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Modern Pummerer-type reactions

Ken S. Feldman

Department of Chemistry, The Pennsylvania State University, University Park, PA 16802, USA

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1. Introduction

Who discovered the Pummerer reaction? A simple, if not rhetorical, question that belies a straightforward answer. Ultimately, provenance for this well-known transformation depends on a second question: what chemical process actually constitutes a Pummerer reaction? Perhaps the original candidate for this role was reported by Fromm and Achert in 1903,[1] who described the decomposition of dibenzylsulfoxide (**1**) upon attempted distillation to furnish the suite of products **2**–**5** (Scheme 1). This study did not include the deliberate treatment of the sulfoxide with an electrophile (i.e., H^+, Ac_2O), a precondition of the modern version of the Pummerer reaction, and so it is likely that adventitious

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E-mail: ksf@chem.psu.edu

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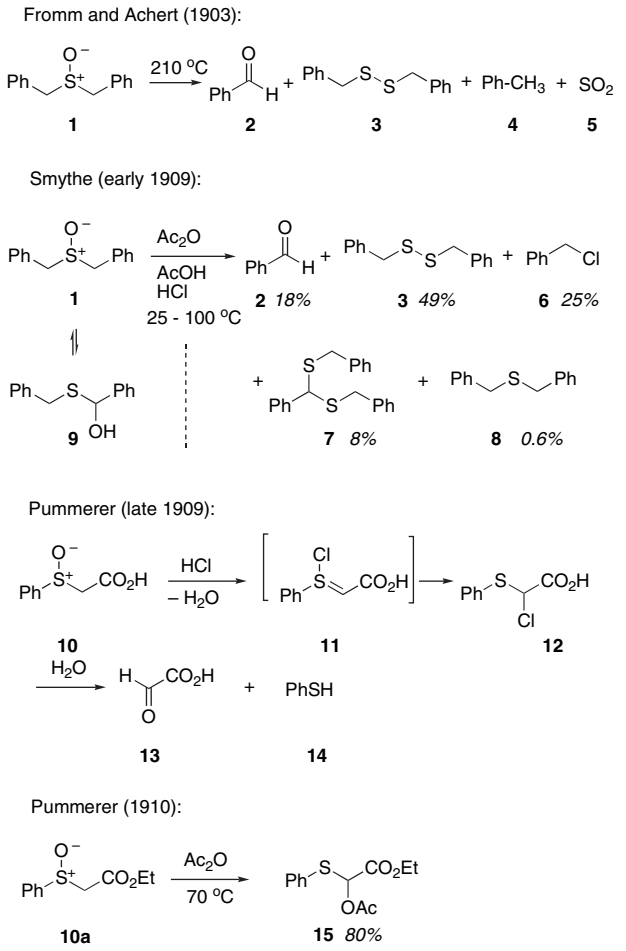


Scheme 1. Early examples of Pummerer (and related) reactions.

and unacknowledged acid autocatalyzed the decomposition. No mechanistic discussion attended this observation, and the surprising formal oxidative transposition that was observed caused the authors to doubt the structure of their starting material: "Der merkwürdige Zerfall des Benzylsulfoxyds bei 210°, insbesondere die Bildung von Benzaldehyd bei dieser Zersetzung, liess Zweifel darüber autkommen, ob die dem Sulfoxyd zugeschriebene Constitutions-formel: $(C_6H_5{\cdot}CH_2)_2S{:}O$, die richtige sei. Es musste in diesem Fall-eja eine Wanderung des Sauerstoffs vom Schwefel an den Kohlenstoff stattgefunden haben. Eine solche Wanderung konnte man ausschliessen, wenn man dem Benzylsulfoxyd die folgende Constitutions-formel, in welcher der Sauerstoff von vornherein an Kohlenstoff gebunden ist, zuschrieb: $C_6H_5{\cdot}CH_2{\cdot}S{\cdot}O{\cdot}CH_2{\cdot}C_6H_5$."[1] (The unusual decomposition of benzylsulfoxide at 210°, in particular the formation of benzaldehyde upon this decomposition, raises concerns about whether the constitutional formula assigned to the sulfoxide, $(C_6H_5{\cdot}CH_2)_2S{:}O$, is correct. If it is so, then migration of the oxygen from sulfur to carbon must have taken place. Such a migration can be excluded if one assigns the following constitutional formula, in which the oxygen is bound at carbon from the outset, to the benzylsulfoxide: $C_6H_5{\cdot}CH_2{\cdot}S{\cdot}O{\cdot}CH_2{\cdot}C_6H_5$.) Six years later in early 1909, Smythe picked up this train of research and described the products detected upon exposing **1** to the undeniable Pummerer activators HCl and Ac_2O.[2] Smythe observed formation of the characteristic Pummerer reaction product benzaldehyde (**2**) (and its derived thioacetal **7**), and his mechanistic speculation started out in a productive vein by suggesting that the hydroxysulfide **9** preceded the aldehyde. However, Smythe was apparently at a loss to rationalize the intermediacy of this alcohol, and he resorted to invoking what he termed 'dynamic isomerism' between **1** and **9**, by analogy with known keto-enol tautomerizations, to justify its presence. Later in that same year, in a paper that cites the work of Smythe, Rudolph Pummerer authored his now famous report on the consequences of treating the sulfinyl acetic acid **10** with HCl.[3a] Pummerer meticulously characterized the product distribution, which included the aldehyde **13** and thiophenol. Once again, a formal oxidation at carbon required explanation, and Pummerer rose to this challenge by invoking the intermediacy of the sulfurane **11** and then its formal 1,2-chloride shift product, the sulfide **12**. The similarity of Pummerer's sulfurane to the currently adopted thionium ion intermediate, Ph(+)S=CH–, should not be overlooked (simple chloride ionization from **11**), and this hypothesis provided for the first time a rational mechanistic framework for discussing sulfoxide decomposition chemistry. Pummerer evaluated and then rejected Smythe's dynamic isomerism explanation, noting that "Auf die ausführlichen Desmotropie-Betrachtungen des Verfassers kann ich nicht näher eingehen, sie stehen in beträchtlichem Gegensatz zur heutigen Kenntnis derartiger Probleme."[3a] (I don't want to elaborate further on the author's detailed discussion of 'desmotropy', as it stands in considerable contrast to modern understanding of such problems.) Thus, while Pummerer was perhaps not the first researcher to observe his eponymous reaction, he appears to be the first to understand what he was observing.

It is unclear whether Pummerer appreciated the significance of his (or Smythe's) discovery. He published only one follow-up report on the topic in 1910,[3b] which did, however, describe the reaction of a sulfoxide **10a** with acetic anhydride in the classical Pummerer sense, before embarking on a long and distinguished career in the general area of industrial organic chemistry. In fact, Pummerer's biographer, R.E. Oesper, wrote a 1951 encomium that noted Pummerer's many contributions to both industrial chemistry and organic mechanistic studies, but failed even to mention the sulfoxide chemistry that now bears his name![4] So, why is the Pummerer reaction called 'The Pummerer reaction'? Perhaps the genesis of this term can be traced to a 1960 supplement for a 1959 article by Horner and Kaiser from Universität Mainz,[5a] who christened the reaction thusly: "Die Analogie zur POLONOVSKI-Reaction liegt auf der Hand. Die Reaktion zwischen Sulfoxyden und Säureanhydriden wollen wir in Zukunft als 'Pummerer-Reaktion' bezeichnen."[5b] (The analogy to the POLONOVSKI reaction is obvious. In the future, we would like to designate the reaction between sulfoxides and acid anhydrides as the 'Pummerer reaction'.)

Research into the electrophile-promoted decomposition of sulfoxides proceeded only fitfully for the 50 years following Pummerer's initial observation, Figure 1. Sporadic reports of Pummerer-like chemistry appeared, but no systematic efforts to explore the process were documented until the 1959 Horner and Kaiser work. Perhaps the Mainz groups' attention to this obscure reaction, coupled with their elevation of the chemistry to 'named reaction' status, piqued the

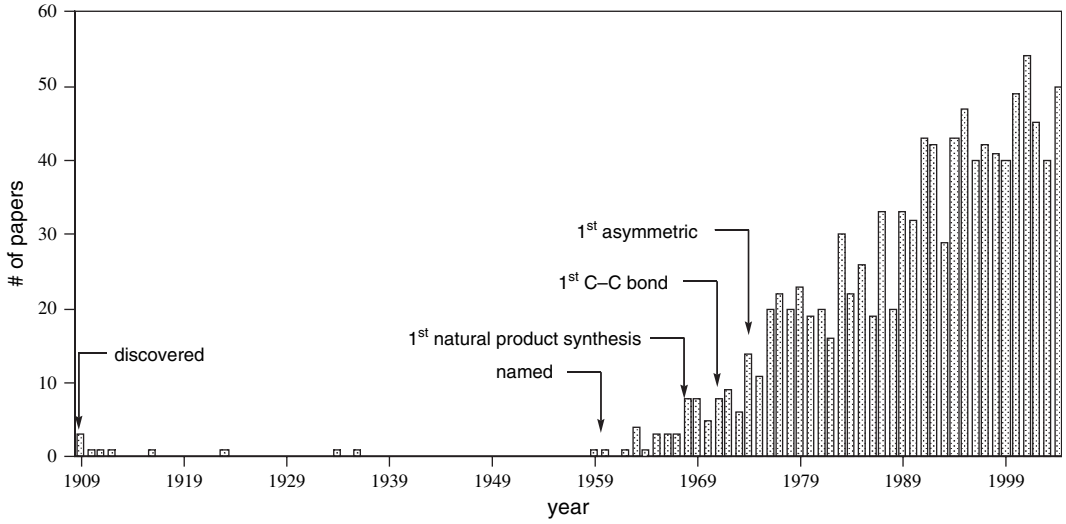
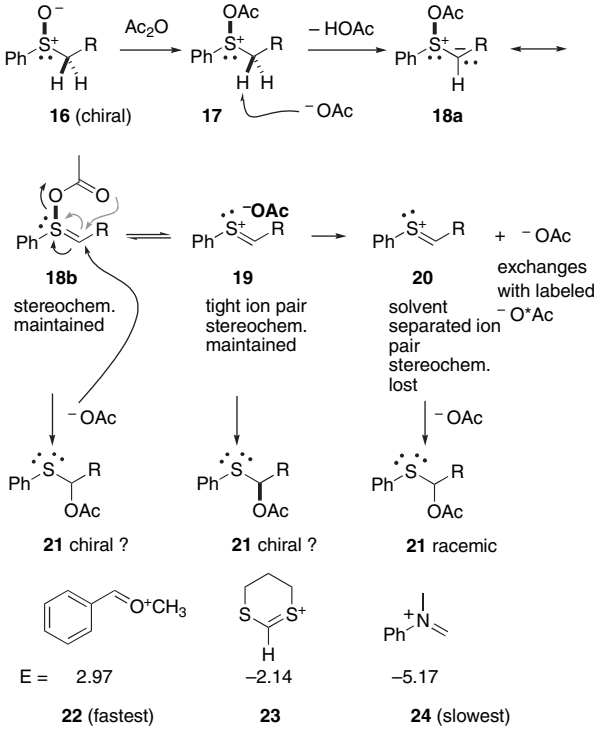


Figure 1. Timeline for Pummerer reaction research.

interest of other researchers, as the 1960s saw the beginning of an upsurge of research work that continues unabated to the present day. Early studies largely focused on mechanistic issues and attempted to explore the scope of the process, leading to elucidation of a detailed reaction mechanism. Other milestones include the first use in a natural product synthesis (illudin M by Matsumoto et al.[6]), the first example of C–C bond formation,[7] and the first claim for asymmetric synthesis from a chiral sulfoxide.[8]

The mechanistic course of the Pummerer rearrangement has been explored through judicious use of deuterium- and O^{18}-labeling experiments, kinetic analysis, and product identification studies.[9] The confluence of results from these studies provides a self-consistent mechanistic picture, Scheme 2.



Scheme 2. Current mechanistic thinking about the Pummerer reaction.

A chiral sulfoxide is invoked to illustrate some of the mechanistic subtleties uncovered by the labeling studies, as the observation of significant levels of asymmetric induction would otherwise be at odds with passage through the commonly cited achiral thionium ion intermediate **20**. Treatment of sulfoxide **16** with Ac_2O rapidly provides the chiral sulfonium salt **17**, which can racemize under certain circumstances (e.g., high acetate concentration) via the intermediacy of a sulfurane $PhS(OAc)_2CH_2R$. To limit this undesirable outcome, the effective acetate trap DCC has been introduced into the Pummerer mixture, albeit at some sacrifice in yield.[10] If acetate acts as a base with **17** instead, ylide **18a** will be formed, itself a resonance form of the sulfurane **18b**. This ylide preserves the chirality at sulfur under standard Pummerer conditions, and it is postulated to serve as a direct precursor to (chiral) α-acetoxysulfide **21** via either intramolecular S-to-C transposition of the acetate group,[11] or by intermolecular addition of exogenous acetate.[12] Ejection of acetate from **18** competes with product formation, and this process can lead first to a tight ion pair **19** and then to a solvent separated ion pair **20**. Both **19** and **20** can serve as precursors to α-acetoxysulfide **21**, although the stereochemical consequences for each path may differ.

The broader utility of the Pummerer reaction in organic synthesis stems, at least in large part, from the capability of the electrophilic intermediate **20** to combine productively with carbon π-nucleophiles and fashion new C–C bonds. The question then can be raised, 'How good of an electrophile is thionium ion **20**?' Many studies have shown that electron rich arenes and alkenes are effective partners for **20**. Some qualitative measure of sulfur-stabilized carbocation **20**'s electrophilicity can be gleaned from the seminal contributions of Mayr, who measured/calculated the electrophilicity parameter E for the species **22**–**24**.[13] By this scale, the doubly sulfur-stabilized carbocation ion **23** reacts with Mayr's reference π-type carbon nucleophiles a few orders of magnitude slower than the phenyl/oxygen stabilized carbocation **22**, but significantly faster than the iminium ion **24**.

The energetics that govern the various competitive pathways that extend from **18** seem to be finely balanced, as variations

of substrate structure/functionality, solvent, additives, etc. appear sufficient to steer the reaction down one channel or another. Oxygen-18 labeling studies provide evidence for the predominant or exclusive operation of each of these pathways under differing circumstances.[9b] From this perspective, it may not be fruitful to define one Pummerer 'mechanism', but rather a more valuable exercise might entail identifying relationships between reaction/substrate parameters and specific mechanistic consequences. Thus, Kita's search for conditions that favor reaction through **18b** or **19** has led to the discovery of a new set of Pummerer activators that proceed with high levels of asymmetric induction (vide infra).[14] The application and extension of these mechanistic considerations underlie all of the recent advances in Pummerer technology, and have led to the development of a broad suite of synthetic methods, which, taken together, establish this chemistry as a fundamental strategy-level reaction in organic synthesis.

From these episodic beginnings, the pace of Pummerer rearrangement-based research has ever quickened as the broad scope and high efficiency of this transform have become apparent. Over 1000 research papers have been published on this topic, with about 40% appearing over the past decade. The five most active groups in the Pummerer field include Oae, who was responsible for many of the fundamental advances in mechanistic understanding in the formative years of Pummerer reaction research, and Furukawa, Bravo, Padwa and Kita, all of whom have made, and continue to make, significant contributions that extend the scope of the reaction in directions that are particularly valuable for organic synthesis.

2. Scope of the review

Numerous reviews of Pummerer chemistry, both focused and exhaustive, have been written.[9,15] These earlier, authoritative accounts of the transformation serve to track its development and to fill in many of the mechanistic intricacies that attend its execution. As the volume of Pummerer research has expanded continually over the more recent decades, so has the emergence of new knowledge and applications that fall under the Pummerer umbrella. It is toward these more contemporary developments that this review is directed.

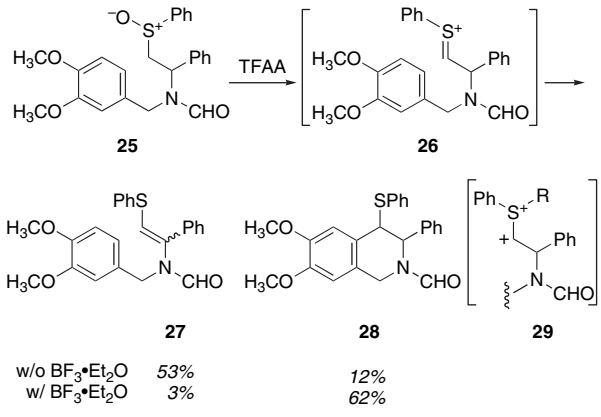
Specifically, discoveries in the area of Pummerer reaction initiation that feature chemistry distinct from the classical sulfoxide acylation trigger have broadened the scope of tolerated substrates, and prominent examples will be discussed. Likewise, recent extensions of the permissible classes of both sulfur-bearing substrates and, independently, the nucleophilic addends, probe the limits of functional group compatibilities and help to define the ultimate utility of the transform. Finally, the use of sulfoxide substrates bearing either adjacent or distal unsaturated moieties has led to novel reaction modes that further extend the scope of the reaction. Many of these newer developments help illuminate some of the mechanistic subtleties of the putative electrophilic Pummerer intermediates as well. This review is organized by reaction component, and will focus, in turn, on initiator, then nucleophile, and finally substrate chemistry. This latter category will include discussions of additive, vinylogous, and cascade-type Pummerer sequences.

3. Initiator chemistry

If the roster of serviceable Pummerer initiators had never expanded beyond the harsh, acidic reagents described in the seminal Fromm/Smythe/Pummerer studies, it is unlikely that this transform would have found much use in organic synthesis. However, much effort has been expended to address this original limitation, and a whole suite of mild and selective initiators have been developed. In particular, electrophilic silyl transfer reagents and hypervalent iodine compounds have extended the reach of Pummerer chemistry to include both thermally labile and acid-labile substrates. In addition, a range of Lewis acids have been brought to bear on the problem of selective initiation, sometimes unintentionally, and these reagents conceivably can introduce a certain level of 'tunability' to the task of chemoselective sulfoxide activation in polyfunctional substrates. A survey of these advances follows.

3.1. Acidic additives with acylative initiators

The classical Pummerer recipe for initiation, treatment of a sulfoxide with a potent acylating agent like trifluoroacetic anhydride (TFAA) in a non-participating solvent, is sufficient to generate the electrophilic thionium ion **20**, but the somewhat muted electrophilicity of this species (cf. **22**–**24**) can limit the range of acceptable carbon π-nucleophiles. This issue is illustrated by the problematic conversion of sulfoxide **25** into the desired tetrahydroisoquinoline product **28**, Scheme 3.[16a] Apparently, when the rate of nucleophile capture is rendered slow by structural (electronic) features, alternative processes, such as deprotonation or even dealkylation,[16,17] can intervene. Sano and co-workers have devised a solution to the problem of insufficient thionium ion electrophilicity by including highly acidic activators in the reaction medium.[15] Both $BF_3 \cdot Et_2O$ and CF_3SO_3H[15b] have shown promise in this regard. For example, treating sulfoxide **25** with TFAA and then with $BF_3 \cdot Et_2O$ leads to isolation of a much improved yield of the Pummerer cyclization product **28**.[15a] Control experiments discounted **27** as a precursor to **28** under the reaction conditions. Sano's group has gone on

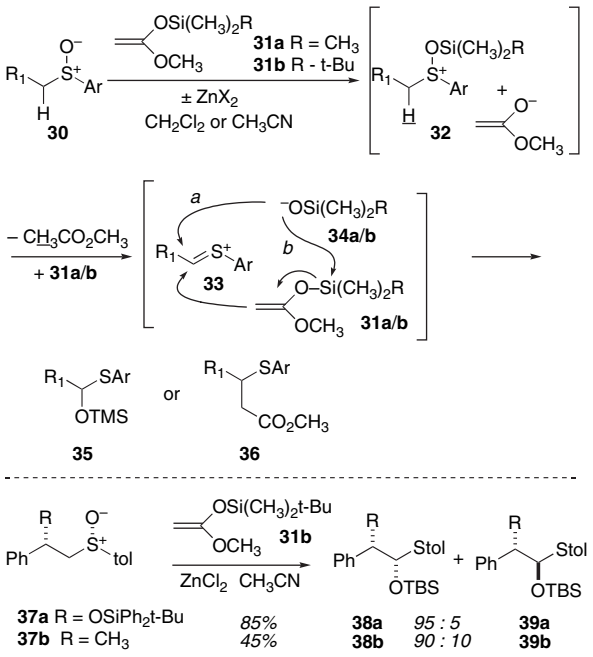


Scheme 3. Examples of Sano's acid promoted acylative Pummerer initiation conditions.

to exploit this enhanced Pummerer reactivity in the synthesis of numerous tetrahydroisoquinoline-containing natural products and related targets.[15c] In mechanistic discussions, Sano entertains the notion that a 'superelectrophilic' dicationic species **29** is the key intermediate, a proposition in alignment with the dicationic intermediate invoked to rationalize certain kinetic data from both Friedel–Crafts and Pictet–Spengler reactions.[18] However, alternative explanations, such as sequestration of the (weak) base/nucleophile CF_3COO^- by the added acid, a scenario in which the lifetime of a singly charged thionium ion might be extended sufficiently to react with the sluggish aryl nucleophile, cannot be dismissed at this point. The scope of this technique for promoting otherwise reluctant Pummerer reactions has yet to be determined, but it holds promise for extending the reaction in directions useful for complex molecule synthesis.

