Phosphoramidites: Marvellous Ligands in Catalytic Asymmetric Conjugate Addition

BEN L. FERINGA

Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands
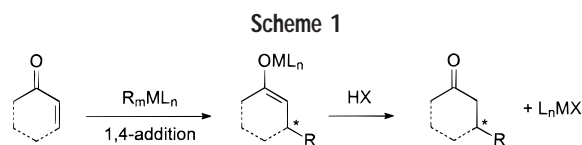
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ABSTRACT

The development of an efficient catalytic system for enantioselective carbon–carbon bond formation by 1,4-addition of organometallic reagents (organolithium, Grignard, and organozinc reagents) to enones is a major challenge in organic synthesis. This Account presents the breakthrough realized in this field using chiral phosphoramidite ligands for copper-catalyzed dialkylzinc additions. Applications in catalytic routes to cycloalkanones as well as tandem and annulation procedures with excellent enantioselectivities are discussed.

Introduction

The challenge to develop new catalytic methods and to replace existing synthetic procedures, which often rely on the use of stoichiometric amounts of auxiliary reagents, by catalytic ones has captivated the chemical community.[1] This so-called "catalytic switch" is expected to have a profound influence on the future of fine chemical manufacturing and can drastically change our synthetic repertoire. It also has stimulated the awareness that ultimately integrated multistep catalytic transformations might be feasible. Few areas in chemistry have seen the pace of progress found in asymmetric catalysis in the past decades. Today a considerable number of catalytic systems are known which provide enantioselectivities exceeding 95%.[2] Catalytic enantioselective carbon–carbon bond-forming reactions include Diels–Alder and ene reactions, dialkylzinc additions to aldehydes, aldol (and related) transformations, coupling reactions, allylic substitutions, and cyclopropanations. Among the most widely used methods for the construction of carbon–carbon bonds are conjugate addition reactions of carbon nucleophiles to α,β-unsaturated compounds.[3] For instance, these additions are key steps in the synthesis of numerous biological active compounds including steroids, prostaglandins, and terpenes. The broad potential, combined with the large variety of donor and acceptor compounds that can be

Scheme 1

employed, has been a strong impetus to develop enantioselective variants.

Major advances in the development of catalytic asymmetric Michael additions[4] and enantioselective conjugate additions of organocopper compounds with chiral non-transferable ligands[5,6] have been reported.

However, despite numerous attempts over more than two decades, it is only recently that chiral metal catalysts have been found that show enantioselectivities up to the 90% level in 1,4-additions of Grignard, organolithium, or organozinc reagents, albeit often with limited scope[2a,6] (Scheme 1).

Following Lippard's seminal report on the asymmetric addition of *n*-BuMgBr to 2-cyclohexen-1-one using a chiral *N,N'*-dialkylaminotropone imine copper(I) catalyst,[7] a variety of ligands were examined, and these studies revealed that the best results are usually obtained with copper(I) complexes with soft sulfur or phosphorus ligands.[2a,8] Challenged by the idea to design a general and enantioselective catalyst for this important class of reactions and fascinated by the spectacular results on the 1,2-addition of dialkylzinc reagents[9] (R_2Zn), we started in 1986 using Zn, Ni, and Cu catalysis. In the quest for chiral ligands and catalysts for 1,4-additions of R_2Zn reagents, we experienced the complex nature of many of these catalytic systems. We decided to deviate our strategy to uncover high reactivity first. The breakthrough came when we introduced phosphoramidites as ligands for asymmetric catalysis. As a result of the remarkable reactivity and selectivity of copper complexes based on these novel chiral ligands, the first catalytic 1,4-additions of R_2Zn reagents with complete enantiocontrol were realized.[10] The use of phosphoramidites in catalytic conjugate addition to cyclic and acyclic enones is the main topic of this Account, with emphasis on the progress made by our research group.
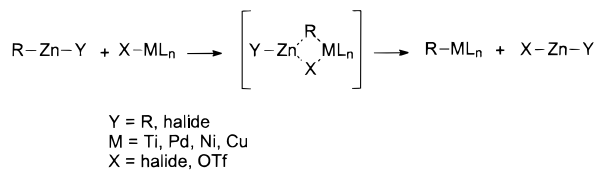
Dialkylzinc Reagents

Recent years have seen a remarkable revival of the use of organozinc reagents in organic synthesis.[11] There were two important considerations in our focus on R_2Zn reagents: (1) Is it possible to use an enone and an alkene as the starting materials? (2) Are functional groups tolerated (a feature not easily accomplished with organolithium or Grignard reagents) (Scheme 2)?

