Modern Organocopper Chemistry. Edited by Norbert Krause

ISBNs: 3-527-29773-1 (Hardcover); 3-527-60008-6 (Electronic)

7
Copper-catalyzed Enantioselective Conjugate Addition Reactions of Organozinc Reagents

Ben L. Feringa, Robert Naasz, Rosalinde Imbos, and Leggy A. Arnold

7.1 Introduction

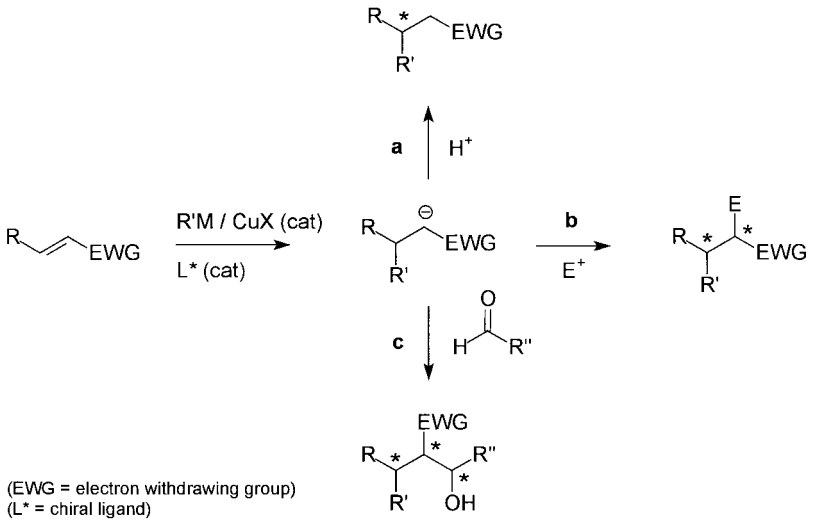
Conjugate addition (1,4-addition) of carbon nucleophiles to α,β-unsaturated compounds is one of the most important carbon–carbon bond-forming strategies in synthetic organic chemistry [1]. The versatility of the conjugate addition is mainly due to the large variety of nucleophiles (organometallic reagents, Michael donors, other carbanions) and acceptors (α,β-unsaturated aldehydes, ketones, nitriles, phosphates, esters, and sulfones, as well as nitroalkenes) that can be used [2]. Recent progress in the development of highly enantioselective Michael additions has been reviewed [3].

The most frequently employed organometallic reagents in conjugate addition reactions are organocuprates derived from organolithium or Grignard reagents [4–12]. A number of other transition metal catalysts (Ni, Co, Pd, Ti) and organometallic reagents (R_2Zn, R_3Al, RBX_2) have been shown to provide valuable alternatives to organocopper chemistry for achieving this transformation [5, 12]. In particular, the exploitation of dialkylzinc reagents has been extremely successful in the development of highly enantioselective catalytic 1,4-additions in recent years [6, 9, 11, 12]. These efforts are summarized in this chapter.

The conjugate addition of organometallic reagents R_nM to an electron-deficient alkene under, for instance, copper catalysis conditions results in a stabilized carbanion that, upon protonation, affords the chiral β-substituted product (Scheme 7.1, path a). Quenching of the anionic intermediate with an electrophile creates a disubstituted product with two new stereocenters (Scheme 1, path b). With a prochiral electrophile, such as an aldehyde, three new stereocenters can be formed in a tandem 1,4-addition-aldol process (Scheme 1, path c).

A number of conjugate additions delivering excellent enantioselectivities through the use of organocuprates in the presence of *stoichiometric* amounts of chiral (nontransferable) ligands are known today [7–9].

A major challenge has been the development of enantioselective 1,4-additions of



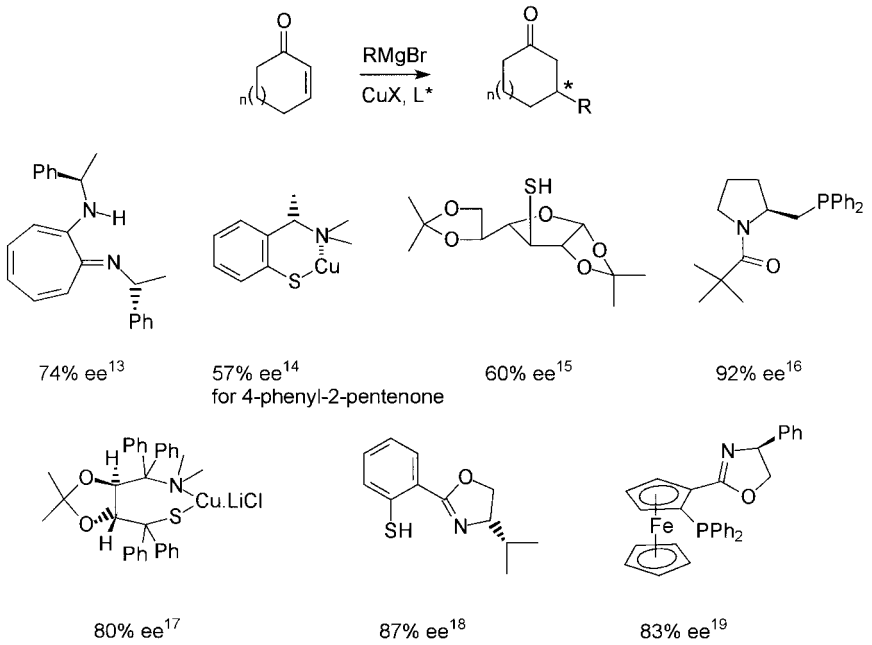
Scheme 7.1. Catalytic conjugate addition and tandem conjugate addition.

organometallic reagents in the presence of only *catalytic* amounts of transition metals and chiral ligands. Only recently have catalytic methods promoting enantioselectivities in 1,4-additions of Grignard, organolithium, and organozinc reagents been found [8–12].

Problems encountered in the rational design of enantioselective catalytic versions of 1,4-additions of organometallic reagents are the frequently observed fast uncatalyzed reaction and the complex nature of the actual catalysts. Factors that can have a strong influence on the 1,4-addition include the nature of the organometallic reagent, the number and nature of the ligands, solvent-dependent aggregation, the presence of salts or halides (distinct differences when using R_2M and RMX, for example), coordinating or noncoordinating solvents and Lewis acid activation of the substrate.

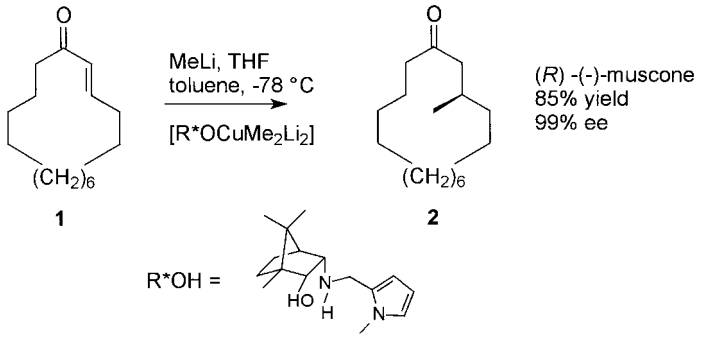
A brief discussion of the most notable achievements obtained with Grignard, organolithium, and organoboron reagents follows. Although Lippard [13] used a chiral *N,N′*-dialkylaminotropone imine copper(I) catalyst in his pioneering work on the asymmetric 1,4-addition of *n*-BuMgBr to 2-cyclohexenone, nearly all subsequent conjugate additions of Grignard reagents with high enantioselectivities have been performed with copper(I) salts in the presence of chiral sulfur or phosphorus ligands. Chiral ligands and catalysts, with the enantioselectivities achieved to date using Grignard reagents, are summarized in Scheme 7.2 [13–19].

A major problem in the development of catalytic asymmetric 1,4-additions of RLi reagents is the high reactivity usually associated with organolithium species. One solution has been found in the stoichiometric formation of the corresponding chiral cuprates; *ee*'s of up to 99% have been reported [20]. An impressive example of the use of a substoichiometric quantity (33 mol%) of chiral ligand is to be found in



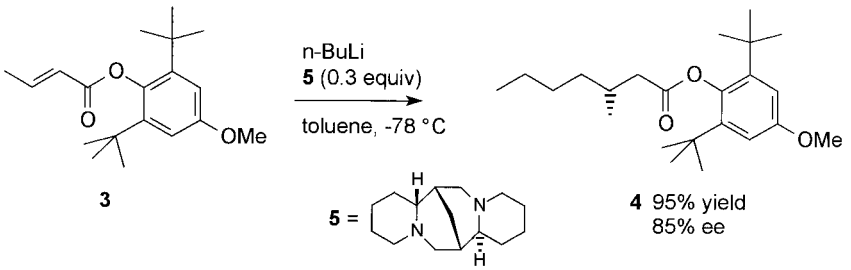
Scheme 7.2. Chiral ligands and catalysts in enantioselective 1,4-additions of Grignard reagents.

the chiral, alkoxycuprate-catalyzed addition of MeLi to (*E*)-2-cyclopentadecenone (**1**) to afford (*R*)-muscone (**2**) with an *ee* of 99% (Scheme 7.3) [21].



Scheme 7.3. Asymmetric synthesis of (*R*)-muscone.

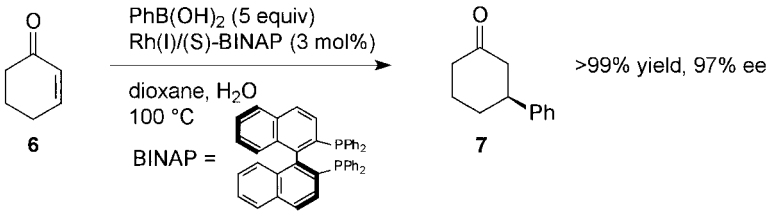
Another successful approach involves the use of chiral donor ligands to affect the aggregation behavior of organolithium species [22]. The oligomeric organolithium reagents are converted by the chiral ligand to more reactive monomeric chiral organolithium species. For instance, the 1,4-addition of *n*-BuLi to **3**, containing a sterically demanding ester moiety, in the presence of a stoichiometric amount of (–)-sparteine (**5**) as a chiral donor ligand, yields (*R*)-**4** with an *ee* of 99% (Scheme 7.4).



Scheme 7.4. 1,4-Addition of *n*-BuLi, using sparteine as a chiral donor ligand.

Reduction of the quantity of sparteine donor ligand used to only 0.3 equivalents still provides an *ee* of 85% in the addition product **4** [23].

Organoboron reagents are particularly well suited for 1,4-additions of aryl and vinyl groups to enones. Hayashi et al. developed a highly enantioselective Rh(I)/BINAP-catalyzed 1,4-addition of phenylboronic acid to cyclic and acyclic enones [24] (Scheme 7.5) and 1-alkenylphosphonates [25].



Scheme 7.5. Rhodium-catalyzed enantioselective 1,4-addition using phenylboronic acid.

7.2
Organozinc Reagents

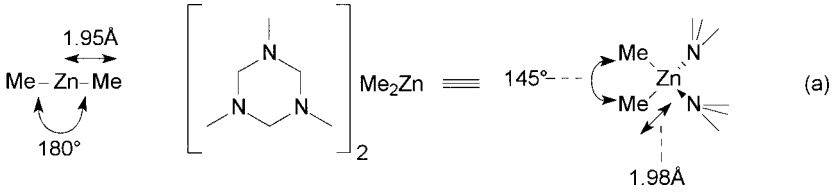
Asymmetric carbon–carbon bond-formation using organozinc reagents has developed into one of the most successful areas of synthetic chemistry in recent years [26]. Although dialkylzinc reagents (R_2Zn) usually react extremely sluggishly with carbonyl compounds and enones [27], effective catalysis may be achieved through the use of various ligands and transition metal complexes [28].

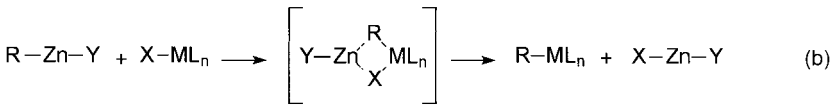
Catalysis can be attributed to two effects:

(1) changes in geometry and bond energy of the zinc reagent [29], and
(2) transmetallation [28]

The first effect has been exploited in numerous ligand-accelerated [30], enantioselective 1,2-additions of R_2Zn reagents to aldehydes [26]. Dimethylzinc, for example, has a linear structure and is not reactive towards aldehydes or ketones. Upon coordination of triazine, however, a tetrahedral configuration is produced at the zinc

atom and an elongated zinc–carbon bond is created, resulting in enhanced reactivity of the dialkylzinc reagent (Scheme 7.6(a)) [29].



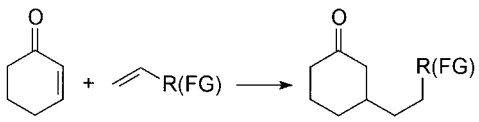


Y = R, halide
M = Ti, Pd, Ni, Cu
X = halide, OTf
L = Ligand

Scheme 7.6. Activation of organozinc reagents.

Organozinc reagents can be converted into more reactive organometallic reagents RML_n [28], as has been demonstrated for Ni, Cu, Pd, and Ti [5, 31]. Transmetalation is therefore most probably the key step in copper-catalyzed 1,4-additions of R_2Zn reagents, with alkyl transfer from Zn to Cu generating organocopper reagents in situ (Scheme 7.6(b)) [28]. In view of the complex nature of many organocopper reagents [32, 41], it needs to be emphasized that other formulations, such as bimetallic Zn/Cu reagents, are perhaps more realistic.

