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Base-Controlled Fe(Pc)-Catalyzed Aerobic Oxidation of Thiols for the Synthesis of S-S and S-P(O) Bond

Hai Huang,[a,b] Jeffrey Ash,[a] Jun Yong Kang*,[a]

A Fe(Pc)-catalyzed aerobic oxidation of thiols for the synthesis of disulfide has been developed under mild reaction conditions. In addition, aerobic oxidative cross-dehydrogenative coupling (CDC) reaction of thiols with P(O)-H compounds (*H*-phosphonates and *H*-phosphine oxide) for the formation of S-P(O) bond has been demonstrated under the Fe(Pc) catalysis system with a base additive. Control experiments revealed that the use of base (DIPA) in this system controls the synthetic pathways in which thiophosphates are formed.

Introduction

Organosulfur compounds possessing S-S and S-P(O) bonds are significant structures in both synthetic chemistry and medicinal chemistry, owing to their unique structures and diverse biological activities.[1] Disulfides containing S-S bond units are commonly found in protein structures and naturally occurring bioactive molecules.[2] They exhibit a wide range of enzyme inhibitions such as acetohydroxyacid synthase (AHAS) inhibitors (**A**, **B**)[3] and anticancer agents (**C**)[4] (Figure 1). Thus, many efforts have been devoted to the synthesis of symmetrical and unsymmetrical disulfides.[1c, 2h, 5] For example, oxidation reaction,[5d, f, j, 6] reduction reaction,[7] substitution reaction,[8] free radical dimerization reaction[5i, 9] and microwave-assisted reaction[5b, f] have been developed over the past decades. However, many synthetic methods still rely on expensive and toxic metal complexes and hazardous halide reagents. Hence, the development of a mild catalytic transformation for the synthesis of disulfides is highly desirable in the study of bioactive small molecules. On the other hand, thiophosphates with S-P(O) bond motifs are also important scaffolds in a variety of biologically active molecules such as anticancer (**D**, **E**) and antibacterial agents (**F**) (Figure 1).[10]
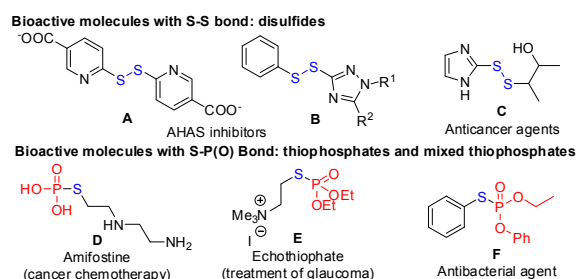

Figure 1. Bioactive organosulfur compounds bearing S-S and S-P(O) bonds.

The conventional approach toward the thiophosphate compounds involves the air and moisture sensitive pre-functionalized $(RO)_2P(O)Cl$, which undergoes nucleophilic substitution with RSX.[11] Recently, cross-dehydrogenative coupling (CDC) reaction of thiols with P(O)H compounds has emerged as a powerful strategy for the S-P(O) bond formation.[9a, 12] For instance, Han and co-workers reported a palladium-catalyzed CDC reaction of thiols with *H*-phosphonates for the synthesis of thiophosphates.[13] The Jiao group also disclosed a Cs_2CO_3-catalyzed oxidative coupling reaction of thiols with *H*-phosphonates.[14] Despite the recent advances in the S-P(O) bond construction, the development of an efficient and mild aerobic oxidative CDC reaction of thiols with P(O)H compounds for the synthesis of biologically important thiophosphate compounds is still highly demanding due to the potential application in pharmaceuticals and bioactive compounds.

To develop an alternative synthetic method for S-S and S-P(O) bond formation, we utilized iron phthalocyanine [Fe(Pc)] as a potential oxidation catalyst.[15] Herein, we report base-controlled selective synthetic methods of (i) Fe(Pc)-catalyzed aerobic oxidation of thiols for the synthesis of disulfides and (ii) Fe(Pc)-catalyzed aerobic oxidative phosphorylation of thiols with P(O)H compounds for the synthesis of thiophosphates.

