Catalysis of Stannane-Mediated Radical Chain Reactions by Benzeneselenol

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ABSTRACT

The discovery and development of the catalysis of stannane-mediated radical chain reactions by benzeneselenol, generated in situ by reduction of diphenyl diselenide with tributyltin hydride, are described. The catalytic sequence is discussed in terms of polarity reversal catalysis of radical chain reactions, and applications to synthesis are presented. These include the prevention of numerous radical rearrangement reactions, the ability to intervene in certain multistep radical rearrangements, especially aryl and vinyl radical cyclizations, at intermediate stages with advantages to the product profile, and the effective trapping of allyl-, benzyl-, and cyclohexadienyl-type radicals, permitting inter alia the isolation of aryl cyclohexadienes and their application in synthesis.

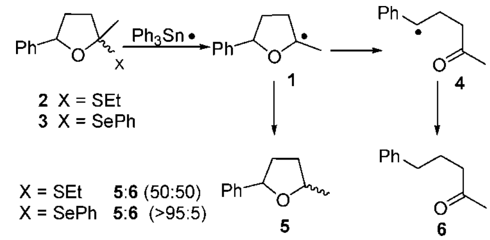
Introduction

Several years ago, we observed that the retro-5-endo-trig ring opening of radical **1**, a potential intermediate in a reaction then of interest to us, was less efficient when the radical was generated from the selenide **3** than from the thioether **2** under tin hydride conditions (Scheme 1).[1] The difference in reactivity was traced to the presence of diphenyl diselenide as an impurity in selenide **3** and led to the hypothesis of the catalysis of stannane-mediated chain reactions by benzeneselenol, derived in situ by the reduction of the diselenide.[1] This hypothesis evolved into a powerful synthetic method, whose scope is delineated below. A closely related sequence employing tributylgermane as the reductant with catalytic thiophenol was subsequently described by Bowman et al.[2]

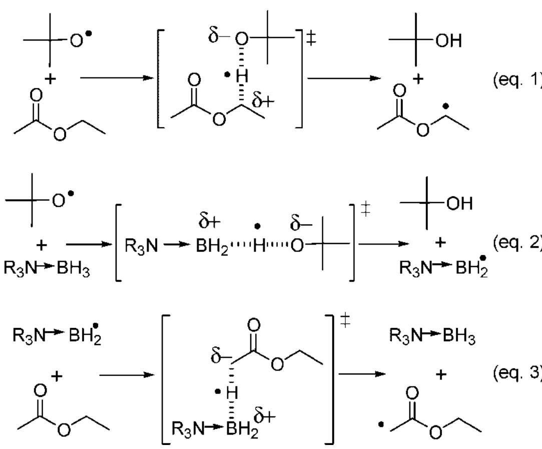
"Polarity Reversal Catalysis"

Roberts coined the term "polarity reversal catalysis" to account for the change in regioselectivity of hydrogen abstraction by the *t*-butoxyl radical from esters upon inclusion of an amine–borane catalyst.[3] Without the catalyst, hydrogen atom abstraction of an hydridic hydrogen α to the ester oxygen occurs to give an acyloxyalkyl radical (eq 1 in Scheme 2). With an amine–borane, the electrophilic *t*-butoxyl radical preferentially removes the more nucleophilic hydride from the B–H bond of the catalyst (eq 2 in Scheme 2). This generates a nucleophilic amine–boryl radical, which abstracts an acidic hydrogen adjacent to the ester carbonyl, completing the two-step catalytic sequence and generating the alkoxycarbonyl radical (eq 3 in Scheme 2). A single polarity-matched step is replaced by two polarity-matched steps in the catalyzed reaction, with a concomitant switch in regioselectivity.[3]

Scheme 1. Tetrahydrofuranyl Radical Fragmentation



Scheme 2. Amine–Borane-Catalyzed Hydrogen Abstraction



A related phenomenon operates in the classic catalysis of aldehyde decarbonylation by thiols.[4] The subsequent work of Roberts on the catalysis of silane reduction of alkyl halides by thiols is another example of the same type. In this process, the slow abstraction of an hydridic silane hydrogen by a nucleophilic alkyl radical, a polarity-mismatched step (eq 6 in Scheme 3), is replaced by two more rapid polarity-matched steps.[3] Thus, the nucleophilic alkyl radical preferentially abstracts the acidic thiol hydrogen to give an electrophilic thiyl radical (eq 4 in Scheme 3), which removes the hydridic hydrogen from the silane (eq 5 in Scheme 3).[3]

The polarity reversal catalysis concept has the advantage of being easily visualized by the ultimate practitioners of the art, synthetic chemists, in view of

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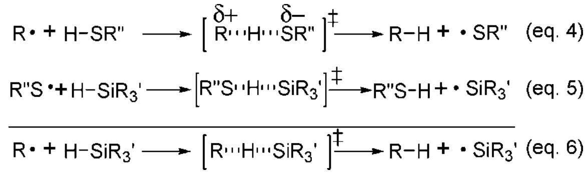
Scheme 3. Thiol Catalysis of Alkyl Radical Trapping by Silanes

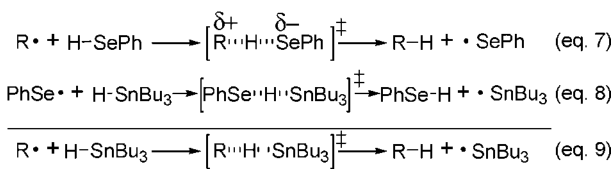


the widespread role of polar effects in governing radical reactions.[5] However, an alternative explanation has been put forward by Zavitsas and Chatgilialoglu, according to which the effect can be understood and the rates of the various hydrogen atom abstractions accurately predicted, by considering the triplet repulsion energy at the transition state for hydrogen atom abstraction as derived from the antibonding energy between the two non-hydrogen atoms.[6] A polemic raged for several years on the relative merits of the two hypotheses with no clear resolution of the issues.[3,7] Without passing judgment, in this Account, we adopt the more graphical description by Roberts.

