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CHAPTER

Progress in the Chemistry of Phosphorothioates

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Abstract: The present review focuses on the synthesis and applications of phosphorothioates (phosphorothioic esters) with the general structure $R_2P(O)SR'$, which are molecules belonging to the large family of organophosphorus compounds. They found important applications as biological active molecules, as well as synthetic intermediates to access valuable phosphorus and/or sulfur-containing structures. The reactivity of both heteroatoms, phosphorus and sulfur, is discussed by showing how they are involved as electrophilic, nucleophilic, or radical species in different transformations. The general methods for the preparation of phosphorothioates are described according to the various strategies involving P-S bond formation from one sulfur-reagent and one phosphorus-reagent, which include recent metal-catalyzed cross-coupling reactions. Particular attention is paid to synthetic applications of phosphorothioates occurring *via* the P-S bond cleavage, including for example anionic rearrangements and cascades, formation of sulfur-heterocycles, homolytic processes for olefins phosphorylation, and metal-catalyzed alkynes thiophosphorylation. The literature of the last two decades is covered, highlighting selected contributions in the chemistry of this class of compounds.

Keywords: phosphorus, sulfur, phosphorothioates, thiophosphates, phosphorothioic esters, mercaptophosphonate, P-S bond formation, P-S coupling, P-S bond cleavage, sigmatropic rearrangement, anionic rearrangement, sulfur heterocycles.

1. INTRODUCTION

Compounds that contain phosphorus and sulfur atoms bonded to each other represent an important class of compounds due to their biological properties and fields of applications, in particular agrochemistry (as pesticides),[1] or in medicinal chemistry (as enzymes inhibitors or antivirals).[2] As the literature covering this topic is very broad, we decided to discuss herein only one among the three categories of PS-compounds illustrated in Figure 1 (phosphorothioates **A**, phosphorothionates **B**, and phosphorodithioates **C**), that

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of phosphorothioates **A**. As far as concerns the chemistry of specific P-S compounds such as the tetraphosphorus decasulfide (P₄S₁₀) or the Lawesson's reagent (LR), it was the topic of recent reviews.[3]

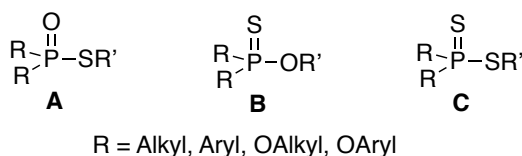
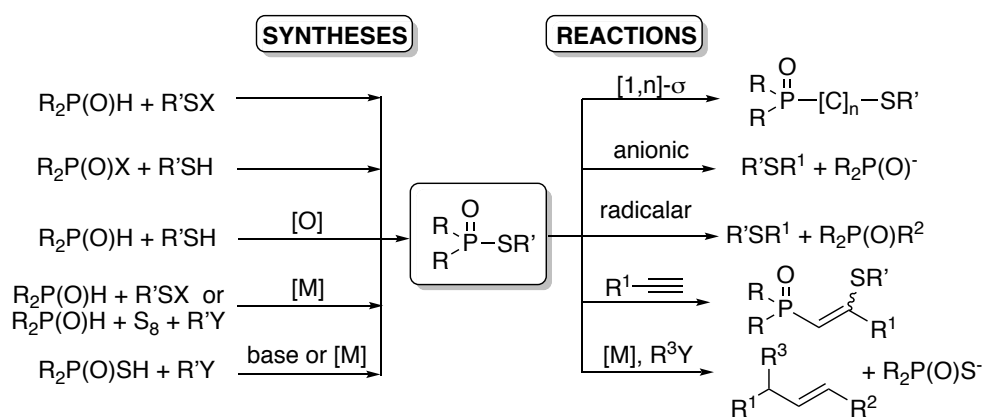


Figure 1. General structures of phosphorothioates **A**, phosphorothionates **B**, and phosphorodithioates **C**.

One widely known example is the incorporation of the P(O)-S moiety as an essential structural element in modified oligonucleotides for therapeutic applications and studies of processes involving RNA.[4] Additionally, phosphorothioates **A** are useful synthetic tools in various chemical transformations, most of them involving the cleavage of the P-S bond. Some enantiopure phosphorothioic acids have been developed for their chiral recognition ability.[5]

In the first section of this chapter, general approaches to access phosphorothioic esters will be described, according to the various methods for the P-S or C-S bond formation (Scheme 1: **Syntheses**). The second section will deal with the rich chemistry of phosphorothioates due to the presence of the both P and S heteroatoms directly linked and their synthetic applications (Scheme 1: **Reactions**). Contributions of the literature of the last two decades have been selected and highlighted, demonstrating the interest and the advances in the chemistry of these compounds.



Scheme 1. Overview of selected syntheses and reactions of phosphorothioates covered in this chapter.

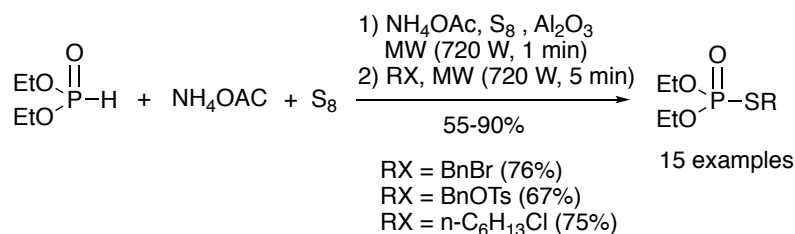
2. SYNTHESSES OF PHOSPHOROTHIOIC ESTERS

The different strategies used to prepare phosphorothioic esters either consist to form a P-S bond by using appropriate phosphorous and sulfur partners as electrophiles, nucleophiles, or radicals, or to introduce the P(O)S-function directly, *via* a C-S bond formation. The overall collection of methods enables access to a broad variety of structures of both S-alkyl and S-aryl phosphorothioate derivatives.

2.1. P-S bond formation from P-nucleophile and S-electrophile

The main phosphorus reagents used in these methods are P(IV) species of type $R_2P(O)H$, with rare cases of P(III) species involved in Arbuzov-type reactions. On the other hand, different sources of sulfur have been used, including elemental sulfur, disulfides, thiocyanates, as well as S-oxidized species.

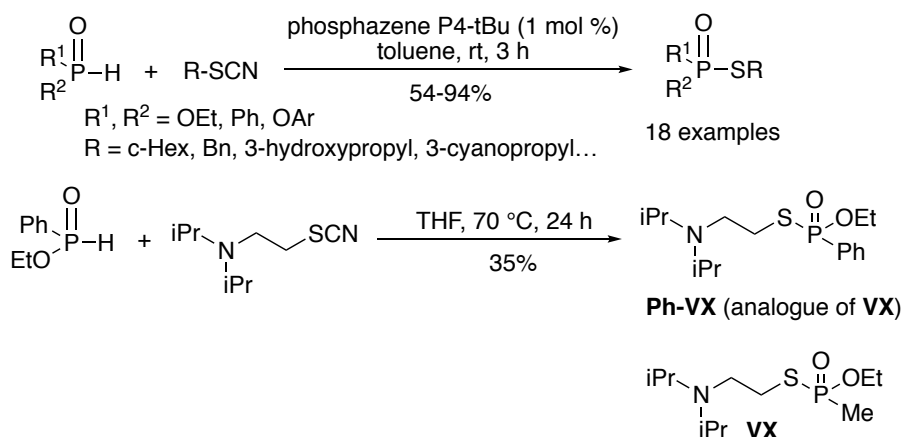
A simple and general method has been developed for the synthesis of S-alkyl and S-benzyl phosphorothioates *via* a one-pot reaction of alkyl or benzyl halides (or tosylates) with a mixture of diethyl phosphite, ammonium acetate, and sulfur powder, in the presence of acidic alumina, under solvent-free conditions, using microwave irradiation (Scheme 2).[6],[7] Less reactive alkyl halides such as 1-hexyl chloride also reacted efficiently.



Scheme 2. One-pot P-S bond formation / S-alkylation.

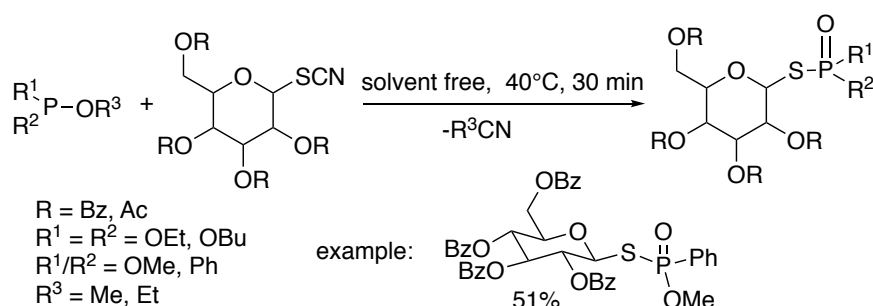
Renard, Mioskowski, and co-workers reported a mild synthetic method involving a thiocyanate as the sulfur-source and H-phosphine oxides, phosphinates, or phosphonates, as the phosphorus-source (Scheme 3).[8] Thiocyanates[9] proved their compatibility with a wider variety of functional groups than other previously described sulfur species. The reaction takes place under catalysis by hindered non-nucleophilic bases, such as phosphazene P4-tBu. The authors applied the method to achieve the synthesis of **Ph-VX** as a substrate for antibody-catalyzed hydrolysis. This phenylphosphorothioate

represents a less toxic analogue of methylphosphorothioate **VX**, which has been described as the most powerful acetylcholinesterase inhibitor. As the thiocyanate partner already bears a basic hindered amine moiety, the use of an additional base was not necessary.



Scheme 3. Thiocyanates as sulfur-source to access phosphorothioates.

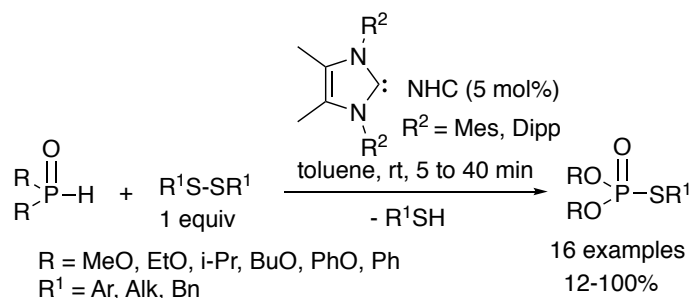
S-glycosyl anomeric thiocyanates have been transformed in the corresponding phosphorothioates by Michaelis-Arbuzov type reaction with triethylphosphite, dimethyl phenylphosphonite, or methyl diphenylphosphinite (Scheme 4).[10]



Scheme 4. Michaelis-Arbuzov type reaction of glycosyl thiocyanates.

