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Catalytic Regiodivergent Kinetic Resolution of Allylic Epoxides: A New Entry to Allylic and Homoallylic Alcohols with High Optical Purity

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A novel regiodivergent kinetic resolution of a series of allylic epoxides with alkylzinc reagents is described. Results demonstrate the potential of chiral copper-phosphoramidite catalysts for enantiomer differentiation of allylic epoxides, allowing a chiral catalyst-stereoregulated synthesis of cyclic allylic and homoallylic alcohols with high optical purities.

Introduction

The development of efficient asymmetric catalysts is a rational, useful way to improve the preparation of chiral compounds with high optical purities. Kinetic resolution of a racemic mixture is a well-established method for the preparation of optically active compounds.[1] However, the major drawback with this approach is that a maximum of only half of the racemic starting material is converted into nonracemic products. Parallel kinetic resolution (PKR) is an interesting strategy recently introduced, in which both enantiomers of a racemate can be converted into different products.[2] This conceptual variation often requires the use of two different stoichiometric chiral reagents in parallel.[3] Conceptually similar to PKR is the so-called regiodivergent kinetic resolution (RKR), which is a process in which a single chiral catalyst or reagent reacts with a racemic substrate to form regioisomers possessing opposite configurations on the newly formed stereogenic centers. To date, there are only a few examples that demonstrate this concept. For example, RKR reactions under nonstoichiometric conditions have previously been described in the Bayer−Villiger oxidation of racemic ketones by means of enzymatic methods[4a−c] or chiral catalysts,[4d,e] and more recently, an interesting allylic substitution of racemic 5-vinyloxazolidininones with phthalimide and a chiral palladium catalyst has been reported.[5] However, RKR-concerning catalytic processes that form carbon−carbon bonds are very rare. The only two examples are the intramolecular cyclopropanation of racemic allylic diazoacetates catalyzed by chiral rhodium complexes[6] and the zirconocene-catalyzed addition of EtMgBr to racemic dihydrofurans.[7] In the context of RKR processes forming carbon−carbon bonds, we recently discovered a highly stereocontrolled transformation of a racemic mixture by an organometallic reagent and a chiral catalyst to give separable regioisomeric products.[8] Our method was based on the addition of dialkylzinc reagents (R = Me or Et) to racemic cyclic allylic epoxides in the presence of copper complexes of nonracemic phosphoramidite (*R*,*R*,*R*)-**1** (Scheme 1).[9]

This chiral catalyst was able to discriminate between the enantiomers of semirigid allylic epoxides to give separable regioisomers. The reaction showed a striking complementary enantiomer-dependent regioselectivity. The allylic alcohols (derived from an S_N2' addition on the faster-reacting enantiomer of the cyclic allylic epoxide) and above all the homoallylic alcohols (derived from an S_N2 addition on the slower-reacting enantiomer) were obtained with good to excellent ee's. We now wish to give a full account of this work.

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(7) Visser, M. S.; Hoveyda, A. H. *Tetrahedron* **1995**, *51*, 4383.

(8) Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 930.

(9) For the kinetic resolution of allylic epoxides with dialkylzinc reagents and copper-phosphoramidite catalyst, see: (a) Badalassi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Arnold, A.; Feringa, B. L. *Tetrahedron Lett.* **1998**, *39*, 7795. (b) Bertozzi, F.; Crotti, P.; Feringa, B. L.; Macchia, F.; Pineschi, M. *Synthesis* **2001**, 483. For the desymmetrization reaction of symmetrical allylic epoxides, see: (c) Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Arnold, A.; Feringa, B. L. *Org. Lett.* **2000**, *2*, 933. (d) Bertozzi, F.; Crotti, P.; Del Moro, F.; Feringa, B. L.; Macchia, F.; Pineschi, M. *Chem. Commun.* **2001**, 2606.

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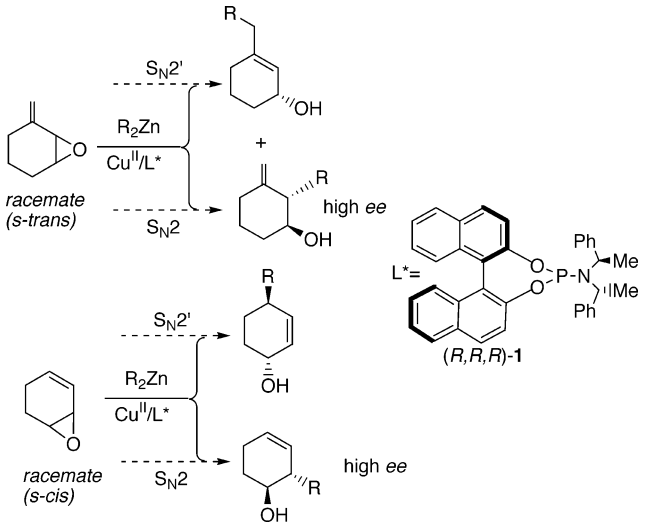
SCHEME 1. Preliminary Results of the Catalytic RKR of Cyclic Allylic Epoxides

