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Enantioselectivity in cyclopropanation catalyzed by Cu(I) complexes increased by π stacking of two monodentate oxazoline ligands

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Abstract

Cu(I) complexes of monodentate ligands *R*-2,4-diphenyloxazoline (**1**) and *R*-2-isopropyl-4-phenyloxazoline (**2**) exhibit significant increase of enantioselectivity in cyclopropanation of styrene versus ligands **3–6**, indicating participation in the catalytic cycles of conformationally distinguishable 2:1 (ligand/Cu) complexes, stabilized by π stacking of phenyl groups on the chiral centre.

Keywords: Monodentate ligands; Oxazoline ligands; π stacking; Cyclopropanation; Enantioselectivity

1. Introduction

Monodentate chiral nitrogen ligands are regularly less effective in the control of the stereochemical outcome of the reactions catalyzed by their metal complexes than the bidentate or tridentate ones. The bidentate, oxazoline ring containing nitrogen ligands with C_2 symmetry are particularly effective in enantioselective catalytic cyclopropanation [1–7], hydrogen transfer [5], palladium-catalyzed allylic alkylations [5,7] and Diels–Alder reactions [8]. To our best knowledge, there is no report about the catalytic activity of the complexes of chiral monodentate, oxazoline ring containing ligands. Assuming that two molecules of suitably substituted monodentate oxazoline ligands possessing π stacking properties [9], bound to the central metal ion, can adopt a helical arrangement which could increase the enantiodifferentiating ability of the complex so as to achieve efficiencies similar to that of catalytic complexes with bidentate C_2-symmetric ligands [1–8].

In order to prove this concept we prepared the oxazolines **1–6** and examined their Cu(I) complexes in the cyclopropanation reaction of styrene with diazoacetate according to the known procedure [6,10], and compared to the

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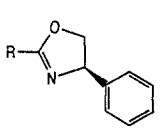
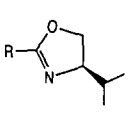
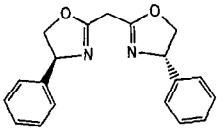
results reported for the C_2-symmetric ligand **7** [4,5].



1 R = Ph
2 R = *i*-Pr
3 R = *t*-But
4 R = 3,5-$(OMe)_2$Ph



5 R = Ph
6 R = *i*-Pr



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2. Experimental

2.1. General

Gas chromatographic analyses were performed by a Hewlett-Packard 5890 chromatograph using nitrogen as a carrier gas. Chiral column CP-Chirasil-DEX CB (25 m × 0.25 mm I.D., Chrompack) was used for separation of enantiomeric *cis* and *trans*-2-phenylcyclopropane carboxylic acid ethyl esters. Characterization of the stereoisomeric products was performed by cyclopropanation with C_2-symmetric ligand (4*S*,4*S*′)-4,4′-diisopropyl-2,2′-methylenebisoxazoline, and determination of the elution order as described by Löwenthal and Masamune [4], and Evans et al. [6]. The elution order was as follows: R_t *cis*-(*1S,2R*) < *cis*-(*1R,2S*) < *trans*-(*1R,2R*) < *trans*-(*1S,2S*).

2.2. Synthesis of ligands

The oxazoline derivatives **1–6** were prepared starting from *R*-phenylglycinol and *R*-valinol, via corresponding β-hydroxyalkylamides which were treated with thionyl chloride and submitted to the base-induced cyclization [5]. All ligands and their precursors have been characterized by IR, ^{1}H- and ^{13}C-NMR spectra. Synthetic studies will be published separately.

2.3. Catalytic cyclopropanation with Cu(I) complexes of 1–6

Ligands **1–6** have been examined in the cyclopropanation of styrene with ethyl diazoacetate, catalyzed by the in situ formed Cu(I) complexes following described procedures [6,10].

To an excess of styrene (0.52 g, 0.57 ml, 5.0 mmol) were added the precatalytic copper (I) trifluoromethanesulphonate benzene complex (15 μmol, available from Fluka) and the corresponding quantity of chiral oxazoline ligand (Table 1). Afterward, alkyl diazoacetate (1 mmol, i.e. 1 ml of the 1 M solution in 1,2 dichlorethane) was added dropwise by a syringe pump over a period of 4.5 h. The reaction was carried out by stirring overnight under an inert argon atmosphere, at room temperature. Diastereomeric mixture of *cis/trans* alkyl 2-phenylcyclopropan-1-carboxylates was isolated on a silica gel column (1 × 15 cm) with ethyl acetate–light petroleum (gradient 0–10%) as eluent. Diastereomeric composition and chemical yield were determined by gas chromatography

