Control of Asymmetry Through Conjugate Addition Reactions

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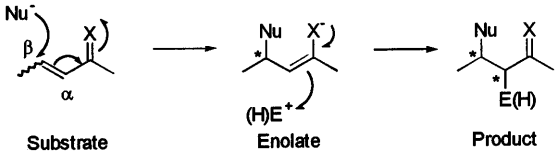
The use of nucleophiles bearing chiral centres, the use of α,β-unsaturated systems with the chirality at the γ position and the presence of chiral ligands or other chiral mediators are the more common sources for the control of asymmetry through Michael addition reactions.

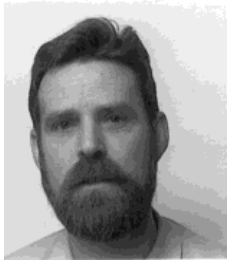
Introduction

The nucleophilic addition of enolates or their analogues to the carbon−carbon double bond of α,β-unsaturated ketones, aldehydes, nitriles, or carboxylic acid derivatives, usually referred to as the Michael reaction, is a fundamental but useful carbon−carbon bond forming reaction (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. For the last decade, there have been great advances for asymmetric Michael reactions. Im-

Scheme 1





Enrique Díez-Barra (top, left) was born in Madrid, Spain in 1954. He received his bachelor of chemistry from the Universidad Complutense, where he also obtained his Ph. D. with M. C. Pardo, working on 1,3-dipolar cycloadditions of azolium ylides in 1982. In 1985 he moved to Ciudad Real, Spain where he created the department of organic chemistry in the new Universidad de Castilla-La Mancha. Alkylation and Michael addition under phase-transfer catalysis conditions have been his preferred topics. Enrique Díez-Barra is now Catedrático of Organic Chemistry and is involved in a new objective: the synthesis of dendrimers.

Sonia Merino (right) was born in Barcelona, Spain in 1971. In 1993 she received her bachelor of chemistry from the Universidad de Castilla-La Mancha, where she also obtained her Ph. D. in 1997 with E. Díez-Barra, working on phase-transfer-catalysed Michael additions. Sonia is now in Toulouse, France as postdoctoral fellow with Professor Jean Pierre Majoral.

John Leonard (bottom, left) was born in Manchester, England in 1954. In 1979 he obtained his Ph. D. with R. Brown, working on biomimetic conversions of secologanin into chincona alkaloids. He spent two years working with G. Stork on the total synthesis of veratrum alkaloids. John is fellow of the RSC and Chartered Chemist, and now senior lecturer in organic chemistry. His research projects are the synthesis of the alkaloid manzamine-A and the development of new methods for asymmetric induction involving chiral lithium amide bases.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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portant aspects of the control of relative stereochemistry through conjugate addition reactions have been discussed in a review paper[1] citing 153 references and covering the literature up to end of March 1994. We will concentrate on more recent literature, but sometimes older data will be used to establish an understanding of these reactions.

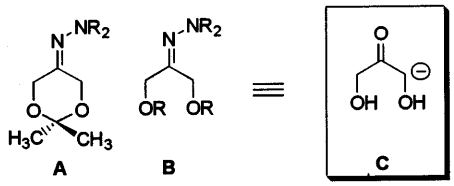
This review is intended to give ways in which the absolute stereochemistry at newly created chiral centres can be controlled. The first part is concerned with an overview of most of the common Michael donors. Sections 2 and 3 of this review will deal with conjugate additions to α,β-unsaturated systems with chirality in the electron-withdrawing group and α,β-unsaturated systems bearing a chiral centre at the γ position. Finally, section 4 is focussed on reactions of achiral nucleophiles to achiral α,β-unsaturated systems in the presence of chiral ligands or other chiral mediators.

1. Conjugate Additions where the Asymmetry is Introduced Via Chiral Centres Covalently Bonded Within the Nucleophile

Enders et al. have developed highly diastereoselective conjugate addition reactions using lithium anions of SAMP [(*S*)-1-amino-2-methoxymethylpyrrolidine] and RAMP [(*R*)-1-amino-2-methoxymethylpyrrolidine] hydrazones. The racemization-free, magnesium monoperphthalate (MMPP) mediated aza Cope elimination of aldehyde SAMP hydrazones generates a CN triple bond. 4-Cyano esters obtained by Michael addition can be converted into *cis*-4,5-disubstituted piperidin-2-ones (*de, ee* > 92%).[2]

In order to obtain the conjugate nucleophilic formylation products, the hydrazones are usually cleaved by ozonolysis followed by reductive workup.[3] Recently, Enders et al.[4] have introduced hydrazones **A** and **B** as useful C_3-building blocks and synthetic equivalents of the dihydroxyacetone d^2-synthon **C** (Figure 1).[5] The addition of a type-A SAMP hydrazone to α,β-unsaturated (*E*)-esters proceeded with a high level of asymmetric induction. Subsequent removal of the chiral auxiliary affords protected 4,6-dihydroxy-5-oxo esters in good overall yields and high diastereo- and enantiomeric excesses.