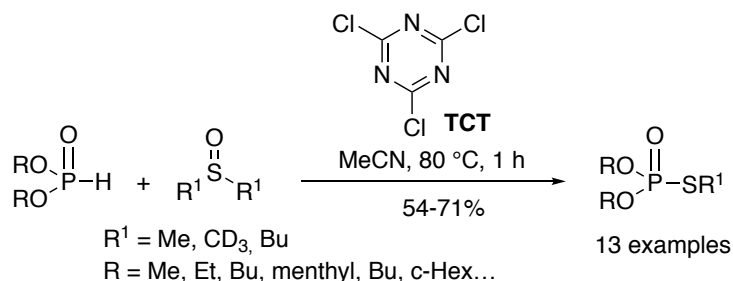
Nguyen et al. described the phosphorylation of disulfides by using N-heterocyclic carbenes (NHCs) as efficient organocatalysts to promote the reaction under mild conditions (Scheme 5).[11] The protocol is simple, metal- and oxidant-free, and needs very short reaction times. Imidazolylidene catalysts (5 mol%) gave the best results for this P-S coupling reaction. In the mechanism proposed by the authors, the NHC acts as a Brønsted base catalyst to activate the phosphorus center *via* a proton-transfer to form an ion-pair intermediate. Then, the nucleophilic phosphorus reacts with the disulfide to

form the phosphorothioate product. Another procedure to prepare S-phenyl phosphonothioate from phosphites and disulfides employed zinc dust, in ethanol, at room temperature.[12]



Scheme 5. NHC-catalyzed reaction of phosphites with disulfides.

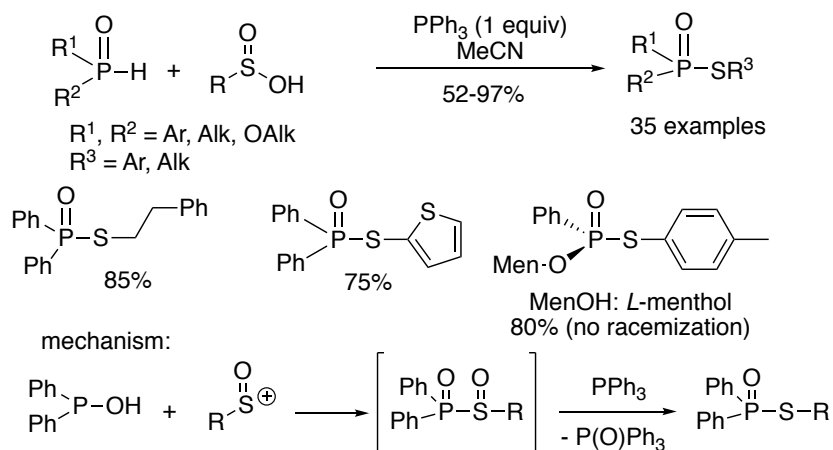
Li et al. have developed a synthesis for S-methyl and S-butyl phosphorothioates starting from various phosphites and dimethyl or dibutyl sulfoxide, activated by 2,4,6-trichloro[1,3,5]-triazine (cyanuric chloride, TCT).[13] The procedure was also applied to the introduction of SCD₃ group into bioactive phosphorothioates. The high purity of the obtained deuterated derivatives allows their use in mechanistic biological studies (Scheme 6).



Scheme 6. Reaction of phosphites with TCT-activated sulfoxides.

A metal- and oxidant-free S–P(O) bond construction has been developed by directly reacting P(O)H compounds with sulfinic acids.[14] The method is compatible with a broad range of substituents on various substrates including aliphatic, aromatic, and heterocyclic moieties, as well as optically active P-chiral partners, which gave a stereospecific coupling (Scheme 7). The authors proposed a mechanism involving the nucleophilic attack of the P(III) form of the phosphite R₂P–OH on the sulfinyl cation, which is generated *in situ* by dehydration of sulfinic acid. Finally, the formed intermediate undergoes

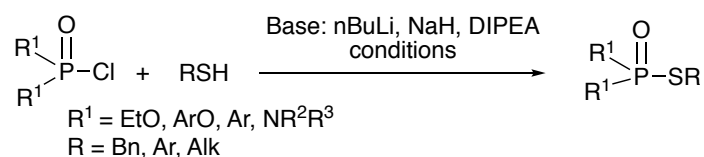
reduction by triphenyl phosphine to afford the desired phosphorothioate. The authors suggested that maybe other electrophilic species could be involved.



Scheme 7. Reaction of phosphites with sulfinic acids.

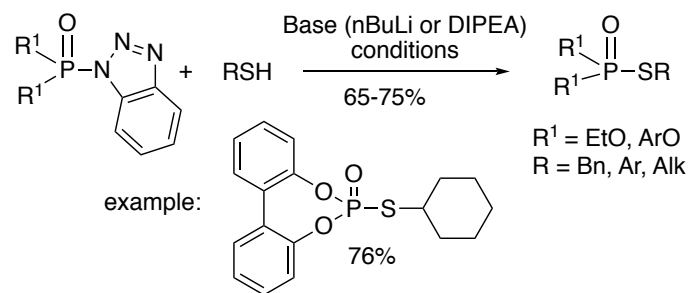
2.2. P-S bond formation from P-electrophile and S-nucleophile

A priori a routine method, the strategy employing a phosphorus-electrophile and a sulfur-nucleophile has been less employed than the previous one, probably because the sensitivity of P(O)X electrophilic reagents. In the main cases the thiolate is generated from the thiol by treatment with a base, then phosphoryl chloride is added to give the expected phosphorothioate (Scheme 8).[15]



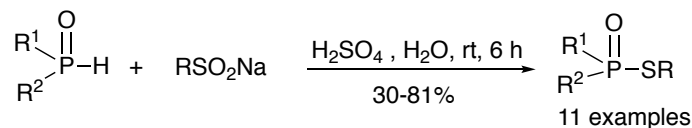
Scheme 8. P-S formation from P(O)Cl reagent and thiolates.

Katritzky et al. used instead chlorophosphates the more stable P-benzotriazole (P-Bzt) derivatives, giving access also to more sensitive biphenol derivatives (Scheme 9).[16]



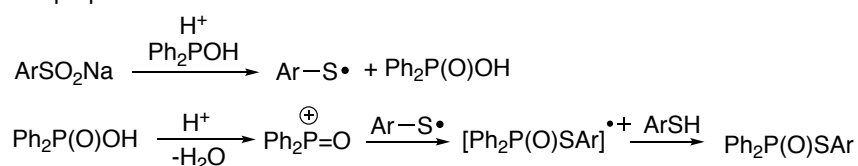
Scheme 9. P-S formation from P(O)Bzt and thiolates.

Odorless and stable sodium arylsulfonates have been used as precursors of arylsulfenyl radicals, which reacted with H-phosphine oxides or dialkyl phosphites to afford phosphorothioates in moderate to good yields (Scheme 10).[17] The yield was poor when sodium methanesulfonate was used instead of a sodium arylsulfonate. The reaction occurred under acidic and reductive conditions, in the presence of sulfuric acid and water, the reducing agent being the phosphorus partner. The mechanism proposed by the authors is also given in Scheme 10. The resulting arylsulfenyl radical reacts with a P-electrophile intermediate leading to the phosphorothioate. The authors showed that the reaction works also by using diaryl chlorophosphines, without acid.



$\text{R}^1, \text{R}^2 = \text{Ph, p-Tol, 4-FC}_6\text{H}_4, 4\text{-CF}_3\text{-C}_6\text{H}_4, 4\text{-naphtyl, EtO, PhO}$
 $\text{R} = \text{Ar, Me}$

proposed mechanism:

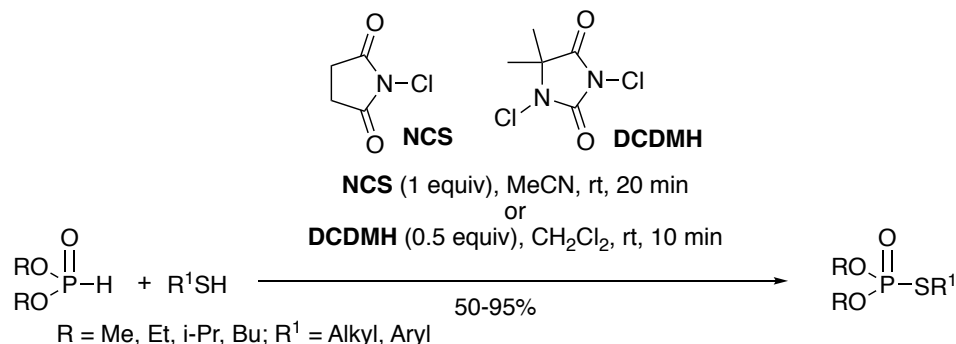


Scheme 10. P-S formation from sodium sulfonates and phosphites.

2.3. Metal-free oxidative P-S bond formation

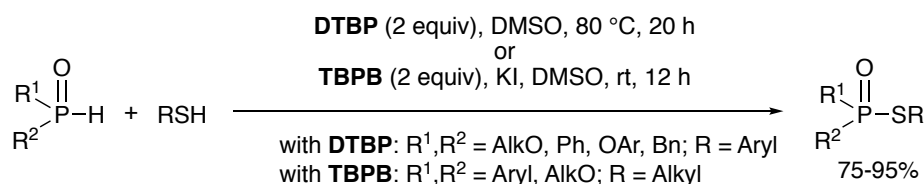
Some methods to access phosphorothioates are based on the P-S formation from phosphites and thiols, both of them nucleophiles, in the presence of an oxidant.

N-chlorosuccinimide (NCS)[18] and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH)[19] have been used by two different research groups to promote the P-S coupling between thiols and dialkylphosphites (Scheme 11). The authors proposed the formation of a sulfenyl chloride (R^1SCl) as the reaction intermediate, which reacted as the electrophile with the nucleophilic phosphorus partner. Both aromatic and aliphatic thiols were tolerated in the reaction conditions.

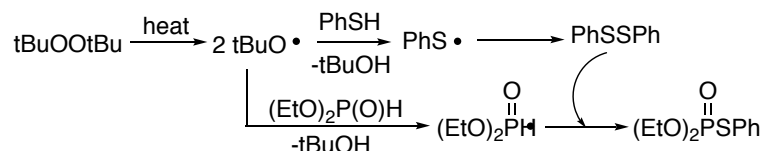


Scheme 11. NCS or DCDMH-promoted reaction between thiols and phosphites.

