Switching On and Off Metalation Sites in Triarylphosphines by Manipulating Substrate Coordination

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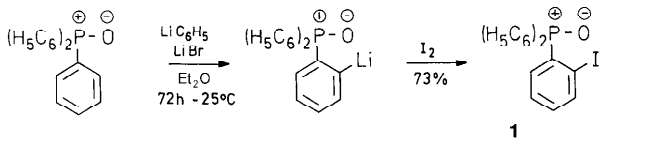
Abstract: The inductive electron-withdrawing effect of the positively charged phosphorus atom in triarylphosphine–borane adducts is largely compensated by the steric congestion caused in its vicinity. Therefore, trihydro(triphenylphosphonio)borate reacts only sluggishly even with superbasic reagents and products derived from *ortho*-metalated intermediates by their trapping with electrophiles are formed only in poor yield. On the other hand, the borane adducts of (3-anisyl)diphenylphosphine and (3-fluorophenyl)diphenylphosphine can be readily deprotonated at the hetero-adjacent *para* position and converted into final products in high yields. The phosphorus-remote regioselectivity of these phosphine–borane zwitterions is complementary to that previously observed with the corresponding phosphine oxides.

Key words: *ortho*-metalation, optional site selectivities, superbases, phosphine–borane adducts, phosphine ligands

Triphenylphosphine oxide undergoes selective monometalation at one of its six *ortho* positions when treated with phenyllithium in diethyl ether or tetrahydrofuran[1, 2] [53% of 2-(diphenylphosphino)benzoic acid[1] and 73% of (2-iodophenyl)diphenylphosphine oxide[2] **(1)** after reaction with dry ice and iodine, respectively]. The simultaneously occurring aryl/aryl exchange remains unnoticed unless isotopically labeled substances are employed.[3, 4] The introduction of an electronegative atom or group into the *meta* position of the substrate enhances the acidity at the doubly activated site flanked by the two substituents to such an extent that deprotonation can already be accomplished with lithium diisopropylamide. Thus, (3-anisyl)diphenylphosphine oxide[5,6] and (3-fluorophenyl)-diphenylphosphine oxide[7] easily undergo *ortho*-lithiation and subsequent iodination to afford precursors to Ullmann-coupled biaryls [76% of (2-iodo-3-methoxyphenyl)diphenylphosphine oxide **(2)**[5] and 85% of (3-fluoro-2-iodophenyl)diphenylphosphine oxide **(3)**[7], respectively].



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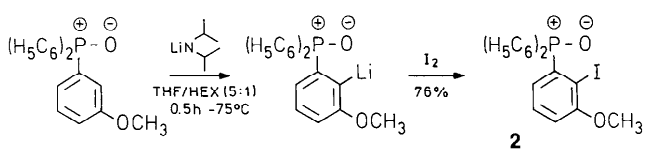

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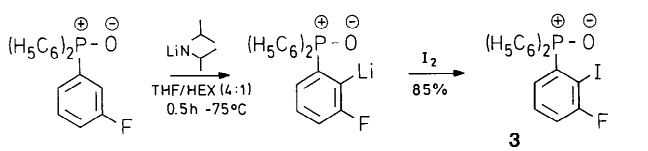

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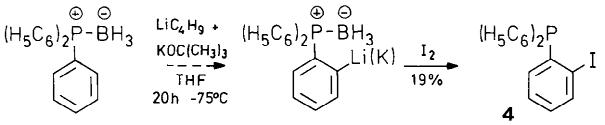
Species structurally related to triphenylphosphine oxide such as *N*-(triphenylphosphonio)anilide[8] and (triphenylphosphonio)methanide[9] can equally be submitted to an *ortho*-selective hydrogen/metal exchange. We wondered how triarylphosphine–borane[10] adducts would behave in this respect. Since the preparation of such zwitterions is as simple as their cleavage back to the components, they could act as turntables promoting the site-controlled electrophilic substitution of aromatic phosphines.

The parent compound trihydro(triphenylphosphonio)borate was found not to react with phenyllithium at all and with the superbasic mixture[11,12] of butyllithium and potassium *tert*-butoxide only sluggishly. While much starting material was recovered, only 19% of (2-iodophenyl)diphenylphosphine **(4)** were obtained after iodination. Extended reaction times had obviously caused an alcoholate assisted deborylation.[13] On the other hand, the superbase promoted metalation proceeded rapidly and smoothly when (3-anisyl)diphenylphosphine–borane was employed as the substrate, and no spontaneous deborylation occurred. However, (4-iodo-3-methoxyphenyl)diphenylphosphine–borane (**5**; 62%) rather than the expected 2-iodo isomer was formed upon iodination. Similarly, the 3-fluoro analog exclusively afforded (3-fluoro-4-iodophenyl)diphenylphosphine–borane (**6**; 78%). This time, *tert*-butyllithium sufficed to bring about the metalation, no superbasic reagent being required.