3.2. Silyl initiators

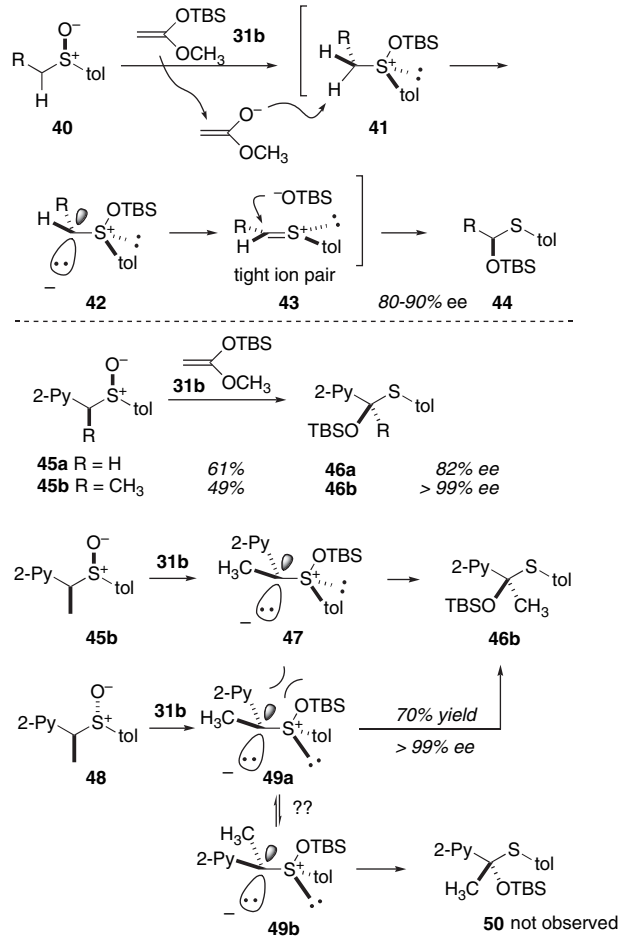
One of the first deviations from sulfoxide acylation orthodoxy can be traced to Kita, who in 1984 introduced the silyl ketene acetals **31a** and **31b** as effective Pummerer initiators, Scheme 4.[14] Related studies by other workers expanded the repertoire of useful silyl electrophiles to include TMSCl(I),[19] TMSOTf,[20] TBSOTf,[21] and $H_2C{=}CHCH_2{-}SiCl_3$,[22] although most of the chemistry that delineated the scope of silicon electrophile initiation was conducted with silyl ketene acetals of the type **31**.



Scheme 4. Kita's introduction of silyl ketene acetal Pummerer initiators.

These reactive silyl cation donors share the desirable characteristics of (1) rapid and chemoselective R_3Si addition to the sulfoxide oxygen under completely neutral conditions, and (2) no requirement for added acid or base, although catalytic ZnX_2 can be used to advantage on occasion. Despite their superficial similarities, the ketene acetals **31a** and **31b** actually proceed to give different products, **36** and **35**, respectively, through the common intermediate **32**. Thus, initial R_3Si transfer driven by the oxophilicity of silicon furnishes the activated sulfonium species **32** in proximity to the basic acetate enolate. Facile proton transfer should promote loss of silanoxide to generate the common thionium ion intermediate **33**, now in the presence of both the silanoxide nucleophile **34** and excess silyl ketene acetal **31**. At this point, the difference between **31a** and **31b**, in terms of the silyl appendages' steric bulk, becomes manifest. Arguably, the less sterically hindered TMS species **31a** (R=CH_3) is more susceptible to attack at silicon by the nucleophilic silanoxide **34a**, and this combination leads to activation of the silyl ketene acetal **31a** for further nucleophilic attack on **33**. The C–C bonded addition product **36** ensues. In contrast, the increased steric bulk around silicon in **31b** apparently suppresses the silanoxide addition of **34b**, and so this nucleophile takes the other option, direct addition to the carbon of thionium ion **33**, to afford the α-siloxysulfide product **35**. The reaction typically proceeds with good yield and with excellent diastereoselectivity if applicable, as exemplified by the conversion of **37a** into predominantly **38a**, and **37b** preferentially into **38b**.[23] The stereochemical outcome of the former reaction can be rationalized by invoking a Felkin–Ahn-type transition state for addition of silanoxide to thionium ion, whereas the bias toward **38b** from **37b** is a bit of a puzzle. The observed preference for diastereomer **38b** is inconsistent with the predictions of the Cram model for nucleophilic addition to α-stereogenic (but otherwise electronically unbiased) aldehydes. Thus, some other effect that overrides the Cram selectivity must be operational. This 'anomalous' result leaves open the possibility that the chirality at sulfur may play a role, a hypothesis not anticipated by the simple thionium intermediate **20** of Scheme 2. This argument is developed further below.

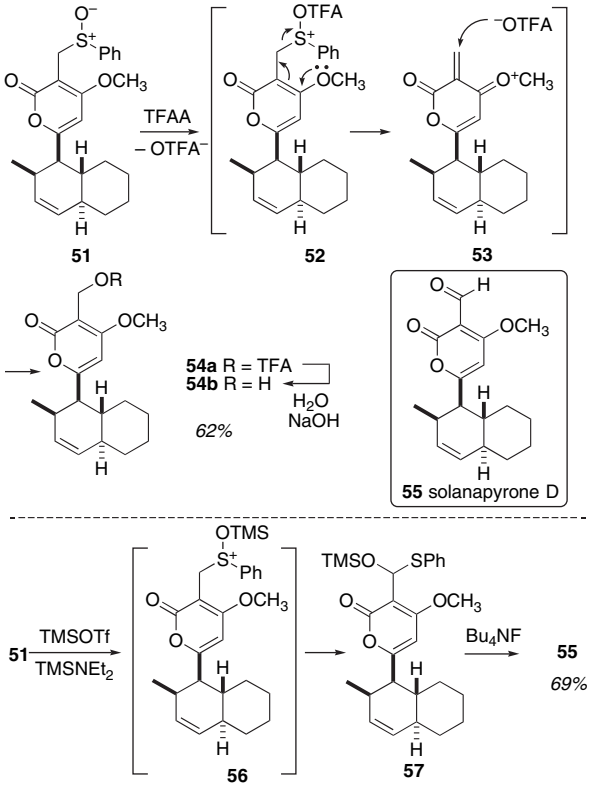
A major advantage of this silicon-based initiator, and a major advance in Pummerer chemistry, derives from its application to chiral sulfoxide substrates in asymmetric syntheses. Whereas the conversion of chiral sulfoxides into chiral α-acyloxysulfides in high ee appears to be beyond the scope of standard acylative activation of the Pummerer process (cf. the discussion with Scheme 2), it is well within the purview of the silyl ketene acetal initiation methodology, as illustrated in Scheme 5. Kita's interpretation of the formation of α-silyloxysulfides **44** in excellent ee from the chiral sulfoxides **40** cites formation of a sulfonium ylide **42** with a strictly antiperiplanar orientation of the anion and S–O bond. This geometrical arrangement presumably leads to facile E2-type elimination of silanoxide to deliver the expected thionium ion **43** as a tight ion pair with the ejected silanoxide. To the extent that this tight ion pair maintains its integrity, internal transfer of alkoxide from sulfur to carbon should lead to a single enantiomer of the α-silyloxysulfide product, as shown for the conversion of **43** into **44**. This argument acknowledges an explicit and central role for the tight ion pair **19** of Scheme 2, rather than the free thionium ion **20**. As an alternative to the E1CB-type mechanism shown for **41** to **43**, Kita also speculates that a formal Stevens-type process involving homolytic scission of the S–O bond, followed by electron reapportionment and radical recombination at carbon, might be operational as well.



Scheme 5. Asymmetric synthesis via chiral sulfoxides and silyl ketene acetal Pummerer initiators.

Successful examples of this self-immolative asymmetric induction process include the chiral sulfoxides **45a** and **45b**.[24] The α-unsubstituted species **45a** performs as indicated with an ee of 82%. Replacing one of the α-hydrogens with a methyl group provides a more challenging example in that a quaternary stereogenic center is now formed. Quite remarkably, this substrate combines with **31b** to provide the isomer **46b** with complete enantioselectivity. The greater selectivity in the more hindered case might be attributable to differences in the initial deprotonation step. For the conversion of **45b** into **46b**, there is only a single proton that can be removed, and so only one intermediate ylide with antiperiplanar alignment of anion and S–O bond is possible, **47**. This single ylide then leads inevitably to a single product, **46b**. However, in the case of the unsubstituted system **45a** (modeled by **40**, R=2-Py), either one of two diastereotopic protons can be removed. Deprotonation from conformer **41** (R=2-Py) leads to minimized *gauche* interactions between the remaining substituents on carbon and sulfur. However, it is possible that the erosion of stereoselectivity for the substrate **45a** may be tied to deprotonation of the alternative and diastereotopic proton through a higher energy conformation that experiences destabilizing steric interactions between the substituent R and the toluene moiety. This stereochemical analysis illuminates a subtlety of the mechanism when applied to the diastereomeric (to **45b**) chiral sulfoxide **48**. In this instance, the single, stereoelectronically aligned ylide that could be formed directly is shown as **49a**, and despite experiencing the unfavorable *gauche* interactions described above (and illustrated on the structure), the observed product **46b** must derive from this species. Therefore, either rotation/anion inversion about the C–S bond to form the presumably more stable ylide **49b** is slower than silanoxide elimination from **49a**, or, in fact, thionium ylide/ion pair **43** (R=2-Py) is formed directly from the sulfonium salt by a concerted E2-type elimination of silanoxide, and there is no intermediate ylide like **49a** on the reaction coordinate.

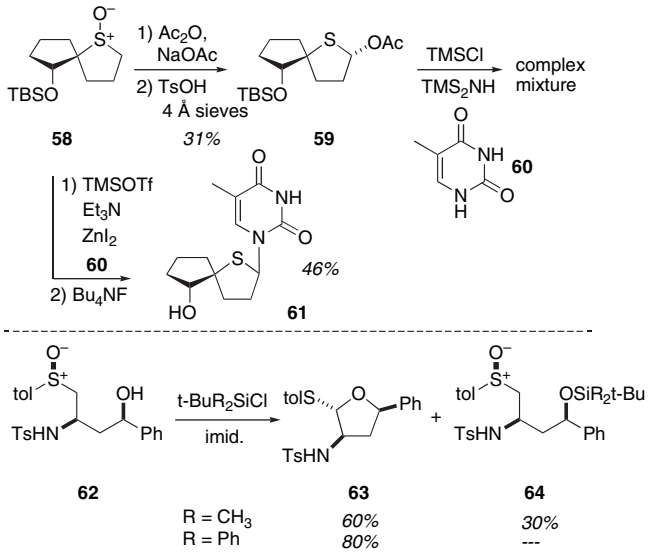
An exploitable difference in the course of the Pummerer process following either silyl electrophile initiation or acylative initiation can be found in Hagiwara's recent synthesis of the phytotoxic principle solanapyrone D (**55**), Scheme 6.[25] Treatment of pyrone sulfoxide **51** with TFAA was pursued with the expectation that Pummerer chemistry would deliver the aldehyde-containing natural product **55**. However, the alcohol **54b** was isolated instead. This deviation from Pummerer convention can be attributed to an oxygen lone pair-promoted elimination of the good leaving group PhSOTFA from **52**, followed by trifluoroacetate conjugate addition to the enone of **53** and eventual OTFA hydrolysis to deliver the alcohol product. In contrast, the use of the silyl initiator TMSOTf with the very same sulfoxide **51** led to the expected 'oxidation' product **55** via the α-trimethylsilyloxy sulfide **57**. Apparently, the diminished nucleofugacity of the silylated sulfonium salt within **56** accounts for its resistance to elimination, and the otherwise slower Pummerer rearrangement can compete effectively.



Scheme 6. An advantage of a silyl Pummerer initiator over the standard acylative initiator.

A second example of reaction rescue by silyl initiation can be found in Paquette's synthesis of the thiothymidine

analogue **61**, Scheme 7.[26] In this instance, the traditional Pummerer sequence with Ac_2O and sulfoxide **58** performed adequately to furnish the anticipated α-acetoxysulfide **59**. However, contrary to expectations, condensation of **59** with thymine under standard Vorbrüggen conditions[27] did not provide the desired thionucleoside **61**. It fell to silyl electrophile initiation to rectify this tactical failure. Treatment of sulfoxide **58** with TMSOTf, base, and a Lewis acid catalyst, all in the presence of thymine (**60**), delivered the thymidine analogue **61** in satisfactory yield.

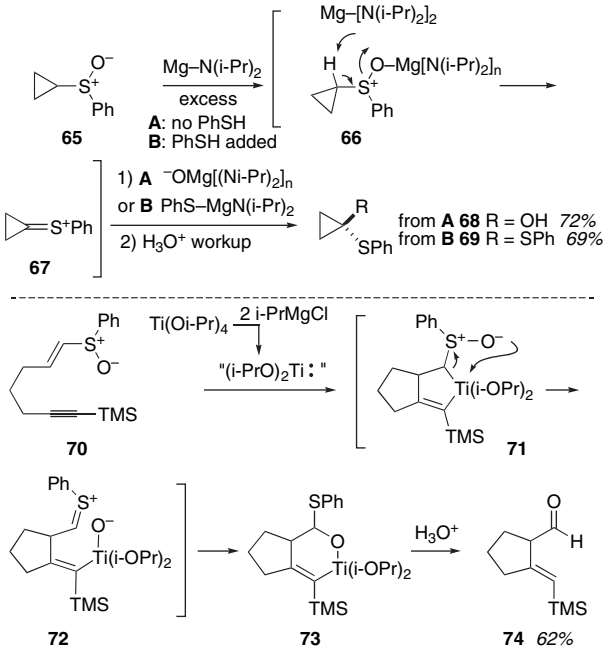


Scheme 7. Further examples of silyl electrophile initiation used to advantage in Pummerer chemistry.

A question of comparative reactivity was explored with substrate **62**.[28] Raghavan and co-workers intended nothing more elaborate than simple alcohol silylation when they treated hydroxy sulfoxide **62** with TBSCl. However, a Pummerer process intervened, leading to formation of the tetrahydrofuran derivative **63** via internal alcohol–thionium ion combination. Use of the sterically more demanding diphenyl analogue *t*-Bu*Ph*$_2$SiCl suppressed even the modest amount of alcohol silylation seen with *t*-Bu*Me*$_2$SiCl, and in this instance the Pummerer cyclization product **63** was the exclusive species observed. The preference for S(+)–O$^-$ silylation over –OH silylation is instructive, as it points to the feasibility of conducting Pummerer reactions on complex substrates without the need for alcohol protection.

3.3. Lewis acidic metal initiators

The discovery that certain Lewis acidic metals promote Pummerer rearrangement seemed to be an unintended benefit of exposing sulfoxide substrates to metal-based reagents with other goals in mind. This chemical serendipity is illustrated by treatment of sulfoxide **65** with the strong base magnesium bis(diisopropylamide), Scheme 8.[29] Kobayashi et al. were exploring sulfoxide deoxygenation protocols, and with *diaryl* sulfoxide substrates, sulfoxide → sulfide reduction was observed as expected.[29a] However, when sulfoxides bearing α-protons were examined, the reaction took a different course and Pummerer-type oxidative transposition products were formed instead. The Pummerer reaction itself was discovered by adding strong mineral acid to a sulfoxide, and potent electrophiles constitute the standard Pummerer triggers. However, in this example the magnesium counterion of the highly basic amide reagent appears sufficient to activate the sulfoxide's oxygen within **65** for departure. Whether deprotonation at the α-position precedes or follows this activation is unclear, and the putative intermediate **66** is shown just for convenience. Whatever the precise sequence of 'H$^+$' and '–OMgX' loss, the intermediate thionium ion **67** so formed is trapped readily by the highly nucleophilic magnesium alkoxides present (Condition A, no added PhSH) to furnish the α-hydroxysulfide **68** following aqueous acidic workup. One advantage of this nonacylative initiation procedure can be seen when substrate **65** is allowed to react with the amide base in the presence of various thiols, including PhSH (Condition B). The magnesium thiolate so generated out-competes the alkoxides for thionium ion **67**, and the dithioketal **69** is formed in good yield. In contrast, use of acylative Pummerer initiation to achieve the same transformation would have to confront the problem of competitive thiol acylation.[30]



Scheme 8. Pummerer initiation with Lewis acidic metals.

A second example of an 'accidental' Pummerer reaction evolved from exposure of the sulfoxide **70** to the formal titanium(II) reagent (*i*-PrO)$_2$Ti: formed by reduction of Ti(*i*-OPr)$_4$.[31] An intermediate titanocycle **71** was expected by analogy to the similar reaction of (*i*-PrO)$_2$Ti: with a sulfone substrate related to **70**. In fact, protonolysis of the intermediate derived from **70** led to formation of the aldehyde **74**. Apparently, the α-titanium sulfoxide intermediate **71** can access a transition state geometry for C-to-O transfer of titanium. The transient thionium ion within the derived **72** can be quenched rapidly by the proximal alkoxide, leading to the titanacycle-containing product **73**. Protonolysis upon acidic workup then delivers the sensitive aldehyde **74**. These adventitious examples of Lewis acidic metal mediated

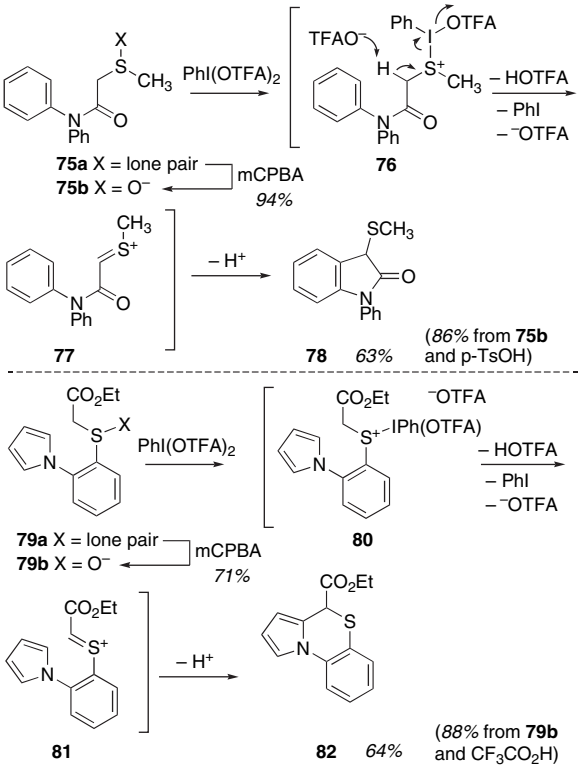
Pummerer initiation by no means define the scope of the chemistry, and it seems within reason to expect that deliberate surveys which test reactions of acidic/oxophilic metals with sulfoxides will uncover further cases of metal mediated Pummerer reactions. For example, Mukaiyama and coworkers have described the results of some preliminary scouting experiments on the utility of $Sn(OTf)_2$, $TiCl_4$, $SnCl_4$, $Cu(OTf)_2$, and $BF_3{\cdot}Et_2O$ for promoting the Pummerer reaction of β-carbonyl sulfoxides.[32] In this series, only $Sn(OTf)_2$ was an effective initiator.

3.4. Iodonium initiators

The introduction of hypervalent iodine-based Pummerer reaction initiators represents a real departure in strategy for this transform. For this family of initiators, a sulfide substrate and not a sulfoxide serves as the starting point, and so the sulfide oxidation and (derived) sulfonium salt rearrangement are no longer temporally separated events. This consolidation of steps leads to greater efficiency in synthesis, but at the cost of possible product oxidation. The sulfide product might, in principle, be susceptible to iodonium-mediated oxidation much as the starting sulfide is. The fact that this 'overoxidation' rarely is observed perhaps can be attributed to the difference in both steric and electronic environments about the starting and final sulfide moieties. The Pummerer sequence replaces a hydrogen α-positioned to the sulfide with a non-hydrogen group, thus increasing the steric shielding of the product sulfide over the less encumbered starting sulfide. Furthermore, to the extent that electronegative nucleophiles are used in the Pummerer reaction, the product sulfide should be protected from further oxidation by virtue of the electron withdrawing inductive influence of the newly attached α-nucleophile unit.

Three hypervalent iodine reagents have been explored as Pummerer initiators: $PhI(OTFA)_2$,[33] PhI(CN)OTf,[34] and tol-IF_2.[35] The former two reagents do not contribute a competitive nucleophile to the reaction medium, and so trapping the putative electrophilic thionium ion with added (or intramoleculary disposed) nucleophiles is feasible. The latter species is used primarily as a fluorinating reagent to form α-fluorosulfides, but a few cases of competitive intramolecular nucleophilic addition have been described, vide infra.

