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(*R*)- and (*S*)-6,6'-Dimethyl- and 6,6'-Dimethoxy-2,2'-diiodo-1,1'-biphenyls: Versatile Intermediates for the Synthesis of Atropisomeric Diphosphine Ligands.[1]

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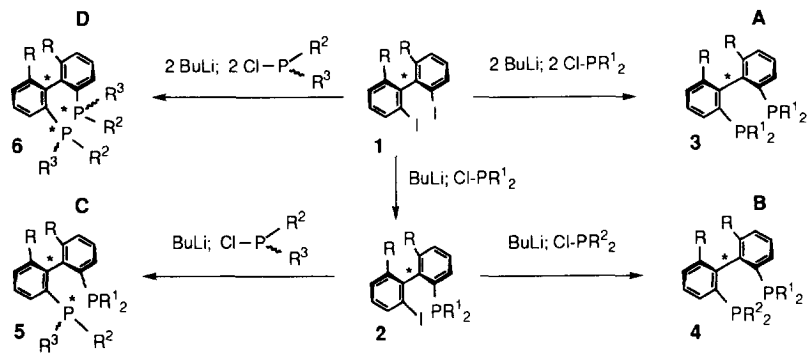
***Abstract**: Starting from enantiomerically pure 6,6'-dimethyl- or 6,6'-dimethoxy-2,2'-diiodo-1,1'-biphenyls (**1a** or **1b**) a variety of atropisomeric diphosphine ligands of defined axial chirality are directly accessible in good yields: asymmetric diphosphines of type **B** and the corresponding diphosphines with one (type **C**) or two (type **D**) stereogenic phosphorus atoms. Pitfalls of the lithiation/phosphination reaction are discussed. The number of P-chiral diastereomers can be reduced by thermal epimerization.* Copyright © 1996 Elsevier Science Ltd

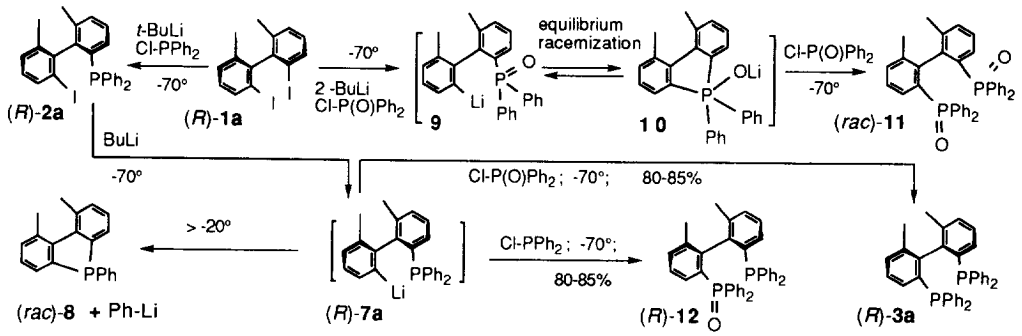
The Rh and Ru complexes of biphenyl diphosphines of type **A**, such as **3a** (R^1 = Ph) or **3b** (R^1 = Ph) are highly efficient catalysts for the asymmetric hydrogenation of standard substrates (e.g. β-keto esters, allylic alcohols etc.)[2]. For the hydrogenation of unconventional substrates (e.g. γ-oxo olefins, α-pyrones)[3a], atropisomeric diphosphines with different steric and electronic properties are often required. As demonstrated, the diphosphine properties can be modified by varying the substitution pattern at the two phosphorus atoms[3b-g]. In the case of biphenyl diphosphines, this would lead to ligands of type **B**, **C** and **D** (*Scheme 1*). So far, one diphosphine of type **B**[3g], but no member of the other two classes combining a stereogenic axis with one or two stereogenic phosphorus atoms has been published[4].