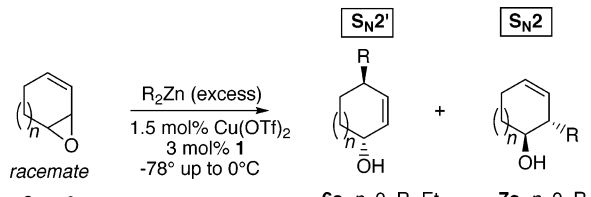


Results and Discussion

To extend the scope and the synthetic utility of our new RKR protocol, we examined several cyclic and aliphatic vinyl oxiranes having different sizes and bearing different substituents, to evaluate the extent of the chiral recognition exhibited by the chiral catalyst with these substrates. As an example of semirigid cyclic allylic epoxides having blocked *s-cis* conformations, allylic epoxides **2**−**5** were examined, and the results are summarized in Table 1. The reactions were carried out under our protocol in order to obtain a *complete conversion* of the starting material (reaction monitored by GC and/or TLC) by the use of an excess of R_2Zn in the presence of a catalytic amount of $Cu(OTf)_2$ (1.5 mol %) and chiral ligand **1** (3.0 mol %) (see the typical procedure in the Experimental Section). It should be noted that the same reactions carried out in the absence of the chiral ligand are sluggish at low temperatures, indicating that these reactions are typical examples of a ligand-accelerated reaction, amenable to adjustment depending on the nature of the chiral ligand. Phosphoramidite **1**, derived from (*R*)-BINOL and (*R*)-bisphenylethylamine,[10] was the chosen ligand because it proved to be slightly superior to its diastereoisomer (*S*,*R*,*R*)-**1**[11] with respect to the extent of regiodivergency and the enantioselectivity of the alcohol reaction products. For these reasons, ligand (*R*,*R*,*R*)-**1** was consistently used throughout this work. The data obtained by the use of ligand **1** confirmed the possibility of obtaining an efficient, highly enantioselective RKR process with all the cyclic substrates **2**−**5**, by the use of commercially available dialkylzinc reagents (entries 1−10, Table 1). The enantioselective introduction of an alkyl chain onto 1,3-cyclopentadiene monoepoxide **2** is of particular importance for the synthesis of chiral nonracemic cyclopentanoids.[12] For this purpose, the enantioselective epoxidation of cyclopentadiene followed by alkylation could be used, as well. However, the moderate enantioselectivity exhibited by the epoxidation step represents a drawback for its effective synthetic utilization.[13]

To the best of our knowledge, the enantioselective reaction of **2** with hard nucleophiles has not been described except for our seminal article which demonstrated the possibility of obtaining the S_N2' adduct of type **6** with good regio- and enantioselectivities when the reaction was performed in accordance with a *kinetic resolution protocol*.[9a] We now report that the reaction of (±)-**2** with *an excess* of dialkylzinc reagents in the presence of the copper-phosphoramidite catalyst afforded a separable mixture of the corresponding regioisomeric alcohols **6a**,**b**

TABLE 1. RKR of Cyclic Allylic Epoxides 2−5 (*s-cis* Conformation) with Dialkylzincs[a]



2, *n*=0
3, *n*=1
4, *n*=2
5, *n*=3

6a, *n*=0, R=Et
6b, *n*=0, R=Bu
8a, *n*=1, R=Me
8b, *n*=1, R=Et
10a, *n*=2, R=Me
10b, *n*=2, R=Et
10c, *n*=2, R=Bu
12a, *n*=3, R=Me
12b, *n*=3, R=Et
12c, *n*=3, R=Bu

7a, *n*=0, R=Et
7b, *n*=0, R=Bu
9a, *n*=1, R=Me
9b, *n*=1, R=Et
11a, *n*=2, R=Me
11b, *n*=2, R=Et
11c, *n*=2, R=Bu
13a, *n*=3, R=Me
13b, *n*=3, R=Et
13c, *n*=3, R=Bu

					ee[c] (%)	
entry	substrate	R	*T* (h)	S_N2'/S_N2[b]	S_N2'	S_N2
1	**2**	Et	5	70/30	40	90
2	**2**	Bu	5	67/33	45	91
3	**3**	Me	3	60/40	64	>97
4	**3**	Et	3	76/24	34	>98
5	**4**	Me	3	50/50	>90	>95
6	**4**	Et	2	53/47	>90	>90
7	**4**	Bu	2	50/50	>90	>95
8	**5**	Me[d]	18	62/38	76	>98
9	**5**	Et[d]	18	66/34	68	>95
10	**5**	Bu[d,e]	18	86/14	56	>95

[a] All reactions were performed in accordance with the typical procedure reported in the Experimental Section (1.5 equiv of R_2Zn, 0.015 equiv of $Cu(OTf)_2$, and 0.03 equiv of ligand **1**). Conversion of >98%, unless stated otherwise. For isolated yields, see the Supporting Information. [b] Determined by ^1H NMR examination of the crude mixture. [c] Determined by GC on chiral stationary phases (see the Supporting Information for further details). [d] 3.0 equiv of Bu_2Zn and Et_2Zn and 4.0 equiv of Me_2Zn were used. [e] Conversion of 83%.

(10) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2620. Chiral ligand **1** was recently used in the iridium-catalyzed allylic etherification and amination of achiral allylic esters: (a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164. (b) Lopez, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426.

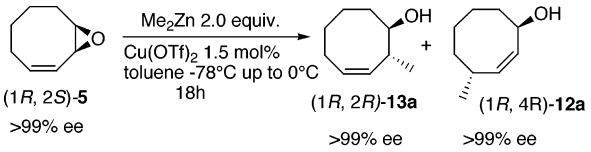
(11) (*S*,*R*,*R*)-Diastereoisomeric phosphoramidite, derived from (*S*)-BINOL and (*R*)-bisphenylethylamine developed by Feringa et al., is to date one of the most effective chiral ligands for the enantioselective addition of dialkylzinc to cyclic enones and for other metal-catalyzed asymmetric processes. For some recent examples, see: (a) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700 and references therein. (b) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262. (c) Jensen, J. F.; Svendsen, B. Y.; la Cour, T. V.; Pedersen, H. L.; Johannsen, M. *J. Am. Chem. Soc.* **2002**, *124*, 4558. For a review, see: (d) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.

