Pergamon

Tetrahedron 56 (2000) 8033–8061

TETRAHEDRON

Tetrahedron Report Number 542

Enantioselective Conjugate Additions

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Received 26 April 2000

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1. Introduction

Enantioselective bond construction is a rapidly growing endeavor in the synthetic community. This is in response to the increasing demand for enantiomerically pure compounds such as pharmaceuticals. Conjugate additions (1,4-additions) involve the addition of nucleophiles (also referred to as donors) to alkenes or alkynes attached to an electron withdrawing group (also referred to as acceptors).[1] This nucleophilic addition is followed by the trapping of the anionic intermediate with an electrophile, which is a proton in the simplest case (Scheme 1).

Conjugate addition is one of the most important bond forming strategies available to the synthetic organic chemist. This is mainly due to the broad spectrum of donors and acceptors that can be employed in this reaction. The nucleophiles can be carbon or heteroatom based (H, N, O, S, Si, P, Se, Sn, I). The diversity in acceptors arises due to the many activating groups possible (ketones, aldehydes, esters, amides, nitriles, nitro, sulfonates, sulfoxides, phosphates, phosphonates etc.).

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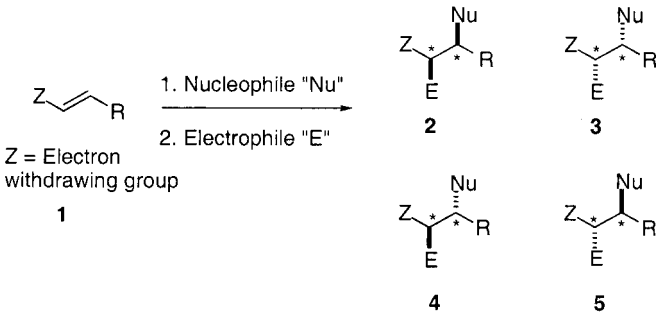


Scheme 1.

In principle, one can establish the stereochemistry at both α and β carbons of the acceptor. When the carbon–nucleophile bond is formed enantioselectively, the process is called enantioselective conjugate addition (ECA). Enantioselectivity in conjugate addition can be achieved in a number of ways:

(a) using a chiral non-transferable group attached to the nucleophile;
(b) using an external chiral ligand, which complexes to the nucleophile;
(c) using a chiral ligand that binds to the acceptor and dictates the approach of the nucleophile;
(d) using a chiral Lewis acid (chiral ligand and metal salt) that activates the acceptor;
(e) using a chiral entity that brings together both the acceptor and donor.

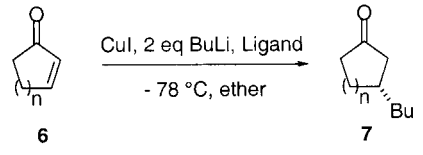
In case (a), catalysis is not possible by virtue of the reaction stoichiometry, whereas in the other four cases there is a possibility for using catalytic amounts of the chiral source. All the variants need a ligand/auxiliary for the chiral source.[2] Most popular among chiral ligands have been those with C_2-symmetry. However, many examples of non C_2-symmetric ligands have come into existence recently. Undoubtedly, the success of ECA and of asymmetric synthesis ultimately depends on the spatial control in proximity to the reaction site in order to dictate a high degree of enantiofacial bias. This review will focus on ECA achieved with various nucleophiles in the past decade with some reference to older literature. Most of the examples involve the formation of a new chiral center at the β-carbon of the acceptor. The previous comprehensive review on asymmetric conjugate addition by Rossiter and Swingle covered the addition of organometallic reagents.[3a] More recently, Feringa and De Vries have reviewed enantioselective carbon–carbon bond formation[4] and Merino et al. have presented a survey of some examples in ECA.[5]

2. Addition of Organocuprate Reagents

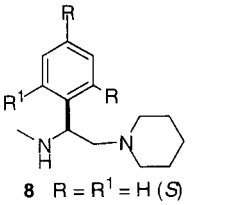
Enantioselective conjugate additions of organocuprates have been realized in two ways: either by the use of a chiral non-transferable ligand or using an external chiral ligand. Several reviews have appeared on the conjugate addition of cuprates, some of them focusing on the mechanistic and structural aspects of cuprates.[6]

2.1. Use of chiral non-transferable ligands

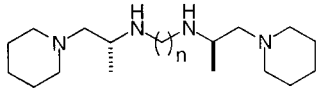
Many examples of diastereoselective and enantioselective conjugate additions with chiral amidocuprates were reviewed by Rossiter and Swingle.[3a] Building upon their previous results on the ECA of amidocuprates using (*S*)-*N*-methyl-1-phenyl-2-(1-piperidinyl)ethanamine [(*S*)-MAPP] ligand **8**, Rossiter et al. prepared new tetraamine ligands, called (*R*,*R*)-DIMAPP-*n* [DIMAPP-4: *N*,*N*′-Di-(1-phenyl-2-(1-piperidinyl)ethyl)-1,4-butanediamine] **11** and **12** where *n* is the number of bridging methylene units. The selectivity for the addition of cuprates to various



entry	n	ligand	yield (%)	ee (%)
1	1	**8**	51	45 (*S*)
2	1	**12**	15	71 (*R*)
3	2	**8**	92	83 (*S*)
4	3	**8**	63	97 (*S*)
5	3	**9**	84	65 (*R*)
6	3	**10**	59	30 (*R*)
7	4	**8**	50	86
8	4	**11**	46	76



8 R = R^1 = H (*S*)
9 R = Me, R^1 = H (*R*)
10 R = R^1 = Me (*R*)



(*R*,*R*)-DIMAPP-n
n = 4, **11**
n = 6, **12**

Scheme 2.

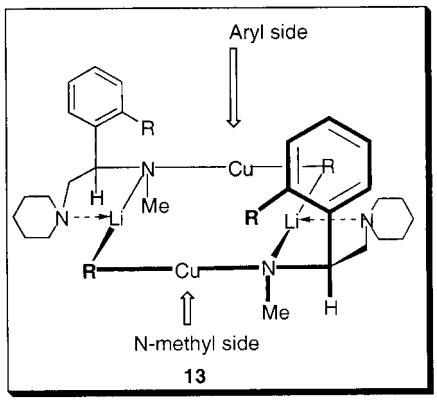


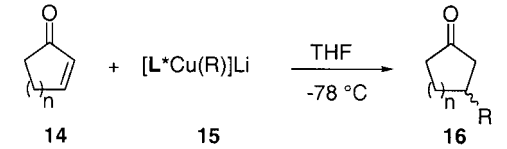
Fig. 1.

cycloalkenones depended on the length of the methylene bridges (Scheme 2).[7] The initial model proposed for enantioselection was corroborated based on variations made to the MAPP ligand: *ortho* substitution of methyl groups to the aromatic ring showed a decrease in enantioselectivity (entries 4–6). Accordingly, cyclohexenone should approach from the aryl side of the complex **13** rather than from the *N*-alkyl side (Fig. 1).[7b]

Initial exploration of cuprate conjugate additions utilized chiral heterocuprates and their efficacy has been demonstrated in many total syntheses. Only recently, chiral carbanionic ligands as non-transferable ligands have received attention. Gais and Boßhammer used cyclic α-sulfonimidoyl carbanions **17** in the conjugate addition of alkylcuprates to cycloalkenones with good ee's (Scheme 3).[8]

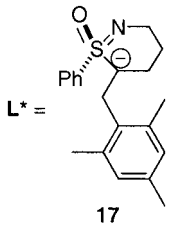
2.2. External chiral ligands in organocuprate additions

Unlike the non-transferable ligands, external ligands can be utilized in substoichiometric amounts. This aspect makes these ligands an attractive alternative. Addition of methyllithium to cyclohexenone in the presence of CuI and bidentate β-amino sulfide ligands **20** and **21** was investigated by Gibson et al. (Scheme 4).[9] The best results obtained (64% ee, 33% yield) were unfortunately irreproducible. The inconsistent results have been attributed to the different batches of methyllithium used. Reactions in toluene gave the opposite enantiomer compared to ethereal solvents. The

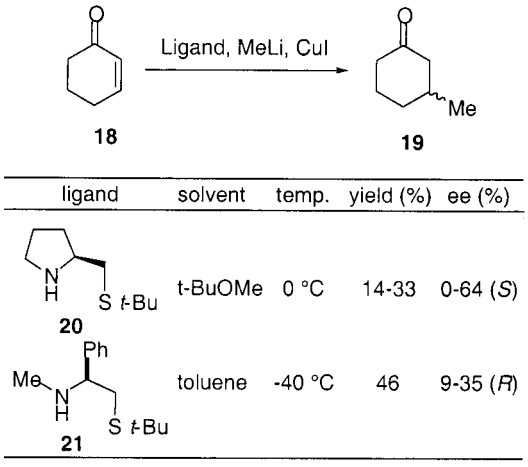


n	R	yield (%)	ee (%)
1	Me	50	86 (*S*)
1	$(CH_2)_3OEE^*$	70	79 (*R*)
1	*n*-Bu	90	99 (*S*)
2	*n*-Bu	80	93 (*S*)
3	*n*-Bu	90	77 (*S*)

* EE = -CH(Me)OEt



Scheme 3.



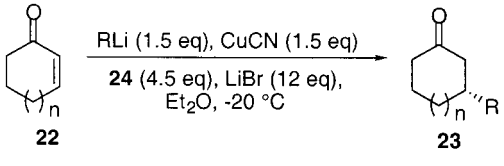
ligand	solvent	temp.	yield (%)	ee (%)
20	t-BuOMe	0 °C	14-33	0-64 (*S*)
21	toluene	-40 °C	46	9-35 (*R*)

Scheme 4.

donor solvents change the geometry around copper and can influence the aggregation of the cuprate reagent.

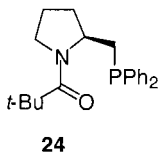
Similar additions of alkylcuprates were investigated by Tomioka and co-workers using chiral amidophosphines and CuCN (Scheme 5).[10] In the absence of lithium salts the addition of methylcopper proceeds with low selectivity. The effect of copper and lithium counterions was found to be crucial. The donor ability of solvent plays an important role: THF produced racemic material whereas ether gave good selectivity.[10b] High ee's were obtained with high loading of the ligand **24** and lithium bromide. As is well established, the addition of TMSCl activated the addition of cuprate in the presence of HMPA. This methodology was extended to other cycloalkenones with reasonable success.

The same authors also studied the addition of lithium organocuprate to chalcone **25** in the presence of chiral amidophosphines **24**, **27** and **28**.[10a] Ligand fine tuning was the major focus of this investigation. Early ^{13}C NMR studies of various ligands in toluene–ether with added lithium or copper salts showed that amido carbonyls are important for coordination to lithium and that the phosphines are required for coordination to copper.[10c] This metal-differentiating coordination provides the structural organization required for selectivity. By varying the substituent on nitrogen and

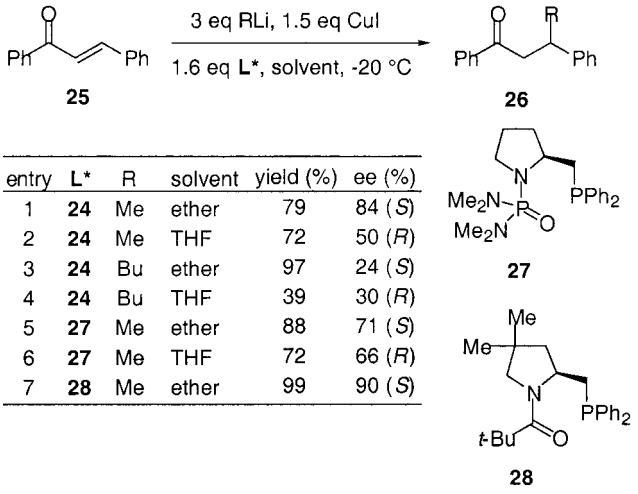


entry	n	R	yield (%)	ee (%)
1*	1	Me	66	92
2	1	Et	89	91
3	1	Ph	63	73
4	0	Et	90	94
5	0	Bu	99	95
6*	3	Me	46	68

* 3 eq of TMSCl/HMPA added

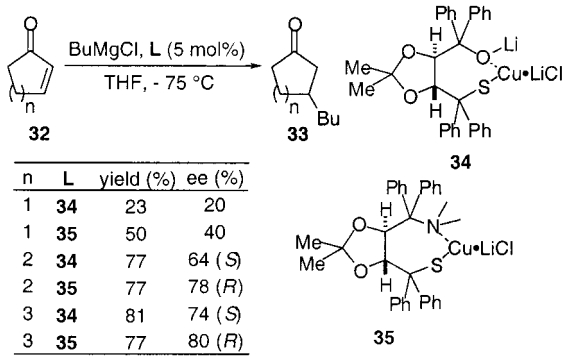


Scheme 5.



entry	L*	R	solvent	yield (%)	ee (%)
1	**24**	Me	ether	79	84 (*S*)
2	**24**	Me	THF	72	50 (*R*)
3	**24**	Bu	ether	97	24 (*S*)
4	**24**	Bu	THF	39	30 (*R*)
5	**27**	Me	ether	88	71 (*S*)
6	**27**	Me	THF	72	66 (*R*)
7	**28**	Me	ether	99	90 (*S*)

Scheme 6.



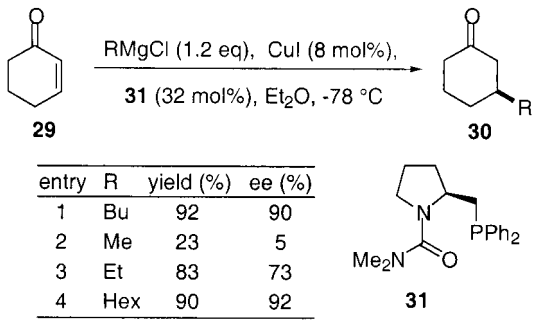
n	L	yield (%)	ee (%)
1	**34**	23	20
1	**35**	50	40
2	**34**	77	64 (*S*)
2	**35**	77	78 (*R*)
3	**34**	81	74 (*S*)
3	**35**	77	80 (*R*)

Scheme 8.

the steric bulk on the pyrrolidinone ring, ligands of various potencies were prepared and tested (Scheme 6). Solvent dependence was two fold: donor solvents were required for enantioselectivity and the strength of the donor solvent was important for high ee's and sense of stereoinduction. THF and DME gave the (*R*) enantiomer while ether, toluene and dimethyl sulfide gave the (*S*) enantiomer. Best results were obtained with the second generation ligand **28** containing 3,3-dimethyl substituents. A model based on an eight centered dimeric cuprate structure has been proposed for the enantioselection in the case of chalcones.