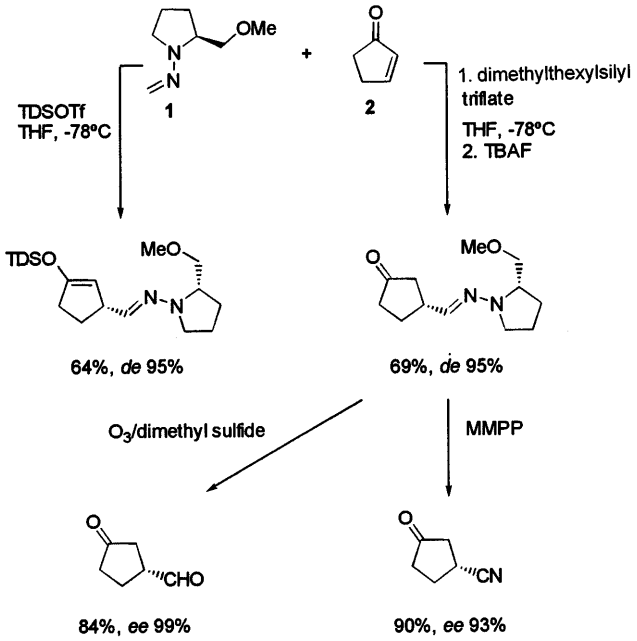
Figure 1



A synthetic method for the asymmetric synthesis of β-amino acids has also been developed by hetero Michael addition of (*S*)-2-methoxymethyl-1-trimetylsilylaminopyrrolidine (TMS-SAMP) and its enantiomer TMS-RAMP to enoates. In this case the SAMP/RAMP reagents act as chiral equivalents of ammonia.[6] The principle of this methodology is the same as that previously developed by Davies et al.[7]

Another example of SAMP hydrazones was developed by Lassaletta et al. They prepared important chiral building blocks, some of them bearing quaternary stereogenic centres, from formaldehyde SAMP hydrazone **1** and the cyclic conjugated enone **2** (Scheme 2).[8] The same workers found that these hydrazones undergo conjugate addition of sugar nitroolefins leading to sugar-derived β-nitro nitriles with high diastereoselective excesses.[9]

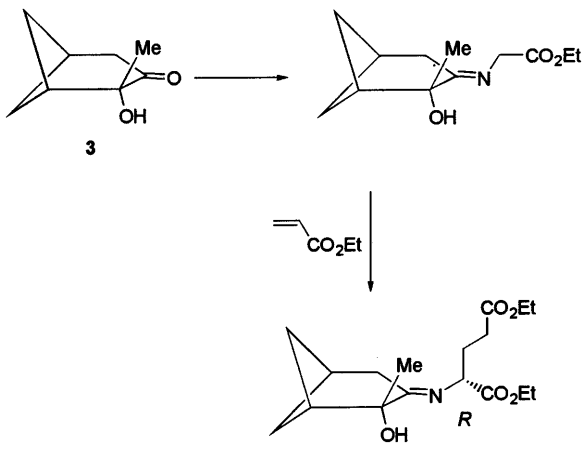
Scheme 2



Enders has also developed a very efficient, highly diastereo- and enantioselective synthesis of 2-substituted 3-aroylcyclohexanones by conjugate addition of metalated amino nitriles to 2-cyclohexenone and subsequent α-alkylation.[10] The title compounds are synthetically useful building blocks, which can be converted into functionalized bicyclic ketones,[11] characteristic structural features of many natural products.

Recently, Solladié-Cavallo et al.[12] utilised hydroxypinanone **3** (Scheme 3) as a powerful chiral auxiliary in

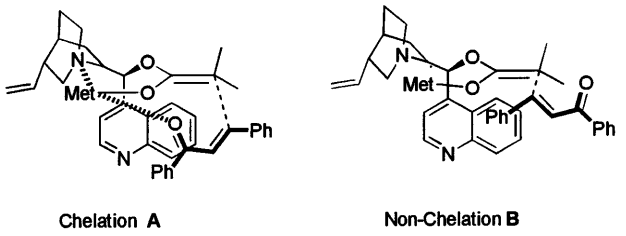
Scheme 3



Michael additions. The outcome of the reaction depends on the starting chiral enolate concentration. High (*R*) diastereoselectivities were obtained under catalytic conditions which can be rationalised through a substrate-directed approach mechanism on a monomeric enolate species. Stoichiometric amounts of DBU/LiBr and DBU/$MgBr_2$ were also used as bases for comparison. The higher (*S*) diastereoselectivity in the case of Mg (98% *S* versus 74% *S* with Li) is probably due to a more rigid and slower exchanging dimeric aggregate.

Fujisawa et al. found that conjugate addition to chalcone of ester enolates having a cinchonyl group as a chiral auxiliary, gave either of the diastereomers selectively by choosing an appropriate enolate metal species.[13] The reversal of the diastereofacial selectivity may be explained in terms of a chelation or non-chelation transition state: the iodozinc enolate formed a chelation state (**A**) with the nitrogen atom of the chiral auxiliary to make *si*-facial attack to enone preferable, whereas the lithium enolate in combination with $SnMe_4$ underwent *re*-facial attack via a non-chelation transition state (**B**) to give the (*R*) isomer (Scheme 4).

Scheme 4



Chelation **A** Non-Chelation **B**

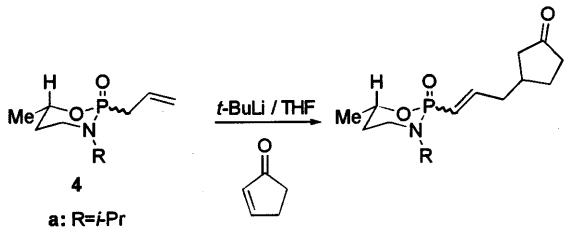
Hoppe et al. have investigated conjugate additions with several enolates bearing auxiliaries derived from oxazolidines.[14] The high diastereoselectivity in the Michael addition of this enolates to 3-buten-2-one, directed by the stereogenic centre at C-2 of the oxazolidine ring, is surprising. The stereochemical result indicates that the enolate carbon atom is attacked from the *si*-face.

Some time ago Wulff reported the first Michael addition reaction of aminocarbene complexes to α,β-unsaturated carbonyl compounds. Unlike their corresponding amide enolates, these anions give exclusive 1,4-addition to a number of enones. The Michael addition of the chiral amino complex**,** derived from prolinol methyl ether with several cyclic enones was investigated and represents the first example of asymmetric reactions of any type of the enolate of either alkoxy- or amino-stabilized group-6 Fischer carbene complexes.[15] Both enantiopodes were examined with cyclohexenone and found to give asymmetric induction in the range of 65−75% *ee* which is comparable with the best induction that has yet been reported for the addition of a chiral acetaldehyde equivalent to cyclohexenone (Scheme 5).