Results and discussion

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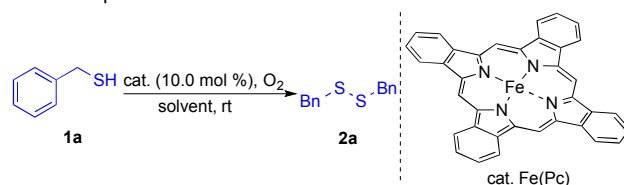
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Benzyl mercaptan **1a** was employed as a model substrate for the optimization of the reaction conditions for the synthesis of disulfides. The study of the catalytic activity of various metal catalysts revealed that the Fe(Pc) catalyst is superior to other metal complexes, providing the desired product **2a** with a quantitative yield under 10 mol % catalyst (Table 1, entries 1-5). Further optimization of the loading of catalyst showed that a 3.0 mol % Fe(Pc) catalyst still affords the disulfide product with 99% yield (Table 1, entry 6). However, no target product was furnished without the catalyst (Table 1, entry 7). The screening of other solvents such as DCM, Et$_2$O, CH$_3$CN, and EtOH exhibited that they require longer reaction time (Table 1, entries 8-11).

**Table 1.** Optimization of reaction conditions for disulfide **2a**[a]

entry	cat.	solvent	time	yield[c]
1	Fe(Pc)	THF	20 min	99%
2	Fe(NO$_3$)$_3$•9H$_2$O	THF	18 h	26%
3	FeCl$_3$	THF	18 h	89%
4	CuCl$_2$•2H$_2$O	THF	18 h	26%
5	MnO$_2$	THF	18 h	<10%
6[b]	Fe(Pc)	THF	20 min	99%
7[b]	--	THF	20 min	--
8[b]	Fe(Pc)	DCM	1 h	92%
9[b]	Fe(Pc)	Et$_2$O	18 h	64%
10[b]	Fe(Pc)	CH$_3$CN	40 min	92%
11[b]	Fe(Pc)	EtOH	30 min	98%

[a]Reaction conditions: **1a** (0.2 mmol), cat. (10.0 mol %) in solvent (1.0 mL) at rt. [b]3.0 mol % of Fe(Pc). [c]Yield was determined by crude ^{1}H NMR using 1,3,5-trimethylbenzene as internal standard.

Having the optimized reaction conditions in hand, we studied the scope of this oxidation reaction by employing different mercaptans (Scheme 1). Both electron-donating groups and electron-deficient substituents on the benzyl group were well tolerated (**2b–2f**). A similar trend was observed with aromatic mercaptans. For example, aromatic thiols with electron-rich groups afforded the target products in near quantitative yields (**2h**, **2i**) and those of electron-poor substituents also provided the corresponding products with excellent yields (**2j–2m**). It is noteworthy that a large-scale reaction (5.0 mmol) using **1g** was performed without sacrificing the product yield (Scheme 1, **2g**, 99%). Importantly, this coupling reaction efficiently tolerates the steric hindrance by yielding the *ortho*, *para*-dimethyl substituted disulfide **2n** with 99% yield. In addition to the aromatic thiols, an aliphatic thiol **1o** was also smoothly transformed to the corresponding disulfide product **2o**. Further, we evaluated this synthetic transformation for the synthesis of unsymmetrical disulfide compounds. A reaction using thiophenol **1g** and 4-methylbenzenethiol **1h** under the standard reaction conditions provided a mixture of all three disulfide products (two symmetrical disulfides and one unsymmetrical disulfide).
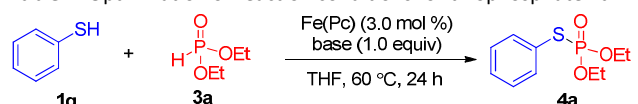
Scheme 1. The scope of aerobic oxidation of thiols.[a]
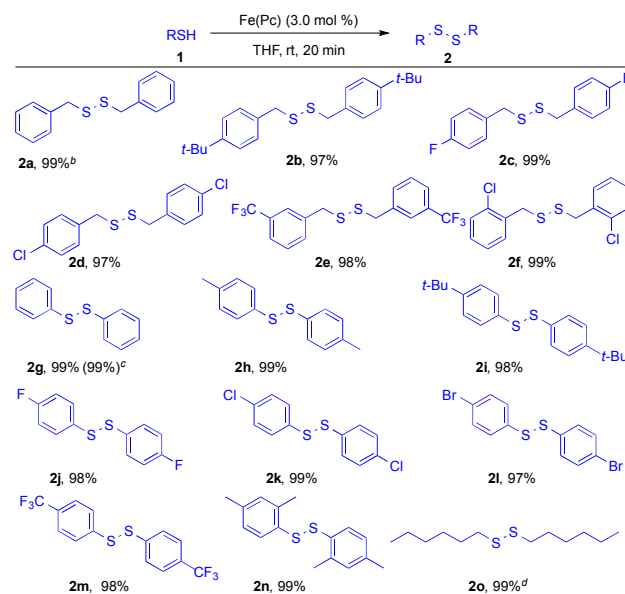
[a]Reaction conditions: **1** (0.2 mmol), Fe(Pc) (3.0 mol %) in THF (1.0 mL) at rt for 20 min. [b]Isolated yield. [c]5.0 mmol of **1g**. [d]2 h reaction

