Evolving Organic Synthesis Fostered by the Pluripotent Phenylsulfone Moiety

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1. Introduction

1.1. Reviewer Philosophy

A comprehensive program for the synthesis of natural (or unnatural) products is analogous to the construction of a pyramid. Careful planning followed by installation of numerous levels of support are required to complete the edifice. Specific "cornerstone" strategies are typically major motivations for undertaking the program. Finally, the venture reflects the desire of the research team to construct a lasting monument to their creativity and hard work (Figure 1).

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Ahmad El-Awa graduated from Cairo University (Cairo, Egypt) in 1999 with a Bachelor's degree in pharmaceutical sciences. From 1999 to 2001, he finished his compulsory military service and briefly worked as a hospital pharmacist and chemistry teaching assistant at Cairo university. He joined Purdue University's chemistry graduate program in 2002 and completed his Ph.D. under the supervision of Philip Fuchs in 2007. The title of his thesis was: Asymmetric synthesis of dipropionate stereotetrads and application towards the total synthesis of Aplyronine A. He is currently a senior research scientist in the chemical development department of AMRI.

Mohammad N. Noshi was born in Alexandria, Egypt, in 1975. He earned his Bachelor's degree in pharmaceutical sciences in 1998 from the school of Pharmacy, Cairo University, where he graduated with honors. He practiced his career as a pharmacist for two years in Seif-Pharmacies, where he worked as the pharmacist in charge. In 2004, he earned his M.Sc. in Medicinal Chemistry from the University of Toledo, Ohio, under the supervision of Prof. P. W. Erhardt. His research involved the design/synthesis of some peptides/peptidomimetics to inhibit an enzyme overexpressed in prostate cancer. He then pursued his Ph.D. studies in organic chemistry at Purdue University,where he joined Prof. P. L. Fuchs' laboratory in the fall of 2003. Since then, he has been working on the total synthesis of the marine anticancer agent, aplyronine A. During his research, he developed a novel synthetic transformation, vinylsulfone to vinylphosphonate transposition. He also developed a new process for large-scale (multidecagram) synthesis of aplyronine A key intermediates that avoids chromatography.

1.2. Attributes of the Phenylsulfone Functional Group[1]

The following are attributes of the phenylsulfone functional group:

• Economical and stable functionality (often crystalline) facilitates purification.

Xavier Mollat du Jourdin was born in Paris, France, in 1980. He received his education in medical and biological sciences from the medical school of Necker Paris V, France, and the University of Versailles Saint Quentin-en-Yvelines, France, where he obtained a D.E.U.G. in biology in 2001. He then spent three years at the school of chemistry of Lyon, CPE, France, where he earned his M.Sc. in organic chemistry/chemical engineering. In 2003, he joined the research group of Professor Philip L. Fuchs at Purdue University where he is currently completing his Ph.D. His research is focused on the synthesis of polyketides via vinyl sulfone chemistry and SAR studies of anticancer agent (+)-Discodermolide.

• UV chromophore of the aryl sulfone allows easy reaction monitoring by thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC).
• Hard anions undergo conjugate-addition to vinyl sulfones without competitive 1,2-addition.
• The strong inductive effect of a sulfone moiety acidifies the γ-position of vinyl sulfones.
• Vinyl sulfones undergo ready base-catalyzed equilibration to allyl sulfones.
• Steric demand of *achiral* tetrahedral sulfone moiety imparts high diasteromeric excess (de) and enantiomeric excess (ee).
• Oxidative cleavage of cyclic vinyl sulfones provides termini-differentiated acyclic segments.
• *Leaving-group ability of sulfinate anion ($\sim 10^{-3}$ vs Cl) provides an almost unique (but specifically limited) added dimension to sulfone functionality.*[2]

1.3. Scope of the Review

The synthetic power of the sulfone functional group has been substantially upgraded over the past 25 years. Previous seminal reviews have been provided by Magnus, Simpkins, Padwa, Bäckvall, Najera, and Yus; Vogel, Cossy, Plumet, and Arjona; and Hassner, Zard, Back, Wicha, and Prilezhaeva.[3] In order to restrict the topic to a manageable level, the primary organizational focus of this review will relate mainly to *conjugate additions to cyclic vinyl sulfones*. However, before engaging the main topic, it is crucial to highlight the less appreciated attribute of the phenylsulfone moiety—its use as a leaving group. While an attempt has been made to document the breadth of this subtopic, many sections only describe one or two examples of a specific transformation.

In 1971, Colter and Miller demonstrated that E_2 elimination of 2-pentyl phenylsulfone **1** afforded alkenes when heated in pyridine or ethylene glycol.[2] More recently, Jenks provided mechanistic information that showed that the intramolecular *syn*-elimination of aryl sulfone **3** requires exceptionally forcing conditions[4] compared to the same reaction of aryl sulfoxide **2**. This compares rather poorly with the well-known sulfoxide pyrolysis, which proceeds under

Philip Fuchs' grade-school education took place in a four-room elementary school in Nashotah, Wisconsin (pop. 237). In 1959, eighth-grade graduation saw the stage decorated in a scientific theme complete with a Fuchs-built Boron atom, foreshadowing both his interest in chemistry and his ultimate university. Fuchs' secondary education took place in Hartland, Wisconsin. At the end of his sophomore year, Fuchs and another student renovated an old one-room building. At the end of that summer, Willow Brook Laboratory, WBL, complete with epoxy-top laboratory benches and a homemade fume hood. During the next two years, the neophyte chemists performed reactions from the literature of organic and inorganic synthesis. Fuchs then attended the University of Wisconsin at Madison and continued summer projects at WBL. WBL sold reagents to Aldrich Chemical Co. in Milwaukee and eventually advertised its chemicals on the back page of the *Journal of the American Chemical Society*. After graduation, Fuchs stayed at UW, beginning graduate studies with Edwin Vedejs in 1968. In the summer of 1971, he received his degree as Vedejs' first Ph.D. and moved to Harvard for a two-year postdoctoral fellowship with E. J. Corey.

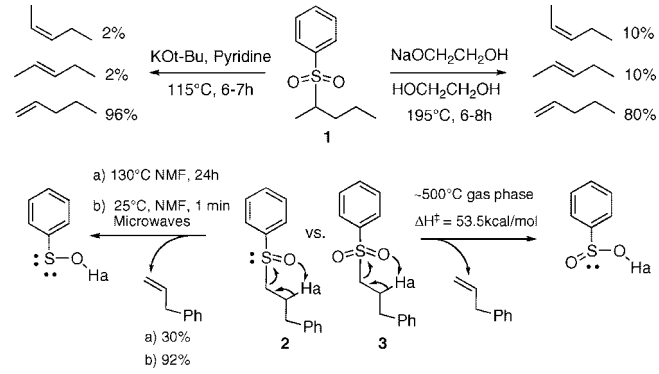
Fuchs has been on the Purdue faculty since 1973, and is the current R. B. Wetherill Professor of Chemistry, with 230 papers published and 62 Ph.D.s granted. His awards and honors include an Eli Lilly young faculty fellowship (1975), an Alfred P. Sloan fellowship (1977), a Pioneer in Laboratory Robotics award (1986), a Martin teaching award (1991), and being voted by the students as one of Top 10 Teachers in School of Science at Purdue (1991, 1993, 1995, 1996). He earned Purdue's highest scientific award, the McCoy Research award in 2003. Fuchs has consulted for Pfizer and Eli Lilly and has served on the editorial board of the *Journal of Organic Chemistry*. Since 2003, Fuchs has been an executive editor for the John Wiley Encyclopedia of Organic Reagents (EROS).

milder conditions and has recently been shown to be vastly improved using microwave heating (Scheme 1).[5]

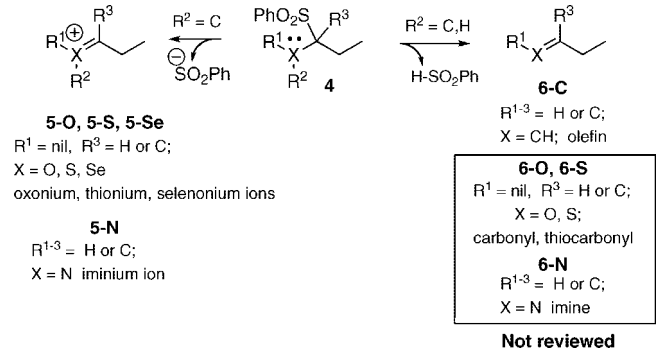
As outlined in the attributes section, the leaving-group ability of the phenylsulfone facilitates a diverse array of synthetic operations, strongly enhancing overall synthetic efficiency. The strong inductive ability of the sulfone group both potentiates the dipolar character of vinyl sulfones and inductively weakens the S−C σ-bond of sp^3-hybridized

Figure 1. Establishing the synthetic pyramid as viewed by the research director. Artwork by artist Ed Blackwell. Scanned image copyright 2009 Philip L. Fuchs.

Scheme 1



Scheme 2



substrates. This latter attribute enables ready access to oxonium, thionium, selenonium, and iminium ion intermediates (**5-O**, **5-S**, **5-Se**, **5-N**) by anchimeric assistance of adjacent heteroatom lone pairs (**4**, Scheme 2). A second reaction that figures prominently in this review is the 1,2-elimination of phenylsulfinic acid to generate alkenes **6-C**. However, the parallel chemistry to afford the *neutral* carbonyls, thiocarbonyls,[6] and imines[7] (**6-O**, **6-S**, **6-N**) will only include a few leading references.

2. Phenylsulfone, a Chemical Chameleon and Nearly Ideal Functional Group

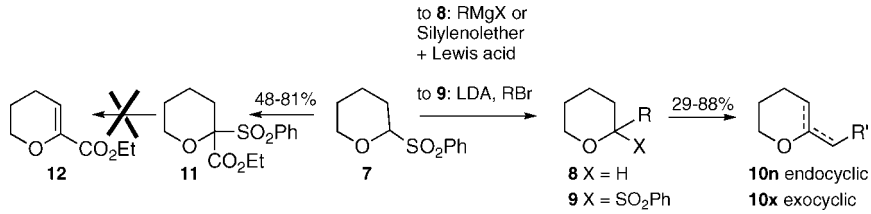
2.1. Alpha-Heteroatom Assisted Expulsion of Phenylsulfinic Acid

2.1.1. Oxygen-Assisted Loss of Phenylsulfinic Acid

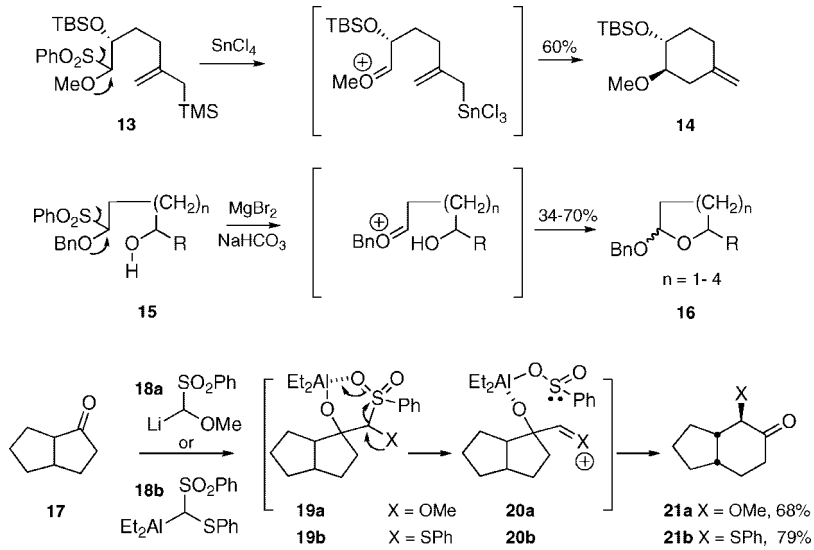
Lone-pair assistance of a proximal heteroatom serves to facilitate departure of sulfinate by scission of the C−S bond. Termed a "chemical chameleon" by Trost,[8] the sulfone may be exploited to great effect under well-defined circumstances. Several reactions from the seminal work of Ley's research group serve to introduce this subject.[9] For example, metalation and alkylation of sulfone **7** affords tertiary α-alkoxysulfones **9**, which readily (often spontaneously) eject phenylsulfinic acid to generate alkylated endocyclic dihydropyrans **10n**. If the side chain of **9** bears a functional group capable of activating the exocyclic C−H bond, (**8**, R = vinyl), exocyclic alkenes **10x** may be obtained (Scheme 3). More highly functionalized substrates were employed to great advantage by Ley to achieve the total syntheses of Avermectin B1a, Milbemycin B1, and okadaic acid.[10] This pyran-based methodology[11] has also been used effectively for the synthesis of furan,[12] butyrolactone,[13] and oxepane[14] intermediates.

Oxonium ions generated from α-alkoxy sulfones have been employed by Ley and Craig as electrophiles in intramolecular

Scheme 3



Scheme 4



C- and O-alkylation reactions.[15] Treatment of sulfone **13** with tin[IV] chloride affords Rapamycin fragment **14**, presumably by the participation of the transmetalated allylic stannane intermediate. In a similar fashion, cyclization of oxonium ions generated from **15** delivers a range of protected hemiacetals **16**. Trost[8] has provided a pinacol-type ring expansion of α-heteroatom (O, S) phenyl sulfones **18a**,**b**. These intermediates undergo rearrangement to α-substituted ketones **21a**,**b** (Scheme 4). Further recent investigation of this pinacol strategy by Taylor reveals that use of zirconium[IV] catalysis delivers a versatile method for one-carbon ring expansion.[9,16]

Noteworthy extensions using α-alkoxy sulfones as precursors to oxonium ions include the preparation of deoxyartemisinin analogues **22**,[17] bridgehead methylation of **24**, a precursor of the GHIJLKM segment **25** of ciguatoxin,[18] and a fiendishly clever sequence for intermediate **30** in the A. B. Smith III synthesis of phorboxazole A (Scheme 5).[19] The latter example exploited coupling the α-halo Grignard reagent **27** with metalated sulfone **26** to provide intermediate **28**. As shown for the parent reaction by Julia,[20] α-alkoxysulfone **28** suffers smooth 1,2-elimination to afford a near-quantitative yield of exoalkylidene-substituted 1,3-dioxane **29**. In this instance, both the alkene diastereomers of **29** converge by Ferrier rearrangement with dimethylaluminum chloride to the targeted ketone **30** in 91% yield.[19]

A final innovation is found in the Ley synthesis of okadaic acid.[10] An *ortho*-methoxy group is used in **31** to enhance the leaving-group ability of the aluminum arylsulfinate by chelation to the acetylenic alane intermediate, resulting in a 70% yield of adduct **32** (Scheme 5).

The α-epoxysulfone moiety **34** is an α-alkoxysulfone capable of serving as an α-keto carbenium ion synthon **37**.[21] Synthesis of this functional group was first achieved by nucleophilic epoxidation of acyclic vinyl sulfones **33**.[22] The stereochemistry of the process is dependent upon the leaving-group ability of the oxidant; with hydrogen peroxide and *t*-butyl hydroperoxide affording the thermodynamic *trans* adducts from *cis*-vinyl sulfones and peracids and hypochlorite giving α-epoxy sulfones of retained configuration.[23] Derivatives of **34b** bearing oxygen functionality in the β'- or γ-positions may often be epoxidized with exceptional selectivity (Scheme 6).[24]

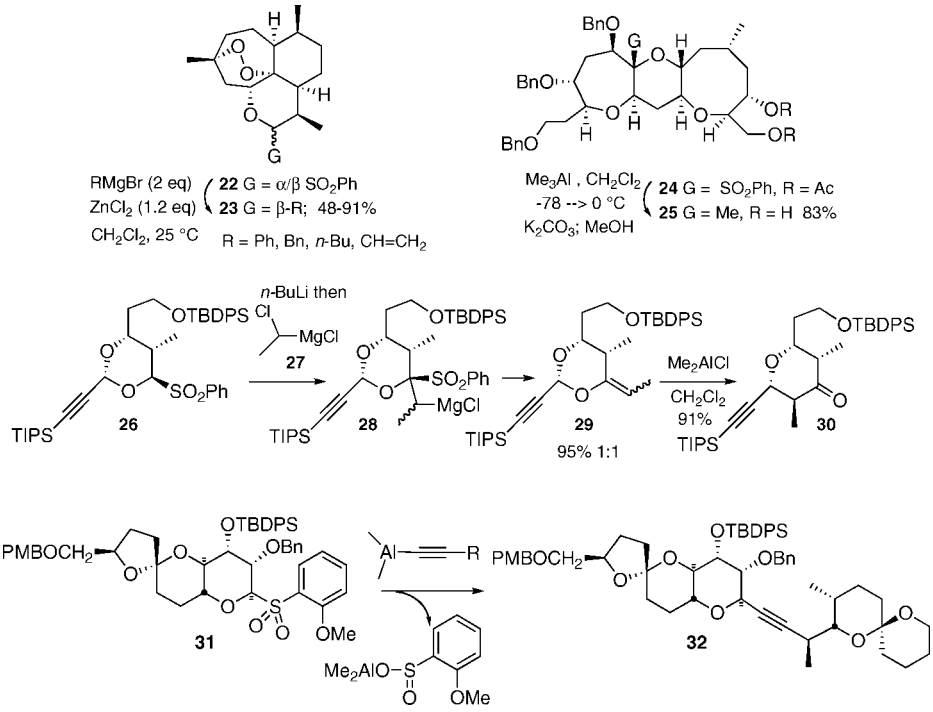
An alternate synthesis of α-epoxy sulfones from addition of α-halosulfone anions **36** to aldehydes and ketones proceeds by a Darzens-type intermediate **35**.[25] An enantiopure alkaloid phase-transfer catalyst has been employed for enantioselective preparation of acyclic α-epoxy sulfones **34a** with ee's up to 81%.[26]

Examples of reactions exploiting α-keto carbenium ion synthon **37** involve transformation of **34a**,**b** to α-substituted aldehydes and ketones and include electrophilic capture of azide, halide, hydroxide, mercaptide, and phosphite.[27] The latter example enables preparation of β-keto phosphonates while avoiding formation of enol phosphonates, a common problem with phosphorylation of α-haloketones.[28] Arjona and Plumet have combined stereoselective vinyl sulfone epoxidation with the α-keto carbenium ion chemistry to prepare a series of intricate cyclohexane derivatives.[29]

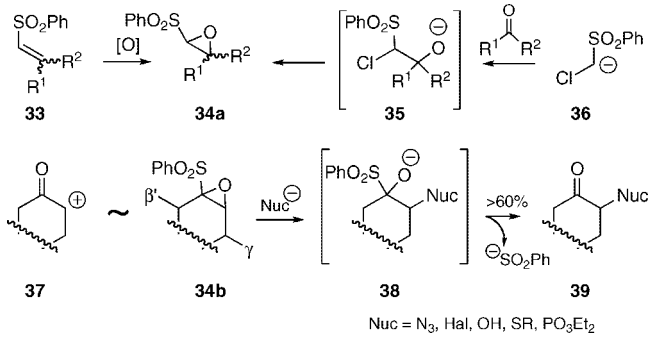
α-Epoxy sulfones are versatile functional groups. Metalation of **34a** at low temperature affords anion **40**,[30] which undergoes efficient reactions with silicon, sulfur, and carbon electrophiles. The trimethylsilyl- (**42**) and alkylthio-substituted (**44**) materials provide ready access to α-haloacyl silanes **41** and α-halothiol esters **43** (Scheme 7).[30]

Arjona, Menchaca, and Plumet have provided an important new protocol for elimination of α-epoxy sulfones to enones. The need for this reaction was revealed in a synthesis where

Scheme 5



Scheme 6

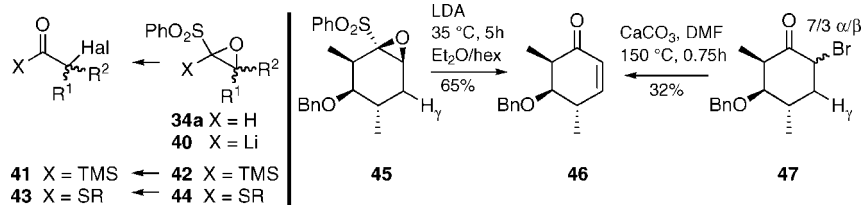


conversion of **45** to α-bromoketone **47** was accomplished in 85% yield, but the subsequent elimination of **47** to enone **46** could only be realized in 32% yield. Thus, direct metalation of **45** in ether−hexane (tetrahydrofuran (THF) fails) provided the requisite enone **46** in a very respectable yield of 65% (Scheme 7).[31]

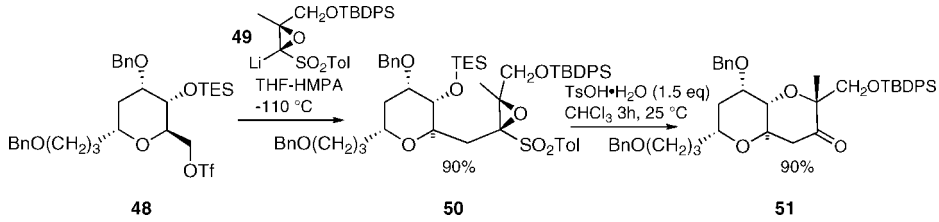
Using the metalation−alkylation chemistry described in Scheme 7, the group of Mori has extensively studied the use of metalated α-epoxy sulfones analogous to **40** for alkylation of appropriately functionalized iodides and triflates. This study was part of a well-conceived intramolecular alcohol alkylation strategy for the synthesis of five- and six-membered endocyclic α-alkoxy ketones.[32] Of particular significance is the reiterative implementation of the Mori chemistry for elaboration of the backbone of hemibrevetoxin B.[33] For example, treatment of triflate **48** (derived from triacetoxy D-glucal in 10 steps) with α-metalated epoxysulfone **49** provided key intermediate **50**, which suffered smooth acid-catalyzed 6-*endo*-cyclization, giving **51** in >80% yield. As is nicely shown in this work, the resultant ketone **51** is easily transformed to another silyloxy triflate appropriate for annulation of subsequent pyran rings of the complex ladder toxin Hemibrevetoxin B (Scheme 8).

