

Intramolecular Addition of Vinyl Radicals to Aldehydes

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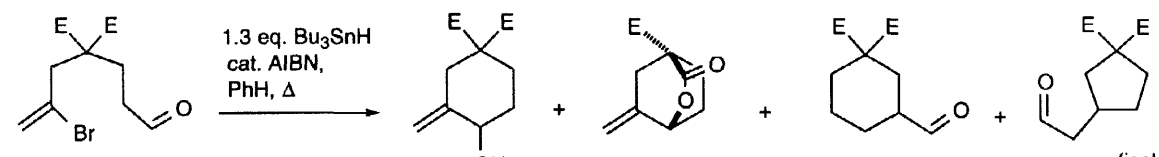
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Abstract : The reaction of aldehydes **1** and **10** with Bu₃SnH has been studied. In thermal conditions, after an initial chemoselective 6-*exo-trig* or 5-*exo-trig* cyclization to the aldehyde, a β -scission reaction takes place, providing rearrangement products. At low temperature, using the Et₃B/O₂ procedure, satisfactory yields of cyclohexanol **2** and cyclopentanol **11** are obtained.

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Aldehydes have mainly been used in radical chemistry as stannyl radical acceptors, to form O-stannyl radical ketyl intermediates that can be reduced¹ to afford alcohols. These intermediates can also be trapped in an intramolecular fashion to form various cyclic compounds,² and are good triggers for tandem reactions, as illustrated by the elegant work of Enholm.³ Though Fraser-Reid and Tsang⁴ have demonstrated that aldehydes are excellent carbon-centered radical acceptors to form cyclohexanols, and in a lesser extent cyclopentanols,⁵ this reaction has still not met its potential success. As pointed out by Curran⁶ : "The problem here is that radical cyclization to carbonyl groups are reversible, and trapping of the closed product is not always easy".⁷

We wanted to investigate the behavior of vinyl radicals towards aldehydes to form α -methylene cycloalkanols. This would represent a radical alternative to the now well-established Nozaki-Kishi coupling of vinyl halides with aldehydes.⁸ Furthermore, we could utilize the resulting alkoxy radicals⁹ in cascade reactions to form oxygenated heteropolycycles. At the inception of this project, a few reports described the reaction of vinyl radicals toward ketones in cyclic series, giving rise to interesting carbocycles.¹⁰ But to the best of our knowledge, the study of simpler system has remained elusive. Thus, we initially focused on aldehyde **1** (Scheme 1), readily available through malonate chemistry, in order to check the previously reported high performance of aldehydes in 6-*exo-trig* cyclizations.⁵

						
Entry	1, E = CO ₂ Me		2 OH	3	4	5 (isolated yield %)
1	0.02 M	slow addition, 2.10 ⁻⁴ mol.h ⁻¹	0	18	28	19
2	0.02 M	t = 2 h	9	21	26	13
3 ^a	1.7 M	t = 2 h	17	32	0	0

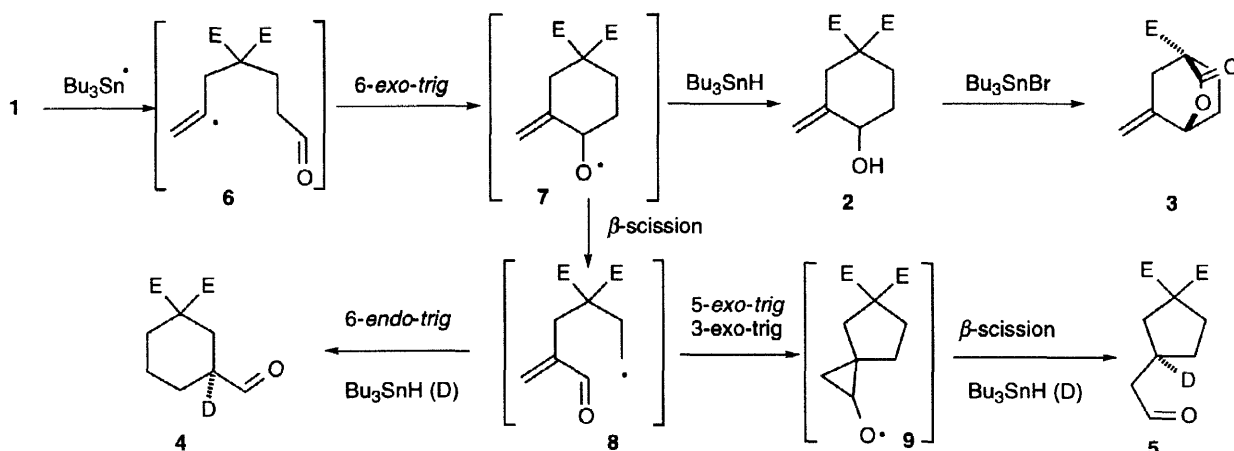
a : In addition, the reduced vinyl radical product, aldehyde **13** is obtained in 20% yield.

