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Tetrahedron Letters 46 (2005) 5957-5959

Tetrahedron Letters

A positive nonlinear effect in catalytic asymmetric cyclopropanation of styrene with ethyl diazoacetate

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Received 4 April 2005; revised 3 June 2005; accepted 10 June 2005

Abstract—The existence of a positive nonlinear effect [(+)-NLE] in the asymmetric cyclopropanation of styrene with ethyl diazoacetate catalysed by a chiral Cu(I)–bisoxazoline complex was observed. This effect can be explained by the possible formation of a catalytically inactive heterochiral *meso*-complex.

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Nonlinear effects (NLE) in catalytic asymmetric reactions are of great interest from a practical synthetic stand point, especially when dealing with positive nonlinear effects [(+)-NLE]. The (+)-NLE is particularly useful in the preparation of chiral compounds with greater enantiomeric purity than that of the chiral catalyst. It has been shown that such effects occur when catalytic complexes of different stoichiometries (i.e., ML*, ML_2^* , etc.; M = metal ion and L* = chiral ligand) exist simultaneously in the reaction system.¹ In the case of enantiomerically nonpure (scalemic) chiral catalysts, the complexes of ML₂* stoichiometry can be homo- or heterochiral, and consequently their stabilities and/or catalytic activities are different due to their diastereomeric relationship. When the heterochiral meso-ML₂* complex is less catalytically active or inactive when compared to the ML* and the homochiral ML_2^* , a positive nonlinear effect will occur, resulting in an increased optical yield. In some cases impressive positive NLEs were observed.²

One of the widely studied catalytic asymmetric reactions is the cyclopropanation of styrene with ethyl diazoacetate catalysed by the complexes of chiral ligands (L^*) with copper(I) or other metal ions (Scheme 1). Two chiral diasteromeric products, *cis*- and *trans*-cyclopropane derivatives are formed in the reaction giving altogether

0040-4039/\$ - see front matter @ 2005 Published by Elsevier Ltd. doi:10.1016/j.tetlet.2005.06.155

four possible stereoisomers. Frequently used chiral ligands in cyclopropanations are C_2 -symmetric bisoxazolines.³⁻⁹ According to the reaction mechanism of cyclopropanation, the Cu(I)L* complex of 1:1 metalto-bisoxazoline stoichiometry represents the only catalytically active species enabling formation of a highly reactive bisoxazoline Cu(I)-carbene complex, which then reacts with styrene.¹⁰ However, we have recently shown that an equilibrium between ML* and ML₂* [M = Cu(I) or Ag(I)] bisoxazoline complexes in acetoni-trile exists with $K_{eq} \approx 10^5 \text{ M}^{-1}$ and $\approx 10^4 \text{ M}^{-1}$, respec-tively.¹¹ This observation suggests that during the catalytic cyclopropanations catalysed by Cu(I)L*, the complex $Cu(I)L_2^*$ could be present in a substantial amount. The latter complex having Cu(I) coordinated with four nitrogens of the two bisoxazoline ligands must be catalytically inactive. Hence, in the case of the enantiomerically nonpure bisoxazoline ligand two homochiral Cu(I)L₂* complexes and also the heterochiral meso-Cu(I)L₂* could be formed (Scheme 2), all being catalytically inactive. Consequently, the occurrence of a (+)-NLE could be expected. To the best of our knowledge, the observation of NLE in cyclopropanations catalysed by chiral Cu(I)-bisoxazoline complexes has not been reported to date. In the context of NLEs, this reaction appears particularly interesting since two chiral diasteromeric products are formed and identical NLE's should be observed for both cis- and trans-products. In a single somewhat related example, Dalko, Cossy and co-workers¹² observed a negative nonlinear effect in the cyclopropanation of 1,1-diphenylethene with (-)-menthyl diazoacetate catalysed by the copper

Keywords: Positive nonlinear effect; Asymmetric cyclopropanation; Bisoxazoline.

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Scheme 1. Catalytic asymmetric cyclopropanation of styrene with ethyl diazoacetate and the enantiomeric diphenylbisoxazoline ligands used for preparation of the Cu(I) catalytic complexes.



Scheme 2. Possible formation of the two enantiomeric homochiral and the heterochiral *meso*- $Cu(I)2_2$ complexes.

complexes of chiral 1,2-diaminoethane-derived ligands. The occurrence of (-)-NLE was attributed to the formation of aggregates or participation of two or more ligands in the active complex.

