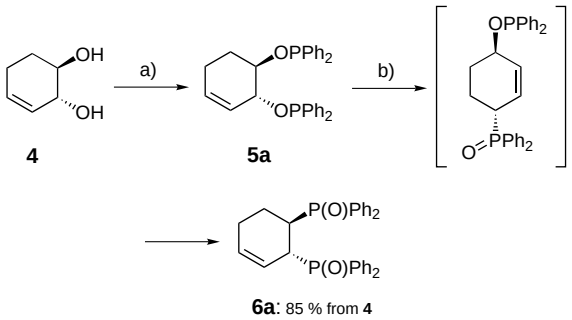
[14] Crystal structure analyses: **1**: monoclinic, space group $C2/c$, $a=2511.8(5)$, $b=1309.2(3)$, $c=4291.8(9)$ pm, $\beta=101.37(3)^\circ$, $V=13.84(1)$ nm^3, $Z=4$; $\rho_{calcd}=1.473$ Mg m^{-3}, $\mu=7.109$ mm^{-1}, $F(000)=6040$. Data collection: $2\theta=3.86-48.14^\circ$, $-18\le h\le 28$, $-13\le k\le 13$, $-49\le l\le 49$, 24666 reflections, of which 9010 were independent ($R_{int}=0.0781$) and 611 refined. All non-hydrogen atoms were refined anisotropically and the H atoms were included in calculated positions, $R_1=0.0663$, $wR_2=0.1794$ ($F>4\sigma(F)$), GOF(F^2) = 1.083; max. residual electron density 2.556 e Å^{-3}. **2**: triclinic, space group $P\bar{1}$, $a=1548.9(3)$, $b=1738.7(4)$, $c=2097.4(4)$ pm, $\alpha=78.37(3)$, $\beta=68.79(3)$, $\gamma=77.12(3)^\circ$, $V=5.0877(18)$ nm^3, $Z=2$; $\rho_{calcd}=1.473$ Mg m^{-3}, $\mu=9.621$ mm^{-1}, $F(000)=2396$. Data collection: $2\theta=4.22-51.84^\circ$, $-18\le h\le 18$, $-21\le k\le 21$, $-25\le l\le 25$, 55309 reflections, of which 18432 were independent ($R_{int}=0.0939$) and 829 refined. All non-hydrogen atoms were refined anisotropically and the H atoms were included in calculated positions, $R_1=0.1313$, $wR_2=0.4136$ ($F>4\sigma(F)$), GOF(F^2) = 1.851; max. residual electron density 17.506 e Å^{-3}. The crystals of **2** are extremely thin, very small platelets, and therefore the data set was strongly influenced by absorption effects. An absorption correction could not be performed. Several maxima of similar size occur which are all located at the periphery of the molecule (60–150 pm from the H atoms). If only data up to $2\theta=44^\circ$ are considered for the refinement of the structure, the structural parameters are altered only slightly: $R_1=0.128$; max. residual electron density 13.40 Å^{-3}. The intensities were measured with a STOE-IPDS diffractometer with a CCD area detector ($Mo_{K\alpha}$ radiation, $\lambda=0.71073$ Å). The crystals were mounted in perfluoropolyether oil; $T=183(2)$ and 193(2) K, respectively. The structures were solved by using direct methods and refined against F^2 for all observed reflections. (Structure solution with SHELXS 94, refinement using SHELXL 93). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-150538 (**1**) and CCDC-150539 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). .

