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Asymmetric Copper-Catalysed Alkene Cyclopropanation and Aziridination Using Tartrate-Derived Bis-Oxazoline Ligands

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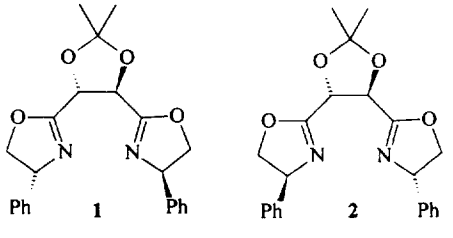
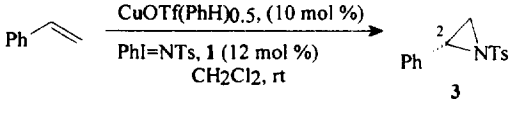
Abstract: The enantioselective cyclopropanation and aziridination of styrene using chiral tartrate-derived bis-oxazoline ligands **1**, **6**, and **7** is reported. The effects of variation of the size of the oxazoline substituent (R^1) and the size of the diazoacetate ester substituent (R^2) on the level and sense of enantioselection is described. Copyright © 1996 Elsevier Science Ltd

The enantioselective cyclopropanation[1-5] and aziridination[6-9] of alkenes is currently an area of significant research activity. We have recently reported[10] the synthesis of new tartrate-derived bis-oxazoline ligands **1** and **2** and their use in the copper catalysed cyclopropanation and aziridination of styrene. We were surprised to find that the configuration of the major enantiomer of the aziridine **3** (2*R*) was opposite to that of the corresponding *trans*-cyclopropane **4** (R^2 = Et; 2*S*) formed using the same catalyst (**1**). This observation seems to contradict the idea that the transition states for aziridination and cyclopropanation are similar.[11]



1 **2**



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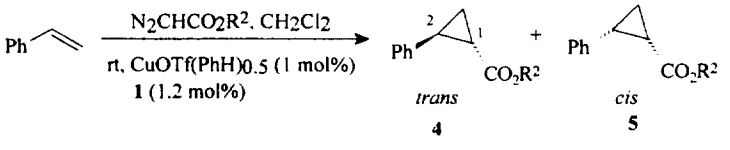
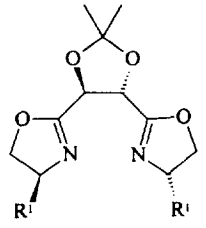


4 **5**

In order to investigate this issue further, we have explored the use of a bulkier diazoacetate which more closely resembles the large tosyl group in size. We have also studied the effect of changing the size of the substituent on the oxazoline rings on the level of enantioselectivity observed in these reactions. The results of these studies are detailed below.

Ligands **6**[12] and **7** bearing ^{i}Pr and ^{t}Bu substituents were prepared from diethyl D-tartrate with (*S*)-valine and (*S*)-*tert*-leucine, respectively, in the same way as reported for the phenyl substituted ligand **1**.[10] Ligands **6** and **7** are in the enantiomeric series to ligand **1**. The results of cyclopropanation and aziridination of styrene using these ligands are shown in **Table 1**.



6 $R^1 = {}^{i}Pr$
7 $R^1 = {}^{t}Bu$

Table 1. Enantioselective Copper-Catalysed Cyclopropanations[a] and Aziridinations[b] of Styrene.

Entry	Ligand (R^1)	Diazoacetate (R^2)	Iodonium ylid	Yield[c] /%	*trans*:*cis* ratio	*trans* ee /% (major isomer[d])	*cis* ee /% (major isomer[d])	aziridine ee /% (major[d])
1[10]	**1** (Ph)	Et	-	69	79:21	49 (1*S*, 2*S*)[e]	34 (1*S*, 2*R*)[e]	-
2	**1** (Ph)	^{t}Bu	-	75	88:12	52 (1*R*, 2*R*)[g]	15 (1*R*, 2*S*)[g]	-
3[10]	**1** (Ph)	-	PhINTs	65	-	-	-	12[f] (2*R*)
4	**6** (^{i}Pr)	Et	-	64	72:28	74 (1*R*, 2*R*)[e]	77 (1*R*, 2*S*)[e]	-
5	**6** (^{i}Pr)	^{t}Bu	-	48	84:16	80 (1*R*, 2*R*)[g]	17 (1*R*, 2*S*)[g]	-
6	**6** (^{i}Pr)	-	PhINTs	73	-	-	-	2[f] (2*S*)
7	**7** (^{t}Bu)	Et	-	56	75:25	49 (1*R*, 2*R*)[g]	38 (1*R*, 2*S*)[g]	-
8	**7** (^{t}Bu)	^{t}Bu	-	75	66:34	36 (1*R*, 2*R*)[g]	7 (1*R*, 2*S*)[g]	-
9	**7** (^{t}Bu)	-	PhINTs	80	-	-	-	<5[d] (2*S*)

The results in entries 1 and 3 are taken from reference 10. [a]Performed as described in reference 3. [b]Performed as described in reference 6. [c]Isolated yields. All products gave the expected ^{1}H, IR, and mass spectra. [d]Determined by optical rotation. [e]Determined by HPLC using a Chiracel OJ, P-615C column. [f]Determined by HPLC using a Whelk O, P-595C column. [g]Determined by GC using a chiral cyclodextrin column.

