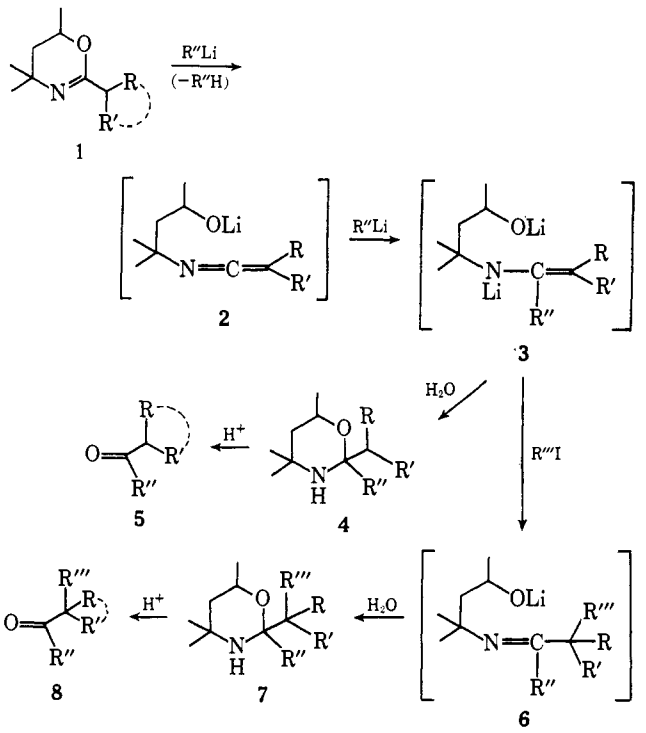
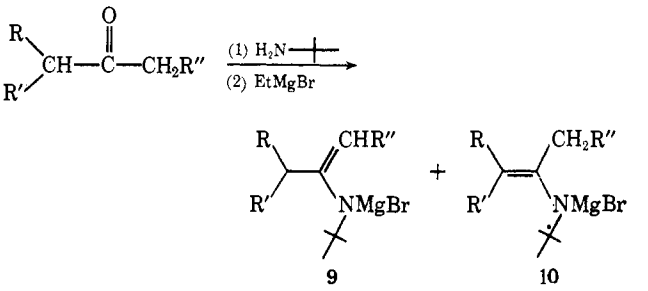


The obvious advantages of this method lie in the fact that not only can a series of unsymmetrical ketones be obtained containing bulky groups but quaternary carbons may be assembled in a stepwise introduction of substituents. The linear geometry of the ketenimine **2** is undoubtedly responsible for allowing sterically endowed organometallics to add smoothly (entries 7 and 8), while the $\alpha$-(tertiary alkyl) groups are formed *via* an enamine alkylation (**3** → **6**). The latter process is akin to Stork's alkylation of magnesium salts of enamines to form $\alpha$-alkyl aldehydes.[7] This sequence, although most elegant for aldehydes and their $\alpha$-(tertiary alkyl) derivatives, gives, for ketones, the enamine derived from the least substituted $\alpha$-carbon, **9**, and not the enamine related to this study, **10**. Thus, the addition of organometallics to the ketenimine **2** provides us with a highly versatile intermediate and nicely complements the method of Stork.[8] Vpc analyses of the



$\alpha$-(tertiary alkyl) ketones **8** indicated no trace of isomeric ketones, which eliminated any concern over the structural integrity of the lithio enamine **3** (and any mobility between lithio-metalated enamines such as **9** and **10**).

(7) G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963).

(8) We have also observed that RMgX adds readily to the ketenimine **2** but cannot be used as the base to remove the proton in **1** in the manner in which RLi is employed. We are therefore investigating methods to prepare **2** as a stable isolable intermediate so that the method may be expanded to include RMgX. In a recent experiment we have successfully converted **1** to the ketenimine *O*-silyl ether [**2**, Li = $(Me)_3Si$] utilizing lithium diisopropylamide followed by trimethylchlorosilane.