New C_2-Symmetrical 1,2-Diphosphanes for the Efficient Rhodium-Catalyzed Asymmetric Hydroboration of Styrene Derivatives**

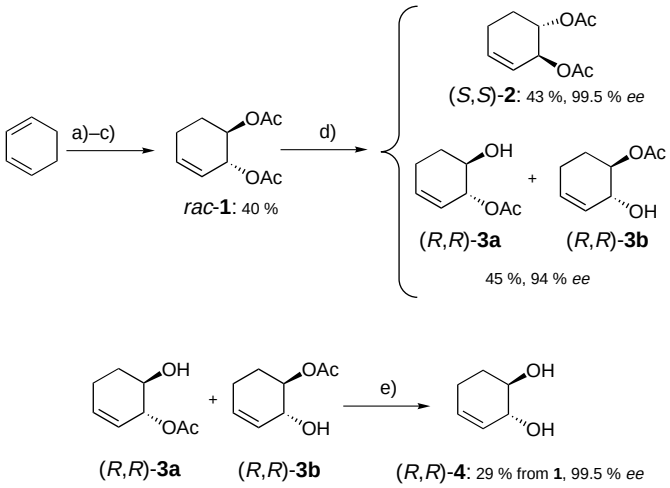
Stéphane Demay, Florence Volant, and Paul Knochel*

Chiral 1,2-diphosphanes are important ligands for asymmetric metal catalysis.[1] Their synthesis is challenging especially if the stereoselective formation of secondary carbon–phosphorus bonds is desired. Recently, we have developed a method[2] that provides a stereoselective synthesis of cyclic 1,2-diphosphane oxides using a tandem [2,3] sigmatropic rearrangement of diphenylphosphinites that are readily available from the corresponding unsaturated 1,2-diols (Scheme 1). Herein we report the use of this rearrangement for a practical preparation of new chiral 1,2-diphosphanes and their application in highly efficient rhodium-catalyzed asymmetric hydroborations.



Scheme 1. Tandem [2,3] sigmatropic rearrangement of diphenylphosphinite. a) $ClPPh_2$, 4-DMAP, Et_2O, RT; b) toluene, reflux, 42 h.

The racemic mixture of the diacetate **1** is prepared in three steps in about 40% overall yield starting from 1,3-cyclohexadiene.[3] This diacetate is easily resolved using *Pseudomonas fluorescens* lipase[4] to afford the chiral diacetate (*S*,*S*)-**2** (43% yield, 99.5% *ee*) and a mixture of monoacetates (*R*,*R*)-**3** (45% yield, 94% *ee*; Scheme 2). The two enantiomeric diols (*R*,*R*)-**4** and (*S*,*S*)-**4** are obtained in optically pure forms after saponification and recrystallization from AcOEt in yields of 29 and 31%, respectively (from **1**). These compounds have been prepared on a multigram scale and are a convenient starting material for a range of new chiral phosphanes of interest for metal catalysis.



Scheme 2. Preparation of the optically pure diol (*R*,*R*)-**4**. a) Br_2 (1 equiv), $CHCl_3$, 5 °C; b) 1M KOH, H_2O, RT, 96 h; c) Ac_2O (2 equiv), pyridine, RT, 12 h; d) *Pseudomonas fluorescens* lipase, pH 7, buffer, 38 °C; e) NaOMe (1 equiv), MeOH, RT, 1 h; f) recrystallization from AcOEt.

The reaction of (*R*,*R*)-**4** with several diarylchlorophosphanes[5] provides the corresponding diphosphinites **5a–c** which undergo a smooth [2,3] sigmatropic rearrangement in

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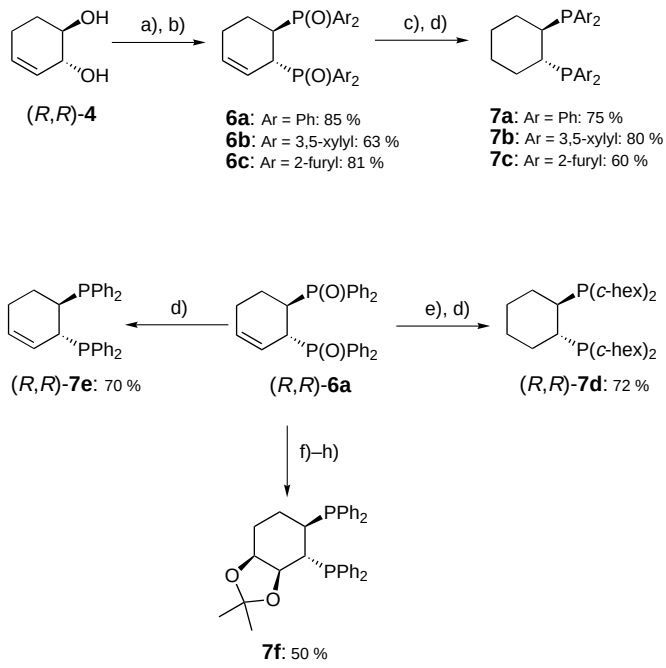
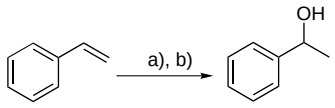
toluene (for **5a** and **5b**; reflux, 42 h) or in mesitylene (for **5c**; 170 °C, 17 h) to afford the corresponding phosphane oxides **6a–c** in 63–85 % yield (Scheme 3). These phosphane oxides



