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TRIBUTYLTIN HYDRIDE-INDUCED O-STANNYL KETYLS IN THE CYCLIZATION OF ALDEHYDES AND KETONES WITH ALKENES

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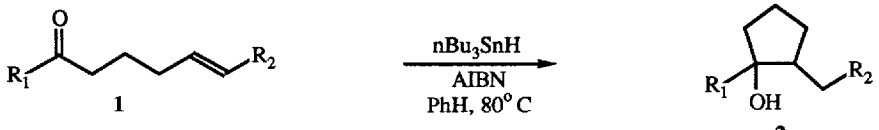
Abstract: An aldehyde or a ketone connected by a tether to an olefin efficiently cyclizes in a free radical reaction mediated by tributyltin hydride. The effects of activated olefins on this reaction, which provides functionalized cyclopentane rings and γ-lactones from O-stannyl ketyls in a mild and regiocontrolled manner, were also studied.

The development of free radical cyclization reactions in total synthesis and in new synthetic methodology has undergone a major increase in recent years.[1] These reactions often involve a variety of well-known precursors to a carbon-centered radicals, such as a halides, thioacyl moieties, olefins, selenides and sulfides, which can be used to produce substituted cyclopentane derivatives when treated with tributyltin hydride.[1,2] O-Stannyl ketyls,[3] produced by the reaction of a carbonyl functional group with a trialkyltin radical,[4] can also provide a carbon-centered radical for these cyclization reactions. To our knowledge, this type of reaction has never been applied to five-membered ring synthesis, nor have various olefin substituents been studied.[5] We now report a mild and regiocontrolled method to construct substituted cyclopentanols and γ-lactones from an aldehyde or a ketone connected to an alkene by a tether.[6]



1 2

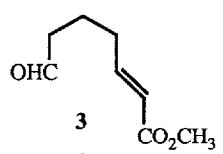
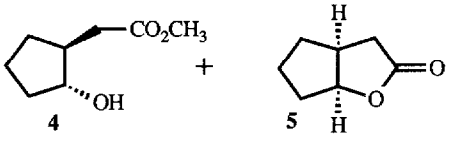
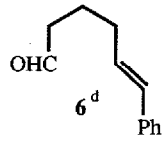
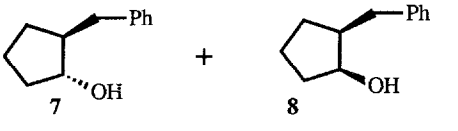
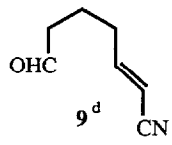
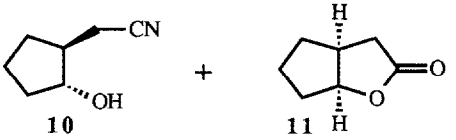
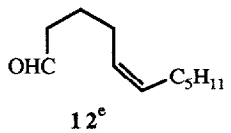
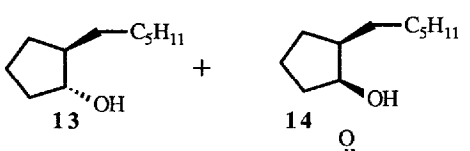
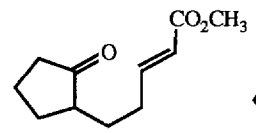
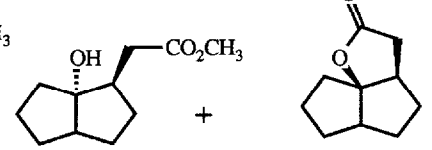
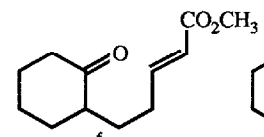
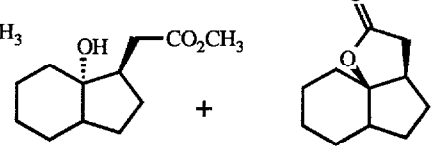
R_1 = H, alkyl
R_2 = alkyl, CO_2R, Ph, CN

We have investigated a number of substrates tabulated in Table 1. Overall, the reaction appears to be quite successful. It is interesting to note that in most cases the olefin was activated to 5-hexenyl-1-oxy free radical cyclization with an electron-withdrawing group. Entry 4 clearly illustrates that this an important condition for success. A substantial amount of the simple reduction of the aldehyde carbonyl in **12** to an alcohol (44% yield) was also obtained, which was not observed in any other five-membered ring precursor. The yields for all of the other reactions with activated olefins ranged from 69-88% and were generally acceptable. In the cases involving a methyl ester or a nitrile, the syn product was always isolated as the γ-lactone. Fairly dilute (0.10 M) reaction conditions were also an important factor in the success of the reaction. A 1,2-pinacol coupled byproduct,[3] presumably formed from quenching the 1,2-bisstannyl pinacol during workup, was observed at increased concentrations.[7]

