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Tin-free radical chemistry: intramolecular addition of alkyl radicals to aldehydes and ketones

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Abstract

The radical cyclization of several ω-iodoaldehydes and a ketone can be accomplished without the use of tributyltin hydride. Triethylborane in presence of oxygen or light from a sun lamp can serve as a radical initiator and terminator. In these conditions, a 5-*exo-trig* cyclization on an aldehyde is faster than on an alkene. © 1999 Published by Elsevier Science Ltd. All rights reserved.

The intramolecular addition of radicals to carbonyl derivatives has witnessed a renaissance over the last couple of years.[1] While the seminal work of Maillard,[2] and of Tsang and Fraser-Reid[3] established that aldehydes are excellent radical acceptors, especially for 6-*exo* ring closures,[4] numerous reports have highlighted the reversibility of such cyclizations,[5] especially in the case of ketones. The kinetics of β-fragmentation of the cyclopentyloxy and the cyclohexyloxy radicals have even been determined.[6] Several methods have been devised to overcome this reversibility and they globally divide into two main families.[7] The first one involves a fast trapping of the intermediate alkoxy radicals (**A** → **B**), using, for instance, triethylborane[8,9] to give cycloalkanols, or phosphines which trigger deoxygenation and provide cycloalkanes.[10] Along the same lines, Fu has developed a radical pinacol sequence, driven by an intramolecular S_H2 pathway of the alkoxy radical on the vicinal stannoxy moiety.[11] Recently, Batey has shown that phenylsilane is particularly well-fitted for the efficient reduction of alkoxy radicals.[12] The second method relies on synthetic artefacts such as acylgermanes,[13] thio- or selenol esters,[14] which, after β-scission, restore the carbonyl functionality (**A** → **C**). An alternative approach has consisted of utilizing acylsilanes,[15] which, after cyclization, undergo a radical Brook rearrangement to furnish cyclic silyl ethers (**A** → **D**) (Scheme 1). In this letter, we are extending our boron-based method to alkyl radicals,[9] and we notably show that these reactions can be run without any tin mediator.

To test this reaction, we focused on the iodomalonates **1** and **3** as starting materials (Scheme 2). Iodides were selected as radical precursors since studies by Oshima and Utimoto have amply demonstrated that alkyl radicals can be generated in the presence of triethylborane and oxygen.[16] While the cyclization of

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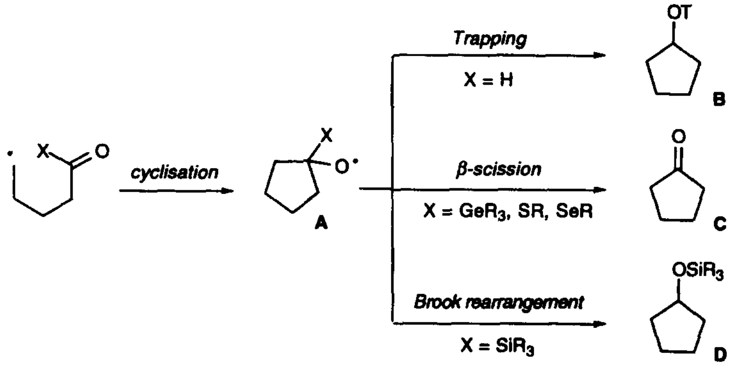
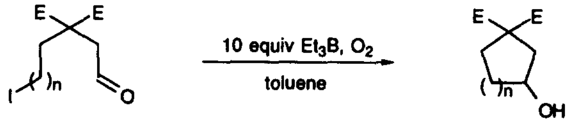


Scheme 1.