(12) For a discussion about the installation of an alkyl chain onto cyclopentanoid systems, see: Ito, M.; Matsuumi, M.; Murugesh, M.; Kobayashi, Y. *J. Org. Chem.* **2001**, *66*, 5881.

(13) Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *35*, 669.

and **7a**,**b**, the latter obtained with a high level of enantioselectivity (>90% ee, entries 1 and 2). Similarly, the addition of Me_2Zn (1.5 equiv) to (±)-**3** catalyzed by $Cu(OTf)_2$/(*R*,*R*,*R*)-**1** afforded a 60/40 mixture of **8a** (S_N2' adduct, 64% ee) and **9a** (S_N2 adduct, >97% ee) (entry 3).[8] The catalyzed addition of Et_2Zn (1.5 equiv) to the same racemate afforded a 76/24 mixture of regioisomers **8a** (34% ee) and **9a** (>98% ee) (entry 4). The RKR process was particularly efficient when 1,3-cycloheptadiene monoepoxide **4** was employed (entries 5−7). With this substrate, the regiodivergency was practically ideal and regioisomeric alcohols **10a**−**c** and **11a**−**c**, having opposite configurations 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 considerable. Moreover, with allylic epoxide **4**, the regiodivergent chiral recognition can be maintained also using different solvents: the addition of Me_2Zn to compound **4** in the presence of a catalytic amount of $Cu(OTf)_2$ (1.5 mol %) and chiral ligand **1** (3.0 mol %) substantially afforded the same results in terms of regio- and enantioselectivies when the reaction was carried out in THF, Et_2O, CH_2Cl_2, or AcOEt.[14] The same reaction carried out in CH_3CN turned out to be sluggish and not regiodivergent, because it afforded the corresponding *syn* S_N2 addition product as the major addition product. The *syn* addition appears to occur without the intervention of the chiral copper complex, via the coordination of zinc to the oxygen of the epoxide and intramolecular transfer of the Me group.[15] The regiodivergency obtained by the application of our protocol to 1,3-cyclooctadiene monoepoxide **5** is not only remarkable (see entries 8−10) but also synthetically useful.[16] In fact, considering that the enantiomerically enriched *trans*-2-alkyl-3-cycloocten-1-ols obtained in this reaction can easily be reduced by catalytic hydrogenation to the corresponding saturated compounds, our protocol offers a new easy route to enantiomerically pure *trans*-2-alkyl-substituted cyclooctanols. These compounds cannot be simply prepared by direct asymmetric alkylation, because the asymmetric ring opening of relatively unreactive cyclooctene oxide is still today a difficult challenge, and our two-step approach is a viable alternative to obtain enantiomerically pure cyclooctanols.[17] It should be mentioned that all the reactions reported in Table 1 can be performed also at 0 °C with only marginal effects on yields and regio- and enantioselectivities, and this represents a significant practical advantage.[18] On the basis

SCHEME 2. Complementary Enantiomer-Dependent Regioselectivity



chiral ligand (*S*,*S*,*S*)-**1**	81	:	19
chiral ligand (*R*,*R*,*R*)-**1**	<2	:	>98

of all the data collected, it seems clear that a chiral recognition occurs in situ between the chiral catalyst and each enantiomer of the allylic epoxide used as the substrate.

We had previously observed that the use of a racemic chiral phosphoramidite catalyst suppresses the regiodivergency and affords only the corresponding S_N2' addition products, that is, the racemic allylic alcohols, from both enantiomers of the epoxide.[8] To obtain more definite evidence that there is a *complementary enantiomer-dependent regioselectivity*, enantiomerically pure epoxide **5** was treated with a copper catalyst derived from either (*S*,*S*,*S*)-**1** or (*R*,*R*,*R*)-**1** (Scheme 2). In the presence of (*R*,*R*,*R*)-**1**, epoxide (1*R*,2*S*)-**5** reacted with Me_2Zn to give with complete regioselectivity the corresponding enantiopure allylic alcohol (1*R*,4*R*)-**12a**, whereas when (*S*,*S*,*S*)-**1** was used, the corresponding homoallylic alcohol (1*R*,2*R*)-**13a** was obtained with a good selectivity.[16] Thus, it is clearly demonstrated that it 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 **1**.

Also, semirigid allylic epoxides such as **14**−**17**, having a blocked *s-trans* conformation, were examined under our reaction protocol (Table 2). Complete conversion of allylic epoxides (±)-**14** and (±)-**15** took place in 3 h and gave, after the usual workup and chromatographic purification, the corresponding allylic and homoallylic alcohols with high yields (entries 1−3, Table 2). Valuable new cyclopentanoid systems **18** and **19** can be obtained in an enantioenriched form through the use of allylic epoxide **14** (entry 1). Actually, it was possible to obtain allylic alcohol **18** with a good enantioselectivity (72% ee), whereas a precise determination of the enantioselectivity of S_N2 adduct **19** was not possible. As for the six-membered allylic epoxide **15**, an accurate examination of its chemical behavior under our protocol with Et_2Zn showed that regioisomeric products **20b** and **21b** derive from the enantiomers of **15** in two clearly distinct phases. The first one is very fast, proceeding with S_N2' regioselectivity to yield **20b** (15 min at −78 °C), while the second slower one which provided **21b** (3 h at −10 °C to arrive at completion) exhibited a complementary S_N2 regioselectivity. It was shown that, after 15 min at −78 °C, the remaining vinyloxirane **15** (62% conversion) was enantiomerically pure (>98% ee) and it reacted with nearly complete regioselectivity at the C-2 oxirane carbon with complete *anti* stereoselectivity to give the final product distribution (S_N2'/S_N2 = 55/45, entry 3). The catalyzed addition of Me_2Zn followed an even more pronounced regiodivergent behavior, affording, after complete conver-

