for suggesting experiments with inosine.

Supplementary Material Available: One figure containing plots of T_M^{-1} vs. log C_T for ICCGGC, CGGCCI, ICCGG, and GGCCI and Table II containing "temperature-independent" and temperature-dependent thermodynamic parameters for the oligomers listed in Table I (2 pages). Ordering information is given on any current masthead page.

Intramolecular Palladium-Catalyzed Cyclizations of Esters Containing Vinyl Triflate and Vinylstannane Groups at the Termini: Synthesis of Large-Ring Lactones

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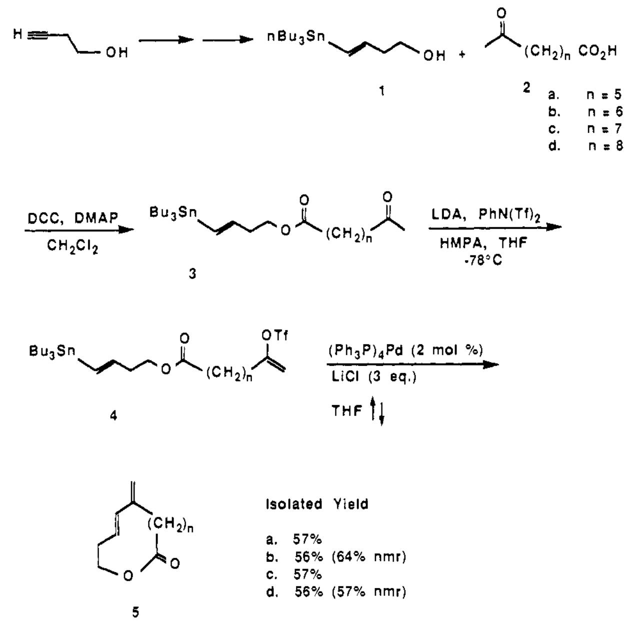
The construction of large-ring compounds, particularly macrocyclic lactones, in relatively high yields is an important procedure, since these compounds occur widely in nature and possess a variety of biological activity.[1] Several approaches to this problem have been utilized, the most prevalent of which is the cyclization of an ω-hydroxy carboxylic acid derivative by some transesterification procedure. An alternate approach to macrolide synthesis is the intramolecular formation of a carbon–carbon bond from an acyclic ester. For example, excellent yields of macrolides can be obtained by reactions such as the Dieckman and Thorpe–Zielger condensations,[2] alkylations,[3] acylations,[4] Horner–Emmons coupling,[5] and Reformatski condensations[6]—particulary that utilizing samarium iodide.[6c] Transition-metal-mediated coupling reactions,[7] especially those arising from the alkylation of an η^3-allylpalladium complex with a soft anion,[7b–e] have the advantage that the reaction occurs under relatively mild conditions.

The palladium-catalyzed reaction of a variety of organic electrophiles and organostannanes takes place to give high yields of cross-coupled products under mild conditions.[8] Furthermore, this reaction is relatively insensitive to moisture and air, tolerates a variety of functional groups on either coupling partner, and is both stereospecific and regioselective. Thus, this reaction appeared to be ideal for the synthesis of a variety of large-ring compounds. As an initial reaction type, the intramolecular coupling of an ester bearing vinyl triflate and vinylstannane[9] groups at the termini was explored. It was anticipated that the palladium catalyst would act as a template to assemble the ends of the molecule through an oxidative addition and coordination of the vinylstannane unit prior to transmetalation. Extrusion of palladium by reductive elimination would simultaneously generate a carbon–carbon bond while reducing the ring size.

Scheme I



The substrates **4** for cyclization were synthesized as shown in Scheme I. The linear esters **3** were obtained by the DCC coupling of the keto acids **2**[10] with an alcohol, (*E*)-4-(tributylstannyl)-3-buten-1-ol (**1**) containing a vinyl tin group. Tin reagent **1** was obtained by the stereospecific stannylmagnesation of 4-(1-ethoxyethoxy)-1-butyne[11] followed by deprotection of the alcohol. The methyl ketone functionality in **3** was converted to the kinetic enolate with LDA at low temperatures and trapped with *N*-phenyltriflimide to give **4**.[9] Both the ketone precursor **3** and the vinyl triflate substrate **4** could be obtained analytically pure by chromatography. The *E*-double-bond geometry was maintained in **4** (J = 19 Hz), the conversion to triflate being carried out without cleavage of the vinnylstannane group.