Although R_2Zn reagents often react sluggishly with carbonyl compounds, effective catalysis can be achieved by complexes based on several ligands and transition metals. The catalytic effect has been explained by changes in geometry and bond energy of the zinc reagents or by transmetalation.[11] In copper-catalyzed 1,4-additions of R_2-
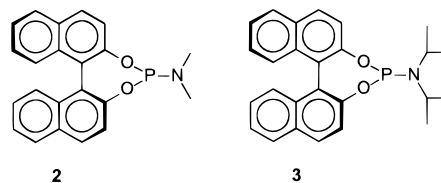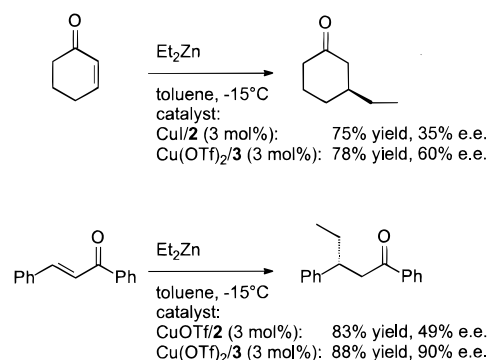
Scheme 2

FG = functional group

Scheme 3

Y = R, halide
M = Ti, Pd, Ni, Cu
X = halide, OTf
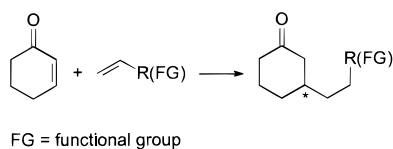
Zn reagents, a key step is alkyl transfer from Zn to Cu to generate in situ an organocopper reagent (Scheme 3), although other formulations such as bimetallic Zn/Cu reagents might be given.[11]

The ability of organozinc reagents to undergo transmetalation permits their conversion in more reactive organometallic reagents RML_n, which has been demonstrated with Ni,[12] Cu,[13] Pd,[14] and Ti.[15] Alkyl transfer from diorganozinc reagents to enones can also be effected by nickel catalysts. Enantioselective versions of these alkyl-transfer reactions to acyclic enones, in particular chalcones, have been reported, employing several chiral ligands including diamines, pyridine methanols, proline amides, and amino alcohols.[16] A notable accomplishment is the 90% enantiomeric excess (ee) reached by Soai in the conjugate addition of Et_2Zn to acyclic enones using a nickel-ephedrine-based catalyst.[16e] Trivalent phosphorus compounds represent another class of ligands that have been used for a considerable time in stoichiometric conjugate additions.[17] The first application in a catalytic addition of Et_2Zn to cyclohexenone, which resulted in 32% ee, was reported by Alexakis.[18] Detailed studies by Bolm[19] and our group[20] revealed that, like the asymmetric copper-catalyzed conjugate addition of Grignard reagents,[8] these carbon−carbon bond formations are highly sensitive to a large number of factors that govern catalyst activity and enantioselectivity. In addition to the structures of the enones and the ligands, these are inter alia the nature of the solvent, Ni−ligand ratio, counterions, temperature, and addition rate.

A very important feature is the apparent lack of one unique and highly reactive catalyst. The dependence of the stereocontrol on the concentration of the catalyst as well as the conversion and the presence of nonlinear effects points to equilibria between several (diastereo-meric) catalytically active species.

## Copper Phosphoramidite Catalysts in Conjugate Addition

The numerous studies, including our own, on asymmetric 1,4-addition of organometallic reagents mentioned above did not clearly show us the key elements for the realization of complete stereocontrol. Apparently, modest enantio-selectivities are rather easily achieved with structurally diverse chiral ligands.

Scheme 4

We realized that several competing catalytically active complexes, including achiral ones, might be present. Therefore, the key question in our design of an enantioselective catalytic system was that of how to achieve very efficient ligand-accelerated catalysis.[21] This concept involves the presence of a chiral ligand that leads to a highly reactive catalyst, strongly favoring an enantioselective pathway over any nonselective pathway.