Vinylogous α-alkoxy sulfones are also well-suited for lone-pair assisted activation of the phenylsulfinate leaving

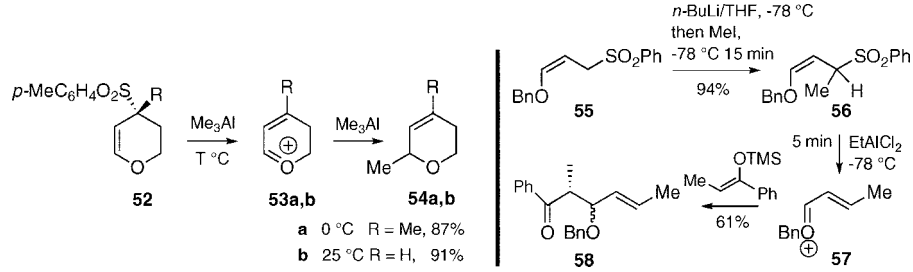
Scheme 7



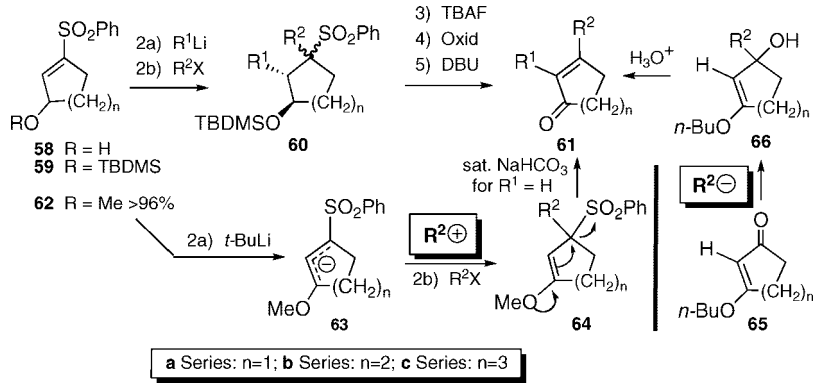
Scheme 8



Scheme 9



Scheme 10



group. Examples of such reactions with cyclic **52** and acyclic substrates **55** have been published from the laboratories of Craig[34] and Trost[35] (Scheme 9).

Conrad reported employing γ-silyloxy vinylsulfones **59** as substrates to achieve the syntheses of α,β-disubstituted enones **61** in 1978 (Scheme 10).[36] A limitation of this strategy existed with respect to the synthesis of β-substituted enones bearing hydrogen in the α-position (**61**, R^1 = H). Jin convincingly solved this problem in 1994 with a one-pot sequence starting from γ-methoxy vinyl sulfones **62b**−**c**, prepared, in turn, by *O*-alkylation of γ-hydroxy vinyl sulfones **58a**−**c**.[37] Metalation (to **63**), *C*-alkylation, and finally hydrolysis of **64b**−**c** provided six- and seven-membered ring enones **61b**,**c** in nearly quantitative yields.[38] As in Schemes 3−5, *the key reaction in Scheme 10* (**64** → **61**) *features the (vinylogous) oxygen-assisted loss of phenylsulfinate*. This procedure, which delivers R^2 as an electrophile (including unactivated primary and secondary halides, S, Se, Si, acyl, and RCHO), is the charge-inverted complement to the classic method of nucleophilic addition of R^2 to vinylogous ester **65**, followed by hydrolysis of vinylogous hemiacetal **66** to enone **61** (Scheme 10).[39]

Evarts and Torres provided the next upgrade of sulfone-based enone syntheses in 2002.[40] As originally demonstrated by Saddler in 1981 in the racemic cyclohexyl series,[41] enantiopure six- and seven-membered ring epoxyvinyl sulfones **66a**,**b** (>98% ee; now available on the mole scale;[42] see section 4.2) react with copper and aluminum reagents to regio- and stereoselectively effect smooth "Lawton"[43] reactions (S_N2' addition to a polarized allylic system[44]) to afford alkylated *trans*-γ-hydroxy vinyl sulfones **67a** and **67b** in very high yield. *O*-methylation of **67a**,**b** provided enantiopure methyl ethers **68a**,**b**, which are substituted analogues of compound **62** (Scheme 10). In comparison to γ-silyloxy vinyl sulfones **59**, which only undergo conjugate addition with *t*-BuLi (Scheme 10), methyl ethers **68a**,**b** are selectively deprotonated in the γ-position by low-temperature treatment with *t*-BuLi. The resulting allylsulfonyl anions **69a**,**b** react with electrophiles adjacent to the sulfonyl moiety to deliver the vinylogously activated sulfones **70a**,**b**, ready for hydrolysis to enones **71a**,**b** (Scheme 11).

Further extension of this concept is possible by 1,4-elimination of epoxyvinyl sulfones **66b** by removal of the allylically activated γ-hydrogen by base. This provides an intermediate that can be directly silylated to enantiopure dienylsulfone **72**.[45] Reaction of **72** with methyllithium followed by aqueous workup gives allyl sulfone **73**, which may be epoxidized to **74**. Elimination (to **75**), *O*-methylation (to **76**), followed by metalation and *C*-methylation yields enone **77** after hydrolysis (Scheme 11).[46]

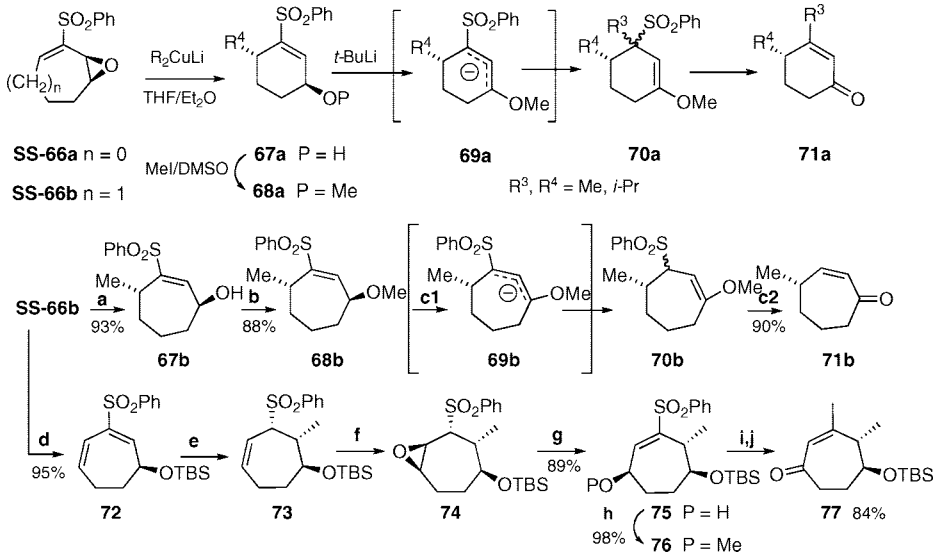
A final example of the vinylogous oxygen-assisted reaction is seen in the efficient, triply convergent prostaglandin E_2 synthesis of Donaldson in 1981.[47] The key C-8 oxime **81** was prepared by Mattox−Kendall[48] elimination of phenylsulfinate from α-sulfonyl oxime **79** followed by conjugate reduction of vinyl nitroso intermediate **80** by borohydride. Deprotection of **81** gave nearly 7 g of enantiopure PGE_2 (Scheme 12).

2.1.2. Sulfur- and Selenium-Assisted Loss of Phenylsulfinic Acid

Sulfones that bear an α-sulfide (or far less commonly, an α-selenide) moiety also experience lone-pair assistance to eject the proximal phenylsulfinic acid residue. For example, Simpkins compared the aluminum[III]-promoted allylation of selenide **82** with sulfide **83**.[49] In the same study, intramolecular Friedel−Crafts-type cyclization of selenonium and thionium ions derived from **86** and **87** suffer smooth cyclization to chlorocyclohexanes **88** and **89** (Scheme 13).

The use of α-thiomethyl sulfone anion **91a** as an acyl-anion synthon was reported by Kotake in 1983.[50] Treatment of the adduct with copper[II] chloride and silica effected hydrolytic release of the carbonyl group by an intermediate thionium ion. Application of the concept by Ley involved addition of α-thiophenylsulfonyl anion **91b** to epoxide **90**

Scheme 11a−j



[a] MeCu (cat), $AlMe_3$, THF, Et_2O, −78 °C, 2 h.

[b] MeI (10 equiv), KOH, DMSO, 5 °C, 15 min.

[c.1] *t*-BuLi, THF, −78 °C, 10 min.

[c.2] Et_3N, THF, H_2O, 3 d.

[d] LiHMDS, THF, −78 °C, 30 min; add TBSCl, warm.

[e] MeLi, THF, −78 °C, 0.5 h.

[f] 2.5 equiv mCPBA, CH_2Cl_2, 24 h, 25 °C.

[g] DBU, THF reflux, 18 h.

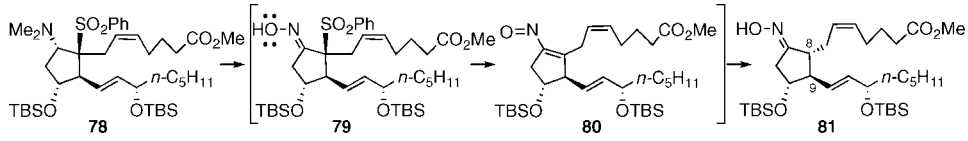
[h] MeI (10 equiv), KOH, DMSO, 5 min.

[i.1] *t*-BuLi, THF −78 °C, 10 min.

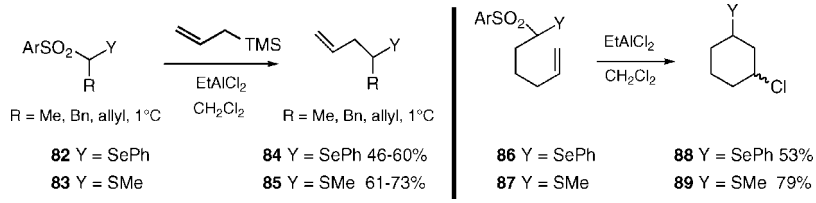
[i.2] MeI, warm to 25 °C, 15 min.

[j] SiO_2, $CHCl_3$, 6 h, 25 °C.

Scheme 12



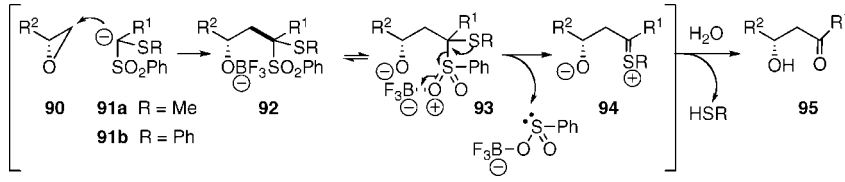
Scheme 13



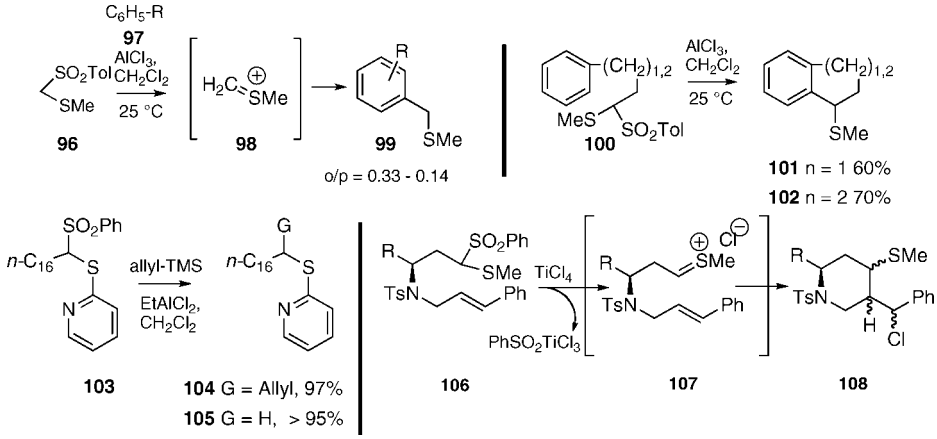
to ultimately deliver Rapamycin fragment **95** after boron trifluoride-mediated generation of thionium ion **94** (Scheme 14).[15]

Additional examples of the value of thionium ion intermediates are seen in the work of Ikegami, who employed sulfone **96** as progenitor of the parent methylthionium ion **98** for thiomethylation of arenes and hetarenes.[51] This study also demonstrated an intramolecular variant of the same reaction for the benzannulation of five- and six-membered ring benzylic sulfides **100**. A result from Barton and Zard employing the thiopyridyl sulfide−sulfone **103** validates the pyridine-substituted thionium ion chemistry as an excellent allyl silane receptor, which affords high yields of homoallyl sulfide **104**.[52] A critical control reaction reported in this publication demonstrated that *in the absence of the allylsilane*, the ethylaluminum reagent provided a near quantitative yield of reduced sulfide **105**, thus raising the possibility of byproduct formation by β-hydrogen donation. Craig employed sulfonamide-protected amine **106** to prepare piperidine **108** by intramolecular alkylation of thionium intermediate **107** (Scheme 15).[53] Finally, the pinacol rearrangement of **19b** → **21b** in Scheme 4 illustrates a further

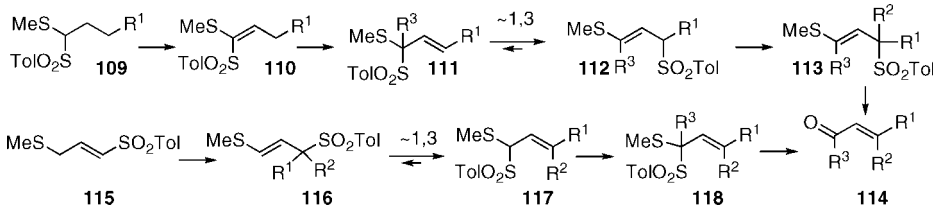
Scheme 14



Scheme 15



Scheme 16



example of a thionium ion generation involving sulfur participation.

Ogura[54] and Trost[35] have examined the vinylogous (and bis-vinylogous)[55] reaction in the sulfur system. For example, both α- and γ-sulfenylated unsaturated sulfones (**110** and **115**) are readily metalated and alkylated to sulfones (**111** and **116**), with the latter requiring two metalation/alkylation cycles. These tertiary allylic sulfones are highly prone to sulfinate anion expulsion and thermodynamic rearrangement to secondary allylic sulfones (**112** and **117**). A final round of alkylation affords γ- and α-sulfenylated allylic sulfones (**113** and **118**), which both suffer ready hydrolysis to enone **114** (Scheme 16).

2.1.3. Nitrogen Assisted Loss of Phenylsulfinic Acid

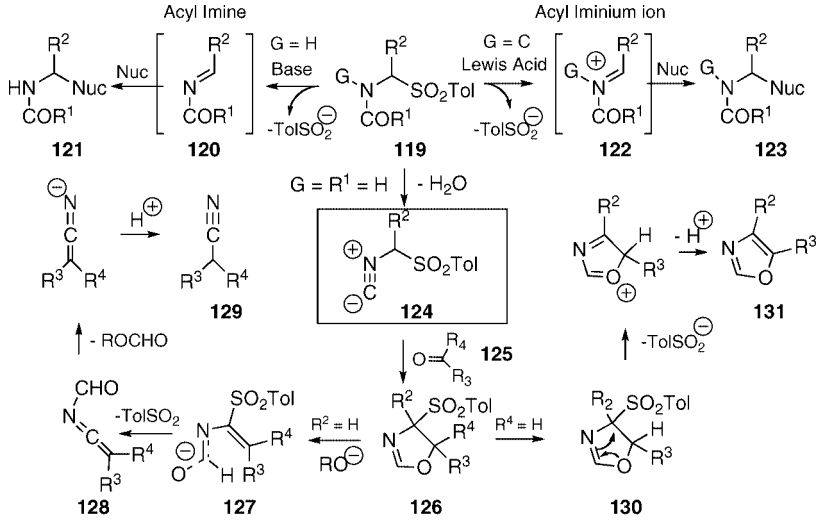
Heteroatom lone-pair assisted loss of phenylsulfinic acid also features sulfones bearing nitrogen in the α-position. In order to maintain a consistent focus, only tertiary nitrogen substrates **119** (G = C), which generate *acyliminium ions* (**122**), will be discussed in this review. The reader is directed to the chemistry of N−H substituted sulfones **119** (G = H), which generate neutral acylimine (**120**) intermediates, followed by in situ addition reactions leading to secondary amides **121**.[56]

A special category of α-nitrogen substituted phenylsulfinic acid loss is seen in the chemistry of TOSMIC **124** (R^2 = H). This well-known reagent[57] undergoes condensations with aldehydes and ketones **125** to provide oxazoles **131** or nitriles **129** as a function of the substitution pattern of the dihydrooxazole sulfone intermediate **126** (Scheme 17). The strategy has been extended with the recent publication of a substantially improved method for the preparation of substituted isonitriles **124** ($R^2 \neq$ H).[58]

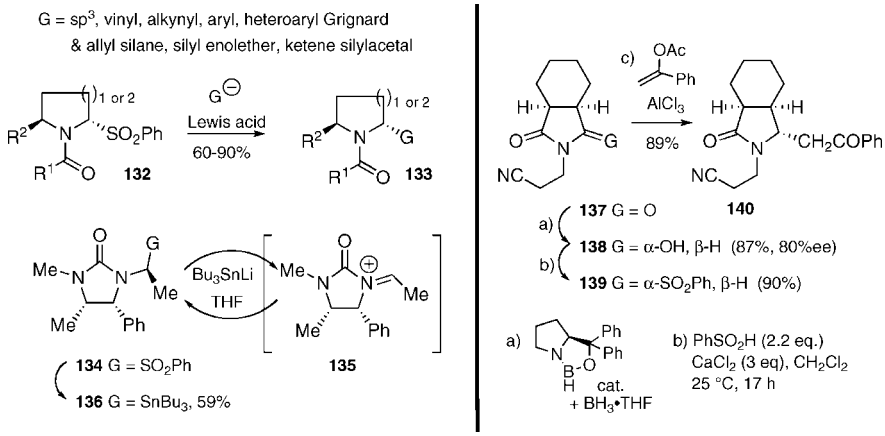
The Ley group was instrumental in generation and trapping of acyliminium ions (**122** → **123**) from α-acylamino sulfones (**119**) as shown in Scheme 17. Specific examples involved functionalization of pyrrolidines and piperidines bearing aryl sulfones adjacent to the acylamino moiety (**132**−**133**, Scheme 18).[59] Pearson demonstrated the value of the urea moiety as chiral auxiliary **134** with his creative synthesis of enantiopure acylamino anions derived from stannane **136**.[60] This enantiopure urea strategy has been adopted by Petrini and employed for the preparation of a wide variety of amine enantiomers.[61] Recent papers exploit this chemistry beginning with reduction of imide **137**, conversion to the enantiopure sulfone **139**, and coupling with an organozinc reagent or enol acetate.[62] The latter example featured reduction of a *meso* imide to ultimately afford an enantiopure keto-lactam (**140**, Scheme 18).

