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Electrophilic Trifluoromethylation of *S*-Hydrogen Phosphorothioates

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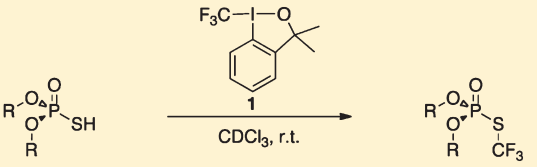
Supporting Information

ABSTRACT: A series of *S*-hydrogen phosphorothioates have been converted to the corresponding *S*-trifluoromethyl derivatives upon reaction with the electrophilic trifluoromethylation reagent **1** (trifluoromethyl 1,3-dihydro-3,3-dimethyl-1,2-benziodoxole). Relative rate data were obtained by ^{19}F NMR monitoring of competition experiments and were evaluated by means of the Taft equation. A high positive polar sensitivity factor of 2.55 was found for electron-rich substrates and a negative one of −0.37 for electron-poor ones, implying the involvement of two different rate-determining steps. Furthermore, the reaction was found to be unaffected by steric factors.



The electrophilic trifluoromethylation of a variety of nucleophiles has attracted considerable attention in the synthetic organic community over the past few years because of the promising physicochemical properties of molecules containing the CF_3 group.[1] To this end, several reagents have been developed, most prominently by Yagupolskii,[2,3] Umemoto,[4−7] and our group.[8,9] We have reported the successful trifluoromethylation of soft nucleophiles, such as phosphines[10] and thiols,[11] and hard ones, such as alcohols,[12] sulfonic acids,[13] and most recently, nitriles,[14] by using hypervalent iodine reagents of type **1**. We wanted to further expand the application scope of our reagents by targeting *S*-hydrogen phosphorothioates, bioisosteres of natural phosphate backbones in DNA and RNA, usually employed to increase the stability of man-made oligo- and polynucleotides toward nucleases in antisense applications.[15,16] Featuring an SH group adjacent to a P−O double bond, the reactivity of these compounds was expected to be between that of thiols and sulfonic acids. Furthermore, because of the inherently acidic nature of the protic functional group it was expected that activation of reagent **1** by strong Brønsted or Lewis acids would be unnecessary.

Examples of *S*-trifluoromethyl phosphorothioates are scarce, and those that are known have mostly been prepared by treating phosphonates with bis(trifluoromethyl)disulfide.[17,18] It has been reported that the products are thermally labile, thereby losing SCF_2 to yield the corresponding fluorophosphates. This elimination may also be induced by treatment with triethylamine.[19,20]

Envisaging a late-stage electrophilic trifluoromethylation of *S*-hydrogen phosphorothioates in biomolecules by our reagent **1**, it was important to evaluate the influence of both steric bulk and inductive properties of the substituents on the reactivity. These aspects were studied by preparing a series of derivatives differing in the nature of the alkyl substituents and by determining relative rates of formation, subsequently analyzed by using the Taft equation (vide infra).[21−23]

Oxidation of phosphonates by elemental sulfur in the presence of a base is known to give access to phosphorothioates that can be readily converted to the corresponding free acids by treatment with excess aqueous HCl.[24,25] If commercially unavailable, phosphonates were prepared in excellent yields by the treatment of PCl_3 with 3 equiv of the desired alcohol at 0 °C in the presence of 2 equiv of pyridine to trap the liberated HCl.[26] Electron-deficient phosphonates (**2h**−**j**) were prepared at ambient temperature while constantly removing HCl by purging the reaction mixture with dry nitrogen.[27] Often, the products were of high enough purity to be used directly in the oxidation step. Thus, substrates **3a**−**k** (Scheme 1 and Table 1) were obtained in yields up to 89% over two steps. It is assumed that compound **3k**, because of its similarity to the MEM protecting group, was partially cleaved during the protonation step to furnish phosphorothioic acid, thus explaining the low yield of ca. 18%.[28]

With substrates **3a**−**k** in hand, the optimal reaction conditions were sought using substrate **3c**. A maximum yield of 76% determined by ^{19}F NMR with α,α,α-trifluorotoluene as internal standard was obtained with 1.25 equiv of substrate and 1 equiv of reagent **1**. Higher loadings led to significant decomposition of reagent **1** and to the formation of substantial amounts of trifluoromethane. Furthermore, it was found that the reaction may be carried out in standard bottled solvents and that rigorous exclusion of moisture is not necessary. Applying the optimized conditions to all substrates gave ^{19}F NMR yields ranging from 8% up to 79%.[29] Isolation of pure products, however, proved to be complicated to nearly impossible, as they decomposed when subjected to chromatographic purification (silica gel, alumina). An exception was found in the case of the cyclohexyl derivative **4g** which was isolated in 63% yield by chromatographic purification on silica gel. Distillation of the reaction mixture was only applicable to the low boiling ethyl (**4a**) and isopropyl derivatives (**4c**). In the other cases, thermal treatment led to dehydration of 2-(2-iodophenyl)propan-2-ol, the byproduct deriving from reagent **1**, yielding

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Scheme 1. Substrate Synthesis and Subsequent Electrophilic Trifluoromethylation

