

Copper-Catalysed Addition of Organometallic Reagents to Vinyl Diepoxides – A Novel Route to Oxa-Bridged Systems and to Substituted Allylic Alcohols

Fabio Bertozzi,^[a] Paolo Crotti,^[a] Federica Del Moro,^[a] Valeria Di Bussolo,^[a]
Franco Macchia,^[a] and Mauro Pineschi*^[a]

Dedicated to the memory of Professor Serena Catalano

Keywords: Catalysis / Copper / Oxabicycles / Oxygen heterocycles

The copper-catalysed addition of organometallic reagents (Grignard and dialkylzinc) to new vinyl diepoxides was examined. Cyclic vinyl diepoxides undergo clean S_N2' reactions to afford oxa-bridged systems of various sizes after a domino intramolecular *O*-alkylation reaction. Acyclic vinyl diepoxides are alkylated in good yields and with good regioselectivities, and a new catalytic enantioselective desymmetrization reaction to afford an enantioenriched allylic epoxy

alcohol by the use of catalytic amounts of a copper phosphoramidite complex was demonstrated. Remarkable differences in terms of reactivity and selectivity are found when different organocopper reagents, generated in situ, are employed.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2003)

Introduction

The reaction of organometallic reagents under copper catalysis conditions is a very popular method for the construction of carbon–carbon bonds.^[1,2] Among their many applications are substitution reactions on a wide variety of allylic substrates by use of Grignard reagents. Regioselectivity and stereoselectivity are of prime importance in such reactions, and many outstanding investigations to elucidate the factors influencing these outcomes have been carried out.^[3] The S_N2' cleavage of vinyloxiranes, which can be regarded as a subclass of allylic substrates, by copper-mediated organometallic addition is a well-established and useful method by which to obtain allylic alcohols.^[4] Among the various ways of introducing chirality in a copper-catalysed organometallic addition reaction, chiral copper complexes of phosphoramidites, developed by Feringa et al.,^[5,6] have been found to be one of the most effective agents, allowing the asymmetric addition of dialkylzinc reagents to several substrates containing activated double bonds.^[7] In this field, we have recently reported a practical, catalytic and enantioselective synthesis of 4-methyl-2-cyclohexenol,^[8] together with a new, regiodivergent and highly enantioselective kinetic resolution of racemic semirigid vinyl-

oxiranes.^[9] Chiral copper complexes of phosphoramidites were also found to be highly effective catalysts for alkylative desymmetrization, with the aid of dialkylzinc reagents, of methylenecycloalkene oxides of type **1**, containing enantiotopic double bonds in the allylic position with respect to the epoxide ring (Figure 1).^[10]

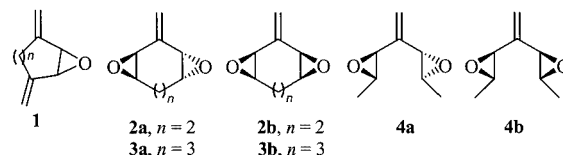


Figure 1. New methyldiene diepoxides **2–4**

This result prompted us to investigate the copper-catalysed addition of organometallic reagents (Grignard and dialkylzinc) to methyldiene diepoxides **2–4**, containing enantiotopic (*cis* compounds **2b**, **3b**, and **4b**) or homotopic (*trans* compounds **2a**, **3a**, and **4a**) oxirane rings in the allylic position with respect to the exocyclic double bond (Figure 1).

Results and Discussion

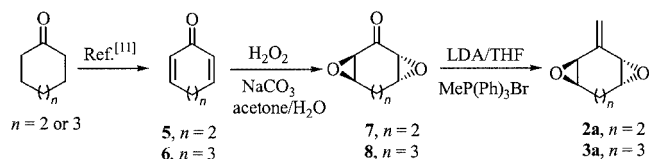
Synthesis of Vinyl Diepoxides **2–4**

The synthesis of cyclic diepoxides **2–3a/b** was accomplished by starting from the readily available cycloheptanone ($n = 2$) and cyclooctanone ($n = 3$) and making use of a known procedure to prepare cycloalkadienones **5** and

^[a] Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy
Fax: (internat.) + 39-050/43321
E-mail: pineschi@farm.unipi.it

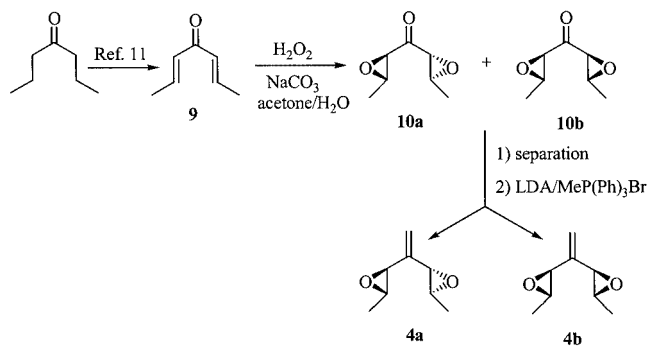
Supporting information for this article is available on the WWW under <http://www.eurjoc.org> or from the author.