Pan, Wu, and coworkers described the use of di-tert-butyl peroxide (DTBP)[20] and tert-butyl peroxybenzoate (TBPB)[21] to promote the P-S bond formation between thiols and phosphites (Scheme 12). In the case of the method using DTBP it was demonstrated that disulfides could be also used instead the corresponding thiols and only aromatic thiols were used as partners, however in a large variety of structures. The authors suggested that the thiyl radical is probably the reaction intermediate (see mechanism in Scheme 12). In the case of TBPB-promoter the reaction has been done mainly between H-phosphine oxides or H-phosphinates and aliphatic thiols, leading to the expected phosphorothioates in good yields.

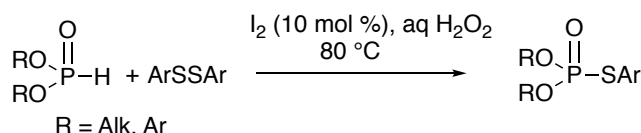


proposed mechanism with **DTBP**:



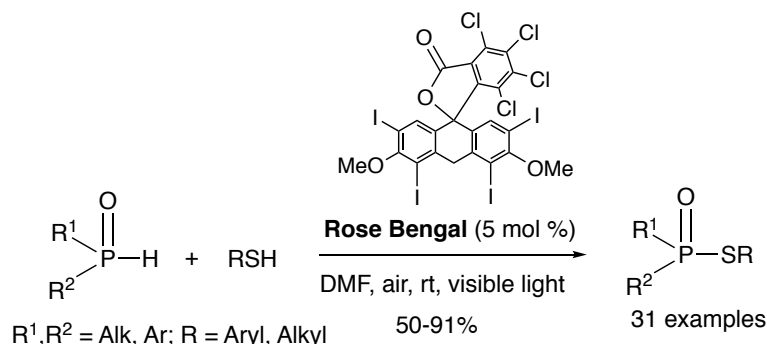
Scheme 12. Peroxide-promoted reaction between thiols and phosphites.

A iodine-catalyzed cross-coupling reaction between phosphonates and diaryl disulfides with H₂O₂ as oxidant was also reported (Scheme 13).[22] Various H-phosphonates were employed for coupling with diaryl disulfides bearing an electron-donating or an electron-withdrawing substituent on para- or meta-position.



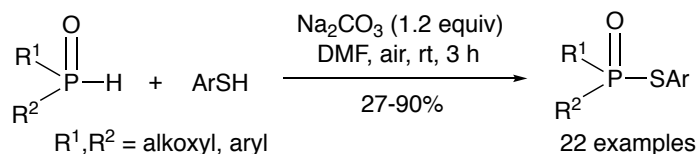
Scheme 13. I₂/H₂O₂ mediated reaction between disulfides and phosphites.

An oxidative cross-coupling of thiols with P(O)H compounds was achieved *via* organic dye-sensitized photocatalysis.[23] The commercially available and inexpensive Rose Bengal was used as the photocatalyst, and air as a convenient green oxidant (Scheme 14). The method was efficient for the synthesis of a range of phosphorothioates in moderate to excellent yields and showed good functional-group tolerance.

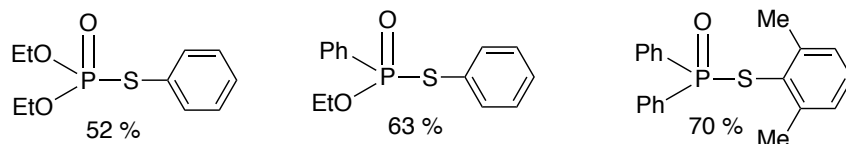


Scheme 14. Visible-light-mediated oxidative coupling between thiols and phosphites.

A cheap method for the synthesis of S-aryl phosphorothioates consisted in the cross-dehydrogenative coupling of P(O)H compounds and aryl thiols, in the presence of Na₂CO₃ as the base and air as the oxidant. The reaction was performed under mild conditions and led to the expected products in moderate to good yields. The proposed mechanism involved the sodium phosphite salt as the nucleophile and the disulfide resulted by the oxidation of the thiol in air, as the electrophile (Scheme 15).[24]

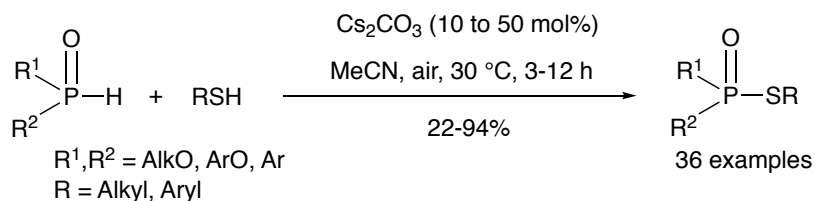


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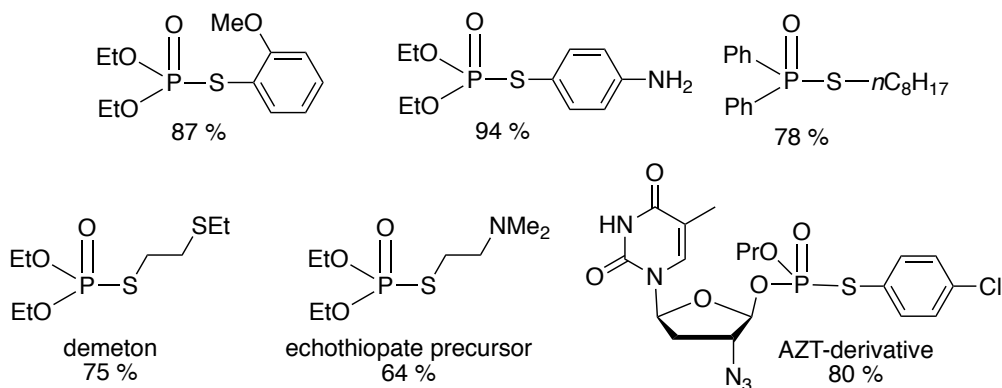


Scheme 15. $\text{Na}_2\text{CO}_3/\text{air}$ mediated reaction between thiols and phosphites.

A catalytic version of the P-S cross-dehydrogenative coupling was described using Cs_2CO_3 as the base-catalyst and molecular oxygen as the oxidant (Scheme 16).[25] The method provided good functional-group tolerance, a broad substrate scope, and could be applied on gram scale and in the preparation of P-S containing bioactive molecules such as demeton, echothiopate, and an AZT-derivative.



selected examples:



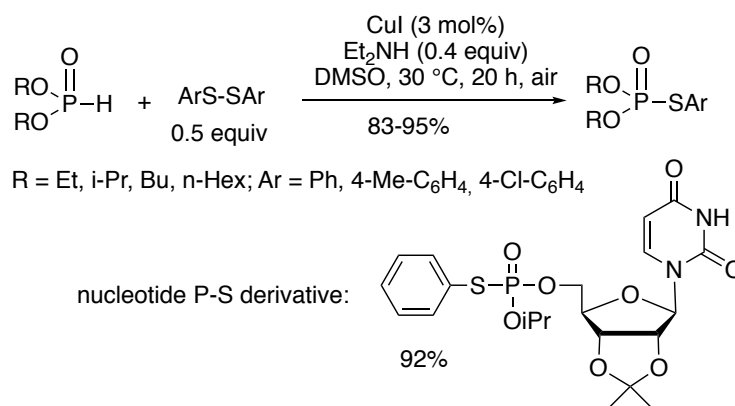
Scheme 16. $\text{Cs}_2\text{CO}_3/\text{air}$ mediated reaction between thiols and phosphites.

2.4. Metal-catalyzed processes involving Phosphorus and Sulfur sources

Transition metals as copper or palladium have been used to form a P-S bond from phosphites and various sulfur-partners. Specifically, efforts have been made to replace thiols by others sulfur reagents that are air-stable and odorless. Another synthetic strategy consists in the one-pot formation of P-S and S-C bonds by using three reaction partners, including the phosphorous and the sulfur sources, and a coupling partner, in the presence of a metal catalyst. In these cases, the metal is mainly necessary for the C-S cross-coupling step.

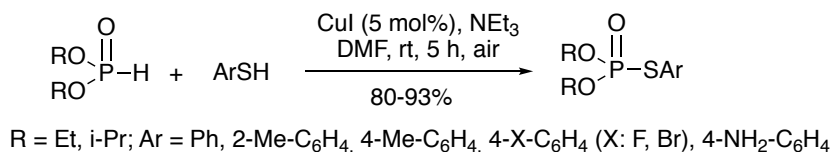
2.4.1. Metal-catalyzed P-S formation

Tang, Zhao, and co-workers reported a practical method for the synthesis of S-aryl phosphorothioates under copper-catalysis.[26] P-S bond was formed by coupling dialkyl phosphites with diaryl disulfides, in the presence of catalytic amounts of copper iodide and diethylamine, in DMSO at 30 °C, in air atmosphere (Scheme 17). A nucleotide P-S derivative was synthesized by this procedure in 92% yield. Moreover, the method was extended to selenium and tellurium counterparts.



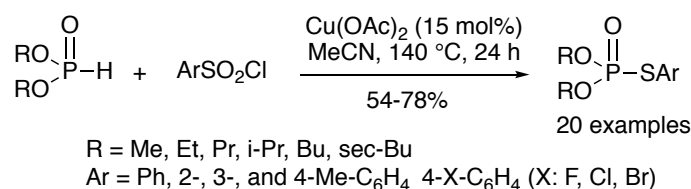
Scheme 17. Cu-catalyzed phosphite/disulfide cross-coupling.

Kaboudin et al. published a copper-catalyzed coupling between phosphites and thiophenols.[27] The reaction took place under mild conditions (room temperature), using copper iodide and triethylamine, in DMF, 5 hours, in air (Scheme 18). The use of different substituents on the aromatic ring had not influence on the yield of S-aryl phosphorothioates.



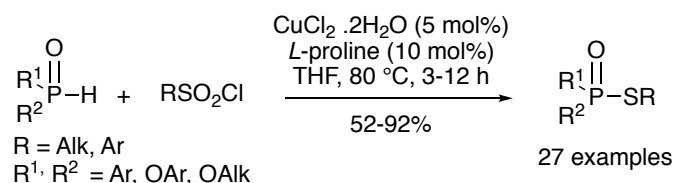
Scheme 18. Cu-catalyzed phosphite/thiophenol cross-coupling.