In effect, this approach also allows for the specific introduction of alkyl groups into ketones having enolizable protons in the $\alpha$ and $\alpha'$ positions (*e.g.*, entries 4 and 5) by *constructing* the ketone from simple fragments. It also provides a useful alternative to ketone syntheses originating from carboxylic acid derivatives and organometallics.[9] Another dividend derived from this method is the ready availability of nonenolizable ketones, which is a major limitation to the Haller–Bauer[10] synthesis of $\alpha$-(tertiary alkyl) acids and amides.

We are investigating further extensions of this process to allow for formation of $\alpha,\alpha$-dialkyl cyclic ketones as well as addition of other nucleophiles to the ketenimine **2**.

**Acknowledgment.** Financial assistance from the National Science Foundation (Grant No. GP-22541), Petroleum Research Fund, administered by the American Chemical Society, and National Institutes of Health (Grant No. GM 06248-10) is gratefully acknowledged. We are also indebted to the Lithium Corporation of America for generous supplies of organolithium reagents used in this study.

(9) D. A. Shirley, *Org. React.*, **8**, 28 (1954).

(10) K. E. Hamlin and A. W. Weston, *ibid.*, **9**, 1 (1957).

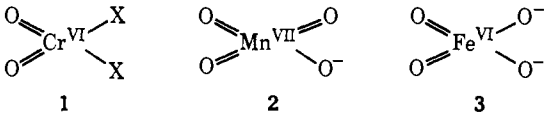
(11) Postdoctoral of the Medical Research Council of Canada, 1968–1970.

**A. I. Meyers,* E. M. Smith,[11] A. F. Jurjevich**
*Department of Chemistry, Wayne State University*
*Detroit, Michigan 48202*
*Received January 30, 1971*

## Oxotransition Metal Oxidants as Mimics for the Action of Mixed-Function Oxygenases. "NIH Shift" with Chromyl Reagents

*Sir:*

In recent years there has been considerable interest and speculation concerning the nature of the biological oxidant in iron-based, mixed-function oxygenases. Surprisingly, no one appears to have noted the striking similarity between reactions catalyzed by oxygenases and those effected by oxotransition metal compounds of chromium (**1**) and manganese (**2**). The most characteristic roles of mixed-function oxygenases are stereo-



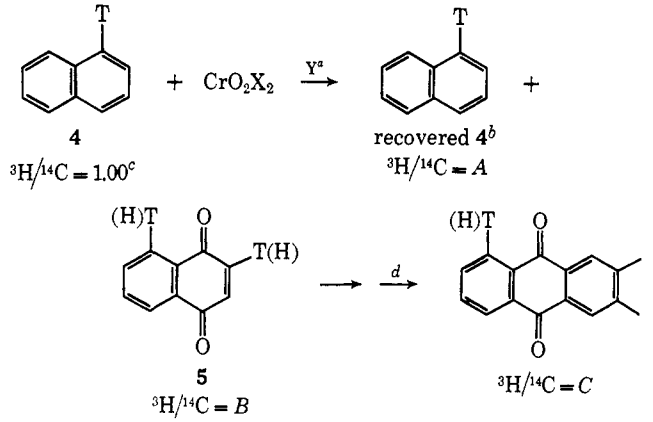
specific hydroxylation of aliphatic hydrocarbons and epoxidation of olefinic and aromatic substances, the last[1] resulting in the celebrated "NIH shift." Permanganate (**2**) and chromyl species (**1**, X = OH, Cl, OAc) have long been known to hydroxylate hydrocarbons with at least partial retention,[2] and chromyl acetate (**1**, X = OAc) epoxidizes olefins with retention of the olefinic geometry.[3] Thus, of the three reactions most typical of mixed-function oxygenases, only the hydroxylation of aromatic substrates with concomitant NIH shift was unknown for these oxotransition metal

(1) D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltzman-Nirenberg, and S. Udenfriend, *J. Amer. Chem. Soc.*, **90**, 6525 (1968).

(2) K. B. Wiberg, "Oxidation in Organic Chemistry," Academic Press, New York, N. Y., 1965.

(3) W. Kruse, *Chem. Commun.*, 1610 (1968).