3. Enantioselective Conjugate Addition of Grignard Reagents: Catalysis

The addition of Grignard reagents in the presence of catalytic amount of Cu(I) salts and chiral amidophosphines was examined by Tomioka et al. (Scheme 7).[11] Selectivities comparable to organocuprate addition (vide supra) were obtained with similar ligands suggesting the possibility of comparable structures of these organometals. However, ligand **31** containing an urea carbonyl is superior to ligands **24** or **28** with amidocarbonyls in enantioinduction. Unlike lithiocuprates, reactions with magnesiocuprates were not enhanced by the addition of an excess of LiBr. It is worth noting the reversal of selectivity in adducts obtained with RMgCl and RLi (compare Schemes 5 and 7). The catalytic version was achieved with CuI and ligand **31**. Good ee's were obtained only when $n>2$ for $R(CH_2)_nMgCl$. The optimum ratio of RMgCl/CuI/ligand=1.2:0.08:0.32 was crucial for catalysis.



entry	R	yield (%)	ee (%)
1	Bu	92	90
2	Me	23	5
3	Et	83	73
4	Hex	90	92

Scheme 7.

Seebach et al. investigated the use of preformed TADDOL derived Cu(I) thiolates in similar transformations (Scheme 8).[12] Slow addition of the Grignard reagent to the mixture of catalyst and substrate provided high selectivity. Interestingly the two complexes **34** and **35** deliver the alkyl group from opposite faces of the cycloalkenone. These copper complexes are bound only to sulfur in a monodentate fashion (Fig. 2). Recent X-ray structures and 2D-NOESY experiments attest to this fact.[13] Also, the orientation of the TADDOL is such that in ligand **35** the NMe_2 group remains far from copper whereas in ligand **34** the OH is closer to the metal. These variations in substituents alter the structure of complexes, resulting in the different face selection observed with these ligands.

Pfaltz et al. utilized catalysts prepared from Cu(I) and mercaptoaryl-oxazolines **39** in conjugate additions to cycloalkenones obtaining moderate selectivities with cyclohexenone and cycloheptenone (Scheme 9, entries 1–3).[14] The Cu(I) thiolate complexes of **39** were found (using FAB MS) to be dimeric and trimeric aggregates with Cu–S–Cu bridges. A complex, non-linear relation was observed between the ee of the ligand and that of the product. Sammakia and Strangeland surveyed ferrocenyl phosphine–oxazoline ligands and found that **40** provided moderate selectivity (Scheme 9, entries 4–6).[15] A point of note is that addition to cyclopentenone was anomalous: the

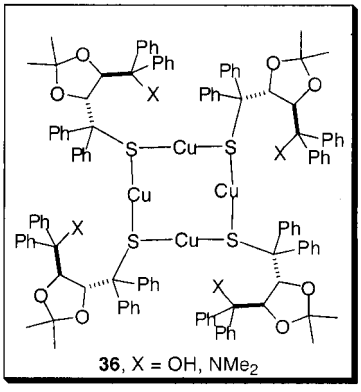
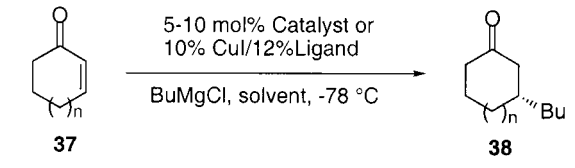
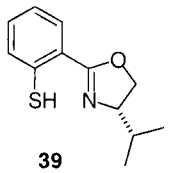


Fig. 2.





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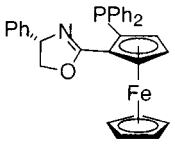


40

entry	n	solvent/additive	ligand	yield (%)	ee (%)	ref.
1	1	THF/HMPA	**39**	67	60	14
2	0	THF/HMPA	**39**	30	16	
3	2	THF/HMPA	**39**	50	83	
4	1	ether	**40**	97	83	15
5	0	ether	**40**	82	-65	
6	2	ether	**40**	82	82	

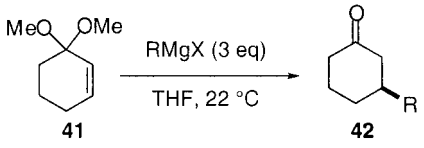
Scheme 9.

sense of stereoinduction was opposite to that of cyclohexenone. The exact nature of the reactive complex in these Cu(I) catalyzed ECA of Grignard reagents is obscure and hence proposing a model for the observed selectivity is difficult.

In a similar vein, addition to unsaturated acetal **41** was achieved with chiraphos and $(PPh_3)_2NiCl_2$ by Hoveyda and co-workers (Scheme 10).[16] The addition was found to give very low ee's in the absence of PPh_3. Adding 2 equiv. of PPh_3 relative to the amount of chiraphos was critical in obtaining selectivity. The exact role of this added PPh_3 is not understood although other phosphines were found to be inferior. The reduction of Ni(II) in the presence of Grignard reagents is well documented.[17] Possibly, a Ni(I) species is involved in the catalytic cycle.

4. Addition of Organolithium Reagents

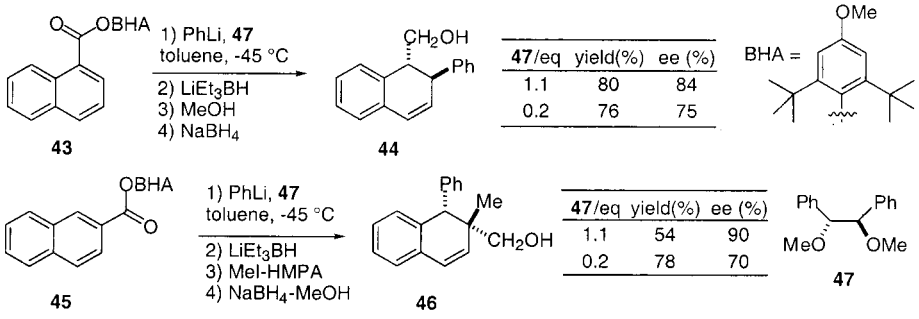
α,β-Unsaturated esters undergo conjugate addition with alkyl and aryllithium reagents. Chemoselectivity (1,4- vs 1,2-addition) in these reactions can be controlled by increasing the steric bulk in the ester substituent. Tomioka has



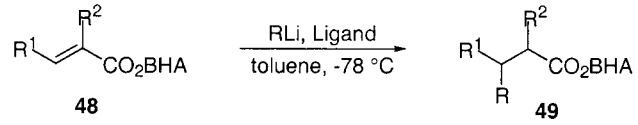
entry	RMgX	condition*	additive	yield (%)	ee (%)
1	EtMgBr	B		90	85
2		A	none	80	10
3	*n*-BuMgCl	A	none	50	0
4		A	PPh_3 (5 mol%)	65	82
5		A	PPh_3 (10 mol%)	85	85
6		A	PPh_3 (20 mol%)	81	76
7	*i*-BuMgCl	B		63	70
8	PhMgBr	B		67	83
9	$Ph(CH_2)_2MgCl$	B		81	84

*A: 5 mol% (*S*,*S*)-(chiraphos)$NiCl_2$
B: 5 mol% (*S*,*S*)-chiraphos, 5 mol% $(PPh_3)_2NiCl_2$

Scheme 10.



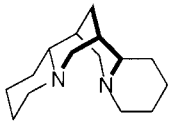
Scheme 11.



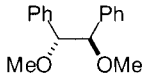
48 49

entry	R^1	R^2	R	ligand (eq)	yield (%)	ee (%)*	R/S
1	Me	H	Bu	**50** (0.3)	95	85 (99)	*R*
2	Me	H	Ph	**50** (4.3)	89	42	*S*
3	Me	H	Ph	**47** (1.0)	99	70 (84)	*S*
4	Me	H	Ph	**47** (0.3)	97	42	*S*
5	Et	H	Bu	**50** (0.3)	94	83 (99)	*R*
6	Et	H	Ph	**47** (0.3)	95	43 (88)	*S*
7	$-(CH_2)_3-$		Bu	**50** (0.3)	82/4†	53 (95)	1*R*, 2*S*
8	$-(CH_2)_4-$		Bu	**50** (0.3)	85/3†	81 (94)	1*R*, 2*S*

* Numbers in parenthesis are for stoichiometric reactions.
† The major product is the *cis*-isomer.



(-) Sparteine, **50**



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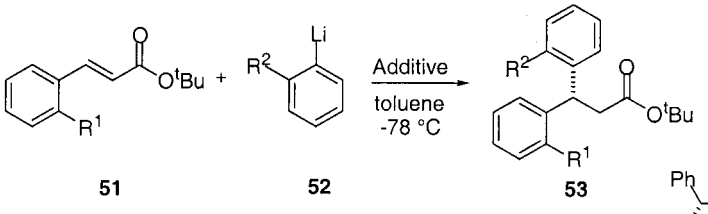
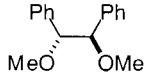
Scheme 12.

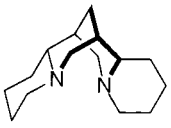


51 **52** **53**



47

entry	R^1	R^2	additive	yield (%)	ee (%)
1	$CH(OMe)_2$	Bn	**50**	92	63
2	$CH(OMe)_2$	Et	**50**	89	56
3	$CH(OMe)_2$	Me	**47**	90	88
4	H	Me	**50**	78	28
5	Ph	Me	**50**	88	78
6	Ph	Bn	**50**	91	74



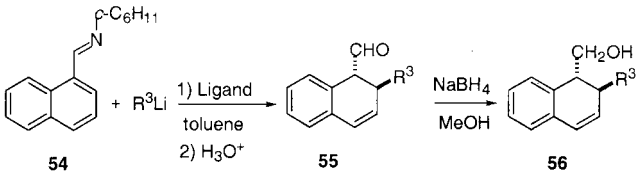
(-) Sparteine, **50**

Scheme 13.

successfully employed 2,6-di-*tert*-butyl-4-methoxyphenyl (BHA) esters in conjugate additions. Organolithium reagents exist as aggregates in hexanes. These oligomeric clusters are broken down in the presence of chiral donor ligands producing monomeric chiral reagents. These monomeric species are more reactive than the oligomeric species. Enantioselective additions use a chiral diether, **47**, which binds to the organolithium resulting in the formation of a chiral nucleophile, which then differentiates the enantiotopic faces in the BHA ester. Tomioka et al. applied this concept in both stoichiometric and catalytic reactions (Scheme 11).[18]

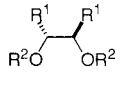
The methodology was extended to other acyclic and cyclic unsaturated BHA esters (Scheme 12).[19] Interestingly, a second function of the BHA ester is to enhance the steric bulk in the lithium enolate intermediate. This allows for favorable ligand exchange towards the chiral reagent preventing the enolate from acting as a sink for the chiral ligand. Another noteworthy observation was that ligand **47** and sparteine **50** were complementary to each other: **47** works best with aryllithium and sparteine works best with alkyllithiums.

Xu and co-workers performed similar transformations on α,β-unsaturated *tert*-butyl esters **51** with aryllithium reagents (Scheme 13).[20] A survey of various ligands showed that the diether ligands were more effective than the aminoether ligands. In many cases they also found that ligand **47** provided the corresponding β,β-diaryl propionates **53** with better selectivity than sparteine. The use



54 **55** **56**

R^3	ligand	yield (%)	ee (%)
Ph	(*S*,*S*)-**57a**	68	90
Bu	(*R*,*R*)-**57a**	92	53
Ph	(*S*,*S*)-**57b**	64	33
Ph	(*S*,*S*)-**57c**	26	20
Ph	(*R*,*R*)-**57d**	82	94
Bu	(*R*,*R*)-**57d**	80	91



	R^1	R^2
57a	Me	Me
57b	Me	Et
57c	Me	Bn
57d	Ph	Me

Scheme 14.

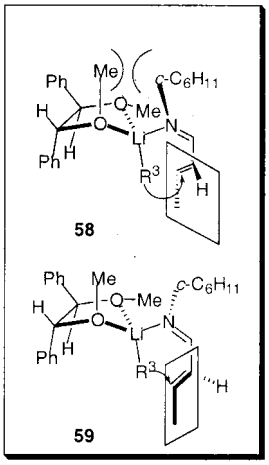
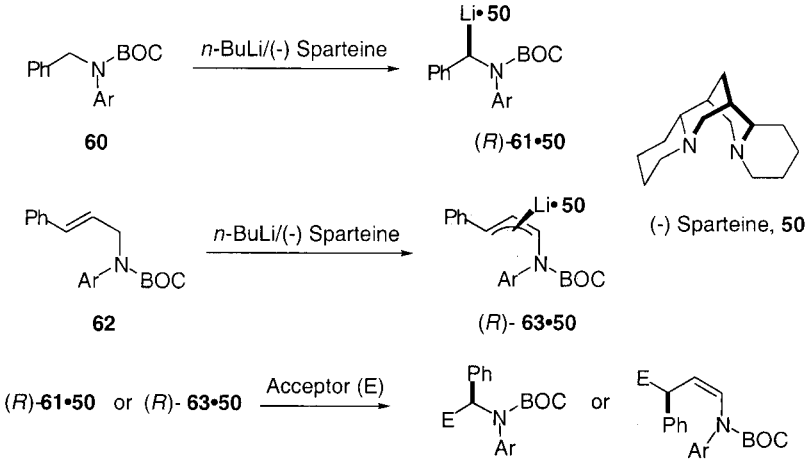
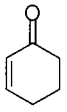
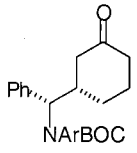
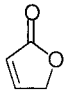
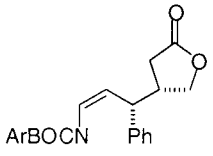
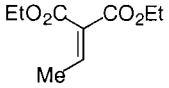
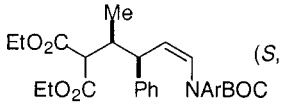
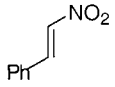
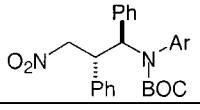


Fig. 3.

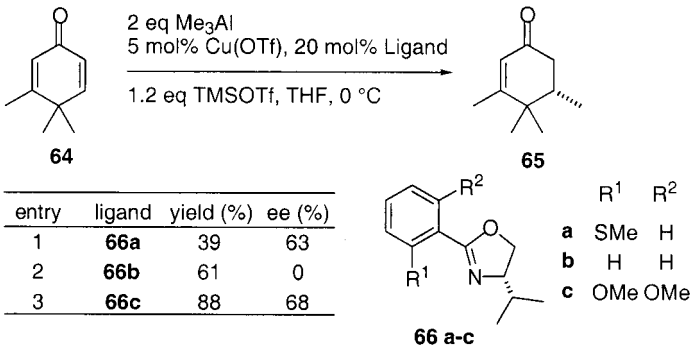
of functionalized substrates and aryllithiums is a feature of this study.