Polarity Reversal Catalysis with Benzeneselenol

In the selenol-catalyzed chemistry, the slow polarity-mismatched reduction of the nucleophilic alkyl radical by the hydridic stannane (eq 9 in Scheme 4) is replaced by two polarity-matched propagation steps. The nucleophilic alkyl radical is quenched by the acidic benzeneselenol, giving an electrophilic selenyl radical (eq 7 in Scheme 4), which abstracts hydrogen from the stannane to regenerate the catalytic selenol (eq 8 in Scheme 4).[1]

Scheme 4. Selenol Catalysis



Alkyl radicals are trapped 500 times faster by benzeneselenol than by tributylstannane (Table 1). It follows that the use of only 5 mol % of a catalytic selenol will result in a 25-fold increase in the rate of trapping of alkyl radicals (Scheme 5).

Table 1. Rate Constants for Primary Alkyl Radical Reduction

reductant	temperature (°C)	k (s^{-1})	reference
Bu_3SnH	25	2.4×10^6	8
PhSeH	25	1.2×10^9	9
PhSH	25	1.4×10^8	10
Bu_3GeH	25	1×10^5	11
1,4-cyclohexadiene	50	2×10^5	12

The catalytic cycle requires the abstraction of the stannane hydrogen by the selenyl radical, with regeneration of the selenol. At the beginning of this investigation, this was not a known reaction, but the demonstration of the catalytic effect of the selenol established its veracity.[1] The experimental Se–H bond strength in benzeneselenol[13] and its similarity to that of tributylstannane (Table 2)[14] provide further grounds for confidence in this key step.

Scheme 5. Catalyzed and Uncatalyzed Reduction

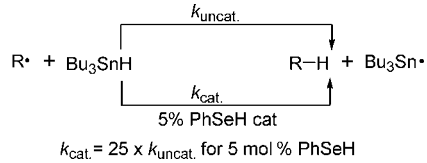


Table 2. Bond Dissociation Energies[13–16]

bond	BDE (kcal mol^{-1})
Bu_3Sn–H	78.6
PhSe–H	78 ± 4
PhS–H	83.5
Bu_3Ge–H	88.6
$PhCH_2$–H	88.5
1,4-cyclohexadien-3-yl–H	76.0
C_6H_5–I	65.0
C_6H_5–Br	80.4
C_6H_5–Se	70 ± 3

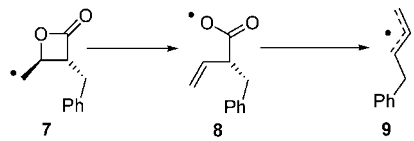
The superlative nature of benzeneselenol as a radical trap was exploited by Newcomb et al.,[9] in their fundamental studies on the rates of alkyl radical rearrangements and fragmentation processes. However, these studies required the use of stoichiometric quantities of selenol, rendering their extension to synthetic protocols impractical. This limitation arises because of the highly air-sensitive nature of the reagent, its noxious odor, and its properties as a vesicant. The catalytic protocol that we established retains the kinetic advantages of benzeneselenol as a radical trap, while minimizing the hazards of working with this substance. The practicality of the method was improved by the realization that diphenyl diselenide is reduced stoichiometrically by tributylstannane (eq 10), removing all need to handle the selenol.[1] The stoichiometry of this reduction was readily established by ^{77}Se and ^{119}Sn nuclear magnetic resonance (NMR) spectroscopy, which also revealed the much slower reaction of benzeneselenol itself with the stannane, something that is essential if the selenol is to persist in the reaction mixture as a working catalyst.[17]

$$PhSe–SePh + Bu_3SnH \rightarrow PhSe–H + PhSe–SnBu_3 \quad (10)$$

Catalytic Selenol as a Radical Clock

The kinetics of radical reactions are often determined by competition methods with the aid of a clock reaction, often the trapping of an alkyl radical by a stannane or benzeneselenol. To satisfy the conditions for pseudo-first-order kinetics, either a large excess of the trap is employed or the reaction is taken to low conversion. It is subsequently necessary to determine the relative amounts of the products in the presence of either a large excess of the trapping reagent or the unreacted starting material.[18] To overcome this potential source of inaccuracy, we devised a protocol in which a known catalytic quantity of benzeneselenol is constantly regenerated by the dropwise addition of tributylstannane as a stoichiometric reagent.[17] The concentration of the selenol is maintained constant throughout the course of the reaction, which is allowed to proceed to full conversion under true pseudo-first-order conditions. The validity of the method was established by redetermination of literature rate constants.[17] Subsequently, we employed this method to determine the kinetic parameters for various rearrangements,[19–21] including the fragmentation of a 2-oxetanon-4-ylcarbinyl radical (Scheme 6).[22]

Scheme 6. Oxetanylmethyl Opening



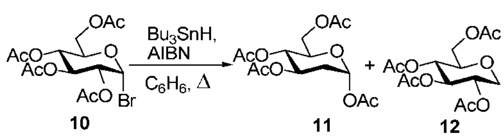
$\log(k_F) = (13.3 \pm 0.2) - (8.7 \pm 1.0)/(2.3RT)$

$\Longrightarrow k_F = 8.2 \times 10^6 s^{-1}$ at 25 °C

Inhibition of Simple Radical Rearrangements

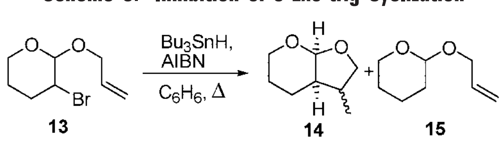
In addition to the original finding (Scheme 1), partial inhibition of several radical rearrangements was demonstrated, as exemplified in Schemes 7 8– 9.[1,20,22]

Scheme 7. Inhibition of Acyloxy Migration



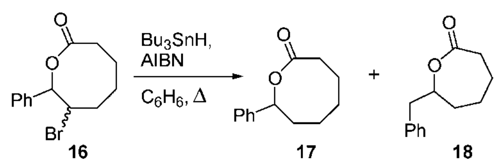
Additive	ratio of **11**:**12**
no additive	89:11
PhSeH	< 5:95
PhSeSePh	< 5:95
PhSH	10:90