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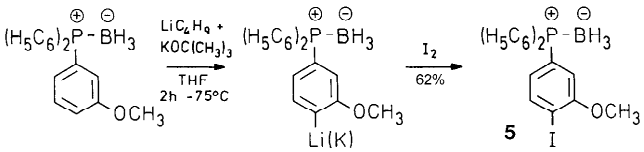

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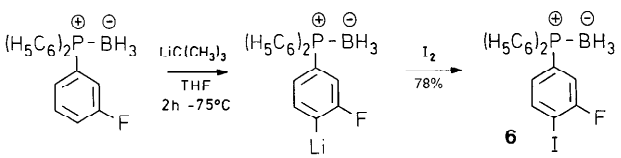

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(3-Anisyl)diphenylphosphine and (3-fluorophenyl)diphenylphosphine can be submitted to a hydrogen/metal interconversion at the 4-position using butyllithium in the presence of potassium *tert*-butoxide and, respectively, *tert*-butyllithium even without prior coordination. Under

the conditions of direct metalation, however, the yields are poor (44% and 37%, respectively) and the structural integrity is imperfect (aryl/alkyl substitution at phosphorus being a major side reaction).

The differences in reactivity and site selectivity exhibited by triarylphosphine oxides and triarylphosphine–borane adducts are striking. Manifestly, efficacious coordination of organometallic reagents requires the presence of nonbonding ("free") electron pairs at the phosphorus-attached center. The electrostatic attraction provided by the negatively charged boron atom is not enough. Obviously, metals seek to get engaged in partially covalent bonds (i.e. space-oriented interactions with electrons) at both ground and transition states. A description of such structures in terms of ion pair or ion multiplet assemblies may lead to wrong conclusions.

In conclusion, the diphenyl(trihydroborato)phosphonio group establishes little, if any, coordinative interaction with organometallic reagents. It does activate an aromatic ring to which it is attached, but it does so only by inductive electron withdrawal. However, this effect is not powerful enough to overcompensate to a sufficient extent the steric hindrance caused by this bulky substituent. As a consequence, no or little *ortho*-metalation is observed. On the other hand, phosphonioborates with an electronegative *meta*-substituent (e.g., fluorine or methoxy) readily undergo a hydrogen/metal exchange reaction at the *para*-position, the phosphonio unit providing long-range assistance. By analogy, *para*-heterosubstituted phosphonioborates can be assumed to be attacked at the *meta* and, again, not at the *ortho* position.

Starting materials were purchased from Fluka (CH-9470 Buchs), Aldrich (D-89552 Steinheim) and Merck (D-64271 Darmstadt), unless literature sources or details of the preparation are given. BuLi in hexane (1.5 M and "11.5 M", i.e. containing the organometallic reagent to the extent of 90%) was supplied by CheMetall (D-60271 Frankfurt), *t*-BuOK by Callery (Pittsburgh, PA 15230). All commercial reagents were used without further purification. Air and moisture sensitive compounds were stored in Schlenk tubes or Schlenk burettes. They were protected by and handled under an atmosphere of 99.995% pure N_2 (glassware: Glasgerätebau Pfeifer, D-98711 Frauenwald). Et_2O and THF were dried by distillation from sodium wire after the characteristic blue color of in situ generated sodium diphenyl ketyl [14] persisted. Ethereal extracts were dried with Na_2SO_4. The temperature of dry ice/MeOH baths is indicated as –75 °C and r.t. (22–26 °C) as 25 °C. Mps are reproducible after resolidification and are corrected. Silica gel (Merck Kieselgel 60) of 70–230 mesh (0.06–0.20 mm) particle size was used for column chromatography. The solid support was suspended in hexane and, when all air bubbles had escaped, was sluiced into the column. When the level of the liquid was still some 3–5 cm above the silica layer, the dry powder, obtained by adsorption of the crude product mixture on 15–20 g silica gel and subsequent evaporation of the solvent, was poured on top of the column.

