Modern Organocopper Chemistry. Edited by Norbert Krause

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Foreword

Copper is one of the oldest transition metals to be used in synthetic organic chemistry. Starting in the 60's, organocopper reagents became among the most popular synthetic tools in the total synthesis of natural product. This is due to the ease of handling and to the chemo-, regio- and stereoselectivities attained with these reagents. Their unique properties for the conjugate addition, for the clean S_N2 substitution, for the mild opening of epoxides, for the carbometallation of triple bonds, etc ... makes them unavoidable reagents for these synthetic transformations.

Over the years, a whole family of reagents evolved with increased selectivity and reactivity. "Homocuprates", "heterocuprates", "higher order cuprates", "mixed cuprates", and others, are terms often employed, and a newcomer chemist may worry about their different properties. Despite a lot of progress in the area of organocopper chemistry there is still a strong lack of knowledge in the mechanistic insights. No reactive intermediates have been trapped, and this "black box" was only considered through analogies with other closely related transition metals or, more recently, through extensive calculations. This is to say that all our knowledge about organocopper chemistry did not came by rational design but through empirical way with experimentation.

Over the years, several review articles appeared on organocopper chemistry. Most often, they cover some aspects or some restricted class of reagents, and they are addressed to chemists knowing already the main reactions of organocopper reagents. In contrast to other transition metals, such as Pd, Ni, Rh etc ... only few books, covering the entire area of organocopper chemistry, have been published. The present book is the most comprehensive and all the most recent advances are extensively discussed: Zn-Cu reagents, Sn and Si-Cu reagents, H-Cu reagents, asymmetric reactions. The reader will learn about the structure of organocopper reagents and about the most updated mechanistic beliefs presently known.

Organocopper chemistry is of wide applicability, very efficient and easy to perform. The main problem is to know the most appropriate reagent to use. The reader will find in this book all the details for the reagent of choice, for the scope and limitations, for the type of substrate needed. This book should be helpful not only to advanced research chemists, but also for teaching this chemistry to younger

students in a comprehensive and modern way. Such a wide coverage of an important piece of chemistry is not only welcome; it was needed!

December 2001
Professor Alexandre Alexakis
University of Geneva
Geneva

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Preface

"When one equivalent of cuprous iodide was treated with one equivalent of methyllithium the yellow, ether-insoluble product was formed. Both the precipitate and the ether solution gave a negative color test with Michler ketone.... However, when one equivalent of cuprous iodide was treated with two equivalents of methyllithium a clear, practically colorless ether solution was formed. This ether solution gave a strong color test."

H. Gilman, R. G. Jones, L. A. Woods, "The Preparation of Methylcopper and some Observations on the Decomposition of Organocopper Compounds", *J. Org. Chem. 1952,* **17**, 1630–1634.

Fifty years ago, *Gilman* and coworkers marked the beginning of the era of organocopper reagents as synthetic tools in organic chemistry by describing the first preparation of an organocuprate, namely lithium dimethylcuprate ($Me_2CuLi{\cdot}LiI$). Nonetheless, it took more than a decade after this discovery until the widespread use of organocuprates was initiated by the seminal work of *House, Corey* and others. Soon, the synthetic versatility of organocopper compounds and in particular those of cuprates (which in the case of the composition $R_2CuLi{\cdot}LiX$ are referred to as Gilman reagents) was exploited and, in its wake, created an abundance of new reagents, methods, and applications.

Notable in this respect are the introduction of heterocuprates, the use of "dummy ligands" in order to improve the "economy" of the reagents, the implementation of "higher-order" and "lower-order" cuprates and the development of chiral organocopper reagents. Last but not least, the refinement of both theoretical and experimental methods (e.g., X-ray, NMR spectroscopy, kinetics) has shed light on the structures of organocopper compounds and the mechanism of their reactions. Although nowadays regarded as indispensable tools in the repertoire of synthetic organic chemists, organocopper chemistry is still a vivid field with numerous new copper-promoted transformations and chiral catalysts being developed over the last years.

This book captures recent advances of organocopper chemistry and serves as a detailed guide to the high standard now reached in the field. Brief summaries of previous achievements as well as thorough discussions of new methods and techniques facilitate (even for students) the entry into *Modern Organocopper Chemistry,* an area that will certainly witness further exciting discoveries in the near future.

Selected authors, all of them being protagonists in the respective area, provide profound expertise about both experimental and theoretical aspects of copper-mediated transformations to a wide range of scientists in academia and industry. Combined with essays about structure and mechanism (chapters 1 and 10), *Modern Organocopper Chemistry* compiles novel techniques for the generation of functionalized organocopper reagents (chapter 2) and heteroatom- as well as heteroatomalkylcuprates (chapter 3). Application of these organometallics in reactions with extended multiple bond systems (chapter 4), in reductions (chapter 5) and in stereoselective conjugate addition and substitution reactions (chapters 6–8), as well as their use for the synthesis of biologically active products (chapter 9), round out this monograph

The idea of this book, bringing together all important aspects of *Modern Organocopper Chemistry* and presenting them in a prolific way, has emerged over the last years in discussions with many colleagues, students and friends. Here, the *European Commission* deserves special mention for genereous support of several projects within the framework *European Cooperation in the Field of Scientific and Technical Research (COST)*. I thank the authors of this volume for their determination to complete their contribution in time of the 50th anniversary of Gilman's groundbreaking discovery. Finally, I dedicate this monograph to the over 2000 scientists mentioned in the author index for their original contributions which made the book possible.

Dortmund, December 2001 Norbert Krause

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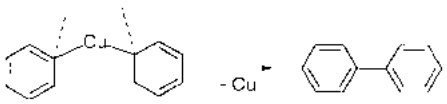
Finally, some organocopper compounds undergo charge disproportionation under the influence of ligands that bind strongly to copper. Treatment of mesitylcopper with 1,2-bis-(diphenylphosphino)ethane (DPPE), for example, results in the formation of bis(mesityl)copper anions and a copper cation to which four phosphorus atoms of two DPPE molecules are coordinated [75].

The selective formation of symmetric biaryls in high yield through thermal or oxidative decomposition is a feature that can be directly associated with the structure of the compound involved. It has been shown that arylcopper compounds with a structure comprising three-center, two-electron-bonded bridging aryl groups undergo this selective reaction (see Scheme **1.13**), while arylcopper compounds in which the Cu atom is η^1-bonded to the aryl group give a mixture of unidentified decomposition products, most probably by a radical pathway. In structures incorporating bridging aryl groups, the carbon atoms are already in close proximity [76], as shown schematically in Scheme **1.13**. Therefore, only a slight further distortion of this geometry is needed to bring the ipso-carbon atoms even closer together, thus promoting the C C bond formation.

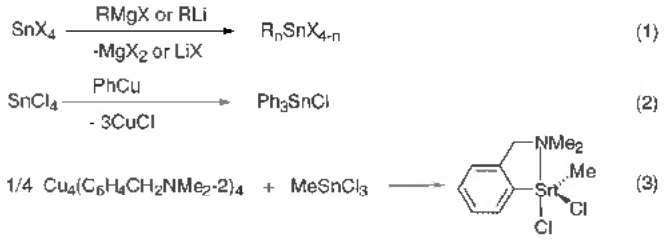


Scheme 1.13.

Furthermore, it has been demonstrated that an increase in the electrophilicity of the copper centers in aggregate structures, by incorporation of Cu^+ into such structures, for example, favors C C bond formation to give biaryls. Treatment of various organocopper compounds with Cu^+ (in the form of CuOTf, OTf = trifluoromethanesulfonate) has been studied [77]. For some compounds containing potential coordinating substituents, it was possible to isolate and study species such as $[(Cu_6R_4)^{2+}][2\ OTf^-]$ [76], but addition of only catalytic amounts of CuOTf to simple arylcopper compounds such as $Cu_4(C_6H_4Me\text{-}2)_4$ and $Cu_4(C_6H_4Me\text{-}4)_4$ affords the corresponding biaryls in quantitative yield. This was explained in terms of a mechanism involving a valence disproportionation reaction of two Cu(I) into Cu(II) and Cu(0) [77].

Finally, pure organocopper compounds have found applications in one-step syntheses of tri- and diorganotin halides. Its has now become well established that treatment of Grignard and organolithium reagents with tin(IV) halides always gives a mixture of products (Eqn. **1** in Scheme **1.14**) rather than the desired tri- or diorganotin halides.

In contrast, treatment of $SnCl_4$ with excess CuPh affords $SnPh_3Cl$ as the only product [78] (Eqn. 2 in Scheme **1.14**). Furthermore, it has been shown that reaction of functionally substituted arylcopper compounds with organotin halides proceeds very selectively to afford a novel type of pentacoordinate organotin compounds possessing interesting structural features [79]. Treatment of $Cu_4(C_6H_4CH_2NMe\text{-}2)_4$ with four equivalents of $SnMeCl_3$, for example, gives



Scheme 1.14.

$SnMeCl_2(C_6H_4CH_2NMe\text{-}2)$ as the only product, in quantitative yield [80] (Eqn. 3 in Scheme 1.14).

1.3 Heteroleptic Organocopper Compounds $Cu_{n+m}R_nX_m$

As outlined previously, aggregation of organocopper compounds is a consequence of the fact that the carbon moieties in these compounds are capable of bridging between two copper atoms. It is therefore to be expected that other anionic ligands capable of bridging between metal centers – halides, for example – might easily become incorporated into such aggregates.

By the early 1970s it was already recognized that the excess CuBr in the red product obtained on treatment of $LiC_6H_4NMe_2\text{-}2$ with CuBr (for which the elemental analysis pointed to a $Cu_3(C_6H_4NMe_2\text{-}2)_2Br$ stoichiometry) is not a contaminant but an integral part of an aggregated species [47]. An X-ray crystal structure determination of this compound showed a structure (see Fig. 1.13) of $Cu_6(C_6H_4NMe_2\text{-}2)_4Br_2$ stoichiometry, with the copper atoms in an octahedral arrangement [44].

Each of the four organic moieties bridges between an equatorial and an axial copper atom through its C(1) atom, while the nitrogen atom in the substituent is coordinated to an adjacent equatorial copper atom. The two bromine atoms bridge, at opposite sites, between two equatorial copper atoms. This structural arrangement has the consequence that the aggregate incorporates two distinct types of

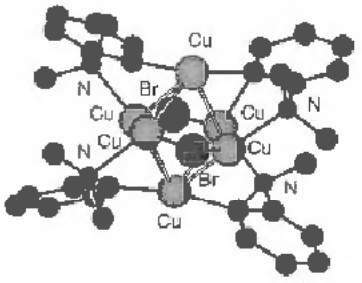
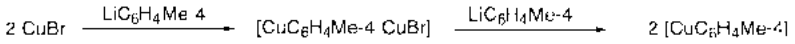


Fig. 1.13. Structure of $Cu_6(C_6H_4NMe_2\text{-}2)_4Br_2$ in the solid state.

copper atoms: four equatorial ones with distorted trigonal coordination geometries, and the two apical ones, with distorted digonal coordination geometries.

It should be noted that a combination of various bonding features – bridging organic groups, bridging anionic ligands such as halogen atoms, and also the presence of potentially coordinating substituents – might give rise to more diverse structural patterns, as has been observed for homoleptic organocopper compounds (vide supra). In addition, though, organocopper compounds that do not contain functional substituents can also aggregate with copper halides, as demonstrated by the following observation:

During the synthesis of $Cu(C_6H_4Me\text{-}4)$, prepared by gradual addition of a solution of $LiC_6H_4Me\text{-}4$ to a suspension of CuBr in Et_2O [16], a completely clear solution is obtained at the stage at which about half of the quantity of $LiC_6H_4Me\text{-}4$ has been added. This indicates that at this point the excess CuBr has been solubilized, most probably as a consequence of aggregation with the $Cu(C_6H_4Me\text{-}4)$ produced (see Scheme 1.15). It was impossible to isolate any well defined compound from this solution, due to the intrinsic low thermal stability of the species formed.



Scheme 1.15.

To discuss all the structures elucidated for heteroleptic organocopper compounds to date [29, 45] is beyond the scope of this chapter, and so only some representative examples of the various kinds of structural motifs are discussed. As outlined in the previous section, the order of addition of the reagents can play an important role in the synthesis of homoleptic organocopper compounds, and might determine the structure of the final product. Similar observations have been made for the synthesis of organocopper-copper halide aggregates. In other cases, however, the same aggregated species is always formed, irrespective of the order of addition or the stoichiometry of the starting materials. This is most probably the result of a large difference in thermodynamic stability of the possible final products, the most stable one acting as a thermodynamic sink.

Organic moieties containing potentially coordinating substituents are largely responsible for the diversity of structures observed in heteroleptic organocopper compounds. The structures observed in compounds containing one of the ligands depicted in Fig. **1.14** demonstrate that important roles are played not only by

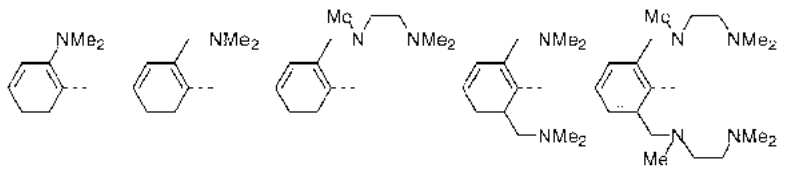


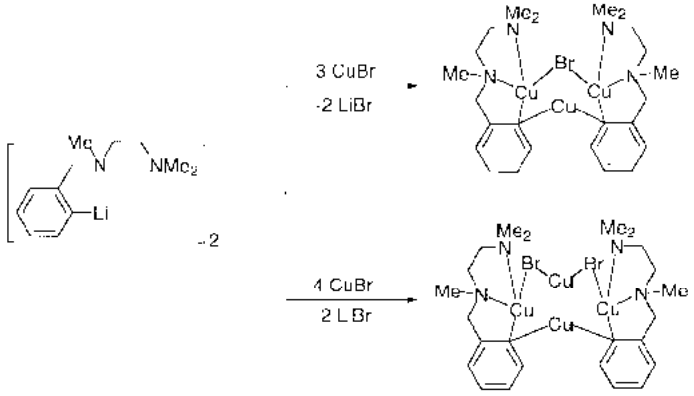
Fig. 1.14. Bidentate-, tridentate- and pentadentate monoanionic ligands applied in the synthesis of various organocopper aggregates.

the number of heteroatoms, but also by the spatial arrangement of the functional groups.

As outlined above, the aggregate $Cu_6(C_6H_4NMe_2\text{-}2)_4Br_2$, incorporating ligand **A**, comprises a structure with six copper atoms in an octahedral arrangement (see Fig. 1.13). It is interesting to note that the other group 11 metals, silver and gold, can also be incorporated into this metal framework. Compounds of compositions $Ag_6(C_6H_4NMe_2\text{-}2)_4X_2$, $Ag_4Cu_2(C_6H_4NMe_2\text{-}2)_4X_2$, $Ag_2Cu_4(C_6H_4NMe_2\text{-}2)_4X_2$, $Au_2Cu_4(C_6H_4NMe_2\text{-}2)_4X_2$, and $Au_2Ag_4(C_6H_4NMe_2\text{-}2)_4X_2$ (X = anionic ligand) [77, 81] have been isolated. On the basis of spectroscopic evidence, structures comparable to that observed for $Cu_6(C_6H_4NMe_2\text{-}2)_4Br_2$ have been proposed. For the latter two compounds it is most likely that the Au atoms occupy axial positions, as a consequence of the tendency of gold(I) to attain a linear digonal coordination geometry.

As mentioned in Section 1.2, the organocopper compound derived from ligand **B** is a discrete, tetranuclear species. Aggregation of this compound with CuCl or CuBr results in an insoluble material with the composition $Cu(C_6H_4CH_2NMe_2\text{-}2)\cdot CuX$ (X = Br, Cl) [35]. Because of its insolubility, which hampers structural characterization, a polymeric structure has been proposed for this compound.

When the (dimeric and structurally characterized [82]) organolithium compound derived from ligand **C** is treated with CuBr, either $Cu_3Br[C_6H_4CH_2N(Me)CH_2CH_2NMe_2\text{-}2]_2$ or $Cu_4Br_2[C_6H_4CH_2N(Me)CH_2CH_2NMe_2\text{-}2]_2$ is formed, depending on the RLi/CuBr molar ratio (see Scheme 1.16).



Scheme 1.16.

The structure of the first compound was unambiguously proven by X-ray crystal structure determination (see Fig. 1.15) [46]. It should be noted that an attempt to prepare and isolate the pure, copper halide-free organocopper compound (by application of less than three equivalents of CuBr) failed, with the 2:1 organocopper-copper bromide aggregate always being isolated, although in lower yield. An interesting structural feature of these compounds is that they may be regarded as

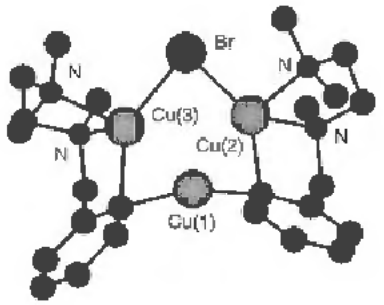


Fig. 1.15. Structure of $Cu_3Br[C_6H_4CH_2N(Me)CH_2CH_2NMe_2\text{-}2]_2$ in the solid state.

consisting of a cuprate anionic moiety R_2Cu^- and either a $[Cu_2Br]^+$ (first compound) or a $[Cu_3Br_2]^+$ (second compound) cationic unit.

Introduction of a second *ortho*-(dimethylamino)methyl substituent, ligand **D** in Figure **1.14**, affords an aggregated species with $Cu_4Br_2R_2$ stoichiometry, established by X-ray crystal structure determination [83]. The structure comprises two organic, monoanionic, terdentate ligands binding four copper atoms (arranged in a butterfly pattern) through C_{ipso} bridge bonding and N → Cu coordination, as well as by two bridging bromine atoms (see Fig. 1.16). This compound may also to be considered as consisting of a R_2Cu^- (cuprate) anionic unit and a $[Cu_3Br_2]^+$ cationic moiety, held together as a consequence of the special spatial arrangement of the heteroatom-containing substituents.

On extension of the coordinating properties of the ligand system to a monoanionic pentadentate representative – ligand **E** in Fig. **1.14** – an even less expected structure was obtained. Treatment of the corresponding organolithium compound (which only exists as an aggregate with LiBr [84]) with CuBr afforded an aggregate, the X-ray structure of which is shown in Fig. 1.17. The structure consists of two monoanionic, pentadentate organic groups, five copper atoms, and three bromine

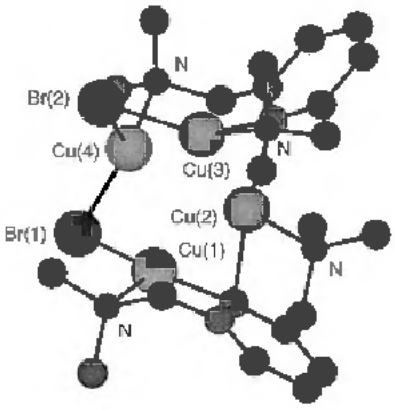


Fig. 1.16. Structure of $Cu_4Br_2[C_6H_3(CH_2NMe_2)_2\text{-}2,6]_2$ in the solid state.

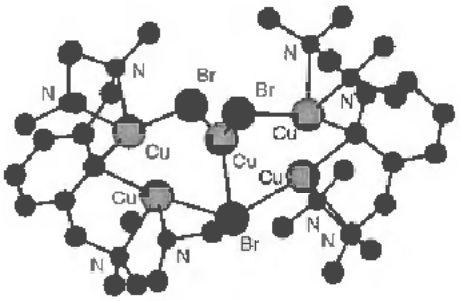
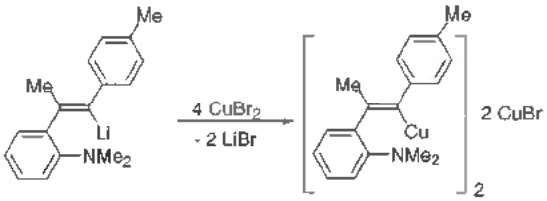


Fig. 1.17. Structure of $Cu_5Br_3[C_6H_3(CH_2N(Me)CH_2CH_2NMe_2)_2\text{-}2,6]_2$ in the solid state.

atoms, and can be described in terms of two $[RCu_2]^+$ cationic building blocks held together by a central $[CuBr_3]^{2-}$ anionic unit [85].

Treatment of a functionalized vinyllithium compound with two equivalents of CuBr (see Scheme 1.17) afforded an aggregate, the structure of which was established by an X-ray crystal structure determination [**41**, **42**] (see Fig. 1.18A).



Scheme 1.17.

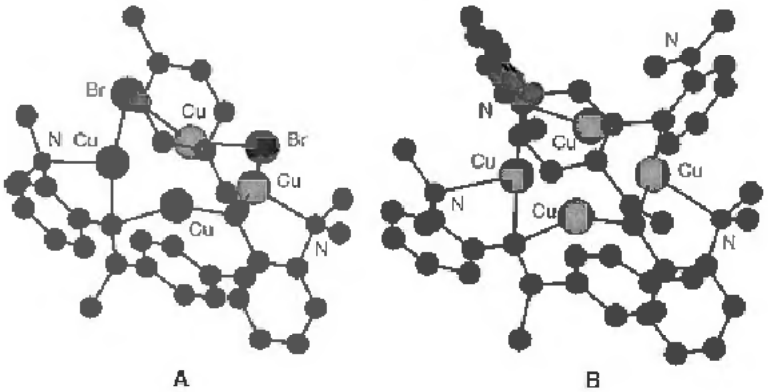
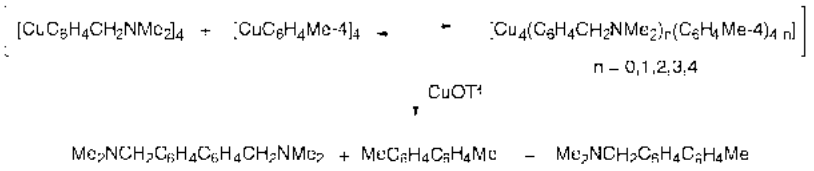


Fig. 1.18. Structures of $Cu_4Br_2[2\text{-}Me_2NC_6H_4C(Me)\text{–}C(C_6H_4Me\text{-}4)]_2$ **(A)** and $Cu_4[2\text{-}Me_2NC_6H_4C(Me)\text{–}C(C_6H_4Me\text{-}4)]_2[C_6H_4NMe_2\text{-}2]_2$ **(B)** in the solid state.

This structure represents the first of the very few examples of structurally characterized organocopper compounds containing vinylic carbon-to-copper bonds. The four copper atoms are arranged in a rhombus-type pattern, while the propenyl groups and the two bromine atoms occupy adjoining edges. As a consequence, the copper atoms are alternately two- and three-coordinate. An interesting feature of this compound is that the two bromine atoms can be replaced by aryl groups on treatment with an aryllithium compound, with retention of the overall structural arrangement [**41**] (see Fig. 1.18B).

This latter compound represents an example of a heteroleptic organocopper compound containing two different organic moieties: aryl groups and vinyl groups. The existence of such heteroleptic organocopper compounds had been proposed earlier, on the basis of spectroscopic and chemical evidence [77]. Thus, it had been shown by NMR spectroscopic studies that organocopper species in solution undergo interaggregate exchange. Mixing of pure $[CuC_6H_4CH_2NMe_2\text{-}2]_4$ with $[CuC_6H_4Me\text{-}\mathbf{4}]_4$, for example, affords an equilibrium mixture of all possible mixed aggregates (Scheme **1.18**).

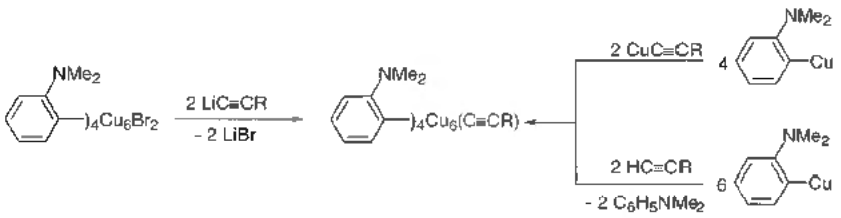


Scheme 1.18.

Decomposition of this equilibrium mixture with catalytic amounts of CuOTf affords a mixture of all three possible biaryls. The formation of the unsymmetrical biaryl 2-$Me_2NCH_2C_6H_4C_6H_4Me$-**4** can only be explained by the occurrence of aggregated copper species in which both the $C_6H_4CH_2NMe_2$-2 and the C_6H_4Me-**4** groups are bound to the same copper core [77]. It was furthermore observed that the ratio of the formed biaryls is not statistical, which points to significant differences in the thermodynamic stabilities of the various mixed aggregates present in solution.

Treatment of $Cu_6(C_6H_4NMe_2\text{-}2)_4Br_2$ (Fig. **1.13**) with two equivalents of a lithium acetylide resulted in selective replacement of the bromide anions with acetylide groups (see Scheme **1.19**) [86]. The aggregate thus formed represents another example of a heteroleptic organocopper compound containing two different organic groups.

Two other synthetic approaches to this type of aggregates are available (Scheme **1.19**). The first involves mixing of the pure arylcopper compound with an appropriate copper acetylide in a suitable solvent [87]. In this regard, it is interesting to note that the aggregate $Cu_6(C_6H_4NMe_2\text{-}2)_4(C{-}CR)_2$ is always obtained irrespective of the stoichiometry of the reagents, thus representing a nice example of selective self-assembly. The second approach involves treatment of a monosubstituted acet-



Scheme 1.19.

ylene with the pure organocopper compound. Partial protonolysis of the organocopper compound produces a copper acetylide, which is immediately trapped by unreacted organocopper compound. The structure of the obtained aggregate was unambiguously proven by an X-ray crystal structure determination (see Fig. 1.19) [88].

An interesting feature of these compounds is that, upon thermolysis in benzene at 80 °C, the unsymmetrical C C coupling product 2-$Me_2NC_6H_4C{-}CR$ is formed exclusively. The selectivity of this reaction is probably directly related to the structural features of this heteroleptic aggregate [89].

There is ample evidence that anions other than halides can also become incorporated in aggregate structures. For example, interaggregate exchange between organocopper compounds and copper carboxylates has been observed in reactions between copper benzoate and mesitylcopper in the appropriate molar ratio [90]. In one reaction, a yellow, crystalline material was isolated in high yield. According to X-ray crystallography [90], it appeared to be a trinuclear aggregate with one mesityl group bridge-bonded between two copper atoms, and with the two benzoate anions each binding in a bridging fashion between one of these copper atoms and a third one (see Fig. 1.20).

Other examples are provided by structures with bridging arenethiolate anions. The application of functionally substituted copper arenethiolates as catalysts in

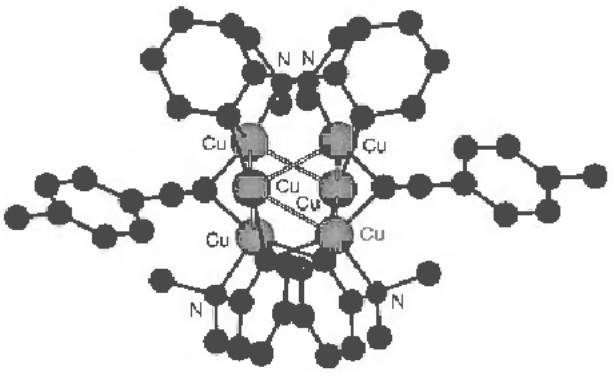


Fig. 1.19. Structure of $Cu_6(C_6H_4NMe_2\text{-}2)_4(C{-}CC_6H_4Me\text{-}4)_2$ in the solid state.

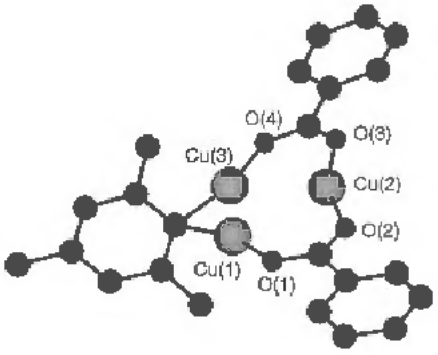


Fig. 1.20. Structure of $Cu_3(Mes)(O_2CC_6H_5)_2$ in the solid state.

copper-mediated C C bond formation reactions is now well established [91, 92], and it has been argued that the formation of mixed arenethiolate alkyl- or aryl-copper aggregates might play a role in these reactions. This assumption is supported by the synthesis of $Cu_4(Mes)_2(SC_6H_4CH_2NMe_2\text{-}2)_2$, which was achieved by treatment of the appropriate copper arene thiolate with mesitylcopper in 1:1 molar ratio. The molecular geometry of this compound was established by X-ray crystal structure determination (Fig. 1.21) [93].

The structure of this compound consists of four copper atoms in a butterfly arrangement, in which the two mesityl groups bridge opposite edges. The remaining two edges are occupied by the arenethiolate ligands through bridging Cu S bonds, while the nitrogen atoms of the substituents are coordinated to two opposite copper atoms. In this way, two of the copper atoms become three-coordinate and the other two copper atoms two-coordinate.

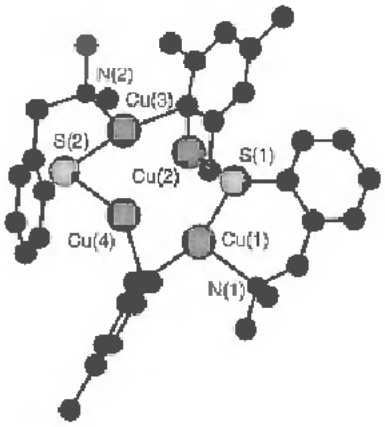


Fig. 1.21. Structure of $Cu_4(Mes)_2(SC_6H_4CH_2NMe_2\text{-}2)_2$ in the solid state.

It is not only heteroatom-functionalized organocopper compounds that give rise to a large diversity of aggregates with copper halides. Organocopper compounds with olefinic substituents, which are also able to coordinate to copper, similarly form aggregates, such as $[Cu_5Br_4(C_6H_4CH{=}CH_2\text{-}2)_2]$ and $[Cu_5Br_2(C_6H_4CH{=}CH_2\text{-}2)_4]$ [94]. These anionic aggregates formally belong to an other class of compounds: the cuprates, discussed in the next section.

The ability of organocopper compounds to form various kinds of aggregated species with metal halides is a factor often overlooked when organocopper compounds are applied as reagents in organic synthesis. It needs to be taken into account that copper halides are often formed during reactions of pure organocopper reagents. It is obvious that these can form aggregates with the organocopper reagent, so that, at a certain stage in the reaction, the initial reagent is no longer present. The organocopper-copper halide aggregate produced probably has a reactivity different to that of the initial organocopper reagent. At the current state of knowledge, the consequences are unpredictable and may well be different for each specific organocopper compound. When an aggregate with much higher stability than the pure organocopper compound is formed, any further reaction may be prevented. If, on the other hand, the aggregate has a considerably reduced thermal stability, extensive decomposition might occur, giving rise to the formation of unwanted side products.

An illustrative example is the formation of the symmetric biaryl from the reaction between $CuC_6H_4NMe_2\text{-}2$ and $IC_6H_4NMe_2\text{-}2$, which has been studied in detail in the authors' laboratory [95]. When this reaction is carried out in benzene as a solvent, the reaction stops when one third of the original organocopper compound has been consumed (Eqn. 1 in Scheme 1.20).

$$6\ CuC_6H_4NMe_2\text{-}2 + 2\ IC_6H_4NMe_2\text{-}2 \xrightarrow{C_6H_6} Cu_6(C_6H_4NMe_2\text{-}2)_4I_2 + 2(C_6H_4NMe_2\text{-}2)_2 \quad (1)$$

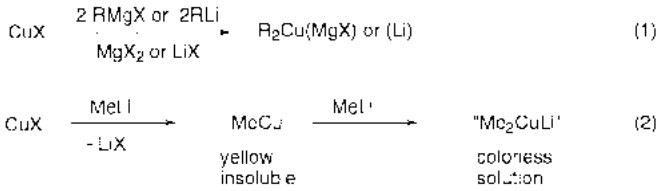
$$CuC_6H_4NMe_2\text{-}2 + IC_6H_4NMe_2\text{-}2 \xrightarrow{DMF} (C_6H_4NMe_2\text{-}2)_2 + CuI \quad (2)$$

Scheme 1.20.

The CuI formed during the reaction is immediately trapped by the unreacted organocopper compound, resulting in the formation of $Cu_6(C_6H_4NMe_2\text{-}2)_4I_2$. This aggregate has a structure similar to that of the corresponding bromine compound (Fig. 1.13). Compared to the parent organocopper compound, this aggregate has considerably greater kinetic stability and so blocks any further reaction even when excess of aryl iodide is present. When, however, the same reaction is carried out in DMF, quantitative formation of the biaryl is observed (Eqn. 2 in Scheme 1.20). It appears likely that the good donor DMF effectively cleaves the aggregated species into the parent organocopper compound and solvated CuI, so that the reaction goes to completion. This observation might also explain why co-solvents such as DMF, NMP, or HMPA are often required to produce high yields in reactions involving organocopper compounds.

1.4 Organocuprates

From the viewpoint of their synthetic potential in organic synthesis, the organocuprates are the most important of all organocopper compound types [13, 96–98]. Organocuprates are commonly obtained by addition of more than one equivalent of an organolithium or Grignard reagent to a copper halide [5] (Eqn. 1 in Scheme 1.21). The existence of such species was discovered after the observation that insoluble MeCu reacts with an additional equivalent of MeLi to afford a clear, colorless solution of a compound represented as "Me_2CuLi" (Eqn. 2 in Scheme 1.21) [6, 7].



Scheme 1.21.

A large variety of cuprates are known nowadays. They include heteroleptic derivatives R(Y)CuM (Y = alkynyl, halide, amido, alkoxide, thiolato, phosphido; M = Li or Mg), and have found widespread application in organic chemistry. Their syntheses and applications are discussed in the other chapters of this book. In addition, compounds in which the copper to lithium (or magnesium) ratio differs from 1:1 are also known; examples are R_3CuLi_2 and the so-called higher order cyanocuprates introduced by Lipshutz et al. [99].

Studies of the structures of cuprate species were initiated to elucidate the mechanisms by which they interact with substrates and to understand their special reactivities. In the early days these investigations were restricted to solution studies by spectroscopic techniques. It was not until 1982 that the first example of a cuprate species – $[(Cu_5Ph_6)(Li(THF_4))]$ – was structurally characterized by X-ray crystal structure determination [100] (vide infra). It should be noted that most of these studies, reviewed previously [29, 45, 101], were limited to "simple" alkyl and aryl derivatives.

In principle, three different types of organocuprates need to be taken account of. These are:

(1) the neutral homoleptic organocuprates, as initially discovered by Gilman,
(2) ionic species, often obtained by adding strongly coordinating molecules such as crown ethers to neutral organocuprates, and
(3) heteroleptic cuprates, of which the cyanocuprates are the most important and most extensively studied representatives.

However, these borderlines should not be taken too strictly.

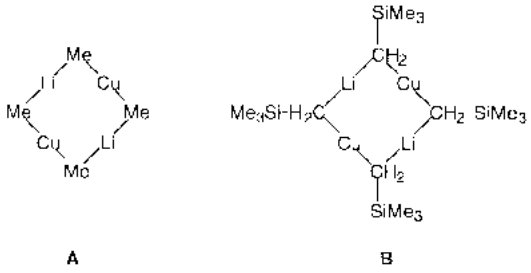


Fig. 1.22. Proposed structures for $Cu_2Li_2Me_4$ (A) and $Cu_2Li_2(CH_2SiMe_3)_4$ (B)

It is beyond the scope of this chapter to discuss the special reactivities associated with each specific type of cuprate; these are covered in other chapters in this book. Here, we will concentrate on the various structural motifs of organocuprates in organic synthesis.

1.4.1
Neutral Homoleptic and Heteroleptic Organocuprates

Molecular weight determination – by vapor pressure depression, ^1H NMR, and solution X-ray scattering data – made it evident that $CuLiMe_2$ exists as a dimer in Et_2O solution [102]. A planar cyclic structure $Cu_2Li_2Me_4$, shown schematically in Fig. 1.22A, has been proposed; it comprises alternating copper and lithium atoms with each of the Me groups bridging between one lithium and one copper atom. Similar conclusions were drawn from variable temperature ^1H NMR studies of $LiCH_2SiMe_3$ and $CuCH_2SiMe_3$ in various ratios. It was shown that the only significant "mixed" species present in solution was the 1:1 aggregate, for which a similar dimeric planar structure was proposed (see Fig. 1.22B) [39, 103]. Furthermore, kinetic data relating to the reaction between $CuLiMe_2$ and MeI implied that the rate-determining step involved the dimeric aggregate, $Cu_2Li_2Me_4$ [102].

The first example of an arylcuprate isolated as a pure compound and studied in detail was the compound of stoichiometry $CuLi(C_6H_4CH_2NMe_2\text{-}2)_2$, incorporating the monoanionic, bidentate $C_6H_4CH_2NMe_2$-2 ligand framework [104]. The synthesis of the corresponding pure aurate, $AuLi(C_6H_4CH_2NMe_2\text{-}2)_2$ [105] and the pure argentate $AgLi(C_6H_4CH_2NMe_2\text{-}2)_2$ [106] were reported by the same authors. Molecular weight determinations by cryoscopy in benzene revealed that these compounds exist in apolar solvents as dimeric aggregates $M_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4$ (M = Cu, Ag, Au). The presence of different magnetically active nuclei (^1H, ^{13}C, $^{107,109}Ag$, and $^{6,7}Li$) in the argentate allowed detailed structural characterization in solution to be carried out by NMR spectroscopy. ^1H and ^{13}C NMR spectroscopy showed the presence of four magnetically equivalent organic moieties over the whole temperature range studied (−70 to +100 °C). At the low exchange limit (< 10 °C), the nitrogen atoms of the substituents are coordinated in pairs to the same type of metal, most probably lithium. Furthermore, the ^{13}C NMR spectrum

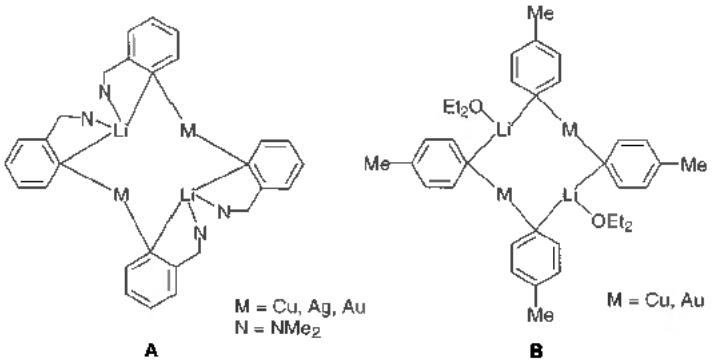


Fig. 1.23. Proposed structures in solution for $M_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4$ **(A)** and $M_2Li_2(C_6H_4Me\text{-}4)_4(OEt_2)_2$ **(B)**.

showed that each of the C_{ipso} atoms is coupled to one Li atom ($^1J(^{13}C, ^7Li) = 7.2$ Hz) and to one Ag atom ($^1J(^{13}C, ^{109}Ag) = 136$ Hz). The ^6Li, ^7Li, and ^{109}Ag NMR spectra pointed to the presence of one type of silver and one type of lithium atom, with each lithium atom being coupled to two silver atoms and each silver atom coupled to two lithium atoms ($^2J(^7Li, ^{109}Ag) = 3.91$ Hz) [107].

On the basis of these data and of spectroscopic similarities between the Cu, Ag, and Au compounds, a structure for these compounds was proposed. This is shown schematically in Fig. 1.23A. This dimeric aggregated structure is not a consequence of the *ortho* functionalization of the aryl anion with a coordinating heteroatom substituent, as became evident from studies of the structural features of the simple arylcuprate Cu_2Li_2 $(C_6H_4Me\text{-}4)_4(OEt_2)_2$ and the corresponding gold compound in solution [108]. For these aggregated species, a structure similar to that of $M_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4$ was proposed (see Fig. 1.23B). However, the lithium atoms are now trigonally coordinated.

The solid state structures of $Cu_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4$ (Fig. 1.24A) [72], $Au_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4$ [109], and $Cu_2Li_2(C_6H_5)_4(OEt_2)_2$ (Fig. 1.24B) [110],

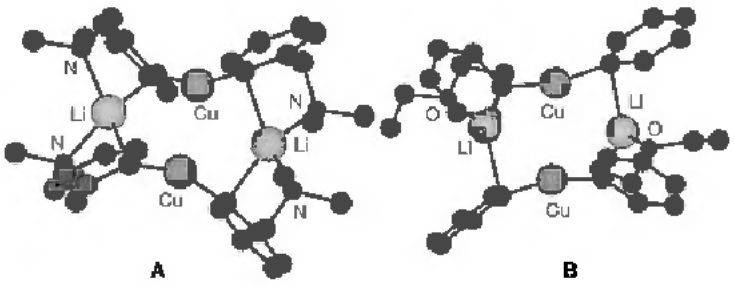


Fig. 1.24. Structures of $Cu_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4$ **(A)** and $Cu_2Li_2(C_6H_5)_4(OEt_2)_2$ **(B)** in the solid state.

were later established by X-ray crystal structure determination and appeared to be in full agreement with the corresponding structures in solution as deduced from spectroscopic data.

$Cu_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4$ was the first neutral cuprate for which the structure could be unambiguously established. A common feature of such structures is the bridging nature of the aryl group. As a consequence of the binding of C_{ipso} to two different metal atoms, this bridging (in comparison with that in homoleptic organocopper compounds) is unsymmetrical (shorter Cu C bond, longer Li C bond). This asymmetry is even more pronounced in the corresponding gold compound [109], which is best described as consisting of two R_2Au anionic units linked together by solvated lithium cations through contact ion-pair formation. Another consequence of the bridging between two different metal atoms is the fact that, if the aryl group is not symmetrically substituted, the bridging carbon atom becomes a center of chirality. This has important stereochemical consequences [111]. A particularly complicated situation arises if the benzylic group in, for example, $Cu_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4$ bears a substituent that gives rise to the presence of different diastereoisomeric units in one aggregate [111]. The pure organocopper compound $Cu_4(C_6H_4CH(Me)NMe_2\text{-}2)_4$, and the corresponding cuprate, $Cu_2Li_2(C_6H_4CH(Me)NMe_2\text{-}2)_4$, were prepared starting both from the enantiopure ligand and from the racemic ligand. It appeared that the organocopper compound $Cu_4(C_6H_4CH(Me)NMe_2\text{-}2)_4$ derived from the racemic ligand exists in solution as a mixture of all possible diastereoisomeric aggregates. This observation, however, contrasts with the situation found for the cuprate $Cu_2Li_2(C_6H_4CH(Me)NMe_2\text{-}2)_4$ derived from the racemic ligand. In this case, only aggregates in which all four bridging and benzylic carbon centers have the same relative stereochemical configuration are formed, in a nice example of diastereoselective self-assembly [112].

That the natures both of the organic group and of the additional donor-solvent molecules are factors that determine the actual cuprate aggregates formed is demonstrated by the structure of $[Cu_2Li_2(CH_2SiMe_3)_4(DMS)_2]_n$ in the solid state [113] (see Fig. 1.25). In this structure, the basic framework consists of repeating central

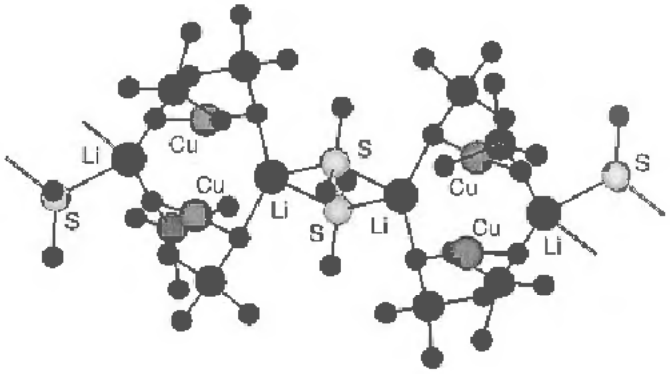


Fig. 1.25. Structure of $[Cu_2Li_2(CH_2SiMe_3)_4(DMS)_2]_n$ in the solid state.

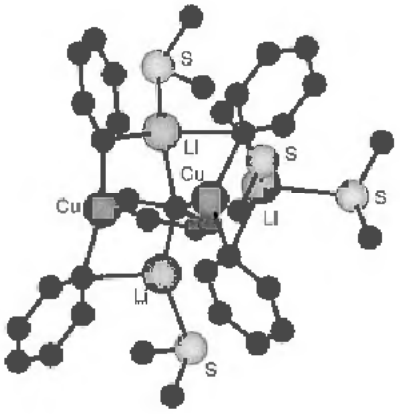


Fig. 1.26. Structure of $Cu_2Li_3Ph_5(DMS)_4$ in the solid state.

Cu_2Li_2 cores with bridging Me_3SiCH_2 groups. These Cu_2Li_2 cores are interlinked to form linear chains through bridging Me_2S ligands between the lithium atoms of two adjacent Cu_2Li_2 cores.

The solid-state structure of $Cu_2Li_2Ph_4(DMS)_3$ is closely related to that observed for $Cu_2Li_2Ph_4(OEt_2)_2$, except that one of the lithium atoms here is now four-coordinate as a result of coordination of two DMS molecules [**114**]. This observation shows that even slight changes in the coordinating properties of donor solvent molecules may change the overall structure of the cuprate.

So far, only cuprates with a 1:1 copper/lithium ratio have been considered. Treatment of phenyllithium with various substoichiometric quantities of copper bromide in DMS as solvent afforded so-called higher order cuprates, of which two were characterizable by X-ray crystallography. These have the overall stoichiometries $Cu_2Li_3Ph_5(DMS)_4$ and $Cu_4Li_5Ph_9(DMS)_4$ [**114, 115**]. The structure of the former compound in the solid state is shown in Fig. 1.26.

The $Cu_4Li_5Ph_9(DMS)_4$ aggregate may be described as consisting of three linear $CuPh_2$ anions, triply bridged by two lithium cations, and of one trigonal Ph_3Cu^2 anion, which is associated with three lithium cations and coordinated by four DMS ligands. The two resulting units – $[(CuPh_2)_3Li_2]$ and $[(CuPh_3)Li_3(DMS)_4]^+$ – are linked together by a bridging phenyl group ipso carbon atom.

The only examples of cuprates in which copper and magnesium atoms are incorporated in one aggregate have the stoichiometries $Cu_2MgPh_4(THF)_n$ [60], $Cu_5Mg_2Ph_4Br_5(THF)_n$ [60], $Cu_4Mg(PhMe\text{-}4)_6(OEt_2)$ [116], and $Cu_4MgPh_6(OEt_2)$ [116]. The structure of $Cu_4MgPh_6(OEt_2)$ in the solid state (Fig. 1.27) was established by X-ray crystal structure determination [117].

The structure of $Cu_4MgPh_6(OEt_2)$ comprises a central core of five metal atoms in a trigonal bipyramidal arrangement, with the magnesium atom at an axial position. The six phenyl groups bridge across the axial–equatorial edges of the trigonal bipyramid. One diethyl ether molecule is coordinated to the magnesium atom,

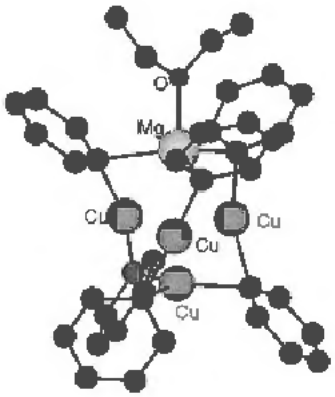


Fig. 1.27. Structure of $Cu_4MgPh_6(OEt_2)$ in the solid state.

to attain coordination saturation. A similar arrangement of the metal framework is observed in the anions $[Cu_5Ph_6]^-$ and $[Cu_3Li_2Ph_6]^-$, discussed in the next section.

For reasons outlined above, the neutral heteroleptic cuprates "RCuLiX" (X = heteroatom-containing ligand) are valuable reagents in organic synthesis. Despite this importance, however, only a very few have been structurally characterized. The structure of $CuLiMe(t\text{-}Bu_2P)(THF)_3$ has been established by X-ray crystal structure determination [118] (Fig. 1.28A). The copper atom has a linear C Cu P geometry. In contrast to most other cuprates, in which lithium is involved in two-electron, three-center bonding with the organic group, the lithium atom is bound in this case to the heteroatom anion (P) and three THF molecules.

Another example of a neutral, heteroleptic cuprate is the arylcopper magnesium arenethiolate $[Cu_4Mes_4][Mg(SC_6H_4CH(Me)NMe_2\text{-}2)_2]_2$ (Fig. 1.28B), formed by self-assembly in solutions of $Cu_3(SC_6H_4CH(Me)NMe_2\text{-}2)_3$ and Mes_2Mg [93]. This copper complex may be regarded as a model compound for a possible active species

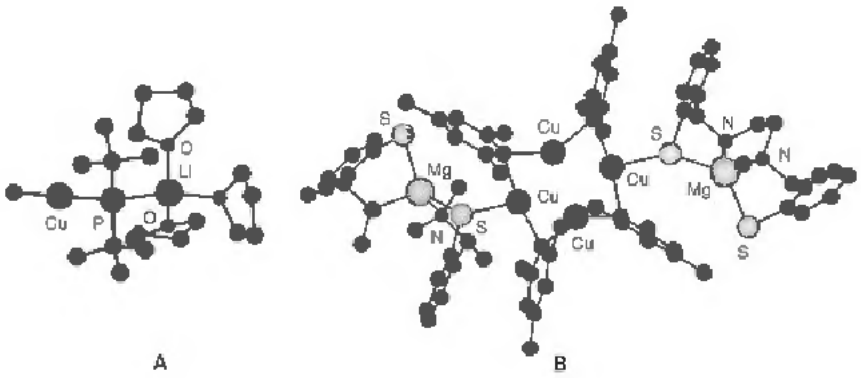
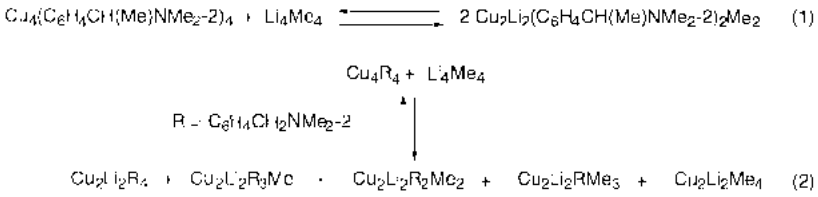


Fig. 1.28. Structures of heteroleptic cuprates $CuLiMe(t\text{-}Bu_2P)\text{-}(THF)_3$ **(A)** and $[Cu_4Mes_4][Mg(SC_6H_4CH(Me)NMe_2\text{-}2)_2]_2$ **(B)** in the solid state.

when $Cu_3(SC_6H_4CH(Me)NMe_2\text{-}2)_3$ is used as a catalyst in enantioselective 1,4-addition reactions of Grignard reagents to enones [91, 92].

The formation of heteroleptic organocuprates "CuLiRR'" in solution has been proposed in, for example, the reaction in diethyl ether between enantiopure $Cu_4(C_6H_4CH(Me)NMe_2\text{-}2)_4$ and Li_4Me_4 (Eqn. 1 in Scheme 1.22) to afford a heteroleptic cuprate $Cu_2Li_2(C_6H_4CH(Me)NMe_2\text{-}2)_2(Me)_2$. These solutions were applied in 1,4-addition reactions. Although methyl transfer to the substrate occurs, no enantioselective induction is observed [119]. A possible explanation for this lack of stereoselectivity involves the occurrence of a disproportionation reaction of the heteroleptic cuprate into the corresponding homoleptic cuprates $Cu_2Li_2(C_6H_4CH(Me)NMe_2\text{-}2)_4$ and $Cu_2Li_2Me_4$. In the authors' laboratory, the reaction between the corresponding achiral organocopper compound $Cu_4(C_6H_4CH_2NMe_2\text{-}2)_4$ and Li_4Me_4 in various ratios has been studied. ^{1}H NMR spectroscopy has shown that such solutions are complicated equilibrium mixtures (Eqn. 2 in Scheme 1.22) of several aggregates, of which the homoleptic cuprates $Cu_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4$ and $Cu_2Li_2Me_4$ are the most abundant. It should be noted that species in which the Cu/Li ratio is different from 1:1 can also not be ruled out a priori.



Scheme 1.22.

Such equilibria are governed by thermodynamics, and so the abundances of the different species in solution are dependent on their relative thermodynamic stabilities. If, however, such a mixture of species is applied in, for example, a conjugate addition reaction, the product formation will be controlled by kinetics, and it is most likely that $Cu_2Li_2Me_4$ would be kinetically the most active species present.

1.4.2
Anionic Homoleptic and Heteroleptic Organocuprates

The first example of a cuprate structurally characterized by X-ray crystal structure determination was the ionic aggregate $[Cu_5Ph_6][Li(THF)_4]$ [100] (Fig. 1.29A). The structural features of the anionic cuprate unit are closely related to those observed in $[Cu_4LiPh_6]$ [117] and $[Cu_3Li_2Ph_6]$ [20]. These aggregates have in common that the metal atoms are arranged in trigonal bipyramidal fashion, and the lithium atoms in the latter two compounds reside in axial positions. The six phenyl groups are bridge-bonded, spanning the axial–equatorial edges of the trigonal bipyramid.

Two peculiar examples of anionic aggregated cuprate species are $[Cu_5Br_4(C_6H_4CH{=}CH_2\text{-}2)_2]$ and $[Cu_5Br_2(C_6H_4CH{=}CH_2\text{-}2)_4]$ (Fig. 1.30). In the first compound,

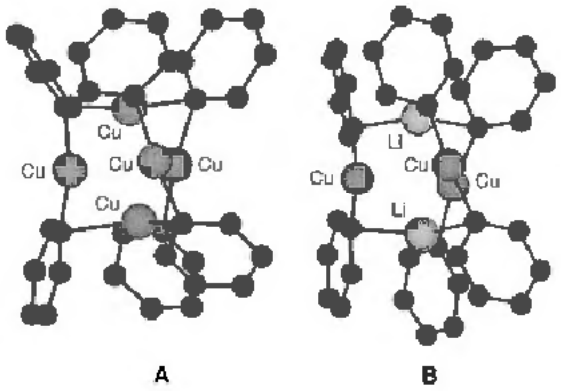


Fig. 1.29. Structures of $[Cu_5Ph_6]$ **(A)** and $[Cu_3Li_2Ph_6]$ **(B)** in the solid state.

both vinylic substituents are π-coordinated to two adjacent copper atoms, whilst in the second compound only one of the four available vinylic substituents is involved in π-coordination [94]. Bridge-bonding by the phenyl groups, however, as well as various types of Br-to-Cu bridging, is also clearly present in these structures.

Addition of the strongly coordinating 1,2-bis(diphenylphosphino)ethane (DPPE) ligand to a solution of Cu_5Mes_5 causes a disproportionation reaction, resulting in the formation of ionic $[CuMes_2][Cu(DPPE)_2]$. This was the first example of a mononuclear cuprate anion for which the structure was established by X-ray crystal structure determination (Fig. 1.31A) [75]. After this discovery, other ionic mononuclear cuprates were prepared by different approaches and structurally characterized. The first approach made use of bulky substituents in the organic groups bound to copper to prevent aggregation. This was achieved in, for example, the crystallization of $CuLi[C(SiMe_3)_3]_2$ from THF, which gave the ionic compound $[Cu(C(SiMe_3)_3)_2][Li(THF)_4]$ [120]. Another approach used an additional ligand

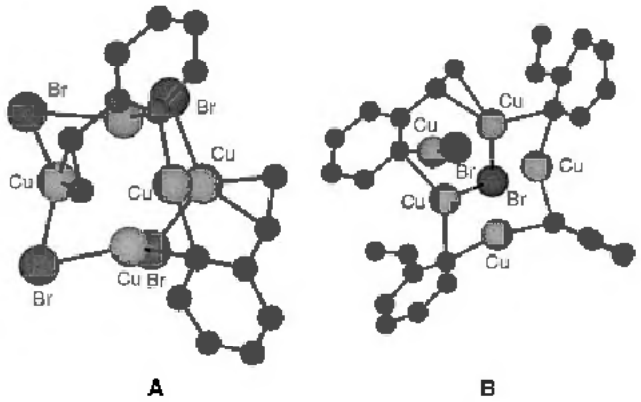


Fig. 1.30. Structures of $[Cu_5Br_4(C_6H_4CH{-}CH_2\text{-}2)_2]$ **(A)** and $[Cu_5Br_2(C_6H_4CH{-}CH_2\text{-}2)_4]$ **(B)** in the solid state.

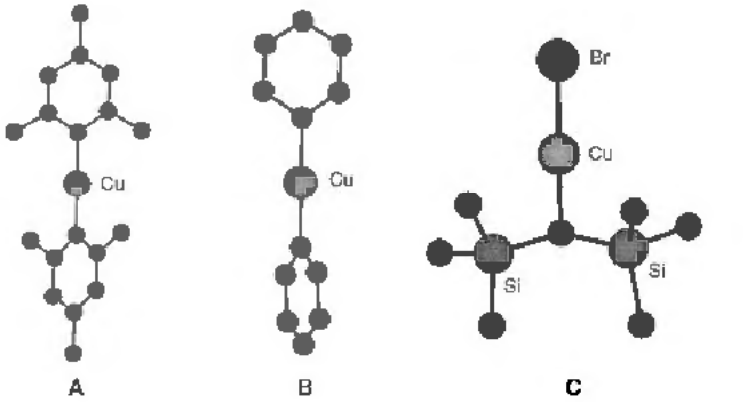


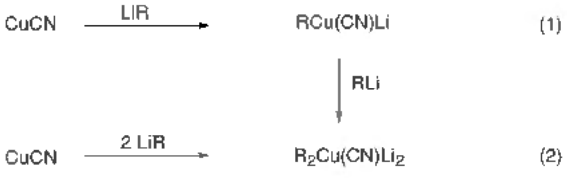
Fig. 1.31. Structures of the mononuclear cuprate anions $[CuMes_2]$ **(A)**, $[CuPh_2]$ **(B)**, and $[Cu(CH(SiMe_3)_2)Br]$ **(C)** in the solid state.

(such as 12-crown-4 or PMDTA (PMDTA = pentamethyldiethylenetriamine)), capable of binding very strongly to the cation; these can break down the aggregated cuprate to form mononuclear ionic species. Examples of mononuclear ionic cuprates obtained in this way are $[CuMe_2][Li(12\text{-crown-}4)_2]$ [121] and $[CuPh_2][Li(12\text{-crown-}4)_2]$ [121] (Fig. 1.31B).

The reaction between equimolar quantities of $LiCH(SiMe_3)_2$ and CuBr in the presence of 12-crown-4 afforded $[Cu(CH(SiMe_3)_2)Br][Li(12\text{-crown-}4)_2]$, the first example of an ionic mononuclear heteroleptic cuprate [121] for which the structure was established by X-ray crystal structure determination (Fig. 1.31C).

1.4.3
Lower- and Higher-order Cyanocuprates

The importance of cyanocuprates as a synthetic tool in organic chemistry is well established. Depending on the amount of organolithium reagent LiR (one or two equivalents) added to CuCN, two different type of cyanocuprates are formed, with stoichiometries of $RCu(CN)Li$ and $R_2Cu(CN)Li_2$, respectively [122] (Scheme 1.23). In order to distinguish between these two different types of cyanocuprates, the term "higher-order" cyanocuprates was introduced by Lipshutz et. al. for the second type of cyanocuprate, and the term "lower-order" cyanocuprate consequently



Scheme 1.23.

Fig. 1.32. Proposed structures for higher-order cyanocuprates.

became established for the first type. The earliest report on cyanocuprates (with a 1:1 stoichiometry) dates from 1973 [123].

The discovery of these cyanocuprates and their application in organic synthesis – particularly of the higher-order cyanocuprates, to which a special reactivity was ascribed [97, 124, 125] – resulted in a scientific controversy concerning the actual structure of these compounds. For a number of years, a large number of reports with appealing titles such as "If the cyano ligand is not on copper, then where is it?" [126] and "It's on Lithium" [127] appeared in the literature. Initially, two models to describe the structure of these cyanocuprates were put forward: (*i*) a bis-anionic species in which two organic groups and the cyanide were bound to the same copper atom (Fig. 1.32A), and (*ii*) a cyano-Gilman cuprate in which only the two organic groups were bound to copper (Fig. 1.32B). The controversy was resolved in 1999 [128], in favor of proposal B.

For lower-order cyanocuprates, it was already clear at an early stage that the organic group and the cyanide were bound to the same copper atom. An elegant NMR study by Bertz [129] on ^{13}C-labeled MeCu(^{13}CN)Li showed that a coupling of 22 Hz was present between the cyanide carbon atom and the methyl group, which could only be the case if both groups were bound to the same copper atom. This spectroscopic evidence was later confirmed by X-ray crystal structure determinations of [*t*-BuCu(CN)Li(OEt)$_2$] [130] (Fig. 1.33) and [2,6-Trip$_2$C$_6$H$_3$Cu(CN)Li] (Trip = 2,4,6-(*i*-C$_3$H$_7$)$_3$C$_6$H$_3$) [131], which appeared in the literature at practically the same time.

It appeared that [*t*-BuCu(CN)Li(OEt)$_2$] exists in the solid state as a dimer [*t*-BuCu(CN)Li(OEt)$_2$]$_2$. Two anionic *t*-BuCu(CN) units, with almost linear geom-

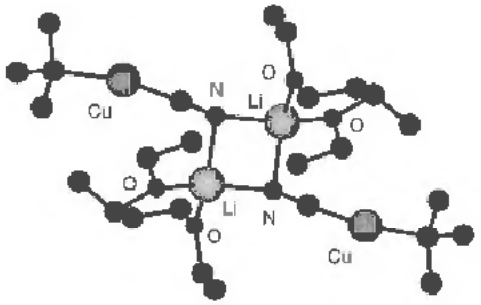


Fig. 1.33. Structure of [*t*-BuCu(CN)Li(OEt)$_2$]$_2$ in the solid state.

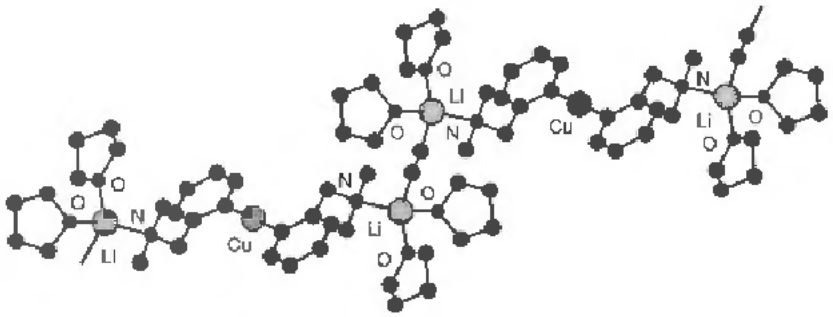


Fig. 1.34. Structure of polymeric $[(C_6H_4CH_2NMe_2\text{-}2)_2Cu(CN)Li_2(THF)_4]_n$ in the solid state.

etries, are linked together through bridging cyanide group nitrogen atoms to two lithium cations. Each lithium cation adopts a tetrahedral coordination geometry as a result of coordination of two diethyl ether molecules. The overall structural features of $[2,6\text{-}Trip_2C_6H_3Cu(CN)Li(OEt)_2]_2$ are very similar to those of $[t\text{-}BuCu(CN)Li(OEt)_2]_2$.

NMR investigations [129, 132, 133], EXAFS and XANES studies [134–136], and theoretical calculations [127, 137, 138] performed on higher-order cyanocuprates strongly suggested that the cyanide anion was not bound to copper in these $R_2Cu(CN)Li_2$ species. Additional evidence was provided by the first X-ray crystal structure determinations of "higher-order" cyanocuprates: $[(C_6H_4CH_2NMe_2\text{-}2)_2Cu(CN)Li_2]$ [139] (Fig. 1.34) and $[(tBu)_2Cu(CN)Li_2]$ [130] (Fig. 1.35).

The molecular structure of the first compound comprises a polymeric chain, consisting of alternating $[(C_6H_4CH_2NMe_2\text{-}2)_2Cu]$ anionic and $[Li_2(CN)(THF)_4]$ cationic units. In the cationic unit, two lithium atoms are end-on bridged by the cyanide group, and two additional THF molecules are coordinated to each lithium atom. The fourth coordination site is occupied by the nitrogen atom of the adjacent (dimethylamino)methylphenyl group of the $[(C_6H_4CH_2NMe_2\text{-}2)_2Cu]$ anionic unit.

On the basis of molecular weight determinations by cryoscopy in THF and conductivity measurements, it was concluded that the polymeric chain breaks up in solution to form smaller aggregates, probably giving rise to solvent-separated

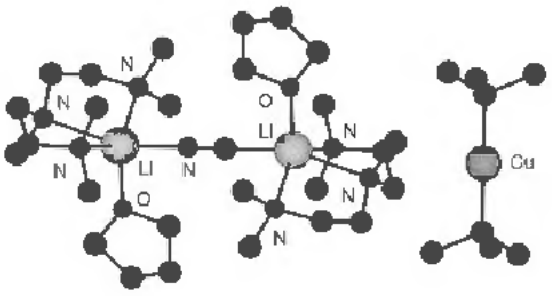


Fig. 1.35. Structure of $[t\text{-}Bu_2Cu][Li_2CN(THF)_2(PMDTA)_2]$ in the solid state.

ion-pairs. The presence of donor solvents, THF in this case, may greatly contribute to the (thermodynamic) stability of a particular structure. This may be inferred from the observation that the use of a less polar solvent such as benzene induces a disproportionation reaction, giving the neutral homoleptic cuprate $[Cu_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4]$ (discussed previously) and LiCN.

The structure of $[t\text{-}Bu_2Cu(CN)Li_2]$ in the solid state consists of isolated $[t\text{-}Bu_2Cu]$ anionic units and $[Li_2CN(THF)_2(PMDTA)_2]$ cationic units (Fig. 1.35). The structural features of the linear R Cu R arrangement are identical to those observed for other $[R_2Cu]$ anionic units discussed previously (cf. Fig. 1.31). The $[Li_2CN(THF)_2(PMDTA)_2]$ cationic unit consists of a central cyanide moiety, to which two lithium atoms are bound in end-on fashion. Coordination saturation at each lithium atom is achieved by coordination of the three nitrogen atoms of the PMDTA molecule and one THF molecule, rendering each lithium atom pentacoordinate. Recent ^1H, ^6Li HOESY experiments showed that this ionic structure found in the solid state is probably retained in polar solvents such as THF [**140**].

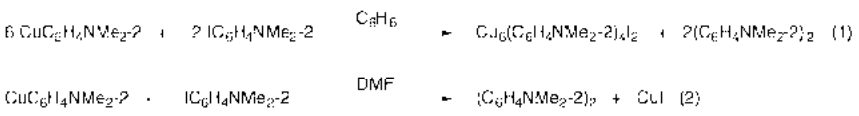
The solution structures of cyano-Gilman cuprates and lower-order cyanocuprates have been studied by cryoscopic measurements in THF [**141**]. The results of this study have in several cases shown ways to obtain useful single crystals of several higher- and lower-order cyanocuprates and consequently to determine their structures in the solid state. It appears that a number of these cyanocuprates retain their observed solid-state structure when dissolved in THF.

1.5 Concluding Remarks

This review substantiates the earlier opinion [29, 45] that the various types of organocopper compounds known today are almost always highly aggregated species. In spite of this structural information, it remains very difficult (and often also incorrect) to correlate a given structural feature of an organocopper or cuprate reagent with its specific reactivity. It always has to be kept in mind that X-ray crystal structural information is generally obtained from crystalline material that selectively crystallized out of a solution existing as a complicated equilibrium mixture of a number of aggregates, rather than as a solution of one pure compound. The aggregate that crystallizes from solution is the thermodynamically most stable one, and this is often the kinetically less reactive species. Indeed, there are only a very few examples of compounds for which it has been proven that the structure as observed in the solid state is retained in solution. One such is $[Cu_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4]$ in apolar solvents such as benzene.

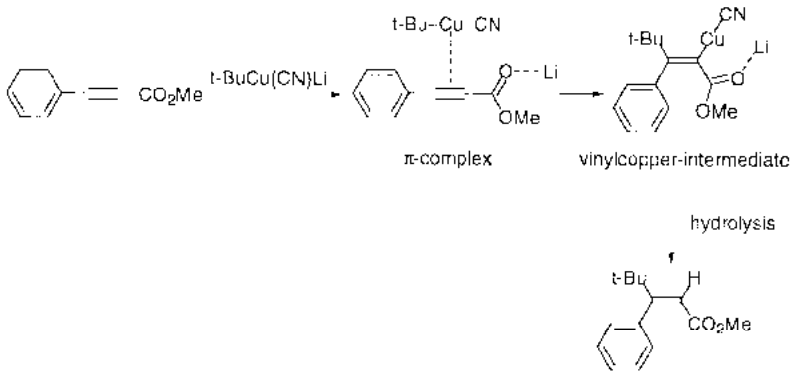
Another factor that complicates understanding of reaction mechanisms and of the actual species involved in reactions of organocopper compounds is the strong tendency of organocopper compounds and cuprates to aggregate with metal halides. These metal halides are often formed as unavoidable co-products when an organocopper compound or an organocuprate is applied as a reagent in organic synthesis. This means that, during a reaction, the initial reagent is gradually con-

verted into another aggregate with different structural features and, consequently, often a different reactivity (cf. Eqns. 1 and 2 in Scheme 1.24) [95].



Scheme 1.24.

To correlate the structural features of a specific copper or cuprate reagent with its reactivity, a better understanding of the interaction of such species with metal halides, ligands, solvents, and, last but not least, substrates is required. Such investigations have already begun and seem to have a promising future. In an elegant NMR study by Krause et. al. [23] it was demonstrated that the reaction between *t*-BuCu(CN)Li and methyl propiolate (see Scheme 1.25) could be monitored by ^{13}C NMR. At −100 °C, resonances attributable to the presence of a π-complex between the organocuprate and the substrate were observed. After the temperature had been raised to −40 °C, the ^{13}C NMR spectrum of a vinylcopper intermediate was observed. Finally, hydrolysis afforded the final product.



Scheme 1.25.

More recently, ^{1}H, ^{6}Li HOESY studies of the structures of cuprates in solution have been undertaken [24, 140]. As outlined in the previous section, the solid-state structures of neutral cuprates such as $Cu_2Li_2Ph_4(OEt_2)_2$ may be described in terms of contact ion-pairs (CIPs) of $[CuPh_2]^-$ and $[Li(OEt_2)]^+$. These studies show that such "simple" cuprates exist in solution in equilibrium between the CIPs and solvent-separated ion-pairs (SSIPs), shown schematically for $CuLiMe_2$ in Fig. 1.36.

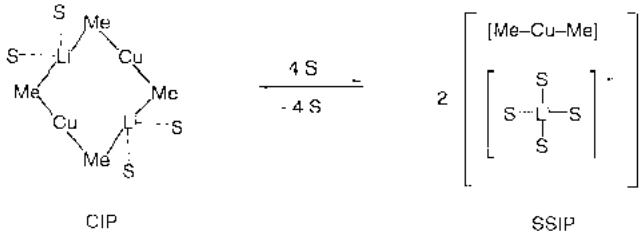


Fig. 1.36. Equilibrium between CIP and SSIP structures.

It has become evident that essentially only the CIP is present in less polar solvents such as diethyl ether, whereas in solvents with a strong affinity for Li^+, such as THF, the major species in the equilibrium is the SSIP. Moreover, this difference in the structural features of the species present in solution could be directly related to its reactivity. In the Michael addition reaction it is most likely that the reactive species is the CIP, as shown by the following experiments. No reaction was observed when $CuLiMe_2$ was treated with 2-cyclohexenone in the presence of two equivalents of 12-crown-**4**; the pure SSIP is present [**142**]. Furthermore, it has been observed that the rate of the reaction between $CuLiMe_2$ and 2-cyclohexenone in THF is considerably slower than that of the same reaction in diethyl ether. Again, this solvent dependence can be explained by a CIP/SSIP equilibrium, which in the case of THF as the solvent lies predominantly on the SSIP side. These data are in perfect agreement with the logarithmic reactivity profiles of reactions between $CuLiR_2$ and enones in diethyl ether and THF as reported by Bertz [**143**, **144**]. Moreover, recent theoretical calculations for this type of reactions [**145**] point to a transition state involving a CIP type of structure for the cuprate moiety (see Fig. 1.37).

The present challenge for scientists is to use modern spectroscopic techniques (such as NMR, in situ IR, in situ EXAFS, and others already available, or which will become available in the near future) in combination with advanced theoretical calculations to obtain new insights into the actual mechanisms and species that play roles in reactions of well known organocopper and cuprate compounds.

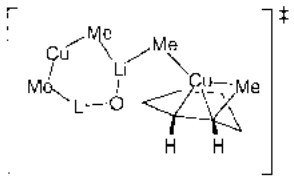


Fig. 1.37. Calculated structure of the transition state in the reaction between $CuLiMe_2$ and 2-cyclohexenone.

Acknowledgement

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2
Transmetalation Reactions Producing Organocopper Reagents

Paul Knochel and Bodo Betzemeier

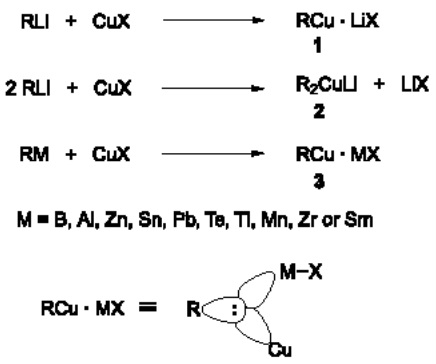
2.1
Introduction

Organocopper reagents constitute a key class of organometallic reagents, with numerous applications in organic synthesis [1]. Their high reactivities and chemoselectivities have made them unique intermediates. Most reports use organocopper reagents of type **1** or **2**, which are prepared from organolithiums. This transmetalation procedure confers optimal reactivity, but in many cases it permits only the preparation of relatively unfunctionalized organocopper reagents. More recently, substantial developments have been taking place in transmetalations to organocopper reagents starting from organometallic species that tolerate the presence of functional groups [2], while synthetic methods permitting the preparation of functionalized organolithiums and organomagnesium compounds have also been developed. All organometallics in which the metal M is less electronegative than copper, and all organometallic species of similar electronegativity but with weaker carbon-metal bonds, are potential candidates for transmetalation reactions [3]. Thus, reaction conditions allowing the transmetalation of organo-boron, -aluminium, -zinc, -tin, -lead, -tellurium, -titanium, -manganese, -zirconium and -samarium compounds have all been found, resulting in a variety of new organocopper reagents of type **3**. Their reactivity is dependent on the nature of the original metal M, which in many cases is still intimately associated with the resulting organocopper reagent (Scheme 2.1) [3–5].

In this chapter, we will emphasize these recent developments, especially those that allow the preparation of organocopper species not accessible through the standard procedures involving organolithiums as precursors and their use in reactions with organic electrophiles.

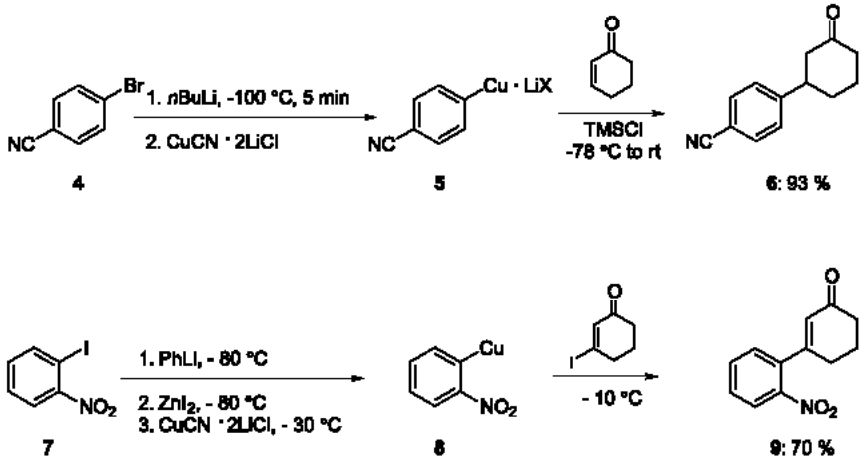
2.2
Transmetalation of Functionalized Organolithium and Organomagnesium Reagents

Many functional groups are incompatible with organolithium reagents. Execution of transmetalations at very low temperatures, however, enables functionalized



Scheme 2.1. Transmetalations producing organocopper reagents.

alkenyllithiums and aryllithiums to be prepared, and subsequent further transmetalation at low temperatures provides the corresponding copper reagents [6]. Thus, treatment of 4-bromobenzonitrile 4 with *n*BuLi at −100 °C in a THF/ether/pentane mixture provides the corresponding aryllithium within 5 min. (Scheme 2.2), and subsequent treatment with the THF-soluble copper salt CuCN·2LiCl [7] then affords the functionalized arylcopper compound 5. Treatment of this with 2-cyclohexenone in the presence of TMSCl [8] furnishes the expected Michael adduct 6 in 93% yield.

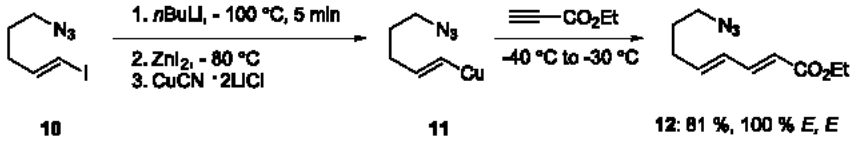


Scheme 2.2. Preparation of functionalized arylcopper reagents from functionalized aryllithiums.

In some cases it can be advantageous first to transmetalate the functionalized aryllithium reagent to the corresponding zinc reagent and then to perform a second transmetalation to afford the corresponding organocopper species. Thus, 2-iodo-1-nitrobenzene 7 is converted into the corresponding lithium reagent by treatment with phenyllithium [9]. Subsequent transmetalation, firstly with ZnI_2 at

−80 °C and then with CuCN·2LiCl [7] at −30 °C, provides the arylcopper **8**. This reacts with 3-iodo-2-cyclohexenone to give the expected addition-elimination product **9** in 70% yield.

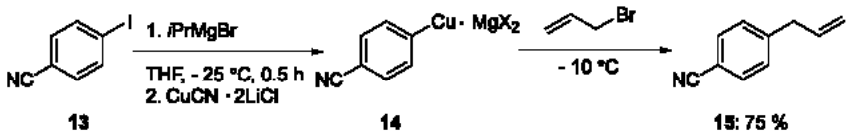
This method can be extended to the preparation of alkenylcopper compounds. Thus, treatment of the iodoalkenyl azide **10** with *n*BuLi at −100 °C (Scheme 2.3), followed by transmetalation with ZnI_2 in THF and then by a second transmetalation with CuCN·2LiCl, produces the copper species **11**. This then effects a *cis*-selective carbocupration of ethyl propiolate to furnish the (*E*,*E*) diene **12** in 81% yield.



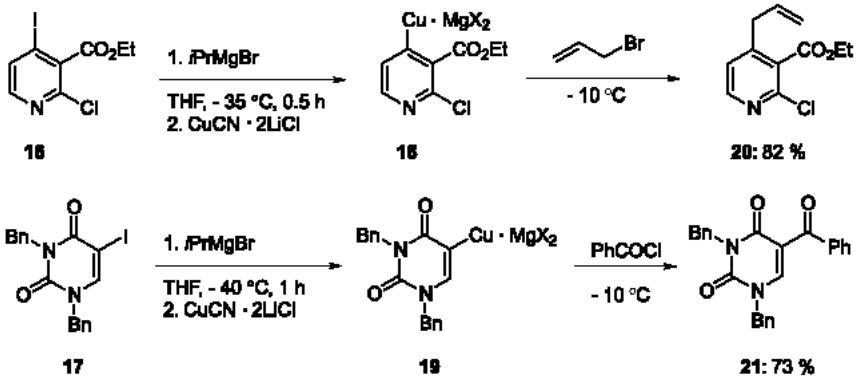
Scheme 2.3. Preparation of an azido-alkenylcopper reagent from an alkenyl iodide.

In general, the preparation of functionalized organolithiums is difficult, although direct lithiation with lithium powder in the presence of a catalytic amount of 4,4′-di-*t*-butylbiphenyl (DTBB) as introduced by Yus [10] is a very general approach to a broad range of polyfunctional organolithiums [11–16], which may be converted into the corresponding organocopper compounds by treatment with CuCN·2LiCl [6]. Organomagnesium compounds are less reactive than organolithiums and tolerate a wider range of functional groups. Mild methods are required for their preparation and excellent results have been obtained by insertion of highly reactive "Rieke-magnesium" into alkyl or aryl halides [17]. Unfortunately, the presence of such important electron-withdrawing functional groups as esters or cyano functions inhibits the formation of Grignard reagents [18]. Complementarily, halogen-magnesium exchange [19] has proven to be an excellent method for preparation of functionalized organomagnesium compounds. Thus, treatment of 4-iodobenzonitrile **13** with *i*PrMgBr or iPr_2Mg in THF at −25 °C furnishes the corresponding organomagnesium reagent, which is transmetalated to produce the desired functionalized organocopper **14**. Treatment of **14** with allyl bromide produces the allylated product **15** in 75% yield (Scheme 2.4) [20].

This iodine-magnesium exchange can also be performed with heterocyclic iodides, such as the functionalized pyridine **16** [21] or the iodouracil derivative **17** (Scheme 2.5) [22]. In both cases, the intermediate organomagnesium reagent can



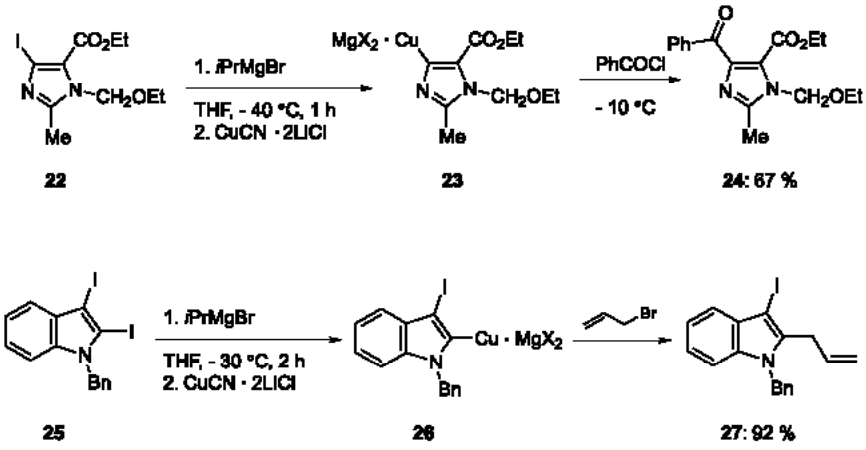
Scheme 2.4. Preparation of functional arylcoppers from functionalized arylmagnesium compounds.



Scheme 2.5. Preparation of highly functionalized, six-membered heterocyclic copper reagents.

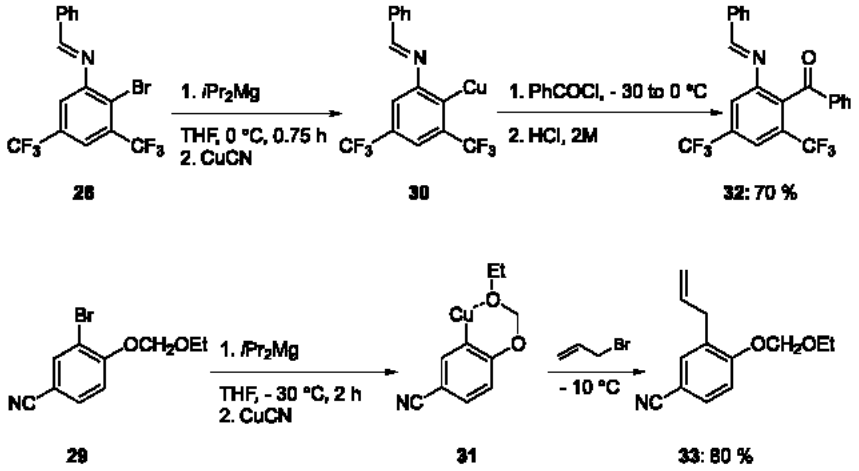
be converted into the corresponding organocopper compound (**18** and **19**, respectively) and then treated with several electrophiles such as allyl bromide or benzoyl chloride, resulting in the expected products **20** and **21** in good yields.

The preparation of polyfunctional 5-membered heterocycles can be achieved in the same manner. The ester-substituted imidazole **22** undergoes a smooth iodine-magnesium exchange at −40 °C within 1 h (Scheme 2.6). After transmetalation with CuCN·2LiCl, the copper reagent **23** is obtained. Treatment of this with benzoyl chloride furnishes the benzoylated imidazole **24** in 67% yield [23]. In the case of the 2,3-iodoindole derivative **25**, it is possible to perform a selective iodine-magnesium exchange at position 2, furnishing the 3-iodo-2-indolylcopper reagent **26** after transmetalation with CuCN·2LiCl. Treatment of **26** with allyl bromide provides the monoallylated indole derivative **27** in 92% yield [24].



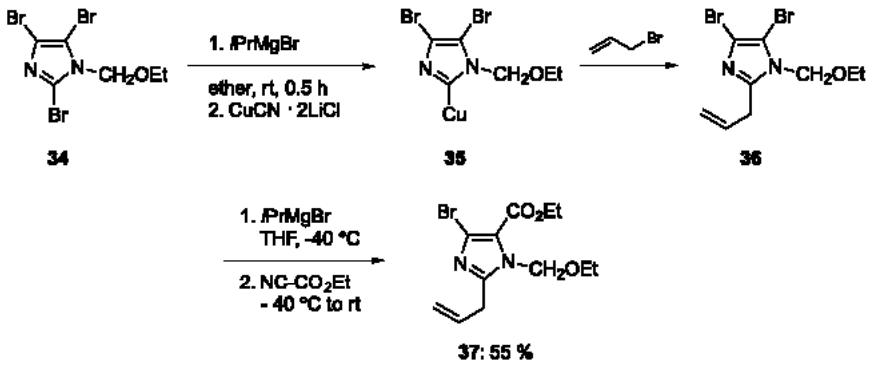
Scheme 2.6. Preparation of highly functionalized, five-membered heterocyclic copper reagents.

Remarkably, halogen-magnesium exchange can also be extended to aryl and heteroaryl bromides [24, 25]. Thus, the functionalized aryl bromides **28** and **29** (Scheme 2.7) were converted, at 0 °C and at −30 °C, respectively, into the corresponding Grignard reagents. After treatment with CuCN, the copper derivative **30** and **31** were obtained. Subsequent treatment with typical electrophiles such as benzoyl bromide or allyl bromide furnished the products **32** and **33**, in 70 and 80% yields.



Scheme 2.7. Preparation of functionalized arylcoppers from aryl bromides.

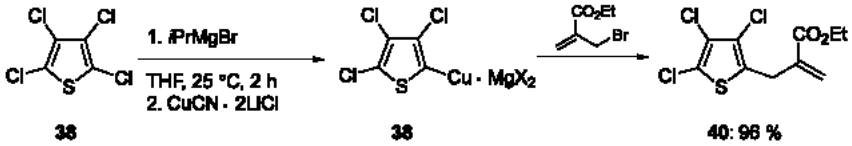
The rate of bromine-magnesium exchange largely depends on the electron density on the aromatic ring, although also being accelerated by the presence of chelating groups [25]. In the case of polyhalogenated heterocycles, these effects enable selective exchange reactions to be accomplished. Thus, the tribromoimidazole **34** (Scheme 2.8) can be successfully converted first into the magnesium derivative and then into the copper reagent **35**, by treatment with *i*PrMgBr followed by



Scheme 2.8. Stepwise Br Mg exchange reactions.

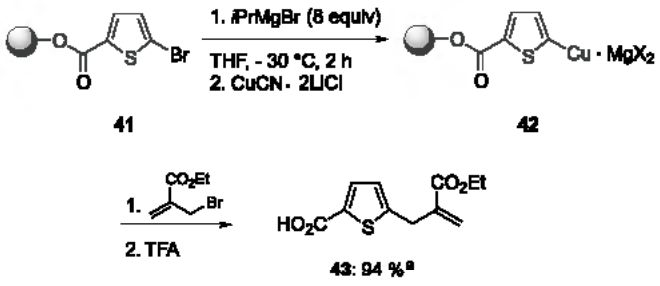
CuCN·2LiCl. This can then be selectively allylated with allyl bromide to provide the dibromoimidazole **36**, which can now be magnesiated by treatment with a further equivalent of *i*PrMgBr, providing the ester-substituted imidazole **37** in 55% yield after carboxylation with ethyl cyanoformate [25].

The halogen-magnesium reaction can be extended to electron-poor heteroaryl chlorides. Thus, tetrachlorothiophene **38** (Scheme 2.9) undergoes chlorine-magnesium exchange at 25 °C, providing the corresponding Grignard reagent in 2 h. Treatment with CuCN·2LiCl gives the copper reagent **39**, and allylation with ethyl (2-bromomethyl)acrylate produces the functionalized thiophene **40** in almost quantitative yield.



Scheme 2.9. Execution of a Cl Mg exchange reaction.

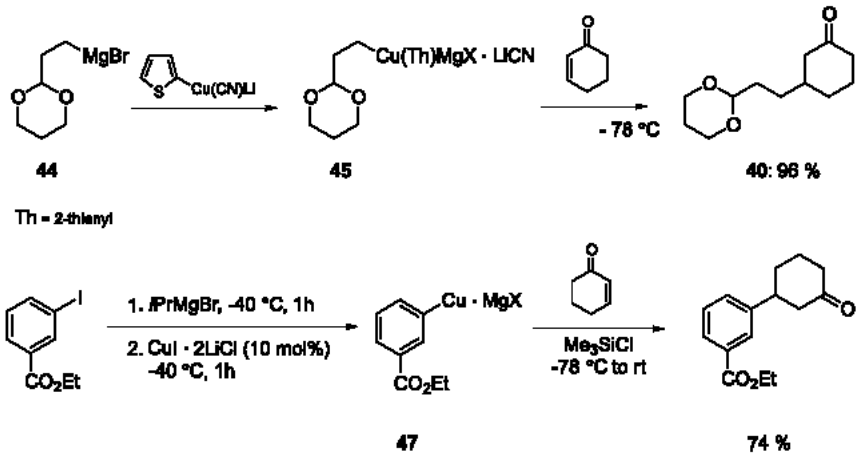
All the allylation reactions can be performed using only catalytic amounts of CuCN·2LiCl, with yields the same as those obtained when a stoichiometric amount of the copper salt is deployed. The halogen-magnesium exchange reaction can also be extended to the solid phase, allowing a variety of polyfunctional copper species to be generated on a resin. Thus, various aryl or heteroaryl iodides or bromides can be attached to Wang resins and treated with an excess of *i*PrMgBr (3–8 equiv.) at −30 °C to −15 °C to provide the expected functionalized Grignard reagent. Transmetalation with CuCN·2LiCl then gives, as expected, the corresponding copper reagent, which can react with various electrophiles such as acid chlorides or allylic halides. After cleavage from the resin, a range of functionalized products may be obtained. Use of the resin-bound bromothiophene **41** as starting material furnishes the copper reagent **42**, which produces the carboxylic acid **43** after allylation and cleavage from the resin (Scheme 2.10) [19, 24].



[a] HPLC-purity (UV, 254 nm)

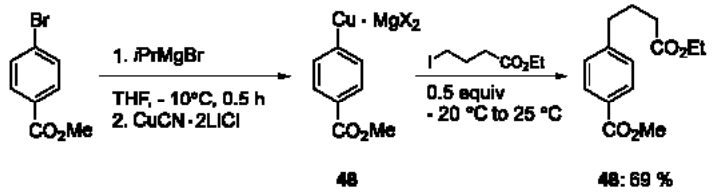
Scheme 2.10. Generation and reaction of functionalized organocopper reagents on the solid phase.

Functionalized organocopper reagents also undergo 1,4-additions. Thus, the alkylcopper 45, prepared from the corresponding Grignard reagent 44, reacts with cyclohexenone at −78 °C to give the expected product 46 [26]. Arylcopper compounds such as 47 add to 2-enones in the presence of TMSCl and CuCN·2LiCl [27] (Scheme 2.11).



Scheme 2.11. Michael additions of functionalized organocopper reagents derived from Grignard compounds.

It is also possible to perform copper-catalyzed alkylation of arylmagnesium compounds. Thus, the copper reagent 48 undergoes a selective cross-coupling [28] with ethyl 4-iodobutyrate to furnish the desired product 49 in 69% yield (Scheme 2.12) [29].

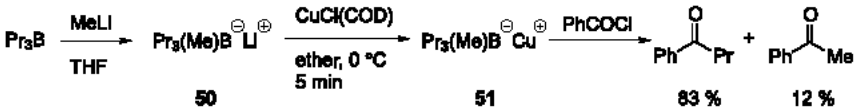


Scheme 2.12. Alkylation of organocopper reagents derived from Grignard compounds.