Scheme 8. Inhibition of 5-Exo-trig Cyclization



Additive	conc (M)	equiv. Bu_3SnH (addn time h)	**14**:**15**
no additive	0.10	2 (0.5)	100:0
PhSeSePh	0.10	2 (0.5)	82:18
no additive	0.20	0.1 (0.5)	100:0
PhSeSePh	0.20	0.1 (0.5)	58:42

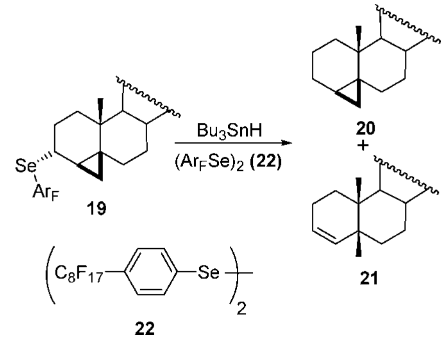
Scheme 9. Inhibition of Lactone Contraction



10^4 [PhSeH] (M)	2.4	4.8	7.1	11.8	14.1
Ratio **17**:**18**	0.42	0.74	1.16	2.00	2.41

Even very rapid rearrangements may be suppressed to a significant extent by increasing the concentration of the selenol. An extreme example was presented by the cyclopropylcarbinyl to homoallyl rearrangement, for which it was calculated that molar concentrations of selenol would be required.[23] To facilitate recovery and recycling of the large quantities of the diselenide, we prepared the fluorous diaryl diselenide **22**. When we worked with a 1.0 M solution of diselenide **22**, reduced in situ to the selenol, a 58:42 mixture of the unrearranged product **20** and the ring-opened product **21** was secured in 65% yield (Scheme 10). The diselenide **22**, regenerated upon work up, was recovered by continuous fluorous extraction.[23]

Scheme 10. Inhibition of Cyclopropylcarbinyl Opening

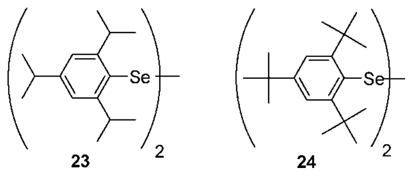


Polarity Reversal Catalysis by Thiols and Tellurols

As expected from its lower rate constant for the trapping of alkyl radicals, as compared to benzeneselenol, thiophenol (Table 1) is a less effective but nevertheless functioning catalyst for the suppression of simple chain reactions (Scheme 7).[1,2] Benzenetellurol, with its expected higher rate of trapping of alkyl radicals, was anticipated to be more effective as a polarity reversal catalyst than benzeneselenol. However, the relative weakness of the Ar–Te bond intervenes, and the tellurol does not persist under the typical reaction conditions.[1]

Selection of Radical Precursors: Bromides or Iodides and the Use of Hindered Selenols as Catalysts

For the benzeneselenol-catalyzed reactions of alkyl radicals, both alkyl bromides and alkyl iodides have been found to be suitable radical precursors.[1] For the reactions of aryl and vinyl radicals, however, the catalytic effect of the selenol is only observed with the iodides.[1,24,25] This is due to the higher bond dissociation energy of sp^2 C–Br bonds than that of sp^2 C–Se bonds (Table 2), resulting in the degradation of the catalyst by the stannane in competition with the generation of the required radical. With the aryl and vinyl iodides, the weaker sp^2 C–I bond is cleaved preferentially, enabling the catalyst to persist in the reaction mixture.[1,24,25] In an attempt to increase the lifetime of the selenol catalyst, diselenides **23** and **24** were prepared, but only minor improvements were seen.[25]

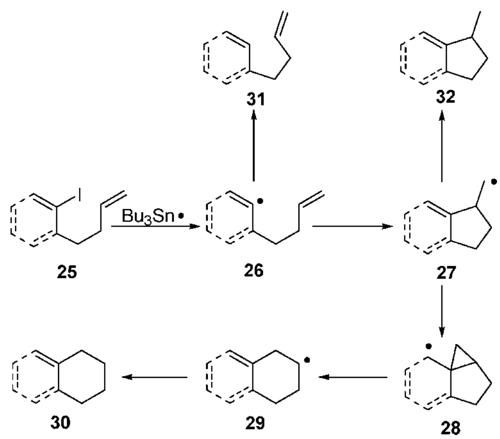


23 24

Intervention in Multistage Radical Rearrangements

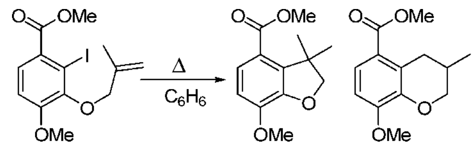
The attractiveness of the catalytic benzeneselenol protocol is enhanced when a single step in a multistage cascade of radical rearrangements can be acted on selectively. This situation arises for the 5-exo-trig cyclizations of aryl and vinyl radicals **26**, wherein the rapid, kinetic 5-exo mode cyclization is followed by a slower rearrangement of the resulting radical **27** to give the thermodynamically more stable 6-endo radical **29**.[26–28] In stannane-mediated chain reactions, mixtures of the 5-exo and 6-endo mode products are usually obtained. To overcome this, the concentration of stannane is usually augmented to suppress the second, slower rearrangement, thereby increasing the yield of the kinetic 5-exo product **32**. Unfortunately, the increased stannane concentration supplements the amount of simple reduction product **31** derived by premature quenching of the initial aryl or vinyl radical **25** (Scheme 11).

