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cis-Selective cyclopropanations using chiral 5,5-diaryl bis(oxazoline) catalysts

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Abstract

A series of 5,5-diaryl bis(oxazolines) have been prepared and used as ligands in the copper catalysed asymmetric cyclopropanation of styrene. Unusually, for bis(oxazolines), the diastereoselectivity of the process favoured the *cis* cyclopropanes with diastereomeric ratios of up to 65:35 being realised. The *cis* selectivity of the process was rationalised in terms of repulsion between the alkene substituent and the *pro-R* 5-aryl group of the bis(oxazoline). © 2000 Published by Elsevier Science Ltd.

Over the last decade a wide range of chiral bis(oxazoline)–metal complexes have been used to catalyse an impressive array of asymmetric transformations.[1] These processes include asymmetric cyclopropanation and aziridination of alkenes, Diels–Alder and cycloadditions, Mukaiyama aldol reactions, allylic substitutions, oxidations and hydrosilylation reactions. One of the most studied procedures has been the bis(oxazoline)–copper and bis(oxazoline)–ruthenium catalysed asymmetric cyclopropanation of alkenes.[2] In general, the procedure is highly diastereoselective for the formation of the *trans* cyclopropanes (*trans:cis* ratios ca. 68:32 to 100:0) and exceptionally high ee's have been realised (up to 99% ee). Access to the *cis* cyclopropanes has been more elusive but very recently there has been growing interest in the development of *cis* diasteroselective processes. These methods have involved alkene cyclopropanations with diazoacetate catalysed by chiral complexes including copper(I) bis(oxazolines) derived from tartrate,[3] metal(II)–salen complexes,[4] dirhodium(II) carboximides[5] and dirhodium(II) carboxylates.[6]

We have previously shown that 5,5-diaryl substituents in chiral oxazolidinone auxiliaries can result in beneficial diastereoselectivity and chemical efficiency.[7] As part of a programme aimed at generating *cis* cyclopropanes, we decided to investigate such 5,5-diaryl substitution in bis(oxazoline) catalysed cyclopropanations. At the outset, we were aware that Singh and co-workers had

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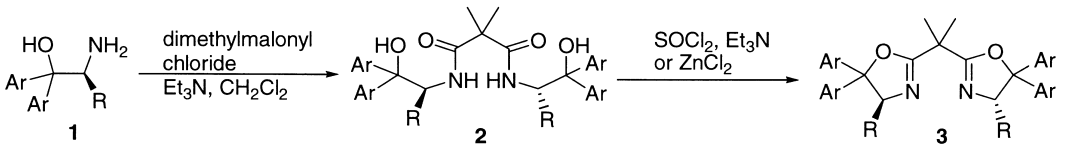
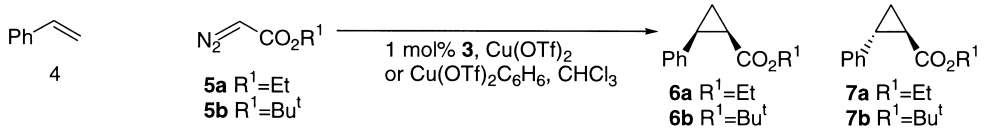
observed very poor enantioselectivities (< 40% ee) in the asymmetric *trans*-selective cyclopropanation of styrene using 5,5-disubstituted pybox catalysts.[8] More recently, Singh[9] and co-workers have used 5,5-disubstituted pybox catalysts in enantioselective allylic oxidations while Andrus et al.[10] have utilised 5,5-dimethyl bis(oxazolines) in the same processes. Originally, Corey et al. employed 5,5-dimethyl bis(oxazolines) in the asymmetric Diels–Alder reaction.[11]

The required starting tertiary amino alcohols **1a–f** were prepared by the reaction of excess Grignard reagent with the appropriate amino ester hydrochloride salt.[7,12] Using the methodology of Denmark et al.[13] the tertiary amino alcohols **1a–f** were converted into the diamides **2a–f** by treatment with dimethylmalonyl chloride and triethylamine (Scheme 1). The subsequent transformation of diamides **2a–f** into bis(oxazolines) **3a–f** initially proved problematic. Using the method of Corey[11] for the cyclisation of tertiary alcohol diamides with methanesulfonic acid and azeotropic removal of water gave the mono cyclised mono dehydrated product. The use of thionyl chloride in toluene at reflux[13] resulted in the dehydrated product being formed. Gratifyingly, treatment of diamides **2a–c** and **2e**,**f** with thionyl chloride at room temperature gave the appropriate bis(oxazolines) **3a–c**,**e**,**f**. However, similar treatment of diamide **2c** gave a complex mixture of products. Fortunately, diamide **2c** could be smoothly converted into the bis(oxazoline) **3c** with zinc chloride in dichloroethane at reflux.



