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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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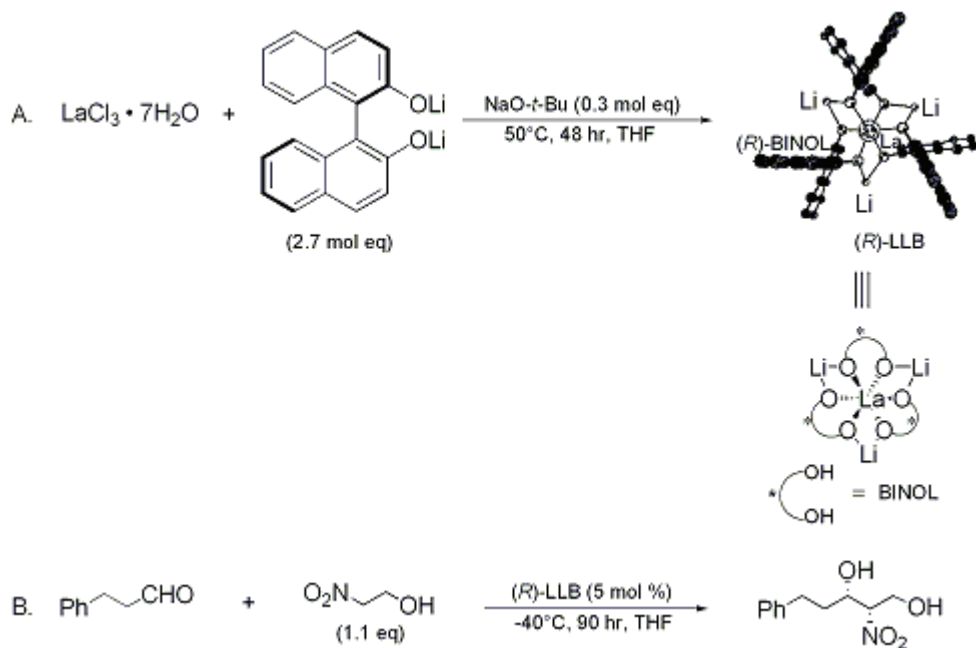
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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CATALYTIC ASYMMETRIC SYNTHESIS OF NITROALDOLS USING A LANTHANUM-LITHIUM-BINOL COMPLEX: (2*S*,3*S*)-2-NITRO-5-PHENYL-1,3-PENTANEDIOL

[*L*-threo-Pentitol, 1,2,4-trideoxy-4-nitro-1-phenyl-]



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Checked by Fabien Havas, Nabi A. Magomedov, and David J. Hart.

1. Procedure

A. Lanthanum-lithium-(R)-BINOL complex (LLB). A dry, 300-mL, three-necked flask equipped with a magnetic stirring bar, septum cap, and a rubber balloon filled with argon, is charged with (*R*)-2,2'-dihydroxy-1,1'-binaphthyl (*R*)-BINOL; 6.49 g, 22.7 mmol, Note 1) and 119 mL of tetrahydrofuran (THF, Note 2) under an argon atmosphere. The system is placed in an ice-water bath and magnetic stirring is initiated. Via syringe, 28.4 mL (45.4 mmol) of a 1.60 M hexane solution of butyllithium (Note 3) is added to the cooled (*R*)-BINOL solution over 7 min and the pale yellow mixture is stirred for an additional 15 min. The cooling bath is removed and the THF solution of (*R*)-BINOL dilithium salt is allowed to reach room temperature.

A 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and a septum cap is charged with 3.12 g of lanthanum trichloride heptahydrate ($\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$, 8.4 mmol, Note 4) and 100 mL of THF. The resulting suspension is sonicated for 30 min at room temperature (Note 5). To this suspension is added the above prepared solution of (*R*)-BINOL dilithium salt via syringe over 5 min with vigorous stirring (Note 6). After this mixture is stirred for 30 min at room temperature, a 0.52 M THF solution of sodium *tert*-butoxide (4.85 mL, 2.52 mmol, Note 7) is added via syringe over 5 min. The resulting suspension is stirred vigorously for 14 hr at room temperature and then stirred for 48 hr at 50°C. The reaction mixture is allowed to cool to room temperature without stirring, and the supernatant is used as a 0.03 M solution of lanthanum-lithium-(*R*)-BINOL catalyst [(*R*)-LLB].