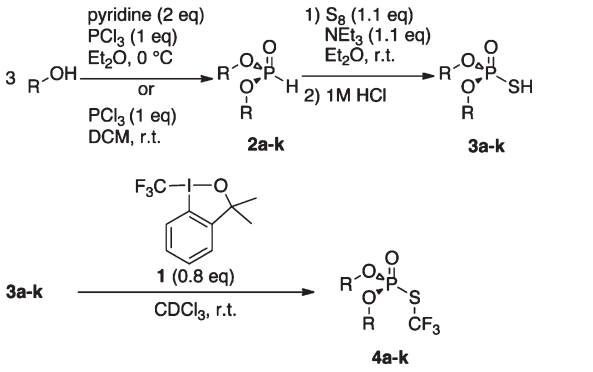


Table 1. Synthesis of 3a−k and 4a−k and Relative Rates k_R/k_{Et}

entry	R	3[a] (%)	4[b] (%)	s^*_{corr}[c]	k_{rel}[d]
a	Et	80.0[e]	64 (22)	0.00	1.000
b	Pr	89.0	67	−0.02	0.899
c	^{i}Pr	81.0	76 (20)	−0.09	0.620
d	Bu	86.0[e]	72	−0.03	0.861
e	^{i}Bu	82.7	68	−0.03	0.821
f	neopentyl	69.7[f]	73	−0.07	0.858
g	Cy	63.0	79 (63)	−0.08	0.629
h	$Cl(CH_2)_2$	62.0	8	0.49	0.842
i	$Cl(CH_2)_3$	51.0	38	0.24	1.038
j	$Cl(CH_2)_4$	69.7	59	0.15[g]	1.101
k	$MeO(CH_2)_2$	17.8	50	0.34	0.520

[a] Isolated yield over two steps. [b] ^{19}F NMR yield determined with α,α,α-trifluorotoluene as internal standard and in parentheses isolated yield. [c] Corrected steric parameters according to eq 1 based on preferred values from ref 30. [d] Relative rates determined by competition experiments using ^{19}F NMR spectroscopy. [e] Commercially available phosphonates were used. [f] Synthesized using a different protocol than the one depicted in Scheme 1. [g] Calculated according to ref 31.

1-iodo-2-(prop-1-en-2-yl)benzene that could not be separated from the desired products.

Using isolated *O,O*-dicyclohexyl *S*-(trifluoromethyl) phosphorothioate (**4g**), trifluoromethylation of the sulfur center was proven unambiguously by inducing SCF_2 elimination through treatment with 3.0 equiv of triethylamine in CH_2Cl_2 at 0 °C. Subsequent HR-ESI-MS analysis of the reaction mixture showed the corresponding fluorophosphate as the ammonium adduct and as its protonated form.

As it was found that dimethyl *S*-hydrogen phosphorothioate slowly decomposes over time, the diethyl derivative was chosen as standard against which the relative rates were to be determined. Thus, a modified Taft equation (eq 1) which accounts for the translated origin due to the ethyl group standardization was used in our study.

$$\log\left(\frac{k_R}{k_{Et}}\right) = \rho^*(\sigma^*_R - \sigma^*_{Et}) + \delta(E_{S,R} - E_{S,Et}) \qquad (1)$$

Relative rates were determined by competition experiments using 5 equiv of substrate and standard **3a**, respectively—the rate thus being reflected by the ratio of the products formed, as monitored by ^{19}F NMR spectroscopy.[32] Initial reproducibility

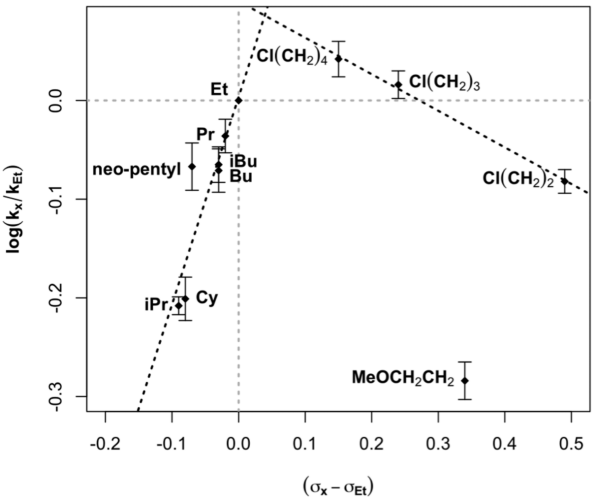
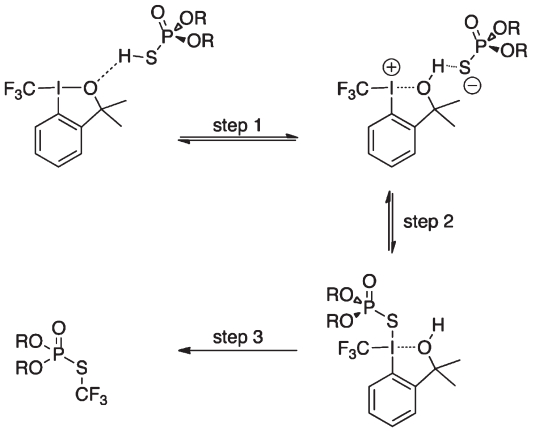


Figure 1. Analysis of the relative rate data using eq 1 shows two distinctly linear relationships suggesting two different rate-determining steps.