More recently, Licandro et al.[16] have reported the synthesis of pentacarbonyl[*trans*-methyl(2,6-dimethyl)morpholinocarbene]chromium(0) complex together with the stereoselective Michael addition of the conjugate base of complex to enones. This complex gives good diastereoselection in the Michael addition reactions regardless of the fact that the stereogenic centres on the morpholine ring are far from the reacting site.

Wulff has also reported that the enolates of chiral imidazolidinone carbene complexes give high asymmetric inductions in their additions to α,β-unsaturated ketones and serve as convenient chiral acetate enolate equivalents since the adducts can be easily and efficiently cleaved to give δ-oxo esters.[17] Denmark et al.[18] found that anions from chiral phosphane oxides react in a highly diastereoselective manner with cyclic enones. For example, the lithium anion of enatiomerically enriched *cis*-**4a−c** reacted with 5-, 6-, and 7-membered enones giving γ-1,4-addition products **5** with a high degree of stereocontrol (Scheme 6).

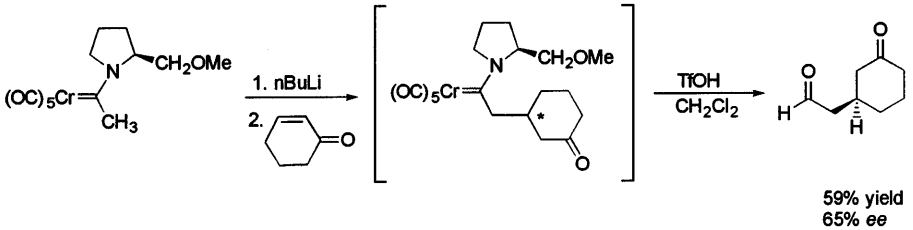
Scheme 6



Lithiated Schöllkopf's bislactim ether also reacted with good facial selectivity as a nucleophile in a conjugate addition to (*E*)-alkenyl phosphonates allowing a direct and stereocontrolled access to a variety of *anti* 2-amino-3-substituted-4-phosphonobutanoic acids, potential agonist of AP4 and mGluRs (metabotropic receptors).[19] The Michael-type addition of chiral imines, derived from racemic α-substituted cyclic ketones and optically active 1-phenylethylamine, to electrophilic alkenes, in neutral conditions, constitutes one of the most efficient methods for the stereocontrolled construction of quaternary carbon centres (Scheme 7).[20]

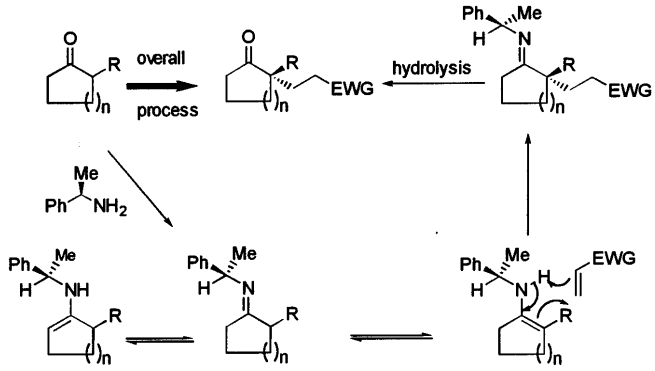
The outcome of these reactions is highly predictable, in terms of both stereochemistry and regiochemistry. It is ap-

Scheme 5



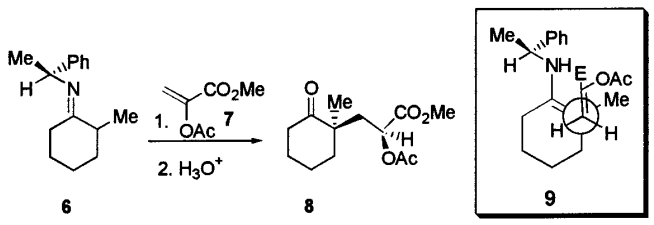
59% yield
65% *ee*

Scheme 7



parent that the mechanism involves a *syn* approach of the reactant partners, and consequently a cyclic (chair-like) transition state. Moreover the proton borne by the nitrogen atom of the enamine should be transferred to the α centre of the electrophile, more or less concertedly with the creation of the C−C bond. d′Angelo et al. reported novel experiments in which the stereochemical course strongly supports this mechanism. For example, addition of imine **6** to **7** proceeded smoothly, leading to adduct (2*S*,1′*R*)-**8** (Scheme 8).[21] The remarkable complete stereocontrol of the two stereogenic centres in adduct **8** was best interpreted by evoking for the addition the compact approach **9** that involves a *synclinal* arrangement of the two partners: electrophile **7** and as nucleophilic species, the more substituted secondary enamine, which is in tautomeric equilibrium with imine **6**. According to such a model, the alkylation takes place *anti* to the phenyl ring of the chiral amine moiety in its energetically preferred conformation (C−H eclipsing the cyclohexane ring), thereby generating the (*R*) configuration at the quaternary carbon centre. The total stereocontrol observed at the tertiary centre requires that the transfer of the N−H proton of the enamine to the C-2 carbon atom of the electrophilic alkene **7** be concerted with the creation of the C−C bond. It is worthy of note that in order to account for the observed (2*S*) configuration, the electrophilic partner **7** needs to be arranged as depicted, namely with the methoxycarbonyl group "*endo*" to the enamine part. This predominant "*endo* preference" can be reasonably interpreted in terms of a cooperative effect between steric and stereoelectronic factors.[22]

