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Asymmetric Synthesis of N-(Diphenylphosphinyl)furfurylamine by the Enantioselective Alkylation of Furfurylimine

Hai Le ZHANG, Xiao Mei ZHANG, Xin LI, Ai Qiao MI*,
Xin CUI, Yao Zhong JIANG

Key Laboratory of Asymmetric Synthesis and Chirotechnology of Sichuan Province and
Union Laboraotry of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry,
Chinese Academy of Sciences, Chengdu 610041

Abstract: Optically active N-(diphenylphosphinyl)furfurylamines **2** with good ee values were obtained by the enantioselective addition of dialkylzincs to furfuryl imine **1** in the presence of chiral aminoalcohol derivatives and oxazolines.

Keywords: Asymmetric, dialkylzinc, N-(diphenylphosphinyl)furfurylamine.

Optically active α-furfuryl amines are important synthetic intermediates for the synthesis of a number of nitrogen containing natural products, such as α-amino acids, β-lactams, indolizilines, quinolizidines and piperidine alkaloids[1]. Zhou and co-workers reported the kinetic resolution of racemic α-furfuryl amine derivatives, using the modified Sharpless asymmetric epoxidation reagent[2]. They also reported the asymmetric synthesis of α-furfuryl amine and its derivatives *via* the addition of organometallic reagents to the chiral imine or its enantiomer[3]. Jiang and co-workers applied the condensation of racemic α-furfuryl amine with chiral auxiliaries, (-)-2-hydroxypinan-3-one or (+)-camphor to the alkylation of chiral imine and gave the corresponding chiral α-furfuryl amine derivatives with 98% *ee*[4]. While the enantioselective alkylation of the imine seems to be a more direct approach to optically active α-furfuryl amine. We[5] and others[6] have recently studied the addition of dialkylzinc reagents to N-(diphenyl-phosphinoyl)imines in the presence of some chiral ligands, and high enantioselectivitis were attained. Herein, we would like to report the enantioselective diethylzinc addition to furfuryl imine **1** in the presence of chiral aminoalcohol derivatives and oxazolines, giving optically active α-furfuryl amine **2** in high yields and reasonable enantioselectivity.

Diethylzinc and imine reacted in toluene in the presence of chiral ligand **3**. The results are shown in **Table1**. The simplest ligand (1R, 2S)-**3a**, induced the addition reaction of **1** with 72% *ee* (entry 1). Further increase in the steric hindrance of the substituents on the nitrogen of the chiral ligands led to a decrease in the enantioselectivity

* E-mail: miaq@cioc.ac.cn

Figure 1 Chiral *β*-amino alcohols

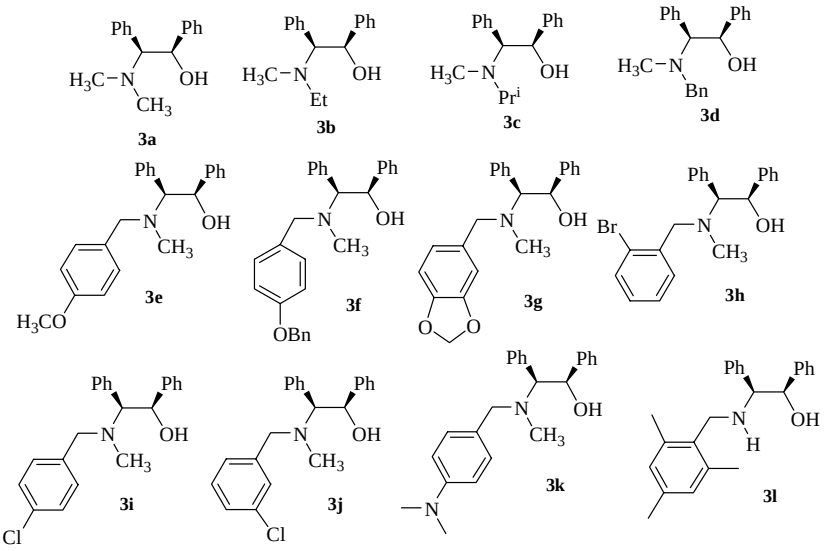
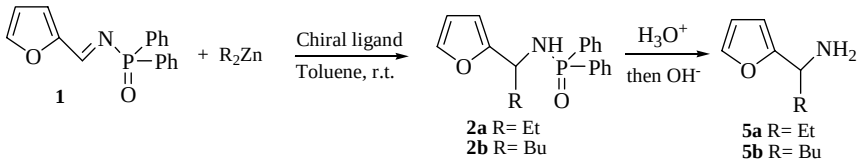


Table 1[a] Asymmetric diethylzinc addition to N-diphenylphosphinoyl furyl imine promoted by the ligands showed in **Figure 1**



Entry	Ligand	R	Time (h)	Yield (%)[b]	e.e (%)[c]	Config.[d]
1	**3a**	Et	28	90	72	R
2	**3b**	Et	48	76	68	R
3	**3c**	Et	48	70	57	R
4	**3d**	Et	28	90	79(97)[e]	R
5	**3d**	Et	24	92	78(98)[e,f]	R
6	**3e**	Et	48	86	74	R
7	**3f**	Et	20	90	77	R
8	**3g**	Et	48	83	75	R
9	**3h**	Et	20	46	74	R
10	**3i**	Et	48	90	74	R
11	**3j**	Et	48	87	74	R
12	**3k**	Et	48	92	73	R
13	**3l**	Et	48	79	81	R
14	**3l**	Bu	48	50	77 (95%)[e,g]	R

[a] Reactions were carried out at room temperature in the presence of stoichiometric amount of amino alcohols (0.1 mmol scale). [b] isolated yields. [c] Determined on HPLC. [d] Determined by comparison of the retention time with the literature[5,6]. [e] E.e. in parentheses are that after recrystallization. [f] The reaction was performed in 1 mmol scale. [g] The reaction was performed in 0.2 mmol scale.

