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Synthesis of symmetrical triarylphosphines from aryl fluorides and red phosphorus: scope and limitations

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Abstract—The reaction of aryl fluorides with phosphide anion, generated in situ from the reduction of red phosphorus by lithium metal in liquid ammonia, gave symmetrical triarylphosphines in fair to good yields. Phosphonodiamide, sulfonamide, 2-oxazolyl, and nitrile groups were stable to the reaction conditions, while nitro and bromo substituents were not. *para*-Substituted aryl fluorides gave higher yields than *meta*-substituted aryl fluorides, and *ortho*-substituted aryl fluorides failed to react. © 2001 Published by Elsevier Science Ltd.

Functionalized triarylphosphines are widely used as ligands for transition metal complexes[1] and as synthetic intermediates for the preparation of novel materials.[2] The classical method for preparing triarylphosphines involves the reaction of Grignard reagents or aryllithium reagents with phosphorus halides.[3] More recent methods include the palladium-catalyzed phosphination of aryl triflates using triarylphosphines,[4] the palladium-catalyzed coupling of aryl halides with trimethylstannyl- or trimethylsilyldiphenylphosphines,[5] nucleophilic phosphanylation of aryl fluorides in superbasic media,[6] palladium-catalyzed P-C cross-coupling reactions of primary and secondary phosphines with functionalized aryl iodides,[7] or a combination of nucleophilic phosphanylation and palladium-catalyzed P-C coupling.[8]

Our interest in the symmetrical triarylphosphine P(4-$C_6H_4PO_3Na_2)_3$, triphenylphosphine triphosphonate (TPPTP), led us to the development of a synthesis of this compound,[9] which combines the nucleophilic aromatic substitution chemistry of aryl fluorides with the in situ formation of phosphide anion in liquid ammonia using red phosphorus and alkali metals.[10] In this way, the use of the very expensive and toxic phosphine gas was avoided.

The surprising result of this preparation was that the triarylphosphine was formed almost exclusively, even when sub-stoichiometric amounts of the aryl fluoride precursor were used. The selectivity of the reaction and convenience of the preparation prompted us to investigate whether this methodology was general in scope.

In a typical reaction,[9] a suspension of red phosphorus in liquid ammonia is stirred with three equivalents of lithium metal in the presence of one equivalent of *tert*-butanol, added slowly as a 10% solution in THF. The presence of a proton donor accelerates the reduction of the red phosphorus and is believed to result in an equilibrium mixture of H_2P^- and $LiNH_2$.[10] A THF solution of the aryl fluoride is then added dropwise and the reaction is stirred at reflux (−33°C).

With reactive substrates, an immediate color change is observed, and the reaction mixture becomes a deep red by the end of the addition. In these cases, the dry ice in the Dewar condenser is not replenished, and the liquid ammonia is allowed to slowly evaporate while stirring the reaction mixture at room temperature overnight. The work-up consists simply of adding water and ether to the residual reaction mixture, filtering if necessary, and separation of the phases.

We have found that the reaction is restricted to activated aryl fluorides containing electron-withdrawing groups in the *para*- or *meta*-position. In contrast to nucleophilic phosphanylations with PH_3 in DMSO[6a] or Ph_2PK in DME or THF,[11] the reaction failed for *ortho*-substituted aryl fluorides, presumably because

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steric or electronic effects unfavorable to nucleophilic aromatic substitution cannot be overcome at the low reaction temperatures. Phosphonodiamide, sulfonamide, and 2-oxazolyl substituents were found to be compatible with the reaction conditions, but a bromo substituent was not. Nitrile groups may be used at low temperatures (−78°C), while nitro groups were not tolerated even at low temperatures. The results are summarized in Table 1.

The use of 2-fluoropyridine as a substrate deserves additional comment. The addition of 2-fluoropyridine to the phosphide solution resulted in darkening of the reaction mixture from yellow to brown to deep red, characteristic of all the successful reactions. After overnight stirring, $^{31}P\{^{1}H\}$ NMR analysis of the reaction mixture showed very little product in the region expected for a triarylphosphine. The major product appeared at 14.6 ppm, with only a small peak at −4.4 ppm, assigned to P(2-Pyr)$_3$, in approximately a 20:1 ratio.

The resonance at 14.6 ppm was consistent with the formation of the known compound [(THF)$_2$Li(μ-Pyr)$_2$P] (**1**), δ 13.0 ($CDCl_3$), an unusual structure with a divalent phosphorus atom.[13]

Heating of the reaction mixture (2 h, reflux) changed the ratio of the areas of the peaks assigned to **1** and P(2-Pyr)$_3$ to 2.5:1. Overnight heating resulted in decomposition.