*B. (2*S*,3*S*)-2-Nitro-5-phenyl-1,3-pentanol*. A 500-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, septum cap, and a rubber balloon filled with argon, is charged

with 119 mL of THF and a 0.03 M THF solution of (R)-LLB catalyst (63.3 mL, 1.90 mmol) under an argon atmosphere. The system is cooled to -40°C and magnetic stirring is initiated (Note 8). The mixture is stirred for 30 min at -40°C , then 2-nitroethanol (3.00 mL, 41.8 mmol, Note 9) is added via syringe over 4 min. After 30 min of stirring at -40°C , 5.00 mL of 3-phenylpropanal (38.0 mmol, Note 10) is added via syringe over 5 min and the resulting solution is stirred for 90 hr. The reaction is monitored by TLC (Note 11). To the reaction mixture is added 150 mL of 1N hydrochloric acid (HCl). To this mixture is added 20 g of sodium chloride (NaCl) and the resulting mixture is transferred to a 2-L separatory funnel. The aqueous phase is extracted three times with ethyl acetate (400, 200, and 200 mL) and the combined organic phases are washed with 350 mL of aqueous saturated NaCl solution and dried over sodium sulfate. The solvent is removed with a rotary evaporator, and the resulting crude product is recrystallized from 1 : 1 hexane: ether (ca. 200 mL) to give 4.31g (50%) of analytically pure (2S,3S)-2-nitro-5-phenyl-1,3-pentanediol (98% ee, Notes 12-15).

2. Notes

1. (R)-BINOL was dried at 50°C for 2 hr under reduced pressure.
2. THF was freshly distilled from sodium benzophenone ketyl under an argon atmosphere.
3. BuLi was purchased from Kanto Chemical Company, Inc. and titrated prior to use.
4. Pulverized lanthanum chloride heptahydrate was purchased from Aldrich Chemical Company, Inc. (purity 99.9%), or Kanto Chemical Company, Inc. (purity 99.99%). The anhydrous salt is very hygroscopic and must be protected against moisture. It can, however, be handled very quickly in air without any special precaution.
5. The checkers used a Branson sonicator.
6. The transfer may also be made via cannula.
7. Sodium tert-butoxide was purchased from Aldrich Chemical Company, Inc.
8. When the checkers conducted the reaction at -30°C , a 45% yield of product with 50% ee was obtained.
9. 2-Nitroethanol was distilled under reduced pressure prior to use.
10. 3-Phenylpropanal was distilled under reduced pressure prior to use.
11. Acetone - hexane (1:2) or dichloromethane-methanol (20 : 1) is used as an eluant. Anisaldehyde is used as an indicator. Silica gel is used as the stationary phase.
12. The submitters indicate that purification of a small amount of crude 2-nitro-5-phenyl-1,3-pentanediol by reverse phase chromatography (Lobar LiChroprep RP-8, $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ 1:1) revealed that the yield, diastereoselectivity, and optical purity of the syn adduct is 79%, syn: anti = 11.5 : 1, and 89% ee, respectively.
13. The submitters obtained a second crop: 0.60 g (7% yield, 91% e.e.).
14. The enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALPAK AD (hexane: i-PrOH 9:1, 0.7 mL/min, 254 nm). The retention times for the (2R,3R)-, (2S,3S)-, (2R,3S)- and (2S,3R)-derivatives are 22.6 min, 24 min, 17 min and 18 min, respectively. The analytical and spectral data of pure (2S,3S)-2-nitro-5-phenyl-1,3-pentanediol are as follows: $[\alpha]_{\text{D}}^{24} -17.7^{\circ}$ (c 0.86, chloroform, 98% ee), mp $101-102^{\circ}\text{C}$; $^1\text{H NMR}$ δ : 1.83-1.95 (m, 2 H), 2.19 (br-t, 1 H, J = 6.2), 2.44 (br-d, 1 H, J = 7.5), 2.75 (m, 1 H), 2.90 (m, 1 H), 4.03-4.23 (m, 3 H), 4.57 (ddd, 1 H, J = 4.0, 5.2, 6.7), 7.17-7.35 (m, 5 H); $^{13}\text{C NMR}$ δ : 31.45 (CH), 35.15 (CH_2), 61.78 (CH_2), 69.53 (CH_2), 92.08 (CH), 126.33 (CH), 128.43 (CH), 128.64 (CH) 140.56 (C); IR (KBr) cm^{-1} : 3332, 1559, 1369; FABMS (glycerol) m/z 226 ($\text{M}^+ + 1$), 161, 91 (base peak). Anal. calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.47; H, 6.77; N, 5.93. The checkers obtained a 53% yield of product, pure by combustion analysis, with 95% ee. One recrystallization of this material (85% recovery) gave product with greater than 98% ee. When the checkers used catalyst aged for 16 days at -20°C , product was obtained in 43% yield with a 95% ee.
15. The submitters recovered BINOL in quantitative yield without racemization. This material was reused after recrystallization from toluene.

