*Allylation*

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# Substituted Allyl Diphenylphosphine Oxides as Radical Allylating Agents**

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Following its discovery nearly a quarter of a century ago,[1] the radical allylation using allylstannanes has proved to be a very powerful synthetic tool. Numerous applications attest to the

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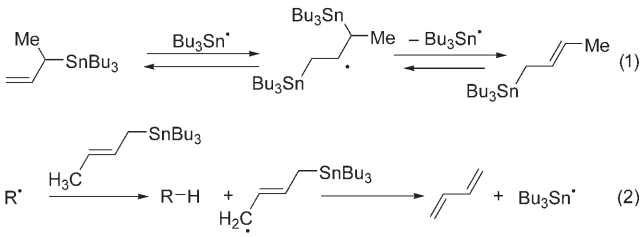
efficiency and compatibility of this methodology with a wide number of functional groups.[2] Nevertheless, the reaction suffers from some limitations, especially in respect to the substitution pattern around the allyl group. γ-Substituted allylstannanes rapidly rearrange under the reaction conditions into their more stable α-isomers [Eq. (1)], and these were found to react mostly through abstraction of the allylic hydrogen atom [Eq. (2)] rather than by the desired addition fragmentation (Scheme 1).[2c,3,4]

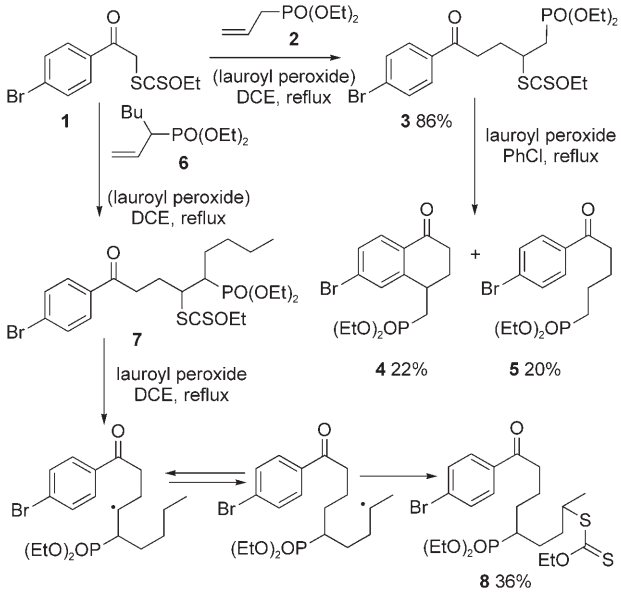



***Scheme 1.*** Some side reactions during allylations with substituted allyltriorganotin reagents.

Several systems using allylcobalt,[5] allylgallium,[6] allylhalogen,[7] or allylsulfur[8] derivatives have been examined in an attempt to overcome these limitations. Nevertheless, most of these processes require a stoichiometric amount of a tin-based promoter[9] (or other heavy-metal derivatives) and have usually been applied to the introduction of simple allyl moieties.[10]

Our method to devise a new, tin-free allylation process was initially to separate the addition and fragmentation steps. This approach would eliminate the possibility of rearrangement of the allylating agent and thus obviate the shortcomings of the previous methods.[11] We thus needed an allylating agent substituted with a relatively poor leaving group (in the radical sense), which would undergo intermolecular addition and transfer of a dithiocarbonate unit and β-elimination in the second step.[12] In this respect, a phosphorus-centered leaving group appeared suitable. The reversible addition of phosphines to olefins is well known.[13] More recently, we and other groups found that a diethylphosphinyl group could be expelled when adjacent to nitrogen- or oxygen-centered radicals.[14] Other related observations include that of Clive and Kang, who reported the elimination of an aryl phosphinyl radical from a cyclohexadienyl system,[15] and the isolation of a minor (8% yield) by-product that arises from an apparent β-elimination of a methylphenylphosphinoyl radical located on a tertiary carbon atom, as reported by Malacria and coworkers.[16] All cases these were especially favorable, but did not foretell the generality of the elimination process in ordinary situations.

