

Michael Addition of Lithiodiphenylphosphine to Menthyloxy-2[5H]-Furanone: Enantioselective Synthesis of *S,S*-CHIRAPHOS

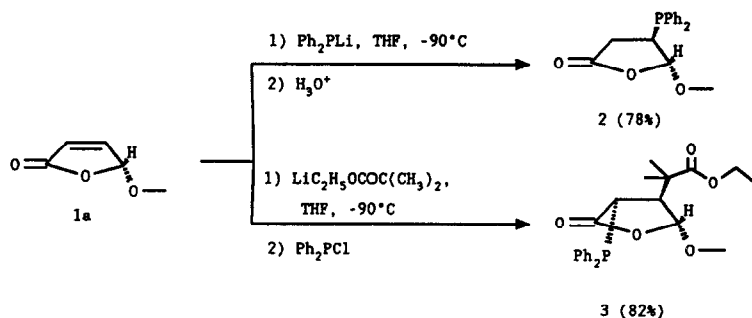
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Abstract: The preparation of enantiomerically pure (2*S*,3*S*)-2,3-bis(diphenylphosphino)-butane (*S,S*-CHIRAPHOS) in 35% overall yield from readily available γ -menthoxybutenolide is described.

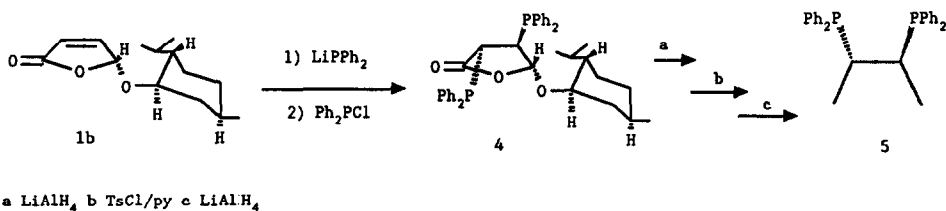
Chiral diphosphines are widely used as ligands in metal mediated asymmetric synthesis. The diphenylphosphine ligands are usually prepared *via* S_N2 type substitutions using tosylates of optically active diols and lithium- or sodium-diphenylphosphide.¹ To our knowledge only very limited use has been made of the Michael addition of phosphide anions; an example being the potassium tertiary butoxide catalyzed addition of diphenylphosphine to diethylvinylphosphonate.² In this communication we present the Michael addition of lithio-diphenylphosphide to γ -alkoxybutenolides³ and its application in the enantioselective synthesis of (*S,S*)-CHIRAPHOS. Initial experiments using methoxy-2[5H]-furanone showed that the 1,4-addition of lithio-diphenylphosphide is a high yielding and *trans*-diastereoselective process to provide the phosphine substituted lactone 2. The lactone enolate, formed by an initial diastereoselective Michael addition of an ester enolate can also be quenched stereoselectively with diphenylphosphine chloride to furnish 3. These results offer a flexible route for the preparation of various functionalized diphenylphosphines (scheme 1).



Scheme 1

Using the enantiomerically pure butenolide synthon (5*R*)-menthyloxy-2[5H]-furanone 1b, the asymmetric Michael addition of lithio-diphenylphosphide forms the key step in an alternative synthesis of (*S,S*)-CHIRAPHOS 5. In a one pot sequential 1,4-addition - quenching reaction with lithio-diphenylphosphide and diphenylphosphine chloride lactone 4 was obtained as a single diastereoisomer. The

adduct was reduced, tosylated and again reduced to give crude (S,S)-CHIRAPHOS. Diphosphine 5 was purified using the NiClO₄ method of Bosnich⁴ after which enantiomerically pure (S,S)-CHIRAPHOS was obtained in 35% overall yield (Scheme 2).^{5,6,7}



Scheme 2

In conclusion we describe here an alternative for the synthesis of (S,S)-CHIRAPHOS by a method which can potentially be applied to many chiral phosphines.

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References and notes:

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- By comparison with ref. 4: lit $[\alpha]_D^{25}$ -211 (c 1.5, CHCl₃), mp 108-109°C; found $[\alpha]_D^{25}$ -212 (c 1.5, CHCl₃), mp 108.2-110°C. All spectral data were identical.
- All compounds showed data in accordance with their proposed structure: the synthesis and spectral data of 4 are as follows: To a stirred solution of 0.93 g (5 mmol) of diphenylphosphine in 30 ml THF (distilled from Na/benzophenone) at -90°C under an Argon atmosphere was added 3.2 ml n-BuLi (1.6N in hexane) and the resulting mixture was stirred for 30 min at -90°C. To the red solution obtained was added, at -90°C during 15 min, a solution of 1.19 g (5 mmol) (5R)-menthyloxy-2[5H]-furanone in 30 ml THF. After stirring for an additional period of 1.5h 1.2 g (5.4 mmol) of diphenylphosphine chloride dissolved in 5 ml THF was added. The temperature was raised slowly (3h) to RT at which temperature the reaction mixture was stirred during 16h before it was poured into 200 ml sat. NH₄Cl solution. After the usual work up 2.8 g (4.6 mmol =92%) of the diphosphine 4 was obtained. IR; neat, cm⁻¹: 1780 (C=O), 1440 (PPh), 740, 690 (monoAr). ¹H-NMR (CDCl₃, 300 MHz); δ 7.8-7.0 (m, 20H); 5.32 (d, 1H, J=8.5 Hz:P); 3.32 (dt, 1H, J=4.0 Hz, J=10.6 Hz); 3.25 (dd, 1H, J=1.1 Hz:P, J=13.9 Hz:P); 2.90 (dd, 1H, J=2.1 Hz:P, J=12.9 Hz:P); 2.4-2.3 (m, 1H); 2.05-1.95 (m, 1H); 1.6-1.40 (m, 2H); 1.31-0.95 (m, 2H); 0.90-0.60 (m, 3H); 0.78 (d, 3H, J=6.2 Hz); 0.71 (d, 3H, J=6.6 Hz); 0.65 (d, 3H, J=6.6Hz) ¹³C- NMR (CDCl₃, 75 MHz; without P-C couplings): δ 172.29 (s), 134.72 (s); 132.21/130.38/130.23/128.61/128.46 (d); 101.22 (d); 77.43 (d); 47.46 (d); 47.30 (d); 39.28 (t); 33.94 (t); 30.88 (d); 30.67 (d); 24.44 (d); 22.31 (t); 21.82 (q); 20.96 (q); 14.95 (q). ³¹P-NMR (CDCl₃): δ 21.43 (m). HRMS; cal: 608.263, exp: 608.261. $[\alpha]_D^{25}$ -22.1 (c 2.6, CHCl₃).
- Using (5S)-menthyloxy-2[5H]-furanone³ the enantiomer of phosphine 5 is accessible.