VOLUME 71, NUMBER 24

JOC Perspective

NOVEMBER 24, 2006

Adventures in Sulfur−Nitrogen Chemistry

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Received May 20, 2006

This account reviews our efforts over the past 37 years to understand the chemistry of a select group of sulfur−nitrogen compounds including sulfinimines (*N*-sulfinyl imines) and *N*-sulfonyloxaziridines. Our early exploration of the thermal properties of sulfenamides, a class of sulfur−nitrogen compounds about which little was known, resulted in a new procedure, the silver-assisted method, for the construction of sulfenimines (*N*-sulfenyl imines). Selective oxidations of these compounds resulted in the production of *N*-sulfinyl imines (sulfinimines) and *N*-sulfonyloxaziridines. *N*-Sulfonyloxaziridines turned out to be a new class of aprotic neutral oxidizing reagents. Enantiomerically pure examples afford high ee values in the oxidation of enolates to α-hydroxy carbonyl compounds and in the oxidation of sulfides and selenides to sulfoxides and selenoxides. Additions of organometallic reagents to enantiomerically pure sulfinimines provide the best and most versatile method for the asymmetric construction of the carbon−nitrogen stereocenters found in many biologically active compounds. Sulfinimine-derived chiral building blocks provide efficient access to many classes of nitrogen heterocycles including aziridines, 2*H*-azirines, pyrrolidines, and piperidines.

Introduction: Early Studies

Prior to the 1960s, molecules containing the sulfur−nitrogen bond were largely unexplored but offered the potential for discovery of new chemistry with useful applications. The genesis for these ideas came from my studies at Syracuse University where my Ph.D. mentor, Donald C. Dittmer, introduced me to the joys and frustrations of heterocyclic organic sulfur chemistry (thiacyclobutene) and from my work as a Welch Postdoctoral Fellow with the late Michael J. S. Dewar at the University of Texas, where I studied boron−nitrogen and boron−oxygen heteroaromatic compounds.

As an assistant professor, my earliest studies focused on the mechanisms of the thermal rearrangements of sulfenamides (ArS-NHAr) a class of sulfur−nitrogen compounds about which little was known at that time.[1,2] We found two types of reactions are characteristic of arenesulfenanilides on heating at 160 °C: (i) homolytic cleavage of the S−N bond to give sulfenyl and amino radicals, which leads to disulfides and azobenzenes, and (ii) intermolecular rearrangement to 2- and 4-aminodiphenyl sulfides via heterolytic cleavage of the S−N bond.

Metal-Assisted Synthesis of Sufenamide Derivatives. Sulfenamides are usually prepared by condensing a sulfenyl chloride (ArSCl) with an amine. The disadvantages of this procedure include the thermal and moisture sensitivity of sulfenyl chlorides and their high reactivity toward nucleophilic substrates such as hydroxy and active methylene groups as well as multiple bonds. These considerations preclude the synthesis of sulfenamides having these reactive functionalities. As a way of circumventing these limitations, we designed a new method for their syntheses called the metal-assisted sulfenamide synthesis.[2,3] This procedure involves treating an aliphatic or aromatic disulfide with a metal salt such as silver nitrate followed by addition of a primary or secondary amine (Scheme 1). Yields are good to excellent for this one-pot procedure. In the course of these studies, we discovered that if ammonia gas is passed through the disulfide/$AgNO_3$ solution and an aldehyde or ketone is added, sulfenimines (*N*-sulfinyl imines) are produced in good to excellent yields for this one-pot reaction sequence (Scheme 1).[4]

Reactions of Sulfenimines. Sulfenimines were another class of sulfur−nitrogen compounds about which little was known.[2,4] Unsymmetrical examples exist as *E* and *Z* isomers with a barrier to syn/anti inversion of about 18 kcal/mol.[5,6] Sulfenimines react with organolithium reagents to form amines and give azaenolates on treatment with LDA. For example, 2-methylhexan-2-amine (**2**) is formed in 57% yield on reaction of *N*-(isopropylidene)benzenesulfenamide (**1**) with *n*-BuLi followed by hydrolysis (Scheme 2).[7] With LDA and benzyl bromide, sulfenimine **3** is obtained in 95% yield.[8]

10.1021/jo061027p CCC: $33.50
Published on Web 08/24/2006

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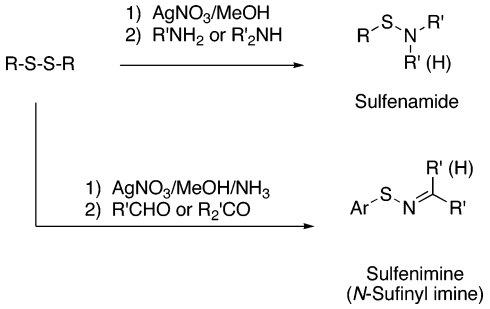

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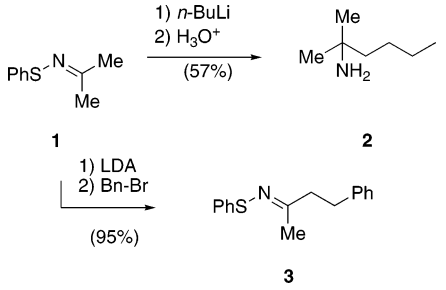

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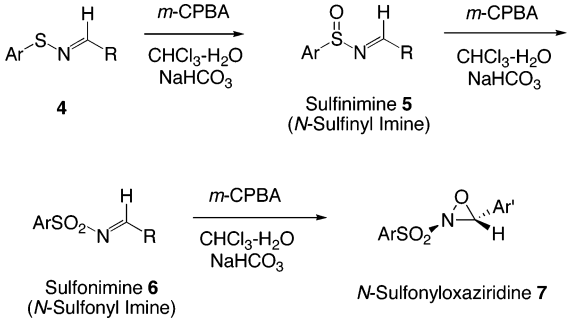

The stage was set for all of our futures studies on sulfur−nitrogen compounds and their derivatives when we began to explore the oxidation chemistry of sulfenimines. Selective oxidation of **4** with *m*-chloroperbenzoic acid (*m*-CPBA) in a two-phase system consisting of $CHCl_3-NaHCO_3-H_2O$ gave the corresponding sulfinimine **5** in excellent yield (Scheme 3).[9] With 2 equiv of *m*-CPBA, the sulfonimine **6** is produced and with excess *m*-CPBA the *N*-sulfonyloxaziridine **7** is obtained.[10] Both sulfinimines (*N*-sulfinyl imines) **5** and *N*-sulfonyloxaziridines **7** were unknown classes of compounds.

