Copper-Catalyzed Aerobic Oxidative Trifluoromethylation of H-Phosphonates Using Trimethyl(trifluoromethyl)silane

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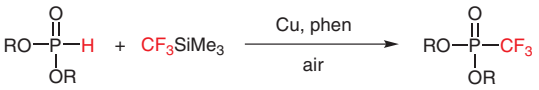
Abstract: Copper-catalyzed aerobic oxidative trifluoromethylation of readily accessible H-phosphonates was demonstrated for the first time. This method not only provides an alternative method for the facile synthesis of a series of biologically important CF_3-phosphonates, but also demonstrates the first example of the efficient construction of a P–CF_3 bond via transition-metal catalysis.

Key words: copper catalysis, phosphonates, trifluoromethylation

The introduction of the trifluoromethyl (CF_3) group into organic molecules can bring about remarkable changes in physical, chemical, and biological properties because of the strongly electron-withdrawing nature and large hydrophobic domain of the trifluoromethyl group.[1] As a consequence, tremendous effort has been devoted to the introduction of the trifluoromethyl group into organic structures. This has led to numerous methods for the efficient incorporation of the trifluoromethyl group into diverse organic molecules using nucleophilic, electrophilic, or radical sources.[2,3] Recently, the transition-metal-mediated or -catalyzed fluoroalkyl cross-coupling reaction has proven to be an attractive and efficient trifluoromethylation protocol.[3] In particular, it is now possible to fulfill the direct trifluoromethylation of C–H bonds of aromatics, alkynes, or olefins in the presence of transition-metal catalysts, precluding the need for the prefunctionalization of substrates.[4] Despite this extensive progress, current trifluoromethylation methods are limited to the construction of C–CF_3 linkages. In contrast, the analogous generation of heteroatom–CF_3 bonds from heteroatom–H bonds without the need for prefunctionalization remains largely unexplored,[5] particularly via transition-metal catalysis. In fact, to the best of our knowledge, the sole protocol involving direct trifluoromethylation at a heteroatom is the electrophilic trifluoromethylation of N-, O-, S, or P-centered nucleophiles developed by Umemoto[5a,b] and Togni.[5c–h] Herein, we disclose a new methodology for catalytically constructing P–CF_3 bonds via aerobic oxidative trifluoromethylation of H-phosphonates with a nucleophilic trifluoromethylating reagent (Scheme 1).



Scheme 1 Oxidative trifluoromethylation of H-phosphonates

Phosphonates are an important class of compounds because of their potential as analogues of biologically important phosphates, and a number of new phosphonates have been investigated for their diverse biological activity.[6] However, there has been relatively little investigation of fluorinated phosphonates,[7] although fluorinated phosphonates were found to be excellent mimics of phosphate esters[6] as well as analogues of enzyme inhibitors.[8] The dearth of fluorinated phosphonates especially trifluoromethylated phosphonates can be attributed to a lack of synthetic methods since common methods used for the preparation of phosphonates cannot be directly applied to trifluoromethylated analogues. For example, chlorotrifluoromethane and trifluoroiodomethane were found to be totally unreactive under the traditional conditions of the Michaelis–Arbuzov reaction, and a photochemical modification of the Arbuzov reaction was required for the preparation of CF_3-phosphonates.[9] In recent years, only rare examples of synthetic methodology for these compounds have been reported.[10–12] In 1997, Burton reported a photochemically induced radical reaction of tetraethyl diphosphite [$(EtO)_2POP(OEt)_2$] and trifluoroiodomethane in the presence of di-*tert*-butyl peroxide providing diethyl trifluoromethylphosphonate in moderate yield.[11] Later, synthesis of CF_3-phosphonates via nucleophilic trifluoromethylation of fluorophosphines followed by oxidation or direct nucleophilic trifluoromethylation of *P*-fluorophosphonates was reported,[12] however, the starting materials are not common and are also not commercially available. Alternatively, Yagupolskii has shown that CF_3-phosphonates can be prepared from readily available H-phosphonates using diaryltrifluoromethylsulfonium salts as the electrophilic trifluoromethylating reagent.[13] Obviously, the development of a simpler and general methodology to

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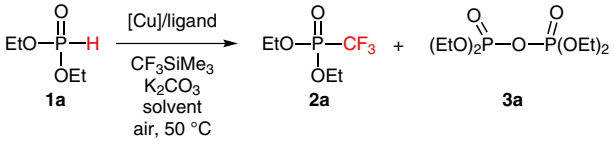
install the trifluoromethyl group into phosphonates is still desired.

