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C_2-Symmetric Bis(Aziridines): A New Class of Chiral Ligands for Transition Metal-Mediated Asymmetric Synthesis

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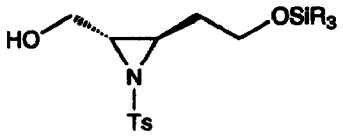
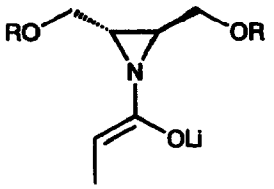
Key Words: Chiral ligands; asymmetric dihydroxylation; catalytic asymmetric allylic substitution; catalytic asymmetric cyclopropanation; catalytic asymmetric aziridination.

Abstract: *The readily available C_2-symmetric bis(aziridines) **1** can act as ligands in a variety of asymmetric transformations mediated by transition metals. In the best cases, >95% ee can be obtained.*

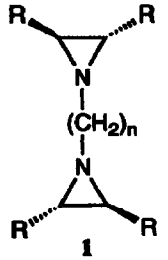
For the past few years we have been exploring the use of chiral aziridines[1a] for asymmetric synthesis and we have shown[1b] how aziridines can function as chiral *substrates* (e.g. for the enantioselective total synthesis of β-lactam antibiotics), and as chiral *auxiliaries* for asymmetric alkylation and aldol reactions. We now wish to report on the use of C_2-symmetric bis(aziridines), **1**, as chiral *ligands* for both stoichiometric and catalytic asymmetric processes mediated by transition metals.



Chiral aziridine *substrate*
(for synthesis of carbapenems)



Chiral aziridine *auxiliary*
(for asymmetric alkylation and aldol)



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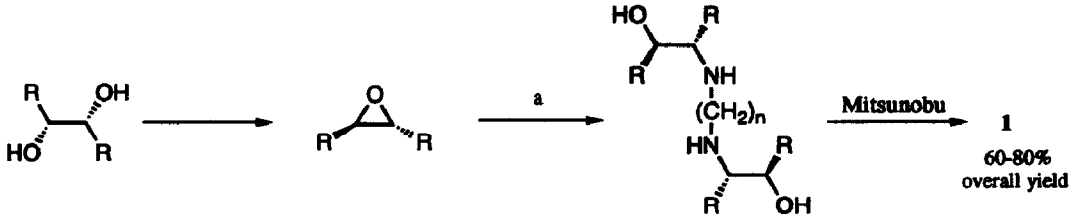
Chiral aziridine *ligand*
R = aryl, alkyl; n = 2, 3, 4.

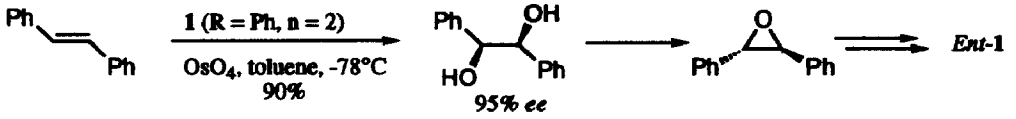
The general route to ligands **1** (Scheme 1) is very simple and is based on the ready availability of enantiomerically pure C_2-symmetric epoxides from chiral 1,2-diols[2a]. The epoxides[2b] (2 eq.) are subjected to ring-opening by a suitable diamine (1 eq.), followed by a double Mitsunobu reaction[3] which gives the desired ligands in good overall yield. The synthetic approach is flexible and allows for *(i)* entry

to both enantiomeric series *(ii)* variation of ring-substituents, *(iii)* different lengths of the spacer chain, *(iv)* introduction of extra stereocentres in the spacer, if required. So far, our studies have concentrated on ligand **1** (R = Ph, n = 2) which has been used in the asymmetric transformations[4] shown in Schemes 2 - 5.



Scheme 1. Synthesis of C_2-symmetric aziridine ligands. (a) 0.5 eq. $H_2N(CH_2)_nNH_2$, Δ.

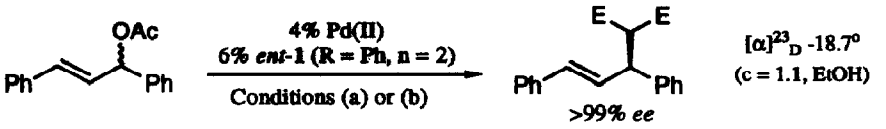
The first reaction we studied was the stoichiometric *syn*-dihydroxylation[5a,b] of *trans*-stilbene mediated by a complex of **1** and OsO_4 (Scheme 2). The bis(aziridine) did indeed function as an accelerative ligand (the reaction could be carried out at low temperature), and the stilbene diol with the absolute configuration shown[5c] was isolated in good chemical yield and in 95% *ee*. (At this stage we prefer not to speculate on possible mechanisms[2a]).



Scheme 2. Stoichiometric asymmetric dihydroxylation using ligand **1**. (2-3 eq. ligand per OsO_4).

