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Novel structure-defined chiral bis(oxazolinyl)thiophenes for Ru-catalyzed asymmetric cyclopropanation ☆

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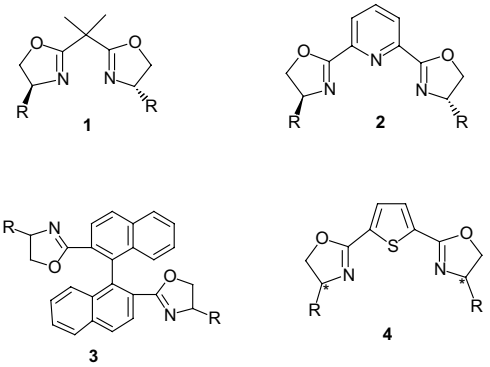
Abstract—The novel structures of sulfur-containing chiral bis(oxazoline) compounds which have been synthesized have been determined by X-ray crystal diffraction analyses. A high enantioselectivity (ee >99%) in the asymmetric cyclopropanation of diphenylethene with diazoester using the bis(oxazoline)-Ru(II) catalyst was obtained.

The catalytic enantioselective synthesis of cyclopropanes has received great attention because of their frequent occurrence in biological compounds and their use as valuable synthetic intermediates.[1] Since the introduction of chiral cyclopropanation catalysts by Noyori and co-workers and Pfaltz and co-workers,[2] the catalyzed asymmetric cyclopropanation by transition-metal complex catalysts has been one of the most efficient synthetic methods for the formation of optically pure cyclopropane compounds.[3] Catalysts containing several metals and various chiral ligands, such as Schiff base–Cu,[4] salen–Co,[5] Rh_2(5S-MEPY),[6] porphyrin–Ru,[7] and especially over the last decade, the C_2-symmetric chiral oxazoline metal complexes have shown desirable enantioselective catalytic effects.[8] They have been successfully employed in asymmetric cyclopropanation.

Currently, several kinds of C_2-symmetric chiral oxazolines, for example, ligand **1** with one carbon spacer,[9] **2** with pyridine nitrogen atom spacer,[10] and **3** with a rigid chiral biaryl skeleton[11] has been synthesized and high enantioselectivity for cyclopropanations has been obtained. The sulfur-containing chiral bis(oxazoline) for the asymmetric cyclopropanation has not yet been described, although sulfur-containing chiral ligands in the other asymmetric catalytic reactions have been reported.[12] Recently, we reported the synthesis of the new chiral bis(oxazolinyl)thiophenes **4**.[13] X-ray structures of these chiral bis(oxazolinyl)thiophenes are herein reported together with their application for catalytic asymmetric cyclopropanation reactions of alkenes with ethyl diazoacetate (EDA) using the Ru(II) complex.



The chiral bis(oxazolines) **4** (thiobox) have been prepared using two methods (Scheme 1):[8,13] The reaction of a diacid chloride with chiral β-amino alcohols to form dihydroxy diamide compounds, which are subsequently treated with thionyl chloride to afford dichloride diamide compounds. The above compounds are transformed into **4** by treatment with a base. The improved route includes one step (e) instead of two steps (c) and (d). This results not only in a simplification of the procedure, but also in an improved the yield of the bis(oxazoline). These new ligands were characterized by IR, NMR, MS, and elemental analysis.[14]

Keywords: Asymmetric cyclopropanation; Bis(oxazoline); Bis(oxazolinyl)thiophene; Ruthenium.

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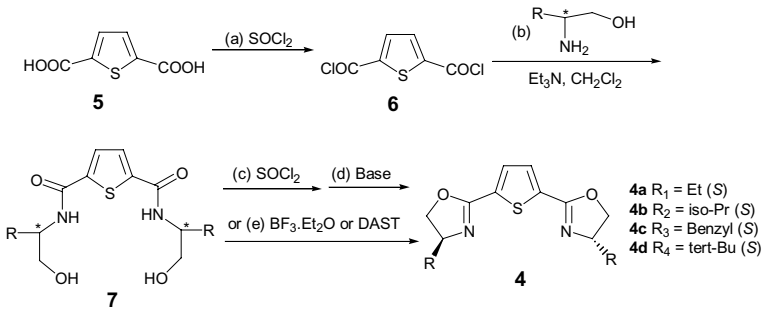


Scheme 1.

