Carbon-Carbon Bond Formation by Catalytic Enantioselective Conjugate Addition

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CARBON–CARBON BOND FORMATION BY CATALYTIC ENANTIOSELECTIVE CONJUGATE ADDITION

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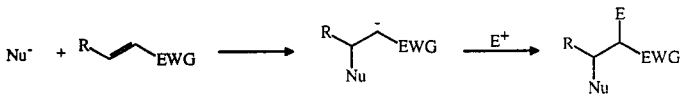
I. INTRODUCTION

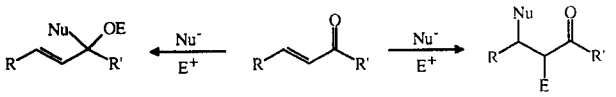
Conjugate addition reactions of carbon nucleophiles to α,β-unsaturated compounds are among the most widely used methods for carbon–carbon bond formation in organic synthesis.[1] It is therefore not surprising that major efforts have been devoted to achieve asymmetric conjugate addition despite the often complicated nature of many 1,4-addition reactions.[2,3] Addition of the nucleophile to the β position of an electron-deficient alkene results in a stabilized carbanion (Eq. 1). After protonation of the carbanion ($E^+ = H^+$) a β-substituted product is formed. Quenching of the stabilized carbanions with electrophiles provides α,β-disubstituted products with two newly created stereocenters, whereas, in the case of a prochiral nucleophile, up to three new stereocenters might be generated in the tandem reaction shown in Eq. 1.



(1)

EWG = CHO, COR, CO_2R, $CONR_2$, CN, SO_2R, NO_2, etc.

As carbon nucleophiles, one can use a variety of organometallic reagents, "classical" Michael donors, carbanions derived from nitroalkanes, nitriles or dithianes and enolates (and derivatives). Common substrates for conjugate addition reactions are α,β-unsaturated aldehydes, ketones, esters, amides, nitriles, sulfones and nitro compounds. Typical problems associated with conjugate addition are regioselectivity and reversibility (in particular with enones as substrates).[4] Competition between 1,2- and 1,4-addition to enones is governed by several parameters, but, in general, the use of soft carbon nucleophiles results in high selectivities for conjugate addition products (Eq. 2).

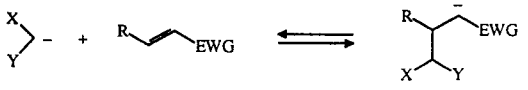


(2)

1,2-addition 1,4-addition

In Michael additions, which are often executed under thermodynamically controlled conditions employing stabilized carbanions, reversibility is not an uncommon feature (Eq. 3). The stereochemistry might be affected by such reversible processes, whereas the presence of a labile

hydrogen at the α-carbon (with respect to EWG) could be another complicating factor since racemization or epimerization can occur.



(3)

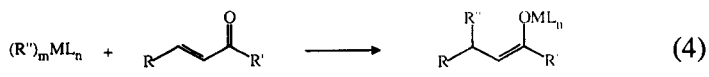
The enormous potential of conjugate addition reactions in synthesis is partly due to the large variety of donor and acceptor compounds that can be employed. Another important aspect is the high diastereoselectivity often observed. These features have been a strong impetus for developing enantioselective 1,4-additions. The use of enantiomerically pure Michael type acceptors based on natural products has been extremely successful, commonly leading to 1,4-adducts with high, predictable stereoselectivities.[2–4,5] *Stoichiometric* asymmetric conjugate additions have been developed along two lines, (i) using a chiral auxiliary-based Michael acceptor i.e., a chiral α,β-unsaturated ester, amide, or sulfoxide,[2,5,6] or (ii) reacting a chiral reagent with a prochiral electron-deficient alkene.[2,3,6] In the latter case, two strategies have mainly been used, namely, chiral auxiliary-based donors, such as enamines and enol derivatives, and chiral ligand-modified organometallic reagents, in particular chiral cuprates, Grignard reagents, organozincates and organolithium reagents. Natural product and synthetic organic ligands and auxiliaries have been successfully employed, but, high diastereoselectivities were also reached with organometallic auxiliaries.[7] Asymmetric conjugate addition reactions using *stoichiometric* chiral auxiliary-based Michael donors and acceptors and chiral organometallic reagents have been extensively covered by reviews and the reader is referred to these papers for specific examples.[1–6]

It should be emphasized that several chiral auxiliary-based acyclic and cyclic α,β-unsaturated substrates, enolates, and enamines are now available that give enantioselectivities exceeding 95% in a variety of reactions. Furthermore, there are a number of organocopper reagents with chiral nontransferable ligands, as well as organocuprates modified by additional chiral ligands known today, that provide 1,4-addition products with >95% ee. High enantioselectivities, however, are reached only with a limited number of prochiral acyclic and cyclic enones (vide infra).[3] Major improvements are necessary, in particular, with respect to the scope of chiral reagent-based methods. This becomes evident when one considers applications in the practical synthesis of enantiomerically pure compounds employing conjugate addition as a key step.

Even more challenging is the development of general methodologies for enantioselective carbon–carbon bond formation using chiral non-racemic catalysts in combination with readily available organometallic reagents and Michael donors. Progress in this area is the subject of this chapter with the emphasis on enantioselective conjugate addition catalyzed by chiral transition-metal complexes.

II. ASYMMETRIC METAL-MEDIATED 1,4-ADDITION

In order to achieve a rational synthesis of new chiral catalysts for enantioselective conjugate addition, it is of prime importance to consider several factors that might govern the 1,4-addition step. Among these are: (i) the nature of the organometallic reagent $(R'')_mM$ (Eq. 4), (ii) the ligands, L_n, associated with it, (iii) the fact that most of these reagents are aggregated in solution (solvent dependent), and (iv) the notion that stereoselectivity (as well as regioselectivity) can be affected by additional ligands, coordinating solvents, and salts.

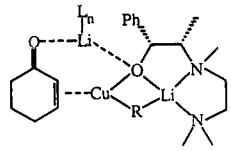


(4)

M = Cu, Li, Zn, Mg

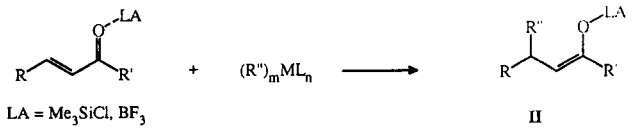
Furthermore, activation of the electron-deficient alkene by Lewis acid or cation complexation to the carbonyl moiety is often proposed as a means to tether the reagent, catalyst, and enone in order to increase stereoselectivity and enhance reactivity toward weaker nucleophiles. The coordinating metal can be from the organometallic reagent, the catalyst (M) or additional metal ions (i.e., salts). The proposed intermediate, **I**, in the highly enantioselective (ee 90%) conjugate addition of the (1*R*,2*S*)-ephedrine-based mixed cuprate, reported by Corey and co-workers,[8] nicely illustrates additional lithium ion coordination between the carbonyl oxygen of the enone and the cuprate ligand (Figure 1).

The use of Lewis acids, in particular Me_3SiCl or BF_3, often results in dramatic increases in reaction rates in 1,4-addition reactions of cuprates presumably by enone activation (Eq. 5a).[9] Increased stereoselectivity, for instance, almost exclusive formation of **IVa** by the addition of Me_2CuLi to **III** in the presence of Me_3SiCl (Eq. 5b),[10] and the formation of enol derivatives, such as **II**, which can subsequently be used in electrophilic additions (tandem 1,4-addition-enolate processes), are important advantages.

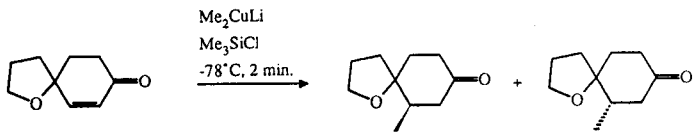


I (L_n = I, THF)

Figure 1. Proposed intermediate in the enantioselective conjugate addition of a mixed cuprate reported by Corey and co-workers.[8]



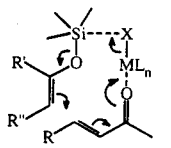
LA = Me_3SiCl, BF_3 II (5a)



III IVa 99 % IVb 1 % (5b)

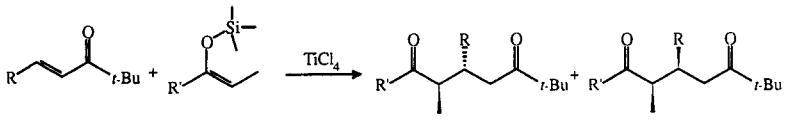
Lewis acid catalysis has been extremely successful in 1,4-additions of enol silyl ethers (and tin analogs).[11] The role of the Lewis acid can be merely an activation of the enone and the silyl enolate leading, via a cyclic transition state, **V**, (Figure 2), to Michael adducts with high stereoselectivities.

The high level of organization that might be reached in these cases offers attractive possibilities for developing new chiral Lewis acid catalysts for 1,4-additions. Moreover, stereoselectivity appears to be strongly Lewis acid and substituent-dependent as illustrated in Eq. 6.[12]



V (XML_n = Lewis acid)

Figure 2. Activation of enone and silyl enolate by a Lewis acid.

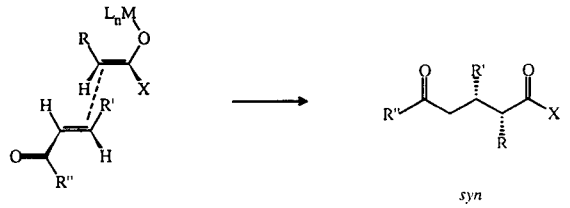


(6)

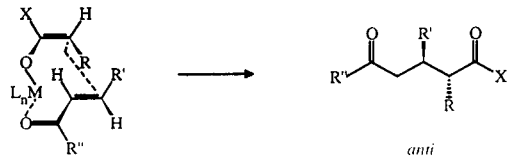
R = *i*-Pr ; R' = OMe	2	:	98
R = Me ; R' = Ph	93	:	7

When enolate anions or other stabilized carbon nucleophiles are involved in conjugate addition reactions in the presence of chiral metal catalysts, the catalysts can exert their stereodirecting effect via formation of chiral metal enolates, **VI**, (Figure 3), or by complexation and activation of the Michael donor, **VII**, (or both donor and acceptor).

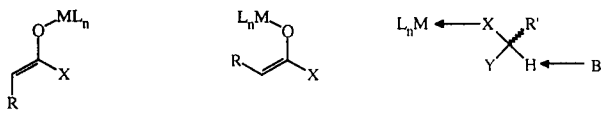
The geometry of the enolate (**VIa** or **VIb**) is also a decisive factor in the π face selectivity and *syn–anti* diastereoselectivity.[13] Finally, it should be noted that the stereochemical result of 1,4-additions of enolate-type carbon nucleophiles strongly depends on chelation or nonchelation control.[6,13] In Eq. 7, the open transition-state model and the closed (chelated) transition-state model for metal enolate additions to enones, leading to *syn* and *anti* adducts respectively, are given for the case of a (*Z*) enolate.



(7a)



(7b)



VIa (*E*-enolate) **VIb** (*Z*-enolate) **VII** (B = base)

Figure 3.

Strongly stimulated by the results of stereoselective aldol reactions, using well defined (*E*)- and (*Z*)-metal enolates, and by exploring the coordination properties of several metals (in particular B, Li, Ti and Mg), a number of highly diastereoselective conjugate additions of metal enolates has been developed.[6,14] Again, enolate geometry, solvent, counterion, metal catalyst, and mode of addition, can strongly influence the stereochemical result. All of these variables need to be considered in designing an effective chiral catalyst for 1,4-addition.

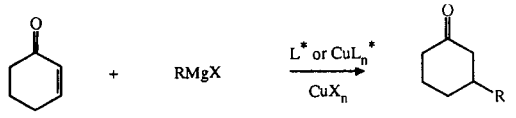
The use of chiral metal catalysts for enantioselective carbon–carbon bond formation, using organometallic reagents and other carbon nucleophiles, will be described in the next sections. For the sake of completeness, conjugate addition reactions using chiral crown ethers and bases are included.

III. CONJUGATE ADDITION OF GRIGNARD REAGENTS

A. Chiral Copper Complexes as Catalysts

Rapid progress has been made, in recent years, toward highly enantioselective conjugate addition of chiral, ligand-modified cuprates and organocopper reagents with nontransferable ligands based on Grignard and organolithium compounds.[3] It is surprising that, despite many attempts, the first examples of successful 1,4-additions of Grignard reagents catalyzed by chiral copper complexes were reported only very recently, albeit modest selectivities and limited scope were reached. Table 1 summarizes the relevant results obtained with cyclic and acyclic enones reported so far. The substrates and chiral catalysts are compiled in Figures 4 and 5, respectively.

