To the Graduate Council:

I am submitting herewith a thesis written by Ian Addison McAlexander entitled "Development of a New Method for the Conversion of Alcohols into Chlorides." I have examined the final copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

Ronald M. Magid, Major Professor

We have read this thesis and recommend its acceptance:

Accepted for the Council:

Associate Vice Chancellor and
Dean of The Graduate School

# Development of a New Method for the Conversion of Alcohols into Chlorides

A Thesis

Presented for the

Master of Science

Degree

The University of Tennessee, Knoxville

Ian Addison McAlexander

August 1997

## Dedication

This thesis is dedicated to my parents

Dr. John Aaron McAlexander

and

Mrs. Glenda Kincaid McAlexander

who have provided opportunities beyond count

and support beyond measure.

## Acknowledgments

There are a number of people at the University of Tennessee to whom I am grateful. I wish to thank my research advisor, Dr. Ron Magid, the legend himself, whose attention to detail is enlightening (if not maddening), skill as an educator inspiring, and love of organic chemistry contagious. Great praise goes to Dr. Fred Schell for revealing the beauty and logic of organic synthesis. I wish to thank Dr. John Bartmess and Dr. Lee Magid for providing the practical tools for figuring out what is happening in the reaction flask. A note of thanks goes to Dr. R. J. Hinde for taking the time to carefully read this work. I also appreciate the technical support of the staff members of the stockroom, glass shop, machine and wood shop, and electronics shop. I am thankful to the University of Tennessee for generous financial support in the form of teaching assistantships.

The path I now follow began at Appalachian State University. I wish to thank Dr. Thomas C. Rhyne and Dr. Grant Holder for their mentorship and for having more confidence in my ability than did I. High expectations breed success.

My highest praise goes to my parents, my grandparents and my sister Emra for their enthusiastic support and unconditional love. I cannot express enough gratitude to my beloved wife Lenore. I am not even certain where I end and she begins.

## Table of Contents

## Chapter 1 - Introduction

The importance of converting alcohols into chlorides is well documented and the methods numerous. A common purpose of this conversion is to generate a synthetic precursor for the formation of organometallic reagents. Also, the chlorine serves as a mobile leaving group in $S_N1$ and $S_N2$ reactions. The conventional methods for instigating this conversion are:

(1) treatment of the alcohol with HCl, perhaps in the presence of a Lewis-acid catalyst such as $ZnCl_2$,

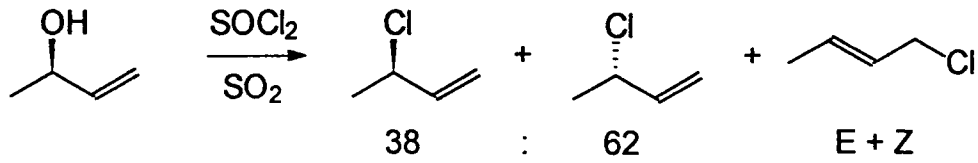
(2) treatment of the alcohol with thionyl chloride, $PCl_3$ or $PCl_5$, or,

(3) conversion into a sulfonate ester such as mesylate or tosylate followed by displacement by chloride.

These methods are generally limited to saturated 1° and 3° alcohols and are not appropriate for sensitive alcohols nor where regiocontrol or stereocontrol must be exercised. Of particular interest to this research group is the regioselective and stereospecific conversion of allylic alcohols into allylic chlorides. This project stems from a long-term interest in the mechanism of the $S_N2'$ reaction.

Allylic alcohols may afford two allylic chloride products, one unrearranged (the α-chloride product) and one allylically rearranged (the γ-chloride product). The example shown below is typical (Equation 1.1).[7]

(1.1)




A more highly substituted alcohol may enrich the product mixture with products from other rearrangements or elimination. The ideal reagent system would afford only one enantiomer (and one stereoisomer in the case of an E or Z alcohol). Conditions should be mild enough that neither elimination nor allylic rearrangement is a problem.

A list of reagent systems is given below. Reagent systems (1) through (4) have been designed to afford as much unrearranged product as possible. The reactive intermediates of systems (2) through (5) are analogous to those of the Arbuzov reaction and will be discussed in Chapter 2.

(1) ROH + $CH_3SO_2Cl$ + LiCl in DMF/collidine [1]

(2) ROH + $CH_3$-S-$CH_3$ + N-chlorosuccinimide [2]

(3) ROH + $Ph_3P$ + $CCl_4$ [3,4]

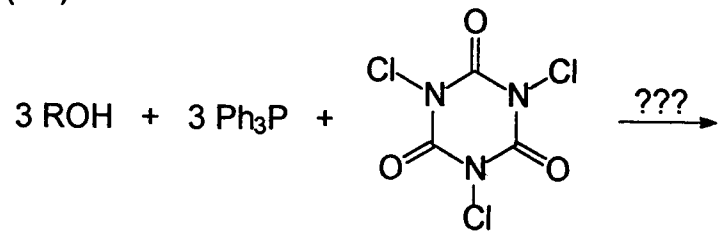
(4) ROH + $Ph_3P$ + hexachloroacetone [5,9]

(5) ROH + $Ph_3P$ + diethylazodicarboxylate + HCl [6]

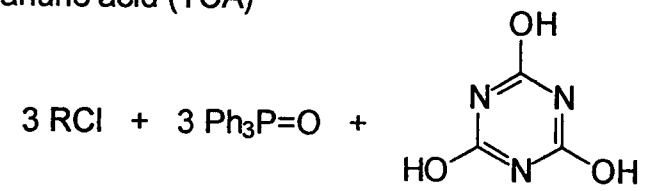
The major goal of this work has been to find an efficient, mild method for converting alcohols into chlorides. Allylic alcohols provide a formidable challenge for any method and therefore help define the scope and usefulness of this reaction. The underlying logic in the choice of reagents came from analogy

with the reactive intermediates in the reagent systems previously listed. The reagent system proposed and examined in this study is shown in Equation 1.2.

(1.2)




Trichlorocyanuric acid (TCA)




Cyanuric acid (CA)

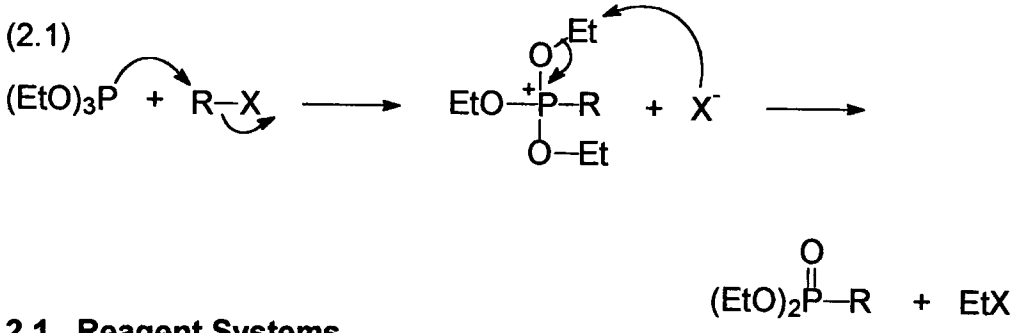
It should be noted that two other minor projects were begun and abandoned prior to the development of this reaction. These are discussed in Chapter 3 - False Starts.

## Chapter 2 - Analogous Reactions

Four reagent systems from Chapter 1 have been used for conversion of allylic alcohols into allylic chlorides. Reagent System 1, employing LiCl in DMF/collidine, will not be discussed as it does not fit the analogy described below.

Each of systems (2) - (5) listed in Chapter 1 contains a nucleophile that removes a "$Cl^+$" from a source of positive halogen. The final step involves displacement on an "onium" species to give the allylic chloride. This displacement is analogous to the product-forming step of the Arbuzov reaction shown in Equation 2.1.

(2.1)

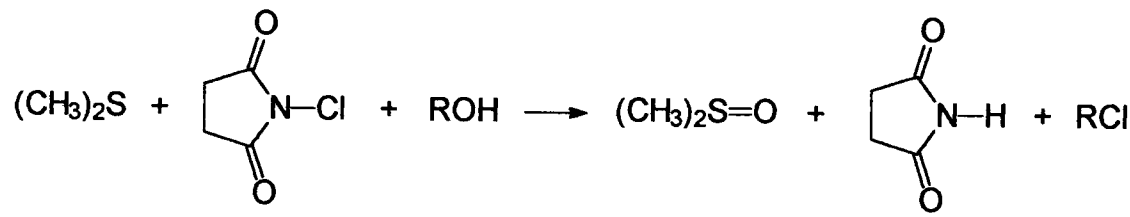


### 2.1. Reagent Systems

#### 2.1.1. Reagent System 2 - Corey's Method [2]

Corey, Kim and Takeda developed the reaction shown in Equation 2.2.