Craig has investigated the vinylogous use of the nitrogen participation chemistry described above for the synthesis of substituted tetrahydropyridines (Scheme 19). It should be noted that the metalated intermediate derived from **141** does not suffer 1,4-elimination of the *N*-sulfonyl moiety under the conditions required for carbon alkylation of the heteroallylic anion.[63]

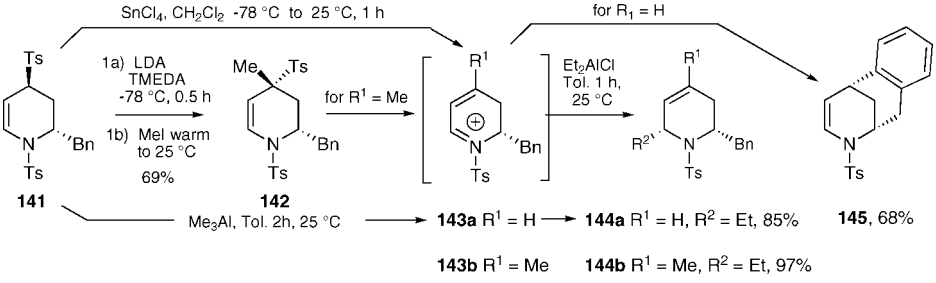
Scheme 17



Scheme 18



Scheme 19



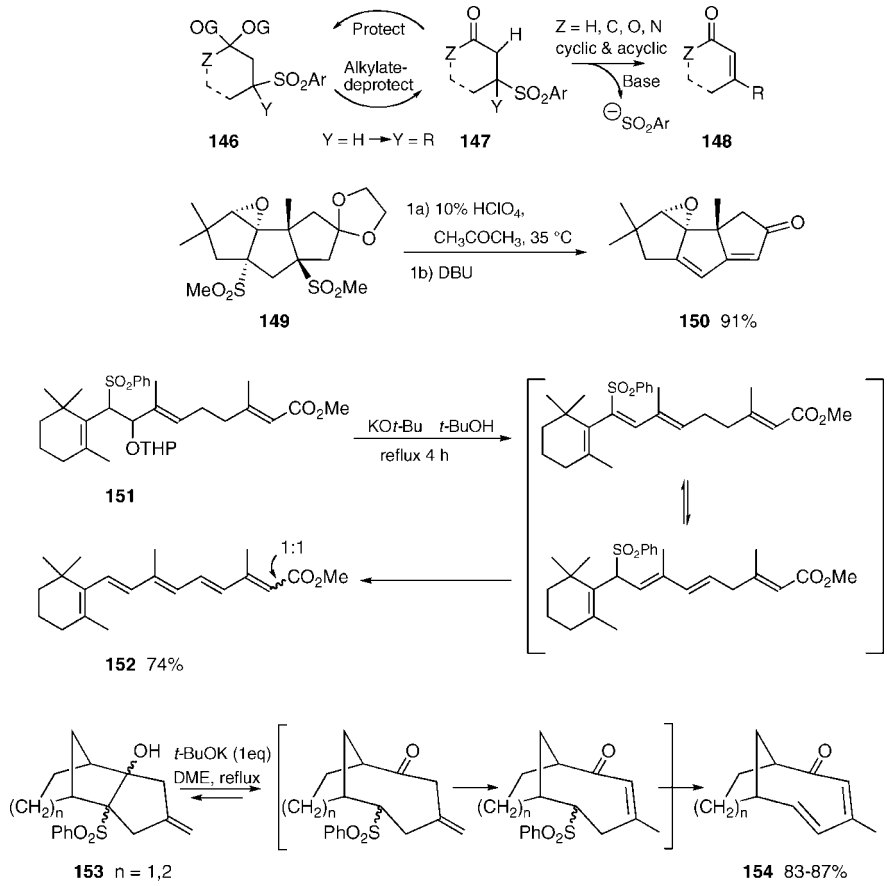
2.2. Other Modes of Loss of Phenylsulfinic Acid from sp^3 Carbon

2.2.1. π-Activation of a C−H Bond β to the Sulfone

Allylic, benzylic, allenic, or propargylic activation of a C−H bond beta to the sulfone moiety enable facile base-promoted elimination of the anion of phenylsulfinic acid (pK_a ≈ 2[64]). Examples of this reaction category are plentiful and include the familiar β-elimination of the phenylsulfonyl moiety from homoallylic aldehydes,[65] ketones,[66,36] esters,[67] orthoesters,[68] acids,[69] amides, lactones,[69] and lactams to afford the unsaturated carbonyl derivatives (**150**, Scheme 20). Temporary protection of the carbonyl group of **147** (as **146** Y = H) provides ready access to the alkylated sulfones **148** (Y = R). The overall sequence clearly exploits both the anion-stabilizing and the leaving-group attributes of the sulfonyl moiety.

Extension of the above concept by Trost and Curran featured a cascade bis-elimination for an efficient synthesis of dienyl ketone **150**.[70] Thermodynamic control can be engaged to great advantage in these eliminations; for example, the Otera group converted protected sulfonyl anion/vinyl aldehyde adduct **151** to pentaenyl ester **152** through β-elimination of the allylically activated alkoxide moiety, isomerization, and 1,6-elimination of phenylsulfinate anion.[71] Similarly, Mi and Maleczka subjected tertiary β-hydroxy sulfones **153** to basic conditions and isolated high yields of dienyl ketones **154**.[72] Presumably the sequence involves a reversible retro-aldol reaction of **153**, followed by formation

Scheme 20



of the enone with an endocyclic double bond and elimination of phenylsulfinate anion to produce **154** (Scheme 20).

In addition to the highly activated (carbonyl enolate) eliminations shown above, alkenes and alkynes are also competent activating functionality for 1,2-elimination of homoallyl and homopropargyl sulfones.[73] Julia is responsible for developing one of the best-known transformations involving sulfone as a leaving group, i.e., the reaction of an allylic alkylating agent with an α-sulfonyl anion followed by elimination of the homoallyl sulfone to afford a diene bearing a new *E*-configured double bond.[74] In an interesting example by the Nicolaou group, the highly functionalized sulfone **155** was converted to diene **156**, which served as a key intermediate in the synthesis of antibiotic X-14547A (Scheme 21). Other synthetically relevant examples include Palmer and Learn's transformation of homoallylic sulfone **157** to exocyclic diene **158**[75] and Toth and Hamann's conversion of tetracyclic morphine intermediate **159** to dienyl ether **160**.[76] Another informative example is seen in the Rhizoxin D synthesis of Williams, Werner, and Feng.[77] These authors found that elimination of the standard *p*-tolylsulfone **161a** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave low yields of bromodiene **162**, whereas KO-*t*-Bu further transformed **162** to 1,3-enyne **163** in high yield. The more activated dichlorophenyl sulfone **161b** satisfactorily afforded target bromodiene **162** in 70% yield (Scheme 21).

Homobenzyl sulfones also undergo the base-promoted elimination reaction. Carpino showed that geminal bis-sulfone **164** is eliminated to vinyl sulfone **165** under relatively mild conditions.[78] An example from the Kametani group is especially revealing; homobenzylsulfone **166** affords benzomorphan nitrile **167** in near-quantitative yield, yet under the basic conditions, the *p*-methoxybenzylic tertiary nitrile **167** did not suffer aromatization by further elimination, even in the face of cooperative double activation of both the cyanide leaving group and the allylic hydrogen (Scheme 22).[79]

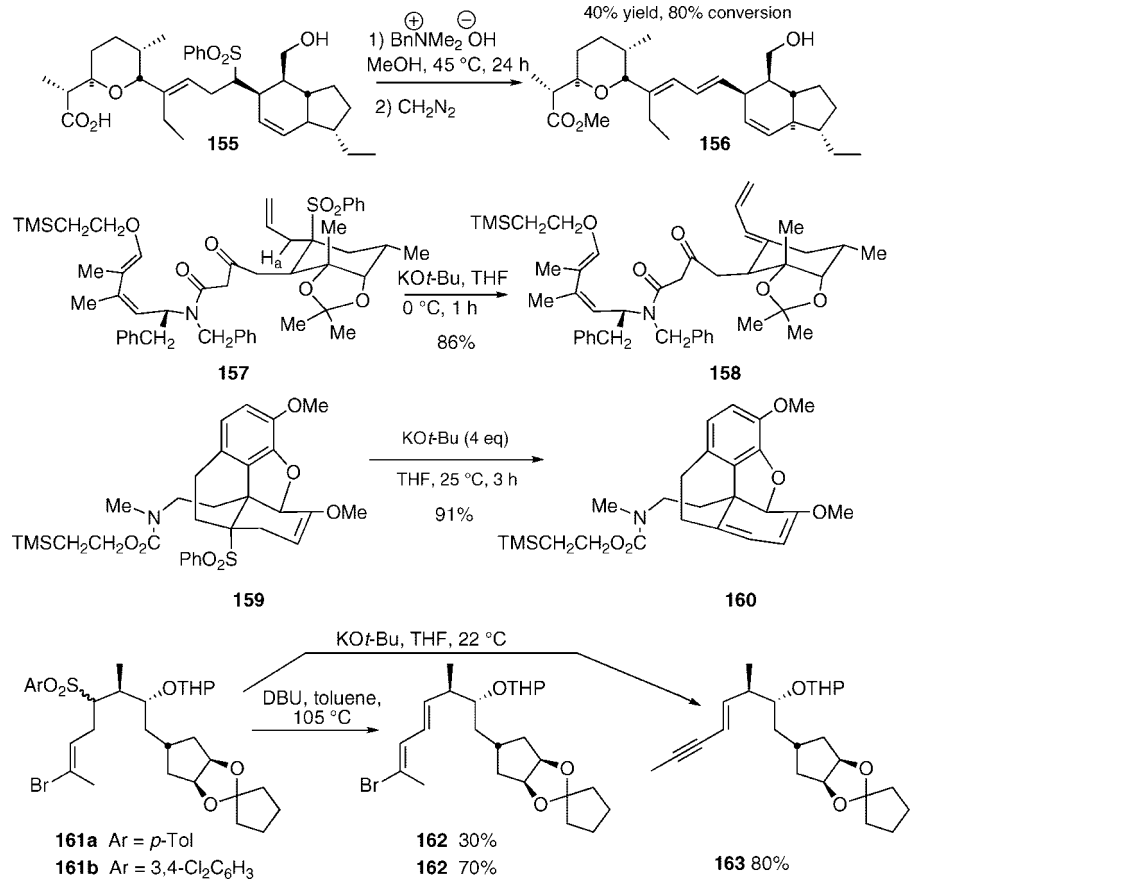
2.2.2. π-Activation of the Phenylsulfone Moiety

A particularly nice application highlighting the amphoteric character of the phenylsulfone functional group was employed by Makosza in 1986 (Scheme 23).[80] This indole annulation involves 10π-electrocyclization of anion **168** to the metalated aniline **171** followed by elimination of the benzylic phenylsulfinate to **170** and isomerization to the aromatized indole **169**.

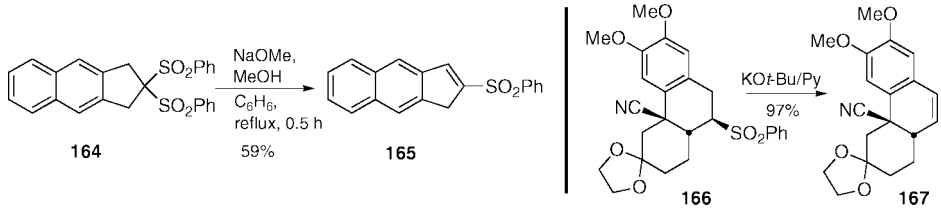
Extension of the above reaction is seen in a 2005 paper by Otera,[81] which reverses the electrocyclization by starting with the aniline anion **173**, cyclization to the benzylic sulfonyl anion **174**, followed by sequential alkylation (to **177**), β-elimination (to **176**), and isomerization to afford indole **175** (Scheme 24).

A related 1,4-elimination of benzylic sulfone **178** requiring excess KO-*t*-Bu was reasonably postulated by Rapoport to involve the initial production of enolate **179**, followed by direct formation of the aromatized phenolate **180**.[82] This example can be contrasted with the failure of tertiary benzylic sulfone **181** to undergo lone-pair assisted ionization/elimination to enone **182**, even upon heating under reflux (Scheme 25).[83]

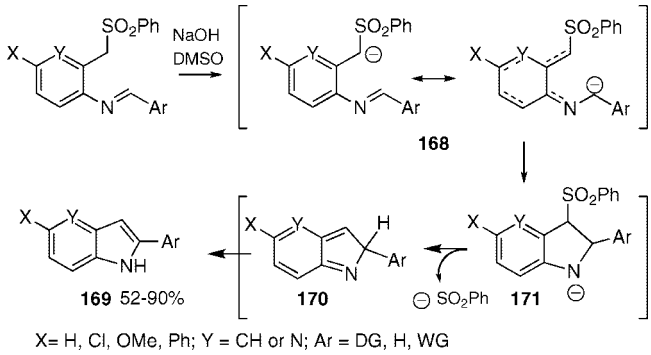
Scheme 21



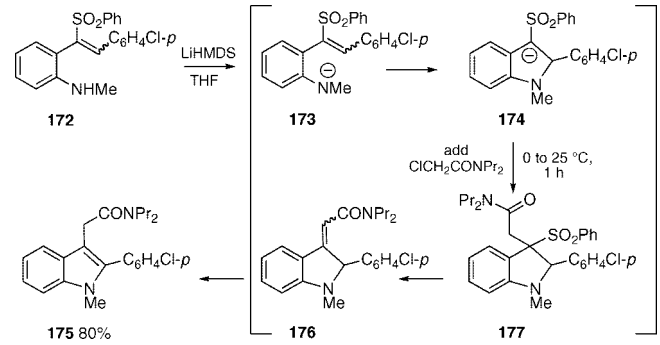
Scheme 22



Scheme 23



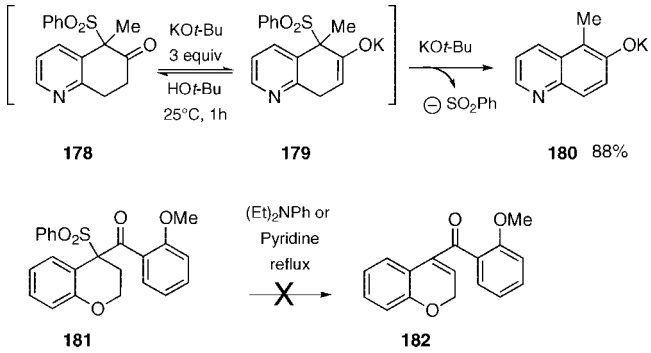
Scheme 24



2.2.3. Oxophilic Lewis-Acid Activation of Allylic and Tertiary Sulfones

Trost and Ghadiri further defined the reactivity of the secondary allylic sulfone functionality in transformation of the naphthyl-substituted allylsulfone **183** to benzannulated product **184** employing Lewis-acid assistance.[8] This transformation was later exploited in the case of sulfone **185** by the Kocienski and Schmalz groups in their study of the synthesis of the pseudopterosin aglycones.[84] Treatment of **185** as a mixture with diethylaluminum chloride provided axial isopropylidene adduct **186** in high yield and diastereomeric excess (Scheme 26). A noteworthy example is provided by Harmata, who showed that the tertiary oxallylic cation formed from sulfone **187** undergoes intramolecular [4 • •3]cycloaddition, forming tricyclic ketone **188** as a mixture of diastereomers.[85] Lewis-acid-mediated sulfone ionization was demonstrated using tertiary (nonallylic) sulfone **189**, which suffered intramolecular Friedel−Crafts reaction, providing **190** under mild conditions (Scheme 27).[8]

Scheme 25



Lewis-acid activation extends to intermolecular alkylation of cyclic and acyclic allylic sulfones. Trost and Ghadiri again were involved in exploring the regioselective coupling of alkynyl- and vinylalanes.[86] For example, secondary and tertiary allylic sulfones **191** and **192** provided 1,4-enynes **193** and **194**, respectively (Scheme 28).

2.2.4. Transition-Metal Activation of Allylic Sulfones

Molybdenum- and nickel-catalyzed reactions of allyl sulfones are known,[87] but this review will only feature the more abundant palladium-catalyzed examples. The catalytic chemistry of π-allyl palladium[0] intermediates is dominated by allylic acetates and carbonates;[88] however, synthetic methodology involving alkylation and alkene-forming reactions of allylic sulfones strongly benefits from the pluripotent character of the sulfone moiety.[89] Two examples from the Trost laboratories highlight the complementary nature of the allylic acetate and allylic sulfone functional groups.[90] The first example converts **197**, the product of palladium-catalyzed alkylation of the "soft" anion **195** to trienyl ketone **198** employing palladium to effect departure of the phenylsulfinate leaving group. Attempts at base-catalyzed elimination of the doubly activated sulfone moiety of **197** were unsuccessful, presumably due to irreversible deprotonation of the highly acidic vinylogous α-sulfonyl ketone **197** (Scheme 29).

The second example is a one-pot palladium-catalyzed double elimination reaction, which arguably sequentially produces the π-allyl intermediate at C16−18 by initial ionization of allyl acetate **199**, undergoes regioselective loss of the H_a (inductively activated by the sulfone) to generate intermediate **200**, ionizes the doubly allylic sulfone to form a new π-allyl intermediate at C20−22, and finally suffers loss of H_b to afford fully conjugated all-*trans*-tetraene **201** (Scheme 30).

Another seminal contribution by the Trost group involves the enantioconvergent catalytic conversion of racemic five-, six-, and seven-membered allyl acetates **202a**−**c** and carbonates **203a**−**c** to enantiopure five-, six-, and seven-membered allyl sulfones **206a**−**c** employing the palladium catalysts in the presence of the versatile Trost ligand **204** (Scheme 31).[91] This strategy can be conveniently employed on large scale[91,92] and is the method of choice for the synthesis of these valuable enantiopure starting materials in exceptionally high yield and enantiomeric excess.

In 1982, Kotake reported the combination of allyl sulfones, Pd[0] catalysis, and $NaBH_4$ as a nucleophilic hydride source.[93] This procedure enables alcohol-directed regioselective reductive cleavage of the sulfone moiety, providing homoallyl alcohol **210** from allyl sulfone anion/aldehyde adducts (Scheme 32).

In a series of follow-up papers, alcohol-free allylic sulfones such as **211**, the precursor to coenzyme Q_{10} side chain **212**, were prepared by regioselective reduction of a palladium π-allyl intermediate using the sterically demanding triethylborohydride reagent (Scheme 32).[94]

In terms of synthetic efficiency, the transformation above involving reductive cleavage of a secondary sulfone is a *net decrease of two units of molecular intricacy*,[95] since both the stereocenter and its pendant heteroatom have been converted to a methylene unit. While the allylic sulfone precursor to **211** (not shown) provided valuable service in establishing the carbon backbone, it can be seen in the recent chemistry of Li and Lantrip[96] that the palladium-catalyzed triethylborohydride reductive cleavage of allylic sulfone **214a**,**b** (a nonconsequential diastereomeric mixture) can be taken to a higher level of performance by adjustment of the ligands on the palladium[0] catalyst. In this instance, both diastereomers of **214** provide the same intermediate **215**, which selectively generates the four dienyl compounds in 70−90% isolated yields using the specified ligands (Scheme 33).[96] Since the four indicated types of 2-alkyl 1,3-dienes comprise the vast majority of 1,3-diene-containing natural products, use of phosphonate sulfone **213** as a conjunctive reagent can be highly advantageous (see section 4.3).

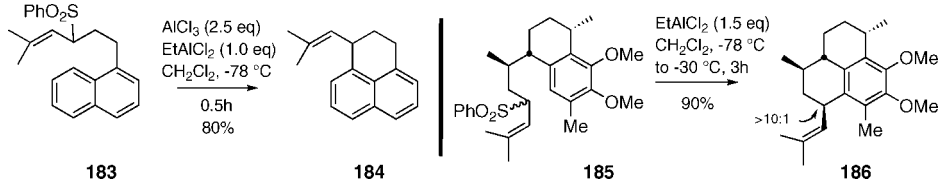
Reaction of **218** (for its synthesis, see Scheme 50) in the presence 10% $Pd(PPh_3)_4$ and 1.1 equiv of tetramethylguanidine (TMG) gave 97% of **219** as compared to 64% using triethylamine.[97] TMG is about 2−3 pK_a units more basic than triethylamine but is not a good nucleophile (Scheme 34).

2.2.5. Phenylsulfone Activation by a Pendant β-Metal or Metalloid

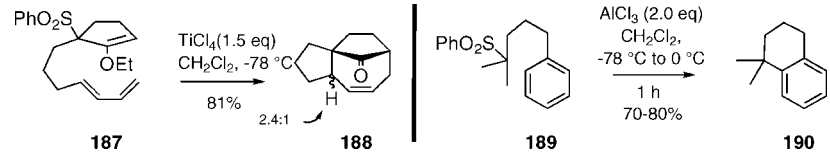
The Kocienski exomethylene−alkene synthesis formally begins with sequential tris-alkylation of methyl sulfone **220** with a pair of alkyl halides and halomethylsilane (or halomethylstannane[98]) **221** to provide β-silyl sulfone **222**. The key elimination features fluoride or alkoxide[99] attack at the silicon moiety, which regioselectively eliminates the phenylsulfinate anion to provide alkene **223** (Scheme 35).[100] The Kocienski alkene synthesis has been used to advantage by Paquette, Schechter, and Najera.[101] β-Silyl sulfones have also been employed in the synthesis of atypical ring systems such as methylenecyclopropanes, including preparation of enantiopure **225**, which is a key intermediate in the Baldwin total synthesis of Hypoglycin A.[102] The Sammes synthesis of bicyclomycin smoothly forms exocyclic alkene **227** by the fluoride-mediated elimination from **226** (Scheme 35) but is especially notable for an additional piece of synthetic information (see Scheme 57).[103]

Kim, Jin, and Ma have employed the Kocienski reaction to provide the formal equivalent of a reductive cleavage of vinyl sulfones to vinyl anions.[104] This transformation features addition of phenyldimethylsilyl lithium or -cuprate to a vinyl sulfone (**228**, **229**, **234**) followed by treatment with tetrabutylammonium fluoride (TBAF). More useful is the example in which the incipient α-sulfonyl anion undergoes a subsequent alkylation to ultimately provide a trisubstituted alkene after the alkene-forming reaction. The second example in Scheme 36 reveals the unexpected formation of allylic sulfone **238**. *anti*-Elimination product **238** may compete with the "normal" allylic alcohol **237** because of the less favorable *cis*-orientation of the PDMS (phenyldimethylsilyl) and sul-

