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[3+3] ANNULATION BY SEQUENTIAL TWO ELECTRON AND ONE ELECTRON ALLYLATION

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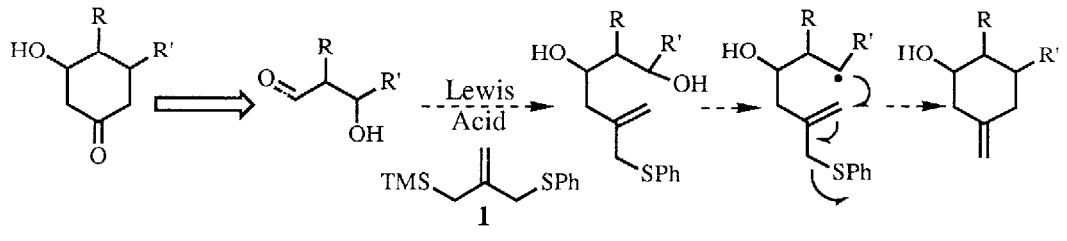
Summary: 3-phenylthio-2-(trimethylsilylmethyl)propene is a convenient conjunctive reagent for the preparation of methylenecyclohexanes via a [3+3] annulation The trimethylsilyl group facilitates the Lewis acid catalyzed allylation of an aldehyde or acetal while the phenylthio group directs a 6-endo-trig radical cyclization reaction.

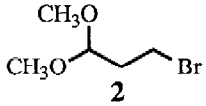
In connection with a synthetic project, we became interested in exploring methods of converting a 3-hydroxyaldehyde into a 3-hydroxycyclohexanone (see Scheme I). While several scenarios can be envisaged for such a transformation[1], the need for stereoselectivity and for mild reaction conditions prompted us to investigate a free radical based protocol.[2]

Our strategy was based on two well known C-allylation reactions Lewis acid catalyzed addition of allylsilanes to aldehydes[3] (formally, a "two electron" process) and free radical mediated allylation using allylic sulfides[2,4,5] (formally, a "one electron" process). The combination of these two processes leads to the consideration of 3-phenylthio-2-(trimethylsilylmethyl)propene (**1**)[6] as a conjunctive reagent in a [3+3] annulation process (see Scheme I).

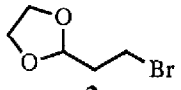
Our plan starts with an aldehyde bearing a substituent capable of conversion into a carbon centered radical at the 3 position. After Lewis acid catalyzed addition of **1** and generation of the radical, a regioselective (6-endo-trig vs 5-exo-trig) radical cyclization is required While there are many examples of highly regioselective ring closure of 5-hexenyl radicals in the 5-exo-trig sense[2], reports of high levels of 6-endo-trig selectivity are less common [2,7] We were hopeful of achieving the desired selectivity[8a] since the presence of the phenylthiomethyl substituent should reduce the rate of 5-exo cyclization relative to that of 6-endo cyclization.[2] Moreover, the presence of the allylic phenylthio group might[8b] increase the rate of 6-endo cyclization and should[8c-e] allow for the use of the fragmentation method[2a] to generate the chain transfer agent This use of this method (as opposed to the tin hydride method[2a]) should increase the lifetimes of intermediate radicals and facilitate the formation of the 6-endo cyclization product

Scheme I





2



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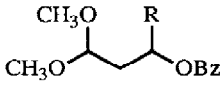
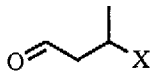
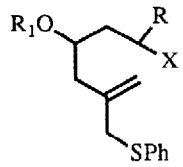


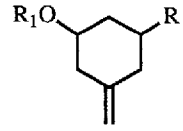
4a R=Ph
4b R=$(CH_2)_4CH_3$
4c R=CH_3



5a X=OBn
5b X=OTBDMS



6 R=H, R_1=CH_3, X=Br
7 R=H, R_1=CH_2CH_2OH, X=Br
8a R=Ph, R_1=CH_3, X=OBz
8b R=Ph, R_1=CH_3, X=Cl
9a R=$(CH_2)_4CH_3$, R_1=CH_3, X=OBz
9b R=$(CH_2)_4CH_3$, R_1=CH_3, X=Br
10a R=CH_3, R_1=CH_3, X=OBz
10b R=CH_3, R_1=CH_3, X=Br
10c R=CH_3, R_1=Bz, X=Br
10d R=CH_3, R_1=Bz, X=OC(S)Im
10e R=CH_3, R_1=TBDMS, X=Br
11a R=CH_3, R_1=H, X=OBn
11b R=CH_3, R_1=H, X=OTBDMS



12 R=H, R_1=CH_3
13 R=H, R_1=CH_2CH_2OH
14 R=Ph, R_1=CH_3
15 R=$(CH_2)_4CH_3$, R_1=CH_3
16 R=CH_3, R_1=CH_3
17 R=CH_3, R_1=Bz
18 R=CH_3, R_1=TBDMS

