

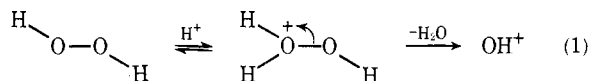
Oxidations with Peroxytrifluoroacetic Acid-Boron Fluoride

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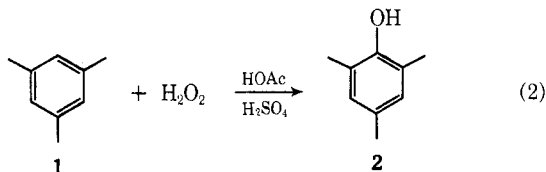
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The common electrophilic aromatic substitution reactions—nitration, halogenation, sulfonation, alkylation and the like—date back to the last century, but it was just over 20 years ago that Derbyshire and Waters¹ first considered the possibility of electrophilic aromatic *hydroxylation*. The direct production of phenols from aromatic hydrocarbons has long been a desirable synthetic goal, both in the laboratory and commercially, but no useful general method was available. The necessary electrophile would presumably have to be a hydroxyl cation,² OH⁺ or its equivalent, analogous to NO₂⁺ (for nitration) or R⁺ (for alkylation). Hydrogen peroxide seemed a logical precursor; it was calculated to be about 1% protonated in 10 N acid, and heterolytic



cleavage of the O-O bond would supply the desired electrophile.

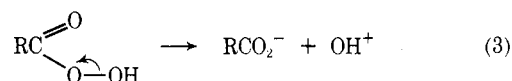
Accordingly, Derbyshire and Waters treated mesitylene (**1**) with hydrogen peroxide in a mixture of acetic and sulfuric acids. They obtained mesitol (**2**) in good yield.³



One serious difficulty in the controlled oxidation of an arene to a phenol is the fact that the products are, in general, more easily oxidized than the reactants. Mesitylene was a fortunate choice of substrate because all positions ortho and para to the hydroxyl group in the product are substituted, thus retarding (but not preventing, *vide infra*) further oxidation.⁴ A Lewis acid

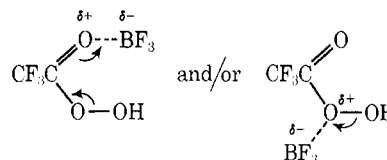
(BF₃·Et₂O) with hydrogen peroxide has also been used as an oxidant,⁷ and although the combination is effective for oxidizing ketones to esters, yields and conversions with aromatic hydrocarbons were low.

Organic peracids constitute a second likely source of electrophilic hydroxyl. Electron-withdrawing R groups should facilitate O-O bond cleavage in the desired sense (eq 3). Musgrave and coworkers, who were



the first to use this approach to direct aromatic hydroxylation,⁸ selected peroxytrifluoroacetic acid (eq 3, R = CF₃) because of its known excellent oxidizing properties.⁹ With mesitylene as the substrate, a good yield of mesitol was obtained (after 24 hr at 0°). However, although the yield was high, the conversion was low (17–25%).¹⁰ The low conversion and long reaction time were somewhat discouraging from the synthetic viewpoint.

It was our good luck to try the fourth remaining combination of reagents, *i.e.*, an organic peracid and a Lewis acid (for example, BF₃). We thought that coordination with either the carbonyl or ether oxygen might facilitate O-O bond cleavage in the desired sense. With this in mind, we tried oxidizing the old standby, mesitylene, with CF₃CO₃H and BF₃. The



reaction was exothermic and virtually complete on mixing the reagents, even at -40°, and the yield of mesitol was essentially quantitative, limited only by the skill of the experimenter. No other Lewis acid that we tried has been so effective or easy to use as BF₃ (gaseous, or more conveniently the ethereate).

We have found peroxytrifluoroacetic acid-boron

(1) D. H. Derbyshire and W. A. Waters, *Nature*, **165**, 401 (1950).

(2) This species has been detected spectroscopically (for references, see G. Herzberg, "Molecular Spectra and Molecular Structure. I. Spectra of Diatomic Molecules," Van Nostrand, New York, N. Y., 1950, p 561), but its existence in solution has never been established. In this paper we will use the symbol OH⁺ for convenience to represent the electrophile. The actual electrophile is probably not OH⁺ (see, for example, R. Curci and J. O. Edwards, *Org. Peroxides*, **1**, 213 (1970)), but leads to an intermediate carbonium ion with the same structure that would be expected were the electrophile OH⁺. Kinetic studies which might establish the true nature of the electrophile have not been performed.

(3) The brief note was never followed by a full paper, and experimental details are lacking, but the result has been verified in our laboratory and yields can be >80%.

