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Synthesis of enantioenriched (*Z*,*E*)-1,2,5-triphenylphospholane oxide by a lithiation–protonation sequence

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Summary — *sec*-Butyllithium/(−)-sparteine mediated deprotonation, followed by reprotonation with various protonating agents, of the *meso* (*E*,*E*)-1,2,5-triphenylphospholane 1-oxide **2** affords the chiral (*E*,*Z*)-1,2,5-triphenylphospholane 1-oxide **4** with up to 45% ee. The results are best explained by a diastereoselective protonation of configurationally stable diastereomeric lithiated species.

phospholane oxide / asymmetric protonation / sparteine-mediated deprotonation

Résumé — Synthèse du (*Z*,*E*)-1,2,5-triphénylphospholane oxyde avec un excès énantiomérique, via une lithiation–protonation. La déprotonation par un système *sec*-butyllithium/(−)-spartéine du (*E*,*E*)-1,2,5-triphénylphospholane 1-oxyde *meso* **2**, suivie d'une reprotonation par divers agents protonants, permet d'obtenir le (*E*,*Z*)-1,2,5-triphénylphospholane 1-oxyde optiquement actif **4** avec des excès énantiomériques atteignant 45 %. La protonation diastéréosélective des intermédiaires lithiés diastéréoisomères permet d'expliquer au mieux les résultats obtenus.

oxyde de phospholane / protonation asymétrique / spartéine

Asymmetric catalysis remains an important issue in modern organic and organometallic chemistry [1]. As a result, the design and synthesis of new chiral ligands is still a field of great activity. Diphosphines, which may function as bidentate ligands, always were and still are among the most efficient ligands. Chiral, optically active monophosphines are less available, probably because they were less involved as being less efficient in reactions where the asymmetric induction arose from the backbone chirality of a chelating ligand [2]. However, optically active monophosphines have been used successfully in some enantioselective hydrogenations [3], hydrovinylations [4], hydrosilylations [5], acylations [6], methoxycarbonylations [7], cross-coupling [8], Pauson–Khand reactions [9] and resolutions [10].

Burk reported the synthesis of optically active 2,5-dialkyl-1-phenylphospholanes **1** [11], which have been used as ligands for asymmetric hydrogenation of unsaturated esters and aminoesters [12] and for the preparation of the DUPHOS ligand and related diphosphines. We described the preparation of the monophosphine 1,2,5-triphenylphospholane and its resolution through preparative chiral liquid chromatography of the corresponding oxide, which could be easily reduced into the optically active phosphine without racemization or epimerization [13]. In the search for a more convenient access to this phosphine, we aimed at investigating the selectivities for a deprotonation–reprotonation sequence of the 1,2,5-triphenylphospholane 1-oxide **2** with a chiral base, on the basis of the appealing reports of the work of D Hoppe [14] and P Beak [15] on enantioselective lithiation–substitution sequences.

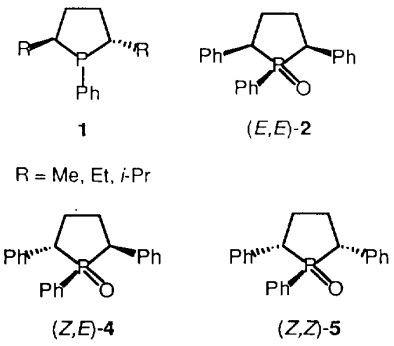

Fig 1

Such a stereoselective sequence should produce the chiral, optically active (*E*,*Z*)-**4** from achiral (*E*,*E*)-**2**, via an organolithium complex **3** (scheme 1).