Scheme 2. Proposed Three-Step Mechanism Unifying Findings for Electron-Rich and Electron-Poor Substrates



problems of the relative rate of substrate **3h**, proposed to stem from slow intramolecular cyclization (nucleophilic displacement of chlorine by sulfur), were solved by storing the substrate at −17 °C and by performing competition experiments immediately after its preparation. All other substrates showed long time stability, and the results were reproducible using the original samples within a time frame of several months. Thus, relative uncertainties ranging from 2.7 to 5.5% were observed.

A Taft plot of the obtained data is given in Figure 1, and a mechanistic interpretation is provided in Scheme 2. By assuming that the steric influence is neglectable and thus considering only polar influences, the Taft plot clearly shows two different mechanistic regimes, one for electron-rich alkyl substrates and one for derivatives containing electron-poor chloroalkyl groups. Moreover, performing multiple linear regression on the data set for the sterically diverse electron-rich substrates corroborated the assumption that the steric sensitivity is unsignificant.[33]

A high positive polar sensitivity factor of 2.55 found in the case of electron-rich substrates is indicative of a negative charge building up during the rate-determining step. As substrates containing electron-rich substituents are expected to be less acidic, their ability to activate reagent **1** by protonation is lower.

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Thus, the proton-transfer equilibrium between reagent **1** and substrate lies to the left (Scheme 2, step 1). In the case of electron-poor substrates, a moderate polar sensitivity factor of −0.37 was found, implying a positive charge buildup during the RDS. Hence, the initial equilibrium is shifted to the right. However, by lowering the electron density on sulfur the substrates become less good donors, such that coordination to the iodonium ion, preceding the reductive elimination step, becomes less favorable (Scheme 2, step 2).

O,O-Bis(2-methoxyethyl) *S*-hydrogen phosphorothioate (**3k**) reacts significantly slower than the chloroalkyl derivatives although an intermediate reactivity between that of 2-chloroethyl (**3h**) and 3-chloropropyl (**3i**) substrates was expected. Thus, it is proposed that, after the protonation of the reagent and coordination to the iodonium core, the remote methoxy group further stabilizes the intermediate, thereby slowing down the reductive elimination step (Scheme 2, step 3), this resulting in a lower overall relative rate. This kind of stabilization has already been noted before in different hypervalent iodine(III) reagents.[34]

In conclusion, we have shown that *S*-hydrogen phosphorothioates are readily trifluoromethylated in moderate to good yields, though isolation remains a practical problem. By running competition experiments and applying the Taft equation it was shown that electronic effects heavily influence the relative rates but steric factors are generally unimportant. The kinetic findings further imply that not only activation of reagent **1** plays a critical role but that nucleophilicity is equally important. If substrates contain suitable donors for iodine(III), the reductive elimination to yield the product may be slower than expected due to additional stabilization of the key intermediate.

EXPERIMENTAL SECTION

All reactions were carried out in standard bottled solvents and without rigorous exclusion of either air or moisture.

General Procedure 1: Synthesis of Alkyl Phosphonates. To a solution of the appropriate alcohol (0.43 mol, 3 equiv) and pyridine (23.2 mL, 0.29 mol, 2 equiv) in Et_2O (50 mL) at 0 °C was added PCl_3 (12.5 mL, 0.14 mol, 1 equiv) over the course of 1 h. After complete addition, the reaction mixture was allowed to slowly warm to ambient temperature, and it was stirred for 16 h. The white suspension was then filtered under suction, and the residual pyridinium chloride was washed twice with Et_2O (50 mL). The combined filtrates were concentrated under reduced pressure and dried under HV to yield the desired phosphonates as colorless liquids. Distillation may be necessary if purity is not satisfactory.

General Procedure 2: Synthesis of Chloroalkyl Phosphonates. To a solution of the appropriate alcohol (0.43 mol, 3 equiv) in CH_2Cl_2 (200 mL) was added PCl_3 (12.5 mL, 0.14 mol, 1 equiv) in CH_2Cl_2 (70 mL) over the course of 1 h. Liberated HCl was removed by a constant nitrogen stream. After completed addition, the dropping funnel was washed with additional CH_2Cl_2 (20 mL) and the reaction mixture was stirred for 16 h while purging nitrogen to remove all dissolved HCl. The solution was then concentrated under reduced pressure and dried under HV to yield the desired phosphonate. Distillation may be necessary if purity is not satisfactory.