Scheme 11. Aryl and Vinyl Radical Cyclization



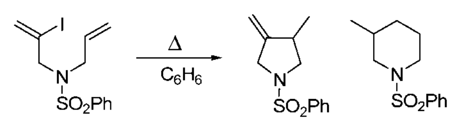
Aryl and presumably vinyl radicals react with tributylstannane at rates approaching the diffusion-controlled limit,[29] indicating that, for a given concentration of stannane, a catalytic quantity of selenol will have no significant impact on the initial ring closure. The ensuing neophyl or homoallyl/cyclopropylcarbinyl rearrangement is, however, one of the slower radical rearrangements,[18,30] rendering it susceptible to suppression by a catalytic quantity of selenol. Effectively, it should be possible to operate with a low concentration of stannane, conditions that normally ensure the formation of significant quantities of the 6-endo mode product, in the presence of catalytic selenol, and completely suppress the second rearrangement while having no effect on the initial ring closure. In other words, the inclusion of the catalytic selenol should lead to increased 5-exo/6-endo product ratios without compromising the overall yield of the cyclized product. This scenario was borne out for both aryl and vinyl radical cyclizations, provided that the aryl and vinyl iodides were employed as radical precursors rather than the corresponding bromides (Scheme 12).[1,24,25]

Scheme 12. Improved Aryl and Vinyl Radical Cyclizations



33 34 35

Bu_3SnH	20:80
Bu_3SnH + 0.01 M $(PhSe)_2$	90:10



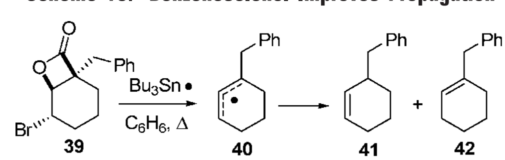
36 37 38

Bu_3SnH	20:80
Bu_3SnH + 2 x 10^{-3} M $(PhSe)_2$	85:15

Enhanced Chain Propagation with Allyl Radicals

In the course of our work on the opening of 2-oxetanon-4-ylcarbinyl radicals (Scheme 6), we studied the reaction of bromolactone **39** with tributylstannane. After fragmentation of the oxetanylcarbinyl radical and decarboxylation, the allyl radical **40** was trapped by the stannane to give the alkenes **41** and **42** in the modest yield of 22%, along with 31% of the various dimers of the allyl radical **40** (Scheme 13).[22,31] In addition, a considerable quantity of azobisisobutyronitrile (AIBN) was required to drive this reaction to completion, all of which pointed to poor chain transfer to the stannane. We reasoned that the inclusion of benzeneselenol, with its more rapid hydrogen transfer capabilities, would facilitate this key propagation step, as was confirmed in practice. Indeed, when the same reaction was conducted in the presence of 10 mol % of in situ generated selenol, only 10 mol % of AIBN was required for the reaction to go to completion and a single product **42** was formed in 85% yield (Scheme 13).[22,31] Similar results were observed with the system studied in Scheme 6, passing through the intermediacy of an allyl radical, which afforded complex reaction mixtures and poor conversion in the absence of the selenol catalyst.[22,31]

Scheme 13. Benzeneselenol Improves Propagation



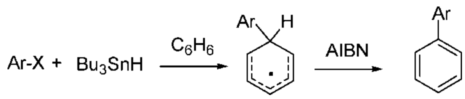
39 40 41 42

Bu_3SnH + AIBN	**41** + **42**: 22 % (12:88)
Bu_3SnH + AIBN + 10 % $(PhSe)_2$ (2x10^{-3} M)	**42:** 85 %

Aryl Radical Addition to Arenes and the Trapping of Cyclohexadienyl Radicals

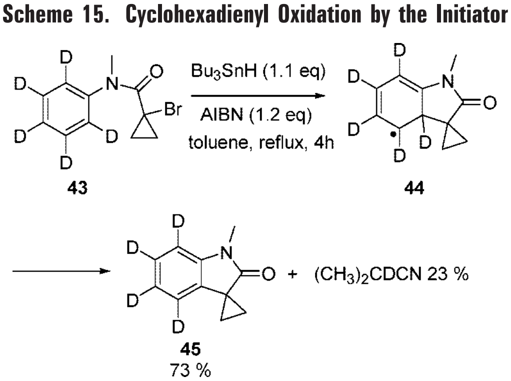
The addition of aryl radicals onto arenes (Scheme 14)[32,33] is frequently applied in organic synthesis, most often in the guise of cyclization.[34,35] The product of these reactions is typically a fully rearomatized system rather than the cyclohexadiene that might be expected from chain transfer of the intermediate cyclohexadienyl radical to the stannane. Reductive radical cyclization onto arenes with the isolation of spirocyclic cyclohexadienes can, however, be achieved with samarium iodide.[36,37] Dearomatized systems also can be obtained when alternative propagation steps for the cyclohexadienyl are designed into the system.[38] In addition to the isolation of aromatized products, the stannane-mediated processes are characterized by poor chain propagation, as is clear from the excessive amounts of initiator employed to achieve full substrate conversion. Excessive amounts of initiator are also required in the tris(trimethylsilyl)silane-promoted oxidative addition of aryl halides to arenes.[39]

Scheme 14. Aryl Radical Addition to Arenes



Although other mechanisms have been proposed, most were invalidated by Beckwith et al.,[40] and it is generally considered that the unreactive cyclohexadienyl is oxidized by the azo-initiator.[41,42] In conjunction with the poor propagation, this accounts for the large amounts of initiator required to achieve high conversion in such reactions. Indeed, Beckwith et al. provided evidence that this pathway is at least partially correct by the isolation of 2-cyano-2-deuteriopropane in 23% yield from the reaction of the pentadeuteriated substrate **43** with tributyltin hydride and AIBN (Scheme 15).[40] Most recently, it has been demonstrated that propagation may be enhanced by working in the presence of oxygen, when the aryl cyclohexadienyl radical is oxidized by oxygen, providing the fully aromatic system and a hydroperoxy radical capable of hydrogen atom abstraction from the stannane.[43]

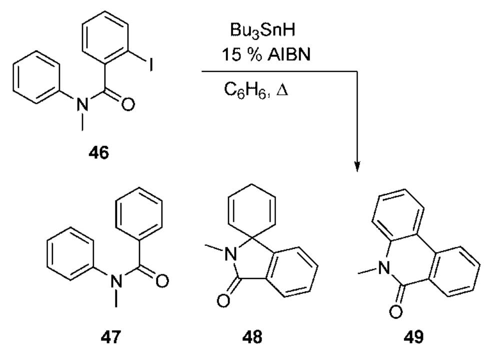
Scheme 15. Cyclohexadienyl Oxidation by the Initiator



Beckwith et al. also made the critical observation that the AIBN-initiated, tributylstannane-promoted reduction of methyl *p*-bromobenzoate proceeded more smoothly and cleanly in cyclohexane as a solvent than in benzene. This was attributed[40] to the inhibition of propagation by cyclohexadienyl radicals, arising from the radical addition to the solvent, in agreement with our general hypothesis. Because rate constants for aryl radical addition to benzene have been determined to be in the range of 4.5×10^5 M^{-1} s^{-1} at 25 °C,[44] it is not surprising that this is a major process in 11.2 M neat benzene.

