functionalized for phosphorylation at position 1 and/or formation of a cyclic phosphate.[5a]

In summary, the results described herein conclusively establish the crucial "directing" effect of an allylic acetate in osmylations of "symmetrical" conduritol B derivatives.[23] Overall, we feel that the process is primarily controlled by stereoelectronic effects that favor osmylation anti to the more electron-donating oxygen.[24] The extension of this methodology to aminoglycosyl derivatives,[25] as well as detailed studies on this mechanistically intriguing osmylation, are being pursued in our laboratories.

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Supplementary Material Available: Experimental and spectroscopic data for **2**, (−)-**3**, (−)-**7**, (−)-**10**, (−)-**11**, (−)-**12**, (+)-**13**, (+)-**14**, and (−)-**15** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(23) For a related stoichiometric osmylation of a substituted cyclopentene, see: King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089–5090. For a detailed study of the bis-hydroxylation of a related conduritol, see: Chida, N.; Ohtsuka, M.; Nakazawa, K.; Ogawa, S. *J. Org. Chem.* **1991**, *56*, 2976–2983.

(24) Halterman, R. L.; McEvory, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 980–985 and references cited therein.

(25) The completion of the synthesis of 1,4- and 1,6-GPI will be addressed on the aminoglycosyl derivatives to ensure the compatibility of protecting groups and functionality and reaction conditions.

Stereoselective Formation of *E*- or *Z*-Exocyclic Alkenes via Radical Cyclization Reactions of Acetylenic Esters

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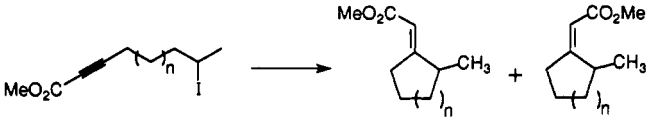
Summary: The intramolecular cyclization of secondary alkyl radicals with α,β-alkynyl esters proceeds stereoselectively to give either *E*- or *Z*-exocyclic alkenes, depending upon the reaction conditions.

Over the last decade, the utility of free-radical reactions for the formation of carbon–carbon bonds has been clearly demonstrated,[2] and currently there is a great deal of interest in the development of methods to control the stereochemistry of reactions of this type, thereby making them even more powerful. As a continuation of our investigations into the stereospecific formation of exocyclic alkenes via radical methods,[3] we would like to report herein the results of our studies on the radical cyclization reactions of the ω-iodo α,β-alkynyl esters **1** and **2** to the corresponding exocyclic alkenes **3a,b** and **4a,b**.



1: n = 1 **2**: n = 2 **3a** (n = 1) **4a** (n=2) **3b** (n = 1) **4b** (n=2)

The purpose of this study was to investigate the effect of reducing agents on the stereochemistry of reduction of vinyl radicals and to study the utility of the methyl substituent in the intermediate radical as a source of stereochemical control.[4] The results of free-radical cyclization of compounds **1** and **2** under a variety of reaction conditions are shown in Table I.

In all cases, the cyclization reactions of compounds **1** and **2** proceeded smoothly to afford the corresponding exocyclic alkenes in good yield. Most interesting, however, is the significant dependence of the stereoselectivity of these cyclizations on the reaction conditions employed. When compound **1** was reacted with the commonly used radical propagator tri(*n*-butyl)tin hydride in refluxing benzene (entry 1, Table I) a clean reaction ensued to give the corresponding *E*-exocyclic alkene **3a** as the predominant product.[5] In contrast, cyclization of **1** under analogous conditions, except employing tris(trimethylsilyl)silane[6] as the radical propagating agent (entry 2, Table I), gave a mixture of the two possible exocyclic alkenes, with the *Z*-isomer predominating. This finding prompted further investigation, and it was discovered that, by lowering the reaction temperature, the selectivity for the *Z*-isomer **3b** could be dramatically enhanced. Indeed, at −78 °C, triethylborane-initiated[7] radical cyclization of **1**, in the presence of tris(trimethylsilyl)silane as the reducing agent, results in a reversal of stereoselectivity to give an 11:89 mixture of **3a,b** in favor of the *Z*-isomer (entry 4, Table I).

The AIBN-initiated cyclization of compound **2** with tri(*n*-butyl)tin hydride was found to be analogous to the cyclization of its lower homologue **1**, favoring the *E*-exocyclic alkene **4a** over the *Z*-isomer **4b** in a ratio of 98:2. However, the low-temperature reaction of **2** with tris(trimethylsilyl)silane proved somewhat more challenging. When carried out at −78 °C, no cyclization was observed even after prolonged reaction time. The only product

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(2) See, for example: (a) Curran, D. P. *Synthesis* **1988**, *9*, 417. (b) Curran, D. P. *Synthesis* **1988**, *9*, 489. (c) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986. (d) Hart, D. J. *Science* **1984**, *223*, 883.

