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# Synthesis and Application of Phosphonothioates, Phosphonodithioates, Phosphorothioates, Phosphinothioates and Related Compounds.

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**Abstract:** Methods for the preparation of phosphonothioates, phosphonodithioates, phosphorothioates, phosphinothioates and related compounds are reviewed. The application of these compounds as synthetic intermediates is also discussed.

**Keywords:** Phosphonothioates; Phosphonodithioates; Phosphorothioates; Phosphinothioates.

## 1. Introduction

The aim of this literature review is to highlight methods for the preparation of phosphonothioates, phosphorothioates, phosphinothioates, phosphonodithioates and related compounds with a particular focus on the construction of S-C bonds. The application of these compounds as synthetic intermediates will also be discussed.

Organophosphorus compounds are particularly important in agrochemicals, where a significant number of pesticides contain phosphorus-sulfur bonds e.g. in the protection of sugar cane from fungal pathogens.[1-6] More recently, medicinal chemistry studies have identified compounds containing the phosphorus-sulfur bond as potential anti-cancer agents,[7] antivirals,[8] cardioprotective therapeutics[9] and acetylcholine esterase inhibitors.[10, 11] The phosphorus-sulfur bond is also found in chemical warfare agents, such as the V-series of organophosphate compounds.[12, 13] Phosphorothioates are widely used in nucleoside chemistry owing to their enhanced *in vivo* and *in vitro* stability against nuclease enzymes[14-17] and their ability to act as labelling agents in metabolism studies.[18-25] Their application in materials chemistry has also been investigated.[26, 27] Zinc salts of dithiophosphonic acids are often employed as lubricants.[28] Tetrathiophosphoric acids and dithiophosphinic esters have been exploited as RAFT (Reversible Addition-Fragmentation Chain Transfer) reagents for controlled styrene polymerisation.[29, 30] Additionally, metal complexes of sulfur-containing organophosphorus compounds often display interesting spectroscopic properties.[31, 32]

The myriad of 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 pertinent organophosphorus functional groups is provided in Figure 1. Dialkyl phosphine oxides, phosphinates and phosphites exist in an prototropic equilibrium between two tautomers.[33] 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.

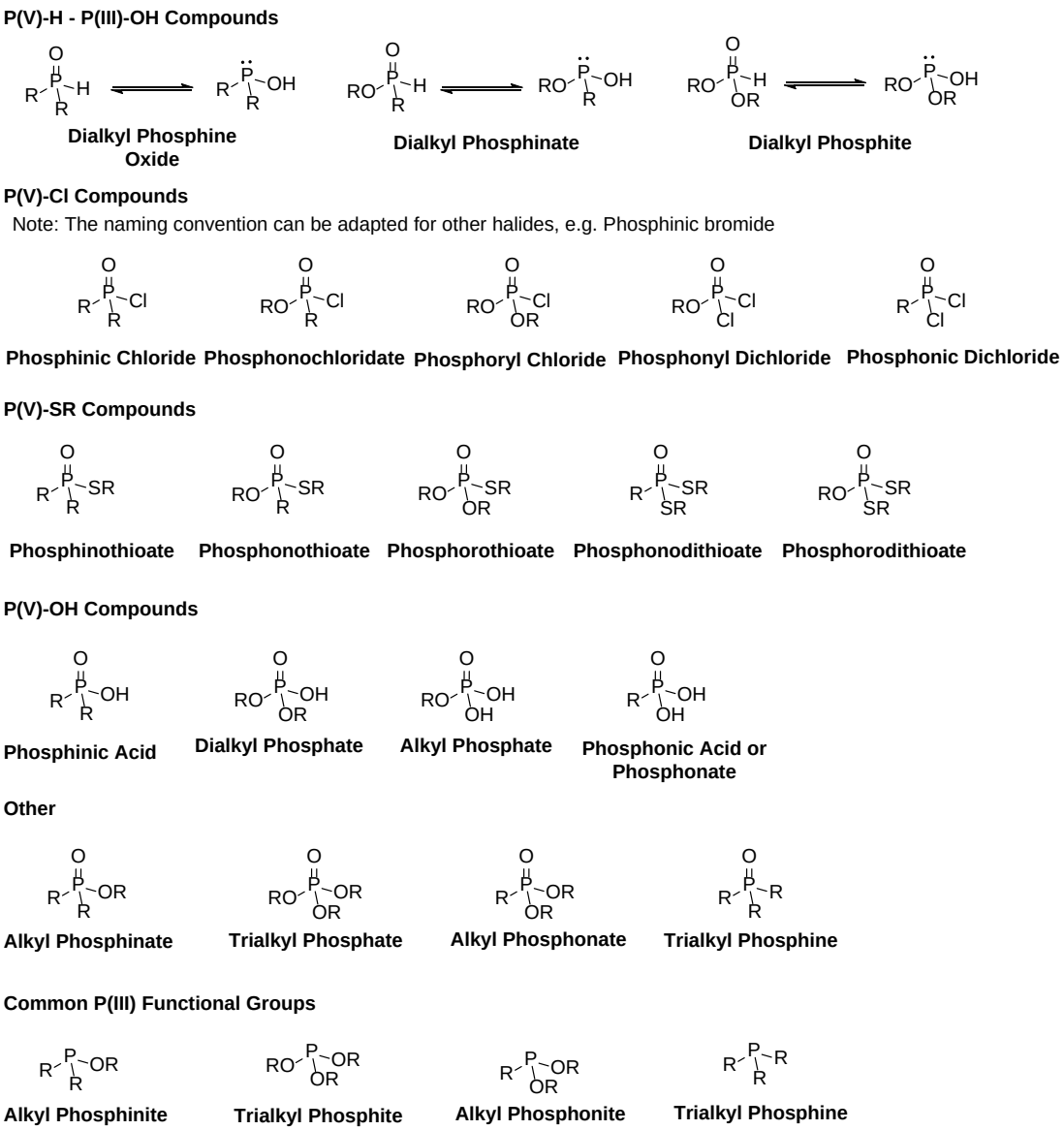



**Figure 1 – Nomenclature of organophosphorus functional groups.[#]**

[#]In general, when P=S, the prefix "Thio-" is appended to the name. i.e. thiophosphine oxide or thiophosphinic chloride. The designation "alkyl" may be replaced with "aryl" where appropriate.

## 2. Synthesis of phosphinothioates, phosphonothioates, phosphorothioates and phosphonodithioates

The initial focus of this digest will be on methods for the construction of the PS-C bond in phosphinothioates, phosphonothioates, phosphorothioates and phosphonodithioates. These reactions are summarised in Figure 2.

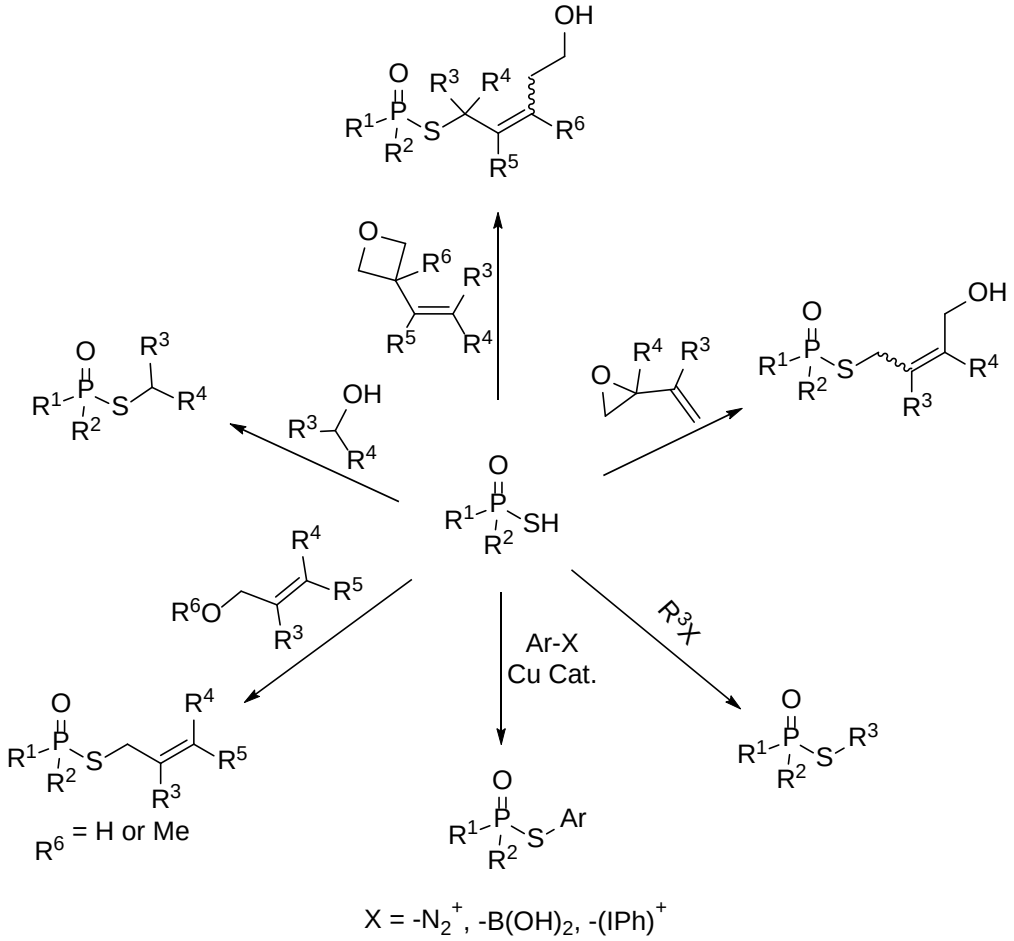
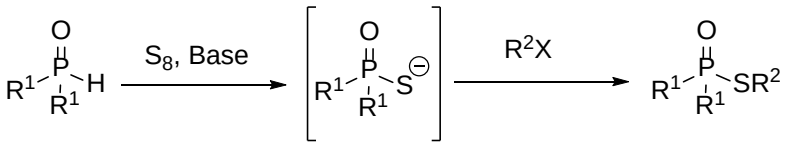



**Figure 2 – Methods for the preparation of phosphinothioates, phosphonothioates, phosphorothioates and phosphonodithioates.**

### 2.1. Alkylation by alkyl halides and alkyl tosylates

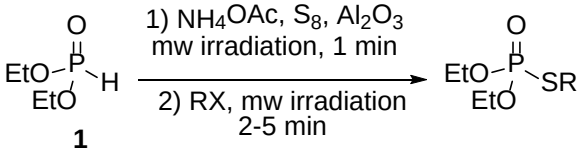
*P*(V)-thiolate anions, generated by treating *P*(V)-H compounds with elemental sulfur in the presence of base, are readily alkylated by alkyl halides (Scheme 1).




