The Di-*t*-Butylphosphinyl Directed *ortho* Metalation Group. Synthesis of Hindered Dialkylarylphosphines

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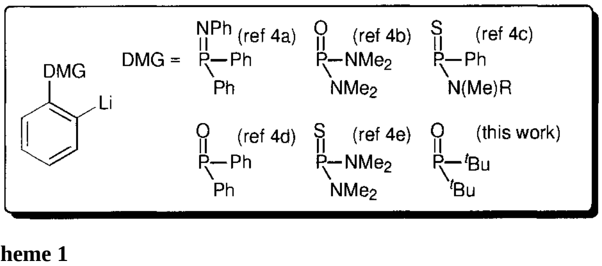
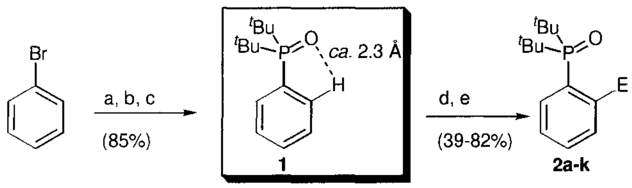
Abstract: Using the new $P(O)^tBu_2$ Directed Metalation Group, a variety of *ortho*-substituted aryl di-*t*-butylphenylphosphine oxides (**2a-k**) have been prepared, its relative metalation ability has been established, and reduction and homocoupling products (Scheme 4) have been obtained.

In the realm of heteroatom-containing Directed Metalation Groups (DMGs),[3] existing phosphorus-based DMGs (Scheme 1) exhibit limitations of synthetic inaccessibility, ineffective directing ability, and competing side reactions.[4] Of particular note is the diphenylphosphinyl DMG which allows access to important phosphino aryl ligands but is plagued with competing attack at phosphorus.[5] To overcome this limitation, Schmid[6] and Brown[7] implemented a cooperative *meta*-OMe DMG effect which allows regioselective in-between metalation using *t*-butyllithium or LDA. Herein we report on the di-*t*-butylphosphinyl DMG, assign its relative metalating position *vis a vis* other useful DMGs, and demonstrate its utility for the synthesis of diversely substituted aromatics, including sterically compromised arylphosphines, systems of increasing interest as ligands in organometallic catalysis.[8,9]



Scheme 1

Di-*t*-butylphenylphosphine oxide (**1**) was chosen for metalation studies based on the absence of α-deprotonation sites and the expectation that the hindered $P(O)^tBu_2$ moiety would serve to minimize P-nucleophilic attack. Furthermore, a calculation (MM2 force field) indicated a proximate oxygen-*ortho*-H distance (2.3 Å) which, with well-recognized *caveat* understood, suggested favorable *ortho* metalation.[10,11] Substrate **1**, readily prepared in good yield by modification of a literature procedure (Scheme 2)[6,12,13] was subjected to metalation with *t*-butyllithium (1-2 equiv), chosen largely for purposes of degeneracy. The resulting suspension of the yellow *ortho*-lithio species was treated with a representative series of electrophiles to give a range of 2-substituted arylphosphinyl derivatives **2a-k** (Table 1).[14] Thus, aside from the classical carbon electrophiles (entries 1-5), quenching with $B(OMe)_3$ followed by oxidation furnished a phosphinyl phenol (entry 7) and treatment with other heteroatom electrophiles led to silicon, phosphorus and halogen arylphosphinyl derivatives (entries 8-11). Treatment of the *ortho*-P/B substituted aromatic (entry 6) with propanediol ($MgSO_4$ / CH_2Cl_2 / rt) afforded the boronate **2f** whose X-ray structure (Figure 1)[11,15] reveals a strong boron-oxygen interaction (B-O distance = 1.67 Å) and thus a planar P-O-B heterocyclic arrangement with a tetrahedral boron atom.[16]



Scheme 2. a) *t*-BuLi / Et_2O / < -40 °C; b) $^tBu_2PCl$ / rt → reflux; c) H_2O_2 / MeOH / 0° C → rt; d) ^tBuLi / THF / -78 ° C; e) E^+

Table 1. Synthesis of Arylphosphinyl Derivatives **2a-k**[14]

entry	E^+	E	Product	Yld, %[a]	δ ^{31}P (ppm)[b]
1	MeI	Me	**2a**	82	57.4
2	EtI	Et	**2b**	39	57.9
3	Ph_2CO	$C(OH)Ph_2$	**2c**	75	59.5
4	CO_2	CO_2H	**2d**	42	60.2
5	DMF	CHO	**2e**	74	60.8
6	$B(OMe)_3$	$B(OR)_2$[c]	**2f**	65	79.5
7	$B(OMe)_3$	OH[d]	**2g**	67	68.9
8	TMSCl	TMS	**2h**	76	56.0
9	$ClPPh_2$	PPh_2	**2i**	63	54.8[e]
10	Cl_3CCCl_3	Cl	**2j**	53	62.1
11	I_2	I	**2k**	76	53.3

a) Yields of chromatographed or crystallized material showing correct analytical and/or HRMS data. b) Relative to external phosphoric acid standard. c) $(OR)_2$ = $-OCH_2CH_2CH_2O-$. d) Obtained by oxidation (NaOH / H_2O_2) of the crude boronic acid. e) ^{31}P NMR chemical shift of Ph_2P = 30.9 ppm ($^3J_{PP}$ = 4.8 Hz)

