Modern synthetic approaches to phosphorus-sulfur bond formation in organophosphorus compounds.

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Abstract:

Phosphorothioates, phosphonothioates, phosphinothioates and phosphonodithioates are organophosphorus compounds with widespread application, especially in the fields of agrochemicals, medicinal chemistry and materials chemistry. Herein, we review modern methods for the construction of the phosphorus-sulfur bonds in these important functional groups. This review is organised on the basis of the different synthetic approaches, with the advantages and disadvantages of each also examined.

Keywords: Phosphorothioate; phosphonothioate; phosphinothioate; phosphonodithioate; phosphorus-sulfur bond formation; organophosphorus chemistry; organosulfur chemistry.

Biographical information:

Dr David J. Jones (1992) was born in London, United Kingdom. He completed his undergraduate training in University College Cork (UCC), Ireland attaining a BSc in the Chemistry of Pharmaceutical Compounds. In 2018 he completed his PhD in organic chemistry under the joint supervision of Dr Tim O'Sullivan and Dr Eileen O'Leary in the area of organophosphorus chemistry. David has since become a PDRA in the laboratory of Dr Gerard McGlacken in UCC, whereupon his research interests have expanded to include transition metal-catalysed cross-coupling chemistry, nanoparticle catalysis in hydrogenation reactions and flow chemistry.

Dr Eileen O'Leary graduated with a BSc (hons) Chemistry in 1999, and subsequently completed a PhD in organic chemistry, with a focus on electrophilic fluorinating agents, with Dr Daniel McCarthy also in UCC. She conducted postdoctoral work in the design and synthesis of anti-cancer

drugs. She subsequently investigated the properties of APIs and how they impact secondary processing. Dr O'Leary held a joint lecturer appointment between the School of Pharmacy and Department of Chemistry in UCC from 2007-2017. She now occupies the role of Lecturer in Chemistry at Cork Institute of Technology and engages in staff development in the Teaching & Learning Unit. Her research interests range from the development of anti-viral drugs to the investigation of improved teaching learning and assessment strategies in higher education.

Dr Tim O'Sullivan received his BSc degree in Industrial Chemistry from the University of Limerick in 1997. He subsequently obtained a PhD degree under Professor Lewis Mander at the Research School of Chemistry, Australian National University focusing on the total synthesis of diterpenoids. He returned to Ireland in 2001 to work as a postdoctoral fellow with Dr Mary Meegan at Trinity College Dublin initially and later as a senior postdoctoral fellow at University College Dublin in the research group of Professor Pat Guiry. He was appointed Lecturer in Pharmaceutical Chemistry in University College Cork in 2006. His current research focus is on the development of new methods for the synthesis of bioactive compounds.

1.1 Introduction

Phosphonothioates, phosphorothioates, phosphinothioates and similar functional groups are increasingly common in the scientific literature. The most significant application of these compounds to date has been in the area of agricultural chemistry, with the development of several potent pesticides containing phosphorus-sulfur bonds.[1] Compounds from this class have also been developed as potential anti-fungal agents.[1c, 1d] Phosphorous sulfur-containing molecules have found application in medicinal chemistry as promising cardioprotective molecules[2], anti-cancer therapies,[3] antiviral medications,[4] and as inhibitors of acetylcholine esterase.[5] Phosphorothioate oligonucleotide analogues are of considerable interest due their enhanced pharmacokinetic properties,[6] and in the elucidation of metabolic pathways.[7] These compounds are also proving attractive to chemists with a view to creating novel materials.[8] More notoriously, these compounds possess high military significance as chemical warfare agents.[9]

The synthetic application of these compounds, in addition to their preparation *via* C–S bond, formation strategies has recently been summarised by us.[10] The aim of this complementary review, therefore, is to examine the preparation of phosphorothioates and related functional groups based on approaches which revolve around the construction of the P–S bond (Figure 1). Reports involving similar organophosphorus or sulfur sources are grouped together and the underlying principles governing each reaction type are discussed. An outlook examining potential areas of future research is provided towards the end of this review.

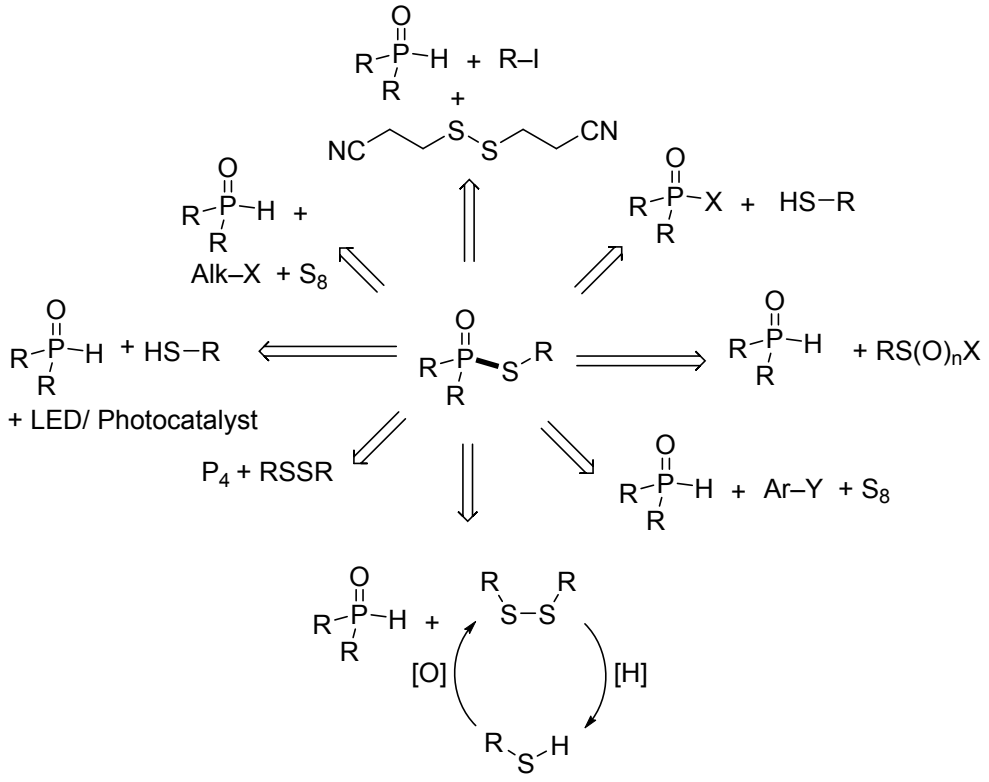


Figure 1. Main approaches to P–S bond formation discussed in this review

1.2 Nomenclature used in this review

The large number of different organophosphorus functional groups commonly encountered in mainstream organic chemistry has led to significant confusion regarding nomenclature. To aid in the understanding of this review, a list of relevant organophosphorus functional groups is provided in Figure 2 and may serve as a useful guide.

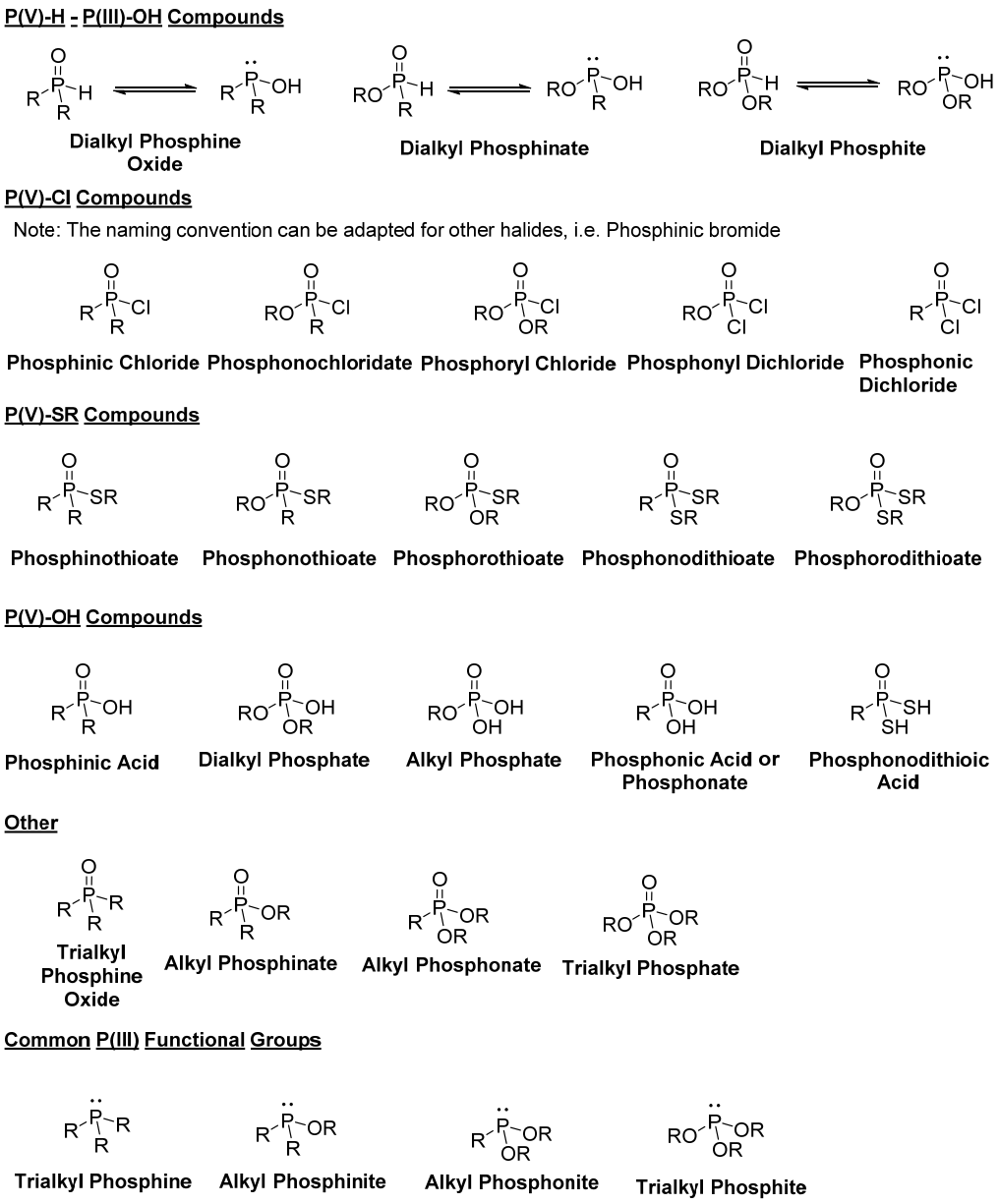


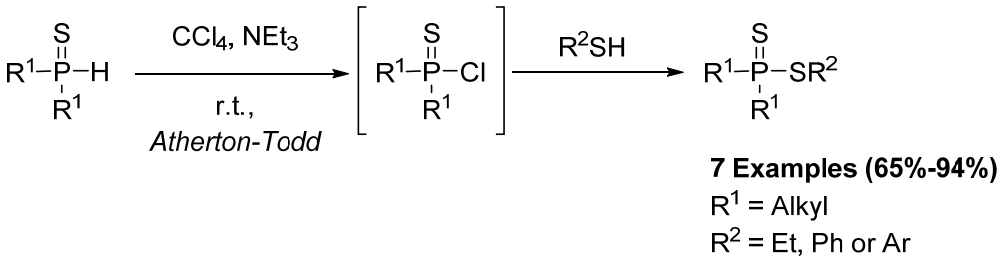
Figure 2. Nomenclature of the main organophosphorus functional groups[1]

Dialkyl phosphines, phosphinates and phosphites exist in an prototropic equilibrium between two tautomers (Figure 2).[11] This tautomerism is broadly similar to that observed between ketones and their enol forms. Where appropriate to the discussion, they will be distinguished from one another as the *P*(V) and the *P*(III) tautomeric forms.

2. P–S bond formation employing electrophilic phosphorus sources

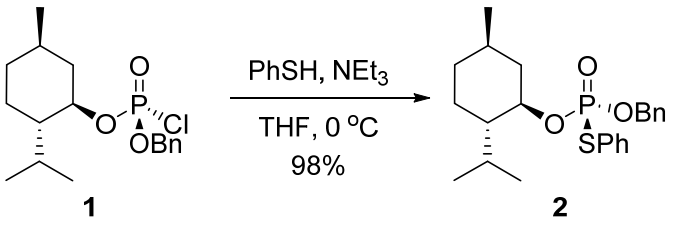
Among the established methods for forming phosphorus-sulfur bonds is the nucleophilic displacement of a halide or pseudohalide leaving group from phosphorus with a sulfur nucleophile. Phosphorus-halide bonds are typically installed through the Atherton-Todd reaction between a Lewis-acidic P–H and a halide source such as CCl_4/NEt_3 or $CHCl_3/LiO^tBu$,[12] either racemically[13] or stereospecifically.[14] The halide can also be introduced through reaction of P-OH with a chlorinating reagent such as oxalyl chloride,[15] thionyl chloride[16] or phosphorus pentachloride.[17]

For example, thiophosphinic chlorides, produced *in situ via* the Atherton-Todd reaction, were treated with a range of thiols to access the corresponding thiophosphinothioates in good to excellent yields (Scheme 1).[18] The yield was lowest when ethanethiol was used owing to its volatility.



Scheme 1

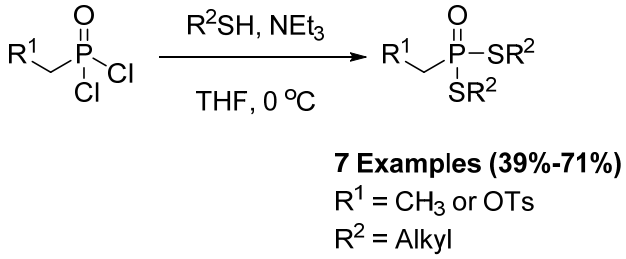
More recently, Zhou *et al*. observed that the nucleophilic displacement of chloride from phosphonic chlorides proceeded cleanly with inversion of stereochemistry (Scheme 2).[19] In the course of this work, they studied the reaction of optically pure menthyl derivative **1**, which can be obtained through an asymmetric Atherton-Todd reaction, with a number of nucleophiles. Phosphorothioate **2** was formed in almost quantitative yield when thiophenol was used as the nucleophile.



Scheme 2

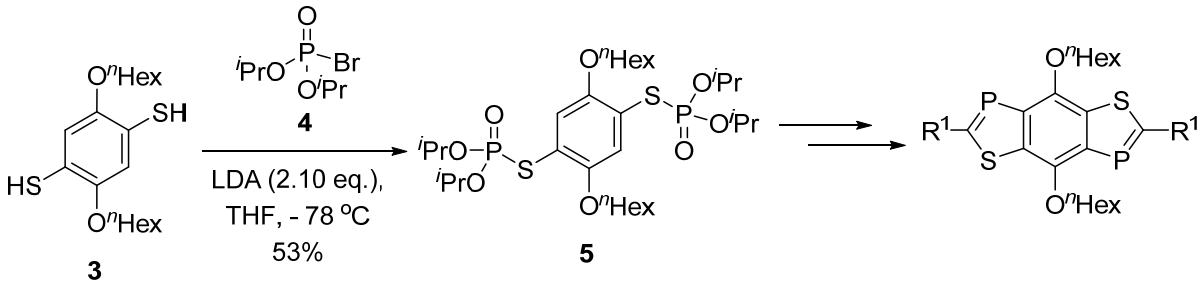
The synthesis of symmetrical phosphonodithioates through the consecutive base-mediated displacement of two chloride ions from a phosphonic dichloride is also possible (Scheme 3).[15]

Anhydrous, deoxygenated solvent is required to maintain consistent yields owing to the hydrolytic instability of the phosphonic dichlorides, as well as the propensity for alkyl thiols to undergo oxidative dimerization to the corresponding disulfides.



Scheme 3

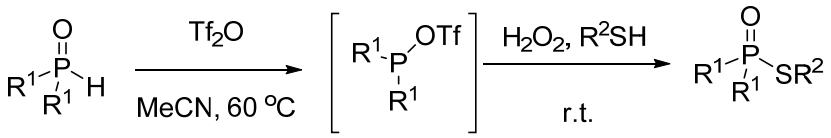
Nucleophilic displacement of bromide has also been successfully exploited as a means of accessing phosphorothioate **5**, an intermediate in the synthesis of a variety of benzobisthiophosphazoles with interesting electrochemical properties (Scheme 4).[8a] Initially, lithium diisopropylamide (LDA) was added to the thiol to generate a dianion, which was subsequently quenched with bromide **4** to afford bisphosphorothioate **5** in 53% yield.



Scheme 4

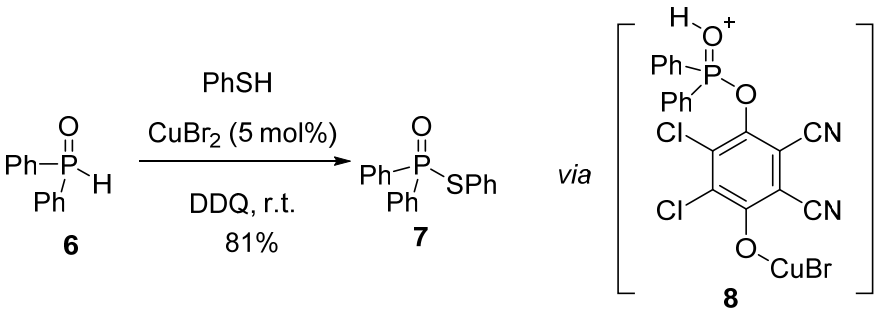
Yuan and co-workers demonstrated that triflic phosphites, formed *in situ* when diaryl phosphonites were treated with triflic anhydride in acetonitrile, gave *S*-aryl phosphinothioates in the presence of hydrogen peroxide in 67%-95% (Table 1).[20] Both electron-rich and electron-poor thiols were well tolerated. However, a slight decrease in reactivity was observed when a 2-napthyl-substituted triflate (Table 1, Entry 7) was used in place of a phenyl or tolyl triflate derivative (Table 1, Entries 4 and 8).

Table 1. Phosphinylation of aromatic thiols using triflic phosphites



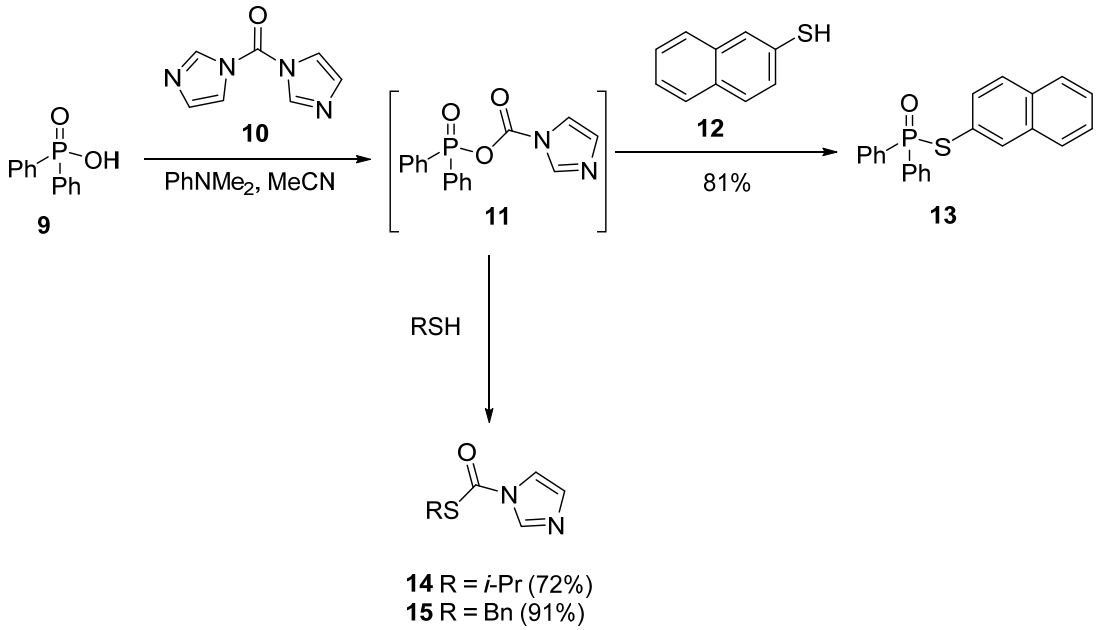
Entry	R^1	R^2	Yield
1	Ph	2-Napthyl	79%
2	Ph	2,4-diMeC_6H_3	89%
3	Ph	3-$MeOC_6H_4$	95%
4	Ph	4-MeC_6H_4	80%
5	Ph	4-*t*-BuC_6H_4	90%
6	Ph	4-ClC_6H_4	81%
7	2-Naphthyl	4-MeC_6H_4	67%
8	4-MeC_6H_4	4-MeC_6H_4	78%

Liu *et al*. studied the activation of diphenyl phosphine oxide (**6**) by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and copper(II) bromide toward attack by thiophenol, in addition to other oxygen and nitrogen nucleophiles (Scheme 5).[21] The authors postulate that DDQ, copper(II) bromide and **6** combine to form the activated complex **8**, increasing the susceptibility of the phosphorus centre to nucleophilic attack, affording **7**.



Scheme 5

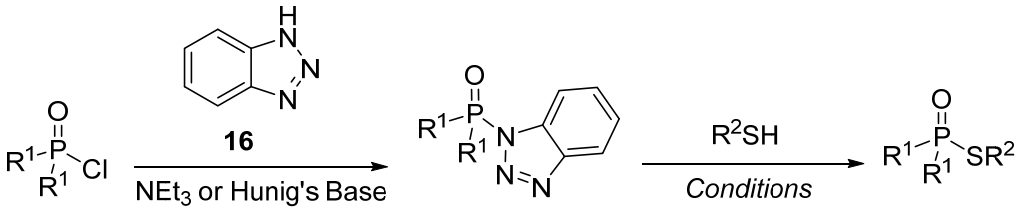
The coupling of phosphinic acids with various phenols using *N*,*N*'-carbonyl diimidazole (CDI) (**10**) was reported by Xiong *et al*. (Scheme 6).[22] When diphenyl phosphinic acid (**9**) was coupled to napthylene-2-thiol (**12**) under these conditions, the corresponding phosphinothioate **13** was formed in 81% yield, proceeding through activated intermediate **11**. This intermediate reacts differently with alkanethiols, however, affording thioesters **14** and **15** instead, making this route unsuitable for aliphatic substrates.

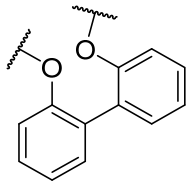


Scheme 6

A recent report by Panmand *et al*. detailed the transformation of a range of phosphoryl chlorides to the corresponding phosphorothioates *via* a benzotriazole intermediate in 65%-76% yields (Table 2).[23] The authors found that the benzotriazole intermediates were considerably more stable towards hydrolysis than their phosphoryl chloride precursors. These benzotriazole intermediates could also be treated with alcohol and amine nucleophiles to form the corresponding substitution products in similar yields.

Table 2. Benzotriazole-mediated phosphorothioate preparation



Entry	R^1	R^2	Conditions	Yield
1	OEt	Cyclohexyl	A	76%
2	OEt	Bn	A	75%
3	OEt	4-MeC_6H_4	A	70%
4		Bn	B	70%
5		4-MeC_6H_4	B	65%

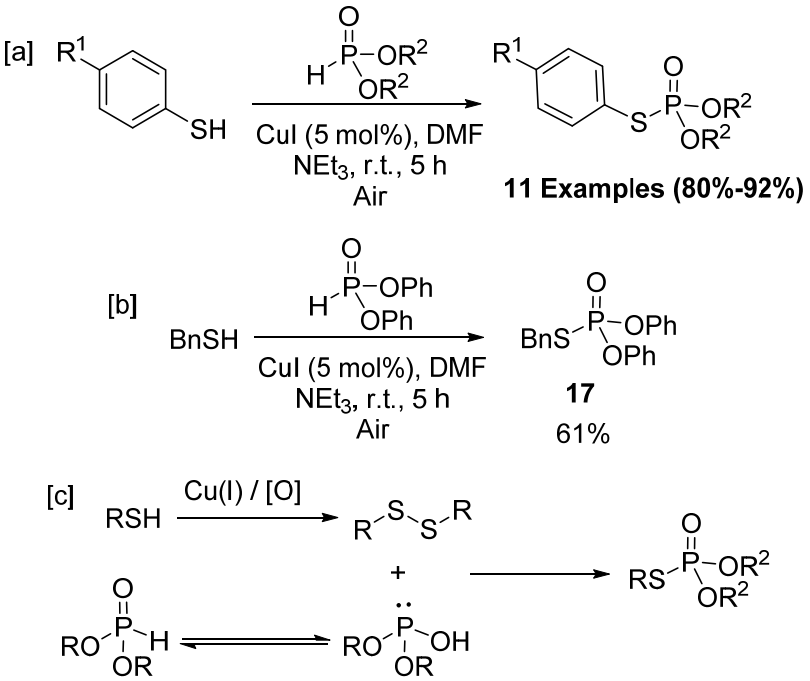
(A) n-BuLi, THF,-78 ^{o}C – r.t., 30 mins (B) DIPEA, r.t., 1 h.

