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Reactions of (R_P)- and (S_P)-*tert*-butylphenylphosphinobromidates and *tert*-butylphenylthionophosphinochloridates with heteroatom nucleophiles; preparation of *P*-chiral binol phosphinates and related compounds

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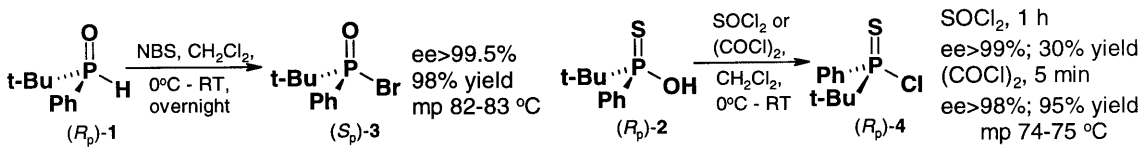
Abstract—Reaction of (R_P)- and (S_P)-*tert*-butylphenylphosphinobromidates and *tert*-butylphenylthionophosphinochloridates with metallated phenol and BINOL alkoxides, thioalkoxides, amides and enolates leading with clean inversion at phosphorus to phosphinates, phosphinothiolates and phosphinoamidates, and the corresponding thionophosphorus compounds are described.

Synthesis of *P*-chiral tertiary phosphines and phosphine oxides relies on stereoselective substitution of *O*- or *S*-alkyl groups at phosphorus by organometallic reagents.[1] Less attention has been focused on the single displacement at a *strictly P*-chiral centre by nucleophiles other than carbanions to give heteroatom P^V substituted compounds. Enantiopure *tert*-butylphenylphosphine oxides (R_P)-**1** and (S_P)-**1** are easily prepared from the readily resolved phosphinothioic acids (R_P)-**2** and (S_P)-**2**, and react as nucleophiles with alkylating agents and carbonyl compounds to provide functionalised tertiary phosphine oxides.[2,3] In order to expand the utility of these reagents, we have examined the reactivity of the derived P^V electrophiles, namely the phosphinobromidate **3** and thionophosphinochloridate **4** with various heteroatom nucleophiles, with the purpose of assessing the ligating properties of the products in asymmetric catalysis.

Phosphinobromidates (R_P)-**3** and (S_P)-**3** have been prepared previously (Scheme 1).[4,5] Whilst thionophosphinochloridate (R_P)-**4** is also known,[6] use of thionyl chloride on (R_P)-**2** in CH_2Cl_2 to give (R_P)-**4** in 30% yield (Scheme 1) with ee >99% as analysed by HPLC (Chiralcel OJ, hexane) represents a far simpler method for its preparation. Absolute configuration of (R_P)-**4** was confirmed by X-ray diffractometry.[7] The yield of (R_P)-**4** becomes near quantitative when oxalyl chloride in CH_2Cl_2 is used, albeit with a slight decline in optical purity (96% ee). A single recrystallization of (R_P)-**4** gives a product of over 98% ee. Reactions of the bromidates **3** with heteroatom nucleophiles are summarised in Table 1. For entries 1–9, a solution of the alcohol, thiol or amine (1.0 mmol) in THF (5 mL) was treated with sodium hydride (1.0 equiv.) at 0°C. After 5–10 min of stirring, the sodiated nucleophile was treated with a solution of racemic, (R_P)- or (S_P)-**3** (1.0



Scheme 1.