Next, we explored a Fe(Pc)-catalyzed oxidative CDC reaction of thiols with P(O)-H substrates (Table 2). To test our hypothesis of the S-P bond formation, we employed thiophenol **1g** and diethyl phosphonate **3a** under the standard reaction conditions. However, the reaction of **1g** and **3a** failed to give the thiophosphate product **4a** but still furnished the disulfide **2a** (Table 2, entry 1). Gratifyingly, when Et$_3$N was added to the reaction media as an additive, the corresponding thiophosphate product **4a** was generated in 73% yield (Table 2, entry 2). Further screening of other bases identified diisopropylamine (DIPA) as an optimum base, which afforded the thiophosphate product **4a** with 90% yield (Table 2, entries 2-5). Importantly, a catalytic amount of base (10 mol %) also provided **4a** with 40% yield (Table 2, entry 6) yet it is less efficient than the stochiometric amount.

Table 2. Optimization of reaction conditions for thiophosphate **4a**.[a]

entry	base	Yield (%)[b]
1	--	--
2	Et$_3$N	73
3	pyridine	trace
4	DBU	20
5	DIPA	90
6	DIPA[c]	44

[a]Reaction conditions: **1g** (0.2 mmol), **3a** (0.2 mmol), Fe(Pc) (3.0 mol %), and base (0.2 mmol) in THF (1.0 mL) at 60 ^{o}C for 24 h. [b]Isolated yield. [c]10 mol % of DIPA.

With the optimized reaction conditions for the S-P(O) bond construction, the scope of this CDC reaction was investigated by

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employing different thiols **1** and P(O)-H compounds **3** described in Scheme 2. An efficient catalytic activity was still observed with a large-scale reaction of **1g**, which provided **4a** with 85% yield. Different P(O)-H scaffolds such as **3b** with methoxy groups and **3c** with phenyl groups also afforded the corresponding thiophosphates **4b** and **4c** in 73% and 63% yields, respectively. Next, we evaluated the scope of aromatic thiols. The electronic effects of the aryl thiols showed a negligible effect on this CDC reaction. Both electron-donating groups (Me, t-Bu) and electron-deficient substituents (F, Cl, Br, CF$_3$) on the phenyl ring afforded the desired thiophosphates **4d**-**4i** in moderate to high yields. To study the steric effect on this transformation, *ortho*-, *para*-dimethyl substituted thiophenol **1n** was employed in this CDC reaction, which efficiently provided the corresponding thiophosphate **4j** with 79% yield. In addition, aliphatic thiols such as benzyl mercaptan **1a** and hexane-1-thiol **1o** furnished the target thiophosphates **4k** and **4l** with 77% and 45% yields, respectively.

Scheme 2. The scope of Fe(Pc)-catalyzed CDC reaction^a
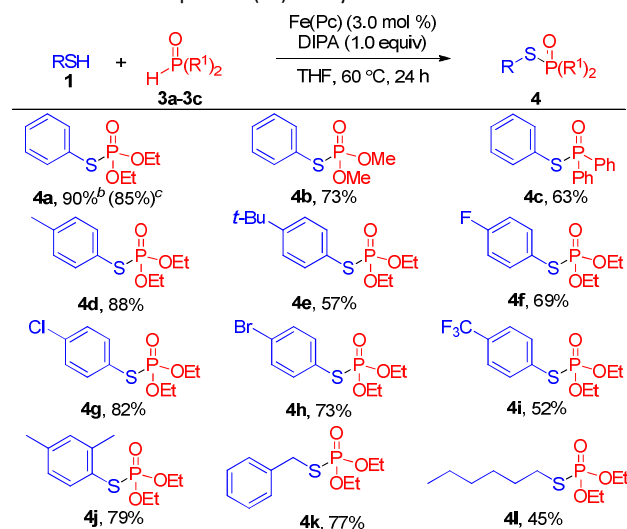
^{a}Reaction conditions: **1** (0.2 mmol), **3** (0.2 mmol), Fe(Pc) (3.0 mol %), and DIPA (0.2 mmol) in THF at 60 ^{o}C for 24 h. ^{b}Isolated yield. ^{c}5.0 mmol of **1g**.