General Procedure 3: Synthesis of *S*-Hydrogen Phosphorothioates. To a suspension of the appropriate phosphonate (1.0 equiv) and solid sulfur (1.1 equiv) in Et_2O in a two-necked round-bottom flask equipped with a reflux condenser and a rubber septum under argon was slowly added NEt_3 (1.1 equiv). After full conversion of the phosphonate, as monitored by ^{31}P NMR spectroscopy, the suspension was diluted with Et_2O to 100 mL and then washed with aqueous HCl (100 mL, 1 M), dried over $MgSO_4$, concentrated under reduced pressure, and finally dried under HV. The resulting suspension was filtered over a small cotton plug to yield the *S*-hydrogen phosphorothioates. If necessary, *S*-hydrogen phosphorothioates may be purified by dissolving in 50% aqueous Na_2CO_3 and washing twice with Et_2O, followed by acidification of the aqueous layer with HCl (1 M) and finally by two extractions with Et_2O. These combined organic layers are then dried over $MgSO_4$, concentrated under reduced pressure, and dried under HV to yield the pure S-hydrogen phosphorothioate.

Dipropyl Phosphonate (2b). According to GP1, 32.0 mL of ^{n}PrOH was reacted to yield 23.7 g (99%) of pure product as a colorless oil: δ_H (250 MHz, $CDCl_3$) 6.78 (d, J = 692.47 Hz, 1 H), 4.00 (dt, J = 8.46, 6.64 Hz, 4 H), 1.69 (sextet, J = 7.03 Hz, 4 H), 0.94 (t, J = 7.40 Hz, 6 H); δ_C (62.9 MHz, $CDCl_3$) 67.2 (d, J = 6.05 Hz), 23.7 (d, J = 6.32 Hz), 10.0; δ_P(101.3 MHz, $CDCl_3$) 7.88; HRMS (ESI) calcd for $C_6H_{16}O_3P$ 167.0832 ($[M + H]^+$), found 167.0830.

Diisopropyl Phosphonate (2c). According to GP1, 33.0 mL of ^{i}PrOH was reacted to yield 23.5 g (99%) of pure product as a colorless oil: δ_H (300 MHz, $CDCl_3$) 6.67 (d, J = 687.08 Hz, 1 H), 4.64−4.48 (m, 2 H), 1.20 (d, J = 1.34 Hz, 6 H), 1.18 (d, J = 1.34 Hz, 6 H); δ_C (75.5 MHz, $CDCl_3$) 70.6 (d, J = 5.73 Hz), 23.8 (d, J = 4.30 Hz), 23.7 (d, J = 4.77 Hz); δ_P (121.5 MHz, $CDCl_3$) 7.29; HRMS (ESI) calcd for $C_6H_{16}O_3P$ 167.0832 ($[M + H]^+$), found 167.0832 (73.9%).

Diisobutyl Phosphonate (2e). According to GP1, 40.0 mL of ^{i}BuOH was reacted to yield 26.3 g (95%) of pure product as a colorless oil: δ_H (300 MHz, $CDCl_3$) 6.80 (d, J = 692.95 Hz, 1 H), 3.84 (ddd, J = 7.91, 6.46, 1.52 Hz, 4 H), 1.96 (nonaplet, J = 6.66 Hz, 2 H), 0.95 (d, J = 6.72 Hz, 12 H); δ_C (75.5 MHz, $CDCl_3$) 71.6 (d, J = 6.33 Hz), 29.2 (d, J = 6.43 Hz), 18.7 (d, J = 1.69 Hz); δ_P (121.5 MHz, $CDCl_3$) 8.03; HRMS (ESI) calcd for $C_8H_{20}O_3P$ 195.1145 ($[M + H]^+$), found 195.1147.

Dineopentyl Phosphonate (2f). *N,N,N′,N′,N″,N″*-Hexamethylphosphinetriamine (9.94 g, 40.2 mmol, 1.0 equiv) was added to a two-necked round-bottom flask equipped with a Teflon-coated magnetic stirring bar, a reflux condenser, and a rubber septum under argon. THF (25 mL) and distilled water (0.72 mL, 40.0 mmol, 1.0 equiv) were added, and the resulting solution was heated to reflux for 3 h. Then, neopentyl alcohol (7.19 g, 81.6 mmol, 2.0 equiv) in THF (30 mL) was added by syringe, and the reaction was continued for an additional 16 h. It was then allowed to cool to ambient temperature and concentrated under reduced pressure to furnish a yellowish oil. Distillation (56 °C, 0.02 mbar) yielded 7.6 g (84%) of pure product as a colorless oil: δ_H (300 MHz, $CDCl_3$) 6.83 (d, J = 693.40 Hz, 1 H), 3.79−3.69 (m, 4 H), 0.97 (s, 18 H); δ_C (75.5 MHz, $CDCl_3$) 74.9 (d, J = 6.71 Hz), 32.1 (d, J = 6.81 Hz), 26.0; δ_P (121.5 MHz, $CDCl_3$) 8.42; HRMS (ESI) calcd for $C_{10}H_{24}O_3P$ 223.1458 ($[M + H]^+$), found 223.1450.

