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Synthesis and easy Racemisation of an Atropisomerically Chiral Phosphinamine

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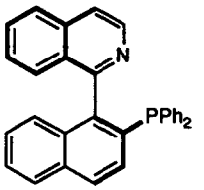
***Abstract**: Both the chelating P-N ligand 1-(2'-diphenylphosphino-3',6'-dimethoxyphenyl)-isoquinoline and its square planar Pd complex (15) atropisomerise readily at room temperature.*

Much recent asymmetric synthesis has been based on the atropisomerically chiral biphosphine BINAP and related compounds[1], although the level of structural variation on the basic 2,2'-diphosphino-1,1'biaryl unit has been quite limited. Chelating aminophosphines are often effective ligands for asymmetric homogeneous catalysis, particularly in cross-coupling chemistry[2]. Following on from earlier mechanistic and synthetic work on asymmetric C-C bond formation[3], we wished to prepare an axially chiral P-N chelate as the first representative of a novel class of ligands.



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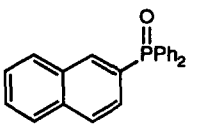

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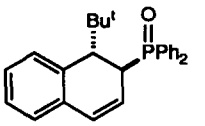

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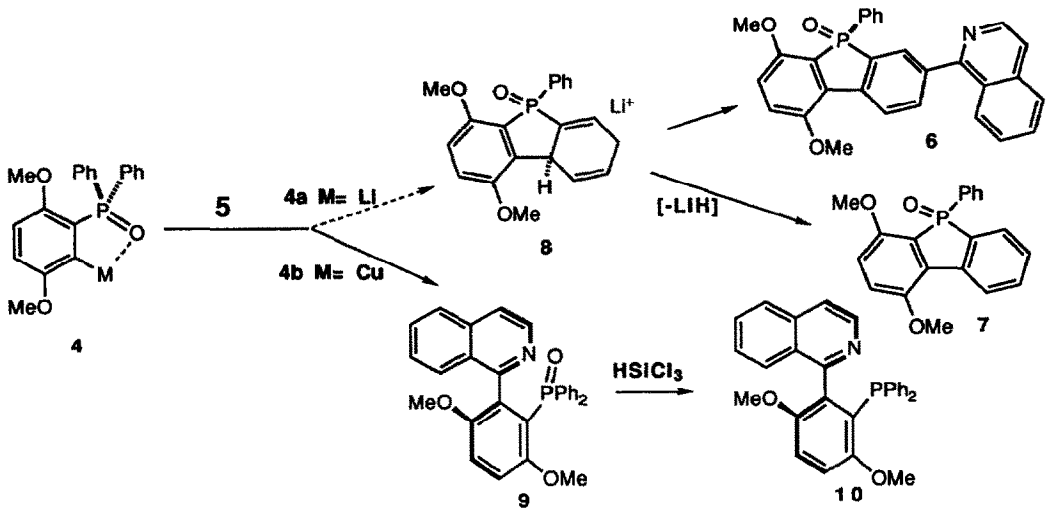
Initial efforts centred on the synthesis of the BINAP P-N analogue (**1**) via established biaryl coupling routes. Thus attempted lithiation of 2-(diphenylphosphinoyl)-naphthalene (**2**) with Bu^{t}Li in thf at -78^{0}C to provide a nucleophilic component for biaryl coupling led only to the addition product (**3**). This is in line with the difficulties previously recorded in ortho-metallation of simple arylphosphine oxides; hence the parent $Ph_3P{=}O$ can only be lithiated with PhLi, which averts alkyl exchange at phosphorus[4]. Such problems can be avoided by using the methoxyl-stabilised lithio-derivative (**4a**)[5], which can be prepared from the corresponding arene with Bu^{t}Li in thf at -100^{0}C, followed by equilibration at -78^{0}C. Attempted cross-coupling of this lithio-derivative directly with 1-iodoisoquinoline (**5**) [ex isoquinoline N-oxide, $POCl_3$, then NaI, HI, MEK; 45% overall] using 1-2 mol% of $Cl_2Ni(PPh_3)_2$ in thf at ambient temperature was unsuccessful. On workup, low yields (< 10%) of the substituted dibenzophosphole oxide (**6**)[6], m.p. 260-2^{0}C were obtained in addition to unreacted phosphine oxide. Comparably low yields of the parent dibenzophosphole oxide (**7**)[6] were obtained in separate experiments. The lithiated species (**4**) is clearly unstable at room temperature - cyclisation to a phosphole oxide intermediate (**8**) which may intercept the electrophile (**4**) evidently represents one decomposition pathway[7].



