

Enantioselective Furylation of Prochiral Aldehydes by Difurylzinc in the Presence of a Chiral Amino Alcohol: Asymmetric Synthesis of 2-Furylmethanols

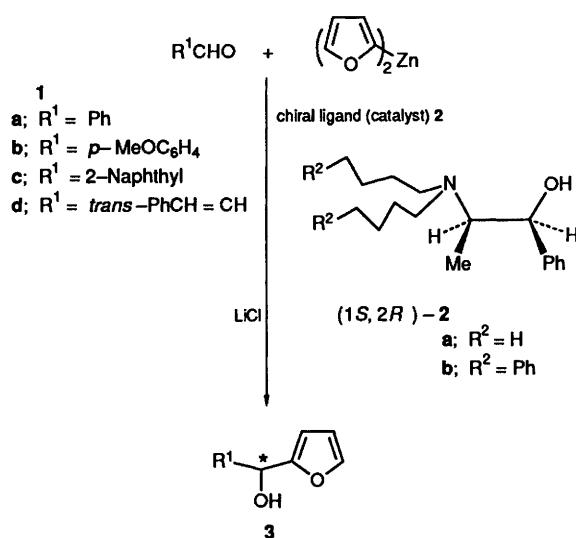
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The first example of the enantioselective furylation of aldehydes is described. Optically active 2-furylmethanols have been synthesized in good enantiomeric excesses (up to 73% e.e.) by the enantioselective addition of difurylzinc to aldehydes using *N,N*-dibutylnorephedrine and *N,N*-di(4-phenylbutyl)norephedrine as either chiral ligands or catalysts.

Although the enantioselective addition of organometallic reagents to aldehydes provide optically active secondary alcohols, in most cases, the structure of organometallic reagents has been limited to alkylmetals.¹ It is a challenging problem to find a new chiral ligand (catalyst) and a new method for the enantioselective addition of organometallic reagent which is sterically and electronically different from alkylmetals. On the other hand, optically active furylmethanols form an important class of compounds, because the furyl group is recognized as an important function for the facile introduction of further functionalities.^{2,3}

We report the first example of the enantioselective furylation of aldehydes. After many experiments, we found that the presence of lithium halide (LiX, X = F, Cl, Br) as an additive enhanced the enantiomeric excess (e.e.) of (*S*)-(2-furyl)phenylmethanol **3a** to 53–56% e.e. in the addition of difurylzinc to benzaldehyde in the presence of (1*S*,2*R*)-(-)-*N,N*-dibutyl-norephedrine (DBNE, **2a**, 1 equiv.). The attempted addition of difurylzinc to benzaldehyde without LiCl as an additive (which are the usual conditions for addition of dialkylzincs)⁴ in the presence of (-)-DBNE (1 equiv.) resulted in low (11%) e.e. of (*S*)-**3a**. In the presence of (-)-DBNE, difurylzinc approaches benzaldehyde from the *Re* face to afford (*S*)-**3a**. This stereo-



chemical course is the reverse of that for dialkylzinc reagents. It was also found that (1*S*,2*R*)-*N,N*-di(4-phenylbutyl)norephe-

Table 1. Enantioselective furylation of aldehydes **1** using **2b** as chiral ligand or catalyst in the presence of lithium chloride.

Entry	Aldehyde 1	Alcohol 3 ^a				
			$[\alpha]_D$ [temp. (°C), c, CHCl ₃]	Yield (%)	E.e. (%) ^b	Config.
1 ^c	a	a	-3.2° [28, 0.99]	62	72	<i>S</i> ^d
2 ^c	b	b	+0.47° [29, 1.0]	58	73	
3 ^c	c	c	-6.3° [25, 1.3]	68	59	
4 ^c	d	d	-4.4° [28, 1.6]	79	45	
5 ^e	a	a	—	53	30	<i>S</i> ^d

^a Satisfactory results were obtained for all new compounds from NMR, IR spectroscopy and high mass spectrometric analyses. ^b Based on HPLC analyses using a chiral column (Daicel Chiralcel OD, 250 mm; 254 nm UV detector). Eluant 3% propan-2-ol in hexane; flow rate 1.0 ml min⁻¹; **3a**, retention time (min), 27.3 for major isomer, 34.6 for minor isomer. For **3b**, retention time (min), 39.3 for major isomer, 50.5 for minor isomer. For **3c**, retention time (min), 40.5 for minor isomer, 46.2 for major isomer. For **3d**, retention time (min), 14.4 for major isomer, 18.9 for minor isomer. ^c Molar ratio. 1:difurylzinc:2:LiCl = 1:2.5:1:4.9–5.0. ^d M. Kusakabe, Y. Kitano, Y. Kobayashi and F. Sato, *J. Org. Chem.*, 1989, **54**, 2085. ^e Molar ratio. 1:difurylzinc:2:LiCl = 1:2.5:0.3:5.7.

drine **2b** [α]_D²⁷ -33.4° (*c* 2.27, MeOH), which possesses phenyl groups at the end of *N*-butyl substituents, was more enantioselective in the furylation. Thus, the reaction of benzaldehyde with difurylzinc† in the presence of the lithium salt of **2b** (1 equiv.) and LiCl afforded (*S*)-(-)-**3a** of 72% e.e. (determined by HPLC analysis using a chiral column) in a yield of 62%.‡ As shown in Table 1, aromatic and unsaturated aldehydes were furylated enantioselectively in moderate to good e.e.s (up to 73%). The reaction using a catalytic amount of **2b** (0.3 equiv.) also afforded optically active **3a** in 30% e.e. (entry 5). Coordination of the lithium cation with the oxygen atom of the furan ring may be one of the possible reactions for the described enantioselective furylation.

† 1.6 M Butyllithium in hexane (1.6 ml, 2.6 mmol) was added dropwise to a THF solution (1.5 ml) of furan (2.6 mmol) at 0 °C. After the reaction mixture had been stirred for 2 h at 0 °C, ZnCl₂ (0.175 g, 1.3 mmol) in THF (2 ml) was added dropwise to the solution. The mixture was then stirred for 30 min, after which it was evaporated under reduced pressure; THF (1 ml) was added to the residue.

‡ A THF solution (1 ml) of (1*S*,2*R*)-**2b** (0.207 g, 0.5 mmol) was added to LiCl (0.107 g, 2.5 mmol) in THF (2 ml) at room temp., and the mixture was stirred for 7 min; a 1.6M hexane solution of butyllithium (0.32 ml, 0.5 mmol) was then added dropwise (formation of the lithium salt of **2b**). After the mixture had been stirred for 10 min, benzaldehyde (0.53 g, 0.5 mmol) in THF (1 ml) was added. The mixture was cooled to 0 °C and then a solution of difurylzinc (1.3 mmol) in THF was added dropwise during 3 min. After the mixture had been stirred for 13 h at 0 °C, saturated aqueous NH₄Cl (10 ml) was added to quench the reaction. The aqueous layer was extracted with Et₂O (5 × 10 ml) and the combined extracts were washed with brine, dried (Na₂SO₄) and evaporated. The residue was purified by silica gel TLC.

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