Table I. Products from the Reactions of 2 with SBLO at 23 °C

pressure O_2, atm	11-LO (%)	15-LO (%)	17-LO (%)	17:15 LO ratio
0.05	2.3	1.3	96.4	74
0.2	2.6	6	92.2	15.4
50	2.3	9	89	9.9

generally *increase* with decreasing temperature. For example, for **2**, TTN values in air changed from 1000 at 33 °C to 2200 at 23 °C to 4300 at 13 °C. The strong variation of TTN with temperature is more easily understood in terms of organoiron rather than free-radical intermediates.

The behavior of substrate **3** falls exactly into line with the results just described for **1** and **2**. In air at 23 °C no conversion of **3** to lipoxygenated product can be observed by ultraviolet absorption measurement. A modest reaction can be initiated by addition of 15-HPETE as activator (TTN ca. 100 in air increasing to 350 in 1 atm of O_2). Although TTN values increase further with pressure, they remain well below those observed for **2** under comparable conditions. Thus **3** was found to be an excellent time dependent inactivator of SBLO as shown by kinetic measurements which reveal K_i 1.0 μM, k_{inact} 0.14 min^{-1} (in air at 23 °C).[7] This result is readily understood in terms of the enhanced susceptibility of the organoiron intermediate from **3** to homolytic decomposition.

The lipoxygenation (LO) products obtained by the action of SBLO on **2** and **3** are of considerable interest from a mechanistic viewpoint,[8] especially because the product distribution was found to depend on O_2 pressure. The distributions of LO products from **2** at various O_2 pressures are summarized in Table I. Although arachidonate (**1**) is converted almost exclusively to the 15-LO product (15-HPETE) by SBLO, **2** affords mainly 17-LO product along with small amounts of 11- and 15-LO products. As O_2 pressure is increased the ratio of 17-LO to 15-LO products decreases, consistent with the trapping of more 15-organoiron intermediate at higher O_2 pressure. The data indicate that the minor 11-LO product probably arises independently of the 15-LO product (e.g., from the 11-organoiron intermediate). In addition it appears that some of the 17-LO product comes from the 15-organoiron intermediate and the remainder from a directly formed (and thermodynamically more stable) 17-organoiron intermediate. The major 17-LO product (after hydroperoxide reduction) has been shown to be the 17-(*S*)-isomer **4**.[8,9] These results are not readily reconciled with the free-radical processes (**a**) and (**b**). The bisdehydroarachidonate analogue **3** is converted by SBLO at 50 atm O_2 and 23 °C mainly into the 19-LO product **5** (94.7%), although smaller amounts of 11-LO (2.9%), 15-LO (0.7%), and 17-LO (1.5%) have been isolated and identified.

Informative results have also been obtained by a study of the "radical clock" substrate analogue **6**. At 23 °C in air **6** behaved not as a substrate but as a time-dependent inactivator of SBLO; K_i 21 μM and k_{inact} 0.28 min^{-1}.[7] At higher O_2 pressures, as with **3**, lipoxygenation could be observed. Thus at 23 °C and 50 atm of O_2 the principal pathway was 15-lipoxygenation *without* cyclopropane cleavage to give (after hydroperoxide reduction) **7** (51%). Analogous products of 11-, 8-, and 5-lipoxygenation *without* cyclopropane cleavage amounted to another 28%. Cyclopropyl cleavage products totaled only 14%. The other reaction product, 14-formyl-5,8,11,13-tetradecatetraenoic acid, was formed in 7% yield. In contrast, peroxide-induced, free-radical chain oxidation of the model olefin **8** in an oxygen atmosphere produced *only* cyclopropyl cleavage products.[10-12]

(7) For method of measurement, see: Corey, E. J.; Lansbury, P. T., Jr.; Cashman, J. R.; Kantner, S. S. *J. Am. Chem. Soc.* **1984**, *106*, 1501-1503.
(8) Syntheses of substrates **2**, **3**, and **6** and the isolation and identification of products of reaction with SBLO are described in a separate paper, see: Corey, E. J.; Nagata, R. *Tetrahedron Lett.*, in press.
(9) Small amounts of the 11,12-(*E*)-isomer of **4** can also be detected.[8]
(10) Griller, D.; Ingold, K. *Acc. Chem. Res.* **1980**, *13*, 317-323.
(11) Conditions: benzene solution, 21 °C, di-*tert*-butyl peroxyoxylate as initiator. HPLC analysis and spectroscopic identification of all products.
(12) Bartlett, P. D.; Benzing, E. P.; Pincock, R. E. *J. Am. Chem. Soc.* **1960**, *82*, 1753-1768.

