

The Iowa connection

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Abstract

A summary of the Fluorinated Ylide Chemistry, Organometallic Chemistry, Phosphonate Chemistry, Single-Electron-Transfer Chemistry and Metal Hydride Chemistry carried out at the University of Iowa is described. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Synthetic methodology; Organofluorine chemistry; Ylides; Organometallics; Phosphonates; SET chemistry

1. Introduction

The research initiated in my group at the University of Iowa was influenced by my associations with Professors W.T. Miller and H.C. Brown, which aroused my interest in fluoro-olefin chemistry and organoborane chemistry, respectively. As the reader will note, we have developed synthetic methodology in several different areas, some which are interrelated, while others stemmed from current trends in organofluorine chemistry. In order to provide some coherence, I have organized the chemistry into general topics, rather than adopt a strict chronological presentation. I have explained why we pursued particular synthetic topics and also how each topic developed from its conception until the present or until we lost interest in it. Because of space limitations, it has not been possible to discuss every research topic pursued during the past 36 years, and I apologize to any coworker whose work is not presented here.

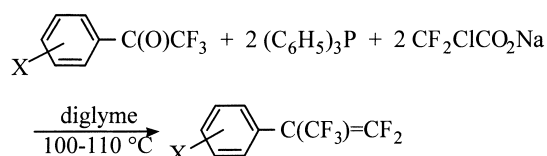
2. Ylide chemistry

My initial research topic, as a graduate student, in Professor Miller's laboratory was the preparation of 2-phenyl-substituted perfluoroallyl halides and a mechanistic study of S_N2' reactions of such halides with fluoride ion. At that time (1956), however, the lack of suitable routes to this class of perfluoroallyl halides caused us to postpone the work. Instead, I pursued the aluminum halide-catalyzed rearrangement and disproportionation of fluorohaloalkanes and

fluorohaloallyl halides as a Ph.D. topic [1]. However, my initial thesis topic continued to be of interest to me, and a stubborn determination to conquer this topic was never abandoned by my subconscious, even though it took us another 15 years to succeed! The key to this research problem was found through our studies on fluorinated phosphorus ylides.

2.1. Fluorohalomethylene ylides from fluorohalomethanes and tertiary phosphines

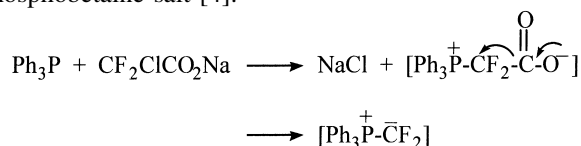
My initial interest in ylide chemistry was piqued by Frank Herkes, one of the first graduate students to join my research group at Iowa in 1962. He pointed out to me that Fuqua and coworkers [2] had prepared 1,1-difluoro-olefins from aldehydes by heating an aldehyde, triphenylphosphine, and sodium chlorodifluoroacetate in a glyme solvent. This approach, however, failed with ketones. The ylide $[\text{Ph}_3\text{P}^+-\text{CF}_2^-]$ was proposed as a transient species in this transformation, formed via capture of $[:\text{CF}_2]$ (from thermolysis of the acetate) by the nucleophilic tertiary phosphine. Since neither one of us knew anything about ylides at that time, Frank and I naively assumed that this ylide was insufficiently nucleophilic to react with standard ketones. However, we anticipated that it would attack the more electrophilic carbonyl group in ketones of the type $\text{ArC}(\text{O})\text{R}_\text{F}$ and thus established a new route to β -phenyl-substituted perfluoro-olefins [3,4]:



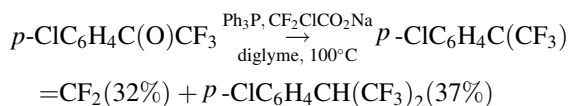
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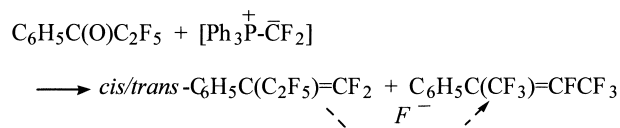
This venture initiated our work in ylide chemistry, which continues to the present time. We were fortunate that the tertiary phosphine, Ph_3P , did *not* react either with the perfluoroalkyl ketones or with the olefinic product. Mechanistic experiments suggested that the ylide was not formed by trapping of $[:\text{CF}_2]$, but was formed via decomposition of a phosphobetaine salt [4]:



With ketones containing a carbanion stabilizing group, it became apparent that significant amounts of fluoride ion were formed in the generation of the ylide, since both the olefin and its HF-addition product were formed, e.g.,

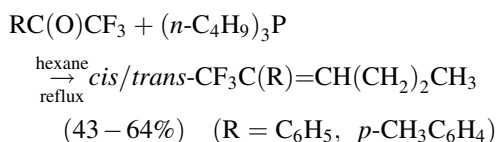


Also, with ketones containing perfluoroalkyl groups of more than one carbon, a mixture of the terminal olefin and internal olefin (isomerized product) was formed [5,6], e.g.,



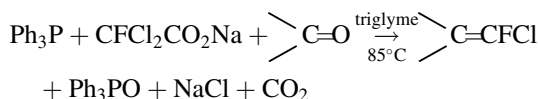
HF-addition and fluoride ion-catalyzed isomerization could be avoided by using lithium chlorodifluoroacetate in DMF to generate the ylide [6]. Attempts to pre-generate the ylide were unsuccessful [4].

Fuqua and coworkers had attempted to prepare 2-phenylpentafluoropropene via the more nucleophilic ylide $n\text{-Bu}_3\text{P}^+-\overset{\ominus}{\text{C}}\text{F}_2^-$ [7]. However, when trifluoroacetophenone was heated with $n\text{-Bu}_3\text{P}$ and sodium chlorodifluoroacetate in *N*-methyl-2-pyrrolidone (NMP), they obtained 1,1,1-trifluoro-2-phenyl-2-hexene in low yield. To account for this, these workers proposed that the difluoromethylene ylide formed initially rearranged before being trapped by ketone. However, Ken Klabunde in our laboratory demonstrated that the products isolated by Fuqua et al. [7] were actually formed via direct reaction of the tertiary trialkylphosphine with the perfluoroalkyl aryl ketone [8]. This work provided the first reported examples of reactions between a perfluoroalkyl ketone and a trialkylphosphine:



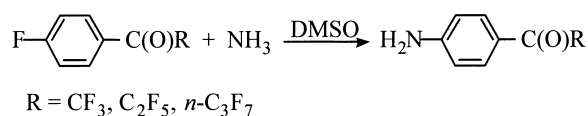
This initial work was extended by Henry Krutzsch, who established that the mixed halogen ylide $[\text{Ph}_3\text{P}^+-\text{CFCl}]^-$

could be generated by two different methods [9,10], as outlined below:



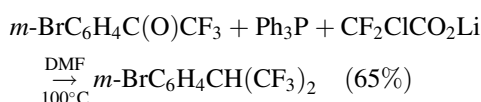
The similarity in the *cis/trans* ratio of fluorochloro olefinic products from the two methods suggested that the mixed ylide was a common intermediate. In contrast to the difluoromethylene ylide, the mixed fluorochloro ylide exhibited some stability and could be pre-generated (albeit in moderate to low yields). Coincident with our work, Ando and coworkers reported the same mixed ylide, formed via the reaction of methyl dichlorofluoroacetate with triphenylphosphine and sodium methoxide [11].

The unavailability of *meta*- and *para*-substituted trifluoroacetophenones, with substituents such as NH_2 , CN , Br , and I , seriously impeded the preparation of β -phenyl-substituted perfluoro-olefins. However, Klabunde developed a simple, useful route to the amino-substituted ketones, which could then be readily transformed into other derivatives by the Sandmeyer reaction [12]:



These ketones were subsequently utilized by Klabunde for the preparation of phenyl-substituted hexafluoropropanes, $\text{CF}_3\text{CHArCF}_3$. The acidity of these propane derivatives was studied by base-catalyzed hydrogen, deuterium and tritium isotope exchange methods to probe fluorine hyperconjugation, intermediate carbanion stability and carbanion geometry [13]. None of this work would have been possible without the ylide route to the olefin precursors required for the 2-hydropropane compounds. Similarly, the availability of fluorochloro-olefin products derived from the mixed halogen ylide provided us with the opportunity to study the stereochemistry of nucleophilic displacement of chloride ion in β -substituted-1-chloroperfluoro-olefins [14]; in all cases, retention of configuration was observed.

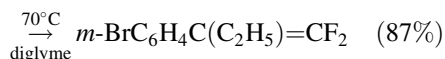
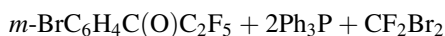
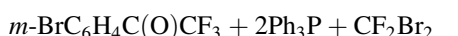
Even though the use of lithium chlorodifluoroacetate in DMF circumvented some of the problems with substituted aryl perfluoroalkyl ketones [6], it did not solve them all. For example, with *m*-bromophenyl trifluoromethyl ketone, only the H-F addition product was isolated:



Similarly, with *m*-bromophenyl pentafluoroethyl ketone, the internal olefin $m\text{-BrC}_6\text{H}_4\text{C}(\text{CF}_3)=\text{CFCF}_3$ was the major

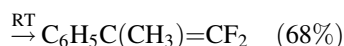
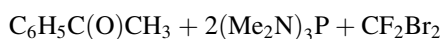
product. With other good carbanion stabilizing groups, such as Br, I, CN, NO₂ in the perfluoroalkyl ketone, similar results were observed with CF₂ClCO₂Li. Clearly, an alternative fluoride-ion free route to these reactive β-substituted-1,1-difluoro-olefins was required.

Rabinowitz had suggested that 1,1-difluoro-olefins could be formed via the interaction of dibromodifluoromethane with Ph₃P and RCHO. However, no details were provided or subsequently published. Doug Naeae subsequently developed a procedure whereby a perfluoroalkyl aryl ketone was treated with CF₂Br₂ and Ph₃P at 70°C in glymes or DMF to give excellent yields of 1,1-difluoro-olefins [15]. No H-F addition products or isomerized olefins were observed, e.g.,

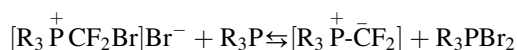


In addition, the yields of olefinic products are generally higher than via the chlorodifluoroacetate method. However, like the acetate route, the CF₂Br₂ route failed with ketones that did not contain an activating perfluoroalkyl group, e.g., acetophenone.

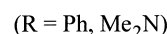
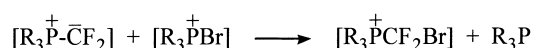
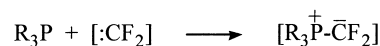
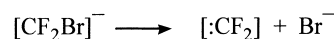
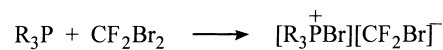
Naeae resolved this problem by employing the more nucleophilic ylide [(Me₂N)₃P⁺-CF₂⁻] generated from (Me₂N)₃P and either CF₂Br₂ or CF₂Cl₂:



Ketones, such as cyclohexanone, other non-activated ethyl phenyl ketones and diethyl ketone also gave good yields of the corresponding 1,1-difluoro-olefins [16,17]. Naeae was able to isolate and identify the bromodifluoromethylphosphonium salts formed initially from the reaction of the tertiary phosphine and CF₂Br₂. Mechanistic experiments demonstrated that these salts were formed via a difluorocarbene route (Scheme 1). A second halophilic attack on the phosphonium salt gave the corresponding ylide:

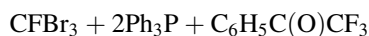


Extension of this methodology to the bromofluoromethylene ylide by Bill Vander Haar [18] provided a new route to bromofluoromethylene olefins directly from aldehyde or ketone precursors. Unfortunately, the bromofluoro ylide olefination route is not stereospecific and gives *cis/trans* mixtures of olefins. The phosphonium salt [Ph₃PCFBr]⁺Br⁻ can be isolated when CFBBr₃ and Ph₃P



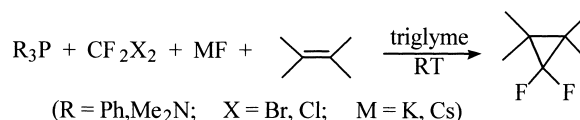
Scheme 1.

are used in equimolar amounts.