3. P–S bond formation using RSH

3.1 Transition metal-catalysed reaction of RSH with P(O)–H

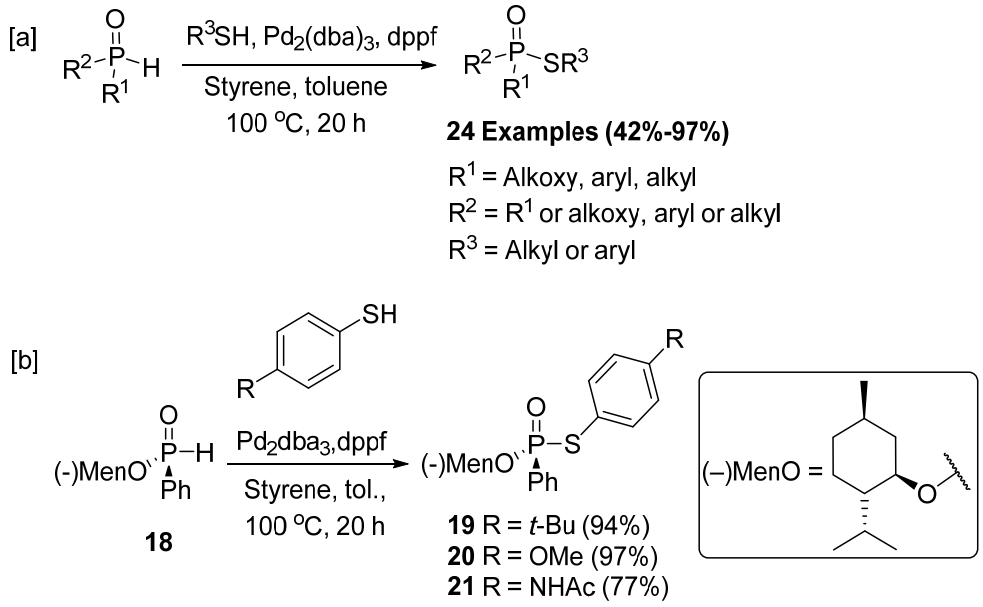
In Section 2, we outlined how P–S bond formation may be achieved *via* activation of an organophosphorus substrate followed by introduction of a sufficiently nucleophilic thiol. Although this strategy represents a practical method for accessing a variety of sulfur-containing organophosphorus compounds, it suffers from several inherent drawbacks. These include the use of stoichiometric activating agents, as well as the instability and toxicity of the activated intermediates. The catalytic activation of stable organophosphorus precursors using a transition metal catalyst overcomes many of these issues.

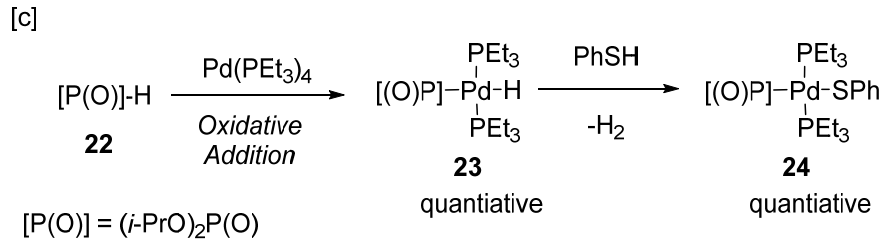
Kaboudin and co-workers employed copper(I) iodide to aerobically couple aromatic thiols and dialkyl phosphites producing phosphorothioates in excellent yields (Scheme 7).[24] Benzyl mercaptan was successfully coupled to diphenyl phosphite to form phosphorothioate **17** under these conditions in 61% yield (Scheme 7 [b]). This result is noteworthy, as it represented one of the few examples of metal-catalysed phosphorus-sulfur bond formation involving an aliphatic thiol until relatively recently. Although the mechanistic details of the transformation are not discussed in this report, it is likely that the thiol undergoes copper-catalysed oxidation to the corresponding disulfide, which then reacts with the phosphite to afford the product (Scheme 7 [C]). By contrast, repeating the reaction under anaerobic conditions in an argon atmosphere proved unsuccessful.

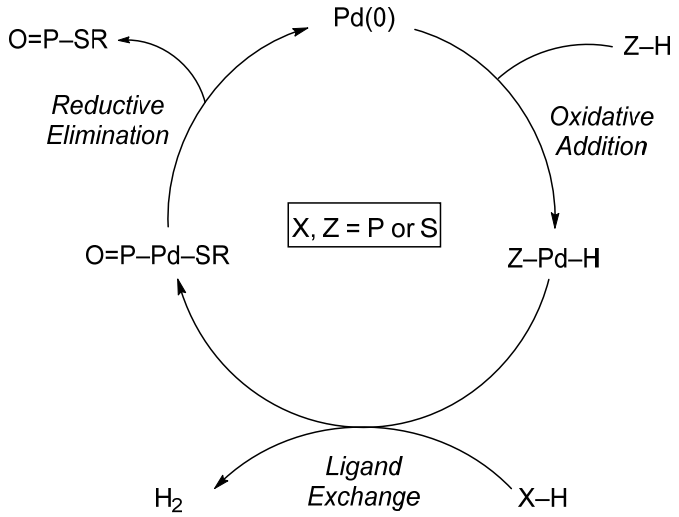


Scheme 7

Dehydrogenative P–S coupling of a range of thiols and *H*-phosphine oxides, phosphinates and phosphites exploiting catalytic $Pd_2(dba)_3$ with 1,1'-ferrocenediyl-bis(diphenylphosphine) (dppf) as the ligand was developed by Zhu *et al*. (Scheme 8).[25] The coupling was conducted in the presence of styrene which scavenges molecular hydrogen, thereby allowing the reaction to reach completion. Yields tended to be lower when 4-nitrothiophenol was used as the sulfur source, likely reflecting its reduced nucleophilicity. Sterically bulky groups on the organophosphorus coupling partner similarly hindered the reaction. Interestingly, the authors also noted that when *P*-chiral *H*-phosphinate **18** and a variety of *para*-substituted thiophenols were subjected to the above reaction conditions, the resulting *S*-aryl phosphonothioates **19-21** were recovered with complete retention of stereochemical configuration (Scheme 8 [b]). This result represents the first synthesis of a *P*-chiral phosphonothioate *via* a catalytic process. The proposed mechanism involves oxidative insertion of the palladium into either the P–H or S–H bond, forming an activated palladium species. This reactive intermediate undergoes a subsequent X–H insertion, and a final reductive elimination, to install the P–S bond. The authors were unable to determine whether the P–H or S–H insertion reaction occurs first, but did demonstrate that P–H insertion is possible. Oxidative addition of tetrakis(triethylphosphine)palladium(0) into the P–H bond of phosphinate **22** afforded tetra-coordinate hydrido complex **23** which was isolated in quantitative yield (Scheme 8 [c]). Quantitative dehydrogenative insertion of **23** into the S–H bond of thiophenol produced complex **24**, the structure of which was confirmed by X-ray crystallography.





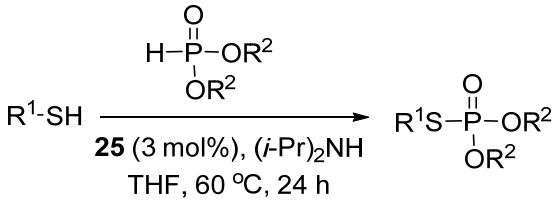


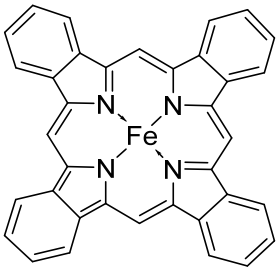
Scheme 8

Oxidative coupling of alkyl thiols with dialkyl phosphites catalysed by iron phthalocyanine (**25**) [Fe(Pc)] was pioneered by Huang as a method for accessing phosphorothioates (Table 3).[26] The products were recovered in yields ranging from 45%-90%. Using dimethyl phosphite in place of diethyl phosphite led to a decrease in yield (Table 3, Entry 1 *vs.* 2). Thiophenol derivatives bearing either electron-donating or electron-withdrawing substituents were also compatible with these

conditions (Table 3, Entries 1-9). Notably, alkyl thiols were also successfully transformed to their corresponding phosphorothioates using this approach (Table 3, Entries 10-11).

Table 3. [Fe(Pc)]-catalysed phosphorothioate synthesis

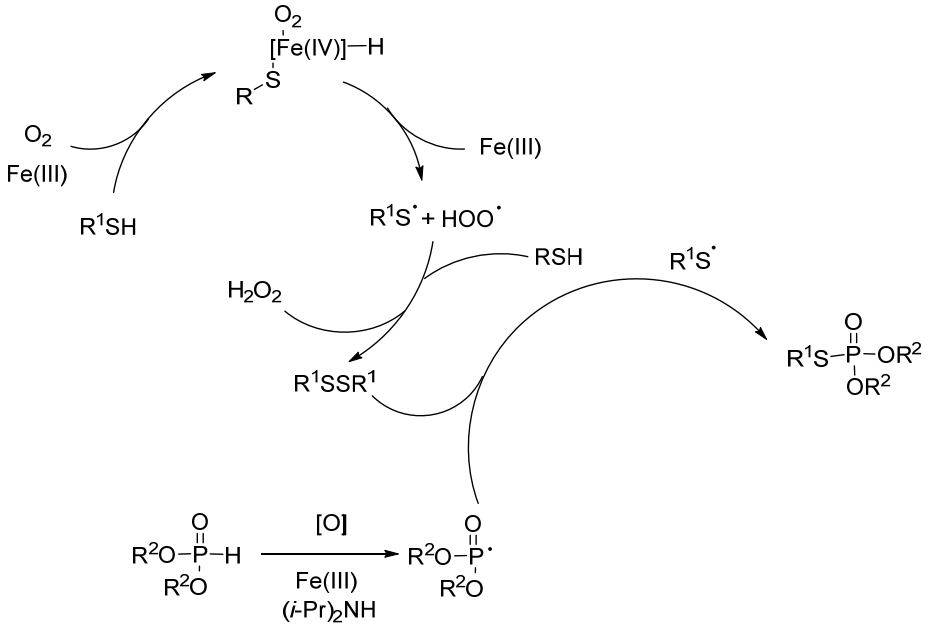




25

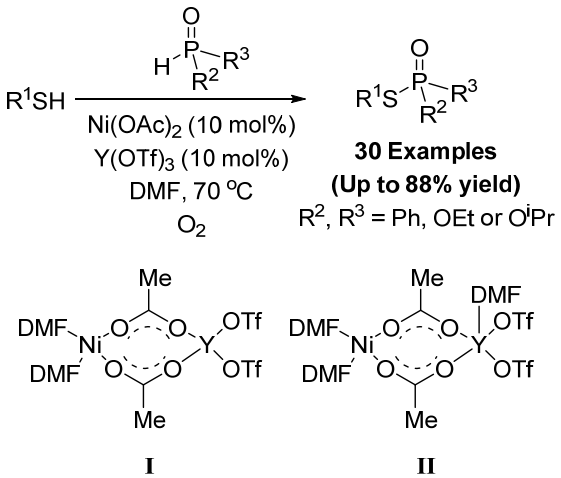
Entry	R^1	R^2	Yield
1	Ph	Et	90%
2	Ph	Me	73%
3	4-MeC_6H_4	Et	88%
4	4-*t*-BuC_6H_4	Et	57%
5	4-FC_6H_4	Et	69%
6	4-ClC_6H_4	Et	82%
7	4-BrC_6H_4	Et	73%
8	4-$CF_3C_6H_4$	Et	52%
9	2,4-$DiMeC_6H_3$	Et	79%
10	Bn	Et	77%
11	*n*-Hexyl	Et	45%

When the above reaction was conducted in the presence of TEMPO or butylated hydroxytoluene (BHT), depressed yields indicated that the reaction likely proceeds *via* a radical mechanism. The authors proposed a catalytic cycle involving concomitant oxidation of the thiol and the phosphite by iron(III), leading to a radical coupling which furnishes the phosphorothioate product (Scheme 9).



Scheme 9

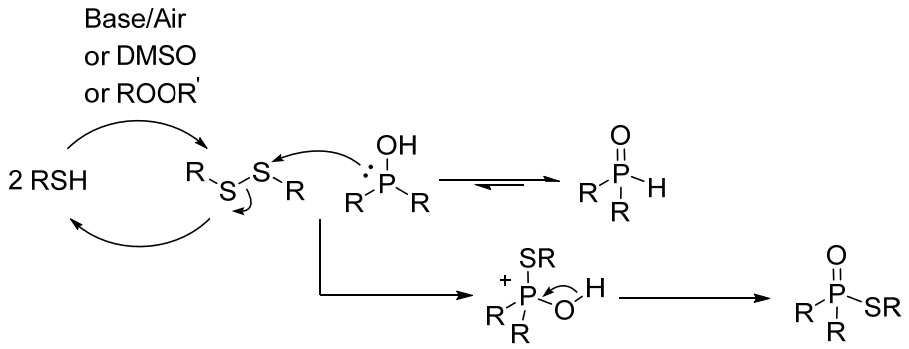
A nickel(II)-catalysed aerobic oxidative coupling using thiols to form phosphorothioates, phosphonothioates and phosphinothioates, invoking an unusual Ni(II)/Y(III) bimetallic species, has been reported by Chen and colleagues (Scheme 10).[27] When nickel(II) acetate was used as the sole catalyst in the presence of oxygen, the reaction proceeded sluggishly, affording only 4% yield of their desired product Addition of yttrium(III) triflate led to a significant rate enhancement, affording the target in 72% yield. A radical-type mechanism was ruled out by the familiar TEMPO experiments suggesting the possibility of a bimetallic Ni(II)/Y(III) catalytic species. Through a combination of ESI-MS and UV-VIS analysis, two plausible bimetallic species, **I** and **II**, were identified during the reaction. Notably, these conditions successfully furnished both *S*-alkyl and *S*-aryl products in good yields.



Scheme 10

3.2. Transition metal-free reaction of RSH with P(O)–H

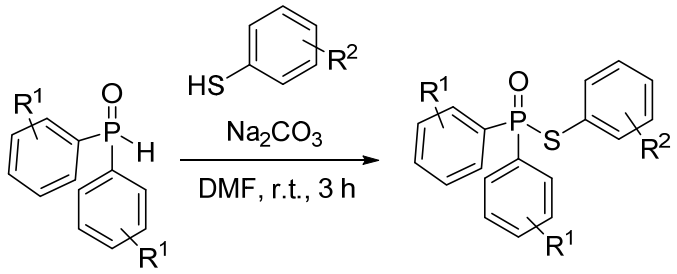
A major goal of modern synthetic chemistry is the development of robust methods which obviate the use of transition metal catalysts, thereby avoiding excessive consumption of a finite resource. In the majority of cases described in section 3.1, the key role of the transition metal was to catalyse the oxidative coupling process. However, the oxidation of thiols and organophosphorus compounds may also be achieved by non-metallic reagents, such as DMSO, iodine or even air in the presence of base. The procedures described in this section typically employ some variation of the fundamental reaction pathway described in Scheme 11. *In situ* oxidation of a thiol to the corresponding disulfide affords an electrophilic sulfur source. Nucleophilic attack by the organophosphorus substrate cleaves the disulfide, forming a new P–S bond accompanied by the release of a thiol molecule. This thiol may be re-oxidised to the disulfide to propagate the reaction.



Scheme 11

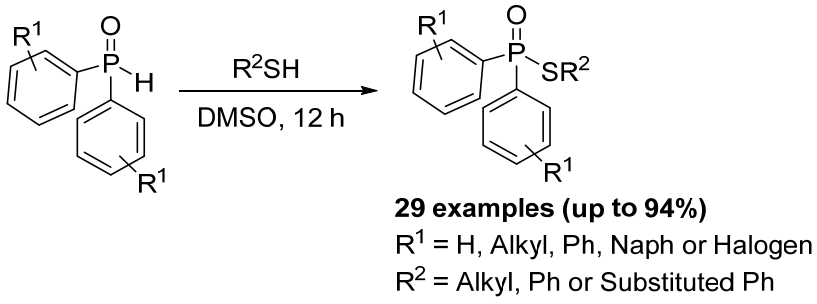
Wallace has previously demonstrated that thiols oxidise readily to the corresponding disulfides when exposed to air under basic conditions.[28] The rate of oxidation is accelerated in polar aprotic solvents such as DMF or DMSO.[28-29] He *et al.* exploited this phenomenon in their synthesis of phosphinothioates (Table 4).[30] The products arising from thiophenols bearing electron-donating groups (Table 4, Entries 1-7) were recovered in good to excellent yields, while those bearing an electron-withdrawing group reacted more sluggishly (Table 4, Entries 8-10). 4-Nitrothiophenol performed particularly poorly (Table 4, Entry 10). This is consistent with previous observations that electron-rich thiols undergo oxidation to the corresponding disulfide more rapidly.[28-29] Both di(4-chlorophenyl) phosphine oxide and di(4-methylphenyl) phosphine oxide were are also subjected to these reaction conditions (Table 4, Entries 11 and 12). The resulting products were recovered in lower yields when compared to reactions of unsubstituted diphenyl phosphine oxide (Table 4, Entry 2).

Table 4. Sodium carbonate-mediated phosphinothioate synthesis



Entry	R^1	R^2	Yield	Entry	R^1	R^2	Yield
1	H	H	88%	**7**	H	3-MeO	77%
2	H	4-Me	87%	**8**	H	4-F	75%
3	H	3-Me	81%	**9**	H	4-Cl	63%
4	H	2-Me	81%	**10**	H	4-NO_2	27%
5	H	2-Et	62%	**11**	4-Me	4-Me	58%
6	H	2-MeO	83%	**12**	4-Cl	4-Me	57%

Interestingly, phosphinothioates may also be prepared in the absence of base when the reaction is conducted in DMSO (Scheme 12).[31] DMSO promotes background oxidation of the thiol to the corresponding disulfide, which then reacts with the dialkyl phosphine oxide starting material, furnishing the desired products. Aryl-substituted phosphinothioates were recovered in 60%-94% yield after 12 hours at room temperature. Alkyl thiols also reacted under these conditions, albeit more sluggishly. The *S*-alkyl-substituted phosphinothioates were isolated in 45%-65% yield after stirring in a sealed tube at 120 ^{o}C.

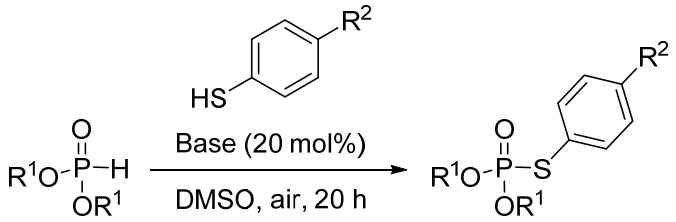


Scheme 12

In contrast to dialkyl phosphines, dialkyl phosphites generally react more slowly with thiols or disulfides due to their reduced nucleophilicity. Consequently, phosphorothioates have proven to be more challenging targets than phosphinothioates, typically requiring extended reaction times or elevated temperatures. The “caesium effect” describes the enhanced solubility, nucleophilicity and

tendency toward oxidation of caesium salts of weak organic acids when compared to other alkali salts.[32] Ouyang showed that caesium hydroxide catalysed the formation of phosphorothioates from dialkyl phosphites and thiophenols (Table 5).[33] A brief screen of caesium hydroxide against other alkali hydroxides highlighted the enhanced catalytic role of caesium (Table 5, Entries 1-5). A series of phosphorothioates was subsequently prepared in 83%-96% yield using this methodology (Table 5, Entries 6-13). A slight decrease in yield was recorded with 4-chlorothiophenol was employed (Table 5, Entries 6, 9 and 12). Interestingly, a similar transformation starting from a disulfide rather than a thiol fails to proceed in the absence of a base (*vide infra* Section 4.1, Scheme 17). This may suggest that deprotonation of the phosphite represents a key step in the underlying reaction mechanism.

Table 5. Alkali metal-mediated phosphorothioate synthesis

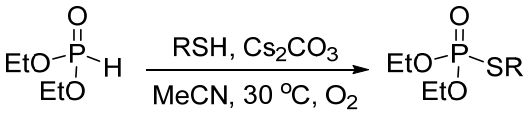


Entry	R^1	R^2	Base	Yield	Entry	R^1	R^2	Base	Yield
1	Me	H	LiOH	0%	**8**	Et	H	CsOH	92%
2	Me	H	NaOH	21%	**9**	Et	Cl	CsOH	86%
3	Me	H	KOH	29%	**10**	Et	Me	CsOH	93%
4	Me	H	RbOH	70%	**11**	*n*-Bu	H	CsOH	92%
5	Me	H	CsOH	91%	**12**	*n*-Bu	Cl	CsOH	83%
6	Me	Cl	CsOH	85%	**13**	*n*-Bu	Me	CsOH	94%
7	Me	Me	CsOH	95%					

Consistent with these findings, Song and co-workers reported that caesium carbonate catalysed the formation of phosphorothioates more effectively than other alkali metal carbonates (Table 6).[34] These reactions were conducted in an oxygen atmosphere to facilitate oxidation of the thiol to the disulfide. The authors demonstrated that both aryl and alkyl thiols were compatible with this approach. Aryl thiols were converted to corresponding phosphorothioate products (Table 6, Entries 1-12) in good to excellent yields using 10 mol% of caesium carbonate. The only notable exception was the 4-nitrophenyl analogue (Table 6, Entry 7) which was isolated in only 22% yield after an extended reaction time, perhaps reflecting the sluggish oxidation of electron-poor thiols to their disulfides. Alkyl thiols were also suitable substrates, but required a higher loading of 50 mol% of

caesium carbonate and extended reaction times (Table 6, Entries 13-24). Benzylic thiols required additional heating in order to force the reaction to completion (Table 6, Entries 17 and 18).

