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Radical Cyclizations of Cyclic Ene Sulfonamides Occur with β-Elimination of Sulfonyl Radicals to Form Polycyclic Imines

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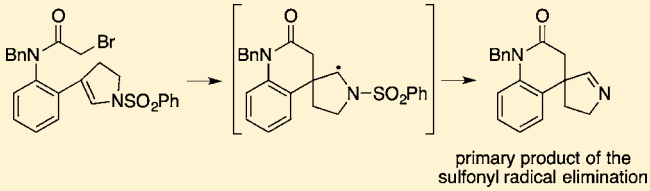
Supporting Information

ABSTRACT: Radical cyclizations of cyclic ene sulfonamides provide stable bicyclic and tricyclic aldimines and ketimines in good yields. Depending on the structure of the precursor, the cyclizations occur to provide fused and spirocyclic imines with five-, six-, and seven-membered rings. The initial radical cyclization produces an α-sulfonamidoyl radical that undergoes elimination to form the imine and a phenylsulfonyl radical. In a related method, 3,4-dihydroquinolines can also be produced by radical translocation reactions of *N*-(2-iodophenylsulfonyl)-tetrahydroiso-quinolines. In either case, very stable sulfonamides are cleaved to form imines (rather than amines) under mild reductive conditions.



INTRODUCTION

The quintessential reaction of β-sulfonyl radicals is fragmentation to form a sulfonyl radical and a multiple bond.[1] Such β-elimination reactions have broad synthetic utility. The radical prior to fragmentation can be centered on either carbon or nitrogen (Figure 1). For example, the elimination reaction of β-sulfonyl alkyl radicals in Figure 1a is commonly applied to make alkenes from β-functionalized sulfones, allyl sulfones and alkenyl sulfones.[2] The example reaction from Zard is a typical addition/fragmentation reaction of an allyl sulfone.[3]

Carbon−nitrogen double bonds can also be made by two different kinds of sulfonyl radical eliminations. The elimination of β-sulfonyl aminyl and related radicals has been developed by Kim and others into a useful method to make assorted imines, hydrazones and, as exemplified in Figure 1b, oximes.[4]

The reverse positioning of the sulfonyl group and the radical (β-elimination of a sulfonyl group from an α-sulfonamidoyl radical; Figure 1c) is less common and has a checkered history. Often, this history involves reactions of *N*-alkenylsulfonamides, hereafter called ene sulfonamides. In 1959, McKusick and coworkers reported that the isomerization of ene sulfonamide **1** to β-sulfonyl enamine **2** was induced by X-rays (Figure 2a).[5] This isomerization can also be triggered by photolysis or thermolysis with AIBN, and studies supported a sulfonyl radical addition/elimination mechanism.[5c]

More recently, Zard[6] and Renaud[7] have introduced transformations based on carbon-radical additions to functionalized ene-sulfonamides to make functionalized ketones or heterocycles, depending on the associated functional groups. In an example from Renaud[7] (Figure 2b), treatment of in situ generated catechol borane **3** (the radical precursor) with ene sulfonamide **4** and di-*t*-butyl hydroperoxide (DTHP) gave α-ketoester **5** in 20% overall yield from 1-octene (the precursor of **3**).

Murphy has also observed that *N*-sulfonyl groups are lost in several transformations.[8]For example, treatment of diazonium ion **9** with tetrakisdimethylaminoethylene (TDAE) provided indole **10** in 33% yield (Figure 2c) as one of several products.[8b]

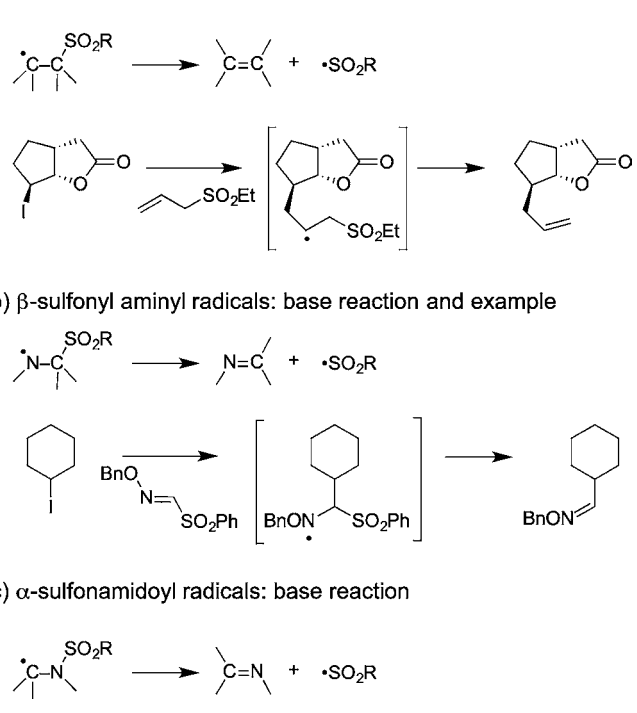


Figure 1. Three classes of radicals that can undergo β-elimination of sulfonyl radicals to make C=C and C=N bonds.

