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Fluoride-mediated phosphination of alkenes and alkynes by silylphosphines

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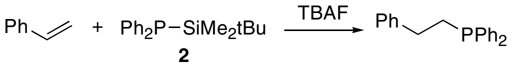
Abstract—Regioselective phosphination of carbon–carbon unsaturated bonds by a fluoride-mediated reaction of silylphosphines is described. Alkenes and alkynes having a directing group, such as an aromatic or a carbonyl group, reacted to form a carbon–phosphorus bond under mild conditions. When an anhydrous fluoride source was applied in the presence of an electrophile, the corresponding three-component coupling product was obtained.

Tertiary phosphines are indispensable as ligands for transition-metal catalysts; therefore, new methods for providing multi-functional phosphine ligands, by forming carbon–phosphorus bonds under mild conditions have received great attention.[1] In general, conventional synthetic methods, including Grignard reagents or alkaline metal phosphides, have been limited to simple alkyl and aryl phosphines due to spontaneous reactivities of these reagents.[2]

Silylphosphines offer considerable potential as synthetic equivalents of phosphines, masked phosphines, or phosphides, for the synthesis of several organophosphorus compounds.[3] The silylphosphines themselves generally have a much lower reactivity, in comparison with other metal phosphides, such as lithium phosphides. However, some silylphosphines easily react with good electrophiles, such as an aldehyde,[4] an acyl halide,[5] α,β-unsaturated carbonyl compounds,[6,7] and an azodicarboxylate.[8] The nucleophilicity of a phosphorus atom of a silylphosphine should increase upon treatment with a fluoride anion and the resulting agent could serve as a powerful phosphorus nucleophile. Despite the great utility of fluoride anion for activation of organosilicon compounds, a fluoride-mediated reaction of silylphosphines has not been reported thus far. In this study, we report a fluoride-mediated reaction of silylphosphines as a novel phosphination of carbon–carbon unsaturated bonds.

We first surveyed the reactivity of silylphosphine **2**[8] toward styrene in the presence of TBAF (commercial 1.0 M solution in THF) under several conditions (Table 1).



The diphenylphosphino group of **2** selectively added to the β-position of styrene resulting in diphenyl(2-phenylethyl)phosphine. The most influential factor in the reaction was the solvent used. In CH_2Cl_2, only 8% of the product was formed even after 4h under reflux. In contrast, the addition proceeded smoothly and rapidly at room temperature in polar solvents, such as DMF and DMSO. Although the use of CH_3CN gave a poor result at rt, the reaction proceeded well at 50 °C. In all the cases, no reaction occurred in the absence of TBAF.

The results of the fluoride-mediated phosphination of several alkenes, including the conjugated ones, are shown in Table 2.[9]

Table 1. Solvent effects on the phosphination reaction

Entry	Solvent	Temp. (°C)	Time (min)	Yield (%)
1	CH_2Cl_2	40	240	8
2	CH_3CN	25	120	36
3	CH_3CN	50	20	81
4	DMF	25	15	89
5	DMSO	25	20	81

Keywords: Silylphosphine; Phosphination; Michael addition; Three-component coupling.

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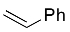
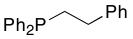
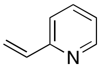
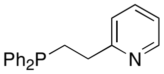
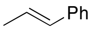
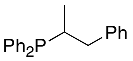
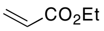
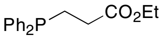
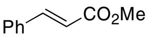
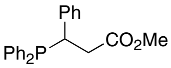
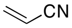
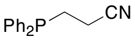
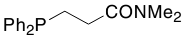
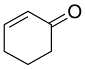
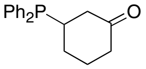
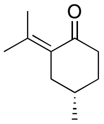
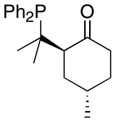
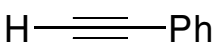
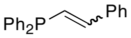
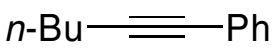
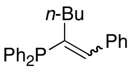
Table 2. Fluoride-mediated phosphination[a]