Table 6. Caesium carbonate-mediated phosphorothioate synthesis



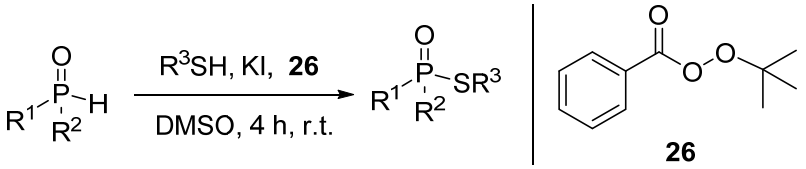
Entry	R	Yield[a]	Entry	R	Yield[b]
1	Ph	76%	**13**	*n*-Bu	69%
2	2-ClC_6H_4	77%[c]	**14**	*i*-Bu	53%
3	3-ClC_6H_4	81%	**15**	*i*-Pent	69%
4	4-ClC_6H_4	86%	**16**	*n*-Oct	76%
5	4-BrC_6H_4	80%	**17**	CH_2Ph	58%[d]
6	4-FC_6H_4	86%	**18**	4-$MeOC_6H_4CH_2$	80%[d]
7	4-$NO_2C_6H_4$	22%[c]	**19**	2-Furyl	72% [e]
8	4-$MeOC_6H_4$	90%	**20**	CH_2CH_2Ph	76% [e]
9	3-$MeOC_6H_4$	89%	**21**	$CH_2CH_2CO_2Me$	68%
10	2-$MeOC_6H_4$	87%	**22**	$CH_2CH_2CONHMe$	61% [f]
11	4-$NH_2C_6H_4$	94%[c]	**23**	$CH_2CH(NHBoc)CO_2Et$	67% [e]
12	4-MeC_6H_4	93%[c]	**24**	cyclohexyl	50% [d]

[a]Unless otherwise stated: Cs_2CO_3 (10 mol%), 3 h [b] Unless otherwise stated: Cs_2CO_3 (50 mol%), 12h, [c] Cs_2CO_3 (10 mol%), 12 h [d] At 80 °C [e] 3 h [f] At 60 °C

The *in situ* oxidation of thiols to disulfides may also be accomplished using peroxides. An initial study by Wang *et al.* demonstrated the application of this chemistry to the synthesis of phosphinothioates and phosphonothioates (Table 7).[35] A screen of oxidants revealed that *tert*-butyl peroxybenzoate (TBPB) (**26**), in presence of potassium iodide, efficiently catalysed the phosphorylation of both alkyl and aryl thiols in good to excellent yields. In the case of aryl thiols, the reaction was successful regardless of the electronic or steric nature of the substrate. Both electron-donating (Table 7, Entries 2-4) and electron-withdrawing substrates (Table 7, Entries 5 and 6) provided almost quantitative yields of the target phosphinothioates. One exception was the reaction of 4-acetamidothiophenol which was noticeably lower yielding (Table 7, Entry 7). Alkyl thiols were also well tolerated. In the case of 1,6-hexanedithiol, where both mono- and diphosphorylation products were possible, only monophosphorylation was observed (Table 7, Entry 15). Phosphinates were also subjected to these conditions and the resulting phosphonothioates were isolated in good yields (Table 7, Entries 19 and

20). It is likely that the peroxide facilitates this transformation *via* a radical mechanism as no reaction was observed in the presence of TEMPO.

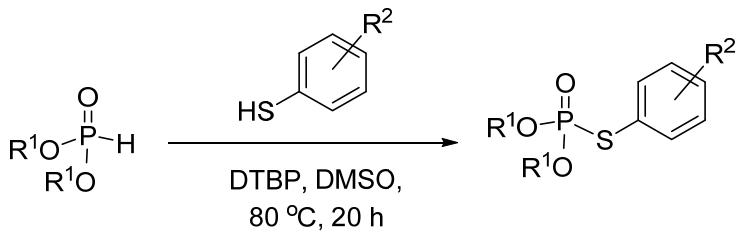
Table 7. Oxidative P(V)-S bond formation using TBPB



Entry	R^1	R^2	R^3	Yield	Entry	R^1	R^2	R^3	Yield
1	Ph	Ph	Ph	96%	**11**	Ph	Ph	*n*-Bu	97%
2	Ph	Ph	4-$MeOC_6H_4$	98%	**12**	Ph	Ph	*t*-Bu	88%
3	Ph	Ph	3-$MeOC_6H_4$	99%	**13**	Ph	Ph	CH_2CO_2H	66%
4	Ph	Ph	2-$MeOC_6H_4$	99%	**14**	Ph	Ph	$(CH_2)_{11}CH_3$	96%
5	Ph	Ph	4-ClC_6H_4	99%	**15**	Ph	Ph	$(CH_2)_6SH$	82%
6	Ph	Ph	2-ClC_6H_4	95%	**16**	2-MeC_6H_4	2-MeC_6H_4	Cyclohexyl	81%
7	Ph	Ph	4-$AcNHC_6H_4$	51%	**17**	2-Naph	Ph	Cyclohexyl	76%
8	Bn	Ph	Ph	71%	**18**	Bn	Ph	Cyclohexyl	65%
9	4-ClC_6H_4	4-ClC_6H_4	Ph	90%	**19**	Ph	OEt	Bn	81%
10	2-Naph	2-Naph	Ph	99%	**20**	Ph	OEt	4-ClBn	84%

A parallel report from the same team outlined how a similar peroxide-based approach, employing di-*tert* butyl peroxide (DTBP), could be also exploited to access phosphorothioates (Table 8).[36] In contrast to the formation of phosphinothioates (Table 7), which proceeded under relatively mild conditions, an elevated temperature of 80 ^{o}C proved necessary, reflecting the reduced nucleophilicity of dialkyl phosphites. Lower yields were obtained when more sterically hindered thiophenols were employed (Table 8, Entries 3-4 and 7-8) or when phosphites bearing longer alkyl chains were introduced (Table 8, Entries 10-14). In accordance with earlier studies which identified 4-nitrothiophenol as a challenging substrate (Table 6, Entry 10 and Table 4, Entry 7), 4-nitrothiophenol did not react under these conditions (Table 8, Entry 9).

Table 8. DTBP-promoted oxidative P(V)-S bond formation



Entry	R^1	R^2	Yield	Entry	R^1	R^2	Yield
1	Et	4-MeO	96%	**8**	Et	2-Cl	81%
2	Et	3-MeO	85%	**9**	Et	4-NO_2	0%
3	Et	2-MeO	32%	**10**	Et	H	92%
4	Et	2-NH_2	77%	**11**	Me	H	90%
5	Et	3-HO	85%	**12**	*n*-Pr	H	82%
6	Et	4-Cl	97%	**13**	Hex	H	55%
7	Et	3-Cl	89%	**14**	Octyl	H	37%

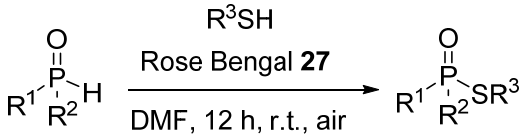
3.3 Radical reactions of RSH with P(O)-H

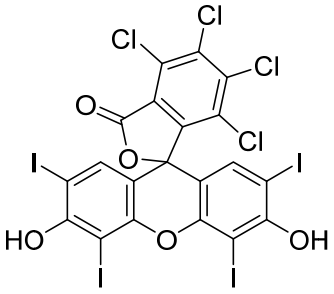
Photoredox catalysis is a powerful synthetic tool for environmentally benign organic transformations.[37] Photocatalytic reactions are generally conducted in the presence of a photosensitiser, such as Rose Bengal, Rhodamine B, Eosin Y or Methylene Blue, which becomes photoexcited when irradiated by visible light.[37] The light sources for these reactions are typically sunlight or light-emitting diodes (LEDs). In this photoexcited state, the photocatalyst enables the generation of various reactive intermediates under mild conditions. In the context of organophosphorus chemistry, photoredox catalysis has been predominantly applied to the construction of phosphorus-carbon bonds.[38]

The first report of the construction of phosphorus-sulfur bonds *via* a photocatalysed approach was that of Sun and co-workers.[39] Rose Bengal (**27**) was chosen as the photocatalyst (Table 9). Irradiation of the photocatalyst with 10 W blue LEDs catalysed the phosphorylation of aryl and alkyl thiols in moderate to excellent yields. The choice of thiol (Table 9, Entries 1-18) and phosphine oxide (Table 9, Entries 19-24) were both investigated. In general, thiophenol derivatives (Table 9, Entries 1-15) were more amenable to these conditions than alkyl-substituted thiols (Table 9, Entries 16-18). Aryl substrates bearing an electron-withdrawing group (Table 9, Entries 9-11) reacted more sluggishly than electron-rich substrates (Table 9, Entries 2-8). The products arising from sterically

hindered *ortho*-substituted thiols (Table 9, Entries 14 and 15) were recovered in lower yields than the corresponding *meta*- (Table 9, Entries 12 and 13) or *para*-substituted thiophenols (Table 9, Entries 2 and 11). Bulkier phosphine oxides afforded lower yields than their less hindered counterparts (Table 9, Entries 19-23). The conversion of a phosphinate to the corresponding phosphonothioate also proved possible, albeit in a low 30% yield following an extended reaction time of 36 hours (Table 9, Entry 24). When 4-hydroxythiophenol (Table 9, Entry 7) and 4-aminothiophenol (Table 9, Entry 8) were subjected to these conditions, the reactions proceeded with high chemoselectivity and exclusive phosphorus-sulfur bond formation.

Table 9. Rose Bengal-catalysed P(V)-S bond formation





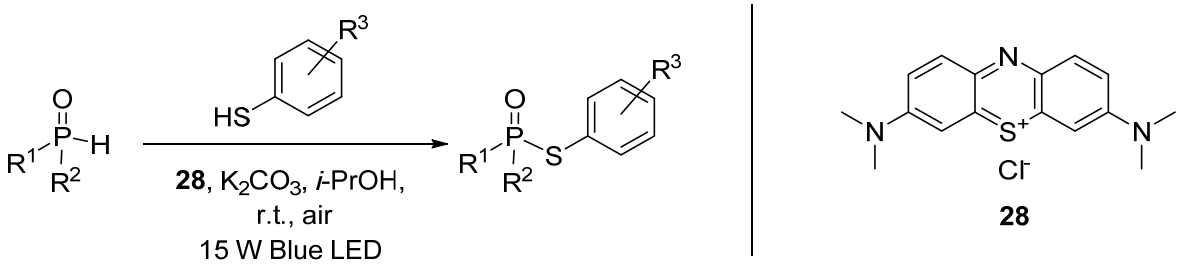
Rose Bengal **27**

Entry	R^1	R^2	R^3	Yield
1	Ph	Ph	Ph	56%
2	Ph	Ph	4-MeC_6H_4	79%
3	Ph	Ph	4-EtC_6H_4	82%
4	Ph	Ph	4-*t*-BuC_6H_4	83%
5	Ph	Ph	4-$MeOC_6H_4$	86%
6	Ph	Ph	4-$AcNHC_6H_4$	73%
7	Ph	Ph	4-HOC_6H_4	77%
8	Ph	Ph	4-$NH_2C_6H_4$	84%
9	Ph	Ph	4-FC_6H_4	58%
10	Ph	Ph	4-ClC_6H_4	40%
11	Ph	Ph	4-BrC_6H_4	54%
12	Ph	Ph	3-MeC_6H_4	82%
13	Ph	Ph	3-$MeOC_6H_4$	91%
14	Ph	Ph	2-MeC_6H_4	60%
15	Ph	Ph	2-$MeOC_6H_4$	55%
16	Ph	Ph	*n*-Pr	46%

17	Ph	Ph	Cyclohexyl	40%
18	Ph	Ph	Bn	50%
19	4-MeC_6H_4	4-MeC_6H_4	4-MeC_6H_4	80%
20	2-MeC_6H_4	2-MeC_6H_4	4-MeC_6H_4	52%
21	4-*t*-BuC_6H_4	4-*t*-BuC_6H_4	4-MeC_6H_4	35%
22	4-FC_6H_4	4-FC_6H_4	4-MeC_6H_4	56%
23	4-ClC_6H_4	4-ClC_6H_4	4-MeC_6H_4	62%
24	Ph	EtO	4-MeC_6H_4	30% (36h)

Zhang later modified this methodology, substituting Methylene Blue (**28**) for Rose Bengal (**27**).[40] The authors further extended the substrate scope, preparing phosphorothioates (Table 10, Entries 1-13) as well as phosphinothioates (Table 10, Entries 14-19). Somewhat surprisingly, *para*-halogenated thiophenols (Table 10, Entries 5-7) afforded higher yields than electron-rich substrates (Table 10, Entries 2-4). This trend contrasted with the findings of Sun and colleagues. Thiols bearing stronger electron-withdrawing groups, such as the 4-cyano or the 4-nitrosubstituted examples (Table 10, Entry 10-11), performed poorly and required extended reaction times. Sterically hindered *ortho*-substituted thiols were also slow to react (Table 10, Entries 12-13). The chemoselective formation of phosphorus-sulfur bonds was again noted (Table 10, Entries 8, 9, 13).

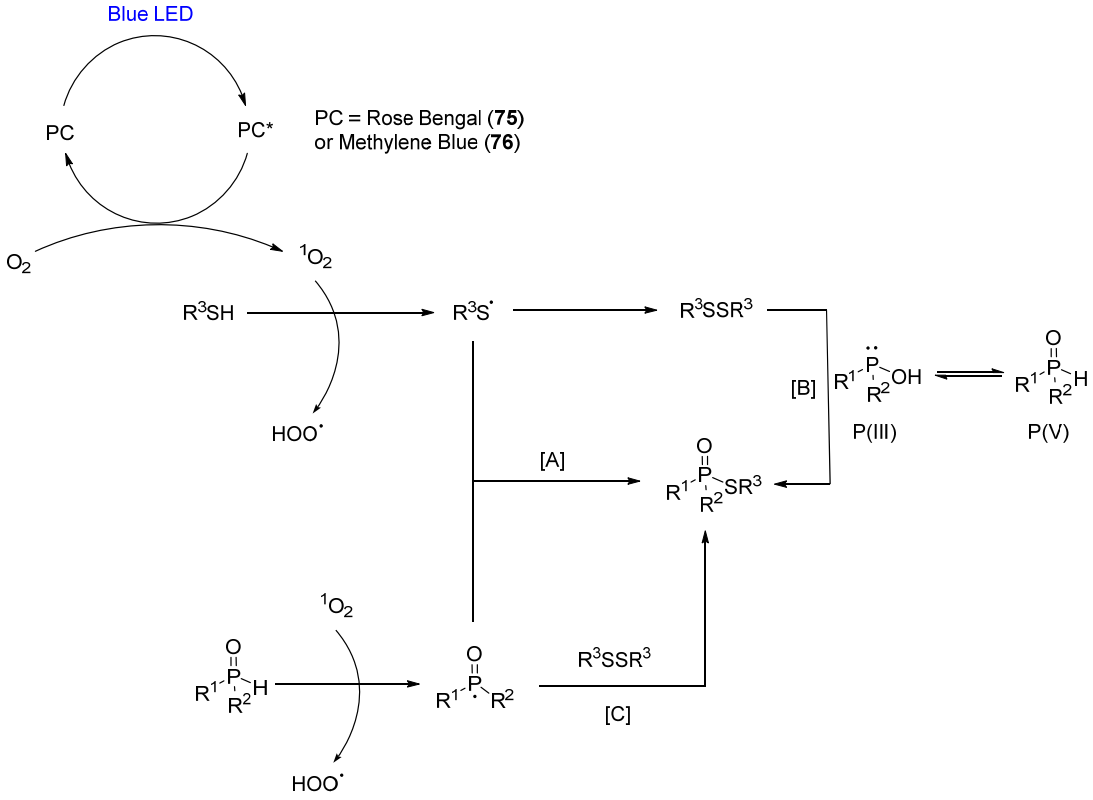
Table 10. Methylene blue-catalysed P(V)-S bond formation



Entry	R^1	R^2	R^3	Time (h)	Yield
1	OEt	OEt	H	24	87%
2	OEt	OEt	4-Me	24	92%
3	OEt	OEt	4-MeO	24	66%
4	OEt	OEt	4-*t*-Bu	24	61%
5	OEt	OEt	4-F	24	64%
6	OEt	OEt	4-Cl	24	95%
7	OEt	OEt	4-Br	24	92%

8	OEt	OEt	4-NH_2	24	67%
9	OEt	OEt	4-HO	24	73%
10	OEt	OEt	4-NC	48	45%
11	OEt	OEt	4-NO_2	48	42%
12	OEt	OEt	2-Br	48	54%
13	OEt	OEt	2-NH_2	48	43%
14	Ph	Ph	4-Cl	24	86%
15	Ph	Ph	4-Me	24	83%
16	4-MeC_6H_4	4-MeC_6H_4	4-Cl	24	76%
17	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-Cl	36	62%
18	Ph	Ph	4-F	48	54%
19	4-MeC_6H_4	4-MeC_6H_4	4-NH_2	24	88%

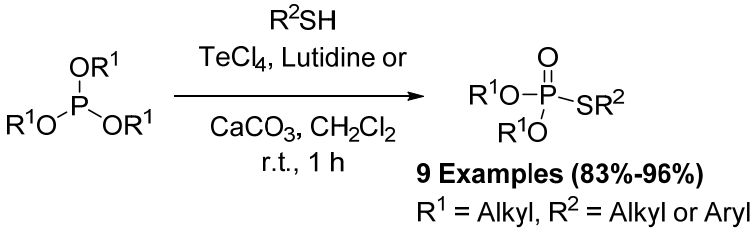
Both Zhang[40] and Sun[39] independently conducted studies to elucidate the mechanism of this transformation, and concluded that three parallel processes were likely at play (Scheme 13). When the photocatalyst (PC) is initially irradiated, it becomes photoexcited (PC*). In this state, the catalyst promotes the formation of singlet oxygen ($^1O_2$), a reactive oxygen species, from molecular oxygen. This was supported by the observation that only trace amounts of the product were formed when the reaction was conducted in the dark, in the absence of the photocatalyst, in an inert atmosphere or in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), a strong physical quencher of singlet oxygen.[41] Both authors observed evidence for radical intermediates. When the reaction was carried out in the presence of radical traps such as TEMPO or styrene, the corresponding thiyl and phosphinyl adducts were detected, suggesting that both thiyl and *P*-centred radicals are involved. The combination of these two radicals is, therefore, one possible route to generating the final product (Scheme 13, Route [A]).



Scheme 13

3.4 Reaction of RSH with R_3P

Trialkyl phosphites are relatively strong nucleophiles and react with disulfides to form the corresponding phosphorothioates. Phosphorothioates were recovered in 83%-96% yields in the presence of sub-stochiometric amounts of tellurium(IV) chloride and a suitable base such as lutidine or calcium carbonate (Scheme 14).[42] In the case of alkane thiols, calcium carbonate afforded significantly higher yields than lutidine, although a possible basis for this observation was not provided.

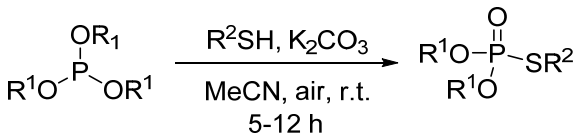


Scheme 14

In a similar vein, Wen and colleagues generated a range of phosphorothioates from trialkyl phosphites and the corresponding aryl thiols (Table 11).[43] *In situ* oxidation of the thiol to the disulfide, mediated by potassium carbonate, and subsequent nucleophilic attack by the trialkyl

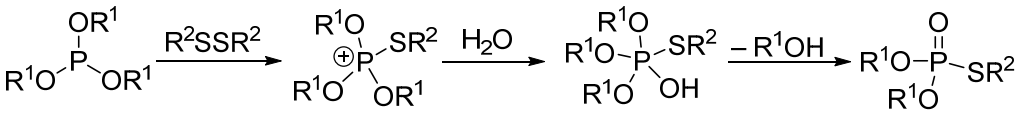
phosphite, installed the desired phosphorus-sulfur bond. Aromatic thiols with either electron-withdrawing or electron-donating substituents were well tolerated, although yields tended to be higher with electron-rich substrates (Table 11, Entries 1-13). Interestingly, *S*-(4-nitrophenyl) diethyl phosphorothioate (Table 1, Entry 12) was isolated in an impressive yield of 85%. Previous studies identified this compound as being particularly difficult to produce using a disulfide-mediated approach (*cf*. Table 4, Entry 10; Table 6, Entry 7; Table 8, Entry 9). 2-Mercaptonapthylene and 2-mercaptothiophene likewise proved to be compatible substrates (Table 11, Entries 16, 17). By contrast, alkyl thiols did not react under these conditions (Table 11, Entry 14, 15). Additionally, when trimethyl phosphite was used in place of triethyl phosphite, the resulting yields were lower (Table 11, Entries 18 and 19). However, excellent yields were recorded with other phosphites (Table 11, Entries 20-24).

Table 11 – Preparation of phosphorothioates from trialkyl phosphites



Entry	R^1	R^2	Yield	Entry	R^1	R^2	Yield
1	Et	4-MeC_6H_4	92%	**13**	Et	2,5-diMeC_6H_3	89%
2	Et	3-MeC_6H_4	71%	**14**	Et	Bn	Trace
3	Et	2-MeC_6H_4	77%	**15**	Et	Cyclohexyl	0%
4	Et	4-$MeOC_6H_4$	70%	**16**	Et	2-Napthyl	55%
5	Et	3-$MeOC_6H_4$	80%	**17**	Et	2-Thiophene	64%
6	Et	4-BrC_6H_4	50%	**18**	Me	4-MeC_6H_4	40%
7	Et	3-BrC_6H_4	52%	**19**	Me	4-ClC_6H_4	15%
8	Et	4-ClC_6H_4	90%	**20**	*i*-Pr	4-MeC_6H_4	91%
9	Et	3-ClC_6H_4	40%	**21**	*i*-Pr	4-ClC_6H_4	88%
10	Et	4-$CF_3C_6H_4$	63%	**22**	*n*-Bu	4-MeC_6H_4	88%
11	Et	3-$CF_3C_6H_4$	48%	**23**	*n*-Bu	4-ClC_6H_4	80%
12	Et	4-$NO_2C_6H_4$	85%	**24**	Ph	4-MeC_6H_4	90%

The authors propose that, following initial oxidative dimerisation of the thiol, subsequent nucleophilic attack by the phosphite generates a tetravalent intermediate (Scheme 15). Collapse of the resulting tetravalent intermediate, facilitated by water, affords the desired product.

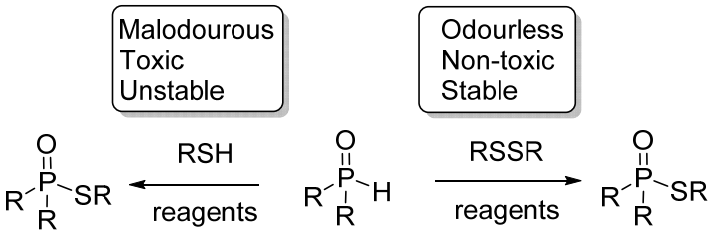


Scheme 15

4. P–S bond formation from disulfides

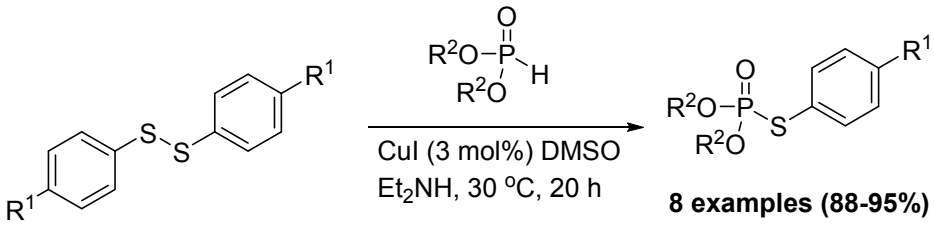
4.1 Reaction of RSSR with P(O)–H

In Section 3.2, the use of disulfides as an electrophilic sulfur source was discussed. These disulfides are typically generated *in situ* by oxidative dimerisation of the corresponding thiols. However, it is often more convenient to employ the disulfides directly as they are generally more stable and less malodorous (Scheme 16). In principle, the reactions described in this section proceed *via* a similar pathway wherein the P(III)-nucleophile attacks the disulfide, forming a new P–S bond and a thiol molecule which can be subsequently recycled.



Scheme 16

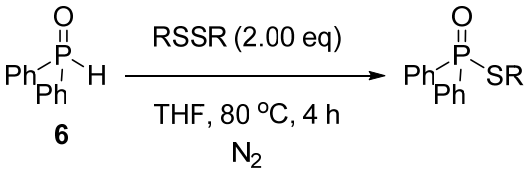
An early example of this approach was reported by Gao and co-workers, who demonstrated the successful application of copper catalysis for the preparation of *S*-aryl phosphorothioates from diaryl disulfides and dialkyl phosphites in excellent yields (Scheme 17).[44] Copper(I) iodide was found to be the most efficient catalyst following extensive optimisation. The reaction stalls in the absence of base, but does proceed in the absence of copper, albeit significantly more slowly. This protocol was also used to access *Se*-aryl phosphoroselenides and *Te*-aryl phosphorotellurides.