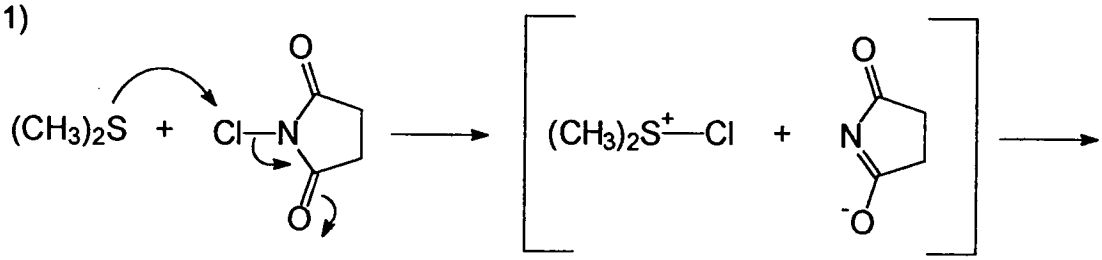
(2.2)



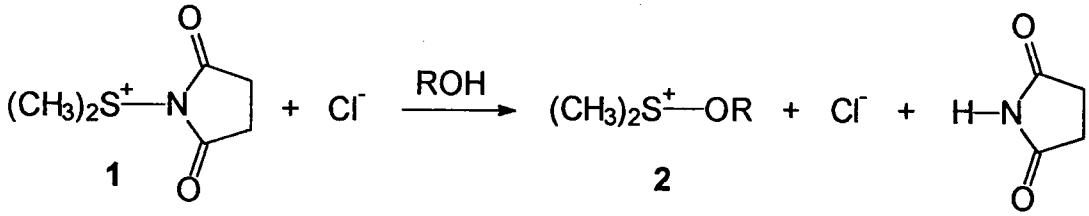
Dimethyl sulfide and N-chlorosuccinimide give reactive intermediate **1** shown in Scheme 2.1 below.[16] Addition of alcohol affords the reactive sulfoxonium intermediate **2**. Once **2** is formed it may undergo $S_N2$ displacement by chloride ion to give the chloride product and dimethyl sulfoxide by-product. Note the analogy with the Arbuzov reaction. The intermediate salt shown in brackets is not suggested in the Corey paper but is inferred by this author. The ability of sulfur to achieve a tetravalent state may make this reaction scheme an over-simplification.

**Scheme 2.1.**

(1)



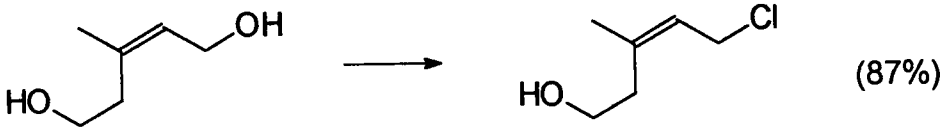
(2)



(3)

Saturated primary and secondary aliphatic alcohols are not reactive. However, alcohols prone to form stabilized cations (such as benzhydrol or allylic alcohols) readily undergo conversion into the chloride. The selectivity of this reaction for one alcohol over another is dramatically demonstrated with Z-3-methyl-2-penten-1,5-diol shown in Equation 2.3.[2]

(2.3)




(87%)

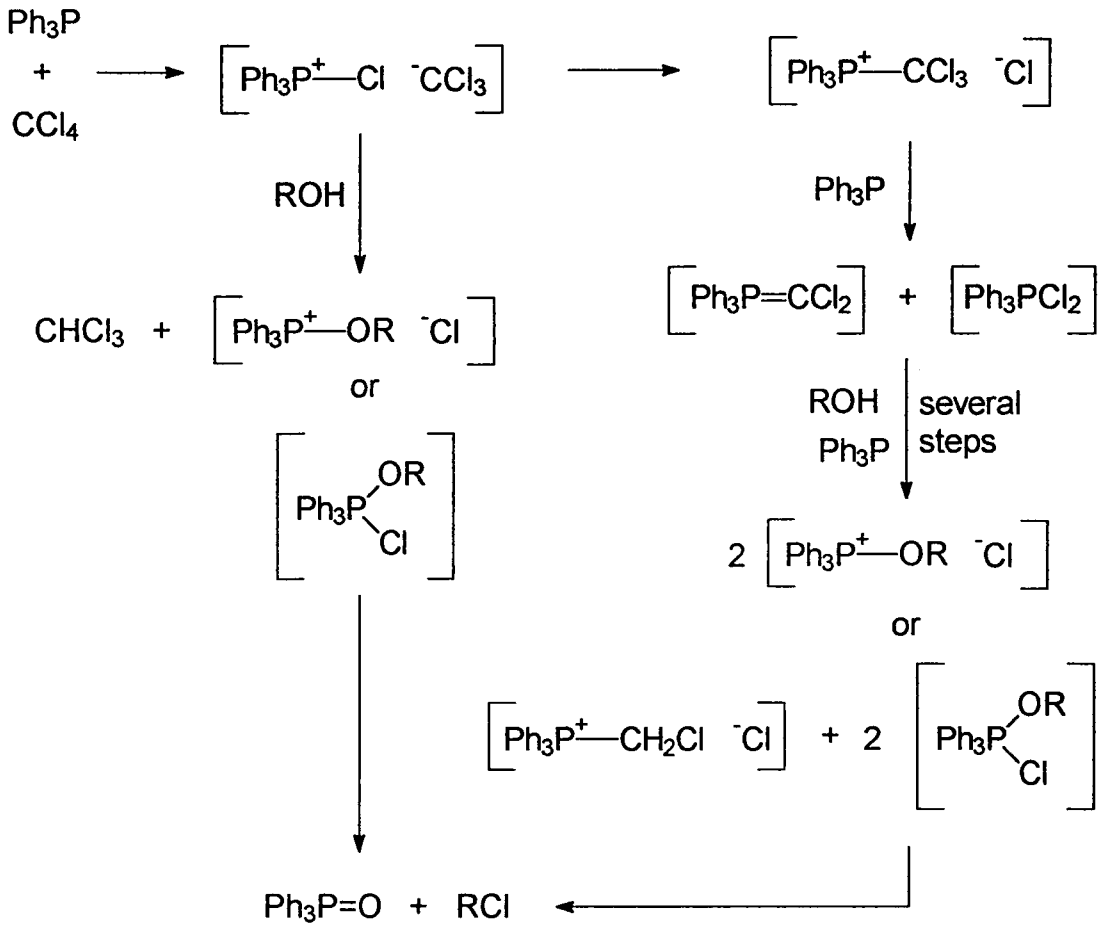
### 2.1.2. Reagent System 3 - Snyder's Method[3]

Snyder applied the triphenylphosphine-carbon tetrachloride reagent system[4] to the formation of allylic chlorides from allylic alcohols as shown in Equation 2.4. The reaction is outlined in Scheme 2.2. For a complete discussion of the complex mechanistic details of this reaction see the review article by Appel.[4] The salient point of this scheme is that the final step is again an Arbuzov-type reaction between $Cl^-$ and an alkoxytriphenylphosphonium ion.

(2.4)

| | | $CH_3CH{=}CHCH_2{-}Cl$ | | $CH_3\underset{\displaystyle Cl}{\underset{\vert}{C}}HCH{=}CH_2$ |
|---|---|---|---|---|
| $CH_3{-}CH{=}CHCH_2OH$ | | 100 | : | 0 |
| | $\xrightarrow[CCl_4]{Ph_3P}$ | | | |
| $CH_3\underset{\displaystyle OH}{\underset{\vert}{C}}HCH{=}CH_2$ | | 11 | : | 89 |

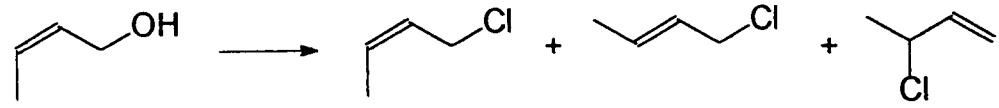
**Scheme 2.2.**


Ph3P
+
CCl4
[Ph3P+—Cl -CCl3]
[Ph3P+—CCl3 -Cl]
ROH
Ph3P
CHCl3 + [Ph3P+—OR -Cl]
or
[Ph3P=CCl2] + [Ph3PCl2]
ROH
Ph3P
several steps
2 [Ph3P+—OR -Cl]
or
[Ph3P+—CH2Cl -Cl] + 2
Ph3P=O + RCl

### 2.1.3. Reagent System 4 - Magid's Method[5,9]

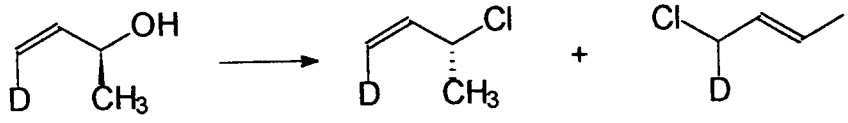
This reagent system is simply a variation on the triphenylphosphine-carbon tetrachloride system previously discussed. Magid and co-workers found that their desired low-boiling allylic chlorides were contaminated by the $CCl_4$ solvent and $CHCl_3$ by-product. Hexachloroacetone (HCA) was proposed as a high-boiling solvent and source of positive chlorine (bp 202 °C). The hope was that up to six equivalents of "$Cl^+$" would be provided giving acetone as the by-product. It was found that when HCA was used as the solvent only one equivalent of "$Cl^+$" was provided. A survey of sixteen allylic alcohols shows the reaction to give excellent yields of allylic chlorides with high regio- and stereoselectivity under mild conditions. In the first example (Equation 2.5) the Z stereochemistry remains essentially unchanged and only a small amount of rearranged product is observed. The secondary optically active allylic alcohol in Equation 2.6 gives complete inversion of configuration in the unrearranged product and, not surprisingly, a small amount of rearranged product.