Tomioka showed that α,β-unsaturated aldimines undergo either 1,2- or 1,4-addition depending on whether the substituent on the imine was an alkyl (1,2-addition) or an aromatic (1,4-addition) group. This result was corroborated with PM3 level calculations for the relative LUMO coefficients at the 2- and 4-positions.[21] Variation of substituents on the ligand **57** in the addition of organolithium reagents to the *N*-cyclohexyl aldimine **54** (Scheme 14) elaborated the importance of substituents on the structure of organolithium–ligand complex.[22] Bulky groups on the ether oxygen (**57c**) lead to unfavorable interactions between R^2 and R^3 (of alkyllithium) hence disturbing the all *trans* arrangement of R^1 and R^2 shown in Fig. 3. This arrangement provides C_2-symmetry to the ligand–alkyllithium complex. On the basis of the steric interactions of the aldimine (an acyclic aldimine is shown in Fig. 3) with this complex the observed selectivity can be explained (**59** favored over **58**). A key point to note is that the chiral information on carbon



entry	acceptor (E)	product		yield (%)	dr	er
1			(*S*,*S*)	82	>99:1	96:4
2			(*S*,*R*)	66	96:4	97:3
3			(*S*,*S*)	93	80:20	98:2 (93:7)
4			(*S*,*R*)	80	90:10	97:3

Scheme 15.



entry	ligand	yield (%)	ee (%)
1	**66a**	39	63
2	**66b**	61	0
3	**66c**	88	68

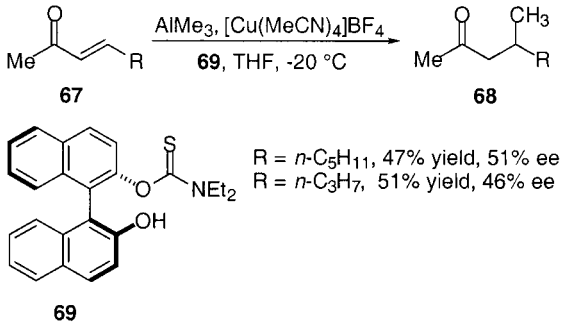
Scheme 16.

is being relayed to the oxygen atom in the RLi–ligand complex.

A relatively more challenging concept is the use of configurationally stable organolithium species in conjugate additions. Here the organolithiums by themselves are capable of undergoing inversion at the carbanionic center. This inversion can be prevented if the lithium is coordinated to a bulky ligand. Beak and co-workers have developed this concept in generating 1,4-adducts with high diastereo- and enantioselectivities (Scheme 15).[23] Various cyclic and acyclic acceptors are compatible in this reaction. Enantioselective deprotonation of *N*-Boc-*N*-arylbenzylamine **60** and *N*-Boc-*N*-arylcinnamylamine **62** with *n*-BuLi/(−)sparteine gives the carbanion–ligand complexes (*R*)-**61**·**50** and (*R*)-**63**·**50** which then add in a 1,4-manner to provide the products. The crystal structure of (*R*)-**63**·**50** was determined and provided a model for the explanation of the stereochemical outcome for the addition.[24]

5. Organoaluminum Reagents

Only a few examples of conjugate additions using trialkylaluminum reagents are known. Here too catalysis by Cu(I) salts prove effective. Iwata et al. showed that trimethylaluminum adds to cyclohexa-2,5-dienone **64** where the reactivity of one of the olefinic bonds is reduced due to the β-methyl substituent (Scheme 16).[25] Conjugate addition proceeded efficiently at the less substituted double bond in the presence of an equivalent of TMSOTf. The two *ortho* substituents on the phenyl ring in **66** are important for obtaining selectivity.



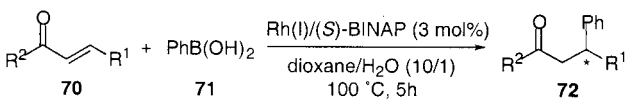
Scheme 17.

Application of Kubas compound, $[Cu(MeCN)_4]BF_4$, with thiourethane based ligand **69** was examined by Woodward et al. for acyclic ketones (Scheme 17).[26] Both yields and enantioselectivity were only moderate. They also obtained similar results with other organometallic reagents and monothiobinol based ligands (not shown).

6. Organoboron Reagents

Organoboronic acids have been extensively used in Suzuki cross-coupling strategies using palladium catalysts.[27] Only in the last three years have conjugate additions with organoboron reagents using Rh(I) catalysts been developed.[28] This reaction involves transmetallation of the organic group from boron to rhodium followed by the coordination of enones to the rhodium through the olefin π-bond. 1,4-Addition then occurs in this assembly of reactants. The enantioselective transformation was made possible using the chiral BINAP ligands (Scheme 18).[29] Phenylboronic acid **71** adds efficiently to various acyclic and cyclic alkenones to provide the products in high ee's. Hayashi and Miyaura have proposed a catalytic cycle involving a rhodium enolate, which then reacts with the boronic acid to produce the catalytically active rhodium–phenyl species. Fig. 4 shows the model (naphthyl groups omitted) for the binding of cyclohexenone, which explains the selectivity.

As a complementary method to the one discussed above, in situ generation of phenylboronic acids was achieved from the corresponding borate esters (stable precursors for boronic acids).[30] 1-Alkenyl phosphonates **74** were also successfully utilized as substrates in this methodology (Scheme 19).[31] Phenylboroxine **75**, the source of the phenyl group, is hydrolyzed in situ using 1 equiv. of water. The



Enone	$PhB(OH)_2$ /eq	yield (%)	ee (%)
2-cyclohexenone	5	>99	97 (*S*)
2-cyclopentenone	1.4	93	97 (*S*)
2-cycloheptenone	1.4	51	93
(*E*)-5-methyl-2-hexenone	5	82	97

Scheme 18.

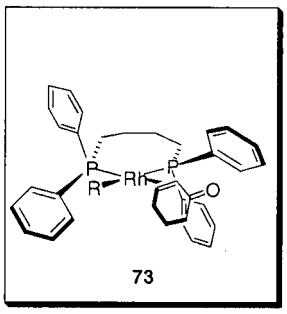


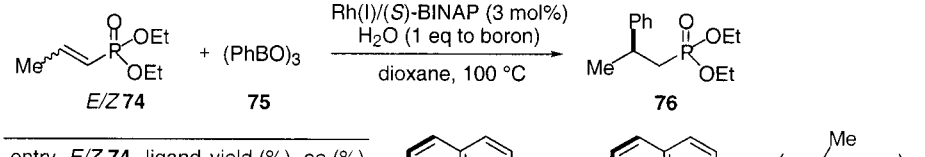
Fig. 4.

E-isomers gave products with (*S*) configuration and the *Z*-isomers gave (*R*) configuration.

Alkynylboronates have long been known to be good reagents in conjugate addition to enones. Chong et al. carried out a transesterification from alkynylborates to a BINOL ligand **79** preparing chiral alkynylboronates **82**, which can then perform the conjugate addition in an enantioselective manner (Scheme 20).[32] **82a–c** are essentially chiral nucleophiles, except that the chiral source is not transferred to the product. Good ee's of the 3-alkynyl enones **84** were obtained. The selectivity has been proposed to originate from steric interactions in the six membered transition state; **85*R*** favored over **85*S*** (Fig. 5).

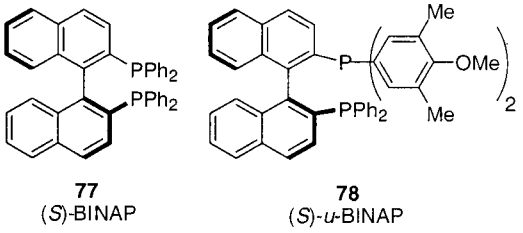
7. Organozinc Reagents: The Ligand Game

Organozinc reagents hold a special place in the development of ECA of organometallic reagents. The reactivity, basicity and the tolerance for other functional groups present on either the substrate or the organozinc reagent are the main reasons for their popularity. Organozinc reagents are much less basic than the other organometallic reagents employed in conjugate addition reaction. Diethylzinc addition to enones and other conjugate acceptors in the absence of additives, either ligands or other transition metal catalysts, is slow. Hence, this reaction has proved most suitable for the development of ligands and to test their efficacy in ECA and other reactions. Two distinct classes of catalysts (for most cases) have been pursued: nickel catalysts for acyclic enones and copper catalysts for cycloalkenones. A possible explanation exists in the different coordinations of Cu and Ni with the substrates. Copper coordinates to the olefin π-bond (**86A**) whereas nickel coordinates to the carbonyl oxygen (**86B**) far from the reaction center and hence cannot deliver the alkyl group in a stereocontrolled fashion. In acyclic enones, nickel can

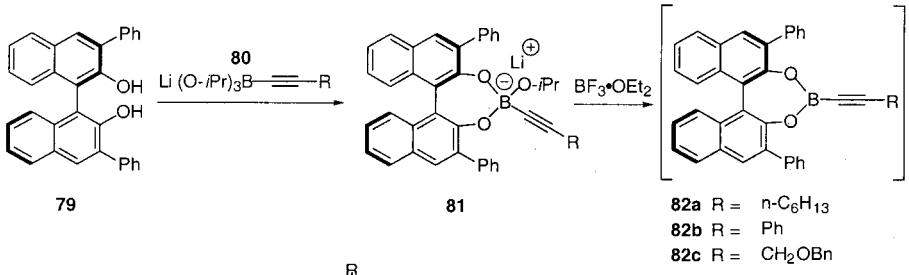


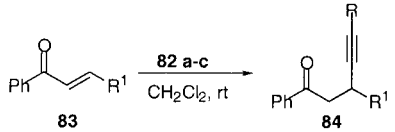
entry	*E/Z* **74**	ligand	yield (%)	ee (%)
1	*E*	**77**	94	96 (*S*)
2*	*E*	**77**	5	-
3	*Z*	**77**	96	89 (*R*)
4	*Z*	**78**	98	92 (*R*)

*no H_2O added.



Scheme 19.





entry	R^1	**82**	yield (%)	ee (%)
1	Ph	**82a**	88	85
2	1-naphthyl	**82a**	91	95
3	1-naphthyl	**82b**	99	98
4	1-naphthyl	**82c**	81	>98

Scheme 20.

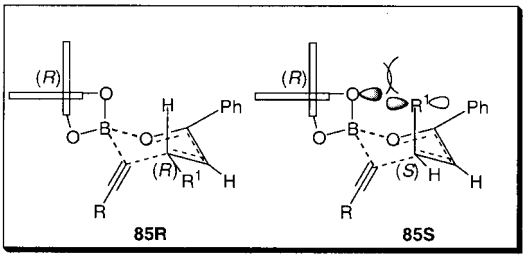


Fig. 5.

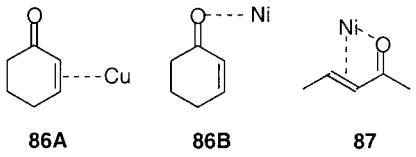


Fig. 6.

coordinate to the carbonyl oxygen and the olefin π-bond in the *s-cis* conformation **87** (Fig. 6).[33b]

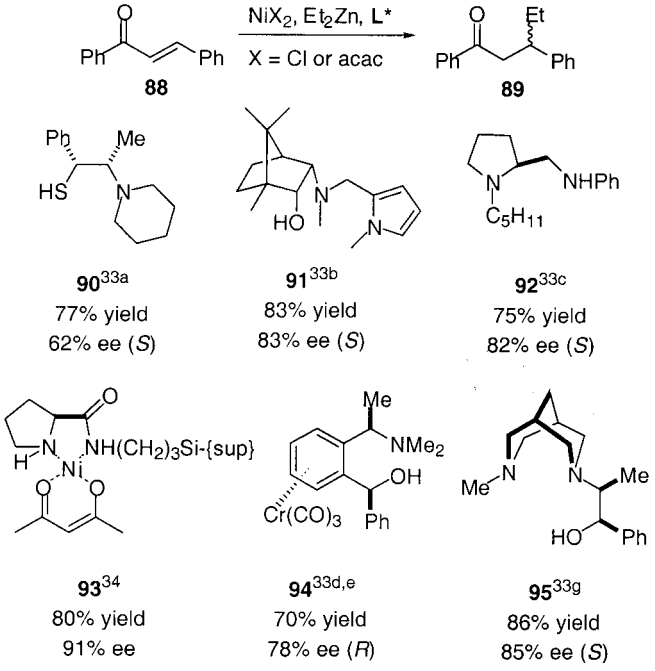
7.1. Nickel catalyzed ECA of diethylzinc to acyclic enones

Ni(II) catalyzes the addition of diethylzinc to chalcones (a popular class of acyclic enones) in the presence of various amine-based ligands (Scheme 21).[33] The best selectivities were obtained by Corma et al. with **93** supported on a USY zeolite.[34] Asami[33c] and Waldmann[33g] observed an increase in the enantioselectivity by the addition of an equivalent of 2,2′-bipyridyl [to Ni(II)]. The additive is thought to improve the stability of the active catalyst but the exact mechanism is not known.

7.2. Copper catalyzed ECA of diethylzinc to cycloalkenones

Alexakis et al. reported the first copper catalyzed conjugate addition of diethylzinc to cyclohexenone using a trivalent phosphorous ligand.[35] The reaction was found to proceed efficiently (70% yield) only in the presence of both Cu(I) and trivalent phosphorous additive [except for CuCN and $Cu(OTf)_2$]; 0.5 mol% of Cu(I) and 1 mol% of the P(III) ligand was found sufficient for catalysis.[37l] Finding a particular ligand that can aid in the copper catalyzed addition of diethylzinc to various enones with high selectivity is difficult. However, comparable selectivities can be obtained by minor modifications within a particular family of ligands. The catalytic cycle involves the reduction of Cu(II), which has two phosphorous atoms bound to it, to Cu(I) **97** with subsequent transmetallation of alkyl group to copper (Fig. 7).[37g] The alkyl transfer to the acceptor occurs after the enone olefin binds to copper (see **100**). Commonly used solvents are toluene and CH_2Cl_2. Donor solvents like ether, THF or acetonitrile lower the selectivity. Cyclopentenone is a troublesome substrate giving low yields of 1,4-adduct due to oligomerization of zinc enolate and the high volatility of the 1,4-adduct. Sewald observed that if CuCN is the copper source, there is a remarkable reversal in the sense of asymmetric induction compared to CuOTf or CuX (X=Cl, I) with a chiral sulfonamide as the ligand.[36] This strongly suggests a complete change in mechanism in the presence of cyanide as the counterion. A collection of ligands and the enantioselectivities obtained with various substrates in the $Cu(OTf)_2$ catalyzed addition of diethyl zinc is presented in Fig. 8.[37]

Some comments on the ligands in Fig. 8 are warranted: (a) Two phosphorous atoms are bound to the copper in the active complex; (b) For ligands that possess stereochemistry on both the diol and the third substituent on phosphorous,



Scheme 21.