The seminal report of hypervalent iodine initiated Pummerer reaction falls to Tamura and colleagues, who showed that $PhI(OTFA)_2$ effectively promotes cyclization of sulfide **75a** into oxindole **78** in good yield, Scheme 9.[33] Presumably, the thiophilic character of the 'soft' iodonium reagent confines initial reaction to the sulfide function, and the authors propose the familiar sulfonium salt and thionium ion intermediates, **76** and **77**, respectively, en route from starting material to product. Whatever the precise mechanistic details, the overall result is competitive with the conventional two-step Pummerer procedure (oxidation of **75a** to give sulfoxide **75b**, and then treatment of this sulfoxide with an acidic initiator).[36] A limited series of sulfide substrates were studied, and in all cases, C–C bond-forming cyclizations proceeded to the exclusion of detectable $CF_3CO_2^-$ addition to the electrophilic intermediate.

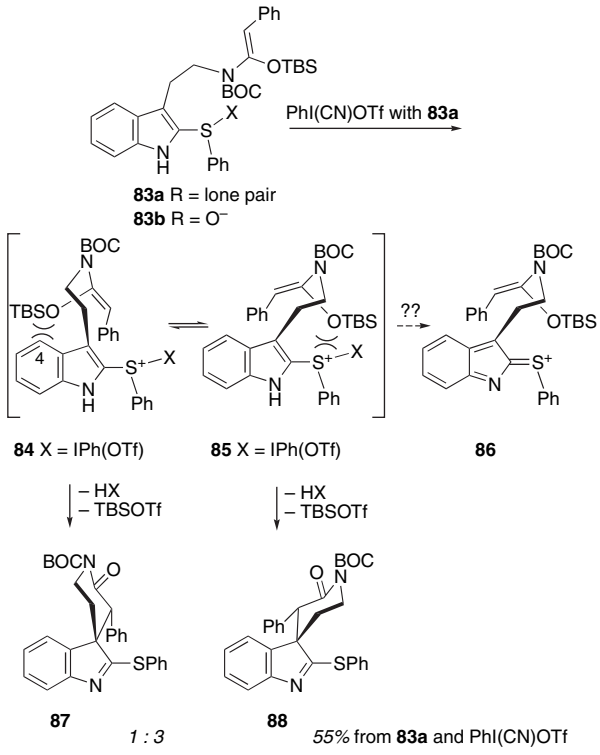


Scheme 9. Use of $PhI(OTFA)_2$ as a Pummerer initiator with sulfide substrates.

A conceptually related example is provided by Chen et al., who demonstrated that the one-step oxidative cyclization of **79a** into **82** compares favorably with the two-step alternative passing through sulfoxide **79b**.[37a] As with the Tamura chemistry, the acidifying β-carbonyl function appears to be an important structural feature. Attempted Pummerer rearrangements on sulfoxide substrates similar to **79b** but lacking the carbonyl moiety were not productive.[37b] This observation seems to have some generality for modestly reactive aryl and alkenyl nucleophiles, although the workaround discussed in Section 3.1 (strongly acidic additives) can be used to promote reaction with these types of reluctant Pummerer substrates.

The study of biomimetic indole oxidative cyclizations has had a long and varied history within the area of tryptophan-derived natural products total synthesis.[38] The use of Pummerer chemistry with a C(2) sulfinyl or sulfide-substituted indole as a trigger for oxidative cyclization was envisioned as a solution to both overoxidation and/or regiochemical problems encountered with standard oxidants (cf. Section 5.4.2 for further discussion) (Scheme 10).[38] For example, hypervalent iodine initiation with the sulfide **83a** was examined. $PhI(OTFA)_2$ did not perform satisfactorily in this regard, and starting material consumption without concomitant product formation was observed under all conditions examined. These failures led to examination of Stang's reagent, PhI(CN)OTf, as an alternative Pummerer initiator with sulfide substrates of the type **83a**.[38] The incorporation of a cyanide unit within PhI(CN)OTf may serve the dual roles of both diminishing the oxidative power and 'softening' the iodonium center even further when compared to $PhI(OTFA)_2$. Both of these characteristics converge favorably when using sensitive and functional rich substrates

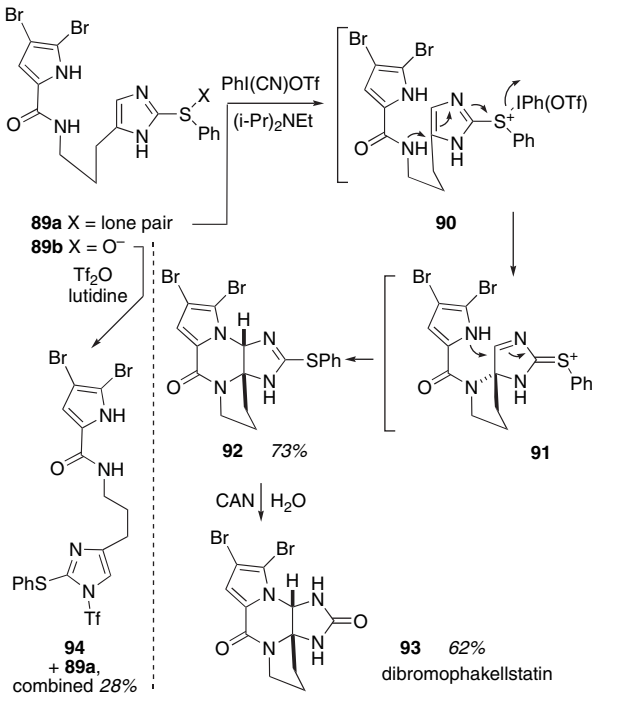
like **83a**, and lead to successful realization of this sulfide-based Pummerer oxidative cyclization.



Scheme 10. Use of PhI(CN)OTf as a Pummerer initiator with a sulfide substrate.

The observation that diastereomer **88** is favored over **87** plausibly can be traced to the differential steric interactions shown in **84** and **85**. Specifically, the key C–C bond formation might pass through either an S_N2'-like displacement within the sulfonium ion intermediates **84** and **85** or through the thionium ion **86**. (This S_N2'-like pathway has been termed an 'additive Pummerer' mechanism, whereas the alternative via **86** is called a 'vinylogous Pummerer' reaction. Both pathways will be discussed further in Section 5.4.1. For simplicity, only the additive pathway is cited in the following discussion, but the same arguments would apply to the vinylogous process as well.) Two salient steric interactions can be identified as shown in **84** and **85**, and the trade-off between these penalizing 1,3-diaxial collisions should, in large measure, determine the stereochemical outcome of cyclization. In general, it appears that the interaction between –OTBS and C(4)–H in **84** is more severe than the –OTBS//–S(X)Ph contact, as diastereomer **88**, evolving from **85**, is favored. Whatever the mechanistic subtleties, the overarching benefit of using PhI(CN)OTf in this sulfide-based Pummerer reaction lies in the facility of oxidative cyclization on the electron rich indole nucleus without interference from either product overoxidation or loss of desired C–C bond formation regioselectivity.

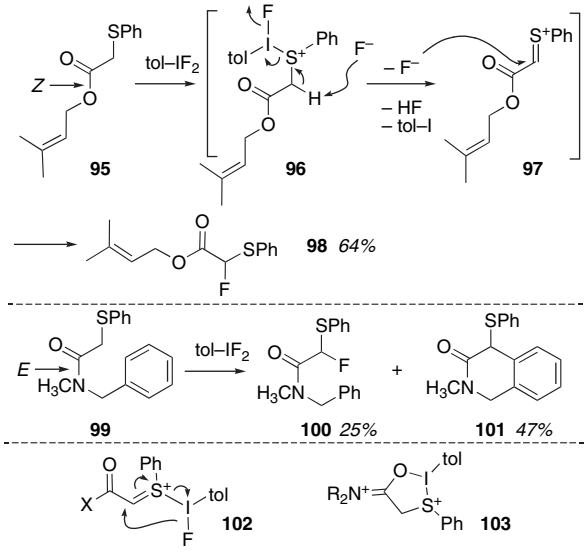
The value of iodonium salt initiation with the Pummerer sequence can be seen in an application to the biomimetic total synthesis of the sponge alkaloid dibromophakellstatin (**93**), Scheme 11.[39] This attempt to extend aromatic heterocycle oxidative cyclization methodology to the imidazole nucleus began with the sulfoxide **89b** and conventional Tf_2O-based Pummerer initiation. Surprisingly, only the deoxygenated sulfide **89a** admixed with its triflamide derivative **94** was isolated. The latter compound presumably arises from the former under the reaction conditions, but the origin of **89a** remains a mystery. Apparently, if a sulfonium salt was accessed from **89b** and Tf_2O, it must have suffered formal reduction rather than productive Pummerer-type rearrangement chemistry. This disappointing turn was reversed by resorting to sulfide/iodonium initiation chemistry. Portionwise treatment of **89a** with PhI(CN)OTf in the presence of base delivered the tetracyclic product **92** as a single diastereomer. Whether sulfide activation leads to a bona fide thionium ion (not shown) or the reaction transpires through the additive mechanistic course **90**→**91**→**92** is not settled at present. The additive mechanism shown below has the advantage of providing a quite electrophilic partner **91** for the sterically hindered and electronically deactivated pyrrole nucleophile. In contrast, a thionium ion-based mechanism would present this modest nucleophile with a neutral imine electrophile. The tetracyclic sulfide **92** is completely inert to further hypervalent iodine-mediated oxidation, but it is susceptible to the stronger oxidant ceric ammonium nitrate, a process that facilitates the hydrolysis of the thioimidate function and furnishes the intact natural product.



Scheme 11. Synthesis of the marine isolate dibromophakellstatin via a PhI(CN)OTf-mediated Pummerer cyclization on an imidazole sulfide substrate.

The Pummerer initiation chemistry of tol-IF_2 has been developed by Motherwell and co-workers as a direct means of introducing fluorine into organic molecules, Scheme 12.[35,40] Exemplifying this strategy is the conversion of alkenyl ester **95** into the α-fluorosulfide **98**.[35] The lack of participation by the alkene nucleophile is a hallmark of this chemistry. This unanticipated result prompted Motherwell to speculate that perhaps an alternative mechanistic path is operational. A formal reductive elimination of iodine,

as illustrated in **102**, was proposed as a rationale for the complete fluoride addition selectivity. Curiously, C–C bond formation in the tol-IF_2-promoted Pummerer reaction was seen for certain amide substrates, for example, **99**→**100**+**101**,[40a] although reaction of the dimethylalkene analogue of **99** (similar to **95**) led only to the fluoride capture product. An explanation for the disparate behavior of amide and ester may be tied to conformational preferences wherein the tertiary amide of **99** can adopt the requisite *E*-amide bond disposition with much less energetic penalty than the ester must pay to access the analogous *E*-O–C(=O) rotomer. As a final twist, observation of alkene-containing elimination products from more complex amide substrates encouraged the authors to speculate that a new intermediate, the cyclization product **103** emerging from internal participation of the nucleophilic amide carbonyl and the electrophilic iodonium center, may play a role in this Pummerer process.[40c] In any event, the tol-IF_2-mediated Pummerer fluorination sequence represents one of the mildest methods for introduction of fluorine into organic substrates, and its value in organofluorine chemistry just is beginning to be assessed.



Scheme 12. Use of tol-IF_2 as a Pummerer initiator with sulfide substrates.

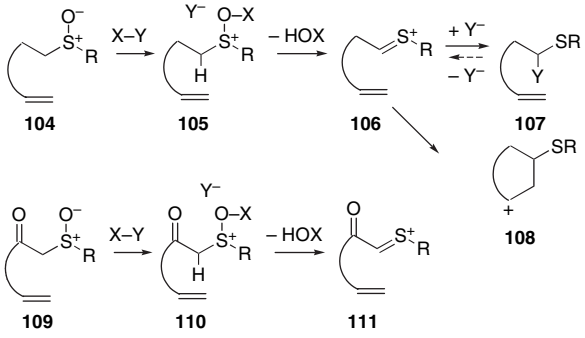
4. Nucleophiles

Successful Pummerer reaction requires that the nucleophilic addend and the electrophilic initiator do not combine destructively prior to initiation of the reaction sequence. Thus, advances in initiation chemistry, which broaden the available palette of useful electrophiles, provide an indirect benefit to the nucleophilic capture portion of the transform as well. Carbon–carbon bond formation holds a place of special prominence in the Pummerer portfolio, and the extension of simple alkene and arene thionium ion traps to include highly functionalized partners is a testament to the successful matching of initiator with nucleophile. Consequently, these effective Pummerer examples have a large and continuing impact on natural product synthesis, as described below. In a separate vein, the productive use of phosphorus nucleophiles in the Pummerer process portends new strategies for organophosphonate synthesis.

4.1. Arenes and alkenes

One of the great virtues of the Pummerer reaction lies in its capacity to form core carbon–carbon bonds within a variety of molecular contexts. The requirement for compatibility between the nucleophile and the initiating electrophile limits carbon nucleophiles to those species that are unreactive to acid and acylating reagents, a significant narrowing of options that rarely falls outside of moderately electron rich alkenes and arenes. Nevertheless, this transformation has been exploited innumerable times in complex molecule synthesis, particularly in the alkaloid arena. Both inter- and intramolecular C–C bond formation have been documented in a wide range of systems, although the latter process has seen the most intense development.

In principle, the generation of a thionium ion **106** from alkene(arene)-bearing sulfoxide **104** sets up a competition between addition of the desired C-nucleophile and the initiator counterion Y^- (Scheme 13). To the extent that Y^- is a competent nucleophile, the reaction may be diverted to the sulfide product **107**. Fortunately, the addition of Y^- is reversible with common initiators, and so if sulfide **107** is treated under sufficiently vigorous reaction conditions to regenerate **106**, productive C–C bond formation may still prevail. A sequestering agent is often employed to prevent Y^- from re-adding to thionium ion **106**. As a matter of practice, many of the C–C bond-forming Pummerer reactions initiated with Ac_2O or TFAA provide a counterion (AcO^- or $TFAO^-$, respectively) that wins the competition for **106** under typical reaction conditions. However, in all cases where the goal is C–C bond formation, conditions have been devised, typically involving higher temperatures and an acidic additive to trap RCO_2^-, to reform, and then redirect, **106** to the carbon nucleophile addition alternative **108**. However, when the initiator counterion is arguably non-nucleophilic (e.g., Y=OTf^-), direct and productive combination of the thionium ion with the alkene(arene) typically ensues.

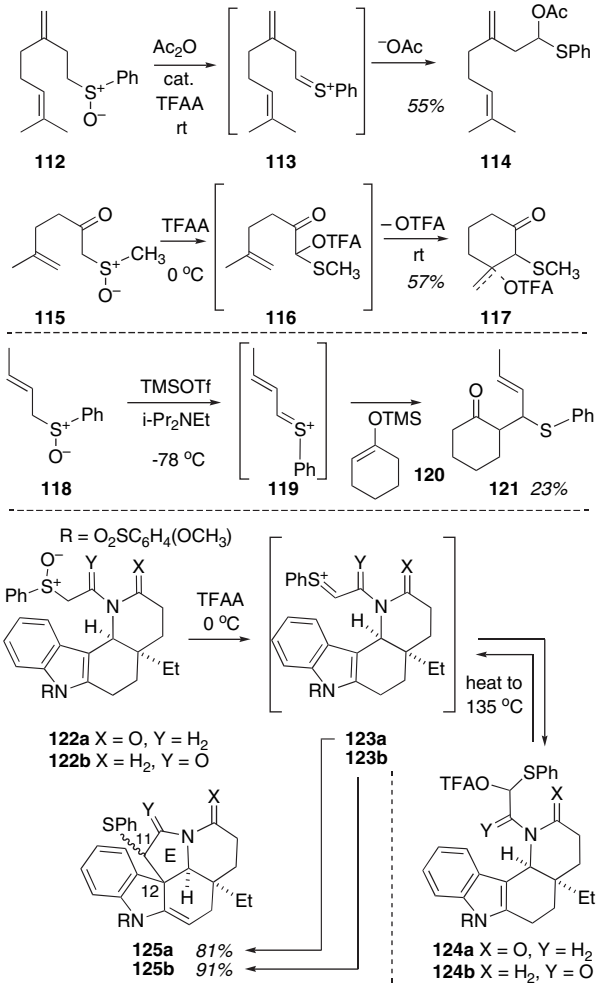


Scheme 13. Mechanistic paradigms for Pummerer reaction-mediated C–C bond formation.

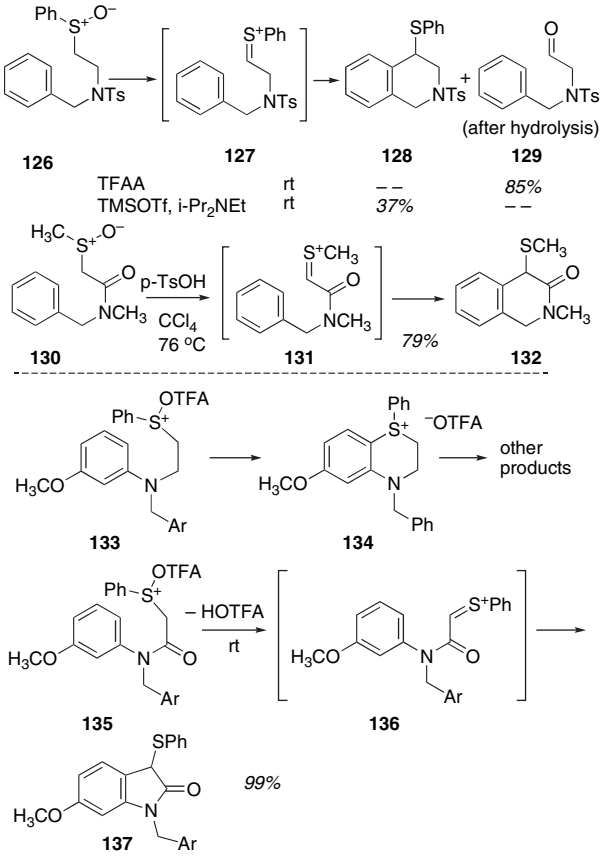
Carbon–carbon bond-forming Pummerer reaction sequences generally fall into one of two classes: with and without a carbonyl function β to the thionium ion intermediate (**109** vs **104**, Scheme 13). The acyl thionium ion **111** derived from **109** has been categorized as being more reactive than the non-acyl version **106**,[15g] but quantitative kinetic data on this question are lacking. Using chemical yield as a criterion for judging reactivity does not provide an unequivocal test of this hypothesis either (vide infra). However, there is much

experimental support for the contention that the enhanced acidity of the α-protons in **110** compared to **105** does have an influence on the reaction course, as it promotes facile loss of H–OX from **110** to the exclusion of other possible but undesired processes. These points are illustrated by examples as detailed in Schemes 14–16.

The trisubstituted and disubstituted alkenes in **112** and **115**, respectively, do not appear to be sufficiently nucleophilic to capture the intermediate thionium ions in preference to the initiator counterions AcO^- and $TFAO^-$, Scheme 14.[41] Apparently, even incorporation of the allegedly activating carbonyl of **115** does not increase the reactivity of this cationic intermediate toward alkene nucleophiles to the extent that C–C bond formation can compete with trifluoroacetate trapping. However, this example is typical of the cases where subsequent reaction of the first-formed trifluoroacetoxy sulfide **116** under more vigorous conditions does lead to productive C–C bond formation, **116**→**117**.[41b] The value of using an initiator bearing a non-nucleophilic counterion is illustrated in the counterpoint example **118**→**121**.[42] In this instance, there is no evidence that the intermediate thionium ion **119** is trapped by any nucleophile other than the silyl enol ether shown. Unfortunately, no systematic studies have been described wherein the initiator counterion and/

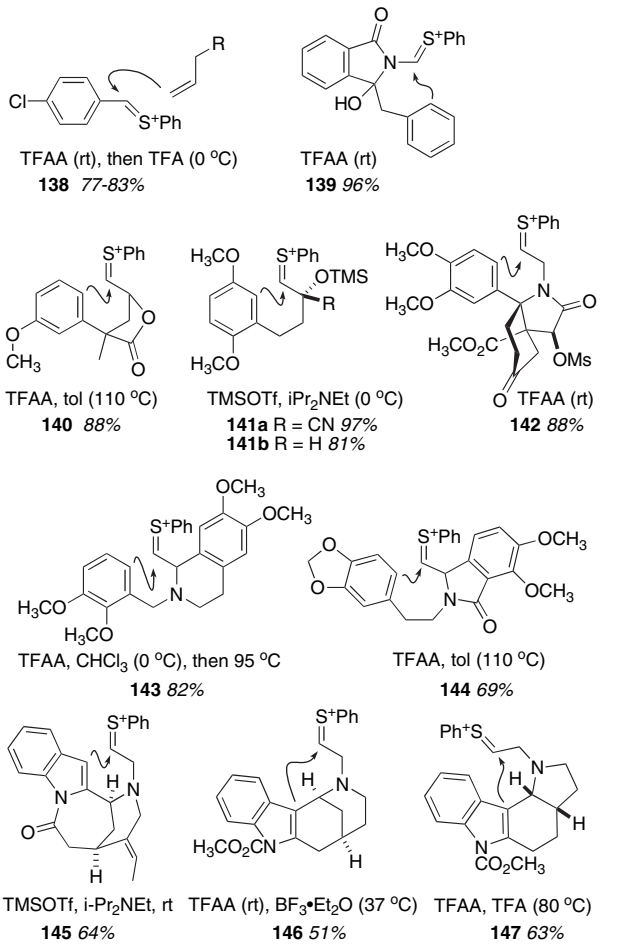


Scheme 14. Direct comparison of acyl- versus non-acyl Pummerer cyclizations for C–C bond formation.