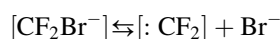
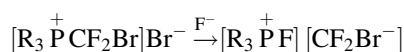
Similar work by Mike Van Hamme [19] provided access to the phosphonium salt [(Me₂N)₃PCFCl₂]⁺Cl⁻ (via reaction of (Me₂N)₃P with CFCl₃) and hence the ylide (Me₂N)₃P⁺-C⁻FCl. He also demonstrated that Ph₃P, CFCl₃, >C=O and zinc dust in DMF at 60°C could provide chlorofluoromethylene olefins in one step [20].

The phosphonium salts prepared in our ylide work provided convenient sources of other transient intermediates, such as dihalocarbenes and trihalomethide ion. Naeae demonstrated that bromodifluorotriphenylphosphonium bromide was readily cleaved by methoxide or fluoride ion to give difluorocarbene [21]. He developed this route as a one-pot procedure to produce difluorocyclopropanes via in situ formation of the phosphonium salt precursor, e.g., [21]



This facile formation and capture of difluorocarbene has been extensively utilized by many workers over the past 25 years and has become the most widely employed mild, non-basic route to difluorocarbene.

The carbene is formed via initial cleavage of the phosphonium salt to give a trihalomethide ion which collapses via α-elimination to the carbene:

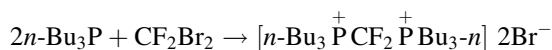


Jack Kesling utilized this methodology to capture [CF₂Br]⁻ with electrophiles, such as alcohols, iodine, fluoro-olefins and acyl fluorides [22]. In related work, Greg Wheaton demonstrated the generation and capture of [CF₂Cl]⁻ with electrophiles, such as trifluoromethyl ketones, pentafluoro

pyridine and fluoro-olefins [23,24]. Previous to these reports, there was no concrete evidence in the literature for the existence of halodifluoromethide ions. This work stimulated others to re-investigate earlier work and to confirm the finite lifetime of these intermediates. Subsequent work by Kesling and Seiji Shin-Ya generated $[\text{CF}_2\text{Br}]^-$, $[\text{CF}_2\text{Cl}]^-$ and $[\text{CFCl}_2]^-$ from analogous phosphonium salts [25].

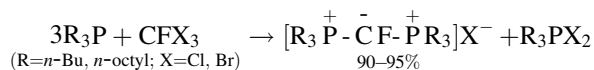
In a collaborative work with the Department of Nuclear Medicine (National Institutes of Health), Rick Flynn and Steve Hansen studied the hydrolysis of $[\text{Ph}_3\text{PCF}_2\text{Br}]^+\text{Br}^-$ and $[\text{Ph}_3\text{PCFBr}_2\text{Br}]^+\text{Br}^-$ in the presence of a radioactive isotope of bromine. With $[\text{Ph}_3\text{PCF}_2\text{Br}]^+\text{Br}^-$, unequivocal evidence was obtained which demonstrated that the mechanism of hydrolysis proceeds through a difluorocarbene intermediate and that decomposition of bromodifluoromethide is reversible [26]: $[\text{CF}_2\text{Br}]^- \rightleftharpoons [\text{:CF}_2] + \text{Br}^-$; with $[\text{Ph}_3\text{PCBr}_2]^+\text{Br}^-$, hydrolysis of the salt proceeds via $[\text{CFBr}_2]^-$, and not $[\text{:CFBr}]^-$ [27].

When Kesling [28] attempted to prepare $[n\text{-Bu}_3\text{PCF}_2\text{Br}]^+\text{Br}^-$ from CF_2Br_2 and $n\text{-Bu}_3\text{P}$, he discovered that the initial reaction between these reactants to form $[n\text{-Bu}_3\text{PCF}_2\text{Br}]^+\text{Br}^-$ was slower than the subsequent reaction of the phosphonium salt with a second equivalent of the trialkyl phosphine. The main product (the exclusive product if two equivalents of $n\text{-Bu}_3\text{P}$ were utilized) was a bis(phosphonium) salt [28]:



Bis(phosphonium) salt formation was not observed with two equivalents of the triarylphosphine, Ph_3P . Kesling rationalized bis(phosphonium) salt formation via nucleophilic attack of the intermediate ylide on dibromotri-*n*-butylphosphorane (Scheme 2). We assumed that the reaction stopped at this stage because any further halophilic reactions would involve abstraction of F^+ from the bis(phosphonium) salt. However, if abstraction of X^+ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) were available, we predicted that the reaction would continue to form a phosphoranium salt, $[\text{R}_3\text{P}^+-\text{CF}-\text{P}^+\text{R}_3]\text{Br}^-$. However, at that time (~ 1974) our NMR capabilities were poor

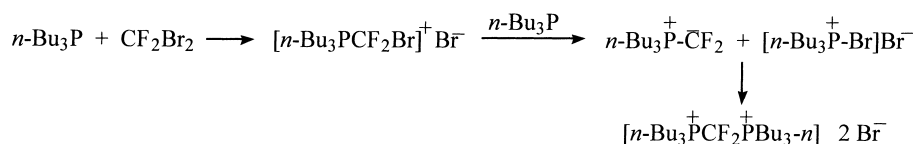
and we could not observe the phosphoranium salt spectroscopically. Consequently, we postponed further work in this direction for a few years until our NMR capabilities improved and allowed Daryl Cox (in the early 1980s) to verify our earlier expectation of phosphoranium salt formation [29]:



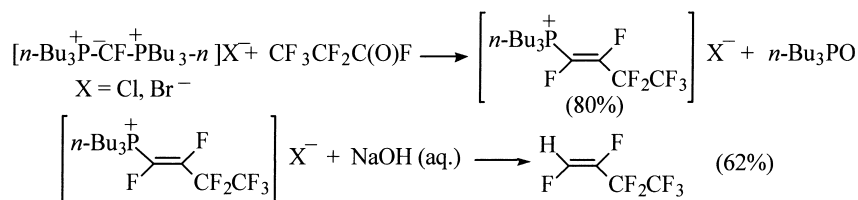
The phosphoranium salts exhibited excellent reactivity with perfluoroacyl fluorides. Ylides generally undergo acylation with acid halides; however, Cox demonstrated that perfluoroacyl fluorides undergo a stereoselective Wittig olefination reaction with the phosphoranium salts to give a (*Z*)-perfluorovinyl phosphonium salt; subsequent basic hydrolysis gave only the (*E*)-1-hydroperfluoro-olefin [30] (Scheme 3). This work illustrates one of the rare examples of a Wittig olefination reaction with an acyl halide and provided the first example of the preparation of a fluoro-olefin directly from an acyl halide.

Subsequent work by Cox and Narayanasamy Gurusamy [31] demonstrated that aldehydes also react with the fluorine-containing phosphoranium salts, derived from $n\text{-Bu}_3\text{P}$, to produce a fluorine-containing vinylphosphonium salt, basic hydrolysis of which gives the corresponding 1-fluoroalkenes with retention of configuration. The stereochemistry of the vinyl phosphonium salt is aldehyde dependent: with aliphatic aldehydes, the major product is the (*E*)-vinylphosphonium salt, which gives the (*Z*)-1-fluoro-alkene exclusively on hydrolysis, while aryl aldehydes give the (*Z*)-phosphonium salt and hence the (*E*)-1-fluoroalkene [31] (Scheme 4). The stereochemistry, in the case of aromatic aldehydes, is judged to be controlled by formation of a through-space charge-transfer complex between the aromatic ring and the positively charged phosphonium center during formation of the oxaphosphetane intermediate [31].

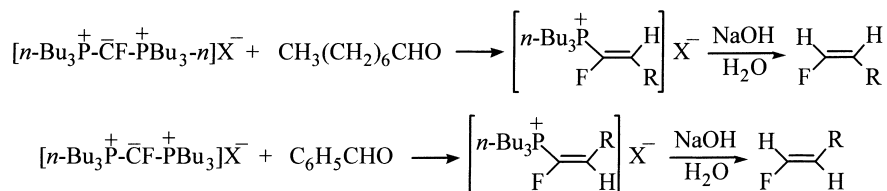
In contrast to the Wittig olefination reaction noted above, In Howa Jeong and Cox [32] observed normal acylation of the fluorine-containing phosphoranium salts with perfluoroacyl chlorides. Jeong subsequently developed this metho-



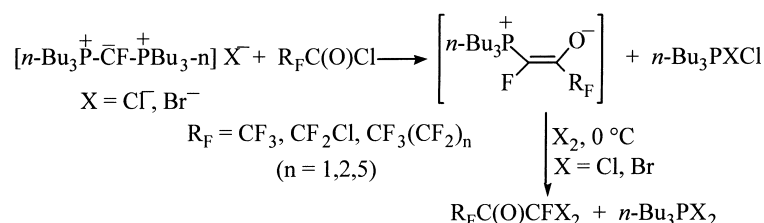
Scheme 2.



Scheme 3.



Scheme 4.



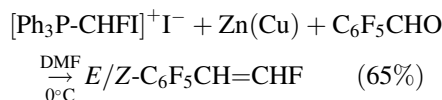
Scheme 5.

dology into a regioselective preparation of α,α -dihalofluoromethyl perfluoroalkyl ketones (Scheme 5) [33]. Treatment of $\text{R}_\text{F}\text{C}(\text{O})\text{CFCl}_2$ with SbF_5 provided a useful route to α -chloroperfluoro-2-alkanones and perfluoro-2-alkanones [34].

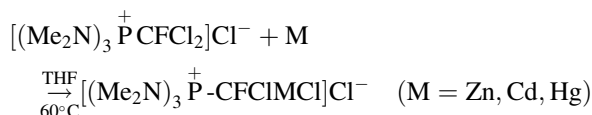
Thus, what began as a simple preparative route to 1,1-difluoro-olefins eventually led us to bis(phosphonium) salts and eventually to the novel fluorine-containing phosphonium salts. We developed an in-depth understanding of the mechanisms of these reactions, which aided us in the development of subsequent phosphonate chemistry. This work provided some unique and novel chemistry and several useful precursors for our studies in organometallic chemistry (see later).

2.2. Ylides via metal dehalogenation of phosphonium salts

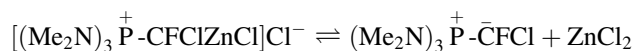
The fluoromethylene ylide $[\text{Ph}_3\text{P}^+\text{-CHF}^-]$ was initially generated by Pete Greenlimb under typical Wittig conditions from $[\text{Ph}_3\text{P-CH}_2\text{F}^+]\text{I}^-$; however, it was not very stable [35], and a better method was developed which involved Zn(Cu)-dehalogenation of an α -halophosphonium salt [36]. Although only modest success was achieved in this work by Greenlimb, e.g.



the metal dehalogenation approach was extended successfully to other ylides. For example, Van Hamme employed this route to form stable ylide complexes with Group IIB metals [37]:

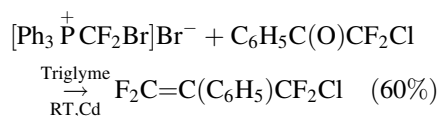


These complexes exhibited surprising stability in ethereal solvents and served as effective chlorofluoromethylene transfer agents in Wittig reactions via dissociation into the corresponding ylide and metal chloride, e.g.



When the metal was zinc, a solution of the complex could be generated on a large scale and utilized in Wittig olefination reactions over a period of weeks.

