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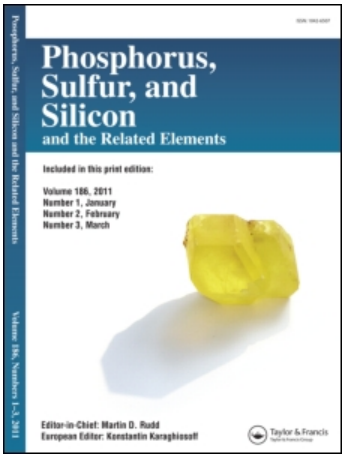

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ON THE DIRECT METALATION OF TERTIARY PHENYLPHOSPHINES

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ON THE DIRECT METALATION OF TERTIARY PHENYLPHOSPHINES

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We have envisaged a route towards ortho-phosphinobenzoic acids via direct ortho-metalation of tertiary phenylphosphines. The direct metalation of tertiary phenylphosphines with BuLi/KOt-Bu or BuLi/TMEDA proves to be an a-selective process. After carbonation mixtures of carboxylic acids are obtained. With BuLi/KOt-Bu/THF the reaction occurs preferably at the meta and para positions. With BuLi/TMEDA/hexane all three possible positions are metalated. Introduction of an auxiliary methoxy group leads to a higher selectivity. Blocking of all meta and para positions with methoxy groups leads to metalation in the ortho position. The rate of metalation at the ortho position is relatively slow. Observed side reactions are: substitution of phenyl groups, α-metalation, and substitution of a methoxy group.

Key words: metalation; butyllithium; phosphinobenzoic acid; phosphine; carbonation; substitution.

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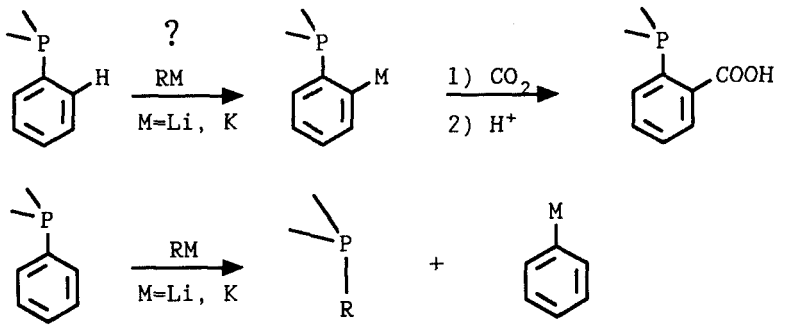
INTRODUCTION

The phosphorus atom of tertiary phosphines binds very weakly to alkali metal ions. This will impede the formation of an intermediate complex of the metalating reagent and the phosphine in which the anionic fragment of the reagent is held in close proximity to the ortho hydrogens. Further, only a weak stabilization, if any at all, of an ortho-metalated species will occur by intramolecular coordination with the phosphorus atom.

Phosphine moieties are mildly electron-withdrawing, however, and thus could promote selective ortho-metalation, as has been observed with other electron-withdrawing substituents (F and CF_3; σ Ph_2P = +0.19,[1,2] σ CF_3 = +0.53).



Only a few examples exist of the direct metalation of tertiary phenylphosphines. Gilman and Brown[3] have obtained 3-diphenylphosphinobenzoic acid in 6% yield by lithiation of triphenylphosphine with butyllithium and subsequent carbonation.

Peterson[4] has reported an a-selective (di)metalation of dimethylphenylphosphine with *t*-butyllithium. Horner and Simons have metalated diphenylphosphinohydroquinone ethers.[5] Kellner and Tzschach[6] have found a selective ortho-metalation using auxiliary dimethylaminomethyl groups attached to the phosphorus atom. Direct metalation of tertiary phenylphosphines may be frustrated because of a nucleophilic displacement reaction at the phosphorus atom,[7] as depicted.

We have used two powerful metalation reagents; "butylpotassium" and BuLi/TMEDA. Butylpotassium was prepared in situ by the addition of BuLi in hexane to a mixture of the phosphine and KOt-Bu in THF at −78°C. In this system metalation of the aryl group has to compete with the reaction of BuK with THF[8] and can only occur when metalation is a fast process (kinetic conditions). Reaction with BuLi/TMEDA in hexane at room temperature allows equilibration of metalated species and the most stable lithium compound will be formed (thermodynamic conditions). The metalated species were carbonated at −78°C by a rapid stream of CO_2. Standard work-up allows a ready separation of carboxylic acids from neutral material.