Scheme 3. Preparation of the diphosphanes **7a–f**. a) $ClPAr_2$ (2.05 equiv), 4-DMAP (2.1 equiv), Et_2O, RT, 30 min; b) toluene or mesitylene, reflux; c) Pd/C, H_2, AcOH, 60 °C, 18 h; d) $HSiCl_3$ (20 equiv), toluene, autoclave, 110 °C, 14 h; e) Raney Ni in excess, 40 bar H_2, EtOH, 90 °C, 12 h; f) OsO_4 (0.1 equiv), NMO (3 equiv), pyridine (3 equiv), *t*BuOH, H_2O, reflux, 6 h; g) $HSiCl_3$ (30 equiv), toluene, autoclave, 130 °C, 18 h; h) $Me_2C(OMe)_2$ (excess), PTSA (cat.), CH_2Cl_2, THF, RT, 12 h.

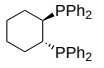
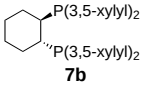
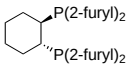
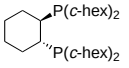
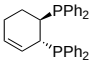
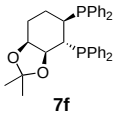
are readily converted into the corresponding saturated phosphanes (**7a–c**) in a two-step sequence (1. H_2, Pd/C, AcOH, 65 °C, 18 h; 2. $HSiCl_3$ (20 equiv), toluene, 110 °C, autoclave, 14 h) in satisfactory overall yield (60–80 %). Alternatively, the phenyl rings can also be readily reduced with a Raney nickel catalyst[6] in 90 % yield to give the (*R*,*R*)-1,2-bis(dicyclohexylphosphanyl)cyclohexane (**7d**) in 80 % yield after subsequent reduction with $HSiCl_3$.[7] The direct reduction of **6a** with $HSiCl_3$ provides the unsaturated diphosphane **7e**. The treatment of **6a** with a catalytic amount of OsO_4 (10 mol %), *N*-methylmorpholine *N*-oxide (NMO; 3 equiv), and pyridine (3 equiv) in *t*BuOH/H_2O (reflux, 6 h) affords stereoselectively[8] a *cis* 1,2-diol, which leads to the diphosphane **7f** in 50 % yield after reduction of the phosphane oxide ($HSiCl_3$, 30 equiv, toluene, 130 °C, 18 h) and ketal formation ($Me_2C(OMe)_2$, *p*-toluenesulfonic acid (PTSA; cat.), CH_2Cl_2, THF, RT, 12 h).

The catalytic activity of rhodium complexes of these new phosphanes in enantioselective hydroboration reactions was investigated.[9] The hydroboration of styrene with catecholborane in the presence of $[Rh(cod)_2]BF_4$ (1 mol %; cod = 1,5-cyclooctadiene) and the chiral diphosphanes **7a–f** (1.2 mol %) furnishes, after oxidative workup (KOH, H_2O_2), 1-phenylethanol with high regioselectivity (> 99:1) and variable enantioselectivity (Scheme 4 and Table 1). The diphos-



Scheme 4. Rhodium-catalyzed asymmetric hydroboration of styrene with ligands **7a–f**. a) $[Rh(cod)_2]BF_4$ (1.0 mol %), **7a–f** (1.2 mol %), catecholborane (1.2 equiv), solvent; b) 3 M KOH, H_2O_2.