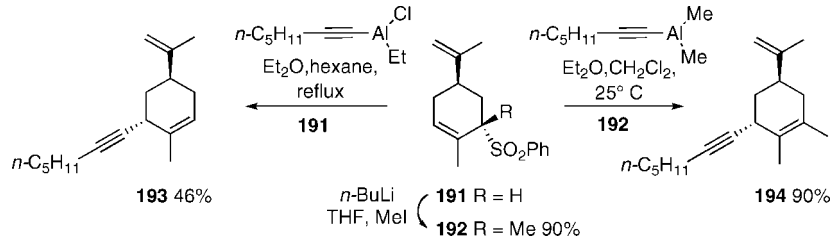
Scheme 26



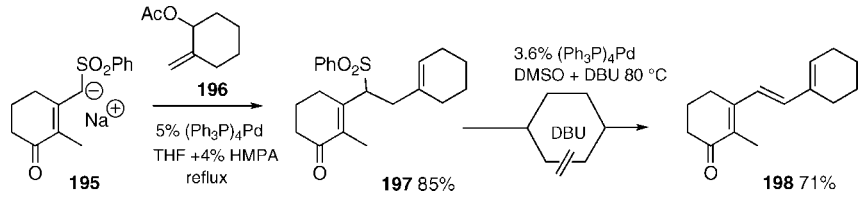
Scheme 27



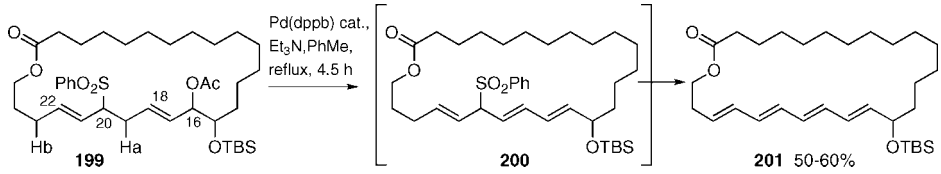
Scheme 28



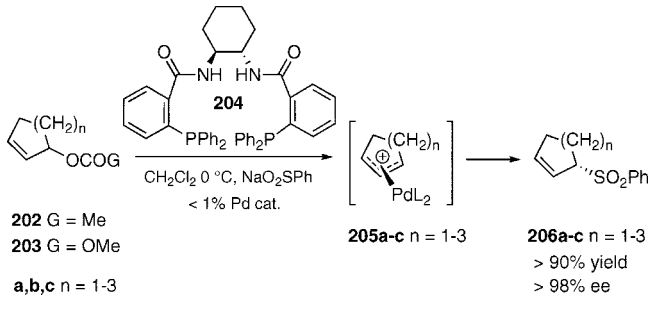
Scheme 29



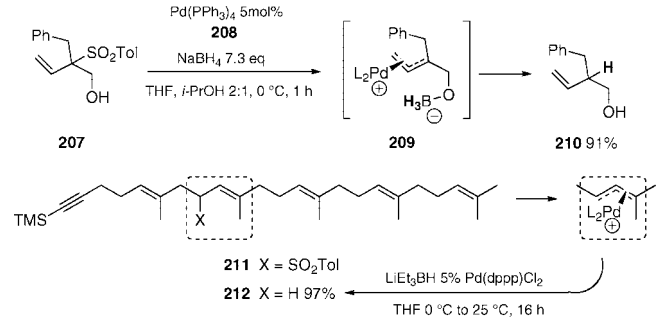
Scheme 30



Scheme 31



Scheme 32



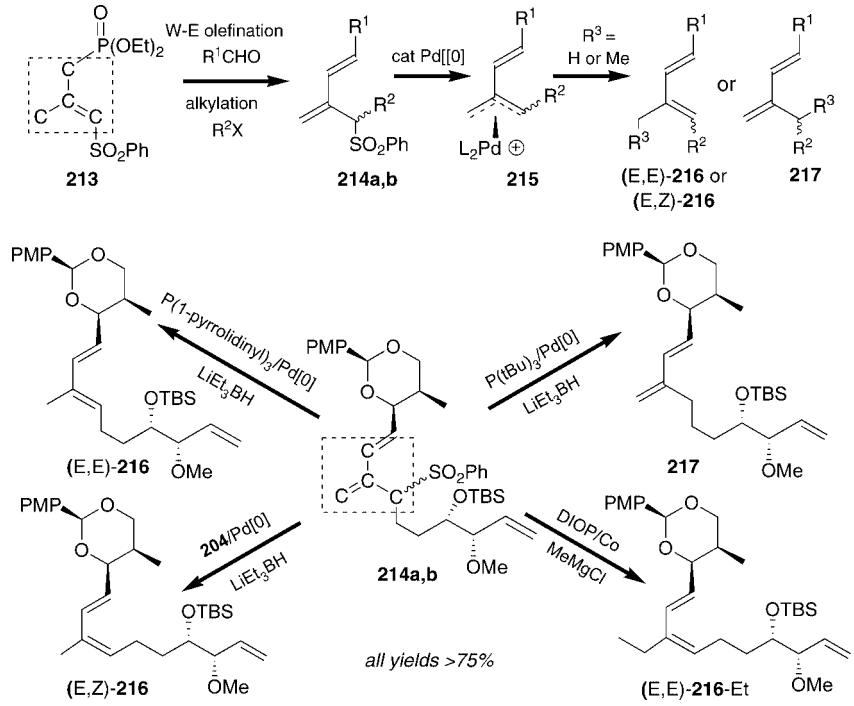
fone moieties in substrate **236**. Since *syn*-elimination is required to form **237**, it is probable that formation of the carbanion-like intermediate from the pentavalent fluorosilicate is more advanced in the transition state, making the pK_a difference between sulfinate and silyloxide leaving groups of lower importance (Scheme 36).

Julia provided a spectacular extension of the 1,2-elimination concept by showing that α-metalated sulfones undergo well-behaved alkylation reactions with α-halomethyl-Grignard reagents, providing the alkenation products by the transient *β*-sulfonyl magnesium halides (**240**).[20] Particularly nice applications of this process are seen in the conversion of the cyclopropylsulfone **239** to the methylenecyclopropane **241** (Scheme 37)[105] and the total synthesis of Phorboxazole A[19] (see **28** ↔ **29**, Scheme 5).

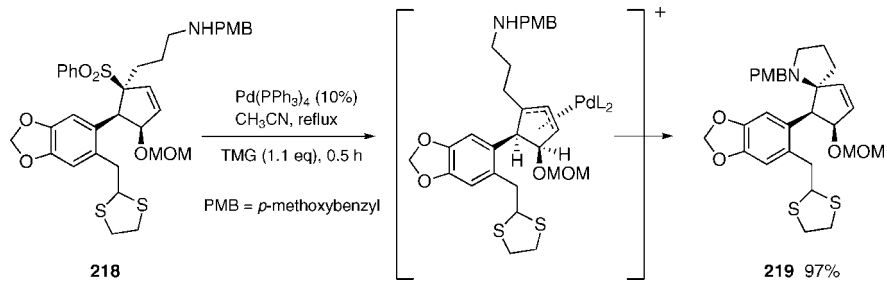
2.2.6. Intramolecular 3-exotet-Cyclopropanation

While the aryl sulfone moiety is an exceedingly ineffective leaving group for traditional S_N2 reactions, the intramolecular

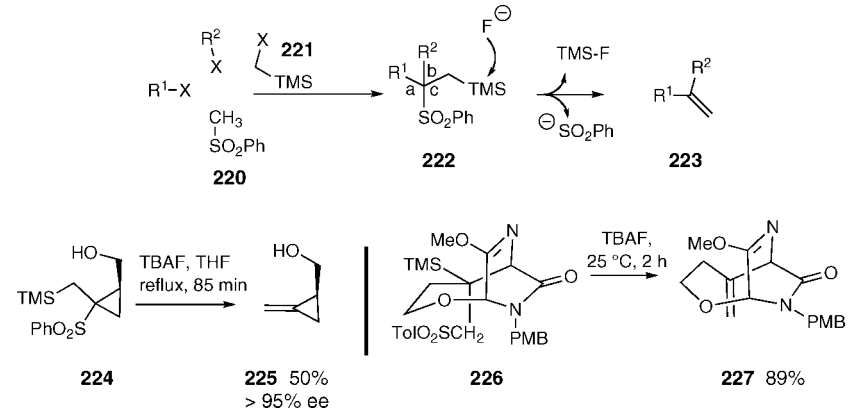
Scheme 33



Scheme 34



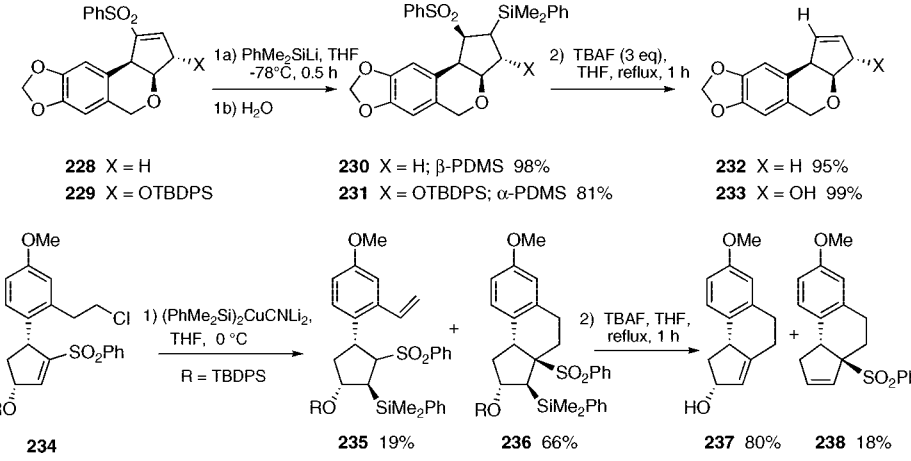
Scheme 35



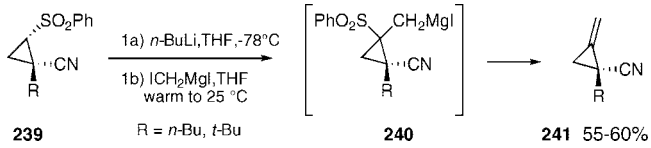
3-*exotet* reaction is, like most similar entropy-limited 3-ring-forming reactions, a viable process. The initial example of this reaction, converting keto-disulfone **242** to pentacyclic ketone **243**, was published by Parker and Woodward in 1969 (Scheme 38).[106] Application of this reaction for the synthesis of the chrysanthemic acid ester **247** and its analogues,[107] fused cyclopropanes **251** and **252**,[108] and the more intricate tricyclic skeleton **256**[109] has also been reported.

Related 3-*exotet* cyclopropanations were observed by Jin during a conjugate-addition study of six- and seven-membered γ-methoxyvinyl sulfones.[38] While these substrates are smoothly metalated with *t*-BuLi to provide well-behaved allylic anions **257a**,**b**, addition to the exceptionally reactive five-membered Michael receptor **258** affords intermediates (**259a**,**b**) prone to ejection of the methoxy-allylically activated tertiary sulfone (cf. Schemes 10 and 11) at about −65 °C to form spirofused cyclopropanes **260a**,**b**. Care is needed to isolate these materials because they are susceptible to fragmentation of the cyclopropane moiety with concomitant generation of δ-sulfonylenones **261a**,**b**. Further treatment of **261a**,**b** with DBU readily completes elimination of the remaining phenylsulfinic acid (Scheme 39). These transfor-

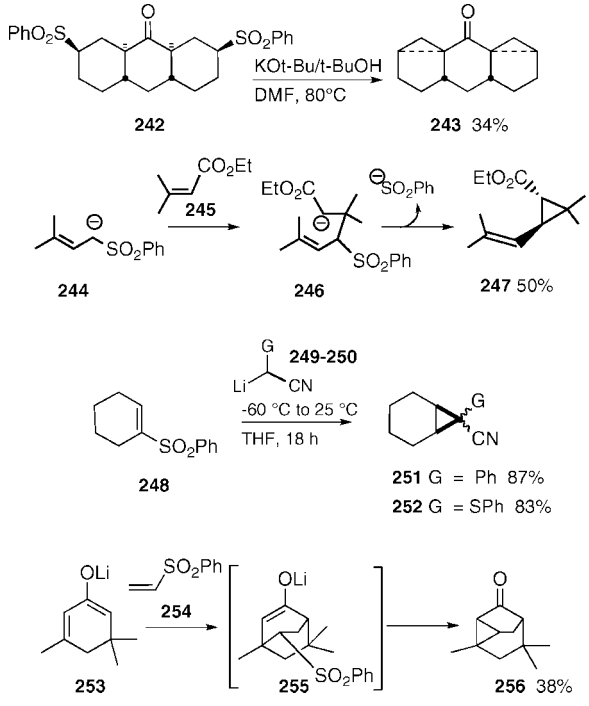
Scheme 36



Scheme 37



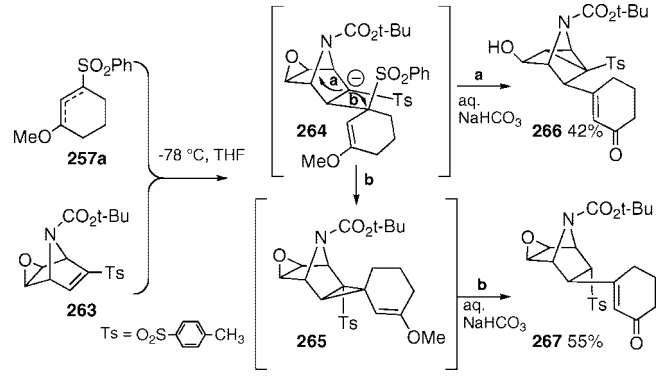
Scheme 38



mations are additional examples of the Trost−Curran cascade synthesis of dienyl ketones[70] (cf. **149** ↔ **150**, Scheme 20).

Scheme 40 reveals an interesting competition between two 3-*exo* processes. Reaction of **257a** with vinyl sulfone **263**

Scheme 40



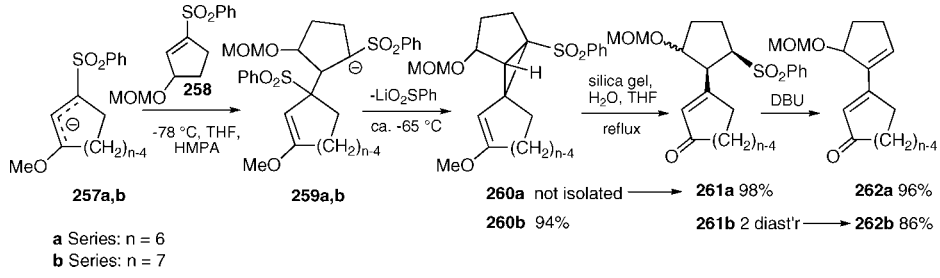
provides **267** as the product anticipated from the above precedent, but the yield is only 55%.[40] The remaining 42% is cyclopropyl sulfone **266**, formed by intramolecular opening of the pendant epoxide by the common α-sulfonyl anion intermediate **264**.[110]

2.2.7. Ramberg−Bäcklund Alkene Synthesis Employing Phenylsulfinic Acid as the Leaving Group

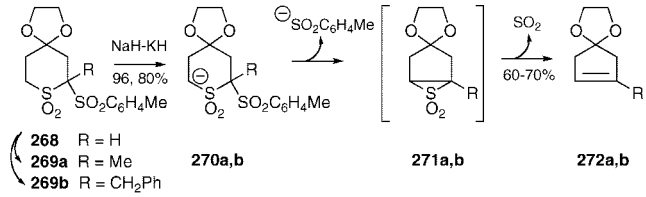
The classical Ramberg−Bäcklund reaction transforms the attached pair of carbon residues of an α-halo sulfone to the sp^2 carbons of a newly formed alkene. The mechanism involves metalation at the less-hindered carbon center with concomitant 3-*exotrig*-elimination of the halide anion to generate a transient episulfone. Cheletropic loss of sulfur dioxide completes the alkene-forming reaction.[111]

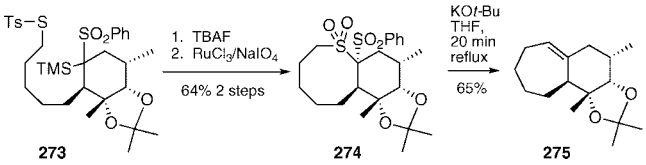
Use of arylsulfinate anion as a leaving group in the 3-*exotrig* reaction enables considerable flexibility with respect to construction of the alkene. For example, alkylation of the doubly activated methine of bis-sulfone **268** smoothly provides alkylated adducts **269a**,**b**. Metalation followed by sequential loss of sulfinate anion and sulfur dioxide gives

Scheme 39



Scheme 41





the trisubstituted alkenes **272a**,**b** in good yields (Scheme 41).[112] In comparison, an annulation procedure by Scarpetti employs fluoride-mediated intramolecular sulfenylation of thiolsulfonate **273** to form the eight-membered sulfide ring. Oxidation to **274** followed by Ramberg−Bäcklund reaction affords the cycloheptenyl-annulated product **275** (Scheme 41).[113]

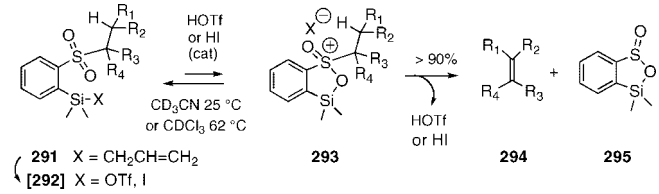
Another example was provided by Ranasinghe.[114] Addition of an aryl anion to vinyl sulfone **59** was combined with sequential sulfenylation using the β-TMS ethyl thiolsulfonate reagent[115] followed by acetal hydrolysis, hydride reduction, and oxidation to **276**. Metalation of **276** keyed 3-*exotet* extrusion of phenylsulfinate giving allylsilane **277** in high yield (Scheme 42).[114]

2.2.8. Phenylsulfone Activation by Covalent Modification

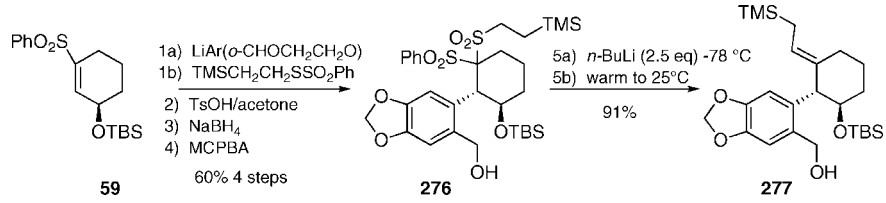
Kwiatkowski, Radisson, and Burkholder have determined that substrates devoid of competitive metalation sites suffer low-temperature, sulfone-directed *ortho*-metalation,[116] which allows self-immolative elimination of homoallylic and homobenzylic sulfones affording dienes and styrenes (the latter not shown). Deuterium labeling has proven that organolithiums **280** and **284** are intermediates en route to exocyclic dienes **282** and **286**. Of additional significance was the observation that the traditional potassium *t*-butoxide elimination with **279** produced trienol **278** as the only identifiable product in very low yield (Scheme 43).[117] Modification of the sulfone moiety was also an important variable. By including an additional *meta*-methoxy group in compound **283**, the metalation occurred at −110 °C and elimination to **286** was complete by −78 °C, with a near-quantitative yield.[117] Wicha has used this self-immolative elimination reaction for preparation of the functionalized cyclopropenylsilane **289** (Scheme 43).[118]

As stated at the outset of this review,[2] examples of elimination of aryl sulfones lacking activated β-protons to alkenes under mild conditions are very rare. The Lewis-acid-catalyzed chemistry described in section 2.2.3, when considered along with reports of intramolecular nucleophilic attack of sulfonyl oxygens at carbon[119] during electrophilic addition to alkenes, led Van Dort to study intramolecular oxygen functionalization.[120] It was found that generation of a silyltriflate or iodide intermediate [**292**] *ortho* to the phenylsulfone moiety smoothly formed cyclic sultinium species **293** as a prelude to alkene **294** and silylsulfinate **295** in near-quantitative yields (Scheme 44).

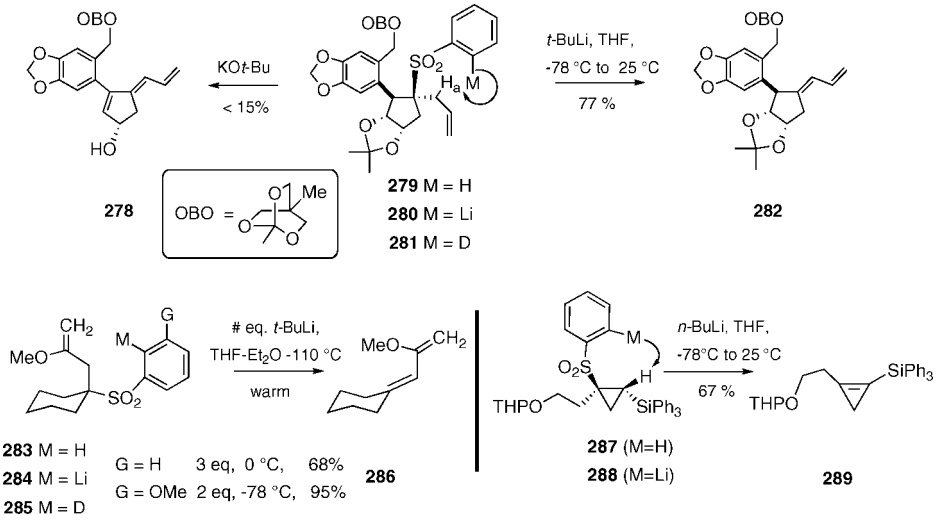
Scheme 44



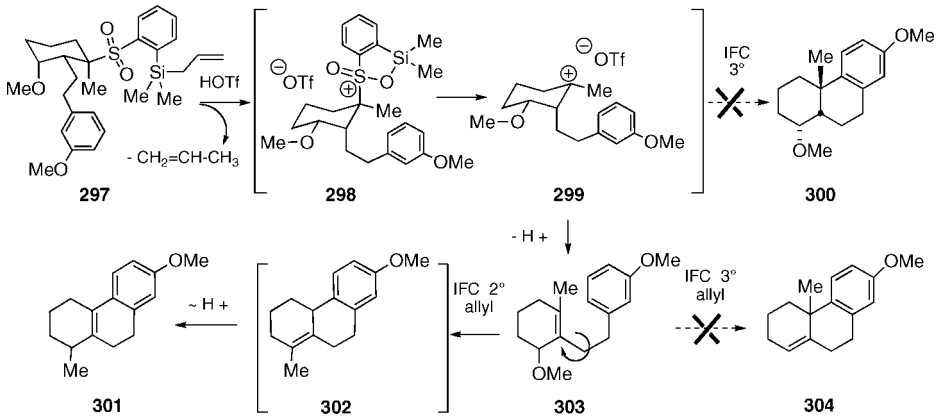
Scheme 42



Scheme 43



Scheme 45



Silyl triflates **292** are easily generated by protodesilylation of allylsilane precursors **291** with catalytic triflic acid. Because of their relative stability, allylsilanes **291** nicely serve as latent silyl triflates. As described in Scheme 43, directed *ortho*-metalation of phenyl sulfones lacking acidic α-protons followed by treatment with allyldimethylchlorosilane provides ready access to allyldimethylsilyl aryl sulfones such as **291**. Alternatively, the silyl group can be introduced early in the sequence by silylation of the S,*ortho*-C dianion of thiophenol.[120,121] Reaction of *m*-methoxyphenethyllithium[122] with 3-methoxycyclohex-1-enyl (*ortho*-allyldimethylsilyl) sulfone followed by quenching with methyl iodide affords **297** in 56% yield.