Scheme 1. **a**: **R = Me**; **b**: **R = OMe** (only *(R)*-enantiomer shown);

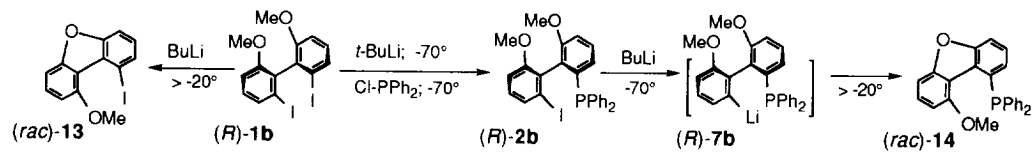
The ready availability of the enantiomerically pure 6,6'-dimethyl- and 6,6'-dimethoxy-2,2'-diiodo-1,1'-biphenyls (**1a** and **1b**) of defined axial chirality[1] has now opened up a direct access to enantiomerically pure diphosphines of type **B-D**. Thus monolithiation of **1**, preferably with *t*-BuLi, and phosphination with dialkyl- or diarylphosphinous chlorides afforded the homochiral iodo monophosphines **2** in 60-80% yield (*Table 1*)[5]. Lithiation of **2** with *n*-BuLi and phosphination with achiral or racemic phosphinous chlorides led to the asymmetric diphosphines **4** (*Table 2*) and **5** (*Table 3*), respectively[6]. In an analogous way, diphosphines **6**, which are stereogenic at both phosphorus atoms, were prepared from **1** and racemic chlorophosphines. When carried out at low temperature (-70°), these reactions gave good yields (60-85%) and proceeded with full retention of the biphenyl stereochemistry. However at higher temperatures (> -20°), under otherwise identical conditions, (*R*)-**2a** and (*R*)-**1a** were converted exclusively to the *racemic* dibenzophosphole (*rac*)-**8**[7] and phenyllithium (*Scheme 2*). The latter reacted with $ClPPh_2$ to give triphenylphosphine or, in the absence of $ClPPh_2$, could be trapped as benzoic acid by adding dry ice to the reaction mixture. Similarly, treatment of (*R*)-**1b** and (*R*)-**2b**

with one equivalent of BuLi (> -20°) led to the new *racemic* dibenzofurans (*rac*)-**13**[7] and (*rac*)-**14**[7], respectively, in 55-85% yield (*Scheme 3*). These results indicate a great tendency of the aryllithium species to undergo intramolecular attack on the hetero atom, favouring oxygen over phosphorus if both are present as in **7b**. The crucial effect of the temperature on the outcome of these lithiation/phosphination reactions is striking and might also explain the contradicting results reported in the literature for the phosphination of 2,2'-dilithiobiphenyl[8].



Scheme 2. (only *(R)*-enantiomer shown)

Intramolecular interaction of the aryllithium species with the phosphorus atom was evident also at low temperature (-70°). The reaction of the chiral diiodide (*R*)-**1a** with BuLi and diphenylphosphinic chloride in lieu of diphenylphosphinous chloride at -70° yielded the *racemic* dioxide (*rac*)-**11**. In contrast, the analogous reaction of monoiodide (*R*)-**2a** gave the monoxide (*R*)-**12** without racemization (*Scheme 2*). These results might be explained by assuming an equilibration of the intermediate **9** via a symmetric dibenzophosphole type intermediate such as **10**.



Scheme 3 (only *(R)*-enantiomer shown)

The heterotopicity of the phosphorus substituents of diphosphines **C** and **D** is reflected in the chemical shifts of the methyl and methoxy groups in the ^{1}HNMR spectra, thus enabling the assignment of the relative configuration of the stereogenic phosphorus atoms, particularly when the ^{1}HNMR spectra of both epimers are known[9]. The relatively high field ^{1}HNMR signals of the methyl (**3a**; 1.40 ppm)[10a] and methoxy (**3b**; 3.15 ppm)[10b] groups at C(6) or C(6') are due to ring current shielding by phenyl rings. Contributing to this shielding are: a) the biphenyl system (depending on the interplanar angle of the biphenyl)[10a,c-e]; b) the aryl substituent on phosphorus at C(2') or C(2) located in a *stacking* position above the methyl or methoxy group of the biphenyl system[10a,11]. In some cases the assigned configuration was confirmed by X-ray crystallography[12].

