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Enantioselective Cyclopropanation of Styrene Catalysed by Copper(I) Complexes with Chiral Oxazolines

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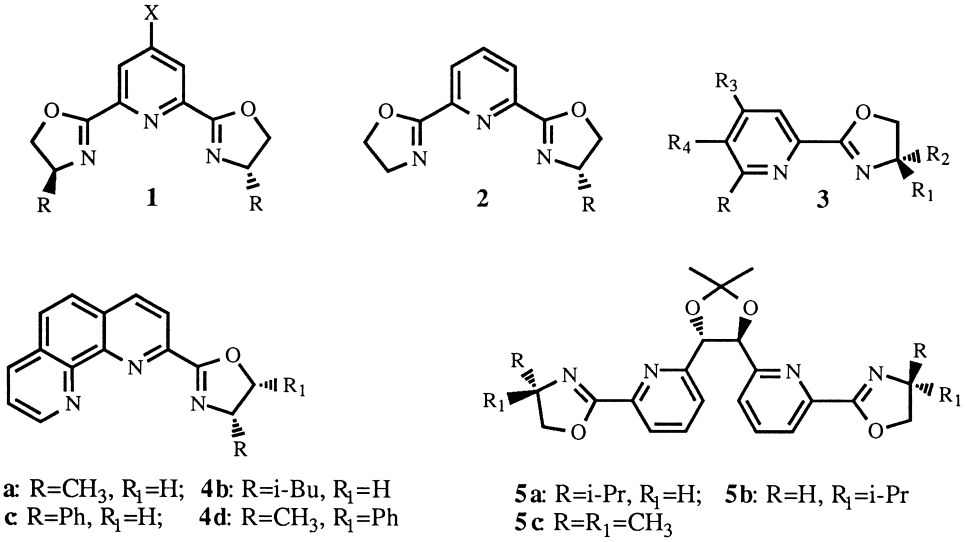
Abstract—A large set of copper complexes, prepared in situ from copper(I)-triflate and a variety enantiopure oxazoline ligands, was assessed as chiral catalysts in the enantioselective cyclopropanation of styrene by ethyl diazoacetate. Enantioselectivities up to 60% and up to 52%, respectively, for *trans*- and *cis*-2-phenylcyclopropanecarboxylate were observed.

Introduction

During the last decade, enantiopure oxazoline ligands have emerged as an effective class of chiral inducers in a wide variety of transition metal catalysed asymmetric processes. High catalytic activities and enantiomeric excesses (e.e.'s) have been obtained in hydrosilylation, allylic alkylation, H-transfer reduction and cyclopropanation, mainly using C_2-symmetric chiral ligands in conjunction with suitable transition metal ions.[1]

Although C_2-symmetric oxazolines usually allow for an improved stereocontrol of the reaction by removing competitive reaction paths which may reduce enantiofidelity,[2] high e.e.'s can be obtained also with ligands devoid of this topology. In the cyclopropanation of olefins by diazoesters, for instance, the Ru(II)-complex with the C_2-symmetry tridentate ligand 2,6-bis(oxazolinyl)pyridine (pybox) **1** is a quite active and enantioselective catalyst,[3] but more recently it has been shown that the unsymmetrical bis(oxazolinyl)pyridine **2** provides similar stereoselection (Scheme 1).[4]

These results stimulated us to investigate the behaviour of



Scheme 1.

Keywords: copper catalysts; asymmetric cyclopropanation; oxazoline ligands.

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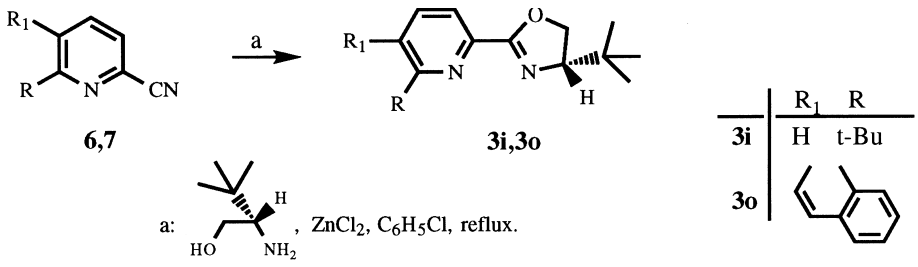


Scheme 2.