An attempt to prepare octahydrophenanthrene **300** by intramolecular Friedel−Crafts alkylation of the *axial* sultinium intermediate **298** involved reaction of tertiary sulfone **297** with 5 mol % triflic acid in $CDCl_3$ at 62 °C. Tricyclic **300** was not detected, but at short reaction times, alkene **303** could be isolated. Longer reaction times (2 h) served to convert **303** to tricyclic alkene **301** in 67% overall yield from **297**, without concomitant production of alkene **304** from alkylation at the more-hindered tertiary position of the putative allylic cation. NMR studies in conjunction with molecular mechanics calculations attributed the failure of **297** to cyclize to **300** to unfavorable conformational factors (Scheme 45).[120]

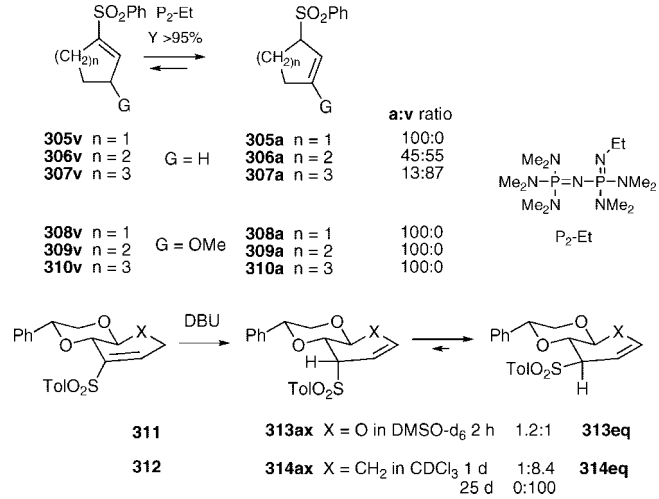
2.3. Opportunities and Limitations

2.3.1. Vinyl Sulfone to Allyl Sulfone Equilibrium

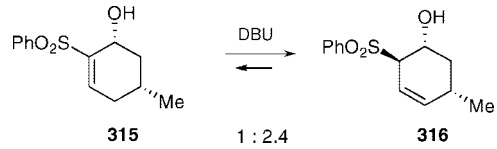
Jin and Kim have demonstrated that DBU or the 13 000 times stronger P_2-Et phosphazene base promotes prototropic equilibration of simple cyclic vinyl sulfones **305v**−**307v**, showing a preference that decreases from 100% allyl **305a** to 13% allyl **307a** as the ring size increases (Scheme 46).[123] This contrasts with the corresponding vinyl sulfides, which show a ∼10:1 preference for the vinyl isomer, irrespective of the ring size.[124] Substitution of a methoxy group at the γ-position guarantees complete equilibration to the γ-methoxy allyl sulfones **308a**−**310a**.[125] The Sakakibara group reports a related study in the carbohydrate series studying equilibration of vinyl sulfones **311**−**312** (Scheme 46).[126]

When isomerization of a vinyl sulfone yields a disubstituted alkene, the energies of the two species are more closely balanced. For example, isomerization of **315** with 5 mol % DBU for 15 h generated a 1:2.4 equilibrium mixture of **315**/**316**, which upon crystallization provided a first-crop 46% yield of pure **316**. The lower solubility of **316** allowed

Scheme 46



Scheme 47

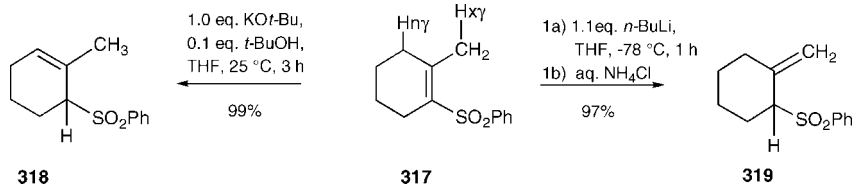


fractional crystallization, and two additional equilibration/crystalization cycles provided a final yield of 79% (Scheme 47).[127]

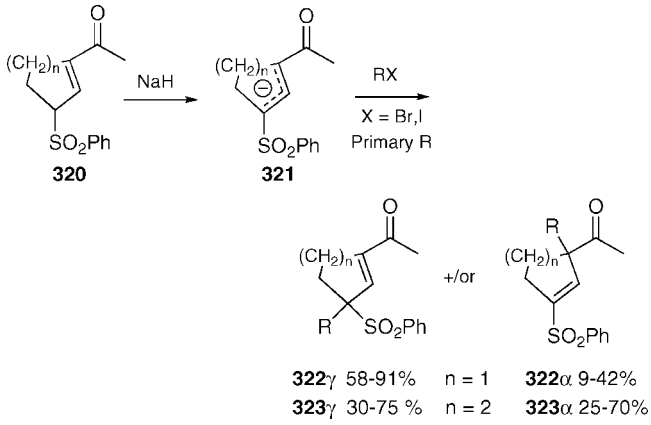
The interplay of kinetic and thermodynamic effects allows an additional measure of control during the isomerization process. Treatment of β-methyl vinyl sulfone **317** with potassium *t*-butoxide in the presence of *t*-butyl alcohol in THF provided the more stable endocyclic allyl sulfone **318** in 99% yield. Alternatively, sulfone-directed kinetic deprotonation at the exocyclic methyl group of **317** using *n*-butyllithium followed by quenching with saturated ammonium chloride solution yielded exocyclic allyl sulfone **319** in 97% yield. Attempts at isomerization of the exocyclic allyl sulfone **319** to the endocyclic allyl sulfone **318** using *p*-toluenesulfonic acid at reflux in THF provided 99% of recovered starting material (Scheme 48).[128]

The thermodynamic preference for allyl sulfones over their vinyl counterparts has been exploited in systems bearing additional carbonyl functionality. Peter Lansbury (*the elder*) showed that alkylations of (exocyclic) metalated vinylogous keto-sulfone **321** favored alkylation proximal to the sulfone moiety, maintaining the enone conjugation in the major adducts **322**γ and **323**γ (Scheme 49).[129]

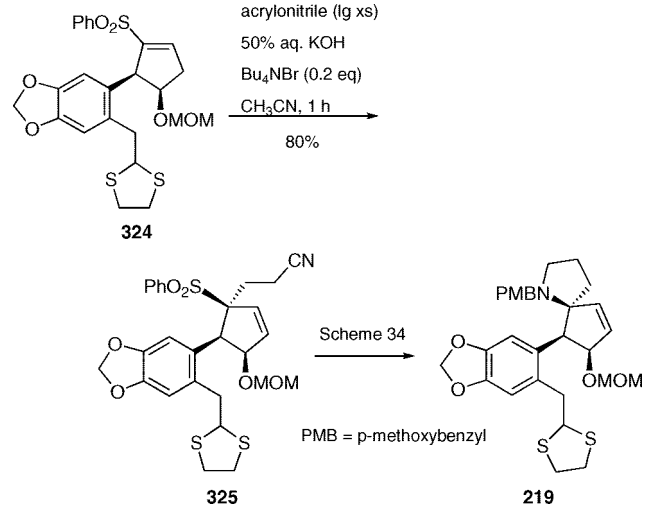
Scheme 48



Scheme 49



Scheme 50



2.3.2. Avoiding and Exploiting Eliminations from α-Sulfonyl Anions

Isomerization and/or alkylation of unsaturated sulfones bearing potential leaving groups present the synthetic chemist an additional challenge. Jin demonstrated that, while low-temperature metalation of **324** with alkyllithium or lithium amide bases initiates rapid elimination of the methoxymethyl (MOM) moiety followed by decomposition, such systems could be successfully alkylated using phosphazene bases.[97] Furthermore, treatment of **324** with 50% aqueous potassium hydroxide and excess acrylonitrile under phase-transfer conditions delivers adduct **325** in excellent yield. Allylic sulfone **325** has been further transformed by a π-allyl intermediate (cf. Scheme 34) to spirocyclic amine **219**, further demonstrating the sulfone's pluripotency (Scheme 50). It appears that vinyl sulfones which normally suffer β-elimination when subjected to metalation with strong bases such as alkyllithium, lithium diisopropylamide (LDA), or KO-*t*-Bu can often be successfully isomerized or alkylated using π-bases such as DBU or the phosphazenes, or by employing weakly basic conditions in protic media.

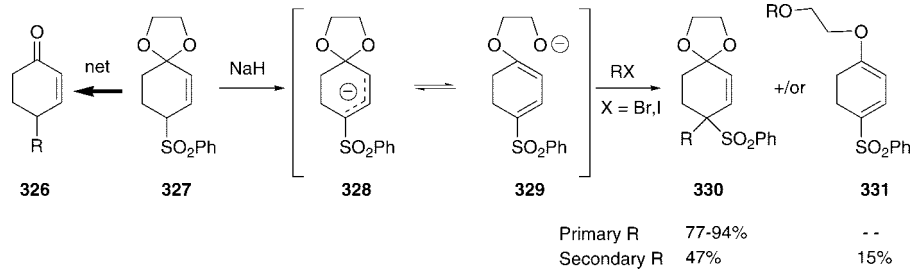
Complementary to the approach shown in Scheme 48, Paquette[130] and co-workers used dioxolane **327** to ensure high equilibrium concentration of allylsulfonyl anion **328**, which was exclusively trapped adjacent to the sulfone moiety when using primary alkyl halides, giving high yields of **330**. Alkylation of **327** with secondary halides was lower yielding, yet still regioselective with regard to C-alkylation, but importantly also provided a small amount of the mechanistically revealing sulfonyl dienyl ether **331**. Deprotection of the acetal functionality and reductive cleavage of sulfone **330** regioselectively provide γ-alkylated enone **326** (Scheme 51).

As previously described in Scheme 11, enantiopure γ-alkylated cyclohexenones and cycloheptenones are even more readily prepared by Lawton S_N2' reactions beginning with epoxy vinyl sulfones.[40]

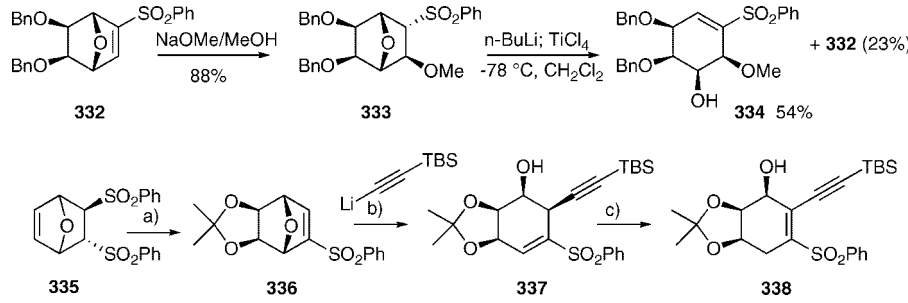
A nice synthesis of highly functionalized cyclohexyl systems has been reviewed by Vogel, Cossy, Plumet, and Arjona.[3] Useful sulfone examples of the Vogel "naked sugar" strategy from the Spanish school of Arjona and Plumet feature purposeful β-eliminations including the titanium[IV]-mediated synthesis of vinyl sulfone **334** in competition with the unwanted regeneration of starting bridged bicyclic vinyl sulfone **332**.[131] The related addition of a lithium acetylide to enantiopure vinyl sulfone **336** initially provides the kinetically favored vinyl sulfone product **337**. Isomerization of this material *in mildly basic protic media* affords conjugated enyne **338** without significant loss of either the acetonide or the alcohol moiety (Scheme 52).[132]

Funk, Umstead, and Brummond have provided a complementary strategy for kinetically controlled conversion of allyl

Scheme 51



Scheme 52a, b, c

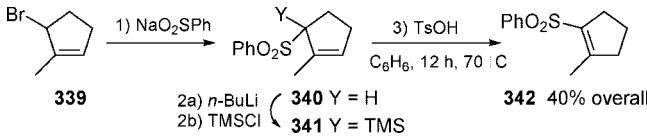


[a] Nine ops including resolution; 14% each enantiomer,

[b] 62%.

[c] NaOMe 0 °C, 71%.

Scheme 53



sulfones to vinyl sulfones.[133] This procedure features acid-catalyzed protodesilylation of α-silylated allyl sulfone **341** to regioselectively provide the less-stable vinyl sulfone **342** (Scheme 53).

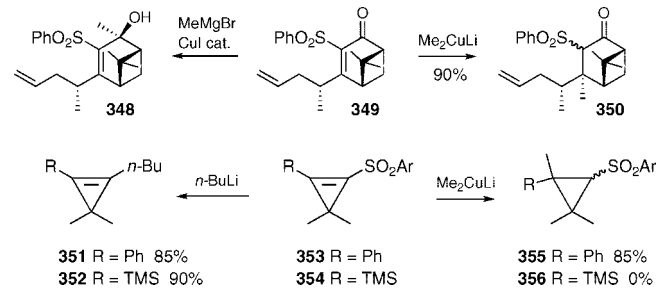
2.3.3. Additions to β,β-Disubstituted Vinyl Sulfones

The conjugate-addition literature is replete with examples illustrating the difficulty of adding basic nucleophiles (Grignard reagents, RLi, etc.) to β,β-disubstituted activated alkenes. Vinyl sulfones are no exception. Even the less challenging acyclic substrate **343** suffered only γ-metalation to allylic sulfonyl anion **344** before forming dimer **346** by conjugate addition.[134] In sharp contrast, the essentially nonbasic vinyl cuprate smoothly provided the desired adduct **347** (Scheme 54).[135]

The only other examples of successful nucleophilic addition to β,β-disubstituted vinyl sulfones are arguably special cases (cf. synthesis of **247**, Scheme 38). Doubly activated sulfone **349** gives the desired adduct **350** in high yield, yet in the catalytic process, the substrate undergoes preferential 1,2-addition, affording tertiary alcohol **348** in unspecified yield.[136] Cyclopropenyl sulfones devoid of γ-hydrogens reveal another interesting dichotomy.[137] While phenyl-substituted cyclopropenyl sulfone **353** reacts with *n*-BuLi to give **351** by replacement of the sulfonyl moiety, methyl cuprate is able to cleanly undergo conjugate addition to afford **355**. In contrast, substrate **354**, bearing the trimethylsilyl "hetero *t*-butyl group", is inert to the dimethylcuprate reagent, even during extended reaction times (Scheme 55).

An example of a successful addition of organolithium reagent to a β,β-disubstituted vinyl sulfone bearing a highly

Scheme 55



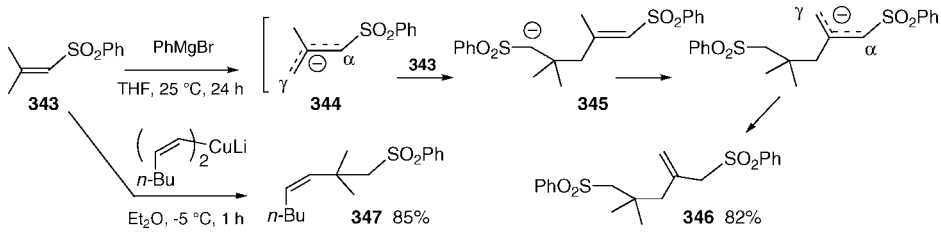
activated γ-hydrogen involves the *intramolecular* double cyclization of intermediate **358**, which yielded a 4:1 mixture of **359** and **360**.[76] Clearly, kinetic formation of the benzotetrahydrofuran ring enabled preferential cyclization to **359** in direct competition with deprotonation of **357** to give unwanted dienylic sulfone **360** (Scheme 56).

A highly noteworthy example features addition of metalated dioxopiperazine **361** to β-silyl vinyl sulfone **362**, which gives alcohol **364** after deprotection of the OTBS (O-*tert*-butyldimethylsilyl) group.[103] This is *the only example of a formally intermolecular C−C bond formation* by addition to a β,β-disubstituted vinyl sulfone bearing allylically activated γ-hydrogens. It seems reasonable to postulate that reversible formation of siliconate **363** makes the reaction an intramolecular 5-*exotrig* addition (Scheme 57). Oxidation of **364** to acyliminium ion **365** triggers intramolecular oxygen alkylation to form ether **226**. Application of the Kocienski reaction (Scheme 35) sets the key exocyclic methylene double bond of the bicyclomycin intermediate **227**.

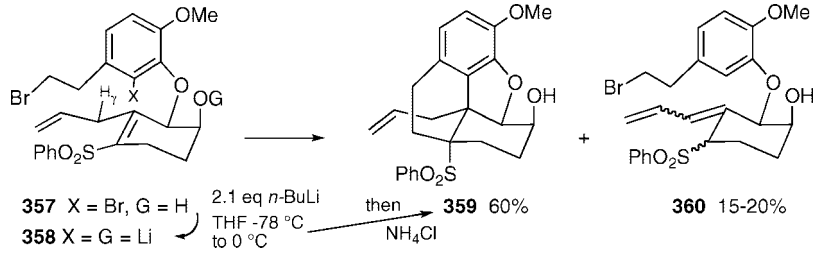
2.3.4. Addition of Radicals to Vinyl Sulfones

Vinyl sulfones having a low-lying LUMO (lowest unoccupied molecular orbital) are good coupling partners for carbon-centered nucleophilic radicals having a high-energy HOMO (highest occupied molecular orbital).[138] The ability

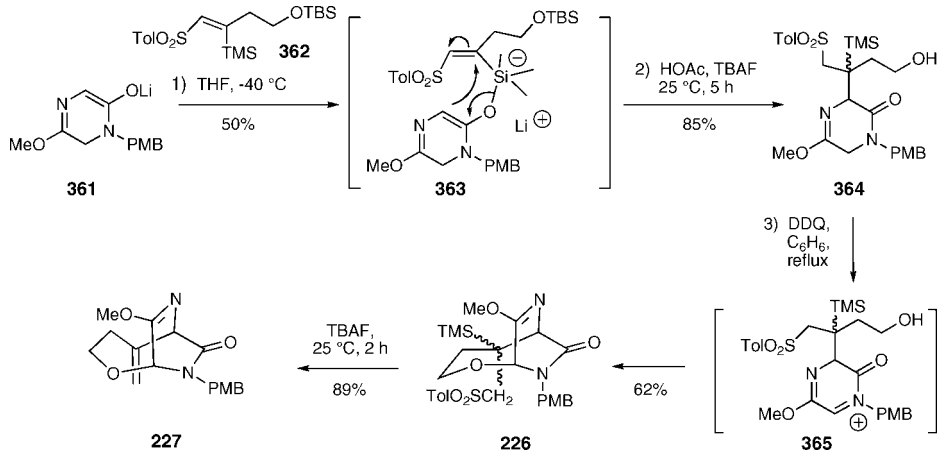
Scheme 54



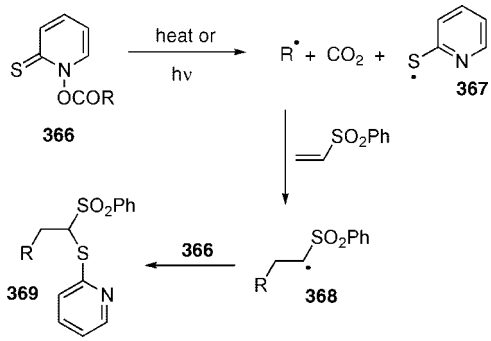
Scheme 56



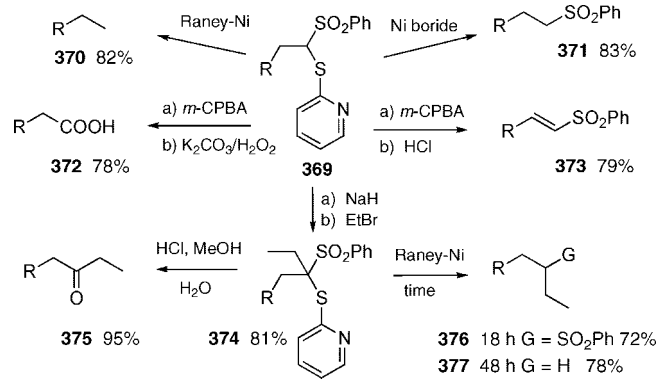
Scheme 57



Scheme 58



Scheme 59

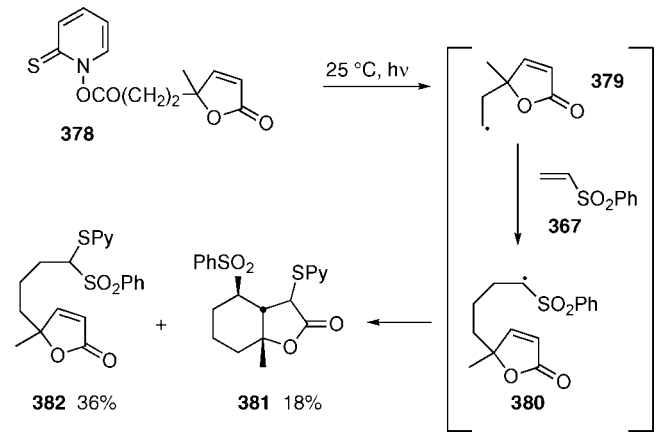


of the sulfone moiety to stabilize α-radicals further expands the repertoire of manipulations available to the synthetic chemist.

