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Copper-catalyzed enantioselective allylic alkylation ring-opening reactions of small-ring heterocycles with hard alkyl metals

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Copper-catalyzed enantioselective allylic substitution reactions with organometallic reagents have aroused a great deal of interest in recent years. Small-ring heterocycles, such as epoxides and aziridines, have proven to be valuable leaving groups in copper-catalyzed asymmetric allylic alkylations with organometallic reagents. Some successful combinations of an organometallic reagent and an external chiral ligand for the enantioselective addition of dialkylzinc reagents to racemic and symmetrical allylic 1,2- and 1,4-epoxides are described. For this purpose, chiral copper complexes of phosphoramidite ligands, having an electron-deficient phosphorus atom, proved to be highly effective catalysts. Our experimental work has shed some light on the mechanism of a copper-catalyzed allylic alkylation and supports the notion that the reductive elimination step is the regio- and stereodetermining step.

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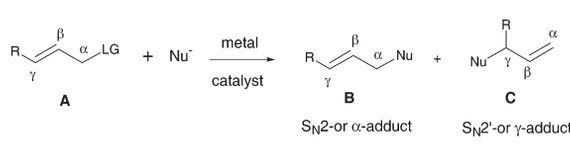
Introduction

The transition metal catalyzed asymmetric carbon-carbon formation reactions are fundamental transformations in synthetic organic chemistry.[1] In this area, metal-catalyzed allylic alkylation is one of the most popular and useful protocols. Allylic alkylation can be catalyzed by many metal complexes deriving from palladium, nickel, copper, platinum, rhodium, iridium, iron, molybdenum and tungsten. From the standpoint of organic synthesis, palladium and copper are the most important metals for selective metal-catalyzed allylic substitution with carbon nucleophiles. Most of the reaction protocols based on the above metals (except for nickel and copper) rely on the use of soft nucleophiles. In particular, spectacular results have been achieved with palladium-catalyzed enantioselective allylic substitutions using soft carbon nucleophiles (for example malonates).[2]

Alternatively, the copper-catalyzed allylic substitution reaction making use of hard nucleophiles (for example organometallic reagents) can be performed and this approach has generated a great deal of interest in recent years. Advantages of the use of copper are that a broad range of organometallic compounds (organolithium, Grignard and organozinc reagents) can be used and that the regioselectivity is often of the S_N2'-type.[3] In general, treatment of an allylic substrate **A**, possessing a suitable leaving group (LG) in its allylic position, 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 **B** and **C**, respectively (Scheme 1). Moreover, despite the intrinsic preference for γ-attack, the regioselectivity can be advantageously tuned by changing the reaction conditions.[3] Copper(I)-promoted asymmetric γ-substitution of allylic substrates bearing a chiral leaving group has been reported,[4] but catalytic procedures employing chiral ligands on copper have emerged only recently. In particular, the enantioselective copper-catalyzed γ-allylation of allylic substrates with Grignard reagents has been described by the groups of Van Koten and Bäckvall,[5] and of Alexakis.[6]

The use of organozinc reagents in copper-catalyzed allylic alkylation has been described only quite recently. Organozinc reagents have the advantages of being broadly tolerant of various functional groups, of transmetallating easily to other transition metals and of possessing an inherently low reactivity. Whereas in some cases catalytic allylic alkylation with Grignard reagents gives only a moderate regioselectivity because of a background S_N2 substitution, it is worth



LG=Br, Cl, OAc,-OCO_2R, -$OPO(OEt)_2$, etc.

Scheme 1

Mauro Pineschi was born in Certaldo (Firenze) in 1964. In 1993 he received his Ph.D at the University of Pisa under the guidance of P. Crotti on the development of new synthetic methodologies making use of epoxides and aziridines. After a postdoctoral position in the group of B. L. Feringa as a Marie Curie Fellowship of the European Community working on asymmetric catalysis, in 1998 he became researcher of organic chemistry at the University of Pisa. In 2002 he was appointed associate professor of organic chemistry at the same University. In 2000 he was the recipient of the Ciamician Medal, a prestigious award of the organic division of the Italian Chemical Society. His research interests include enantioselective catalysis and the development of new synthetic methodologies involving small-medium ring heterocycles.

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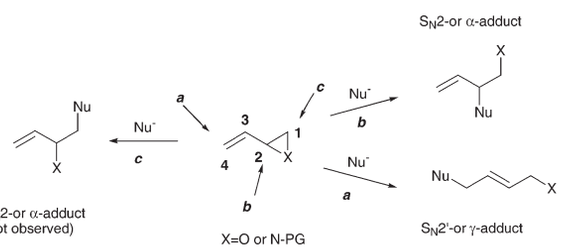
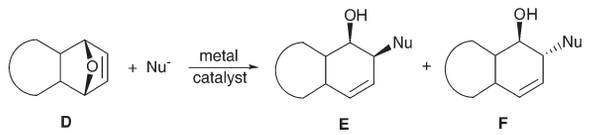
mentioning that organozinc reagents do not react with most allylic substrates in the absence of copper salts. Recently, Dübner and Knochel introduced a new, highly regio- and enantioselective copper-catalyzed alkylation of allyl chlorides with sterically demanding organozinc reagents.[7] Feringa *et al.* recently described an enantioselective allylic alkylation of cinnamyl bromide with linear dialkylzincs proceeding with moderate regio- and enantioselectivities.[8] The most successful Cu-catalyzed allylic substitution reaction with "hard" alkylating agent has been developed by Hoveyda and coworkers, using peptide-based ligands and dialkylzincs.[9] Allylic phosphates were found to be the most suitable leaving group and very recently this strategy has also been applied to the asymmetric synthesis of α-alkyl-β,γ-unsaturated esters.[10] The use of phosphates as leaving group has been also reported by Piarulli, Gennari and coworkers in a new highly regio- and enantioselective allylic desymmetrization of *meso*-cyclic allylic bisdiethylphosphates.[11]

While the development of a new copper-catalyzed enantioselective alkylation of classical allylic substrates (such as **A**) has been the target of research efforts in many different research groups, the same is not true when the leaving group consists of a samll-ring heterocycle, such as an epoxide or an aziridine. For example, allylic epoxides and aziridines can be considered as a particular class of allylic substrates. As substrates they are special because they combine the reactivity of epoxides and aziridines and that of allylic substrates, allowing a wide range of synthetic transformations. Nucleophilic attack can, in principle, take place on three of the four consecutive functionalized carbon atoms (pathways *a*, *b*, *c* in Scheme 2) and the allylic alkylation is accompanied by a ring-opening process in which the leaving group is maintained in the final product. Nucleophilic addition to the least hindered oxirane carbon (carbon 1) affords the 1,2-addition product (path *c*). Nucleophilic attack on the oxirane carbon adjacent to the carbon-carbon double bond (carbon 2, allylic position) affords the regioisomeric S_N2 addition product, usually obtained in ring-opening reactions (path *b*). Finally, conjugate addition of the nucleophile to the vinyl carbon 4 gives the corresponding S_N2' addition product (path *a*). Much work has centered on developing conditions to obtain each of these three products selectively. While path *c* is not commonly observed, paths *a* and *b* have been widely used in the synthesis of natural products.[12] The factors that favor nucleophilic attack by route *b* (direct addition or S_N2) and/or route *a* (conjugate addition or S_N2') usually rely heavily on the type of reagent.

As dialkylzincs are hard alkyl nucleophiles, but usually too weak to react with these conjugate systems, it is tempting to consider the possibility of generating a cuprate *in situ* by a transmetallation reaction, leading to more reactive and selective species. The first novel procedure for the selective S_N2' addition of organozinc reagents to vinyloxiranes was reported by Lipshutz *et al.*, who described an effective alkylation of allylic epoxides with functionalized organozinc reagents under mild conditions.[13] However, to the best of our knowledge, there have not been any reports about the catalytic enantioselective addition of organometallic reagents to these carbon



Scheme 2 Possible reaction pathways for the nucleophilic ring opening of an allylic epoxide or aziridine (PG = protecting group).



