by using the well-established method of Saegusa.[17] Comparison of material prepared in this way with an authentic sample of **17** generously supplied to us by Professor Koreeda indicated that the formal synthesis was complete and our objectives had been achieved.

Efforts are underway to prepare biologically active analogues of coriolin and to utilize the diyl trapping reaction in the construction of other natural products. The results of these studies will be reported in due course.

Acknowledgment. We gratefully acknowledge the continued support of the Public Health Service (National Cancer Institute). L.V.H. thanks the Belgian National Fund for Scientific Research for a Senior Research Assistantship. The initial synthetic efforts to prepare coriolin by Dr. Olof Wallquist are acknowledged with pleasure. Finally, both of us thank Professors Koreeda, Trost, Danishefsky, and Mehta for copies of spectral data and/or authentic samples which were used for comparison purposes.

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(16) (a) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5959. (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. *Tetrahedron* **1984**, *40*, 5005.

(17) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. Lithium diisopropylamide (LDA) provided ca. a 3:2 mixture of silyl enol ethers while lithium tetramethylpiperidide affords the same enol ethers in a 6:1 ratio (personal communication from Professor Raymond Funk, University of Nebraska). The major product in each case results from enolate formation toward C_5. The minor product is converted back to the starting ketone after being treated with palladium acetate and workup.

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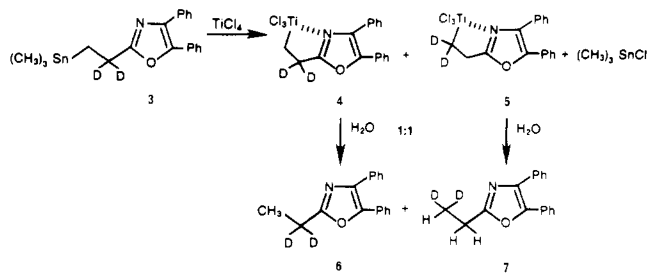
Metalation of 4,5-Diphenyl-2-[2-(trimethylstannyl)ethyl]oxazole with Titanium Tetrachloride. A New Carbon–Carbon Bond Forming Methodology Based on Organotitanium Reagents[1]

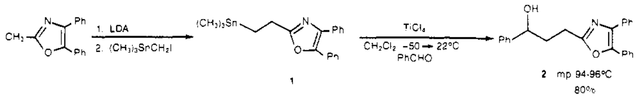
Summary: The reaction of 4,5-diphenyl-2-[2-(trimethylstannyl)ethyl]oxazole (1) with titanium tetrachloride produces, by a chelation controlled mechanism, a trichlorotitanium intermediate which reacts with benzaldehyde to afford a secondary alcohol.

Sir: In connection with a program directed toward the preparation of new pharmaceuticals, we required a synthesis of γ-hydroxy carboxylic acids. A proposed entry into these types of molecules was the addition of a propionate homoenolate equivalent to an aldehyde.[2,3] 4,5-Diphenyl-2-[2-(trimethylstannyl)ethyl]oxazole (1)[4] was developed as a homoenolate equivalent. In this communication we report the first example of a metalation reaction of an alkyl carbon–tin σ bond with titanium tetrachloride. A mechanistic interpretation of this novel reaction will be presented.

Scheme I



4,5-Diphenyl-2-[2-(trimethylstannyl)ethyl]oxazole (1) was prepared in 70% yield by alkylation of 4,5-diphenyl-2-methyloxazole[5] (LDA, 1 equiv, THF −50 °C, 30 min) with (iodomethyl)trimethyltin[6] (1 equiv, −50 °C to 0 °C). When titanium tetrachloride (1 equiv) was added to a solution containing benzaldehyde (1.1 equiv) and tin-oxazole 1 (1 equiv) in dry dichloromethane at −50 °C and the resulting red wine colored reaction mixture was warmed to 22 °C for 2 h, only the crystalline hydroxy oxazole 2 (mp 94–96 °C) was isolated in 80% yield (eq 1).



(1)

The high-field (360 MHz) proton magnetic resonance spectrum of 1 in CD_2Cl_2 exhibited a pair of A_2X_2 triplets. Absorptions for the major isotope (^{118}Sn) and the minor isotopes (^{117}Sn and ^{119}Sn) of oxazole 1 were observed. The methylene protons adjacent to tin and the oxazole ring appeared at 1.27 and 3.05 ppm, respectively. The low-temperature proton spectrum of oxazole 1 and titanium tetrachloride showed dramatic changes in the methylene proton region.[7] Two A_2M_2 triplets were found at 3.12 and 3.50 ppm (J = 6.8 Hz) without the associated coupling to the isotopes of tin. A new singlet appeared at 0.69 ppm. When a solution of trimethyltin chloride was added, a new singlet did not appear and only the peak at 0.69 ppm became enhanced. When the sample was warmed to 22 °C, the proton spectrum remained unchanged. These results indicated that titanium tetrachloride had reacted with oxazole 1 between −60 °C to −1 °C and formed trimethyltin chloride and an organotitanium species. The proton signals at 3.12 and 3.50 ppm were consistent with values cited in the literature for the methylene protons of (trichloroethyl)titanium.[8] When the metalation reaction was repeated and monitored by TLC (1:3 ethyl acetate/hexane), the addition of the organotitanium species to benzaldehyde occurred between 0 °C to 22 °C. We con-