**Scheme I**




[a] In all reactions the chromyl reagent was added at 0°; after 0.5 hr the mixtures were warmed to room temperature. [b] The per cent of recovered naphthalene from experiments 1, 2, and 3 was *ca.* 78, 81, and 16, respectively. [c] The starting naphthalene had a $^3H/^{14}C$ ratio of 10.95; all ratios have been normalized to this number to facilitate interpretation. [d] This conversion was effected essentially quantitatively by Diels–Alder reaction with 2,3-dimethylbutadiene followed by air oxidation (C. F. H. Allen and A. Bell, "Organic Synthesis," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 310).

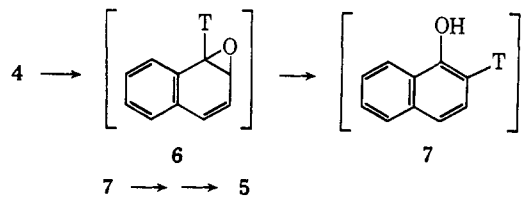
**Table I**

| Expt | Reagent $CrO_2X_2$ | Conditions (Y) | *A* | *B* | *C* | Yield of **5**,[a] % |
|---|---|---|---|---|---|---|
| 1 | $CrO_2(OAc)_2$[b] | $CCl_4$ | 1.00 | 0.70 | 0.51 | 36 |
| 2 | $CrO_2(OAc)_2$ | $CCl_4$, 50% HOAc | 0.99 | 0.70 | 0.52 | 57 |
| 3 | $CrO_2Cl_2$ | $CCl_4$ | 1.04 | 0.75 | 0.52 | 24 |

[a] Yield based on unrecovered napthalene. [b] For the preparation, see H. L. Krauss, *Angew. Chem.*, **70**, 502 (1958).

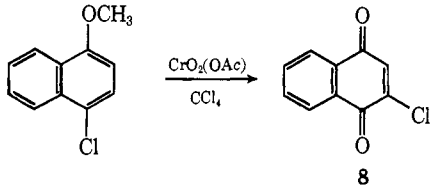
compounds (**1** and **2**). We now report that this last mode of reactivity is also exhibited by certain chromyl oxidants (**1**, X = Cl, OAc), making them the first nonenzymatic oxidants to mimic mixed-function oxygenases in all important respects. We also describe the stereoselective epoxidation of squalene by the iron(VI) oxidant **3**, providing the first example of an iron-based, nonenzymatic oxidation of olefins that is not radical in character.

When [1-$^3H$,1-$^{14}C$]naphthalene (**4**) is oxidized by chromyl acetate or chromyl chloride in $CCl_4$, 1,4-naphthoquinone is produced in fair yield (Scheme I and Table I). Of the tritium remaining in quinone **5**, 26–31% (*i.e.*, $(B - C)/B$) has migrated to the 2 position, since in the absence of any tritium shift the $^3H/^{14}C$ ratio *B* should be the same as the ratio *C*, *ca.* 0.50. This represents a large NIH shift[4] which we feel provides strong evidence for the intermediacy of epoxide **6**.[1]




Failure to observe intermediates such as **6** or the naphthol **7** is not unexpected as they are much more sensitive to reaction than is the starting naphthalene. In fact, when an 8:3 *M* mixture of [$^{14}C$]naphthalene and unlabeled 1-naphthol (**7**) was oxidized by chromyl acetate in $CCl_4$ (chromyl acetate was added until only a trace of 1-naphthol remained), the 1,4-naphthoquinone isolated contained no significant activity. Experiment 2 reveals that the presence of a proton source (HOAc) has no effect on the magnitude of the shift, ruling out tritium incorporation into the 2 position by any protonic exchange mechanism. In order to establish that the value of ratio *B* in excess of *C* was not the result of a large tritium isotope effect in the oxidative destruction of quinone **5**, a sample of **5** from experiment 1 ($B$ = 0.70) was subjected to partial destruction by chromyl acetate in $CCl_4$. The unreacted quinone (30% was recovered) actually showed a slight decrease in the $^3H/^{14}C$ ratio ($B$ = 0.67).