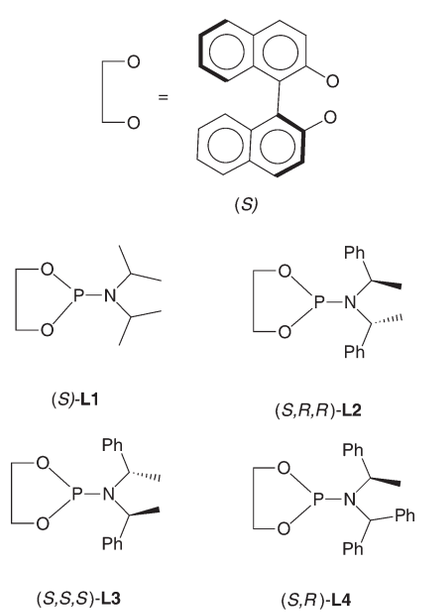
Scheme 3 Nucleophilic ring opening of [2.2.1]-oxabicyclic alkene **D**.

allylic electrophiles, even if this approach could be an intriguing challenge in organic synthesis.

Among the different strategies for the construction of highly functionalized molecules, the ring opening of oxabicyclic alkenes with organometallic reagents, has provided different approaches to the synthesis of both monocyclic and acyclic compounds with control of the relative and absolute stereochemistry.[14] These approaches usually utilize a nucleophilic attack on the double bond with concomitant expulsion of the bridging oxygen in a regio- and stereocontrolled manner to give the corresponding *syn*- and *anti*-adducts **E** and **F**, respectively (Scheme 3).

However, the enantioselective symmetry-breaking of symmetrical oxabicyclic compounds has not been described until recently.[15] In this area, Lautens and coworkers reported a highly enantioselective palladium-catalyzed ring opening of oxabicyclic alkenes with dialkylzincs.[16] More recently, the same author has described a high enantioselective rhodium-catalyzed ring opening of meso oxabicyclic alkenes with aryl-alkenyl boron compounds.[17,18] Waymouth described an asymmetric zirconium-catalyzed addition of Et_3Al to oxabicyclic alkenes.[19] It should be noted that these asymmetric transformations afford the *syn*-addition products.

The remarkable results previously obtained in the addition of organozinc reagents to enones by Feringa *et al.* and others[20] prompted us to verify the effectiveness of the chiral copper complexes of Binol-based phosphoramidites (such as ligands **L1**–**L4**, Scheme 4) in the stereoselective conjugate addition of organozinc reagents to allylic 1,2- and 1,4-epoxides and more recently to allylic aziridines. A "critical" description of these efforts constitutes the topic of the present article.



Scheme 4 Ligands used for the copper-catalyzed enantioselective allylic alkylation ring-opening reactions of samll-ring heterocycles with dialkylzincs.

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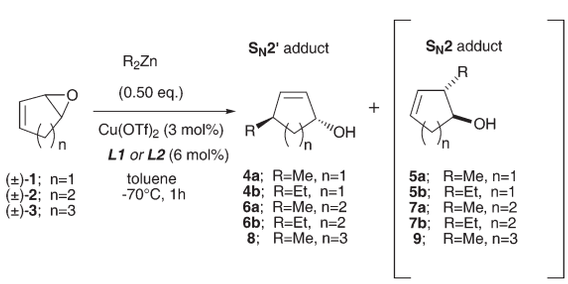
Copper-catalyzed kinetic resolution of allylic 1,2- and 1,4-epoxides and aziridines

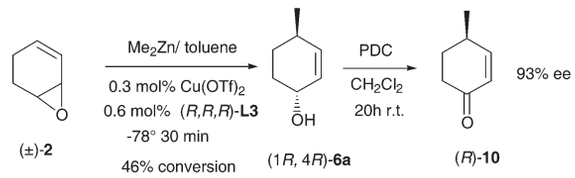
The S_N2' displacement of allylic epoxides affords synthetically useful allylic alcohols and the ratio of S_N2'/S_N2 products in the nucleophilic addition to cyclic allylic epoxides is very sensitive on the type of organometallic reagent or catalyst used.[12] Our preliminary results showed that the reaction of 1,3-cyclohexadiene monoepoxide **2** with Me_2Zn (1.5 equiv.) in the presence of $Cu(OTf)_2$ (3 mol %) afforded a complex reaction mixture containing a small amount (8% combined yield) of a *ca.* 1:1 mixture of allylic alcohols **6a** (*anti*-S_N2' pathway) and **7a** (*anti*-S_N2 pathway) (Scheme 5).

This result can be drastically changed when a phosphoramidite is used as the chiral ligand.[20a] For example, the preventive addition to the reaction mixture of a catalytic amount (6 mol %) of chiral phosphoramidite (*S*)-**L1** gave a dramatic increase in the conjugate addition pathway.[20] Thus, allylic alcohol **6a** was obtained with a good regio- ($S_N2'/S_N2 = 13$) and enantioselectivity (62% ee). This is a typical example of a ligand-accelerated catalysis effect:[22] without the ligand, the reaction is much slower and proceeds without regio- and stereoselectivity. The best results (>90% ee) were obtained by the use of (*S*,*R*,*R*)-**L2**, derived from (*S*)-2,2′-binaphthol and the sterically demanding bis-(*R*)-1-phenylethylamine,[20b] especially when six- and seven-membered monoepoxides **2** and **3** were used. The highest enantioselectivity was observed in the addition of Me_2Zn to **3** (96% ee). In this case, the regioselectivity (S_N2'/S_N2 ratio) was even better than that obtained in the stoichiometric addition of MeCu(CN)Li to vinyloxirane **3**.[12a]

The synthetic utility and practicality of this new procedure was soon after demonstrated through the first catalytic asymmetric synthesis of both (*R*)-(+)- and (*S*)-(−)-2-cyclohexen-1-one (**10**).[23] Chiral non-racemic 2-cyclohexenones are attractive building blocks for the synthesis of a variety of natural products and are usually obtained from the "chiral pool", from (*R*)-(+)-pulegone or (*S*)-(+)-carvone or by means of conventional racemate resolution methods. These procedures are often long and tedious and the overall yields obtained are generally quite low. The key step of our straightforward approach is the S_N2' addition of Me_2Zn to racemic **2** to give enantiomerically enriched allylic alcohol **6a** (93% ee, 89% yield based on the reacted epoxide), which can easily be oxidized to the target compound (Scheme 6). This step has been optimized as far as enantio- and regioselectivities and work-up procedures are concerned. The striking ligand-accelerated catalysis by the chiral copper complexes with phosphoramidite **L3** permitted a very low catalyst loading (0.6 mol %). Very similar results can be obtained by the use of chiral ligand **L2**. Compared with other multistep syntheses, our two-step procedure is simple and starts from commercially cheap and readily available reagents.[24] Moreover, our simple work-up procedure, based on filtration and distillation, qualifies for further scale-up. As a large number of dialkylzinc reagents are available by standard methods,[25] it is reasonable to assume that other optically active 4-alkyl-2-cyclohexenones (and 4-alkyl-2-cyclohexenols)



Scheme 5 Kinetic resolution of 1,3-cycloalkadiene monoepoxides. Redrawn from ref. 21. Copyright 1998, Elsevier.



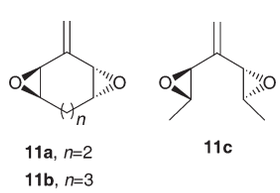
Scheme 6 Multigram catalytic synthesis of **10**. Redrawn from ref. 23. Copyright 2001, Georg Thieme Verlag.

can be synthesized by this procedure, allowing a novel, easy, flexible and practical multigram-scale synthesis of this interesting class of compounds by the use of minimal amounts of Binol-derived phosphoramidites.