Finally, an independent study has provided a chemical analogy for the organoiron-mediated process (**c**).[13] Although, further research is required to establish the pathway of the lipoxygenation of fatty acids, the feasibility of mechanism (**c**) is strongly supported by the results outlined above.[14]

(13) Corey, E. J.; Walker, J. C., following publication.
(14) This research was supported in part by grants from the National Institutes of Health and the National Science Foundation.

Organoiron-Mediated Oxygenation of Allylic Organotin Compounds. A Possible Chemical Model for Enzymatic Lipoxygenation

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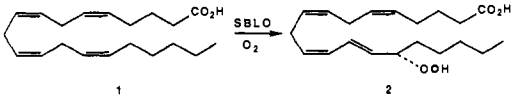
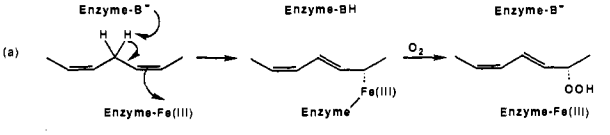
Evidence has been presented in the preceding paper[1] that the allylic dioxygenation of fatty acids by soybean lipoxygenase (SBLO), for example, the conversion of arachidonic acid (**1**) to the 15(*S*)-hydroperoxide **2**, follows the pathway summarized in (**a**). The rate-limiting C–H cleavage step in this scheme involves





proton abstraction by a basic group on the enzyme which is facilitated by concurrent electrophilic attack by the Fe(III) unit at the catalytic site. The allylic organoiron intermediate which results can then react with O_2 by σ-bond insertion to form product. A consequence of enzymatic control of the attachment of iron to the substrate would be position and stereospecific delivery of oxygen. Because there are no previously known purely chemical analogues of this lipoxygenation process and, indeed, essentially no knowledge of organoiron-mediated oxygenation reactions of this general sort, the studies described herein were undertaken. The results obtained in this investigation support the feasibility of mechanism (**a**) for enzymatic lipoxygenation and, at the same time, demonstrate a new approach to transition-metal-mediated chemical oxidation.

The realization of a biomimetic chemical allylic oxidation by the mechanism outlined in (**a**) is complicated by the difficulty of arranging for the concerted attack on the substrate of two species which are incompatible in solution, i.e., a potent base (B^-) and a strong Lewis acid (Fe(III) having a vacant coordination site). For this reason a simpler system was chosen for study which consisted of $FeBr_3$ as the Fe(III) electrophile and the allylic tin compounds **3** and **4** as substrates. Because of the excellence of cationic tin as a leaving group, it seemed likely that the required organoiron intermediate could be generated in organic solvents without assistance from a strongly basic reagent. 1-Phenylprop-2-enyltributyltin (**3**) was prepared as previously described.[2]

(1) Corey, E. J.; Nagata, R. *J. Am. Chem. Soc.*, preceding paper in this issue.

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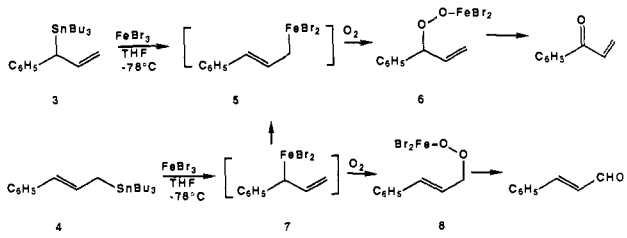


3-Phenylprop-2-enyltributyltin (**4**) was synthesized in 81% yield by the reaction of phenylpropenyllithium[3] with tri-*n*-butyltin triflate[4] in tetrahydrofuran (THF) at −78 °C initially and then at −78 °C to 23 °C over 10 min. Although **3** undergoes isomerization to **4** upon heating to 80 °C in benzene,[2] no interconversion of **3** and **4** occurred under the conditions of any of the experiments described herein.