Waste Disposal Information


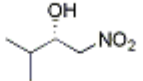

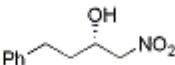
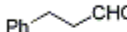

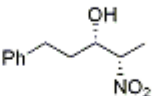
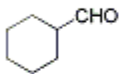
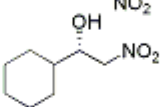
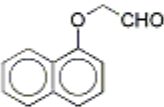
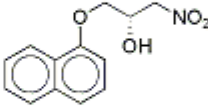
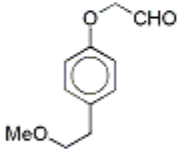
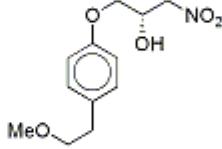
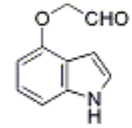
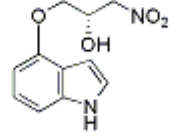

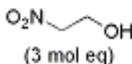
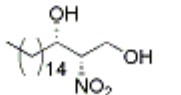
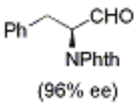
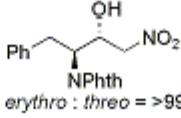
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The lanthanum-lithium-BINOL (LLB) catalyst² can be prepared by three different methods that start with lanthanum trichloride,³ lanthanum trichloride heptahydrate (procedure A),⁴ or lanthanum tris(2-propoxide).^{5,6} From a practical perspective, the most important method is procedure A, since this procedure is easy to perform, and the starting lanthanum trichloride heptahydrate is much cheaper than the corresponding anhydride or lanthanum tris(2-propoxide). Using methods similar to those for LLB, other rare earth-lithium-BINOL complexes can be prepared. For example, praseodymium-lithium-BINOL complex (PrLB) and neodymium-lithium-BINOL complex (NdLB) can be prepared from praseodymium tris(2-propoxide) and neodymium tris(2-propoxide), respectively. In some cases, these rare earth-lithium-BINOL complexes promote the nitroaldol reaction more efficiently than LLB to give nitroaldols in higher optical purities.^{6,7} Furthermore, samarium-lithium-BINOL complex (SmLB), europium-lithium-BINOL complex (EuLB) and gadolinium-lithium-BINOL complex (GdLB) are effective in the asymmetric nitroaldol reaction of aromatic aldehydes with nitromethane.^{6,7} The purity of rare earth tris(2-propoxide) may vary with supplier. The submitters have obtained their best results using rare earth tris(2-propoxide) purchased from Kojundo Chemical Laboratory Co., Ltd., Japan.

