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Boron Trifluoride-Mediated Alkylation of Diphenylphosphine with *tert*-Alkyl Fluoride

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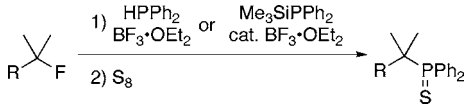
ABSTRACT



Treatment of tertiary alkyl fluoride with diphenylphosphine in the presence of a stoichiometric amount of boron trifluoride etherate yields the corresponding *tert*-alkyldiphenylphosphine despite the coexistence of the strong Lewis acid and the highly coordinating phosphine. Use of diphenyl(trimethylsilyl)phosphine as a nucleophile makes the reaction catalytic in boron trifluoride.

Organophosphorus compounds play important roles in various fields of chemistry as synthetic reagents, ligands for transition metal complexes, advanced materials, and building blocks of supramolecular assemblies. Among them, phosphines having a bulky alkyl group on phosphorus provide transition metals with unique reactivity in catalysis.[1] Synthesis of phosphines having a *tert*-alkyl group thus deserves further exploitation. Installation of *tert*-alkyl group often requires highly basic conditions.[2] For instance, *tert*-butyldiphenylphosphine was prepared from *tert*-butyl Grignard reagent and chlorodiphenylphosphine.[3] *tert*-Butyl chloride reacts with lithium diphenylphosphide to afford the same phosphine under UV irradiation.[4] Such syntheses always suffer from functional group compatibility. Development of mild and efficient methods has been awaited.

Recently, we reported that boron trifluoride chemoselectively activates the carbon−fluorine bonds of *tert*-alkyl fluorides in the presence of ether, ketone, and ester moieties to generate the corresponding tertiary carbocations.[5] The cations were efficiently trapped with nucleophiles such as silyl enolates and allylsilanes. The unusually strong fluorophilicity of boron trifluoride prompted us to employ a highly coordinating nucleophile. We report herein the use of diphenylphosphine, known to form adducts with boron compounds,[6] as the nucleophile. The reaction offers a mild procedure for the synthesis of *tert*-alkyldiphenylphosphine.

Treatment of 3-fluoro-3-methyl-1-phenylbutane (**1a**) with diphenylphosphine (1.2 equiv) in the presence of a stoichiometric amount of boron trifluoride etherate (1.0 equiv) at −20 °C for 6 h afforded (1,1-dimethyl-3-phenylpropyl)-diphenylphosphonium tetrafluoroborate (**2a**) (Table 1, Method A). Since *tert*-alkyldiphenylphosphine was generally sensitive to oxygen, the product was isolated as phosphine sulfide **3a** after treatment with elemental sulfur in 73% yield (Table 1,

(1) For recent examples: (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett*. **1998**, *39*, 617−620. (b) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367−2370. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (d) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc*. **2001**, *123*, 2677−2678. (e) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2413−2416.

(2) (a) Elsner, G. In *Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1982; Vol. E1, pp 106−159. (b) Kawashima, T. In *The Fourth Series of Experimental Chemistry*; Akiba, K., Ed.; Maruzen: Tokyo, 1992; Vol. 24, pp 229−243.

(3) Hoffmann, H.; Schellenberg, P. *Chem. Ber*. **1966**, *99*, 1134−1142.

(4) Santiago, A. N.; Rossi, R. A. *J. Chem. Soc., Chem. Commun*. **1990**, 206−208.

(5) Hirano, K.; Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2004**, *45*, 2555−2557.

(6) Complex formation between BF_3 and phosphines was investigated. (a) Graham, W. A. G.; Stone, F. G. A. *J. Inorg. Nucl. Chem*. **1956**, *3*, 164−177. (b) VanPaasschen, J. M.; Geanangel, R. A. *Inorg. Chem*. **1978**, *17*, 3302−3304. (c) Rapp, B.; Drake, J. E. *Inorg. Chem.* **1973**, *12*, 2868−2873. For review of phosphine-borane adducts, see: (d) Ohff, M.; Holz, J.; Quirmbach, M.; Börner, A. *Synthesis* **1998**, 1391−1415. (e) Imamoto, T. *Pure Appl. Chem*. **1993**, *65*, 655−660.