Another important feature is the reduced basicity of R_2Zn reagents [27, 29]. The tolerance of organozinc reagents for functional groups (esters, nitriles) set them apart from many other organometallic systems, such as organolithium and Grignard reagents [28]. A number of R_2Zn reagents are commercially available, but an important practical consideration in the use of organozinc reagents in 1,4-addition is the option of starting with an enone and an alkene (Scheme 7.7).

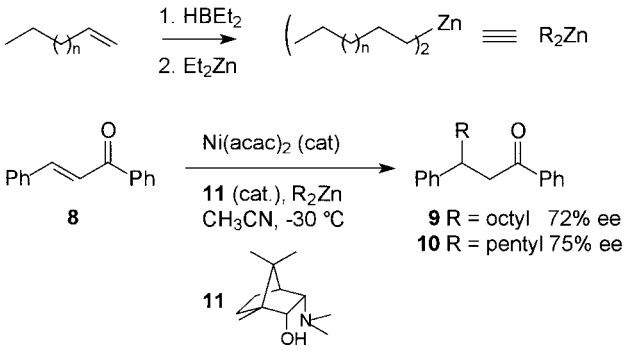


FG = functional group

Scheme 7.7. Alkenes as starting materials in 1,4-additions involving (functionalized) organozinc reagents.

The R_2Zn reagents are readily prepared from the corresponding (functionalized) alkene by hydroboration and subsequent boron-zinc exchange, according to the

procedure of Knochel et al. (Scheme 7.8) [8, 28, 33]. Alternatively, they are accessible from the Grignard reagents by transmetalation, following the method introduced by Seebach et al. [5c, 34], but removal of halide is required since the presence of salts is usually detrimental in the subsequent catalytic asymmetric C–C bond-formation.



Scheme 7.8. Nickel-catalyzed 1,4-addition, using alkene hydroboration and boron-zinc exchange.

7.3
Copper-catalyzed 1,4-Addition

7.3.1
Phosphoramidite-based Catalysts

The numerous studies prior to 1996 on Cu-catalyzed additions of Grignard reagents to cyclohexenone as a model substrate revealed that, with a few exceptions, enantioselectivity was exclusively found with either cyclic substrates (Grignard reagents) or acyclic substrates (dialkylzinc reagents) (Scheme 7.2).

The first application of a copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone, using chiral phosphorous ligand **12**, was reported by Alexakis (Fig. 7.1) [35]. An *ee* of 32% was obtained.

It appears from these early studies that modest to rather high yields and enantioselectivities can be achieved with structurally very diverse chiral ligands. Furthermore, both relatively hard (amino alcohols) and soft (thiols, phosphines) ligands

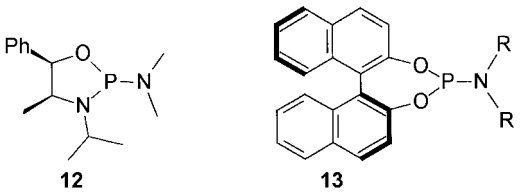
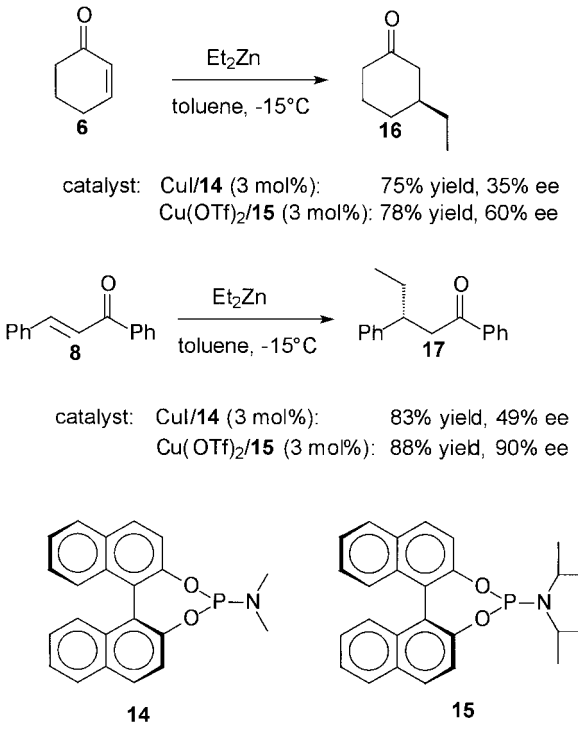


Fig. 7.1. Structures of phosphorus ligands **12** and **13**.

produce active catalysts for 1,4-additions of Grignard and R_2Zn reagents. A critical analysis of copper-catalyzed 1,4-additions revealed that several competing catalytically active complexes, including achiral ones, might be present. A question that therefore played a decisive role in our discovery of the first catalytic, enantioselective 1,4-addition of an organometallic reagent with *ee*s exceeding 98% was that of how efficient ligand-accelerated catalysis might be achieved [30]. In anticipation that the catalytic activity might be enhanced by fine-tuning of the steric and electronic properties of the ligands, phosphoramidites were introduced as a novel class of chiral ligands for copper [36].

Phosphoramidites **13**, derived from 2,2′-binaphthol, proved to be versatile ligands for copper-catalyzed 1,4-additions of Et_2Zn to chalcone and 2-cyclohexenone (Scheme 7.9) [37].



Scheme 7.9. Copper-catalyzed 1,4-addition to cyclohexenone and chalcone, with phosphoramidites as chiral ligands.

With these catalysts (3 mol%), prepared in situ from CuI or CuOTf and ligand **14**, the following observations were made:

(1) high activity; complete conversions were reached in less than 3 h at −35 °C (isolated yields 75–88%),

(2) excellent chemoselectivities and regioselectivities (> 95%) for 1,4-addition,
(3) significant *ee*s both with cyclic and with acyclic enones; a feature notably absent with previous catalysts.

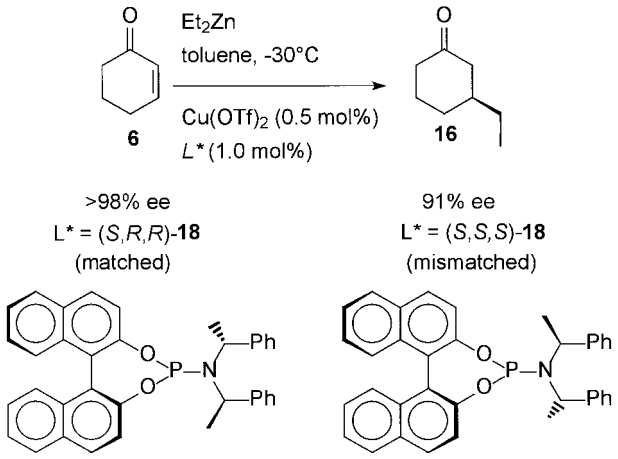
Use of ligand **15**, with a sterically more demanding diisopropylamine moiety, further increased the enantioselectivity.

Another significant improvement, resulting in better catalyst solubility and slightly enhanced *ee* values, was found when $Cu(OTf)_2$ was used. The ease of handling of $Cu(OTf)_2$, compared to that of CuOTf, is a major advantage for applications of this catalytic system in synthesis. The copper(II) complex is most probably reduced in situ to a copper(I) complex, which functions as the actual catalyst.

The most important findings using the catalytic system based on Cu-ligand **15** are:

(1) strongly ligand-accelerated catalysis, and
(2) Et_2Zn addition to 4,4-dimethyl-2-cyclohexenone and chalcone with 81% *ee* and 90% *ee*, respectively.

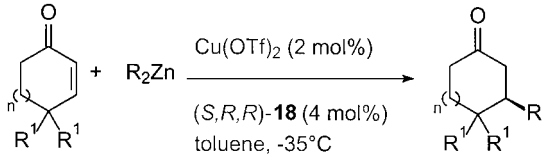
A breakthrough was achieved with chiral phosphoramidite (*S*, *R*, *R*)-**18**, in which a C_2-symmetric (*S*)-binaphthyl unit and a C_2-symmetric (*R*, *R*)-bis-(1-phenylethyl)-amine unit are present (Scheme 7.10), resulting in the enantioselective catalytic 1,4-addition of Et_2Zn to 2-cyclohexenone (**6**) with >98% *ee* [38].



Scheme 7.10. Enantioselective 1,4-addition of Et_2Zn to cyclohexenone with $Cu(OTf)_2$-matched (S, R, R)-**18** and $Cu(OTf)_2$-mismatched (S, S, S)-**18** phosphoramidites.

The presence of two chiral units in ligand **18** results in a matched (*S*, *R*, *R*) and a mismatched (*S*, *S*, *S*) combination. The absolute stereochemistry of the product is controlled by the BINOL moiety and the amine component has a distinct effect in

Tab. 7.1. Enantioselective 1,4-addition of R_2Zn reagents to cyclic enones, catalyzed by $Cu(OTf)_2$/(*S*, *R*, *R*)-**18**.

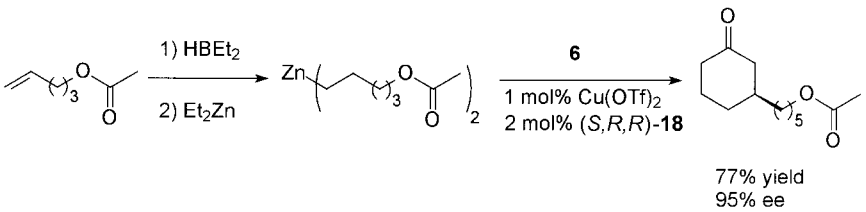


R	R^1	*n*	*Yield (%)*	*ee (%)*
C_2H_5	H	1	94	>98
C_2H_5	H	0	75	10
C_2H_5	H	2	95	>98
C_2H_5	H	3	95	97
C_2H_5	CH_3	1	74	>98
C_2H_5	C_6H_5	1	93	>98
CH_3	H	1	72	>98
CH_3	CH_3	1	68	>98
C_7H_{15}	H	1	95	95
i-C_3H_7	H	1	95	94
$(CH_2)_3C_6H_5$	H	1	53	95
$(CH_2)_3CH(OC_2H_5)_2$	H	1	91	97

fine-tuning the enantioselectivity. However, even the diastereomeric Cu catalyst derived from (*S*, *S*, *S*)-**18** still gave an *ee* of 91% [39]. The high selectivity and reactivity in this ligand-accelerated catalytic 1,4-addition was retained when the amount of catalyst used was reduced. When **6** was used as a substrate, turnover numbers larger than 3000 (95% *ee*) were found.

The examples given in Tab. 7.1 illustrate the scope of the $Cu(OTf)_2$/(*S*, *R*, *R*)-**18**-catalyzed 1,4-addition. With various R_2Zn reagents, excellent yields and enantioselectivities are obtained for cyclic enones (except for cyclopentenone, vide infra) [6, 38, 80].

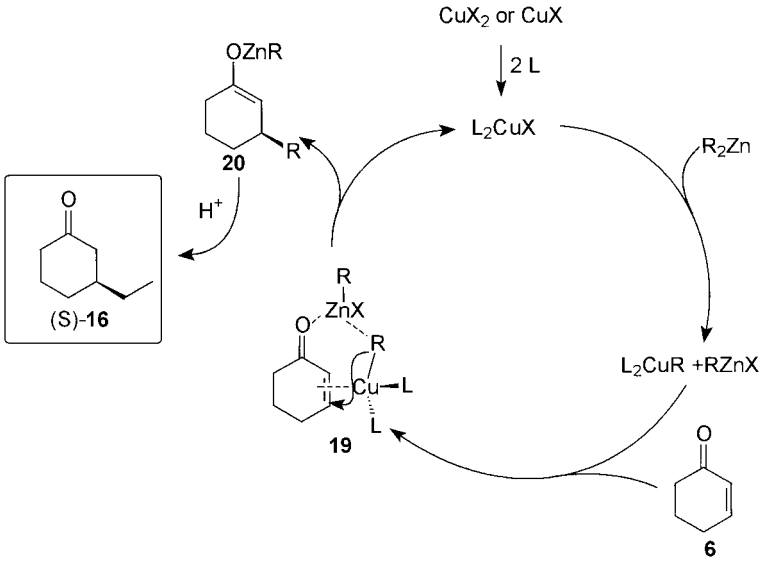
Functionalized alkyl groups are readily introduced through this catalytic procedure, while the level of stereoselectivity is not affected by, for instance, the presence of an ester functionality in the R_2Zn reagent (Scheme 7.11).



Scheme 7.11. Copper-catalyzed enantioselective 1,4-addition of a functionalized zinc reagent.

