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Remarkable cumulative stereoselectivity in cyclopropanation with supramolecular Cu(I) catalytic complexes

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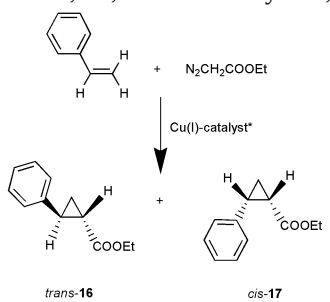
Supramolecular Cu(I) catalyst 1 exhibited 77% cumulative (dia- and enantio-) stereoselectivity and one of the highest diastereoselectivities (86% de) obtained to date in the cyclopropanation of styrene with ethyl diazoacetate.

Enantioselective transformations based on the use of chiral organometallic catalysts present one of the most important strategies for production of enantiomerically pure compounds.[1,2] On the other hand, extensive development of supramolecular chemistry enabled syntheses of the cavity-containing receptor molecules capable of binding and recognition of selected substrate molecules.[3,4] Design of cavity-containing supramolecular catalysts with a built in organometallic catalytic center presents an attractive but until now lesser explored possibility.[5]

Here we describe the first approach to a chiral supramolecular catalyst for enantioselective cyclopropanation. In the classical cyclopropanation of styrene with ethyl diazoacetate (Scheme 1), chiral bidentate bisoxazoline–Cu(I) catalytic complexes possessing C_2-symmetry are most frequently used.[2a–d] The cumulative stereochemical outcome of the reaction is evaluated by ee and de of the formed cyclopropanes. While with some catalysts very high enantioselectivity (more than 90% ee) is achieved, diastereoselectivity is usually low to medium, in the range 40–50% de. Our new strategy toward supramolecular catalysts for cyclopropanation is based on the design of cavity-containing ligands with a built-in bisoxazoline unit (Fig. 1). Since the bridge connects two centers of C_2-symmetric bisoxazoline unit, a certain degree of helicity is induced to the bridge. According to the proposed reaction mechanism of bisoxazoline–Cu(I) catalyzed cyclopropanations, a cyclopropane ring forms by the electrophilic attack of Cu(I) bound carbene to prochiral alkene.[6] Consequently, with a macrocyclic supramolecular catalyst of sufficient size, the reaction should occur inside the helical cavity. In this way, the local C_2 chirality at the metallic center is to a certain degree extended to the reaction space defined by the size of the cavity. Compared to classical acyclic bisoxazoline–Cu(I) catalysts, this strategy offers the advantage of stereochemically more defined catalyst topology beyond the catalytic site that could result in the improved diastereo- and enantioselectivity of the cyclopropanation reaction.

To test this hypothesis, the macrocyclic ligands **1**–**4** (Scheme 2, **1**–**4** obtained in 29, 27, 49 and 25% yields, respectively),



trans-**16** *cis*-**17**

Scheme 1 Cyclopropanation of styrene with ethyl diazoacetate catalysed by chiral bisoxazoline–Cu(I) complexes.

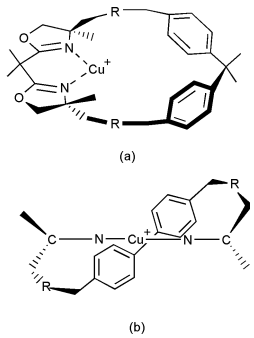


Fig. 1 General structure of C_2-symmetric supramolecular Cu(I) catalyst (*a*); helicity of the macrocycle connecting stereogenic centers of the bisoxazoline unit (*b*).

possessing different sizes of the macrocyclic ring, have been prepared and their Cu(I) complexes used in cyclopropanation of styrene with diazoacetate.[7]

The enantio- and diastereoselectivities obtained in the cyclopropanations with Cu(I) complexes of the macrocyclic ligands **1**–**4** at two standard ligand/Cu(I) ratios,[2b] are collected in Table 1 and compared to those obtained with the Cu(I) complexes of the acyclic bisoxazoline ligands **14** and **15**.[2b] It turns out that the complexes of the two smallest macrocyclic ligands, **1** and **2**, exibit the highest diastereoselectivity (86% de for **1**) and enantioselectivity (81% ee for **2**) affording nearly the same cumulative stereoselectivity (75–77%). For the two larger macrocycles **3** and **4** both de and ee dropped; for the former de is somewhat higher (50–54% de) than for the latter (42% de), whereas ee in both cases remains quite similar (66–68%). As compared to acyclic precursor **14**, however, the cumulative stereoselectivity for the *trans*-**16** isomer obtained with **1** and **2** is 20% higher than that for **14** (57–58%) and also higher than that obtained with the best bisoxazoline in the acyclic series, ligand **15**[2b] (69–70%). The cumulative stereoselectivity increase for **1**–**4** shows clear dependence on the size of the macrocycle cavity being the lowest for the most flexible, **4**, and the highest for the most rigid, **1**. In the series acyclic **14**–macrocyclic **4** to **1** the remarkable increase of de from 38 to 86% is observed. Interestingly the ee's in the series are rather similar (65–68%) except for the peak value for **2** (81%). These results reveal the importance of the catalyst topology for the diastereoselectivity outcome of the reaction and show the advantage of macrocyclic over acyclic catalysts. The exceptional diastereoselectivity observed for the **1**–Cu(I) catalyst can be explained by high degree of stereoselection induced by the helicity of the bridge which strongly favors formation of *trans*-**16** over *cis*-**17** (Fig. 2).