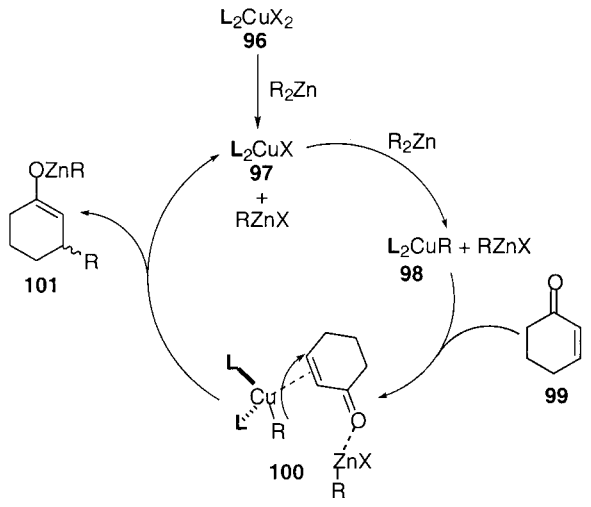


Fig. 7.

there is a cooperative effect of the stereochemistry of these substituents on the enantioselectivity. The third substituent determines the level of ee and the stereochemistry of the diol moiety determines the sense of stereoselection. Examples include TADDOL–phosphite: **109** which gives 96% ee whereas **110** gives 0% ee[37m] and Feringa's phosphorous amidite: (*S*,*R*,*R*)-**102** produces 98% ee with cyclohexenone while the (*S*,*S*,*S*)-isomer produces 75% ee;[37g] (c) Gennari et al. have screened a combinatorial library of about 140 ligands of type **111** and identified two ligands which provide good ee's for cycloalkenones;[37o] (d) Diphosphine ligands **107** and **108**, capable of forming a 4-membered chelate with metals, gave good selectivities.[37n] The advantage of these smaller chelating ligands is that the chirality information is present very near to the copper atom, allowing for a greater degree of stereocontrol. Other chiral phosphine ligands like chiraphos, norphos, BINAP, duphos failed to produce good stereoselection;[37k]

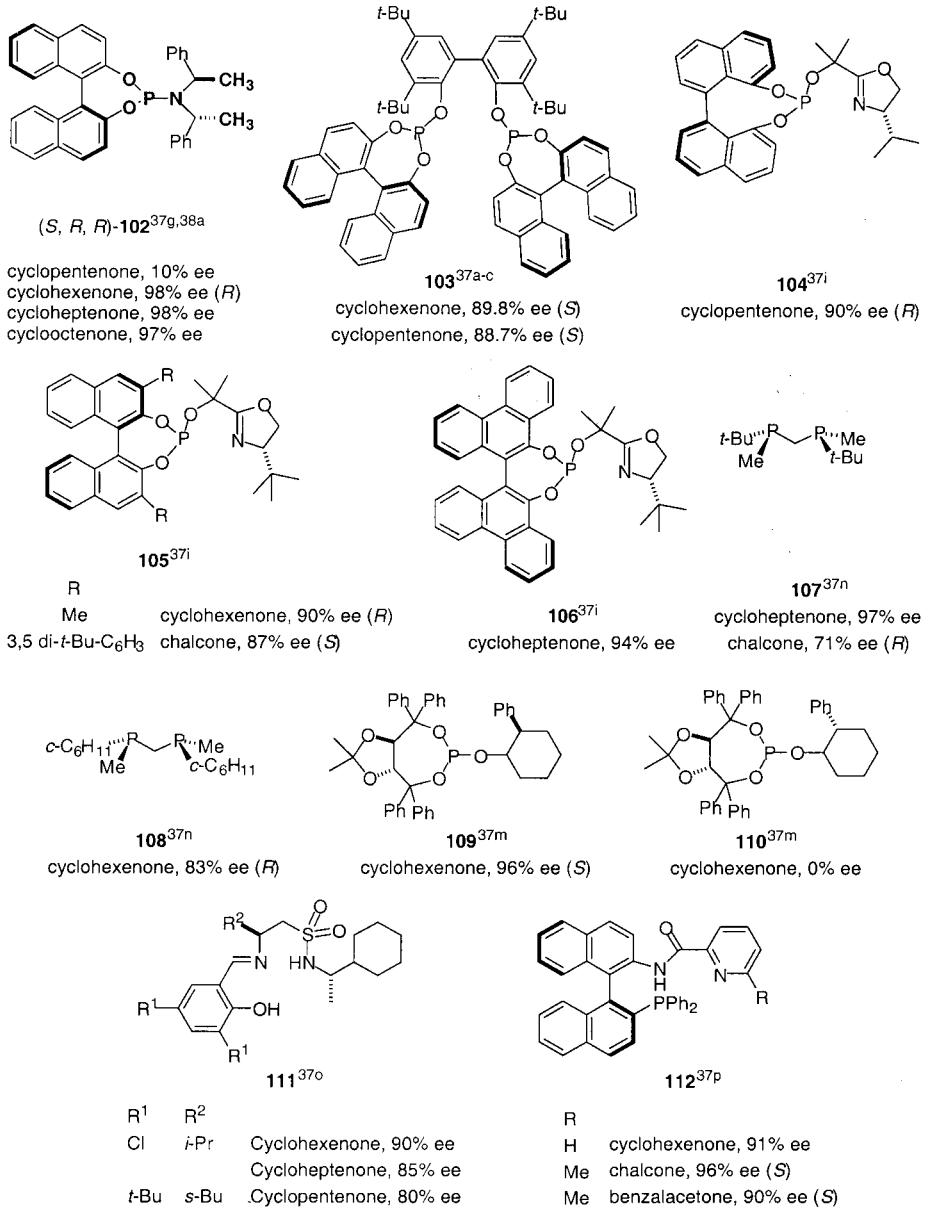
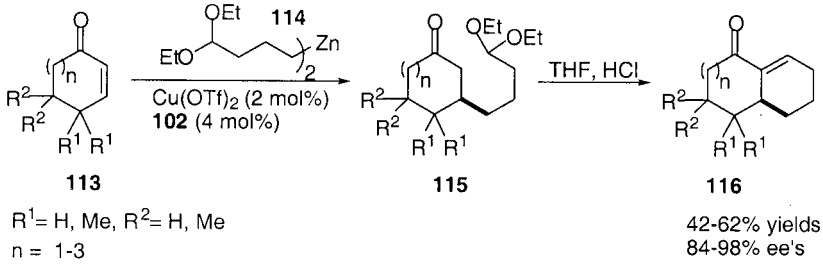


Fig. 8.



Scheme 22.

(e) A promising feature is that a variety of ligands have been utilized hinting at the tolerance by copper for donor atom on the ligand in this reaction.

Feringa and co-workers applied a tandem addition–cyclization protocol using organozinc reagents containing an aldehyde protected as an acetal that, after conjugate addition, undergo intramolecular aldol cyclization to give 6,6-, 6,7- and 6,8-annulated bicyclic systems **116** (Scheme 22).[38] Feringa has also reported the regio and enantioselective reactions on cyclohexadienones.[38b]

Recently, Alexakis et al. synthesized (*R*)-muscone (53% yield, 79% ee) which has been an attractive target for demonstrating conjugate addition of organometallic reagents to macrocyclic enones.[39] Chan has shown that diethylzinc can be added to lactones especially, six membered lactone, in up to 92% ee using ligand **103**.[40]

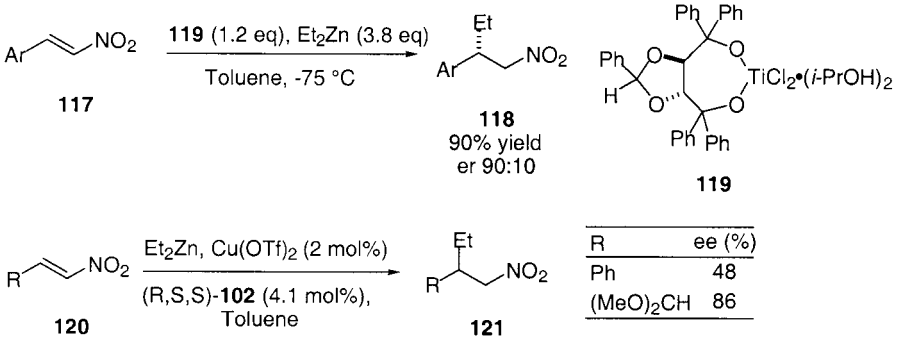
7.3. Addition of diethylzinc to nitroolefins

Nitroolefins are very good acceptors in conjugate addition reactions. Their reactivity towards diethylzinc is very different depending on the presence or absence of Lewis acids. Seebach and Schäfer found that dialkylzinc reagents replace the nitro group in the absence of Lewis acids whereas in the presence of Lewis acids ($MgBr_2$ or Ti–TADDOLates) 1,4-addition proceeds very effectively. Expanding on this observation, 2-aryl-1-nitroalkanes were prepared enantioselectively using a slight excess of Ti–TADDLOLate **119** and four-fold excess of dialkylzinc reagent. Good ee's were obtained with various ω-nitroarenes (Scheme 23).[41] A puzzling result was obtained: use of $MgBr_2$ gave 40% ee of (*S*) product while MgI_2 gave a 50% ee of the (*R*) product. A catalytic variant of this transformation utilizing Cu(I) and the (*R*,*S*,*S*) diastereomer of Feringa's ligand **102** resulting in moderate ee's was reported by Sewald and Wendisch.[42]

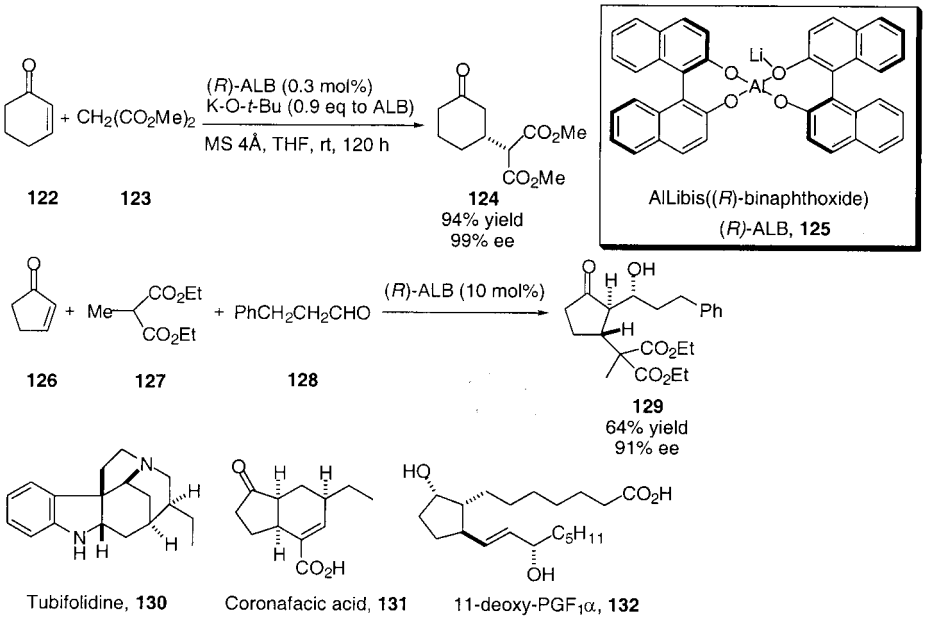
8. Addition of Neutral Carbon Nucleophiles

8.1. Addition of 1,3 dicarbonyls: The Michael reaction

The addition of 1,3-dicarbonyl compounds to conjugate acceptors, the classic Michael reaction, has been rendered asymmetric with heterobimetallic catalysts.[43] Heterobimetallic catalysts, extensively investigated by Shibasaki, contain two metal centers where one of them is Lewis acidic (lanthanides or group 13 elements) capable of activating the acceptor, while the second metal center (alkali metals bound to a Brønsted base) coordinates to the enolate. (*R*)-Aluminumlithium bis(binaphthoxide), (*R*)-ALB **125**, prepared from $LiAlH_4$ and BINOL (2 equiv.) catalyzes the Michael reaction of malonate esters with cyclohexenone with high yields and ee's (Scheme 24).[44] The reaction is very efficient in that only 0.3 mol% of ALB is required. Potassium *t*-butoxide helps in accelerating the reaction and molecular sieves prevent the decomposition of catalyst by moisture. The structure of the catalyst **125** has been determined by X-ray crystallography. In the proposed model for stereoinduction, the cycloalkenone coordinates strongly to the aluminum and reacts with the lithium enolate (Fig. 9). The aluminum enolate, obtained after the initial conjugate addition reaction, can further undergo aldol reaction with aldehyde **128** in high selectivity. Both cyclohexenone and cyclopentenone give good selectivities. These Michael additions have been utilized in the synthesis of tubifolidine **130**[45] and coronafacic acid **131**.[46] Prostaglandin 11-deoxy-$PGF_1\alpha$ **132** has been synthesized from the tandem Michael–aldol protocol.[47]



Scheme 23.



Scheme 24.

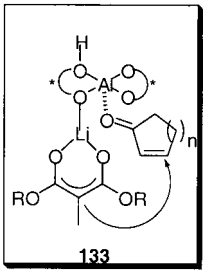
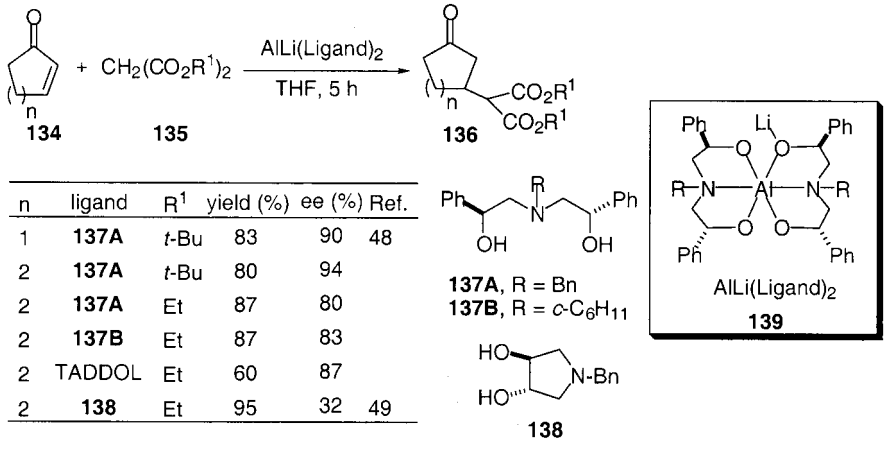


Fig. 9.