7.3.2 Catalytic Cycle

We have proposed a pathway, based on mechanistic studies in organocuprate and zincate chemistry [40–42] and the results of several catalytic experiments [37, 38], for the catalytic 1,4-addition (Scheme 7.12). Most probably, in situ reduction of $Cu(OTf)_2$ takes place prior to the formation of the Cu(I)-phosphoramidite complex L_2CuX. Subsequent alkyl transfer from zinc to copper gives L_2CuR and RZnX. Complexation of the RZnX to the carbonyl group and formation of the π-complex between L_2CuR and the enone results in complex **19**. This step is followed by alkyl transfer, and the resulting zinc enolate **20**, upon protonation, affords β-substituted cycloalkanone **16**. Alternatively, the enolate can be trapped with other electrophiles in tandem procedures (vide infra). The proposed mechanism is in accordance with the significant increases in reaction rates of 1,4-additions of cuprates produced by enone activation using Lewis acids [40–43] and with the well known π-complexation ability of organocopper species [20, 44]. In view of the high selectivities observed and taking into account that dinuclear species are involved in catalytic 1,2-additions of R_2Zn reagents [26], **19** might well be formulated as a bimetallic complex in which the enone is bound in a fixed conformation that affords highly π-face-selective addition.



Scheme 7.12. Catalytic cycle for 1,4-additions of R_2Zn reagents.

The presence of two ligands in the active catalyst is proposed on the basis of the optimum ligand-to-copper ratio of 2 and the nearly identical selectivities of monodentate and bidentate phosphoramidites in the 1,4-addition of Et_2Zn to 2-cyclohexenone [45].

The observation of nonlinear effects, both with chalcone and with cyclohexenone, further supports this catalyst stoichiometry. The nonlinear effects can be explained by the involvement of diastereomeric complexes L_2CuR, with two chiral ligands bound to copper (Fig. 7.2) [45].

The X-ray structure of the CuI complex **21** of phosphoramidite **14** provides additional insight into a possible mechanism for stereocontrol (Fig. 7.3). The formation of the L_2CuEt-enone complex involves substitution of the iodide in **21** for the alkyl moiety and of one of the ligands for the π-coordinated enone. Coordination of RZnX results in the bimetallic intermediate **19** (Fig. 7.3). The absolute configuration of the two phosphoramidite ligands and the pseudo-C_2-symmetric arrangement dictate the formation of (*S*)-3-ethyl-cyclohexanone.

7.3.3 Variation of Ligands

A remarkable number of new BINOL- and TADDOL-based chiral ligands for the copper-catalyzed conjugate addition of R_2Zn reagents have recently been introduced, with both monodentate and bidentate ligands having proven capable of inducing high enantioselectivities [6, 11, 12, 46].

Yields and selectivities of BINOL-derived ligands in additions of Et_2Zn and Me_2Zn to 2-cyclohexenone are compiled in Tab. 7.2.

Pfaltz introduced phosphite ligands **22**, with BINOL and chiral oxazoline units, which gives excellent enantioselectivities [47]. In phosphoramidites **14** and **15** (Scheme 7.9) the structure of the amine moiety is crucial, but substituents at the 3,3′-positions of the BINOL unit had only minor influences on the enantioselectivity of the 1,4-addition to cyclohexenone. In contrast, the introduction of the two 3,3′-methyl substituents in ligand **22** increased the *ee* drastically: from 54% to 90%.

Bidentate phosphorus ligands based on BINOL, such as phosphonite **23**, phosphites **24** and **25**, and phosphoramidite **26** (Tab. 7.2), with various bridging units were introduced by the groups of Reetz, Chan, and Waldmann [48–50]. Excellent enantioselectivities – up to 96% for ligand **23**, for instance – were found.

Although the presence of BINOL in the ligands so far discussed has shown itself to be particular effective, modification of the diol moiety provides new classes of ligands for this addition reaction. Alexakis, screening a number of chiral phosphites in the $Cu(OTf)_2$-catalyzed 1,4-addition, showed that an *ee* of 40% could be obtained for the addition of Et_2Zn to 2-cyclohexenone and of 65% for addition to chalcone, by using cyclic phosphites derived from diethyl tartrate [51].

The use of TADDOL-based ligands offers an important alternative for copper-catalyzed asymmetric 1,4-additions. TADDOLs ($\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol compounds), introduced by Seebach, are among the most successful currently known ligands in asymmetric catalysis. Seebach also developed the first copper-catalyzed 1,4-addition of a Grignard reagent using a TADDOL derivative as a chiral ligand (see Scheme 7.2) [17]. We have reported TADDOL-based

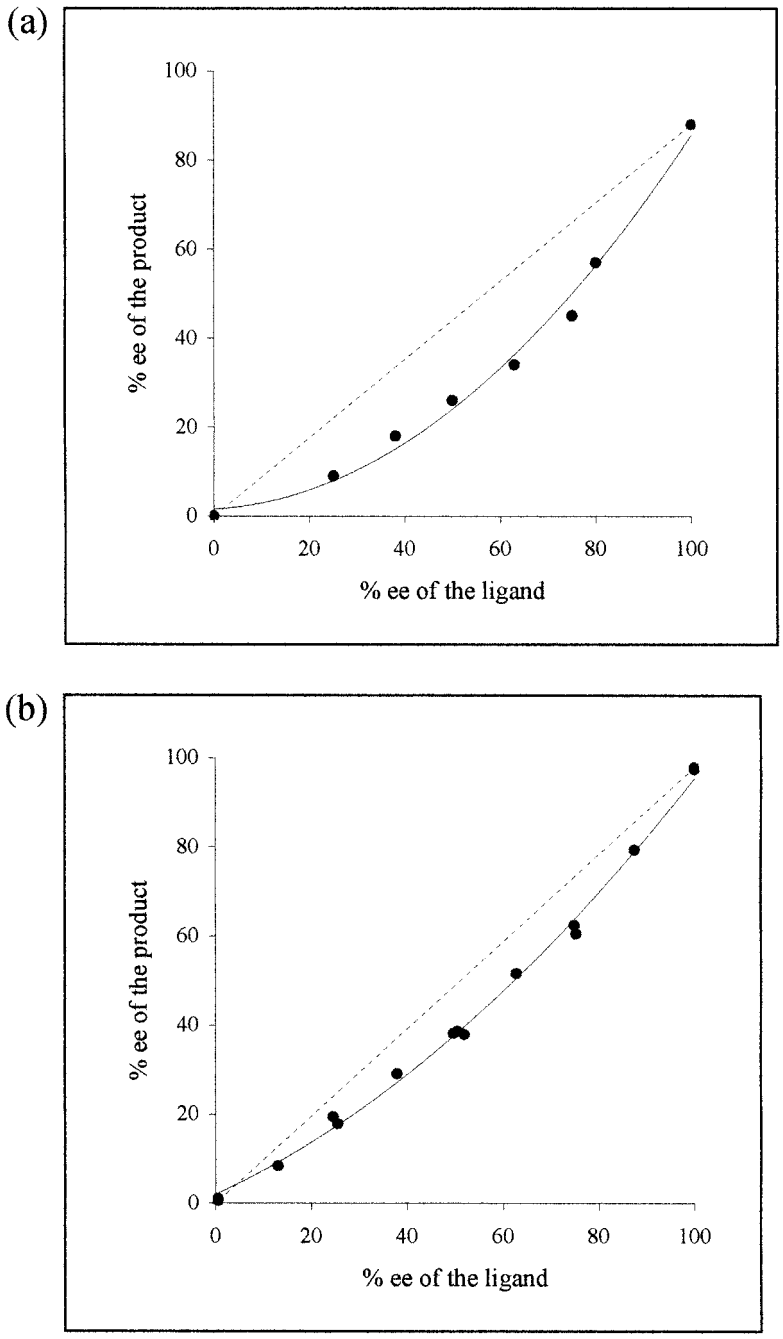
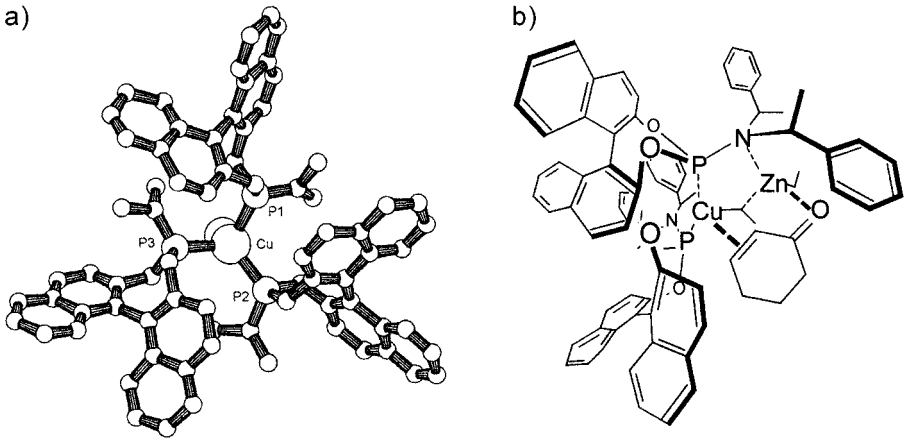


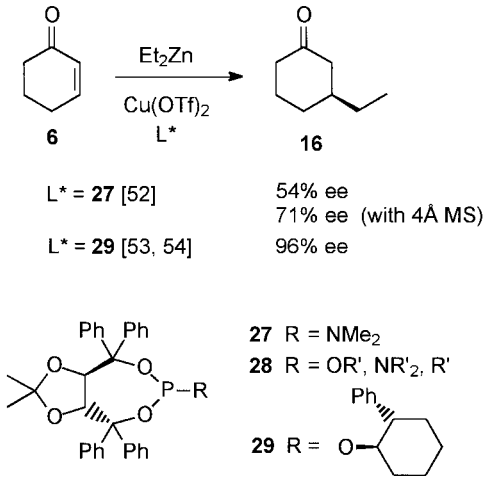
Fig. 7.2. Correlation between the *ee* of the ligand and that of the 1,4-addition product: a) chalcone (ligand **15**) and b) 2-cyclohexenone (ligand **18**).



21 **19**

Fig. 7.3. a) X-ray structure of the CuI complex **21** of ligand **14**; b) Possible bimetallic intermediate involved **19** in si-face-selective ethyl transfer to 2-cyclohexenone.

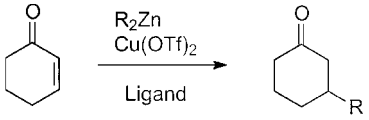
phosphoramidite **27** as a chiral ligand for $Cu(OTf)_2$-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone, affording an *ee* of 54% (Scheme 7.13) [52].



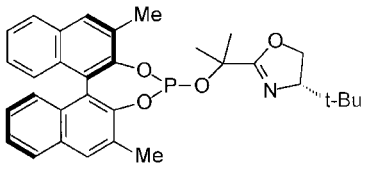
Scheme 7.13. TADDOL-based phosphoramidite ligands in the catalytic 1,4-addition.

Surprisingly, the enantioselectivity could be increased to 71% when powdered molecular sieves (4 Å) were present during the reaction. This effect might be due to traces of water, resulting in the formation of mixed zinc hydroxides and affecting the stereoselectivity, or might be attributable to a catalytic reaction at the surface of the molecular sieves. A remarkable difference between ligand **27** and BINOL phosphoramidite **18** is that with **27** the highest enantioselectivity is found with the

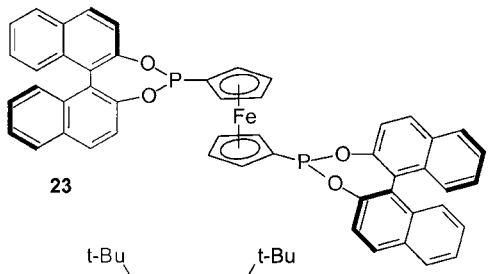
Tab. 7.2. Copper-catalyzed enantioselective 1,4-addition of R_2Zn to 2-cyclohexenone using BINOL-type ligands.



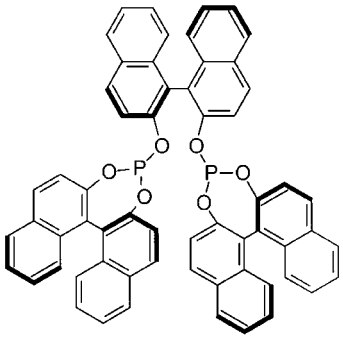
Ligand	*Catalyst (mol%)*	*R*	*ee (%)*	*Ref.*
22	3	Et	90	47
		Me	96	47
23	1	Et	96	48
24	1	Et	90	49
25	1	Et	90	49
26	1	Me	82	50



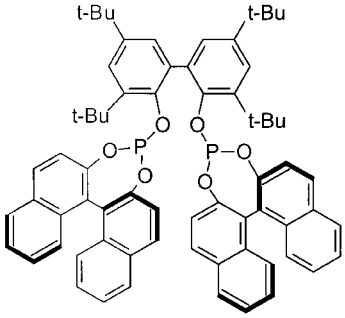
22



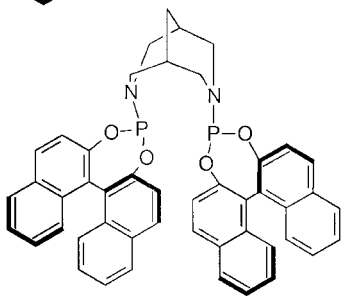
23



24



25



26

smallest amine substituent (Me_2N) at phosphorus, whereas in the case of ligand **18** a bulky amine is essential.

Alexakis et al. synthesized a large variety of TADDOL-based phosphites, phosphoramidites, and phosphonites **28**, and screened these ligands in the Et_2Zn addition to 2-cyclohexenone (Scheme 7.13) [53, 54]. While only modest *ee*s were reported for most of these ligands, an excellent yield (95%) and enantioselectivity (96%) was observed with ligand **29**. The stereocontrol in these ligands is mainly due to the TADDOL moiety.