To investigate the reaction mechanism, a number of control experiments were conducted (Scheme 3). We confirmed that the oxidation reaction of thiols to form disulfides is significantly inhibited by radical scavengers such as TEMPO and BHT by providing only 36% and 42% yields, respectively (Scheme 3, eq 1). Further control experiments revealed that the oxidative CDC reaction of phenyl disulfide **2g** with diethyl phosphonate **3a** is also inhibited by radical scavengers (Scheme 3, eq 2), which indicates that a phosphorus radical could be involved in this transformation. Additionally, unsymmetrical disulfide **2p**[16] was treated with **3a** under the standard reaction conditions in which an equal amount of **4a** and **4d** was generated. The outcomes of these experiments suggest that this oxidative coupling reaction may follow a free radical reaction.

Scheme 3. Control experiments
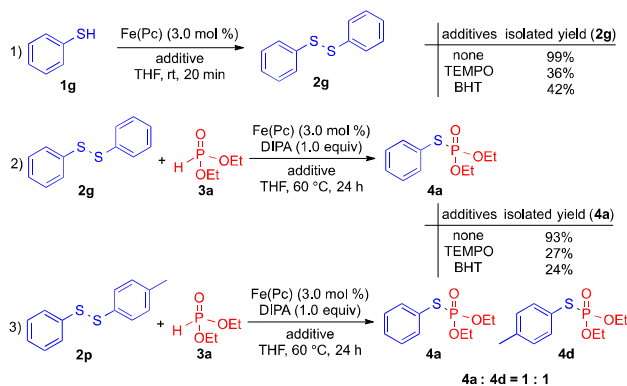
On the basis of the results of our experimental outcomes and previous reports,[15a] a plausible mechanism of the aerobic oxidation reaction is described in Scheme 4. A Fe(III) species which is generated from Fe(II)(Pc) by aerobic oxidation would participate in a catalytic cycle.[15a] The catalytic cycle is initiated by a complexation between the thiol **1** and Fe(III) species to provide an iron complex **A** (Scheme 4, path a).[15a, 17] Then, the resulting iron complex **A** is converted into a thiyl radical (RS·) and a hydroperoxy radical (HOO·), which are responsible for the formation of a disulfide product **2** and a hydrogen peroxide.[9a] For the S-P bond formation shown in path b, a phosphorus radical **B** could be generated from the phosphonate **3** in the presence of DIPA and Fe(III) species. The base additive presumably helps the phosphonate-phosphite tautomeric equilibrium to shift toward a nucleophilic phosphite form,[18] which would form a complex with Fe(III) species to produce a phosphorus radical **B**.[9a] Then, the phosphorus radical **B** undergoes a coupling reaction with the disulfide **2** to form a thiophosphate product **4**.

Scheme 4. Proposed mechanism
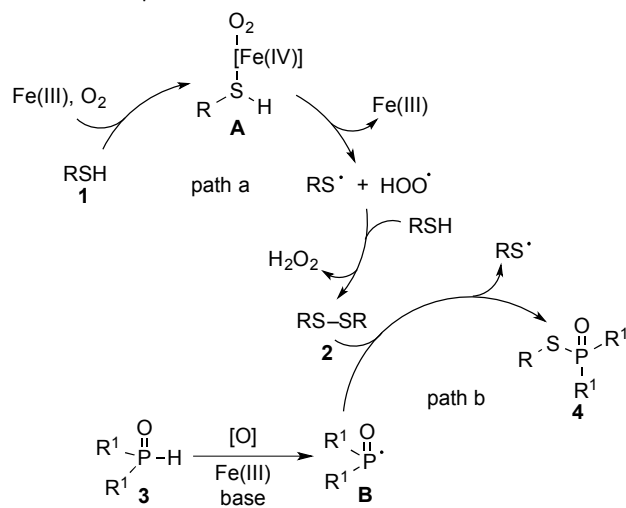
Conclusions

In summary, a base-controlled Fe(Pc)-catalyzed selective synthesis of disulfides and thiophosphates has been developed. An aerobic oxidation reaction of thiols with the Fe(Pc) catalyst has been established as an efficient, practical method for the synthesis

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of disulfides with excellent yields in which a simple filtration is sufficient for the purification of products. In addition, a Fe(Pc)-catalyzed CDC reaction of thiols with P(O)-H compounds for the synthesis of thiophosphates in presence of base has been demonstrated. A series of control experiments revealed that the base additive is a key reagent for the S-P(O) bond formation. This synthetic transformation would provide a practical route for the synthesis of biologically important disulfides and thiophosphates.