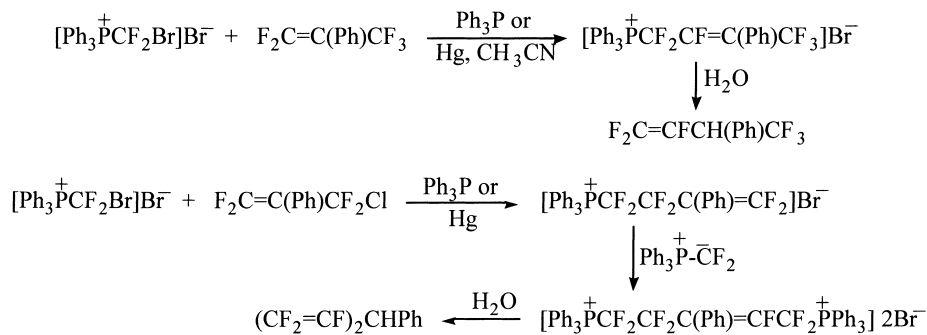
When the difluoromethylene ylide, $[\text{R}_3\text{P}^+\text{-}\bar{\text{C}}\text{F}_2]$, was generated from $[\text{R}_3\text{P}^+\text{CF}_2\text{Br}]\text{Br}^-$ and a tertiary phosphine (R_3P) in the presence of substrates such as $\text{C}_6\text{F}_5\text{CHO}$, $\text{C}_6\text{F}_5\text{C}(\text{O})\text{CF}_3$, $\text{C}_6\text{H}_5\text{C}(\text{O})\text{CF}_2\text{Cl}$ and $\text{C}_6\text{F}_5\text{C}(\text{O})\text{CF}_2\text{Cl}$, low yields of the 1,1-difluoroolefins were obtained since the ketones reacted with the tertiary phosphine used. Kesling and Naae, however, found that when the ylide was generated via dehalogenation of the phosphonium salt in the presence of these substrates, good yields of 1,1-difluoro-olefins were obtained [38], e.g.



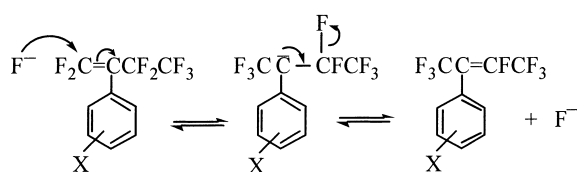
Similar dehalogenation of $[\text{Ph}_3\text{PCFBr}_2]^+\text{Br}^-$ provided a useful route to $[\text{Ph}_3\text{P}^+\text{-}\bar{\text{C}}\text{FBr}]$ [39].

2.3. Chain-extension reactions

Yoshio Inouye and Jim Headley demonstrated that nucleophilic difluoromethylene ylides reacted with 1,1-difluoro-olefins to give chain-extended phosphonium salts, which on hydrolysis gave chain-extended fluorinated alkenes or alkadienes [40]. With an allyl halide derivative, the initial $\text{S}_\text{N}2'$ product reacted with a second equivalent of the ylide to give chain-extension by two CF_2 units (Scheme 6).



Scheme 6.



Scheme 7.

2.4. Fluoride ion-catalyzed isomerization of 2-aryl-F-butenes

Our success with the difluoromethylene ylide chemistry permitted us to prepare a series of β -phenyl-substituted perfluoro-1-butenes. This finally enabled us to accomplish my initial PhD thesis topic, namely to investigate the mechanism of fluoride ion-involved catalyzed $\text{S}_{\text{N}}2'$ reactions in such systems. Headley [41] carried out a detailed kinetic study of the isomerization. The resultant Hammett plot was non-linear with a concave downward break near $\sigma = 0$, and a two-step mechanism involving formation of a carbanionic intermediate best explained the data (Scheme 7). A change in the rate-limiting step caused the break in the Hammett plot.

2.5. Ylide-carbene chemistry

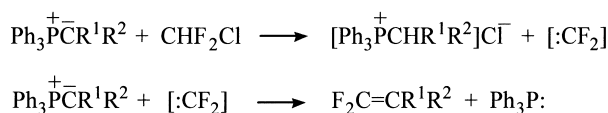
In an attempt to prepare 1,1-difluoro-olefins without formation of Ph_3PO (the main byproduct in Wittig chemistry), Wheaton developed a novel reaction between non-stabilized ylides and chlorodifluoromethane [42,43]. The idea was to utilize the basic ylides in a two-fold way: (i) as a

base to generate the electrophilic difluorocarbene in situ; and (ii), to trap the electrophilic carbene with the nucleophilic ylide (Scheme 8). The triphenylphosphine can be readily recovered and utilized to prepare more $[\text{Ph}_3\text{PCHR}^1\text{R}^2]^+\text{Cl}^-$ (ylide precursor). The $[\text{Ph}_3\text{PCHR}^1\text{R}^2]^+\text{Cl}^-$ formed in the reaction can be recovered and recycled to prepare more ylide. Consequently, olefin formation involves one equivalent of phosphonium ylide and one equivalent of CHF_2Cl . No Ph_3PO is formed. This reaction can also be accomplished with polymer-supported phosphonium ylide, which makes recycling of the tertiary phosphine and phosphonium salt more efficient [44]. This approach to 1,1-difluoro-olefins is an example of Trost's atom economy concept.

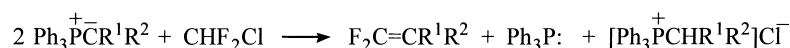
In the above discussion of the highlights of our ylide chemistry, many details and examples were of necessity omitted. For a more thorough presentation of the work, the reader should consult our *Chemical Reviews* article on this topic [45].

2.6. Cyclic fluorinated ylides

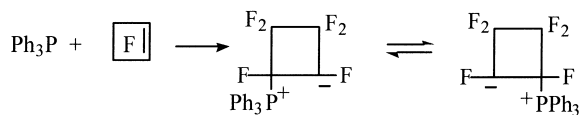
In addition to the fluoromethylene ylides, we also pioneered the preparation and identification of *stable* fluorinated cyclic ylides. Our interest in this subject was stimulated by a report by Stockel and coworkers, who proposed that the 1 : 1 adduct between triphenylphosphine and perfluorocyclobutene was a rapidly equilibrating set of 1,3-dipolar species [46] (Scheme 9). Our knowledge of fluorinated carbanions (in 1970) led us to suspect that these 1,3-dipolar species would be unstable and easily lose fluor-



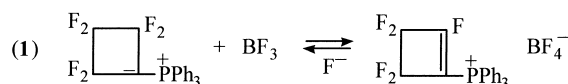
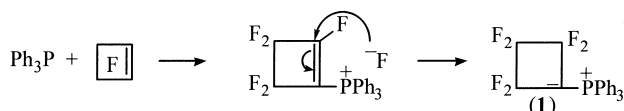
Overall Reaction:



Scheme 8.



Scheme 9.

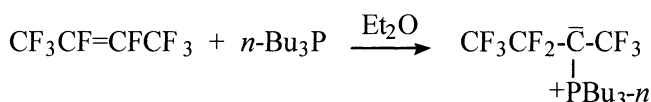


Scheme 10.

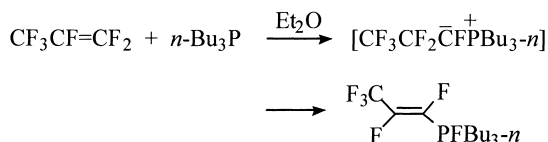
ide ion. Consequently, we prepared the 1 : 1 adduct and, finding its ^{19}F NMR spectrum ambiguous, carried out an X-ray analysis and unequivocally demonstrated the compound to be the *stable* cyclic ylide **1** [47], formed as shown in Scheme 10. (Perfluorocyclopentene and related four and five-membered perfluorinated cycloalkenes behave similarly [45].)

When the cyclic ylide **1** is treated with BF_3 , the corresponding vinyl phosphonium tetrafluoroborate is formed and can be isolated. However, treatment of the tetrafluoroborate salt with fluoride ion reforms the ylide [45,48,49] (Scheme 10). Cyclic ylides like **1** are stabilized by the phosphonium centre and the beta fluorines. It's not necessary to invoke any stabilization by 'd' orbitals on phosphorus. In fact, trialkylamines form analogous stable ammonium ylides, as demonstrated by work of Dick Howells and Paul Vander Valk in our laboratory [50,51]. Later work by Vander Valk demonstrated the applicability of this method to analogous arsonium ylides [52] (Scheme 11). Note that this work provided not only the first stable fluorinated ylides but also the first examples of stable fluorinated carbanions. Subsequent work by others has demonstrated the generality of this seminal work.

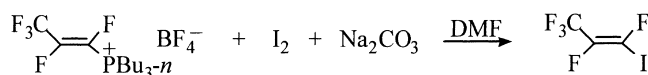
Extension of this work to acyclic olefins by Seiji Shin-Ya and Howells [53] demonstrated that stable ylide formation was possible when only β -fluorines are present in the ylide. Thus, perfluoro-2-butene reacts with $n\text{-Bu}_3\text{P}$ to give a stable ylide (in solution):



However, when both α - and β -fluorines are present in the ylide, the ylide is unstable and collapses to a vinylphosphorane [53]. Hydrolysis of the vinylphosphorane derived from hexafluoropropene gives only (*E*)-1-hydropentafluoropropene [54,55]:

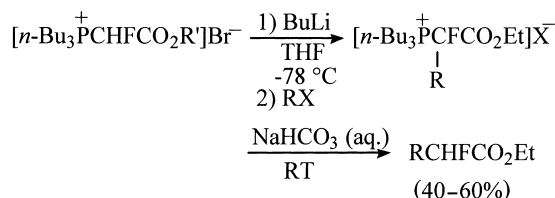


Shin-Ya and Howells demonstrated the generality and utility of this methodology as a stereoselective reductive route to polyfluorinated olefins. We and others have employed this method as a one-pot route to many 1-hydroperfluoro-olefins. The vinylphosphonium tetrafluoroborates are also readily cleaved by KF/I_2 or $\text{Na}_2\text{CO}_3/\text{I}_2$ to give perfluorovinyl iodides with retention of geometry [56]. This methodology has also been used by others to prepare the analogous SF_5 derivatives.

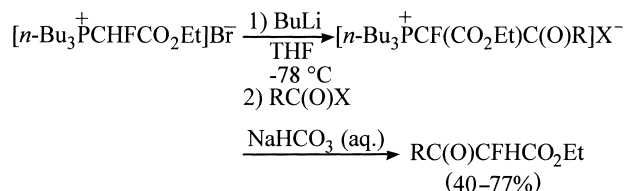


2.7. Ylide functionalization

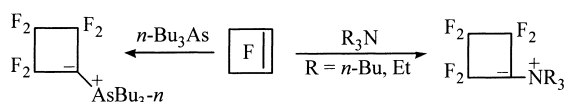
In addition to the typical Wittig reaction to directly give olefinic products, we became interested in more complex in situ functionalization of fluorine-containing ylides. The main architect of this work in our laboratory was Alagappan Thenappan. Initially he developed a route to α -fluoroalkanoates *via* alkylation of (fluorocarboalkoxymethylene)tri-*n*-butylphosphorane [57,58]. The conversion can be carried out as a one-pot reaction:



Similarly, Thenappan developed a convenient route to α -fluoro- β -ketoesters *via* acylation of (fluorocarboethoxymethylene)tri-*n*-butylphosphorane [59,60]:

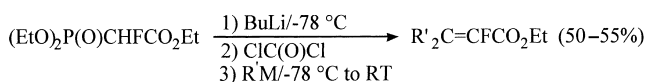
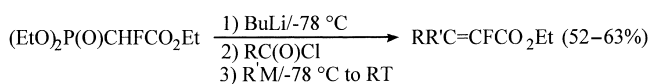


The R group in the acyl halide can be alkyl, aryl, perfluoroalkyl or cycloalkyl, and the phosphonium bromide starting material is easily made from $n\text{-Bu}_3\text{P}$ and $\text{BrCH}\text{F}\text{CO}_2\text{Et}$. This mild method can be carried out as a one-pot reaction *via* sequential addition of the reagents.

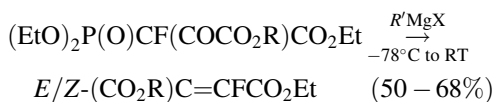
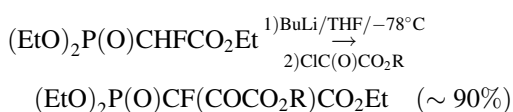


Scheme 11.

