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Studies in Heteroelement-Based Synthesis

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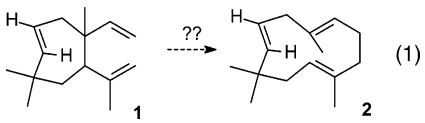
An account of studies in our group over 30 years is presented, with highlights taken from events that began with our plans for medium ring synthesis, but were soon diverted to organophosphorus chemistry, and that eventually resulted in the investigation of sulfur ylide ring expansions, thiocarbonyl chemistry, azomethine ylides, organotin and organoboron methodology, and control of relative and absolute configuration.

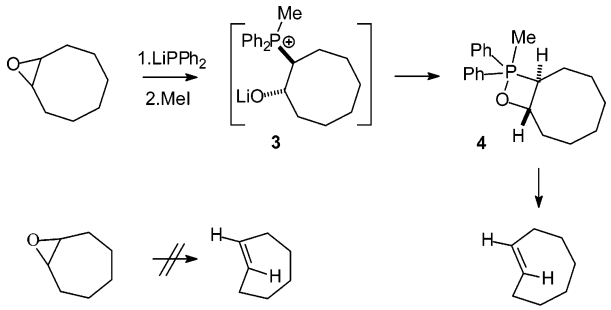
Like so many research programs in academics, my group's work in heteroatom-mediated synthetic methodology had its roots in a student research proposal, tracing back to advanced graduate courses. During my second and third years in graduate school, I was fortunate to attend courses by Peter Wharton and Jerome Berson in close succession, lectures that produced an early fascination with thermal rearrangement chemistry. Wharton spoke in depth about medium-sized ring sesquiterpenes, while Berson focused more on strained-ring hydrocarbons, but both addressed the factors that control the Cope rearrangement.[1] These ideas reappeared in my third-year research proposal, the hypothetical (and still untested) sequence shown in eq 1 from a divinyl *trans*-cycloheptene **1** to the sesquiterpene cycloundecatriene humulene, **2**. Of course, neither the reactant nor the product of eq 1 contains any heteroatoms. That connection for our work came unexpectedly as we were trying to identify new methods that might generate the strained *trans*-cycloheptene of eq 1.



(1)

In the third year of my faculty appointment at Wisconsin, we started to address the *trans*-cycloalkene problem. During a group seminar discussion, a phosphorus-based approach was suggested on the basis of the inversion of a *cis*-alkene oxide into the *trans*-alkene. The key steps assumed trans-ring opening of the epoxide with lithium diphenylphosphide, followed by syn-elimination via the betaine **3** (Scheme 1). I do not remember what prompted the idea. Most likely, it was Ireland's use of lithium diphenylphosphide as a potent nucleophile to cleave the C−O bond of a methyl phenyl ether in the alnusenone synthesis.[2] I do recall that our knowledge of phosphorus chemistry did not extend much beyond this example, although we knew a few basics of the Wittig reaction as a way to make alkenes. In particular, we did not know that Trippett had already studied an acyclic example related to Scheme 1 and had encountered stereochemical complications.[3] If we had known this background, we would not have pursued an organophosphorus approach because there was good reason to question stereospecificity. Fortunately, we did not know, and went ahead. Within days, the key events of Scheme 1 had been tested in a simple case. Soon thereafter, an experiment with *cis*-cyclooctene oxide gave *trans*-cyclooctene with high selectivity (ca. 97% trans).

SCHEME 1. Cyclooctene Inversion Using the Betaine Method



For reasons we never fully understood, many subsequent attempts to reproduce the *trans*-cyclooctene preparation gave mixtures of both the *cis*- and the *trans*-alkenes. Eventually, after more precautions were taken to purify reactants, the problem disappeared. The difficulty was overcome, but it raised concerns about the betaine method and stimulated a much closer look at the issues.

One consequence of the reproducibility problem was that we visited the library to see if anything was already

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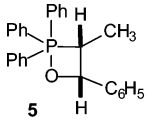
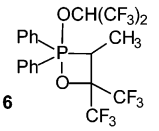
known regarding the decomposition of stereodefined phosphorus betaines. The brief answer is yes, but that is another story.[3,4] More important, the problem stimulated attempts to monitor the betaine intermediate by ^{31}P NMR spectroscopy. Hours were spent looking at baseline noise in the tetravalent phosphorus region hoping to find the betaine **3**. Finally, the sweep width was increased enough to see a strong signal in the pentavalent phosphorus region (δ −62.8 ppm) that proved to be the oxaphosphetane **4**.[5] By this time, we had read enough phosphorus chemistry to know that formation of an observable oxaphosphetane was significant, but not quite enough to forget about eq 1 and humulene. That took several added developments.

First, we found that the betaine decomposition process was quite general and could be used to invert the stereochemistry of a variety of acyclic olefins via the epoxides.[6] The synthetic potential was clear and had to be pursued. Second, our attempts to extend the betaine method to 7-membered rings failed completely. No evidence for generation of *trans*-cycloheptenes was found. Instead, the betaine decomposed via elimination to the cycloheptenylphosphonium salt.[5] Last, and most important, we were able to detect the oxaphosphetane **5** in a representative Wittig reaction. The first attempts encountered experimental difficulties because we had not yet understood that lithium-free ylides are easier to work with,and much better for spectroscopy as well as for nearly all preparative Wittig reactions. As a result, it took some months to get the experiments under control and to obtain definitive spectra for the reaction of benzaldehyde with ethylidenetriphenylphosphorane. The ^{31}P spectrum of **5** was very similar to that of **3** and confirmed that the oxaphosphetane is the low-temperature intermediate. The only other observable oxaphosphetanes that we could find in the literature had been prepared from hexafluoroacetone,[7] as in structure **6**.[7b] Stabilization of pentavalent phosphorus by the trifluoromethyl substituents had been noted, and apparently **6** was regarded as a special case and had not attracted much attention as a Wittig intermediate. In contrast, oxaphosphetane **5** contains typical substituents, and we were soon convinced that it would be representative of other Wittig reactions.