^{1}H NMR spectra were recorded at 400 MHz and ^{31}P NMR spectra were recorded at 162 MHz, chemical shifts (δ scale) referring to TMS (internal standard) and 85% aq H_3PO_3 (external standard), respectively. All samples were dissolved in $CDCl_3$. Coupling constants (J) are measured in Hz. Coupling patterns are abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), td (triplet of doublets), and m (multiplet). MS were obtained by chemical ionization in an ammonia atmosphere at 100 °C source temperature. Elemental analyses were executed by the laboratory of I. Beetz, D-96301 Kronach.

(3-Fluorophenyl)diphenylphosphine–Borane:
A solution of (3-fluorophenyl)diphenylphosphine[7] (56 g, 0.20 mol) in THF (0.25 L) was added, over the course of 30 min, to an ice-cold suspension of borane (0.21 mol) in THF (0.37 L) which had been prepared[15] from $NaBH_4$ (8.1 g, 0.21 mol) and BF_3•OEt_2 (30 mL, 34 g, 0.24 mol). After 3 h at 0 °C, the mixture was filtered and the solvent evaporated. The white powder left behind was washed with chilled water (2 × 0.20 L) and dried on burned clay. The crude product was triturated with hot i-PrOH (40 mL) to afford white crystals; mp 108–111 °C (mp 109–111 °C after recrystallization from hexane/toluene 2:1); yield: 48 g (81%).
^{1}H NMR: δ = 7.2 (6 H, m), 7.4 (6 H, m), 7.3 (1 H, m), 7.19 (1 H, t, J = 8.2 Hz, broad), 1.3 (3 H, m, broad).
^{31}P NMR: δ = 21.8.
MS (CI): *m/z* (%) = 310 (0.8, $M^+ + NH_4 - 2$), 294 (0.9, M^+), 293 (4.1, $M^+ - 1$), 280 (100), 201 (8.1), 183 (13).
Anal. calcd for $C_{18}H_{17}BFP$ (294.12) C 73.51, H 5.83; found C 73.76, H 5.79.

(3-Methoxyphenyl)diphenylphosphine–Borane:
Obtained analogously by allowing (3-methoxyphenyl)diphenylphosphine[5] (60 g, 0.20 mol) to react with borane (0.21 mol) in THF (0.37 L). After 1 h at 0 °C, the mixture was worked up as described above to afford white crystals; mp 125–127 °C (mp 126.5–128 °C after recrystallization from benzene/hexane 1:1); yield: 56 g (91%).
^{1}H NMR: δ = 7.58 (4 H, ddm, J = 10.9, 7.0 Hz), 7.51 (2 H, tq, J = 7.5, 1.4 Hz), 7.43 (4 H, tm, J = 7.3 Hz), 7.35 (1 H, td, J = 7.8, 3.1 Hz), 7.1 (2 H, m), 7.03 (1 H, dm, J = 8.2 Hz), 3.77 (3 H, s), 1.3 (3 H, m, broad).
^{31}P NMR: δ = 21.7.
MS (CI): *m/z* (%) = 307 (100, $M^+ + 1$), 293 (1.9), 231 (3.2), 199 (3.1), 152 (2.5).
Anal. calcd for $C_{19}H_{20}BOP$ (306.15) C 74.54, H 6.58; found C 74.80, H 6.53.

(2-Iodophenyl)diphenylphosphine (4):
At –75 °C, *t*-BuOK (2.2 g, 20 mmol) in THF (20 mL) and a solution of triphenylphosphine–borane[15] (5.5 g, 20 mmol) in THF (50 mL) were consecutively added to BuLi, from which the commercial solvent (hexane) had been stripped off (20 mmol). After 20 h at –75 °C, the mixture was treated with I_2 (5.1 g, 20 mmol) in THF (20 mL) before the temperature was raised to 0 °C. After vigorous shaking with 10% aq $Na_2S_2O_3$ (50 mL), the organic solvent was evaporated and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (80 mL) and dried. Evaporation of the solvent afforded 5.7 g of yellow needles. The ^{31}P NMR spectrum revealed the presence of triphenylphosphine–borane (δ = 20.8) and a new product (δ = 8.3) in the approximate ratio of 4:3. The latter was obtained pure after chromatography (silica gel, 0.15 kg, Et_2O/pentane 1:9). Adduct **4** was isolated as a white crystalline material (platelets); mp 117–120 °C (lit.[16] mp 119–120 °C); yield:1.5 g (19%).
^{1}H NMR: δ = 7.89 (1 H, ddd, J = 8.0, 3.2, 1.2 Hz), 7.3 (11 H, m), 6.99 (1 H, td, J = 7.7, 1.7 Hz), 6.79 (1 H, dt, J = 7.6, 1.2 Hz).
^{31}P NMR: δ = 8.8.
Upon oxidation with H_2O_2 (see below) and recrystallization from EtOAc, (2-iodophenyl)diphenylphosphine oxide **(1)** was obtained; mp 157–160 °C (lit.[2] mp 159–161 °C); yield: 0.46 g (30%).

