

ENANTIOSELECTIVE SYNTHESIS OF SECONDARY ALCOHOLS IN THE PRESENCE OF CHIRAL LIGANDS

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Abstract—The synthesis of two S-proline derivatives is described together with their use as chiral ligands for lithium in reactions of n-butyllithium with benzaldehyde to give 1-phenyl-1-pentanol with moderate optical purity. The presence of lithium salts in the reaction mixture causes a decrease in asymmetric induction.

The formation of chiral secondary alcohols from carbonyl compounds has been fairly widely studied either by reduction of ketones with chiral hydride reagents¹⁻⁴ or by reactions of aldehydes with organometallic reagents in the presence of chiral ligands.⁵⁻⁸ Using the latter approach Cram *et al.*⁹ and Mukaiyama *et al.*⁵ obtained excellent results (up to 92% e.e.) in stoichiometric catalysis of additions of organometallics to aldehydes.

We have studied the proline derivatives (4') and (6) as chiral ligands in the reaction of n-butyllithium with benzaldehyde. Our approach to the design of the ligands for lithium was based on these considerations: the ligand had to bear two amine functions separated by two carbons, plus two methoxy groups (in 6) or lithium alkoxides (in 4') capable of further coordination.

These chiral catalysts can be easily recovered in 90% yield without any loss of optical purity by washing the reaction mixtures with 3N HCl, normal work-up, and bulb-to-bulb distillation. Two synthetic routes were used to obtain the ligands starting from the readily available S-proline (see Scheme 1).

Reduction of S-proline (1) with LiAlH₄ gave prolinol (2).⁹ Condensation of prolinol (2) with ethyl oxalate afforded amide (3) in quantitative yield. Treatment of (3)

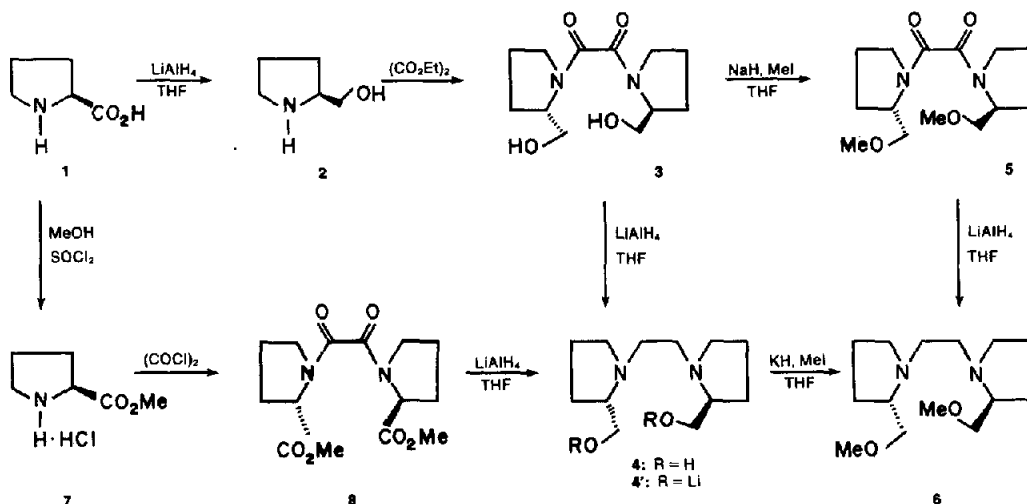
with LiAlH₄ in THF gave the pre-ligand (4) in 50% yield, the by-product being prolinol which can be recycled. The compound (5), obtained in 51% yield from (3) by treatment with NaH, CH₃I in THF, was reduced with LiAlH₄ in THF to give the ligand (6) in 85% yield.

Alternatively, condensation of S-proline methylester hydrochloride with oxalyl chloride in benzene gave the compound (8) in 80% yield. Reduction of (8) with LiAlH₄ in THF gave (4) in 70% yield. The ligand (6) can also be obtained by direct methylation of (4) in low yield.

In the first place we examined the detailed reaction conditions such as molar ratio of reactants, temperature, solvent, and ligand concentration in the asymmetric addition of n-BuLi to benzaldehyde using (4') and (6) as chiral ligands. The best optical purity (36%) was obtained with a molar ratio benzaldehyde: n-BuLi: ligand (4') 1:2:3 respectively, at -85°, and using 0.2 M solutions of the ligand in dimethoxymethane (DMM) (entry 10, Table 1).

1-Phenyl-1-pentanol was obtained with R-configuration using (4') as catalyst and S-configuration using (6).

On seeing some intriguing and non-reproducible data, we performed other reactions, under the best conditions (entry 10, Table 1), testing the molarity of n-BuLi solutions with more care. The organolithium was tested either



Scheme 1.