(14) However, this is not always true for all the examined substrates. For example, the use of THF with 1,3-cyclohexadiene monoepoxide **3** afforded a more complex reaction mixture containing also variable amounts of *syn* adducts.

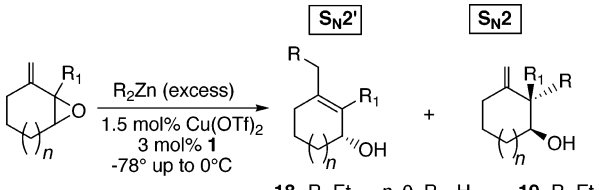
(15) For a recent example concerning the *syn* addition of organozinc species to cyclic 1,3-diene monoepoxides, see: Xue, S.; Li, Y.; Ha, K.; Yin, W.; Wang, M.; Guo, Q. *Org. Lett.* **2002**, *4*, 905.

(16) For the determination of absolute and relative configurations of 4-alkylcyclooctanols, see: Del Moro, F.; Crotti, P.; Di Bussolo, V.; Macchia, F.; Pineschi, M. *Org. Lett.* **2003**, *5*, 1971.

(17) For some recent reports, see: (a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (b) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428. (c) Denmark, S. E.; Wynn, T.; Jellerichs, B. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 2225.

(18) Attempts to perform the reaction entirely at rt gave 3-cycloheptenone as the major product and only trace amounts of addition compounds.

TABLE 2. RKR of Cyclic Allylic Epoxides (*s-trans* Conformation)[a]



14, *n*=0, R_1=H
15, *n*=1, R_1=H
16, *n*=1, R_1=Bu
17, *n*=2, R_1=H

18, R=Et, *n*=0, R_1=H, **19**, R=Et
20a, R=Me, *n*=0, R_1=H, **21a**, R=Me
20b, R=Et, *n*=0, R_1=H, **21b**, R=Et
22, R=Et, *n*=1, R_1=Bu, **23**, R=Et
24a, R=Me, *n*=2, R_1=H, **25a**, R=Me
24b, R=Et, *n*=2, R_1=H, **25b**, R=Et
24c, R=Bu, *n*=2, R_1=H, **25c**, R=Bu

					ee[c] (%)	
entry	substrate	R	*T* (h)	S_N2'/S_N2[b]	S_N2'	S_N2
1	**14**	Et	3	56/44	72	nd
2	**15**	Me	3	49/51	96	92
3	**15**	Et	3	55/45	80	99
4	**16**	Et[d]	18	>95/<5	13	
5	**17**	Me	18	23/77	>97	32
6	**17**	Et	18	56/44	72	88
7	**17**	Bu	18	52/48	82	90

[a−c] See corresponding footnotes in Table 1. [d] Conversion of 34%. Unreacted allylic epoxide **16** was recovered with 2% ee. nd = not determined.

sion of (±)-**15**, allylic alcohol **20a** (96% ee) and homoallylic alcohol **21a** (92% ee) (entry 2).[8] Considering that the construction of a quaternary stereocenter by a catalytic asymmetric reaction is certainly a topic of current interest, we examined allylic epoxide **16**, which contains a butyl group at the C-2 oxirane carbon.[19] Unfortunately, epoxide **16** turned out to be particularly unreactive when treated with an excess of Et_2Zn under our usual reaction protocol, and only S_N2' adduct **22** and unreacted allylic epoxide were recovered, both with low enantioselectivities. No trace of the desired corresponding S_N2 adduct **23** was observed (entry 4). The copper-catalyzed addition of Et_2Zn to the unprecedented cycloheptenyl allylic epoxide **17** afforded, after complete conversion, the corresponding allylic and homoallylic alcohols **24b** and **25b**, respectively, with high yields and enantioselectivities (entry 6). An even more regiodivergent reaction was obtained in the copper-catalyzed addition of Bu_2Zn, giving compounds **24c** and **25c** with high enantioselectivities (entry 7). In general, in the catalyzed addition of dialkylzinc reagents to allylic epoxides, the allylic alcohol (S_N2' adduct) is the main reaction product and there is a clear tendency of Me_2Zn, with respect to Et_2Zn, to give increased amounts of S_N2 adducts for all the substrates examined. In this sense, it is interesting to note the regiodivergent behavior favoring the formation of homoallylic alcohol **25a** (S_N2 adduct) exhibited by Me_2Zn in the reaction with epoxide **17** (entry 5). In this case, the minor regioisomeric allylic alcohol **24a** was obtained with a very high enantioselectivity (>97% ee), and when the reaction was carried out in accordance with a kinetic resolution protocol (0.50 equiv of Me_2Zn), **25a** was the main reaction product. Moreover, the reaction performed with Me_2Zn (1.5 equiv) in the presence of racemic chiral catalyst **1** gave homoallylic alcohol **25a** as the main reaction product (>90% of the crude reaction mixture). Considering that, in an enantioselective RKR process, the product obtained with the higher ee is commonly associated with the slower reaction, the above observations for epoxide **17** tend to indicate that, under our reaction protocol, the S_N2' addition can be, in some cases, the slower pathway in the addition process.