6 (Scheme 1).^[11] Alkaline epoxidation of **5** and **6** with H_2O_2 in acetone/ H_2O in the presence of Na_2CO_3 afforded the corresponding *trans*-diepoxy ketones **7** and **8** (67 and 56% isolated yields, respectively). It is known from the literature that *cis/trans* isomerization of related diepoxy ketones may take place in a basic medium,^[12] and also in our case it was only possible to isolate the *trans* isomers **7** and **8**. Wittig olefination of **7** and **8** with methyltriphenylphosphonium bromide in the presence of LDA in THF afforded the new *trans*-vinyl diepoxides **2a** and **3a** (32 and 56% isolated yields, respectively).^[13]



Scheme 1

The synthesis of aliphatic diepoxides **4a** and **4b** was similarly accomplished by starting from readily available 4-heptanone, which was smoothly converted into (*E,E*)-hepta-2,5-dien-4-one (**9**) by a known procedure (Scheme 2).^[11] The alkaline epoxidation ($\text{H}_2\text{O}_2/\text{Na}_2\text{CO}_3$) of dienone **9** in this case afforded an almost equimolar mixture of the diepoxy ketones **10a** and **10b**, which were separated by flash chromatography and subjected to olefination with methyltriphenylphosphonium bromide in the presence of LDA in THF to afford the new vinyl diepoxides **4a** and **4b** (44 and 62% isolated yields, respectively).

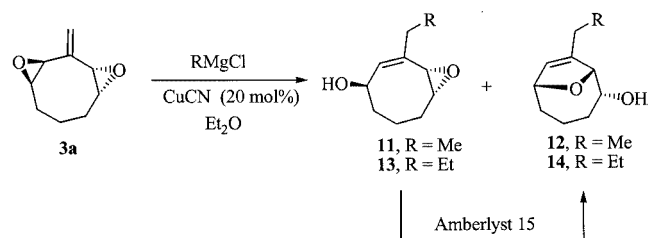


Scheme 2

Copper-Catalysed Additions of Grignard Reagents to Vinyl Diepoxides 2–4

On the basis of the well-documented role of Cu^{I} salts in promoting conjugate additions of Grignard reagents to α,β -unsaturated carbonyl compounds and to allylic halides and acetates,^[3] we speculated that copper(I)-catalysed addition of commercially available Grignard reagents to vinyl diepoxides **2–4** should be feasible. The CuCN -catalysed addition of MeMgCl (3.0 equiv.) to the *trans*-vinyl diepoxide **3a** occurred smoothly in Et_2O (2 h, from -40°C up to 0°C) to afford a 62:38 mixture of the allylic epoxy alcohol **11** and the oxabicyclic compound **12**, as determined by ^1H NMR in C_6D_6 (Scheme 3).^[14] CuCN -catalysed addition of

EtMgCl proceeded in a similar way, affording a 72:28 mixture of $\text{S}_{\text{N}}2'$ -alkylated products **13** and **14** (^1H NMR in C_6D_6).^[14]



Scheme 3

The above observations clearly indicated that the organometallic reagent produced *in situ* reacted with complete $\text{S}_{\text{N}}2'$ regioselectivity to give the allylic epoxy alcohols **11** and **13** as the primary reaction products. Moreover, the oxabicyclic compounds **12** and **14** are simply derived from the corresponding allylic epoxy alcohols **11** and **13**, respectively, by intramolecular nucleophilic opening of the epoxide ring by the oxygenated functionality. The intramolecular *O*-alkylation clearly demonstrates the *trans* relationship of the two interacting groups (OH and the remaining oxirane functionality) and as a consequence the *trans* relationship of the two oxirane functionalities in the starting diepoxide **3a**. The intramolecular *O*-alkylation occurs with complete regioselectivity at the allylic position of the remaining vinyl-oxirane, affording the bicyclo[4.2.1]nonane skeleton. The quantitative formation of the oxa-bridged systems **12** and **14** can be achieved simply by treating the initially obtained crude reaction mixtures with Amberlyst 15 in CH_2Cl_2 for 5 min at room temperature.