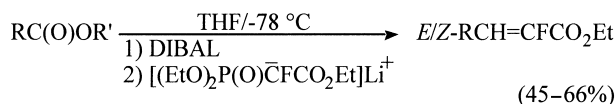
This methodology was subsequently modified by Thenappan and Hou-Jen Tsai to provide a one-pot synthesis of unsymmetrical and symmetrical tetrasubstituted α -fluoro- α,β -unsaturated esters from α -fluorophosphonates, as illustrated below [61]:



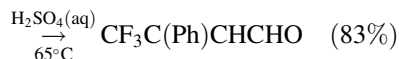
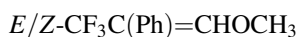
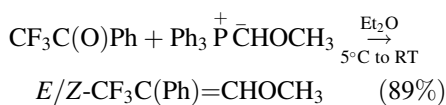
When alkyloxalyl chlorides were used as the acylating agent, the above procedure provided an expedient synthesis of α -fluoro- α,β -unsaturated diesters [62,63]:



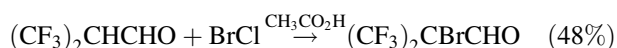
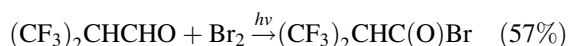
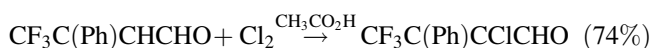
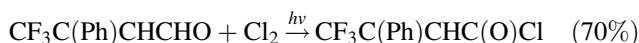
An additional modification introduced by Thenappan was the low-temperature in situ reduction of an ester to an aldehyde with di-isobutylaluminum hydride, followed by in situ reaction of the aldehyde with a fluorine-containing phosphonate anion to give α -fluoro- α,β -unsaturated esters [64,65]. The ester's R group can be alkyl, aryl, perfluoroalkyl or fluoroalkyl. With ethyl formate this procedure provides a facile preparation of ethyl 2-fluoroacrylate [66].



A series of fluorine-containing aldehydes was prepared by Don Wiebe via Wittig chemistry [67], e.g.

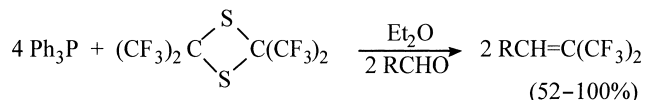


Halogenation of these aldehydes could be regioselectively controlled via the enol or free-radical halogenation at the formyl hydrogen:



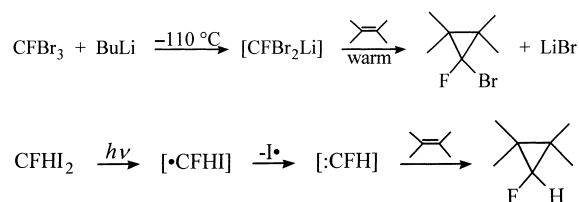
This selective halogenation work provides a facile route to either α -halopolyfluorinated aldehydes or polyfluorinated acyl halides, and demonstrates the effect of CF_3 groups on the formation of free-radical sites at an adjacent carbon atom.

Inouye developed a simple in situ preparation of $\text{Ph}_3\text{P}^+\text{C}^-(\text{CF}_3)_2$ from tetrakis(trifluoromethyl)-1,3-dithietane, which is readily prepared from hexafluoropropene. In situ capture of this ylide with aldehydes gave good yields of the bis(trifluoromethyl)olefins [68]. Ketones do not capture this ylide.



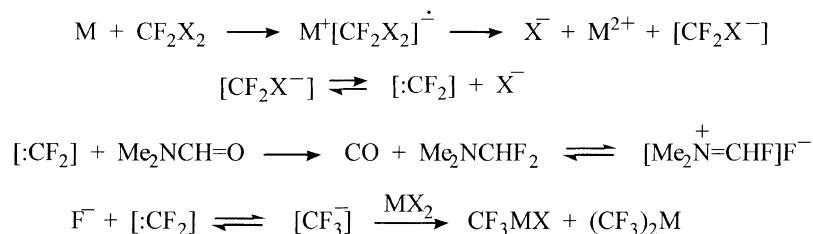
3. Organometallic chemistry

Our initial ventures in organometallic chemistry were quite straightforward and provided useful but not especially novel results. In the early 1970s, Jerry Hahnfeld explored some fluorinated vinyl-lithium reagents and demonstrated that these retained their configuration — contrary to an earlier report in the literature [69]. As part of our interest at that time, he also explored the low-temperature preparation and utility of trihalomethyl-lithium reagents such as CFCl_2Li and CFBr_2Li as fluorochloro- and fluorobromocarbene precursors [70]. Hahnfeld also developed a photochemical route to fluorocarbene from di-iodofluoromethane [71].

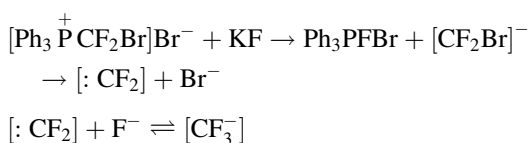


3.1. Perfluoroalkyl, perfluoroallyl and perfluoroaryl organometallics

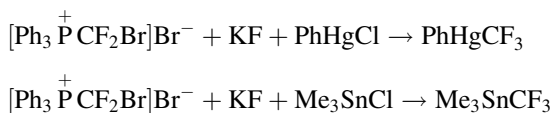
Our interest in carbene chemistry [21] and the frustration of dealing with exotherms during scale-up of recipes involving low-temperature lithium reagents provided the impetus for our more novel work on organometallic reagents. From our previous ylide work in which we utilized phosphonium salts as difluorocarbene precursors, Jack Kesling developed a new route to trifluoromethyl derivatives of mercury and tin [28,45]. He reasoned that the fluoride ion utilized in carbene generation (see p. 3) could reversibly trap $[:\text{CF}_2]$ to form trifluoromethide, hence if decomposition of the phosphonium salt was triggered with F^- in the presence of an electrophile rather than a nucleophilic olefin, capture of $[\text{CF}_3^-]$ would produce a trifluoromethylated product:



Scheme 12.

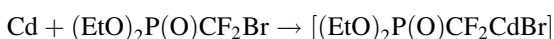


The two electrophilic reagents successfully utilized by Kesling were phenylmercuric chloride and chlorotrimethyltin:



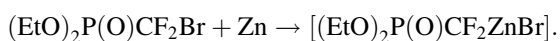
This important advance by Kesling provided the impetus for later work on the preparation of trifluoromethyl zinc, cadmium and copper reagents.

As part of our phosphonate chemistry, Ryutaro Takei and Shin-Ya prepared a stable cadmium reagent from diethyl (bromodifluoromethyl)phosphonate:

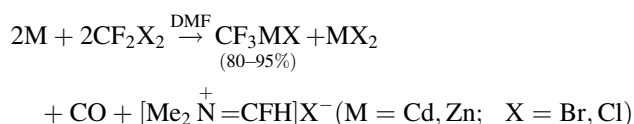


We chose to explore cadmium for two reasons: (i) we were not aware of the use of cadmium in any coupling (dimerization) reactions; and (ii) we needed a way to demonstrate the formation (in solution) of the organometallic reagent, being well aware (from literature precedent) that cadmium NMR could assist our structural assignments [72].

In later work, Takashi Ishihara and Masamichi Maruta [73] prepared the analogous zinc reagent:



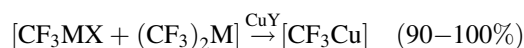
In the course of investigating the chemistry of this reagent, we often encountered an unknown singlet in the ^{19}F NMR spectrum at ca. 44 ppm upfield from CFCl_3 . Denise Wiemers proposed that this signal could be a trifluoromethylzinc reagent. Hence we devised an experiment to generate difluorocarbene from dihalodifluoromethanes with concomitant formation of a metal halide, arguing that if the in situ generated $[:\text{CF}_2]$ could be captured by fluoride ion, trifluoromethide would become available to attack the in situ generated metal halide. Thus was born our simple preparation of trifluoromethyl cadmium and zinc reagents from dihalodifluoromethanes [74], i.e.



DMF is not a neutral partner in this reaction: it serves as both the solvent and the reactant needed to produce the fluoride ion required for trifluoromethide formation from difluorocarbene produced via an electron transfer route (Scheme 12). Detailed mechanistic experiments provided evidence for the electron transfer step, the formation of $[:\text{CF}_2]$, CO and Me_2NCHF_2 [74,75].

Thus, the earlier work of Kesling, Takei, Shin-Ya, Ishihara and Maruta culminated in the development of this novel route to trifluoromethylated organometallic reagents [74,76].

In subsequent work, Wiemers utilized her reagents, particularly the cadmium reagent, in:



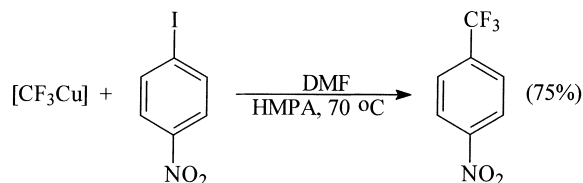
Y = I, Br, Cl, CN

exchange reactions with Cu(I) salts to achieve the first pre-generation and spectroscopic detection of trifluoromethylcopper [77]. Using dihalodifluoromethanes, $[\text{CF}_3\text{Cu}]$ could be pre-generated via a one-pot reaction:



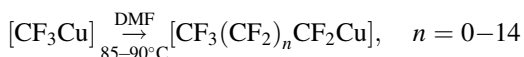
Several interesting observations were made during this work. Firstly, following the exchange reaction with $\text{Cu}(\text{I})\text{Y}$, we detected three singlets in the ^{19}F NMR spectrum of the product — suggesting the presence in the DMF solution of three different copper reagents! Obviously, we were surprised and puzzled at this observation. When oxygen was vigorously excluded, one of these signals disappeared, suggesting that it belonged to an oxidation product of $[\text{CF}_3\text{Cu}]$. Later work by Monica Willert-Porada demonstrated that the oxidation product was in fact a perfluoroalkyl copper (III) species, $[(\text{CF}_3)_4\text{Cu}^-]$, [78]. Subsequent X-ray work by Nauman confirmed this. Secondly, when the initially formed $[\text{CF}_3\text{Cu}]/\text{DMF}$ solution was stored overnight, the reagent was converted to $[\text{CF}_3\text{CF}_2\text{Cu}]$ — an observation made earlier by Kobayashi in the preparation of $[\text{CF}_3\text{Cu}]$ from CF_3I [79]. However, when HMPA was added to stabilize the $[\text{CF}_3\text{Cu}]$ reagent, coupling reactions

with aryl iodides could be effected at 70°C without formation of trifluoroethylcopper, e.g.