In the search for new allylic epoxides as substrates for our reaction protocol, we recently developed a new copper-catalyzed addition of Grignard and dialkylzinc reagents to the new vinyl diepoxides **11a–c**, which contain homotopic oxirane rings in the allylic position with respect to the exocyclic double bond (Scheme 7). Cyclic vinyl diepoxides **11a,b** undergo clean S_N2' reactions, delivering oxa-bridged systems of various sizes after a domino intramolecular *O*-alkylation reaction. For example, the CuCN catalyzed reaction of Grignard reagents with vinyl diepoxide **11b** proceeded with complete S_N2' regioselectivity to give the allylic epoxy alcohols **12a,b** as the primary reaction products. Subsequent intramolecular *O*-alkylation occurred with complete regioselectivity at the allylic position of the remaining allylic epoxide, affording the bicyclo[4.2.1]-nonane skeleton, present in **13a,b** (Scheme 8).[26]

The application of the same copper-catalyzed addition protocol of Grignard reagents to the seven-membered vinyl diepoxide **11a** proved to be strongly influenced by the type of RMgX and reaction conditions utilized. However, when the reaction was performed with a threefold excess of the Grignard reagent in THF, it invariably afforded diols **14a–d** as the major product. Interestingly, these compounds are derived from a double alkylation process in which the alkyl moiety is transferred twice. A similar control of reactivity, depending on the reagents and solvent used for the reaction, was also observed with the aliphatic vinyl diepoxide **11c**, which was (doubly) alkylated with a good yield when an excess of EtMgBr was used in THF. With substrate **11a** an intramolecular *O*-alkylation also occurred, affording regioisomeric bicyclo[3.2.1] compounds of type **15** in which the attack has occurred at the less activated allylic position of the oxirane moiety (Scheme 8). Unfortunately, the copper phosphoramidite-catalyzed kinetic resolution of compounds **11a–c** with dialkylzincs proved not to be enantioselective.[26]

As organocuprates are effective in the ring opening of oxabicycles[14] and copper-phosphoramidite catalysts show high regio- and enantioselectivities in the ring opening of allylic epoxides with dialkylzinc reagents, we envisioned that the copper-catalyzed asymmetric ring opening of [2.2.1]-oxabicyclic alkenes (otherwise called 1,4-epoxides) might be feasible. An interesting mechanistic study of the palladium-catalyzed ring opening of oxabicyclic compounds with dialkylzincs was recently reported by Lautens and coworkers.[27] The regioselectivity found with the unsymmetrical substrate **16** was one of the experiments that ruled out the intervention of a π-allyl



Scheme 7 New cyclic vinyl diepoxides. Redrawn from ref. 26. Copyright 2003, Wiley–VCH.

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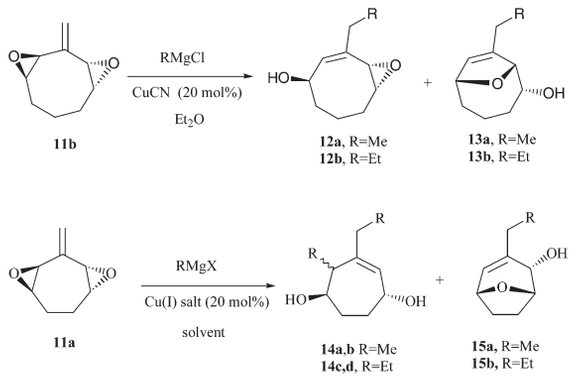
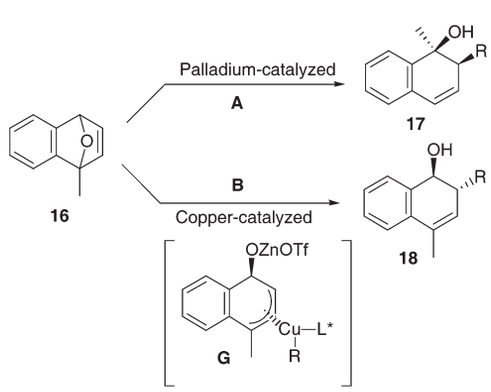


Scheme 8 Copper-catalyzed reaction of vinyl diepoxides **11a,b** with Grignard reagents. Redrawn from ref. 26. Copyright 2003, Wiley–VCH.

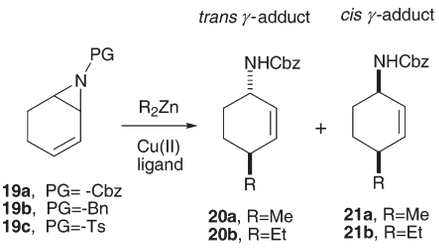
palladium intermediate. In fact, *syn*-dihydronaphthol **17** with overall retention of configuration was selectively obtained (pathway A in Scheme 9), thus excluding an ionization mechanism. In contrast, our copper phosphoramidite-catalyzed kinetic resolution of **16** exclusively afforded dihydronaphthol **18**, which is regioisomeric with the tertiary alcohol **17** obtained by the Pd-catalyzed protocol (pathway B).[28]

Reasonably, the complete regioselectivity observed points to a π-allyl pathway involving selective ionization at the tertiary center of **16**. Subsequently, the allyl intermediate **G** undergoes a reductive elimination, with retention of configuration, at the less hindered secondary terminus to give compound **18**.[29] Even if it is difficult to explain this complete regioselectivity, an *endo* mode of addition of the *in situ* formed organocuprate to the alkene in an *anti* fashion to the leaving group cannot be ruled out.[30]

Very recently, as a natural extension of our work on allylic epoxides, some racemic cyclic allylic aziridines have also been synthesized and studied. In the past few years great advances have been reported in the development of synthetic methods for the nucleophilic ring opening of 2-alkenyl aziridines.[31] In particular, the use of organocuprates as nucleophiles has emerged as a powerful and stereoselective synthetic method for the preparation of aliphatic (*E*)-allylic amines.[12b–e] Enantiomerically pure aliphatic allylic aziridines can be obtained by means of a chiral pool approach starting from non-racemic amino acids. However, to the best of our knowledge, there are no reports about the catalytic and enantioselective addition of organometallic reagents to these carbon electrophiles. The nature of the protecting group on alkenyl aziridines proved to be critical for their reactivity. Whereas the *N*-tosyl aziridine **19c** could not be isolated because it was not stable during chromatographic purification, the Cbz protecting group proved to be



Scheme 9 Complementary regio- and stereoselectivity of the ring opening of unsymmetrical oxabicyclic **16** with dialkylzincs with different metal catalysts.



Scheme 10 Regio- and enantioselective copper-catalyzed addition of dialkylzinc reagents to cyclic allylic aziridines. Redrawn from ref. 32. Copyright 2003, Elsevier.

optimal with respect to stability and reactivity. The benzyl-protected aziridine **19b** proved not to be reactive enough in our reaction conditions and only trace amounts of addition products were obtained, even using an excess of Et_2Zn and a prolonged reaction time. It should be noted that unlike the related epoxide **2**, the alkylative addition of Et_2Zn (1.5 equiv.) to allylic aziridine **19a** in the presence of $Cu(OTf)_2$ (0.03 equiv.) occurred smoothly (>95% conversion in 3 h, at −78 °C up to −10 °C) and afforded an equimolar mixture of the *cis*,*trans*-allylic amines **20b** and **21b**, (γ-adducts), as the major reaction products (Scheme 10).

Usually a copper-catalyzed allylic alkylation occurs in an *anti* fashion but a *syn* stereoselective process has already been found in copper allylic substitution reactions with a reagent-coordinating leaving group.[4] Interestingly, the *syn* stereoselective pathway can be drastically suppressed through the use of an external (chiral) ligand for copper. For example, the use of catalytic amounts of chiral copper complexes with racemic chiral ligand **L2** (Scheme 4) as a catalyst for the addition of Et_2Zn (1.5 equiv.) to **19a** made it possible to obtain a 95:5 *anti*:*syn* stereoselectivity. As for the kinetic resolution process, the best enantioselectivity in the allylic amine reaction product **20a** was obtained through the use of Me_2Zn and chiral ligand **L3** (83% ee at 48% conversion). This process is particularly valuable, considering that the new cyclic primary allylic amine of type **20** in its enantioenriched form is not easily accessible by other synthetic routes.[32]

Copper-catalyzed enantioselective desymmetrization of symmetrical allylic 1,2- and 1,4-epoxides

