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CsOH-promoted P-alkylation: a convenient and highly efficient synthesis of tertiary phosphines

Matthew T. Honaker, Benjamin J. Sandefur, James L. Hargett, Alicia L. McDaniel and Ralph Nicholas Salvatore*

Department of Chemistry, Western Kentucky University, 1 Big Red Way, Bowling Green, KY 42101-3576, USA

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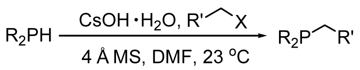
Abstract—A mild and efficient method for the synthesis of tertiary phosphines and ditertiary phosphines has been developed. In the presence of cesium hydroxide, molecular sieves and DMF at room temperature, various secondary phosphines and alkyl bromides were examined, and the results have demonstrated that this methodology offers a general synthetic procedure to produce tertiary phosphines in moderate to high yields. Optically active tertiary phosphine synthesis is also described.

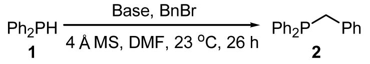
Tertiary phosphines have emerged as an preeminent class of organic compounds which hold ubiquitous applications serving as versatile ligands for transition-metal catalyzed reactions and as useful reagents in a wide array of organic transformations.[1] Triarylphosphines (e.g. PPh_3) dominate most common applications, although, the more electron-rich trialkylphosphines or alkyl diarylphosphines, may offer special advantages in more demanding cases.[2] General synthetic methods for the preparation of such tertiary phosphines have included the reduction of phosphine oxides (or phosphonic acid esters),[3] reaction of organometallic reagents with phosphorus dihalides,[4] coupling between a metal phosphide anion and an alkyl halide,[5] or via the addition of P–H reagents to olefins.[6] However, many of these protocols suffer from several disadvantages such as significant, if not exclusive, oxidation of the phosphine, tedious procedures, harsh reaction conditions, poor product yields or employ the use of protecting groups at phosphorus.[7] During the course of our synthesis toward phosphine macrocycles and related phosphorus crowns, we envisioned that a milder and more convenient approach for the construction of the C–P bond would be of considerable interest. Therefore, in an effort to circumvent the mentioned shortcomings, we report in this letter, a general and efficient direct coupling of a secondary phosphine with an alkyl halide. Under a dry nitrogen atmosphere, using cesium hydroxide in the presence of powdered 4 Å molecular sieves[8] and anhydrous DMF, secondary phosphines were united with alkyl halides for the exclusive synthesis of tertiary phosphines at ambient temperature (Scheme 1).

At the outset of this work, we began our approach by screening a variety of different bases for the monoalkylation of diphenylphosphine (**1**) using a slight excess of benzyl bromide (1.2 equiv.) as the coupling partner (Table 1). Of the alkali bases examined, cesium hydroxide monohydrate was by far the most efficient base



Scheme 1.

Table 1. P-Alkylation of **1** using various bases



entry	base (1 equiv)	yield (**2**)
1	LiOH	3%
2	NaOH	31%
3	KOH	35%
4	RbOH	41%
5	CsOH	93%

Keywords: tertiary phosphine; ditertiary phosphine; secondary phosphine; cesium hydroxide; molecular sieves.

* Corresponding author. Tel.: +1-270-745-3271; fax: +1-270-745-5361; e-mail: ralph.salvatore@wku.edu

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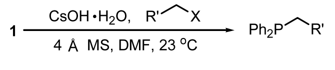
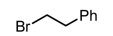
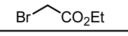
delivering benzyldiphenylphosphine (**2**) exclusively, in high yield (entry 5).[9,10] Whereas, lithium, sodium, potassium and rubidium hydroxide under the same procedure, failed, giving low conversion of **1** (entries 1–4). Although not shown in Table 1, organic bases including Et_3N and DBU gave no reaction. We attribute this high yield and chemoselectivity in favor of tertiary phosphine formation as further evidence of the 'cesium effect'.[11] Numerous efficient *O*- and *N*-alkylations have been reported using cesium bases,[12] however, to our knowledge, this report is the first regarding a chemoselective P-alkylation protocol.

Solvent selection was also crucial for the efficient cesium hydroxide mediated P-alkylation of secondary phosphines. We found anhydrous DMF was the solvent of choice, whereas various other solvents, encompassing dry DMSO, NMP and DMAC did not prove advantageous. Solvents including ether, EtOAc, CH_3CN, and CH_2Cl_2 were less suitable. With the optimized conditions determined, various halides and secondary phosphines were then subjected to P-alkylations to evaluate the scope and limitations of the reaction procedure.