The two diastereomeric products arise from the syn- or anti-dispositions of the alcohol and substituted methylene appendage and reflect the formation of two new sp^3 centers from the two sp^2 centers of the carbonyl and the olefin. The ratios ranged from approximately a 1:1 to 3:1 for all entries. Lower temperature (23° C)

Table 1

Intramolecular Radical Cyclizations of Aldehydes and Ketones With Olefins

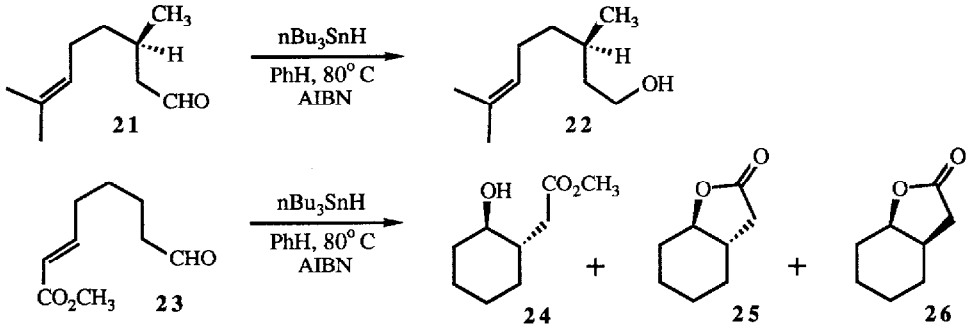
Entry	Starting Substrate[a]	Products	Anti:Syn[b]	Yield[c]
1	 **3**	 **4** + **5**	58:42	81%
2	 **6**[d]	 **7** + **8**	53:47	80%
3	 **9**[d]	 **10** + **11**	52:48	73%
4	 **12**[e]	 **13** + **14**	66:34	32%
5	 **15**	 **16** + **17**	76:24	69%
6	 **18**[f]	 **19** + **20**	58:42	88%

[a]All new compounds give IR, ^{1}H NMR, ^{13}C NMR, mass spectrum and combustion analysis and/or accurate mass data consistent with the structure shown; other compounds were compared with known[6(c),(e)] spectral data; [b]Ratio determined on the crude reaction mixture by capillary GC using a 30 m J&W DB1701 column; [c]Yield data is for the mixture of both syn and anti products; [d]The starting substrate was a 2:1 trans:cis mixture; [e]The starting substrate was a 5:1 cis:trans mixture; [f]The starting substrate was a 10:1 trans:cis mixture.

photochemical initiation did not alter these ratios to any significant extent.

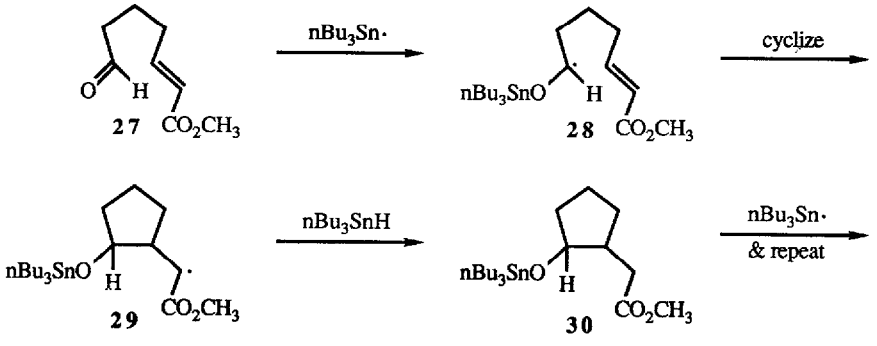
We have also examined the effect of an activated olefin with two 6-heptenyl-1-oxy modes of cyclization. When citronellal (**21**) was treated under the same conditions as the reactions above,[9] citronellol (**22**) was produced in 95% yield. This cyclization can be predicted to be less favorable than the 5-hexenyl-1-oxy case in Table entry 4, and, as expected, no cyclized products (< 2%) were observed. The ester **23**, conversely, underwent a facile 6-heptenyl-1-oxy cyclization to render six-membered ring compounds **24**, **25**, and **26** in a 19:39:42 ratio,

respectively, in 69% yield and a correspondingly smaller amount (12%) of the simple reduction product. Thus, we conclude that the activation of the olefin appears to also be an important factor for success in the 6-heptenyl-1-oxy cyclization as well.