A more successful approach involved the cuprate (**4b**), prepared by reaction of lithium compound (**4a**) with $CuBr;SMe_2$ at low temperature. When this was reacted with compound (**5**) [thf; 0^0C then reflux 15h.] the desired product (**9**)[6] was formed in 35% yield, after chromatographic separation from some recovered reactants and recrystallisation. This was reduced to crystalline racemic phosphine (**10**)[6] with $HSiCl_3$ in 85% yield.

Reaction of the ligand rac-(**10**) with $(MeCN)_2PdCl_2$ in CH_2Cl_2 gave the corresponding racemic chelate complex (**11**) with displacement of MeCN. An X-ray crystallographic analysis confirmed the cis-chelate square-planar structure (Figure 1A). There is some distortion towards tetrahedral palladium, most clearly demonstrated in the Cl-Pd-P angle of 172^0 and Cl-Pd-N angle of 169^0 as illustrated in Figure 1B; similar features are apparent in other X-ray structures of palladium P-N chelates, although the generality of this distortion has not been recognised[8]. The complex (**11**) [2mol% in thf] proved to be an effective catalyst for the cross-coupling of $PhCH_2MgCl$ with halide (**12**) leading to the expected stilbene (**13**)[3] with a rate of 8 turnovers / h at 30^0C.

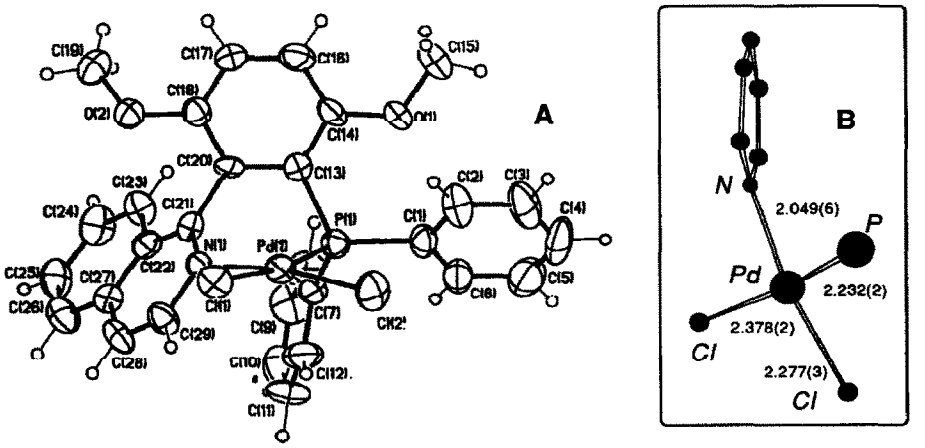
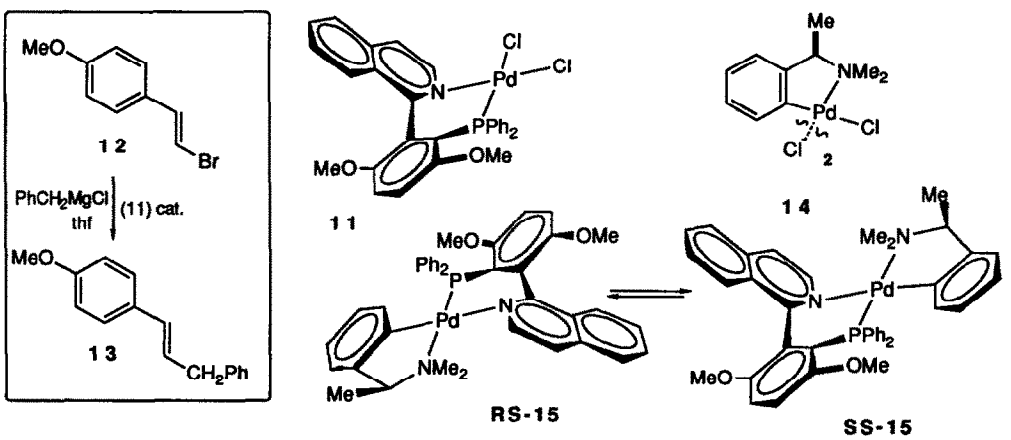


Figure 1A. X-ray structure of complex (11), $MeNO_2$, Et_2O, 0^0C. $C_{29}H_{24}NO_2Cl_2PPd$, M=626.8, Monoclinic, $P2_1/n$, a= 11.501(4) b=13.310(7), c= 17.692(6) , U= 2669(1) A^3, Z= 4, D_c= 1.56 g cm^3, Mo-Kα radiation, λ= 0.71069 A, μ(Mo-Kα)= 9.7 cm^{-1}, T= 290K, R= 0.042 for 1926 unique observed reflections($I/\sigma(I)$) > 2.0. Figure 1B. Distortions from ideality around palladium.