As delineated in Table 2, primary and secondary halides were examined and found to be generally applicable to the newly developed techniques. Various halides were efficiently ligated with diphenylphosphine (**1**) generating the corresponding tertiary phosphines exclusively. Primary aliphatic bromides reacted efficiently providing the subsequent substituted phosphines within 29 h in remarkable yields (entries 1–4). In turn, 1-bromodecane (**7**), a lipophilic bromide, afforded the desired product in moderate yield (42%) after nearly the same time period (entry 5). Interestingly, sterically more demanding secondary bromides, including 2-iodopropane (**8**) and 2-bromobutane (**9**) offered similar results, however, longer reaction times were required for the desired transformations (entries 6, 7). As expected, tertiary halides were resistant to alkylations under these conditions. Also, halides containing base-sensitive functional groups, such as ethyl bromoacetate (**10**), which is vulnerable to hydrolysis, was tolerant to this method, proceeding smoothly without complication. It is noteworthy to mention, no phosphonium salt was detected in any case, demonstrating this procedure is highly chemoselective.[13] Furthermore, side products stemming from elimination and oxidation were circumvented.[13]

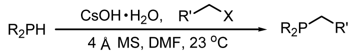
Table 2. Tertiary phosphine synthesis using various halides

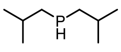
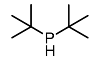
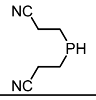


entry	halide (R'X)		time (h)	yield (%)
1	EtBr	(**3**)	24	83
2	*n*-BuBr	(**4**)	26	90
3		(**5**)	29	99
4		(**6**)	26	82
5	1-bromodecane	(**7**)	29	42
6	2-iodopropane	(**8**)	72	63
7	2-bromobutane	(**9**)	62	61
8		(**10**)	20	63

Having established the efficacy of this process, our attention was next focused on the alkylation of structurally diverse phosphines using alkyl halides in order to demonstrate substrate versatility. Dialkyl and diarylphosphines, as well as sterically demanding dialkylphosphines were found to be highly compatible under the identified conditions. As demonstrated in Table 3, dicyclopentylphosphine (**11**) underwent consolidation with both a reactive halide and an unreactive bromide generating the corresponding tertiary phosphines in good yield (entries 1–2). In a similar fashion, $(c\text{-}C_6H_{11})_2PH$ (**13**) also proved successful (entries 3–5). We were delighted to observe di-*p*-tolylphosphine (**14**), an electron-rich secondary phosphine, reacted extremely efficiently affording various substituted phosphines in nearly quantitative yield, despite the nature of the halide (entries 6–9). Moreover, we were pleased to find that our procedures were highly applicable in the synthesis of sterically congested tertiary phosphines. For instance, *i*-Bu_2PH (**16**) was united with both benzyl bromide (**12**) and 1-bromo-3-phenylpropane (**6**) affording the respective phosphines in similar yields (entries 10–11). More importantly, *t*-Bu_2PH, (**17**), a bulky phosphine, was also a compatible coupling partner, albeit longer time was required for the transformations (entries 12–13). Finally, bis(2-cyanoethyl)phosphine (**18**), a phosphine that contains an electron-withdrawing group, underwent benzylation successfully to afford the tertiary phosphine in 88% yield (entry 14).

Table 3. CsOH-promoted P-alkylation of secondary phosphines with halides

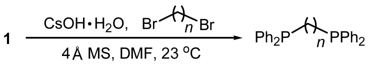


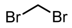
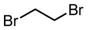
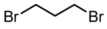
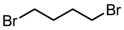
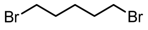
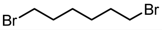
entry	phosphine (R_2PH)		halide (R'X)	time (h)	yield (%)
1	dicyclopentylphosphine	(**11**)	BnBr (**12**)	24	74
2	**11**		**6**	23	70
3	dicyclohexylphosphine	(**13**)	**12**	21	96
4	**13**		**5**	21	83
5	**13**		**6**	21	86
6	di-*p*-tolylphosphine	(**14**)	**12**	43	97
7	**14**		**3**	43	quant.
8	**14**		*n*-PrI (**15**)	48	97
9	**14**		**4**	48	99
10		(**16**)	**12**	20	87
11	**16**		**6**	29	87
12		(**17**)	**12**	96	68
13	**17**		**6**	120	47
14		(**18**)	**12**	23	88