At this point, we thought it interesting to check the behavior of acyclic allylic epoxides such as **26**−**34** under our reaction protocol (Table 3). The conformational mobility typically associated with these compounds could give a better insight into the reaction mechanism. Stereoelectronic considerations require the epoxide and vinylic carbon centers to assume a nearly coplanar disposition in the course of the reaction, even if we recently demonstrated that different arrangements are also possible.[16] In open noncyclic allylic epoxides, the required coplanarity necessary for an effective interaction between the π-orbitals and the breaking oxirane allylic C−O bond can be matched in the corresponding *s-cis* and *s-trans* conformers. Assuming a more favorable *anti* stereoselective mode of attack by the nucleophile, the conformational equilibrium between the *s-trans* and *s-cis* forms swaps the face of the double bond presented to the chiral catalyst, thus rendering an effective chiral recognition as a really challenging event. Several acyclic allylic epoxides with different substitution patterns (type and geometry of the double bond and/or of the epoxide) were therefore synthesized and examined under our reaction condition protocol.

The use of commercially available 1,3-butadiene monoepoxide **26** under our RKR protocol gave mainly achiral conjugate addition products **35a**,**b** with moderate *E*/*Z* diastereoselectivities and only minor amounts (3−5%) of S_N2 addition products **36a**,**b** (entries 1 and 2, Table 3). When isoprene monoepoxide **27** was used, a slightly better *E*/*Z* diastereoselectivity (*E* isomer > 91%) was obtained for S_N2' adducts **37a**,**b**. Moreover, it is also significant that with isoprene monoepoxide it was possible to obtain greater amounts (12−15%) of the S_N2 addition products, homoallylic alcohols **38a**,**b**, containing quaternary stereocenters, with respect to the use of butadiene monoepoxide under the same reaction conditions.[20] Allylic epoxide (*E*)-**28**, bearing a terminal oxirane function, is of special interest because the double bond is in conjugation with the aromatic ring. This structural arrangement is known to favor the formation of the S_N2 addition product, when related copper-mediated allylic alkylation of cynnamylic substrates has been used.[21] Contrary to this expectation, the Cu(II)/ligand **1**-catalyzed addition of Me_2Zn to epoxide **28** gave an inseparable 65/35 mixture of alcohols (*E*)-**39** (S_N2' adduct) and **40** (S_N2 adduct),[22] respectively, both obtained with very low ee's

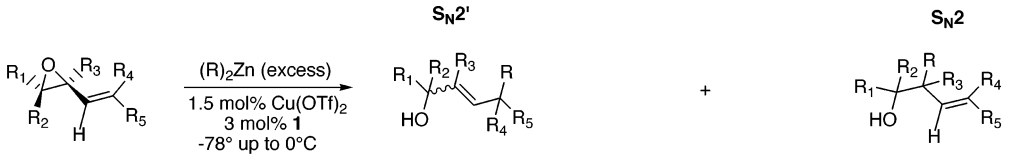
(19) For reviews on the enantioselective formation of quaternary carbon stereocenters, see: (a) Corey, E. J.; Guzmán-Pérez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591.

(20) Regioisomeric alcohols **37a**,**b** and **38a**,**b** were obtained as an inseparable mixture, and a precise determination of their enantioselectivity was not possible. However, when the reaction was performed in the presence of racemic chiral ligand **1**, an increase in S_N2' adducts **37a**,**b** (95% of the crude mixture) was observed. This is a clear, even if indirect, indication that a chiral recognition is present to some extent for isoprene monoepoxide.

(21) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884.

(22) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834.

TABLE 3. RKR of Conformationally Mobile Allylic Epoxides[a]



26, R_1=R_2=R_3=R_4=R_5=H
27, R_1=R_2=R_4=H, R_3=Me
28, R_1=R_2=R_3=R_5=H, R_5=Ph
29, R_2=Ph, R_1=R_3=R_4=R_5=H
30, R_2=-CH_2OTBDPS, R_1=R_3=R_5=H, R_4=Et
31, R_1=-$(CH_2)_2$-CH_3, R_2=R_3=R_5=H, R_4=Et
32, R_2=R_3=R_4=H, R_1=-CH_3, R_5=-CH_2OBn
33, R_1=R_2=R_3=H, R_4=-$(CH_2)_2$(CH=C)(Me)$_2$, R_5=Me
34, R_2=R_4=R_5=H, R_1=R_3=-CH_2-$(CH_2)_2$-CH_2-