Scheme 1

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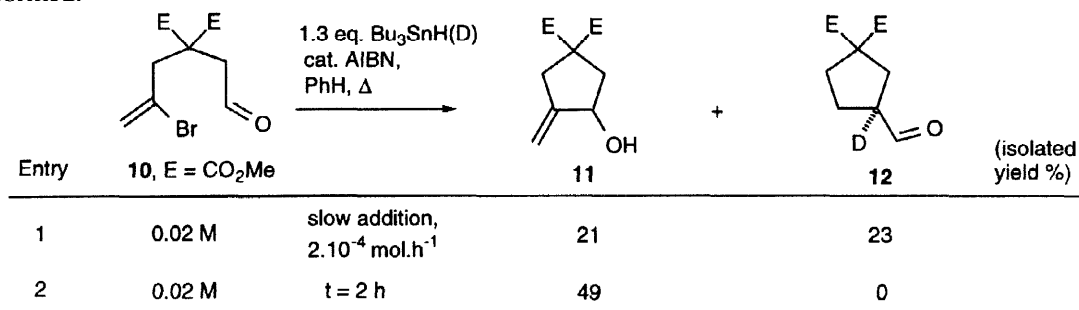
Heating a mixture of aldehyde **1** and Bu_3SnH (1.3 equiv.) for 2 hours (Scheme 1, entry 2) afforded a mixture of 4 products, whose diversity of functionalities allowed a separation by column chromatography. Based on deuterium labelling with Bu_3SnD , we could propose a radical mechanism for the formation of aldehydes **4** and **5** (Scheme 2). After an initial 6-*exo-trig* cyclization of the vinyl radical to the aldehyde, generating alkoxy radical **7**, a β -scission reaction takes place to form enal intermediate **8**. A 6-*endo-trig* ring closure, based on a favorable Michael addition of the nucleophilic methylene radical, affords cyclohexylaldehyde **4**. As a minor pathway from **8**, a tandem 5-*exo-trig*, 3-*exo-trig* to form bicyclic alkoxy radical **9**, followed by a β -scission would also give aldehyde **5**. Moreover, we could determine that lactone **3**, was formed through a polar process, and probably not through a radical reaction.¹¹ Indeed, when heated in refluxing benzene, in presence of Bu_3SnCl ,¹² alcohol **2**¹³ was cleanly converted to lactone **3**.

We then found that the product distribution was highly dependent on the stannane concentration in the reaction medium. At high concentrations (Scheme 1, entry 3), only alcohol **2** and derived lactone **3** are observed, whereas low stannane concentrations allow the β -scission pathway and favor the formation of rearrangement products **4** and **5**. This observation is consistent with the fact that all products derive¹⁴ from alkoxy radical **7**, and that the reaction of aldehyde **1** with Bu_3SnH , would be completely chemoselective in favor of the 6-*exo-trig* cyclization of the vinyl radical to the aldehyde. No 1,5-H transfer¹⁵ or 1,6-H transfer⁵ is observed.



Scheme 2

Encouraged by this finding, we then turned to aldehyde **10**,¹⁶ for which a 5-*exo-trig* cyclization of the vinyl radical was expected. Once again, the product distribution (Scheme 3) was highly dependent on the tin hydride concentration. However, global isolated yields in this series were rather low and some minor compounds could also be formed.



Scheme 3

In slow stannane addition conditions, aldehyde **12** is obtained in 23% yield. Incorporation of deuterium in adjacent position to the carbonyl group suggests us that this product originates exclusively from a pathway similar to the formation of **4**. In this case a sequence of a 5-*exo-trig* cyclization, followed by a β -scission of the alkoxy radical and a final unusual 5-*endo-trig* cyclization¹⁷ would take place. At higher concentration of tin hydride, however, only cyclopentanol **11**¹⁸ is isolated, thus confirming our previous findings.