**Scheme 1**

Using ammonium acetate as a base, Kaboudin has employed this strategy to access a range of phosphorothioates in 75-90% yield (Table 1).[34] Conducting the reaction under microwave conditions facilitated shorter reaction times. Acidic alumina was used as a solid-support for the reaction, acting as a Lewis-acid catalyst.[35, 36] An initial screening of bases revealed that ammonium acetate was the only effective base in this reaction. No product was recovered when bases such as ammonium formate and ammonium hexafluorophosphate were used. Both alkyl chlorides and alkyl bromides may be employed as the alkylating agent. Kaboudin later adopted a similar approach in his synthesis of a range of potential choline esterase inhibitors.[10]

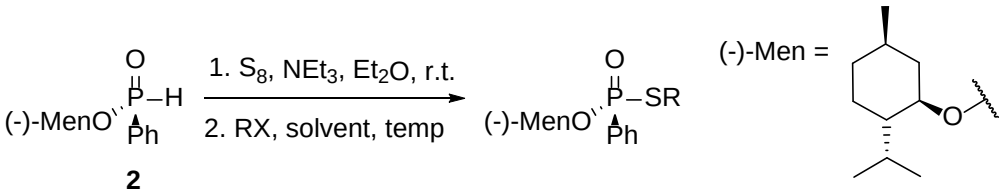
**Table 1 – Microwave-assisted sulfuration-alkylation**




| Entry | R | X | Yield |
|---|---|---|---|
| **1** | Bn | Br | 76% |
| **2** | Bn | Cl | 82% |
| **3** | $Ph_2CH$ | Br | 88% |
| **4** | $PhCH_2CH_2$ | Br | 75% |
| **5** | $4\text{-}NO_2C_6H_4CH_2$ | Br | 90% |
| **6** | $4\text{-}MeC_6H_4CH_2$ | Cl | 88% |
| **7** | $3\text{-}MeC_6H_4CH_2$ | Cl | 85% |
| **8** | $2\text{-}MeC_6H_4CH_2$ | Cl | 76% |
| **9** | $PhCH_2CH_2CH_2$ | Cl | 80% |

Wang *et al.* subsequently showed that when menthyl derivative **2** was subjected to similar conditions, the stereochemical configuration at the phosphorus was retained in the product (Table 2).[37] In the synthesis of the *S*-methyl substituted product (Table 2, entry 1) methyl iodide was used as the alkylating agent. In all other cases the corresponding alkyl bromides were used (Table 2, entries 2-7). Less reactive, sterically hindered alkyl halides required longer reaction times at elevated temperatures in order to drive the reaction to completion (Table 2, Entries 3-6).

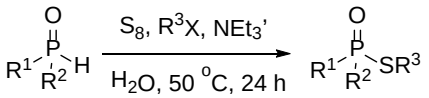
**Table 2 - Stereospecific synthesis of *P*-chiral phosphonothioates**




**2**

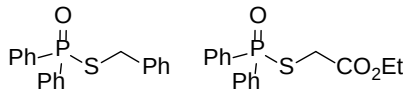
| Entry | R | Temp (°C) | Time (h) | Solvent | Yield |
|---|---|---|---|---|---|
| **1** | Me | r.t. | 2 | Diethyl Ether | 99% |
| **2** | Et | r.t. | 72 | Diethyl Ether | 99% |
| **3** | *i*-Pr | 50 | 120 | Neat | 93% |
| **4** | *sec*-Bu | 50 | 72 | Neat | 89% |
| **5** | Cyclohexyl | 50 | 72 | Neat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

Zhang demonstrated that the above transformations can also be conducted in water in comparable yields (Scheme 2).[38] In this instance, triethylamine was found to be the optimal base. The substrate scope was investigated by altering both the phosphorus-containing starting material as well as the electrophile. A variety of different leaving groups was used including bromide, chloride and tosylate. Phosphinothioates **3-5**, phosphorothioates **6-7** and phosphonothioates **8-11** were prepared *via* this methodology. In accordance with the earlier findings of Wang[37], the stereochemical configuration of enantiopure starting materials was conserved in the final products (**8** and **9**). While the yields for phosphinothioates and phosphonothioates were generally good to excellent, phosphorothioates **6** and **7** were isolated in poor yields of 11% and 6% respectively.




**Selected Examples:**

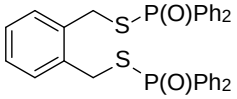
**Phosphinothioates:**



**3** 80%

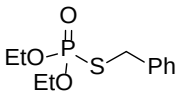


**4** 64%

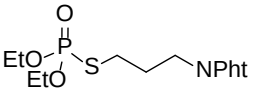


**5** 71%

**Phosphorothioates**

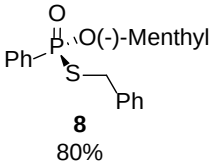


**6** 11%

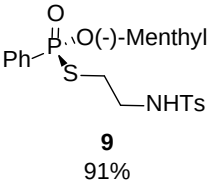


**7** 6%

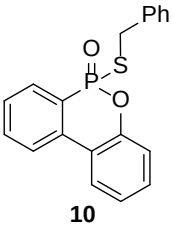
**Phosphonothioates:**



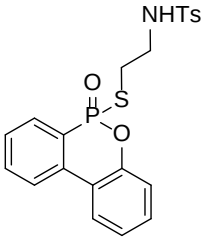
**8** 80%



**9** 91%



**10** 46%

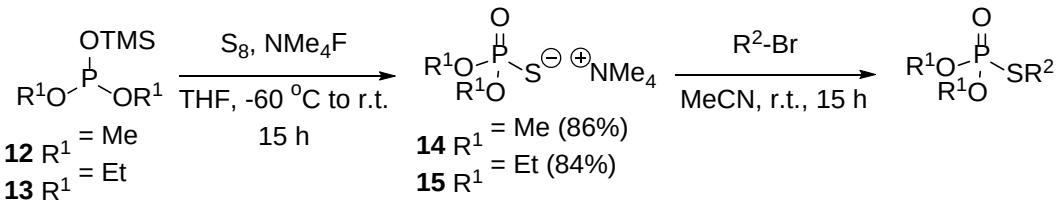


**11** 82%

**Scheme 2**

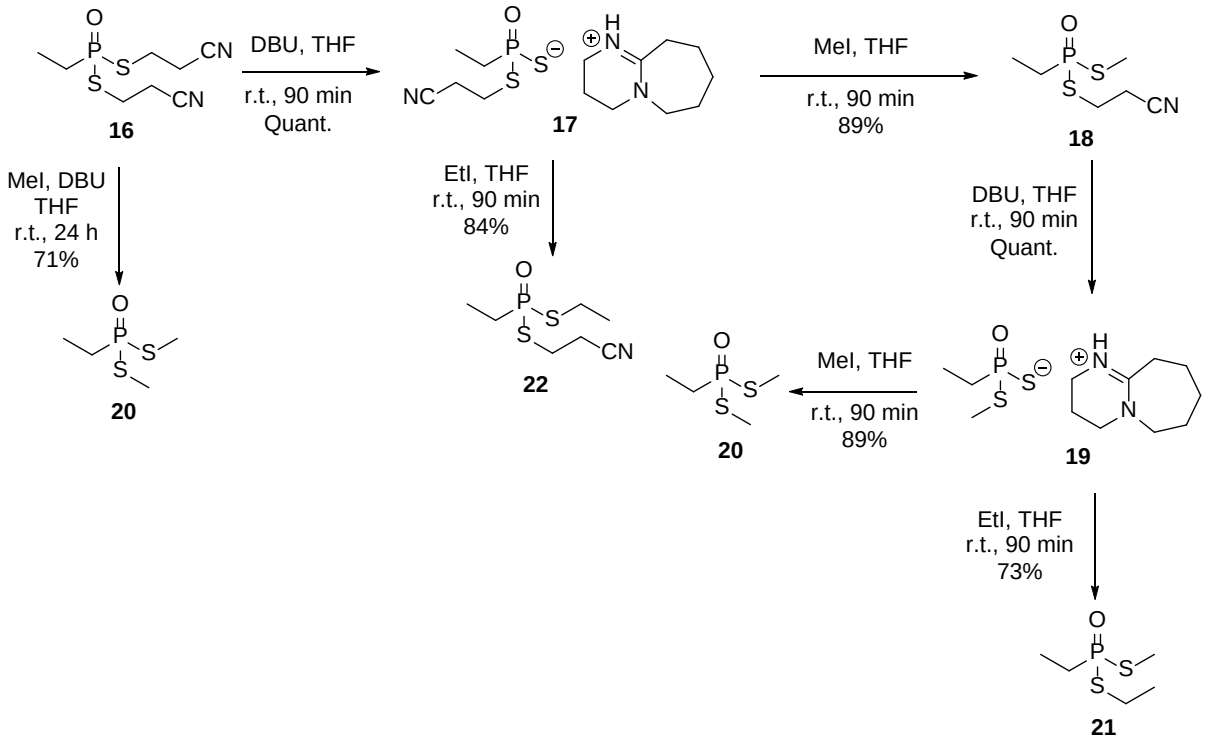
Silyl phosphites are highly versatile intermediates in organophosphorus chemistry.[39] They react readily with electrophiles to afford a variety of *P*(V) compounds, most notably in the Abramov reaction.[40] Kovacs *et al*. confirmed that silyl phosphites **12** and **13** are cleanly sulfurized on treatment with $S_8$ in the presence of tetramethylammonium fluoride to furnish the corresponding tetramethylammonium phosphorothiolate salts **14** and **15** in excellent yields (Table 3).[41] The authors found that the tetramethylammonium salts were particularly convenient to work with, as they were more soluble and shelf-stable than salts bearing other counter-ions. This facilitated their subsequent alkylation under mild conditions.

**Table 3 – Preparation of phosphorothioates from silyl phosphites**




| 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% |

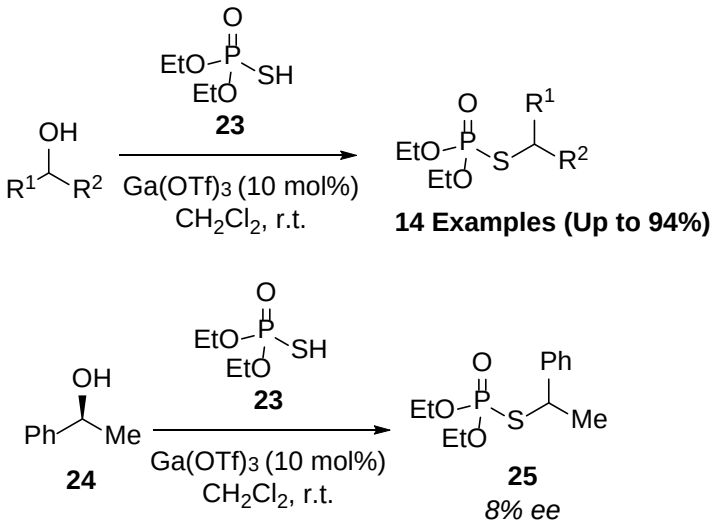
The 2-cyanoethyl moiety has been widely exploited as a base-labile protecting group.[42] In the course of our investigation into the synthesis of novel phosphonodithioates, we discovered that treatment of di(2-cyanoethyl) ethylphosphonodithioate (**16**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) quantitatively affords DBU salt **17** (Scheme 3).[43] An E1cB-type mechanism was proposed, consistent with similar cyanoethyl deprotections reported previously in the literature.[44] However, when the deprotection of **16** was carried out in the presence of a large excess of methyl iodide, both cyanoethyl groups were removed to form phosphonodithioate **20** in 71% yield. It is likely that methylation of anionic intermediates formed during the reaction enables the removal of the second cyanoethyl group. Interestingly, this approach can be extended to the formation of unsymmetrically substituted phosphorodithioates bearing low molecular weight side-chains. This avoids the use of the corresponding alkanethiols which are toxic and malodorous.




