The development of simple, efficient procedures for the stereoselective formation of carbon-carbon bonds by the use of organometallic reagents is one of the major challenges in organic chemistry. Recently, we have introduced some new copper-catalyzed enantioselective allylic alkylation ring-opening reactions of small ring heterocycles with hard alkyl metals. The regio- and stereocchemical outcome of the copper-phosphoramidite catalyzed enantioselective addition of dialkylzinc reagents to cyclic allylic epoxides \(2a-d\) depended on the substrate and reaction conditions used (see Scheme 1). Phosphoramidite \((R,R,R)-1\) derived from \((R)\)-BINOL and \((R)\)-bis-phenyl-ethyamine,\(^2\) was the chosen ligand because it proved to be slightly superior to its diastereoisomer \((S,R,R)\)\(^3\) with respect to the extent of regiodivergency, and the enantioselectivity of the alcohol reaction products.

When reactions were performed in accordance with a classic kinetic resolution (KR) protocol (Equation a, Scheme 1), it was possible to obtain with a high regioselectivity the corresponding allylic alcohol \((S_N2^\circ\) pathway) and to recover the unreacted allylic epoxide with a high optical purity.\(^5\) Very interestingly, if reactions were performed up to completion of the allylic epoxide (Equation b, Scheme 1), it was possible to obtain both the corresponding regioisomeric allylic and homoallylic alcohols \((S_N2\) pathway) with a high enantioselectivity.\(^5\) To avoid
the inherent limitations of resolution processes, also some novel procedures for the enantioselective desymmetrization of symmetrical allylic epoxides were devised. For example, we recently demonstrated the first alkylating and enantioselective ring-opening of 1,3,5,7-cyclooctatetraene (COT) monoepoxide (3) to give previously unknown 4-alkylcyclooctatrienols (Equation c, Scheme 1). From a synthetic point of view, it should be noted that cyclic allylic- (bis-allylic-) and homoallylic alcohols with high optical purity cannot be prepared by alternative straightforward synthetic procedures. Sharpless’ kinetic resolution of racemic cyclic allylic alcohols with an endocyclic double bond is known to proceed with a modest enantioselectivity. Moreover, the enantioselective epoxidation of cis-olefins of conjugated dienes, followed by a subsequent regioselective installation of the alkyl chain, is potentially able to give only moderate values of optical purity. On the other hand, racemic cyclic allylic epoxides 2a–d and symmetrical COT-monoepoxide 3 can easily be prepared on a multigram scale by mono-epoxidation of the corresponding commercially available 1,3-diienes or COT, respectively.

The KR protocol was recently used by our group for a novel catalytic high regio- and enantioselective synthesis of 4-methyl-2-cyclohexen-1-ol (4) in a multigram scale reaction (Procedure 1, Scheme 2). Alloytic alcohol 4 was then transformed into the corresponding α,β-unsaturated ketone by a simple oxidation reaction. Compared with other multistep syntheses of optically active 4-methyl-2-cyclohexen-1-ones, which are useful chiral building blocks, our two-step procedure is straightforward, simple and practical. The major drawback of this protocol is the reduced degree of conversion (46%) necessary to obtain the 2° addition product 4 with a high regio- and enantioselectivity. However, the simple work-up procedure, based on filtration and distillation, qualifies for a further scale-up.

A complete conversion of a racemic allylic epoxide into constitutionally different enantiomerically enriched ring-opened products can be simply obtained by means of an excess of the dialkylic reagent and a chiral catalyst in a carbon-carbon bond-forming reaction. Very recently, we have shown that the RKR can be successfully applied to a variety of semicyclic rigid allylic epoxides and, in some specific cases, also to conformationally mobile allylic epoxides. Like most catalytic asymmetric reactions, our RKR protocol is substrate-dependent and 1,3-cycloheptadiene monoepoxide proved to be an ideal substrate. Evidently, with this substrate, the asymmetric matching of the chiral ligand with the enantiomers of the substrate is considerable. Also by the use of reduced amounts of the chiral copper catalyst (0.5 mol%) in a gram scale reaction entirely performed at 0 °C, regioisomeric alcohols 5 and 6, having opposite configurations at the hydroxyl group-bearing carbon, were obtained in almost equal amounts, with high enantiomeric excesses (Procedure 2, Scheme 3). In this case, a chromatographic purification (SiO2) proved to be necessary for the separation of allylic alcohol 5 and homoallylic alcohol 6.