Table 1. Rhodium-catalyzed enantioselective hydroboration of styrene using ligands **7a–f**.

Entry	Ligand	Solvent	*T* [°C]	*ee* [%] (config.)
1	 **7a**	Et_2O:CH_2Cl_2 (4:1)	– 60	8 (*S*)
2	 **7b**	Et_2O:CH_2Cl_2 (4:1)	– 60	65 (*R*)
3	 **7c**	Et_2O:CH_2Cl_2 (4:1)	– 60	65 (*S*)
4	 **7d**	DME	– 35	92 (*S*)
5	 **7e**	DME	– 40	8 (*R*)
6	 **7f**	DME	– 40	15 (*R*)

phanes **7a**, **7e**, and **7f** (entries 1, 5, and 6 of Table 1) produce low enantioselectivities which are independent of the reaction conditions. However, the electron-rich diphosphane **7b** provides (*R*)-1-phenylethanol with 65 % *ee* using a mixture of diethyl ether and CH_2Cl_2 (4:1) as the solvent for the reaction. This mixture was found to be superior to THF, dimethoxyethane (DME), *tert*-butyl methyl ether, toluene, and mixtures of these solvents. Interestingly the electron-poor diphosphane **7c** (entry 3, Table 1) provides the (*S*)-alcohol; this result shows the importance of the electron density of the phosphorus center on the enantioselectivity.[10] Finally, the best results are obtained with the very electron-rich diphosphane **7d**. In this case, (*S*)-1-phenylethanol is obtained in 92 % *ee* (DME, – 35 °C, 3 h) with a regioselectivity greater than 99:1 (Table 1, entry 4). A lower reaction temperature results in no reaction, while a higher temperature results in lower enantioselectivity and regioselectivity.

The diphosphane **7d** has been applied to the hydroboration of other styrene derivatives to evaluate the scope of this new ligand under standard conditions (1 mol % of catalyst in DME at – 35 °C; Table 2). In all cases the regioselectivity is excellent. Irrespective of the electronic nature of the substituents, their position and size have a profound effect on the enantioselectivity. Indeed, all the styrene derivatives with a

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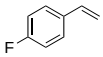
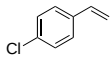
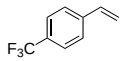
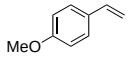
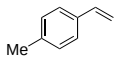
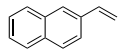
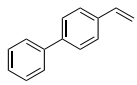
Table 2. Rhodium-catalyzed enantioselective hydroboration of styrene derivatives using ligand **7d**.

Entry	Substrate	Conversion [%] (t [h])	Regio-selectivity	*ee* [%] (config.)	Yield[c] [%]
1	 **8a**	100 (3)	>99:1	92 (*S*)	85
2	 **8b**	100 (3)	>99:1	93 (*S*)	81
3	 **8c**	86 (15)	>99:1	76 (*S*)	62
4	 **8d**	100 (2)	>99:1	85 (*S*)	84
5	 **8e**	98 (4)	98:2	58 (*S*)	80
6	 **8f**	84 (17)	99:1	93 (*S*)	69
7	 **8g**	98 (4)	98:2	92 (*S*)	82
8	 **8h**	100 (5)	>99:1	91 (*S*)	83
9	 **8i**	74 (17)[a]	97:3	74 (*S*)	64
10	 **8j**	62 (17)[b]	97:3	84 (*S*)	50

[a] Reaction performed with 2 mol% of catalyst at −28 °C. [b] Reaction performed with 2 mol% of catalyst at −35 °C. [c] Yield of the analytically pure product.