Although BINOL- and TADDOL-based ligands have been used most frequently in copper-catalyzed 1,4-additions of R_2Zn reagents (Tab. 7.2, Scheme 7.13), a number of other chiral ligands have been reported (Fig. 7.4). The *ee*s obtained in the 1,4-addition of Et_2Zn to 2-cyclohexenone (**6**) are indicated for each ligand. Zhang et al. described binaphthalene phosphine **30**, with an additional pyridine moiety, and an *ee* of 92% was attained with this ligand [55]. Tomioka reported 70% enantioselectivity in the 1,4-addition of Et_2Zn to 4,4-dimethyl-2-cyclohexenone using bisaminophosphine **31** [56], whereas Imamoto obtained an *ee* of 70% with the chiral bisphosphine **32** [57]. Furanose-derived hydroxysulfide **33** was used by Pàmies to obtain an *ee* of 62% [58]. In addition, Buono et al. reported a catalytic system based on the quinoline–phosphorus ligand **34** and CuI [59]. Once again a remarkable

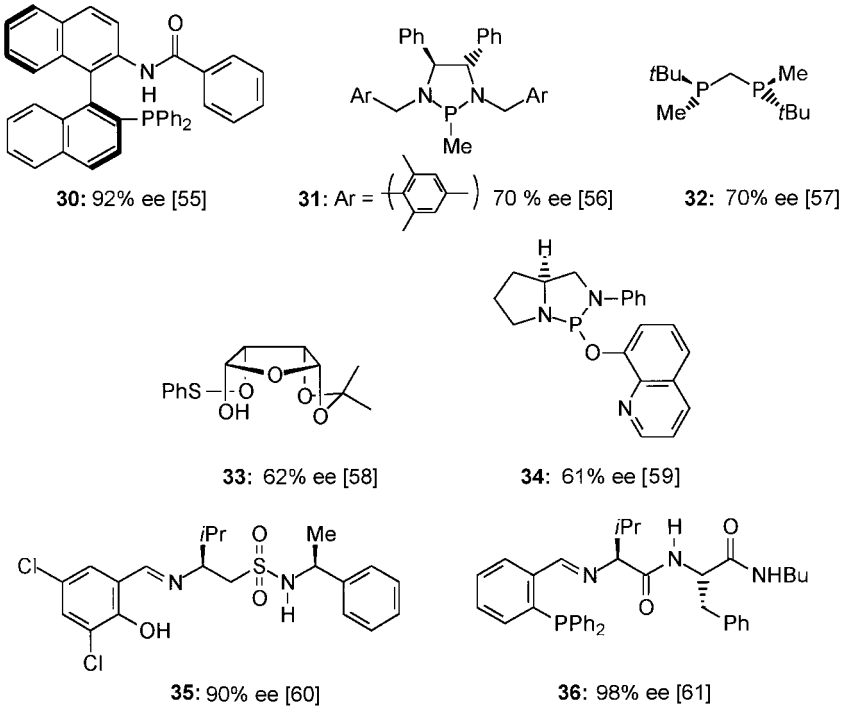


Fig. 7.4. Various chiral ligands used in the copper-catalyzed 1,4-addition of Et_2Zn to 2-cyclohexenone.

enhancement of the stereoselectivity was observed in the presence of H_2O, resulting in an *ee* of 61%.

Gennari et al. have recently used a combinatorial approach to identify new ligands for the catalytic enantioselective 1,4-addition of organozinc reagents [60]. Screening of a library of 100 salicylimine-sulfonamide-type ligands found ligand **35** to be the most selective for 2-cyclohexenone (90% *ee*). An interesting aspect of this approach is the option of screening the library of ligands in 1,4-additions to different enones, in order to determine optimal combinations of ligand and substrate.

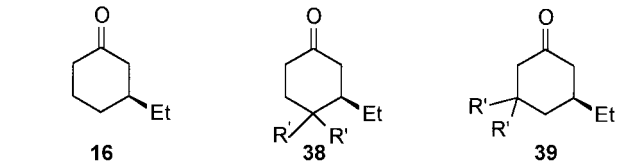
Modular peptide-based phosphine ligands were introduced by Hoveyda, providing excellent stereocontrol in 1,4-additions to cyclic enones [61]. Enantioselectivities of 97–98% were attained in alkylations of six- and seven-membered cyclic enones using ligand **36**. A major breakthrough in the 1,4-addition of R_2Zn reagents to 2-cyclopentenone was accomplished, achieving an *ee* of 97% for the first time with this notoriously difficult substrate (see Fig. 7.6, below). The most suitable ligands and catalysts, and the enantioselectivities so far attained, are summarized below for three important subclasses of enones.

7.3.4 Cyclic Enones

In copper-catalyzed 1,4-additions of R_2Zn reagents to cyclic enones, the corresponding 3-alkyl-cycloalkanones can be obtained with enantioselectivities exceeding 90% with a number of chiral ligands (Fig. 7.5) [6, 10–12, 38, 47, 48, 53, 61–63, 80]. Using phosphoramidite **18**, 3-methyl- and 3-ethylcyclohexanone and 3-ethylcycloheptanone are obtained with *ee*s of >98% (same level of *ee* also with ligand **36**) [61]. 3-Ethylcyclooctanone was formed with an *ee* of 97% [80]. Steric effects of reagent and cycloalkenones were small; transfer of an isopropyl group proceeded with an *ee* of 94% and even the use of 4,4′-disubstituted cyclohexenones gave adducts **38** (R′ = alkyl, phenyl) with the same high level of stereocontrol as with the unsubstituted substrates. Only for 5,5′-dimethylcyclohexenone, giving **39**, was a slightly lower *ee* value observed, presumably because of unfavorable 1,3-diaxial interactions.

Excellent enantioselectivities (96% *ee*) for 2-cyclohexenone were also obtained with the ligands **22**, **23**, and **29**, introduced by the groups of Pfaltz [47], Reetz [48], and Alexakis [63], respectively. *Ee*s in the range of 90–92% were found with ligands **24**, **25**, **30**, and **35** [49, 55, 60].

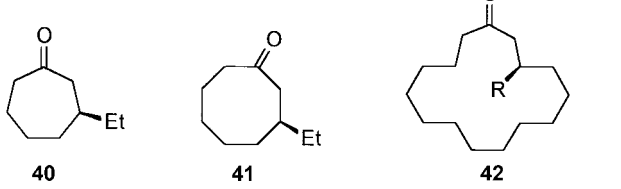
Optically active 3-ethylcycloheptanone, with *ee*s ranging from 93% to >98%, can now be obtained with five different types of ligands, including phosphoramidites [6], phosphines [57, 61], and phosphites (Fig. 7.5) [47, 48]. It appears that the structural requirements of the chiral ligands are not especially limited. In particular, the formation of 3-methylcycloheptanone in 97% *ee* with the chiral bisphosphine ligand **32** recently introduced by Imamoto [57] should be emphasized, together with the finding that both monodentate and bidentate ligands give high enantioselectivities.



Ligand:	ee:
18, 36	≥ 98%
22, 23, 29	96%
24, 25, 30, 35	90-92%

18 ≥ 98%

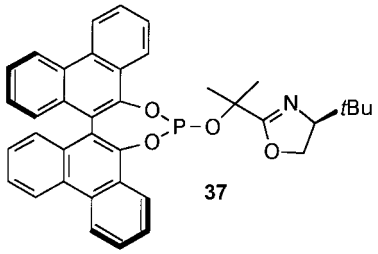
18 84-88%

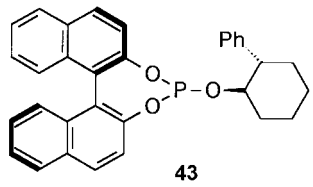


18, 36	≥ 98%
32	97%
37	94%
23	93%

18 97%

43 79% (R = Me)
43 87% (R = Et)





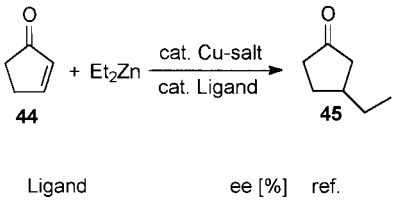
(for structures of other ligands, see table 7.2)

Fig. 7.5. Conjugate addition products.

The formation of 3-ethylcyclooctanone **41** (97% *ee*) [6, 80] and muscone **42** (R = Me, 79% *ee*) [63] are illustrative for our present purposes.

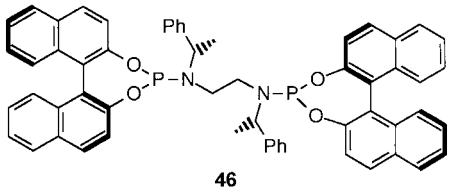
7.3.5
2-Cyclopentenone

Optically active cyclopentanes are among the structural units most frequently encountered in natural products such as steroids, terpenoids, and prostaglandins. Not unexpectedly, the development of a highly enantioselective catalytic 1,4-addition reactions to 2-cyclopentenones has proven to be a challenging goal. In contrast with the high enantioselectivity observed in the copper-phosphoramidite-catalyzed 1,4-

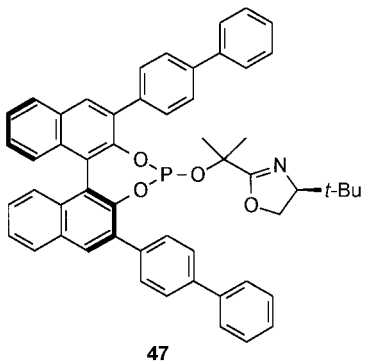


44 **45**

Ligand	ee [%]	ref.
(*R,S,S*) – **18**	10	38
(*S,S,S*) – **18**	30	38
27 (with 4 Å sieves)	62	52
22	72	47a
24	77	49a
46	83	62
25	89	49b
47	94	47b
36	97	61



46



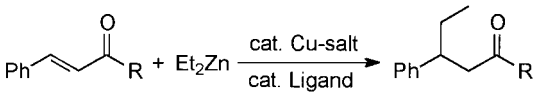
47

Fig. 7.6. Enantioselective conjugate addition to 2-cyclopentenone.

addition of Et_2Zn to 2-cyclohexenone and larger cyclic enones, an *ee* of only 10% is found when the same ligand (*S,R,R*)-**18** is applied to 2-cyclopentenone **44** (30% *ee* for the (*S,S,S*)-ligand **18**) (Fig. 7.6) [38].

Besides the very low stereoselectivities, a major problem encountered with this substrate is the low chemical yield (due to subsequent reaction between the resulting zinc enolate and the starting material) and the high volatility of the product. Using TADDOL-phosphoramidite **27** in a tandem 1,4-addition-aldol condensation to cyclopentenone, we were only able to obtain an *ee* of 37%, but the enantioselectivity was raised to 62% in the presence of wet powdered molecular sieves (4 Å) [52]. This beneficial effect of water and molecular sieves in some catalytic 1,4-additions has been observed in other cases recently [52, 59]. Important to note is that the yields in the tandem version are dramatically increased, presumably due to in situ trapping of the reactive enolate (vide infra). Pfaltz et al. reported a 72% *ee* in the addition of Et_2Zn to **44** when using BINOL-oxazoline phosphite ligand **22** [47].

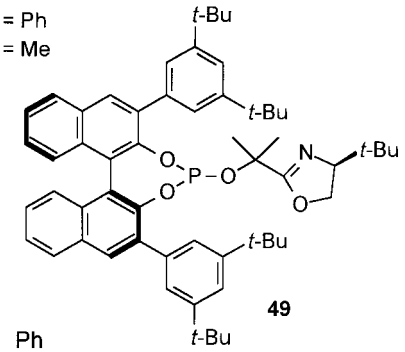
High enantioselectivities (83–89% *ee*) have been obtained with the bidentate ligands **46** [62] and **25** [49b]. The first catalytic 1,4-addition of diethylzinc to 2-cyclopentenone with an *ee* exceeding 90% was reported by Pfaltz, who employed phosphite **47**, bearing biaryl groups at the 3,3′-positions of the BINOL moiety [47]. Hoveyda et al., using ligand **36**, have recently had success with highly enantioselective 1,4-additions (97% *ee*) of dialkyl zinc reagents to 2-cyclopentenones [61]. This is an exciting result as it should allow the catalytic asymmetric synthesis of substituted cyclopentanes (including prostaglandins) with enantioselectivities exceeding 95%.



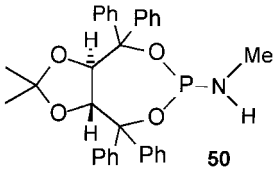
17 R = Ph
48 R = Me

Ligand	ee [%] **17**	ee [%] **48**
15	89	60
49		87
26	78	
30	96	90
32	71	
29	50	35
50		49

(For structures of other ligands, see Table 7.2 and Scheme 7.13)



49



50

Fig. 7.7. Enantioselective conjugate addition to acyclic enones.

7.3.6
Acyclic Enones

Aryl-substituted enones (chalcones in particular) have been used as model substrates in studies of catalytic 1,4-additions with organozinc reagents. Fig. 7.7 summarizes typical enantioselectivities achieved with various chiral ligands.