Scheme 17

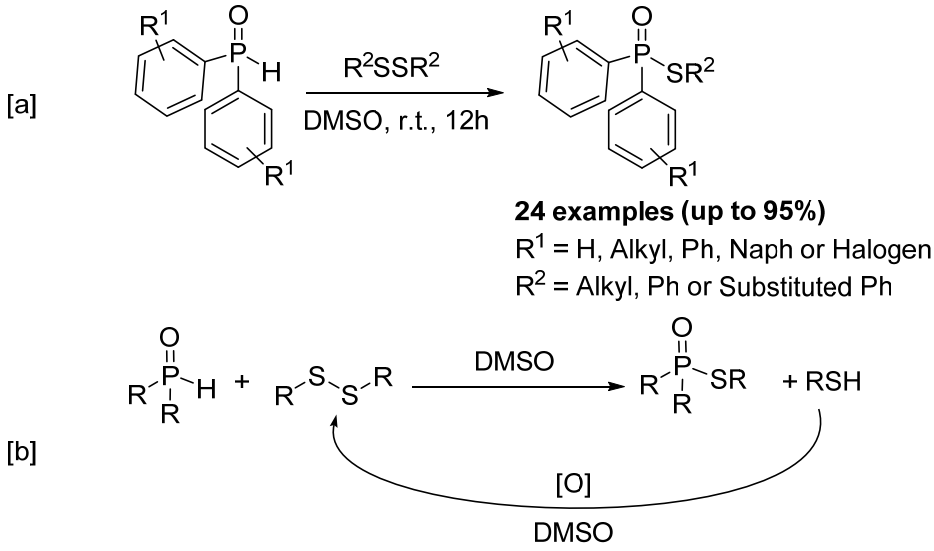
As previously observed, diaryl phosphine oxides react faster with disulfides than dialkyl phosphites. This precedents a report by Xia and Cheng, which demonstrated that treating diphenyl phosphine (**6**) with a range of aryl and alkyl disulfides in THF at reflux, in the absence of a base, furnished the corresponding phosphinothioates in 40%-95% yields (Table 12).[45] Aryl disulfides were generally recovered in good to excellent yields (Table 12, Entries 1-10). Alkyl derivatives were also recovered in satisfactory yields (Table 12, Entries 11-15).

Table 12. Synthesis of phosphinothioates from disulfides



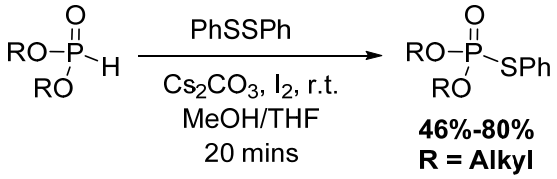
Entry	R	Yield	Entry	R	Yield	Entry	R	Yield
1	Ph	95%	**6**	4-ClC_6H_4	72%	**11**	Me	73%
2	4-MeC_6H_4	94%	**7**	4-BrC_6H_4	80%	**12**	Octyl	48%
3	4-$MeOC_6H_4$	95%	**8**	3-ClC_6H_4	58%	**13**	*i*-Bu	88%
4	2-MeC_6H_4	82%	**9**	4-*t*-$BuOCOC_6H_4$	89%	**14**	Bn	48%
5	2-FC_6H_4	80%	**10**	4-HOC_6H_4	40%	**15**	Allyl	78%

Sun *et al*. described a similar transformation under ambient conditions employing dimethyl sulfoxide (DMSO) as the reaction medium, which facilitates the formation of phosphinothioates in comparable yields to those reported by Xia and Cheng (Scheme 18 [a]).[31] The authors extended the substrate scope of this reaction to include substituted diphenyl phosphine oxides. In general, alkyl-substituted aryl rings proved more reactive than their halogenated analogues. It is likely that DMSO serves to re-oxidise the thiol by-product which results from initial nucleophilic attack by the phosphine (Scheme 18 [b]).



Scheme 18

Caesium carbonate, in the presence of molecular iodine, accelerated the formation of *S*-phenyl phosphorothioates in 46%-80% yield from diphenyl disulfide and various phosphites (Scheme 19).[46] The combination of caesium base (*vide supra*, Section 3.2) and molecular iodine, which acts as a co-oxidant, rapidly re-oxidises the thiolate intermediate, with the reaction reaching completion in 20 minutes. This approach can be further modified to access *Se*-phenyl and *Te*-phenyl phosphonochalcogens using the corresponding dichalcogenides in place of the disulfide.

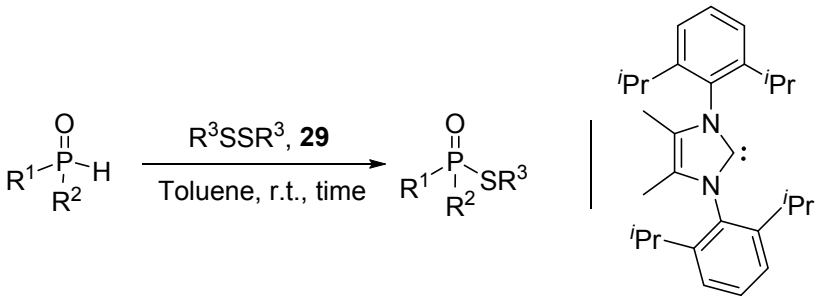


Scheme 19

N-Heterocyclic carbenes (NHCs) are an important class of organocatalyst which have widespread application in organic chemistry.[47] A 10 mol% loading of imidazolylidene **29** catalysed the phosphorylation of a range of disulfides (Table 13).[48] Although other NHC catalysts were examined, **29** proved to be the most efficient. Phosphites (Table 13, Entries 1-8), phosphinates (Table 13, Entries 9-13) and phosphine oxides (Table 13, Entries 14-16) were transformed over 5-40 minutes. The phosphorylation of di(4-tolyl) disulfide (Table 13, Entries 2, 6, 10 and 15) proceeded relatively slowly, mostly likely due to increased steric hindrance. The coupling of *O*-butyl phenylphosphinate with dibenzyl disulfide (Table 13, Entry 13) required an extended reaction time of 24 hours to generate the desired product in 12% yield. This result contrasts sharply with the analogous transformation with *O*-methyl phenylphosphinate (Table 13, Entry 9), which returned a 100% yield

after 15 minutes. The increased steric hindrance of the bulkier *O*-butyl group accounts for the reduced reactivity.

Table 13. NHC-catalysed phosphorylation of disulfides

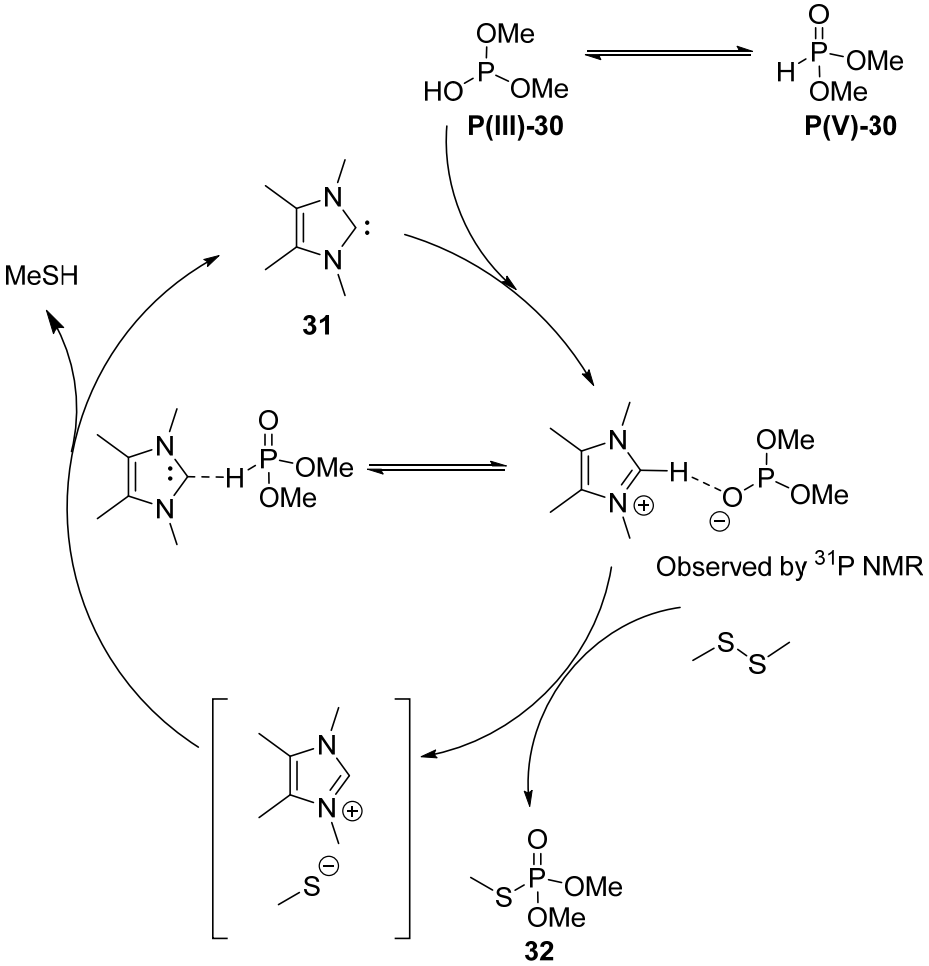


29

Entry	R^1	R^2	R^3	Yield	Time (min)
1	*n*-BuO	*n*-BuO	Bn	83%	5
2	*n*-BuO	*n*-BuO	4-Tol	34%	40
3	*n*-BuO	*n*-BuO	Et	84%	5
4	PhO	PhO	Bn	94%	30
5	MeO	MeO	Bn	89%	5
6	MeO	MeO	4-Tol	19%	40
7	MeO	MeO	Et	68%	5
8	MeO	MeO	*n*-Bu	76%	5
9	Ph	MeO	Bn	100%	15
10	Ph	MeO	4-Tol	45%	40
11	Ph	MeO	Et	68%	5
12	Ph	MeO	Cyclohexyl	Trace	n/a
13	Ph	*n*-BuO	Bn	12%	24 hr
14	Ph	Ph	Bn	94%	5
15	Ph	Ph	4-Tol	79%	40
16	Ph	Ph	Et	96%	5

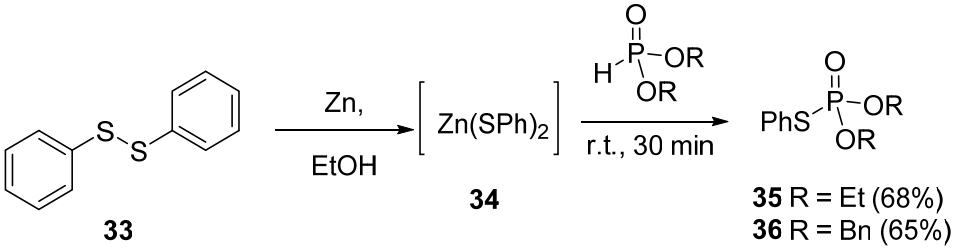
Monitoring of these reactions by ^{1}H and ^{31}P NMR in deuterated toluene led to the identification of transient reaction intermediates. This work, in conjunction with computational experiments, supported the mechanism outlined by the authors (Scheme 20). It is believed that the *N*-heterocyclic

carbene **31** acts as a Lewis-base which deprotonates phosphite starting material **30**. The resulting adduct adds across the disulfide bond forming phosphorothioate **32**.



Scheme 20

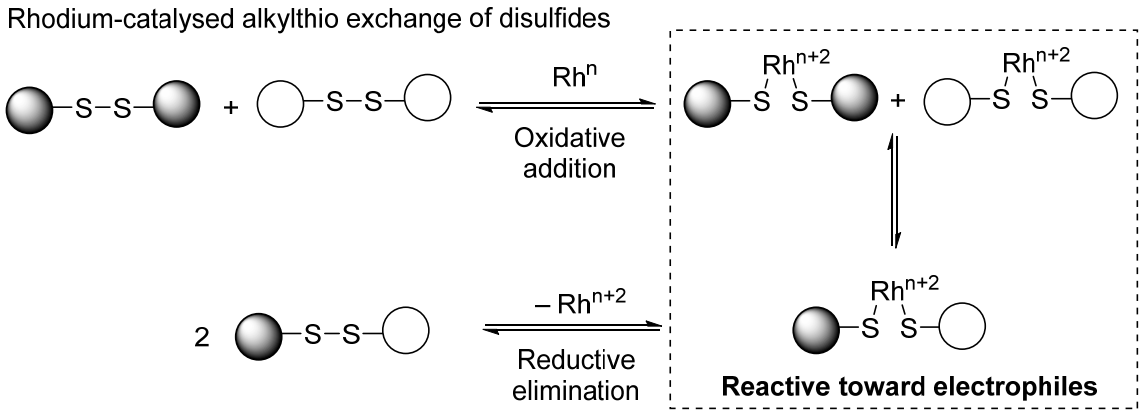
In the course of their studies on the antimicrobial activity of phosphonoselenides and phosphorothioates, Mitra and co-workers developed a zinc-mediated reductive coupling which was subsequently exploited to produce phosphorothioates **35** and **36** in 68% and 65% yields respectively (Scheme 21).[49] The authors suggest that the zinc acts *via* reduction of the disulfide bond, generating zinc(II) species **34**, which then couples with the phosphite, installing the phosphorus-sulfur bond.



Scheme 21

4.2 P–S bond formation using rhodium-catalysed alkylthio exchange with RSSR

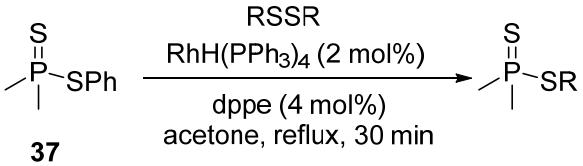
Arisawa and Yamaguchi have extensively investigated the reactivity of disulfides in the presence of rhodium catalysts.[50] They discovered that rhodium-catalysed oxidative addition across a disulfide bond may be harnessed to effect alkylthio exchange reactions with a variety of electrophiles (Scheme 22).



Scheme 22

An early application of this approach was illustrated in their synthesis of a library of dimethylthiophosphinates (Table 14).[51] A rhodium(I) catalyst (2 mol%), along with 1,2-bis(diphenylphosphino)ethane (dppe) (4 mol%) as a ligand, was employed to oxidatively cleave the starting disulfides. The resulting rhodium thiolate displaced the thiophenol group from thiophosphinothioate **37** furnishing the desired products. Both aryl (Table 14, Entries 1-2) and alkyl thiophosphinothioates (Table 14, Entry 3-6) were successfully prepared in good yields.

Table 14. Rhodium-catalysed alkylthio-exchange reactions of 37 with disulfides



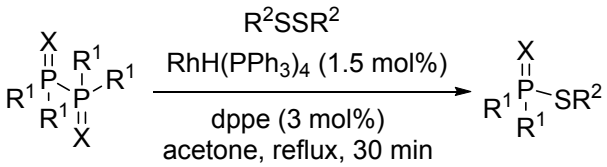
37

Entry	R	Yield
1	4-ClC_6H_4	68%
2	4-MeC_6H_4	69%
3	*n*-Octyl	71%

4	*t*-BuOCONH$_2$(CH$_2$)$_2$	81%
5	MeO$_2$C(CH$_2$)$_3$	70%
6	MeO(CH$_2$)$_4$	74%

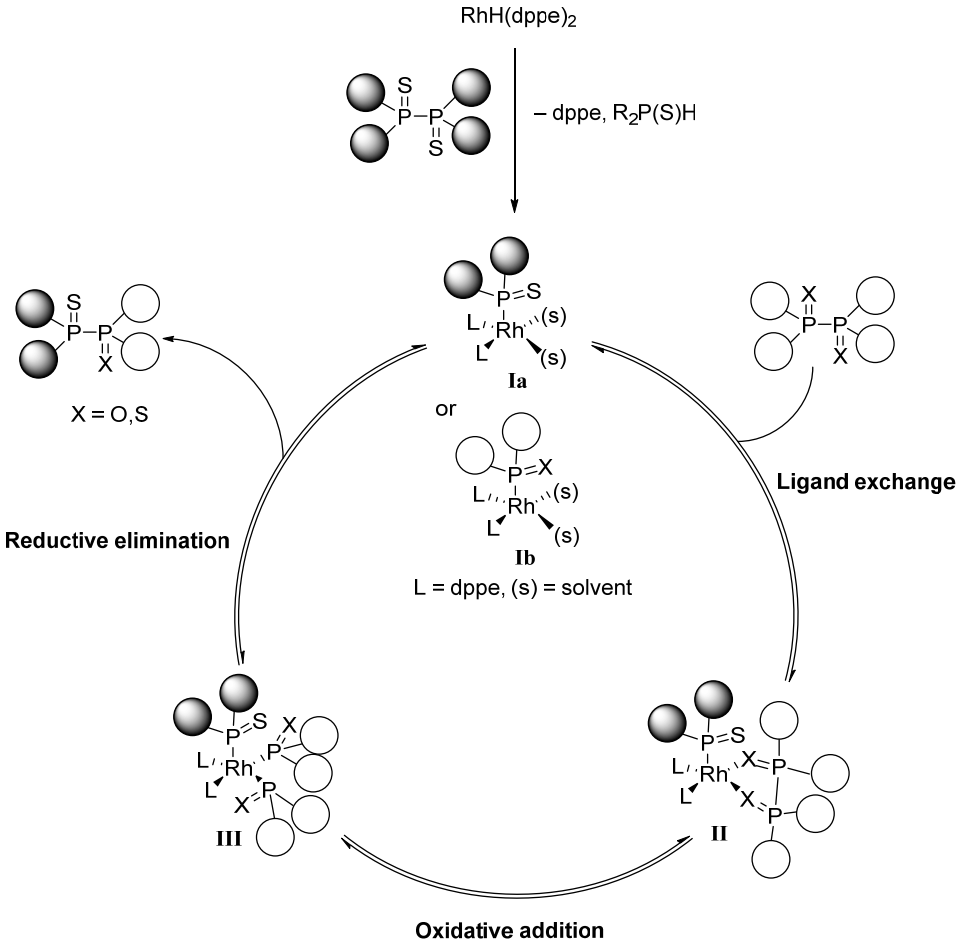
The authors also demonstrated how the phosphorus-phosphorus bonds in tetraalkyl phosphane dioxides and disulfides may be cleaved to undergo rhodium-catalysed metathesis with disulfides (Table 15).[51] This transformation worked well for a broad range of substrates, affording the corresponding thiophosphinothioates (Table 15, Entries 1-9) or phosphinothioates (Table 15, Entries 10-15) in good to excellent yields. A notable exception was the 4-chlorophenyl derivative (Table 15, Entry 3) which was recovered in a low yield of 8%. The yield of this particular product could be increased to 50% by doubling the loading of both the catalyst and ligand, in addition to extending the reaction time from thirty minutes to two hours. However, the corresponding reaction with thiophosphinothioate **37** was significantly higher yielding (Table 14, Entry 1).

Table 15. Rhodium-catalysed P–S bond metathesis



Entry	X	R^1	R^2	Yield	Entry	X	R^1	R^2	Yield
1	S	Me	Ph	91%	**9**	S	*n*-Pr	$BocNH(CH_2)_2$	100%
2	S	Me	4-MeC_6H_4	86%	**10**	O	Ph	Ph	97%
3	S	Me	4-ClC_6H_4	8%	**11**	O	Ph	4-MeC_6H_4	90%
4	S	Me	*n*-Octyl	97%	**12**	O	Ph	*n*-Octyl	83%
5	S	Me	$BocNH(CH_2)_2$	98%	**13**	O	Ph	*t*-$BuOCONH_2(CH_2)_2$	97%
6	S	Me	$MeO_2C(CH_2)_3$	100%	**14**	O	Ph	$MeO_2C(CH_2)_3$	91%
7	S	Me	$MeO(CH_2)_4$	99%	**15**	O	Ph	$PhCO_2(CH_2)_3$	95%
8	S	Et	$BocNH(CH_2)_2$	98%					

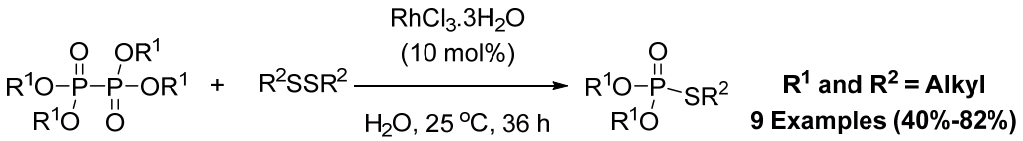
Arisawa and colleagues later reported a rhodium(I)-catalysed phosphorus-phosphorus bond metathesis.[52] Over the course of this study, the authors identified a possible mechanism which may offer some insights into the chemistry of phosphorus-sulfur bond formation (Scheme 23). Initially, the Rh(I) pre-catalyst reacts with the starting phosphane disulfide to generate the active catalyst **Ia**. Ligand exchange with the other phosphane metathesis partner forms intermediate **II**, which then undergoes oxidative addition to produce **III**. Reductive elimination from **III** furnishes the metathesis product and regenerates **Ia**. As each step of the mechanism is reversible, **Ib** may also act as catalytic species.



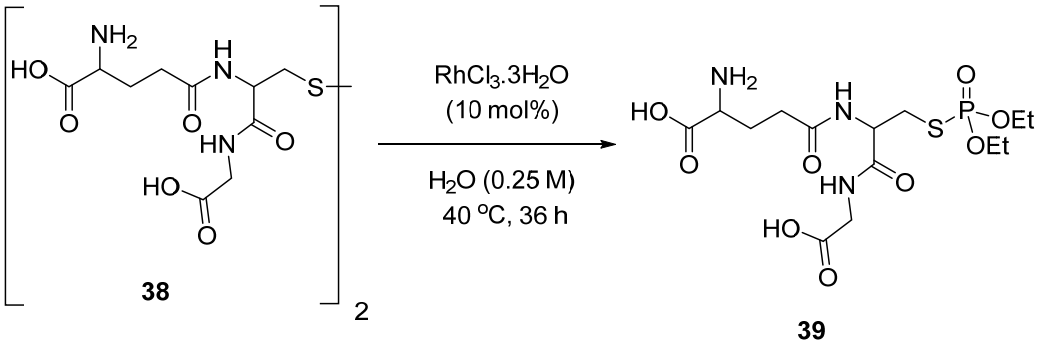
Scheme 23

The scope of above Rh(I)-catalysed process has been largely limited to phosphinothioate analogues. More recently, Arisawa and co-workers extended the substrate scope of this transformation to encompass phosphorothioates (Scheme 24 [A]).[53] Rhodium(III) chloride was used in place of *tetrakis*(triphenylphosphine)rhodium hydride as the pre-catalyst and the reaction could be conducted in water under relatively mild conditions. This procedure was developed in an effort to phosphorylate the biomolecule, glutathione (**38**) (Scheme 24 [B]). Glutathione (**38**) had previously proven to be a challenging substrate due to its limited solubility in most organic solvents. Gratifyingly, glutathione was successfully converted to phosphorothioate **39** in 77% yield using a relatively dilute aqueous reaction solution (0.25 M). A Rh(III) to Rh(I) catalytic cycle has been posited as a possible mechanism (Scheme 24 [C]). Initially, rhodium chloride inserts across the phosphorus-phosphorus bond affording Rh(I) intermediate **I**. Oxidative addition of intermediate **I** to another molecule of phosphane dioxide generates Rh(III) intermediate **II** as per Scheme 23. Ligand metathesis with the disulfide furnishes the phosphorothioate product and intermediate **III**, which can reductively eliminate to afford an additional phosphorothioate molecule and regenerate the active catalyst.