Table 1: Iodo monophosphines

	R	R^1	δMe ppm	$[\alpha]_D^{20°}$ (*R*)	$[\alpha]_D^{20°}$ (*S*)	mp (°C)	(*rac*); mp (°C)
(*R*) & (*S*)-**2a**	Me	Ph	1.94; 1.54	-44.8	+43.5	167-168	166-167
(*S*)-**2a**	Me	Tol	1.93; 1.55	-.-	+55.7	136.4	-.-
(*S*)-**2a**	Me	Cyhex	2.02; 1.94	-.-	+8.7	138-144(dec.)	-.-
			δOMe ppm				
(*S*)-**2b**	OMe	Ph	3.75; 3.09	-.-	-9.0	125.7	194-195

For Tables 1-3: $[\alpha]_D^{20°}$ (c = 0.5-1, $CHCl_3$).

Table 2: Diphosphines of class **B** lacking C_2-symmetry .

	R	R^1	R^2	δ_{Me} ppm	$[\alpha]_D^{20°}$ (*R*)	$[\alpha]_D^{20°}$ (*S*)	mp (°C)
(*R*) or (*S*)-**4a**	Me	Ph	α-Thienyl	1.44; 1.36	+71.9	-70.2	149-151
(*S*)-**4a**	Me	Tol	α-Thienyl	1.44; 1.39	-.-	-48.0	foam
(*R*) or (*S*)-**4a**	Me	Ph	α-Furyl	1.50; 1.37	-66.3	+66.7	123-125
(*R*) or (*S*)-**4a**	Me	Ph	Cypent	1.91; 1.31	-39.5	+40.4	129-130
(*R*) or (*S*)-**4a**	Me	Ph	Et	1.92; 1.42	-24.8	+25.5	107.5-108
(*S*)-**4a**	Me	Ph	Cyhex	1.92; 1.27	-.-	+52.3	185-186
(*R*) or (*S*)-**4a**	Me	Tol	Cyhex	1.91; 1.28	-71.5	+69.4	166-167
				δ_{OMe} ppm			
(*R*)-**4b**	OMe	Ph	Cyhex	3.68; 3.08	+10.3	-.-	238-239
(*S*)-**4b**	OMe	Ph	Et	3.69; 3.18	-.-	-40.0	foam
(*S*)-**4b**	OMe	Ph	Cypent	3.66; 3.07	-.-	-15.7	210-211
(*S*)-**4b**	OMe	Ph	α-Furyl	3.44; 3.11	-.-	-28.4	213-214
(*S*)-**4b**	OMe	Ph	iPr	3.67; 3.01	-.-	-29.0	147.5-148
(*S*)-**4b**	OMe	Ph	α-Thienyl	3.27; 3.13	-.-	-102.0	223.5-223
(*S*)-**4b**	OMe	Ph	3,5-^{t}Bu$_2$Ph	3.29; 2.98	-.-	-56.8	106-107

Table 3: Diphosphines of class **C** or **D**, with *one* or *two* stereogenic P-atoms