Desymmetrization of a symmetrical molecule to yield an enantiomerically enriched product is a widely used and rational synthetic strategy. One area for which examples of desymmetrization reactions are scarce is the catalytic enantioselective construction of C–C bonds.[33] Encouraged by the results obtained with racemic allylic epoxides[21] we were intrigued by the possibility of the addition of dialkylzincs to the enantiotopic faces of prochiral symmetrical allylic 1,2-epoxides, thus avoiding the intrinsic limitations of a kinetic resolution process. With this aim, the previously unknown *meso*-methylidene cycloalkane epoxides **22a–c**, bearing enantiotopic methylidene moieties in an allylic position with respect to the endocyclic oxirane ring, were synthesized and studied (Scheme 11).[34] The symmetrical epoxide **22a**, which can easily be obtained from naphthoquinone in two steps, was our model substrate. By studying this substrate we soon realized that ligand **L3**, derived from (*S*)-Binol and (*S*)-bisphenylethylamine, resulted in a matched combination.[35] The corresponding bis-allylic alcohols **23a–c** were obtained with good yield and a high regio- and enantioselectivity. The highest selectivity was obtained when the conformationally less constrained vinyloxirane **22c** was used. In this case, the addition product, the bis-allylic alcohol **23c**, was obtained (90% yield) with a 97% ee and a regioisomeric ratio of 98:2. Evidently, in this case, the chiral

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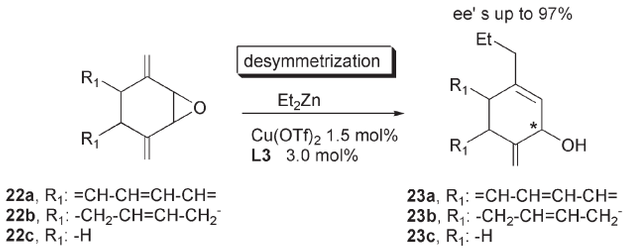
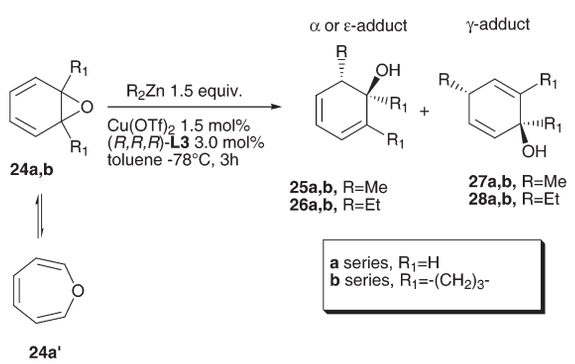


Scheme 11 Catalytic and enantioselective desymmetrization of symmetrical methylidene cycloalkene oxides **22a–c**.

catalyst's ability to discriminate between the enantiotopic reaction sites is maximized.

The effective chiral recognition of two enantiotopic faces of prochiral symmetrical allylic epoxides prompted us to search for even more appealing desymmetrization reactions. For example, arene oxides are very reactive compounds that have been subjected to several studies since the demonstration that these compounds are formed from aromatic hydrocarbons by the microsomial enzyme fraction from mammalian liver.[36] There are only a few, dated reports dealing with ring-opening reactions of arene oxides carried out with organometallic reagents.[37] Moreover, none of these procedures employing organometallic reagents are catalytic or enantioselective. We have recently described an unprecedented catalytic and enantioselective trapping of highly reactive symmetrical arene oxides offering a new route to enantioenriched dihydroaromatic alcohols, not easily accessible by means of other synthetic methods.[38] Benzene oxide (**24a**) and indan-8,9-oxide (**24b**) were examined as symmetrical arene oxide substrates (Scheme 12). Benzene oxide is known to exist in equilibrium with its tautomeric valence structure, the oxepin **24a′**. This compound exists mainly as oxepin at room temperature, even if the oxide component **24a** determines the reactions of the system with most agents. Epoxide **24a** was allowed to react at −78 °C (1 h, 95% conversion) with Me_2Zn (1.5 equiv) in the presence of a catalytic amount of $Cu(OTf)_2$ (0.015 equiv) and the chiral ligand (*R*,*R*,*R*)-**L3** (0.030 equiv) to give a crude reaction mixture consisting of the previously unsynthesized regioisomeric dienols **25a** (α-adduct) and **26a** (γ-adduct). The reaction with Et_2Zn gave a slightly different result, with a predominance of the achiral γ-adduct **28a**. The substituted enantioenriched dihydroaromatic α-adducts **25a** (93% ee) and **26a** (64% ee) were obtained with a complete *anti* stereoselectivity. Indan-8,9-oxide (**24b**), containing a tetrasubstituted epoxide, is known to exist only in the oxide form. The copper-phosphoramidite catalyzed addition of R_2Zn at −78 °C to **24b** (3 h, 95% conversion) gave a *ca.* 80:20 mixture of the corresponding α- and γ-adducts **25b**:**27b** (R = Me) and **26b**:**28b** (R = Et) (Scheme 12). It is remarkable that the α-adducts **25b** (≥95% ee) and **26b** exclusively derive from an *anti*-stereoselective



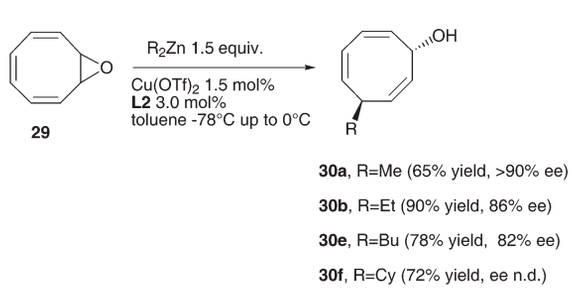
Scheme 12 Catalytic enantioselective trapping of arene oxides with dialkylzincs.

1,6-addition pathway and therefore have been more appropriately called ε-adducts.

The monoepoxide of 1,3,5,7-cyclooctatetraene (COT) is also a symmetrical molecule and it has several distinctive features with respect to the other symmetrical vinyl oxirane substrates examined. In fact, COT-monoepoxide (**29**) has a special structure imposed by three conjugated double bonds where the double bonds and the epoxide ring are not in the same plane. Moreover, there were very few reports in the literature about the ring opening of this epoxide. The ring contraction isomerization to the seven-membered trienyl carboxaldehyde that in turn added the organometallic reagents, forming substituted cycloheptatrienyl alcohols, was the most common reaction observed when organometallic reagents were employed with this substrate.[39] Moreover, Matsuda *et al.* reported that the reaction with Et_2CuLi in Et_2O under various reaction conditions resulted in the formation of polymeric material.[40] The only reported addition of an alkyl group to COT-monoepoxide without ring contraction made use of RLi in Et_2O and afforded 4-alkyl-2,6-cyclooctadien-1-ones through a 1,5-sigmatropic rearrangement.[41] We have recently found that the combination of Grignard reagents together with a catalytic amount of CuCN gave cleanly the corresponding trienyl alcohol addition product in a high yield and with complete conjugate regioselectivity.[42] Even better results were obtained by the use of stoichiometric amounts of copper salts in combination with Grignard reagents. Moreover, a highly enantioselective desymmetrization of **29** with dialkylzinc reagents and chiral copper complexes of phosphoramidite ligand **L2** has been reported as well (Scheme 13).[43] The less reactive Me_2Zn delivered the corresponding S_N2'-adduct **30a** (65% yield) with the best enantioselectivity (> 90% ee).

The dihedral angle between the adjacent double bond and the median plane containing the two oxirane carbons in epoxide **29** is *ca.* 60°. It is noticeable that in spite of this remarkable geometric constraint, an S_N2'-cuprate addition is achieved by the appropriate *in situ* generation of an organocopper reagent. This is the highest deviation from coplanarity ever observed in an allylic-type alkylation reaction.[44]

As regards the study of the desymmetrization reaction of 1,4-epoxides, oxabenzonorbornadiene **31** was considered as our model substrate.[29] It should be noted that the copper-phosphoramidite catalyst is essential to obtain the *anti* stereoselective pathway and in the absence of this catalyst, no significant reaction takes place. In fact, the addition of Et_2Zn alone (140 h, r.t.) gave only the starting material and a trace amount of the *syn*-adduct **33a**. On the other hand, the addition of Et_2Zn to **31** catalyzed by $Cu(OTf)_2$ (3.0 mol %) gave only the *syn*-adduct **33a** (full conversion, 55% isolated yield after 18 h at r.t.). All the minor *syn*-adducts obtained throughout this work are racemic and probably derive from an uncatalyzed reaction pathway. Facing the low reactivity of Et_2Zn in the copper-catalyzed alkylative ring opening of **31**, we varied the reaction parameters (solvent, Lewis acid, copper salt and ligand) and found that anhydrous $Zn(OTf)_2$ was highly



Scheme 13 Copper-phosphoramidite catalyzed desymmetrization of COT-monoepoxide. Redrawn from ref. 43. Copyright 2003, American Chemical Society.