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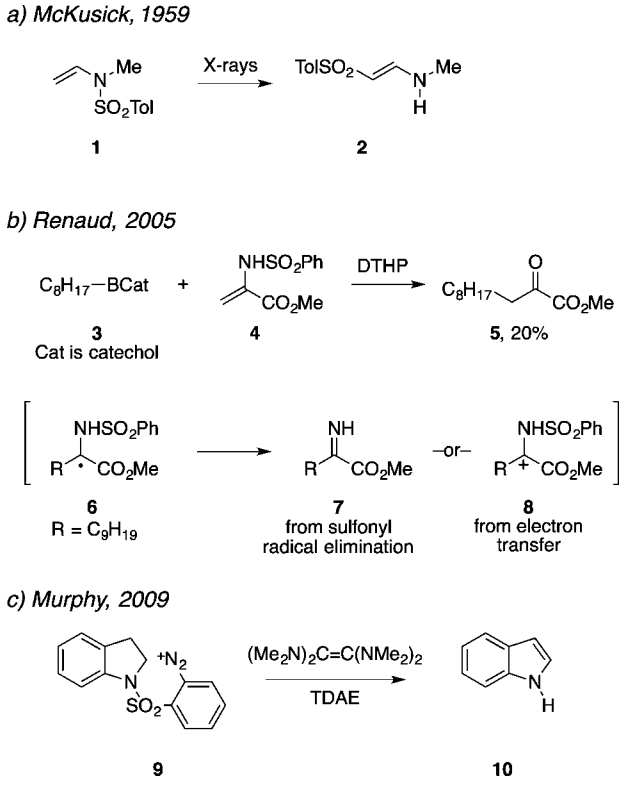

Figure 2. Possible examples of sulfonyl radical eliminations to make imine intermediates under nonreducing conditions.

All of the transformations in Figure 2 are multistep processes that may or may not include sulfonyl radical elimination steps. Take Renaud's reaction (b), for example. Addition of the radical derived from **3** to alkene **4** provides α-benzenesulfonamidoyl radical **6**. One sensible route to the product **5** is sulfonyl radical elimination to an imine **7** followed by hydrolysis. However, the conditions are oxidizing, so direct oxidation of **6** to a sulfonyl iminium ion **8**[9] and then hydrolysis could provide a path to the product **5** that does not involve sulfonyl radical elimination.

The evidence for such sulfonyl radical eliminations under reducing conditions is even less clear-cut, as shown by the two examples in Figure 3.[10] In an approach to (−)-kainic acid, Cossy reported in 1999 that cyclization of enantiopure **11** with tributyltin hydride unexpectedly provided imine **13** (Figure 3a).[11] She had expected a cyclative hydrostannation to occur starting with tin radical addition to the alkyne. The actual product **13** was indeed cyclized, but it contained neither tin nor the sulfonyl group. This, and Somfai's result coming up in Figure 3b, led Cossy to suggest that enamidyl radical **12** was the key intermediate in this reaction.

Somfai in turn had reported in 1994 that syringe pump addition of tin hydride to ene sulfonamide **14** provided the reduced spirocyclic sulfonamide **16** in 57% isolated yield.[12] This reaction presumably involves α-sulfonamidoyl radical **15**, which apparently abstracts hydrogen from tin hydride even under syringe pump conditions. Likewise, a homologue of **14** with a six-membered ring ene sulfonamide underwent reductive cyclization in similar yield.

The collective evidence in Figures 2 and 3 for the β-sulfonyl radical elimination reaction to form imines is circumstantial because the direct products of such reactions are not isolated. Further, the low yields and formation of competing products in

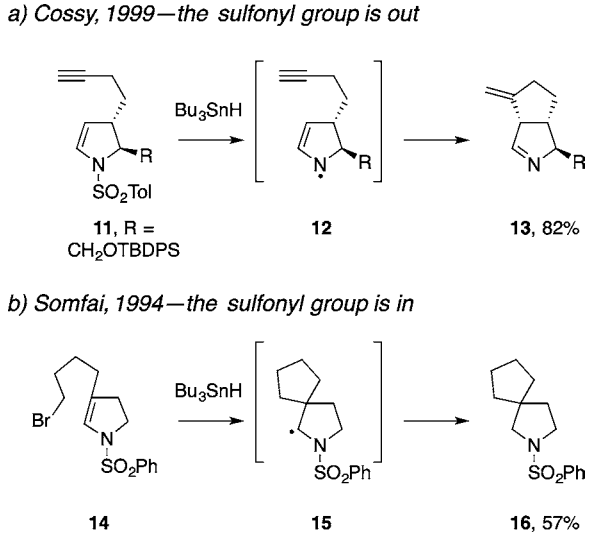

Figure 3. Tin hydride cyclizations of similar ene sulfonamides give contrasting results.

some reactions combine to suggest that even if this elimination does occur at times, it is not very efficient.

We now report that we have found strong evidence in the search for evidence of β-sulfonyl radical eliminations from α-sulfonamidoyl radicals. Specifically, we have isolated members of a family of stable imines, the primary products of such reactions, in good yields. The elimination has good synthetic potential because a strong N−SO_2Ar bond is cleaved under mild conditions with concomitant ring formation. We also introduce a radical translocation variant that has value as a new deprotection reaction. Lastly, we revisit the contrasting results of Cossy and Somfai to better understand whether β-sulfonyl radical eliminations are involved.

