Pergamon

Tetrahedron Letters 42 (2001) 457–460

TETRAHEDRON LETTERS

Completely stereoselective P–C bond formation via base-induced [1,3]- and [1,2]-intramolecular rearrangements of aryl phosphinates, phosphinoamidates and related compounds: generation of *P*-chiral β-hydroxy, β-mercapto- and α-amino tertiary phosphine oxides and phosphine sulfides

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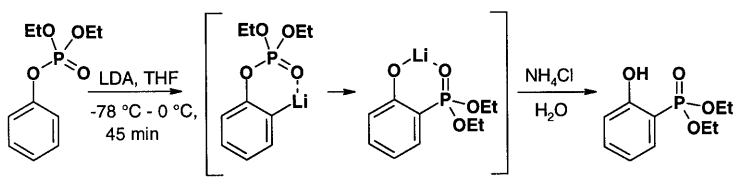
Received 25 August 2000; revised 23 October 2000; accepted 2 November 2000

Abstract—Upon treatment with LDA or alkyllithium, enantiomers of *P*-chiral phosphinates, phosphinothioates, phosphinoamidates, thionophosphinates, thionophosphinothioates and thionophosphinoamidates undergo clean [1,3]- and [1,2]-rearrangements with complete stereoselectivity, with retention of configuration at phosphorus, to provide functionalised tertiary phosphine oxides and phosphine sulfides; the [1,2]-rearrangements of the phosphinoamidates are previously unrecorded. © 2001 Elsevier Science Ltd. All rights reserved.

Displacement of halogen from (R_P)- and (S_P)-*tert*-butylphenylphosphinobromidates[1,2] and *tert*-butylphenylthionophosphinochloridates[2] by heteroatom nucleophiles is completely stereoselective in leading to aryl phosphinates, phosphinothioates and the corresponding thionophosphorus compounds.[2] These products are amenable to an intramolecular rearrangement first described for the conversion of a diethyl aryl phosphate to diethyl *o*-hydroxyarylphosphonate (Scheme 1) by treatment with LDA in THF (Scheme 1).[3] The [1,3]-rearrangement proceeds via heteroatom-facilitated *ortho*-lithiation and thermodynamically-driven rearrangement to the less basic aryloxide. Chiral 1,3,2-oxazaphospholidine oxides derived from ephedrine rearrange with strict retention of configuration at phosphorus.[4] Similarly, *P*-chiral *o*-phosphonic phenols and analogues are obtained from (aryloxy)phospholidines, (aryloxy)phosphates and analogues bearing chiral ligands attached to phosphorus.[5] In these special cases, it may be argued that retention of configuration at phosphorus is under control of chirality in the attached ligands. Phosphorodiamidothioates[6] and dialkyl thiophosphates[7] derived from thiophenol rearrange in the presence of alkyllithium or LDA. The analogous rearrangement of enol phosphates derived from ketones to β-ketophosphonates has also been examined.[8]

Unlike the foregoing examples,[4,5] our *P*-chiral phosphinates and related compounds[1,2] do not have chirality in the attached ligands. *It is therefore of interest to examine just how stereoselective this rearrangement is at phosphorus in the absence of any 'external' chiral control element*. More particularly we wish to acquire enan-



Scheme 1.

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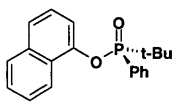
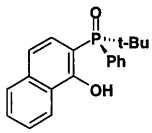
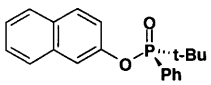
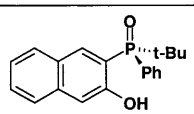
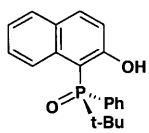
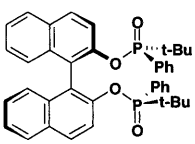
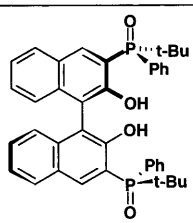
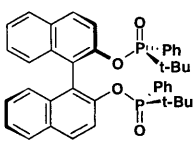
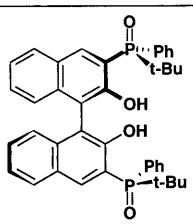
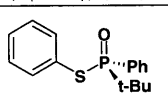
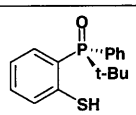
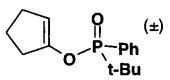
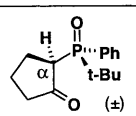
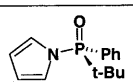
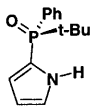
PII: S0040-4039(00)01952-3

tiomers of the rearrangement products, β-hydroxy- and β-mercaptoarylphosphine oxides and sulfides as ligands for asymmetric catalysis. Accordingly, each of the compounds[2] of Table 1 (0.2–1 mmol) in THF (1 mL) were added to an excess of LDA (from 2.5 M *n*-butyllithium in hexane and equivalent *N*,*N*-diisopropylamine), or *n*-butyllithium, under nitrogen at −78°C, and stirred for 30 min to 12 h. Warming to room temperature was required for some substrates. The β-functionalised tertiary phosphine oxides **1**–**8** are obtained in moderate to excellent yields.