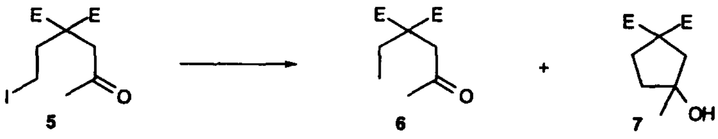
1, in the presence of tributyltin hydride gave a quantitative yield of cyclopentanol **2**, we were pleased to confirm that a high yield of **2** could also be obtained without the stannane mediator in a satisfactory yield (88%).[17] Similarly, the cyclohexanol **4** was isolated after treatment and chromatography in almost quantitative yield. We noticed that this reaction was highly sensitive to the quality of the triethylborane. A freshly open bottle of the commercial solution in hexanes, or a freshly 'home-made' solution from pure material, generally resulted in higher yields.



1, n = 1	Bu_3SnH, - 78 °C	**2**, 99%
1	no Bu_3SnH, 0 °C	**2**, 88%
3, n = 2	no Bu_3SnH, 0 °C	**4**, 98%

Scheme 2.

We next tackled the reactivity of ketones in these reactions. Examples of cyclizations of ketones to yield tertiary alcohols are rare.[3,18–21] Our initial results with precursor **5** reflected this difficulty (Scheme 3). In fact, we showed that tributyltin hydride was detrimental for this reaction to occur (Table 1, entries 1 and 2). With 1.3 equivalents of tin hydride, only the reduction product **6** was observed. In the absence of the stannane, carbinol **7** could now be formed in 52% yield, the reduction product **6** being still present (entry 3). We had to dope the system by adding ten more equivalents of triethylborane. This guaranteed a high yield of the tertiary alcohol **7**. To the best of our knowledge, this constitutes the highest yield observed for a cyclization onto a ketone, and it has to be compared with the one recorded by Batey on the same substrate: 36% in the presence of phenylsilane.[12]



Scheme 3.

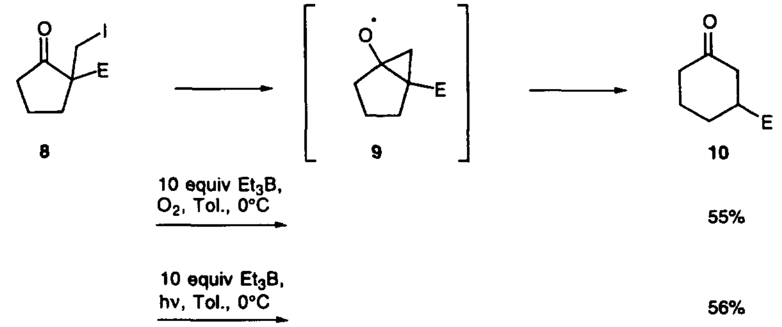
The behavior of iodoketoester **8** was also investigated in the presence of triethylborane (Scheme 4). Two reactions were run: the first one in the presence of oxygen, the second one by irradiating with a sun lamp (no oxygen was necessary in this case). The same rearranged product **10** was obtained in similar yields. No cyclopropanol derivative was detected in these reactions. This could suggest that no

Table 1

entry	reagents	T °C	6 % yield	7 % yield
1	1.3 equiv Bu_3SnH 10 equiv Et_3B/O_2	- 78	100	0
2	1.3 equiv Bu_3SnH 10 equiv Et_3B/O_2	0	81	0
3	10 equiv Et_3B/O2	0	-[a]	52
4	20 equiv Et_3B/O_2	0	0	92

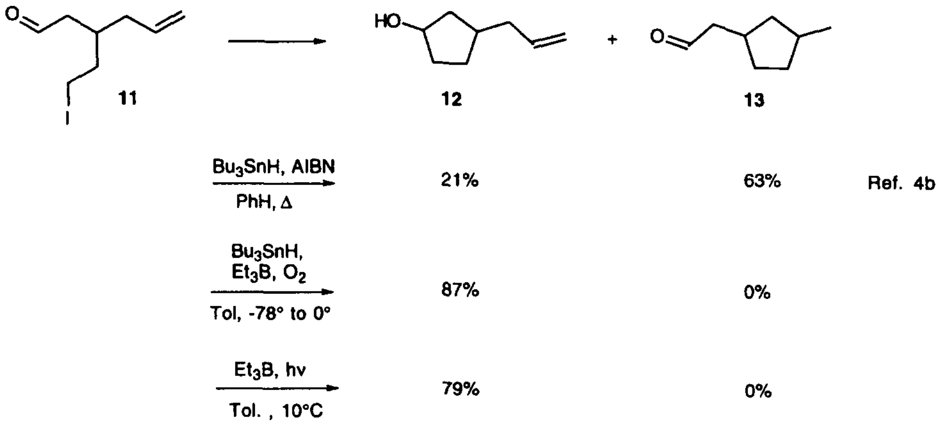
[a] A mixture of **5** and **6** (1 : 4) was isolated in 45% yield. The hydrogen source for the reduction of **5** is probably the solvent.

