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Atropo-enantioselective synthesis of an axially chiral C_1-symmetric phosphine ligand and its application in the asymmetric hydrosilylation of styrenes[1]

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Abstract

The axially chiral monodentate phosphine *P*-**8** was synthesized in enantiomerically pure form, starting from the readily available, configurationally unstable lactone **1**. Furthermore, its application as a ligand in the Pd-catalyzed stereoselective hydrosilylation of styrenes was investigated. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Over the past 20 years, axially chiral 2,2′-disubstituted-1,1′-binaphthyls have proved to be most useful agents in asymmetric synthesis,[2] typical examples being BINAL-H in the stereoselective reduction of ketones[3] and BINAP as a ligand for transition metals in asymmetric catalysis.[4] However, comparatively little attention has been paid to the stereoselective preparation of such enantiopure biaryls, in particular if they are constitutionally unsymmetric and thus C_1-symmetric.[5] For this attractive goal, we have developed a novel concept[6] which is based on rapidly interconverting lactone-bridged biaryls such as *P*-**1**⇌*M*-**1** (Scheme 1) as synthetic intermediates. They can be cleaved atropo-enantioselectively using, for example, chiral hydride transfer reagents, to give the stereochemically stable biaryls **2** with excellent enantiomeric ratios of up to 98.5:1.5 (97% ee),[7] or atropo-diastereoselectively using either metallated chiral *N*-nucleophiles such as 1-arylethylamides (drs of up to 95:5, de ≤90%)[8] or chiral metal alkoxides, e.g. derived from menthol (drs of up to 99:1, de ≤98%),[9] to give biaryl amides or esters **3**.

The potential of the ‘lactone methodology’ has, meanwhile, been demonstrated in the synthesis of more than 20 natural biaryls[6] and axially chiral auxiliaries.[10] In this paper, we report on the synthesis

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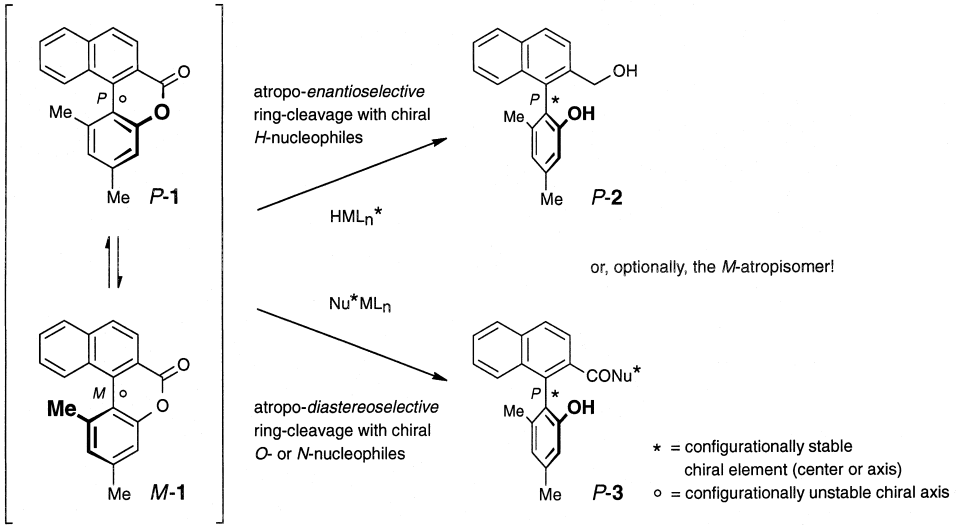


Scheme 1. Alternative pathways to axially chiral biaryls **2** and **3** by atropo-enantio- or -diastereoselective cleavage of **1**

of an enantiopure monodentate biaryl phosphine ligand and its application in the enantioselective hydrosilylation of styrene derivatives.

