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2-Aryl-5,5-bisoxazolin-2-yl[1,3]dioxanes as solution phase and immobilised ligands for highly enantioselective cyclopropanations

Julian G. Knight* and Paul E. Belcher

School of Natural Sciences, Bedson Building, University of Newcastle upon Tyne, NE1 7RU, UK

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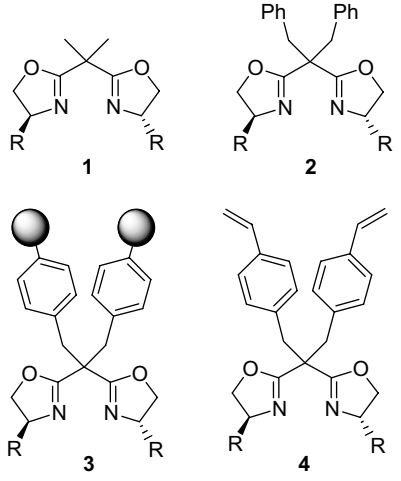
Abstract—2-Aryl-5,5-bisoxazolin-2-yl[1,3]dioxanes **5**, which can be easily prepared in three steps from diethyl bishydroxymethylmalonate, amino alcohol and an aromatic aldehyde, have been used for the copper catalysed asymmetric cyclopropanation of styrene with ethyl diazoacetate in up to 99% ee for the *trans*-cyclopropane. Grafting onto a bromo-Wang resin produced an immobilised ligand **9** which gave the *trans*-cyclopropane in 65% ee.

1. Introduction

The design of efficient asymmetric catalytic reactions that proceed with high enantioselectivities is an important goal in organic synthesis. Since first reported by Lowenthal and Masamune[1] and Evans et al.[2] in 1991, chiral bisoxazolines have been successfully used in the asymmetric catalysis of a number of reactions due to their ability to coordinate to a large number of metal ions in different oxidation states.[3] However these catalytic systems often require high catalyst-to-substrate loading (typically up to 10 mol%) and, as a result of this, separation and recycling of the catalyst is desirable. Catalyst immobilisation renders separation from the products and recycling simple.[4,5] Several different methods of immobilisation of bisoxazolines have been explored and these can be divided into three main categories: covalent heterogenisation on insoluble supports;[6–12] covalent heterogenisation onto soluble organic polymers;[13,14] and heterogenisation using non-covalent bonding.[15–21]

The immobilisation of bisoxazolines and their subsequent use as catalysts in cyclopropanation reactions has been the subject of several reports.[22] With a few notable exceptions, the enantioselectivities achieved with these immobilised complexes have not equalled the excellent levels of enantiocontrol exhibited by ligands **1** under homogeneous conditions.[2]



Mayoral has reported the immobilisation of bisoxazolines by either grafting onto commercially available resins **3** or by direct polymerisation of monomer **4** with styrene and various different cross linking agents.[6,8,9] It was found that in the cyclopropanation of styrene with ethyl diazoacetate (see Scheme above Table 1), the bisoxazoline grafted onto Merrifield resin (**3**, R = Ph) gave the *trans*-cyclopropane in only 26% ee. However, polymers, in which the chiral ligand was the only cross linker present, gave up to 78% ee (R = *t*-Bu). Interestingly the homogeneous analogue of polymer **2** afforded a similar enantioselectivity of 70% (R = *t*-Bu). More recently, Salvadori and co-workers

* Corresponding author. Tel./fax: +44 (0) 191 222 7068; e-mail: j.g.knight@ncl.ac.uk

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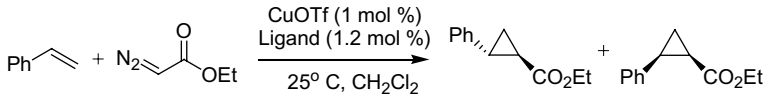
Table 1. Cyclopropanation[a] of styrene with ethyl diazoacetate