Dicyclohexyl Phosphonate (2g). According to GP1, 45.4 mL of CyOH was reacted to give the crude phosphonate that was distilled (120−130 °C, 0.02 mbar) to yield 29.4 g (94%) of pure product as a colorless oil: δ_H (300 MHz, $CDCl_3$) 6.89 (d, J = 687.81 Hz, 1 H), 4.45 (qt, J = 8.71, 4.27 Hz, 2 H), 2.02−1.87 (m, 4 H), 1.81−1.66 (m, 6 H), 1.67−1.45 (m, 6 H), 1.44−1.17 (m, 6 H); δ_C (75.5 MHz, $CDCl_3$) 75.7 (d, J = 6.04 Hz), 33.8 (d, J = 3.93 Hz), 33.6 (d, J = 4.46 Hz), 25.1, 23.5; δ_P (121.5 MHz, $CDCl_3$) 4.54; HRMS (ESI) calcd for $C_{12}H_{23}NaO_3P$ 269.1276 ($[M + Na]^+$), found 269.1271

Bis(2-chloroethyl) Phosphonate (2h). According to GP2, 29.0 mL of 2-chloroethanol was reacted to yield 29.4 g (99%) of pure product as a slightly yellow oil: δ_H (300 MHz, $CDCl_3$) 6.97 (d, J = 719.72 Hz, 1 H), 4.36−4.30 (m, 4 H), 3.71 (t, J = 5.56 Hz, 4 H); δ_C (75.5 MHz, $CDCl_3$) 65.4 (d, J = 5.81 Hz), 42.7 (d, J = 6.37 Hz); δ_P (121.5 MHz, $CDCl_3$) 8.25; HRMS (ESI) calcd for $C_4H_{10}Cl_2O_3P$ 206.9739 ($[M + H]^+$), found 206.9736 (29.7%)

Bis(3-chloropropyl) Phosphonate (2i). According to GP2, 36.0 mL of 3-chloropropanol was reacted to give the crude phosphonate that was distilled (110 °C, 0.02 mbar) to yield 30.7 g (91%) of pure

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product as a colorless oil: δ_H (300 MHz, $CDCl_3$) 6.86 (d, J = 701.20 Hz, 1 H), 4.26 (dt, J = 7.96, 5.92 Hz, 4 H), 3.67 (t, J = 6.19 Hz, 4 H), 2.15 (quintet, J = 6.03 Hz, 4 H); δ_C (75.5 MHz, $CDCl_3$) 62.3 (d, J = 5.60 Hz), 40.5, 33.0 (d, J = 6.69 Hz); δ_P (121.5 MHz, $CDCl_3$) 8.08; HRMS (ESI) calcd for $C_6H_{14}Cl_2O_3P$ 235.0052 ($[M + H]^+$), found 235.0051.

Bis(4-chlorobutyl) Phosphonate (2j). According to GP2, 20.2 mL of 4-chlorobutanol (ABCR-Chemicals, technical grade, 85%) in CH_2Cl_2 (100 mL) was reacted with PCl_3 (5 mL) in CH_2Cl_2 (30 mL) to give crude phosphonate that was distilled (140 °C, 0.02 mbar) to yield 12.7 g (84%) of pure product as a colorless oil: δ_H (300 MHz, $CDCl_3$) 6.82 (d, J = 696.88 Hz, 1 H), 4.12 (dt, J = 8.11, 5.74 Hz, 4 H), 3.58 (t, J = 5.93 Hz, 4 H), 1.88 (t, J = 3.00 Hz, 8 H); δ_C (75.5 MHz, $CDCl_3$) 64.9 (d, J = 5.84 Hz), 44.3, 28.6, 27.8 (d, J = 6.39 Hz); δ_P (121.5 MHz, $CDCl_3$) 7.81; HRMS (ESI) calcd for $C_8H_{18}Cl_2O_3P$ 263.0365 ($[M + H]^+$), found 263.0356.

Bis(2-methoxyethyl) Phosphonate (2k). According to GP1, 33.9 mL of 2-methoxyethanol was reacted to give the crude phosphonate that was distilled (85 °C, 0.02 mbar) to yield 15.7 g (81%) of pure product as a colorless oil: δ_H (300 MHz, $CDCl_3$) 6.91 (d, J = 715.61 Hz, 1 H), 4.31−4.12 (m, 4 H), 3.59 (t, J = 4.61 Hz, 4 H), 3.38 (s, 6 H); δ_C (75.5 MHz, $CDCl_3$) 71.4 (d, J = 5.40 Hz), 64.6 (d, J = 6.14 Hz), 58.9; δ_P (121.5 MHz, $CDCl_3$) 9.20; HRMS (ESI) calcd for $C_6H_{16}O_5P$ 199.0730 ($[M + H]^+$), found 199.0725.

***O,O*-Diethyl *S*-Hydrogen Phosphorothioate (3a).** According to GP3, 10.0 mL of diethyl phosphonate and 2.74 g of sulfur in 50 mL of Et_2O were reacted with 11.9 mL of NEt_3 to yield 10.48 g (80%) of product as a yellow oil: δ_H (250 MHz, $CDCl_3$) 7.99 (bs, 1 H), 4.09 (dq, J = 9.36, 7.09 Hz, 4 H), 1.27 (t, J = 7.08 Hz, 6 H); δ_C (62.9 MHz, $CDCl_3$) 64.3 (d, J = 5.57 Hz), 15.8 (d, J = 7.70 Hz, CH_3); δ_P (101.3 MHz, $CDCl_3$) 58.0; HRMS (ESI) calcd for $C_4H_{12}O_3PS$ 171.0239 ($[M + H]^+$), found 171.0234 (33.1%).

