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

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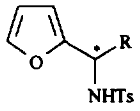
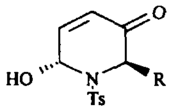
Abstract: A new method to prepare chiral α-substituted furfuryl amines was achieved in high d.e. values and chemical yields. © 1997 Elsevier Science Ltd

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

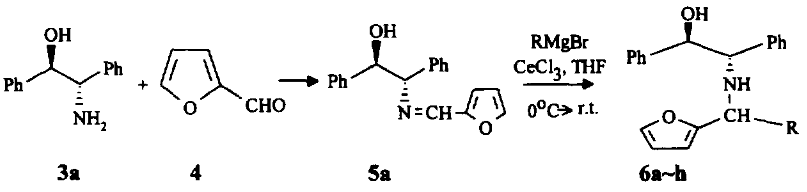


1



2

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).



Scheme 1.

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

The absolute configuration of **6b** was further confirmed by hydrogenation in the presence of formic acid and methanol with Pd/C.[11] Protection of the resulting amino group gave the known (S)-N-tosyl-α-butyl furfuryl amine **7**. ($[\alpha]_D^{20}=-4.9$ (c, 9.0, EtOH). {Lit.[3]: $[\alpha]_D^{20}=-5.0$ (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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Table 1. Nucleophilic addition of organometallic reagents to chiral aldimine (1R,2S)-**5a**[a]

Entry	Comp.	RMgBr	yield(%)[b]	*d.e.*(%)[c]	Config.[d]
1	**6a**	Et	90.6	92.4	*S*
2	**6b**	^{n}Bu	85.1	97.8	*S*
3	**6c**	cHex	69.2	98.7	*S*
4	**6d**	Allyl	82.5	99.6	*S*
5	**6e**	^{n}Pent	87.0	98.5	*S*
6	**6f**	^{n}Pr	79.5	83.9	*S*
7	**6g**	^{n}Hex	83.0	97.8	*S*
8	**6h**	Bn	78.4	99.5	*S*

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'~6d'** are deduced from **6b** and **6d** and from comparision of sign of specific rotations with **6b** and **6d**.[10]

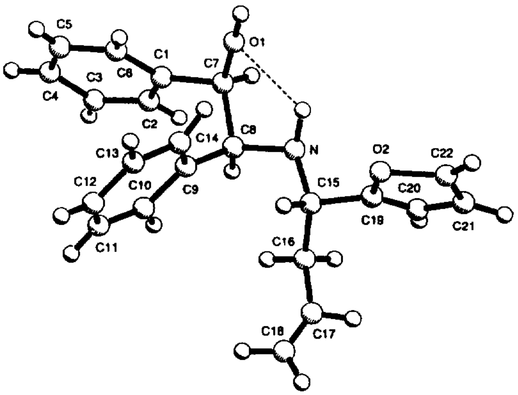
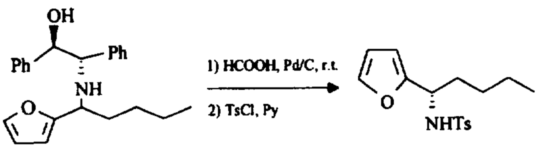


Figure 1. The molecular structure of **6d**.

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).

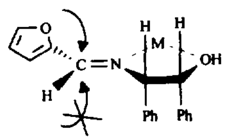


6b **7**

Scheme 2.

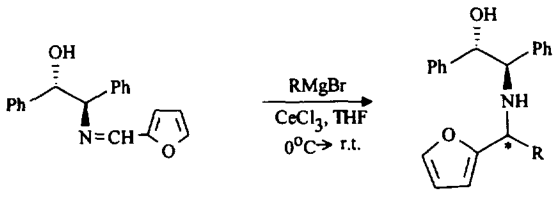
In addition, when the aldimine **5b**, the enantiomer of **5a**, was subjected to reaction with the alkyl Grignard reagents in the similar manner (Scheme 3), the enantiomer of amino derivative **6a–d'** was also obtained in high diastereomeric excess and high chemical yield (Table 2).

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



5a

Figure 2.



5b **6a'-d'**

Scheme 3.

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

Entry	Comp.	R	yield(%)	*d.e.*^{a}(%)	Config.
1	**6a'**	Et	79	94.2	*R*
2	**6b'**	^{n}Bu	75.0	96.3	*R*
3	**6c'**	cHex	76.8	98.5	*R*
4	**6d'**	Allyl	85.7	99.3	*R*

a. *d.e.* values were determined by HPLC in UBondapak C_{18} column.

Acknowledgements

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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 $P2_12_12_1$ (#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^{-1}.

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