^{31}P NMR;
δ -62.7 ppm

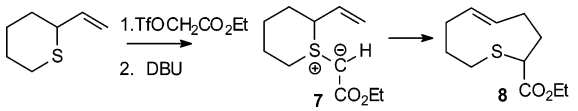


^{31}P NMR;
δ -32.1 ppm

At this point, our first research proposal on mechanistic Wittig chemistry was sent to the National Science Foundation. On a similar time scale, more ^{31}P NMR spectra of oxaphosphetanes were recorded, sufficient to document their intermediacy in several other Wittig reactions as the sole observable intermediates. Soon, there was enough material to submit a communication to *J. Am. Chem. Soc.*[8] The communication reviewed well, but the NSF proposal did not. We were told that there was already a consensus regarding the Wittig mechanism dating back by 10 years or more and featuring the ionic (betaine) intermediate. The NMR detection of pentavalent phosphorus species might be due to various other structures or anomalies, perhaps related to our lack of experience with ^{31}P NMR. The reviewers commented rather briefly and recommended control experiments and kinetic studies. In short, the expected funding did not materialize.

We were faced with unpleasant choices. Finances could be stretched for another 6−9 months, but then what? In 1973, it was difficult to believe that committing scarce graduate student resources to an unfunded mechanistic study was wise. The centrally important discipline of physical organic chemistry was taking hits, while synthetic chemistry was on the rise. I had misgivings about the long-term potential of research activities covered by the already familiar phrase "synthesis of biologically active ...", but funding was a short-term issue.

My misgivings about synthesis proved to be unfounded, but there was no mistaking the trend in 1973. The next NSF proposal went out with no mention of phosphorus or mechanistic studies. Instead, the focus was placed on sulfur ylides as intermediates in ring expansion (eq 2) and on applications in the synthesis of macrolides. The reviewers expressed interest and raised no unwelcome issues. As our finances approached zero, the grant was approved and the immediate crisis was resolved.



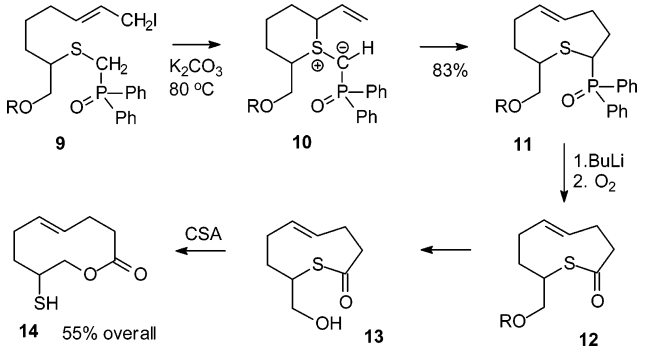
(2)

Of course, the key ring expansion of eq 2 has the same roots as in the original plan of eq 1. This is the same project (medium-ring synthesis) and the same concept (sigmatropic ring expansion), but a different driving force (neutralization of opposite charges in the ylide **7**). With much precedent in acyclic ylide rearrangements, a successful outcome was predictable.

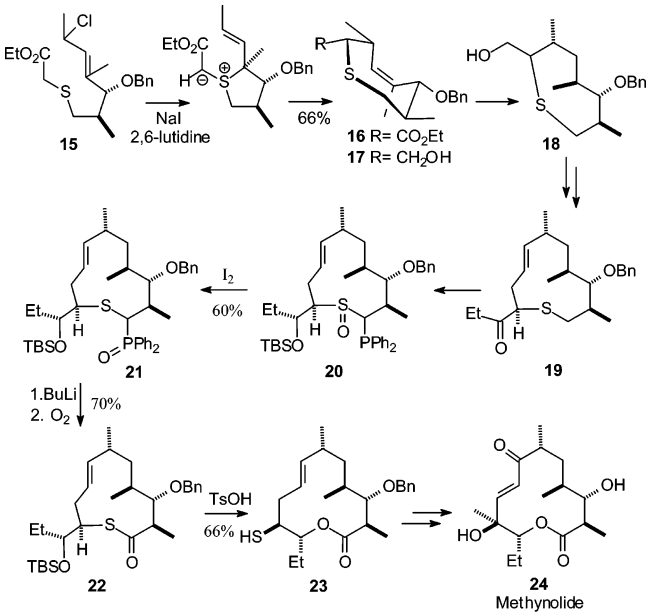
The sulfur ylide chemistry went as expected. Early studies established efficient examples including conversion of the 6-membered ylide **7** to the 9-membered cyclic sulfide **8**.[9] Other ring sizes from 8 to 12 members could be accessed by the same method, and the classical Ramberg−Backlund method for sulfur extrusion could be used to prepare medium-ring carbocycles.[9,10] In the meanwhile, the phosphorus project did not move at all, except when I could find a few hours to do ^{31}P NMR spectroscopy.