**Scheme 3**

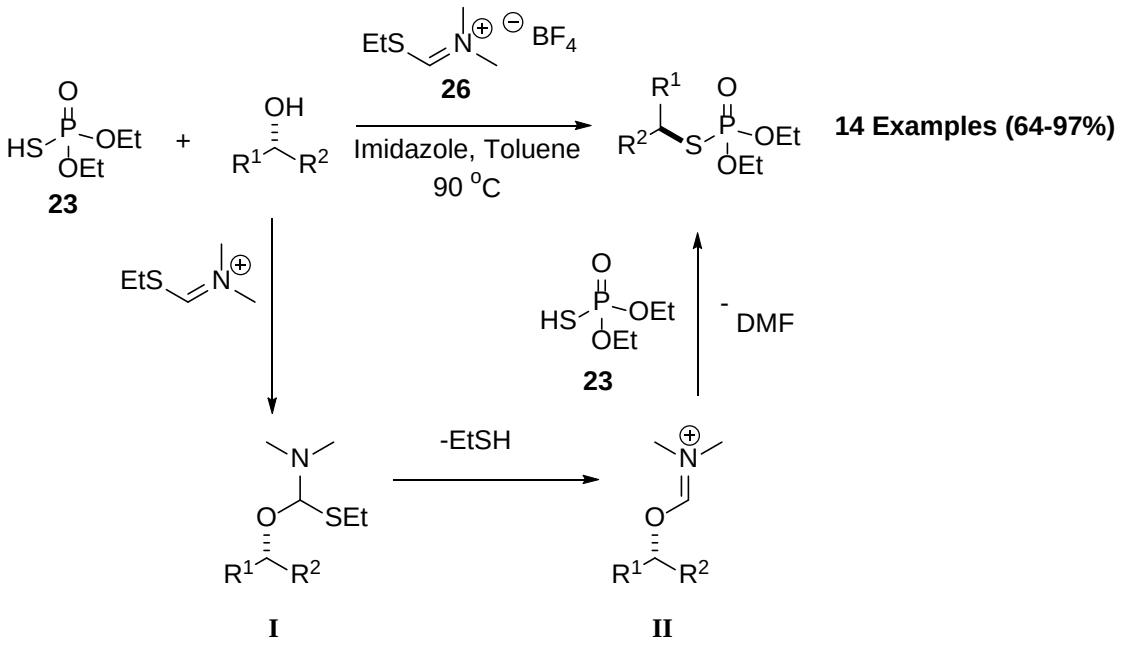
### 2.2. Alkylation by other electrophiles

While alkyl halides have been extensively employed as alkylating agents, , alternative alkylation strategies involving alcohols, epoxides and oxetanes have more recently come to the fore. Wu has shown that gallium(III) triflate catalyses the reaction of phosphorothioic acid **23** with alcohols to form phosphonothioates under mild conditions (Scheme 4).[45] The substrate scope for this reaction encompasses both primary and secondary alcohols, including a variety of benzylic and heterobenzylic alcohols. It is likely that the gallium(III) triflate is acting as a Lewis acid, enabling displacement of the alcohol by **23**. A series of control experiments demonstrated that no reaction occurred in the absence of a Lewis acid and that yields were inferior when indium(III) catalysts were employed. When enantiopure **24** was subjected to these reaction conditions, the expected product **25** was formed in only 8% *ee.* The configuration of the major enantiomer was not reported.




**Scheme 4**

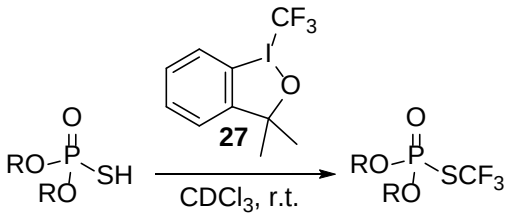
The use of thioiminium salts as activating agents for the nucleophilic substitution of alcohols has been extensively studied by Porter and co-workers.[46-48] This methodology has recently been applied to the preparation of phosphorothioates from thioic acid **23** and various alcohols, using tetrafluoroborate salt **26** (Scheme 5). This approach proceeds with complete inversion of the stereocentre bearing the alcohol moiety in contrast to the gallium(III)-catalysed methodology described by Wu. The authors have proposed that initial attack of the alcohol on the iminium cation forms intermediate **I**. Rapid elimination of ethanethiol, assisted by the neighbouring amine, forms Vilsmeier-type intermediate **II** which is a potent electrophile. Nucleophilic displacement of dimethylformamide by **23** forms the key sulfur-carbon bond. The authors chose to use tetrafluoroborate salt **27**, rather than the corresponding iodide, as it contains a less nucleophilic counteranion.[48] If the corresponding iodide is used instead, substitution of intermediate **II** by iodide would lead to the corresponding alkyl iodides.[47]




**Scheme 5**

*S*-Trifluoromethylphosphorothioates and *O*-trifluoromethylphosphates are versatile intermediates which undergo thermal- or base-induced thiocarbonyl extrusion to afford the corresponding phosphorofluoridates (Table 4).[49, 50] Santschi and Togni reported the trifluoromethylation of phosphorothioic acids using trifluoromethylbenziodoxole **27** (Table 4).[51] The majority of the resulting trifluoromethylated products were too unstable to be isolated as they decomposed rapidly on silica, with the exception of the cyclohexyl derivative (Table 4, Entry 7) which was recovered in a modest yield of 63%. Consequently, the conversion to the products was reported based on quantitative $^{19}F$ NMR analysis of the crude reaction mixture using trifluoromethylbenzene as an internal standard. The ethyl and isopropyl analogues were isolated by distillation (Table 4, Entries 1 and 3) but the other substrates simply decomposed on heating.

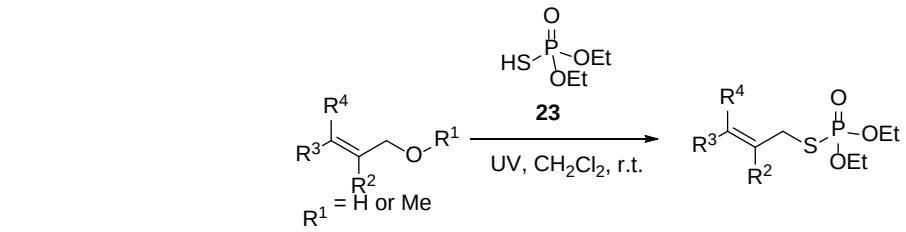
**Table 4 – Trifluoromethylation of phosphorothioic acids**



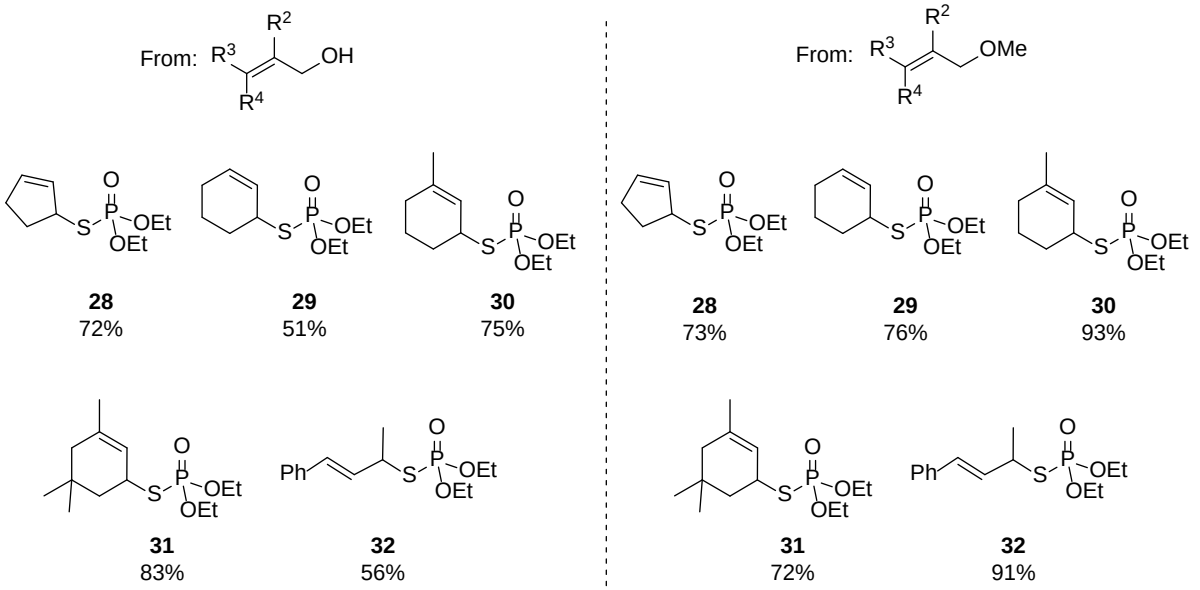

| Entry | R | Conversion | Yield | Entry | R | Conversion | Yield |
|---|---|---|---|---|---|---|---|
| **1** | Et | 64% | 22% | **6** | Neopentyl | 73% | -- |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **2** | *n*-Pr | 67% | -- | **7** | Cy | 79% | 63% |
| **3** | *i*-Pr | 76% | 20% | **8** | $ClCH_2CH_2$ | 8% | -- |
| **4** | *n*-Bu | 72% | -- | **9** | $ClCH_2(CH_2)_2$ | 38% | -- |
| **5** | *i*-Bu | 68% | -- | **10** | $MeOCH_2CH_2$ | 50% | -- |

While attempting to perform a thiol-ene reaction between cyclopentyl methyl ether and a phosphorothioic acid under UV-irradiation, Wu and co-workers observed that allylic substitution of the methyl ether was preferred.[52] The authors then subjected other allylic methyl ethers and alcohols to these conditions to afford the corresponding phosphorothioates **28-32** in 51%-93% yields (Scheme 6). In general, the products originating from methyl ether substrates were recovered in higher yields than those from alcohol precursors. The mechanism likely involves homolytic cleavage of the allylic C-O bond and trapping of the resulting cation by **23**.



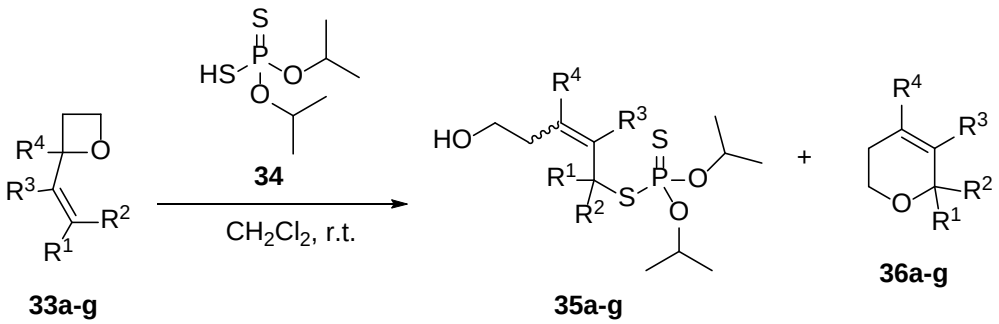

**Selected examples:**




**Scheme 6**

The nucleophilic ring-opening of vinyl oxetanes is a convenient route to homoallylic alcohols, a highly versatile class of synthetic intermediate.[53] Larock and co-workers demonstrated that carbon, nitrogen and oxygen nucleophiles undergo ring-opening to give predominantly *E*-products.[54, 55] In contrast, Guo and Njardarson showed that dithiophosphoric acid **34** opens a range of vinyl oxetanes in a *Z*-selective fashion (Table 5).[56] Replacing the isopropyl groups in **34** with methyl or ethyl groups led to a decrease in stereoselectivity. When terminal alkenes are used in this reaction (Table 5, Entries 1, 2, 4 and 6), the resulting homoallylic alcohols are recovered in excellent yields with high selectively for the *Z*-product. Exclusive formation of the *Z*-product was observed when sterically demanding groups were placed adjacent to the oxetane ring (Table 5, Entry 4). Substitution at the terminus of the alkene led to increasing formation of dihydropyran by-products (Table 5, Entries 3, 5 and 7).