Scheme 8



The tolerance of the process to other substituents at the α position of the ketone has been explored. The addition of enamino ester **11** to methacrylate **10** furnished adduct **12** as a single compound (*de* and *ee* > 95%), thereby allowing the simultaneous, complete stereocontrol of a quaternary carbon centre and a tertiary one in the β position (Scheme 9).[23] Examples which indicate the scope of these conjugate addition reactions were also reported.[24][25]

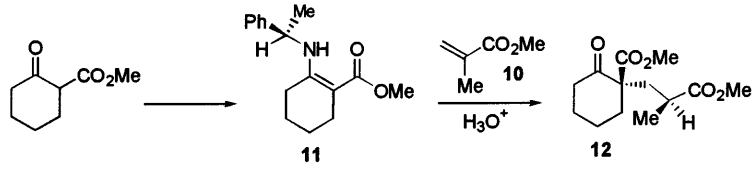
Koga et al.[26] carried out asymmetric Michael reaction of chiral enamines prepared from α-alkyl β-oxo esters and (*S*)-valine *tert*-butyl ester. They discovered that the diastereoselectivity of this reaction is highly sensitive to the solvent system. The lithiated chiral enamines react with di-*tert*-butyl methylenemalonate in toluene/HMPA to give α,α-dialkylated β-oxo esters in 87−92% *ee* after hydrolysis. On the other hand, the reactions in THF give the corresponding antipodes in 84−95% *ee*.

This type of asymmetric reaction has been widely applied to the enantioselective synthesis of various compounds of natural origin, including terpenes, steroids and alkaloids. d′Angelo et al. have recently developed a concise, direct approach for the total enantioselective synthesis of (+)-vincamine.[27] The key tactical element was the asymmetric Michael addition of a chiral enamino lactam to methyl acrylate to create stereoselectively the crucial quaternary carbon centre at C-20. Thus, according to the strategy that was ultimately adopted, involving the Wolff-Kishner reduction of the oxo group of the intermediate adduct, (+)-vincamine has been synthesised by a linear sequence of 15 chemical operations, with an overall yield of 1.2% (mean yield per step: 74%), from commercially available tryptamine.

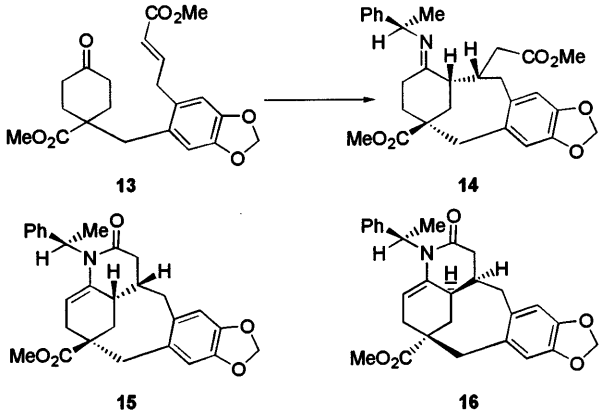
Also oxo ester **13** led to a 2:1 mixture of "*all-cis*" polycyclic adducts **15** and **16**, structurally related to the taxane series. The major Michael adduct **14** was the initial product, which then lactamised to give **15** (Scheme 10).[28]

Mayrargue et al.[29] have developed a novel application of the Michael addition to optically active enamines for the preliminary steps in the synthesis of the artemisinin analogues. Quite recently, Pfau et al. have reported an enantioselective synthesis of (−)-Polywood through Michael-type reaction of chiral imines.[30] Fortunak et al. have reported the synthesis of (*S*)-10-hydroxycamptothecin. The chiral centre is derived utilising Seebach's chemistry[31] for the

Scheme 9



Scheme 10



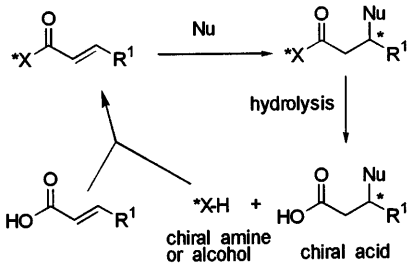
diastereoselective Michael addition of a chiral dioxolanone enolate to a methylene malonate acceptor.[32] Diastereoselective Michael reactions of methyl (2-trialkylsilyl)-tetrahydrofuran-3-carboxylates with methyl cinnamate have been reported.[33] The silicon group can be removed under mild oxidative conditions to generate an oxonium cation which is capable of intramolecular nucleophilic capture.

2. Conjugate Additions to α,β-Unsaturated Systems with Chirality in the Electron-Withdrawing Group

2.1. Conjugate Additions to α,β-Unsaturated Esters and Amides Derived from Chiral Alcohols and Chiral Amines

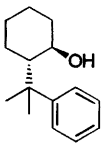
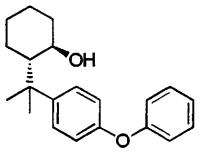
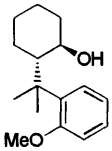
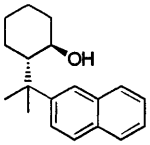
A variety of nucleophiles add to α,β-unsaturated esters and amides in a conjugate manner. If the alcohol or amide from which the system is derived is a chiral unit, there is a potential for asymmetric induction. Hydrolysis would then release the original chiral auxiliary group as well as a chiral acid (Scheme 11).

Scheme 11



The ability of cyclohexyl-based chiral auxiliaries to control the interaction of reagents with tethered substrates has been extensively exploited for asymmetric synthesis.[34] d′Angelo and Dumas have reported that an almost complete stereocontrol can be obtained in the conjugate addition of diphenylmethanamine to chiral crotonates derived from certain "arylmenthol-type" auxiliaries (Scheme 12).[35] This high efficiency has been attributed to the predominance, in such crotonates, of stacked conformations. Thus, the presence of a one-carbon spacer substituted by a dimethyl group, between the aryl nucleus and the cyclohexane ring in the chiral auxiliary component, is crucial in order to gain a good facial selectivity.