Having achieved the successful synthesis of an atropisomerically chiral ligand, its resolution was attempted. Following established methodology for diphosphines[9], resolution of the ligand rac-(**10**) was attempted by reaction with the enantiomerically pure palladium amine complex (**S-14**). The resulting isolated complex (**15**), m.p. 162-4^{0}C (dec) was clearly a 1:1 mixture of diastereomers with most signals duplicated in the ^{13}C and ^{1}H NMR spectra [e.g. CH*Me*, 1.46, 1.90; C*H*Me, 3.76, 5.03 ppm; ^{31}P NMR 30.4, 30.7 ppm; i.e P trans to N]. This ratio was always maintained on recrystallisation from acetone/Et_2O, but on standing in acetone solution, (**RS-15**) and (**SS-15**) slowly interconverted, and one diastereomer eventually became predominant by 4:1. On evaporation and recrystallisation this reverted to 1:1, indicating that the thermodynamic preference for one diastereomer in solution is not maintained in the solid state. In addition, the ligand must be epimerising within the complex. Since the chiral auxiliary is configurationally stable, this requires prior dissociation of one ligating atom with ready rotation about the biaryl bond before recoordination, and the isoquinoline nitrogen is the likely candidate. Rapid racemisation of the free ligand was confirmed by an NMR magnetisation transfer experiment in toluene-d_8 at 500 MHz. The diastereotopic m-PPh_2 protons are clearly separated and sharp at [δ 7.32, 7.47 ppm].



Irradiation of one leads to diminution of the other, and by varying the delay between the excitation and observation pulses a rate constant for magnetisation transfer (i.e. racemisation) of about 0.2 s^{-1} was obtained. This corresponds to an energy barrier for atropisomerism of around 93 KJ mol^{-1}, corresponding to an extrapolated lifetime for a single enantiomer of only a few minutes at ambient temperature. Given the bulk of the -PPh_2 group, this easy racemisation is surprising; the racemisation barrier in 1-(1'-naphtho)isoquinoline is however much lower than that in 1,1'-binaphthyl[10], and OMe is a small substituent in terms of its effect on biaryl rotation barriers[11]. Even more surprising is the ready epimerisation of complex (**15**), which requires that one of the ligating atoms dissociate first. Some insight may be derived from analysis of the X-ray structure of (**11**), since the Pd-N bond is 30^0 out of the isoquinoline ring plane, as illustrated in Figure 1B - to accommodate the constraints of the rigid chelate unit. This attenuates the lone-pair coordination and assists dissociation of this bond[12].

Thus the synthesis of a chelating ligand of the desired type has been achieved, and its catalytic potential demonstrated. Further structural constraints are required to raise the rotational barrier before asymmetric catalysis can be broached.

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6) Key data : (**6**): white needles mp 260-262^{0}C; IR (KBr) ν 1262 cm^{-1} (P=O); *m/z* (DCI (NH_3)) 464 ($(M+1)^+$,100%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.76 (s, 3H, OMe), 4.01 (s, 3H, OMe), 6.84 (dd, $J_{P,H}$ 5.7, $J_{7,8}$ 9 Hz, 1H, 3-H), 7.13 (d, 1H, 2-H), 7.34 (dt, J 7.2, 2.9 Hz, 2H, *m*-Ph), 7.44 (t, J 7.2 Hz, 1H, *p*-Ph), 7.53 (t, J 7.2 Hz, 1H, 6'-H), 7.63 (d, 1H, 4'-H), 7.70 (m, 3H, 7'-H+*o*-Ph), 7.85 (d, $J_{8',7'}$ 8.7 Hz, 1H, 8'-H), 7.91 (d, 1H, 8-H), 8.00 (d, $J_{1,2}$ 8.7 Hz, 1H, 9-H), 8.08 (d, $J_{5',6'}$ 7.2 Hz, 1H, 5'-H), 8.54 (dd, $J_{P,H}$ 2.9 Hz, 1H, 6-H), 8.56 (d, $J_{3',4'}$ 5.8 Hz, 1H, 3'-H); ^{13}C NMR (62.9 MHz, $CDCl_3$) : δ 56.24, 56.34 (OCH_3) 112.94 ($J_{C,P}$ = 7 Hz, C3) 118.65 (C2) 120.27 (C4') 126-160 (Ar); ^{31}P NMR (101.2 MHz, $CDCl_3$): δ 29.8.