2.3
Transmetalation of Organoboron and Organoaluminium Reagents

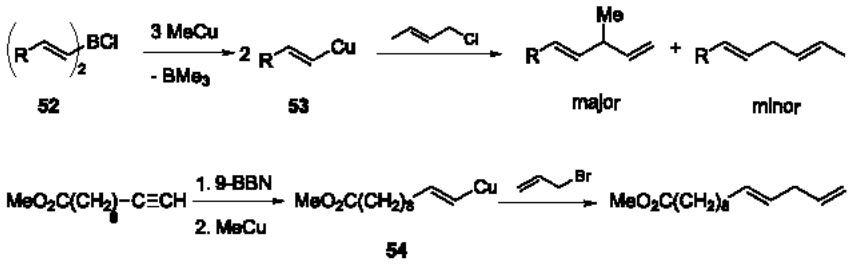
Direct transmetalation of organoboranes to organocopper reagents is not a general reaction. Because of their similar bond energies and electronegativities, this transmetalation is limited to the preparation of alkenylcopper and unfunctionalized

alkylcopper compounds. In the latter case, the reaction is favored by the formation of an ate-complex [30]. Thus, treatment of tripropylborane with MeLi produces the lithium organoboronate **50**, which is converted into the copper boronate **51**. Treatment of **51** with benzoyl chloride is not selective, since both the methyl group and the propyl group are transferred, affording a mixture of two ketones (Scheme 2.13).



Scheme 2.13. Acylation of organocopper reagents derived from organoboranes.

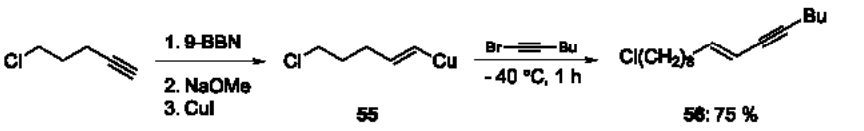
The transmetalation of dialkenylchloroboranes of type **52** with methylcopper (3 equiv.) provides an alkenylcopper compound **53**, which undergoes cross-coupling with allylic halides to produce mixtures of S_N2 and S_N2' products. Interestingly, this method is also useful for the preparation of functionalized alkenylcoppers such as **54** (Scheme 2.14) [31].



Scheme 2.14. Allylation of alkenylcopper species derived from alkenylboranes.

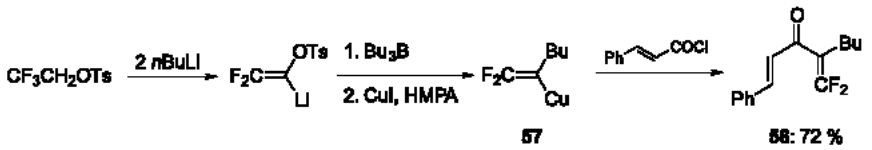
Better results can be obtained by generating the boronate species with the aid of sodium methoxide. In this case, satisfactory transmetalation occurs on treatment with CuI. Thus, the functionalized copper reagent **55** can be alkynylated with 1-bromo-1-hexyne at −40 °C, furnishing the enyne **56** in 75% yield (Scheme 2.15) [32].

In the presence of a polar cosolvent such as hexamethylphosphoric triamide (HMPA), it is possible to generate the fluorine-substituted copper compound **57**,



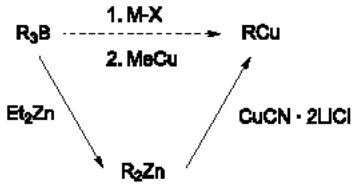
Scheme 2.15. Alkynylation of alkenylcopper reagents obtained from alkenylboranes.

obtained through a 1,2-migration of a butyl group. After acylation, this provides useful unsaturated ketones such as 58 (Scheme 2.16) [33].



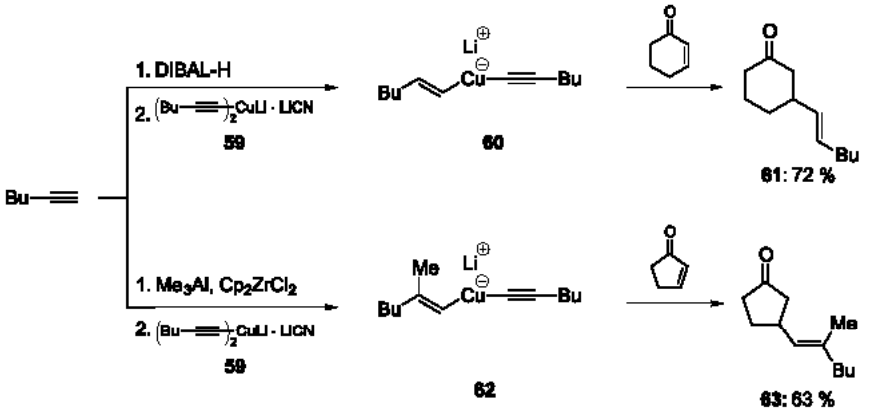
Scheme 2.16. Preparation of fluorinated ketones by way of fluorinated alkenylcopper species.

Thus, direct transmetalation of organoboranes to form organocopper compounds is a capricious reaction, not really generally applicable. Much more general access to organocopper compounds can, on the other hand, be achieved by prior conversion of the organoboranes into organozinc compounds. After addition of CuCN·2LiCl [7], the desired copper compounds are then cleanly generated and can be treated with a broad range of electrophiles, giving excellent yields (Scheme 2.17; see also Sect. 2.4) [34].



Scheme 2.17. Preparation of organocopper reagents from organoboranes.

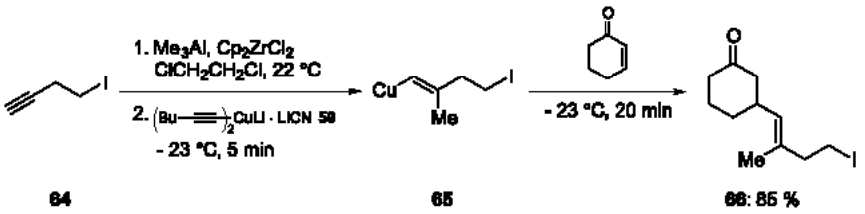
A smoother transmetalation procedure should be ensured by the more electronegative character of aluminium, as first demonstrated by Wipf and Ireland [35]. Thus, hydroalumination of 1-hexyne with DIBAL-H, followed by addition of the cuprate 59, bearing non-transferable alkynyl groups, provides the copper intermediate 60. This adds smoothly to 2-cyclohexenone to produce the Michael adduct 61, in 72% yield (Scheme 2.18) [36].



Scheme 2.18. Michael additions using alkenylcopper species derived from alkenylaluminiums.

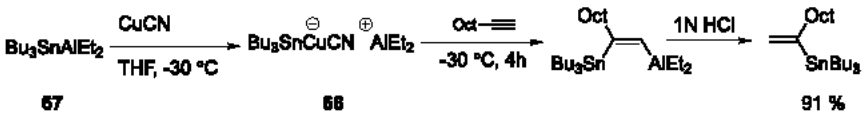
Alternatively, by performing a zirconium-catalyzed Negishi methylalumination on 1-hexyne, it is possible to produce stereochemically pure alkenylcopper species **62**, which adds to enones in a 1,4-fashion, to give compounds such as **63** (Scheme 2.18) [35, 36].

Wipf has shown that this method is quite general and tolerates several functional groups, such as ethers, thioethers, silanes, halides, aromatic rings, and olefins. The iodoalkyne **64** is readily carbometalated and after treatment with the dialkynylcuprate **59** furnishes the functionalized copper reagent **65**, which smoothly undergoes 1,4-addition reactions with enones. Thus, in the case of 2-cyclohexenone, the functionalized ketone **66** is produced in 85% yield (Scheme 2.19) [2, 36].



Scheme 2.19. Michael addition of a functionalized alkenylcopper species.

The scope of this transmetalation is very much a function of the availability of interesting alkenylaluminium species [37]. Stannylalumination of alkynes also proceeds through a stannylcopper intermediate **68**, obtained by transmetalation of the stannylated aluminium precursor **67**. This reaction enables regioselective stannylation of alkynes to be accomplished (Scheme 2.20) [38].



Scheme 2.20. Stannylation of terminal alkynes with stannylcopper reagents derived from stannylated aluminium compounds.

2.4
Transmetalation of Functionalized Organozinc Reagents

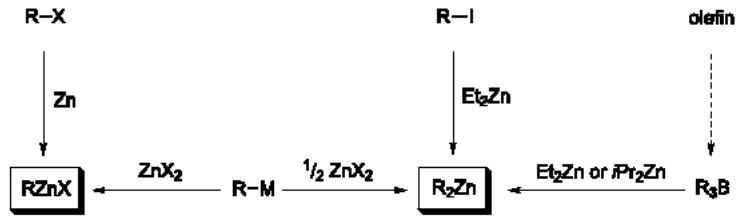
2.4.1
Preparation of Organozinc Reagents

Organozinc compounds have been known for more than 150 years, but their application in organic synthesis was formerly rather limited [39], due to their

moderate reactivity. Only when it was realized that organozincs undergo smooth transmetalations to give a broad range of organometallics did their synthetic applications begin to increase exponentially. Transmetalation of organozinc reagents to give organopalladium intermediates [40] and their transmetalation to organocopper compounds proved to be particularly important [7, 34, 41, 42]. Since it is possible to prepare organozinc compounds bearing a large range of organic functional groups, this methodology broadens the scope of organocopper chemistry considerably. This high functional group compatibility is a function of the pronounced covalent character of the carbon-zinc bond, while the excellent transmetalation capability of organozincs for production of other organometallics is a consequence of the presence of low-lying empty *p*-orbitals. Especially useful for this transmetalation are THF-soluble copper salts of the type CuCN·2LiX [7, 41]. After transmetalation, the resulting copper species, tentatively represented as RCu(CN)ZnX, reacts with most of those electrophiles E^+ that also react with the more classical diorganolithium cuprates (R_2CuLi), to afford products of type R-E (Scheme 2.21).

Scheme 2.21. Preparation of zinc-copper reagents.

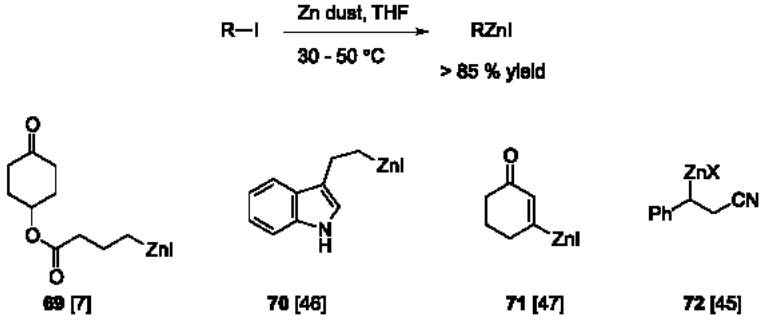
Notable exceptions are epoxides and alkyl halides, which do not react directly with RCu(CN)ZnX, although reaction conditions for performing alkylation reactions are available [43]. There are two classes of organozinc compounds: organozinc halides (RZnX) and diorganozincs (R_2Zn). The reactivity of diorganozincs is slightly higher, but the major difference relevant to this second class of organozinc compounds is the absence of zinc salts (ZnX_2), which is highly important for applications in asymmetric addition reactions [44]. The preparation methods are different. Whereas organozinc halides are obtained either by transmetalation reactions or by direct insertion of zinc dust into alkyl halides, diorganozincs are best prepared by means either of an iodine-zinc exchange reaction or of a boron-zinc exchange reaction (Scheme 2.22).



Scheme 2.22. Preparation of organozinc reagents.

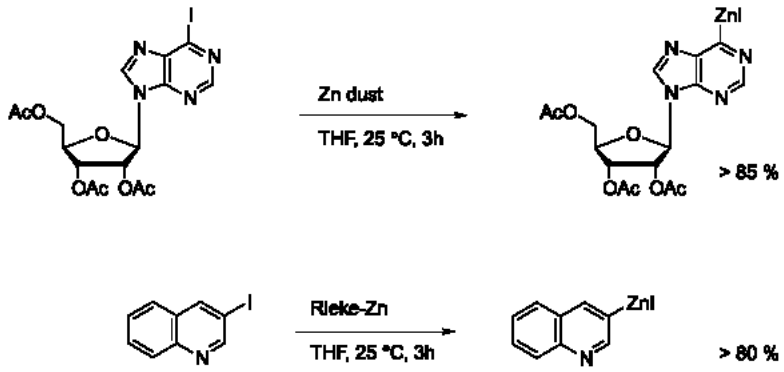
2.4.1.1 Preparation of Organozinc Halides

Functionalized organozinc halides are best prepared by direct insertion of zinc dust into alkyl iodides. The insertion reaction is usually performed by addition of a concentrated solution (approx. 3 M) of the alkyl iodide in THF to a suspension of zinc dust activated with a few mol% of 1,2-dibromoethane and Me_3SiCl [7]. Primary alkyl iodides react at 40 °C under these conditions, whereas secondary alkyl iodides undergo the zinc insertion process even at room temperature, while allylic bromides and benzylic bromides react under still milder conditions (0 °C to 10 °C). The amount of Wurtz homocoupling products is usually limited, but increases with increased electron density in benzylic or allylic moieties [45]. A range of polyfunctional organozinc compounds, such as **69–72**, can be prepared under these conditions (Scheme 2.23) [41].



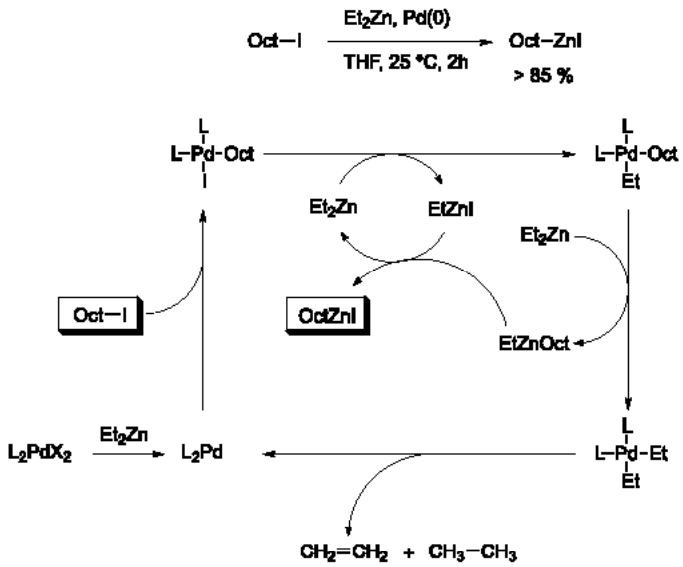
Scheme 2.23. Preparation of functionalized zinc reagents by direct insertion of zinc.

Insertion of zinc dust into aryl or heteroaryl iodides is also possible, but polar cosolvents are required in some cases [48, 49]. The use of highly activated zinc (Rieke zinc) prepared by reduction of zinc halides with lithium results in faster insertion (Scheme 2.24) [50–52].



Scheme 2.24. Preparation of functionalized arylzinc reagents.

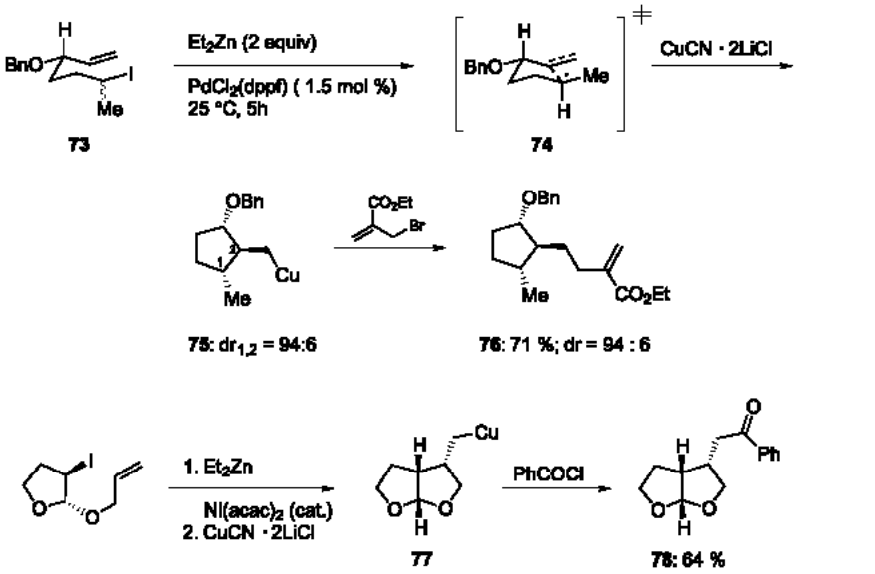
Crucially, this allows organozinc reagents to be prepared from less reactive aryl bromides and secondary or tertiary alkyl bromides. Alternatively, organozinc iodides can be prepared by means of a palladium(0)-catalyzed reaction between alkyl iodides and Et_2Zn (Scheme 2.25) [53–56].



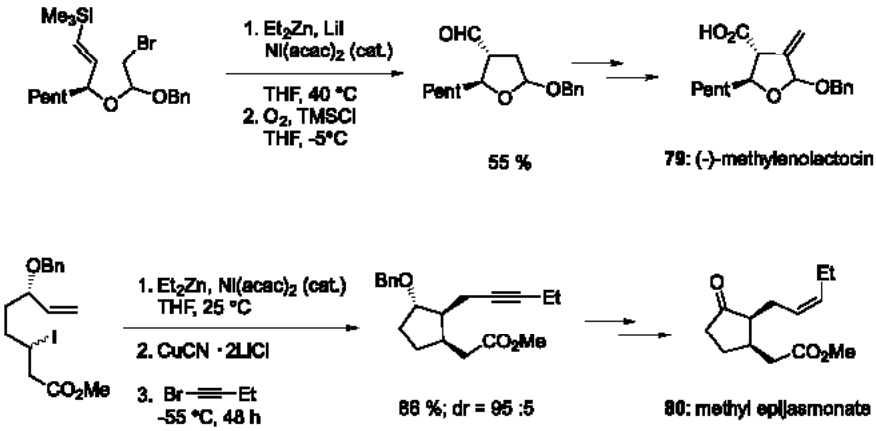
Scheme 2.25. Pd(0)-catalyzed formation of alkylzinc iodides.

The palladium(0)-catalyzed insertion proceeds through a radical insertion mechanism, allowing radical cyclizations to be performed. This procedure constitutes a new, stereoselective preparation of cyclic zinc reagents from unsaturated, open-chain compounds. Since the cyclization is radical in nature, the relative stereochemistry of the starting alkyl iodide does not need to be controlled. Thus, the unsaturated iodide **73**, used as a 1:1 mixture of diastereomers, produces a cyclic organozinc reagent after Pd(0)-catalyzed iodine-zinc exchange, by way of the transition state **74**. This then, after transmetalation with CuCN·2LiCl, gives the stereomerically pure organocopper **75**. Allylation with ethyl 2-(bromomethyl)acrylate affords the cyclopentane derivative **76** almost as a single stereoisomer (Scheme 2.26) [54].

This reaction can also be applied to the preparation of heterocyclic organocopper reagents such as **77** from readily available secondary alkyl iodides. Ring-closure in this case is catalyzed by $Ni(acac)_2$ rather than by Pd(0), affording new heterocyclic molecules such as **78** (Scheme 2.26) [55]. These cyclization reactions are key steps in the preparation of such natural products as (–)-methylenolactocin **79** [57] and methyl epijasmonate **80** [58] (Scheme 2.27).

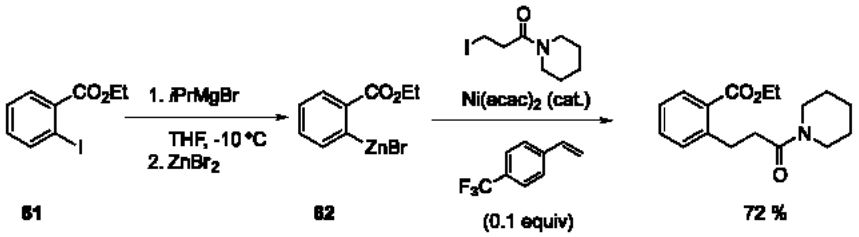


Scheme 2.26. Radical cyclizations resulting in cyclic copper organometallics (dppf = 1,1′-bis (diphenylphosphino)ferrocene).



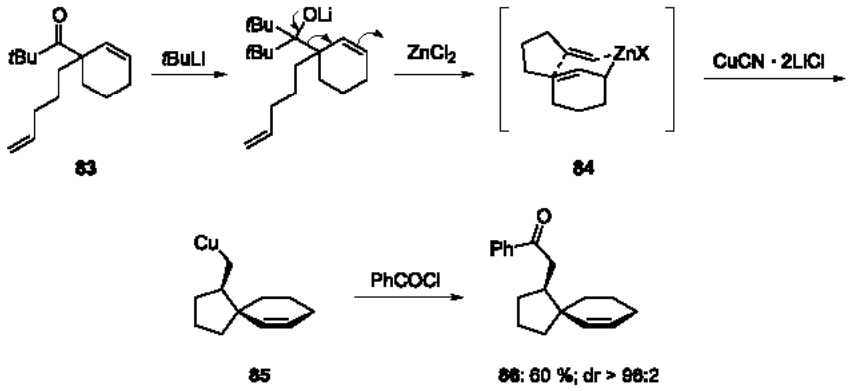
Scheme 2.27. Preparation of (–)-methylenolactocin 79 and methyl epijasmonate 80.

Various other less general methods for the preparation of organozinc halides are available, transmetalation from organomagnesium compounds being of interest. Thus, iodine-magnesium exchange in ethyl 2-iodobenzoate 81 produces a magnesium intermediate, which is transmetalated with $ZnBr_2$ to give the corresponding zinc reagent 82. This undergoes smooth Ni(0)-catalyzed cross-coupling with functionalized alkyl iodides (Scheme 2.28) [59].



Scheme 2.28. Preparation of a functionalized arylzinc halide by transmetalation of an organomagnesium compound.

Finally, the use of homoallylic zinc alcoholates as masked allylic zinc reagents has been described [60]. Thus, the ketone **83** was treated with *n*BuLi, producing a highly sterically hindered lithium alkoxide that, after conversion to the corresponding zinc alkoxide, underwent a fragmentation reaction to form the allylic zinc reagent **84**. After transmetalation with CuCN·2LiCl, this organozinc species underwent an intermolecular addition to the double bond, furnishing the spiroorganometallic compound **85**. Benzoylation of this produced the ketone **86**, in a diastereomeric ratio of >98:2 and in 60% yield (Scheme 2.29) [61].

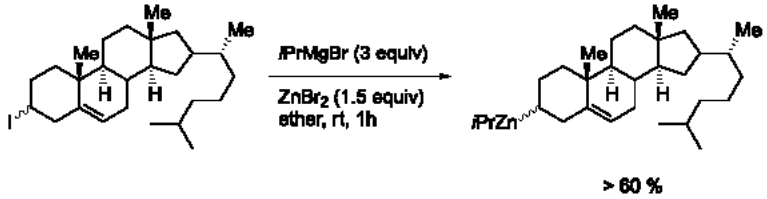


Scheme 2.29. Organozinc reagent prepared by an ene reaction.

2.4.1.2 Preparation of Diorganozinc Reagents

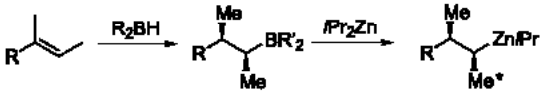
Other than transmetalation reactions from organolithium and organomaganesium compounds, there are two general methods for preparing diorganozincs. These are boron-zinc exchange and iodine-zinc exchange [42]. The iodine-zinc exchange reaction is catalyzed by the presence of copper(I) salts and is radical in nature. It is best performed with Et_2Zn [62, 63], and usually takes place within 12 h at 50 °C. It is also possible to perform the exchange under irradiation conditions [64]. Provided that the presence of metal salts does not perturb the further course of the reaction, iodine-zinc exchange can be performed by using iPr_2Zn generated in situ by treat-

ment of *i*PrMgBr with $ZnBr_2$ (0.5 equiv.). With this reagent, the exchange reaction occurs very rapidly (25 °C, 1 h), allowing complex secondary diorganozincs to be prepared (Scheme 2.30) [65].



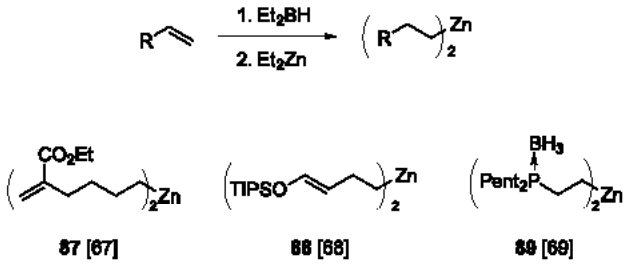
Scheme 2.30. Preparation of a diorganozinc compound by iodine-zinc exchange.

Because of the radical character of the exchange, it is not possible to prepare chiral diorganozinc reagents in this way [66]. The most general and practical preparation of diorganozincs is the boron-zinc exchange reaction, which has several advantages. It tolerates various functional groups and, since the starting organoboranes used for the exchange are prepared from olefins, numerous functionalized olefins are available as starting materials. More importantly, boron-zinc exchange proceeds with retention of configuration. Thus, chiral organoboranes are excellent precursors for chiral secondary alkylzinc reagents (Scheme 2.31) [42].



Scheme 2.31. Boron-zinc exchange for the preparation of chiral organozinc reagents.

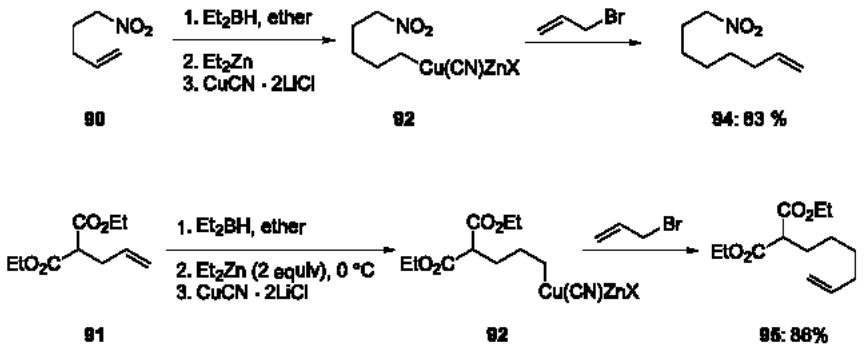
In the case of primary organoboranes, the exchange reaction is best performed with Et_2Zn, whereas less reactive secondary organoboranes require the use of iPr_2Zn. Thus, a wide variety of terminal olefins have been converted into primary diorganozincs such as **87**–**89** (Scheme 2.32).



87 [67] **88** [68] **89** [69]

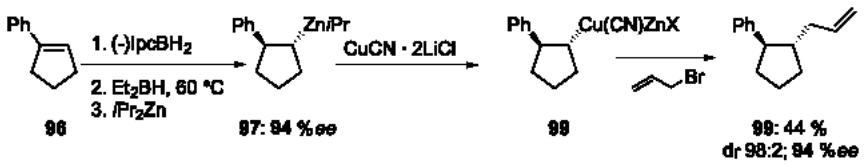
Scheme 2.32. Preparation of polyfunctional primary dialkylzinc compounds by boron-zinc exchange.

Remarkably, this reaction sequence permits the preparation of diorganozincs bearing acidic hydrogen atoms in the molecule. The unsaturated nitroalkane **90** and the unsaturated alkylidenemalonate **91** are smoothly converted into the corresponding diorganozinc reagents by the sequence shown in Scheme 2.33. Transmetalation with CuCN·2LiCl provides the expected organocopper reagents **92** and **93**. After allylation with an excess of allyl bromide, the desired products **94** and **95** are obtained in excellent yields [70].



Scheme 2.33. Preparation of organocopper reagents bearing acidic hydrogens.

As mentioned above, chiral diorganozincs can be prepared by this procedure. Thus, treatment of 1-phenylcyclopentene (**96**) with (–)-IpcBH$_2$ provides a chiral organoborane (99% *ee* after recrystallization). Treatment of this with Et$_2$BH at 60 °C for 16 h gives a diethylorganoborane, which undergoes transmetalation with *i*Pr$_2$Zn to afford the chiral organozinc reagent **97**. After further transmetalation with CuCN·2LiCl, the chiral secondary organocopper reagent **98** is formed. Allylation of this with allyl bromide gives the cyclopentane **99** in 44% overall yield (94% *ee* and 98:2 *trans*:*cis* ratio; Scheme 2.34) [71].

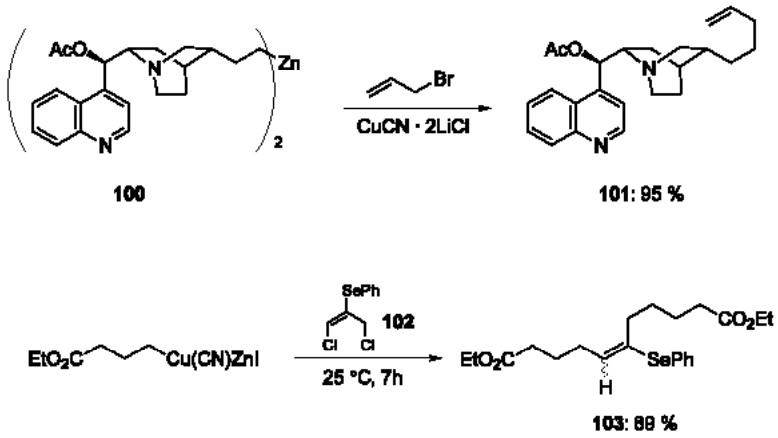


Scheme 2.34. Preparation of chiral alkylcopper reagents (Ipc = isopinocampheyl).

The same method can be applied to the preparation of chiral acyclic organocopper reagents of somewhat lower configurational stability [72]. Chiral cyclic organocopper compounds can also be prepared by diastereoselective hydroboration of prochiral allylic ethers [73]. Mixed secondary organozinc reagents of the type FG RZnCH$_2$SiMe$_3$ (FG = functional group; CH$_2$SiMe$_3$: non-transferable group) can also be prepared [74–76].

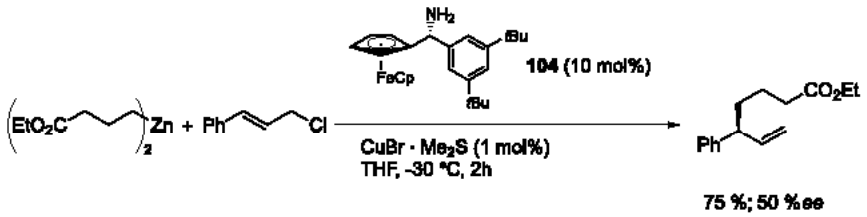
2.4.2
Substitution Reactions with Copper-Zinc Reagents

Organocopper reagents prepared from organozinc species undergo S_N2' reactions with allylic halides or allylic phosphates in high yields. These reactions display excellent S_N2' regioselectivity. The polyfunctional organozinc species **100**, obtained from the corresponding olefin by a hydroboration/boron-zinc exchange sequence, can be smoothly allylated in the presence of the THF-soluble salt CuCN·2LiCl [7, 70] to give the polyfunctional quinoline derivative **101**. Selective double S_N2' reaction is observed with 1,3-dichloropropene reagent **102**, producing the unsaturated selenide **103** in 89% yield and with high regioselectivity (Scheme 2.35) [77].

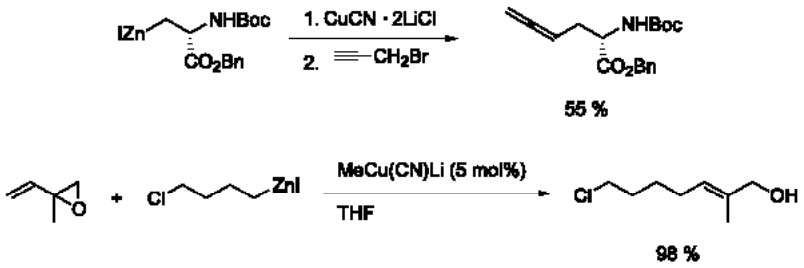


Scheme 2.35. Copper(I)-mediated allylation reactions.

In most allylation reactions, only a catalytic amount of CuCN·2LiCl is required [41]. Use of the chiral ferrocenylamine **104** as a catalyst makes enables asymmetric allylation of diorganozinc reagents to be effected with allylic chlorides (Scheme 2.36) [78]. Related electrophiles such as propargylic bromides [79] and unsaturated epoxides [80] also undergo S_N2'-substitution reactions (Scheme 2.37).

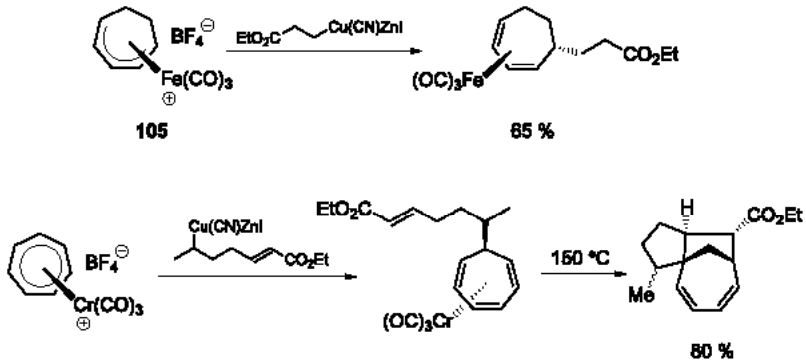


Scheme 2.36. Enantioselective allylation with diorganozinc reagents.



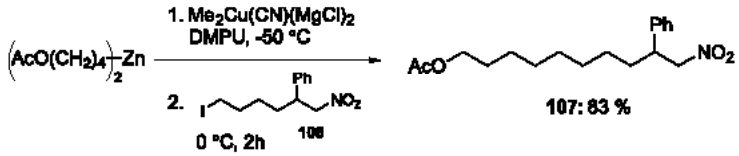
Scheme 2.37. Substitution reactions of propargylic bromides and unsaturated epoxides with organozinc reagents.

Substitution reactions also proceed well with cationic η^5-cycloheptadienyliron complexes such as **105** [81] and related chromium complexes [82], and have found applications in natural product synthesis (Scheme 2.38).



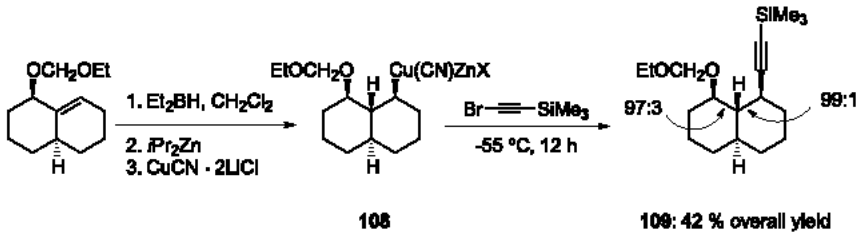
Scheme 2.38. Reactions between copper-zinc reagents and cationic metal complexes.

Alkyl iodides do not react with zinc-copper reagents. However, use of copper species $R_2Cu(CN)(MgX)_2 \cdot Me_2Zn$, obtained by treatment of the cuprate $Me_2Cu(CN)(MgCl)_2$ with a diorganozinc compound R_2Zn, results in a cross-coupling reaction at 0 °C in DMPU. The reaction tolerates a number of functional groups, as well as alkyl iodides containing acidic hydrogens, such as **106**. The desired cross-coupling product **107** is produced in good yield (Scheme 2.39) [43].



Scheme 2.39. Cross-coupling between copper-zinc reagents and alkyl iodides.

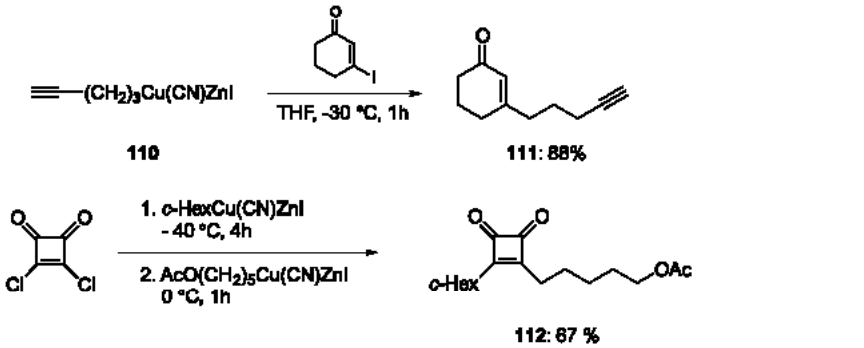
Cross-coupling between functionalized zinc-copper reagents and 1-iodoalkynes or 1-bromoalkynes is very fast [83]. This smooth cross-coupling occurs at low temperatures (−55 °C) and offers high stereoselectivity in reactions with chiral secondary organozinc-copper reagents such as **108** (obtained by a hydroboration/boron-zinc exchange sequence), producing the alkyne **109** in 42% overall yield (Scheme 2.40) [73].



Scheme 2.40. Alkynylation of chiral secondary copper-zinc reagents.

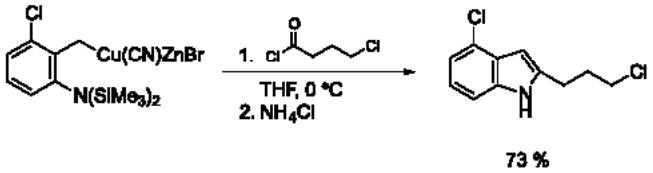
Alkynylation of zinc-copper compounds has been used for the synthesis of polyfunctional acetylenic ethers [84] and for the preparation of building blocks for pharmaceutically active compounds [85]. Whereas cross-coupling between non-activated iodoalkenes and zinc-copper reagents only proceeds at elevated temperatures and in polar solvents such as NMP or DMPU (60 °C, 12 h) [86], alkenyl iodides conjugated with electron-withdrawing groups react under milder conditions. Thus, 3-iodo-2-cyclohexenone undergoes the addition-elimination reaction with the zinc-copper reagent **110** at −30 °C within 1 h, affording the functionalized enone **111** in excellent yield (Scheme 2.41) [46].

The same mechanism is operative for the preparation of squaric acid derivatives of type **112**. Treatment of 3,4-dichlorocyclobutene-1,2-dione with two different zinc-copper reagents provides the double addition-elimination product **112** in 67% yield (Scheme 2.41) [87].



Scheme 2.41. Substitution reactions with copper-zinc reagents by addition-elimination mechanisms.

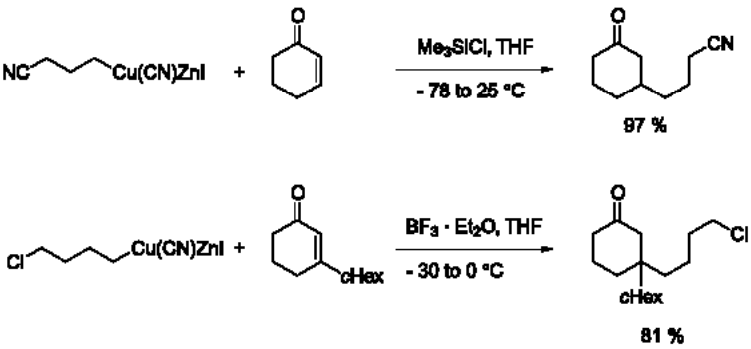
The reaction between zinc-copper reagents and acid chlorides is very general and provides a useful synthesis of ketones [7, 34, 41, 42]. This acylation has also been used to prepare various indoles substituted in position 2 (Scheme 2.42) [88].



Scheme 2.42. Synthesis of 2-substituted indoles by acylation of functionalized organozinc reagents.

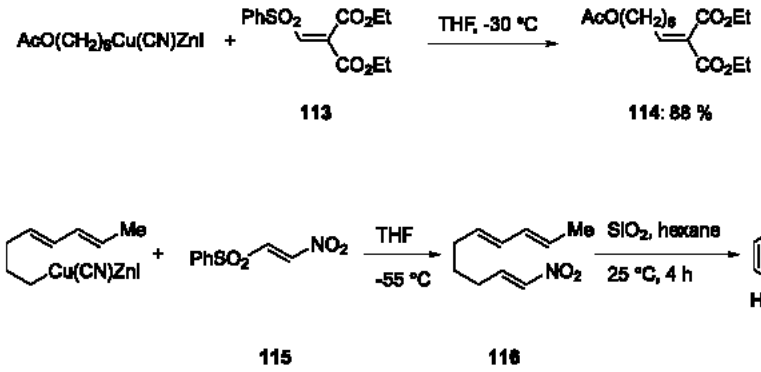
2.4.3
Addition Reactions with Copper-Zinc Reagents

Zinc-copper compounds readily undergo Michael addition reactions in the presence of TMSCl, selectively affording 1,4-adducts [7, 34, 41, 42]. In the case of β-disubstituted enones, the 1,4-addition proceeds well in the presence of $BF_3{\cdot}OEt_2$ (Scheme 2.43) [89].



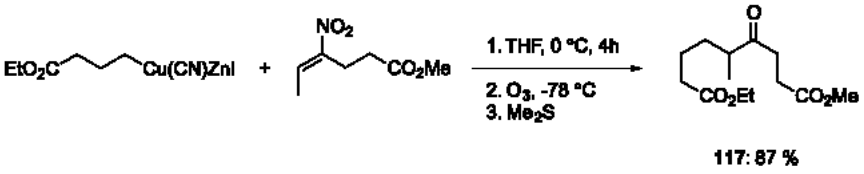
Scheme 2.43. Michael additions of copper-zinc reagents to enones.

Prostaglandin derivatives may be prepared by the addition of copper-zinc reagents to substituted cyclopentenones [90–92]. In the presence of a copper(I)-monosubstituted sulfonamide, dialkylzincs also add to enones [93]. The addition of zinc-copper compounds to unsaturated esters is difficult, and only efficient if a leaving group is present in the β-position. Alkylidenemalonates, on the other hand, readily undergo Michael additions [94]. The β-phenylsulfonylalkylidenemalonate **113** undergoes an addition-elimination process to provide functionalized alkylidenemalonates such as **114** in excellent yields [95]. Similarly, the β-phenylsulfonylnitroolefin **115** readily reacts with copper-zinc organometallics to provide nitro compounds such as **116**, which readily undergo intramolecular Diels-Alder reactions (Scheme 2.44) [96].



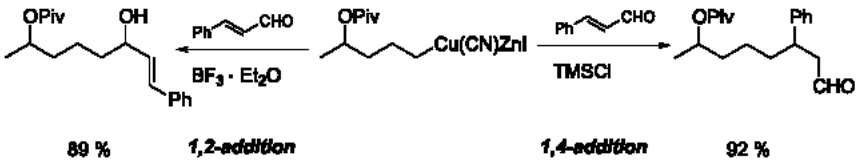
Scheme 2.44. Addition-elimination reactions involving copper-zinc reagents.

In general, copper-zinc compounds, unlike organolithium-derived organocopper reagents, undergo clean addition reactions to nitroolefins. After Michael addition, the resulting zinc nitronates can be oxidatively converted into polyfunctional ketones, such as **117** (Scheme 2.45) [96].



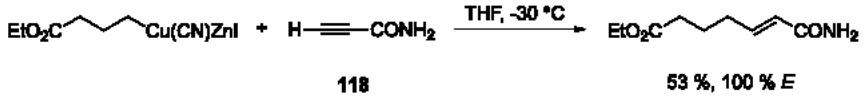
Scheme 2.45. Addition of zinc-copper reagents to nitroolefins.

Addition to unsaturated aldehydes results either in the 1,2- or in the 1,4-addition product, depending on the reaction conditions. Thus, in the case of cinnamaldehyde, the 1,2-addition product is produced in the presence of $BF_3 \cdot OEt_2$ and the 1,4-addition product is obtained in the presence of Me_3SiCl (Scheme 2.46) [97].



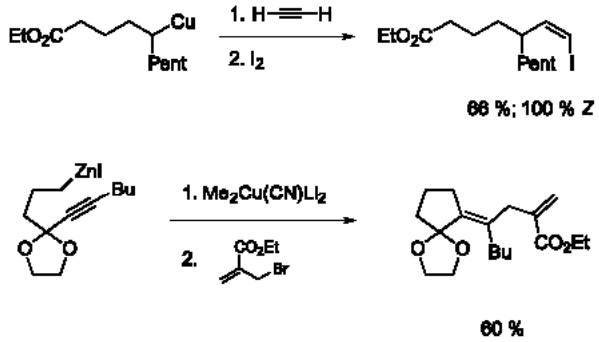
Scheme 2.46. Reactions between zinc-copper compounds and unsaturated aldehydes.

Acetylenic esters react well with copper-zinc compounds. Propiolic esters are especially reactive [83], but other acetylenecarboxylic acid derivatives such as dimethyl acetylenedicarboxylate or propiolamide **118** undergo highly stereoselective *cis* addition (Scheme 2.47) [46].



Scheme 2.47. Addition of zinc-copper compounds to propiolic acid derivatives.

Finally, zinc-copper exchange by treatment of FG RZnI with $Me_2Cu(CN)Li_2$ provides copper species that add smoothly to various alkynes and which can also be used to perform cyclization reactions (Scheme 2.48) [98].

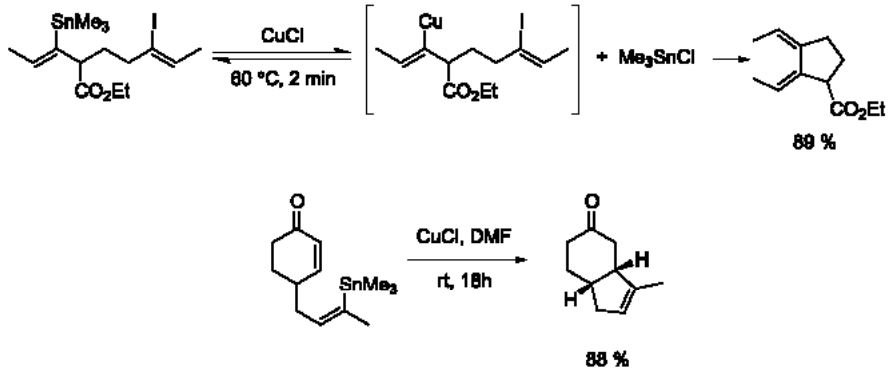


Scheme 2.48. Intermolecular and intramolecular carbometalation of alkynes with copper-zinc reagents.

Organozinc copper reagents have very broad synthetic potential and a number of typical experimental procedures have recently been published [99, 100].

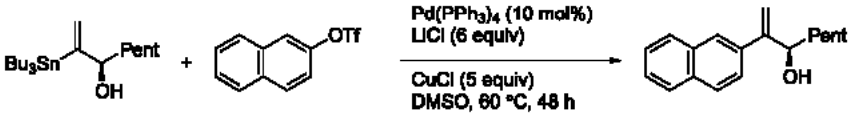
2.5
Transmetalation of Organotin, Organosulfur, and Organotellurium Reagents

Transmetalations of alkenylstannanes with copper salts are reversible if they are performed with CuCl in polar solvents [101]. This has found application in cyclization reactions (Scheme 2.49) [102].



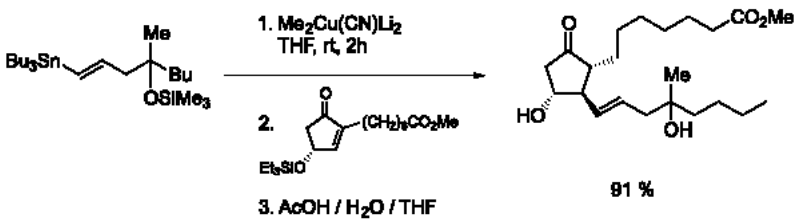
Scheme 2.49. Cyclization of alkenylcopper compounds generated from organostannanes.

Transmetalation of this type has also been used to assist palladium(0)-catalyzed cross-coupling reactions in sterically congested substrates. Transmetalation of stannanes into alkenylcopper intermediates considerably accelerates subsequent palladium(0)-catalyzed cross-coupling with arylsulfonates (Scheme 2.50) [103].



Scheme 2.50. Copper(I) chloride as a promoter of Stille cross-coupling.

These transmetalations may be performed not only with copper(I) halides in DMF [104], but also by using $Me_2CuLi{\cdot}LiCN$. This transmetalation has been used in the synthesis of prostaglandin derivatives (Scheme 2.51) [105].



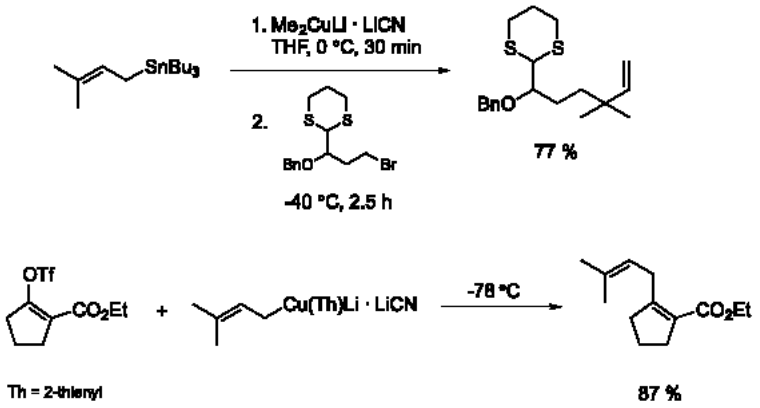
Scheme 2.51. Prostaglandin synthesis using Sn Cu transmetalation.

As well as alkenylstannanes [106–108], other classes such as α-heteroatom-substituted alkyltributylstannanes [109] and, more importantly, allylic stannanes [110, 111] also undergo these Sn Cu transmetalations. Otherwise difficult to prepare, allylic copper reagents may, however, be obtained by treatment of allylic stannanes (produced in turn from organolithium, magnesium, or zinc organometallics) with $Me_2CuLi{\cdot}LiCN$. They enter into cross-coupling reactions with alkyl bromides [110] or vinyl triflates (Scheme 2.52) [111].

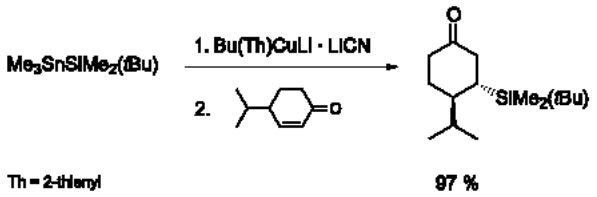
Michael additions [112] and other reactions typical of organocopper species can also be performed with silylcopper reagents such as TBDMSCu, prepared by Sn/Cu exchange [113] between $Me_3SnSiMe_2(t\text{Bu})$ and Bu(Th)CuLi·LiCN (Th = 2-thienyl) (Scheme 2.53) [113, 114].

Transmetalation of thioethers to organocopper compounds can also be performed in some special cases. Thus, treatment of the ester **119** with $Me_2CuLi{\cdot}LiCN$ provides the copper reagent **120**, which can be treated successfully with several electrophiles such as allyl bromide or acid chlorides to afford the expected products such as **121** (Scheme 2.54) [115, 116].

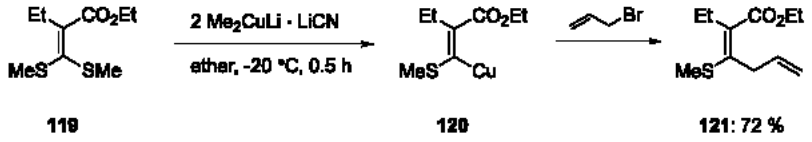
This reaction can be extended to cyanoketone dithioacetals [117]. Alkenyltellu-



Scheme 2.52. Cross-coupling of allylic copper compounds.

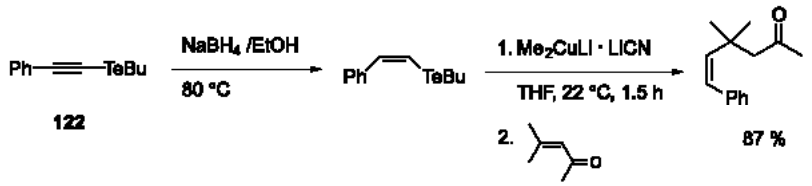


Scheme 2.53. Preparation of silylcuprates by Sn/Cu-transmetalation.



Scheme 2.54. Sulfur/copper exchange reaction.

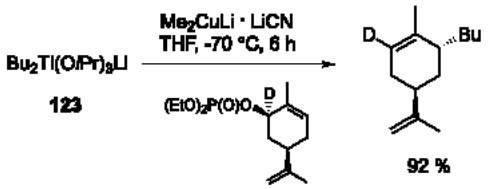
rium species also undergo exchange with $Me_2CuLi{\cdot}LiCN$. The synthetic importance of this exchange is due to the easy availability of (*Z*)-alkenyltellurium species by reduction of alkynyl tellurides such as **122** (Scheme 2.55) [118].



Scheme 2.55. Te/Cu exchange reactions of (*Z*)-alkenyltellurium species.

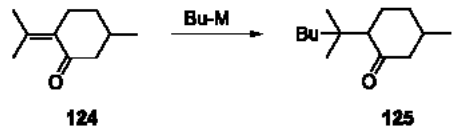
2.6
Transmetalation of Organotitanium and Organomanganese Reagents

Transmetalations with first row transition metal elements such as titanium or manganese have produced useful synthetic applications. Organotitanate species of type **123** show the advantage of high S_N2' selectivity in the *anti* stereochemistry of the resulting copper(I) intermediates (Scheme 2.56) [119, 120].



Scheme 2.56. Copper(I)-catalyzed *anti*-S_N2' substitution of allylic phosphates.

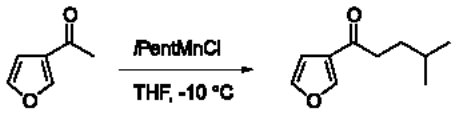
Organomanganese reagents are very useful organometallics, reacting with high chemoselectivity with acid chlorides [121] and several other classes of electrophiles [122]. The scope of organomanganese reagents can be greatly increased by use of copper(I) catalysis. Especially impressive is the performance of Michael additions [123–128]. Thus, the Michael addition between BuMnCl and pulegone **124**, furnishing **125**, proceeds in excellent yield in the presence of Li_2CuCl_4 (3 mol%) (Scheme 2.57) [128].



BuMnCl, THF, -30 °C to rt: < 5 %
BuMnCl, Li_2CuCl_4 (3 mol%), THF, 0 °C, 1h: 95 %
BuMgCl, Li_2CuCl_4 (3 mol%), THF, 0 °C, 2h: 51 %

Scheme 2.57. Copper-catalyzed Michael addition reactions between organomanganese reagents and pulegone.

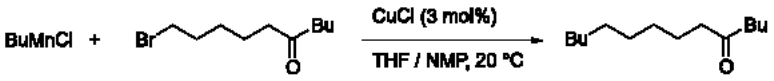
Acylation reactions can also be greatly improved in this way, with *t*-alkyl- or *sec*-alkyl-manganese reagents reacting with acid chlorides in excellent yields [123]. The related addition-elimination to 3-ethoxy-2-cyclohexenone is also improved, resulting after acidic aqueous workup in 3-methyl-2-cyclohexenone [125]. The perillaketone **126** was prepared in an improved yield using copper(I) catalysis (Scheme 2.58) [129].



126: 94 % in presence of CuCl (1 mol%)
63 % without CuCl

Scheme 2.58. Preparation of perilla-ketone using copper-catalyzed acylation.

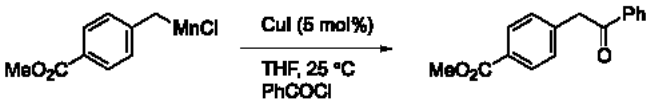
Alkylation of organomanganese reagents with alkyl bromides can also be improved by addition of CuCl (3 mol%). The reactions proceed at room temperature and are complete within a few hours [123, 130]. The opening of epoxides is also improved under these conditions. The reaction also features good chemoselectivity, tolerating the presence of sensitive functions such as ketones (Scheme 2.59) [130].



90 %

Scheme 2.59. Copper-catalyzed alkylation of alkyl manganese reagents.

Benzylic organomanganese reagents prepared by direct insertion of activated manganese metal display the same behavior (Scheme 2.60) [131]. Excellent results are also obtained for 1,4-additions of organomanganese reagents to unsaturated esters in the presence of CuCl (3 mol%) [127].

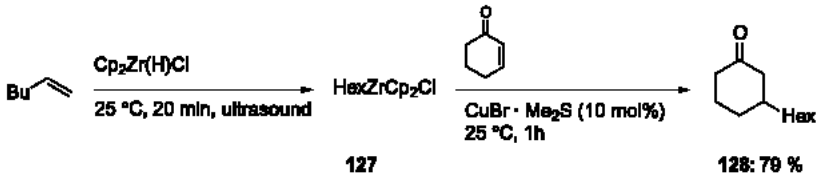


75 %

Scheme 2.60. Copper-catalyzed acylation of benzylic manganese reagents.

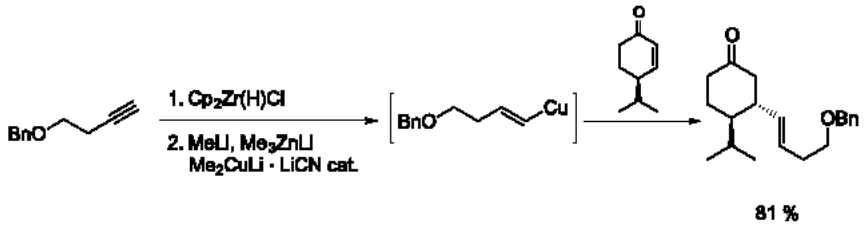
2.7
Transmetalation of Organozirconium and Organosamarium Reagents

Transmetalation reactions of organozirconium reagents were pioneered by Schwartz [130–132], with improved procedures developed more recently by Lipshutz [133] and Wipf [134]. The hydrozirconation of 1-hexene with $H(Cl)ZrCp_2$ at 25 °C under sonication conditions produces the *n*-hexylzirconium complex **127**, which adds to cyclohexenone in the presence of $CuBr{\cdot}Me_2S$ (10 mol%) to afford the desired product **128** in 79% isolated yield (Scheme 2.61) [134].

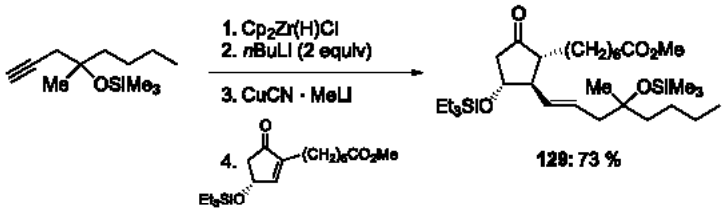


Scheme 2.61. Copper-catalyzed 1,4-addition of alkylzirconium derivatives.

Similarly, alkenylzirconium species prepared by the hydrozirconation of alkynes add in a conjugated fashion to enones. Formation of an intermediate zincate prior to transmetalation to the copper species facilitates the Michael addition (Scheme 2.62) [135]. This methodology has been applied to the preparation of protected misoprostol **129** (Scheme 2.63) [136, 137].

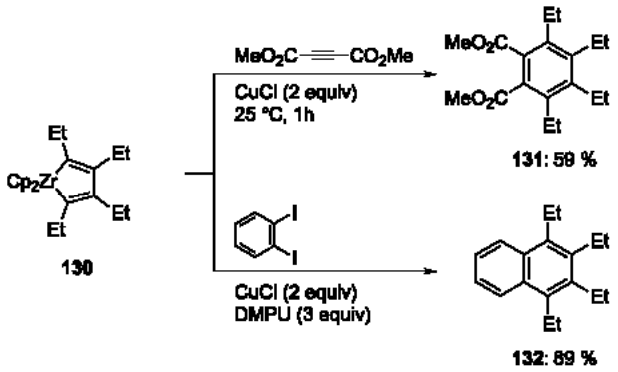


Scheme 2.62. "Michael addition of an alkenylzirconium compound", by successive transmetalation into zinc and copper intermediates.



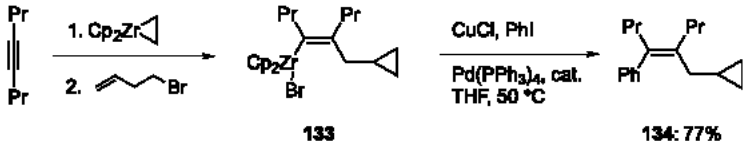
Scheme 2.63. Synthesis of protected misoprostol **129**.

The mechanism and the nature of the reaction intermediates have been carefully studied by Wipf, revealing an activation of the carbonyl group of the enone by the zirconium complex. Remarkably, a variety of primary and secondary alkylzirconium complexes can be added to enones in 1,4-fashion under mild conditions [134, 138]. Interestingly, treatment of zirconocyclopentadienes such as **130** with alkynes such as dimethyl acetylenedicarboxylate in the presence of CuCl gives benzene derivatives such as **131** [136, 137]. A transmetalation from Zr to Cu has been postulated in this reaction. Annelation reactions involving a similar transmetalation of **130** and cross-coupling with 1,2-diodobenzene proceeds in high yield to afford **132** (Scheme 2.64) [139, 140].



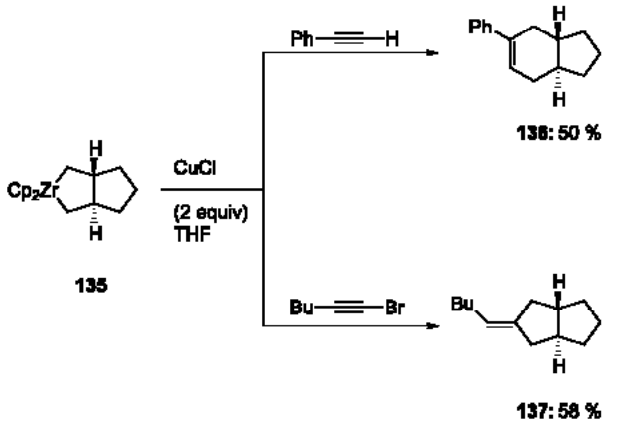
Scheme 2.64. Copper-catalyzed reactions of zirconocyclopentadienes.

Cross-coupling reactions between alkenylzirconocenes such as **133** and aryl or alkenyl iodides occur readily in the presence of CuCl and $Pd(PPh_3)_4$, producing tetrasubstituted olefins such as **134** in good yields (Scheme 2.65) [141, 142].



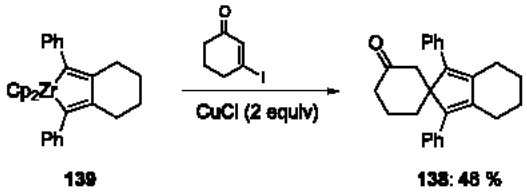
Scheme 2.65. Cross-coupling between alkenylzirconocene complexes and aryl iodides.

Carbocupration of alkynes by zirconacyclopentane derivatives can be performed according to the same procedure. Thus, the zirconocyclopentane **135**, obtained by treatment of Bu_2ZrCp_2 with 1,6-heptadiene, reacts at room temperature with phenylacetylene to afford the adduct **136** through a carbocupration-reductive elimination mechanism. Cross-coupling followed by intramolecular carbocupration takes place in the case of the reaction with 1-bromohexyne, producing **137** (Scheme 2.66) [143].



Scheme 2.66. Copper-catalyzed reactions of zirconacyclopentane derivatives.

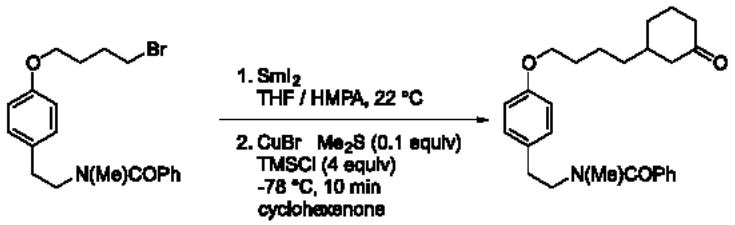
Finally, spiro-compounds such as **138** can be prepared by treatment of zirconacylopentadienes such as **139** with 3-iodo-2-cyclohexenone in the presence of CuCl (2 equiv.) (Scheme 2.67) [144].



139 **138: 46 %**

Scheme 2.67. Spirometalation of zirconacyclopentadienes.

Very few transmetalations between organolanthanides and organocopper reagents have been reported. Organosamarium(III) reagents, prepared by treatment of SmI_2 with alkyl halides in THF/HMPA, undergo easy conjugate addition to unsaturated ketones and nitriles in the presence of TMSCl, producing the corresponding Michael adducts. Functionalized alkyl bromides such as **140** react chemoselectively with cyclohexenone in the presence of TMSCl and $CuBr{\cdot}Me_2S$ (0.1 equiv.) to afford the polyfunctional ketone **141** in 60% yield (Scheme 2.68) [145].



140 **141: 60 %**

Scheme 2.68. Copper-catalyzed 1,4-addition of organosamarium reagents.

2.8 Conclusion

Transmetalations of various organometallic species with copper salts have been found to produce highly useful organocopper reagents of great synthetic interest. Many different organometallic precursors have proved valuable, depending on the functionality present in the copper reagent. The scope of organocopper chemistry has been greatly enhanced by these new transmetalation reactions and these reagents have found many applications in organic synthesis.

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3
Heteroatomcuprates and α-Heteroatomalkylcuprates in Organic Synthesis

R. Karl Dieter

3.1
Introduction

Organocopper(I) chemistry slowly emerged from Reich's preparation of phenyl copper (1923) and Gilman's subsequent reports on ethyl copper (1936) and lithium dimethylcuprate (1952) [1]. The conjugate addition reactions [2] of Kharasch (RMgX/cat CuX, 1941) and House (R_2CuLi, 1966) and the substitution reactions of Corey and Posner [3] inaugurated a period of rapid development in organocopper chemistry. Simple alkylcopper or lithium dialkylcuprate reagents increasingly became employed for the introduction of simple, non-functionalized alkyl groups in natural product synthesis. The fact that only one of the alkyl groups was transferred from lithium dialkylcuprates to carbon electrophiles stimulated the development of heteroatom(alkyl)cuprates. In these reagents, the heteroatom bound to copper served as a non-transferable or residual ligand, enabling the transferable alkyl groups to be conserved [4]. Chiral, non-transferable heteroatom ligands also saw service in asymmetric organocopper reactions [5]. Although earlier reports had referred to silylcopper and stannylcopper reagents, the development and synthetic applications of these reagents was stimulated by the reports of Fleming (1978) and Piers (1980) [6]. Developments in the chemistry of silicon and tin resulted in the exploration of silylcuprates and stannylcuprates, where the synthetic value of the copper-mediated reactions lay in subsequent transformations involving the resultant C Si and C Sn bonds. The silyl and stannyl substituents were exploited as tools for regiocontrol and stereocontrol, and in the subsequent construction of C C bonds.

Utilization of heteroatom-functionalized organocopper reagents posed a major hurdle. The nature of the preparation of organocopper reagents, from organolithium and Grignard reagents, severely limited the type of alkyl ligand that could be introduced onto copper. Copper-mediated transfer of complex heteroatom-functionalized alkyl ligands, however, is a particularly attractive synthetic goal, since the organocopper transformations are often complementary to the organolithium and Grignard reactions. Successes in this field came with the development of procedures for oxidative addition of metallic copper with organic electrophiles [7], lithiation [8], and developments in transition metal chemistry that permitted

preparation of cuprate reagents from organometallic species other than lithium and Grignard reagents. Transmetalation from a variety of transition organometallic reagents to copper has developed into a powerful tool for uniting copper chemistry and highly functionalized alkyl ligands [9]. While Knochel's copper-mediated organozinc reactions [10] have admirably solved many problems in this area, lithium α-aminoalkylcuprates have provided a useful expansion of the corresponding organolithium chemistry [11].

This chapter focuses on heteroatomcuprates and α-heteroatomalkylcuprates and the potential they offer in the development of synthetic strategies. Alkylcuprate chemistry involving heteroatom functionality at a location other than the α-position is the topic of Chapt. 2.

3.2 Heteroatomcuprates

Heteroatom copper and cuprate reagents contain a ligand bound to copper through a heteroatom, which may either be transferred to an organic electrophile or serve as a non-transferable or residual ligand. Reagents derived from copper in its low valent oxidation state [that is, Cu(I)] readily transfer Group IVA ligands to a wide range of organic electrophiles, while Group VA ligands commonly act as residual ligands. Nevertheless, a limited number of Group VA ligand transfer reactions have been reported (vide infra).

3.2.1 Group IVA Heteroatoms (Si, Ge, Sn)

While organocopper(I) (RCu) and organocuprate reagents [RCu(L)Li] have been known for over half a century, the corresponding silyl and stannyl reagents are of recent origin. Like their carbon analogues, these reagents [6, 12, 13] can be prepared by the addition of silyllithium or stannyllithium reagents to Cu(I) salts in ethereal solvents [14, 15], tetrahydrofuran (THF) being the solvent most often used. The combination of Cu(I) salt, substitution pattern of the silyl or stannyl ligand, use of non-transferable residual ligands, and ligand:copper stoichiometries can result in a bewildering array of reagents (Tab. 3.1), which are likely to display different reactivities, regioselectivities, and stereoselectivities in their reactions with carbon electrophiles. The silylcuprates and stannylcuprates appear to be more thermally stable than the organocuprates, and preferentially transfer the Si [6, 14b, i] or Sn [14b, 16] heteroatom in mixed alkyl(heteroatom)cuprates [$(R_3M)CuRLi$; M = Si, Sn]. The preferential transfer of the silyl or stannyl group has been attributed to weaker Cu Si or Cu Sn bonds or alternatively to copper ligand HOMO/electrophile LUMO orbital interactions [14i]. The higher energy Cu M (M = Si, Sn) HOMO orbital will be closer in energy to the electrophile LUMO orbital than the energetically lower lying Cu C HOMO orbital, which is consistent with the observed selectivity. The mixed $(R_3M)Cu(alkyl)CNLi_2$ (M = Si, Sn) reagents con-

Tab. 3.1. Representative silyl and stannylcuprate reagents.

Silylcuprate Reagents	*C–Si to C–OH*	*Ref.*	*Stannylcuprate Reagents*	*Ref.*
$(Me_3Si)_2CuLi$	No	14a	$Me_3SnCu{\cdot}SMe_2$	15a, 6
$(PhMe_2Si)_2CuLi$	Yes	22a	n-$Bu_3SnCu{\cdot}SMe_2$	15b
$PhMe_2SiCu(CN)Li$	Yes	14b–c	$Me_3SnCu(CN)Li$	14b, 6
$(PhMe_2Si)_2CuLi{\cdot}LiCN$	Yes	14b–c, 24, 6	$(Bu_3Sn)_2CuLi$	15c, 37b
$PhMe_2SiCu(Me)CuLi{\cdot}LiCN$	Yes	14b,d	$(Me_3Sn)_2CuLi$	15d
$[(MeHC{-}CMeCH_2)Ph_2Si]_2CuLi$	Yes	14e	$(Bu_3Sn)Cu(n\text{-}Bu)Li{\cdot}LiCN$	16b, 6
$Et_2NPh_2SiCu(CN)Li$	Yes	14f, 6	$(Bu_3Sn)Cu(Me)Li{\cdot}LiCN$	14b, 15d
t-$BuMe_2SiCu(n\text{-}Bu)Li{\cdot}LiCN$	No	14g, 6	$Me_3SnCu(Bu)Li{\cdot}LiCN$	16c
$(t\text{-}BuPh_2Si)_2CuLi$	Yes	14g	$Me_3SnCu(SPh)Li$	15e
$[(Me_3Si)_3Si]_2CuLi$	—	14h	$(Ph_3Sn)_2CuLi$	15f

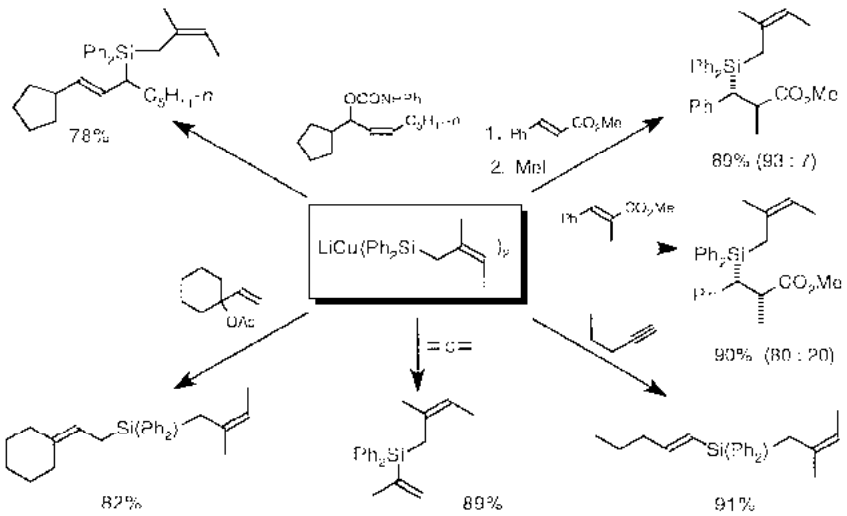
serve silyl and stannyl ligands, which are not always completely transferred from $(R_3M)_2CuLi$ reagents, and minimize Group IVA by-products (such as R_3MMR_3, R_3MH, R_3MOH) formed with the latter reagents. Although the greater thermal stability renders formation of silylcuprates and stannylcuprates less capricious than that of the carbon-centered reagents, the mode and method of preparation may play important roles. The $(PhMe_2Si)_2CuLi$ reagent is generally employed, due to difficulties in preparing trimethylsilyllithium and because the $PhMe_2Si$ group is readily converted into a hydroxy substituent [6].

Mixed alkyl(silyl)cuprates or alkyl(stannyl)cuprates are readily prepared by ligand exchange with lithium dialkylcuprates and $R_3SnSi(R^1)_3$ [16a], Me_3SnH [16b, c], $Me_3SiSnMe_3$ [16d], and $Me_3SnSnMe_3$ [16e]. $R_3SnSi(R^1)_3$ reagents can afford either silylcuprates or stannylcuprates, depending upon the steric bulk of R and R^1. The ligand exchange procedures obviate the necessity of generating silyllithium and stannyllithium reagents. Procedures catalytic in copper have been developed [17], while a procedure using disilane and $(CuOTf)_2{\cdot}PhH$ also avoids the use of silyllithium reagents [18]. For cuprate preparations, the use of CuCN is generally more reliable than that of CuI or CuCl, perhaps because of diminished yields with purified CuI [19] and the sensitivity of CuCl to light, air, and moisture. NMR studies (^1H, ^{13}C, ^{119}Sn, and ^{31}P for HMPA additive) of silylcuprates [14b, c, i] and stannylcuprates [14b] reveal rapid dynamic ligand exchange, with the $R_3MCu(R')CNLi_2$ composition as the thermodynamic sink. While these mixed heteroatomcuprates are often depicted as "higher order" cuprate reagents $[R_3MCu(R')CuCNLi_2]$ [14b, c, i, 16] and several "higher order" organocuprates have been confirmed both by NMR spectroscopy and by X-ray analysis [20], this formulation may be open to reappraisal [21]. Although these NMR studies reveal multiple species, depending upon $R_3M/RLi/CuCN$ stoichiometry, the "higher order" compositions need not necessarily have three ligands bound to copper. Alternative complexation arrays are possible and ligand exchange faster than the NMR timescale [14i] might preclude firm structural conclusions. In this account, the formulations $(R_3M)_2CuCNLi_2$ and

$(R_3M)_2CuLi{\cdot}LiCN$ are used interchangeably, reflecting the original literature, and serve only to convey the stoichiometry of reagent preparation. Although free lithium species may be present (depending upon stoichiometries [14i]), the less basic silyllithium and stannyllithium reagents generally pose fewer problems than the more basic alkyllithium reagents.

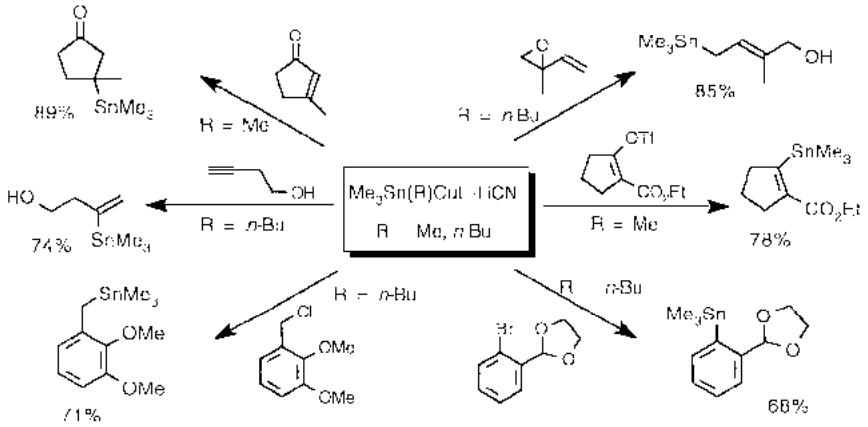
Early work on silylcopper and stannylcopper reagents found the same reaction profiles as exhibited by carbon-ligated copper reagents [6]. These include conjugate addition reactions [22, 23], silylcupration [24] and stannylcupration [15d, 25] of alkynes, and substitution reactions with acid chlorides [26, 27], allylic [28, 29] and propargylic [30, 31] substrates, vinyl substrates [32, 33], epoxides [26c, 34], alkyl electrofuges [34, 16b, d], and iminium salts [35]. While allenes generally fail to undergo carbocupration, they are readily amenable to silylcupration [27, 30, 36] and stannylcupration [36c, 37] reactions.

The synthetic power of these silylcuprate and stannylcuprate reactions lies in the synthetic utility of the product silanes and stannanes for carbon-carbon bond formation and also in the utilization of the silyl [38] or stannyl substituents as agents for stereocontrol and regiocontrol. Additionally, use of appropriate silylcuprates permits conversion of the produced C Si bond into a C OH bond (Tab. 3.1) [39]. This C Si to C OH conversion is a particularly difficult transformation for an allyl silane, and the development of lithium diphenyl(2-methyl-2-butenyl)silylcuprate for this purpose illustrates the characteristic transformations of silylcuprates (Scheme 3.1) [14e]. Several silyl substituents convertible into hydroxy groups are not amenable to the cuprate methodology [14e]. Allyl and vinyl silanes – generated by treatment of silylcuprates with allylic substrates and by silylcupration of alkynes, respectively – are synthetically powerful nucleophiles for carbon-carbon bond construction [40]. The corresponding stannylcuprates undergo similar transforma-



Scheme 3.1. Reactivity profile of silylcuprates with carbon electrophiles [14e].

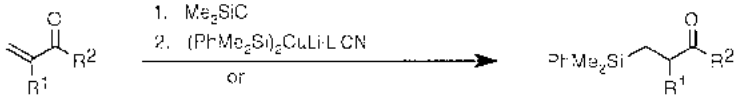
tions, independent of the method of cuprate preparation [16b, d] (Scheme 3.2). While allyl stannanes can be used as allylic nucleophiles [41], vinyl and aryl stannanes are frequently employed in the palladium-catalyzed Stille coupling, with vinyl, aryl, and alkynyl halides and sulfonates [42].



Scheme 3.2. Reactivity profile of stannylcuprates with carbon electrophiles [16b, d].

3.2.1.1 Conjugate Addition Reactions

Although trialkylstannyllithium reagents undergo conjugate addition reactions with 2-enones and enoates, the trialkylsilyllithium reagents are limited to 2-enones [6]. Silylcuprate conjugate adducts are sometimes formed in low yields if the intermediate enolate participates in a subsequent Michael reaction with the starting α,β-unsaturated substrate [43]. Sterically unhindered substrates and unsaturated aldehydes and ketones are particularly susceptible. This side reaction can be suppressed by addition of trimethylsilylchloride (TMSCl) or by use of zincate reagents (Scheme 3.3). The TMSCl presumably works either by trapping the enolate anion as the silyl enol ether or by accelerating the conjugate addition reaction (or both),

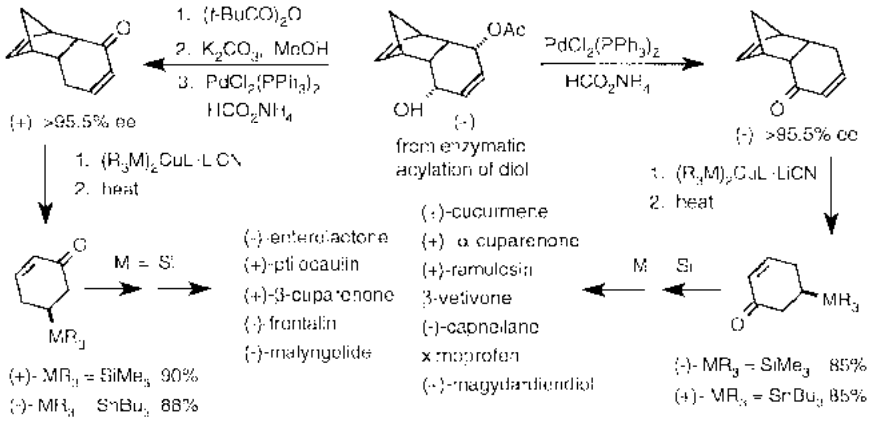


	% yield			
	cuprate		zincate	
	with TMSCl	without TMSCl	with TMSCl	without TMSCl
R^1 H, Me; R^2 Me, MeO, NMe_2, H	57-80	6-42	64-78	5-37
R^1, R^2 = H, CN or $Me_2C{=}CHCH_2$, OEt	50-83	23-29	75-93	21-35
methyl crotonate	72	95	72	80

Scheme 3.3. Conjugate addition reactions of silylcuprates and zincates in the presence and absence of TMSCl [43].

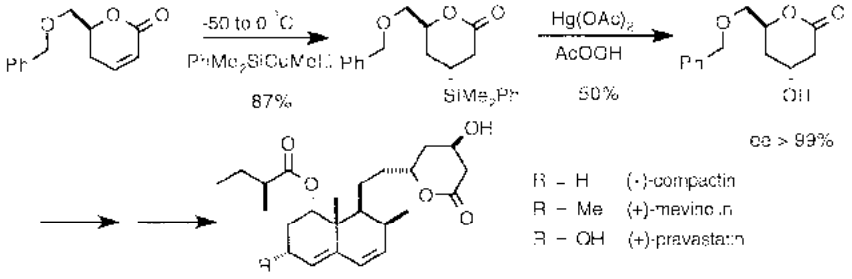
while the zincate gives rise to formation of a less reactive zinc enolate anion. The use of TMSCl with methyl crotonate, however, afforded lower yields than those achieved without the additive, this procedure being used in the synthesis of (±)-lavandulol [43].

The silylcuprate conjugate addition reaction has been used for the protection of an enone double bond, which can be regenerated with $CuBr_2$ [22a], and for the strategic introduction of the silyl substituent for stereocontrol and regiocontrol purposes. Enantiopure 5-trimethylsilyl-2-cyclohexenone can be prepared by conjugate addition reaction [44] and the appropriate enantiomer has been converted into a number of natural products (Scheme 3.4) [38]. These synthetic strategies exploit



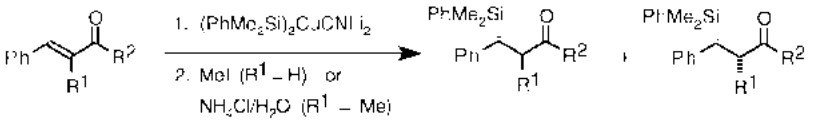
Scheme 3.4. Synthesis of enantiopure (+)- and ( )-5-trimethylsilyl- and 5-tri-*n*-butylstannyl-2-cyclohexenone [44] and natural products prepared from the silyl synthons [38].

the *anti* directing effect of the silyl substituent in subsequent conjugate addition reactions. It also proved possible to prepare the corresponding enantiopure 5-tri-*n*-butylstannyl-2-cyclohexenone. Alternatively, the stereoselectivity of the silylcuprate 1,4-addition can be directed by an existing substituent, as illustrated by the syntheses of (+)-compactin, (+)-mevinolin, and (+)-pravastatin (Scheme 3.5) [45].

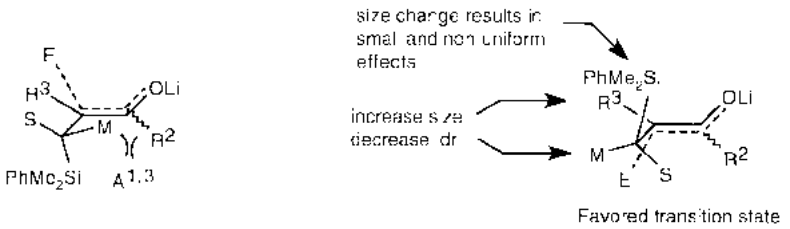


Scheme 3.5. Silylcuprate conjugate addition in syntheses of (+)-compactin, (+)-mevinolin, and (+)-pravastatin [45].

The enolate anions resulting from silylcuprate conjugate addition to α,β-unsaturated systems can be trapped with a wide variety of electrophiles, providing opportunities for relative asymmetric induction [46]. Conjugate addition to an α-alkyl-substituted α,β-unsaturated system generally gives the *syn* (aldol notation) diastereomer, while the *anti* diastereomer is produced from enolate alkylation of the substrate unsubstituted in the α-position (Schemes 3.1 and 3.6). The ease of the former reaction is in marked contrast to the reluctance of carbon cuprates to transfer alkyl groups to α-alkyl-substituted enones and enoates. The evidence suggests that this stereoselectivity is the result of a favored transition state in which the silyl substituent is *anti*-periplanar to the enolate π-system, the medium-sized group on the stereo center is "away" from the enolate group and thus can avoid $A^{1,3}$ interactions, and approach of the electrophile is from the side *anti* to the silyl substituent (Scheme 3.6).



R^2	*anti* : *syn* (R^1 = H)	% yield Methylation	*anti* : *syn* (R^1 = Me)	% yield protonation
OMe	97:3	88	15:85	84
Me	98:2	57	30:70	-
H	92:8	74	11:89	93
Ph	high	70	-	-
NMe_2	97:3	86	18:82	83
Cl	64:36	63	-	-
CN in place of COR^2	54:46	65	14:86	77

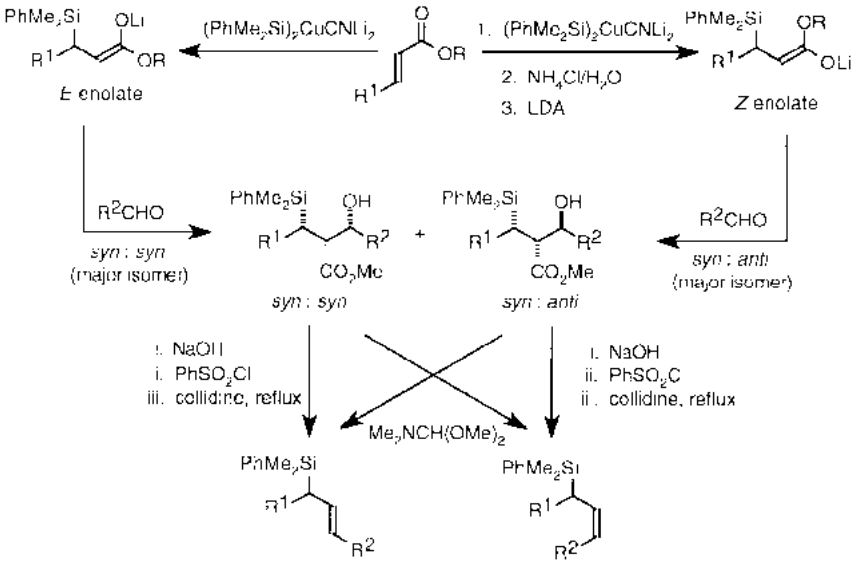


Scheme 3.6. Diastereoselectivity in silylcuprate conjugate addition-alkylation (alkyl halides) or protonation reactions with α,β-enoates [46].

The geometry of the enolate double bond appears to play no role in the diastereoselectivity of electrophile quenching of the enolate, as long as there is a group larger than hydrogen (R^2) *syn* to the stereocenter. This accounts for the diminished diastereoselectivity in the methylation reaction with unsaturated aldehydes and the loss of selectivity with unsaturated nitriles. Similar diastereoselectivities (94:6 to 92:8) were observed for a series of alkyl halides (RX, where R = Me, Et, *n*-Bu, *i*-Pr, $PhCH_2$, CH_2=$CHCH_2$, and MeO_2CCH_2; X = I, Br). Substrates undergoing protonation may have different transition state geometries, due to unfavorable R^3/silyl

gauche interactions, but they take place with the same sense even for nitrile substrates. This strategy has been employed in a synthesis of the Prelog–Dejerassi lactone [47]. Quaternary centers at the α-position can be generated with good diastereoselectivity when small α-substituents (R^3 = Me, Et, $CH_2C{=}CH_2$, CH_2CO_2Me; E^+ = EtI, *i*-PrI, $CH_2{=}CHCH_2Br$, $BrCH_2CO_2Me$: 80:20 to 90:10 dr, 63–95% yields) are present, while moderately sized α-substituents (such as *i*-Pr: 60:40 dr) give poor diastereoselectivity [46].

Similar diastereoselectivities have been observed for trigonal electrophiles [48] [for example, *anti*:*syn* ratios from the *E* enolate and *Z* enolate respectively (*E*, *Z*): $E^+ = CH_2O$ (71:29, 81:19), $CH_2{=}C(SiMe_3)COMe$ (93:7, 91:9), $(CH_2{=}NMe_2)^+I$ (87:13, 82:18)], with the *E* and *Z* enolates again giving the same major diastereomer in modest yields (43–78%). It was also possible to carry out alkylations on the resultant silyl enol ethers in the presence of Lewis acids, but diastereoselectivities ranged from excellent to poor, depending upon the electrophile. Silylcuprate conjugate addition to 2-enoates produces *E* enolates directly, while quenching of the enolate and regeneration of it with lithium diisopropylamide affords the *Z* enolate. The direct formation of the *E* enolate implies that the conjugate addition reaction proceeds preferentially from the *s-cis* enoate conformer. The *E* and *Z* enolates display normal stereoselectivities in the aldol reaction with aldehydes, which can be accounted for in terms of the Zimmerman–Traxler chair transition state, and this permits the synthesis of a major diastereomer with control over three contiguous stereogenic centers (Scheme 3.7, Tab. 3.2). Similar diastereoselectivities



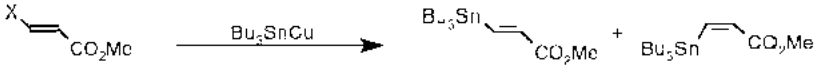
Scheme 3.7. Diastereoselective formation of β-silyl (*E*)- or (*Z*)-ester enolates by silylcuprate conjugate addition followed by alkylation with aldehydes [49]. Stereoselective synthesis of (*E*)- and (*Z*)-allyl silanes [50].

Tab. 3.2. Diastereoselectivity in the aldol reactions between (*E*)- or (*Z*)-β-silyl ester enolates and aldehydes (Scheme 3.7).

	From E enolate		*From Z enolate*	
	syn, syn:syn, anti	*% Yield*	*syn, syn:syn, anti*	*% Yield*
$R = R^1 = R^2 = Me$	89:11	73	6:94	81
$R = R^1 = Me$; $R^2 = Ph$	94:6	90	9:91	79
$R = Me$; $R^1 = Ph$; $R^2 = Me$	85:15	81	9:91	78
$R = Me$; $R^1 = R^2 = Ph$	91:9	81	10:90	79

are observed for the stannylcuprate conjugate addition and subsequent aldol reaction, although the selective formation of one major diastereomer is not as high. Stereospecific *syn* [49a] or *anti* [49b] decarboxylative elimination of the β-hydroxy acids selectively affords either the *E* or the *Z* allylsilane (Scheme 3.7) [50].

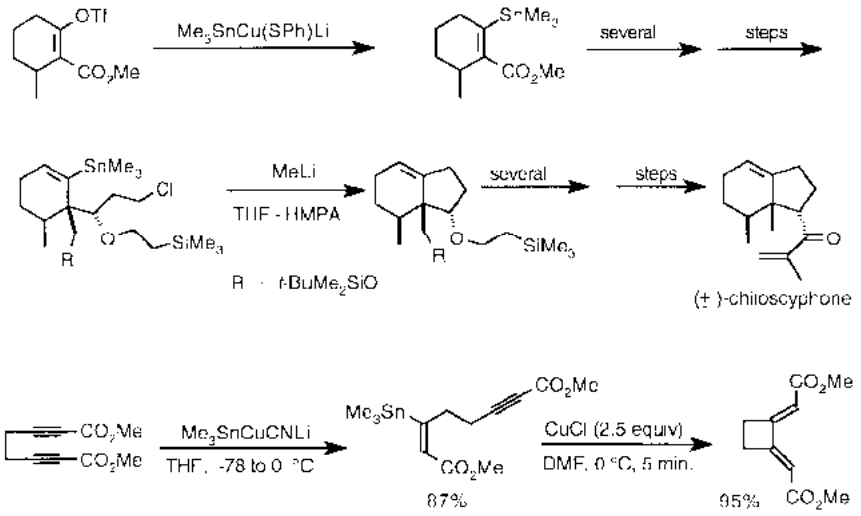
Stannylcuprates participate in conjugate addition reactions with 2-enones [16, 23e, 51–53], enals [51], enoates [51, 52], and enamides [54]. They also undergo substitution reactions with 3-iodo-2-enones [53], enol triflates of cyclic β-keto esters [16d, 55], and 2-enoates [56] containing good leaving groups (such as Cl, I, PhS) at the β-position. These substitution reactions may proceed through a conjugate addition-elimination pathway or by direct substitution. β-Haloacrylates and β-phenylthioacrylates afford 2:1 adducts with the stannyllithum reagent and diminished yields with the cuprate reagents [56a]. Optimal yields and stereocontrol, with retention of configuration, were achieved with the tributylstannylcopper reagent, while the poor stereoselectivity obtained with 3-phenylthioacrylate appears to be related to leaving group ability (Scheme 3.8). A similar substitution reaction has been achieved with Bu_3SnCu(2-thienyl)Li·LiCN and a 3-sulfonyl-substituted 2-enoate [56b]. The resulting 3-stannyl-2-enones and enoates undergo oxidative homo coupling with CuCl [55c]. The substitution reaction fails with coumarin-derived triflates; the stannylcuprates [Me_3SnCu(L)Li·LiCN, L = Me, 2-thienyl] either transfer the methyl ligand preferentially or give complex product mixtures [57]. Palladium-catalyzed coupling of the triflate and hexamethylditin gave the 4-stannylcoumarins in good yields.



substrate	reaction conc.	% yield	*E*:*Z*
E (X = Cl, I)	-78 °C, 40 min	58-62	100:0
E (X = Cl, I)	-78 °C, 1 h; 0 °C, 4 h; 25 °C, 4 h	50	25:75
Z (X = Cl, I)	-78 °C, 40 min	47-62	0:100
Z (X = OTs)	-78 °C, 1 h; 0 °C, 4 h; 25 °C, 4 h	59	0:100
E (X = SPh)	-78 °C, 1 h; 0 °C, 4 h; 25 °C, 1 h	50	25:75

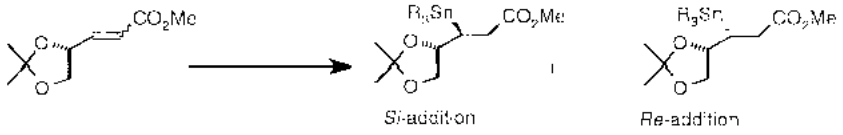
Scheme 3.8. Stereospecific substitution of (*E*)- and (*Z*)-β-substituted acrylates with Bu_3SnCu [56a].