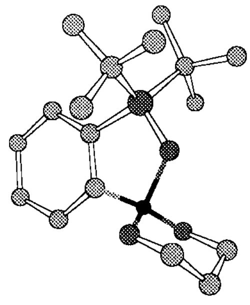
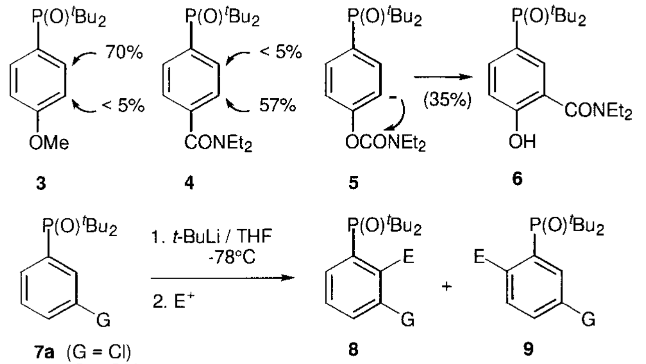


Figure 1 - X-ray structure of boronate **2f** [11,15]

In order to evaluate the relative metalating power of $P(O)^tBu_2$ in the DMG hierarchy,[3] intra- and inter-molecular competition experiments were performed on substrates **3** - **5** (Scheme 3).[17] Using kinetically limiting conditions (*t*-BuLi / THF / -78°C / 5 min)[18] and TMSCl quench, substrates **3** and **4** underwent exclusive metalation *ortho* to the phosphinyl and *ortho* to the amide group respectively (^1H NMR analysis, isolated % yields of products are shown). Metalation of **5** afforded the anionic *ortho* Fries rearrangement product **6**.[19] In intermolecular competition experiments, a 1:1 mixture of **1** and PhOMe, $PhCONEt_2$, and $PhOCONEt_2$ were allowed to compete for 1 equiv of *t*-BuLi (THF / -78°C / 5 min) followed by excess TMSCl quench. Product analysis indicates the following results: **1**:PhOMe = > 95: < 5;

1:PhCONEt$_2$ = 2:8; **1**:PhOCONEt$_2$ = < 5: > 95. With the appropriate *caveat*,[18] these results suggest an order of metalation power, DMG = OCONEt$_2$ > CONEt$_2$ > P(O)^{t}Bu$_2$ > OMe.

As an initial indication of cooperative metalation effects of the P(O)^{t}Bu$_2$ DMG, lithiation - ^{t}BuNCO quench of **7a**[17] provided a 8:1 ratio (56% combined isolated yield) of **8** and **9**. Similarly, metalation - TMSCl quench of **7b**,[17] afforded **8** as the only isolable product.

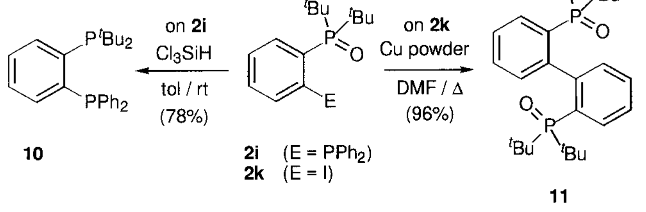


7a (G = Cl)
7b (G = OMe)

G	E	yld, %	8:9
Cl	CONH^{t}Bu	56	8:1
OMe	TMS	67	> 95:5

Scheme 3

In pursuit of chemistry of potential value for ligand studies, phosphine oxide **2i** (Scheme 4) was reduced with trichlorosilane to give the unsymmetrical bisphosphine **10** and **2k** was subjected to typical Ullmann homocoupling conditions to afford the 2,2'-bisphosphinyl biaryl **11** in excellent yield. Attempts to further metalate **11** were unsuccessful, results which may be understood on the basis of the single crystal X-ray analysis of **11**[11] which shows alignment of both oxygens towards the centres of the opposite rings thereby placing them in unfavourable orientation for directing *ortho*-deprotonation.



2i (E = PPh$_2$)
2k (E = I)

Scheme 4

In summary, this work has introduced the P(O)^{t}Bu$_2$ *ortho*-metalation group for the regiospecific synthesis of new P-based aromatics, evaluated its relative hierarchy with respect to several other DMGs, and revealed its potential for the construction of new phosphorus ligands. Extension and application of these preliminary results is under active study.

