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Chiral Imidazoles and Imidazole *N*-Oxides as Ligands for Stereoselective Cyclopropanation Reactions

Grzegorz Mlostoń*,[a], Paulina Mucha[a,[1]] and Heinz Heimgartner*,[b]

[a]*University of Łódź, Department of Organic and Applied Chemistry, Tamka 12, PL-91-403 Łódź, Poland*

[b]*University of Zurich, Institute of Organic Chemistry, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland*

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Abstract: New, optically active ligands derived from imidazole were tested in the cyclopropanation reaction of styrene using ethyl diazoacetate and copper(I) triflate as a catalyst.

Keywords: Cyclopropanation, diazo compounds, imidazole *N*-oxides, styrene.

INTRODUCTION

Cyclopropanation reactions are well known and widely applied in modern organic synthesis [2]. On the one hand, diverse cylopropane derivatives are important building blocks for the preparation of more complex molecules, e.g. natural products [3], and on the other hand, cyclopropanations are frequently used as test reactions in basic research. Special attention is focused on stereoselective formation of the cyclopropane ring, and both diastereoselectivity and enantioselectivity are of interest [4]. A favorite procedure for the examination of new chiral ligands is the metal complex catalyzed cyclopropanation of prochiral olefins with α-diazo compounds. The most popular substrates for these reactions are styrene and its derivatives and α-diazo esters [4e].

In recent times, chiral *N*-heterocycles and their *N*-oxides have attracted attention as ligands for asymmetric synthesis [5]. However, there are only a few reports on the application of imidazoles and imidazole *N*-oxides [6]. In a series of recent papers, we reported on the synthesis of differently substituted, optically active, 2-unsubstituted imidazole 3-oxides and their conversion into other imidazole derivatives, *e.g.* imidazole-2-thiones [7]. To the best of our knowledge, neither imidazoles nor their *N*-oxides have been used in asymmetric cyclopropanation.

The goal of the present study was to test selected bis-imidazoles and the corresponding *N,N′*-dioxides, derived from enantiomerically pure *trans*-1,2-diaminocyclohexane, as ligands in the Cu(I)-catalyzed reaction of styrene with ethyl diazoacetate (EDA).

RESULTS AND DISCUSSION

The preparation of the chiral ligands **1**-**4** (Fig. (**1**)) has been reported previously [7].

The first cyclopropanation reaction, in which styrene and EDA in a ratio of 4:1 were reacted in the presence of Cu(I) triflate as a catalyst, was carried out at room temperature without the addition of a ligand. The progress of the reaction was monitored by IR spectroscopy and the disappearance of the strong diazo absorption at 2111cm^{-1} evidenced the completion of the reaction. The mixture of *trans*- and *cis*-2-phenylcyclopropanecarboxylate **5** was isolated in 60% yield, and the ratio of the *trans*- and *cis*-isomer was established by ^{1}H-NMR spectroscopy as 2:1 (Scheme **1**) (see *e.g.* [8]).

An analogous experiment performed in the presence of catalytic amounts (4 mol % relative to EDA used) of the bis-imidazole 3,3′-dioxide (*S,S*)-**1a** led to a complex mixture of products. The reaction to give the desired cyclopropane derivatives occurred smoothly only in the presence of trace amounts of hydrazine hydrate [9, 10]. After chromatographic workup, the determination of the *ee*-values for *trans*- and *cis*-**5** was carried out by HPLC on a chiral solid phase (Chiralcel OD). This method was applied for all studied ligands (Table **1**).

In general, the diastereoisomeric excess (*de*) observed in the reactions performed in the presence of the chiral ligands **1**-**4** was slightly higher than in their absence.

The highest *de* value (81%) was obtained with (*S,S*)-**1c**. The determined *ee*-values were rather low, but they were higher in the case of *cis*-**5** than in *trans*-**5**. The best induction for *cis*-**5** (94% *ee*) was achieved with the ligand (*R,R*)-**2b**. On the other hand, the highest *ee* of *trans*-**5** (20%) was observed in the reaction with (*S,S*)-**1d**.