The reaction between stannylcuprates and enol triflates of cyclic β-keto esters has been exploited in an annulation strategy culminating in the synthesis of (±)-chiloscyphone [55a] (Scheme 3.9). Stannylcuprate conjugate additions to 2-ynoates affords vinylstannes, which upon transmetalation to vinylcuprates can react intramolecularly with an original or subsequently introduced electrophile in a versatile ring-forming procedure [55d].



Scheme 3.9. Annulation and ring-formation strategies based on reactions between stannylcuprates and triflates of cyclic β-keto esters [55a] and functionalized ynoates [55d].

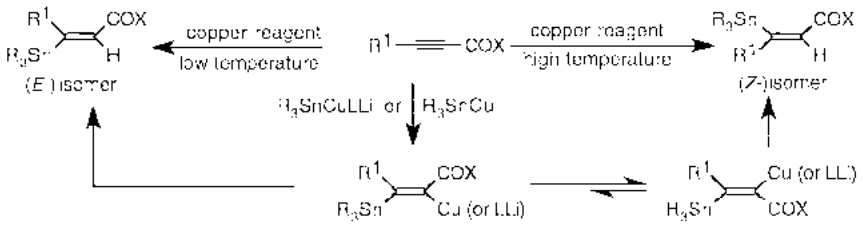
Stannylcuprates generally offer no advantage over stannyllithium reagents for conjugate additions to simple 2-enones and enoates. The stannyllithium reagents successfully undergo 1,4-addition to 3,3-dialkyl-2-enoates, which are unreactive toward the cuprate reagents [53]. Although stannylcuprate additions to enantiopure conjugated SAMP [(*S*)-1-amino-2-methoxymethylpyrrolidine] hydrazones proceeded with high diastereoselectivities, the major product was that arising from conjugate addition of the resultant enolate to the starting hydrazone [58], a common problem with 1,4-additions of silylcuprates and stannylcuprates to Michael acceptors. Chiral 4-heteroatom-substituted 2-enoates also provide opportunities for diastereoselection, now arising in the initial conjugate addition process and induced by the adjacent stereogenic center [59]. Comparisons of the stannyllithium, cuprate, and zincate reagents provided no useful predictive model because of wide variation in the reaction conditions. In general, the *Z* enoates gave excellent but opposite diastereoselectivities with the lithium and cuprate reagents, while the *E* enoates gave poor selectivities. The zincates gave excellent selectivities in the same sense with both the *E* and the *Z* enoates (Scheme 3.10).



	Z-enoate		E-enoate	
reagent	% yield	(Si:Re)	% yield	(Si:Re)
Bu_3SnLi	58	100:0	50	74:26
n-Bu_3Sn(Bu)CuLi·LiCN	37	10:90	84	43:57
n-$Bu_3Sn(Et)_2ZnLi$	84	0:100	73	10:90

Scheme 3.10. Diastereoselectivity in 1,4-addition of stannyllithium, cuprate, and zincate reagents to enantiopure 4-heteroatom-substituted 2-enoates [59].

Conjugate addition reactions of stannylcopper(I) reagents are most often employed with 2-ynoates, to afford *E*:*Z* mixtures of 3-stannyl-2-enoates [6, 23a–d, 51, 54, 60]. Several cuprate reagents [$Me_3SnCuLLi$, L = SPh, $SnMe_3$, C–CC(OMe)Me_2, CN], and also the organocopper reagent $Me_3SnCu{\cdot}SMe_2$, transfer the stannyl group to 2-ynoates and the reaction works well with protected 4-hydroxyalkynoates [51, 61]. The phenylthiocuprate reagent selectively affords the *E* isomer, through *syn* addition, when added to ynoates [60a] at low temperatures in the presence of a proton source, and the *Z* isomer at higher temperatures (−48 °C). The organocuprate reagent, $(Me_3Sn)_2CuLi$, and an acetylenic mixed cuprate stereoselectively gave *E* isomers through *syn* addition, although the former reagent is commonly the one of choice (Scheme 3.11, Tab. 3.3). Excellent stereoselectivites are also achieved with the cyanocuprate, which is less capricious than $Me_3SnCu(SPh)Li$ [60c]. These *E*:*Z* diastereoselectivities can also be achieved with chiral 4-amino-2-ynoates; the *E* diastereomers can be converted into 4-tributylstannylpyrrolin-2-ones (Scheme 3.12) [61]. The unprotected lactams were unstable and generally isolated as the *t*-butoxycarbonyl (Boc)-protected derivatives. These vinyl stannanes underwent effective palladium-catalyzed coupling with vinyl halides and acid chlorides [61b].

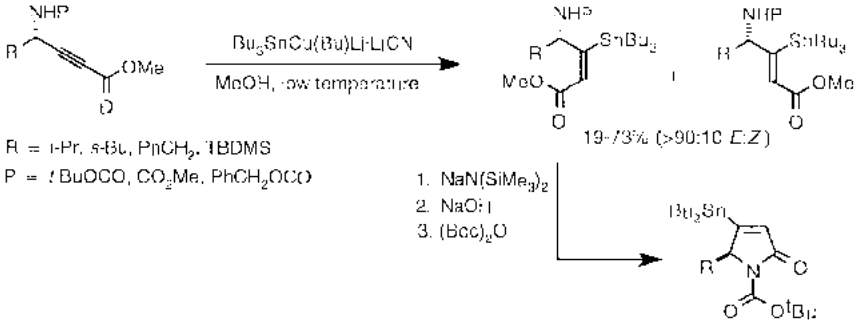


Scheme 3.11. *E*:*Z* Diastereoselectivities in conjugate additions of stannylcuprates to α,β-unsaturated derivatives.

Tab. 3.3. Stereoselectivity in stannylcopper or cuprate additions to 2-ynonates (Scheme 3.11).

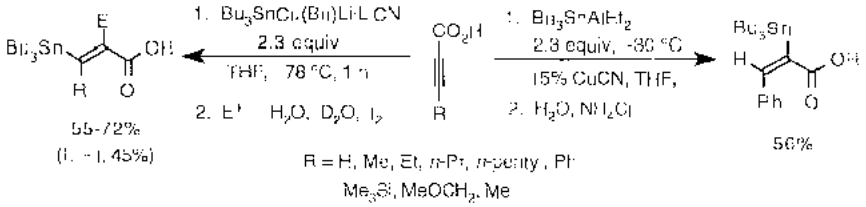
R^7	X	Cuprate	Reaction conditions	% Yield	E:Z	Ref.
Me, $RO(CH_2)_2$ [a]	NMe_2	$Me_3SnCu{\cdot}SMe_2$	THF, 78 °C, 3 h	77–83	>99:1	54
	NMe_2	$Me_3SnCuSPhLi$	THF, 48 °C, 1 h 20 °C, 1 h; 0 °C, 2 h	68–72	7:93	54
Me, Et, $R_3SiO(CH_2)_2$ [a]	OMe, OEt	$Me_3SnCuSPhLi$	cuprate (2), MeOH (1.7), 100 °C, 15 min; 78 °C, 3 h	78–82	≥96:4	60a
	OMe OEt	$Me_3SnCuSPhLi$	i. cuprate (1.3), 78 °C, 15 min; 48 °C, 4 h ii. MeOH	76–81	≥4:96	60a
Me	OEt	$Me_3SnCuSPhLi$	48 °C, 4 h	76	2:98	60a
		$(Me_3Sn)_2CuLi$	48 °C, 4 h	74	32:68	60a
		$Me_3SnCRLi$ [b]	48 °C, 4 h	82	99:1	60a
		$Me_3SnCu{\cdot}SMe_2$	48 °C, 4 h	68	99:1	60a
Et	OEt	$Me_3SnCuCNLi$	i. THF, 48 °C, 2 h; 0 °C, 2 h ii. NH_4Cl, NH_4OH, H_2O	72	1:99	60c
		$Me_3SnCuCNLi$	i. THF, MeOH, 78 °C, 4 h ii. NH_4Cl, NH_4OH, H_2O	74	99:1	60c
n-Pr	OMe	$Bu_3SnCu(Bu)Li{\cdot}LiCN$	50 °C, 2 h	80–85	15:85	60d
		$Bu_3SnCu(2\text{-Th})Li{\cdot}LiCN$	25 °C, 2 h	80–85	10:90	60d
		$Bu_3SnCu(N\text{-imid})Li{\cdot}LiCN$	25 °C, 2 h	>85	4:96	60d
CH_2NHBoc	OMe	$Bu_3SnCu(Bu)Li{\cdot}LiCN$	78 °C, 10 min	72	50:50	61b
			MeOH, 78 °C, 10 min	79	100:0	61b
OTHP	OMe		78 °C, 10 min	66	0:100	61b
			MeOH, 78 °C, 10 min	75	100:0	61b

a) R = *t*-$BuMe_2Si$
b) R = C≡CC $(OMe)Me_2$
(Th = thienyl, imid = imidazole)



Scheme 3.12. Synthesis of chiral 4-stannylpyrrolin-2-ones by means of stannylcuprate additions to chiral 2-ynoates [61a] (Boc = *t*-butoxycarbonyl).

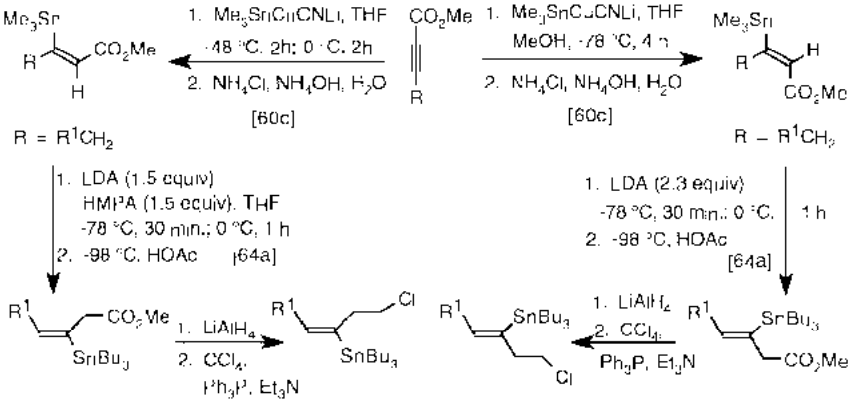
These observed stereoselectivites can be interpreted in terms of an α-cuprio ester formed by *syn* addition at low temperature and intercepted by proton quenching [60a] to afford the *E* adduct. Selective formation of the *Z* diastereomer at higher temperatures, requires either formation and stereoselective protonation of an allenyl enolate or isomerization of the *Z* α-cuprio ester to the *E* α-cuprio ester and stereoselective protonation. Recent mechanistic studies involving alkylcuprates and alkynoates have found isomerization between *E* and *Z* α-cuprio esters through the allenolate intermediate, with the resulting adduct *E*:*Z* diastereomeric ratio reflecting the alkenyl cuprate equilibrium *E*:*Z* ratio (Scheme 3.11) [62]. Application of this argument to the stannylcuprate reactions requires the *E* α-cuprio esters to be thermodynamically more stable than the *Z* isomers, and sufficiently so as to account for the high stereoselectivity. Stannylcuprate additions have been shown to be reversible and can sometimes give the 2-stannyl regioisomers. The initial conjugate adduct obtained from alkynyl esters cannot generally be trapped with electrophiles other than a proton, although the adduct obtained with Me_3SnCu(2-thienyl)Li and ethyl 4-*t*-butyldimethylsilyloxy-2-butynoate has been trapped with reactive electrophiles such as methyl iodide, allyl bromide, and propargyl bromide to afford the *Z* diastereomers in moderate yields (40–65%) [51]. Higher yields of trapping products can be achieved with 2-alkynyl amides [54] which, in contrast, afford the *E* diastereomers. Similarly, treatment of 1-triphenylsilyl-1-propynone with $Bu_3SnCu(Bu)Li{\cdot}LiCN$ gives an adduct that can be trapped with acid chlorides, allyl halides, and carbon dioxide to afford the *E* α,β-unsaturated acylsilane [27]. Trapping can also be achieved intramolecularly, to afford a β-trimethylstannyl-cyclopentenecarboxylate (77%), although the higher homologue gave the cyclohexenecarboxylate in low yield (3%) together with 1-trimethylstannyl-1-carbomethoxymethylenecyclopropane (45%). The formation of the latter product illustrates the reversibility of the reaction, formation of the 2-stannyl regioisomer, and subsequent cyclization [60a]. The formation of either trialkylstannyl regioisomer can be achieved with judicious choice of reagents. Addition of $Bu_3SnCu(Bu)Li$ to alkynyl acids affords the 3-stannylenoic acids, which can be trapped with iodine, while treatment with diethyl(tributylstannyl)aluminium in the presence of CuCN reverses the regioselectivity (Scheme 3.13) [63].

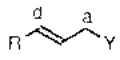
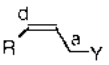
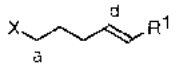
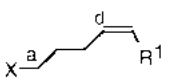


Scheme 3.13. Reagent regioselectivity in the stannylcupration of 2-ynoic acids [63].

Piers has exploited these 2-ynoate stannylcupration reactions in the preparation of donor and dipolar synthons (Scheme 3.14) [64]. Stereoselective stannylcupration followed by deconjugation provides a stereocontrolled route to vinyl 1,3-dipolar

synthons (i.e., donor/acceptor sites) which has been employed in synthetic routes to dolastane-type diterpenoids, (±)-amijitrienol [64c], and the marine sesterterpenoid (±)-palouolide [64e].



synthon	R	R^1 or Y	synthon
	alkyl, H	alkyl, H	
	alkyl, H	OH, I	
	$X(CH_2)_3$- (X = Cl, I)	CO_2Me, CH_2OMOM $CH_2OTBDMS$, CH_2OAc, Et	

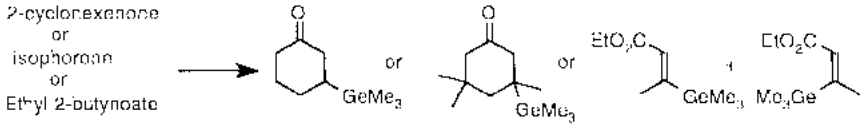
d = donor site, a = acceptor site

Scheme 3.14. Selected synthons available through stannylcuprate additions to 2-ynoates [64].

Silylcuprates have been reported to undergo reactions with a number of miscellaneous Michael acceptors [65]. Conjugate addition to 3-carbomethoxy acyl pyridinium salts [65a] affords 4-silyl-1,4-dihydropyridines. Oxidation with *p*-chloranil generates a 4-acyl pyridinium salt that gives the 4-silylnicotinate upon quenching with water, and methyl 4-silyl-2-substituted dihydronicotinates upon quenching with nucleophiles (nucleophilic addition at the 6-position). The stabilized anion formed by conjugate addition to an α,β-unsaturated sulfone could be trapped intramolecularly by an alkyl chloride [65b].

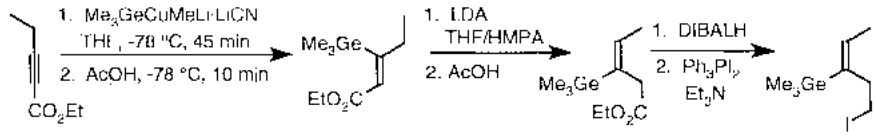
The conjugate addition reactions of trimethylgermylcopper and cuprate reagents have only been explored recently [66] (Scheme 3.15). In cuprate reagents containing two trimethylgermyl ligands, both ligands are transferred, promoting efficient ligand utilization. While Me_3SnLi exclusively gives conjugate addition with 2-cyclohexenone, Me_3GeLi gives a 1:3.8 mixture of the 1,4 and 1:2-adducts. The conjugate addition of germylcuprates to isophorone was not enhanced with TMSCl as an additive, although TMSBr proved effective. With 2-ynoates, the germylcopper

and cyanocuprate reagents gave the *E* diastereomeric product with excellent stereoselectivity, while the mixed cuprate reagent gave the *Z* diastereomer with modest stereoselectivity. *E* Stereoselectivity appears to result from *syn* addition of the copper reagent and thermal stability of the intermediate vinylcopper (cuprate) intermediate, while *Z* diastereoselectivity is a product of vinylcuprate intermediates prone to isomerization to the allenolate intermediate and subsequent protonation of the allenolate *anti* to the large germyl substituent. The conjugate addition reaction to ynoates can be used for the stereoselective synthesis of trisubstituted double bonds and has been exploited in a synthesis of (±)-sarcodonin G [66b].



Reagent	% yield from 2-cyclohexenone	% yield from isophorone	% yield from ethyl 2-butynoate (dr)
$Me_3GeCu{\cdot}Me_2S$	77		81 (99:1)
$(Me_3Ge)_2CuLi$	86[a]		90 (1.7:1)
Me_3GeCu_2CNLi	90		90 (99:1)
$(Me_3Ge)_2Cu(I){\cdot}LiCN$	85[a]		
$Me_3GeCuMeCNLi$	87	33	86 (1:3.9)
		33[b]	
		66[c]	

[a] Reagent employed (0.65 equiv). [b] TMSCl (1.5 equiv). [c] TMSBr (4 equiv).

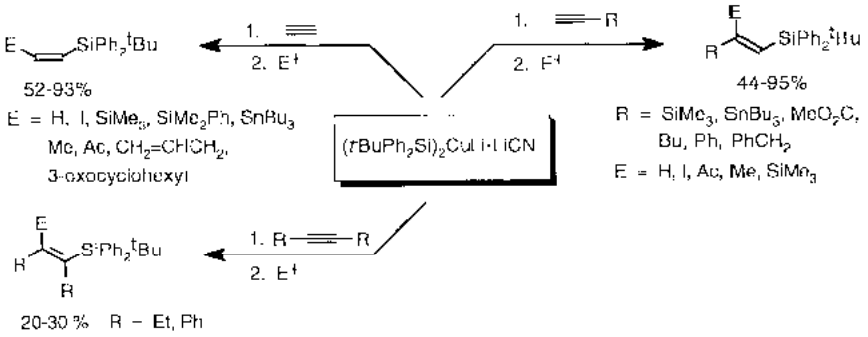


Scheme 3.15. Conjugate addition reactions of germylcopper and cuprate reagents [66a].

3.2.1.2 Silylcupration and Stannylcupration of Alkynes and Allenes

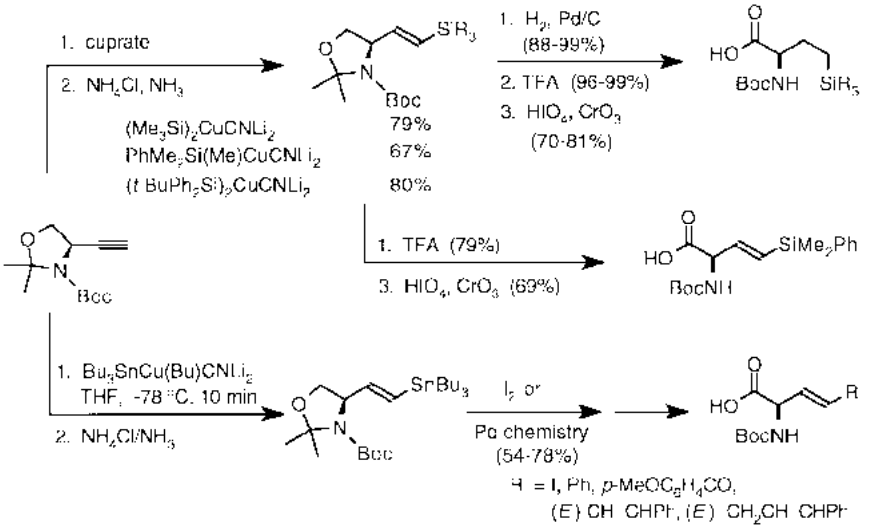
The silylcupration and stannylcupration of unactivated alkyne and allene π-bonds has been reviewed [67], focusing on the work of Fleming and Pulido. Silylcupration of terminal alkynes proceeds uneventfully with $(PhMe_2Si)_2CuLi{\cdot}LiCN$, regiospecifically affording intermediate 2-cuprio alkene reagents that can be trapped with a variety of electrophiles [24, 68], although modest regioselectivity (60:40) has been observed with $PhMe_2SiCuCNLi$ [14c]. Only the 1-lithio alkyne afforded small amounts of the regioisomeric 2-silylalkene (10:1 ratio, 80% yield). With reactive electrophiles (such as I_2, CO_2, MeCOCl, MeI at 0 °C; 71–94%), the vinylcuprate intermediate can be trapped directly, but activation with hexamethylphosphoramide (HMPA) or hexynyllithium is required for less reactive electrophiles (such as *n*-BuI, 2-cyclohexenone, and propylene oxide, 54–69%). An excess of the terminal alkyne will protonate the vinylcuprate intermediate. Assuming formation of a

vinyl(silyl)cuprate intermediate, the results suggest preferential transfer of a vinyl ligand over a silyl ligand. Comparable or superior yields are obtained with (*t*-$BuPh_2Si)_2CuLi{\cdot}LiCN$ in silylcupration of alkynes followed by electrophilic trapping, and this methodology has been used to produce vicinal vinyldisilanes and vinyl-(silyl)stannanes (Scheme 3.16) [69]. Disubstituted alkynes are less reactive and give vinylsilanes in low yields.



Scheme 3.16. Silylcupration of alkynes with (*t*-$BuPh_2Si)_2CuLi{\cdot}LiCN$ and electrophilic trapping of the vinylcuprate reagent [69].

Silylcupration also works with 1-aminoalkynes [70], propargyl sulfides [71], propargyl amines [14a, 72] – where it has been exploited in the synthesis of saturated and unsaturated *γ*-silyl-α-amino acids (Scheme 3.17) – and propargyl ethers, where



Scheme 3.17. Synthesis of functionalized α-amino acids by silylcupration [72a] or stannylcupration [81c] of chiral propargyl amines (Boc = *t*-butoxycarbonyl; TFA = trifluoroacetic acid).

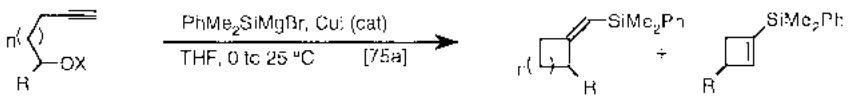
it has been exploited in syntheses of α-dietyopterol [73a] and (+)-crotanecine [73b]. Modest regioselectivity was achieved in the low temperature silylcupration of a chiral cyclohexyl ethynyl ether, used in the synthesis of (+)-crotanecine, although good selectivity was achievable at 0 °C. The single intermediate regioisomer (1-trimethylsilyl-2-alkenyl)(trimethylsilyl)cuprate obtained from propargyl amines has been trapped with electrophiles (such as vinyl halides, 2-halothiophenes, CO_2, methyl chloroformate, allyl halides, and propargyl halides, I_2; 58–95%) [**14a**]. Trapping of the vinylcuprate derived from homopropargyl amines with carbon dioxide provides a synthetic route to 3-(trimethylsilylmethylidine)-2-pyrrolidinones. Vinyl silanes prepared from propargyl amines can also participate in carbodesilylation reactions under Hiyama [tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) or $Bu_4NF/PdCl_2$)] conditions, or in Heck reactions, regioselectively and stereoselectively producing aryl-substituted olefins [72c, **74**].

Intramolecular trapping of the intermediate vinylcuprate provides opportunities for ring-formation, depending upon the relative reactivities of the alkyne and the participating electrophilic functionality with the silylcuprate reagent. These silylcupration-cyclization reactions have been achieved in modest to good yields with ω-alkynyl tosylates, mesylates, ketones, and epoxides (Scheme 3.18), and in low yields with ω-alkynyl-2-enoates and acetylenes [75]. Although the copper-catalyzed reactions were described as involving addition of the silylmagnesium reagent across the triple bond, the presence of copper(I) salts seems more consistent with silylcupration [75a]. The actual species involved would be dependent upon the relative rates of silylcupration and silylmagnesiation in any potential catalytic cycle. These studies have found that silylcupration of an alkyne is:

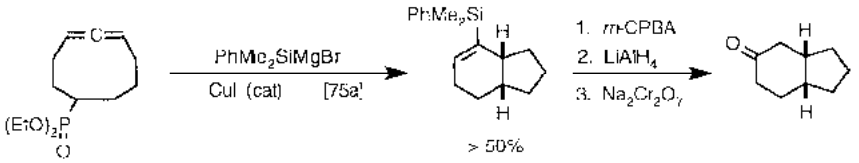
- generally faster than reaction of the silylcuprate with sulfonate esters, ketones, and epoxides when cyclization is successful,
- comparable in rate with **1,4**-additions to 2-enones when low yields of cyclized products are obtained,
- and slower than reaction of the silylcuprate with allylic acetates and aldehydes when the cyclization reaction fails [75b].

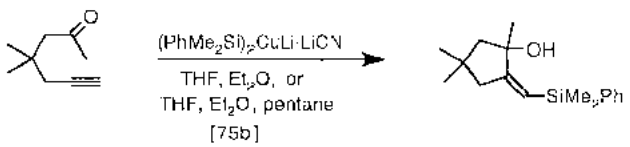
In successful cyclization reactions, transfer of the silyl ligand to both electrophilic centers is sometimes a competing reaction, which can be minimized by use of the less reactive mixed cuprate $PhMe_2SiCuMeLi{\cdot}LiCN$. The presence of a *gem*-dimethyl group in the backbone facilitates cyclization to small rings through the Thorpe–Ingold effect (that is, a decrease in angle deformation or ring strain, relative to that in the system lacking the *gem*-dialkyl group, upon cyclization). A similar stannylcupration-cyclization has also been observed [75c].

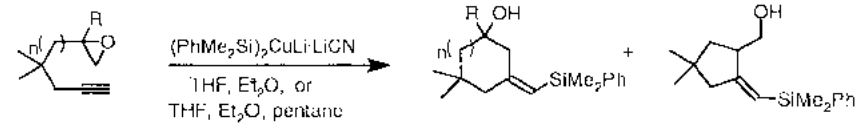
The initial reports in 1982–83 by Westmijze et. al. [25a] and Piers [25b] on the addition of stannylcopper and cuprate reagents to simple alkynes were followed by full studies [76] and reports from several laboratories [**14b**, 16b–e, 25c, 77–78]. In the earlier studies, the vinylcopper species could only be trapped with a proton. Marino achieved success in the addition to cyclohexenone of the vinyl cuprate generated by addition of $Bu_3SnCuCNLi$ to acetylene [79a–b], and Fleming [79c]



R	n	X	% yield	
H	0	Ms	45	41
Me	0	Ms	30	10
H	1	Ts	28	
H	2	Ts	91	
Me	2	Ts	46	
Bu	2	Ts	43	
H	5	Ts	60	







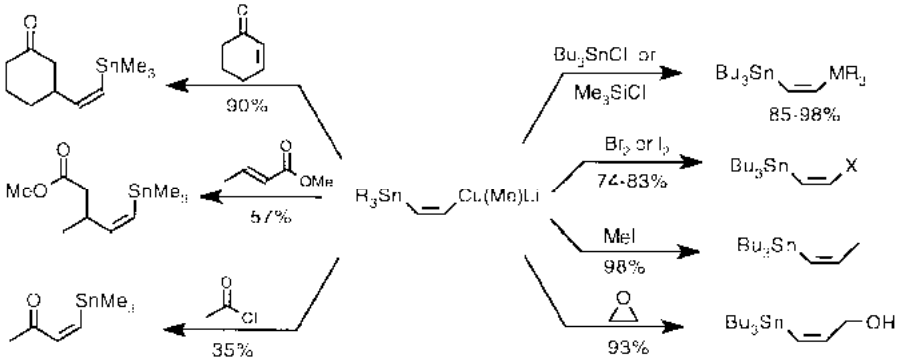
n	R	% yield	
0	H	83	
1	H	20	64
1	Me	65	

[75b]

Scheme 3.18. Ring-formation by intramolecular trapping of the vinylcuprates resulting from silylcupration of alkynes with magnesium silylcuprates [75a] or lithium silylcuprates (*m*CPBA = *m*-chloroperbenzoic acid) [75b].

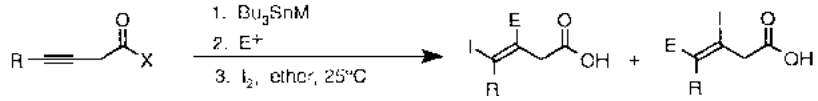
generalized the procedure using $Bu_3SnCu(Me)Li$ and trapping the vinyl cuprate with a variety of electrophiles (Scheme 3.19).

The reaction has been incorporated into a synthetic approach to enediynes [77]. Structural and mechanistic studies by Oehlschlager established the reversibility of these stannylcupration reactions [25c]. Although the resultant vinylcopper reagents were thermodynamically favored, crossover experiments found facile ligand exchange processes. Efforts to control the regiochemistry of the addition were met



Scheme 3.19. Stannylcupration of acetylene and trapping of the vinylcuprate with electrophiles [79c].

with only modest success. Stannylcupration of 3-butynoic acid or 3-hexynoic acid regioselectively afforded the 4-stannyl-3-enolates, which were stereoselectively converted into the vinyl iodides (Scheme 3.20). The regiochemistry could be reversed by use of a cuprate reagent prepared from a stannylaluminium reagent or by use of stannyl esters [63a].

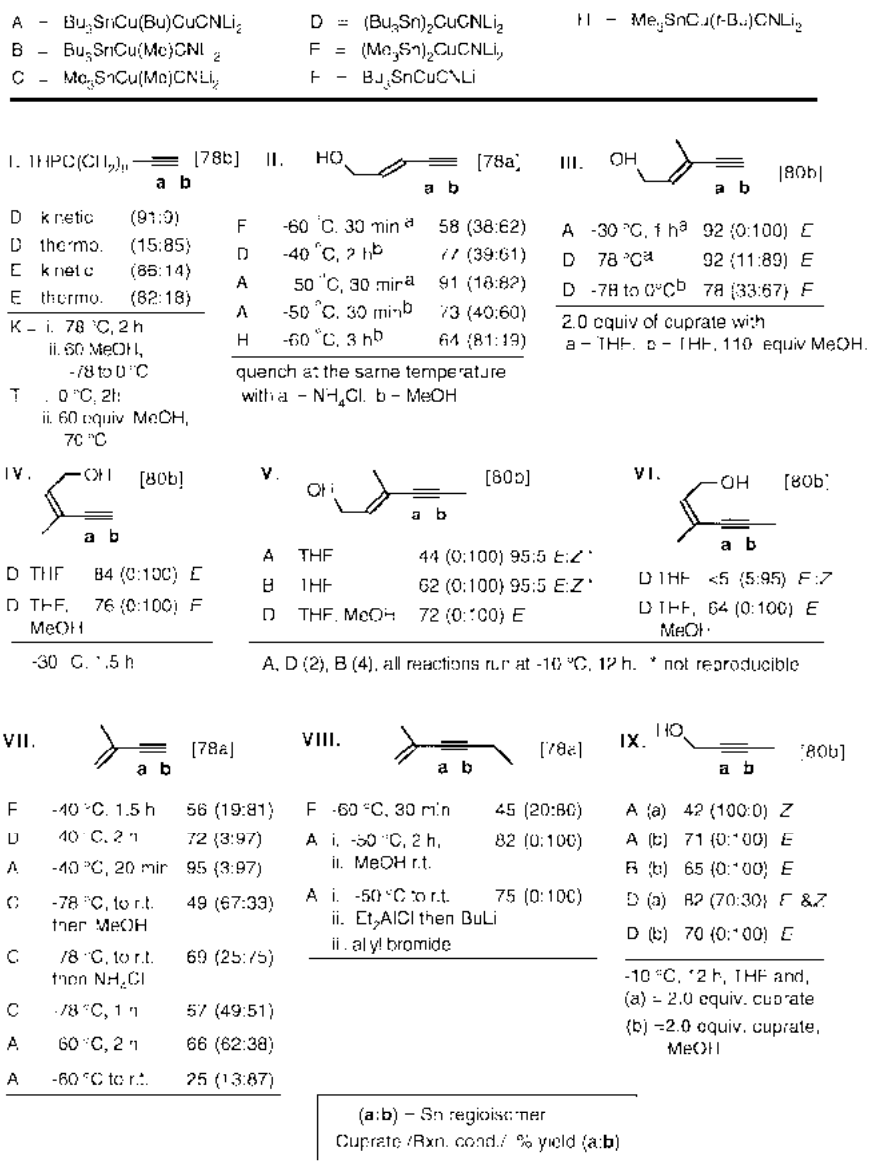


R	X	E^+	reagent (M)	% yield	ratio
H	OH	H	Cu(Bu)Li, LiCN	55	95:5
H	OH	H	$AlEt_2$, 15% CuCN	28	20:80
H	$OSnBu_3$	H	Cu(Bu)Li, LiCN	47	5:95
Et	OH	H	Cu(Bu)Li, LiCN	40	90:10
H	OH	Me	Cu(Bu)Li, LiCN	55	98:2

Scheme 3.20. Regioselective stannylcupration of 3-ynoic acids or esters [63a].

Although excellent regioselectivity could, at times, be achieved with terminal alkynes, enynes, and propargyl systems, it proved to be extremely sensitive to copper reagent, substrate structure, reaction temperatures, proton sources, and the temperature at which the reaction was quenched (Scheme 3.21). Steric factors, both in the cuprate reagent and in the substrate, influenced regiochemical outcomes, while use of alcohols as proton sources gave rise to deeply colored solutions suggestive of the formation of mixed alkoxy(stannyl)cuprate intermediates. The use of mixed stannyl(alkyl)cuprate reagents sometimes resulted in lower yields, and this was attributed to deprotonation of the 1-alkynes by these more basic cuprate reagents. Optimal reaction conditions for regiocontrol in stannylcupration of 1-alkynes, ω-hydroxy-1-alkynes, enynes, and propargyl alcohols were developed by Oehschlager and Pancrazi [78, 80]. The complexity of these reactions is illustrated by the results

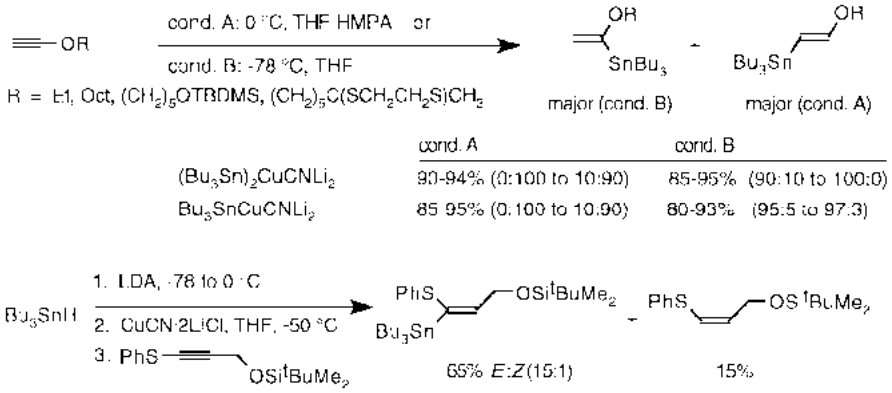
tabulated in Scheme 3.21. Similar results have also been obtained with propargyl amines [81–82], propargyl acetals [83], and higher homologue 1-alkynyl acetals [83b, 84]. Stannylcupration of chiral propargyl amines followed by coupling reactions mediated by vinyl iodide or vinylstannane provides a versatile synthetic route



Scheme 3.21. Regioselectivity in the stannylcupration of 1-alkynes, -hydroxy-1-alkynes, enynes, and propargyl alcohols.

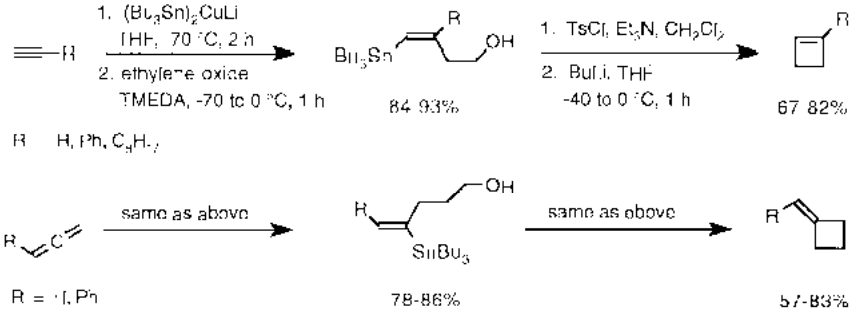
to β,γ-unsaturated-α-amino acids (Scheme 3.17) [81c] or the saturated analogues. Copper-catalyzed addition of stannylmagnesium reagents to 1-alkynes [85] provides excellent, regioselective formation of 1-stannylalkenes and, although used infrequently, has been employed with terminal alkynyl enynes [86a] and enynyl acetals [86b]. With enynyl acetals, identical regioselectivity was achieved by use of $Bu_3SnMgBr/CuCN$ (15 mol%) and of $Bu_3SnCuBuLi{\cdot}LiCN$ [i.e., 1-stannyl:2-stannyl dienes: 80:20 versus 85:15 respectively], although better regioselectivity could be achieved by modification of the acetal functionality. The 1,3-dioxolane acetal gave a 98:2 regioselectivity, which was attributed to dimer formation through intermolecular complexation between the acetal oxygens and the copper center. As expected, the selectivity diminished with decreasing concentration.

Complexation effects have also been seen in the stannylcupration of alkynyl ethers and thio ethers (Scheme 3.22) [87]. (*E*)-2-Stannylvinyl ethers are regioselectively prepared under thermodynamic conditions, while stannylcupration at low temperatures affords the 2-stannyl-2-alkoxyalkenes [87a]. In the latter case, the (*E*)-2-alkoxyvinylcuprate undergoes *trans* elimination above −20 °C to afford ethynyl(tributyl)tin. The addition of HMPA stabilizes the (*E*)-2-alkoxyvinylcuprate intermediate, allowing isomerization at higher temperatures to the 1-alkoxyvinylcuprate, the greater stability of which is attributed to intramolecular oxygen/copper complexation. Deuterium labeling studies have indicated *E*:*Z* isomerization during methanolysis of the 2-alkoxyvinylcuprate generated from $Bu_3SnCuMeLi{\cdot}LiCN$, but not from that produced from $(Bu_3Sn)_2CuLi{\cdot}LiCN$. This was interpreted in terms of protonation of the enol ether to give a β-cuprio cation, with elimination of a cuprate after 60° rotation giving retention of configuration, while elimination after 120° rotation gave the product with inversion of configuration.



Scheme 3.22. Stannylcupration of alkynyl ethers [87a] and alkynyl thioethers (TBDMS = *t*-butyldimethylsilyl) [87b].

Regioselective stannylcupration of terminal alkynes and allenes, followed by quenching of the cuprate intermediate with ethylene oxide, provides a facile synthesis of cyclobutene and alkylidine cyclobutane derivatives, respectively (Scheme 3.23) [15c]. A number of total syntheses have exploited regioselective stannylcup-

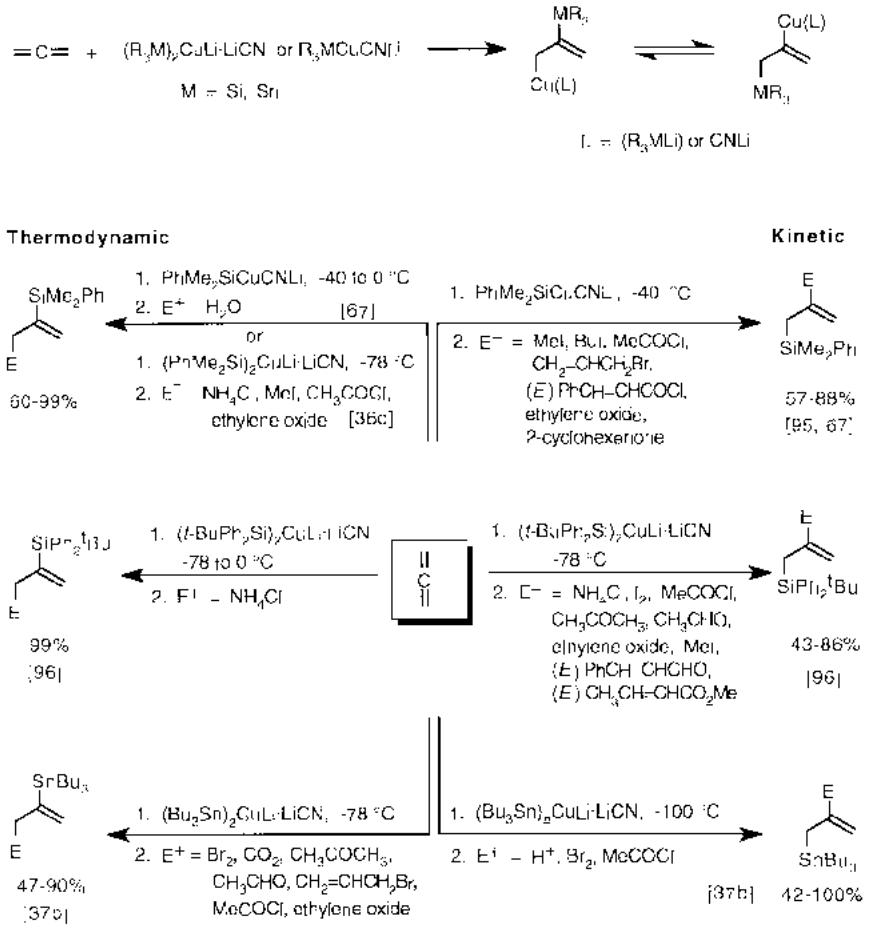


Scheme 3.23. Cyclobutene and alkylidine cyclobutane synthesis by stannylcupration of alkynes and trapping of the resultant vinylcuprate with epoxides [15c].

ration reactions. Stannylcupration of endiynes has been used in the synthesis of (13*E*)-trifluoromethylretinoates [88], (all *E*)- and (8*Z*)-anhydroretinols [89a], and the polyene alarm pheromone of the Cephalaspidean mollusks [89b]. The stannylcupration of propargyl ethers has been used in the synthesis of the C14–C26 segment of the macrolide antitumor agent rhizoxin [90a] and in the synthesis of the tetrahydrofuran fragment of the elfamycin antibiotic aurodox [90b], while the stannylcupration of a homopropargyl acetal was employed in the synthesis of macrolactin A [91]. Regioselective and stereoselective stannylcupration of 1-trimethylsilyl-1,3-pentadiyne was exploited in the synthesis of (−)-rapamycin [92]. Vinyl stannanes prepared by stannylcupration have been utilized in copper chloride-promoted coupling reactions [93].

Germylcupration of terminal alkynes was reported nearly sixteen years ago [94] and can be achieved with several cuprate reagents [such as $(Ph_3Ge)_2CuLi{\cdot}LiCN$, $(Ph_3Ge)_2CuLi$ from CuI or $CuBr{\cdot}SMe_2$], but only in the presence of proton donor such as alcohols, water, aldehydes, or ketones for the reagent $(Ph_3Ge)_2CuLi{\cdot}LiCN$. Here, the equilibrium of a reversible reaction lies toward the starting alkynes and germylcuprates and the presence of a weak acid is required to trap the vinylcuprate intermediate. Germylcupration of alkynes with the triethyl derivatives (such as $(Et_3Ge)_2CuLi{\cdot}SMe_2$), unlike the triphenylgermylcuprate case, proceeds to completion and the vinylcuprate can be trapped with electrophiles (such as D_2O, MeI, allyl bromide; 82–96%). Regioselectivity varies as a function of cuprate preparation and alkyne structure; 2-germyl-1-alkenes are favored with 1-dodecyne and cuprate reagents prepared from CuCN and either Ph_3GeLi or Et_3GeLi, while phenylacetylene or enynes favor formation of the 1-germyl-1-alkenes.

Silylcupration [36] and stannylcupration [36c, 37] of allenes afford intermediate vinyl or allyl copper species (Scheme 3.24), depending upon the copper reagent, temperature, and the electrophile employed to trap the copper intermediate [67]. Treatment of allene with $(PhMe_2Si)_2CuLi{\cdot}LiCN$ affords vinyl silanes upon quenching with alkyl halides, acid chlorides, epoxides, enones, or chlorine. Allyl silanes are formed upon quenching with bromine or iodine [36c]. This electrophile-induced regioselectivity appears not to involve equilibrating allyl and vinylcuprate



Scheme 3.24. Silylcupration and stannylcupration of allenes under kinetic and thermodynamic control [37c, 67, 95, 96].

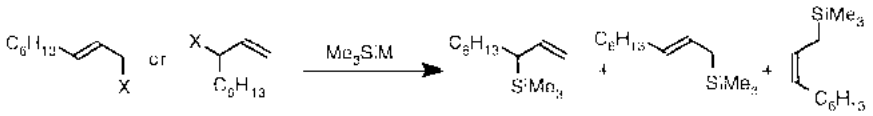
reagents and is not understood. Quenching of the intermediate cuprate with enones results in 1,2-nucleophilic addition to the ketone carbonyl rather than the conjugate addition reaction characteristic of organocopper reagents. Although 1-substituted vinyl silanes are available by direct silylcupration of allene with $(PhMe_2Si)_2CuLi{\cdot}LiCN$, substituted allyl silanes must be prepared indirectly, via the vinyl iodide. Alternatively, use of the cyanocuprate reagent $PhMe_2SiCuCNLi$ under thermodynamic control affords the allyl cyanocuprate reagent, but produces the vinyl cyanocuprate reagent under kinetic control [95]. Only the latter reagent can be alkylated with a variety of carbon electrophiles (Scheme 3.24). Although these reagents are depicted as silylcopper species (R_3SiCu), their preparation from one equivalent of silyllithium and one equivalent of CuCN corresponds to the mixed cuprate composition $R_3SiCuCNLi$ as normally written for lithium organo(cyano)-cuprates. Since copper reagents RCu are generally produced without removal of the

resultant lithium salts (LiX, X = Cl, Br, I, etc.), it seems likely that the reactivities of these species reflect mixed heteroatomcupratess of the type RCuXLi. Use of the sterically more hindered cuprate $(t\text{-BuPh}_2\text{Si})_2\text{CuLi}\cdot\text{LiCN}$ [96] gives the same thermodynamic and kinetic selectivity and, once more, the allylic cuprate produced under thermodynamic control cannot be trapped with electrophiles other than a proton. The counterpart vinylcuprate reacts with a range of electrophiles (Scheme 3.24). Vinyl cyanocuprate reagents generated from allene and PhMe_2SiLi [95] or $t\text{-BuPh}_2\text{SiLi}$ [67] and CuCN undergo 1,4-addition reactions with 2-enones or enals, although BF_3 is employed with the latter reagent. This contrasts with the bis(stannyl)cuprate reagents [36c, 96], which transfer the vinyl ligand in 1,2-fashion to 2-enones and enals and the $t\text{-BuPh}_2\text{Si}$ ligand in a 1,4-fashion to 2-enoates. The reactions between vinyl cyanocuprate reagents generated from allene and $\text{PhMe}_2\text{SiCuCNLi}$ and acid chlorides, 2-enals, and enones [97] provide opportunities, respectively, for silicon-directed Nazarov cyclizations or for cyclizations and annulations involving Lewis acid-promoted addition of allyl silanes to aldehyde and ketone carbonyls. Silylcupration of terminal allenes followed by treatment of the intermediate vinylcuprates with allyl phosphonates provides a facile synthesis of silylated 1,4-dienes [98a]. A catalytic version of the reaction using 20 mol% CuCN afforded a 50% yield of diene, corresponding to a catalyst turnover of 2.5. The first examples of silylcupration of alkenes were reported in 2001 for styrenes [98b] and 1,3-dienes [98c]. The intermediate cuprate arising in the latter reaction could be trapped with allylic phosphates in a highly regioselective fashion.

The stannylcuprate reagent $(\text{Bu}_3\text{Sn})_2\text{CuLi}\cdot\text{LiCN}$ displays the same thermodynamic and kinetic selectivity with allene, but the allylcuprate can in this case be trapped with a variety of electrophiles, while the vinylcuprate reacts only with reactive electrophiles (Scheme 3.24) [37, 67]. The vinyl to allylcuprate equilibrium takes place at −78 °C effectively limiting the procedure to the preparation of allylcuprates. Quenching with MeI gives irreproducible results, while methyl propiolate affords a conjugate adduct and 2-enones afford 1,2-addition products. Substituted allenes generally give either vinyl metal or allyl metal derivatives ($M = SiR_3$ [36c, 96, 99]; $M = SnR_3$ [36c, 37, 100]), depending upon the substitution pattern of the allene, although mixtures sometimes occur. In general, the trialkylmetal ligand adds to the least substituted carbon atom of the allene functionality.

3.2.1.3 Substitution Reactions

Reactions between allylic electrophiles and organometallic reagents pose problems of regiocontrol and stereocontrol. Nucleophilic substitution can proceed with (S_N2') or without (S_N2) allylic rearrangement, and the configuration of the product olefin may be affected. Regioselective S_N2' allylic substitution occurs with $(\text{PhMe}_2\text{Si})_2\text{CuLi}$ and tertiary allylic acetates [28a, b], while labeling studies on allylic chlorides found a regioselective and stereoselective *anti*-S_N2' process as the predominant pathway [101]. A detailed study on allylic substitutions with Me_3SiCu identified some interesting patterns (Scheme 3.25) [102]. The silylcopper reagent promoted allylic rearrangement, while regioselectivity decreased with increased solvent polarity and with better leaving groups. Better regiocontrol could be achieved



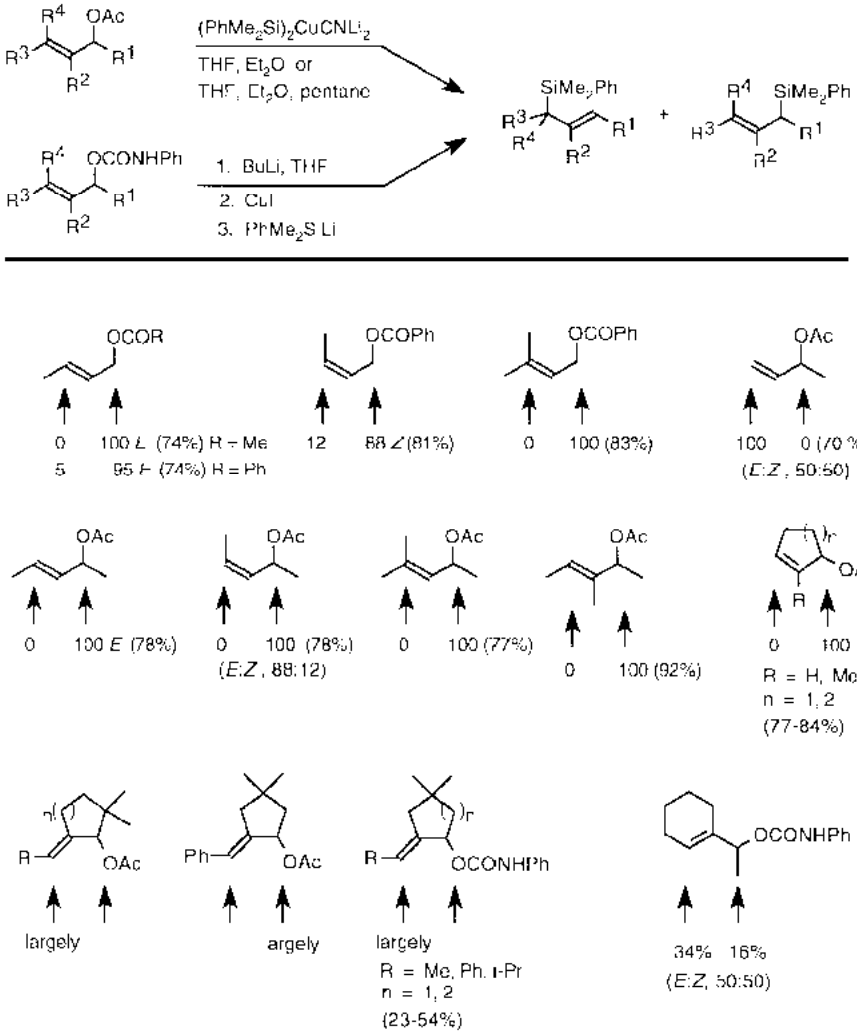
X	X	M	solvent	% yield	distribution
I		Cu	HMPA	75	57:33:10
Br		Cu	HMPA	80	60:13:27
Cl		Cu	HMPA	80	87:13:0
Cl		Cu	HMPA-Et_2O	87	98:2:0
Cl		Li	HMPA-Et_2O	78	0:100:0
	OMs	Cu	THF	52	6.5:32:61.5

Scheme 3.25. Reactions between silylcopper reagent and allylic substrates [102].

with allylic chlorides than with allylic sulfonate esters, the latter substrates giving mixtures of *E* and *Z* diastereomers with poor stereocontrol.

Regiocontrol and stereocontrol can be achieved with $(PhMe_2Si)_2CuLi{\cdot}LiCN$ and a wide range of allylic acetates and benzoates containing primary, secondary, or tertiary centers at the leaving group site or at the other end of the allyl system and secondary or tertiary centers at the central carbon atom (Scheme 3.26) [103]. The cuprates $(PhMe_2Si)_2CuLi{\cdot}LiCN$ and $(PhMe_2Si)_2CuLi$, however, failed to react with secondary allylic acetates [101, 103]. Since the CuCN-derived cuprate can only be prepared in THF, addition of ether or of ether-pentane solvent mixtures was necessary to induce reaction with secondary allylic acetates, where regiochemical control is more challenging. Good regiocontrol can be achieved when one end of the allylic system is more substituted than the other end or has a neopentyl 'like' substitution pattern and the silyl ligand adds to the least sterically hindered site. Although the allylic ester-cuprate combination shows no great bias either towards the S_N2 pathway or towards the S_N2' one, there may be a slight preference for direct substitution, in contrast to the silylcopper-allylic chloride reactions (Scheme 3.25). When the substitution is secondary at both ends of the allylic system in disubstituted olefins, *Z* diastereomers generally give reasonable and *E* diastereomers poor regiocontrol, while both give *E*:*Z* diastereomeric mixtures of allyl silanes.

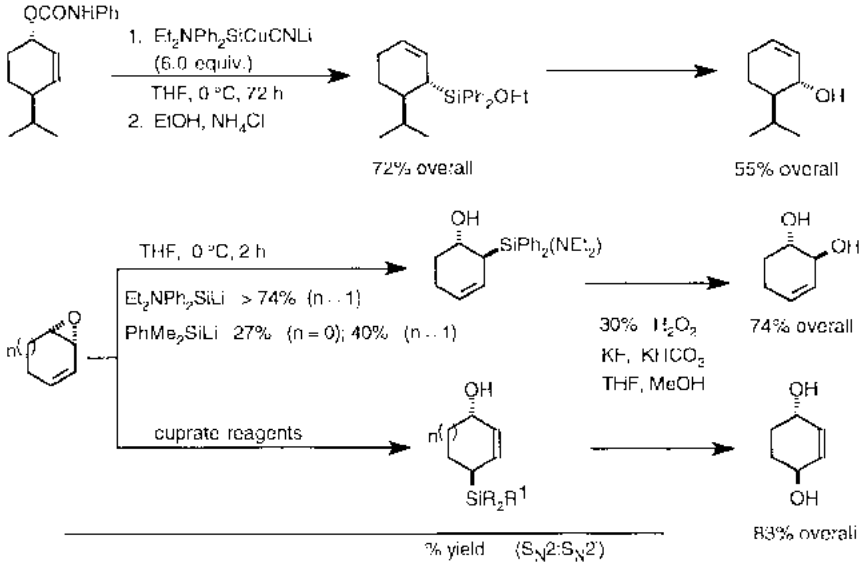
The silyl ligand can be directed to the more substituted end of the allyl system by use of a carbamate methodology that delivers the silyl group in an intramolecular fashion, by way of an amido(silyl)cuprate reagent generated in situ. These reactions proceed in low to modest yields with significant recovery of starting carbamate. Good yields can be achieved by use of excess reagent though, and excellent regiocontrol and stereocontrol can be achieved in some instances (Scheme 3.27) [104a]. Use of $Et_2NPh_2SiCuCNLi$ transfers a heteroatom-substituted silyl group that, in the presence of an allylic double bond, can be converted into an alcohol functionality. The aminosilane is unstable to chromatography, however, and is sometimes converted into a silyloxy group [104a]. Treatment of allylic epoxides with silyllithium reagents proceeds with direct substitution, while the cuprate reagents act with allylic rearrangement (Scheme 3.27) [104], offering complementary proce-



Scheme 3.26. Regioselectivity in reactions between silylcuprate reagents and allylic acetates and carbamates [103].

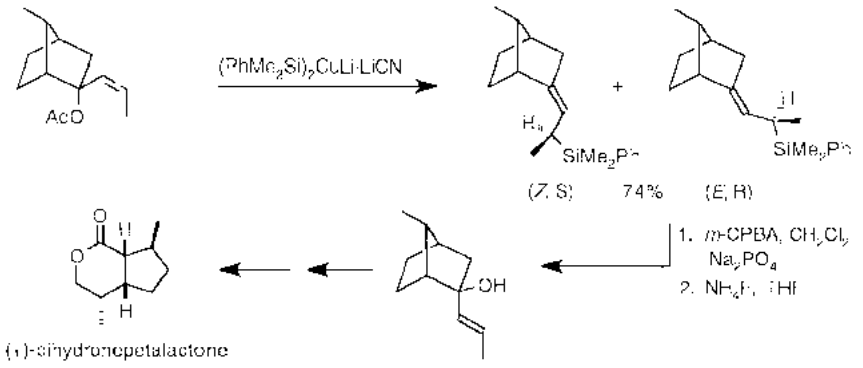
dures for the preparation of regioisomeric cycloalkenediols. The regioselectivity of the latter process is dependent upon the cuprate reagent. Like organocuprates, silylcuprates effect preferential allylic substitution on 4-bromo-2-enoates [105].

A consequence of the *anti*-S_N2' pathways, both in the silylcuprate substitution reaction and in the allyl silane protiodesilylation, is that a mixture of allylic substrates differing in configuration at both the olefin and stereogenic center will all stereoselectively afford the same diastereomeric product [28b]. Propargyl substrates would give enantiomers if appropriately substituted [28b]. This feature of *anti*-S_N2' pathways has been exploited in syntheses of the Prelog–Dejerassi lactone [47] and of (±)-dihydronepetalactone (Scheme 3.28) [106], while regiocontrol and stereo-



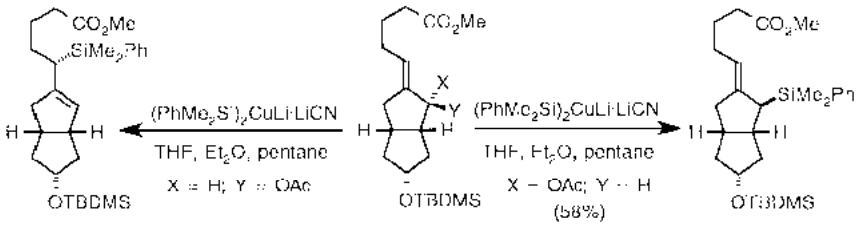
	% yield (S_N2:S_N2')	
cuprate reagent	n = 0	n = 1
$PhMe_2SiCuCNLi$	72 (0:100) 85:15 *trans*:*cis*	70 (0:100)
$(PhMe_2Si)_2CuLi{\cdot}LiCN$	79 (47:53)	94 (27:73)
3 $PhMe_2SiLi$ + CuCN	70 (60:40)	90 (60:40)
$Et_2NPh_2SiCuCNLi$	>83 (8:92) at -78 °C	
	>83 (50:50) at -0 °C	

Scheme 3.27. Regioselectivity in reactions of silyllithium and silyl cuprate reagents with allylic carbamates and epoxides [104].



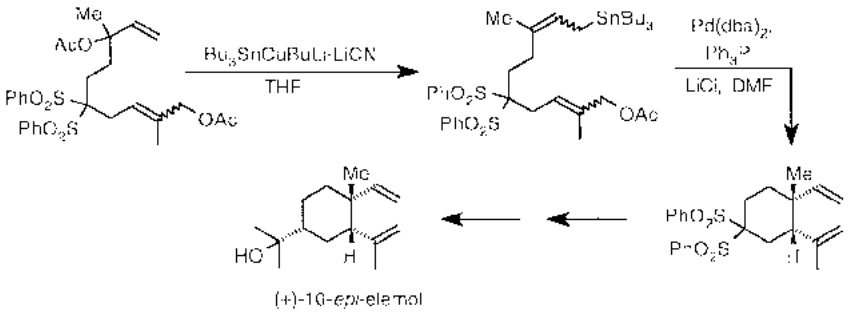
Scheme 3.28. Stereochemical aspects of allylic substitution and application in the synthesis of (+)-dihydronepetalactone (*m*-CPBA = *m*-chloroperbenzoic acid) [106].

control were also easily achieved in a rigid bicyclic system used in the synthesis of (±)-carbacyclin analogues (Scheme 3.29) [107]. Allyl silanes prepared from allylic substrates and silylcuprates have been used in syntheses of (−)- and (+)-dihydrocodeinone and (−)- and (+)-morphine [108], (+)-14-deoxyisoamijiol [109], and (+)-lanostenol [110]. The opening of an *endo* cyclic allylic lactone with the Fleming silylcuprate was employed in the synthesis of *epi*-widdrol and widdrol as a 3:1 mixture [111]. Allylic substitution using [Ph_2((*Z*)-2-methyl-2-butenyl)Si]$_2$CuLi (cf. Scheme 3.1) was used in a prostanoid synthesis requiring the conversion of an allyl silane into an allylic alcohol [14e].



Scheme 3.29. Silylcuprate substitutions in the synthesis of (±)-carbacyclin analogues (TBDMS = *t*-butyldimethylsilyl) [107].

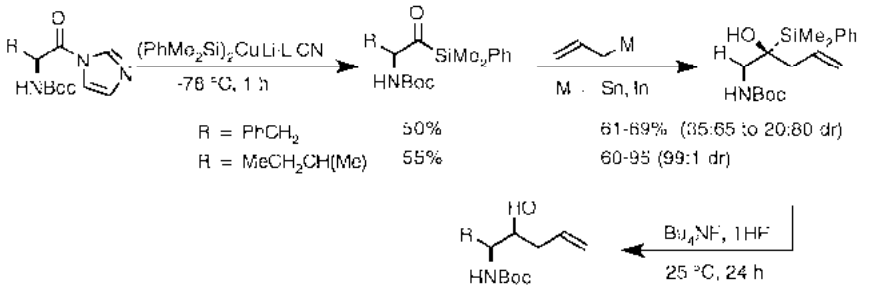
Stannylcuprates [112] and germylcuprates [113] also participate in allylic substitution reactions, and an allyl stannane prepared in this manner was exploited in the synthesis of (±)-10-epi-elemol [112b]. A mixed stannyl cuprate reagent reacted chemoselectively with a tertiary allylic acetate (Scheme 3.30), providing an allyl stannane that was cyclized to an intermediate 1,2-dienylcyclohexane. Although allylic chlorides afford only low yields, allyltriethylgermanes are readily prepared by treatment of allylic acetates or allylic phenyl sulfides with lithium bis(triethylgermyl)cuprate. The addition is highly regioselective, favoring addition of the germyl substituent to the least sterically hindered site in the allyl system. Primary allylic acetates give direct S_N2 substitution with retention of olefin configuration, while secondary and tertiary allylic acetates containing a terminal olefin give products of allylic rearrangement as mixtures of *E* and *Z* diastereomers. The reaction of the allylic acetates shows high regioselectivity, favoring direct substitution



Scheme 3.30. Stannylcuprate allylic substitution in the synthesis of (+)-10-epi-elemol (dba = dibenzylideneacetone) [112b].

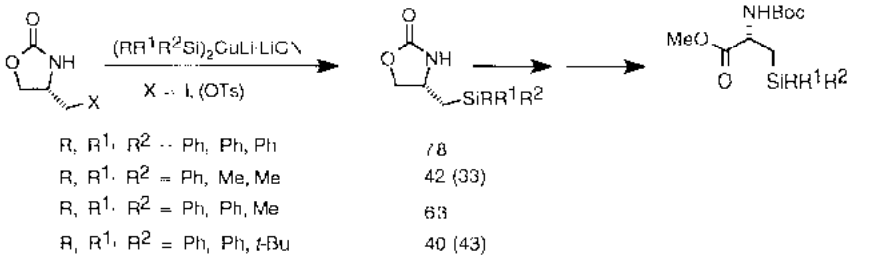
(S_N2:S_N2' = ca. 9:1), when both ends of the allylic system correspond to secondary centers [113], while the corresponding allylic sulfide reactions proceed without regioselectivity.

Silylcuprates also participate in substitution reactions with acid chlorides [26, 27, **114**], or with acyl imidazoles [115]. The zinc cuprate reagents $(PhMe_2Si)_2CuCN(ZnCl)_2$ and $PhMe_2SiCuCN(ZnCl)$ are significantly less reactive than the corresponding lithium reagents. Although the latter reagent gives low yields of acylsilanes, the former one gives higher yields than the lithium silylcuprates (0 to 25 °C, 10 h) with highly functionalized acid chlorides [**114a**]. Treatment with α- or β-amino acid chlorides or imidazoles affords α- or β-aminoacylsilanes, which can be utilized in synthetic routes to enantiopure β- [**114d**, 115a] (Scheme 3.31) or γ-amino alcohols [**114d**]. Alkylation of silylcuprates with alkyl halides and



Scheme 3.31. Synthesis of β-amino alcohols by acylation of silylcuprates (Boc = *t*-butoxycarbonyl) [114d, 115a].

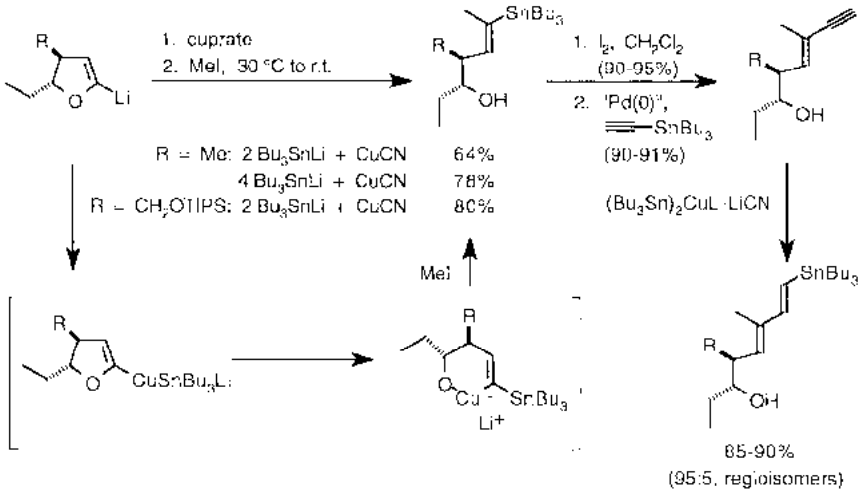
sulfonates has been exploited in a synthesis of silicon-containing alanines for use as non-protenogenic amino acids (Scheme 3.32) [116a]. Seebach's procedure ($Bu_2CuLi{\cdot}LiCN + R_3SiCl$ [116b]), which transfers the silyl group to 2-enoates or lactones, failed to effect coupling with these alkyl halides, and the silylcuprates were generated from the silyllithium reagents.



Scheme 3.32. Synthesis of silylalanines by means of alkyl halide alkylation of silylcuprates [116a].

Stannyl cuprates couple with vinyl halides or triflates [16c–d, 85], and a vinyl stannane produced this way has been used in the synthesis of 7-[(*E*)-alkylidene]-cephalosporins [117]. Vinyl substitution reactions starting from dihydrofurans are

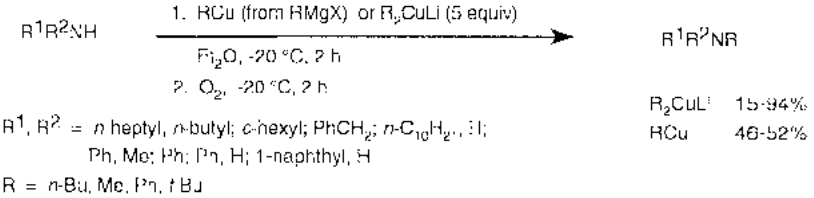
also possible (Scheme 3.33) and the reaction has been used in a synthetic approach to the C10–C15 fragments of (±)-tylosin aglycon [118a] and des-epoxy-rosaramycin (Scheme 3.33) [118b]. Dihydropyrroles undergo the same reaction [118c].



Scheme 3.33. Metalate rearrangement of a mixed vinyl(stannyl)cuprate derived from a 2,3-dihydrofuran (TIPS = triisopropylsilyl) [118b].

3.2.2
Group VA and VIA Heteroatoms (N, O, P)

Although heteroatoms of Group VA and VIA frequently serve as non-transferable ligands in cuprate chemistry, there are a few studies that have explored the synthesis of amines and ethers from these reagents. Treatment of primary or secondary amines with lithium dialkylcuprates (or alkylcopper species from Grignard reagents) followed by treatment with molecular oxygen affords substituted amines in modest to good yields, with ethereal solvents giving higher yields than hydrocarbon solvents (Scheme 3.34) [119]. Similar yields were achieved by addition of a lithiated amide to butylcopper and subsequent oxidation, suggesting the intermediacy of lithium (alkyl)amidocuprates. Amine alkylation could be achieved with 2-anilinoethanol without protecting the alcohol functionality, although the use of five equiv-



Scheme 3.34. Alkylation or arylation of amines by treatment of organocopper reagents with amines [119].

alents of cuprate reagent should have deprotonated both the arylamine and alcohol functional groups. Coupling of arylamidocuprates [Ar(Me)NCuXLi, X = Cl, CN (5 equiv.)] with *ortho*-lithiated benzamides generated by directed *ortho* metalation (DOM) provides a synthesis of *N*-arylanthranilamides (23–63%) which may be cyclized to acridones (25–95%) [120]. Efficient ligand utilization was achieved with lithium and zinc cyanocuprates (RCuCNM: M = Li, ZnCl) and lithium amides, and the procedure was extended to the synthesis of hydrazines [121]. EPR studies indicated the formation of aminyl radicals upon addition of molecular oxygen to the amidocuprate solutions, suggesting product formation by radical coupling [121a]. Improvements were obtained by judicious combination of cuprate and oxidation reagents. Oxidation of the less reactive zinc cuprates with an oxygen/*o*-dinitrobenzene (20 mol%) combination and use of the milder oxidizing system $Cu(NO_3)_2/O_2$ with the more reactive lithium cuprates proved particularly effective [121b]. The procedure provides for the alkylation, arylation, and vinylation of amines, but may not be synthetically competitive with the corresponding palladium chemistry. A recent Cu(I) catalyzed amine arylation is general [121c].

Treatment of *N*-alkoxyamines or *N*-silyloxyamines with cuprate reagents affords substituted amines, through displacement of the alkoxy [122a] or siloxy group [122] by an alkyl or aryl ligand from the cuprate reagent. Gilman and $R_2CuLi{\cdot}LiCN$ reagents are employed, and presumably one ligand is sacrificed to deprotonate the amine; the resultant amido(aryl or alkyl)cuprate undergoing reductive elimination to afford the substituted amine [122b]. Primary amines can be prepared by treatment of lithium dialkyl cuprates or alkylcopper reagents with 4,4′-bis(trifluoromethyl)benzophenone *o*-methylsulfonyloxime [122c]. Yields can be improved by addition of HMPA, while alkylcopper reagents generated from either Grignard or organolithium species afford the amines without the need for oxidation with molecular oxygen. Use of Grignard reagents offers a procedure catalytic in copper, affording primary amines containing primary, secondary, or tertiary alkyl groups in good to excellent yields (61–96%). Oxidative addition of the alkylcopper or cuprate reagent into the N O bond, followed by reductive elimination, accounts for the observed products. In the absence of copper, Grignard or lithium reagents fail to give substitution products. Treatment of amido- or α-heteroarylcopper reagents with ICH_2ZnI affords α-aminomethyl- (vide infra) or heteroarylmethylcuprates, which react with allylic halides to afford homoallylic amines or 2-(3-alkenyl)furans and thiophenes [123]. A detailed mechanistic study of the copper-catalyzed reaction between sodium methoxide and aryl bromides to afford anisole derivatives implicates a cuprate intermediate, $Na[Cu(OMe)_2]$, and a mechanism involving electron transfer [124].

3.3 α-Heteroatomalkylcuprates

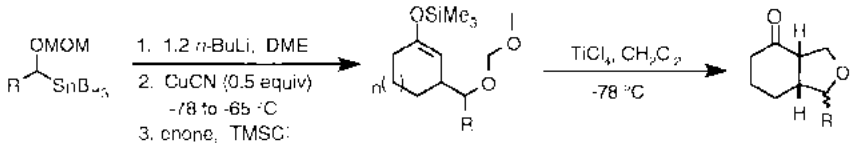
Ligands containing a heteroatom at the organometallic site generally exhibit lower cuprate reagent reactivity and introduce difficulties in cuprate preparation. Devel-

opments in α-heteroatomalkylcuprate chemistry have generally followed advances in the preparation of the corresponding organolithium and/or transition metal reagents. The synthetic potential of these heteroatom-functionalized cuprate reagents remains largely unexplored, awaiting solutions to the problems of reactivity and preparation.

3.3.1 Group VI Heteroatoms (O, S, Se)

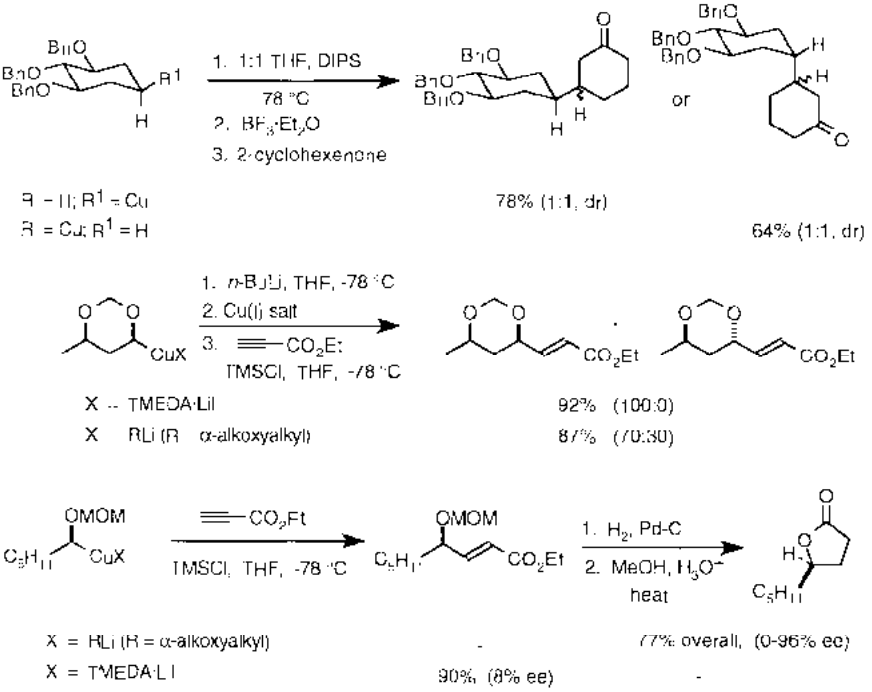
The first example of an α-alkoxyalkylcuprate was provided by direct deprotonation of *t*-butyl methyl ether (*sec*-BuLi/KO^{t}Bu), lithium bromide-induced conversion to the lithium reagent, and treatment with CuBr·SMe$_2$. High yields were achieved in the use of this reagent with an acid chloride and 2-cyclohexenone (90%) [125a] and it has also been utilized in the synthesis of (−)-aristermycin and (−)-neopanocin A [125b]. Linderman [126] and Fuchs [127] concurrently prepared α-alkoxyalkylcuprates from organolithium reagents generated by transmetalation of organostannanes. Good yields of enone conjugate adducts could be obtained with the cuprate reagent R$_2$CuLi·LiCN in the presence of TMSCl, while the absence of TMSCl or the use of RCuCNLi resulted in low yields. Good yields of conjugate adducts could also be obtained either with two equivalents of alkyl copper reagents (RCu) and BF$_3$·Et$_2$O, or, if BF$_3$·Et$_2$O was added after the enone, with only one equivalent of the copper reagent [127]. These reactions were complicated by the formation of homo-coupled dimers arising from the cuprate reagents and the side reaction was attributed to impurities in the organostannanes [126] and Cu(I) salt [127]. Impure organostannane precursors gave rise to heterogenous cuprate solutions. Use of highly pure organostannanes or in situ treatment of commercial CuCN (which contains 6–8% CuCl) with 5 mole% isopropylmagnesium chloride to scavenge Cu(II) trace impurities minimized the amounts of homo-coupling products. Cuprate formation was further complicated by the thermal lability of the α-alkoxylithium reagents, and use of solid CuCN requiring elevated temperatures for cuprate formation was sometimes problematic. The THF/diisopropyl sulfide-soluble CuBr·SMe$_2$ complex permitted cuprates to be formed at −78 °C and to be obtained free of Cu(II) impurities. Conjugate addition of R$_2$CuLi·LiCN reagents to 2-enals in the presence of TMSCl (added to both the cuprate and the enal solutions) afforded the *syn* conjugate adducts (*syn*:*anti*, 45:1 to 250:1) in modest yields (18–46%); substantial amounts of alcohols arising from 1,2-additions were also formed [128]. Use of TMSCl in combination with HMPA, DMAP, or TMEDA all favored 1,2-addition over 1,4-addition. Sequential α-alkoxyalkylcuprate conjugate addition, enolate trapping with TMSCl, and silyl enol ether alkylation provides a one-pot synthesis of tetrahydrofurans (Scheme 3.35) [129]. Cyclic enones afford *cis*-fused tetrahydrofurans, while acyclic systems give complex mixtures of diastereomers. α-Alkoxyalkylcopper reagents also participate in allylic substitution reactions with ammonium salts [127].

At low temperatures, α-alkoxyalkyllithium reagents are configurationally stable and the resultant alkylcopper or alkylcuprate reagents can transfer the ligand with



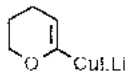
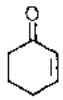
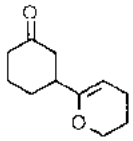
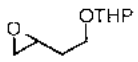
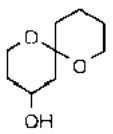
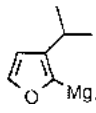
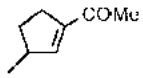
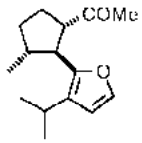
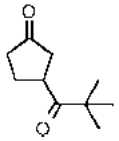
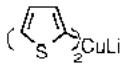
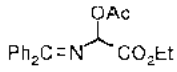
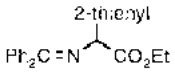
Scheme 3.35. Tetrahydrofuran synthesis by means of MOM α-alkoxyalkylcuprate conjugate additions followed by Lewis acid-promoted cyclization (MOM = methoxymethyl) [129].

retention of configuration. This methodology has been utilized in the transfer of enantiopure glucosyl [127] and α-alkoxyalkyl ligands [130] in conjugate addition reactions (Scheme 3.36). Cyclic α-alkoxyalkylcuprates prepared from the corresponding enantiopure stannanes [127, 130] can sometimes transfer the α-alkoxyalkyl ligand with retention of configuration. In acyclic systems, stereocontrol is capricious [130a], and racemization or isomerization occurs at higher temperatures both in cyclic and in acyclic systems. Oxygen-induced dimer formation with retention of configuration from an enantiopure α-alkoxyalkylcuprate (40% yield, >90% retention) suggests that racemization does not occur during the transmetalation step. The degree of racemization increases with increasing amounts of dimer and both events may be induced by trace amounts of oxygen [130]. The conjugate ad-



Scheme 3.36. Conjugate addition reactions of enantiopure α-alkoxyalkylcuprates (DIPS = diisopropylsulfide) [127, 130].

Tab. 3.4. Reactions of α-alkoxyalkenyl-, α-heteroaryl-, and acylcuprate reagents [180].

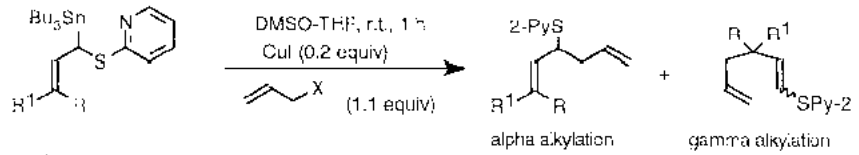
Cuprate	*Electrophile*	*Reaction conditions*	*Product*	*% Yield*	*Ref.*
 L = C–CC_3H_7		—		91	133c
L = 2-dihydropyranyl		i. THF, 0–20 °C ii. $H^{\oplus}$, H_2O		64	133b
		THF, 0–20 °C		25	134
^{t}BuCOCuCNLi		THF, Et_2O, pentane 110 to 25 °C		82	136
		THF, 5 °C, 6 h		71	135

dition does not proceed by a radical pathway and racemization could conceivably occur in a reversible d–π^* complexation event. In the cyclic systems, enantiopure alkylcopper reagents prepared from CuBr·SMe_2 or CuI·TMSI give retention of configuration in conjugate addition reactions to a greater extent than R_2CuLi·LiCN reagents do. Either poor or no stereocontrol is achieved at the newly created stereocenter β to the carbonyl group.

Geminal α-dialkoxyalkylcopper reagents prepared via stannanes also participate in conjugate additions to 2-enones, but fail with methyl crotonate. The copper reagent prepared from CuI·PBu_3 gives better yields than the corresponding cuprate reagent (92% versus 25%) [131]. Phenylation of a cuprate derived from a mixed O,S-acetal has also been reported [132]. Although these reagents add to enones and ynoates, they have not been extended to other Michael acceptors or to other reactions characteristic of cuprate reagents. A number of α-alkoxyalkenylcuprates and α-heteroarylcuprates have been used in synthesis (Tab. 3.4) [133–135]. The yields are generally good, reflecting the propensity of alkenyl ligands to participate in cuprate reactions (the preferential transfer of alkenyl ligands relative to easily transferred silyl ligands, for example) and the α-alkoxyalkenylcuprates undergo substitution reactions with epoxides and acetates. Acyl cuprates, generated by treatment of primary, secondary, or tertiary alkyl cuprates (R_2CuLi·LiCN [136a] or RCuCNLi [136b]) with carbon monoxide, selectively transfer the acyl group in conjugate ad-

dition reactions with 2-enones and enals. Only the *t*-butyl ligand competitively transfers, albeit in low yields (**14–24%**), again illustrating the ease with which sp^2-hybridized ligands preferentially participate in cuprate reactions. The former reagent is unstable at −78 °C, decomposing within 30 minutes, while the latter can be utilized at room temperature. The technique has been extended to allylic cuprates [137], employing a mixed homocuprate [(allyl)MeCuLi·LiCN]. Use of TMSCl results in formation of products resulting from alkyl ligand transfer. Diacylation of enones can be achieved by quenching the enolate resulting from acyl ligand transfer with an acid chloride [138].

α-Thionocarbamoyl stannanes [$R_2NC(=S)OCHR(SnBu_3)$] undergo in situ transmetalation with catalytic amounts of CuCN between room temperature and 23–50 °C, and the resultant α-alkoxy(cyano)cuprate reagents undergo conjugate addition reactions with 2-enones and enals and substitution reactions with allylic epoxides [139]. Successful conjugate addition required the use of TMSCl; poor yields were obtained with CuCl, $CuBr_2$, or $[ICu{\cdot}PBu_3]_4$. The reaction gave good yields of **1,4**-addition products as mixtures of diastereomers (dr = **1:1.2–2.4**) in THF or DME, but poor yields in Et_2O, benzene, DMSO, or HMPA; acceptable yields sometimes required the use of THF/acetone. Deuterium incorporation into the destannylation products from THF-d_8 suggests a radical pathway in the formation of these by-products. In situ transmetalation of α-(2-pyridylthio)allylstannanes can also be achieved with catalytic amounts of CuI in DMSO-THF, although the reaction fails with simple allyl stannanes (Scheme 3.37) [**140**]. Regioselective alkylation of the allyl copper reagent with allylic halides takes place γ to the sulfur atom for allylic chlorides and bromides, and α to sulfur for allylic iodides. Increased substitution at either the β- or the γ-positions in the allylic halide increases the degree of allyl copper α-alkylation (α:γ = 87:13 for 1-chloro-3-methyl-2-butene, $S_N2:S_N2' = 37:63$). Low chemical yields and α-selectivity on the allyl copper reagent are observed with the phenylthio analogues. These observations suggest that the pyridine nitrogen facilitates transmetalation and or cuprate reactivity and plays a role in the regioselectivity of the reaction.



Scheme 3.37. Reaction of α-thioallylcuprates generated in situ from stannanes and allylic halides [140].

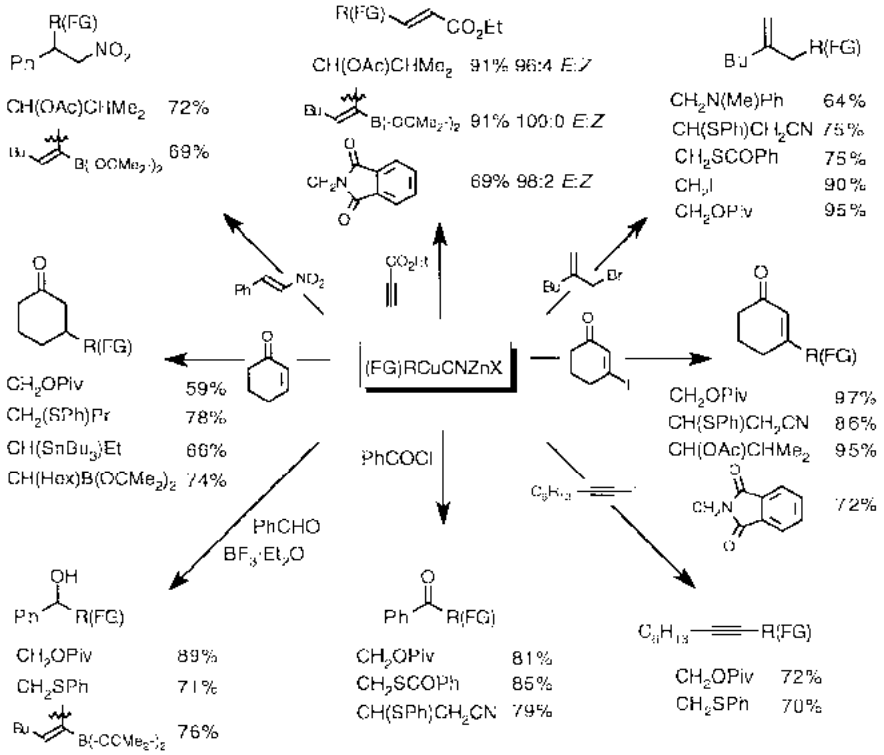
Mukaiyama reported the conjugate addition of α-dithioalkylcuprates to 2-enones (73–94% yields) for the synthesis of **1,4**-diketones, and the reaction was exploited in a synthesis of (±)-dihydrojasmone [**141**]. Few reports on α-thioalkylcuprates have appeared since then. Cuprates formed from lithiated ketene dithioacetals and

CuI·P(OMe)$_3$ undergo 1,4-addition to cyclohexenone with α-regioselectivity (98:2), while the lithium reagents display γ-selectivity (3:1 to 35:1) on the allylic organometallic reagent [142]. The cuprate reagent prepared from [phenylthio(trimethylsilyl)]methyllithium and CuI at low temperatures over one hour undergoes conjugate addition to simple enones in good yields (such as 2-cyclohexenone, 2-pentenone, isophorone; 52–83%); shorter times for cuprate preparation and higher temperatures resulted in 1,2-addition products and dimerization of the cuprate ligands occurred at −23 °C [143].

Although α-lithio alkoxides and sulfides are readily available, this approach requires the use of strong bases and affords lithium α-heteroatomalkylcuprates prone to side reactions and limited in effective cuprate/electrophile combinations. The lithium cuprates are most effective when the α-heteroatom is part of an sp^2-hybridized ligand (Tab. 3.4). Exploiting organozinc chemistry and the Zn Cu transmetalation technique [10], Knochel has developed effective procedures for the generation of α-alkoxy- [144] and α-thioalkylcuprates [145]. Acylation of α-arylselenoalkylcuprates, prepared in similar fashion, affords α-arylselenoketones [146]. The addition of THF-soluble CuCN·2LiCl to solutions of zinc reagents (RZnX or R_2Zn) presumably affords the corresponding zinc cuprate reagents (−30 °C, 5 min), which are both more stable and less reactive than the corresponding lithium cuprate reagents. Although less reactive than zinc alkylcuprates, these zinc α-heteroatomalkylcuprates react with a wide range of electrophiles (such as allyl halides, 2-enones, 3-halo-2-enones, acid chlorides, 2-ynoates, 1-halo-1-alkynes, nitroalkenes, and aldehydes (Scheme 3.38). Nevertheless, individual combinations of α-heteroatomalkylcuprate and electrophile can prove troublesome [144]; this appears to be related to proximity of the heteroatom and copper centers. Zinc α-alkoxyalkylcuprates have been utilized in the synthesis of (±)-rhopaloic acid A [147] and dynemicin [148] and added to cationic iron tricarbonyl pentadienyl complexes [149]. They also participate in conjugate addition reactions with nitroolefins, although the corresponding cuprates containing α-sulfur, nitrogen, or boron atoms fail to add [144b].

3.3.2
Group V Heteroatoms (N, P) and Silicon

Although zinc phthalimidomethylcuprate reacted with 3-iodo-2-cyclohexenone in good yield (72%) [144] (Scheme 3.8), the reagent was unreactive with other electrophiles. An α-aminomethyl zinc cuprate prepared from piperidinylcopper and ICH_2ZnI was readily alkylated with allyl halides [123], although other electrophiles appear not to have been examined. In contrast to these limited applications, α-heteroarylzinc cuprates prepared from 2-iodoimidazoles, 2-iodothiazoles, 2-iodopyridines, or 2-iodoquinolines react with allylic halides, 1-iodo-1-alkynes, and 3-iodo-2-enones to afford coupled products in good yields [150]. Coupling of the heteroarylzinc reagents with vinyl iodides, aryl halides, and heteroaryl halides required the use of palladium catalysis. These results once more illustrate the facility with which sp^2 centers bound to copper participate in ligand transfer, even in systems of

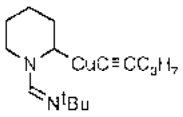
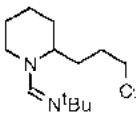
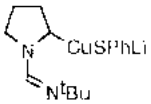
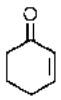
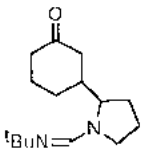
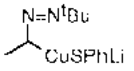
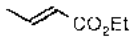
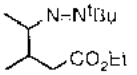
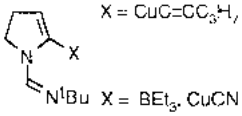
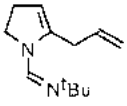
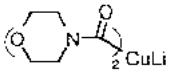
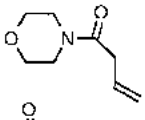
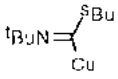
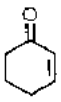
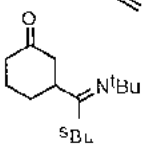
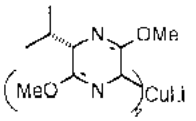
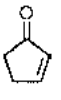
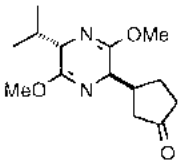
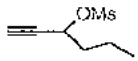
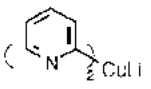
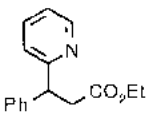
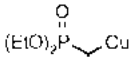
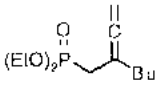


Scheme 3.38. Reactions of zinc α-alkoxy-, α-acyloxy-, α-arylthio-, α-acylthio-, and α-amino-, α-stannyl-, or α-borylalkylcuprates with various electrophiles [144a, 145].

reduced reactivity. Early work on cuprate reagents containing an α-nitrogen atom consistently involved sp^2 centers bound to copper [11a, 151–154], although good yields of conjugate addition products could also be obtained from allylic type systems (Tab. 3.5) [155–156]. Carbamoylation can be achieved with carbamoyl cuprates prepared from lithium amides, copper halides, and carbon monoxide [152]. The first examples of α-aminoalkylcuprates (sp^3 centers bound to copper) were employed by Meyers [157] and Gawley [158] in an effort to avoid SET events in alkylations of the corresponding lithium reagents and were limited to reactions with alkyl and allyl halides [157]. Dieter and Alexander reported the first examples of α-aminoalkylcuprate conjugate addition reactions (Tab. 3.5) involving hydrazone- [156] and formamidine-derived cuprates [11b]. The inability to remove either protecting group in the presence of the ketone functionality prompted an examination of Beak's α-lithiated carbamates [159] for the preparation of α-aminoalkylcuprates [11c, 160].