Concerning the source of the chiral catalysts, the introduction of trialkylsilylethynyl groups at the 6,6'-position of BINOL is effective for obtaining nitroaldols in higher enantiomeric excesses.⁸ In the case of diastereo- and enantioselective nitroaldol reactions using nitroethane, nitropropane, and 2-nitroethanol, higher diastereomeric excesses are also observed using 6,6'-bis(triethylsilylethynyl)BINOL as a ligand.⁸ Furthermore, the submitters have synthesized several therapeutically or biologically important compounds such as β -blockers,^{7,9,10,11} norstatine derivative,¹² and threo-dihydrosphingosine.⁸ Representative results are shown in Table I. To the best of the submitter's knowledge, rare earth-lithium-BINOL complexes are the only catalysts that efficiently promote asymmetric nitroaldol reactions.

TABLE I
ASYMMETRIC NITROALDOL REACTION USING LANTHANUM-LITHIUM-BINOL
DERIVATIVE COMPLEX AS A CATALYST

Entry	Aldehyde	Nitro compound ^a	Conditions ^{b,c}	Nitroaldol	Yield (%)	syn / anti	ee (%) (of syn)
1		MeNO ₂	(<i>R</i>)-LLB (3.3 mol%), -42 °C, 18 hr		80	—	85
2		MeNO ₂	(<i>R</i>)-LLB* (3.3 mol%), -40 °C, 91 hr		84	—	85
3			(<i>R</i>)-LLB* (3.3 mol%), -20 °C, 75 hr		70	89 / 11	93
4		MeNO ₂	(<i>R</i>)-LLB (3.3 mol%), -60 °C, 25 hr		73	—	93
5		MeNO ₂	(<i>R</i>)-LLB (3.3 mol%), -50 °C, 60 hr		80	—	92
6		MeNO ₂	(<i>R</i>)-LLB (5 mol%), -50 °C, 60 hr		90	—	94
7		MeNO ₂	(<i>R</i>)-LLB (10 mol%), -50 °C, 96 hr		76	—	92
8		 (3 mol eq)	(<i>R</i>)-LLB* (10 mol%), -40 °C, 163 hr		78	91 / 9	97
9	 (96% ee)	MeNO ₂	(<i>R</i>)-LLB (3.3 mol%), -40 °C, 72 hr	 erythro : threo = >99 : 1	92% (erythro: 96% ee)		

a) Otherwise noted, 10 mol eq of nitro compound was used. b) All reactions were carried out in THF. c) LLB* : lanthanum-lithium-(*R*)-6,6'-bis(triethylsilylethynyl)BINOL.

References and Notes

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- (*R*) or (*S*)-LLB catalyst can be purchased from Fluka Chemie AG as a 0.03M THF solution. See, [tri-Lithium tris\[\(*R*\)-1,1'-bi\(2-naphtholato\)\]lanthanate](#) solution, CAS: 161444-03-7 , [tri-Lithium tris\[\(*S*\)-1,1'-bis\(2-naphtholato\)\]lanthanate](#) solution, CAS: 151736-98-0 .

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

(2S,3S)-2-Nitro-5-phenyl-1,3-pentanediol:
L-threo-Pentitol, 1,2,4-trideoxy-4-nitro-1-phenyl- (9); (172171-05-0)

(R)-2,2'-Dihydroxy-1,1'-binaphthyl [
(R)-BINOL]:
[1,1'-Binaphthalene]-2,2'-diol, (R)- (+)- (8);
[1,1'-Binaphthalene]-2,2'-diol, (R)- (9); (18531-94-7)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)

Lanthanum trichloride heptahydrate: Aldrich:
Lanthanum chloride heptahydrate (8);
Lanthanum chloride, heptahydrate (9); (10025-84-0)

Sodium tert-butoxide:
tert-Butyl alcohol, sodium salt (8);
2-Propanol, 2-methyl-, sodium salt (9); (865-48-5)

2-Nitroethanol:
Ethanol, 2-nitro- (8,9); (625-48-9)

3-Phenylpropanal: Aldrich:
Hydrocinnamaldehyde (8);
Benzenepropanal (9); (104-53-0)