Scheme 15. Further examples of the influence of an α-acyl group on thionium ion chemistry.

or the β-carbonyl presence have been varied within the same substrate, and so it is impossible to draw broad conclusions from these examples. Differences in alkene nucleophilicities (Mayr *N* values: 2-methyl-2-butene (0.65), 2-methylpent-1-ene (0.96), cyclohexanone trimethylsilylenol ether (5.21))[13a] may play a role in some instances as well. Two related examples particularly germane to the question of β-carbonyl activation of a thionium ion are provided by Magnus as part of his comprehensive program on indole alkaloid synthesis via Pummerer chemistry.[43] Work toward the aspidosperma alkaloids required the means to close the E-ring at a late stage of the synthesis, **122**→**125**, Scheme 14. Much prior art[44] had met with only limited success in identifying competent electrophiles for the indole C(12) nucleophile (aspidosperma numbering, see structure **125**), and so it is particularly gratifying to note that the Pummerer reaction stood alone in its capacity to close this demanding bond in excellent yield. Both the β-carbonyl version **122b** and its β- $-CH_2-$ analogue **122a** were explored, but with neither substrate was the indole nucleophilic enough (Mayr N=7.81 for N,2-dimethylindole)[45] to capture the first-formed thionium ions **123a/b** prior to $TFAO^-$ trapping. Thus, trifluoroacetoxy sulfides **124b** and **124a**, respectively, were formed first. Upon heating to 135 °C, however, both species presumably entered into an equilibrium with **123a/b**, and under these more forcing conditions, cyclization to fashion the sterically encumbered C(11)–C(12) bond proceeded smoothly. Interestingly, there did not appear to be any advantage attending the use of the β-carbonyl version



Scheme 16. Examples of non-acyl-containing Pummerer substrates for C–C bond formation.

of the substrate **122b**, as yields from both series were similarly high.

Some further examples reinforce the value of excluding nucleophilic initiator counterions, and in addition bring out the indisputable advantage of a β-carbonyl group in acidifying the α-proton, Scheme 15. Sulfoxides **126** and **130** differ principally by the incorporation of the β-carbonyl function in the latter species. In the presence of TsOH, the β-carbonyl-containing sulfoxide **130** at elevated temperature proceeded to cyclized product through the expected Pummerer process.[46] The carbonyl-less analogue **126** with the standard initiator TFAA delivered only the $TFAO^-$ trapping product, isolated after hydrolysis as the aldehyde **129**.[47] No C–C bond-forming cyclization product **128** was detected, an observation in line with the Pummerer transformations discussed in Scheme 14. An interesting feature of these similar examples was revealed when substrate **126** was treated with TMSOTf, an initiator that lacks a nucleophilic counterion. In this example, the thionium ion generated from **126** is both long-lived enough and reactive enough to trap the proximate nucleophilic aryl ring to form exclusively the cyclized product **128**.

The comparison between attempted Pummerer reactions of **133** and its β-carbonyl-containing analogue **135** highlights the importance of acidifying the α-proton.[48] Sulfonium intermediate **135**, with the acidifying carbonyl, performed as expected and favored C–C bond formation to form **137**. In this case, loss of trifluoroacetic acid from **135** generated putative thionium ion **136**, which apparently cyclized either directly or after diversion to an unobserved trifluoroacetoxy sulfide intermediate, in excellent yield. The similar substrate lacking this acidifying carbonyl never got to the thionium ion intermediate. The now only weakly basic α-proton was not susceptible to the usual TFAOH elimination. Rather, the sulfonium salt **133** persisted long enough for its intrinsic electrophilicity to be expressed through C–S cyclization onto the adjacent aryl ring in essentially a Friedel–Crafts thionation reaction. The nascent sulfonium salt **134** then proceeded to a suite of products. No experiments that described the results of incorporating a hindered base (e.g., *i*-Pr_2NEt, cf. **126**→**128**) to overcome the diminished acidity of the α-proton were reported.

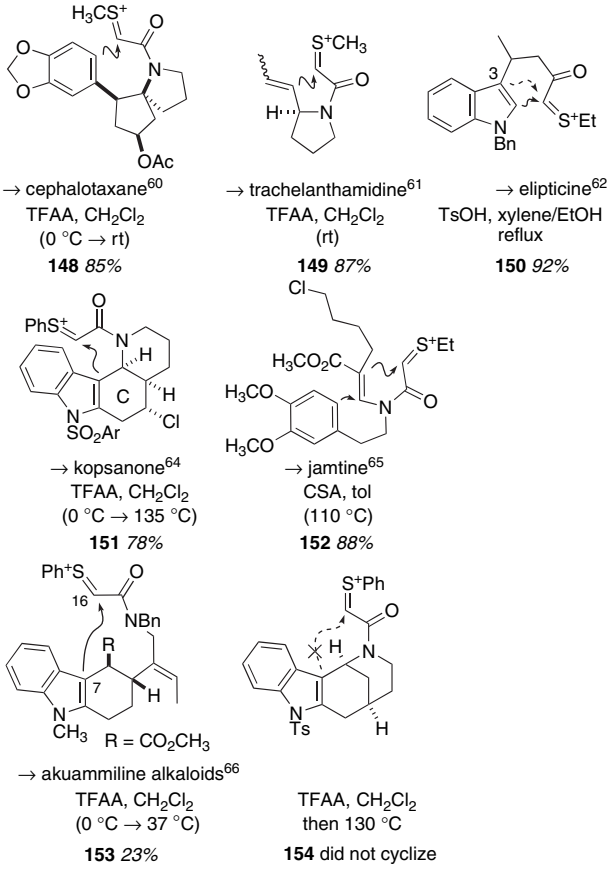
A survey of C–C bond-forming reactions with non-β-carbonyl-containing Pummerer substrates bearing mostly internal arene and alkene nucleophiles is shown in Scheme 16. Reaction of a *p*-chlorobenzyl, phenyl sulfoxide precursor to **138** proceeded through an α-trifluoroacetoxy sulfide intermediate. Treatment of this labile species with further strong acid (TFA) was required to reformulate a thionium intermediate **138** that was capable of being intercepted by external alkenes.[49] This two-step procedure, discussed in detail along with Scheme 14, is characteristic of most (**140**,[50] **143**,[51] **144**,[52] **146**,[53] and **147**[54]) but not all (**139**, **142**) TFAA-initiated Pummerer reactions. Substrate **142**, a key intermediate in Sano's erythrina alkaloid synthesis program,[55a] may enjoy a uniquely favorable convergence of both preorganization for cyclization and minimal strain in the product. The facile room temperature cyclization of thionium ion **139** is a bit anomalous, given the lack of defined conformational restrictions, but this species may benefit from an electronic advantage not shared by the other examples in Scheme 14.[56] In a resonance form, this electrophile can be viewed as an *N*-acyl iminium ion, a species that can be expected to display different (and perhaps greater) electrophilicity than the simple thionium moiety.

The extension of Magnus' seminal indole C(12) (aspidosperma numbering) functionalization chemistry beyond the aspidosperma alkaloids attests to its potential for impacting on many related problems, as exemplified by **145** (geissoschizine),[57] **146** (strychnos alkaloids),[53,58] and **147** (ibophyllidine alkaloids),[54] inter alia. Thus, C(3) of the indole nucleus appears to be a well-matched nucleophilic partner for thionium ion electrophiles, and even some rather strained and otherwise difficult ring closures (e.g., **145**, **146**) can be achieved. The Pummerer thionium ions formed from TMSOTf/*i*-Pr_2NEt initiation, **141a/b**,[59] and **145**,[57] all proceed to product under much milder experimental conditions than those typically necessary for the TFAA-initiated processes. Again, the value of using an initiator bearing a non-nucleophilic counterion is evident.

It should not escape notice that with **138** and **139** as exceptions, all of the thionium ions listed in Scheme 16 bear an inductively electron withdrawing atom (N or O) in a position adjacent to the electrophilic carbon. Even **138** and **139** arguably can fall under this classification by noting the inductive

effect of the chloride in **138** and the carbonyl in **139**. Is this feature critical for success in C–C bond-forming reactions, or is it largely just an artifact of the synthesis plans that utilize the Pummerer reaction? Many examples of Pummerer reactions proceeding through the thionium ion formed from DMSO, or thionium ions derived from other simple sulfoxides that do not contain a β-electron withdrawing group, have been documented.[15e] Therefore, this common structural/electronic feature of the systems in Scheme 16 does not appear crucial for success.

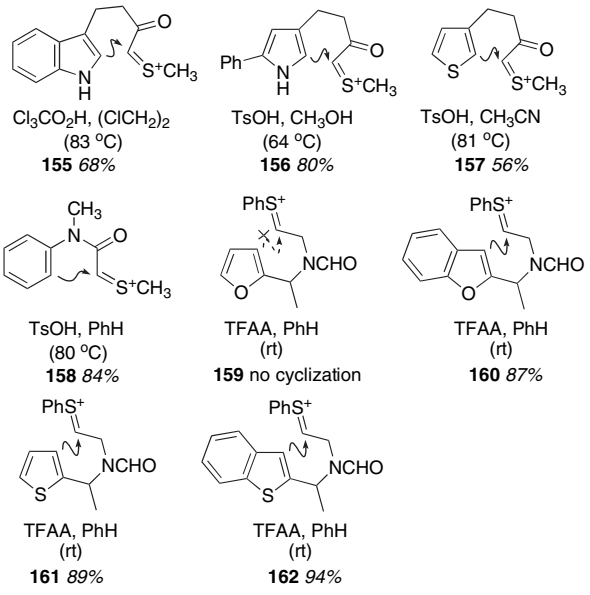
The number of successful C–C bond-forming Pummerer transformations that employ a β-carbonyl sulfoxide greatly exceeds the number reported without the carbonyl, as detailed by several earlier reviews.[15g,k] The use of β-carbonyl-containing thionium ions in carbocyclization reactions directed toward natural product targets is illustrated in Scheme 17. Ikeda's concise synthesis of cephalotaxine (cf. **148**) benefited enormously from the Pummerer reaction's ability to fashion seven-membered rings upon thionium ion initiated cyclization.[60] The extension of this methodology beyond the common five- and six-membered ring domain (cf. **144** also) distinguishes Pummerer chemistry from many other acyclic closure strategies. Ishibashi's trachelanthamidine synthesis (cf. **149**) is notable for the complete regiocontrol exhibited upon thionium ion cyclization to afford the desired five-membered ring product instead of the six-membered ring alternative.[61] The authors favor an explanation that cites greater strain in the six-membered ring transition state as a consequence of incorporating five sp^2 atoms within the forming ring. The five-membered ring alternative transition state would only contain four sp^2 atoms and perhaps pay a lesser energetic penalty to conform to the stereoelectronic requirements for C–C bond formation embodied in Baldwin's rules. This distinction is not general, as many successful Pummerer cyclizations that form the six-membered ring product have been documented.[15e] The elipticine cyclization substrate **150** presents an interesting mechanistic puzzle in light of the trachelanthamidine cyclization result.[62] In this case, the regiochemistry of cyclization favors the six-membered ring product, despite (1) the greater nucleophilicity of the C(3) position of *N*-alkyl indoles, and (2) the stereoelectronic preference for five-membered ring formation (cf. **149**). It is possible that initial kinetically favored cyclization occurs at C(3) to form a spirocyclic indolenine intermediate, but then under the vigorous reaction conditions, rearrangement proceeds via a 1,2-alkyl shift to afford the observed six-membered ring product. This mechanistic course finds precedence in Pictet–Spengler and Bischler–Napieralski cyclizations on tryptamine derivatives.[63] Magnus' syntheses of the kopsane alkaloids (cf. **151**) extend his earlier aspidosperma work to systems that have a higher oxidation level in the C ring.[64] The yield decreases slightly compared to the simpler case **125b** (Scheme 14). The jamtine synthesis by Padwa (cf. **152**), in contrast, breaks new ground by employing the Pummerer-generated thionium ion intermediate as an initiator of a polyene cascade cyclization.[65] This extension of Pummerer chemistry will be explored in more depth in Section 6.1. Bosch's approach to members of the akuammiline family of indole alkaloids exemplifies his many contributions that use Pummerer chemistry to forge C–C bonds to C(3) of the indole core within the context of complex alkaloid synthesis.[66] This substrate demonstrates that even eight-membered rings, usually a significant challenge for acyclic closure methodologies, can be accessed via Pummerer chemistry and thionium ion capture. As in previous indole C(3) additions, a first-formed α-trifluoroacetoxy sulfide intermediate is then heated to promote subsequent trifluoroacetate loss and cyclization. Whereas the yield suffers compared to other indole–thionium ion cyclizations, the formation of the highly sterically encumbered C(7)–C(16) bond (akuammiline numbering) sets this strategy apart from several other unrewarded attempts at this key segment of the target. The curious failure of thionium ion **154** to cyclize, in contrast to the successful closure of the related species **146**, is a reminder that intrinsic and energetically penalizing features of the substrate can trump even the usually favorable indole-Pummerer cyclization.[67] In this instance, the planarity of the amide linkage is postulated to misalign the nucleophile's approach to such an extent that a low energy path is no longer available. The amine analogue **146** does not suffer from this conformational rigidity and apparently can access a geometry conducive to nucleophile–electrophile union.



Scheme 17. Examples of acyl-containing Pummerer substrates for C–C bond formation.

The electrophilicity of both non-acyl thionium ion intermediates and the β-acyl analogues generated in Pummerer processes appears sufficient to combine with heteroaromatic nucleophiles, Scheme 18.[68–70] Note that in each successful case, relatively elevated temperatures are required to achieve acceptable yields of cyclization products in the acyl thionium ion series, whereas the non-acyl series realizes equivalently high yields at room temperature. These apparent rate

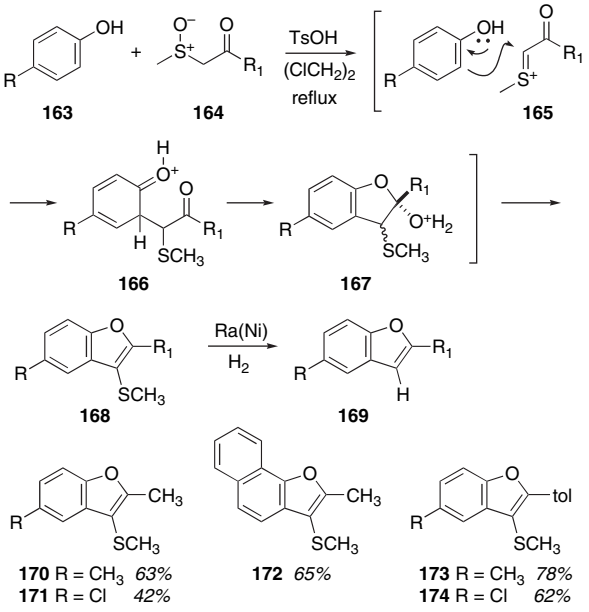
differences just might reflect the variation in initiation protocols. Comparing the reaction yields with Mayr nucleophilicities within each series, or between series (N=5.80 for indole; 4.63 for pyrrole; 1.26 for 2-methylthiophene; 5.5 for *N*,*N*-dimethylaniline)[13a,45] does not reveal any trend between the heteroaryl rings' intrinsic nucleophilicity and the reaction yield, an observation that does not conflict with the hypothesis of slow (S_N1-like) thionium ion formation followed by rapid electrophile quenching by any proximal and competent nucleophile. The authors present no data that bear on the question of whether the six-membered ring forms by direct cyclization, or, alternatively, by spirocyclization followed by 1,2-shift. The failure of the furan-containing system **159** to furnish cyclized product was attributed to the sensitivity of the furan nucleus to the generated TFA.[70]



Scheme 18. Examples of acyl and non-acyl thionium ion cyclizations with aromatic and heteroaromatic partners.

4.2. Phenols

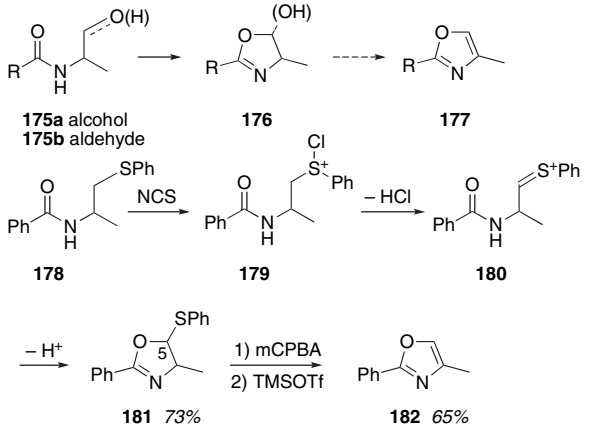
An application of Pummerer reactions with arene nucleophiles can be seen in an expedient preparation of benzofurans, Scheme 19.[71] In these instances, the doubly nucleophilic character of the phenol species **163** enables a formal [3-atom+2-atom] cyclocondensation with the doubly electrophilic Pummerer intermediate **165**. This first-formed thionium ion appears to favor initial addition to the phenol's carbon center rather than the hydroxyl, a result in accord with the expectations of hard–soft acid/base theory.[72] The *para*-positioned substituent directs addition to the *ortho* site of the phenol. From the addition product **166**, thermodynamically driven proton transfers and dehydration then deliver the intact benzofuran nucleus in **168**. Sulfur removal can be accomplished by simple Raney nickel-mediated hydrogenolysis to furnish the parent benzofuran **169**. The scope of the reaction includes both electron rich and electron deficient phenolic substrates, cf. **170** and **171**, respectively. The yields tend to be higher with the more electron rich phenols, **170** versus **171** and **173** versus **174**, but the fact that the reaction works at all with the electron deficient species **171** and **174** is a notable observation. Both alkyl (**170/171**) and aryl (**173/174**) ketones perform satisfactorily in the transform. The only major limitations encountered thus far involve the need to block the *para* position of the phenolic substrate from reaction, and the requirement for product refunctionalization to generate a sulfur-free compound.



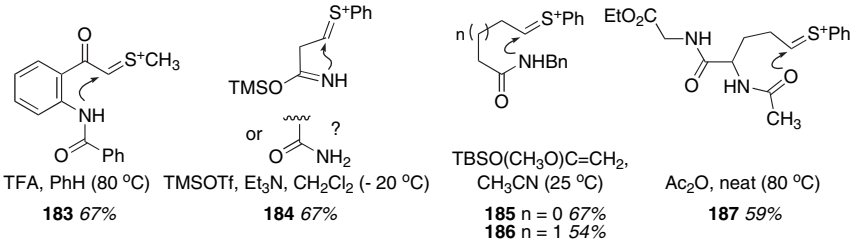
Scheme 19. Benzofuran formation from Pummerer reactions with phenol substrates.

4.3. Amides

The observation of amide participation in Pummerer-derived thionium ion trapping reactions dates back at least to the early work of Connor (Scheme 21),[73] and Magnus recently has developed a concise synthesis of oxazoles that exploits this process,[74] Scheme 20. This chemistry grew out of frustrated attempts to convert either the alcohol **175a** or the aldehyde **175b** into the oxazole product. A Pummerer-based strategy accomplishes the difficult oxidation (equivalent of **176** (no hydroxyl)→**177**) in advance of cyclization by transposing the relatively easy S→S(X) oxidative charge to the more challenging C(H)→C(X) goal. Thus, exposure



Scheme 20. Oxazole synthesis via Pummerer reaction on an amide substrate.

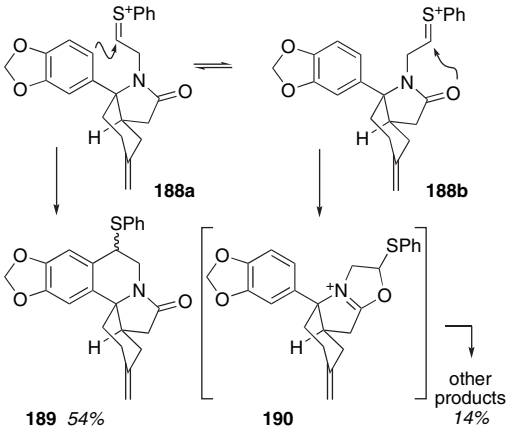


Scheme 21. N- versus O-cyclization in Pummerer reactions with amide nucleophiles.

of sulfide **178** to a Cl^+ source led to a presumed thionium ion intermediate **180**, which is sufficiently electrophilic to trap the proximal amide function on oxygen. The product retains the oxidation level increase at C(5), and through somewhat unorthodox TMSOTF assisted sulfoxide elimination, the oxazole product **182** is formed in good yield.