Nearly identical *ee*s (87–89%) were found by Feringa and Pfaltz on employing bulky phorphoramidite [37, 38] and phosphite ligands [47] in 1,4-additions to chalcone and benzalacetone. Alexakis employed TADDOL-based chiral ligand **29** in catalytic 1,4-additions to chalcone and benzalacetone (50% and 35% *ee*, respectively) [54]. A variety of chiral phosphoramidites based on BINOL were tested by Feringa and co-workers in the same reaction (*ee*s of up to 89% with ligand **15**) [45]. The most significant structural features with the phosphoramidite ligands are:

(1) Sterically demanding substituents at the amine moiety enhance the enantioselectivities,
(2) The introduction of methyl substituents at the 3,3′-positions of the BINOL moiety produces comparable enantioselectivities, except in the case of small amine groups,
(3) In contrast to the 1,4-addition to cyclic enones, the presence of a chiral amine is not a prerequisite for high enantioselectivity. The highest enantioselectivities so far observed for the two acyclic adducts **17** and **48** (96% *ee* and 90% *ee*, respectively) are with the pyridine–phosphine ligand **30**, introduced in 1999 by Zhang [55]. This is the first ligand that gives enantioselectivities of >90%, both for cyclic and for acyclic enones, in copper-catalyzed 1,4-additions of R_2Zn re-

agents. It should be noted that Alexakis attained *ee*s of up to 92% for a number of alkyl-substituted enones using both phosphoramidite and phosphite ligands (**18**, **43**) [63].

With the chiral copper catalysts based on phosphorus ligands, enantioselectivities in excess of 90% are now possible for all three different classes of substrates: 2-cyclohexenones and larger rings, 2-cyclopentenones, and acyclic enones. However, it appears that each class requires a specific ligand. The modular structures of the phosphoramidite-, phosphite-, and iminophosphine-type ligands are advantageous in the fine-tuning of the ligands. For phosphoramidites this can be achieved by modifying the amine component, while stereocontrol in the phosphites can be regulated through variation in the 3,3′-positions in the BINOL moiety. In the iminophosphines introduced by Hoveyda [61], peptide modification permits specific ligand optimization.

7.4 Synthetic Applications

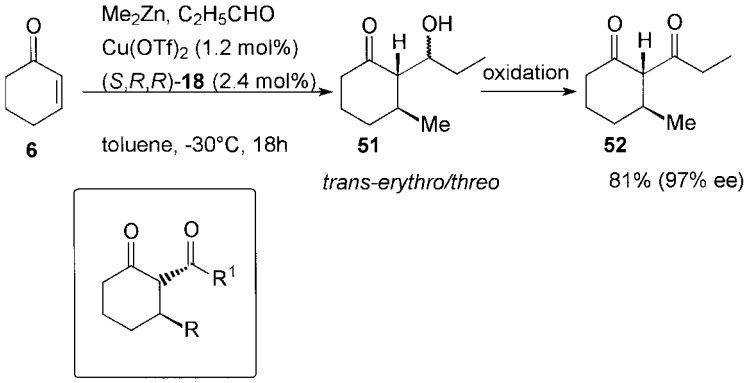
7.4.1 Tandem Conjugate Addition-Aldol Reactions

Tandem 1,4-addition to cycloalkenones constitutes an extremely versatile and elegant methodology for the synthesis of 2,3-disubstituted cycloalkanones, as is evident from its application in areas such as prostaglandin synthesis. Noyori et al. have reported the use of organozinc reagents in copper-catalyzed tandem additions [64]. The zinc enolate resulting from the catalytic enantioselective 1,4-addition of Et_2Zn to cyclohexenone reacts readily with an aldehyde in a subsequent aldol condensation.

The first asymmetric procedure consists of the addition of R_2Zn to a mixture of aldehyde and enone in the presence of the chiral copper catalyst (Scheme 7.14) [38, 52]. For instance, the tandem addition of Me_2Zn and propanal to 2-cyclohexenone in the presence of 1.2 mol% chiral catalyst (*S*, *R*, *R*)-**18** gave, after oxidation of the alcohol **51**, the diketone **52** in 81% yield and with an *ee* of 97%. The formation of *erythro* and *threo* isomers is due to poor stereocontrol in the aldol step. A variety of *trans*-2,3-disubstituted cyclohexanones are obtained in this regioselective and enantioselective three-component organozinc reagent coupling.

7.4.2 Kinetic Resolution of 2-Cyclohexenones

We have recently discovered that phosphoramidite **18** is also an excellent ligand for copper-catalyzed kinetic resolution of chiral 2-cyclohexenones (Scheme 7.15). Chiral 2-cyclohexenones are attractive building blocks for a variety of natural products, but their synthesis usually requires multistep routes from chiral starting materials [65]. The development of the new kinetic resolution was the product of two impor-

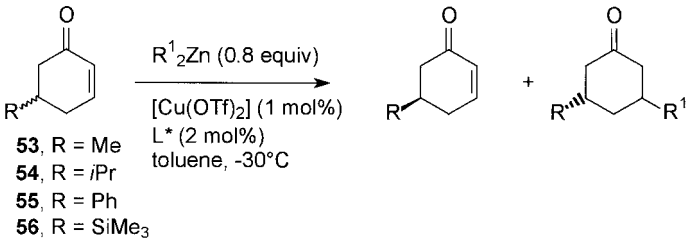


Scheme 7.14. Enantioselective tandem conjugate addition-aldol reactions.

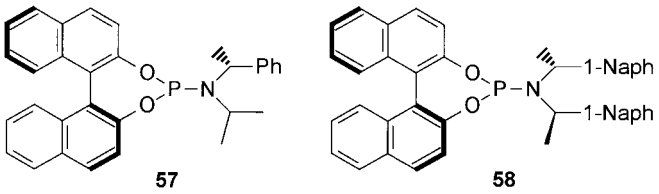
Tab. 7.3. Kinetic resolution of 5-substituted 2-cyclohexenones **53–56** according to Scheme 7.15 (s: stereoselectivity factor).

Ligand	*Enone*	*R¹*	*t (min)*	*Convn. (%)*	*ee (%)*	*s*	*Conf.*[a]
(*S*, *R*, *R*)-**18**	**53**	Et	15	48	88	120	R
(*S*, *R*, *R*)-**18**	**53**	Et	**20**	**53**	**99**		
(*S*, *S*, *S*)-**18**	**53**	Et	15	42	62	24	*R*
(*S*, *R*)-**57**	**53**	Et	90	49	86	50	*R*
(*S*, *S*)-**57**	**53**	Et	45	51	90	42	*R*
(*S*, *R*, *R*)-**58**	**53**	Et	45	46	76	40	*R*
(*S*, *S*, *S*)-**58**	**53**	Et	90	19	12	3	*R*
(*S*, *R*, *R*)-**18**	**54**	Et	10	54	96	39	—
(*S*, *R*, *R*)-**18**	**55**	Et	—	55	89	19	*R*
(*S*, *R*, *R*)-**18**	**56**	Et	5	56	86	14	—
(*S*, *R*, *R*)-**18**	**53**	*i*-Pr	60	55	84	14	*R*
(*S*, *R*, *R*)-**18**	**53**	*n*-Bu	15	49	93	>200	*R*
(*S*, *R*, *R*)-**18**	**53**		**30**	**54**	>**99**		
(*S*, *R*, *R*)-**18**	**54**	*n*-Bu	60	50	93	94	—
(*S*, *R*, *R*)-**18**	**54**		**90**	**53**	**99**		
(*S*, *R*, *R*)-**18**	**56**	*n*-Bu	15	44	78	>200	—
(*S*, *R*, *R*)-**18**	**56**		**45**	**52**	>**99**		
(*S*, *R*, *R*)-**18**	**53**	Me	20	50	93	94	*R*

a) Configuration of the unreacted enone



Scheme 7.15. Enantioselective kinetic resolution of 5-substituted 2-cyclohexenones.



57 58

Fig. 7.8. Ligands used in the kinetic resolution of 5-substituted 2-cyclohexenones.

tant considerations [66, 67]: i) many racemic cyclohexenones are readily available, and ii) high *trans* diastereoselectivity is found in the addition of organometallic reagents to 5-alkyl-2-cyclohexenones [68].

Results from catalytic kinetic resolutions (1 mol% catalyst) of 5-substituted cyclohexenones **53–56** using a number of phosphoramidite ligands are compiled in Tab. 7.3 [69]. There was a good correlation found between the selectivity of the ligands in the 1,4-addition to 2-cyclohexenone and that in the kinetic resolution of 5-methyl-2-cyclohexenone **53**. Once again the most selective ligand is (*S*, *R*, *R*)-**18**, while particularly noteworthy in comparison with all the other phosphoramidite ligands is the high reactivity (48% conversion of **53** at −40 °C in 15 min.) of the copper catalyst based on **18**. High selectivity factors (s) up to and over 200 are found, making this kinetic resolution synthetically interesting, as was demonstrated by a resolution of **53** on an 11 g scale [69].

The nature of the R^1_2Zn reagents has a profound influence on the selectivity in this process (Tab. 7.3). Contrary to expectations, the use of the bulkier *i*-Pr_2Zn reagent in place of Et_2Zn results in a lower selectivity, but with *n*-Bu_2Zn the selectivity increases, providing unconverted **53** with an *ee* of >99% at 52–54% conversion (Fig. 7.9). High *trans* diastereoselectivity had previously been observed for

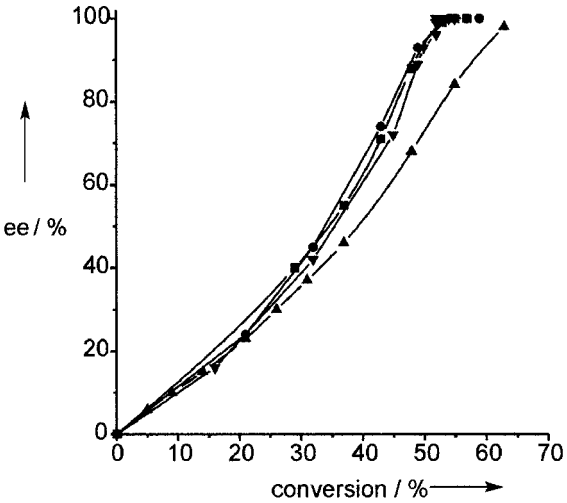
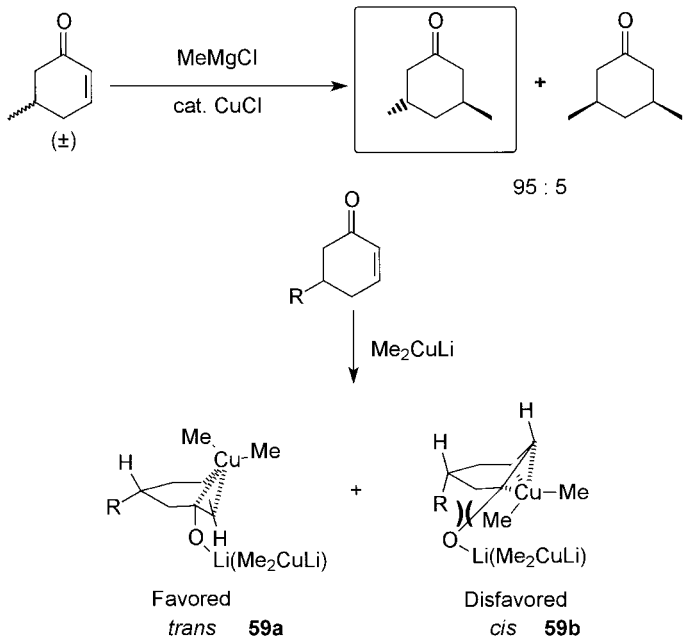


Fig. 7.9. *Ee* against conversion for the kinetic resolution of **53** with (*S*, *R*, *R*)-**18**, $Cu(OTf)_2$, and Et_2Zn (–■–), *i*Pr_2Zn (–▲–), *n*Bu_2Zn (–●–), and Me_2Zn (–▼–).

the copper-catalyzed Grignard addition to 5-methyl-2-cyclohexenone (Scheme 7.16) [68]. The *trans* diastereoselectivity in these 1,4-additions might be explained by the involvement of preferred conformations and a copper intermediate such as **59**, as proposed by Corey [68a] (cf. Chapter 6).



Scheme 7.16. Favored and disfavored copper intermediates as proposed by Corey et al. [68a].

In an ideal kinetic resolution (common in enzyme-catalyzed processes), one enantiomer of a racemic substrate is converted while the other is unreactive [70]. In such a kinetic resolution of 5-methyl-2-cyclohexenone, even with 1 equivalent of Me_2Zn, the reaction should virtually stop after 50% conversion. This near perfect situation is found with ligand **18** (Fig. 7.10) [71]. Kinetic resolutions of 4-methyl-2-cyclohexenone proceed less selectively ($s = 10–27$), as might be expected from the lower *trans* selectivity in 1,4-additions to 4-substituted 2-cyclohexenones [69].

7.4.3
Sequential 1,4-Additions to 2,5-Cyclohexadienones

2,5-Cyclohexadienones **61** and **64** are readily available from monoprotected hydroquinones or *para*-substituted phenols, respectively. Conjugate additions to these symmetrical dienones result in desymmetrization of the prochiral dienone moieties, providing access to multifunctional chiral synthons in two steps from the aromatic precursors (Scheme 7.17) [72].