Both **3** and **4** are stable against reaction with O_2 (1 atm) in various solvents for prolonged periods at room temperature. However, slow addition of a cold (−78 °C) solution of **3** in THF to a stirred solution of 1.2 equiv of anhydrous $FeBr_3$ in THF saturated with O_2 (1 atm) at −78 °C resulted in a very rapid reaction which produced in less than 1 min phenyl vinyl ketone as the only volatile product in 70% yield.[5] In contrast, under the same conditions **4** was converted mainly to cinnamaldehyde (60%) with phenyl vinyl ketone as a minor product (10% yield).[6] Both cinnamaldehyde and phenyl vinyl ketone are stable under both reaction and isolation conditions. This result immediately renders a free-radical mechanism improbable as a major pathway since **3** and **4** clearly should give the same product(s) via the common allyl radical.[7] In fact, when the phenylallyl radical is generated in THF at −78 °C under 1 atm of O_2 by the reaction of 3-phenylprop-2-enylmercuric bromide[3] with tri-*n*-butyltin hydride approximately equal amounts of primary and secondary benzylic oxygenation products (cinnamaldehyde, cinnamyl alcohol, and phenyl vinyl ketone) are formed.

The most reasonable nonradical mechanism for formation of the above described oxidation products from **3** or **4** involves electrophilic S_E2' attack by $FeBr_3(\cdot 2THF)$ on the allylic tin compound to generate a σ-organoiron intermediate which is then trapped by O_2.[8] The nature of the products suggests that the metalloene reaction with O_2 via a six-membered cyclic transition state is somewhat faster than σ-insertion of O_2 (four-membered transition state) at −78 °C in this particular system. Thus **3** would be converted to the organoiron intermediate **5** which would be transformed into phenyl vinyl ketone via **6**. Similarly S_E2' reaction of $FeBr_3$ with **4** would give **7**, which by metalloene reaction with O_2 would form **8**, the precursor of the major product cinnamaldehyde. The pathway from **4** to the minor product phenyl vinyl ketone appears to involve a 1,3-iron rearrangement which converts **7** to the more stable primary organoiron compound **5** at a rate that is roughly one-sixth that for oxygenation of **7**. Support for this possibility was obtained from an experiment in which **4** and $FeBr_3$ were allowed to react in THF at −78 °C with 2 equiv of O_2 as a 20:1 mixture of Ar–O_2 at 1 atm. Under these conditions phenyl vinyl ketone predominated over cinnamaldehyde by a factor of 3. This experimental result clearly argues against the formation of *both* cinnamaldehyde and phenyl vinyl ketone from **7** by competing metalloene and σ-O_2 insertion processes since the balance between these would be independent of O_2 concentration.

Interestingly, slow addition of either **3** or **4** to a solution of $FeBr_3$ in THF at 0 °C under an atmosphere of O_2 afforded essentially the *same* mixture of products: cinnamaldehyde (60% yield) and phenyl vinyl ketone (10% yield). It seems likely that under these conditions the products formed from **3** and **4** derive from the same organoiron intermediate. A free-radical-mediated process again seems unlikely since the product ratio is far from the expected 1:1. Whether the organoiron intermediate is the primary σ compound **5** or a π-allyl organoiron structure cannot be decided at present. Nonetheless it is clear that this organoiron system is one of delicate balance either between σ- and π-organoiron structures or metalloene and σ-bond–O_2 insertion pathways, with major perturbations possible with changing temperature or metal ligands.