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RESULTS

As expected,[7] reaction of triphenylphosphine **1** with BuLi/MOt-Bu at −78°C in THF leads to substitution of phenyl groups.

$$\underset{\mathbf{1}}{Ph_3P} + BuLi/MOt\text{-}Bu \rightarrow Bu_nPh_{(3-n)}P$$

$M = Na, \quad n = 1$
$M = K, \quad n = 1, 2$

Upon carbonation, a very small amount of an acidic fraction is obtained ($M = K$) which according to ^{31}P NMR consists of butylphosphinobenzoic acids. The substitution reaction is strongly suppressed when phenyl groups are replaced by an electron-releasing alkyl group. We have found that isopropyldiphenylphosphine **2** and dibutylphenylphosphine **5** are metalated by BuLi/KOt-Bu, but a mixture of carboxylic acids is obtained after carbonation (30–40% total yield). Compound **2** gives a mixture of two acids, the meta and para benzoic acids **3** and **4** (ratio ca. 1:1). Dibutylphenylphosphine **5** gives a mixture of four acids: the meta and para benzoic acids **7** and **8** (1:1) and two compounds which were tentatively assigned as two diastereoisomers of phosphinoacetic acid **15** on the basis of their respective ^{31}P chemical shifts (δ ^{31}P −12.6 and −13.2; yield ca. 10%) and their ready conversion to the starting material **5** on warming[9] of the solution. The latter compounds are formed through α-metalation of a butyl group. Thus from both **2** and **5** none of the ortho acid is obtained.

Metalation of **5** with BuLi/TMEDA in hexane and subsequent carbonation leads to a mixture of five carboxylic acids, **7** (55%), **8** (25%), **15** (10%, two diastereomers, see above), and the ortho-benzoic acid **6** (10%). Warming of the mixture leads to decarboxylation of **15**. The Figure shows the ^1H COSY spectrum of the mixture of the three benzoic acids **6**, **7**, and **8** in C_6D_6; the data are presented in the Table.

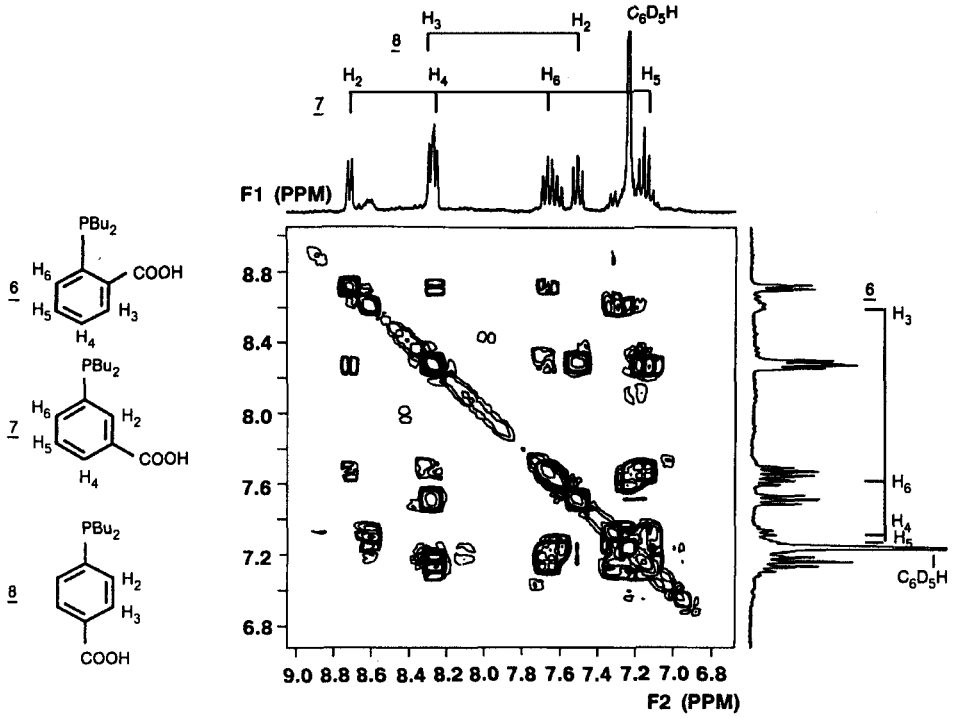

FIGURE ^1H COSY spectrum of 6, 7 and 8 in C_6D_6 at 300 MHz.