Cyclization of **4** containing the vinyl tin and vinyl triflate groups at the termini of the ester chain was accomplished with tetrakis(triphenylphosphine)palladium (2 mol %) in the presence of lithium chloride under high dilution (10^{-3} M) in refluxing THF. Good yields of pure products **5** could be obtained; remarkably, the yield was insensitive to the ring size. Especially noteworthy was the observation that a 57% *isolated yield* of the 12-membered ring was achieved, since this is a ring size that is difficult to generate, the rate of cyclization being the slowest of the 12- through 21-membered rings.[12] Under these mild reaction con-

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(1) For reviews, see: (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (b) Back, T. G. *Tetrahedron* **1977**, *33*, 3041. (c) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (d) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.

(2) Hurd, R. N.; Shah, D. H. *J. Org. Chem.* **1973**, *38*, 390.

(3) (a) Takahashi, T.; Hashiguchi, S.; Kasuga, K.; Tsuji, J. *J. Am. Chem. Soc.* **1978**, *100*, 7424. (b) Takahashi, T.; Kasuga, K.; Tsuji, J. *Tetrahedron Lett.* **1978**, *19*, 4917. (c) Takahashi, T.; Kasuga, K.; Takahashi, M.; Tsuji, J. *J. Am. Chem. Soc.* **1979**, *101*, 5072. (d) Takahashi, T.; Nagashima, T.; Tsuji, J. *Chem. Lett.* **1980**,. 369. (e) Takahashi, T.; Minami, I.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 2651. (f) Takahashi, T.; Ikeda, H.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 1363. (g) Sims, R. J.; Tischler, S. A.; Weiler, L. *Tetrahedron Lett.* **1983**, *24*, 253. (h) Trost, B. M.; Sato, T. *J. Am. Chem. Soc.* **1985**, *107*, 719.

(4) Gerlach, H. *Helv. Chim. Acta* **1977**, *60*, 3039.

(5) (a) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069. (b) Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010. (c) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011. (d) Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 4732. (e) Meyers, A. I.; Comins, D. L.; Roland, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 7104. (f) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1224. (g) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030. (h) Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148. (i) Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3651. (j) Oikawa, Y.; Tanaka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3647. (k) Nakajima, N.; Hamada, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 4645.

(6) (a) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705. (b) Tsuji, J.; Mandai, T. *Tetrahedron Lett.* **1978**, *19*, 1817. (c) Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889.

(7) (a) Corey, E. J.; Krist, H. A. *J. Am. Chem. Soc.* **1972**, *94*, 667. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1977**, *99*, 3867. (c) Trost, B. M.; Verhoeven, T. R. *Tetrahedron Lett.* **1978**, *26*, 2275. (d) Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 568. (e) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1983**, *105*, 5940. (f) Ziegler, F. E.; Chakraborty, U. R.; Weisenfeld, R. B. *Tetrahedron* **1981**, *37*, 4035.

(8) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(9) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

(10) (a) Bestmann, H. J.; Kunstmann, R.; Schultz, H. *Justus Liebigs Ann. Chem.* **1966**, *699*, 33 (n = 5). (b) Burgstahler, A. W.; Weigel, L. O.; Bell, W. J.; Rust, M. K. *J. Org. Chem.* **1975**, *40*, 3456 (n = 6). (c) Tsuji, J.; Kaito, M.; Yamada, T.; Mandai, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1915 (n = 6). (d) Citterio, A.; Vismara, E. *Synthesis* **1980**, 751 (n = 7, 8).

(11) Hibino, J.; Matsubara, S.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetetrahedron Lett.* **1984**, *25*, 2151.

(12) Corey, E. J.; Brunelle, D. J.; Stork, P. J. *Tetrahedron Lett.* **1976**, *17*, 3405.

0002-7863/87/1509-3785$01.50/0

ditions, no *E* to *Z* isomerization and no rearrangement of the exocyclic double bond occurred [exo methylene protons **5a–d** δ 4.14–4.98 and 4.89–4.98; *E* internal for **5a–d** δ 5.57–5.72 (J = 16 Hz) and 5.93–6.16 (J = 16 Hz)].

The palladium-catalyzed cyclization of other substrates bearing different functional groups by the coupling of various organostannane and electrophilic termini is being explored.

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The Selective Oxidation of Primary Alcohols to Aldehydes by O_2 Employing a Trinuclear Ruthenium Carboxylate Catalyst

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Though many reports describe trinuclear ruthenium carboxylates as catalysts,[1] none of these systems utilize dioxygen as the primary oxidant. We have found $Ru_3O(O_2CR)_6L_3{}^n$ (R = CH_3 or C_2H_5; L = H_2O or PPh_3; n = 0, +1) to be an efficient catalyst for the selective oxidation of primary alcohols to aldehydes and secondary alcohols to ketones by O_2 under mild conditions.