35a, R=Et,	R_1=R_2=R_3=R_4=R_5=H,		**36a**, R=Et
35b, R=Bu,	R_1=R_2=R_3=R_4=R_5=H,		**36b**, R=Bu
37a, R=Et,	R_1=R_2=R_4=H, R_3=Me,		**38a**, R=Et
37b, R=Bu,	R_1=R_2=R_4=H, R_3=Me,		**38b**, R=Bu
39, R=Me,	R_1=R_2=R_3=R_5=H, R_5=Ph,		**40**, R=Me
41, R=Et,	R_2=Ph, R_1=R_3=R_4=R_5=H		**42**, R=Et
43, R=Et,	R_2=-CH_2OTBDPS,R_1=R_3=R_5=H, R_4=Et,		**44**, R=Et
45, R=Et,	R_1=-$(CH_2)_2$-CH_3, R_2=R_3=R_5=H, R_4=Et		**46**, R=Et
47, R=Et,	R_1=Me, R_2=R_3=R_4=H, R_5=-CH_2OBn,		**48**, R=Et
49, R=Et,	R_1=R_2=R_3=H, R_4=-$(CH_2)_2$(CH=C)(Me)$_2$,R_5=Me,		**50**, R=Et
51a, R=Me,	R_2=R_4=R_5=H, R_1=R_3=-CH_2-$(CH_2)_2$-CH_2-,		**52a**, R=Me
51b, R=Et,	R_2=R_4=R_5=H, R_1=R_3=-CH_2-$(CH_2)_2$-CH_2-,		**52b**, R=Et
51c, R=Bu,	R_2=R_4=R_5=H, R_1=R_3=-CH_2-$(CH_2)_2$-CH_2-,		**52c**, R=Bu

						ee[c] (%)	
entry	substrate	R	*T* (h)	S_N2'/S_N2[b]	*E* / *Z*[b] (S_N2')	S_N2'	S_N2
1	**26**	Et	5	97/3	82/18		
2	**26**	Bu	5	95/5	85/15		
3	**27**	Et	5	85/15	93/7		nd
4	**27**	Bu	5	87/13	91/9		nd
5	**28**	Me	4	65/35	>95/<5	2	6
6	**29**	Et	4	68/32	>95/<5	6	15
7	**30**	Et	5[d]	75/25	>95/<5	rac	2
8	**31**	Et	4	66/34	>95/<5	52	97
9	**32**	Et	18[e]	85/15	87/13	nd[f]	nd[f]
10	**33**	Et	4[e]	90/10	nd	10	nd
11	**34**	Me[g]	3	53/47	>95/<5	94	nd
12	**34**	Et[g]	1	55/45	>95/<5	90	92
13	**34**	Bu[g]	4	57/43	>95/<5	89	95

[a–c] See corresponding footnotes in Table 1. [d] Conversion of 30%. [e] Reaction performed with 3.0 equiv of Et_2Zn. [f] The enantioselectivity (4%) was determined only of the starting epoxide **32** by HPLC (Daicel Chiralcel OD-H). [g] Reaction performed entirely at −78 °C.

(entry 5). Similarly, the catalyzed addition of Et_2Zn to *cis*-epoxide **29**, bearing a terminal double bond, afforded a 68/32 mixture of regioisomeric alcohols (*E*)-**41** and **42**, respectively, with poor stereoselectivities (entry 6). With epoxides **28** and **29**, the use of racemic chiral ligand (*S*,*S*,*S*)(*R*,*R*,*R*)-**1** afforded almost the same regioisomeric ratio, thus indicating that a chiral recognition is not operative with this substrate (data not shown in Table 3). Allylic *cis*-epoxide **30**, possessing a *Z* configuration of the double bond, turned out to be relatively unreactive under our reaction conditions (30% conversion after 5 h at 0 °C), and the corresponding ring-opened products (*E*)-**43** (S_N2' adduct) and (*Z*)-**44** (S_N2 adduct) were obtained as racemates (entry 7). However, it is to be noted that within S_N2' adduct **43**, deriving from an allylic rearrangement, the new double bond had an *E* configuration, whereas in S_N2 adduct **44** the original *Z* double bond configuration present in the starting epoxide was fully maintained.[23] The preservation of the *Z* geometry of the starting allylic epoxide was also observed in homoallylic alcohol **46** (S_N2 adduct), deriving from the regiodivergent catalyzed addition of Et_2Zn to *trans*-epoxide **31**.

In this case, we were delighted by the good enantioselectivities found in the corresponding ring-opening products **45** (52% ee) and **46** (97% ee) (entry 8), in accordance with the incursion of an efficient RKR process absent in the other acyclic substrates so far examined. In particular, the behavior of allylic epoxide **31** was markedly different from that of the closely related epoxide **30**, the only differences being the *cis* geometry of the epoxide and the presence of an ethereal functionality in the latter compound. In sharp contrast with the good results obtained with compound **31**, the copper-phosphoramidite-catalyzed reaction with Et_2Zn of *trans*-allylic epoxide **32**,[24] bearing an *E* double bond, gave an 85/15 mixture of two regioisomeric S_N2' adducts **47a**,**b** (as an 87/13 *E*/*Z* mixture) and **48** (S_N2 adduct), respectively (entry 9). In this case, it was possible to obtain in a pure state also a substantial amount of (*Z*)-S_N2' adduct **47b**. Unfortunately, it was not possible to determine the enantioselectivity of alcohols **47a**,**b** and **48**. However, an examination of the reaction mixture composition after ∼4 h at 0 °C revealed that the starting allylic epoxide **32** was essentially racemic at this point (75% of conversion), thus excluding the incursion of an effective RKR process. We also explored the reactivity of epoxide **33**, deriving from geraniol, in view of the possibility of forming a quaternary center by means of an S_N2' reaction. Actually, the addition of Et_2Zn to epoxide **33** performed under our protocol afforded the desired allylic alcohol **49** (S_N2 adduct) with a good regioselectivity (90%) but unfortunately with a low ee (10% ee, entry 10). The same reaction afforded only a minor amount (∼10%) of regio-

(23) For a study on the relationship of the double bond configuration between reactants and products in the cross-coupling reactions of allylic substrates with organocopper reagents, see: Underiner, T. L.; Paisley, S. D.; Schmitter, J.; Leshesky, L.; Goering, H. L. *J. Org. Chem.* **1989**, *54*, 2369.