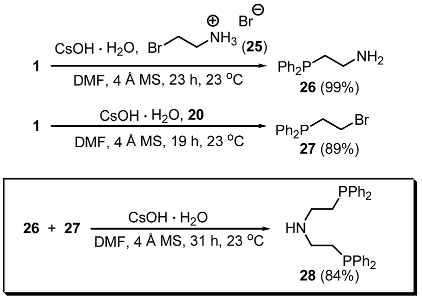
After substantiating the generality of this approach, we then directed our efforts toward the synthesis of ditertiary phosphines. Ditertiary phosphines are known to be excellent ligands in metal complexes, which act as robust catalysts.[14] Keeping this in mind, we extended the above preliminary results using various dibromides (1 equiv.) with 2 equiv. of the prototypical phosphine, **1** (Table 4). As shown in entry 1, dibromomethane (**19**), underwent P-alkylation to afford the corresponding ditertiary phosphine in excellent yield (95%) after 16 h. Likewise, 1,2-dibromoethane (**20**) was found to react efficiently generating dppe in high yield (entry 2). In addition, 1,3-dibromopropane (**21**) and 1,4-dibromobutane (**22**) exhibited similar trends producing the bis-phosphine products, 1,3-dppp and 1,4-dppb, respectively (entries 3, 4). To this end, extension of the alkyl chain length to 5 and 6 carbon fragments on the dibromide moiety were also examined and demonstrated to be facile (entries 5, 6).

Encouraged by the aforementioned results and to broaden the scope of the study, we next investigated the synthesis of a phosphorus–nitrogen–phosphorus (P-N-P) ligand (Scheme 2). Under the suggested conditions, diphenylphosphine (**1**) underwent coupling with 2-bromoethylamine·HBr (**25**) generating diphenyl(phosphinoethyl)amine (**26**) in excellent yield. Notably, protection of the primary amine proved unnecessary, further emphasizing issues of chemoselectivity of this protocol. In a similar fashion, 1 equiv. of 1,2-dibromoethane (**20**) underwent monoalkylation with **1** (1 equiv.) to provide bromo-phosphine **27** in high yield. Subsequent treatment of phosphine adduct **26** with bromo-phosphine precursor **27** via the same strategy commenced the synthesis of symmetrical P-N-P ligand **28** cleanly.

Table 4. Synthesis of ditertiary phosphines



entry	dihalide		time (h)	yield (%)
1		(**19**)	16	95
2		(**20**)	36	78
3		(**21**)	45	83
4		(**22**)	47	87
5		(**23**)	72	63
6		(**24**)	72	69



Scheme 2.

Taking into account the importance of optically active phosphines in organic synthesis at this juncture, we investigated our approach in the synthesis of tertiary phosphines possessing a chiral center at the phosphorus atom. As shown in Scheme 3, alkylation of commercially available methylphenylphosphine (**29**) proceeded smoothly with *n*-PrI (**15**) delivering optically active tertiary phosphine **30** in moderate yield after 20 h using CsOH.[15] In comparison, reaction of (−)-menthyl chloride (**31**) with **1** proved promising providing the chiral monodentate ligand (+)-neomenthyldiphenylphosphine (NMDPP, **32**), after 63 h in a greater yield than previously reported (70%).[16] Owing to the mild conditions, racemizations or E_2-elimination were not observed during alkylation of these phosphines, making this protocol highly attractive.[15,16]

In conclusion, we have developed a general synthetic method for the exclusive synthesis of tertiary phosphines using a secondary phosphine and alkyl halide in the presence of cesium hydroxide, 4 Å molecular sieves and DMF. Our convenient and improved reaction conditions are generally applicable with a wide array of secondary phosphines and alkyl halides which, in most cases, has shown a dramatic improvement in overall yields, as well as common drawbacks seen using existing protocols. Furthermore, our mild procedure (room temperature) is of particular value given its experimental simplicity and diverse functional group compatibility. The synthesis of sterically hindered phosphines, ditertiary phosphines, and optically active phosphines were particularly successful offering numerous potential applications in the realm of asymmetric synthesis and catalysis. Further studies regarding the mechanism and applications of these techniques will be reported in due course. In addition, efforts are currently underway to extend this procedure to the synthesis of secondary phosphines and phosphine macrocycles.