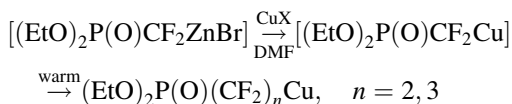


Based on related work by Willert-Porada and Haridassan Nair, the three ^{19}F signals mentioned above were assigned to the species $\text{CF}_3\text{Cu}\cdot\text{L}$ (L = metal halide), $\text{CdI}^+[\text{CF}_3)_2\text{Cu}]^-$ and $\text{CdI}^+[\text{CF}_3)_4\text{Cu}]^-$ [80,81]

The spontaneous conversion of $[\text{CF}_3\text{Cu}]$ to $[\text{CF}_3\text{CF}_2\text{Cu}]$ in DMF at room temperature accelerated at higher temperatures, and surprisingly the oligomerization did not stop at the perfluoroethylcopper stage. Thus, at 85–95°C (in DMF), chains of 14–16 carbons were formed, all possible values of n (to 14) being found — both odd and even values. Hence, the chain growth:

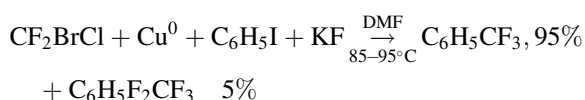


must occur by insertion of CF_2 units, not by dimerization of $[:\text{CF}_2]$ to $\text{F}_2\text{C}=\text{CF}_2$ (TFE) followed by oligomerization of TFE with $[\text{CF}_3\text{Cu}]$. This chain-extension process is not unique to trifluoromethyl copper; for example, $(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{Cu}$ undergoes a similar process when heated [81]:



This initial work by Wiemers on the oligomerization of $[\text{CF}_3\text{Cu}]$ was subsequently taken up by Jerry Easdon, who also prepared a similar oligomeric copper reagent directly from dibromodifluoromethane or bromochlorodifluoromethane and Cu^0 [82]: $\text{CF}_2\text{XY} + \text{Cu}^0$ (X, Y = Br, Cl) (in DMF at 85–95°C) $\rightarrow [\text{CF}_3(\text{CF}_2)_n\text{CF}_2\text{Cu}]$, where n varies from 0 to 14. The distribution of oligomeric chains was determined by coupling of the oligomeric copper reagent with iodobenzene and subsequent analysis of the (perfluoroalkyl)benzenes formed by GLPC and mass spectrometry. This unprecedented oligomerization process complimented the oligomerization of TFE as an entry to longer chain perfluoroalkyl derivatives, since the copper reagent is easily functionalized. TFE oligomerization reactions can give only even numbered products, whereas the copper reagent gives both odd and even products. The University of Iowa patented this novel process [83–86], which delayed its announcement, although it was revealed in several conference presentations. Easdon also developed a protocol for the preparation of trifluoromethylated aromatics via direct reaction of dihalodifluoromethanes, copper metal, and aryl iodides [82]. Initial experiments indicated that oligomerization of the initially formed $[\text{CF}_3\text{Cu}]$ competed with coupling of trifluoromethylcopper with iodobenzene, as perfluoro-

alkyl chains from 0 to 9 carbons were detected in the product. After a search for an additive which would effectively suppresses the rate of oligomerization relative to the rate of coupling of trifluoromethylcopper with the iodoaromatic, Easdon found that fluoride ion worked best. Thus, when coupling was carried out in the presence of KF or CsF, 95% of the coupled product was the trifluoromethyl derivative [82–86]:



Since the initial discovery of the formation of $[\text{CF}_3\text{M}]$, where M = Cd, Zn or Cu, from difluorodihalomethanes and the elucidation of the oligomerization of the copper derivative mechanism by Wiemers, several other workers have prepared $[\text{CF}_3\text{Cu}]$ by utilizing a different source of $[:\text{CF}_2]$ [87–89]. The seminal work of Wiemers led the way.

The ease with which $[\text{CF}_3\text{M}]$ oligomerized suggested that it might be employed as a $[\text{CF}_2]$ transfer agent. Work by Zhen-Yu Yang and Wiemers [90] demonstrated that in a competition between pentafluorophenylcopper and trifluoromethylcopper, selective transfer (insertion) of $[\text{CF}_2]$ occurred with pentafluorophenylcopper at low temperature:

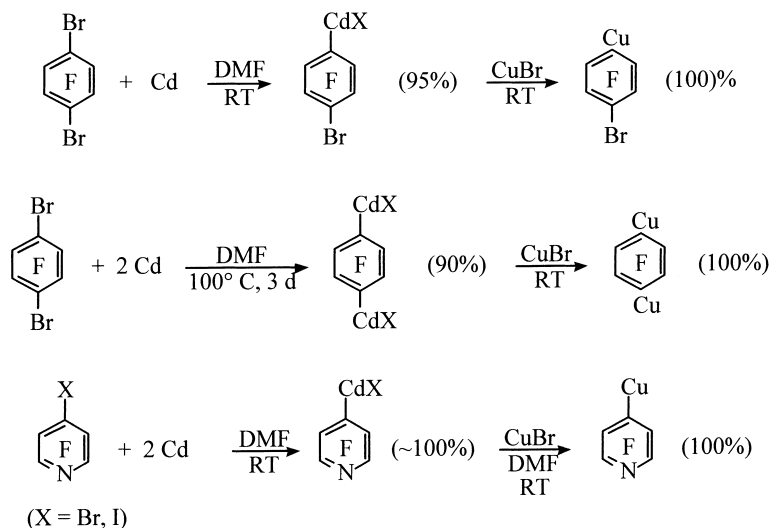


The perfluorobenzylcopper presumably forms first but is more reactive than $\text{C}_6\text{F}_5\text{Cu}$ where $[\text{CF}_2]$ insertion is concerned. This perfluoro(phenethyl)copper could also be directly prepared from the trifluoromethyl cadmium reagent [90]. Interestingly, multiple insertions of $[\text{CF}_2]$ units into $\text{C}_6\text{F}_5\text{CF}_2\text{CF}_2\text{Cu}$ were not observed, even when a large excess of $[\text{CF}_3\text{Cu}]$ was utilized at room temperature. Perfluoro(phenethyl)copper is readily functionalized with allyl halides and halogens, couples smoothly with vinyl halides and iodoaromatics, and readily undergoes SO_2 insertion at the C–Cu bond [90].

Our success with trifluoromethylcadmium halides as synthetic reagents prompted us to explore other compounds of this class. Pam Heinze studied the direct preparation of perfluoroalkyl cadmiums from perfluoroalkyl iodides [91], in DMF at room temperature: $\text{R}_\text{F}\text{I} + \text{Cd} \rightarrow \text{R}_\text{F}\text{CdI} + (\text{R}_\text{F})_2\text{Cd}$; yields were good to excellent when $\text{R}_\text{F} = \text{CF}_3$, C_2F_5 , or $n\text{-C}_3\text{F}_7$ and moderate for higher homologues. The reaction also worked well with bromopentafluorobenzene. The reaction was later exploited by Kathy MacNeil, who generated pentafluorophenylcopper via copper(I) halide exchange with the $[\text{C}_6\text{F}_5\text{CdBr}]$ produced [92].

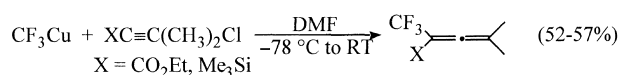
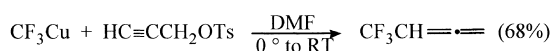
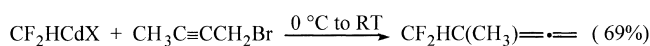
Greg Hartgraves prepared difluoromethylcadmium via similar methodology [93] and used ^{113}Cd NMR to characterize the mono and bis reagents formed:





Scheme 13.

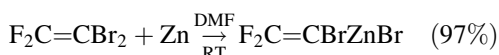
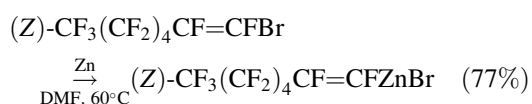
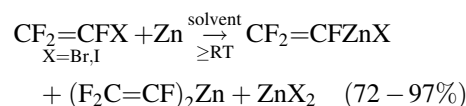
These difluoromethylcadmium reagents react with Cu(I) bromide to give difluoromethylcopper [94,95]; both types of reagent and perfluoroalkylcopper species were used by Hartgraves to synthesize a range of fluoroalkylated allenes [96,97], e.g.



Heinze, with Yasuo Tarumi, used perfluoroallyl cadmium and copper reagents from CF₂=CFCF₂I [98], while Yang and MacNeil [99] and Ba Van Nguyen [100] extended the work to the aromatic series (Scheme 13).

3.2. Perfluorovinyl zinc, cadmium and copper reagents

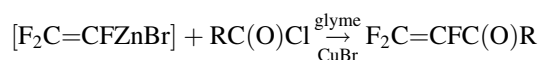
Steve Hansen and Terry Spawn developed a general, direct stereospecific preparation of stable fluorinated vinylzinc reagents from the corresponding fluorinated vinyl iodides or bromides and zinc metal [101]. Solvents such as DMF, THF, DMAC, CH₃CN and glymes were employed.



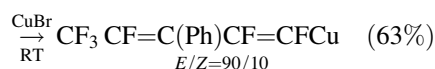
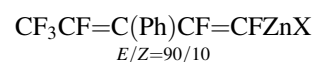
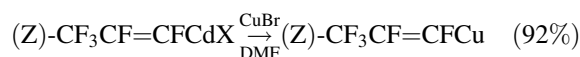
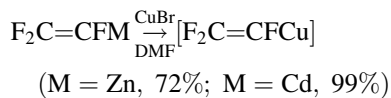
The corresponding vinylcadmium reagents were prepared by Hansen using similar methodology [102]. These vinylcadmium reagents exhibit excellent thermal stability, and we have isolated (CF₂=CF)₂Cd and (Z)-(CF₃CF=CF)₂Cd as DMF or triglyme solvates via distillation [103].

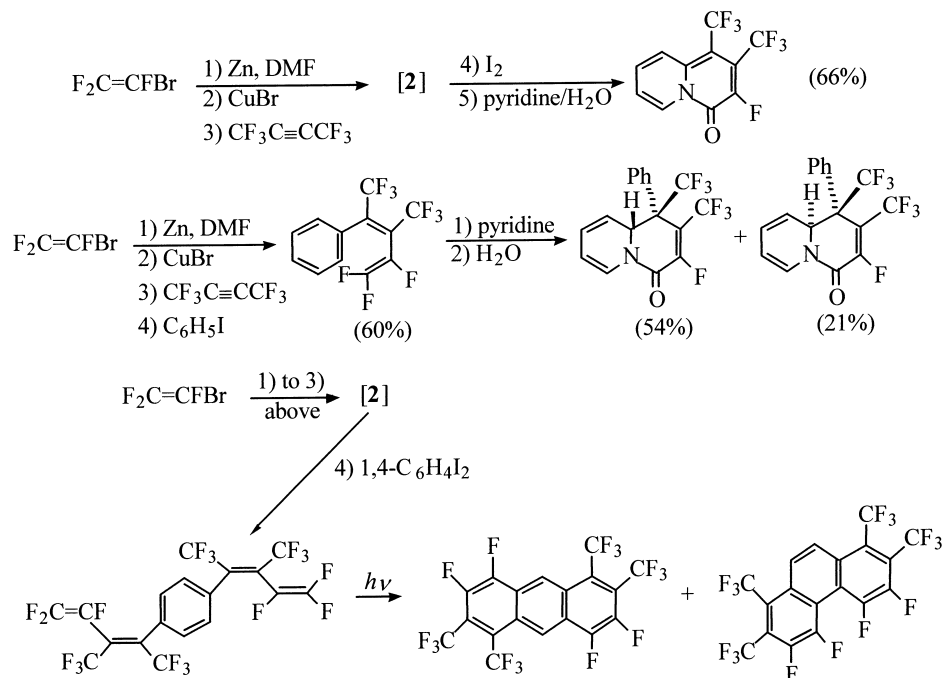


The bis-cadmium species are low-melting, moisture sensitive white solids. The fluorovinyl zinc and cadmium reagents are very useful synthons. Spawn, for example, developed a high yield, general route to trifluorovinyl ketones via the copper(I) mediated acylation of trifluorovinylzinc reagents [104]; these ketones are excellent Michael acceptors.



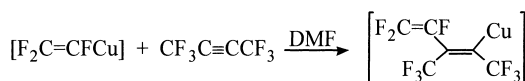
Although numerous literature reports describe attempts to pregenerate fluorinated vinyl copper reagents, success was not achieved until Hansen demonstrated that a copper(I) metathesis reaction of the corresponding vinyl cadmium and/or zinc reagents proceeds stereospecifically to give *stable* polyfluorinated vinylcopper reagents in excellent yields [105]. His work provided the first *unequivocal* route to fluorinated vinylcopper reagents.



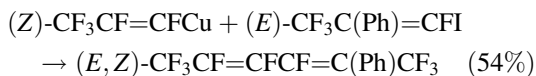


Scheme 14.

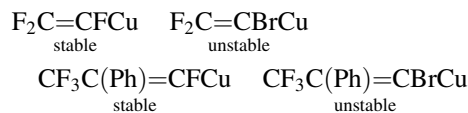
Subsequent work by Hansen demonstrated that these vinyl copper reagents add stereospecifically to perfluoro-2-butyne [103], e.g.