Sulfenic Acids

On heating at 80−100 °C, sulfinimines derived from aldehydes undergo a [2,3] sigmatropic rearrangement to give the nitrile and unstable sulfenic acids **8** as evidenced by trapping experiments with methyl propiolate to give the vinyl sulfoxide **9** (Scheme 4).[9] In the presence of TMS-Cl, thermolysis of **5** (Ar = 2-nitrophenyl) gives trimethylsilyl arenesulfenate **10**, which is a useful source of stable sulfenate ions ($ArSO^-$) on treatment with alkoxides.[11]

The importance of sulfenic acids as transient intermediates in organic and bioorganic sulfur reactions is well recognized, and the diversity of reactions attributed to this species is extraordinary.[12] The difficulty in studying sulfenic acids stems

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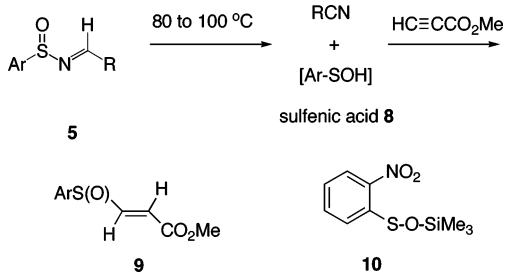

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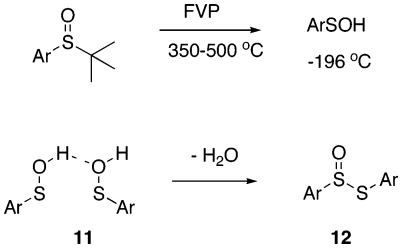

from the high reactivity of the acids and of their reaction products but also from the lack of mild methods to generate them.[13] Neither the hydrolysis of sulfenyl derivatives nor the thermolysis of sulfinimines or sulfoxides leads to stable sulfenic acids with the result that most of their chemistry has been inferred from studies of their end reaction products.[12]

To prepare sulfenic acids in good concentration under conditions where they are stable enough to be studied, we employed flash vacuum pyrolysis (FVP).[13] FVP of *tert*-butyl sulfoxides at 340−500 °C with condensation of the sulfenic acid on a liquid nitrogen coldfinger afforded these species in moderate to good yields as determined by trapping experiments with methyl propiolate (Scheme 5). From these studies, we concluded that the principal reaction of sulfenic acids is thiosulfinate **12** formation via a hydrogen bond dimer **11**, which illustrates their ability to function as both electrophiles and nucleophiles.[13,14] We suggested that the steric and electronic factors that inhibit formation of the sulfenic acid dimer **11** would lead to stable sulfenic acids.[15] While we never prepared an isolatable sulfenic acid the stability of recently reported sulfenic acids has been attributed to steric factors that inhibit formation of the dimer.[16]

N-Sulfonyloxaziridines: A New Class of Oxidizing Reagents

N-Sulfonyloxaziridines **7** were the first examples of an oxaziridine to have a substituent other than carbon or hydrogen attached to nitrogen.[17] These stable oxaziridines are readily prepared by biphasic-buffered oxidation of sulfonimines **6** with *m*-CPBA or potassium peroxymonosulfate (Oxone) (Scheme 3).[10,18,19] Sulfonimines (*N*-sulfonyl imines) **6** are conveniently prepared by heating sulfonamides (RSO_2NH_2) with aromatic aldehydes in the presence of an acid catalyst such as $TiCl_4$ or heating at 150−180 °C with the diethyl acetal of an aromatic aldehyde.[10b] Although *N*-alkyl and *N*-aryl oxaziridines are active oxygen compounds able to oxidize I^- to I_2, they are not reactive enough to oxidize other substrates. By contrast, we discovered that *N*-sulfonyloxaziridines **7** are able to oxidize nucleophilic substrates with reactivities similar to peracids (Figure 1).[17b]

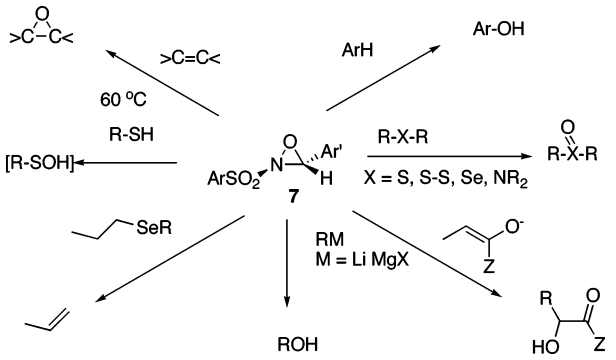

FIGURE 1. Oxygen-transfer reactions of *N*-sulfonyloxaziridines **7**.

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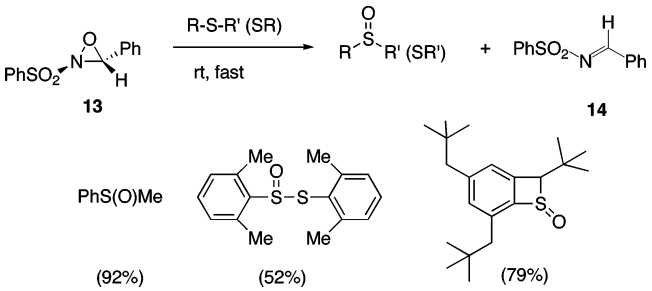

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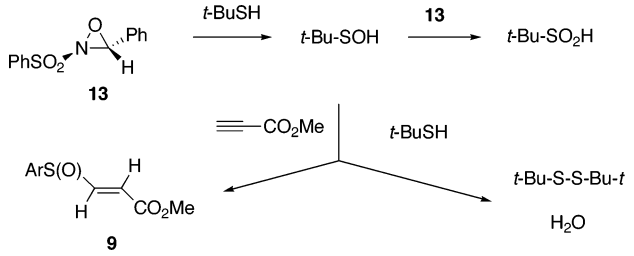

Oxidation of Organosulfur Compounds. *N*-Sulfonyloxaziridines such as 2-phenylsufonyl-3-phenyloxaziridine (**13**) rapidly oxidize sulfides and disulfides to sulfoxides and thiosulfinates without over oxidation (Scheme 6).[20−22] We demonstrated that the mechanism of oxygen transfer involves an S_N2-type attack of the nucleophile on the oxaziridine oxygen with displacement of the sulfonimine **14**.[23] We also devised a catalytic process for the selective oxidation of sulfides to sulfoxides.[22]

Because *N*-sulfonyloxaziridines are aprotic, neutral oxidizing reagents and do not react with alkynes, it was possible to obtained the first direct evidence that sulfenic acid intermediates are involved in the oxidation of thiols to higher sulfur oxides (RSO_xH) and to disulfides.[24] These transformations are among the most important biological reactions of thiols. Oxidation of 2-methyl-2-propanethiol (*t*-BuSH) with **13** in the presence of methyl propiolate affords the corresponding sulfenic acid as evidenced by isolation of the vinyl sulfoxide **9** (Scheme 7). In the absence of the trapping reagent, methyl propiolate, the sulfenic acid, which is an α-effect nucleophile, is rapidly oxidized to the sulfinic acid (*t*-$BuSO_2H$). The acid reacts with excess *t*-BuSH to give the disulfide and water.[24]

Oxidation of Carbon−Carbon Double Bonds. Like peracids, *N*-sulfonyloxaziridines epoxidize alkenes in a syn stereospecific manner.[17b,25] In contrast to peracids, oxidations using these reagents are much slower and require heating for 3−12 h

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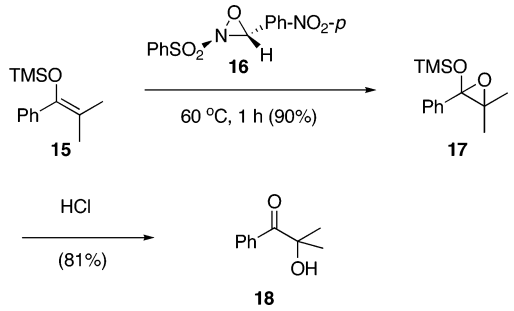