Since relatively hard (amino alcohols) as well as soft (thiols, phosphines) chiral ligands result in active catalysts for 1,4-additions, we anticipated that the catalytic activity might be enhanced by fine-tuning the electronic properties of trivalent phosphorus ligands. Toward this goal we have introduced phosphoramidites,[22] which have electron donor−acceptor properties typically between those of arylphosphines and arylphosphites.

In contrast to the large number of phosphines and phosphites frequently employed as ligands in asymmetric catalysis, phosphoramidites have not been used, presumably because of the sensitivity toward hydrolysis attributed to this class of compounds.

We discovered that chiral phosphoramidites **1** based on 2,2′-binaphthol are, however, not only remarkably stable but also excellent ligands for Cu-catalyzed 1,4-addition of R_2Zn to cyclic and acyclic enones, as shown in Scheme 4.[23]

1, R = alkyl
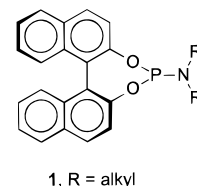
Detailed examination of the Et_2Zn addition to model substrates chalcone and cyclohexenone employing **1**−**3** mol % of catalyst, prepared in situ from CuI or CuOTf and phosphoramidite **2**, revealed the following features: (1)
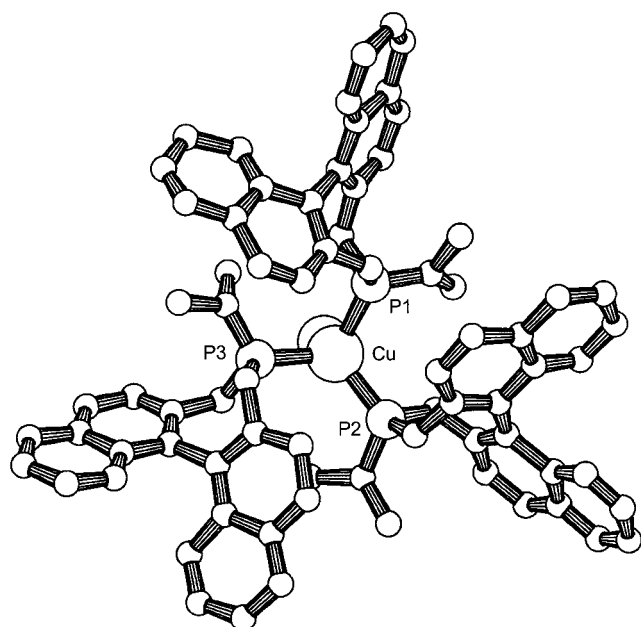
FIGURE 1. X-ray structure of the CuI complex of ligand **2**.

Excellent chemo- and regioselectivities (>95%) for the 1,4-adducts. (2) Relatively short reaction times, as complete conversions are reached in less than 3 h, even at −35 °C. (3) Significant enantioselectivities for both cyclic and acyclic enones using the same catalyst. This was an exciting observation, as the latter feature is notably absent with almost all other catalysts for asymmetric 1,4-addition of organometallic reagents.

Of all the 1,4-additions to enones we had been studying so far, the copper−phosphoramidite catalyst turned out to be by far the best in providing a clean and fast formation of β-alkylated ketones. We were delighted to find that the high catalytic activity was the result of a strong ligand accelerating effect.

Important improvements, including better solubility of the catalyst and slightly enhanced ee values, were found when Cu(OTf)$_2$ was used for the in situ preparation of the catalyst instead of CuI or CuOTf. Apparently, in situ reduction to the corresponding Cu(I) complex takes place. For application in synthesis, the easy handling of Cu(OTf)$_2$ compared to CuOTf is probably most significant.

Once we had realized our first major goal—efficient ligand-accelerated catalysis—we focused on reaching high enantioselectivity by ligand modification. Structural variations of the phosphoramidites can be easily explored by a modular variation of the amine and binaphthol moieties. The X-ray structure of the CuI complex of phosphoramidite **2** guided us, as it shows that the obvious positions for ligand modification are the amine moiety and the 3,3′-positions of the binaphthyl part of the ligand. Substituents at these positions will point toward an alkyl moiety or an enone bound to copper (vide infra) (Figure 1).