We initially envisaged the use of a simple diethyl phosphonate as the departing group and chose to study the behavior of phosphonate **3** derived from the addition of *p*-bromophenacyl dithiocarbonate **1** to diethyl allylphosphonate **2**. The choice was dictated by the possibility of the intermediate radical undergoing closure to the aromatic ring to give tetralone **4**, and this process, although unwanted in the present case, should act as an internal clock and give us an idea of the rate of β-elimination.[17] We also chose to use the higher-boiling chlorobenzene as the solvent to favor the fragmentation pathway, which has a large, positive entropy of activation. In the event, heating adduct **3** with lauroyl peroxide in chlorobenzene resulted in the formation of **4** and the reduced derivative **5** as the major products. No elimination of the phosphonate group was observed (Scheme 2).

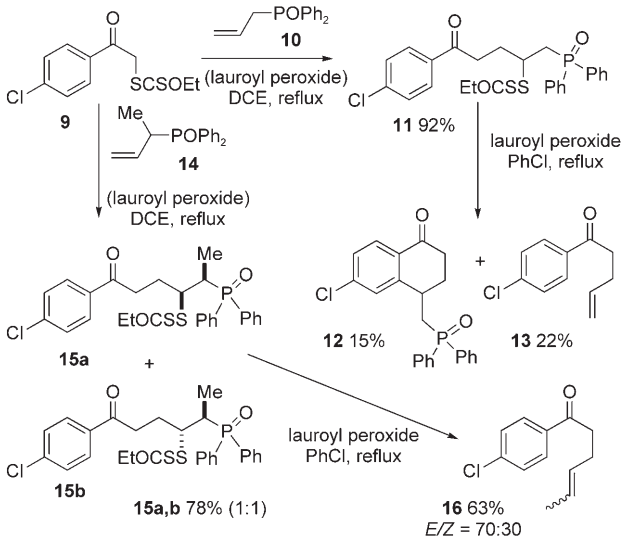



***Scheme 2.*** Negative experiments with allyl phosphonate reagents. DCE = 1,2-dichloroethane.

Weakening the carbon–phosphorus bond by substitution of the phosphonate group was the next logical step. Obtaining substituted derivatives was also more interesting synthetically and the purpose of our study in the first place. The radical addition of the same dithiocarbonate **1** to allylphosphonate **6** occurred fairly efficiently to give adduct **7** in 60% yield, but when this product was heated in 1,2-dichloroethane with lauroyl peroxide, neither elimination nor ring closure to the tetralone was observed. Instead, hydrogen abstraction from the side chain occurred to ultimately give compound **8** in 36% yield (Scheme 3). Steric hindrance in this case had clearly slowed down tetralone formation, and a Thorpe–Ingold effect had facilitated the 1,5-hydrogen shift. Switching to a higher-boiling solvent was obviously not going to overcome this unwanted radical translocation.

Decidedly, the phosphonate entity was too poor a leaving group for our objectives. It remained for us to examine the influence of the substituents around the phosphorus center on its leaving ability. The use of a diphenylphosphine oxide group seemed the most judicious choice as, in addition to ready availability, the bond we wanted to break would now acquire some benzylic character and perhaps be weakened sufficiently to undergo β-scission. Strain relief upon cleavage of such a bulky group should provide an extra driving force. Radical addition of dithiocarbonate **9** to allyl diphenylphosphine oxide **10** took place in high yield, and exposure to