With no funds and no co-workers for Wittig chemistry from 1975 to 1978, our group had lost momentum and something had to be done. My attempts to sell the Wittig topic to prospective students produced no takers, so an indirect approach was needed. A phosphorus-mediated end game strategy for macrolide synthesis was inserted into the sulfur ylide project. Every possible connection with sulfur, nitrogen, and phosphorus ylides was built into other projects under the umbrella of biologically active targets. Predictably, this produced no Ph.D. theses focused on phosphorus, but it did result in one individual who agreed to complete the ^{31}P NMR study of oxaphosphetanes. After an 8-year delay, the full paper finally appeared.[11]

SCHEME 2. Medium Ring Lactones by Ring Expansion and S to O Acyl Transfer



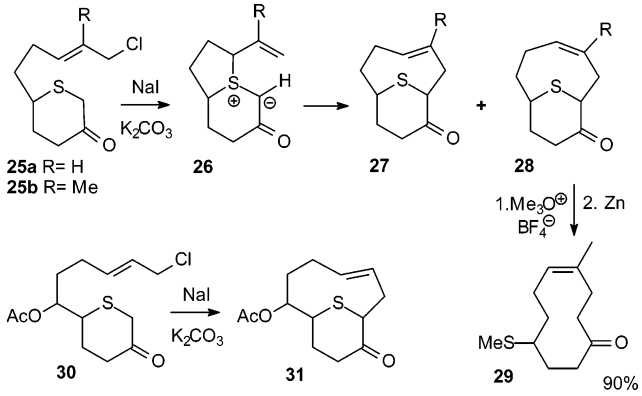
SCHEME 3. Sulfur-Based Synthesis of Methynolide



By 1980, our NSF renewal included phosphorus chemistry in the last stages of a proposed methynolide synthesis. The key transformation from a cyclic sulfide to a macrolide was demonstrated in feasibility studies (Scheme 2),[12] based on the oxygenation of a phosphorus-stabilized anion derived from **11** to the thiolactone **12**, followed by deprotection to **13** and acyl migration to give **14**. Desulfurization was then used to convert **14** into the parent macrolide, phoracantholide I.[12]

The synthesis of methynolide by a similar scheme proved far more challenging (Scheme 3). Ylide ring expansion worked well considering the increase in complexity and afforded **16** (66%) in one operation from **15**. On the other hand, the hydrogenation of the hindered double bond in **17** required a major effort. Eventually, a solution was found using diimide at temperatures above 120 °C to give the desired stereoisomer **18**. Stereochemistry is controlled by the local conformation near the double bond in the illustrated geometry. This was our first proposed example of the local conformer effect in medium ring stereocontrol, involving diimide hydrogenation from the backside of the alkene (peripheral attack),[13] and dating back to the funded 1973 proposal.[14] In any event, the immediate obstacle was overcome, and the remaining problems in the synthesis could be addressed.

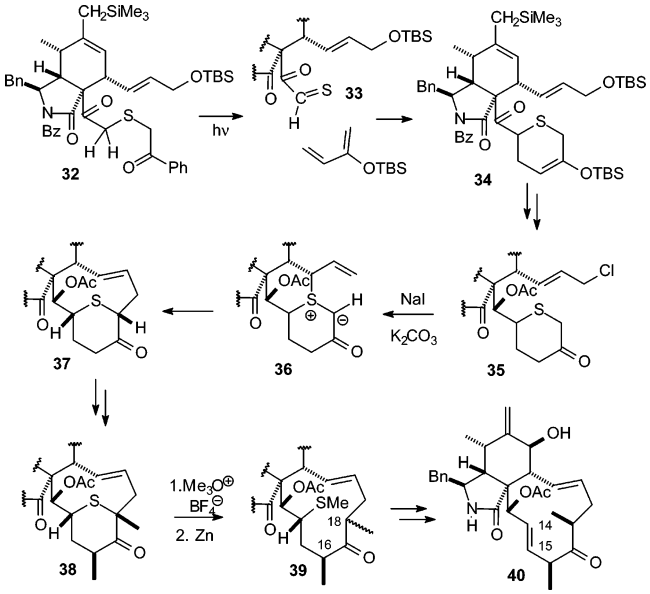
SCHEME 4. Medium-Sized Carbocycles by Sulfur Ylide Ring Expansion



Ring expansion from **18** to the 11-membered ring stage **19** and introduction of phosphorus via phosphinylation of the sulfoxide anion were relatively uneventful. Internal oxygen transfer from **20** to **21** followed by deprotonation of **21** and oxygenation then gave the thiolactone **22**. The oxidative activation sequence was challenging, but the critical acyl transfer process from thiolactone **22** to the macrolide **23** was successful and the methynolide synthesis was completed after much effort.[15] The sulfur ylides had performed their strategic role, and so had phosphorus.

A second sulfur-based synthetic project had been initiated some years earlier as part of the effort to expand the focus on ylide chemistry in our group. In this case, phosphorus did not enter the picture, but the objective was to access medium ring carbocycles, the same goal that was mentioned in the hypothetical example of eq 1. The plan was to exploit internal S-alkylation followed by sulfur ylide rearrangement (Scheme 4). Thus, sulfur-bridged cyclodecenones could be prepared by heating the allylic chlorides **25** with NaI in the presence of K_2CO_3. The case with R = H gave a 1:1.6 *E*/*Z* mixture of **27a** and **28a**, but **25b** produced the *Z*-alkene **28b** exclusively (88−93%). Reductive C−S bond cleavage was then used to convert **28b** into the cyclodecenone **29** (90%).[16] Starting with the homologous substrate **30**, a similar sequence of internal S-alkylation and ylide rearrangement afforded the sulfur-bridged 11-membered carbocycle **31**, exclusively as the *E*-olefin isomer (60%).[17] This system had been designed as a model study for the synthesis of 11-membered carbocyclic cytochalasin derivatives.[18] Selected highlights from this project involving the sulfur-intensive steps are illustrated in Scheme 5, taken from our synthesis of zygosporin E (Scheme 5).[19] Photolytic generation of a complex thioaldehyde **33** from the phenacyl sulfide **32** initiates the most important events. As demonstrated in extensive supporting studies, the thioaldehyde is a highly reactive heterodienophile that is trapped by 2 + 4 cycloaddition using an excess of the 2-siloxybutadiene.[20] After cycloaddition and diastereomer equilibration, 57% of the enol silane **34** was isolated as a single isomer. Enol silane hydrolysis and functionality adjustments eventually produced the ketone **35**, the starting point for ylide rearrangement chemistry. Ketone **35** was then subjected to the NaI/K_2CO_3 conditions for internal