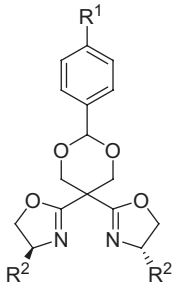


Entry	Ligand	Yield (%)[c]	*trans*/*cis*[d]	*trans* ee[e]% (config.)[f]	*cis* ee[e] % (config.)[f]
1	**1a** (R = *i*-Pr)	—	69/31[2]	49 (1*R*,2*R*)[2]	45 (1*R*,2*S*)[2]
2	**1b** (R = *t*-Bu)	77[2]	77/23 (lit.,[2] 73/27)	99 (1*R*,2*R*) (lit.,[2] 99)	99 (1*R*,2*S*) (lit.,[2] 97)
3	**2** (R = *t*- Bu)	46[6,8]	32/68[6,8]	70 (1*R*,2*R*)[6,8]	79 (1*R*,2*S*)[6,8]
4	**5a** (R^1 = H, R^2 = *i*-Pr)	84	66/34	64 (1*R*,2*R*)	20 (1*R*,2*S*)
5	**5b** (R^1 = H, R^2 = Ph)	90	70/30	41 (1*R*,2*R*)	28 (1*R*,2*S*)
6	**5c** (R^1 = H, R^2 = *t*-Bu)	60	67/33	99 (1*R*,2*R*)	89 (1*R*,2*S*)
7	**5d** (R^1 = $CH_2OTBDMS$, R^2 = *t*-Bu)	95	67/33	95 (1*R*,2*R*)	90 (1*R*,2*S*)
8	**9** (R^1 = CH_2O-Wang, R^2 = *t*-Bu)[b]	60	64/36	65 (1*R*,2*R*)	58 (1*R*,2*S*)

[a] Performed as described in Ref. 2.
[b] Cu content 0.018 mmol g^{-1}, determined by ICP analysis.
[c] Isolated yield.
[d] Determined by ^{1}H NMR.
[e] Determined by GC analysis using a chiral β-cyclodextrin 120 column (SUPELCO Beta Dex™ 120, 30 M × 0.25 mm, 0.25 μm film).
[f] Determined by specific rotation.

have reported enantiomeric excesses up to 93% using an oxazoline (R = *t*-Bu) in which the C_1 bridge was incorporated into an insoluble support via a simple alkyl chain.[12] These results indicate that the nature and size of the groups on the C_1 bridge between the oxazoline rings, as well as the nature of the immobilisation, has a significant effect on the level of enantiocontrol. A comparison of the enantioselectivities obtained in the cyclopropanation with bisoxazoline **1** (R = *t*-Bu) and **2** (R = *t*-Bu) (Table 1, entry 2 vs 3) shows that the presence of bulkier groups on the C_1 bridge causes a significant decrease in the level of enantiocontrol. The magnitude of this decrease in the enantioselectivity is possibly linked to the ability of the groups on the C_1 bridge to rotate into the space around the metal. We reasoned that incorporating the substituents on the C_1 bridge into a ring system would serve to restrict the rotation of these groups and hence reduce their ability to adversely affect the enantioselectivity.

Herein we report the synthesis of bisoxazolines **5**, in which a 1,3-dioxane restricts the conformational mobility of the groups on the C_1 bridge, and the subsequent use of these ligands in the copper(I) catalysed cyclopropanation of styrene with ethyl diazoacetate. The design of **5** allows for simple modification of the dioxane bridge to allow for ligand immobilisation onto an insoluble solid support.