The most significant improvements of the ligands with respect to the enantioselectivity in the catalytic 1,4-addition are observed when sterically demanding substituents are introduced at nitrogen. When the diisopropylamine derived ligand **3** is employed, ee's of 60% and 90%
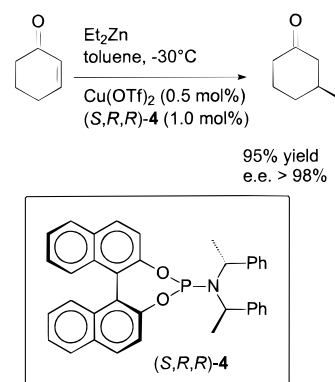
Scheme 5

Table 1. Enantioselective 1,4-Addition of R$_2$Zn Compounds to Cyclic Enones Catalyzed by Cu(OTf)$_2$/4

R	R^1	n	yield (%)	ee (%)
C$_2$H$_5$	H	1	94	>98
C$_2$H$_5$	H	0	75	10
C$_2$H$_5$	H	2	95	>98
C$_2$H$_5$	H	3	95	97
C$_2$H$_5$	CH$_3$	1	74	>98
C$_2$H$_5$	C$_6$H$_5$	1	93	>98
CH$_3$	H	1	72	>98
CH$_3$	CH$_3$	1	68	>98
C$_7$H$_{15}$	H	1	95	95
i-C$_3$H$_7$	H	1	95	94
(CH$_2$)C$_6$H$_5$	H	1	53	95
(CH$_2$)$_5$OAc	H	1	77	95
(CH$_2$)$_3$CH(OC$_2$H$_5$)$_2$	H	1	91	97

for cyclohexenone and chalcone, respectively, are reached (Scheme 4).

A breakthrough was achieved when the nonchiral amine moiety in the (S)-2,2′-binaphthol-based phosphoramidite ligand was replaced by a second chiral structural unit, that is, the sterically demanding (R,R)-bis-(1-phenylethyl)amine, resulting in phosphoramidite **4**. A matched combination results in a highly selective catalyst for the addition of diorganozinc reagents to cyclohexenone (Scheme 5).[10]

Even when only 0.5 mol % catalyst (Cu-to-ligand ratio 1:2) is employed, excellent yields and ee values exceeding 98% are obtained, and recently turnover numbers greater than 3000 were realized.[24] The scope and efficiency of this novel monodentate ligand **4** is remarkable, as is illustrated in Table 1 for cyclic enones.

When the new chiral copper phosphoramidite catalyst is used, enantioselectivities up to 90% for acyclic enones (chalcones)[25] and >98% for cyclic enones (cyclohexenones)[10] are now routinely obtained.[26]

Catalytic Cycle

A proposed pathway for the catalytic 1,4-addition, based on mechanistic studies in organocuprate and zincate chemistry[6,11] and the results obtained by us so far,[10,23,25]
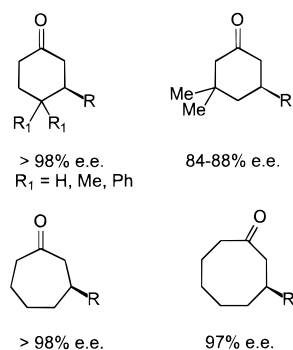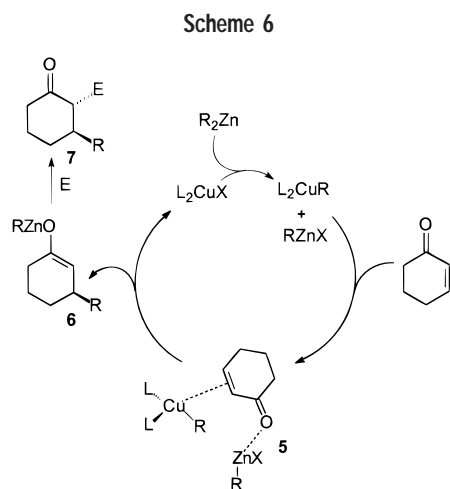
FIGURE 2. Cycloalkanones obtained by enantioselective catalytic 1,4-addition using R$_2$Zn and catalyst Cu^{II}(OTf)$_2$/**4**. Substituents R are given in Table 1.