C_1-symmetric oxazolinylpyridines **3** in the cyclopropanation of styrene. These ligands are capable of excellent asymmetric inductions in Rh-catalysed hydrosilylation[5] and in the Pd-catalysed allylic substitution reactions.[6] We have further pursued our study to evaluate the utility in this reaction of the potentially tridentate and tetradentate oxazoline derivatives **4** and **5**, respectively.

In this paper we report the results obtained in the application of a set of 28 enantiopure oxazoline derivatives as ligands in copper(I)-catalysed asymmetric cyclopropanation of styrene.

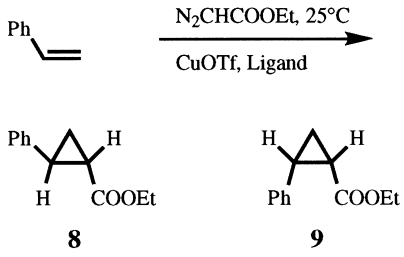
Results and Discussion

Synthesis of the ligands

All but two of the oxazoline ligands used throughout this study were already known and have been prepared according to the procedures reported in the literature. The oxazolinylpyridine **3i** and the oxazolinylphenanthridine **3o** which were not yet known, have been expressly prepared for this study by heating under reflux a chlorobenzene solution of the 2-cyano-6-(1,1-dimethylethyl)pyridine (**6**) or of the 2-cyanobenzo[*h*]quinoline (**7**) with (S)-*tert*-leucinol in the presence of a catalytic amount of zinc chloride[7] (Scheme 2).

Copper(I)-catalysed asymmetric cyclopropanation

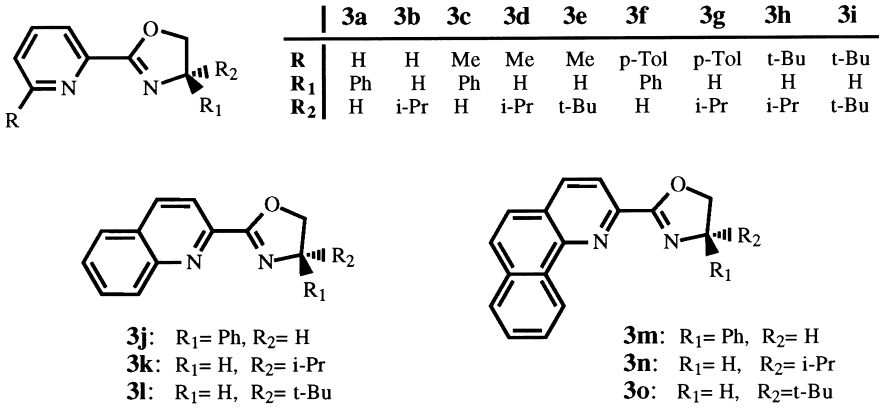
The reaction of styrene with ethyl diazoacetate[8] to give the *trans* and *cis* cyclopropanes **8** and **9** was chosen as the model for the evaluation of the efficiency of these oxazoline ligands in the copper(I)-catalysed asymmetric cyclopropanation of olefins.



The reaction was carried out at room temperature by slow addition of ethyl diazoacetate to a solution of styrene in methylene chloride containing the copper(I)-oxazoline catalyst. This was prepared in situ by adding the appropriate amount of ligand to copper(I) trifluoromethanesulfonate–benzene complex $[Cu(OTf)(C_6H_6)_{0.5}]$.

At the outset of the catalytic screening, our attention was focussed on ligands **3** (Scheme 1) bearing substituents of different steric demand or electronic property on the oxazoline and/or pyridine rings. This follows from the consideration that the introduction of a substituent on the 6-position of the pyridine ring of oxazolinylpyridines is the cause of a chiral switch in the Rh-catalysed hydrosilylation[9] and exerts a dramatic effect on the enantioselectivity of the Pd-catalysed allylic alkylation.[6]

The first set of catalytic runs has been performed with ligands **3a–o** substituted with groups of increasing steric demand on the pyridine and/or the oxazoline ring (Scheme 3).