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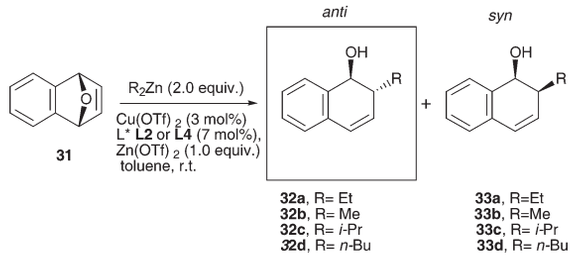
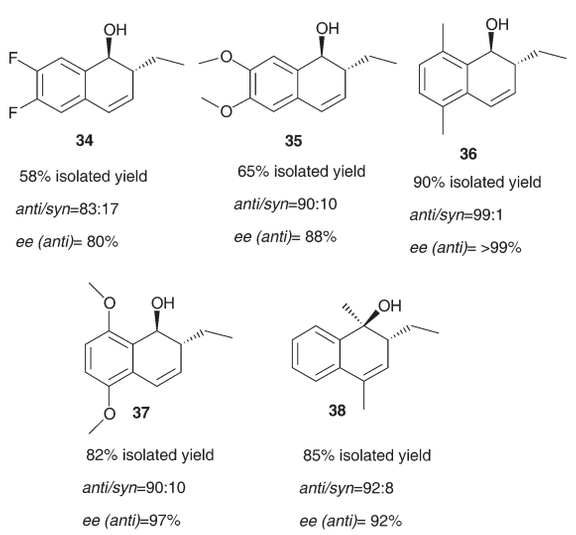


Scheme 14 Copper-catalyzed enantioselective ring opening of oxabenzonorbornadiene **31**. Redrawn from ref. 29. Copyright 2002, American Chemical Society.

beneficial for obtaining the *anti*-adducts **32a–d** with a high yield and stereoselectivity (Scheme 14).[29] The role of this additive in the ring-opening reactions of oxabicyclic compounds seems to be that of a Lewis acid favoring ionization of the bridgehead carbon–oxygen bond. The enantioselectivity of the reaction can also be improved by the use of the new phosphoramidite **L4**. With this ligand compound **32a** can be obtained with 92% yield and 94% ee in 13 h.

Next, the ring opening with Et_2Zn of other oxabenzonorbornadienes bearing substituents in various positions with respect to the endocyclic oxygen was undertaken. Chiral phosphoramidites **L2** (7 mol %) and $Cu(OTf)_2$ (3 mol %) gave the best results with these substrates in terms of the stereoselectivities obtained. Scheme 15 indicates all the enantioenriched dihydronaphthols that can be obtained with uniformly high *anti* stereo- and enantioselectivities. In particular, it is possible to obtain adduct **36** as a single diastereoisomer with $>99\%$ ee. Furthermore, it should be noted that was possible to obtain adduct **38**, containing a tertiary benzylic carbon atom, with a high level of diastereo- and enantioselectivity.

It is remarkable that our protocol is the only current example of an enantioselective *anti* ring opening of oxabicyclic alkenes with a carbon nucleophile.[29] The addition is complementary to the palladium-catalyzed *syn*-selective ring opening with dialkylzincs reported by Lautens and coworkers,[15,27] allowing a new entry to *anti*-dihydronaphthols with a high enantioselectivity. However, the synthetic scope of our reaction seems to be limited to the case of oxabenzonorbornadienes. In fact, our copper-catalyzed protocol gave only very low yields of addition products when non-benzylic oxabicyclic alkenes were employed. The situation can be changed by the use of the more robust Grignard reagents. During the development of our enantioselective procedure, we commonly used a CuCN (20 mol %) catalyzed addition of Grignard reagents for the ring opening of oxabicyclic alkenes to obtain the racemic *anti* stereoisomers.[45] Very recently, a copper-catalyzed *anti* stereocontrolled ring opening of oxabicyclic alkenes with Grignard reagents has been described.[30] The reaction proceeds in the presence of sub-stoichiometric amounts of copper salts and triphenyl phosphine. However, this procedure is more general in that several [2.2.1]-oxabicyclic alkenes can be opened and, moreover, it is the first *anti* ring opening arylation of oxa-bridged systems reported to date, albeit in racemic form.



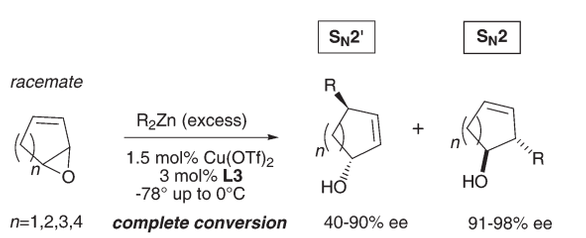
Scheme 15 Enantioenriched dihydronaphthols obtainable by the copper-catalyzed ring opening of different substituted oxabenzonorbornadienes.

Regiodivergent kinetic resolution of allylic epoxides

Kinetic resolution of a racemic mixture is a well-established methodology for the preparation of optically active compounds.[46] However, the major drawback with this approach is that a maximum of only one-half of the racemic starting material is converted into non-racemic products. Parallel kinetic resolution (PKR) is an interesting strategy recently introduced, in which both enantiomers of a racemate can be converted into different products.[47] This conceptual variation usually requires the use of two different stoichiometric chiral reagents in parallel. PKR concerning catalytic processes that form carbon-carbon bonds are, however, very rare.[48,49] During our study on the copper-catalyzed enantioselective kinetic resolution of cyclic 1,2-allylic epoxides, we took notice of the following: the amount of the homoallylic alcohol S_N2-adduct increased with the increase of conversion of the allylic epoxide and furthermore the ee of this homoallylic alcohol was always greater than 90%! Moreover, the regioselectivity of the reaction could be drastically changed in favor of the S_N2' addition product when a racemic chiral ligand was used, indicating that it is the chirality of the chiral ligand that determines the regioselectivity outcome. This striking and unexpected result led to the discovery of a new, highly stereocontrolled transformation of a racemic mixture by an organometallic reagent and chiral catalyst to give separable regioisomeric products.[50]

After this initial finding we have recently shown that enantioselective regiodivergent kinetic resolution (RKR) is also effective for a variety of cyclic 1,3-diene monoepoxides ($n = 1$–4, R = Me, Et, Bu) having a blocked s-*cis* conformation (Scheme 16).[51] The RKR process was particularly efficient when 1,3-cycloheptadiene monoepoxide ($n = 2$) was employed. With this substrate, the regiodivergency is practically ideal and regioisomeric alcohols of type S_N2' and S_N2, having opposite configuration at the hydroxyl-group-bearing carbon, were obtained in almost equal amounts and with a high enantiomeric excess ($>90\%$ ee) with all the dialkylzincs used. Evidently with this substrate, the asymmetric matching of the chiral ligand with the enantiomers of the substrate is noteworthy. Highly reactive racemic naphthalene oxide was also successfully trapped with Et_2Zn in an RKR process with a complementary enantiomer-dependent regioselectivity.[38]

In order to obtain more definite evidence that there is *a complementary enantiomer-dependent regioselectivity*, enantiomerically pure epoxide **39** was treated with a copper catalyst



Scheme 16 Copper-catalyzed RKR of cyclic 1,3-diene monoepoxides. Redrawn from ref. 51. Copyright 2004, American Chemical Society.