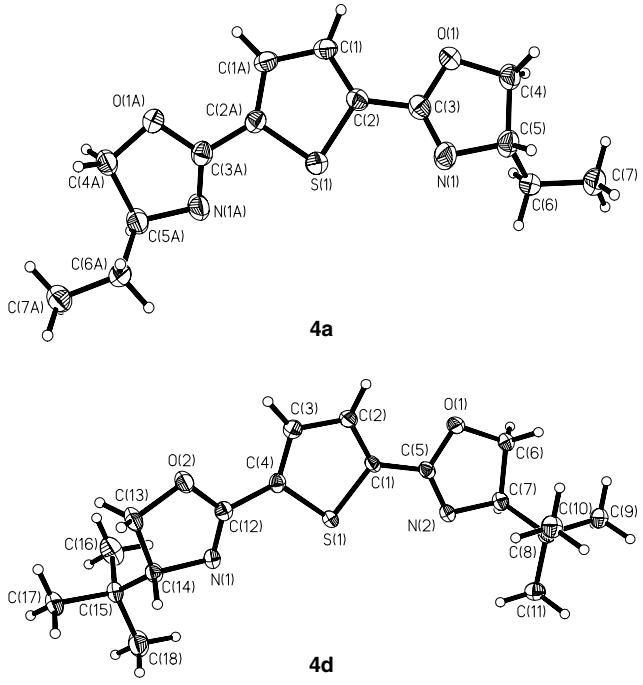


Figure 1. Molecular structures of **4** with atom labeling.

In order to obtain a direct understanding of the structure of the new chiral bis(oxazoline) ligands **4**, the structures of the ligands **4a**,**d** were determined by X-ray crystallography. Compounds **4a** and **4d** were obtained as air-stable, colorless crystals by slow evaporation from solutions of **4** in acetone–hexane (v/v 1:3). The perspective views of compounds **4a** and **4d** are shown in Figure 1.

From the view of the crystal structures of **4a** and **4d**, the thiophene unit with two oxazolines moieties possesses a twist angle and they do not lie in the same plane, and it is found that the N–S–N bond angle is quite large. This differs from the structure of previously reported pybox.[10,15] In **4**, the thiophene functions as a backbone, where the sulfur atom is part of strong π-donor system. The chirality has been introduced by two oxazoline moieties near the sulfur. These C_2-symmetric bis(oxazolines) offer the possibility for a new group of N–S–N chelating tridentate ligands.

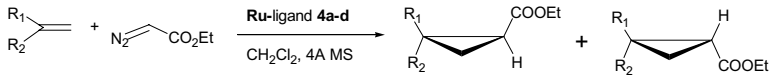
These ligands were successfully utilized for Ru-catalyzed cyclopropanation of alkenes with ethyl diazoacetate. This is the commonly investigated model reaction with chiral ligands.[10,16] The asymmetric cyclopropanation was carried out in CH_2Cl_2 in the presence of 4 mol % of ruthenium(II) catalyst by mixing $[RuCl_2(p\text{-cymene})]_2$ and the bis(oxazoline) ligands **4** to give cyclopropanecarboxylate as a mixture of *trans* and *cis* isomers (Scheme 2).[†]

The ratio of *trans* to *cis* isomers was determined by ^1H NMR analysis, and enantiomeric excess of these mixtures was determined by HPLC analysis using a chiral column (Chiralcel OD-H or OJ). The results are summarized in Table 1. Using ligand **4a** and substrate 1,1-diphenylethene, studies were carried out to determine the optimum reaction conditions. The choice of the solvents has a significant effect on both the enantioselectivity and the yield. Dichloromethane was found to give the best results. Slightly lower enantioselectivities were obtained in chloroform and dichloroethane, and the enantioselectivity and yield decreased in THF (entry 1). Reduction of the reaction temperature from 40 to 0 °C, did not noticeably affect the reaction, but increased enantioselectivity from 92% ee (entry 4) to >99% ee (entry 6) and lowered the yield from 91% to 70%. Changing the ligand (**4b**,**c**,**d**) has a little effect on the enantioselectivity of 2,2-phenyl-cyclopropanecarboxylate.[‡]

Variation of the ligand on the cyclopropanation of other alkenes has a great effect on the *trans*/*cis* diastereo-

[†] The ligand **4** (0.21 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (0.1 mmol) were mixed in 4 mL CH_2Cl_2 and refluxed for 40 min, cooled to rt, 1,1-diphenylethene or other alkenes (10.0 mmol, excess) and 4 Å molecular sieves (MS) were added to the above mixture. Then, a solution of the diazoester (5.0 mmol) in 3 mL CH_2Cl_2 was slowly added at rt over 4 h. The reaction was stirred for another 16 h. The solvent was removed and the crude product was separated by flash chromatography over silica gel to give cyclopropyl ester products in 63–91% isolated yield.