(4-Iodo-3-methoxyphenyl)diphenylphosphine–Borane (5):
At –75 °C, THF (25 mL) and *t*-BuOK (2.8 g, 25 mmol) were added to BuLi, from which the commercial solvent (hexane) had been stripped off (25 mmol). A solution of (3-methoxyphenyl)diphenylphosphine–borane (7.7 g, 25 mmol) in THF (25 mL) was added dropwise over the course of 20 min. After 2 h at –75 °C, the mixture was treated

with I_2 (6.3 g, 25 mmol), as described in the preceding procedure. After washing with 10% aq $Na_2S_2O_3$ (50 mL), the product was extracted with CH_2Cl_2 (3 × 30 mL). The ^1H NMR spectrum of the yellow oil obtained revealed the presence of the starting material (methoxy signal at δ = 3.77) and of (4-iodo-3-methoxyphenyl)diphenylphosphine–borane (methoxy signal at δ = 3.81) in ca. ratio of 1:5. The former impurity was removed by trituration with hot i-PrOH (10 mL) to give an off-white fine powder; mp 120–123 °C (mp 130–132 °C after recrystallization from hexane/benzene 1: 1); yield: 6.7 g (62%).
^1H NMR: δ = 7.82 (1 H, dd *J* = 7.9, 2.6 Hz), 7.6 (6 H, m), 7.5 (4 H, m), 7.11 (1 H, dd, *J* = 12.1, 1.7 Hz), 6.74 (1 H, ddd, *J* = 10.1, 7.8, 1.6 Hz), 3.81 (3 H, s), 1.2 (3 H, large m).
^{31}P NMR: δ = 21.9.
MS (CI): *m/z* (%) = 448 (2.2, $M^+ + NH_4 - 2$), 432 (1.8, M^+), 431 (5.2), 418 (71), 292 (100).
Anal. calcd for $C_{19}H_{19}BIOP$ (432.05) C 52.82, H 4.43; found C 53.21, H 4.35.

(3-Fluoro-4-iodophenyl)diphenylphosphine–Borane (6):
At –75 °C, THF (50 mL) was added to *t*-BuLi (25 mmol), from which the commercial solvent (pentane) had been stripped off. This solution was siphoned through a cannula in the course of 30 min to (3-fluorophenyl)diphenylphosphine–borane (7.4 g, 25 mmol) in THF (50 mL) kept at –75 °C. After 2 h at –75 °C, I_2 (6.3 g, 25 mmol) in THF (25 mL) was added, the dry ice bath removed and the mixture allowed to reach 0 °C. After vigorous shaking with 10% aq $Na_2S_2O_3$ (50 mL), the organic solvent was evaporated and the aqueous phase extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (60 mL) and dried. Evaporation to dryness afforded the crude product (9.7 g) which was triturated with hot i-PrOH (7 mL); mp 117–121 °C (mp 124–125 °C after recrystallization hexane/toluene 2:1); yield: 8.2 g (78%).
^1H NMR: δ = 7.82 (1 H, ddd *J* = 8.0, 6.1, 2.6 Hz), 7.6 (6 H, m), 7.5 (4 H, m), 7.20 (1 H, ddd, *J* = 10.9, 8.0, 1.8 Hz), 7.08 (1 H, ddd, *J* = 10.1, 8.0, 1.8 Hz), 1.3 (3 H, m, broad).
^{31}P NMR: δ = 22.1.
MS (CI): *m/z* (%) = 436 (1.3, $M^+ + NH_4^+ - 2$), 420 (1.5, M^+), 406 (100), 280 (49), 183 (21).
Anal. calcd for $C_{18}H_{16}BFIP$ (420.01) C 51.47, H 3.84; found C 51.46, H 4.01.