(**7**): *m/z* (DCI (NH_3)) 337 ($(M+1)^+$, 100%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.76 (s, 3H, OMe), 3.98 (s, 3H, OMe), 6.80 (dd, $J_{P,H}$ 5.9 Hz, 1H, 3-H), 7.10 (d, $J_{2,3}$ 8.8 Hz, 1H, 2-H), 7.37 (m, 3H, 7-H+*m*-Ph), 7.48 (t, J 7.4 Hz, 1H, *p*-Ph), 7.55 (t, J 7.4 Hz, 1H, 8-H), 7.70 (d, $J_{9,8}$ 7.4 Hz, 1H, 9-H), 7.73 (d, J 6.5 Hz, 2H, *o*-Ph), 8.40 (dd, $J_{P,H}$ 2.9, $J_{6,7}$ 8.8 Hz, 1H, 6-H).^{13}C NMR (62.9 MHz, $CDCl_3$) : δ 56.24, 56.34 (OCH_3) 112.94 ($J_{C,P}$ = 7 Hz, C3) 118.65 (C2) 120.27 (C4') 126-160 (Ar)

(**10**) M.p. 195-196^{0}C (CH_2Cl_2-Et_2O). ν_{max} (KBr) 1258s (C=C), and 1187s (P=O) cm^{-1}; *m/z* (DCI (NH_3)) 337 ($(M+1)^+$; δ_H (500 MHz, $CDCl_3$) 3.38 (3 H, s, OMe), 3.54 (3 H, s, OMe), 7.00 (1 H, dd, $J_{4',5'}$ 9.1 Hz, J_{PH} 5.5 Hz, 4'-H), 7.15-7.20 (3 H, m, Ph-*m*+5'-H), 7.24-7.28 (3 H, m, Ph-m+p), 7.32-7.34 (1 H, m, Ph-*p*), 7.38 (1 H, ddd, $J_{5,6}$ 8.3 Hz, $J_{6,7}$ 6.9 Hz, $J_{6,8}$ 1.1 Hz, 6-H), 7.46-7.52 (5 H, m, Ph-*o*+4-H), 7.56 (1 H, ddd, $J_{7,8}$ 8.2 Hz, $J_{6,7}$ 6.9 Hz, $J_{5,7}$ 1.2 Hz, 7-H), 7.61 (1 H, dd, $J_{5,6}$ 8.3 Hz, $J_{5,7}$ 1.2 Hz, 5-H), 7.72 (1 H, dd, $J_{7,8}$ 8.2 Hz, $J_{6,8}$ 1.1 Hz, 8-H), 8.42 (1 H, d, $J_{3,4}$ 5.7 Hz, 3-H); δ_C (62.9 MHz, $CDCl_3$) 55.8 (OMe), 56.6 (OMe), 113.1 (d, J_{PC} 7 Hz, 4'-C), 116.6 (5'-C), 120.1 (C_9H_6N), 122.3 (d, J_{PC} 102 Hz, 2'-C), 126.4-135.7 (m, Ph+C_9H_6N+1'-C), 141.7 (3-C), 152.5 (d, J_{PC} 13 Hz, 3'-C), 155.2 (6'-C), 157.6 (d, J_{PC} 3 Hz, 1-C); δ_P (101.3 MHz, $CDCl_3$) 23.8 (P=O).

(**11**):M.p. 170-171^{0}C (CH_2Cl_2-hexane); ν (KBr) 1255 cm^{-1} s (C=C); ^{1}H NMR (500 MHz, C_6D_6): δ 2.96 (s, 3H, OCH_3), 3.12 (s, 3H, OCH_3), 6.53 (d, $J_{4',5'}$ 8.9 Hz, 1H, 4'-H), 6.69 (d,, 1H, 5'-H), 6.96-7.11 (m, 8H, *o*+*p*-Ph overlapped with 6-H+7-H), 7.18 (d, $J_{3,4}$ 5.9 Hz, 1H, 4-H), 7.39 (d, $J_{5,6}$ 8.2Hz, 1H, 5-H), 7.43-7.46 (m, 2H, *m*-Ph), 7.62-7.65 (m, 2H, *m*- Ph), 7.81 (d, $J_{7,8}$ 8.1 Hz, 1H, 8-H), 7.61 (dd, $J_{5,6}$ 8.3, $J_{5,7}$ 1.2 Hz, 1H, 5-H), 7.72 (dd, $J_{7,8}$ 8.2, $J_{6,8}$ 1.1 Hz, 1H, 8-H), 8.60 (d, $J_{3,4}$ 5.9 Hz, 1H, 3-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 55.4 (OCH_3), 56.4 (OCH_3), 112.8 (4'-C), 120.0 (C_9H_6N), 126.1-137.3 (Ph+C_9H_6N+1'-C+2'-C), 141.9 (3-C), 151.8 (d, $J_{P,C}$ 11 Hz, 3'-C), 156.2 (6'-C), 159.6 (1-C); ^{31}P NMR (101.2 MHz, $CDCl_3$): δ -17.4 ; (**10**), (**11**) and derived complexes were obtained analytically pure.
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