Mixtures of isomeric cyclopropanecarboxylates **5** obtained in the presence of catalytic amounts of catalysts (*S,S*)-**1d** and (*R,R*)-**2b**, respectively, were separated and fractions containing analytically pure *trans*-**5** were obtained. In both cases, the optical rotatory power was measured. Whereas in the first case the $[\alpha]_D$ value was +57 (*c* 0.2; $CHCl_3$), in the second case it was –31 (*c* 0.2; $CHCl_3$). Based on the literature data for the optical rotation of (1*S*,2*S*)-*trans*-**5** ($[\alpha]_D$ = +269) and (1*R*,2*R*)-*trans*-**5** ($[\alpha]_D$ = –279) [12], one can conclude that in the experiments with (*S,S*)-**1d** the first enantiomer predominated and, in the case of (*R*,*R*)-**2b** used

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*Address correspondence to these authors at the University of Łódź, Department of Organic and Applied Chemistry, Tamka 12, PL-91-403 Łódź, Poland; Tel: +48 42 635 57 61; Fax: +48 42 665 51 62;
E-mail: gmloston@uni.lodz.pl

University of Zurich, Institute of Organic Chemistry, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland; Tel: +41 44 635 42 82 , Fax: +41 44 635 68 12; E-mail: heimgart@oci.uzh.ch

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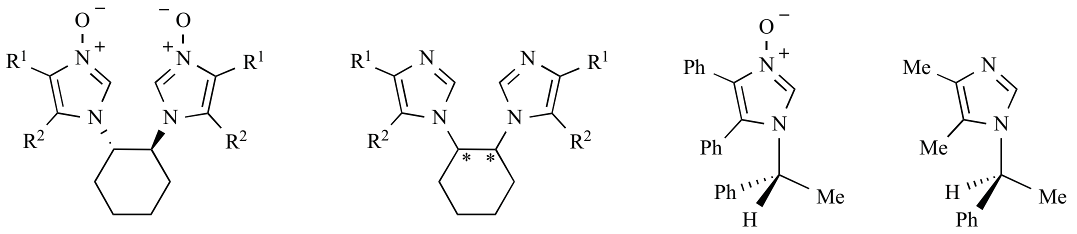


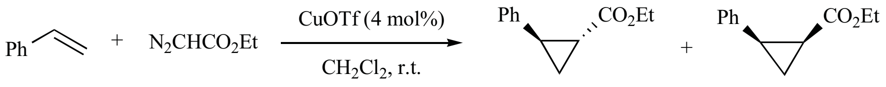
(*S*,*S*)-**1a** R^1 = R^2 = Me
b R^1 = Ph, R^2 = Me
c R^1 = Me, R^2 = Ph
d R^1 = R^2 = Ph

(*R*,*R*)-**2b** R^1 = Ph, R^2 = Me
(*S*,*S*)-**2c** R^1 = Me, R^2 = Ph

(*R*)-**3**

(*S*)-**4**

Fig. (1). Imidazole derived ligands **1-4** used in the study.



trans-**5** *cis*-**5**

Scheme 1. Cyclopropanation of styrene with ethyl diazoacetate (EDA) in the presence of CuOTf.

Table 1. Efficiency of Imidazole Ligands 1-4 in the Cyclopropanation Reaction of Styrene Using Ethyl Diazoacetate

Ligand	Yield [%]	*trans*-5:*cis*-5	*ee trans*-5 [%]	*ee cis*-5 [%]
(*S*,*S*)-**1a**	52	3:1	-	-
(*S*,*S*)-**1b**	34	2.3:1	4	31
(*S*,*S*)-**1c**	60	4.4:1	2	34
(*S*,*S*)-**1d**	50	2:1	20	40
(*R*,*R*)-**2b**	48	2.5:1	14	94
(*S*,*S*)-**2c**	29	2.3:1	8	34
(*R*)-**3**	41	3:1	-	-
(*S*)-**4**	54	3:1	1	4

as a catalyst, the second enantiomer was the major component.