Copper-catalysis to access S-aryl phosphorothioates was successfully used in the case of coupling of dialkyl phosphites with arylsulfonyl chlorides.[28] The best reaction conditions have been found to be Cu(OAc)₂ as the catalyst and acetonitrile as the solvent, at 140 °C, for 24 hours, in air (Scheme 19). The reaction works well with electron donating or withdrawing substituents on the aromatic ring. 2-Naphtyl and 2-thienyl derivatives have been also obtained in good yields. The authors proposed a mechanism based on single-electron transfer (SET) involving a ArS-Cu^{III}(OAc)P(O) species.



Scheme 19. Cu-catalyzed phosphite/sulfonyl chloride cross-coupling.

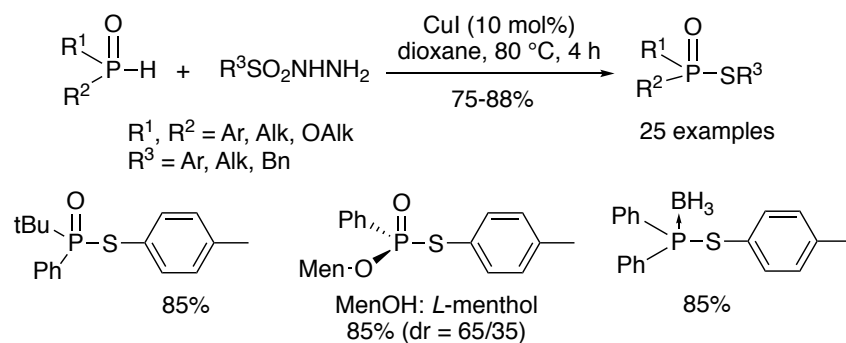
An improved procedure for the Cu(II)-catalyzed coupling of sulfonyl chloride with P(O)-H was recently described (Scheme 20).[29] L-proline was used as the ligand of choice, which allowed a smaller catalyst loading and also expanded the substrate scope, in particular the sulfur-partner. Moreover, the Cu^{II}(proline)₂ catalyst complex can be prepared in gram-scale, is easy to handle, and could be recovered and reused up to ten runs.



Scheme 20. Cu(II)/proline-catalyzed phosphite/sulfonyl chloride cross-coupling.

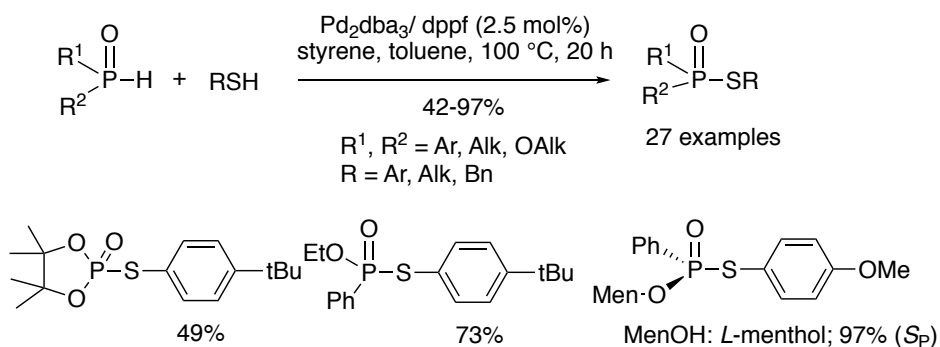
Sulfonyl hydrazides have also been used as a thiol surrogate in the copper-catalyzed P-S cross-coupling with various phosphorous P-H partners (phosphites, phosphinites, phosphine oxides, phosphine boranes).[30] The optimized reaction conditions were the following: copper iodide as the catalyst, in 1,4-dioxane, at 80 °C, in air (Scheme 21). The presence of a base was not necessary, whereas the use of a Boc-protected hydrazide function

inhibited the reaction. In this case not only variously substituted S-aryl phosphorothioates have been obtained, but also S-alkyl and S-benzyl derivatives were accessible in good yields. In the case of the use of a P-stereogenic enantiopure substrate, the P-configuration was not preserved during the transformation.



Scheme 21. Cu-catalyzed phosphite/sulfonyl hydrazide cross-coupling.

A general access to a large variety of phosphorothioates consist in the Pd-catalyzed dehydrogenative phosphorylation of thiols (Scheme 22).[31] Both aromatic and aliphatic thiols coupled with three kinds of P(O)H compounds: phosphites (including cyclic derivatives), phosphinates, and secondary phosphine oxides. Electron-rich and electron-deficient thiophenols with various functional groups worked efficiently. Notably, this catalytic process allowed access to P-chiral phosphorothioates, the reaction occurring with retention of configuration at phosphorus.

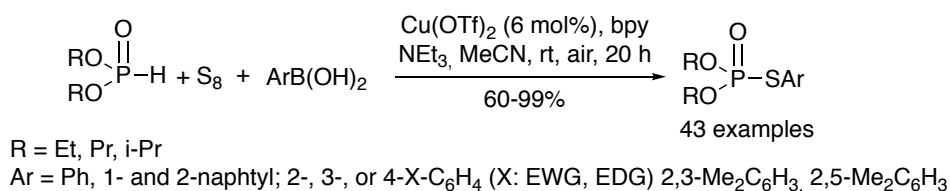


Scheme 22. Pd-catalyzed phosphite/thiol cross-coupling.

A publication mentioned the palladium-catalyzed formation of an S-aryl phosphorothioate from a phosphite and a sodium arylsulfinate, in the presence of silver acetate.[32] The product was in this case undesired, as the expected reaction was the desulfitative C-P coupling leading to the aryl phosphonate.

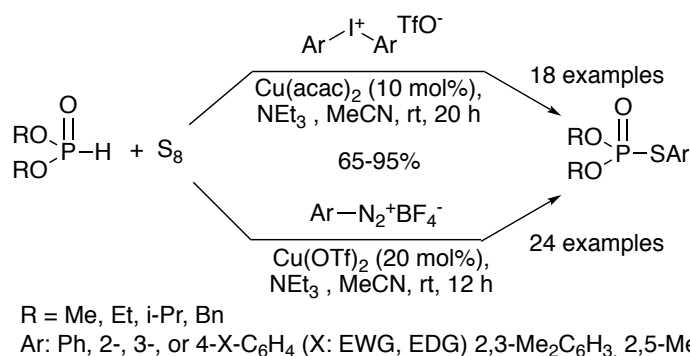
2.4.2. Metal-catalyzed three-component reactions

A highly efficient three-component copper-catalyzed reaction has been developed to access S-aryl phosphorothioates from phosphites, elemental sulfur, and aryl boronic acids (Scheme 23).[33] A broad variety of functionalized boronic acids have been used successfully, including electron rich and deficient aromatics, as well as sterically hindered substrates such as 2,6-dimethyl phenylboronic acid. The authors showed that diethyl phosphite and octasulfur react first in the presence of triethylamine to give the phosphorothioic acid ammonium salt, which then reacts with the phenylboronic acid under Chan-Evans-Lam copper-catalyzed conditions to give S-phenyl phosphorothioate.



Scheme 23. Cu-catalyzed three-component reaction of phosphite, sulfur, and boronic acid

Another three-component copper-catalyzed ligand-free reaction has been developed to access S-aryl phosphorothioates from phosphites, sulfur powder, and diaryliodonium or aryl diazonium salts (Scheme 24).[34] The aryl coupling partners can be readily prepared from simple corresponding arene precursors, aryl iodides or aromatic amines. The method covers a broad scope of substrates. When diphenylphosphine oxide was used instead dialkyl phosphite, a yield of only 22% was obtained.



Scheme 24. Cu-catalyzed three-component reaction of phosphite, sulfur, and diaryliodonium or diazonium salt.

A Fe₃O₄-functionalized Cu-BTC (H₃BTC = 1,3,5-benzenetricarboxylic acid) was prepared and used as a heterogeneous catalyst in the synthesis of S-aryl phosphorothioates (Scheme 25).[35] The catalyst could be magnetically recovered and reused without significant loss of its activity after six cycles. The reaction involves three components: aniline, phosphite, and elemental sulfur. Aryl diazonium salt is generated *in situ* from aniline in the presence of tBuONO and MeSO₃H, then reacted with the phosphite and the sulfur powder under copper-catalysis. A large variety of substrates have been successfully used, including electron-rich and -deficient aryl amines, and various phosphites. Moreover, gram-scale synthesis was performed with high yield (82%), which provides the possibility to apply this method in practical scale-up synthesis.

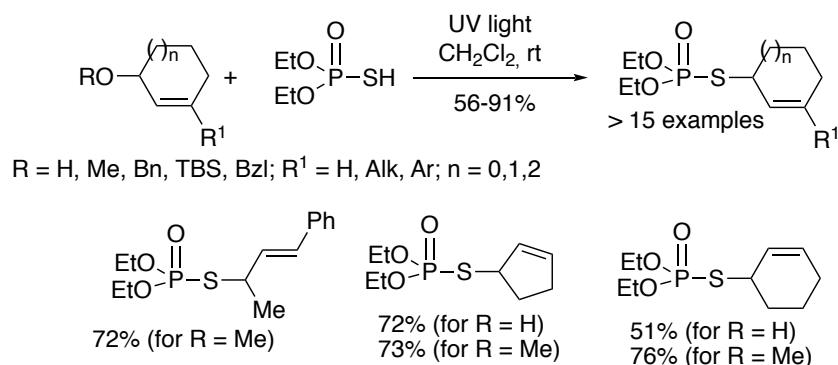


Scheme 25. Three-component reaction catalyzed by a Cu-composite of phosphite, aniline, and sulfur.