It has been observed that chloride also has a strong tendency for 1,2 migration in biological aromatic hydroxylations.[6] Here too, we have found that chromyl acetate effects the same result as the biological oxidant affording **8** in 4% yield[7]




**8**

(4) Aromatic substrates containing groups which deprotonate (*e.g.*, phenols, anilines, etc.) exhibit little or no deuterium retention during enzymatic hydroxylations.[5] A naphthol intermediate such as **7** (or perhaps its metal-coordinated anion) might be expected to analogously give very little tritium retention upon further oxidation under our conditions. The $^3H/^{14}C$ ratio *B* would then have a maximum value of *ca.* 0.75 rather than unity.

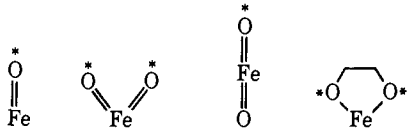
(5) J. Daly, D. Jerina, and B. Witkop, *Arch. Biochem. Biophys.*, **128**, 517 (1968).

(6) E. W. Thomas, B. C. Loughman, and R. G. Powell, *Nature (London)*, **204**, 884 (1964); J. K. Faulkner and D. Woodcock, *J. Chem. Soc.*, 1187 (1965); G. Guroff, K. Kondo, and J. Daly, *Biochem. Biophys. Res. Commun.*, **25**, 622 (1966).

(7) The yield of chloroquinone **8** isolated from the complex reaction mixture is low, and traces of quinone **5** may have been formed. Since **8** is probably more oxidatively stable than **5**, nothing can be said about the percentage of chloride migration in this reaction.

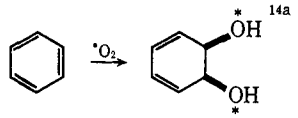
Although ferrate ion (**3**) was first prepared in 1702, there is little known concerning its reactivity with organic substrates.[8] Like its isostructural relative manganate ($MnO_4^{2-}$), ferrate is only stable in strongly alkaline solution. Unlike manganate,[9] we find that it reacts very slowly with oleic acid to produce complex product mixtures in low yield. The only products identified were *erythro*- and *threo*-9,10-dihydroxystearic acid, formed in the ratio 7:3. All ferrate salts are instantaneously decomposed by mineral acids, but barium ferrate is unique in exhibiting stability toward acetic acid, in which it is reported to give a red solution.[8] When a slight excess of squalene was treated with a suspension of barium ferrate in glacial acetic acid, epoxidation was the only detectable mode of oxidative attack. Monoepoxysqualenes were formed in 10% yield, based on ferrate.[10] The internal oxides were found by nmr analysis to be a mixture of isomers (90% trans and 10% cis). Thus, the ferrate epoxidation is not completely stereospecific. Chromyl acetate was found to produce only epoxides with squalene in carbon disulfide, and nmr analysis of the internal monoepoxides in this case showed that only trans epoxides had formed. Whatever the mechanism of epoxidation by chromyl acetate might be, it cannot involve the development of significant positive charge on the olefinic carbon atoms since cationic cyclizations are very favorable for such 1,5-dienes.

The above results suggest that some kind of oxoiron (Fe=O) species may play the role of active oxidant in mixed function oxygenase reactions. We feel that partial structures **9**, **10**, and **11** are possible candidates for the natural oxidant.[12] Formulae **9**, **10**, and **11**



**9** **10** **11** **12**

represent monooxo, cis dioxo, and trans dioxo structural types, respectively (* = derived from molecular oxygen). All three types could in principal epoxidize olefins by direct atom transfer, but epoxidation *via* a cyclic ester (*i.e.*, **12**) is only possible for cis dioxo formulations such as **10**.[13] The recent observations of cis hydroxylation of aromatic nuclei by oxygenases in several[14a,b] microorganisms are not inconsistent with an intermediate such as **12**. Our work on oxotransition



metal compounds is continuing with special emphasis on distinguishing between monooxo (**9**) and dioxo (**10** and **11**) structures for the natural iron oxidant.

**Acknowledgments.** One of us (K. B. S.) gratefully acknowledges Professor James P. Collman for many stimulating discussions of oxygenase chemistry. We thank a Du Pont Fundamental Research Grant for providing financial support.

(8) J. T. Riley, Ph.D. Thesis, University of Kentucky, 1968.