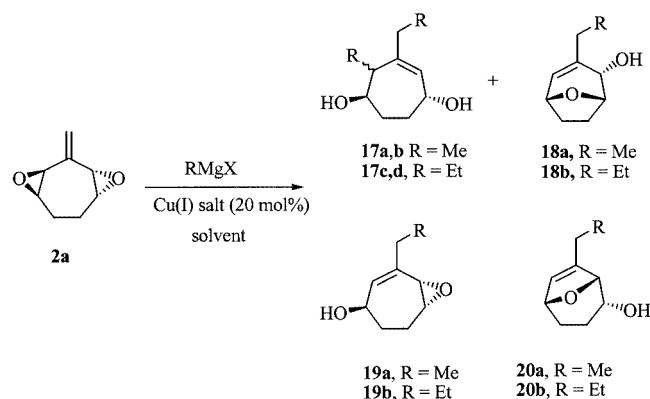
We subsequently applied the same copper-catalysed addition of Grignard reagents to the seven-membered vinyl diepoxide **2a** (Scheme 4). While the reactivity displayed by this substrate seemed to be similar to that of the homologue **3a** (complete conversion in 2 h at 0°C), examination of the composition of the crude reaction mixture clearly indicated that the behaviour of **2a** was very different: in this case reactions performed with a threefold excess of the Grignard reagent (see Table 1) afforded the diols **17a–d**, deriving from a double alkylation process, as the main reaction product. The diol adducts of type **17** are always obtained as an approximately equimolar and inseparable mixture of diastereoisomers and are accompanied by variable amounts of alcohols **18–20a/20b**, depending on the type of RMgX and reaction conditions used (Table 1).

The allylic epoxy alcohols **19a** and **19b**, common intermediates deriving from the first $\text{S}_{\text{N}}2'$ process for the formation of compounds **17a–d**, **18a**, **18b**, **20a**, and **20b**, were in this case obtained only when RMgCl in Et_2O was used (see Entries 2 and 4, Table 1). The use of RMgBr , on the other hand, did not offer any possibility to isolate the intermediate epoxide **19** under any of the reaction conditions examined (Entries 1, 3, 5–9). Use of THF as the solvent drastically reduced the complexity of the reaction mixture, which then turned out to be constituted essentially only of com-

Table 1. Copper(I)-catalysed addition of Grignard reagents to vinyl diepoxide **2a**

Entry ^[a]	RMgX	Solvent	Copper salt	Conversion	Product distribution ^[b]
1	MeMgBr	Et ₂ O	CuCN	> 98%	17a,b (75%), 18a (17%) 19a (< 1%), 20a (7%)
2	MeMgCl	Et ₂ O	CuCN	> 95%	17a,b (49%), 18a (21%) 19a (25%), 20a (5%)
3	MeMgBr (1.2 equiv.)	Et ₂ O	CuCN	76% ^[c]	17a,b (59%), 18a (35%) 19a (4%), 20a (6%)
4	MeMgCl (1.2 equiv.)	Et ₂ O	CuCN	82%	17a,b (20%), 18a (20%) 19a (50%), 20a (10%)
5	MeMgCl	THF	CuCN	> 98%	17a,b (86%), 18a (10%) 19a (1%), 20a (4%)
6	MeMgBr	THF	CuCN	> 98%	17a,b (81%), 18a (14%) 19a (< 1%), 20a (4%)
7	MeMgCl	THF	CuBr·Me ₂ S	> 95%	17a,b (80%), 18a (16%) 19a (< 1%), 20a (3%)
8	EtMgBr	THF	CuCN	> 98% ^[d]	17c,d (88%), 18b (8%) 19b (< 1%), 20b (3%)
9	EtMgBr	THF	CuBr·Me ₂ S	> 95%	17c,d (76%), 18b (17%) 19b (< 1%), 20b (6%)

[a] All reactions were performed in accordance with the typical procedure [Cu^I salt (20 mol %), RMgX (3.0 equiv.)] see the Exp. Sect. [b] Determined by ¹H NMR and GC analysis of the crude reaction mixtures. [c] A relatively complex reaction mixture containing some unidentified by-products was obtained. [d] 3-Propyl-2,4-cycloheptadien-1-ol (a deoxygenated product) was also obtained in this reaction (see the Supporting Information for further details).