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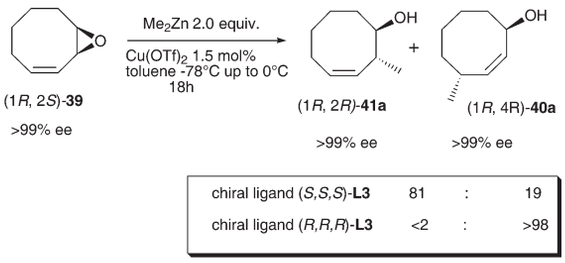


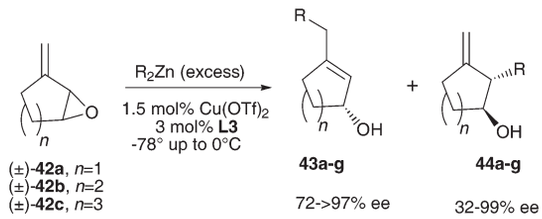
Scheme 17 Complementary enantiomer-dependent regioselectivity. Redrawn from ref. 51. Copyright 2004, American Chemical Society.

derived from both (*S*,*S*,*S*)-**L3** or (*R*,*R*,*R*)-**L3** (Scheme 17). In the presence of (*R*,*R*,*R*)-**L3**, (1*R*, 2*S*)-**39** reacted with Me_2Zn to give with complete regioselectivity the corresponding enantiopure allylic alcohol (1*R*,4*R*)-**40a**, whereas when (*S*,*S*,*S*)-**L3** was used, the corresponding homoallylic alcohol (1*R*,2*R*)-**41a** was obtained with a good selectivity.[51] Thus, it is clearly demonstrated that is possible to control the regioselectivity of the copper-catalyzed addition reaction of dialkylzincs to an enantiomerically pure cyclic allylic epoxide simply by choosing the appropriate enantiomer of phosphoramidite **L3**.

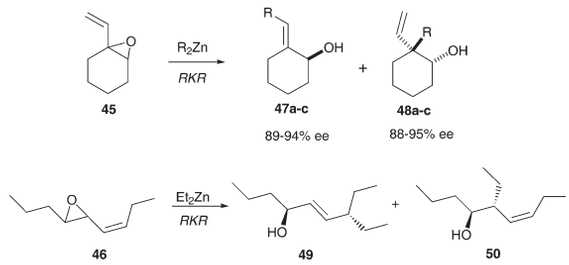
The enantioselective regiodivergency is operative also when racemic exo-methylene epoxides **42a–c**, which possess a blocked s-*trans*-conformation, are used (Scheme 18). Particularly worthy of note is the regiodivergent behavior in favor of the formation of the homoallylic alcohol of type **44** (S_N2-adduct) exhibited by Me_2Zn in the reaction with epoxide **42c**. In this case, the minor regioisomeric allylic alcohol **43e** ($n = 2$, R = Me) was obtained with a very high enantioselectivity (>97% ee) and when the reaction was carried out in accordance with a kinetic resolution protocol (Me_2Zn, 0.50 equiv), **44e** ($n = 2$, R = Me) was the main reaction product.

Considering that in an enantioselective RKR process the product obtained with the higher ee is commonly associated with the slower reaction, the above observations about epoxide **42c** would indicate that under our reaction protocol, the S_N2' addition can be, in some cases, the slower pathway within the addition process.

The comparison of the regiochemical outcomes obtained with a racemic catalyst *vs.* an optically pure one has been used in our experimentation to prove, when different, an *in situ* chiral recognition of the allylic epoxides. For example, many acyclic allylic epoxides examined showed only a modest complementary enantiomer chiral recognition and proved not to be suitable substrates for the RKR process. However, the asymmetric matching of ligand **L3** with the conformational mobility typically associated with acyclic allylic epoxides was in some cases successful. For example, we were delighted by the high enantioselectivity found in the ring-opened products, the allylic alcohols **47a–c** and homoallylic alcohols **48a–c** (R = Me, Et, Bu), when 1-vinyl cyclohexene oxide **45** was used as the substrate in our reaction protocol (Scheme 19). Considering that the construction of a quaternary stereocenter by means of a catalytic asymmetric reaction is certainly a topic



Scheme 18 Copper-catalyzed RKR of racemic exo-methylene allylic epoxides. Redrawn from ref. 51. Copyright 2004, American Chemical Society.



Scheme 19 Successful RKR of conformationally mobile allylic epoxides.

of current interest,[52] it is to be noted that the S_N2-addition products **48a–c**, containing a quaternary carbon stereocenter, were obtained with a high enantioselectivity.

The acyclic allylic epoxide **46** also gave a nice RKR reaction when treated with Et_2Zn in our reaction protocol. In this case it is important to point out that in the S_N2'-adduct **49**, deriving from an allylic rearrangement, the new double bond has an *E* configuration, whereas in the S_N2-adduct **50**, the original *Z* double bond configuration present in the starting epoxide is fully maintained. The preservation of the original double bond configuration of the starting epoxide in the S_N2-adduct seems to indicate that during the reaction the double bond is partly retained. Such a relationship of double bond configuration between reactant and product has been explained by Goering *et al.* by an oxidative addition that leads directly to a π-allyl copper(III) complex.[53] The most fascinating and unusual aspect of this RKR is certainly that the regioselectivity of the reaction depends directly on the absolute configuration of the chiral catalyst. This new process allows the formation of several new allylic and homoallylic alcohols with a good-to-excellent enantioselectivity. In most cases, the allylic and homoallylic alcohol reaction products can easily be separated by chromatography on silica gel. This method is also amenable for a novel synthesis of a quaternary carbon stereocenter with a high enantioselectivity. These facts, together with the ease of the reaction procedure, give a good level of practicality to our method and the possibility to access several allylic and homoallylic alcohols in an enantioenriched form.[51]

Considerations on the reaction mechanism

In sharp contrast with the palladium-catalyzed allylic alkylation, the mechanism for copper-catalyzed allylic alkylation has not been fully established yet and scant information is available as regards the transition state.[54] This is mainly due to the scarcity of direct methods to investigate the reaction pathway and to the lack of any intermediate that can be isolated. Most probably, the dialkylzinc reagent reduces *in situ* the copper(II) to the copper(I) salt, which is the true catalytic species. Moreover, it is generally admitted that an oxidative addition occurs to form a copper(III) intermediate[55] and that the rate-determining step of a cuprate conjugate addition is the last stage of the reaction, that is the reductive elimination process.[56] Our experimental work regarding the study of the copper-catalyzed allylic alkylation of 1,2- and 1,4-allylic epoxides has shown the following important points.

(i) The presence of an olefin is required for the reaction to occur, since cyclohexene oxide and styrene oxide are not alkylated in our reaction conditions.

(ii) The complete regioselectivity obtained in the copper-phosphoramidite catalyzed kinetic resolution with Et_2Zn of an unsymmetrical oxabicyclic compound such as **16** points to a π-allyl pathway, even if other mechanisms cannot be ruled out (*vide supra*, Scheme 9).

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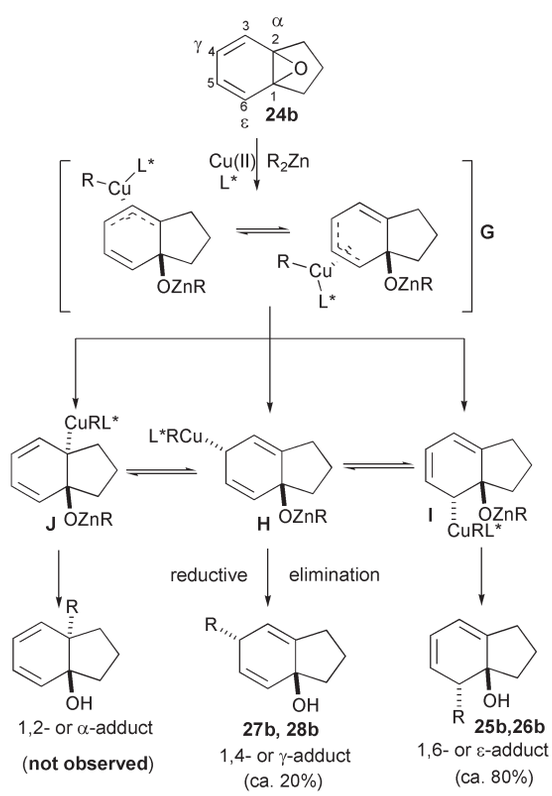
(iii) A fundamental role is exhibited by the chiral ligand: the absolute configuration of the chiral ligand determines the regiochemical outcome of the reaction.[51] It is difficult to imagine a scenario in which each enantiomer of the allylic substrate reacts with a completely different regiochemistry, without any common intermediates, simply by choosing the absolute configuration of a chiral ligand.