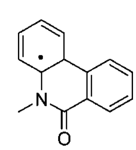
We conceived that the cyclohexadienyl radicals might be efficiently quenched by benzeneselenol, enabling the isolation of cyclohexadienes and a reduction in the quantity of initiator required. This hypothesis was readily established with a dramatic shift in the product spectrum and conversion of substrate **46** in the presence of catalytic selenol (Scheme 16).[45] With only 15 mol % AIBN, the conversion of **46** is dramatically improved and the formation of various dimers is almost completely suppressed in the presence of the catalytic selenol. More importantly, the spirocyclic cyclohexadiene **48**, a minor product in the absence of the selenol, is the major product in the presence of the catalyst, clearly indicating the quenching of the intermediate cyclohexadienyl radical by the selenol. The analogous cyclization, with the isolation of the spirocyclohexadiene **48**, was subsequently conducted under samarium iodide conditions.[37]

Scheme 16. Improved Aryl Radical Cyclization



	46	47	48	49
Bu_3SnH + AIBN	37 %	23 %	<5 %	12 % + dimers
Bu_3SnH + AIBN + 4×10^{-3} M PhSeH	30 %	22 %	43 %	22 %

The limits of the method are clear from the isolation of phenanthridinone **49**, which suggests that the aminocyclohexadienyl radical **50** gains sufficient stabilization from the amido group to prevent hydrogen abstraction from the selenol.[45] The formation of considerable amounts of the simple deiodination product **47** also provides evidence of the less than perfect chain transfer and the corresponding buildup of unreacted stannane in the reaction mixture over the course of the addition. We also studied the stannane-

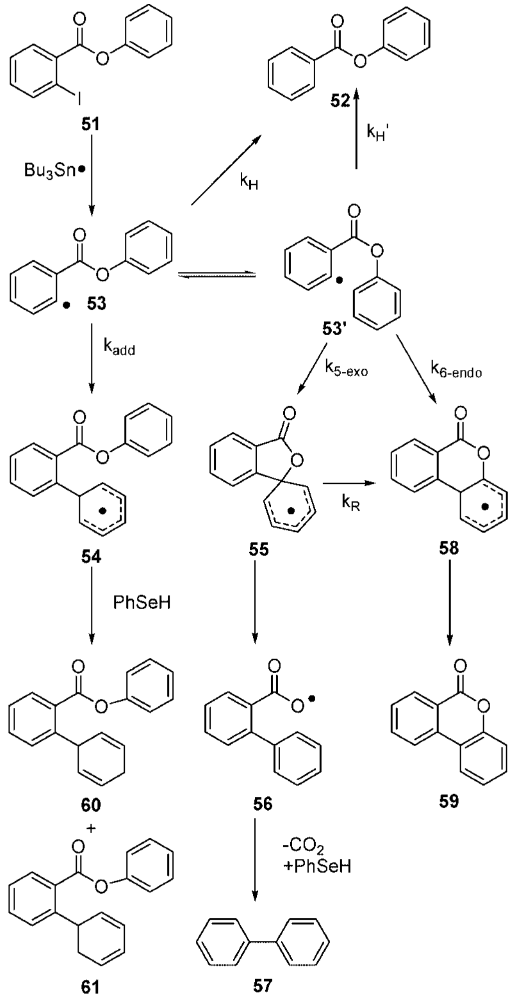


50

mediated reaction of the phenyl iodobenzoate **51** in the presence and absence of catalytic benzeneselenol (Scheme

17).[45] A complex reaction mixture was obtained, owing to the existence of two reaction manifolds arising from the two rotamers about the ester bond. One series of products resulted from trapping of the *trans* conformation **53** by the solvent benzene, whereas a second series was derived from the *cis* conformation **53′** and the intended cyclization process. The most significant difference between the uncatalyzed and catalyzed reactions was in the quantity of the cyclohexadienes **60** and **61**, which increased from essentially 0% in the uncatalyzed process to 40% in the presence of the selenol. The acyloxycyclohexadienyl radical **58** suffered oxidation even in the presence of the selenol, again pointing to the limits of the hydrogen transfer reaction.[45] The expulsion of acyloxy radicals from cyclohexadienyl radicals, as in the fragmentation of **55** to **56**, was subsequently exploited by Studer and Walton in their quest for alternative radical sources.[46]

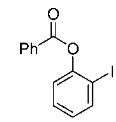
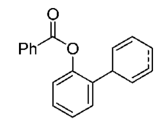
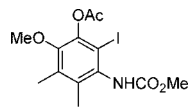
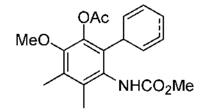
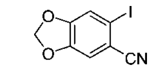
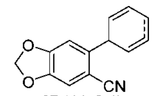
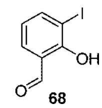
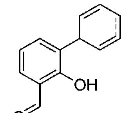
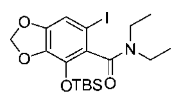
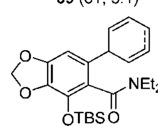
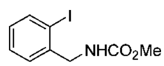
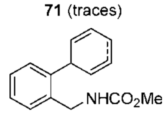
Scheme 17. Reaction of Phenyl Iodobenzoate



substrate [conc, M]	$(PhSe)_2$ (M%)	recovered substrate	products (% yield)
51 [0.02]	0	27%	**52** (25), **59** (5), **57** (3)
51 [0.02]	0.004	0 %	**52** (17), **60**+ **61** (40; 6.8:1), **59** (12), **57** (21)

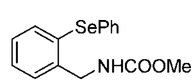
With the isomeric iodophenyl benzoate **62**, only one series of products arising from the intermolecular addition of the intermediate radical *o*-(benzoyloxy)phenyl to benzene was observed.[45] In the absence of the selenol, the fully aromatic 2-benzoyloxybiphenyl was the major product, while in the presence of the selenol, the cyclohexadiene **63** was favored (Table 3).