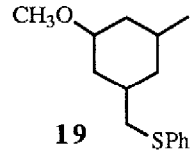


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Table I. [3+3] Annulation with **1**

Entry	Substrate	Method[a]	Product[b]	Entry	Substrate	Method[a]	Product[b]
			Lewis Acid Catalyzed Addition				
1.	**2**	$TiCl_4$	**6** (95%)	6	**5a**	$TiCl_4$	**11a** (>9 1, 56%)[d]
2	**3**	$TiCl_4$	**7** (32%)[c]	7.	**5a**	$SnCl_4$	**11a** (>9·1, 70%)[d]
3.	**4a**	$TiCl_4$	**8a** (1 1, 95%)	8.	**5b**	$TiCl_4$	**11b** (4 1, 32%)[d]
4.	**4b**	$TiCl_4$	**9a** (1 1, 87%)	9.	**5b**	$SnCl_4$	**11b** (2 1, 50%)[d]
5	**4c**	$TiCl_4$	**10a** (1:1, 83%)				
			Free Radical Cyclization				
10	**6**	A	**12** (35%)	16.	**10c**	B	**17** (1.3:1, 61%)[e]
11	**7**	A	**13** (75%)	17.	**10d**	B	**17** (1.3:1, 17%)[e]
12.	**8b**	A	**14** (1.2:1, 60%)[e]	18.	**10d**	C	**17** (1.2 1, 61%)[e]
13.	**9b**	A	**15** (1.3:1, 44%)[e]	19.	**10e**	B	**18** (1.4.1, 48%)[e]
14.	**10b**	A	**16** (1.1:1, 55%)[e]	20.	**10e**	C	**18** (1.3:1, 58%)[e]
15.	**10c**	A	**17** (1.5.1, 25%)[e]				

(a) A· $(Bu_3Sn)_2$, hν (Hg lamp), PhH, 10°C; B: $(Me_3Sn)_2$, Ph_2CO, hν (Hg lamp or Rayonette [300 nm]), PhH, 10°C, C. $(Me_3SnOCPh_2)_2$, PhH, 80°C (b) Values in parentheses refer to the ratio of diastereomers and the isolated yield. (c) The dioxepane formed by intramolecular displacement of the bromide was also formed (30%). No attempt was made to optimize the formation of **7**. (d) The major isomer is assumed to be *anti* on the basis of analogy.[3,10a] (e) The major isomer is *cis* on the basis of ratio of the axial vs equatorial CHOR protons in the ^1H NMR spectrum.

To test our hypothesis, the readily available **2**[9a] was coupled[3] with **1** in the presence of $TiCl_4$ to give the adduct **6** in 95% yield. Treatment of **6** with Bu_3SnH (1.5 eq.) in refluxing benzene containing AIBN provided **12** (30%) together with the reduced product **6** (X=H; 17%). By contrast, irradiation of a benzene solution of **6** and $(Bu_3Sn)_2$ with a medium pressure Hg lamp gave the cyclized product **12** (35%) in the absence of the reduced product. That the low isolated yield of was due to the volatility of **12** was evident when analogous treatment of **7** provided the 6-endo-trig cyclization product **13** in 75% yield. The results of [3+3] annulation obtained with **1** and other acetals and aldehydes are presented in the Table I.[9,11]

The reagent **1** (1 1 eq.) couples with acetals under $TiCl_4$ (1 eq., -78°C) catalysis to give adducts in high yield (Table I, Entries 1-5) The addition of **1** to β-hydroxyaldehyde derivatives (Table I, Entries 6-9) is less efficient. The lower yields obtained in these cases is due to the instability of the substrates towards the Lewis acid.[10] Improved yields (and diastereoselectivity) were obtained with the benzyl ether derivative **5a**, presumably due to the formation of a stable chelate.[10b] In our hands, best results were obtained in CH_2Cl_2 with 1.1 eq. of **1**, 1.5 eq. of $SnCl_4$, at -78--->0°C (Table I, Entry 7).

Suitable substrates[11] underwent 6-endo-trig free radical cyclization using the fragmentation method.[2a] We typically employed $(Bu_3Sn)_2$ (1 eq.) with photochemical initiation (Hg lamp) as the source of the chain carrying organotin radicals (Method A) Because of the sensitivity of some substrates to prolonged irradiation, we also investigated alternative methods for generating organotin radicals (Methods B, C).[12] By comparison, using the tin hydride method always gave a mixture of cyclized and reduced products. For example, reaction of **10b** with Ph_3SnH (PhH, AIBN, 80°C) gave **16**, **19** (as a 1:1 mixture of 2 diastereomers), and the reduced products **10b** (X=H) and the S_H2' substitution[13] congener **10b** (X=H, SPh--->$SnPh_3$).[14] In no case were we able to detect or isolate products derived from a 5-exo-trig cyclization.[15]