(iv) The maintenance of the original double-bond geometry observed in the acyclic allylic epoxides series within the corresponding S_N2-adducts (for example, the *Z* double bond in homoallylic alcohol **50**) supports the notion that the configuration of the double bond is partly retained throughout the reaction and points to a direct formation of a (π-allyl)copper(III) system.[53]

(v) The examination of the regiochemical outcome indicates that a 1,6-addition mode may be operative in a biased system such as indan-8,9-oxide (**24b**). The 1,6-addition process can be reasonably explained only by admitting an interconversion between regioisomeric (σ-allyl)copper(III) species.

Considering the conjugate nature of the starting epoxide, this interconversion between the regioisomeric (σ-allyl)copper(III) complexes of types **H**–**J** probably occurs by means of an intermediate delocalized (π-allyl)copper(III) species of type **G** (Scheme 20).[57] In this biased framework, the attack at the tertiary carbon terminus atom of **G** to give **J** is not favorable for steric reasons, while the attack at the secondary terminus of the **G** species to give the (σ-allyl)copper(III) complex **I** could be highly favored. The subsequent rate-limiting reductive elimination step on **I** affords the ε-adducts **25**, **26–b** (1,6-addition products) as the major products.[38]

Moreover, the remarkable *chiral recognition* of the enantiomers of a racemic allylic substrate by the chiral ligand (point iii) cannot be easily explained by a kinetically controlled formation of the corresponding regioisomeric (σ-allyl)copper(III) species by a selective nucleophilic cuprate addition to each enantiomer of the allylic epoxide, without the intervention of any equilibria between these species.[58,51] Probably it is the phosphoramidite chiral ligand that plays an important role in the acceleration of the carbon–carbon bond formation during the reductive elimination step, which should be the stereo- and regio-determining step.[56]



Scheme 20 Postulated mechanism for the enantioselective trapping of indan-8,9-oxide.

Conclusions and future prospects

It is worth mentioning that while there are several successful examples of asymmetric ring-opening reactions of epoxides with heteronucleophiles,[59] there are very few reports dealing with the enantioselective ring opening of epoxides with organometallic reagents.[60,61] We envisaged that flanking a double bond to an oxirane (or aziridine) ring could give rise to more possibilities of asymmetric nucleophilic ring opening of the heterocyclic ring by an organometallic reagent. This strategy has been demonstrated to be a viable alternative to the commonly used allylic alkylations in which the leaving group is lost in the final product. We have succeeded in developing one of the few successful combinations of an organometallic reagent and an external chiral ligand for the enantioselective addition of dialkylzinc reagents to allylic 1,2- and 1,4-epoxides. Chiral copper complexes of phosphoramidite ligands, having an electron-deficient phosphorus atom, proved to be highly effective catalysts for effectuating these transformations. However, detailed mechanistic studies are necessary to elucidate the origin of the high stereocontrol. Furthermore, the challenge remains for the effective development of new, stereocontrolled protocols making use of Grignard reagents, which are the most readily available carbon nucleophiles. The addition of sp^2-hybridized organometallics in a enantioselective fashion to allylic 1,2-epoxides and aziridines remains to be addressed, too. In this connection, the use of mild organometallic reagents, such as organoboron compounds, in an enantioselective allylic alkylation ring-opening reaction of allylic epoxides and aziridines would be of particular value. Our current studies are focused on expanding the scope of our procedure to other small-ring heterocycles and to other primary organometallic reagents.

References

1 B. M. Trost and C. Lee, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH Publishers, New York, 2nd edn., 2000, p. 593.
2 B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921.
3 A. S. E. Karlström and J.-E. Bäckvall, in *Modern Organocopper Chemistry*, ed. N. Krause, Wiley–VCH, Weinheim, 2001, p. 259 and references cited therein.
4 B. Breit and P. Demel, in *Modern Organocopper Chemistry*, ed. N. Krause, Wiley–VCH, Weinheim, 2001, p. 210 and references cited therein.
5 (*a*) G. J. Meuzelaar, A. S. E. Karlström, M. van Klaveren, E. S. M. Persson, A. del Villar, G. Van Koten and J.-E. Bäckvall, *Tetrahedron*, 2000, **56**, 2895; (*b*) A. S. E. Karlström, F. F. Huerta, G. J. Meuzelaar and J.-E. Bäckvall, *Synlett*, 2001, 923.
6 (*a*) A. Alexakis, C. Malan, L. Lea, C. Benhaim and X. Fournioux, *Synlett*, 2001, 927; (*b*) A. Alexakis and K. Croset, *Org. Lett.*, 2002, **4**, 4147.
7 F. Dübner and P. Knochel, *Angew. Chem., Int. Ed.*, 1999, **38**, 379.
8 H. Malda, A. W. van Zijl, L. A. Arnold and B. L. Feringa, *Org. Lett.*, 2001, **3**, 1169.
9 C. A. Luchaco-Cullis, H. Mizutani, K. E. Murphy and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2001, **40**, 1456.
10 K. E. Murphy and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2003, **125**, 4690.
11 U. Piarulli, P. Daubos, C. Claverie, M. Roux and C. Gennari, *Angew. Chem., Int. Ed.*, 2003, **42**, 234.
12 For a review of allylic epoxide ring openings with organocuprates, see: (*a*) J. A. Marshall, *Chem. Rev.*, 1989, **89**, 1503 and references cited therein; for selected examples of allylic aziridine ring openings with organocuprates, see (*b*) P. Wipf and P. C. Fritch, *J. Org. Chem.*, 1994, **59**, 4875; (*c*) T. Ibuka, K. Nakai, H. Habashita, Y. Hotta, N. Fujii, N. Mimura, Y. Miwa, T. Taga and Y. Yamamoto, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 652;

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(*d*) A. A. Cantrill, A. N. Jarvis, H. M. I. Osborn, A. Ouadi and J. B. Sweeney, *Synlett*, 1996, 847; (*e*) A. Toda, H. Aoyama, N. Mimura, H. Ohno, N. Fujii and T. Ibuka, *J. Org. Chem.*, 1998, **63**, 7053 and references therein; (*f*) C. S. Penkett and I. D. Simpson, *Tetrahedron Lett.*, 2001, **42**, 1179.

13 B. H. Lipshutz, K. Woo, T. Gross, D. J. Buzard and R. Tirado, *Synlett*, 1997, 477.

14 For reviews, see: (*a*) P. Chiu and M. Lautens, *Top. Curr. Chem.*, 1997, **190**, 1; (*b*) M. Lautens, *Synlett*, 1993, 177.

15 For a recent rview, see: M. Lautens, K. Fagnou and S. Hiebert, *Acc. Chem. Res.*, 2003, **36**, 48.

16 M. Lautens, J.-L. Renaud and S. Hiebert, *J. Am. Chem Soc.*, 2000, **122**, 1804.

17 M. Lautens, C. Dockendorff, K. Fagnou and A. Malicki, *Org. Lett.*, 2002, **4**, 1311.

18 K. Fagnou and M. Lautens, *Chem. Rev.*, 2003, **103**, 169.

19 D. B. Millward, G. Sammis and R. M. Waymouth, *J. Org. Chem.*, 2000, **65**, 3902.

20 (*a*) A. H. M. de Vries, A. Meetsma and B. L. Feringa, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2374; (*b*) B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos and A. H. M. de Vries, *Angew. Chem., Int. Ed.*, 1997, **36**, 2620; ; for overviews of phosphoramidites in catalytic asymmetric conjugate additions, see (*c*) B. L. Feringa, *Acc. Chem. Res.*, 2000, **33**, 346; (*d*) A. Alexakis and C. Benhaim, *Eur. J. Org. Chem.*, 2002, 3221.