2.5. From phosphorothioic acids or their salts

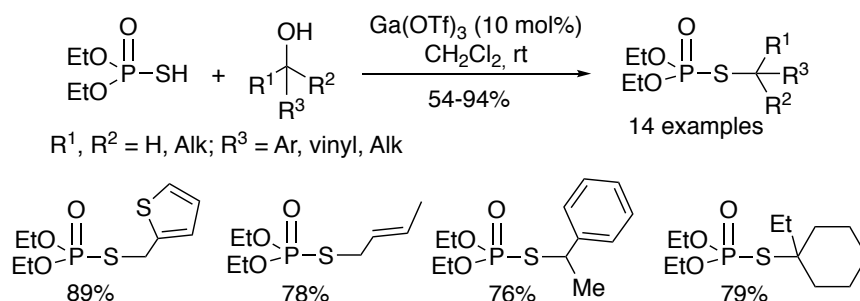
2.5.1. By *S*-alkylation

Wu and coworkers reported a transition-metal-free synthetic method to access phosphorothioate esters from allylic alcohols or their ethers and phosphorothioic acids (Scheme 26).[36] The reaction was performed under photochemical conditions (UV light). A wide range of acyclic and cyclic substituted allylic alcohols and methyl ethers have been used with good results. The reaction scope was then expanded to involve alcohols protected with groups such as benzyl, *tert*-butyldimethylsilyl (TBS), and benzoyl ethers (Bzl). To determine the reaction stereospecificity, one experiment was carried out using an enantioenriched (53% ee) allylic ether. A nearly racemic (< 10% ee) phosphorothioate ester was obtained. The authors explained this result by postulating intermediates such as allylic carbocations and/or allylic radicals generated from the photochemical cleavage of the C-S bond of the product.



Scheme 26. Photochemical-promoted reaction of alcohols/ethers with phosphorothioic acid.

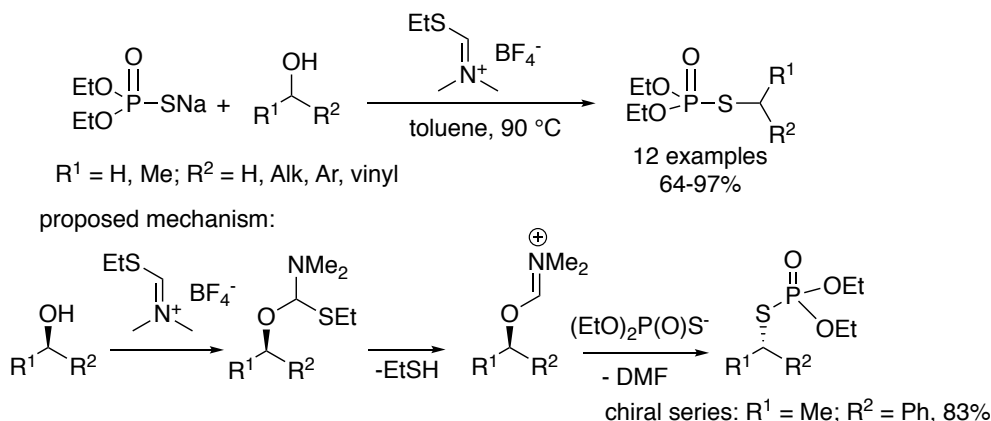
The same research group reported the direct substitution of various alcohols with *O,O*-diethyl phosphorothioic acid, catalyzed by $\text{Ga}(\text{OTf})_3$ as an inexpensive, hydrolytically stable Lewis acid (Scheme 27).[37] A wide range of primary and secondary alcohols has been successfully used, however only in benzylic or allylic series. The method was applicable for tertiary alcohols bearing alkyl substituents. When the reaction was done on the enantiopure (*S*)- α -methylbenzyl alcohol the expected phosphorothioate was isolated in nearly racemic form (8% ee).



Scheme 27. $\text{Ga}(\text{OTf})_3$ -catalyzed reaction of phosphorothioic acid with alcohols.

Porter and coworkers used the thioiminium salt prepared from *N,N*-dimethylthioformamide and Meerwein's salt as the coupling agent for the direct conversion of primary and secondary alcohols to the corresponding phosphorothioic esters by reaction with sodium phosphorothioate (Scheme 28).[38] Alternatively, the reaction can be performed with phosphorothioic acid in the presence of imidazole, under vigorous stirring. The mechanism proposed by the authors consists in the nucleophilic addition of the alcohol to the thioiminium salt with loss of ethanethiolate, then nucleophilic displacement of dimethylformamide (DMF) by the phosphorothioate salt to

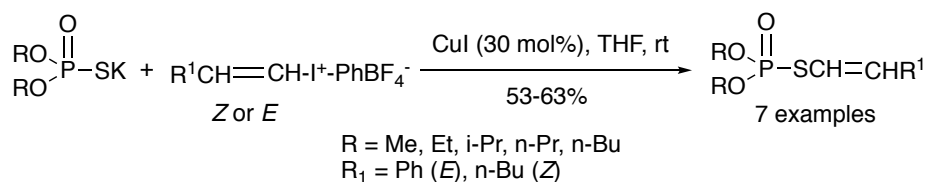
afford the phosphorothioic ester. Both of primary and secondary alcohols were converted to the corresponding phosphorothioates in good yields. (*E*)-Cinnamyl alcohol could be converted to the desired product, without allylic rearrangement. The stereochemical course of the reaction was studied by using (*S*)- α -methylbenzyl alcohol. The corresponding phosphorothioate was obtained with inversion of configuration.



Scheme 28. Ga(OTf)₃-catalyzed Conversion of alcohols to phosphorothioates using a thioiminium coupling agent.

2.5.2. By metal-mediated C-S bond formation

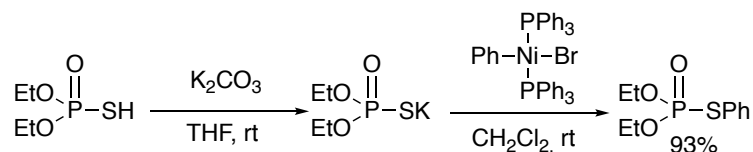
Some publications described metal-catalyzed reactions consisting in the direct C-S coupling between a phosphorothioate salt and an aryl or vinyl partner. S-vinyl phosphorothioates have been prepared in good yields, under mild reaction conditions, from potassium phosphorothioate and vinyl(phenyl) iodonium salts, under copper-catalysis (Scheme 29).[39] The process occurred with retention of the double bond geometry.



Scheme 29. Cu-catalyzed C-S coupling of phosphorothioate salts and hypervalent iodine.

In one publication the phosphorothioate disulfide species was involved in C-S Ni- or Pd-catalyzed reactions with aryl halides to afford S-aryl phosphorothioates.[40] For the mechanistic study, potassium phosphorothioate

was reacted with the nickel(II)-complex obtained from bromobenzene in the presence of triphenylphosphine ligand, affording S-phenyl phosphorothioate in good yield (Scheme 30).



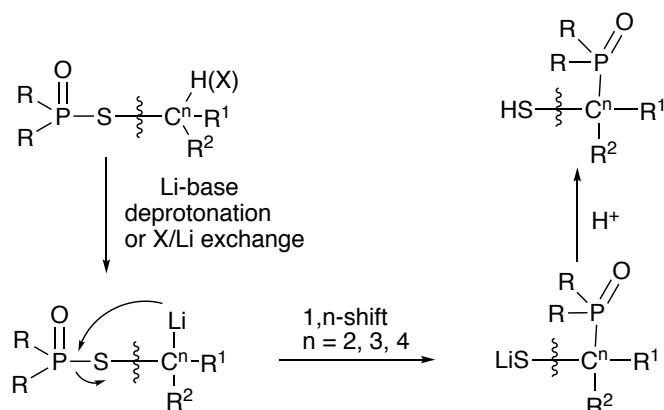
Scheme 30. Ni-mediated C-S coupling of phosphorothioate salts.

3. REACTIONS OF PHOSPHOROTHIOIC ESTERS

Specific reactivities of phosphorothioates are based on the ionic, radical, or metal-mediated cleavage of the P-S bond. In processes involving an anionic P-S cleavage that include the rearrangement reactions, the nucleophilic attack of a lithium carbanion or of an alkoxide, takes place on the phosphorus atom, with releasing of a thiolate. In the case of a homolytic P-S cleavage, the radical species attacks the sulfur atom, with releasing of a P-centered radical. The metal-mediated P-S cleavage was less studied and probably involves an S-M-P(O) intermediate (M = Pd, Pt). Phosphorothioate was also used as a living group in allylic substitutions with carbon-nucleophiles (Grignard reagents) and fluorine nucleophiles, and the differences and benefits in comparison with other leaving groups (i.e. chloride, carbonate) were demonstrated.

3.1. Rearrangement reactions

The different types of anionic rearrangements described below consist in the migration of the electrophilic phosphorus from the sulfur-atom to the carbanion generated in the 2-, 3-, or 4- position of the sulfur by treatment with a lithium-base (*via* deprotonation or halogen/lithium exchange), with release of the thiolate function that can be trapped by protonation or alkylation to afford the corresponding P,S-difunctionalized products (Scheme 31).[41] Several of the obtained compounds have shown interesting metal-chelating properties due to both P and S functionalities, and have been used in the synthesis of metal complexes such as platinum complexes[42],[43],[44] (Figure 2) or as enzymes inhibitors (metallo-enzymes) that are based on Zn-chelation.[45]



Scheme 31. General reaction for the anionic rearrangement of phosphorothioate into mercaptophosphonate.

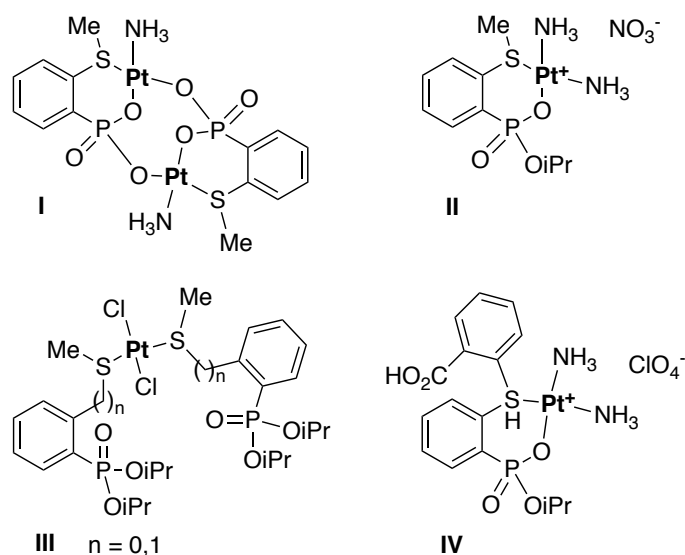
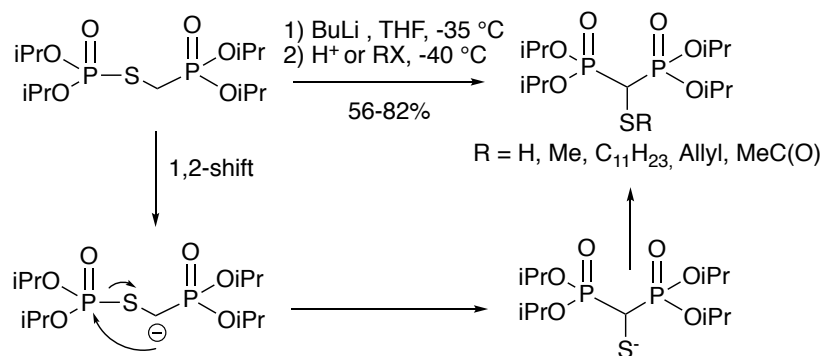


Figure 2. Examples of Pt-complexes with difunctionalized P,S-compounds obtained via anionic P-S to P-C rearrangement.