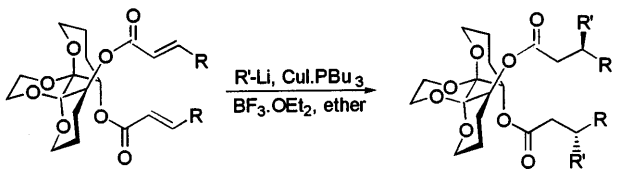
Scheme 12

Chiral Auxiliary R*OH	de (%)	Chiral Auxiliary R*OH	de (%)
	60		97
	99		98

Chiral α,α-disubstituted β-oxo esters are versatile building blocks for the synthesis of many natural compounds containing stereogenic quaternary carbon centres. Guingant et al. have developed a new method for the preparation of α,α-disubstituted β-oxo esters of high enantiomeric purity.[36] Their methodology involved the addition of β-enamino ester to chiral acrylates followed by treatment of the primary adduct with an excess of Meerwein′s reagent in order to remove the chiral auxiliary. Recently, Chiappe et al.[37] utilised naphthyl 3,4,6-tri-*O*-methyl-β-D-glucopyranoside as a chiral auxiliary in an asymmetric Michael addition to the 2-*O*-crotonyl glucopyranoside derivative, showing that this compound can be a valid alternative to the use of 8-aryl menthol derivatives as chiral auxiliaries.

A bifunctional, C_2-symmetrical chiral auxiliary derived from dihydroxylated dispiro ketals has been used by Ley[38] to induce a high degree of asymmetry in Michael additions of cuprates to a variety of di-α,β-unsaturated ester systems (Scheme 13).

Scheme 13



Guingant et al. have also investigated conjugate addition on several α,β-unsaturated amides bearing auxiliaries derived from proline.[39] They achieved fairly good *de* values using β-enamino esters with α,β-unsaturated amide derivates in Lewis acid promotor′s presence.

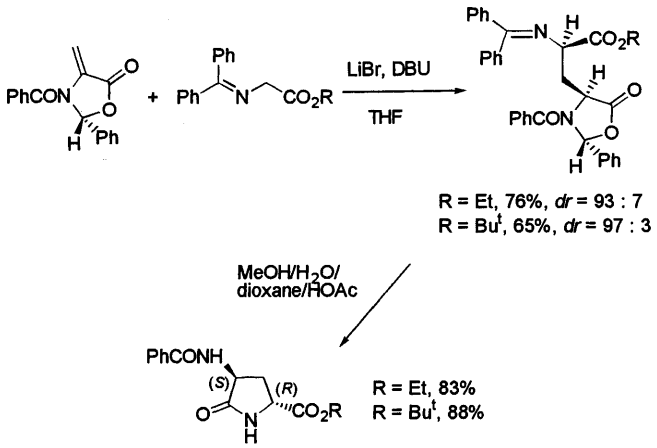
Hruby et al. achieved fairly good diastereoselectivity through conjugate Grignard additions to 4-phenyl-2-oxazolidinone-derived α,β-unsaturated amides. This methodology was an efficient procedure to prepare sterically hindered β-branched isohexanoic acid derivatives.[40] In more recent studies amino acids like β-isopropyl-2′,6′-dimethyltyrosines have been synthesised by a catalytic asymmetric

Michael addition of an organocuprate to a chiral α,β-unsaturated acyloxazolidinone.[41] The reactions generally proceeded in good stereoselectivities (75−95% *ee*/*de*) and yields (70−90%), making these optically active amino acids available on a large scale for the practical synthesis of peptides.

2.2. Other Types of Chiral Michael Acceptors

Jackson et al.[42] have established that nucleophilic addition of a range of simple alkyl and aryl organometallics (lithium, copper-lithium and Grignard reagents) to (α-silylvinyl)sulfoximines proceeds in good yield and, in many cases, with high stereoselectivity, to give the Michael adducts. The reactions of (2*R*)-phenyl-4-methyleneoxazolidin-5-ones with imines giving Michael adducts with the (2′*R*) stereochemistry have been reported.[43] Thus a practical method has been developed for the synthesis of 4-benzamidopyroglutamate (Scheme 14).

Scheme 14



The Michael addition reactions of ketone and ester lithium enolates to optically active Fischer vinylcarbene complexes derived from (−)-8-phenylmenthol take place with high *syn* selectivity and high levels of asymmetric induction. The initial Michael adducts can be further elaborated through diastereoselective addition of organometallic reagents to ketones and aldol reactions. Removal of the metal fragment and chiral auxiliary group leads to cyclic enol ethers with three or five contiguous stereogenic centres and of high enantiomeric purity.[44] The chiral (−)-8-phenylmenthyloxy-substituted Fischer vinylcarbenes show better *syn* diastereoselectivity than the corresponding methoxy and ethoxy derivatives[45][46] or the *O*-chelated imidazolidinone carbene complexes[47] in the reactions with lithium enolates. This is presumably because they are sterically more encumbered and therefore discriminate more effectively between the diastereomeric transition states, regardless of whether these chiral complexes undergo Michael addition in an *s-trans* conformation or an *s-cis* conformation of the vinylcarbene moiety.

