

Solvent and counterion effects in the asymmetric cyclopropanation catalysed by bis(oxazoline)–copper complexes

José M. Fraile, José I. García, José A. Mayoral^{*}, Tibor Tarnai

Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Universidad de Zaragoza-C.S.I.C., Pedro Cerbuna 12, E-50009 Zaragoza, Spain

Received 8 July 1998; accepted 13 October 1998

Abstract

The reaction of styrene with ethyl diazoacetate, promoted by the complexes of two bis(oxazolines) with Cu(I) and Cu(II) salts (chloride and triflate), was studied in CH_2Cl_2 and nitroethane. The use of nitroethane reduces the selectivity with regard to the diazoacetate, and also slightly reduces the *trans/cis* selectivity. In the reactions carried out with triflates the use of nitroethane gives rise to a slight decrease in the enantioselectivity, whereas the reverse is true for copper chlorides. The influence of the solvent and the counterion on the enantioselectivity is explained on the basis of their influence in the disproportionation of Cu(I) to Cu(II) and Cu(0), the latter acting as a non-chiral catalyst. The rate of this side reaction also depends on the structure of the bis(oxazoline) ligand. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Asymmetric cyclopropanation; Chiral homogeneous catalysis; Bis(oxazoline)–copper; Solvent effects; Counterion effects

1. Introduction

Catalytic enantioselective cyclopropanation of olefins is of great interest in organic chemistry due to the role of cyclopropanes as valuable intermediates in organic synthesis and to the frequent presence of these structures in biologically active compounds [1,2]. In this respect, a good number of metal complexes bearing chiral ligands are able to promote the transfer of carbene from diazo compounds to alkenes, through metal–carbene complexes, with high enantioselectivities (for a recent review, see Ref. [3]).

Bis(oxazoline)–copper complexes are among the best catalysts for this kind of reaction [4–6], and enantiomeric excesses of up to 99% have been reported.

Recently we have shown [7] that cationic bis(oxazoline)–Cu(II) complexes, supported by cation exchange into clays, are efficient heterogeneous catalysts for these reactions. The solvent used to carry out the cationic exchange has a noticeable influence on the results of the reaction, the best being obtained using nitroethane. It has also been reported that the use of nitromethane and nitroethane leads to significant improvement in the catalytic properties of bis(oxazoline)–Cu(II) complexes in a hetero-Diels–Alder reaction [8]. The role of nitroethane

^{*} Corresponding author. Tel./Fax: +34-976762077; E-mail: mayoral@posta.unizar.es

in the clay-catalysed reactions may be related to the creation of microenvironments of this solvent surrounding the cationic complexes in the clay. We therefore considered it of interest to assess the influence of this solvent, as compared with methylene chloride, in the benchmark reaction of styrene (**1**) with ethyl diazoacetate (**2**), promoted by bis(oxazoline)–copper complexes under homogeneous conditions.

2. Experimental

The appropriate copper salt (0.25 mmol) was added to a solution of bis(oxazoline) (0.25 mmol) in the appropriate solvent (10 ml) under argon and the mixture was stirred for 15 min. After this time, styrene (2.5 mmol) and *n*-decane (500 mg) in 15 ml of the same solvent was added, and then ethyl diazoacetate (1.25 mmol) was added during 2 h using a syringe pump. The reaction was monitored by gas chromatography and, after the consumption of the diazoacetate, a second portion of this reagent was added in the same way. When the CuCl_2 had been used, the solution of the complex was heated at 40°C for several minutes with a few drops of ethyl diazoacetate, prior to the addition of styrene.

The results of the reactions were determined by gas chromatography. FID from Hewlett-Packard 5890-II; cross-linked methyl silicone column: 25 m \times 0.2 mm \times 0.33 μm ; helium as carrier gas, 20 p.s.i.; injector temperature: 230°C; detector temperature: 250°C; oven temperature program: 70°C (3 min), heat at 15°C min^{-1} to 200°C (5 min); retention times: ethyl diazoacetate (**2**) 4.28 min, styrene (**1**) 5.03 min, *n*-decane 6.93 min, diethyl fumarate 8.73 min, diethyl maleate 9.04 min, **6**, **7** 9.38 and 9.54 min, *cis*-cyclopropanes (**5**) 11.84 min, *trans*-cyclopropanes (**4**) 12.35 min.