Lippard and co-workers described the first catalytic conjugate addition of *n*-BuMgBr to 2-cyclohexen-1-one (**2**) (Eq. 8).[15] Using a copper(I) complex derived *in situ* from chiral *N,N'*-dialkyl aminotropone imine [H-(*R*)-CHIRAMT, **14**], 3-butyl-cyclohexanone was obtained with 14% enantiomeric excess (ee) (Table 1, Entry 1).

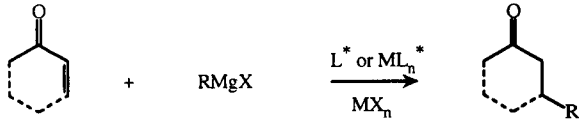


(8)

2

The enantioselectivity of the reaction is significantly increased by the addition of hexamethyl phosphoric triamide (HMPA) and silyl reagents

Table 1. Catalytic Enantioselective Conjugate Addition of Grignard Reagents



Entry	*Enone*	*L*orML$_n$**	*MX$_n$*	*RMgX*	*Additives*	*Reaction conditions*	*% Yield*	*% ee (conf.)*	*Reference*
1	**2**	**14**[a] (0.08)	CuBr[b] (0.04)	*n*-BuMgCl		THF, –78 °C	94	14 (*S*)	15
2	**2**	**14**[a] (0.04)	CuBr[b] (0.04)	*n*-BuMgCl		THF, –78 °C	96	20 (*S*)	15
3	**2**	**15**[a] (0.04)	CuBr[b] (0.04)	*n*-BuMgCl		THF, –78 °C	89	15 (*S*)	15
4	**2**	**15**[a] (0.04)	CuBr[b] (0.04)	*n*-BuMgCl	HMPA,Me_3SiCl (1.9)	THF, –78 °C	95	51 (*S*)	16
5	**2**	**15**[a] (0.04)	CuBr[b] (0.04)	*n*-BuMgCl	HMPA,Ph_2(*t*-Bu)SiCl (1.9)	THF, –78 °C	53	74 (*S*)	16
6	**2**	**14**[a] (0.04)	CuBr[b] (0.04)	*n*-BuMgCl	HMPA,Ph_2(*t*-Bu)SiCl (1.9)	THF, –78 °C	57	74 (*S*)	16
7	**2**	**14**[a] (1.0)	CuBr[b] (1.0)	*n*-BuMgCl	HMPA,Ph_2(*t*-Bu)SiCl (1.9)	THF, –78 °C	97	78 (*S*)	16
8	**2**	**14**[a] (0.04)	CuBr[b] (0.04)	MeMgCl	HMPA,Me_3SiCl (1.9)	THF, –78 °C	54	30 (*R*)	16
9	**2**	**14**[a] (0.04)	CuBr[b] (0.04)	EtMgCl	HMPA,Me_3SiCl (1.9)	THF, –78 °C	87	14 (*S*)	16
10	**6**	**16** (0.03)		MeMgI	HMPA,Me_3SiCl (1.9)	Et_2O, 0 °C	80	57 (*S*)	17
11	**2**	**17**[a] (0.06)	CuI (0.05)	*n*-BuMgCl	HMPA (2.0)	THF, –78 °C	nr[c]	58 (*R*)	19
12	**2**	**18**[a] (0.06)	CuI (0.05)	*n*-BuMgCl	HMPA (2.0)	THF, –78 °C	67	60 (*R*)	19
13	**2**	**19**[a] (0.06)	CuI (0.05)	*n*-BuMgCl	HMPA (2.0)	THF, –78 °C	nr[c]	15 (*R*)	19
14	**2**	**20**[a] (0.06)	CuI (0.05)	*n*-BuMgCl	HMPA (2.0)	THF, –78 °C	nr[c]	52 (*R*)	19
15	**2**	**18**[a] (0.06)	CuI (0.05)	*i*-PrMgCl	HMPA (2.0)	THF, –78 °C	71	72 (*R*)	19

16	**1**	**18**[a] (0.06)	CuI (0.05)	*i*-PrMgCl	HMPA (2.0)	THF, –78 °C	43	37 (*R*)	19
17	**3**	**18**[a] (0.06)	CuI (0.05)	*n*-BuMgCl	HMPA (2.0)	THF, –78 °C	24	83 (*R*)	19
18	**3**	**18**[a] (0.12)	CuI (0.10)	*n*-BuMgCl	HMPA (2.0)	THF, –78 °C	50	83 (*R*)	19
19	**3**	**18**[a] (0.12)	CuI (0.10)	*i*-PrMgCl	HMPA (2.0)	THF, –78 °C	55	87 (*R*)	19
20	**2**	**21** (0.03)	CuI[d] (0.03)	*n*-BuMgCl		Et_2O, –78 °C	90	50 nr[c]	20
21	**2**	**21** (0.03)	CuI[d] (0.03)	PhMgBr		Et_2O, –78 °C	60	20 nr[c]	20
22	**2**	**22** (0.01)		*i*-PrMgCl		THF, –90 °C	97	17 (*R*)	24
23	**2**	**23** (0.01)		*i*-PrMgCl	LiO*t*-Bu (0.01)	THF, –90 °C	95	21 (*R*)	24
24	**2**	**24** (0.01)	$ZnCl_2$ (0.01)	*i*-PrMgCl		THF, –90 °C	97	22 (*R*)	25
25	**2**	**25**[e] (0.01)	$ZnCl_2$ (0.01)	*i*-PrMgCl		THF, –90 °C	97	17 (*R*)	25
26	**2**	**26** (0.01)	$ZnCl_2$ (0.01)	*i*-PrMgCl		THF, –90 °C	91	21 (*R*)	25
27	**2**	**27** (0.01)	$ZnCl_2$ (0.01)	*i*-PrMgCl		THF, –90 °C	95	15 (*R*)	25
28	**2**	**28** (0.01)	$ZnCl_2$ (0.01)	*i*-PrMgCl		THF, –90 °C	91	21 (*R*)	25
29	**2**	**25**[e] (0.05)	$ZnCl_2$ (0.05)	*i*-PrMgBr		THF, –90 °C	92	33 (*R*)	25

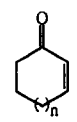
Notes: [a]Chiral ligand used as lithium salt.

[b]Actually, CuBr·Me_2S was used as metal source.

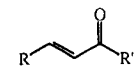
[c]nr, not reported.

[d]An additional 3 equivalents of BuLi was added (with respect to CuI).

[e]An additional equivalent of BuLi was added (with respect to $ZnCl_2$).

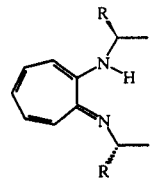


1 n = 0
2 n = 1
3 n = 2
4 n = 10

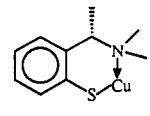


5 R, R' = Ph
6 R = Ph ; R' = Me
7 R = Me ; R' = Ph
8 R = Ph ; R' = CPh_3
9 R = Ph ; R' = *t*-Bu
10 R = Ph ; R' = *p*-MeOPh
11 R = *p*-MeOPh ; R' = Ph
12 R = *p*-ClPh ; R' = Ph
13 R = Ph ; R' = *p*-ClPh

Figure 4. Substrates used in catalytic enantioselective conjugate addition reactions (see sections III and V).



14 R = Ph (H-(*R*)-CHIRAMT)
15 R = 1'-Naph (H-(*R*)-NEAT)



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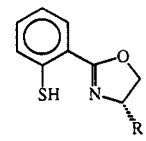
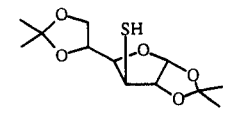


17 R = Me
18 R = *i*-Pr
19 R = *t*-Bu
20 R = Benzyl



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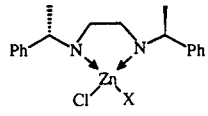
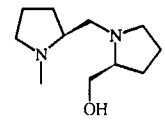


22 X = Cl
23 X = O*t*-Bu



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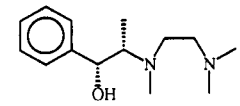

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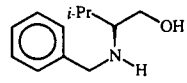

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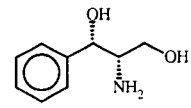

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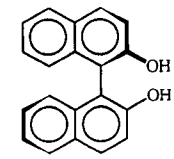

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Figure 5. Chiral ligands and complexes used as catalysts in the conjugate addition of Grignard reagents to enones.

(Table 1, Entries 4–6 and section II).[16] Both HMPA and a bulky silyl reagent seem essential to reach high ee's. The highest enantioselectivity (ee 74%, c.y. 53–57%) is obtained using 2 equiv. of *t*-butyldiphenylsilyl-chloride, 2 equiv. of HMPA and 4 mol% of chiral ligands **14** or **15**. The role of HMPA and the silyl reagent remains rather obscure at present, but it appears that these additives suppress the uncatalyzed conjugate addition. A slightly higher ee is obtained when a stoichiometric amount of catalyst is used (Table 1, Entry 7). Compared to *n*-BuMgCl, poor enantioselectivities were found with other Grignard reagents (Table 1, Entries 8 and 9). Interestingly, the reaction with MeMgCl gave (*R*)-3-methylcyclohexanone in excess, instead of the *S* enantiomer observed in the reaction with *n*-BuMgCl. This reversal indicates that the Grignard reagent is involved in the rate-determining step of the reaction. Other enones are converted as well, though no enantioselectivity was observed. All of these effects clearly demonstrate the complex nature of the catalytic sequence. Further study of additive effects will be necessary.

Van Koten and co-workers have reported the use of chiral copper(I) arenethiolate {2-[1-(*R*)-(dimethylamino)ethyl]phenyl thiolate copper(I)} (**16**) as a catalyst for the enantioselective addition (ee 57%) of MeMgI to benzylidene acetone (**6**) (Table 1, Entry 10).[17] The enantioselectivity is highly dependent on the mode of addition. Only slow addition of MeMgI to a preformed solution of **6** and 3 mol% of **16** in Et_2O produced high enantioselectivity. This indicates that a cuprate reagent rather than free MeMgI is involved in the reaction. The copper complex probably exists in solution as a trinuclear aggregate. The X-ray structure of a related achiral copper complex has been obtained and is shown in Figure 6.[18]

Zhou and Pfaltz reported that copper(I) thiolate complexes derived *in situ* from chiral mercaptophenyloxazolines, **17–20**, were effective in the 1,4-addition of *n*-BuMgCl to cyclic enone **2** (Table 1, Entries 11–14).[19] Again, the highest selectivities were reached only when the Grignard reagent was added slowly at –78°C to the solution of enone, catalyst and two equivalents of HMPA. The methyl and isopropyl derivatives, **17** and **18**, were the most effective ligands whereas the bulky derivative, **19**, gave markedly lower enantioselectivity. Significant enantioselectivities were found only in the presence of HMPA. The use of trialkylchlorosilanes as additives (vide supra) resulted in substantial loss of selectivity. For cyclic enones, the enantioselectivity increased with ring size from cyclopentenone (16–37%), to cyclohexenone (60–72%), and to cycloheptenone (83–87%) (Table 1, Entries 15–19).[19] With respect to the

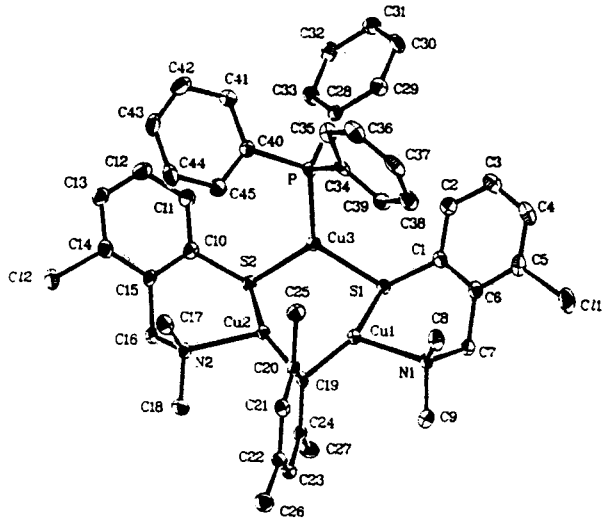


Figure 6. ORTEP drawing of achiral $\{Cu_3[SC_6H_3(CH_2NMe_2)\text{-}2\text{-}Cl\text{-}3]_2(C_6H_2Me_3\text{-}2,4,6)(PPh_3)\}$ (reprinted from ref. 18; copyright 1992 American Chemical Society).

