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Highly enantioselective asymmetric reactions involving zinc ions promoted by chiral aziridine alcohols

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ABSTRACT

Enantiomerically pure, chiral secondary and tertiary aziridine alcohols (including the aziridine analogue of ProPhenol—AziPhenol) have proven to be highly effective catalysts for enantioselective asymmetric reactions in the presence of zinc ions, including arylation of aromatic aldehydes, epoxidation of chalcone and addition of diethylzinc to aldehydes, leading to the desired chiral products in high chemical yields (up to 90%) and with *ee*'s up to 90%. A higher catalytic activity of Prophenol-type bis(aziridine alcohol) in the aforementioned asymmetric transformations has been demonstrated.

1. Introduction

The enantioselective formation of carbon–carbon bonds is one of the most essential strategies in modern organic chemistry.[1,2] Among them, asymmetric reactions involving zinc cations constitute current and extensively studied topics in synthetic organic chemistry. Typical examples of zinc(II)-mediated stereocontrolled transformations are asymmetric arylation of aldehydes[3] and epoxidation of α,β-unsaturated carbonyl compounds (e.g. chalcone).[4] Both processes are of great importance due to a high significance of potential applications of their chiral products. Thus, diarylmethanols can act as precursors of many biologically and pharmacologically relevant compounds,[3] e.g. (*R*)-orphenadrine and (*R*)-neobenodine,[5] (*S*)-cetirizine[6] or (*S*)-BMS 184394[7,8] (Fig. 1).

In turn, chiral epoxides are a structural part of many natural products, fragrances (epoxides of carvone), pheromones ((+)-disparlure) or alkaloids (scopolamine). Moreover, chiral epoxides find applications in the synthesis of other natural products such as (−)-Cleistenolide[9] and cascarillic acid,[10] and in many other asymmetric transformations.[11] Chiral epoxides are also present in many biologically relevant molecules such as Neocarzinostatin,[12] Ovalicin[13] or Epothilones (Fig. 2).[14,15]

ProPhenol dinuclear ligands containing proline[16–19] or azetidine[20] can form complexes with zinc ions facilitating various asymmetric transformations such as direct aldol reactions,[16,19] 1,4-additions of diethyl phosphite to enones,[17] nitroaldol (Henry) reactions,[18] or Friedel–Crafts alkylations of pyrrole with chalcones.[20]

In order to continue our studies on stereocontrolled reactions including the formation of carbon–carbon bonds,[21–25] having advantageous results in the asymmetric arylation of aldehydes using secondary and tertiary aziridine alcohols[3] we decided to synthesize a novel ProPhenol-type ligand (AziPhenol) containing chiral aziridine moieties and to compare its catalytic activity with those exhibiting by the aforementioned simple aziridine alcohols. Similar studies have been conducted using azetidine analogues of ProPhenol ligands in Friedel–Crafts reaction.[20] These analogues exhibited much higher catalytic activity in comparison with those found with simple chiral azetidine alcohols.[20] First of all, we decided to check the catalytic activity of all designed ligands in the asymmetric epoxidation of chalcone.

2. Results and discussion

2.1. Synthesis of the ligands

Chiral aziridine alcohols **L1**–**L4** (Fig. 3) were synthesized as described previously.[26,27] AziPhenol ligand **L5** was prepared *via* a three-step synthetic route (Scheme 1).

In the first step, *p*-cresol was treated with formaldehyde in aqueous NaOH solution affording the corresponding diol **2**.[18] To the above diol, HBr in acetic acid was added at room temperature, which gave compound **3** in 80% yield.[18] Dibromide **3** was reacted with aziridine alcohol **4**[26] in dry DMF, in the presence of potassium carbonate at 0 °C. Pure ligand **L5** was obtained after purification *via* column chromatography in 86% yield.