(4-Iodo-3-methoxyphenyl)diphenylphosphine:
A solution of (4-iodo-3-methoxyphenyl)diphenylphosphine–borane (10 g, 23 mmol) in Et_2NH (80 mL) was heated under reflux for 4 h. After evaporation to dryness, the residue was dissolved in CH_2Cl_2 (100 mL), washed with 2 M HCl (2 × 50 mL) and brine (2 × 50 mL) and dried. Evaporation of the solvent afforded the product as a white powder which was crystallized from i-PrOH; mp 124–127 °C (mp 127–128 °C after recrystallization from EtOH/benzene 4:3); yield: 5.1 g (53%).
^1H NMR: δ = 7.71 (1 H, dd, *J* = 7.9, 1.6 Hz), 7.3 (10 H, m), 6.75 (1 H, dd, *J* = 8.1, 1.7 Hz), 6.58 (1 H, ddd, *J* = 8.1, 6.4, 1.6 Hz), 3.72 (3 H, s).
^{31}P NMR: δ = –4.2.
MS (CI): *m/z* (%) = 434 (0.6, $M^+ + NH_4 - 2$), 418 (100, M^+), 341 (2.8), 292 (25).
Anal. calcd for $C_{19}H_{16}IOP$ (418.21) C 54.57, H 3.86; found C 54.83, H 3.91.

(3-Fluoro-4-iodophenyl)diphenylphosphine:
Obtained analogously from (3-fluoro-4-iodophenyl)diphenylphosphine–borane (9.2 g, 22 mol); mp 63–64 °C; yield: 5.2 g (58%).
^1H NMR: δ = 7.69 (1 H, ddd, *J* = 8.1, 6.2, 1.6 Hz), 7.4 (6 H, m), 7.3 (4 H, m), 6.90 (1 H, ddd, *J* = 8.2, 6.3, 1.5 Hz), 6.82 (1 H, ddd, *J* = 9.5, 7.2, 1.8 Hz).
^{31}P NMR: δ = –5.4.
MS (CI): *m/z* (%) = 423 (0.4, $M^+ + NH_4$), 406 (100, M^+), 329 (2.8), 280 (30).
Anal. calcd for $C_{18}H_{13}FIP$ (406.17) C 53.23, H 3.23; found C 53.28, H 3.20.

(4-Iodo-3-methoxyphenyl)diphenylphosphine Oxide:
Under stirring, 30% aq H_2O_2 (1.1 mL, 1.2 g, 11 mmol) was slowly added to a suspension of (4-iodo-3-methoxyphenyl)diphenylphosphine (4.2 g, 10 mmol) in MeOH (15 mL) kept at 0 °C. After 1 h at 25 °C, sat. aq Na_2SO_3 (4 mL) and 2 M HCl (1 mL) were added. After 1 h, the organic solvent was evaporated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried. Evaporation of the solvent afforded white crystals; mp 180–183 °C (mp 186–187.5 °C after recrystallization from benzene); yield: 3.7 g (86%).
^1H NMR: δ = 7.83 (1 H, dd, *J* = 7.8, 3.3 Hz), 7.66 (4 H, ddt, *J* = 12.1, 7.0, 1.5 Hz), 7.55 (2 H, tq, *J* = 7.4, 1.5 Hz), 7.5 (4 H, m), 7.30 (1 H, dd, *J* = 12.8, 1.6 Hz), 6.76 (1 H, ddd, *J* = 11.6, 7.9, 1.7 Hz), 3.86 (3 H, s).
^{31}P NMR: δ = 28.8.
MS (CI): *m/z* (%) = 450 (0.2, $M^+ + NH_4^+ - 2$), 434 (70, M^+), 433 (100), 307 (21).
Anal. calcd for $C_{19}H_{16}IO_2P$ (434.21) C 52.56, H 3.71; found C 52.79, H 3.92.

(3-Fluoro-4-iodophenyl)diphenylphosphine Oxide:
Obtained analogously from (3-fluoro-4-iodophenyl)diphenylphosphine (4.7 g, 12 mmol); mp 116–119 °C (mp 119–120 °C after recrystallization from hexane/toluene 1:2); yield: 4.5 g (93%).
^1H NMR: δ = 7.87 (1 H, ddd, *J* = 8.2, 6.1, 3.3 Hz), 7.66 (4 H, ddt, *J* = 12.3, 7.1, 1.7 Hz), 7.59 (2 H, tq, *J* = 7.7, 1.7 Hz), 7.49 (4 H, tdt, *J* = 8.1, 3.2, 1.6 Hz), 7.33 (1 H, ddd, *J* = 12.2, 7.8, 1.7 Hz), 7.20 (1 H, ddd, *J* = 11.2, 8.1, 1.7 Hz).
^{31}P NMR: δ = 27.9.
MS (CI): *m/z* (%) = 422 (63, M^+), 421 (100), 345 (6.6), 295 (74).
Anal. calcd for $C_{18}H_{13}FIOP$ (422.17) C 51.21, H 3.10; found C 51.10, H 3.19.

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