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A New Class of Bis-Oxazoline Ligands for the Cu-Catalysed Asymmetric Cyclopropanation of Olefins

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Abstract: A set of new chiral bis-oxazolines, **5a-b** and **6a-c**, has been synthesised from *D* and *L*-diethyl 2,3-*O*-isopropylidene tartrates and chiral amino alcohols. These ligands were found to be efficient in the Cu(I)-catalysed asymmetric cyclopropanation of olefins. Bis-oxazolines of this type based on readily available valine were found comparable with previous ligands based on the more expensive *tert*-leucine.
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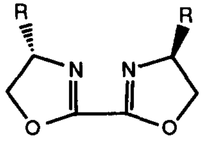
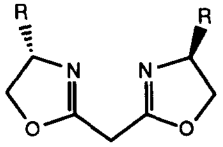
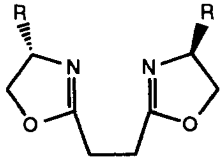
The C_2-symmetric chiral bis-oxazolines have emerged as an efficient class of ligands for a variety of metal catalysed asymmetric reactions in the last few years.[1] The most widely studied ligand of this series is **2** where the two oxazolines are separated by a methylene bridge and which forms a six membered chelate with the metal. Evans[2,3] has previously reported the cyclopropanation of styrene with ethyl diazoacetate in the presence of the catalyst generated *in situ* from copper(I)triflate and bisoxazoline **2c** (R=*t*-Bu) with very high asymmetric induction. However, other derivatives of **1** and **2** with less bulky stereogenic groups were found to be much less effective. The use of a *t*-Bu derivative of **2** has also been found to be crucial in order to achieve high asymmetric induction in several other catalytic reactions.[4,5] In this preliminary communication we report on a new class of bis-oxazolines where the two oxazolines are separated by a tartrate backbone and thus form a seven membered chelate with the metal.



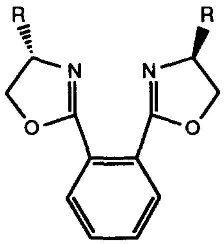
1a; R=CHMe$_2$



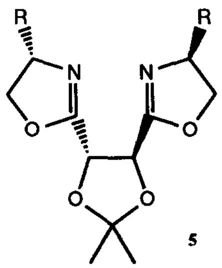
2a; R=CH$_2$Ph
2b; R=CHMe$_2$
2c; R=CMe$_3$



3; R=CHMe$_2$



4; R=CHMe$_2$



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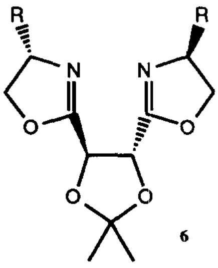

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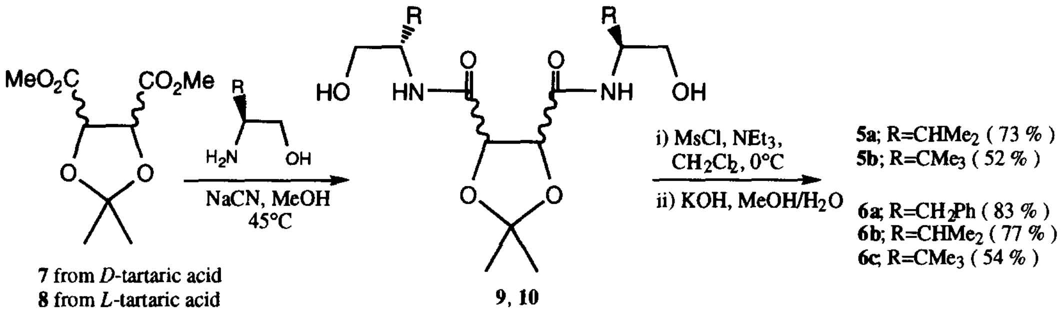
The bis-oxazolines, **5a-b** and **6a-c**, were synthesised from the corresponding *D* and *L* dimethyl 2,3-*O*-isopropylidene tartrates **7** and **8** as shown in Scheme 1. The intermediate bis-amidoalcohols **9** and **10** were prepared under NaCN catalysed neutral conditions[6] and were subsequently cyclised into bis-oxazolines in good overall yields according to the procedure reported by Denmark.[1f]



Scheme 1

The model study of cyclopropanation was done on styrene with ethyl diazoacetate in the presence of the catalyst generated *in situ* using 1 % Cu(I)OTf[7] and 1.05 % of ligand. The results are summarized in Table I.

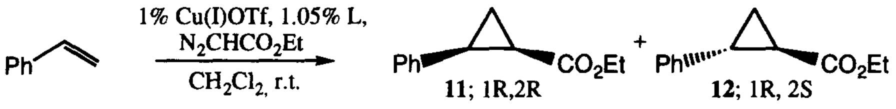
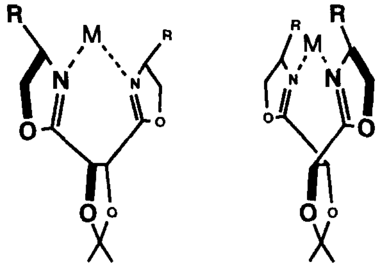