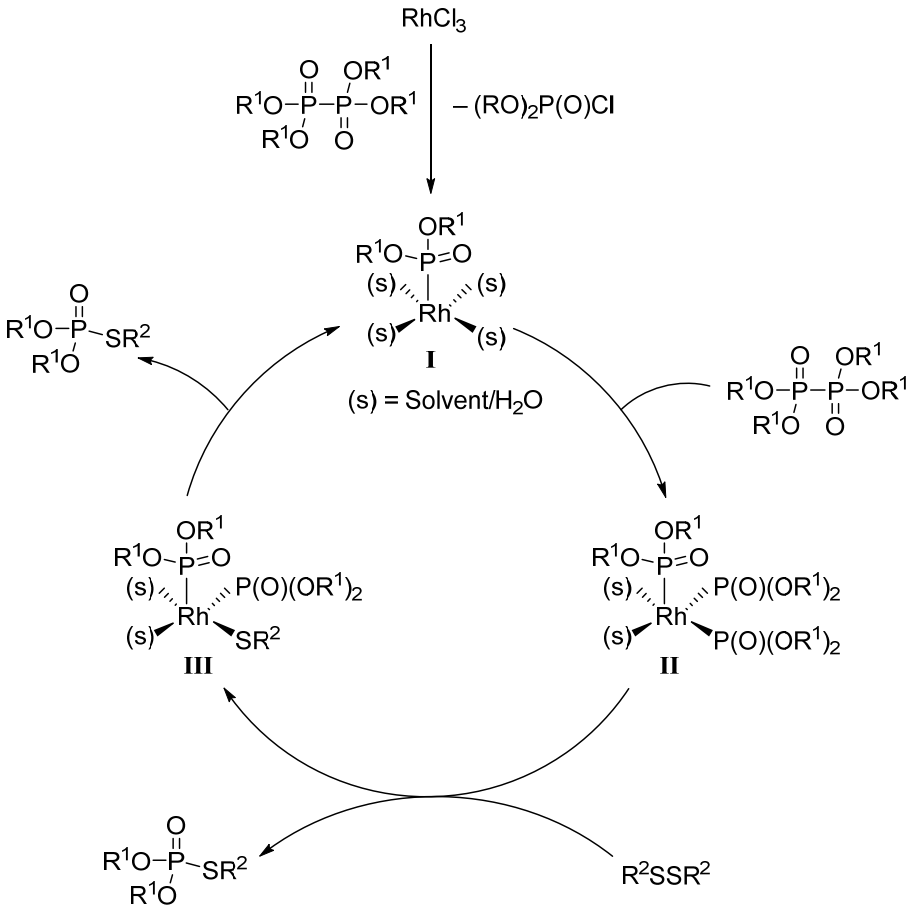
[A]



[B]



[C]

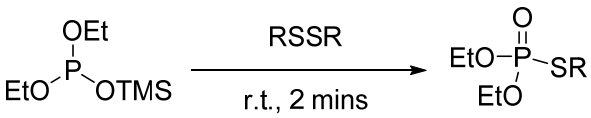


Scheme 24

4.3 Reaction of RSSR with R_3P

A recent report by Zhan *et al*. outlines a solvent- and catalyst-free approach for preparing phosphorothioates.[54] Treatment of commercially available trimethylsilyl diethyl phosphite (**40**) with a range of disulfides in the absence of solvent afforded the corresponding phosphorothioates in excellent yields almost instantaneously (Table 16). Most substitution patterns on the aromatic ring were well tolerated (Table 16, Entries 1-9). Benzyl mercaptan (Table 16, Entry 10), 2-mercaptonapthylene (Table 16, Entry 11) and *N*-methyl 4-mercaptophenylsulfonamide (Table 16, Entry 12) all required slightly longer reaction times. Heteroaromatic disulfides also proved amenable to this transformation (Table 16, Entry 14-16). The use of other silyl groups, such as triethylsilyl or triisopropylsilyl, was observed to have a negligible impact on reaction performance.

Table 16. Preparation of phosphorothioates from silyl phosphites

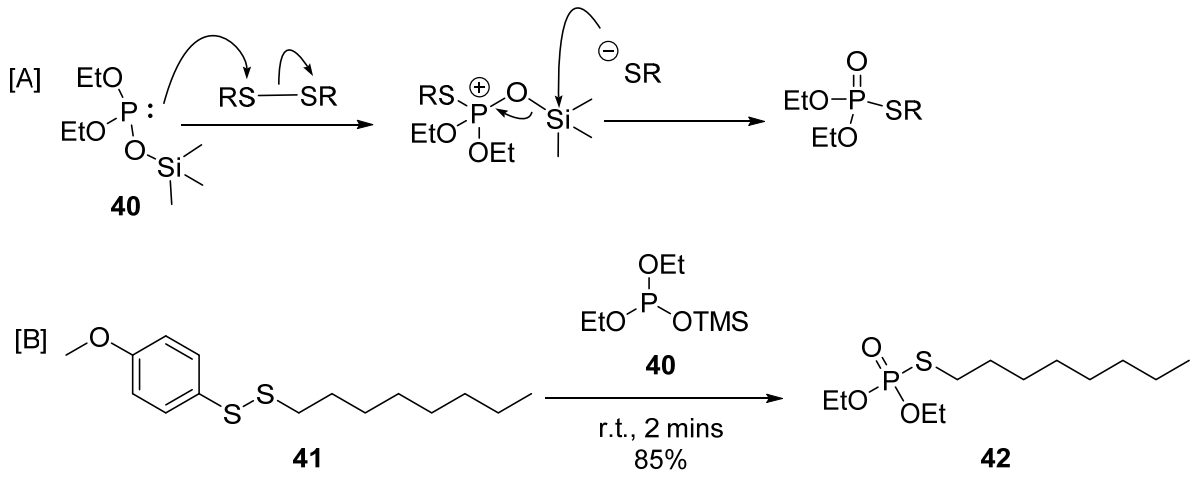


40

Entry	R	Yield	Entry	R	Yield
1	Ph	80%	**9**	4-$AcOC_6H_4$	93%
2	4-MeC_6H_4	85%	**10**	Bn	45% [a]
3	4-(AllylO)C_6H_4	94%	**11**	2-Naphyl	35% [a]
4	4-$MeOC_6H_4$	93%	**12**	4-($MeSO_2NH$)C_6H_4	65% [b]
5	4-ClC_6H_4	95%	**13**	4-(TFANH)C_6H_4	94%
6	4-HOC_6H_4	75%	**14**	2-Pyridyl	51%
7	4-$NH_2C_6H_4$	89%	**15**	2-Benzamidazolyl	83%
8	4-AcC_6H_4	84%	**16**	2-Thiophenyl	92%

[a] 10 mins [b] 5 mins

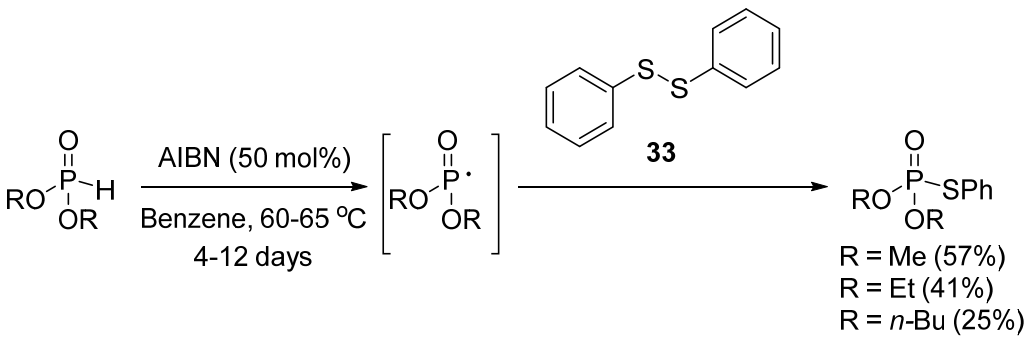
The proposed mechanism strongly resembles that of the Michaelis-Arbuzov rearrangement (Scheme 25 [A]). Initial attack of phosphite **40** on the disulfide forms a tetravalent phosphonium species along with a thiolate anion. Desilylation of the phosphonium intermediate by the thiolate affords the target molecule. Interestingly, when unsymmetrically substituted disulfide **41** was subjected to these same conditions, there was a clear preference for the formation of *S*-alkylated adduct **42** rather than the corresponding *S*-arylated product (Scheme 25 [B]).



Scheme 25

4.4 Reaction of RSSR with *P*-centred radicals

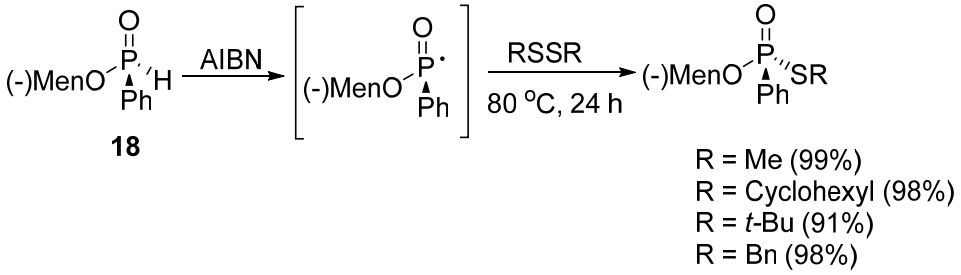
The generation of *P*-centred radicals *via* the homolytic cleavage of Lewis-acidic P-H bonds has been widely exploited as a route to highly functionalised organophosphorus compounds.[55] Xu and co-workers found that *P*-centred radicals, generated *in situ* from dialkyl phosphites and azobisisobutyronitrile (AIBN), reacted with diphenyl disulfide **33** to form a series of phosphorothioates in poor to moderate yields (Scheme 26).[56] The low yields from this reaction were ascribed to the stability of the disulfide bond which was slow to undergo homolytic fission under these conditions. Consequently, reaction times of up to 12 days were required.



Scheme 26

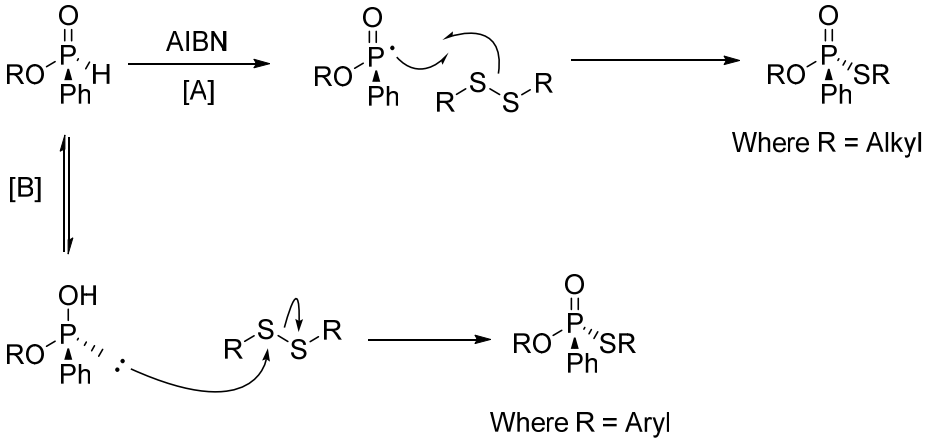
Wu also discovered that treating phosphinate **18** with AIBN led to the formation of a *P*-centred radical which subsequently combined with various disulfides to furnish several phosphinothioates in 91%-99% yields (Scheme 27).[57] The reaction of dialkyl disulfides failed in the absence of AIBN, confirming that a radical mechanism is at play. The stereochemical configuration of the starting

material was retained in the products, indicating that the homolytic fission of the P–H bond proceeds with retention of stereochemistry.



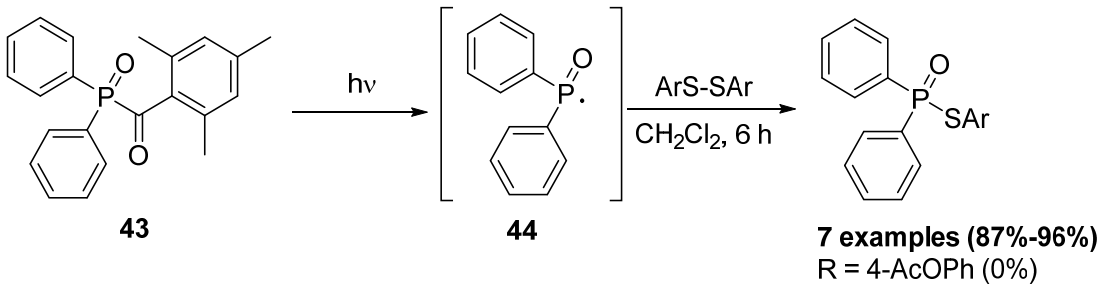
Scheme 27

Diaryl disulfides were observed to react with **18** to form *S*-aryl phosphonothioates in the absence of AIBN. The reaction likely proceeds *via* nucleophilic attack of **18** on the disulfide (Scheme 28 – Pathway [B]). Dialkyl disulfides are more electron-rich than diaryl disulfides and, consequently, are weaker electrophiles, making them more amenable to a radical-based transformation (Scheme 28 – Pathway [A]).



Scheme 28

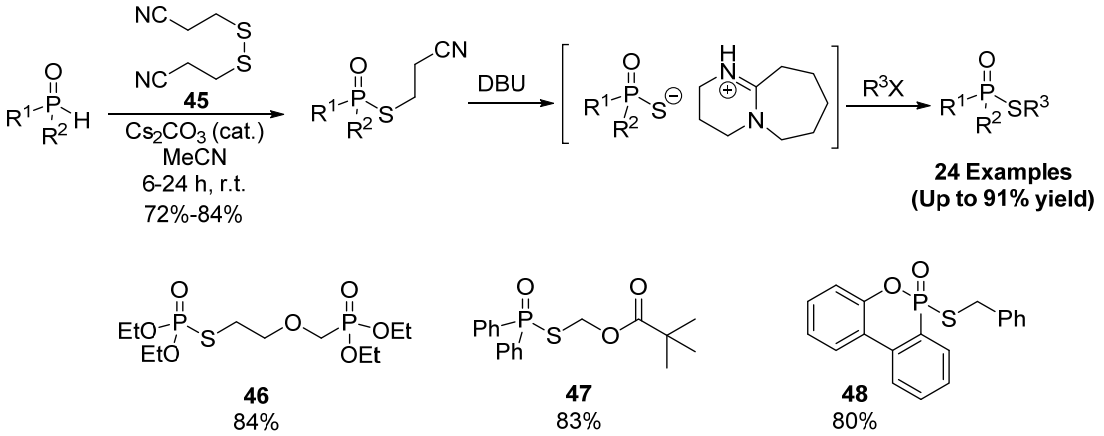
Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (TMDPO) (**43**) is a radical initiator widely used in macromolecular chemistry for various applications (e.g. surface processing) (Scheme 29).[58] Sato demonstrated that TDMPO is an attractive source of *P*-centred radicals as it is air stable and does not require special handling.[59] Upon photo-irradiation with a xenon lamp, homolytic cleavage of the P–C bond generated phosphinyl radical **44**. This radical intermediate combined with various aryl and alkyl disulfides to afford the corresponding diphenyl phosphinothioates in 87%-96% yields.



Scheme 29

4.5 Thiolate formation through E1cB elimination of acrylonitrile

Utilising 3,3'-dithiobispropionitrile (**45**), *S*-(2-cyanoethyl)-substituted phosphinothioates, phosphorothioates and phosphonothioates can be prepared from the corresponding P(O)–H substrates by exploiting the caesium effect (Scheme 30).[60] The resulting products are noteworthy as subsequent addition of DBU quantitatively affords the thioate intermediates as their DBU salts, which may be alkylated *in situ* to produce the target phosphinothioates, phosphorothioates and phosphonothioates in a one-pot fashion. We have employed this methodology to synthesise phosphorothioate **46**, thus confirming its applicability to the preparation of drug-like molecules for which the corresponding thiol is unknown.[61] Similarly, the pivaloxymethyl (POM) prodrug group may be introduced using iodomethyl pivalate as the alkylating agent [62] with the resulting *S*-(pivaloxymethyl) esters (e.g. phosphinothioate **47**) recovered in excellent yields. In certain cases (e.g. phosphonothioate **48**), this methodology affords significantly higher yields than other similar approaches (*cf.* Scheme 52).



Scheme 30

Harnessing the chemistry of the *S*-(2-cyanoethyl) group constitutes a useful method for preparing symmetrically and unsymmetrically substituted *S,S*-dialkyl phosphonodithioates (Scheme 31).[15] Thus, treatment of phosphonodithioate **49** with DBU furnished monodeprotected intermediate **50**.

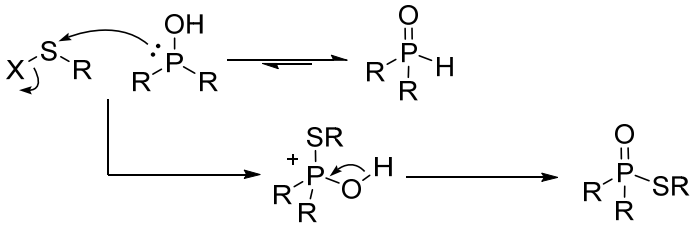
Subsequent alkylation of **50** facilitated the removal of the second cyanoethyl group and formation of DBU salt **52**. This DBU salt, **52**, served as a common intermediate from which either symmetrical *S,S*-dialkyl phosphonodithioate **54** or unsymmetrical phosphonodithioate **55** could be synthesised as required. Alternatively, direct conversion of **49** to symmetrical phosphonodithioate **54** proved possible using an excess of methyl iodide.

S

Scheme 31

5. P–S bond formation from RS–X

Although disulfides have been proven to be highly reliable electrophilic sulfur transfer reagents for P–S bond formation, sulfides bearing a nucleofuge such as a halogen or an imide group may be employed in a similar manner (Scheme 32).

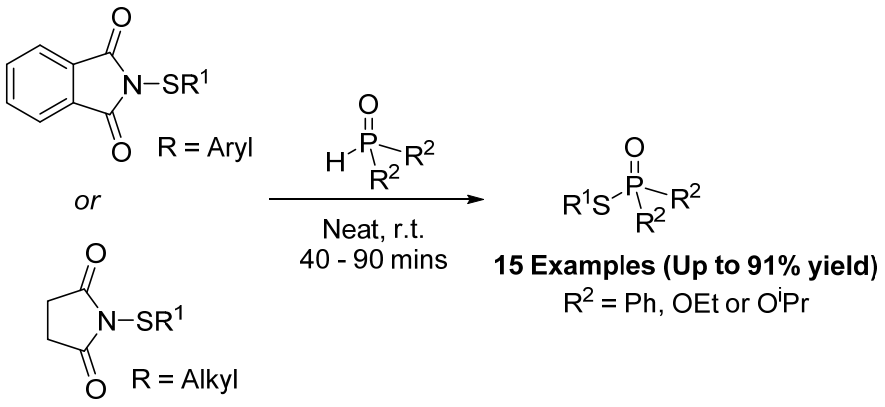


X = Cl, phthalimide, succinimide, CN

Scheme 32

5.1 P–S bond formation from *N*-thioimide precursors

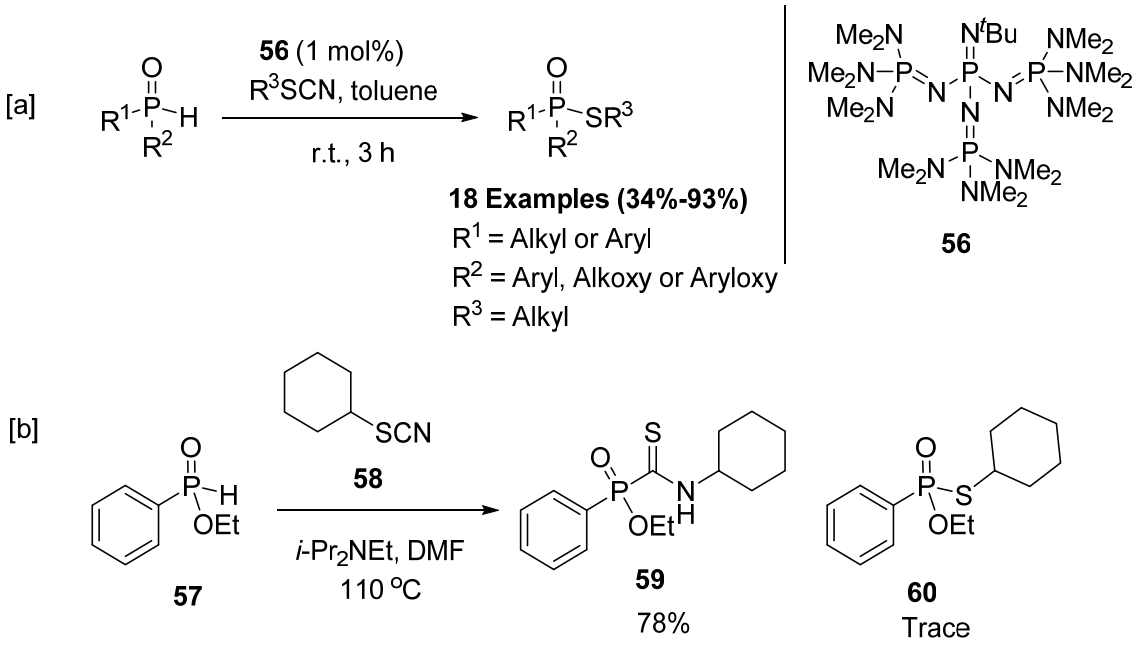
A recent study by Mondal and Saha explored the electrophilic sulfuration of dialkyl phosphites and phosphine oxides in solvent-free conditions employing *N*-thioimides as a sulfur source (Scheme 33).[63] This protocol provided access to both *S*-alkyl and *S*-aryl products, from the corresponding succinimide or phthalimide precursor respectively, in good yields. The reaction performed best when conducted neat. By contrast, the addition of polar or non-polar solvents resulted in extensive by-product formation and depressed yields.



Scheme 33

5.2 P–S bond formation from alkyl thiocyanates

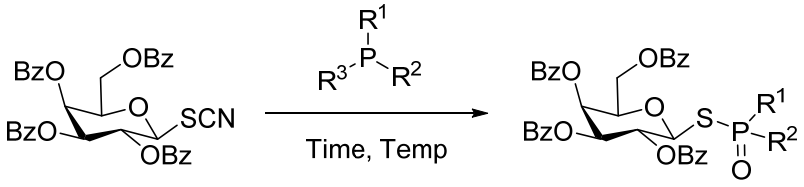
Alkyl thiocyanates are important synthetic intermediates for the preparation of sulfur-containing organic compounds.[64] In the course of their research on VX nerve agents, Renard *et al*. discovered that the presence of sterically hindered phosphazene **56** (1 mol%), or DBU (5 mol%), catalyses the conversion of thiocyanates to the corresponding phosphonothioates (Scheme 34 [a]).[65] The authors suggest that the mechanism resembles a modified Pudovik reaction.[66] During their optimisation studies, the authors observed that the reaction of **57** with cyclohexyl thiocyanate (**58**) at higher temperatures produced adduct **59** instead of expected phosphonothioate **60** (Scheme 34 [b]). Side-product **59** forms when nucleophilic attack of the starting phosphinate occurs at the thiocyanate carbon, as opposed to the sulfur atom, which is favoured at elevated temperatures.



Scheme 34

Piekutowska and Pakulski have successfully prepared a range of *S*-glycosyl phosphonothioates, phosphorothioates and phosphinothioates by modifying the Michaelis-Arbuzov rearrangement.[67] Treatment of glycosyl thiocyanate **61** with various phosphites and phosphonites afforded *S*-glycosylated products **62a-e** in 20%-85% yield (Table 17). In general, when *O*-trimethylsilylated substrates were used in place of *O*-alkyl derivatives, higher yields resulted (e.g. Table 17 Entries 1 and 3, Entries 6, 7, 10 and 11). This presumably reflects their greater reactivity in the Michaelis-Arbuzov rearrangement due to the more labile nature of the oxygen-silicon bond. This study was expanded to encompass other epimers of **61** which returned broadly similar results.