α-Aminoalkylcuprates, prepared from α-aminoalkylstannanes by way of an Sn to Li to Cu transmetalation sequence, reacted with acyclic and cyclic enones in THF to afford good to excellent yields of conjugate adducts [$R_2CuCN{\cdot}LiCN$ (50–99%),

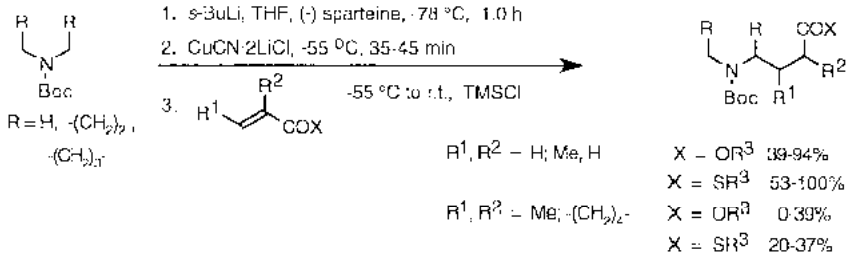
Tab. 3.5. Reactions of α-nitrogen and phosphorus alkyl-, alkenyl-, and acylcuprate reagents [180].

Cuprate	*Electrophile*	*Reaction conditions*	*Product*	*% Yield*	*Ref.*
	$Br(CH_2)_3Cl$	THF, 20 °C		76	157
		THF, 78 °, 1 h, 10 h r.t.		86	11b
		THF 78 °C to r.t., 3 h		88 (35:65 dr)	156
		THF, Et_2O 20 °C, 4 h		87	151a
		THF 20 °C, 20 min		60	151b
		THF, HMPA CO, 25 °C, 12 h		93	152a
		Et_2O 78 to 0 °C		65	153
		THF, DMS 70 °C		71	155a
$Ph_2C{=}NCH_2Cu{\cdot}SMe_2$		THF, 50 °C 45 min	$Ph_2C{=}NCH_2CH{=}C(H)Pr\text{-}n$	49	155b
		Et_2O 0 °C, 20 min		82	154
		THF, 16 h 35 to 25 °C		70	176a

(DMS = dimethylsulfide, HMPA = hexamethylphosphoramide)

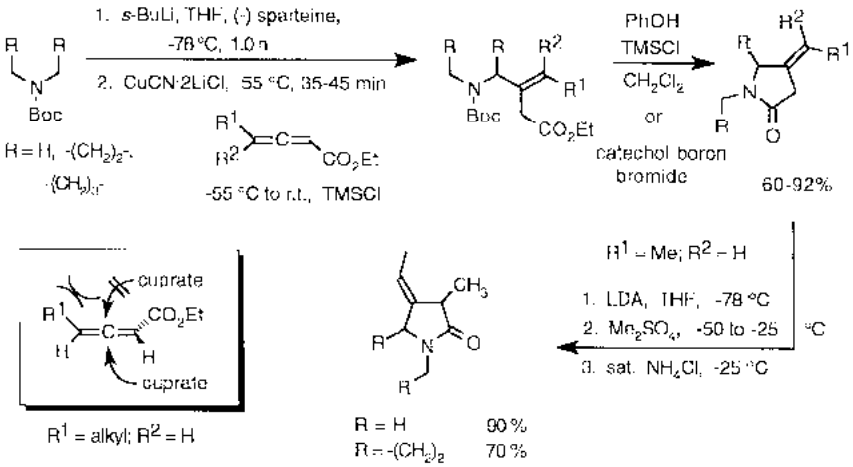
RCuCNLi (25–62%)]. Successful conjugate addition required the activating influence of TMSCl [11c], and rather modest yields (25–64%) were obtained with β,β-dialkyl-substituted 2-enones. Cuprate preparation directly from the organolithium

species, available by *s*-butyllithium deprotonation of the carbamate [159], by utilization of THF-soluble CuCN·2LiCl, afforded a procedure less sensitive to the effects of diamine (added to assist deprotonation), temperature, manner of organolithium preparation and *s*-butyllithium quality [160]. The use of CuCN·2LiCl resulted in the first successful examples of α-aminoalkylcuprate conjugate addition to α,β-unsaturated carboxylic acid derivatives [161] (2-enoates, thiol esters, imides) (Scheme 3.39) and gave significantly higher yields of 1,4-adducts with 2-enals,



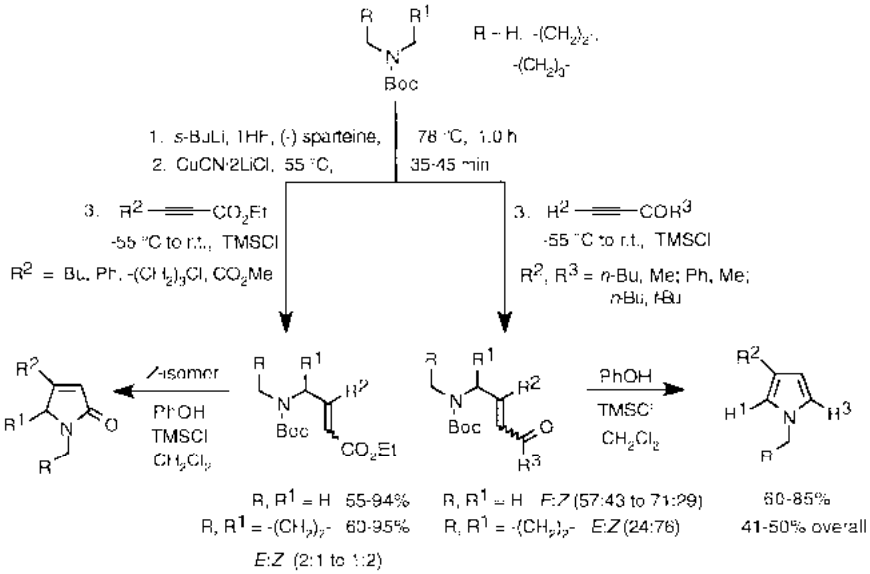
Scheme 3.39. Reactions between α-aminoalkylcuprates and α,β-unsaturated carboxylic acid derivatives [161].

accompanied by smaller amounts of 1,2-addition products [160]. Conjugate addition of α-aminoalkylcuprates to allenic esters occurred stereoselectively, *anti* to the substituent at the γ-carbon atom to afford (*E*)-3-aminoalkyl-β,γ-unsaturated esters [162]. Carbamate deprotection and lactonization with PhOH/TMSCl regioselectively and stereoselectively afforded 4-alkylidene-2-pyrrolidinones, 4-alkylidene-2-pyrrolizidinones, and 4-alkylidene-2-indolizidinones. These products could be alkylated at the 3-position of the γ-lactam through the lactam enolate (Scheme 3.40).



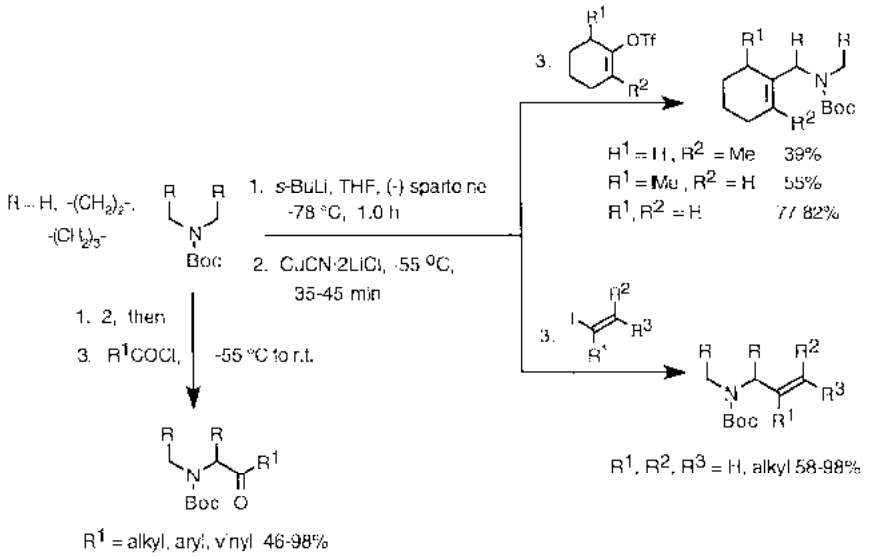
Scheme 3.40. Stereoselective reaction between α-aminoalkylcuprates and allenic esters, with formation of 4-alkylidine-2-pyrrolidinones [162].

Conjugate addition of RCuCNLi reagents to 2-ynoates gave *E*:*Z* mixtures of 4-amino-2-enoates. Although the *Z* isomers could be directly cyclized to pyrrolidinones, *E* isomers needed to be heated neat with thiophenol. Conjugate addition to 2-ynones afforded *E*:*Z* mixtures of 4-amino-2-enones, but treatment of the adducts with PhOH/TMSCl effected Boc deprotection and cyclization to pyrroles [163]. The procedure is versatile, permitting introduction of substituents at three of the four carbon atoms of the pyrrole ring system (Scheme 3.41). The reaction between cuprates and alkynyl ketones or esters may well proceed by way of a 1,2-addition or carbocupration process [62] (vida supra) and the use of TMSCl and CuCN·2LiCl in the α-aminoalkylcuprate reactions facilitates *E*:*Z* isomerization of the intermediate α-cuprio-α,β-unsaturated ketones and alkynes. The poor stereoselectivity in the ynoate reactions may be circumvented with the aid of the stereospecific substitution reaction between α-aminoalkylcuprates and 3-iodo-2-enoates [164]. Although the less reactive zinc phthalimidomethylcuprate failed to undergo 1,4-addition to nitro-olefins [144b], the reaction was successful with α-aminoalkylcuprates containing a single electron-withdrawing substituent on nitrogen, this procedure being used in the preparation of triplex DNA-specific intercalators [165].



Scheme 3.41. Reactions between α-aminoalkylcuprates and alkynyl ketones [163] or esters [161b], and formation of pyrroles and pyrrolidinones (Boc = *t*-butoxycarbonyl).

α-Aminoalkylcuprates also participate in a variety of substitution reactions (Scheme 3.42). Reagents prepared from copper cyanide ($R_2CuLi{\cdot}LiCN$ or RCuCNLi) or CuCl (RCu·LiCl) react with alkyl, aryl, and alkenyl acid chlorides to afford α-amino ketones in good to excellent yields [166]. Use of the latter two reagents is efficient in α-aminoalkyl ligand, although yields are slightly lower than



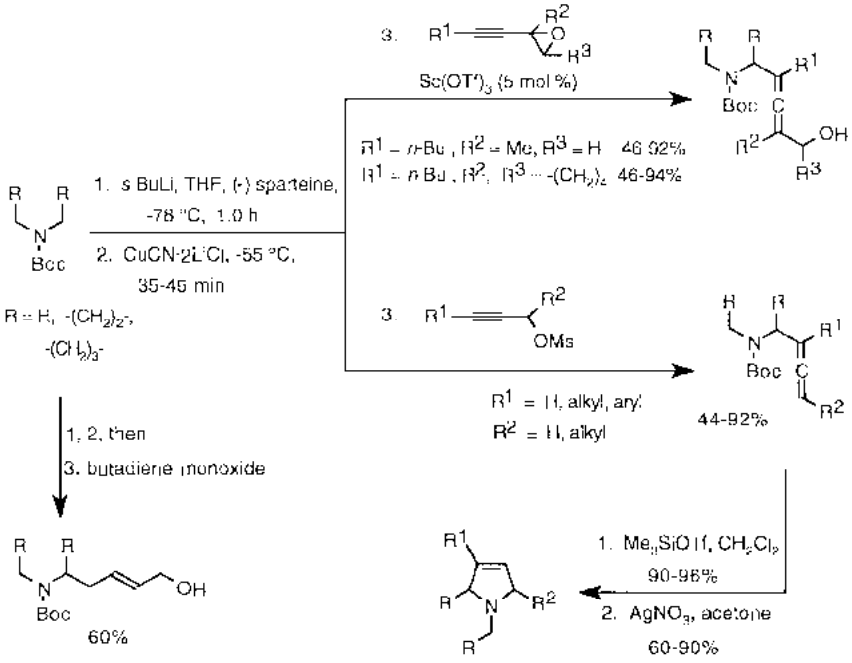
Scheme 3.42. Substitution reactions between α-aminoalkylcuprates and acid chlorides [166], vinyl triflates [167], and vinyl iodides (Boc = *t*-butoxycarbonyl) [168].

those obtained with $R_2CuLi{\cdot}LiCN$. α-Aminoalkylcuprates prepared from CuI, $Cu{-}CC_4H_9$, CuMe, or $CuPPh_2$ and α-lithiocarbamates gave low to moderate yields of allylic amines on treatment with vinyl triflates prepared from cyclic ketones [167]. Good to excellent yields could be achieved with the $R_2CuLi{\cdot}LiCN$ reagent, although the reaction was sensitive to steric factors, giving low to modest yields of allylic amines with the vinyl triflates derived from camphor and 2-methylcyclohexanone. Failure to prepare acyclic vinyl triflates stereoselectively prompted an examination of vinyl iodides, which can be prepared stereoselectively from alkynes. Initially, successful stereospecific vinylation of α-aminoalkylcuprates with vinyl iodides required use of THF-soluble CuCN·2LiCl [168]. Good to excellent yields of allylic amines were obtained with $R_2CuLi{\cdot}LiCN$, while slightly lower yields were obtained in two cases with the RCuCNLi and RCu·LiCl reagents. The methodology was employed in a stereoselective synthesis of (±)-norruspoline.

A study of the factors affecting α-aminoalkylcuprate chemistry examined the influence of *s*-BuLi quality, the role of alkoxide impurities in the *s*-BuLi, temperature, and Cu(I) source (e.g., insoluble CuCN versus THF-soluble CuCN·2LiCl) [169]. α-Aminoalkylcuprates prepared from α-lithiocarbamates with poor quality *s*-BuLi containing LiH and/or *s*-BuOLi gave good yields of the conjugate addition product with methyl vinyl ketone or the substitution product with (*E*)-1-iodo-1-hexene, although nearly quantitative yields could be obtained when high quality *s*-BuLi was employed. When prepared with high quality *s*-BuLi, α-aminoalkylcuprates displayed good thermal stability (3 h at 25 °C, for example), which decreased when poorer quality *s*-BuLi was employed. The vinylation reaction and 1,4-addition to methyl

crotonate could be achieved in nearly quantitative yields using either solid CuCN or THF-soluble CuCN·2LiCl, although use of solid CuCN required elevated temperatures for complete cuprate formation. The α-lithiocarbamates appear to be significantly less thermally stable than the α-aminoalkylcuprates, and use of THF-soluble CuCN·2LiX permitted rapid cuprate formation at −78 °C, minimizing α-lithiocarbamate decomposition.

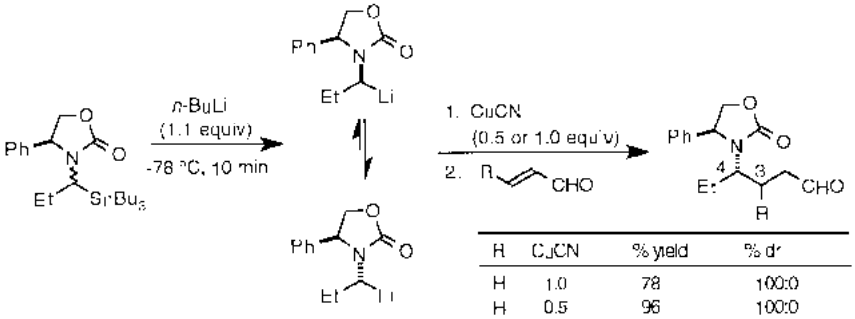
Substitution reactions with allyl halides or phosphonates afforded mixtures of rearranged (S_N2') and unrearranged (S_N2) products and little regioselective control could be achieved [170]. These results are consistent with initial formation of an olefin-copper π-complex, followed by allylic inversion (i.e., S_N2', generally with *anti* stereoselectivity) to give a σ-alkylcopper complex. This σ-allyl complex can undergo reductive elimination to afford the S_N2' substitution product, or isomerize through a π-allyl complex to give a rearranged σ-allyl complex, which on reductive elimination affords the S_N2 substitution product. Alkylation of α-aminoalkylcuprate reagents with allylic sulfides prepared from benzothiazole-2-thiol resulted in regiospecific S_N2 substitution in modest to good yields (31–80%). Excellent regiocontrol could also be achieved with allylic epoxides [171] and with propargyl sulfonates and epoxides [172], resulting in exclusive S_N2' substitution in most systems (Scheme 3.43). Propargyl acetates were unreactive. Substitution without allylic rearrangement (i.e., S_N2) was only observed when severe steric crowding was present in the α-amino alkyl ligand or in the propargyl substrate. The resultant allenyl carbamates



Scheme 3.43. Reactions of α-aminoalkylcuprates with allylic epoxides [171] and propargylic substrates (Boc = *t*-butoxycarbonyl) [172].

can be deprotected with trimethylsilyltriflate to afford the allenyl amines [172], which can be cyclized to pyrrolines in excellent overall yields by use of $AgNO_3$ [173]. When coupled with non-racemic propargyl alcohols, this synthetic methodology provides an excellent route to enantiopure pyrroline derivatives, which can be exploited for the synthesis of a variety of heterocyclic compounds such as aza sugars.

Beak's extensive studies on asymmetric deprotonation of carbamates with (−)-sparteine [159] raise the intriguing prospect of maintaining configuration stability of the C M bond during lithiation, cuprate formation, and cuprate reaction. In preliminary studies, the enantiomeric excess ranged from excellent in the vinylation reaction (85–89% *ee*), to modest in the propargyl systems (54% *ee*) while conjugate addition reactions with esters gave racemic products [174]. Successful application of this strategy will require a balance of substrate and cuprate reactivity, and the use of non-polar solvents to minimize racemization of the organolithium reagents prior to cuprate formation. Transmetalation of diastereomeric N-(α-stannylalkyl) lactams epimeric at the alkylstannane stereocenter affords an epimeric mixture of organolithium reagents that rapidly equilibrates to the more stable epimer (Scheme 3.44). Treatment of the lithium reagent with CuCN (1.0 or 0.5 equivs.) affords enantiopure α-aminoalkylcuprates that give single diastereomers on treatment with acrolein [175]. Conjugate addition to 2-enones gave mixtures of diastereomers epimeric at the β-carbon of the original enone. Diastereoselectivities are poor with acyclic enones (56:44 dr) and modest to excellent with cyclic enones. The poor diasteroselectivity at the β-carbon of cyclic enones arises from poor facial selectivity during cuprate addition. Acyclic enones may also give poor diastereoselectivity at the β-carbon center because of *E*:*Z* isomerization arising from an equilibrium between an enone-cuprate d–π^* complex and starting materials. Much work remains to be done in the development of asymmetric variations in α-aminoalkylcuprate chemistry.



R	CuCN	% yield	% dr
H	1.0	78	100:0
H	0.5	96	100:0
Me	1.0	85	100:0 (C4) 71:29 (C3)

Scheme 3.44. Reactions of enantiopure α-aminoalkylcuprate with 2-enals [175].

Relatively few examples involving a phosphorous atom in the α-heteroatomalkylcuprate have appeared [176]. Such cuprates have been treated with allylic and propargylic substrates, but have not been reported to undergo conjugate addition

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4
Copper-mediated Addition and Substitution Reactions of Extended Multiple Bond Systems

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4.1
Introduction

Since the pioneering work of Gilman et al., who carried out the first investigations into organocopper compounds RCu [1] and lithium diorganocuprates R_2CuLi [2], the latter reagents (still referred to even today as Gilman reagents) have been becoming widespread among organometallic reagents used for carbon-carbon bond formation. In particular, the seminal work of House et al. and Corey et al. has served to establish organocuprates as the reagents of choice not only for substitution reactions of many saturated (haloalkanes, acid chlorides, oxiranes) and unsaturated (allylic and propargylic derivatives) electrophiles, but also for 1,4-addition reactions to α,β-unsaturated carbonyl compounds and, last but not least, for carbocuprations of non-activated alkynes [3]. In these processes, the unique reactivity of organocuprates relies on the interplay of the "soft", nucleophilic copper and the "hard", electrophilic lithium ion, offering control over reactivity and selectivity through "fine-tuning" of the reagent. Most of the tremendous achievements in various fields of organocopper chemistry over the last few decades are highlighted in this book. These include the elucidation of the structures of organocopper compounds [4] and the mechanism of their transformations [5] (Chapts. 1 and 10), new copper-mediated and copper-catalyzed processes [6] (Chapts. 2, 3, and 5), diastereoselective reactions (Chapt. 6), and highly enantioselective substitution and conjugate addition reactions [7] (Chapts. 7 and 8). The high standards attained in these fields are documented in numerous applications of copper-promoted transformations in total synthesis (Chapt. 9).

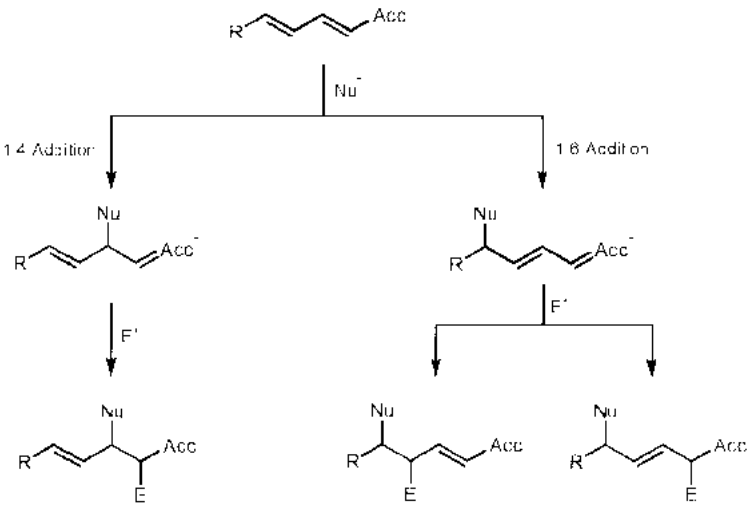
As far as substrates are concerned, while the usual 1,4-addition and 1,3-substitution (S_N2') reactions of simple unsaturated substrates have so far predominated, analogous transformations of ambident substrates with extended multiple bond systems (i.e., with two or more reactive positions) have come to attention only recently. Here, systematic investigations have shown that such 1,5-substitutions and even 1,6- and 1,8-addition reactions proceed highly regioselectively and stereoselectively, in particular when the substrate contains at least one triple bond besides one or more conjugated double bonds. These unusual reaction types not

only open up novel routes to interesting target molecules, but also provide deeper insights into the mechanism of copper-mediated carbon-carbon bond formation [3o, 8].

4.2
Copper-mediated Addition Reactions to Extended Michael Acceptors

4.2.1
Acceptor-substituted Dienes

Thanks to their ambident character, acceptor-substituted dienes can provide several isomeric products in copper-mediated Michael additions, therefore making it particular important to control not only the regioselectivity but also the stereoselectivity of these transformations (Scheme **4.1**).

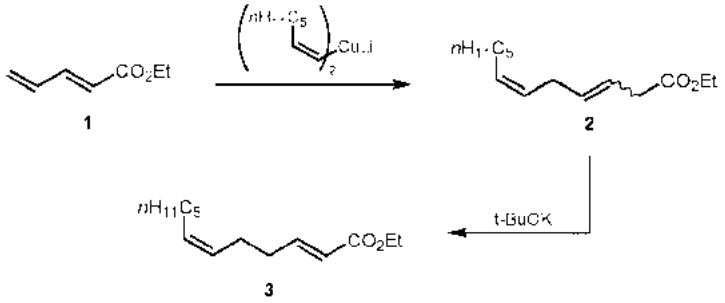


Scheme 4.1. Regioselectivity in conjugate addition reactions to acceptor-substituted dienes.

Besides direct nucleophilic attack onto the acceptor group, an activated diene may also undergo **1,4**- or **1,6**-addition; in the latter case, capture of the ambident enolate with a soft electrophile can take place at two different positions. Hence, the nucleophilic addition can result in the formation of three regioisomeric alkenes, which may in addition be formed as *E*/*Z* isomers. Moreover, depending on the nature of nucleophile and electrophile, the addition products may contain one or two stereogenic centers, and, as a further complication, basic conditions may give rise to the isomerization of the initially formed *β*,*γ*-unsaturated carbonyl compounds (and other acceptor-substituted alkenes of this type) to the thermodynamically more stable conjugated isomer (Eq. **4.1**).

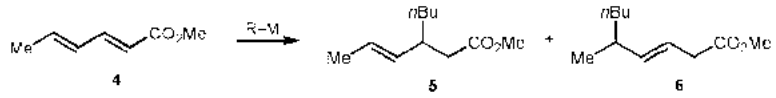
(4.1)

The first example of a cuprate addition to an acceptor-substituted diene was reported by Näf et al. [9], who used lithium di-(*Z*)-1-heptenylcuprate in a Michael addition to dienoate **1** (Eq. 4.2). The reaction proceeded highly regioselectively, furnishing a 1:1 mixture of the two isomeric 1,6-adducts **2**, which were converted into the Bartlett pear constituent ethyl (2*E*,6*Z*)-2,6-dodecadienoate (**3**) by basic isomerization.



(4.2)

In analogous reactions, several other groups reported the exclusive formation of 1,6-addition products, suggesting that not even the choice of the organocopper reagent affected the regioselectivity of the transformation [10]. Whereas the use of monoorganocopper compounds predominantly resulted in the formation of adducts with *E* configurations, the corresponding Gilman cuprates R_2CuLi yielded only 1:1 mixtures of the *E* and *Z* isomers [10b]. Ultimately, Yamamoto et al. [3f, 11] were able to show in their seminal contributions that even 1,4-additions of organocopper reagents to activated dienes are feasible: while the reaction between methyl sorbate (**4**) and the reagent formed from *n*-butylcopper and boron trifluoride mainly gave the 1,4-adduct **5**, the corresponding Gilman cuprate nBu_2CuLi again exclusively provided the 1,6-addition product **6** (Eq. 4.3). The organocopper compounds $RCu{\cdot}BF_3$ are synthetically very useful (in natural product synthesis, for example; cf. Chapt. 9) and so have become commonly referred to as Yamamoto reagents [3f].

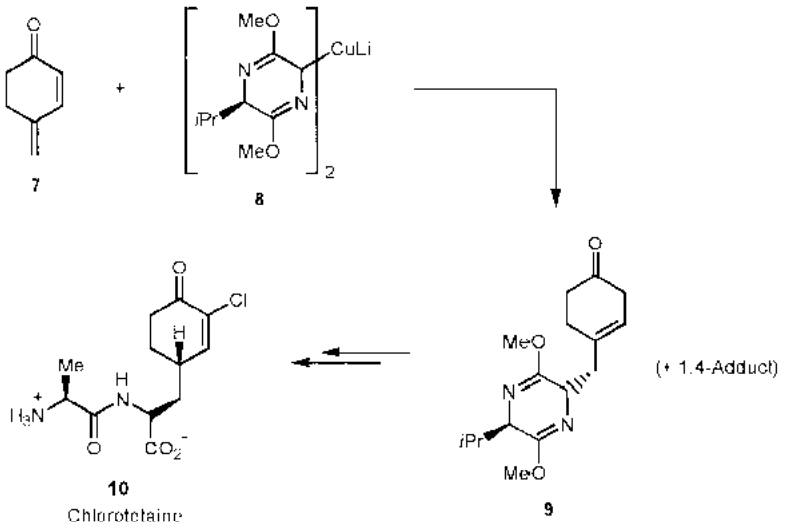


(4.3)

R–M	5 : 6
$nBuCu \cdot BF_3$	93 : 7
nBu_2CuLi	< 1 : > 99

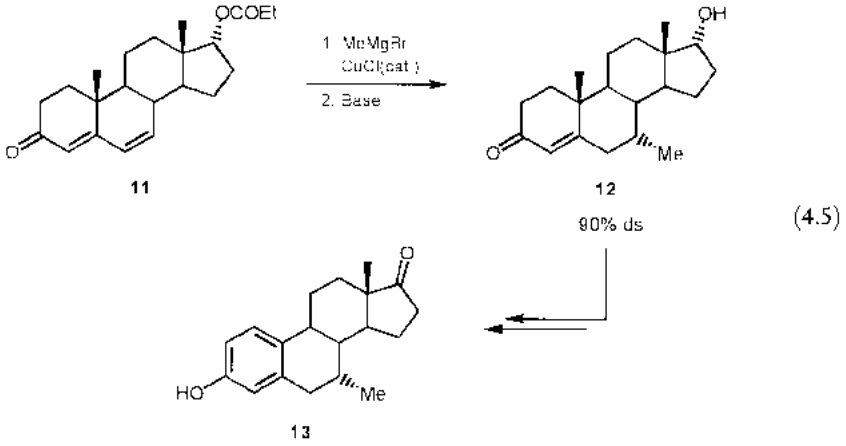
Michael additions of organocopper reagents to acceptor-substituted dienes have found widespread application in target-oriented stereoselective synthesis [12]. For

example, the chiral cuprate **8**, containing a Schöllkopf bislactim ether moiety, was used in the first total synthesis of the antimycotic dipeptide chlorotetaine (**10**; Eq. **4.4**) [12d]. Although the nucleophilic addition to dienone **7** in this case did not proceed regioselectively, furnishing only a 63:37 mixture of the 1,6- and 1,4-adducts, the former compound was successfully converted over several steps into diastereomerically and enantiomerically pure chlorotetaine (**10**).



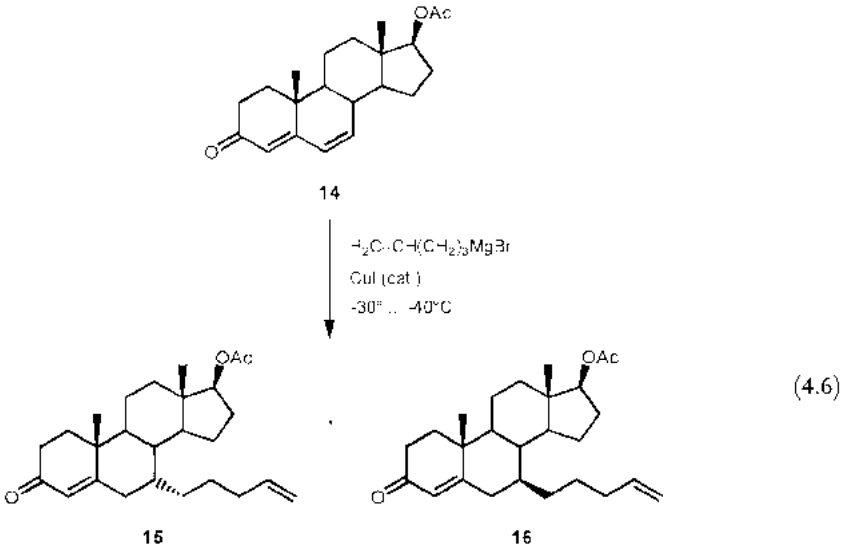
(**4.4**)

While copper-catalyzed Michael additions to acceptor-substituted dienes using Grignard reagents as nucleophiles were reported even earlier than the corresponding additions of (stoichiometric) organocuprates, the former transformations have largely been restricted to the synthesis of steroid hormones. In this context, in addition to tetrahydro-3*H*-naphthalen-2-ones, which were used as model substrates for doubly unsaturated steroids [13, **14**], estradiol derivatives bearing an alkyl chain in the 7α-position are especially interesting target molecules, due to their high affinity for and specificity towards estrogen receptors [15, 16]. These unsaturated steroids may thus be particularly useful for the treatment of mammary tumors (breast cancer) [15]. As regards preparative aspects, however, the nucleophilic 1,6-addition to doubly unsaturated $\Delta^{4,6}$-steroids should proceed not only with the desired regioselectivity [13, **14**, 15b, 16], but also in a diastereoselective manner, since only the 7α isomers are effective enzyme inhibitors [15b]. Although the diastereoselectivity of the copper-catalyzed 1,6-addition of methyl Grignard reagents to $\Delta^{4,6}$-steroids may be dependent on the substitution pattern of the substrate [13a], general preference for attack from the α side has frequently been observed [13]. Wieland and Auner [13e], for example, reported an α selectivity of 90% in the copper-catalyzed 1,6-addition of MeMgBr to dienone **11** (Eq. **4.5**). The product **12** was converted over several steps into 7α-methylestrone (**13**), a precursor of several highly active steroidal hormones.



(4.5)

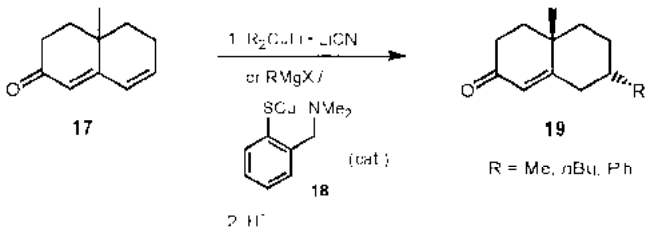
In contrast to this, the introduction of longer alkyl chains with the aid of copper-promoted 1,6-addition reactions to $\Delta^{4,6}$-steroids normally proceeds with unsatisfactory α:β ratios [15b, 16]. In some cases, improvement of the diastereoselectivity by "fine tuning" of the reaction conditions has been possible. The ratio of the epimeric products **15** and **16** in the copper-catalyzed 1,6-addition of 4-pentenylmagnesium bromide to dienone **14**, for example, was improved from 58:42 to 82:18 by adjustments to the quantity of nucleophile and the solvent composition (Eq. 4.6) [16f].



(4.6)

Eq. Grignard	Ratio THF / diethyl ether	**15** : **16**
12	1 : 9	58 : 42
12	1 : 4	60 : 40
12	1 : 1	78 : 22
4	1 : 1	82 : 18

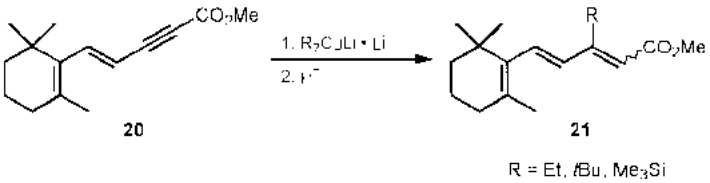
Aberrant behavior, however, has been observed when using bicyclic tetrahydro-3*H*-naphthalen-2-ones as Michael acceptors: the 1,6-addition of cyano-Gilman cuprates or Grignard reagents (catalyzed by copper arene thiolate **18**) proceeds with high *trans* selectivity, irrespective of the transferred group (Eq. **4.7**) [17]. NMR spectroscopic investigations have found that formation of π-complexes at the double bond adjacent to the carbonyl group, similar to those observed in 1,6-cuprate additions to acceptor-substituted enynes (Sect. **4.2.3**), are involved in these transformations. Nevertheless, deeper insight into mechanistic features, which should be highly rewarding for preparative applications, is still awaited.



(4.7)

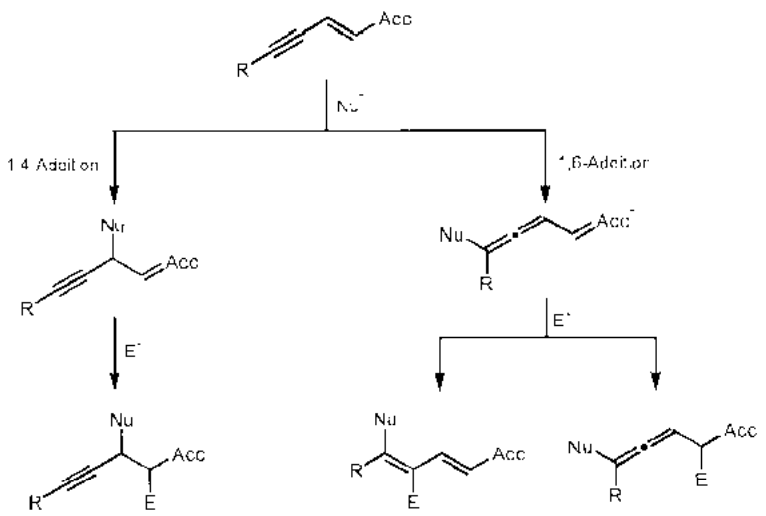
4.2.2
Acceptor-substituted Enynes

As for conjugate addition reactions of carbon nucleophiles to activated dienes, organocopper compounds represent the reagents of choice for regioselective and stereoselective Michael additions to acceptor-substituted enynes. Whereas substrates bearing an acceptor-substituted triple bond in conjugation with one or even more double bonds (such as **20**) react with organocuprates exclusively by 1,4-addition (Eq. **4.8**) [18], the corresponding additions to enynes bearing acceptor substituents at the double bond can result in the formation of several regioisomeric products [3o, 8, 19].



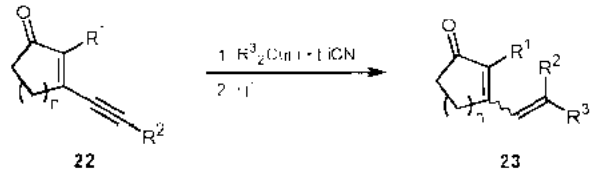
(4.8)

Analogously to the acceptor-substituted dienes (Scheme **4.1**), the outcome of the reaction depends strongly on the regioselectivity of both the nucleophilic attack of the copper reagent (1,4- or 1,6-addition) and of the electrophilic trapping of the enolate formed (Scheme **4.2**). Since the allenyl enolate formed by 1,6-addition can furnish either an allene or a conjugated diene upon reaction with a soft electrophile, and so offers the possibility of creating axial chirality, this transformation is of special interest from the preparative and also the mechanistic points of view. Recent investigations have demonstrated that the regioselectivities and stereoselectivities of both steps can be controlled by the choice of the reactants, in particular by "fine-tuning" of the organocopper reagent and the electrophile.



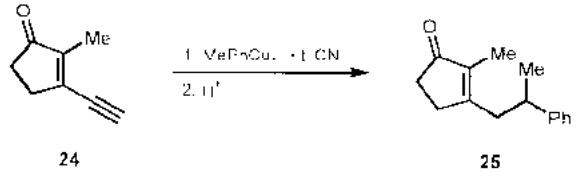
Scheme 4.2. Regioselectivity in conjugate addition reactions to acceptor-substituted enynes.

The first copper-mediated addition reactions to enynes with an acceptor group at the triple bond were reported by Hulce [19, 20], who found that 3-alkynyl-2-cycloalkenones **22** react regioselectively with cuprates, in a 1,6-addition at the triple bond (Eq. 4.9). The allenyl enolates thus formed are protonated at C-4 to provide conjugated dienones **23** as mixtures of *E* and *Z* isomers. Interestingly, substrates of this type can also undergo tandem 1,6- and 5,6-additions, indicating that the allenyl enolate is sufficiently nucleophilic to react with another organometallic reagent in a carbometalation of the allenic double bond distal to the electron-releasing enolate moiety (Eq. 4.10) [20b]. Hence, it is even possible to introduce two different groups at the Michael acceptor, either by successive use of two organocopper reagents or by employing a mixed cuprate.



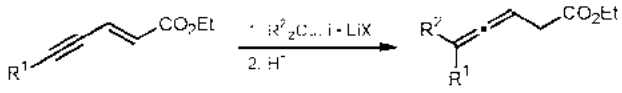
22 **23** (4.9)

n = 1, 2; R^1 = H, Me; R^2 = H, Ph, Me_3Si; R^3 = Me, Et



24 **25** (4.10)

With regard to preparative applications, however, shifting the regioselectivity of the electrophilic quenching reaction towards the formation of allenes would be far more interesting, since the scope of synthetic methods for the preparation of functionalized allenes has hitherto been rather limited [21]. Moreover, a stereoselective reaction of this type would open up a route to these axially chiral compounds in enantiomerically enriched or even pure form. The Gilman cuprate $Me_2CuLi{\cdot}LiI$ and cyano-Gilman reagents $R_2CuLi{\cdot}LiCN$ ($R \neq Me$) in diethyl ether did indeed react regioselectively in a 1,6-fashion with various substituted 2-en-4-ynoates **26**. After protonation with dilute sulfuric acid, the β-allenic esters **27**, with alkyl, alkenyl, aryl, and silyl substituents, were obtained in good chemical yields (Eq. **4.11**) [22].

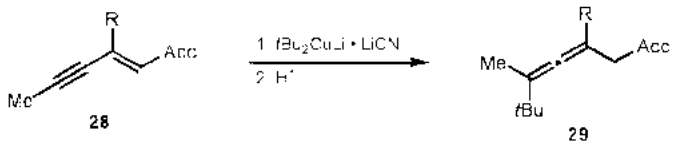


26 **27**

R^1 = Ph, R^2 = Me:	79%
R^1 = Ph, R^2 = *t*Bu:	81%
R^1 = *n*Bu, R^2 = Ph:	62%
R^1 = Me_3Si, R^2 = Me:	57%

(**4.11**)

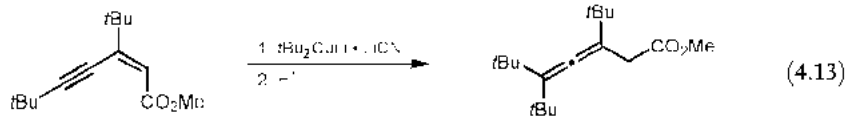
The nature of the acceptor substituent exerts hardly any influence on the regioselectivity of the cuprate addition to acceptor-substituted enynes. Enynes **28**, variously incorporating thioester, lactone, dioxanone, keto, sulfonyl, sulfinyl, cyano, and oxazolidino groups, all react in a 1,6-manner to furnish functionalized allenes **29** (Eq. **4.12**). In contrast, though, 1-nitro-1-en-3-ynes are attacked at the C=C double bond, with formation of the corresponding 1,4-adducts [22c]. The differences in reactivity can be described qualitatively by the following reactivity scale: Acceptor (Acc) = NO_2 > COR, CO_2R, COSR > CN, SO_3R, oxazolidino > SO_2R > SOR ≫ $CONR_2$. Remarkably, the regioselectivity of the cuprate addition to acceptor-substituted enynes is also insensitive to the steric properties of the substrate. Thus, enynes with *t*-butyl substituents at the triple bond (e.g., **30**) undergo 1,6-additions even when the cuprate itself is sterically demanding (Eq. **4.13**) [22b]. This method is therefore highly useful for the preparation of sterically encumbered allenes of type **31**.



28 **29**

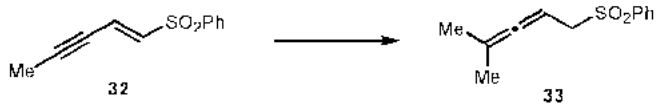
(**4.12**)

Acc = CN, R = Me:	79%
Acc = SO_2Ph, R = H:	91%
Acc = SO_2Et, R = H:	49%



30 31 (4.13)

In order to achieve acceptable chemical yields with less reactive Michael acceptors, such as sulfones and sulfoxides, it is often necessary to use more reactive organocopper reagents or to activate the substrate by Lewis acid catalysis. Thus, treatment of enyne sulfone **32** with five equivalents of the Gilman cuprate Me_2CuLi alone gave no trace of the addition product, whereas the analogous reaction with Me_3CuLi_2 provided the desired allene **33** only in a disappointing 16% yield (Eq. **4.14**) [22c]. With two equivalents of Me_2CuLi in the presence of one equivalent of Me_3SiI, however, the yield was increased to 45%, although with Me_3SiOTf as additive the allene **33** was isolated in only 29% yield. Unfortunately, enyne amides completely fail to form 1,6-adducts even under these conditions.

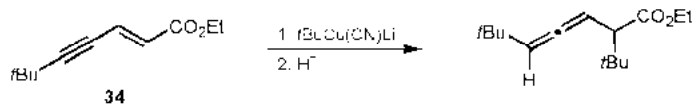


32 33

$Me_2CuLi \cdot LiI$:	0%
$Me_3CuLi_2 \cdot LiI$:	16%
$Me_2CuLi \cdot LiI / Me_3SiI$:	45%
$Me_2CuLi \cdot LiI / Me_3SiOTf$:	29%

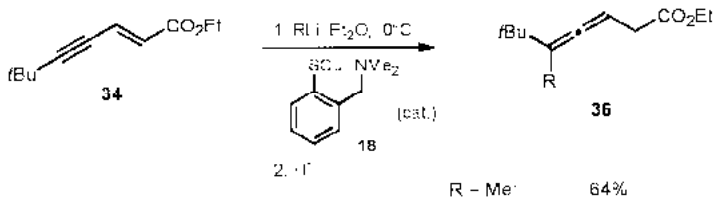
(4.14)

Unlike the substrate, the organocuprate component has a pronounced influence on the regiochemical course of the addition to acceptor-substituted enynes. While the Gilman cuprate $Me_2CuLi \cdot LiI$ as well as cyano-Gilman reagents $R_2CuLi \cdot LiCN$ ($R \neq Me$) readily undergo 1,6-additions, the Yamamoto reagents $RCu \cdot BF_3$ [3f] and organocopper compounds RCu activated by Me_3SiI [23] both afford 1,4-adducts [3o]. In some cases, even 1,4- and 1,6-reduction products are observed; these may be the result of electron transfer from the cuprate to the substrate or of hydrolysis of a stable copper(III) intermediate [19, 24]. Lower order cyanocuprates RCu(CN)Li again show a different behavior; although these do not usually react with acceptor-substituted enynes, the cuprate *t*BuCu(CN)Li nevertheless undergoes anti-Michael additions with 2-en-4-ynoates and nitriles (Eq. **4.15**) [25]. A satisfactory interpretation of the capricious behavior of organocuprates in these conjugate addition reactions to acceptor-substituted enynes is unfortunately still awaited, and so identification of the appropriate reaction conditions for each cuprate often has to rely upon a "trial and error" search.



34 35 70% (4.15)

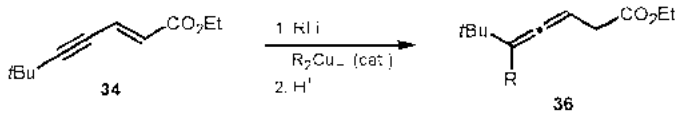
Like the copper-catalyzed 1,4-Michael additions of Grignard reagents to enones and activated dienes, the corresponding 1,6-additions to acceptor-substituted enynes can also be conducted catalytically. However, only very carefully controlled reaction conditions furnish the 1,6-adduct as the major product. Hence, the use of copper (2-dimethylaminomethyl)thiophenolate (**18**) as catalyst and simultaneous addition of the substrate (e.g., **34**) and an organolithium reagent to a suspension of the catalyst **18** in diethyl ether at 0 °C resulted in the formation of various substituted β-allenylcarboxylates **36** (Eq. **4.16**) [26]. The yields were comparable to those obtained in analogous stoichiometric procedures, whereas only low yields of the 1,6-addition products were found if other copper(I) salts were employed as catalyst, or other Grignard reagents as nucleophile.



R = Me: 64%
*n*Bu: 59%
*t*Bu: 83%

(4.16)

As is implicit in the fact that the products of the (stoichiometric) 1,6-cuprate addition – the lithium allenyl enolate and the organocopper compound – are formed as independent species, it is also possible to conduct the reaction catalytically through in situ regeneration of the cuprate. The reaction can thus be run in a continuous mode, with only catalytic amounts of the preformed cuprate being necessary (with simultaneous addition of the substrate and the organolithium compound) enabling the desired allenes to be prepared even on larger scales (Eq. **4.17**) [30].

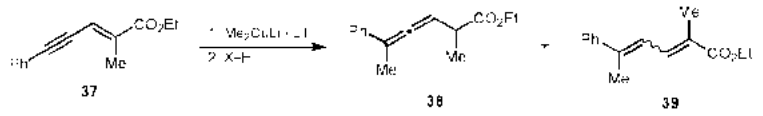


R = Me: 68%
*n*Bu: 83%
*t*Bu: 53%

(4.17)

As previously mentioned, allenes can only be obtained by 1,6-addition to acceptor-substituted enynes when the intermediate allenyl enolate reacts regioselectively with an electrophile at C-2 (or at the enolate oxygen atom to give an allenyl ketene acetal; see Scheme **4.2**). The regioselectivity of the simplest trapping reaction, the protonation, depends on the steric and electronic properties of the substrate, as well as the proton source. Whereas the allenyl enolates obtained from alkynyl enones **22** always provide conjugated dienones **23** by protonation at C-**4** (possibly

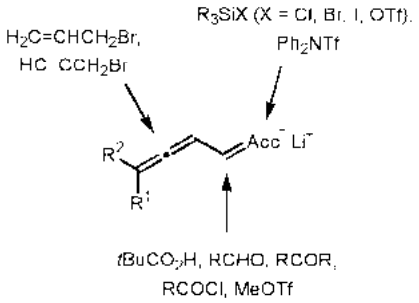
through allenyl enols; see Eq. **4.9**) [19, 20], the corresponding ester enolates are usually protonated at C-2 (Eq. **4.11**), especially if sterically demanding groups at C-5 block the attack of a proton at C-**4** (Eq. **4.13**) [3o, 22]. In the presence of a substituent at C-2 of the enolate, however, mixtures of both allenes and conjugated dienes are formed for steric reasons (Eq. **4.18**). Nevertheless, this problem can be solved by using weak organic acids as a proton source. In particular, pivalic acid (2,2-dimethylpropionic acid) at low temperatures gives rise to exclusive formation of allenes [22a].



(4.18)

X–H	38	39
2N H_2SO_4, 25°C	50	50
AcOH, 25°C	64	36
$tBuCO_2H$, 25°C	82	18
$tBuCO_2H$, -80°C	> 99	< 1

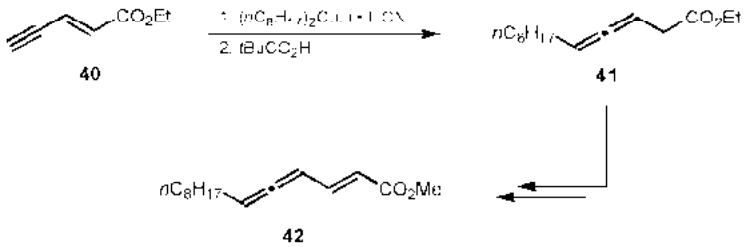
In contrast to the protonation, the regioselectivity of reactions between other electrophiles and allenyl enolates derived from 2-en-**4**-ynoates is independent of the steric and electronic properties of the reaction partners (Scheme **4.3**) [3o, 27]. As expected according to the HSAB principle, hard electrophiles such as silyl halides and triflates react at the enolate oxygen atom to form allenyl ketene acetals, while soft electrophiles such as carbonyl compounds attack at C-2. Only allylic and propargylic halides react regioselectively at C-**4** of the allenyl enolate to give substituted conjugated dienes. Again, cyclic allenyl enolates obtained through 1,6-cuprate addition to 3-alkynyl-2-cycloalkenones **22** show a deviant behavior; treatment with iodomethane gave product mixtures derived from attack of the electrophile at C-2 and C-**4**, while the reaction with aldehydes and silyl halides took place exclusively at C-**4** [19, 28].



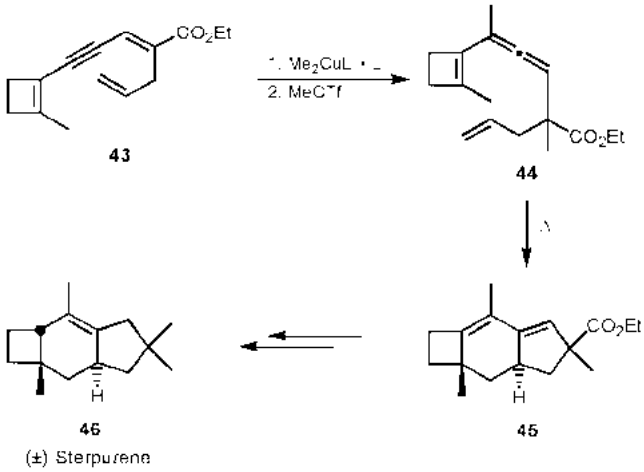
Scheme 4.3. Regioselectivity of trapping reactions of acyclic allenyl enolates with different electrophiles.

Several preparative applications of the 1,6-cuprate addition to acceptor-substituted enynes have been described in recent years. In addition to its use in the formation of

sterically encumbered allenes (Eq. 4.13) [22b] and simple terpenes such as pseudoionone [22a], this method is also the synthesis of valuable for access to allenic natural products (Eq. 4.19) [3o]. For example, 1,6-addition of lithium di-*n*-octylcuprate to enynoate **40**, followed by regioselective protonation with pivalic acid, yielded allene **41**, which was then readily convertible into the insect pheromone methyl 2,4,5-tetradecatrienoate (**42**). Further applications of 1,6-additions in natural product synthesis rely upon vinylallenes as diene components in the Diels–Alder reactions (Eq. 4.20). Hence, the synthesis of the fungal metabolite (±)-sterpurene (**46**) and some oxygenated metabolites started with the 1,6-addition of lithium dimethylcuprate to enynoate **43** and subsequent regioselective enolate trapping with methyl triflate [29]. The vinylallene **44** thus formed underwent an intramolecular [4+2] cycloaddition to give the tricyclic product **45**, which was finally converted into the target molecule **46**.



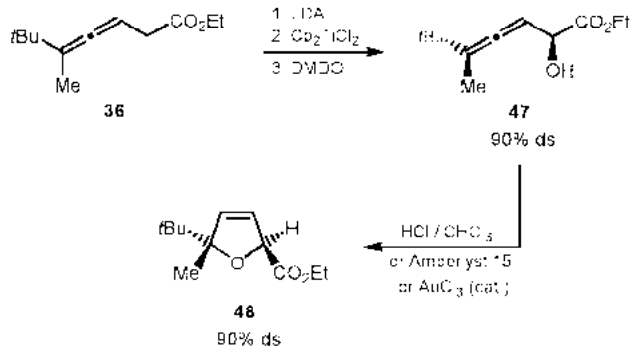
(4.19)



(4.20)

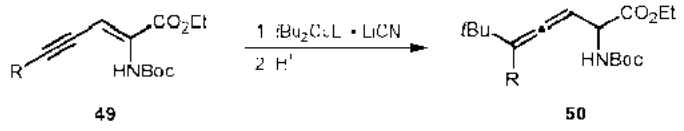
The Diels–Alder reaction outlined above is a typical example of the way in which axially chiral allenes, accessible through 1,6-addition, can be utilized to generate new stereogenic centers in a selective fashion. This transfer of chirality is also possible by means of intermolecular Diels–Alder reactions of vinylallenes [30], aldol reactions of allenyl enolates [31], and Ireland–Claisen rearrangements of silyl allenylketene acetals [32].

Recently, the oxidation of titanium allenyl enolates (formed by deprotonation of β-allenylcarboxylates of type **36** and transmetalation with titanocene dichloride) with dimethyl dioxirane (DMDO) was found to proceed regioselectively at C-2. In this way, depending on the steric demand of the substituents at the allenic moiety, the corresponding 2-hydroxy-3,4-dienoates were obtained diastereoselectively with up to 90% ds (Eq. **4.21**) [33]. α-Hydroxyallenes of this type are synthetically valuable precursors for 2,5-dihydrofurans, found not only in several natural products but also in biologically active compounds [34]. Thus, the cyclization of allene **47** to heterocycle **48** took place with complete axis-to-center chirality transfer, being easily achieved by treatment with HCl gas in chloroform, acidic ion exchange resins such as Amberlyst **15**, or, last but not least, with catalytic amounts of gold(III) chloride (this last method is particularly useful for α-hydroxyallenes containing acid-sensitive groups [33b]).



(4.21)

Allenic amino acid derivatives **50**, which are of special interest as selective vitamin B_6 decarboxylase inhibitors [35], are accessible through 1,6-cuprate addition to 2-amino-substituted enynes **49** (Eq. **4.22**) [36]. Because of the low reactivity of these Michael acceptors, however, the reaction succeeds only with the most reactive cuprate: the *t*-butyl cyano-Gilman reagent $tBu_2CuLi{\cdot}LiCN$. Nevertheless, the addition products are obtained with good chemical yields, and selective deprotection of either the ester or the amino functionality under acidic conditions provides the desired target molecules.

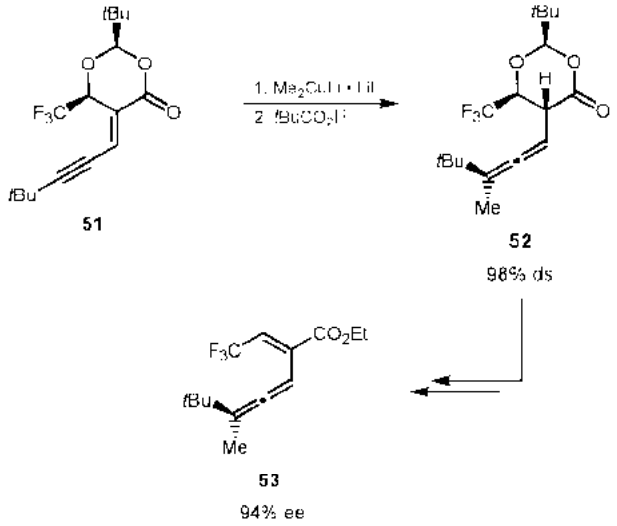


(4.22)

R = *t*Bu, Ph, Me_3Si, 1-cyclohexenyl

By starting with enantiomerically enriched or pure β-allenylcarboxylates, it is possible to carry out several of the transformations mentioned above stereoselectively. With regard to the required substrates, chiral 5-alkynylidene-1,3-dioxan-4-ones of

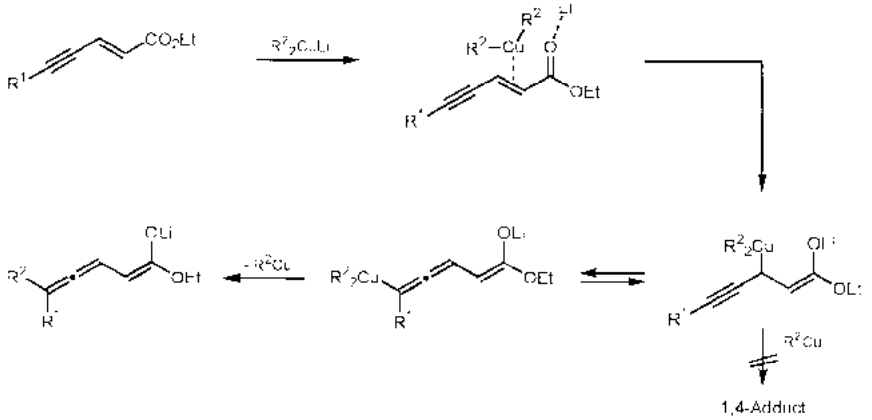
type **51** have proven to be valuable synthetic precursors, since these Michael acceptors adopt a very rigid conformation. Because of the equatorial position of the *t*-butyl group, the trifluoromethyl residue shields the top face of the enyne moiety, exposing the underside of the molecule to preferential attack by the nucleophile (Eq. **4.23**) [30, 37]. Treatment with lithium dimethylcuprate and pivalic acid therefore gave the allene **52** with a diastereoselectivity of 98% ds, and the stereochemical information generated in this step remained intact during the conversion into the chiral vinylallene **53**.



(4.23)

In contrast to nucleophilic addition reactions to activated dienes (Sect. **4.2.1**), the mechanism of **1,6**-cuprate additions to acceptor-substituted enynes is quite well understood, largely thanks to kinetic and NMR spectroscopic investigations [30]. ^{13}C NMR spectroscopic studies have revealed that these transformations proceed through π-complexes, with an interaction between the π-system of the C=C double bond and the nucleophilic copper atom (a soft-soft interaction in terms of the HSAB principle), together with a second interaction between the hard lithium ion of the cuprate and the hard carbonyl oxygen atom (Scheme **4.4**) [38]. In particular, the use of ^{13}C-labeled substrates has shed light on the structure of the metal-containing part of these π-complexes, indicating, for example, that the cuprate does not interact with the triple bond [38b, c]. Recently determined ^{13}C kinetic isotope effects prove that bond formation between C-5 of the acceptor-substituted enyne and the cuprate occurs in the rate-determining step [39]. Moreover, with the aid of kinetic measurements with a variety of different substrates, even activation parameters for these transformations have been determined experimentally [40]. A mechanistic model in accordance with all these experimental data (Scheme **4.4**) involves the formation of σ-copper(III) species, which might be in equilibrium with an allenic copper(III) intermediate. Both intermediates can undergo reductive elimination to produce the **1,4**- and **1,6**-adduct, respectively. The experimentally observed exclu-

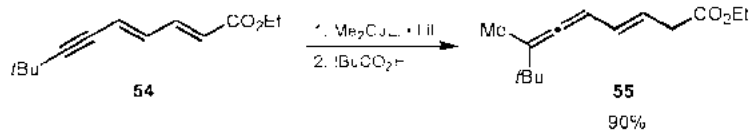
sive formation of the 1,6-addition product, however, may indicate that the latter reductive elimination occurs much more rapidly than that from the first intermediate.



Scheme 4.4. Proposed mechanism for the 1,6-addition of organocuprates to acceptor-substituted enynes.

4.2.3
Acceptor-substituted Polyenynes

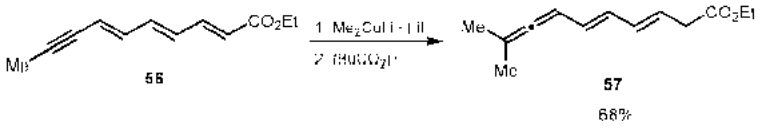
In view of the high regioselectivity observed in the addition of organocuprates to acceptor-substituted enynes, it seems interesting to determine whether the preference of these reagents for triple bonds persists even when the distance between the acceptor group and the triple bond is increased by the introduction of further C=C double bonds. Of course, the number of possible regioisomeric products rises with increasing length of the Michael acceptor. The 2,4-dien-6-ynoate **54**, for example, can be attacked by an organocopper reagent at C-3, C-5, or C-7, the latter possibility producing a vinylogous allenyl enolate possessing four reactive positions (enolate oxygen, C-2, C-4, C-6). The high regioselectivity of the reaction between **54** and lithium dimethylcuprate was therefore striking; the cuprate attacked the triple bond exclusively and protonation with pivalic acid occurred at C-2 of the enolate, giving the 1,8-addition product **55** as the only isolable regioisomer in 90% yield (Eq. 4.24) [30].



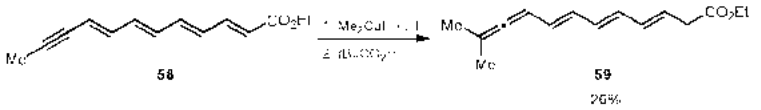
(4.24)

In an analogous manner, the trienynoate **56** reacted in a 1,10-fashion to give the 3,5,7,8-tetraenoate **57** (Eq. 4.25), and it was even possible to obtain the 1,12-

adduct **59** from the Michael acceptor **58**, containing four double bonds between the triple bond and the acceptor substituent (Eq. **4.26**). In the latter case, however, the yield was only 26%; this is probably due to the reduced thermal stabilities of the starting material and the addition product (the 1,12-adduct was the only isolable reaction product apart from polymeric compounds) [30, 30].



55 **57** 68% (4.25)



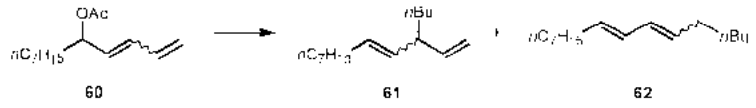
58 **59** 26% (4.26)

These transformations and those summarized in the previous chapter indicate that Michael acceptors containing any combination of double and triple bonds undergo highly regioselective copper-mediated addition reactions. The following rule holds: *Michael acceptors with any given arrangement of conjugated double and triple bonds react regioselectively with organocuprates at the triple bond closest to the acceptor substituent.* Like the 1,6-cuprate addition to acceptor-substituted enynes (Scheme **4.4**), these reactions start with the formation of a cuprate π-complex at the double bond adjacent to the acceptor group [38]. Subsequently, an equilibrating mixture of σ-copper(III) intermediates is probably formed, and the regioselectivity of the reaction may then be governed by the different relative rates of the reductive elimination of these intermediates.

4.3
Copper-mediated Substitution Reactions of Extended Substrates

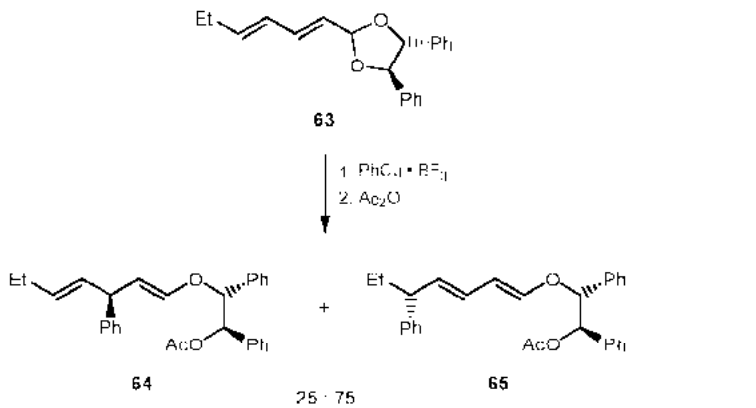
In contrast to the addition reactions discussed so far, only a few examples of copper-mediated substitutions of extended electrophiles have been reported to date. Investigations into substitution reactions of various dienylic carboxylates with organocuprates (and Grignard reagents in the presence of catalytic amounts of copper salts) indicated that the ratio of the three possible regioisomers (that is, α-, γ-, and ε-alkylated products) depends strongly on the substrate and reaction conditions [41]. For example, treatment of dienyl acetate **60** with *n*BuMgBr and stoichiometric quantities of CuI mainly furnished the S_N2' (1,3) substitution product **61** (Eq. **4.27**), whereas with catalytic quantities of CuI and THF as solvent the conjugated diene **62** was formed exclusively (or in other words, S_N2'' (1,5) substitution takes place under these conditions) [42]. The dependence of the reaction course on the *n*BuMgBr:CuI ratio gives again credence to the postulate that different organocopper species are responsible for the formation of the regioisomeric products. With equimolar amounts of Grignard reagent and copper salt, the active species is

probably the monoalkylcopper compound *n*BuCu·MgBrI, which produces **61**. Contrarily, an excess of the Grignard reagent should produce the magnesium cuprate $n\mathrm{Bu}_2\mathrm{CuMgBr}$ as the reactive nucleophile, providing the 1,5-substitution product **62**.



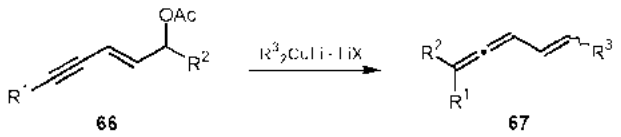
(4.27)

Stereoselective substitution reactions of chiral dienyl electrophiles have also been carried out. In analogy to the copper-promoted S_N2' reactions of simple allylic electrophiles [3], the corresponding S_N2' (1,3) substitutions of dienyl carbonates [**43**] have been reported to proceed with high *anti* selectivity. Interestingly, treatment of chiral dienyl acetal **63** with the Yamamoto reagent $PhCu{\cdot}BF_3$ gave rise to the formation of a 1:3 mixture of the *anti*-S_N2' substitution product **64** and the *syn*-S_N2'' (1,5) substitution product **65** (Eq. **4.28**) [**44**]. A mechanistic explanation of this puzzling result has yet to be put forward, however.



(4.28)

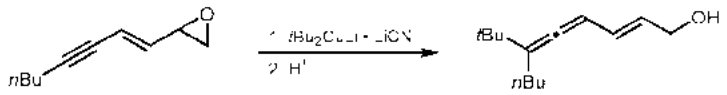
The corresponding copper-mediated S_N2'' (1,5) substitution reactions of conjugated enyne acetates **66** also take place with high regioselectivities, furnishing vinylallenes **67** with variable substitution patterns (Eq. **4.29**) [**45**]. Although the substitution products are usually obtained as mixtures of the *E* and *Z* isomers, complete stereoselection with regard to the olefinic double bond of the vinylallene has been achieved in some cases. Analogous 1,5-substitutions can also be carried out with enyne oxiranes, which are transformed into synthetically useful hydroxy-substituted vinylallenes (Eq. **4.30**; Sect. **4.2.2**) [**45**]. Moreover, these transformations can be performed under copper catalysis conditions, by simultaneous addition of the organolithium compound and the substrate to catalytic amounts of the cuprate.



66 67

(4.29)

$R^1 = R^2 = Me$, $R^3 = n$Bu: 90% ($E : Z = 67 : 33$)
$R^1 = R^2 = Me$, $R^3 = t$Bu: 93% ($E : Z = 25 : 75$)
$R^1 = Me_3Si$, $R^2 = Me$, $R^3 = t$Bu: 96% ($E : Z = 40 : 60$)
$R^1 = n$Bu, $R^2 = t$Bu, $R^3 = Me$: 92% ($E : Z = > 99 : < 1$)

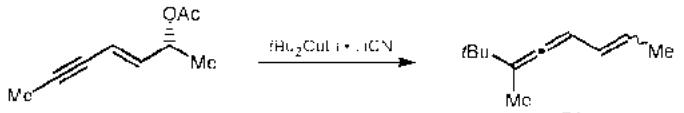


68 69

72%

(4.30)

Highly enantioselective 1,5-substitution reactions of enyne acetates are also possible under carefully controlled conditions (Eq. 4.31) [46]. For example, treatment of enantiomerically pure substrate **70** with the cyano-Gilman reagent tBu$_2$CuLi·LiCN at −90 °C provided vinylallene **71** as a 1:3 mixture of *E* and *Z* isomers with 20% and 74% *ee*, respectively. This mediocre selectivity might be attributable to racemization of the allene by the cuprate or other reactive copper species formed in the reaction mixture. The use of phosphines as additives, however, can effectively prevent such racemizations (which probably occur by one-electron transfer steps) [47]. Indeed, vinylallene **71** was obtained with an *ee* of 92% for the *E* isomer and of 93% for the *Z* isomer if the substitution was performed at −80 °C in the presence of 4 eq. of nBu$_3$P. Use of this method enabled various substituted vinylallenes (which are interesting substrates for subsequent Diels–Alder reactions; Sect. 4.2.2) to be prepared with >90% *ee*.



70 71

(4.31)

$E : Z = 25 : 75$
Without Additive: 20% ee (*E*) / 74% ee (*Z*)
With 4 eq. nBu$_3$P: 92% ee (*E*) / 93% ee (*Z*)

4.4 Conclusion

Over the last 30 years, organocopper reagents have been utilized with great success in organic synthesis. The results presented in this chapter highlight the excellent

performance of these organometallic compounds in regioselective and stereoselective transformations of compounds with extended π-systems, in particular in 1,6-, 1,8-, 1,10-, and 1,12-additions and in 1,5-substitution reactions of acetylenic substrates derivatives. These transformations not only provide new information regarding the mechanisms of copper-mediated carbon-carbon bond formation, but they also open up new opportunities in target-oriented synthesis.

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5
Copper(I)-mediated 1,2- and 1,4-Reductions

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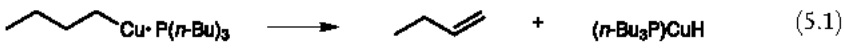
5.1
Introduction and Background

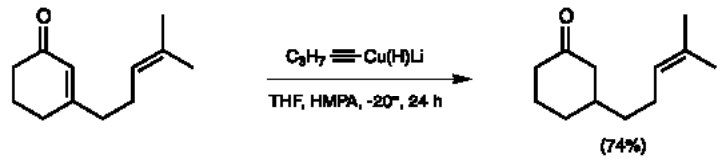
Long before Kharasch's seminal paper on copper-catalyzed additions of Grignard reagents to conjugated enones (1941) [1] and Gilman's first report on formation of a lithiocuprate (Me_2CuLi; 1952) [2] appeared, Cu(I) hydride had been characterized by Wurtz as a red-brown solid [3]. Thus, "CuH" is among the oldest metal hydrides to have been properly documented, dating back to 1844. Although studied sporadically for many decades since, including an early X-ray determination [4], most of the initial 'press' on copper hydride was not suggestive of it having potential as a reagent in organic synthesis. In fact, it was Whitesides who demonstrated that this unstable material is often an unfortunate result of a β-elimination, which occurs to varying degrees as a thermal decomposition pathway of alkylcopper species bearing an available β-hydrogen (such as *n*-BuCu; Eq. 5.1) [5]. Stabilized forms of CuH, most notably Osborn's hexameric $[(Ph_3P)CuH]_6$ [6], for which an X-ray structure appeared in 1972, for years saw virtually no usage in organic synthesis even in a stoichiometric sense, let alone a catalytic one. Several groups in the 1970s and early 80s, however, recognized the value of hydride delivery to α,β-unsaturated frameworks with the aid of copper complexes. This interest resulted in several hydrido cuprates of widely varying constitution, each intended for use as a stoichiometric 1,4-reductant.



(5.1)

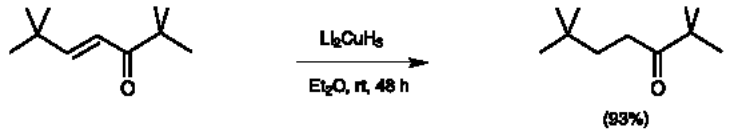
The mixed hydrido cuprate "$R_rCu(H)Li$", designed to contain a nontransferable or 'dummy' group R_r (such as 1-pentynyl, *t*-butoxide, or thiophenoxide) [7], was found by Boeckman et al. to effect conjugate reductions of enones in good yields [8]. The preferred ligand R_r is the 1-pentynyl group, which is likely to impart a reactivity greater than that of the corresponding heteroatom-based mixed hydrido complex (Eq. 5.2). The reagents are made by initial treatment of CuI with DIBAL in toluene at −50 °C, to which the lithium salt of the dummy ligand is then added. Similar treatment of CuI with potassium tri-*sec*-butylborohydride has been suggested by

Negishi to give rise to "$KCuH_2$", which reduces ketones and other functional groups [9].



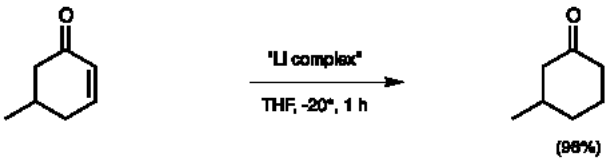
(5.2)

Reduction of "Me_3CuLi_2" with LAH was described by Ashby and co-workers as a means to produce the powerful reducing reagent "Li_2CuH_3" [10], which can be used in either THF or Et_2O at room temperature for conjugate reductions (Eq. 5.3). Strangely, the species analogous to Gilman's reagent, "$LiCuH_2$", delivers hydride to an enone in THF in a predominantly 1,2-sense.



(5.3)

Semmelhack et al. chose CuBr, together with either Red-Al or $LiAl(OMe)_3H$ in a 1:2 ratio, to afford presumed hydrido cuprates, albeit of unknown composition [11]. In THF, both the former "Na complex" and the latter "Li complex" are heterogeneous (and of differing reactivities), yet each is capable of 1,4-reductions of unsaturated ketones and methyl esters (Eq. 5.4). Commins has used a modified version, prepared from lithium tri-*t*-butoxy-aluminium hydride and CuBr (in a 3:4.4 ratio), to reduce a 3-substituted-*N*-acylated pyridine regioselectively at the α-site [12].



(5.4)

5.2
More Recent Developments: Stoichiometric Copper Hydride Reagents

While these and related reagents have seen occasional use, none has been the overwhelming choice over another, perhaps due to questions of functional group tolerance and/or a general lack of structural information. In 1988, however, Stryker et al. described (in communication form) results from a study on the remarkable tendency of the Osborn complex $[(Ph_3P)CuH]_6$ [6a, b] to effect highly regioselective conjugate reductions of various carbonyl derivatives, including unsaturated ketones, esters, and aldehydes [13]. The properties of this phosphine-stabilized reagent

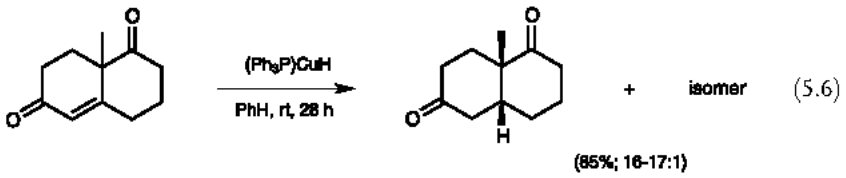
(mildness of reaction conditions, functional group compatibility, excellent overall efficiencies, etc.) were deemed so impressive that this beautifully crystalline red solid was quickly propelled to the status of "Reagent of the Year" in 1991. It is now commonly referred to, and sold commercially, as "Stryker's Reagent" [14].

Among its salient features, this copper hydride (written for simplicity from now on as the monomer $(Ph_3P)CuH$) can be prepared in multi-gram quantities from four precursor compounds (CuCl, NaO-*t*-Bu, PPh_3, and H_2) that are not only readily available but also very inexpensive (Eq. 5.5) [15]. It is also noteworthy that the by-products of formation (NaCl and *t*-BuOH) are especially "environmentally friendly".

$$\mathrm{CuCl} + \mathrm{NaO\text{-}t\text{-}Bu} + \mathrm{PPh_3} \xrightarrow[15\text{-}24\ \mathrm{h}]{\mathrm{H_2,\ PhH,\ rt}} [(\mathrm{Ph_3P})\mathrm{CuH}]_6 + \mathrm{NaCl} + \mathrm{t\text{-}BuOH} \quad (5.5)$$

The quality of $(Ph_3P)CuH$ can vary, depending upon the care taken in the crystallization step. An unknown impurity – that shows broad signals at δ 7.78, 7.40, and 7.04 in the ^1H NMR spectrum in dry, degassed, benzene-d_6 – is usually present in all batches of the reagent, although small amounts are not deleterious to its reduction chemistry. The hydride signal, a broad multiplet, occurs at 3.52 ppm (Fig. 5.1). Proton NMR data reported by Caulton on the related $[(tol)_3P]CuH$ include a "broad but structured multiplet centered on δ +3.50 in C_6D_6" [16].

Either hexane or pentane can replace acetonitrile to induce crystallization without impact on yield or purity. The hexamer can be weighed in air for very short periods of time, but must be stored protected under an inert atmosphere. Curiously, $(Ph_3P)CuH$ as originally studied may occasionally be most effective when used in the presence of moist organic solvent(s), the water providing an abundant source of protons, some of which ultimately find their way into the neutral carbonyl adduct (Eq. 5.6). When TMSCl (= 3 equiv.) is present in place of water, in situ trapping of the presumed copper enolates results; on workup these afford carbonyl products directly [13, 16]. More hindered silyl chlorides (such as *t*-$BuMe_2SiCl$) produce isolable silyl enol ethers, as is to be expected [13b]. Unlike cuprates, the reagent is of low basicity. Reactions are highly chemoselective, with 1,4-reductions of enones proceeding in the presence of halides and sulfonates, as well as sulfide residues in the γ-position [17].



(5.6)

Preparation of $[(Ph_3P)CuH]_6$ [15]

Triphenylphosphine (100.3 g, 0.3825 mol) and copper(I) chloride (15.14 g, 0.1529 mol) were added to a dry, septum-capped 2 L Schlenk flask and placed under nitrogen. Benzene (distilled and deoxygenated, approximately

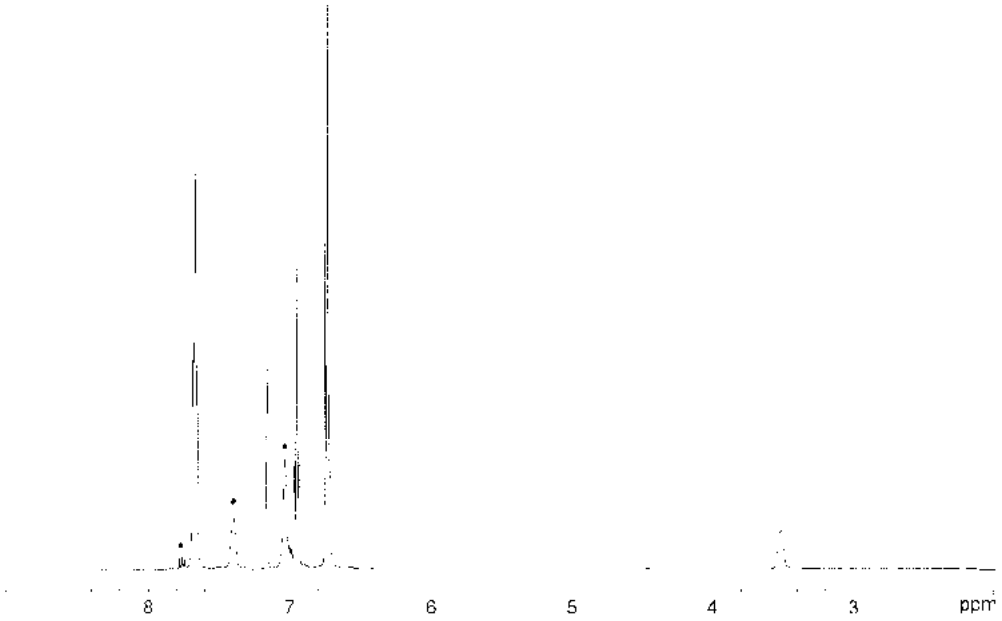


Fig. 5.1. ^{1}H NMR spectrum of $[(Ph_3P)CuH]_6$ in C_6D_6. Chemical shifts: δ 7.67, 6.95, 6.74, and 3.52. Signals marked by · indicate impurities.

800 mL) was added by cannula, and the resultant suspension was stirred. The NaO-*t*-Bu/toluene suspension was transferred by wide-bore cannula to the reaction flask, washing if necessary with additional toluene or benzene, and the yellow, nearly homogeneous mixture was placed under positive hydrogen pressure (1 atm) and stirred vigorously for 15 24 h. During this period the residual solids dissolved, the solution turned red, typically within one hour, then dark red, and some gray or brown material precipitated. The reaction mixture was transferred under nitrogen pressure through a wide-bore Teflon cannula to a large Schleulk filter containing several layers of sand and Celite. The reaction flask was rinsed with several portions of benzene, which were then passed through the filter. The very dark red filtrate was concentrated under vacuum to approximately one-third of its original volume, and acetonitrile (dry and deoxygenated, 300 mL) was layered onto the benzene, promoting crystallization of the product. The yellow-brown supernatant was removed by cannula, and the product was washed several times with acetonitrile and dried under high vacuum to give 25.0 32.5 g (50 65%) of bright red to dark-red crystals.

The yields obtained by this procedure are roughly comparable to those obtained starting directly with purified $(CuO\text{-}t\text{-}Bu)_4$ and one atmosphere of hydrogen, although higher yields (ca. 80%) have been reported under 1500 psi of hydrogen pressure [16].

Representative procedure for conjugate reduction of an enone [13]

$[(Ph_3P)CuH]_6$ (1.16 g, 0.82 mmol), weighed under inert atmosphere, and Wieland Miescher ketone (0.400 g, 2.24 mmol) were added to a 100 mL, two-necked flask under positive nitrogen pressure. Deoxygenated benzene (60 mL) containing 100 μL of H_2O (deoxygenated by nitrogen purge for 10 min) was added by cannula, and the resulting red solution was allowed to stir at room temperature until starting material had been consumed (TLC monitoring; 8 h). The cloudy red-brown reaction mixture was opened to air, and stirring was continued for 1 h, during which time copper-containing decomposition products precipitated. Filtration through Celite and removal of the solvent in vacuo gave crude material which was purified by flash chromatography to afford the product in 85% yield.

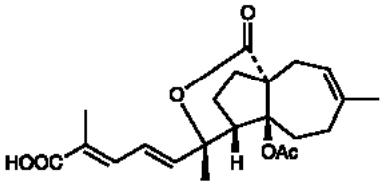
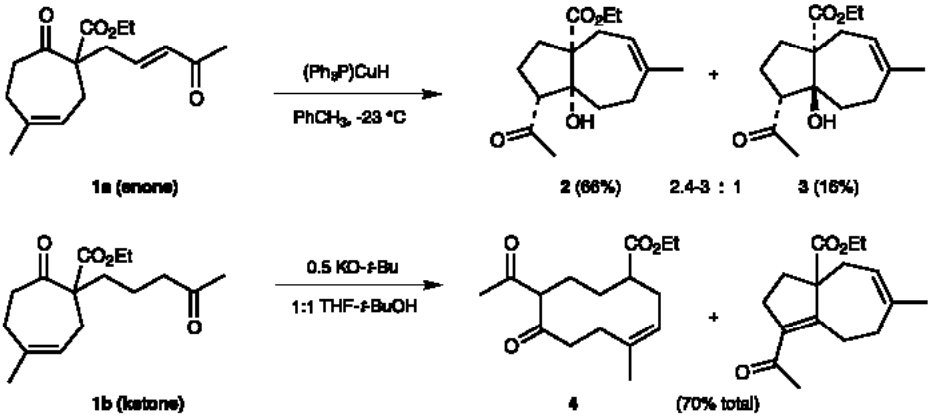


Fig. 5.2. Pseudolaric acid A.

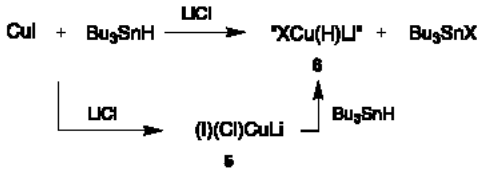
An insightful application of Stryker's reagent can be found in efforts by Chiu aimed at the total synthesis of pseudolaric acid A (Fig. 5.2), where a conjugate reduction-intramolecular aldol strategy was invoked [18]. Treatment of precursor enone **1a** with $(Ph_3P)CuH$ (two equivalents) in toluene at sub-ambient temperatures quickly afforded the annulated aldol products **2** and **3** in a 2.4–3:1 ratio (Scheme 5.1). The same treatment in THF produced a higher percentage (6:1) of the undesired *cis*-fused isomer **2**. Earlier attempts under basic conditions to form the required *trans*-fused aldol based on the saturated analog of **1b** met with failure, the 10-membered skeleton **4** forming from second-stage decomposition of the initially derived mix of **2** and **3**. The switch to copper hydride, used at uncharacter-



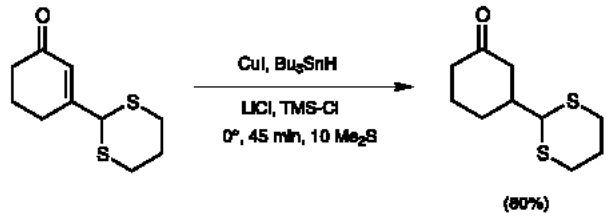
Scheme 5.1. Intramolecular 1,4-addition-aldol reactions.

istically low temperatures (−23°), ultimately provided entry to the bicyclic array by virtue both of the directed 1,4-hydride delivery to enone **1a**, and also of the relatively non-basic nature of the intermediate copper alkoxide.

Soon after the appearance of the series of papers from the Stryker labs [13, 15, 17, 19a], an alternative method for the presumed generation of stoichiometric halohydrido cuprate "XCu(H)Li" (X = Cl or I) was reported (Scheme 5.2) [20]. It relies on a transmetalation between Bu_3SnH and CuI/LiCl, the inorganic salts combining to form a mixed dihalocuprate (**5**) [21], which may then undergo a ligand exchange with the tin hydride to afford halohydrido species **6**.

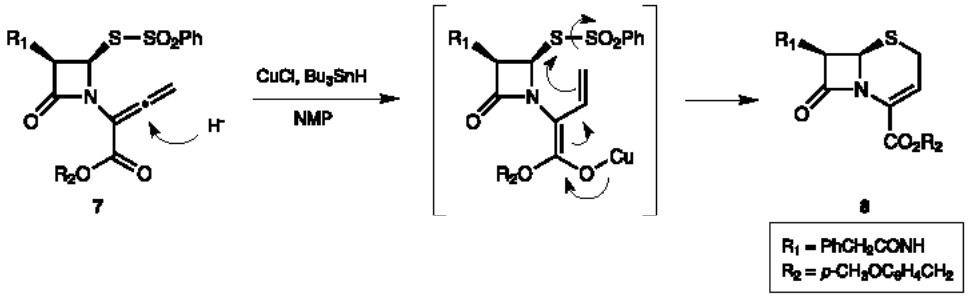


Scheme 5.2. In situ generation of hydrido cuprates.



(5.7)

Selective 1,4-reduction of unsaturated aldehydes and ketones by **6** occurs smoothly in THF between −25 °C and room temperature within a few hours (Eq. 5.7). Particularly noteworthy is the realization that phosphines are noticeably absent from the reaction medium. The analogous combination of $CuCl/Bu_3SnH$ in *N*-methyl-2-pyrrolidinone (NMP) or DMF does not behave identically [22], failing to react with the hindered substrate isophorone, whereas a 72% yield of the corresponding reduced ketone is formed with reagents $XCu(H)Li/Bu_3SnH$. Nonetheless, a form of "CuH" is being generated in this more polar medium, effectively utilized by Tanaka to arrive at 3-norcephalosporin **8** upon reaction with allenic ester **7** (Scheme 5.3).



Scheme 5.3. Conversion of allenyl ester **7** to 3-norcephalosporin **8**.

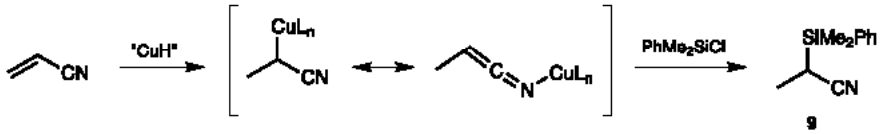
Representative procedure for Bu_3SnH/CuI/LiCl conjugate reduction [20]

(*E*,*E*)-8-Acetoxy-2,6-dimethyl-2,6-octadienal (80 mg, 0.391 mmol) was added at −60 °C to a solution of CuI (190.4 mg, 1.00 mmol) and LiCl (100.8 mg, 2.38 mmol) in THF (4.5 mL), followed by Me_3SiCl (0.27 mL, 2.09 mmol). After 10 min, Bu_3SnH (0.30 mL, 1.10 mmol) was added dropwise, producing a cloudy yellow slurry. The reaction mixture was then allowed to warm gradually to 0 °C over 2 h. A concurrent darkening to a reddish-brown color was observed. Quenching was carried out with 10% aq. KF solution (3 mL), resulting in an orange precipitate. The organic layer was filtered through Celite and evaporated, and the residue was rapidly stirred with additional quantities of 10% KF for ca. 30 min before diluting with ether. The organic layer was then washed with saturated aq. NaCl solution and dried over anhydrous Na_2SO_4. The solvent was then removed in vacuo and the material was chromatographed on silica gel. Elution with EtOAc/hexanes (10:90) gave 82 mg (100%) of (*E*)-8-acetoxy-2,6-dimethyl-6-octenal as a colorless oil; TLC (15% EtOAc/hexanes) R_f 0.22.

Interestingly, the CuCl/$PhMe_2SiH$ reagent pair was reported by Hosomi and coworkers to generate what was presumed to be CuH, also uncomplexed by phosphine [23]. The choice of solvent is critical, with ligand exchange occurring at room temperature in DMF or DMI (1,3-dimethylimidazolidinone), but not in THF, CH_3CN, or CH_2Cl_2, suggesting a stabilizing, Lewis basic role for the solvent in place of phosphine. Neither CuCN nor CuI are acceptable replacements for CuCl. When ratios of 4:2 silane:CuCl are used, along with one equivalent of substrate, excellent yields of 1,4-adducts may be anticipated (Eq. 5.8).

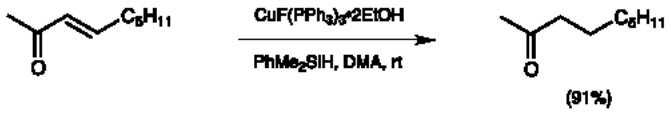
(5.8)

Although unhindered enones and enoates work well, attempted 1,4-reduction of acrylonitrile afforded α-silylated product **9** (Scheme 5.4). Presumably this unexpected product results from a 1,4-reduction/α-anion trapping by the $PhMe_2SiCl$ present in solution. Curiously, there was no mention of any similar quenching of intermediate enolates on either carbon or oxygen when unsaturated ketones or esters were involved.



Scheme 5.4. 1,4-Reduction/α-silylation of acrylonitrile.

On the basis of the identical O Cu to O Si transmetalation, Mori and Hiyama examined alternative Cu(I) salts in the presence of Michael acceptors [24, 25]. This study produced the finding that $PhMe_2SiH/CuF(PPh_3)_3 \cdot 2EtOH$ (1.5 equivalents) in DMA (*N,N*-dimethylacetamide) is effective for conjugate reductions (Eq. 5.9). Triethylsilane could also be employed in place of $PhMe_2SiH$, but other silyl hydrides gave either undesired mixtures of 1,4- and 1,2-products (with Ph_2SiH_2 and $(EtO)_3SiH$, for example) or no reaction (with $PhCl_2SiH$, for example). Hindered enones, such as isophorone and pulegone, were not reduced under these conditions. Most efforts at trapping intermediate enolates were essentially unproductive, aside from modest outcomes when D_2O and allyl bromide were used [25].