Table I. Cyclopropanation of styrene with ethyldiazoacetate

Ligand[a]	Yield[b]	Diastereoselectivity[c] trans : cis	% *ee*[d] trans	% *ee*[e] cis	Configuration[f] trans / cis
6a	77	68 : 32	50	39	1R,2R / 1R,2S
6b	76	70 : 30	84	65	1R,2R / 1R,2S
6c	78	64 : 36	2	ND	ND
5a	77	67 : 33	68	73	1R,2R / 1R,2S
5b	85	70 : 30	84	85	1R,2R / 1R,2S
3	49	64 : 36	59	30	1R,2R / 1R,2S
4	12	64 : 36	8	ND	ND
1[2]	g	66 : 34	3	8	1R,2R / 1R,2S
2a[4]	76	71 : 29	36	15	1R,2R / 1S,2R
2a[5]	g	86 : 14	19	9	1R,2R / 1R,2S
2b[4]	72	71 : 29	46	31	1R,2R / 1S,2R
2b[5]	g	84 : 16	13	5	1R,2R / 1R,2S
2c[2]	g	77 : 23	98	93	1R.2R / 1R.2S

[a] For the last six entries the values are taken from the literature as indicated; [b] Isolated yield; [c] Determined by ^{1}H NMR of the crude product; [d] By chiral HPLC using Chiralcel OD-H; [e] By optical rotation; [f] Based on the sign of optical rotation.[8] [g] Not mentioned.

Four bis-oxazolines with different tethers were compared, the flexible ethane unit (ligand **3**), the rigid and planar ortho substituted benzene ring (ligand **4**) and the rigid and twisted tartrates (ligands **5** and **6**). The beneficiary effect of using a 7-membered chelate[9] was clearly demonstrated with ligand **3**[10] which resulted in 59% *ee* for the *trans* cyclopropane **11** (compared to 3% *ee* using ligand **1a** and 13-46% for **2b**). The more rigid benzene derived ligand **4**, on the other hand, resulted in considerably lower enantioselectivity and yield (8% *ee*, 12% yield). A plausible explanation for this might be the electron withdrawing character of the aromatic ring. In the rigid tartrate derived ligands **5** and **6**, the two oxazoline rings are no longer co-planar but slightly twisted pushing the oxazolinyl R groups either towards the metal ion (using the amino alcohol derived from *L*-amino acid and *L*-tartrate **6**, Fig. 1) or away from it (*L*-amino acid and *D*-tartrate, **5**). Rigid bis-oxazolines **5a** with a wide angle between the R-groups led to an enantioselectivity of 68% for the *trans* product and this could be further increased by using ligand **6b**, in which the R-groups are brought closer to the metal (84% *ee* for the major product). If the isopropyl group in **6** is replaced by a *t*-Bu group, there will no longer be sufficient space for the copper to coordinate to the bis-oxazoline and as a result, low enantioselectivity is observed. In the case of ligand **5** where the R groups are not in such close proximity, the trend was opposite and higher enantioselectivity was observed when *i*-Pr (68% ee) was replaced by *t*-Bu (84% ee).



5 **6**

Figure 1

The conclusion that ligand **6c** failed to form a complex with Cu(I)OTf due to its large oxazolinyl substituents was also supported by separate experiments in which the ligands were treated with various cuprous complexes and their ^1H NMR spectra observed. The isopropyl ligand **6b** showed a single set of signals in ^1H NMR with downfield shift of the oxazolyl protons indicating rapid complex formation while the *t*-Bu derivative **6c** gave rise to two sets of signals on addition of cuprous complexes demonstrating unsymmetric oxazoline copper complexes. On the other hand, ligand **5b** did indeed form the symmetrical complex and produced both *cis* and *trans* cyclopropanated products with high optical purity.

The effect of the diazoacetate in the cyclopropanation of styrene was also studied using various diazoacetates in the presence of **6b** (Table II). Increasing the steric bulk of the diazoacetate from ethyl to *t*-Bu led to an *ee* of 88%. This could be improved further by using (-)-menthyldiazoacetate (89% *ee*) or (-)-8-phenylmenthyldiazoacetate (96% *ee*).

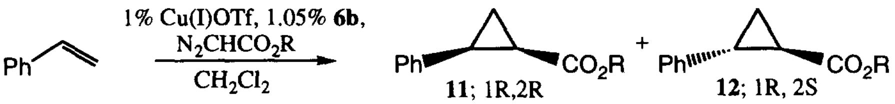
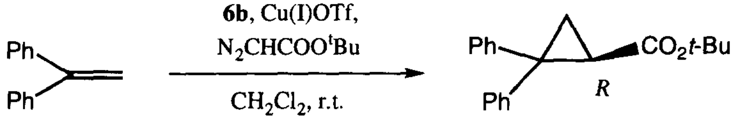


Table II. Cyclopropanation of styrene with various diazoacetates

Diazoacetate[ref]	% Yield[a]	Diastereoselectivity[b] trans : cis	% *ee* trans	% *ee* cis
Ethyl	76	70 : 30	84	65
t-Butyl[11]	84	82 : 18	88[c]	84[d]
(-)-Menthyl[12]	86	85 : 15	89[e]	89[e]
(-)-8-Phenyl menthyl[13]	80	80 : 20	96[d]	91[d]

[a] Isolated yield; [b] Determined by ^1H NMR of the crude product; [c] By optical rotation of acid; [d] By chiral HPLC using Chiralcel OD-H; [e] By GLC analysis.

This new set of ligands has also been investigated for cyclopropanation of other olefins (eq. 1). Cyclopropanation of 1,1-diphenylstyrene with *t*-Bu diazoacetate gave the product in 90% yield and with 92% optical purity.



eq. 1.

90% yield, 92% *ee*

By introducing a tartrate backbone between the two oxazoline rings we have synthesised a new class of bis-oxazolines which have shown high enantioselectivity in the cyclopropanation of olefins compared to the corresponding conventional ligands having a methylene bridge between the two oxazoline rings. The valine derived ligand **6b** was found comparable with the analogous ligand **2c** derived from more expensive *tert*-leucine. Work is in progress to compare this new system for other asymmetric transformations.

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