The nature of the diol in the heterobimetallic catalyst plays a major role in determining the selectivity. Sundararajan and Manickam[48] used C_2-symmetric chiral aminodiols **137** in place of BINOL and obtained reasonable success. In contrast, Choudary et al. obtained the Michael adducts in only low ee's with **138** as the diol (Scheme 25).[49] The structure of the heterobimetallic catalyst **139** derived from ligand **137** has been established by NMR. The low ee's obtained with ligand **138** can be explained by the lack of steric shielding farther away from the metal center.

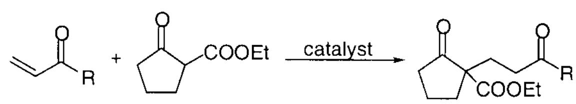
The addition of β-ketoesters to acyclic enones generates Michael adducts with stereochemistry at the γ-carbon (a quaternary center). Catalysis with Ni(II) in the presence of a chiral diamine produces good selectivities (Scheme 26).[50] The diamine **143** forms an enamine with **141** in the presence of nickel, forming a chiral nucleophile, which then coordinates to the enone **140** and efficient transfer of the donor takes place. Chiral bases like cinchonidine can catalyze this transformation efficiently although the reaction is sluggish (~500 h).[51] d'Angelo et al. showed that **144**, a resin supported quinine with a seven atom spacer catalyzes the formation of Michael adduct from 2-carbomethoxyindanone and methyl vinyl ketone (MVK) with 87% ee and 85% yield.[52]

Pfaltz et al. synthesized chiral bis(dihydroxazolylphenyl)-



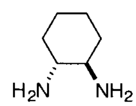
n	ligand	R^1	yield (%)	ee (%)	Ref.
1	**137A**	*t*-Bu	83	90	48
2	**137A**	*t*-Bu	80	94	
2	**137A**	Et	87	80	
2	**137B**	Et	87	83	
2	TADDOL	Et	60	87	
2	**138**	Et	95	32	49

Scheme 25.

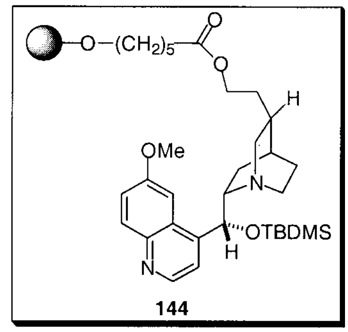


140 141 142

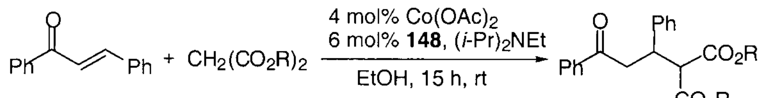
R	catalyst	yield (%)	ee (%)	ref.
Me	Ni(OAc)$_2$/**143**	37	91	50
Me	Ni(OAc)$_2$/**143**	31	74	
H	Cinchonidine	88	72	51



143

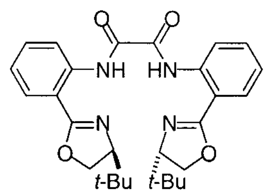


Scheme 26.



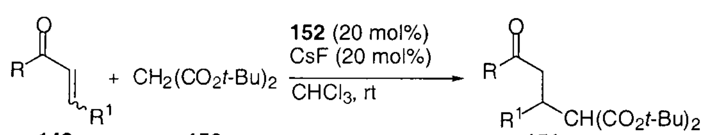
145 146

entry	R	yield (%)	ee (%)
1	Et	17	75
2	*i*-Pr	12	82
3	*t*-Bu	13	89



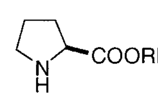
148

Scheme 27.



149 150 151

entry	Enone	yield (%)	ee (%)
1	(*E*)-CH$_3$CH=CHCOCH$_3$	65	88 (*S*)
2	(*E*)-Ph(CH$_2$)$_2$CH=CHCOCH$_3$	73	60 (*S*)
3	2-cyclohexenone	84	65 (*R*)
4	2-cycloheptenone	75	74 (*R*)
5	(*E*)-2-cyclopentadecenone	54	82 (*S*)

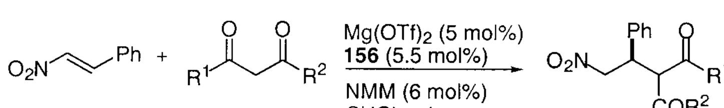


152

Scheme 28.

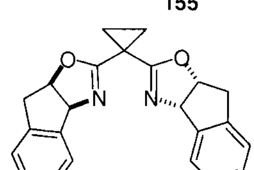
oxalamide **148** which was found to assist Co(II) in catalyzing the addition of dialkyl malonates to chalcone in the presence of Hünig's base with moderate selectivities but low yields (Scheme 27).[53] The reactions were not allowed to proceed to completion as the ee's dropped significantly with increase in time.

Rubidium prolinate **152** can act as a chiral catalyst in



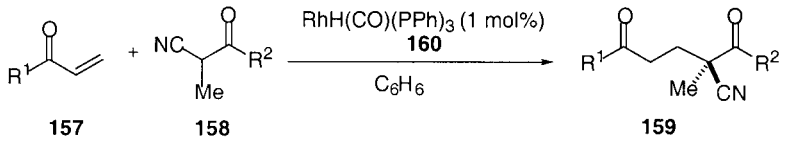
153 154 155

entry	R^1	R^2	yield (%)	ee (%)
1	Me	OEt	95	90
2	Me	O*t*-Bu	94	29
3	CHMe$_2$	OEt	90	94
4	OEt	OEt	92	95

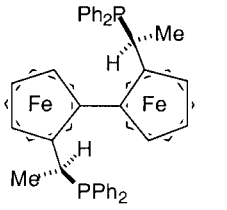


156

Scheme 29.



entry	R^1	R^2	yield (%)	ee (%)
1	Me	OMe	99	73
2	Me	O*t*-Bu	95	81
3	Et	OCH(*i*-Pr)$_2$	99	91
4	Ph	O*i*-Pr	95	83
5	H	OCH(*i*-Pr)$_2$	88	92
6	Me	NMe(OMe)	98	93



(*S*,*S*)-(*R*,*R*)-PhTRAP

160

Scheme 30.

activating enones via in situ formation of an imine. Yamaguchi showed that this reaction proceeds with moderate to good ee's in the presence of CsF as an additive (Scheme 28).[54] CsF is thought to aid in the enolization of the malonate and to hold the enolate in a fixed conformation. The sense of facial bias is the same in additions to both acyclic and cyclic enones.

The addition of active methylene compounds to nitroolefins requires much less activation. Ji et al. demonstrated this reaction with considerable success in the presence of $Mg(OTf)_2$ and aminoindanol derived bisoxazoline ligand **156** (Scheme 29).[55] The β-ketoesters enolize upon coordination to the Lewis acid–ligand complex, forming a chiral nucleophile. This complex adds to the nitroolefin in a selective manner. The use of a base stronger than *N*-methylmorpholine (NMM) leads to lower ee's probably due to the increase in base catalyzed reaction, prior to complexation with the catalyst, which leads to racemic product.

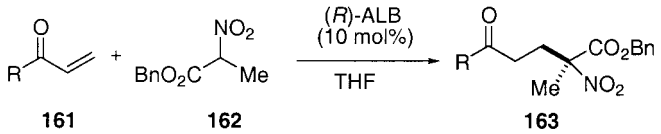
α-Cyano carboxylates and α-cyano Weinreb amides undergo enantioselective Michael reactions with enones and enals readily with Rh(I) and a *trans*-chelating ligand **160** (Scheme 30).[56] The enolate of the nitrile coordinates to the Rh–PhTRAP complex and the electrophile approaches from the sterically less hindered *re*-face of the enolate to give (*R*)-**159**. Adducts **159** can then be converted into α-methyl-α-amino acids. Williams et al. performed a similar transformation with a Pt–phosphino–oxazoline complex but with much less success (<25% ee).[57]

8.2. Addition of nitroalkanes

Addition of α-nitroesters to acyclic enones proceeds with good chemical efficiency in the presence of 10 mol% (*R*)-ALB similar to **125** (Scheme 31).[58] The lithium naphthoxide in the heterobimetallic catalyst acts as the Brønsted base in enolizing the nitroester which coordinates in a bidentate fashion to lithium (similar to that in Fig. 9) and reacts with the enone which is bound to the Lewis acidic aluminum. Interesting in this study is the observation of at least three different signals for Al in the ^{27}Al NMR of the ALB catalysts prepared. This suggests the existence of complexes with different ratios of aluminum and lithium binaphthoxide. A significantly different X-ray structure (compared to Shibasaki's catalyst **125**) was observed for a compositionally different complex, $AlLi_3BINOL_3$. Although the crystals of $AlLi_3BINOL_3$ were able to effect the transformation, it is doubtful whether it was the catalytically active species.

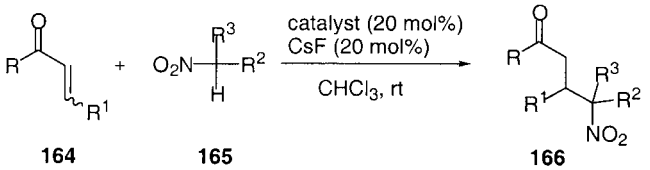
Nitroalkanes were added to prochiral enones using various rubidium prolinates **167**–**169** as catalysts with moderate ee's by Yamaguchi et al. (Scheme 32).[59] The enantioselectivity obtained for different substrates is dependent on the catalyst. Bulkier nitroalkanes give better selectivity. Changing the size of the 5-membered ring in **167** to a 4-membered ring results in lower asymmetric induction (not shown).

Nitroalkanes can be added to chalcone using sugar



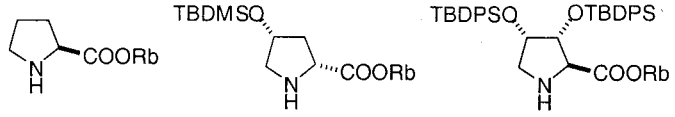
entry	R	temp./ °C	yield (%)	ee (%)
1	Me	-30	83	74
2	Et	-23	84	49
3	Ph	rt	87	8

Scheme 31.



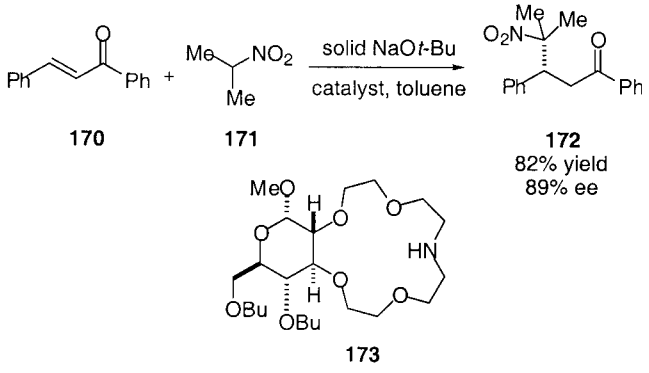
164 165 166

entry	Enone	nitroalkane	catalyst	yield (%)	ee (%)
1	(*E*)-CH_3CH=$CHCOCH_3$	*i*-$PrNO_2$	**167**	74	68
2	2-cyclohexenone	*i*-$PrNO_2$	**168**	94	60
3	2-cycloheptenone	*i*-$PrNO_2$	**169**	41	82
4	2-cycloheptenone	c-$C_6H_{11}NO_2$	**168**	74	86



167 168 169

Scheme 32.



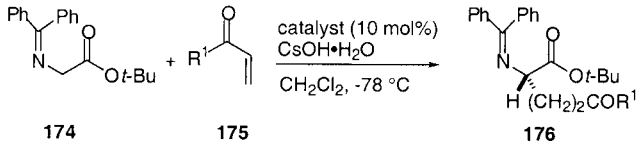
170 171 172 173

Scheme 33.

derived chiral crown ethers (7 mol%) and solid potassium *t*-butoxide (35 mol%) (Scheme 33).[60] The free secondary amine in the crown ether **173** is important for selectivity. If the secondary amine is converted to a tertiary amine, the enantioselectivities decrease dramatically. Hydrogen bonding of the substrate with the free NH has been proposed as a key factor in obtaining selectivity.

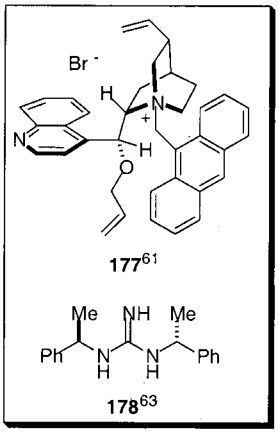
The Schiff's base **174** derived from glycine *t*-butylester and benzophenone has been utilized in phase transfer catalyzed 1,4-addition to enones. Corey and co-workers have formed the salt of cinchonidine alkaloid **177**, which effectively catalyzes the Michael addition with up to 400:1 selectivity (Scheme 34).[61] The structure of the catalyst has been developed with careful analysis of each structural feature. $CsOH{\cdot}H_2O$ was used as the base in the solid form. This methodology provides a simple route to many α-amino acids and has been recently extended to the synthesis of (*S*)-ornithine.[62] Similar transformation was reported by Ma and Cheng using chiral guanidine catalyst **178** albeit with low ee's.[63]

A novel reaction was observed by Shibasaki et al. wherein the Horner–Wadsworth–Emmons reagent **180** underwent 1,4-addition in the presence of ALB **125** and a base (Scheme 35).[64] The reactions are sluggish even at high temperatures. The 1,2-addition could be suppressed and yield of 1,4-addition product could be increased by using sodium *t*-butoxide as base instead of alkyllithiums. Excellent selectivities were observed for cycloalkenones.



174 175 176

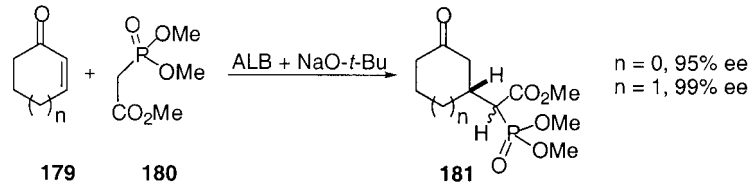
acceptor	catalyst	yield (%)	ee (%)
methylacrylate	**177**	85	95
cyclohexenone		88	99
CH_2=$CHCOCH_2CH_3$		85	91
t-butylacrylate	**178**	98	30.1



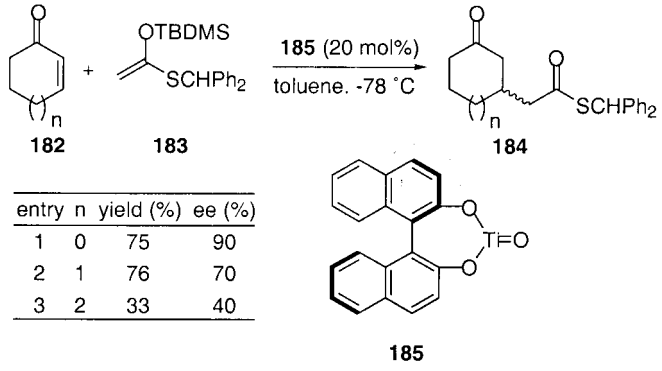
177[61]

178[63]

Scheme 34.