RESULTS AND DISCUSSION

Discovery and Mechanism of the Imine-Forming Reaction. We first encountered the imine-forming reaction during pilot studies directed toward the synthesis of the meloscine/epimeloscine (**17a,b**) class of natural products.[13,14] The goal was to learn how to make the B-ring of ABD tricycles like **18** by radical cyclizations and to determine the favored configuration of such cyclizations when R ≠ H (Figure 4).

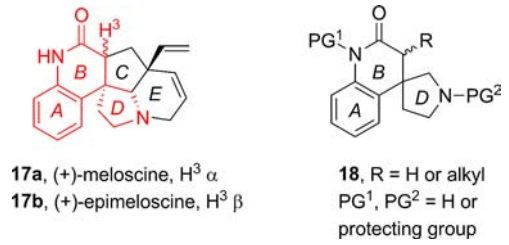

Figure 4. Structures of meloscine natural products **17** and target tricyclic analogues **18**.

Scheme 1 shows the synthesis of two key precursors and the results of the first radical cyclizations. Initially we made precursors like **23** by a reliable Stille coupling route (detailed in the Supporting Information), but we later switched to the Suzuki coupling route in Scheme 1 because it was more flexible for varying substituents in target radical precursors. Coupling of

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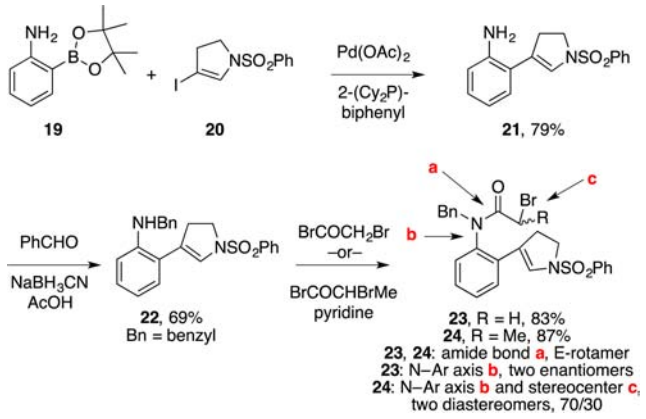
Scheme 1. Syntheses of 23 and 24 Typify the Synthesis of the Various Radical Precursors in This Study



2-(pinacolatoboranyl)aniline **19** with readily available 4-iodo-1-(phenylsulfonyl)-2,3-dihydro-1*H*-pyrrole **20**[15] provided aniline **21** in 79% yield. Reductive *N*-benzylation to give **22** (69% yield) was followed by acylation with bromoacetyl bromide and 2-bromopropanoyl bromide. The α-bromoacetanilides **23** and **24** were obtained in 83 and 87% yields.

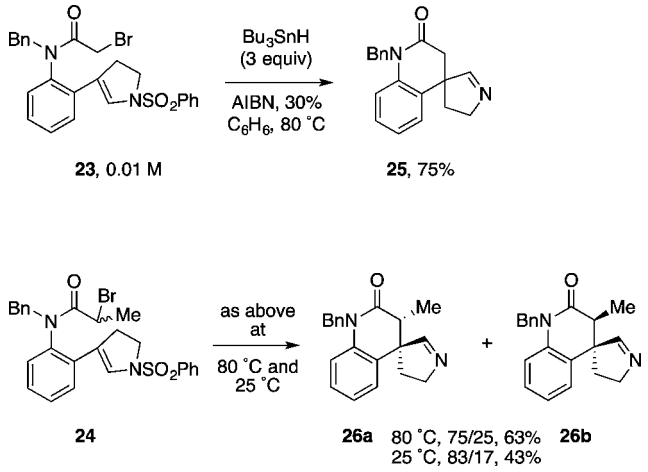
Bromoacetamide **23** has two axes that can provide rotational isomers. Rotation of the N—C(=O) bond (a) is a standard amide rotation that can provide *E* and *Z* isomers, while rotation of the N–Ar bond (b) provides a pair of enantiomers. There is only one set of signals in the ^{1}H NMR spectrum of **23** (>95%), which we assign to the depicted *E*-amide rotamer (C=O and N–Ar *trans*).[16] All the geminal methylene protons of **23** are diastereotopic, confirming that it is a mixture of enantiomers about the N–Ar axis on the NMR time scale.

The corresponding α-bromopropanamide **24** adds a stereocenter to the rotatable amide and N–Ar bonds, so four diastereomers of **24** are possible.[17] This amide is a 70/30 mixtures of diastereomers according to ^{1}H NMR analysis. These must be the *E*-rotamers of the two possible diastereomers created by the stereocenter and the N–Ar axis. The diastereomers cannot be separated by chromatography, so the barrier to N–Ar bond rotation is less than about 22 kcal/mol. Related diastereomers with higher N–Ar rotation barriers have been separated and shown to give the same products on radical cyclization.[17a] So separation is pointless because the two diastereomers of **24** will give the same radical and hence the same result on radical cyclization.

