A novel synthesis of unsymmetrical tertiary phosphines: selective nucleophilic substitution on phosphorus(III)

Sumita Singh and Kenneth M. Nicholas*

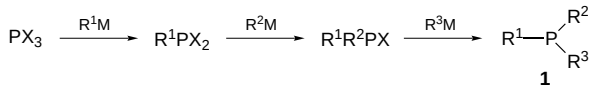
Department of Chemistry and Biochemistry, University of Oklahoma, Norman, OK, 73019, USA

A new synthesis of unsymmetrical tertiary phosphines has been developed employing selective, sequential alkylation of chloroaminophosphines by Grignard and organolithium reagents.

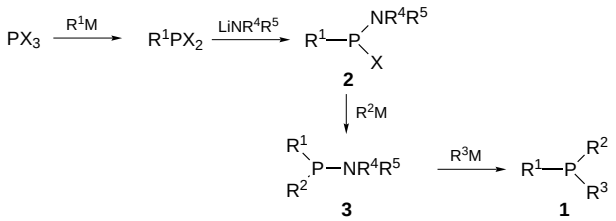
Phosphines constitute the most important class of ligands used in transition metal catalysed reactions.[1] The activity and selectivity of such catalysts are often acutely sensitive to the structure of the phosphine, necessitating the synthesis and testing of a variety of ligands to optimize the catalyst. Hence, the development of efficient and selective preparative routes to structurally diverse phosphine libraries, both in solution and on solid supports, is an important objective. Initial approaches to high throughput parallel syntheses of peptide-derived chiral phosphines[2] and of other ligands[3] and catalysts[4] for asymmetric synthesis have been reported recently.

We sought to develop a general and efficient preparation of tertiary phosphines which ultimately would be adaptable for solid phase parallel synthesis. Solution phase preparation of phosphines usually involves displacement of halide or alkoxide using organometallic reagents[5] (Scheme 1) but access to unsymmetrical tertiary phosphines **1** is complicated by polysubstitution. Selective displacement of chloride in the presence of alkoxide is sometimes possible using a combination of organocadmium and Grignard reagents,[6] organozinc and organolithium reagents,[7] and *via* other approaches[8] but these methods often employ inconvenient organometallics, require multiple steps, and/or lack selectivity or generality. We describe herein a new approach (Scheme 2) which exploits the vastly different leaving group abilities of chloride *vs.* amide and the differential reactivity of organolithium *vs.* organomagnesium reagents.

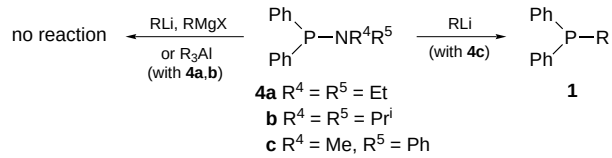
To first establish the leaving group ability of the dialkylamino unit, the interaction of **4a**–**c**[9] with representative RLi, RMgX, and R_3Al reagents was investigated. Dialkylaminophosphines **4a**,**b** proved unreactive even when these organometallics were employed in excess at elevated temperature.† *N*-Methyl-*N*-phenylaminodiphenylphosphine **4c**[9] possessing an expectedly better leaving group, however, reacted extremely slowly with excess MeMgCl at high temperature but rapidly



Scheme 1



Scheme 2



Scheme 3

with MeLi at room temperature, yielding the desired phosphine (Scheme 3).

The key chloroaminophosphines **2** (**a** R = Ph; **b** R = Et) are efficiently prepared (*ca.* 75%) by reaction of readily available organodichlorophosphines‡§ with LiNMePh[9] (THF, 20 °C, Scheme 2).¶ These, in turn undergo selective reaction with Grignard reagents (1.5 equiv, THF, 20 °C) producing aminophosphines **3a**–**j** in excellent yields following aqueous workup (Table 1).‖ A variety of substituents, including alkyl, vinyl and aryl groups, are efficiently incorporated.

Organolithium reagents readily react with the aminophosphines **3** (THF, 20 °C) giving unsymmetrical tertiary phosphines **1a**–**j** (Scheme 2, Table 1).** Although isolated yields of volatile dialkylaryl phosphines were only fair, diarylalkyl derivatives, including sterically hindered ones (*e.g.* **1e**–**g**), could be obtained in high yield.

Finally, we note that the complete sequence from PR^1Cl_2 to $PR^1R^2R^3$ can be conveniently accomplished without the isolation of intermediates. In this way phosphine **1f** was obtained in 59% yield by sequential treatment of $PhPCl_2$ with LiNMePh, *o*-tolMgBr and then MeLi.††

Application of this methodology for the solid-phase synthesis of phosphine libraries is under investigation.

