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Asymmetric aziridination of chalcones catalyzed by a novel backbone 1,8-bisoxazolinylanthracene (AnBOX)-copper complex†

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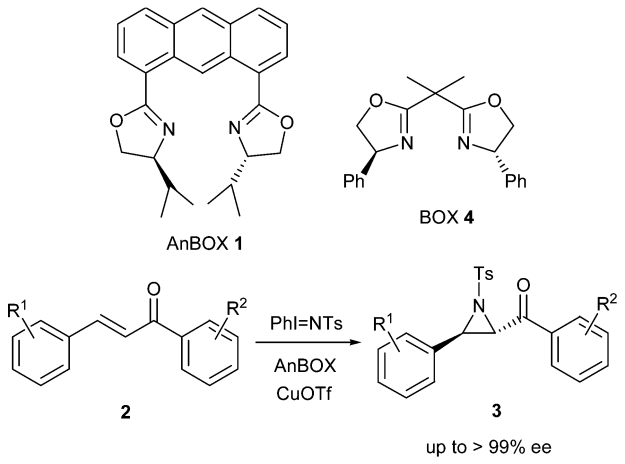
Highly enantioselective aziridination of chalcones catalyzed by a novel backbone 1,8-bisoxazolidinylanthracene (AnBOX) and CuOTf with up to > 99% ee and the opposite enantioselectivity compared with the ligands of Evans are described.

Aziridines are the nitrogen analogues of epoxides and exhibit similar reactivity patterns as electrophilic reagents.[1] They undergo highly regio- and stereoselective transformations and are very useful intermediates in organic synthesis.[2] The aziridines, especially chiral aziridine derivatives, have been attractive synthetic targets in their own right recently.[1,2a] There have been three major approaches for catalytic asymmetric aziridinations developed during the past decade,[2a,3] including nitrene transfer to olefins[4,5] and carbene transfer to imines[6] under the catalysis of chiral ligands and transition metals,[7] and carbene transfer to imines *via* chiral sulfonium ylides.[8] Among them, the nitrene transfer to olefins is a powerful strategy for the synthesis of enantiomerically enriched aziridines with a variety of functional groups.[4,5] In transition metal–chiral ligand catalyzed asymmetric aziridinations, the C_2 symmetric chiral bisoxazolines have emerged as one of the most efficient classes of ligands and Cu(I) has been proven to be an effective metal.[4] Recently numerous chiral bisoxazoline ligands have been synthesized from readily available diacid and chiral amino alcohols and they have been applied widely in catalytic asymmetric reactions.[9] The influence of substitutions both on the oxazoline ring and on the backbone moiety has been investigated previously.[10] Some conformationally rigid backbone-containing bisoxazoline ligands, in which the two oxazoline rings were linked by benzene,[11] pyridine,[12] dibenzofuran,[13] dibenzothiophen,[14] and bicyclic compounds,[15] have also been synthesized and evaluated in some asymmetric catalytic reactions. However, highly enantioselective aziridination of chalcones still remains a challenging problem.[16] This promotes us to search for novel bisoxazoline ligands for the asymmetric aziridination.

Our design for this ligand focuses on a backbone possessing some different structural features from previously reported bisoxazoline ligands.[9–15] Our ligand, the two oxazoline rings of which are attached on the 1,8-positions of a rigid anthracene ring, possesses only bidentate, instead of tridentate in the rigid bisoxazoline ligands with pyridine, dibenzofuran, or dibenzothiophen as the backbones. Thus, it has a different chiral environment near the reaction center from the reported ones.[11–15] We have investigated the asymmetric aziridination of chalcones employing [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) as the nitrene source with our ligand 1,8-bisoxazolinylanthracene (AnBOX) **1** and copper complex as catalyst. Although the aziridinated products are *N*-sulfonylated, the synthetic utility of sulfonylated products has recently been enhanced by the development of methods for the selective cleavage of the protecting group.[17] Herein, we wish to report our preliminary efforts on this subject.

Our ligand **1** was synthesized and evaluated in the asymmetric aziridination of chalcones.[18] The results are summarized in Table 1. The ee values obviously depend on the substituents on both phenyl groups in the chalcones. The chalcones with electron-donating substituents show higher enantioselectivities than those with electron-withdrawing substituents in the asymmetric aziridination. More than 98% ee values were obtained for mono- and dimethyl substituted chalcones (Table 1, entries 2, 7 and 8). To our best knowledge, this is the highest enantioselectivity reported in the asymmetric aziridination of chalcones.

In comparison with the asymmetric aziridination catalyzed by bisoxazoline (BOX) **4** of Evans *et al.* (Table 1, entry 10),[4] it is very interesting to note that our ligand AnBOX **1** showed different stereoselectivity, with which chalcones were aziridinated in an opposite configuration (2*S*,3*R*) although AnBOX was derived from the L-amino alcohol as used in the BOX ligands of Evans *et al.*[4] The different orientation in the enantioselectivity could be presumed to be due to the fact that AnBOX has a more crowded environment



Scheme 1 Asymmetric aziridination of chalcones **2**.