(2.5)




>99 : <1 trace

(2.6)

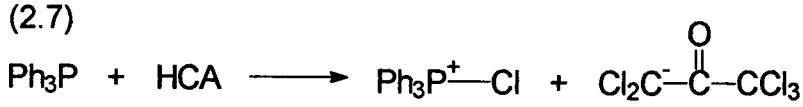


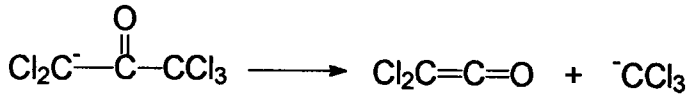

94% 6% (E only)

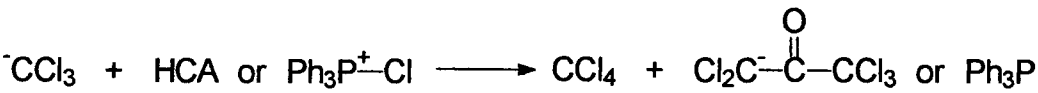
In some cases $CCl_4$ was found to be a minor by-product. The mechanism for the formation of $CCl_4$ has not been determined though two reasonable mechanisms (Equations 2.7 and 2.8) have been eliminated. Note that alcohol must be present for $CCl_4$ to form.

**Reasonable (but wrong) mechanism I.**

(2.7)



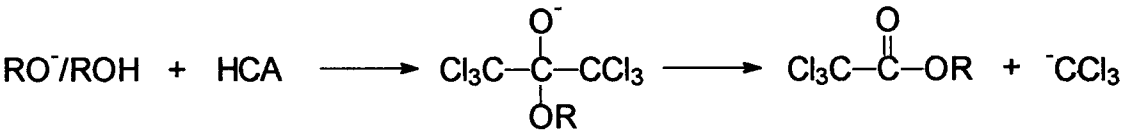


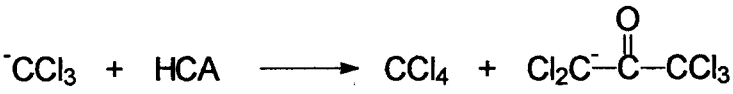


This mechanism does not explain why the alcohol must be present. Also, dichloroketene was not trapped in the presence of excess cyclopentadiene.

**Reasonable (but wrong) mechanism II.**

(2.8)





In this experiment the ester is formed suggesting that $^{-}CCl_3$ is indeed the leaving group. However, $^{-}CCl_3$ removes a proton from the alcohol faster than it can abstract "$Cl^{+}$". The product found in this case, in high yield, is $CHCl_3$, not $CCl_4$. Also, an equivalent of alcohol is needed for the formation of one equivalent of $CCl_4$. This contradicts the nearly quantitative yields of allylic chloride recovered in other experiments.[5]

This reaction, though a great improvement over $Ph_3P/CCl_4$, fails to completely resolve the purification difficulties. It was found that use of the high boiling solvent sulfolane (tetramethylene sulfone, bp 285°C) improved the reaction in the following ways:[9]

(1) Hexachloroacetone now provides two equivalents of positive chloride and may be used in stoichiometric amounts.

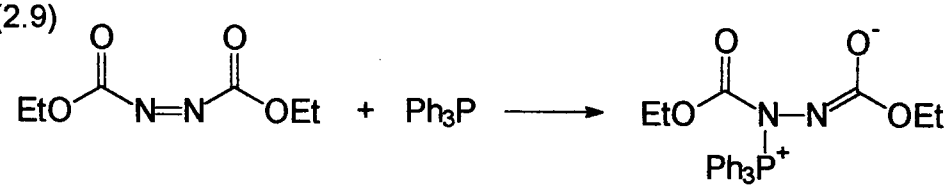
(2) Contamination by $CCl_4$ is no longer a problem.

### 2.1.4. Reagent System 5 - The Mitsunobu Reaction[6]

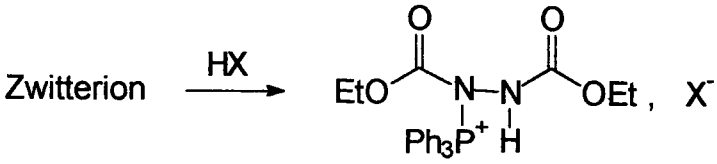
The Mitsunobu reaction has enjoyed mushrooming popularity over the last twenty years. This is due to the versatility of the reaction allowing for an array of functional group exchanges with predictable stereochemistry. The mechanism of the reaction is shown in Steps 1, 2, and 3.

**Step 1. Adduct formation.**

(2.9)



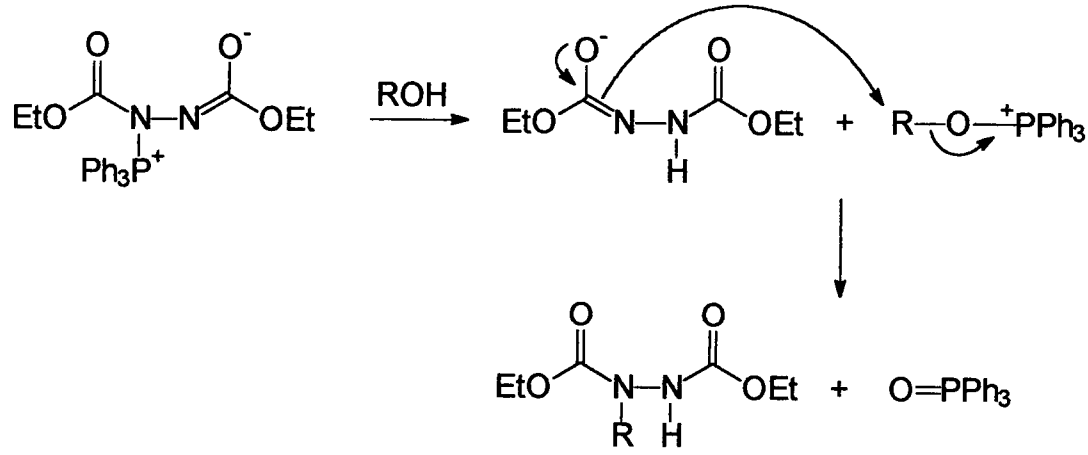
DEAD Zwitterion



Azaphosphonium salt

The Mitsunobu reagent is an azaphosphonium salt. The conjugate base (halide, carboxylate, etc.) of the acid component H-X needs to be weakly nucleophilic. If the zwitterion is formed in the presence of an alcohol instead of H-X, the N-alkylated diethylazodicarboxylate (DEAD) results.

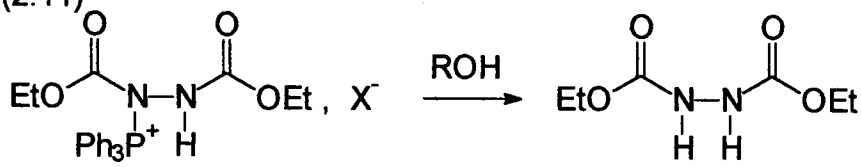
(2.10)



The point is that the alcohol must be introduced after the azaphosphonium salt is formed.

**Step 2. Alcohol activation.**

(2.11)



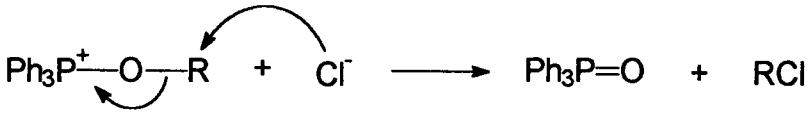

+ $Ph_3P^+—OR$ , $X^-$

Oxyphosphonium salt

The nature of the activated alcohol is still under debate and is dependent upon the alcohol structure and reaction conditions. The activated alcohol may exist as an oxyphosphonium salt (as shown above), as a pentavalent species (several have been isolated[11]) or as an equilibrium mixture. Still, whatever the intermediate species and associated equilibria, the primary suspect as key intermediate is the oxyphosphonium salt. These salts too have been isolated.[12]

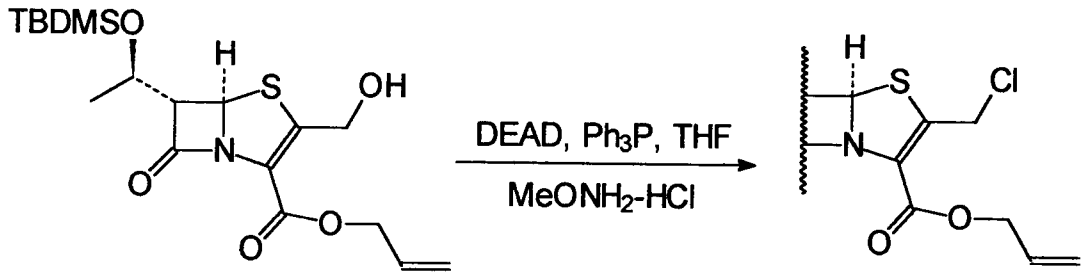
**Step 3. $S_N2$ Reaction:**

(2.12)




Note that this step is analogous to the Arbuzov reaction previously discussed. What the Mitsunobu reaction comes down to then is the formation of an oxyphosphonium salt that can undergo $S_N2$ attack. The nucleophile is chosen depending upon the product desired. Clearly, then, for the formation of chlorides, the nucleophile would be chloride ion. The efficacy of this reaction is evidenced by the transformation in Equation 2.13.