Barton, Togo, and Zard[139] have shown that vinyl sulfones react with carbon-centered radicals produced from the homolysis of thiohydroxamic acid ester **366**. The nucleophilic alkyl radical adds to phenyl vinyl sulfone, yielding radical **368** stabilized by the strong inductive effect of the sulfone (Scheme 58). By avoiding reductive quenching, **368** combines with **367** or the alkyl radical, allowing a plethora of further synthetic manipulations (Scheme 59). Yields of **369** vary from 70 to 100%.[140]

The importance of a matched HOMO−LUMO interaction was demonstrated by showing that intermolecular reaction of radical **380** with thiohydroxamate ester **378** occurred at twice the rate of the intramolecular cyclization of **380**, leading to **381** even in the presence of an excess of vinyl sulfone **367** (Scheme 60).[141] The desired pathway leading to **381** was favored only when the reaction conditions favored fast homolysis of **378**, so that it was no longer available to compete with the intramolecular process.[142] On the other

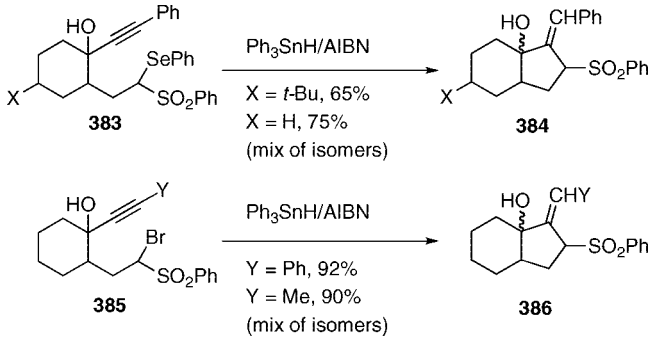
Scheme 60



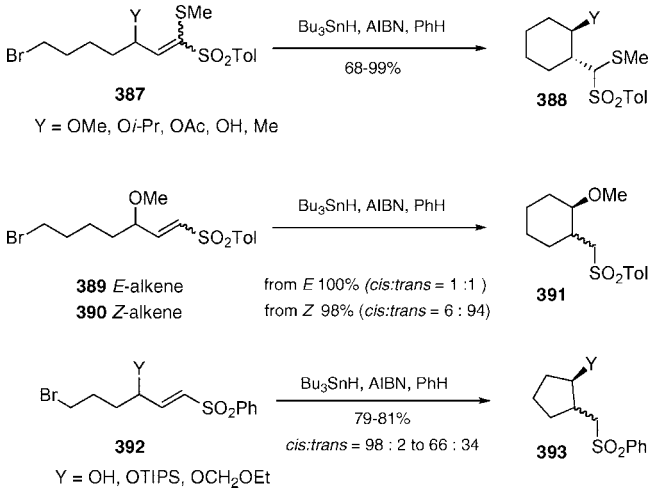
hand, when an electron-deficient radical reacts with an electron-rich multiple bond, good yields are realized (Scheme 61).[143]

Intramolecular addition of electron-rich radicals to vinyl sulfones has been successfully demonstrated with systems

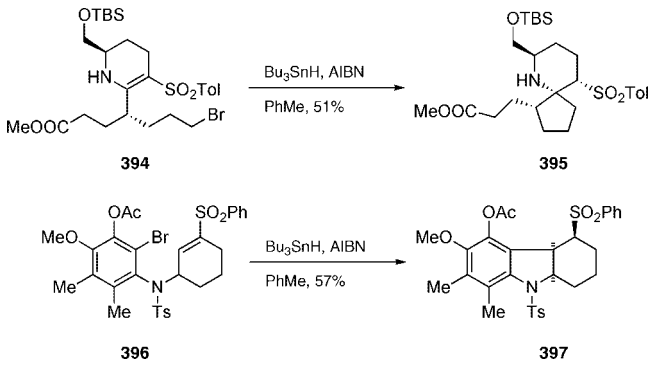
Scheme 61



Scheme 62



Scheme 63



of varying degrees of complexity. The presence of the vinyl sulfone results in efficient 6-*exotrig* ring closure[144,145] in addition to the more common 5-*exotrig* closures (Scheme 62).[146] In the former case, *trans*-configured products prevailed, while in the latter, *cis* products were preferred. Similar cyclizations were performed in good yields, yet with low *cis/trans* selectivities.[145] Scheme 63 provides two examples of radical addition/cyclization in natural product syntheses, including formation of spirocyclic piperidine **395** by *intramolecular* addition of the primary radical at the β,β-disubstituted vinyl sulfone of **394**.[147]

Finally, acyl radicals generated from acyl selenides have been shown to effectively undergo intramolecular addition to vinylogous sulfonates, affording cyclic ethers in high yields and with *cis* selectivity (Scheme 64).[148] It was shown that both *cis*- and *trans*-configured vinylogous sulfonates (β-alkoxyvinyl sulfones) favor the *cis* product, although the selectivity is much higher in the case of the *cis* alkene by virtue of the 1,3-diaxial interaction in the transition state.

3. Synthetic Efficiency

3.1. Enantiopure Targets Increase Synthetic Difficulty

Achieving high material throughput is further exacerbated when targeting pure enantiomers. While asymmetric syntheses employing chiral catalysts with prochiral substrates are attractive because one molecule of catalyst generates many chiral progeny, issues such as catalyst cost and recovery may detract from this inherent advantage. The problem is further compounded by syntheses requiring remote centers of chirality, because one may have to repeatedly access the chiral pool. Furthermore, if the chemist is forced to adopt one of the stoichiometric reactions to achieve enantiopure products, the choice is often nonobvious (Scheme 65).[95]

3.2. Multiply Convergent Syntheses

The design of a synthetic blueprint has profound mathematical consequences on synthetic efficiency. In general, individual units of approximately equivalent complexity are best assembled "late" in the synthesis (Scheme 66). Careful selection of the number of segments adopted and the timing of their unification is intimately connected with the specific chemical strategy.

3.3. Exploiting Cyclic Vinyl Sulfones in Multiply Convergent Syntheses

A 1986 review by Braish[149] featured γ-oxygenated cyclic vinyl sulfones **58** and **59** as the focal point for multiply convergent conjugate addition/alkylation sequences (Scheme 67) to establish highly functionalized adducts **60**, which were subsequently elaborated to natural and non-natural products **407**−**411**. The strategic value of the phenylsulfone was that it allowed three (or more) highly functionalized segments to be rapidly assembled, followed by stereoselective desulfonylation (**407**−**409**) or elimination of the sulfone to an alkene for further functionalization (**410** and **411**).

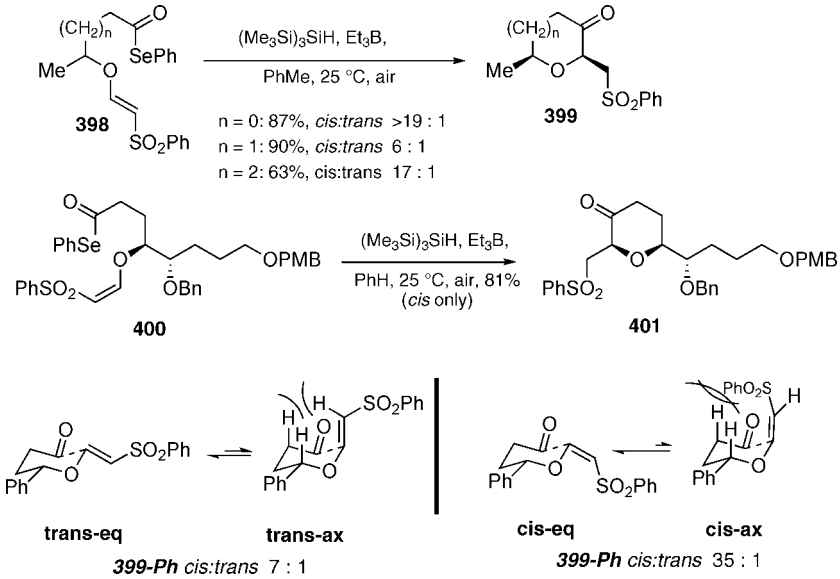
4. Cyclic Sulfones as Precursors to Termini-Differentiated Enantiopure Acyclic Arrays

4.1. Introduction to the Chiral Carbon Catalog

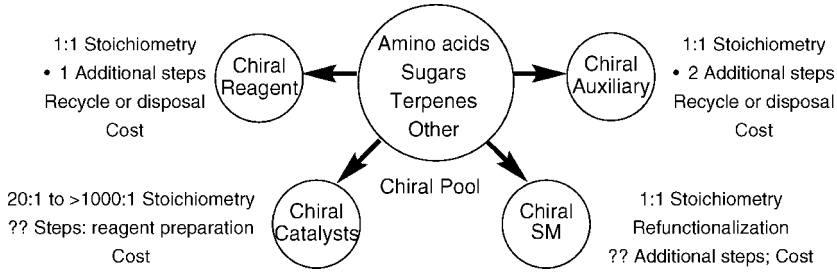
4.1.1. Polypropionates as Conformational Control Elements

It has long been recognized that peptides, nucleotides, and glycosides are recognition elements for many biological processes. This perception also applies to other classes of compounds like steroids, prostaglandins, β-lactams, etc. While the ability of DNA to code for the production of specific peptide sequences is a fundamental aspect of biochemistry, the hypothesis that polypropionate sequences impart biological information by serving as conformational control elements has yet to be explored on a systematic basis. The interplay between internal and external H-bonding interactions in combination with minimization of Me−Me *syn*-pentane overlap is likely to be an absolutely crucial factor in determining substrate−receptor binding of macrocyclic

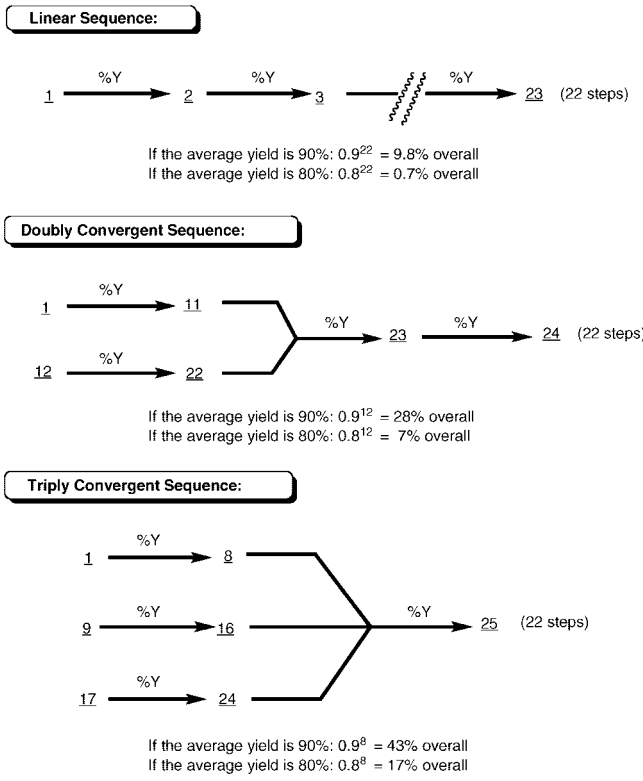
Scheme 64



Scheme 65



Scheme 66



drugs. Backbone stereochemical effects of individual natural products have largely been treated on an ad hoc basis, with systematic exploration seldom being undertaken.

The *R,R,R,R*-configured trimethyldiol stereopentad **412** (Scheme 68) is a polypropionate sequence found in many biologically active natural products.[152] Although stereopentads can exist in 32 stereoisomeric forms, it appears from examination of structure-searchable databases that *only 5 of these possibilities currently appear in natural products*. Even if additional permutations have been overlooked, it is clear that only a small number of stereoisomers are utilized by Nature in the construction of polypropionate natural products. *Because evolution has limited Nature's biological armamentarium, chemists are currently restricted with respect to examining collections of potential drugs bearing non-natural polypropionate stereopentad backbones.*

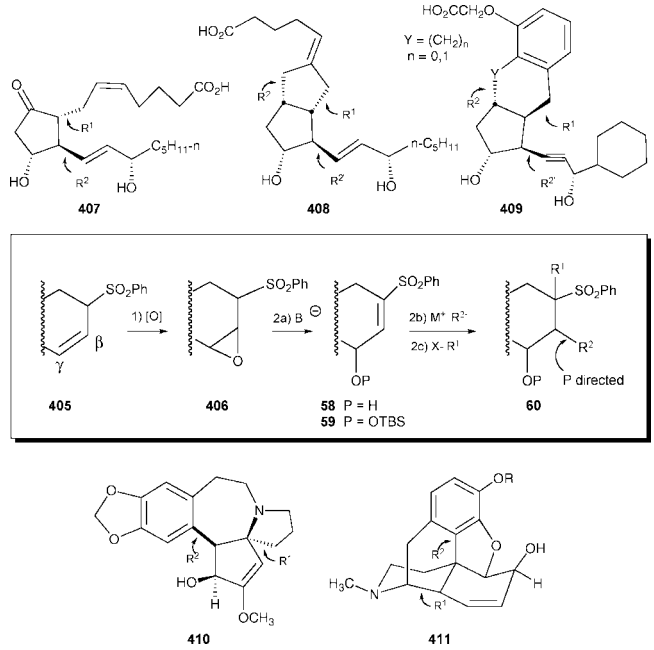
4.1.2. Segment Connection Strategy

A paper by Torres, Chen, and Kim describes uses of cyclic stereoselection followed by oxidative cleavage of 6- and 7-membered ring vinyl sulfones to efficiently access termini-differentiated 6- and 7-carbon backbone segments bearing up to 5 stereocenters.[46] These valuable materials can then be incorporated into advanced intermediates by conjunctive alkenylation reactions (Scheme 69).

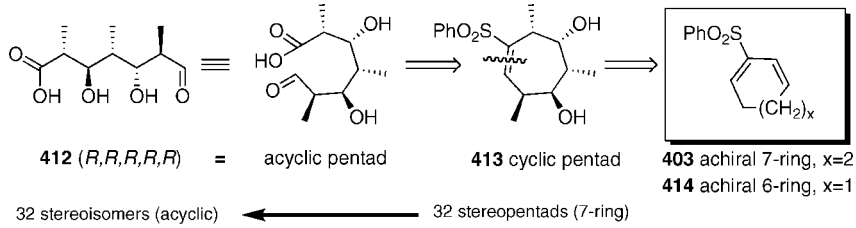
4.2. Large-Scale Synthesis and Enantioselective Epoxidation of Dienyl Sulfones

Achiral cross-conjugated dienyl sulfone **403** can conceptually serve as a starting material for all of the 32 stereoisomers of **412** implied in Scheme 68. Improved (10 mol) syntheses of dienyl sulfones **403** and **414** from thiophenol **420** and the corresponding cycloalkanones have been published by Park

Scheme 67



Scheme 68



and Torres.[42] For example, in a single operation without purification of intermediates, cycloheptanone **402** (Scheme 66) is successively converted to 1-phenylthiocycloheptene **421**, brominated to a mixture of **422**/**423**, oxidized to bromosulfones **424**/**425**, and treated with 1 equiv of pyridine. The S_N2' reaction of pyridine generates insoluble pyridinium salt **426** accompanied by a toluene solution of the unreactive minor β-bromovinyl sulfone **424**, which is easily removed. Dissolution of **426** in warm water, cooling, and addition of DABCO effects 1,4-elimination of the pyridine moiety, giving >1.1 kg of 98% pure sulfone **403** by simple filtration. Optimized, catalytic (1% loading in methanol) Jacobsen asymmetric epoxidation of **403** delivers either enantiomer of **66b** in *79% yield and >98% ee on the multimole scale* (Scheme 70).[42]

4.3. Epoxyvinyl Sulfone Stereodiads as Progenitors of Polypropionate Segments

4.3.1. First-Generation Synthesis of Dienyl Sulfide Stereodiads[42,46]

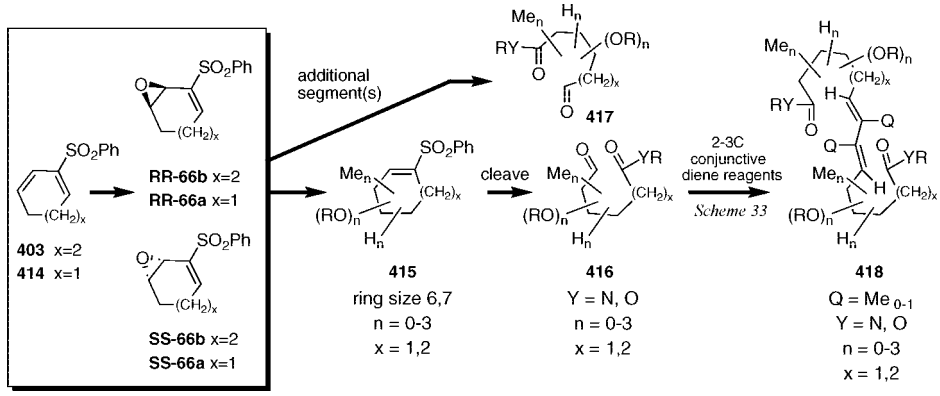
Reaction of oxygenated dienylsulfones *ent*-**404** with 2 equiv of methyllithium or methyl Grignard followed by diphenyl disulfide afforded *syn* methylated alcohol *syn*-**431** after warming to room temperature. This transformation is noteworthy in that the allyl sulfonyl anion intermediate *syn*-**427** underwent regioselective sulfenylation at the γ-position, affording vinyl sulfone *syn*-**429**. Monitoring of the reaction reveals that isomerization of intermediate vinyl sulfone *syn*-**429** to allyl sulfone *syn*-**431** occurs under the basic reaction conditions. Reaction of *syn*-**431** with aluminum trichloride in the presence of triethylamine effects regioselective elimination to dienyl sulfide *syn*-**433**. This elimination was formerly conducted using the more-costly trimethylsilyl triflate and triethylamine in methylene chloride at reflux.[150] This transformation again relies upon the unique *amphoteric nature of the sulfone moiety* (cf. Scheme 15).

Repeating this sequence using 1 equiv of methyl anion on TBS ether *ent*-**72** followed by addition of DBU to effect equilibration of *anti*-**430** to *anti*-**432** gives the complementary *anti* stereodiad *anti*-**434** by steric-directed *anti* methyl addition followed by parallel processing. This provides the pair of stereodiads *syn*-**433** and *anti*-**434** in 55−65% overall yield, from epoxide **66b** on >20 g scale (Scheme 71).