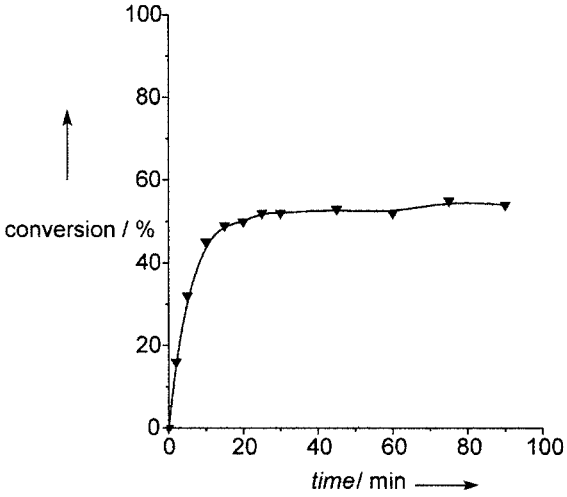
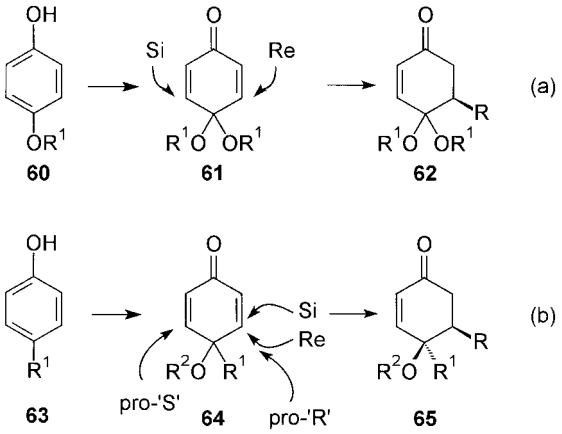


Fig. 7.10. Conversion against time for the kinetic resolution of **53** with 1 equivalent of Me_2Zn under standard conditions.

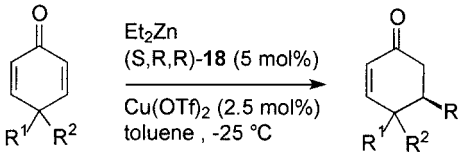


Scheme 7.17. Possible modes of attack by R_2Zn on dienones **61** and **64**.

In the case of benzoquinone monoacetals **61**, the two substituents at the 4-position are equal, and side-selective addition (*Re* versus *Si* face) creates a single stereocenter (Scheme 7.17(a)). In the (*S*, *R*, *R*)-**18**/$Cu(OTf)_2$-catalyzed 1,4-addition, depending on the nature of the R_2Zn reagent and the size of the acetal moiety, enantioselectivities ranging from 85–99% were found (Table 7.4). The highest *ee*s are provided by a combination of a small acetal moiety and Me_2Zn; 99% *ee* was obtained with 4,4-dimethoxy-5-methyl-2-cyclohexenone, for example.

When an alkyl and an alkoxy moiety are present at the 4-position of the dienone (Scheme 7.17(b)), desymmetrization during the 1,4-addition produces two stereocenters in a single step. The chiral copper-phosphoramidite catalyst derived from

Tab. 7.4. Conjugate additions to 2,5-cyclohexadienone monoacetals and ethers.

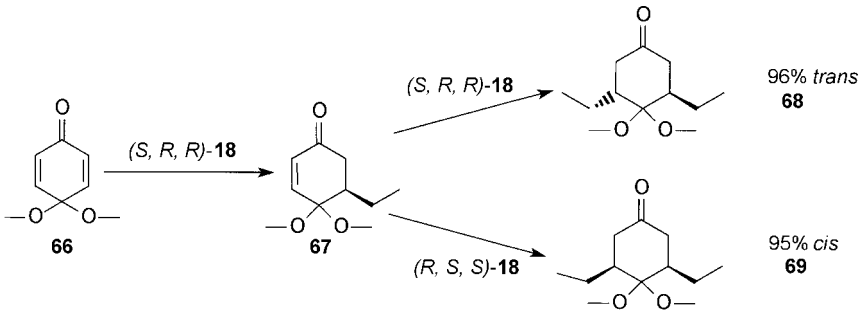


R_1	R_2	R	Yield (%)	dr	ee (%)
OMe	OMe	Et	65	—	97
OEt	OEt	Et	59	—	92
$-OCH_2CH_2O-$		Et	68	—	92
$-OCH_2CH_2CH_2O-$		Et	62	—	89
$-OCH_2C(Me)_2CH_2O-$		Et	75	—	85
OMe	OMe	Me	76	—	99
OMe	Me	Et	60	90/10	97[a)]
OMe	CH_2Ph	Et	53	97/3	93[a)]
$-CH_2CH_2CH_2O-$		Et	66	99/1	65[a)]
OMe	OCH_2Ph	Et	58	1/1	98/98

a) The ee for the major diastereoisomer is given

ligand **18** can indeed readily distinguish the *Re* and *Si* faces and the pro-*R* and pro-*S* positions in the dienone. It was found with **64** that the C-5 alkyl group was introduced syn to the alkoxy moiety. The selectivity again depended on the substituents at the 4-position, with *ee*s of up to 97% and ratios of up to 99:1 being found for the major diastereoisomer of **65**.

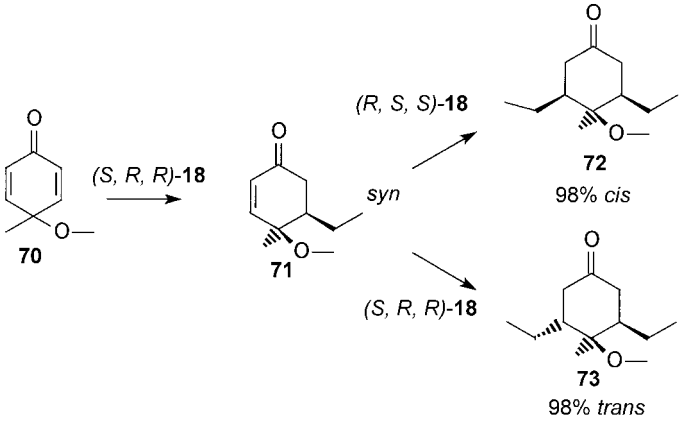
The products of this catalytic enantioselective 1,4-addition still contain an enone moiety, prone to subsequent 1,4-addition [73]. An intriguing question regarding stereocontrol was posed; would the stereoselectivity in the second addition step be governed by the catalyst or would there be a major effect from the stereocenters already present? Sequential 1,4-addition to dimethoxy-substituted cyclohexadienone **66** (Scheme 7.18) using the copper catalyst based on (*S*, *R*, *R*)-ligand **18** both in the



Scheme 7.18. Selective *cis* or *trans* double conjugate addition of Et_2Zn to cyclohexadienone monoacetal **66**.

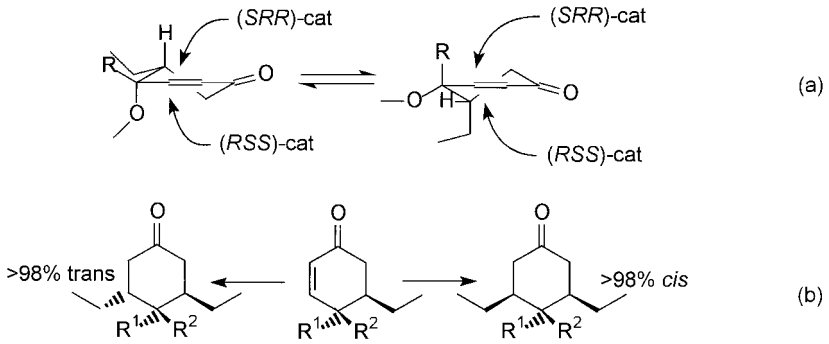
first step (97% *ee*) and in the second gave a 96% selectivity for *trans*-3,5-diethyl-4,4-dimethoxycyclohexanone (**68**). In contrast, use of (*S*, *R*, *R*)-ligand **18** followed by (*R*, *S*, *S*)-**18** resulted in (*meso*)-*cis*-**69** (95% selectivity).

In the case of 2,5-cyclohexadienone **70**, with a methoxy and a methyl substituent (Scheme 7.19), the *syn* monoadduct **71** gave 3,4,4,5-tetrasubstituted cyclohexanones, with three consecutive stereocenters. On employing the (*R*, *S*, *S*)-ligand **18** in the second addition step, *cis*-**72** (98% *de*) was found, whereas with (*S*, *R*, *R*)-**18** in the second step *trans*-**73** (98% *de*) was obtained [73].



Scheme 7.19. Selective *cis* or *trans* double conjugate addition of Et_2Zn to cyclohexadienone ether **70**.

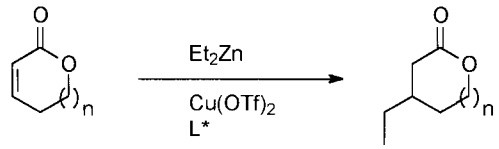
The lack of any directing effect from the 4-methoxy and the 5-ethyl substituents at the two stereocenters already present in **71** is a remarkable finding, and points to strong catalyst-dependence in the stereocontrol (Scheme 7.20). On the basis of these findings, various stereoisomers of 3,4,4,5-tetrasubstituted cyclohexanones are now accessible through sequential catalytic 1,4-additions, with control over the relative and absolute configurations possible simply by judicious selection of the appropriate enantiomer of the chiral ligand in each step.



Scheme 7.20. The selectivity of the second conjugate addition depends solely on the configuration of the chiral catalyst used.

7.4.4 Lactones

Unsaturated lactone **74** (Scheme 7.21) can be viewed as an oxygen heterocyclic analogue of 2-cyclohexenone, and it has recently been reported that catalytic 1,4-additions of Et_2Zn to **74** can indeed be accomplished with high enantioselectivity. For adduct **76**, Reetz achieved a remarkable 98% *ee* when employing ferrocene-based diphosphonate ligand **23** [48]. Using diphosphite **24**, Chan et al. achieved an *ee* of 92% for the six-membered lactone **74** and a 56% *ee* for the five-membered lactone **25** [49c].

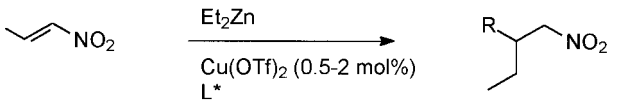


	L*	
74 (n = 1)	**23**	**76** 98% ee
74 (n = 1)	**24**	**76** 92% ee
75 (n = 0)	**24**	**77** 56% ee

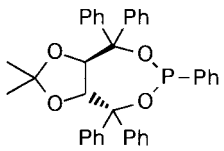
Scheme 7.21. Enantioselective conjugate addition to lactones.

7.4.5 Nitroalkenes

Nitroalkenes are excellent Michael acceptors, and asymmetric 1,4-additions to nitroalkenes (Scheme 7.22) provide access to highly versatile synthons, since the nitro group is readily reduced to the corresponding amine [74]. Seebach, employing a



	L*	
78 R = Ph	**18**	**83** 48% ee
79 R = $CH(OMe)_2$	**18**	**84** 86% ee
80 R = cyclohexyl	**18**	**85** 94% ee
81 R = 4-MeC_6H_4	**82**	**86** 86% ee



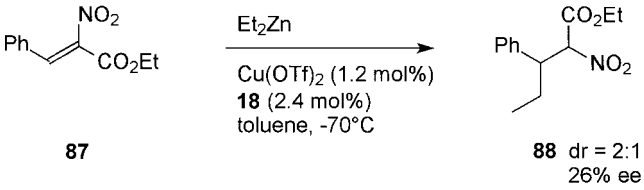
82

Scheme 7.22. Enantioselective conjugate addition to nitroalkenes.

stoichiometric chiral TADDOL-based titanium Lewis acid, reported highly enantioselective 1,4-additions of R_2Zn reagents to nitrostyrenes (90% *ee*) [75]. The first copper-catalyzed enantioselective 1,4-additions of Et_2Zn to nitroalkenes **78** and **79**, with *ee*s of up to 86%, were described by Sewald et al. (Scheme 7.22) [76].

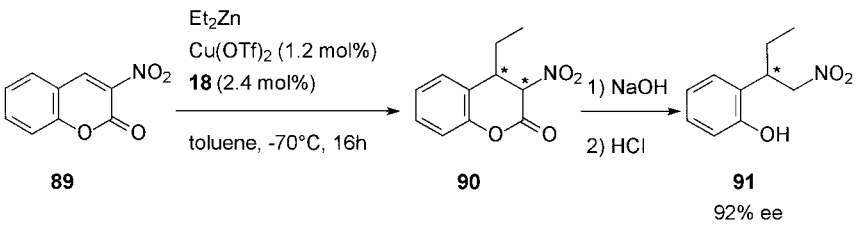
Alexakis, employing various chiral trivalent phosphorus ligands, has recently described $Cu(OTf)_2$-catalyzed 1,4-additions of Et_2Zn to a number of nitroalkenes (Scheme 7.22) [77]. TADDOL-based phosphonite **82** gave the highest *ee*s for arylnitroalkenes (up to 86%), whereas phosphoramidite **18** is the ligand of choice for alkylnitroalkenes (*ee*s of up to 94%).