(9) W. Rigby (*J. Chem. Soc.*, 2452 (1956)) reports a 32% yield of *erythro*-9,10-dihydroxystearic acid from the action of manganate on oleic acid.

(10) Since under the conditions of the oxidation the epoxide products were partially opened to the corresponding hydroxyacetates, the reaction mixture was stirred until tlc revealed complete acetolysis of the oxides. Following lithium aluminum hydride reduction of the crude hydroxyacetate mixture, the monointernal diols were isolated by preparative tlc. The diols were transformed to the corresponding oxides using our published procedure.[11] A control experiment established that authentic *trans*-monointernal squalene oxides proceeded through the above sequence (acetolysis and reclosure) with complete retention of the original geometry.

(11) K. B. Sharpless, *Chem. Commun.*, 1450 (1970).

(12) It is generally argued that the active oxidant derives from reduction of a ferroporphyrin oxygen complex. However, since either one- or two-electron reduction is possible, we have avoided specifying oxidation states for **9**, **10**, and **11**. There are other more subtle problems related to assigning the oxidation state of the metal. For example, even if one knew that **10** was a dianion resulting from two-electron reduction, the oxidation state of the iron would not be apparent; it would be somewhere between IV and VI depending on whether the negative changes resided principally on the metal or on the ligands (porphyrin and oxygens). *A priori* there is no reason to doubt that any iron IV, V, or VI oxidant would be potent enough to effect all known oxygenase reactions.

(13) We have recently found that thermolysis of the esters formed by reaction of osmium tetroxide with olefins leads in part to epoxides.

(14) (a) D. T. Gibson, G. E. Cardin, F. C. Maseles, and R. E. Kallio, *Biochemistry*, **9**, 1631 (1970), and references contained therein; (b) D. M. Jerina, T. W. Daly, A. M. Jeffrey, and D. T. Gibson, *Arch. Biochem. Biophys.*, **142**, 394 (1971).

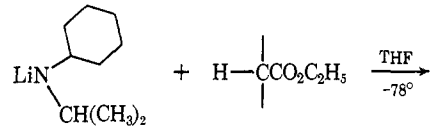
(15) Fannie and John Hertz Foundation Fellow, 1969–1971.

**K. Barry Sharpless,* Thomas C. Flood**[15]
*Department of Chemistry*
*Massachusetts Institute of Technology*
*Cambridge, Massachusetts 02139*
*Received February 4, 1971*

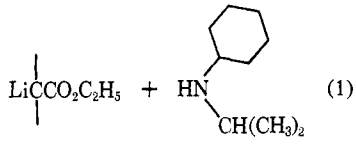
## The Reaction of Lithium *N*-Isopropylcyclohexylamide with Esters. A Method for the Formation and Alkylation of Ester Enolates

*Sir:*

Lithium *N*-isopropylcyclohexylamide (LiICA) reacts with a wide variety of esters at low temperatures in tetrahydrofuran to produce solutions of the corresponding lithium ester enolates (eq 1). Self-condensa-



(LiICA)



(1)

tion of the ester does not occur, even when such solutions are allowed to reach room temperature. This represents the first general method for the preparation of stable solutions of ester enolates.[1] At room tem-

(1) Ester enolates have previously been generated by the reaction of esters with 1 and 2 equiv of lithium amide in liquid ammonia[2] and with the alkali metal salts of triphenylmethane.[3] These bases are most successful with relatively unreactive esters such as ethyl isobutyrate or *tert*-butyl esters. Even in these cases the enolate solutions must be utilized soon after their formation to prevent appreciable self-condensation.

(2) W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960); C. R. Hauser and J. K. Lindsay, *J. Amer. Chem. Soc.*, **77**, 1050 (1955); C. R. Hauser and W. H. Puterbaugh, *ibid.*, **75**, 1068 (1953).

(3) W. Schlenk, H. Hilleman, and I. Rodloff, *Justus Liebigs Ann. Chem.*, **487**, 135 (1931); D. F. Thomas, P. L. Bayless, and C. R. Hauser, *J. Org. Chem.*, **19**, 1490 (1954); B. E. Hudson, Jr., and C. R. Hauser, *J. Amer. Chem. Soc.*, **63**, 3156 (1941).