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Optimizing the 5-exo/6-endo Ratio of Vinyl Radical Cyclizations Through Catalysis with Diphenyl Diselenide

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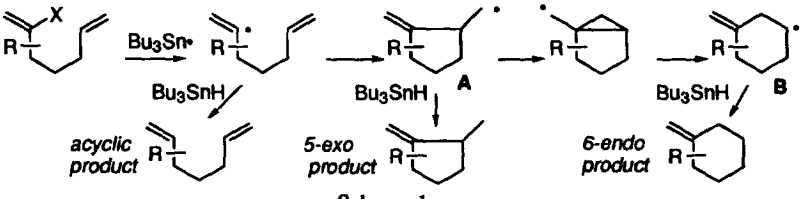
Abstract: *The 5-exo/6-endo product ratio in the stannane mediated cyclizations of vinyl iodides is very significantly improved by operating in the presence of catalytic PhSeSePh with no loss in overall cyclization yield.*

Since their introduction in 1982[1] vinyl radical cyclizations, particularly the 5-exo-variety, have proved to be extremely popular in organic synthesis,[2] even permitting high degrees of stereocontrol.[3] However, the utility of such vinyl radical cyclizations is frequently offset by the formation of mixtures of the 5-exo and formal 6-endo mode products. The formal 6-endo mode product typically arises by rearrangement of the kinetically closed radical (**A**) to the more stable **B**. As such the 5-exo/6-endo ratio is a function of stannane concentration with higher concentrations giving more of the kinetic 5-exo product (Scheme 1).[4] Unfortunately, as clearly demonstrated by Beckwith,[4a] the use of high concentrations of stannane needed to suppress the unwanted rearrangement also leads to increased amounts of acyclic product due to trapping of the vinyl radical.



Scheme 1

As we have demonstrated in an extension of Roberts' concept[5,6] of polarity reversal catalysis of radical chain reactions, catalytic quantites of diphenyl diselenide, reduced *in situ* to benzeneselenol (eq. 1), are extremely efficient at preventing rearrangements of nucleophilic alkyl radicals in stannane mediated chain sequences, yet have little effect on the rearrangements of more reactive aryl radicals.[7] The catalytic effect of benzeneselenol on the reduction of nucleophilic alkyl radicals is readily understood in terms the sequence of propagation steps (eqs. 2-4) and the rate constants for trapping of primary alkyl radicals by tributyltin hydride (k_{25} = 2.4 x 10^6 s^{-1})[8] and benzeneselenol (k_{25} = 2.1 x 10^9 s^{-1}).[9] The failure of benzeneselenol to catalyse the reduction of aryl radicals may be due to an unfavorable polarization of the transition state for hydrogen atom

abstraction from the selenol by the aryl radical, or to the compression of rates against the diffusion controlled limit.[10]

$Bu_3SnH + PhSeSePh$	$\rightarrow$	$Bu_3SnSePh + PhSeH$	eq. 1.
$Bu_3Sn\bullet + RX$	$\rightarrow$	$Bu_3SnX + R\bullet$	eq. 2.
$R\bullet + PhSeH$	$\rightarrow$	$RH + PhSe\bullet$	eq. 3.
$PhSe\bullet + Bu_3SnH$	$\rightarrow$	$PhSeH + Bu_3Sn\bullet$	eq. 4.

We therefore reasoned that conducting cyclizations of analogous vinyl radicals at low stannane concentrations, but in the presence of catalytic diphenyl diselenide, would lead to preparatively important, improved 5-exo/6-endo ratios without the drawback of acyclic product formation seen at higher stannane concentrations. To test this hypothesis we have taken three examples of vinyl radical cyclizations from the literature and examined the effect of a catalytic quantity of PhSeSePh on the exo/endo product ratios, as set out in Table 1. Preliminary experiments with vinyl bromides revealed PhSeH to be consumed by Bu_3SnH more rapidly than the substrate, neccesitating use of the more reactive vinyl iodides in this sequence. With the vinyl iodides the catalyst persists until the substrate is consumed, after which it is decomposed by reaction with the stannane as signaled by the appearance of a faint, grey, metallic precipitate in the reaction mixture.[11,12]