Grignard reagent, it was found that *i*-PrMgCl gave consistently higher ee's than *n*-BuMgCl, whereas PhMgBr gave virtually racemic products. Despite the strong analogy between chiral catalyst, **16**, and the copper catalysts derived from ligands **17–20**, only low enantioselectivities (ee <20%) with acyclic enones were reported in the latter case.

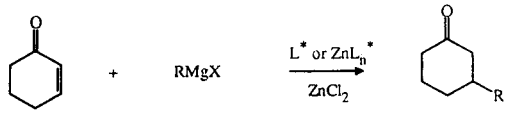
A third catalytic system, based on chiral copper(I) thiolate complexes, was described by Spescha and Rihs.[20] The Cu(I) complex prepared *in situ* from the lithium salt of 1,2,5,6-di-*O*-isopropylidene-3-thio-α-*O*-glucofuranose (**21**) gave high yields and regioselectivities exceeding 98% in the addition of *n*-BuMgCl to enone **2**. The enantioselectivity is strongly dependent on the reaction conditions. Variation of a large number of reaction parameters resulted in ee's up to 60%. A typical example is given in Table 1, Entry 20. In order to avoid an excess of reagents, the catalytic reaction was carried out by slow, simultaneous addition of a solution of *n*-butyl magnesium halide and a solution of enone to a solution of the cuprate. Remarkable dependency on the halide in the Grignard reagent was observed. Using PhMgBr, an ee of only 20% was found (Table 1, entry 21). Reproducible results were found upon addition of a radical scavenger [2,2,6,6-tetramethylpiperidin-*N*-oxyl

(TEMPO)]. Together with the dependency of the enantioselectivity on the yields, salts, and solvents, these findings typically illustrate the complex nature of these catalytic systems. Without doubt, the copper catalysts, based on chiral thiol ligands, are highly promising in enantioselective conjugate additions of Grignard reagents. The first examples of ee's exceeding 95% seem within close reach.

One of the major problems to deal with, besides tuning of ligand and reaction conditions, are the different aggregates of the catalyst, in equilibrium with each other, and apparently formed in the reaction medium. The aggregate formation probably depends on the concentration of reactants and additives, resulting in different, catalytically active species with differing enantioselectivities.

B. Chiral Zinc Complexes as Catalysts

The development of chiral zinc(II) complexes as catalysts for 1,4-addition reactions was based on the discovery by Isobe and co-workers[21] of the facile conjugate addition of lithium triorganozincates. Subsequent studies resulted in selective alkyl group transfer from mixed trialkylzincates,[22] the use of alkoxides as nontransferable ligands, and 1,4-additions of Grignard reagents mediated by *N,N,N′,N′*-tetramethylenediamine zinc dichloride as reported by Jansen and Feringa.[23] Inspired by these results, we have used chiral diamine zinc complexes, **22** and **23** (Figure 5), and observed enantioselectivity in the 1,4-addition of *i*-PrMgBr to cyclohexenone (**2**). Subsequently, we found that catalytic amounts (1 mol%) of zinc(II) complexes, **22** and **23**, substantially increase yields, regioselectivities toward 1,4-adducts, and enantioselectivities of the conjugate addition (Eq. 9 and Table 1, Entries 21 and 22).[24] The use of an alkoxide as a nontransferable ligand increases both regio- and enantioselectivity.



2 (9)

A number of chiral catalysts, prepared *in situ* from chiral ligands **24–28** and $ZnCl_2$, were screened in the model reaction (Eq. 9).[25] A selection of the results is given in Table 1, Entries 24–29. In all cases, the yields and regioselectivities were excellent, and the highest enantioselectivity (33%) was found with 5 mol% of chiral ligand **25** and *i*-PrMgBr as the Grignard reagent.

The enantioselectivity depends on a number of variables:[25]

1. With other alkyl and aryl Grignard reagents, lower ee's, as compared to *i*-PrMgX, were found.
2. Both regio- and enantioselectivity improved by decreasing the temperature.
3. The effect of chloride or bromide (in RMgX) on the enantioselectivity reverses with different chiral ligands. Similar effects have been observed in cuprate additions.[20]
4. A significant improvement of enantioselectivity due to the presence of lithium ions was observed. Preferentially, the catalyst has to be prepared from the lithium salt of the ligand (for the lithium ion effect; see also section II).
5. Higher enantioselectivities were attained by slow addition of *i*-PrMgX to a solution containing substrate and catalyst. It appears essential to maintain a low concentration of the organometallic species to prevent rapid, uncatalyzed addition. Comparison of the catalyzed and uncatalyzed conversion of **2** with *i*PrMgBr at –90°C, shown in Figure 7, illustrates the general problem.

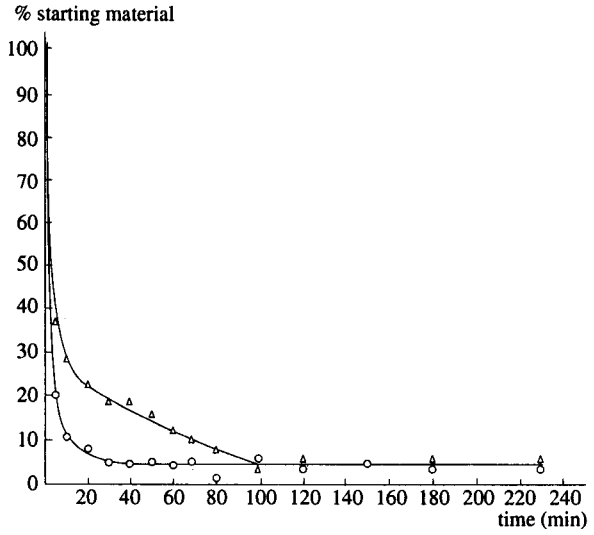


Figure 7. Decrease of 2-cyclohexenone (**2**) versus time in the reaction with iPrMgBr at –90 °C in THF: (Δ) no catalyst, (o) using 1 mol% TMEDAZn(O*t*-Bu)Cl (reprinted from ref. 25; copyright 1990 American Chemical Society.).

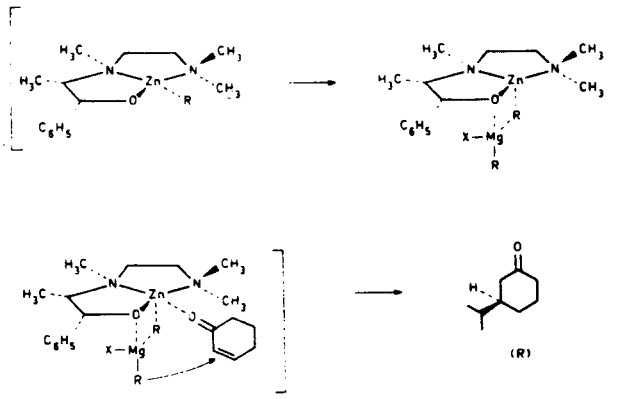


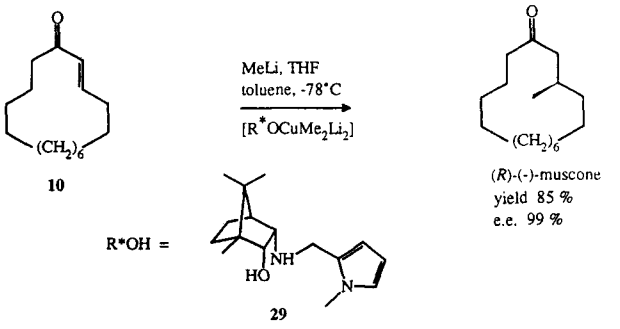
Figure 8. Proposed mechanism in the zinc-catalyzed conjugate addition of Grignard reagents to **2** (reprinted from ref. 25; copyright 1990 American Chemical Society.).

The modest selectivities and the sensitivity to a large number of variables make it difficult to postulate a catalytic cycle. The enantioselective 1,4-addition can be rationalized by a model, shown in Figure 8, for the catalyst based on ligand **25**. The chiral tetracoordinated alkylzinc complex may be one among various complexes in equilibrium.[25] Binding of the Grignard reagent via coordination of magnesium to the alkoxide, *exo* to the bicyclic zinc complex, can take place. Activation of the substrate, via coordination to zinc, involves a pentacoordinated zinc(II) intermediate bringing Grignard reagent and enone in close proximity to allow alkyl transfer. In this stage, a third metal (i.e., lithium) could be involved as proposed for cuprate additions (see also section II). It should be noted that scrambling of both alkyl groups has been observed. The zinc-catalyzed 1,4-addition of Grignard reagents is attractive for high yields and regioselectivities, although it is obvious that the enantioselectivity needs substantial improvement.

IV. CATALYTIC CONJUGATE ADDITION OF ORGANOLITHIUM REAGENTS

The high reactivity commonly found for organolithium reagents compared to Grignard reagents and the preference for 1,2-addition make the development of an efficient catalyst for conjugate addition of RLi a

particularly challenging goal. Significant enantioselectivities in catalytic alkyllithium additions had not been reported until Tanaka and co-workers[26] recently achieved the chiral alkoxycuprate-catalyzed addition of MeLi to (*E*)-cyclopentadec-2-en-1-one (**10**) affording (*R*)-(-)-muscone with 99% ee (Eq. 10).

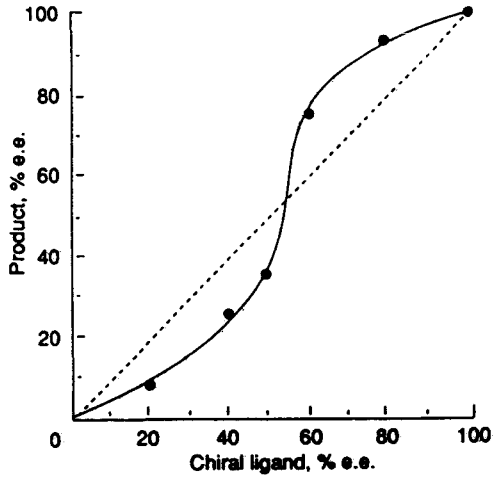


(10)

The chiral catalyst was prepared from amino alcohol ligand, **29**, by sequential addition of MeLi, CuI and MeLi. The conditions for the catalyst preparation seem critical to reach high enantioselectivities. The use of 1 equivalent of THF, presumably as an external ligand to the chiral cuprate, increases the ee significantly. Under optimized conditions, 33 mol% of chiral ligand **29** provides muscone, virtually enantiomerically pure and in high yield (Eq. 10). A nonlinear correlation between the enantiomeric excess of the ligand **29** and the ee of muscone was observed (Figure 9a).[26] The chiral amplification can be explained by the involvement of homochiral dimeric complexes of ($R^*OCuMe_2Li_2$).[26–29] The structure shown in Figure 9b has been proposed for this C_2-symmetric dimer whereas related heterochiral dimers can also be present in the case of scalemic **29**.

The chiral amplification indicates that the homochiral dimer is more reactive than the heterochiral dimer.[26–29] It should be noted that the amplification effects and enantioselectivities are strongly dependent on catalyst concentration. Despite impressive ee's in this case, further implementation awaits effective catalysis at lower catalyst concentration and high selectivities with other enones.

The enantioselective addition of phenyl- and 1-naphthyllithium to 1- and 2-naphthalenecarboxylic esters of 2,6-di-*t*-butyl-4-methoxyphenol (BHA), catalyzed by the chiral diether, **30**, was reported by Tomioka and co-workers (Eq. 11).[30] This is an interesting case of ligand-accelerated, organometallic carbon–carbon bond formation.[31] The 1,4-addition in the



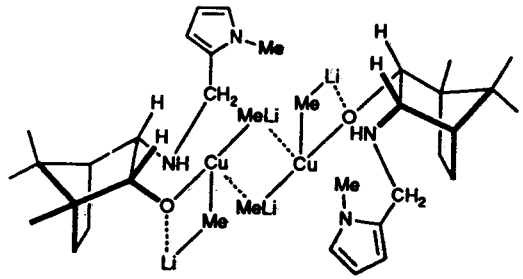
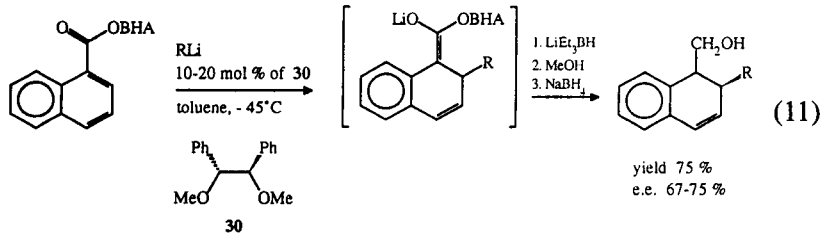


Figure 9. (**a**) Nonlinear correlation between % ee of the chiral ligand, **29**, and % ee of the product in the enantioselective conjugate addition of the chiral alkoxydimethylcuprate. (**b**) The proposed homochiral dimeric structure of the chiral alkoxydimethylcuprate (reprinted from ref. 26; copyright 1993 Royal Chemical Society.).

absence of chiral ligand **30** was sluggish. Both 1- and 2-hydroxymethyl substituted dihydronaphthalene derivatives can be obtained via this catalytic process.