5

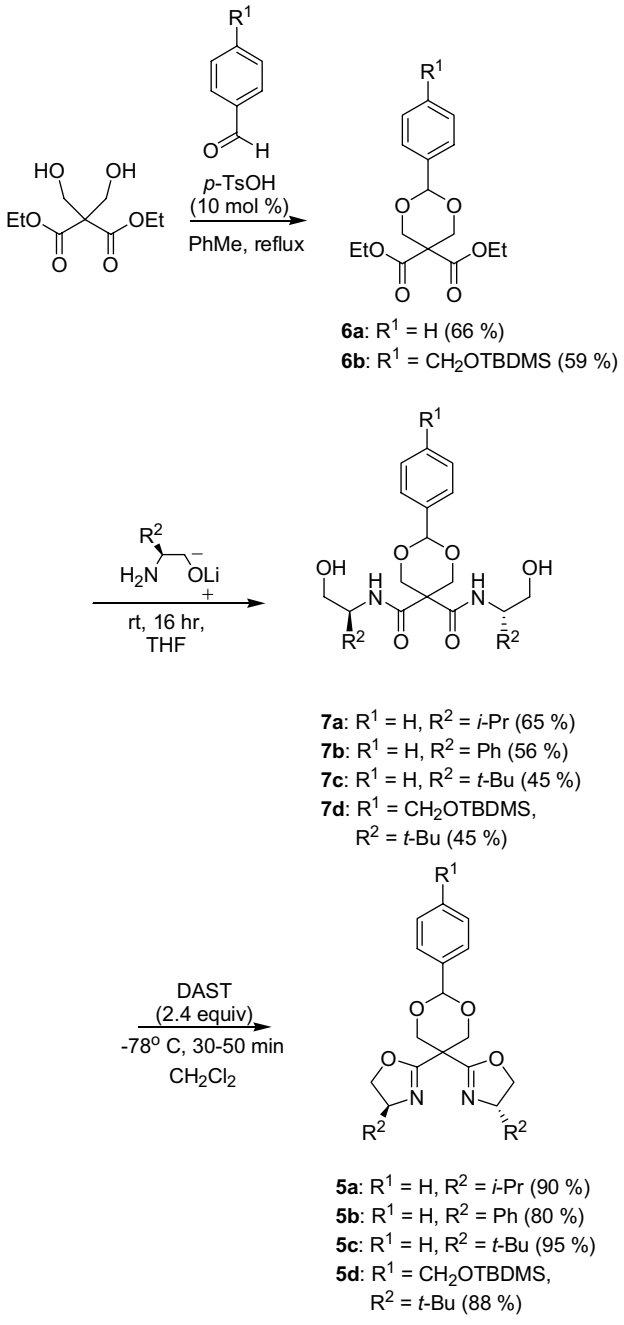
2. Results and discussion

Bisoxazolines **5a–c** were synthesised as shown in Scheme 1. Dioxane diester **6a** was obtained in 66% yield by the acid catalysed condensation of diethyl bishydroxymethylmalonate and benzaldehyde under Dean–Stark conditions.[23–25] Bis-amido alcohols **7a–c** were prepared using a modification of Dodd's[26] conditions from diester **6a** and the corresponding amino alcohols. Bisoxazolines **5a–c** were subsequently obtained in excellent yield by treatment of bishydroxyamides **7a–c** with diethylaminosulfur trifluoride (DAST).[27,28]

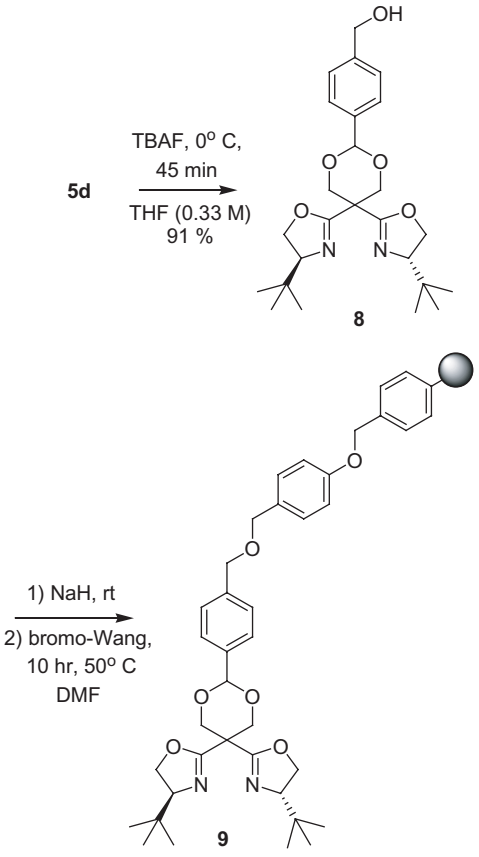
The bisoxazolines **5a–c** were evaluated as ligands in the cyclopropanation reaction of styrene with ethyl diazoacetate (Table 1).