Entry	Substrate		Product		Yield (%)[b]
1		**1a**		**3a**	89
2		**1b**		**3b**	95
3		**1c**		**3c**	78
4		**1d**		**3d**	82
5		**1e**		**3e**	76[c]
6		**1f**		**3f**	81
7		**1g**		**3g**	76
8		**1h**		**3h**	78[c]
9		**1i**		**3i**	75[c,d,e]
10		**4a**		**5a**	75[d,f]
11		**4b**		**5b**	62[d,g]

[a] All reactions were conducted in DMF at rt for 15 min, using 1.2 equiv of silylphosphine and TBAF each. A commercial 1.0 M THF solution of TBAF (contains ca. 5% of water) was used.

[b] Isolated yields.

[c] Phosphine adducts formed initially were easily oxidized after purification.

[d] The ratio of the isomers was determined by ^{31}P NMR.

[e] The ratio of isomers was *trans*/*cis* >95:5.

[f] The ratio of the *E* and *Z* isomers was ca. 5:1.

[g] The ratio of the *E* and *Z* isomers was ca. 3:2.

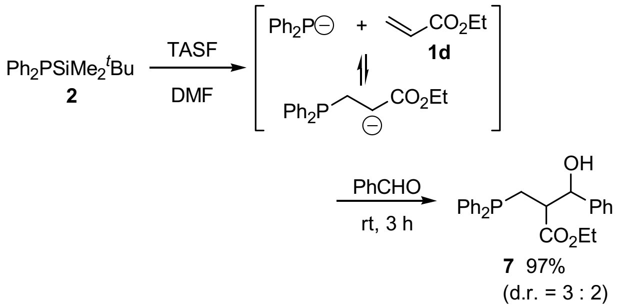
This reaction required an aromatic group or an electron-withdrawing group on the alkene; an alkene having only an alkyl group did not react with **2** at all. This was probably due to lack of stabilization of an anionic intermediate during addition. Aromatic alkenes, α, β-unsaturated carbonyls, and a nitrile reacted in 15 min resulting in good yields of the corresponding β-phosphino adducts (entries 1–9).[10] Substituents on the β-carbon did not affect the addition (entries 3, 5, 8, and 9). Methyl cinnamate gave methyl 3-phenyl-3-(diphenylphosphino)propionate, which indicated that the carbonyl group is a better directing group than the phenyl group of the cinnamate (entry 5).

This fluoride-mediated phosphination could be successfully applied to alkynes. Alkynes **4a** and **4b** resulted in the corresponding adducts **5a** and **5b** in a regioselective manner, as a mixture of *E*/*Z* isomers (entries 10 and 11). At least one directing group was also required in the case of alkynes; a terminal aliphatic alkyne did not react at all.

In addition, the reactivity did not depend on the substituents on the silyl group of the silylphosphine. Use of trimethylsilyldiphenylphosphine **6** instead of **2** provided almost the same results; for example, addition of **6** to ethyl acrylate **1d** and ethynylbenzene **4a** under the same conditions gave **3d** (78%) and **5a** (64%), respectively.

The reaction appeared to proceed through tetra-*n*-butylammonium diphenylphosphide generated in situ from silylphosphine and TBAF. The characteristic red color of the diphenylphosphide appeared on addition of TBAF to the solution of silylphosphine and this soon faded as the reaction progressed. Since the commercial TBAF solution contains a small amount of water, the substituent-stabilized intermediate, which is formed by subsequent addition to an alkene, may be trapped by protonation. When an additional electrophile exists in the absence of a proton source, the intermediate should be trapped by the electrophile. In fact, the three-component coupling reaction of benzaldehyde, **2**, and **1d** was accomplished using TASF as an anhydrous fluoride resulting in good yields of **7** (Scheme 1) as a mixture of diastereomers.[11]

The addition did not proceed without a second electrophile, such as an aldehyde or a proton source. These



Scheme 1.

results clearly suggested that equilibrium may exist at the first addition step. Then, the stabilized intermediate successively added to the electrophile resulting in the adduct.