Experimental

General Information

All reactions were carried out under atmospheric conditions in oven-dried glassware with magnetic stirring bar. Dry solvents (THF, toluene, and DCM) were obtained by solvent purification system under argon. All commercially available reagents were used as received without further purification. Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 0.25 mm aluminum-backed silica gel 60-F plates. Visualization was accompanied with UV light and $KMnO_4$ solution. Concentration under reduced pressure refers to the removal of volatiles using a rotary evaporator attached to a dry diaphragm pump (10-15 mm Hg) followed by pumping to a constant weight with an oil pump (<300 mTorr). Infrared (IR) spectra were recorded on an IR spectrometer with KBr wafers or a film on KBr plate. High-resolution mass spectra (HRMS) were recorded on LCMS-IT-TOF mass spectrometer using ESI (electrospray ionization). ^1H NMR spectra were recorded in $CDCl_3$ on 400 MHz NMR spectrometer. The ^1H chemical shifts are referenced to residual solvent signals at δ 7.26 ($CHCl_3$) or δ 0.00 (TMS). ^1H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicities are indicated as follows: s (singlet), bs (broad singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet). ^{13}C NMR spectra were proton decoupled and recorded in $CDCl_3$ on 100.5 MHz NMR spectrometer. The ^{13}C chemical shifts are referenced to solvent signals at δ 77.16 ($CDCl_3$). ^{31}P NMR spectra were proton decoupled and recorded in $CDCl_3$ on 162 MHz NMR spectrometer. ^{31}P chemical shifts are reported relative to 85% H_3PO_4 (0.00 ppm) as an external standard.

General Procedure for the Synthesis of Disulfides 2

Thiols **1** (0.2 mmol) and Fe(Pc) (3.0 mol%) were dissolved in THF (1.0 mL) in a 2 dram vial. The resulting reaction mixture was stirred at room temperature for 20 min – 2 h. After stirring for 20 min – 2 h, Fe(Pc) was removed by filtration and the volatiles were removed under reduced pressure to give pure corresponding products **2**.

1,2-Dibenzyldisulfane (**2a**):[19] 24.6 mg, 99%; As a yellow oil; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (m, 10H), 3.60 (m, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 137.4, 129.4, 128.5, 127.4, 43.3.

1,2-Bis(4-(tert-butyl)benzyl)disulfane (**2b**):[20] 34.8 mg, 97%; As a yellow oil; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (dt, J = 8.4, 2.0 Hz, 4H), 7.17 (dt, J = 8.4, 2.0 Hz, 4H), 3.59 (m, 4H), 1.31 (s, 18H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 150.5, 134.2, 129.1, 125.4, 43.0, 34.5, 31.4.

1,2-Bis(4-fluorobenzyl)disulfane (**2c**):[21] 28.7 mg, 99%; As a yellow oil; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, J = 8.8, 5.6 Hz, 4H), 7.00 (t, J = 8.4 Hz, 4H), 3.58 (m, 4H); ^{13}C NMR (100.5

MHz, $CDCl_3$) δ 162.2 (d, J = 245.6 Hz), 133.1 (d, J = 3.8 Hz), 130.9 (d, J = 8.2 Hz), 115.4 (d, J = 21.5 Hz), 43.0, 34.5, 31.4.

1,2-Bis(4-chlorobenzyl)disulfane (**2d**):[20] 30.7 mg, 97%; As a yellow oil; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.4 Hz, 4H), 7.15 (t, J = 8.4 Hz, 4H), 3.57 (m, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 135.8, 133.4, 130.6, 128.7, 42.5.

1,2-Bis(3-(trifluoromethyl)benzyl)disulfane (**2e**):[22] 37.3 mg, 98%; As a yellow oil; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.6 Hz, 2H), 7.48-7.37 (m, 6H), 3.61 (m, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 138.2, 132.6, 131.0 (q, J = 32.0 Hz), 129.0, 126.0 (m), 124.3 (m), 123.9 (q, J = 270.9 Hz), 42.5.

1,2-Bis(2-chlorobenzyl)disulfane (**2f**):[19] 32.2 mg, 99%; As a yellow oil; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.36 (m, 2H), 7.28-7.18 (m, 6H), 3.78 (m, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 135.0, 134.1, 131.6, 129.7, 128.9, 126.7, 41.1.

1,2-Diphenyldisulfane (**2g**):[23] 21.6 mg, 99%; As a white solid; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.47 (m, 4H), 7.32-7.26 (m, 4H), 7.21 (tt, J = 7.2, 1.6 Hz, 2H), 3.78 (m, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 137.0, 129.0, 127.5, 127.1.

1,2-Di-p-tolyldisulfane (**2h**):[23] 24.1 mg, 99%; As a white solid; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 4H), 7.10 (d, J = 8.0 Hz, 4H), 2.31 (m, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 137.4, 133.9, 129.8, 128.5, 21.0.