(11)

V. CONJUGATE ADDITION OF DIALKYLZINC REAGENTS CATALYZED BY CHIRAL NICKEL COMPLEXES

In recent years, enantioselective carbon–carbon bond formation by the 1,2-addition of organozinc reagents to aldehydes has become one of the most successful and active areas of asymmetric synthesis.[31] Although dialkylzinc reagents react extremely sluggishly with carbonyl compounds, effective catalysis can be achieved with several ligands and transition-metal complexes. The catalytic effect has been explained by changes in the geometry and bond energy of the zinc reagents.[32] For example, dimethylzinc has a linear structure and is not reactive with aldehydes or ketones (Figure 10). Upon coordination of triazine, a tetrahedral configuration at the zinc atom and an elongated zinc–carbon bond are found, resulting in enhanced reactivity of the dialkylzinc reagent.

Several catalytic 1,4-additions of dialkylzinc reagents to acyclic enones employing chiral nickel complexes have been developed (Eq. 12 and Table 2). The substrates and chiral catalysts are compiled in Figures 4 and 11, respectively. Based on the work of Greene and co-workers,[33]

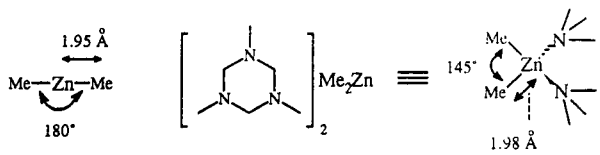
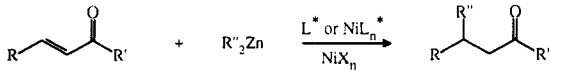


Figure 10. Structures of dimethylzinc and its adduct with 1,3,5-trimethylhexahydro-1,3,5-triazine.

an enantioselective modification of the nickel-catalyzed alkyl transfer from diorganozinc reagents to enones was found by Soai and co-workers.[34] The chiral catalyst, prepared *in situ* from $NiBr_2$ and (1*S*,2*R*)-*N*,*N*-di-*n*-butyl-norephedrine (**31**), produced (*R*)-1,3-diphenylpentan-1-one with 32% yield and 48% enantiomeric excess (Table 2, Entry 1). Higher yields were achieved with $Ni(acac)_2$ instead of $NiBr_2$ (Table 2, Entries 2–4),[35] although large amounts of chiral ligand are required.



(12)

A remarkable achiral ligand effect was observed. Preparation of the chiral catalyst from $Ni(acac)_2$, chiral ligands **31**, **32**, or **33**, and an achiral ligand in acetonitrile raised the enantioselectivity up to 90% (Table 2, Entries 5–9).[36] Comparable enantioselectivities could be reached with nickel catalysts prepared *in situ* from C_2-symmetric bipyridine, **34**,[37] chiral pyridines **35** and **36**, as reported by Bolm and co-workers[38] (Table 2, Entries 10–19), and amino alcohols **37** and **38** described by Feringa and co-workers[39] (Table 2, Entries 20–32).

Detailed studies with ligands **34–36**, by Bolm's group, and **37** and **38**, in our group, revealed the following about a large number of factors that govern catalyst activity and enantioselectivity:[38,39]

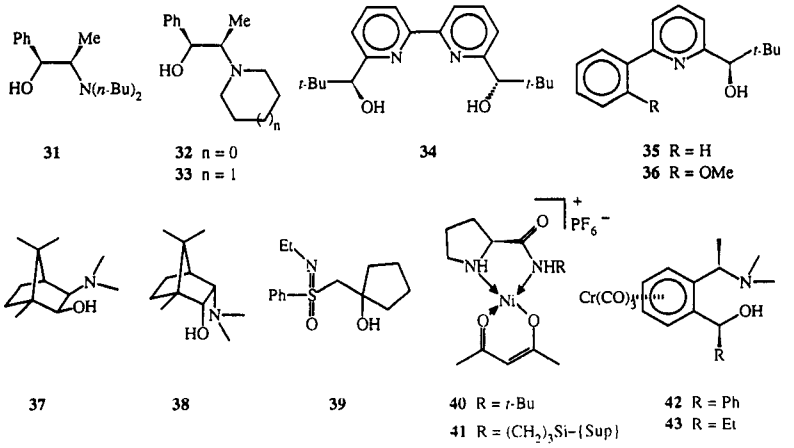
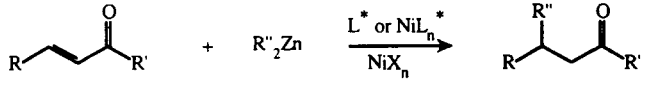


Figure 11. Chiral ligands and complexes used as catalysts in the conjugate addition of dialkylzinc reagents to enones.

Table 2. Catalytic Enantioselective Conjugate Addition of Dialkylzinc Reagents



Entry	Enone	L^* or NiL_n^*	NiX_n	R	Reaction conditions	% Yield	% ee (conf.)	Reference
1	**5**	**31** (0.30)	$NiBr_2$ (0.25)	Et	toluene/hexane, –30 °C	32	48 (*R*)	34
2	**5**	**31** (0.60)	$Ni(acac)_2$ (0.50)	Et	toluene/hexane, –30 °C	75	45 (*R*)	35
3	**6**	**31** (0.60)	$Ni(acac)_2$ (0.50)	Et	toluene/hexane, –30 °C	63	12 (*R*)	35
4	**7**	**31** (0.60)	$Ni(acac)_2$ (0.50)	Et	toluene/hexane, –30 °C	78	44 (*R*)	35
5	**5**	**31** (0.17), 2,2′-bipyridine (0.07)	$Ni(acac)_2$ (0.07)	Et	MeCN/toluene, –30 °C	47	90 (*R*)	36
6	**5**	**32** (0.14), 2,2′-bipyridine (0.06)	$Ni(acac)_2$ (0.06)	Et	MeCN/toluene, –30 °C	63	82 (*R*)	36
7	**5**	**31** (0.14), piperazine (0.06)	$Ni(acac)_2$ (0.06)	Et	MeCN/toluene, –30 °C	44	87 (*R*)	36
8	**5**	**31** (0.14), pyridine (0.12)	$Ni(acac)_2$ (0.06)	Et	MeCN/toluene, –30 °C	84	71 (*R*)	36
9	**10**	**33** (0.17), 2,2′-bipyridine (0.07)	$Ni(acac)_2$ (0.07)	Et	MeCN/toluene, –30 °C	58	80 (*R*)	36
10	**5**	**34** (0.20)	$Ni(acac)_2$ (0.01)	Et	MeCN/hexane, –30 °C	75	72 (*R*)	37
11	**5**	**34** (0.05)	$Ni(acac)_2$ (0.01)	Et	MeCN/hexane, –30 °C	74	20 (*R*)	37
12	**5**	**35** (0.19)	$Ni(acac)_2$ (0.01)	Et	MeCN/hexane, –30 °C	79	82 (*R*)	38
13	**5**	**36** (0.20)	$Ni(acac)_2$ (0.01)	Et	MeCN/hexane, –30 °C	64	82 (*R*)	38
14	**12**	**35** (0.20)	$Ni(acac)_2$ (0.01)	Et	MeCN/hexane, –30 °C	78	90 Nr[a]	38
15	**13**	**35** (0.20)	$Ni(acac)_2$ (0.01)	Et	MeCN/hexane, –30 °C	71	72 Nr[a]	38
16	**11**	**35** (0.20)	$Ni(acac)_2$ (0.01)	Et	MeCN/hexane, –30 °C	75	80 Nr[a]	38
17	**10**	**35** (0.20)	$Ni(acac)_2$ (0.01)	Et	MeCN/hexane, –30 °C	61	86 Nr[a]	38
18	**6**	**34** (0.10)	$Ni(acac)_2$ (0.02)	Et	MeCN/hexane, –30 °C	76	2 Nr[a]	38
19	**2**	**35** (0.20)	$Ni(acac)_2$ (0.01)	Et	MeCN/hexane, –30 °C	35	0 Nr[a]	38
20	**5**	**37** (0.16)	$Ni(acac)_2$ (0.07)	Et	MeCN/hexane, –30 °C	81	65 (*R*)	39

21	**5**	**37** (0.16)	$Ni(acac)_2$ (0.01)	Et	MeCN/hexane, –30 °C	69	72 (*R*)	39
22	**5**	**37** (0.02)	$Ni(acac)_2$ (0.004)	Et	MeCN/hexane, –30 °C	69	31 (*R*)	39
23	**5**	**37** (0.16)	$NiBr_2$ (0.07)	Et	MeCN/hexane, –30 °C	80	39 (*R*)	39
24	**5**	**38** (0.16)	$Ni(acac)_2$ (0.07)	Et	MeCN/hexane, –30 °C	82	79 (*S*)	39
25	**5**	**38** (0.16)	$Ni(acac)_2$ (0.01)	Et	MeCN/hexane, –30 °C	74	84 (*S*)	39
26	**11**	**37** (0.16)	$Ni(acac)_2$ (0.07)	Et	MeCN/hexane, –30 °C	Nr[a]	57 Nr[a]	39
27	**10**	**37** (0.16)	$Ni(acac)_2$ (0.07)	Et	MeCN/hexane, –30 °C	Nr[a]	51 Nr[a]	39
28	**12**	**37** (0.16)	$Ni(acac)_2$ (0.07)	Et	MeCN/hexane, –30 °C	Nr[a]	61 Nr[a]	39
29	**13**	**37** (0.16)	$Ni(acac)_2$ (0.07)	Et	MeCN/hexane, –30 °C	Nr[a]	59 Nr[a]	39
30	**5**	**37** (0.16)	$Ni(acac)_2$ (0.07)	Et	*n*-PrCN/hexane, –50 °C	84	81 (*R*)	39
31	**5**	**38** (0.16)	$Ni(acac)_2$ (0.07)	Et	*n*-PrCN/hexane, –50 °C	82	84 (*S*)	39
32	**5**	**37** (0.16)	$Ni(acac)_2$ (0.07)	Me	MeCN/hexane, –30 °C	Nr[a]	59 (*R*)	39
33	**8**	**33** (0.25)		Et	hexane, rt	81	80 Nr[a]	41
34	**9**	**33** (0.25)		Et	hexane, rt	82	72 (*R*)	41
35	**5**	**37** (0.20)		Et	hexane, rt	Nr[a]	15 (*S*)	39
36	**5**	**39** (0.20)	$Ni(acac)_2$ (0.01)	Et	EtCN/hexane, –30 °C	71	70 (*R*)	42
37	**5**	**40** (0.05)		Et	hexane/THF, –10 °C	75	77 Nr[a]	43
38	**6**	**40** (0.05)		Et	hexane/THF, –10 °C	85	75 Nr[a]	43
39	**5**	**41**[b] (0.05)		Et	hexane/THF, –10 °C	80	91 Nr[a]	43
40	**6**	**41**[b] (0.05)		Et	hexane/THF, –10 °C	74	95 Nr[a]	43
41	**5**	**42** (0.50)	$Ni(acac)_2$ (0.05)	Et	MeCN/hexane, –30 °C	90	62 (*R*)	44
42	**5**	**42** (0.10)	$Ni(acac)_2$ (0.01)	Et	MeCN/hexane, –30 °C	66	36 (*R*)	44
43	**5**	**43** (0.50)	$Ni(acac)_2$ (0.05)	Et	MeCN/hexane, –30 °C	91	43 (*R*)	44

Notes: [a]Nr, not reported.
[b]Chiral nickel complex supported on USY zeolite.

