given by Schmiedekamp et al.[9] are given in parentheses): A(VI)–X = 113.0° (111.6–114.9, average 113.8), A(VI)–Y = 103.0° (102.2–107.1, average 104.0), A(V)–X = 116.9° (113.3, 122.3), and A(V)–Y = 104.9° (103.5, 108.0). In all cases predicted angles from eq 3 lie close to the mean values given by Schmiedekamp et al.[9]

Calculating the angles in the charged species NH_2^- and NF_2^- is not quite as straightforward since one must make assumptions about the distribution of net charge. Assuming that the lone pairs and the ligands carry an equal charge, that is, they each use 0.25 valence units to form external bonds, the bond valences will be 1.75 for the lone pairs and 0.75 for the ligands. This leads to $\langle\theta\rangle$ = 113.3 and 101.3°, respectively, compared with the values of 115.0, 113.8 and 102.0, 103.8 calculated by Schmiedekamp et al.[9] In a solid-state complex the valences of the bonds to the ligands (including the lone pairs) will be affected by whether the nitrogen or the ligands form the stronger external bonds and in that case the observed angles may well be different.

The conclusions that can be drawn from the above discussion are that for certain purposes it is convenient to treat a stereoactive lone pair of electrons as a divalent base. The atom that it belongs to must then be treated as if it were in its highest oxidation state; thus S(IV) is treated as the complex S(VI)–(lone pair). An incidental advantage of this approach is that it separates the Lewis acid and base functions of S(IV) into an acid function (S(VI)) and a base function (lone pair), a concept that is particularly helpful when the lone pair also forms a coordinate bond to a metal or other Lewis acid. Using this formalism the angular space occupied by a ligand or a lone pair can be predicted from simple geometric considerations if the strength (valence) of the bond that it forms with the central atom is known. In the case of isolated neutral molecules, such as those treated by Schmiedekamp et al.,[1] the bond valence is the same as the bond order and can be assigned by inspection, but in the solid state nonintegral bond valences will result from the bonding between the tetrahedral group and adjacent ions and thus the geometry of the group will depend in a predictable way on the environment.[4]

Acknowledgment. I thank the National Research Council of Canada for financial support.

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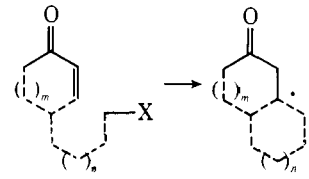
Alkyltin(IV)-Mediated Carbocyclization

Sir:

The synthesis of complex organic molecules requires methods for the formation of carbocyclic rings.[1,2] Although a number of carbocyclization methods have been developed which employ concerted, ionic, or radical processes, conjugate addition to α,β-enones, a central reaction type in intermolecular carbon–carbon bond formation, has witnessed limited utility in carbocyclization (e.g., **1** → **2**).[3] This approach to



1 **2**

cyclization has been constrained by the substantial stabilization of the carbanionic nucleophile required for effective intramolecular anionic enone addition[3a,b] and by the effective competition of α,β-enone polymerization with desired cyclization in radicaloid processes. The internal addition of an unactivated, carbanionic nucleophile to the electrophilic β site of an enone is the vinylogous counterpart of the halocarbonyl reductive cyclization.[4]

We report here a method for effecting intramolecular conjugate addition to 2-cyclohexenones of unactivated carbon nucleophiles which proceeds through the mediation of novel alkyltin(IV) chemistry. This method of carbocyclization illustrates the use of the carbon–tin σ bond as a latent carbanionic nucleophile in internal carbon–carbon bond formation.[5] As illustrated here, the overall sequence corresponds to the annulation of variable-sized rings onto a preexisting cyclohexanone ring system.

The cyclization method employs activation of the α,β-enone moiety with Lewis acids to engender a β-electrophilic site (e.g., **4**) which is sufficiently potent to react with a stereoproximate carbon–tin σ bond. A synthetically useful feature of this approach to carbocyclization is that the weakly polarized nature of the carbon–tin σ bond ($C^{\delta-}$–$Sn^{\delta+}$) ensures compatibility of the α-enone and tetraalkyltin moieties until electrophilic activation. Thus a model 2-cyclohexenone substrate **3**[6] yields a mixture of 2-decalone isomers **5** and **6**[6a] upon treatment with Lewis acids (Scheme I). When the cyclization is conducted in methylene chloride with titanium tetrachloride as acid catalyst, a temperature dependence of 2-decalone isomer distribution is observed. The ratio of *cis*-2-decalone (**5**) to *trans*-2-decalone (**6**) varied from 93:7 at 40 °C (2-min reaction period) to 33:67 at −78 °C (30 min). The formation of products was established to be kinetic and not reversible and could be a consequence in part of the distribution of pseudoaxial:pseudoequatorial (4′-trimethylstannyl)butyl side-chain conformers.[7] The preparation of 4-(4′-trimethylstannyl)butyl-2-cyclohexenone (**3**) was effected by the method of Stork and Danheiser[8] through alkylation of the kinetic enolate of 3-ethoxy-2-cyclohexenone (**7**) with 1-iodo-4-(trimethylstannyl)butane[9] followed by reduction and acid-catalyzed hydrolysis.