The results of tin hydride reactions with **23** and **24** are summarized in Scheme 2. In a typical cyclization experiment, a benzene solution of **23** (1 equiv, 0.01 M), Bu_3SnH (3 equiv), and AIBN (0.3 equiv) was heated at 80 °C for 30 min. The starting material was consumed, and a single major new product was evident on TLC analysis. Evaporation of the solvent and flash chromatography provided the new product in 75% yield. This was not the expected product of reductive cyclization (see **18** in Figure 2), but instead the stable spirocyclic aldimine **25**. The imine structure of **25** was clear from the various spectra. For example, the sulfonyl group was absent, and correlated resonances at 7.51 ppm (singlet) in the ^{1}H NMR spectrum and 167.8 ppm in the ^{13}C NMR are diagnostic of the imine CH atoms. Other NMR and HRMS data are fully consistent with structure **25**.

Cyclization of **24** was conducted under similar conditions at both 80 °C (AIBN initiation) and room temperature (rt, Et_3B initiation[18]). The 80 °C experiment gave imine epimers **26a** and **26b** as a 75/25 mixture in 63% isolated yield. This ratio increased to 83/17 in the rt experiment, and the isolated yield was 43%.

Scheme 2. Radical Cyclizations to Ene Sulfonamides Provide Stable Cyclic Aldimines



The configuration of the major isomer from cyclization of **24** was initially assigned as **26a** based on NOESY experiments on the mixture. Later we succeeded in crystallizing the major diastereomer from the mixture, and its X-ray crystal structure confirmed both the constitution and the configuration. This structure, shown in Figure 5, provides clues as to why these

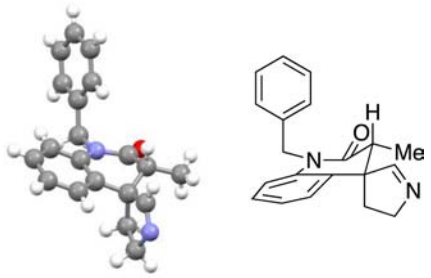


Figure 5. X-ray crystal structure of **26a** (left) along with standard representation focusing on the lactam ring conformation and substituents (right).

imines are so stable. The lactam ring (B) of **26a** adopts a distorted half-chair conformation in which the smaller imine CH-group on the spiro carbon atom is pseudoequatorial and the larger CH_2-group is pseudoaxial. The larger group adopts the pseudoaxial location because of A-strain[19] and because there are no 1,3-diaxial interactions. In the pseudoequatorial location, the imine carbon atom is shielded by the fused aromatic ring (especially the adjacent *ortho*-hydrogen) on one side and by the substituents on C3 of the lactam on the other side.

The mechanism for formation of these products is illustrated in Figure 6a with the simpler precursor **23**. A tributyltin radical abstracts bromine from **23** to give α-amide radical **27**, which then undergoes 6-*exo* cyclization by adding to the β-carbon atom of the ene sulfonamide. The resulting α-sulfonamidoyl radical **28** ejects the phenylsulfonyl radical ($PhSO_2\bullet$) in a β-fragmentation reaction to give imine **25**. This imine is robust, and it survives both heating with excess tin hydride (a potential

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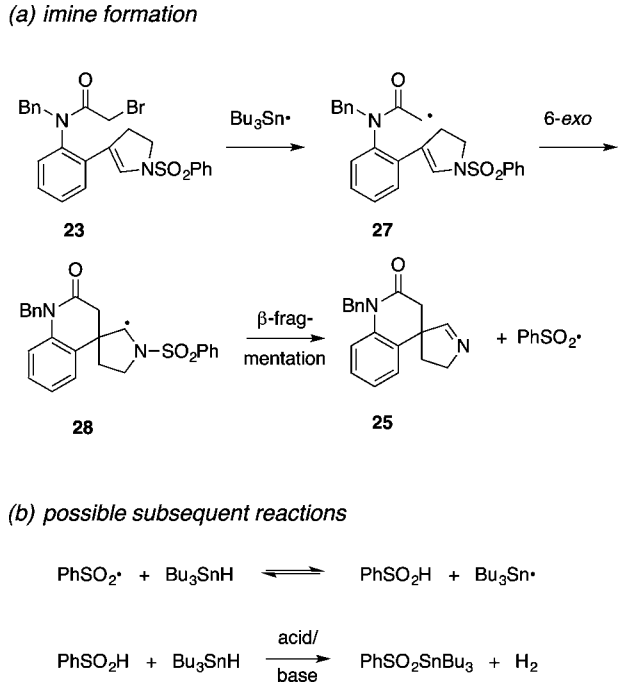


Figure 6. Evidence for β-fragmentation: (a) suggested steps and intermediates for formation of the imine and (b) possible fates of the tin and sulfur reaction components (right).

