Enantioselective epoxidation catalysed by ruthenium complexes with chiral tetradentate bisamide ligands

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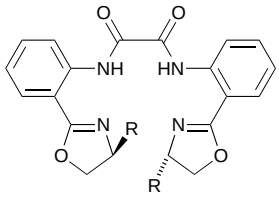
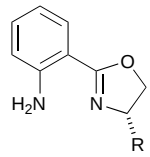
Ruthenium complexes with chiral bis(dihydrooxazolylphenyl)oxalamide ligands catalyse the epoxidation of (*E*)-stilbene and (*E*)-1-phenylpropene with 69 and 58% ee, respectively, using $NaIO_4$ as oxidant.

The development of efficient catalytic methods for the enantioselective preparation of epoxides is an important objective of current research.[1–6] The most general and most effective catalysts available today are titanium–tartrate complexes for the epoxidation of allylic alcohols[6] and manganese–salen complexes[3,5] which allow the preparation of epoxides from certain *cis*-disubstituted, tri- and tetra-substituted alkenes with high ees. However, for other important classes of substrates such as terminal and *trans*-disubstituted olefins efficient enantioselective epoxidation catalysts are still lacking.

A method for the epoxidation of alkenes using $RuCl_3$, 2,2′-bipyridyl and $NaIO_4$ in a two-phase reaction medium has been reported.[7] Several attempts were made to render this system enantioselective by replacing bipyridyl with chiral ligands.[8,9] However, only low enantioselectivities have been obtained so far.



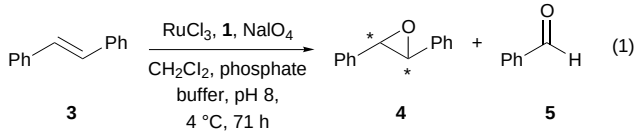
1a–e



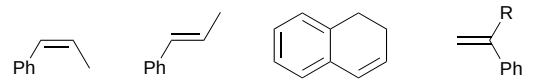
2a–e

a R = Me, **b** R = Pr^i, **c** R = Bu^t, **d** R = Bn, **e** R = Ph

We have recently developed an efficient synthesis of chiral C_2-symmetric oxalamides **1**, starting from readily available 2-(2-aminophenyl)oxazolines **2** and oxalyl chloride.[10] Oxalamides of this type possess a number of features which make them attractive ligands for enantiocontrol of metal-catalysed reactions, in particular for oxidations. A variety of differently substituted derivatives can be readily prepared in both enantiomeric forms starting from commercially available enantiopure precursors. The doubly deprotonated oxalamide **1** can act as a tetradentate ligand. Due to the π-acceptor properties of the α-dicarbonyl unit and the oxazoline rings, these ligands are expected to be quite resistant to oxidation and hence suitable for the formation of stable high-valent metal complexes. Here we report that ligands **1** can be used for the enantiocontrol of ruthenium-catalysed epoxidations.



In preliminary experiments, following Balavoine's procedure,[7a] with 2 mol% of $RuCl_3 \cdot H_2O$ and 2 equiv. of $NaIO_4$ in the presence of 12 mol% of ligand **1b**, (*E*)-stilbene was epoxidised in 31% yield with an ee of 43%. Higher ees and somewhat better yields were obtained when an aqueous buffer was used instead of water [Table 1, reaction (1)]. In addition to the desired



6 **7** **8** **9** R = H **10** R = Me

epoxide, significant amounts of benzaldehyde were formed. Control experiments showed that the epoxide **4** is stable under the reaction conditions. This implies that benzaldehyde is formed directly by oxidative cleavage of the olefin rather than by degradation of the epoxide.

Among the different oxalamides **1a–e**, the isopropyloxazoline derivative **1b** was found to be the most effective ligand. In contrast, the *tert*-butyloxazoline derivative **1c** gave poor ees and low yields of epoxide due to the formation of benzaldehyde, which is the main reaction in this case. Ligands **1a** and **1d** gave similar yields of epoxides as **1b** but somewhat lower ees. Interestingly, with ligand **1e** the opposite enantiomer of **4** was formed in 21% ee. In the absence of catalyst, (*E*)-stilbene was not oxidised by $NaIO_4$ under otherwise identical conditions. Replacing $NaIO_4$ by NaOCl resulted in very low yield and enantiomeric excess.