3. Conjugate Addition to α,β-Unsaturated Systems Bearing a Stereocentre at the γ Position

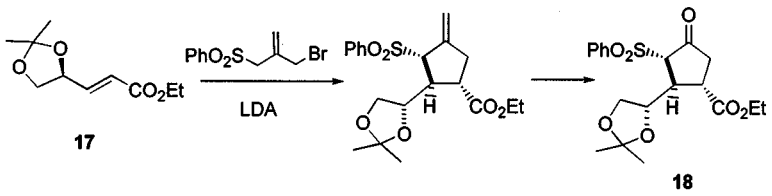
3.1. Reactions with Acyclic α,β-Unsaturated System

Extensive studies conducted in recent years have shown that γ-oxygen substitution in acyclic α,β-unsaturated carbonyl derivatives can sometimes exert a high degree of stereocontrol in conjugate additions. Among the factors influencing the stereochemical outcome, the structure of the organometallic reagent seems of utmost importance. Reversal of the stereochemical outcome in these reactions has often been observed and the rationalisation of sometimes confusing results is not yet conclusive. For instance, utilisation of allyllithium reagents[48] as well as of alkyl-[49] and vinylcopper reagents[50] resulted predominantly in *anti* adducts whereas alkyllithium reagents[51] and allylic cuprates[52] afforded mostly *syn* adducts. A very recent paper on the use of lithium dialkylamides as nucleophiles showed a high *syn* diastereoselection induced by the presence of bulky alkoxy groups at the γ position.[53]

Ghera and Hassner[54] have explored γ-oxygenated α,β-unsaturated (*E*)-enoates as acceptors for eventual asymmetric cyclopentanation. Good diastereofacial *anti* selectivity has been achieved in Michael reaction initiated ring closure reactions of the conjunctive reagent with γ-oxygenated enoates which afforded *trans-trans*-trisubstituted methylenecyclopentanes. The use of a nonracemic acceptor **17** led to the synthesis of the optically active cyclopentanone **18** with a very good *de* value (Scheme 15).

Lassaletta et al. studied the addition of nitro olefin groups within sugar derivatives to formaldehyde *N,N*-dimethylhydrazone and found that the reaction proceeds at room temperature without any need of base or catalyst. By mixing the reagents, β-nitro dimethylhydrazones are formed in good yields and high stereoselectivities and no epimerization occurred in the cleavage of the dimethylhydrazone group. Several Michael adducts have been successfully

Scheme 15



17 18

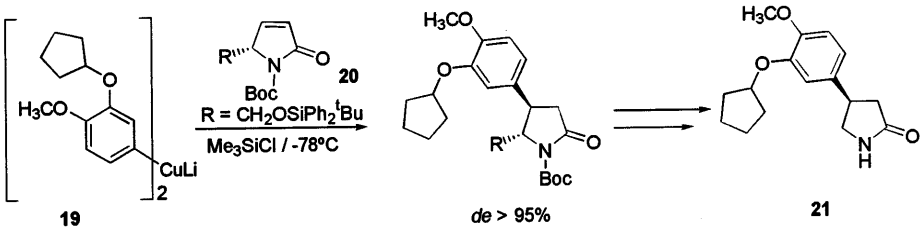
transformed into β-nitro aldehydes by ozonolysis and into β-nitro nitriles in excellent yields by treatment with MMPP.[55]

3.2. Reactions with Cyclic α,β-Unsaturated Systems

The stereochemical course of Lewis acid catalysed Michael reaction of 4-siloxycyclopentenone with ketene silyl acetals has been reported.[56] These reactions are shown to proceed with sterically unfavourable *syn* preference (to the siloxy group) when steric demand of the acetals is slight, whereas β substitution of acetals results in reversal of diastereoselection. These results are discussed in terms of the stereoelectronic vs. steric effects.

(*R*)-(−)-Rolipram (**21**), which is of great interest as a therapeutic agent for the treatment of central nervous system disorders,[57] was prepared using a type of Michael reaction approach from readily available starting materials.[58] The key step is a stereoselective Michael addition of an arylcuprate **19** to a modified pyroglutamic derivative **20** which acts as the template to induce the stereoselectivity. Facile manipulation of the enantiomerically pure Michael product afforded the expected therapeutic agent (Scheme 16).

Scheme 16



4. Conjugate Additions of Achiral Nucleophiles to Achiral α,β-Unsaturated Systems in the Presence of Chiral Ligands or other Chiral Mediators

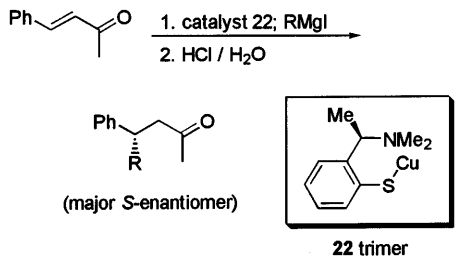
Enantioselective reactions of achiral substrates in the presence of chiral additives is a very attractive prospect, especially if the chiral additive can be used as a catalyst. This is an area of study that has attracted a good deal of attention in recent years. Recent reviews[1][59] have covered the literature up to end of March 1994 and this review will therefore highlight processes that proceed with high enantioselectivity and novel methods that have been reported recently.

4.1. Modification of Cuprate and Magnesium Reagents

An array of chiral alcohols and amines have been incorporated within cuprate reagents as non-transferable ligands. Several groups investigated asymmetric conjugate addition using (*S*)-2-methoxymethylpyrrolidine (SMP) as chiral auxiliary ligand.[60] Quinkert et al.[61] employed the enantioselective conjugate addition of chiral-ligand-modified organocuprates to 2-methylcyclopent-2-en-1-one in the total synthesis of the pseudoguainolide (+)-confertin. Good yields (76%) and enantioselectivities (*ee* = 75%) were observed when SMP was used.

Koten et al.[62] found that (arenethiolato)copper(I) complexes **22** act as efficient homogeneous catalysts in Michael addition reactions of several Grignard reagents to acyclic enones. The addition products are formed with excellent chemoselectivity (> 99%) and good enantioselectivity (76% *ee*) (Scheme 17).