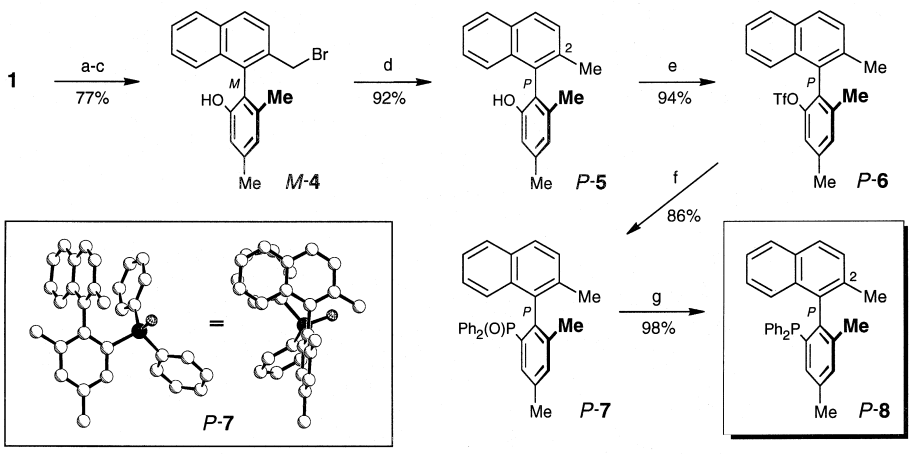
2. Results and discussion

The catalytic asymmetric hydrosilylation of olefins constitutes an important method for the preparation of optically active compounds.[11] Uozumi and Hayashi[12] observed that palladium coordinated to a chelating bisphosphine such as BINAP did not catalyze the hydrosilylation of 1-alkenes even at 80°C, while the reaction took place smoothly at 40°C when using *monodentate* phosphine ligands, instead. In further efforts they extended the field of application of these ligands to enantioselective hydrosilylation and allylic alkylation reactions.[13,14]

Based on these earlier investigations, we envisaged the synthesis of a C_1-symmetric monodentate phosphine ligand *P*-**8** by the lactone concept: atropo-diastereoselective cleavage of the lactone **1** using lithium 1*R*-mentholate as a chiral *O*-nucleophile[9] (dr 89:11, 78% de), separation of the diastereomeric menthyl esters by column chromatography, reduction of the pure major isomer with $LiAlH_4$, and subsequent benzylic hydroxy–halogen exchange gave the known[10] bromo compound *M*-**4** in an enantiomerically pure form (Scheme 2). By a second reduction step, *M*-**4** was transformed into the (still phenolic) 2-methyl compound *P*-**5**,[15] which was then converted into the corresponding triflate *P*-**6** by treatment with triflic anhydride.

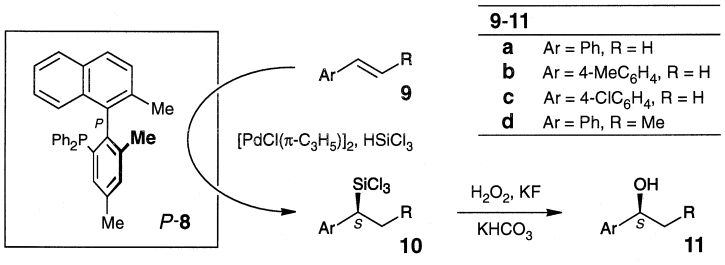
Palladium-mediated phosphinylation of *P*-**6** to the phosphine oxide *P*-**7** and final reductive *P*-deoxygenation gave the required axially chiral biaryl phosphine *P*-**8** in 56% overall yield from **1**. An X-ray structural analysis of *P*-**7**[16] confirmed the anticipated constitution. Further, as can be seen, the array at the configurationally stable biaryl axis is additionally fixed by π-stacking of the distal (i.e. 'outer') naphthalene ring to one of the two diastereotopic phenyl substituents on the *P*-atom (see the righthand crystal structure in Scheme 2).

For an evaluation of the potential of the phosphine *P*-**8** as a reagent in asymmetric synthesis, we selected the hydrosilylation of styrenes **9a–d** (Scheme 3). In accordance with previous work in the literature,[13] we used $[PdCl(\pi\text{-}C_3H_5)]_2$ as the catalyst precursor, now with *P*-**8** as the chiral ligand. In our



Scheme 2. Synthesis of the axially chiral phosphine ligand *P*-**8** and crystal structure of its direct precursor, *P*-**7**. Reaction conditions: (a) *n*BuLi, 1*R*-menthol, toluene, 0°C; (b) $LiAlH_4$, Et_2O, rt; (c) $(CCl_2Br)_2$, PPh_3, CH_2Cl_2, 0°C; (d) $LiAlH_4$, Et_2O, rt; (e) Tf_2O, DABCO, CH_2Cl_2, 0°C; (f) $Pd(OAc)_2$, $HP(O)Ph_2$, dppb, $^iPrNEt_2$, DMSO, 100°C; (g) $HSiCl_3$, xylene, 120°C

first attempts, the reactions were carried out at room temperature, regioselectively yielding the silanes **10a**–**d** in 84–99% chemical yields after distillation. Oxidation with H_2O_2 delivered the benzylic alcohols **11a**–**d**, the enantiomeric ratios of which were determined by HPLC on a chiral phase (see experimental).