The 'amide-endo' nature of the cyclization substrate **180** guaranteed that only O–C and not N–C bond formation could occur. However, this preference is not general, and, in fact, C–N bond formation appears to be favored when that option is accessible geometrically, Scheme 21. Connor's seminal effort **183** demonstrated that C–N bond formation was feasible, but the 5-enol(*exo*)-*exo*-trig cyclization shown should enjoy sufficient stereoelectronic benefits over the alternative 7-enol (*endo*)-*exo*-trig O→C closure to diminish the importance of the latter process under any circumstance. The trade-offs become less clear-cut with the four-, five-, and six-membered ring closures **184**–**186**, respectively.[75,76] In each of these cases, the cyclization of either N or O of the amide function forms the same-sized ring, and so the aforementioned stereoelectronic differences are not applicable. In each case, only N→C bond formation is observed. Curiously, this preference switches again with the acetamide substrate **187**.[77] In this case, the 7-enol(*endo*)-*exo*-trig cyclization appears to be preferred. The fact that the O→C cyclization product is kinetically favored can be deduced from the results of a control experiment wherein the alternative N→C cyclization product, prepared by an independent route, remains unchanged when exposed to reaction conditions.

Numerous β-amido thionium ions were generated as substrates in C–C bond-forming reactions via chemistry discussed in Section 4.1. For example, either **123a** or **142** could have cyclized as per **180**→**181**, but rather they exclusively followed the C–C bond-forming alternative instead. The underlying structural and electronic features that steer a thionium ion intermediate toward either arene or amide nucleophiles are difficult to disentangle with these substrates, and so a simple set of predictive tools is not yet in hand. This point is emphasized by the observations of Desmaële in his approach to the erythrina alkaloids,[78] Scheme 22. Thionium ion **188**, generated by treatment of a precursor sulfoxide with TMSOTf/*i*-Pr_2NEt, is quite similar to the related species **142** invoked by Sano et al. in their erythrina alkaloid work, but the subsequent cyclization chemistry is quite different. Sano's thionium ion **142** proceeded uneventfully and in high yield to a C–C bonded product via an internal Friedel–Crafts alkylation process. In contrast, the thionium ion **188** apparently partitions between the two proximal nucleophiles present, and a mixture of products derived from both C–C and C–O bond formation ensues.

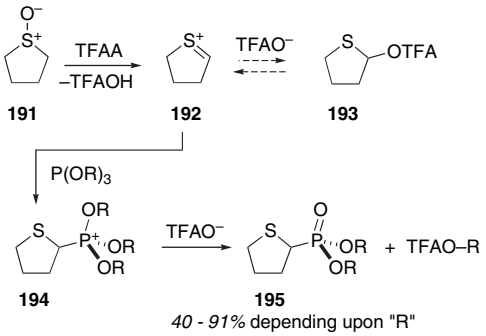


Scheme 22. Carbon–carbon versus O–C bond formation upon Pummerer-mediated cyclization in the erythrina alkaloid series.

The basis for this divergent reactivity may be related to the presence of the mesylate in **142**. The electron-withdrawing character of this moiety could suppress the nucleophilicity of the amide carbonyl in **142** sufficiently to steer the reaction to the alternative Friedel–Crafts process. Perhaps thionium ion **188**, lacking this governor on the amide's reactivity, can engage both nearby nucleophiles in productive cyclocondensations. Whatever the reason, the observation of competition between an arene and an amide is a reminder of the subtle effects that, collectively, contribute to the reactivity profile of Pummerer-derived thionium ions.

4.4. Phosphites

It was not until 2001 that phosphorus was explored as a nucleophile in Pummerer reactions,[79] Scheme 23. In this study, Masson et al. demonstrated that a concatenation of Pummerer and Arbuzov reactions leads to the formation of α-thiophosphonates from sulfoxide **191** and trialkyl



Scheme 23. Phosphite as a nucleophile in the Pummerer transform.

phosphites. The yield of phosphonate product **195** is responsive to the steric and electronic character of the phosphite's 'R' group. The highest yield attended use of the triisopropyl phosphite substrate. The authors speculate that the trialkylphosphite itself serves as a base in this sequence by promoting the loss of the elements of triflic acid from the sulfonium salt derived from **191**. The scope of this Pummerer transform with respect to the sulfoxide component may be rather restricted, as pentamethylene sulfoxide, dimethyl sulfoxide, and phenyl methyl sulfoxide all failed to deliver phosphonate product under similar treatment.

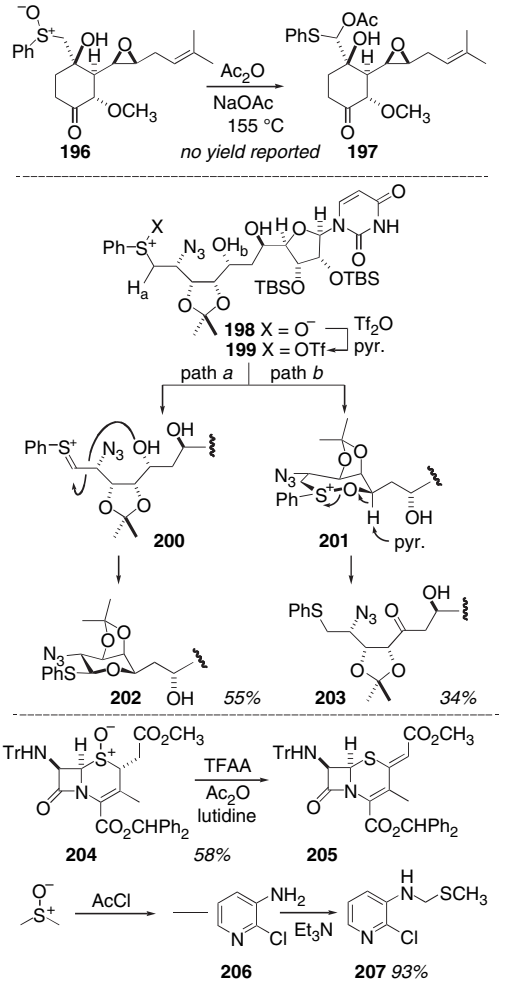
5. Substrates

The expansion of Pummerer chemistry into the natural products synthesis arena inevitably has led to the examination of substrates of ever increasing complexity in transformations that test the limits of functional group compatibility and tolerance. In addition, exploration of regioselectivity control elements in unsymmetrical dialkyl sulfoxides has added mechanistic nuance to an overall understanding of the process. Finally, extensions of Pummerer chemistry to sulfoxide analogues (e.g., sulfilimines), and in separate studies, to the solid state, add to the burgeoning versatility of this reaction. Each of these topics will be addressed in turn, and illustrated with examples from the recent literature.

5.1. Functional group compatibilities

The presence of nucleophiles in the Pummerer reaction solution is inevitable, given the second-step quenching of the electrophilic thionium ion, but just what nucleophiles can be tolerated? The competition between the sulfoxide oxygen and the resident nucleophile(s)for the acylating (or silylating) initiator is the key, and it is no surprise that the carbon nucleophiles discussed earlier (alkenes, arenes) fail to offer any challenge to the sulfoxide. On the other hand, nucleophiles that do react with acylating/silylating agents readily, such as alcohols and amines, raise the possibility that the reaction may be diverted down undesired pathways.

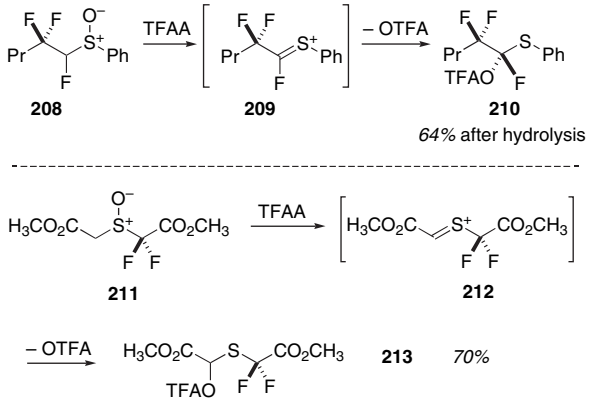
Several examples of hydroxyl-containing Pummerer substrates that do undergo uneventful reaction at the sulfoxide, followed by standard thionium ion trapping suggest that, in general, initiation conditions can be identified that favor reaction at sulfoxide rather than hydroxyl.[15e] One illustration of this phenomenon can be seen with the fumagolone precursor **196**,[80] Scheme 24. In this instance, reaction of the acylating agent, even under rather forcing conditions, is localized at the sulfoxide oxygen, despite the presence of the tertiary alcohol and the sensitive (to the NaOAc present) epoxide. A more revealing example can be found in Matsuda's tunicaminyluracil synthesis work, **198**→**202/203**.[81] Treatment of **198** with Tf_2O leads only to acylation at the sulfoxide function, despite the presence of the nucleophilic secondary alcohols and the imide residue. In contrast, use of TFAA led to competitive alcohol trifluoroacetylation, an observation perhaps consistent with the dogma that the 'harder' sulfoxide alkoxide prefers reaction with the 'harder' acylating agent, and vice versa. The sulfonium salt **199** unexpectedly partitions between the conventional Pummerer reaction (path a, **199**→**200**→**202**) and a formal Swern-type oxidation (path b, **199**→**201**→**203**) promoted, presumably, by the proximity of alcohol and sulfonium salt within **199**. It is possible that the divergence in reaction pathways from **199** is tied to the relative acidities of H_a and H_b, but the authors did not report the results of experiments that might test this premise.



Scheme 24. Examples of alcohol and amine compatibility with Pummerer reaction conditions.

There does not appear to be any systematic studies that probe the compatibility of amines with Pummerer conditions. Sporadic application of the Pummerer reaction to amine-containing substrates reveals that, at the very least, amines are not incompatible with the desired reaction path. Tertiary amine-containing substrates (e.g., **143**, Scheme 16) and the N–H indole and pyrrole species **155** and **156**, respectively, (Scheme 18) are perhaps the best-represented classes of amine-bearing compounds that survive the Pummerer process unchanged. Extension of this immunity to secondary or primary amines is suggested by the specific cases **204** and **206**, but cannot be claimed as general without substantiation through more examples. The secondary amine of **204** is not acylated under the Pummerer conditions, but that lack of reactivity can be attributed to steric hindrance as much as any inherent reactivity difference between N: and O^-.[82] Similarly, the lack of acylation with the primary amine of **206** is intriguing, but may be due to no more than the sequence of mixing.[83]

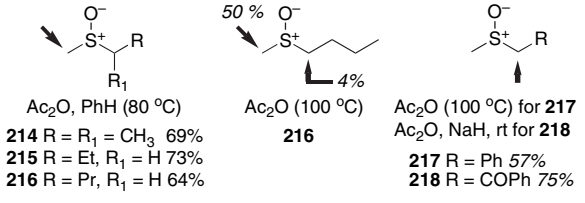
One of the more remarkable attributes of the Pummerer reaction is its ability to access exceedingly electron deficient carbocations derived from fluorinated substrates, Scheme 25. Nucleophile substitution chemistry on highly fluorinated compounds is often plagued by slow rates due to the inductive electron-withdrawing character of the fluorine atoms. Therefore, the observation that these types of compounds function in the Pummerer process is not without its merits, as it opens up a host of nucleophilic substitution possibilities for the preparation of highly functionalized fluorinated compounds. Fluorinated thionium ions that feature fluorine on either side of the carbocationic site are accessible, and the nucleophile trapping products **210** and **213**, respectively, are formed in good yield.[84,85]



Scheme 25. Highly electrophilic thionium ions generated from fluorinated Pummerer substrates.

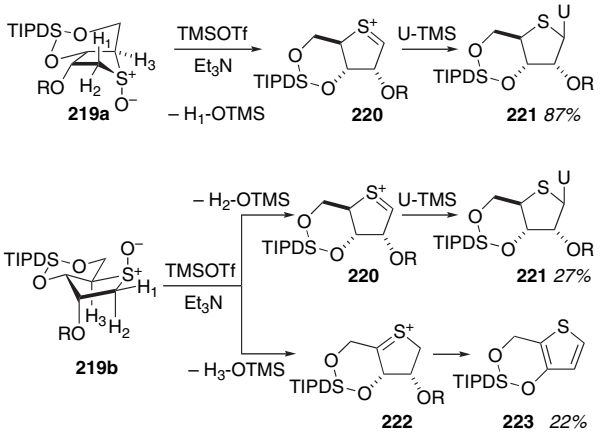
5.2. Regioselectivity

Pummerer reactions on unsymmetrical dialkyl sulfoxides bearing α and α′ protons can lead, in principle, to two different sulfide products, depending on the direction of proton loss. Numerous studies during the formative stages of Pummerer investigations provide guidance on the question of which proton loss is preferred, as illustrated by the canonical examples in Scheme 26. In all cases, elimination of the elements of HOAc occurred exclusively or greatly favoring loss of the more acidic proton, an observation consistent with either an E2- or E1CB-type mechanistic course. In sulfoxides without an acidifying β-group (**214–216**),[86] elimination occurs at the less substituted side (= most stable anion = most acidic proton). With sulfoxides where there is an identifiable β-acidifying group, (e.g., **217** and **218**),[86b,87] elimination favors that position. Subsequent deuterium labeling studies on rigid cyclic sulfoxides revealed that there is a strong preference for *anti* elimination of HOAc from a conformation where antiperiplanar alignment of H and OAc can be achieved (cf. Scheme 5).[88]



Scheme 26. Historical basis for the observation that Pummerer reaction regioselectivity is responsive to proton acidity.

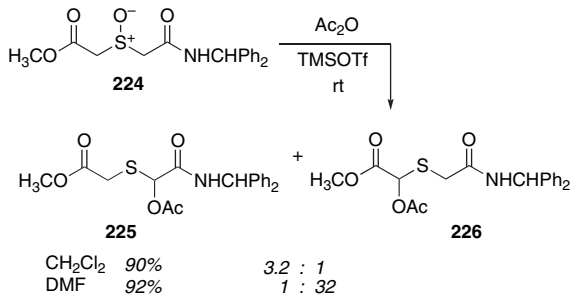
The influence of this stereoelectronic preference for elimination on Pummerer reaction regioselectivity can be seen in a more recent example in the thionucleoside field, Scheme 27.[89] Matsuda et al. demonstrated that the sulfoxides **219a** and **219b**, which differ only at the sulfur configuration, undergo Pummerer reaction to form protected thiouracil derivatives (Vorbrüggen reaction) with markedly different results. The α-sulfoxide **219a** can achieve the necessary stereoelectronic overlap between S-OTMS (derived from **219a** and TMSOTf) and H_1, leading to thionium ion formation away from the ring juncture, **220**. An excellent yield for uracil attachment ensued. In contrast, the diastereomer (at sulfur) **219b** has two protons, H_2 and H_3, which can meet the strict stereoelectronic criterion for alignment, and two products in roughly equal amounts were formed. The desired product **221** derives from elimination of H_2-OTMS, but the equally accessible H_3 elimination diverts sulfoxide to the undesired thionium **222**, and thence to the aromatized thiophene elimination product **223**. Thus, careful consideration of the stereoelectronic requirements for HX elimination from an activated sulfonium salt can provide insight into both the regiochemical outcome, and the facility, of a Pummerer process.



Scheme 27. Pummerer reaction regioselectivity dictated by stereoelectronic effects.

An interesting addendum to the settled theory of Pummerer regioselectivity can be found in the examples reported by Nagao,[90] Scheme 28. In this instance, the sulfoxide **224** has two flanking acidifying groups, and conventional wisdom would dictate that the ester, being more acidic than the amide (pK_a's in DMSO: ethyl acetate=30.5; dimethyl acetamide=34.5)[91], would direct proton loss with a preference for forming sulfide **226**. However, in CH_2Cl_2 solvent, the opposite result is observed! The reaction regioselectivity returns to 'normal' (**226** favored) when DMF is used as a solvent. This profound solvent effect can be traced to the competition between the various carbonyls for the added activator TMSOTf. In the non-participating solvent CH_2Cl_2, both the ester and amide carbonyls will bind TMS+ to slightly differing extents. The more basic amide should be preferred, and that differential carbonyl activation favoring the amide will translate to the differential acidities that are expressed in the **225/226** ratio. In DMF, however, the solvent's carbonyl appears to swamp out substrate carbonyl binding to TMS+, and the natural preference for deprotonation toward the ester function dominates. This example illustrates one method

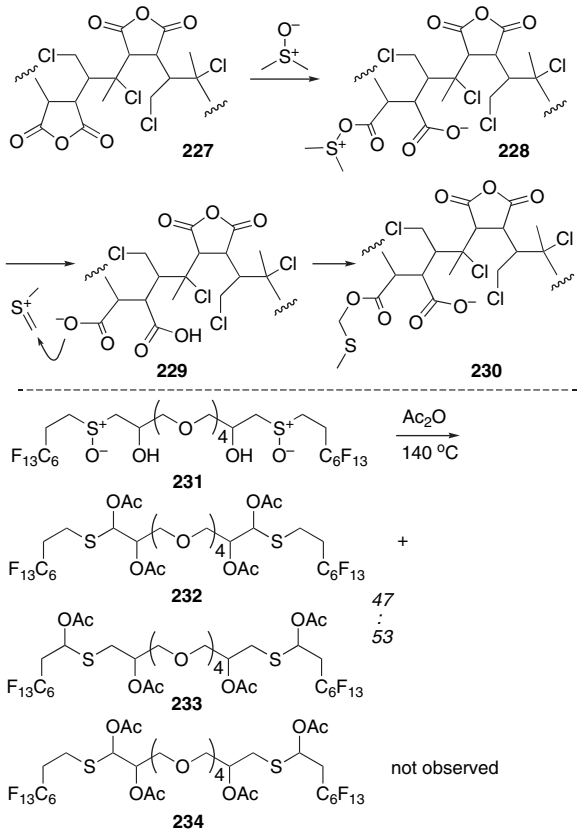
wherein the regioselectivity of a Pummerer reaction can be manipulated in a predictable manner by experimental design.



Scheme 28. Pummerer reaction regioselectivity is responsive to Lewis acid additives.

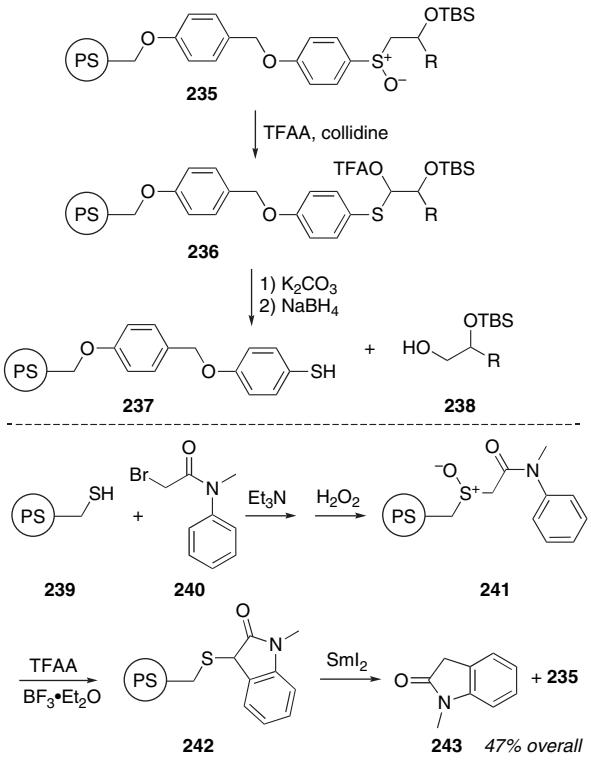
5.3. Polymer and solid-state chemistry

The Pummerer reaction has not yet had a significant impact in the area of macromolecular chemistry, although there does not appear to be any fundamental reason why this chemistry can't translate into the realm of polymer reactions, Scheme 29. Markarian et al. have observed, quite by accident, that dissolving a maleic anhydride/1,3-dichlorobutadiene copolymer **227** in DMSO leads to a modification of the polymer's functionality.[92] This structural change was characterized as resulting from the intervention of essentially a Pummerer reaction on DMSO using the polymeric anhydride as an initiator, **227**→**230**. The complimentary process, a Pummerer reaction on a polymeric (oligomeric) sulfoxide substrate, was investigated by Hedhli and colleagues.[93] They observed that treatment of a series of oligoethyleneglycol bis sulfoxides, including the tetrameric species **231**, with the initiator Ac_2O led to the isolation of two products in roughly equal amounts, as exemplified by the two regioisomeric bis sulfides **232** and **233**. The almost equal partitioning between the fluorinated and non-fluorinated sides of the sulfoxide is a bit surprising, but perhaps is just a reflection of the trade-off between the acidifying effects of the inductively electron withdrawing groups on either side of the sulfoxide. By far, the bigger surprise is a complete absence of any of the unsymmetrical regioisomer **234**. The basis of this remarkable claim by the authors remains obscure, given the almost equal facility with which either side of the sulfoxide group apparently participates in the Pummerer reaction to form **232** or **233**. In short, this result must reflect the operation of a completely dominant electronic effect that is exerted over 16 non-conjugated atoms, a phenomenon likely to have little precedence in all of organic chemistry.