Table 1. Chiral catalysis in addition of *n*-BuLi to benzaldehyde at -85°

Entry	Molar ratio			Ligand	Solvent	Ligand concentration [M] ^{a)}	Optical purity (%) ^{b)}	Absolute configuration
	PhCHO	<i>n</i> -BuLi ^{d)}	ligand					
1	1	1	1	(4')	Et ₂ O	0.2	15	R
2	1	1	1	(4')	DME	0.2	19	R
3	1	1	1	(4')	DMM	0.2	22	R
4	1	1	1	(4')	DMM	0.05	20	R
5 ^{c)}	1	1	1	(4')	DMM	0.2	15	R
6	1	1	2	(4')	DMM	0.2	30	R
7	1	1	2	(4')	DMM	0.05	26	R
8 ^{c)}	1	1	2	(4')	DMM	0.2	20	R
9	1	2	2	(4')	DMM	0.2	26	R
10	1	2	3	(4')	DMM	0.2	36	R
11	1	3	3	(4')	DMM	0.2	30	R
12	1	4	3	(4')	DMM	0.2	25	R
13	1	2	4	(4')	DMM	0.2	33	R
14	1	2	3	(6)	<i>n</i> -hexane	0.2	15	S
15	1	2	3	(6)	Et ₂ O	0.2	13	S
16	1	2	3	(6)	THF	0.2	4	S

a) This concentration does not take into consideration the amounts of *n*-hexane introduced in the reaction with commercial *n*-BuLi.

b) On the basis of the highest value available in literature: $[\alpha]_D^{25} 35.7^{\circ}$ (c 3, C₆H₆) (ref. 8).

c) Reaction performed at -60°C .

d) 1.5 M *n*-BuLi in *n*-hexane, tested by direct titration (see ref. 11).

by hydrolysis and acid titration¹⁰ or by a direct one,¹¹ the difference indicating the amount of lithium hydroxide and alkoxides¹⁰ present in the reagent. We found a decrease in asymmetric induction proportional to the amount of the poisoning lithium salts.

By using low molarity *n*-BuLi an increasing amount of *n*-hexane was introduced in the reaction mixture. This fact was not thought to be fundamental in decreasing the optical purities, on the basis of previous experiments (Table 1, entries 4,7) which clearly show that diminishing the concentration of *n*-hexane by adding larger amounts of DMM does not improve optical yields. Further confirmation of the negative salt-effect on the asymmetric induction was given by two other reactions performed in the presence of LiI and LiClO₄ (Table 2).

EXPERIMENTAL

¹H NMR spectra were recorded on a Varian XL-100 instrument (solvent CDCl₃ unless otherwise stated, Me₄Si as internal standard), mass spectra with a Varian MAT 112 spectrometer, IR spectra (CHCl₃) with a Perkin-Elmer 257 spectrophotometer, optical rotations were measured at 25° with a Perkin-Elmer 141 polarimeter. Commercial 60 F₂₅₄ (Merck) silica gel plates were used for tlc; 230-400 mesh silica gel (Merck) was used for "flash" chromatography.

Materials

Benzaldehyde was distilled under reduced pressure in an atmosphere of dry oxygen-free nitrogen before use. Commercial *n*-BuLi in *n*-hexane (Merck or Fluka) was used. Et₂O, DME, DMM, THF, and *n*-hexane were freshly distilled from LiAlH₄ under nitrogen prior to use.

Table 2. Negative salt-effect in the addition of *n*-BuLi to benzaldehyde in the presence of the chiral catalyst (4')^{a)}

Entry	Acid titration [M]	Direct titration [M]	Added salt	Optical purity (%)
1	1.6	1.5	-	34-36 ^{b)}
2	1.6	1.3	-	28-30 ^{b)}
3	1.6	1.0	-	15-18 ^{b)}
4	1.6	1.5	LiClO ₄ ^{c)}	8
5	1.6	1.5	LiI ^{c)}	1

a) Reaction conditions as in entry 10, table 1.

b) Average values obtained from at least ten experiments.

c) Molar ratio added salt:(4') 1:1.

General procedure

The ligand was treated with *n*-BuLi at 0° for 30 min in the proper solvent and cooled to -85°. Benzaldehyde (1 mmol) was then added and the reaction mixture was stirred for 1 h. The reaction was quenched with 3N HCl, and the product extracted with ether. Separation by silica gel preparative tic (CH₂Cl₂) and further purification by bulb-to-bulb distillation gave 1-phenyl-1-pentanol. Yields of the isolated product were generally 60–80%.

Recovery of the chiral ligands

The acidic solution from above was neutralized with solid NaHCO₃ and then concentrated in vacuo. The residue was washed with CH₂Cl₂ and the organic solution dried (K₂CO₃) and concentrated. Distillation gave the pure ligands in over 90% recovery and examination of the [α]_D values indicated that no racemization had occurred.

Compound 3

L-Prolinol (2)⁹ (50 g, 0.495 mol) was treated with ethyl oxalate (38 g, 0.26 mol) at 0° with stirring. The reaction mixture was stirred at room temperature for 2 h and then evaporated under vacuum. The crude product was crystallized from ethyl acetate to give the compound 3 (66 g) in quantitative yield, mp 85°; [α]_D (c 1.14, MeOH) -131.4°; ν_{max} 3340, 3260, 1640, 1620 cm⁻¹; δ (CD₃OD) 1.7–2.2 (m, 8H, CH₂CH₂), 3.2–3.8 (m, 10H, CH₂N, CH₂O), 4.1–4.3 (br. t, 2H, CHN); found: C, 56.0; H, 7.9; N, 11.0. C₁₂H₂₀N₂O₄ requires C, 56.2; H, 7.8; N, 10.9%.