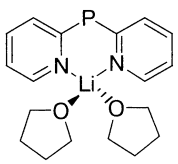

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Table 1. The reaction of phosphide anion with aryl fluorides in liquid ammonia/THF

Entry	Substrate	Product[a]	Yield[b]
1	2-FC_5H_4N	[Li(2-Pyr)$_2$P·2THF][c]	(Not isolated)
2	2-FC_6H_4OMe	No reaction	
3	2-$FC_6H_4P(O)(NEt_2)_2$	No reaction	
4	3-$FC_6H_4P(O)(NMe_2)_2$	P[3-$C_6H_4PO_3H_2$]$_3$·2H_2O	37[d]
5	3-FC_6H_4-ox[e]	No reaction	
6	4-$FC_6H_4P(O)(NMe_2)_2$	P[4-$C_6H_4P(O)(NMe_2)_2$]$_3$	60
7	4-FC_6H_4-ox	P(4-C_6H_4-ox)$_3$	36
8	4-$FC_6H_4SO_2NEt_2$	P(4-$C_6H_4SO_2NEt_2$)$_3$	54
9	4-FC_6H_4CN	P(4-C_6H_4CN)$_3$	37[f]
10	4-FC_6H_4Br	Uncharacterized mixture	
11	4-$FC_6H_4NO_2$	Uncharacterized mixture	

[a] All products had satisfactory ^{31}P and ^{1}H NMR spectra.[12]
[b] Isolated yield after work-up and purification by column chromatography or crystallization.
[c] Identified from ^{31}P NMR analysis of reaction mixture (cf. Ref. 13).
[d] Isolated as phosphonic acid dihydrate after hydrolysis of crude phosphonodiamide in 2.4 M HCl and crystallization.
[e] ox = 4,5-dimethyl-2-oxazol-2-yl.
[f] Reaction carried out at −78°C.

The method is somewhat limited by the availability of aryl fluoride precursors. For the preparation of phosphonate-substituted triaryl phosphines, fluoroaryl phosphonodiamides are the precursors of choice. In contrast to phosphonodiesters,[8,9,14] the phosphonodiamide moiety is stable to the reaction conditions, yet can be readily hydrolyzed to the corresponding phosphonic acid by refluxing in dilute HCl.

Aryl phosphonodiamides are most easily prepared by the reaction of an aryllithium reagent with *N*,*N*,*N*′,*N*′-tetraalkylphosphonodiamidic halides. Thus, *N*,*N*,*N*′,*N*′-tetramethyl-(4-fluorophenyl) phosphonodiamide was readily prepared by metal–halogen exchange of 1-bromo-4-fluorobenzene with *n*-butyllithium, and reaction of the resulting 4-fluorophenyllithium with *N*,*N*,*N*′,*N*′-tetramethyl phosphonodiamidic chloride in THF at −78°C.[9] However, this method failed for *ortho*- or *meta*-bromofluorobenzenes because of competing benzyne formation.

The *meta*-substituted aryl fluoride precursor *N*,*N*,*N*′,*N*′-tetramethyl-(3-fluorophenyl)phosphonodiamide was prepared in low yield by the reaction of the Grignard reagent derived from 1-bromo-3-fluorobenzene and *N*,*N*,*N*′,*N*′-tetramethylphosphono diamidic chloride in THF at reflux. A significant amount of the Grignard homocoupling product difluorobiphenyl was formed instead, which was identified by GC/MS analysis. The sluggish reaction of Grignard reagents with the phosphonodiamidic chloride is in sharp contrast to the reaction with aryllithium reagents.

The *ortho*-substituted aryl fluoride precursor *N*,*N*,*N*′,*N*′-tetraethyl-(2-fluorophenyl)phosphonodiamide was prepared in a multistep sequence: Diethyl 2-fluorophenyl phosphonate was prepared by the palladium-catalyzed reaction of 1-bromo-2-fluorobenzene and diethyl phosphite.[15] The ester was cleaved by transesterification with bromotrimethylsilane[16] followed by methanolysis to give the free acid. The phosphonic acid was converted to the phosphonyl dichloride by refluxing in thionyl chloride, and finally to the diamide by treatment with diethylamine.