Table 17. Michaelis-Arbuzov rearrangement of glycosyl thiocyanate 65

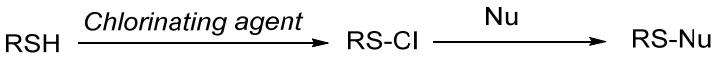


61 **62a-e**

Entry	R^1	R^2	R^3	Product	Temp	Time (h)	Yield
1	OEt	OEt	OEt	**62a**	80 °C	2	30%
2	OEt	OEt	OTMS	**62a**	r.t.	24	68%
3	OEt	OEt	OTMS	**62a**	60 °C	2	77%
4	OBu	OBu	OBu	**62b**	80 °C	8	30%
5	Ph	OMe	OMe	**62c**	40 °C	1	53%
6	Ph	OEt	OTMS	**62d**	r.t.	18	85%
7	Ph	OEt	OTMS	**62d**	40 °C	1	83%
8	Ph	Ph	OMe	**62e**	r.t.	24	20%
9	Ph	Ph	OMe	**62e**	40 °C	0.5	25%
10	Ph	Ph	OTMS	**62e**	r.t.	18	74%
11	Ph	Ph	OTMS	**62e**	40 °C	1	71%

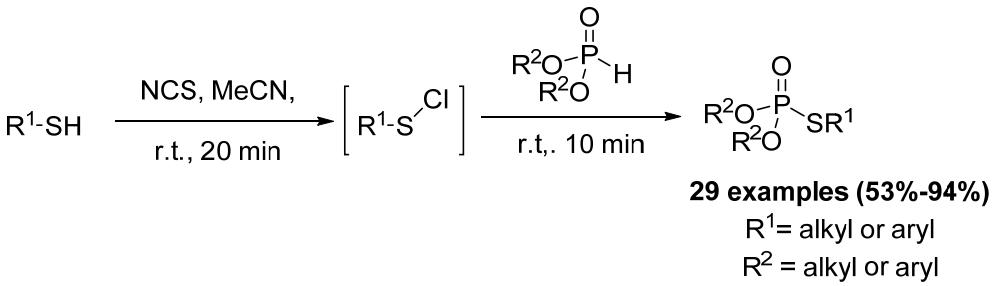
5.3 P–S bond formation from sulfenyl halides

The chlorination of thiols to the corresponding sulfenyl chlorides is an important transformation in mainstream organosulfur chemistry (Scheme 35).[68] Sulfenyl chlorides are typically prepared *in situ*, prior to treatment with a nucleophile, owing to their instability toward hydrolysis.



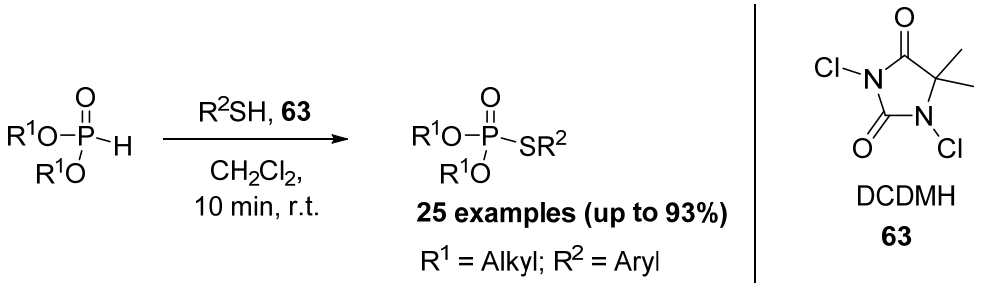
Scheme 35

The *N*-chlorosuccinimide-mediated synthesis of phosphorothioates from thiols and phosphonates under mild conditions was first reported by Liu and Lee.[69] *In situ* conversion of a range of alkyl and aryl thiols to the corresponding sulfenyl chlorides, followed by condensation with various dialkyl phosphites, furnished the target products in good to excellent yields (Scheme 36). This methodology was reasonably general with good substrate scope although yields tended to suffer when aryl thiols with bulky *ortho* substituents or electron-withdrawing substituents were employed. *N*-Iodosuccinimide and *N*-bromosuccinimide were also investigated but were found to be significantly less effective.



Scheme 36

A similar approach, using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) (**63**) as the chlorinating agent, was described by Bi and co-workers. (Scheme 37).[70] This transformation was quite rapid, reaching completion within 10 minutes. A variety of substituents on the phosphorus and sulfur atoms were well tolerated, and both alkyl and aryl thiols were compatible with these conditions. Thiols bearing a carboxylic acid as part of their side-chain did not react. The authors suggest that the limited solubility of these substrates hinders their transformation.

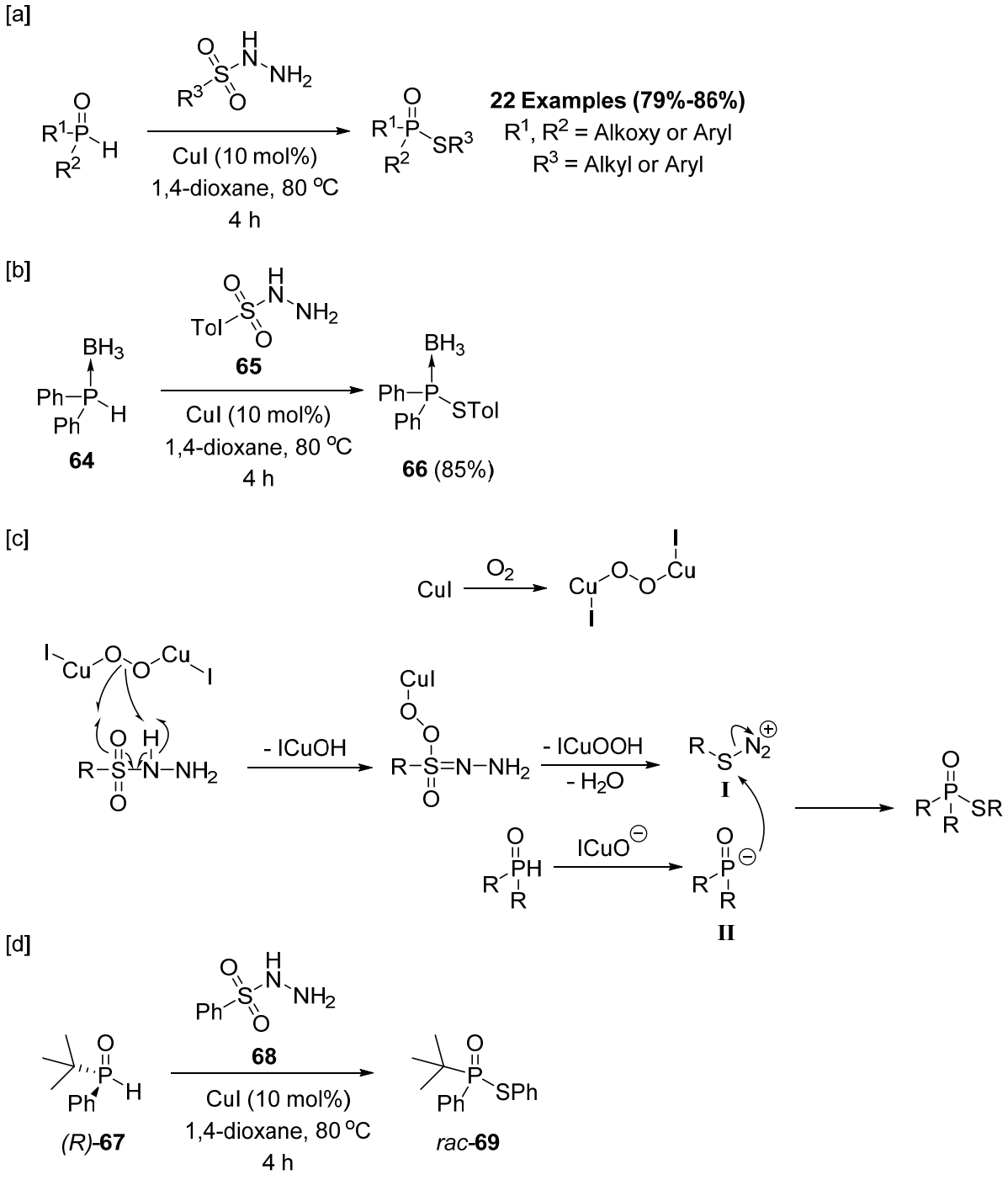


Scheme 37

6. P–S bond formation from $RS(O)_nX$

6.1 From sulfonyl hydrazides

Kumaraswamy and Raju have explored the copper-catalysed construction of phosphorus-sulfur bonds using sulfonylhydrazides as the sulfur source (Scheme 38 [a]).[71] *S*-Alkyl thioates were prepared in high yields *via* this approach in contrast to similar copper-catalysed methods reported by Xu and Zhang (*vide infra* Scheme 47, Scheme 50). In the case of aryl thiols, the coupling reaction tolerates electron-rich or electron-poor substrates equally well. The reaction appears to be insensitive to increased steric hindrance resulting from *ortho*-substitution on the aryl substituent. Interestingly, boranophosphonothioate **66** was also synthesised using this methodology by coupling boranophosphite **64** with tosylhydrazine (**65**) (Scheme 38 [b]). Boranophosphates and related compounds are often utilised in oligonucleotide chemistry and are otherwise difficult to access owing to their reactivity towards electrophiles.[72] The proposed mechanism involves initial oxidation of copper(I) iodide to the corresponding copper(II) peroxide which subsequently oxidises the sulfonylhydrazide to diazonium sulfide intermediate **I** (Scheme 38 [c]). Deprotonation of the organophosphorus starting material, followed by nucleophilic attack on the diazonium sulfide, affords the coupled product. A copper-free variant was later reported by Cheng and co-workers substituting catalytic tetrabutylammonium iodide for copper iodide to generate diazonium sulfide intermediate **I**. [73] The formation of planar anionic intermediate **II** may also account for the racemisation observed on conversion of *(R)*-**67** to *(rac)*-**69** (Scheme 38 [d]).

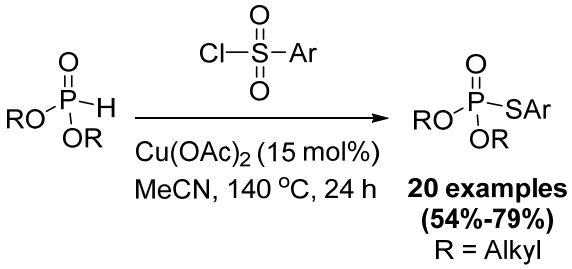


Scheme 38

6.2 From sulfonyl chlorides

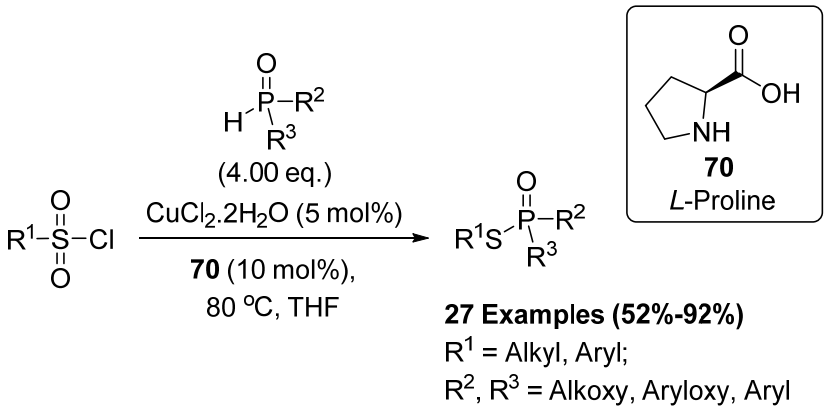
Bai *et al.* explored the copper-catalysed reductive coupling of aryl sulfonyl chlorides to dialkyl phosphonates to prepare *S*-aryl phosphorothioates (Scheme 39).[74] Screening of copper(I)/(II) additives revealed that copper(II) acetate was an efficient catalyst whereas the reaction does not proceed in the absence of a catalyst. Interestingly, no product was formed when palladium(II) acetate was tested. The reaction is relatively insensitive to electronic effects as high yields were

recorded when either electron-rich or electron-poor substituents were introduced. Lower yields were observed with sterically hindered *ortho*-substituted sulfonyl chlorides.



Scheme 39

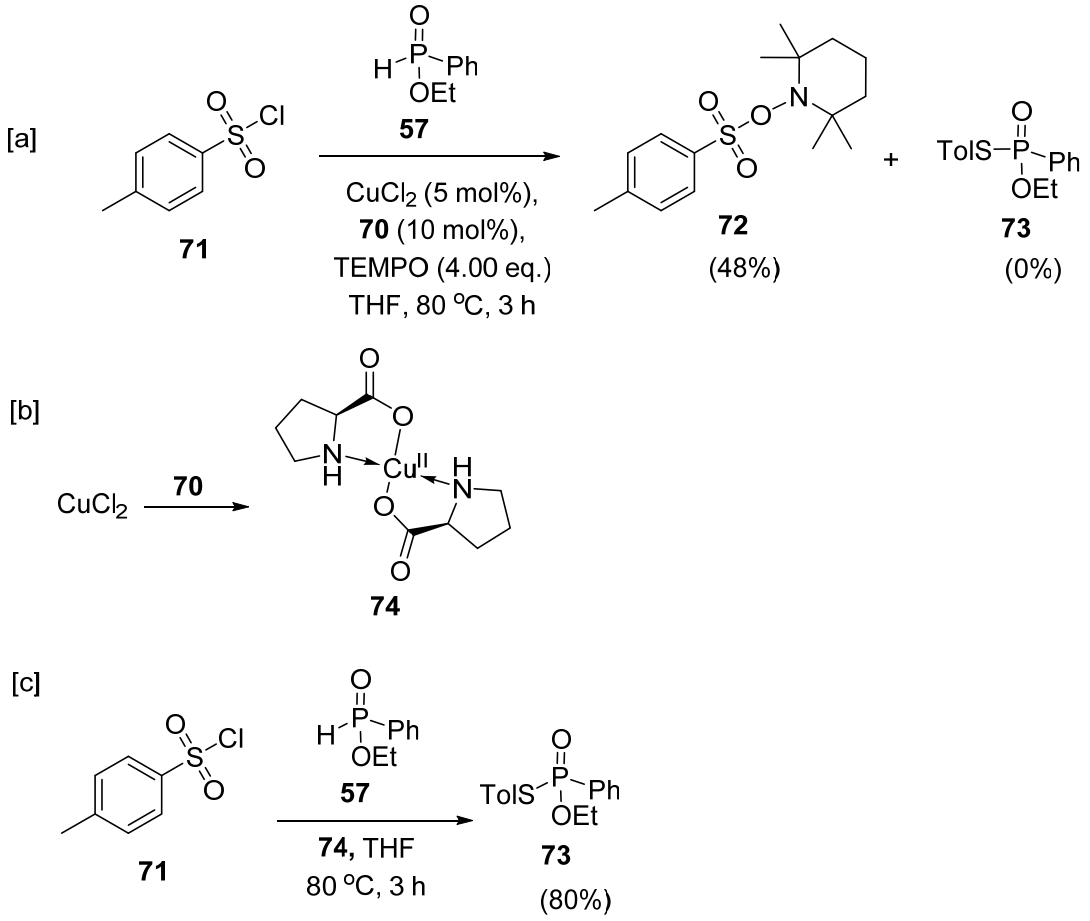
A common feature of many copper-catalysed phosphorus-sulfur bond forming reactions is the high loading of the copper catalyst typically required. The use of readily available *L*-proline (**70**) as a ligand enabled Zhang and co-workers to employ a modest 5 mol% loading of copper(II) chloride in the reductive coupling of a range of sulfonyl chlorides to form phosphorothioates and phosphonothioates (Scheme 40).[75] They discovered that four equivalents of the phosphorus-containing starting material were required to ensure complete consumption of the sulfonyl chloride. Both alkyl and aryl thioates may be prepared using this approach. The catalyst system showed no significant decline in activity after ten uses.



Scheme 40

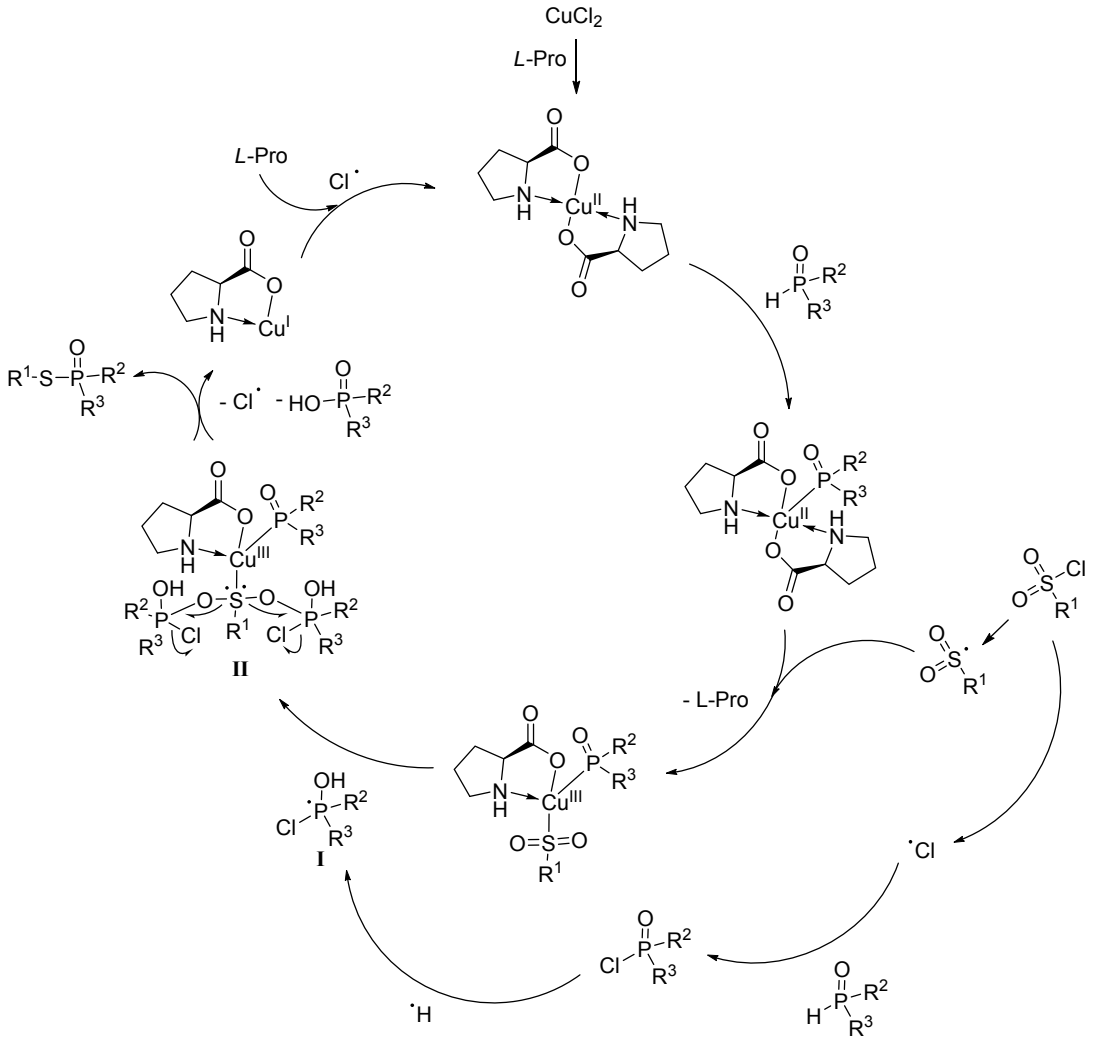
Several experiments were performed in order to elucidate the exact role of *L*-proline (**70**) in the reaction (Scheme 41). When the reaction was repeated in the presence of TEMPO, no product formed, indicating that a radical process was likely at play. The isolation of tosylated TEMPO adduct **72** suggested that a sulfonyl radical was generated during the reaction (Scheme 41 [a]). The authors also discovered that treating copper(II) chloride with *L*-proline at elevated temperatures led to the formation of prolinate/Cu complex **74** (Scheme 41 [b]). Prolinate **74** was subsequently found to

catalyse the reductive coupling of tosyl chloride (**71**) with phosphinate **73**, confirming it to be the active catalytic species (Scheme 41 [c]).



Scheme 41

Based on these observations, the authors proposed the mechanism outlined in Scheme 42. The participation of two equivalents of radical intermediate **I** in the reductive elimination step *via* intemediate **II** possibly explains the requirement for a four equivalents excess of the phosphorus-containing starting material in this reaction.

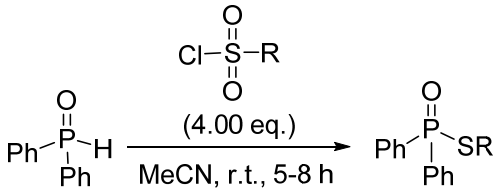


Scheme 42

Copper-catalysed reductive coupling of aryl sulfonyl chlorides was discussed previously in the context of metal-catalysed phosphorus-sulfur bond formation.[74-75] Parallel work by He[76] and Wang[77] demonstrated that a similar reductive coupling could be performed under mild conditions in the absence of a catalyst.

The initial report by He described how treating four equivalents of diphenyl phosphine (**6**) with a series of aryl (Table 18, Entries 1-12) and alkyl (Table 18, Entries 13 and 14) sulfonyl chlorides furnished the corresponding phosphinothioates in 47%-94% yields. Alkyl-containing substrates generally afforded lower yields than aryl substrates. The best performing substrate was the 4-methylphenyl derivative which was isolated in 94% yield (Table 18, Entry 12). Strongly electron-withdrawing groups, such as 4-nitrophenyl or 4-cyanophenyl (Table 18, Entries 2-4), impacted negatively on yields while 4-halophenyl derivatives were isolated in up to 84% yields (Table 18, Entries 6-10).

Table 18. Reactions of diphenyl phosphine oxide with sulfonyl chlorides in MeCN

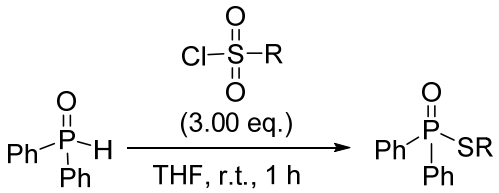


6

Entry	R	Yield	Entry	R	Yield
1	Ph	88%	**8**	4-BrC_6H_4	84%
2	4-$NO_2C_6H_4$	62%	**9**	3-BrC_6H_4	82%
3	2-Me-5-$NO_2C_6H_3$	50%	**10**	2-BrC_6H_4	75%
4	4-CNC_6H_4	60%	**11**	4-$MeOC_6H_4$	68%
5	4-$NHAcC_6H_4$	70%	**12**	4-MeC_6H_4	94%
6	4-FC_6H_4	83%	**13**	CH_2Ph	70%
7	4-ClC_6H_4	84%	**14**	*n*-Bu	47%

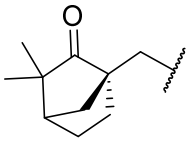
The yields reported by Wang (Table 19) for this transformation were broadly comparable those described by He (Table 18). However, Wang's methodology requires only three equivalents of the phosphine starting material and a shorter reaction time of one hour. Of particular note, phosphinothioates from alkyl sulfonyl chlorides were isolated in moderate to excellent yields (Table 19, Entries 10-14).

Table 19. Reactions of diphenyl phosphine oxide (6) with sulfonyl chlorides in THF



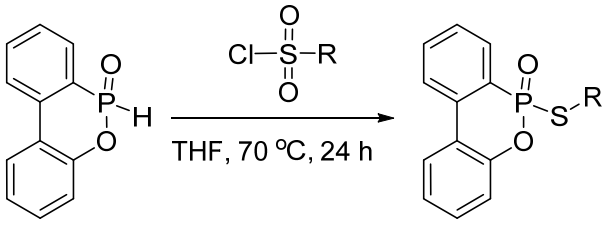
6

Entry	R	Yield	Entry	R	Yield
1	Ph	81%	**8**	3-BrC_6H_4	71%
2	4-MeC_6H_4	92%	**9**	4-*t*-BuC_6H_4	90%
3	4-$MeOC_6H_4$	83%	**10**	Me	82%
4	4-$CF_3C_6H_4$	66%	**11**	*n*-Bu	68%

5	4-$AcNHC_6H_4$	87%	**12**	Cyclopropyl	88%
6	4-ClC_6H_4	74%	**13**	2-Chloroethyl	82%
7	4-BrC_6H_4	84%	**14**		78%

In a similar vein, Wang *et al*. investigated the reaction of phosphinane **74** with various sulfonyl chlorides (Table 20).[77] Heterocycle **74** was slow to react with sulfonyl chlorides at room temperature. However, the authors found that elevating the temperature and prolonging the reaction time successfully furnished the products in 32%-77% yield. Electron-rich sulfonyl chlorides (Table 20, Entries 1-4) reacted more readily than those containing an electron-withdrawing group (Table 20, Entries 6-8). A butyl-containing analogue (Table 20, Entry 10) was also prepared using this procedure, although it was isolated in a modest 32% yield.