Scheme 6

Scheme 7

is shown in Scheme 6. Starting either with a Cu(I)−phosphoramidite complex or preferably the Cu(OTf)$_2$−phosphoramidite complex, transfer of an alkyl fragment from R$_2$Zn to the copper center takes place. Complexation of the alkylzinc fragment to the enone carbonyl and formation of the π-complex of the copper alkyl species with the enone results in complex **5**. Due to the high levels of stereocontrol reached in this catalytic cycle, **5** might well be formulated as a bimetallic complex, leading to a fixed conformation of the enone. Subsequent alkyl transfer generates zinc enolate **6**, which upon protonation affords the β-substituted cycloalkanone **7**, or alternatively **6** may be trapped in tandem protocols (vide infra).

The optimum ligand-to-copper ratio of 2, the nearly identical selectivities with mono- and bidentate phosphoramidites (except for cyclopentenones),[23,25b] and the observation of nonlinear effects[25a] strongly point to the presence of two ligands in the active catalyst.

Cyclic Enones

The scope of the novel catalytic 1,4-addition includes cyclic enones with different ring sizes and substituent patterns leading to 3-substituted cyclohexanones, cycloheptanones, and cyclooctanones with ee's exceeding 97% (Figure 2).[10,27] Surprisingly, the enantioselectivity is not affected in the case of 4,4′-disubstituted cyclohexenones (e.g., dialkyl, diphenyl), whereas for 5,5′-disubstituted
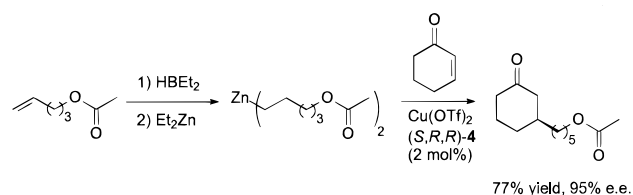
cyclohexenones a slight depletion of ee is observed, presumably due to unfavorable 1,3-diaxial interactions.

The catalytic 1,4-addition of a variety of functionalized dialkylzinc reagents proceeds with comparable enantioselectivities (Scheme 7, Table 1). Starting with the corresponding alkenes, the R$_2$Zn reagents are readily prepared by hydroboration and subsequent zinc exchange according to the procedure of Knochel[28] or via the corresponding Grignard reagent. It is particularly noteworthy that the catalyst tolerates ester and acetal functionalities.

In sharp contrast with the uniformly high enantioselectivity obtained when the ring size of the enone is increased, the very low selectivity (10% ee with ligand **4**) that is found in the 1,4-addition of diethylzinc to cyclopentenone is remarkable. Employing a binaphthol-based phosphite ligand, Pfaltz was able to raise the ee to 72% in this addition.[29] We followed two approaches involving ligand modifications that led to significant improvements in the case of cyclopentenone. The first approach involves a Taddol-based phosphoramidite (**8**) in the presence of molecular sieves,[32] whereas the second is based on bis-phosphoramidite ligand **9**, leading to 83% ee.[25b]
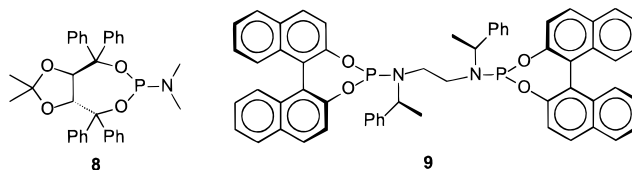
However, raising enantioselectivities to the >95% level in catalytic routes to the (synthetically important) cyclopentanone building blocks is a still major challenge.

Conjugate Additions to Cyclohexadienones

Chiral synthons derived from 4,4-disubstituted cyclohexadienones are highly attractive due to their multifunctional nature. Conjugate addition to symmetric dienones results in desymmetrization of the prochiral dienone moiety[30] (Scheme 8a). When the two substituents are equal, as is the case with benzoquinone monoacetals **10**, side selective—Re versus Si face—addition of the organometallic reagent will afford a single stereocenter. Enantioselectivities ranging from 85% to 99% were found, depending on the size of the acetal moiety and the nature of the R$_2$Zn reagents. For example, 4,4′-dimethoxy-5-methylcyclohexenone (**16**) is readily obtained in 76% isolated yield with a rewarding 99% ee (Figure 3).