(24) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574.

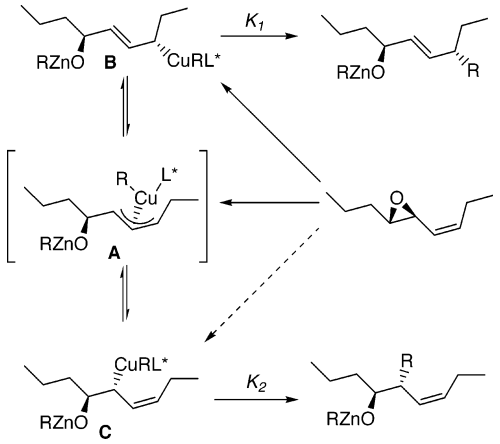
isomeric homoallylic alcohol **50** (ee not determined). Much to our surprise, we were able to create a quaternary stereocenter efficiently and with a high enantioselectivity when 1-vinyl-1-cyclohexene oxide (**34**)[25] was used as the substrate for our RKR procedure. This conformationally mobile substrate gave a very fast reaction with dialkylzincs in the presence of catalytic amounts of Cu(II)/ligand **1**, to the point that the reaction could be completely performed at −78 °C, giving an almost equimolar mixture of (*E*)-allylic alcohols **51a**−**c**[26] and homoallylic alcohols **52a**,**c**, both with high optical purities (89−95% ee's) and quantitative yields (entries 11−13 and the Supporting Information). It should be noted that the S_N2 addition pathway to **34** allows the obtainment of a quaternary carbon stereocenter with a high enantioselectivity.[19] Like most of the semirigid substrates examined in Tables 1 and 2, the reaction of epoxide **34** with 0.50 equiv of R_2Zn catalyzed by Cu(II)/(*S*,*S*,*S*)-**1**, according to a kinetic resolution protocol, and with R_2Zn (1.5 equiv, catalyzed by racemic **1**) afforded compounds of type (*E*)-**51** with high levels of S_N2' regioselectivity (>90%).

The asymmetric matching of the ligand with acyclic allylic epoxide substrates is somewhat puzzling and substrate-dependent, and it is difficult to give a complete and coherent rationalization. However, good levels of *E* stereoselectivity were uniformly obtained for the S_N2' adducts when conformationally mobile allylic epoxides **26**−**34** were used. Even if the ground state conformers are not necessarily the same, it is reasonable that the corresponding *s-trans* conformers are the reactive ones.

Considerations on the Reaction Mechanism. The mechanism of a copper-catalyzed allylic alkylation has not been fully established yet, and scant information is available in regard to the transition state. 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 Cu(II) salt to the Cu(I) salt, which is the true catalytic species. Moreover, it is generally admitted that an oxidative addition occurs to form a Cu(III) intermediate[27] and that the rate-determining step of a cuprate conjugate addition is the last stage of the reaction, that is, the reductive elimination process.[28]

Steric factors do not seem to play an important role in the regiochemical outcome of the copper-catalyzed regiodivergent additions to the allylic epoxides examined by us. In fact, unlike the related use of stoichiometric cuprates,[29] the presence of alkyl substituents in the allylic position does not hinder S_N2 addition when conformationally mobile allylic epoxides are used. On the contrary, it seems that a substituent in this position leads to an increase of the S_N2 adduct (entries 3, 4, and 11−13, Table 3). We have now shown that the slower reaction is usually, but not exclusively, the S_N2 addition pathway, and it is this reaction (i.e., the slower reaction) that is invariably associated with the formation of the product with the higher enantioselectivity. The maintenance of the *Z* double bond geometry present in allylic epoxides **30** and **31** in the corresponding S_N2 adducts (compounds **44** and **46**, entries 7 and 8) supports the notion that the configuration of the double bond is partly retained throughout the reaction.[23] As shown in Scheme 3 for the reaction of one enantiomer of epoxide **31**, taken as a model for all examined noncyclic allylic epoxides **26**−**34**, this experimental evidence might be consistent with an oxidative addition process leading directly to a Cu(III)−π-allyl system of type **A**[30] in equilibrium with the corresponding regioisomeric σ-allyl−copper(III) species **B** and **C**. The subsequent reductive elimination steps, K_1 and K_2, from **B** and **C**, respectively, probably play a crucial role in determining the stereo- and regioselectivities observed (Scheme 3).[28]

SCHEME 3. Postulated Mechanism for the RKR (Only One Enantiomer of the Allylic Epoxide Is Shown)



In this framework, the fundamental importance of the sense of chirality of the chiral ligand, when the RKR is operative, should be noted. Probably, the fact that the absolute configuration of the chiral ligand, having matched and mismatched combinations with the enantiomers of the allylic substrate, determines the regiochemical outcome seems to indicate that the nonracemic phosphoramidite ligand plays a fundamental role in the acceleration of the carbon−carbon bond formation during the reductive elimination step.[28] Moreover, the presence of an olefin is required for the reaction to occur, since cyclohexene oxide and also the more reactive styrene oxide do not give the corresponding ring-opened products under the reaction conditions commonly used. These data seem to indicate that a kinetically controlled obtainment of the corresponding σ-allyl−copper(III) species **B** and **C** in a totally independent way, by means of a selective nucleophilic cuprate addition to each enantiomer of the allylic

(25) Annis, G. D.; Ley, S. V.; Self, C. R.; Sivaramakrishnan, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 270.

