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Asymmetric synthesis of optically active fluorine-containing alcohols using chiral catalysts

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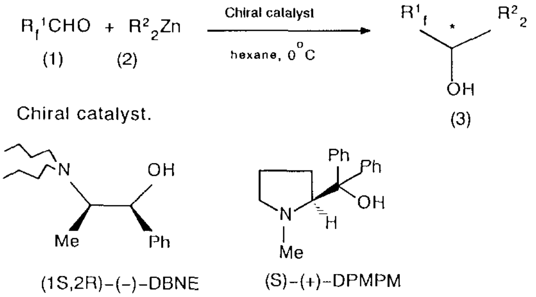
Abstract

Optically active fluorine-containing alcohols have been synthesized in high enantiomeric excess by the catalytic enantioselective addition of dialkylzincs to fluorine-containing aldehydes.

Optically active fluorine-containing compounds have attracted considerable interest in many fields [1] such as biologically active compounds [2], liquid crystals [3], polymers [4], etc. Among fluorine-containing compounds, optically active fluorine-containing alcohols (**3**) are one of the most important synthetic intermediates. However, the methodology for the asymmetric synthesis of **3** has been limited to certain biological methods [5] and the enantioselective reduction of fluorine-containing ketones using a stoichiometric amount of a chiral auxiliary [6].

In contrast, we have reported the enantioselective addition of organozinc reagents to aldehydes using *N*,*N*-dibutylnorephedrine (DBNE) [7] and (*S*)-(+)-diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM) [8] as chiral catalysts.



Scheme 1. Catalytic enantioselective addition of dialkylzincs to fluorine-containing aldehydes.

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TABLE 1

Asymmetric synthesis of fluorine-containing optically active alcohols

Entry[a]	R^1_f in compound **1**	R^2(equiv.)[b] in compound **2**		Chiral catalyst	Time (h)	Alcohols (**3**)		
						$[\alpha]_D$ (c, solvent)	Yield[c] (%)	Enantiomeric Excess[d] (config.)
1	p-$CF_3C_6H_4$	Et	2.2	(−)-DBNE	22	−19.4(5.0,C_6H_6)	92	91(*S*)
2	p-$CF_3C_6H_4$	Me	2.2	(−)-DBNE	190	−24.7(1.9,CH_3OH)	31	84(*S*)
3	p-$CF_3C_6H_4$	Me	3.0	(−)-DBNE	214	−21.3(1.7,CH_3OH)	80	81(*S*)
4	p-$CF_3C_6H_4$	Bu^n	2.2	(−)-DBNE	44	−18.7(3.5,$CHCl_3$)	28	77
5	p-$CF_3C_6H_4$	Et	2.2	(+)-DPMPM[e]	22		80	91(*S*)
6	p-FC_6H_4	Et	2.2	(−)-DBNE	24	−36.6(5.0,$CHCl_3$)	83	93
7	o-FC_6H_4	Et	2.2	(−)-DBNE	24	−24.0(5.0,$CHCl_3$)	65	85
8	p-F-m-BrC_6H_4	Et	2.2	(−)-DBNE	22	−23.7(5.0,$CHCl_3$)	89	85
9	$F(CH_2)_7$	Et	2.2	(−)-DBNE	14	+7.9(4.2,$CHCl_3$)	36	83
10	$CF_3(CF_2)_5(CH_2)_2$	Et	2.2	(−)-DBNE	12		43	73

[a] Solvent, hexane; reaction temperature, 0 °C.

[b] Based on the fluorine-containing aldehydes.

[c] Isolated yields.

[d] Determined by HPLC analysis of the corresponding (−)-MTPA esters using chiral columns (Chiral OJ and Chiralpak AD) or ^1H NMR analyses of the corresponding (−)-MTPA esters.

[e] Lithium salt of DPMPM (prepared *in situ* by reaction with n-butyllithium) was used.

We report here the catalytic asymmetric synthesis of **3** by the highly enantioselective addition of dialkylzincs to fluorine-containing aldehydes using DBNE and DPMPM as chiral catalysts (Scheme 1).

When *p*-trifluoromethylbenzaldehyde was treated with diethylzinc in hexane at 0°C in the presence of (1*S*,2*R*)-(−)-DBNE (6 mol%), (*S*)-1-(*p*-trifluoromethyl)phenylpropanol was obtained in 92% yield and 91% enantiomeric excess (Table 1, entry 1). It was found that the lithium salt of (S)-(+)-DPMPM was also effective in affording the corresponding fluorine-containing alcohol in 91% enantiomeric excess (Table 1, entry 5).

On the other hand, treatment of other dialkylzincs (Me_2Zn, nBu_2Zn) with *p*-trifluoromethylbenzaldehyde at 0 °C in the presence of 6 mol% of (1*S*,2*R*)-(−)-DBNE in hexane afforded the corresponding fluorine-containing optically active alcohols in high enantiomeric excess (entries 2–4).

The method was also applicable to the asymmetric synthesis of optically active fluorine-containing aliphatic alcohols. Thus, the enantioselective addition of Et_2Zn to the aliphatic fluorine-containing aldehydes using 6 mol% of (1*S*,2*R*)-(−)-DBNE afforded the corresponding optically active aliphatic alcohols in good to high enantiomeric excesses (entries 9,10).

The following procedure is typical (Table 1, entry 6). To a solution of (−)-DBNE (6 mol%, 0.06 mmol) in hexane (2.0 ml) was added *p*-fluorobenzaldehyde (1 mmol). The mixture was stirred at room temperature for 20 min, then Et_2Zn (2.2 mmol, 2.2 ml of 1 M hexane solution) was added at 0 °C. The reaction mixture was stirred at 0 °C for 24 h, and was quenched with 1 M HCl. The mixture was extracted with dichloromethane, the extract dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by silica gel TLC [hexane–AcOEt 4:1 (v/v) as developing solvent].

As described above, optically active fluorine-containing alcohols were obtained by the enantioselective addition of dialkylzincs to fluorine-containing aldehydes in good to high enantiomeric excesses using DBNE and DPMPM as chiral catalysts. Because both enantiomers of DBNE and DPMPM are available*, either enantiomer of **3** of the desired configuration can be synthesized using the appropriate enantiomer of the chiral catalysts.

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