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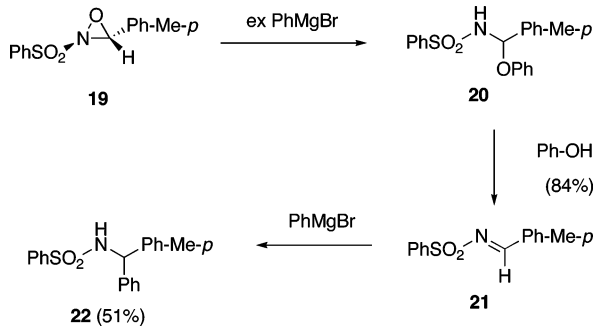
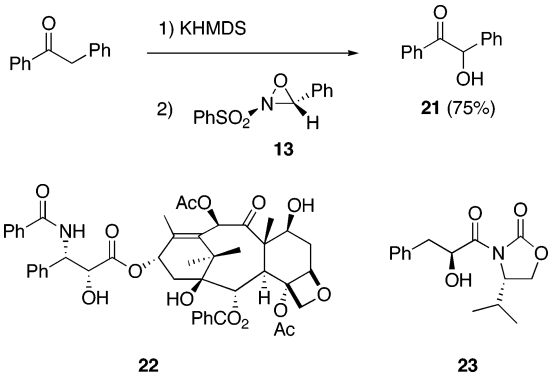


at 60 °C for useful yields. For this reason, the thermally more stable 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine (**16**) is employed. Using this reagent means that more nucleophilic substrates such as sulfides, selenides, and amines can be oxidized in the presence of C═C double bonds. Because *N*-sulfonyloxaziridines are neutral and aprotic, it is possible to prepare acid-labile epoxides. For example, heating silyl enol ether **15** at 60 °C for 1 h with oxaziridine **16** resulted in a 90% isolated yield of α-siloxy epoxide **17** (Scheme 8).[26] Elusive α-siloxy epoxides have been proposed as key intermediates in the Rubottom oxidation, the oxidation of silyl enol ethers to α-hydroxy aldehydes and ketone.[27] Indeed, treatment of **17** with trace acid afforded **18** in 81% yield.

Oxidation of Organometallic Reagents. Because *N*-sulfonyloxaziridines are neutral and aprotic they among the few reagents able to hydroxylate lithium and Grignard reagents (RM) to alcohols and phenols.[17a,28] For example, with excess phenylmagnesium bromide, oxaziridine **19** gives phenol in 84% yield (Scheme 9).[17a,29] Oxygen transfer is envisioned as attack of RM on the oxaziridine oxygen atom to give a hemiaminal intermediate **20**, which collapses to products. Sulfonamide **22** is formed by reaction of the organometallic reagent with the intermediate *N*-sulfonylimine **21**. The formation of this byproduct can be avoided by using one of the bulky (camphorylsulfonyl)oxaziridine reagents (see below).[29]

Without a doubt, the most widely used application of *N*-sulfonyloxaziridines is the α-hydroxylation of metal enolates to the α-hydroxy carbonyl functionality found in many biologically active natural products. The hydroxylation of enolates by *N*-sulfonyloxaziridines is the subject of a number of reviews.[17,28,30−32] Yields of α-hydroxylation are generally good to excellent. For example, the reaction of the potassium enolate of deoxybenzoin with oxaziridine **13** gave benzoin (**21**) in 75% isolated yield (Scheme 10).[32] Other prominent examples of the use of *N*-sulfonyloxaziridines to prepare α-hydroxy carbonyl compounds are found in Holton's Taxol (**22**) synthesis[33] and Evans' diastereoselective hydroxylation of chiral imide enolates **23**.[34]

SCHEME 10



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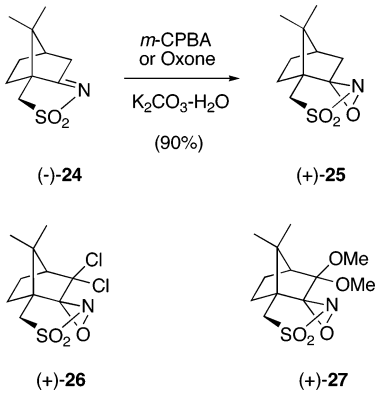

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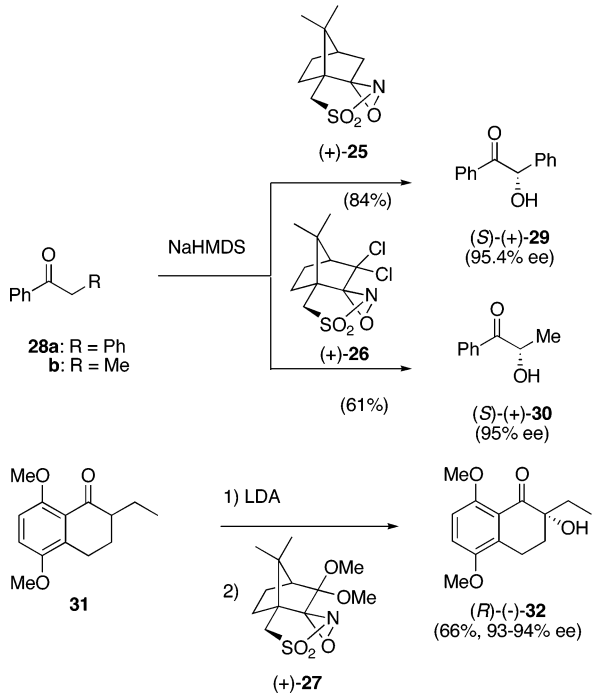


Asymmetric Oxidations Using *N*-Sulfonyloxaziridines

Our interest in asymmetric synthesis resulted from the realization that oxaziridines are unique among nitrogen-containing compounds in that they have a configurationally stable nitrogen atom at ordinary temperatures.[17] We saw that asymmetric oxidations would be possible with an optically active *N*-sulfonyloxaziridine, and because the nitrogen and carbon stereocenters are adjacent to the active-site oxygen atom, the asymmetric induction was predicted to be quite high.

(Camphorylsulfonyl)oxaziridine (+)-**25** is available by oxidation of the corresponding camphorsulfonylimine (−)-**24** with buffered potassium monopersulfate (Oxone) (Scheme 11).[35,36] Because of steric blocking of the exo face, oxidation can only take place from the endo-face of the C−N double bond and a single oxaziridine isomer is obtained. Sulfonimine (−)-**24** can be prepared on a large scale from camphor-10-sulfonic acid.[35c] Because the configuration of the oxaziridine three-membered ring controls the stereochemistry of the product, it is possible to "tune" the selectivity of these reagents by manipulation of the α-imino carbon in the sulfonimine prior to oxidation. This approach provides (camphorsulfonyl)oxaziridine derivatives such as (+)-**26**[37] and (+)-**27**,[38] several of which are commercially available.