As regards symmetrical substrates, we recently reported that COT-monoepoxide (3), despite its non-planar tube form, can be successfully alkylated with appropriate organocopper reagents, without the occurrence of any ring-contraction-isomerization. The enantioselective desymmetrization reaction of 3 with Et₂Zn can be improved with respect to our original report and performed on a gram scale in the presence of catalytic amounts of Cu(OTf)2/(R,R,R)-1 to give a clean crude reaction mixture containing (1R,4R)-4-ethyl-2,5,7-cyclooctatrienol (7) (Procedure 3, Scheme 4). Bis-allylic alcohol 7 can be obtained in a pure state by flash chromatography with a satisfactory 68% isolated yield and a high enantioselectivity of 94%.

**Scheme 2** Multigram catalytic enantioselective synthesis of 4-methyl-2-cyclohexen-1-ol via kinetic resolution of racemic 1,3-cyclohexadiene monoepoxide.

**Scheme 3** Regiodivergent kinetic resolution of racemic 1,3-cycloheptadiene monoepoxide with Et₂Zn.

**Scheme 4** Catalytic enantioselective desymmetrization of COT-monoepoxide.
In summary, several optically active allylic and homoolylic alcohols can be synthesized by these procedures, allowing a flexible and practical gram-scale synthesis of this interesting class of compounds by the use of small amounts of BINOL-derived phosphoramidites.

All reactions were conducted in flame-dried glassware with magnetic stirring under an Ar atmosphere. Toluene was distilled from sodium/benzophenone ketyl and stored under Ar. ²H NMR spectra were recorded on a Bruker AC-200 spectrometer. Chemical shifts are reported in ppm downfield from TMS as the internal standard (CDCl₃; δ = 7.26). ¹³C NMR spectra were recorded on a Bruker AC-200 (50 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm downfield from TMS as the internal standard (CDCl₃; δ = 77.7). Silica gel 60 (Macherey-Nagel 230–400 mesh) was used for flash chromatography.

(1R,4R)-(−)-4-Methyl-2-cyclohexen-1-ol (4): Kinetic Resolution Protocol (Procedure 1); Typical Procedure
A solution of Cu(OTf)₂ (54.3 mg, 0.15 mmol) and (R,R,R)-4 (0.160 g, 0.3 mmol) in anhyd toluene (30 mL) was stirred for 40 min. The colorless solution was cooled to −78 °C and freshly distilled racemic 1,3-cyclohexadiene monoepoxide (2b) (4.80 g, 50 mmol) in anhyd toluene (5 mL) was added. The solution was cooled to 0 °C, and subsequently a solution of Me₂Zn in toluene (5 mL) and isopropylbenzene (1.80 g, 30 mmol) in anhyd toluene (7.0 mL) was stirred at r.t. for 40 min. The solution was cooled to 0 °C, and subsequently a solution of Cu(OTf)₂ (16.4 mg, 0.045 mmol) and (R,R)-4 (0.160 g, 0.3 mmol) in anhyd toluene (5 mL) was added and the stirred reaction mixture was allowed to stand at r.t. for 40 min. The solution was cooled to −78 °C and a solution of Cu(OTf)₂ (54.3 mg, 0.15 mmol) and chiral ligand (162.0 mg, 0.3 mmol) in anhyd toluene (5 mL) was stirred at r.t. for 40 min. The solution was cooled to −78 °C and a solution of freshly distilled 2a (containing 7% of unreacted COT, 1.2 g, ca. 10.0 mmol) in toluene (1 mL) was added. After 5 min., Et₂Zn (13.6 mL, 15 mmol) was added and the stirred reaction mixture was allowed to warm slowly up to 0 °C. The mixture was quenched after 3 h (95% conversion) at 0 °C with sat. aq NH₄Cl solution (10 mL). Extraction with Et₂O (3 × 30 mL) and evaporation of the dried (MgSO₄) organic phase afforded a crude liquid reaction mixture (1.020 g, 68% yield) as a pale yellow oil by flash chromatography (SiO₂) eluting with hexanes containing 15% of EtOAc and 2% Et₃N. The enantiomeric excess of 5 (83%) was determined by chiral GC (β-cyclodextrin column, iso-thermal 110 °C); tₚ 34.06 min (minor), tₚ 32.96 min (major); [α]₂₀° = +325 (c = 1.0, MeOH); Rₜ 0.27 (20% EtOAc in hexanes).

3H NMR: δ = 6.07–6.17 (m, 2 H), 5.55–5.61 (m, 1 H), 5.15–5.43 (m, 3 H), 4.82–4.93 (m, 1 H, CH(OH), 2.65–2.75 (m, 1 H, 1.51–1.65 (m, 2 H), 0.90 (t, J = 7.3 Hz, 3 H).

13C NMR: δ = 133.5, 133.0, 132.6, 131.5, 128.3, 127.0, 70.5, 39.6, 29.6, 12.4.


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