Scheme 4

pounds of type **17** (main product) and **18**, together with some minor amounts of oxa-bridged systems of type **20** (Entries 5–9). The use of a catalytic amount of CuBr·Me₂S in place of CuCN gave similar results (Entries 7 and 9). We were intrigued by the presence of the diol adducts of type **17** as the main reaction products in all reactions examined (except for Entry 4). Theoretically, the diastereoisomeric diols **17a** and **17b**, deriving from a double alkylation process in which the alkyl moiety of the Grignard reagent is transferred twice, could form in two ways: (i) by alkylative *anti*-stereoselective S_N2 and S_N2' ring-openings of the intermediate vinyl oxirane **19**, or (ii) by an alkylative, nonstereoselective ring-opening of the oxa bridged compound **20**, deriving in turn from **19** through an intramolecular *O*-alkylation in the allylic position (Figure 2).^[15] In order to obtain evidence of the process associated with the formation of the diols **17a** and **17b**, an almost equimolar mixture of **19a** and **20a** was subjected to the standard procedure (MeMgBr/THF/CuCN 20 mol %) and after 2 h at 0 °C the diols **17a**

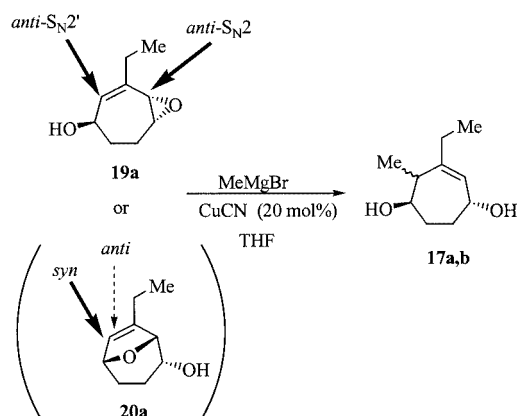


Figure 2. Possible reaction pathways for the double alkylation process

and **17b** had been formed at the exclusive expense of vinyl-oxirane **19a**, clearly indicating that alkylative ring-opening of **19a** was responsible for the formation of **17a** and **17b**. The predominant active catalytic species in Et₂O is probably RCu(CN)MgX, whereas in THF “higher order” magnesium cyanocuprates such as R₂Cu(CN)(MgX)₂ could also be involved.^[16] It is known that dialkylcopper reagents exhibit different reactivity and an increased preference for S_N2 substitution with respect to “lower order” cyanocuprates.^[1,17]

The different product distributions observed in the alkylation reactions between the seven- and eight-membered vinyloxiranes **2a** and **2b** could reasonably be explained by comparison of the reactive conformations in the two systems. In general, the prerequisite for allylic substitution to occur is the ability of the system to adopt a conformation in which the π-orbitals of the double bond and the σ-bond

connecting the leaving group to the allylic carbon atom are aligned.^[18] In the case of a vinyl oxirane (such as **11** and **19a**), the coplanarity necessary to attain the overlap between the nucleophilic d-orbitals of the copper and the π^* -orbital of the double bond and of the σ^* -orbital of the oxirane moiety (as shown in **A**, Figure 3),^[4] is seriously hindered in the eight-membered vinyl diepoxide **11** by the steric repulsion between the hydrogen atoms present in positions 2 and 5 (conformation **B**, Figure 3). The seven-membered analogue, on the other hand, does not suffer from any negative steric repulsion (see, for example, conformation **C**, Figure 3) thus allowing the copper-catalysed addition of Grignard reagents to the intermediate vinyl epoxide of type **19** to occur, as found experimentally.

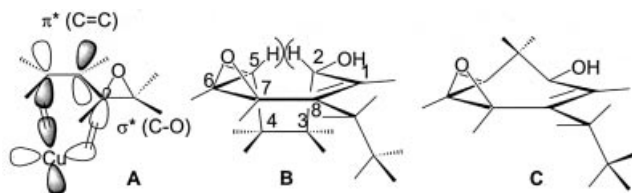


Figure 3. Orbital overlaps and reactive conformation for the S_N2' -cuprate alkylation of vinyl oxiranes **11** (see **B**) and **19a** (see **C**)

The regioselectivity of the intramolecular *O*-alkylation of **19a** and **19b** was somewhat surprising, considering that it delivered regioisomeric bicyclo[3.2.1] compounds of type **18** in which the attack had occurred at the less activated homo-allylic position of the oxirane moiety (path b, Figure 4). The oxa-bridged system of type **20**, deriving from intramolecular oxygen alkylation of the intermediate epoxy alcohol **19** in the more activated allylic position was observed only in very small amounts (path a, Figure 4). Recently, the regioselective intramolecular alkylation observed in cycloheptadienyl epoxyvinyl sulfones was explained in terms of a bidentate coordination of the acid catalyst with both the epoxide and the sulfonyl oxygen atoms.^[19] Our results indicate that there is an intrinsic preference, albeit modest, for a bicyclic 6/5 ring system over the other (path b vs. path a, Figure 4), without the intervention of any chelated activating functionality.