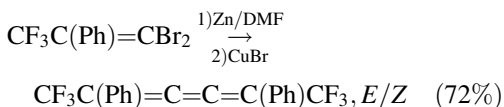
The synthetic utility of the prototypical *syn* adduct 2 is exemplified in Scheme 14 (one-pot techniques are used). These few examples demonstrate the wealth of chemistry now available via these copper reagents. As expected, these fluorinated vinylcopper reagents are readily acylated, allylated, alkylated, benzylated and stereospecifically coupled with vinyl halides, as demonstrated by Hansen [105–108]:



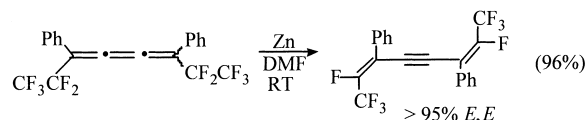
In contrast to the stability of the perfluorinated vinyl zinc and copper reagents, those containing an α -halogen other than fluorine exhibit diminished stability, especially the copper reagents. Thus, when $CF_3C(Ph)=CBrZnX$ (stable) was treated with $Cu(I)Br$, Peter Morken found



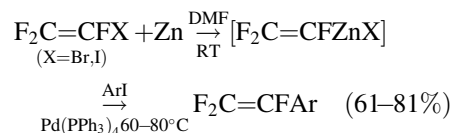
that the product immediately dimerized to a mixture of (*E*- and (*Z*)-butatrienes [109–111] which are readily separated by silica gel chromatography:



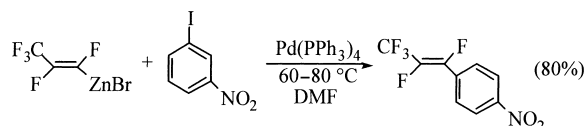
Morken also demonstrated that zinc dehalogenation of the isomeric trienes provides a convenient entry to divinyl acetylenes derived from $C_2F_5C(Ph)=CBr_2$ and its higher R_F homologues [112,113], e.g.



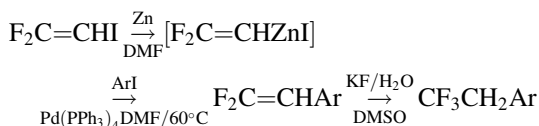
Heinze recognized that the perfluorovinylzinc reagents could be utilized in palladium-catalyzed coupling sequences with aryl iodides and vinyl halides, and she developed this methodology to provide a useful, mild route to trifluorovinyl styrenes [114,115].



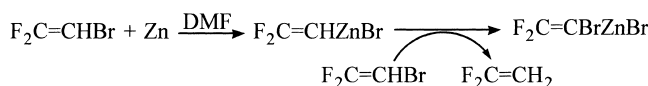
A wide variety of functional groups are tolerated in this approach, and the mild conditions prevent cyclodimerization of the styrene product. This route to (trifluorovinyl)-benzenes has received wide acceptance and has been utilized on a large scale. With longer chain perfluorovinylzinc reagents, the coupling reaction proceeds stereospecifically. Use of perfluoro-2-propenylzinc bromide [$CF_3C(ZnBr)=CF_2$ from $CF_3CBr_2CF_3$ and Zn] provides ready access to β,β -difluoro- α -trifluoromethyl styrenes, $CF_3C(Ar)=CF_2$ [116,117]:



This approach was extended by Nguyen for the facile preparation of β,β -difluorostyrenes and (2,2,2-trifluoroethyl)benzenes from $\text{F}_2\text{C}=\text{CHI}$ [118]:

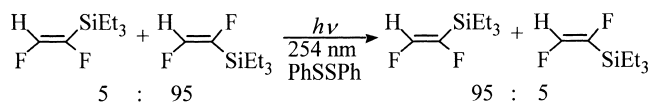


The corresponding bromoethylene is not suitable for conversion to the zinc reagent: using $\text{CF}_2=\text{CHBr}$, Nguyen discovered one of the first examples of an acid-base reaction during vinylzinc formation, i.e.

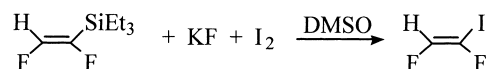


Useful extensions of this work are outlined in Scheme 15 [118,119].

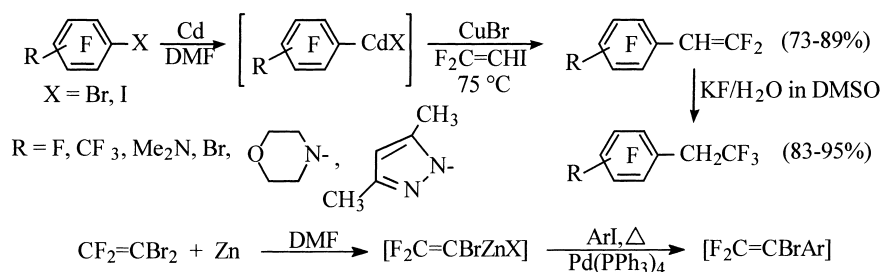
Charles Davis developed a stereospecific route to (*Z*)- α,β -difluorostyrenes via the vinylzinc/palladium coupling methodology. The requisite zinc reagent was prepared from (*E*)- $\text{HFC}=\text{CFSiEt}_3$, which was prepared by a novel photochemical isomerization developed by:



Simonetta Fontana and Davis in our laboratory [120]. This work provided the first general route to *cis*-1,2-difluoroolefin precursors. On a large scale, the *E/Z*-vinyl silanes can be separated by fractional distillation; iododesilylation then provides the requisite (*E*)-vinyl iodide for zinc reagent formation [121]:

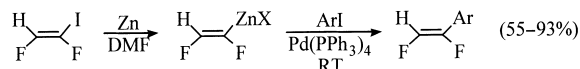


Subsequent formation of the zinc reagent followed by palladium catalyzed coupling with aryl iodides stereoselec-

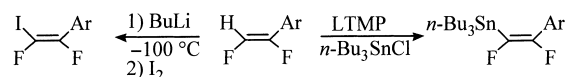


Scheme 15.

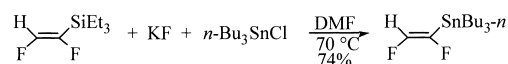
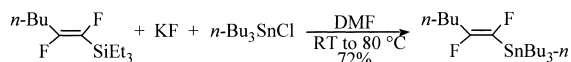
tively gave the (*Z*)- α,β -difluorostyrenes [122]. The styrenes can be readily:



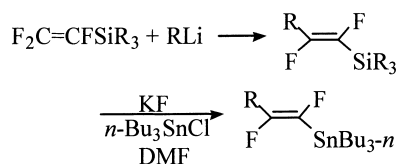
converted to (*E*)- α,β -difluoro- β -iodostyrenes or the analogous vinylstannanes, useful precursors for elaboration into other *cis* analogues.



One of the most useful synthetic transformations in our laboratory was developed by Ling Xue, who demonstrated that 1,2-difluorovinylsilanes can be stereospecifically converted into the corresponding 1,2-difluorovinyl stannanes [123,124]:

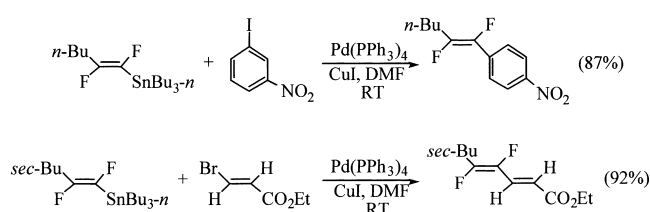


This work readily permits the preparation of fluorinated vinylstannanes from the corresponding fluorinated vinylsilanes, which are readily prepared from trifluorovinylsilanes via addition-elimination reactions:



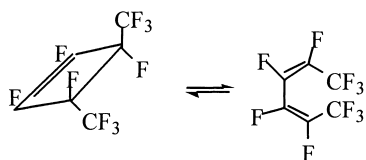
The corresponding vinylstannanes cannot be easily prepared via similar methodology, since the stannane group easily exchanges with the alkyl lithium reagent: $\text{F}_2\text{C}=\text{CFSnR}_3 + \text{R}'\text{Li} \rightarrow [\text{F}_2\text{C}=\text{CFLi}] + \text{R}_3\text{SnR}'$. This approach permits the facile preparation of almost any (*E*)- or (*Z*)-fluorinated vinylstannane, which readily participates in

palladium-catalyzed coupling reactions under Liebeskind conditions, as demonstrated by Long Lu [125], e.g.,

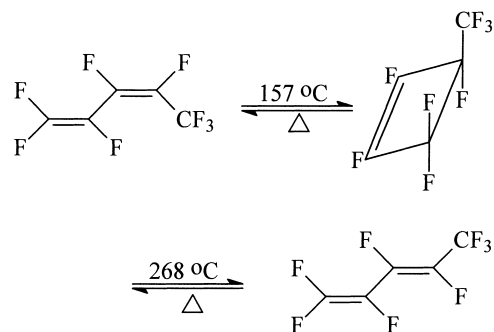


We believe that this silane/stannane conversion discovered in our laboratory and its extensions will become a general stereospecific entry to fluorinated dienes, trienes and polyenes.

The vinylcopper chemistry and the palladium-catalyzed coupling chemistry of fluorinated vinylzinc reagents in our laboratory led to a fruitful collaboration with Professor Bill Dolbier's group at the University of Florida. In earlier work of Guan-Su Shaw in our laboratory, we had noted that the ring closure and ring opening of fluorinated dienes and fluorinated cyclobutenes did not appear to follow the usual selection rules promulgated for the analogous hydrocarbon analogues. When this work was presented at a Winter ACS Fluorine Conference in 1983, a serious and protracted discussion on the interpretation of our results ensued [126]. Current physical-organic orbital symmetry control arguments (in 1983) regarding the ring opening of *cis*- and *trans*-1,2,3,4-tetramethylcyclobutenes attributed the direction of ring opening to probable repulsive steric interactions that would be present in the transition state due to the two methyl groups rotating simultaneously inwards. This argument had been uniformly applied in the interpretation of virtually all electrocyclic ring-opening reactions of hydrocarbon cyclobutenes. In order to resolve the argument produced in our presentation, Bill graciously offered to collaborate with us on this problem. We carried out the synthesis of model dienes and Bill and his coworkers carried out the gas-phase reactions. This collaboration resulted in several seminal papers on this topic [127–129] and unequivocally demonstrated that trifluoromethyl groups (CF₃) in the 3,4-position of cyclobutenes preferentially moved inwards on ring-opening:

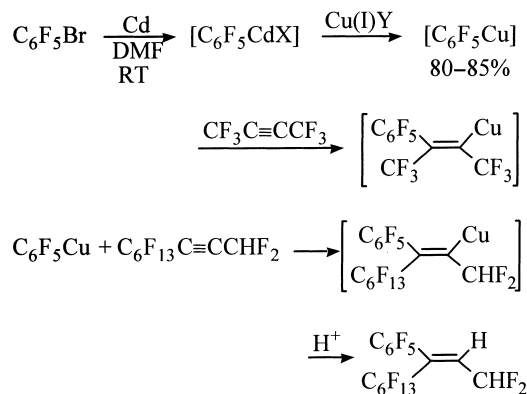


The cyclobutene opens to the *Z,Z*-diene with an activation energy ~18 kcal less than when it ring opens to the *E,E*-diene. Similar results were found with the (*E*)- and (*Z*)-1,3-pentadiene system. It was found that the (*Z*)-diene underwent cyclization much more readily than the (*E*)-diene:

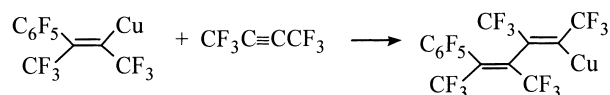


It was gratifying to see that our copper and zinc chemistry not only contributed to useful and novel synthetic methodology but also to the advancement of mechanistic organic chemistry. The role of Bill Dolbier was crucial in this work and contributed to its ultimate success. The collaborative effort was indeed greater than the sum of its parts!