***Scheme 3.*** First successful allylations with allyl diphenylphosphine oxides.

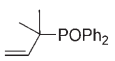
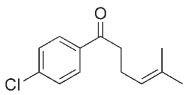
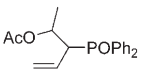
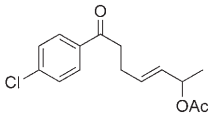
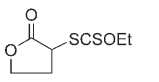
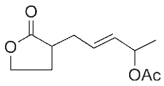
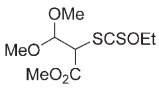
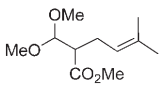
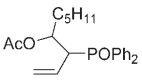
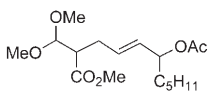
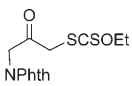
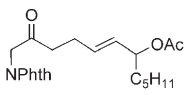
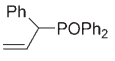
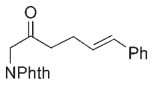
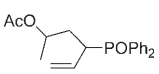
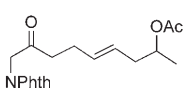
peroxide in refluxing chlorobenzene gave the corresponding tetralone **12** and the desired elimination product **13**, both in low yield. The formation of allylated derivative **13** was nevertheless a good start, as it was expected that substitution would make the elimination step more efficient. Indeed, when substituted diphenylphosphine oxide **14** was employed as the radical trap, the intermolecular addition proceeded quite satisfactorily; more pleasing, it was observed that smooth elimination of the diphenylphosphinoyl group took place upon heating **15** with lauroyl peroxide in refluxing chlorobenzene to give unsaturated ketone **16** in 63% yield as a mixture of geometric isomers with the expected preponderance of the *E* isomer.[18]

The diphenylphosphine oxide group thus possessed the requisite properties we sought, and the desired allylation could at last be achieved. In principle, the process can be a chain reaction, propagated by the reaction of the diphenylphosphinoyl radical with the dithiocarbonate moiety. The addition–fragmentation of phosphorus-centered radicals on thiocarbonyl derivatives is well documented in the pioneering studies of Barton et al.[19] In practice, however, this approach did not turn out to be efficient, and nearly stoichiometric amounts of the peroxide (0.5 equiv) were needed. It seems that the properties that make the diphenylphosphinoyl radical a good "leaving group" cause it to be a poor chain-propagating agent. All our attempts at determining the fate of the phosphorus species failed.

No elimination occurred in the absence of peroxide, so a purely thermal mechanism can be discarded. Furthermore, the mixture of the two diastereoisomers of **15** could be separated, and only one of the two was in fact subjected to the fragmentation process. Monitoring by thin layer chromatography (tlc) indicated that a rapid equilibration occurred between the two diastereoisomers **15a** and **15b** before elimination of the diphenylphosphinoyl group. Thus, the relative stereochemistry of the initial addition product will have no consequence on the elimination process. Finally, it turns out that it is not even necessary to isolate the addition product **15**, as the allylation can be accomplished directly by heating dithiocarbonate **9** and phosphine oxide **14** in chlorobenzene at reflux using the much longer lasting di-*tert*-butyl peroxide instead of lauroyl peroxide. The yield of enone **16** was 69%, based on **9**, thus representing a significant improvement on the two-step procedure.

We next explored the scope of this reaction by varying the dithiocarbonate and allylic diphenylphosphine oxide. The

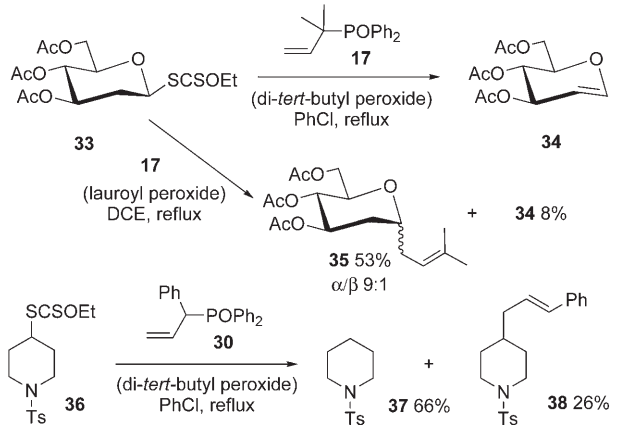
***Table 1:*** Examples of allylations with branched allyl diphenylphosphine oxides.

| Dithiocarbonate | | Phosphine oxide | | Allylation product | | Yield [%][a] |
|---|---|---|---|---|---|---|
| | **9** |  | **17** |  | **18** | 58 |
| | **9** |  | **19** |  | **20** | 52 |
|  | **21** | | **19** |  | **22** | 72 |
|  | **23** | | **17** |  | **24** | 68 |
| | **23** |  | **25** |  | **26** | 67 (9:1) |
|  | **27** | | **25** |  | **28** | 70 |
| | **27** |  | **30** |  | **31** | 66 |
| | **27** |  | **30** |  | **32** | 71 (83:17) |

[a] Ratio of the *E*/*Z* isomers is given in brackets.