Ethanol, *n*-propyl alcohol, isopropyl alcohol, *n*-butyl alcohol, *tert*-butyl alcohol, and cyclohexanol were investigated as substrates. The primary alcohols were oxidized more rapidly than secondary alcohols, while tertiary alcohols were unreactive under the conditions employed. Typical oxidations utilized 50 mL of substrate/solvent, 1 mL of a ketone standard, and generally were 10^{-3} M in catalyst. Reactions were run in a 65 °C oil bath under an initial pressure of 40 psi of dioxygen and monitored over a 12- or 24-h period by GC and GCMS. At 25 °C, ethanol was not oxidized while *n*-propyl alcohol was oxidized only slightly. All the other substrates except *tert*-butyl alcohol were oxidized at 65 °C. Increasing the temperature to 100 °C increased the rate of the reaction but also increased the rate of catalyst deactivation. No induction period was observed in these reactions and in all cases the oxidations were 100% selective for the carbonyl product. Further oxidation of product aldehydes to acids was not observed, and acetal or ketal formation was only observed when acetaldehyde was formed in ethanol solution. Several different ruthenium carboxylate complexes were found to be effective catalysts. The mixed-valence, neutral carboxylates, $Ru_3O(prop)_6(H_2O)_3$ (prop = $CH_2CH_2CO_2^-$) and $Ru_3O(prop)_6(PPh_3)_3$, were slightly more active[2a] than their cationic congeners, $Ru_3O(OAc)_6(H_2O)_3^+$ and $Ru_3O(prop)_6(H_2O)_3^+$.

For mechanistic studies we chose the $Ru_3O(prop)_6(H_2O)_3^+$-catalyzed oxidation of isopropyl alcohol. This catalyst was prepared by using a modification of the original synthesis.[3] Liquid chromatography on a Sephadex gel was used instead of precipitating the complex from a solution of the crude carboxylate. Three bands resulted which were characterized by elemental analysis, IR, NMR, and UV–visible spectroscopy. The middle fraction corresponded most closely[4] to the complex reported by Wilkinson and was the only catalytic fraction.

The trinuclear complex was compared with two monomeric ruthenium compounds reported to catalyze alcohol oxidations. Hydrated ruthenium trichloride has been reported to oxidize secondary alcohols at 100 °C and 1 atm of O_2, albeit slowly.[5] The other compound studied, $RuCl_2(PPh_3)_3$, has been used to dehydrogenate secondary alcohols to ketones and primary alcohols to aldehydes and acetal mixtures under a variety of conditions.[6] The trinuclear carboxylate complex is as selective as either $RuCl_3(H_2O)_x$ or $RuCl_2(PPh_3)_3$ and approximately 10 times more active.[2b]

UV–visible spectroscopy has been very informative in determining the active species in solution. Since no induction period is observed for this reaction, either the trinuclear carboxylate is the active catalytic species or it is a precursor that converts rapidly to the active species in solution. A distinct color change is observed when an alcoholic solution of the catalyst is heated to 43 °C under an inert atmosphere; the changes in the spectra correspond to the conversion of the ruthenium(III,III,III) to the ruthenium(III,III,II) complex as reported by Wilkinson.[3] However, if ketone were produced during this reduction, the amount produced (assuming a stoichiometric conversion either per mole of catalyst or per mole of ruthenium) was too small to be detected by GC. This change is reversible; the addition of either O_2, 30% H_2O_2, or air to the warm alcohol solution immediately oxidizes the (III,III,II) to the (III,III,III) species. The color change corresponding to the reduced (III,III,II) complex is not observed under our catalytic conditions (40 psi O_2); however, this complex could be a transient species.

Attempts to characterize the spent catalyst were unsuccessful. After 1000 turnovers were achieved (143 h), the UV–vis spectrum showed essentially no change in the catalyst. The solid recovered after 135 turnovers (43 h) contained a small amount of unidentified impurity, but both ^1H NMR and FTIR confirmed the presence of starting material. None of these results identify the nature or the nuclearity of the active species in solution.

To eliminate the possibility of a free radical chain mechanism, several reactions were carried out with use of free radical initiators and free radical traps. ABMP (2,2′-azobis(2-methylpropionitrile)), a free radical initiator, was used in place of the catalyst and produced insignificant amounts of product after 12 h. The addition of the free radical trap, benzoquinone, to a typical oxidation with catalyst present had no effect on the reaction.

