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Palladium-Catalyzed Synthesis of Aqueous, Fluorous, and Supercritical CO_2-Soluble Phosphines

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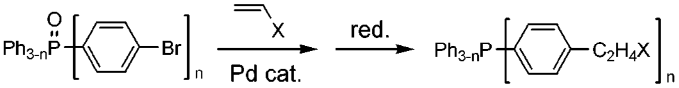
ABSTRACT



A generic, simple, and economical route has been developed for the synthesis of phosphines soluble in aqueous, fluorous, and supercritical CO_2 phases. The methodology is based on the palladium-catalyzed Heck olefination of haloarylphosphine oxides followed by reduction, affording various arylphosphines in high yields.

One of the current frontiers in homogeneous catalysis is concerned with using as reaction media nontraditional solvents such as water, room-temperature ionic liquids, supercritical carbon dioxide ($scCO_2$), and perfluorocarbons.[1] Phosphines are the most widely utilized ligands in metal-catalyzed homogeneous reactions. To make their metal complexes soluble in these solvents and facilitate catalyst/product separation, the phosphines will normally need to be modified. For catalysis in an aqueous phase, this can be done by appending the phosphines with hydrophilic groups such as $-SO_3Na$, $-CO_2Na$, and $-NR_3Cl$,[1a] whereas by attaching to perfluorinated moieties or long alkyl chains the phosphines become $scCO_2$-soluble or fluorous-soluble in the case of the former.[1c−h] However, few such functionalized phosphines are commercially available and their synthesis is generally not an easy undertaking,[2,3] thus impeding the development of catalytic processes in emerging solvents in particular and green chemistry in general. Indeed, there appear to be, until now, no generic methods that allow for the synthesis of phosphines applicable to catalysis in these nontraditional media. We report herein that the palladium-catalyzed Heck reaction provides a simple, versatile route to all such phosphines.[4]

Our methodology is based on a three-step synthesis, that is, the C−C coupling of haloarylphosphine oxide **1** with an olefinic substrate and hydrogenation of the resulting oxide−substituted olefin **2** followed by reduction of the saturated oxide **3** to give the free phosphine **4** (Scheme 1). The palladium-catalyzed Heck olefination of the halophosphine

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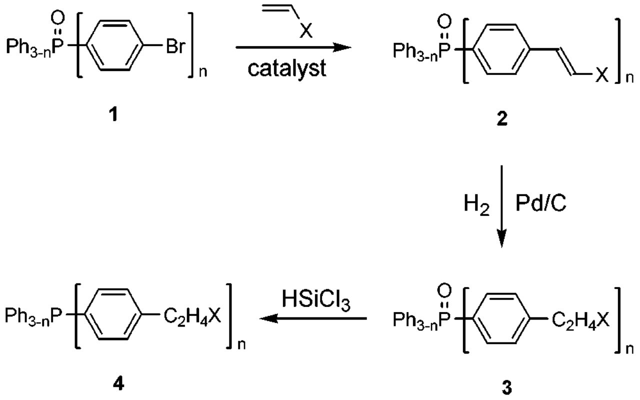
Scheme 1[a]



[a] Formation of **2**: 1.1 - 1.5 equiv olefin (relative to bromine), ca 1.3 equiv NaOAc, 0.5 - 1 mol% palladacycle, 125 °C for 15 - 24 h in DMF. Formation of **3**: 10 bar H_2, 10% Pd/C, ambient temperature for 5 h in EtOAc. Formation of **4**: 5 equiv $HSiCl_3$, 5 - 10 equiv NEt_3, 120 °C for 5 h in toluene.

oxides comprises the essential part of the chemistry. This divergent approach, with the haloarylphosphine oxides as modular building blocks, was expected to offer a much-simplified yet generic route to phosphines soluble in aqueous, fluorous, and $scCO_2$ phases, since olefins with various functionalities are known to couple with aromatic halides and the phosphine oxides **1** are readily available with established procedures and require no special cautions to handle.[5,6] To our delight, indeed, the oxides **1** ($n = 1-3$) could be olefinated with a variety of olefinic substrates $H_2C{=}CHX$ (X = *n*-perfluorohexyl, *n*-butyl, *n*-octyl, *n*-trtradecyl, butoxycarbonyl, phenyl, 4-chlorophenyl) to give **2**. In a typical reaction, a phosphine oxide was mixed with 1.1 equiv of an olefin (relative to bromine), ca. 1.3 equiv of NaOAc, and 0.5−1 mol % of the Herrmann−Beller palladacycle catalyst in DMF.[7] The coupling reaction proceeded smoothly at 125 °C to give the olefinated phosphine oxides **2a**−**i** in more than 90% isolated yields in most cases without optimization (Table 1). Most of the reactions completed in 24 h reaction time regardless of the number of bromide substituents in the starting oxide. The O=P substituted phenyl bromides thus behave like activated aryl bromides such as 4-bromoacetophenone in the Heck reaction. Activation of bromobenzene itself requires more stringent conditions with the same palladacycle catalyst.[7] This may not be surprising given the strong electron withdrawing capability of the O=P substituent.[8] ^{1}H NMR studies indicate that the electron-withdrawing effect of the phosphoryl group on the *para* position of a phenyl ring lies between those of a carbonyl and a bromide group.[6] In line with this argument, tris(4-bromophenyl)phosphine failed to couple with *n*-butyl acrylate under conditions similar to those employed for the corresponding oxide, although this could also arise from possible poisoning of active palladium species by the excessive phosphines, and the borane-protected tris(4-bromophenyl)-phosphine did not react with the same olefin. As with other Heck reactions, substitution of the vinylic protons by the arylphosphine oxides occurs at the less substituted side of the C=C double bond leading to *trans* olefins. With the more electron rich 1-hexene, 1-decene, and 1-hexadecene, however, about 10% of the product resulted from 2-substitution, as judged by the ^{1}H and ^{13}C NMR spectra. The oxides **2a**−**i** all have been characterized by NMR, MS, and satisfactory elemental analysis. Thus, with this simple modular approach, potentially water, $scCO_2$, and fluorous-soluble phosphines could all readily be obtained. The versatility of the methodology is further demonstrated by the olefination of **1** with styrenes to give **2h** and **2i**.