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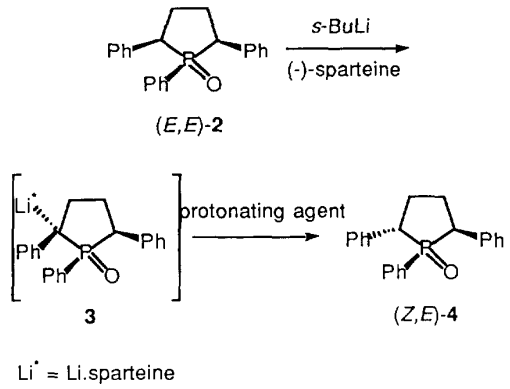


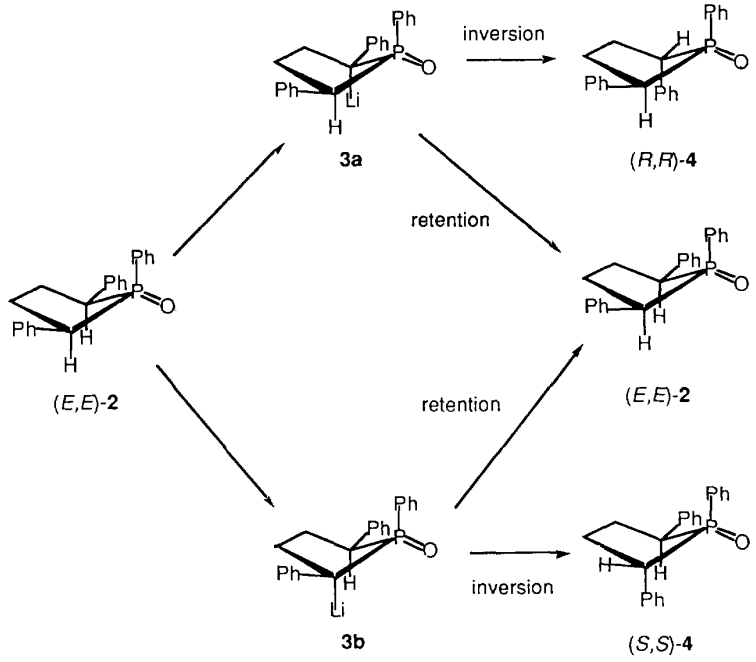
Scheme 1. Access to (*E*,*Z*)-**4** from (*E*,*E*)-**2** by an asymmetric deprotonation–reprotonation procedure.

As the deprotonation by lithium bases at a benzylic position is known to occur with stereoretention [16], the success of this strategy requires an invertive substitution for the protonation step.

Selective deprotonation of enantiotopic benzylic protons at C-2 and C-5 positions by a chiral base (organolithium complexed by a chiral ligand) will provide diastereomeric organolithium **3a** and **3b**. On the assumption that these complexes show substantial configurational stability under the reaction conditions, subsequent protonation with inversion will provide (*R*,*R*)-**4** from **3a** and the enantiomer (*S*,*S*)-**4** from **3b** (scheme 2). According to this hypothesis, the enantioselectivity recorded would arise from the deprotonation step, as a selection between enantiotopic sites by a chiral reagent.

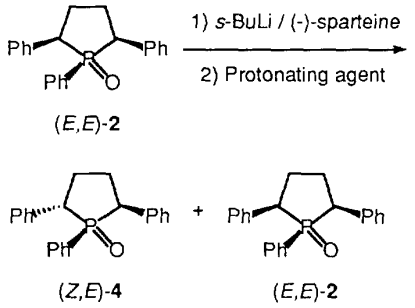
We first investigated the *sec*-BuLi/sparteine deprotonating system and different proton sources for the protonation step. Reactions were conducted as follows in a Schlenk tube under an inert atmosphere (argon): into freshly distilled THF (1 mL) were added successively at −78 °C (−)-sparteine (83 μL, 0.36 mmol), *sec*-butyllithium (1.3 M in cyclohexane, 254 μL, 0.33 mmol). After 15 min stirring at this temperature, (*E*,*E*)-**2** (100 mg, 0.3 mmol) in THF (3 mL) was added dropwise. The homogeneous orange-red solution was stirred for 0.5 h at −78 °C. The reaction was quenched by the protonating agent (10 equiv) and the colorless mixture allowed to warm to room temperature. Aqueous work-up followed by flash chromatography gave a mixture of (*E*,*Z*)-**4** and (*E*,*E*)-**2**. The ratio of these two diastereomers and the ee of (*E*,*Z*)-**4** were measured by chiral HPLC. Results are collected in table I.