Table 20. Synthesis of phosphonothioates from sulfonyl chlorides

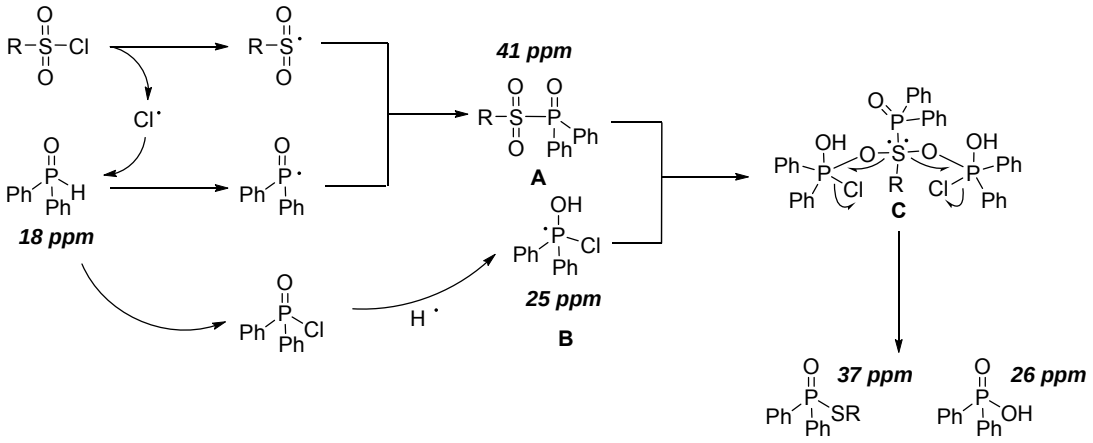


74

Entry	R	Yield	Entry	R	Yield
1	Ph	77%	**6**	4-ClC_6H_4	63%
2	4-MeC_6H_4	73%	**7**	4-BrC_6H_4	57%
3	4-$MeOC_6H_4$	77%	**8**	3-BrC_6H_4	65%
4	4-*t*-BuC_6H_4	68%	**9**	2-Napthyl	75%
5	4-$AcNHC_6H_4$	70%	**10**	*n*-Bu	32%

The reaction likely proceeds *via* a radical mechanism as no product formed on addition of TEMPO. Analysis of the ^{31}P NMR spectrum of the crude reaction mixture revealed that diphenyl phosphinic acid was consistently present as a by-product (Scheme 43). The suggested mechanism is consistent with that subsequently proposed by Zhang[75] for the related copper-assisted process above. Homolytic cleavage of the sulfur-chlorine bond in the sulfonyl chloride produces sulfonyl and chloride radicals. The chloride radical abstracts hydrogen from the phosphine, creating a *P*-centred

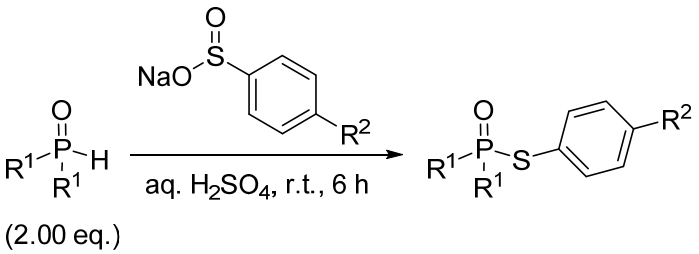
radical, which then combines with the sulfonyl radical, resulting in intermediate **A**. Intermediate **B** simultaneously forms through a parallel radical transfer process. Reductive elimination of the oxygen atoms from **A**, enabled by intermediate **B**, forms the product and accounts for the formation of diphenyl phosphinic acid **9**. This also explains why three equivalents of the phosphine starting material are required.



Scheme 43

Lin *et al.* have described the acid-mediated reductive coupling of sodium sulfinate salts with dialkyl phosphine oxides and dialkyl phosphonites. (Table 21).[78] The reaction proceeds under mild conditions but requires two equivalents of the phosphorus-containing starting material to reach completion. The yields obtained for phosphine oxides (Table 21, Entries 1-8) were considerably higher than those obtained for phosphites (Table 21, Entries 9-10). Phosphites gave higher yields when the reaction was conducted in DMF at 100 ^{o}C. The authors tentatively proposed that the reaction likely proceeds *via* a radical mechanism involving the reduction of the sulfinate salt by the organophosphorus starting material based on radical trapping experiments with TEMPO.

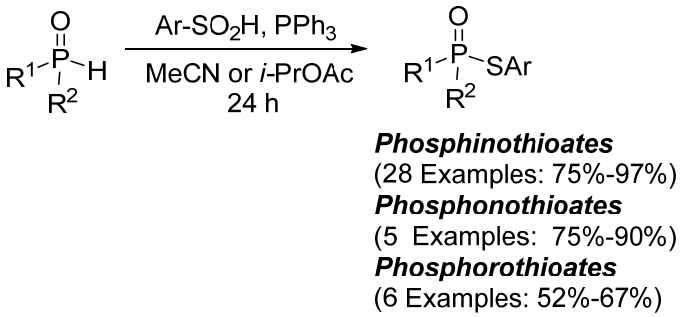
Table 21. P(V)-S bond formation from sodium arylsulfinates



Entry	R^1	R^2	Yield
1	Ph	Me	78%
2	Ph	MeO	62%

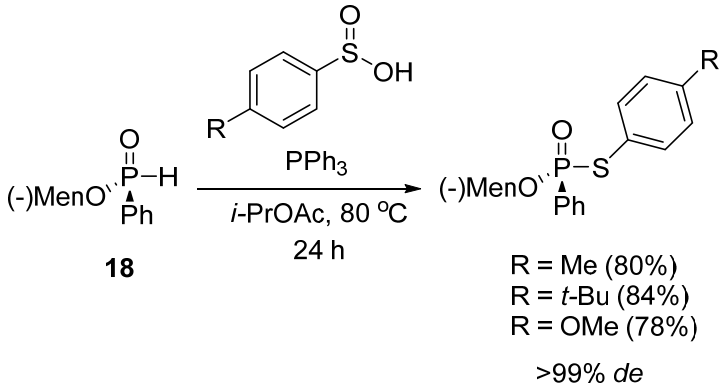
3	Ph	Cl	81%
4	Ph	Br	70%
5	4-MeC_6H_4	Me	69%
6	4-FC_6H_4	Me	75%
7	4-$CF_3C_6H_4$	Me	76%
8	4-NaphthylC_6H_4	Me	60%
9	EtO	Me	12%
10	PhO	MeO	15%

A significant drawback of this approach is the necessity for two equivalents of the phosphorus-containing starting material. Moon and colleagues managed to reduce this requirement to a single equivalent by the introduction of triphenylphosphine as a sacrificial reductant (Scheme 44).[79] The authors significantly extended the substrate scope beyond that of Lin's original report, with both phosphinothioates and phosphorothioates recovered in good to excellent yields



Scheme 44

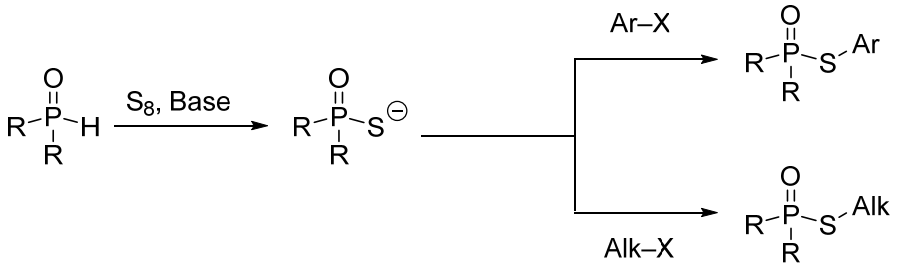
In contrast to Lin's findings, the authors concluded that the underlying mechanism was not radical-based, as addition of TEMPO did not significantly inhibit the reaction. This suggests that these two similar methodologies may proceed *via* different mechanisms. Furthermore, when menthol-derived **18** was subjected to these reaction conditions, the stereochemical configuration at the phosphorus was retained in the product, making this a particularly convenient method for the formation of *P*-chiral phosphonothioates (Scheme 45).



Scheme 45

7. P–S bond formation using elemental sulfur

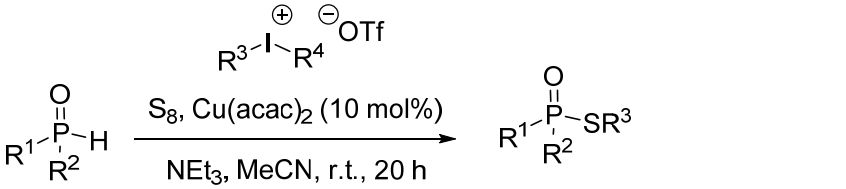
When treated with elemental sulfur in the presence of base, P(O)–H compounds are readily transformed to the corresponding thioate species (Scheme 46). These thioates constitute versatile intermediates in the synthesis of sulfur-containing organophosphorus compounds as they can be either arylated or alkylated to afford the *S*-aryl or *S*-alkyl targets.



Scheme 46

7.1 P–S(Aryl) bond formation from elemental sulfur and P(O)–H

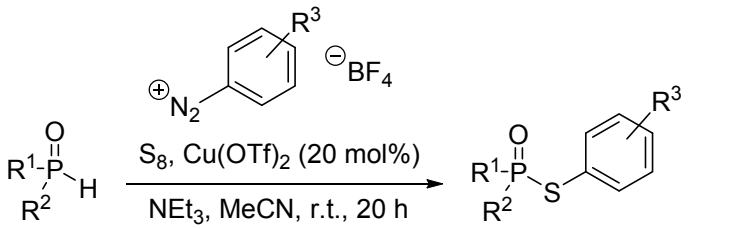
A multicomponent preparation of *S*-aryl phosphorothioates and phosphonothioates by copper-catalysed phosphorothiolation of both symmetric and unsymmetric diaryliodonium salts has been described by Zhang *et al*. (Scheme 47).[80] While copper(II) triflate and copper(II) acetate both promote the reaction, copper(II) acetylacetonate was found to be the most effective catalyst. In the absence of elemental sulfur, rapid *P*-arylation instead occurs with the side-product formed in yields of up to 70%. The presence of elemental sulfur suppresses this side reaction and the phosphorothioate product is formed exclusively.



18 Examples (65%-95%)
R^1 = Alkoxy, R^2 = Alkoxy or Ph
R^3 = Aryl; R^4 = R^3 or mesityl

Scheme 47

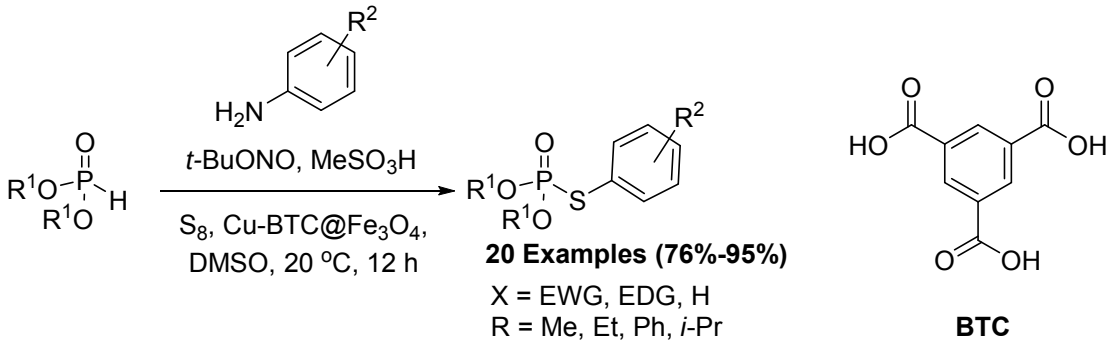
The same authors also employed copper catalysis in the coupling of aryl diazonium tetrafluoroborate salts to dialkyl phosphonites, phosphine oxides and phosphonates, again using elemental sulfur (Scheme 48).[80] Both electron-withdrawing and electron-donating substituents were well tolerated, although yields tended to be lower for *ortho*-substituted diazonium salts. Copper(II) triflate was found to be the best catalyst of those screened. Interestingly, this reaction required a higher loading of 20 mol% of the catalyst in comparison to the 10 mol% of copper(II) acetylacetonate required for diaryl iodonium triflate substrates (*cf*. Scheme 47).



24 Examples (22%-96%)
R^1 = Alkoxy,
R^2 = Alkoxy, Aryl
R^3 = EWG or EDG

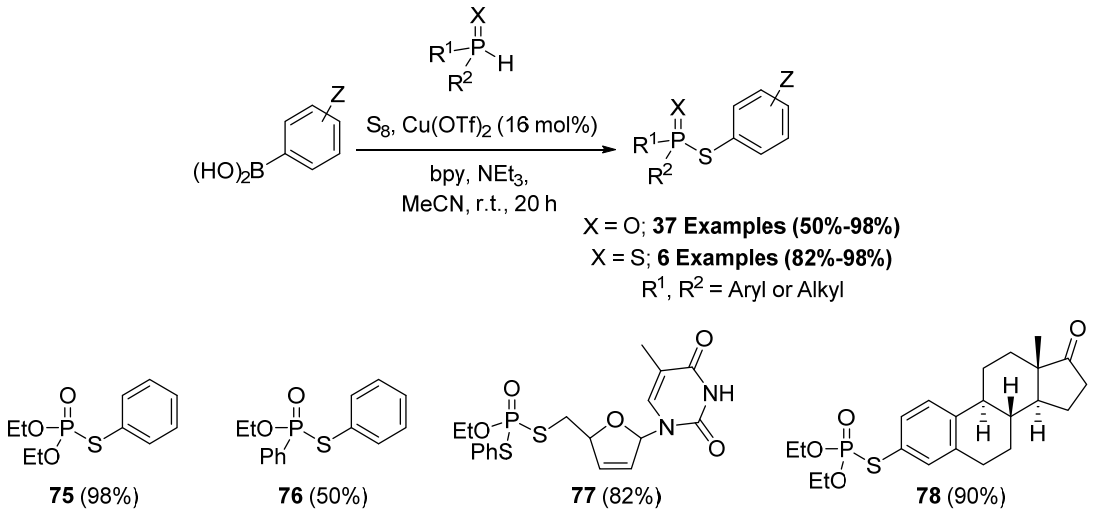
Scheme 48

Wang and colleagues, adapting the methodology of Zhang *et al*., successfully synthesised phosphorothioates from diazonium mesylate salts, generated *in situ* by the oxidation of substituted anilines with *tert*-butyl nitrite (Scheme 49).[81] A magnetically recyclable Cu-BTC@Fe_3O_4 composite facilitated the recovery and reuse of the catalyst a further six times with no detectable loss in catalytic efficiency. During their investigation, the authors noted that none of the desired *S*-aryl phosphorothioate product was formed in the presence of TEMPO, a radical scavenger. This result suggests that the underlying mechanism of this reaction is radical-based, although the exact details remain unclear.



Scheme 49

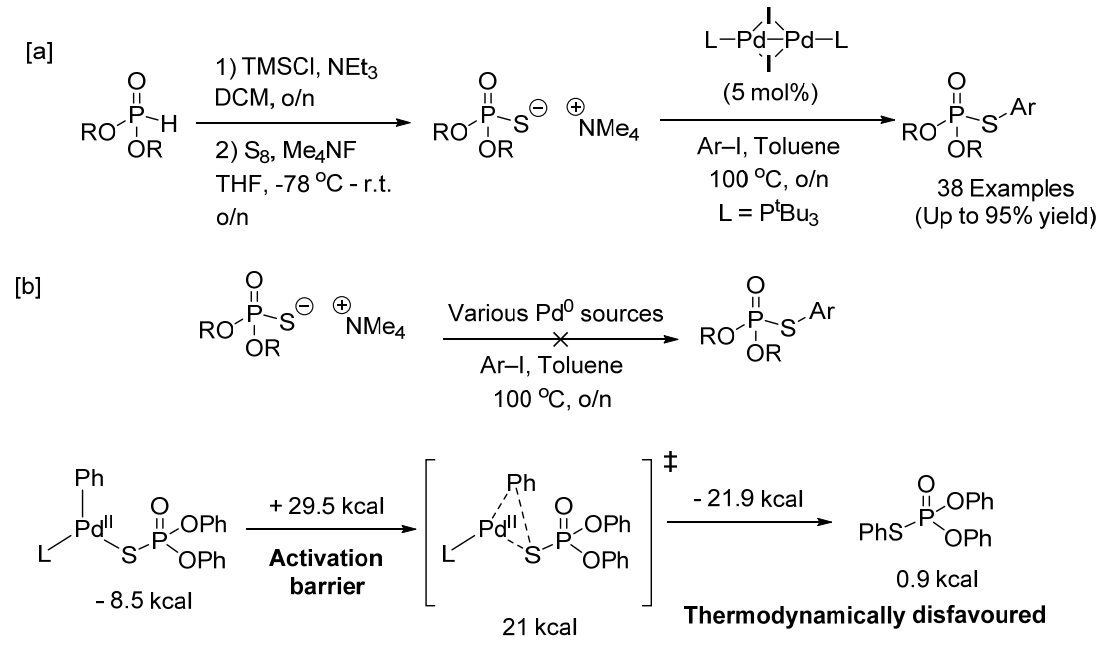
A similar transformation using aryl boronic acids instead of aryl diazonium salts was reported by Xu and co-workers (Scheme 50).[82] 2,2'-Bipyridine (bpy) was found to be the optimal ligand for this transformation. Similar to the findings of Zhang *et al*., phosphorothioate **75** was recovered in a significantly higher yield than phosphonothioate **76**, suggesting that electron-poor phosphorus substrates are more compatible with these conditions. This chemistry is highly scalable with **25** being prepared in almost quantitative yield on a 5.00 g scale. Analogues of complex biological molecules such as thymidine derivative **77** and steroid **78** were also produced in high yields using this methodology.

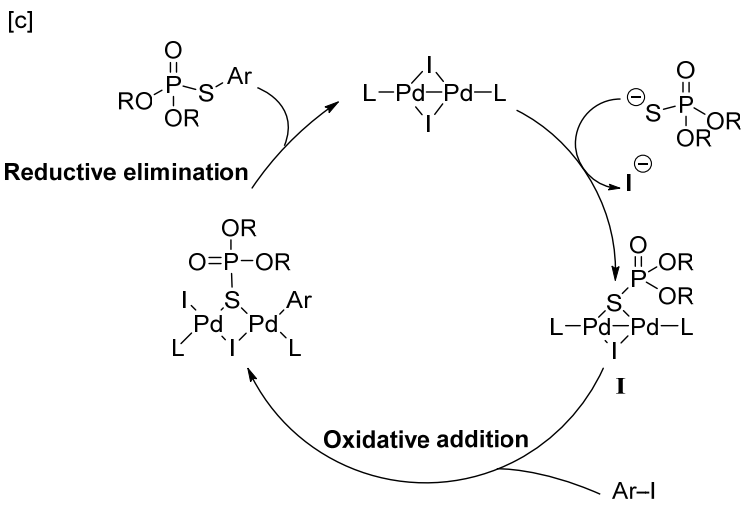


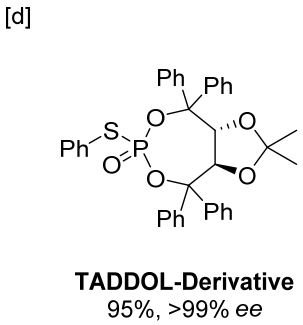
Scheme 50

Although the Pd(0)/Pd(II)-catalysed cross-coupling reaction reported by Zhu *et al*. (*vide supra* Scheme 8) furnishes phosphinothioates in good yields when thiols are coupled with dialkyl phosphites, this approach was found to be unsuitable for the coupling of phosphorothioates and aryl iodides (Scheme 51 [b]) and recourse to Pd(I) chemistry was instead required (Scheme 51 [a]).[83] The authors conducted computational studies to understand the lack of observed reactivity in this instance and concluded that reductive elimination of Ar–SP(=O)R_2 from Ar–Pd(II)I–SP(=O)OR_2 is a

high energy process (Scheme 50 [b]). This observation prompted an investigation of a possible Pd(I)/Pd(II) catalytic cycle with a lower activation barrier. In order for Pd(I)-dimer catalysis to be successful, the coupling partner must stabilise the bridging unit of the dimer. The authors confirmed that ammonium tetramethylphosphorothioate was a competent coupling partner by recording the formation of an intermediate similar to **I** by ^{31}P NMR (Scheme 50 [c]). The addition of a suitable aryl iodide coupling partner allowed turnover of the catalytic cycle and the successful formation of the desired phosphorothioate. Various aryl iodides were well tolerated irrespective of their steric or electronic properties. Notably, the configuration of the chiral centres in the starting materials was preserved in the products. Several α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol (TADDOL)-derived phosphorothioates were successfully prepared by this approach (e.g. Scheme 50 [d]).





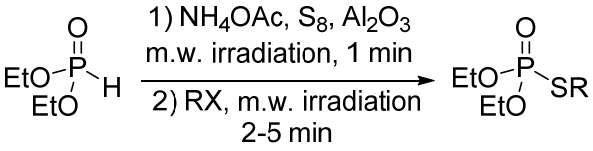


Scheme 51

7.2 P–S(Alkyl) bond formation from elemental sulfur and P(O)–H

An early example of this approach was reported by Kaboudin (Table 22).[84] A range of phosphorothioates was generated in 75%-90% yields employing ammonium acetate as base in conjunction with acidic alumina as a solid support.[85] Both alkyl chlorides and alkyl bromides were found to be suitable alkylating reagents. Kaboudin later adopted a similar approach in the preparation of potential choline esterase inhibitors.[5a]

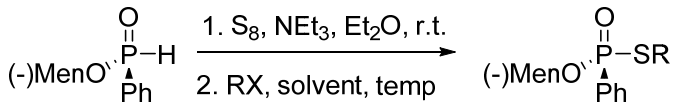
Table 22. Microwave-assisted sulfuration-alkylation



Entry	R	X	Yield
1	Bn	Br	76%
2	Bn	Cl	82%
3	Ph_2CH	Br	88%
4	$BnCH_2$	Br	75%
5	4-$NO_2C_6H_4CH_2$	Br	90%
6	4-$MeC_6H_4CH_2$	Cl	88%
7	3-$MeC_6H_4CH_2$	Cl	85%
8	2-$MeC_6H_4CH_2$	Cl	76%
9	$BnCH_2CH_2$	Cl	80%

When menthol derivative **18** was subjected to similar conditions, Wang *et al.* discovered that the stereochemical configuration at the phosphorus was retained in the product (Table 23).[57] Although methyl iodide was used to prepare the *S*-methyl-substituted product (Table 23, Entry 1), in all other cases the corresponding alkyl bromides proved effective (Table 23, Entries 2-7). Sterically hindered alkyl halides generally required longer reaction times at elevated temperatures in order to reach completion (Table 23, Entries 3-6).

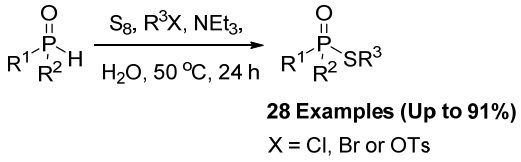
Table 23. Stereospecific preparations of *P*-Chiral phosphonothioates



18

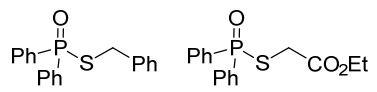
Entry	R	X	Temp	Time (h)	Solvent	Yield
1	Me	I	r.t.	2	Diethyl ether	99%
2	Et	Br	r.t.	72	Diethyl ether	99%
3	*i*-Pr	Br	50 °C	120	Neat	93%
4	*sec*-Bu	Br	50 °C	72	Neat	89%
5	Cyclohexyl	Br	50 °C	72	Neat	88%
6	*t*-Bu	Br	60 °C	72	Neat	83%
7	Bn	Br	r.t.	3	Diethyl ether	95%

Zhang demonstrated that the above transformations may also be conducted in water in comparable yields (Scheme 52).[86] Triethylamine was found to be the optimal base following an initial screening study. Phosphinothioates **79-81**, phosphorothioates **82** and **83**, and phosphonothioates **48**, **84-86** were successfully prepared *via* this methodology. As previously observed by Wang[57], the stereochemical configuration of enantiopure starting materials was conserved in the final products (**84** and **85**). While the yields of phosphinothioates and phosphonothioates were generally good to excellent, phosphorothioates **82** and **83** were isolated in poor yields of 11% and 6% respectively.