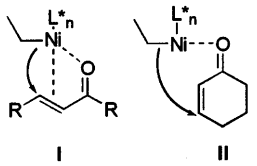
Scheme 17



4.2. Modification of Organozinc Reagents

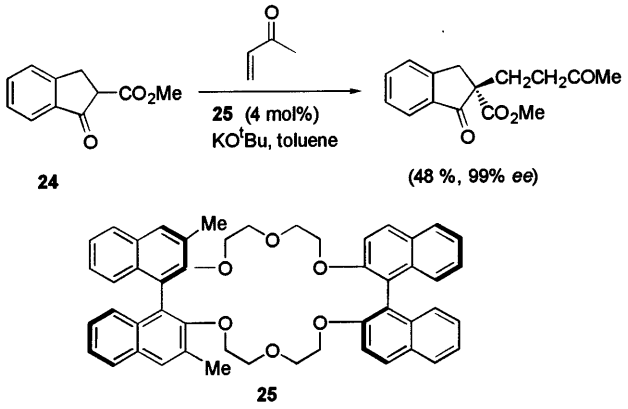
Feringa et al. carried out conjugate additions using chiral zinc complexes in conjunction with Grignard reagents, but the enantioselectivities of such reactions were generally very low.[63] Recently, the same workers have used catalytic quantities of several novel tri- and tetradentate amino alcohol ligands, all derived from (+)-camphor, in the nickel-catalysed conjugate additions of diethylzinc to chalcone and cyclohexenone.[64] However, the goal to develop a catalytic system, capable of enantioselective conjugate addition of diethylzinc to both cyclic and acyclic substrates failed. Apparently, in the nickel-catalysed alkyl transfer a chiral alkylnickel species is formed with affinity to the carbonyl oxygen atom resulting in an enantioselective alkyl transfer in the case of *s-cis* enones, i.e. chalcone, as is shown in Figure 2 (**I**). In the case of cyclohexenone, intermediate **II** will probably be formed with the chiral alkylnickel species too far away from the β position and therefore not able to introduce any asymmetry in the conjugate addition.

Figure 2



Catalytic enantioselective conjugate addition reactions of diethylzinc to chalcone using $Co(acac)_2$ and chiral amino alcohols derived from (+)-camphor have also been reported. Enantioselectivities up to 83% were achieved with these reagents.[65]

Scheme 19

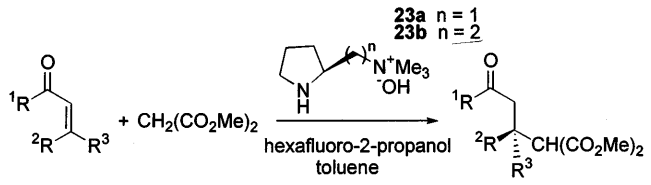


4.3. Modification of 1,3-Dicarbonyl Compounds and other Activated Nucleophiles

Loupy and Zaparucha found that various quaternary ammonium salts catalysed the enantioselective Michael addition of *N*-acetylaminomalonate to chalcone under phase-transfer catalysis conditions without solvent.[66] In more recent studies the same group discovered that ultrasound irradiation enhances the rate and improves the yield of the heterogeneous asymmetric Michael reaction without any modification of the enantioselectivity with respect to standard procedure. These improvements are assigned to ultrasonic mechanical effects.[67]

Moderate enantioselectivities have been achieved for additions of malonates to enones using the ammonium hydroxides **23a** and **23b**, easily prepared from (*S*)-proline, as chiral catalysts (Scheme 18).[68]

Scheme 18



A spectacular asymmetric induction (99% *ee*) has been achieved in the Michael addition of the cyclic substrate **24** to methyl vinyl ketone in the presence of 4 mol-% each of crown ether **25** and KO*t*Bu at −78°C (Scheme 19).[69]

Several other asymmetric inductions have been reported using chiral crown ethers as catalyst. Brunet et al. explored the use of optically active crown ethers derived from (1*R*)-(+)-camphor in the Michael addition of phenylacetate to acrylate. The mechanism of their catalytic effect is discussed in terms of kinetic vs. thermodynamic control in the formation of the catalytic ion-pair complexes. The relative basicity of the complexes formed between the alkaline metals and the unprotonated chiral crown ethers plays an important role in the stereochemical outcome. AMBER and AM1 calculations support that the reaction in which the best *ee* (83%) is obtained proceeds under kinetic control.[70]

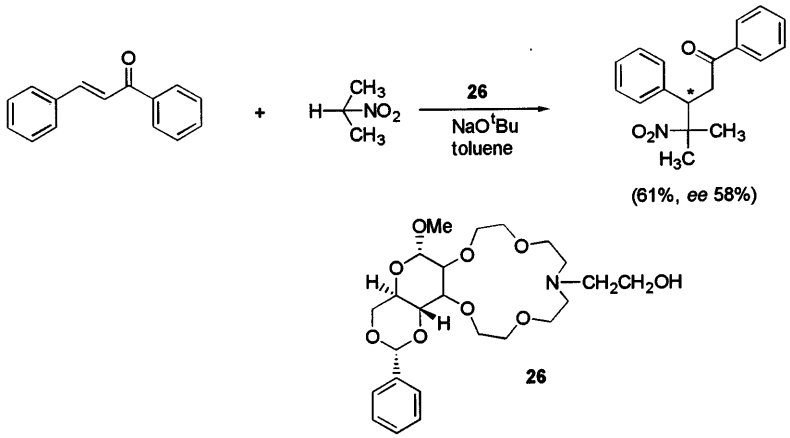
A novel class of crown ether derivatives incorporating D-glucose has also been synthesised. Catalytic activity of macrocycles in asymmetric Michael addition reaction was also studied. The average cavity size of these macrocycles was determined by the application of the MMX programme.[71] Töke et al. have used crown ethers anellated to sugar units to catalyse the enantioselective carbon−carbon bond-forming reaction of methyl phenylacetate with methyl acrylate with *ee* values up to 80%.[72] In a similar fashion, crown ether **26** shows significant asymmetric induction as phase-transfer catalyst in the Michael addition of 2-nitropropane to chalcone (Scheme 20).[73]

Several important new organometallic catalysts for conjugate additions have been reported recently. Ito et al.[74] found that a rhodium complex involving *trans*-chelating chiral diphosphane ligand (*S*,*S*)-(*R*,*R*)-PhTRAP (PhTRAP: 2,2′′-bis[1-(diphenylphosphanyl)ethyl]-1,1′′-biferrocene) is an effective catalyst for the Michael reaction of 2-cyano-*N*-methoxy-*N*-methylpropionamide with vinyl ketones or acrolein to produce optically active Michael adducts with high enantiomeric excesses (89−94%) in high yields.