Hydroxylation of Metal Enolates. The enantioselective hydroxylation of prochiral enolates with (camphorylsulfonyl)-oxaziridines produces the corresponding α-hydroxy compounds in good yield and high ee.[30−32] For example, hydroxylation of the sodium enolate of deoxybenzoin (**28a**) with (+)-(camphorsulfonyl)oxaziridine (**25**) at −78 °C affords (+)-(*S*)-benzoin (**29**) in 84% yield and >95% ee (Scheme 12).[39−41] Similarly, (*S*)-2-hydroxy-1-phenyl-1-propanone (**30**) is produced in 95% ee by oxidation of the sodium enolate of propiophenone (**28b**), this time using (+)-8,8-(dichlorocamphorsulfonyl)oxaziridine (**26**).[37] Oxidation of the lithium enolate of tetralone **31** to (−)-**32**, the AB ring synthon of the antitumor antibiotic rhodomycinones, with (+)-[8,8-dimethoxy dicamphoryl)sulfonyl]-oxaziridine (**27**) resulted in much better ee values (>94%) than did hydroxylation with (+)-**25** or (+)-**26** (Scheme 12)[38]

The stereoselectivity for enolate hydroxylations depends on the configuration of the oxaziridine three-membered ring, which means either enantiomer is readily available by using either the (+)- or (−)-oxaziridines. For hydroxylation of acyclic ketone enolates, the molecular recognition depends on the enolate geometry, the counterion, and the oxaziridine structure. Generally better selectivity was noted for the sodium *Z* enolates.[41] We suggest that these hydroxylations are consistent with an S_N2-type substitution of the enolate on the oxaziridine oxygen atom via an "open" transition state controlled by steric factors. *N*-Sulfonyloxaziridine asymmetric oxidations of metal enoaltes have been the subject of several reviews.[28,30,31]

Asymmetric Oxidation of Sulfides to Sulfoxides. Asymmetric oxidation of methyl 9-anthryl and *p*-tolyl sulfides with camphorylsulfonyloxaziridines (+)-**25** (3 and 73% ee)[35a] and (+)-**26** (54 and 42% ee)[42] produces the corresponding sulfoxides with poor to modest levels of asymmetric induction. To improve the enantioselectivity, we designed (−)-*N*-(phenylsufonyl)(3,3-dichlorocamphoryl)oxaziridine (**33**), which is one of the best and most general reagents for the asymmetric oxidation of diverse sulfides to sulfoxides (Figure 2).[43,44] As long as the difference in size of the two groups attached to the sulfur atom is large high ee's are observed. The absolute stereochemistry of the sulfoxide is controlled by the structure of oxaziridine.

Asymmetric Oxidations of Selenides to Selenoxides. In 1983, we reported the first example of an optically active selenoxide prepared in low ee (5−11%) by asymmetric oxidation of methyl aryl selenides with an optically active oxaziridine.[45] At that time, we demonstrated that selenoxide's con-

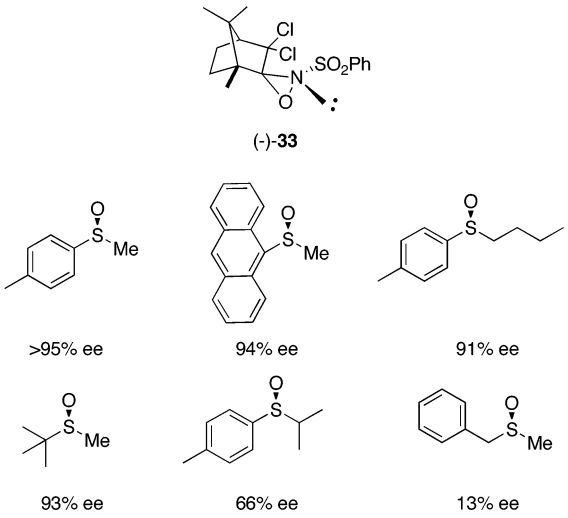


FIGURE 2. Asymmetric oxidation of sulfides using oxaziridine (−)-**33**.

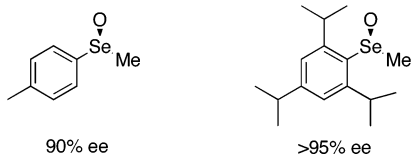
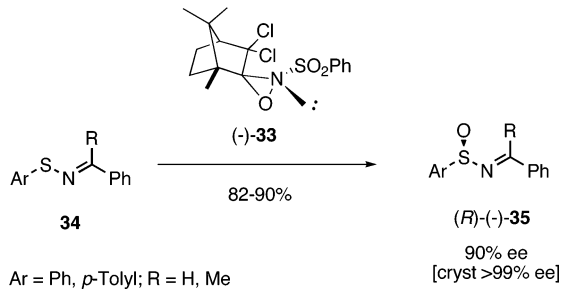


FIGURE 3. Asymmetric oxidation of selenides to selenoxides using (−)-**37**.

SCHEME 13



figurational liability was due to achiral hydrate formation, which is strongly acid catalyzed.[45,46] With oxaziridine (−)-**33**, asymmetric oxidation of selenides, under rigorously anhydrous conditions, produces selenoxides in high enantiomeric purity (90−95% ee) (Figure 3).[47] Bulky ortho substituents, which inhibit hydrate formation, where shown to slow racemization.

Asymmetric Oxidation of Sulfenimines to Sulfinimines. In 1992, we prepared the first examples of optically active sulfinimines (*N*-sulfinyl imines) (*R*)-(−)-**35**, derived from aldehydes, by asymmetric oxidation of sulfenimines **34** with oxaziridine (−)-**33** (Scheme 13).[48] The sulfinimines were obtained enantiomerically pure by crystallization.

Sulfinimines (*N*-Sulfinyl Imines): New Chiral Imine Building Blocks

Sulfinimines **36** provide a general solution to the problem of addition of organometallic reagents to chiral imines (Figure 4). In **36**, the electron-attracting sulfinyl group activates the C═N bond for nucleophilic addition. The sulfinyl auxiliary also exerts powerful and predictable stereodirecting effects, which results in addition of organometallic reagents to both enolizable and nonenolizable sulfinimines with high diastereoselectivities. Epimerization of the newly created carbon stereocenters in the sulfinamide product is inhibited because the sulfinyl group stabilizes anions at nitrogen. In contrast to aliphatic imines, aliphatic sulfinimines are stable and not particularly susceptible to deprotonation or self-condensation. Moreover, unlike other imine *N*-auxiliaries, the sulfinyl group in the product sulfinamide is easily removed under comparatively mild acid conditions and can be recycled into the Andersen reagent precursor.[49] The utility of sulfinimines **36** in the highly diastereoselective asymmetric syntheses of amine derivatives has been conclusively demonstrated by us[50] and more recently by the Ellman[51] and Senanayake[52] groups (Figure 4). The chemistry of sulfinimines has been reviewed.[50,51,52a]

Employing sulfinimine **36**, we introduced general methodology for the highly diastereoselective asymmetric syntheses of α-amino acids,[53] α-amino phosphonates,[54] *β*-amino acids,[55] *syn*- and *anti*-2,3-diamino esters,[56] α-amino aldehydes and ketones,[57] *β*-amino ketones,[58] 1,2,3,4-tetrahydroisoquinolines,[59] aziridine carboxylates,[60] and aziridine phosphonates[61] (Figure 4). *Indeed, the most direct and reliable method for the asymmetric construction of diverse amine derivatives having a nitrogen attached to a stereogenic center is the addition of an organometallic reagent to the C═N bond of enantiopure sulfinimines.*[50−52]

Synthesis of Sulfinimines. It was impractical to prepared sulfinimines by asymmetric oxidation of sulfenimines with oxaziridines (Scheme 13). If their full potential as chiral imine building blocks were to be realized, a more general and more concise methods for their preparation was essential. We realized this objective using the Andersen reagent, (+)- or (−)-menthyl *p*-toluenesulfinate (**37**), which is commercially available and can be produced on a large scale using the Solladie modification.[62,63] When **36** was treated with LiHMDS in the presence of various aldehydes, the corresponding enantiopure sulfinimines **36** (R^1 = H) were isolated in good to excellent yields (Scheme 14).[64] Although this one-pot procedure was general for aldehydes, it failed with ketones, and separation of the menthol byproduct was sometimes problematic. A much better method for sulfinimine synthesis is to condense *p*-toluenesulfinamide (**38**) with aldehydes and ketones using the mild Lewis acid dehydrating reagent $Ti(OEt)_4$.[65] Our synthesis of sulfinimines by this method with diverse aldehyde and ketones proved to be remarkably general, affording **36** in high yield and enantiomeric purity (Scheme 14). Both (+)- and (−)-**38** are commercially available and can be produced on a large scale.[66] 2-Methyl-2-propanesulfinamide introduced by Ellman[51] and Senanayake's[52] method for preparing diverse enantiopure sulfinamides, including **38**, represents important recent contributions to the chemistry of sulfinimines.