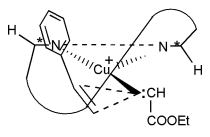


Fig. 2 Schematic presentation of helical topology and *trans*-position of the larger groups of reactants in the **1**–Cu(I) carbene catalytic complex reaction with styrene.

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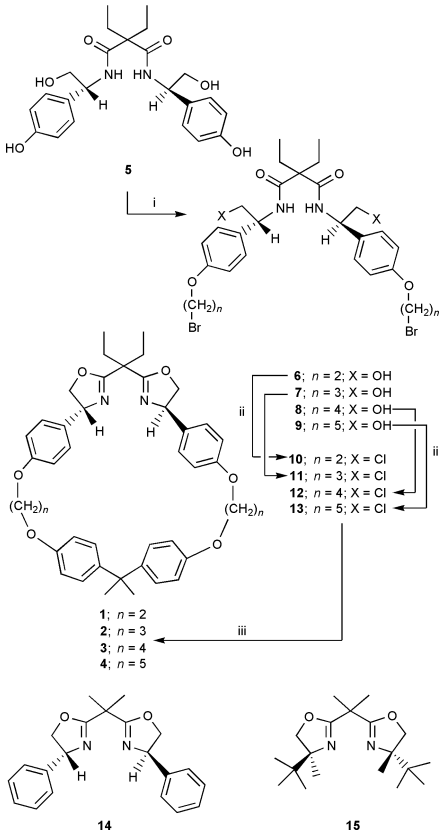
Table 1 Cyclopropanation reaction of styrene with ethyl diazoacetate in 1,2-dichloroethane solution catalysed by macrocyclic **1**–**4**- and **14**, **15**-Cu(I) complexes

Ligand	Ligand/Cu(I)	Yield[a]	*cis*-**17**–*trans*-**16** ratio[b]; (de %)	*cis*-**17**[b] ee %	*trans*-**16**[b] ee %	Cumulative stereoselectivity[c] (%)
1, *n* = 2	1.2	58	7:93; (86)	60.0 (1*S*,2*R*)	65.1 (1*S*,2*S*)	77
	2.0	55	7:93; (86)	59.4 (1*S*,2*R*)	65.0 (1*S*,2*S*)	77
2, *n* = 3	1.2	55	17:83; (66)	70.1 (1*S*,2*R*)	80.5 (1*S*,2*S*)	75
	2.0	58	16:84; (68)	72.9 (1*S*,2*R*)	81.3 (1*S*,2*S*)	76
3, *n* = 4	1.2	54	25:75; (50)	51.0 (1*S*,2*R*)	66.1 (1*S*,2*S*)	62
	2.0	57	23:77; (54)	53.5 (1*S*,2*R*)	68.7 (1*S*,2*S*)	65
4, *n* = 5	1.2	67	29:71; (42)	60.5 (1*S*,2*R*)	66.5 (1*S*,2*S*)	59
	2.0	62	29:71; (42)	62.3 (1*S*,2*R*)	67.7 (1*S*,2*S*)	59
14	1.2	77	30:70; (40)	54.0 (1*S*,2*R*)	64.8 (1*S*,2*S*)	58
	2.0	79	31:69, (38)	54.2 (1*S*,2*R*)	65.3 (1*S*,2*S*)	57
15	1.2	75	28:72; (44)	95 (1*R*,2*S*)	96 (1*R*,2*R*)	70
	2.0	80	29:71; (42)	95 (1*R*,2*S*)	96 (1*R*,2*R*)	69

[a] Isolated, not optimised yields. [b] Determined by chiral GC analysis, using Chirasil Dex-CB column. [c] Cumulative (diastereo- and enantio-) selectivity calculated in % of (1*S*,2*S*)-*trans*-**16** and (1*R*,2*R*)-*trans*-**16** formed in catalytic reactions by using ligands **1**–**4**, **14** and the ligand **15**, respectively.



Scheme 2 (i) $Br(CH_2)_nBr$ (*n* = 2-5); K_2CO_3,MeCN; (ii) $(Cl_3CO)_2CO$; PPh_3, CH_2Cl_2 or $SOCl_2$; (iii) Cs_2CO_3, MeCN. Structures of the reference ligands **14** and **15**. All prepared compounds have correct spectroscopic and elemental analysis data.

In conclusion, we report on the synthesis of the first supramolecular Cu(I) catalysts comprising macrocyclic ligands **1**–**4** and their application in stereoselective cyclopropanations of styrene with ethyl diazoacetate. The macrocyclisation principle used with such catalysts which produced the highest cumulative stereoselectivity in cyclopropanations reported to date could be of general value considering variety of catalytic transformations based on C_2-symmetric organometallic ligands.[1,2] Our work on the cavity-tuning of the supramolecular Cu(I) catalysts, and their applications in other catalytic enantioselective reactions is in progress.

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