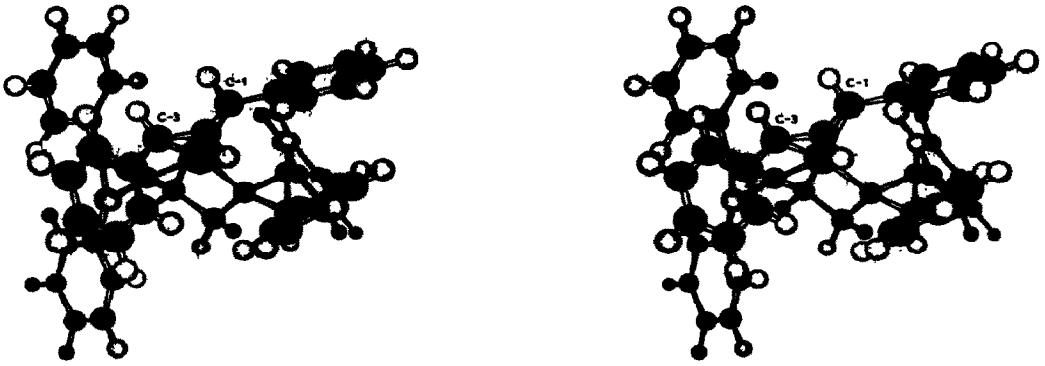
If desired, the intermediate osmate ester complex of **1** can be isolated; after hydrolytic work-up and flash chromatography, the ligand is easily recovered for re-use. It is also noteworthy that the product of this reaction actually serves as the starting material for synthesis of the enantiomeric ligand!

With this encouraging result in hand, we turned our attention to the more demanding issue of *catalytic* asymmetric synthesis in the form of the palladium-mediated reaction[6a,b,c] shown in Scheme 3.



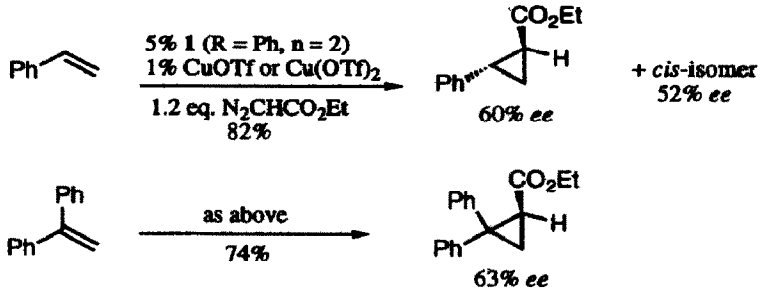
Scheme 3. Catalytic asymmetric nucleophilic substitution using *ent*-**1**. Pd(II) = $(\pi\text{-allyl})_2PdCl_2$, E = CO_2Me.
Conditions (a): 1.5 eq. $CH_2(CO_2Me)_2$, 1.5 eq. *N, O*-bis(trimethylsilyl)acetamide, 0.1 eq. KOAc, THF, rt, 77%.
Conditions (b): 1.2 eq. $NaCH(CO_2Me)_2$, THF, rt, 89%.

This process involves nucleophilic attack by the malonate anion on a (distorted) square-planar complex formed from the chiral ligand, Pd(II), and racemic 1,3-diphenyl-2-propenyl acetate. The absolute stereochemistry of the product[6d] is consistent with the intermediacy of the structure shown below (Chem 3D representation) in which non-bonded interactions are minimized. The nucleophile approaches *anti* with respect to palladium, and attacks the less-hindered terminus (C-1) of the π-allyl system. Attack at C-3 is hindered by one of the phenyl groups on the nearest aziridine ring. (We are currently engaged on the isolation and structure determination of the putative π-allyl intermediate).



The reaction can be run under two different sets of conditions[6a], an experimental advantage of the present system being that preformed sodium malonate can be used (conditions *b* in Scheme 3).

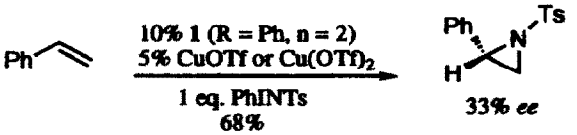
Recently, much attention has been paid to copper-catalyzed asymmetric cyclopropanation[7a,b,c] and aziridination[8a,b], and it was therefore of interest to test our ligands in such reactions (Scheme 4).



Scheme 4. Catalytic asymmetric cyclopropanation using ligand 1.

Although the levels of *ee* obtained[7d] so far are modest in comparison to the best literature values[7a-c], we are hopeful that the necessary improvements can be made by fine-tuning of the ligand structure. (For example, in his impressive study of asymmetric cyclopropanation, Evans[7a] has pointed out the advantage of having 6- rather than 5-membered chelates as the catalytic species). With 1, in contrast to the Evans ligands, the more easily handled Cu(II) triflate can be used in place of the corresponding copper(I) species. The process is nevertheless presumed to involve a Cu(I) complex as the catalyst, with the diazoester acting as the reducing agent[9]. Mechanistic speculation pertaining to the stereochemical course of the reaction must await further experimentation.

Finally, copper catalysis of the reaction between PhI=NTs and olefins in the presence of ligands 1 offers the amusing possibility of using one chiral aziridine to mediate formation of another (Scheme 5).



Scheme 5. Catalytic asymmetric aziridination using ligand 1.

As for cyclopropanation using the same ligand 1, it is apparently immaterial if one starts with Cu(I) or Cu(II); the latter has been suggested[8b] to be the true catalytic species, with PhI=NTs acting as oxidant. The enantioselective aziridination of styrene has also proved problematic for others[8a,b] and the detailed reaction mechanism remains obscure; thus, while the *ee* shown above[8c] is not impressive it is nevertheless encouraging. Modification of the catalytic system and ligand structure, in order to improve enantioselectivity, is under way[10].

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10. The ligand is recovered unchanged from the reactions shown in Schemes 3 - 5.

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