(2.13)




(85%)

This reaction worked where no other reaction had been successful.[10] The use of the Mitsunobu reaction for the conversion of allylic alcohols into chlorides has been little used and perhaps should be explored further.

**Summary of Reagent Systems (2) - (5)**

In reagent systems (2) through (5) the step affording the chloride product is an Arbuzov type $S_N2$ reaction.

## 2.2. Proposal

Trichlorocyanuric acid (TCA) appears to be a promising reagent for the conversion of allylic alcohols into allylic chlorides for several reasons:

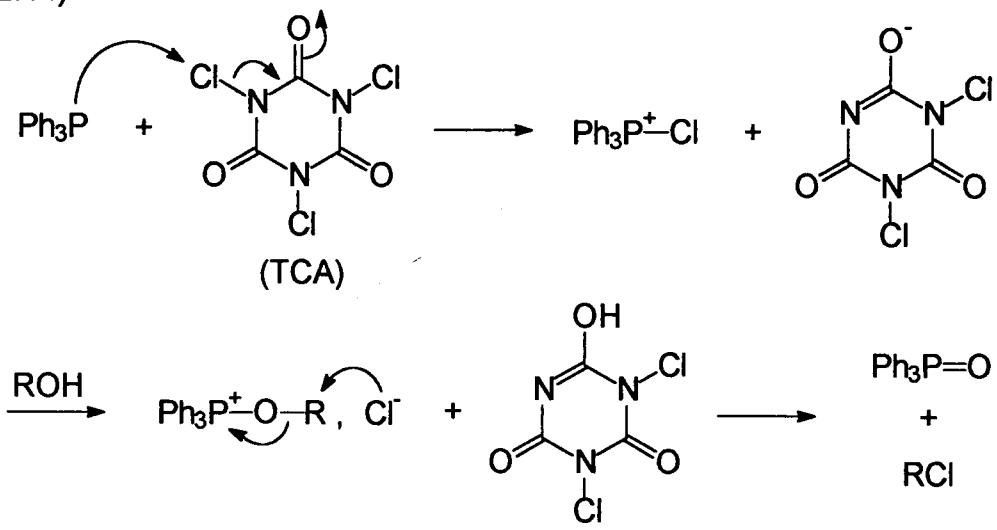
(1) TCA has the potential to be a source of up to three equivalents of positive chlorine. Loss of three "$Cl^+$" followed by protonation would give rise to the inert, aromatic by-product cyanuric acid (CA).

(2) TCA is commercially available as a fine white solid and is easy to handle (though quite reactive).

(3) There is no opportunity for problematic by-products $CHCl_3$ or $CCl_4$ to form.

The anticipated mechanism for one eq of $Ph_3P$ is shown in Equation 2.14.

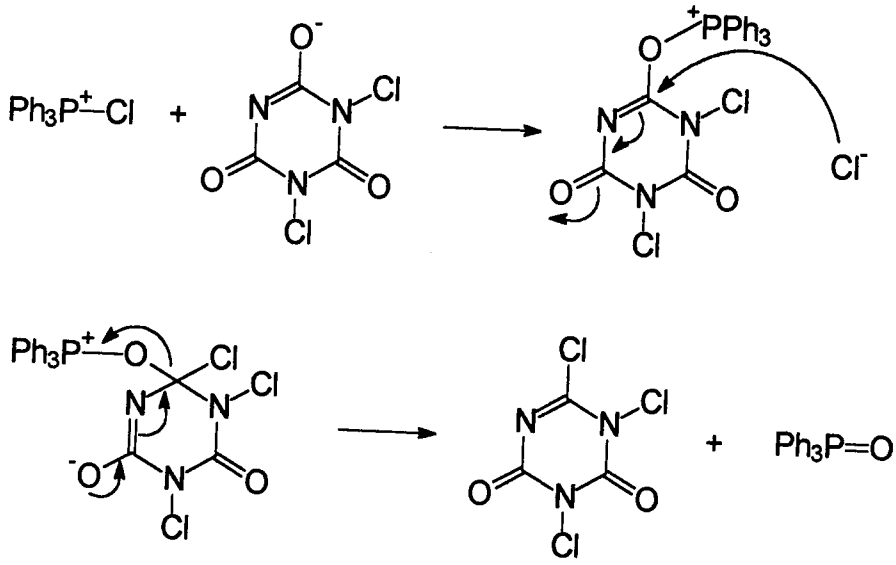
(2.14)




Repetition with two more equivalents each of $Ph_3P$ and ROH should provide a total of three equivalents of RCl and one equivalent of cyanuric acid.

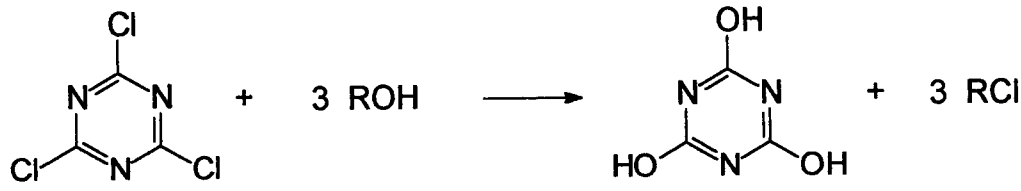
One can theorize about an alternative fate for one of the intermediates. It is conceivable that the conjugate base of TCA could attack the triphenylphosphonium chloride to form either a pentavalent species or an oxyphosphonium salt. Subsequent attack by chloride (Equation 2.15) would lead to the expulsion of triphenylphosphine oxide and the formation of a carbon-chlorine bond.

(2.15)



Repetition with two more equivalents of $Ph_3P$ would give a total of three equivalents of $Ph_3P{=}O$ and an equivalent of cyanuric chloride (CC) before the alcohol has ever been added. This is an important consideration as cyanuric chloride has already been employed for the chlorination of alcohols.[13] The reaction between cyanuric chloride and an alcohol, in which CC is converted into cyanuric acid, is given in Equation 2.16.

(2.16)

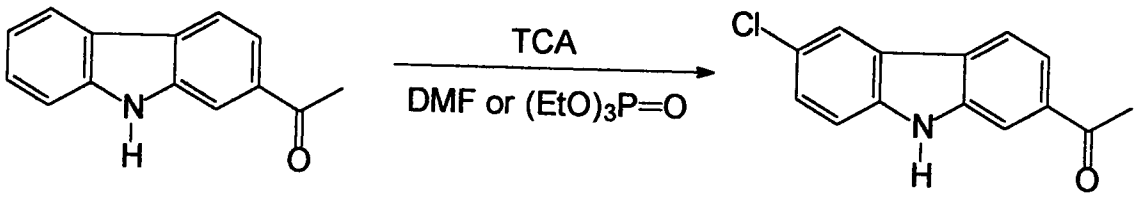


Cyanuric chloride (CC)

Cyanuric acid (CA)

It should also be noted that TCA has been employed as a chlorinating agent though not for the conversion of alcohols into chlorides. Its use has been for an uncatalyzed electrophilic aromatic substitution reaction (Equation 2.17).[14]

(2.17)



## Chapter 3 - False Starts

### 3.1. False Start I.

Can the HCA-$Ph_3P$ reagent system be used to convert alcohols into some functional group other than alkyl chlorides? The system works well for the conversion of allylic alcohols and simple saturated alcohols into chlorides.[5, 9] As noted earlier, the final step in the reaction sequence is $S_N2$ attack on the oxyphosphonium species by chloride to give the alkyl chloride product. It was hypothesized that if a stronger nucleophile ($Nu^-$) were present, preference would be to form R-Nu. The stronger nucleophile could compete with the chloride for a reactive intermediate or, if alkyl chloride were forming, could displace the chloride by an $S_N2$ path. The nucleophile chosen for this investigation was cyanide.

(3.1)

$$R{-}O{-}\overset{+}{P}Ph_3\ ,\ Cl^- \ +\ K^+,\ {}^-CN \xrightarrow{\ ?\ } R{-}CN \ +\ K^+,\ Cl^-$$

**Formation of Valeronitrile, Attempt I.** An equivalent each of dry KCN, crushed $Ph_3P$, 1-butanol, and a small amount of sulfolane were combined and stirred. An equivalent of HCA was added last. Solubility problems between the potassium cyanide salt and organic solvents were expected and indeed encountered. It was hoped that KCN would be at least partially soluble in sulfolane ($\epsilon$=43). The white slurry was stirred for three days. Flash distillation,

followed by analysis by GC-MS, revealed chlorobutane, chloroform and $CCl_4$. No nitrile product was observed.