	R	R^1	R^2	R^3	stack[a]	δ_{Me} ppm	$[\alpha]_D^{20°}$ [b]	mp (°C)	P*-config.
(*R*)(*S*)-**5a** [c]	Me	Ph	Ph	^{t}Bu	Ph	1.35; 1.06	+154.3	140-141	Δ stable
(*S*)(*S*)-**5a** [d]	Me	Ph	Ph	^{t}Bu	^{t}Bu	2.04; 1.28	-121.0	142-143	Δ unstable
(*R*)(*R*)-**5a** [d]	Me	Ph	Ph	^{t}Bu	^{t}Bu	2.05; 1.28		147-149	Δ unstable
(*S*)(*S*)-**5a** [e]	Me	pTol	Ph	^{t}Bu	^{t}Bu	2.04; 1.32		142-143	Δ unstable
(*R*)(*S*)-**5a** [f]	Me	pTol	Ph	^{t}Bu	Ph	1.36; 1.06	+168.6	161-162	Δ stable [12]
(*R*)(*S*)-**5a**	Me	Ph	Ph	Cyhex	Ph	1.33, 1.00	+129.0	187-188	Δ stable [12]
(*R*)(*R*)-**5a**	Me	Ph	Ph	Cyhex	Cyhex	not isol.			Δ unstable
(*R,R*)(*S*)-**6a** [g]	Me	-.-	Ph	Cyhex	Ph	0.92	+164.8	187-188	Δ stable [12]
(*S,S*)(*R*)-**6a** [g]	Me	-.-	Ph	Cyhex	Ph	0.92	-166.6	190-191	Δ stable
(*S,S*)(*S*)-**6a** [h]	Me	-.-	Ph	Cyhex	Cyhex.	1.97	-56.0	(159°) 190	Δ unstable
(*S,R*)(*S*)-**6a** [i]	Me	-.-	Ph	Cyhex	Ph/Cy	not isol.			
(*R,R*)(*S*)-**6a** [k]	Me	-.-	Ph	^{t}Bu	Ph	0.98	+183.5	138-139	Δ stable
(*S,S*)(*S*)-**6a** [l]	Me	-.-	Ph	^{t}Bu	^{t}Bu	2.01	-246.0	143-144	Δ unstable [12]
(*S,R*)(*S*)-**6a** [m]	Me	-.-	Ph	^{t}Bu	Ph/^{t}Bu	1.96; 1.05	+34.6	120-121	

[a] Stack = stacking position[11], e.g. one of the substituents on phosphorus is situated in an nearly parallel position above the adjacent phenyl ring of the biphenyl backbone (cf. the stereoscopic drawing of (*R*)-**3a** (R1 = Ph)[10a]. [b] (c = 0.5-1, $CHCl_3$). [c] Δ Stable; apolar, major product; ^{t}Bu: 1.11 ppm (d, *J* = 12.6 Hz). [d] (*R*)(*R*) or (*S*)(*S*); polar, minor product; ^{t}Bu: 1.10 ppm (d, *J* = 12.3 Hz); on heating at 100° complete epimerization to (*S*)(*R*)- and (*R*)(*S*)-**5a**, respectively. [e] Polar, minor prod.; on heating at 100° complete epimerization to (*R*)(*S*)-**5a**; ^{t}Bu: 1.08 ppm (d, *J* = 12.0 Hz). [f] Δ Stable; apolar, major prod.; ^{t}Bu: 1.11 ppm (d, *J* = 12.6 Hz). [g] Δ Stable; C_2-symmetry. [h] First mp: 159°, second mp: 190°; during melting (159° → 190°) full conversion to (*R,R*)(*S*)-**6a** and (*S,R*)(*S*)-**6a**. [i] Not isolated. [k] Δ Stable; C_2-symmetry; ^{t}Bu: 1.20 ppm (A-part of $A_9A'_9XX'$-spectrum, X = P; *J* ~ 12.0 Hz). [l] ^{t}Bu: 0.91 ppm (d, *J* = 12.0 Hz). [m] "Meso", ^{t}Bu: 1.06 (d, *J* = 12.0 Hz) and 0.63 ppm (d, *J* = 12.0 Hz).

The diastereomers with the sterically more encumbered substituent in the *stacking* position epimerized at elevated temperatures to the less strained, more stable isomers with the sterically less demanding substituent in this position. Thus the labile diastereomer (*S,S*)(*S*)-**6a** (R^2 = Ph, R^3 = Cyhex) (*Cy-stacking*; *Table 3*) exhibits melting points at 159° and 190°, which indicates epimerization to the higher melting diastereomers having one or two phenyl groups in a *stacking* position (*Ph-stacking*). Accordingly on heating, the (*S,S*)(*S*)-diastereomer was completely converted to a mixture of the (*S,R*)(*S*)- and (*R,R*)(*S*)- diastereomers. Similarly, the thermally labile compounds (*S*)(*S*)-**5a** (R^1 = Ph or pTol, R^2 = Ph, R^3 = ^{t}Bu) (*^{t}Bu-stacking*; *Table 3*) epimerized completely to the stable (*R*)(*S*)-isomers (*Ph-stacking*).