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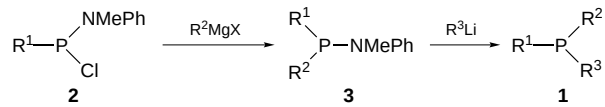
Table 1 Preparation of unsymmetrical tertiary phosphines



2	R^1	R^2	X	3	Yield[a] (%)	R^3	1	Yield[a] (%)
2a	Ph	Pr^i	Cl	**3a**	86	Me	**1a**	16
2a	Ph	Me	Cl	**3b**	83	Bu^t	**1b**	44
2a	Ph	Vinyl	Br	**3c**	95	Me	**1c**	54
2a	Ph	*p*-tol	Br	**3d**	94	Me	**1d**	95
2a	Ph	*p*-tol	Br	**3e**	94	Bu^t	**1e**	76
2a	Ph	*o*-tol	Br	**3f**	96	Me	**1f**	93
2a	Ph	2,6-$Me_2C_6H_3$	Br	**3g**	89	Me	**1g**	70
2a	Ph	Me_3SiCH_2	Cl	**3h**	87	Me	**1h**	98[b]
2b	Et	*p*-tol	Br	**3i**	90	Ph	**1i**	99
2b	Et	Bn	Cl	**3j**	77	Ph	**1j**	78

[a] Isolated yield. [b] Mixture of phosphine and PhNHMe (3 : 1) by ^{1}H NMR spectroscopy. Yield calculated *via* integration.

Footnotes and References

* E-mail: knicholas@ou.edu

† Synthesis of tertiary phosphines *via* reaction of Grignard reagents with aminoarylphosphines bearing a coordinating heteroatomic group at the *ortho* position on the phenyl ring has been previously reported (ref. 10). Based on the non-reactivity of unsubstituted aryldialkylaminophosphines observed by us, the ligating *ortho* substituent seems to be a prerequisite.

‡ Some organodichlorophosphines are commercially available; they also can be obtained *via* reaction of phosphorus trichloride with organometallic reagents (ref. 5).

§ Reactions and transfers for the preparation of **1**–**3** were conducted under N_2. All compounds exhibited satisfactory ^{1}H and ^{31}P NMR spectra.

¶ *Preparation* of **2**: Bu^{n}Li (35 mmol in hexane) was added slowly to PhNHMe (30 mmol) in THF (5 ml) at 0 °C and the resulting white suspension was stirred at room temp. for 45 min. The solvent was evaporated, the white solid was dissolved in THF (150 ml), and the solution was added dropwise to $RPCl_2$ in THF (1.25 M, R = Et, Ph) at 0 °C. After stirring at room temp. for 2 h, the solvent was evaporated, CH_2Cl_2 (40 ml) was added, the mixture filtered, and the solvent evaporated to provide crude **2a**,**b** which could be purified by vacuum distillation.

‖ *Preparation* of **3**: To a stirred solution of **2a** or **b** in THF (1 M) at 0 °C was added 1.5 equiv. of Grignard reagent. The mixture was stirred at room temp. until all of **2** had reacted (by ^{1}H and ^{31}P NMR spectroscopy). The mixture was then cooled in ice and 1 M NH_4Cl was added slowly for complete neutralization. The organic layer was separated, dried over Na_2SO_4, and the solvent evaporated to give the aminophosphines **3a**–**j** as pale yellow liquids which could be used in the next step without further purification.

** *Preparation* of **1**: To a solution of **3** in THF (1 M) at 0 °C was added 1.5 equiv. of RLi. After warming to room temp., the mixture was stirred until reaction completion was indicated (by ^{1}H and ^{31}P NMR spectroscopy). The solvent was evaporated and hexane (30–40 ml) was added. After stirring for a few minutes, the mixture was filtered, and the solvent was evaporated to yield the phosphines.

†† *'No isolation' preparation* of **1**: PhMeNLi was prepared and added to $PhPCl_2$ in THF as described for the preparation of **2**. When the starting material was consumed (2 h, by NMR spectroscopy), *o*-tolylMgBr (1.5 equiv.) was added at 0 °C and the reaction mixture was then warmed to room temperature. Once the formation of aminophosphine was complete (1.5 h), the solvent was evaporated and the residue was triturated with 50 ml benzene. The combined extracts were evaporated and the residue was dissolved in 10 ml THF, treated with MeLi (5.5 equiv.) at 0 °C, and then stirred at room temperature for 3 h. Phosphine **1f** was isolated as described for the preparation of **1** above.

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