We have studied the $Cu(OTf)_2$-phosphoramidite-catalyzed conjugate addition of Et_2Zn to α,β-unsaturated nitroacetate **87** (Scheme 7.23) [78, 79]. The nitroacetate moiety is a synthetic equivalent of an α-amino acid, and reduction of the nitro group in the 1,4-adduct provides access to α- and β-alkylated amino acids. Although the 1,4-adduct **88** is obtained in high yield, the enantioselectivity has so far been disappointingly low (26% *ee*) when using a mixture of *E* and *Z* isomers of the nitroalkene. With isomerically pure (*Z*)-**87**, a complete lack of enantioselectivity was observed, suggesting that a *cis* orientation of aryl and nitro groups is unfavorable for the selective formation of the catalyst-substrate complex.



Scheme 7.23. Enantioselective conjugate addition to α,β-unsaturated nitroacetates **87**.

Correspondingly, the catalytic 1,4-addition of dialkylzinc reagents to 3-nitrocoumarin **89** (Scheme 7.24), with a fixed *trans* orientation of the aryl and nitro groups, proceeds with excellent yields (90–99%), high diastereoselectivity (d.r. up to 20:1), and enantioselectivities of up to 92%. Hydrolysis of the lactone moiety in **90** was accompanied by decarboxylation, providing an asymmetric synthesis of β-arylnitroalkane **91**.

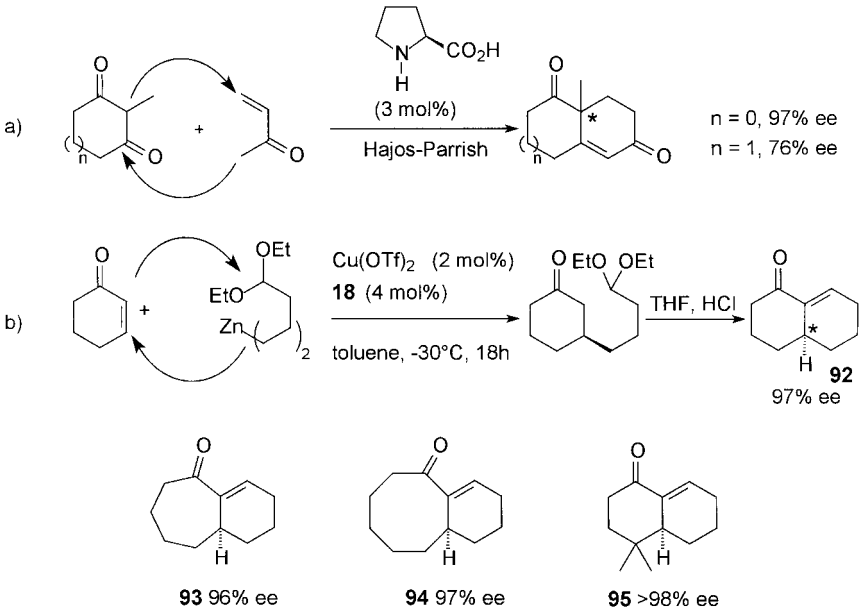


Scheme 7.24. Enantioselective conjugate addition to 3-nitrocoumarin (**89**).

7.4.6
Annulation Methodology

The construction of carbocyclic compounds by ring-annulation procedures frequently plays a prominent role in total synthesis. The tolerance of various functional groups in the zinc reagents employed in copper-catalyzed asymmetric 1,4-additions forms the basis for three novel catalytic enantioselective annulation methods discussed here.

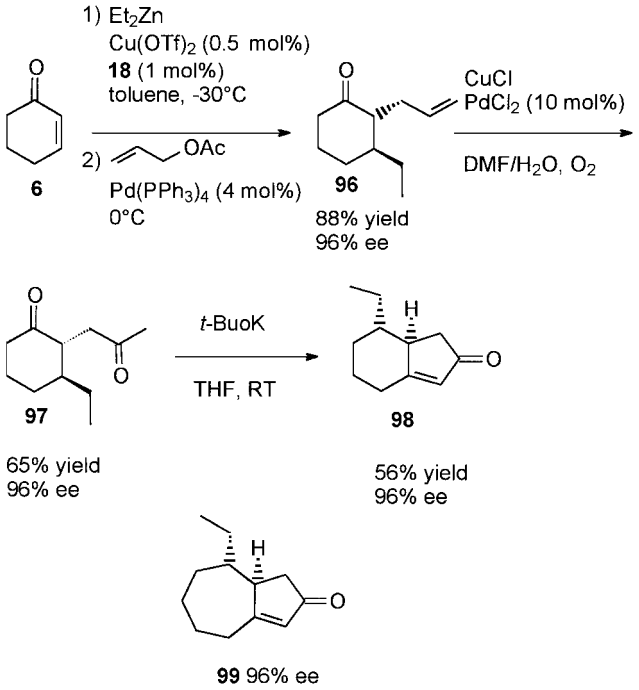
In the first method, a dialkylzinc reagent bearing an acetal moiety at the δ-position is used (Scheme 7.25(b)). The catalytic 1,4-addition is followed by acetal hydrolysis and aldol cyclization of the 4-substituted cycloalkanone, affording 6,6- (**92**), 6,7-, (**93**) and 6,8- (**94**) annulated ring systems with high enantioselectivities (> 96% *ee*s) [80]. In addition, dimethyl-substituted decalone **95**, with a structure frequently found in natural products, is readily obtained in enantiomerically pure form.



Scheme 7.25. Annulation methodology: a) Hajosh–Parrish version of the Robinson annulation, b) catalytic enantioselective annulation with functionalised organozinc reagents.

Comparison with the Hajos–Parrish asymmetric version of the Robinson annulation [81] (Scheme 7.25(a)) shows the following distinct differences between the two methods. Firstly, the cycloalkenone in the $Cu(OTf)_2$/ligand **18**-catalyzed procedure is the Michael acceptor, whereas the cycloalkanone is the Michael donor in the proline-mediated annulation. Secondly, the asymmetric induction occurs in the 1,4-addition step in the new method, in contrast to the asymmetric aldol-cyclization in the Hajos–Parrish procedure.

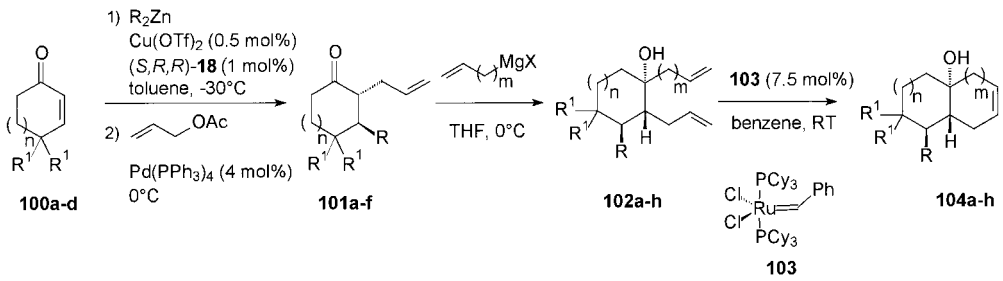
Bicyclo[4.3.0]nonenes, thanks to their frequent appearance in natural products, are other important targets for novel annulation methodology. A six-membered ring-annulation to cyclopentenones has yet to be developed, the main reason for this being that, until very recently, the levels of enantioselectivity in catalytic 1,4-additions to 2-cyclopentenone were too low for a synthetically useful procedure. However, a highly enantioselective annulation of a five-membered ring to 2-cyclohexenone has been developed (Scheme 7.26) [80].



Scheme 7.26. Catalytic enantioselective annulations of five-membered rings.

The method involves a regioselective, *trans*-diastereoselective, and enantioselective three-component coupling, as shown in Scheme 7.26. In this case, the zinc enolate resulting from the 1,4-addition is trapped in a palladium-catalyzed allylation [64] to afford *trans*-2,3-disubstituted cyclohexanone **96**. Subsequent palladium-catalyzed Wacker oxidation [82] yields the methylketone **97**, which in the presence of *t*-BuOK undergoes an aldol cyclization. This catalytic sequence provides the 5,6- (**98**) and 5,7- (**99**) annulated structures with *ee*s of 96%.

The third annulation method is again based on asymmetric tandem 1,4-addition and palladium-catalyzed allylation [83]. The key step is a ring-closing metathesis using Grubbs' catalyst **103** (Scheme 7.27). Advantage is taken of the presence of the ketone moiety in the adduct **101**, which permits a subsequent 1,2-addition of a Grignard or organolithium reagent. In this way a second alkene moiety is introduced. Ring-closing metathesis of **102** affords the bicyclic structures **104**. A wide



Scheme 7.27. Catalytic enantioselective annulations using RCM (ring-closing metathesis).

variety of annulated ring systems is accessible through this catalytic methodology (Table 7.5).

Tab. 7.5. Enantioselective annulations using RCM.

R	*R¹*	*n*	*m*	*Product*	*Ring system*	*Yield*[a] *(%)*	*ee (%)*
Et	H	1	1	**104a**	[6, 6]	49	96
Et	H	2	1	**104b**	[7, 6]	58	96
Et	H	3	1	**104c**	[8, 6]	32	97
Et	Me	1	1	**104d**	[6, 6]	45	97
Me	H	1	1	**104e**	[6, 6]	34	96
Bu	H	1	1	**104f**	[6, 6]	52	93
Et	H	1	0	**104g**	[6, 5]	—[b]	—
Et	H	1	2	**104h**	[6, 7]	56	96

a) Isolated yield over three steps of all-*trans* isomer.
b) Only a small amount (< 10%) of *cis*-fused **104g** was detected by GC.

Very recently, a catalytic enantioselective route to prostaglandin E_1 methyl ester was developed based on a tandem 1,4-addition-aldol reaction [84].

7.5 Conclusions

Organozinc reagents have played an important role in the development of efficient catalysts for enantioselective carbon–carbon bond-formation by 1,4-addition to α,β-unsaturated compounds. Important advantages of the use of organozinc reagents are the option of starting with alkenes (through hydroboration-zinc transfer procedures) and the tolerance towards functional groups.

The use of copper catalysts based on chiral phosphorus ligands to assist 1,4-additions of dialkylzinc reagents has in recent years produced major breakthroughs, with excellent enantioselectivities. A number of monodentate and bidentate phosphoramidites, phosphites, phosphonites, and phosphines are now available as chiral ligands for alkyl transfer to a variety of cyclic and acyclic enones. So far,

excellent stereocontrol has proven especially attainable in alkyl transfer to various cyclic enones. The modular structures of most of these chiral phosphorus ligands should be highly beneficial for the future fine-tuning of the catalysts to deliver high enantioselectivities for specific classes of substrates.

A few catalysts display activity and selectivity levels sufficiently high for application in organic synthesis. Their utilization in the synthesis of a number of chiral building blocks and target molecules is emerging as summarized in the second part of this chapter.

For the transfer of aryl and alkenyl groups to enones, Hayashi's procedure, employing the corresponding boronic acids and a rhodium-BINAP catalyst, is the method of choice at present [24, 25]. For the transfer of alkyl groups to cyclic enones the use of dialkylzinc reagents in the presence of copper-phosphoramidite catalysts is superior. Although the first examples of highly enantioselective 1,4-additions of R_2Zn reagents to nitroalkenes have been reported, similar catalytic methods for numerous other classes of α,β-unsaturated compounds still need to be developed.

Furthermore, the recent successes with R_2Zn reagents should certainly stimulate new investigations into enantioselective 1,4-additions of Grignard and organolithium reagents. The elucidation of the mechanisms and the factors governing stereocontrol in these catalytic systems are other major challenges for the near future.

Acknowledgements

We are grateful to the co-workers who participated in the studies summarized in this chapter; their names are given in the references. We thank Ing. Marc van Gelder for his contributions with numerous HPLC and GC separations and Dr. A. J. Minnaard for suggestions and discussions. Financial support from The Netherlands Foundation for Scientific Research and from the European Community is gratefully acknowledged.

References and Notes

1 Comprehensive Organic Synthesis, B. M. Trost, I. Fleming (Eds.), Pergamon, Oxford, **1991**, Vol. 4.

2 P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press, Oxford, **1992**.

3 a) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290; *Angew. Chem. Int. Ed.* **1997**, *36*, 1236; b) J. Leonard, *Contemp. Org. Synth.* **1994**, *1*, 387.

4 a) *Organocopper Reagents, A Practical Approach*, R. J. K. Taylor (Ed.), Oxford University press, Oxford, **1994**; b) B. H. Lipshutz in *Organometallics in Synthesis*, M. Schlosser (Ed.), Wiley, Chichester, **1994**; c) B. H. Lipshutz, *Acc. Chem. Res.* **1997**, *30*, 277.

5 a) M. Kumada, *Pure Appl. Chem.* **1980**, *52*, 669; b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; c) D. Seebach, L.