In conclusion, enantiomerically pure diphosphines of type **A** and **B** and P-chiral diphosphines of type **C** and **D** have become easily available in one step starting from the pivotal intermediates **1** and **2**. Diphosphines of type **C** and **D** can undergo thermal epimerization at the chiral P-atoms. In case of type **C** diphosphines this allows the conversion of diastereomer mixtures to diastereomerically pure compounds.

References and Notes

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4. Phosphorus chirality is rare due to the synthetic difficulty of controlling stereogenicity at phosphorus. For the synthesis of the P-chiral diphosphine ligand DIPAMP ephedrine was recently used as a chiral auxiliary: a) Carey, J.V.; Barker, M.D.; Brown, J.M.; Russell, M.J.H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 831; b) Brown, J.M.; Carey, J.V.; Russell, M.J.H. *Tetrahedron* **1990**, *46*, 4877; c) Jugé, S.; Stephan, M.; Laffitte, J.A.; Genet, J.P. *Tetrahedron Lett.* **1990**, *31*, 6357; d) Jugé, S.; Stephan, M.; Merdès, R.; Genet, J.P.; Halut-Desportes, S. *J. Chem. Soc., Chem. Commun.* **1993**, 531. Factors affecting epimerization of chiral phosphines have been discussed by Mislow: e) Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7012.
5. In monometallations, *t*-BuLi gave higher yields than *n*-BuLi. Achiwa utilized *t*-BuLi for the monometallation of a racemic 6,6'-disubstituted 2,2'-dibromobiphenyl.[3g]
6. General procedure: To a solution of 14.4 g (28.7 mmol) (*S*)-diphenyl-(2'-iodo-6,6'-dimethylbiphenyl-2-yl)phosphine [(*S*)-**2a**)] in 200 ml toluene and 50 ml ether under Ar was added at -70° 30 ml BuLi solution (1.6 M in hexane; 0.048 mol) and the mixture was stirred at -68° for 3/4 h. Then a solution of 16.0 g (78.6 mmol) (*rac*)-t-butylphenylchlorophosphine in 50 ml toluene was added within 15 min and the greyish-brown suspension was stirred for 1.5 h at -65° and over night at r.t. After addition of water (85 ml) and 3N NaOH (30 ml) the mixture was stirred for 1/4 h and then extracted with 300 ml toluene. The organic phase was washed with water (2 x 150 ml), dried over Na_2SO_4, filtered, and evaporated. Chromatography of the residue on silica gel (hexane-toluene) gave 7.32 g (47%) (*R*)(*S*)-**4a** and 3.90 g (25%) (*S*)(*S*)-**4a**. Single crystallizations from AcOEt/MeOH afforded 3.5 g of (*R*)(*S*)-**4a** (100% de) and 2.3 g (*S*)(*S*)-**4a** (100% de according to HPLC analysis on a Chiracel OD-phase), respectively.
7. (*rac*)-**8**, mp.: 75-76°, δ_{OMe}: 2.56 ppm; (*rac*)-**13**, mp.: 100-101°, δ_{OMe}: 4.00 ppm; (*rac*)-**14**, mp.: 225°, δ_{OMe}: 3.56 ppm; specific rotations at 365-589 nm of all three compounds were zero.
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9. In chromatography, configuration at phosphorus affected the retention time and R_f-values of the diastereomers, notably of those with alkyl and aryl substituted phosphorus. Diphosphines with the aryl in lieu of the alkyl group in the *stacking* position were less polar.
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11. Extending the terminology of Rebek, Jr. and others, we named a group that exerts a (aromatic) "stacking interaction" to be in a "stacking position". Aryl- as well as alkyl groups may occupy this position, e.g. *Ph*-; *Cyhex*-; ^tBu-*stacking*. See a) Rebek, Jr., J. *Angew. Chem.* **1990**, *102*, 261; b) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K.-S.; Jones, S.; Nemeth, D.; Williams, K.; Rebek, Jr., J. *J. Am. Chem. Soc.* **1989**, *111*, 1090; c) Jones, G.B.; Chapman, B.J. *Synthesis* **1995**, 475.
12. Coordinates and thermal parameters of the X-ray structures have been deposited at the *Crystallographic Data Centre*, Cambridge, University Chemical Lab., Cambridge CB2 1EW, England.

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