It was decided that a more polar solvent was needed if the KCN were to dissolve to any appreciable extent. Dimethyl sulfoxide (DMSO) was chosen since it is slightly more polar ($\epsilon$=47) than sulfolane.

**Formation of Valeronitrile, Attempt II.** An equivalent each of KCN and 1-butanol and 2 mL of DMSO were combined. The KCN was observably soluble in the DMSO though it did not dissolve completely. Crushed $Ph_3P$ was added followed by HCA. Flash distillation, followed by analysis by GC-MS, revealed a mixture of 1-butanol, DMSO and $(CH_3)_2S$ (dimethyl sulfide). The odor of the product mixture left little doubt as to the presence of the dimethyl sulfide. Again, no nitrile product was observed.

### 3.2. False Start II.

A primary alcohol notoriously prone to rearrangement is neopentyl alcohol (2,2-dimethyl-1-propanol). It seemed that reaction of this alcohol would complement the previous work on allylic alcohols[5] and perhaps widen the scope of the reaction.

This experiment was first performed in 1978 by Allen and Magid.[15] Products were collected by flash distillation and analyzed by $^1$H-NMR. The question of formation of $CCl_4$ as a by-product remains since it is unobservable

by this technique. If the product was pure neopentyl chloride then the yield was 77%.

**Formation and Analysis of Neopentyl chloride, Attempt I.** Neopentyl alcohol and a great excess of HCA (acting as both solvent and source of positive chlorine) were combined, stirred, and cooled in an ice-bath. A slight excess of $Ph_3P$ was then added and allowed to stir until mostly dissolved (2 hours). Product was collected by flash distillation. Analysis was by GC (GOW-MAC, TCD detector, 20% Carbowax 20M on Chromosorb-P 80/100 mesh).

Two peaks were revealed whose retention times corresponded with authentic samples of neopentyl chloride and $CCl_4$. A series of mixed standards of neopentyl chloride (98%, Lancaster) and $CCl_4$ were prepared. Standards of seven different mole ratios were run, the peak heights recorded and a correlation plot constructed. Interpolation of the product peak heights suggested a product ratio of 50:50 neopentyl chloride:$CCl_4$. Based on the mass of product collected by flash distillation this corresponds to an overall yield of ~25% neopentyl chloride.

**Formation and Analysis of Neopentyl chloride, Attempt II.** Neopentyl alcohol and HCA, acting as both solvent and source of positive chlorine, were mixed and cooled in an ice-bath. A slight excess of crushed $Ph_3P$ was added very slowly (2 hours). Once addition was complete the ice-bath was removed and the reaction mixture stirred until most of the $Ph_3P$ had dissolved (5 hours).

Product was collected by flash distillation and analyzed by gas chromatography (HP 5890 GC with FID detector, PEG fused silica capillary column, HP 3392 A Integrator). Samples of the product were spiked with authentic neopentyl chloride, carbon tetrachloride, and chloroform and analyzed by GC. The two major peaks observed in the product mixture were identified as neopentyl chloride and $CCl_4$. Electronic integration suggested yields of approximately 84% neopentyl chloride, 11% $CCl_4$, and 5% other unidentified by-products.

Hesitant to impart too much value to the integration percentages, it seemed appropriate to construct a Beer's-Law plot from the integration of a series of twelve mixed standards. The standards were a mixture of authentic neopentyl chloride and $CCl_4$. The results were horrible. Repeated injections of the same sample gave reproducible peak heights for neopentyl chloride but not for $CCl_4$. There was no trend in the peak height of the standards that represented the change in $CCl_4$ concentration. *The peak heights for $CCl_4$ appeared random.* The reason for this is simple. The instrument employed a flame ionization detector (FID). The sample injected literally passes through a flame. Incomplete combustion equates to irreproducible results. Carbon tetrachloride is a flame retardant and cannot be analyzed with an FID. There was no other detector available for a GC compatible with capillary columns. The project was abandoned in favor of the proposed reaction employing trichlorocyanuric acid (Equation 2.14). If neopentyl chloride could be produced by this new reaction without $CCl_4$ as a by-product then the efforts here would have been in vain.

## Chapter 4 - Results and Discussion

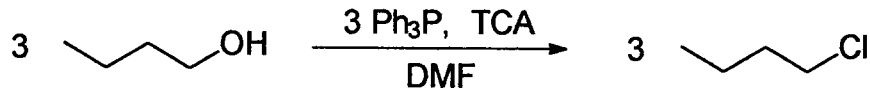
The efficacy of the reagent system, $Ph_3P$/TCA (Equation 2.14), for the conversion of alcohols into chlorides was explored. Reaction conditions and protocol were determined by reaction with a simple saturated primary alcohol. Once a promising method was devised, attention was turned to the reactivity of secondary alcohols, an allylic and a benzylic alcohol.

### 4.1. The Reactions.

#### 4.1.1. Reactions with a 1° Alcohol.

The alcohol of choice for developing this method was 1-butanol. The proposed reaction is shown in Equation 4.1.

(4.1)




Dimethyl formamide (DMF) was chosen as the solvent initially since TCA had been used successfully in this medium by other workers.[14] Products were collected by flash distillation employing a pump table which allows the pressure to be varied. The best yield of 1-chlorobutane was 60%. A small amount of DMF was present in every distillate collected. It was reasoned that the higher boiling analog of DMF, N–methylpyrrolidinone, would resolve the purification

difficulty and perhaps serendipitously increase product yield. In the next trial with 1-butanol, contamination was not a problem. However, the yield of 1-chlorobutane dropped to 27%.

Sulfolane was the solvent of choice for the $Ph_3P$/HCA method and was logically included in the survey. Its high boiling point (285 °C) makes collection of low boiling products particularly simple. With sulfolane as solvent, pure 1-chlorobutane was obtained in 73% yield. With a promising solvent chosen, attention could be turned to reagent protocol.

The highest yield of 1-chlorobutane (82%) was obtained when a slight excess of TCA (11% excess of "$Cl^+$") was added to a solution of 1-butanol and $Ph_3P$ (11% excess) in sulfolane. A white gas and white precipitate were produced instantly. The white precipitate has shown up in a number of reactions. This will be discussed in greater detail later.

Recall that the final step in the formation of alkyl chloride is an $S_N2$ reaction with chloride acting as the nucleophile. It was thought that the reaction might be improved by increasing the concentration of $Cl^-$. LiCl, $Ph_3P$, and 1-butanol were dissolved in sulfolane prior to addition of TCA. Again, a white gas was evolved, a white precipitate was formed and the collected product was pure. A 67% yield of 1-chlorobutane was obtained. This was certainly not an improvement but it is difficult to say if the LiCl was responsible for the small decrease.

In summary, the general reaction conditions and protocol developed with 1-butanol are: $Ph_3P$ (1.1 eq) and alcohol (1 eq) are dissolved in a minimum of

warm sulfolane. TCA (1.1 eq) is added all at once to the stirred solution. Product is flash-distilled into a dry ice-acetone trap until boiling stops within the reaction flask.

### 4.1.2. Reactions with 2° Alcohols.

Employing the method summarized above, but allowing the reaction mixture to stir for 48 hours, a 50% yield of 2-chloropropane was obtained from 2-propanol. A small amount of unreacted alcohol co-distilled with the chloride product. The more sterically hindered 2° alcohols were anticipated to give lower yields than the 1° alcohol 1-butanol.

Cyclohexanol was expected to behave similarly to 2-propanol. Disturbingly, the reaction using cyclohexanol produced only a trace of cyclohexyl chloride whereas the elimination product, cyclohexene, was obtained in 34% yield. The reaction mixture was refluxed to encourage complete conversion; the reflux period probably contributed to the competition from elimination.

### 4.1.3. Reaction of an Alcohol Prone to Rearrangement.

The difficulties associated with neopentyl alcohol were described in Chapter 3 - False Start II. The anticipated by-product from rearrangement is 2-chloro-2-methylbutane. Elimination should not be a problem though overall yield may be depressed due to the bulky nature of the alcohol. Analysis of the isolated product showed exclusively neopentyl chloride in 51.6% yield. The lack

of any rearranged product supports the proposed final $S_N2$ step.

### 4.1.4. Reaction of an Allylic Alcohol.

The allylic alcohol 3-buten-2-ol provides several challenges. As a 2° alcohol it is somewhat hindered and as an allylic alcohol it is prone to rearrangement. There is also the opportunity for elimination. A low yield, 26%, of 3-chloro-1-butene was obtained. Spectral analysis revealed a small amount of the rearranged product 1-chloro-2-butene.

### 4.1.5. Reaction of Benzyl Alcohol.

Benzyl alcohol presents a new challenge. Recall that flash-distillation of low-boiling chlorides was a relatively simple matter in the high-boiling solvent sulfolane. The method had to be altered to isolate the high-boiling product benzyl chloride (bp 179 °C).