1. The presence of acetonitrile (or another nitrile) as solvent, and presumably as a stabilizing ligand to nickel, appears essential in all cases.
2. Improvement of the enantioselectivity by using additional achiral ligands was not observed.
3. The enantioselectivity strongly depends on the ligand-to-nickel ratio and the concentration of the *in situ* prepared chiral catalyst. For **34–36**, the ligand-to-nickel ratio should be 20, whereas for **37** and **38**, a ligand-to-nickel ratio >2.2 is essential. The ee drops drastically with less than 1 mol% catalyst.[39] These effects point to an equilibrium between various catalytically active (chiral) nickel complexes (Eq. 13).

$$Ni(acac)_2 + 2\,L^* \quad Ni(acac)L^* + L^* \quad NiL_2^* \qquad (13)$$

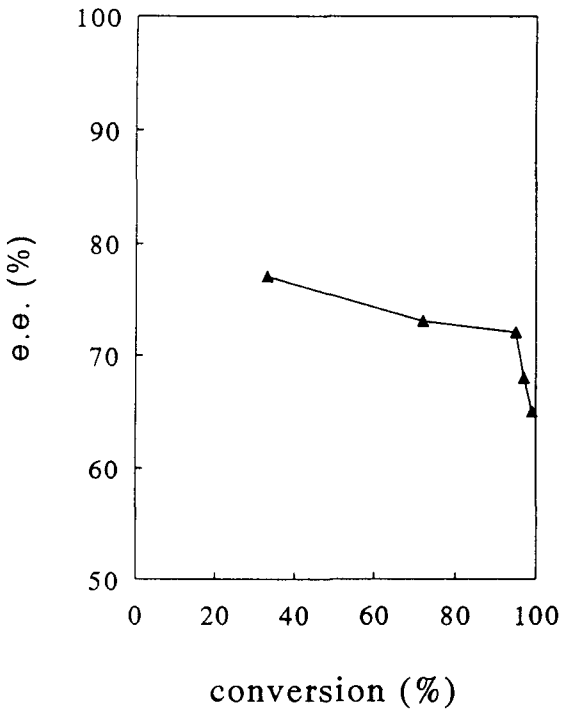


Figure 12. Effect of reaction time on enantiomeric excess of product.

4. The enantiomeric excess decreases significantly with reaction time and the conversion of chalcone (Figure 12). A mechanism proposed by Bolm might explain the time dependency.[38] The organozinc reagent is capable of reducing nickel(II) to nickel(I) and nickel(0) to generate a number of reactive nickel catalysts. Nickel(I) is most likely responsible for efficient catalysis by electron transfer and, in combination with chiral amino alcohol ligands, appears highly enantioselective. After a certain time, the selective catalyst is transformed into species which are still active, but produce racemic material. As a result, the overall ee of the product decreases as the reaction progresses.
5. Asymmetric amplification was observed (Figure 13). The use of 1 mol% $Ni(acac)_2$ with scalemic DAIB, **37**, (ee 25%) gave the 1,4-adduct with an ee of 34%.[39] With ligand **35**, Bolm and

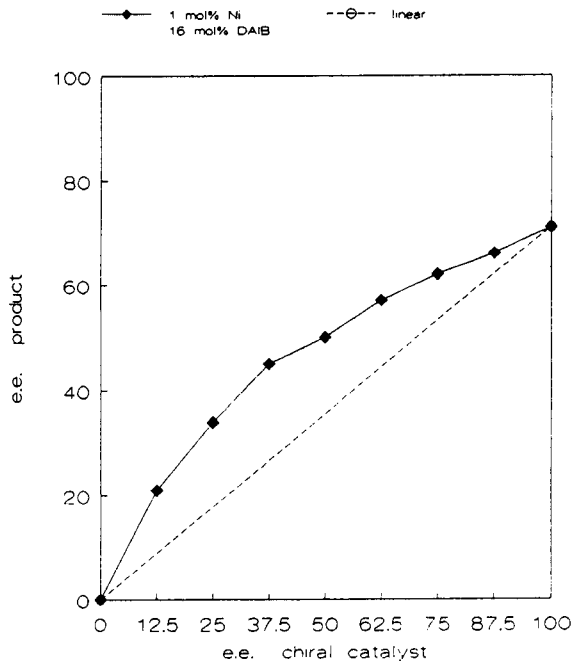
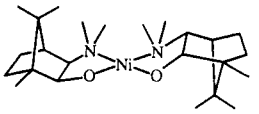
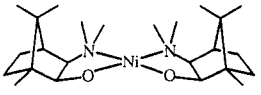


Figure 13. Nonlinear correlation between % ee of the chiral ligand, **37**, and % ee of the product in the enantioselective conjugate addition of Et_2Zn to chalcone (**5**) (1 mol% of $Ni(acac)_2$ and 16 mol% of **37**).



homochiral



meso

Figure 14. Possible diastereomeric nickel complexes (only *cis*-complexes are shown).

co-workers observed an even stronger amplification factor (up to 4.4).[40]

In asymmetric catalysis, nonlinear relationships between ee's of ligands and products have been interpreted in terms of differences in the chemical behavior of diastereomeric complexes.[27–29] These can be diastereomeric dinuclear complexes, i.e., dinuclear zinc-[31a] or dinuclear nickel-zinc-complexes of the chiral ligands. More appropriate in the case discussed here is the formation of diastereomeric mononuclear nickel complexes from scalemic ligands (Figure 14, ligand **37**).[38,39] Predominant reaction of dialkylzinc with the less stable, optically active complex would lead to the formation of a homochiral, catalytically active species. The minor enantiomer of the chiral ligand will be trapped in the more stable *meso* complex.

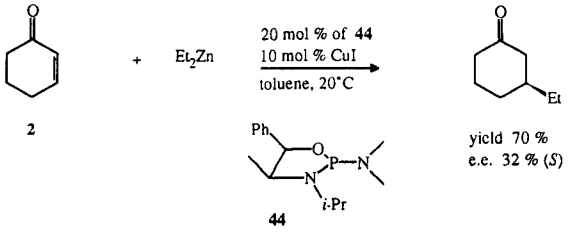
Soai and co-workers reported that enantioselective conjugate addition to enones also proceeds with chiral amino alcohol as a catalyst without the use of transition metals although at much lower rates.[41] After 4 days of reaction time, 1,4-adducts with ee's of 70–80% were obtained using 25 mol% of **33**. We found that with 20 mol% of **37**, and without a metal salt, the reaction proceeds in 4 days.[39] The (*S*)-enantiomer is formed in a slight excess (Table 2, Entry 35), whereas with $Ni(acac)_2$ and **37**, the *R* enantiomer is found in excess.

Variation of the ligand structure in the three classes of chiral ligands revealed that only limited modification in each class is allowed. For ephedrine-based ligands, **31–33**, *N,N*-di-*n*-butyl, piperidinyl and pyrrolidinyl groups are allowed. The steric bulk of the *t*-butyl group is essential in the pyridine-based ligands, **34–36**. We found that both *cis-exo-* and *cis-endo-N,N*-dimethylamino(iso-)borneols (**37** and **38**) are excellent ligands. The *N,N*-dimethyl group is crucial to reach high enantioselectivity.

The nickel-catalyzed enantioselective conjugate addition of diethylzinc to chalcone was also performed using optically active β-hydroxy sulfoximines as chiral ligands.[42] The ligand structure was optimized and an ee up to 70% was reached with ligand **39** (Table 2, Entry 36). Sánchez and co-workers reported the conjugate addition of diethylzinc to enones by homogeneous and supported, cationic chiral nickel complexes, **40** and **41**, based on proline amide ligands.[43] Under homogeneous conditions, ee's of 75–77% were reached using 5 mol% of catalyst **40** at –10 °C (Table 2, Entries 37 and 38). Though the addition reactions were slower with the supported chiral complexes, **41**, the enantioselectivities were raised to 95% (Table 2, Entries 39 and 40). The relatively high enantioselectivities observed with a chiral ligand-to-nickel ratio of 1, compared to ratios of more than 2 in other studies,[36–42,44] are explained by the fact that a single chiral complex is used. Competing catalysis by achiral $Ni(acac)_2$ (or other complexes; see Eq. 13) presumably cannot take place as happens in other catalytic reactions (vide supra). An attractive feature of this system is also the easy removal and recovery of the chiral catalyst.

1,2-Disubstituted arene-chromium complexes, **42** and **43**, were also employed as chiral ligands in the nickel-catalyzed 1,4-addition.[44] Modest ee's were strongly dependent on the amount of catalyst and the structure of the chromium complex (Table 2, Entries 41–43).

A very limited number of alkylzinc reagents and substrates has been successfully used so far in the 1,4-addition reactions described here. Various chalcones (**5–13**, Figure 4) give high ee's but 2-cyclohexenone and α,β-unsaturated esters gave racemic products and low yields. Very recently, Alexakis and co-workers reported the first example of copper-catalyzed enantioselective conjugate addition of diethylzinc to 2-cyclohexenone (Eq. 14).[45] The use of 10 mol% of CuI and 20 mol% of trivalent phosphorous ligand, **44**, resulted in an enantioselectivity of 32%. Chalcone gave racemic material under the same conditions.



2

44

yield 70 %
e.e. 32 % (*S*)

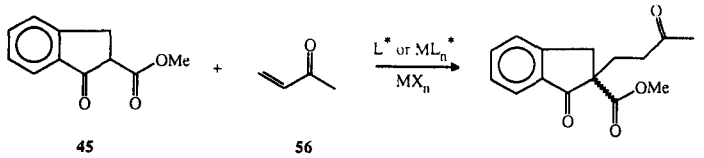
(14)

VI. MICHAEL ADDITIONS

A. Chiral Metal Complexes as Catalysts

Carbon–carbon bond formation via Michael additions are most frequently performed under conditions of base catalysis. The conjugate addition of 1,3-dicarbonyl compounds to enones can also be efficiently catalyzed by metal complexes. Among the advantages of transition-metal-catalyzed Michael additions are the high yields often found under mild reaction conditions, whereas side reactions, frequently encountered in base-catalyzed Michael additions, are avoided. Several catalytic Michael additions employing chiral metal complexes have been developed (Eq. 15 and Table 3). The Michael donors and acceptors and chiral catalysts are compiled in Figures 16 and 17, respectively. Brunner and Hammer were the first to report significant enantioselectivity in a transition-metal-catalyzed Michael addition.[46]

The addition of methyl-1-oxo-2-indanecarboxylate (**45**) to methyl vinyl ketone (MVK, **56**) in the presence of 3 mol% of a chiral cobalt(II) complex, derived *in situ* from $Co(acac)_2$ and (-)-1,2-diphenyl-1,2-ethanediamine (**62**), provided the 1,4-adduct with an enantioselectivity of 66% (see Eq. 15 and Table 3, Entries 1–3).



45 56 (15)

An octahedral cobalt complex was proposed, coordinating two Michael donors and chiral diamine as the ligand (Figure 15). It was proposed that the (*R*) adduct is formed from the $\Delta(\lambda)$ form of the octahedral cobalt complex if the ester carbonyl occupies an equatorial position and MVK adds from the si side of the bound substrate. This model also accounts for the low enantioselectivity with acyclic Michael donors.

In further investigations, the $Co(acac)_2$-(+)- or (-)-1,2-diphenylethylenediamine catalysts were examined in the Michael addition of unsymmetrical 1,3-dicarbonyl donors under various conditions.[47] Using MVK, di-*t*-butyl methylenemalonate (**60**) and acrolein (**57**) as Michael acceptors, and Michael donors, **46–48**, enantioselectivities up to 37% were reached (Table 3, Entries 4–7). Under the reaction conditions, the enan-

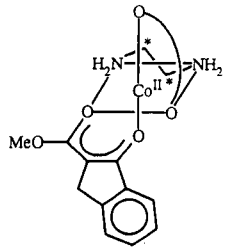


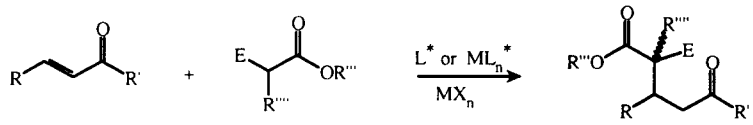
Figure 15.

tioselectivity was almost temperature independent, no racemization took place, and the conjugate addition was irreversible.

Nickel(II) Schiff base complexes also showed catalytic activity in the Michael addition of β-ketoesters to MVK.[48] Yields and reaction rates strongly depend on the geometry of the nickel complex and the structure of the Michael donor. With 1 mol% of chiral nickel(II) complex, **63**, the addition of 2-methylethyl acetoacetate (**47**) to MVK proceeds with 71% yield and 6% ee at room temperature without solvent (Table 3, Entry 8). Although enantioselectivity is very low, the observation that the square, planar nickel complex, **63**, has considerably higher activity in the conjugate addition than tetrahedral nickel analogues is valuable for further development of an efficient chiral nickel catalyst.