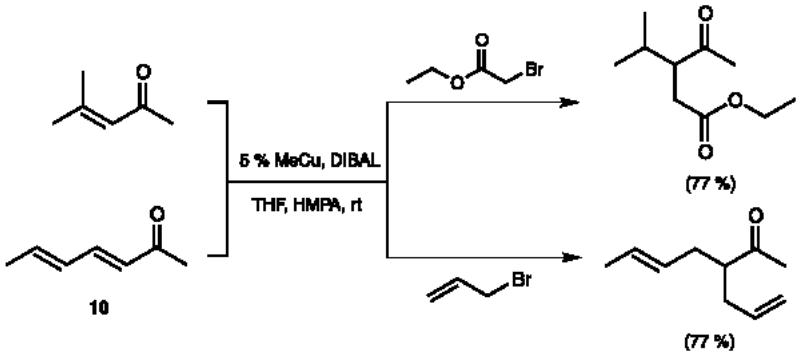


(5.9)

The successes described above notwithstanding, synthetic chemistry in the 1990s was in large measure characterized by 'catalysis', which encouraged development of organocopper processes that were in line with the times. The cost associated with the metal was far from the driving force; that was more (and continues to be) a question of transition metal waste. In other words, proper disposal of copper salt by-products is costly, and so precludes industrial applications based on stoichiometric copper hydrides.

5.3
1,4-Reductions Catalytic in Cu(I)

Prior to the advent of triphenylphosphine-stabilized CuH [6a, b, 13], Tsuda and Saegusa described use of five mole percent MeCu/DIBAL in THF/HMPA to effect hydroalumination of conjugated ketones and esters [26]. The likely aluminium enolate intermediate could be quenched with water or TMSCl, or alkylated/acylated with various electrophiles (such as MeI, allyl bromide, etc.; Scheme 5.5). More

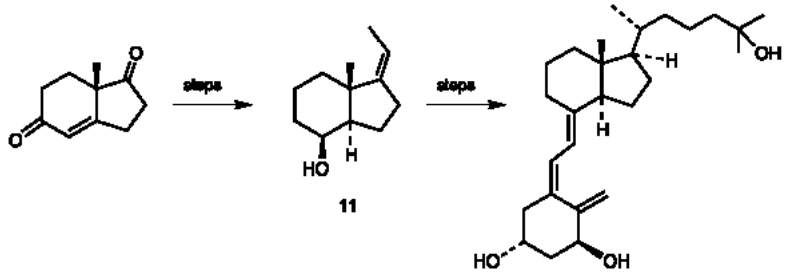


Scheme 5.5. Reductive alkylations of enones using catalytic MeCu.

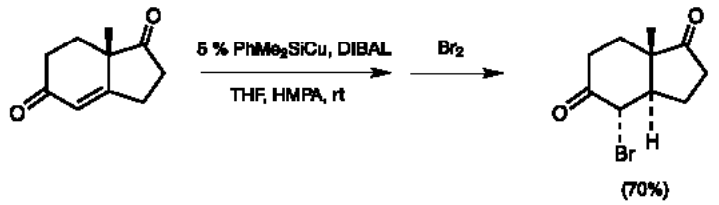
highly conjugated networks, such as in **10**, were reduced in a 1,6 fashion, with the enolate being alkylated at the expected α-site.

t-BuCu has been used extensively in place of MeCu en route to synthons (such as **11**) of value in the construction of the D vitamins (Eq. 5.10) [27]. Very recently, replacement of *t*-BuCu by a more stable silyl analogue, $PhMe_2SiCu$, has been reported:

(1) to minimize the amount of copper required for this reductive bromination (6.5 versus 20 mol%; Eq. 5.11),
(2) to afford enhanced regioselectivity (> 19:1 ratio for 1,4-reduction versus 1,2-addition to the isolated keto group),
(3) to produce higher overall yields (70 versus 57%), and
(4) to be readily usable in large scale reactions [28].



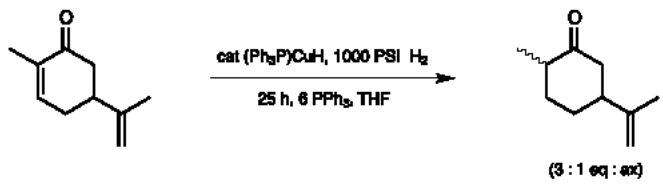
(5.10)



(70%)

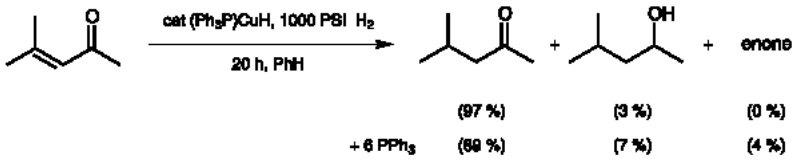
(5.11)

Not long after Stryker's initial report on $(Ph_3P)CuH$ [13], that group discovered that it was possible to establish a catalytic cycle in which molecular hydrogen serves as the hydride source [19]. Although yields are very good, very high pressures (ca. 500–1000 psi) are unfortunately needed, at which products of overreduction are occasionally noted in varying amounts (Eqs. 5.12, 5.13). Addition of PPh_3 stabilizes the catalyst, although turnover appears to be slowed. The inconveniently high pressures can be avoided by the introduction of *t*-BuOH (10–20 equiv./copper), which promotes clean hydrogenation at one atmosphere of hydrogen, presumably by protonolysis of the unstable copper(I) enolate intermediate to give the more stable copper *t*-butoxide complex (vide infra).



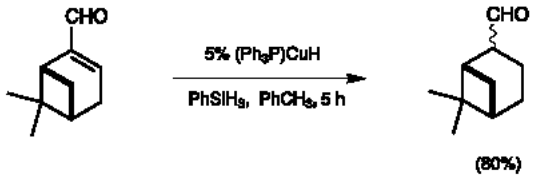
(3 : 1 eq : ax)

(5.12)



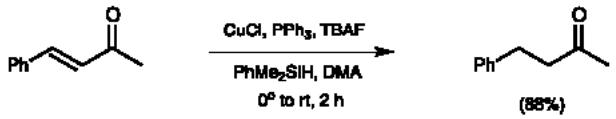
(5.13)

The continued search for methods to effect 1,4-reductions using catalytic quantities of CuH produced several reports late in the last decade. The basis for these new developments lies in an appreciation for the facility with which various silyl hydrides undergo transmetalation with copper enolates. Thus, a limited amount of $(Ph_3P)CuH$ (0.5–5 mol%) in the presence of $PhSiH_3$ (1.5 equivalents relative to substrate) reduces a variety of unsaturated aldehydes and ketones in high yields (Eq. 5.14) [29]. Limitations exist with respect to the extent of steric hindrance in the educt. Similar results can be achieved using Bu_3SnH in place of $PhSiH_3$, although the latter hydride source is the appropriate (albeit expensive) choice from the environmental perspective.



(5.14)

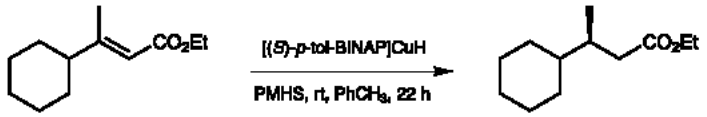
An alternative, in situ source of $(Ph_3P)CuH$ can be fashioned from $CuCl/PPh_3$/TBAF and $PhMe_2SiH$ (1.2 equivalents) in DMA, initially made at 0° with the reaction then being run at room temperature [25]. Unhindered acyclic enones require 20 mol% of CuCl, PPh_3, and TBAF for best results (Eq. 5.15). Cyclic examples are more demanding, with substituted cyclohexenones such as carvone undergoing reduction when excess reagents are present (1.6 equivalents). Acetylcyclohexene was unreactive to the catalytic conditions above.



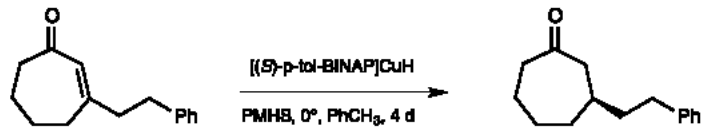
(5.15)

Use of the Stryker protocol (CuCl + NaO-*t*-Bu under H_2) for generating a copper hydride, but replacing PPh_3 with *p*-tol-BINAP and H_2 with four equivalents of polymethylhydrosiloxane (PMHS) [30], is presumed to produce the corresponding reagent bearing a nonracemic bidentate phosphine ligand, (*p*-tol-BINAP)CuH. This species, derived in situ and first described by Buchwald, is capable of delivering hydride to β,β-disubstituted-α,β-unsaturated esters, with control over the absolute stereochemistry at the resulting β-site (Eq. 5.16) [31]. Likewise, conjugated cyclic enones can be reduced with asymmetric induction by the same technique [32], although either (*S*)-(BINAP)CuH or Roche's [(*S*)-BIPHEMP]CuH can be em-

ployed here as well as (*p*-tol-BINAP)CuH (Eq. 5.17) [33]. In both methods, PMHS functions as the stoichiometric source of hydride, which participates in a transmetalation step involving the likely copper enolate to regenerate the copper hydride catalyst [34]. Enoates require ambient temperatures, excess PMHS (4 equivalents), and reaction times of the order of a day, while enones react at 0 °C and require only 1.05 equivalents of silyl hydride, to prevent overreduction. The *ee* values obtained range from 80–92% for the newly formed esters, while those for ketones are generally higher (92–98%).



(5.16)



(5.17)

General procedure for asymmetric conjugate reduction of α,β-unsaturated esters [31]

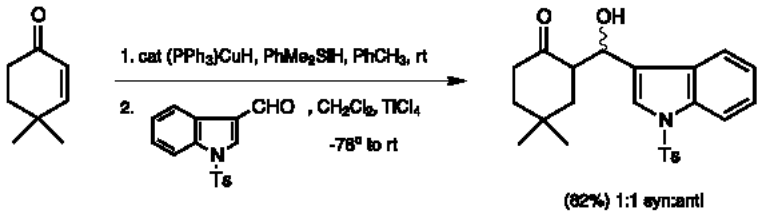
(*S*)-*p*-tol-BINAP (10 mg, 0.162 mmol) was placed in a flame-dried Schlenk flask, and dissolved in toluene (6 mL). The solution was degassed by briefly opening the flask to vacuum, then backfilling with argon (this degassing procedure was repeated 3 more times). The Schlenk flask was transferred into an argon-filled glovebox. NaO-*t*-Bu (8 mg, 0.083 mmol) and CuCl (8 mg, 0.081 mmol) were placed in a vial, and dissolved in the reaction solution. The resulting mixture was stirred for 10 20 min. The Schlenk flask was removed from the glovebox, and PMHS (0.36 mL, 6 mmol) was added to the reaction solution under an argon purge. The resulting solution turned a reddish-orange color. The α,β-unsaturated ester (1.5 mmol) was added to the reaction solution under argon purging and the resulting solution was stirred until reaction was complete, as monitored by GC. The Schlenk flask was then opened and ethanol (0.3 mL) was added dropwise to the reaction (CAUTION! Rapid addition of ethanol caused extensive bubbling and foaming of the solution). The resulting solution was diluted with ethyl ether, washed once with water and once with brine, and back-extracted with ethyl ether. The organic layer was then dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. The product was then purified by silica column chromatography.

General procedure for the asymmetric reduction of α,β-unsaturated ketones [32]

A chiral bis-phosphine ((*S*)-*p*-tol-BINAP, (*S*)-BINAP, or (*S*)-BIPHEMP) (0.05 mmol) was placed in a flame-dried Schlenk tube and dissolved in toluene (2 mL). The Schlenk tube was transferred to a nitrogen-filled

glovebox. In the glovebox, NaO*t*-Bu (5 mg, 0.05 mmol) and CuCl (5 mg, 0.05 mmol) were weighed into a vial. The toluene solution of the chiral bisphosphine was added by pipette to the vial to dissolve solids and the resulting solution was then transferred back into the Schlenk tube. The Schlenk tube was removed from the glovebox, the solution was stirred for 10–20 min, and PMHS (0.063 mL, 1.05 mmol) was added to the solution with argon purging. The resulting solution turned reddish orange in color. The solution was then cooled to the specified temperature. The α,β-unsaturated ketone (1.0 mmol) was added to the reaction mixture with argon purging and the resulting solution was stirred at room temperature (18–27 h). Consumption of the α,β-unsaturated ketone was monitored by GC. When the reaction was complete, the Schlenk tube was opened and water (1 mL) was added. The resulting solution was diluted with diethyl ether, washed once with water and once with brine, and back-extracted with diethyl ether. TBAF (1 mmol, 1 M in THF) was added to the combined organic extracts and the resulting solution was stirred for 3 h. The solution was then washed once with water and once with brine, back-extracted with diethyl ether, and the organic layer was dried over anhydrous $MgSO_4$. The solvent was then removed in vacuo and the product was purified by silica column chromatography. In order to determine the *ee*, the product was converted into the corresponding (*R*,*R*)-2,3-dimethylethylene ketal and then analyzed by GC analysis (Chiraldex G-TA) for the diastereomeric ketals.

Intermediate silyl enol ethers can be trapped and isolated from initial conjugate reductions of enones with Stryker's reagent, or they may be used directly in Mukaiyama-type aldol constructions (i.e, in 3-component constructions; 3-CC) [35]. Thus, in a one-pot sequence using toluene as the initial solvent and 1–5 mol% $(Ph_3P)CuH$ relative to enone, any of a number of silyl hydrides (such as $PhMe_2SiH$, Ph_2MeSiH, tetramethyldisiloxane (TMDS), or PMHS) can be employed to produce the corresponding silyl enol ether. Dilution with CH_2Cl_2 without isolation, followed by cooling to −78 °C and introduction of an aldehyde, followed by a Lewis acid ($TiCl_4$ or $BF_3{\cdot}OEt_2$) results in good yields of aldol adducts (Eq. 5.18). Unfortunately, there is no acyclic stereocontrol (*syn* versus *anti* selectivity) in these 3-CC reactions [34b].



(5.18)

Representative procedure for conjugate reduction-aldol 3-CC: 2-{Hydroxy-[1-(toluene-4-sulfonyl)-1H-indol-3-yl]-methyl}-4,4-dimethylcyclohexanone [35]

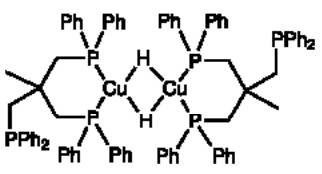
Dimethylphenylsilane (0.23 mL, 1.5 mmol, 1.5 equiv.) was added dropwise to a homogeneous, red solution of $[CuH(PPh_3)]_6$ (16.0 mg, 0.008 mmol, 5 mol% Cu) in toluene (2.0 mL) and the solution was stirred at room temperature for ca. 5 min. 4,4-Dimethylcylohexenone (0.13 mL, 1.0 mmol) was

added dropwise to the resulting red solution, which was stirred at room temperature. After ca. 7 min, the solution had darkened to a heterogeneous brown/black. Monitoring of the reaction by TLC showed that the enone had been consumed after 3 h, forming the corresponding silyl enol ether. The solution was diluted with CH_2Cl_2 (5.0 mL) and added by cannula to a solution of *N*-tosyl-indole-3-carboxaldehyde (0.45 g, 1.5 mmol, 1.5 equiv.) and $TiCl_4$ (1.5 mL of 1.0 M solution in CH_2Cl_2, 1 equiv.), in CH_2Cl_2 (7.0 mL) at −78 °C. Stirring was continued for 1 h and the reaction was quenched with saturated $NaHCO_3$ solution (6.0 mL) at −78 °C, and allowed to warm to room temperature. A blue precipitate was filtered using a Buchner funnel, and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic portions were washed with brine (2 × 50 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. Purification by flash chromatography (1:9 EtOAc/PE to 1:4 EtOAc/PE) afforded diastereomers as a yellow oil (combined yield 0.35 g, 82%).

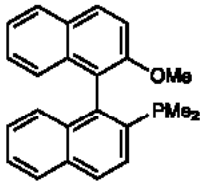
5.4
1,2-Reductions Catalyzed by Copper Hydride

Reductions of non-conjugated aldehydes and ketones based on copper chemistry are relatively rare. Hydrogenations and hydrosilylations of carbonyl groups are usually effected by transition metals such as Ti [36], Rh [37], and Ru [38], and in one case, Cu [39]. An early report using catalytic $[(tol)_3P]CuH$ in reactions with formaldehyde, in which disproportionation characteristic of a Tishchenko reaction took place, is indicative of a copper(I) alkoxide intermediate [16]. Almost two decades later, variations in the nature of the triphenylphosphine analogue (Strykers' reagent), principally induced by introduction of alternative phosphine ligands, have resulted in remarkable changes in the chemoselectivity of this family of reducing agents [40, 41]. Although not as yet fully understood, subtle differences even between alkyl substituents on phosphorus can bring about dramatic shifts in reactivity patterns. Changes in the composition of $[(Ph_3P)CuH]_6$ caused by ligands such as tripod (1,1,1-tris-(diphenylphosphinomethyl)-ethane), which forms a dinuclear bidentate complex (Fig. 5.3) [42], have been used by Stryker to great advantage to reduce ketones in a 1,2-fashion.

Both conjugated and non-conjugated ketones, as well as conjugated aldehydes, undergo clean 1,2-addition in the presence of CuH modified by Me_2PhP (Eq. 5.19). Ketones react under an atmosphere of hydrogen over a roughly 24 hour period. The presence of *t*-BuOH (10–20 equiv./copper) is important for increasing catalyst life-



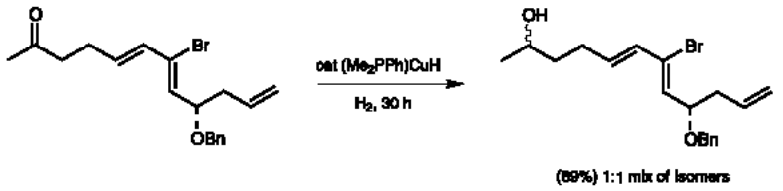
$[(\eta^2\text{-tripod})CuH]_2$



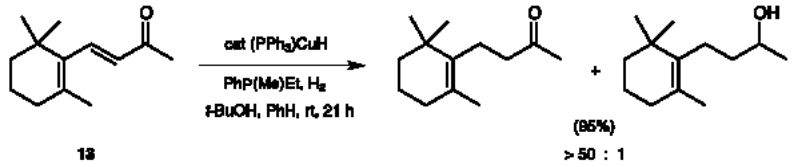
12

Fig. 5.3. Ligands tested for 1,2-reductions.

time, as in the corresponding cases of 1,4-reductions (vide supra), presumably by conversion of the initially formed copper alkoxide to the alcohol product in exchange for a thermally more stable $[Cu(O\text{-}t\text{-}Bu)]_4$. This complex is then hydrogenolyzed to reform the copper hydride catalyst. In most cases, isolated olefins are untouched, as is true for dienes, esters, epoxides, alkynes, and acetals. Rates are slower in substrates bearing free alkenes, probably a consequence of d–π^* interactions with the metal. Acyclic conjugated enones afford a high degree of control for generation of allylic alcohol products, with only small percentages of over-reduced material formed when using $PhMe_2P$-modified reagent. The corresponding $PhEt_2P$-altered Stryker's reagent, however, does not function as a catalyst for this chemistry (this is also the case with the novel biaryl P,O-ligand **12**, the dimethylphosphino analog of MOP) [43], while the mixed dialkylphenyl case Me(Et)PPh is unexpectedly effective (e.g., for β-ionone, **13**: >50:1; 95% yield; Eq. 5.20).

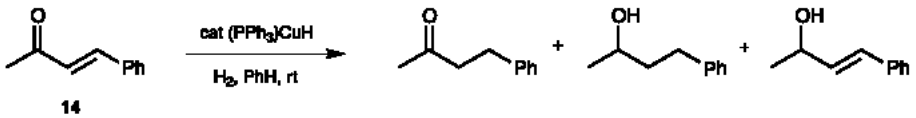


(5.19)



(5.20)

With these new levels of appreciation of the nuances associated with CuH-phosphine interactions, considerable fine-tuning of Stryker's reagent is now possible. One case in point involves enone **14**, which can be converted predominately into any one of three possible products (Scheme 5.6) [40].



Conditions				yield (%)
No added phosphine, 10h (A) 16% $(PPh_3)CuH$ 1000 PSI H_2	91	9	0	89
PPh_3 (12 equiv / Cu), 2 h (B) 16% $(PPh_3)CuH$ 1700 PSI H_2	0	92	8	95
Me_2PPh (6 equiv / Cu) 18 h (C) 5% $(PPh_3)CuH$ 500 PSI H_2	0	8	92	91

Scheme 5.6. Selective reductions as a function of phosphine.

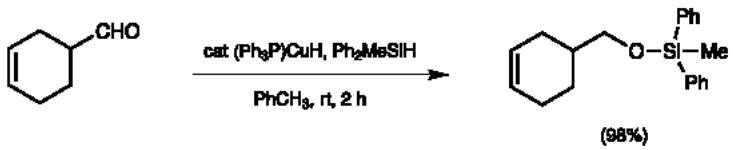
General procedure for reduction of saturated ketones using $[(Ph_3P)CuH]_6$ and Me_2PPh [40]

In a glovebox, $[(Ph_3P)CuH]_6$ (1 10 mol% Cu), Me_2PPh (6 equiv./Cu), and *t*-butanol (10 20 equiv./Cu) were combined in a Schlenk flask and dissolved in benzene. A solution of the substrate (10 100 equiv./Cu) in benzene (0.4 0.8 M in substrate) was added to this solution. The flask was sealed, removed from the drybox and, after one freeze-pump-thaw degassing cycle, placed under a slight positive pressure of hydrogen. The resulting yellow-orange homogeneous solution was allowed to stir until completion, as monitored by TLC. The reaction mixture was exposed to air, diluted with ether, and treated with a small amount of silica gel. This mixture was stirred in air for ≥0.5 h, filtered, concentrated in vacuo, and purified by flash chromatography. If the polarity of the product was similar to that of the residual phosphine, the crude mixture was treated with sodium hypochlorite (5% aqueous solution) and filtered through silica gel/$MgSO_4$ prior to chromatography.

General procedure for reduction of saturated ketones using $(PhMe_2P)CuH$ produced in situ [40]

Under an inert atmosphere, a solution of the substrate in benzene was added to a slurry of freshly purified CuCl (5 mol%), Me_2PPh (6 equiv./Cu), and *t*-butanol (10 equiv./Cu) in benzene (final concentration: 0.4 0.8 M in substrate). After degassing with one freeze-pump-thaw cycle, the suspension was placed under a slight positive pressure of hydrogen and allowed to stir until completion, as monitored by TLC. The product was isolated and purified as described above.

Further alterations in the above reaction conditions, notably the replacement of H_2 with various silanes as the hydride source, results in a net hydrosilylation of nonconjugated aldehydes and ketones [44]. The catalytic $(PPh_3)CuH$/excess R_3SiH combination is highly effective at converting aldehydes directly into protected primary alcohols, with silanes ranging from $PhMe_2SiH$ – which produces a relatively labile silyl ether – to Hanessian's especially hydrolytically stable *t*-$BuPh_2Si$ derivatives [45], all from the corresponding precursor silanes (Eq. 5.21). Levels of CuH used tend to be in the 1–3 mol% range, although from the few cases studied to date, one tenth as much may be sufficient to drive the reaction to completion. The more reactive PMHS [30] appears to be the ideal choice of silane for catalyst usage in the <1 mol% category, although the use of this polymeric hydride source necessitates workup under basic conditions.

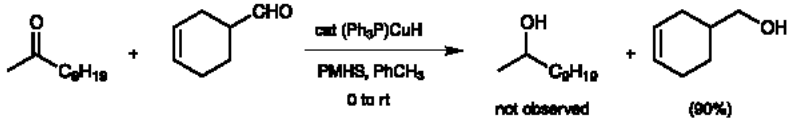


(5.21)

Representative 1,2-reduction/silylation of an aldehyde, giving (2-bromobenzyloxy)-diphenylmethylsilane [44]

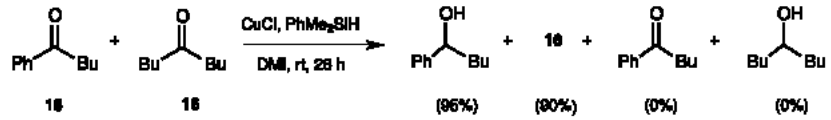
A dried 25 mL flask with a rubber septum top was flushed with argon and charged with $[PPh_3(CuH)]_6$ (53 mg, 0.162 mmol), as a red solid. Toluene (5.4 mL) was added, followed by neat diphenylmethylsilane (1.4 mL, 7.0 mmol), resulting in a homogeneous red solution. In a second dry, argon-flushed vessel (10 mL), fitted with a rubber septum, 2-bromobenzaldehyde (0.63 mL, 5.4 mmol) and toluene (4 mL) were mixed together, and the solution was transferred by cannula, with stirring, into the solution (at room temperature) of copper reagent and silane. The reaction mixture was monitored by TLC (elution with 5% diethyl ether/hexane, R_f — 0.74); the aldehyde was consumed after 30 min. The reaction was filtered through a pad of Celite/charcoal, washed with EtOAc (2 × 15 mL), and the filtrate concentrated to an oil in vacuo. Kugelrohr distillation (168 °C, 0.2 0.3 Torr) yielded the title compound as a colorless oil (1.98 g, 95%).

Ketones take considerably longer to reduce than aldehydes (10–24 h), although yields are not compromised. Differences in reactivity toward aldehydes and ketones can be used to advantage, with highly chemoselective reduction occurring at the aldehyde in the presence even of a methyl ketone (Eq. 5.22) [44].



(5.22)

In situ production of phosphine-free CuH from CuCl or CuOAc (0.3–1.0 equivalents), in the presence of an excess of $PhMe_2SiH$ in DMI at room temperature, displays a remarkable preference for reductions of aryl ketones (e.g., **15**) over aliphatic ones such as **16** (Eq. 5.23) [46]. Reactions require a day or more to reach completion, concentrations of 0.5 M notwithstanding, but yields have been uniformly good (77–88%) for the few cases examined. Aldehydes, however, show no such selectivity and are reduced to the corresponding primary alcohols, albeit in high yields.

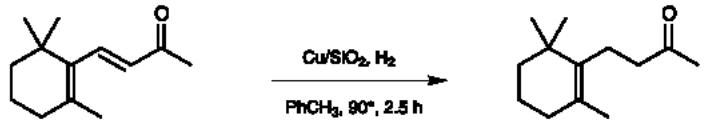


(5.23)

5.5 Heterogeneous CuH-Catalyzed Reductions

Catalysts such as copper chromite, first prepared and utilized for carbonyl 1,2-reductions back in 1931 [47], have given way to more modern reagents for effecting

related transformations under heterogeneous conditions. Ravasio first described Cu/Al_2O_3 in steroid reductions (steroid-4-en-3-ones), examining the regioselectivities, stereoselectivities, and chemoselectivities of this supported reductant at 60 °C under a hydrogen pressure of one atmosphere [48]. A follow-up study by that group, described in 1996, promotes the more generally useful Cu/SiO_2 [48]. Under an atmosphere of H_2 at 90 °C in toluene, this catalyst effects 1,4-reductions of conjugated enones while leaving isolated olefins intact. Although the preparation of the catalyst is fairly involved (cf. the procedure below), the method results in excellent levels of conversion, and high yields of the corresponding ketones. The featured example in this work is that of β-ionone, from which the desired keto product, reflecting reduction of the α,β-site, was provided with high levels of regiocontrol (Eq. 5.24). Removal of the catalyst by filtration, followed by reactivation at 270 °C, essentially did not result in any change in selectivity after four consecutive cycles. These reactions are believed to involve CuH, generated on the surface of pyrogenic silica.



β-ionone (13) (98%) (5.24)

Catalyst preparation [49]

Concentrated NH_4OH was added to a solution of $Cu(NO_3)_2 \cdot 3H_2O$ (25 mL, 160 g/L) until pH – 9 was reached, the support (silica, 10 g) was then added, and the mixture was slowly diluted to 3 L in order to allow hydrolysis of the $Cu[NH_3]_4^{++}$ complex and deposition of the finely dispersed product to occur. The solid was separated by filtration, washed with water, dried overnight at 120 °C, and calcined in air at 350 °C for 3 hours. In this way, 8% Cu samples, 308 m^2/g BET surface area, were obtained. The catalyst was reduced with H_2 at 270 °C at atmospheric pressure, the water formed being removed under reduced pressure, before the hydrogenation reaction.

Experimental conditions

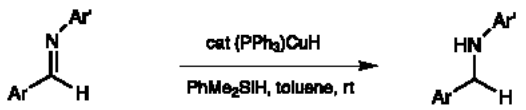
The substrates (2 mmol) were dissolved in toluene (12 mL) and the solution was transferred under H_2 into a glass reaction vessel in which the catalyst (0.3 g) had been reduced previously. Reactions were carried out at 90 °C and at atmospheric pressure, with magnetic stirring, the final charge of hydrogen being adjusted to 1 atm with a mercury leveling bulb, and monitored by withdrawing 20 µL samples through a viton septum and analyzing them by capillary GLC. After completion, the catalyst was filtered off, the solvent removed, and the reaction mixture analyzed by NMR. Superatmospheric pressure (1.5 5 atm) could conveniently be used to speed up the reaction without loss in selectivity when higher substrate/Cu ratios were used. For the recycling tests, the catalyst was washed with diethyl ether, dried, and reactivated at 270 °C.

A fascinating study on the surface science of copper hydride on SiO_2, as well as on Al_2O_3, ceria (cerium oxide), and ZnO, has appeared [50]. Pure, yet thermally unstable, CuH can be precipitated as a red-brown solid from aqueous cupric sulfate and hypophosphorous acid in the presence of H_2SO_4, and has been characterized by powder X-ray diffraction (PXRD) (Eq. 5.25). Transmission electron microscopy (TEM) data suggest that it is most stable when deposited on acidic SiO_2.

$$4Cu^{+2} + 6H_2PO_2^- + 6H_2O \xrightarrow{H^+} 4CuH_{ppt} + 6H_2PO_3^- + 8H^+ \qquad (5.25)$$

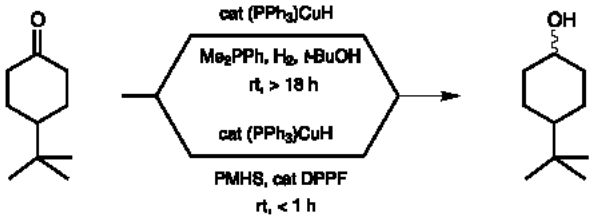
5.6 Overview and Future Developments

Although many variations on reagents bearing hydride ligated to copper(I) have been developed, it was the advent of Stryker's reagent that provided a well defined, easily handled, and crystalline source of CuH. This hexameric copper hydride, $[(Ph_3P)CuH]_6$, has been enthusiastically embraced by the synthetic community as a highly reliable means of effecting fundamental conjugate reductions of unsaturated aldehydes, ketones, and esters. Unlike the procedures previously in use, in which presumed *ate* complexes of CuH required manipulations of multiple reagents and gave rise to highly basic species, $(Ph_3P)CuH$ is relatively non-basic and is available commercially, or can be readily prepared in multigram quantities. Moreover, when stored under an inert atmosphere, it can last for months without significant decomposition. That $(Ph_3P)CuH$ derives from readily accessible and inexpensive precursors is a bonus, and as it is regarded as a base metal catalyst, in association with either molecular hydrogen or silanes as sources of stoichiometric hydride, the economics involved in its use are highly favorable. Also not to be overlooked among the virtues of $(Ph_3P)CuH$ is its tolerance to moisture, as well as many to functional groups – including isolated, unsaturated carbon-carbon bonds – which otherwise preclude normal modes of catalytic hydrogenation. The noteworthy impact exerted by various achiral monodentate and bidentate phosphine ligands on CuH reactions can be used to tremendous advantage in controlling resulting regioselectivities and chemoselectivities. Replacement of the PPh_3 in Stryker's reagent with selected chiral, nonracemic bidentate phosphines has enabled enantioselective 1,4-reductions to be achieved. Still more recently, the 1,2-addition mode of Stryker's reagent has been evolving rapidly. These reactions have similarly proven to be quite effective under conditions catalytic in CuH. Further recognition and greater appreciation of such elements of reactivity and selectivity, associated with both the 1,2- and the 1,4-reduction patterns of $(Ph_3P)CuH$, are likely to give rise to future improvements, new methodologies, and synthetic applications.



(5.26)

An aldimine reduction already "in the pipeline" has been tested using catalytic Stryker's reagent along with various silanes, the preliminary data suggesting that such 1,2-additions do indeed take place, albeit far more slowly that those on the corresponding carbonyl derivatives (Eq. 5.26) [51]. In line with observations made concerning the effects of phosphines on CuH [40, 41], a remarkable rate enhancement has also been noted in ketone hydrosilylations under the influence either of racemic BINAP or DPPF (bis(diphenylphosphino)ferrocene). Thus, while 4-*t*-butylcyclohexanone takes a day to be reduced when catalytic $(PPh_3)CuH$ is used with either H_2 [40, 41] or PMHS [44], simple addition of either of these bidentate ligands results in complete conversion in less than one hour at identical concentrations (Scheme 5.7) [44]. This key observation has generated considerable enthusiasm for development of a highly effective method for asymmetric hydrosilylations [52] of aryl ketones using catalytic CuH ligated by a nonracemic bidentate phosphine (Roches' 3.5-xyl-MEO-BIPHEP) [53]. It thus seems reasonable to conclude that the story of reductions by CuH in organic synthesis, whether under homogeneous or heterogeneous conditions, is far from complete.



Scheme 5.7. Effect of DPPF on reductions with Stryker's reagent.

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6
Copper-mediated Diastereoselective Conjugate Addition and Allylic Substitution Reactions

Bernhard Breit and Peter Demel

Abstract

Conjugate additions and allylic substitution reactions of organocopper reagents are synthetically valuable C C bond-forming reactions. New stereogenic centers may be introduced in the course of either reaction. Their selective formation may be controlled either by the reagent or by the substrate, the latter being the focus of this review. The subject has recently been summarized comprehensively [1], and so this chapter focuses on important basic principles and the most recent progress, with emphasis on reactions of potential value in organic synthesis.

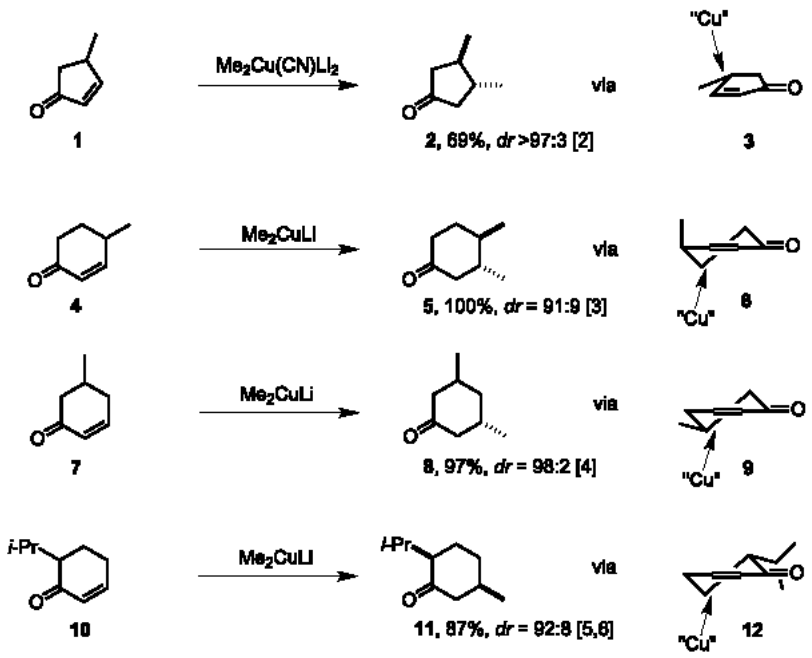
6.1
Conjugate Addition

6.1.1
Stereocontrol in Cyclic Derivatives

Cyclic systems usually adopt distinct preferred conformations, which frequently allow them to pass through a single reactive conformation in the course of a chemical reaction; this may result in the formation of a single product. In this context, addition of organocuprates to a number of chiral, cyclic enone systems frequently occurs with high levels of stereoselectivity. Historically, this chemistry has had a major impact on the field of total synthesis of steroids and prostaglandins [1a, k]. In this chapter we would thus like to present an overview of the most general stereochemical trends underlying the addition of organocuprates to chiral cyclic enones.

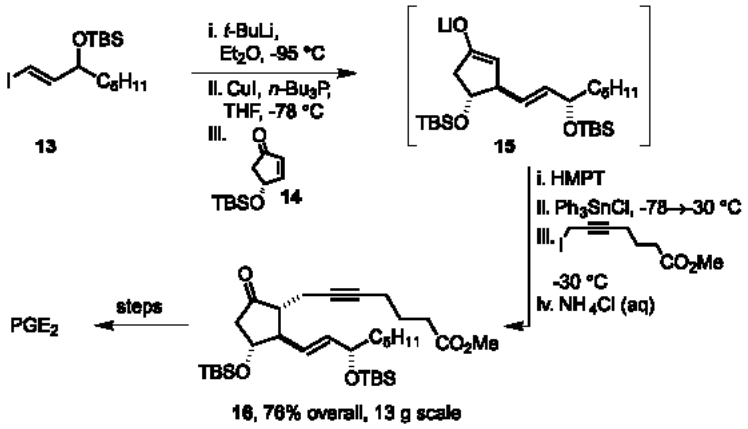
When organocuprates are added either to 4-substituted cyclopentenones **1**, or to 4-substituted or 5-substituted cyclohexenones (**4** and **7**), the *trans* addition product is generally obtained with good to excellent levels of diastereoselectivity (Scheme 6.1) [2–4]. The 6-substituted cyclohexenone **10**, however, predominantly gave the *syn* addition product [5, 6].

A beautiful illustration of the power of diastereoselective cuprate addition to cyclopentenone systems is given in the course of the synthesis of the prostaglandin E_2 (PGE_2) (Scheme 6.2) [7]. Thus, addition of the functionalized organocuprate



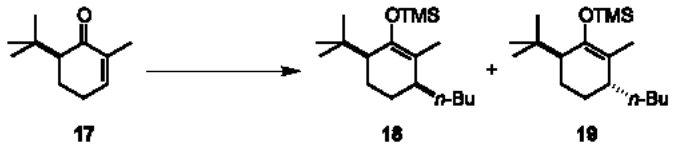
Scheme 6.1. Diastereoselectivity in conjugate addition of organocuprates to chiral cyclic enones.

reagent obtained from iodide **13** to the chiral cyclopentenone **14** occurred in *trans* selective fashion to give enolate **15**. Transmetalation to the tin enolate, followed by stereoselective propargylation, furnished a 76% overall yield of cyclopentanone **16**, which was transformed into prostaglandin E_2 [7c].



Scheme 6.2. Diastereoselective addition of a functionalized cuprate to cyclopentenone **14** in the synthesis of prostaglandin E_2 (PGE_2) (TBS = *t*-butyldimethylsilyl, HMPT = hexamethylphosphoric triamide).

Addition of Lewis acids may not only accelerate the reaction rate of a conjugate addition but may also alter the stereochemical outcome of a cuprate addition. Interestingly, when the 6-*t*-butyl-substituted cyclohexenone derivative **17** was exposed to dibutylcuprate, followed by silylation of the resulting enolate, the *cis* enol ether **18** was obtained (Scheme 6.3) [8]. If, however, the cuprate addition was performed in the presence of chlorotrimethylsilane, the stereochemical outcome of the conjugate addition reaction was reversed to give *trans* enol ether **19**.



Scheme 6.3. Influence of added TMSCl on the diastereoselectivity of the conjugate addition of dibutylcuprate to enone **17** (TMS = trimethylsilyl, HMPT = hexamethylphosphoric triamide).

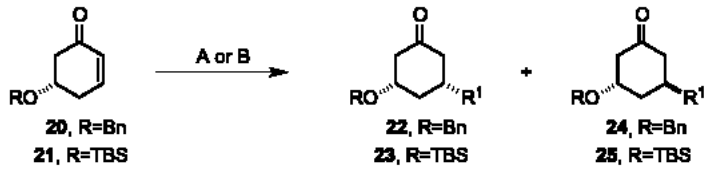
It has recently been shown that the intrinsic substrate-directing capability of 5-substituted chiral cyclohexenenones can be overruled by making use of active substrate direction. Proper choice of the cuprate reagent made it possible to switch between standard passive substrate control and an alternative active substrate control, and hence to reverse the stereochemical outcome of the conjugate addition reaction [9]. Thus, treatment of 5-oxygen-substituted cyclohexenones **20** and **21** with a cyano-Gilman reagent gave the expected *trans* addition products **24** and **25**, respectively (entries 1, 4, 6, Tab. 6.1, Scheme 6.4). Conversely, when the corresponding lower order cyanocuprate was employed, diastereoselectivity was reversed and the *cis* addition products **22** and **23**, respectively, were formed with high selectivities (entries 2, 3, 5). A very reasonable explanation for this result is a benzyloxy- or silyloxy-directed cuprate addition through transition state **26** (Scheme 6.5) [9b–e, 10].

Tab. 6.1. Results of conjugate addition of organocopper reagents to enones **20** and **21**.

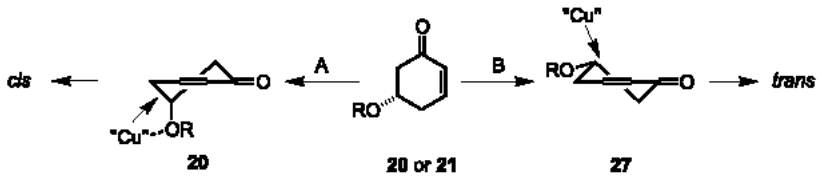
Entry	*Substrate*	*R*^{1}	*Method*[a)]	*cis:trans*	*Yield [%]*	*Ref.*
1	**20**	*n*-Bu	B	10:90	87	9b
2	**20**	*n*-Bu	A	>98:2	80	9b
3	**21**	*n*-Bu	A[b)]	>99:1	92	9b
4	**21**	*n*-Bu	B	2:98	92	9a, b
5	**21**	Me	A	>99:1	83	9b
6	**21**	Me	B	3:97	83	9a, b

a) Et_2O, –78 °C, 2.4 eq. of cuprate reagent (A: $R^1Cu(CN)Li$; B: $R^1_2CuLi{\cdot}LiCN$).

b) 1.2 eq. of cuprate reagent.

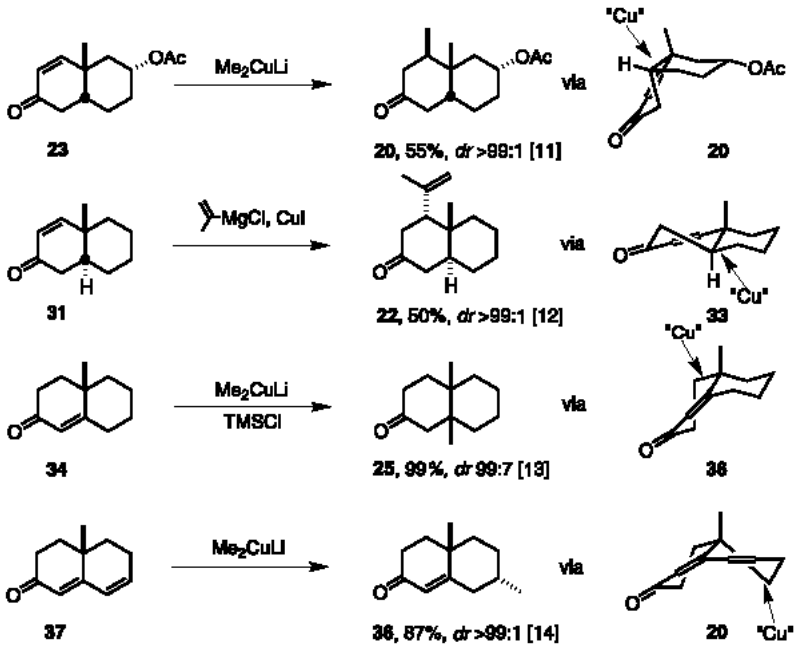


Scheme 6.4. Diastereoselectivity in conjugate addition of organocopper reagents to alkoxy-substituted cyclohexenones **20** and **21** (Bn = benzyl, TBS = *t*-butyldimethylsilyl).



Scheme 6.5. Rationale for the stereochemical outcome of diastereoselective conjugate addition to cyclohexenones **20** and **21**.

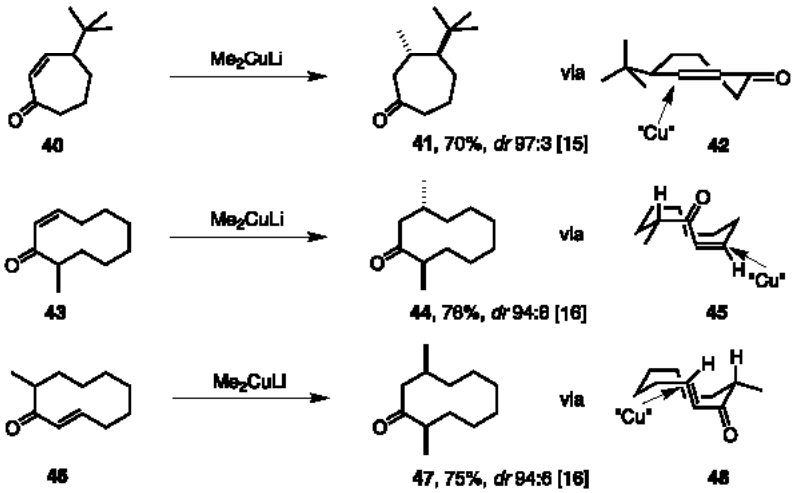
The addition of organocuprates to chiral decalin enone systems has been explored in the context of steroid synthesis. For the addition of lithium dimethylcuprate to enones **28**, **31**, and **34**, the major diastereomer obtained can easily be predicted by employment of a qualitative conformational analysis (Scheme 6.6) [11–13]. Thus,



Scheme 6.6. Diastereoselectivity in conjugate additions of organocuprates to chiral bicyclic cyclohexenones (TMS = trimethylsilyl).

attack of the copper nucleophile occurs in all cases through the most stable half-chair conformation to give the corresponding addition products. A similar analysis also accounts for the 1,6-addition to dienone **37** [14].

Rather less information on addition of cuprates to larger cyclic enone systems is available. 4-Substituted cycloheptenones (such as **40**) have been shown to give the *trans* addition products preferentially (Scheme 6.7) [15]. Furthermore, interesting selectivities have been noted upon addition of lithium dimethylcuprate to cyclodecanone systems **43** and **46**. These systems should adopt the preferred conformations **45** and **48**, which on addition of the nucleophile provide either the *trans* adduct **44** or the *cis* product **47**, respectively [16]. Similar results have been obtained from conjugate additions of organocopper reagents to medium- and large-ringed α,β-unsaturated lactone systems. This field has been reviewed recently [1i].



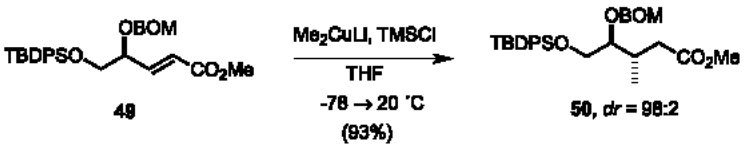
Scheme 6.7. Diastereoselectivity in conjugate addition of organocuprates to chiral cyclic enones of medium ring size.

6.1.2 Stereocontrol in Acyclic Derivatives

6.1.2.1 γ-Heteroatom-substituted Michael Acceptors

Conjugate addition reactions of acyclic Michael acceptors possessing heteroatom-substituted stereogenic centers in their γ-positions may provide useful levels of diastereoselectivity. A typical example is given with the γ-alkoxy-substituted enoate **49** in Scheme 6.8 [17]. High levels of diastereoselectivity in favor of the *anti* addition product **50** were found in the course of dimethylcuprate addition.

To account for the observed diastereoselectivity, a "modified" Felkin–Anh model has been proposed [18]. In analogy to the classical Felkin–Anh model, originally developed for the addition of organometallic reagents to aldehydes possessing a



Scheme 6.8. Diastereoselective addition of lithium dimethylcuprate to acyclic enoate **49** (TBDPS = *t*-butyldiphenylsilyl, BOM = benzyloxymethyl, TMS = trimethylsilyl).

stereogenic center in the α-position, the largest substituent or, more precisely, the substituent with the lowest lying σ*-orbital (L in Fig. 6.1), should be orientated so as to allow efficient overlap with the π-system of the Michael acceptor. As a consequence, the LUMO (π*-C=C) should be lowered in energy, which provides a more reactive conformation. This holds for both rotamers **51** and **52**. Rotamer **51**, however, suffers to a greater extent from repulsive allylic $A^{1,3}$ strain [19]. Accordingly, for *Z*-configured π-systems, $A^{1,3}$ strain should become the decisive factor. Conversely, nucleophile attack is more hindered for rotamer **52**. Hence, for *E*-configured Michael acceptors in particular, a subtle balance of these two repulsive interactions should govern the overall stereochemical outcome of the conjugate addition reaction. Finally, it should be kept in mind that this model relies on the basic assumption that nucleophile attack is the step that determines stereoselectivity. This notion has been challenged, however, both in recent high level calculations and in experimental studies [20–22]. Nevertheless, this simple model provides at least a rough first order analysis for the stereochemical outcome that should be expected in the course of a conjugate addition reaction to γ-chiral Michael acceptors.

Stereoselective addition of cuprates to γ-alkoxy enoates of type **49** [17] (see Schemes 6.8 and 6.9) has been used in the construction of polypropionate-type structures. Thus, a sequence of diastereoselective cuprate addition, enolate formation, and diastereoselective oxygenation with Davis's reagent has been applied iteratively to provide a C_{19}–C_{28} segment of Rifamycin S (**60**) [17c, d].

Chlorotrimethylsilane-accelerated divinylcuprate addition to enal **61**, followed by a Wittig olefination, provided enoate **62** as a single stereoisomer in excellent yield (Scheme 6.10) [23]. The enoate **62** could be transformed in further steps into olivin (**63**), the aglygon of olivomycin.

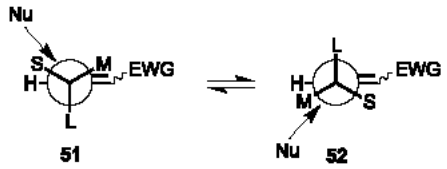
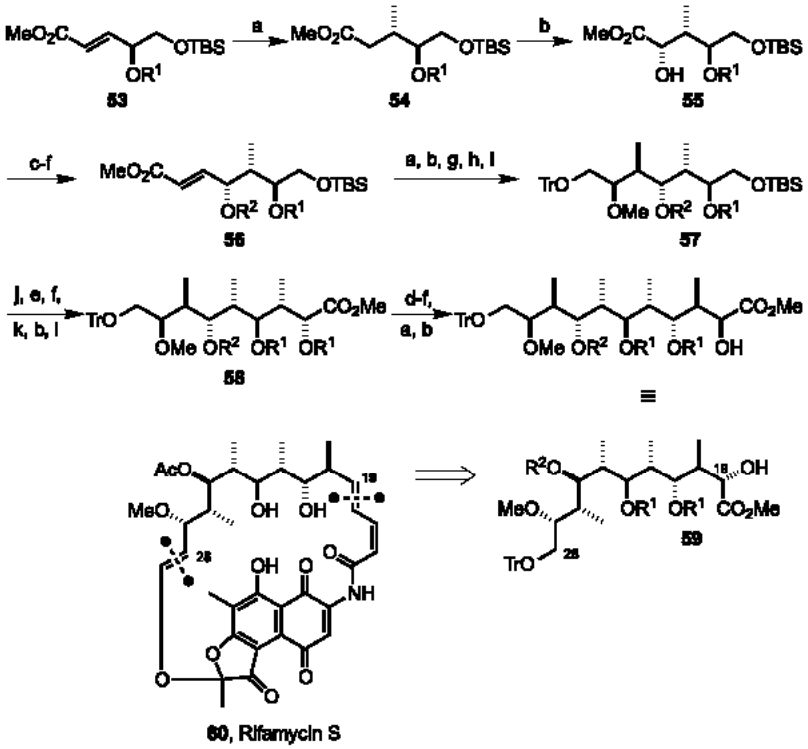


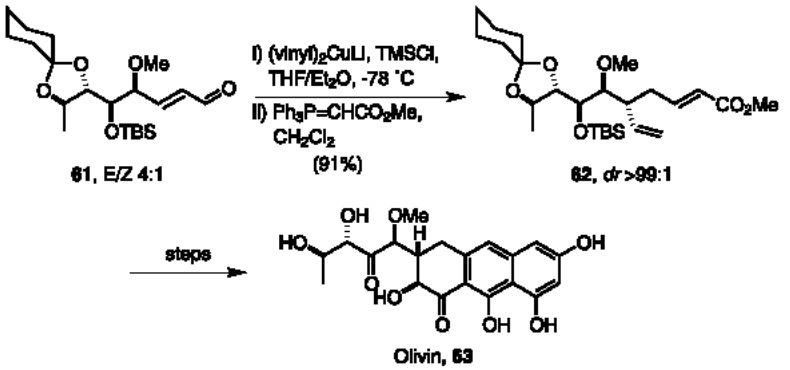
Fig. 6.1. "Modified" Felkin–Anh model to account for the observed diastereoselectivity in conjugate addition reactions to γ-chiral Michael acceptors.



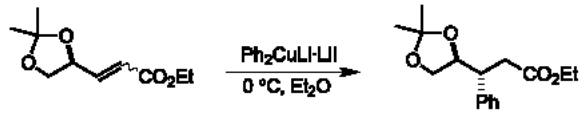
Scheme 6.9. Construction of the polypropionate segment of Rifamycin S through iterative diastereoselective cuprate addition to acyclic enoates. a) Me_2CuLi, TMSCl, THF, 78 °C; b) KHMDS, THF, 78 °C; Davis oxaziridine; c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; d) DIBAL-H; e) Swern oxidation, f) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2; g) $NaBH_4$, THF/H_2O; h) TrCl, DMAP, CH_2Cl_2; i) NaH, MeI, DMF; j) TBAF, THF; k) $CuBr{\cdot}SMe_2$, MeLi·LiBr, TMSCl, THF; l) BOMCl, *i*-Pr_2NEt, CH_2Cl_2; R^1 = BOM, R^2 = MOM. (TMS = trimethylsilyl, KHMDS = potassium hexamethyldisilazide, MOM = methoxymethyl, DIBAL-H = diisobutylaluminium hydride, Tr = triphenylmethyl, DMAP = 4-*N*,*N*-dimethylaminopyridine, TBAF = tetrabutylammonium fluoride, BOM = benzyloxymethyl)

With glyceraldehyde-derived enones and enoates, it has been found that addition of aryl or alkenyl copper reagents is almost independent of the enone geometry [24, 25]. In agreement with the "modified" Felkin–Anh model, *Z* enoates usually provide high levels of *anti* selectivity (Scheme 6.11). Hence, the *Z* derivative **64** reacted with complete stereochemical control, whereas the *E*-enoate **64** gave a lower selectivity of **4:1** in favor of the *anti*-conjugate adduct [25].

A drawback of the *Z* enoates is usually lower reactivity, reflected in prolonged reaction times and higher reaction temperatures. This may be overcome by switching to more reactive enone systems. Thus, addition of the functionalized cyano-Gilman cuprate system **67** to *Z* enone **66** proceeded smoothly at low temperatures, with excellent acyclic stereocontrol at the β-stereocenter [26, 27]. Stereocontrol upon

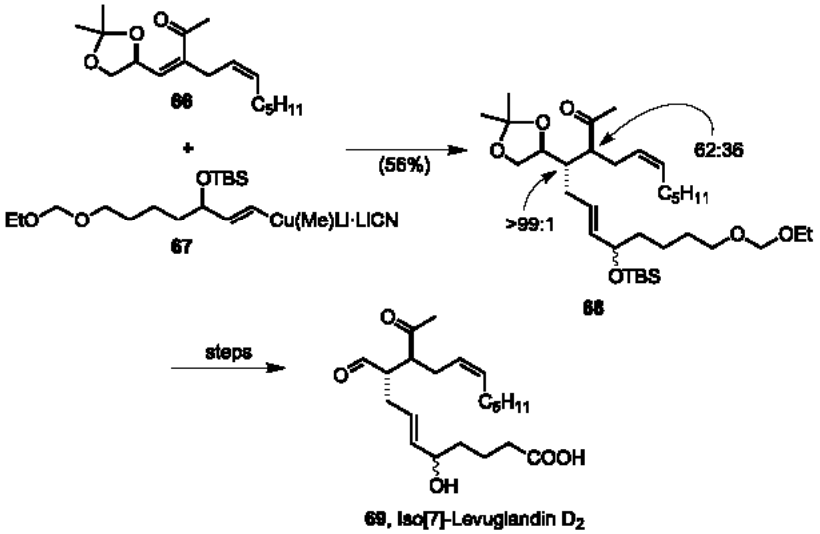


Scheme 6.10. Stereoselective cuprate addition to enal 61 – the key step towards the synthesis of olivin. (TBS = *t*-butyldimethylsilyl, TMS = trimethylsilyl)



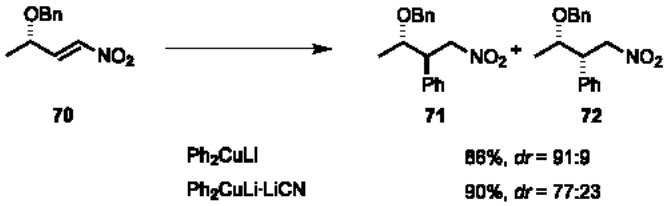
Scheme 6.11. Influence of double bond geometry upon addition of diphenylcuprate to enoate 64.

enolate protonation, however, was only moderate. Conjugate adduct 68 was further transformed to give iso[7]-levuglandin D_2 (Scheme 6.12) [26].



Scheme 6.12. Diastereoselective cuprate addition to Z enone 61 – key step towards the synthesis of iso[7]-levuglandin D_2. (TBS = *t*-butyldimethylsilyl)

The stereochemical trends discussed above are not limited to α,β-unsaturated carbonyl compounds; other Michael acceptors such as nitroalkenes and unsaturated phosphane oxides display similar behavior. A representative example for the nitroalkene class of Michael acceptors is shown with substrate **70** in Scheme 6.13 [28]. The best results were thus obtained for arylcuprates. Other organocuprates were much less selective, which severely restricts their application in organic synthesis.



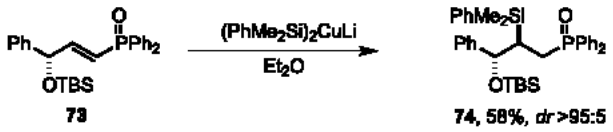
70 **71** **72**

88%, *dr* = 91:9

90%, *dr* = 77:23

Scheme 6.13. Diastereoselective cuprate addition to nitroalkene **70**.

Similar observations were made in a related series of unsaturated phosphane oxides (such as **73**, Scheme 6.14) [29]. Whereas dialkylcuprates mostly reacted non-selectively, the best diastereoselectivities were observed for disilylcuprates (**74**).



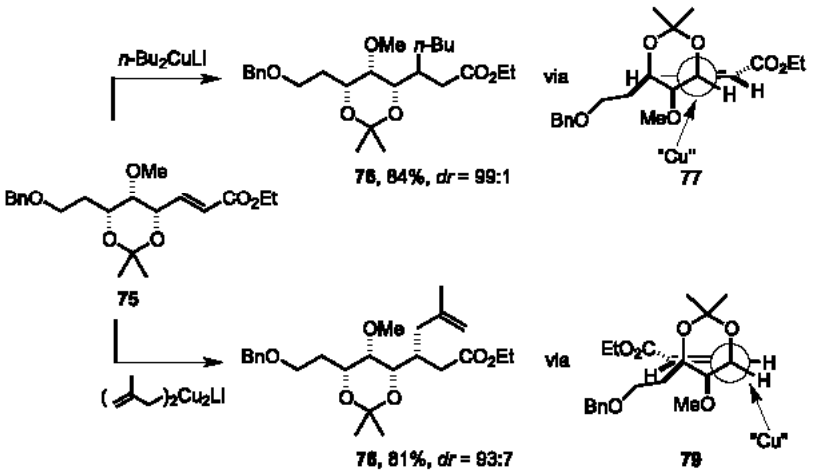
73 **74, 58%, *dr* >95:5**

Scheme 6.14. Diastereoselective cuprate addition to α,β-unsaturated phosphane oxide **73** (TBS = *t*-butyldimethylsilyl).

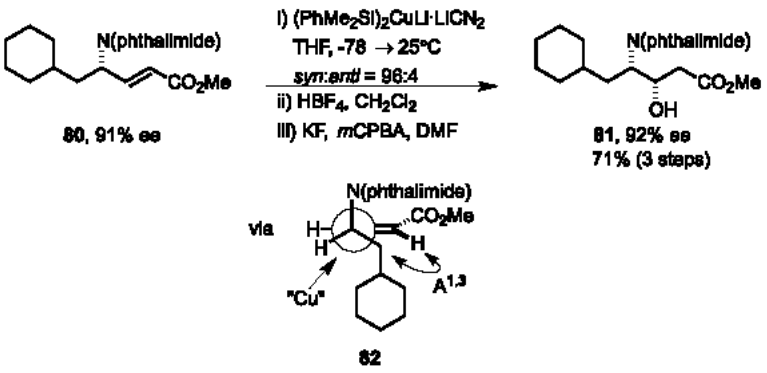
Obviously, the nature of the organocopper reagent is an important factor with respect to the stereochemical outcome of the cuprate addition. This is nicely illustrated for the cuprate addition reaction of enoate **75** (Scheme 6.15). Here, lithium di-*n*-butylcuprate reacted as expected by way of the "modified" Felkin–Anh transition state **77** (compare also **52**), which minimizes allylic $A^{1,3}$ strain, to give the *anti* adduct **76** with excellent diastereoselectivity [30]. Conversely, the bulkier lithium bis-(methylallyl)cuprate preferentially yielded the *syn* diastereomer **78** [30, 31]. It can be argued that the bulkier cuprate reagent experiences pronounced repulsive interactions when approaching the enoate system past the alkyl side chain, as shown in transition state **77**. Instead, preference is given to transition state **79**, in which repulsive interactions to the nucleophile trajectory are minimized.

A similar explanation may also hold for the result of conjugate addition to γ-phthalimido enoate **80** (Scheme 6.16). Thus, addition of the bulky cyano-Gilman silyl cuprate gave the *syn* diastereomer **81** (*dr* = 96:4) [32, 33]. Preference for the sterically least hindered nucleophile trajectory seems to dictate the overall stereochemical outcome (transition state **82**).

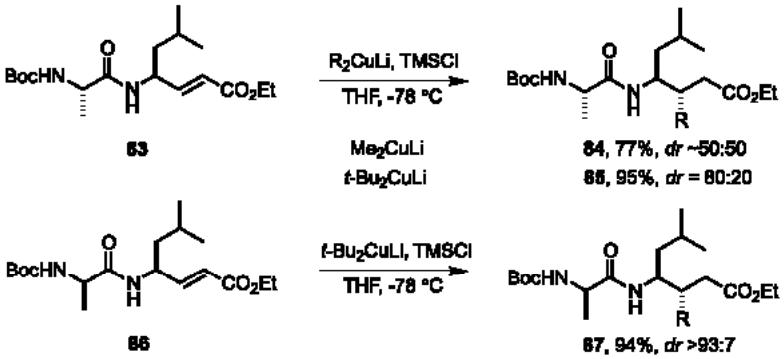
The results for conjugate additions to pseudodipeptides **83** and **86** may be interpreted along similar lines. Thus, addition of the fairly "slim" lithium dimethylcuprate nucleophile proceeded non-selectively (**84**, Scheme 6.17) [34, 35]. Con-



Scheme 6.15. Conjugate addition to enoate 75; influence of the nature of the cuprate reagent on diastereoselectivity.



Scheme 6.16. Diastereoselective cuprate addition to γ-phthalimido enoate 80.



Scheme 6.17. Diastereoselective cuprate addition to pseudopeptides 83 and 86.

versely, the bulky lithium di-*t*-butylcuprate displayed 4:1 selectivity in favor of the *anti* diastereomer of **85**. Interestingly, the stereogenic center in the 5-position had a significant influence, as the *syn* derivative **86** provided the conjugate adduct **87** with significantly higher diastereoselectivity under otherwise identical reaction conditions ($dr > 93{:}7$). Furthermore, investigations with analogous pseudotripeptide derivatives (*L,L,L* and *D,L,L*, respectively) found that an unusual remote 1,8-induction may even be operative in some cases [35].

For a cuprate addition reaction to a diester derivative such as **88**, it might be expected that the *anti* addition product would be favored, since a pronounced allylic $A^{1,3}$ strain in these substrates along "modified" Felkin–Anh lines should favor transition state **52** (see Fig. 6.1). However, experiments produced the opposite result, with the *syn* product **89** being obtained as the major diastereomer (Scheme 6.18) [36, 37].

88 **89**

(vinyl)Cu·BF_3	72%, dr = 78:22
n-BuCu·BF_3	52%, dr = 95:5
(methallyl)Cu(CN)Li·BF_3	95%, dr = 96:4

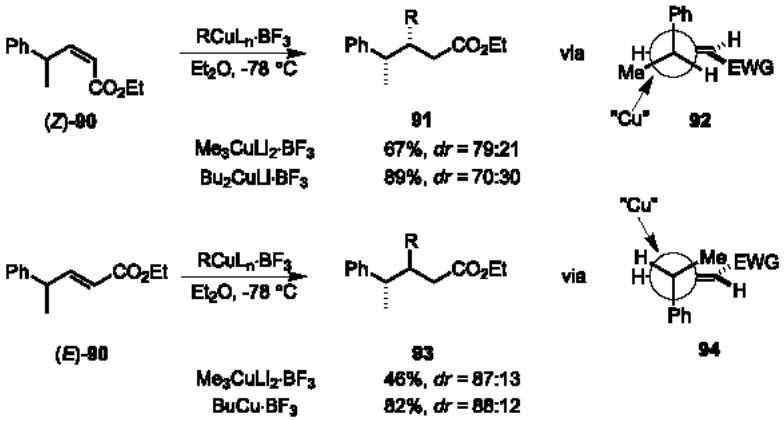
Scheme 6.18. Diastereoselective cuprate addition to diester **88**.

This result clearly marks the difficulties and limitations inherent in the "modified" Felkin–Anh model, which so far is nothing more than a rule of thumb. To account for these results, a switch in mechanism towards a "π-complex" model has been proposed [36b, 37].

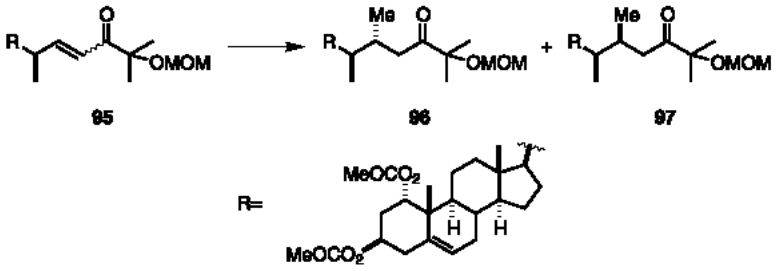
6.1.2.2 *γ*-Alkyl-substituted *α,β*-Unsaturated Carbonyl Derivatives

Diastereofacial selection on addition of organocoppper reagents to chiral *γ*-alkyl-substituted Michael acceptors has been investigated less extensively, due to the usually low selectivities generally observed for these systems [38, 39]. This is exemplified by the reaction of *E* and *Z* enoates **90** (Scheme 6.19). Thus, either *syn*-**91** or *anti*-**93** is formed upon conjugate addition with BF_3-modified reagents, as a function of enoate geometry. The stereochemistry of the reaction is in accordance with the "modified" Felkin–Anh model [40].

Better stereoselectivities have been noted for conjugate addition reactions to the steroidal enone **95** (Scheme 6.20, Tab. 6.2). Irrespective of the enone geometry, addition of lithium dimethylcuprate provided the *anti* addition product **96** in high yield and with good diastereoselectivity (Tab. 6.2, entries 1 and 2). Interestingly, addition of chlorotrimethylsilane to the reaction mixture had a dramatic effect. The *E* isomer of enone **95** still gave the *anti* addition product **96** with perfect stereoselectivity (entry 3). With the *Z* isomer of the enone, however, the *syn* addition product **97** was formed in good yield and with high diastereoselectivity (entry 4)



Scheme 6.19. Diastereoselective cuprate addition to γ-methyl-substituted enoates **90**.



Scheme 6.20. Diastereoselective cuprate addition to steroidal enone **95** (MOM = methoxymethyl).

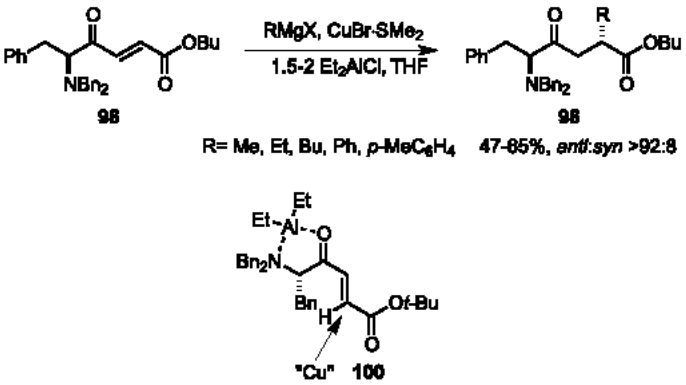
[41]. This result fits with the notion that addition of chlorotrimethylsilane changes the rate and selectivity-determining step of the conjugate addition reaction [22, 42].

Tab. 6.2. Results of diastereoselective cuprate additions to enone **95** (TMS = trimethylsilyl, HMPT = hexamethylphosphoric triamide).

Entry	*Substrate*	*Reagents*	96:97	*Yield [%]*
1	(*E*)-95	Me_2CuLi 0 °C, THF	98:2	91
2	(*Z*)-95	Me_2CuLi 0 °C, THF	98:2	78
3	(*E*)-95	Me_2CuLi, TMSCl, HMPT 78 °C, THF	100:0	95
4	(*Z*)-95	Me_2CuLi, TMSCl, HMPT 78 °C, THF	3:97	75

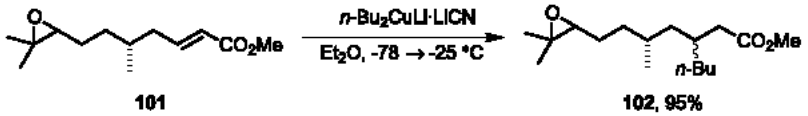
6.1.2.3 α,β-Unsaturated Carbonyl Derivatives with Stereogenic Centers in Positions other than the γ-Position

When the chiral α,β-enone enoate **98** was treated with magnesiocuprates in the presence of 1.5–2 equivalents of diethylaluminium chloride, the *anti* addition product **99** was obtained in moderate yield and with good diastereoselectivity (Scheme 6.21) [43, 44]. A reasonable explanation might assume a chelating coordination of the aluminium reagent [45]. Thus, if the enone **98** were to adopt an *s-trans* conformation, as indicated for complex **100**, subsequent front side attack of the nucleophile would furnish the major diastereomer *anti*-**99**.



Scheme 6.21. Lewis acid-promoted diastereoselective conjugate addition to enone **98** (Bn = benzyl).

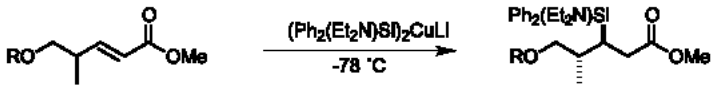
Michael acceptors possessing stereogenic centers in their δ-position or in any position further remote do not exhibit significant levels of stereochemical control if passive substrate control is relied on exclusively. The δ-methyl-substituted epoxyenoate **101**, for example, reacted with lithum dibutylcyanocuprate in a chemoselective but stereorandom fashion (Scheme 6.22) [46, 47].



Scheme 6.22. Non-stereoselective conjugate addition to the δ-chiral enoate **102**.

6.1.2.4 Directed Conjugate Addition Reactions

As discussed, conjugate addition reactions involving chiral γ-alkyl-substituted α,β-unsaturated carbonyl derivatives usually occur with low levels of diastereoselectivity. In accord with this general trend, the benzyloxy and silyloxy derivatives **103** and **104** (Scheme 6.23) both reacted with a silyl cuprate in non-selective fashion, to give the conjugate adducts **108** and **109**, respectively (entries 1 and 2, Tab. 6.3) [39]. Conversely, high levels of diastereoselectivity were found for the corresponding carbamates, and even better results were obtained for carbonates, giving the *anti* esters **110**–**112** as the major diastereomers (entries 3–5) [39].



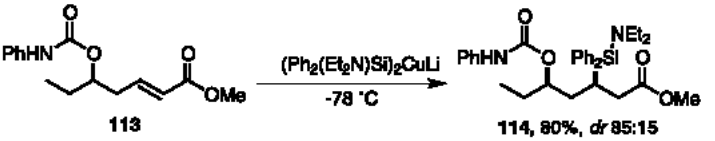
103-107 **103-112**

Scheme 6.23. Diastereoselective cuprate addition to δ-functionalized enoates **103–107**.

Tab. 6.3. Results of diastereoselective cuprate addition to δ-functionalized enoates **103–107** (TBS = *t*-butyldimethylsilyl, Bn = benzyl).

Entry	*Substrate*	*R*	*Product*	*anti:syn*	*Yield [%]*
1	**103**	Bn	**108**	50:50	95
2	**104**	TBS	**109**	50:50	45
3	**105**	CONHPh	**110**	89:11	77
4	**106**	COOMe	**111**	>95:5	80
5	**107**	COOBn	**112**	>95:5	85

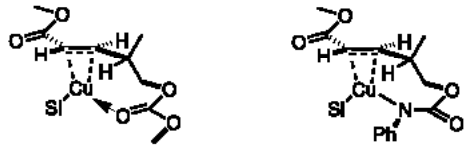
Interestingly, even derivative **113**, with the carbamate-functionalized stereogenic center in the δ-position, exhibited significant levels of diastereoselectivity to give ester **114** (Scheme 6.24). In this case, however, the *syn* addition product **114** was formed as the major isomer.



113 **114, 80%, *dr* 85:15**

Scheme 6.24. Diastereoselective cuprate addition to δ-carbamate-functionalized enoate **113**.

It has been proposed that a directed cuprate addition with a carbamate or a carbonate serving as a reagent-directing functional group may account for the stereochemical outcome of these reactions (see models **115** and **116** in Scheme 6.25) [39, 48].



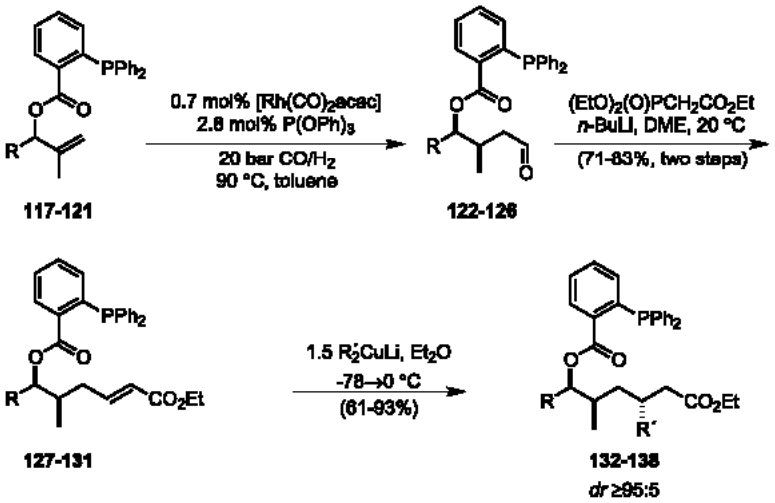
115 **116**

Scheme 6.25. Proposed explanation for directed cuprate addition to carbonates **106** and **107** and carbamate **105**.

A new concept, employing a specifically introduced reagent-directing group [49], allowed more efficient use to be made of substrate direction in conjugate addition of cuprates to acyclic enoates [50]. The *ortho*-diphenylphosphinobenzoyl (*o*-DPPB) functionality was identified as an ideal directing group. This group is easily attached to the substrate through esterification of an appropriate alcohol function. The multifunctional character of this group is notable; it can act as an efficient directing

group for a number of late transition metal-mediated or -catalyzed reactions. To date, directed hydroformylations [51], rhodium-catalyzed domino-type processes [52, 53], and a palladium-catalyzed atropselective biaryl coupling [54] have been described.

Thus, enoates **127–131** were prepared efficiently by means of a combination of an *o*-DPPB-directed stereoselective hydroformylation and a Horner–Wadsworth–Emmons (HWE) olefination (Scheme 6.26). In general, chiral δ-methyl-substituted enoates are known to react non-selectively in lithium dimethylcuprate additions [46]. Conjugate addition reactions between enoates **127–131** and lithium dialkylcuprates, however, gave the corresponding *anti* 1,4-addition products **132–138** in good yields and with high diastereoselectivities [50]. Thus, the combination of *o*-DPPB-directed hydroformylation and *o*-DPPB-directed cuprate addition afforded useful building blocks, with up to four stereogenic centers, for polyketide synthesis (**132–138**, see Scheme 6.26, Tab. 6.4). Control experiments with a corresponding phosphane oxide suggested that the *o*-DPPB group controls both reactivity and stereoselectivity in the course of this conjugate addition reaction. However, it has been found that the stereoselectivity of the *o*-DPPB-directed cuprate addition is a sensitive function of the enoate structure and so is so far limited to the *E* enoates of the general structure shown in Scheme 6.26 [50b].

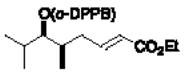
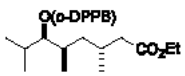
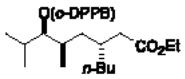
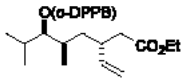
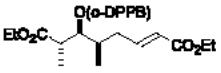
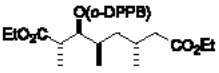
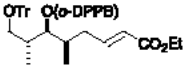
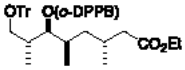
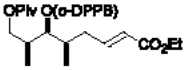
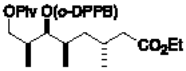
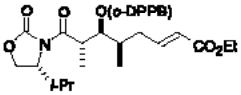
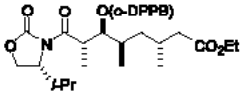


Scheme 6.26. Construction of polyketide building blocks by sequential directed stereoselective hydroformylation and directed cuprate addition with the aid of the reagent-directing *o*-DPPB group. (*o*-DPPB = *ortho*-diphenylbenzoylphosphanyl, DME = dimethoxyethane)

6.1.3
Auxiliary-bound Chiral Michael Acceptors and Auxiliary Chiral Metal Complexes

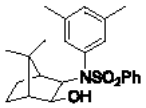
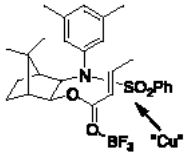
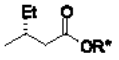
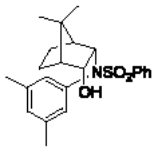
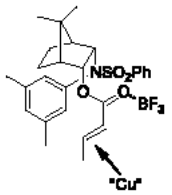
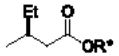
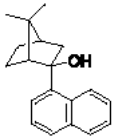
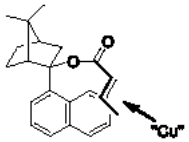
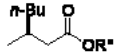
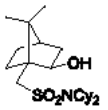
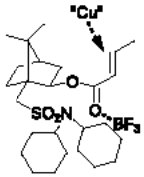
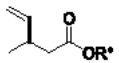
Diastereoselective conjugate additions to chiral Michael acceptors in which the part initially bearing the chiral information is removable (i.e., a chiral auxiliary) provides a means to synthesize enantiomerically pure conjugate adducts. Chiral auxiliaries should ideally be readily available in both enantiomeric forms. They should

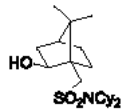
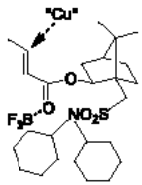
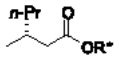
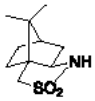
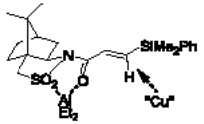
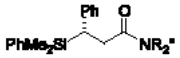
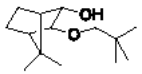
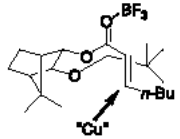
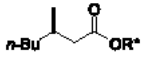
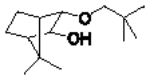
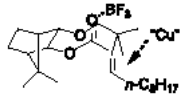
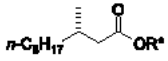
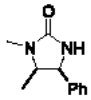
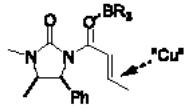
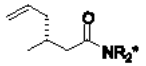
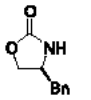
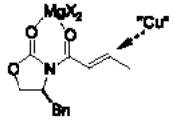
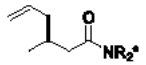
Tab. 6.4. Results of *o*-DPPB-directed cuprate addition to acyclic enoates **127–131** (*o*-DPPB = *ortho*-diphenylphosphinobenzoyl, Tr = triphenylmethyl, Piv = pivaloyl).

Entry	*Enoate*	*Product*	*Yield [%]*	*anti:syn*
1	 **127**	 **132**	93	95:5
2	**127**	 **133**	68	95:5
3	**127**	 **134**	61	80:20
4	 **128**	 **135**	68	95:5
5	 **129**	 **136**	71	86:14
6	 **130**	 **137**	60	85:15
7	 **(–)-131**	 **(–)-138**	75	95:5

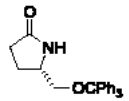
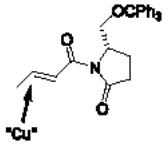
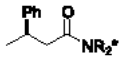
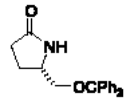
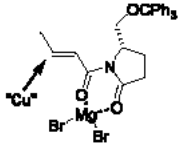
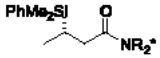
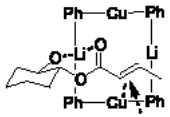
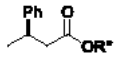
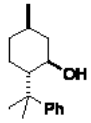
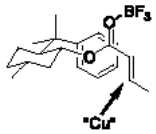
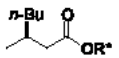
furthermore be easily introducible into the substrate and removable from the product. Thus, the most common attachment of an appropriate auxiliary occurs by means of an ester or an amide linkage to the carbonyl group of an α,β-unsaturated carbonyl derivative. A number of auxiliaries have been developed for this purpose and a comprehensive review up to 1992 is available [1g]. A personal selection of useful auxiliaries for achieving high levels of stereoselectivity is given in Tab. 6.5. In each case the assumed reactive conformation is provided, allowing the major stereoisomer to be predicted for each substrate type.

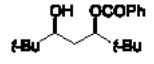
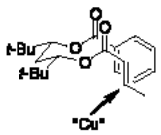
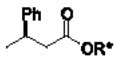
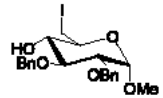
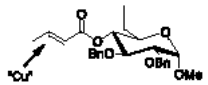
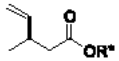
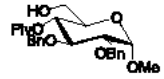
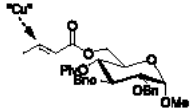
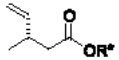
Tab. 6.5. A selection of auxiliary controlled diastereoselective conjugate additions with organocopper reagents. (TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine, Piv = pivaloyl)

Entry	*Auxiliary R**	*Reagents*	*Assumed Reactive Conformation*[a]	*Product*	*de [%]*	*Ref.*
1		EtCu $BF_3{\cdot}OEt_3$			>99	55c–e
2		EtCu $BF_3{\cdot}OEt_3$			>99	55c–e
3		*n*-BuCu, TMSI			98	56
4		(vinyl)Cu $P(n\text{-}Bu)_3$ $BF_3{\cdot}OEt_3$			98	55a, b

5		*n*-PrCu P(*n*-Bu)$_3$ BF_3·OEt_3			97	55a, b
6		Ph_2CuLi P(*n*-Bu)$_3$ $EtAlCl_2$			95	57
7		MeCu P(*n*-Bu)$_3$ BF_3·OEt_3			94	58
8		MeCu P(*n*-Bu)$_3$ BF_3·OEt_3			98	58
9		(allyl)Cu TMEDA Bu_2BOTf			98	59
10		(allyl)MgCl CuBr·SMe_2 BF_3·OEt_2			97	60

Tab. 6.5 (continued)

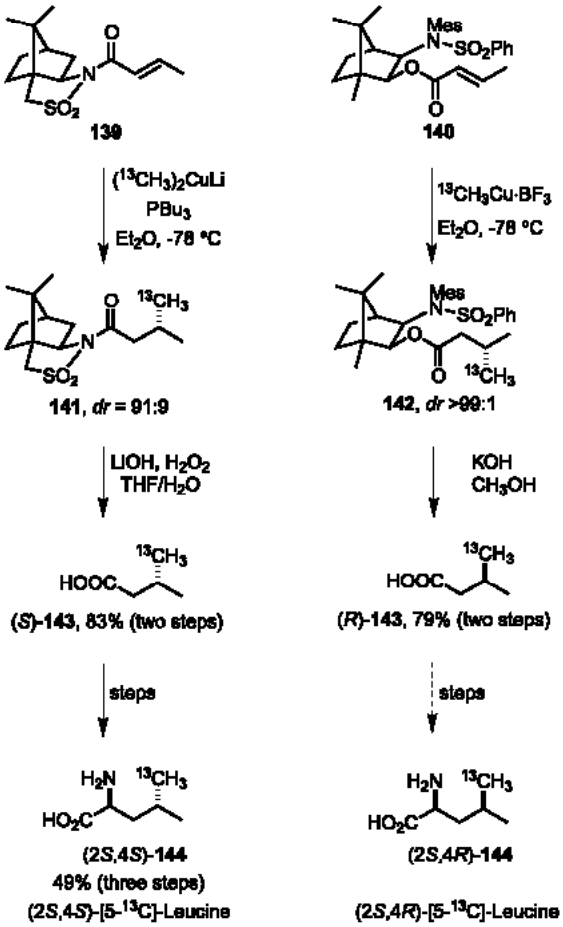
Entry	Auxiliary R*	Reagents	Assumed Reactive Conformation[a]	Product	de [%]	Ref.
11		PhMgCl $CuBr \cdot SMe_2$			95	61a
12		$MgBr_2$ $(PhMe_2Si)_2CuLi$			78	61b
13		Ph_2CuLi			88	62
14		*n*-BuCu $BF_3 \cdot OEt_2$			>99	63

15		Ph_2CuLi $BF_3{\cdot}OEt_3$			92	64
16		(vinyl)MgBr $CuBr{\cdot}SMe_2$			>98	65
17		(vinyl)MgBr $CuBr{\cdot}SMe_2$			72	65

a) A bold arrow indicates attack from the upper side or the front side, respectively. A dashed arrow indicates attack from the lower or the back side, respectively.

Most of the useful auxiliaries are chiral amine or alcohol derivatives readily available from the chiral pool, and most of them possess rigid cyclic or bicyclic structures to allow efficient differentiation of the two competing diastereomorphic transition states. In some cases, additional rigidity was achieved with the aid of an external chelating Lewis acid (entries 6, 10, 12). In certain cases, however, acyclic auxiliaries may also be useful (see entry 15).

Selective labelling of the two diastereotopic methyl groups of L-leucine (144) has enabled their fates during secondary metabolic reactions to be elucidated [66]. Moreover, in the context of protein interactions, differentiation of the leucine *pro-R* and *pro-S* methyl groups in protein NMR spectra allows molecular recognition phenomena to be studied [67]. Recently, efficient routes to both forms of ^{13}C-labeled leucine, based on application of an auxiliary-controlled stereoselective conjugate addition reaction (Scheme 6.27) have been described [68]. Thus, starting

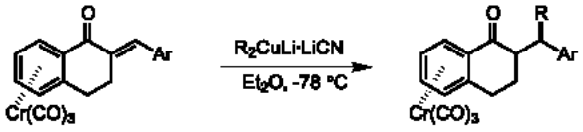


Scheme 6.27. Auxiliary-controlled stereoselective cuprate addition as the key step for the construction of both diastereomeric forms of [5-^{13}C]-leucine 144.

from either enamide **139** or **140**, it was possible to obtain both enantiomers of the [5-^{13}C]-3-methylbutanoic acid **143**. An additional three steps transformed the acids **143** into the desired leucines **144**.

As well as organic chiral auxiliaries, organometallic fragments have found some application as chiral auxiliaries in conjugate addition reactions. Particularly noteworthy are chiral molybdenum allyl complexes [69], chiral iron complexes [70], and planar chiral arene chromium species [71].

An interesting chromium system example is represented by complex **145**. Addition of cyano-Gilman cuprates occurred with complete diastereoselectivity to give conjugate adducts **146** (Scheme 6.28). Interestingly, the opposite diastereomer was accessible by treatment of enone **145** with a titanium tetrachloride/Grignard reagent combination [71c].

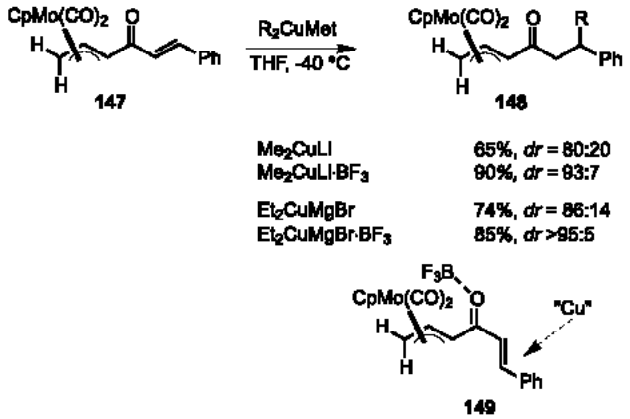


145 **146**

Ar= Ph, *p*-MePh, *o*-MePh **85-95%, *dr*>99:1**
R = allyl, Me, Ph, cyclopropyl, *n*-butyl

Scheme 6.28. Diastereoselective cuprate addition to a planar chiral arylchromium enone complex **145**.

When the chiral molybdenum π-allyl-substituted enone **147** was treated with lithium dimethylcuprate, formation of adduct **148** with fair selectivity was observed (Scheme 6.29) [69]. Interestingly, higher selectivities were obtained in the presence of boron trifluoride etherate. It is assumed that Lewis acid coordination induces the *s-trans* reactive conformation **149** [64]. Consequently, nucleophile attack *anti* to the molybdenum fragment should afford the major diastereomer **148**.



147 **148**

Me_2CuLi **65%, *dr* = 80:20**
$Me_2CuLi{\cdot}BF_3$ **90%, *dr* = 93:7**

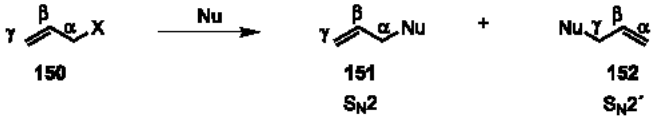
$Et_2CuMgBr$ **74%, *dr* = 86:14**
$Et_2CuMgBr{\cdot}BF_3$ **85%, *dr*>95:5**

149

Scheme 6.29. Diastereoselective cuprate addition to chiral molybdenum π-allyl enone complex **147**.

6.2 Allylic Substitution

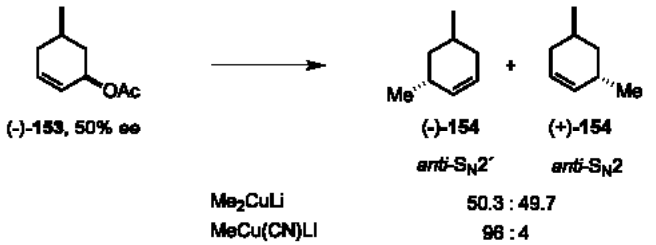
Treatment of allylic substrates **150**, possessing suitable leaving groups X in their allylic positions, with organocopper reagents may result either in an S_N2-type process (α-attack) or alternatively in an S_N2' one (γ-attack), giving the substitution products **151** and **152**, respectively (Scheme 6.30) [1j].



X = Hal, OH, OCOR, OR, OCONHR, $OP(O)(OR)_2$, OSO_2R, SO_2R, SR_4, NR_3^+, O/S-benzothiazol-2-yl, etc.

Scheme 6.30. Potential reaction products from allylic substitution with organocopper reagents (= Nu).

The ratio of α-attack to γ-attack is a subtle function of substrate structure (steric and electronic properties), the leaving group, and also the nature of the organocopper reagent employed. Like the S_N2 process, the S_N2' reaction with organocopper reagents generally occurs with inversion of configuration, resulting from the attack of the organocopper reagent *anti* to the leaving group in the allylic position. An instructive example is offered in the reaction of substrate **153** in Scheme 6.31. Treatment of the enantiomerically enriched cyclohexenyl acetate **153** with lithium dimethylcuprate yielded the racemate **154**. Hence, for the sterically unbiased substrate **153**, both S_N2 and S_N2' attacks took place, in a ratio of approximately 1:1. Interestingly, when the organocopper reagent was changed to the lower order methylcyanocuprate, a clear preference for the S_N2' pathway was found [72].



Scheme 6.31. Different results of allylic substitution of cyclohexenyl acetate ( )-**153** with dimethylcuprate and with a lower order cyano cuprate.