Sulfinimine-Derived Chiral Building Blocks. The current focus of our research is the design and synthesis of sulfinimine-derived polyfunctionalized chiral building blocks, templates, and scaffolds for the asymmetric synthesis of multisubstituted nitrogen heterocycles, amino acids, and amino phosphonates (Figure 5).[67] We require these building blocks to be easily prepared in both enantiomerically pure forms and provide efficient access to diverse classes of amine derivatives with a minimum of chemical manipulation and protecting group chemistry.

In the above context, we introduced *N*-sulfinyl aziridine 2-carboxylates for the synthesis of 2*H*-azirine 2-carboxylates

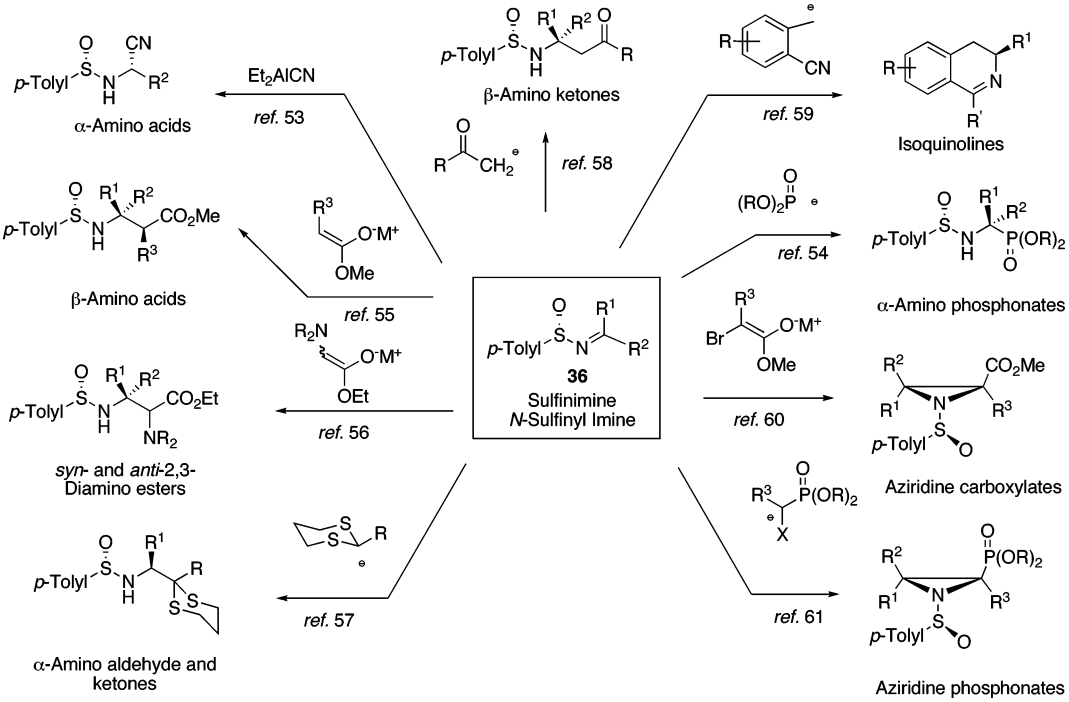
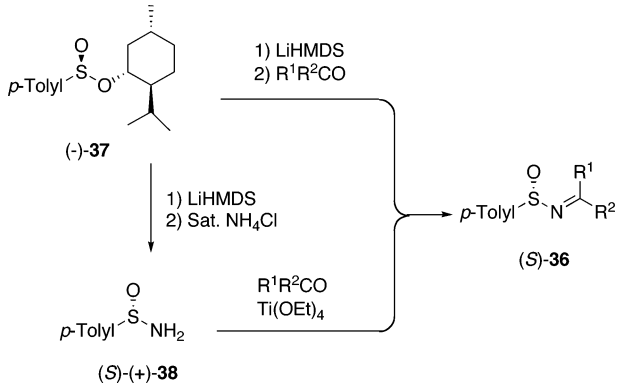


FIGURE 4. Reactions of sulfinimines with organometallic reagents to produce chiral nonracemic amine derivatives.

SCHEME 14



and α- and *β*-amino acids;[60a,d,68] 2*H*-azirine-3-phosphonates for the synthesis of aziridine 2-phosphonates and α-amino phosphonates;[69] α-amino 1,3-dithianes for the synthesis of α-amino aldehydes and ketones (useful in the preparation of pyrrolidines);[57] *N*-sulfinyl *β*-amino aldehydes and ketones[58] for the synthesis of 2,3,6-trisubstitued 4-piperidones,[58b] 2,3,5,6-tetrasubstituted 4-piperidones,[58c] and *trans*-2,5-disubstituted pyrrolidines;[70] *N*-sulfinyl *δ*-amino *β*-ketoesters[71] for the asymmetric synthesis of 2,4,6-trisubstituted piperidines[72] and 2,3,5-trisubstituted pyrrolidines (prolines);[73−75] and *δ*-amino *β*-ketophosphonates for the asymmetric synthesis carbocyclic nucleosides[76] and pyrrolidines.[77,78] Generally, these building blocks are prepared in one or two steps by addition of an enolate species to a sulfinimine or a sulfinimine-derived building block.

2*H*-Azirines. *N*-Sulfinylaziridine 2-carboxylate esters such as (+)-**39**, available via the one-pot aza-Darzens reaction of α-bromo enolates with a sulfinimines (Figure 4),[60] on treatment with TMSCl and LDA afforded the corresponding 2*H*-azirine 2-carboxylate (+)-**40** in 77% yield (Scheme 15).[68a,c] This procedure was the first general method for the asymmetric synthesis of 2*H*-azirines, the smallest of the unsaturated nitrogen heterocycles. The reaction sequence involves a base-induced elimination of sulfenic acid (*p*-TolylSOH) from (+)-**39**, and this