SCHEME 5. A Synthesis of Zygosporin E by Thioaldehyde Cycloaddition and Sulfur Ylide Ring Expansion



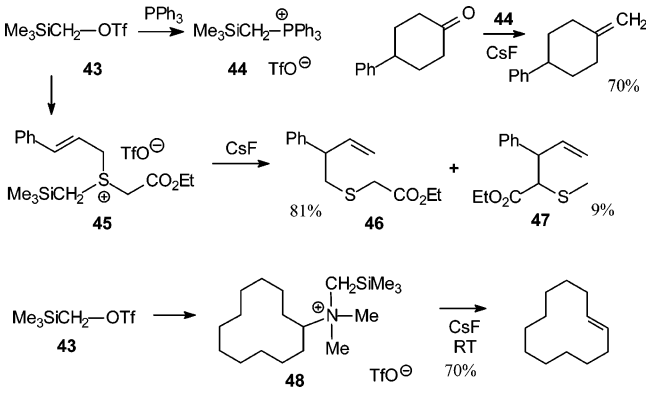
S-alkylation and formation of the ylide **36**. This resulted in spontaneous 2,3-sigmatropic rearrangement and gave the sulfur-bridged carbocycle **37** (65%), together with 6% of a diastereomer (not shown).

The remaining steps to zygosporin E required the introduction of two methyl groups and peripheral adjustments. In a pleasant surprise, the bridgehead position of **37** was easily enolized and methylated using the standard LDA/MeI procedure. However, introduction of the second (C_{16}) methyl group to give **38** required protecting group adjustments that will not be detailed here. Suffice to say that sulfur had served its purpose and now had to be removed. Reductive cleavage of the C−S bond next to the activating ketone carbonyl function of **38** was carried out as in our model studies (Scheme 4), but the result was formation of **39** as a mixture of two C_{18} diastereomers. As luck would have it, the required isomer was the minor component in a 1:2.6 mixture. Nevertheless, sufficient material was obtained to complete the synthesis of zygosporin E by sulfoxide pyrolysis to introduce the C_{14}−C_{15} double bond.[19]

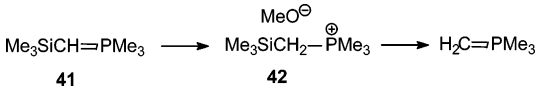
The above outcome, along with a completed synthesis of otonecine using thiocarbonyl cycloaddition chemistry,[21] signaled the end of major efforts in our group involving sulfur-based methodology. Completion of the natural products was among the high points of this effort, but that was not the scientific justification. I would point to the S-acyl to O-acyl migrations, the thiocarbonyl chemistry, and the ylide ring expansions as the most important advances. The latter topics have been developed further in the literature.[22]

As mentioned in an earlier section, synthetic projects focusing on a range of ylides had been initiated in the 1970s, partly to attract research funding, and partly to attract co-workers who might become interested in the Wittig problem. By 1979, these efforts had produced a new technique for ylide generation. We had noticed Schmidbaur's report describing the conversion from a

SCHEME 6. Ylide Generation by Desilylation of Onium Salts



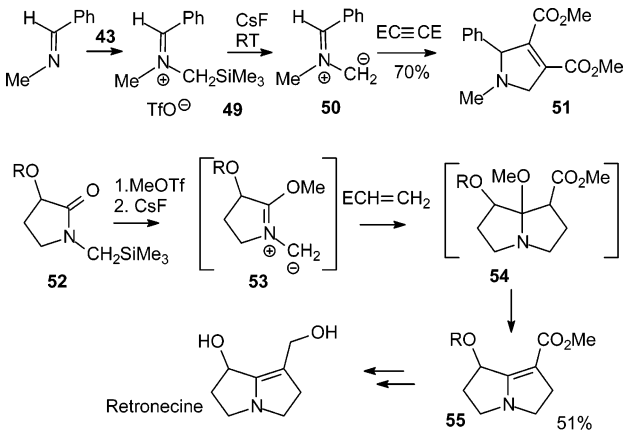
trimethylsilyl-substituted phosphorane **41** to the parent ylide ($Me_3P{=}CH_2$) upon treatment with methanol (eq 3).