***O,O*-Dipropyl *S*-Hydrogen Phosphorothioate (3b).** According to GP3, 10.0 g of dipropyl phosphonate and 2.12 g of sulfur in 45 mL of Et_2O were reacted with 9.2 mL of NEt_3 to yield 10.62 g (89%) of product as a yellow oil: δ_H (300 MHz, $CDCl_3$) 6.85 (bs, 1 H), 4.07 (dt, J = 8.47, 6.71 Hz, 4 H), 1.74 (sextet, J = 7.06 Hz, 4 H), 0.98 (t, J = 7.41 Hz, 6 H); δ_C (75.5 MHz, $CDCl_3$) 69.9 (d, J = 5.91 Hz), 23.4 (d, J = 7.84 Hz), 10.0; δ_P (121.5 MHz, $CDCl_3$) 59.1; HRMS (ESI) calcd for $C_6H_{16}O_3PS$ 199.0552 ($[M + H]^+$), found 199.0557.

***O,O*-Diisopropyl *S*-Hydrogen Phosphorothioate (3c).** According to GP3, 10.0 mL of diisopropyl phosphonate and 2.12 g of sulfur in 45 mL of Et_2O were reacted with 9.2 mL of NEt_3 to yield 9.59 g (81%) of product as a yellow oil: δ_H (300 MHz, $CDCl_3$) 7.10 (bs, 1 H), 4.86−4.69 (m, 2 H), 1.36 (d, J = 2.96 Hz, 6 H), 1.34 (d, J = 2.95 Hz, 6 H); δ_C (75.5 MHz, $CDCl_3$) 73.5 (d, J = 5.71 Hz), 23.5 (d, J = 5.51 Hz), 23.5 (d, J = 5.64 Hz); δ_P (121.5 MHz, $CDCl_3$) 56.3; HRMS (ESI) calcd for $C_6H_{16}O_3PS$: 199.0552 ($[M + H]^+$), found 199.0545.

***O,O*-Dibutyl *S*-Hydrogen Phosphorothioate (3d).** According to GP3, 10.0 mL of dibutyl phosphonate and 1.81 g of sulfur in 50 mL of Et_2O were reacted with 7.8 mL of NEt_3 to yield 9.93 g (86%) of product as a yellow oil: δ_H (300 MHz, $CDCl_3$) 7.41 (bs, 1 H), 4.10 (q, J = 7.46 Hz, 4 H), 1.69 (quintet, J = 7.18 Hz, 4 H), 1.42 (sextet, J = 7.44 Hz, 4 H), 0.94 (t, J = 7.36, 6 H); δ_C (75.5 MHz, $CDCl_3$) 68.1 (d, J = 5.93 Hz), 32.0 (d, J = 7.75 Hz), 18.7, 13.6; δ_P (121.5 MHz, $CDCl_3$) 58.4; HRMS (ESI) calcd for $C_8H_{19}NaO_3PS$ 249.0685 ($[M + Na]^+$), found 249.0683.

***O,O*-Diisobutyl *S*-Hydrogen Phosphorothioate (3e).** According to GP3, 10.0 g of diisobutyl phosphonate and 1.82 g of sulfur in 40 mL of Et_2O were reacted with 8.0 mL of NEt_3 to yield 10.15 g (87%) of product as a yellow oil: δ_H (300 MHz, $CDCl_3$) 6.72 (bs, 1 H), 3.87 (dd, J = 7.67, 6.68 Hz, 4 H), 2.00 (nonaplet, J = 6.69 Hz, 2 H), 0.97 (d, J = 6.72 Hz, 12 H); δ_C (75.5 MHz, $CDCl_3$) 74.2 (d, J = 6.30 Hz), 28.9 (d, J = 7.98 Hz), 18.7; δ_P (121.5 MHz, $CDCl_3$) 59.2; HRMS (ESI) calcd for $C_8H_{20}O_3PS$ 227.0865 ($[M + H]^+$), found 227.0857.

***O,O*-Dineopentyl *S*-Hydrogen Phosphorothioate (3f).** According to GP3, 3.0 g of dineopentyl phosphonate and 0.48 g of sulfur in 16 mL of Et_2O were reacted with 2.1 mL of NEt_3 to yield 2.85 g (83%) of product as a viscous slightly yellow oil that crystallized over time: δ_H (300 MHz, $CDCl_3$) 3.76 (d, J = 6.15 Hz, 4 H), 0.98 (s, 18 H); δ_C (75.5 MHz, $CDCl_3$) 77.5 (d, J = 6.77 Hz), 32.1 (d, J = 8.57 Hz), 26.1; δ_P (121.5 MHz, $CDCl_3$) 60.1; HRMS (ESI) calcd for $C_{10}H_{24}O_3PS$ 255.1178 ($[M + H]^+$) found 255.1177.