**Table 5 – Nucleophilic ring opening of vinyl oxetanes**

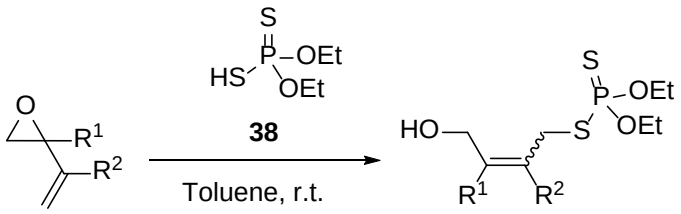



**33a-g** **35a-g** **36a-g**

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield | 35:36 | *Z*-35:*E*-35 |
|---|---|---|---|---|---|---|---|
| **1** | H | H | H | $PhCH_2CH_2$ | 87% | **35a** Only | 4.3:1 |
| **2** | H | H | Me | $PhCH_2CH_2$ | 92% | **35b** Only | 2.5:1 |
| **3** | Me | H | H | $PhCH_2CH_2$ | 78% | 4.9:1 | 6.7:1 |
| **4** | H | H | H | $PhCH_2C(CH_3)_2$ | 98% | **35d** Only | *Z*-**35d** Only |
| **5** | Me | Me | H | $PhCH_2CH_2$ | 86% | **36e** Only | -- |
| **6** | H | H | H | Ph | 90% | **35f** Only | 5.8:1 |
| **7** | Me | Me | H | Ph | 90% | **36g** Only | -- |

A similar ring-opening of vinyl epoxides by thioic acid **38** was described by the same authors (Table 6).[57] When 1,1-disubstituted epoxides **37a-e** were treated with **38** in toluene, conjugate addition at the alkene was observed and the resulting allylic alcohols **39a-e** were recovered in 81%-87% yields predominantly as the *Z*-isomer (Table 6). Substitution on the alkene bond led to a decrease in *Z*-selectivity (Table 6, Entry 5) while bulkier groups on the epoxide improved *Z*-selectivity (Table 6, Entry 4).

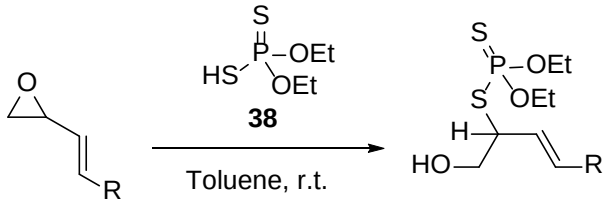
**Table 6 – Nucleophilic ring opening of vinyl epoxides by dithioic acid 38**




**37a-e** **39a-e**

| Entry | $R^1$ | $R^2$ | Yield | *Z*-39:*E*-39 |
|---|---|---|---|---|
| **1** | $PhCH_2CH_2$ | H | 87% | 15:1 |
| **2** | Ph | H | 85% | 17:1 |
| **3** | $PhCH_2CH_2$ | Me | 85% | 6:1 |
| **4** | $PhCH_2C(CH_3)_2$ | H | 81% | *Z*-39 Only |
| **5** | Me | *n*-Pentyl | 82% | 1.5:1 |

Interestingly, when monosubstituted epoxides **40a-c** were subjected to these same conditions, nucleophilic attack on the epoxide was preferred over conjugate addition leading to the formation of homoallylic alcohols **41a-c** respectively (Scheme 7).



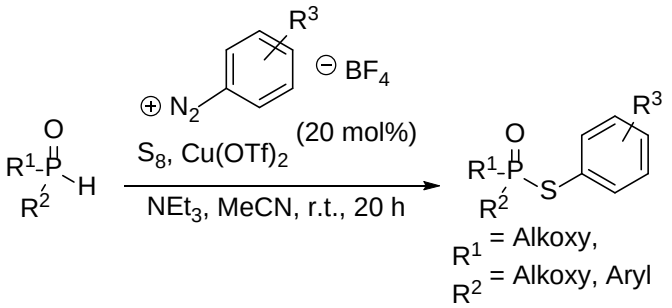

**40a** (R ≡ $C_7H_{15}$) **41a** (R ≡ $C_7H_{15}$) 71%
**40b** (R = Ph) **41b** (R = Ph) 83%
**40c** (R = H) **41c** (R = H) 75%

**Scheme 7**

### 2.3. Copper-catalysed arylations

The construction of PS-C bonds *via* copper-catalysed arylation reactions has been the subject of considerable study in recent times. In general, these protocols display broad substrate scope and have been successfully applied to the preparation of bioactive compounds. Zhang and co-workers have extensively studied the copper-catalysed *S*-arylation of organophosphorus compounds.[58] In a recent study, they discovered that sulfurization of dialkyl phosphonites, phosphine oxides and phosphonates under basic conditions and subsequent copper-catalysed coupling to a series of arenediazonium salts afforded a range of thioate products (Table 7). Different copper catalysts were initially screened, with copper(II) triflate proving most effective. In general, phosphorothioates (Table 7, Entries 1-6) were recovered in higher yields than either phosphonothioates (e.g. Table 7, Entry 7) or phosphinothioates (e.g. Table 7, Entry 8). Yields tended to be lower when *ortho*-substituted diazonium salts were employed (Table 7, Entry 2 and 3) although the electronic nature of the substituent had little impact on yields (Table 7, Entry 2 and 3). In the case of phosphorothioates, bulkier substituents on the phosphorus impacted negatively on yields obtained (Table 7, Entry 1, 4, 5 and 6).

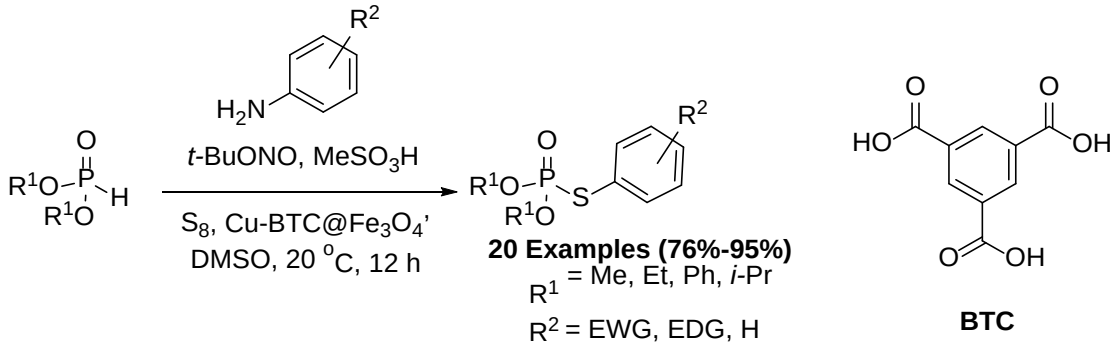
**Table 7 – Copper-catalysed arylation using diazonium salts**




| Entry | $R^1$ | $R^2$ | $R^3$ | Yield | Entry | $R^1$ | $R^2$ | $R^3$ | Yield |
|---|---|---|---|---|---|---|---|---|---|
| **1** | OEt | OEt | H | 98% | **5** | O*i*-Pr | O*i*-Pr | H | 70% |
| **2** | OEt | OEt | 2-Me | 74% | **6** | OBn | OBn | H | 77% |
| **3** | OEt | OEt | 2-F | 77% | **7** | OEt | Ph | H | 67% |
| **4** | OMe | OMe | H | 81% | **8** | Ph | Ph | H | 22% |

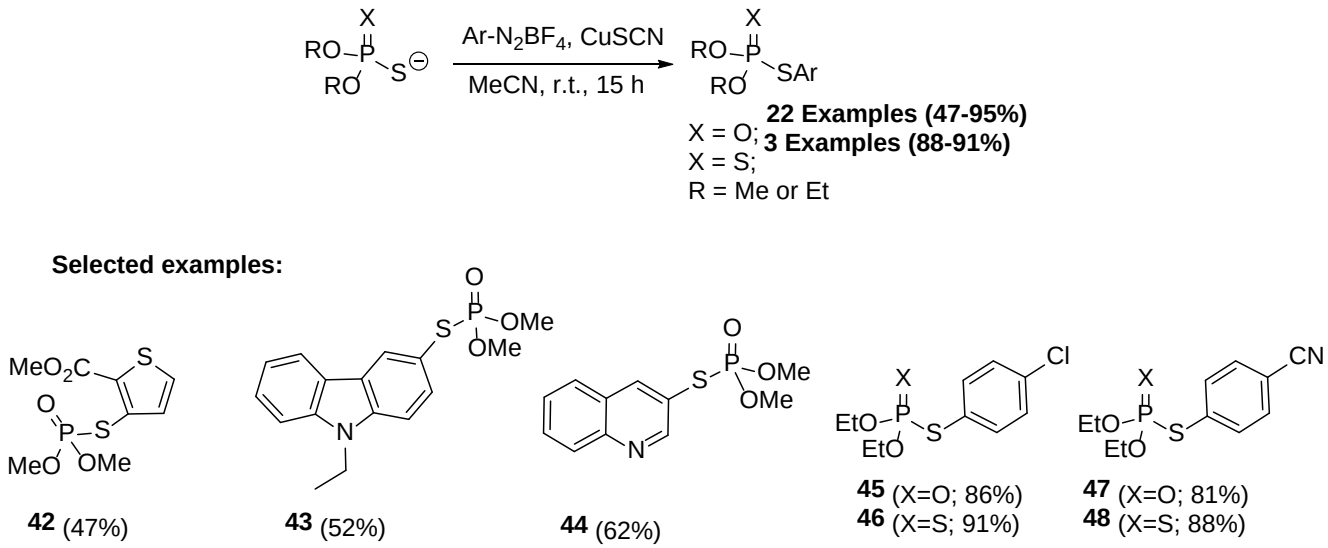
Adapting the methodology of Zhang, Wang and colleagues successfully synthesised phosphorothioates from diazonium mesylate salts, generated *in situ* by the oxidation of substituted anilines with *tert*-butyl nitrite (Scheme 8).[59] An interesting feature of this procedure is the use of a magnetically recyclable Cu-BTC@$Fe_3O_4$ composite which was recovered after the reaction and used

a further six times with no detectable loss in catalytic efficiency. No product was obtained when the reaction was attempted in the presence of TEMPO, a radical scavenger. It is likely, therefore, that this reaction proceeds *via* a radical mechanism, although the exact mechanistic details remain unclear.




**Scheme 8**

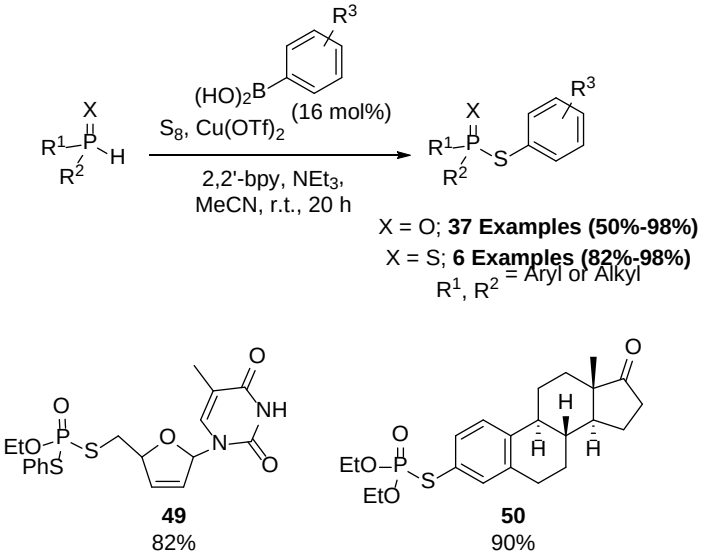
Kovacs *et al*. subsequently confirmed that a preformed phosphorothioate or thiophosphorothioate can also undergo this transformation (Scheme 9).[41] Systematic optimisation confirmed that copper(I) thiocyanate was the best catalyst, although copper(I) iodide and copper(II) acetate performed reasonably well. Kovacs expanded the scope of this transformation to prepare several novel derivatives including functionalised heterocycles.