substituent in the *para* position give enantioselectivities between 84 and 93% *ee* (Table 2, entries 2, 4, 6, 7, and 10), except for the *para*-trifluoromethylstyrene (58% *ee*; Table 2, entry 5), which is the only styrene bearing a pure electron-withdrawing group (only −I, no +M effect). Enantioselectivities lay between 74 and 91% *ee* when the substituents are in the *meta* position (Table 2, entries 3, 8, and 9). *ortho*-Fluorostyrene is hydroborated under these conditions with a regioselectivity greater than 99:1, but with only 56% *ee*. Remarkably, the use of ligand **7c** solves the problem of the hydroboration of 2-substituted styrenes (Table 3). Reactions were performed with 1 mol% of catalyst in a mixture of DME and toluene (3:2) at −75 °C. The high rate of these hydroborations is surprising, with most reactions being completed within 1 h at this low temperature. Enantioselectivities lay between 77 and 82% and regioselectivities are also good.

Table 3. Rhodium-catalyzed enantioselective hydroboration of 2-substituted styrene derivatives using ligand **7c**.[a]

Entry	Substrate	Regio-selectivity	*ee* [%] (config.)	Yield[b] [%]
1	 **8k**	86:14	77 (*S*)	75
2	 **8l**	97:3	82 (*S*)	84
3	 **8m**	97:3	81 (*S*)	86
4	 **8n**	94:6	82 (*S*)	81

[a] Reaction is performed with 2 mmol of styrene derivatives, 1 mol% of $[Rh(cod)_2]BF_4$, 1.05 mol% of ligand **7c**, and 1.2 equivalents of catecholborane in a mixture of DME and toluene (3:2) at −75 °C; the conversion was 100% after 1 h. [b] Yield of analytically pure product.

In summary, the [2,3] sigmatropic rearrangement of chiral unsaturated 1,2-diphosphinites allows an effective and original preparation of chiral diphosphanes. We have also shown the high efficiency of these diphosphanes in the asymmetric hydroboration of styrene derivatives. The modular approach for the preparation of these ligands is a great advantage since various substituents can be attached to the phosphorus center.

Experimental Section

Typical procedure for the double [2,3] sigmatropic rearrangement: Preparation of (1*R*,2*R*)-1,2-bis(diphenylphosphanyl)-3-cyclohexene (**6a**): (1*R*,2*R*)-1,2-dihydroxy-3-cyclohexene (**4**, 10 mmol, 1.14 g), 4-dimethylaminopyridine (DMAP; 21 mmol, 2.1 equiv, 2.57 g), and diethyl ether (120 mL) were added under argon to a 250-mL flask equipped with a magnetic stirrer. Pure chlorodiphenylphosphane (20.5 mmol, 2.05 equiv, 4.60 g) was added dropwise to the homogeneous solution. The resulting suspension was stirred for 0.5 h and then filtered under argon over a short pad of dry silica gel. The precipitate was washed twice with diethyl ether (20 mL). The ether solution was evaporated under reduced pressure and the resulting crude diphosphinite was diluted with toluene (80 mL). This solution was heated under argon to reflux for 42 h. The solvent was evaporated after cooling the reaction mixture to RT. Crude **6a** was recrystallized from AcOEt to yield a colorless crystalline solid (4.09 g, m.p. 201–202 °C, 85% yield from **4**).

Typical procedure for the preparation of (1*R*,2*R*)-1,2-bis(dicyclohexylphosphanyl)cyclohexane (**7d**): Unsaturated phosphane oxide **6a** (2.41 g, 5 mmol), Raney nickel (5 g, rinsed with ethanol prior to use), and ethanol (20 mL) were placed in an autoclave under argon. The autoclave was heated at 90 °C for 20 h with vigorous magnetic stirring under hydrogen (40 bar). After cooling the autoclave and purging with argon, the Raney nickel was filtered off and rinsed with AcOEt. The solvents were evaporated under reduced pressure. The reaction was complete and gave only one product as judged by ^{31}P NMR spectroscopic analysis of the crude reaction mixture. The white and waxy residue was recrystallized from *n*-heptane/CH_2Cl_2 to give **6h** as colorless needles (2.29 g, 90% yield). The phosphane oxide **6h** (2 mmol) was placed under argon in an autoclave with toluene (30 mL) and trichlorosilane (4 mL, 40 mmol, 20 equiv) and heated for 14 h at 110 °C. After cooling the reaction mixture to RT, it was transferred in a 100-mL flask filled with argon. The excess toluene and trichlorosilane were evaporated under a high vacuum (10–2 Torr). The residue was dissolved in toluene (25 mL) and carefully hydrolyzed at 0 °C