An intriguing question was posed to us in the case of cyclohexadienones with two different substituents, i.e., an alkoxy group and an alkyl group, at the 4-position (Scheme
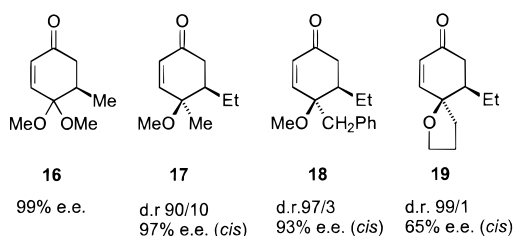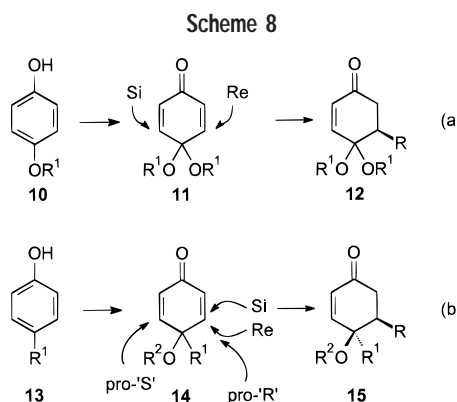
FIGURE 3. Cyclohexenones from the catalytic 1,4-addition to cyclohexadienones

Scheme 8

8b). Will the chiral copper−phosphoramidite catalyst be able to distinguish the *Re/Si* faces and the *pro-R/pro-S* positions in dienone **14**, leading to two stereocenters in a single step? It was gratifying to find that, indeed, the C5-alkyl group was introduced cis to the alkoxy moiety at the C4-position.[30] Diastereoselectivities up to 99/1 and ee's up to 97% for the major diastereoisomers are found (Figure 3).

This catalytic procedure allows an attractive two-step route to nearly enantiomerically pure cyclohexenones starting from phenols.

Tandem Conjugate Addition−Aldol Reactions

Inspired by Noyori's results on tandem additions of organozinc reagents,[31] we anticipated that the zinc enolate, resulting from the conjugate addition, might be trapped by an aldehyde in a subsequent aldol reaction.[32] The first catalytic regio- and enantioselective three-component coupling of organozinc reagents was, indeed, achieved, affording *trans*-2,3-disubstituted cyclohexanones with ee's exceeding 90% in all cases examined (Scheme 9).[10] The formation of *erythro−threo* mixtures (1:1−1:2 ratios) is the result of poor stereocontrol at the exocyclic stereocenter in the aldol step. The tandem addition (1.2 mol % catalyst) of Me$_2$Zn and propanal to cyclohexenone, providing diketone **20** (after oxidation) in 81% yield with 97% ee, is an illustrative example.

Catalytic Enantioselective Annulation Methodology

The finding that the copper−phosphoramidite catalyst tolerated functionalized dialkylzinc reagents constitutes the foundation for novel catalytic enantioselective annulation methods. The Hajos−Parrish asymmetric version

Scheme 9
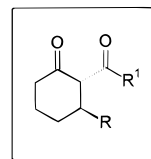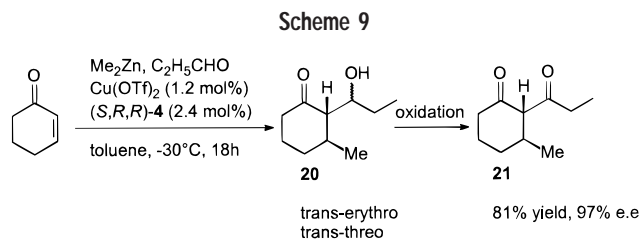
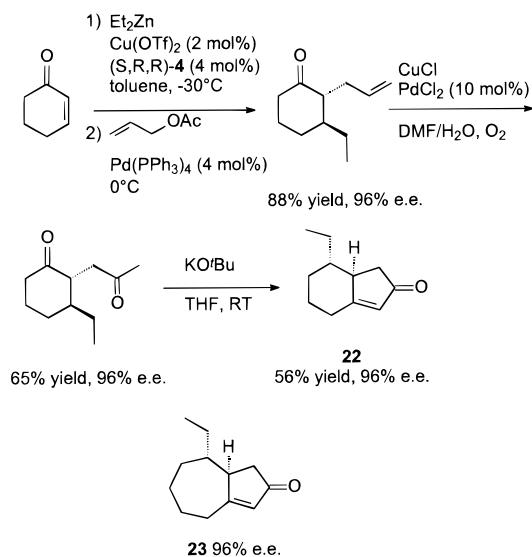| R	R^1	yield (%)	e.e. (%)
C$_2$H$_5$	C$_6$H$_5$	88	95
CH$_3$	C$_2$H$_5$	81	97
CH$_3$	m-BrC$_6$H$_4$	81	97
CH$_3$	C$_6$H$_5$	67	91
C$_2$H$_5$	CHCH$_2$	92	95
CH$_3$	CHCH$_2$	75	97