Desimoni and co-workers also investigated the model reaction given in Eq. 15, employing chiral copper(II) complexes **64–67**.[49] All copper complexes are based on Schiff base ligands derived from salicylaldehyde and chiral amino alcohols and are presumably dimeric structures. Furthermore, there is evidence that H_2O is bound to the copper atom in these complexes, resulting in six coordination bonds around each copper atom. Typical results of copper(II)-catalyzed addition reactions are summarized in Table 3. The enantioselectivity strongly depends on the solvent (Table 3, Entries 9–11). A negative factor seems to be the ability of the solvent to compete with the chiral ligand for metal complexation. With catalyst **64** enantioselectivities up to 54% were reached, but introduction of a phenyl substituent drastically reduces the ee (Table 3, Entry 12). Increasing the rigidity of the catalyst by incorporating an additional hydroxyl group, that can act as an axial ligand in **66** and **67**, raised the ee to 70% (Table 3, Entries 13–17).[49] Nearly quantitative yields are observed with 1–10 mol% of copper(II) catalyst at –20 °C in CCl_4. A

Table 3. Catalytic Enantioselective Michael Additions

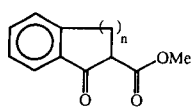


Entry	*Michael donor*	*Michael acceptor*	*L* or ML$_n$**	*MX$_n$*	*Reaction conditions*	*% Yield*	*% ee (conf.)*	*Reference*
1	**45**	**56**	**61** (0.05)		toluene, 20 °C	18	6 (*R*)	46
2	**45**	**56**	**62** (0.03)	Co(acac)$_2$ (0.03)	toluene, 20 °C	72	21 (*R*)	46
3	**45**	**56**	**62** (0.05)	Co(acac)$_2$ (0.05)	toluene, –50 °C	50	66 (*R*)	46
4	**47**	**56**	**62** (0.005)	Co(acac)$_2$ (0.005)	toluene, 20 °C	62	5 (*S*)	47
5	**46**	**56**	**61** (0.03)	Co(acac)$_2$ (0.03)	toluene, –50 °C	36	20 Nr	47
6	**46**	**60**	**61** (0.03)	Co(acac)$_2$ (0.03)	toluene, –50 °C	83	25 Nr	47
7	**48**	**57**	**61** (0.03)	Co(acac)$_2$ (0.03)	toluene, 20 °C	38	37 Nr	47
8	**47**	**56**	**63** (0.01)		, 20 °C	71	6 (*S*)	48
9	**45**	**56**	**64** (0.10)		dioxane, 20 °C	Nr[a]	13 (*R*)	49
10	**45**	**56**	**64** (0.10)		toluene, –70 °C	Nr[a]	19 (*R*)	49
11	**45**	**56**	**64** (0.10)		CCl_4, 20 °C	Nr[a]	54 (*R*)	49
12	**45**	**56**	**65** (0.10)		CCl_4, 20 °C	Nr[a]	7 (*S*)	49
13	**45**	**56**	**66** (0.10)		CCl_4, 20 °C	Nr[a]	60 (*S*)	49
14	**45**	**56**	**66** (0.10)		CCl_4, –20 °C	Nr[a]	69 (*S*)	49
15	**45**	**56**	**66** (0.01)		CCl_4, –20 °C	Nr[a]	70 (*S*)	49
16	**45**	**56**	**67**[b] (0.10)		CCl_4, –20 °C	Nr[a]	68 (*S*)	49

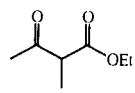
17	**45**	**56**	**67**[b] (0.01)		CCl_4, –20 °C	Nr[a]	70 (*S*)	49
18	**45**	**56**	**68** (0.04)	$Co(acac)_2$ (0.04)	toluene, 25 °C	81	4 (*R*)	50
19	**45**	**56**	**68** (0.14)		toluene, 0 °C	75	3 (*S*)	50
20	**45**	**56**	**68** (0.07)	$Co(acac)_2$ (0.07)	toluene, –80–50 °C	46	38 (*R*)	50
21	**45**	**56**	**68** (0.07)	$Ni(acac)_2$ (0.07)	benzene, –50 °C	44	14 (*R*)	50
22	**49**	**56**	**69** (0.01)	$RhH(CO)(PPh_3)_3$ (0.011)	benzene, 5 °C	99	72 (*R*)	51
23	**50**	**56**	**69** (0.01)	$RhH(CO)(PPh_3)_3$ (0.011)	benzene, 5 °C	95	81 (*R*)	51
24	**51**	**56**	**69** (0.01)	$RhH(CO)(PPh_3)_3$ (0.011)	benzene, 5 °C	99	84 (*R*)	51
25	**52**	**56**	**69** (0.01)	$RhH(CO)(PPh_3)_3$ (0.011)	benzene, 5 °C	95	81 (*R*)	51
26	**51**	**57**	**69** (0.01)	$RhH(CO)(PPh_3)_3$ (0.011)	benzene, 3 °C	88	87 (*R*)	51
27	**51**	**57**	**69** (0.001)	$RhH(CO)(PPh_3)_3$ (0.0011)	benzene, 3 °C	89	84 (*R*)	51
28	**53**	**59**	**70** (0.10)		chloroform, 25 °C	88	40 (*R*)	53
29	**54**	**59**	**70** (0.05)		chloroform, 25 °C	71	76 (*S*)	53
30	**55**	**59**	**70** (0.10)		chloroform, 25 °C	39	65 (*R*)	53
31	**54**	**6**	**70** (0.20)		chloroform, 25 °C	79	53 (*S*)	53
32	**54**	**3**	**70** (0.05)		chloroform, 25 °C	91	59 (*R*)	53
33	**54**	**2**	**70** (0.05)		chloroform, 25 °C	87	49 (*R*)	53
34	**54**	**58**	**70** (0.05)		chloroform, 25 °C	63	35 (*S*)	53

Notes: [a]Nr, not reported.
[b]Hydrated complex.

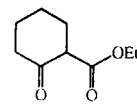
Michael donors :



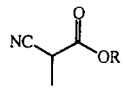
45 n = 1
46 n = 2



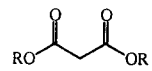
47



48

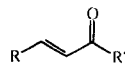


49 R = Me
50 R = Et
51 R = *i*-Pr
52 R = *t*-Bu

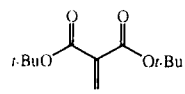


53 R = Me
54 R = *i*-Pr
55 R = *t*-Bu

Michael acceptors :

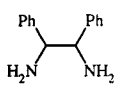


56 R = H ; R' = Me
57 R = H ; R' = H
58 R = Me ; R' = H
59 R = Me ; R' = Me

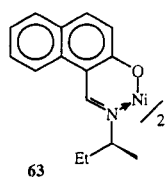


60

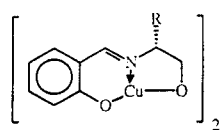
Figure 16. Michael donors and acceptors used in enantioselective Michael additions.



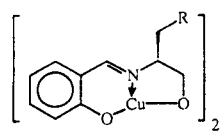
61 (-)-(*RR*)
62 (+)-(*SS*)



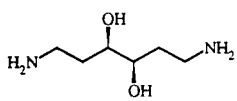
63



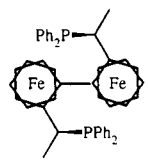
64 R = Et
65 R = Ph



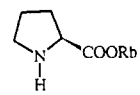
66 R = $(CH_2)_2OH$
67 R = OH



68



69 TRAP



70

Figure 17. Chiral ligands and complexes used as catalysts in enantioselective Michael additions.

model, comparable to that described by Brunner and Hammer,[46] was proposed to account for the observed enantioselectivity.

An *in situ* prepared chiral cobalt(II) catalyst, derived from $Co(acac)_2$ and diaminodiol ligand, **68**, was also tested in the addition of methyl-1-oxo-2-indanecarboxylate (**45**) to MVK (Eq. 15).[50] With 4–14 mol% of **68**, acceptable yields (46–81%) but modest ee's (3–38%) were found (Entries 18–20). This asymmetric catalysis is a property of the metal-ligand complex and not of the ligand itself. This is proven by the results in Table 3, Entries 18 and 19, in which the free ligand, **68**, appears to favor the opposite absolute stereochemistry. Remarkably, the dianilino derivative of **68** results in an inefficient catalyst. With $Ni(acac)_2$, instead of $Co(acac)_2$, a lower enantioselectivity was found (Table 3, Entry 21).[50]

Recently Ito and co-workers reported a rhodium-catalyzed enantioselective Michael addition of α-cyanocarboxylates to vinyl ketones.[51] The chiral catalyst was prepared *in situ* from $RhH(CO)(Pph_3)_3$ and the *trans* chelating chiral diphosphine ligand 2,2″-bis[1-(diphenylphosphino)ethyl]-1,1″-biferrocene (TRAP, **69**). The use of *i*-propyl-α-cyanocarboxylate, as Michael donor, gave the highest enantioselectivity in the addition to MVK (see Table 3, Entries 22–25). The reactions of **51** with a large variety of vinyl ketones or acrolein (**57**) proceeds with enantioselectivities ranging from 83–89% (see, for example, Entry 26). High catalyst efficiency was observed even with 0.1 mol% of **69** (Table 3, Entry 27), and high yields are generally found. *Trans* chelation of the chiral ligand to rhodium appears essential for high ee's since common *cis* chelating diphosphines, such as BINAP, DIOP or Chiraphos, resulted in low enantioselectivities. It is proposed that the activated cyanoacetic ester is bound to rhodium through the cyano nitrogen and that, in the enolate intermediate (Figure 18a), the enantioselective carbon–carbon bond formation occurs at the carbon atom rather distant from the metal center. Only a concave chiral ligand, such as TRAP, would effect the remote enantiofacial differentiation. The X-ray crystal structure of *trans*-{RhCl(CO)[(*R*,*R*)-(*S*,*S*)-*n*-BuTRAP]}, which bears a *n*-Bu group instead of a Ph group as in **69**, reveals that rhodium has a nearly planar coordination geometry (Figure 18b).[52]

The conformation of the ligand is essentially C_2-symmetric, and the chloro and carbonyl groups on rhodium, which may be replaced by a prochiral substrate in a catalytic asymmetric reaction, are completely buried in the chiral cavity created by the ferrocenyl backbone and the *n*-Bu groups.

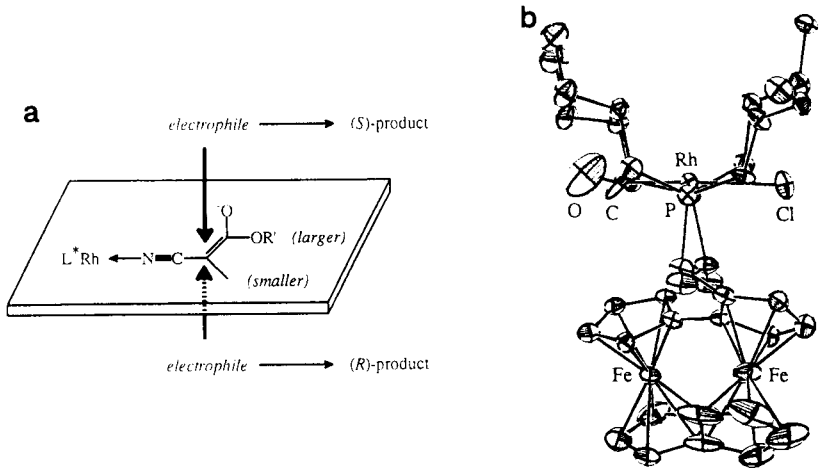


Figure 18. (**a**) Proposed mechanism in the rhodium-catalyzed Michael addition. (**b**) ORTEP plot of *trans*-{RhCl(CO)[(*R,R*)-(*S,S*)-*n*-BuTRAP]} (reprinted from ref. 52; copyright 1994 Verlag Chemie.).

Yamaquchi and co-workers reported the first catalytic asymmetric Michael addition of simple malonate ions to prochiral enones and enals.[53] Asymmetric induction was observed when the Michael addition of dimethyl malonate (**53**) to prochiral acceptors, catalyzed by the lithium salt of L-proline, was carried out in chloroform. Higher catalytic activity and enantioselectivity were attained with the rubidium salt, **70** (Table 3, Entry 28). Enantioselectivities up to 76% were achieved with 5 mol% of **70** (10–20 mol% with the less reactive substrates), di-*i*-propyl malonate (**54**) and various Michael acceptors, such as aliphatic and aromatic enones, cyclic enones and enals (Table 3, Entries 29 and 31–34). A small amount of water promotes the reaction. Yields of adducts were very low

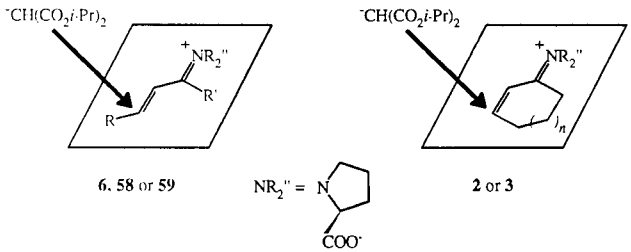


Figure 19. Proposed mechanism in the rubidium-catalyzed Michael addition.

with catalytic amounts of the rubidium salt of *N*-methyl-L-proline or free L-proline. Thus, both the secondary amine moiety and the metal carboxylate moiety of **70** are essential for high catalytic activities. Reversible iminium salt formation to provide chiral Michael acceptors could account for the above asymmetric inductions (see Figure 19). Independent experiments demonstrated a high reactivity of an unsaturated iminium salt, derived of **6** and pyrrolidine, toward malonate addition.[53]

B. Chiral Amines and Crown Ethers as Catalysts

The use of chiral amines as catalysts in the Michael addition reaction was first reported by Långström and Bergson in 1973.[54] The addition of methyl-1-oxo-2-indanecarboxylate (**45**) to acrolein (**57**) using optically active 2-(hydroxymethyl)-quinuclidine (**71**) provided the optically active 1,4-adduct (see Eq. 15).