(3) (a) Lowinger, T. B.; Weiler, L. *Can. J. Chem.* **1990**, *68*, 1636. (b) Harris, F.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 2941.

(4) For additional, recent examples of stereoselective radical cyclizations to form trisubstituted olefins, see: (a) Journet, M.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 1893. (b) Journet, M.; Malacria, M. *J. Org. Chem.* **1992**, *57*, 3085.

(5) Stereochemical assignment of the products was based on the chemical shifts of the allylic protons; see: Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon: Oxford, 1969. In the case of **3a,b** these assignments were further verified by comparison of ^{1}H NMR spectra with those reported previously; see ref 11.

(6) (a) Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* **1990**, *31*, 3641. (b) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

(7) (a) Oshima, K.; Ichinose, Y.; Fugami, K. *Tetrahedron Lett.* **1989**, *30*, 3155. (b) Oshima, K.; Nozaki, K.; Utimoto, K. *Tetrahedron* **1989**, *45*, 923.

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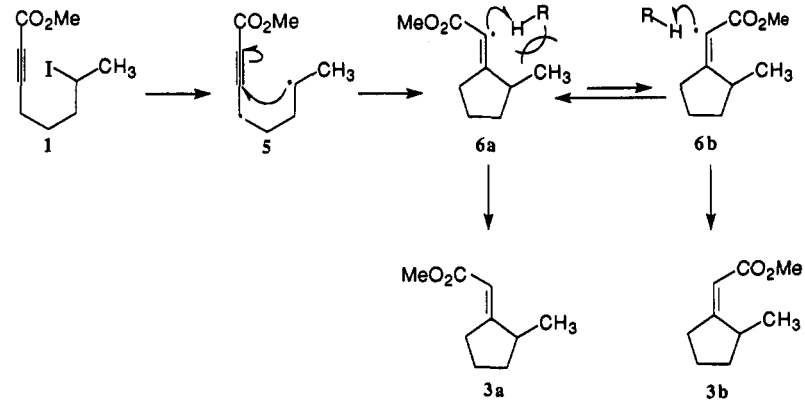
Table I. Radical Cyclization Reactions of Compounds 1 and 2

entry	radical precursor	chain transfer reagent	initiator	temp (°C)	*E*:*Z* ratio[a]	combined[b] yield (%)
1	1	Bu_3SnH	AIBN	80	98:2	82
2	1	$(TMS)_3SiH$	AIBN	80	34:66	86
3	1	Bu_3SnH	Et_3B/air	−78	60:40	84
4	1	$(TMS)_3SiH$	Et_3B/air	−78	11:89	85
5	2	Bu_3SnH	AIBN	80	98:2	79
6	2	$(TMS)_3SiH$	Et_3Br/air	−78 → 25	9:91	82

[a] As determined by gas chromatography. [b] Based on isolated material.



observed was the corresponding reduced acyclic acetylenic ester. This observation was not completely unexpected, as it is well-known that radical cyclization to form cyclohexane derivatives is significantly slower than the analogous cyclization to cyclopentane derivatives. This difficulty was overcome by initiating the reaction at −78 °C and then allowing it to warm to room temperature over a period of 45 min. In this manner good yields of cyclic products were obtained, and the stereoselectivity in favor of the *Z*-isomer **4b** was preserved.

The high stereoselectivity for the *E*-exocyclic alkene in the reactions with tri(*n*-butyl)tin hydride at high temperature is easily understood in light of the fact that tri(*n*-butyl)tin hydride is known to isomerize alkenes. Therefore, under these conditions the predicted thermodynamic product, i.e., the *E*-exocyclic alkene, is obtained.[8] To verify that isomerization does indeed occur under these reaction conditions, control experiments were performed. When pure samples of the *Z*-alkenes **3b** and **4b** were independently resubjected to the reaction conditions (Bu_3SnH, AIBN, benzene, Δ) a rapid isomerization was observed, and after purification by radial chromatography the isomerized alkenes (*E*)-**3a** and (*E*)-**4a** were isolated in near-quantitative yield. In contrast, similar experiments conducted with tris(trimethylsilyl)silane showed no isomerization of these compounds, even after several hours.