3.1.1. Anionic 1,2-rearrangement

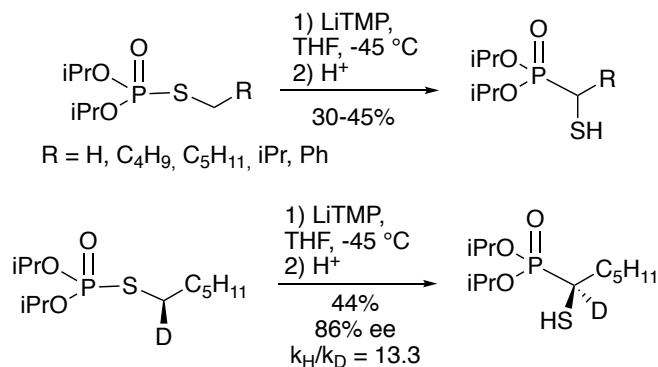
While the rearrangement of the hydroxymethylene bis(phosphonate) into the corresponding phosphonomethyl phosphate occurring in basic media is the favored process in the oxygen series, the reverse rearrangement, S-phosphonomethyl phosphorothioate into the α -thiolato bis(phosphonate), has been described in the sulfur series (Scheme 32).[46] The 1,2-shift occurred at -35 °C from the carbanion generated by deprotonation of the S-phosphonomethyl phosphorothioate by BuLi. The thiolate can readily loose

sulfur at higher temperature leading to the methylene bis(phosphonate) carbanion, however the corresponding thiol and various sulfides have been prepared by rapid protonation or addition of alkylating agents at $-40\text{ }^{\circ}\text{C}$.



Scheme 32. Phosphorothioate-mercaptophosphonate rearrangement.

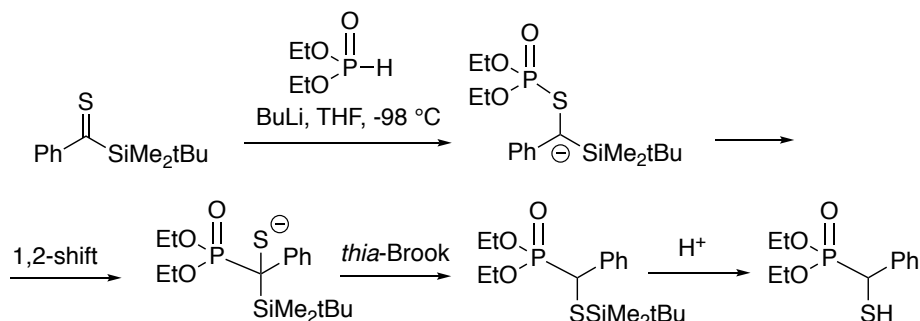
After several years, the rearrangement of *S*-alkyl *O,O*-dialkyl phosphorothioates to α -mercaptophosphonates and its mechanism have been studied.[47] The *S*-benzyl phosphorothioate was metallated α to the *S*-atom at low temperature by trityllithium and LiTMP (lithium 2,2,6,6-tetramethylpiperidide) to give a stabilized carbanion, which rearranged to α -mercaptophosphonate in 45% yield (Scheme 33). The mechanistic study using the chiral enantiopure substrate monodeuterated in α -position to the *S*-atom, showed that the 1,2-migration proceeds with retention of configuration.



Scheme 33. Phosphorothioate-mercaptophosphonate rearrangement.

Another method to generate the carbanion in α -position to the *S*-atom, consisted in the thiophilic attack of silyl thioketones with lithium diethylphosphite.[48] Then, the reaction proceeded in the phosphorothioate to mercaptophosphonate rearrangement followed by the migration of the silyl

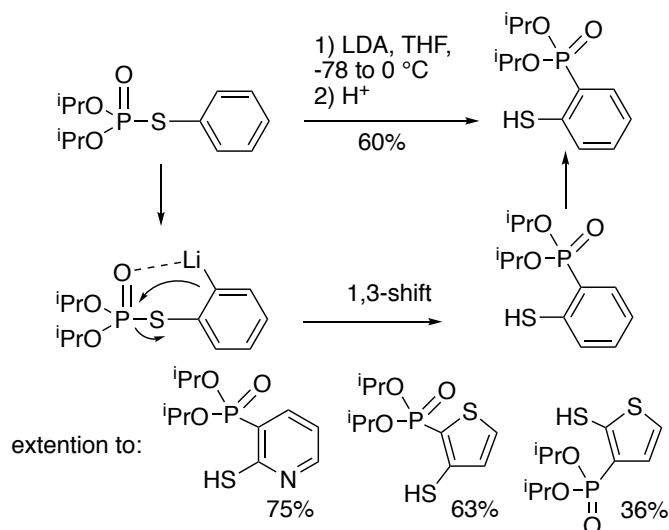
group from the carbon to the sulfur atom (thia-Brook rearrangement), leading to the S-silylated sulfanylphosphonate carbanion (Scheme 34).



Scheme 34. Phosphorothioate-mercaptoposphonate/thia-Brook rearrangements.

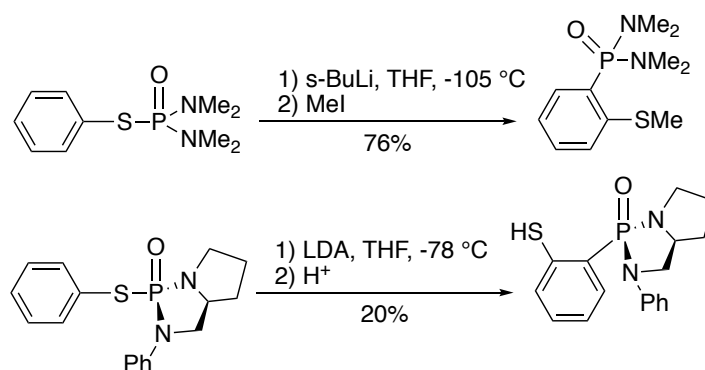
3.1.2. Anionic 1,3-rearrangement

The P-S to P-C 1,3-rearrangement of aryl or heteroaryl (such as pyridyl and thienyl) phosphorothioates into ortho-sulfanyl (hetero)aryl phosphonates has been developed by Masson and co-workers.[49] For the success of this anionic rearrangement which takes place after ortho-lithiation, it was necessary to use bulky isopropoxy groups on the phosphorus atom, as this prevents direct nucleophilic attack of the base at the P-atom (Scheme 35).



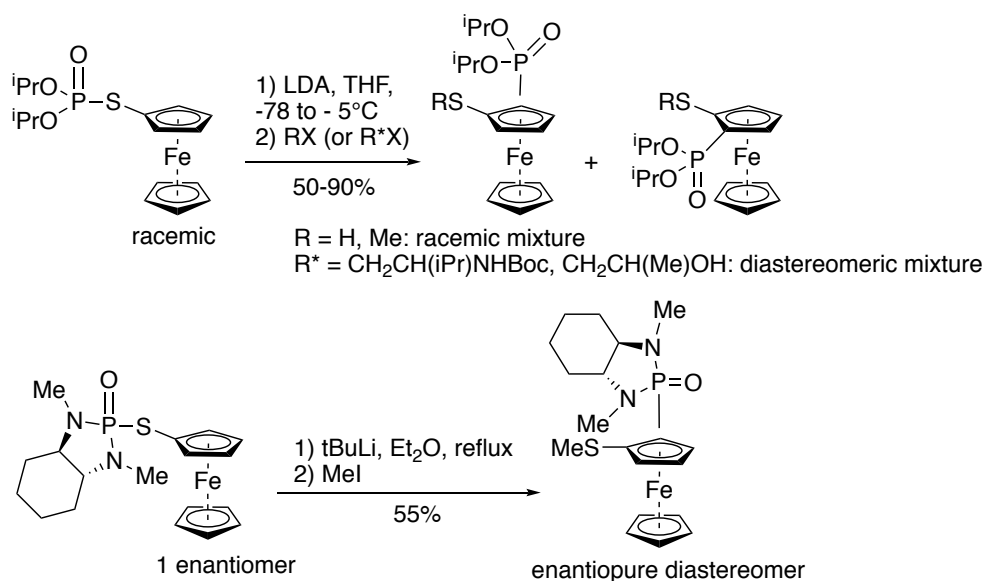
Scheme 35. 1,3-Rearrangement of phosphorothioate into mercaptophosphonate

The same type of rearrangement has also been studied in phosphoramidate series (Scheme 36). By treatment of the substrate with *sec*-BuLi and subsequent methylation of the thiolate resulted after the P-S to P-C shift, the corresponding 2-methylsulfanyl phenylphosphoramidate was obtained.[50] In an asymmetric version, starting from the chiral substrate derived from (*S*)-(+)-2-(anilinomethyl)-pyrrolidine, the ortho-lithiation by LDA, followed by 1,3-rearrangement and protonation, led to the expected thiophenol derivative in low yield (20%).[51]



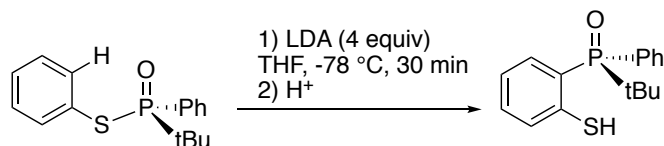
Scheme 36. 1,3-Rearrangement in phosphoramidate series.

The rearrangement has been extended by Bonini et al.[52] in ferrocenyl phosphorothioate series and the resulting thiolate was trapped by protonation or methylation to give a racemic mixture of products (Scheme 37). When the thiolate was tosylated with a chiral aminoalcohol derivative, or was used as the nucleophile for the ring-opening of a chiral epoxide, a mixture of separable diastereomers was obtained. An asymmetric version using a chiral phosphoramidate enabled access to enantiomerically pure planar ferrocenyl derivatives. In this case the rearrangement required the use of *t*BuLi in refluxing ether.



