Mild electrophilic trifluoromethylation of secondary and primary aryl- and alkylphosphines using hypervalent iodine(III)–CF_3 reagents†

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A direct, mild and efficient trifluoromethylation of primary and secondary phosphines is achieved with easily accessible, cheap hypervalent iodine compounds acting as electrophilic CF_3-transfer reagents.

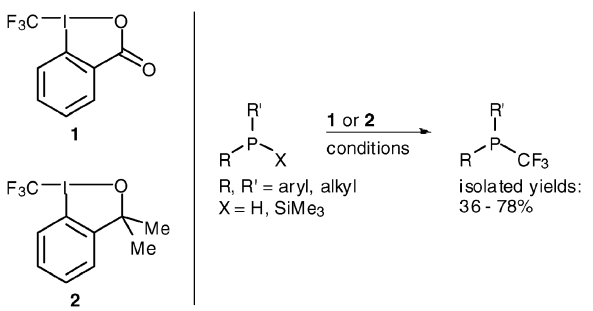
Organophosphorus compounds containing a trivalent P-centre are of great importance in many areas of chemistry—in particular as ligands in transition-metal complexes. The introduction of small, strongly electron withdrawing substituents at phosphorus is an important aspect since it allows the bonding behavior of the P-donor atom towards the metal atom in a complex to be altered. Thus, the introduction of a CF_3 fragment on phosphorus(III) is interesting for the reason that the smallest member of the perfluoroalkyl series leads to phosphine ligands with altered σ-donating and π-accepting properties. Such phosphines can thus serve as surrogates of CO, NO or PF_3 from an electronic point of view at the expense of an increased steric demand.[1] The direct, late stage introduction of a CF_3 functional group at phosphorus is a task with little precedence in the literature. The first reports on the synthesis of $R_2P(CF_3)$ date back to the middle of the last century and utilize trifluoroiodomethane in a radical reaction with suitable phosphorus precursors such as Me_3P[2] or $Ph_2P–PPh_2$.[3] The concomitantly formed equimolar amount of $Me_4P^+ I^-$ or Ph_2PI and the handling of gaseous ICF_3 render this method problematic, inefficient and somewhat limited with respect to generality.

Alternatively, nucleophilic trifluoromethylation reactions using Me_3SiCF_3 (known as Ruppert–Prakash reagent) have been reported for *P*-fluorophosphines and -phosphates,[4] *P*-cyano phosphines,[5] and fluorinated phosphazenes.[6] These methods require rather uncommon starting materials which are not commercially available and have to be accessed in multistep procedures. The synthesis of $P(CF_3)_3$ from cheap $P(OPh)_3$ and Me_3SiCF_3 rather represents an exception.[7]

Umemoto has shown that *S*-trifluoromethyl dibenzothiophenium salts as electrophilic trifluoromethylating reagents give *P*-trifluoromethyltriphenylphosphonium salts starting from triphenylphosphine.[8] However, the same approach has never been applied to the synthesis of tertiary phosphines from the corresponding secondary derivatives.

We recently succeeded in accessing a new class of electrophilic trifluoromethylating reagents based on hypervalent λ^3-organoiodine exhibiting good to excellent reactivity toward several classes of nucleophiles, such as β-keto esters, α-nitro esters and mercaptanes.[9] Two members of this reagent class, **1** and **2** (Scheme 1), both derived from 2-iodobenzoic acid, are typically applied in electrophilic trifluoromethylations in our laboratory.