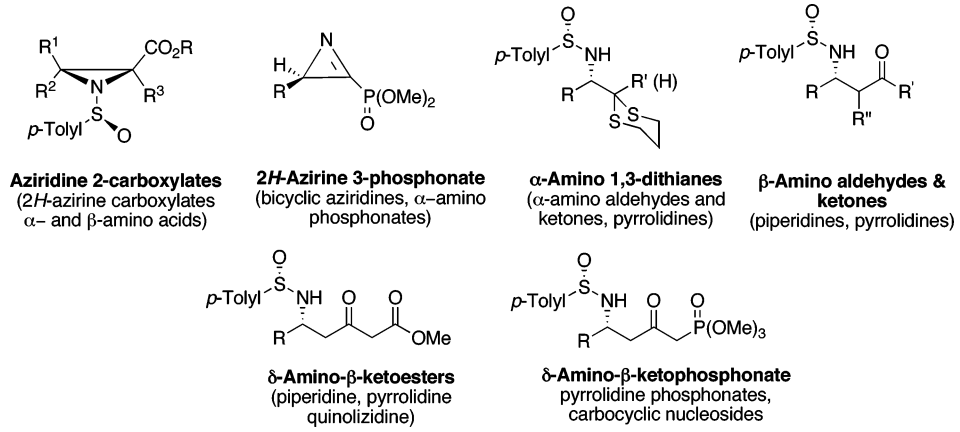
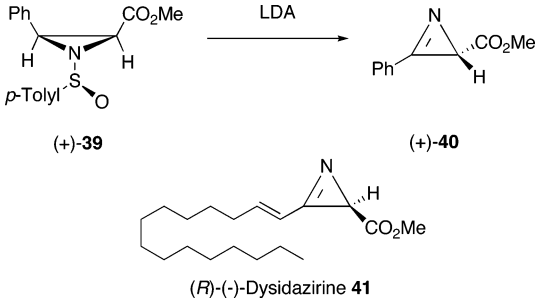
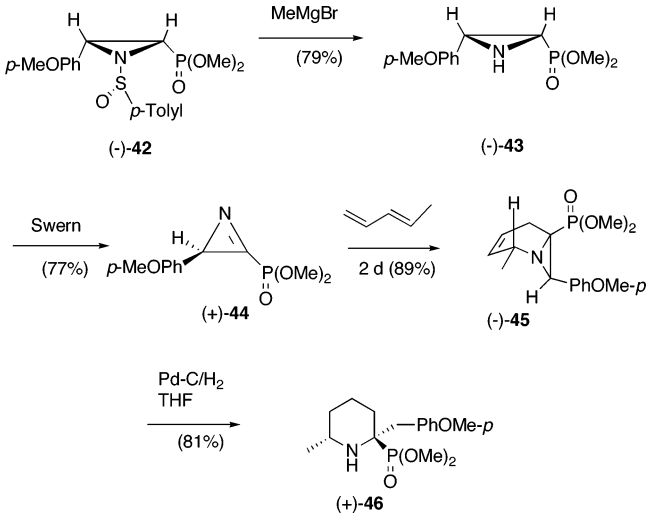


FIGURE 5. Examples of sulfinimine-derived chiral building blocks and templates for the asymmetric synthesis of amine derivatives.

SCHEME 15



SCHEME 16

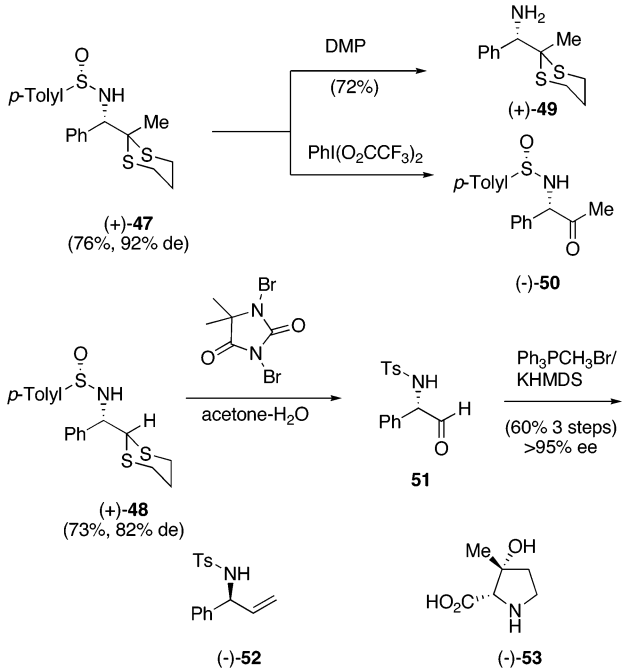


methodology was extended to the first synthesis of (*R*)-(−)-dysidazirine (**41**), a cytotoxic antibiotic isolated from a marine sponge (Scheme 15).[68a,c] The addition of Grignard reagents to 2*H*-azirine 2-carboxylates is a useful method for the synthesis of 3,3-disubstituted aziridine 2-carboxylate esters which on reductive ring opening afford *β*-substituted α-amino acids.[68b,d]

N-Sulfinylaziridine 2-phosphonates such as (−)-**42** give the corresponding NH-aziridines (−)-**43** in good yield on reaction with MeMgBr (Scheme 16).[61d] The major product in the Swern oxidation of **43** is 2*H*-azirine 3-phosphonate (+)-**44**, which was obtained in 77% yield and is the first example of this type of heterocycle.[69] 2*H*-Azirine 3-phosphonates are a new class of chiral iminodienophiles that on reaction with dienes such as *trans*-piperylene afford the bicyclic aziridine adduct in excellent yield (Scheme 16). Selective ring opening of **45** produces enantiopure quaternary piperidine phosphonates such as (+)-**47**, which are amino acid surrogates.[69]

***N*-Sulfinyl α-Amino 1,3-Dithianes.** *N*-Sulfinyl α-amino-1,3-dithioketals **47**[57a] and acetals **48**[57b] are prepared in good yield and high de values by treating sulfinimines with lithio-1,3-dithianes (Scheme 17). These compounds are important new sources of α-amino aldehydes and ketones which are valuable chiral building blocks for asymmetric synthesis and are usually prepared from α-amino acids. Selective removal of the *N*-sulfinyl and ketal groups of (+)-**47** gave (+)-**49** and (−)-**50**, respectively.[57a] However, similar attempts to remove the thioacetal group in (−)-**48** resulted in decomposition. Removal was accomplished with aqueous 1,3-dibromo-5,5-dimethylhydantoin, which affords an α-amino aldehyde **51** in which the *N*-sulfinyl group had been oxidized to an *N*-tosyl group.[57b] Performing the Wittig reaction on this α-amino aldehyde gives the enantiopure allylic amine (−)-**52** in 60% yield for the three-step sequence. We have employed our *N*-sulfinyl α-amino 1,3-dithianes derived from α-amino aldehydes and ketones in the asymmetric synthesis of functionalized prolines including (2*S*,3*R*)-(−)-3-hydroxy-3-methylproline (**53**), a segment of the antitumor polyoxopeptins.[57]

SCHEME 17



***N*-Sulfinyl *β*-Amino Aldehydes and Ketones.** In contrast to α-amino aldehydes and ketones, *β*-amino aldehydes and ketones have been much less utilized as chiral building blocks. Undoubtedly, this is due to the lack of efficient methods to prepare them as single enantiomers. A general solution to this problem is the addition of organometallic reagents to *N*-sulfinyl *β*-amino Weinreb amides (Figure 6).[58,6a,d] We prepared the Weinreb amides by addition of the potassium enolate of *N*-methoxy-*N*-methylacetamide to sulfinimines and by reaction of lithium *N*,*O*-dimethylhydroxyamine to *N*-sulfinyl *β*-amino esters. With DIBAL-H and Grignard reagents the corresponding enantiopure *N*-sulfinyl *β*-amino aldehydes and ketones, respectively, are formed in good to excellent yields (Figure 6).[58] We employed these new *β*-amino ketones in the concise enantioselective syntheses of the sedum piperidine alkaloids (+)-sedridine and (−)-allosedridine.[58a]

Alternatively *β*-amino ketones **54** can be prepared directly, in high diastereoselectivity, by addition of the potassium enolates of methyl ketones to sulfinimines (Scheme 18).[58b,c] When the prochiral lithium enolate of 4-heptanone was added to sulfinimine (+)-**55**, only two of the possible four diastereoisomers were detected, *syn*-**56** and *anti*-**57** (Scheme 18).[58c] In diethyl ether, the enolate *E*/*Z* ratio was 15:1 but dropped to 1:2.5 in THF. These results were interpreted in terms of Ireland's transition-state model and preferential formation of the *E* enolate.[58c]