Similar control over reactivity, depending on the reagents and solvent used for the reaction, was also observed in the aliphatic series of vinyl diepoxides of type **4**: when **4a** and **4b** were treated with EtMgCl (3.0 equiv.) in Et₂O in the presence of catalytic amounts of CuCN (20 mol %), the epoxy allylic alcohols (*E*)-**21a** and **23a** were obtained as the

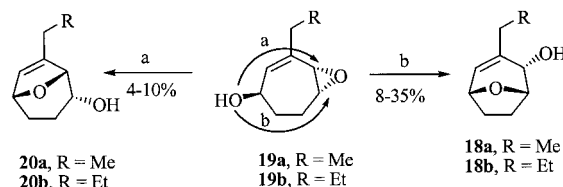
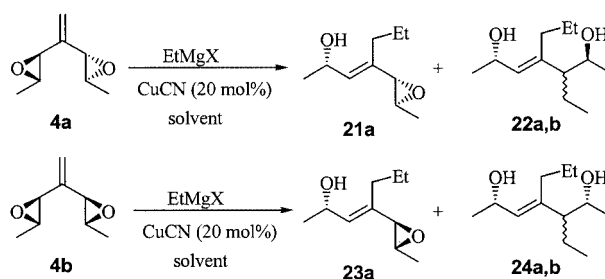


Figure 4. Possible reaction pathways for the intramolecular *O*-alkylation of compounds **19a** and **19b**

main reaction products (Scheme 5, Entries 1 and 2, Table 2). The use of EtMgBr in THF, on the other hand, in this case also gave a mixture of the diastereoisomeric diols **22a** and **22b** (from **4a**) and **24a** and **24b** (from **4b**) deriving from a double alkylation process in which the allylic epoxy alcohols of types **21** and **23** are the corresponding most likely intermediates (Entries 3 and 4).



Scheme 5

With *meso* substrate **4b**, and in sharp contrast with substrate **4a**, the commonly observed *anti*- S_N2 and *anti*- S_N2' ring-opening of the intermediate epoxy allylic alcohol **23a** give the same product. The addition on **23a** can reasonably occur both in an *anti*- and in a *syn*- S_N2' fashion to give a ca. 80:20 mixture of the two diastereoisomers **24a** and **24b**, as observed experimentally. The oxygen functionality probably directs the *syn*- S_N2' addition mode.^[20]

Copper Phosphoramidite Catalysed Addition of R₂Zn to Vinyl Diepoxides **2a**, **3a**, and **4b**

The addition of Et₂Zn (1.5 equiv.) to racemic vinyl diepoxide **3a**, catalysed by a copper complex obtained by mixing Cu(OTf)₂ (1.5 mol %) with phosphoramidite (*S,S,S*)-**15** (3.0 mol %) in toluene (3 h, -78 °C up to -10 °C, 45% conversion), afforded a ca. 8:2 mixture (¹H NMR in C₆D₆)^[14] of S_N2' adducts **13** and **14** with complete regioselectivity (for formulas see Schemes 3 and 6). Chiral GC

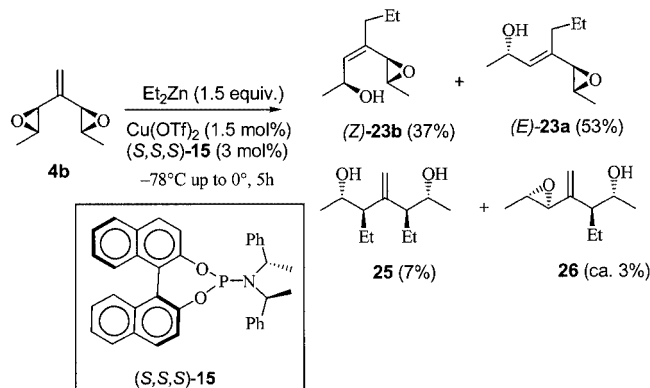
Table 2. Copper(I)-catalysed addition of EtMgX to vinyl diepoxides **4a** and **4b**

Entry ^[a]	Substrate	EtMgX	Solvent	Conversion	Product distribution ^[b]
1	4a	EtMgCl	Et ₂ O	92%	21a (58%), 22a,b (42%)
2	4b	EtMgCl	Et ₂ O	> 95%	23a (57%), 24a,b (43%)
3	4a	EtMgBr	THF	> 95%	21a (< 3%), 22a,b (> 97%)
4	4b	EtMgBr	THF	> 95%	23a (ca. 5%), 24a,b (ca. 95%)

^[a] All reactions were performed in accordance with the typical procedure [Cu^I salt (20 mol %), RMgX (3.0 equiv.)] see the Exp. Sect.

^[b] Determined by ¹H NMR and GC analysis of the crude reaction mixtures.

analysis showed that the vinyl diepoxide **3a** was essentially racemic, indicating that a kinetic resolution of **3a** was not effective with this chiral catalyst.



Scheme 6

The copper phosphoramidite-catalysed addition of Me_2Zn to the seven-membered vinyl diepoxide **2a** afforded a complex reaction mixture in which the double alkylated diols **17a** and **17b** were not present (GC) even in trace amounts (Scheme 4).