Table 3. Selenol-Catalyzed Addition of Aryl Radicals to Benzene[45,47–49]

substrate	product (percent yield, 1,4:1,3)
 **62**	 **63** (77; 2.5:1)
 **64**	 **65** (40)
 **66**	 **67** (44; 3:1)
 **68**	 **69** (61; 5:1)
 **70**	 **71** (traces)
 **72**	 **73** (0)

Selenol quenching of cyclohexadienyl radicals takes place predominantly at the central position, leading preferentially to the formation of 1,4-cyclohexadienes rather than the more stable conjugated dienes. This regioselectivity agrees with that seen in the quenching of cyclohexadienyl radicals by oxygen.[50] It appears that there is a considerable steric interaction between the selenol and aryl moieties when the hydrogen is delivered to the terminal position, and that the change in the 1,4/1,3 ratio with the substrate is related to the changing steric environments. It is also possible that the quenching regioselectivity is related to the uneven spin distribution in the cyclohexadienyl radicals, as hinted at by electron spin resonance (ESR) spectroscopy.[51]

Various functional groups are tolerated (Tables 3 and 4), but it is evident that steric hinderance stymies the addition of **70** to benzene.[48] Another failure was observed with the *N*-benzyl carbamate **72** when the major product was the selenide **74**.[48] The addition of *ortho*-functionalized



74

aryl iodides to benzene, followed up with an electrophilic ring closure onto the cyclohexadiene, presents the opportunity for facile and direct syntheses of partially reduced tricyclic heterocycles (Scheme 18).[52] A number of systems were synthesized in this way as exemplified in Table 4.

Scheme 18. Aryl Radical Addition and Cyclofunctionalization

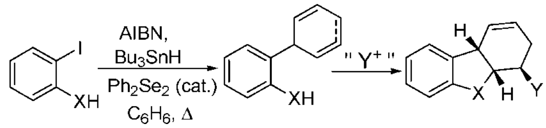
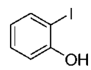
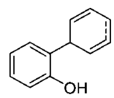
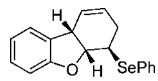
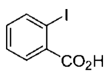
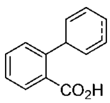
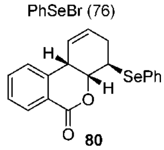
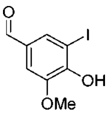
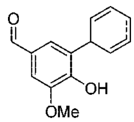
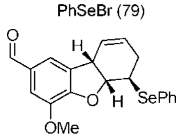
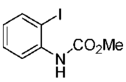
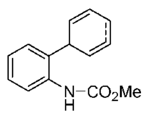
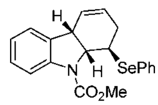
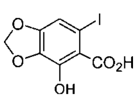
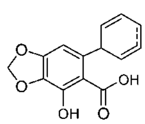
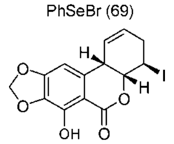


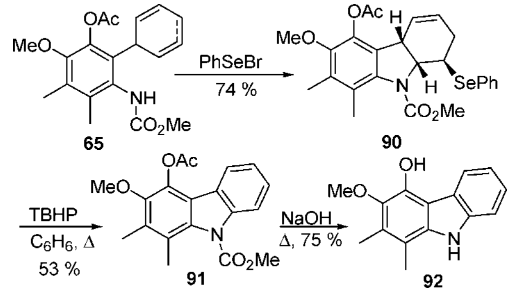
Table 4. Aryl Radical Addition and Cyclofunctionalization[48,52]

substrate	diene (percent yield, 1,4:1,3)	cyclized product, electrophile (percent yield)
 75	 76 (48,10:1)	 77 PhSeBr (76)
 78	 79 (54, 10:1)	 80 PhSeBr (79)
 81	 82 (44, 10:1)	 83 PhSeBr (71)
 84	 85 (41, 3:2)	 86 PhSeBr (69)
 87	 88 (30, >10:1)	 89 I_2 (71)

In an application of this process to synthesis, the highly functionalized tetrahydrocarbazole **90** was converted to carbazomycin B by heating in the presence of *tert*-butyl hydroperoxide, followed by saponification (Scheme 19).[47] The aromatization of the cyclohexadiene formed upon *syn* elimination of the intermediate selenoxide is achieved with benzeneseleninic acid, which itself arises from disproportionation of the *syn*-elimination byproduct, benzeneselenenic acid. The selenium moiety therefore has triple usage, provoking the electrophilic cyclization, then permitting the *syn* elimination, and subsequent aromatization.

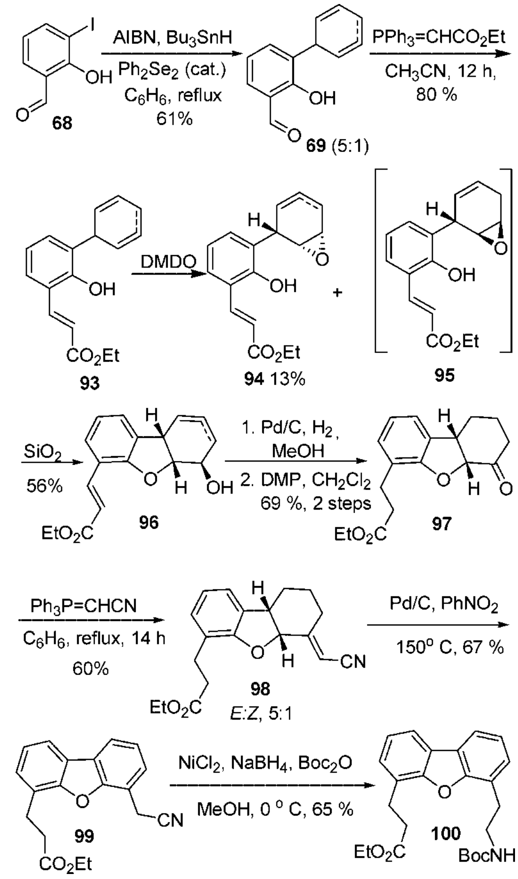
The aryl radical addition/cyclofunctionalization reaction also provides the opportunity to prepare dibenzoheterocycles substituted in both benzenoid rings, by

