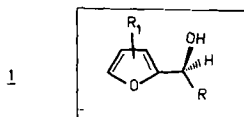


ENANTIOSELECTIVE SYNTHESIS OF FURYLALCOHOLS BY CATALYTIC  
ASYMMETRIC ADDITION OF DIETHYLZINC TO FURANALDEHYDES

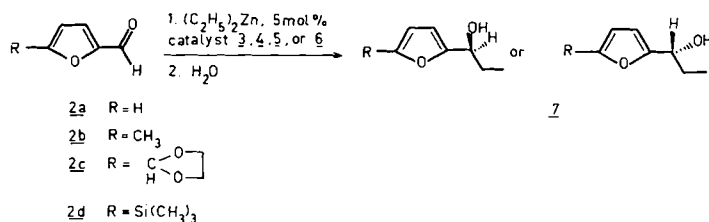
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**Abstract.** Optically active 2-furylcarbinols with up to 97% enantiomeric excess were prepared by highly  $\pi$ -face selective addition of diethylzinc to furan aldehydes catalyzed by aminoalcohol ligands 3 to 6.

Substituted furans have gained importance as versatile multifunctional building blocks in synthesis.<sup>1</sup> For example strategies based on photochemically mediated [2+2] cycloadditions to furans,<sup>2</sup> and conversions of furans to cyclopentenones<sup>3</sup> and chiral butenolides<sup>4</sup> have been developed. Further application in the synthesis of natural products would be considerably stimulated if homochiral 2-furylcarbinols 1 were readily accessible.

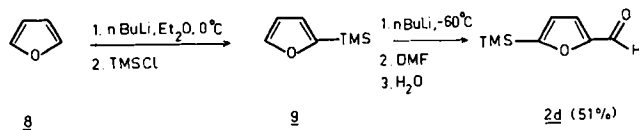


Recently methodology for the preparation of optically active 2-furylcarbinols by kinetic resolution using the Sharpless epoxidation procedure was described.<sup>5</sup> Herein we describe a catalytic asymmetric synthesis of 5-substituted-2-furylcarbinols 7 by the chiral ligand induced addition of diethylzinc to 5-substituted-2-furan aldehydes 2 (eq. 1).



Following Oguni's report on the enantioselective addition of diethylzinc to benzaldehyde catalyzed by chiral 2-amino-1-alcohols much progress has been made in the asymmetric addition of alkyl- and vinyl groups to aryl- and  $\alpha,\beta$ -unsaturated aldehydes using this procedure.<sup>7-11</sup> In order to find a practical synthetic route to optically active furylcarbinols of high optical purity (e.e. > 90%) we examined furanaldehydes 2a-2d and chiral catalysts 3-

6.<sup>12,13</sup> 5-Trimethylsilyl-2-furaldehyde (2d)<sup>14,15</sup> was prepared in a new one pot procedure via sequential lithiation of furan (eq. 2).



The catalysts (S)-(+)-diphenyl-(1-methylpyrrolidin-2-yl) methanol (DPMPM) 4<sup>9</sup> and N,N-dibutylaminonorephedrine (DBNE) 6<sup>10</sup> were prepared following literature procedures. (-)-3-Exo dimethylaminoisoborneol (DAIB) 5<sup>9</sup> was synthesized from (+)-camphor following a slightly modified procedure as reported<sup>9</sup> using K<sub>2</sub>OtBu as a base in the first step and MeI as the methylating agent in the final step. When 2-furaldehyde (2a) was treated with diethylzinc at +4°C for 16 h using quinine 3 (5 mol %) as a catalyst (R)-2-furyl-1-propanol (7a) was obtained in 83% isolated yield and 60% enantiomeric excess (e.e.) after distillation.

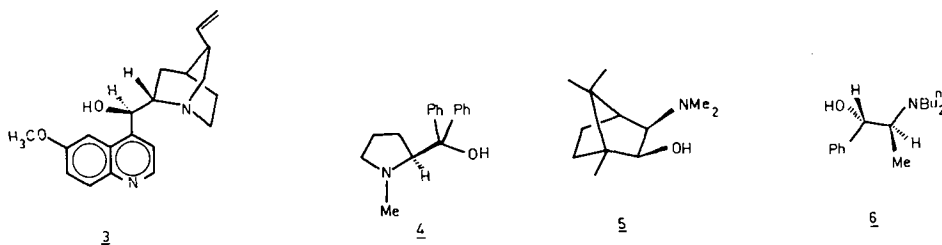


Table Catalytic asymmetric synthesis of furylcarbinols 7a-7d and 7e.