Removal of the sulfinyl group in the *N*-sulfinyl *β*-amino ketone with TFA/MeOH gives the corresponding intermediate *β*-amino ketone salt that on reaction with aldehydes undergoes an acid-catalyzed highly stereoselective intramolecular Mannich reaction to produce multisubstituted piperidones (Figure 7). This

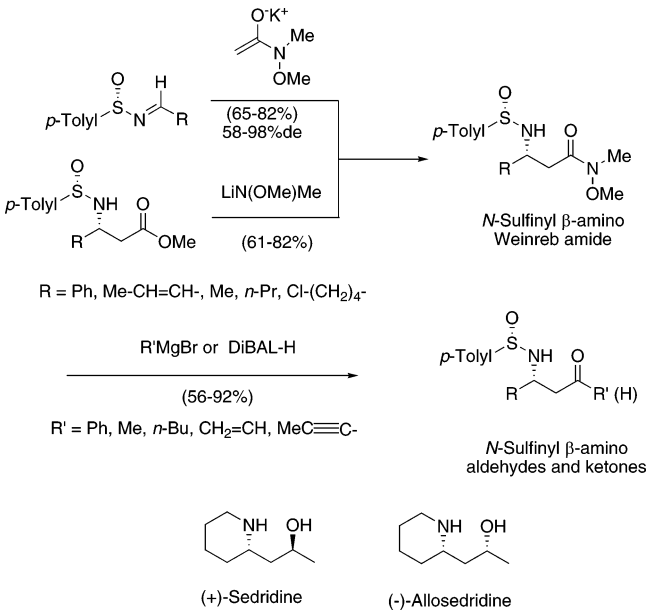
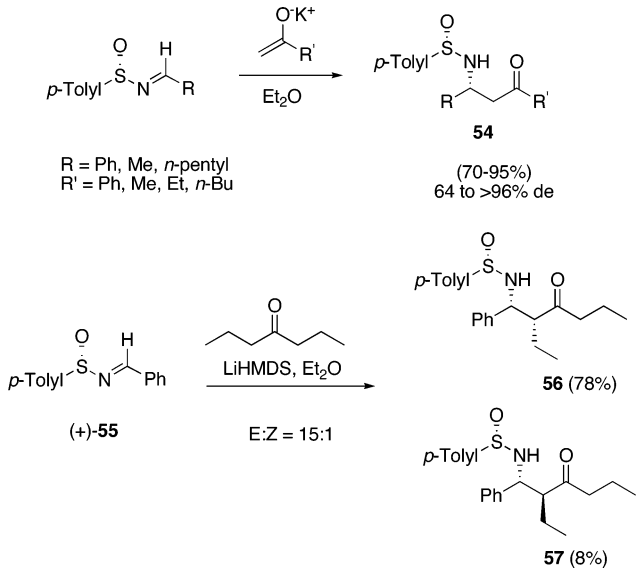


FIGURE 6. Asymmetric synthesis of β-amino aldehydes and ketones from β-amino Weinreb amides.

SCHEME 18



process represents one with the most efficient methods for the rapid and stereoselective assembly of multi-substituted piperidines (Figure 7). We have used our new β-amino ketones in the highly stereoselective asymmetric synthesis of the dendrobatide frog skin toxins (−)-indolizidine 209B and (−)-223A.[58b,c]

***N*-Sulfinyl δ-Amino β-Ketoesters.** On treatment with enolates, *N*-sulfinyl β-amino esters **58** provide *N*-sulfinyl δ-amino β-ketoesters **59** (Scheme 19).[71] These compounds can often be prepared in one pot by reaction of the sulfinimine with an excess of the enolate. With acid and an aldehyde, **59** undergoes a one-pot, highly stereoselective, intramolecular Mannich cyclization to produce the functionalized piperidine template **60**. This methodology provides general access to structurally diverse piperidines, a common structural feature of natural products and medicinally important compounds. We employed this method in the asymmetric syntheses of monosubstituted piperidines such as (*R*)-(+)-2-phenylpiperidine;[71] disubstituted piperidines such

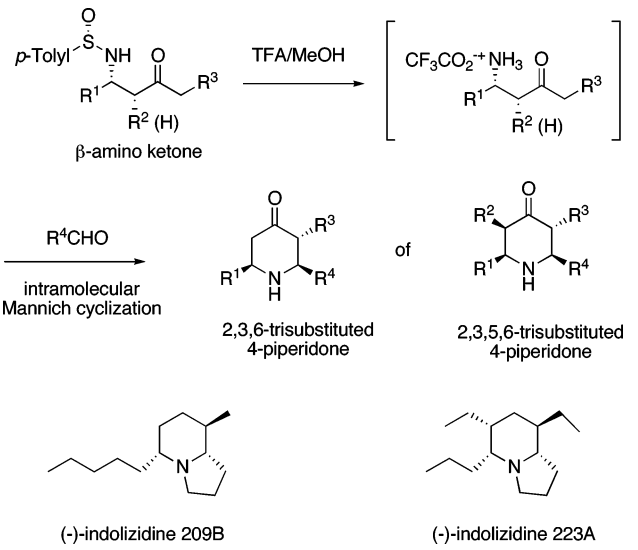
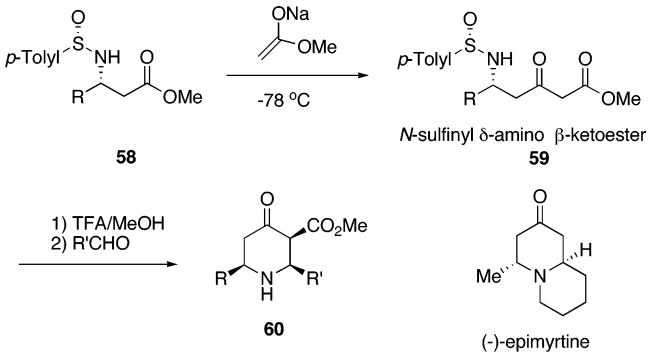
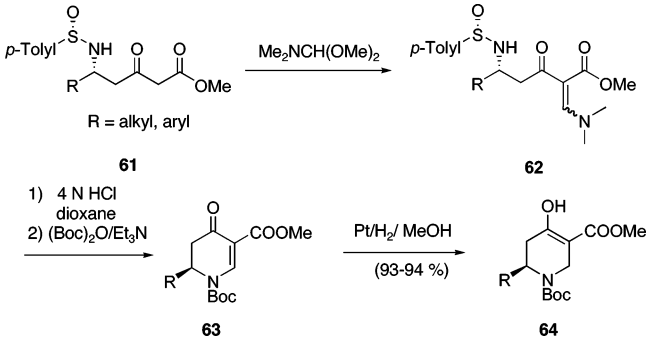


FIGURE 7. Synthesis of piperidines using *N*-sulfinyl β-amino ketones and the intramolecular Mannich reaction.