Scheme 1. (a) R = Pr^i, Ar = 4-tolyl; (b) R = Pr^i, Ar = 2-naphthyl; (c) R = Bu^t, Ar = 4-tolyl; (d) R = Ph, Ar = 4-tolyl; (e) R = CH_2Ph, Ar = 4-tolyl; (f) R = CH_2Ph, Ar = 2-naphthyl

The efficacy of 1:1 mixtures of bis(oxazolines) **3** and appropriate copper salts to catalyse the asymmetric cyclopropanation of styrene **4** with diazoesters **5** was investigated (Scheme 2, Table 1). Initially, a wide range of reaction parameters were investigated for the isopropyl 5,5-ditolyl bis(oxazoline) **3a** (entries 1–7, Table 1). In the cases using ethyl diazoacetate as the carbene source there is a preference (up to 65:35) for the *cis* cyclopropane **6a** over the *trans* cyclopropane **7a** (entries 1–5, Table 1). The use of *tert*-butyl diazoacetate **5b** as the carbene source results in a diminishing of the *cis* selectivity (ca 1:1) but an increase in the enantioselectivity of the process (entries 6 and 7).



Scheme 2.

Clearly, the structure of the bis(oxazoline) ligand influences the diastereoselectivity of the cyclopropanation. This is in contrast to the observations of Pfalz et al. for the semicorrin catalysed asymmetric cyclopropanations where the *trans* diastereoselectivity was attributed solely to interactions between the alkene and the carbene ester group.[14] However, we believe that the

Table 1
Asymmetric cyclopropanation of styrene **4** using 1 mol% of bis(oxazolines) **3**

Entry	**3**	Salt[a]	Temp (°C)	**5**	Yield (%)	Ratio **6**:**7**[b]	% ee **6**[c]	% ee **7**[d]
1	a	Cu(II)	20	a	83	61:39	58	56
2[e]	a	Cu(II)	20	a	49	61:39	58	54
3	a	Cu(II)	0	a	68	65:35	64	66
4	a	Cu(I)	20	a	100	65:35	60	59
5	a	Cu(I)	0	a	85	63:37	63	64
6	a	Cu(II)	0	b	80	48:52	76	75
7	a	Cu(I)	0	b	85	50:50	73	81
8	b	Cu(I)	0	a	42	59:41	44	36
9	c	Cu(I)	20	a	87	52:48	63	55
10	d	Cu(I)	20	a	63	42:58	45	51
11	e	Cu(I)	0	a	36	38:62	36	26
12	f	Cu(I)	0	a	46	46:54	76	72

[a]Cu(II) refers to the use of $Cu(OTf)_2$, while Cu(I) refers to $Cu(OTf)_2C_6H_6$. [b]Determined by ^1H nmr. [c]Determined by hplc of the pure *cis* ethyl ester using a Chiralcel OJ column. [d]Determined by hplc of the pure *trans* ethyl ester using a Chiralcel OD column. [e]Using 0.1 mol% of **3a**.

general mechanistic protocol is similar to that delineated by Pfalz et al.[14] and extended by Singh and co-workers.[9] Here the enantioselectivity can be understood from the attack of the *Re* face of the electrophilic carbenoid by the alkene. This avoids steric repulsion at the transition state between the carbene ester group and the C-4 substituent at the stereogenic centre. However, to understand the unusual *cis* diastereoselectivity we carried out a molecular mechanics based modelling study.[15] This modelling suggested that the carbene is distorted from being orthogonal to the bis(oxazoline) ring and this further favours alkene attack at the *Re* face of the carbene. Additionally, there is potentially an unfavourable steric interaction between the styrene phenyl group and the *pro-R* aryl group at C-5 for *ul* addition which leads to the *trans* cyclopropane **7**. This adverse steric interaction is avoided for the *lk* addition and results in the preferential formation of the *cis* cyclopropane **6**. However, this adverse steric interaction is counter balanced by a steric repulsion between the styrene phenyl and the ester alkyl group on the carbene in the favourable *lk* addition. Thus, the use of *tert*-butyl diazoacetate **5b** results in an increase in the proportion of the *trans* isomer **7**.

In contrast to previously reported[2] bis(oxazoline) catalysis with copper(II) salts, the use of bis(oxazoline) **3a** with copper(II) triflate did not require heat or the addition of phenylhydrazine to initiate the carbene insertion reaction (entries 1–3 and 6). However, in the case of bis(oxazoline) **3a**, the best selectivities were obtained using copper(I) triflate when the reaction was carried out at 0°C. Under these conditions the use of ethyl diazoacetate **5a** afforded a 63:37 mixture of *cis* cyclopropane **6a** and *trans* cyclopropane **7a** in ee's of 63% and 64%, respectively (entry 5). Similar conditions with *tert*-butyl diazoacetate **5b** afforded the corresponding *cis* **6b** and *trans* **7b** products in a 1:1 ratio with ee's of 73 and 81%, respectively (entry 7).

All the initial reactions with bis(oxazoline) **3a** were conducted using 1 mol% of the catalyst system. However, changing the substrate:catalyst ratio to 1000:1 does not appear to compromise the stereochemical outcome of the reaction, but results in a lower yield (entry 2).

The influence of the steric requirements at C-4 and C-5 in the enantioselective cyclopropanation of styrene **4** using copper(I) triflate and ethyl diazoacetate **5a** was investigated. These results indicated that increasing the steric requirements of the 5,5-substituents resulted in little change in

the *cis:trans* ratio but diminished the enantioselectivity (entries 5 and 8). However, for the 4-benzyl bis(oxazolines) **3e** and **3f** there is an increase in both the enantioselectivity and the *cis* diastereoselectivity on increasing the steric demand at the 5-positions (entries 11 and 12). On the other hand, increasing the steric requirements at the stereogenic centres resulted in a decrease in the *cis* diastereoselectivity (entries 5, 9 and 10)

Acknowledgements

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