We have found that these reagents are suited for the formal exchange of a H^+ with CF_3^+ at the phosphorus atom of a phosphine, in close analogy to the synthesis of trifluoromethylthioethers from thiols. Thus, mixing equimolar amounts of either one of the reagents **1–2** and diphenylphosphine at ambient or at low temperature (−78 °C) in CH_2Cl_2 gave the desired diphenyl(trifluoromethyl)phosphine (**7**) in 78% or 74% isolated yield after purification by column chromatography (Table 1, Entries 3 and 4). Similarly, the more basic, nucleophilic and sterically demanding dicyclohexylphosphine reacted readily under the same reaction conditions and was isolated as the corresponding phosphine sulfide (**6**) in 52% isolated yield after stirring with S_8 to avoid rapid oxidation during work-up and isolation (Entry 1). Interestingly, in addition to diphenylphosphine, the corresponding *P*-trimethylsilylated derivative[10] underwent trifluoromethylation under the same reaction conditions in comparable yield (**7**, 69%, Entries 9–11). As a side product, trimethylsilyl 2-iodobenzoate was detected by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy. Increasing the steric bulk on the *ortho*-position of the aryl substituents of the phosphine resulted in diminished product yields with both reagents (Table 1, Entries 12 and 13). Notably, the corresponding lithium and potassium phosphides ($MPPh_2$, M = Li, K) did only produce trace amounts of the



Scheme 1 Left: Electrophilic trifluoromethylation reagents **1** and **2**. Right: Trifluoromethylation of P(III)-centres using λ^3-iodanes **1** or **2**.

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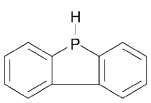
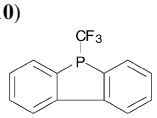
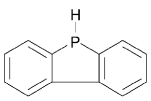
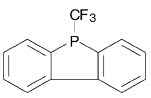
† Electronic supplementary information (ESI) available: Detailed experimental procedures including characterization and spectroscopic data for compounds **6–15**. See DOI: 10.1039/b801424h

Table 1 Electrophilic trifluoromethylation of phosphines using **1** or **2**

	Substrate	Conditions	Product	Yield[a]
1	Cy_2PH	**2**, CH_2Cl_2, −78 °C → r.t.	$Cy_2(CF_3)P{=}S$[b] (**6**)	52%
2	$CyPH_2$	**1**, CD_2Cl_2, r.t.	$CyPH(CF_3)$ (**15**)	54%[d,e]
3	Ph_2PH	**1**, CH_2Cl_2, r.t.	$Ph_2P(CF_3)$ (**7**)	78%
4	Ph_2PH	**2**, CH_2Cl_2, −78 °C → r.t.	$Ph_2P(CF_3)$ (**7**)	74%
5	Ph_2PH	**2**, MeOH, −78 °C → r.t.	$Ph_2P(CF_3)$ (**7**)	65%
6	Ph_2PH	**2**, MeCN, −78 °C → r.t.	$Ph_2P(CF_3)$ (**7**)	70%
7	Ph_2PH	**2**, Toluene, −78 °C → r.t.	$Ph_2P(CF_3)$ (**7**)	55%
8	$PhPH_2$	**1**, CD_2Cl_2, r.t.	$PhPH(CF_3)$ (**14**)	84%[d]
9	$Ph_2P(SiMe_3)$	**1**, CD_2Cl_2, r.t.	$Ph_2P(CF_3)$ (**7**)	92%[d]
10	$Ph_2P(SiMe_3)$	**2**, CH_2Cl_2, −78 °C → r.t.	$Ph_2P(CF_3)$ (**7**)	69%
11	$Ph_2P(SiMe_3)$	**2**, CD_2Cl_2, r.t.	$Ph_2P(CF_3)$ (**7**)	66%
12	$(o\text{-Tol})_2PH$	**1**, CH_2Cl_2, r.t.	$(o\text{-Tol})_2P(CF_3)$ (**8**)	48%
13	$(o\text{-Tol})_2PH$	**2**, CH_2Cl_2, −78 °C → r.t.	$(o\text{-Tol})_2P(CF_3)$ (**8**)	50%
14	$(p\text{-Tol})_2PH$	**1**, CH_2Cl_2, r.t.	$(p\text{-Tol})_2P(CF_3)$ (**9**)	78%
15	$(p\text{-Tol})_2PH$	**2**, CH_2Cl_2, −78 °C → r.t.	$(p\text{-Tol})_2P(CF_3)$ (**9**)	70%
16	$(p\text{-Tol})_2PH$	**2**, CH_2Cl_2, 0 °C Syringe pump[c]	$(p\text{-Tol})_2P(CF_3)$ (**9**)	66%
17	$(\beta\text{-Np})_2PH$	**1**, CH_2Cl_2, 0 °C → r.t.	$(\beta\text{-Np})_2P(CF_3)$ (**10**)	58%
18	$(\beta\text{-Np})_2PH$	**2**, CH_2Cl_2, −78 °C → r.t.	$(\beta\text{-Np})_2P(CF_3)$ (**10**)	53%
19	 (**5**)	**1**, CH_2Cl_2, r.t.	 (**11**)	41%
20	 (**5**)	**2**, CH_2Cl_2, −78 °C → r.t.	 (**11**)	44%
21	$(p\text{-OMePh})_2PH$	**1**, CH_2Cl_2, r.t.	$(p\text{-OMePh})_2P(CF_3)$ (**12**)	36%
22	$(p\text{-OMePh})_2PH$	**2**, CH_2Cl_2, −78 °C → r.t.	$(p\text{-OMePh})_2P(CF_3)$ (**12**)	58%
23	*rac*-(*o*-anisyl)PhPH	**2**, CH_2Cl_2, −78 °C → r.t.	*rac*-(*o*-anisyl)$PhP(CF_3)$ (**13**)	63%