Scheme 29. Pummerer reactions with polymeric and oligomeric components.

The push to identify chemical transformations that work with functionality tethered to a solid support has led to testing of the Pummerer process in this environment, Scheme 30. In the initial foray, Solladié and co-workers demonstrated that the resin-bound sulfoxide **235** participates in a conventional Pummerer reaction upon treatment with TFAA to furnish an initial sulfide product **236** and then the desired resin-free alcohol **238** upon hydrolysis/reduction.[94] This sequence has the net effect of cleaving the molecule of interest from the resin, and so it falls under the category of 'traceless linker' technology. No yields were reported, and so the overall efficiency of the strategy cannot be judged.



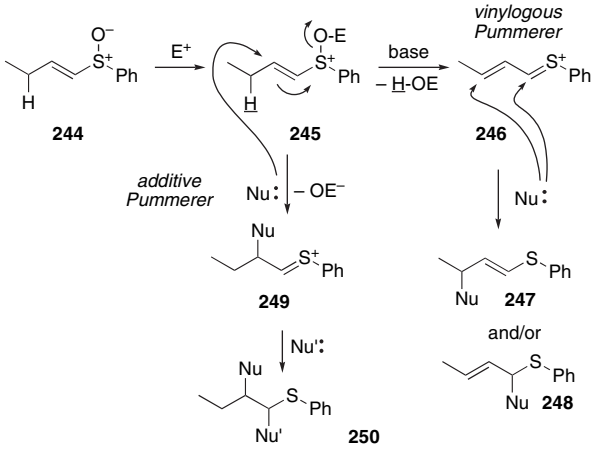
Scheme 30. Pummerer chemistry on beads.

The use of Pummerer chemistry to effect a desired cyclization within a resin-bound substrate was probed by Proctor et al., **241**→**242**.[95] The Glasgow group employed chemistry very similar to that described by Sano (Scheme 15, **135**→**137**) to effect closure of the oxindole nucleus. In a second independent step, the heterocycle was cleaved from the resin under reductive conditions. This example illustrates how the Pummerer reaction can be an asset to library synthesis by virtue of its productive use in 'on-bead' chemistry.

5.4. α,β-Unsaturated sulfoxides

The introduction of alkenyl and aryl sulfoxides as substrates in Pummerer chemistry has expanded the basic repertoire of useful processes for oxidative transposition in significant and fundamental ways, particularly in the area of heterocycle synthesis. The alkene adjacent to the sulfoxide function efficiently extends the thionium ion's electrophilicity down the molecular framework and introduces many new options for single and double nucleophile capture. With this multiplexed reactivity, of course, comes issues of both regioselectivity and stereoselectivity of bond formation. These questions are often cast in terms of the grand mechanistic dichotomy that defines this area of Pummerer chemistry, vinylogous versus additive pathways for nucleophile–electrophile pairing. A survey of historical precedents, and the current trends that have evolved from them, follows.

5.4.1. Vinylogous and additive mechanisms. Captured in Scheme 31 is the essence of the underlying mechanistic picture for Pummerer reaction with unsaturated sulfoxides. Whereas an alkenyl substrate **244** is shown for convenience, these pathways extend to the aromatic versions as well. Initiation of the Pummerer sequence by activation of the sulfoxide in **244** leads to the branch point in this mechanistic proposal, sulfonium ion **245**. If this sulfonium salt bears a γ-proton whose C–H bond can maintain overlap with the π-system of the alkene, then simple E2-like elimination of the elements of H–OE follows from direct analogy with the alkyl Pummerer substrates. The product of this elimination is the electrophilic unsaturated thionium ion **246**, which is capable of trapping nucleophiles at either the α- or γ-positions to deliver **248** or **247**, respectively. This pathway has been termed the 'vinylogous Pummerer reaction'.[96] The factors



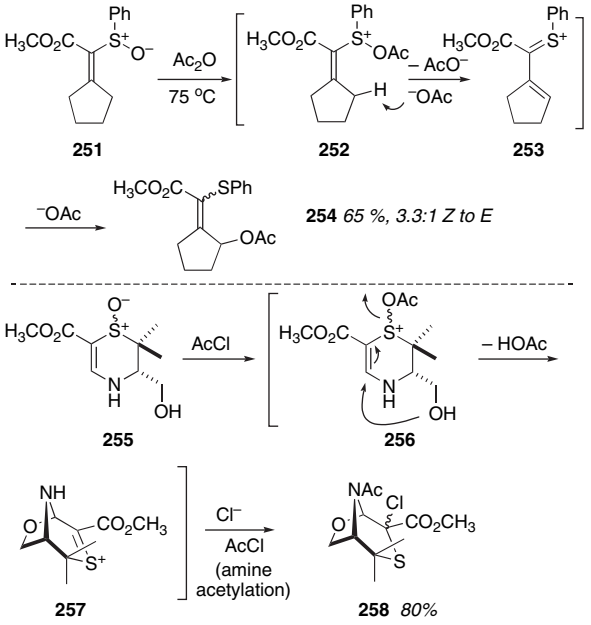
Scheme 31. Vinylogous and additive mechanistic pathways for the unsaturated sulfoxide Pummerer reaction.

that govern the choice of α or γ nucleophile attack are not well understood, and examples exist that favor either outcome. Built in biases have been used to steer the nucleophile to one site or the other, as illustrated by example below. Despite the fact that the elimination of H–OE is most likely to be bimolecular with respect to base, the overall vinylogous Pummerer sequence bears a strong resemblance to S_N1-type chemistry in that the leaving group departs to form a high-energy electrophilic intermediate prior to nucleophile addition.

The sulfonium salt **245** can engage the nucleophile directly in a process competitive with the vinylogous channel to afford the thionium ion **249**. The nascent thionium ion in **249**, like any Pummerer-generated thionium ion, will react rapidly with available nucleophiles to furnish the double adduct **250**. Depending on the particulars, the two nucleophiles can be the same or different, and clever substrate design has been used to serve up a specific sequence of nucleophiles for controlled introduction of the two addends. This mechanistic pathway had been labeled the 'additive Pummerer reaction'.[97] In contrast to the vinylogous alternative, this reaction scheme most closely aligns with an S_N2'-type process in that the introduction of the first nucleophile occurs in concert with departure of the leaving group OE. In some of the examples described below, the mechanistic path is unambiguous. However, other Pummerer transforms on unsaturated sulfoxides could proceed by either mechanism, and in none of the ambiguous cases has any evidence been presented that allows for a definitive conclusion about which might be operational.

The inaugural example of a vinylogous Pummerer reaction on an unsaturated substrate can be ascribed to Uda and coworkers (1975),[96] who demonstrated that the alkenyl sulfoxide **251**, upon reaction with acetic anhydride, leads to the vinylogous acetate addition product **254**, Scheme 32. The fact that no acetate addition occurred at the ring juncture excludes an additive mechanism from further consideration. The additive mechanism was known at the time, although not yet christened as such, through Stoodley's study of the Pummerer reaction of the unsaturated sulfoxide **255** (1972).[98] This example features the double nucleophilic addition characteristic of the additive mechanism, with first hydroxyl and then chloride quenching electrophilic sites on the substrate. These rather humble Pummerer 'curiosities' have spawned a great deal of the modern Pummerer literature, as many research groups have actively pursued the development and exploitation of the myriad reactions that stem from treatment of unsaturated sulfoxides with activators, as detailed in the following sections.

5.4.2. Aromatic Pummerer substrates. The sub-field of aromatic sulfoxide Pummerer rearrangement chemistry has seen more development than the aliphatic counterpart, presumably because of the ready availability of the starting aryl sulfoxides, and the role that such transformations might play in total synthesis endeavors. The seminal report by King demonstrated no more than the fact that aryl ring oxidation was possible (**259**→**262**) via the agency of a Pummerer reaction on a phenolic substrate,[99] Scheme 33. No arguments were advanced that supported one mechanistic path over another, but the acidity of the phenolic hydroxyl in **260** would tend to lend weight to a vinylogous Pummerer

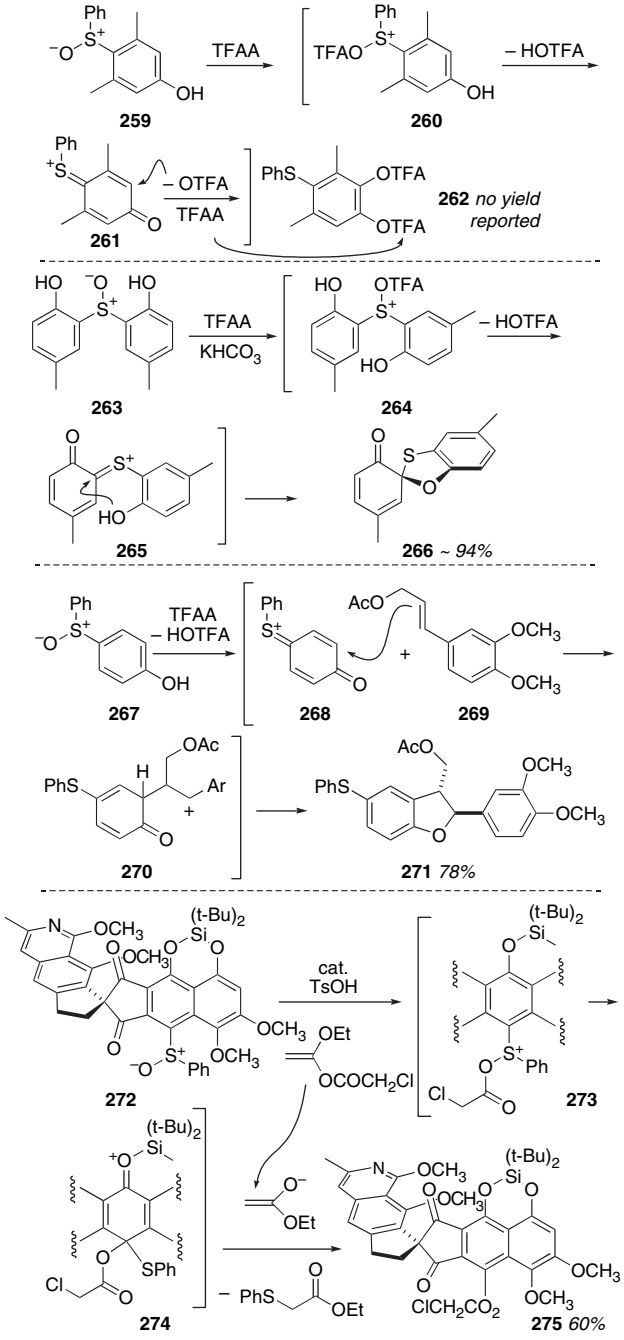


Scheme 32. Early examples of the unsaturated sulfoxide Pummerer reaction.

mechanistic sequence over the additive alternative. Kita, and independently, Jung, picked up on this line of inquiry and fleshed out much of the scope of the process within the context of phenol oxidative addition chemistry.

Jung, for example, showed that the bis phenolic sulfoxide **263**, upon subjection to TFAA-mediated Pummerer initiation, furnished the spirocyclic cyclohexadienone product **266** in excellent yield,[100] Scheme 33. A vinylogous Pummerer process was proposed to rationalize this result. The facile loss of the elements of trifluoroacetic acid from **264** presumably leads to the electrophilic orthoquinone analogue **265** that plays a central role in this transformation. The product **266** can be reductively desulfurized to provide a bis phenolic ether, a common structural element of many phenol (e.g., tyrosine)-derived natural products. As with the work of King, these phenol sulfoxide substrates combined with the TFAA electrophile preferentially on the sulfoxide oxygen and not the phenol hydroxyl.

Kita et al. extended the phenolic sulfoxide Pummerer chemistry through systematic investigations that probed the role of activator, nucleophile, and solvent on the facility and the scope of the process.[101] His group identified conditions that supported the addition of a carbon (alkene) nucleophile to the intermediate (thionio)quinone electrophile, as exemplified by the combination of sulfoxide **267** with styrene derivative **269** to provide good yields of the formal [3-atom+2-atom] addition product dihydrobenzofuran **271**,[102] Scheme 33. This reaction provides facile access to neolignan-type structures with excellent stereochemical control. The value and selectivity of this aryl Pummerer rearrangement chemistry can be seem in Kita's efforts directed toward the antitumor antibiotic fredericamycin via an Ar–S(O)Ph → Ar–OCOR transformation (**272** → **275**, Scheme 33).[103] This sequence was executed in good yield and without interference from undesired degradative pathways, despite the presence of a nucleophile sensitive

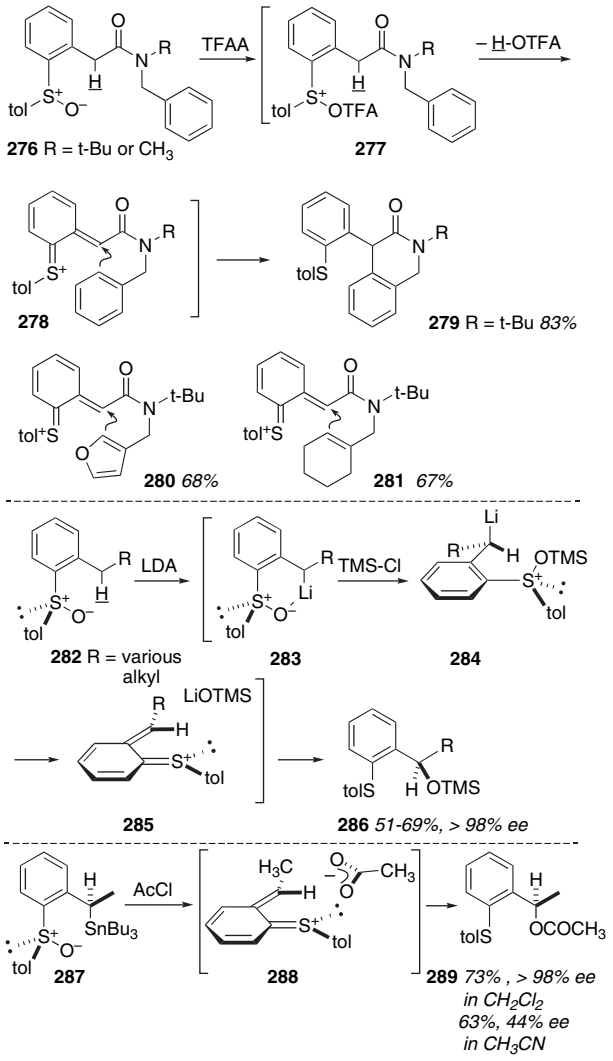


Scheme 33. Examples of phenolic sulfoxide Pummerer reactions.

quaternary β-dicarbonyl and oxidation sensitive masked hydroquinones.

Contemporaneous studies by Padwa and co-workers on a non-phenolic variant of the aryl Pummerer reaction led to the development of a benzylic C–H activation strategy to trigger the Pummerer sequence,[104] Scheme 34. In a representative example, the aryl sulfoxide **276** bearing a pendant aryl nucleophile was exposed to standard Pummerer initiation conditions to deliver the cyclized material **279**.[104a] In this instance, loss of H–OTFA through a vinylogous mechanistic pathway is required to activate the benzylic position for C–C bond formation. The highly electrophilic *ortho*-(thionio)quinone methide intermediate **278** is reactive

enough to trap even the unactivated aryl ring in good yield. The fate of this transformation rests on the identity of the amide's 'R' substituent. When R=*t*-Bu (large), an amide rotomer favoring juxtaposition of the two aryl rings is preferred. When R=CH_3 (small), the alternative rotomer is preferred, and aryl trapping of the electrophilic species is not seen. In this instance, the *ortho*(thionio)quinone methide is quenched by simple $TFAO^-$ addition. Extension of this chemistry to more nucleophilic (furan, **280**) and less nucleophilic (alkene, **281**) traps speaks to the promise of generality for the transform.

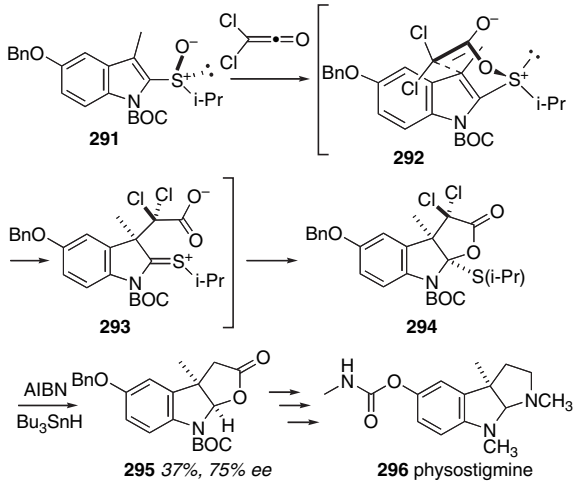


Scheme 34. Padwa's exploration of benzylic activation through aromatic Pummerer reactions.

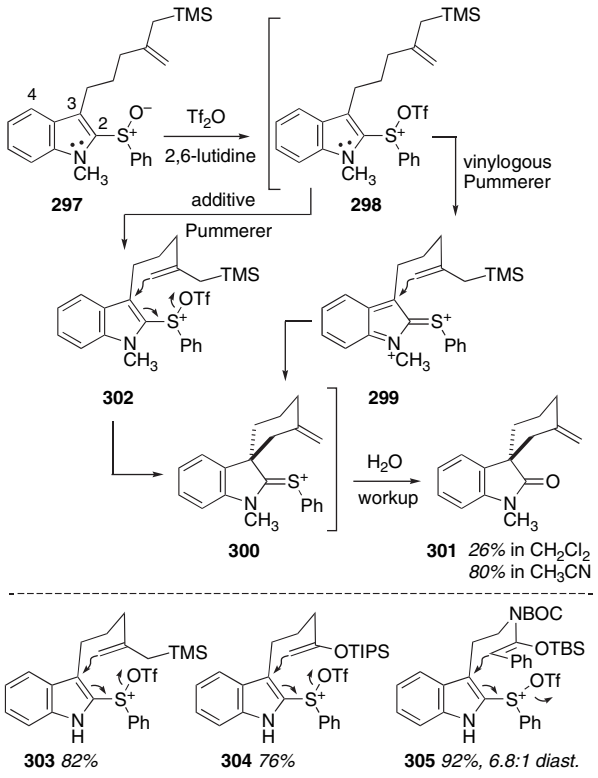
An intriguing variant on the benzylic activation theme recently has emerged from the Padwa lab, **282**→**286**, and the related **287**→**289**,[105] Scheme 34. In these examples, sulfoxide activation of the benzylic position is aided by chelation rather than by the carbonyl-induced acidification within **277**, but the net result, formation of a *ortho*(thionio)-quinone methide intermediate, is the same. In the key advance of this work, a high level of chirality transfer from stereogenic sulfoxide to the benzylic position was detected. This observation was explained by invoking a tight ion pair (**285** in the case of **282** and **288** from **287**) that preserved the original stereochemical information despite having only sp^2 centers. The tight ion pair has sufficient integrity to sustain the apparent planar chirality of **285/288** and enable this transfer. This speculation is supported by the solvent effects seen with **287**, wherein use of a more polar solvent, which presumably would better promote ion separation, provides product with lower ee. Given the planar nature of the typical thionium ion electrophile, Pummerer reactions on chiral sulfoxides that proceed with high levels of asymmetric induction are rare (cf. Kita's work, Scheme 5), and so these examples may presage the opening of new vistas in the field.

The expansion of aryl sulfoxide Pummerer chemistry into heteroaromatic systems was led by Marino and colleagues, who explored the use of indole sulfoxide substrates with ketene initiators,[106] Scheme 35. The goal of the synthesis involved preparation of 3,3-disubstituted indoline products en route to members of the physostigmine family of medicinally active alkaloids. Toward this end, treatment of the chiral sulfoxide **291** with dichloroketene led to a transient sulfonium intermediate that is poised to reorganize via [3,3] sigmatropy to furnish the C(3) disubstituted lactone **294** following cyclization within **293** of the carboxylate nucleophile into the thionium ion electrophile. Further functional group transformations led ultimately to physostigmine itself. The modest yield of Pummerer rearrangement was offset somewhat by the favorable level of asymmetric induction in the key C–C bond formation. The authors cite a transition state resembling **292** as the vehicle for establishing absolute stereochemistry at C(3), and they note that the sterically bulky isopropyl group serves as a conformational anchor for this assembly. Smaller sulfoxide substituents (e.g., CH_3) proceeded with much lower ee's. It is not clear whether the minor enantiomer emerges from a similar chair-like transition state construct with an axial isopropyl group, or from a boat-like alternative with an equatorial isopropyl. The sequential addition of two nucleophiles to the sulfonium/thionium ion intermediates is characteristic of the additive Pummerer mechanistic pathway.