Table 1 Asymmetric aziridination of chalcones

Entry	Chalcone	R^1	R^2	Ligand	Yield[a] (%)	Ee (%)[b]
1	**2a**	H	H	**1**	80	96[c]
2	**2b**	4-Me	H	**1**	86	98[d]
3	**2c**	4-Cl	H	**1**	70	76[d]
4	**2d**	3-Cl	H	**1**	76	84[d]
5	**2e**	2-Cl	H	**1**	91	79[d]
6	**2f**	3-F	H	**1**	85	71[d]
7	**2g**	H	4-Me	**1**	92	> 99[d]
8	**2h**	4-Me	4-Me	**1**	59	> 99[d]
9	**2i**	4-Me	4-Cl	**1**	51	68[d]
10	**2a**	H	H	**4**	38	86[ce]

[a] Isolated yield after flash silica gel chromatographic separation. [b] Enantiomeric excess was determined by HPLC analysis using chiral columns. [c] The absolute configuration was determined by comparing the measured optical rotations with the reported one.[16] [d] The absolute configurations were tentatively assumed according to the reaction mechanism and their relative retention times on chiral columns. [e] The opposite absolute configuration as shown in Scheme 1 was obtained.

† Electronic supplementary information (ESI) available: characterization data, ^{1}H NMR and ^{13}C NMR spectra for the ligand AnBOX **1** and all unknown compounds **3**, and HPLC chromatograms for the determination of the ee values of all the aziridine derivatives **3**. See http://www.rsc.org/suppdata/cc/b4/b404134h/

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between the two oxazoline rings than the BOXes of Evans *et al.* Copper has to locate above or below the anthrancene ring after it coordinates with AnBOX. Actually, the two locations are the same because of the C_2 symmetry of the AnBOX ligand. The oxazoline rings rotate certain angles and exist in a non-planar mode to the anthrancene ring; unlike in the BOX ligands of Evans *et al.*, where the copper locates between two oxazoline rings. Proposed transition states for the asymmetric aziridination of chalcones for reactions catalyzed by BOX and AnBOX are shown in Schemes 2 and 3, respectively. The coordination of the oxyatom of the carbonyl group in chalcones with copper in the catalyst seems to play an important role to give rise to high enantioselectivity in the asymmetric aziridination.[19] To verify the coordination, 1,3-diphenylpropene, a structural analogue of chalcone, just without carbonyl group, was aziridinated under the same reaction conditions and only 6% ee was obtained. This supports the existence of the coordination. The scope and limitation of this asymmetric aziridination, and the mechanism of the enantioselectivity are currently being investigated in this laboratory.

In summary, the asymmetric aziridination of chalcones using 1,8-bisoxazolinylanthracene (AnBOX) as the chiral ligand has been investigated. Encouragingly high ee values with an opposite configuration, as compared with the bisoxazoline ligands of Evans *et al.*,[4] have been achieved. In addition, the results indicate that the enantioselectivity is substituent-dependent to chalcones. The chalcones with electron-donating substituents show higher enantioselectivities than those with electron-withdrawing substituents. The coordination of the oxyatom of the carbonyl group in chalcones and copper in the catalyst seems to play an important role in the high enantioselectivity in the asymmetric aziridination. It is very interesting that a backbone-controlled stereoselectivity was observed for the AnBOX ligand in the asymmetric aziridination. This provides very important information for designing novel ligands.

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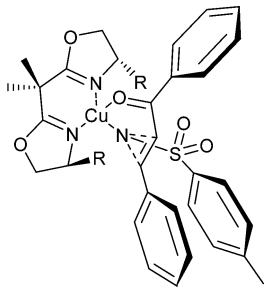
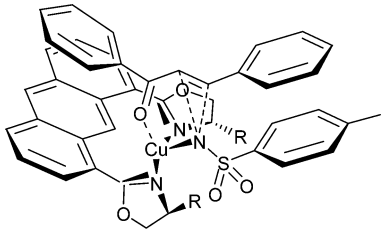


Scheme 2 Proposed transition state in the asymmetric aziridination of chalcone catalyzed by BOX **4** of Evans *et al.*[4] [The nitrene attacks from the bottom, (2*R*,3*S*)-aziridine produced].



Scheme 3 Proposed transition state in the asymmetric aziridination of chalcone catalyzed by our AnBOX **1**. [The nitrene attacks from the top, (2*S*,3*R*)-aziridine produced].

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18 **Asymmetric aziridination of chalcones, general procedure**: to a stirring solution of chalcone **2a** (312 mg, 1.50 mmol), AnBOX **1** (24 mg, 0.06 mmol) and the CuOTf·0.5C_6H_6 (13 mg, 0.05 mmol) in CH_2Cl_2 (8 mL) was added PhI=NTs (373 mg, 1.00 mmol) portionwise under nitrogen atmosphere at 24 °C over 2 h. After the addition, the reaction mixture was kept stirring for another 3 h. The aziridine product was obtained after flash chromatography with petroleum ether (60–90 °C) and ethyl acetate (6 : 1, v/v) as an eluent.

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