Then, aiming at optimizing this reaction, we focused on low temperature conditions, using the Et₃B/O₂ system as an initiator.¹⁹ Although, Et₃B can be theoretically used only in a catalytical amount, as AIBN, we found the reaction highly sensitive to the amount that was used. Thus, this amount has to be increased to 10 equivalents to observe the disappearance of the aldehyde **13** (Scheme 4, entries 1 and 3), suggesting that Et₃B may also play the role of a Lewis acid. The TLCs of the crude products of entries 3 and 5 showed only one product, whose R_f corresponds to the expected alcohols **2** and **11**. However, after a standard work-up (KF, MeOH) to eliminate tin residues, chromatography afforded in both cases a mixture of two products : alcohols **2** and **11**, contaminated by the dimeric boron adducts **15** (CIMS, MNH₄⁺ = 512) and **14** (CIMS, MNH₄⁺ = 484). Brown²⁰ has reported the affinity of alkoxy radicals towards trialkylboron derivatives. In our case, the Et₃B boron appears as a radical quencher of the intermediate alkoxy radicals, and would prevent the β -scission pathway. A simple aqueous treatment is sufficient to cleave these boronic esters, and pure alcohols **2** and **11** can be obtained in satisfactory yields (entries 4 and 6).

Entry	precursor	conditions ^a	2, 50	13	14, n=1 15, n=2	(isolated yield %)
1	1	A	2, 50	13	0	
2	1	B	2, 51	13	0	
3	1	C	2, 16	0	15, 24	
4	1	D	2, 79	0	0	
5	10	C	11, 34	-	14, 18	
6	10	D	11, 64	-	0	

a : The precursor **1** or **10** (0.02 M in toluene) is treated with Bu₃SnH, in conditions A (Et₃B, 1 eq. at 0°C), in conditions B (Et₃B, 4eq. at T = -78° to 0° C), conditions C (Et₃B, 10 eq. at T = -78° to 0° C), or conditions D (Et₃B, 10 eq. at T = -78° to 0° C, followed by an aqueous work-up). The crude product is then treated with KF in MeOH, and purified by flash chromatography.

Scheme 4

In conclusion, the reaction of aldehydes **1** and **10** has proven to be totally chemoselective in favor of the 6-*exo-trig* and 5-*exo-trig* cyclization processes. In thermal conditions, the resulting alkoxy radicals fragment to afford various rearrangement products. Using low temperature conditions, based on the Et₃B/O₂ system, appears as a method of choice to trap the intermediate alkoxy radicals and this results in an efficient synthesis of α -

methylene cyclopentanols and cyclohexanols. Further work is now in progress, focusing on chiral boron derivatives, in order to develop an asymmetric version of this cyclization.

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- 13) **2** : ^1H NMR (CDCl_3 , 200 MHz) 1.60-1.70 (m, 1H), 1.80-1.95 (m, 2H), 2.25-2.35 (m, 1H), 2.53 (d, $J = 13.7$ Hz, 1H), 2.92 (d, $J = 13.7$ Hz, 1H), 3.65 (s, 6H), 4.05 (m, 1H), 4.82 (s, 1H), 4.95 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) 28.4, 32.4, 37.3, 52.6, 52.7, 56.4, 71.1, 109.8, 145.9, 171.0, 171.5; IR 3450, 2950, 2850, 1730, 1250 cm^{-1} ; Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_5$: C, 57.89, H, 7.07. Found: C, 57.87, H, 7.15.
- 14) We can not yet completely rule away another minor pathway for **2**, involving an *O*-ketyl radical, cyclizing in a 6-*exo-trig* mode followed by a bromide β -elimination.
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- 18) **11** : ^1H NMR (CDCl_3 , 400 MHz) 2.27 (ddd, $J = 14.0, 5.0, 0.8$ Hz, 1H), 2.52 (dd, $J = 13.9, 6.9$ Hz, 1H), 2.87 (dt, $J = 17.1, 2.4$ Hz, 1H), 3.11 (dd, $J = 17.1, 1.2$ Hz, 1H), 3.73 (s, 3H), 3.74 (s, 3H), 4.52 (m, 1H), 5.09 (q, $J = 2$ Hz, 1H), 5.21 (q, $J = 2$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) 38.8, 42.6, 53.0, 53.1, 57.5, 73.3, 110.2, 151.0, 172.0, 172.8; IR 3500, 3050, 2840, 1725, 1430 cm^{-1} ; Anal. Calcd. for $\text{C}_{10}\text{H}_{14}\text{O}_5$: C, 56.07, H, 6.59. Found: C, 56.00, H, 6.65.
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