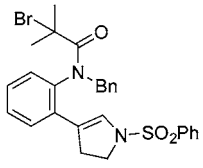
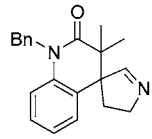
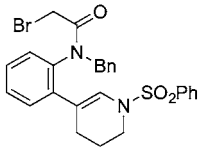
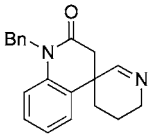
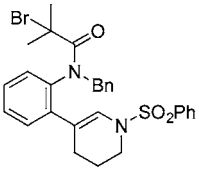
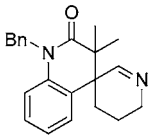
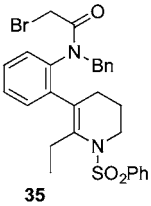
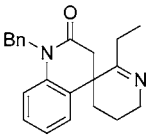
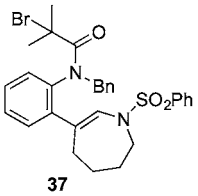
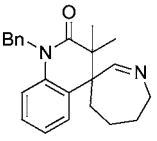
ionic hydride source) and silica gel chromatography. It cannot tautomerize to an enamine. Its isolation is strong evidence implicating the β-elimination of α-sulfonamidoyl radicals because it is the primary product this reaction.

Focusing on the phenylsulfonyl radical product[1a,2a] of the β-fragmentation reaction, we can further speculate that this abstracts a hydrogen atom from tin hydride to generate tributyltin radical ($Bu_3Sn\bullet$) and benzenesulfinic acid ($PhSO_2H$).[20a,b] This is a chain transfer step provided that the original bromine abstraction reaction by the tin radical (**23** → **27**) competes effectively with possible back hydrogen atom transfer.[21]

Benzenesulfinic acid is an unstable compound prone to disproportionation and other reactions.[2a] And with a pK_a of about 2.7, it can also be expected to undergo an acid/base reaction with Bu_3SnH as shown in Figure 6b. If this reaction is quantitative, then 2 equiv of Bu_3SnH are needed for the overall reaction. Indeed, the use of 1 equiv of Bu_3SnH in the pilot reductions in Scheme 1 did not provide high conversions of precursor **24**.[22a] Likewise, tin hydide addition/elimination reactions of allyl sulfones require 2 equiv of tin hydride.[23] This suggests that a significant amount of tin hydride is consumed either by the indicated acid/base reaction or by other reactions with the sulfur-derived product(s).[20b]

Scope of the Imine-Forming Reaction. Next we surveyed the scope of the imine-forming reaction by varying substituents and ring sizes, and the results of these studies are summarized in Table 1. The precursors were all made by suitable variations of the route outlined in Scheme 1, and complete details (experimental procedures, characterization of intermediates) are in the Supporting Information. The radicals derived from the precursors in Table 1 may undergo the initial cyclization at different rates. To maximize the chances for cyclization rather than direct reductive debromination, we switched to a standard syringe pump procedure for these

Table 1. Scope of the New Imine Forming Reaction[a]

entry	precursor	product	yield
1	 **29**	 **30**	81%
2	 **31**	 **32**	73%
3	 **33**	 **34**	50%
4	 **35**	 **36**	61%
5	 **37**	 **38**	40%

[a]Isolated yields after flash chromatography are recorded.

reactions. The crude products were purified by flash chromatography to provide the isolated yields in Table 1.

Cyclization of 2-bromo-2-methylpropanamide **29**, a more substituted analogue of **23** and **24**, provided imine **30** with a quaternary center adjacent to the spirocenter in 81% yield (entry 1). Precursors **31** and **33** have a six-membered ene sulfonamide ring, one without (**31**) and one with (**33**) additional methyl groups on the carbon bearing the radical precursor. Isolated yields of six-membered cyclic imines **32** and **34** were 73 and 50% (entries 2 and 3). These precursors all form spirocyclic aldimines on tin hydride reaction. The precursor **35** bears an additional ethyl group on the α-carbon atom of the ene sulfonamide. This gives spirocyclic ketimine product **36** in 61% yield.

Finally, we prepared a 2-bromo-2-methylpropanamide precursor **37** that has the ene sulfonamide as part of a seven-membered ring. Cyclization of **37** provided imine **38** with spirofused six- and seven-membered rings in 40% isolated yield (entry 5). In this seven-membered ring series, the geminal dimethyl group adjacent to the spiro-carbon was important for product stability.[22b] In contrast, the five- and six-membered imines were stable regardless of amide substitution pattern.

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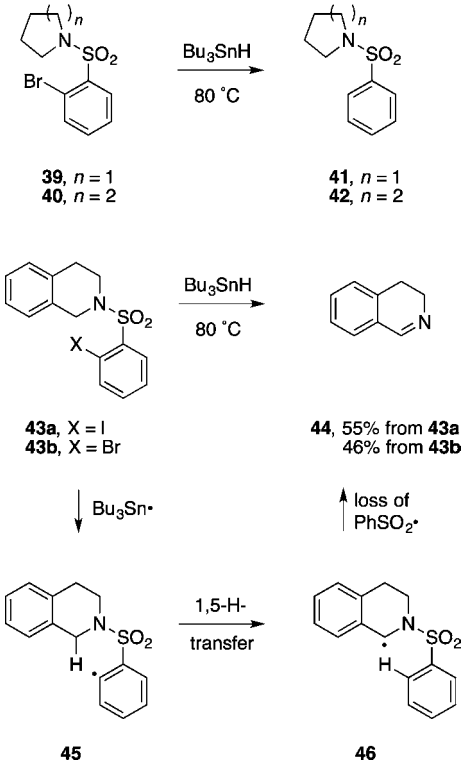
Imine products predominated in every case in Scheme 2 and Table 1, so this suggests that the β-fragmentation reaction of the intermediate α-sulfonamidoyl radicals is rather general. All the imines in Table 1 were again stable and easily isolable. Overall, this is an appealing method to make functionalized spirocyclic imines.