Entry	Aldehyde (R <sup>1</sup> )	Solvent <sup>1</sup>	Catalyst	Product	Yield <sup>2</sup> (%)	[α] <sub>D</sub> <sup>20</sup> (c, CHCl <sub>3</sub> )	o.p. <sup>3</sup> (%)	e.e. <sup>3</sup> (%)
1	<u>2a</u> H	T	<u>3</u>	<u>7a</u>	83	+11.6 (1.00)	60	57 <sup>4</sup>
2	<u>2a</u> H	H	<u>4</u>	<u>7a</u>	81	-16.5 (0.98)	85	
3	<u>2a</u> H	T	<u>5</u>	<u>7a</u>	68	-12.6 (1.02)	65	
4	<u>2a</u> H	H	<u>6</u>	<u>7a</u>	82	-17.9 (1.75)	92	93(91) <sup>4</sup>
5	<u>2b</u> CH <sub>3</sub>	T	<u>3</u>	<u>7b</u>	85	+ 7.5 (1.72)	62.5	62.5
6	<u>2b</u> CH <sub>3</sub>	T	<u>5</u>	<u>7b</u>	90.5	-11.6 (0.99)	97	
7	<u>2b</u> CH <sub>3</sub>	H	<u>6</u>	<u>7b</u>	88	-10.9(1.17)	91	91.1(89) <sup>4</sup>
8	<u>2c</u> CHOCH <sub>2</sub> CH <sub>2</sub> O	T	<u>3</u>	<u>7c</u>	96	+ 5.2(1.07)	51	51
9	<u>2c</u> CHOCH <sub>2</sub> CH <sub>2</sub> O	H	<u>4</u>	<u>7c</u>	77	- 7.3(1.07)	72	
10	<u>2c</u> CHOCH <sub>2</sub> CH <sub>2</sub> O	T	<u>5</u>	<u>7c</u>	56	- 4.7(1.12)	46	
11	<u>2c</u> CHOCH <sub>2</sub> CH <sub>2</sub> O	H	<u>6</u>	<u>7c</u>	- <sup>5</sup>	-		
12	<u>2d</u> Si(CH <sub>3</sub> ) <sub>3</sub>	T	<u>3</u>	<u>7d</u>	78	+ 5.1(1.00)	51	51
13	<u>2d</u> Si(CH <sub>3</sub> ) <sub>3</sub>	H	<u>4</u>	<u>7d</u>	84	- 9.4(1.04)	94	
14	<u>2d</u> Si(CH <sub>3</sub> ) <sub>3</sub>	T	<u>5</u>	<u>7d</u>	78	- 9.0(1.00)	90	89 <sup>3</sup>
15	<u>2d</u> Si(CH <sub>3</sub> ) <sub>3</sub>	H	<u>6</u>	<u>7d</u>	82	- 8.5(1.00)	85	85
16	<u>2c</u> <sup>5</sup>		<u>3</u>	<u>7e</u> (R <sub>1</sub> =CHO)	93	+18.7(1.03)	51	
17	<u>2c</u> <sup>5</sup>		<u>6</u>	<u>7e</u> (R <sub>1</sub> =CHO)	92	-29.9(0.98)	83	83

1) T = toluene; H = n-hexane; 2) isolated yields of pure furylcarbinols after distillation; 3) o.p. = optical purity; e.e. = enantiomeric excess; e.e. based on <sup>1</sup>H NMR via complexation with quinine.<sup>17</sup> 4) e.e. based on <sup>19</sup>F NMR of the (-)-MTPA esters.<sup>16</sup> 5) the dioxolane 7c was directly converted into 7e (see text).

A Re-face selective addition takes place and the enantio- and Re-face-selectivities are in accordance with the result of the addition of  $\text{Et}_2\text{Zn}$  to benzaldehyde using quinine.<sup>11</sup> Employing **6** as a catalyst the optical yield can be raised to 92% while Si-face addition leads now to (S)-**7a** (table, entry 4).

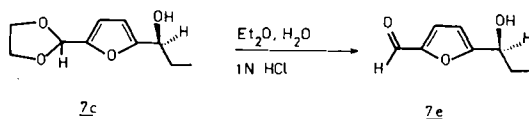
The e.e. of **7a** ( $[\alpha]_D^{25} -17.9^\circ$  (c 1.75,  $\text{CHCl}_3$ )) was determined by  $^{19}\text{F}$  NMR of the corresponding (-)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic (MTPA) ester<sup>16</sup> and independently by  $^1\text{H}$  NMR using complexation with quinine.<sup>17</sup> The use of quinine as a chiral solvating agent in  $\text{CDCl}_3$  proved to be an operationally extremely simple way of e.e. determination of furyl alcohols with base line separations in various cases.

Using the same four catalysts **3** - **6** the addition of  $\text{Et}_2\text{Zn}$  was also carried out with substrates **2b** - **2d**. The results are given in the table. It has to be noted that the reaction conditions were identical using the same catalyst for the different furanaldehydes **2a** - **2d**.

It is interesting to see that the substituent in position 5 at the furan ring has little influence on the catalytic asymmetric addition; for the quinine catalyzed reaction e.e.'s of 51-62% are observed (entries 1, 5, 8, 12). When furan aldehydes are used as substrates for the diethylzinc addition additional coordination via the furan oxygen can be envisaged which could influence the stereochemical bias of this reaction.

Comparable enantioselectivities for benzaldehydes<sup>7,11</sup> and furanaldehyde however indicate that such an effect, if it exists, has only a minor stereochemical consequence. The results with different catalysts show that high e.e.'s (92-97%) are reached by the proper combination of aminoalcohol and furan aldehyde.

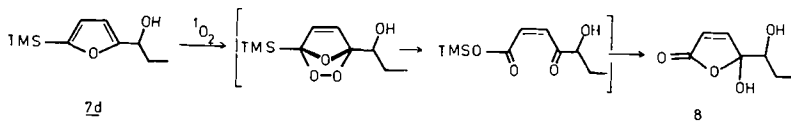
The deprotection of the aldehyde functionality in furylcarbinol **7c** is readily accomplished in situ (eq. 3).



The addition of  $\text{Et}_2\text{Zn}$  to **2c** using catalyst **6** followed by a washing procedure of the ethereal solution of **7c** using aqueous 1N HCl provided **7e** in 92% yield (e.e. = 83%, entry 17). Optically active furanaldehyde **7e** is an interesting starting material for various homochiral furans.

The access to furyl alcohols with synthetically useful e.e.'s which contain a 5-trimethylsilyl-substituent allow for an attractive route to chiral butenolides via oxidative methods.

Thus singlet oxygen photooxidation of **7d** resulted in a fast and quantitative addition leading to butenolide **8**.



The initial  $^1\text{O}_2$  addition to **7d** is presumably followed by a silotropic shift and cyclization to **8** in accordance with reported experiments with silylfurans.<sup>18</sup> Further studies along these lines are in progress.

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