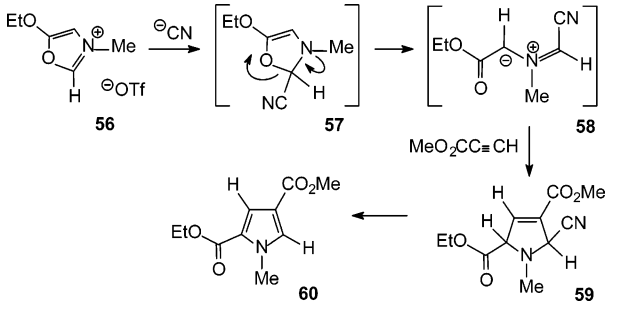
This conversion involves desilylation of an intermediate α-silylphosphonium salt **42** by methoxide acting as the silaphile.[23] A related process was tested in our laboratory where the silylphosphonium salt **44** was prepared by alkylation of Ph_3P with Me_3SiCH_2OTf (**43**), and ylide generation was accomplished using fluoride ion as the silaphile.[24] Olefination of cyclohexanone was demonstrated, but serious applications in the phosphorus series were difficult to justify because the standard deprotonation route to phosphorus ylides is so easy. Sulfonium and ammonium ylide applications were more promising. For example, a nonstabilized sulfonium ylide could be generated from the salt **45** and trapped by a 2,3-shift to give **46** (Scheme 6). The 9:1 ratio of **46**/**47** indicates that sigmatropic rearrangement is faster than equilibration of the intermediate ylides by proton transfer. A nonstabilized ammonium ylide could also be accessed by treatment of the ammonium salt **48** with CsF, resulting in 5-center elimination to the alkene. Analogous ammonium ylide eliminations were well-known, but strongly basic conditions had been used in the earlier studies.[25]

The most important application of the desilylation approach proved to be in the generation of nonstabilized azomethine ylides (Scheme 7).[24] Deprotonation approaches are difficult to control in the azomethine series, apparently due to the sensitivity of the reactants as well as the ylides, but desilylation of iminium salts is a general process having broad utility.[26,27] In the first experiments, the salt **49** was formed by alkylation using **43**. Desilylation with CsF in the presence of dimethyl acetylenedicarboxylate as the dipolarophile resulted in trapping of ylide **50** to give the cycloadduct **51**. Access to azomethine ylides was also demonstrated starting from *N*-trimethylsilylmethyl lactams or thiolactams, as illustrated in the sequence from **52** to **55** via the labile cycloadduct **54**.[27] Subsequent studies by other groups developed several related desilylation techniques for nonstabilized azomethine ylide generation from imine or amide derivatives and numerous applications are now known.[24−28]

SCHEME 7. Imidate Ylide-Based Synthesis of Retronecine



SCHEME 8. Stabilized Azomethine Ylides from 4-Oxazolines

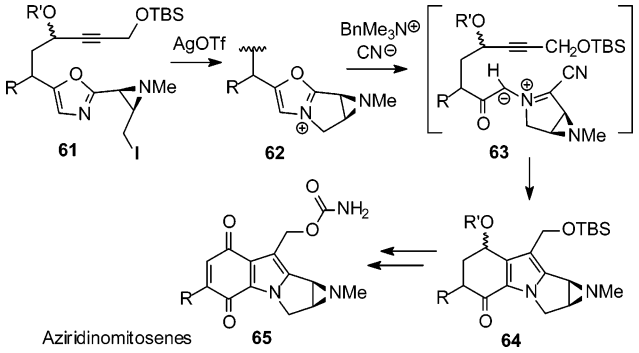


Our involvement with azomethine ylides continued, but attention was turned to the development of new methods for room temperature access to the carbonyl-stabilized ylide family that might be used in the synthesis of highly reactive target structures. The key event is illustrated in the conversion from oxazolium salt **56** to the pyrrole **60** (Scheme 8).[29] Addition of cyanide ion to **56** affords a labile 4-oxazoline intermediate **57**, and electrocyclic ring opening gives the transient azomethine ylide **58**. After 2+3 dipolar cycloaddition, the initially formed pyrroline **59** undergoes spontaneous aromatization to pyrrole **60**. All of these steps proceed at room temperature or below, in contrast to the alternative of aziridine pyrolysis as a method for azomethine ylide generation.[30]

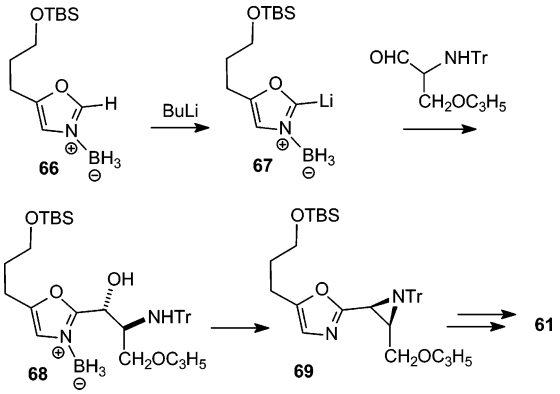
In the ultimate test for the 4-oxazoline method of azomethine ylide generation, the aziridinyl oxazole **61** was converted into an oxazolium salt **62** by internal alkylation (Scheme 9). Addition of a soluble cyanide source to **62** resulted in ylide formation, internal [2 + 3] cycloaddition, and aromatization to **64**. Survival of the sensitive pyrrole-activated aziridine over this sequence of events reflects the mild conditions for ylide formation. Further conversion into the quinone **65** has been demonstrated, and provides an entry into the aziridinomitosene series in work that is ongoing in our laboratory.[31]

The aziridinomitosene project stimulated the investigation of several other topics, including methodology for metalation of oxazoles or aziridines as potential precursors of the key intermediate **61**. At the outset, it was not clear whether it would be better to metalate the oxazole or the aziridine, so studies were initiated to explore both

SCHEME 9. A Synthesis of Aziridinomitosenes



SCHEME 10. Oxazole Borane Complex Lithiation



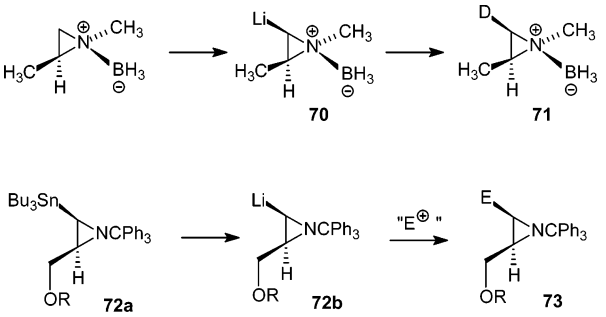
approaches. Both were eventually demonstrated (Schemes 10 and 11).

