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Chiral Dialkyl Thiophosphoramidates as Highly Enantioselective Catalysts for the Alkylation of Aldehydes

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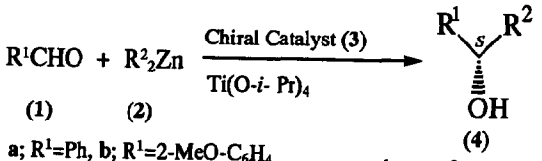
Abstract: Chiral dialkyl thiophosphoramidates derived from norephedrine are highly enantioselective catalysts for the addition of dialkylzincs to aldehydes in the presence of titanium(IV) isopropoxide, and optically active *sec* -alcohols with up to 97% e.e. being obtained.

Increasing interest has been centered on catalytic enantioselective addition of dialkylzinc reagents to aldehydes.[1] On the other hand, we recently reported the enantioselective synthesis of chiral phosphoramides (and chiral amines after the hydrolysis) by the alkylation of phosphinoylimines.[2] We are interested in the use of chiral phosphoramide derivatives as chiral catalysts and, although dialkyl thiophosphoramidates[3] and dimethyl thiophosphinamide[4] are utilized as protecting groups of amines, to the best of our knowledge, they have rarely been utilized as chiral catalysts in asymmetric synthesis.[5]

We now report that chiral dialkyl thiophosphoramidates (**3a,b**) derived from norephedrine (which is available in either enantiomeric form) are highly enantioselective chiral catalysts for the addition of dialkylzincs to aldehydes. When benzaldehyde (**1a**) was reacted with diethylzinc using 5 mol% (1*S*, 2*R*)-(+)-*N* - dimethoxyphosphinothioyl norephedrine (**3a**) ($[\alpha]_D^{22}$ +12.8 (*c* 1.0, MeOH), prepared in 79% yield from dimethyl chlorothiophosphate and (+)-norephedrine using triethylamine) in the presence of titanium(IV) isopropoxide [Ti(O-*i* -Pr)$_4$] in toluene/hexane at -50°C, (*S*)-(-)-1-phenyl-1-propanol (**4b**) with 95% e.e. was obtained in 93% yield (Table, entry 1). Furthermore, **4b** with 97% e.e. was obtained using 15 mol% of (1*S*, 2*R*)-(+)-**3a** in the presence of Ti(O-*i* -Pr)$_4$ (entry 2). On the other hand, treatment of dimethylzinc with **1a** in the presence of (+)-**3a** afforded (*S*)-1-phenylethanol (**4a**) in 95% e.e. (entry 3). 2-Methoxybenzaldehyde (**1b**) and α,β-unsaturated aldehyde (cinnamaldehyde) (**1c**) were ethylated in 90 - 95% e.e.'s (entries 4 and 5).

In a typical experiment (Table, entry 2): 0.8 mmol of Ti(O-*i* -Pr)$_4$ was added to a toluene solution (1 ml) of (+)-**3a** (0.15 mmol, 0.041g) and the mixture was refluxed for 20 min. The mixture was cooled to -50°C and a



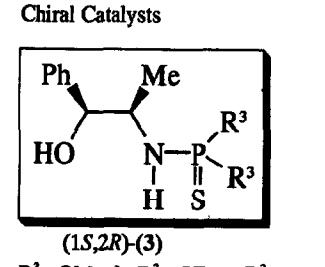


Table. Enantioselective synthesis of (*S*)-**4** using chiral catalysts (**3**).[a]

Entry	Aldehyde	R^2	Catalyst	Temperature/°C	Time/h	4	$[\alpha]_D$(*c*, solvent, temperature)	Yield/%	E.e./%[b]
1	**1a**	Et	**3a**	-50	2.3	**4b**	-42.9 (2.0, $CHCl_3$, 24)	93	95
2	**1a**	Et	**3a**	-30	2.9	**4b**	-44.9 (1.0, $CHCl_3$, 23)	80	97
3	**1a**	Me	**3a**	-30 → 0	3.8	**4a**	-37.9 (1.0, *cyclo*-C_6H_{12}, 23)	52	95
4	**1b**	Et	**3a**	-50 → 0	5.0	**4c**	-46.1 (1.0, toluene, 24)	82	95
5	**1c**	Et	**3a**	-50	2.2	**4d**	-4.3 (2.5, $CHCl_3$, 22)	75	90
6	**1a**	Et	**3b**	-35 → -20	1.3	**4b**		97	88
7	**1a**	Et	**3c**	-35 → -20	3.0	**4b**		98	74

[a] Molar ratio. **1** : **2** : **3** : Ti(O-*i*-Pr)$_4$ = 1 : 1.5 : 0.05 : 1.5 (for entries 1, 6 and 7); 1 : 1.5 : 0.15 : 0.8 (for entries 2, 4 and 5); 1 : 1.5 : 0.15 : 1.5 (for entry 3). [b] Determined by HPLC analysis using chiral column. Daicel Chiralcel OB for **4b** and **4c**; Chiralcel OD for **4a** and **4d**.

hexane solution of Et_2Zn (1 M, 1.5 ml, 1.5 mmol) was added. The reaction mixture was stirred at -50°C for 20 min, **1a** (0.106g, 1 mmol) was added, stirring continued for 2.9 h at -30°C, and the reaction quenched with saturated aq. NH_4Cl solution. The mixture was extracted with dichloromethane, the extract was dried (Na_2SO_4), and the solvent was evaporated under a reduced pressure. The residue was purified by silica gel TLC [developing solvent, hexane-AcOEt 4:1 (v/v)]. (*S*)-(-)-**4b** with 97% e.e. was obtained in 80% yield.

As to the structural effect of the chiral catalysts, (1*S*,2*R*)-diethyl thiophosphoramidate (**3b**) also shows high asymmetric induction [(*S*)-**4b**, 88% e.e., entry 6). (1*S*,2*R*)-*N*-Dimethylphosphinothioyl norephedrine (**3c**) afforded (*S*)-**4b** with good e.e. (74% e.e., entry 7).

As described, chiral dialkyl thiophosphoramidates derived from norephedrine are highly enantioselective catalysts for the alkylation of aldehydes. The present results may open the way to the use of chiral thiophosphoramidates in asymmetric synthesis.

References and Notes

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