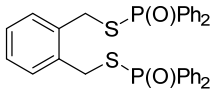
Selected Examples:

Phosphinothioates:



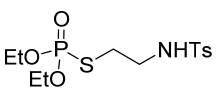
79 80%

80 64%

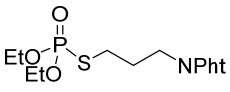


81 71%

Phosphorothioates

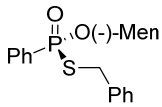


82 6%

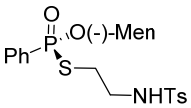


83 11%

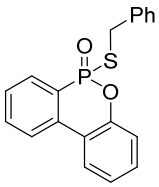
Phosphonothioates:



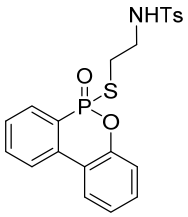
84 80%



85 91%



48 46%

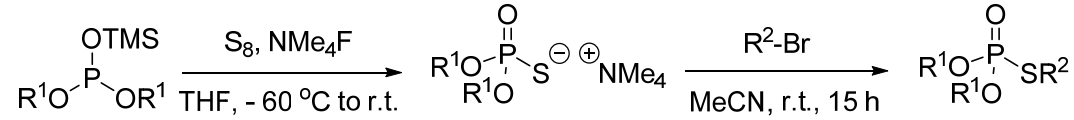


86 82%

Scheme 52

Silyl phosphites are highly versatile intermediates in organophosphorus chemistry.[66] They readily react with electrophiles to afford a variety of *P*(V) compounds, most notably in the Abramov reaction.[87] Kovacs *et al*. showed that silyl phosphites **87** and **40** were cleanly sulfurized using S_8 in the presence of tetramethylammonium fluoride to furnish the corresponding tetramethylammonium phosphorothiolate salts **88** and **89** in excellent yields (Table 24).[88] Tetramethylammonium salts proved particularly convenient to work with, as they were more soluble and shelf-stable than other salts, and this facilitated their subsequent alkylation under mild conditions.

Table 24. Preparation of phosphorothioates from silyl phosphites



87 R^1 = Me
40 R^1 = Et

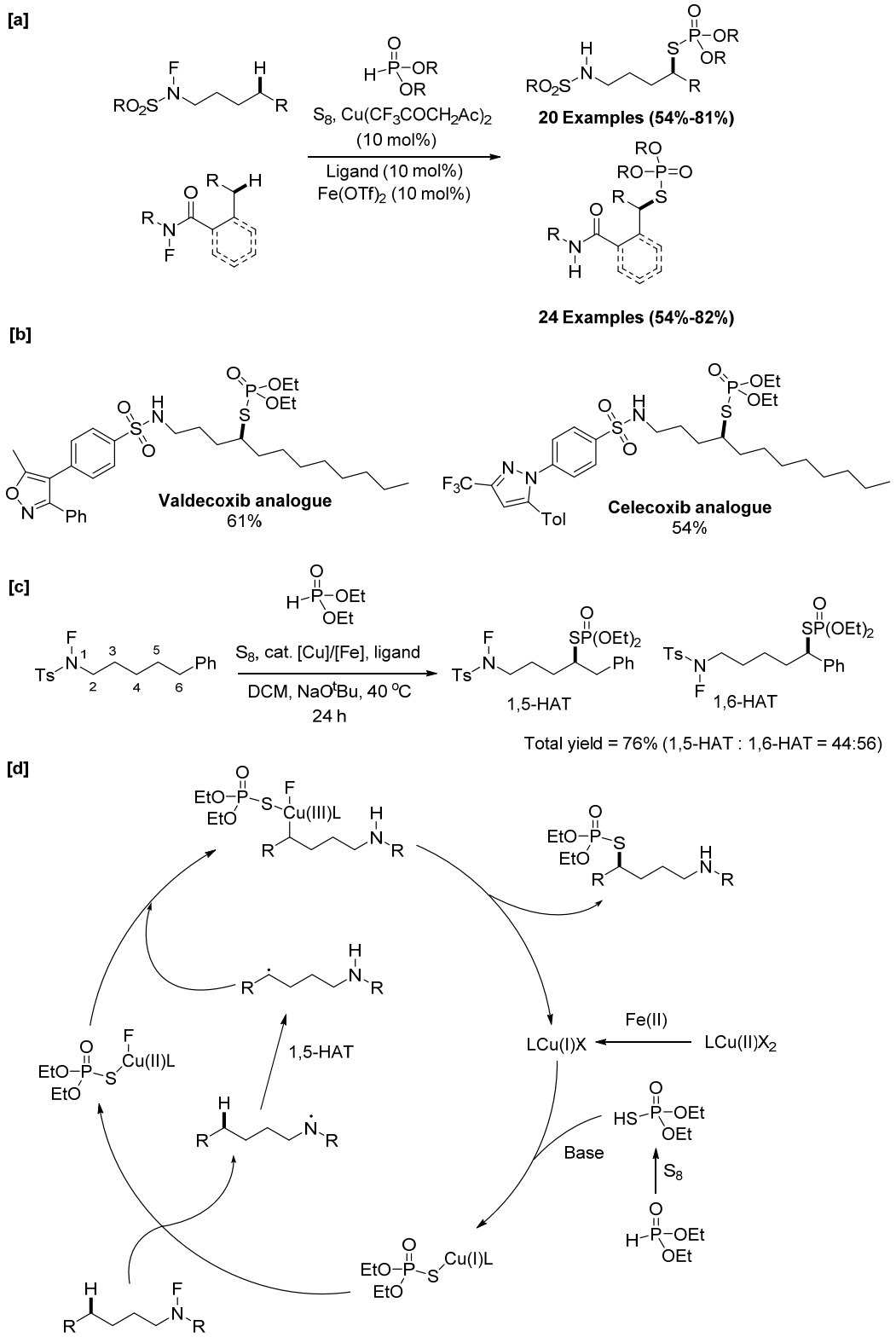
88 R^1 = Me (86%)
89 R^1 = Et (84%)

Entry	R^1	R^2	Yield
1	Me	Bn	98%
2	Me	4-$CF_3C_6H_4CH_2$	69%

3	Me	$PhC(O)CH_2$	78%
4	Me	*n*-Bu	80%
5	Et	Bn	77%
6	Et	*n*-Bu	89%
7	Et	$CH_3CH_2SCH_2CH_2$	89%

7.3 Unreactive C–H phosphorothiolation involving elemental sulfur

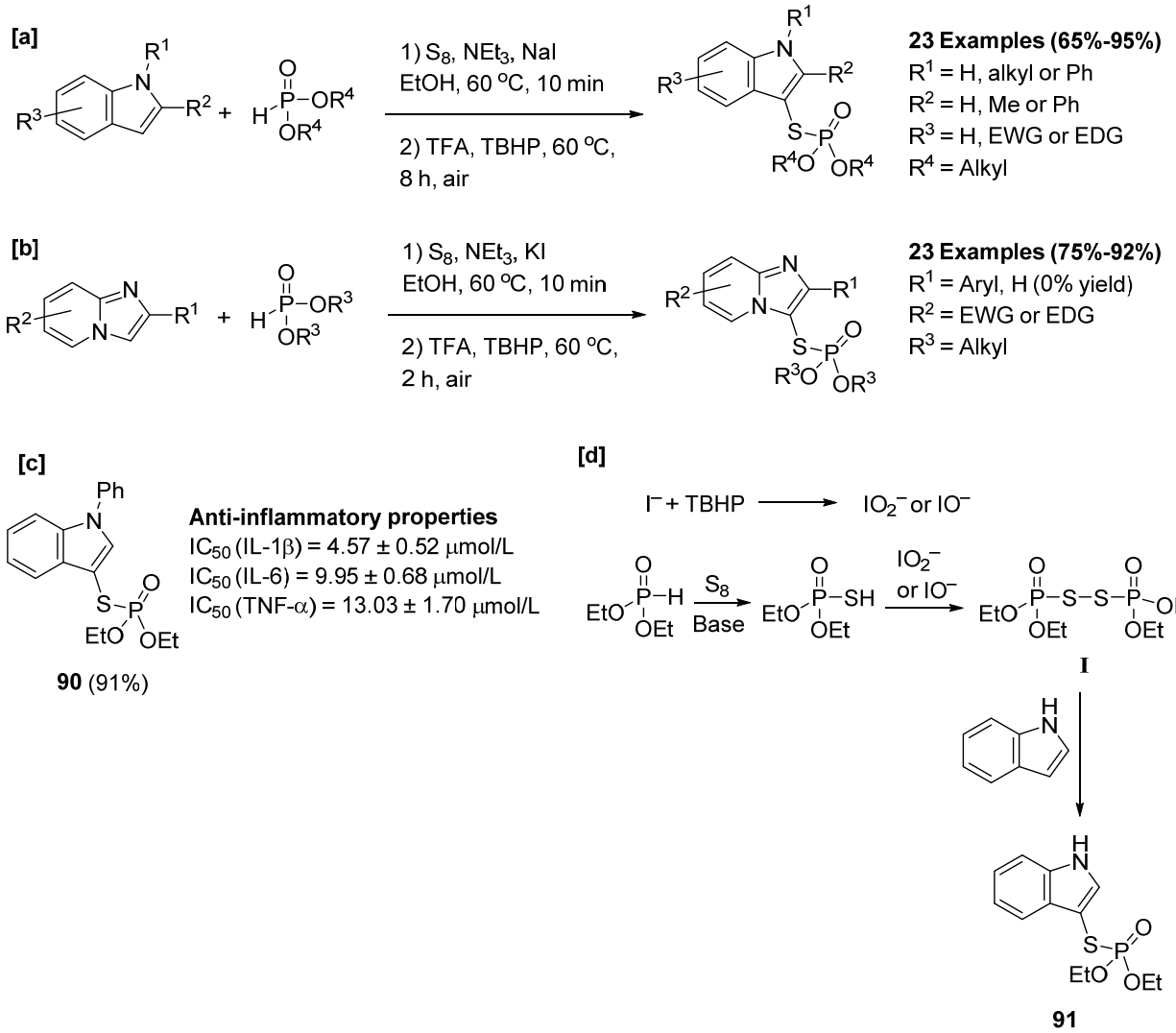
In Sections 7.1 and 7.2, the reaction of phosphorous thioate anions with activated C–X bonds was discussed. An obvious drawback to this approach is the requirement to stoichiometrically pre-activate the coupling partner, which is inherently wasteful. Functionalising unactivated C–H bonds would be far more attractive from an atom economy perspective. To that end, the multicomponent radical-based phosphorothiolation strategy for sulfonamide and carboxamide derivatives reported by Shi *et al*. is noteworthy (Scheme 53 [a]).[89] Heterolytic cleavage of the N–F bond followed by 1,5-hydrogen atom transfer (1,5-HAT) activates the adjacent ð-carbon. Both iron triflate and copper trifluoroacetoacetonate are involved in the generation of the reactive radical species. The reaction is reasonably general and both electron-rich as well as electron-poor amides are tolerated. In most instances, there is a clear preference for the ð-phosphorothiolation product arising from the 1,5-HAT process, which is perhaps best exemplified by the application of this approach to the derivatisation of the COX-2 inhibitors Valdecoxib and Celecoxib in 61% and 54% yields respectively (Scheme 53 [b]). The authors also demonstrated how the regiospecificity of the transformation may be altered to preferentially form a ω-phosphorothiolation product *via* a 1,6-HAT process, likely owing to the improved stability of the resulting benzylic radical intermediate (Scheme 53 [c]). The multi-component mechanism tentatively proposed by the authors is initiated by the reduction of Cu(II) to Cu(I) by iron triflate (Scheme 53 [d]). The phosphorothiolation reagent, generated *in situ*, then ligates the Cu(I), triggering the 1,5-HAT process and the subsequent cross-coupling reaction.



Scheme 53

Shi *et al*. also described an oxidative phosphorothiolation procedure for indoles (Scheme 54 [a]) and imidazole[1,2-a]pyridines (Scheme 54 [b]) using elemental sulfur and a range of phosphites.[90] As functionalised indoles and imidazo[1,2-a]pyridines are among the most valuable structural motifs in

biologically active molecules, the direct phosphorothiolation of these core structures represents a significant advance for medicinal chemistry.[91] The authors confirmed the significance of this new class of compounds by studying their potential as anti-inflammatory agents. Indole **90** was identified as a promising inhibitor of a number of pro-inflammatory cytokines, displaying low nanomolar IC_{50} values against interleukins IL-1β and IL-6, in addition to tumour necrosis factor alpha (TNF-α), both of which are strong hallmarks of anti-inflammatory ability (Scheme 54 [c]).[92] Mechanistic experiments performed by the authors suggested that dimer **I** was likely to be the active phosphorothiolation species (Scheme 54 [d]). The subsequent reaction of indole presumably occurs regioselectively at the 3-position *via* electrophilic substitution.



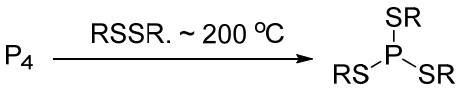
Scheme 54

8. White phosphorus

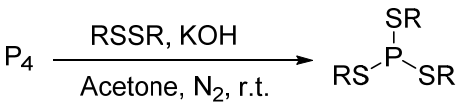
White phosphorus represents one of the most abundant allotropes of elemental phosphorus. The instability of white phosphorus towards elevated temperatures and moisture can make handling difficult. Indeed, white phosphorus is pyrophoric on exposure to air above ambient temperatures. Despite these limitations, white phosphorus has been utilised in the production of sulfur-containing organophosphorus compounds.[93] White phosphorus is routinely converted into phosphorus trichloride using gaseous chlorine, which is an entryway into most organophosphorus compounds *via* nucleophilic substitution.[94] The process of white phosphorus valorisation is highly energy intensive and environmentally damaging. In 2017, the European Union designated white phosphorus a critical raw material and noted that 100% of its supply of the material is imported from Kazakhstan, China and Vietnam.[95] Consequently, more efficient use of this valuable resource through direct functionalisation is highly desirable.

In an early patent filing, Stevens treated a range of symmetrical and unsymmetrical disulfides with white phosphorus at very high temperatures to produce the corresponding trithiophosphites (Scheme 55).[96] It is likely that either homolytic or heterolytic cleavage of the disulfide generates the thiolating reagent which then reacts with the white phosphorus to afford the product. Wu later demonstrated that this process could be conducted under much milder conditions in the presence of basic potassium hydroxide (Scheme 55).[97] A significant drawback of this approach, however, was the requirement for a large excess of the disulfide (approximately ninety-fold molar excess) to reach completion.

Stevens (1951):



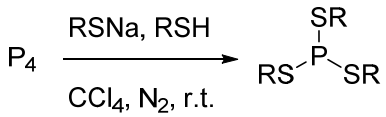
Wu (1965):



Scheme 55

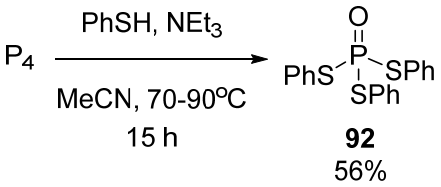
A later report by Brown *et al*. in 1978 represented a significant improvement on these early efforts.[98] In Brown's procedure, finely divided white phosphorus is treated with a mixture of two equivalents of thiolate salt, the parent thiol and carbon tetrachloride (Scheme 56). Carbon tetrachloride facilitates the reaction by chlorinating the anionic products of the initial nucleophilic attack of the thiolate at phosphorus. This renders the immediate products more electrophilic,

thereby allowing the reaction to reach completion. Although this approach represents a major advance, the use of carbon tetrachloride as a solvent is problematic.



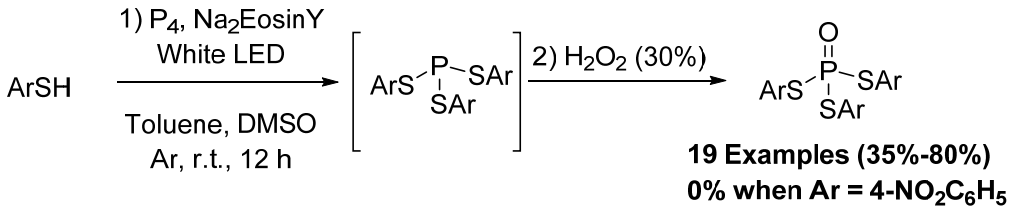
Scheme 56

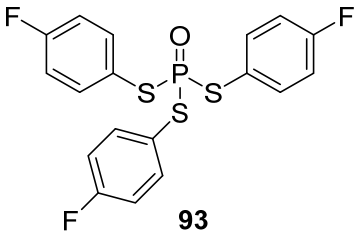
Seeking to avoid carbon tetrachloride, Badeeva *et al*. successfully prepared phosphorotrithioate **92** using white phosphorus and thiophenol in acetonitrile (Scheme 57). Conducting the reaction in air, as opposed to a nitrogen atmosphere, resulted in the formation of the oxidised P(V) product instead of the usual P(III) product. A modest yield of 56% of **92** was recovered from this reaction.



Scheme 57

Lu and colleagues discovered a highly efficient photochemical process for accessing phosphorotrithioates using visible light and Eosin Y as a photosensitiser (Scheme 58).[99] A variety of substitution patterns were tolerated on the aromatic ring, although the reaction was less efficient when *ortho*-substituted thiophenols were introduced. Interestingly, no product resulted from 4-nitrothiophenol and only trace products were observed when alkyl thiols were investigated. Initially, aryl thiyl radicals are formed *in situ* from the reaction of the aryl thiol precursor with the photoexcited Eosin Y. White phosphorus then quenches these radicals, and the process terminates by generating the corresponding trithiophosphite. Addition of hydrogen peroxide oxidises the trithiophosphite to the target phosphorotrithioate. No product formed when the reaction was attempted in the presence of TEMPO, confirming the mechanism to be radical based. Highlighting the potential of this chemistry, novel phosphorotrithioate **93** was found to possess favourable anti-inflammatory properties with low nanomolar inhibition of IL-1β and IL-6 and TNF-α (*cf.* Scheme 54 [c]).[92]





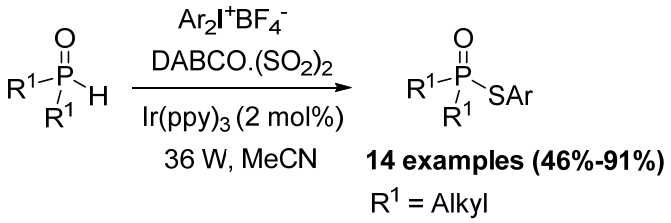
93

Anti-inflammatory properties
IC_{50} (IL-1β) = 0.15 μmol/L
IC_{50} (IL-6) = 1.18 μmol/L
IC_{50} (TNF-α) = 2.44 μmol/L

Scheme 58

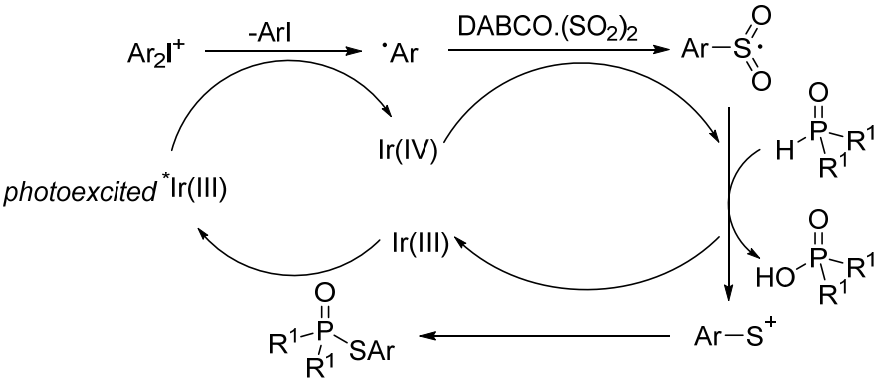
9. Miscellaneous methods

Gong *et al*. recently described how iridium photocatalysis offers a viable route to phosphinothioates in moderate to excellent yields employing the 1,4-diazabicyclo[2.2.2]oxetane-bis(sulfur dioxide) adduct (DABCO.$(SO_2)_2$) (Scheme 59).[100] Electron-poor aryl iodonium salts were observed to be more amenable to these conditions than electron-rich substrates which reacted sluggishly.



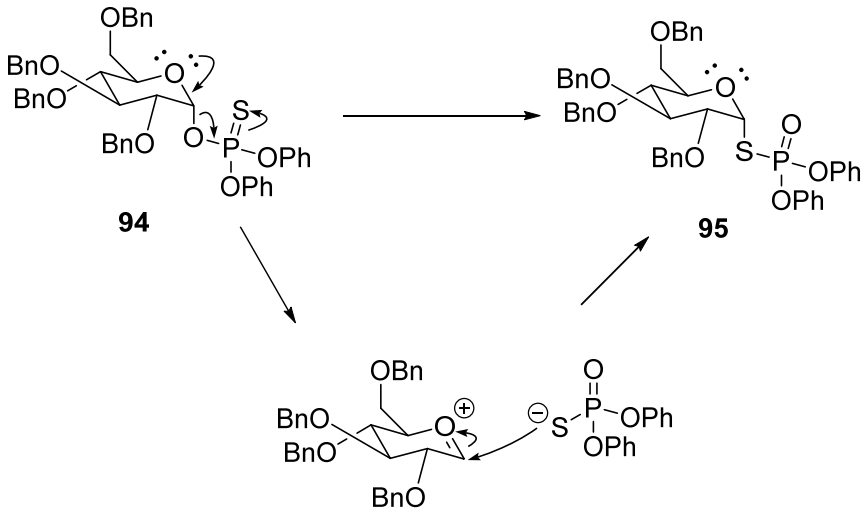
Scheme 59

The reaction is believed to proceed *via* a single-electron transfer type mechanism facilitated by the iridium(III) photocatalyst, which is photoexcited *via* visible-light irradiation (Scheme 60). Evidence supporting a radical mechanism lies in the absence of product formation on addition of three equivalents of TEMPO.



Scheme 60

Loranger *et al*. observed the isomerisation of *O*-linked thiophosphates to the corresponding *S*-linked phosphorothioates while investigating novel analogues of glucose-1-phosphate (Scheme 61).[101] Elimination of the anomeric substituent from **94** forms an oxonium cation and phosphorothioate anion. The anion then recombines *via* the sulfur atom, owing to its enhanced nucleophilicity relative to oxygen, producing **95**.



Scheme 61

10. Outlook

The ever-increasing importance of sulfur-containing organophosphorus compounds has led to a surge of recent publications and an expanded menu of reactions available to chemists for P–S bond formation. A wide array of phosphorothioate, phosphonothioate and phosphinothioate compounds may be readily prepared, alongside their closely related analogues, using one of the many methods described in this review. As there now exists several strategies for the incorporation of these motifs

into relatively simple molecules, it is likely that future studies will increasingly examine the application of these approaches to the late stage functionalisation of relatively complex substrates. Indeed, several groups have already demonstrated the utility of their methodologies by synthesising highly functionalised, biologically relevant molecules, including nucleoside, steroid and other natural product derivatives. In addition, the phosphorothiolation/phosphinothiolation/phosphonothiolation of relatively unreactive C–H bonds remains largely unexplored, and is likely to be a fruitful space for future discovery. Only two recent literature examples examine the phosphorothiolation of alkyl C–H bonds through a 1,5-HAT approach and a highly nucleophilic aryl C–H of nitrogen heterocycles. It is also somewhat surprising, given the recent explosion of interest in flow chemistry, that P–S bond formation has not yet been explored in flow.

Several groups have proposed detailed mechanisms to underpin their synthetic methodologies. Generally, authors have relied on familiar radical trapping experiments or on the *in situ* detection of unstable reaction intermediates to support their hypotheses. To date, there are relatively few computational studies on P–S bond formation. As demonstrated by Schoenebeck and co-workers (*vide supra* Scheme 51), robust theoretical work can support the development of fundamentally new chemical processes. Adopting a similar approach will support the future discovery of novel patterns of reactivity.

Acknowledgments

The UCC Strategic Research Fund is gratefully acknowledged for funding of a PhD Scholarship (DJJ).

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Graphical Abstract