The results in Table 1 show that catalysts based on the dioxane-bridged ligands **5** give comparable enantioselectivity to the simple ligands **1** (Table 1 entries 1 and 2 vs 4 and 6, respectively). This observation supports the proposal that constraining the groups on the C_1 bridge into a ring restricts their ability to adversely influence the selectivity (compare entries 3 vs 6).

In order to enable attachment to a solid support, the corresponding silyl protected 4-hydroxymethyl benzaldehyde **6b** was prepared in two steps from 4-bromo benzyl alcohol.[24,25,29] Following a similar route to that used for the synthesis of ligands **5a–c**, the 4-siloxymethylphenyl derived dioxane-bridged bisoxazoline **5d** was prepared (Scheme 1). Desilylation with tetrabutyl ammonium fluoride gave the corresponding alcohol **8**, which was attached to bromo-Wang resin (benzyloxybenzyl bromide, 0.7 mmol Br g^{-1}) to give the supported ligand **9** (Scheme 2). Micro-analysis of **9** showed that about a third of the active sites on the resin had been taken up by the ligand (0.26 mmol g^{-1}). The catalyst complex was obtained by treatment of the resin bound ligand with CuOTf and the copper content determined by ICP analysis (0.018 mmol g^{-1}).



Scheme 1.



Scheme 2.

Bisoxazoline **5d** gave the *trans*-cyclopropane in 95% ee (Table 1, entry 7) demonstrating that the addition of the silyloxymethyl group to the 4-position of the aromatic ring leads to only a slight decrease in the level of enantiocontrol. In contrast, immobilised ligand **9** gave the *trans*-cyclopropane in 65% ee (Table 1, entry 8). While immobilisation leads to a substantial drop in selectivity, this represents the highest reported enantioselectivity for this cyclopropanation using a bisoxazoline grafted to a preformed organic polymer support.

It should be noted that since the dioxane ring will presumably adopt a chair conformation in which the aromatic ring at the 2-position is equatorial, ligands **5** are not C_2 symmetrical. One oxazoline ring is axial, and will suffer an interaction between the oxazoline oxygen and the axial lone pairs of the two dioxane oxygens; the other oxazoline is equatorial and avoids this interaction. Although a retention of C_2-symmetry has been stated to be important in designing immobilised bisoxazolines,[22] non-C_2-symmetrical ligands designed to minimise the increase in steric hindrance at the bridging methylene carbon when compared to **1**, have proven to form highly enantioselective catalysts,[12] and hence C_2-symmetry is not essential for good enantiocontrol.

3. Conclusion

In summary, under homogeneous conditions, the introduction of a dioxane ring at the C_1 bridge of the bisoxazoline overcomes the drop in enantioselectivity often observed with the introduction of groups other than methyl at this position.[6] The selectivity obtained with the immobilised ligand **9** represents a significant improvement over ligand **2** bearing larger and more flexible groups at C_1.[8] Since immobilised bisoxazoline ligands which have been prepared by polymerisation of oxazoline containing monomers are reported to give higher enantioselectivities for cyclopropanation than those prepared by grafting onto a preformed polymer,[22,12] we are currently investigating the polymerisation of dioxane-bridged bisoxazoline monomers. The results of this work will be published in due course.

Acknowledgements

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