[‡] Single crystals of **4a** and **4d** were scanned at 110 K on a Bruker Smart CCD-1000 diffractometer (Mo-K_α, $\lambda = 0.71069$ Å). The structures were solved using direct methods and refined with full-matrix least-squares (SHELX-97) with atomic coordinates and anisotropic thermal parameters for all nonhydrogen atoms.[18] CCDC reference number 232493 and 232495.



Scheme 2.

Table 1. Enantioselective cyclopropanation catalyzed by the Ru-bis(oxazolines)

Entry	Ligand	R_1	R_2	T (°C)	Solvent	*trans*:*cis*[a]	%Ee (*trans*)[b]	%Ee (*cis*)	Yield%[c]
1	**4a**	Ph	Ph	rt	THF	—	81	81	66
2	**4a**	Ph	Ph	rt	$ClCH_2CH_2Cl$	—	96	96	82
3	**4a**	Ph	Ph	rt	$CHCl_3$	—	95	95	83
4	**4a**	Ph	Ph	40	CH_2Cl_2	—	92	92	91
5	**4a**	Ph	Ph	rt	CH_2Cl_2	—	99	99	85
6	**4a**	Ph	Ph	0	CH_2Cl_2	—	>99	>99	70
7	**4b**	Ph	Ph	rt	CH_2Cl_2	—	98	98	77
8	**4c**	Ph	Ph	rt	CH_2Cl_2	—	96	96	72
9	**4d**	Ph	Ph	rt	CH_2Cl_2	—	98	98	63
10	**4a**	H	Ph	rt	CH_2Cl_2	67:33	62	66	90
11	**4b**	H	Ph	rt	CH_2Cl_2	76:24	81	84	83
12	**4c**	H	Ph	rt	CH_2Cl_2	72:28	75	79	80
13	**4d**	H	Ph	rt	CH_2Cl_2	79:21	89	82	79
14	**4d**	H	4-MeO-Ph	rt	CH_2Cl_2	82:18	91	85	78
15	**4d**	H	4-Cl-Ph	rt	CH_2Cl_2	80:20	87	83	82

[a] The ratio of *trans* and *cis* was determined by ^1H NMR.
[b] Ee values were determined by chiral HPLC analysis(Chiralcel OD-H or OJ column).
[c] Isolated yield of a mixture of *trans* and *cis* based on EDA.

selectivity and enantioselectivity. As can be seen from entries 10–15 in Table 1, when the R groups of the ligand are changed from ethyl to bulkier groups (*iso*-Pr; benzyl; *tert*-butyl), all reaction give higher *trans*:*cis* ratios for the cyclopropanation products of styrene, *p*-chlorostyrene and 4-vinylanisole. The best results were obtained with the *tert*-butyl group, where a *trans*:*cis* ratio of 82:18 (entry 14) and 91% ee of *trans* product were obtained. This is consistent with the results previously reported.[17] Apart from styrene substrate, *p*-chlorostyrene and 4-vinylanisole were also selected as substrates. There was no obvious improvement on the enantioselectivity of the cyclopropyl ester product.

Compared with results reported for the catalyst Ru-pybox,[10] with respect to ee values and yield of cyclopropanation of 1,1-diphenylethene, better results are reported herein by the use of the catalyst Ru-thiobox. In the case of styrene and substituent styrenes, the ee values of the cyclopropanation product are similar, but the *trans*/*cis* stereoselectivity is somewhat lower with Ru-thiobox. These differences may result from the different catalyst structure. With respect to the structure of the catalyst, it is expected that the N–S–N bonds coordinated to Ru have a larger and longer angle than that of N–N–N bonds coordinated to Ru. This may result in easier access of the reactive substrate and is favorable for a larger sterically bulky substrate. In addition, Ru–S coordination is much stronger than Ru–N coordination, because sulfur and ruthenium are both soft centers. The Ru–N coordination represents a soft to hard interaction, and a soft–soft interaction is expected to be much stronger.

In conclusion, a series of new chiral sulfur-containing bis(oxazolines) with thiophene as the backbone has been synthesized and some structures have been determined by X-ray crystal diffraction analyses. Preliminary results in the asymmetric cyclopropanation of alkenes with diazoacetate have been obtained. A high enantioselectivity has been obtained in the cyclopropanation of diphenylethene using the Ru(II)-bis(oxazoline) catalyst, the *trans*:*cis* stereoselectivity and enantioselectivity are also good. The preliminary results suggest that these novel bis(oxazolines) posses potential as new catalysts for asymmetric reactions. Further studies on the asymmetric reactions are currently being investigated.

See *Supplemental materials* for crystallographic data in CIF or other electronic format.

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