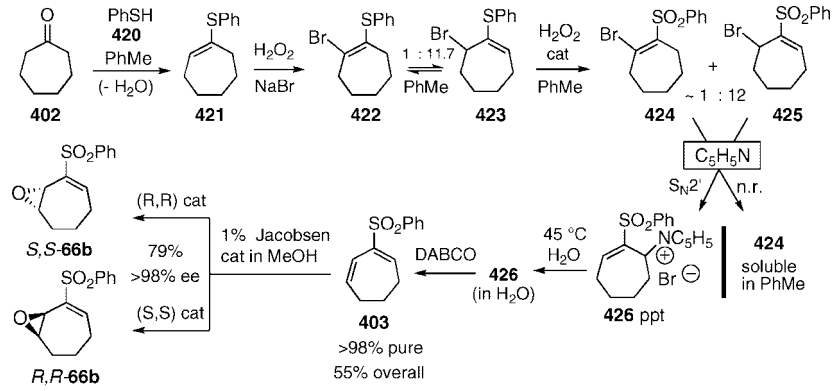
4.3.2. Second-Generation Synthesis of the Dienyl Sulfide Stereodiads

Although *anti*-**432** could be successfully prepared from *ent*-**72**, the reaction yielded a mixture of *anti*- and *syn*-diastereomers. The best result was 10:1 in favor of *anti* and the typical ratio was 7:1. Thus, it was desirable to prepare *anti*-**434** by opening the epoxide **66b** by direct *anti*-methylation. Reaction of *R,R*-**66b** with $AlMe_3/H_2O$ in dichloromethane exclusively afforded hydroxy vinyl sulfone *anti*-**435** in 93−99% yield. Treating *anti*-**435** with 3 equiv of base forms intermediate dianion *anti*-**427**, which gives vinyl sulfone *anti*-**436** upon reaction with diphenyl disulfide. The sulfenylation is regioselective at the γ-position but affords *anti*-**436** (Scheme 71) as a mixture of γ-sulfide diastereomers. Interestingly, dianion formation could be monitored by TLC, because *anti*-**437** is quantitatively

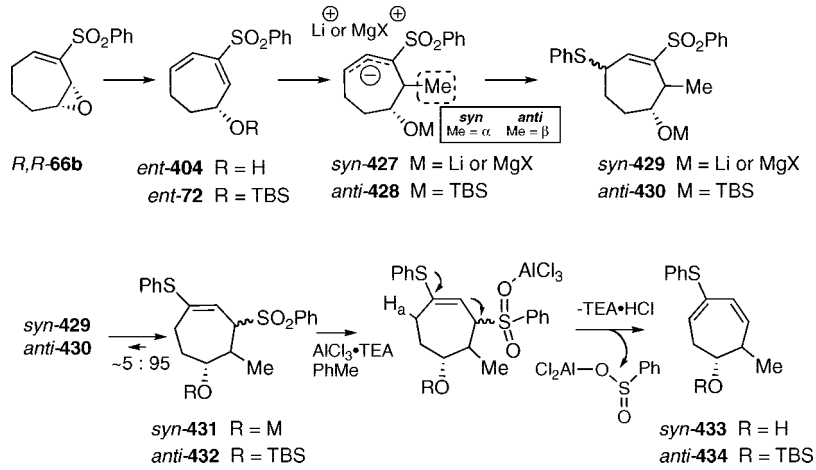
Scheme 69



Scheme 70



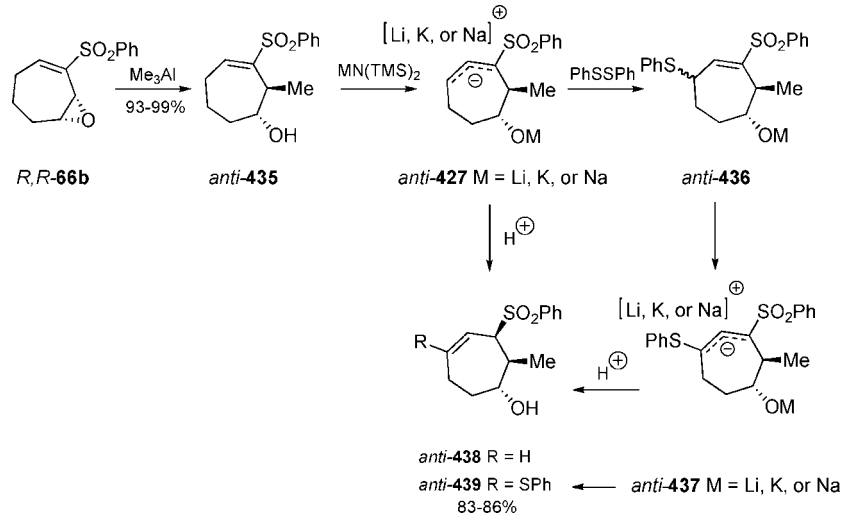
Scheme 71



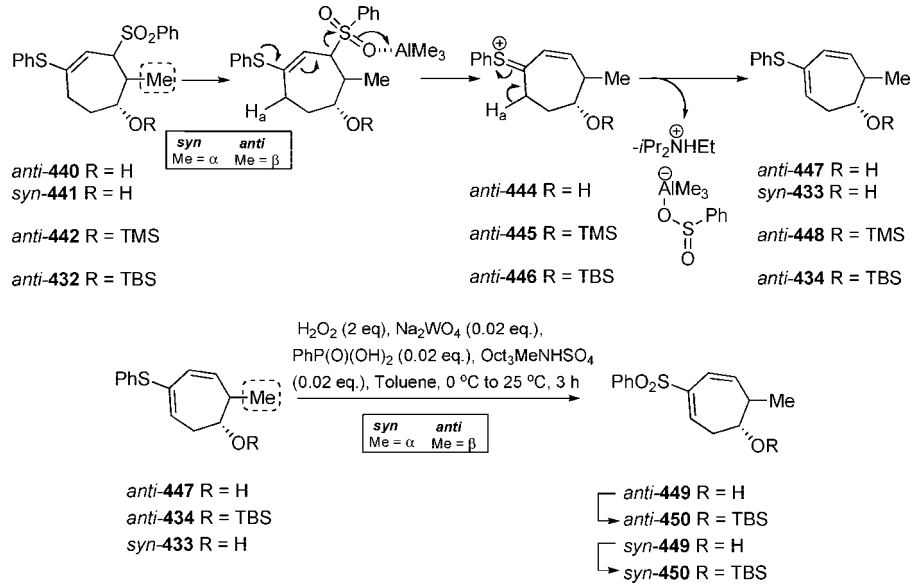
quenched on TLC to allyl sulfone *anti*-**438**. Na or K bases were comparable regarding dianion formation, with KHMDS being faster than NaHMDS (HMDS = hexamethyldisilazane). In contrast, LDA fails to effect the second metalation unless hexamethylphosphoramide (HMPA) is added. Under the optimal conditions, *anti*-**435** is deprotonated to dianion *anti*-**427**, sulfenylated, further deprotonated to dianion *anti*-**437**, and finally quenched regio- and stereoselectively to γ-phenylsulfonyl vinyl sulfide *anti*-**439** in 83−86% yield (Scheme 72).

As described in Scheme 71, treating *syn*-**431** and *anti*-**432** with $AlCl_3$/triethylamine affords dienyl sulfides *syn*-**433** and *anti*-**434** as the major products. However, application of this protocol to *anti*-**440** faced technical difficulties that demanded a more-convenient combination of reagents. The problems included using hygroscopic $AlCl_3$ on large scales, its short shelf life, and its irreversible complexation with triethylamine, which deactivated both species. Moreover, triethylammonium hydrochloride precipitates from solution, making stirring especially difficult at low temperature. $AlMe_3$/*i*Pr_2NEt avoids the aforementioned problems and reduces reaction time from 18 to 2 h. Thus, treating *anti*-**440** with $AlMe_3$/*i*Pr_2NEt triggers the regioselective elimination of sulfonyl moiety to give vinyl thionium ion *anti*-**444**. Proton H_a in *anti*-**444** is abstracted by *i*Pr_2NEt to afford *anti*-**447** almost exclusively. Similarly, *syn*-**441**, *anti*-**442**, and *anti*-**432** smoothly provided dienyl sulfides *syn*-**433**, *anti*-**448**, and *anti*-**434** in yields of 90−100%. Finally, subjecting dienyl sulfide *anti*-**447** to the seminal Noyori sulfide oxidation protocol[151] delivered dienyl sulfone *anti*-**449** in quantitative yield. TBS protection of *anti*-**449** affords *anti*-**450** in quantitative yield. Similarly, *anti*-**434** quantitatively affords

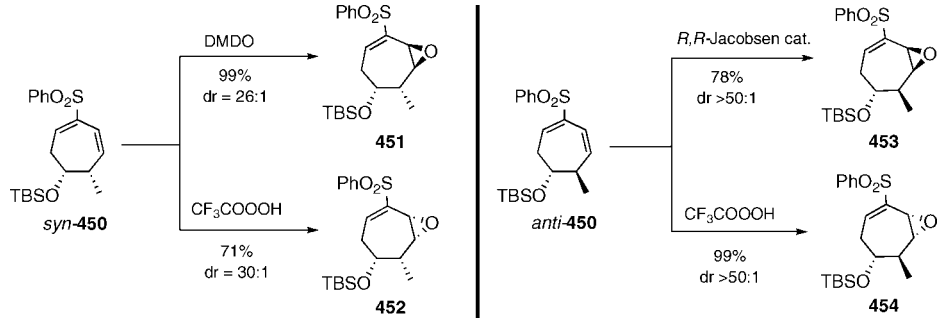
Scheme 72



Scheme 73



Scheme 74

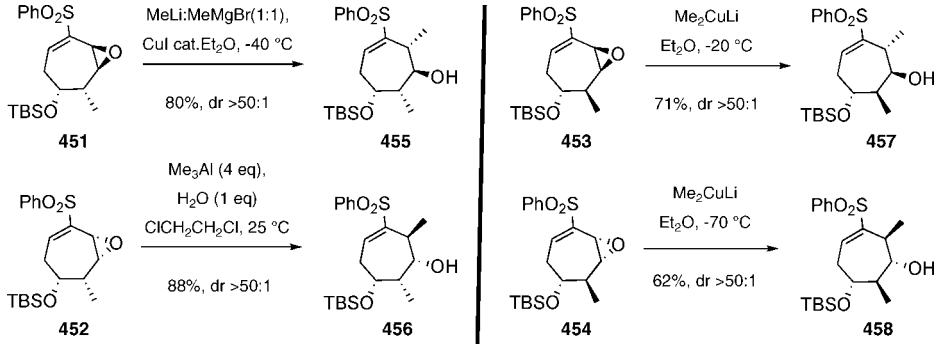


anti-**450** under the Noyori conditions. Applying the same sequence to the *syn* series, Noyori oxidation of dienyl sulfide *syn*-**433** affords dienyl sulfone *syn*-**449** quantitatively. The TBS protection of *syn*-**449** to *syn*-**450** is also quantitative. This modified sequence generates dienyl sulfone *anti*-**450** in 80−85% *overall yield* from epoxide **66b**. Conveniently, this second-generation strategy affords the *anti*-diastereomer, avoids chromatography, and is reproducible on >75 g scale (Scheme 73).

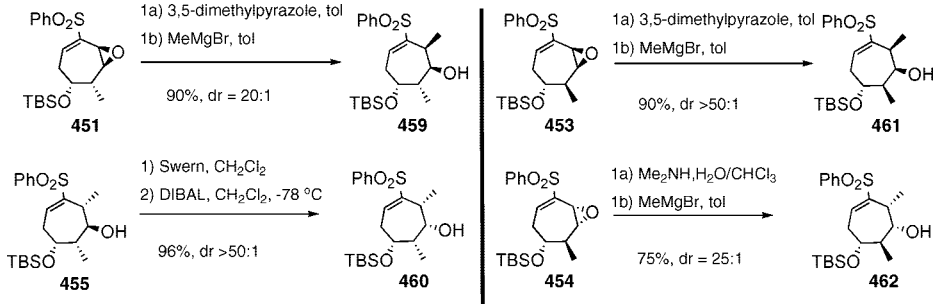
4.3.3. Synthesis of a 7-Carbon Sulfone Family of Stereotetrads

As a logical extension to the chemistry of Torres, Chen, and Kim (Scheme 11),[46] El-Awa and Mollat du Jourdin developed a systematic approach for the stereocontrolled synthesis of all eight diastereomeric dipropionate stereotetrads.[152] The approach featured stereoselective epoxidations of dienylsulfones *syn*-**450** and *anti*-**450** producing all four

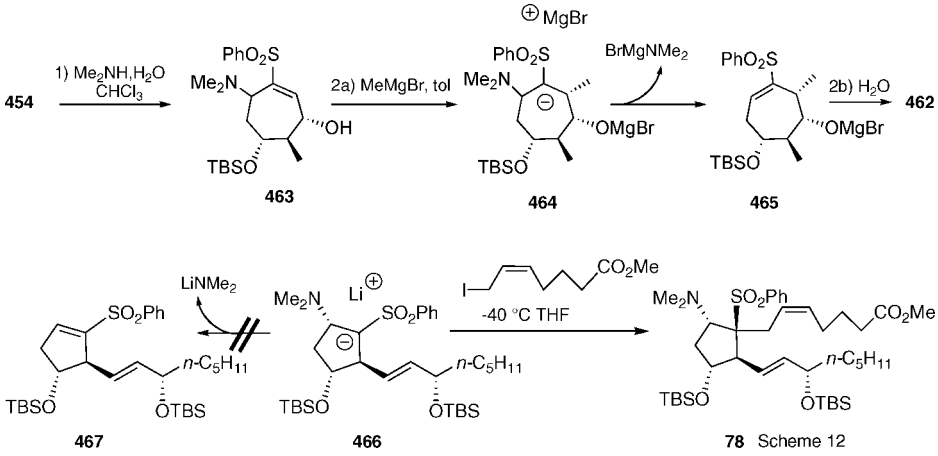
Scheme 75



Scheme 76



Scheme 77



78 Scheme 12

epoxides **451**, **452**, **453** and **454** in high diastereomeric ratios. In three of the four epoxidations, substrate control was successfully employed, while double diastereoselection with the (*R,R*)-Jacobsen catalyst[153] was necessary to achieve stereoselective synthesis of **453** (Scheme 74).

Reaction of epoxides **451**, **452**, **453** and **454** with various nucleophilic methylation reagents afforded stereotetrads **455**, **456**, **457** and **458** in high diastereomeric purities (Scheme 75).

syn-Methylation of the epoxide set required a more subtle approach. Hence, these epoxides were first treated with a soft nucleophile that effected clean 1,4-addition, and the intermediates were subsequently treated with MeMgBr in situ resulting in net 1,2-*syn*-methylation. This protocol was successfully applied to epoxides **451**, **453** and **454**; however, epoxide **452** gave the undesired 1,2-*anti* product **456**. Consequently, stereotetrad **460** was accessed by oxidation/reduction of tetrad **455** (Scheme 76).

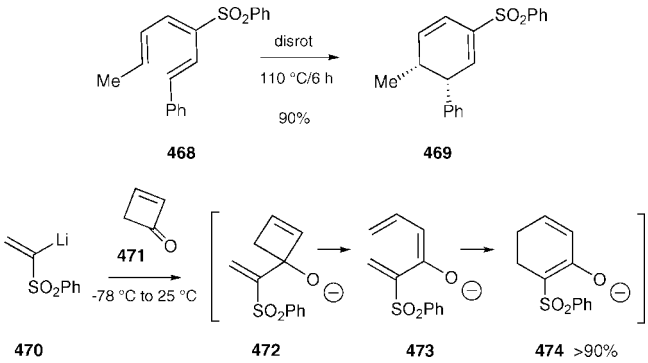
In the cases of **451** and **453**, the 3,5-dimethylpyrazole group serves as an excellent leaving group because of its anion-stabilizing capability. In stark contrast, it was completely unexpected that the dimethylamino moiety of anion **464** would act equivalently, since it had been previously established that lithiated α-sulfonyl anion intermediate **466** was impervious to β-elimination of $LiNMe_2$.[47] In retrospect, it appears that the elimination reaction of **464** is driven by the enhanced strength of the Mg−N bond, which exceeds that of the Li−N bond by 13 kcal/mol (Scheme 77).[152]

4.4. Alternative Access to Functionalized 6-Ring Vinyl Sulfones

4.4.1. Electrocyclization of Acyclic Trienyl Sulfones

While the synthesis of the parent cross-conjugated cyclohexadienyl sulfone **414** is readily achieved on a large scale either by Bäckvall's phenylsulfonyl mercuration of 1,3-cyclohexadiene followed by the β−elimination of mercury[0][154] or as shown in Scheme 69, several interesting electrocyclizations provide highly functionalized (racemic) cyclohexadienyl sulfones. For example, in 2004 Brandänge

Scheme 78



and Leijonmarck reported a concise route to cross-conjugated cyclohexadienyl sulfone **469** using a 1,6-electrocyclic reaction of triene **468** (Scheme 78).[155] In the same year, Magomedov demonstrated that metalated vinyl sulfone **470** adds to cyclobutenone **471** to afford alkoxide intermediate **472**, which suffers conrotatory opening to trienolate **473** followed by facile (presumably charge-accelerated) disrotatory cyclization to the cyclohexadienolate **474** (Scheme 78).[156]

4.4.2. 7-Oxabicyclo[2.2.1]hexane-Based Strategies

The use of 7-oxabicyclo[2.2.1]hexanes developed by Vogel, termed the "naked sugar strategy",[157] has evolved by inclusion of the vinyl sulfone moiety and has been effectively advanced by the Spanish School of Arjona and Plumet at Madrid.[30,32,44g,h,132,133,158] Application of this approach for the synthesis of enantiopure 6-carbon polypropionates as shown in Scheme 79 is extensively documented in the references given. The synthesis begins with asymmetric Diels−Alder reactions of furan **475** to ultimately give the key bicyclic vinyl sulfones **477** and **482**. Oxygen-directed conjugate addition/β-elimination of the strain-activated ether moiety gives **478** and **483** with simultaneous creation of a new vinyl sulfone bearing the *syn* methyl/alcohol configuration. Further processing with oxidative cleavage of the six-membered ring delivers the fully elaborated stereotetrads **479** and **485** in 12 and 13 operations, respectively.

4.5. Synthesis of Functionalized 5-Ring Vinyl Sulfones[149]

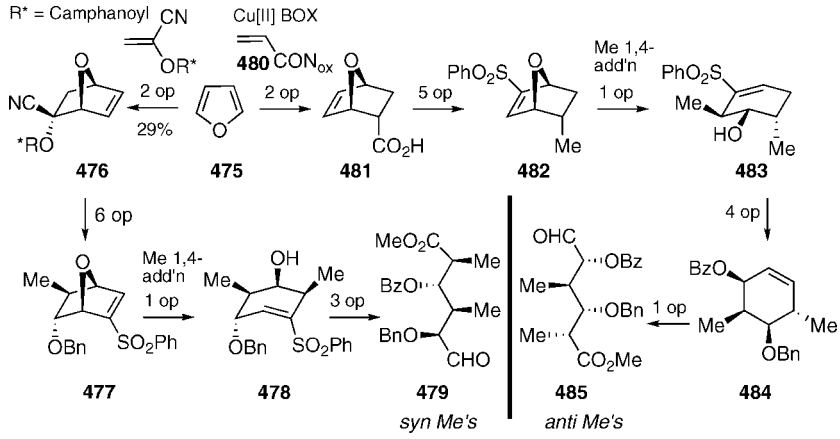
4.5.1. First-Generation Synthesis of 5-Ring Vinyl Sulfone Stereodiads

Derivatives of enantiopure vinyl sulfone **492** are useful intermediates for the synthesis of cephalotaxine, prostaglandin, carbacyclin, and its analogues.[117,159] Synthesis of this material, while achievable on the >100 g scale, involved nine operations and included a classical resolution, factors unattractive to organic chemists in the new millennium (Scheme 80).

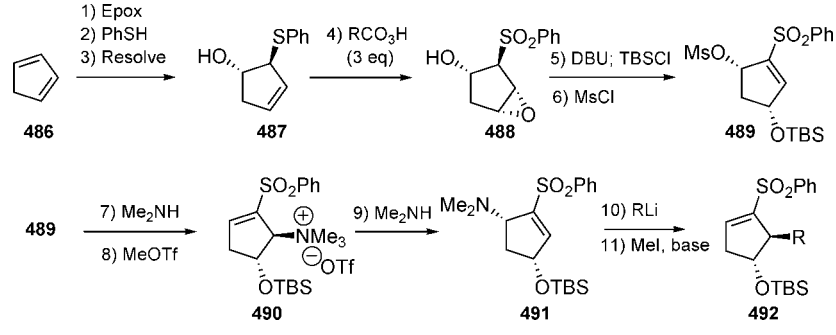
4.5.2. Second-Generation Synthesis of 5-Ring Vinyl Sulfone Stereodiads

A more satisfactory synthesis of enantiopure 5-ring starting materials was accomplished on a large scale with minimal financial expenditure.[92] HCl gas was added to neat cyclopentadiene **486** to generate 3-chlorocyclopent-1-ene. Immediate treatment of this exceptionally reactive allylic halide (not shown) with sodium acetate provided racemic allylic acetate **493** in 60% yield. Application of the Trost catalytic deracemization protocol gives the known allylic sulfone **494** in >90% yield and with >95% ee.[91] Epoxidation of **494** with MCPBA followed by treatment with base provides an

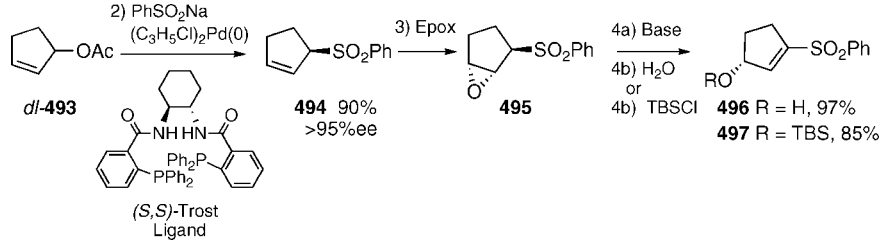
Scheme 79



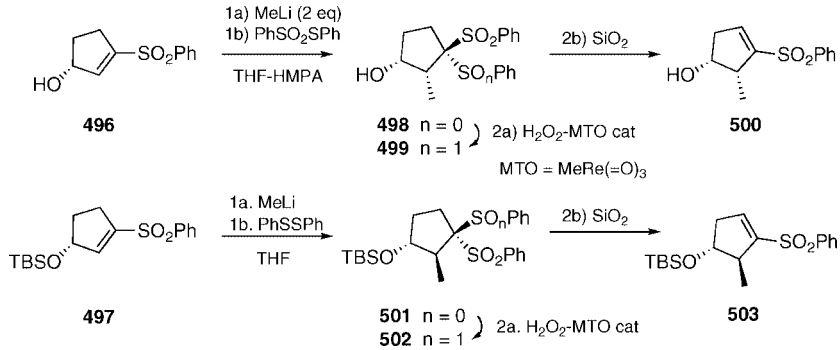
Scheme 80



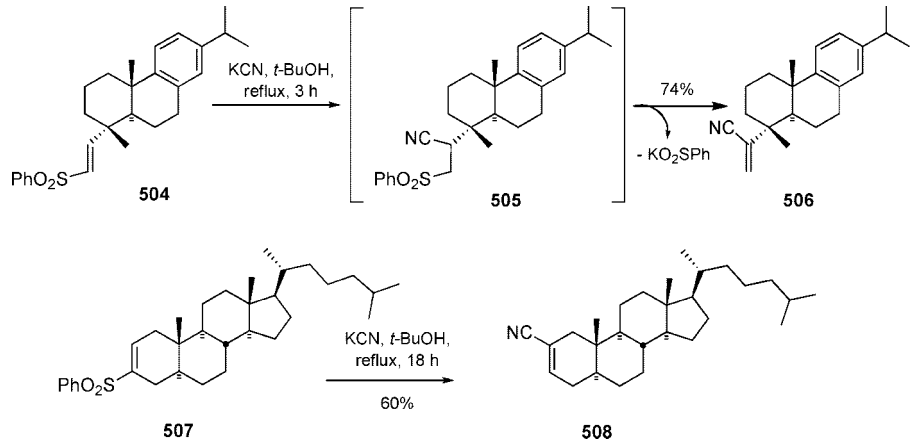
Scheme 81



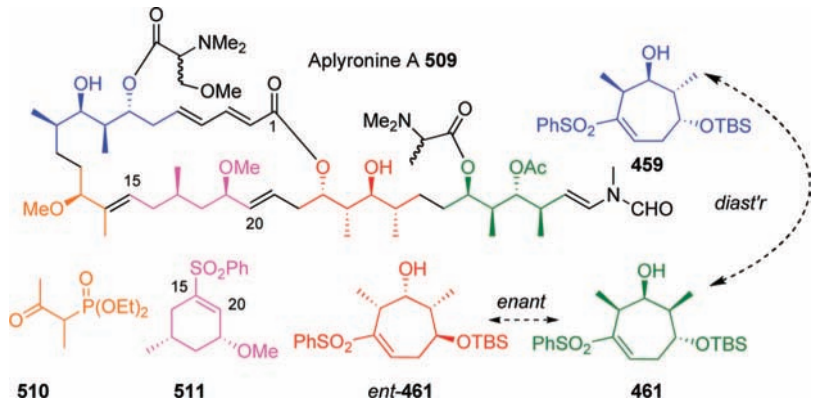
Scheme 82



Scheme 83



Scheme 84

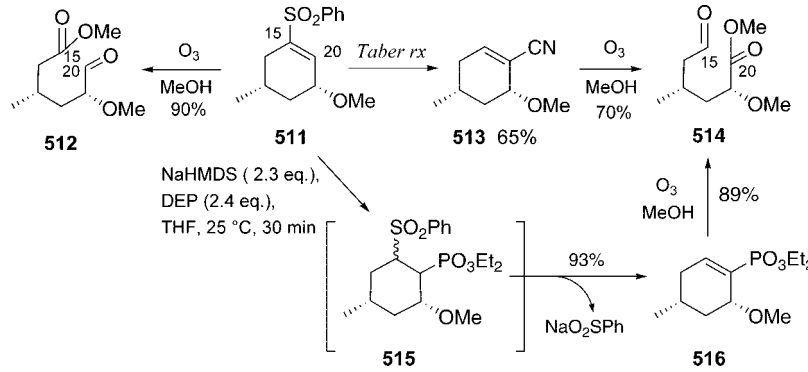


efficient synthesis of alcohol **496** or TBS ether **497** as a function of the quenching protocol employed (Scheme 81).