Acknowledgements

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References and Footnotes

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10. Supported by X-ray crystal structure data (2.498 Å).
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13. Compound **1** was also prepared (44% yield) by treatment of phenyldichlorophosphine with *t*-BuLi (2 equiv) in toluene at 0°C followed by reflux (12 h) and hydrogen peroxide oxidation. Although less general, this method is particularly useful for preparation of large quantities of **1**. The use of toluene as the solvent is crucial; in THF or Et$_2$O, no product was isolated.
14. *Typical Experimental Procedure.* To a solution of di-*t*-butylphenylphosphine oxide (**1**) (302 mg, 1.27 mmol) in anhyd THF (8 mL) at < -70°C (CO$_2$/acetone bath) was added dropwise *t*-BuLi (0.99 mL, 1.39 mmol, 1.4 M in pentane) and the reaction mixture was stirred (80 min). The yellow suspension was treated via cannula with a solution of I$_2$ (354 mg, 1.39 mmol) in THF (5 mL) and the resulting red solution was warmed to rt over 8-10 h. Addition of aq Na$_2$S$_2$O$_3$ and standard work up, followed by flash chromatography (5:1 EtOAc/hexane eluent) afforded 352 mg (76% yield) of **2k** as a colourless solid, mp 164.5-165°C (Et$_2$O/CH$_2$Cl$_2$); IR (KBr) 1164 cm^{-1}; ^{1}H NMR (CDCl$_3$, 250 MHz) δ 8.15 (ddd, 1H, J = 1.3, 2.1, 8.0 Hz), 7.54 (ddd, 1H, J = 1.5, 7.6, 7.7 Hz), 7.37 (dddd, 1H, J = 1.4, 2.2, 7.5, 7.7 Hz), 7.09 (dddd, 1H, J = 1.5, 3.0, 7.6, 7.7 Hz), 1.33 (d, 18H, J = 13.6 Hz); ^{13}C NMR (CDCl$_3$, 63 MHz) 144.4 (d, J = 8.0 Hz), 132.5 (d, J = 11.4 Hz), 131.7, 131.3 (d, J = 76.5 Hz), 125.8 (d, J = 10.0 Hz), 98.7, 37.2 (d, J = 59.1 Hz), 27.5; m/z (EI) 364 (M$^+$); Anal Calcd for $C_{14}H_{22}IOP$: C, 46.17; H, 6.09; P, 8.50. Found: C, 45.95; H, 5.89; P, 8.69.
15. Crystal data for **2f**: $C_{20}H_{35}BO_3P$, M_r = 365.28, monoclinic, C2/c, a = 20.663(2), b = 13.337(1), c = 15.604(2) Å, β = 101.745(7)°, V = 4210.0(10) Å^3, Z = 8, F(000) = 1592, D_c = 1.153 g/cm^3, T = 160K. Data were collected on a Siemens P4 Diffractometer with MoKα radiation (λ = 0.71073 Å). A total of 3689 independant reflections were measured. The structure was solved using direct

methods (SHELXTL IRIS) and refined by full-matrix least-squares on F (270 parameters) resulting in final R, wR, and GoF values of 4.17, 5.32, and 3.56 respectively [for 2731 data with $F > 6.0\sigma(F)$]. The compound co-crystallized with a disordered hexane molecule (compound : solvent = 2:1).

16. Comparison with structures of other phosphine oxides (Haque, M.-u.; Ahmed, J.; Horne, W. *Acta Cryst.* **1983**, *C39*, 383; Campbell, J.A.; Caughlan, C.N.; Fitzgerald, A.; Campana, C.; Cremer, S.E. *Acta Cryst.* **1984**, *C40*, 1918) shows a slightly longer than average P-O bond length (1.533 Å). Similar comparison with trigonal planar boronate esters (Matsubara, H.; Tanaka, T.; Takai, Y.; Sawada, M.; Seto, K.; Imazaki, H.; Takahashi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2103; Kliegel, W.; Preu, L.; Rettig, S.J.; Trotter, J. *Can. J. Chem.* **1986**, *64*, 1855) and tetrahedral borates (Ahlenstiel, E.; Kliegel, W.; Rettig, S.J.; Trotter, J. *Can. J. Chem.* **1993**, *71*, 263) shows that the ester B-O bond lengths are longer than would be expected for trigonal planar boronates and are more in line with a tetrahedral arrangement. Furthermore, the ^{31}P NMR chemical shift (79.5 ppm) suggests that the tetrahedral structure dominates in solution as well as in the solid state.

17. Compound **4** was obtained from the corresponding acid which was prepared according to a literature procedure (Malakhova, I.G.; Tsvetkov, E.N.; Kabachnik, M.I. *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1975**, *24*, 164). Compounds **5** and **3** were prepared by metal-halogen exchange (*t*-BuLi / THF / -78 °C) of the *t*-butyldimethylsilyl ether of 4-bromophenol followed by ClP^tBu_2 quench and H_2O_2 oxidation, desilylation (CsF / THF-DMF) and carbamoylation ($ClCONEt_2$ / K_2CO_3 / MeCN) and methylation (MeI / K_2CO_3 / MeCN) in 60% and 63% overall yields respectively. Compounds **7a** and **7b** were prepared from the corresponding bromo derivatives according to the protocol in Scheme 2 (73 and 58% yields respectively).

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