Mechanistically, the reaction is probably mediated by a homolytic chain mechanism and proceeds by the addition of a tributyltin radical to the aldehyde carbonyl in **27** to produce O-stannyl ketyl intermediate **28**.[5] This type of trialkyltin radical addition to a carbonyl to produce O-stannyl ketyl intermediates in simple carbonyl reductions by trialkylstannanes has been reported.[4,8] A subsequent free radical cyclization by addition to the olefin produces the carbon-centered free radical intermediate **29**. A transfer of hydrogen from tributyltin hydride then renders **30** and tributyltin radical which repeats the process. It is noteworthy that prior to workup, intermediate **30** contains a useful tin alkoxide functionality and can be alkylated and acylated to afford other useful addends.

At the outset of these studies we recognized that the α,β-unsaturated ester could also be reduced, and this has been documented to be a facile process.[8,10] When tributyltin hydride reacts with this functional group, the olefin is hydrostannylated in preference to ester carbonyl reduction and results in a product bearing a tributyltin moiety β- to the ester. Such tin products are then generally not easily protodestannylated.[4] These adducts were not observed as byproducts in any of the examples attempted.



In conclusion, a new method for the construction of substituted cyclopentane rings and γ-lactones has been developed. This reaction uses tributyltin hydride in a free radical reaction to form O-stannyl ketyls which undergo intramolecular addition to activated olefins in a mild and regiocontrolled manner.

ACKNOWLEDGEMENT. We gratefully thank the University of Florida Division of Sponsored Research and the Department of Chemistry for their generous support of this research.

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(1) "Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds," Bernd Giese, Pergammon Press, New York, **1986**.

(2) (a) Neumann, W.P. Synthesis **1987**, 665; (b) Ramaiah, M. Tetrahedron **1987**, *43*, 1987; (c) Curran, D. P. Synthesis **1988**, 417, 489; (d) Hart, D. J. Science **1984**, *223*, 883.

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(4) For a review of this topic see: Pereyre, M.; Quintard, J.-P.; Rahm, A. "Tin in Organic Synthesis," Butterworths, Boston, **1987**, pp. 69-80.

(5) Sugawara, T.; Otter, B. A.; Ueda, T. Tetrahedron Lett. **1988**, 75.

(6) Other methods for the intramolecular coupling of an olefin and a carbonyl include: (a) Pradhan, S. K.; Kadam, S. R.; Kolhe, J. N.; Radhakrishnan, T. V.; Sohani, S. V. Thaker, V. B. J. Org. Chem. **1981**, *46*, 2622; (b) Corey, E. J.; Pyne, S. G. Tetrahedron Lett. **1983**, 2821; (c) Enholm, E. J.; Trivellas, A. Tetrahedron Lett. **1989**, 1063; (d) Molander, G. A., Kenny, C. Tetrahedron Lett. **1987**, 4367; (e) Little, R. D.; Fox, D. P.; Hijfte, L. V.; Dannecker, R.; Sowell, G.; Wolin, R. L.; Moëns, L.; Baizer, M. M. J. Org. Chem. **1988**, *53*, 2287; (f) Shono, T.; Mitani, M. J. Am. Chem. Soc. **1971**, *93*, 5284; (g) Shono, T.; Nishiguchi, I.; Ohmizu, H.; Mitani, M. J. Am. Chem. Soc. **1978**, *100*, 545; (h) Little, R. D.; Baizer, M. M. in "The Chemistry of Enones," Patai, S.; Rappoport, Z., eds., Wiley, New York, **1989**, pp 615-618, and references therein.

(7) When compound **3** was treated under the same conditions[9] except at 0.50 M in benzene, compounds **4** and **5** and the 1,2-pinacol byproduct were present in the crude reaction mixture in a 34:27:39 ratio, respectively.

(8) (a) Kuivila, H. G. Adv. Organometal. Chem. **1964**, *1*, 47; (b) Ingold, K. U.; Lusztyk, J.; Scaiano, J. C. J. Am. Chem. Soc. **1984**, *106*, 343; (c) Quintard, J. P.; Pereyre, M. Bull. Soc. Chim. Fr. **1972**, 1950; (d) Neumann, W. P.; Heymann, E. Justus Liebigs Ann. Chem. **1965**, *683*, 11.

(9) Procedure: A solution of the aldehyde or ketone in benzene (0.10 M) with AIBN (0.01 eq.) and tributyltin hydride (1.50 eq.) was carefully degassed with argon and heated to 80° C (bath temperature). After 5-8 hours, thin layer chromatography indicated that the reaction was done. The solvents were removed and the crude oil was subjected to flash chromatography to isolate the desired products.

(10) (a) Neumann, W. P.; Sommer, R. Justus Liebigs Ann. Chem. **1964**, *675*, 10; (b) Leusink, A. J.; Budding, H. A.; Drenth, W. J. Organometal. Chem. **1968**, *11*, 541.

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