Scheme 37. 1,3-Rearrangement in ferrocenyl series.

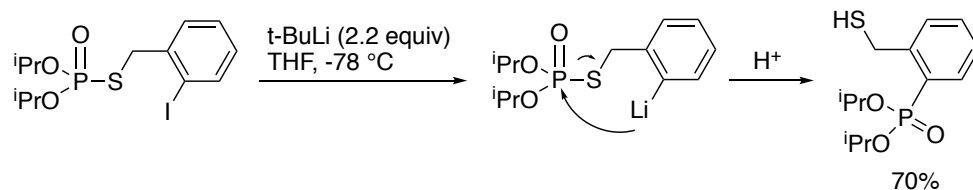
The migration of the phosphinyl group from the sulfur to the carbon atom has also been extended to P-stereogenic phosphinothioate, leading stereoselectively to the corresponding ortho-mercaptophenyl phenyl-tert-butyl phosphine oxide, with retention of configuration at phosphorus (Scheme 38).[53]



Scheme 38. Phenyl phosphinothioate to 2-mercaptophenyl phosphine oxide rearrangement.

3.1.3. Anionic 1,4-rearrangement

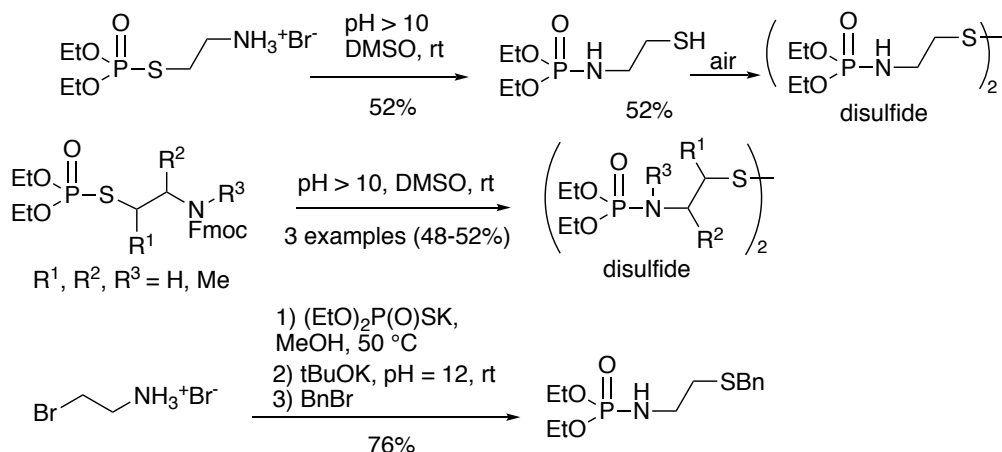
The 1,4-sigmatropic rearrangement was used to transform *S*-(2-iodobenzyl) *O,O*-dialkyl phosphorothioate into the corresponding 2-(sulfanylmethyl)phenylphosphonate.[44] The iodide-lithium exchange by reacting the iodoaryl precursor with tert-butyllithium is followed by the 1,4-migration of the phosphoryl group from the sulfur atom to the carbanion of the aromatic ring (Scheme 39). At the end of the reaction, the acidic hydrolysis of the sulfanyl led to the benzylic thiol derivative in 70% yield. This example of 1,4 P-S to P-C shift appears to be the only one of this type.



Scheme 39. 1,4-Rearrangement of phosphorothioate into mercaptophosphonate

3.1.4. Thiophosphate to phosphoramidate rearrangement

The rearrangement of *S*-(2-aminoethyl) phosphorothioates to *N*-(2-mercaptoethyl) phosphoramidates has been studied by Gothelf and co-workers (Scheme 40).[54] The transformation took place at room temperature, under basic conditions and the resulting thiols were rapidly oxidized into the corresponding disulfides. Alternatively, in a *one-pot* procedure starting from 2-bromoethylamine hydrobromide and potassium phosphorothioate, the thiol resulting from the P-S to P-N rearrangement has been subsequently *S*-benzylated.

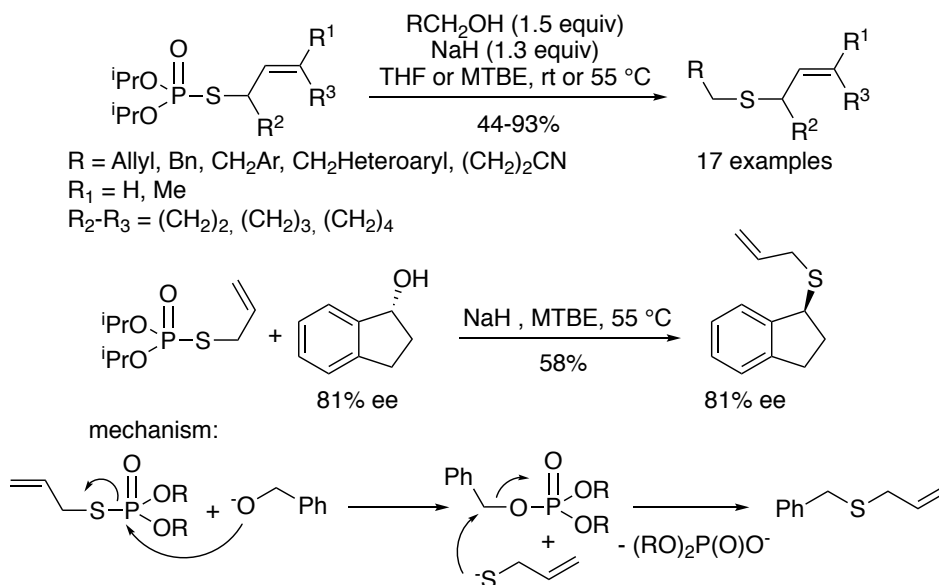


Scheme 40. Phosphorothioate to phosphoramidate rearrangement.

3.2. Anionic P-S bond cleavage with C-S bond formation

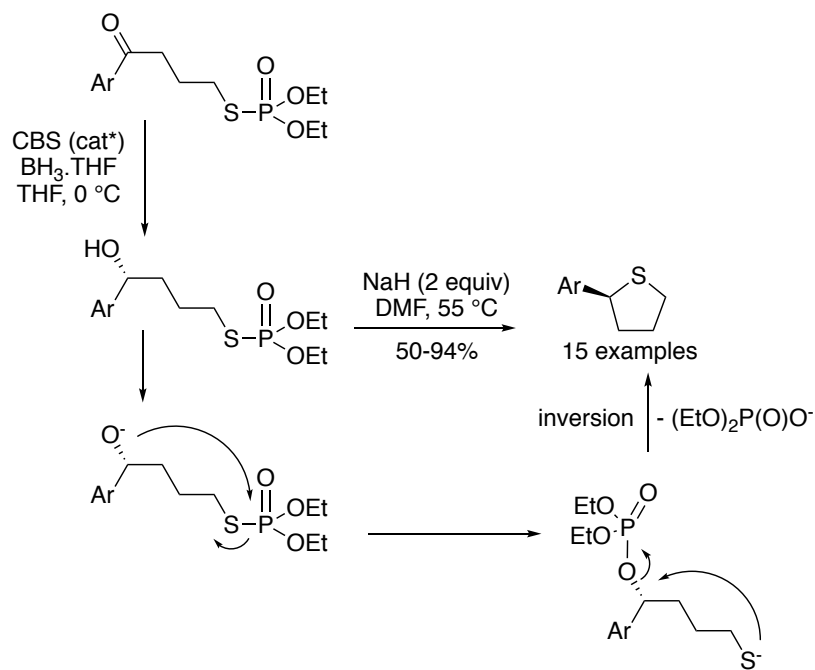
Wu and Robertson developed a methodology to access sulfides (thioethers) by using the phosphorothioic acid as a safer and odorless surrogate for H_2S . First they described the synthesis of allylic sulfides starting from the corresponding phosphorothioic esters and alcohols (Scheme 41). The reaction occurred *via* a double substitution process: the attack of the alkoxide to the P-atom of the corresponding acyclic or cyclic allylic phosphorothioate with release of the thiolate and subsequent displacement by this latter of the phosphate group.

Mainly allylic and benzylic alcohols have been used, and various functional groups were tolerated. It was demonstrated that the reaction is stereospecific leading to enantioenriched sulfides from the corresponding chiral secondary alcohols.[55]



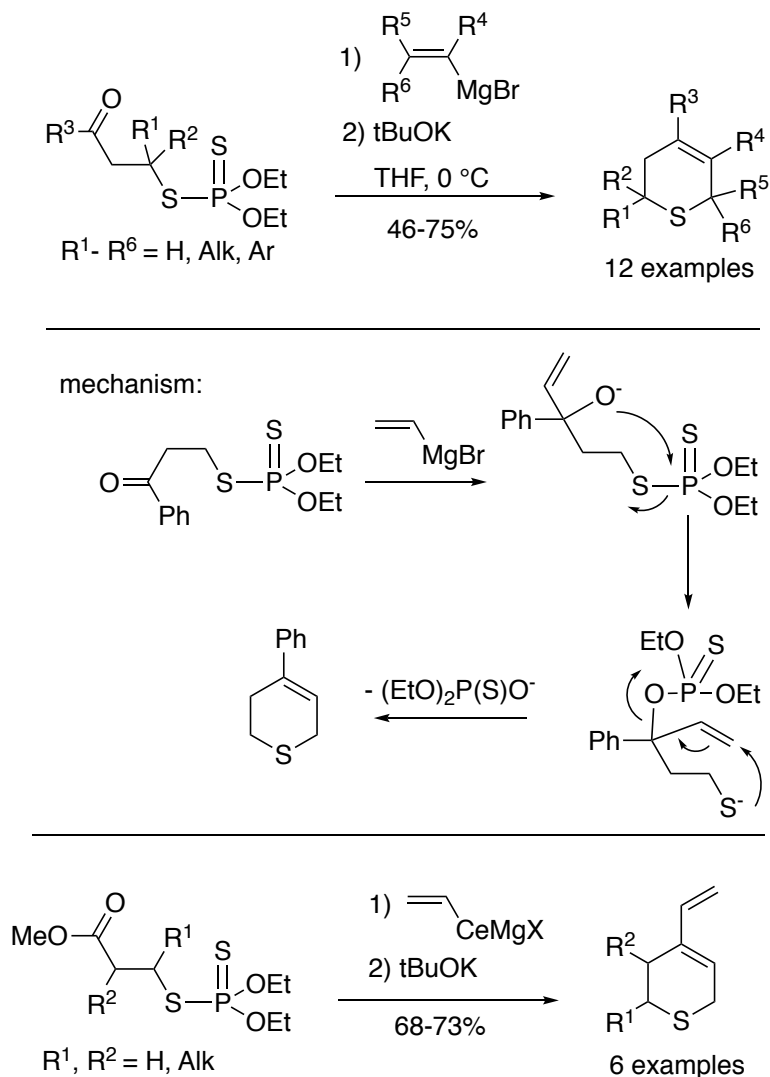
Scheme 41. Synthesis of allylic sulfides from phosphorothioates and alcohols.