1,2-Bis(4-(tert-butyl)phenyl)disulfane (**2i**):[23] 32.4 mg, 98%; As a white solid; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (dt, J = 8.8, 2.4 Hz, 4H), 7.32 (dt, J = 8.4, 2.4 Hz, 4H), 1.29 (s, 18H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 150.5, 134.0, 127.7, 126.1, 34.5, 31.3.

1,2-bis(4-fluorophenyl)disulfane (**2j**):[23] 24.8 mg, 98%; As a white solid; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.40 (m, 4H), 7.03-6.97 (m, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 162.5 (d, J = 246.3 Hz), 132.2 (d, J = 2.9 Hz), 131.3 (d, J = 8.2 Hz), 116.3 (d, J = 22.4 Hz).

1,2-bis(4-chlorophenyl)disulfane (**2k**):[23] 29.6 mg, 99%; As a white solid; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.4 Hz, 4H), 7.27 (d, J = 8.8 Hz, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 135.1, 133.6, 129.3, 129.2.

1,2-bis(4-bromophenyl)disulfane (**2l**):[23] 36.6 mg, 97%; As a white solid; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 4H), 7.33 (d, J = 8.4 Hz, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 135.7, 132.2, 129.4, 121.6.

1,2-bis(4-(trifluoromethyl)phenyl)disulfane (**2m**):[5g] 34.8 mg, 98%; As a white solid; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.58 (m, 8H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 140.8, 129.4 (d, J = 32.7 Hz), 126.6, 126.1 (m), 123.8 (d, J = 270.9 Hz).

1,2-bis(2,4-dimethylphenyl)disulfane (**2n**):[24] 28.2 mg, 99%; As a yellow oil; R_f = 0.3 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.0 Hz, 2H), 6.98 (s, 2H), 6.92 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 138.3, 137.8, 132.3, 131.2, 130.5, 127.3, 21.0, 20.1.

1,2-Dihexyldisulfane (**2o**):[6e] 23.7 mg, 99%; As a yellow oil; R_f = 0.6 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 2.68 (t, J = 7.2 Hz, 4H), 1.72-1.62 (m, 4H), 1.43-1.24 (m, 12H), 0.89 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 39.2, 31.4, 29.2, 28.2, 22.5, 14.0.

General Procedure for the Synthesis of Thiophophonates 4.

Thiols **1** (0.2 mmol), P(O)-H compounds **3** (0.2 mmol), DIPA (0.2 mmol) and Fe(Pc) (3.0 mol%) were dissolved in THF (1.0 mL) in a 2 dram vial. The resulting reaction mixture was stirred at 60 °C for 24 h. After stirring for 24 h, the volatiles were removed under reduced

pressure. The residue was subjected to column chromatography on silica gel to give corresponding thiophosphates **4**.

O,O-Diethyl S-phenyl phosphorothioate (**4a**):[9a] 44.2 mg, 90 %; As a colorless oil; R_f = 0.2 (v_{Hexane}/v_{EA}= 4:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59-7.55 (m, 2H), 7.37-7.32 (m, 3H), 4.27-4.11 (m, 4H), 1.31 (td, *J* = 7.2, 0.8 Hz, 6H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 134.5 (d, *J* = 5.2 Hz), 129.3 (d, *J* = 2.2 Hz), 128.9 (d, *J* = 2.9 Hz), 126.6 (d, *J* = 7.5 Hz), 64.0 (d, *J* = 6.7 Hz), 16.0 (d, *J* = 6.7 Hz).

O,O-Dimethyl S-phenyl phosphorothioate (**4b**):[11c] 31.8 mg, 73%; As a colorless oil; R_f = 0.1 (v_{Hexane}/v_{EA}= 4:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59-7.54 (m, 2H), 7.39-7.33 (m, 3H), 3,82 (d, *J* = 12.8 Hz, 6H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 134.6 (d, *J* = 5.2 Hz), 129.5 (d, *J* = 2.2 Hz), 129.1 (d, *J* = 2.9 Hz), 126.1, 54.2 (d, *J* = 6.0 Hz).

S-Phenyl diphenylphosphinothioate (**4c**):[12d] 39.1 mg, 63 %; As a colorless oil; R_f = 0.2 (v_{Hexane}/v_{EA}= 4:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89-7.81 (m, 4H), 7.53-7.47 (m, 2H), 7.47-7.40 (m, 6H), 7.26-7.16 (m, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 135.3 (d, *J* = 3.7 Hz), 132.6 (d, *J* = 106.4 Hz), 132.3 (d, *J* = 2.9 Hz), 131.6 (d, *J* = 10.4 Hz), 129.1 (d, *J* = 1.5 Hz), 128.9 (d, *J* = 2.2 Hz), 128.5 (d, *J* = 13.4 Hz), 126.2 (d, *J* = 5.2Hz).