One of the problems in this reaction is the formation of benzaldehyde, which is rapid in the beginning (Fig. 1). In the initial period up to *ca*. 60% conversion, the alkene is consumed at about the same rate as benzaldehyde is formed while the formation of epoxide is much slower. The ee is very low in the beginning but increases significantly during the course of the reaction. We thought that these problems could possibly be overcome if the catalyst was treated with the oxidant prior to addition of the substrate. Indeed, the catalytic performance could be significantly improved using the following protocol. A suspension of $RuCl_3 \cdot H_2O$ (3.5 mg, 14 μmol) and ligand **1**

Table 1 Ruthenium-catalysed epoxidation of **3** using ligands **1a–e**

Entry	Ligand	Conversion (%)	Yields[a] (%) **4**	Yields[a] (%) **5**	Ee[b] (%)	Abs. Config.[c]
1	**1a**	> 99	42	21	42	(1*R*,2*R*)
2	**1b**	> 99	37	31	62	(1*R*,2*R*)
3	**1c**	> 99	4	65	21	(1*R*,2*R*)
4	**1d**	> 99	43	27	38	(1*R*,2*R*)
5	**1e**	69	19	34	21	(1*S*,2*S*)

[a] Determined by GC integration based on tridecane as internal standard. The yields of **4** and **5** are based on the conversion of alkene. [b] Determined by GC using a chiral capillary column (Chiraldex γ-CD-TFA, 30 m × 0.25 mm, 1 bar H_2, 150–157 °C (0.5° min^{-1}), 157 °C (1 min), 157–180 °C (30° min^{-1}), t_R = 11.9/12.1 min). [c] The absolute configuration was determined based on the sign of the optical rotation, see ref. 13.

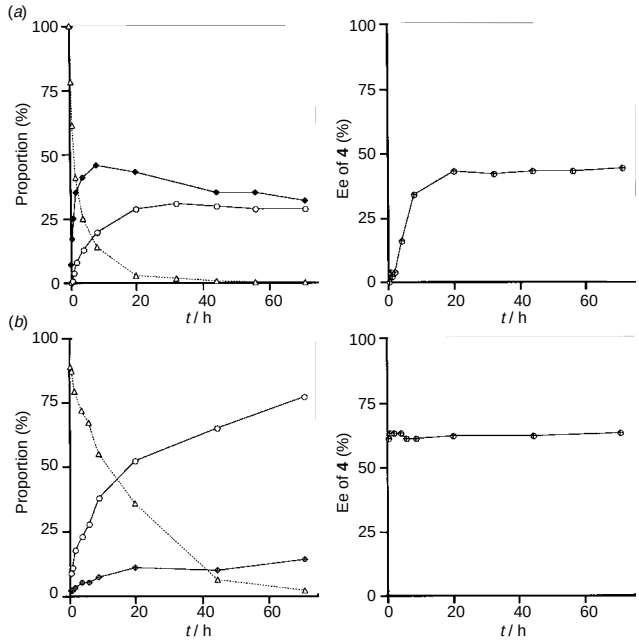


Fig. 1 Epoxidation of (*E*)-stilbene using ligand **1b** under (*a*) non-optimised (see text) and (*b*) optimised conditions: (△) **3**, (○) **4** and (◇) benzaldehyde **5**

(80 μmol) in aqueous buffer (2 ml, pH 8, 20 mM sodium phosphate) was stirred for 30 min at 4 °C. Subsequently, CH_2Cl_2 (3 ml) was added, followed by $NaIO_4$ (300 mg, 1.403 mmol). The resulting two-phase system was vigorously stirred for 4 h at 4 °C. Then (*E*)-stilbene (**3**) (125 mg, 0.694 mmol) was added and stirring continued for another 67 h. As shown in Fig. 1(*b*), the epoxide is now the major product and the enantiomeric excess remains constant during the reaction. Under these conditions **3** was converted to **4** in 74% yield (determined by GC based on tridecane as internal standard) with 69% ee. In a larger scale experiment with 3.5 mmol of **3**, the product **4** was isolated in 60% yield with the same ee after column chromatography. This is the best result obtained so far in the ruthenium-catalysed epoxidation of **3** with $NaIO_4$. After completion of this work, a ruthenium catalyst derived from a chiral bis(oxazolinyl)pyridine ligand was reported which gave up to 74% ee in the epoxidation of **3** with $PhI(OAc)_2$.[11] Interestingly, only benzaldehyde formation but no epoxidation was observed in this case when $NaIO_4$ was used as oxidant.

Using the same procedure, other alkenes were tested as substrates in the ruthenium-catalysed epoxidation with ligand **1b**. The epoxidation was found to be stereospecific for both (*E*)- and (*Z*)-alkenes. (*Z*)-1-Phenylpropene **6** was converted to the *cis*-epoxide in 50% yield with 25% ee. Significantly higher enantioselectivity was achieved for the epoxidation of the corresponding (*E*)-isomer **7** (58% ee, 40% yield). In this respect the ruthenium–oxalamide complexes resemble chromium–salen complexes[12] which also give higher ees with **7** than with the (*Z*)-isomer **6**, but differ from related manganese–salen or –porphyrin complexes[3–5] which afford higher ees for (*Z*)- than for (*E*)-olefins. Olefins **8**–**10** could not be used as substrates because the corresponding epoxides were not stable under the reaction conditions.

Notes and References

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