Recent reports from our group regarding a copper-mediated or -catalyzed oxidative trifluoromethylation protocol using the nucleophilic trifluoromethylating reagent trimethyl(trifluoromethyl)silane (Ruppert–Prakash reagent, CF_3SiMe_3), have allowed direct and efficient introduction of the trifluoromethyl group into various substrates such as terminal alkynes,[4b] aryl boronic acids[3h] and heteroaromatics.[4k] In light of these results, we hypothesized that a similar copper-catalyzed oxidative trifluoromethylation protocol might allow the formation of a P(O)–CF_3 bond.

We first examined the ability of various copper salts to catalyze the oxidative trifluoromethylation of diethyl phosphonate (**1a**) using trimethyl(trifluoromethyl)silane as the trifluoromethylating reagent and potassium carbonate as the base under an air atmosphere (Table 1). The result showed that copper(II) hydroxide was a good catalyst for the reaction affording the desired product **2a** in 63% yield together with the remaining starting material (entry 1). In contrast, **1a** was totally consumed in the presence of other Cu(I) or Cu(II) salts while the formation of side product **3a** (detected by GC-MS)[14] diminished the reaction efficiency (entries 2–5). The complete transformation of the starting material **1a** was fulfilled by simply prolonging the reaction time from 24 hours to 36 hours and **2a** could be obtained in 78% yield (entry 6). The use of 1,10-phenanthroline (phen) as the ligand is essential for this transformation (entry 6). Switching to other ligands such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), 2,2′-bipyridine, and 2,4,6-trimethylpyridine led to no observed formation of **2a** (entries 7–9). Further optimization of the solvent suggested that the solvent highly affected this reaction. Although toluene gave a comparable yield of **2a**, dichloromethane, *N*,*N*-dimethylformamide, and tetrahydrofuran dramatically suppressed the reaction (entries 10–13).

With the optimized condition in hand, we next tested the scope of the reaction with other H-phosphonates. The copper-catalyzed aerobic oxidative trifluoromethylation protocol can be applied to other H-phosphonates to produce the corresponding CF_3-phosphonates (Table 2). However, the reaction efficiency was highly dependent on the substrate. In the presence of 30 mol% copper(II) hydroxide, only substrates **1a** and **1f** readily gave the desired coupling products in moderate yields (entries 1, 6), while other H-phosphonates were almost unreactive (entries 2–5, 7). Increasing the loading of copper(II) hydroxide from 30 mol% to 60 mol% only encouraged the desired oxidative trifluoromethylation of the two substrates (**1b**, **1e**) and led to moderate yields of the corresponding CF_3-phosphonates (entries 2, 5). To our delight, switching the catalyst copper(II) hydroxide to the more reactive copper(II) ethoxide dramatically facilitated the transformation of

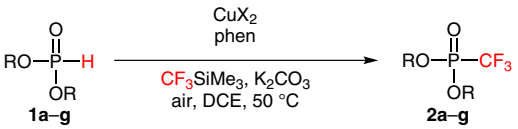
Table 1 Copper-Catalyzed Aerobic Trifluoromethylation of Diethyl Phosphonate[a]



Entry	Cu catalyst (30 mol%)	Ligand (30 mol%)	Solvent (0.3 M)	Yield[b] (%)
1	$Cu(OH)_2$	phen	DCE	63
2	$Cu(OEt)_2$	phen	DCE	60
3	$Cu(OAc)_2$	phen	DCE	29
4	CuOAc	phen	DCE	54
5	$CuCl_2$	phen	DCE	20
6	$Cu(OH)_2$	phen	DCE	56 (78)[c]
7	$Cu(OH)_2$	TMEDA	DCE	–
8	$Cu(OH)_2$	2,2′-bipyridine	DCE	–
9	$Cu(OH)_2$	2,4,6-trimethylpyridine	DCE	–
10	$Cu(OH)_2$	phen	CH_2Cl_2	trace
11	$Cu(OH)_2$	phen	toluene	77
12	$Cu(OH)_2$	phen	DMF	–
13	$Cu(OH)_2$	phen	THF	15

[a] Reaction conditions: **1a** (0.3 mmol), copper catalyst (0.09 mmol), ligand (0.09 mmol), CF_3SiMe_3 (1.2 mmol), K_2CO_3 (1.2 mmol), solvent (1 mL), 50 °C, 24 h, under air.
[b] Yield was determined by ^{19}F NMR analysis using (trifluoromethyl)benzene as an internal standard.
[c] The reaction was conducted for 36 h.