The 3-methyl-2-cyclohexenone derivative **9**,[6] in which the preferred conformation has the (4′-trimethylstannyl)butyl side chain in a pseudoaxial position, did not undergo the expected carbocyclization. Instead, transfer of a hydride β to the trimethyltin moiety occurred generating a single, stereoisomeric cyclohexenone **11** (Scheme II).[6b] The lack of carbon–carbon bond formation is presumably a consequence of the substantial steric interactions which occur in the six-membered transition state for coupling of the encumbered, trimethylstannyl-bound carbon nucleophile to the electrophilic, disubstituted β-enone position. The hydride transfer process is facilitated by the ca-

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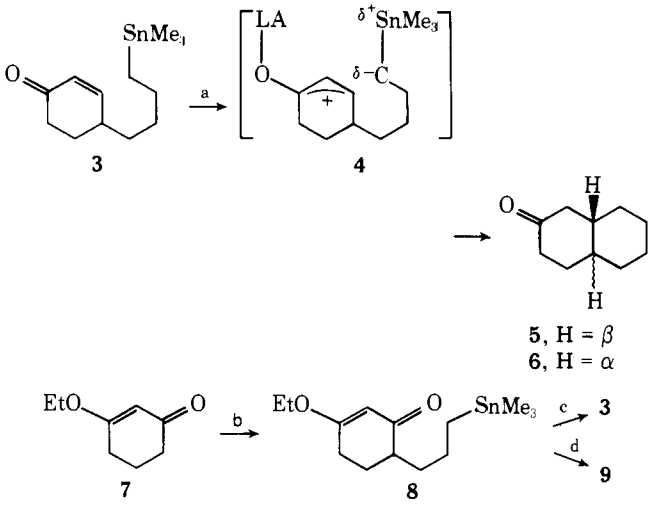
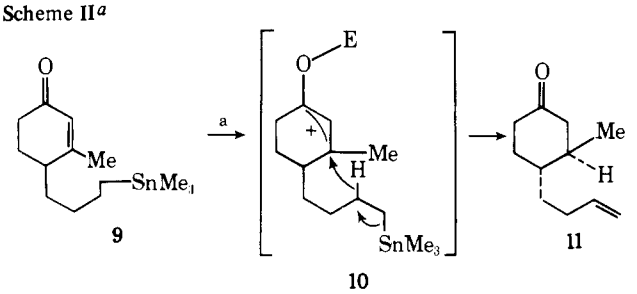
Scheme I[a]



[a] Conditions: (a) $TiCl_4$ (1%), CH_2Cl_2 (92%); (b) (i) LiDA, THF, −78 °C, (ii) HMPA, THF, $I(CH_2)_4SnMe_3$ (91%); (c) (i) $LiAlH_4$, THF, (ii) 2% aqueous H_2SO_4, 0 °C (60%); (d) (i) MeLi, THF, 0 °C, (ii) 2% H_2SO_4, 0 °C (85%).

Scheme II[a]



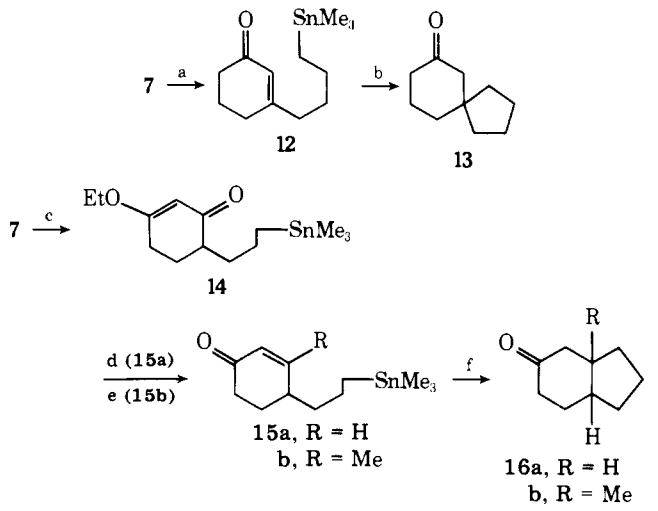
[a] Conditions: (a) CH_2Cl_2, $TiCl_4$ (1%), 20 °C, 1 h (94%).

pability of the trialkyltin unit to stablize a β-carbocationic site[10] and does not encounter the magnitude of steric interactions in the carbon–carbon bond-forming process (cf. **10** vs. **4**). This β-hydride transfer is not the intrinsically preferred mode of reaction in these trimethyltin mediated reactions (vide infra) and appears not to have been observed previously for reactions of tetraalkyltin molecules. The stereoisomeric reduction product, *cis*-**11**, was not found over a span of reaction temperatures.