21 F. Badalassi, P. Crotti, F. Macchia, M. Pineschi, A. Arnold and B. L. Feringa, *Tetrahedron Lett.*, 1998, **39**, 7795.

22 D. J. Berrisford, C. Bolm and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1059.

23 F. Bertozzi, P. Crotti, B. L. Feringa, F. Macchia and M. Pineschi, *Synthesis*, 2001, 483 and references cited therein.

24 For an alternative approach based on the KR of racemic 4-methyl-2-cyclohexen-1-one, see: R. Naasz, L. A. Arnold, A. J. Minnaard and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2001, **40**, 927.

25 P. Knochel, J. J. Almena Perea and P. Jones, *Tetrahedron*, 1998, **54**, 8275.

26 F. Bertozzi, P. Crotti, F. Del Moro, V. Di Bussolo, F. Macchia and M. Pineschi, *Eur. J. Org. Chem.*, 2003, 1264.

27 M. Lautens, S. Hiebert and J.-L. Renaud, *J. Am. Chem Soc.*, 2001, **123**, 6834.

28 The reaction of **16** with Et_2Zn (0.75 equiv.) in the presence of $Cu(OTf)_2$ (3.0 mol %) and chiral ligand **L2** (7 mol %) afforded, after 60 h at r.t., unreacted **16** with 92% ee at 56% conversion and exclusively *anti*-dihydronaphthol **18** (86% ee).

29 F. Bertozzi, M. Pineschi, F. Macchia, L. A. Arnold, A. J. Minnaard and B. L. Feringa, *Org. Lett.*, 2002, **4**, 2703.

30 R. G. Arrayas, S. Cabrera and J. C. Carretero, *Org. Lett.*, 2003, **5**, 1333.

31 For some recent reports, see: (*a*) B. Olofsson and P. Somfai, *J. Org. Chem.*, 2003, **68**, 2514 and references therein; (*b*) B. J. Paul, E. Hobbs, P. Buccino and T. Hudlicky, *Tetrahedron Lett.*, 2001, **42**, 6433; (*c*) D. C. D. Butler, G. A. Inman and H. Alper, *J. Org. Chem.*, 2000, **65**, 5887.

32 F. Gini, F. Del Moro, F. Macchia and M. Pineschi, *Tetrahedron Lett.*, 2003, **44**, 8559.

33 For a review of enantioselective desymmetrization reactions, see: M. C. Willis, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1765.

34 F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi, A. Arnold and B. L. Feringa, *Org. Lett.*, 2000, **2**, 933.

35 For the first preparation of chiral ligand **L3**, see ref. 20*b*. Chiral ligand **L3** has recently been used in the iridium-catalyzed allylic etherification and amination of achiral allylic esters: (*a*) T. Ohmura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 15 164; (*b*) F. Lopez, T. Ohmura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 3426.

36 For reviews, see: (*a*) T. C. Bruice and P. Y. Bruice, *Acc. Chem. Res.*, 1976, **9**, 378; (*b*) D. R. Boyd and D. M. Jerina, in *Small Ring Heterocycles, Part 3, Chemistry of Heterocyclic Compounds*, ed. A. Hassner, Wiley, New York, 1985, vol. 42, p. 197.

37 See, for example: A. M. Jeffrey, H. J. C. Yeh, D. M. Jerina, R. M. DeMarinis, C. H. Foster, D. E. Piccolo and G. A. Berchtold, *J. Am. Chem. Soc.*, 1974, **96**, 6929.

38 F. Bertozzi, P. Crotti, F. Del Moro, B. L. Feringa, F. Macchia and M. Pineschi, *Chem. Commun.*, 2001, 2606 and references therein.

39 T. Matsuda and M. Sugishita, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 174.

40 M. Ogawa, M. Sugishita, M. Takagi and T. Matsuda, *Tetrahedron*, 1975, **31**, 299.

41 M. J. Miller, M. H. Lyttle and A. Streitwieser, Jr., *J. Org. Chem.*, 1981, **46**, 1977.

42 For a review regarding the structure and reactivity of cyanocuprates, see: N. Krause, *Angew. Chem., Int. Ed.*, 1999, **38**, 79.

43 F. Del Moro, P. Crotti, V. Di Bussolo, F. Macchia and M. Pineschi, *Org. Lett.*, 2003, **5**, 1971.

44 The maximum tolerated deviation from the perfect alignment seems to be *ca.* 30°. In general, the prerequisite for an allylic alkylation to occur is the ability of the system to attain a conformation in which the π orbitals of the double bond and the σ bond connecting the leaving group are aligned. For example, see: C. N. Farthing and P. Kocovsky, *J. Am. Chem. Soc.*, 1998, **120**, 6661 and pertinent references therein.

45 F. Bertozzi, M. Pineschi, F. Macchia, L. A. Arnold, A. J. Minnaard and B. L. Feringa, unpublished results.

46 For a recent review on kinetic resolution, see: J. M. Keith, J. F. Larrow and E. N. Jacobsen, *Adv. Synth. Catal.*, 2001, **1**, 5 and references therein.

47 For reviews, see: (*a*) J. R. Dehli and V. Gotor, *Chem. Soc. Rev.*, 2002, **31**, 365; (*b*) J. Eames, *Angew. Chem., Int. Ed.*, 2000, **39**, 885.

48 (*a*) M. P. Doyle, A. B. Dyatkin, A. V. Kalinin, Q. A. Ruppar, S. F. Martin, M. R. Spaller and S. Liras, *J. Am. Chem. Soc.*, 1995, **117**, 11 021; (*b*) K. Tanaka and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 8078.

49 For the only previous example of a RKR making use of a hard alkyl metal (EtMgBr), see: M. S. Visser and A. H. Hoveyda, *Tetrahedron*, 1995, **51**, 4383.

50 F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2001, **40**, 930 and references therein.

51 M. Pineschi, F. Del Moro, P. Crotti, V. Di Bussolo and F. Macchia, *J. Org. Chem.*, 2004, **69**, 2099.

52 For reviews on enantioselective formation of quaternary carbon stereocenters, see: (*a*) E. J. Corey and A. Guzmán-Pérez, *Angew. Chem., Int. Ed.*, 1998, **37**, 388; (*b*) J. Christoffers and A. Mann, *Angew. Chem., Int. Ed.*, 2001, **40**, 4591.

53 For a related explanation, see: T. L. Underiner, S. D. Paisley, J. Schmitter, L. Leshesky and H. L. Goering, *J. Org. Chem.*, 1989, **54**, 2369.

54 For a recent review, see: E. Nakamura and S. Mori, *Angew. Chem., Int. Ed.*, 2000, **39**, 3750.

55 A. S. E. Karlström and J.-E. Bäckwall, *Chem.-Eur. J.*, 2001, **7**, 1981 and references therein.

56 E. Nakamura, M. Yamanaka and S. Mori, *J. Am. Chem Soc.*, 2000, **122**, 1826.

57 The interconversion between the regioisomeric (σ-allyl)copper(III) complexes of type **H**–**J** could also be reasonably explained by the intervention of suprafacial 1,3-shifts.

58 For an alternative explanation, see: M. Ito, M. Matsuumi, M. G. Murugesh and Y. Kobayashi, *J. Org. Chem.*, 2001, **66**, 5881 and references therein.

59 E. N. Jacobsen and M. H. Wu, in *Comprehensive Asymmetric Catalysis*, eds. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, New York, 1999, ch. 35.

60 For asymmetric epoxide ring openings with sp^2-hybridized organometallic reagents, see: (*a*) M. Mizuno, M. Kanai, M. A. Iida and K. Tomioka, *Tetrahedron*, 1997, **53**, 10 699; (*b*) A. Alexakis, E. Vrancken and P. Mangeney, *Synlett*, 1998, 1165; (*c*) N. Oguni, Y. Miyagi and K. Itoh, *Tetrahedron Lett.*, 1998, **39**, 9023.

61 For the catalytic asymmetric ring opening of activated aziridines, see: P. Müller and P. Nury, *Org. Lett.*, 1999, **1**, 439.

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