O,O-diethyl S-*p*-tolyl phosphorothioate (**4d**):[9a] 45.9 mg, 88 %; As a colorless oil; R_f = 0.2 (v_{Hexane}/v_{EA}= 4:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47-7.41 (m, 2H), 7.18-7.12 (m, 2H), 4.27-4.10 (m, 4H), 2.35 (s, 3H), 1.31 (td, *J* = 6.8, 2.8 Hz, 6H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 139.2, 134.6 (d, *J* = 5.2 Hz), 130.1 (d, *J* = 2.2 Hz), 122.8 (d, *J* = 7.4 Hz), 63.9 (d, *J* = 6.0 Hz), 21.2 (d, *J* = 2.2 Hz), 16.0 (d, *J* = 7.4 Hz).

S-(4-(*tert*-Butyl)phenyl) *O,O*-diethyl phosphorothioate (**4e**):[13] 34.2 mg, 57 %; As a colorless oil; R_f = 0.2 (v_{Hexane}/v_{EA}= 4:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48-7.43 (m, 2H), 7.35-7.31 (m, 2H), 4.24-4.08 (m, 4H), 1.31-1.24 (m, 15H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 152.3 (d, J = 3.0 Hz), 134.3 (d, *J* = 5.2 Hz), 126.4 (d, *J* = 2.2 Hz), 122.8 (d, *J* = 7.4 Hz), 63.9 (d, *J* = 5.9 Hz), 34.6, 31.1, 16.0 (d, *J* = 7.4 Hz).

O,O-Diethyl *S*-(4-fluorophenyl) phosphorothioate (**4f**):[9a] 36.2 mg, 69%; As a colorless oil; R_f = 0.2 (v_{Hexane}/v_{EA}= 4:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.58-7.52 (m, 2H), 7.09-7.02 (m, 2H), 4.27-4.11 (m, 4H), 1.32 (td, *J* = 7.2, 0.8 Hz, 6H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 163.3 (dd, *J* = 245.6, 3.0 Hz), 136.6 (dd, *J* = 8.9, 5.2 Hz), 121.7 (d, *J* = 7.5 Hz), 116.6 (dd, *J* = 22.4, 3.0 Hz), 64.1 (d, *J* = 6.7 Hz), 16.0 (d, *J* = 7.4 Hz).

S-(4-Chlorophenyl) *O,O*-diethyl phosphorothioate (**4g**):[9a] 45.7 mg, 82 %; As a colorless oil; R_f = 0.2 (v_{Hexane}/v_{EA}= 4:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53-7.48 (m, 2H), 7.35-7.31 (m, 2H), 4.28-4.11 (m, 4H), 1.35-1.28 (m, 6H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 135.7 (d, *J* = 5.2 Hz), 135.5 (d, *J* = 3.7 Hz), 129.5 (d, *J* = 2.2 Hz), 125.1, 64.2 (d, *J* = 6.0 Hz), 16.0 (d, *J* = 6.7 Hz).

S-(4-Bromophenyl) *O,O*-diethyl phosphorothioate (**4h**):[9a] 47.3 mg, 73%; As a colorless oil; R_f = 0.2 (v_{Hexane}/v_{EA}= 4:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50-7.41 (m, 4H), 4.28-4.10 (m, 4H), 1.32 (tt, *J* = 6.8, 0.8 Hz, 6H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 135.9 (d, *J* = 5.2 Hz), 132.5 (d, *J* = 2.3 Hz), 125.8 (d, *J* = 7.2 Hz), 123.6 (d, *J* = 3.7 Hz), 64.2 (d, *J* = 6.0 Hz), 16.0 (d, *J* = 7.5 Hz).

O,O-Diethyl *S*-(4-(trifluoromethyl)phenyl) phosphorothioate (**4i**):[14] 32.6 mg, 52 %; As a colorless oil; R_f = 0.2 (v_{Hexane}/v_{EA}= 4:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 (d, *J* = 8.0 Hz, 4H), 7.61 (d, *J* = 8.0 Hz, 4H), 4.30-4.14 (m, 4H), 1.33 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 134.2 (d, *J* = 5.3 Hz), 131.9 (dd, *J* = 6.7, 1.5 Hz), 130.8 (dd, *J* = 32.8,