A reactive mixture was prepared by dissolving $Ph_3P$ and TCA in methylene chloride ($CH_2Cl_2$). This mixture could be cooled in an ice-bath whereas sulfolane could not (mp 27 °C). Upon addition of benzyl alcohol a white precipitate formed instantly. The white precipitate was collected and the $CH_2Cl_2$ removed by simple distillation. Benzyl chloride was collected by simple distillation but decomposition in the reaction flask quickly became a problem. However, the high purity of the product and the 60% isolated yield were encouraging.

To determine if complete conversion of the alcohol into the chloride was taking place, the reaction was repeated and a sample of the reaction mixture was analyzed after addition of the alcohol. The $^{1}$H-NMR spectrum showed benzyl chloride and no remaining benzyl alcohol. A summary of the reactions used in the development of this method is given in Table 4.1.

## 4.2. The By-products.

A white precipitate formed in five reactions. No clear pattern to its formation was observed. Repeated attempts at obtaining a melting point showed that the compound decomposes at 350 - 400 °C. The white precipitate collected from the reaction of benzyl alcohol (Experiment 15) was dissolved in DMSO-$d_6$ and analyzed by $^{13}$C-NMR. The single peak at δ150 corresponds with the literature spectrum (Sadtler) of cyanuric acid (s-triazine-2,4,6-triol).

$Ph_3P{=}O$ has been isolated from reaction of $Ph_3P$, TCA and alcohol. The $Ph_3P{=}O$ was recrystallized from ether (mp 156 - 159 °C, lit. mp 156 - 158 °C) and analyzed by NMR spectroscopy (see Spectral Data section).

## 4.3. The Reaction Mixture.

### 4.3.1. The Reactive Species.

Recall from the Proposal (Chapter 2.2.) that there is concern that the true reactive species is cyanuric chloride (CC), which has served in this type of conversion before.[13] Attempts were made to identify cyanuric chloride in the

**Table 4.1. Reaction Summary.**

| Exp. # | Alcohol (1 eq.) | Eq. $Ph_3P$ | Eq. $Cl^+$ | Solvent | % Yield RCl |
|---|---|---|---|---|---|
| 1 | 1-butanol | 1 | 1 | DMF | 48 |
| 2 | 1-butanol | 1 | 1.1 | DMF | 60 |
| 3 | 1-butanol | 1.4 | 1.35 | DMF | 50 |
| 4 | 1-butanol | 1.07 | 1.08 | N-methylpy. | 27 |
| 5 | 1-butanol | 1 | 1 | Sulfolane | 73 |
| 6 | 1-butanol | 1.11 | 1.11 | Sulfolane | 82.4 |
| 7 | 1-butanol + LiCl | 1.02 | 1.03 | Sulfolane | 67.2 |
| 8 | 1-butanol | 1.49 | 1.54 | Sulfolane | 75 |
| 9 | 2-propanol | 1.13 | 1.13 | Sulfolane | 50 |
| 10 | cyclohexanol | 1.09 | 1.15 | Sulfolane | 34 Elimination |
| 11 | neopentyl alc. | 1.09 | 1.23 | Sulfolane | 51.6 |
| 12 | 3-buten-2-ol | 1.1 | 1.1 | Sulfolane | 26 |
| 13 | benzyl alc. | 1 | 1 | $CH_2Cl_2$ | 60 |
| 14 | benzyl alc. | 1.27 | 1.28 | $CH_2Cl_2$ | see discussion |

mixture of $Ph_3P$, TCA and $CH_2Cl_2$ ("the reaction mixture"). A literature spectrum of cyanuric chloride could not be found so a sample of the authentic material was purchased from Aldrich. Our observations are listed below.

(1) Authentic cyanuric chloride is soluble in $C_6D_6$ but is not soluble in DMSO-$d_6$. The $^{13}C$ spectrum shows a single peak at δ172.

(2) Cyanuric acid (CA) is soluble in DMSO-$d_6$ but is not soluble in $CDCl_3$ or $C_6D_6$. The $^{13}C$ spectrum shows a single peak at δ150.

(3) $CDCl_3$ plus reaction mixture gives a white precipitate. The $^{13}C$ spectrum shows what may be $Ph_3P=O$ in the reaction mixture (see Spectral Data section).

Neither cyanuric chloride nor any other intermediate reactive species could be identified in the reaction mixture. The presence of $Ph_3P=O$ is strong evidence for the formation of cyanuric chloride. Unfortunately, the spectrum purporting to show $Ph_3P=O$ is complex and is dependent upon the NMR solvent. It is possible that the aromatic alkoxyphosphonium chloride (or its salt) is responsible for a spectrum very similar to that of $Ph_3P=O$. This consideration is discussed further in Section 4.3.2.

### 4.3.2. $^{13}C$ Spectra of $Ph_3P$ and $Ph_3P=O$.

We are looking to verify the presence of $Ph_3P$, $Ph_3P=O$, or an aromatic alkoxyphosphonium salt by $^{13}C$-NMR spectroscopy in the $Ph_3P$/TCA reaction mixture. Complete conversion of $Ph_3P$ into $Ph_3P=O$ would be strong support for the formation of cyanuric chloride in situ. The stoichiometry of each reaction was 3 moles $Ph_3P$ to 1 mole TCA. The solvent in each reaction below was

$CH_2Cl_2$. Recall that the driving force of this reaction is the formation of an aromatic ring.

**Spectral Data in $CDCl_3$.**

(1) $Ph_3P$ in $CDCl_3$ (Aldrich lit. spectrum); 7 peaks (137.27, 137.12, 133.79, 133.53, 128.60, 128.44, 128.35).

(2) $Ph_3P=O$ in $CDCl_3$ (Aldrich lit. spectrum); 7 peaks (133.30, 132.07, 131.94, 131.83, 131.80, 128.48, 128.32).

(3) Newly purchased TCA + $Ph_3P$ in $CDCl_3$; White ppt; 13 peaks (137.2, 136.6, 133.6, 133.4, 133.3, 133.1, 132.0, 131.8, 131.0, 130.8, 130.5, 128.4, 128.3).

There is reasonable argument for the presence of both $Ph_3P$ and $Ph_3P=O$ in (3) above. Most of the literature shifts match up with those in the reaction mixture. A mixture of $Ph_3P$ and $Ph_3P=O$ is exactly what is not expected. No clear conclusion about what species are present in the reaction mixture can be made.

**Spectral Data in $C_6D_6$.**

(4) $Ph_3P$ in $C_6D_6$; 4 peaks (134.3, 134.0, 128.8, 128.7).

(5) $Ph_3P=O$ in $C_6D_6$; 3 peaks (132.9, 132.7, 131.9).

(6) TCA + $Ph_3P$ in $C_6D_6$; White ppt; 7 peaks (134.4, 134.2, 132.5, 132.3, 131.8, 129.6, 129.4).

We have exactly the same dilemma as above: good evidence for a mixture of $Ph_3P$ and $Ph_3P=O$. Conspicuously missing from the spectrum is cyanuric chloride at δ172. But what does this mean?

**Spectral Data in DMSO-$d_6$.**

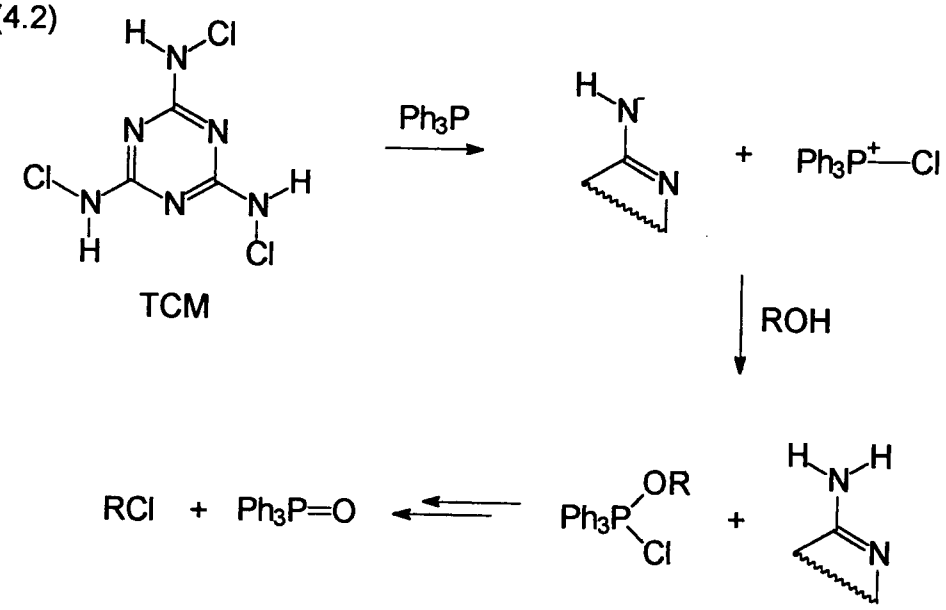
(7) TCA + $Ph_3P$ in DMSO-$d_6$; No white ppt but there was a reaction (heat, loss of color, a few bubbles); 1 peak at δ150.0; 13 peaks (134.5, 133.4, 132.8, 132.6, 132.0, 131.5, 129.8, 129.6, 128.7, 128.5, 124.1, 122.3).