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[1] Dedicated to Professor Robert M. Coates on the occasion of his 20th anniversary at the University of Illinois, Champaign–Urbana.

[2] For some recent examples of propionate homoenolate equivalents, see: (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360. (b) Caine, D.; Frobese, A. S. *Tetrahedron Lett.* **1978**, 883. (c) Jacobson, R. M.; Lahm, G. P. *J. Org. Chem.* **1980**, *45*, 395. (d) Goswami, R.; Corcoran, D. E. *Tetrahedron Lett.* **1982**, *23*, 1463. (e) Hoppe, D.; Bronneke, A. *Tetrahedron Lett.* **1983**, *24*, 1687. (f) Taylor, E. C.; Davies, H. M. L. *Tetrahedron Lett* **1983**, *24*, 5453. (g) Nakamura, F.; Kuwajima, I. *J. Am. Chem. Soc.* **1983**, *105*, 651. (h) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368.

[3] For a general review of homoenolate anions and homoenolate anion equivalents, see: Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205.

[4] All isolated compounds have yielded spectral and analytical data consistent with the assigned structures.

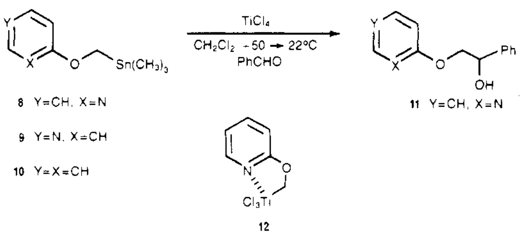
[5] 4,5-Diphenyl-2-methyloxazole was prepared by two procedures: (a) Davidson, D.; Weiss, M.; Jelling, M. *J. Org. Chem.* **1937**, *2*, 328. (b) Jeffreys, R. A. *J. Chem. Soc.* **1952**, 4823. Alternatively, 4,5-diphenyl-2-methyloxazole can be obtained from the Aldrich Chemical Co.

[6] Seyferth, D.; Andrews, B. *J. Organomet. Chem.* **1971**, *30*, 151.

[7] The low-temperature ^{1}H NMR (360 MHz) experiment was performed as follows: a solution of oxazole 1 in CD_2Cl_2 (CH_2Cl_2 internal standard) was placed in an NMR tube and cooled to −60 °C (dry ice–acetone bath). Excess titanium tetrachloride (neat liquid) was added to the NMR tube. A red wine colored solution appeared immediately. The tube was quickly transferred to a cooled probe (−1 °C) and the low-temperature spectrum was obtained.

[8] Hanlan, J.; McCorvan, J. D. *Can. J. Chem.* **1972**, *50*, 747.

Scheme II



cluded that a discrete organotitanium species was produced from oxazole 1.[9]

The metalation of 4,5-diphenyl-2-[2-(trimethylstannyl)ethyl]oxazole-d_2 is shown in Scheme I.[10] Deuterated intermediates **4** and **5** can be directly observed by proton magnetic resonance and trapped by protonation to give oxazoles **6** and **7**. The deuterated oxazole **3** was prepared by synthesis of 4,5-diphenyl-2-(trideuteriomethyl)oxazole from benzoin, acetonitrile-d_3, and sulfuric acid-d_2 using the procedure of Jeffereys.[5b] Alkylation of the (trideuteriomethyl)oxazole afforded **3** in 85% isolated yield. When **3** was allowed to react with titanium tetrachloride in CD_2Cl_2, *only one* new singlet was observed at 3.12 ppm. When water was added to the reaction mixture, one 4,5-diphenyl-2-ethyloxazole-d_2 (**6**) (mp 32–34 °C) was isolated in 64% yield. The proton nuclear magnetic resonance spectrum of **6** showed only one broad singlet at 1.44 ppm. From this data, it was concluded that only one titanium reagent was derived from **3**, and the 4,5-diphenyl-2-ethyloxazole-d_2 (**6**) was produced from **3** by protonation of intermediate **4**. The metalation reaction did not proceed through a cyclopropyl intermediate.

In order to determine the need for a heteroatom in the substrate, three new compounds were prepared and submitted to the metalation reaction conditions (Scheme II).