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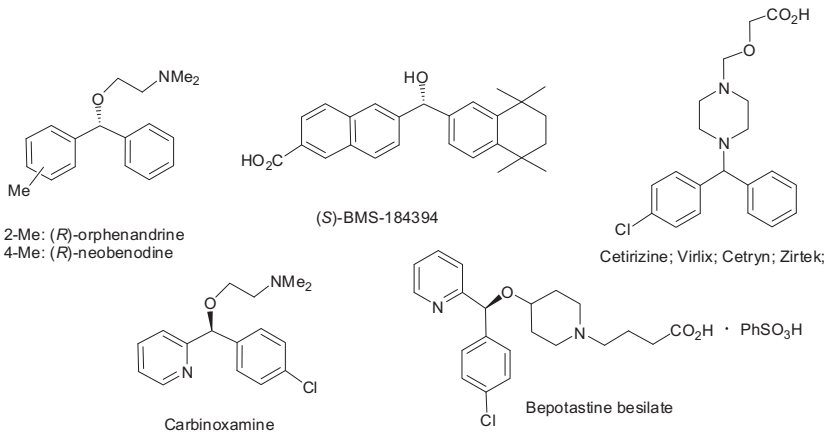


Figure 1. Diarylmethane-based drugs.

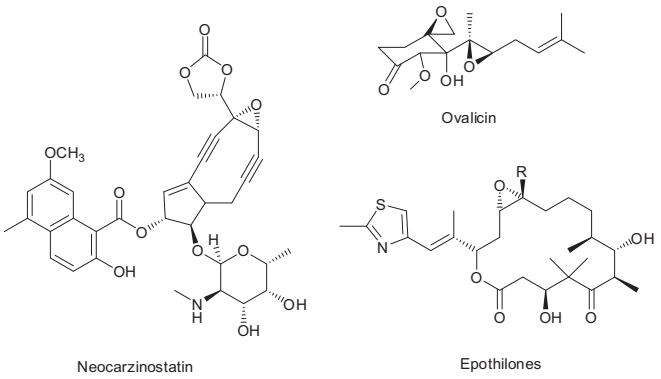
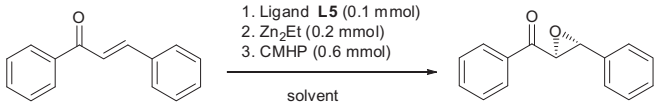


Figure 2. Drugs containing a chiral epoxide.

2.2. Asymmetric epoxidation of chalcone—screening of the conditions and ligands

The designed aziridine alcohol **L5** was tested as a chiral ligand in the asymmetric epoxidation of chalcone following the procedure described by Ulukanli et al.[4] (Scheme 2).[17] The reactions were carried out in various solvents and at 0 °C or 20 °C, respectively, in the



Scheme 2. Asymmetric epoxidation of chalcone catalyzed by ligand **L5** under various conditions.

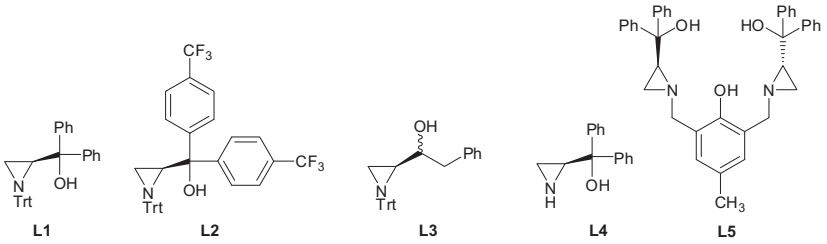
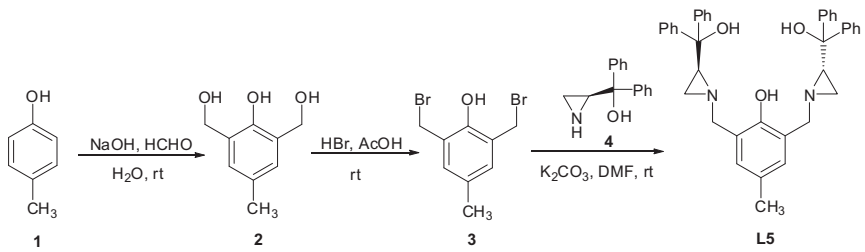


Figure 3. Chiral aziridine alcohols **L1**–**L5**.



Scheme 1. Synthesis of ProPhenol ligand **L5**.