***O,O*-Dicyclohexyl *S*-Hydrogen Phosphorothioate (3g).** According to GP3, 5.0 g of dicyclohexyl phosphonate and 0.68 g of sulfur in 15 mL of Et_2O were reacted with 3.0 mL of NEt_3 to yield 3.81 g (67%) of product as a yellow, highly viscous oil: δ_H (300 MHz, $CDCl_3$) 5.76 (bs, 1 H), 4.49 (qt, J = 9.04, 4.39 Hz, 1 H), 1.98−1.89 (m, 4 H), 1.78−1.68 (m, 4 H), 1.65−1.45 (m, 6 H), 1.45−1.19 (m, 6 H); δ_C (75.5 MHz, $CDCl_3$) 78.2 (d, J = 6.15 Hz), 33.2 (d, J = 4.41 Hz), 33.1 (d, J = 4.91 Hz), 25.2, 23.6; δ_P (121.5 MHz, $CDCl_3$) 57.2; HRMS (MALDI) calcd for $C_{12}H_{24}O_3PS$: 279.1178 ($[M + H]^+$), found 279.1165

***O,O*-Bis(2-chloroethyl) *S*-Hydrogen Phosphorothioate (3h).** According to GP3, 10.0 g of bis(2-chloroethyl) phosphonate and 1.70 g of sulfur in 35 mL of Et_2O were reacted with 7.4 mL of NEt_3 to yield 7.11 g (62%) of product as a yellow viscous oil: δ_H (300 MHz, $CDCl_3$) 6.85 (bs, 1 H), 4.26 (dt, J = 9.51, 5.76 Hz, 4 H), 3.75 (t, J = 5.80 Hz, 4 H); δ_C (75.5 MHz, $CDCl_3$) 67.7 (d, J = 5.00 Hz), 42.2 (d, J = 8.65 Hz); δ_P (121.5 MHz, $CDCl_3$) 59.0; HRMS (ESI) calcd for $C_4H_{10}Cl_2O_3PS$ 238.9460 ($[M + H]^+$), found 238.9455.

***O,O*-Bis(3-chloropropyl) *S*-Hydrogen Phosphorothioate (3i).** According to GP3, 10.0 g of bis(3-chloropropyl) phosphonate and 1.50 g of sulfur in 30 mL of Et_2O were reacted with 6.50 mL of NEt_3 to yield 6.33 g (56%) of product as a yellow viscous oil: δ_H (300 MHz, $CDCl_3$) 6.42 (bs, 1 H), 4.28 (dt, J = 8.46, 5.90 Hz, 4 H), 3.69 (t, J = 6.27 Hz, 4 H), 2.17 (quintet, J = 5.97 Hz, 4 H); δ_C (75.5 MHz, $CDCl_3$) 64.9 (d, J = 5.36 Hz), 40.7, 32.8 (d, J = 8.06 Hz); δ_P (121.5 MHz, $CDCl_3$) 60.1; HRMS (ESI) calcd for $C_6H_{14}Cl_2O_3PS$ 266.9773 ($[M + H]^+$), found 266.9779.

***O,O*-Bis(4-chlorobutyl) *S*-Hydrogen Phosphorothioate (3j).** According to GP3, 4.03 g of bis(4-chlorobutyl) phosphonate and 0.54 g of sulfur in 15 mL of Et_2O were reacted with 2.32 mL of NEt_3 to yield 3.73 g (83%) of product as a yellow oil: δ_H (300 MHz, $CDCl_3$) 6.28 (bs, 1 H), 4.15 (dt, J = 8.39, 5.80 Hz, 4 H), 3.60 (t, J = 6.06 Hz, 4 H), 1.90 (m, 8 H); δ_C (75.5 MHz, $CDCl_3$) 67.5 (d, J = 5.68 Hz), 44.4, 28.7, 27.4 (d, J = 7.92 Hz); δ_P (121.5 MHz, $CDCl_3$) 59.5; HRMS (ESI) calcd for $C_8H_{18}Cl_2O_3PS$ 295.0086 ($[M + H]^+$), found 295.0091.

***O,O*-Bis(2-methoxyethyl) *S*-Hydrogen Phosphorothioate (3k).** According to GP3, 10.0 g of bis(2-methoxyethyl) phosphonate and 1.78 g of sulfur in 40 mL of Et_2O were reacted with 7.72 mL of NEt_3 to yield 2.50 g (22%) of product as a yellow viscous oil: δ_H (300 MHz, $CDCl_3$) 7.09 (bs, 1 H), 4.36−4.17 (m, 4 H), 3.70 (t, J = 4.53 Hz, 4 H), 3.46 (s, 6 H); δ_C (75.5 MHz, $CDCl_3$) 71.6 (d, J = 6.63 Hz), 66.3 (d, J = 5.51 Hz), 59.0; δ_P (121.5 MHz, $CDCl_3$) 66.7; HRMS (ESI) calcd for $C_6H_{15}NaO_5PS$ 253.0270 ($[M + Na]^+$), found 253.0261 (34.1).