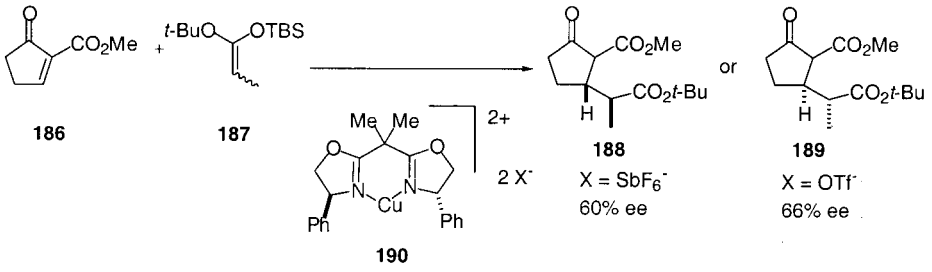


Scheme 35.



entry	n	yield (%)	ee (%)
1	0	75	90
2	1	76	70
3	2	33	40

Scheme 36.

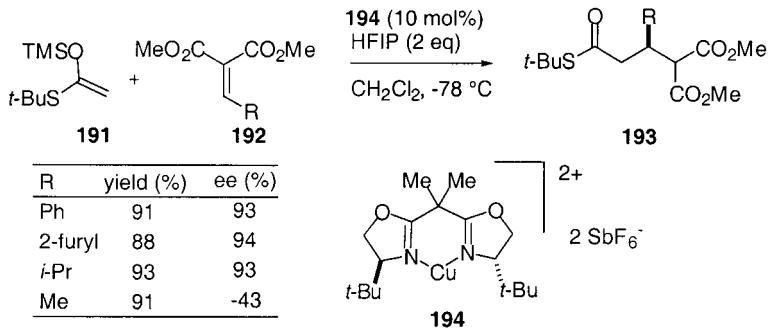


Scheme 37.

8.3. Mukaiyama–Michael reactions

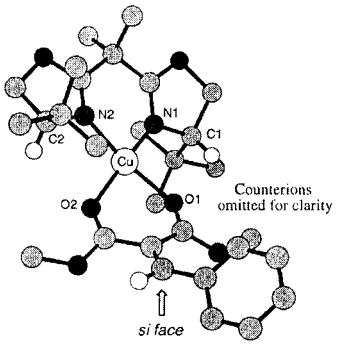
The conjugate addition of enol silanes or silylketene acetals to enones, the Mukaiyama–Michael reaction, has been studied by several groups. Mukaiyama et al. have used a BINOL derived titanium oxide **185** to generate the Michael adduct with cyclopentenone in good ee's (Scheme 36).[65] Higher cycloalkenones produced lower ee's. The titanium oxide merely acts as a chiral Lewis acid and activates the cycloalkenones. The high ee's obtained with cyclopentenone is surprising as one would not expect to form a rigid Lewis acid–substrate complex in the presence of a monodentate donor.

Bidentate binding of the substrate to the Lewis acid can be accomplished with two carbonyl groups: 2-carbomethoxy cyclopentenone **186** is an example. Propionate silylketene acetal adds to **186** in the presence of a Cu–bis(oxazoline) complex **190** to produce the *syn* diastereomers as major products (moderate *syn*/*anti* ratios) with moderate ee's (Scheme 37).[66] There is a large effect on the product stereochemistry depending on the counterion: antimony



R	yield (%)	ee (%)
Ph	91	93
2-furyl	88	94
i-Pr	93	93
Me	91	-43

Scheme 38.



195

Fig. 10. X-Ray crystal structure of alkylidene malonte (R=Ph)–**194** complex. Reprinted with permission from Ref. 68. © 1997 American Chemical Society.

hexafluoride provides **188** whereas triflate provides the other *syn* isomer **189**. Bernardi and Scolastico found that the choice of the substituents on the bis(oxazoline) was crucial in determining the level of enantioselection. The reaction was also catalyzed in the presence of Ti–TADDOLates with moderate ee's for the *syn* products.[67]

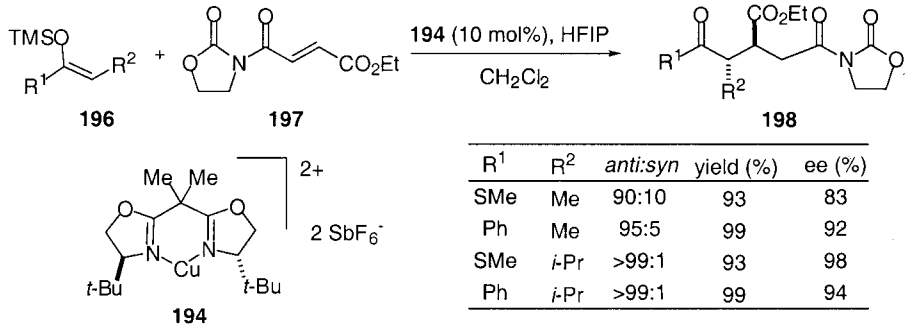
Evans and co-workers explored the ECA of thioester derived silylketene acetals to doubly activated system **192** using Cu(II)bis(oxazolines) **194** (Scheme 38).[68] The C–C bond formation occurred with high enantioselectivity for bulky substituents at the β-position. The process was made catalytic in **194** with the use of two equivalents of hexafluoroisopropanol (HFIP). HFIP, which is weakly acidic, aids not only in the release of the malonyl enolate formed after the conjugate addition but also hydrolyzes the silylketene acetal **191**. This hydrolysis could be minimized by the use of toluene as a co-solvent (methylene chloride was the solvent).

The X-ray crystal structure of the substrate–Cu–bis(oxazoline) complex **195** (Fig. 10) was obtained which shows a distorted square-planar arrangement at copper and the copper–substrate chelation, a 6-membered ring, is in a half-open envelope conformation with the copper at the apex. This arrangement favors the approach of the silylketene acetal only from the *si* face of the olefin, which accounts for the product configuration. In a related study, Evans et al. reported the addition of enol silanes to oxazolidinone fumarates **197** in the presence of Cu(II)bis(oxazoline) catalyst (Scheme 39).[69] (*Z*)-enol silanes gave *syn* adducts whereas (*E*)-enol silanes gave *anti* adducts. HFIP was again helpful in improving the rates. The reaction was studied by in situ infrared spectroscopy which revealed that the first step in the reaction was a hetero Diels–Alder reaction followed by the hydrolysis of the dihydropyran ring to the observed product.

8.4. Radical based ECA

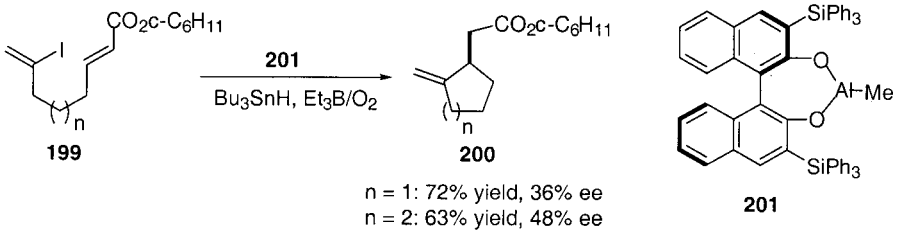
Enantioselective conjugate addition of radicals is a recently developing field. Only four years ago was this concept initiated.[70] A first example in the intramolecular radical addition was reported by Nishida et al., using a BINOL based chiral aluminum Lewis acid **201** (Scheme 40).[71] Formation of a vinylic radical followed by a 5-*exo* or 6-*exo* (for $n=1$ or 2) cyclization controlled by the chiral Lewis acid provides enantiofacial selection. Four equivalents of the Lewis acid was employed in these reactions for obtaining maximum selectivity. Lower yields of the 6-membered ring products are due to difficulty in the 6-*exo* cyclizations.

Intermolecular reactions are relatively difficult because one needs to tinker with the reactivity of the substrate so that the chiral source–substrate complex is more reactive than the uncomplexed substrate. Sibi, Porter and co-workers showed

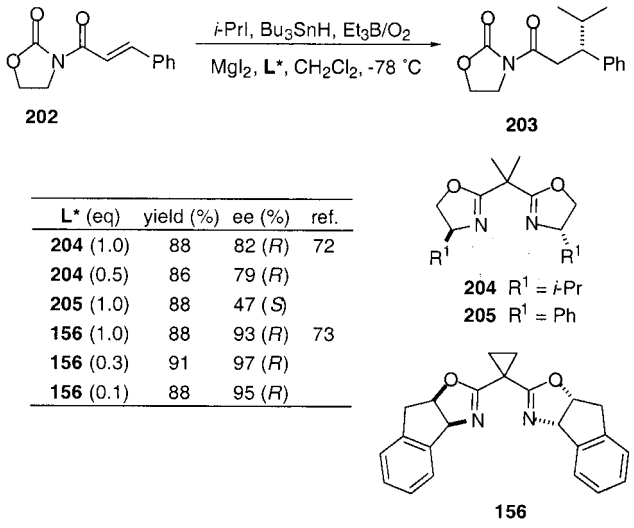


R^1	R^2	*anti:syn*	yield (%)	ee (%)
SMe	Me	90:10	93	83
Ph	Me	95:5	99	92
SMe	*i*-Pr	>99:1	93	98
Ph	*i*-Pr	>99:1	99	94

Scheme 39.



Scheme 40.



L* (eq)	yield (%)	ee (%)	ref.
204 (1.0)	88	82 (*R*)	72
204 (0.5)	86	79 (*R*)	
205 (1.0)	88	47 (*S*)	
156 (1.0)	88	93 (*R*)	73
156 (0.3)	91	97 (*R*)	
156 (0.1)	88	95 (*R*)	

Scheme 41.

that it was indeed possible to achieve enantioselective transformations with radicals using chiral Lewis acids (Scheme 41).[72] The addition of isopropyl radical to cinnamoyl oxazolidinone **202** with MgI_2–bisoxazoline ligand **204** (50 mol%) gave the adduct **203** in 86% yield and 79% ee. Interestingly, face selection depends on whether the C-4 substituent on the bisoxazoline ligand has an alkyl (**204**) or an aryl (**205**) group. Using only 10 mol% of MgI_2 and **156**, high levels of selectivity were obtained by Sibi and Ji.[73] A model **206** with *cis*-octahedral geometry around the Lewis acid accounts for selectivity with the ligand **156** while a *trans*-octahedral complex **207** is postulated with **205** (Fig. 11). Furthermore, these reactions could be conducted at room temperature without much loss in selectivity.

In $Zn(OTf)_2$ mediated reaction of **202** with ligand **156**, 53% ee of (*R*)-**203** was obtained (data not shown in Scheme 41). In contrast, the use of pyrazole as an achiral template instead of oxazolidinone leads to an inversion in selectivity in the

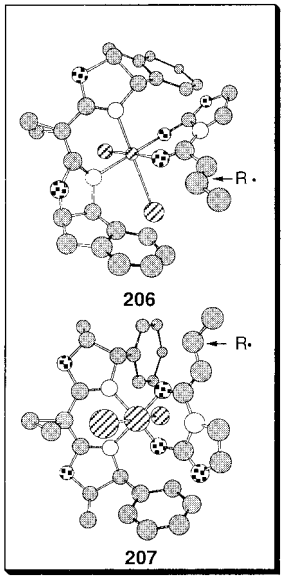
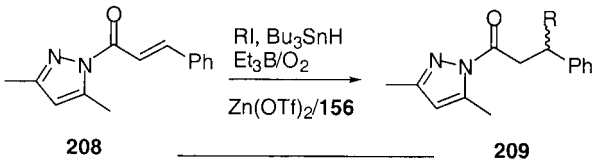


Fig. 11.



R	yield (%)	ee (%)
i-Pr	76	51 (*S*)
Et	80	39 (*R*)
c-C_6H_{11}	81	81

Scheme 42.

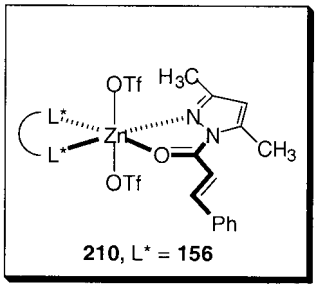


Fig. 12.

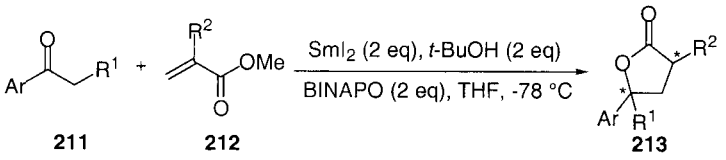
presence of $Zn(OTf)_2$ (Scheme 42).[74] These acylated pyrazoles **208** form 5-membered chelates unlike the 6-membered chelate formed with oxazolidinones. This change in chelate ring size, accompanied by a *trans*-octahedral geometry with **156**, has been proposed for the reversal of enantioselectivity (Fig. 12). Similar transformation was investigated by Curran and Kanemasa with the DBFOX–Ph ligand (vide infra, **253**) and moderate selectivity (75% ee) was obtained.[75] DBFOX, a tridentate ligand, increases the electron density on Mg and makes it a weaker Lewis acid. This leads to the non-selective background reaction (non-Lewis acid catalyzed) and hence to the lowering of enantioselectivity.

Ketyl radicals generated from aryl ketones **211** and SmI_2, the Kagan reagent, can add to olefins. Mikami and Yamaoka have taken advantage of complexing the samarium with chiral 2,2′-bis(diphenylphosphinyl)-1,1′-binaphthyl (BINAPO) **214** to make this addition process enantioselective (Scheme 43).[76]

9. Nitrogen Based Nucleophiles

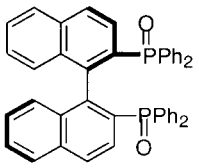
Addition of nitrogen nucleophiles to α,β-unsaturated esters lead to the synthesis of β-amino acid derivatives. Jørgensen et al. reported the enantioselective $TiCl_2$–BINOL **217** catalyzed addition of benzylhydroxylamine to *N*-acyloxazolidinones **215** (Scheme 44).[77] However, only modest enantioselectivity was obtained (maximum ee of 42%).

