

## A new synthesis of chiral α-substituted furfuryl amines by diastereoselective addition of organometallic reagents

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Abstract: A new method to prepare chiral  $\alpha$ -substituted furfuryl amines was achieved in high d.e. values and chemical yields. © 1997 Elsevier Science Ltd

Recently, the synthesis of chiral amines through the addition of organometallic reagents to the imines<sup>1</sup> with chiral amino alcohols as auxiliaries was reported.<sup>2a-d</sup> In our previous works, we reported that in the kinetic resolution of  $\alpha'$ -alkyl  $\alpha$ -furfuryl amides using modified Sharpless epoxidation reagents, two versatile chiral building blocks were obtained, one of them is the chiral  $\alpha$ -substituted furfuryl amine 1, the other is the chiral dihydropyridone 2, both in high enantioselectivity (90–100%) and high chemical yield (40–45%).<sup>3</sup> These are very useful chiral building blocks for the total synthesis of natural products.<sup>4-8</sup> The synthesis of chiral  $\alpha$ -substituted furfuryl amine 1, via the alkylation of chiral ketimine was also reported.<sup>9</sup> In this paper, we wish to report a new asymmetric synthesis of  $\alpha$ -substituted furfuryl amine 1, which could easily be oxidized to dihydropyridone 2, via the addition to aldimine 5a and 5b derived from furaldehyde 4 and the chiral amino alcohol (1S,2R)-2-amino-1,2-diphenylethanol 3b as chiral auxiliaries.



Alkylation of chiral aldimine 5a with various Grignard reagents yielded the amine derivatives 6a-h (Scheme 1). In all cases, the excellent diastereoselectivity and high chemical yields were obtained (Table 1).



The *anti*-configuration of the major product **6d** was determined by X-ray diffraction analysis<sup>12</sup> (Figure 1).

The absolute configuration of **6b** was further confirmed by hydrogenation in the presence of formic acid and methanol with Pd/C.<sup>11</sup> Protection of the resulting amino group gave the known (S)-N-tosyl- $\alpha$ -butyl furfuryl amine 7. ([ $\alpha$ ]<sub>D</sub><sup>20</sup>=-4.9 (c, 9.0, EtOH). {Lit.<sup>3</sup>: [ $\alpha$ ]<sub>D</sub><sup>20</sup>=-5.0 (c, EtOH)}) (Scheme 2). The highly stereoselective addition of compound **5a** was due to the steric effects of the two phenyl

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Entry	Comp.	RMgBr	yield(%) <sup>b</sup>	d.e.(%) <sup>c</sup>	Config. <sup>d</sup>
1	68	Et	90.6	92.4	S
2	6b	"Bu	85.1	97.8	S
3	6c	cHex	69.2	98.7	S
4	6d	Allyl	82.5	99.6	S
5	6e	"Pent	87.0	98.5	S
6	6f	"Pr	79.5	83.9	S
7	6g	"Hex	83.0	97.8	S
8	6h	Bn	78.4	99.5	S

Table 1. Nucleophilic addition of organometallic reagents to chiral aldimine (1R,2S)-5a<sup>a</sup>

a. The reaction was carried out in THF using alkyl Grignard reagents (2.5eq.) in the presence of cerium trichloride (1.0eq.) at 0°C to r.t.. b. The isolated yields were obtained after chromatography on silica gel as mixture. c. *d.e.* values were determined by HPLC in UBondapak  $C_{18}$  column. d. The absolute configurations of **6b** was determined by the conversion of **6b** to the known compound 7 (Scheme 2). The absolute configuration of **6d** was determined by X-ray diffraction (Fig. 1). The absolute configuration of **6a**, **6c**, **6e**-**6h** and **6a**<sup>2</sup>-**6d**<sup>4</sup> are deduced from **6b** and **6d** and from comparision of sign of specific rotations with **6b** and **6d**.<sup>10</sup>



Figure 1. The molecular structure of 6d.

rings, so that the alkyl group could attack the imine group from the top of **6a**. A transition state of the reaction is proposed as follows (Figure 2).



In addition, when the aldimine **5b**, the enantiomer of **5a**, was subjected to reaction with the alkyl Grignard reagents in the similar manner (Scheme 3), the enantiomer of amino derivative 6a-d' was also obtained in high diastereometric excess and high chemical yield (Table 2).

In summary, a new method to prepare non-racemic  $\alpha$ -furfuryl amines was achieved in high d.e. values and high chemical yields. The work for the synthesis of alkaloids from these  $\alpha$ -furfuryl amines is in progress.



Figure 2.



## Scheme 3.

Table 2. Nucleophilic addition of organometallic reagents to chiral aldimine (1S,2R)-5b

Comp.	R	yield(%)	d.e.*(%)	Config.
6a'	Et	79	94.2	R
6b'	"Bu	75.0	96.3	R
6c'	cHex	76.8	98.5	R
6d'	Allyl	85.7	99.3	
	Comp.   6a'   6b'   6c'   6d'	K K   6a' Et   6b' "Bu   6c' cHex   6d' Allyl	K yield(%)   6a' Et 79   6b' "Bu 75.0   6c' cHex 76.8   6d' Allyl 85.7	Comp. R yread(70) a.e. (70)   6a' Et 79 94.2   6b' "Bu 75.0 96.3   6c' cHex 76.8 98.5   6d' Allyl 85.7 99.3

a. d.e. values were determined by HPLC in UBondapak C<sub>18</sub> column.

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- 10. Optical rotations were measured on an Autopol spectrometer III automatic polarimeter. The solvent is the ethanol and the concentration range is between 1 and 3. Specific rotations ( $[\alpha]_D^{20}$ ) of **6a**: -65.2 (c, 2.1) **6b**: -51.1 (c, 0.53) **6c**: -55.6 (c, 1.8) **6d**: -46.2 (c, 0.80) **6e**: -43.0 (c, 0.6) **6f**:

-56.7 (c, 0.87) **6g**: -40.2 (c, 0.6) **6h**: -43.4 (c, 0.87) **6a**': +71.6 (c, 0.67) **6b**': +49.6 (c, 0.86) **6c**': +48.3 (c, 0.73) **6d**': +49.9 (c, 1.0).

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- 12. The crystal of **6f** was in the orthorhombic system with the space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (#19) and the lattice parameters were precisely determined as a=12.517(2), b=23.612(8), c=6.253(3), U=1848(1), Z=4, Dc=1.198 g/cm<sup>-1</sup>.

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