Recently, chiral Rh^I catalysts containing a novel chiral bisphosphane ligand have been reported.[75] Moderate enantioselectivities (73% *ee*) have been achieved for additions of 2-cyanopropionates to methyl vinyl ketone in the presence of 1 mol-% of the catalyst. A Lewis acid promoted Michael addition of 2-(trimethylsilyloxy)furan to 3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one was recently published. A 1:1 complex prepared from scandium triflate and 3,3′-bis(diethylaminomethyl)-1,1′-bi-2-naphthol in situ showed excellent *anti* selectivity and moderate enantioselectivity, while bis(oxazoline)Cu^{II} complexes exhibited excellent enantioselectivity and moderate to good *anti* selectivity.[76] This is the first example of asymmetric and catalytic Michael addition of 2-(trimethylsilyloxy)furans.

Several biscopper(II) complexes with chiral ligands derived from 2-substituted 2-(salicylideneamino)ethanols have also been tested as catalysts of enantioselective Michael re-

Scheme 20



actions between methyl 1-oxoindan-2-carboxylate and 3-buten-2-one.[77] The degree of enantioselection is strongly affected by the architecture of the ligand. The best result (75% *ee*) was obtained for a ligand having a substituent potentially suitable to induce the formation of a bis-tetradentate copper(II) complex with a square-pyramidal coordination.

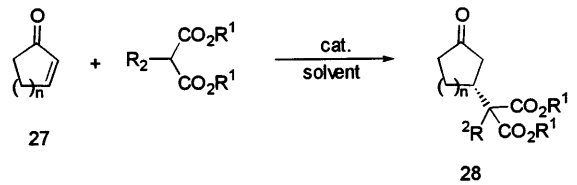
Bernardi and Scolastico found that Cu^{II} complexes of the bis(oxazolines) are effective promoters for the diastereo- and enantioselective conjugate addition of propionate silylketene acetal to 2-(methoxycarbonyl)cyclopentenone,[78] although *ee* values were modest. The same workers reported Michael-Mukaiyama additions promoted by TADDOL-derived Ti chlorides (TADDOL: 2,2-dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol) with excellent *de* values and *ee* values up to 47%.[79] Jorgensen et al. used TiX_2-TADDOLate and $TiCl_2$-BINOLate complexes (BINOL: 1,1′-naphtalene-2,2′-diol) to catalyse the addition of *O*-benzylhydroxylamine to α,β-unsaturated *N*-acylated 1,3-oxazolidinones giving β-amino acid precursors.[80]

Yamaguchi et al. found that rubidium salts of L-proline promotes the catalytic asymmetric Michael addition of malonate anions to enones and enals.[81] This reaction can be applied to a wide range of acceptors and gives adducts with a predictable absolute configurations. For example rubidium salts of proline catalyse the asymmetric Michael addition of nitro alkanes to prochiral acceptors. When (2*S*)-L-prolines were used, acyclic (*E*)-enones gave (*S*) adducts and cyclic (*Z*)-enones gave (*R*) adducts predominantly. Enantiomeric excesses exceeding 80% were attained in some reactions of secondary nitro alkanes. The nitro group of the adducts can be replaced with hydrogen by Bu_3SnH reduction. The overall transformation is equivalent to an asymmetric β-alkylation of the enone.[82]

Very high enantioselectivities for a range of reactions were reported by Sasai et al. using lithium-free lanthanum sodium BINOL complex (LSB) as an asymmetric catalyst for Michael reaction of various enones with malonates to give Michael adducts in up to 92% *ee* and almost quantitative yield.[83] LSB was also applied to a catalytic asymmetric Michael reaction in which the asymmetric centre is induced on the side of the adduct originating from the Michael donor. Moreover, the reaction was not so affected by the choice of rare-earth metal.[84]

The new heterobimetallic asymmetric catalyst consisting of aluminum, lithium, and BINOL has been also reported. This catalyst was effective in the Michael reaction of cycloalkenones **27** with dialkyl malonates providing high yields of **28** in 99% *ee*. Mechanistic studies on AlLi-(*R*)-BINOL complex also acts as a multifunctional heterobimetallic asymmetric catalyst. Furthermore, three-component coupling reactions were achieved by trapping the aluminium enolate intermediate with an aldehyde for the first time (Scheme 21).[85]

Scheme 21



Recently, the C_2-symmetric chiral amino diol (1*R*,5*R*)-3-benzyl-1,5-diphenyl-3-azapentane-1,5-diol [(*R*,*R*)-I] has been synthesised. The heterobimetallic catalyst [I_2-Al-Li] obtained by reaction of the amino diol (*R*,*R*)-I with $LiAlH_4$, promotes the asymmetric Michael addition of malonic esters to α,β-unsaturated compounds with high enantiomeric excess.[86] Chiral lithium alkoxides were designed and applied to enantioselective Michael reaction of methyl phenylacetate and methyl acrylate to give the corresponding adduct in enantiomeric excess up to 84%.[87] The same workers have also studied the enantioselective Michael reaction of ketone lithium enolates as the Michael donors using a chiral imine as an external ligand. The adducts were obtained in 52−100% yield and the *ee* values of up to 94%.[88]

5. Conclusion

Chiral auxiliaries based on carbohydrates, crown ethers and heterobimetalic compounds have appeared as new and efficient tools for asymmetric Michael additions. The developement of new auxiliaries and modifications of the classical ones for more specific reactions and the research on new reagents with wide applicability are important challenges for the future.

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