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Chiral 8-substituted 10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-trien-8-ols as enantioselective catalysts in the addition of diethylzinc to substituted benzaldehydes

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Abstract

Chiral 8-substituted 10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.$0^{2,7}$] undeca-2(7),3,5-trien-8-ols were prepared from highly enantiopure (>97% ee) (1*R*)-(+)-α-pinene. The enantioselectivity was assessed in the addition of diethylzinc to substituted benzaldehydes to yield alcohols of the (*S*)-configuration, with an enantiomeric excess that typically ranges from 45 to 79%. Importantly, the electron-releasing substituents at the *meta*-position of the substituted benzaldehydes exhibited high enantioselectivity during alkylation using diethylzinc.

Keywords: Enantioselective catalyst; Diethylzinc; Asymmetric alkylation; Chiral ligand; Enantiomeric excess

1. Introduction

The asymmetric catalysis of organic reactions to provide enantiomerically enriched products is extremely important in modern synthetic and pharmaceutical chemistry [1–7]. The catalyzed asymmetric C–C bond-forming reaction in which diorganozinc reagents are enantioselectively added to aldehydes, represents one of the most important and fundamental asymmetric reactions [8,9]. Since the first work in this area by Oguni and Omi [10], various chiral ligands, including β-amino alcohols [11–40], BINOL [41–54], salen [55–57], TADDOL [58–67], pyridyl alcohol [68–79] and their derivatives have been employed in such reactions. Chiral ligands with diol generally need a Lewis acid, such as $Ti(O{-}i{-}Pr)_4$ to establish a chiral environment for the asymmetric addition of diethylzinc to aldehydes. While chiral ligands with amino alcohol or pyridyl alcohol constitute an asymmetric environment with two molecules of diethylzinc, one acts as a Lewis acid, and the other acts as a nucleophile [80–83]. The interaction between diethylzinc and an amino alcohol generates a chelated ethylzinc alkoxide (A), which is in equilibrium with a dimeric species (B) [81]. Only the monomer is catalytically active, and the adjacent Zn and O ring atoms, displaying complementary Lewis acid and Lewis base characteristics, are believed to coordinate with one molecule of aldehyde and one molecule of diethylzinc, respectively, to assemble the key species (C) where the ethyl group is transferred (Scheme 1).

The authors are interested in synthesizing and applying of chiral bipyridine derivatives as ligands for metal complexes in enantioselective catalysis [84], and are attracted by the possibility of modifying the structures of (D) and (E) by altering the position of the hydroxyl group (Fig. 1). This substitution leads to a new class of ligands **5–9**, **13** and **14**, substantially influencing the steric interactions between the ligand and the substrate, both of which are coordinated to the metal, so the stereoselectivity is expected to improve as the chirogenic element of the ligand gets closer to the metal center.

This study reports the synthesis of diastereomeric pure 8-substituted 10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-trien-8-ols (**5**–**9**), and **13**–**14**. These ligands in the enantioselectively catalyzed addition of diethylzinc to substituted benzaldehydes were investigated.

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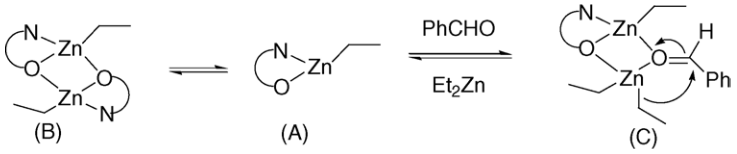


Scheme 1.

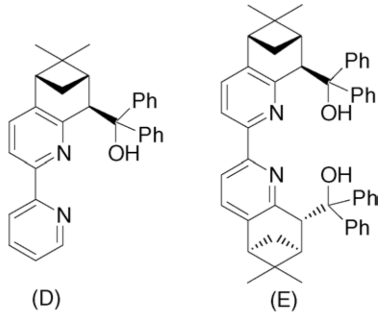
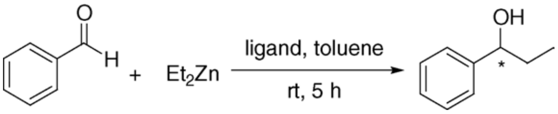


Fig. 1. The structures of chiral bipyridyl-type ligand (D) and (E).