CONCLUSIONS

The cyclopropanation reaction of styrene with EDA in the presence of CuOTf and catalytic amounts of hydrazine was studied in order to test the efficiency of chiral imidazole derivatives as ligands with respect to the stereoselectivity of the process. In comparison with the ‘ligand-free’ reaction, the *de*-value in favour of *trans*-**5** in general increased slightly, and in the case of (*S*,*S*)-**1c** achieved the value of 81%. The influence of the ligands **1-4** on the *ee*-value was modest and only in the case of (*R*,*R*)-**2b** was an attractive result (94%) for the *cis*-isomer obtained. It is very likely that the observed chiral induction in reactions catalyzed by enantiopure ligands derived from imidazole *N*-oxides and imidazole derivatives results from complexation of the Cu(I) salt and formation of a chiral complex, which is incorporated in the structure of the intermediate carbenoide. The structures of some chiral carbenoids have been proposed for metal catalyzed cyclopropanation reactions with diazoacetates and styrene [4e]. To the best of our knowledge, the presented ligands are the first imidazole derivatives tested in the cyclopropanation reaction. In spite of the relatively modest selectivities observed, the presented results are encouraging for further modifications of the substitution pattern in chiral imidazole derivatives.

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[10] **Typical procedure for the synthesis of 5:** A mixture of a bis-imidazole or imidazole ligand **1-4** (0.04 mmol), a drop of hydrazine hydrate, and CuOTf (toluene complex) (0.02 mmol) in CH_2Cl_2 (2 ml), was stirred magnetically at room temperature for 0.5 h. To this solution was added styrene (416 mg, 4 mmol), and stirring was continued for 10 min. From a solution of ethyl diazoacetate (114 mg, 1 mmol) in CH_2Cl_2 (0.5 ml), prepared in a syringe, a few drops were added in order to start the reaction. The mixture was warmed to 40 °C and stirring was continued at this temperature for 0.5 h, and then cooled to ca. 20 °C. The rest of the ethyl diazoacetate solution was added drop-wise within 4 h, and the mixture was stirred overnight. After removing of the solvent under reduced pressure, the crude product was purified by column chromatography (hexane/AcOEt 95:5). Analytically pure isomers of ethyl 2-phenylcyclopropane-1-carboxylate **5** were obtained as colorless oils and their spectroscopic data fitted well with literature data (*e.g.* ref. [11]). **IR** (KBr): ν 3087*w*, 3064*w*, 3030*w*, 2981*w*, 2933*w*, 2908*w*, 2872*w*, 1719*s*, 1603*w*, 1496*w*, 1457*m*, 1412*m*, 1336*m*, 1191*s*, 1078*m*, 1040*s*, 1018*m,* 937*m*, 850*w*, 762*s*, 703*s*, 529*w*. ^{1}**H-NMR** ($CDCl_3$): *trans*-**5**: δ 7.29–7.10 (m, 5H, 5 arom. **H**); 4.18 (q, $J_{\text{H-H}}$ = 7.2, 2H, C**H**$_2$CH$_3$); 2.54–2.51 (m, 1H, **H**C(1)); 1.92–1.89 (m, 1H, **H**C(2)); 1.62–1.59 (m, 1H, **H**C(3)); 1.33–1.27 (m, 1H, **H**C(3)); 1.29 (t, $J_{\text{H-H}}$ = 7.2, 3H, CH$_2$C**H**$_3$). *cis*-**5**: δ7.35–7.08 (m, 5H, 5 arom. **H**); 3.86 (q, $J_{\text{H-H}}$ = 7.2, 2H, C**H**$_2$CH$_3$); 2.72–2.38 (m, 1H, **H**C(1)); 2.20–1.87 (m, 1H, **H**C(2)); 1.80–1.48 (m, 1H, **H**C(3)); 1.42–1.11 (m, 1H, **H**C(3)); 0.95 (t, $J_{\text{H-H}}$ = 7.2, 3H, CH$_2$C**H**$_3$,). ^{13}**C-NMR** ($CDCl_3$): (*trans*)-**5**: δ173.37 (**C**O); 140.12 (1 arom. **C**); 128.48, 126.48, 126.19 (5 arom. **C**H); 60.70 (**C**H$_2$CH$_3$); 26.17 (**C**(2)); 24.17 (**C**(1)); 17.00 (**C**(3)); 14.28 (CH$_2$**C**H$_3$).

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