***O,O*-Diethyl *S*-Trifluoromethyl Phosphorothioate (4a).** To a solution of reagent **1** (257.2 mg, 0.78 mmol) in CH_2Cl_2 (4.0 mL) was added a solution of **3a** (165.8 mg, 0.97 mmol) in CH_2Cl_2 (3.6 mL) which subsequently was stirred for 16 h. The solution was concentrated under HV and then distilled (45 °C, 0.02 mbar) to yield *O,O*-diethyl *S*-trifluoromethyl phosphorothioate (**4a**) (41.5 mg, 22%) as a colorless oil: δ_H (300 MHz, $CDCl_3$) 4.40−4.20 (m, 5 H), 1.41 (td, J = 7.08, 0.94 Hz, 6 H); δ_C (75.5 MHz, $CDCl_3$) 127.8 (qd, J = 310.43, 5.39 Hz), 65.2 (d, J = 5.70 Hz), 15.75 (d, J = 7.48 Hz); δ_P (121.5 MHz, $CDCl_3$) 13.3 (q, J = 7.56 Hz); δ_F (188.3 MHz, $CDCl_3$) −34.33 (d, J = 7.60 Hz).

***O,O*-Diisopropyl *S*-Trifluoromethyl Phosphorothioate (4c).** To a solution of reagent **1** (252.6 mg, 0.77 mmol) in CH_2Cl_2 (4.0 mL) was added a solution of **3c** (188.6 mg, 0.95 mmol) in CH_2Cl_2 (3.6 mL) which subsequently was stirred for 48 h. The solution was concentrated under HV and then distilled (45 °C, 0.02 mbar) to yield *O,O*-diisopropyl *S*-trifluoromethyl phosphorothioate (**4c**) (39.8 mg, 20%)

as a colorless oil: δ_H (300 MHz, $CDCl_3$) 4.95−4.80 (m, 2 H), 1.41 (d, J = 6.19 Hz, 6 H), 1.38 (d, J = 6.23 Hz, 6 H); δ_C (75.5 MHz, $CDCl_3$) 127.8 (qd, J = 310.22, 5.46 Hz), 75.2 (d, J = 6.41 Hz), 23.8 (d, J = 3.94 Hz), 23.2 (d, J = 6.22 Hz); δ_P (121.5 MHz, $CDCl_3$) 10.6 (q, J = 7.72 Hz); δ_F (188.3 MHz, $CDCl_3$) −34.01 (d, J = 7.73 Hz); HRMS (ESI) calcd for $C_7H_{15}F_3O_3PS$ 267.0426 ($[M + H]^+$), found 267.0421 (82).

***O,O*-Dicyclohexyl *S*-Trifluoromethyl Phosphorothioate (4g).** To a solution of reagent **1** (251.7 mg, 0.76 mmol) in CH_2Cl_2 (4.0 mL) was added a solution of **3c** (263.5 mg, 0.95 mmol) in CH_2Cl_2 (3.6 mL) which subsequently was stirred for 23 h. $BF_3 \cdot OEt_2$ (0.11 mL, 0.91 mmol) was added dropwise, and stirring was continued for 2 h. The organic layer was diluted with CH_2Cl_2 (20 mL) and washed with water (20 mL). The aqueous layer was back-extracted once with CH_2Cl_2 (20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under HV. Chromatographic purification (silica gel, pentane/ether = 9:1, r_f = 0.51 in pentane/ether = 4:1) yielded *O,O*-dicyclohexyl *S*-trifluoromethyl phosphorothioate (**4g**) (166.8 mg, 63%) as a colorless oil: δ_H (300 MHz, $CDCl_3$) 4.60 (qt, J = 8.63, 4.23 Hz, 2 H), 2.06−1.85 (m, 4 H), 1.83−1.67 (m, 4 H), 1.67−1.45 (m, 6 H), 1.45−1.13 (m, 6 H); δ_C (75.5 MHz, $CDCl_3$) 127.9 (qd, J = 310.36, 5.42 Hz), 79.8 (d, J = 7.07 Hz), 33.4 (d, J = 3.57 Hz), 32.9 (d, J = 5.42 Hz) 24.9, 23.4; δ_P (121.5 MHz, $CDCl_3$) 10.7 (q, J = 7.75 Hz); δ_F (188.3 MHz, $CDCl_3$) −33.79 (d, J = 7.66 Hz); HRMS (ESI) calcd for $C_{13}H_{23}F_3O_3PS$ 347.1052($[M + H]^+$), found 347.1052.

General Procedure for Determining the Relative Rates. To a mixture of 0.2 mL of a solution of **3c** (117.6 mg in 0.490 mL of $CDCl_3$, 1.21 M) and 0.2 mL of a solution of **3a** (224.3 mg in 1.090 mL of $CDCl_3$, 1.21 M) in an NMR tube was added 0.1 mL of a solution of reagent **1** (124.7 mg in 0.780 mL of $CDCl_3$ and 45.0 μL of α,α,α-trifluorotoluene, 0.48 M). The reaction was sampled at three different times by ^{19}F NMR spectroscopy. The ratio of the products formed reflects the relative rate.

■ ASSOCIATED CONTENT

Supporting Information. Kinetic data and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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