The ability of this method to create quaternary carbon–carbon bonds was demonstrated by the formation of spirocycle **13**[6c] from the β-substituted enone **12**[6] (Scheme III). The syntheses of the 3- and 4-substituted-2-cyclohexenone substrates **3** and **12** illustrate the capability of the halo trimethylstannylalkane unit to act as either an electrophile in enolate alkylation or as a nucleophile in Grignard addition. This ambident capability for introduction of the pendant (trimethylstannyl)alkyl chain and the compatability of the α,β-enone system and the tetraalkyltin unit under a variety of conditions enhances the versatility of this annulation operation. In addition, this spiroannulation sequence (**7** → **12** → **13**) exemplifies a generally observed phenomenon in these cyclization reactions—that the formation of a five-membered ring relative to the homologous six-membered ring was kinetically faster and less sensitive to steric considerations.

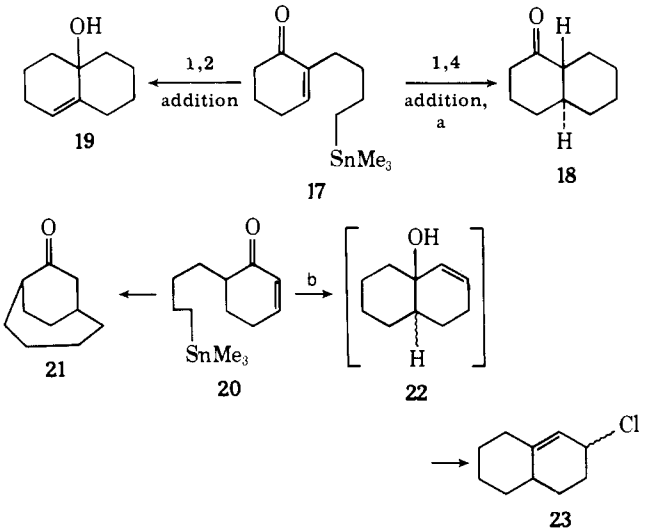
The efficacy of five-membered ring formation with respect to six-membered ring generation was reinforced by examining the synthesis of the *cis*-hydrindanones **16.** The cyclization substrates **15**[6] were synthesized via the method of Stork and Danheiser.[8] The hydrogen-containing substrate **15a** could not be isolated and cyclized spontaneously in situ to *cis*-hydrindanone (**16a**).[6d] The methylcyclohexenone substrate **15b** underwent smooth conversion into *cis*-methylhydrindanone

Scheme III[a]



[a] Conditions: (a) (i) $Me_3Sn(CH_2)_4MgCl$,[9] THF, 20 °C, (ii) 2% H_2SO_4, 0 °C (61%); (b) CH_2Cl_2, $TiCl_4$ (1%), 40 °C, 30 min (82%); (c) (i) LiDA, THF–HMPA, −78 °C, (ii) $Me_3Sn(CH_2)_3I$, HMPA (78%); (d) (i) $LiAlH_4$, THF, 20 °C, (ii) 2% H_2SO_4 (**16a**, 53%); (e) (i) MeLi, THF, 0 °C, (ii) 2% H_2SO_4 (92%); (f) CH_2Cl_2, $TiCl_4$ (1%), 20 °C, 30 min (68%).

Scheme IV[a]



[a] Conditions: (a) CH_2Cl_2, $TiCl_4$ (1%), 40 °C, 2 h (73%); (b) CH_2Cl_2, $TiCl_4$ (1%), 40 °C, 15 min.

(**16b**)[6d] with no trace of the β-hydride transfer product analogous to **11.** Only the *cis*-hydrindanone isomers **16** could be detected in these cyclization reactions.