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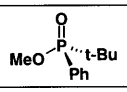
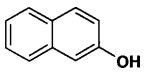
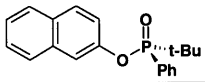
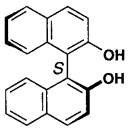
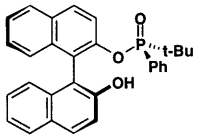
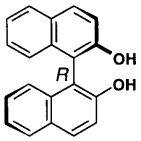
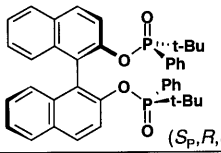
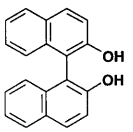
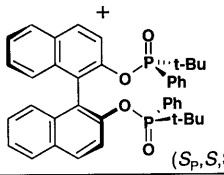
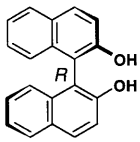
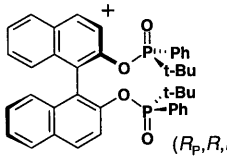
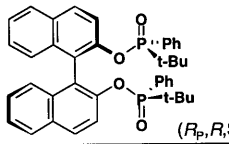
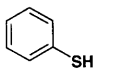
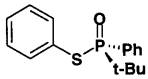
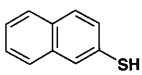
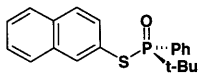
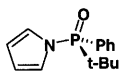
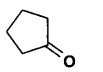
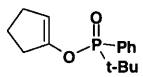
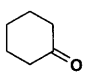
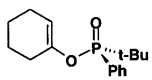
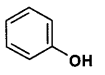
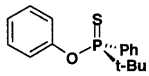
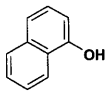
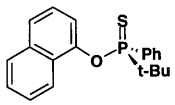
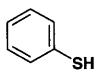
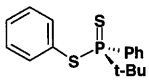
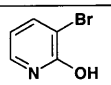
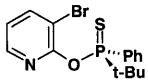
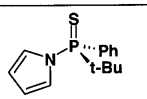
or 2.0 equiv.) in THF (5 mL) at the same temperature. The reaction time ranged from 5 min for pyrrole (entry 9) to 12 h for BINOL (entries 3–6). For entries 10 and 11, the ketone (1.2 mmol) in THF (5 mL) was treated with LDA (1.2 mmol) at 0°C and stirred for 15 min followed by the dropwise addition of the bromidate (1.0 mmol) in THF (5 ml) at −78 °C, and workup after 1 h.

Table 1. Reaction of bromidates *Rac*-**3**, (R_P)-**3** and (S_P)-**3** with heteroatom nucleophiles

Entry	Nucleophile	Config. of 3	Products		Yield %[a]	$[\alpha]_D^{23}$ (*c*, $CHCl_3$) m.p. °C	δ_P ppm[b]
1	MeOH	S_P		**5**	quant.	+58° (*c* 1.11) 60-1	52.0
2		S_P		**6**	quant.	+40° (*c* 1.03) 95-6	49.3
3		S_P (1 eq.)		**7**	85[d]	-252° (*c* 1.08) 199-201	51.4
4		S_P		**8** (S_P,*R*,S_P)	75	-407° (*c* 1.19) 192-193	49.4
5	 *rac*	S_P	**8** + 	**9** (S_P,*S*,S_P)	50 19	see above -135° (*c* 0.31) 225-227	- 49.4
6		*Rac*	**8** + 	**10** (R_P,*R*,R_P)	28 3[c,d]	see above [**10** and **11** inseparable]	49.4
				**11** (R_P,*R*,S_P)	37[c]		48.4, 50.1
7		R_P		**12**	quant.	- 231° (*c* 1.0) 79-80	64.4
8		R_P		**13**	quant[d]	- 269° (*c*. 1.03) 108-109	64.2
9		R_P		**14**	50 (ee 78)[a]	----	41.8
10		*Rac*		**15**	80	---- 83-4	48.6
11		S_P		**16**	97	+51.8° (*c* 1.05) 58-9	47.2

[a] ee, estimated by ^1H NMR (300 MHz) (see text), is ≥98.5% except for entry 9; [b] in $CDCl_3$ relative to $(MeO)_3P$; [c] (R_P,*R*,R_P) - and (R_P,*R*,S_P)- compounds **10** and **11** were an inseparable mixture; [d] absolute configuration by X-ray crystallography.