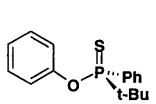
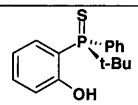
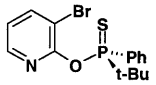
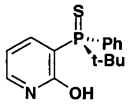
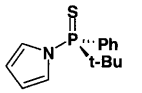
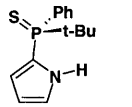
The rearrangement is completely stereoselective and proceeds with strict retention of configuration, as indicated by X-ray crystallography of selected products[9] and ^{1}H NMR (300 MHz) spectroscopy admixed with (S_p)-*tert*-butylphosphinothioic acid.[1] The 2-naphthyl phosphinate (entry 3) provides a mixture of products **2** and **3** from which the major isomer **2** is isolated by fractional recrystallisation; HPLC of the mother liquors enables the minor isomer to be isolated. Rearrangement of *O*-2-naphthyl phosphate[10] and *O*-2-naphthyl phospholidine[5b] also provides predominantly the 3-sub-

Table 1. Base-induced rearrangement of phosphinates, phosphinothiolates and phosphinoamidates

Entry	Starting compound	Reaction conditions	Products		Yield %[a]	$[\alpha]_D^{23}$ (c, $CHCl_3$) m.p. °C	δ_p ppm[b]
1		1.0 mmol; 3 equiv. LDA; -78 °C; ½ h		**1**	94	-143° (*c* 0.65) 165-6	51.3
2		1.0 mmol; 3 equiv. LDA; -78 °C; ½ h		**2**	84[c,d]	-102° (*c* 0.83) 222-3	50.3
				**3**	14[d,e]		58.6
3	 (S_p,*R*,S_p)	0.5 mmol; 10 equiv. LDA; -78 °C - RT; 12 h		**4**	88	- 208° (*c* 0.83) 233-6	50.0
4	 (R_p,*R*,S_p) (94%) + (R_p,*R*,R_p) (6%)	0.3 mmol; 10 equiv. LDA; -78 °C - RT; 12 h		**5**	25[f]	+84° (*c* 3.78) 202-205	49.5, 49.8
5		0.5 mmol; 4 equiv. LDA; -78 °C; ½ h		**6**	45	+ 180° (*c* 1.29)	46.8
6		0.5 mmol; 3 equiv. LDA; -78 °C - RT; 12 h		**7**	85[f,g]	----	45.3
7	 (ee 78%)	0.2 mmol; 3 equiv. *n*-BuLi; -78 °C; ½ h		**8**	50% (ee 78%)	----	36.2

[a]ee by ^{1}H NMR spectroscopy (300 MHz) (see text) is ≥98.5%, except for entry 7; [b]in $CDCl_3$ relative to $(MeO)_3P$; [c]absolute configuration by X-ray crystallography; [d] yields estimated by ^{1}H and ^{31}P (121 MHz) NMR spectroscopy; [e]compounds separated by HPLC: CHIRALPAK AD column, hexanes/*i*-propanol 95:5, 1 mL min^{-1}, t, 14.6 min, minor, 26.3 min, major isomer; [f]structure by X-ray crystallography; [g]product is unstable with respect to epimerization at C-α.

Table 2. Base-induced rearrangement of thionophosphinothiolates and thionophosphinoamidates

Entry	Starting Compound	Reaction conditions	Rearranged Product		Yield% (e.e.)[a]	$[\alpha]_D^{23}$ ($CHCl_3$) m.p. °C	δ_p ppm,[b]
1		5 equiv. *t*-BuLi, -78 – 20 C°; 18 h		**9**	22 (98)	+7° (*c* 0.87) oil	54.1
2		5 equiv. *n*-BuLi, -78 – 20 C°; 5 h		**10**	76 (97)	+33° (*c* 1.32) 124-127	44.7
3		5 equiv. *n*-BuLi, -78 – 20 C°; 4 h		**11**	81[c] (89)	+61 (*c* 1.72) 107-111	60.9