Scheme 19. Carbazomycin B Synthesis



exploitation of the C–electrophile bond. This was illustrated through a synthesis of a β-turn mimic (Scheme 20), which also highlights the resistance of the cyclohexadiene moiety to the conditions of the Wittig reaction.[49]

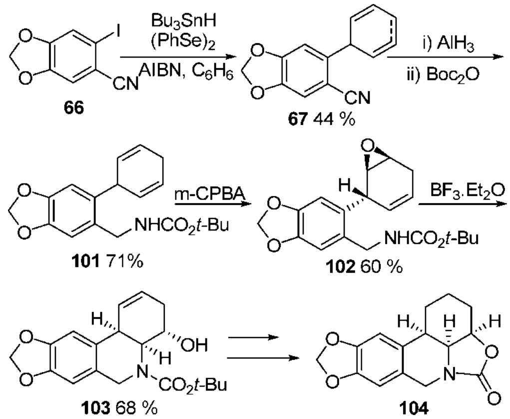
Scheme 20. 4,6-Disubstituted Dibenzofuran Synthesis



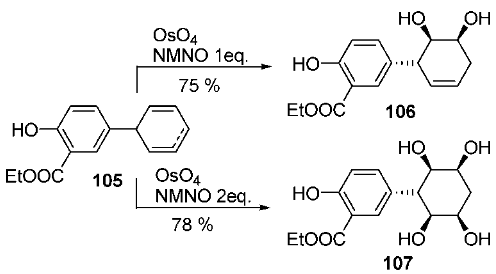
The aryl radical addition/cycloaromatization sequence was also applied to the synthesis of a number of phenanthridine derivatives related to the *Amaryllidaceae* alkaloids (Scheme 21). The aluminum hydride reduction of the nitrile group in the presence of the cyclohexadiene is noteworthy.[48]

Catalytic osmoylation of the aryl cyclohexadienes provides a very direct, two-step synthesis of aryl-substituted cyclitols from aryl iodides and benzene (Scheme 22).[53]

Scheme 21. Phenanthridine Synthesis



Scheme 22. Cyclitol Synthesis



Aryl Radical Addition to Other Arenes

The addition of aryl radicals to arenes other than benzene is more complex, owing to the possibility of *ortho*, *meta*, *para*, and *ipso* addition, coupled with the potential variance of the 1,4-/1,3-diene ratio according to the substituent. Nevertheless, the considerable body of early work carried out upon the addition of aryl radicals onto a wide variety of arenes and heteroarenes, for the most part under nonchain conditions and typically with rearomatizarion of the cyclohexadienes,[32,33] prompted a brief exploration. Typically, the addition products were obtained in modest yield and in the fully aromatic form (Table 5), consistent with the failure of substituted, stabilized cyclohexadienyl radicals to undergo chain propagation with the selenol, as noted for radicals **50** and **58**.[54] Nevertheless, with both chlorobenzene and naphthalene, cyclohexadienes were isolated. In the additions of *o*-iodophenol and *o*-iodobenzoic acid to anisole, the products from attacked *ortho* to the methoxy group underwent in situ acid-promoted cyclization to give tricyclic products, clearly indicating chain transfer and cyclohexadiene formation in these cases.

Aryl Addition to Heterocycles

Previous work on the oxidative addition of aryl radicals to neutral pyridines indicated a slight preference for the reaction at the *ortho* position.[55] Tris(trimethylsilyl)silane promoted addition of aryl halides to nitrogen heterocycles, by a process requiring large amounts of initiator and leading to fully aromatic products, has also been

Table 5. Radical Addition to Arenes[54]

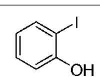
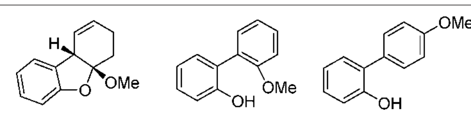
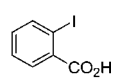
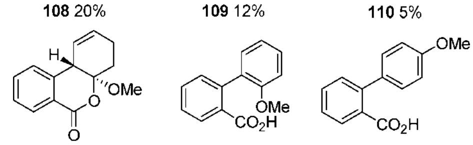
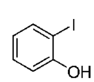
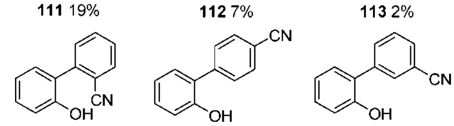
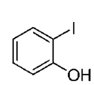
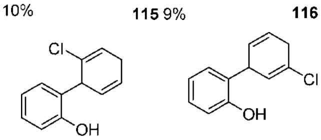
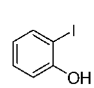
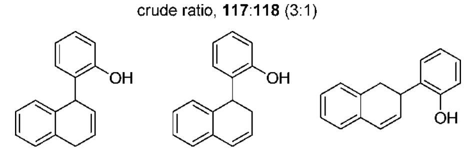
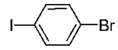
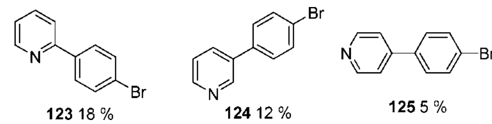
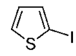
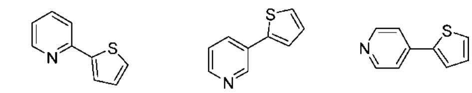
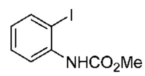
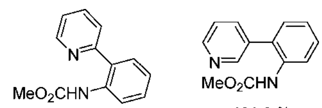
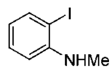
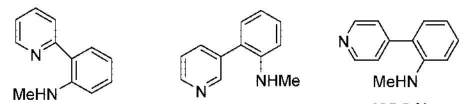
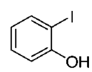
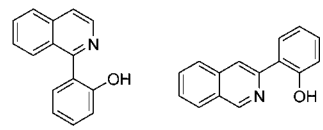
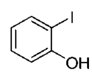
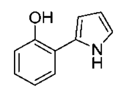
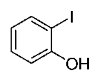
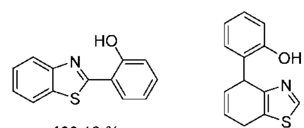
arene	substate	products
anisole	 75	 **108** 20% **109** 12% **110** 5%
anisole	 78	 **111** 19% **112** 7% **113** 2%
benzonitrile	 75	 **114** 10% **115** 9% **116** 5%
chlorobenzene	 75	 **117** 17% **118** 3% crude ratio, **117**:**118** (3:1)
naphthalene	 75	 **119** **120** **121** 40 %, **119**:**120**:**121** (1.4:1.4:1)

