Currently, we do not have an explanation as to why the selectivity factor is not higher (s > 200) in this resolution as could be expected from Figure 2. A possible explanation is that the kinetics are more complicated with Me₂Zn than with the other zinc reagents in which case the formula given in reference [9] is no longer valid.


Highly Enantioselective Regiodivergent and Catalytic Parallel Kinetic Resolution**

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The development of new methodologies for the preparation of chiral compounds of high optical purity by means of asymmetric catalysis is presently an area of great importance in organic chemistry. Kinetic resolution of a racemic mixture with a chiral reagent is a well-documented strategy in which a maximum of only one half of the racemic starting material is converted into non-racemic products.[1] Parallel kinetic resolution (PKR) is an interesting strategy recently introduced, in which both enantiomers of a racemate can be converted into achiral compounds.[2] This conceptual variation often requires the use of two different stoichiometric chiral reagents in parallel.[3] Parallel reactions under non-stoichiometric conditions using two different stoichiometric chiral reagents in parallel.[3] The latter is the only example of a PKR reaction involving the formation of a C–C bond. In this special case, there are distinct reactivities for both enantiomers: one enantiomer gave intramolecular cyclopropanation, whereas the other enantiomer was transformed by means of a hydride abstraction/elimination into achiral compounds.

Herein we report the first highly stereocontrolled transformation of a racemic mixture by an organometallic reagent and a chiral catalyst to give separable regiosomeric products.

Recently, we described a new catalytic kinetic resolution of racemic vinylxiranes with dialkylzinc reagents (0.50 equiv) by using copper complexes of non-racemic phosphoramidite as chiral catalysts.[4] When racemic vinyl epoxide 2 was treated with excess Et₂Zn (1.5 equiv) in the presence of the catalyst prepared in situ from [Cu(OtF)₂] (1.5 mol %) (TF = trflate = OSO₂CF₃) and (R,R,R)-1 (3 mol %), complete conversion of 2 took place in 3 h to give, after usual work-up and chromatographic purification (see Experimental Section), the corresponding S₀₂⁻addition product (R)-3a (46% yield, 80% ee; Scheme 1) together with the regiosomeric alcohol (S,S,S)-4a (37% yield) having a surprising 99% ee! The progress of the reaction in terms of the the conversion and enantioselectivities (Figure 1a and 1b, respectively) was therefore closely monitored.[10] The peculiarity of this reaction stems from the fact that regiosomeric products were derived from opposite enantiomers of 2 in two clearly distinct phases: The first one was very fast, proceeding with S₀₂⁻regioselectivity to yield (R)-3a (15 min at −78°C), whereas the second slower one which provided (1,S,2)-4a (−10°C and 3 h to go to completion) exhibited a complementary S₀₂⁻regioselectivity. In fact, after 15 min at −78°C, the remaining vinylxirane (1,S,2)-2 (62% conversion) was enantiomerically pure, (>98% ee)[10] and it reacted with nearly complete regioselectivity, and with complete anti stereoselectivity, at the 2-position. The catalyzed addition of Me₂Zn followed an even more pronounced regiodivergent behavior, affording, after complete conversion of 2, (R)-3b (9% GC yield, 96% ee) and (1,S,2)-4b (51% GC yield, 92% ee) (Scheme 1).

The complementary enantiomer-dependent regioselectivity was also demonstrated by a reaction carried out with the racemic catalyst (R,R,R)(S,S,S)-1. In this case, the conjugate-addition product 3 was obtained with almost complete regioselectivity (S₀₂⁻/S₂₀⁻ = 98:2), clearly indicating that chiral recognition leads to enantio- and regiodivergent reactivity when the reaction is performed with the chiral catalyst.

The mechanism for the copper-catalyzed organometallic addition reactions has been discussed in a number of reports.[11,12] Probably the initially formed π complex 2A[13][12] undergoes an oxidative addition resulting in the formation of 2001 Angew. Chem. Int. Ed. 40, No. 5}

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[**] This work was supported by the Ministero dell’Università e della Ricerca Scientifica e Tecnologica (MURST, Roma) and by the University of Pisa. We gratefully acknowledge Merck for the generous financial support derived from the 2000 ADP Chemistry Award.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.
Figure 1. GC yield Y [%] (a) and enantiomeric excesses ee [%] (b) of compounds 2 (●), 3a (●●●), 4a (●●●●) present in the reaction mixture at different conversions X of 2. Values determined by GC using a β-cyclodextrin column (see Supporting Information).

Scheme 2. Postulated mechanism of the regiodivergent PKR.

The efficient catalytic conversion of a racemic compound to two different and separable chiral products of high isomeric purity has been accomplished also by the use of a vinylxirane having a blocked s-cis conformation such as 1,3-cyclohexadiene monoepoxide 5 (Scheme 3). The addition of Me₂Zn (1.5 equiv) to (rac)-5 catalyzed by [Cu(OTf)₂]/(R,R,R)-1 afforded a 60:40 mixture of (1R,2S)-6b (S₂2-adduct, 64 % ee) and (1S,2S)-7b (S₂2-adduct, > 97 % ee).[15] The catalyzed addition of Et₂Zn (1.5 equiv) to the same racemate afforded a 76:24 mixture of regioisomer (1R,2S)-6a (34 % ee) and (1S,2S)-7a (98 % ee). Evidently with this substrate, while keeping the corresponding k₁/k₄ for one enantiomer of the substrate, the rates of reductive elimination versus isomerization for the other one (k₂ vs. k₃ of Scheme 2) are not very different, thus allowing the formation of regioisomeric S₂2 adducts 7a, b with very high ee, together with large amounts of S₂2 substitution products 6a, b with a reduced enantioselectivity.
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, this unprecedented regiodivergent catalytic parallel kinetic resolution with an organometallic reagent supports the notion that the oxidative addition might be a very fast process and reductive elimination is instead a regio- and stereodetermining step.

Experimental Section

General procedure: A solution of [Cu(OtBu)] (10.83 mg, 0.030 mmol) and I (32.3 mg, 0.06 mmol) in anhydrous toluene (4.0 mL) was stirred at room temperature for 40 min. The colorless solution was cooled to –78 °C, and subsequently solutions of racemic vinyl bromide (2.0 mmol) in toluene (1.0 mL) and R-Zn (3.0 mmol) in toluene were added. The resulting light yellow solution was quenched with saturated aqueous NH₄Cl (5.0 mL) once the reaction reached completion (GC analysis). Extraction with Et₂O and evaporation of the dried (MgSO₄) organic phase gave the crude product, which was subjected to flash chromatography (see Supporting Information). Enantioselectivities were determined by chiral GC (CP-cyclodex-β-column).

Received: October 30, 2000 [Z 16011]

[1] For a review of kinetic resolution processes, see: H. B. Kagan, J. C. Fiaux, Top. Stereochem. 1988, 18, 249. As an alternative, the overall yield can be improved to 100% by conducting a dynamic kinetic resolution. For example, see: B. A. Persson, F. E. Fuerta, J. E. Bäckvall, J. Org. Chem. 1999, 64, 5237, and references therein.


[9] The reaction was also carried out in CH₂Cl₂ instead of toluene to obtain vinylxirane (1S,2R)-2 in an enantioselective manner (–98% ee) by distillation, stopping the reaction after the first fast-phase.


[12] For an examination of nonlinear effects in the related copper–phosphoramidite catalyzed addition reaction of dialkylzinc reagents to enones, see reference [7c].