TABLE

Selected NMR data of alkylphosphinobenzoic acids[a]

^{13}C[b]	3	4	7	8	^1H[b]	6	7	8
1	138.6(15.3)	145.2(18.4)	140.3(18.2)	147.3(19.6)	H2		8.67(6)	7.46(6)
2	134.6(19.1)	132.8(18)	133.6(16.6)	131.8(17.6)	H3	8.56		8.23
3	129.6(6)	c	129.5(7.1)	129.6(6.4)	H4	7.27	8.22	
4	c	129.4	129.1	130.1	H5	7.2	7.11	
5	c		128.3(9)		H6	7.57	7.62(7)	
6	138.3(21)		137.7(20.4)					
CO	171.0	171.0	172.0	172.0				

[a] ^{13}C data in $CDCl_3$; ^1H data in C_6D_6.
[b] CP is C_1 and so on, for numbering of hydrogens see the Figure.
[c] Resonates in the expected region, no assignment possible due to overlap with other peaks.

The structure of **6** which is formed in a relative small amount was tentatively assigned on the basis of its ^1H NMR spectrum. The COSY experiment shows that the molecule contains four CH fragments in an arrangement as required for **6**.

We have attempted to make the metalation reaction more selective by the introduction of a methoxy group in the meta position. Methoxy groups strongly favor ortho-metalation, which in compound **9** could occur in an ortho or a para position with respect to the phosphorus atom. We have found that metalation of **9** is favored

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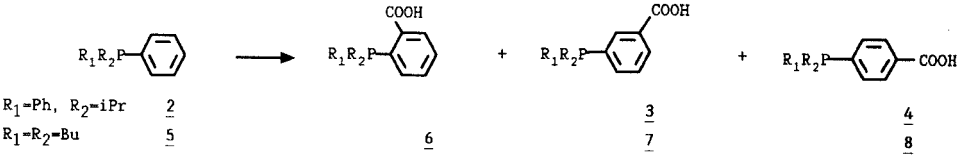
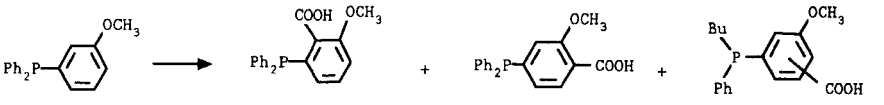
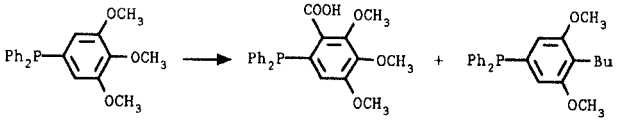
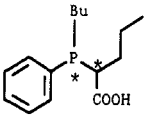
over nucleophilic substitution of phenyl groups (vide supra); a high yield of carboxylic acid is obtained after carbonation of the metalated species. Thus it would appear that the rate of metalation has been increased with respect to that of triphenylphosphine by the introduction of the methoxy group. Reaction with BuLi/KOt-Bu and subsequent carbonation leads to para-substituted benzoic acid **11** in ca. 75% yield. None of the corresponding ortho isomer **10** is formed. A similar selectivity was reported by Horner and Simons in the reaction of phosphinohydroquinone ethers and BuLi in THF.[5]

In contrast to reactions in THF, the reaction of **9** with BuLi/TMEDA in hexane at room temperature followed by carbonation at −78°C leads to a mixture of the ortho and para benzoic acids (ratio **10**:**11** = 2:3). The compounds were separated chromatographically and their structures were assigned unambiguously on the basis of their ^{1}H, ^{13}C and ^{31}P NMR spectra. Further blocking of the remaining meta and para positions with methoxy groups, as in diphenylphosphino-3,4,5-trimethoxybenzene **12**, leaves only the ortho positions available for metalation. Compound **12** indeed gives the ortho benzoic acid after metalation with BuLi/TMEDA/hexane and subsequent carbonation but only in ca. 30% yield. In addition, **14** is obtained by substitution of a methoxy group. The yield of this side reaction can be improved to virtually 100% by reaction of **12** and BuLi in hexane without TMEDA.[10] We have not observed products that would result from a nucleophilic substitution of phenyl groups. With KOt-Bu/BuLi/THF a very low yield (<1%) of the acid **13** is formed and most of the starting material is recovered. This suggests that the rate of ortho-metalation is lower than that of metalation of THF.









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We have not observed products that arise from metalation of the unsubstituted phenyl rings with either of the two metalating agents.