Behrendt, D. Felix, *Angew. Chem.* **1991**, *103*, 991; *Angew. Chem. Int., Ed. Engl.* **1991**, *30*, 1008; d) R. O. Duthaler, A. Hafner, *Chem. Rev.* **1992**, *92*, 807.
6 B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346.
7 B. E. Rossiter, N. M. Swingle, *Chem. Rev.* **1992**, *92*, 771.
8 B. L. Feringa, A. H. M. de Vries in *Asymmetric Chemical Transformations*, M. D. Doyle (Ed.), *Advances in Catalytic Processes 1*, Jai Press, Greenwich, CT, **1995**, 151.
9 K. Tomioka, Y. Nagaoka in *Comprehensive Asymmetric Catalysis*, E. N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Springer, Berlin, **1999**, pp 1105–1120.
10 N. Krause, *Angew. Chem. Int. Ed.* **1998**, *37*, 283.
11 M. P. Sibi, S. Manyem, *Tetrahedron*, **2000**, *56*, 8033.
12 N. Krause, A. Hoffmann-Röder, *Synthesis*, **2001**, 171.
13 G. M. Villacorta, C. P. Rao, S. J. Lippard, *J. Am. Chem. Soc.* **1988**, *110*, 3175.
14 F. Lambert, D. M. Knotter, M. D. Janssen, M. van Klaveren, J. Boersma, G. van Koten, *Tetrahedron: Asymmetry* **1991**, *2*, 1097.
15 M. Spescha, G. Rihs, *Helv. Chim. Acta* **1993**, *76*, 1219.
16 a) M. Kanai, K. Tomioka, *Tetrahedron Lett.* **1995**, *36*, 4275; b) Y. Nakagawa, M. Kanai, Y. Nagaoka, K. Tomioka, *Tetrahedron* **1998**, *54*, 10295; c) M. Kanai, Y. Nagakawa, K. Tomioka, *ibid.* **1999**, *55*, 3843; d) K. Tomioka, Y. Nagakawa, *Heterocycles* **2000**, *52*, 95; e) Y. Nagakawa, K. Matsumoto, K. Tomioka, *Tetrahedron* **2000**, *56*, 2857.
17 a) D. Seebach, G. Jaeschke, A. Pichota, L. Audergon, *Helv. Chim. Acta* **1997**, *80*, 2515; b) A. Pichota, P. S. Pregosin, M. Valentini, M. Wörle, D. Seebach, *Angew. Chem. Int. Ed.* **2000**, *39*, 153.
18 a) Q.-L. Zhou, A. Pfaltz, *Tetrahedron Lett.* **1993**, *34*, 7725; b) Q.-L. Zhou, A. Pfaltz, *Tetrahedron* **1994**, *50*, 4467.
19 E. L. Stangeland, T. Sammiaka, *Tetrahedron* **1997**, *53*, 16503.
20 E. J. Corey, R. Naef, F. Hannon, *J. Am. Chem. Soc.* **1986**, *108*, 7114.
21 K. Tanaka, J. Matsui, H. Suzuki, *J. Chem. Soc., Perkin Trans. 1*, **1993**, 153.
22 a) M. Shindo, K. Koga, K. Tomioka, *J. Am. Chem. Soc.* **1992**, *114*, 8732; b) K. Tomioka, M. Shindo, K. Koga, *Tetrahedron Lett.* **1993**, *34*, 681.
23 a) Y. Asano, A. Iida, K. Tomioka, *Tetrahedron Lett.* **1997**, *38*, 8973; b) Y. Asano, A. Iida, K. Tomioka, *Chem Pharm. Bull.* **1998**, *46*, 184.
24 a) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579; b) Y. Takaya, M. Ogasawara, T. Hayashi, *Tetrahedron Lett.* **1999**, *40*, 6957.
25 T. Hayashi, T. Senda, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **1999**, *121*, 11591.
26 a) R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49; b) K. Soai, T. Shibata in *Comprehensive Asymmetric Catalysis*, E. N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Springer, Berlin, **1999**, pp 911–922; c) K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833.
27 W. Carruthers in *Comprehensive Organometallic Chemistry*, G. Wilkinson, F. G. A. Stone, E. W. Abel (Eds.), Pergamon, Oxford, **1982**, Vol. 7, pp 661–729.
28 P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.
29 J. Boersma in *Comprehensive Organometallic Chemistry*, G. Wilkinson, F. G. A. Stone, E. W. Abel (Eds.), Pergamon, Oxford, **1982**, Vol. 2, pp 823–862.
30 D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059.
31 a) A. E. Greene, J.-P. Lansard, J.-L. Luche, C. Petrier, *J. Org. Chem.* **1984**, *49*, 931; b) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; c) Y. Tamaru, H. Tanigawa, T. Yamamoto, Z. Yoshida, *Angew. Chem.* **1989**, *101*, 358; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 351; d) L. Zhu, R. M. Wehmeyer,

R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445; e) B. H. Lipshutz, M. R. Wood, R. Tirado, *J. Am. Chem. Soc.* **1995**, *117*, 6126; f) M. J. Rozema, C. Eisenberg, H. Lütjens, R. Ostwald, K. Belyk, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 3115.

32 B. H. Lipshutz, *Synthesis* **1987**, 325.

33 F. Langer, A. Devasagayaraj, P.-Y. Chavant, P. Knochel, *Synlett* **1994**, 410.

34 a) B. Weber, D. Seebach, *Angew. Chem.* **1992**, *104*, 961; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 84; b) J. L. von dem Bussche-Hünnefeld, D. Seebach, *Tetrahedron* **1992**, *48*, 5719.

35 A. Alexakis, J. Frutos, P. Mangeney, *Tetrahedron: Asymmetry* **1993**, *4*, 2427.

36 R. Hulst, N. K. de Vries, B. L. Feringa, *Tetrahedron: Asymmetry* **1994**, *5*, 699.

37 A. H. M. de Vries, A. Meetsma, B. L. Feringa, *Angew. Chem.* **1996**, *108*, 2526; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2374.

38 B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. de Vries, *Angew. Chem.* **1997**, *109*, 2733; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2620.

39 For ligand (*S*, *S*, *S*)-**18** the *ee* was incorrectly reported to be 75% (see reference 38)

40 N. Krause, A. Gerold, *Angew. Chem.* **1997**, *109*, 184; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 187.

41 E. Nakamura, S. Mori, *Angew. Chem.* **2000**, *112*, 3902; *Angew. Chem. Int. Ed.* **2000**, *39*, 3750.

42 M. Kitamura, T. Miki, K. Nakano, R. Noyori, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 999.

43 a) Y. Aoki, I. Kuwajima, *Tetrahedron Lett.* **1990**, *31*, 7457; b) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1985**, *26*, 6015, 6019.

44 a) C. Ullenius, B. Christenson, *Pure Appl. Chem.* **1988**, *60*, 57; b) N. Krause, R. Wagner, A. Gerold, *J. Am. Chem. Soc.* **1994**, *116*, 381.

45 L. A. Arnold, R. Imbos, A. Mandoli, A. H. M. de Vries, R. Naasz, B. L. Feringa, *Tetrahedron* **2000**, *56*, 2865.

46 F.-Y. Zhang, A. S. C. Chan, *Tetrahedron: Asymmetry* **1998**, *9*, 1179.

47 a) A. K. H. Knöbel, I. H. Escher, A. Pfaltz, *Synlett* **1997**, 1429; b) I. H. Escher, A. Pfaltz, *Tetrahedron* **2000**, *56*, 2879.

48 M. T. Reetz, *Pure Appl. Chem.* **1999**, *71*, 1503.

49 a) M. Yan, L.-W. Yang, K.-Y. Wong, A. S. C. Chan, *Chem. Commun.* **1999**, 11; b) M. Yan, A. S. C. Chan, *Tetrahedron Lett.* **1999**, *40*, 6645; c) M. Yan, Z.-Y. Zhou, A. S. C. Chan, *Chem. Commun.* **2000**, 115.

50 O. Huttenloch, J. Spieler, H. Waldmann, *Chem. Eur. J.* **2000**, *6*, 671.

51 A. Alexakis, J. Burton, J. Vastra, P. Mangeney, *Tetrahedron: Asymmetry* **1997**, *8*, 3987.

52 E. Keller, J. Maurer, R. Naasz, T. Schrader, A. Meetsma, B. L. Feringa, *Tetrahedron: Asymmetry* **1998**, *9*, 2409.

53 A. Alexakis, J. Vastra, J. Burton, C. Benhaim, P. Mangeney, *Tetrahedron Lett.* **1998**, *39*, 7869.

54 A. Alexakis, J. Burton, J. Vastra, C. Benhaim, X. Fournioux, A. van den Heuvel, J.-M. Levêque, F. Mazé, S. Rosset, *Eur. J. Org. Chem.* **2000**, 4011.

55 X. Hu, H. Chen, X. Zhang, *Angew. Chem.* **1999**, *111*, 3720; *Angew. Chem. Int. Ed.* **1999**, *38*, 3518.

56 T. Mori, K. Kosaka, Y. Nagakawa, Y. Nagaoka, K. Tomioka, *Tetrahedron Asymmetry* **1998**, *9*, 3175.

57 Y. Yamanoi, T. Imamoto, *J. Org. Chem.* **1999**, *64*, 2988.

58 a) O. Pàmies, G. Net, A. Ruiz, C. Claver, S. Woodward, *Tetrahedron: Asymmetry* **2000**, *11*, 871; b) O. Pàmies, G. Net, A. Ruiz, C. Claver, *Tetrahedron: Asymmetry* **1999**, *10*, 2007.

59 G. Delapierre, T. Constantieux, J. M. Brunel, G. Buono, *Eur. J. Org. Chem.* **2000**, 2507.

60 I. Chataigner, C. Gennari, U. Piarulli, S. Ceccarelli, *Angew. Chem.* **2000**, *112*, 953; *Angew. Chem. Int. Ed.* **2000**, *39*, 916.

61 S. J. Degrado, H. Mizutani, A. M. Hoveyda, *J. Am. Chem. Soc.* **2001**, *123*, 755.

62 A. Mandoli, L. A. Arnold, A. H. M. de Vries, P. Salvadori, B. L. Feringa, *Tetrahedron: Asymmetry* **2001**, *12*, 1929.

63 A. Alexakis, C. Benhaim, X. Fournioux, A. van den Heuvel, J.-M. Levêque, S. March, S. Rosset, *Synlett* **1999**, 1811.

64 M. Kitamura, T. Miki, K. Nakano, R. Noyori, *Tetrahedron Lett.* **1996**, *37*, 5154.

65 a) G. Sarakinos, E. J. Corey, *Org. Lett.* **1999**, *1*, 811; b) G. P. J. Hareau, M. Koiwa, S. Hikichi, F. Sato, *J. Am. Chem. Soc.* **1999**, *121*, 3640; c) T. Hanazawa, M. Koiwa, G. P. J. Hareau, F. Sato, *Tetrahedron Lett.* **2000**, *41*, 2659 and references cited therein.

66 Recent non-enzymatic kinetic resolutions, c.f.: a) E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421; b) S. Bellemin-Laponnaz, J. Tweddell, G. Ruble, F. M. Breitling, G. C. Fu, *Chem. Commun.* **2000**, 1009; c) J. Yun, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 767; d) X. Feng, L. Shu, Y. Shi, *J. Am. Chem. Soc.* **1999**, *121*, 11002.

67 a) H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249; b) A. H. Hoveyda, M. T. Didiuk, *Curr. Org. Chem.* **1998**, *2*, 489.

68 a) E. J. Corey, F. J. Hannon, *Tetrahedron Lett.* **1990**, *31*, 1393; b) T. A. Blumenkopf, C. H. Heathcock, *J. Am. Chem. Soc.* **1983**, *105*, 2354; c) N. L. Allinger, C. K. Riew, *Tetrahedron Lett.* **1966**, 1269; d) C. H. Heathcock, T. C. Germroth, S. L. Graham, *J. Org. Chem.* **1979**, *44*, 4481.

69 R. Naasz, L. A. Arnold, A. J. Minnaard, B. L. Feringa, *Angew. Chem.* **2001**, *113*, 953; *Angew. Chem. Int. Ed.* **2001**, *40*, 927.

70 a) C. H. Wong, G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Elsevier, London, **1994**; b) H. van der Deen, A. D. Cuiper, R. P. Hof, A. van Oeveren, B. L. Feringa, R. M. Kellogg, *J. Am. Chem. Soc.* **1996**, *118*, 3801.

71 It is not clear why the selectivity factor is not higher in this resolution, as might be expected from Fig. 7.10. One possible explanation is that the kinetics with Me_2Zn might be more complicated than with the other zinc reagents, in which case the formula in Ref. 67a would no longer be valid; see also: D. G. Blackmond, *J. Am. Chem. Soc.* **2001**, *123*, 545.

72 R. Imbos, M. H. G. Brilman, M. Pineschi, B. L. Feringa, *Org. Lett.* **1999**, *1*, 623.

73 R. Imbos, A. J. Minnaard, B. L. Feringa, *Tetrahedron*, **2001**, *57*, 2485.

74 P. Knochel, D. Seebach, *Synthesis*, **1982**, 1017.

75 H. Schäfer, D. Seebach, *Tetrahedron* **1995**, *51*, 2305.

76 N. Sewald, V. Wendisch, *Tetrahedron: Asymmetry* **1998**, *9*, 1341.

77 A. Alexakis, C. Benhaim, *Org. Lett.* **2000**, *2*, 2579.

78 J. P. G. Versleijen, PhD Thesis, University of Groningen, 2001.

79 J. P. G. Versleijen, A. M. van Leusen, B. L. Feringa, *Tetrahedron Lett.* **1999**, *40*, 5803.

80 R. Naasz, L. A. Arnold, M. Pineschi, E. Keller, B. L. Feringa, *J. Am. Chem. Soc.* **1999**, *121*, 1104.

81 Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615.

82 B. L. Feringa in *Transition Metals for Organic Synthesis*, M. Beller, C. Bolm (Eds.), Wiley, Weinheim, **1998**, Vol. 2, pp. 307–315.

83 R. Naasz, L. A. Arnold, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2001**, 735.

84 L. A. Arnold, R. Naasz, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2001**, *123*, 5841.