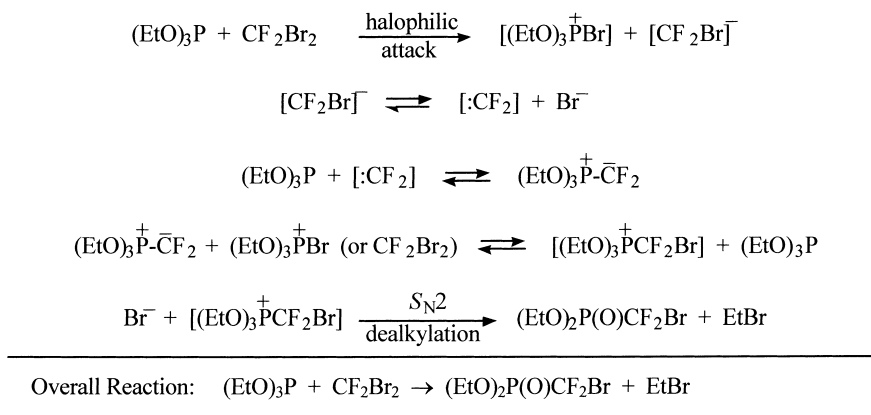
It would be remiss if I did not comment on the work of MacNeil and its contribution to our more recent ventures. She combined the earlier work of Heinze and Hansen to prepare [C₆F₅Cu] from [C₆F₅CdX] and studied its *syn* addition to fluorinated alkynes [92]. The resultant adduct was readily functionalized with electrophiles, such as H⁺, I₂, allylic halides, alkyl halides, aryl halides, vinyl halides, and acyl halides. With an unsymmetrical alkyne, regio-specific addition was observed:



Fluoride ion-catalyzed isomerization of the acylated product, and PhSSPh/*hν* catalyzed the isomerization of the protonated copper reagent. In a few cases, the initial vinyl-copper adduct could undergo a second *syn* addition to a second equivalent of perfluoro-2-butyne [92,130], e.g.,



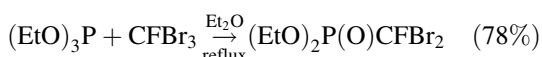
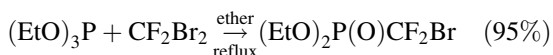
When the product from coupling with perfluorovinyl iodides was treated with fluoride ion, sequential isomerization occurred; initially at the C₆F₅ terminus and then at the perfluorovinyl terminus to give the *cis* propenyl group:



Scheme 16.

blocks, we decided to pursue the preparation of this important, yet unexplored, class of phosphorus derivatives.

Richard Flynn initially chose to investigate halofluoromethanes that we knew were susceptible to halophilic attack by phosphorus (tertiary phosphines). We anticipated that the halofluoromethide ion would be produced and lead to the corresponding fluorinated phosphonate. In retrospect, this study was more successful than we could have anticipated. Flynn discovered that merely refluxing trialkyl phosphites with dibromodifluoromethane or tribromodifluoromethane in ether or triglyme gave good to excellent yields of the respective fluorinated phosphonates [137]. The reactions are exothermic, but can be easily and safely carried out in solvents like ether

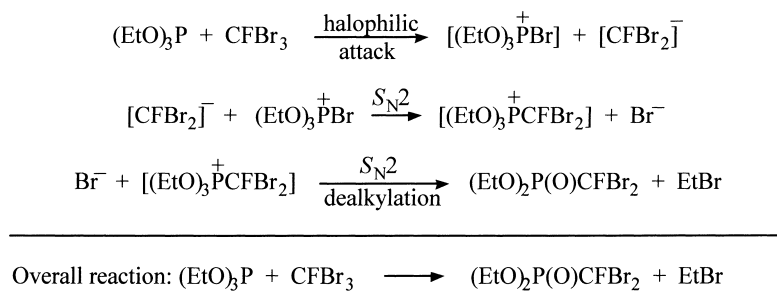
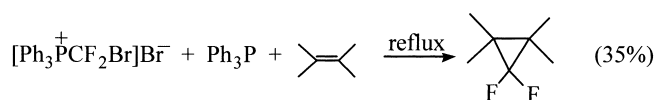


or triglyme, and are readily scaled-up. Subsequent work by Flynn demonstrated that analogues, such as $\text{Ph}_2\text{P}(\text{O})\text{CF}_2\text{Br}$ and $\text{EtO}(\text{Ph})\text{P}(\text{O})\text{CF}_2\text{Br}$ could be prepared by similar methodology from Ph_2POEt and $\text{PhP}(\text{OEt})_2$ respectively [45,138]. The mechanism of the formation of these phosphonates was investigated by Flynn [138] and is dependent on the halofluoromethane precursor. With CF_2Br_2 , the mechanism is similar to that of difluoromethylene ylide

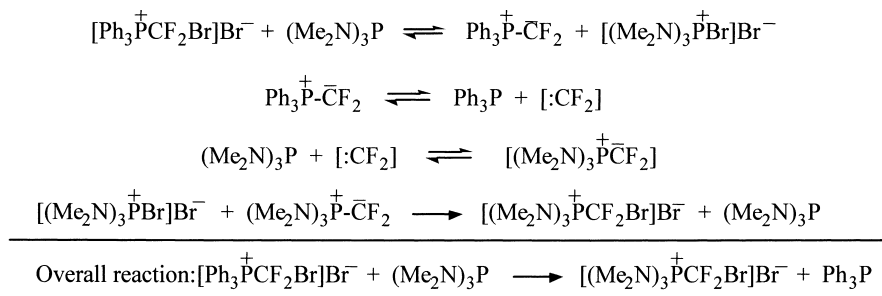
formation from this precursor, and is outlined in Scheme 16. The main difference between phosphonate formation and ylide formation is that the dealkylation step is irreversible and shifts all equilibria to product. Other CF_2XY analogues behave similarly.

In the CFBr_3 case, the initial step is similar (halophilic attack). However, subsequent steps, as expected [27], do not invoke carbene intermediates and the mechanism is more reminiscent of the Michaelis-Arbusov reaction (Scheme 17). Consequently, the key to success is the presence of a polarizable halogen in the methane and the formation of a stabilized fluoromethide ion or carbene. With precursors such as CF_3I and $\text{C}_6\text{F}_5\text{I}$, only one of these requirements is met, consequently they are unreactive towards trialkylphosphites. However, Flynn developed a photochemical procedure for the preparation of $(\text{EtO})_2\text{P}(\text{O})\text{CF}_3$ and $(\text{EtO})_2\text{P}(\text{O})\text{C}_6\text{F}_5$ in moderate yields [139].

Later collaborative work with Bruce Smart's group at DuPont, corroborated our proposal that ylide formation is reversible and produces $[:\text{CF}_2]$. Thus, when the reaction of $[\text{Ph}_3\overset{\oplus}{\text{P}}\text{CF}_2\text{Br}]^+\text{Br}^-$ with triphenylphosphine is carried out in a large excess (21 equivalents) of tetramethylethylene, the corresponding difluorocyclopropane is formed [140]:

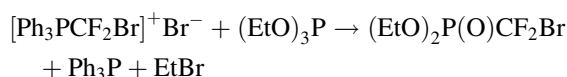


Scheme 17.



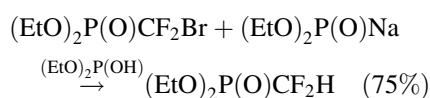
Scheme 18.

Similar conclusions had been earlier reached by Naeef [45,141], who proposed a dissociation mechanism in the exchange of the $[\text{CF}_2\text{Br}]$ group when bromodifluoromethylphosphonium salts were treated with a more nucleophilic tertiary phosphine (Scheme 18). Flynn observed a similar exchange with trialkylphosphites [138,140]:



The dealkylation step rapidly shifts all equilibria to the phosphonate product [140].

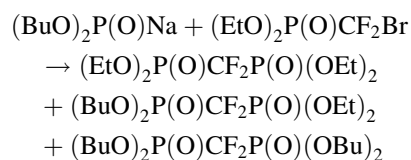
We became intrigued by the mechanism of phosphonate formation from CF_2Br_2 : why did the phosphonate anion $[(\text{EtO})_2\text{P}(\text{O})\text{CF}_2]^-$ not attack the $[(\text{EtO})_3\text{PBr}]^+$ cation and form a bisphosphonate? Presumably, we deduced, halogen abstraction from the cation or CF_2Br_2 occurs faster than bisphosphonate formation. However, Flynn devised an in situ reaction, whereby phosphonate anion formation simultaneously produced the corresponding $(\text{EtO})_2\text{P}(\text{O})\text{Br}$ so that in situ phosphorylation would give the bisphosphonate. The simultaneous generation of the two intermediates required was tested by the following reaction:



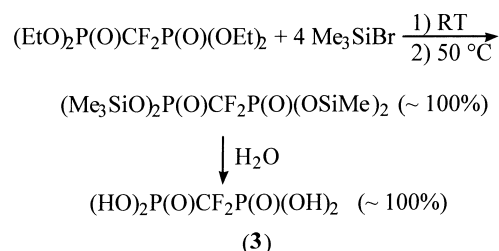
Abstraction of positive halogen gave the phosphonate anion and phosphoryl halide. Rapid quenching of the anion by diethylphosphite gave the observed difluoromethylphosphonate. When the reaction is repeated in the absence of the dialkyl phosphite, in situ phosphorylation becomes the dominant reaction and bisphosphonate formation is observed [142]. Our initial yields were not spectacular — 47% in hexane. However, later work using toluene gave significantly better results (60% for the diethyl analogue) [143–146]. Flynn also demonstrated that the bisphosphonate could be obtained via direct reaction of CF_2Br_2 with an excess of sodium dialkylphosphite [142]. Nevertheless, the design of the synthetic approach was demonstrated very nicely by Flynn and provided the first synthesis of this class of bisphosphonates.

The preliminary work by Flynn to produce the phosphonate anion from the bromodifluoromethylphosphonate via

reaction with a dialkyl phosphite anion also demonstrated again the ease of dissociation of the difluoromethylphosphonate anions. Thus, when the groups on phosphorus were different, rapid exchange of $[\text{CF}_2]$ occurred to give a mixture of bisphosphonates via scrambling of $[\text{CF}_2]$ among all possible phosphite anions in solution [147]:

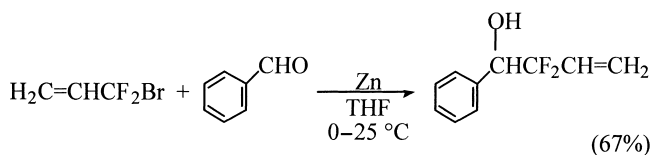


Hydrolysis of the bisphosphonates is readily accomplished via the silylestere and the bisphosphonic acid (**3**) is formed in good yield [148]:



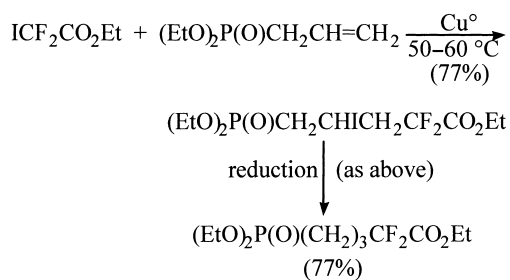
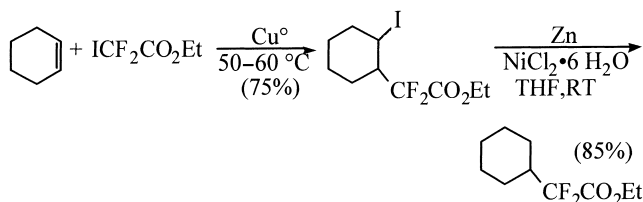
We investigated this acid as a chelating agent for calcium in collaboration with Professor Donald Pietrzyk, one of my Analytical Chemistry colleagues [149]. Dorothy Rowe in our Dental School also investigated **3** as a chelating agent for calcium in bone [150]. Blackburn and coworkers proposed that **3** can mimic pyrophosphate in biological substrates and touched off an explosion of activity with its analogues.

In our laboratory, we tried to develop methodology to bisphosphonates (and acids) of the type $(\text{RO})_2\text{P}(\text{O})(\text{CF}_2)_n\text{P}(\text{O})(\text{OR})_2$, where $n > 1$. Initial success, utilizing a solution free-radical approach achieved some success [151], but the chemistry was difficult and yields were variable. Our interest in these compounds at this time were their potential utility as fuel cell electrolytes or electrolyte additives. One of these compounds, $(\text{HO})_2\text{P}(\text{O})\text{CF}_2\text{CF}_2\text{P}(\text{O})(\text{OH})_2$, did show good activity in a H_2/O_2 fuel cell in collaborative work with Professor Ernest Yeager's group at Case Western Reserve University [152].