**Scheme 9**

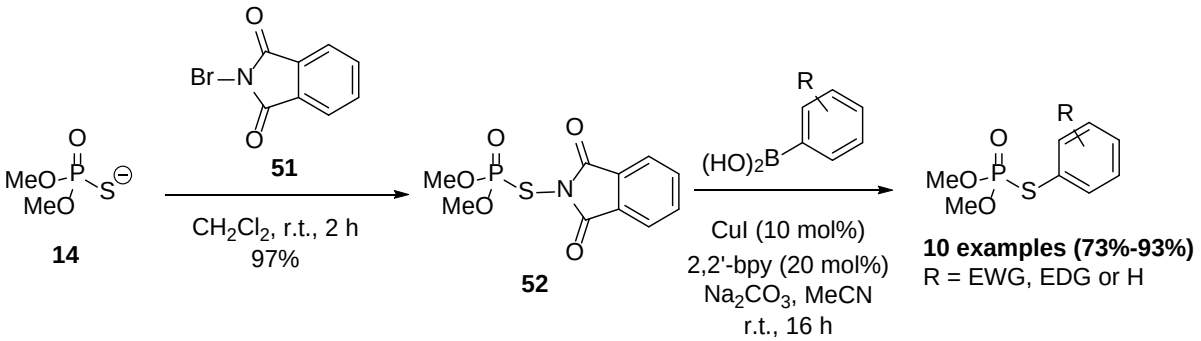
A similar transformation which uses aryl boronic acids instead of arenediazonium salts was reported by Xu and co-workers (Scheme 10).[60] 2,2'-Bipyridine (2,2'-bpy) was determined to be the optimal ligand for this transformation. Phosphonothioates were recovered in significantly lower yields than

phosphorothioates. Analogues of complex biological molecules such as thymidine derivative **49** and steroid **50** were produced in high yields with this approach




**Scheme 10**

The application of phthalimide derivatives as coupling partners in Chan-Lam couplings has been previously reported.[61, 62] A key advantage of these reagents is their long term stability.[61] Kovacs *et al*. discovered that phthalimide **52**, formed by treating phosphorothioate **14** with *N*-bromophthalimide (**51**), is also a suitable substrate for Chan-Lam couplings (Scheme 11). Sodium carbonate proved superior to triethylamine as the base. Both electron-rich and electron-poor boronic acids were compatible with these conditions and the resulting phosphorothioate products were isolated in 73%-93% yield.

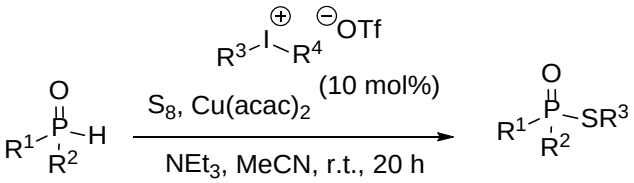



**Scheme 11**

A multicomponent preparation of *S*-aryl phosphorothioates and phosphonothioates by copper-catalysed phosphorothiolation of diaryliodonium salts has been developed by Zhang *et al*. (Table 8).[58] While copper(II) triflate and copper(II) acetate do catalyse the reaction, copper(II)

acetylacetonate was identified as the most effective catalyst. In the absence of elemental sulfur, rapid *P*-arylation occurs in yields of up to 70%. The presence of elemental sulfur suppresses this side reaction and the phosphorothioate product is obtained exclusively. Consistent with previous findings, phosphorothioates (Table 7, Entry 1-4 and 7-8) were recovered in higher yields than phosphonothioates (Table 8, Entry 5) or phosphinothioates (Table 8, Entry 6). Diaryliodonium salts were better coupling partners than diazonium salts and afforded higher overall yields. Selective coupling of the smaller aryl ring to the thioate was possible when bulky mesityl-containing diaryliodonium salts were employed (Table 8, Entry 7 and 8).

**Table 8 – Arylation using diaryliodonium salts**




| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield |
|---|---|---|---|---|---|
| **1** | OEt | OEt | Ph | Ph | 95% |
| **2** | OMe | OMe | Ph | Ph | 80% |
| **3** | OBn | OBn | Ph | Ph | 85% |
| **4** | O*i*-Pr | O*i*-Pr | Ph | Ph | 71% |
| **5** | Ph | OEt | Ph | Ph | 74% |
| **6** | Ph | Ph | Ph | Ph | 65% |
| **7** | OEt | OEt | 4-$FC_6H_4$ | Mes | 90% |
| **8** | OEt | OEt | 4-$(EtO_2C)C_6H_4$ | Mes | 94% |

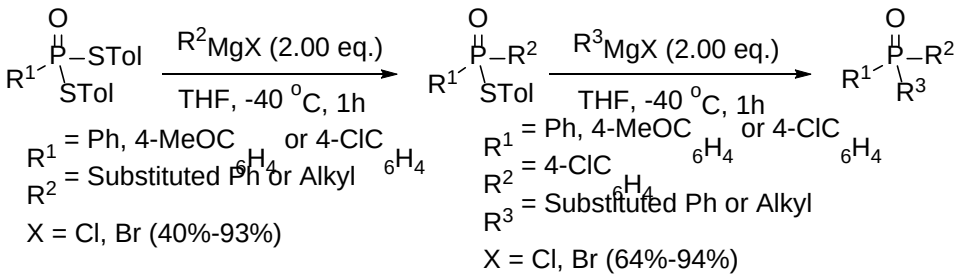
## 3. Application of phosphinothioates, phosphonothioates, phosphorothioates, phosphonodithioates and related compounds

In this section, we outline the synthetic utility of phosphinothioates, phosphonothioates and phosphorothioates in the preparation of phosphine oxides, phosphonates, phosphoramidates and various sulfur-containing heterocycles. We also examine their application in allylic substitution reactions.

### 3.1. Conversion to phosphine oxides, phosphonates and phosphoramidates

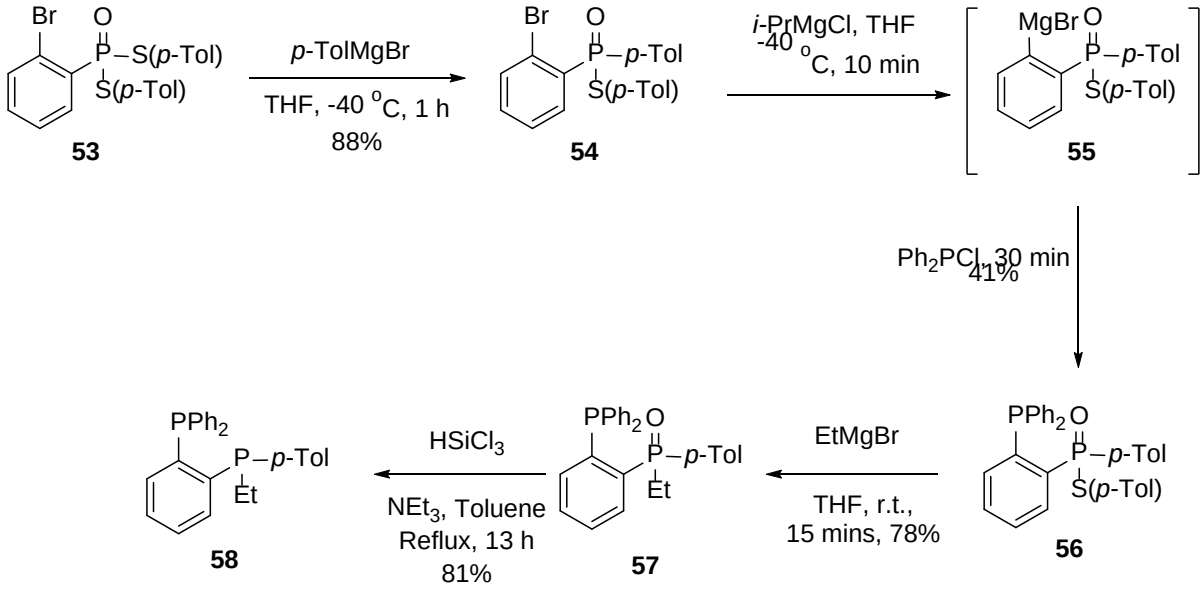
The unique reactivity of the phosphorus-sulfur bond has enabled researchers to successfully access targets which are otherwise challenging, or impossible, using conventional organophosphorus chemistry. These targets include phosphine oxides, phosphonates and phosphoramidates which are ubiquitous as ligands in various metal-catalysed reactions.[63-66]

Nishiyama and co-workers have exploited phosphonodithioates to prepare unsymmetrically substituted tertiary phosphine oxides *via* sequential reaction with Grignard reagents (Scheme 12).[67] The reaction was generally high yielding except when *tert*-butyl Grignard reagents were used. This result is notable as stepwise introduction of different carbon substituents on phosphorus is otherwise difficult to achieve when displacing conventional leaving groups such as halides.




**Scheme 12**

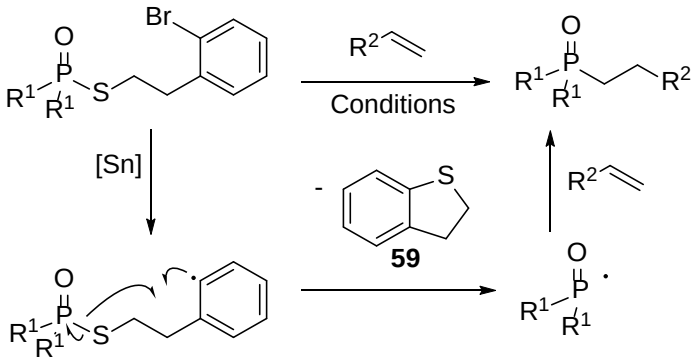
An interesting application of this chemistry is in the synthesis of diphosphinobenzene derivative **58** (Scheme 13). Treatment of **53** with 4-methylphenylmagnesium bromide afforded phosphinothioate **54** in 88% yield. Metalation of **54** with isopropylmagnesium chloride furnished Grignard reagent **55**, which reacted with diphenylphosphine chloride to give phosphine **56** in 41% yield over two steps. A final substitution reaction using ethylmagnesium chloride, followed by silane reduction, furnished unsymmetrically substituted phosphine **58**.