Scheme 3. Enantioselective hydrosilylation of styrenes **9a**–**d** and oxidation of the resulting silanes **10a**–**d** to the benzylic alcohols **11a**–**d**

Under these conditions, the best asymmetric inductions were achieved for the alcohol **11d**, which gave an enantiomeric ratio of 62:38 (24% ee) (see Table 1). At 0°C, by contrast, the best results were attained with **11c**, giving an er of up to 75:25 (50% ee). In all these reactions, the *S*-enantiomeric products were formed preferentially.

The results obtained are in good agreement with those of Hayashi and co-workers,[13] who reported excellent enantiomeric ratios of up to 98:2 (96% ee) if related binaphthyl-based monodentate phosphine ligands *without* a substituent in the 2-position were used, while for Et, CN, CO_2Me, and OH substituents at C-2, the enantiomeric purities of the products decreased to 18, 26, 30, and 34%, respectively. Presumably, the dihedral angle between the naphthyl and phenyl rings, which is controlled by the size of the substituent located at C-2, has a decisive influence on the enantioselectivity. In our case, a lower steric hindrance at the axis, hopefully giving rise to higher asymmetric inductions, might be achieved by decreasing the steric demand of the alkyl substituent in the phenyl part of *P*-**8**, by starting from an analog of the biaryl lactone precursor **1** in which the methyl groups are missing.

Table 1
Enantioselective hydrosilylation of styrenes **9a–d**

styrene	temp. [°C]	t [h]	yield **10** [%] [a]	yield **11** [%] [a]	er [b] **11** (*S*:*R*) [c]	ee (%)
9a	23	18	84	91	55:45	10
9b	23	18	99	96	58:42	16
9c	23	24	88	91	60:40	20
9d	23	48	93	92	62:38	24
9a	0	24	86	91	68:32	36
9b	0	24	99	94	64:36	28
9c	0	96	87	92	75:25	50
9d	0	144	88	91	65:35	30

[a] Isolated yield after distillation.

[b] Determined by HPLC on a Chiralcel OD-H phase, with a commercially available racemate as a standard.

[c] Established by comparison of the specific rotation with the literature value.[17]

3. Conclusion

The facile atropo-enantioselective synthesis of the new enantiopure monodentate biarylphosphine *P*-**8** described in this paper, is achieved smoothly and in a very good overall yield of 56% starting from **1**. This underlines the efficiency and flexibility of the 'lactone methodology', giving rise to virtually any substitution pattern (here a *P*-substituent) in the proximity of the biaryl axis. As shown for the Pd-catalyzed enantioselective hydrosilylation of styrene derivatives (ee ≤50%), the potential of *P*-**8** as a ligand for catalysts in asymmetric synthesis has been demonstrated.

4. Experimental

Optical rotations were measured with a Perkin–Elmer polarimeter. Melting points were determined in a Kofler melting point apparatus. The IR spectra were scanned from KBr pellets using a Perkin–Elmer spectrophotometer model 1420. The NMR spectra were recorded with a Bruker AC 250 (250 MHz) instrument. Elemental analyses were performed in the Institute of Inorganic Chemistry of the University of Würzburg using a Leco CHNS-932. Mass spectra were measured on a Finnigan MAT 2000 mass spectrometer at 70 eV. All reactions were carried out under an Ar atmosphere using freshly dried solvents. The reagents were of commercial grade and used as supplied. HPLC analyses were carried out using a combination of a Waters M 510 pump, a Chiralcel OD-H column (Daicel Chem. Ind. Ltd., 4.6×250 mm), and an ERC-7215 UV-detector. Compound *M*-**4c** was prepared as described previously.[10] The styrenes **9a–d** and the racemic alcohols **11a–d** were purchased from Aldrich.

4.1. P-*1-(4′,6′-Dimethyl-2′-hydroxyphenyl)-2-methylnaphthalene* P-***5***

To a solution of *M*-**4** (440 mg, 1.29 mmol) in diethyl ether (20 mL), $LiAlH_4$ (196 mg, 5.16 mmol) was added and the reaction was stirred for 1 h (monitored by TLC). After hydrolysis with H_2O and acidification with 2N HCl, the aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by