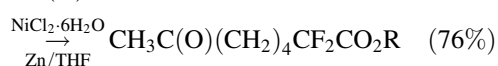
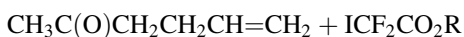
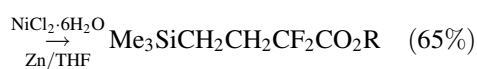


The reaction was easy to carry out experimentally, avoided low temperature reactions with unstable allylic intermediates (lithium reagents), and gave the addition product regioselectively with the CF₂ terminus bonded to the carbonyl carbon, similar to earlier observations by Seyferth and Hiyama. Other metals, such as Cd or Sn, also catalyzed the reaction. Interestingly, in the presence of aluminum and catalytic amounts of tin dichloride, the reaction was successful in protic solvents; for example, with benzaldehyde in ethanol instead of THF, the benzyl alcohol shown above was obtained in 56% yield.

Yang also utilized copper powder to initiate the addition of iododifluoroacetates to alkenes. The reaction is suppressed by *p*-dinitrobenzene and di-*tert*-butyl nitroxide and gives cyclized products with diallyl ether, which is consistent with an SET mechanism. Reductive deiodination of the adduct was achieved with Zn/NiCl₂·6 H₂O [164, 165]:

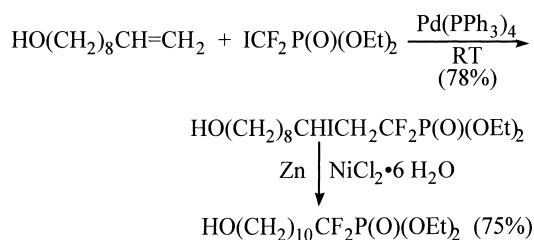


Yang [166,167] also demonstrated that zinc in the presence of nickel chloride hexahydrate in moist THF could give the α,α -difluoroesters in a one-pot reaction. Zinc reduces the nickel chloride to Ni⁰, which catalyzes both the addition and reduction reactions. A wide variety of functional groups,

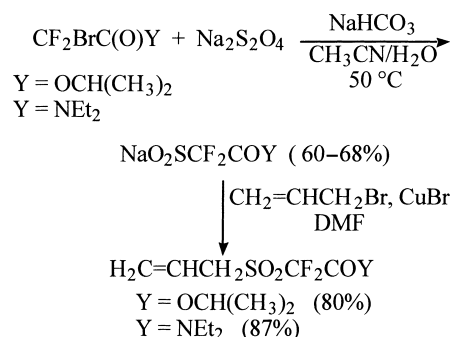


such as OH, OAc, ketone, ester, and silyl, are tolerated in this reaction, and the overall reaction is a facile entry to functionalized α,α -difluoroesters. Mechanistic experiments are in agreement with an SET pathway. Extension of this approach to iododifluoroacetates (ICHFCO₂R) gives α -fluoroesters in moderate to good yields [168].

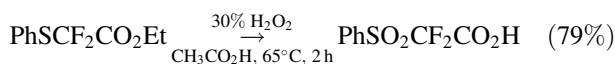
Use of diethyl iododifluoromethylphosphonate by Yang provided an excellent route to α,α -difluorofunctionalized phosphonates [169,170] from alkenes containing functional groups, such as Me₃Si, OH, epoxy, OAc, ketone and ester; dienes gave the corresponding bisphosphonates. Both copper metal and Pd(Ph₃)₄ initiated the reactions. Mechanistic evidence was again in agreement with an SET mechanism.



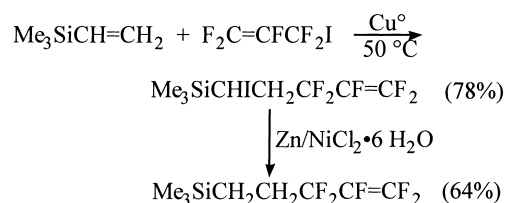
Yang also developed a route to α,α -difluoromethylene functionalized sulfones via sulfination of bromodifluoroacetate or acetamide with sodium dithionite, followed by cuprous bromide catalyzed allylation [171,172]:



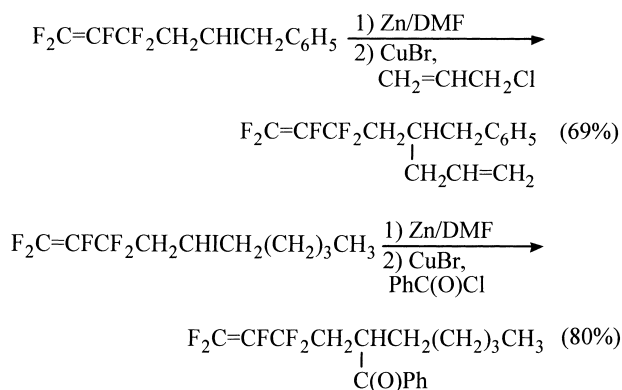
The aryl analogues were prepared by reaction of the bromodifluoroester or amide with appropriate mercaptides to give sulfides, which were oxidized to give the sulfones, e.g.,



Nguyen and Yang [173,174] utilized SET chemistry to achieve perfluoroallylation of olefins, e.g.

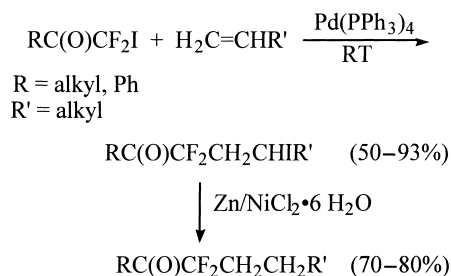


As expected, a wide variety of functional groups are tolerated in this approach. The initial adducts readily form a zinc reagent, which can be elaborated further via reaction with electrophiles, e.g.

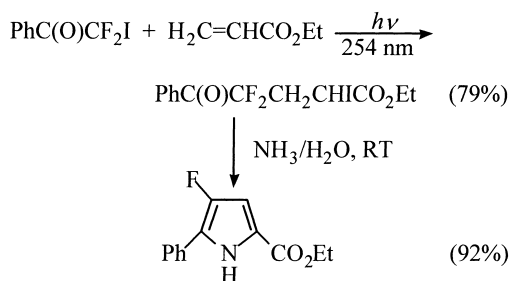


This work demonstrates that the SET approach can not only provide ready access to a variety of iodine-free functionalized α - or α,α -difluoro derivatives, but also that the initial adducts can be further elaborated via a zinc derivative.

Zai-Ming Qiu utilized an SET approach to develop a general route to α,α -difluoroketones from iododifluoromethyl ketones [175,176]; as usual, this method tolerates many functional groups, e.g.



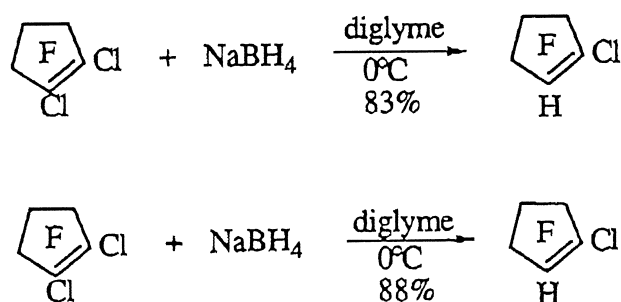
In related work, he studied the photochemical addition of iododifluoromethyl ketones or perfluoroalkyl iodides to electron-deficient olefins [177–179], and utilized the products to develop a clever route to α -substituted β -fluoropyrroles [180,181], e.g.



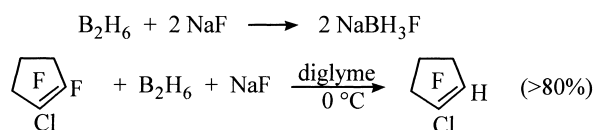
When the corresponding silyl derivatives are utilized in the reaction with aqueous ammonia, the reaction sequences stop at the 1-pyrroline stage.

6. Metal hydride chemistry

From my experience in Professor H.C. Brown's laboratory, I carried an interest in metal hydride and borane chemistry with me to the University of Iowa. At that time (1962), lithium aluminum hydride (LAH) was the reagent generally employed for reduction of polyfluoro-olefins. However, it was difficult to prevent over-reduction with this reagent, so product separation problems often arose. Richard Johnson then introduced sodium borohydride as a selective reagent to accomplish the olefin reduction process [182].

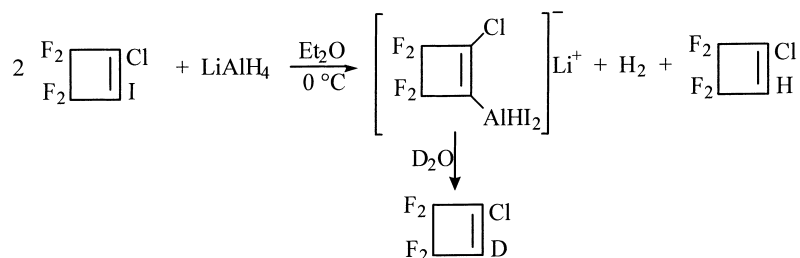


Although fluoro-olefins were inert to diborane under normal hydroboration conditions, diborane/MF solutions readily reduced polyfluoro-olefins, via in situ formation of the $[\text{BH}_3\text{F}]^-$ ion [183]. An article in Fluorine Chemistry Reviews [184] summarizes our initial work with NaBH_4 and the earlier work with LAH.

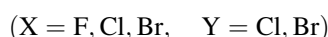
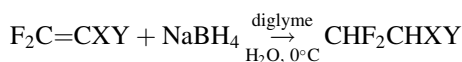


In later work with LAH, we found that when vinylic iodine was present, attack by the reducing agent occurred at iodine — not at carbon. We proposed that a stable aluminum complex was formed and in one case, (Scheme 20) attempted to isolate the complex. However, attempts to remove the last vestiges of solvent caused an explosion, presumably via elimination of the aluminum complex to form a cycloalkyne [185]. Since the reduced olefin could be easily removed under vacuum before hydrolysis, addition of D_2O to the aluminum complex gave a simple route to the deuterated olefin. Subsequent work by Frank Mettite with sodium aluminum hydride in diglyme provided an improved procedure for the preparation of the deuterated olefin [186].

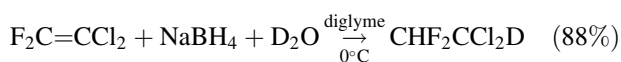
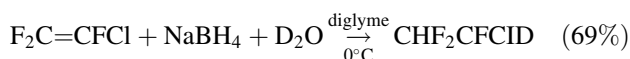
Lynn Anderson developed a useful method for the hydrogenation of fluorinated ethylenes with sodium borohydride in protic media [187,188]. Since sodium borohydride is soluble (and stable) in water or alcohols, the ethylenes could be treated with NaBH_4 in diglyme with added water, ethanol or *t*-butyl alcohol. The major product does not arise via displacement of vinylic halogen but through the addition of the elements of H_2 to the fluorinated olefin.



Scheme 20.



The reaction can be utilized to add HD to fluorinated ethylenes regioselectively, since one of the hydrogens comes from the borohydride reagent and the other from the protic solvent.



6.1. Epilogue

In this review of my group's research activities in Iowa, I have attempted to present the genesis of ideas conceived and developed during the period 1962–1997. Any success we have achieved is due to the hard work, dedication, talent and creativity of the students and postdoctoral associates with whom it has been my pleasure to have shared many chemical adventures. They have made my laboratories a pleasant and exciting place, and have constantly initiated, challenged, extended and developed research ideas. Over the years, the students and postdocs in our laboratory continuously change, and each new group has brought its own ideas and enthusiasm to bear on the research effort. I would be remiss, however, not to acknowledge the one coworker who has been the constant in all our endeavours and to whom I dedicate this article — my wife, Margaret. Over the past 40 years, Margaret has assumed numerous duties and responsibilities in order that I could devote my time and efforts to my mistress, chemistry. She has used her talents and energy unstintingly to assist the coworkers in my research group in numerous ways, and without her help, understanding and sacrifices there is no possible way that I could have attempted and/or accomplished the many endeavours in synthetic methodology described above.

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