Wynberg and co-workers studied the model reaction of the same Michael donor with MVK, as Michael acceptor, and quinine (**72**), as chiral base (1 mol%).[55] The 1,4-adduct is produced in almost quantitative yield with ee's up to 76% depending on solvent and temperature (see Eq. 15). Several variations of chiral base, Michael donor and acceptor, and reaction conditions were examined, but enantioselectivities exceeding 76% were not reached in these studies.[56,57]

Several attempts were reported to facilitate removal of the chiral catalyst from the reaction mixture by attaching it to a polymer. With alkaloids **72**, **74**, and **75** anchored to cross-linked polystyrene[58] or copolymerized with acrylonitrile,[59] the 1,4-additions, given in Eq. 15, proceed with low and moderate ee's, respectively. Insertion of spacer groups between the alkaloid and the polymer backbone improves the enantioselectivity to 65%.[60] This is almost the same value found in the reaction with nonpolymer-bound alkaloid. When the model reaction (Eq. 15) was performed under high pressure, lower ee's were found.[61]

The model reaction was also performed under phase transfer conditions. With quaternary ammonium halides, derived from methionine, the reaction is sluggish and hardly enantioselective.[62] Substantial improvements were achieved with [p-(trifluoromethyl)benzyl]-chinchoninium-bromide (**75**), as phase transfer catalyst, and 2-propylindanone as Michael donor (Eq. 16),[63] under solid–liquid phase transfer conditions in the presence of quaternary ammonium salts, **78–80**, derived from *N*-methylephedrine. A typical example is given in Eq. 17.[64]

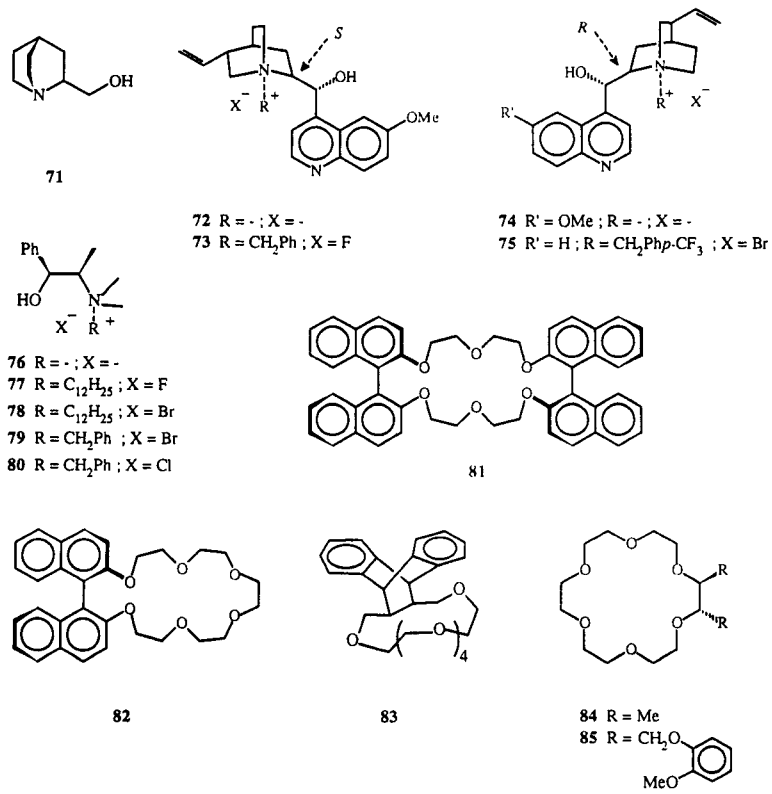
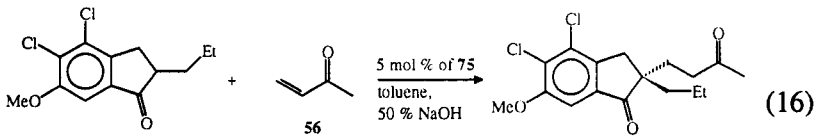
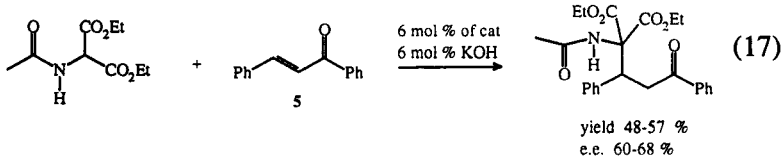


Figure 20. Chiral amines and crown ethers used in Michael additions.

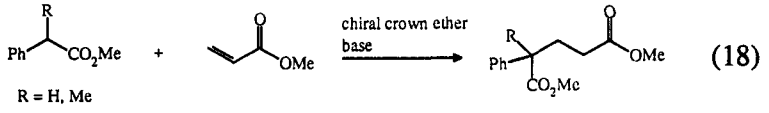


(16)



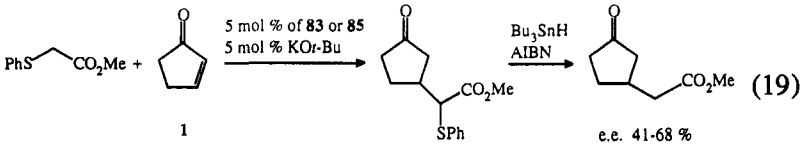
(17)

Higher enantioselectivities have been reached using chiral catalysts prepared by complexation of a base to a chiral crown ether. Cram and Sogah found that, with 4 mol% of a bis-β-naphthol-derived, optically active crown ether **81** and potassium *t*-butoxide as the base, the 1,4-adduct (Eq. 15) could be isolated with 48% yield and an ee of 99%.[65] Crown ether **82** was used similarly in the reaction of methyl acrylate and methyl 2-phenylpropionate or methyl phenylacetate (Eq. 18).[65] The highest ee's in these last reactions were achieved with potassium amide as base (83% and 65%, respectively). In both cases the *R* crown ether gave the *S* adduct. In the presence of KO*t*-Bu, crown ethers, **81 and 82**, were also used as chiral catalysts in the anionic (Michael type) polymerization of methacrylate esters to give highly isotactic helical polymers.[66]



(18)

Following these fascinating reports, several groups have investigated other chiral crown ethers as catalysts in the reaction given in Eq. 18.[67] Enantioselectivities did not increase above 81%. A remarkably high enantioselectivity of 79% was achieved with simple C_2-symmetric chiral crown ether **84** derived from (2*S*,3*S*)-butanediol.[67d] Using chiral crown ether **83**, Yamamoto and co-workers investigated the Michael addition of methyl phenylthioacetate to cyclopentenone to give the 1,4-adduct with 60% yield and an ee of 41% (Eq. 19).[67c] Using crown ether **85**, Koga and co-workers were able to raise the enantioselectivity to 68% in this reaction.[68]



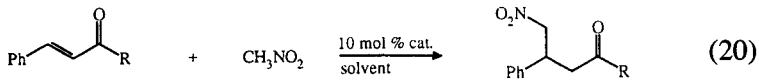
(19)

VII. NITROALKANE ADDITIONS

In recent years, Michael addition reactions of nitroalkanes to activated olefins have attracted considerable attention in part due to the availability of various synthetic methods for the conversion of the nitro group to other functional groups.[69]

Only a few enantioselective nitromethane additions to enones, catalyzed by alkaloids and derivatives, have been reported. Using quaternary

salts derived from quinine or *N*-methylephedrine (**73**, **77–79**, Figure 20), as chiral phase transfer catalysts, and an excess of inorganic salts (KF, NaOH or KO*t*-Bu), enantiomeric excesses up to 26% were reached in the addition of nitromethane to chalcone (Eq. 20).[70] No reaction takes place in aprotic solvents with the free alkaloids as chiral bases. Addition takes place in methanol although without enantioselectivity.



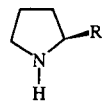
R = Ph, Me

(20)

Under high pressure (900 MPa), both quinine (**72**) and quinidine (**74**) (10 mol%) catalyze the nitromethane addition in aprotic solvents, such as toluene, with high conversion and ee's up to 60%.[61,71] These results shows that high pressure is actually advantageous in performing sluggish asymmetric reactions composed of rather inert reactants and/or a catalyst.

Botteghi and co-workers reported the first example of a transition-metal-catalyzed enantioselective nitroalkane addition to enones.[72] The catalyst was prepared *in situ* from $Ni(acac)_2$ and proline-derived ligands **86–88** (Figure 21). Using a large excess of nitromethane, enantioselectivities up to 17% were reached, although long reaction times are required. Slightly higher ee's (24%), but low yields, were found with benzalacetone.

A decrease of the Michael donor-to-acceptor ratio appears to increase asymmetric induction. With equimolar amounts of donor and acceptor, the chemical yield of the 1,4-adduct is rather low but an enantioselectivity of 61% is found (ligand **87**).[50] The observed increase in ee may well be a solvent effect. An increase in solvent polarity (nitromethane vs. benzene) produces a decrease in stereoselectivity in the same reaction



86 R = CH_2NHPh
87 R = $CONH_2$
88 R = CH_2OH

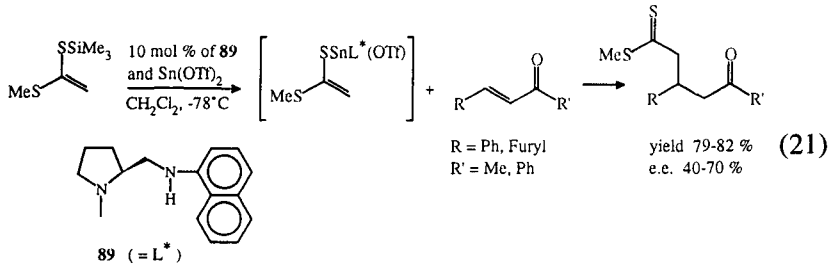
Figure 21.

catalyzed by alkaloid bases under phase transfer conditions.[56b] In this case, asymmetric catalysis is confirmed as a property of metal complexes since the ligands alone do not catalyze the reactions.

Yamaguchi and co-workers noted a reaction of 2-nitropropane and 2-cyclohexenone (**2**) or (*E*)-3-penten-2-one (**59**) in the presence of 5 mol% of rubidium salt, **70**.[53] The adducts were obtained with yields of 61 and 48% and ee's of 58 and 69%, respectively.

VIII. MISCELLANEOUS

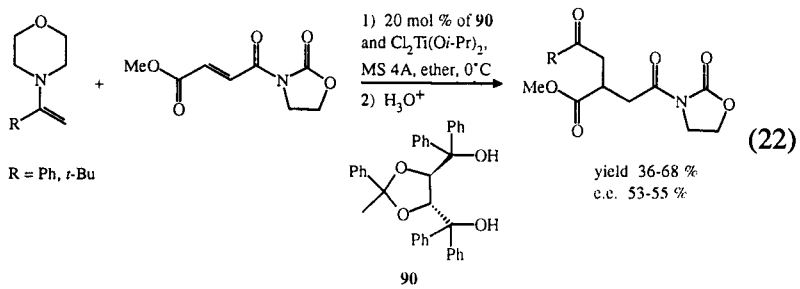
Two additional successful approaches to catalytic asymmetric Michael addition need to be mentioned, using chiral Lewis acids as catalysts. Mukaiyama and co-workers used a chiral tin complex, derived *in situ* from tin(II) triflate and chiral diamine, **89**, in the Michael addition of trimethylsilyl ene thiolate to enones (Eq. 21).[73] When the trimethylsilyl ene thiolate was added slowly to the reaction mixture, in order to suppress the competing uncatalyzed addition, enantioselectivities up to 70% were reached.