We have 13 peaks though the shifts are a bit different from those of Spectrum 3. The peak at δ150.0 indicates the presence of cyanuric acid. This is surprising since there should not be a proton source. It is assumed that the protons came from water present in the solvent DMSO-$d_6$.

### 4.4. Another Source of Positive Chlorine.

For formation of cyanuric chloride (CC) to occur the conjugate base of TCA would have to attack the $Ph_3P^+$-Cl species as shown in Equation 2.15. This step is not necessary (though it may well still occur) for the proposed reaction shown in Equation 2.14. It seemed reasonable that an oxygen-free source of positive chlorine would kill the opportunity for CC to form by never allowing $Ph_3P=O$ to act as a leaving group prior to addition of the alcohol. The reagent trichlormelamine (TCM) was chosen for this purpose. The anticipated reaction is shown in Equation 4.2.

(4.2)




Analysis of the reaction mixture by $^{13}$C-NMR shows that no reaction took place. It would appear that $Ph_3P$ is not a strong enough base to remove the chlorine. Work with this reagent was abandoned. Experimental details are given at the end of Chapter 5.

## 4.5. Conclusions and a Hypothesis.

Cyanuric chloride (CC) does not appear to be forming in the reaction mixture. Supporting evidence is that there is no clear formation of $Ph_3P=O$ in the reaction mixture prior to the addition of alcohol. Also, we know CC to be soluble in $C_6D_6$ and Spectrum 6 revealed no confirming peak at δ172.

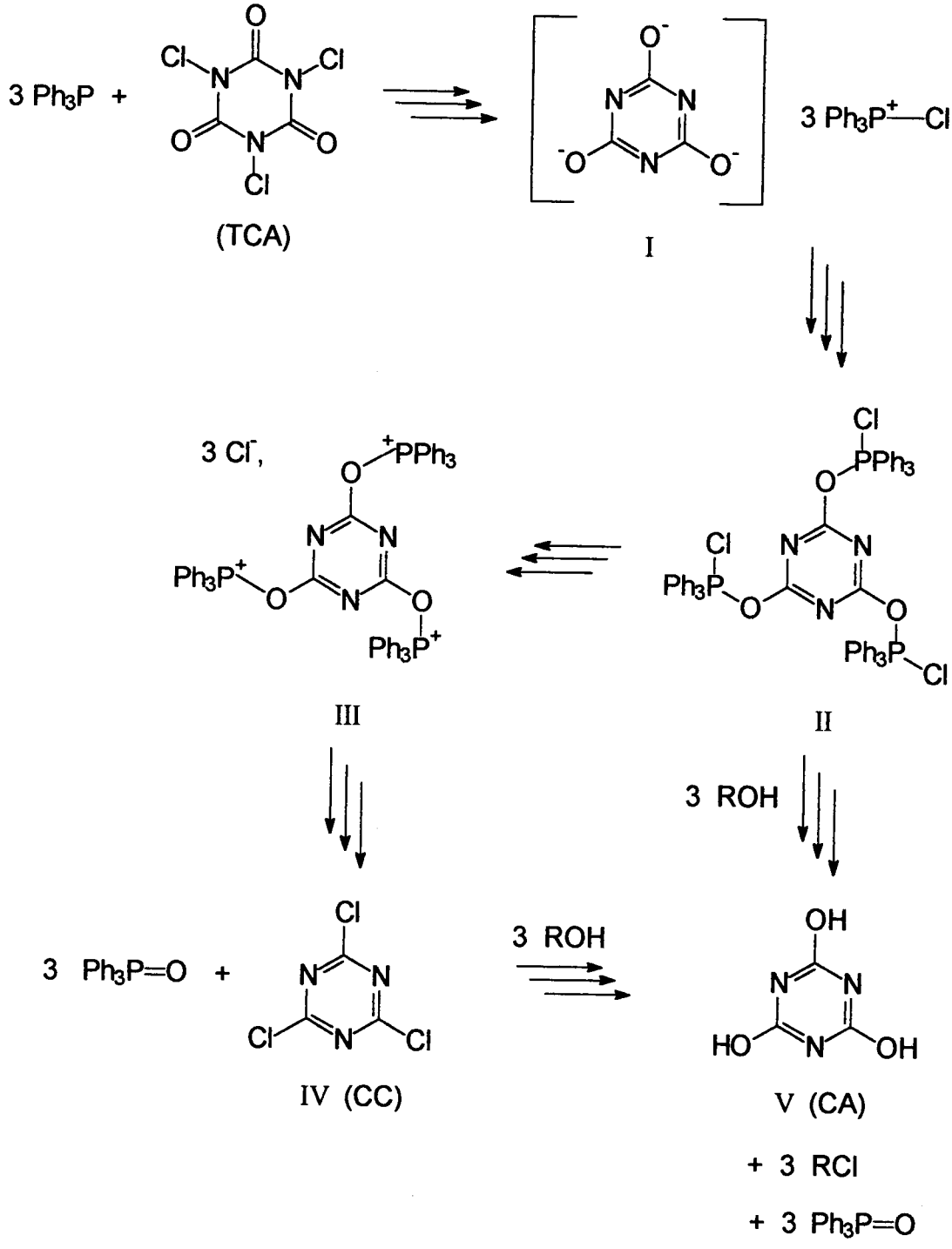
The identity of the white precipitate formed upon addition of NMR solvents $CDCl_3$ and $C_6D_6$ remains a mystery. It could be cyanuric acid if the NMR solvent is wet, water being a proton source just like an alcohol.

My hypothesis as to the identity of the reactive intermediate is shown in

Scheme 4.1. I propose that the spectral data disprove path **II** → **III** → **IV** and that the reactive intermediate is **II** or perhaps **III** as a tight ion pair. Perhaps the spectral data are representative of the equilibria among species **I**, **II**, and **III**. Note that for formation of cyanuric chloride (**IV**), chloride ion, a relatively weak nucleophile, must disrupt the aromatic ring. The good resonance stabilization through the ring system and the excellent leaving group are the only reasons this is considered at all. By path **II** → **V**, once the aromatic ring is formed in the first step it need never be disrupted. We simply await a nucleophile that can act as a proton source.

In conclusion, this method has excellent potential for the conversion of alcohols into chlorides. The reaction works with problematic alcohols. Yields may possibly be improved by preparing and chilling the reaction mixture prior to introduction of the alcohol. Product isolation needs to be improved and the scope of the reaction needs to be expanded. The results obtained here justify further investigation.

**Scheme 4.1.**


3 Ph3P +
(TCA)
I
3 Ph3P+—Cl
3 Cl-,
III
II
3 ROH
3 Ph3P=O +
IV (CC)
3 ROH
V (CA)
+ 3 RCl
+ 3 Ph3P=O

## Chapter 5 - Experimental Details

### General Procedure.

All products were collected by flash distillation and analyzed by $^1$H-NMR in $CDCl_3$, unless otherwise noted, on a Bruker AC-250 spectrometer. All solvents were either newly purchased (Aldrich) or freshly distilled by rotary evaporation and stored over 4 Å molecular sieves. The purity of each solvent was checked by $^1$H-NMR prior to use. TCA was stored in a desiccator. All reported yields are isolated yields unless stated otherwise.

### Reaction of 1-Butanol with $Ph_3P$-TCA in Dimethyl Formamide (DMF).

**Experiment 1.** TCA (1.741 g, 21.80 mequiv. "$Cl^+$") was dissolved in a minimum of DMF. This solution was added dropwise to a stirred solution of $Ph_3P$ (5.790 g, 21.86 mmol) and 2 mL of 1-butanol (~22 mmol) in a minimum of DMF. Stirring was continued for 1 hour at room temperature and 0.5 hours at gentle reflux. Analysis by $^1$H- and $^{13}$C-NMR revealed only 1-chlorobutane (48% yield by mass) and a small amount of DMF.

**Experiment 2.** TCA (1.929 g, 24.16 mequiv "$Cl^+$", 10% excess) was dissolved in 5 mL of DMF. This solution was added dropwise over 1 hour to a stirred solution of $Ph_3P$ (5.813 g, 21.94 mmol) and 1-butanol (1.630 g, 21.99 mmol) in 10 mL of DMF. Stirring was continued for 1 hour at room temperature

and 0.5 hours at gentle reflux. Analysis revealed 1-chlorobutane (60% yield) and a small amount of DMF.

**Experiment 3.** TCA (2.156 g, 27.00 mequiv "$Cl^+$", 35% excess) was dissolved in 7 mL of DMF. This solution was added dropwise over a period of 15 minutes to a stirred solution of $Ph_3P$ (7.420 g, 28.01 mmol, 40% excess) and 1-butanol (1.480 g, 19.97 mmol) in 15 mL of DMF. The temperature of the clear yellow solution was never allowed to rise above 40 °C. Near the end of the addition a white precipitate formed. Analysis revealed 1-chlorobutane (50% yield) contaminated by a small amount of DMF. Collection of a second fraction afforded mostly DMF and some 1-chlorobutane.