Tert-butanol showed an excellent stereoselectivity for the protonation with inversion, giving 98% (*E*,*Z*)-**4**, but nearly racemic. This result is indicative of a ready deprotonation by the base and, on assumption of some configurational stability for the organolithium compound, of a very poor selection of the base for the enantiotopic protons of (*E*,*E*)-**2**. The less sterically hindered methanol gave again a poor enantioselectivity, but more significantly a worse selectivity for the protonation step. The efficiency for the inversion process is even worse with acetic acid since only 33% of (*E*,*Z*)-**4** was produced. However, the enantiomeric purity of this sample is significantly higher (45%). Both trifluoroacetic acid and triphenylmethane were poorly selective in terms of invertive substitution. The variations of the (*E*,*Z*)-**4**/(*E*,*E*)-**2** ratio and the ee of (*E*,*Z*)-**4** thus seem to be opposite. As the protonating agent, acetic acid ap-



Scheme 2. Mechanism of the (*S*,*S*)-**4**, (*R*,*R*)-**4** and (*E*,*E*)-**2** formation.

Table I. Reactions of (*E*,*E*)-**2** with *sec*-BuLi/(−)-sparteine followed by protonation[a].



Protonating agent	*(E,Z)-4/(E,E)-2*[b]	*(E,Z)-4 ee*[c] *(%)*
tert-BuOH	98:2	2
MeOH	85:15	5
CH_3COOH	33:66	45
CF_3COOH	5:95	51
Ph_3CH[d]	5:95	58

[a] Experimental conditions: see text. [b] Combined yield of (*E*,*E*)-**2** and (*E*,*Z*)-**4** was above 95% in all runs. [c] Determined by chiral HPLC (Chiralcel OD-H®, hexane/isopropanol 3:1); the major enantiomer is first eluted unless stated otherwise. [d] As a 3M THF solution.

peared to be the best compromise in terms of chemical and optical yields for (*E*,*Z*)-**4**.

To investigate the role of the basic alcoholates generated when methanol or *tert*-butanol were used as proton source, the evolution of the reacting mixture at −78 °C was studied. Addition of acetic acid immediately after quenching by methanol (the disappearance of the bright red-orange colour indicating a complete protonation of the intermediate lithiated species), followed by warming to room temperature, gave a 96:4 mixture of (*E*,*E*)-**2** and (*E*,*Z*)-**4**, whereas warming the reaction mixture without addition of acetic acid gave 85% of nearly racemic **4**. Methanolate ions appeared to be basic enough to isomerize the (*E*,*E*) phospholane oxide **2** into the more stable (*E*,*Z*)-**4** [13] upon warming to room temperature.

Further experiments were carried out in order to provide insight into the stereoselectivities recorded. Experiments carried out with various sparteine/base systems showed that *sec*-BuLi/sparteine is the best deprotonating system (table II).

Modification of the reaction conditions (solvent) or of the experimental protocol did not bring any improvement [17] (table III).

Toluene as a solvent afforded a better yield for (*E*,*Z*)-**4** but a lower ee. This result contrasts with Beak's results obtained in an intramolecular enantioselective cyclisation where toluene proved to give a much higher ee than THF [18].

The 'inverse' procedure, where the base/sparteine is added to the phospholane oxide solution at −78 °C, gave neither higher yields nor improved ee's for (*E*,*Z*)-**4**. This, along with the results obtained with an

Table II. Reactions of (*E*,*E*)-**2** with base/(−)-sparteine followed by protonation with AcOH[a].