[a]By HPLC, OJ column, hexane-*i*-propanol: **9** hexane-*i*-propanol 99:1 0.5 mL min^{-1}; **10** 95:5 1 mL min^{-1}; **11** 95:5 1 mL min^{-1}; [b]in $CDCl_3$ relative to $(MeO)_3P$; [c]absolute configuration by X-ray crystallography.

stituted product. The rearrangements of the BINOL bisphosphinates are noteworthy. The (S_P,*R*,S_P)-BINOL bisphosphinate (entry 3) gives the 3,3′-bisphosphine oxide **4**, which possesses both axial chirality and chirality at phosphorus. The 94:6 mixture of the (R_P,*R*,S_P)- and (R_P,*R*,R_P)-BINOL bisphosphinates[2] (entry 4) gives only **5** arising via rearrangement of the (R_P,*R*,S_P)-bisphosphinate. The racemic enol phosphinate (entry 6) gives the ketophosphine oxide **7**; relative configuration was confirmed by X-ray crystallography. The pyrrole phosphinoamidate rearranged rapidly to the 2-pyrrolo phosphine oxide **8** (entry 7). A [1,2]-shift of this kind has not been reported previously.

Rearrangements of the thionophosphinates were difficult to induce. Thus the phenyl thionophosphinate (entry 1, Table 2) was unaffected by LDA, *n*- or *sec*-butyllithium. Although use of *tert*-butyllithium was only partially successful in providing **9**, attempts to improve the yield by using base combinations—e.g. *tert*-butyllithium/potassium *tert*-butoxide—were unsuccessful. In line with mechanistic considerations (cf. Scheme 1), the thionophosphinate group is less effective in inducing *ortho*-metallation than is phosphinate. However, metallation by halogen–metal exchange, as in treatment of *O*-2-bromopyridyl thionophosphinate (entry 2) with *n*-butyllithium, results in smooth rearrangement to **10**. This observation is consistent with Buono's findings.[5d]

In contrast, direct metallation of the thionophosphinoamidate (entry 3) is obviously facile, as rearrangement to **11** proceeds easily. X-Ray structural analysis of **11** reveals that configuration at phosphorus is retained.[9] As in the case of the phosphinoamidate of entry 7, Table 1, the rearrangement is new. Because of ring strain, a TBP intermediate leading to **8** or **11** is unlikely to be involved, as proposed for the [1,3]-rearrangements by Buono.[5a] *o*-Lithiation is directed by the dipolar phosphine oxide group, and this group becomes coordinated with lithium at the *ortho* position (cf. Scheme 1); indeed it is not possible to locate an energy minimum for that conformer with the phosphine oxide group directed away from lithium.[11] Migration with retention of configuration of the phosphinyl group corresponds to 'equatorial' addition *syn* to the phosphine oxide at phosphorus to generate a putative three-membered azaphosphirane intermediate; this will undergo fast ring opening via 'equatorial' elimination, rather than permutational isomerism. The homogeneity of the stereochemical outcome of the [1,2]- and [1,3]-shifts also suggests that the latter proceed via a related pathway; that is, permutational isomerism is not involved.

In conclusion, the rearrangement of *P*-chiral phosphinates, phosphinothiolates, phosphinoamidates and their thionophosphorous analogues bearing achiral substituents is completely stereoselective, and has synthetic importance in providing access to multifunctional chelating *P*-chiral phosphine oxides and phosphine sulfides. Use of these products as ligands in catalytic asymmetric reactions will be reported elsewhere.

Acknowledgements

We thank the Hong Kong Research Grants Council (Grants HKUST 706/96P and HKUST 6170/97P) for generous support of this work. Development of the reactions to provide the BINOL bisphosphinates for asymmetric catalysis was carried out under the RGC Central Allocation Grant (Grant 'Open Laboratory for Asymmetric Synthesis'; E-RB03).

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9. CIF files for **2**, **7** and **11** have been submitted to CSD. Absolute configurations were unambiguously determined from anomalous scattering of Mo-Kα radiation by P and S in the compounds studied, and gave Flack parameters close to zero.
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11. PM3 (Titan, Wavefunction Inc.; Schrödinger, Inc., Version 1, 1999) calculation on minimised conformers of the Buono compound **5** (Ref. 5a) with solvation of vacant coordination sites on (tetrahedral) Li by THF indicate that steric crowding by substituents on phosphorus prevents complete solvation by THF around Li in the '*anti*' conformer (PO pointing towards opposite *o*-position); attempts to locate local conformational minima in the unsolvated '*anti*' conformer results in interconversion into the '*syn*' conformer.