Two additional examples illustrate the sensitive control of this α-enone cyclization process by entropic and electronic factors. 2-(4′-Trimethylstannyl)butyl-2-cyclohexenone (**17**),[6] synthesized by the method of Taber[11] via alkylation of dihydro-*o*-anisic acid dianion with 1-iodo-4-trimethylstannylbutane, followed by acid-catalyzed hydrolysis and decarboxylation (52%), underwent carbocyclization exclusively to the thermodynamically more stable *trans*-1-decalone isomer **18.**[6a] This cyclization proceeded with a substantially slower rate in comparison with the related six-membered ring formation in 2-decalones **5** and **6,** which could be a manifestation of a relatively less favorable mode of ring closure.[12]

The lack of a substantial 1,2-addition product (e.g., **19,** hexalins, etc.) in the carbocyclization of cyclohexenone **17** demonstrates a central synthetic and mechanistic feature of this internal coupling process—that conjugate enone addition is intrinsically favored over direct 1,2 addition. The stereo-

electronic considerations are identical for internal 1,2 and 1,4 addition of the latent carbon nucleophile to the activated enone in **17** (Scheme IV). A priori analysis of this carbon–carbon bond-forming operation would suggest that either 1,2 or 1,4 addition could be the favored mode. That direct 1,2 addition could occur was shown in the cyclizative reaction of 6-substituted cyclohexenone **20**, prepared via alkylation of 3-dimethylaminocyclohexanone with 1-iodo-4-trimethylstannylbutane[9] (KH, THF, 0 °C), followed by quaternization (MeI) and β elimination (DBU, benzene, 20 °C; 70% overall).[13]

When confronted with internal cyclization either transannularly via the conjugate addition mode to a strained, eight-membered ring **21**[14] or via the direct addition mode to a fused, six-membered ring (e.g., **22**), cyclohexenone **20** prefers the latter. The intermediate, direct addition product(s), octalinol(s) **22**, generated a mixture of octalinyl chlorides **23**[6e] (63%). In addition, the conjugate addition product, bicyclic ketone **21**,[15] was observed (10%). These data demonstrate that direct carbonyl, nucleophilic addition will occur when entropic (or presumably other) features of the cyclization substrate inhibit the intrinsically preferred, conjugate addition process and when 1,2 addition is a favorable ring closure.[12] However, medium-sized carbocyclic rings, often synthetically inaccessible through direct annulation processes, can be prepared via this carbocyclization scheme.

Owing to the ease of tetraalkyltin unit incorporation into the precyclization molecule, to the stability of the alkyltin unit, and to the possible polyfunctionality generated in the cyclization product, we anticipate that alkyltin-enone carbocyclization will have broad utility in complex molecule synthesis. The principal constraint would appear to be the stereoelectronic, enthalpic, and entropic requirements for ring closure.[12] We are currently examining the use of different carbon-centered electrophiles and carbon–tin nucleophiles in this carbocyclization process and the implementation of this annulative strategy in natural product synthesis.

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Supplementary Material Available: Appendix I, spectral characteristics of compounds **3, 8, 9, 12, 14, 15b, 17**, and **20** (2 pages). Ordering information is given on any current masthead page.

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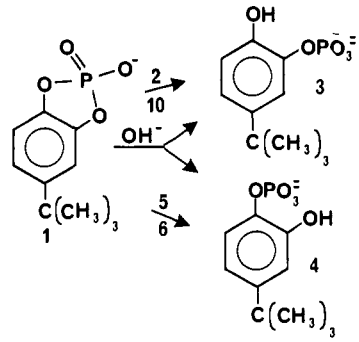
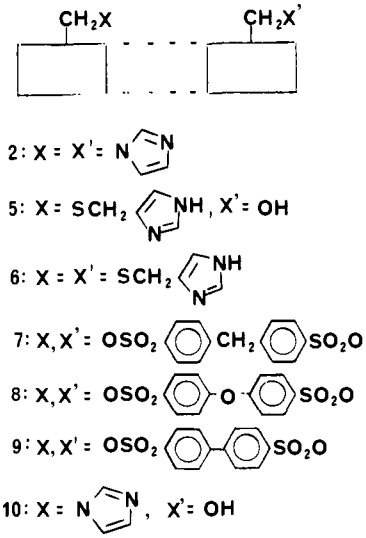
Reversing the Selectivity of Cyclodextrin Bisimidazole Ribonuclease Mimics by Changing the Catalyst Geometry

Sir:

We have described[1] the catalytic cleavage of the cyclic phosphate (**1**) of 4-*tert*-butylcatechol on complexing with a



β-cyclodextrinyl-6,6′-bisimidazole (**2**). The kinetics showed a bell-shaped pH vs. rate profile, indicating that there was cooperative catalysis by a basic imidazole group and an acidic imidazolium group. The enzyme ribonuclease[2] also catalyti-



cally hydrolyzes certain cyclic phosphates using these two catalytic groups in this way. Most strikingly, our enzyme

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