(entries 2, 3). Most of chiral N-methyl-N-aryl amino alcohols **(3d-j)** gave good enantioselectivities with up to 74% *ee* (entries 4-11). From the wide range of chiral

aminoalcohols showed in **Figure 1**, N-monosubstituted amino alcohol **3l** containing a 2, 4, 6-trimethybenzyl group gave the highest enantioselectivity of 81% (**Table 1**, entry 13), the same phenomena as we expected[5c]. The enantioselective butylation of **1** with $Bu^n{}_2Zn$ using 1 equiv. of **3l** afforded the corresponding phosphoramides in 77% *ee* (entry 14). Although a stoichiometric amount of the chiral ligands were used, chiral *β*-amino alcohols could be easily recovered by the flash chromatography. Optically active furfurylamine **5** was easily obtained by the acidic hydrolysis of the N-(diphenylphosphinyl)furfurylamine **2**[7]. It should be noted that the N-(diphenylphosphinyl)-furfurylamine **2** obtained is white crystalline and that their optical purity could be enhanced by recrystallization. For example, the enantiomeric purity of compound **2a** (79% *ee*, entry 4) was increased to 97% *ee* by recrystallization from a mixed solvent of hexane and acetone.

Chiral oxazoline ligands have been extensively employed in metal-catalyzed asymmetric reaction. We designed and developed a set of chiral oxazolines **4** (**Figure 2**) which started from commercially available (1S, 2S)-2-amino-1-phenylpropanediol **6**[5a,5e]. Because of importance of optically active *α*-furfuryl amines we examined the stereo-differentiating abilities of these chiral oxazolines and used them for the asymmetric diethylzinc addition to the furfurylimine. From the **Table 2**, we can see this set of chiral oxazoline ligands were also quite efficient for the enantioselective ethylation of N-diphenylphosphinoyl furyl imine. Among **4a**-**e**, ligand **4a** showed the highest chiral

Figure 2 Chiral oxazolines

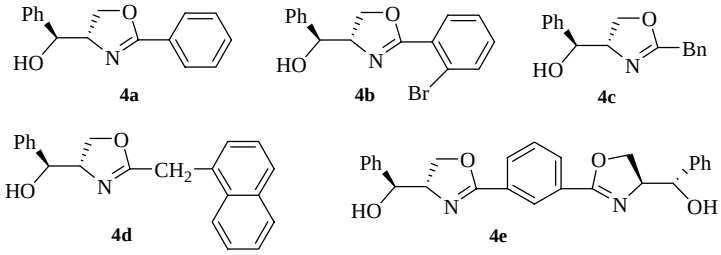
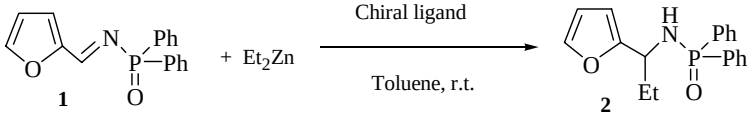


Table 2[a] Asymmetric diethylzinc addition to *N*-diphenylphosphinoyl furyl imine promoted by the ligands showed in **Figure 2**



Entry	Ligand (equiv.)	Time (h)	Yield (%)[b]	e.e (%)[c]	Config.
1	**4a**	28	77	72	S
2	**4b**	48	59	41	S
3	**4c**	28	71	69	S
4	**4d**	28	67	66	S
5[d]	**4e**	48	62	67	S

[a] The reaction was carried out at room temperature in the presence of stoichiometric amount of oxazolines, unless specified. [b] isolated yields. [c] Determined on HPLC. [d] The reaction was promoted by 50mol% of ligand **4e**.

introduction for the addition reaction, giving 72% *ee* (**Table 2**, entry 1). While oxazoline **4b**, having an *o*-bromophenyl group, leading to poor enantioselectivity (entry 2, 41% *ee*). This observation is in agreement with our previous analysis[5d]. The phosphoramide **2e** was obtained in 67% *ee* when 0.5 equiv. of bis(oxazoline) **4e** was used(entry 5). This is also the example using C_2-symmetric chiral bis(oxazoline) to promote the dialkylzinc addition to N-diphenylphosphinoylimine.

Typical procedure (**Table 1**, entry 5): The furfuryldiphenylphosphinyl imine **1**[8a] (295 mg, 1 mmol) and chiral ligand **3d** (317 mg, 1 mmol) were dissolved in dry toluene (20 mL) under Ar. To the mixture was added Et_2Zn (1 mmol, 1 mol/L hexane solution 4 mL) at room temperature, and then the mixture was stirred for 24 h. The reaction was quenched by adding satd. aq. NH_4Cl, and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (eluent, acetone – petroleum ether, 1:3 v/v) to give **2a**[8b] as a white solid in 92% yield with 78% *ee* by HPLC analysis with a chiral column(254 nm UV detector; eluent, 5% propan-2-ol in hexane; flow rate, 1.0 mL min^{-1}). The enantiomeric purity of compound **2a** was increased to 98% ee by recrystallization from the mixture of hexane and acetone.

In summary, a family of chiral *β*-amino alcohols and oxazolines were screened for addition of diethylzinc to furyl imine, satisfactory enantioselectivities of up to 81% were obtained.

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8. (a) The furfuryldiphenylphosphinyl imine **1** was synthesized according to the literature, see ref. 6c. (b) The data of the product **2a** are in agreement with the data of N-(diphenylphosphinyl)-fururylamine in ref.6c.

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