with degassed 3 M KOH (10 mL). The mixture was stirred at RT for 30 min. The two layers were then separated and the organic phase dried ($MgSO_4$) under argon. The resulting clear yellow organic phase was filtered and transferred by cannulation into a second flask flushed with argon. The toluene was evaporated and the crude diphosphane **7d** washed with dried degassed methanol (2 × 5 mL). After filtration, traces of the solvent were removed under high vacuum (2 h) to yield **7d** as a white microcrystalline solid (m.p. 126–128 °C), which was stored under argon (0.76 g, 80 % yield).

Typical procedure for the hydroboration with **7d**: A mixture of $[Rh(cod)_2]BF_4$ (8.1 mg, 0.020 mmol) and diphosphane **7d** (11.5 mg, 0.024 mmol) in dry DME (5 mL) was stirred for 10 min at RT in a 10-mL Schlenk tube under argon. Styrene or a derivative (2 mmol) was added to the resulting orange solution. The homogeneous mixture was cooled to −35 °C and stirred at this temperature for 15 min before adding freshly distilled catecholborane dropwise (2.4 mmol, 0.26 mL). The catecholborane dissolved in the DME and some gas evolved from the reaction mixture. The reaction was monitored by sampling. Aliquots were taken, treated with KOH (3 M) and 30 % H_2O_2, and extracted with diethyl ether or dichloromethane. The samples were then analyzed by chiral GC (Chiralsil DEX-CB column) or chiral HPLC (OD or OJ columns) to determine the conversion (using *n*-decane as an internal reference) and enantiomeric excess. The regioselectivity was determined by ^{1}H NMR spectroscopic analysis of the final crude reaction mixture after oxidative work-up. The products were purified by chromatography on silica (pentane/diethyl ether) to afford the corresponding alcohols.

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The First Crystallographic Evidence for the Structures of *ortho*-Lithiated Aromatic Tertiary Amides**

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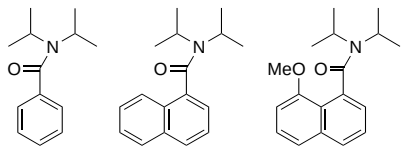
Directed metalation is arguably the most selective way of making regiospecifically substituted aromatic rings. The use of directed *ortho*-metalation involving amide-type functional groups (secondary and tertiary amides, carbamates, and oxazolines) has revolutionized the synthesis of complex benzenoid aromatic compounds over the last 15 years:[1] several recent total syntheses have involved important *ortho*-lithiation steps.[2] The four classes of substituents mentioned are not only the best directors of lithiation—with their electron-rich oxygen centers which promote the "complex-induced proximity effect"[3] and withdraw electron density from the ring—but also the most versatile.[2c]

It is, therefore, surprising how little is known of the products of *ortho*-lithiation reactions. Kinetic-isotope-effect evidence[4] suggests the reaction proceeds by a rate-determining deprotonation of an initial substrate–organolithium complex. It is assumed that O–Li coordination is maintained from reactive complex through to products, though for tertiary amides (the best directing group of all[5]) such coordination poses severe geometric difficulties. Even in the simple benzamide **1**, the tertiary amide group lies twisted out of the aromatic ring plane for steric reasons,[6, 7] inhibiting direct O-coordination to a 2-lithio group. The angle of twist affects the rate of lithiation,[6] but even amides which have little flexibility to rotate far from perpendicular, for example, **2** and **3**, still undergo efficient *ortho*-lithiation.[7, 8]



1 **2** **3**

Herein we report the first crystal structures of the products of tertiary-amide-directed *ortho*-metalation reactions. These go some way towards clarifying the nature of the O–Li coordination in *ortho*-lithiated amides, and also towards

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