CONCLUDING REMARKS

Phosphino groups do not lead to a selective otho-metalation reaction. This is in contrast to substituents containing five-valent phosphorus atoms (ylides,[11] phosphine oxides,[11] and phosphates).[12] Also, the effects are remarkably different from those of $(CH_3)_2N$ and *t*-BuS groups[8] which promote metalation of the ortho position. Reaction of BuLi/TMEDA/hexane leads to metalation in the ortho position whereas reaction of BuLi/KOt-Bu/THF does not. This suggests that the metalation of the ortho position is slow with respect to metalation of the meta and para positions or of THF.

The selectivity of the direct metalation of phenylphosphines appears to be similar to that of alkyl-[13,14] or silylbenzenes.[14]

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EXPERIMENTAL

Starting materials were obtained commercially or were prepared by well established literature methods. In all experiments with phosphorus compounds oxygen was excluded using Schlenk-type glassware. THF was distilled from sodium/benzophenone.

The NMR spectra were recorded on Varian 200 and 300 MHz instruments. The data are presented below and in the Table. Coupling constants are given in Hz; coupling with phosphorus is given in parentheses and *J*(CH) in square brackets. Chemical shifts are reported in ppm. The CP carbon is numbered C_1, H_2 is the hydrogen atom attached to C_2, and so on. Phosphine oxides were prepared by the addition of *t*-BuOOH to a solution of the phosphine; sulfides were prepared by the addition of elemental sulfur. These derivatives were not isolated and were prepared for spectroscopic characterization of the structure of the parent compound.

Metalation of **9** *with KOt-Bu/BuLi/THF.* To a mixture of 10.0 g (34.25 mmol) of **9**, 3.85 g (34.4 mmol) of KOt-Bu, and 100 ml of dry THF 21.5 ml of BuLi (1.6 M in hexane) was added in 10 minutes at −78°C. The solution was left for 1 h at this temperature and subsequently carbonated with a rapid stream of CO_2. The THF was removed in vacuum. Ether and water were added to the residue. The water layer was separated off and filtered. Acidification with HCl until pH = 3 gave 8.55 g of carboxylic acids (ca. 90% of **11** and 10% of an acid with one butyl group attached to the phosphorus atom (see the Scheme), δ ^{31}P −13.8, δ ^1H 0.9 (3H), 1.4 (4H), 2.05 (2H)). The ether layer yielded 1.4 g of a neutral fraction, which consisted of the starting material (ca. 50%) and various butylphosphines (δ ^{31}P −15.7, −16.6 and −24.8 ppm).

Metalation of **9** *with BuLi/TMEDA/hexane.* To a mixture of 10.48 g (35.9 mmol) of **9**, 5.4 ml TMEDA, and 50 ml of hexane 23 ml of BuLi (1.6 M in hexane) was added at −78°C. The cooling bath was removed and the mixture was stirred at room temperature for 70 h. After cooling to −78°C a rapid stream of CO_2 was passed through the mixture. Subsequently, the cooling bath was removed and at room temperature water was added. The water layer was separated off and filtered. Acidification with HCl gave a thick oil. Stirring for two days while a gentle stream of argon was passed over the two-phase system afforded to a white solid material. This was filtered off, washed with water and dried in vacuum. Yield 8.4 g (25.0 mmol, 70%) of a mixture of **10** and **11** (2:3). The compounds were separated by chromatography over Kieselgel 60 (Merck). As eluent we used $CHCl_3$ with 1% of methanol. The para compound **11** eluted faster than the ortho acid **10**.

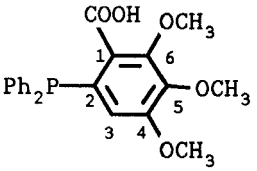
Analytical data of **10**: According to elemental analysis this compound contains some inorganic material from the column (ca. 3% by weight, calculated as SiO_2). Solutions were centrifuged before the NMR spectrum was recorded.

NMR ($CDCl_3$): ^1H, H_4 7.00, H_5 7.35, H_6 6.67 (3.5), CH_3O 4.00, Ph 7.3; ^{13}C, (J_{CP}), C_1 142.2 (25.3), C_2 124.6 (25.1), C_3 157.7 (6.6), C_4 111.7, C_5 131.9, C_6 127.4, CH_3O 56.6, CO 167.4, *i* 137.6 (10.7), *o* 133.8 (20.4), *m* 128.4 (7.1), *p* 128.6; ^{31}P, −5.2.