Table 1
Asymmetric alkylation of benzaldehyde using diethylzinc, in the presence of various chiral ligands



Entry	Ligands	Yield (%)	Ee (%)
1	**5**	86	30
2	**6**	81	70
3	**7**	76	28
4	**8**	61	30
5	**9**	62	30
6	**13**	73	70
7	**14**	<5	53

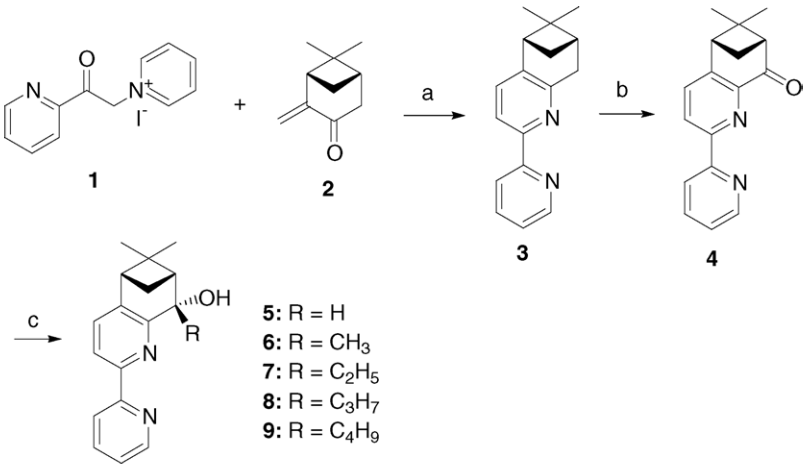
2. Results and discussion

2.1. Synthesis of the ligands 5–9 and 13–14

Scheme 2 outlines the synthesis of ligands **5**–**9**. (1*R*)-(+)-α-Pinene was readily photooxygenated in the presence of acetic anhydride, pyridine, DMAP and TPP to produce directly α,β-unsaturated ketone **2** [85]. Moreover, 2-acetylpyridine was heated with iodine in pyridine at 100–110 °C for 3 h and recrystallized from ethanol to yield pyridinium salt **1** [86]. Compounds **1** and **2** were heated with ammonium acetate in glacial acetic acid at 100–110 °C overnight to yield bipyridyl-type compound **3** [87–88]. Compound **3** was oxidized to ketone **4** using potassium permanganate, and then reduced using sodium borohydride, lithium aluminum hydride or diisobutylaluminum hydride to yield the corresponding alcohol **5** (NaBH$_4$, 97% de; LiAlH$_4$, 97% de; DIBAL-H, 81% de). When sodium borohydride and lithium aluminum hydride were used as reductants, more diastereoselective products were produced. Compounds **6**–**9** were prepared by reacting compound **4** with the corresponding Grignard reagents. Compound **10** [84] was treated with potassium permanganate to produce ketone **11** (24% yield) and diketone **12** (33% yield), and to recover the starting material (15%). Subsequently, compounds **11** and **12** reacted with methylmagnesium iodide to yield the corresponding alcohol **13** and diol **14** (Scheme 3).

2.2. Asymmetric addition of diethylzinc to benzaldehyde in the presence of various ligands

The asymmetric alkylation of benzaldehyde using diethylzinc in hexane at room temperature in the presence of 5 mol% of ligands yielded enantiomeric excesses of 1-phenyl-1-propanol, as shown in Table 1. The stereochemical outcome depends mainly



Scheme 2. (a) NH$_4$OAc, AcOH, 100–110 °C, 16 h; (b) KMnO$_4$, *t*-BuOH, 75–80 °C, 24 h; (c) (1) **5**: NaBH$_4$ or LiAlH$_4$ or DIBAL-H, THF; (2) **6**: MeMgI, Et$_2$O, rt, 1 h; (3) **7**: EtMgBr, Et$_2$O, rt, 1 h; (4) **8**: PrMgBr, Et$_2$O, rt, 1 h; (5) **9**: BuMgBr, Et$_2$O, rt, 1 h.