A dual GC analysis (using FID and TCD detectors) of an isopropyl alcohol reaction revealed that for every mole of acetone produced, 1 mol of water was formed. Monitoring the O_2 consumption revealed that 2 mol of product were formed for every mole of O_2 consumed, indicating the four-electron reduction of O_2 to H_2O. One four-electron step seemed unlikely; two two-electron steps with H_2O_2 as an intermediate are more probable, even though identification of H_2O_2 in the reaction mixture was unsuccessful. Added H_2O_2 is rapidly consumed with accelerated carbonyl formation and thus would not be expected to exist in appreciable concentrations during the catalysis.

Isopropyl alcohol oxidations catalyzed by $Ru_3O(prop)_6(H_2O)_3^+$ exhibit a slight rate dependence upon acidity. Brønsted acids, $HClO_4$ and CF_3SO_3H, had an inhibiting effect as did Cu(II) and Zn(II). Isopropyl alcohol oxidation was accelerated by sodium

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(1) (a) Legzdins, P.; Mitchell, R. W.; Rempel, G. L.; Ruddick, J. D.; Wilkinson, G. *J. Chem. Soc. A* **1970**, 3322. (b) Mitchell, R. W.; Spencer, A.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1973**, 846. (c) Sasson, Y.; Rempel, G. L. *Tetrahedron Lett.* **1974**, *47*, 4133. (d) Sasson, Y.; Rempel, G. L. *Can. J. Chem.* **1974**, *52*, 3825. (e) Fouda, S. A.; Hui, B. C. Y.; Rempel, G. L. *Inorg. Chem.* **1978**, *17*, 3213. (f) Milner, D. J.; Whelan, R. *J. Organomet. Chem.* **1978**, *152*, 193. (g) Fouda, S. A.; Rempel, G. L. *Inorg. Chem.* **1979**, *18*, 1. (h) Sasson, Y.; Zoran, A.; Blum, J. *J. Mol. Catal.* **1979**, *6*, 289. (i) Trzeciak, A. M.; Ziolkowski, J. J. *Oxid. Commun.* **1980**, *1*, 295. (j) Trzeciak, A. M.; Szymanska-Buzar, T.; Ziolkowski, J. J. *J. Mol. Catal.* **1981**, *10*, 69. (k) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (l) Shibaeva, L. V.; Ariko, N. G.; Gudimenko, Yu, I.; Mitskevich, N. I. *Vestsi Akad. Navuk BSSR, Ser. Khim. Navuk* **1982**, 40. (m) Thivolle-Cazat, J.; Tkatchenko, I. *J. Chem. Soc., Chem. Commun.* **1982**, 1128. (n) Ito, S.; Aihara, K.; Matsumoto, M. *Tetrahedron Lett.* **1983**, *24*, 5249. (o) Nicolaides, C. P.; Coville, N. J. *J. Mol. Catal.* **1984**, *24*, 375.

(2) Isopropyl alcohol oxidation under standard conditions. Turnover numbers (t.o.) = (mmol of product)/(mmol of catalyst). (a) $Ru_3O(OAc)_6(H_2O)_3^+$, 270 t.o./24 h; $Ru_3O(prop)_6(H_2O)_3^+$, 254 t.o./24 h; $Ru_3O(prop)_6(H_2O)_3$, 764 t.o./24 h; $Ru_3O(prop)_6(PPh)_3$, 904 t.o./24 h. (b) $Ru_3O(prop)_6(H_2O)_3^+$, 112 t.o./12 h; $RuCl_3$, 5.5 t.o./12 h (3 × 10^{-3} M catalyst); $RuCl_2(PPh_3)_2$, 12 t.o./12 h.

(3) Spencer, A.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1972**, *13*, 1570.

(4) Anal. Calcd: C, 28.49; H, 4.68; N, 0.00. Found: C, 27.34; H, 4.32; N, 0.44. ^1H NMR δ 2.18 (q, 2 H, anion), 1.42 (q, 12 H, bridge), 1.08 (t, 3 H, anion), 0.80 (t, 18 H, bridge).

(5) Tang, R.; Diamond, S. E.; Neary, N.; Mares, F. *J. Chem. Soc., Chem. Commun.* **1978**, 562.

(6) Jardin, F. H. *Prog. Inorg. Chem.* **1984**, *31*, 265.

0002-7863/87/1509-3786$01.50/0