NMR phosphine sulfide ($CDCl_3$): ^1H, H_4 7.12 (1), H_5 7.36 (3.5), H_6 6.95 (14), CH_3O 3.88: ^{31}P, 43.7.
Analytical data of **11**: melting point 195°C. Elemental analysis: $C_{20}H_{17}O_3P$ requires C 71.42, H 5.10, P 9.21%. Found: C 71.30, H 5.19, P 9.24%.
NMR ($CDCl_3$): ^1H, H_2 6.92 (8), H_5 8.09 (6.5), H_6 6.97 (1.5), CH_3O 3.89, COOH 10.6, Ph 7.3–7.4; ^{13}C, (J_{CP}), C_1 146.8 (16.7), C_2 115.9 (22.8), C_3 157.7 (7.4), C_4 117.2, C_5 132.7 (6.4), C_6 125.7 (15.8), CO 166.2, CH_3O 56.1, *i* 135.3 (10), *o* 133.6 (20.2), *m* 128.4 (7.3), *p* 129.1; ^{31}P, −4.3.
NMR phosphine oxide ($CDCl_3$): ^{31}P, 29.8.
NMR phosphine sulfide ($CDCl_3$): ^1H, H_2 7.79 (17), H_5 8.13 (4), H_6 7.13 (11.4), CH_3O 4.02; ^{31}P, 42.6.

Diphenylphosphino-3,4,5-trimethoxybenzene **12**. Lithio-3,4,5-trimethoxybenzene was prepared from the bromide[8] (25.0 g, 101.2 mmol) in ether (80 ml). At −78°C a solution of 18.4 ml Ph_2PCl (100.8 mmol) in 100 ml of ether was added, after the addition the cooling bath was removed and the mixture was refluxed for 10 min. Standard work-up and crystallization from hexane gave 27.7 g (78.7 mmol; 77.8%) of pure product. Reaction of the lithium compound with Ph_2PCl in THF or of a Grignard reagent with Ph_2PCl led to a less pure product.
Exact mass: calc. 352.1228; found 352.1218
NMR phosphine ($CDCl_3$): ^1H, CH 6.51 (8), OCH_3 (6H) 3.70, (3H) 3.84; ^{13}C, (J_{CP}), C_1 131.8 (10.7), C_2 110.8 (22.0) [160.9, 8.4], C_3 153.2 (9.6), C_4 138.6, *i* 137.3 (11.5), *o* 133.5 (19.4) [160.1], *m* 128.4 (6.8) [158.5], 128.7 [160.9], CH_3O at C_3 56.0 [142.8], CH_3O at C_4 60.8 [142.8], ^{31}P, −3.4.
NMR phosphine sulfide ($CDCl_3$): ^1H, CH 6.90, OCH_3 (6H) 3.74, (3H) 3.87, Ar 7.5 and 7.7; ^{31}P, +43.9.
NMR phosphine oxide ($CDCl_3$): ^{13}C, (J_{CP}), C_1 126.4 (106.6), C_2 109.0 (11.7), C_3 153.0 (17.7), C_4 140.9 (2.8), CH_3O at C_3 55.9, CH_3O at C_4 60.5.

Metalation of **12**. To a mixture of 4.36 g (12.4 mmol) of **12** and 2.5 ml of TMEDA in 100 ml hexane 7.6 ml of BuLi (1.6 M in hexane) was added. The mixture was kept at room temperature for four hours. Then the suspension was cooled to −78°C, 100 ml of THF was added, a clear solution was obtained, and a rapid stream of CO_2 was passed through. Work-up gave crude **13**, washing with diethyl ether afforded the pure material (1.57 g; 32%). A longer reaction time (20 h) did not lead to an improved yield.
Melting point 150°C. Elemental analysis: $C_{22}H_{21}O_5P$ requires C 66.66, H 5.34, P 7.81%. Found: C 66.42, H 5.52, P 7.90.
NMR ($CDCl_3$) phosphine: ^1H, 6.28 (3.5), OCH_3 4.08, 3.89, 3.52, Ar 7.3; ^{13}C, (J_{CP}), C_1 122.0 (23.3), C_2 136.7 (27), C_3 114.1 [162], C_4 155.1, C_5 141.6, C_6 152.7 (6.7), COOH 166.8, CH_3O 62.5, 60.9 and 55.5, *i* 138.0 (11.9), *o* 133.7 (20.5) [160], *m* 128.4 (7.0) [161], *p* 128.6 [161]; ^{31}P −3.2.
NMR ($CDCl_3$) phosphine sulfide: ^1H, 6.99 (16), OCH_3 3.91, 3.87, and 3.64, Ar 7.4 and 7.7; ^{31}P, +44.9.



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