Sibi and co-workers, utilizing pyrazole templates **218**, were able to perform the conjugate addition of *O*-benzylhydroxylamine in good yields and ee's up to 97% (Scheme 45).[78] The high ee's obtained in these reactions with **218** (R=Me) is a consequence of selective addition of amine (~9:1) followed by a kinetic resolution



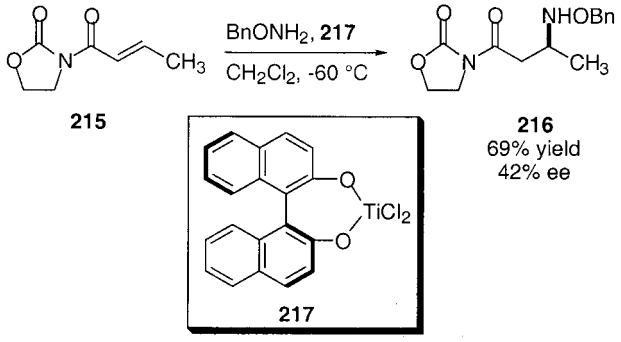
211 212 213

Ar	R^1	R^2	yield (%)	*cis* : *trans*	ee (%) *cis/trans*
Ph	H	H	46		67
Ph	H	Me	42	66:34	89/55
Ph	Me	H	18		63



(*R*)- BINAPO, **214**

Scheme 43.

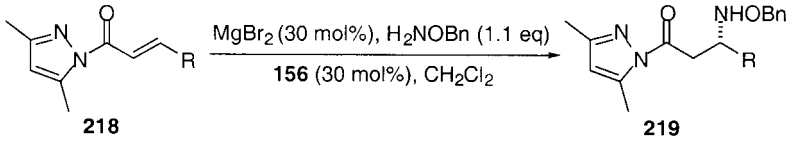


215 **216** 69% yield 42% ee **217**

Scheme 44.

wherein the minor enantiomer of **219** (R=Me) is preferentially converted to **220** by amidolysis. Substoichiometric amounts of the Lewis acid (30 mol%) gave better yields (due to less amidolysis) and only a slight decrease in ee's. The use of lanthanide Lewis acids leads to the reversal of product stereochemistry.

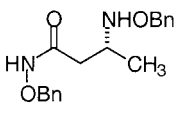
Recently, Jacobsen and Myers have succeeded in the addition of hydrazoic acids (6.6 equiv.) to unsaturated imides **221** using 5 mol% of chiral (salen)Al(III) complex **223** (Scheme 46).[79] A single point binding of the substrate through the imide carbonyl closer to the olefin has been suggested to account for the observed selectivity.



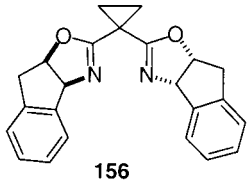
218 **219**

R	yield (%)	ee (%)
Me	80	92 (*R*)
Me*	60	97 (*R*)
CH_2Ph	80	95 (*R*)
i-Pr	76	87 (*R*)
Me†	67	59 (*S*)

* 1eq $MgBr_2$ used.
† 1 eq $Y(OTf)_3$ used.

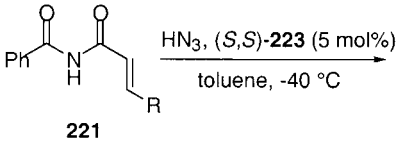


220



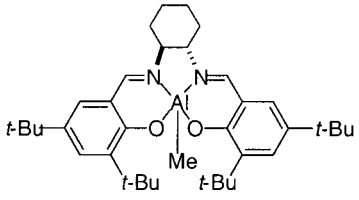
156

Scheme 45.



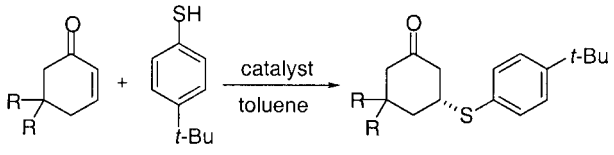
221 **222**

R	yield (%)	ee (%)
Me	96	96
t-Bu	99	97
CH_2Bn	93	96
Ph	60	58

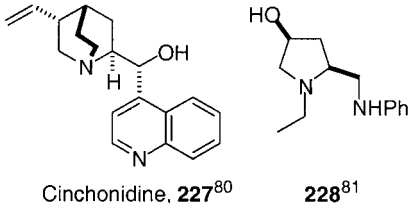


(*S*,*S*)-**223**

Scheme 46.

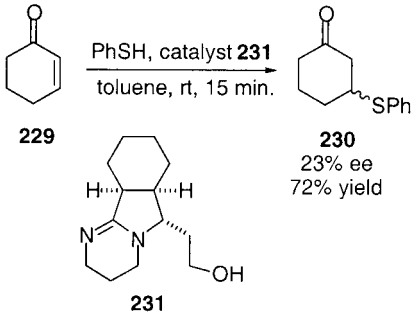


R	catalyst	yield (%)	ee (%)
Me	**227** (1 mol%)	98	70
H	**228**	74	88

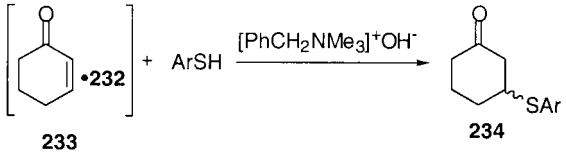


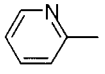
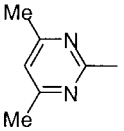
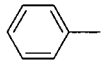
Cinchonidine, **227**[80] **228**[81]

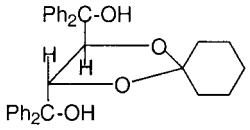
Scheme 47.



Scheme 48.



Ar	yield (%)	ee (%)
	51	80
	77	78
	100	0



(*R*,*R*)-(-)-**232**

Scheme 49.

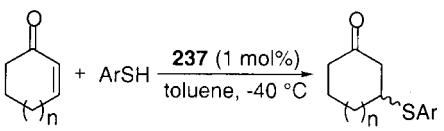
10. Thiol Additions

Earliest reports on the ECA of thiols utilized cinchona alkaloids and chiral amino alcohols (Scheme 47). A detailed mechanistic study by Wynberg and Hiemstra showed that the β-hydroxy amine functionality is required for higher ee's.[80] Cinchonidine **227** acts as a bifunctional catalyst bringing both the reactants together; the carbonyl oxygen of enone forms a hydrogen bond to the hydroxyl group and the thiol anion is bound through electrostatic interaction with the ammonium cation. Non-polar solvents work best in enhancing these catalyst–reactant interactions. Catalyst **228**, containing a β-hydroxy amine moiety, was prepared by Mukaiyama et al. from hydroxyproline.[81] These catalysts were efficient in catalyzing thiol addition to cyclohexenone producing up to 88% ee's.

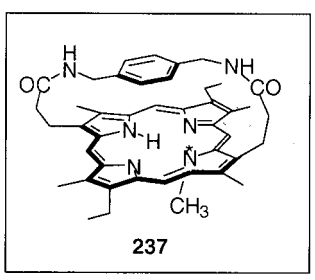
Optically active bases were recently revisited as catalysts for thiol additions with poor success. Addition of thiophenol to cyclohexenone proceeded with low ee's in the presence of chiral amidine **231** (Scheme 48).[82]

An interesting use of inclusion crystals of cyclohexenone and optically active host compound **232** in addition of thiols was reported by Toda et al. (Scheme 49).[83] Heteroaryl thiols gave good selectivities in the reactions with benzyltrimethylammonium hydroxide as catalyst. This bulky catalyst acts to deliver the thiols through a salt-like interaction of the heteroatom on the aryl ring and the ammonium ion. A decrease in the steric bulk of the ammonium salt lowers the selectivity.

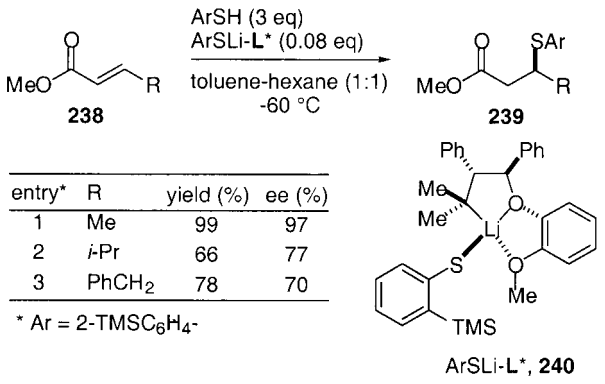
Chiral porphyrins have been shown to catalyze the addition of thiols to cycloalkenones (Scheme 50).[84] Moderate



entry	n	Ar	ee (%)
1	1	Ph	47
2	1	4-*t*-BuC$_6$H$_4$	51
3	2	4-*t*-BuC$_6$H$_4$	49



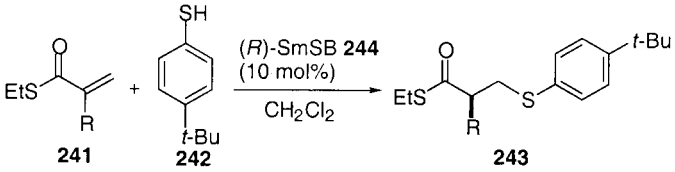
Scheme 50.



entry*	R	yield (%)	ee (%)
1	Me	99	97
2	*i*-Pr	66	77
3	$PhCH_2$	78	70

* Ar = 2-$TMSC_6H_4$-

Scheme 51.



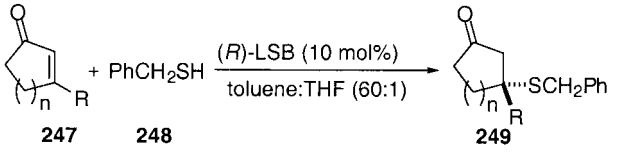
entry	R	yield (%)	ee (%)
1	Me	96	93
2	*i*-Pr	78	90
3	$PhCH_2$	89	87
4	Ph	98	84

Scheme 52.

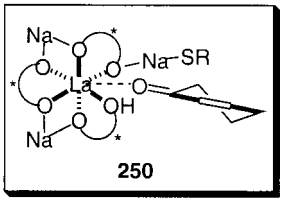
selectivities were obtained. The hydrogen bonding of the enone to the exocyclic amido NH of **237** activates the substrate and provides steric shielding leading to selectivity.

Thiols undergo conjugate additions with α,β-unsaturated esters in excellent ee's in the presence of chiral lithium catalysts (Scheme 51).[85] The chiral arenethiolato–lithium complex **240** is the active catalyst in the addition.

Shibasaki et al. have extended the scope of their hetero-bimetallic catalysts to the addition of thiols.[86] Both acyclic thio esters (Scheme 52) and cycloalkenones (Scheme 53) gave good selectivities. The lanthanum based catalyst $LaNa_3$tris(binaphthoxide), (*R*)-LSB, was efficient with the cycloalkenones and the samarium based catalyst $SmNa_3$-tris(binaphthoxide), (*R*)-SmSB, was good for the thio esters. In case of α-substituted substrates (**241**) selectivity arises



entry	n	R	yield (%)	ee (%)
1	1	H	86	90
2	2	H	94	56
3	3	H	87	83
4	1	Me	56	85



Scheme 53.

from asymmetric protonation of intermediate **246** by the acidic hydroxyl generated during the complexation of thiol to the catalyst (Fig. 13). This protocol has been utilized in the catalytic kinetic resolution of a bicyclic enone.[87] The catalytic cycle for the addition of thiols to cycloalkenones is similar to that of thio esters. The stereoselectivity at the β-position of the acceptor is determined by the controlled delivery of thiol as shown in **250**.

Kanemasa and co-workers added arene thiols enantioselectively to *N*-crotonyl oxazolidinones **251** with Ni(II) and DBFOX/Ph **253** (Scheme 54).[88] The ee's are very dependent on the reaction conditions. Proton sponge (*N*,*N*,*N*′,*N*′-tetramethyl-1,8-diaminonaphthalene, 10 mol%) helps in achieving high selectivity. The aqua complexes are necessary; the use of anhydrous complex leads to racemic material. Lewis acid activation of the substrate plays an important role rather than the complexation of the thiol to Ni, though thiols have been known to poison nickel catalysts in many reactions.

11. Miscellaneous Reactions

11.1. Conjugate reduction

The enantioselective 1,4-addition of a hydride ion, conjugate reduction, has been recently achieved by Buchwald and

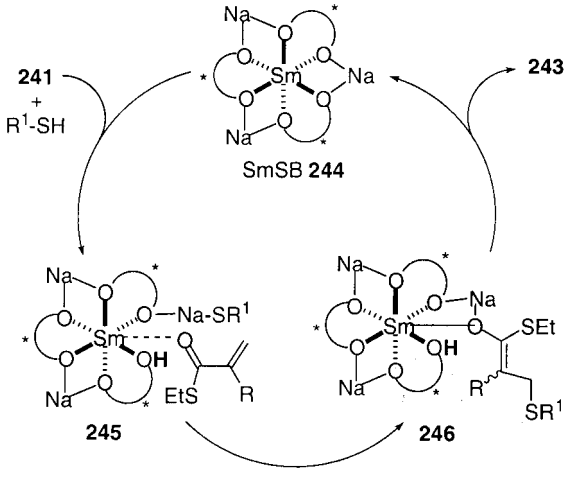
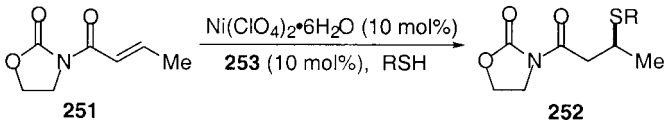


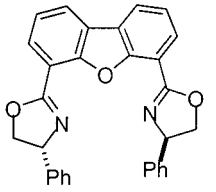
Fig. 13.



251 252

entry*	R	yield (%)	ee (%)
1	Ph	84	94
2	mesityl	36	96
3	2-naphthyl	88	91

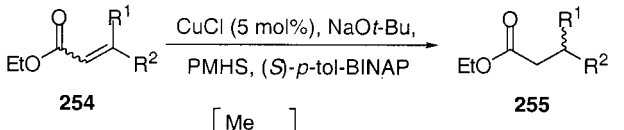
* At 0 °C in CH_2Cl_2/THF (10:1) + proton sponge (10 mol%).



(*R*,*R*)-DBFOX/Ph, **253**

Scheme 54.