To explain the stereochemistry of the allylic substitution reaction, a simple stereoelectronic model based on frontier molecular orbital considerations has been proposed (**155**, Fig. 6.2). Organocopper reagents, unlike C-nucleophiles, possess filled d-orbitals (d^{10} configuration), which can interact both with the π^*-(C=C) orbital at the γ-carbon and to a minor extent with the σ^*-(C X) orbital, as depicted

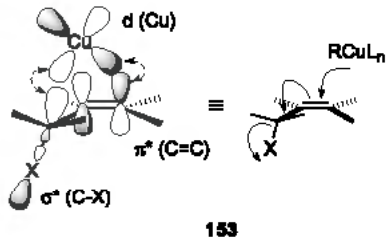
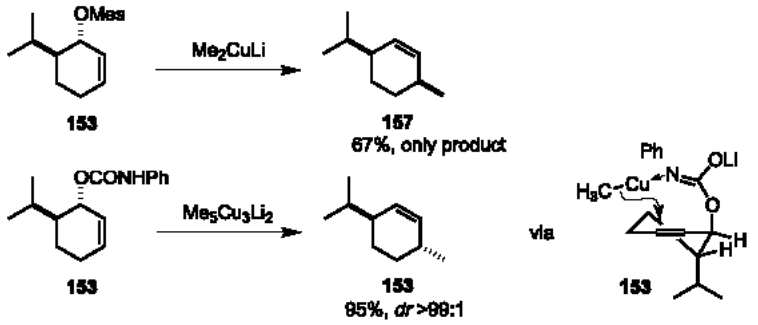


Fig. 6.2. Frontier orbital-based model to explain the stereochemistry of allylic substitution.

in Fig. 6.2 [73]. To achieve optimal orbital overlap, the σ^*-orbital of the C X bond should be aligned coplanar to the alkene π-system.

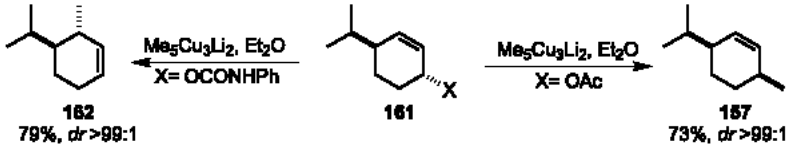
Interestingly, this intrinsic stereoelectronic control over allylic substitution can be overridden when a reagent-coordinating leaving group is employed. Suitable leaving groups have been found in carbamates [74, 75], (O/S)-benzothiazoles [76, 77] (Scheme 6.32) and, very recently, the *ortho*-diphenylphosphinobenzoyl (*o*-DPPB)-group was identified as an efficient reagent-directing leaving group (Scheme 6.44) [91].



Scheme 6.32. Different stereochemical results with mesylate (156) and carbamate (158) leaving groups upon allylic substitution with organocuprates.

When the non-coordinating mesitoate system **156** was treated with lithium dimethylcuprate, formation of the *anti*-S_N2' substitution product **157** was observed. Notably, the exclusive formation of the γ-substitution product is the result of severe steric hindrance at the α-position, originating from the adjacent isopropyl group [78]. Conversely, the corresponding carbamate **158** was reported, on treatment with a higher order cuprate, to form the *syn*-S_N2' product **159** exclusively [74]. The lithiated carbamate is assumed to coordinate the cuprate reagent (see **160**), which forces the *syn* attack and gives *trans*-menthene (**159**).

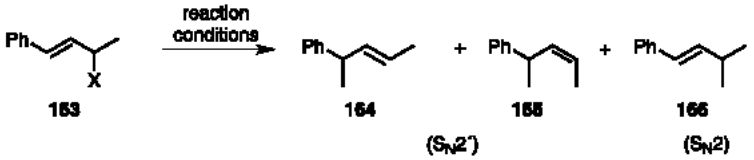
Associated with the propensity to intramolecular delivery of the organocopper reagent is the benefit of high regioselectivity, since an intramolecular trajectory prohibits the alternative α-attack. This is best exemplified by the reaction behavior of the cyclic system **161** (Scheme 6.33). For this substrate, γ-attack is sterically hindered. Hence, treatment of the acetate of **161** with a higher order methyl cuprate



Scheme 6.33. Different stereochemical and regiochemical results with acetate (→**157**) and carbamate (→**162**) leaving groups on allylic substitution of **161** with a higher order methylcuprate.

exclusively gave the S_N2-type product **157**. Conversely, the carbamate of **161** is able not only to direct the stereochemistry to produce a *syn*-attack but also permits the exclusive formation of the S_N2' product **162** [74]. Similar results were obtained upon treatment of **161** with silylcuprates [79]. The generalization can therefore be made that carbamate leaving groups induce high γ-selectivity in allylic substitution with organocuprates, irrespective of steric hindrance at the γ-position in the allylic framework.

For acyclic allylic substrates the situation is more complex, since a larger number of reactive conformations, and hence corresponding transition states, compete. Thus, methyl cinnamyl derivatives **163** (X = OAc), upon treatment with lithium dimethylcuprate, mainly gave the S_N2 substitution product **166** (entry 1, Tab. 6.6 and Scheme 6.34) [80]. The preference for the S_N2 product is expected, since deconjugation of the alkene system is electronically unfavorable.



Scheme 6.34. Leaving group and reagent dependence of allylic substitution in acyclic derivative **163**.

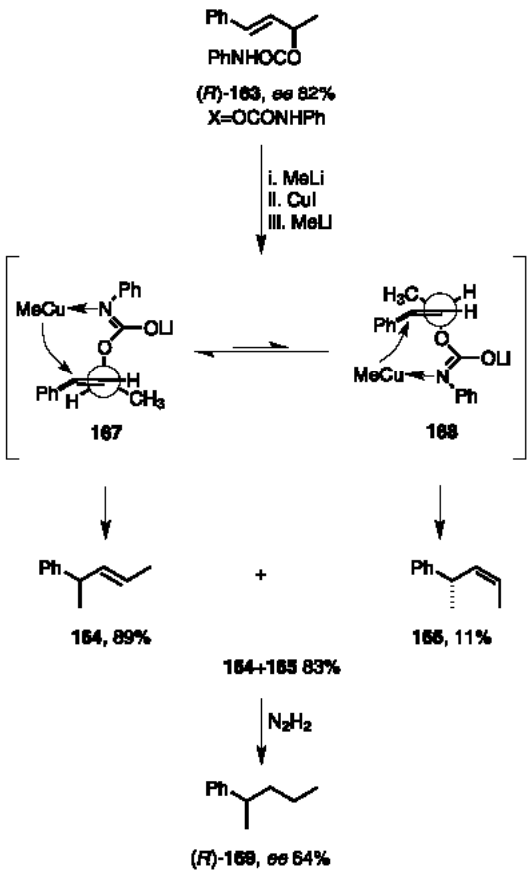
Tab. 6.6. Results of allylic substitution of styrene system **163** with organocopper reagents.

Entry	*X*	*Reaction conditions*	164:165:166	*Yield [%]*	*Ref.*
1	OAc	Me_2CuLi[a]	4:0:96	>99	80
2	OAc	MeCu(CN)Li[a]	39:12:49	—[c]	81
3	OCONHPh	i. MeLi, ii. CuI, iii. MeLi[b]	89:11:0	—[c]	75, 80

a) Et_2O.
b) THF.
c) Yields are not given in the original literature.

As already noted, lower order cyanocuprates are more S_N2'-selective reagents. On treatment with acetate **163**, however, a mixture of the two regioisomers was obtained (entry 2) [81]. In addition, γ-alkylation had taken place with ca. 25% loss of double bond configuration [82].

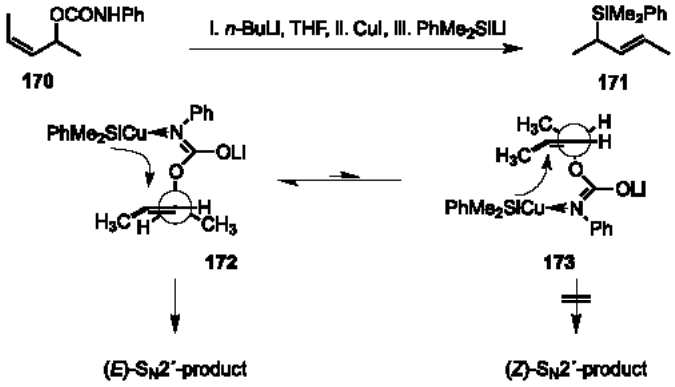
Better results were obtained for the carbamate of **163** (entry 3) [75, 80]. Thus, deprotonation of the carbamate **163** with a lithium base, followed by complexation with copper iodide and treatment with one equivalent of an alkyllithium, provided exclusive γ-alkylation. Double bond configuration was only partially maintained, however, giving **164** and **165** in a ratio of 89:11. The formation of both alkene isomers is explained in terms of two competing transition states: **167** and **168** (Scheme 6.35). Minimization of allylic $A^{1,3}$ strain should to some extent favor transition state **167**. Employing the enantiomerically enriched carbamate (*R*)-**163** (82% *ee*) as the starting material, the proposed *syn*-attack of the organocopper nucleophile could then be as shown. Thus, after substitution and subsequent hydrogenation, (*R*)-2-phenylpentane (**169**) was obtained in 64% *ee* [75].



Scheme 6.35. Interpretation of the chirality transfer during the course of allylic substitution of acyclic carbamate derivative (*R*)-**163**.

As a consequence of this model, it should be foreseeable that increasing allylic $A^{1,3}$ strain – arising from employment of a *Z* alkene system, for example – should favor transition state **167** even more, giving higher levels of *E* selectivity for the

corresponding allylic substitution product. Accordingly, treatment of the *Z* allylic carbamate **170** with the mixed silyl cuprate resulted in exclusive formation of the *E* alkene **171** (Scheme 6.36) [83]. Interestingly, the *Z* allylic substrates also provide higher *E* selectivities in the case of non-directed allylic substitutions.



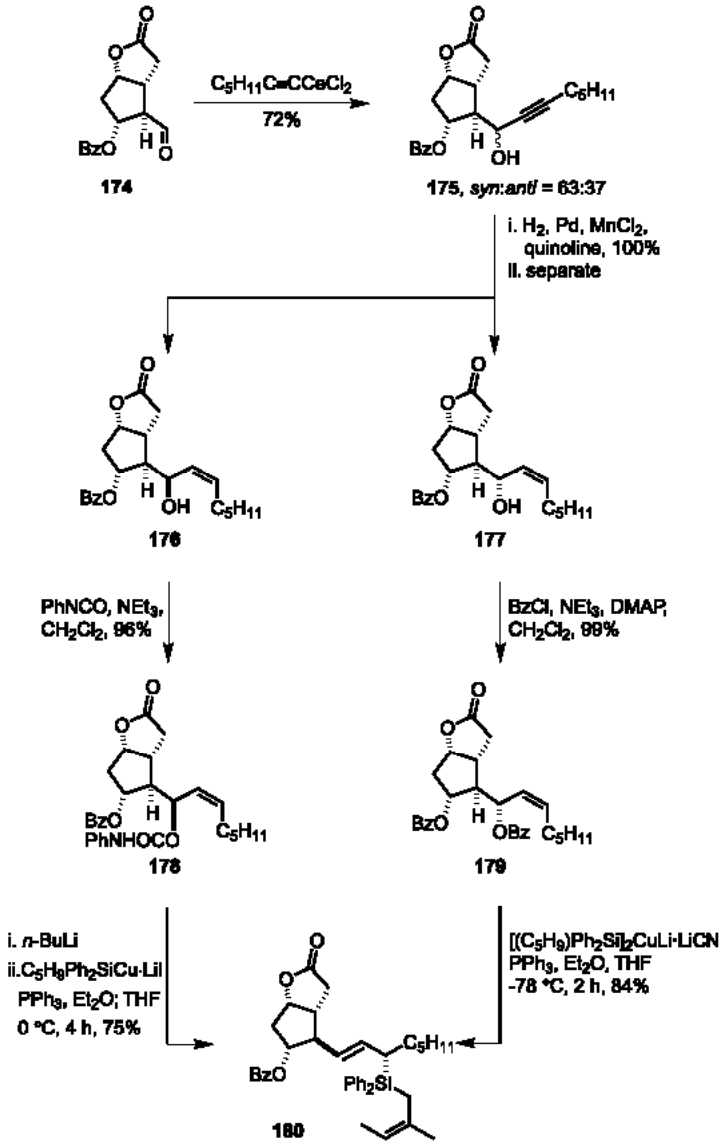
Scheme 6.36. Regioselective allylic substitution of *Z* carbamate **170** with a silylcuprate reagent.

This knowledge was elegantly exploited in a recent synthesis of prostaglandins (Scheme 6.37). The starting point was a mixture of diastereomeric propargylic alcohols **175**, obtained from a non-selective 1,2-addition of an alkynylcerium reagent to aldehyde **174**. Subsequent *cis* hydrogenation with a palladium catalyst gave the diastereomeric *Z* allylic alcohols **176** and **177**. The two diastereomers were separated and transformed either into the carbamate **178** or into the benzoate **179**. Allylic substitution of both substrates with phosphine-modified silylcuprate reagents converged to the formation of a single allyl silane **180** [84].

Upon allylic substitution with organocopper reagents, both *E* and *Z* allylic carbamates generally furnish *E* alkene systems, either exclusively or preferentially. In contrast, it was recently found that *E* allylic carbamates bearing silyl groups in their *γ*-positions provide remarkable *Z* selectivities under reaction conditions involving mixed organomagnesium/copper reagents (Scheme 6.38) [85].

Thus, enantiomerically pure carbamate (*E*)-**181** furnished the *Z* allylsilane **182** in high yield and with good *Z* selectivity. After transformation into the saturated alcohol **184**, an enantiomeric excess of 88% was determined, consistent with the *E*:*Z* ratio of the allylsilane with respect to the *ee* of the starting compound (entry **1**, Tab. 6.7). On switching to an isobutyl organocopper reagent obtained from the corresponding isobutyllithium, however, the carbamate (*E*)-**181** furnished the *E* allylsilane **183** (entry 2). Conversely, both reagent types reacted with the *Z* isomer of **181** to give the *E* allylsilane **183** (entries 3 and **4**). To explain the inverse stereochemical outcome of allylic substitution of the *E* vinylsilane **181** with the magnesium/copper reagents, two arguments have been put forward (Scheme 6.39).

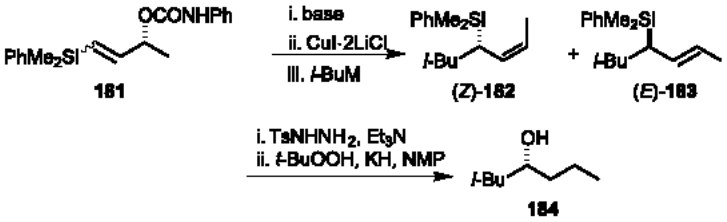
According to these, reaction takes place either through the sterically less favorable transition state **185** or by a pathway involving an *exo* attack of the Grignard reagent on the copper-complexed carbamate, as shown in **187** [75, 85]. For *Z* car-



Scheme 6.37. Allylic substitution with silylcuprates in the course of a prostaglandin synthesis.

barnate **181**, minimization of allylic $A^{1,3}$ strain again seems to dictate the stereochemical outcome of the allylic substitution, irrespective of the reagent employed [85].

As well as coordinating leaving groups, a second general solution to the problem of obtaining high S_N2' selectivities makes use of sulfonate leaving groups in combination with Lewis acid-activated organocopper reagents [86–89]. For example, the *Z* γ-mesyloxy enoate **189** reacted with lithium methylcyanocuprate-boron trifluoride

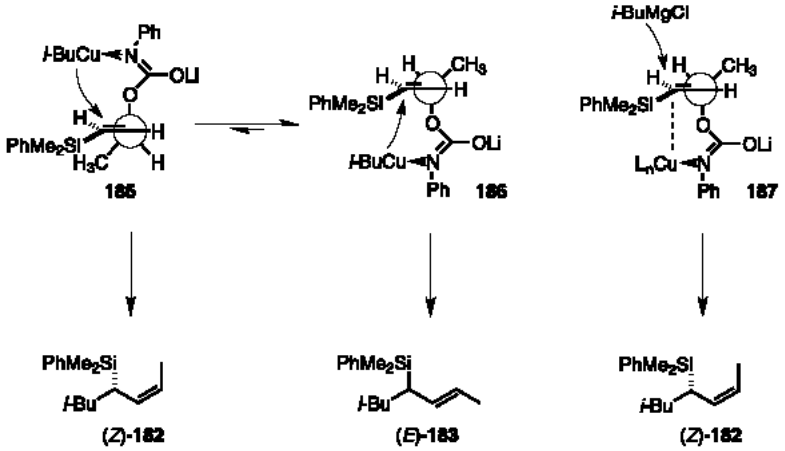


Scheme 6.38. Influence of reagent and alkene geometry on allylic substitution of γ-silyl-substituted allylic carbamates **181** (Ts = *para*-toluenesulfonyl, NMP = *N*-methylpyrrolidinone).

Tab. 6.7. Results of allylic substitution of γ-silyl-substituted allylic carbamates **181** with organocopper reagents.

Entry	*Substrate*	*Base*[a]	*M*	182:183	*Yield*[b] *[%]*	*ee* 184 *[%]*
1	(*E*)-**181**	*n*-BuLi	MgCl	94:6	90	88
2	(*E*)-**181**[c]	*n*-BuLi	Li	9:91	69	—
3	(*Z*)-**181**[d]	MeLi	MgCl	3:97	93	92
4	(*Z*)-**181**[d]	MeLi	Li	<1:99	93	94

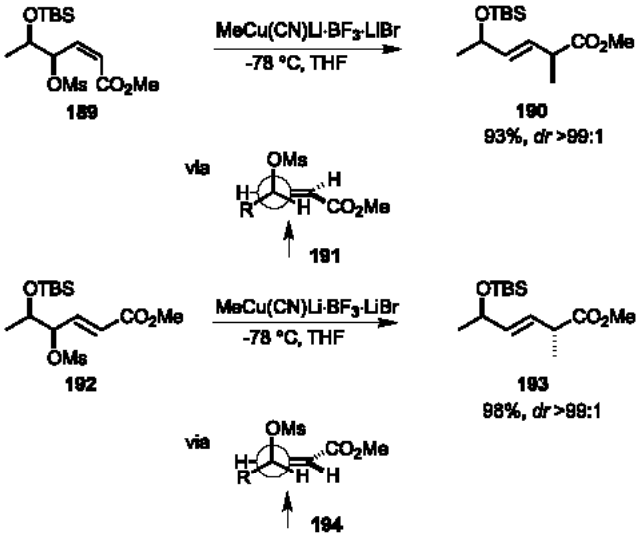
a) THF, 0 °C.
b) yield of **182** and **183**.
c) Racemic starting material was employed.
d) 96% *ee*, *E*:*Z* — 3:97.



Scheme 6.39. Interpretation of the results of allylic substitution of γ-silyl-substituted allylic carbamates.

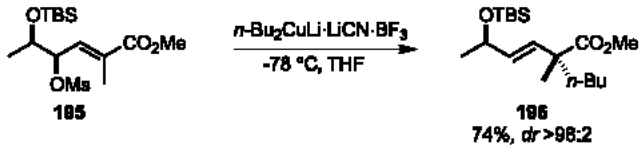
to give the 1,4-*syn*-configured β,γ-unsaturated ester **190** in high yield and with good stereoselectivity (Scheme 6.40). Interestingly, the corresponding *E* enoate **192**, under identical conditions, gave the 1,4-*anti*-configured product **193** [86]. Thus, olefin geometry provides a convenient handle with which to control the configuration of the newly formed stereogenic center [88].

Transition state models that minimize allylic $A^{1,3}$ strain (**191** and **194**) provide



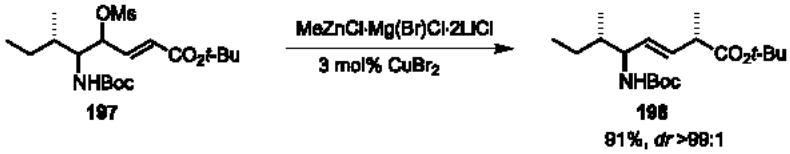
Scheme 6.40. Influence of alkene geometry on stereoselectivity of allylic substitution of mesylates 189 and 192 with boron trifluoride-modified lower order cyanocuprate reagents.

interpretations of the stereochemical outcome of both reactions [86b]. Interestingly, it has been possible to use the method for stereoselective construction of quaternary carbon centers (Scheme 6.41) [87].



Scheme 6.41. Stereoselective construction of a quaternary stereocenter by allylic substitution of mesylate 195 with a boron trifluoride-modified cyano-Gilman cuprate reagent.

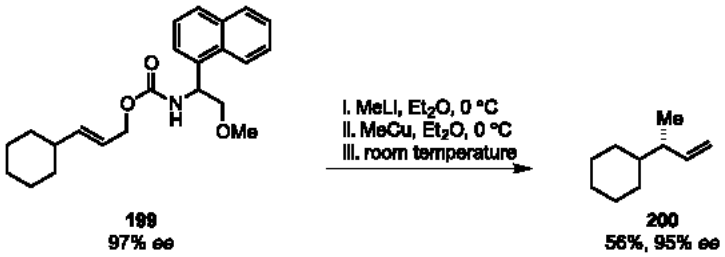
More recent investigations have shown that this reaction operates even under catalytic conditions (3–10 mol% of copper(II) salt), with alkylzinc reagents as the stoichiometric organometallic source (Scheme 6.42) [89].



Scheme 6.42. Copper-catalyzed allylic substitution of mesylate 197 with an organozinc reagent.

To achieve diastereoselectivity in the course of allylic substitution, the controlling chiral information may not only reside in the substrate skeleton but may also be part of the allylic leaving group. Thus, a chiral carbamate has been developed as a

chiral reagent-directing leaving group (as in **199**), transforming an achiral allylic alcohol into the corresponding chiral allylic substitution product **200** with a high degree of enantioselective stereocontrol (Scheme 6.43) [90].



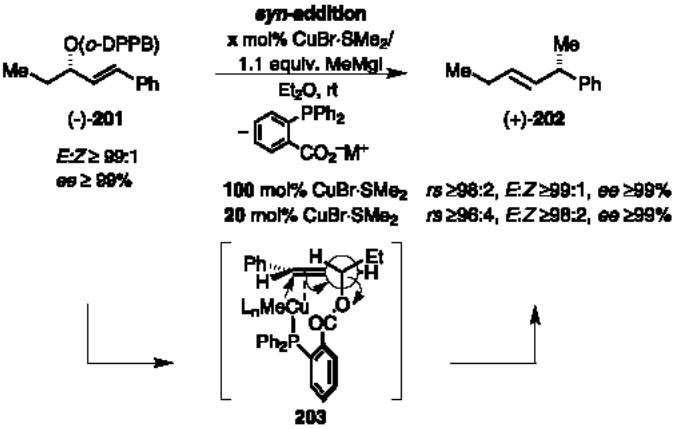
199
97% *ee*

200
56%, 95% *ee*

Scheme 6.43. Control of allylic substitution stereochemistry with the aid of a chiral carbamate leaving group.

Although carbamates and benzothiazoles have proven to be useful reagent-directing leaving groups for allylic substitution with organocopper reagents, the previous discussion has shown that both systems suffer from a number of drawbacks. For instance, control over alkene geometry upon reaction of acyclic derivatives is often unsatisfactory in particular for substrates with *E*-configuration (see Scheme 6.35). As a consequence chirality transfer will be incomplete.

Very recently the *ortho*-diphenylphosphanylbenzoyl (*o*-DPPB) function (see chapter 6.1.2, Scheme 6.26) has been identified as an alternative reagent-directing leaving group which resolves the above described problems [91]. Thus, cinnamyl derivative (−)-**201** gave upon successive treatment with CuBr·SMe_2 and MeMgI the S_N2' substitution product (+)-**202**. The reaction occured with complete control of chemo-, regio- and stereoselectivity which is easily explained via reactive conformation **203**. Interestingly, the amount of copper could be lowered to 20 mol-% without significant loss of selectivity. Noteworthy, to our knowledge this is also the first example of a directed *syn*-selective substitution employing catalytic reaction conditions.



Scheme 6.44. *ortho*-Diphenylphosphinobenzoyl (*o*-DPPB)-group directed allylic substitution with Grignard reagents.

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7
Copper-catalyzed Enantioselective Conjugate Addition Reactions of Organozinc Reagents

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

7.1 Introduction

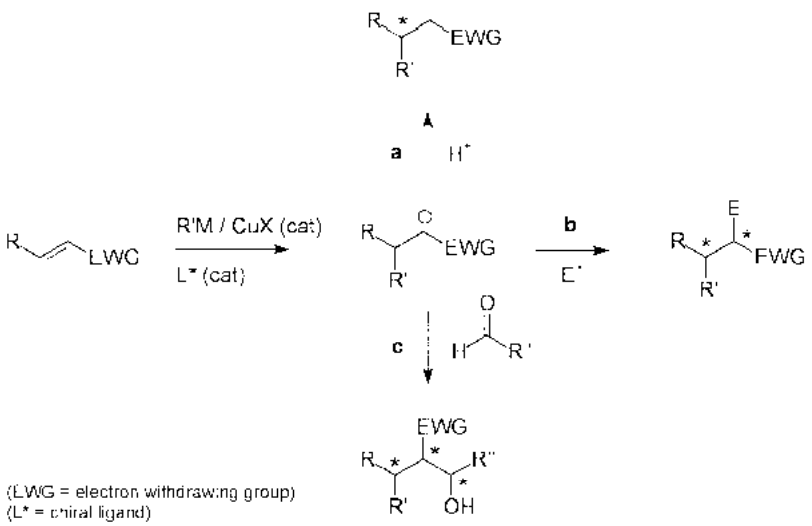
Conjugate addition (1,4-addition) of carbon nucleophiles to α,β-unsaturated compounds is one of the most important carbon–carbon bond-forming strategies in synthetic organic chemistry [1]. The versatility of the conjugate addition is mainly due to the large variety of nucleophiles (organometallic reagents, 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 (non-transferable) ligands are known today [7–9].

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



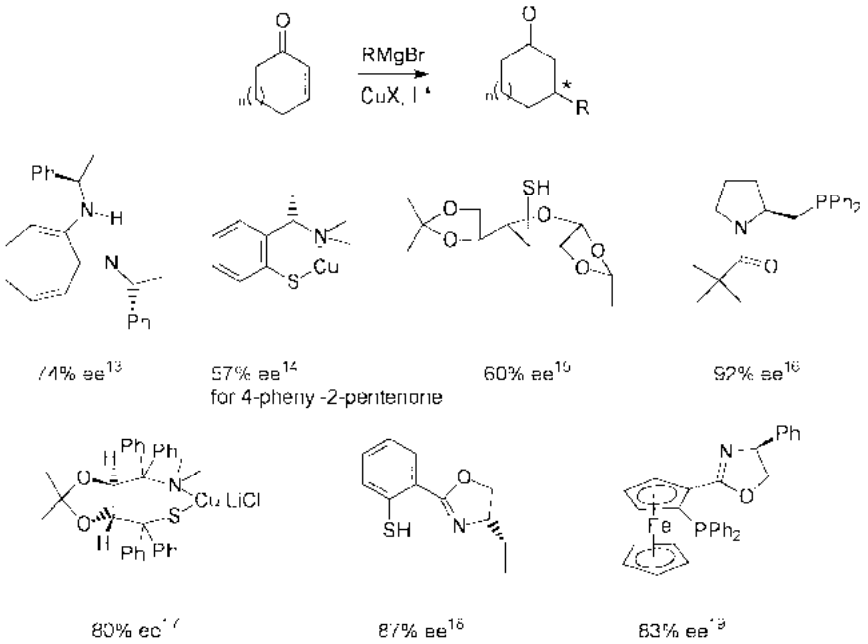
Scheme 7.1. Catalytic conjugate addition and tandem conjugate addition.

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.

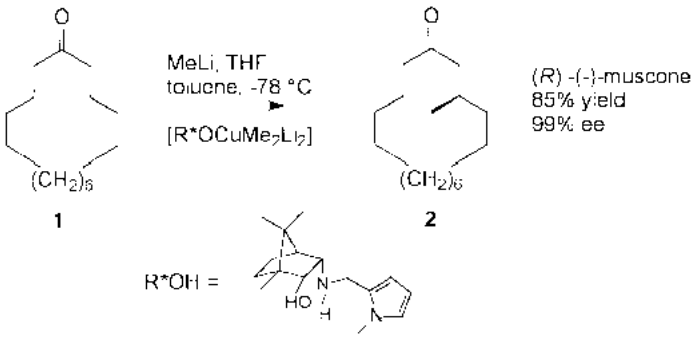
A brief discussion of the most notable achievements obtained with Grignard, organolithium, and organoboron reagents follows. Although Lippard [13] used a chiral *N,N'*-dialkylaminotropone imine copper(I) catalyst in his pioneering work on the asymmetric 1,4-addition of *n*-BuMgBr to 2-cyclohexenone, 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



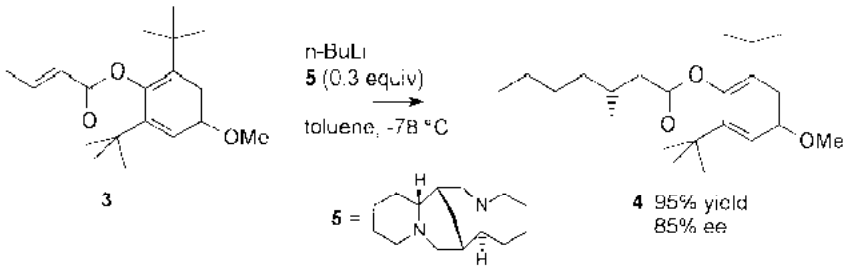
Scheme 7.2. Chiral ligands and catalysts in enantioselective 1,4-additions of Grignard reagents.

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.

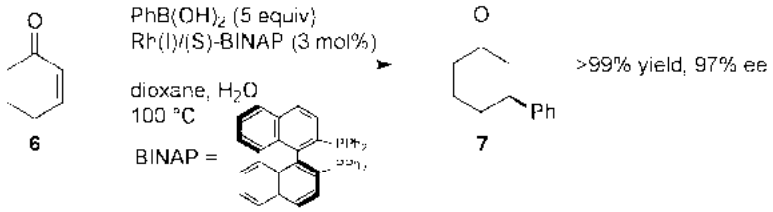
Another successful approach involves the use of chiral donor ligands to affect the aggregation behavior of organolithium species [22]. The oligomeric organolithium reagents are converted by the chiral ligand to more reactive monomeric chiral organolithium species. For instance, the 1,4-addition of *n*-BuLi 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

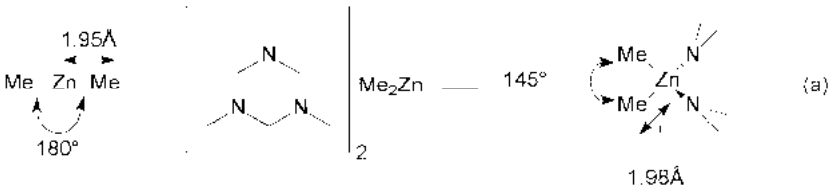
Asymmetric carbon–carbon bond-formation using organozinc reagents has developed into one of the most successful areas of synthetic chemistry in recent years [26]. Although dialkylzinc reagents (R_2Zn) usually react extremely sluggishly with carbonyl compounds and enones [27], effective catalysis may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

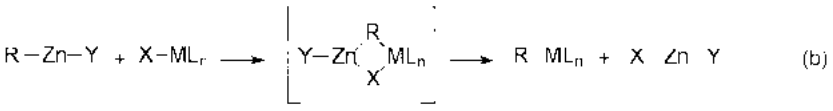
Catalysis can be attributed to two effects:

(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].



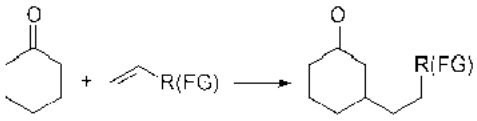


Y = R, halide
M = Ti, Pd, Ni, Cu
X = halide, OTf
L = Ligand

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).

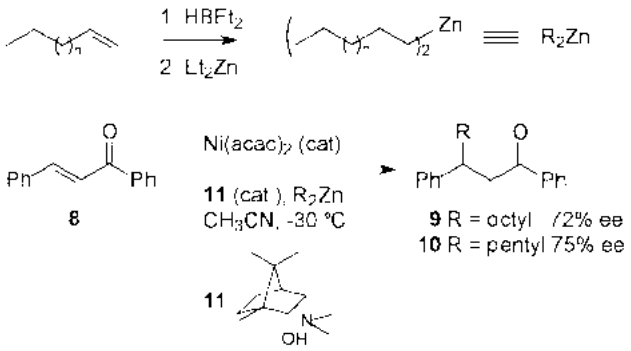


FG – functional group

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

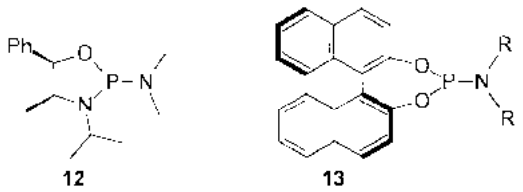
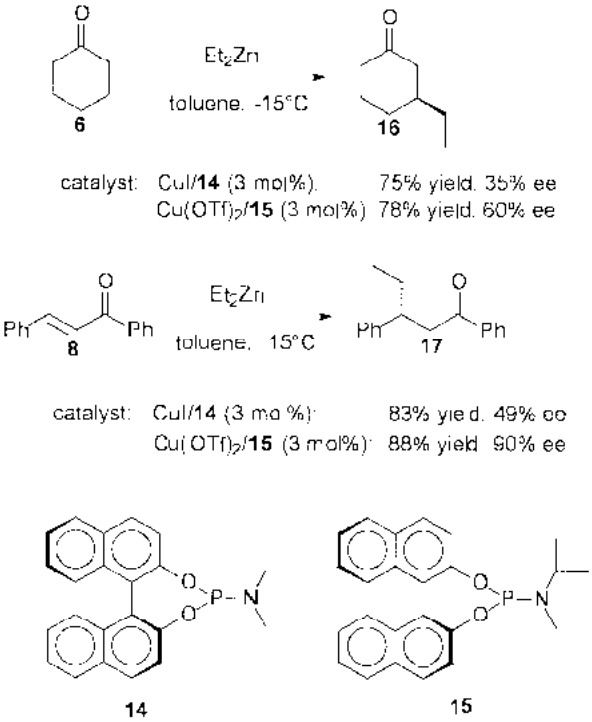


Fig. 7.1. Structures of phosphorus ligands **12** and **13**.

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 *ees* 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 *ees* both with cyclic and with acyclic enones; a feature notably absent with previous catalysts.

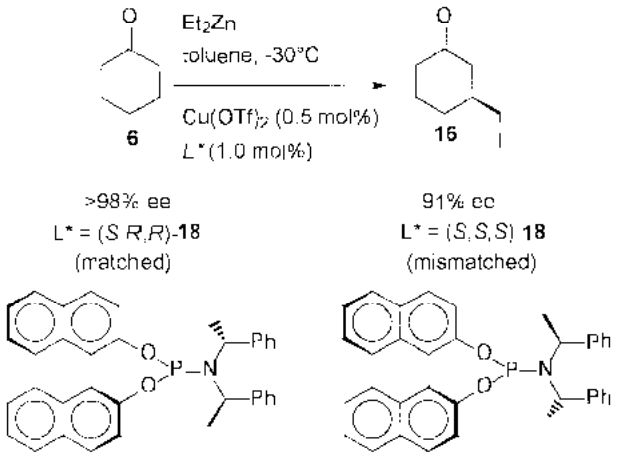
Use of ligand **15**, with a sterically more demanding diisopropylamine moiety, further increased the enantioselectivity.

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.

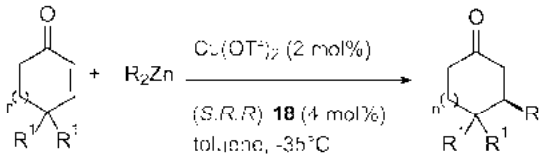
A breakthrough was achieved with chiral phosphoramidite (*S*, *R*, *R*)-**18**, in which a C_2-symmetric (*S*)-binaphthyl unit and a C_2-symmetric (*R*, *R*)-bis-(1-phenylethyl)-amine unit are present (Scheme 7.10), resulting in the enantioselective catalytic **1,4**-addition of Et_2Zn to 2-cyclohexenone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

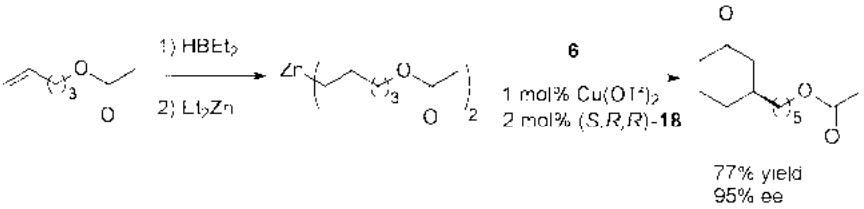


R	R^1	*n*	*Yield (%)*	*ee (%)*
C_2H_5	H	1	94	>98
C_2H_5	H	0	75	10
C_2H_5	H	2	95	>98
C_2H_5	H	3	95	97
C_2H_5	CH_3	1	74	>98
C_2H_5	C_6H_5	1	93	>98
CH_3	H	1	72	>98
CH_3	CH_3	1	68	>98
C_7H_{15}	H	1	95	95
i-C_3H_7	H	1	95	94
$(CH_2)_3C_6H_5$	H	1	53	95
$(CH_2)_3CH(OC_2H_5)_2$	H	1	91	97

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].

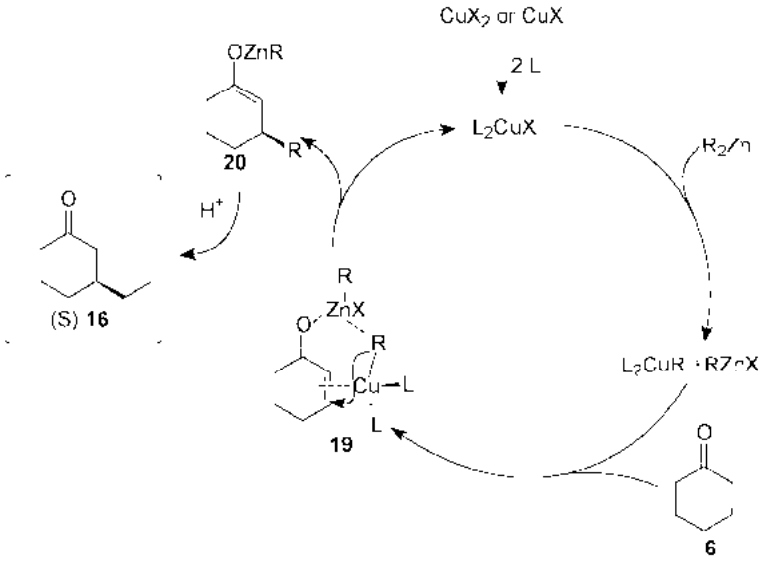
Functionalized alkyl groups are readily introduced through this catalytic procedure, while the level of stereoselectivity is not affected by, for instance, the presence of an ester functionality in the R_2Zn reagent (Scheme 7.11).



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

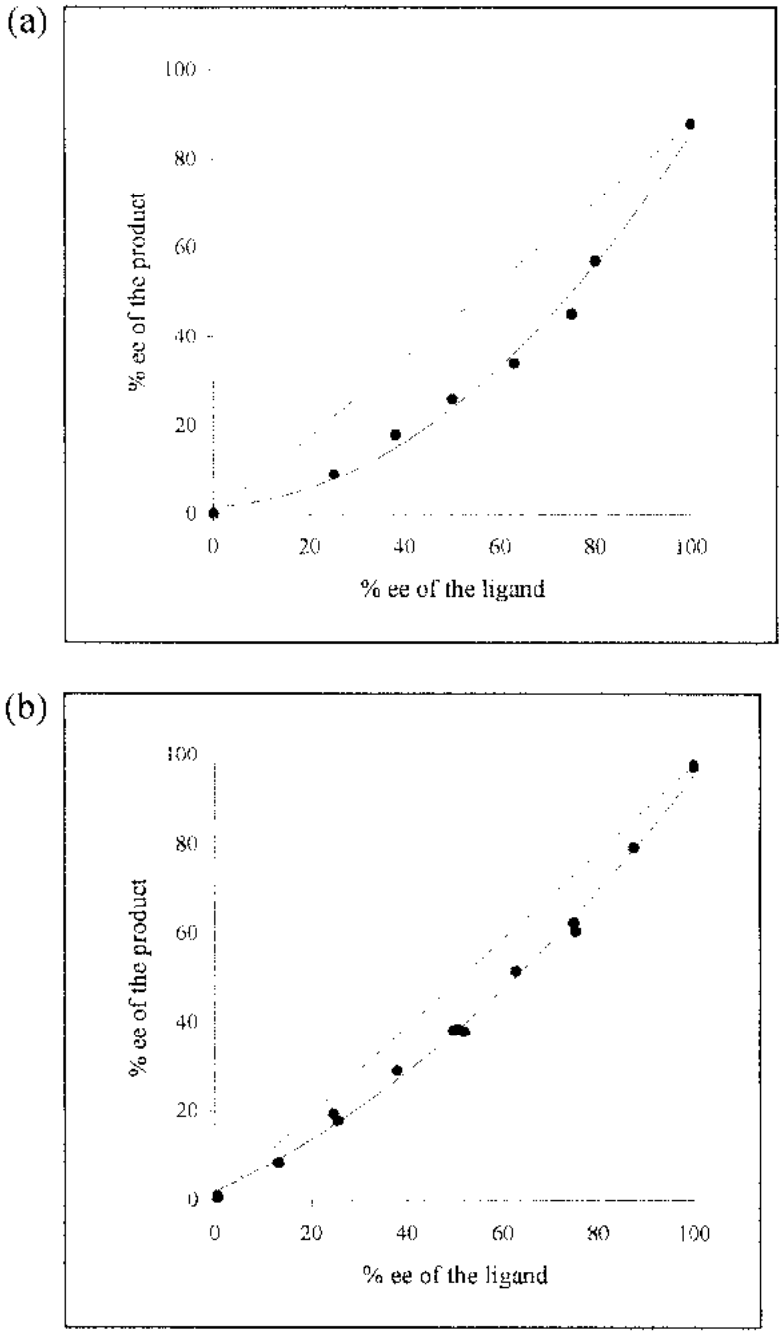


Fig. 7.2. Correlation between the *ee* of the ligand and that of the 1,4-addition product: a) chalcone (ligand **15**) and b) 2-cyclohexenone (ligand **18**).

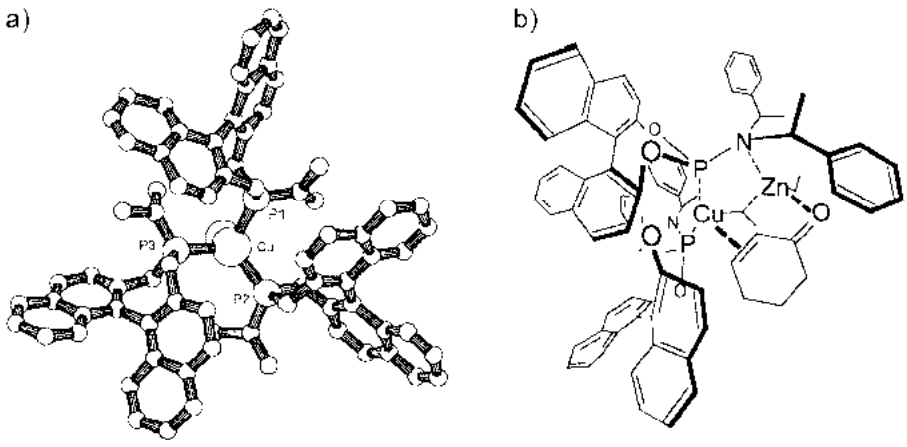
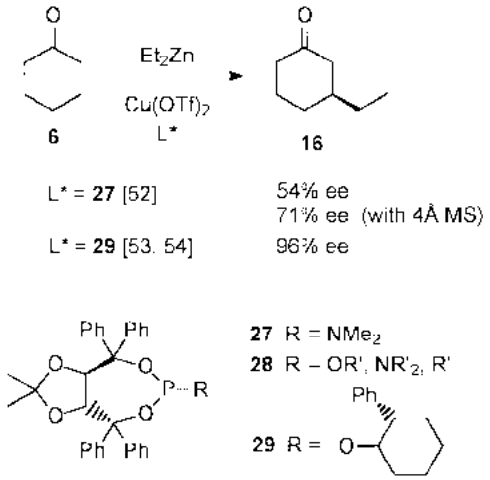


Fig. 7.3. a) X-ray structure of the CuI complex **21** of ligand **14**; b) Possible bimetallic intermediate involved **19** in si-face-selective ethyl transfer to 2-cyclohexenone.

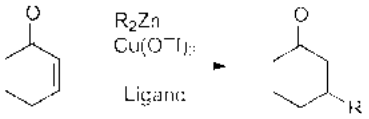
phosphoramidite **27** as a chiral ligand for $Cu(OTf)_2$-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone, affording an *ee* of 54% (Scheme 7.13) [52].



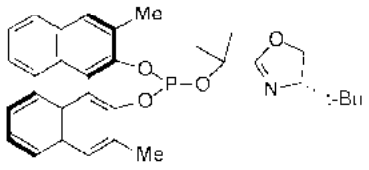
Scheme 7.13. TADDOL-based phosphoramidite ligands in the catalytic 1,4-addition.

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



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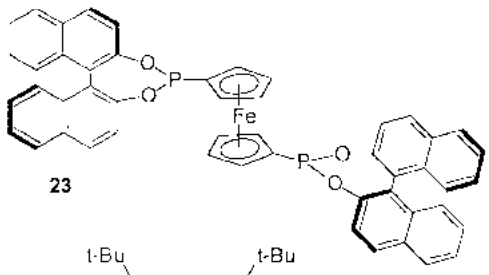

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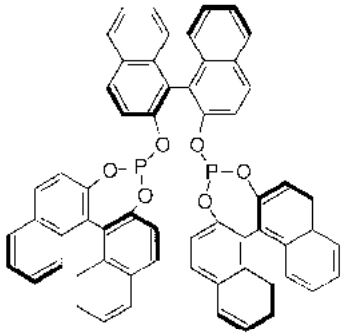

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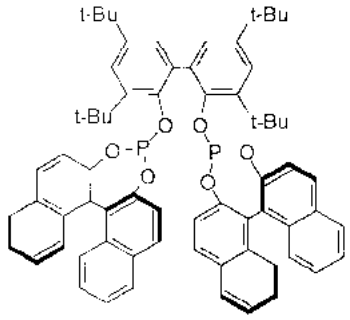

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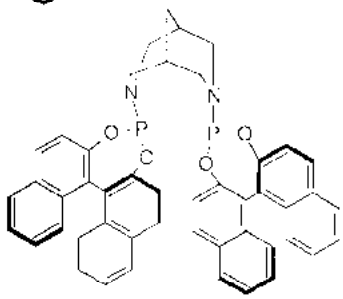

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smallest amine substituent (Me_2N) at phosphorus, whereas in the case of ligand **18** a bulky amine is essential.

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 *ees* 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 *ees* 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

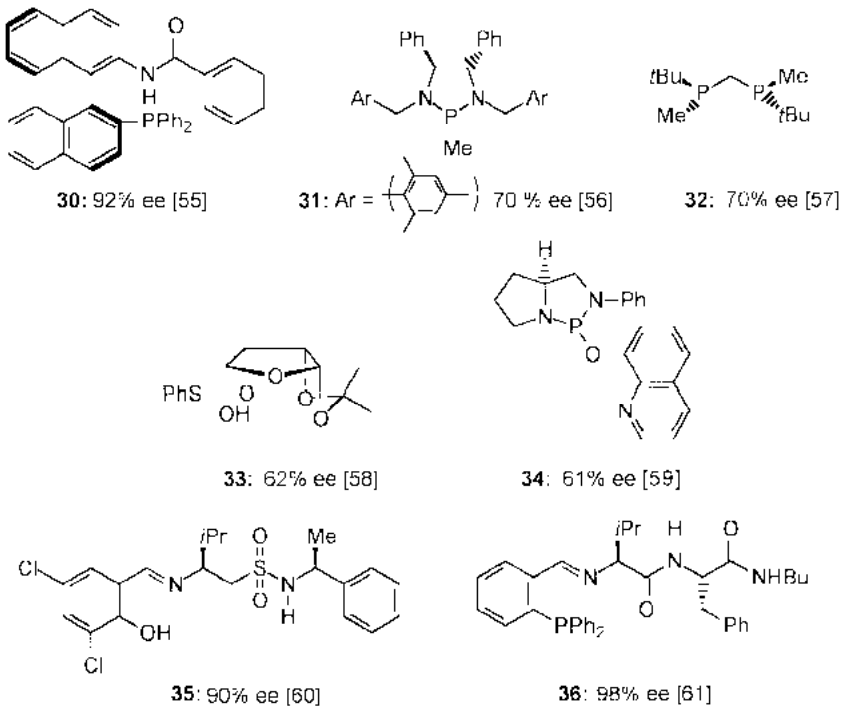


Fig. 7.4. Various chiral ligands used in the copper-catalyzed 1,4-addition of Et_2Zn to 2-cyclohexenone.

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.

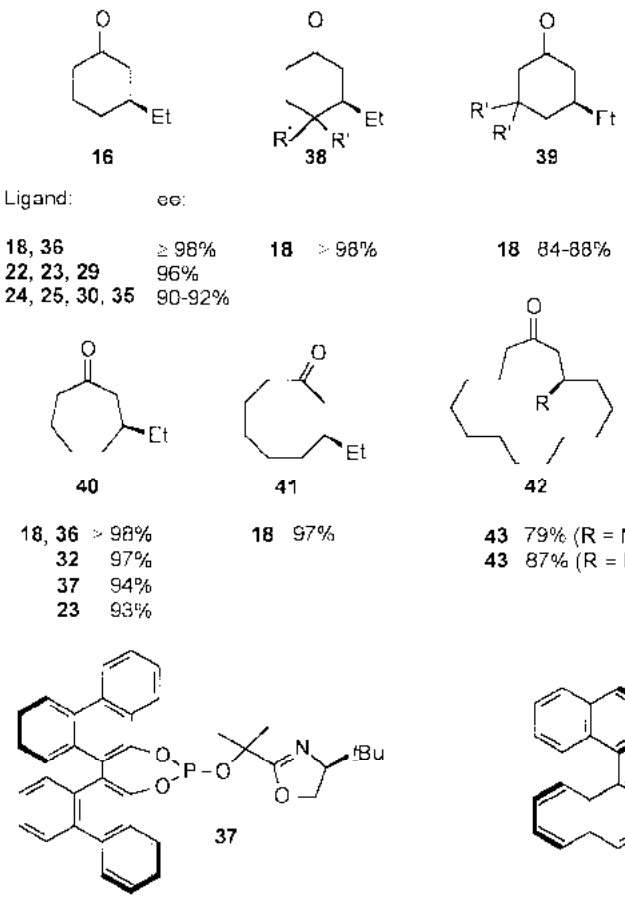
Modular peptide-based phosphine ligands were introduced by Hoveyda, providing excellent stereocontrol in **1,4**-additions to cyclic enones [61]. Enantioselectivities of 97–98% were attained in alkylations of six- and seven-membered cyclic enones using ligand **36**. A major breakthrough in the **1,4**-addition 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 *ees* 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. *Ees* in the range of 90–92% were found with ligands **24**, **25**, **30**, and **35** [49, 55, 60].

Optically active 3-ethylcycloheptanone, with *ees* 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.



(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-

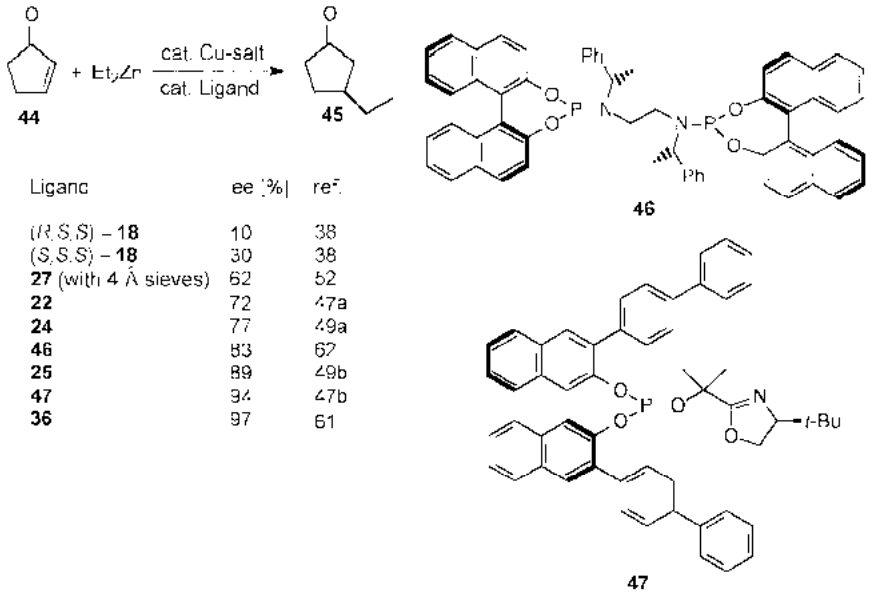
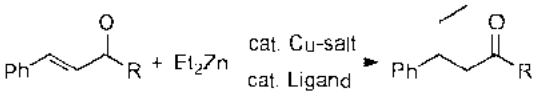


Fig. 7.6. Enantioselective conjugate addition to 2-cyclopentenone.

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].

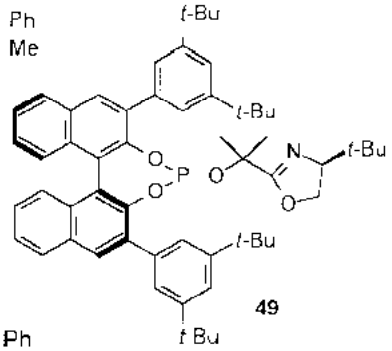
High enantioselectivities (83–89% *ee*) have been obtained with the bidentate ligands **46** [62] and **25** [49b]. The first catalytic 1,4-addition of diethylzinc to 2-cyclopentenone with an *ee* exceeding 90% was reported by Pfaltz, who employed phosphite **47**, bearing biaryl groups at the 3,3′-positions 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)



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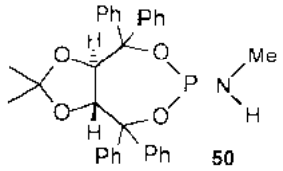

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Fig. 7.7. Enantioselective conjugate addition to acyclic enones.

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 *ees* (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 (*ees* 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 *ees* 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

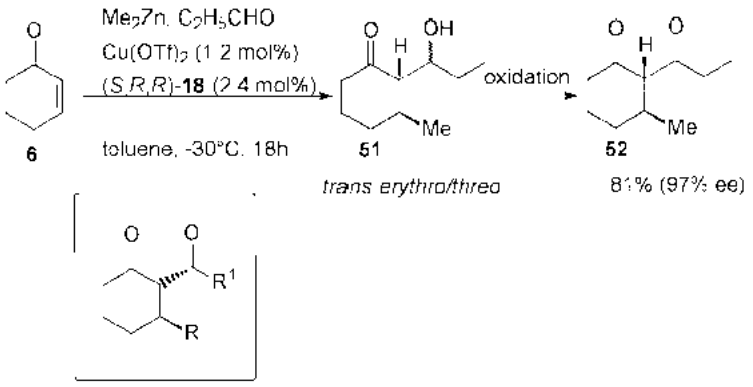
7.4.1 Tandem Conjugate Addition-Aldol Reactions

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-

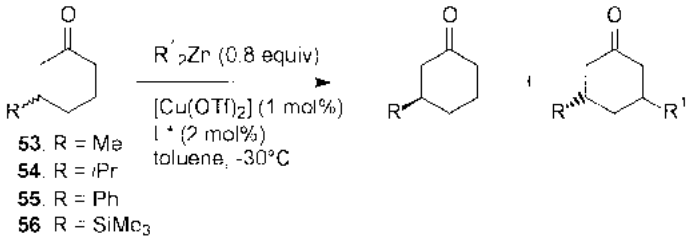


Scheme 7.14. Enantioselective tandem conjugate addition-aldol reactions.

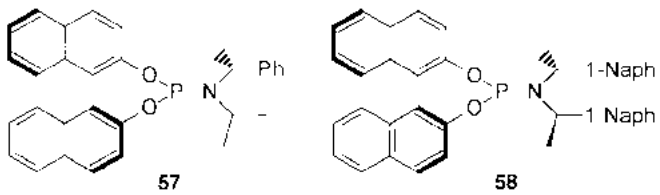
Tab. 7.3. Kinetic resolution of 5-substituted 2-cyclohexenones **53–56** according to Scheme 7.15 (s: stereoselectivity factor).

Ligand	*Enone*	*R'*	*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

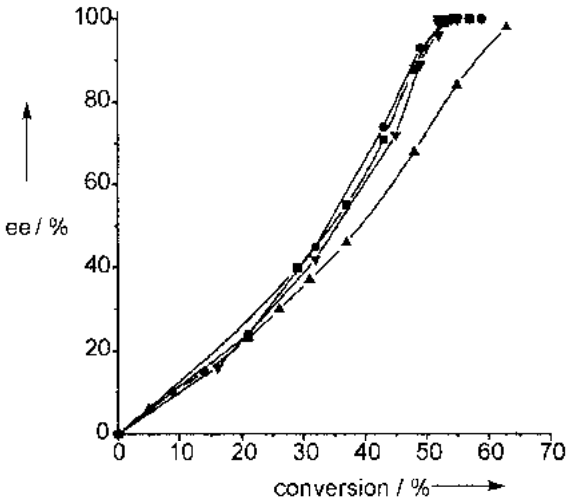
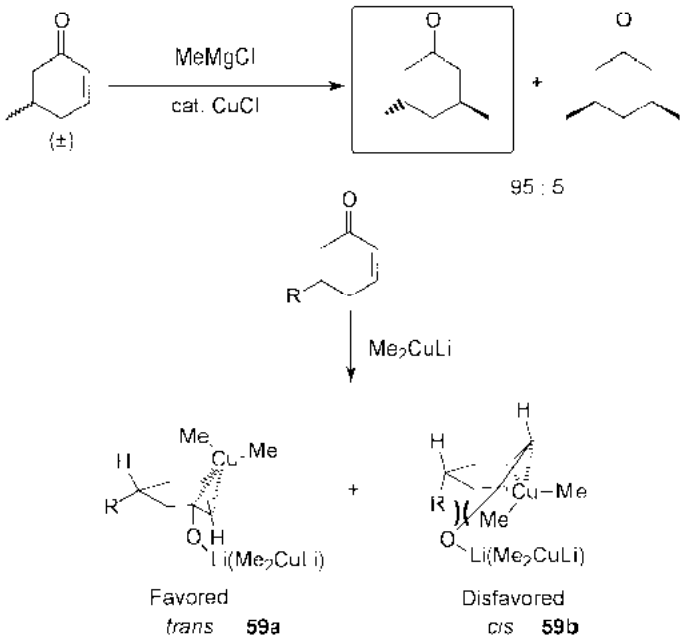


Fig. 7.9. *Ee* against conversion for the kinetic resolution of **53** with (*S*, *R*, *R*)-**18**, $Cu(OTf)_2$, and Et_2Zn (–■–), *i*Pr_2Zn (–▲–), *n*Bu_2Zn (–●–), and Me_2Zn (–▼–).

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].

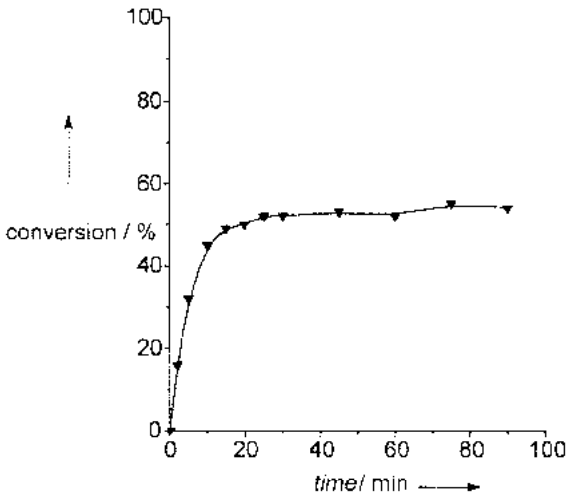
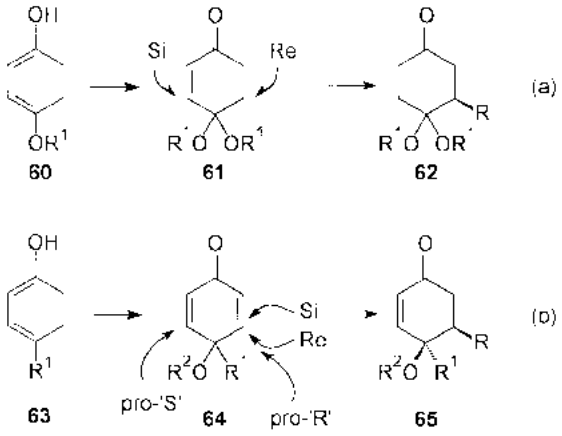


Fig. 7.10. Conversion against time for the kinetic resolution of **53** with 1 equivalent of Me_2Zn under standard conditions.

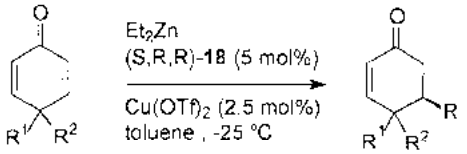


Scheme 7.17. Possible modes of attack by R_2Zn on dienones **61** and **64**.

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 *ees* 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.

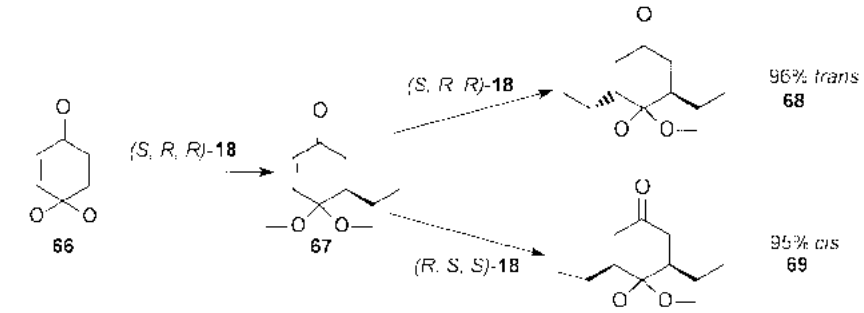


R_1	R_2	R	Yield (%)	dr	ee (%)
OMe	OMe	Et	65	—	97
OEt	OEt	Et	59	—	92
OCH_2CH_2O		Et	68	—	92
$OCH_2CH_2CH_2O$		Et	62	—	89
$OCH_2C(Me)_2CH_2O$		Et	75	—	85
OMe	OMe	Me	76	—	99
OMe	Me	Et	60	90/10	97[a]
OMe	CH_2Ph	Et	53	97/3	93[a]
$CH_2CH_2CH_2O$		Et	66	99/1	65[a]
OMe	OCH_2Ph	Et	58	1/1	98/98

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 *ees* of up to 97% and ratios of up to 99:1 being found for the major diastereoisomer of **65**.

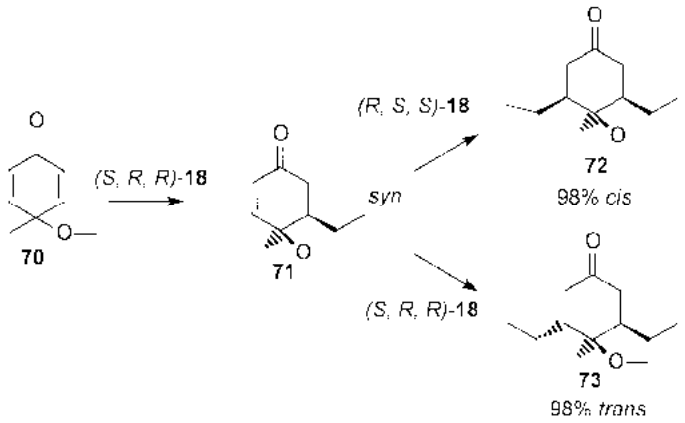
The products of this catalytic enantioselective 1,4-addition still contain an enone moiety, prone to subsequent 1,4-addition [73]. An intriguing question regarding stereocontrol was posed; would the stereoselectivity in the second addition step be governed by the catalyst or would there be a major effect 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**.

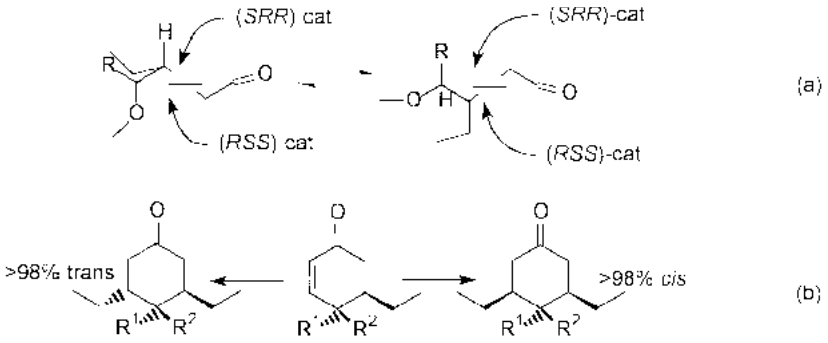
first step (97% *ee*) and in the second gave a 96% selectivity for *trans*-3,5-diethyl-**4**,**4**-dimethoxycyclohexanone (**68**). In contrast, use of (*S*, *R*, *R*)-ligand **18** followed by (*R*, *S*, *S*)-**18** resulted in (*meso*)-*cis*-**69** (95% selectivity).

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**.

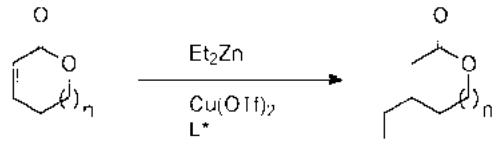
The lack of any directing effect from the **4**-methoxy and the 5-ethyl substituents at the two stereocenters already present in **71** is a remarkable finding, and points to strong catalyst-dependence in the stereocontrol (Scheme 7.20). On the basis of these findings, various stereoisomers of 3,**4**,**4**,5-tetrasubstituted 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].

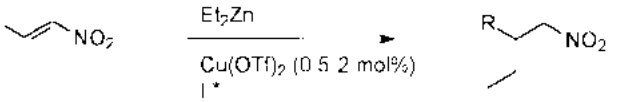


	L*	
74 (n = 1)	**23**	**76** 98% ee
74 (n = 1)	**24**	**76** 92% ee
75 (n = 0)	**24**	**77** 56% ee

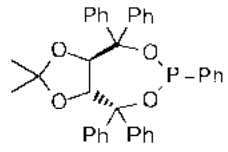
Scheme 7.21. Enantioselective conjugate addition to lactones.

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



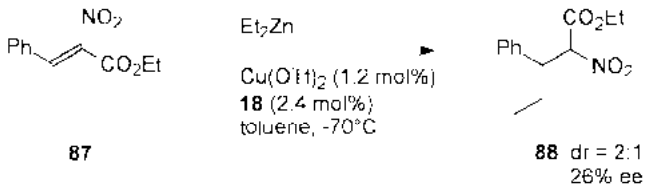
82

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 *ees* of up to 86%, were described by Sewald et al. (Scheme 7.22) [76].

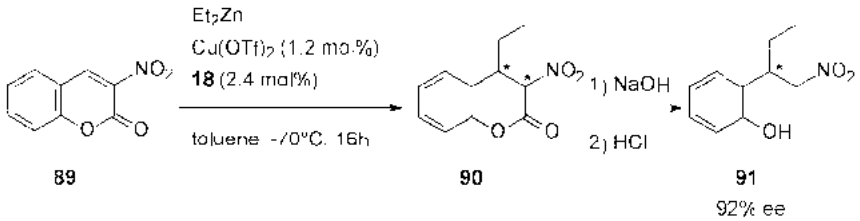
Alexakis, employing various chiral trivalent phosphorus ligands, has recently described $Cu(OTf)_2$-catalyzed 1,4-additions of Et_2Zn to a number of nitroalkenes (Scheme 7.22) [77]. TADDOL-based phosphonite **82** gave the highest *ees* for arylnitroalkenes (up to 86%), whereas phosphoramidite **18**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



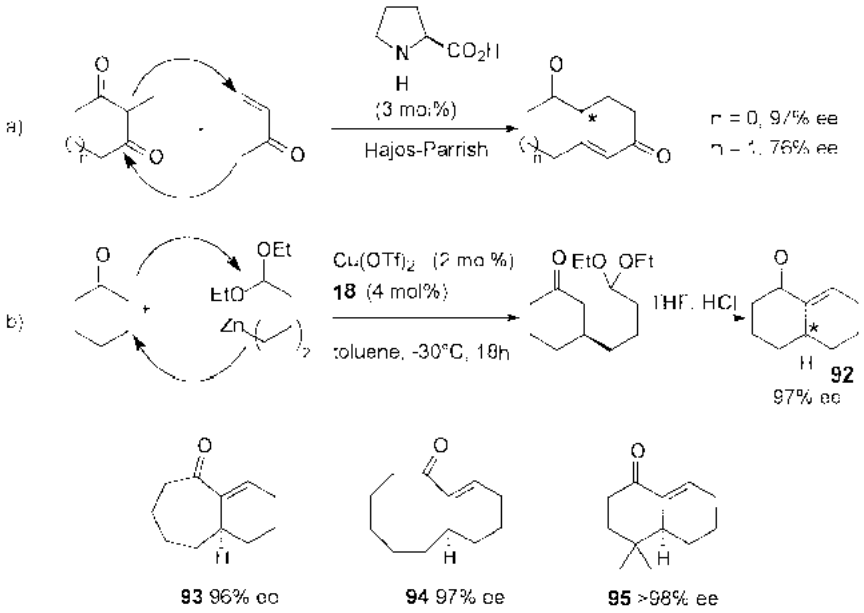
Scheme 7.24. Enantioselective conjugate addition to 3-nitrocoumarin (**89**).

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.

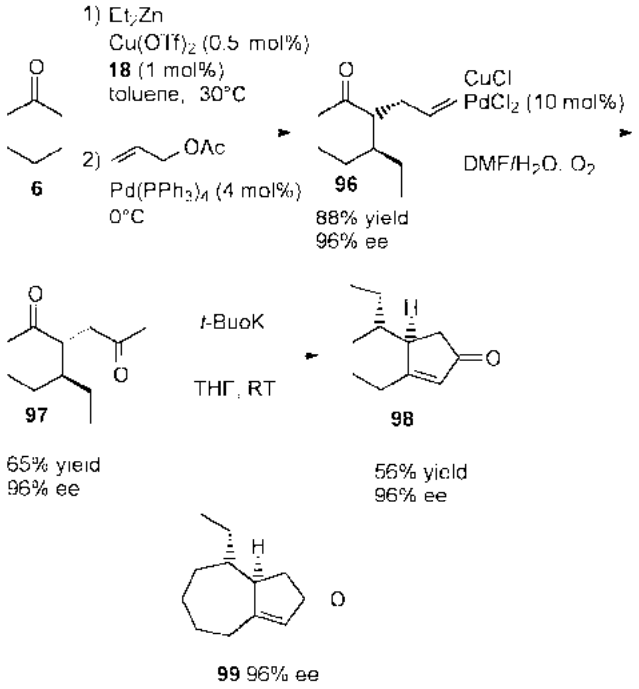
In the first method, a dialkylzinc reagent bearing an acetal moiety at the δ-position is used (Scheme 7.25(b)). The catalytic 1,4-addition is followed by acetal hydrolysis and aldol cyclization of the 4-substituted cycloalkanone, affording 6,6- (**92**), 6,7-, (**93**) and 6,8- (**94**) annulated ring systems with high enantioselectivities (>96% *ees*) [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.

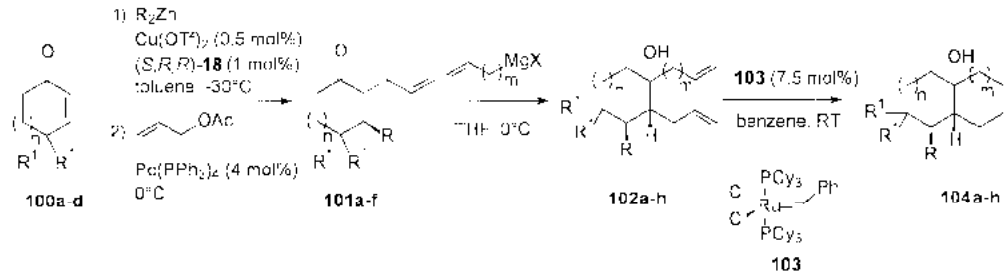
Bicyclo[4.3.0]nonenes, thanks to their frequent appearance in natural products, are other important targets for novel annulation methodology. A six-membered ring-annulation to cyclopentenones has yet to be developed, the main reason for this being that, until very recently, the levels of enantioselectivity 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 *ees* 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	*R*^{1}	*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.

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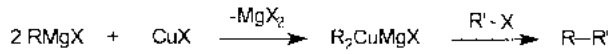
8
Copper-Mediated Enantioselective Substitution Reactions

A. Sofia E. Karlström and Jan-Erling Bäckvall

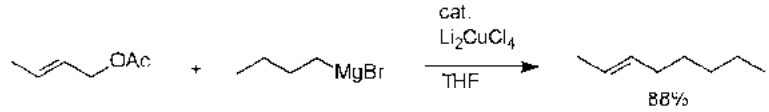
8.1
Introduction

Copper-mediated substitution reactions constitute an important, and much used, tool for the construction of new carbon–carbon bonds in organic synthesis [1]. Many different types of substitution and addition reactions mediated by organocopper reagents have been established as fundamental reactions in the repertoire available to the synthetic chemist. The first example of a copper-mediated substitution reaction was described by Gilman in 1936 [2], and involved reactions between phenylcopper – PhCu – and acid chlorides and allylic halides. Copper-mediated substitution reactions at saturated carbon were reported in 1952, also by Gilman [3], who found that the copper-catalyzed reaction between methyl iodide and methylmagnesium reagents gave ethane. These copper-catalyzed coupling reactions between alkyl halides and Grignard reagents were later studied in more detail (Eq. 1) [4, 5].



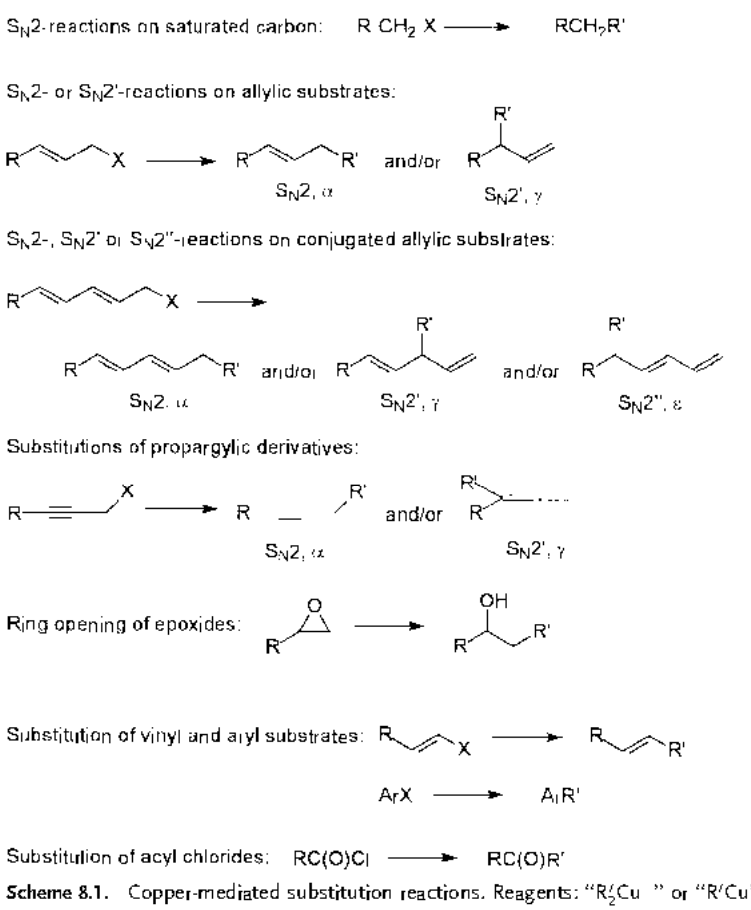
(1)

In the 1952 paper mentioned above [3], Gilman reported on the formation of lithium dimethylcuprate from polymeric methylcopper and methyllithium. These so-called Gilman cuprates were later used for substitution reactions on both saturated [6] and unsaturated [7, 8, 9] substrates. The first example of a cuprate substitution on an allylic acetate (allylic ester) was reported in 1969 [8], while Schlosser reported the corresponding copper-catalyzed reaction between an allylic acetate and a Grignard reagent (Eq. 2) a few years later [10].



(2)

Copper-mediated or copper-catalyzed substitution reactions can be performed on a number of different substrates (Scheme 8.1). Stoichiometric organocopper reagents



Scheme 8.1. Copper-mediated substitution reactions. Reagents: "R'_2Cu^-" or "R'Cu".

R'Cu, or lithium or magnesium homocuprates R'_2CuM (M = Li, MgX), are frequently used, but a number of catalytic processes have also been developed. These processes normally utilize a catalytic amount of a copper salt CuY and a stoichiometric amount of an organometallic reagent R'M (M = Li, MgX, ZnX, etc.). The leaving groups used include halides, esters, sulfonates, and epoxides, among others.

Copper-catalyzed asymmetric substitution reactions can be classified into three major types:

(1) diastereoselective reaction of achiral nucleophiles with chiral substrates,
(2) diastereoselective reaction of chiral nucleophiles with prochiral substrates, and
(3) enantioselective reaction of achiral nucleophiles with prochiral substrates in the presence of chiral catalysts.

From the data available it is clear that diastereoselective reactions of type (1) are very useful for control over absolute stereochemistry, but they require stoichiometric amounts of the chiral auxiliary. Reactions of type (3), on the other hand, have so far

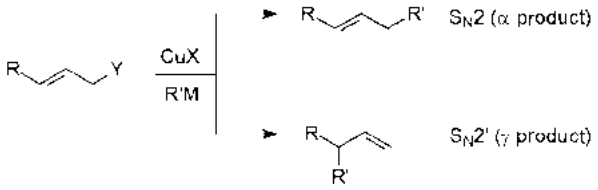
been less used, but they have the advantage that only a small amount of chiral material is required, and that a chiral auxiliary does not have to be cleaved off and recovered after the reaction.

As discussed in Chapt. 6, copper-mediated diastereoselective addition and substitution reactions are well studied methods for the construction of chiral centers in organic molecules. The development of copper-mediated enantioselective substitution reactions, however, is still at an early stage.

The use of chiral catalysts as an approach to enantiomerically enriched products by means of copper-mediated substitution reactions is covered in this chapter. Reactions in which a chiral auxiliary resides in the leaving group of the substrate will also be dealt with, since these reactions provide direct and efficient routes to single enantiomers of the desired products. Most studies so far have been concerned with allylic substrates, with a new chiral center being produced in the course of a selective S_N2' reaction.

8.2 Allylic Substitution

The copper-mediated allylic substitution reaction has been the target of research efforts from many different research groups during the last 30 years. This transformation is fascinating since the substitution reaction of a substrate with a leaving group in the allylic position can occur in two different modes. These two modes are: (i) direct displacement of the leaving group in an S_N2 fashion, often also referred to as α substitution, and (ii) S_N2' displacement of the leaving group involving an allylic shift of the double bond, also referred to as γ substitution (Scheme 8.2). In a more highly conjugated allylic system, such as a 1,3-pentadienol derivative, the substitution can occur even further away from the leaving group.



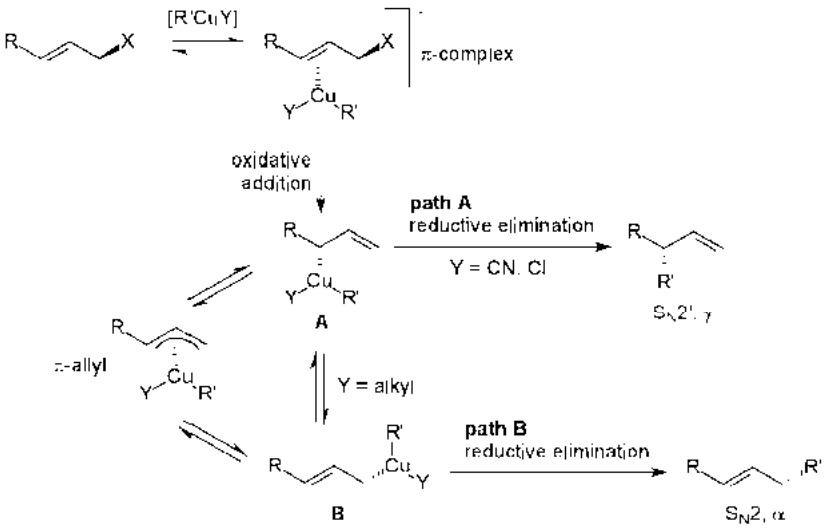
R' = alkyl, aryl, vinyl, allyl
M = Li, MgX, $Ti(OR)_3$, ZnX, etc.
Y = Cl, Br, OC(O)R'', SO_2Ph, OR'', $OP(O)(OR'')_2$, etc.

Scheme 8.2. Copper-catalyzed allylic substitution.

Depending on the substrate and the other reaction parameters, very high regioselectivities towards either α or γ substitution can be obtained. In certain cases, the regioselectivity can easily be switched between the two modes by changing the reaction conditions [11]. Compared to, for example, palladium(0)-catalyzed allylic substitution reactions, the possibility of switching between S_N2 and S_N2' selectivity

in copper-mediated reactions is an advantage. A further advantage is that a fairly broad range of organometallic reagents can be used: lithium, magnesium, and zinc reagents, for example. In this way, both nonfunctionalized and functionalized substituents can be introduced.

Mechanistically, these reactions are considered to proceed by way of oxidative addition of the organocopper reagent to yield Cu(III) intermediates [9, 11–13], giving the final substitution products through reductive elimination as presented schematically in Scheme 8.3. The oxidative addition is thought to be highly γ-selective, which would initially produce the σ-allyl complex **A**. A fast reductive elimination from this complex (that is, when Y is electron-withdrawing) would give the γ product. Under slow reductive elimination conditions (Y = electron-donating), the σ-allyl complex **A** would have time to rearrange to the more stable σ-allyl complex **B**. Reductive elimination from the latter would give the α product.



Scheme 8.3. Proposed mechanisms of allylic substitution reactions.

S_N2'-selective reactions between primary allylic substrates and organocopper reagents result in the creation of new chirality in previously achiral molecules, and it is tempting to try to take advantage of this for the development of enantioselective allylic substitution reactions.

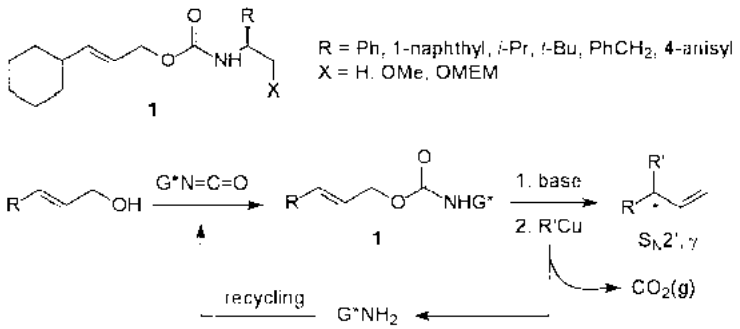
8.2.1
Allylic Substrates with Chiral Leaving Groups

Most asymmetric induction processes with chiral auxiliaries involve a stereodifferentiating reaction that affords one diastereomer as the primary product. To obtain the desired enantiomer, the chiral auxiliary must be removed. Highly diastereoselective reactions between organocopper reagents and allylic substrates with

chiral auxiliaries attached to the allylic backbone have been developed [14]. If, however, an allylic substrate with a chiral leaving group can be utilized, the enantiomerically pure product can be obtained directly.

The first attempts to develop reactions offering control over the absolute stereochemistry of a chiral center, created by γ-selective substitution of an achiral allylic alcohol-derived substrate, involved the use of chiral auxiliaries incorporated in the nucleofuge. The types of stereodirecting groups utilized vary, and have included sulfoximines [15], carbamates [16], and chiral heterocyclic sulfides [17–19].

Denmark and co-workers reported the first example in 1990 [16], using substrates **1**, synthesized from achiral allylic alcohols and readily available optically active amine auxiliaries. Substrates **1** were then employed in copper-mediated allylic substitution reactions, as shown in Scheme 8.4.

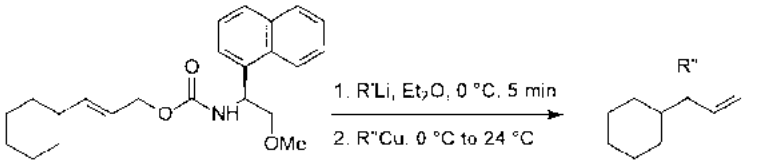


Scheme 8.4. Employment of allylic carbamates **1** in copper-mediated asymmetric substitution.

Substitution reactions of achiral allylic carbamates have been studied previously, by Gallina and Goering, for example [20]. An intriguing feature of these substrates is the preference for formation of the S_N2' product in which the newly introduced group appears on the same side as the leaving group was previously (*syn* selectivity). As has been shown in several independent studies, the more commonly used substrates, such as allylic esters and halides, usually react with *anti* selectivity. The opposite *syn* stereochemistry observed for carbamates has been explained by coordination of the copper reagent to the leaving group, followed by an intramolecular delivery of the nucleophile. This would be consistent with the fact that a chiral carbamate of type **1**, as designed by Denmark et al., can produce significant asymmetric induction in the γ-position even though that involves a 1,7-transfer of chirality in this case.

Optimization of the reaction conditions was undertaken in order to find the best S_N2'/S_N2 ratio and the best substrate conversion. Initial formation of a lithium carbamate salt of **1** on treatment with MeLi, followed by treatment with a stoichiometric amount of MeCu in Et_2O at 0 °C, produced clean S_N2' selectivity and isolation of the desired alkene in 75% yield. A variety of chiral carbamates **1** were investigated, the substrate with R = 1-naphthyl and X = OMe being chosen as the candidate for further studies. It is noteworthy that substrates in which X = H gave

very low selectivity, and also that incorporation of a coordinating oxygen functionality seems to be necessary for high enantioselectivity. A striking difference between aliphatic and aromatic auxiliaries, in favor of the latter, was also noted. Fine-tuning of the reaction parameters resulted in high enantiomeric excesses (≥ 88% *ee*) in reactions with MeCu, *n*-BuCu, and PhCu (Scheme 8.5). Et_2O had to be used as solvent since the use of THF dramatically reduced the enantiomeric excesses.



1

2 R" = Me 95% ee
3 R" = Bu, 88% ee
4 R" = Ph, 91% ee

Scheme 8.5. Optimized reaction conditions for reactions between allylic carbamate **1** (R = 1-naphthyl, X = OMe) and organocopper reagents $R''Cu$.

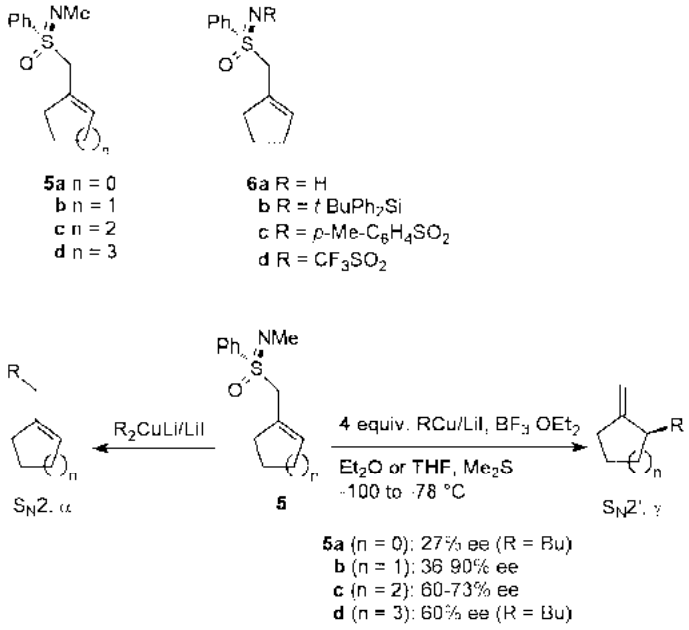
The main disadvantage of this reaction is that it is necessary to use stoichiometric amounts, or more, of the organocopper reagent, together with stoichiometric amounts of the chiral auxiliary. The leaving group chiral auxiliary, however, can be recovered and recycled after the reaction.

Another highly selective system was designed by Gais et al. in the course of the synthesis of isocarbacyclin [15a]. In conjunction with this study it was found that optically pure allylic sulfoximines undergo regioselective and enantioselective allylic substitution reactions with organocopper reagents [15b]. Since the chirality is at the sulfur atom, the chiral center is directly connected to the allylic fragment in sulfoximes **5** and **6**, used in this study (Scheme 8.6).

Endocyclic allylic sulfoximines **5** were synthesized from cycloalkanones and lithiated enantiomerically pure (*S*)-*S*-methyl-*S*-phenylsulfoximine, by addition and subsequent elimination and isomerization of the intermediate vinylic sulfoximines.

The allylic sulfoximines **5** were subjected to treatment with organocopper reagents. The regioselectivity could be controlled by variation of the reaction conditions, and a highly α-selective reaction was obtained with homocuprates R_2CuLi/LiI. Organocopper reagents RCu/LiI in the presence of $BF_3{\cdot}OEt_2$ (Yamamoto conditions) [**14**, 21], on the other hand, gave γ-selective reactions producing exocyclic alkene products (Scheme 8.6). Regioselectivity showed no clear dependence on the solvent, since both Et_2O/Me_2S and THF/Me_2S were suitable for highly selective reactions.

For **5b**, derived from cyclopentanone, a maximum *ee* of 90% was achieved with the bulky copper reagent t-$BuPh_2SiO(CH_2)_4Cu$/LiI. Et_2O had to be used as solvent for optimal results in this case, but THF was the best solvent in others. Low temperature conditions (−100 °C, or from −100 to −78 °C) were used for all the enan-



Scheme 8.6. Reactions between endocyclic sulfoximines **5** and organocopper reagents.

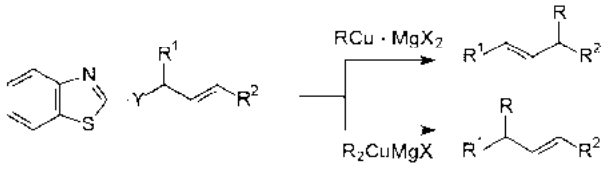
tioselective reactions. Organocopper reagents functionalized with ether groups in the γ- or δ-positions gave *ees* of 63–71%. Simple *n*-alkylcopper reagents also produced enantioselectivities of around 70%. Further investigation of copper reagents using $TMSCH_2Cu$ and $PhCH_2Cu$ met with little success, since the γ selectivity was lost. The loss of γ selectivity in the case of $TMSCH_2Cu/LiI$ was attributed to an equilibrium process with the corresponding homocuprate, which in parallel experiments was shown to give high α selectivity. For **5c** (n = 2), *ees* between 60 and 73% were observed for all Grignard reagents studied (both functionalized and nonfunctionalized), together with high γ selectivities. Further enlargement of the cycloalkene ring, as in **5d**, did not produce any improvement, with treatment with $BuCu/LiI/BF_3 \cdot OEt_2$ in Et_2O giving an *ee* of 60%. A smaller cyclobutene ring in the allylic sulfoximine, as in **5a**, gave only a 27% *ee* with the butylcopper reagent.

It was demonstrated that the chiral auxiliary can be recovered after the reaction as the corresponding sulfinamide Me(H)NS(O)Ph, with virtually complete retention of configuration at the sulfur atom.

To explore the influence of the nitrogen substituent in the sulfonimidoyl group, substrates **6** were synthesized and tested. Sulfoximines bearing a silyl group (**6b**) or hydrogen (**6a**) on nitrogen, however, did not react at all; neither with RCu, nor with R_2CuLi. The *N*-tosyl-substituted (**6c**) and *N*-CF_3SO_2-substituted (**6d**) substrates were less reactive than **5b**, but afforded similar regioselectivities under both α-selective and γ-selective conditions. The observed *ees* for these substrates were lower (around 30%), however.

Gais et al. also investigated the mechanism of the reaction, with respect to the influence of additives. It was concluded, at least for the organocopper reagent $TMSCH_2Cu$, that LiI and $BF_3{\cdot}OEt_2$ are necessary additives for reaction with an allylic sulfoximine. The role of metal halide could be to promote formation of heteroleptic cuprates RCu·MHal or $(RCu)_m(MHal)_n$. Organocopper reagents prepared in the absence of lithium salts were unreactive. BF_3 probably acts through substrate or intermediate activation. NMR experiments in the presence of BF_3 showed that BF_3 coordinates to the nitrogen atom in sulfoximines bearing the NMe group, but not in the triflyl- or tosyl-substituted substrates **6d** and **6c**, in which the electronegative substituent on nitrogen prevents coordination.

Calò et al. have thoroughly investigated the use of allylic electrophiles containing heterocyclic leaving groups in regioselective allylic substitution (Scheme 8.7) [22].

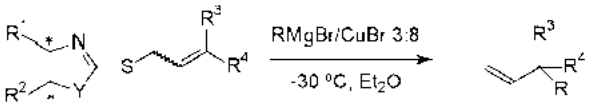


Y = O, S
R′ and R^2 = H or alkyl

Scheme 8.7. Substitution of heterocyclic allylic substrates.

From the data obtained under various conditions it was concluded that the selectivity is governed by preliminary chelation of the leaving group to the organocopper reagent $RCu{\cdot}MgX_2$. The organocopper reagents $RCu{\cdot}MgX_2$, prepared from a Grignard reagent and an excess of a copper salt, selectively gave the S_N2' products, while homocuprates R_2CuMgX were S_N2-selective. The more electrophilic nature of $RCu{\cdot}MgX_2$ results in better coordinating properties than in the R_2CuMgX reagent and it was suggested that the S_N2'-selective reaction is due to intramolecular delivery of the coordinated RCu reagent.