The asymmetric inductions of the reactions were also determined by gas chromatography. FID from Hewlett-Packard 5890-II, Cyclodex B column: 30 m \times 0.25 mm \times 0.25 μm ; helium as

carrier gas, 20 p.s.i.; injector temperature: 230°C; detector temperature: 250°C; oven temperature program: 125°C isotherm; retention times: (1*S*,2*R*)-cyclopropane (**5b**) 28.9 min, (1*R*,2*S*)-cyclopropane (**5a**) 29.8 min, (1*R*,2*R*)-cyclopropane (**4a**) 34.3 min, (1*S*,2*S*)-cyclopropane (**4b**) 34.9 min. The peaks were assigned to the corresponding enantiomers by comparison with previously described results [6]. The *cis* and *trans* stereochemistry was assigned by comparison of the peak ratios with those obtained with the non-chiral column.

3. Results and discussion

Table 1 shows the results obtained in the reaction of styrene (**1**) with ethyl diazoacetate (**2**) catalysed by bis(oxazoline)–Cu(I) and Cu(II) complexes, using two different counterions (Scheme 1), in methylene chloride and nitroethane.

As can be seen, the use of Cu(II) or Cu(I) does not have a significant influence on the reaction results. Although Cu(I) is the active species, it is known that Cu(II) is reduced to Cu(I) by diazoesters. This reduction is confirmed by the disappearance of the UV–VIS band at a λ_{max} near to 730 nm, which corresponds to the d–d transition [9]. Given the small proportion of catalyst used, the only effect of using Cu(II) is, in some cases, a slight decrease in the selectivity with regard to diazoacetate. The effects of the solvent and the counterion are far more important, and there is a close relationship between the nature of the ligand, the counterion and the solvent.

With $\text{Cu}(\text{TfO})_2$ the replacement of CH_2Cl_2 by nitroethane leads to a slight decrease in both the *trans/cis* and the enantioselectivities, and to a marked decrease in the selectivity with regard to diazoacetate (56 to 18% with **3a** and 53 to 14% with **3b**). Given that the amount of maleate and fumarate formed does not depend on the solvent used, the lower selectivity with regard to diazoacetate may be due to the forma-

Table 1
Results obtained in the reaction of styrene (**1**) with ethyl diazoacetate (**2**)

Ligand	CuX _n	Solvent	1:2	<i>t</i> (h)	% Conversion ^a (styrene)	% Selectivity (1) ^a	% Selectivity (2)	4:5 ^b	% ee 4 ^{b,c}	% ee 5 ^{b,c}
3a	CuTfO	CH ₂ Cl ₂	2	2	32	86	55	2.1	69	63
			1	7	73	79	58	2.0	65	59
3a	Cu(TfO) ₂	CH ₂ Cl ₂	2	2	34	83	56	2.1	62	56
			1	7	69	85	58	2.1	59	53
3a	Cu(TfO) ₂	EtNO ₂	2	2	10	90	18	2.0	57	48
			1	7	19	89	17	1.8	55	45
3a	CuCl	CH ₂ Cl ₂	2	5	7	82	12	2.6	4	6
			1	21	18	81	14	2.7	2	4
3a	CuCl	EtNO ₂	2	5	12	43	11	1.8	37	35
			1	7	14	88	13	1.8	35	32
3a	CuCl ₂	CH ₂ Cl ₂	2	5	13	48	12	2.4	5	8
			1	21	24	60	15	2.5	5	3
3a	CuCl ₂	EtNO ₂	2	5	5	60	6	1.7	47	42
			1	8	16	70	11	1.8	46	41
3b	CuTfO	CH ₂ Cl ₂	2	2	42	84	70	2.5	94	92
			1	7	89	82	72	2.4	94	91
3b	Cu(TfO) ₂	CH ₂ Cl ₂	2	2	36	74	53	2.4	90	87
			1	7	81	75	61	2.4	91	88
3b	Cu(TfO) ₂	EtNO ₂	2	2	17	41	14	2.1	80	77
			1	7	22	61	13	2.1	78	74
3b	CuCl	CH ₂ Cl ₂	2	5	18	73	27	2.3	3	8
			1	21	40	74	29	2.4	3	7
3b	CuCl	EtNO ₂	2	5	10	74	14	2.0	26	25
			1	21	21	75	16	2.0	13	12
3b	CuCl ₂	CH ₂ Cl ₂	2	5	18	60	22	2.2	2	7
			1	21	33	74	24	2.3	2	7
3b	CuCl ₂	EtNO ₂	2	5	13	72	19	2.2	18	17
			1	21	22	89	20	2.2	5	4