(21)

It is proposed that the metal exchange of tin and silicon takes place initially to generate a chiral tin(II) enethiolate and Me_3SiOTf. Activation of the enone by Me_3SiOTf induces the Michael addition of the chiral tin(II) ene thiolate along with regeneration of the tin(II) triflate-diamine complex.

Catalytic asymmetric Michael additions of morpholine-derived enamines to methyl-(*E*)-4-oxo-4-(2-oxo-1,3-oxazolidin-3-yl)-2-butenoate, with modest yields but promising ee's, were found by Narasaka and co-workers (Eq. 22).[74] The chiral catalyst is prepared *in situ* from $Cl_2Ti(O\textit{i}\text{-}Pr)_2$ and (2*R*,3*R*)-1,4-diol, **90**, derived from tartaric acid.



(22)

The course of the titanium-catalyzed addition reaction of enamines with unsaturated acid derivatives was strongly dependent on the enamine structure. Contrary to the Michael reaction of the enamines given above, the reactions of 2,2-disubstituted enamines with the same Michael acceptor produced optically active cyclobutanes. The *in situ* prepared chiral catalyst was also used successfully in Diels–Alder and 2+2 cycloadditions, ene reactions, and hydrocyanations.

IX. CONCLUSIONS

The current stage of the enantioselective synthesis of β-substituted carbonyl compounds, using chiral catalysts, has been reviewed in this chapter. Remarkable progress has been made in the last few years on the enantioselective synthesis of β-substituted carbonyl compounds through conjugate addition catalyzed by chiral metal complexes. Except for an early report by Brunner on cobalt-catalyzed Michael additions, the first successful enantioselective conjugate addition reactions catalyzed by metal complexes were reported in 1988. A number of examples are currently known of both Michael type additions and 1,4-additions of organometallic reagents catalyzed by chiral metal complexes with enantioselectivities exceeding 80%. The large variety of chiral metal complexes and ligands, that have shown modest enantioselectivities, are the stepping stones for developing highly selective catalysts in the near future.

A wealth of information has already been gathered about the factors affecting catalytic activity and selectivity. A picture emerges showing that conjugate addition reactions are often extremely delicate and complex processes, in particular due to the appearance of various catalytically active complexes (in equilibrium) during the reaction and sensitivity to the reaction conditions. The scope of organometallic re-

agents, Michael donors and electron-deficient alkenes in these enantioselective processes has been limited so far. With a few exceptions, only model reactions have been studied. It is evident that the development of highly selective catalysts for conjugate addition with a broad scope is a major challenge in current asymmetric synthesis.

REFERENCES

1. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series, No. 9; Pergamon: Oxford, 1992; (b) Winterfeldt, E. *Kontakte* **1987**, 20; **1987**, 37.
2. (a) Schmalz, H.-G. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 1.5; (b) Wynberg, H. In *Topics in Stereochemistry*; Eliel, E. L.; Wilen, S., Eds.; Wiley-Interscience: New York, 1986; Vol. 16, p 87; (c) Tomioka, K.; Koga, K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, p 201.
3. Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
4. House, H. O. *Modern Synthetic Reactions*, 2 ed.; W. A. Benjamin: Menlo Park, California, 1972; Chapter 9.
5. Feringa, B. L.; de Lange, B.; Jansen, J. F. G. A.; de Jong, J. C.; Lubben, M.; Faber, W.; Schudde, E. P. *Pure & Appl. Chem.* **1992**, *64*, 1865.
6. (a) Jansen, J. F. G. A.; Feringa, B. L. In *Houben-Weyl, Stereoselective Synthesis of Organic Compounds*; Hoffmann, R. W., Ed.; Georg Thieme: Stuttgart-New York, Chapter 1.5 (in press); (b) Nogradi, M. *Stereoselective Synthesis*; VCH: Weinheim, Germany, 1987.
7. See for instance: (a) Davies, S. G.; Walker, J. C. *J. Chem. Soc., Chem. Commun.* **1985**, 209; (b) Liebeskind, L. S.; Welker, M. E. *Tetrahedron Lett.* **1985**, *26*, 3079.
8. Corey, E. J.; Naef, R.; Hannon, F. *J. Am. Chem. Soc.* **1986**, *108*, 7114.
9. Aoki, Y.; Kuwajima, I. *Tetrahedron Lett.* **1990**, *31*, 7457 and references cited therein.
10. Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015 and 6019.
11. Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1986**, 1017 and references cited therein.
12. Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797.
13. Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499.
14. (a) Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025; (b) Corey, E. J.; Magriotis, P. A. *J. Am. Chem. Soc.* **1987**, *109*, 287; (c) Yamaguchi, M.; Hasebe, K.; Tanaka, S.; Minami, T. *Tetrahedron Lett.* **1986**, *27*, 959; (d) Enders, D.; Müller, S.; Demir, A. S. *Tetrahedron Lett.* **1988**, *29*, 6437 and references cited therein.
15. Villacorta, G. M.; Rao, C. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175.
16. Ahn, K.-H.; Klassen, R. B.; Lippard, S. J. *Organometallics* **1990**, *9*, 3178.

17. Lambert, F.; Knotter, D. M.; Janssen, M. D.; van Klaveren, M.; Boersma, J.; van Koten, G. *Tetrahedron: Asym.* **1991**, *2*, 1097.
18. Knotter, D. M.; Grove, D. M.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc.* **1992**, *114*, 3400.
19. Zhou, Q.-L.; Pfaltz, A. *Tetrahedron Lett.* **1993**, *34*, 7725.
20. Spescha, M.; Rihs, G. *Helv. Chim. Acta* **1993**, *76*, 1219.
21. Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679.
22. (a) Watson, R. A.; Kjonaas, R. A. *Tetrahedron Lett.* **1986**, *27*, 1437; (b) Kjonaas, R. A.; Hoffer, R. K. *J. Org. Chem.* **1988**, *53*, 4133.
23. Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron Lett.* **1988**, *29*, 3593.
24. Jansen, J. F. G. A.; Feringa, B. L. *J. Chem. Soc., Chem. Commun.* **1989**, 741.
25. Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.* **1990**, *55*, 4168.
26. Tanaka, K.; Matsui, J.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 153.
27. Wynberg, H.; Feringa, B. L. *Tetrahedron* **1976**, *32*, 2831.
28. Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353.
29. For nonlinear effects in stoichiometric conjugate addition reactions of organocuprates to enones, see: ref. 3 and Rossiter, B. E.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernández, A. E.; Vickers, D.; Fluckiger, E.; Patterson, R. G.; Reddy, K. V. *Tetrahedron* **1993**, *49*, 965.
30. Tomioka, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 681.
31. For reviews of ligand accelerated carbon–carbon bond formation, see: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49; (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
32. (a) Carruthers, W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 7, Chapter 49; (b) Hursthouse, M. B.; Motevaili, M.; O'Brien, P.; Walsh, J. R.; Jones, A. C. *J. Mater. Chem.* **1991**, *1*, 139.
33. Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931.
34. Soai, K.; Hayasaka, T.; Ugajin, S.; Yokoyama, S. *Chem. Lett.* **1988**, 1571.
35. Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *J. Org. Chem.* **1988**, *53*, 4148.
36. Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc., Chem. Commun.* **1989**, 516.
37. Bolm, C.; Ewald, M. *Tetrahedron Lett.* **1990**, *31*, 5011.
38. Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205.
39. de Vries, A. H. M.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4479. see also: Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron: Asym.* **1992**, *3*, 581.
40. Bolm, C. *Tetrahedron: Asym.* **1991**, *2*, 701.
41. Soai, K.; Okudo, M.; Okamoto, M. *Tetrahedron Lett.* **1991**, *32*, 95.
42. Bolm, C.; Felder, M.; Müller, J. *Synlett* **1992**, 439.
43. Corma, A.; Iglesias, M.; Martín, V.; Rubio, J.; Sánchez, F. *Tetrahedron: Asym.* **1992**, *3*, 845; for the synthesis of **40** and **41** see: Corma, A.; Iglesias, M.; del Pino, C.; Sánchez, F. *J. Organomet. Chem.* **1992**, *431*, 233.
44. Uemura, M.; Miyake, R.; Nakayama, K.; Hayashi, Y. *Tetrahedron: Asym.* **1992**, *3*, 713.
45. Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asym.* **1993**, *4*, 2427.
46. Brunner, H.; Hammer, B. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 312.
47. Brunner, H.; Kraus, J. *J. Mol. Cat.* **1989**, *49*, 133.

48. Botteghi, C.; Schionata, A.; Rosini, O.; Salvadori, P. *J. Mol. Cat.* **1990**, *63*, 155.
49. Desimoni, G.; Quadrelli, P.; Righetti, P. P. *Tetrahedron* **1990**, *46*, 2927.
50. Botteghi, C.; Paganelli, S.; Schionata, A.; Boga, C.; Fava, A. *J. Mol. Cat.* **1991**, *66*, 7.
51. Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295.
52. Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 111.
53. Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176.
54. Långström, B.; Bergson, G. *Acta Chem. Scand.* **1973**, *27*, 3118.
55. Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238.
56. (a) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057; (b) Wynberg, H.; Greijdanus, B. *J. Chem. Soc., Chem. Commun.* **1978**, 427; (c) Kobayashi, N.; Iwai, K. *J. Polym. Sci., Polym. Lett. Ed.* **1982**, *20*, 85; (d) Heisler, T.; Janowski, K.; Prager, R. H.; Thompson, M. J. *Aust. J. Chem.* **1989**, *42*, 37.
57. For related enantioselective Michael addition of α-*i*-propyl-3,4-dimethoxybenzyl cyanide to several enones with ee <11%, see Brunner, H.; Zintl, H. *Monatsh. Chem.* **1991**, *122*, 841; for conjugate cyanide addition to enones with ee <45%, see: Dehmlow, E. V.; Sauerbier, C. *Liebigs Ann. Chem.* **1989**, 181.
58. (a) Hermann, K.; Wynberg, H. *Helv. Chim. Acta* **1977**, *60*, 2208; (b) Hodge, P.; Khoshdel, E.; Waterhouse, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2205.
59. (a) Kobayashi, N.; Iwai, K. *J. Am. Chem. Soc.* **1978**, *100*, 7071; (b) Kobayashi, N.; Iwai, K. *J. Polym. Sci., Polym. Chem. Ed.* **1980**, *18*, 923.
60. Inagaki, M.; Hiratake, J.; Yamamoto, Y.; Oda, J. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4121.
61. Sera, A.; Takagi, K.; Katayama, H.; Yamada, H.; Matsumoto, K. *J. Org. Chem.* **1988**, *53*, 1157.
62. Banfi, S.; Cinquini, M.; Colonna, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1841.
63. Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710.
64. Loupy, A.; Sansoulet, J.; Zaparucha, A.; Merienne, C. *Tetrahedron Lett.* **1989**, *30*, 333.
65. Cram, D. J.; Sogah, D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625.
66. Cram, D. J.; Sogah, D. Y. *J. Am. Chem. Soc.* **1985**, *107*, 8301.
67. (a) Alonso-López, M.; Martín-Lomas, M.; Penadés, S. *Tetrahedron Lett.* **1986**, *27*, 3551; (b) Alonso-López, M.; Jiminez-Barbero, J.; Martín-Lomas, M.; Penadés, S. *Tetrahedron* **1988**, *44*, 1535; (c) Takasu, M.; Wakabayashi, H.; Furuta, K.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 6943; (d) Aoki, S.; Sasaki, S.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 7229; (e) Maarschalkerwaart, D. A. H.; Willard, N. P.; Pandit, U. K. *Tetrahedron* **1992**, *48*, 8825; (f) Crosby, J.; Stoddart, J. F.; Sun, X.; Venner, M. R. W. *Synthesis*, **1993**, 141.
68. Aoki, S.; Sasaki, S.; Koga, K. *Heterocycles*, **1992**, *33*, 493.
69. (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1; (b) Ono, N.; Kaji, A. *Synthesis* **1986**, 693; (c) Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625.

70. (a) Colonna, S.; Hiemstra, H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1978**, 238; (b) Annunziata, R.; Cinquini, M.; Colonna, S. *Chem. Ind.* **1980**, 238; (c) Colonna, S.; Re, A.; Wynberg, H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 547.
71. Matsumoto, K.; Uchida, T. *Chem. Lett.* **1981**, 1673.
72. Schionata, A.; Paganelli, S.; Botteghi, C.; Chelucci, G. *J. Mol. Cat.* **1989**, *50*, 11.
73. (a) Yura, T.; Iwasawa, N.; Narasaka, K.; Mukaiyama, T. *Chem. Lett.* **1988**, 1025; (b) Iwasawa, N.; Yura, T.; Mukaiyama, T. *Tetrahedron* **1989**, *45*, 1197.
74. Hayashi, Y.; Otaka, K.; Saito, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2122.