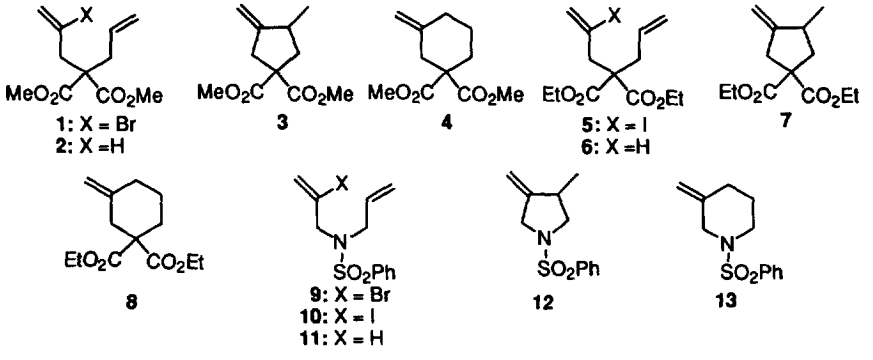
Entries 1 - 5 of Table 1 demonstrate the effect of stannane concentration on the uncatalysed cyclization of the radical derived from **1** or **5**. Thus, Stork reported cyclization of **1** with 2.2×10^{-2} M Bu_3SnH to give a 3:1 ratio of the 5-exo and 6-endo products **3** and **4**, respectively, with no reduction product **2** (Table 1, entry 1). With the iodide **5**, as the stannane concentration is augmented from 4.8×10^{-3} through 1.2×10^{-2} to 1.2×10^{-1} the ratio of **7**:**8** increases, in agreement with the mechanism of Scheme 1, without the formation of a significant amount of **6** (Table 1, entries 2 - 4). However, in order to obtain a **7**:**8** ratio of >95:5 it was necessary to go to 4.9×10^{-1} M Bu_3SnH by which time reduction of the vinyl radical to give **6** was a competing process (Table 1, entry 5). In contrast, entries 6 - 7 (Table 1) show that, with a Bu_3SnH concentration of 1.2×10^{-2} M and below, catalytic PhSeSePh ($\leq 10^{-3}$ M) more or less completely suppresses the formation of **8** without giving rise to **6**. Indeed, it is necessary to go to 10^{-2} M PhSeSePh before reduction of the vinyl radical becomes a competing process (Table 1, entry 8). Thus, it is readily seen that a catalytic quantity of PhSeSePh has a very significant effect on the 5-exo/6-endo product ratio without leading to the formation of significant recduction product.

A second example contrasts the bromide **9**/Bu_3SnH reaction to that of the corresponding iodide **10** with Bu_3SnH and catalytic PhSeSePh. It was reported[13] that treatment of the bromide **9** with Bu_3SnH (4.6×10^{-2} M) in benzene at reflux led to the isolation of **12** and **13** in the ratio 28:56 (Table 1, entry 9).[14] When the experiment was conducted with **10**, under more dilute conditions, we obtained 1:4 mixtures in favor of the 6-membered ring **13** (Table 1, entries 10 and 11). Operating in the presence of 10 mol% PhSeSePh (10^{-3} M) the ratio was adjusted to 55:45, and by going to 20 mol% PhSeSePh a much more favorable 85:15 ratio of products was obtained, again without formation of a significant quantity of the reduction product (Table 1, entries 12 and 13).