Alkylation of 2-pyridone and 4-hydroxypyridine with (iodomethyl)trimethyltin and silver carbonate in pentane using the procedure of Hopkins[11] gave **8** and **9** as clear oils. The phenyl ether **10** was prepared by alkylation of phenol (NaH, DMF, 50 °C) with (iodomethyl)trimethyltin. When compounds **8**, **9**, and **10** were submitted to the metalation conditions ($TiCl_4$, 1.2 equiv, PhCHO, 1 equiv, CH_2Cl_2, −50 °C to 22 °C), only the pyridyl ether **8** afforded the addition product **11** in 50% yield. Compounds **9** and **10** did not react and only starting material was observed by TLC. The proton magnetic resonance spectrum (360 MHz) of **8** possessed a singlet at 4.16 ppm (^{118}Sn) and a doublet (J = 12.6 Hz, ^{117}Sn and ^{119}Sn) for the methylene protons. These peaks disappeared and a new singlet at 4.97 ppm was observed when titanium tetrachloride was added. Again, this result was indicative of the formation of an organotitanium intermediate (**12**). The preceding data suggest that the pyridine and oxazole nitrogen was involved in the transition state for metalation. Furthermore, the metalation reaction did not proceed by an electronic effect due to the nitrogen atom as demonstrated by the unreactivity of isomer **9**. A mechanistic interpretation for this reaction is shown in Figure 1.

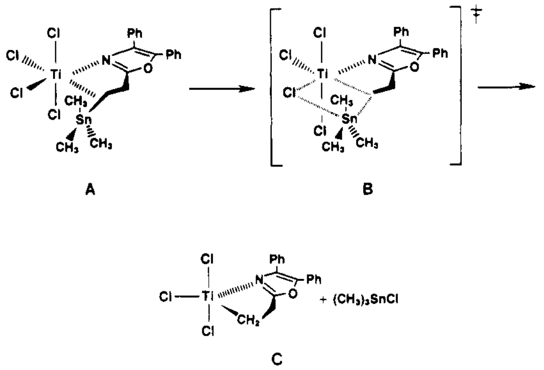


Figure 1. Reaction pathway of the metalation of 4,5-diphenyl-2-[2-(trimethylstannyl)ethyl]oxazole with titanium tetrachloride showing (a) the tin-oxazole–titanium tetrachloride complex, (b) the transition state, (c) the organotitanium product.

The metalation reaction involves the coordination of titanium tetrachloride with the carbon–tin σ bond and the nitrogen atom. The tin atom also coordinates with a chloride atom. It is hypothesized that the nitrogen atom and the carbon–tin σ bond form a chelate ring in the transition state. Since the organotitanium product possesses a chelate ring,[12] then the transition state must also experience enhanced stability (product development in the transition state). The decrease in entropy of activation obtained by chelation is a contributing factor for the metalation reaction to occur. The scope of this new reaction process is being developed.

Acknowledgment. The author would like to thank Dr. Stephen Spanton for recording the high-field proton magnetic resonance spectra and for valuable discussions during the course of this investigation.

Supplementary Material Available: High-field proton nuclear magnetic resonance spectra (360 MHz) for compounds 1, 3, 4, 6, 8, and 12 are available (8 pages). Ordering information is given on any current masthead page.

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Received June 7, 1985

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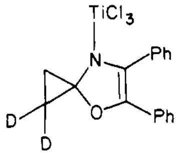
[9] For recent reviews of organotitanium chemistry, see: (a) Reetz, M. *Top. Curr. Chem.* **1982**, *106*, 1. (b) Weidman, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31.

[10] If the formation of the organotitanium species proceeds through a cyclopropyl intermediate, then by symmetry, intermediate i must open to produce a one-to-one mixture of two titanium species, 4 and 5. Secondary isotope effects should not effect this ratio.



i

[11] Hopkins, G. C.; Jonak, J. P.; Minnemeyer, H. J.; Tieckelmann, H. *J. Org. Chem.* **1967**, *32*, 4040.

[12] The crystal structure of methyl 3-(trichlorostannyl)propionate, which contains intramolecularly chelating ligands, has shown the tin atom to be occupying a trigonal bipyramidal geometry with the organic group in an equitorial site. Harrison, P. G.; King, T. J.; Healy, M. A. *J. Organomet. Chem.* **1979**, *182*, 17.

An Approach to the Bakkanes. A Short, Stereocontrolled Total Synthesis of (±)-Bakkenolide A[1]

Summary: A stereoselective total synthesis of (±)-bakkenolide A (fukinanolide) has been efficiently achieved in six steps.

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[1] Presented in part at the Fourth French–Japanese Symposium, Antibes Sophia-Antipolis, Sept 1984 (A.E.G.).

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