(26) The *E* configuration of the double bonds in compounds **51a**−**c** has been established by 1D ROESY spectra (see the Supporting Information).

(27) For very recent experimental evidence supporting the incursion of Cu(III) intermediates, see: Karlström, A. S. E.; Bäckwall, J.-E. *Chem.*−*Eur. J.* **2001**, *7*, 1981 and references therein.

(28) For the importance of the reductive elimination step in a copper-catalyzed conjugate addition, see: Nakamura, E.; Yamanaka, M.; Mori, S. *J. Am. Chem. Soc.* **2000**, *122*, 1826.

(29) For a review, see: Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503 and pertinent references therein.

(30) Due to the scarcity of direct methods to investigate the reaction pathway, the obtainment of σ-allyl−copper(III) species **B**, in equilibrium with regioisomeric σ-allyl−copper(III) species **C**, through a π-allyl complex or a suprafacial 1,3-sigmatropic shift cannot be ruled out. However, the substantial preservation of the stereochemical integrity of the original double bonds present in the S_N2 adducts seems to indicate that the reductive elimination step is faster than the eventual incursion of *syn*/*anti* isomerization processes.

epoxide, is not likely.[12] It is difficult to imagine a scenario in which a *complementary enantiomer-dependent regioselectivity* having the described peculiarities can be obtained, without the incursion of any common intermediates.

In conclusion, we have shown that the outcome of the enantioselective regiodivergent kinetic resolution of racemic allylic epoxides with dialkylzinc reagents is effective for a variety of cyclic substrates, and also for some acyclic substrates. The most fascinating and unusual aspect is certainly that the regioselectivity of the reaction depends directly on the absolute configuration of the chiral catalyst. This new process allows the obtainment of several new allylic and homoallylic alcohols with good to excellent enantioselectivities. 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 obtainment 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. The mechanism of this reaction and the exact nature of the copper species involved in this highly efficient catalytic process still need to be established. Nevertheless, the data obtained support the notion that the reductive elimination is the regio- and stereodetermining step.

Experimental Section

Materials and Methods. For general information, see refs 8 and 16. The *E* configuration of the double bonds of compounds **51a**−**c** was established by proton 1D ROESY spectra. 1D ROESY spectra were recorded on a spectrometer operating at 599.69 MHz using a 5 mm broadband inverse probe with a *z*-axis gradient, with a spectral width of 5400 Hz and a mixing time of 0.6 s.

Typical Procedure: Preparation of (1*R*,4*R*)-4-Ethyl-2-cyclohepten-1-ol (10b) and of (1*S*,2*S*)-2-Ethyl-3-cyclohepten-1-ol (11b). A solution of $Cu(OTf)_2$ (5.40 mg, 0.015 mmol) and chiral ligand (*R*,*R*,*R*)-**1** (16.2 mg, 0.03 mmol) in anhydrous toluene (1.5 mL) was stirred at rt for 40 min. The colorless solution was cooled to −78 °C, followed by subsequent addition of a solution of **1** (110 mg, 1.0 mmol) in toluene (0.5 mL). After 5 min, Et_2Zn (1.36 mL of a 1.1 M solution in toluene, 1.5 mmol) was added, and the stirred reaction mixture was allowed to warm slowly up to 0 °C. After 3 h (>98% conversion), the mixture was quenched with saturated aqueous NH_4Cl solution (5 mL). Extraction with Et_2O (2 × 35 mL) and evaporation of the dried ($MgSO_4$) organic phase afforded a very clean crude mixture consisting only of alcohols **10b** and **11b** (>90% crude yield). The crude reaction mixture was subjected to flash chromatography (SiO_2) with 20% EtOAc in hexanes to give, as the second eluting fractions, 56 mg of pure **10b** (40%), as a liquid. R_f = 0.20. ^{1}H NMR δ 5.43−5.77 (m, 2H), 4.29−4.49 (m, 1H), 1.18−2.32 (m, 9H), 0.90 (t, 3H, J = 7.2 Hz). ^{13}C NMR δ 136.5, 135.3, 70.9, 40.2, 36.3, 32.2, 29.1, 22.7, 12.3. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.88; H, 11.39. The enantiomeric excess of **10b** (>90%) was determined by chiral GC (β-cyclodextrin column): isothermal 110 °C, 22.0 psig; t_R 43.82 min (minor), t_R 44.36 min (major). The first eluting fractions of the flash chromatography afforded 35 mg of pure **11b** (25%), as a liquid. R_f = 0.26 (20% AcOEt in hexanes). ^{1}H NMR δ 5.81−5.97 (m, 1H), 5.40−5.52 (m, 1H), 3.47−3.61 (m, 1H), 1.19−2.39 (m, 9H), 0.93 (t, 3H, J = 7.4 Hz). ^{13}C NMR δ 133.7, 132.7, 71.7, 47.8, 39.0, 29.0, 25.0, 24.0, 11.7. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.21; H, 11.33. The enantiomeric excess of **11b** (>90%) was determined by chiral GC (β-cyclodextrin column): isothermal 110 °C, 22.0 psig; t_R 34.06 min (minor), t_R 34.56 min (major).

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Note Added after ASAP Posting. This article was released ASAP on 2/13/2004. Two entries in Table 1 were changed. The paper was reposted on 2/16/2004.

Supporting Information Available: Text giving experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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