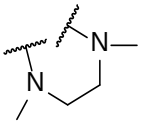



**Scheme 13**

*P*-centred radicals are a versatile class of reactive intermediates which have been widely exploited in organic chemistry.[68, 69] These radicals are typically produced by the homolytic cleavage of a Lewis-acidic P-H bond in the presence of a radical initiator. Carta *et al*. developed a new strategy for accessing *P*-centred radicals.[70] Tin-mediated halide extraction gives an aryl radical intermediate which induces cleavage of an adjacent phosphorus-sulfur bond to form the desired *P*-centred radicals on elimination of dihydrobenzothiophene (**59**) (Table 9). The radical is then quenched by addition of an alkene furnishing the corresponding phosphine oxides (Table 9, Entries 1-6), phosphonates (Table 9, Entries 7-10) and phosphoramidates (Table 9, Entries 11-14). The generation of phosphoramidates by this approach is especially noteworthy as phosphoramidate radicals were hitherto unknown. Phosphoramidates have diverse pharmacological indications.[71]

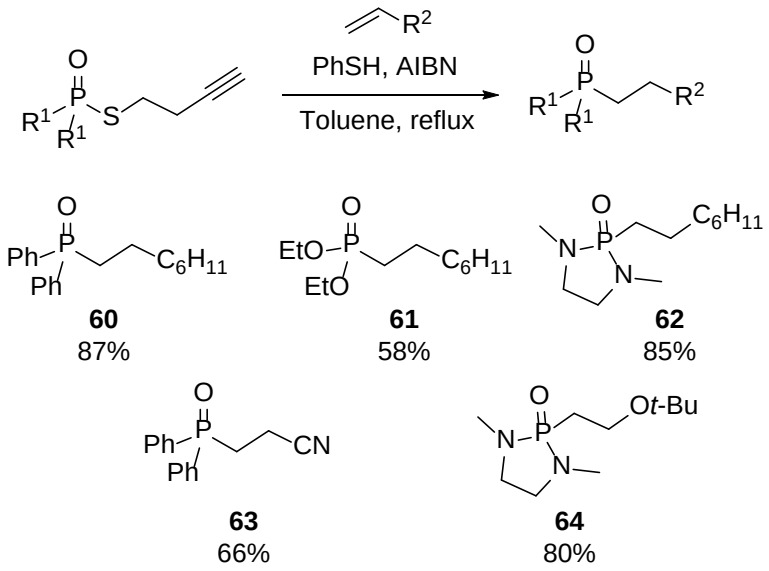
**Table 9 – Generation of *P*-centred radicals *via* tin-mediated homolytic P-S bond cleavage**




| Entry | $R^1$ | $R^2$ | Conditions | Yield |
|---|---|---|---|---|
| **1** | Ph | Hexyl | A | 84% |
| **2** | Ph | Hexyl | B | 58% |
| **3** | Ph | CN | A | 39% |
| **4** | Ph | CN | B | 50% |
| **5** | Ph | O*t*-Bu | A | 71% |
| **6** | Ph | O*t*-Bu | B | 47% |
| **7** | OEt | Hexyl | A | 75% |
| **8** | OEt | Hexyl | B | 70% |
| **9** | OEt | CN | A | 74% |
| **10** | OEt | O*t*-Bu | B | 56% |
| **11** |  | Hexyl | A | 60% |
| **12** | | Hexyl | B | 48% |
| **13** | | CN | A | 82% |
| **14** | | O*t*-Bu | A | 40% |

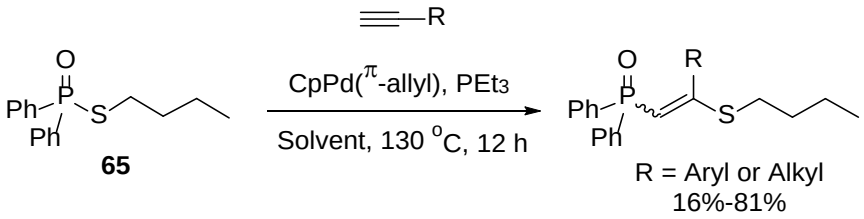
A: $Bu_3SnH$, AIBN, toluene, reflux. B: $Bu_3SnCl$, $NaBH_4$, *t*-BuOH, reflux.

A disadvantage of the above methodology is that removal of the tin by-products can sometimes be difficult. Carta and colleagues further demonstrated that when a terminal alkyne replaces the 2-bromophenyl ring in the above example, thiophenol may be used instead of tin as a means of generating the *P*-centred radical (Scheme 14). The resulting products **60-64** were isolated in 58%-87% yields.




**Scheme 14**

The stereoselective phosphinylthiolation of terminal alkynes with phosphorothioate **65** in the presence of CpPd-$PEt_3$ has been reported (Scheme 15).[72] Triethylphopshine was the best ligand for this transformation and led to near complete consumption of starting material. Bulkier ligands, such as triphenylphosphine, were ineffective. Conducting the reaction in ethylbenzene favoured the formation of the *E*-isomer. In contrast, when the reaction was conducted in either hexanol or isoamyl alcohol, the *Z*-isomer was generally preferred. The authors proposed that the *Z*-isomer is likely the kinetic product of the reaction and that isomerisation to the *E*-alkene occurs in ethylbenzene but not in alcohol solvents.

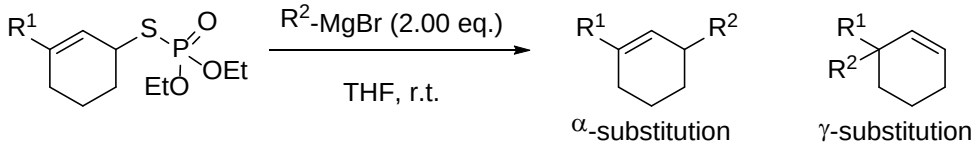



**Scheme 15**

### 3.2. Utility as leaving groups in substitution reactions

The displacement of allylic leaving groups is complicated by the possibility of forming two regioisomeric products. In particular, allylic substitution using hard nucleophiles such as Grignard reagents tends to be poorly regioselective. Ligand directed γ-substitution by Grignard reagents is known[73] but few methods for selective α-substitution have been reported.[74] Preliminary work by Wu and co-workers established that allylic displacement of phosphorothioates by Grignard reagents could occur regioselectively (Table 10).[52] Aryl Grignard reagents preferentially underwent α-substitution and the resulting cyclohexenes could be isolated in 55%-81% yields (Table 10, Entries 1-6). Interestingly, the opposite regioselectivity was observed for secondary alkyl Grignard reagents (Table 10, Entries 7-11). No selectivity for either regioisomer was observed when *tert*-butylmagnesium bromide was employed (Table 10, Entry 12).

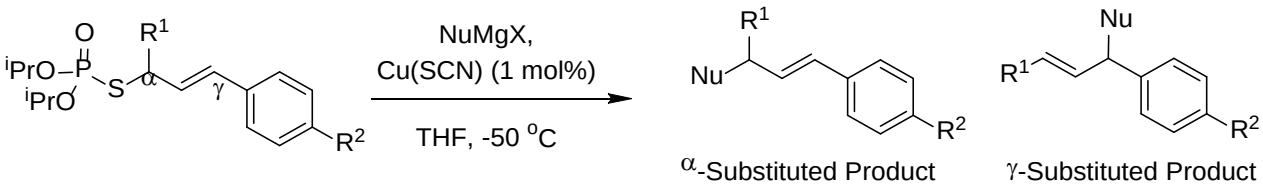
**Table 10 – Regioselective Grignard coupling reactions**




| Entry | $R^1$ | $R^2$ | α:γ | Yield | Entry | $R^1$ | $R^2$ | α:γ | Yield |
|---|---|---|---|---|---|---|---|---|---|
| **1** | Me | Ph | >95:5 | -- | **7** | Me | Cy | <5:95 | 81% |
| **2** | Me | 4-$CF_3C_6H_4$ | >95:5 | 81% | **8** | 4-$FC_6H_4$ | Cy | 15:85 | 47% |
| **3** | Me | 4-$FC_6H_4$ | >95:5 | 75% | **9** | Me | Cyp | 13:87 | 80% |
| **4** | *i*-Pr | 4-$FC_6H_4$ | >95:5 | 70% | **10** | Me | *i*-Pr | <5:95 | 86% |
| **5** | 4-$FC_6H_4$ | 4-$FC_6H_4$ | >95:5 | 70% | **11** | 4-$FC_6H_4$ | *i*-Pr | 15:85 | 61% |
| **6** | Me | 1-styrene | >95:5 | 55% | **12** | 4-$FC_6H_4$ | *t*-Bu | 1:1 | 48% |

Wu and co-workers later demonstrated that allylic substitutions of phosphorothioates are efficiently catalysed by copper(I) thiocyanate (Table 11).[75] Interestingly, the reaction proceeds with excellent α-selectivity, regardless of the nature of the Grignard reagent used. Both linear (Table 11, Entries 1-3) and branched (Table 11, Entries 4-12) allylic substrates are compatible with these conditions.

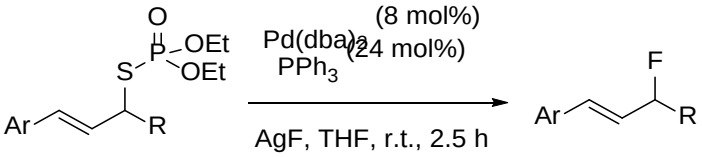
**Table 11 – Copper-catalysed allylic substitution**




| Entry | $R^1$ | $R^2$ | Nu | α:γ | Yield |
|---|---|---|---|---|---|
| **1** | H | H | *i*-Pr | >95:5 | 84% |
| **2** | H | H | Bn | 94:6 | 86% |
| **3** | H | H | Ph | >95:5 | 90% |
| **4** | Me | H | *i*-Pr | >95:5 | 91% |
| **5** | Me | H | Bn | >95:5 | 67% |
| **6** | Me | H | Ph | >95:5 | 83% |
| **7** | Me | F | *i*-Pr | 92:8 | 85% |
| **8** | Me | F | Bn | 90:10 | 73% |
| **9** | Me | F | Ph | >95:5 | 81% |
| **10** | Me | MeO | *i*-Pr | 75:25 | 88% |
| **11** | Me | MeO | Bn | 70:30 | 69% |
| **12** | Me | MeO | Ph | >95:5 | 92% |

Allylic fluorides are an important class of compounds due to their applications in medicinal chemistry, reaction mechanism elucidation and chemical biology.[76-79] Until recently, the most effective method for palladium-catalysed allylic fluorination employed primary allylic 4-nitrobenzoates as leaving groups.[80] Unfortunately, this approach was determined to be unsuitable for the fluorination of secondary allylic substrates. Lauer and Wu have shown that secondary allylic phosphorothioates undergo palladium-catalysed fluorination in the presence of silver fluoride affording a range of allylic fluorides in 53%-75% yields (Table 12).[81] Both electron-withdrawing and electron-donating substituents were equally well tolerated.