In order to evaluate the (+)-NLE in the cyclopropanation of styrene with diazoacetate we used diphenylbisoxazoline (2)-Cu(I) catalytic complexes prepared by mixing 2 and CuOTf in a 2:1 molar ratio. The stereochemical outcome of the reaction was followed by chiral GC analysis using a Chirasil Dex-CB column. The ee of the (R)-2 ligand was varied from 0% to 100% by mixing it with defined amounts of the (S)-2 enantiomer. Formation of three types of $Cu(I)2_2$ complexes in different ratios may be expected: two enantiomeric homochiral complexes and the heterochiral meso-complex (Scheme 2). According to the theory of NLE, the formation of the homochiral and the heterochiral meso-Cu(I) $\mathbf{2}_2$ complexes, being catalytically inactive, should result from a decrease in the concentration of the catalytically active Cu(I)(S)-2, by an increase of the optical purity of Cu(I)(R)-2 and hence occurrence of (+)-NLE. By changing the ee of (R)-2 from 0% to 100%, the ee's of the diasteromeric *cis*- and *trans*-cyclopropane products 1 changed from 0% to 54% and 0% to 66% (Table 1). The results from Table 1 show that for both diastereo-

Table 1. Enantiomeric excesses^a of *cis*-1 and *trans*-1 versus the ee of the chiral catalyst (R)-2

Entry	(<i>R</i>)-2 % ee	<i>cis</i> -(1 <i>S</i> ,2 <i>R</i>)-1 % ee	<i>trans-</i> (1 <i>S</i> ,2 <i>S</i>)- 1 % ee
1	0	-3	0
2	10	7	12
3	20	25	35
4	30	38	49
5	40	44	59
6	50	47	61
7	60	49	63
8	70	51	67
9	80	51	65
10	90	52	67
11	100	54	66

^a Estimated experimental error \pm 5% due to small overlap of the GC peaks for the *trans*-1 enantiomers.



Figure 1. Relationship of normalised ee's of *trans*-1 (\blacksquare) and *cis*-1 (\bigcirc) versus % ee of (*R*)-2 showing identical (+)-NLE's for both diasteromers of 1.

mers of a 1, higher ee's were obtained than those calculated for the linear ee 1 versus ee (R)-2 relationship. Hence, a clear positive NLE is observed (Fig. 1). The *cis*-1/*trans*-1 diastereoselectivity in all cases was 30:70 and the chemical yields were in the range of 87–98%.

The observation of (+)-NLEs is in accordance with the formation of the catalytically inactive meso-Cu(I) 2_2 complex. Since the optical purity of the catalytic Cu(I)(R)-2 complex influences the enantioselectivity and not the diastereoselectivity of reaction, the magnitudes of the (+)-NLEs should be the same for both diastereomers of 1. As shown in Figure 1, the normalised ee's of trans- and cis-1 versus optical purity of (R)-2 show identical curves within the experimental error. This result is of significance demonstrating for the first time that identical (+)-NLEs are obtained for two diasteromeric chiral products formed in a single reaction step. Desimoni and co-workers¹³ performed Diels-Alder and 1,3-cycloaddition reactions catalysed by zinc and magnesium complexes of 2, respectively. Only in the case of zinc complex the (+)-NLE was observed. The effect was explained by the formation of a stable heterochiral meso-Zn(II) 2_2 complex; its X-ray structure is analogous to that of the proposed meso-Cu(I) 2_2 complex shown in Scheme 2.

In conclusion, we report the first observation of a (+)-NLE in the cyclopropanation of styrene with ethyl diazoacetate catalysed by Cu(I)–bisoxazoline–2 catalytic complex. Experimental evidence shows that the nonlinear effects are identical within experimental error for both chiral diastereomeric products, *cis*- and *trans*-1.¹⁴ The occurrence of a (+)-NLE is explained by the formation of two catalytically inactive enantiomeric Cu(I)2₂ complexes and by one inactive heterochiral *meso*-Cu(I)2₂ complex, the latter being responsible for the occurrence of the (+)-NLE.

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- 14. To a 1,2-dichloroethane solution (1 mL) of styrene (0.26 g; 2.5 mmol), CuOTf·1/2 PhMe (2.6 mg; 0.01 mmol) and 2 (6.7 mg; 0.02 mmol) of defined optical purity 0.5 mL of a 1 M ethyl diazoacetate solution in 1,2-dichloroethane was slowly added under argon at room temperature over 4 h using a syringe pump. Samples were taken and analysed by chiral GC using a Chirasil Dex-CB column.