chromatography on silica gel (eluent: diethyl ether:petroleum ether, 1:2) yielded *P*-**5** as a slightly yellow solid, which was recrystallized from diethyl ether:petroleum ether as colorless needles (310 mg, 1.27 mmol, 92%): mp 88°C; $[\alpha]_D^{20}$ −58.2 (*c* 1.0, $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3450, 3020, 2930, 2890, 2830, 1600, 1550, 1290, 1035, 830, 810, 780, 750; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.82 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.36 (s, 1H, OH), 6.76, 6.79 (s, s, 1H each, 3′-H and 5′-H), 7.35–7.48 (m, 3H, Ar-H), 7.48 (d, *J*=8.2 Hz, 1H, 4-H), 7.85 (d, *J*=8.2 Hz, 1H, 3-H), 7.87 (d, *J*=7.9 Hz, 1H, 8-H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 19.56 (CH_3), 20.00 (CH_3), 21.36 (CH_3), 113.3, 121.7, 123.0, 125.0, 125.4, 126.7, 128.1, 128.5, 130.2, 132.5, 132.8, 136.0, 136.1, 137.7, 138.8, 152.9 (Ar-C); MS: *m/z* (%) 262 (100) [M^+], 247 (46) [M^+-CH_3], 232 (16) [247−CH_3], 202 (13) [232−CO]. Anal. calcd for $C_{19}H_{18}O$ (262.4): C, 86.49; H, 6.92. Found: C, 86.53; H, 6.85.

4.2. P-*1-(4′,6′-Dimethyl-2′-trifluoromethylsulfonyloxyphenyl)-2-methylnaphthalene* P-***6***

A solution of the phenol *P*-**5** (240 mg, 914 μmol) and DABCO (204 mg, 1.83 mmol) in CH_2Cl_2 (8 mL) was cooled to 0°C and stirred for 30 min. Tf_2O (230 μl, 1.37 mmol) was added and the reaction mixture was stirred for 30 min until completion of the reaction (TLC). Removal of the solvent followed by chromatography on silica gel (eluent: diethyl ether:petroleum ether, 1:2) gave *P*-**6** as a colorless oil (354 mg, 898 μmol, 98%): $[\alpha]_D^{20}$ +31.4 (*c* 1.0, $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3020, 3000, 2960, 2930, 2900, 1610, 1580, 1490, 1400, 1250, 1110, 730; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.84 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.03, 7.09 (s, s, 1H each, 3′-H and 5′-H), 7.14 (m, 1H, Ar-H), 7.22–7.34 (m, 2H, Ar-H), 7.35 (d, *J*=8.2 Hz, 1H, 4-H), 7.75 (d, *J*=8.2 Hz, 1H, 3-H), 7.77 (m, 1H, 8-H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 19.71 (CH_3), 20.04 (CH_3), 21.20 (CH_3), 119.4 (q, *J*=318 Hz, C-F), 120.6, 122.1, 122.6, 124.6, 124.9, 125.0, 126.2, 128.0, 128.4, 129.3, 130.7, 132.0, 132.1, 134.7, 139.4, 147.6 (Ar-C); MS: *m/z* (%) 394 (61) [M^+], 246 (100) [$M^+-OSO_2CF_3$], 231 (19) [246−CH_3], 216 (5) [231−CH_3], 201 (4) [216−CH_3]. Anal. calcd for $C_{20}H_{17}F_3O_3S$ (394.4): C, 60.91; H, 4.34; S, 8.13. Found: C, 61.12; H, 4.37; S, 7.94.

4.3. P-*1-(4′,6′-Dimethyl-2′-diphenylphosphanylphenyl)-2-methylnaphthalene* P-***7***

A mixture of the triflate *P*-**6** (200 mg, 507 μmol), $HP(O)Ph_2$ (205 mg, 1.10 mmol), $Pd(OAc)_2$ (5.7 mg, 26 μmol), dppb (10.9 mg, 26 μmol) and $(i\text{Pr})_2$NEt (425 μl, 2.6 mmol) in DMSO (5 mL) was heated to 100°C for 6 h, cooled to room temperature and concentrated in vacuo. After addition of ethyl acetate (40 mL), the precipitated solid was removed by filtration. The organic layer was extracted with H_2O (3×30 mL), dried over Na_2SO_4 and the solvent was removed. Chromatography on silica gel (eluent: hexane:ethyl acetate, 1:1) of the resulting red oil yielded the product *P*-**7**. From petroleum ether:ethyl acetate, the phosphine oxide *P*-**7** was obtained as colorless crystals (194 mg, 434 μmol, 86%): mp 195–196°C; $[\alpha]_D^{20}$ +85.5 (*c* 1.0, $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3020, 2980, 2920, 2900, 2820, 1600, 1570, 1420, 1170; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.74 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 6.79–7.19 (m, 10H, Ar-H), 7.21–7.64 (8H, Ar-H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 19.75 (CH_3), 20.97 (CH_3), 21.20 (CH_3), 124.1, 125.3, 125.6, 126.9, 127.6, 127.9, 128.0, 128.3, 130.1, 130.2, 130.6, 130.7, 131.0, 131.4, 131.7, 132.2, 132.7, 132.8, 134.3, 134.8, 135.3, 136.7, 138.7, 140.0 (Ar-C); ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.60; MS: *m/z* (%) 446 (23) [M^+], 431 (4) [M^+-CH_3], 355 (100) [431−C_6H_4]. Anal. calcd for $C_{31}H_{27}OP$ (446.5): C, 83.39; H, 6.09. Found: C, 82.99; H, 6.28.