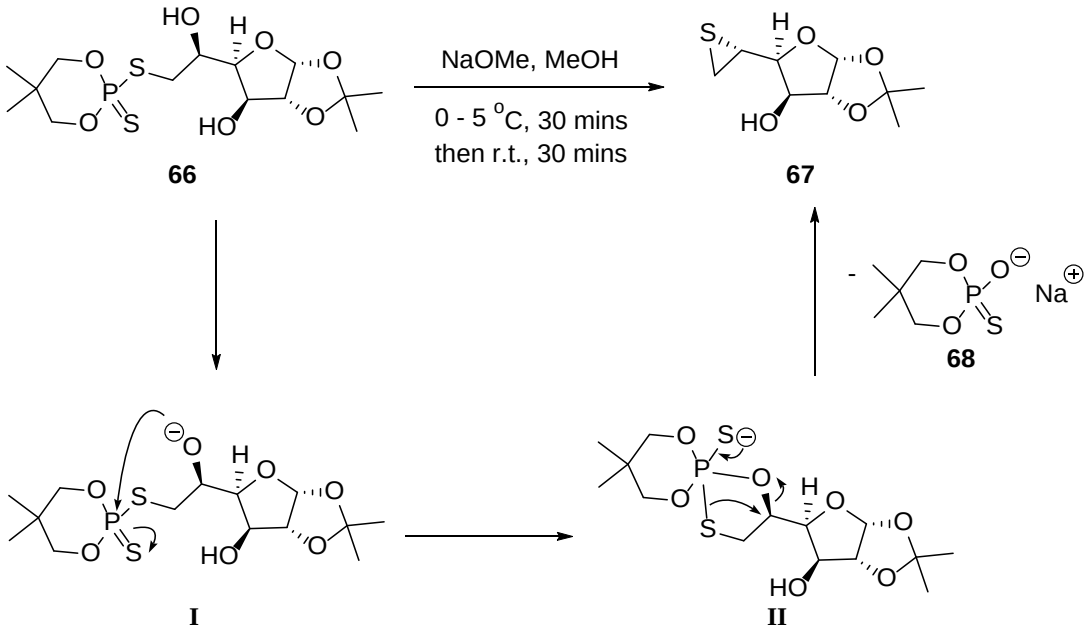
**Table 12 – Palladium-catalysed allylic fluorination**




| Entry | Ar | R | Yield | Entry | Ar | R | Yield |
|---|---|---|---|---|---|---|---|
| **1** | Ph | Me | 75% | **7** | 4-$MeOC_6H_4$ | Me | 65% |
| **2** | Ph | Et | 63% | **8** | 4-$(BnOCH_2)C_6H_4$ | Me | 60% |
| **3** | Ph | *i*-Pr | 68% | **9** | 4-($t$-$BuO_2C)C_6H_4$ | Me | 53% |
| **4** | Ph | *t*-Bu | 74% | **10** | 2-Thienyl | Me | 65% |
| **5** | Ph | Ph | 67% | **11** | 4-$(CH_3CH(OTIPS))C_6H_4$ | Me | 79% |
| **6** | 4-$FC_6H_4$ | Me | 66% | **12** | 3,5-di$(CF_3)C_6H_3$ | Me | 66% |

### 3.3. Synthesis of sulfur-containing heterocycles

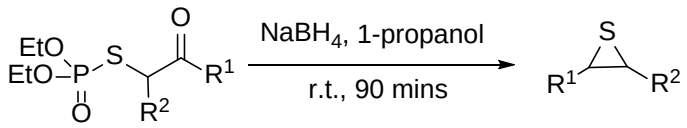
Intramolecular anionic cascades allow for the formation of thiiranes under mild conditions by exploiting the labile nature of phosphorus-sulfur bond. An early example of this approach was reported by Kudelska.[82] Conversion of dithiophosphinate **66** to thiirane **67** was accomplished by deprotonating **66** with sodium methoxide to generate intermediate **I** (Scheme 16). Rearrangement of **I** to **II** and expulsion of **68** produced the thiirane with complete inversion of configuration. No yields were reported for this reaction.




**Scheme 16**

Maciągiewicz later demonstrated that borohydride-mediated reduction of the ketone moiety in phosphorothioates **69a-f** furnished thiiranes **70a-f** in 78%-94% yields (Table 13).[83] This approach was subsequently applied by the same authors to the preparation of vinyl[84] and propargyl[85] thiiranes.

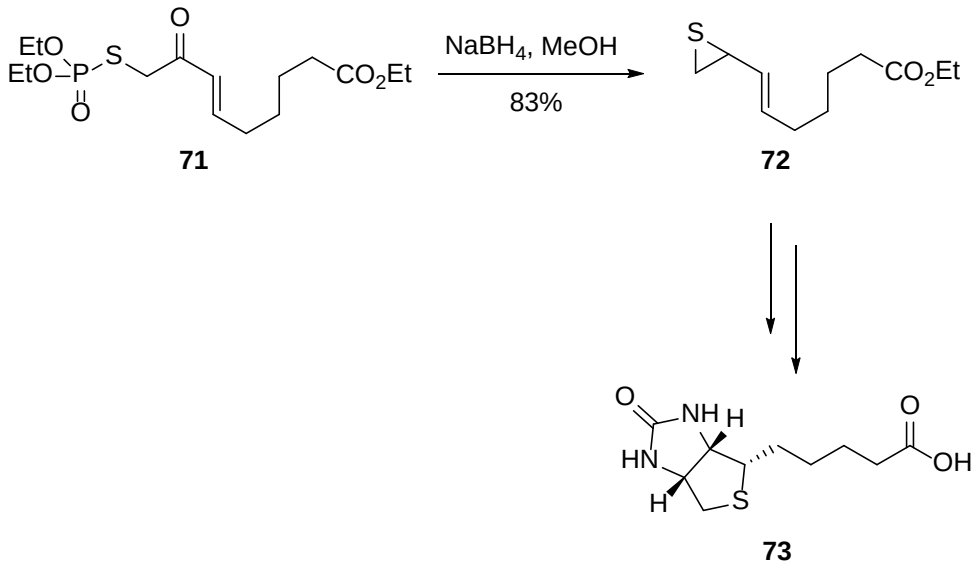
**Table 13 – Borohydride-mediated reductive thiirane formation**




**69a-f** **70a-f**

| Entry | Phosphinothioate | $R^1$ | $R^2$ | Thiirane | Yield |
|---|---|---|---|---|---|
| **1** | **69a** | Et | Me | **70a** | 82% |
| **2** | **69b** | *n*-Pr | Et | **70b** | 78% |
| **3** | **69c** | *i*-Bu | *i*-Pr | **70c** | 85% |
| **4** | **69d** | *p*-$FC_6H_4$ | Me | **70d** | 86% |
| **5** | **69e** | Ph | Me | **70e** | 84% |
| **6** | **69f** | 4-$BnOC_6H_4$ | Me | **70f** | 94% |

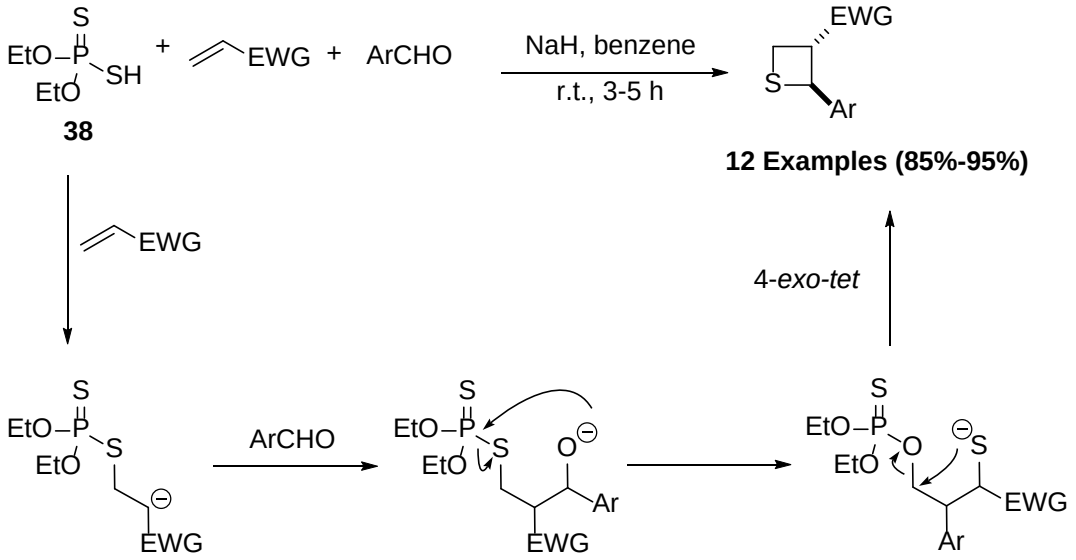
Njardarson and co-workers adopted a similar strategy in their total synthesis of biotin (**73**), a co-factor and B-vitamin widely studied in biochemistry and chemical biology (Scheme 17).[86, 87] The authors prepared **72** in 83% yield from phosphorothioate **71**. Thiirane **72** could then be converted to **73** over several steps.




**71** **72** **73**

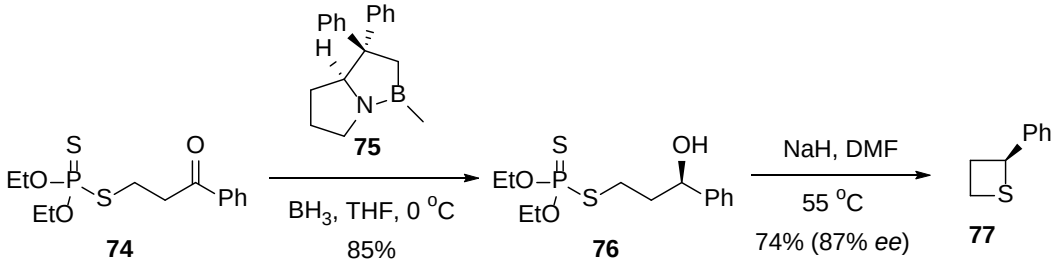
**Scheme 17**

Yadav described the synthesis of 2,3-disubstituted thietanes from **38** and alkenes bearing an electron withdrawing group in a Baylis-Hillman-type reaction (Scheme 18).[88] An initial conjugate addition at the alkene and subsequent alkylation formed an alkoxide intermediate which underwent *S*-/*O*-rearrangement and elimination to afford the thietane. The products were recovered in excellent yields of 85%-95%. The *trans*-products was formed almost exclusively with only trace amounts of the *cis*-products evident in the $^{1}$H NMR spectra.




**Scheme 18**

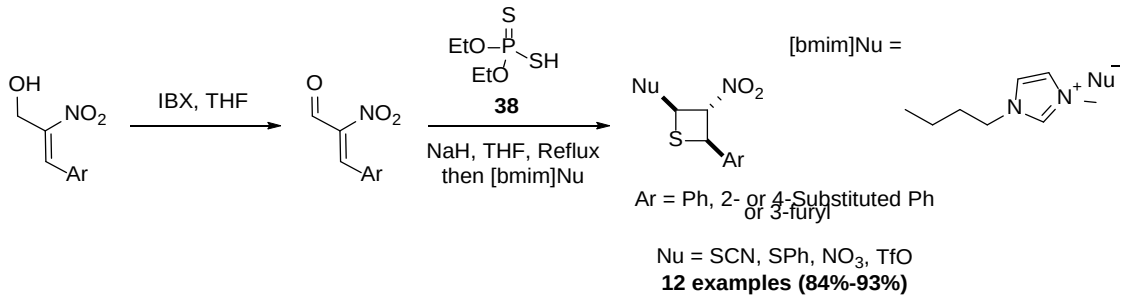
An asymmetric route to thietane **77** was developed by Wu.[89] Stereoselective reduction of thiophosphorothioate **74** using the (-)-Corey-Bakshi-Shibata (CBS) reagent **75** afforded **76** which underwent a base-promoted 4-*exo*-tet cyclisation to thietane **77** in 74% yield and 88% *ee* (Scheme 19).