Table 1
Enantioselectivity in cyclopropanation of styrene with ethyl diazoacetate catalyzed by Cu(I) complexes of **1–7**

Ligand	Ligand/Cu	Yield (%)	*cis/trans*	*cis* (ee %) [a]	*trans* (ee%) [a]
–	0 [b]	59	53/47	0	0
1	1.0:1	86	38/62	7 (*1S,2R*)	10 (*1S,2S*)
	1.3:1	80	37/63	6 (*1S,2R*)	25 (*1S,2S*)
	2.0:1	84	38/62	5 (*1S,2R*)	38 (*1S,2S*)
	3.0:1	71	38/62	5 (*1S,2R*)	38 (*1S,2S*)
	5.0:1	32	37/63	7 (*1S,2R*)	32 (*1S,2S*)
	∞ [c]	ca. 1	41/59	6 (*1R,2S*)	5 (*1S,2S*)
2	1.0:1	81	32/68	1 (*1S,2R*)	1 (*1S,2S*)
	1.3:1	76	35/65	4 (*1S,2R*)	4 (*1S,2S*)
	2.0:1	63	35/65	19 (*1S,2R*)	18 (*1S,2S*)
	3.0:1	61	35/65	19 (*1S,2R*)	17 (*1S,2S*)
	5.0:1	49	36/64	12 (*1S,2R*)	12 (*1S,2S*)
	∞ [c]	ca. 1	37/63	0	1 (*1R,2R*)
3	2.0:1	37	37/63	0	1 (*1R,2R*)
4	2.0:1	76	38/62	0	4 (*1R,2R*)
5	2.0:1	74	37/63	7 (*1R,2S*)	4 (*1R,2R*)
6	2.0:1	76	38/62	1 (*1R,2S*)	4 (*1R,2R*)
7 [4]	1:1	81	30/70	52 (*1R,2S*)	60 (*1R,2R*)

[a] The ee's are the average values of at least two experiments that differ for ca. ±1%, as determined by GLC chiral capillary column CP-Chirasil-Dex CB (25 m×0.25 mm I.D.), reaction time: 24 h.
[b] Experiments were performed in the absence of the ligand.
[c] Experiments were performed in the presence of 3 mol% of the ligand and in the absence of Cu(I) ions.

on the HP-1 capillary column with biphenyl as an internal standard.

3. Results and discussion

Six structurally related monodentate ligands (**1–6**), derivatives of 4*R*-phenyloxazoline (**1–4**) or 4*R*-isopropyloxazoline (**5**, **6**), exhibited notably different behaviour in enantioselective cyclopropanation. In spite of low to medium enantioselectivities, their dependence on the L/Cu ratio, and the opposite direction of induction obtained by the ligands **1**, **2** and **3–6** indicate different absolute conformations of their catalytic complexes. The results presented in Table 1 reveal that ligand **1** affords *cis* isomer of 2-phenylcyclopropane-1-carboxylic acid ethyl ester with low enantioselectivity, which does not change with the L:Cu molar ratio, whereas using ligand **2** the enantioselectivity changes significantly, reaching 19% ee at the 2–3:1 L/Cu molar ratio. For the *trans* isomer, however, with both ligands **1** and **2** the achieved enantioselectivities reaches 38% ee and 18% ee, respectively, at the 2–3:1 L/Cu molar ratio. Complexes of **3–6** exhibited very low enantioselectivities for both diastereomers at all examined molar ratios of the ligand.

The last runs for **1** and **2** in Table 1 confirm the requirement for chiral catalytic species in these reactions, small asymmetric induction by chiral medium can be noticed at an extremely low rate.