The oxazole metalations had to contend with the well-known tendency of 2-metalated oxazoles to equilibrate with acyclic valence bond tautomers.[32] Because the undesired ring opening pathway involves the unshared electron pair on nitrogen, it could be suppressed by the simple expedient of converting the oxazole into the corresponding borane complex **66** prior to lithiation (Scheme 10).[33] Simpler analogues of **67** could be reacted with representative electrophiles, including iodomethane, positive halogen sources, and aldehydes to give the substituted oxazoles.[33] Using the same approach, **67** was reacted with a protected serinal derivative to afford the amino alcohol **68**. Mitsunobu conditions were then used to convert the crude **68** into the aziridine **69**, a key precursor of the oxazole aziridine **61** in our aziridinomitosene project (Scheme 9). This proved to be the best approach for connecting the oxazole and aziridine subunits.

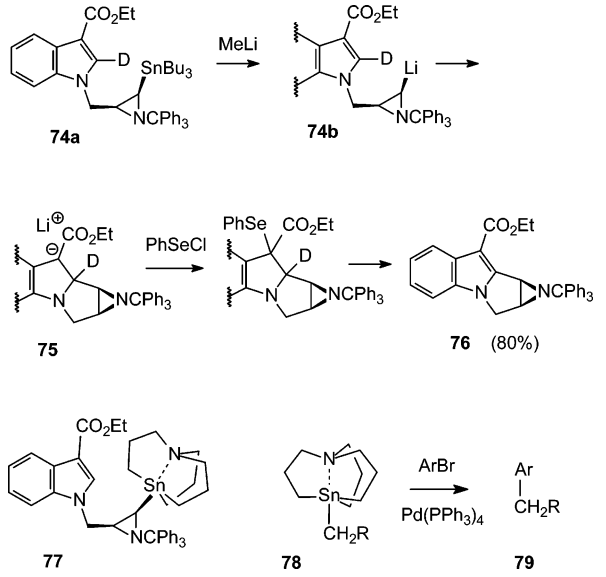
The alternative approach via aziridine lithiation was demonstrated in model studies using two different methods (Scheme 11). The first relies on lithiation of an aziridine borane complex with *s*-BuLi to produce **70**. Quenching with D_2O results in >90% of the deuterated **71**, indicating that the lithiation occurs syn to the activating borane subunit.[34,35] Although the lithiation of aziridine boranes is fundamentally interesting, the strongly basic conditions proved to be an unwelcome limitation. A second approach was therefore developed using tin−lithium exchange from a stannylated aziridine **72a**.

At first glance, the methyllithium conditions used for metal exchange from **72a** to **72b** would also appear to

SCHEME 11. Aziridine Lithiation



SCHEME 12. Internal Michael Addition Approach to Aziridinomitosenes

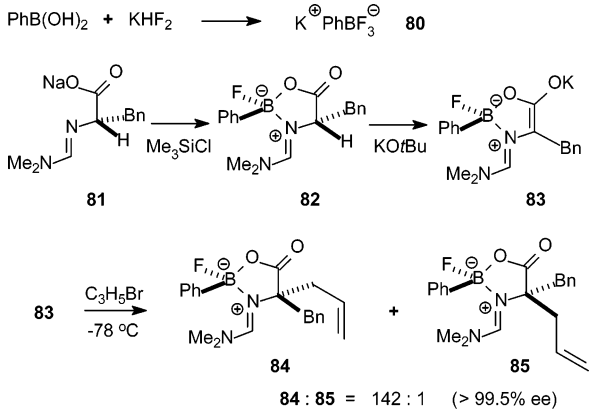


be rather basic. However, they proved to be well suited for introduction of representative electrophiles to afford **73**, and also for more demanding aziridinomitosene applications. As shown in Scheme 12, the conversion of **74a** into **76** was effected by internal Michael addition from the lithioaziridine **74b** to the enolate **75**, followed by aromatization via a labile selenide intermediate. Addition of the methyllithium reagent to the ester was not observed, but we did encounter low yields due to competing lithiation of the indole ring in the parent (replace D by H) series. Fortunately, the deuterated substrate **74** is protected against this undesired pathway by a factor of at least 30 due to a kinetic isotope effect, and cyclization occurs in 80% yield.[36]

We had also initiated work on another organotin approach for activation of aziridine bonds, based on the conjecture that transannular N···Sn interaction in a deoxastannatrane derivative **77** might result in a C−Sn bond having sufficient reactivity for internal Michael reaction in the presence of a Lewis acid. Preliminary tests of this possibility were not promising. However, the transannular effect did result in enhanced reactivity for the exocyclic bond in simpler structures **78**, sufficient for selective Stille coupling to give **79**.[37a] Interesting applications of **78** for the palladium-catalyzed coupling of more highly functionalized substrates have been reported.[37b]

The lithiation of the aziridine borane complex **69** is an example where the configuration of a potentially labile