Recent cyclizations on propargyl ethers suggest that the stereochemistry of such cyclizations results from isomerization of the radical intermediate.[4] We believe that a combination of a temperature-sensitive reduction of the vinyl radical intermediates **6a** and **6b** along with an isomerization of the cyclized products **3** or **4** at higher temperatures explains our results. For example, the reversal in stereoselectivity at low temperature in the tris(trimethylsilyl)silane-mediated reactions can be understood if one considers the individual steps in the reaction, as depicted below.

Abstraction of the iodine atom from **1** affords the secondary alkyl radical **5**. Addition of this radical to the alkyne gives a vinyl radical, which can exist in two isomeric forms, **6a** and **6b**.[9] The final step required in the reaction is the abstraction of a hydrogen atom from the reducing agent. Previous data for alkyl- and silyl-substituted alkenyl radicals suggest that inversion of the alkenyl radical is faster than atom transfer even at −78 °C.[10,11] However, since tri(*n*-butyl)tin hydride leads to product isomerization, in our case we are unable to make a quantitative statement about the relative rates of alkenyl-radical inversion and atom abstraction from Bu_3SnH (Table I, entries 1, 3, and 5), although the data in entry 3 suggest that the rate of inversion is comparable to reduction at −78 °C which is consistent with Kuivila's observation.[12]

Chatgilialoglu et al. have shown that the rate of hydrogen abstraction from tris(trimethylsilyl)silane to an unhindered alkyl radical is four times slower than that from tri(*n*-butyl)tin hydride.[13] Our data (entries 4 and 6) suggest that hydrogen atom transfer from tris(trimethylsilyl)silane is slow relative to inversion and is consistent with these results.[13] In the reduction of isomer **6a**, leading to the *E*-exocyclic alkene **3a**, the bulky reducing agent must approach the molecule from the side bearing the methyl group. This trajectory is disfavored because of a severe steric interaction between the bulky reducing agent and the methyl group. However, for reduction of **6b**, leading to the *Z*-exocyclic alkene **3b**, the reducing agent approaches the molecule from the side opposite the methyl group avoiding the steric interaction between the bulky reducing agent and the methyl group. The lower reactivity of tris(trimethylsilyl)silane relative to tri(*n*-butyl)tin hy-

(8) Molecular mechanics calculations (Model KS 2.96 and MacroModel using the MM2 force field) suggest that the *E*-isomer **4a** is more stable than the *Z*-isomer **4b** by 0.2 kcal/mol.

(9) (a) Curran, D. P.; Kim, D. *Tetrahedron* **1991**, *47*, 6171. (b) Jenkins, P. R.; Symons, M. C. R.; Booth, S. E.; Swain, C. J. *Tetrahedron Lett.* **1992**, *33*, 3543.
(10) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379.
(11) Curran, D. P.; Chen, M. H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265.
(12) Kuivila, H. G. *Acc. Chem. Res.* **1968**, *1*, 299.
(13) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641.

dride[14] would lead to enhanced selectivity in the silane reduction. These results show that steric hindrance from the hydrogen atom source can effect the stereoselectivity of atom transfer to alkenyl radicals in the same way that steric hindrance on the radical itself alters the stereoselectivity.[11]

Thus, it has been shown that steric requirements in the transition state for radical cyclization reactions can be exploited to control the stereoselectivity of exocyclic alkene formation[15] and that by judicious choice of reaction temperature and reducing agent high stereoselectivity for either the *E*- or the *Z*-isomer can be obtained. This represents one of the first examples of control of olefin stereochemistry in a radical cyclization by the reducing agent. Investigations of the scope and limitations of this methodology are continuing, and the results of these studies will be presented in due course.

Acknowledgment. We thank the Natural Science and Engineering Research Council (NSERC) of Canada for financial support of this work.

Supplementary Material Available: Experimental procedures, compound characterization data, and spectra (31 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Chatgilialoglu, C.; Dickhaut, J.; Giese, B. *J. Org. Chem.* **1991**, *56*, 6399.

(15) For additional examples of the influence of temperature and H-donor on the stereoselectivity of radical reactions, see: Giese, B.; Gonzalez-Gomez, J. A.; Lachhein, S.; Metzger, J. O. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 479.

Tin(II) Amides: New Reagents for the Conversion of Esters to Amides

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Summary: Mixed tin(II) amides are generated, in situ, via addition of aliphatic amines to $Sn[N(TMS)_2]_2$. Condensation of these reagents with esters yields amides.

Tin(II) amides provide a convenient source of nucleophilic amines. Recently, we reported the utility of these reagents for the chemo- and stereoselective synthesis of enamines from aldehydes.[1] We now describe a facile, in situ procedure for the generation of tin(II) amides, and their subsequent application for the conversion of esters to amides.