Scheme 10

a) 1,4-addition, b) aldol
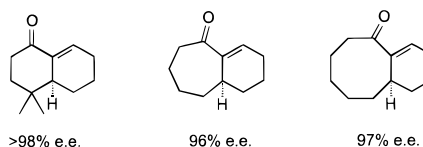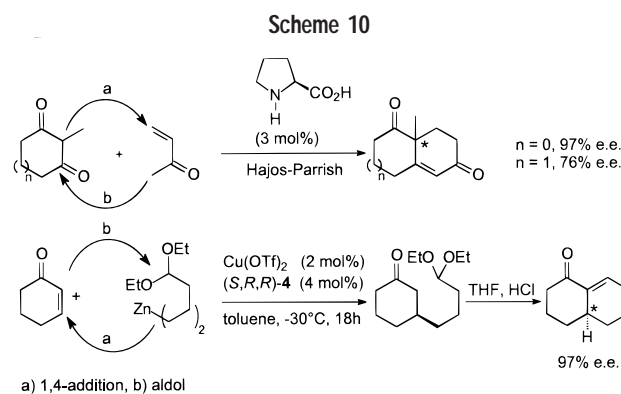
of the Robinson annulation is one of the most prominent protocols in the construction of carbocyclic compounds (Scheme 10a), frequenty used in the synthesis of steroids and terpenes.[33] We envisioned that an alternative method might be developed employing a C4-acetal-functionalized dialkylzinc reagent followed by in situ acetal hydrolysis and ring closure of the resulting 4-substituted cyclohexanone (Scheme 10b).

Although the substituent pattern in the decalone products is different, both methods shown in Scheme 10 involve conjugate addition and aldol cyclization steps. The essential differences between the two methods are that (i) the cycloalkanone is the Michael donor in the first case and the Michael acceptor in the new procedure and (ii) the stereocontrol is exerted in the aldol cyclization step or in the catalytic 1,4-addition step, respectively.

This new protocol affords 6,6-, 6,7-, and 6,8-annulated ring systems with ee's in all cases exceeding 96%.[27] We were particularly pleased to observe that the annulation to 4,4-dimethylcyclohexenone afforded the corresponding decalone in enantiomerically pure form, as this product has a structural feature that is prominent in many natural products.

The formation of carbobicyclic structures with a five- as well as a six-membered ring—the bicyclo[4,3,0]nonene

Scheme 11

88% yield, 96% e.e.

65% yield, 96% e.e.

22
56% yield, 96% e.e.

23 96% e.e.

Scheme 12

(R = C$_6$H$_5$, R^1 = C$_2$H$_5$, 26% e.e.)

24

25
79% yield, 92% e.e.

Scheme 13

n = 0,1,2

50-96% e.e. (S$_N$2'/S$_N$2 = 3-59)

24% yield, 54% e.e.   66% yield, 92% e.e.   76% yield, 96% e.e.

skeleton—is without doubt an important goal. As the levels of enantioselectivity in catalytic 1,4-addition of R$_2$Zn reagents to cyclopentenones were still insufficient for synthetically useful six-membered-ring annulation procedures, we anticipated that the reverse sequence, i.e., annulation of a five-membered ring to a cyclic enone, might be accomplished. Accordingly, a new method was developed based on the regioselective, *trans*-diastereoselective, and enantioselective three-component coupling shown in Scheme 11.[27] The in situ-prepared zinc enolate from the cyclohexenone is trapped in a palladium-catalyzed allylation, which is followed by a palladium-catalyzed Wacker oxidation and aldol cyclization, affording the desired 5,6-annulated product **22**. The same catalytic sequence starting with cycloheptenone affords the 5,7-carbobicyclic product **23**. Excellent diastereo- and enantioselectivities for a variety of bicyclic structures are the most prominent features of these new catalytic annulation procedures (Schemes 10 and 11).