Scheme 3.

Table 1. Enantioselective cyclopropanation of styrene by ethyl diazoacetate using ligands **3a–o**

Entry	Ligand	Yield[a] (%) **8+9**	*trans*/*cis* ratio[b] **8:9**	% e.e.[b]		Configuration[c]	
				8	**9**	**8**	**9**
1	**3a**	67	68:32	2	4	1*R*, 2*R*	1*S*, 2*R*
2	**3b**	74	68:32	4	9	1*S*, 2*S*	1R, 2*S*
3	**3c**	76	68:32	5	7	1*R*, 2*R*	1*S*, 2*R*
4	**3d**	66	68:32	34	39	1*S*, 2*S*	1*R*, 2*S*
5	**3e**	88	70:30	43	44	1*S*, 2*S*	1*R*, 2*S*
6	**3f**	89	71:29	29	42	1*R*, 2*R*	1*S*, 2*R*
7	**3g**	78	64:36	29	30	1*S*, 2*S*	1*R*, 2*S*
8	**3h**	77	61:39	27	50	1*S*, 2*S*	1*R*, 2*S*
9	**3i**	89	62:38	60	51	1*S*, 2*S*	1*R*, 2*S*
10	**3j**	71	77:23	12	23	1*R*, 2*R*	1*S*, 2*R*
11	**3k**	75	69:31	39	39	1*S*, 2*S*	1*R*, 2*S*
12	**3l**	77	69:31	45	41	1*S*, 2*S*	1*R*, 2*S*
13	**3m**	66	67:33	20	6	1*S*, 2*S*	1*S*, 2*R*
14	**3n**	73	75:25	51	15	1*R*, 2*R*	1*R*, 2*S*
15	**3o**	69	67:33	21	8	1*R*, 2*R*	1*S*, 2*R*

[a] Isolated yield, based on ethyl diazoacetate, for the mixture of *trans* and *cis* cyclopropanes.
[b] Determined by GC analysis (see Experimental).
[c] Assignment according to Ref. 13.

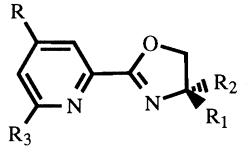
From the results reported in Table 1, the following considerations can be made on the mutual cross-effects of the substitution pattern.

(i) The diastereoselectivity of the reaction is negligibly affected by the structure of the ligand.
(ii) The enantioselectivity of the reaction is positively affected by the presence of substituents of increasing steric demand on the stereogenic carbon of the oxazoline ring as in the case of **3a–b** (entries 1–2), **3d–e** (entries 3–5), **3h–i** (entries 8–9), **3j–k–l** (entries 10–12) and **3m–n** (entries 13–14). The sole exception to this trend was observed with **3o** which was less stereoselective than **3n** (entries 15–14).
(iii) The introduction of an achiral substituent in the 6-position of the pyridine ring has a pronounced effect on the enantioselectivity of the reaction. Substitution of the hydrogen by a methyl (**3a–c**; entries 1–3 and **3b–d**; entries 2–4) or by a *p*-tolyl group (**3a–f**; entries 1–6 and **3b–g**; entries 2–7) leads to a sharp increase of the e.e. The stereoselectivity improves further when the size of the substituent on the pyridine ring increases from methyl to *t*-butyl, as in the case of **3d–h** (entries 4–8) and **3e–i** (entries 5–9). Substitution of the hydrogen by a benzo-fused ring, as in the case of **3a–j** (entries 1–10), **3b–k** (entries 2–11), **3j–m** (entries 10–13), **3k–n** (entries 11–14) and **3l–o** (entries 12–15), has contrasting effects.

These results indicate that steric encumbering in the proximity of the pyridine nitrogen donor aids a more efficient transmission of the chiral information from the oxazoline pendant of the ligand. We may speculate that the presence of a substituent on the 6-position can push the metal closer to the oxazoline nitrogen in the transition state or that it can prevent the approach of the substrate from the pyridine side.