The above results indicate that ligands **1**, **2** can form catalytic complexes with 2:1 stoichiometry. The enantioselectivity of *trans*-cyclopropanation with the complex of **1** approaches the values obtained with **7**, for which bidentate nature and C_2 symmetry of Cu(I) complex is firmly established [1,2], and C_2 symmetry of 2:1 complex of (**1**, **2**):Cu can be assumed. Due to the dissociative ligand-exchange process known for polydentate nitrogen ligands, two monodentate ligands which bind under self-assembling into 2:1 complex could exert nearly the same overall stability as the bidentate ligand with relatively high 'first arm' dissociation constant [11]. 3D molecular model of catalytic complex of **1** with 2:1 stoichiometry, as outlined in Fig. 1 [12], shows overlapping two phenyl groups at the chiral centre. Coplanarity of C(2) phenyl groups and oxazoline ring is presumably maintained in the catalytic complex, though the energy lost for perturbed coplanarity could be estimated to only ca. 2.4 kcal/mol [13], whereas the energy gain by π stacking in **1** and **2** should be well above this value [14]. This indicates that dimeric mode of binding for **1** and **2** in the 2:1 catalytic Cu(I) complex is stabilized by the π stacking of the two phenyl groups on the chiral centre, affording nearly C_2 symmetric arrangement in the inner sphere of the complex. Similar topology was found in efficient catalysts with the C_2 symmetric bidentate ligands described by Pfaltz [1,2], Masamune [4] and Evans [6]. A molecular model of the C_2 symmetric ligand **7**, according to data in Ref. [2] is also presented in Fig. 1. An almost total absence of enantioselectivity with ligands **5** and **6** additionally proves the impor-

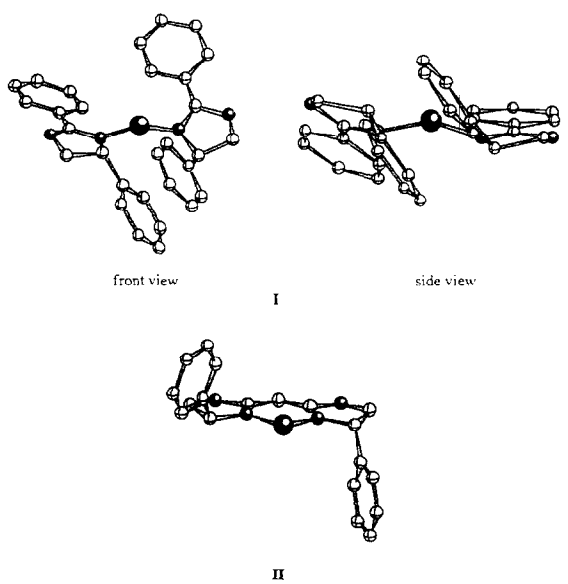

Fig. 1. 3D molecular models of Cu(I) dimeric complex of ligand **1** (**I**) and monomeric complex of ligand **7** (**II**), according to data in Ref. [2].

tance of the stacking of the phenyl group on the chiral C(4) atom. Considering the fact that ligands **1**, **2** and **7** have opposite configurations on the chiral C(4) atom, the opposite enantioselectivity for both isomers in the cyclopropanation reaction is obtained, Table 1. The higher enantioselectivity obtained with **7** as compared to **1** and **2** indicates deviation of the 2:1 complexes from the ideal C_2-symmetric ('fence') arrangement adopted by **7** [2,4,5]. This relation is emphasized by the side view projection of **I** as compared to **II**, Fig. 1. Almost total absence of enantioselectivity with ligands **3** and **4** can be explained by the hindrance to dimerization by the bulky groups on C(2).

Highly relevant to our results is the observed inversion of enantioselectivity, caused by different conformations of two structurally similar catalytic species, recently reported for asymmetric addition of hydrogen cyanide to aldehydes catalyzed by two chiral derivatives of diketopiperazine [15,16]. Two groups on the chiral centre in diketopiperazines, phenylmethyl and isopropylmethyl, are structurally closely related to phenyl and isopropyl in **1** and **5**. In the reported case the origin of the opposite enantioselectivity is also proved to result from different $\pi-\pi$ interactions between diketopiperazine and the aromatic groups, stabilizing two catalytic species with opposite conformations [17].

4. Conclusion

Our preliminary results indicate that 2:1 ligand/Cu(I) complexes exist as catalytic species when an excess of mononitrogen ligand is used. Such complexes possess chiral topology that determines enantioselective bias and raises the enantiomeric excess to a value comparable to that obtained with to 1:1 complex of C_2 symmetric bidentate ligand. Properly designed chiral monodentate nitrogen ligands, possessing even stronger 'outer-sphere interaction' than π stacking between two benzene rings, e.g. coulombic interactions between two charged groups or $\pi-\pi$ interaction between polycondensed (hetero)aromatics, could additionally stabilize the 2:1 L/Cu(I) complexes of pseudo C_2 symmetry. Their thermodynamic stability or reactivity needs to be sufficiently high to provide an efficient chirality transfer in the catalytic step. At present our efforts are focused on the design and synthesis of such nitrogen ligands.

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