The heterocyclic component in the leaving group offers possibilities for introduction of chirality. Optically active oxazolin-2-yl and thiazolin-2-yl allyl thioethers **7** were thus chosen as substrates (Scheme 8.8) [17].



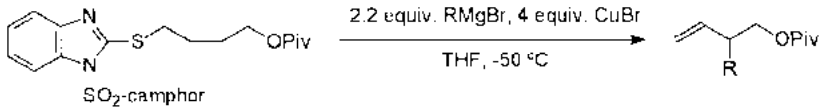
7

R = *i*-Pr, Bu
R^1 = CH_2OPiv, CH(OPiv)Ph, *i*-Pr
R^2 = H, Ph
R^3 = H, Me, $(CH_2)_2CH{=}CMe_2$
R^4 = Me, Ph, $(CH_2)_2CH{=}CMe_2$

Scheme 8.8. Enantioselective substitution of oxazolin-2-yl and thiazolin-2-yl allyl thioethers.

The regioselectivity of the reaction was found to be solvent-dependent, with Et_2O favoring S_N2' products, and THF favoring S_N2 products, in accordance with results from studies of similar systems [22]. As expected, a high ratio of CuBr to Grignard reagent favored the S_N2' path. Various chiral heterocyclic sulfides **7** were thus treated with *i*-PrMgBr or *n*-BuMgBr in Et_2O in the presence of excess CuBr, yielding the desired *γ*-products with *ee*s ranging from 50 to 98%, depending on the substrate used. From the results obtained, it was concluded that steric hindrance around the leaving group nitrogen atom resulted in higher enantioselectivity. The geometry of the allylic double bond (*E* or *Z*) plays a decisive role, as shown by one example in which the two double bond isomers gave opposite enantiomers with comparable enantioselectivities, even though the leaving group was of the same absolute stereochemistry.

Chelate formation between the leaving group and the organocopper reagent can also be used to increase the reactivity of the leaving group so that it reacts chemoselectively, in preference to a different potential leaving group [18]. In this way, an allylic substrate bearing a pivalate and a sulfide of benzothiazole can, through a *γ*-selective reaction, yield homoallylic pivalates exclusively. With a chiral allylic sulfide, the reaction could produce optically active homoallylic pivalates in chemoselective, regioselective, and enantioselective fashion. Use of a chiral benzimidazole sulfide as the leaving group, as in **8**, resulted in selective replacement of the benzimidazole to give homoallylic pivalates in 32–59% *ee* (Scheme 8.9) [18].

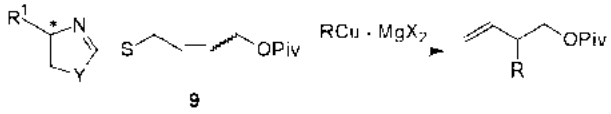


8

R	*n*-Bu	*n*-C_8H_{17}	*i*-Pr	*c*-C_6H_{11}
ee (%)	43	59	30	32

Scheme 8.9. Enantioselective substitution of allylic sulfide **8**.

It was argued that the relatively low *ee* in this case could be attributed to the large separation between the source of chirality and the reactive center, and so the reaction in Scheme 8.10 was investigated [19]. The chirality in the leaving group in compound **9** is closer to the reaction center than in the first studied substrate **8**, since the stereocenter in **9** is in the position *α* to the coordinating nitrogen.



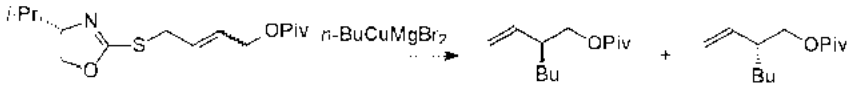
9

R^1 = EtO_2C, *i*-Pr, *t*-$BuMe_2SiOCH_2$
Y = S, O, CH_2

Scheme 8.10. Enantioselective substitution of allylic sulfide **9**.

To obtain good S_N2' selectivity, a high ratio of copper to Grignard reagent (**4**:**1**) also had to be used in this system. *Ee*s of up to 98% were achieved with *n*-BuMgBr

Tab. 8.1. Dependence on double bond geometry in **10**.



(*S*) (*Z*) **10** or (*S*)-(*E*)-**10** (*S*)-**11** (*R*)-**11**

10	***(R)*-11**	***(S)*-11**	***ee* (%)**
(*S*)-(*Z*)	1	99	98 (*S*)
(*S*)-(*E*)	99	1	98 (*R*)
(*S*)-(*Z*)/(*S*)-(*E*) 90:10	10	90	80 (*S*)

in combination with CuBr for **9** with $R^1 = i$-Pr and Y = O. Although the azomethine group is crucial for the selectivity, group Y can be changed from O to S or CH_2 without any large drop in obtained *ee*s. Substrate **9** with $R^1 = EtO_2C$ was not suitable under the reaction conditions studied, with racemization of the heterocyclic stereocenter taking place.

As in the case of the substitution reaction of compound **7**, the absolute configuration of the product depends on the double bond geometry of the starting material, as shown by the example in Tab. 8.1.

The selectivity in this process is governed by preliminary chelation of the RCu species by the azomethine group and the allylic double bond. The proposed chelates for the cases of (*S*)-(*Z*)-**10** and (*S*)-(*E*)-**10** are shown in Fig. 8.1.

8.2.2
Chiral Auxiliary that is Cleaved off after the Reaction

Reaction between C_2 symmetric diols and α,β-unsaturated aldehydes yield chiral ethylenic acetals that undergo copper-mediated substitution reactions. With aryl or

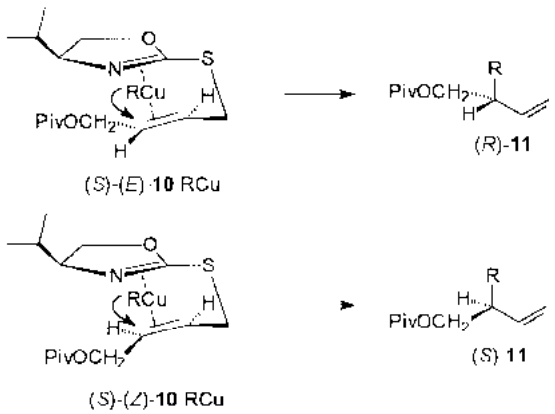
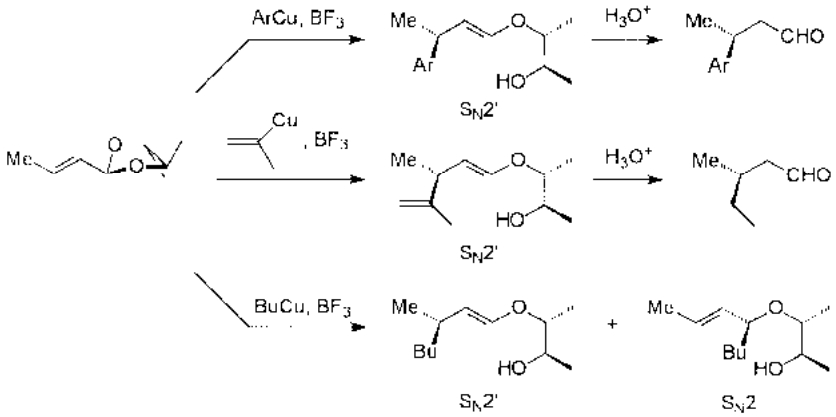


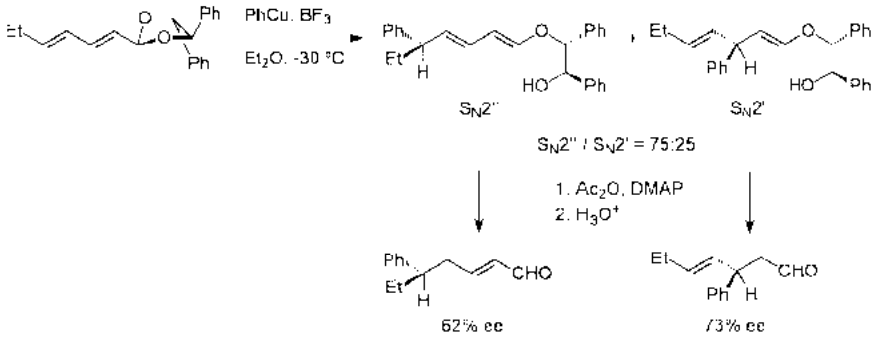
Fig. 8.1. Proposed chelate structures.

vinylcopper reagents this reaction, as studied by Alexakis et al. (Scheme 8.11), is highly *anti* S_N2'-selective. With alkyl copper reagents, however, a mixture of S_N2' and S_N2 substitution results [23, 24]. The copper approaches from the face of the double bond that is on the side of the equatorial substituent in the acetal, and the C O bond nearest to the axial substituent is cleaved. The initial S_N2' product is an enol ether, which is hydrolyzed to a chiral β-substituted aldehyde. The reaction sequence starting from an α,β-unsaturated aldehyde can be viewed overall as a conjugate addition of RLi.



Scheme 8.11. Reactions between an ethylenic acetal and organocopper reagents.

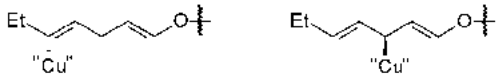
With the reagent PhCu in the presence of the additives BF_3 and PBu_3, *ees* of up to 95% were obtained, while values of up to 85% were achievable with a vinyl copper reagent. Chiral dienic acetals have also been studied; three regioisomeric products could be obtained in this case as the result of S_N2, S_N2', or S_N2'' attack of the organocopper reagent [25]. Mixtures were indeed obtained with alkyl copper reagents, but PhCu·BF_3 resulted in formation of only the S_N2' and S_N2'' products, with selectivity for the latter (Scheme 8.12).



Scheme 8.12. Substitution of a dienyl acetal.

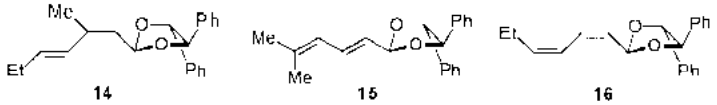
Hydrolysis of the enol ethers obtained from the substitution reaction with the organocopper reagent yielded chiral δ-substituted aldehydes with *ee*s of 62 and 73% for the S_N2'' and S_N2' products, respectively.

The S_N2'' product was shown to be the result of a *syn*-selective reaction, the stereochemistry being opposite to that of the S_N2' product, which has the incoming group *anti* to the leaving group. The reason for the observed *syn* selectivity is not clear, but the authors proposed the initial formation of the two distinct Cu(III)-σ-allyl complexes **12** and **13** for the S_N2'' and S_N2' pathways in Scheme 8.12.



12, S_N2'' **13**, S_N2'

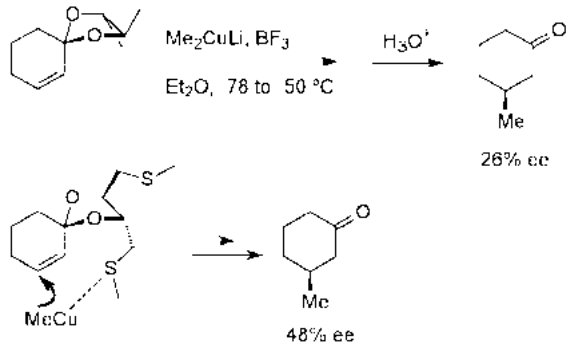
The regioselectivity was found to be highly dependent on the substitution pattern of the starting acetal, and the configurations of its double bonds (Scheme 8.13). The best result was obtained with the β-substituted acetal **14**, which exclusively yielded the S_N2'' product, in 83% *ee*. Substitution in the δ-position instead (**15**) yielded 90% of the S_N2' product, in 61% *ee*. It seems that the regioselectivity is governed by steric factors and that the attack of the organocopper reagent takes place at the less hindered site. The (*Z*, *Z*) substrate **16** was highly S_N2''-selective, with the resulting product being formed in 58% *ee*. Other substrates investigated were less selective.



	14	**15**	**16**
S_N2' / S_N2'	100:0	10:90	100:0
ee of S_N2'' (%)	83	-	58
ee of S_N2 (%)	-	61	-

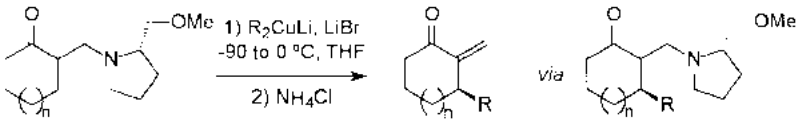
Scheme 8.13. Selectivity dependence on the acetal structure.

When the reaction was applied to a chiral cyclic ketal instead, very low selectivities were obtained. Introduction of chelating substituents into the ketal made improvement possible, though (Scheme 8.14) [23, 26].



Scheme 8.14. Substitution of chiral cyclic ketals.

A result equivalent to an allylic substitution reaction with a chiral leaving group can also be achieved by a two-step procedure involving a conjugate addition reaction and a subsequent elimination reaction, as demonstrated by Tamura et al., who studied the reaction shown in Scheme 8.15 [27].

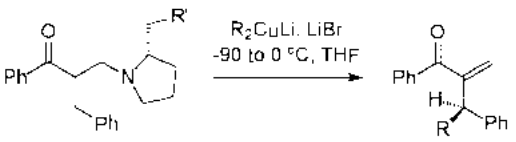


17a (n = 0)
b (n = 1)
c (n = 2)

n = 0	n = 1	n = 2
R = Bu, 82% ee	R = Bu, 95% ee	R = Bu, 96% ee
R = Et, 85% ee	R = Me, 95% ee	R = Me, 96% ee
R = Ph, 47% ee	R = Et, 95% ee	R = Et, 97% ee
R = vinyl, 79% ee		R = Ph, 97% ee
		R = vinyl, 96% ee

Scheme 8.15. Conjugate addition and elimination sequence, resulting in overall S_N2' substitution.

A diastereomerically differentiating addition-elimination sequence involving 1,5-transfer of chirality has been used to effect an overall allylic S_N2' substitution of a chiral amine auxiliary by organocuprates. Several different types of organocopper reagents, including RCu·LiBr, R_2CuLi·LiBr, RCu(CN)Li, R_2CuLi·LiCN, and $R_2CuMgCl$·MgCl(Br), were investigated in the presence or absence of Lewis acids such as LiBr and $ZnBr_2$. The optimal reaction conditions were found to be the use of one equivalent of R_2CuLi·LiBr and two equivalents of LiBr. Using these conditions, excellent enantioselectivities, of ≥95% *ee*, were achieved for the introduction of *n*-butyl, methyl, ethyl, phenyl, and vinyl groups into substrate **17c** (n = 2). In the case of a six-membered ring (**17b**) these high levels of enantioselectivity could be obtained for the introduction of saturated substituents such as *n*-butyl, methyl, and ethyl. Here it was shown that the use of LiBr as an additive invariably produced higher enantioselectivities than $ZnBr_2$ did (95% *ee* versus 90% *ee*). The products with unsaturated substituents (phenyl and vinyl) were too unstable to be isolated in this case. A substrate with a smaller ring (**17a**) gave generally lower *ees*. This investigation also included acyclic substrates **18** (Scheme 8.16), but these afforded lower *ees*, with an *ee* of 70% being obtained in the best case, using dibutylcuprate.



18

Scheme 8.16. The use of acyclic substrates **18**.

It was concluded that an oxygen functionality in the C(2)-side chain of the pyrrolidinyl chiral auxiliary was of great importance for the achievement of high *ees*.

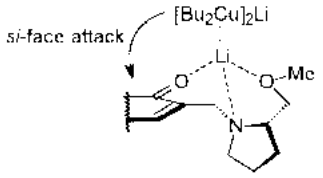


Fig. 8.2. Transition state model for the enantioselective substitution of **17**.

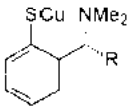
On the basis of this conclusion and on NMR studies of complexes of **17b** with Lewis acids, a transition state model to explain the observed selectivity was proposed. This involved initial complexation of a cuprate lithium ion to the three different heteroatoms in the substrate, followed by formation of a d-π^* complexation product from the less hindered *si* face, the *re* face being shielded by the pyrrolidine ring (Fig. 8.2).

8.2.3
Catalytic Reactions with Chiral Ligands

Compared to the intensive and successful development of copper catalysts for asymmetric 1,4-addition reactions, discussed in Chapt. 7, catalytic asymmetric allylic substitution reactions have been the subjects of only a few studies. Difficulties arise because, in the asymmetric γ substitution of unsymmetrical allylic electrophiles, the catalyst has to be capable of controlling both regioselectivity and enantioselectivity.

In 1995, Bäckvall and van Koten reported the first example of a catalytic, enantioselective S_N2' substitution of a primary allylic acetate in the presence of a chiral copper complex [28, 29].

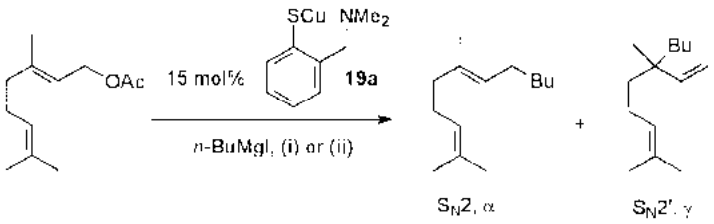
The copper(I) arenethiolate complexes **19** [30], first developed and studied by van Koten's group, can be used as catalysts for a number of copper-mediated reactions such as 1,4-addition reactions to enones [31] and 1,6-addition reactions to enynes [32].



19a R = H
b R = Me

Initial studies on the application of these catalysts to allylic substitution reactions showed that the arenethiolate moiety functions as an excellent nontransferable group, and that the regioselectivity can be completely reversed by suitable changes in the reaction parameters [33]. If the reaction between geranyl acetate and *n*-BuMgI was carried out in THF at −30 °C with fast addition of the Grignard reagent to the reaction mixture, complete α selectivity was obtained. Raising the tempera-

ture to 0 °C and use of Et_2O as solvent, with slow addition of the Grignard reagent, gave 100% of the γ product (Scheme 8.17).

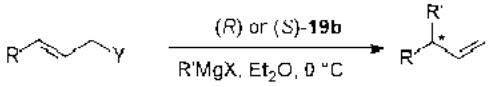


(i): Et_2O, 0 °C, 120 min addition time of *n* BuMgI, 100% γ product
(ii): THF, -30 °C, 5 min addition time of *n*-BuMgI, 100% α product

Scheme 8.17. Control of regioselectivity with catalyst **19a**.

These catalysts also give a remarkable reversal in leaving group ability. An allylic acetate becomes more reactive than an allylic chloride in the presence of **19a**, a fact that can be explained by chelate formation with the catalyst and Grignard reagent, with the acetate group becoming activated by coordination of oxygen to magnesium [33b].

The use of the chiral catalyst **19b** for asymmetric allylic substitution of allylic substrates has been studied in some detail (Scheme 8.18) and, under γ-selective reaction conditions, asymmetric induction was indeed obtained [28, 34].



20 R = $PhOCH_2$, **a** Y = OAc, **b** *t* BuC(O)O, **c** $CF_3C(O)O$, **d** $(EtO)_2P(O)O$
21 R = *c*-C_6H_{11}, Y = OAc
22 R = Ph, Y = OAc
R'MgX = *n*-BuMgI, *n*-BuMgBr, Me_3SiCH_2MgI

Scheme 8.18. Enantioselective substitution with catalyst **19b**.

To optimize the enantioselectivity it was necessary to use a rather high catalyst loading (ca. 15 mol%), with reactions being carried out at fairly low substrate concentrations, with slow addition of the Grignard reagent over 2 hrs. The effect of the leaving group was studied using substrates **20**, in their reactions with *n*-BuMgI. Both the acetate **20a** and the pivalate **20b** underwent highly regioselective reactions, with 34% *ee* for the acetate and 25% *ee* for the more bulky pivalate. Trifluoroacetate (**20c**) or diethylphosphate (**20d**) as leaving groups resulted in slightly lower regioselectivities (ca. 90:10) and the *ees* were severely diminished to around 10%. The substituent on the allylic double bond had only a minor influence on the *ee*; $PhOCH_2$ (**20a**) and cyclohexyl (**21**) gave *ees* of 34 and 41% respectively. A slightly lower *ee* of 28% was obtained with cinnamyl acetate (**22**). The mode of addition was important for the outcome, the best results being obtained when both the Grignard reagent and the substrate were added slowly to the reaction mixture. With this

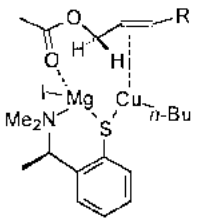


Fig. 8.3. Proposed chelate structure for the catalytically active intermediate.

technique, the *ee* in the case of the reaction between cyclohexyl-substituted allylic acetate **21** and *n*-BuMgI was 42%. This implies that a 1:1 ratio of substrate to Grignard reagent at all times is important for the selectivity. Excess substrate can disrupt the bidentate coordination necessary for the proposed chelate. The difference here, however, was very small in comparison to the situation when the Grignard reagent alone was added over 2 h. A still larger difference was observed when the substrate was added to a mixture of catalyst and *n*-BuMgI, conditions favoring formation of a homocuprate, R_2CuM. In that case only 18% *ee* was achieved. The reaction has to be performed at a rather high temperature if maximum enantioselectivity is to be achieved. Reaction temperatures of 0 °C or 20 °C produced similar *ees*, but an *ee* of only 7% was obtained at a lower temperature (−20 °C). This supports the hypothesis that chelate formation is important for the enantioselectivity.

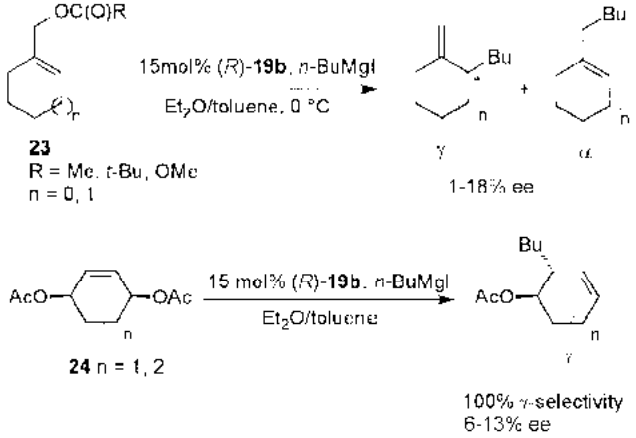
The results obtained can be explained in terms of a catalytic intermediate made up of a chelate between Grignard reagent, catalyst, and substrate. The allylic substrate anchors in a bidentate fashion, through carbonyl coordination to magnesium and copper-alkene π-interaction, as represented schematically in Fig. 8.3. The chelate constitutes a rigid structure, incorporating a six-membered ring with a chiral magnesium atom. The chelate shown would produce preferential coordination from the face of the olefin indicated in Fig. 8.3, in accord with the observation that *R* ligands result in *R* products.

The coordination of the acetate in this fashion should result in enhanced leaving group reactivity, while the effect of changes in the leaving group on enantioselectivity further supports the idea of chelate formation. The more bulky pivalate should give a less stable chelate, and a lower *ee* is indeed observed. The electron-withdrawing trifluoromethyl group in the trifluoroacetate moiety would weaken coordination and give a less stable chelate, which would explain the low enantioselectivity (10% *ee*) with the allylic trifluoroacetate. (It is also possible that the high reactivity of trifluoroacetate as a leaving group results in reaction before chelate formation takes place.) The same arguments also apply to the phosphate leaving group.

The reaction of cyclohexyl-substituted allylic acetate **21** with different Grignard reagents was investigated [34]. As already mentioned, a 41% *ee* had been obtained with *n*-BuMgI. Changing the counter-ion in the Grignard reagent to Br , under otherwise identical reaction conditions, gave an *ee* of 50%. The sterically hindered Grignard reagent Me_3SiCH_2MgI underwent only slow reaction, giving a moderate

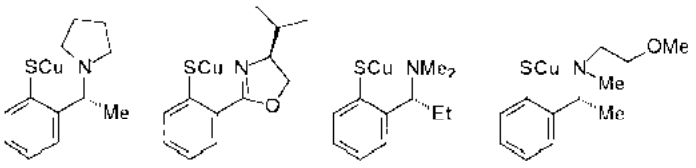
yield of the γ product, but the observed *ee*, 53%, was the highest so far obtained with catalyst **19b**.

To study the effect of conformationally more rigid substrates, some cyclic allylic esters (**23** and **24**) were employed as substrates. Reaction of these with *n*-BuMgI, employing **19b** as catalyst, produced very low *ees*, however (Scheme 8.19) [35].



Scheme 8.19. Reactions of cyclic allylic esters **23** and **24**, with catalysis by **19b**.

To investigate the effect of the substituents in the arenethiolate structure, four differently substituted copper arenethiolates, **25**–**28**, were tested as catalysts, but very low *ees* were obtained in all cases [34]. The oxazolidine complex **26**, developed by Pfaltz et al. [36] and used successfully in asymmetric conjugate addition reactions to cyclic enones, gave a completely racemic product with allylic substrate **20a**.



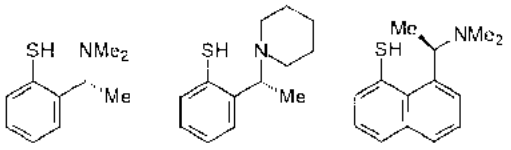
25 **26** **27** **28**

To avoid the difficulties in handling the highly air-sensitive copper arenethiolates, a method for their preparation and utilization in situ has been developed, the arenethiol **29** being deprotonated with *n*-BuLi and mixed with a copper(I) salt to yield the active catalyst [34].

Use of this technique results in an equivalent of lithium halide being present in the reaction mixture, unlike when the isolated copper arenethiolates are employed. Lithium salts can have very profound effects on copper-mediated reactions, but in this case a similar *ee* (40%) and complete γ selectivity were still obtained for the reaction between **21** and *n*-BuMgI when the catalyst was prepared from CuI. Nei-

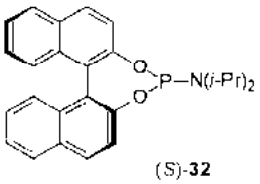
ther a change of the Cu:ligand ratio to 1:2 nor an increase in the temperature (cf. the work with the preformed catalyst) affected the outcome of the reaction. The effect of the arenethiolate ligand on the reactivity was confirmed by performing the reaction with only CuI as catalyst, in the absence of the ligand. In this case, the allylic acetate **21** was partly recovered, and formation of the corresponding alcohol was observed, which indicates that the reaction was much slower. The regioselectivity was also no longer complete ($\gamma/\alpha = 95:5$). The source of the copper can also have a dramatic influence on the stereochemical outcome; a change from CuI to CuBr·SMe2 resulted in an *ee* of only 7%. This can be explained in terms of coordination of the dimethyl sulfide to copper, hampering formation of the catalytic intermediate. CuCl could be employed with the same efficiency as CuI, but $Cu(OTf)_2$ gave a lower enantioselectivity.

Investigation of different Grignard reagents was also carried out. In contrast to the result obtained with the isolated catalyst **19b**, the in situ generation technique here gave a lower *ee* for BuMgBr (30% *ee*) than for BuMgI (40% *ee*). Use of CuBr instead of CuI allowed this *ee* to be increased somewhat, to 36%. Some bulkier Grignard reagents, such as *i*-PrMgI, *i*-PrMgBr, *i*-BuMgBr, and Me_3SiCH_2MgI, were also investigated, but no *ees* higher than 40% could be obtained. No allylic substitution at all was observed with PhMgI. Cinnamyl acetate (**22**) as the substrate gave slightly lower *ees* than obtained with **21**, in line with the results with the preformed catalyst. Variation of the ligand structure (as in **30** and **31**) produced lower *ees* than obtained with **29**. Use of ligand **30** resulted in a very low *ee* of 10% for the reaction between **21** and *n*-BuMgI, but **31** gave a reasonable *ee* of 35%. Interestingly, the major enantiomers were of opposite configurations when (*R*)-**29** and (*R*)-**31** were used.



29 **30** **31**

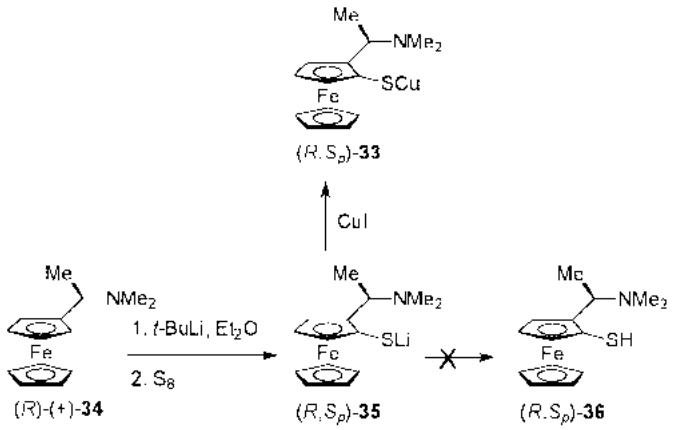
The moderate *ees* obtained with the copper arenethiolate ligands discussed above prompted a search for new chiral ligands for use in asymmetric allylic substitution reactions. The binaphthol-derived phosphoramidite ligand **32**, used successfully by Feringa et al. in copper-catalyzed 1,4-addition reactions [37], was accordingly tested in the reaction between **21** and *n*-BuMgI.



(S)-**32**

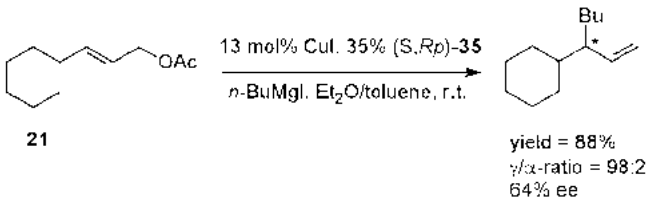
The presence of ligand **32**, however, resulted in much slower allylic substitution [38], as could be seen by the formation of large amounts of the alcohol produced by carbonyl attack of the Grignard reagent on the acetate. S_N2' selectivities were also lower than those obtained with copper arenethiolate catalysts. Optimization of the conditions (10% each of $Cu(OTf)_2$ and **32**, slow addition of *n*-BuMgI in Et_2O at −20 °C) made it possible to obtain a 97:3 ratio of S_N2' and S_N2 products with less than 10% attack on the carbonyl, but the S_N2' product was racemic [35]. However, it cannot be ruled out that this class of ligands might be useful for the allylic substitution reaction under reaction conditions different to those tested.

Chiral ferrocenes have received much attention as ligands in metal-catalyzed reactions [39], but their use in copper chemistry has been very limited [**40**, **41**]. The ferrocene moiety offers the possibility of utilizing both central and planar chirality in the ligand. By analogy with the copper arenethiolates described above, ferrocenyl copper complex **33** (Scheme 8.20) is extremely interesting.



Scheme 8.20. Ferrocene thiolates.

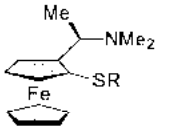
The synthesis of the corresponding ferrocene thiol **36** was therefore undertaken (Scheme 8.20) [**42**]. This thiol proved to be too unstable and could not be isolated, but the precursor lithium thiolate **35** could be isolated and stored under an argon atmosphere. Treatment of **35** with CuI produced a catalytically active species that gave up to 64% *ee* in the reaction between allylic acetates and *n*-BuMgI (Scheme 8.21). A rather large ratio of ligand to copper gave better results; it was concluded that this was due to the low stability of the ligand towards oxidation.



Scheme 8.21. Allylic substitution in the presence of ferrocene ligand **35**.

The *ee*s obtained in reactions between **21** and different Grignard reagents using copper arenethiolate **19b** (isolated complex or prepared in situ from **29** and CuX) were improved in all cases when the ferrocenyl system was used. Thus, MeMgI, EtMgI, *n*-PrMgI, and *i*-PrMgBr gave *ee*s of **44**, 62, **54**, and 52% respectively. The enantiomeric excesses obtained using this ligand are the highest so far reported for copper-catalyzed allylic substitution reactions between allylic esters and Grignard reagents.

The necessity of an anionic thiolate ligand was established by performing reactions with ferrocene thioethers **37** as ligands. Here, essentially racemic products were obtained.



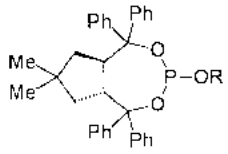
R = Ph, *t*-Bu

(R,S_p)-**37**

Alexakis et al. have also recently studied allylic substitution reactions in the presence of chiral ligands [**43**]. Their experience with phosphorus-based ligands for copper in conjugate addition reactions [**44**] prompted them to study these systems in substitution reactions as well. Reactions between cinnamyl chloride and Grignard reagents were chosen as a suitable test system. It turned out to be a challenge to obtain a regioselective reaction with this system in the presence of the ligand triethyl phosphite $P(OEt)_3$. However, it proved possible to obtain a γ/α ratio of 97:3 by addition of ethyl magnesium bromide to cinnamyl chloride, CuCN (1 mol%), and $P(OEt)_3$ (2 mol%) in CH_2Cl_2 at −80 °C. By using EtMgCl, with $Cu(OTf)_2$ as catalyst, and carrying out inverse addition of the substrate to a mixture of the catalyst, ligand, and Grignard reagent, the regioselectivity could be switched in favor of the α product (γ/α 7:93) [**45**]. Use of other solvents, such as Et_2O, THF, or toluene, produced very low selectivities. Use of cinnamyl acetate (**22**) as substrate favored the α product.

In total, 29 phosphorus-containing chiral ligands of various structures were screened under the optimized γ-selective conditions, but most of them gave little or no chiral induction. The four ligands **38a–d**, all derived from (−)-TADDOL, depicted in Fig. 8.4 gave *ee*s in excess of 30% in the reaction between ethyl magnesium bromide and cinnamyl chloride.

Ligand **38a**, bearing an (−)-*N*-methylephedrine substituent, was superior, and gave an *ee* of 51% and a γ/α ratio of 91:9. Further fine-tuning of the reaction conditions gave an improvement to 73% *ee* and a γ/α ratio of 94:6. Optimum enantioselectivity was favored here by a CuCN:ligand ratio of 1:1 and the use of only 1 mol% of each. Slower addition of the Grignard reagent (40 min) also produced improvements. It should be noted, however, that with 2.5 mol% of CuCN, 5 mol% of ligand, and addition of the Grignard reagent over only 20 min, the γ/α ratio was 100:0, with an only slightly lower *ee* (67%).



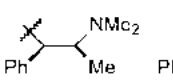
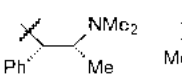
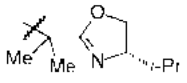
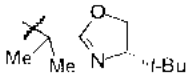
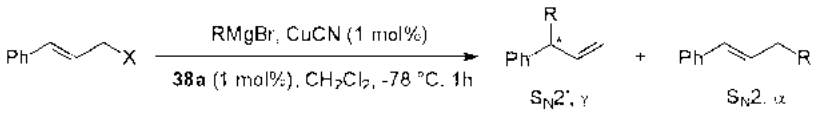
	38a	38b	38c	38d
R =				
$S_N2':S_N2$	91:9	95:5	95:5	95:5
ee (%)	51	34	32	32

Fig. 8.4. Ligands **38** employed in allylic substitution reactions between cinnamyl chloride and EtMgBr.

With suitable conditions for the test system established, variations in the structures of the substrate and the Grignard reagent were examined (Scheme 8.22).



X = Cl, Br, $OP(O)(OMe)_2$, OAc
R = Et, *n*-Pr, *n*-Bu, *n*-C_5H_{11}, Me, *c*-C_6H_{11}, *c*-C_5H_9, *c*-$C_6H_{11}CH_2$, *i*-Pr, *i*-Bu, Me_3SiCH_2, neopentyl, 4-F C_6H_4, 2 MeO C_6H_4

Scheme 8.22. Investigation of substrate and Grignard reagent structure.

The effect of the leaving group was briefly examined, but cinnamyl bromide gave a substantially lower *ee* (38%). Cinnamyl dimethyl phosphonate, or acetate, gave very poor results. The cyclohexyl-substituted allylic acetate **21**, on the other hand, afforded a completely *γ*-selective reaction, but the product turned out to be racemic. Changing the Grignard reagent halide from bromide to either chloride or iodide resulted in very low *ees*.

The scope of the reaction with cinnamyl chloride was assessed by testing a number of different Grignard reagents, including *n*-alkyl, methyl, aryl, cycloalkyl, isopropyl, and isobutyl derivatives, $TMSCH_2MgBr$, and the sterically crowded neopentylMgBr. Increased steric hindrance, however, resulted in lower *ees* and none of the tested reagents gave *ees* as high as EtMgBr had. The bulky neopentyl Grignard reagent gave almost racemic S_N2' product. The *n*-alkyl Grignard reagents *n*-PrMgBr and *n*-BuMgBr gave *ees* of 57 and 52%, respectively. Interestingly, the reaction could also be performed with an aromatic Grignard reagent, but with low *ees* (21% for 2-MeO C_6H_4MgBr).

The reported results show that the reaction is very sensitive to small changes in the reaction conditions, such as temperature. Just a few degrees difference in the reaction temperature could have a dramatic influence on the outcome of the reaction. No single set of reaction conditions was applicable to all cases, and the depen-

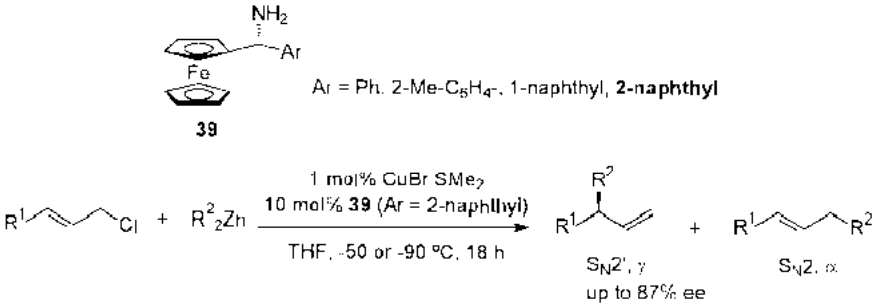
dence of the selectivity on the structure of the Grignard reagent and substrate is hard to interpret.

Organozinc reagents in combination with a catalytic amount of copper catalyst and ligand can be used in place of Grignard reagents. In this case, however, the allylic electrophile has to carry a relatively reactive leaving group, such as a halide; allylic esters do not normally react with organozinc reagents. Knochel et al. discovered that chiral primary amines could function as useful ligands to copper for catalysis of allylic substitution reactions between unsymmetrical allylic chlorides and diorganozinc reagents [41a]. Primary ferrocenyl amines **39** were the most efficient of the ligands studied. These ligands may be obtained easily and with high optical purity from ferrocenyl aryl ketones, by reduction with $BH_3 \cdot SMe_2$ in the presence of a chiral ligand.

The Ar group in the ligand is very important for the enantioselectivity in the S_N2' product. In a screening reaction between cinnamyl chloride and dineopentylzinc, the ligand bearing a 2-naphthyl substituent produced the highest *ee* (42%). Furthermore, a high ratio of ligand to copper of 10:1 increased the *ee* to 67% at −50 °C, while a reduction in the reaction temperature to −90 °C resulted in a further increase, to 82% *ee*. Interestingly, the enantioselectivity showed an almost linear dependence on temperature and only 25% *ee* was achieved at 25 °C.

The influence of the leaving group in the substrate was also investigated, but changes from the Cl in cinnamyl chloride to Br, carbonate, xanthate, or phosphate all resulted in diminished selectivity. The type of organometallic reagent was also very important, and no reaction at all was observed with organozinc reagents of the type RZnX.

To conclude the study, combinations of differently substituted substrates and diorganozinc reagents were investigated (Scheme 8.23).

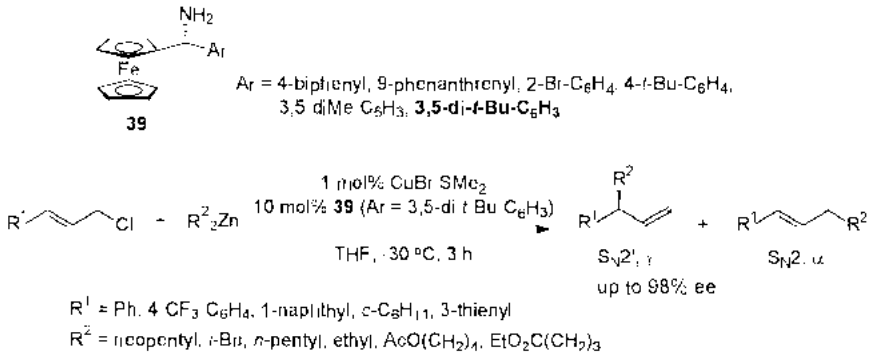


Scheme 8.23. Asymmetric allylic substitution catalyzed by **39** (Ar = 2-naphthyl).

The reactions were regioselective in all cases, with γ:α ratios of >90:10. The maximum *ee*, 87%, was obtained by treatment of a substrate containing the electron-withdrawing R^1 substituent 4-CF_3 C_6H_4 with dineopentylzinc. Changing the

substrate R^1 group to naphthyl, cyclohexyl, or functionalized substituents such as 3-thienyl or silylethers resulted in lower *ees* being obtained. A change of the R^2 group in the diorganozinc reagent from the bulky neopentyl invariably produced lower *ees*. Bis(trialkylsilylmethyl)zinc gave 42–67% *ee*. Bis(myrtanyl)zinc reagents of both possible configurations, (+) and (−), were also employed, and afforded diastereomeric substitution products with *ees* of around 40%. The asymmetric induction seems to be highly influenced by steric hindrance and sterically demanding diorganozincs were necessary for obtainment of high *ees*.

The ferrocenyl amine ligands **39** could be improved further by changing the Ar substituent (Scheme 8.24) [41b].

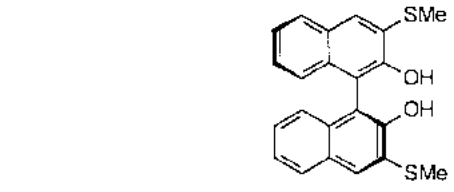


Scheme 8.24. Improvements of ligand **39**.

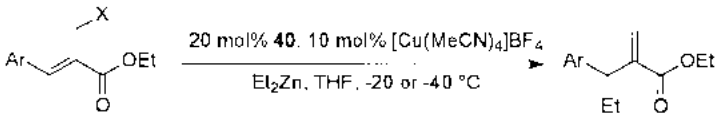
Steric hindrance in the ligand **39** proved to be very important, and the best results were obtained by introducing sterically demanding substituents on the phenyl ring; 3,5-di-*t*-butylphenyl, for example, gave a 92% *ee* in the reaction between cinnamyl chloride and dineopentylzinc. This ligand also gave the best S_N2' selectivity, at 98:2. Further optimization, including simultaneous addition of R_2Zn and the allylic chloride over 3 h, resulted in an improvement to a 96% *ee*. Under these conditions a higher reaction temperature (−30 °C) could also be employed without any decrease in *ee*. With the 2-naphthyl-substituted ligand, the combination of 4-CF_3-cinnamyl chloride and dineopentylzinc resulted in the highest *ee* (98%) of all the substrate combinations studied. This optimized ligand system in all cases produced enantioselectivities higher than those obtained with the 2-naphthyl-substituted ligand employed in the first study. It is also noteworthy that, with this ligand, significant *ees* (44–65%) could be obtained from the di-*n*-alkylzinc reagents diethylzinc and dipentylzinc. Further improvements were obtained by the use of a mixed reagent, ethylneopentylzinc, which selectively transferred the ethyl group with an *ee* of 52%, compared to 44% for Et_2Zn.

Functionalized diorganozinc reagents $[AcO(CH_2)_4]_2Zn$ and $[EtO_2C(CH_2)_3]_2Zn$ were also employed, giving complete γ selectivity in both cases, with *ees* of 50%.

Woodward et al. have used the binaphthol-derived ligand **40** in asymmetric conjugate addition reactions of dialkylzinc to enones [46]. Compound **40** has also been studied as a ligand in allylic substitutions with diorganozinc reagents [47]. To allow better control over selectivity in γ substitution of the allylic electrophiles studied, Woodward et al. investigated the influence of an additional ester substituent in the β-position (Scheme 8.25).



40



41

X = Br, Cl, OCHO, OSO_2Me
Ar = Ph, 4-NO_2-C_6H_4-, 4-Cl-C_6H_4-, 4-Me-C_6H_4-, 1-naphthyl

Scheme 8.25. Allylic substitution of **41** in the presence of ligand **40**.

The reaction between allylic substrates **41** and Et_2Zn, catalyzed by $[Cu(MeCN)_4]BF_4$, was indeed very fast, and proceeded with excellent γ selectivity. Inclusion of the ligand **40** in the reaction mixture resulted in some enantioselectivity, but rather large quantities of catalyst (10 mol%) and ligand (20 mol%) had to be used to maximize asymmetric induction. The effect of the leaving group was examined; chloride produced higher *ees* than bromide did, but the yields obtained were significantly lower. With a mesylate the reaction gave a high yield, but an almost racemic product was obtained, while an allylic formate was unreactive under these conditions. With different aryl-substituted allylic chlorides and Et_2Zn a maximum of 64% *ee* was achieved. Changes in temperature between −20 and −40 °C had a minor influence on the enantioselectivity. The highest *ee* was obtained with Ar = 4-$O_2NC_6H_4$, and the reaction seems to be controlled more by electronic factors than by steric ones. For the other γ-aryl-substituted substrates **41** investigated, the *ees* varied between 22% and 36%. The asymmetric version of this reaction is unfortunately characterized by low isolated yields.

It may be concluded from the different examples shown here that the enantioselective copper-catalyzed allylic substitution reaction needs further improvement. High enantioselectivities can be obtained if chirality is present in the leaving group of the substrate, but with external chiral ligands, enantioselectivities in excess of 90% *ee* have only been obtained in one system, limited to the introduction of the sterically hindered neopentyl group.

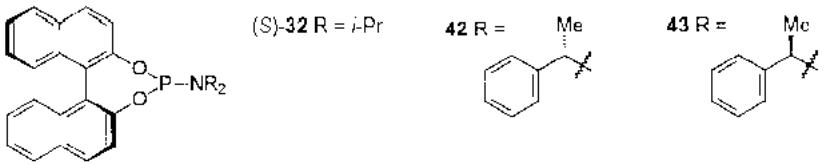


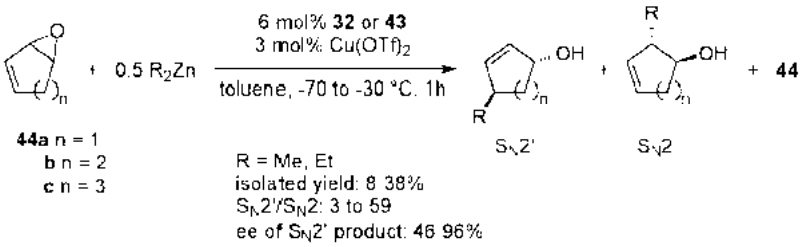
Fig. 8.5. Binaphthol-derived phosphoramidite ligands developed by Feringa et al.

8.3
Epoxides and Related Substrates

Ring-opening of oxiranes with organocopper reagents is a well known process in organocopper chemistry, usually proceeding with high selectivity. For vinyl oxiranes, both S_N2 and S_N2' reaction types are possible and the selectivity can be controlled. Optically active allylic alcohol products can be obtained when starting from nonracemic vinyloxiranes [48].

Asymmetric ring-opening of saturated epoxides by organocuprates has been studied, but only low enantioselectivities (< 15% *ee*) have so far been obtained [49, 50]. Müller et al., for example, have reported that the reaction between cyclohexene oxide and MeMgBr, catalyzed by 10% of a chiral Schiff base copper complex, gave *trans*-2-methylcyclohexanol in 50% yield and with 10% *ee* [50].

The use of vinyl epoxides as substrates in enantioselective copper-catalyzed reactions, on the other hand, has met with more success. An interesting chiral ligand effect on $Cu(OTf)_2$-catalyzed reactions between cyclic vinyloxiranes and dialkylzinc reagents was noted by Feringa et al. [51]. The 2,2′-binaphthyl phosphorus amidite ligands **32** and **43** (Fig. 8.5), which have been successfully used in copper-catalyzed enantioselective conjugate additions to enones [37], allowed kinetic resolution of racemic cyclic vinyloxiranes (Scheme 8.26).



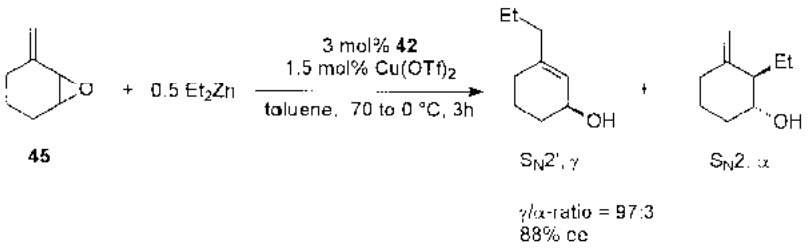
Scheme 8.26. Kinetic resolution of cyclic vinyl oxiranes **44**.

The process was S_N2'-selective in the presence of catalytic amounts of ligands (*S*)-**32** or (*S*, *R*, *R*)-**43** and $Cu(OTf)_2$. This is another example of ligand-accelerated catalysis; without the ligand the reaction was much slower and proceeded with low regioselectivity.

When 0.5 equivalents of dialkylzinc were used, *ees* of more than 90% were obtained, with reasonable isolated yields of up to 38% [52] of the S_N2'-substituted

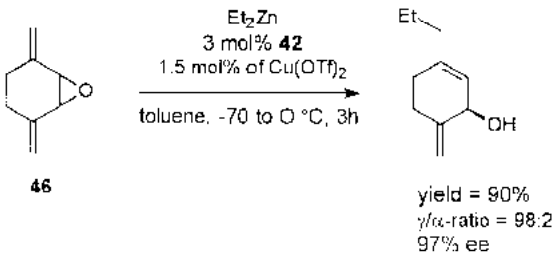
products arising from the 1,3-cyclohexadiene monoepoxide **44b** and the 1,3-cycloheptadiene monoepoxide **44c**. The substrate **44a**, with a five-membered ring, gave much lower asymmetric induction and the maximum *ee* was 54%. Ligand **43** was superior to **32** in all cases studied. The yield and *ee* of the remaining unreacted vinyloxirane was not mentioned.

The vinyloxirane reaction was later extended to methylidene cyclohexene oxide and to related *meso* derivatives [53]. The effects of the diastereomeric ligands **42** and **43** (Fig. 8.5), derived from (*S*)-binaphthol and (*S*, *S*)- or (*R*, *R*)-*bis*-phenylethylamine respectively, were investigated. In the case of kinetic resolution of racemic methylidene cyclohexane epoxide **45** with Et_2Zn, ligand **42** produced better yields, regioselectivity, and enantioselectivity than **43** (Scheme 8.27).



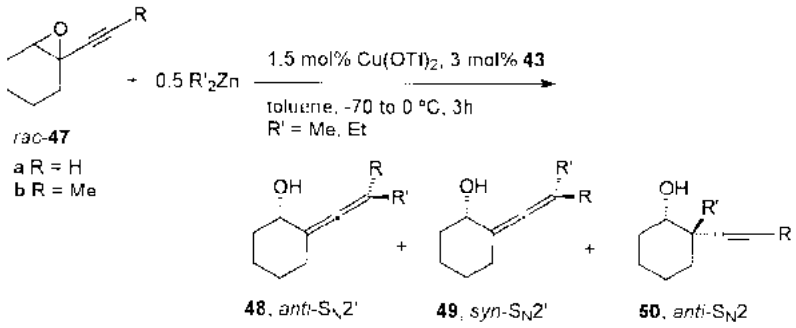
Scheme 8.27. Reaction between epoxide **45** and Et_2Zn, catalyzed by $Cu(OTf)_2$ and ligand **42**.

To avoid the inherent limitations of a kinetic resolution process, the reaction was extended to desymmetrization of prochiral *meso* epoxides. A number of cyclic dimethylidene epoxides were synthesized and subjected to treatment with Et_2Zn in the presence of $Cu(OTf)_2$ and ligands **42** or **43**. As in the case mentioned above, ligand **42** was superior in terms of selectivity. Cyclohexane derivative **46** gave the ring-opened product with a 97% *ee* and in a 90% isolated yield, with a γ/α ratio of 98:2 (Scheme 8.28). The other substrates investigated produced significantly lower *ee*s of between 66% and 85%.



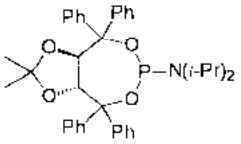
Scheme 8.28. Reaction between **46** and Et_2Zn.

The same authors also studied the alkylation of alkynyl epoxides for formation of optically active α-allenic alcohols under kinetic resolution conditions (Scheme 8.29) [54].



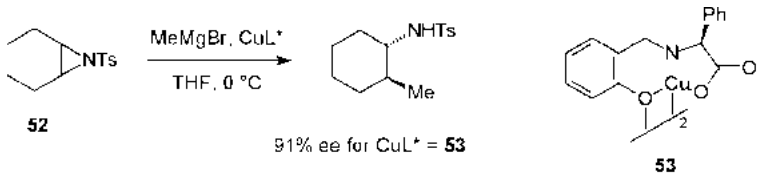
Scheme 8.29. Reactions of alkynyl epoxides **47** with R_2Zn.

With ligand **43** the reaction between **47** and 0.5 equivalent of R_2Zn was highly diastereoselective, proceeding in an *anti* fashion (**48**/**49** ≥ 97:3). The regioselectivity depended on the diorganozinc reagent, a low S_N2'/S_N2 ratio of 55:45 being obtained with **47a** (R = H) and Me_2Zn, but ratios of more than 90:10 with Et_2Zn. *Ee*s of up to 38% were obtained for the *anti*-S_N2' product **48** (R′ = Et). The influence of the ligand was investigated for the reaction between **47a** and Et_2Zn. Compound **42** gave a highly *anti*- and S_N2'-selective reaction (**48**/**49** > 99:1, (**48** + **49**)/**50** = 97:3), but **48** was almost racemic. The use of TADDOL-derived ligand **51** resulted in a *syn*- and S_N2'-selective reaction to give **49** in 36% *ee*.



51

Copper-catalyzed desymmetrization of *N*-tosylaziridine **52** with Grignard reagents has been reported (Scheme 8.30) [50].



Scheme 8.30. Desymmetrisation of *N*-tosylaziridine **52**.

A number of structurally very different copper complexes were employed as catalysts. The copper complex of binaphthol-derived phosphoramidite **32** and the Schiff base complex **53** (derived from salicylaldehyde and phenylglycine) gave promising results in a screening reaction between **52** and MeMgBr, and **53** was chosen as the candidate for optimization. The effect of solvent (THF or Et_2O),

variation of the metal in the organometallic reagent (Mg or Li), and variation of the Grignard reagent counter-ion (Cl^-, Br^-, or I^-) were studied, but it was difficult to find any systematic trends. The best conditions consisted of a slow addition (10 min.) of MeMgBr to **52** and 30 mol% of complex **53**. In this way, an *ee* of 91% was obtained (Scheme 8.30).

8.4 Concluding Remarks

Copper-mediated enantioselective substitution reactions have undergone an interesting development during the last decade. For allylic substitution, high *ees* have been obtained for stoichiometric reactions and for the corresponding catalytic reactions with allylic chlorides and sterically hindered carbon nucleophiles. For nonhindered carbon nucleophiles (bearing *n*-alkyl groups), copper-catalyzed reactions with allylic chlorides give *ees* in the 50–73% range. With allylic acetate, the highest enantioselectivity obtained in copper-catalyzed allylic substitution is 64%, also obtained with nonhindered carbon nucleophiles. For vinylepoxides and aziridines, high *ees* have recently been obtained in copper-catalyzed reactions with Et_2Zn and MeMgBr, respectively. In conclusion, the developments made during the last few years look very promising, but there is still a lot more to be done in the field. Further improvement in the copper-catalyzed enantioselective substitution of allylic acetates, for example, would be of great synthetic interest.

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9
Copper-Mediated Synthesis of Natural and Unnatural Products

Yukiyasu Chounan and Yoshinori Yamamoto

Abstract

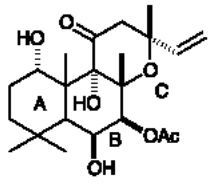
The true value of organotransition metal reagents and reactions in organic synthesis is measured by the extent of their usage in the synthesis of complicated natural products. From this point of view, the importance of the organocopper reagents is comparable to that of palladium reagents. This chapter highlights some of the most important advances in this field published from about 1995 onwards, as several excellent reviews [1] already cover papers published before then.

Applications of organocopper reagents and reactions to natural product synthesis are classified by reaction type: conjugate addition, S_N2 substitution, S_N2' substitution, 1,2-metalate rearrangement, and carbocupration.

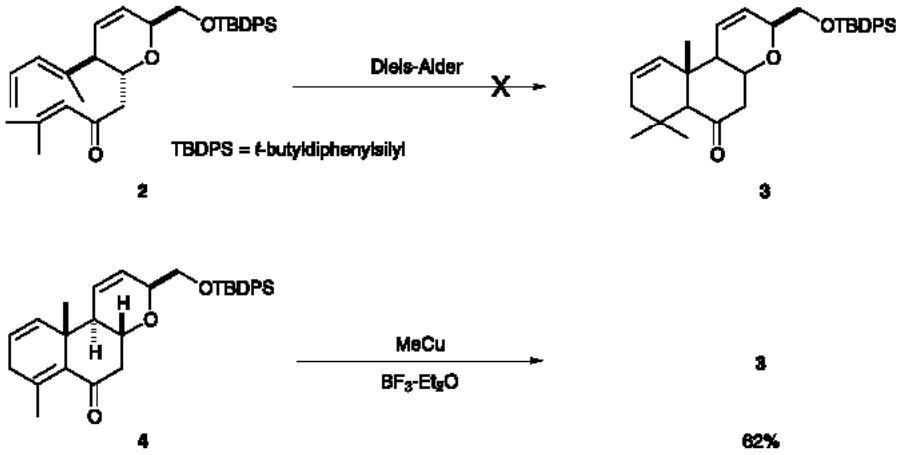
9.1
Conjugate Addition

Conjugate addition [2] to Michael acceptors is the most important and useful reaction in organocopper chemistry, and the reaction is often used as the key step in the synthesis of numerous natural and unnatural products. Perhaps one of the most efficient methods for the synthesis of quaternary carbon centers is organocopper-mediated conjugate addition to β,β-disubstituted enones.

An example of the construction of quaternary carbon can be seen in a synthetic approach to forskolin (**1**) [3]. Forskolin, a highly oxygenated labdane diterpene, exhibits a broad range of physiological activities thanks to its ability to activate adenylate cyclase. Hanna's group's synthetic strategy (Scheme 9.1) involved an intramolecular Diels–Alder cyclization of trienone **2**, which should have assembled the A and B rings of the tricyclic forskolin skeleton simultaneously. The approach failed to give the desired product, however, owing to the steric bulkiness of the system. In order to overcome this difficulty, the construction of the forskolin framework from tricyclic ketone **4** by 1,4-addition of methyl copper reagent was successfully investigated. Subsequent treatment of **4** with MeCu BF_3 in ether, according to Yamamoto's procedure [4], provided **3** in 62% yield.

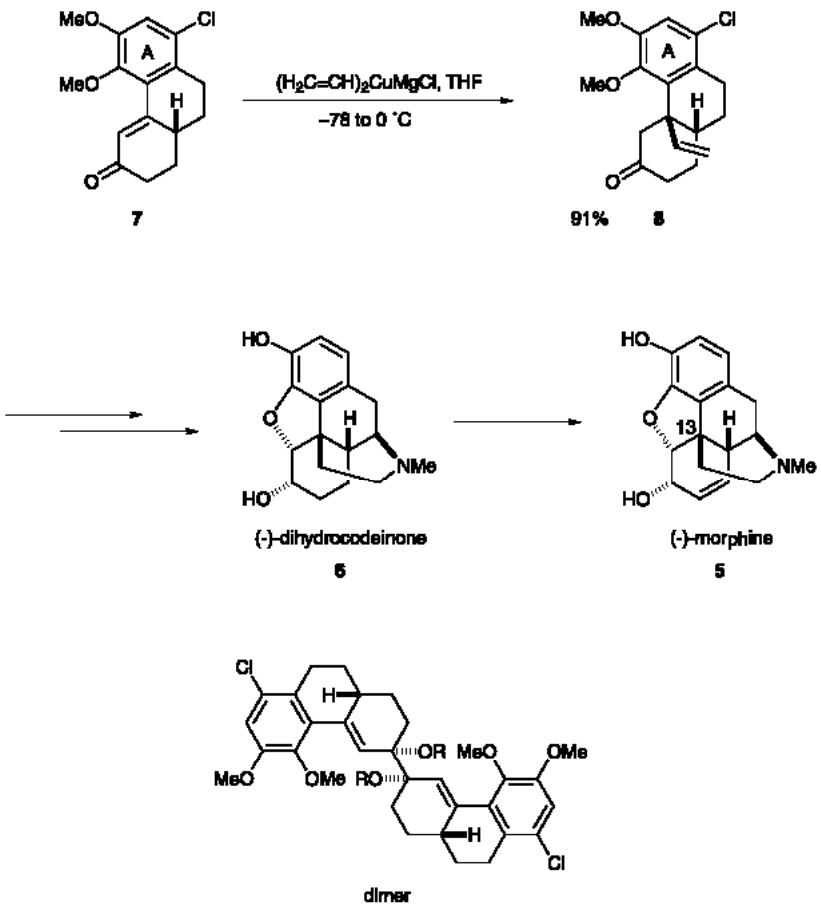


Forskolin
1



Scheme 9.1.

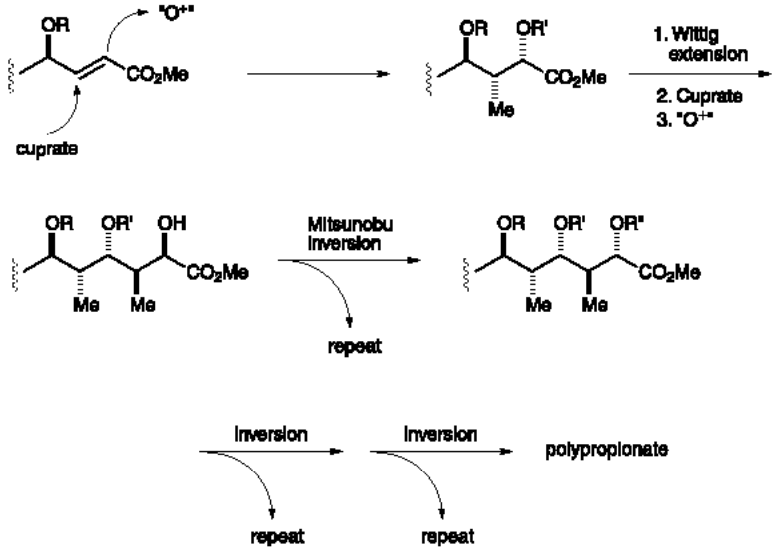
One of the advantages of conjugate addition is that it may be used to introduce sp^2 carbon side chains, for example in the synthesis of (–)-morphine (5) [5]. Opium alkaloids of the (–)-morphine type have long represented challenges for natural products synthesis because of their complex molecular architecture, involving a dense network of three carbocycles and two heterocycles containing five vicinal stereogenic carbons. One of these stereocenters (C13) is a quaternary benzylic carbon atom and therefore difficult to create. The synthetic strategy of Mulzer's group [6] was the first to provide a functionalized phenanthrene derivative of type **7**, with a correctly substituted aromatic ring A, and then to employ conjugate addition of an sp^2-unit (vinyl group) to establish this quaternary benzylic stereocenter (Scheme 9.2). The conjugate addition of a vinyl cuprate to **7**, with activation of the vinyl cuprates by chlorotrimethylsilane (TMSCl) [7], was troubled by low yields of **8** and by a non-polar C_2 symmetrical dimer byproduct. As a subsequent refinement, the simple vinyl magnesiocuprate $(CH_2{=}CH)_2CuMgCl$ [8], in the absence of TMSCl, afforded precursor **8** as a single diastereomer in 91% yield without any dimeric byproducts. This chirally economic asymmetric total synthesis is linear

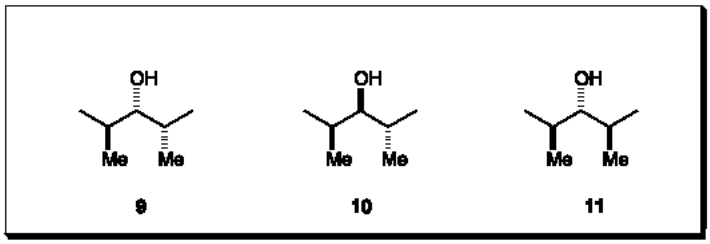


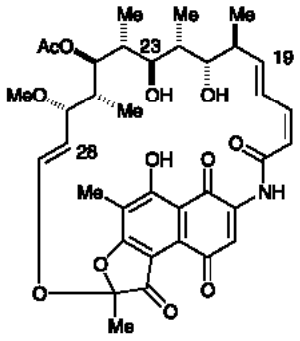
Scheme 9.2.

but very short, with 1,4-addition of the sp^2 carbon unit with the aid of a vinyl cuprate as the key reaction.

Another of the merits of organocopper reagents is the high degree of stereocontrol in conjugate addition. The polypropionate pathway is a biosynthetic route to important classes of antibiotics and the basic structures of a number of natural products. In practice, each propionate-derived stereocenter [9] can be constructed individually by adopting the aldol condensation in its numerous asymmetric versions [10]. The alternative method, which consists of the stereocontrolled addition of a cuprate to an enantiopure γ-alkoxy-α,β-unsaturated ester followed by hydroxylation of the corresponding enolate, has been reported by Hanessian et al. [11], who applied this method to the construction of the C19–C28 acyclic chain of rifamycin S (**12**) [12]. This simple strategy, shown in Scheme 9.3, is admirable, with sequential reactions proceeding in a stereocontrolled fashion through iterative cycles of





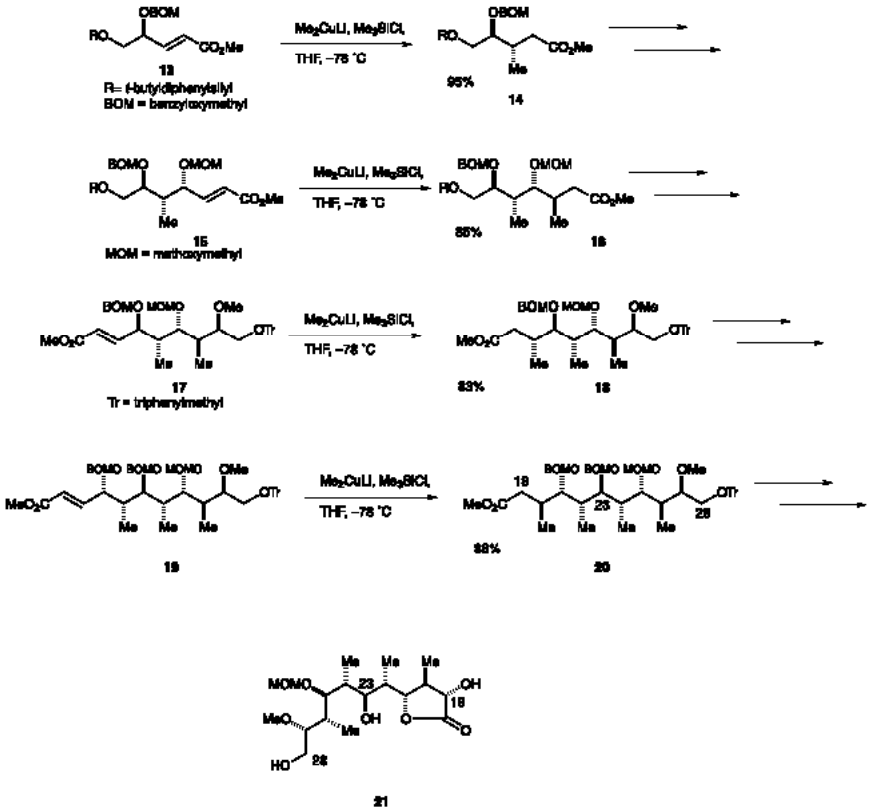


12 Rifamycin S

Scheme 9.3. Stereocontrolled strategy for iterative assembly of enantiopure polypropionate subunits.

cuprate additions, hydroxylations, Wittig chain extensions, and Mitsunobu reactions. This simple approach can give rise to all the combinations of stereotriads shown as types **9**, **10**, and **11**.

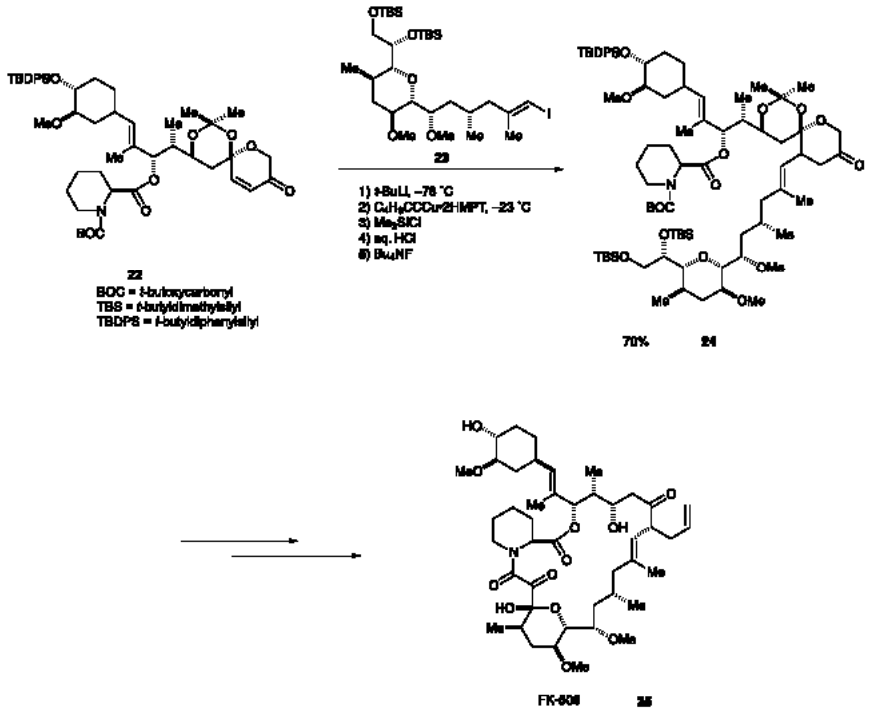
In the case at hand, the γ-alkoxy-α,β-unsaturated esters **13**, **15**, **17**, and **19** were treated with lithium dimethylcuprate in the presence of excess TMSCl in THF at −78 °C, producing the adducts **14**, **16**, **18**, and **20** in 95, 85, 83, and 86% yields, respectively (Scheme 9.4). It was thus possible to assemble the acyclic C19–C28 subunit **21** of rifamycin S (**12**), which represents the longest sequence of contiguous propionate-derived units among the macrolides and ansa antibiotics. The strategy has also successfully been applied to the syntheses of the (all propionate)-derived segments of such natural products as bafilomycin A_1 [13], hygrolidin [**14**], elaiophylin [15], and scytophycin C [16].



Scheme 9.4.

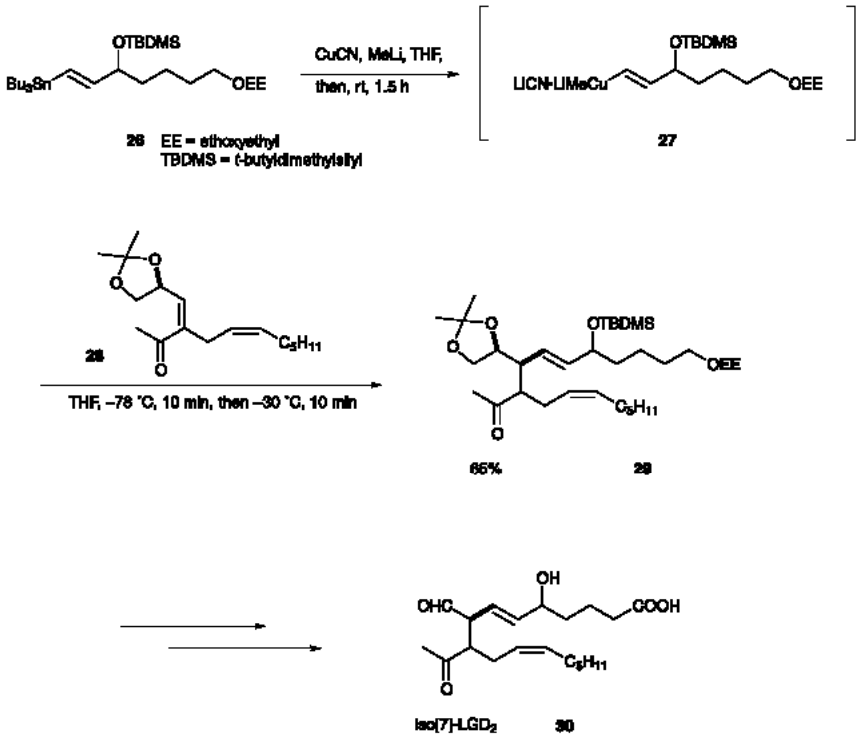
Conjugate addition of organocopper reagents has also been used to introduce multifunctional groups in the final carbon–carbon bond-forming step. The immunosuppressant FK-506 (**25**) [17] was noteworthy in its activity, which was found

to be approximately 100 times higher than that of cyclosporin A, the favored drug at that time [18]. In the total synthesis of **25**, by Ireland et al., addition of a vinyl cuprate was a key step [19]. Their strategy was to couple two large building blocks, the "top half" and "bottom half" fragments (Scheme 9.5), and conjugate addition of the bottom half vinyl iodide **23** to the top half spiroenone **22** was investigated in this context. Use variously of lower order cuprates and homo- and mixed-cyano-Gilman cuprates [20] gave the desired adduct **24** in yields no better than 30–40%. An improved methodology involved the use of a dummy group, hexynylcopper, as its bis-HMPT complex [21]. This reaction required only 1.1 equiv. of the vinyl lithium derived from **23**, and gave a 70% yield of the ketone **24**. High facial selectivity was formed and no diastereomeric conjugate addition products were formed [22]. The success of this coupling procedure provides an ideal solution to the problems of trisubstituted olefin synthesis that had been prominent in previous syntheses [23].



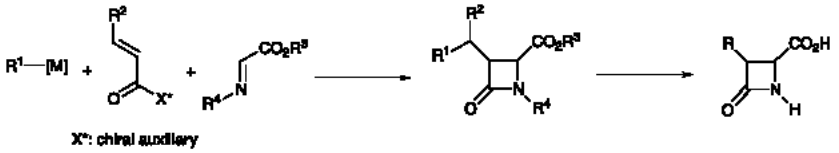
Scheme 9.5.

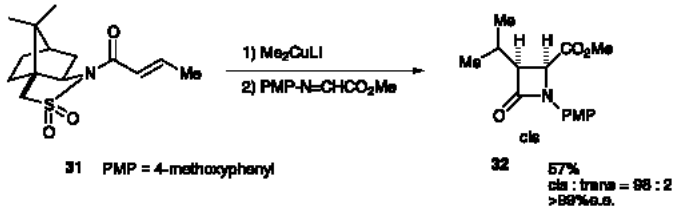
Another example is found in the total synthesis of iso[7]-levuglandin D_2 (**30**) by Salomon et al. [24]. The cyanocuprate **27** was prepared by transmetalation of multifunctional vinylstannane **26** with $Me_2CuLi{\cdot}LiCN$ (Scheme 9.6) [25]. Addition of the enone **28** to the multifunctional vinylcuprate **27** provided the conjugate addition product **29** in 65% yield (based on the enone consumed).



Scheme 9.6.

A typical one-pot, three-component coupling sequence can be found in the preparation of the prostaglandin skeleton [26] in a remarkably rapid fashion by the conjugate addition of an organocopper reagent to a substituted cyclopentanone, followed by enolate trapping. That chemistry is not discussed here though, since there have been many excellent reviews in the past ten years [1, 27]. Yamamoto et al. first accomplished three-component coupling using organocopper compounds in the field of β-lactam synthesis [28], the key steps being addition of nitrogen nucleophiles to enoates with the aid of copper amides and subsequent enolate trapping with an electrophile. Palomo et al. have recently reported an alternative synthetic method [29]. Their strategy was based on an efficient combination of three reactants, in the form of addition of organocuprate reagents to α,β-unsaturated carboxylic acid derivatives and subsequent condensation of the resulting enolates with an imine, as shown in Scheme 9.7. Treatment, for example, of the Gilman reagent Me_2CuLi with *N*-enoyl-sultam **31**, followed by one-pot enolate trapping with the imine, produced a 57% chemical yield of the *cis* β-lactam adduct **32**, with high diastereoselectivity (98:2), and in excellent enantiomeric purity (>99% *ee*). The stepwise process, by way of metal enolates generated by deprotonation, provided the expected adduct in lower chemical yields and with poorer diastereomeric and enantiomeric ratios than those attained using this method.



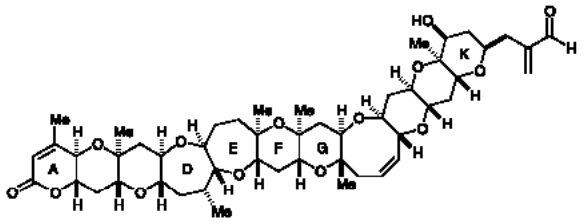


Scheme 9.7. An asymmetric, three-component synthetic strategy for β-lactam synthesis.

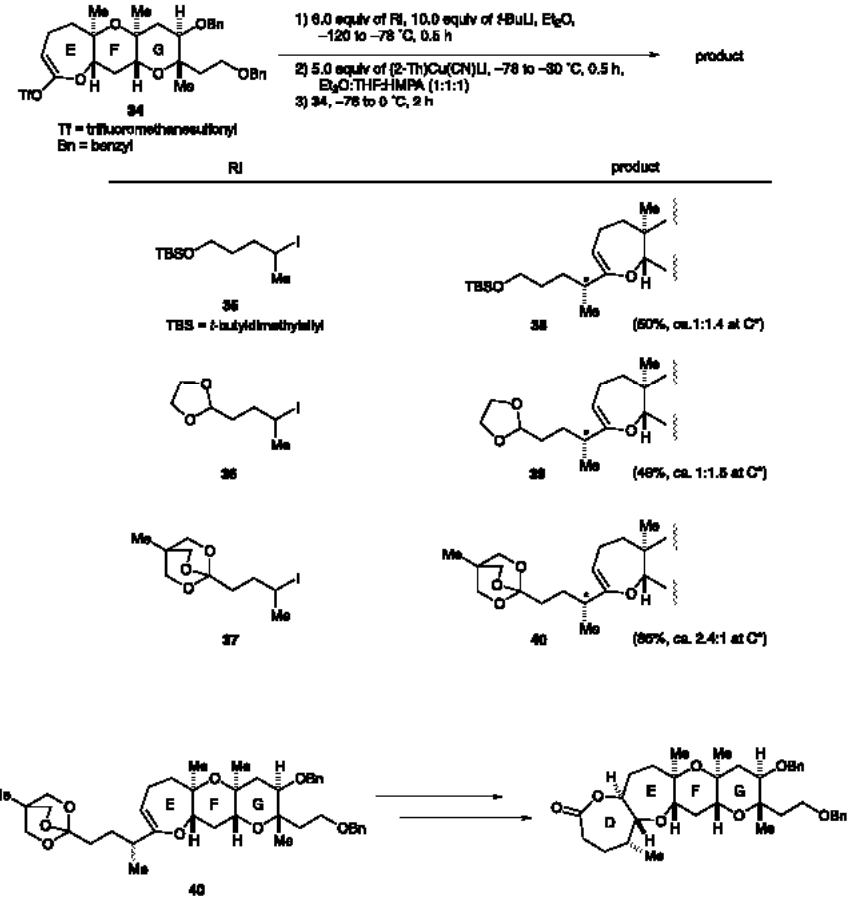
9.2
S_N2 Substitution [30]

As well as conjugate additions, S_N2 substitution reactions with organocopper reagents are frequently used in various synthetic processes. In a total synthesis of brevetoxin B (**33**), an active principle of the poisonous waters associated with the red tide phenomenon, substitution on an sp^2 carbon center by a functional organocopper reagent is employed as one of the key reactions (Scheme 9.8) [31]. To carry out the formation of the D ring, alkyl iodides **35** and **36** were transformed into their lithio derivatives by halogen-metal exchange with *t*-BuLi and into the cyano-Gilman reagents R(2-thienyl)CuLi·LiCN [32], which coupled easily with the lactone-derived enol triflate **34** to afford desired oxepenes **38** and **39** in 50% and 49% yields, respectively. In view of the lack of stereoselectivity in these substitution reactions, the orthoester iodide **37** was prepared and utilized in order to improve the stereochemical outcome of the process. Its coupling with the enol triflate **34** by way of the cyanocuprate afforded **40** in an 85% total yield and with a diastereoselectivity of *ca.* 2.4:1 in favor of the desired stereoisomer. The diastereoselectivity is quite superior to that obtained in the two preceding cases. It should be noted here the use of the solvent system Et_2O:THF:HMPA (1:1:1) in this coupling reaction was important for the stereoselectivity observed. Compound **40** was converted to the DEFG lactone segment in several steps.

S_N2 substitution using organocopper reagents is an efficient method for the synthesis of 3-substituted olefins. In the synthesis of farnesyl diphosphate analogues (**43**, **45**) as potential inhibitors of the enzyme protein-farnesyl transferase, for example, organocopper methodology was compared with the Stille reaction [33] and the Suzuki reaction [34], frequently used in the coupling of vinyl triflates with



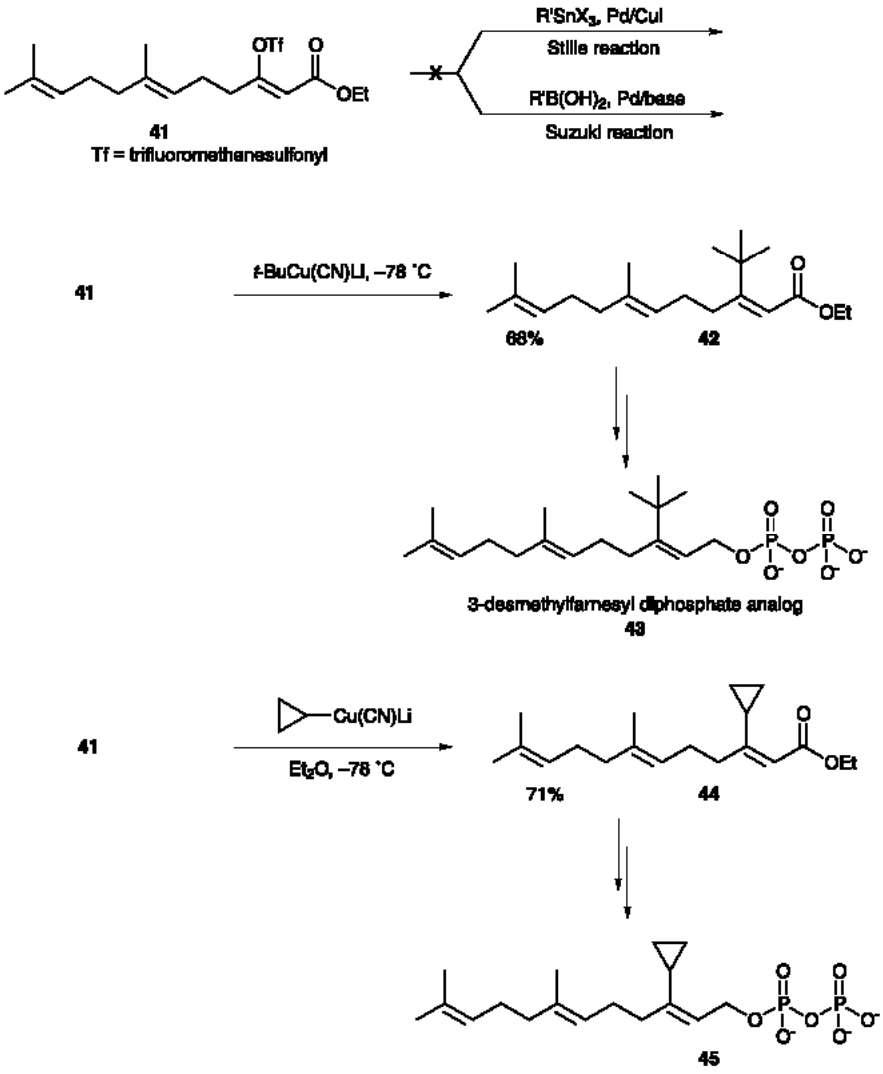
33 brevetoxin B



Scheme 9.8.

a variety of organotin nucleophiles and boronic acids to introduce functional groups onto sp^2 carbon atoms [35]. In this case, neither of these palladium-catalyzed coupling reactions was amenable to the introduction of a cyclopropyl or *t*-butyl nucle-

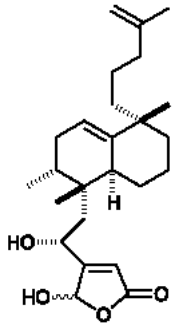
ophile. On the other hand, treatment of vinyl triflate **41** with 1.5 equiv. of *t*-BuCu(CN)Li [36] in ether at −78 °C for 1 h produced the desired ester **42** in 68% yield (Scheme 9.9). Coupling of **41** with the lower order cyclopropyl cyanocuprate reagent at −78 °C for 1.5 h also afforded **44**, in 71% yield. The double bond geometry was maintained during all these cuprate coupling reactions, and none of the undesired but more stable *trans* isomers of **42** and **44** were isolated.



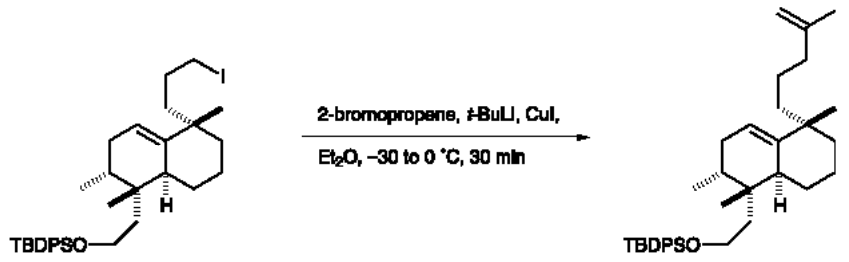
Scheme 9.9.

In a total synthesis of cdc25A protein phosphatase inhibitor dysidiolide (**46**) [37], substitution on an sp^3 carbon center by vinyl cuprate was used to accom-

plish elaboration of the side chain (Scheme 9.10) [38]. The C-1 side chain was set in place by means of iodide displacement with the vinyl cuprate derived from 2-lithiopropene (10 equiv. of 2-bromopropene, 21 equiv. of *t*-BuLi, 5 equiv. of CuI, Et_2O, −30 to 0 °C, then 0 °C for 30 min) to afford **48** in 97% yield.



46 Dysidiolide

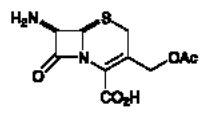


47
TBDPS = *t*-butyldiphenylsilyl

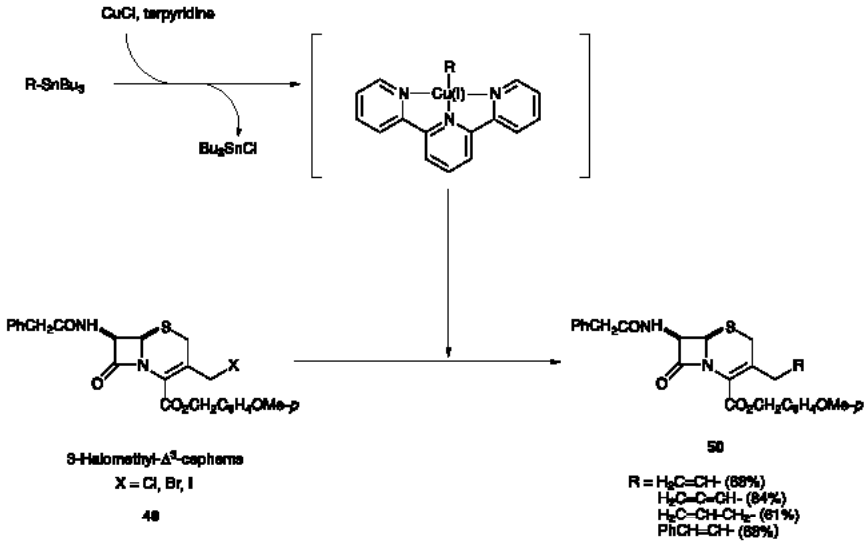
97% **48**

Scheme 9.10.

Several groups have recently accomplished various intramolecular and intermolecular Stille-type reactions [39] with the aid of a copper(I) salt in the absence of palladium catalysts, with transmetalation of organostannanes with the copper(I) salt serving to generate organocopper(I) species [40]. To explore the cephalosporin analogues as β-lactam antibiotics possessing high antibacterial activity, a non-palladium Stille-type reaction was used in the synthesis of C(3)-substituted Δ^3-cephems [41]. Treatment of the 3-halomethyl-Δ^3-cephems **49** with tributylvinyltin (1.5 equiv.) and copper chloride (1.0 equiv.) in the presence of terpyridine (1.0 equiv., added for coordinative stabilization of the generated vinylcopper species) in *N*-methyl-2-pyrrolidinone at room temperature predominantly afforded the 3-allyl-Δ^3-cephem **50** in 68% yield (Scheme 9.11). Copper-promoted reactions with allenyltributyltin, allyltributyltin, and styryltributyltin were also successfully applied to the synthesis of cephem derivatives, giving the desired coupling products in 84%, 61%, and 50% yields, respectively.



7-Aminocephalosporanic Acid (7-ACA)

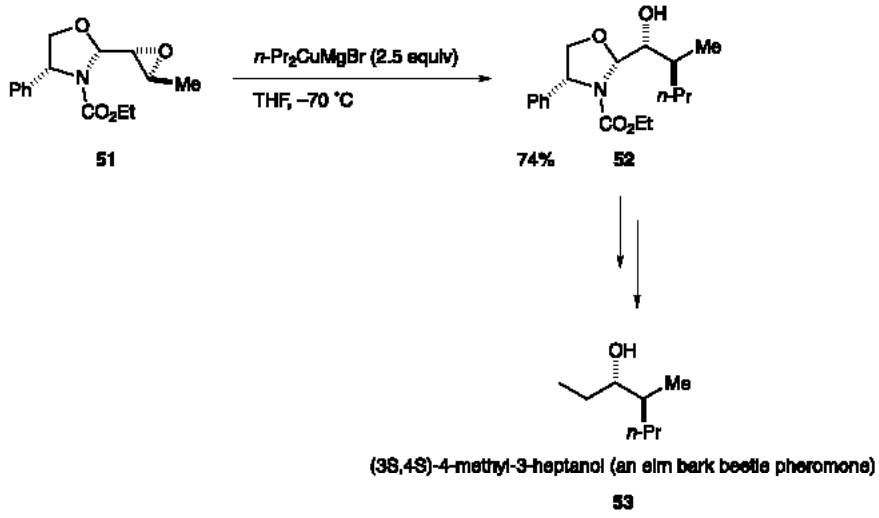


Scheme 9.11.

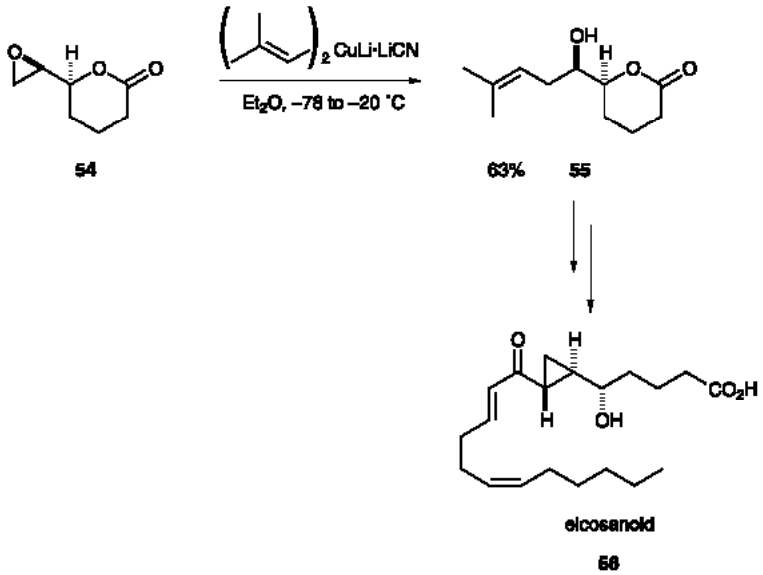
S_N2 Reactions with epoxides and aziridines are also synthetically useful. An example of epoxide cleavage with an organocopper reagent with sp^3 carbon moieties is the enantioselective synthesis of (3*S*,4*S*)-4-methyl-3-heptanol (**53**), an elm bark beetle (*Scolytus multistriatus*) pheromone [42]. The chiral epoxy oxazolidine **51** [43], prepared from (*R*)-phenylglycinol, reacted with a propylmagnesium bromide-derived cuprate at −70 °C to afford the oxazolidine **52** in 74% yield (Scheme 9.12). Compound **52** was converted into the target molecular **53** by conventional procedures.

Epoxide ring-opening with transfer of an sp^2 carbon moiety was applied in a short synthesis [44] of eicosanoid **56** [45], relevant in marine prostanoid biosynthesis (Scheme 9.13). Homoallyl alcohol **55** was obtained in good yield from **54** by use of a cyano-Gilman alkenylcuprate [46].