The next set of catalytic experiments was devoted to clear out the presence, if any, of an 'electronic control' on the outcome of the reaction. This follows from recent observations that even substituents remote from the active site of the chiral ligand can influence the catalytic activity and the

Table 2. Enantioselective cyclopropanation of styrene by ethyl diazoacetate using ligands **3p–u**



3p: R= Cl, R_1= Ph, R_2= R_3= H
3q: R= OCH_3, R_1= Ph, R_2= R_3= H
3r: R= Cl, R_1= H, R_2= i-Pr, R_3= H
3s: R= OCH_3, R_1= H, R_2= i-Pr, R_3= H
3t: R= OCH_3, R_1= H, R_2= t-Bu, R_3= CH_3
3u: R= H, R_1= H, R_2= i-Pr, R_3= CN

Entry	Ligand	Yield[a] (%) **8+9**	*trans*/*cis* ratio[b] **8:9**	% e.e.[b]		Configuration[c]	
				8	**9**	**8**	**9**
1	**3p**	78	66:34	0	0	–,–	–,–
2	**3q**	74	73:21	4	8	1*R*, 2*R*	1*R*, 2*S*
3	**3r**	88	65:35	10	3	1*R*, 2*R*	1*R*, 2*S*
4	**3s**	75	64:36	26	19	1*R*, 2*R*	1*R*, 2*S*
5	**3t**	75	63:37	50	45	1*S*, 2*S*	1*R*, 2*S*
6	**3u**	86	61:39	8	11	1*S*, 2*S*	1*R*, 2*S*

[a] Isolated yield, based on ethyl diazoacetate, for the mixture of *trans* and *cis* cyclopropanes.
[b] Determined by GC analysis (see Experimental).
[c] Assignment according to Ref. 13.

Table 3. Enantioselective cyclopropanation of styrene by ethyl diazoacetate using ligands **4** and **5**

Entry	Ligand	Yield[a] (%) **8**+**9**	*trans*/*cis* ratio[b] **8**:**9**	% e.e.[b]		Configuration[c]	
				8	**9**	**8**	**9**
1	**4a**	67	62:38	9	0	1*R*, 2*R*	–,–
2	**4b**	88	60:40	2	2	1*R*, 2*R*	1*S*, 2*R*
3	**4c**	78	58:42	6	0	1*R*, 2*R*	–, –
4	**4d**	77	58:42	2	41	1*R*, 2*R*	1*R*, 2*S*
5	**5a**	78	62:38	41	52	1*S*, 2*S*	1*R*, 2*S*
6	**5b**	76	61:39	7	8	1*R*, 2*R*	1*R*, 2*S*
7	**5c**	78	55:45	17	40	1*S*, 2*S*	1*R*, 2*S*

[a] Isolated yield, based on ethyl diazoacetate, for the mixture of *trans* and *cis* cyclopropanes.
[b] Determined by GC analysis (see Experimental).
[c] Assignment according to Ref. 13.

enantioselectivity of the process through their electronic effect.[6a,10] To this purpose, a variety of oxazoline ligands substituted with electron-withdrawing (**3p**–**r**) or electron-releasing (**3q**–**s**) groups in 4-position of the pyridine ring were assessed in the cyclopropanation of styrene. While for these derivatives we can confidently assume a pure electronic effect for the substituent, steric and electronic properties can hardly be separated in ligands **3t**–**u** where the carbon adjacent to the pyridine nitrogen is substituted (Table 2).

The data reported in Table 2 show that a 4-chloro substituent has a negligible effect on the e.e. (**3p**–**r**; entries 1–3), whereas a methoxy substituent in the same position leads to a sharp increase of the stereoselectivity (**3q**–**s**; entries 2–4) and even to a chiral switch in comparison with the unsubstituted oxazolines **3a**–**b** (entries 1–2, Table 1). A slight positive effect of the electron-releasing substituent is observed even when a methyl substituent is present in position-6 (compare entries 5 of this table and Table 1). Finally, ligand **3u** (entry 6) gives an e.e. lower than the one recorded with the roughly related ligand **3d** (entry 4, Table 1). This provides further confirmation to the negative influence of electron-withdrawing groups.