intermediate cyclopropyloxy radical of type **9** is formed in this reaction and corroborates some recent literature data questioning the existence of intermediates of type **9** in these sequences.[22] But this could simply indicate that in this case the trapping with triethylborane cannot beat the β-scission process.



Scheme 4.

Finally, this reaction proved useful for reversing the chemoselectivity of the radical cyclization of enal precursor **11** (Scheme 5). Fraser-Reid showed that the 5-*exo-trig* cyclization involving the alkene moiety was the major pathway in refluxing benzene. In the presence of triethylborane and at lower temperature, only the diastereomeric mixture (70:30) of cyclopentanols **12** was isolated. This result could be an illustration of the Lewis acidity displayed by triethylborane. Lewis acids have been introduced for some time now in radical chemistry[23] and have already been exploited to alter the reactivity of several systems.



Scheme 5.

In conclusion, we have shown that the radical cyclization of ω-iodoaldehydes or ketones in the presence of triethylborane as a radical initiator and terminator is an efficient process. No tin mediator is necessary.[24] The high reactivity of carbonyl derivatives in these conditions may be attributed to the Lewis acidity of triethylborane and it could serve to reverse the chemoselectivity of the cyclization of an enal precursor. Examination of secondary and tertiary iodides in order to study the diastereoselectivity of this cyclization, as well as modifications of the borane derivative in order to increase its efficiency and to exploit its use in asymmetric cyclizations, are under active investigations in our laboratory.

Acknowledgements

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17. Typical procedure for radical cyclizations without tin: a 0.02 M toluene solution of aldehyde **3** (171 mg, 0.5 mmol) was treated at 0°C with 5 mL (5 mmol, 10 equiv.) of a 1 M solution of triethylborane in hexanes and a few milliliters of air was added via syringe. The reaction mixture was stirred for 1 h at this temperature and then treated with ammonium chloride and brine. Purification by flash chromatography on silica gel (PE:EtOAc, 60:40) furnished the alcohol **4** as a colorless oil (106 mg, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.35–1.42 (m, 2H), 1.70–1.80 (m, 4H), 2.20–2.30 (m, 2H), 2.61 (bs, 1H), 3.63 (m, 1H), 3.63 (s, 3H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 28.6, 31.2, 52.6, 52.7, 54.2, 67.9, 171.6, 172.4; IR 3500, 2940, 2850, 1720, 1445, 1430 cm^{-1}; CIMS NH_3 *m/z* (rel. int.) 217 (MH^+, 100). As additional evidence for the structure, alcohol **4** was refluxed in toluene (0.04 M) for 40 h with 5 mol% of the distannoxane catalyst described by Otera (Otera, J., Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307–5311) to furnish the corresponding lactone in quantitative yield. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.75–1.80 (m, 2H), 1.85–1.95 (m, 2H), 2.00–2.10 (m, 2H), 2.28–2.36 (m, 2H), 3.75 (s, 3H), 4.72 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 25.2, 26.1, 48.6, 52.7, 75.8, 170.4, 172.8; IR 3050, 2970, 2950, 2870, 1740, 1070, 735 cm^{-1}; anal calcd for $C_9H_{12}O_4$: C, 58.69, H, 6.57. Found: C, 58.86, H, 6.75.
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