Imine-Formation by Radical Translocation. If β-fragmentation is a core reaction of α-sulfonamidoyl radicals, then it should be possible to make such radicals by another route and again observe the formation of imines. We chose radical translocation[24] to generate such radicals based in part on Murphy's minor product in Figure 2c.[25] However, we used halide rather than diazo radical precursors to retain the opportunity for tin hydride mediated reactions.

The results of four simple but informative experiments are summarized in Scheme 3. Reduction of *N*-(2-bromophenylsulfonyl)pyrrolidine **39** and the corresponding piperidine homologue **40** with Bu_3SnH at 80 °C under the usual thermal conditions provided principally the directly debrominated products **41** and **42**. We suspected that these products formed because the radical translocation (a 1,5-hydrogen atom transfer reaction) failed, not because the elimination reaction failed.

To address this problem, we made the two *N*-(2-halophenylsulfonyl)tetrahydroisoquinolines **43a** (X = I) and **43b** (X = Br). These have a pair of C−H bonds that are additionally activated for radical translocation by the adjacent aryl ring. Reduction of **43a,b** with Bu_3SnH under the standard thermal conditions followed by flash chromatography provided the stable 3,4-dihydroisoquinoline **44** in 55 and 46% yield, repectively.

Scheme 3. Radical Translocation Reactions Lead to Oxidative Removal of *N*-(2-Halosulfonyl) Groups Under Mild Reductive Conditions Provided That the Precursors Have Suitably Activated C−H Bonds



The dihydroisoquinoline product **44** arises from a sequence of iodine atom abstraction to give aryl radical **45** followed by radical translocation to give **46** and then β-fragmentation to give the imine functional group embedded in the products **44**. These results show that the imine-forming reaction is a characteristic of α-sulfonamidoyl radicals that is independent of their method of generation. Beyond that, such reactions could have value in synthesis. Sulfonyl groups are attractive N-protecting groups because sulfonamides are so stable.[26] The knock on N-sulfonyl groups is that they are hard to remove by either hydrolysis or reduction.[27] Here the 2-halosulfonyl group functions as "self-oxidizing protecting group";[28] it is removed under mild reductive conditions to give a valuable imine product that is oxidized on the carbon skeleton with respect to the precursor.

Understanding the Contrasting Prior Results. To complete the study, we came full circle to the contrasting results of Cossy and Somfai (Figure 3). Recall that starting from similar ene sulfonamide precursors, Cossy obtained a fused imine **13** lacking the *N*-sulfonyl group,[11] but Somfai obtained a standard reduced spricycle **16** retaining the *N*-sulfonyl group.[12]

Figure 7 shows possible products in tin hydride reactions of Cossy's substrate **11**. At issue is which functional group in **11** is the radical precursor in the cyclization and which is the radical acceptor. Cossy had planned a hydrostannation reaction in which the alkyne is the radical precursor and the ene sulfonamide is the acceptor, path (a) (going downward from **11**). Addition of tributyltin radical to **11** gives alkenyl radical **47**. The expected final product of cyclization of **47** at that time was reduced alkenyl stannane **48**, but this was not isolated.

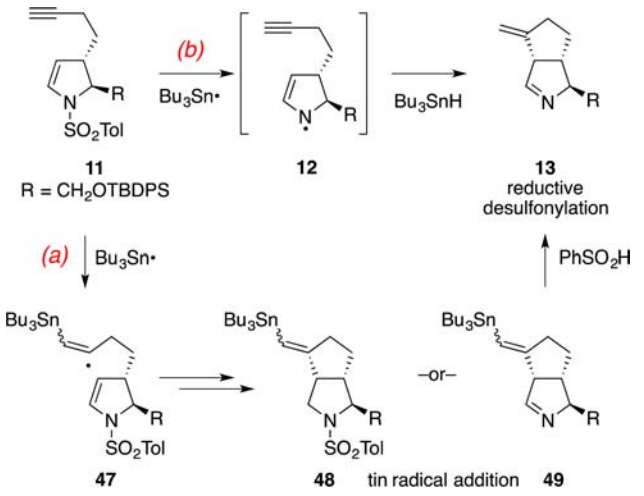


Figure 7. Products in the cyclization of **11** depend on which functional group is the precursor in the cyclization and which is the acceptor. Path (a), the alkyne is the precursor and the ene sulfonamide is the acceptor. Path (b), the ene sulfonamide is the precursor and the alkyne is the acceptor. The isolated product **13** is a secondary product of path (a) derived from **49**, not a primary product from reductive desulfonylation path (b).