**Reaction of 1-Butanol with $Ph_3P$-TCA in N-Methylpyrrolidinone.**

**Experiment 4.** $Ph_3P$ (3.928 g, 14.83 mmol, 7% excess) and 1-butanol (1.025 g, 13.82 mmol) were dissolved in 15 mL of N-methylpyrrolidinone and cooled in an ice-bath (16 °C). The solid TCA (1.187 g, 14.86 mequiv. "$Cl^+$", 8% excess) was added all at once. A white gas evolved, the temperature jumped to 42 °C and the solution became clear purple-gray. Stirring was continued for 30 minutes. Analysis revealed 1-chlorobutane (27% yield) and a small amount of unreacted alcohol.

**Reaction of 1-Butanol with $Ph_3P$-TCA in Sulfolane.**

**Experiment 5.** $Ph_3P$ (3.583 g, 13.52 mmol) was dissolved in a minimum of warm sulfolane (60 °C). 1-butanol (1.002 g, 13.51 mmol) was added followed by TCA (1.186 g, 14.85 mequiv. "$Cl^+$", 10% excess). The temperature jumped from ambient to 88 °C and was stirred for 2 hours without external heating. Product was collected in two sessions. Analysis of both fractions revealed pure 1-chlorobutane (73% yield).

**Experiment 6.** $Ph_3P$ (3.931 g, 14.84 mmol, 11% excess) and 1-butanol (0.989 g, 13.35 mmol) were dissolved in 15 mL of warm sulfolane (50 °C). The reaction flask was equipped with a water cooled condenser. The TCA (1.179 g, 14.76 mequiv. "$Cl^+$", 11% excess) was added as the solid all at once. The exothermic reaction instantly produced a white gas and white precipitate. Analysis revealed pure 1-chlorobutane (82.4% yield).

**Experiment 7.** $Ph_3P$ (4.008 g, 15.13 mmol, 2% excess), LiCl (0.628 g, 14.81 mmol), and 1-butanol (0.950 g, 12.82 mmol) were dissolved in 20 mL of warm sulfolane. The flask was immersed in a room-temperature water bath. The TCA (1.214 g, 15.20 mequiv. "$Cl^+$", 3% excess) was added all at once to the stirred solution. A white gas evolved and a white precipitate formed instantly. Analysis revealed pure 1-chlorobutane (67.2% yield). Vacuum filtration (washed with acetone) afforded 1.746 g of white precipitate.

**Experiment 8.** $Ph_3P$ (5.127 g, 19.35 mmol, 49% excess) was dissolved in 20 mL of sulfolane. TCA (1.589 g, 19.90 mequiv. "$Cl^+$", 54% excess) was added all at once to the stirred solution. The reaction mixture became very hot and turned golden-yellow. Once cooled to room temperature, the 1-butanol (0.960 g, 12.95 mmol) was added in one aliquot and the reaction mixture refluxed for 1 hour turning the solution slightly brown. Analysis revealed pure 1-chlorobutane in 75% yield.

**Reaction of 2-Propanol with $Ph_3P$-TCA in Sulfolane.**

**Experiment 9.** $Ph_3P$ (3.920 g, 14.80 mmol, 13% excess) and 2-propanol (0.785 g, 13.1 mmol) were dissolved in a minimum of sulfolane and cooled in an ice-bath. After addition of TCA (1.182 g, 14.80 mequiv. "$Cl^+$", 13% excess) the reaction mixture was allowed to stir for 48 hours. Analysis revealed 2-chloropropane (50% yield) and a small amount of unreacted alcohol.

**Reaction of Cyclohexanol with $Ph_3P$-TCA in Sulfolane.**

**Experiment 10.** $Ph_3P$ (4.366 g, 16.50 mmol, 9% excess) and cyclohexanol (1.518 g, 15.16 mmol) were dissolved in 15 mL of warm sulfolane (50 °C) and cooled briefly in an ice-bath to 20 °C. The TCA (1.394 g, 17.5 mequiv. "$Cl^+$", 15% excess) was added in several portions. The temperature increased to 50 °C (no white gas evolved). Stirring was continued for 1.5 hours at room temperature and 0.5 hours at gentle reflux (140 °C). Analysis revealed

cyclohexene (34% yield) and a small amount of cyclohexyl chloride.

**Reaction of Neopentyl Alcohol with $Ph_3P$-TCA in Sulfolane.**

**Experiment 11.** $Ph_3P$ (4.367 g, 16.48 mmol, 9% excess) and neopentyl alcohol (1.348 g, 15.14 mmol) were dissolved and stirred in a minimum of sulfolane. TCA (1.339 g, 18.63 mequiv. "$Cl^+$", 23% excess) was added in one portion. White gas was produced instantly and the temperature increased from 28 °C to 82 °C. Stirring was continued for 2 hours. Analysis revealed the product to be exclusively neopentyl chloride (51.6% yield).

**Reaction of 3-Buten-2-ol with $Ph_3P$-TCA in Sulfolane.**

**Experiment 12.** $Ph_3P$ (3.962 g, 14.95 mmol, 10% excess) and 3-buten-2-ol (1.000 g, 13.59 mmol) were dissolved in a minimum of sulfolane. The TCA (1.196 g, 14.98 mequiv. "$Cl^+$", 10% excess) was added all at once. The reaction was exothermic and accompanied by a small amount of white gas. Stirring was continued for 1.5 hours. Analysis revealed mostly 3-chloro-1-butene (26% yield) and a small amount of 1-chloro-2-butene.

**Reaction of Benzyl Alcohol with $Ph_3P$-TCA in $CH_2Cl_2$.**

**Experiment 13.** TCA (2.096 g, 26.24 mequiv. "$Cl^+$") was added to 20 mL $CH_2Cl_2$. The TCA would not dissolve completely. The mixture was immersed in an ice-bath and the $Ph_3P$ (6.938 g, 26.19 mmol) was added slowly. The solution

became clear pale-yellow and yet a small amount of white precipitate remained. A sample of the solution was removed for $^{13}C$-NMR analysis.

With the ice-bath in place, benzyl alcohol (2.826 g, 26.13 mmol) was added to the stirred solution. A white precipitate formed instantly. Stirring was continued for 30 minutes at gentle reflux. The white precipitate was collected by gravity filtration. Products were collected by simple distillation, the first fraction ($CH_2Cl_2$) over a range of 40 - 60 °C and the second fraction (benzyl chloride, 60% yield) over a range of 174 - 176 °C. A large amount of decomposition product (black and yellow tar) remained in the pot.

**Experiment 14.** $Ph_3P$ (1.948 g, 7.353 mmol, 27% excess) was dissolved in 10 mL of $CH_2Cl_2$ and cooled in an ice-bath. The TCA (0.593 g, 7.425 mequiv. "$Cl^+$", 28% excess) was added all at once causing the solution to boil and reflux within the cold flask. The solution turned from clear and colorless to clear pale-yellow. Samples were removed for analysis by $^{13}C$-NMR.

Benzyl alcohol (0.626 g, 5.789 mmol) was added to the reaction mixture again causing the solvent to reflux within the cold flask and a large quantity of white precipitate quickly formed. The ppt. was collected by vacuum filtration, washed with $CH_2Cl_2$ and dried in an oven at 60 °C. $^1H$-NMR analysis in DMSO-$d_6$ showed the white precipitate to be cyanuric acid. Analysis of the reaction mixture ($CDCl_3$) showed benzyl chloride but no benzyl alcohol.

**Reaction of 1-Butanol with $Ph_3P$ and Trichloromelamine (TCM) in Sulfolane.**

**Experiment 15.** $Ph_3P$ (1.624 g, 6.130 mmol, 4% excess) was dissolved in 10 mL of warm sulfolane. A water bath kept the solution at 40 - 50 °C. TCM (0.488 g, 6.253 mequiv. "$Cl^+$", 6% excess) was added all at once to the stirred solution changing it from clear and colorless to clear yellow. A small amount of TCM remained undissolved after 1 hour of stirring even after adding a 5 mL aliquot of additional sulfolane. The 1-butanol (0.438 g, 5.909 mmol) was added and stirring was continued for 0.5 hours. Once cool, a sample of the reaction mixture was taken for analysis ($^{13}C$-NMR, DMSO-$d_6$) revealing unreacted 1-butanol and no 1-chlorobutane.

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## Vita

Ian McAlexander was born in Charlotte, North Carolina on February 3, 1968. He survived the Mecklenburg County Public School System graduating from Independence Senior High School in June, 1986. He attended Montreat College in Montreat, North Carolina for two years receiving the Associate in Science, Natural Science degree in May of 1988. Proceeding to Appalachian State University in Boone, North Carolina, he completed his Bachelor of Science in Chemistry, ACS Certification, in May of 1992. He spent the next two years as an Analytical Technologist with Chemical Specialties, Inc. in Harrisburg, North Carolina. Well motivated for graduate school, he entered The University of Tennessee, Knoxville in August of 1994. En route to completing his Master of Science degree he collected a Graduate Teaching Award and completed the cumulative exam system. The Master's degree was awarded in August of 1997.