As the aliphatic series included the symmetrical substrate like **4b**, possessing enantiotopic oxirane moieties, a study was made of a catalytic alkylative desymmetrization reaction, previously explored with methylenecycloalkene oxides of type **1** (Figure 1).^[10] At full conversion (5 h, from $-78\text{ }^\circ\text{C}$ up to $0\text{ }^\circ\text{C}$) the desymmetrization reaction of *meso*-vinyl diepoxide **4b** with Et_2Zn in the presence of a catalytic chiral copper complex of phosphoramidite (*S,S,S*)-**15**, gave a mixture of different ring-opening products: the allylic alcohols **23b** and **23a** ($\text{S}_\text{N}2'$ addition pathway, 90%), diol **25** (double *anti*- $\text{S}_\text{N}2$ addition, 7%) and epoxy alcohol **26** (single *anti*- $\text{S}_\text{N}2$ addition, ca. 3%) (Scheme 6). The homoallylic diol **25** and the epoxyallylic alcohol **26** were easily separated by flash chromatography from the crude reaction mixture containing the allylic alcohols **23a** and **23b**. Pure samples of stereoisomers **23a** and **23b** could only be obtained by subsequent semipreparative TLC. These compounds showed (GC analysis on chiral stationary phase) moderate enantiomeric excesses (**23b**: 48% *ee*; **23a**: 52% *ee*), thus indicating that enantioselective desymmetrization of *meso*-vinyl diepoxide **4a** had occurred to some extent. In this case, consistently with the results of the ring-openings observed previously, the epoxy allylic alcohols **23a** and **23b** do not undergo a subsequent conjugate alkylation to give the corresponding diastereoisomeric diols **24a** and **24b** (Scheme 6). However, it was possible to isolate minor quantities of the diol **25** and of the alcohol **26**, originating from direct alkylation in the allylic position, in which the exomethylidene unit had been maintained.

Another interesting feature of this addition reaction is the formation of a 40:60 mixture of both (*Z*)-**23b** and (*E*)-**23a** isomeric epoxy allylic alcohols ($\text{S}_\text{N}2'$ addition products) when the reaction is performed with Et_2Zn in the presence of the chiral copper phosphoramidite catalyst. In contrast, the use of EtMgX in the presence of a catalytic amount of

CuCN substantially delivered only the isomeric (*E*)-epoxy allylic alcohol **23a** (Scheme 5 and Table 2). It is likely that the different reaction conditions may also give rise to a change in the active catalytic species in this case. In copper-catalysed organometallic addition to allylic substrates, the (*E*) isomer is usually formed preferentially.^[21] In the copper phosphoramidite catalysed addition of Et_2Zn , an almost equimolar (*E*)/(*Z*) mixture of the epoxy allylic alcohols **23a** and **23b** (with essentially the same *ee* values) was formed and this could be an indication that the ratio of *s-trans*/*s-cis* conformers of vinyl diepoxide **4b** does not affect the enantiomeric excesses of epoxy allylic alcohols **23a** and **23b**.^[22]

Conclusion

In summary, we have examined the copper-catalysed addition of Grignard and dialkylzinc reagents to some new methylenediepoxydes. Cyclic *trans*-vinyl diepoxydes **2a** and **3a** undergo $\text{S}_\text{N}2'$ addition reactions with organocopper reagents produced in situ with a high degree of regioselectivity, thus allowing a new alkylative approach to oxabridged systems of different sizes. Acyclic vinyl epoxides **4a** and **4b** are alkylated with good yields and regioselectivities. A new catalytic enantioselective desymmetrization reaction of a *meso*-symmetrical system to give an enantioenriched epoxy allylic alcohol has been accomplished by the use of Et_2Zn and catalytic amounts of a chiral copper complex of phosphoramidite **15**. The nature of the organometallic reagent plays an important role in determining the outcome of the reaction. While the copper phosphoramidite addition of dialkylzinc reagents was not able to alkylate the intermediate epoxyallylic alcohols of type **19**, **21**, and **23**, the addition of Grignard reagents resulted in a new double alkylation process. The remarkable solvent effect on the product distribution of the CuCN -catalysed cross-coupling reactions of methylenediepoxydes **2a** and **4a** and **4b** with Grignard reagents can be reasonably explained by assuming the involvement of different active catalytic species. Furthermore, the different (*E*)/(*Z*) product ratios exhibited by **4b** when different organocopper reagents are generated in situ seems difficult to explain in terms of simply steric interactions in reactant-like transition state conformers.