The absence of **48** led to the suggestion that the observed product **13** arose from a cyclization in which the ene sulfonamide was the radical precursor and the alkyne was the radical acceptor, path (b) (going to the right from **11**). This is a reductive desulfonylation, not a hydrostannation. The problem with this suggestion is that the conversion of **11** to **12** is a

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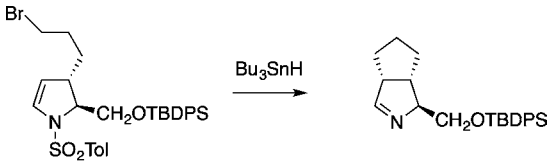
homolytic substitution reaction at a sulfonyl group, a reaction that is widely thought to be unfavorable.[29] Previous suggestions of such reactions have been refuted both experimentally[30] and computationally.[31] However, the focus of much of this prior work has been on substitution of sulfonyl groups by second-row radicals (especially carbon radicals) rather than tin radicals. In contrast, homolytic substitutions at sulfur atoms in lower oxidation states (for example, ArSR and ArS(O)R) with carbon, tin, and other radicals are common.[32]

With the hindsight provided by the new results, we can see that Cossy's original line of thinking (the alkyne is the precursor, path (a)) could well be correct. However, we now see that the expected product of the tin radical addition to the alkyne is imine **49** resulting from sulfonyl radical elimination rather than reduced sulfonamide **48** from hydrogen transfer. Could it be that imine **49** was formed in Cossy's reaction and then protodestannylated to **13** by the in situ generated benzenesulfinic acid?[33]

To address this issue, we synthesized bromide **50** (Scheme 4) as described fully in the Supporting Information. The

Scheme 4. Tin Hydride Reduction of 50[a]



50 **51**, 54%

[a]The bromide, not the ene sulfonamide, functions as a radical precursor.

bromine atom in **50** that replaces the alkyne in **11** can only serve as a radical precursor, not a radical acceptor. Thus, the origin of any cyclized product formed in reduction of **50** is straightforward to determine.

Reduction of **50** with Bu_3SnH was conducted at room temperature under conditions similar to Cossy's (Et_3B initiation). The major product was the imine **51** (Scheme 4), which was isolated in 54% yield by flash chromatography and fully characterized. Clearly in substrate **50**, the bromide functioned as the radical precursor and the ene sulfonamide functioned as the radical acceptor.

The results of this experiment suggest that the imine product **13** in Cossy's reaction was formed by the path (b) in Figure 7 with the steps of (1) tin radical addition to the alkyne **11** to give **47**, (2) 5-*exo* cyclization, and (3) β-fragmentation to eliminate the sulfonyl group and form the imine **49**. Finally, (4) ionic protodestannylation of this primary product **49** produces the isolated product **13**.

With new understanding of Cossy's reaction, it is now Somfai's result (no imine formation in Figure 3b) that with hindsight looks out of place. Thus, we resynthesized bromide **14** by Somfai's published procedures[12] to revisit its cyclization chemistry.

Syringe pump addition of tributyltin hydride to bromide **14** as described by Somfai gave somewhat variable results, as summarized in Figure 8 and described more fully in the Ph.D. thesis of H. Zhang.[34] Two products were consistently formed: an unstable product and stable product. The inconsistencies were with percent conversion and the ratio of the two products;

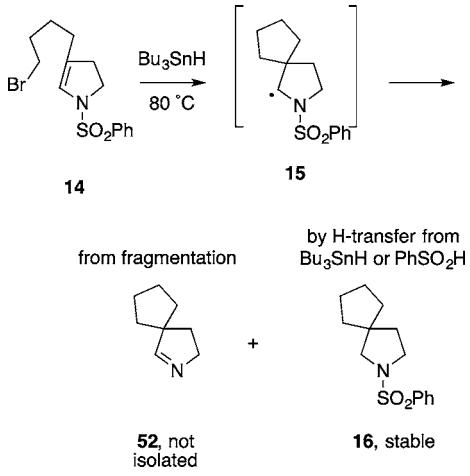


Figure 8. Syringe pump addition of tin hydride to **14** gives not one but two products: one stable to chromatography (**16**) and one unstable (**52**).

however, the ratio trend was consistent: the unstable product was always major and the stable product was always minor.

In a typical syringe pump experiment, the stable product was isolated in 15% yield by flash chromatography and proved to be Somfai's reduced product **16** retaining the *N*-sulfonyl group. The ^{1}H NMR spectra of several crude mixtures recorded before chromatography showed that the unstable product was spirocyclic imine **52**.[35] For example, the protons of the N–CH_2 group resonated as a doublet of triplets, J = 2.1 and 6.9 Hz at 3.86 ppm, in the ^{1}H NMR spectrum. When an integration standard was added (1,3,5-trimethoxybenzene), the calculated yield of the imine **52** was typically 45–60%.

Syringe pump experiments like these are difficult to reproduce in the best of cases because there are many variables. And the cyclization of **14** is far from a best case scenario for two reasons. First, the benzenesulfinic acid byproduct is a good hydrogen atom donor that is nicely matched with the α-sulfonylamidoyl radical **15** for polarity reverse catalysis.[36] This acid may be consumed less efficiently under syringe pump conditions because tin hydride is always deficient. Thus, the syringe pump procedure might provide more powerfully reducing conditions rather than less. Second, alkyl bromides are electrophiles and ene sulfonamides are nucleophiles, so nonradical reactions may compete, especially under the long heating involved in the syringe pump procedure.