The phosphination of carbon–carbon unsaturated bonds is of interest in recent times, due to the wide use of functional phosphines as ligands in catalysis.[12,13] Base-catalyzed,[14] metal-catalyzed,[15] and uncatalyzed[16] phosphination of alkenes and alkynes have been extensively studied in recent years. The present fluoride-mediated phosphination proceeded smoothly under quite mild conditions. It produced results similar to other methods for simple addition, in terms of yields and selectivities. Moreover, it has the advantage that the carbon frame of the adduct can be extended through the subsequent coupling reaction in one pot, thereby resulting in more functionalized phosphines.

In conclusion, we have developed a novel phosphination reaction of alkenes and alkynes by silylphosphines that is mediated by TBAF. Formation of a carbon–phosphorus bond through a mild and convenient procedure has paved the way for obtaining a variety of new multi-functional organophosphorus compounds, particularly ligands of transition metal catalysts.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.10.098.

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9. *Typical procedure*: Silylphosphine **2** (72 mg, 0.24 mmol) in DMF (1.5 mL) and THF solution of tetra-*n*-butylammonium fluoride (1.0 M, 0.2 mL) were added to a stirred mixture of styrene **1a** (21 mg, 0.2 mmol) at rt. After stirring for 15 min at rt, the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (eluent: $CHCl_3$/*n*-hexane = 1:4, R_f 0.4) resulting in adduct **3a** (47 mg, 89%), which is a colorless oil.
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11. *Typical procedure*: TASF (134 mg, 0.50 mmol) was added to a stirred mixture of **1d** (42 mg, 0.42 mmol), silylphosphine **2** (150 mg, 0.50 mmol), and benzaldehyde (43 mg, 0.42 mmol) in DMF (3 mL) at rt. After stirring for 3 h at rt, the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (eluent: AcOEt/*n*-hexane = 1:4) resulting in adduct **7** (160 mg, 97%) as a mixture of diastereomers (isomer ratio = 3:2), which is difficult to separate; (major isomer) ^{1}H NMR δ 1.14 (t, $J = 7.7$ Hz, 3 H), 2.81 (t, $J = 5.1$ Hz, 2H), 3.10 (dt, $J = 7.6, 5.1$ Hz, 1H), 3.92 (m, 2H), 4.90 (d, $J = 7.6$ Hz, 1H), 7.27–7.51 (m, 10H), 7.60–7.73 (m, 5H); ^{13}C NMR δ 13.6, 29.1 (d, $J = 70.8$ Hz), 47.9 (d, $J = 2.5$ Hz), 60.9, 75.2 (d, $J = 8.5$ Hz), 126.5, 127.9, 128.6 (d, $J = 4.1$ Hz), 128.8, 130.7 (d, $J = 9.6$ Hz), 131.2 (d, $J = 9.7$ Hz), 132.1 (d, $J = 2.4$ Hz), 132.7, 141.2, 172.8 (d, $J = 6.7$ Hz); ^{31}P NMR δ −18.4; IR (neat) 3091, 3048, 3004, 2956, 1730, 1591, 1448, 1320, 1251, 1032, 781, 704 cm^{-1}; FABMS calcd for $C_{24}H_{25}O_3P$, 392; found 393 (M + H). (minor isomer) ^{1}H NMR δ 1.05 (t, $J = 8.0$ Hz, 3 H), 2.35 (m, 2H), 3.80 (m, 2H), 5.14 (d, $J = 4.8$ Hz, 1H), 7.23–7.51 (m, 10H), 7.60–7.73 (m, 5H); ^{31}P NMR δ −19.2. These two diastereomers could be separated by a column chromatography on silica gel (eluent: AcOEt/*n*-hexane = 3:2) as their phosphine oxides after oxidation by *m*CPBA.
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16. (a) Mimeau, D.; Delacroix, O.; Gaumont, A. C. *Chem. Commun.* **2003**, 2928–2929; (b) Mimeau, D.; Gaumont, A. C. *J. Org. Chem.* **2003**, *68*, 7016–7022.