SCHEME 13. Asymmetric Memory at Stereogenic Boron



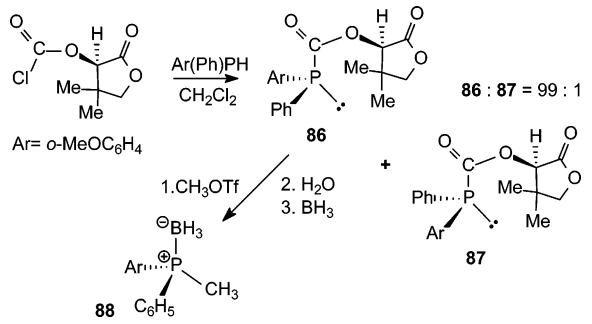
stereocenter (the aziridine nitrogen) can be temporarily stabilized by formation of a Lewis acid−Lewis base complex. As long as the nitrogen is tetravalent, its configuration can be exploited to control stereochemistry at an adjacent carbon in the lithiation step. Other projects had been initiated in our group where the same principle could be used to control absolute configuration. In one interesting case, the phenylalanine-derived imine carboxylate **81** was converted into a boron complex **82** using the potassium trifluoroborate salt **80** as an in situ source of $PhBF_2$ (Scheme 13).[38] At temperatures where the boronate complex is stable, the boron stereocenter can be used to store stereochemical information. Thus, conversion into the enolate **83** occurs without racemization of the phenylalanine, and enolate alkylation with allyl bromide affords the isomer **84** with excellent stereoselectivity (142:1 **84**/**85**).[39]

The use of tetravalent boron for asymmetric memory[40] was the initial motivation for this work, but a more important consequence may be the development of the convenient KHF_2 method for preparation of potassium trifluoroborate salts related to **80**.[38] In contrast to other boron halide derivatives, the potassium trifluoroborate salts are easy to handle because they are strongly favored by thermodynamic factors. The aryl and alkenyl trifluoroborates have attracted considerable interest for applications in organometallic coupling chemistry.[41]

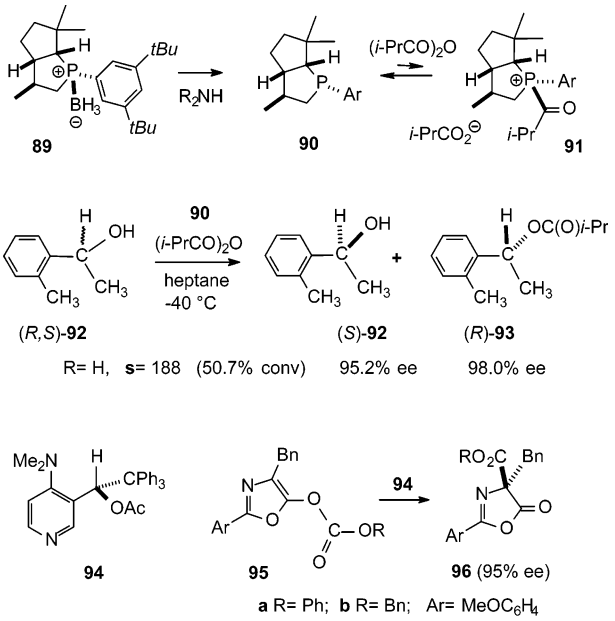
The conversion from **81** to a single diastereomer **82** is a consequence of crystallization-induced asymmetric transformation during product isolation. The initially formed product is a mixture of boron epimers, but **82** is more stable in the crystal lattice and accumulates during crystallization if the conditions are chosen to allow isomer equilibration. This probably occurs via trivalent boron intermediates resulting from TMSCl-catalyzed heterolysis of a B−F or B−O bond. Several other organoboron environments have been identified in our group where related equilibration events could be used to control boron configuration.[39b]

Crystallization-induced asymmetric transformation has interesting preparative implications for configuration control in chiral structures that contain potentially labile stereogenic heteroelements. A logical extrapolation from this principle was to investigate chiral phosphine derivatives where pyramidal inversion provides a mechanism for interconversion of epimers (Scheme 14). We were able

SCHEME 14. Crystallization-Induced Asymmetric Transformation at Stereogenic Phosphorus



SCHEME 15. Chiral Nucleophilic Acyl Transfer Catalysts



to demonstrate phosphorus stereocontrol in the case of the alkoxycarbonylphosphine **86** (1:1 **86**/**87** prior to asymmetric transformation; 99:1 **86**: **87** after crystallization and warming the solid to 50 °C).[42] The crystallization method relies on the presence of a chiral auxiliary, but it is highly effective for the synthesis of enantioenriched phosphine derivatives, as in the conversion from **86** to the tertiary phosphine borane **88** by a sequence of *P*-alkylation and hydrolysis (84% recovery; >99.5% ee).

A second project involving chiral phosphines was initiated to follow up a preliminary study where simple phosphines had been shown to activate anhydrides for the esterification of alcohols.[43,44] The most highly selective catalyst to emerge from our study was the phosphabicyclo-[3.3.0]octane (PBO) derivative **90** (Scheme 15). Phosphine **90** activates anhydrides via the *P*-acylphosphonium carboxylate **91**, a reactive intermediate that discriminates between enantiomers of substrate alcohols in the acyl transfer step. Enantioselectivity is optimum for highly substituted benzylic or allylic alcohols, resulting in efficient kinetic resolution as shown for one of the best substrates **92** to afford the isobutyrate ester **93**.[45,46]

The mechanistic analogy between phosphine-catalyzed and *p*-(dimethylamino)pyridine-catalyzed acyl transfer was recognized early in this effort, and stimulated the exploration of chiral DMAP derivatives in our group. In the first attempts, highly enantioselective reagents were encountered,[47] but catalytic turnover was not achieved. More recently, a new family of readily accessible DMAP structures has been identified, and the first member of the series (**94**; TADMAP) has been shown to induce enantioselective carboxyl transfer from oxygen to carbon, as in the conversion of an oxazolyl phenoxycarbonate **95a** to the azlactone **96a**.[48] The chiral phosphine **90** is also an effective catalyst for the analogous carboxyl transfer process, although the preferred substrate is the benzyloxycarbonyl derivative **95b** and the product is the enantiomer of **96b**. Both catalysts **90** and **94** are comparable to Fu's chiral DMAP derivative in terms of enantioselectivity for the carboxyl migrations.[49]