4.4. P-*1-(4′,6′-Dimethyl-2′-diphenylphosphanophenyl)-2-methylnaphthalene* P-***8***

A solution of the phosphine oxide *P*-**7** (100 mg, 224 μmol) and NEt_3 (490 μl, 4.46 mmol) in xylene (5 mL) was cooled to 0°C, treated with $HSiCl_3$ (114 μl, 1.12 μmol), and heated to reflux for 24 h. After cooling to room temperature, the reaction mixture was hydrolyzed with a saturated $NaHCO_3$ solution. The obtained residue was separated by filtration over Celite and washed with diethyl ether (3×10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed. Purification of the crude product succeeded by chromatography on silica gel (eluent: diethyl ether) to give *P*-**8**, which was recrystallized from diethyl ether:petroleum ether yielding a white powder (94 mg, 218 μmol, 98%): mp 134°C; $[\alpha]_D^{20}$ +104.3 (*c* 1.0, $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3040, 3020, 2930, 2900, 2830, 1620, 1600, 1560, 1420, 730, 690; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.73 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 6.85–7.14 (m, 12H, Ar-H), 7.16–7.27 (m, 4H, Ar-H), 7.67–7.72 (m, 2H, 8-H and 4-H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 19.82, (CH_3), 20.95 (CH_3), 21.33 (CH_3), 124.5, 125.5, 127.4, 127.7, 128.0, 128.1, 128.2, 128.3, 128.9, 131.8, 132.3, 132.7, 133.4, 133.6, 133.9, 134.0, 134.7, 136.9, 137.4, 137.5, 137.7, 137.9, 138.1, 142.4 (Ar-C); ^{31}P NMR (162 MHz, $CDCl_3$): δ −14.25; MS: *m/z* (%) 430 (27) [M^+], 415 (8) [M^+-CH_3], 400 (34) [415−CH_3], 324 (100) [400−C_6H_4]. Anal. calcd for $C_{31}H_{27}P$ (430.5): C, 86.48; H, 6.32. Found: C, 86.07; H, 6.06.

4.5. *General procedure for the asymmetric hydrosilylation of the styrenes* ***9a–d***

In analogy to the literature[14] styrene **9** (3.80 mmol), $[PdCl(\pi\text{-}C_3H_5)]_2$ (38.0 μmol), and chiral phosphine *P*-**8** (76.0 μmol) were stirred for 30 min. Then $HSiCl_3$ (4.56 mmol) was added and the solution stirred until completion of the reaction (TLC). The silane **10** obtained by distillation from the reaction mixture was dissolved in THF:MeOH (1:1) and treated with KF (22.8 mmol) and $KHCO_3$ (45.6 mmol). After 10 min stirring at room temperature and addition of 30% H_2O_2 (22.8 mmol), the suspension was heated under reflux. Upon completion of the oxidation according to TLC, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$, and the residue was removed by filtration. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Column chromatography of the crude product on silica gel (eluent: diethyl ether:petroleum ether, 1:1) gave a pure material. The ers of the benzyl alcohols **11** were determined by HPLC on a chiral phase (Daicel Chiralcel OD-H, detection at 254 nm, flow rate 0.5 mL/min, eluent: ^{i}PrOH:hexane, 1:9). The predominant absolute configurations of all of the products obtained were assigned to be *S* by the signs of their optical rotations (all negative), as reported for (*S*)-**11a**–**d** in the literature.[17]

Acknowledgements

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16. Cell data for **7**: $C_{31}H_{27}P$, orthorhombic, space group $P2_12_12_1$, a=962.3(1) pm, b=1488.6(1) pm, c=1739.5(2) pm. Additional data for this structure have been deposited at the Cambridge Crystallographic Data Centre.
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