Acknowledgements

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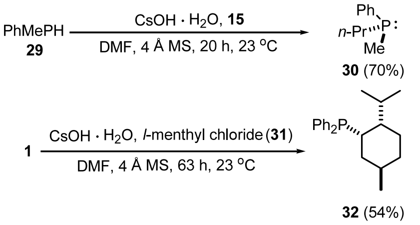

Scheme 3.

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8. Molecular sieves accelerated the alkylation by removal of water from the reaction media. When molecular sieves were not activated, reactions were sluggish resulting in diminished product yield with recovery of the starting phosphine predominately.
9. It is plausible the reaction proceeds via the diphenylphosphide anion, which is prepared in situ by reaction of Ph$_2$PH and CsOH. The anion, presumably is weakly coordinated to the cesium cation, hence, a 'naked anion' demonstrating enhanced nucleophilicity, as defined by the 'cesium effect'. Preliminary observations are consistent with previously reported examples using other alkali metal counterparts. Currently, the mechanism is under investigation and these results will be reported in due course. For formation of 'naked anions' by solvation of cesium ions which has been previously postulated and studied extensively in other systems; see: Dijkstra, G.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1987**, *52*, 4230. For formation of alkyl metal diphenylphosphides, see: (a) Aguiar, A. M.; Greenberg, H. J.; Rubenstein, K. E. *J. Org. Chem.* **1963**, *28*, 2091; (b) Fisher, C.; Mosher H. S. *Tetrahedron Lett.* **1977**, *29*, 2487; (c) Chatt, J.; Hart, F. A. *J. Chem. Soc.* **1960**, 1378. (d) For Ph$_2$PCs, see: Fluck, E.; Issleib, K. *Z. Naturforsch., B* **1965**, *20*, 1123.
10. Representative experimental procedure: To a suspension containing activated powdered 4 Å molecular sieves (500 mg) in anhydrous *N*,*N*-dimethylformamide (8.3 mL) cesium hydroxide monohydrate (180 mg, 1.07 mmol) was added and the mixture was stirred under a dry nitrogen atmosphere. After **1** (0.19 mL, 1.07 mmol) was added, the reaction mixture was stirred for 1 h resulting in a dark red–orange solution. Benzyl bromide (**12**) (0.15 mL, 1.29 mmol) was added in one portion, at which point, the mixture turned immediately to milky white. The reaction was allowed to proceed at room temperature for 26 h, at which point **1** was consumed (TLC). Degassed basic water (30 mL) was added and the mixture was subsequently extracted with CH$_2$Cl$_2$ (3×30 mL). The combined organic layers were then washed with degassed basic water (3×30 mL), dried using anhydrous sodium sulfate, decanted, and the solvent was removed in vacuo. Purification via recrystallization from benzene afforded **2** as an air-sensitive white powder (275 mg, 93%).
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13. ^{31}P NMR spectra were obtained for both crude and purified products substantiating the claim for complete specificity and purity for each tertiary phosphine. Phosphonium salt and side products stemming from elimination and oxidation of the phosphine were not detected in an example. In addition, ^{1}H, ^{13}C NMR, GC/MS and elemental analysis were carried out on all synthetic samples. All isolated final products gave analytical and spectroscopic data in agreement with the proposed structures.
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15. Phosphine **30** was dissolved in deoxygenated benzene and quarternized with benzyl bromide. The solvent and excess BnBr was evaporated in vacuo and the resulting oily residue was triturated with ether, whereupon it immediately crystallized. The optical rotation of the resulting phosphonium salt was compared to the known literature value, see: Horner, L.; Winkler, H.; Rapp, A.; Mentrup, A.; Hoffmann, H.; Beck, P. *Tetrahedron Lett.* **1961**, 161. The optical rotation of the synthetic sample was +37.0° (methanol); reported: 36.8°.
16. Phosphine **32** was recrystallized from degassed 95% EtOH and the optical rotation of was taken and matched to the known value, see: Morrison, J. D.; Masler, W. F. *J. Org. Chem.* **1974**, *39*, 270. The observed value was +94° (*c* 1.26 CH_2Cl_2); reported: + 95.5°. Mp 97–99°C. Competing E_2-elimination was not detected. In this example, **1** was not completely consumed during the reaction, accounting for the additional mass balance.