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are more complicated with Me2Zn than with the other zinc reagents in which case the formula given in reference [9] is no longer valid.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 useful products.[2] This conceptual variation often requires the use of two different stoichiometric chiral reagents in parallel.[3] Parallel reactions under non-stoichiometric conditions have previously been described in the asymmetric Bayer–Villiger oxidation of racemic ketones, by means of enzymatic methods[4] or chiral catalysts,[5] and in the intramolecular cyclopropanation of racemic allylic diazoacetates catalyzed by chiral rhodium complexes.[6] 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 regioisomeric 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(Otbf)2] (1.5 mol %) (Ti = triflate = OSO2CF3) and (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 S=S2-addition product (R)-3a (46 % yield, 80 % ee; Scheme 1) together with the regioisomeric alcohol (1,S2,5)-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.[8] The peculiarity of this reaction stems from the fact that regioisomeric products were derived from opposite enantiomers of 2 in two clearly distinct phases: The first one was very fast, proceeding with S=S2-regioselectivity to yield (R)-3a (15 min at −78 °C), whereas the second slower one which provided (1,S2,5)-4a (−10 °C and 3 h to go to completion) exhibited a complementary S=S2 regioselectivity. In fact, after 15 min at −78 °C, the remaining vinylxirane (1,S2,5)-2 (62 % conversion) was enantiomerically pure, (>98 % ee)[8] 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 (49 % GC yield, 96 % ee) and (1,S2,5)-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 (S=S2/S=S2 = 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.[10] Probably the initially formed π complex 2A[11][12] undergoes an oxidative addition resulting in the formation of
Figure 1. GC yield $Y$ [%] (a) and enantiomeric excesses [%] (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 vinyloxirane having a blocked $s$-$cis$ conformation such as 1,3-cyclohexadiene monoepoxide 5 (Scheme 3). The addition of Me$_2$Zn (1.5 equiv) to the same racemate afforded a 76:24 mixture of regioisomer (‡)-(1R,4R)-6a ($S_02$-adduct, >98 % ee) and (‡)-(1S,2S)-7a ($S_02$-adduct, >97 % ee). Evidently with this substrate, while keeping the corresponding $k_1$ vs. $k_2$ for one enantiomer of the substrate, the rates of reductive elimination versus isomerization for the other one ($k_3$ of Scheme 2) are not very different, thus allowing the formation of regiosomeric $S_02$ adducts 7a, b with very high ee, together with large amounts of $S_02$ 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)2] (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 epoxide (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).

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[9] The reaction was also carried out in CH2Cl2 instead of toluene to obtain vinylxirane (1 ee), in an enantioselectively pure form (>98% ee) by distillation, stopping the reaction after the first faster-phase.


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