To mitigate the first problem, we switched to the standard fixed concentration conditions so that tin hydride is never deficient during the reaction course.[37] To eliminate the possibility of a competing intramolecular S_N2 reaction, we replaced the bromide **14** by the analogous phenylselenide **53**.

The results of two key experiments with **53** are summarized in Scheme 5. In both experiments, **53** (0.01 M) was reduced with 3 equiv of tin hydride at 80 °C (AIBN initiation). After 30 min, TLC analysis showed that the precursor was largely consumed. In the first reaction, the solvent was evaporated and the crude product was dissolved in $CDCl_3$ with an integration standard. The major product was imine **52** in 60% yield. Resonances from the reduced product **16** were not evident in this spectrum.

In the second reaction, a solution of sodium borohydride in ethanol was added after tin hydride treatment to reduce any imine present to an amine. This crude mixture was exposed to

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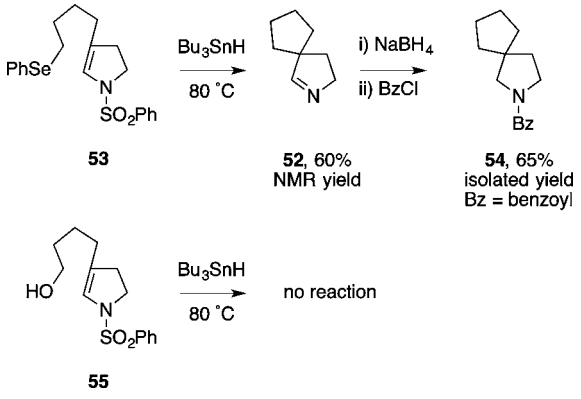
Scheme 5. Results of Tin Hydride Reactions of Phenylselenide 53 and Alcohol 55



benzoyl chloride and pyridine, and then the resulting product was purified by flash chromatography to provide benzamide **54** in 59% yield.

These results show that the formation of imine **51** by sulfonyl radical elimination is more rapid than hydrogen atom abstraction from tin hydride under fixed tin hydride conditions and syringe pump conditions. We understand why Somfai did not observe the imine **51** (because he purified his products by flash chromatography), though we are not sure why he isolated about 30% more reduced product **16** from his syringe pump experiment than we typically observed. From the vantage point of the β-fragmentation reaction, the key observation is that the cyclization results with **14** are generally consistent with Cossy's prior results and with our new results.

Finally, to test whether ene sulfonamides are competent radical precursors at all under these conditions, we treated alcohol **55** (Scheme 5) with tributyltin hydride under the standard thermal conditions (80 °C). No new products was detected, and most of the starting material was recovered. Thus, the sulfonyl groups of ene sulfonamides are not subject to facile homolytic substition reactions by tin radicals.[29−31]

CONCLUSIONS

Tin hydride mediated radical cyclizations of ene sulfonamides are general reactions that provide bicyclic and tricyclic aldimines and ketimines in good yields. Depending on the structure of the precursor, the cyclizations occur in 5-*exo* or 6-*exo* modes to provide fused or spirocyclic imines. With the exception of the small spirocyclic imine **52**, all of the cyclic imines herein are robust compounds that are not reduced ionically by tin hydride under the reaction conditions and that are readily purified by flash chromatography. Reinvestigation of the contrasting prior results from Cossy[11] and Somfai[12] showed that imine products predominated in both cases.

Mechanistically, the initial radical cyclization produces an α-sulfonamidoyl radical that undergoes elimination to form the imine and a phenylsulfonyl radical. This β-elimination reaction has been postulated in the past based on the structures of downstream products that have been isolated in related reactions (Figures 2 and 3). The isolation of the many primary imine products in this work does not prove that imines are intermediates in all of these prior reactions. However, it cements the case for the β-elimination as a core reaction of α-sulfonamidoyl radicals.

In a related method, 3,4-dihydroquinolines can also be produced by radical translocation reactions of *N*-(2-halophenylsulfonyl)-tetrahydroisoquinolines. Accordingly, readily available *N*-(2-halophenylsulfonyl) groups can now serve as so-called self-oxidizing protecting groups,[28] although C−H bonds that are activated toward 1,5-hydrogen transfer seem to be an important prerequisite. As with the cyclative transformation, very stable sulfonamides are cleaved to form imines (rather than amines) under mild reductive conditions.

Imines are synthetic intermediates in a vast collection of two-component and multicomponent addition reactions.[38] By far the most common way to make imines, whether stable species or transient reaction intermediates, is by the condensation of aldehydes or ketones with amines.[39] The ability to made imines by a sulfonyl radical elimination, especially when coupled with a prior radical reaction (here, the cyclizations), provides a powerful alternative to the usual condensation route that differs both in the bonds that are formed and in the reaction conditions. These differences promise to offer expanded opportunities for imine chemistry in synthesis.

ASSOCIATED CONTENT

Supporting Information

Details of all new experiments, spectral data, and crystal data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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