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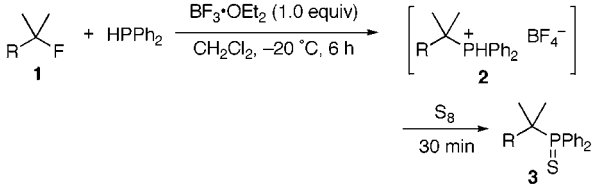
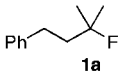
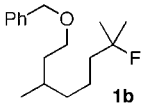
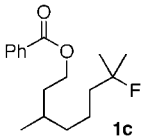
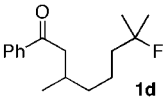
Table 1. Phosphination of *tert*-Alkyl Fluorides with Diphenylphosphine or Diphenyl(trimethylsilyl)phosphine in the Presence of Boron Trifluoride

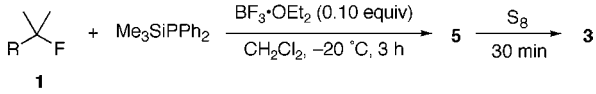
Method A



1 2 3

entry	substrate	$HPPh_2$	product	yield[a]
1	 **1a**	1.2 equiv	**3a**	73% (82%)
2	 **1b**	1.2 equiv	**3b**	53%
3	**1b**	3.0 equiv	**3b**	80%
4	 **1c**	1.2 equiv	**3c**	65%
5	 **1d**	3.0 equiv	**3d**	64%
6	**1a**	3.0 equiv[b]	**3a'**	52%

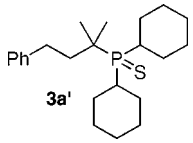
Method B



1

7	**1a**	1.2 equiv	**3a**	68%
8	**1b**	3.0 equiv	**3b**	53%
9	**1c**	3.0 equiv	**3c**	58%
10	**1d**	3.0 equiv	**3d**	40%

[a] Isolated yield. The yield in parentheses was determined by NMR. [b] Dicyclohexylphosphine was used instead of diphenylphosphine.

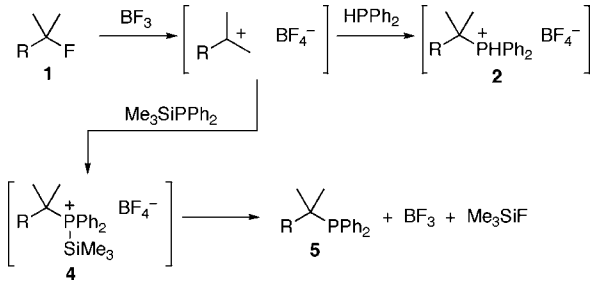


3a'

entry 1). Alkenes formed by the elimination of hydrogen fluoride were the only detectable byproducts. Ether, ester, and keto functional groups were tolerant under the reaction conditions (entries 2−5). Although, in some cases, an excess of diphenylphosphine was essential to attain a satisfactory yield, the present procedure offers functionalized phosphines unavailable by conventional phosphine synthesis. To our delight, the more basic dicyclohexylphosphine underwent alkylation (entry 6). Use of *tert*-alkyl chloride resulted in no conversion.

The requirement of a stoichiometric amount of boron trifluoride would stem from the formation of stable phosphonium tetrafluoroborate **2**, which prevents regeneration of boron trifluoride (Scheme 1). Attempted removal of hydrogen fluoride from **2** in the presence of various bases failed to regenerate boron trifluoride. We anticipated that diphenyl(trimethylsilyl)phosphine, instead of diphenylphosphine, would act as a nucleophile to yield intermediate **5** and that generation of a strong silicon−fluorine bond would facilitate liberation of boron trifluoride with concomitant production of trimethylsilyl fluoride. This was indeed the case and 0.10 equiv of boron trifluoride effected the alkylation (Table 1, entries 7−10, Method B).