Changing the oxazoline substituent (R^1) from phenyl to *iso*-propyl leads to an increase in the enantioselectivity of cyclopropanation (compare entries 1 and 4, or 2 and 5) without significantly affecting the *trans:cis* ratio. Increasing the size of the oxazoline substituent still further (to *tert*-butyl) leads to an unexpected drop in the level of enantioselectivity (entries 4 and 7; or 5 and 8). A similar pronounced drop in enantioselectivity is also seen in the aziridination reactions on increasing the size of R^1 (entries 3, 6, and 9). These observations suggest that the transition state is becoming overcrowded as the groups on the ligand become larger and that this leads to poorer selectivity.

In agreement with this idea is the effect of increasing the size of the diazoacetate substituent (R^2). Increasing the size of the ester is reported to lead to improved *trans:cis* ratios.[3-5] In our case, changing from ethyl- to *tert*-butyl- diazoacetate does improve the *trans:cis* ratio for ligands **1** and **6** (entries 1 and 2; or 4 and 5). For the *tert*-butyl substituted ligand **7**, however, increasing the size of the diazoacetate leads to a *decrease* in the *trans:cis* ratio (entries 7 and 8) again suggesting an effect due to overcrowding. The size of the diazoacetate substituent does not normally change the level or sense of enantioselection significantly.[3-5] The *iso*-propyl (**6**) and *tert*-butyl ligands (**7**) behave normally in this respect; changing the diazoacetate does not affect the sense of enantioselection (entries 4 and 5; or 7 and 8) and the major cyclopropane isomers have the 1*R* configuration. Although the level of enantioselection is affected only slightly for the *trans* isomers, the ee for the *cis* isomers drops dramatically on increasing the size of the diazoacetate. Since the transition state leading to the *cis* isomer is expected to me more congested than that leading to the *trans*, this could again be due to overcrowding.

The phenyl substituted ligand **1**, however, seems to behave in an unexpected way (entries 1 and 2). Increasing the size of the diazoacetate does indeed lead to a moderate increase in the *trans:cis* ratio but this is accompanied by a change in the sense of enantioselection. The configuration of the major cyclopropane isomers changes from 1*S* (entry 1) to 1*R* (entry 2). *To our knowledge this is the first observation of a change in the size of the diazoacetate leading to a reversal of the sense of enantioselection using the same catalyst.* This observation again points to steric effects in the transition states although the precise reason for the reversal remains unclear.

Interestingly, this result allows us to rationalise the previously reported[10] difference in the sense of asymmetric induction between the cyclopropanation and aziridination using ligand **1**. It can be seen that, although the aziridination (entry 3) and cyclopropanation using ethyl diazoacetate (entry 1) give opposite product configurations, when the size of the diazoacetate is increased (entry 2) the sense of induction becomes the same. This supports the notion that the transition states for aziridination and cyclopropanation are similar, but clearly one must compare reactions in which the sizes of the carbenoid and nitrenoid substituents are similar.

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12. Data for **6**: Colourless prisms; $[\alpha]_D^{22}$-45.2° (c 0.86, $CHCl_3$); m.p. 68-70°C; ν_{max}/cm^{-1} (KBr disc) 2986, 2967, 1675; δ_H (400 MHz, $CDCl_3$) 0.87 (6H, d, *J* 6.5, **Me**CH), 0.95 (6H, d, *J* 6.5, **Me**CH), 1.50 [6H, s, OC**Me**$_2$], 1.78 (1H, octet, *J* 6.5, C**H**Me$_2$), 4.0 (2H, m, NC**H**), 4.31 (2H, dd, *J* 8, 8.5, **H**CHO), 4.34 (2H, dd, *J* 10, 8.5, HC**H**O), 4.96 [2H, s, C(NOC)**H**O]; δ_C (100 MHz, $CDCl_3$) 17.89, 18.67, 26.29, 32.30, 70.66, 72.10, 74.12, 112.60, and 163.08; m/z (EI) 325 (M^+ + H, 5%), 309 (20), 267 (25), 223 (55), 154 (100), and 43 (80). The identity of this compound was confirmed by X-ray crystal structure determination.

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