The synthesis of 3,3-dialkyl indolone derivatives from indole-2-sulfoxides also can be realized when the nucleophilic



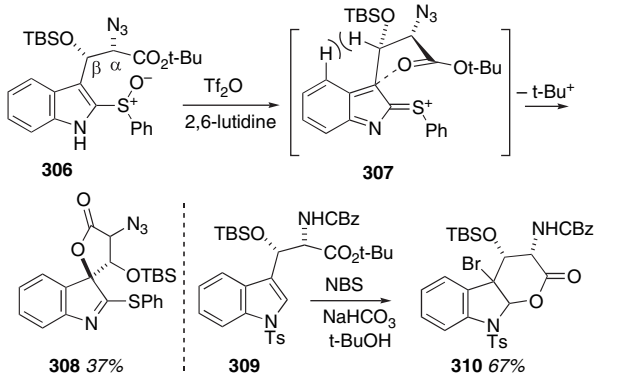
Scheme 35. Marino's Pummerer rearrangement on the indole platform, directed toward physostigmine synthesis.



Scheme 36. Oxidative carbocyclizations extending from indole-2-sulfoxides.

entity is tethered to the indole framework,[38] Scheme 36. The allylsilane of substrate **297** is a relatively poor nucleophile (Mayr N=1.8)[13a] yet the transformation proceeds in high yield, again a reminder of the functionally useful levels of electrophilicity that can be achieved under mild conditions via Pummerer chemistry. The vinylogous versus additive mechanistic dichotomy is brought into sharp relief with the *N*-methyl substrate shown. A putative vinylogous path would proceed inescapably through the dicationic intermediate **299**, whereas the additive alternative would avoid this presumably high-energy species by favoring an S_N2'-type displacement (**302**→**300**) without any involvement of the nitrogen's lone pair. In both scenarios, the same thionium-bearing species **300** would result, and hydrolysis upon workup then affords the oxindole product in excellent yield (in CH_3CN). No independent evidence exists that allows discrimination between these two mechanistic hypotheses at this juncture. Only the vague unease at invoking a doubly cationic intermediate, despite Sano's reliance on same (cf. Scheme 3 and accompanying discussion), tends to shade mechanistic thinking toward the additive pathway. This transformation formally represents an oxidative cyclization onto a heteroaromatic nucleus with complete control of (1) oxidant delivery and (2) regiochemistry of nucleophilic attack. Many prior studies on oxidation-initiated aromatic heterocycle functionalizations have been attempted, and the not infrequent observations of product (over)oxidation, and/or lack of regiochemical control upon nucleophile addition have compromised the value of these transforms in the past.[107] With **297** and related substrates, the site of oxidation is completely controlled by the starting sulfide's (precursor to **297**) unmatched susceptibility to oxidants. The regiochemistry of nucleophile addition is governed by the intermediate's energy gain by rearomatization, as alternative addition sites, such as C(2) or C(4), would not lead to aromatic products. Only the C(3) addition shown, either by additive or vinylogous mechanistic paths, preserves (or returns) the benzene ring to full aromaticity. Successful cyclizations with alternative nucleophiles have been documented as well. The silyl enol ether of **304** and the silyl ketene iminal function in **305** both participate satisfactorily in this Pummerer reaction. Since each of these species has a proton on the indole nitrogen, the first-formed and isolated products are 2-thiophenyl indolenines. The thioimidate function of these compounds can be readily hydrolyzed to the carbonyl (indolone) product in a second step. In this way, a range of functionalized 3,3-spirocyclic indolones are available from simple indole precursors. A detailed mechanistic picture of the cyclization of **305**, with the sulfur activated by hypervalent iodine rather than sulfoxide sulfonylation, has been presented in Scheme 10.

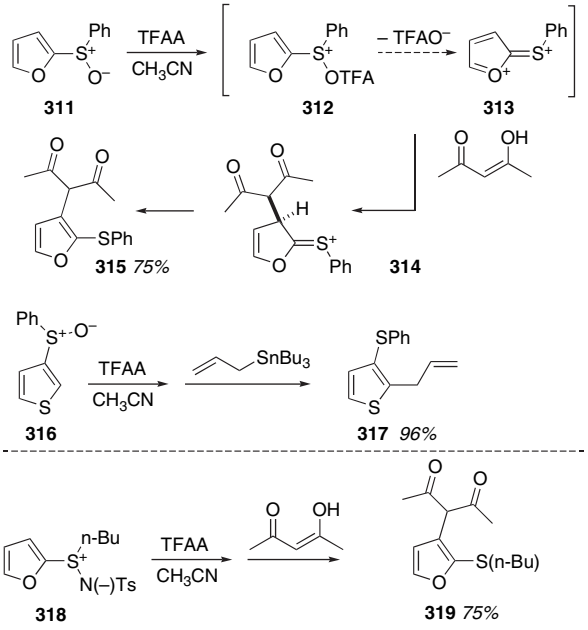
An example of an errant regiochemical result can be found in the tryptophan cyclization literature, where the β-*O*-silyl tryptophan diastereomer **309** leads to C(2) bond formation upon treatment with a bromonium ion source, **309**→**310**,[38] Scheme 37. The C(3) spirocyclic butyrolactone product was desired for a synthesis project, and was expected based upon much precedent.[108] In contrast, the β-*O*-silyl diastereomer of **309** (not shown) does provide the butyrolactone product (C(3) bond formation) under the same conditions, although that diastereomer was not useful for the synthesis objective. This undesired regiochemical outcome with **309** can be corrected by turning to Pummerer chemistry, which forces C(3) bond formation in a tryptophan-derived substrate that bears the same erythro stereochemical relationship between C(α) and C(β). Exposure of sulfoxide **306** to Tf_2O leads to a single diastereomeric product, **308**, in modest yield. The stereochemical outcome can be rationalized by focusing on the steric interaction between the C(β) substituents and the *peri* positioned aryl hydrogen as indicated in **307**. The alternative transition state model would place the TBSO– group in steric conflict with the *peri* hydrogen, and presumably the energetic penalty associated with that A[1,3] interaction disfavors that option. The generally poorer yield of carboxylate C(3) cyclization[38] as compared to the C–C bond-forming cyclizations of Scheme 36 might be attributable to a mismatch between the soft



Scheme 37. Oxidative cyclizations of tryptophan derivatives: Pummerer chemistry versus bromonium ion initiation.

electrophile and the harder nucleophile oxygen compared with the alkene nucleophiles of Scheme 36.

Exploration of the scope of Pummerer-based oxidative activation of heteroaromatic species for C–C bond formation is just beginning. Along with the indole-based examples described above and the imidazole-based system featured in Scheme 11, furan and thiophene rings apparently participate in this chemistry with great ease,[109] Scheme 38. Kita's furan sulfoxide system **311** can be activated with trifluoroacetic anhydride to provide an electrophilic intermediate that is susceptible to nucleophilic capture by carbon nucleophiles like the β-dicarbonyl shown, or allyl tributylstannane.[109a] The Osaka group portrays this chemistry as proceeding through the vinylogous pathway, although there is no reason, a priori, to exclude the additive route at this time.

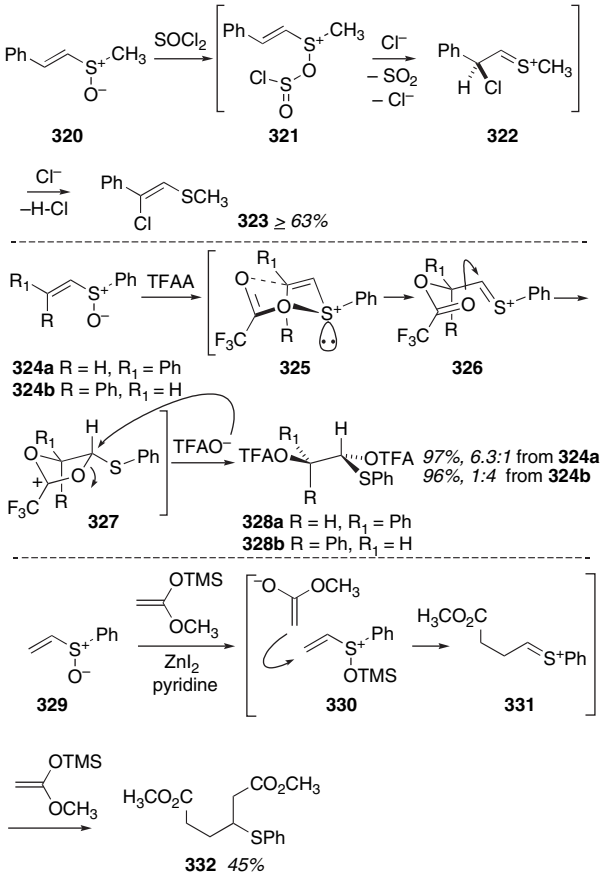


Scheme 38. Pummerer chemistry for functionalization of furan and thiophene rings.

A similar study by Padwa et al. exploited the nitrogen analogue of a sulfoxide, an *N*-tosyl sulfilimine, in a related transform.[109b] Furan, benzofuran and thiophene cores were examined with the Kita nucleophiles, and in all cases the reaction proceeded smoothly with clean C–C bond formation, as exemplified by the conversion of **318** into **319**. Since the nitrogen (or oxygen function) is lost upon Pummerer reaction and the overall yields are similar, the advantages of the sulfilimine system over the archetypal sulfoxide case remain to be established.

5.4.3. Alkenyl Pummerer substrates. Much of the alkenyl sulfoxide Pummerer chemistry that has been developed within the context of synthesis programs was designed to proceed through an additive pathway, as this process yields the largest increase in molecular complexity upon rearrangement/double nucleophile addition. The two nucleophiles that add to the α- and β-alkenyl sulfoxide positions, respectively, can be the same or different, and intramolecular variants add another level of control to the double addition sequencing. The discovery of the unsaturated sulfoxide/dichloroketene [3-atom+2-atom] butyrolactone annelation (cf. Scheme 35) by Marino served as the launch point for much of this chemistry, and several variations have seen use in natural products synthesis, vide infra.

The initial observation of alkenyl sulfoxide Pummerer chemistry germane to the additive process might be found in Russell's 1966 report on the consequences of treating vinyl sulfoxide **320** with thionyl chloride,[110] Scheme 39. The β-chlorovinyl sulfide product **323** plausibly arises from the beginning of the additive sequence **321**→**322**, but the process is interrupted by proton loss to form the alkene product **323**. This cryptic example of additive Pummerer chemistry was not appreciated as such at that time, but it did reveal that the alkene function of vinyl sulfoxides can be engaged in productive bond formation upon sulfoxide activation.



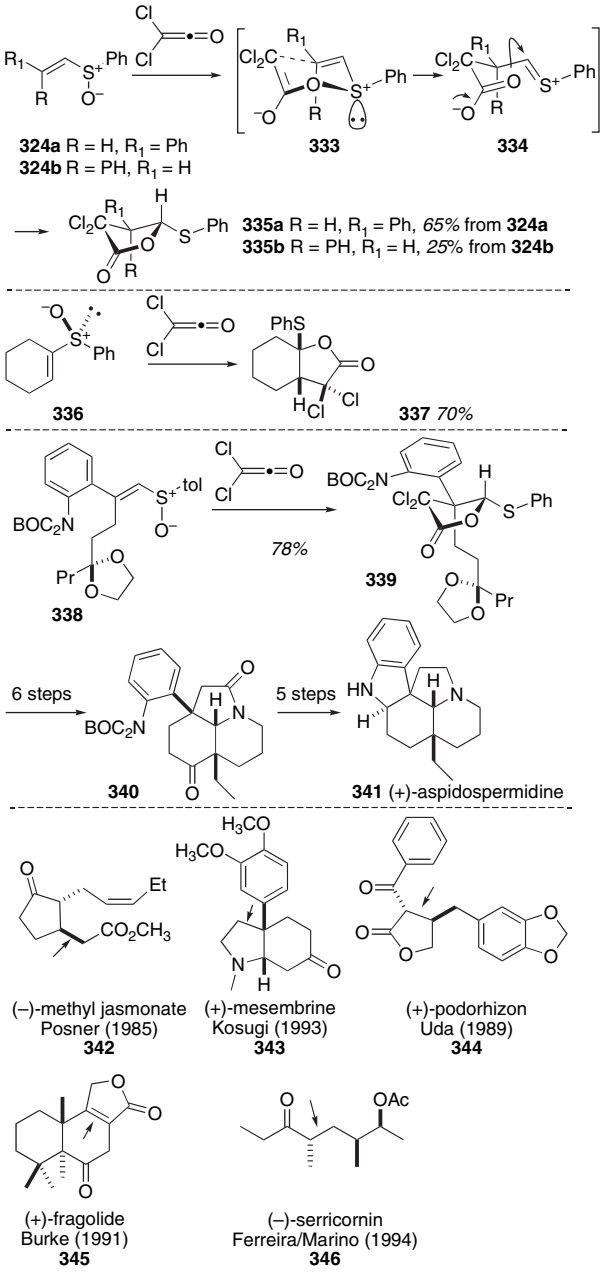
Scheme 39. Some early examples of additive Pummerer rearrangements on alkenyl sulfoxide substrates.

An example of double trifluoroacetate addition was described by Craig and Daniels,[111] **324**→**328**. Of particular interest is the observation that the different geometrical isomers of the starting alkene **324a/324b** furnish distinct and stereochemically opposite major and minor bis trifluoroacetate adducts **328a/328b**, respectively. Unfortunately, the relative stereochemistry of these adducts was not assigned, precluding any definitive mechanistic conclusions. Speculation can fill this gap, and it is possible to rationalize this conservation of stereochemical information by citing first a concerted [3,3]-sigmatropic shift within the intermediate sulfonium salt **325**, anchored by an equatorial phenyl substituent, to deliver the transient thionium ion **326**. In what

will become a common theme in the discussion of alkenyl sulfoxide Pummerer chemistry to follow, a mechanistic course for nucleophile addition that preserves the alkene's geometrical information now is required. Perhaps facile intramolecular cyclization of the pendant trifluoroacetate within **326** can fill this requirement. This transition state geometry modeled by **326** includes a Felkin–Ahn-type alignment of the σ^*_{C-O} and $\pi^*_{C=S(+)}$ orbitals, but also includes an unfavorable steric clash between the 'R' substituent and =S(+)Ph. When R=H (from the *E*-alkene precursor **324a**), no further convolutions are necessary to justify formation of a single stereoisomer. However, when R=Ph (from the *Z*-alkene precursor **324b**), there must be a reason why C–C bond rotation to exchange the positions of R and R_1 does not compete with direct nucleophilic addition, or the same stereoisomer that was formed from the *E*-alkene precursor would be formed here as well. The reason may be supplied by the relatively long C=S bond length, which could mitigate the severity of the Ph/=S(+)Ph steric interaction. This moderation of an otherwise significant steric clash could promote facile nucleophilic addition at a rate faster than bond rotation.

Kita et al. have documented that carbon-based nucleophiles can serve as effective components of the alkenyl sulfoxide additive Pummerer reaction,[112] **329→332**. The great benefit of using silyl ketene acetals as group transfer initiators is illustrated by this chemistry, as these species, almost uniquely, maintain compatibility with the requirements of sulfoxide electrophilic activation without themselves consuming the carbon-based nucleophile. The net result is formation of two new C–C bonds to adjacent carbons under exceedingly mild experimental conditions, a sequence of great potential value in synthesis.

An arguably transforming event in this area of Pummerer chemistry was supplied in a 1981 report by Marino and colleagues that details their alkenyl sulfoxide/dichloroketene cyclocondensation sequence, **324a/b→335a/b**,[113] Scheme 40. Similar to the Craig work, different geometric isomers of the alkenyl sulfoxide substrate lead predictably to distinct and mutually exclusive stereoisomers of product butyrolactone. The mechanistic picture of this transformation emerged over the course of several subsequent studies, and it features the [3,3]-sigmatropic shift/facile intramolecular cyclization sequence (**333→334→335**) discussed in detail earlier. In general, the yield improves when the dichloroketene is prepared by zinc-mediated reduction of trichloroacetyl chloride as compared to triethylamine-promoted dehydrohalogenation of $Cl_2CHCOCl$. Marino attributes this difference to the formation of the Bronsted acidic byproduct $Et_3N\cdot HCl$ in the latter case, which might consume intermediate anions **333/334** by protonation.[113] In addition, a beneficial role for the $ZnCl_2$ produced in the former process might be anticipated from the Kita work (ZnI_2-catalysis). The overall butyrolactone-forming reaction displays sufficient versatility and substrate scope to qualify as one of the more valuable [3-atom+2-atom] annelation procedures currently available. Extensions to chiral sulfoxide substrates might be expected to provide butyrolactone products with high levels of asymmetric induction, given the exquisitely organized transition states involved, and indeed this expectation is borne out experimentally, as illustrated by the conversion of **336→337** with complete control of absolute stereochemistry.[114]

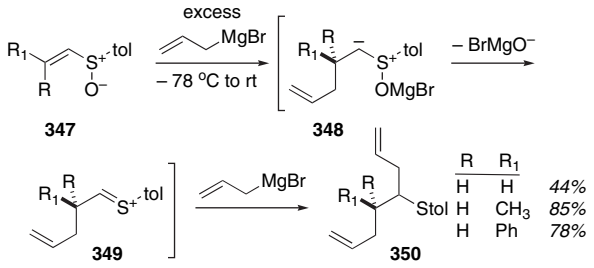


Scheme 40. Marino's butyrolactone annelation via an additive Pummerer rearrangement on alkenyl sulfoxide substrates.

The value of this reaction can be gauged by its impact in total synthesis endeavors. Marino's aspidospermidine synthesis **338→341** speaks to this point, as the readily available chiral sulfoxide **338** is converted to the chiral lactone **339** in good yield and with complete and predictable stereochemical fidelity.[115] This pivotal intermediate led to aspidospermidine in 11 further manipulations. The Marino chemistry was quickly adopted by several other researchers, who capitalized on the reliable chirality transfer of the Pummerer reaction to fix absolute stereochemistry in the lactone product as part of the syntheses of (−)-methyl jasmonate (**342**),[116] (+)-mesembrine (**343**),[117] (+)-podorhizon (**344**),[118] (+)-fragolide (**345**),[119] and (−)-serricornin (**346**).[120] The key C–C

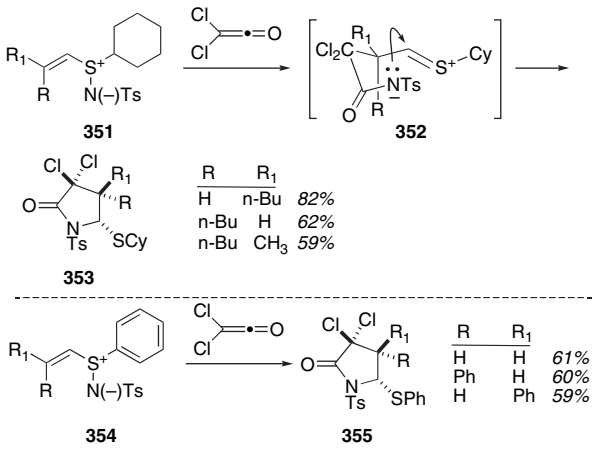
bond formed by the additive Pummerer reaction is indicated by an arrow in each structure. These total syntheses from the 1980s to 1990s cemented the value of this Pummerer-based transform in natural product synthesis by providing the first legitimate bridge between the original developmental/exploratory studies of additive Pummerer chemistry and the later applications phase of the field.

In 1991, Iwata described the observation of additive Pummerer chemistry when attempting to develop the 1,4-conjugate addition reaction of Grignard reagents and alkenyl sulfoxides,[121] Scheme 41. This chemistry emphasizes the doubly electrophilic character of the alkenyl sulfoxide synthon, and illustrates how the two very different electrophiles involved (vinyl sulfonium salt derived from **347** and thionium ion **349**) both are satisfactory partners for a Grignard reagent. No proton transfer/deprotonation products were reported with the acyclic substrates, but cyclohexenyl sulfoxides did provide substantial alkenyl sulfide byproducts. The sulfoxide activation by a magnesium Lewis acid in **348** is reminiscent of the later $Mg(N(i\text{-}Pr_2))_2$ Pummerer activation chemistry of Kobayashi (Scheme 8).



Scheme 41. Iwata's additive Pummerer rearrangement using the Lewis acid '$MgBr^{+}$' as an activator.

Recent extrapolations from the Marino butyrolactone synthesis have involved sulfilimine substrates applied to the analogous lactam construction, Scheme 42. Marino observed that a competition existed within the thionium ion intermediate **352** between N–C bond formation to provide the desired lactam **353**, and O–C bond formation to deliver a lactone imine byproduct.[122] An exploration of the effects of sulfur and nitrogen substituents on this partitioning led to the conclusions that (1) the electron donating or electron-withdrawing character of the nitrogen substituent does not affect the lactam/lactone imine ratio much, but (2) the product ratio was responsive to the electronic contributions of the sulfur moiety. The optimum substituent pairing appeared to be a tosyl unit on the nitrogen and a cyclohexyl group on the sulfur, and with this combination, ratios as high as 20:1 favoring the lactam were observed with no compromise in overall product yield. As with all of the other Marino-type [3-atom+2-atom] annelations, the geometric information in the starting alkene is accurately and predictably translated to product stereochemistry. At the same time, Padwa and colleagues pursued similar studies,[123] and the Emory group found that the *phenyl* substituted sulfilimines **354** performed comparably with the (saturated) *cyclohexyl* analogues of Marino, **354**→**355**. No discussion on the lactam/lactone imine dichotomy was presented in this work.