2.3 Hz), 126.0 (m), 123.7 (d, *J* = 270.9 Hz), 64.4 (d, *J* = 6.7 Hz), 15.9 (d, *J* = 6.7 Hz).

S-(2,4-dimethylphenyl) *O,O*-diethyl phosphorothioate (**4j**):[11a] 43.3 mg, 79 %; As a colorless oil; R_f = 0.2 (v_{Hexane}/v_{EA}= 4:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.08 (s, 1H), 7.00-6.96 (m, 1H), 4.23-4.08 (m, 4H), 2.48 (s, 3H), 2.31 (d, *J* = 2.0 Hz, 3H), 1.30 (td, *J* = 7.2, 0.8 Hz, 6H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 142.0 (d, *J* = 5.2 Hz), 139.6 (d, *J* = 3.7 Hz), 136.2 (d, *J* = 4.4 Hz), 131.7 (d, *J* = 2.9 Hz), 127.6 (d, J = 3.0 Hz), 122.0 (d, J = 7.5 Hz), 64.0 (d, *J* = 6.7 Hz), 21.2, 21.1, 16.0 (d, *J* = 6.7 Hz).

S-benzyl *O,O*-diethyl phosphorothioate (**4k**):[14] 38.6 mg, 77 %; As a colorless oil; R_f = 0.2 (v_{Hexane}/v_{EA}= 4:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38-7.23 (m, 5H), 4.27-3.96 (m, 6H), 1.28 (tt, *J* = 8.0, 0.8 Hz, 6H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 137.5 (d, *J* = 5.2 Hz), 128.9, 128.6, 127.6, 63.5 (d, *J* = 5.2 Hz), 34.9 (d, *J* = 4.5 Hz), 15.9 (d, *J* = 7.4 Hz).

O,O-Diethyl *S*-hexyl phosphorothioate (**4l**):[14] 22.4 mg, 45 %; As a colorless oil; R_f = 0.2 (v_{Hexane}/v_{EA}= 4:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.24-4.09 (m, 4H), 2.87-2.79 (m, 2H), 1.73-1.64 (m, 2H), 1.44-1.26 (m, 12H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 63.3 (d, *J* = 6.0 Hz), 31.1, 30.9 (d, *J* = 3.7 Hz), 30.7 (d, *J* = 6.0 Hz), 28.2, 22.4, 16.0 (d, *J* = 7.5 Hz), 13.9.

Large-scale Experiment

Benzenethiol **1g** (510 µL, 5.0 mmol) and Fe(Pc) (86.2 mg, 0.15 mmol) were dissolved in THF (25 mL) in a 50 mL flask. The resulting reaction mixture was stirred at room temperature for 20 min. After completion, Fe(Pc) was removed by filtration and the volatiles were removed under reduced pressure to give pure 1,2-diphenyldisulfane **2g** (545 mg, 99%).

Benzenethiol **1g** (510 µL, 5.0 mmol), diethyl phosphonate **3a** (645 µL, 5.0 mmol), DIPA (700 µL, 5.0 mmol) and Fe(Pc) (84.6 mg, 0.15 mmol) were dissolved in THF (25 mL) in a 50 mL flask. The resulting reaction mixture was stirred at 60 ^{o}C for 24 h. After stirring for 24 h, the volatiles were removed under reduced pressure. The residue was subjected to column chromatography on silica gel to give corresponding thiophosphate **4a** (1.04g, 85%).

Control Experiment

Control experiment 1.

Thiols **1g** (0.4 mmol), additives (0.4 mmol) and Fe(Pc) (3.0 mol%) were dissolved in THF (2.0 mL) in a 2 dram vial. The resulting reaction mixture was stirred at rt for 20 min. After stirring for 20 min, the volatiles were removed under reduced pressure. The residue was subjected to column chromatography on silica gel to give disulfide **2g** [TEMPO as additive, 15.6 mg, 36%; BHT as additive, 18.4 mg, 42%].

Control experiment 2.

Disulfide **2g** (0.2 mmol), *H*-diethyl phosphonate **3a** (0.2 mmol), additives (0.2 mmol), DIPA (0.1 mmol) and Fe(Pc) (3.0 mol%) were dissolved in THF (1.0 mL) in a 2 dram vial. The resulting reaction mixture was stirred at 60 ^{o}C for 24 h. After stirring for 24 h, the volatiles were removed under reduced pressure. The residue was subjected to column chromatography on silica gel to give corresponding thiophosphate **4a** [TEMPO as additive, 13.5 mg, 27%; BHT as additive, 11.8 mg, 24%].

Conflicts of interest

There are no conflicts to declare.

ARTICLE

Journal Name

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Base-controlled Fe(Pc)-catalyzed S–S/S–P(O) bond formation

12 examples
up to 90% yield

15 examples
up to 99% yield

Iron phthalocyanine (Fe(Pc))