results are summarized in Table 1. It can be seen that prenylation is readily accomplished with phosphine oxide **17**, whereas allyl and homoallyl acetates can be introduced with the corresponding phosphine oxides **19**, **25**, and **30**. The dithiocarbonate moiety itself can bear a number of useful functional groups. Besides the initial phenacyl derivative **9**, substrates can contain a lactone (as in **21**), a protected aldehyde ester (as in **23**), or, perhaps most interestingly, a masked α-aminoketone (as in **27**; Phth = phthalimido). α-Aminoketones are at the centre of several classical syntheses of heteroaromatic rings, such as pyrroles and pyridines, and are not always readily accessible. Moreover, the introduction of many of these allylic fragments would not be trivial by the more common ionic processes, especially with the more functionalized substrates.

Our initial attempt to extend this approach to the formation of C–C bonds at the anomeric position of carbohydrates, such in the 2-deoxyglucose derivative **33**, was frustrated by the premature elimination of the dithiocarbonate group at the temperature of refluxing chlorobenzene to give glucal **34** as the major product (Scheme 4). The C–S bond




***Scheme 4.*** Two special cases. Ts = *p*-toluenesulfonyl.

is weakened by an anomeric effect of the lone pair of electrons on the oxygen atom and thus introduces an element of fragility into the substrate. This complication could be circumvented in a large measure by reverting to the lower-boiling 1,2-dichloroethane as the reaction solvent. In this unprecedented anomeric prenylation of a carbohydrate, the phosphine oxide is tertiary and therefore the addition–fragmentation occurs readily at 80 °C.

A preliminary reaction that involved a simple secondary dithiocarbonate moiety gave rather disappointing results. Thus, the attempted allylation of dithiocarbonate **36** gave mostly reduced piperidine **37** and only a low yield of the normal product **38**. Hydrogen abstraction could take place from the solvent or from the benzylic position of the phosphine oxide reagent **30**. Further studies are needed to ascertain the source of the hydrogen atom.

These preliminary results represent a promising approach to a generalized allylation process and highlight the importance of the substitution around the phosphorus center in determining its leaving-group ability. From a synthetic standpoint, access to numerous substituted allyl diphenylphosphine oxides can be accomplished by direct reaction of the anion derived from the simplest member **10** with various electrophiles (alkylating agents, epoxides, aldehydes, and so forth).[20] Another powerful route is through the Arbuzov–Tripett rearrangement starting from allylic alcohols.[21] The radical reaction itself is flexible, convergent, and takes place under mild neutral conditions.

## *Experimental Section*

Typical procedure for the radical allylation: Di-*tert*-butyl peroxide (a few drops, ca. 100 mg) was added to a solution of the dithiocarbonate (1.0 mmol) and allyl phosphine oxide (2.0 mmol) in refluxing degassed chlorobenzene (10 mL) in a nitrogen atmosphere. A few more drops (ca. 100 mg) of di-*tert*-butyl peroxide were added after 4 h at reflux if the reaction is not yet complete (tlc). The reaction mixture was then cooled to room temperature, concentrated in vacuo, and purified by flash chromatography.

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[18] The results reported herein are taken from chapter 4 of PhD thesis of G. Ouvry, which was defended on December 12th, 2002 (G. Ouvry, *Synthèses d'Oléfines par Voie Radicalaire*, Thèse, Ecole Polytechnique, **2002**); the use of the diphenylphosphinoyl entity as a "new" radical leaving group was recently reported by Malacria et al. (D. Leca, L. Fensterbank, E. Lacôte, M. Malacria, *Angew. Chem.* **2004**, *116*, 4316–4318; *Angew. Chem. Int. Ed.* **2004**, *43*, 4220–4222). One of the senior authors (L. Fensterbank) was a principal examiner of the thesis of G. Ouvry, yet no reference is made to the thesis in this paper, nor was there any acknowledgement in the full paper, which appeared shortly afterwards (D. Leca, K. Song, M. Albert, M. Grangeio Gonçalves, L. Fensterbank, E. Lacôte, M. Malacria, *Synthesis* **2005**, 1405–1420) despite a prior exchange of correspondence with the authors on the matter.
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