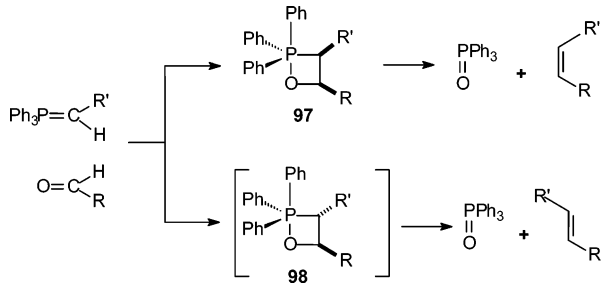
This account of our studies in heteroelement-based methodology began with phosphorus chemistry and has returned to phosphorus in our most recent work by following the evolution of several different lines of investigation featuring sulfonium ylides, azomethine ylides, and studies involving stereogenic heteroatoms. It seems fitting to close with further comment on the phosphorus theme, and to look back at the outcome of the Wittig story.

By the mid-1980s, the major sulfur ylide synthesis projects were nearing completion, and resources could be directed to the long-delayed Wittig chemistry. The first NSF funds to explicitly support this work appeared in 1986 and allowed us to pursue stereocontrolled oxaphosphetane generation from hydroxyphosphonium salts. The experiments were used to probe the reversibility of oxaphosphetane formation, and to monitor stereochemistry at phosphorus[50] as well as at carbon[51] using procedures that are closely related to the betaine method for olefin inversion that had introduced our group to ylide chemistry over 30 years ago (Scheme 1). These more recent studies have already been reviewed,[4,45] so the discussion here will mention only a few historical highlights and the most important mechanistic conclusions.

When we became involved with phosphorus in the early 1970s, textbooks and reviews described the Wittig reaction as an ionic process. The standard stereochemical rationale invoked formation of an *anti*-betaine intermediate and regarded the oxaphosphetane as a transient species of higher energy, or perhaps as the transition state leading to the alkene. To explain stereochemistry, it was assumed that the betaine precursor of the *Z*-alkene decomposes with dominant kinetic control (minimal reversal or equilibration of stereochemistry) when R′ = alkyl (nonstabilized ylides). In the case of stabilized ylides where R′ = CO_2Et, acyl, etc., the formation of *E*-alkene products was attributed to reversible betaine formation, and a kinetic advantage for the decomposition of that betaine isomer which leads to the *E*-alkene. However, none of these generalizations has proven to be consistent with evidence from studies by Maryanoff et al. or the work in our laboratory (Scheme 16). [4]

Both oxaphosphetanes **97** (cis) and **98** (trans) are formed under kinetic control according to experiments based on independent betaine generation.[51] When R′ = alkyl, the reactions with aldehydes are among the fastest 2 + 2 cycloadditions and can be conducted at −78 °C to reach the oxaphosphetane stage. Decomposition to the

SCHEME 16. Reactivity and Stereospecificity in Wittig Reactions



alkene is a slower process, but takes place as a stereospecific cycloreversion at temperatures of ca. −10 °C or above.[51a] In the case where R′ = CO_2Et, the initial step leading to **98** is much slower and becomes rate limiting. On the other hand, the cycloreversion step from **98** to products is exceedingly fast according to the control experiments,[51b] and ranks with the fastest known cycloreversions.

No example of a lithium-free Wittig reaction has been reported where a betaine can be detected. The oxaphosphetane is always more stable, unless Lewis acids are present to cleave the P−O bond. No other intermediates are required by the data to account for the lithium-free Wittig reactions. The above statements may surprise readers who have seen betaines featured in most undergraduate (and some graduate) textbooks to this day. It has intrigued me for 30 years to see that the betaine lives on, despite what one might expect based on the high reactivity of $Ph_3P{=}CHCH_3$ + RCHO in toluene at −78 °C, not to mention high P−O bonding energy that should be a significant factor in the transition state as well as in the ground state. Perhaps this was one cost of that unfunded proposal many years ago. A focused mechanistic study completed within a few years of the first observation of the oxaphosphetane intermediates might have been more decisive than the slowly evolving phosphorus story that has been described in my account, but this was a small price to pay. That longer, slower process has taken our work to adventures in heteroelement chemistry that I could not have imagined in 1973.

Acknowledgment. I would like to express my appreciation to all of the students who have contributed to the research in my group over many years. The stimulus of our conversations was the source of much of the science described in this account. Many of their contributions could not be mentioned, especially those from our early studies of thermal rearrangement and organopalladium chemistry, molybdenum peroxide carbanion hydroxylation studies, total synthesis and methodology efforts not easily connected to the main heteroelement themes, the investigation of stereoelectronic and conformational directing effects, and the work on enantioselective protonation. The willingness of so many individuals to take on unusual problems has been a continuing source of fascination and inspiration for me. Support from the National Science Foundation for 30 years and from the National Institutes of Health (CA17918) for nearly as long is gratefully acknowledged. Unrestricted grants from Eli Lilly and from the Upjohn Co. at a critical moment were greatly appreciated and kept our phosphorus effort alive. Later contributions from Upjohn and Pharmacia provided the freedom to try new directions and to follow where the science leads. Finally, I would like to thank Dr. J. Atkins for helpful comments on the manuscript and for the cover design that appears in this issue.

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