An intramolecular version has been then reported by the same authors starting from γ -thiophosphoryl ketones and enabled the synthesis of enantioenriched 2-substituted tetrahydrothiophenes (thiolanes) (Scheme 42).[56] The transformation consists in the asymmetric CBS reduction of the ketone into the enantioenriched alcohol of which alkoxide attacks in intramolecular on the phosphorus center releasing the thiolate. Then, the intramolecular substitution ($\text{S}_{\text{N}}2$ -type) of the phosphate by the thiolate led to the five-membered sulfur-heterocycle. The method was extended to the synthesis of a chiral thietane (four-membered thiacycle).



Scheme 42. Synthesis of chiral thiolanes from phosphorothioates.

Njardarson and co-workers reported a nice anionic cascade consisting in the: (1) addition of a vinyl Grignard reagent to a carbonyl ketone substituted in β -position with a dithiophosphoryl group, (2) attack of the formed alkoxide to the P-atom with release of the thiolate, (3) 6-*endo*-trig cyclization by addition of the S-nucleophile to the double bond of the vinyl group with elimination of the thiophosphate group.[57] The overall process led to the formation of the thiopyran ring (Scheme 43). Depending on the substrates and on the reaction conditions the 4-*exo* cyclization can also occur, leading to the corresponding 4-membered thietanes. By using a carboxylic ester instead the ketone and a vinyl cerium reagent, 4-vinyl thiopyran products have been obtained.

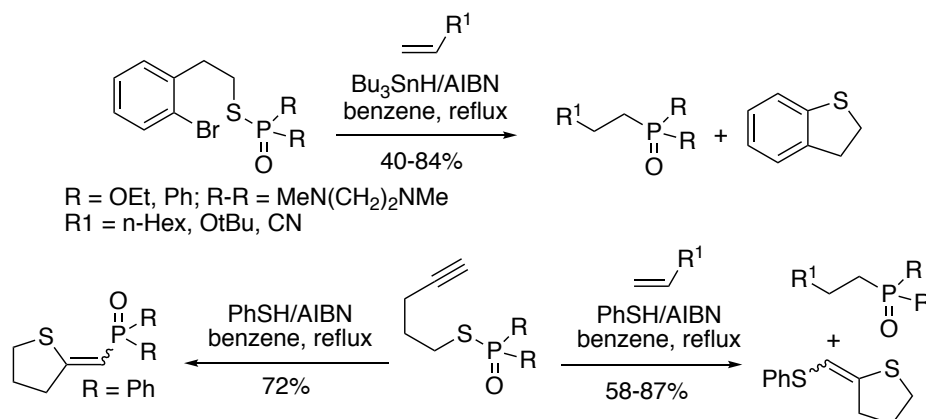


Scheme 43. Synthesis thiopyrans from phosphorodithioates *via* an anionic cascade.

3.3. Homolytic P-S cleavage

Fensterbank, Lacôte, Malacria and co-workers employed phosphorothioate bromobenzene substrates to generate a phosphorus-centered radical *via* a homolytic substitution at the sulfur atom (Scheme 44).[58],[59] The P-radical was trapped *in-situ* by an olefin to give the desired phosphorylated adduct and the dihydrobenzothiophene as the by-product. Phosphonyl, phosphinoyl and diaminothiophonyl radicals have been successfully produced and reacted with both rich and poor double bonds. A tin-free version was then proposed starting from a phosphorothioate linked to a terminal alkyne. In this case the reaction

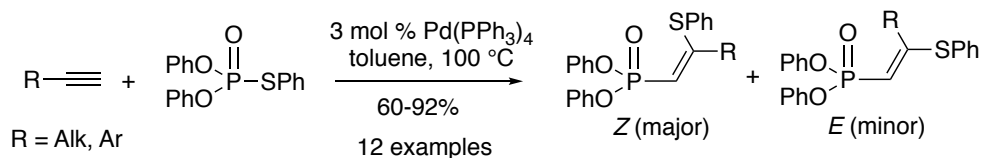
is initiated by a thiyl radical (from thiophenol) in the presence of the olefin, and sulfanylated thiolane is obtained together with the P-adduct. If the substrate is placed in the same reactions conditions without the olefin, a phosphorylated sulfur-heterocycle is obtained as the product of the radical thiophosphinylation of triple bond.



Scheme 44. Domino radical process *via* homolytic P-S cleavage.

3.4. Metal-catalyzed P-S cleavage; Thiophosphorylation of triple bonds

Han and Tanaka reported the Pd-catalyzed thiophosphorylation of terminal alkynes.[60] The 1-phosphonylated 2-sulfanylated alkenes were obtained with good yields (Scheme 45). Functionalized aliphatic alkynes led to excellent results in terms of stereoselectivity (major *Z*) and regioselectivity, whereas arylacetylene gave a mixture of *Z/E* isomers. Internal alkenes were unreactive. The authors proposed a mechanism involving Pd-insertion in the P-S bond with formation of [S-Pd-P] species.

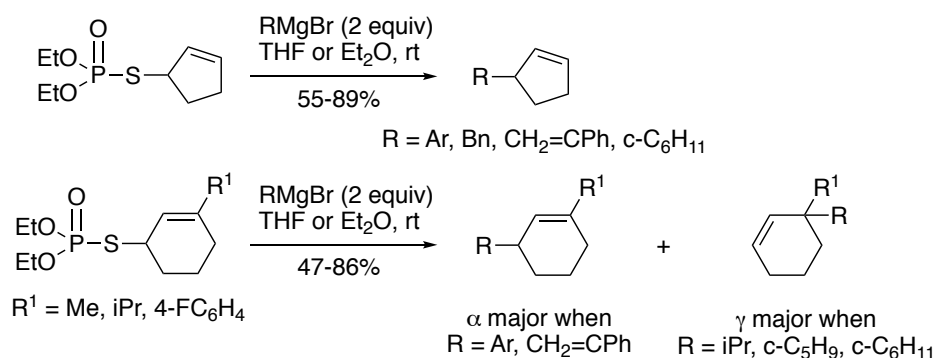


Scheme 45. Pd-catalyzed thiophosphorylation of terminal alkynes.

3.5. Allylic substitution of phosphorothioate group

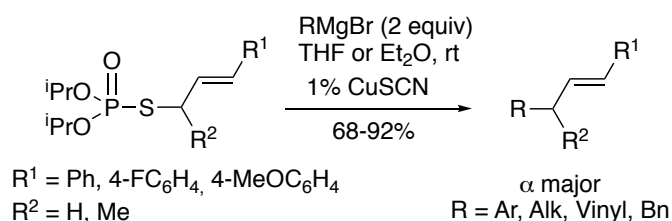
Wu and coworkers developed metal-free or metal-catalyzed allylic substitution reactions, which employ a phosphorothioate as the leaving group.

The first example consisted in the transition-metal-free allylic substitution reaction between Grignard reagents as carbon-nucleophiles and allylic phosphorothioate esters (Scheme 46).[36] The reaction worked with various aryl Grignard reagents with both electron-withdrawing and donating groups, with vinyl derivatives, as well as with both primary and secondary alkyl Grignard reagents. As in principle the reaction can lead to two regioisomers, it was demonstrated by the authors that the use of aromatic and alkenyl nucleophiles led to the α -regioisomer, whereas the use of secondary aliphatic ones resulted in the favored opposite γ -regioselectivity. These regioselectivities have been partially rationalized by a radical-based mechanism in the case of aliphatic Grignard reagents and an ionic mechanism in the case of aromatic counterparts.



Scheme 46. Metal-free allylic substitution with Grignard reagents.

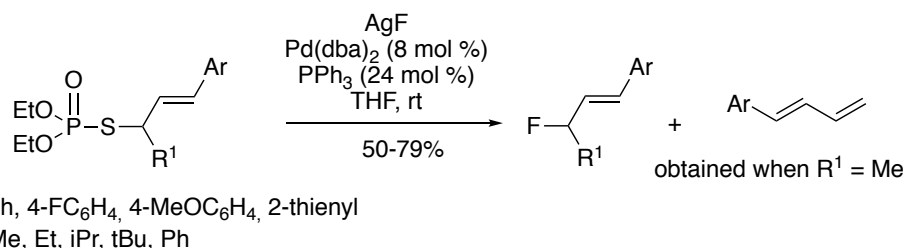
Then, a version using Cu(I)-catalyzed allylic substitution of secondary and primary phosphorothioates with Grignard reagents was reported (Scheme 47).[61] The reaction is highly α -regioselective. The authors compared the phosphorothioate with other leaving groups such chloride or pivalate and obtained a better yield and a higher regioselectivity with the phosphorothioate.



Scheme 47. Cu-catalyzed allylic substitution with Grignard reagents.

The same research group reported the regioselective, palladium-catalyzed allylic fluorination of phosphorothioates with silver fluoride (Scheme 48).[62] The method is efficient compared to other ones used to introduce fluorine in

allylic position, by reducing the undesired diene formation, which is obtained in this case as a minor product. When R¹ = Me, the ratio allyl fluoride/diene in the crude mixture varied between 4:1 and 5:1. The mechanistic studies show that the process proceeds through a palladium π -allyl intermediate and is stereospecific, providing fluorinated products with retention of stereochemical configuration.



Scheme 48. Pd-catalyzed allylic fluorination.

CONCLUSION

The excellent contributions reported in this chapter clearly demonstrate the remarkable efforts and progress made in the past 20 years in the chemistry of phosphorothioates. Due to the development of elegant and efficient access to these species, as well as of diverse innovative and useful synthetic transformations, it is obvious that a larger scientific community will be attracted by this versatile functional group.

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CONFLICT OF INTEREST

The author confirms that he has no conflict of interest to declare for this publication.

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