Base	*(E,Z)-4/(E,E)-2*[b]	*(E,Z)-4 ee*[c] *(%)*
MeLi	29:71	21
LDA	34:66	29
sec-BuLi (1 equiv)	33:66	45
sec-BuLi (2 equiv)	30:70	38

[a] Experimental conditions: see text. [b] Combined yield of (*E*,*E*)-**2** and (*E*,*Z*)-**4** was above 95% in all runs. [c] Determined by chiral HPLC (Chiralcel OD-H®, hexane/isopropanol 3:1); the major enantiomer is first eluted unless stated otherwise.

Table III. Reactions of (*E*,*E*)-**2** with *sec*-BuLi/(−)-sparteine followed by protonation with AcOH.

Procedure[a]	*Solvent*	*(E,Z)-4/(E,E)-2*[b]	*(E,Z)-4 ee*[c] *(%)*
A	THF	33:66	45
A	Toluene	51:49	21
B	THF	28:72	38
B	Toluene	37:63	18

[a] Procedure A: as in [a] of table I; procedure B: the base is added in the solution of phospholane (inverse addition). [b] Combined yield of (*E*,*E*)-**2** and (*E*,*Z*)-**4** was above 95% in all runs. [c] Determined by chiral HPLC (Chiralcel OD-H®, hexane/isopropanol 3:1); the major enantiomer is first eluted unless stated otherwise.

excess of lithium base (table II), allows to rule out the formation of a dianion as a rationalization for the low enantioselectivity and/or diastereoselectivity of the reaction.

Although a lot of work has been done on the configurational stability of benzylic carbanions [10, 19], and a little on α-lithiated phosphine oxides [20], no information is presently available about the structure, the stereochemistry and the configurational stability at the benzylic centers of the diamine chelated organolithium species for the phospholane oxide anions. In particular, it is not possible to determine whether lithiated species **3a** and **3b** epimerize to give **6a** and **6b**, respectively, and (or) may interconvert into each other.

Deprotonation of the (*E*,*E*)-**2** phospholane oxide by *sec*-butyllithium in THF, followed by addition of

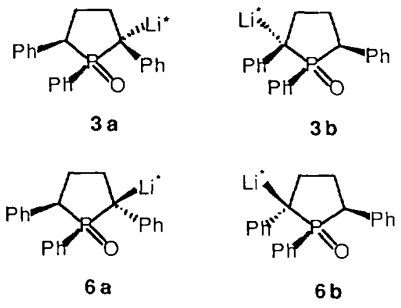


Fig 2

(−)-sparteine and reprotonation by acetic acid, afforded 30% of (*E*,*Z*)-**4** with 43% ee. These values, compared with the 33% yield and 45% ee obtained with the usual procedure, indicate that selective deprotonation at enantiotopic sites can be ruled out as the origin for asymmetric induction.

Two other mechanisms may then account for the enantiomeric induction: i) Selection by an achiral protonating agent of rapidly equilibrating diastereomeric complexes **3a**, **3b**, **6a** and **6b**. This mechanism is also unlikely, since the deprotonation–protonation sequence carried out under the same conditions on (*E*,*E*)-**2**, (*Z*,*Z*)-**5** and (*E*,*Z*)-**4** gave different results for the ee's and distribution of the obtained products (table IV).

Table IV. Reactions of (*E*,*E*)-**2**, (*E*,*Z*)-**4** and (*Z*,*Z*)-**5** with *sec*-BuLi/(−)-sparteine in THF followed by protonation with AcOH[a].

Reactant	*(E,Z)-4/(E,E)-2*[b]	*(E,Z)-4 ee*[c] *(%)*
(*E*,*E*)-**2**	33:66	45
(*E*,*Z*)-**4**	> 99:1	2,5
(*Z*,*Z*)-**5**	5:95	8[d]

[a] Experimental conditions: see text. [b] Combined yield of (*E*,*E*)-**2** and (*E*,*Z*)-**4** was above 95% in all runs. [c] Determined by chiral HPLC (Chiralcel OD-H®, hexane/isopropanol 3:1); the major enantiomer is first eluted unless stated otherwise. [d] Minor enantiomer eluted first.

ii) Selection by a difference in protonation stereoselectivity for the two diastereomers **3a** and **3b**.