Experimental Section

General Remarks: All reactions were carried out in flame-dried glassware with magnetic stirring under argon. Toluene, diethyl ether, and THF were distilled from sodium/benzophenone ketyl and stored under argon. Diisopropylamine was freshly distilled from CaH_2 . Analytical TLC was performed on Alugram SIL G/UV 254 silica gel sheets (Macherey–Nagel) with detection by 0.5% phosphomolybdic acid solution in 95% EtOH. Silica gel 60 (Macherey–Nagel, 230–400 mesh) was used for flash chromatography. Solvents for extraction and chromatography were of HPLC grade. ^1H NMR spectra were recorded with a Bruker AC 200 spectrometer on CDCl_3 or C_6D_6 solutions. Chemical shifts are reported

in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (CDCl_3 ; $\delta = 7.26$ ppm). ^{13}C NMR spectra were recorded with a Bruker AC 200 (50 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (CDCl_3 ; $\delta = 77.7$ ppm). Infrared spectra (IR) were obtained with a Mattson 3000 FTIR spectrometer. Enantioselectivities were determined with a Perkin–Elmer 8420 apparatus (FI detector) with a Chromopak fused silica $25\text{ m} \times 0.25\text{ mm}$ column, coated with CP-Cyclodextrin-B-236-M-19. In all cases the injector and detector temperatures were 250°C and a ca. 0.9 mL/min helium flow was employed. Conversions and regioselectivities were determined with an HP-5890 instrument fitted with an HP-5 capillary column ($30\text{ m} \times 0.25\text{ mm}$). The following compounds were commercially available and were used without purification: Et_2Zn (1.1 M solution in toluene, Aldrich), EtMgCl (2.0 M solution in THF, Aldrich), EtMgBr (3.0 M solution in Et_2O , Aldrich), MeMgCl (3.0 M in THF), MeMgBr (3.0 M in Et_2O), and $\text{Cu}(\text{OTf})_2$ ($> 98\%$, Aldrich), CuCN and $\text{CuBr} \cdot \text{Me}_2\text{S}$ (Fluka), butyllithium (1.6 M solution in hexanes, Aldrich) and methyltriphenylphosphonium bromide (98%) (Aldrich).

Typical Procedure for the Copper-Catalyzed Addition of Grignard Reagents to Vinyl Diepoxides 2a, 3a, 4a and 4b (Table 1 and Table 2): To a stirred suspension of CuCN (9.0 mg, 0.1 mmol) in anhydrous Et_2O or THF (1.0 mL), at -40°C , was added dropwise a solution of RMgX (1.5 mmol), and the heterogeneous mixture was stirred at the same temperature for 30 min. A solution of the vinyl diepoxide (0.5 mmol) in Et_2O or THF (1.0 mL) was slowly added, and the resulting mixture was allowed to warm to 0°C . The reaction was monitored by TLC and quenched at 0°C with saturated aqueous NH_4Cl . Extraction with Et_2O and concentration of the dried (MgSO_4) organic phase gave a crude reaction product which was subjected to chromatography (SiO_2). See Supporting Information for further details.

Typical Procedure for the Copper-Catalyzed Addition of Et_2Zn to Vinyl Diepoxides 3a, 4b: In a 25-mL Schlenk flask, under argon, a solution of $\text{Cu}(\text{OTf})_2$ (5.5 mg, 0.015 mmol) and chiral ligand (*S,S,S*)-**15** (16 mg, 0.03 mmol) in anhydrous toluene (2 mL) was stirred at room temp. 40 min. The colorless solution was cooled to -78°C , treated with a solution of vinyloxirane (1.0 mmol) in anhydrous toluene (0.5 mL) and then with a 1.1 M solution of Et_2Zn in toluene (1.35 mL, 1.5 mmol). The reaction was monitored by TLC and quenched at 0°C with saturated aqueous NH_4Cl . Extraction with Et_2O and concentration of the dried (MgSO_4) organic phase gave a crude reaction product which was subjected to chromatography (SiO_2).

Acknowledgments

We gratefully acknowledge funding by the M. I. U. R. (Rome), by the University of Pisa and by Merck (2002 ADP Chemistry Award to P. C.).

[1] *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, 2002.

[2] B. H. Lipshutz, in: *Organometallics in Synthesis* (Ed.: M. Schlosser), John Wiley & Sons Ltd., Chichester, 1994, pp. 283–382.

[3] E. S. M. Persson, M. van Klaveren, D. M. Grove, J.-E.

Bäckvall, G. van Koten, *Chem. Eur. J.* **1995**, 351–359 and references therein.

[4] For a review, see: J. A. Marshall, *Chem. Rev.* **1989**, 89, 1503–1511.

[5] A. H. M. de Vries, A. Meetsma, B. L. Feringa, *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2374–2376; *Angew. Chem.* **1996**, 108, 2526–2528.