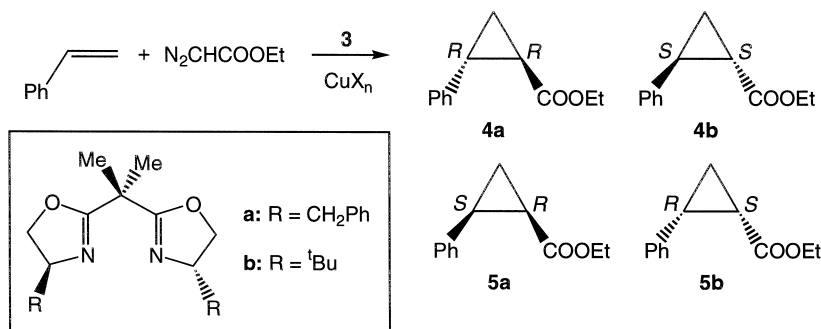
^a Determined by gas chromatography using *n*-decane as the internal standard.

^b Determined by gas chromatography.

^c **4a** and **5a** are the major enantiomers.

tion of some other by-products. These solvent effects are observed with both ligands, **3a** and

3b, but the influence of the solvent on the enantioselectivity is more noticeable with **3b**.



Scheme 1.

solution has a red–brown colour due to colloidal Cu(0) from the outset of the reaction, and the Cu(0) promotes the non-asymmetric cyclopropanation. This mechanism also accounts for part of the decrease in selectivity with regard to diazoacetate because, in this case, the amount of diazocompound consumed in the reduction of Cu(II) to Cu(I) increases. The use of a polar solvent, such as nitroethane, has the effect of decreasing the rate of disproportionation, and hence a higher enantioselectivity is obtained. However, the side reaction of disproportionation is not completely eliminated and, in the case of **3b**, the asymmetric induction decreases with reaction time. The use of a polar solvent will increase the ionic character of the copper–chloride bond, and this may be the cause of this behaviour. In fact, the use of a less-coordinating counterion, such as triflate, inhibits this undesirable side reaction.

Finally, the rate of disproportionation is also influenced by the structure of the bis(oxazoline) ligand. This process is faster with **3b** than with **3a**, which justifies the surprisingly higher enantioselectivity obtained with **3a** and copper chlorides.

4. Conclusion

It can be concluded that the inhibition of the disproportionation of Cu(I) is of prime importance in obtaining good results in asymmetric

cyclopropanation reactions catalysed by chiral Cu(I) complexes, and that this reaction is not only affected by the nature of the counterion, but also by the nature of the solvent and the chiral ligand.

Acknowledgements

This work was made possible by the generous financial support of the Comisión Interministerial de Ciencia y Tecnología (Project MAT96-1053). One of us (T.T.) acknowledges the Spanish Ministerio de Educación y Cultura for a post-doctoral fellowship.

References

- [1] M. Elliot, A.W. Farnham, N.F. James, P.H. Needham, A. Pulman, J.H. Stevenson, *Nature* 246 (1973) 169.
- [2] D. Arlt, M. Jantelatand, R. Lantzsh, *Angew. Chem., Int. Ed. Engl.* 8 (1981) 719.
- [3] V.K. Singh, A. Datta Gupta, G. Sekar, *Synthesis* (1997) 137.
- [4] R.E. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.* 31 (1990) 6005.
- [5] R.E. Lowenthal, S. Masamune, *Tetrahedron Lett.* 32 (1991) 7373.
- [6] D.A. Evans, K.A. Woerpel, M.M. Hinman, M.M. Faul, *J. Am. Chem. Soc.* 113 (1991) 726.
- [7] J.M. Fraile, J.I. García, J.A. Mayoral, T. Tarnai, *Tetrahedron: Asymmetry* 8 (1997) 2089.
- [8] M. Johannsen, K.A. Jørgensen, *Tetrahedron* 52 (1996) 7321.
- [9] A. Datta Gupta, D. Bhuniya, V.K. Singh, *Tetrahedron* 50 (1994) 13725.
- [10] I. Sagasser, G. Helmchen, *Tetrahedron Lett.* 39 (1998) 261.