Enantioenriched (*E*,*Z*)-1,2,5-triphenylphospholane oxide was obtained (33%, 45% ee), through a *sec*-BuLi/sparteine deprotonation–AcOH protonation sequence, from the *meso* (*E*,*E*)-1,2,5-triphenylphospholane oxide. The stereochemical outcome and the origin of the asymmetric induction are presently best explained by a stereoselection of configurationally stable organolithium/sparteine intermediates by AcOH in the protonation step. Further work is being done to get insight into the mechanism of this enantioselective substitution and to set up parameters allowing an improvement of the asymmetric induction.

References

1 a) Brunner H, In: *The Chemistry of Metal-Carbon Bonds* (Hartley FR, Ed), Wiley, New York, 1989, p 109
b) *Asymmetric Synthesis* (Morrison JD, Ed), Academic Press, Orlando, 1985, Vol 5
c) Noyori R, *Chem Soc Rev* (1989) 18, 187

2 Kagan HB, Sasaki M, In: *The Chemistry of Organophosphorus Compounds* (Hartley FR, Ed), Wiley, New York, 1990, Vol 1, pp 51-102

3 Knowles WS, Sabacky MJ, Vineyard BD, *J Chem Soc, Chem Commun* (1972) 10

4 Bogdanovic B, *Angew Chem, Int Ed Engl* (1973) 12, 954

5 a) Marinetti A, *Tetrahedron Lett* (1994) 35, 5861
b) Marinetti A, Ricard L, *Organometallics* (1994) 13, 3956

6 Vedejs E, Daugulis O, Diver ST, *J Org Chem* (1996) 61, 430

7 Cometti G, Chiusoli GP, *J Organomet Chem* (1982) 236, C31

8 Hayashi T, Hayashizaki K, Kiyoi T, Ito Y, *J Am Chem Soc* (1988) 110, 8153

9 Hay AM, Kerr WJ, Kirk GG, Midlemiss D, *Organometallics* (1995) 14, 4986

10 Wilke G, *Angew Chem, Int Ed Engl* (1988) 27, 186

11 Burk MJ, Feaster JE, Harlow RL, *Organometallics* (1990) 9, 2653

12 Burk MJ, Feaster JE, Harlow RL, *Tetrahedron: Asymmetry* (1991) 2, 569

13 Fiaud J-C, Legros J-Y, *Tetrahedron Lett* (1991) 32, 5089

14 Hoppe D, Hintze F, Tebben P, Paetow M, Arhens H, Schwerdtfeger J, Sommerfeld P, Haller J, Guarnieri W, Kolczewski S, Hense T, Hoppe I, *Pure Appl Chem* (1994) 50, 6049

15 Beak P, Basu A, Gallagher DJ, Park YS, Thayumanavan P, *Acc Chem Res* (1996) 29, 552

16 Carstens A, Hoppe D, *Tetrahedron* (1994) 50, 6097

17 Phospholane oxides **2**, **4** and **5** are unsoluble in most of the commonly used solvents (in asymmetric lithiation–substitution reactions), ie, alkanes or diethyl ether.

18 Wu S, Lee S, Beak P, *J Am Chem Soc* (1996) 118, 715

19 Hoffman RW, Rühl T, Harbach J, *Liebigs Ann Chem* (1992) 725

20 a) O'Brien P, Warren S, *Tetrahedron Lett* (1995) 36, 8473
b) O'Brien P, Warren S, *Tetrahedron Lett* (1996) 37, 4271
c) Vedejs E, Garcia-Rivas JA, *J Org Chem* (1994) 59, 6517