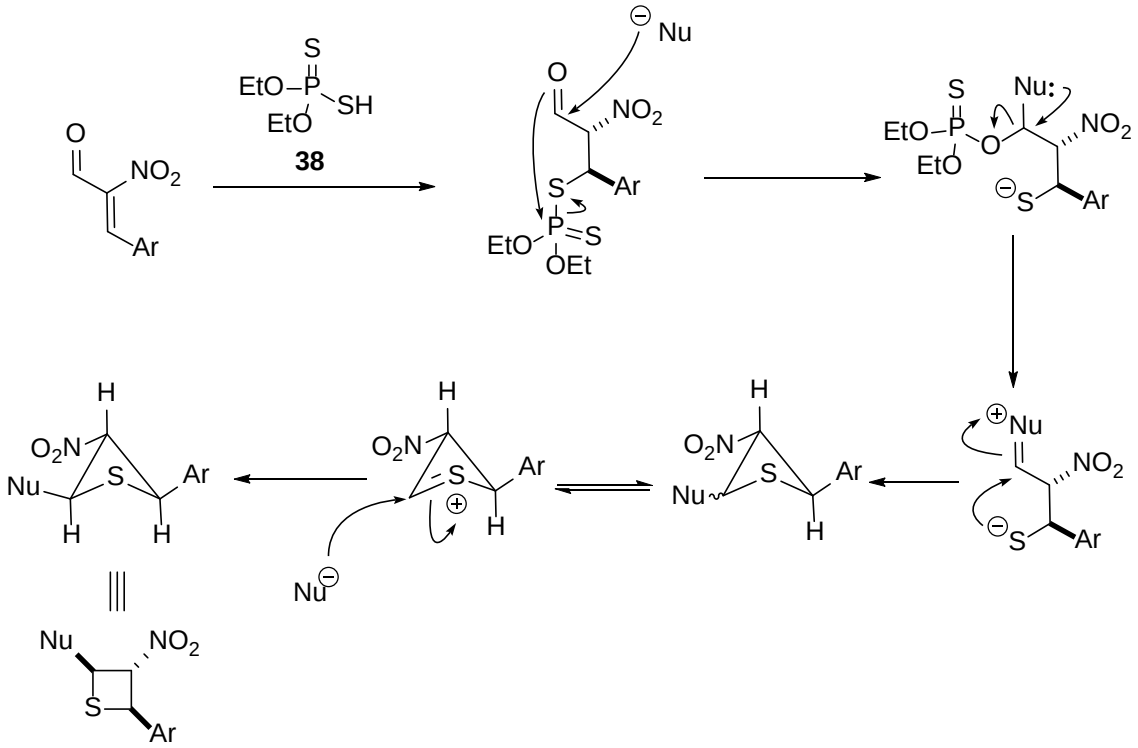

**Scheme 19**

Further expansion of the substrate scope to include β-nitrostyrenes, allowed Yadav to access highly functionalised 2,3,4-trisubstituted thietanes in excellent yields of 84%-93% (Scheme 20).[90] An interesting feature of this reaction is that only a single diastereomer is generated. The mechanism proposed by the authors involves conjugate addition to the nitrostyrene by **38**. This is followed by

nucleophile-assisted *4-exo-tet* cyclisation, thereby eliminating the thiophosphate and forming the thietane (Scheme 21). The exclusive formation of the *trans* isomer of the conjugate addition product is understandable as conjugate additions typically afford *trans* products.[91] The authors suggest that an equilibrium involving a sulfenium ion intermediate, favouring the more thermodynamically stable *trans*-*trans* product, accounted for the stereochemical outcome at the final stereogenic centre.



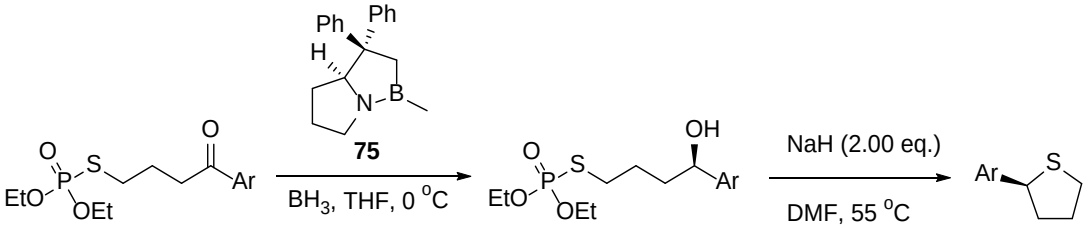

**Scheme 20**




**Scheme 21**

The thiolane ring-structure is found in several natural products including breynin A, breynin B and epibreynin B[92-94], biotin[86] and a variety of α-glucosidase inhibitors[95] such as salacinol and salprinol. Wu has demonstrated that chiral thiolanes may be generated in two steps from the appropriate phosphorothioate (Table 14).[89] A range of chiral alcohols **79a-o** was prepared by CBS-reduction of phosphorothioates **78a-o**. Subsequent addition of sodium hydride afforded enantioenriched thiolanes **80a-o** in yields of 50%-94% and *ee*s from 10%-97%. The substrate scope for this transformation encompassed both substituted aryl (Table 14, entries 2-9) and heteroaryl compounds (Table 14, entries 11-13). The poor enantioselectivity observed for nitrile **80h** (Table 14, Entry 8) and ester **80j** (Table 14, Entry 10) was improved by lowering the loading of sodium hydride from 2 to 1.2 equivalents. It is likely that the enhanced acidity of the benzylic position due to potential delocalisation of the resulting anion into the nitrile or ester promoted unwanted racemisation.

**Table 14 – Synthesis of thiolanes 80a-o**

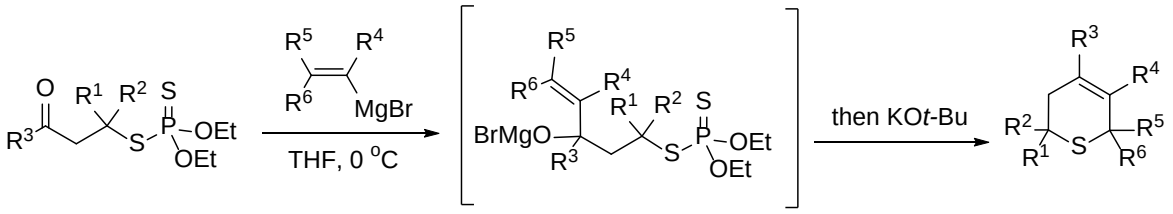


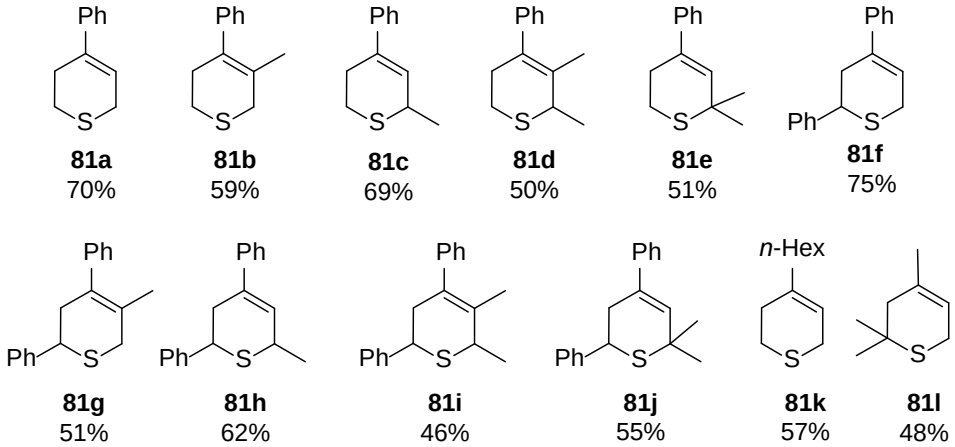

**78a-o** **79a-o** **80a-o**

| Entry | Alcohol | Ar | Yield | Thiolane | Yield | ee |
|---|---|---|---|---|---|---|
| 1 | **79a** | Ph | 94% | **80a** | 92% | 97% |
| 2 | **79b** | 4-$MeC_6H_4$ | 98% | **80b** | 84% | 97% |
| 3 | **79c** | 2-$MeOC_6H_4$ | 97% | **80c** | 78% | 89% |
| 4 | **79d** | 3,4-di$MeC_6H_3$ | 92% | **80d** | 80% | 92% |
| 5 | **79e** | 4-*t*-$BuC_6H_4$ | 92% | **80e** | 84% | 91% |
| 6 | **79f** | 4-$FC_6H_4$ | 97% | **80f** | 79% | 97% |
| 7 | **79g** | 4-$ClC_6H_4$ | 93% | **80g** | 89% | 97% |
| 8 | **79h** | 4-$CNC_6H_4$ | 97% | **80h** | 60% | 0% |
| 9 | **79i** | 4-$MeOC_6H_4$ | 97% | **80i** | 73% | 94% |

| | | | | | | |
|---|---|---|---|---|---|---|
| 10 | **79j** | 4-*t*-$BuO_2C$ | 91% | **80j** | 50% | 10% |
| 11 | **79k** | 2-(*N*-Methylindolyl) | 76% | **80k** | 86% | 74% |
| 12 | **79l** | 2-Furyl | 78% | **80l** | 74% | 96% |
| 13 | **79m** | 2-Thiophenyl | 87% | **80m** | 94% | 91% |
| 14 | **79n** | 4-($CH_3CH(OCH_2CH_3)C_6H_4$ | 97% | **80n** | 83% | 92% |
| 15 | **79o** | 4-(*i*-$Pr_2NC(O)$) | 83% | **80o** | 70% | 85% |

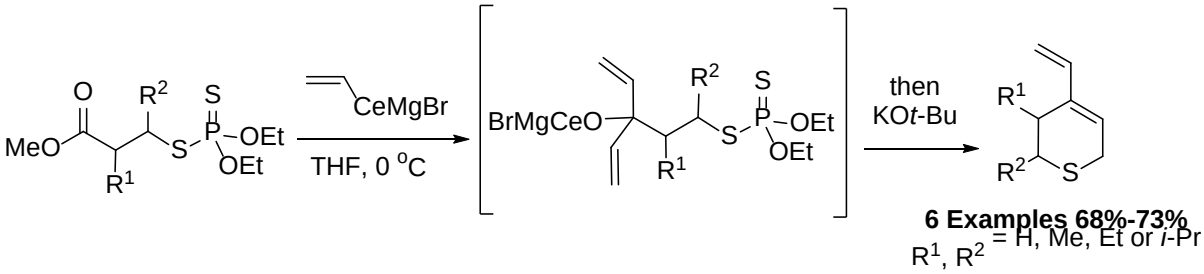
A concise route to thianes has been developed by Njardarson and co-workers.[96] They initially treated thiophosphorothioates with vinyl Grignard reagents generating an alkoxide intermediate with the aim of triggering an intramolecular cyclisation to the target thianes (Scheme 22). However, the magnesium alkoxides were not sufficiently reactive to undergo the requisite *6-endo-trig* cyclisation. Addition of potassium *tert*-butoxide facilitated cation exchange, forming a more reactive nucleophile, which drove the reaction to completion. Thianes **81a-l** were subsequently isolated in yields of 46%-75%.




**Scheme 22**

Njardarson further expanded this approach to encompass methyl ester substrates (Scheme 23). Treatment of the methyl ester with six equivalents of an organocerium reagent led to the *in situ* formation of a divinyl carbinol intermediate. Cation exchange with potassium *tert*-butoxide and subsequent cyclisation afforded the vinyl thiopyrans in 68%-73% yield.




**Scheme 23**

## 4. Conclusion

There has been significant growth in the number of different methods for the preparation of phosphonothioates and related compounds reported in the literature in recent years. The majority of these routes have been shown to be sufficiently broad in substrate scope to enable access to many complex products. The resulting structures have enjoyed widespread application in synthetic chemistry and have been identified as versatile synthetic intermediates. It is clear that further study in this area will reveal more diverse ways to harness the unique reactivity of the phosphorus-sulfur bond.

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