Miscellaneous Applications

The remarkable effect of phosphoramidites, resulting in highly efficient ligand-accelerated catalysis in copper-catalyzed 1,4-additions of organozinc reagents, was also exploited in a number of related C–C bond-forming reactions. When α,β-unsaturated nitroacetates are employed, catalytic 1,4-addition results in β-alkylnitroacetates and, after subsequent Michael addition, α,β-dialkyl-nitroacetates (Scheme 12).[34] Although the stereoselectivity in this process is still rather low, the fact that the nitro group can simply be reduced holds considerable promise for a short catalytic route to a diversity of amino acids and α-alkylated amino acids.

Furthermore, the stereochemical observations made during these studies led us to examine the conjugate addition reaction to 3-nitrocoumarins **24**, with a fixed trans orientation of the aryl and nitro moieties. Much to our delight, high enantioselectivities (up to 92%) were
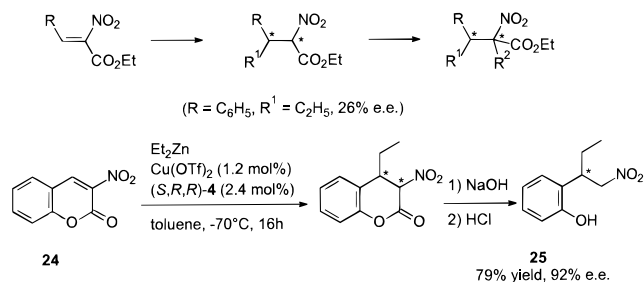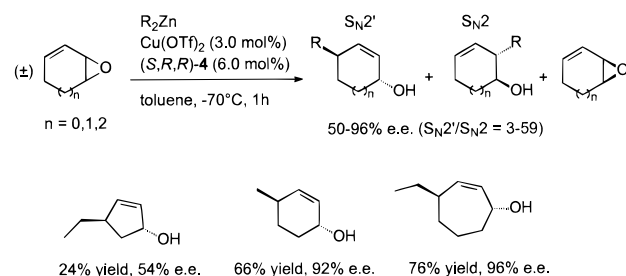
obtained, and subsequent mild decarboxylation afforded a new route to optically active β-arylnitroalkanes.[34]

The report by Lipshutz[35] on a copper-catalyzed cross coupling of functionalized zinc reagents with vinyloxiranes triggered our study toward catalytic enantioselective ring-opening of racemic cyclic 1,3-diene monoepoxides (Scheme 13).[36]

The corresponding allylic alcohols arising from the S$_N$2' pathway were obtained with moderate to high regioselectivity. Both S$_N$2 and S$_N$2' reactions proceed with complete *anti*-selectivity, and the enantioselectivity in these additions reactions, following a kinetic resolution protocol, turned out to be very promising (>90% ee) for 1,3-cyclohexadiene and 1,3-heptadiene monoepoxides. We also found that copper complexes of phosphoramidites are highly effective catalysts for alkylation of related alkynyl epoxides, albeit with modest ee's, affording α-allenic alcohols.[37]

Conclusions

The introduction of chiral phosphoramidites as ligands in copper-catalyzed conjugate addition of organozinc reagents was a delightful event in our long-standing efforts to develop an efficient catalyst for enantioselective carbon–carbon bond formation via 1,4-addition of organometallic reagents. High enantioselectivities are seen in a number of 1,4-additions, related tandem reactions, and annulation methods derived thereof. In particular, the R$_2$Zn addition to cycloalkenones using these catalysts shows activity and selectivity levels sufficiently high for this to be considered as a practical method in organic synthesis. Detailed mechanistic studies are necessary to elucidate the origin of the strong ligand acceleration and excellent stereocontrol found. In view of the remarkable success with phosphoramidites, it is not too far-fetched to predict that many new applications of this class of chiral ligands will be discovered in the near future. The challenge to develop

catalysts with similar activities and selectivities in related carbon–carbon bond formation using organolithium and Grignard reagents remains as vivid as before.

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