Ligand 4 by reduction of 3

A stirred suspension of LiAlH₄ (5.9 g, 0.156 mol) in THF (200 ml) was heated at reflux and then treated with small portions of compound 3 (10 g, 39.1 mmol). The mixture was stirred at reflux for 4 h and then cooled, treated with aqueous KOH and filtered. The aluminum salts were submitted to Soxhlet extraction (overnight) using CH₂Cl₂. The collected organic extracts were dried (Na₂SO₄) and evaporated under vacuum to give a crude mixture which was purified by distillation to give 4 (8.9 g) in 50% yield, b.p. 150° (0.1 mmHg); [α]_D -53.4° (c 0.5, CHCl₃); ν_{max} 3650, 3350, 3160, 1135, 1105, 1060; *m/e* 228 (M⁺), 226, 209, 196, 179, 178, 128, 114 (M/2, 100%); δ 1.2–2.1 (m, 8H, CH₂C), 2.1–3.4 (m, 10H, CH₂N), 3.4–4.0 (m, 5H, CH₂O and OH), 5.0 (br. s, 1H, OH); found: C, 63.02; H, 10.41; N, 12.06. C₁₂H₂₄N₂O₂ requires C, 63.16; H, 10.53; N, 12.28%.

Compound 5

Compound 3 (43 g, 0.168 mol) was added in small portions to a mixture of CH₃I (95.4 g, 0.672 mol) and NaH (16.2 g, 0.672 mol) in THF (400 ml). After 1 h at room temperature the mixture was treated with saturated brine and extracted with ethyl acetate to give a crude product which was purified by "flash" chromatography (CHCl₃; MeOH 9:1) to give compound 5 (24 g, 51%); ν_{max} 1625 cm⁻¹; δ 1.8–2.1 (m, 8H, CH₂CH₂), 3.2–3.7 (m, 8H, CH₂O and CH₂N), 3.4 (s, 6H, OCH₃), 4.1–4.6 (m, 2H, CHN); found: C, 59.0; H, 8.35; N, 10.1. C₁₄H₂₄N₂O₄ requires C, 59.2; H, 8.5; N, 9.9%.

Ligand 6 by reduction of 5

A stirred suspension of LiAlH₄ (5.62 g, 0.148 mol) in THF (300 ml) was heated at reflux and then treated with compound 5 (17 g,

0.06 mol). The mixture was refluxed for 2 h and then worked up as previously described to give a crude product which was purified by distillation to give 6 (13 g, 85%), b.p. 130° (0.1 mmHg); [α]_D -124.2° (c 1.6, CHCl₃); selected δ value: 3.4 (s, 6H, OCH₃), found: C, 65.21; H, 11.04; N, 10.56. C₁₄H₂₈N₂O₂ requires C, 65.63; H, 10.94; N, 10.94%.

Compound 8

A stirred suspension of proline methylester hydrochloride 7¹² (28.7 g, 0.174 mol) in dry benzene (350 ml) was treated with oxalyl chloride (14.7 g, 0.116 mol) and then heated at reflux for 4 h. After cooling, the benzene solution was washed with a saturated NaHCO₃ solution, dried (Na₂SO₄) and evaporated under vacuum. The resulting crude product was crystallized from ethyl acetate to give 8 (21.7 g, 80%), m.p. 154–155°; [α]_D -79.5° (c, 2.0, CHCl₃); ν_{max} 1740, 1660, 1640, 1165; δ 1.6–2.7 (m, 8H, CH₂CH₂), 3.7–4.2 (m, 4H, CH₂N), 4.0 (s, 6H, OCH₃), 4.6–5.0 (m, 2H, CHN); found: C, 54.0; H, 6.3; N, 9.1. C₁₄H₂₀N₂O₆ requires C, 53.8; H, 6.4; N, 9.0%.

Ligand 4 by reduction of 8

A stirred suspension of LiAlH₄ (12 g) in THF (320 ml) was heated at reflux in a Soxhlet apparatus, the scarcely soluble diamide (17.5 g) being continuously extracted by refluxing THF. After 5 h the mixture was cooled, treated with aqueous KOH and worked up as previously described to give 4 in 70% yield (10.2 g).

Ligand 6 by methylation of 4

A THF (40 ml) solution of 4 (4.5 g, 20 mmol) was added to a stirred suspension of KH (1.76 g, 44 mmol) in THF (10 ml) at room temperature and stirred for 1 h. A THF (20 ml) solution of CH₃I (5.68 g, 40 mmol) was added dropwise and stirred overnight. The reaction mixture was quenched with saturated brine (50 ml), extracted with ether, dried (K₂CO₃), and concentrated. Distillation gave 4 (1.1 g, 21%).

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