Table 2 Copper-Catalyzed Oxidative Trifluoromethylation of H-Phosphonates[a]



Entry	Substrate	R	Copper salt (mol%)	Product	Yield[b] (%)
1	**1a**	Et	$Cu(OH)_2$ (30)	**2a**	56
2	**1b**	Pr	$Cu(OH)_2$ (60)	**2b**	73
3	**1c**	Bu	$Cu(OEt)_2$ (30)	**2c**	87
4	**1d**	*i*-Bu	$Cu(OEt)_2$ (30)	**2d**	85
5	**1e**	$(CH_2)_5Me$	$Cu(OH)_2$ (60)	**2e**	90
6	**1f**	$(CH_2)_4Cl$	$Cu(OH)_2$ (30)	**2f**	70
7	**1g**	cyclohexyl	$Cu(OEt)_2$ (30)	**2g**	76

[a] Reaction conditions: **1** (0.3 mmol), copper catalyst (0.09 mmol or 0.18 mmol), phen (0.09 mmol or 0.18 mmol), CF_3SiMe_3 (1.2 mmol), K_2CO_3 (1.2 mmol), DCE (1 mL), 50 °C, 36 h, under air, sealed tube.
[b] Isolated yield.

substrates **1c**, **1d**, and **1g**, providing the corresponding products in high to excellent yields (entries 3, 4, 7). The reason for the high substrate-dependence remains obscure.

In summary, a copper-catalyzed oxidative trifluoromethylation of readily accessible H-phosphonates with trimethyl(trifluoromethyl)silane was revealed for the first time. The new methodology not only allows for the facile synthesis of biologically important trifluoromethylphosphonates without the need for prefunctionalization, but also has potential for the formation other new transition-metal-catalyzed heteroatom–CF_3 bonds, such as N–CF_3, O–CF_3, and S–CF_3 bonds. Ongoing studies are focused on the clarification of the reaction mechanism and expanding the scope of this transformation.

Unless otherwise noted, all reactions were heated on hot plates with oil baths calibrated to an external thermometer. Prior to starting experiments, the hot plate was turned on, and the oil bath was allowed to equilibrate to the desired temperature over 30 min. ^{1}H and ^{19}F NMR spectra ($CFCl_3$ as outside standard and low field is positive) were recorded on a Bruker AM300 spectrometer. ^{13}C NMR was recorded on a Bruker AM400 spectrometer. Unless otherwise noted, all reagents were obtained commercially and used without further purification. Substrates **1a**–**d** were purchased from commercial sources (Aldrich, Alfa and TCI) and used as received. Substrates **1e**–**g** were prepared according to literature procedures.[5g] Reactions were performed under an atmosphere of air using glassware that was flame-dried under vacuum.

Trifluoromethylphosphonates 2a–g; General Procedure

To an oven-dried 40-mL sealed tube containing a magnetic stir bar in air, were added $Cu(OH)_2$ (0.09 mmol or 0.18 mmol) or $Cu(OEt)_2$ (0.09 mmol), 1,10-phenanthroline (0.09 mmol or 0.18 mmol), K_2CO_3 (1.20 mmol), DCE (1 mL), then substrate **1** (0.03 mmol) and CF_3SiMe_3 (1.20 mmol) (see also Table 2). The vessel was sealed with a Teflon-lined septum, and was vigorously stirred at 50 °C for 36 h. The mixture was cooled to r.t. and diluted with CH_2Cl_2, filtered through a short pad of Celite, washed with CH_2Cl_2, and concentrated in vacuo. The resulting residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 100:1 to 10:1, depending on the substrate).

Diethyl Trifluoromethylphosphonate (2a)

Yellow oil; yield: 35 mg (56%).

IR (neat): 1233, 1146, 1045, 420 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.39–4.31 (m, 4 H), 1.42 (t, J = 5.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.89 (dq, J = 282.5 Hz, J = 307.9 Hz), 65.68 (d, J = 6.2 Hz), 16.12 (d, J = 5.0 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.06 (d, $^2J_{P,F}$ = 122 Hz, 3 F).

^{31}P{^{1}H} NMR ($CDCl_3$): δ = –2.56 (q, $^2J_{P,F}$ = 124 Hz).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_5H_{10}F_3NaO_3P$: 229.0212; found: 229.0216.

Dipropyl Trifluoromethylphosphonate (2b)

Yellow oil; yield: 51 mg (73%).

IR (neat): 1736, 1217, 1206, 423 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.26–4.18 (m, 4 H), 1.76 (sextet, J = 5.1 Hz, 4 H), 0.99 (t, J = 5.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.95 (dq, J = 283.2 Hz, J = 307.9 Hz), 70.03 (d, J = 6.6 Hz), 23.03 (d, J = 5.9 Hz), 9.6.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –72.74 (d, $^2J_{P,F}$ = 123 Hz, 3 F).