In all cases examined, free radical cyclization proceeded with poor stereoselectivity [15] Changing the steric bulk of the substituents had little effect on the ratio of diastereomers produced (Table I, compare Entries 14, 15, 19 and 12-14) Similarly, changing the reaction temperature had only a modest effect on the stereoselectivity (Table I, compare Entries 17-20). As expected, subjecting the individual diastereomers to cyclization gave identical results.[17]

Further applications of this methodology will be reported in due course.[18]

Acknowledgement: Financial support from the Natural Sciences and Engineering Research Council (Canada) and the University of Saskatchewan is gratefully acknowledged

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6. Readily prepared [i) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C (89%); ii) PhSH, BuLi, THF, 0°C (97%)] from the known (Trost, B.M.; Chan, D M.T.; Nanninga, T.N. *Org. Syntheses*, **1984**, *62*, 58.) 2-trimethylsilylmethyl-2-propen-1-ol. For other preparations and applications of **1** see: (a) Hunter, R., Simon, C.D. *Tetrahedron Lett*, **1988**, *29*, 2257. (b) Xiao, X.-Y.; Park, S-K.; Prestwich, G.D. *J. Org. Chem*, **1988**, *53*, 4869. (c) Lee, T.V.; Channon, J.A.; Cregg, C.; Roden, F.S.; Yeoh, H.T-L. *Tetrahedron*, **1989**, *45*, 5877 (d) Similar reagents based on tin should also be feasible, for example see. Keck, G.E.; Enholm, E.J.; Kachensky, D.F. *Tetrahedron Lett*, **1984**, *25*, 1867.
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9. (a) Preparation of **2**: Gribble, G.W.; Soll, R.M. *J. Org Chem*, **1981**, *46*, 2433.(b) Preparation of **3**: Buchi, G.; Wüest, H. *J Org Chem.*, **1969**, *34*, 1122. (c) **4** and **5** were prepared from RCHO (R=CH_3, Ph, n-C_5H_{11}) by the sequence: i) CH_2=$CHCH_2MgBr$, ether, 0°C (60-95%). ii) C_6H_5COCl, C_5H_5N (≥95%), or $C_6H_5CH_2Br$, NaH, Bu_4NI, THF, 67°C (96%) or TBDMSCl, imidazole, DMF (98%). iii) O_3, CH_2Cl_2/MeOH, -78°C; Me_2S, C_5H_5N (for **5**, 90-95%) or Me_2S then TsOH, $(MeO)_3CH$ (for **4**, 90-95%).
10. We have observed substantial decomposition of **5b** to unidentified products within 5 min. at -78°C in the presence of $TiCl_4$. See for example: (a) Reetz, M.T.; Kessler, K.; Jung, A. *Tetrahedron Lett*, **1984**, *25*, 729. (b) Keck, G.E.; Castellino, S. *Tetrahedron Lett.*, **1987**, *28*, 281.
11. **8b**, **9b**, and **10b**, were prepared form the corresponding benzoates by the sequence: i) NaOH, MeOH, 65°C (90-95%) ii) MsCl, pyr, 0°C (90-95%) [**8b** was produced by these conditions]. iii) LiBr, THF, 67°C (85-90%). **10c**, **10d**, and **10e**, were prepared from **11a** by the sequence: i) C_6H_5COCl, C_5H_5N (92%). ii) BBr_3, CH_2Cl_2, 0°C (65%). iii) MsCl, pyr, 0°C; LiBr, THF, 67°C (85%) or Im_2CS, PhH, 80°C (93%) or MsCl, pyr, 0°C; NaOH, MeOH, r.t.; TBDMSCl, imidazole, DMF; LiBr, THF, 67°C (45%).
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14 The ratio of products [**16**·**19**:**10b** (X=H):**10b** (X=H, SPh-->$SnPh_3$)] obtained was dependent on the tin hydride concentration For example, using 1.5 eq. of Ph_3SnH ([0.0075 M]) gave products in the ratio 10:6:3:trace. With 3 eq. of Ph_3SnH ([0.015 M]) the product ratio was 3:3:1:2.
15. Since not all of the starting material is accounted for, this mode of reaction can not be ruled out.
16 See ref 5j and references cited therein for a discussion of stereoselectivity in 6-exo free radical cyclizations.
17 The **9b** diastereomers were separable. Subjecting the isomers individually to cyclization (Method A) produced, in each case, **15** as a 1.3:1 mixture of *cis*·*trans* isomers
18. A preliminary account of this work has been reported: Ward, D.E.; Kaller, B.F. 73rd Canadian Chemical Conference, July, **1990**, Halifax, N.S., abstract number 910 OR-H17.

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