Table 1. Olefination of OPPh$_{3-n}$(4-C$_6$H$_4$-Br)$_n$ with $H_2C{=}CHX$ To Give OPPh$_{3-n}$(4-C$_6$H$_4$-Ch=CHX)$_n$[a]

compd	X	*n*	time, h	yield, %[b]
2a	*n*-C_6F_{13}	1	20	93
2b	*n*-C_6F_{13}	2	24	94
2c	*n*-C_6F_{13}	3	24	91
2d	*n*-C_4H_9	3	24	91[c]
2e	*n*-C_8H_{17}	3	24	93[c]
2f	*n*-$C_{14}H_{29}$	3	30	86[c]
2g	CO_2*n*Bu	3	15	98
2h	Ph	3	24	91
2i	4-ClC_6H_4	3	24	89

[a] For general reaction conditions, see Scheme 1. [b] Isolated yield. [c] Containing ca. 10% of 2-substituted isomer.

To obtain the free phosphines **4**, the substituted phosphine oxides were first subjected to hydrogenation and then reduced by treatment with trichlorosilane.[8] The feasibility of the chemistry is shown by the following examples involving phosphine oxides with distinct substituents. Hydrogenation of **2c**, **2d**, and **2g** catalyzed by Pd/C under 10 bar of H_2 afforded the saturated oxides **3c**, **3d**, and **3g**. ^{1}H and ^{31}P NMR spectrum of the oxides so obtained shows no byproducts. The oxides were therefore taken directly to the next step for reduction after filtering out the Pd/C catalyst. The removal of the oxygen was performed by refluxing a mixture of an alkylated phosphine oxide, trichlorosilane, and triethylamine in toluene at 120 °C for a few hours, affording the free phosphines **4c**, **4d**, and **4g** in over 90% isolated yields. **4c**

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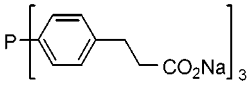
and related phosphines have recently been prepared by a process starting with the preparation of the corresponding fluoroalkylated aryl halides followed by metathesis with $PPh_{3-n}Cl_n$ ($n = 1-3$) using moisture-sensitive and pyrophoric organometallic reagents, resulting in relatively inefficient utilization of the perfluoroalkyl reagents, often the most expensive of all reagents involved.[3a,c,f−h] By way of contrast, close to 90% of the perfluoroalkyl reagents were effectively incorporated into the desired product with the present methodology. The alkylated phosphine **4d** was previously prepared via a multistep reaction starting from 4-bromobenzaldehyde, with an overall yield of only 30%.[9] The presence of the ethylene spacer in **4c** attenuates the strong electron withdrawing effect of the perfluoroalkyl moiety on the phosphorus. Analogous fluorophosphines without a spacer group can be accessed by an organolithium-mediated reaction or more easily by copper-mediated cross coupling of **1** with perfluoroalkyl iodides.[3f,h,k] The utility of fluoroalkylated and alkylated phosphines has been demonstrated by a number of examples of reactions catalyzed by their metal complexes in $scCO_2$ and perfluorocarbon and hydrocarbon solvents.[1c−h,3,10]

The water-soluble sodium salt of tris[4-(2-carboxylethyl)-phenyl]phosphine **5** was obtained by hydrolysis of the oily **4g** in the presence of NaOH as a white powder in 89% isolated yield. While water-soluble phosphines such as $P(3\text{-}C_6H_4SO_3Na)_3$ and $P(4\text{-}C_6H_4CO_2Na)_3$ have long been known,[1a] our methodology provides an easy entry to such phosphines in which the electronic effects of the ionic groups can now be readily minimized by a spacer group.



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In conclusion, we have developed a generic methodology that allows for the easy and economical synthesis of phosphine ligands applicable to catalysis in such diverse solvents as water, ionic liquids, $scCO_2$, and perfluorocarbons. The key aspect of the chemistry involves the Heck olefination of a haloarylphosphine oxide. The introduction of the C═C double bonds into the oxides also makes further functionalization of the ligands possible.

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Supporting Information Available: Experimental procedures and characterization for compounds **2c**, **3c**, **4c**, **2g**, **3g**, **4g**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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