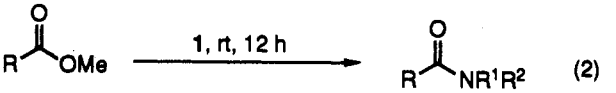
Bis[bis(trimethylsilyl)amido]tin(II), $Sn[N(TMS)_2]_2$, is readily obtained from the reaction of $SnCl_2$ with $LiN(TMS)_2$.[2] We previously demonstrated that this silyl amide reacts chemoselectively with primary aldehydes, to the exclusion of secondary aldehydes, ketones, and esters, to give *N,N*-bis(trimethylsilyl) enamines. We also found that tin(II) amides prepared from dialkylamines were more reactive than silyl amides and converted both aldehydes and ketones to enamines. In this paper, we describe a new procedure for preparing tin(II) amides and their utility for the direct conversion of esters to amides.[3,4]

When a solution of $Sn[N(TMS)_2]_2$ in hexane is treated with 1 equiv of a primary or secondary aliphatic amine, a mixed tin(II) amide is generated via a metathesis reaction (eq 1).[5,6] The hexamethyldisilazane that is liberated in

$$Sn[N(TMS)_2]_2 \xrightarrow[-\,HN(TMS)_2]{HNR^1R^2,\ \text{hexane}} \left[\ (TMS)_2N\text{-}Sn\text{-}NR^1R^2\ \right] \quad (1)$$

1

this process does not interfere with any further condensations of the tin(II) amide and need not be removed. Subsequent reaction of an ester with this mixed tin(II) amide results in formation of an amide *via transfer of the aliphatic amine* (eq 2 and Table I). In all cases we have



(2)

examined, the bis(trimethylsilyl)amino group serves as a nontransferrable ligand.[7]

The following procedure is representative: to a hexane solution of $Sn[N(TMS)_2]_2$ (0.53 g, 1.2 mmol, 0.10 M in hexane),[8] at room temperature and under a nitrogen atmosphere, was added 0.15 g of methyl phenylacetate (1.0 mmol). The reaction mixture was stirred for ca. 10 min, treated with 0.12 mL of piperidine (1.2 mmol), and then monitored by TLC or GC until the reaction had gone to completion.[9] After 12 h, the reaction solution was quenched with 1 mL of methanol in order to precipitate $[Sn(OMe)_2]_n$, diluted with 100 mL of ethyl acetate, and then decanted. The organic layer was washed twice with 5 mL of aqueous KF solution (5 M) and once with 10 mL

(1) Burnell-Curty, C.; Roskamp, E. J. *J. Org. Chem.* **1992**, *59*, 5063.

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(3) Other methods for the conversion of esters to amides: (a) Via alkyl aluminum reagents; Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171. Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989. Lipton, M. F.; Basha, A.; Weinreb, S. M. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 492. (b) Via tin(IV) reagents; George, T. A.; Lappert, M. F. *J. Chem. Soc. A* **1969**, 992. Chandra, G.; George, T. A.; Lappert, M. F. *J. Chem. Soc. C* **1969**, 2566. (c) Via lithium, sodium, and magnesium anions; Ruggeri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 5745. Singh, B. *Tetrahedron Lett.* **1971**, 321. Bassett, H. LI.; Thomas, C. R. *J. Chem. Soc.* **1954**, 1188.

(4) For related chemistry with phosphonates, see: Froneman, M.; Modro, T. A.; Vather, S. M. *Inorg. Chim. Acta* **1989**, *164*, 17. Froneman, M.; Modro, T. A.; Qaba, L.; Vather, S. M. *Tetrahedron Lett.* **1987**, *28*, 2979.

(5) Further studies using ^{119}Sn NMR are in progress to determine the nature of the tin(II) amide in solution.

(6) A dramatic color change in the reaction solution, from orange to lemon yellow, is observed during this step.

(7) Stannylenes, of the type $Sn[NR_2]_2$, R = Et, will also react with esters to give amides; however, more than 0.5 equiv of $Sn[NR_2]_2$ is needed for the reaction to go to completion. This appears to be due to the fact that after the first amide substituent is transferred a $MeOSnNR_2$ stannylene is generated and that stannylenes with methoxy or ethoxy substituents tend to be insoluble.

(8) Etheral solvents can also be used. In THF the reactions are slower and with more sensitive substrates, e.g., methyl phenylacetate, minor amounts (ca. 5%) of Claisen condensation products are observed.

(9) The order of addition of the reagents is not critical.

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