Notably, the trend observed with our pyridyloxazolines is opposite to the case of 4-substituted pybox **1** (Scheme 1) where electron-withdrawing substituents provide higher e.e.'s than electron-donating groups.[10b]

The oxazolinylphenanthrolines **4**[11] and the C_2-symmetric pyridyloxazolines **5**[12] were the last set of chiral modifiers we have tested in the cyclopropanation of styrene. Compounds **4** and **5** are both capable of bidentate and terdentate binding to the metal centre (tetradentate coordination of **5** to Cu(I) is possible as well, but should inactivate the catalyst). Moreover, for both ligands two different modes of bidentate coordination are conceivable: the first involving both the pyridine nitrogen donors and the second involving only one pyridine and the oxazoline nitrogen.

Ligands **4** were poor chiral inducers and gave negligible e.e.'s, much lower than the ones observed with the structurally related ligands **3m**–**n** (compare with entries 13–14 of Table 1), in all cases but one. A moderate e.e. (41%) for the *cis*-diastereoisomer was recorded in the presence of the ligand **4d** possessing two stereocentres on the oxazoline ring. This last result seems to support the view that the oxazoline nitrogen donor is not involved in the coordination at the metal centre and acts as a mere chiral target.

In the series of C_2-symmetric pyridyloxazolines, the epimeric ligands **5a**–**b** were exploited in order to explore the chiral matching–mismatching of the stereogenic elements appended onto the pyridine and oxazoline rings. The best enantioselection, both for the *cis*- and the *trans*-isomer, was obtained with the (*R*,*S*,*S*,*R*)-compound **5a**.

The use of the epimeric (*S*,*S*,*S*,*S*)-derivative **5b**, which has opposite configuration at the oxazoline stereocentres, gave products of much lower e.e. (entries 5–6) and brought about a chiral switch in the *trans*-cyclopropane. This indicates that the stereoselection process is mainly dictated by the sterogenic elements of the dioxolane moiety. This assumption is corroborated by the result obtained with the (*S*,*S*)-ligand **5c** which has no stereocentre in the oxazoline rings. In this reaction the e.e.'s were slightly lower than the ones obtained with **5a**, but the sense of the chiral induction for both *cis* and *trans* isomers was the same.

The results obtained with ligands **4** and **5** lend support to the view that these ligands bind to the metal in a bidentate rather than in a tridentate fashion (Table 3). Coordination seems to occur most probably at the pyridine nitrogen donors. In this case the oxazoline substituent should act merely as a chiral pendant without being directly involved in the coordination.

In conclusion, we have assessed in the Cu(I)-catalysed enantioselective cyclopropanation of styrene a large variety of chelating oxazoline ligands which were investigated with respect to their steric and electronic features. The results obtained indicate that the efficiency of these ligands is moderate, the best e.e. being 60% given by the bis-*t*-butyl substituted derivative **3i**. This value is much higher than the one obtained with C_2-symmetric bis-oxazolines (3–8%),[14] but it is far from the best e.e.'s obtained with C_2-symmetric bipyridines (92–98%).[15] Thus, the C_1-symmetry hybrid pyridine–oxazoline ligands seem to retain half of the positive and half of the negative properties of their C_2-symmetry counterparts.

Experimental

General

Gas chromatographic analyses were performed on a HP 5900 chromatograph using He (60 kPa) as the carrier gas. The *trans/cis* ratio and enantiomeric excesses of ethyl *trans*- and *cis*-2-phenyl-cyclopropane-1-carboxylates **8** and **9** were determined by GC analysis on a 25 m×0.25 mm capillary column coated with diethyl-*t*-butylsilyl β-cyclodextrin operated at 60°C for 5 min, then programmed at 3°C/min to 160°C. The configurations of the prevailing enantiomers were attributed according to the literature.[13]

Copper(I) trifluoromethanesulfonate benzene complex $[Cu(OTf)(C_6H_6)_{0.5}]$ and ethyl diazoacetate were purchased from Aldrich. The ligands **3a–e**,[6a] **3f–h**,[6b] **3j–n**,[6b] **3p–t**,[6c] **3u**,[6c] **4a–d**,[11] **5a–c**,[12] 2-cyano-6-(1,1-dimethylethyl)pyridine (**6**)[6b] and 2-cyanobenzo[*h*]quinoline (**7**)[6b] were prepared according to reported procedures.