Scheme 42. Extension of Marino's dichloroketene–alkenyl sulfoxide Pummerer transform to sulfilimine analogues.

The more than two-dozen examples of unsaturated sulfoxide Pummerer chemistry presented in Section 5 are not comprehensive but are arguably representative of the scope of this area of chemistry. Taken collectively, they help to define the structural and experimental parameters that steer the transform down either the vinylogous or the additive path, but also reveal unresolved mechanistic aspects of this topic. Many systems fall into unambiguous territory where either (1) a lack of γ-protons or severe steric hindrance at the β-position excludes the vinylogous route, or (2) intramolecular delivery of the nucleophile from a sulfoxide oxygen attachment point guarantees that only the additive process can be accessed (e.g., Marino, Iwata, and Craig chemistry). The weight of evidence with arene sulfoxide derivatives points to a vinylogous pathway, perhaps reflecting the reluctance of a phenyl ring to suffer direct nucleophilic attack with the attendant loss of aromaticity (e.g., Kita and Padwa chemistry). The mechanistically unassigned cases mostly evolve from treating *heteroaryl* sulfoxides with activators/nucleophiles. In these cases, the loss of aromatic resonance energy via an additive process might not be so debilitating, while at the same time offering the prospect of proceeding through presumably lower energy singly cationic intermediates (cf. **302** vs **299**, and **312** vs **313**). This question has more than pedagogical interest, as opportunities for achieving asymmetric C–C bond formation from readily available unsaturated chiral sulfoxides may depend on the precise mechanistic course of the transformation.

6. Pummerer-initiated cascade cyclizations

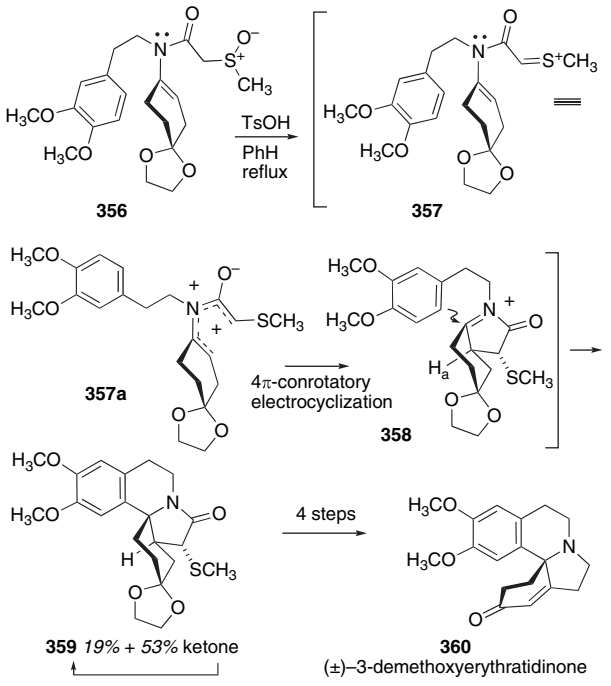
The development of Pummerer chemistry as an enabling technology for multi-part cascade sequences has ensured that this field will have a continuing impact on strategy-level synthesis design. Most of the recent thrusts in this burgeoning area have originated from Padwa and co-workers, and the promise implicit in their preliminary studies seems likely to fuel much additional research on this topic. At present, the Emory group has identified two different and distinct mechanistic venues to reduce this concept to practice: (1) using the Pummerer-generated thionium ion to initiate a cationic polyolefin cyclization, and (2) using the Pummerer-generated thionium ion to fashion a transient 4π electron component for [4π+2π] cycloaddition. Both approaches to cascade

chemistry require compatibility between the acidic/electrophilic Pummerer initiator and the remainder of the functionality that is incorporated to complete the multi-part sequence, and the remarkably high yields obtained (vide infra) attest to the clever substrate design and careful optimization that undergirds these efforts.

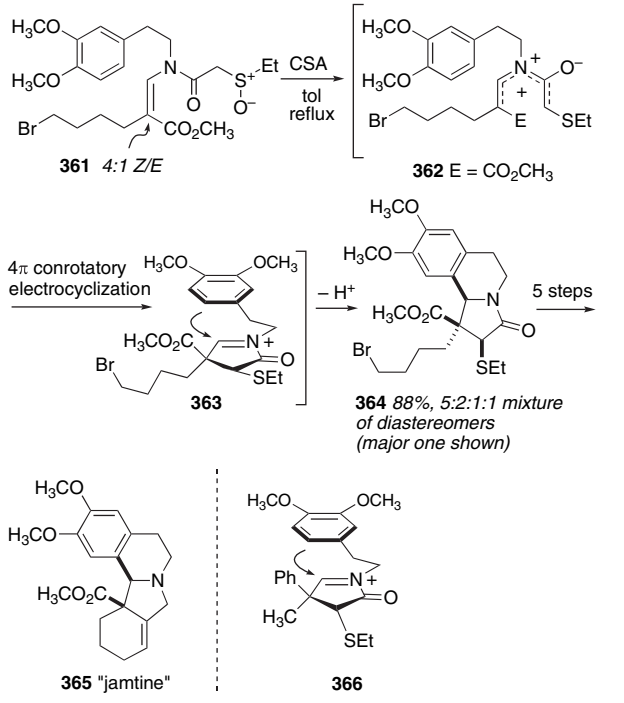
6.1. Cationic polyene-type cyclizations

The development of biomimetic cationic polyene cyclizations for terpenoid assembly, and later, the related iminium ion analogues for alkaloid preparation, have unarguably advanced the whole field of organic synthesis. The fact that Pummerer-derived thionium ions can contribute to this area preceded Padwa's work and was first recognized by Tamura and Ishibashi in the early 1980s,[124] Scheme 43. They developed this chemistry in the area of erythrina alkaloid synthesis, and eventually recorded a concise preparation of the representative member (±)-demethoxyerythratidinone (**360**).[124d] Initiation of the Pummerer sequence with β-carbonyl sulfoxide **356** and tosic acid led to the putative thionium ion **357**, which is faced with a choice: combine with the cyclohexenyl alkene (likely distorted from enamide resonance in the transition state for addition), or with the electron rich aryl appendage. Not surprisingly, five-membered ring closure is favored over seven-membered ring formation, although in preliminary model studies,[124a] a 7.5:1 ratio of the alkene-to-arene cyclization products was observed. The closure of **357** to **358** proceeded with exquisite control for strictly the *cis* cyclopentenone-iminium ion (H_a and SCH_3 *cis* in **358**), a level of stereoselectivity that might not have been anticipated on strictly steric/stereoelectronic grounds. However, Padwa has provided a retrospective explanation for this observation that cites the intervention of a 4π-conrotatory electrocyclization within **357a** to rationalize the result.[125a] The electrophilic iminium ion so derived is poised perfectly to capture the juxtaposed electron rich aryl ring and form the key quaternary C–C bond of the erythrina framework. Some of the ketal function was lost upon reaction, but its reinstallation and then further functional group manipulations led efficiently to the target. It is noteworthy that nothing was 'wasted' in this synthesis design, as the obligatory thioether residue resulting from the Pummerer process played a productive role as well: it served as an oxidation placeholder for the cyclohexene moiety of the final product.

Padwa and co-workers have executed a version of the Pummerer-initiated cationic cyclization cascade that bears some resemblance to the Tamura conceptualization, but in this case leads to a synthesis of the structure assigned to the polycyclic alkaloid jamtine (**365**),[125b,c] Scheme 44. Thus, an enamide **361** bearing the β-sulfoxide trigger was exposed to a Bronsted acid, leading to the 4π-electron pentadiene moiety within **362**. As with the Tamura/Ishibashi precedent, conrotatory cyclization within this unit provided the acyliminium electrophile of **363** with a cis stereochemical disposition between ester and thioether. Friedel–Crafts alkylation of the pendant electron rich arene completes the cascade to afford the tricyclic framework of jamtine, **364**, in excellent yield, as a mixture of diastereomers. The major isomer (shown) resulted from arene ring addition *syn* to the ester function, a preference that the Emory group attributed to steric effects. Available *A*-value data support this sterically based interpretation of stereoselectivity (ethyl=1.75, CO_2CH_3=1.27).[126] Curiously, a similar cyclization within the model substrate **366** led to a single product stereoisomer wherein the new Ar–C bond and the resident phenyl ring are *syn* disposed. Again, a reaction trajectory that minimizes steric hindrance was proposed to explain this observation,[125a] but in this instance the *A*-values (Ph=3.0, Et=1.75) do not appear to be consistent with this interpretation. Perhaps



Scheme 43. Ishibashi's synthesis of (±)-3-demethoxyerythratidinone by use of the Pummerer reaction to initiate a polyene cyclization.



Scheme 44. Padwa's synthesis of the structure assigned to the alkaloid jamtine by use of the Pummerer reaction to initiate a polyene cyclization.

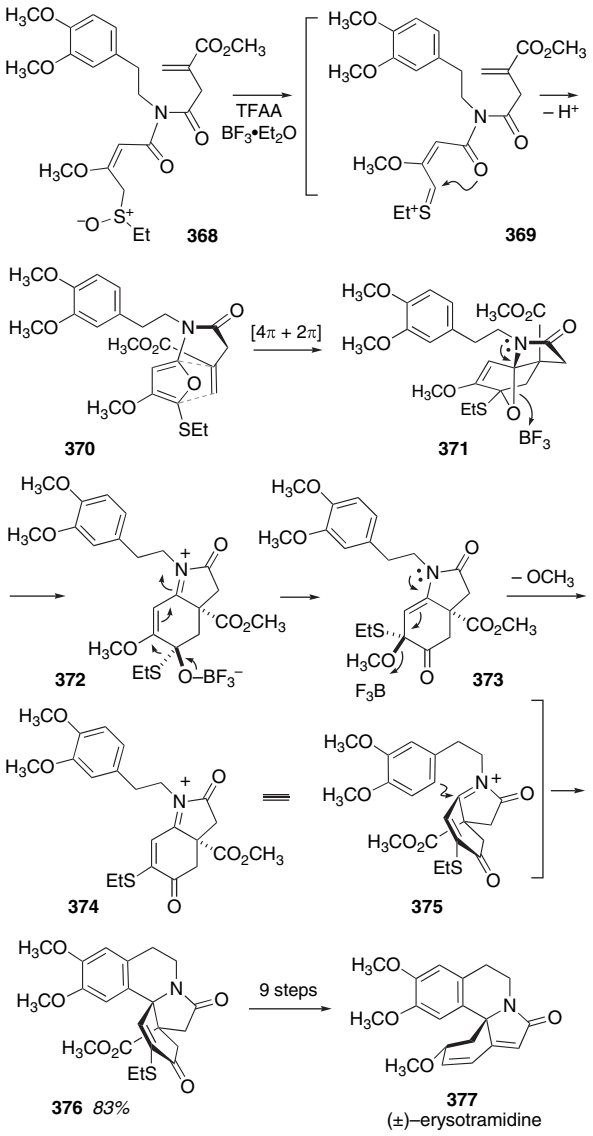
this dilemma can be resolved by noting that these *A*-values can be no more than imperfect measures of what is essentially a torsional (i.e., 1,2)-type interaction.

With tricycle **364** in hand, five additional steps were required to access compound **365**, the putative structure of jamtine. Unfortunately, a lack of congruence between the spectral data of the amine oxide derived from **365** and the natural product jamtine *N*-oxide raises doubts about the legitimacy of the original structural assignment.[125c] Nevertheless, Padwa's work and the earlier Ishibashi's chemistry begins to bring into focus the possibilities that Pummerer-initiated polyene cyclization has to offer natural products synthesis. Compatibility issues can be minimized with prudent substrate design, and the apparent participation of several stereochemical control elements raises the prospects for obtaining cyclization products with high levels of relative asymmetric induction.

6.2. Cationic cyclization–cycloaddition–fragmentation sequences

The redirection of Pummerer-initiated polyene cyclizations to a cycloaddition-mediated cascade could be accomplished by the expedient of replacing the central linchpin alkene with a carbonyl unit,[127] Scheme 45. In this scenario, the nascent thionium ion is captured by the carbonyl oxygen, leading to a five-membered oxygen-containing heterocycle bearing 4π electrons (e.g., furan or carbonyl ylide). This reactive unit then engages an appropriately situated 2π addend in intramolecular [4π+2π] cycloaddition. The cycloadducts so formed are designed to be labile and they readily convert to other structures of interest.

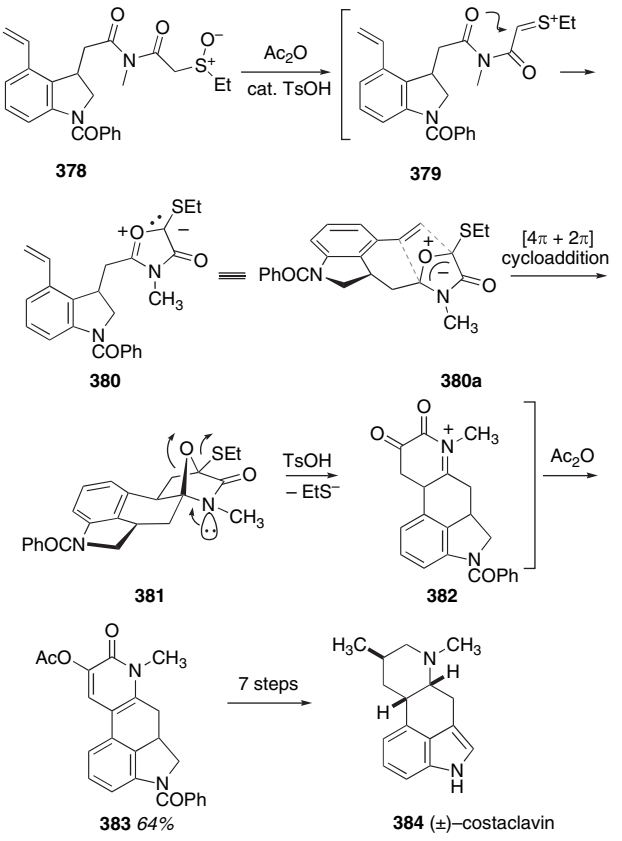
Padwa's construction of the erythrina alkaloid (±)-erysotramidine (**377**) exemplifies the application of this complex multi-step process to target directed synthesis.[127] In this reduction to practice, treatment of the imidosulfoxide **368** with the standard Pummerer initiator trifluoroacetic anhydride and the Lewis acid $BF_3\cdot Et_2O$ leads to the expected thionium ion-containing species **369**, which is poised to cyclize into the adjacent imide carbonyl. This cyclization delivers an intermediate electron rich furan ring following loss of a proton. The proximity of an activated alkene dienophile encourages facile Diels–Alder-type [4π+2π] cycloaddition to forge a short-lived oxonorbornane product **371**. At this point in the mechanistic speculation, the Lewis acid's role becomes prominent. The electrophilic boron presumably triggers rupture of the strained bicyclic system with an assist from the amide's stereoelectronically aligned lone pair, and an intermediate iminium ion **372** is generated. A pinacol-type shift within this species fashions a transient mixed ketal **373**, which suffers loss of methoxide to regenerate the iminium ion. The loss of the oxygen bearing nucleofuge rather than the sulfur-containing alternative might be traced to the oxophilicity of the BF_3 available to assist in this process. Finally, an iminium ion electrophile that lacks a facile decomposition pathway is accessed, and this species can now trap the tethered arene ring in a transformation that is reminiscent of Ishibashi's final erythrina alkaloid closure to deliver the tetracyclic product **376** in an astonishing 83% yield for a seven-step sequence that features the formation of three new C–C bonds. Support for this mechanistic hypothesis



Scheme 45. Padwa's synthesis of an erythrina alkaloid via a Pummerer-initiated cyclization/cycloaddition/cyclization cascade sequence.

can be found in the isolation of a water-trapped adduct of iminium ion **374**, and its further conversion into **376** under $BF_3\cdot Et_2O$ treatment.

A variation of this theme[128] was developed for the synthesis of the ergot alkaloid (±)-costaclavin (**384**),[128c] Scheme 46. In this study, the Pummerer sequence begins by treatment of the imidosulfoxide **378** with acetic anhydride to provide the anticipated thionium ion in **379**. As with the erysotramidine work, cyclization into the adjacent imide carbonyl quenches the sulfur-stabilized carbocation and furnishes a five-membered ring oxoheterocycle bearing 4π electrons. In this manifestation of the cycloaddition partner, however, the 4π-system is expressed as an isomünchnone dipole **380**. Deployment of the requisite 2π electron addend at C(4) of the indoline framework ensures that facile cycloaddition can be achieved, and the pentacyclic product **381** is formed as a transient intermediate. The stereochemical course of this cycloaddition has not been elucidated, and the formulation of **381** as an *endo* adduct is based strictly on mechanistic grounds and limited precedent,[128b] and is



Scheme 46. A Pummerer-initiated cyclization–cycloaddition–fragmentation sequence developed by Padwa for the synthesis of (±)-costaclavin.

offered only as a convenience. As with the erythrina alkaloid synthesis, the bicylo[2.2.1]heptane's inherent strain and favorable stereoelectronic overlap between the oxo bridge and the nitrogen's lone pair converge to promote facile C–O bond scission, possibly assisted by the strong Bronsted acid TsOH present. Acylation of the derived enol formed from tautomerization within **382** then delivers the observed product tetracycle **383** in excellent yield for the putative six-step sequence. This intermediate can be processed on to the target (±)-costaclavin (**384**) in seven additional steps. These seminal examples of cation-initiated cyclization–cycloaddition–fragmentation cascade sequences for rapid assembly of polycyclic materials from simple precursors demonstrate some of the power of Pummerer chemistry to impact on complex molecule synthesis. The merging of strong electrophile chemistry with the essentially orthogonal reactivity found in cycloadditions raises all types of compatibility issues, but the unique aspect of the Pummerer reaction, the generation of a reactive carbon electrophile under exceedingly mild conditions, provides the means to overcome or avoid many potential pitfalls that could be envisioned. Furthermore, these types of cascade sequences, with their obvious benefits for efficiency in synthesis, are likely to come into even greater prominence as more opportunities to link Pummerer chemistry with other types of downstream reactions are identified and then implemented.

7. Conclusion and perspectives

The arc of the Pummerer story is far from complete. While this chemistry lay dormant for nearly a half-century, the explosion of recent activity has more than compensated for the slow start. It is difficult to identify one transforming incident that catapulted this reaction to the fore, but rather the field seemed to benefit from the convergence of three historical events in the late 1950s–1960s: (1) the official 'naming' of the reaction by Horner and Kaiser, (2) the illuminating mechanistic studies by Oae, Russell, and others, and (3) the emergence of the new field of 'natural products synthesis', with its requirements for effective transforms on complex, highly functionalized substrates. The recognition that the Pummerer reaction can provide useful carbocationic intermediates under mild and essentially neutral or even slightly basic conditions opened up whole new opportunities for designing synthesis strategies that formed C–X bonds between carbon electrophiles and a wide range of nucleophiles with a high degree of chemoselectivity. Further developments in the areas of initiator chemistry, substrate scope and compatibilities, and linked, multi-part reaction sequences have continued to add to the value of the transformation. The future looks very bright, as advances in each of these areas might be merged in unforeseen ways to expand the scope, and hence, the impact, of the Pummerer reaction.

It is interesting to speculate what Pummerer might have thought about the vibrant and influential field of organic chemistry that has evolved from his (and his contemporary's) modest initial reports on sulfoxide decomposition. Over the course of his academic lifespan, this chemistry gained little traction. Almost no follow-up work appeared in the literature, perhaps (falsely!) corroborating a sense that the transform was little more than a curiosity of limited interest. Would he have been amazed, or perhaps would he feel a sense of vindication, a time-lapsed "I told you so?"

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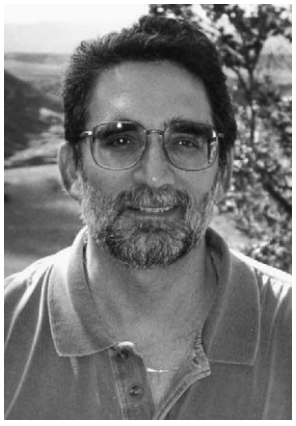
Biographical sketch



Ken Feldman was born and raised in Miami Beach, Florida. In 1978, he obtained his B.S. degree in chemistry while exploring the *ipso* nitration reaction of substituted aromatics in Philip Myhre's lab at Harvey Mudd College. His Ph.D. work at Stanford University with E.E. van Tamelen focused on biomimetic syntheses of marine and terrestrial natural products. After a yearlong stint as a postdoctoral fellow at Dupont, he joined the faculty of the Chemistry Department at Penn State as an Assistant Professor in 1984, where he currently holds the rank of Professor. His research interests include the total synthesis of natural products via Pummerer chemistry, the development of azatrimethylenemethane diyl reactions for alkaloid synthesis, and biological mechanism-of-action studies for the kinamycin family of diazo-containing antibacterial and anticancer terrestrial and marine metabolites.