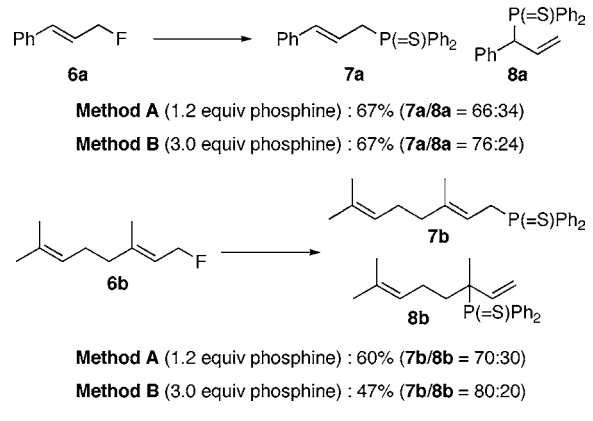
Scheme 1



1 2 4 5

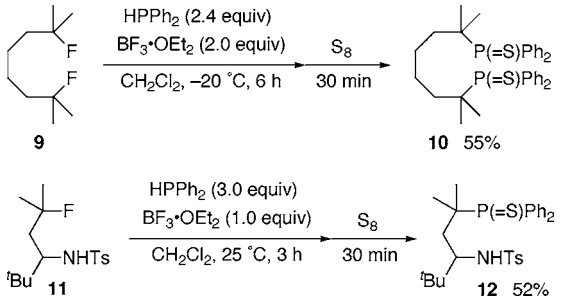
Besides tertiary alkyl fluoride, allylic fluoride participated in a similar reaction to afford allylic phosphine sulfide (Scheme 2). Unfortunately, the reaction yielded a mixture of regioisomers **7** and **8**, which were readily separable from each other by silica gel column chromatography.

Scheme 2

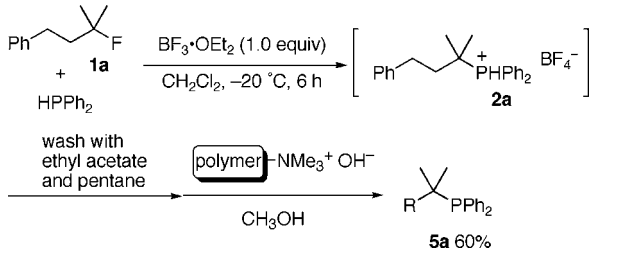


Taking advantage of the mildness and efficiency of this reaction, the present procedure is applicable to the synthesis

Scheme 3



Scheme 4



of precursors of bidentate ligands. Treatment of difluoride **9** with 2.4 equiv of diphenylphosphine in the presence of boron trifluoride provided diphosphine disulfide **10** in good yield (Scheme 3). Aminophosphine derivative **12** was obtained in the reaction of **11** with diphenylphosphine.

We have developed a mild method for the synthesis of *tert*-alkyldiphenylphosphine sulfides. With a proper desulfidation procedure,[7] trivalent phosphines that are useful for ligands and catalysts in organic synthesis would be available. However, the conventional desulfidation requires harsh conditions. Development of mild and easy-to-operate methods for the isolation of trivalent phosphines is now requested in organophosphorus chemistry. Gratifyingly, we could isolate a free phosphine **5a** from the reaction mixture (Scheme 4). Namely, after the alkylation of **1a** was completed, the solvent was removed to obtain a solid containing **2a** and contaminations such as the remaining $HPPh_2$. Since phosphonium salt **2a** was hardly soluble in ethyl acetate, the solid was washed with ethyl acetate to afford pure **2a**. Treatment of **2a** with basic ion-exchange resin, Amberlyte, provided (1,1-dimethyl-3-phenylpropyl)diphenylphosphine (**5a**) in 60% overall yield, although we were unable to prevent concomitant formation of ca. 20% of the phosphine oxide of **5a** (See Supporting Information). Phosphonium salts such as **2a**, in place of free phosphines, are also a useful form of ligands for transition metals, since the free phosphines can be generated in situ in the presence of a base.[8]

In summary, we have developed a mild procedure for alkylation of diorganophosphine with tertiary alkyl fluoride. Radical addition of diorganophosphine or its sulfide to alkene resulted in the completely opposite regioselectivity to the present reaction, that is, anti-Markovnikov selectivity, which the present method can compensate for.[9]

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Supporting Information Available: Detailed experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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