Table 6. Radical Addition to Nitrogen Heterocycles[54,57]

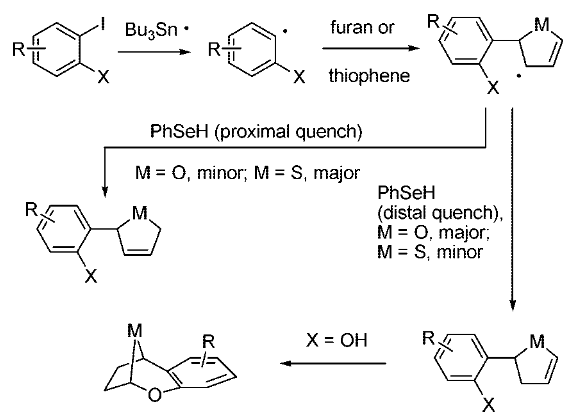
arene	substrate	products
pyridine	 **122**	 **123** 18 %; **124** 12 %; **125** 5 %
pyridine	 **126**	 **127** 19 %; **128** 24%; **129** 7 %
pyridine	 **84**	 **129** 38%; **131** 3 %
pyridine	 **132**	 **133** 25 %; **134** 7 %; **135** 5 %
isoquinoline	 **75**	 **136** 44 %; **137** 4 %
pyrrole	 **75**	 **138** 17 %
benzothiazole	 **75**	 **139** 19 %; **140** 7 %

described.[56] Results from the selenol-catalyzed stannane method were in agreement with the earlier finding of limited regioselectivity, until iodoarenes carrying potential hydrogen-bond donors at the *ortho* position were examined. The higher *ortho* selectivity obtained in these cases is attributed to the pseudo-intramolecular nature of the reaction arising from hydrogen bonding between the donor and the substrate (Table 6),[54,57] consistent with the high *ortho* selectivity seen with protonated pyridines.[35,55] All additions to nitrogen heterocycles afforded fully aromatized products, with no evidence for the intermediate formation of cyclohexadienes even in the crude reaction mixtures.

Additions to furan and thiophene, again on the basis of early literature precedent,[58,59] were more interesting once an initiator compatible with the lower boiling point of the substrate was selected. In all cases, the addition adjacent to the heteroatom was preferred (Table 7).[54,60] However, the regioselectivity of the trapping step changed from furan to thiophene, consistent with the differing degrees of spin delocalization in 1-oxa- and 1-thia-allyl radicals (Scheme 23).[61,62]

Although the yields were only moderate, the most interesting results were obtained with the *o*-iodophenol-type radical precursors when the radical addition was followed by immediate cyclization to give a one-pot synthesis of the 2,3,4,5-tetrahydro-2,3-epoxy-1-benzoxepins (Scheme 23 and Table 7).[54,60]

Scheme 23. Aryl Radical Addition to Furan and Thiophene

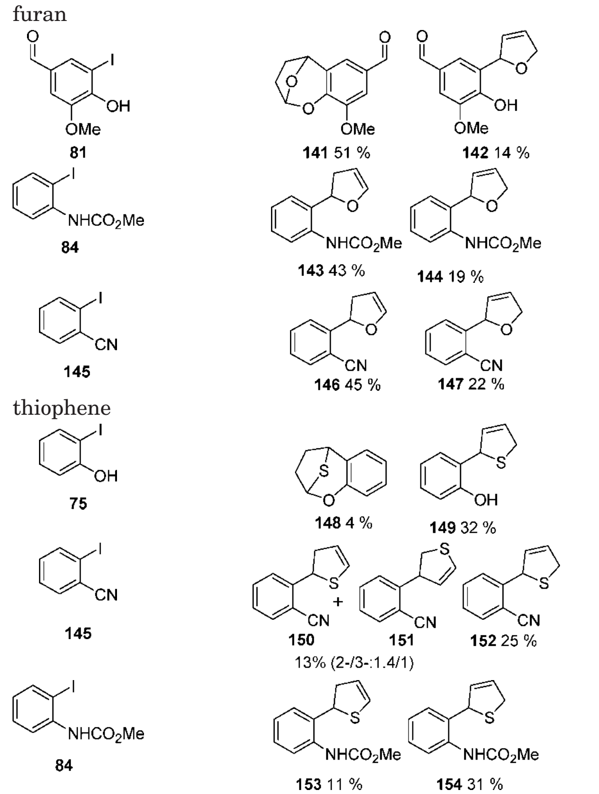


Conclusion

The catalysis of stannane-mediated radical chain reactions by benzeneselenol once again demonstrates that a single, inefficient propagation step may be advantageously replaced by two well-matched steps. The application of this

Table 7. Aryl Radical Addition to Furan and Thiophene[54,60]

substrate	products



concept opens numerous doors previously closed to the synthetic chemist.

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