Cleavage of aziridines has been employed in the asymmetric total synthesis of pancratistatin **57** [47], a compound that is the object of considerable attention thanks to its broad spectrum of antineoplastic activities [48]. The chemistry of vinylaziridines has for the most part been confined to their use in rearrangement sequences resulting in functionalized pyrrolines. Hence, because of the lack of data concerning the ring-opening of vinylaziridines with carbon nucleophiles,



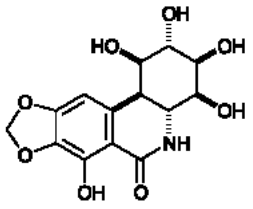
Scheme 9.12.



Scheme 9.13.

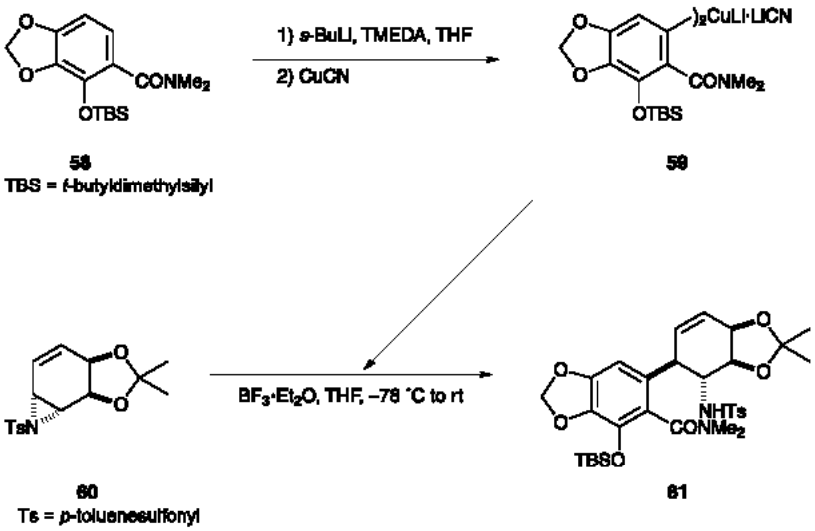
there was a need for a preliminary study of the opening of aziridines with different organometallic species. According to this, whereas lithium diphenylcyanocuprate only shows *anti*-S_N2 substitution, organometallic reagents predominantly react by *syn*-S_N2' substitution; no explanation for this divergent reactivity is given. *Ortho*-

lithiation [49] of a dimethylamide species **58**, followed by cuprate formation according to Lipshutz et al. [50], provided the required cyano-Gilman reagent **59** (Scheme 9.14). The reaction between **59** and the activated aziridine **60** gave a 75% yield of the product **61**. This is the first example of the preparation of cyano-Gilman cuprates by amide group-directed *ortho*-metalation.



pancratistatin

57



58
TBS = *t*-butyldimethylsilyl

59

60
Ts = *p*-toluenesulfonyl

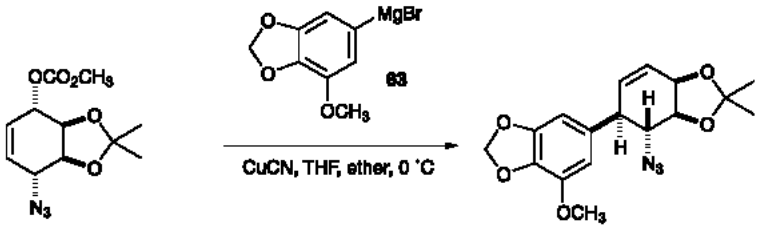
61

Scheme 9.14.

9.3
S_N2' Substitution [51]

Organocuprates react rapidly with allylic halides (or acetates), propargyl halides (or acetates), and vinyloxiranes, frequently with S_N2' regioselectivity. The reaction ordinarily takes place with *anti* (with respect to the leaving group) stereochemistry.

In an alternative synthesis of pancratistatin (**57**) by Trost et al. [52], (Scheme 9.15) addition of the Grignard reagent **63** [53] to a mixture of the azide **62** and copper cyanide reproducibly gave the desired adduct **64**. Because of the difficulties associated with purification of adduct, the overall yield of the two steps (the next being dihydroxylation of the olefin) was 62%.

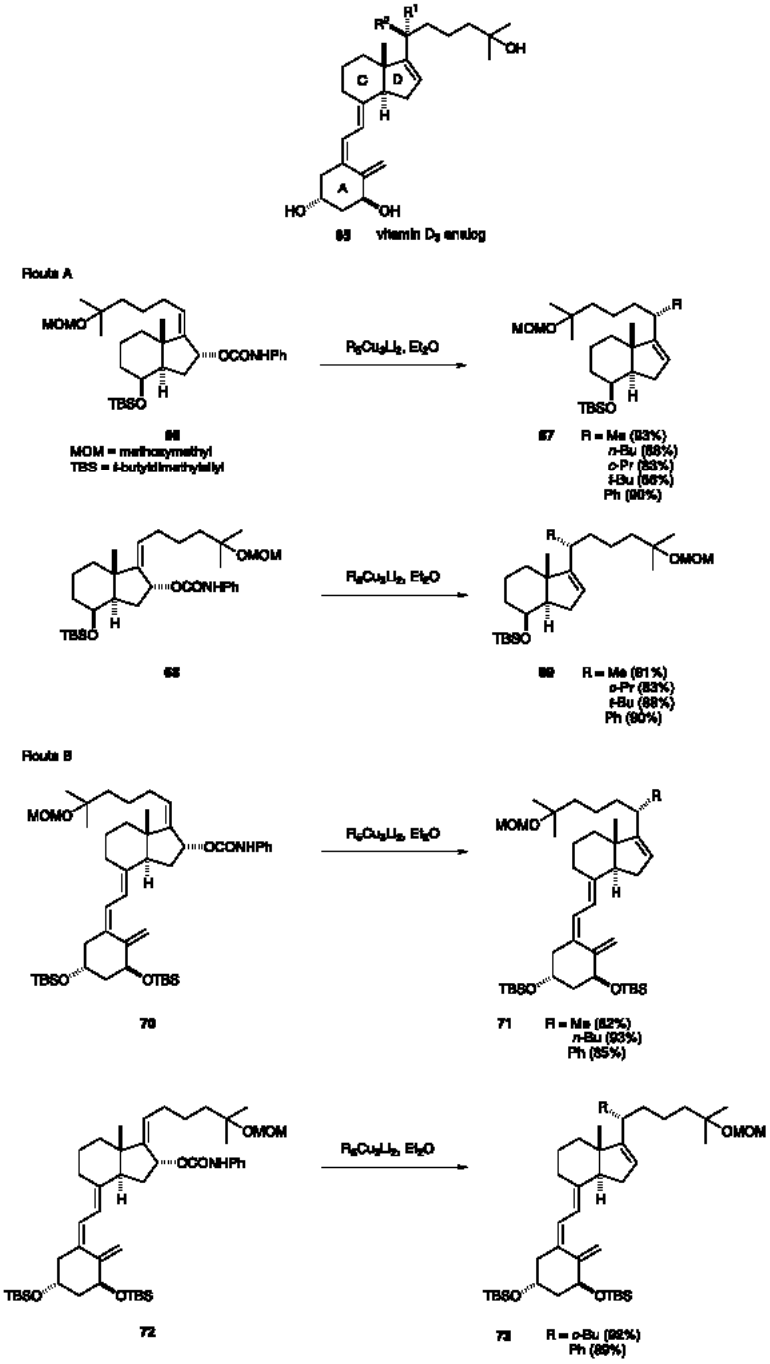


62 **64**

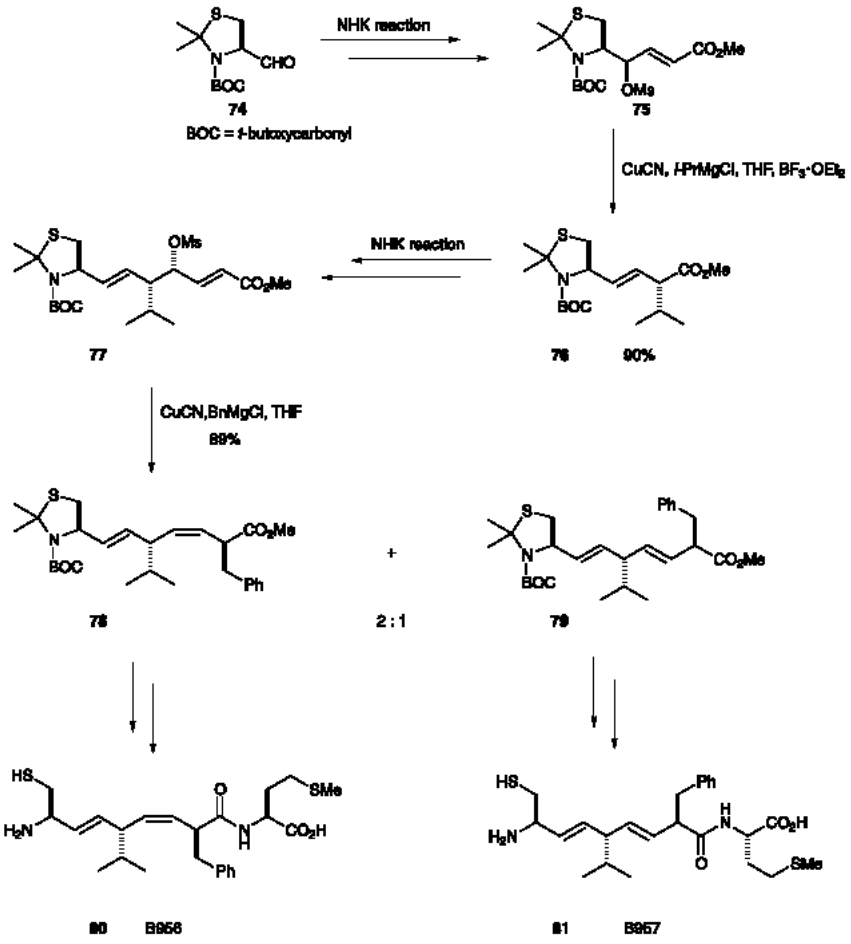
Scheme 9.15.

When an allylic carbamate is employed as a substrate, on the other hand, *syn* substitution occurs [54]. For example, two efficient synthetic routes to 1α,25-dihydroxy-16-ene-vitamin D_3 (**65**) and its analogues have been developed (Scheme 9.16) [55]. In route A, the CD side chain fragments **67** and **69** were prepared by S_N2' *syn* substitution of allylic carbamates **66** and **68** with $R_5Cu_3Li_2$, and the triene unit was then constructed by coupling with the A ring fragment. In route B, S_N2' *syn* allylation of the carbamate moiety took place on the intermediates **70** and **72**, already possessing the vitamin D triene unit, to afford the precursors **71** and **73**. Both routes gave the desired allyl products in high yields.

In syntheses of the potent tetrapeptide mimetic farnesyl transferase inhibitors B956 (**80**) and B957 (**81**), the double bond pairs were constructed by application of iterative Nozaki–Hiyama–Kishi (NHK) and cuprate S_N2' reactions (Scheme 9.17) [56]. The preparation of the precursor **75** for the Ibuka–Yamamoto S_N2' replacement reaction [57] was carried out starting from **74**, by means of the already mentioned NHK reaction [58]. The construction of the olefinic moiety of the peptide isostere **76** was effected by copper-mediated displacement with alkyl nucleophiles. In practice, *anti*-S_N2' diastereoselectivity with high *E* olefin selectivity was observed for the first iteration, on treatment of **75** with the reagent produced by addition of $BF_3{\cdot}Et_2O$ to a mixture of *i*-PrMgCl and CuCN. In the second iteration, the unusual *Z* olefin **78** – not the *E* olefinic product **79** expected from the normal *anti* pathway – was obtained as the major isomer from the S_N2' reaction of **77**, again prepared through an NHK sequence. Compounds B956 and B957 were prepared in high yields from **78** and **79** by the usual sequence, both with >95% purity. This iterative NHK reaction followed by S_N2' substitution thus demonstrates the widespread utility of organocopper reagents in the preparation of olefinic peptide mimetics of other interesting peptides.


65 vitamin D3 analog
Route A
MOMO
OCONHPh
TBSO
66
MOM = methoxymethyl
TBS = t-butyldimethylsilyl
R2Cu3Li3, Et2O
67 R = Me (93%)
n-Bu (88%)
c-Pr (83%)
t-Bu (86%)
Ph (90%)
OMOM
68
69 R = Me (81%)
c-Pr (83%)
t-Bu (88%)
Ph (90%)
Route B
70
71 R = Me (82%)
n-Bu (93%)
Ph (85%)
72
73 R = c-Bu (92%)
Ph (89%)

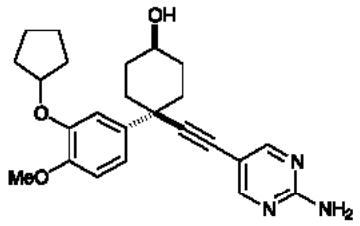
Scheme 9.16.



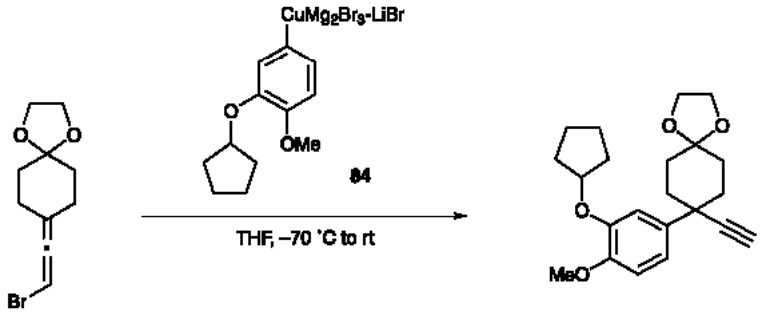
Scheme 9.17.

The propargyl structure of PDE IV inhibitor SB 222618 (**82**) was prepared with the aid of a regioselective S_N2' substitution of the allenic compound **83** (Scheme 9.18) [59]. The most critical step in the synthesis of **82** is the preparation of the intermediate **85**. Aryl copper reagent **84** was prepared as the substitution partner, since it is known that Vermeer-type organocopper species [60] of formula $RCuMg_2Br_3$ LiBr exhibit good regioselectivity in S_N2' reactions [61]. Treatment of **84** with the bromoallene **83** gave the desired propargyl product **85** in 60% yield.

Aziridine cleavage based on an S_N2' reaction was used for the synthesis of peptides bearing *E* alkene dipeptide isosteres, a novel class of potent bombesin receptor antagonists [62]. Treatment of the vinylaziridine **86** (Scheme 9.19) with isobutyl and isopentyl magnesiocyanocuprates in THF at −78 °C for 30 min. stereospecifically gave the desired *E* alkene isosteres **87** in high isolated yields [63].

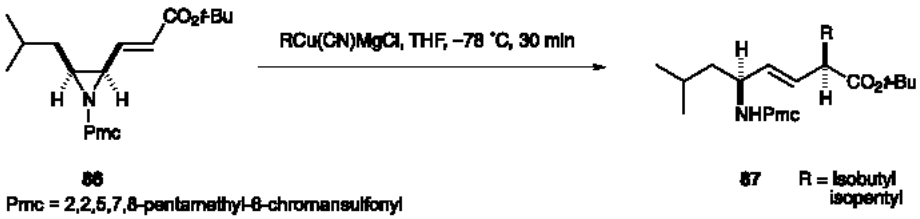


82 SB 222618



83 84 85 60%

Scheme 9.18.



86 87 R = Isobutyl, Isopentyl

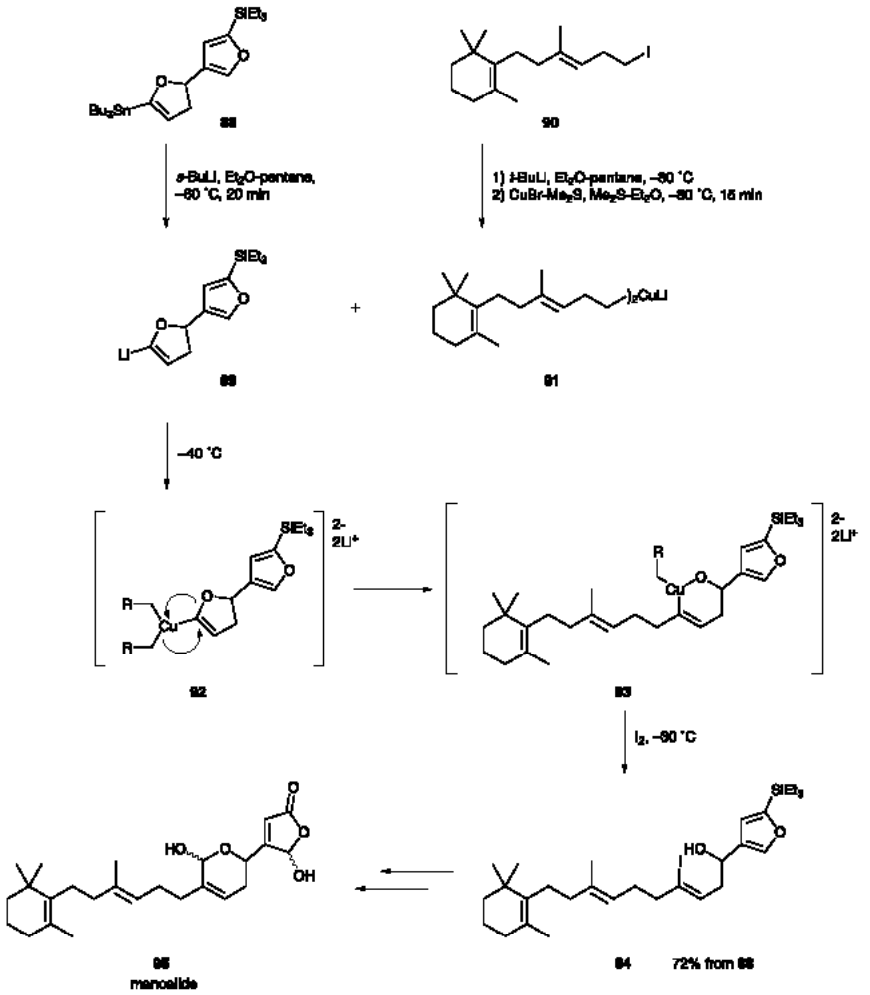
Pmc = 2,2,5,7,8-pentamethyl-6-chromansulfonyl

Scheme 9.19.

9.4
1,2-Metalate Rearrangements

A 1,2-metalate rearrangement of a higher order cuprate, known as a Kocienski rearrangement [64], was used as a key step in the synthesis of the marine anti-inflammatory sesterterpenoid manoalide 95 (Scheme 9.20) [65]. Treatment of the alkenyl lithium 89 (prepared from the alkenylstannane 88 with *s*-BuLi in a diethyl ether-pentane mixture) with the homocuprate 91 (produced from iodoalkane 90) gave the iodoalkene 94 in 72% overall yield from 88. The reaction proceeds as fol-

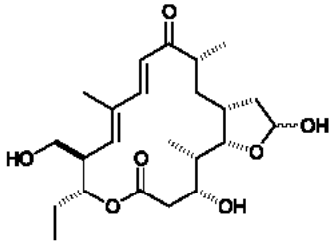
lows. The cuprate reagent **92** is first formed from **89** and **91**, and 1,2-metalate rearrangement then takes place as shown by the arrows in **92** to give **93**. Iodonolysis of **93** results in **94**.



Scheme 9.20.

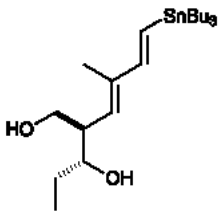
The "western part" **97** of tylosin aglycon (**96**), a 16-membered macrolide, has also been synthesized using this Kocienski metalate rearrangement [66]. Treatment of the lithiated dihydrofuran **99** with the stannyl cuprate [67] obtained from Bu_3SnLi and CuCN, followed by MeI alkylation, exclusively gave the *E* vinyl stannane **100**, in 80% yield. In the last stage, stannyl cupration [68] of the deprotected enyne diol **101** afforded the desired (*E*, *E*) stannyl diene **97** in 85% yield.

The advantage of this strategy is thus the subsequent trapping of the metalate rearrangement product to provide a clean, efficient, and highly stereoselective route to the trisubstitued alkenes.



tylonolide (tylosin aglycon)

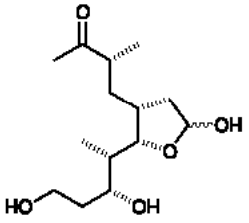
96



Western Part

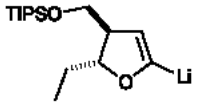
97

+



Eastern Part

98



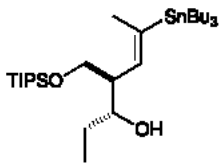
99

TIPS = triisopropylsilyl

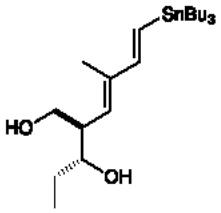
1) $(Bu_3Sn)_2CuLi{\cdot}LiCN$

2) MeI

Kocienski rearrangement



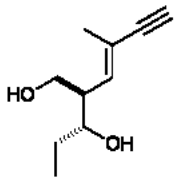
80% **100**



97 85%

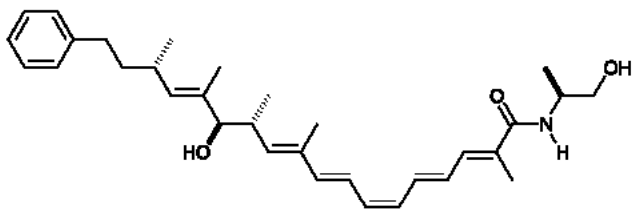
$(Bu_3Sn)(Bu)CuLi{\cdot}LiCN$

stannyl cupration

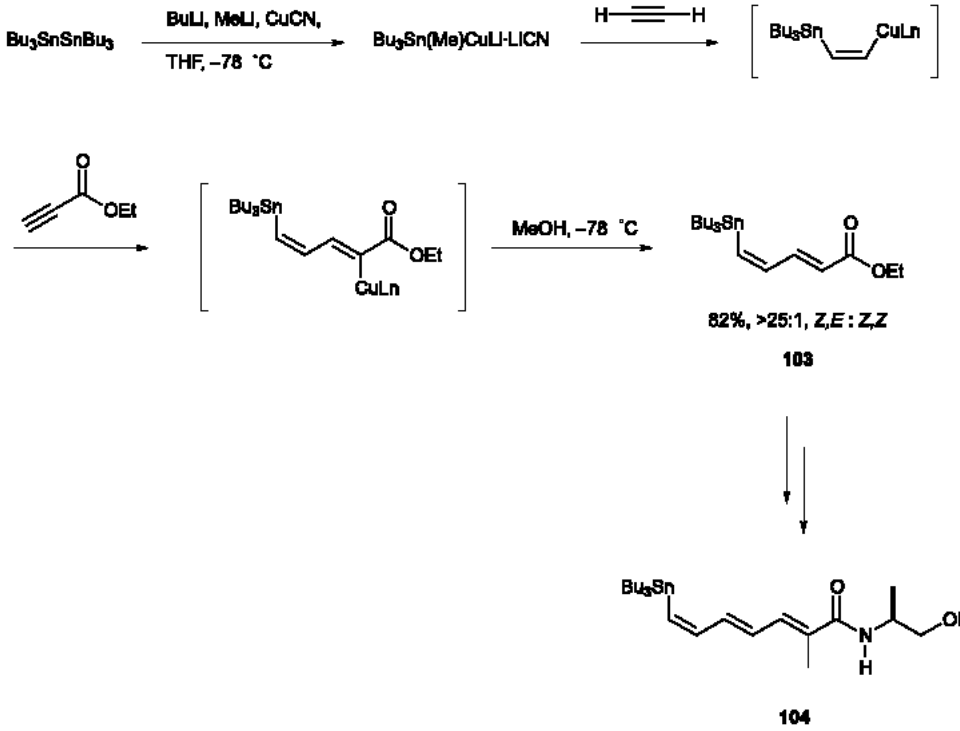


101

Scheme 9.21.



stiplamide 102



Scheme 9.22.

9.5
Carbocupration [69]

The carbocupration of alkynes occurs in a *cis* fashion to afford the synthetically useful *cis* alkenyl products. Recently, copper-mediated introduction of heteroatoms such as stannyl and silyl groups has become frequently used in place of introduction of carbon units as an efficient strategy to build important precursors in syn-

thesis. The synthesis of stipiamide **102** [70], possessing anti-HIV and antifungal activities, was accomplished with high selectivity in a single operation, using sequential tin-copper *syn* additions [71] of tributylstannyl cuprate to acetylene, followed by conjugate addition to ethyl propionate. The stannyl cuprate was prepared first, by treatment of hexabutylditin with butyllithium, methyllithium, and copper cyanide in THF at −78 °C [72] (Scheme 9.22). Excess acetylene gas was added directly to the cold solution, and ethyl propionate was then added. After quenching with methanol [73], the diene ester **103**, intended as the precursor for a Stille coupling, was obtained in 82% yield based on ethyl propionate, with greater than 25:1 *Z,E*:*Z,Z* selectivity. The stipiamide (*E,E,Z,E,E*) olefin structure was subsequently achieved, using the Stille coupling as the final step.

As described above, many copper-mediated reactions play important roles in the syntheses of natural and unnatural products. To date natural product syntheses using organocopper reagents have been accomplished, and will undoubtedly be increasing greatly from now on.

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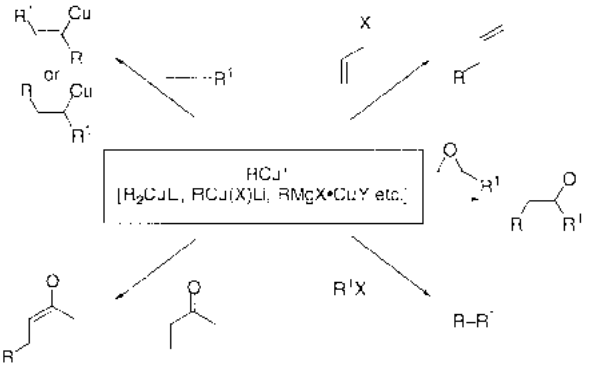
10
Mechanisms of Copper-mediated Addition and Substitution Reactions

Seiji Mori and Eiichi Nakamura

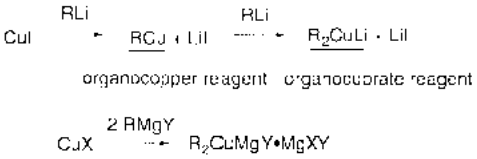
10.1
Introduction

The use of organocopper chemistry in synthesis dates back to the nineteenth century, when Glaser developed copper-catalyzed coupling of terminal alkynes [1]. Half a century after Kharasch's initial discoveries in the 1940s [2], copper reagents are still the most useful synthetic reagents among the transition metal complexes [3], the key roles of copper having become widely recognized in organic synthesis [4–10]. Conjugate addition [11–14], carbocupration [15], alkylation [16], and allylation [17] represent the reactions that can be achieved readily with organocopper reagents but not with other organometallics. The most important utility of copper in organic chemistry is in the form of nucleophilic organocopper(I) reagents used either in a catalytic or a stoichiometric manner. Generally formulated as $[R_2Cu]M$, with a variety of metal M and R groups, organocuprate(I) complexes and related species are uniquely effective synthetic reagents for nucleophilic delivery of hard anionic nucleophiles such as alkyl, vinyl, and aryl anions (Scheme 10.1).



Scheme 10.1. Nucleophilic reactivities of organocopper reagents. R = sp^2, sp^3 carbon anionic centers; X, Y = halogen, etc.

Gilman reported in 1952 that addition of one equivalent of MeLi to a Cu^I salt results in the formation of yellow precipitates, which then afford colorless solutions upon addition of another equivalent of MeLi (Scheme 10.2) [18]. In 1966, Costa isolated a complex between phenylcopper(I) and magnesium, as well as crystals of a lithium diphenylcuprate(I) complex [19]. Although the organocopper reagents derived from Grignard reagents are widely used and may be described as R_2CuMgX, the extent to which to this reflects the reality in solution is still uncertain.



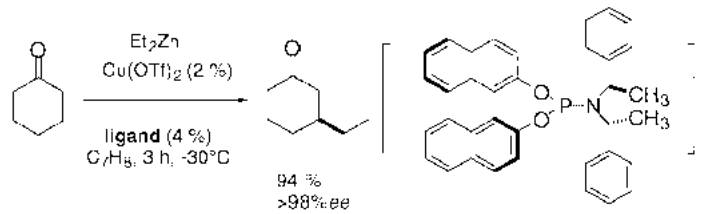
Scheme 10.2. Preparation of organocopper reagents.

The organic chemistry of organocuprates started its rapid development in 1966, when House showed that the reactive species in conjugate addition is the lithium diorganocuprate(I) called a Gilman reagent [20]. The foundations for vigorous subsequent synthetic development were laid by Corey, and important initial developments such as substitution reactions on sp^2 carbon atoms or in allylic systems [16, 17, 21–23], and carbocupration of acetylene [24] had been reported by the mid-1970s.

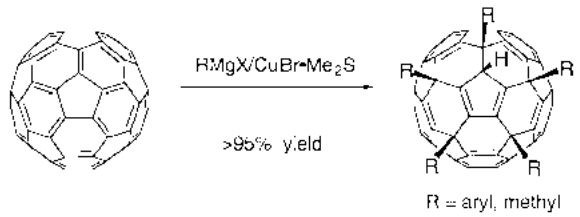
The nature of "Gilman reagents" now needs some careful definition. While numerous reports (older ones in particular) describe Gilman reagents as R_2CuLi, a vast majority of them actually used a LiX complex $R_2CuLi{\cdot}LiX$, prepared by in situ treatment of RLi with CuX (X = bromide, iodide, or cyanide, sometimes with a ligand such as Me_2S and PR_3). Although R_2CuLi and $R_2CuLi{\cdot}LiX$ may display largely the same reactivities, Lipshutz [25] showed that they are in fact different species by analysis of reactivities and spectroscopic properties (the case of X = CN (cyano-Gilman cuprate) is discussed in Sect. 10.6.4). Even small solvent differences may affect the composition of the reagent and hence reactivity [26]. Because of this complexity, it is now customary to indicate all ingredients used when describing a reagent (for example, $R_2CuLi{\cdot}LiI{\cdot}Me_2S/BF_3{\cdot}Et_2O$ in THF/hexane). Understanding of the aggregation state is fundamental for discussion of the reaction mechanism (see Chapt. 1) [27, 28]. In diethyl ether, Gilman reagents largely exist as dimers, but in THF solution, they exist as $R_2CuLi{\cdot}LiX$ or ion-pair species ($R_2Cu^- + Li^+$). These species are in equilibrium with each other [29]. It has been suggested that aggregation of copper species affects enantioselectivities of stoichiometric and catalytic asymmetric conjugate additions [30]. RCu itself is not reactive, and addition of a Lewis acid such as BF_3 is necessary to obtain high reactivities [5, 31]. The latter approach is often used in organic synthesis (see Sect. 10.6.1) in which the identification of the true reactive species has yet to be achieved [32].

Organocopper chemistry is still rapidly expanding its synthetic scope. The scope of carbocupration, previously limited to acetylenes, has recently been extended to olefins [33–36]. 1,6-, 1,8-, 1,10-, and 1,12-Addition and 1,5-S_N2'' substitution reac-

tions of substrates with extended conjugates have been developed (see Chapt. 4) [14, 37–39]. Enantioselective conjugate addition [40] has become truly useful with the aid of dialkylzinc, cationic copper catalyst, and a chiral ligand (Eq. 1, see also Chapt. 7) [41]. Magnesium-based reagents have found use in quantitative fivefold arylation of C_{60} (Eq. 10.2) [42] and threefold arylation of C_{70} [43], paving ways to new classes of cyclopentadienyl and indenyl ligands with unusual chemical properties.

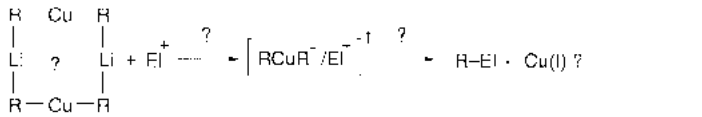


(10.1)



(10.2)

Numerous investigations have been made into the reaction mechanisms of organocopper reactions and the design of efficient copper-mediated reactions, resulting in the reporting of many crystallographic and spectroscopic studies of reactants and products (for analysis of organocopper(I) complexes see Chapt. 1.), as well as examination of solvent effects, substituent effects, kinetics, and NMR spectroscopic data of reactive intermediates. Nevertheless, information about the nature of reactive species in solution and their reactivities is fragmentary and incomplete [44]. The most widely accepted "resting state" of lithium organocuprate(I) species in solution is represented by the eight-centered dimer $(R_2CuLi)_2$ shown in Eq. 10.3, but there is little consensus on the "reactive conformation of a true reactive species" (see Chapt. 1). Making matters worse, the structures of the final copper-containing products are generally unknown. Those exploring the frontiers of organocopper chemistry in industry and academia desperately require better mechanistic understanding.



(10.3)

Two sources of mechanistic information, new analytical and new theoretical methods, have surfaced in the past several years. The former class includes new methods in the study of kinetic isotope effects, in NMR spectroscopy, and in X-ray

absorption spectroscopy [EXAFS (extended X-ray absorption fine structure spectroscopy) and XANES (X-ray absorption near edge structure spectroscopy)]. The latter category includes new developments in ab initio and density functional theories. In this chapter, recent progress on mechanisms of copper-mediated addition and substitution reactions is discussed in the context of the following topics:

(1) conventional mechanistic schemes for copper-mediated reactions,
(2) reaction pathways of organocopper-organometallic aggregates as analyzed through combination of theoretical and experimental data,
(3) mechanisms of copper-catalyzed reactions [45, 46].

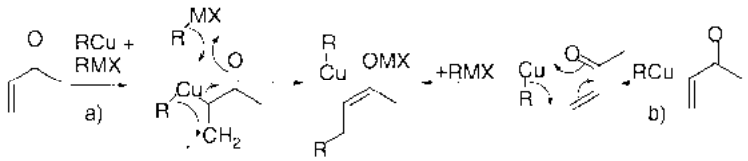
Three important categories of copper reactions – conjugate addition, carbocupration, and alkylation – are discussed.

10.2
Conjugate Addition Reaction

Copper-mediated conjugate addition of alkyl anions to α,β-unsaturated carbonyl or related compounds (hereafter called enones) has long attracted chemists' interest because of its synthetic importance and its obscure mechanism. The difficulties inherent in the elucidation of the mechanisms of conjugate additions are due to the complexity of cluster structures of organocopper species. In the light of contrasting reports (one reporting conjugate addition to be slower in THF than in ether [47, 48], another reporting faster reaction in toluene, and further additional reports that, in toluene, 1,4-addition can be promoted over 1,2-addition in the presence of Me_2O [49] and Me_2S [50]), solvent effects are a difficult subject to deal with. Nevertheless, there have been extensive experimental studies on the reaction mechanisms of conjugate addition.

10.2.1
Four-centered and Six-centered Mechanisms

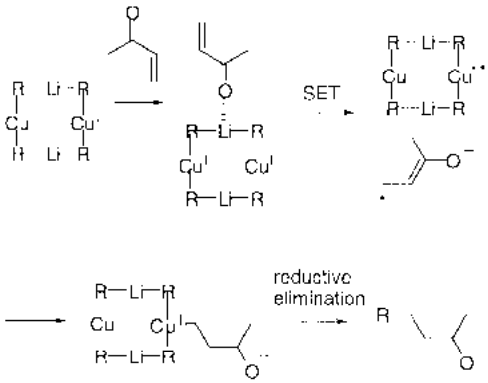
Four-centered addition of RCu to an enone was widely discussed in the 1960s (Scheme 10.3a) [51–53], while discussions on six-centered transition states have continued until recent times (Scheme 10.3b) [54]. These mechanisms do not, however, explain the formation of E/Z mixtures of enolate stereoisomers [20, 55] and must now be considered obsolete.



Scheme 10.3. a) 1,2-Addition and b) 1,4-addition proposals.

10.2.2
Single-electron Transfer Theorem

House pioneered synthetic and mechanistic studies of cuprate reactions in the 1970s. His papers proposed a mechanism (Scheme 10.4) that assumes a single-electron transfer (SET) from the dimer, producing a Cu^{III} intermediate [56, 57]. The SET/Cu^{III} theorem had a strong following for many years. However, most of the experimental facts listed below, once considered to support the SET process, are now no longer accepted as evidence of SET. Only the Cu^{III} hypothesis has survived the test of time.

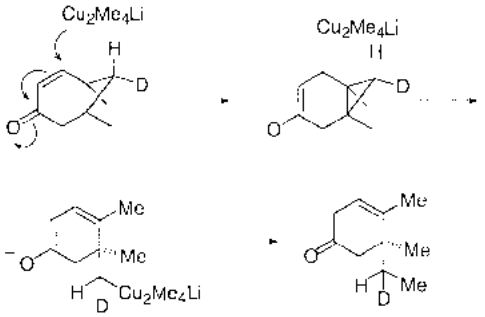


Scheme 10.4. House's 1,4-addition mechanism.

(1) E/Z isomerization of the olefinic part of an enone was once taken as evidence for reversible electron transfer. It was later reported, however, that this isomerization takes place even in the presence of LiI, a common component of the Gilman cluster reagent (for example, $Me_2CuLi{\cdot}LiI$) [58]. Such an isomerization is also possible through reversible generation of an advanced d-π^* copper/enone complex along the reaction pathway [42, 59], and hence does not represent strong evidence for SET.

(2) Qualitative correlation of the apparent rate of 1,4-addition with the reduction potential of the enone was later proven to be only superficial, through quantitative kinetic studies by Krauss and Smith [60].

(3) β-Cyclopropyl α,β-unsaturated ketones such as the one shown below often give ring-opening products, which was taken as strong evidence for radical anion formation by SET. An elegant study by Casey and Cesa, using a deuterium-labeled substrate, indicated stereospecificity in the cyclopropane ring-opening, which hence refutes the radical mechanism (Eq. 10.4) [61]. On the basis of a series of control experiments, Bertz reinterpreted the results in terms of Cu^{III} intermediates formed by two-electron transfer [62].



(10.4)

(4) ESR and CIDNP studies intended to detect the radical intermediates failed [63]. Conjugate addition of a vinylcuprate reagent to an enone takes place with retention of the vinyl geometry, indicating that no vinyl radical intermediate is involved [64, 65]. Kinetic isotope effects and substituent effects in cuprate addition to benzophenone indicate that C C bond formation is rate-determining, which is not consistent with the involvement of a radical ion pair intermediate [66].

SET processes do not occur among moderately electrophilic olefinic acceptors, but are likely to be involved in highly electrophilic substrates. Some recent examples are the polyadditions of cuprate to fullerenes (Sect. 10.1.1). Fluorenone ketyl radical has been detected in a cuprate reaction of fluorenone [20]. Doubly activated olefins [67–69] and bromonaphthoquinone [70] also probably react through SET.

10.2.3
Kinetic and Spectroscopic Analysis of Intermediates

Conjugate additions to α,β-unsaturated ketones and esters are the most important cuprate reactions. Kinetic studies by Krauss and Smith on Me_2CuLi and a variety of ketones revealed the following kinetic characteristics (Eq. 10.5), first order both in cuprate dimer and in the enone [60].

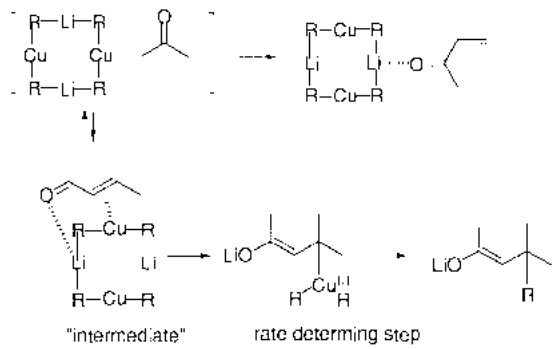
$$(Me_2CuLi)_2 + \text{enone} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{intermediate} \xrightarrow{k_2} \text{product}$$

$$K \quad k_1/k_{-1}$$

$$-\frac{d[\text{intermediate}]}{dt} = \frac{kK[(CH_3)_2CuLi]}{1 + K[(CH_3)_2CuLi]}[\text{enone}] \qquad (10.5)$$

This rate expression is consistent with the reaction scheme shown in Eq. 10.6, formulated on the basis of the Krauss–Smith paper. Thus, the initially formed cuprate dimer/enone complex with lithium/carbonyl and copper/olefin coordinations [71, 72] transforms into the product via an intermediate or intermediates. A lithium/carbonyl complex also forms, but this is a dead-end intermediate. Though detailed

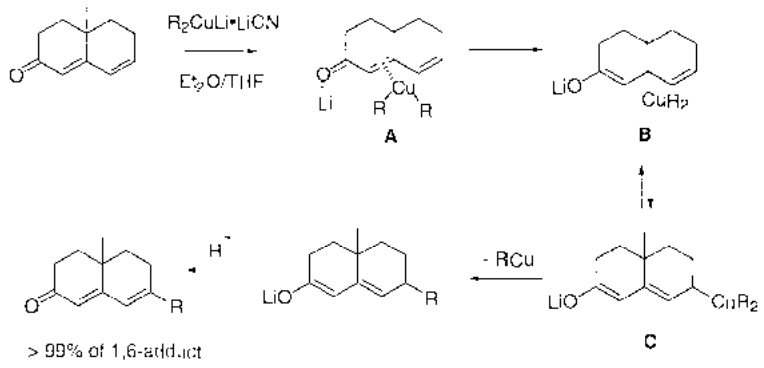
structures of the intermediates were unknown for a long time, the essence of this scheme was supported by subsequent NMR and XANES spectroscopic studies and recent theoretical investigation. The key "intermediate" is now considered to be an organocopper(III) species formed by two-electron, inner sphere electron transfer (Eq. 10.6) (see Sect. 10.2.5).



(10.6)

Corey explicitly proposed a Dewar–Chatt–Duncanson (DCD) interaction for such a Cu^{III}/olefin complex [73]. XANES investigation of a complex formed between a *trans*-cinnamate ester and $Me_2CuLi{\cdot}LiI$ in THF indicated elongation of the C=C double bond and an increase in the coordination number of the copper atom. NMR studies on the organic component in the complexes indicated loosening of the olefinic bond [72, 74]. Very recently, Krause has determined the kinetic activation energies ($E_a = 17$–18 kcal mol^{-1}) of some conjugate addition reactions for the first time [75].

An intermediate formed on 1,6-addition of a cuprate to a dienone has recently been examined by low-temperature NMR spectroscopy. This reaction passes though a Cu/olefin π-complex intermediate **A**, in which cuprate binds to the α- and the β-carbon. Further 1,3-rearrangement from another intermediate (**B**) to still another (**C**) is proposed (Eq. 10.7) [76].



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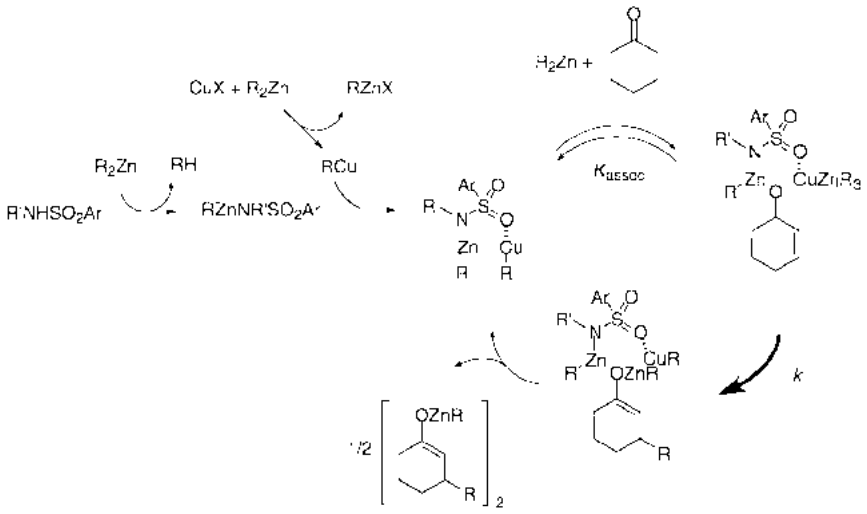


Fig. 10.1. Proposed catalytic cycle of copper-catalyzed conjugate addition.

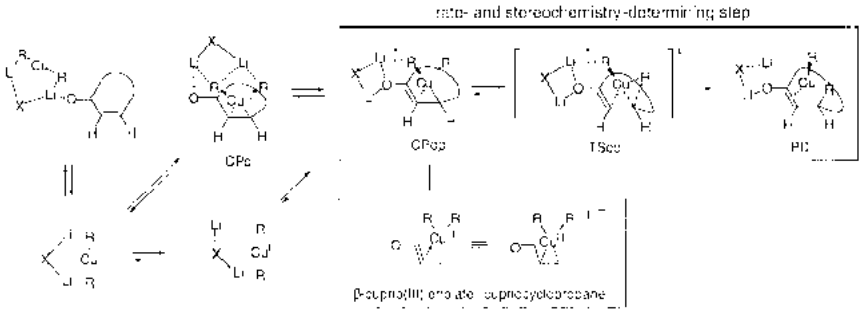
10.2.4
Catalytic Conjugate Addition

There are a large number of reports on copper(I)-catalyzed conjugate additions, yet there is only scant information available about their reaction mechanisms. Recently, the conjugate addition of organozinc compounds to enones was found by Kitamura, Noyori, et al. to be catalyzed by *N*-benzylbenzenesulfonamide and CuCN, and the mechanism was scrutinized (Fig. 10.1). The kinetic rate was found to be first order in the concentrations of the catalyst that exist in equilibrium with R_2Zn and enone [77].

In the enantioselective copper(I)-catalyzed conjugate addition of a cyclic enone with a chiral ligand, the observed nonlinear effects indicate that Cu(I) aggregates participate in the reaction [78].

10.2.5
Theoretically Based Conjugate Addition Reaction Pathway

The reaction pathways of conjugate addition of Me_2CuLi and $Me_2CuLi{\cdot}LiCl$ have been studied for acrolein [79] and cyclohexenone [80] with the aid of density functional methods, and fit favorably with the ^{13}C NMR properties of intermediates, kinetic isotope effects [81], and the diastereofacial selectivity. A similar mechanism also operates in this reaction, as summarized in Scheme 10.5. The rate-determining step of the reaction (**TScc**) is the C C bond formation caused by reductive elimination from Cu^{III} to give Cu^{I}.



Scheme 10.5. Plausible pathway of conjugate addition of $(R_2CuLi)_2$ to enones. Solvent molecules are omitted for clarity. The lithium atoms are fully solvated and the R Li association indicated with a broken line (⁻⁻) in **CPop** and **TScc** may be extremely small or nonexistent in solution. Here, in Schemes 10.7, 10.9, and 10.10, and in Fig. 10.5, the X group can be RCuR, halogen, etc.

TScc is also the stage at which the enantiofacial selectivity of the reaction is determined [80]. This conflicts with the conventional assumption that the face selectivity is established in the initial π-complexation [**40a**], which is now shown to represent a preequilibrium state preceding **TScc**. The calculated activation energy taking the solvation of the lithium atoms into account shows reasonable agreement with recently determined experimental data [75].

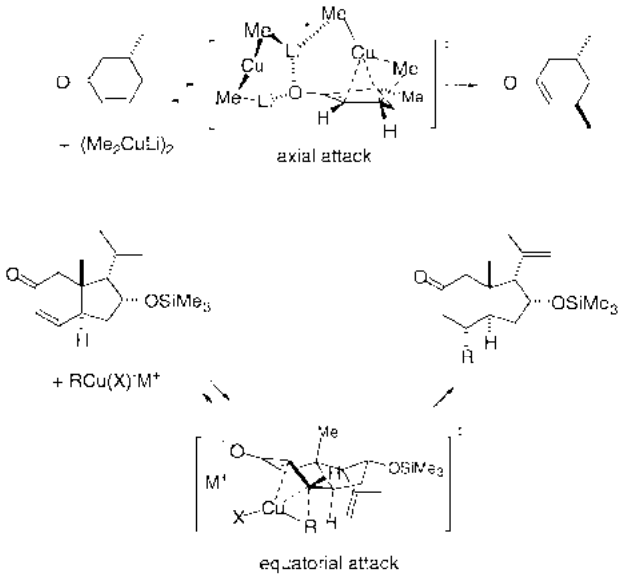
The central feature of the mechanism is the 3-cuprio(III) enolate **Cpop**, of an open, dimeric nature, as shown by comparison of theory with experimentation involving ^{13}C NMR and KIEs [80, 81]. This species serves as the direct precursor to the product (Scheme 10.5, top box). In this critical **CPop** complex, copper/olefin (soft/soft) and a lithium/carbonyl (hard/hard) interactions are present. The open complex may be formed directly, by way of an open cluster (bottom left of Scheme 10.5), or by complexation of a closed cluster with the enone (**CPd**). Experiments have shown that the enone/lithium complex (top left of Scheme **10.11**) is a dead-end species [60, 74].

The **CPop** intermediate is the "β-cuprio ketone" intermediate widely debated in mechanistic discussions of conjugate addition (cf. Scheme 10.3). On the basis of recent theoretical analysis, two limiting structures for CPop may now be considered; these are shown in the bottom box in Scheme 10.5. The reason for the exceptional stability of **CPop** as a trialkylcopper(III) species can be readily understood in terms of the "β-cuprio(III) enolate" structure, with the internal enolate anion acting as a strong stabilizing ligand for the Cu^{III} state [82].

In spite of the apparent difference between conjugate addition and carbocupration reactions (Sect. 10.3.2), the similarities between the key organometallic features of the two reactions are now evident. In both reactions, inner sphere electron-transfer converts the stable C Cu^{I} bond into an unstable C Cu^{III} bond, and the cluster-opening generates a nucleophilic, tetracoordinated alkyl group. The difference is that the product of conjugate addition (**PD**) remains as a lithium enolate complexed with RCu^{I} (Scheme 10.5), while the initial product of carbocupration

(**INT2**, Scheme 10.7) undergoes further reaction (Li/Cu transmetalation) and generates a new organocuprate compound. (Note however that this difference could become more subtle since the product of conjugate addition (**PD**) might behave more like an α-cuprio(I) ketone complexed with a lithium cation [52] than a lithium enolate complexed with copper(I)). In neither reaction was any evidence of radical intermediates (i.e., SET) found by theoretical calculations [79].

Synthetic chemists can now work with three-dimensional pictures of the conjugate addition available on a website [80]. In the absence of steric hindrance (5-methylcyclohexenone, for example), an "axial attack" through a half-chair conformation is favored, while in the cortisone synthesis an "equatorial attack" through a half-boat conformation is favored because of the constraint imposed by the bicyclic rings [83].



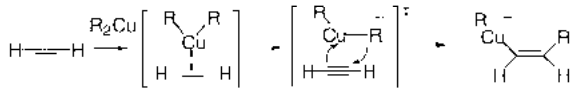
Scheme 10.6. Transition states for diastereoselective conjugate additions. In solution, the lithium and M cations must be fully solvated with solvent molecules. The Me Li association (indicated with an asterisk) will be extremely weak or nonexistent in solution.

10.3
Carbocupration Reactions of Acetylenes and Olefins

10.3.1
Experimental Facts

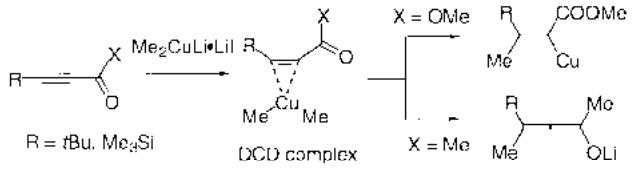
The carbocupration of acetylene takes place smoothly in a *cis* fashion, providing a reliable synthetic route to vinyl copper species (Eq. 10.8) [24]. Magnesium and zinc,

which are more Lewis acidic than lithium, are better counter-cations for this reaction, and strong coordination of a lithium dialkylcuprate(I) with a crown ether dramatically slows down the reaction [84]. This reaction used to be generally considered to proceed through a four-centered mechanism, and hence to be mechanistically different from conjugate addition.



(10.8)

In the addition of Me_2CuLi reagents to electron-deficient acetylenes [85–88], DCD-type complexes have been identified by NMR [84, 89]. As shown below, an ynoate affords a vinylcopper intermediate, while an ynone instead affords an allenolate (Eq. 10.9). The origin of this diversity remains unclear. A related carbocupration mechanism has also been proposed for the reaction with allenylphosphine oxide [53]. Olefin carbocupration of dienes [90] and cyclopropenes [34, 36] is known, but these mechanisms also remain unclear.



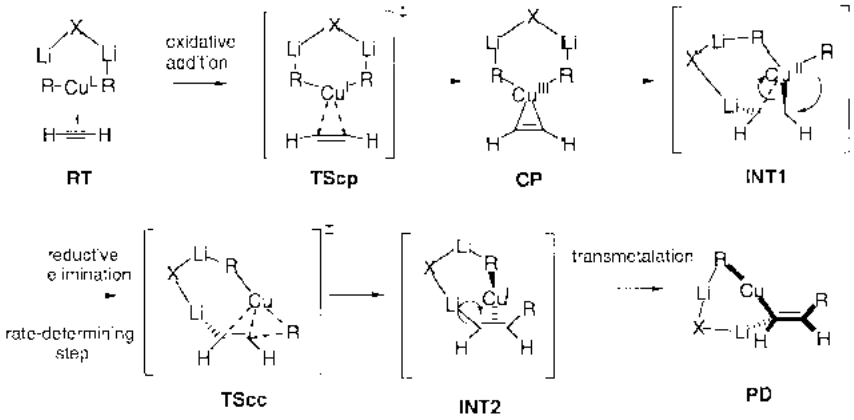
(10.9)

10.3.2

Theoretically Based Carbocupration Reaction Pathway

The carbocupration of acetylene has been studied systematically for five model species – MeCu, Me_2Cu , Me_2CuLi, $Me_2CuLi{\cdot}LiCl$, and $(Me_2CuLi)_2$ [91] – all of which have been invoked once in a while in discussions of cuprate mechanisms. A few general conclusions have been made regarding the reactivities of these reagents with π-acceptors:

(1) The copper d-orbital being very low-lying (hence no redox chemistry available) [92], MeCu can undergo addition only through a four-centered mechanism (Eq. 10.8).
(2) This four-centered pathway requires a large amount of energy, since the covalent Me Cu bond (55 kcal mol^{-1} [93]) must be cleaved. A neutral RCu species is therefore not a reactive nucleophile.
(3) Being electron-rich (thus with high-lying d-orbitals), lithium cuprates such as $(R_2CuLi)_2$ bind tightly to acetylene through two-electron donation from a copper atom (cf. **CP** in Scheme 10.7). In such complex formation, a cluster structure certainly larger than the parent species R_2CuLi is necessary to achieve cooperation of lithium and copper.



Scheme 10.7. Trap-and-bite pathway of carbocupration.

The reaction pathway may be viewed as a "trap-and-bite" mechanism; the structures involved are shown in Scheme 10.7. The cluster opens up and traps the acetylene (**INT1**), transfers electrons, and then "bites" the substrate to form a C C bond (**TScc**). The important events include formation of a DCD-complex (**CP**) via a low energy **TS** (**TScp**) [94], inner-sphere electron transfer to form a transient intermediate **INT1**, C C bond formation through the rate-determining stage **TScc**, and intra-cluster transmetalation from lithium to copper(I) (**INT2**). The DCD character of **CP** is shown by the localized molecular orbitals (LMOs, Fig. 10.2), and has also been found in conjugate addition reactions to enals and enones [79]. Since the C Cu^{III} bond is very unstable, the activation energy for C C bond formation via **TScc** becomes small (<20 kcal mol^{-1}). In solution, the reaction may go directly to **INT1**, or to related species through an open cluster.

It should be noted that the depictions of the "organic" arrows and the indications of the valence of the metal as in Scheme 10.7 (and others in the following para-

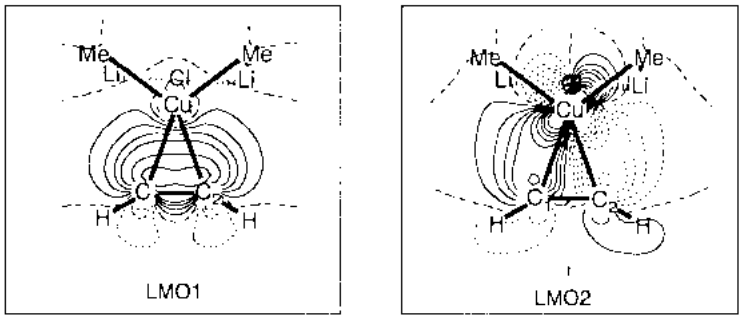


Fig. 10.2. Localized molecular orbitals of the complex (**CP**) between $Me_2CuLi{\cdot}LiCl$ and acetylene.

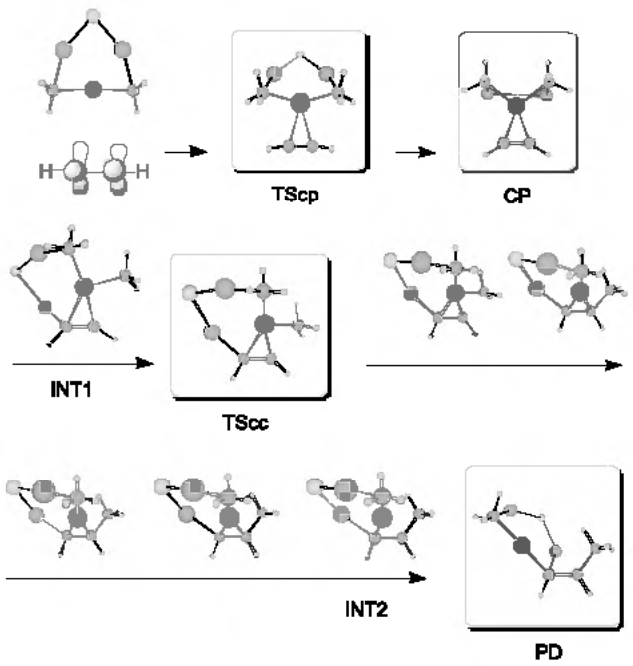


Fig. 10.3. "Snapshots" of intermediates on the potential energy surface of carbocupration of acetylene.

graphs) are necessarily inaccurate from a purely inorganic or theoretical viewpoint. We have nonetheless indicated them, to put the theoretical results into the context of conventional organic chemistry, and to facilitate understanding of the chemistry by organic chemists using the reagents in everyday research.

Figure 10.3 shows "snapshots" of intermediary species on the potential surface of carbocupration to illustrate the transformation of the reacting complex. The formation of the transient carbolithiated intermediate **INT2** is the most striking feature, because recognition of this intermediate provides the key to understanding of the kinship of carbocupration, S_N2' allylation (Sect. 10.4.2), and conjugate addition.

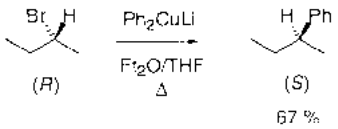
10.4
Substitution Reactions on Carbon Atoms

10.4.1
S_N2 Mechanism of Stoichiometric Substitution Reactions

S_N2 substitution reactions of alkyl halides with hard nucleophiles such as alkyl anions can be achieved most readily with the aid of organocopper chemistry [95]. S_N2 reactions with epoxides and aziridines are also synthetically useful [96]. The

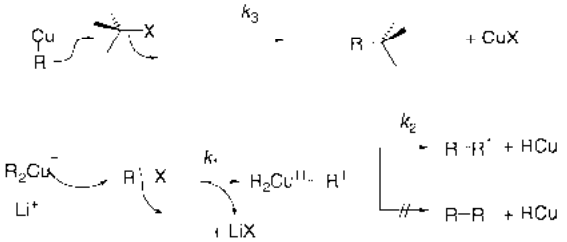
accelerating effects of $BF_3{\cdot}Et_2O$ in the latter reactions indicate the importance of substrate activation (see Sect. 10.6.1) [97].

The alkylation of an alkyl bromide or tosylate, or of an epoxide, with organocuprates takes places with 100% inversion of the stereochemistry at the electrophilic carbon, as shown below (Eq. 10.10) [22, 98]. The magnitudes of primary and secondary kinetic isotope effects in the reaction between $Me_2CuLi{\cdot}LiI{\cdot}PBu_3$ and CH_3I strongly suggested that the rate-determining step of the reaction is the S_N2 displacement stage [99]. Reactions between R_2CuLi and alkyl halides, aryl halides, and alkyl tosylates have been shown to be first order in the concentration of the R_2CuLi dimer and the alkylating reagent [97, 100, 101]. RCu and $RCu(PBu_3)$ do not react with epoxides [96]. Alkylation reactions of R_2CuLi do not take place in the presence of a crown ether, demonstrating the importance of a Lewis acidic LiX component associated with the cuprate moiety. On the other hand, moderately basic and polar THF is a better solvent than diethylether for alkylation [22].



(10.10)

Two mechanistic possibilities for the substitution reactions have been suggested (Scheme 10.8). The first assumes simple S_N2 substitution of the R anion group. The second assumes rate-determining displacement of the leaving group with copper bearing a formal negative charge, and subsequent formation of a trialkylcopper(III) intermediate [82]. This then undergoes reductive elimination to give the cross-coupling product. Though the second mechanism may look pleasing enough to a copper specialist, it leaves a few important questions unanswered; namely the role of the lithium cation, the relative magnitude of k_1 and k_2, and, among other things, the reason why exclusive production of a cross-coupled product R R^1 by way of a symmetrical $R_2(R^1)Cu^{III}$ intermediate is always observed.

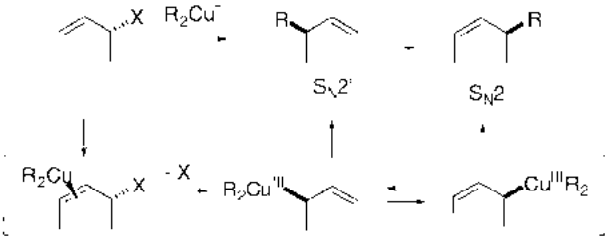


Scheme 10.8. Two proposed alkylation reaction mechanisms.

The proposed participation of a Cu^{III} intermediate is based on an analogy with the chemistry of lithium diorganoaurate(I), R_2Au^ILi [102, 103]. Recent crystallographic data for Cu^{III} species [104] have further supported the similarity between Au^{III} and Cu^{III} [105].

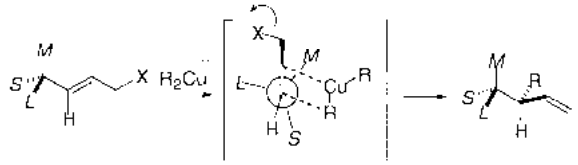
10.4.2
S_N2' Allylation Reactions

Cuprates react rapidly with allylic halides (or acetates) [17, 23], propargyl halides (or acetates) [106–108], and vinyloxiranes, often with S_N2' regioselectivity (Scheme 10.9) [17]. The reaction takes place with *anti* stereochemistry (with respect to the leaving group), while *syn* substitution occurs when an allylic carbamate is employed as the substrate [109].



Scheme 10.9. *Anti*-S_N2' Allylation reaction with competing S_N2 reaction pathway. X = halogen, OAc, $OP(O)Y_2$.

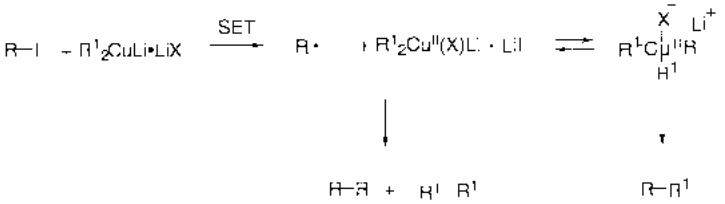
Reactions of R_2CuLi tend to give mixtures of S_N2 and S_N2' products, which it has been suggested is due to the involvement of regioisomeric σ-allylic Cu^{III} species, shown bracketed in Scheme 10.9 [106, 110]. Studies on substituent effects in competitive reactions suggested that the rate-determining stage might involve a two-electron transfer from copper to the allylic substrate [107]. The S_N2 selectivity of the reaction of $Bu_2Cu(X)(MgBr)_2$ is higher with X = I and OTs than with X = Cl and Br, and also higher in ether than in THF [111]. A combination of an organocopper compound and a Lewis acid, such as $RCu{\cdot}BF_3$ [5], $R_2CuLi{\cdot}ZnCl_2$ [112], $R_2CuLi{\cdot}Ti^{IV}$ [113], or $R_2CuLi{\cdot}AlCl_3$ [114], greatly enhances the S_N2' selectivity. Cu(I)-mediated reactions of organozinc species also afford high S_N2' selectivities [112, 115–117]. NMR studies on $R_2CuLi{\cdot}ZnCl_2$ and $R_2CuLi{\cdot}Ti^{IV}$ reagents showed only rapid transmetalation from Cu to Zn or Ti, giving little information on any putative Cu/Zn or Cu/Ti mixed species. Scant information is available for the transition state. The stereoselectivity of the S_N2' reaction of δ-substituted allylic halide of the S_N2 reaction suggested that the transition state geometry for the delivery of an R group from copper has a four-centered character, as shown below (Eq. 10.11) [112]. This conjecture was supported by theoretical comparison between the TS geometries of olefin carbolithiation and those of acetylene carbocupration (cf. Scheme 10.7) [91].



(10.11)

10.4.3
Radical Substitution Reaction Mechanisms

The SET mechanism has been suggested for the alkylation reaction of secondary alkyl iodides, in which the substitution reaction takes place in stereorandom fashion [22, 118]. The reaction between triphenylmethyl bromide and Me_2CuLi generated an ESR-active triphenylmethyl radical, although this may be regarded as a special case [119]. On the basis of trapping experiments using styrene, it was concluded that dialkylcuprate substitution reactions of primary and secondary alkyl iodides may proceed by an SET mechanism, whereas those of primary and secondary bromides do not [120]. This reaction also produces self-coupling products, which is consistent with radicals being involved (Scheme 10.10). The intramolecular cyclization of an olefinic iodide in the presence of an organocopper reagent has been taken as possible but not conclusive evidence of SET [120].



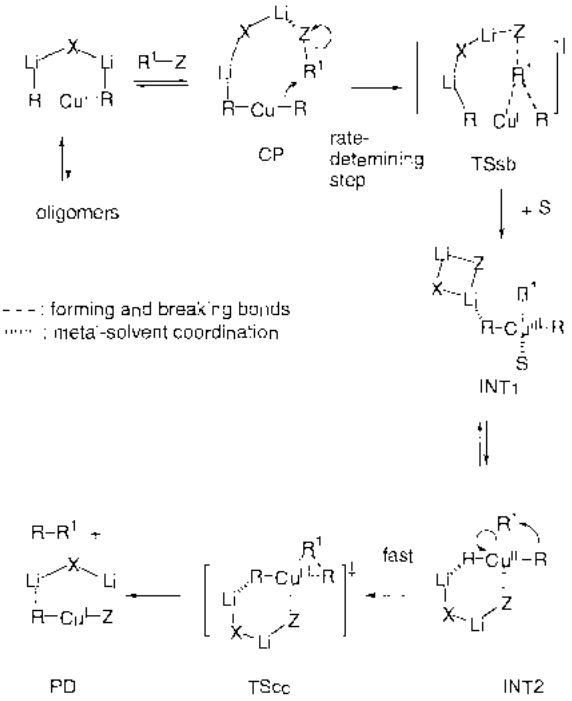
Scheme 10.10. Radical mechanism in alkylation reactions with alkyl halides.

10.4.4
Catalytic Substitution Reactions

Kinetic experiments have been performed on a copper-catalyzed substitution reaction of an alkyl halide, and the reaction rate was found to be first order in the copper salt, the halide, and the Grignard reagent [121]. This was not the case for a silver-catalyzed substitution reaction with a primary bromide, in which the reaction was found to be zero order in Grignard reagents [122]. A radical mechanism might be operative in the case of the silver-catalyzed reaction, whereas a nucleophilic substitution mechanism is suggested in the copper-catalyzed reaction [122]. The same behavior was also observed in the stoichiometric conjugate addition (Sect. 10.2.1) [30].

10.4.5
Theoretically Based Alkylation Reaction Pathways

Alkylation reactions reveal a mechanistic aspect of the cuprate reactions different from that of addition reactions. Theoretical analyses of reactions of alkyl halides (MeI and MeBr) [123, 124] and epoxides (ethylene oxide and cyclohexene oxide) [124] with lithium cuprate clusters (Me_2CuLi dimer or Me_2CuLi·LiCl, Scheme 10.11) resolved long-standing questions on the mechanism of the alkylation reaction. Density functional calculations showed that the rate-determining step of the



Scheme 10.11. Reaction between $R_2CuLi{\cdot}LiX$ and an alkylating agent R^1Z. Solvent coordinated to lithium atoms is omitted.

alkylation reaction (**TSsb**) is the substitution of the C Br bond with an incoming Me Cu σ-bond. The linear $3d_{z2}$ orbital of copper acts as the nucleophile here, as shown by the LMO in Fig. 10.4. The computed and experimental kinetic isotope effects for the reaction of methyl iodide showed good agreement with each other, supporting this conclusion. It is notable that it is again possible to identify an open cluster structure in **TSsb**, with the lithium atom electrophilically activating the leaving group. A trialkylcopper(III) intermediate (**INT**) may form after the rate-

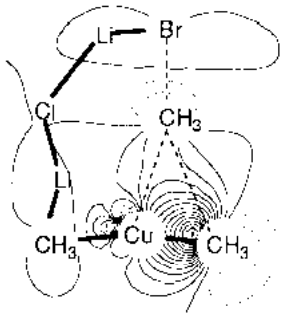
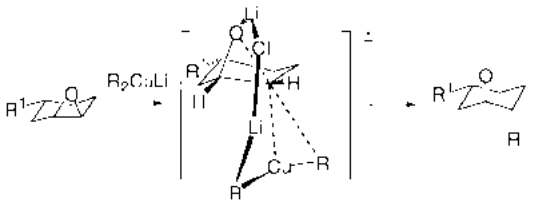


Fig. 10.4. Localized transition structure molecular orbital in the S_N2 reaction between $Me_2CuLi{\cdot}LiCl$ and MeBr.

determining, halide displacement step but only as an unstable transient species **INT1** or **INT2** (Scheme 10.11). These are trialkylcopper(III) complexes of T-shape geometry, with the fourth ligand (solvent of a halide) making the square planar structure [82]. The *trans* relationship of the two alkyl groups (R) is assured by the linear geometry of the cuprate moiety in the transition state **TSsb**, which guarantees cross-coupling between R and R^1 in **TSαα**. Interestingly, this mechanism is a hybrid of the two previous proposals shown in Scheme 10.8.

A similar reaction pathway was found for the S_N2 substitution of an epoxide with a lithium cuprate cluster [124]. In contrast to that in the MeBr reaction, the stereochemistry of the electrophilic carbon center is already inverted in the transition state, providing the reason for the preferred "*trans*-diaxial epoxide-opening" widely observed in synthetic studies. The TS for the S_N2 reaction of cyclohexene oxide is shown in Eq. 10.12.



(10.12)

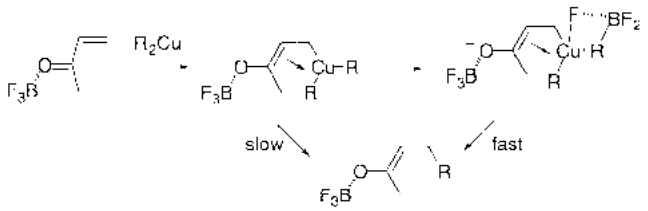
10.6 Other Issues

10.6.1 Counter-cation Lewis Acid Effects

For all major categories of lithium cuprate reactions, it has been shown that addition of a crown ether results in significant retardation [79, 94, 125]. In addition to this, sodium cuprates are much inferior to lithium cuprates for conjugate addition [126]. $BF_3{\cdot}Et_2O$, on the other hand, accelerates conjugate additions [31] and alkylations of epoxides and aziridines [97, 127]. In allylation chemistry, zinc-based [128], titanium-based [113], and aluminum-based [114] organocopper reagents show much higher S_N2' selectivities than lithium cuprate does. The Lewis acidities of cuprate counter-cations are undoubtedly important, but their mechanistic roles still need further investigation (Eq. 10.7).

Recent theoretical studies of reductive elimination from $Me_3Cu{\cdot}S$ in the presence of BF_3 suggest that reaction rate of the conjugate addition can increase if one of the Me groups is detached from the copper(III) to bind with a boron atom (Scheme 10.12) [129].

The origin of the acceleration produced by BF_3 in epoxide alkylation reactions has been examined theoretically [124]. A plausible pathway for BF_3 participation in the epoxide-opening is shown in Fig. 10.5. An epoxide/BF_3 complex **CP1** may encounter the cuprate cluster to form a ternary complex **CP2**, or such a complex may



Scheme 10.12. Proposed mechanism of BF_3 activation in the conjugate addition.

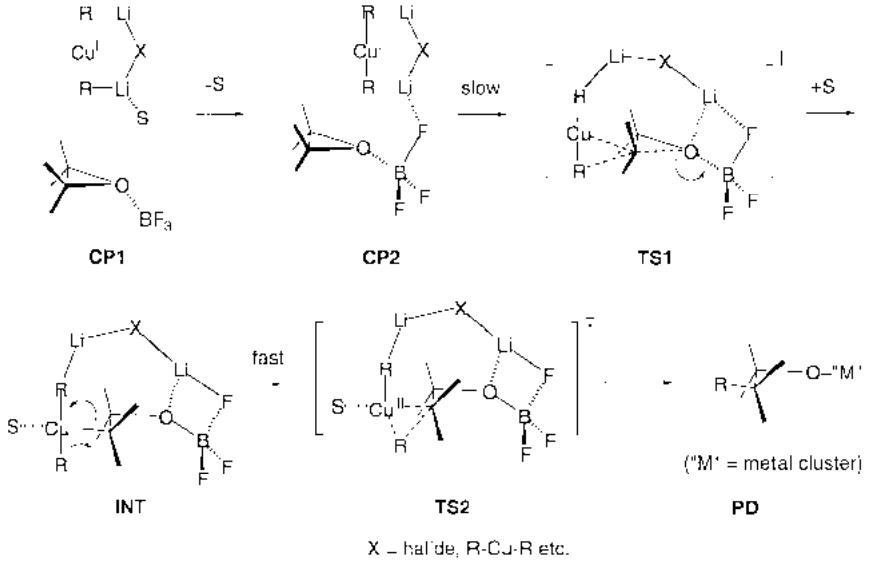


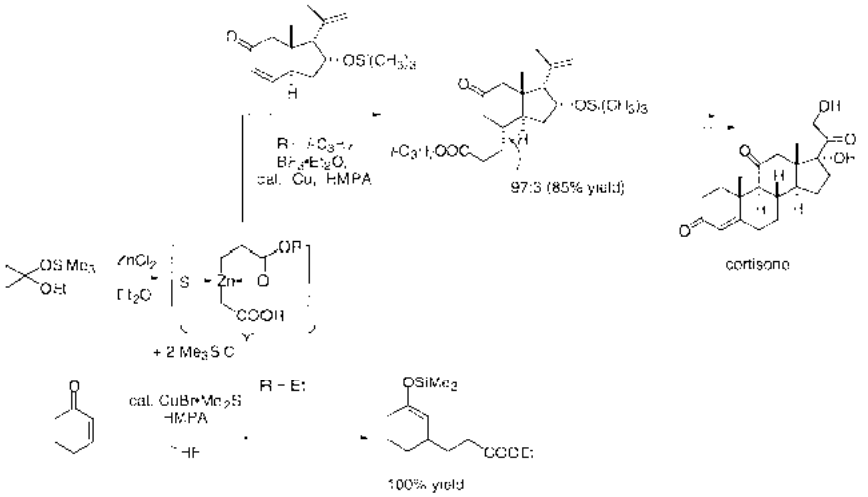
Fig. 10.5. Mechanism for the acceleration of an epoxide alkylation reaction by BF_3.

also be formed from a cuprate/BF_3 complex and the epoxide. Displacement to TS (**TS1**), followed by the formation of a Cu(III) intermediate (**INT**), gives the alkylation product **PD**. The cooperative interaction of BF_3 fluorine and boron atoms with the cuprate and epoxide system is responsible for the acceleration and stabilization of products. The activation energy is reduced by ca. 10 kcal mol $^{-1}$ compared to the process in the absence of BF_3.

10.6.2
Me_3SiCl Acceleration

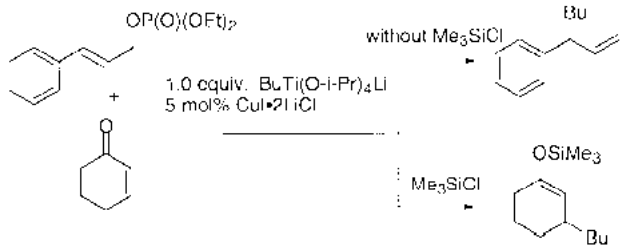
Since Nakamura and Kuwajima's initial discovery in 1984 [130], Me_3SiCl has become a standard reagent for acceleration of conjugate additions. The effect was first reported for copper-catalyzed conjugate additions of the zinc homoenolate of propionic acid esters, as shown in Scheme 10.13, and utilized in a total synthesis of cortisone [131]. Application to Grignard-based catalytic reagents and stoichiometric lithium diorganocuprate(I) followed [132]. Acceleration of conjugate additions and

modification of their selectivities by means of silylating agents are now well established [132].



Scheme 10.13. Me_3SiCl- and BF_3-accelerated catalytic conjugate addition and a cortisone synthesis.

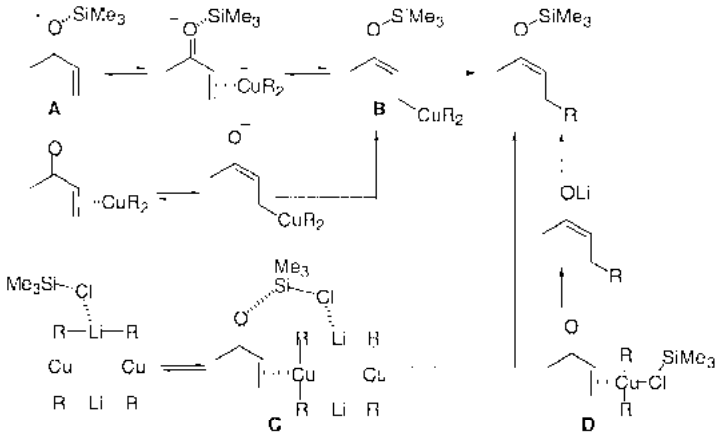
Me_3SiCl also affects the stereoselectivity of 1,2-additions to carbonyl compounds [133]. With the aid of suitable activators, these mildly reactive reagents show selectivities unattainable by the conventional reagents, as illustrated below for Me_3SiCl-dependent chemoselectivity (Eq. 10.13) [134].



(10.13)

Considerable mechanistic discussion has appeared in the literature [135]. One argument assumes simple Lewis acid activation of the starting enone with Me_3SiCl [136] (**A** in Scheme 10.14), although it is supported neither by experiment nor by theory [137]. On the contrary, Me_3SiCl has indeed been shown to be Lewis acidic but rather to act as a base toward the lithium atom in the lithium cuprate cluster [135a] (**C** in Scheme 10.14). The second proposal, by Corey [73], which takes into account an inner sphere electron-transfer hypothesis, assumes in situ trapping of an enolate-like intermediate by the silylating agents, making the process irreversible (**B** in Scheme 10.14). The third and most recent proposal assumes theoretical

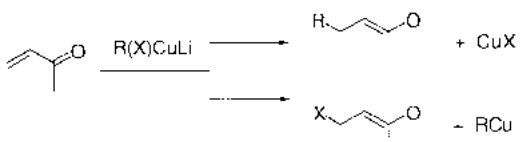
justification for chloride coordination to copper (**D** in Scheme 10.14) [135b]. The magnitude of such coordination, however, was recently shown to be very small [129]. While these proposals failed to provide a direct answer to the mechanism of Me_3SiCl acceleration, the positive correlation between the silylating power of the reagent and the magnitude of rate acceleration [138] strongly suggests that the rate-determining step of the reaction is the silylation step rather than the C C bond-forming step. Recent studies of kinetic isotope effects by Singleton fully supported this observation [139]. Mechanistic data – such as reaction rate, stereochemistry, and theoretical analysis – are still awaited, however.



Scheme 10.14. Various proposed mechanisms for Me_3SiCl acceleration of conjugate additions to enones (X = Me_3SiCl).

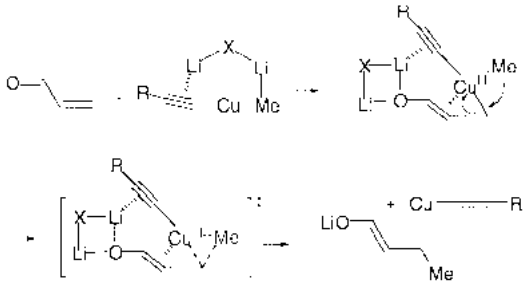
10.6.3
Dummy Ligands

A synthetic problem associated with the use of homocuprates R_2Cu is that the reagent can transfer only one of the two possibly precious R ligands to the target electrophile (E^+, for example, to α,β-unsaturated carbonyl compounds), with one R ligand being lost as an unreactive RCu species. The introduction in 1972 of mixed organocuprates [RCu(X)] [140], in which the X group acts as a nontransferable dummy ligand, provided the first general solution to this problem (Eq. 10.14). Typical dummy ligands include alkynyl [141], cyano [142], phenylthio [143], dialkylamino, and phosphino groups (Chapt. 3) [143, 144]. The selectivity of ligand transfer was considered to be a function of the ligand-ligand coupling process in an intermediate bearing three ligands: R, X and E. A widely accepted hypothesis was that an X group forming a stronger Cu X bond acts as a better dummy ligand (resisting transfer). While this hypothesis has successfully been applied to the design of dummy ligands, recent theoretical studies by Nakamura revealed an entirely different controlling factor in dummy ligand chemistry [145].



(10.14)

The recognition of the importance of cluster structure has resulted in a new understanding of the role of a dummy ligand (Y) in the chemistry of mixed cuprates MeCu(Y)Li [145]. As shown in Scheme 10.15 for the case of Y = alkynyl, the



Scheme 10.15. Dummy ligands: selective transfer of the methyl (or alkyl, alkenyl, aryl) group in preference to transfer of the alkynyl group.

transfer of the methyl group is overwhelmingly favored over the transfer of the alkynyl group. This is because the alkynyl group acts as a tight bridge between Cu^{III} and Li^{+} (Fig. 10.6). In other words, the alkynyl dummy group simultaneously binds to Cu and Li atoms (strong electrostatic interaction between the Li and the alkynyl group), and so remains on the copper atom. By default, the much less effective bridging organic ligand is transferred to the enone substrate. This runs

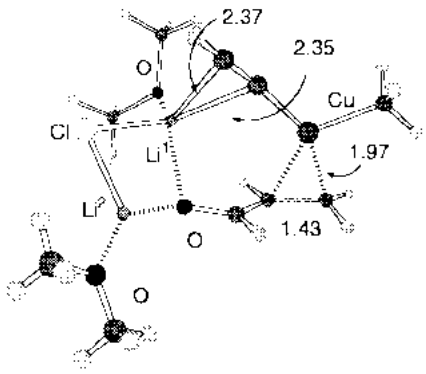
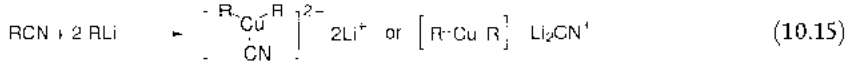


Fig. 10.6. 3D structure of the open complex between acrolein and Me(ethynyl)CuLi·LiCl, with Me_2O coordinated to each lithium atom (B3LYP/631A). Bond lengths are in ångstroms.

contrary to the conventional hypothesis that the Y group forming a stronger Cu Y bond acts as a better dummy ligand (resisting transfer), and has provided an further illustration of the critical roles of cluster structures in organocopper chemistry.

10.6.4
The "Higher Order" Cuprate Controversy

Organocopper(I) species bearing three anionic groups, ($[R_3Cu]^{2-}$), are termed "higher order" cuprates [146, 147]. For purposes of differentiation, conventional cuprate(I) species (R_2Cu^-) may be referred to as "lower order" cuprates. Whether or not a "higher order cyanocuprate ($R_2Cu(CN)Li_2$)", bearing two carbanionic residues and a cyanide anion on copper, exists as a stable species has been the subject of controversy (Eq. 10.15). This controversy has also spawned numerous mechanistic and structural studies on cuprates in general.



(10.15)

It was reported in the 1970s that a "higher order" cuprate reagent, prepared by the use of more than two equivalents of an alkyllithium reagent with a copper(I) salt, was more reactive [20, 146] and more selective than ordinary cuprates [148]. Using NMR and cryoscopy, Ashby showed that species that could be regarded as higher order cuprates were formed [149]. Bertz demonstrated the presence of a triply coordinated Cu(I) complex ($[R_3Cu]^{2-}$) for the first time, by solution NMR studies [150], while Power demonstrated the existence of a triply coordinated cuprate $[Ph_5Cu_2Li_3(SMe_2)_4]$ in the crystalline state [151, 152].

Lipshutz reported in 1981 that reagents formed by addition of two equivalents of RLi to CuCN give higher yields than the corresponding Gilman cuprates (R_2CuLi) or lower order cyanocuprates (RCu(CN)Li), and described them as "$R_2Cu(CN)Li_2$" to imply a triply coordinated structure [147]. With the aid of ^{13}C, ^{6}Li, and ^{15}N NMR data [153], Bertz was able to point out that cyanide was not attached to copper(I) in the Lipshutz mix, and started the controversy [154, 155]. Physical measurements by Penner-Hahn [156] and Lipshutz [157], and theoretical studies by Snyder [158], Penner-Hahn, and Frenking [159] contributed much to the discussion. All the crystallographic data for cyanocuprates of "higher-order stoichiometry" recently reported by Boche [160] and van Koten [161] indicated that the cyanide anion is coordinated to lithium and not to copper. Evidence along the same lines was found in sodium and potassium derivatives [162]. The consensus, therefore, after many years of studies, is that triply coordinated $[Cu(CN)R_2]^{2-}$ is not a stable structure in ethereal solution [153, 163–165]. Despite this conclusion, the Lipshutz mixed reagent still remains the one of choice in many synthetic transformations, and the presence of a triply coordinated cuprate(I) dianion was recently indicated by ^{13}C ^{13}CN carbon coupling in cyanostannylvinylcuprate(I) dianion in a THF/HMPA mixture [166]. In addition, the cyanide anion finds its way onto copper at the end of the reaction, forming RCu(CN)Li, while it is not known when the

cyanide/copper coordination starts. The true role of the cyano group in the reactions of "higher order cyanocuprates" remains obscure [164, 167].

10.6.5
Further Issues

While a large number of studies have been reported for conjugate addition and S_N2 alkylation reactions, the mechanisms of many important organocopper-promoted reactions have not been discussed. These include substitution on sp^2 carbons, acylation with acyl halides [168], additions to carbonyl compounds, oxidative couplings [169], nucleophilic opening of electrophilic cyclopropanes [170], and the Kocienski reaction [171]. The chemistry of organocopper(II) species has rarely been studied experimentally [172–174], nor theoretically, save for some trapping experiments on the reaction of alkyl radicals with Cu(I) species in aqueous solution [175].

10.7
Orbital Interactions in Copper-mediated Reactions

Recent theoretical analysis has revealed an intriguing difference between the addition reactions and the S_N2 alkylation reactions, in the geometry of the nucleophilic C Cu C moiety. As summarized in Sect. 10.2, the C Cu C bonding in doubly coordinated organocuprate(I) anions found in stable structures is always linear. As the HOMOs of linear R_2Cu^- molecules are largely $3d_{z2}$ copper orbitals [92, 94], linear C Cu C groups are suitable for interaction with the σ^*-orbital of MeBr, as illustrated in Fig. 10.7a [94]. Bending of the C Cu C bond to <150° causes mixing of the $3d_{xz}$ copper orbital with the 2p methyl orbital, to make it the HOMO of the cuprate (Fig. 10.7b), which is now suitable for interaction with the π^*-orbitals of enones and acetylenes. The energy gain through back-donation largely compensates for the energy loss associated with the bending (ca. 20 kcal mol^{-1} to achieve an angle of 120°).

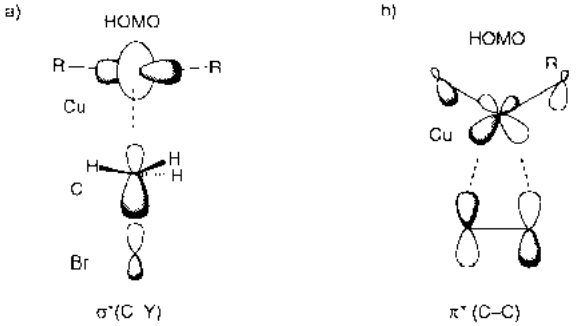


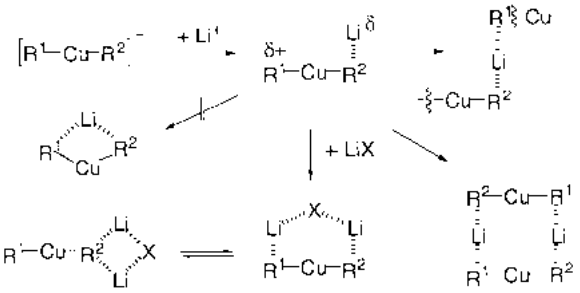
Fig. 10.7. Orbital interactions between R_2Cu^- and substrates in (a) an early stage of interaction of the cuprate with methyl bromide, and (b) π-complexation to acetylene or olefin.

The above analysis for copper chemistry also applies to the same-class element gold, which, however, forms much more stable C Au^{I} bonds [176] and so is unreactive. On the other hand, the d-orbitals of zinc(II), a main group neighbor, are too low-lying to make organozinc compounds as nucleophilic as organocopper compounds [92].

10.8
The Roles of Cluster Structure in Copper-mediated Reactions

The experimental and theoretical data below indicate several important characteristics of cuprate structures and their reaction mechanisms.

(1) The C Cu C angle in a covalently bound R_2Cu fragment in a stationary state is always close to 180° [94]. In ethereal solution, R_2CuLi exists as higher aggregates, the Li R bonds of which are fractional [26, 177–179]. It is invariably possible to identify a neutral fragment, R Cu R Li, in crystals of cyclic oligomers and higher polymers (Scheme 10.16). Depending on the nature of the reacting electrophiles (σ^* or π^*), either linear or bent conformations of the C Cu C moiety become important in nucleophilic reactions (Fig. 10.7) [94].



Scheme 10.16. Various structural possibilities for cuprates. Solid lines indicate (largely) covalent bonds, and dashed lines (largely) electrostatic bonds between a metal cation and an organic or heteroatomic anion. X = RCuR, halogen, CN, etc.

(2) Because of the fractional R Li bond, clusters and polymers can reversibly form an open cluster, which traps the unsaturated substrate through multiple-point bonding (cf. Schemes 10.5 and 10.7). Lithium cations assist the electron flow from the cuprate to the electrophile and, to achieve such cooperative action, a cluster of a particular size may be necessary. Lewis acid metals other than lithium (Zn^{II}, for example) will also play similar roles.

(3) A C Cu^{I} bond is a stable covalent bond, and is difficult to cleave by itself [93]. After charge transfer from cuprate(I) to substrate, however, cleavage of the resulting R Cu^{III} bond becomes easy. The reductive elimination reaction regenerates RCu^{I}, which may take part in further catalytic cycles. Thus, in copper-

catalyzed reactions, excess R anion will react with RCu to regenerate the necessary cuprate species.

(4) Although acetylene carbocupration and conjugate addition have previously been considered to be two separate reactions, they have been shown to share essentially the same reaction mechanism. The kinship of carbocupration, conjugate addition, S_N2' allylation, and S_N2 alkylation has now been established, through the theoretical studies of Nakamura, Mori, and Morokuma.

(5) Demonstration of the critical roles of the open conformations of polymetallic clusters highlights theoretical analysis in cuprate chemistry. Polymetallic clusters in various synthetic reactions are currently attracting the attention of synthetic and mechanistic chemists alike [40, 180–183].

10.9 Summary and Outlook

As summarized in the preceding sections, numerous experimental studies have indicated active participation by large organocopper clusters. These typically bear nucleophilic alkyl residues, copper(I) atoms, and counter-cations (typically lithium). The uniqueness of organocopper chemistry stems primarily from the fact that it lies on the border line between main group elements and transition metals. Comparisons may be made for the neighboring elements – Ni^0, Cu^I, Ag^I, Au^I and Zn^{II} – all of which exist in d^{10} configurations. The energy levels of the copper(I) 3d orbitals are much higher than those in zinc(II), and become even higher upon mixing with the 2p orbital of the alkyl ligand through R_2Cu formation [94]. Redox systems like the Cu^I/Cu^{III} cycle are unavailable for zinc(II). Organonickel and silver species are less stable, and so much less synthetically viable than organocopper(I) reagents, while organogold(I) species are too stable to be synthetically useful. The C Cu C angle is intimately connected with the reactivities of diorganocuprate(I) species, and the Lewis acid (Li^+) in cuprate clusters provides push-pull electronic assistance for charge transfer from Cu^I to the electrophile. The diversity of coordination structures revealed by calculations indicates that organocopper chemistry represents the ultimate "supramolecular chemistry", long but unwittingly exploited by chemists. Numerous other aspects of organocopper chemistry await further mechanistic study. The importance of R_3Cu^{III} species is now fully recognized, and needs more careful attention in future studies of mechanistic and synthetic organocopper chemistry.

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