[6] B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. de Vries, *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2620–2623; *Angew. Chem.* **1997**, 109, 2733–2736.

[7] For an overview of phosphoramidites in catalytic asymmetric conjugate additions, see: B. L. Feringa, *Acc. Chem. Res.* **2000**, 33, 346–353. For the use of phosphoramidites in asymmetric conjugate addition reactions, see also: A. Alexakis, C. Benhaim, S. Rosset, M. Human, *J. Am. Chem. Soc.* **2002**, 124, 5262–5263 and pertinent references therein.

[8] F. Bertozzi, P. Crotti, B. L. Feringa, F. Macchia, M. Pineschi, *Synthesis* **2001**, 483–486.

[9] F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi, B. L. Feringa, *Angew. Chem. Int. Ed.* **2001**, 40, 930–932.

[10] F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi, A. Arnold, B. L. Feringa, *Org. Lett.* **2000**, 2, 933–936.

[11] H. O. Krabbenhoft, *J. Org. Chem.* **1979**, 44, 4285–4294.

[12] H. Prinzbach, W. Seppelt, H. Frintz, *Angew. Chem. Int. Ed. Engl.* **1976**, 16, 198–199; *Angew. Chem.* **1977**, 89, 174–175.

[13] The relative *trans* configuration of the oxirane functionalities present in **2a** and **3a** was later confirmed on the basis of their chemical behaviour. Therefore, in the cyclic case under examination (Scheme 1), it was not possible to obtain significant amounts of the corresponding *cis*-diepoxides **2b** and **3b**, which could be more challenging to study in a possible desymmetrization reaction with organometallic reagents in the presence of a chiral catalyst.

[14] The **11/12** and **13/14** ratio (determined by ^1H NMR) depended on the solvent in which the spectra were recorded: C_6D_6 gave the highest proportions of compound **11**, while the same compound was almost negligible when the spectra were recorded in CDCl_3 .

[15] It is known that oxabicyclic compounds can react with organometallic reagents in both *syn* and *anti* fashion. For an extensive review concerning the ring-opening of oxabicyclic compounds, see: P. Chiu, M. Lautens, *Top. Curr. Chem.* **1997**, 190, 1–85.

[16] We are not concerned about the exact constitution of the species involved in this reaction, but with the reactive species as a reagent system. For a review regarding the structure and reactivity of cyanocuprates, see: N. Krause, *Angew. Chem. Int. Ed.* **1999**, 38, 79–81; *Angew. Chem.* **1998**, 110, 83. For a recent discussion about the decisive influence of the composition of the reagents and the solvent used in a metal-catalysed addition of Grignard reagents to allylic acetates, see: M. Ito, M. Matsunami, M. G. Murugesu, Y. Kobayashi, *J. Org. Chem.* **2001**, 66, 5881–5889 and references therein.

[17] For example, see: J.-E. Bäckvall, M. Sellén, B. Grant, *J. Am. Chem. Soc.* **1990**, 112, 6615–6621.

[18] For example, see: C. N. Farthing, P. Kocovsky, *J. Am. Chem. Soc.* **1998**, 120, 6661–6672 and pertinent references therein.

[19] W. Jiang, D. A. Lantrip, P. L. Fuchs, *Org. Lett.* **2000**, 2, 2181–2184.

[20] For a recent example of a *O*-directed conjugate addition of Grignard reagents, see: K. A. Swiss, D. C. Liotta, *J. Am. Chem. Soc.* **1990**, 112, 9393–9394. For a review on substrate-directable chemical reactions, see: A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, 93, 1307–1370.

[21] For a recent example of an (*E*)-selective [(*E*)/(*Z*) ratios > 4] copper-catalysed ring-opening of vinyloxiranes with organozinc reagents, see: B. H. Lipshutz, K. Woo, T. Gross, D. J. Buzard, R. Tirado, *Synlett* **1997**, 477–478.

[22] Needless to say, the ground state and the reactive conformer are not necessarily the same. Although it is not possible to use direct methods firmly to establish the formation of a π -allyl

complex, it seems reasonable that its formation and subsequent isomerization may give a different product distribution when different organometallic reagents are employed. For an interpretation of the different behaviour of a copper-catalysed alkylation of dialkylzinc reagents with vinyloxiranes through the involvement of regioisomeric σ -allylic Cu^{III} species, see ref.^[9] and references therein. In general, a metal-bound allyl

ligand can undergo geometric interconversion by changing its hapticity. However, the well-known π - σ - π isomerization, which could explain the double bond isomerization, is often found in Pd-catalysed allylic alkylations, but has never been invoked in a Cu-catalysed allylic alkylation.

Received November 12, 2002
[O02628]