^{31}P{^{1}H} NMR ($CDCl_3$): δ = –2.38 (q, $^2J_{P,F}$ = 123 Hz).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_7H_{14}F_3NaO_3P$: 257.0526; found: 257.0531.

Dibutyl Trifluoromethylphosphonate (2c)

Yellow oil; yield: 68 mg (87%).

IR (neat): 1470, 1226, 419 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.30–4.22 (m, 4 H), 1.71 (quint, J = 5.7 Hz, 4 H), 1.71 (quint, J = 5.7 Hz, 4 H), 1.42 (sextet, J = 5.4 Hz, 4 H), 0.94 (t, J = 5.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.95 (dq, J = 282.9 Hz, J = 307.9 Hz), 69.19 (d, J = 6.7 Hz), 32.11 (d, J = 5.4 Hz), 18.29, 13.24.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –72.71 (d, $^2J_{P,F}$ = 123 Hz, 3 F).

^{31}P{^{1}H} NMR ($CDCl_3$): δ = –2.38 (q, $^2J_{P,F}$ = 123 Hz).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_9H_{18}F_3NaO_3P$: 285.0838; found: 285.0839.

Diisobutyl Trifluoromethylphosphonate (2d)

Yellow oil; yield: 66 mg (85%).

IR (neat): 1738, 1372, 1217, 1032, 421 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.05–3.97 (m, 4 H), 2.03–1.94 (m, 2 H), 0.95 (d, J = 5.7 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 120.09 (dq, J = 279.6 Hz, J = 307.9 Hz), 75.12 (d, J = 6.9 Hz), 29.73 (d, J = 6.3 Hz), 18.28, 18.26.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –72.51 (d, $^2J_{P,F}$ = 123 Hz, 3 F).

^{31}P{^{1}H} NMR ($CDCl_3$): –2.44 (q, $^2J_{P,F}$ = 123 Hz).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_9H_{18}F_3NaO_3P$: 285.0838; found: 285.0845.

Dihexyl Trifluoromethylphosphonate (2e)

Yellow oil; yield: 86 mg (90%).

IR (neat): 2933, 1137, 1020, 420 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.30–4.22 (m, 4 H), 1.72 (quint, J = 6.8 Hz, 4 H), 1.43–1.37 (m, 4 H), 1.33–1.29 (m, 8 H), 0.90 (t, J = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 120.03 (dq, J = 284.8 Hz, J = 310.7 Hz), 69.59 (d, J = 6.4 Hz), 31.09, 30.19 (d, J = 5.6 Hz), 24.79, 22.39, 13.82.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –72.24 (d, $^2J_{P,F}$ = 122 Hz, 3 F).

^{31}P{^{1}H} NMR ($CDCl_3$): δ = –2.34 (q, $^2J_{P,F}$ = 124 Hz).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{13}H_{26}F_3NaO_3P$: 341.1464; found: 341.1469.

Bis(4-chlorobutyl) Trifluoromethylphosphonate (2f)

Yellow oil; yield: 69 mg (70%).

IR (neat): 2964, 1282, 1141, 1027, 431 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.36–4.31 (m, 4 H), 3.59 (t, J = 5.4 Hz, 4 H), 1.93–1.89 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.89 (dq, J = 284.1 Hz, J = 308.02 Hz), 68.76 (d, J = 5.9 Hz), 44.01, 29.27, 27.59 (d, J = 6.1 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –72.21 (d, $^2J_{P,F}$ = 124 Hz, 3 F).

^{31}P{^{1}H} NMR ($CDCl_3$): δ = –2.26 (q, $^2J_{P,F}$ = 124 Hz).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_9H_{16}Cl_2F_3NaO_3P$: 353.0058; found: 353.0062.

Dicyclohexyl Trifluoromethylphosphonate (2g)

Yellow oil; yield: 71 mg (76%).

IR (neat): 2942, 1453, 1138, 420 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.69–4.61 (m, 2 H), 1.97–1.94 (m, 4 H), 1.78–1.74 (m, 4 H), 1.68–1.58 (m, 4 H), 1.55–1.48 (m, 2 H), 1.42–1.23 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.99 (dq, J = 284.6 Hz, J = 307.9 Hz), 79.77 (d, J = 7.0 Hz), 33.60 (d, J = 3.2 Hz), 33.05 (d, J = 4.9 Hz), 24.81, 23.20 (d, J = 3.5 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.35 (d, $^2J_{P,F}$ = 122 Hz, 3 F).

^{31}P{^{1}H} NMR ($CDCl_3$): δ = –4.60 (q, $^2J_{P,F}$ = 123 Hz).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{22}F_3NaO_3P$: 337.1151; found: 337.1148.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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