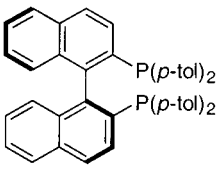
co-workers using Cu(I)-*p*-tol–BINAP as catalyst and polymethylhydrosiloxane (PMHS) as the hydride source (Scheme 55).[89] Both *E* and *Z* **254** react efficiently each providing the opposite enantiomer. PMHS plays a dual role: as the source for hydride and as a trap for the copper enolate generated after the hydride transfer in forming the silylketene acetal which is transformed to **255** during work-up.



254 255

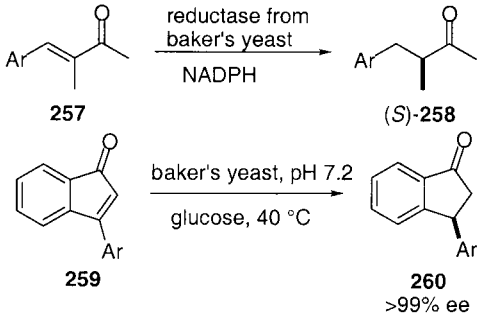
PMHS = $Me_3Si-O-[Si(Me)(H)-O]_n-SiMe_3$

R^1	R^2	*E*/*Z*	yield (%)	ee (%)
Me	*c*-C_6H_{11}	*E*	89	92 (*R*)
Et	Ph	*E*	98	91 (*S*)
Et	Ph	*Z*	98	83 (*R*)



(*S*)-*p*-tol-BINAP **256**

Scheme 55.



257 (*S*)-258 259 260 >99% ee

Scheme 56.

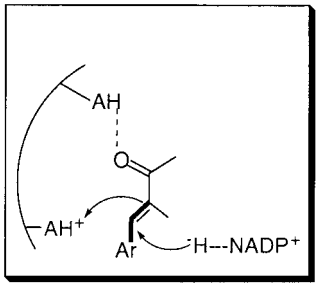


Fig. 14.

Enzymes, chemists' enviable catalysts, are capable of performing conjugate reductions. These transformations provide the saturated ketone products in good enantioselectivities. Kawai et al. showed that **257** could undergo conjugate reduction in the presence of a reductase isolated from baker's yeast with up to 99% ee for (*S*)-**258** (Scheme 56).[90] NAD(P)H delivers the hydride to the β-position and the trapping of the enolate with a proton source, from either water or the enzyme (Fig. 14). The process is equivalent to *trans* hydrogenation. Clark and co-workers have utilized this process in the synthesis of (*S*)-3-arylindan-1-ones **260** in excellent ee's.[91]

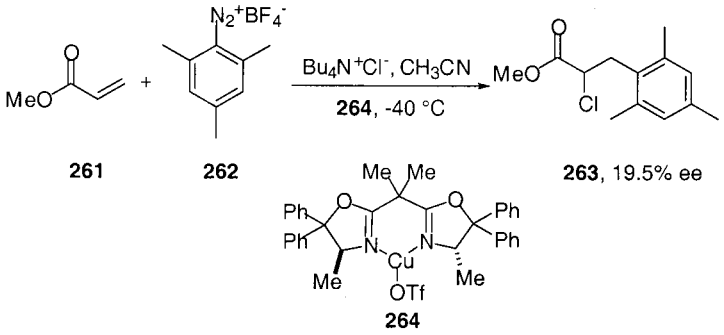
11.2. Enantioselective Meerwin reaction

Arylation of activated double bonds with diazonium salts in the presence of copper catalysts is known as the Meerwin reaction. Brunner and Doyle carried out the addition of mesityldiazonium tetrafluoroborate **262** with methyl acrylate using catalytic amounts of Cu(I)bis(oxazoline) **264** and were able to obtain low ee's for the product **263** (Scheme 57).[92] Since the mechanism of the Meerwin reaction is unclear, it is difficult to rationalize the low ee's obtained and to plan for further modifications.

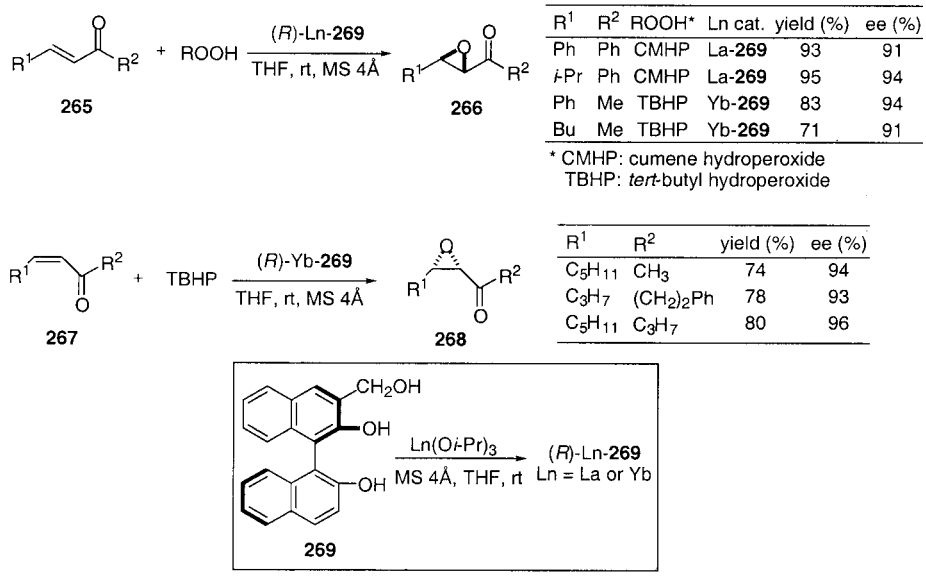
11.3. Epoxidations

Epoxidation of α,β-unsaturated ketones involves the conjugate addition of peroxide anion as the initial step. Using catalyst Ln-**269**, prepared from 3-hydroxymethyl–BINOL **269** and $Ln(O-iPr)_3$, Shibasaki et al. have achieved the stereoselective epoxidation of both *cis* and *trans*-enones (Scheme 58).[93] *cis*-Enones capable of isomerization to the *trans*-enones gave the *cis*-epoxides in good yields. Such control is possible only if the catalyst is able to restrain the rotation of the substrate. Although the actual catalyst structure is not known, a positive non-linear effect observed in these reactions suggests the involvement of oligomeric structures in catalytic process.

Polybinaphthyl ligands, developed by Pu and co-workers, catalyze the asymmetric epoxidation of acyclic enones **270** with *t*-butyl hydroperoxide and diethylzinc (Scheme 59).[94] A *t*-butyl–peroxy complex of polymer bound zinc has been proposed as the active complex. Substoichiometric amounts



Scheme 57.

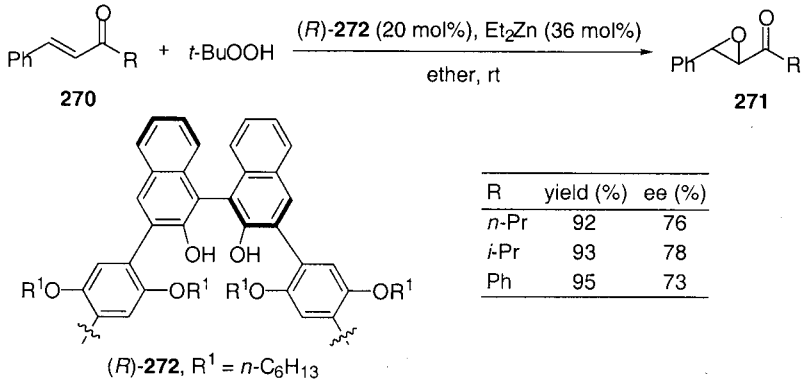


R^1	R^2	ROOH*	Ln cat.	yield (%)	ee (%)
Ph	Ph	CMHP	La-**269**	93	91
i-Pr	Ph	CMHP	La-**269**	95	94
Ph	Me	TBHP	Yb-**269**	83	94
Bu	Me	TBHP	Yb-**269**	71	91

* CMHP: cumene hydroperoxide
TBHP: *tert*-butyl hydroperoxide

R^1	R^2	yield (%)	ee (%)
C_5H_{11}	CH_3	74	94
C_3H_7	$(CH_2)_2Ph$	78	93
C_5H_{11}	C_3H_7	80	96

Scheme 58.



R	yield (%)	ee (%)
n-Pr	92	76
i-Pr	93	78
Ph	95	73

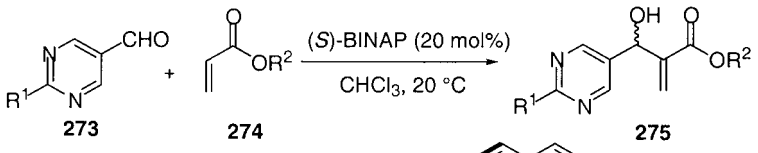
Scheme 59.

of the polymeric ligand **272** were found sufficient. The polymeric ligands were superior to the monomeric ligands in stereoinduction hinting at a cooperative effect of these polymers.

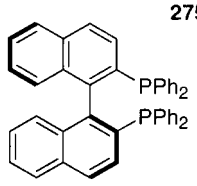
11.4. Baylis–Hillman reaction

The Baylis–Hillman reaction involves the conjugate addition of a base (usually a tertiary amine) followed by the trapping of the resulting enolate with an aldehyde and concomitant release of the amine.[95] Chiral bases have been recently utilized in the enantioselective Baylis–Hillman reaction with considerable success. Chiral phosphine, for example, (*S*)-BINAP was used by Soai et al. with moderate ee's for the products obtained from pyrimidine 5-carbaldehydes **273** and various alkyl acrylates (Scheme 60).[96]

The use of the β-hydroxy amine moiety to provide

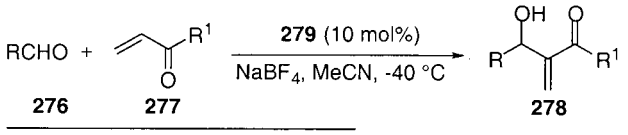


R^1	R^2	yield (%)	ee (%)
H	*i*-Pr	8	9
H	Et	12	25
H	Me	24	44
Me	Me	18	37

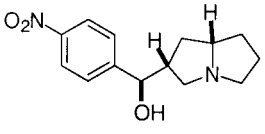


(*S*)- BINAP **77**

Scheme 60.



R	R^1	yield (%)	ee (%)
2-$O_2NC_6H_4$	Et	71	67
2-$O_2NC_6H_4$	Me	71	53
2-ClC_6H_4	Et	58	72
3-pyridyl	Et	93	49
4-$O_2NC_6H_4$	Et	17	39



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Scheme 61.

organization in conjugate addition of nucleophiles seems to be a recurring idea. Barrett and co-workers have used pyrrolizidine based catalyst **279** for the reaction of aromatic aldehydes with enones (Scheme 61).[97] These catalysts also enhance the rate of the reaction (which usually proceeds in about 3 days) although the stereoinduction is only moderate.

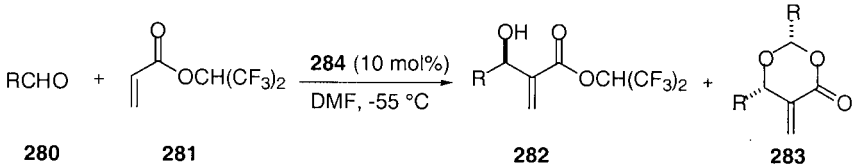
Similar results were obtained with quinidines **284** as catalysts by Hatakeyama. High ee's were obtained although the yields of the Baylis–Hillman products **282** were low due to the competitive formation of the dioxanones **283** through the consecutive reaction of two aldehyde molecules (Scheme 62).[98]

12. Conclusions

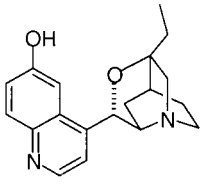
The last decade has witnessed enormous growth in enantioselective conjugate addition methodology. Many nucleophiles can now be added with good stereochemical control. Various concepts in ligand design and the activation and organization of reactants by Lewis acids seem to be the forerunners in achieving asymmetric catalysis in these reactions. Modular variation of structure has been a useful approach in ligand evolution. This, coupled with high-throughput screening, will help in developing a new generation of efficient ligands. We hope that this review has placed the prevalent themes of enantioselective bond construction strategy using conjugate addition in perspective.

Acknowledgements

We thank NIH (GM-54656), NSF (OSR-9452892), NSF (9983680), DuPont, and North Dakota State University for financial support of our programs. We would also like to thank Dr Jianguo Ji, Prof. Craig Jasperse, Dr John Shay, Ms Mei Liu, Dr Jianxie Chen, Dr Yasutomi Asano, Ms Tara Ternes and Mr Justin Sausker for their contribution to our program on conjugate additions. We would also like to thank Profs James Takacs (University of Nebraska) and Russell Linderman (North Carolina State University) for helpful discussions.



R	time	% yield (% ee)	
		ester	dioxanone
4-$NO_2C_6H_4$	1 h	58 (91)	11 (4)
Ph	48 h	57 (95)	-
(*E*)-PhCH=CH_2	72 h	50 (92)	-
Et	4 h	40 (97)	22 (27)
i-Pr	16 h	36 (99)	25 (70)



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Scheme 62.

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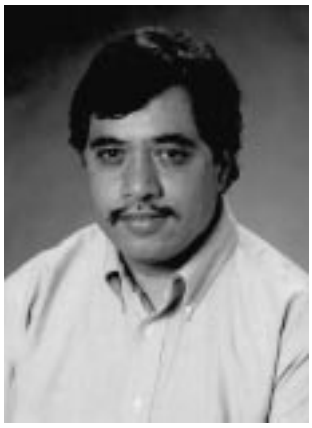
Biographical Sketch



Mukund Sibi hails from Bangalore, India. After undergraduate studies in Bangalore, he joined Hunter College, CUNY, and received his PhD degree under the guidance of Prof. Robert Lichter. He carried out postdoctoral studies with Profs Gordon Gribble, Victor Snieckus and Robert Holton. He joined North Dakota State University in 1987, where he is currently Professor of Chemistry. His research interests include the development of new asymmetric processes, total synthesis of natural products, chiral catalysis, and non-food uses of agricultural materials.

Shankar Manyem obtained his BSc in 1993 from the University of Madras, India. He went on to Indian Institute of Technology, Madras for his MSc (Chemistry). His MSc thesis under Dr D. Loganathan and Dr T.S. Chandra involved screening of microbial sources for β-D-Xylosidases. He was the recipient of Rajiv Gandhi science talent research fellowship (1993) from Jawaharlal Nehru Center for Advanced Scientific Research (JNCASR, Bangalore) and worked with Prof. G. Mehta during summer of 1993. He is currently pursuing his doctoral degree at North Dakota State University with Prof. Mukund Sibi working on enantioselective conjugate addition of organometallic reagents to enamides. He is interested in asymmetric synthesis, especially catalysis.