General procedure for the preparation of oxazolinylmethylpyridines 3

In a 25 ml two-necked flask, zinc chloride (14 mg, 0.10 mmol) was melted under high vacuum and cooled under argon. After cooling to room temperature, chlorobenzene (12 ml) was added, followed by the nitrile (2 mmol) and the amino alcohol (3.0 mmol). The resulting mixture was heated under reflux for the proper time (vide infra) and then the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (6 ml) and the resulting solution was washed with water (3×4 ml). The aqueous solution was extracted with CH_2Cl_2 (6 ml), the combined organic phases were dried over anhydrous Na_2SO_4 and the solvent evaporated. The residue was purified by chromatography on a silica gel column (eluent: ethyl acetate/petroleum ether=2:1).

(*S*)-2-[4,5-Dihydro-4-(1,1-dimethylethyl)oxazol-2-yl]-6-(1,1-dimethylethyl)pyridine (3i). Reaction time: 48 h; 0.42 g (46%); oil; $[\alpha]_D^{25}$ −124.4 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.94 (dd, 1H, *J*=7.5, 0.9 Hz), 7.66 (t, 1H, *J*=7.5 Hz), 7.45 (dd, 1H, *J*=7.5, 0.9 Hz), 4.47 (dd, 1H, *J*=10.2, 8.4 Hz), 4.31 (t, 1H, *J*=8.4 Hz), 4.09 (dd, 1H, *J*=10.2, 8.4 Hz), 1.40 (s, 9H), 0.97 (s, 9H). Anal. Calcd for $C_{16}H_{24}N_2O$: C, 73.81; H, 9.29; N, 10.76;. Found: C, 73.91; H, 9.15; N, 10.84;

(*S*)-2-[4,5-Dihydro-4-(1,1-dimethylethyl)oxazol-2-yl]-benzo[*h*]quinoline (3o). Reaction time: 24 h; 0.494 g (81%); mp 115°C; $[\alpha]_D^{25}$ −85.1 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 9.39 (d, 1H, *J*=7.2 Hz), 8.38 (d, 1H, *J*=8.1 Hz), 8.23 (d, 1H, *J*=8.1 Hz), 7.92–7.68 (m, 5H), 4.59 (dd, 1H, *J*=10.5, 9.0 Hz), 4.44 (t, 1H, *J*=9.0 Hz), 4.22 (dd, 1H, *J*=10.5, 9.0 Hz), 1.03 (s, 9H). Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.2. Found: C, 78.64; H, 6.45; N, 9.35.

Asymmetric cyclopropanation of styrene: typical procedure

A solution of the ligand (34 μmol) in CH_2Cl_2 (2.5 ml) was added to a suspension of $[Cu(OTf)(C_6H_6)_{0.5}]$ (8 mg, 32 μmol) in CH_2Cl_2 (2.5 ml). After 30 min, the mixture was filtered through packed adsorbent cotton under argon, and to the filtrate was added styrene (1.59 ml, 13.87 mmol). Then a solution of ethyl diazoacetate (285 mg, 2.5 μmol) in CH_2Cl_2 (2.5 ml) was added dropwise over a period of 1 h. The mixture was stirred for 12-14 h and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate=15:1) to afford a mixture of ethyl *trans*- and *cis*-2-phenyl-cyclopropane-1-carboxylates as a colourless oil. This mixture was analysed by GC. The diastereomeric and enantiomeric excess was determined by capillary GC with a chiral column [T_r: 33.2 (1*S*,2*S*) and 33.5 (1*R*,2*R*) min for *trans* **8**; T_r: 31.4 (1*R*,2*S*) and 31.8 (1*S*,2*R*) min for *cis* **9**].

Acknowledgements

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