SCHEME 19



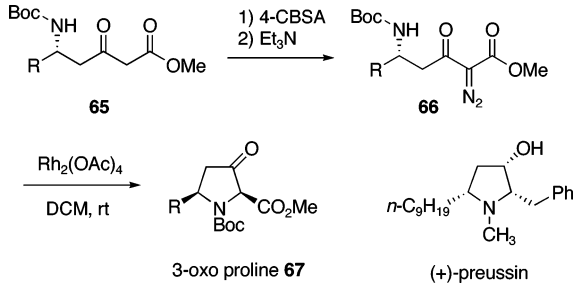
SCHEME 20



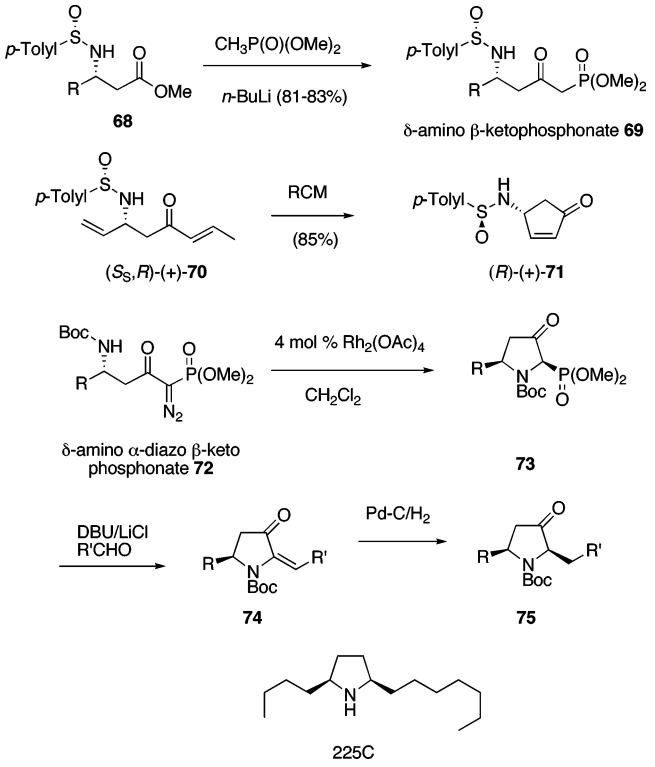
as the four isomers of 4-hydroxypipecolic acid[1c] and (−)-SS20846A;[72a] and trisubstituted piperidines including the frog skin toxin (+)-241D[72c] and the quinolizidine alkaloids (+)-lasubine II,[72b] (−)-lasubine I,[72d] and (−)-epimyrtine.[72e]

N-Sulfinyl δ-amino β-ketoester enaminones **62** are prepared by reaction of **61** with dimethylformamide dimethyl acetal (Scheme 20).[70] On hydrolysis, **62** undergoes, in one pot, an intramolecular Michael addition followed by a retro-Michael-type elimination to produce enantiopure **63**. Hydrogenation of **63** resulted in the 2,4,5-trisubstituted piperidine **64** a structural motif found in numerous biologically active alkaloids. This new building block was employed in a formal synthesis of the marine alkaloid pseudodistomin B.[70]

SCHEME 21



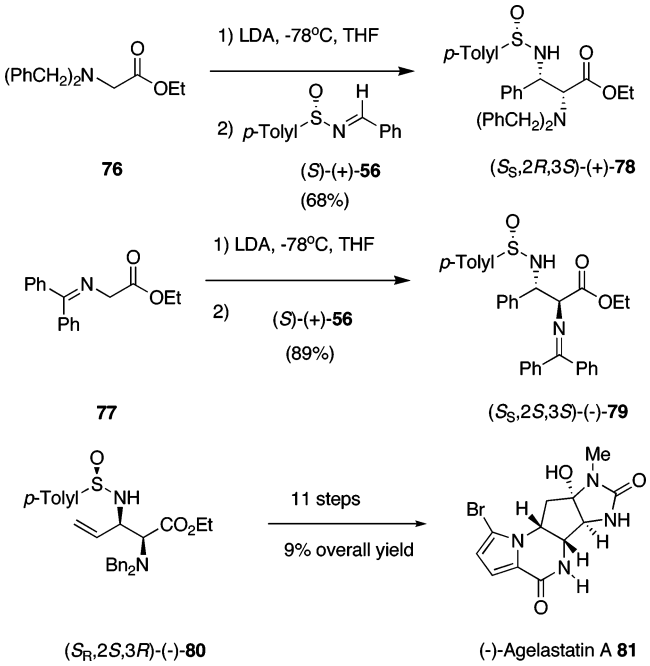
SCHEME 22



N-Boc δ-amino β-keto-α-diazoester **66** is prepared by reaction of *N*-Boc δ-amino β-keto esters **65** with (4-carboxybenzenesulfonyl) azide (4-CBSA) (Scheme 21).[73] On treatment with 3 mol % of $Rh_2(OAc)_4$, these α-diazo compounds undergo a highly stereoselective intramolecular metal carbenoid NH insertion reaction to give *cis*-5-substituted 3-oxo prolines **67**. These building blocks are readily elaborated to *cis*-2,5-disubstituted prolines[73,74] and pyrrolidines such as the antifungal, antitumor agent (+)-preussin.[75]

***N*-Sulfinyl δ-Amino β-Ketophosphonates.** Enantiopure *N*-sulfinyl δ-amino β-ketophosphonates **69** are prepared by reacting dimethyl lithiomethylphosphonate with *N*-sulfinyl β-amino esters **68**[76] or with *N*-sulfinyl β-amino Weinreb amides (Scheme 22).[58d] These new building blocks undergo the Horner−Wadsworth−Emmons (HWE) reaction with aldehydes to give, for example, amino ketodienes such as (+)-**70**.[76] We employed this diene and Grubbs ring-closing metathesis chemistry to produce (*R*)-(+)-4-aminocyclopentenone (**71**), a valuable intermediate for the asymmetric construction of carbocyclic nucleosides. With 4 mol % of $Rh_2(OAc)_4$, *N*-sulfinyl δ-amino α-diazo β-ketophosphonate **72** produces *cis*-5-substituted 3-oxopyrrolidine 2-phosphonates **73**.[77] These undergo the HWE reaction with DBU/LiCl and aldehydes to give enones **74** which

SCHEME 23



are reduced to *cis*-2,5-disubstituted pyrrolidine **74**.[78] We utilized this chemistry in the synthesis of pyrrolidine 225C, an alkaloid detected in the trail pheromones of the pharaoh ant.

***N*-Sulfinyl 2,3-Diamino Esters.** Differentially *N*-protected glycine enolates derived from **76** and **77** add to sulfinimines such as (*S*)-(+)-**56** to give *syn*- and *anti*-*N*-sulfinyl 2,3-diamino esters (+)-**78** and (−)-**79**, respectively (Scheme 23).[56a] Of the four diastereoisomers possible, these prochiral enolates preferentially give the syn and anti diamino esters. The high diastereoselectivities were interpreted in terms of **76** and **77** forming the *E*- and *Z*-enolates, respectively. We elaborated the unsaturated *syn*-2,3-diamino ester (−)-**80** into the architecturally unique cytotoxic tetracyclic marine alkaloid (−)-agelastatin A (**81**) in 11 steps, under eight operations from (−)-**80** (Scheme 23).[56b]

Conclusions. Curiosity-inspired basic research drives discovery. As little was known about the chemistry sulfenamides, I was motivated to understand their reactions and properties. The seeds of my ideas came from my doctoral studies of sulfur heterocycles and postdoctoral studies of boron−oxygen and boron−nitrogen heteroaromatic compounds. One discovery led to another. The exploration of sulfenamides led to the discovery of sulfenimines and sulfinimines and, ultimately, to the invention of *N*-sulfonyloxaziridines and enantiopure sulfinimines. These compounds and their related methodologies are now used in academic and industrial laboratories worldwide. I was fortunate to have many talented, observant, and particularly curious coworkers who contributed to the discoveries. Their keen insights often resulted in new research directions including sulfenic acid and chiral organofluorine chemistries.[80] Without the generous support of the National Science Foundation, the National Institutes of Health, the Petroleum Research Foundation, Merck, AstraZeneca, and GlaxoSmithKline our work would not have been possible.

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JO061027P