The iron-mediated oxygenation reaction described above shows that the reaction of allylic organoiron intermediates with O_2 is a very facile process, fully able to compete with homolytic cleavage of the carbon–iron bond. Although it was not possible to demonstrate direct insertion of O_2 into the carbon–iron bond in the reactions of **3** or **4** with $FeBr_3$ and O_2, such insertions are known for other σ-carbon–transition-metal compounds.[9] Obviously, in the case of enzymatic lipoxygenation of unsaturated acids the balance between the reaction paths available to an organoiron intermediate will differ from the simple chemical system described herein, since major metal ligand and protein-binding effects can be expected. Further research is in progress to extend this study to other allylic systems and Fe(III) reagents.[10]

(2) Jephcote, V. J.; Thomas, E. J. *Tetrahedron Lett.* **1985**, *26*, 5327–5330.

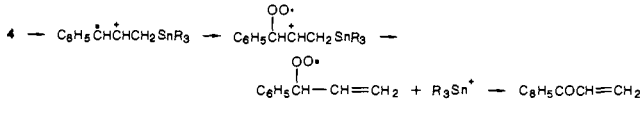
(3) A deep red solution of this lithium reagent in THF was prepared by reaction of 3-phenyl-1-propene with *n*-butyllithium at −20 °C for 1 h, see: Herbrandson, H. F.; Mooney, D. S. *J. Am. Chem. Soc.* **1957**, *79*, 5809–5814. Reaction of the lithium reagent with trimethylchlorosilane gave exclusively the primary trimethylsilyl derivative. Similarly, reaction with mercuric acetate at −20 °C followed by workup with aqueous sodium bromide gave the primary bromomercuric derivative as a crystalline solid.

(4) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2415–2418.

(5) Capillary gas chromatographic analysis using a DB-1 silicone column at 40 °C (5 min), rising to 100 °C over 5 min, and maintained at 100 °C. Cinnamaldehyde and phenyl vinyl ketone had retention times of 11.2 and 9.4 min, respectively.

(6) 5-Phenyl-(2*Z*)-pentenyltri-*n*-butyltin, the analogue of **4** with 2-phenylethyl in place of phenyl, underwent reaction with $FeBr_3$ and O_2 (1 atm) in THF solution at −78 °C to form 69% of 5-phenyl-(2*Z*)-pentenal and 11% of 5-phenyl-1-penten-3-one, an almost identical result with that reported above for **4**. In addition, the dependence of product ratio on O_2 pressure at −78 °C in THF was essentially the same for **4** and the (2-phenylethyl) analogue.

(7) (a) It is conceivable that the phenylallyl radical could result from **3** and **4** by electron transfer to $FeBr_3$ which would also produce $FeBr_2$ and Bu_3SnBr. (b) A radical–cation mechanism is also implausible for the observed iron-mediated oxidation of **3** or **4**, since it leads to incorrect prediction of products: for example, from **4** the formation of phenyl vinyl ketone is predicted (contrary to the experimental results) via the sequence



(8) The strong preference for S_E2' over S_E2 attack by electrophiles on allylstannanes and allylsilanes is heavily documented in the literature.

(9) See, for example: Duong, K. N. V.; Fontaine, C.; Gianotti, C.; Goudemer, A. *Tetrahedron Lett.* **1971**, 1187–1189.

(10) This work was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

Carbon–Hydrogen Bond Activation by Electrophilic Transition-Metal Compounds. Palladium(II)-Mediated Oxidation of Arenes and Alkanes Including Methane

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The activation of carbon–hydrogen bonds by transition metals that leads to the *selective functionalization* of hydrocarbons, especially alkanes, is one of the most challenging problems in organometallic chemistry.[2] Herein, we report our results on the

(1) Alfred P. Sloan Research Fellow, 1984–1988.

(2) Reviews: (a) Halpern, J. In *Fundamental Research in Homogeneous Catalysis*; Shilov, A. E., Ed.; Gordon and Breach: New York, 1986; Vol. 1, p 393. (b) Shilov, A. E. *Activation of Saturated Hydrocarbons by Transition-Metal Complexes*; D. Reidel: Dordrecht, 1984. (c) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (d) Bergman, R. G. *Science (Washington, D.C.)* **1984**, *223*, 902.

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