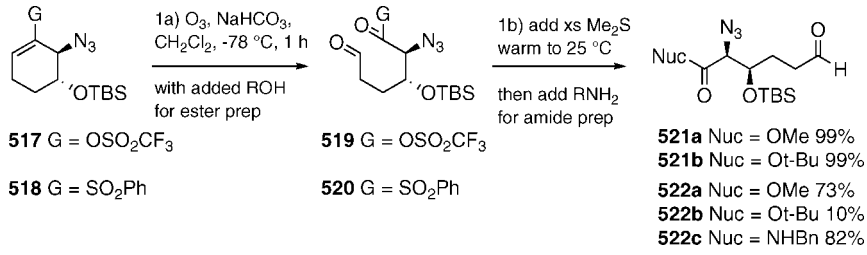
Compounds **496** and **497** are useful enantiopure intermediates for stereoselective synthesis of termini-differentiated five-carbon fragments. As previously demonstrated, treatment of alcohol **496** with 2 equiv of methyllithium results in oxygen-directed methylation; sulfenylation of the α-sulfonyl anion with phenylthiothiolsulfonate affords α-thiophenyl sulfone **498** as a 6:1 mixture with its chromatographically separable diastereomer (not shown). Oxidation of **498** to **499** and treatment with silica gives *syn* adduct **500** in 74% yield (Scheme 82).[92]

Silyl ether **497** provides access to the complementary stereodiad **503**. For example, treatment of **497** with methyllithium in THF at −78 °C followed by addition of diphenyl disulfide gives sulfide **501** in 78% yield. This material need

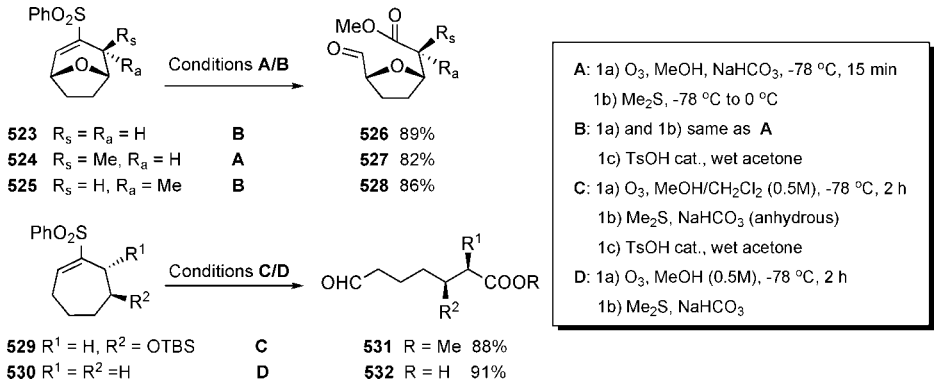
Scheme 85



Scheme 86



Scheme 87



not be isolated but is directly oxidized to sulfoxide **502** after the sulfenylation reaction. Chromatography of **502** on silica gel affords the desired vinyl sulfone **503** in quantitative yield (Scheme 82).

4.6. Vinyl Sulfone Transpositions Resulting in Reversal of Alkene Polarity

4.6.1. Vinyl Sulfone to Vinyl Nitrile Transposition

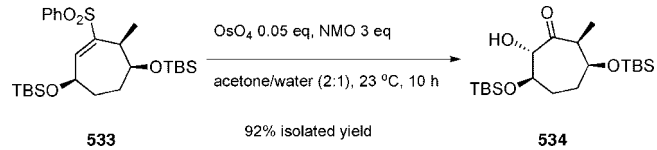
Similar to α,β-unsaturated carbonyl compounds, the β-position of vinyl sulfones is activated toward nucleophilic addition. Taber and Saleh first demonstrated that β-addition of cyanide to a vinyl sulfone followed by elimination of sulfinate anion provides a transposed acrylonitrile with reversed polarity (Scheme 83).[160] The reaction is fastest with acyclic terminal vinyl sulfones and needs only 2.5−3.0 h to give acrylonitriles (cf. **506**) in good yield. Although the transposition is also successful with acyclic internal and cyclic vinyl sulfones, protracted reaction times are needed to furnish transposed acrylonitriles such as **508**.

4.6.2. Vinyl Sulfone to Vinylphosphonate Transposition

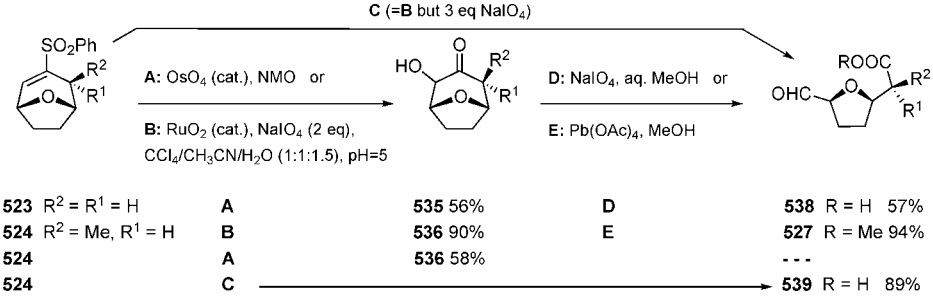
In conjunction with a sulfone-based approach to Aplyronine A **509**, it was desirable to oxidatively cleave vinyl sulfone **511** in order to furnish the termini-differentiated aldehyde ester **512** (Schemes 84, 85).

Although this sequence was successful,[161] a modification in the final coupling strategy necessitated preparation of the end-to-end "reversed" aldehyde ester **514**. Taber's transposition offered a ready solution, and vinyl sulfone **511** was successfully converted to acrylonitrile **513** in 65% yield. In order to avoid the use of KCN for large-scale reactions, phosphite anions were evaluated as "greener" nucleophiles to effect an equivalent transposition. Indeed, Noshi et al. showed that treating vinyl sulfone **511** in anhydrous THF with a mixture of diethyl phosphite (2.4 equiv) and NaHMDS (2.3 equiv) at 25 °C rapidly furnished vinylphosphonate **516** in 93% yield. Ozonolysis of **516** gave **514** in 89% yield as compared to 70% from **513** (Schemes 84, 85).[161]

Scheme 88



Scheme 89



4.7. Oxidative Cleavage of Vinyl Sulfones and Vinylphosphonates

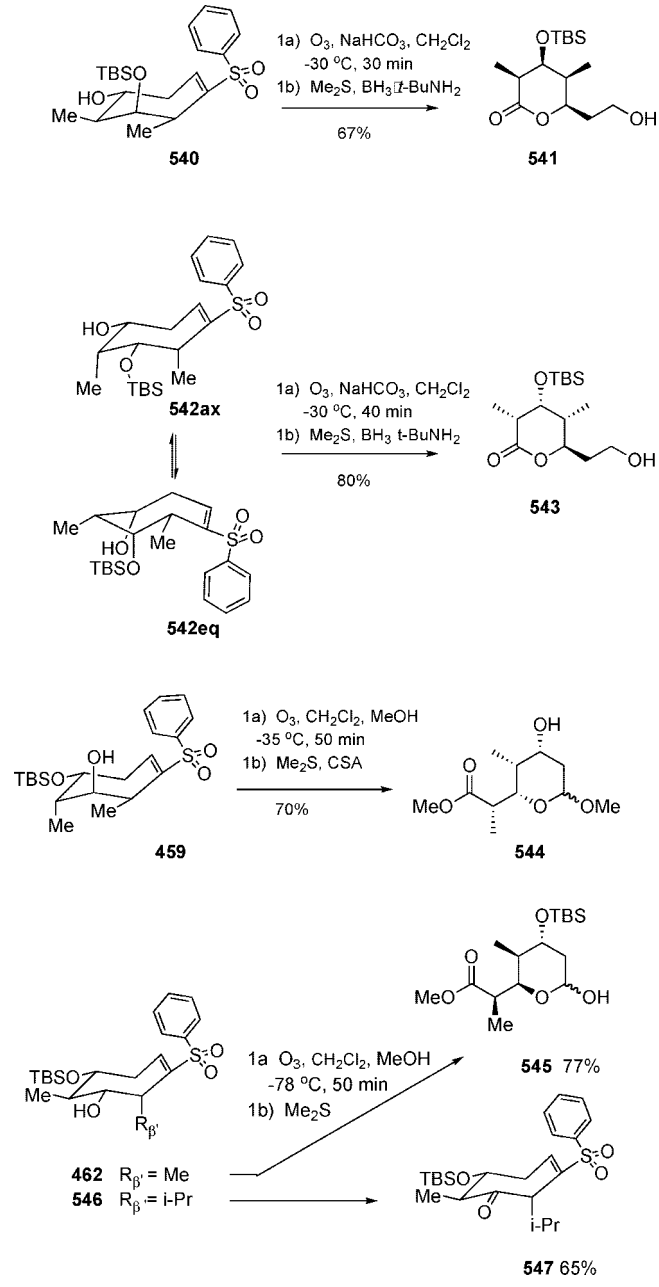
Although ozonolytic cleavage of simple and electron-rich alkenes is well-documented in the literature,[162] the reactivity of enol triflates (cf. **517**) or vinyl sulfones (**518**) was largely unexplored until Hentemann's work in the late 1990s.[163] In spite of their low reactivity, enol triflates and vinyl sulfones can be successfully cleaved to provide a wide variety of termini-differentiated products by varying the nature of the nucleophile (MeOH, *t*-BuOH, and $BnNH_2$) (Scheme 86). Enol triflates are generally more effective with regards to esterification than vinyl sulfones, where *t*-BuOH is ineffective in providing the *t*-butyl ester−aldehyde **522b**. It is significant that amide−aldehydes such as **522c** can also be prepared by ozonolysis of vinyl sulfones provided that the residual ozone is destroyed with dimethyl sulfide prior to addition of the nucleophilic amine.[45] While ozonolysis of the enol triflate may occur by nucleophilic addition to the molozonide rather than the mixed triflic anhydride **519**, ozonolysis of vinyl sulfones likely involves formation of acyl sulfone **520**, which reacts readily with water or other nucleophiles[164] to provide carboxylic acids, esters, and amides.

Jiang[165] expanded the scope of ozonolysis to cycloheptenyl sulfone substrates, showing oxabicyclic vinyl sulfones **523**−**525** can also be successfully cleaved (Scheme 87). Vinyl sulfones **529** and **530** require strictly anhydrous conditions to avoid formation of unwanted carboxylic acid and/or hemiacetal side products. Furthermore, vinyl sulfones **529** and **530** are relatively unreactive, requiring concentrations higher than 0.1 M to proceed at a reasonable rate.[166]

Alternative methods have been employed to circumvent the limitations of ozonolysis. For example, Bäckvall has shown that reaction of **523** with OsO_4 performs dihydroxylation paired with elimination of phenylsulfinic acid to provide α-hydroxyketone **535** in modest yield. Subsequent oxidative cleavage then affords the corresponding carboxylic acid−aldehyde **538** (Scheme 89, method A).[167] In a synthetic approach to IKD-8344, Jiang employed this osmylation protocol with **533** to deliver α-hydroxyketone **534** (Scheme 88).[168] Unfortunately, this method cannot be used on a regular basis as sterically encumbered vinyl sulfones suffer low yields. Later, Jiang showed that the stronger and smaller oxidant RuO_4 is able to accomplish the same transformation with a higher reaction rate and in excellent yields.[168] RuO_4 provides the α-hydroxyketone **536**, which can be cleaved by $Pb(OAc)_4$ to give the desired methyl ester−aldehyde **527** (Scheme 89, methods B/E) or the carboxylic acid−aldehyde **539** by sequential in situ dihydroxylation/oxidative cleavage (Scheme 89, method C).

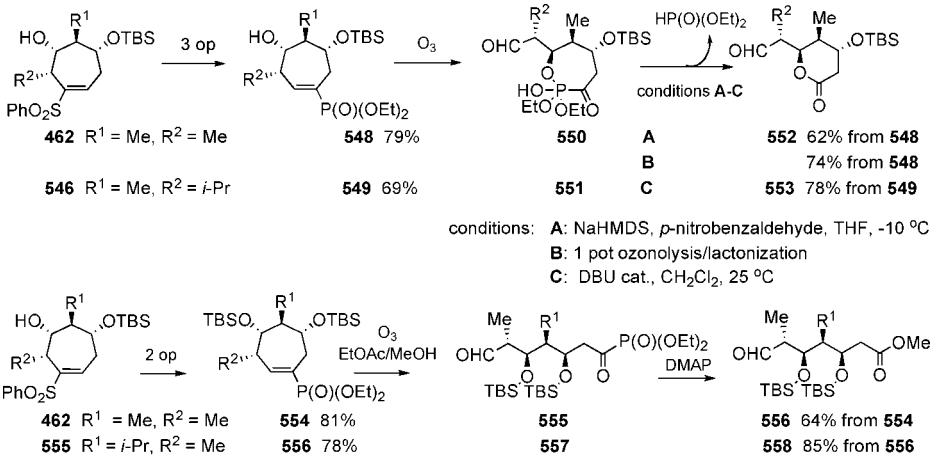
The high yields and reaction rates combined with the simplicity of the RuO_4 protocol are noteworthy. However, the low cost of ozone, the straightforward reaction conditions, and the absence of toxic byproduct provide advantages over RuO_4; therefore, ozone still remains the initial reagent explored for oxidative cleavage of vinyl sulfones.

Scheme 90

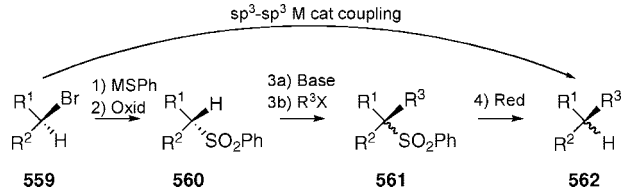


Ozonolysis of tetrasubstituted cycloheptenyl sulfones is generally effective for providing acyclic polypropionate segments (Scheme 90).[152] However, substituents located in the β' position of the vinyl sulfone substantially diminish

Scheme 91



Scheme 92



reactivity. While cycloheptenyl sulfones (not shown) bearing no alkyl group at β'-position smoothly undergo high-yield ozonolysis within 15 min at −78 °C, cleavage of substrates **540**, **542**, **459**, and **462** bearing methyl at this position require 30−50 min at −30 °C to deliver products **541**, **543**, **544**, and **545**. However, ozone treatment of substrate **546** bearing an *axial i-propyl group* results in oxidation of the secondary alcohol to afford ketone **547** in complete preference to ring cleavage at −78 °C (Scheme 90).

To circumvent the aforementioned lack of reactivity, vinyl sulfones **462**, **546**, and **555** were converted to vinylphosphonates **548**, **549**, **554**, and **556** in 69−82% yield using Noshi's conditions (Scheme 85; cf. **511** → **516**).[161] Interestingly, ozonolysis of **554** and **556** in CH_2Cl_2/MeOH does not provide aldehyde−methyl ester **556** and **558** but rather give the easily isolable aldehyde−acylphosphonates **555** and **557** in near-quantitative yield, consistent with the greater stability of acylphosphonates[169] relative to acyl sulfones. Detailed exploration of the ozonolysis of these vinylphosphonates by Mollat du Jourdin showed that the desired methyl esters could be obtained as sole reaction products as a function of the order of addition of solvent ($EtOAc/CH_2Cl_2$, MeOH) and base (DMAP, $NaHCO_3$) by phosphite/MeOH exchange (Scheme 91).[170]

Ozonolysis of intermediates **548** and **549** is complete at −78 °C within 5 min. However, aldehydes **550** and **551** are obtained along with the desired lactones **552** and **553** in ∼6:1 ratio. These α-hydroxyphosphonates, whose structure was known since the late 1990s,[171] are known to expel diethylphosphite under mildly basic conditions[172] or during purification by flash chromatography.[173] In the present case, lactonization to **553** can be driven to completion in high yield by treatment with DBU in dichloromethane,[174] whereas base-sensitive substrate **550** is converted to **552** in 62% yield at low temperature in the presence of NaHMDS with an added sacrificial aldehyde to trap the liberated diethylphosphite. It was found later that **552** could be obtained directly from **548** in 74% yield after optimization of the experimental protocol (Scheme 91).

5. Conclusions

The lessons that Trost teaches about atom economy have occasionally prompted questions about the strategic validity of the phenyl sulfone methodology since the sulfone moiety is not retained in the final product.[175] When considering the efficiency of *any synthesis*, one must evaluate all "indirect" methods, including those employing phenyl sulfones. For example, conversion of generic bromide **559** to phenyl sulfone **560**, C−C bond formation to **561**, followed by reductive cleavage to **562** has failed to exploit the pluripo-

Scheme 93

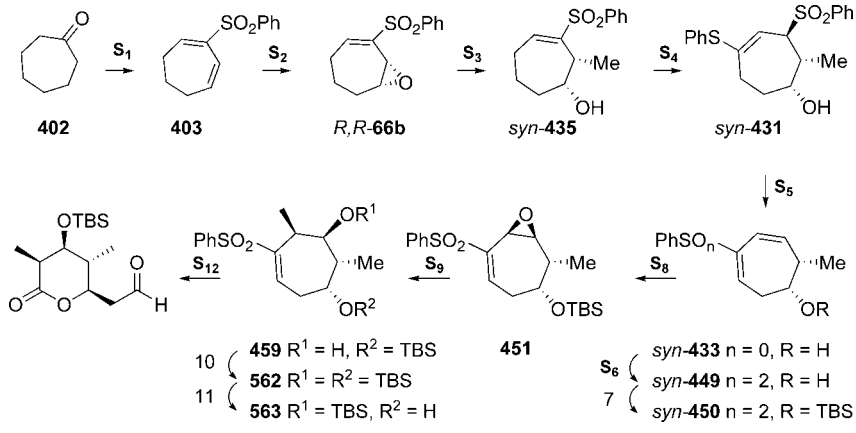


Figure 2. Establishing the synthetic pyramid as viewed by the research associate in the laboratory. Artwork by artist Ed Blackwell. Scanned image copyright 2009 Philip L. Fuchs.

tentcy of the phenyl sulfone. The overall operation requires an introduction/removal of the activating function simply to install a single C−C bond (probably without stereochemical control). This limitation is especially obvious in the 21st century, where synthesis of **562** from **559** would likely be achieved by a single metal-catalyzed stereocontrolled operation (Scheme 92).

The cumulative power of the sulfur functionality is nicely illustrated in the synthesis of enantiopure lactone **564** (Scheme 93). In this sequence, 9 of the 12 operations are either unique to organosulfur intermediates (mainly the phenyl sulfone) or are powerfully enhanced relative to what is currently achievable using other functional groups. The major criticism of the sequence mainly resides with the three steps (7, 10, and 11) that involve protecting-group manipulation.

As evidenced by the entire review, the authors assert that the pluripotent phenyl sulfone is arguably the most versatile functional group available to the synthetic organic chemist.

6. Acknowledgments

This review includes more than 200 person-years of phenyl sulfone research in the Fuchs group and is dedicated to the outstanding individuals whose names are given in the accompanying citations. This work is further dedicated to the memory of Ed Blackwell, whose whimsical and creative water color paintings, including Figures 1 and 2, have reminded the PI and his students of the inherent danger in trying to match wits with Mother Nature.[176]

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(176) To further appreciate the art of Ed Blackwell, and his Purdue influence, see: http://www.agriculture.purdue.edu/connections/fall2005/pg05_01.htm.

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