Table 1

Entry	Substrate (conc, M)	Bu_3SnH (mol%, conc [M])	PhSeSePh (mol%, conc [M])	Acyclic Product[a]	5-exo:6endo ratio[a]
1 (lit[1])	1 (2×10^{-2})	110, 2.2×10^{-2}	0	2[b]	3:4 = 3:1
2	5 (4×10^{-3})	120, 4.8×10^{-3}	0	6 (<5%)	7:8 = 25:75
3	5 (1×10^{-2})	120, 1.2×10^{-2}	0	6 (<5%)	7:8 = 55:45
4	5 (9×10^{-2})	120, 1.2×10^{-1}	0	6 (<5%)	7:8 = 87:13
5	5 (3×10^{-1})	120, 4.9×10^{-1}	0	6 (15%)	7:8 = >95:5
6	5 (4×10^{-3})	120, 4.8×10^{-3}	10, 4×10^{-4}	6 (<5%)	7:8 = >95:5
7	5 (1×10^{-2})	120, 1.2×10^{-2}	10, 1×10^{-3}	6 (<5%)	7:8 = >95:5
8	5 (9×10^{-2})	120, 1.2×10^{-1}	20, 1.8×10^{-2}	6 (5%)	7:8 = >95:5
9 (lit[14])	9 (4.6×10^{-2})	100, 4.6×10^{-2}	0	11[b]	12:13 = 28:56
10	10 (4×10^{-3})	120, 4.8×10^{-3}	0	11 (<5%)	12:13 = 20:80
11	10 (1×10^{-2})	120, 1.2×10^{-2}	0	11 (<5%)	12:13 = 20:80
12	10 (1×10^{-2})	120, 1.2×10^{-2}	10, 1×10^{-3}	11 (<5%)	12:13 = 55:45
13	10 (1×10^{-2})	120, 1.2×10^{-2}	20, 2×10^{-3}	11 (<5%)	12:13 = 85:15
14 (lit[1])	14 (2×10^{-2})	110, 2.2×10^{-2}	0	15[b]	16:17 = 2:1
15	14 (2×10^{-2})	110, 2.2×10^{-2}	0	15 (<5%)	16:17 = 3:1
16	14 (2×10^{-2})	110, 2.2×10^{-2}	10, 2×10^{-3}	15 (<5%)	16:17 = 5:1

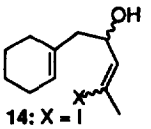
a: Ratios were measured by ^{1}H-NMR spectroscopy on the crude reaction mixtures which were clean and devoid of other products; b: Not reported



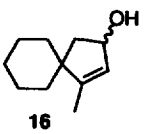
A final example is provided by the literature iodide **14** which was reported[1] to yield **16** and **17** in a 2:1 ratio (Table 1, entry 14). In our hands, under the conditions outlined in the literature, the ratio was 3:1 in favor of **16** (Table 1, entry 15).[15] Again, addition of only 10 mol% of PhSeSePh resulted in the much improved **16**:**17** ratio of 5:1 (Table 1, entry 16).

In summary, we have demonstrated that catalytic quantities of PhSeSePh, reduced *in situ* to PhSeH, have very beneficial effects on the 5-exo/6-endo product ratios in the stannane mediated cyclization of vinyl

iodides. These preparatively significant improvements are achieved without the requirement for an increase in stannane concentration and do not lead to increased reduction product.



14: X = I
15: X = H



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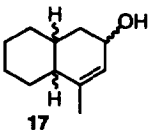

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6. For an alternative explanation of the catalytic effects of thiols and selenols in radical chain reactions see: Zavitsas, A.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1995**, *117*, 10645.
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10. We thank Professor D. P. Curran, Pittsburgh, for this suggestion.
11. It should be noted that this caveat does not apply to the catalysis of the reactions of alkyl halides wherein the use of alkyl bromides is perfectly satisfactory.[7]
12. Vinyl iodides **5** and **10** were prepared by standard alkylations of diethyl allylmalonate and *N*-allylbenzenesulfonamide, respectively, with the mesylate of 2-iodo-2-propenol which in turn was prepared by standard mesylation of 2-iodo-2-propenol (eg Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett.* **1990**, 675)
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14. This ratio is taken from the experimental of the original publication.[14] A different ratio (**12**:**13** = 3:1) is given in the text, but with no details of conditions.
15. As suggested by Stork, the **16**:**17** ratio was determined after oxidation to the corresponding ketones, although we oxidized with TPAP/NMNO (Ley, S. V.; Norman, J.; Griffith, W. P. *Synthesis* **1994**, 639). No attempt was made to determine stereochemistry of **16** or **17** or of the ketones.

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