Table 2. Reaction of thionophosphinochloridate (R_P)-**4** with heteroatom nucleophiles

Entry	Nucleophile	Config. of 4	Product		Yield % (ee)[a]	$[\alpha]_D^{23}$ (*c*, $CHCl_3$) m.p. °C	δ, ppm[b]
1		R_P		**17**	98 (96)	-27° (*c* 2.24) 59-63	105.3
2		R_P		**18**	92[b] (97)	+152° (*c* 2.00) 110-111	103.5
3		R_P		**19**	90[b] (94)	-127.8° (*c* 2.27) 113-117	94.6
4		R_P		**20**	85 (97)	+125.6° (*c* 1.98) 74-75	108.4
5		R_P		**21**	91 (89)	+21.8° (*c* 1.84) oil	82.1

[a]by HPLC, OJ column 0.5 mL min^{-1}: **17** and **18**, hexane/*i*-propanol, 99:1; **19** 93:7; **20** 98:2; **21** 95:5; [b]in $CDCl_3$ relative to $(MeO)_3P$; [b]absolute configuration by X-ray crystallography.

The products had enantiomeric excesses (ee) $\geq 98.5\%$ as assayed by ^1H NMR spectroscopy with (S_p)-*tert*-butylphosphinothioic acid.[2] The exception was in the product from pyrrole (entry 9), for which the ee was 78%. Absolute configuration at phosphorus in products **7**, **10** and **13** (entries 3, 6 and 8) as determined by X-ray crystallography is inverted with respect to that in bromidate **3**.[7] Racemic BINOL and (S_p)-**3** gave phosphinates **8** and **9**, easily separated by chromatography (entry 5); the former was prepared from (*R*)-BINOL and (S_p)-**3** (entry 4). The reaction represents an easy way to resolve racemic BINOL, as the product phosphinates may be hydrolysed. Related, although less straightforward, methods for resolution have been described elsewhere.[8] On the other hand, (*R*)-BINOL with racemic bromidate **3** afforded phosphinates **8**, **10** and **11** (entry 6). While phosphinate **8** was easily isolated as a result of its different polarity, **10** and **11** could not be separated by chromatography or fractional crystallisation; however, a single crystal of **10** was obtainable from the mixture for crystallography. The ^{31}P NMR spectrum of the mixture has a signal due to **10** at δ 49.4, and two other signals of equal intensity at δ 48.4 and 50.1 ppm, due to the R_P- and S_P-centres in the (R_P,*R*,S_P)-isomer **11**. The compounds, in possessing axial chirality and two chiral phosphorus atoms, are representative of a compound class of which very few other examples are known.[9] Enolates react with bromidate **3** exclusively through the oxygen atom (entries 10 and 11).

For thionophosphinochloridates (R_P)- and (S_P)-**4**, use of DMF as solvent with the sodiated nucleophile was required. Thus, treatment of sodium phenoxide (generated from phenol, 1.2 mmol, and NaH) with (R_P)-**4** (1.0 mmol) in DMF (5 ml) overnight afforded the thionophosphinate (entry 1, Table 2) in excellent yield. Other products (Table 2) were also obtained in good yields. X-Ray crystallographic determination of the structures of **18** and **19** (entries 2 and 3)[7] indicate that displacement of chloride from (*R*)-**4** proceeds with inversion of configuration. As in the previous case involving the reaction of pyrrole with bromidate (entry 9, Table 1), displacement of chloride in (*R*)-**4** is not completely stereoselective (entry 5).

In summary, the P^V *P*-chiral electrophilic halidates **3** and **4** react with O-, S-, and N-nucleophiles with inversion of configuration at phosphorus to provide phosphinates, phosphinothiolates, phosphinamides and the corresponding thionophosphorus compounds in good to excellent yields. One application of these products is described in the following communication.

Acknowledgements

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Yeung, L.-L.; Chan, E. W.-K. *Tetrahedron Lett*. **1996**, *37*, 4733.
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5. Haynes, R. K.; Lam, W. W.-L.; Williams, I. D.; Yeung, L.-L. *Chem. Eur. J*. **1997**, *3*, 2052.
6. Skrzypczyński, Z.; Michalski, J. *J. Org. Chem*. **1988**, *53*, 4549.
7. CIF files for (R_P)-**4**, **7**, **10**, **13**, **18** and **19** have been submitted to CSD. Absolute configurations were unambiguously determined from anomalous scattering of Mo-Kα radiation by P, S and Cl in the compounds studied, and gave Flack parameters close to zero.
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