Attempts to prepare aryl phosphonodiamides by the palladium(0)-catalyzed coupling of bis(diethylamido)-phosphite, $(Et_2N)_2P(O)H$,[17] with aryl iodides ($Pd(PPh_3)_4/Et_3N$/THF or $Pd(OAc)_2$-dppe/Et_3N/THF) were unsuccessful, as was the use of a Hiyama-type cross-coupling reaction[18] with $(Et_2N)_2P(O)SiMe_3$[19] ($Pd_2(dba)_3/AsPh_3$/TBAF/THF).

In our previous attempts to react a fluoroaryl phosphonate salt directly with phosphide anion in NH_3/THF,[9] it was found that the low solubility of the disodium salt led to no reaction of the aryl fluoride. In this study we observed that the lithium salt of 4-fluorobenzoic acid, prepared by carefully titrating a THF solution of 4-fluorobenzoic acid with *n*-BuLi at −78°C, was soluble in the reaction mixture. The lithium carboxylate was

not soluble in THF alone, so it was added in small portions directly to the reaction mixture. The reaction was quite sluggish, however, and did not go to completion. ^{31}P NMR analysis of the crude product after work-up showed approximately a 4:1 ratio of tertiary and secondary phosphines, along with a small amount of diarylphosphine oxide. ^{19}F NMR analysis confirmed the presence of some unreacted starting material as well.[20] The mixture of carboxylated phosphines and starting material could not be satisfactorily purified. For this reason we chose to prepare the more soluble oxazoline derivatives of 3- and 4-fluorobenzoic acids.

Several attempts were made to convert 4-fluorobenzoic acid to its 2-oxazoline derivative, either by refluxing the benzoic acid with 2-amino-2-methylpropanol in toluene,[21] or conversion of the benzoic acid to the acid chloride, followed by condensation with 2-amino-2-methylpropanol to form the amide, and cyclization with thionyl chloride.[22] In our hands, neither of these procedures worked very well. The 2-oxazoline derivatives, 4,4-dimethyl-2-(4-fluorophenyl)-2-oxazoline and 4,4-dimethyl-2-(3-fluorophenyl)-2-oxazoline, were eventually prepared by the palladium(0)-catalyzed coupling[23] of 4,4-dimethyl-2-(tri-*n*-butylstannyl)-2-oxazoline with 1-bromo-4-fluorobenzene and 1-bromo-3-fluorobenzene, respectively. Surprisingly, while the *para*-substituted aryl fluoride reacted cleanly with phosphide anion, the *meta*-isomer did not react at all.

In summary, we have shown that activated aryl fluorides can react with phosphide anion in liquid ammonia/THF to give tertiary phosphines in fair to good yields. Although limited in scope, this method can provide easy access to some functionalized triarylphosphines without the use of phosphine gas.

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Hz, 22 Hz), 133.8 (dd, $J=7$ Hz, 185 Hz), 132.8 (d, $J=10$ Hz), 130.0 (dd, $J=6$ Hz, 15 Hz). The chemical structure was confirmed by single-crystal XRD (crystallographic data to be published elsewhere). P(4-C_6H_4-ox)$_3$: ^{31}P NMR ($CDCl_3$): δ −4.8 (s); ^{1}H NMR ($CDCl_3$): δ 7.93 (dd, $J=7.4$ Hz, 13.2 Hz, 6H), 7.34 (m, 6H), 4.11 (s, 6H), 1.39 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 161.4 (s), 139.8 (d, $J=13$ Hz), 133.3 (d, $J=20$ Hz), 128.5 (s), 128.1 (d, $J=7$ Hz); ES-MS: m/z 554.4 $[M+H]^+$ (100%), 555.3 (34%). P(4-$C_6H_4SO_2NEt_2$)$_3$: ^{31}P NMR ($CDCl_3$): δ −5.5 (s); ^{1}H NMR($CDCl_3$): δ 7.80 (dd, $J=1.2$ Hz, 8.4 Hz, 6H), 7.39 (m, 6H), 3.26 (q, $J=7.1$ Hz, 12H), 1.15 (t, $J=7.1$ Hz, 18H); ^{13}C NMR ($CDCl_3$): δ 141.5 (s), 140.4 (d, $J=20$ Hz), 134.0 (d, $J=81$ Hz), 127.0 (d, $J=7$ Hz); ES-MS: m/z 668.4 $[M+H]^+$ (100%), 669.4 (48%), 670.3 (26%). P(4-C_6H_4CN)$_3$ has been previously described: Ravindar, V.; Hemling, H.; Schumann, H.; Blum, J. *Synth. Commun.* **1992**, *22*, 841–851.

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