[a] Isolated yields, unless otherwise stated. [b] S_8 as oxidant. [c] A solution of the phosphine was added to a solution of **2** over the course of 45 min. [d] Conversion calculated based on ^{19}F NMR spectroscopy with $PhCF_3$ as internal reference. [e] Sum of $CyPH(CF_3)$ and $CyPH_2(CF_3)^+$.

trifluoromethylated product as observed by ^{19}F NMR spectroscopy. Interestingly, mixing primary phosphines such as phenyl- or cyclohexylphosphine with equimolar amounts of **1** in CD_2Cl_2 at ambient temperature resulted in the formation of the corresponding monotrifluoromethylated phosphines exclusively (Table 1, Entries 2 and 8). This constitutes a direct and very convenient synthesis of such secondary racemic *P*-trifluoromethylated phosphines. Experimental details are provided as Electronic Supplementary Information.†

At present, the chromatographic separation of the trifluoromethylphosphines from the byproduct deriving from the reagents is not yet optimal and explains the relatively low yields of isolated product in some cases.

From a mechanistic point of view, it seems reasonable to exclude the involvement of phosphides as intermediates. The two reagents **1** and **2** generate bases of very different strengths (a carboxylate and an alcoholate, respectively) and yet afford similar yields. This interpretation is further supported by the

fact that, as mentioned above, neither Li or K diphenylphosphide leads to any significant product formation. Furthermore, it can be speculated that a radical pathway might be operating, based on the observation that the reaction of Cy_2PH with **2** leads to the formation of $CyP(CF_3)_2$ and $CyP(CF_3)H$ in trace amounts, together with the main product $Cy_2P(CF_3)$ as detected by $^{31}P\{^1H\}$ NMR spectroscopy. This can be rationalized by assuming a homolytic cleavage of a C–P bond (P–Cy) after the attack of Cy_2PH by a CF_3-radical instead of P–H bond cleavage.

In conclusion, we have demonstrated that secondary and tertiary P(III) compounds containing only one CF_3-substituent can be conveniently obtained using hypervalent electrophilic λ^3 I–CF_3 compounds starting from readily accessible or even commercially available primary and secondary phosphines. Thus, the method allows for selective alteration of the electronic properties of the phosphorus donor atom. The trifluoromethylated phosphines were found to serve as suitable ligands for transition-metals in several oxidation states forming stable, crystalline complexes with appropriate Pd(II),[11] Ru(II), Rh(I) and Ir(III) precursors, respectively. We are currently pursuing the application of these newly accessible P–CF_3 ligands in catalytic reactions.[12]

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