(4) Recently diisopropyl peroxydicarbonate-cupric chloride⁵ and HF-H₂O₂ in the presence of CO₂ under pressure⁶ have been found effective with less substituted arenes such as benzene and toluene. See also S. Hashimoto and W. Koike, *Bull. Chem. Soc. Jap.*, **43**, 293 (1970).

(5) M. E. Kurz and P. Kovacic, *J. Amer. Chem. Soc.*, **89**, 4960 (1967).

(6) J. A. Vesely and L. Schmerling, *J. Org. Chem.*, **35**, 4028 (1970).

(7) J. D. McClure and P. H. Williams, *ibid.*, **27**, 24 (1962).

(8) R. D. Chambers, P. Goggin, and W. K. R. Musgrave, *J. Chem. Soc.*, 1804 (1959).

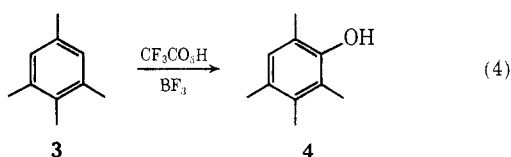
(9) W. D. Emmons and A. S. Pagano, *J. Amer. Chem. Soc.*, **77**, 4557 (1955), and earlier papers.

(10) The reagent reacted more efficiently with more reactive substrates. Thus 2,6-xyleneol was converted (77%) to 2,6-dimethyl-1,4-benzoquinone. This illustrates, incidentally, the ease of further oxidation when a position para to the hydroxyl group is unsubstituted.

fluoride to be a useful, versatile oxidant of π systems. The reagent¹¹ delivers a potent electrophile which attacks substituted as well as unsubstituted positions on aromatic rings. The oxidation products are frequently difficult to obtain in other ways and certain of them, especially highly substituted cyclohexadienones, have proved valuable as synthetic intermediates for aromatic, small-ring, and bicyclic compounds. Recent use of the reagent with alkenes suggests that it may also be useful in aliphatic syntheses. We present here a brief account of this development and a summary of results to date.

Direct Aromatic Hydroxylation

Although the initial driving force for devising the $\text{CF}_3\text{CO}_2\text{H}-\text{BF}_3$ reagent was to effect one-step electrophilic hydroxylation of arenes to phenols, this application has not, in fact, become its most important use. Although mesitylene (**1**) and isodurene (**3**) were readily hydroxylated in good yield, less substituted hydrocarbons (benzene, toluene, etc.) gave mainly tars, due to

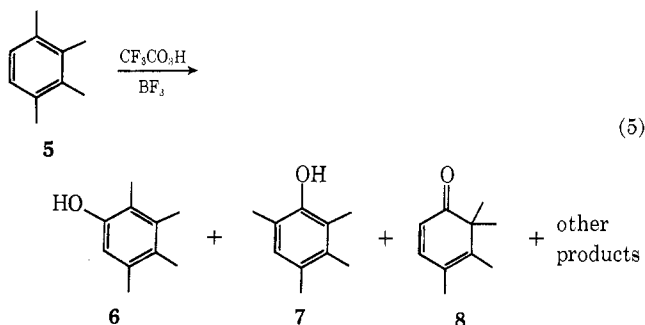


further oxidation of the initially produced phenols.⁴⁻⁶

Extension of the reaction to other highly substituted arenes disclosed the fact that the reagent was sufficiently "hot" to attack already substituted positions. This reaction proved particularly useful synthetically and diverted our attention to the extent that the potential of the reagent for synthesizing phenols has really not yet been fully explored.

Electrophilic Attack at Substituted Positions

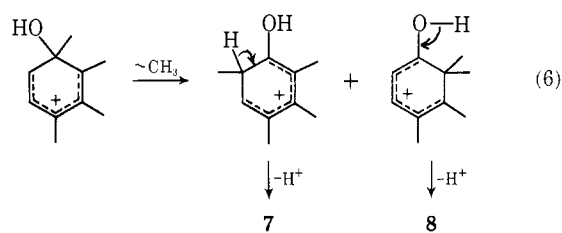
Oxidation of prehnitene (**5**) gave¹² not only the expected phenol **6**, but small amounts of an isomeric phenol, **7**, and cyclohexadienone **8** (as well as other



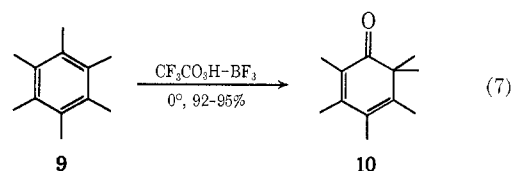
products, discussed in the following section). Products **7** and **8** are most easily rationalized by assuming electrophilic attack at an already substituted position, followed by Wagner-Meerwein methyl migration in either of the two possible senses and proton loss.¹³

(11) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., Vol. I, 1967, pp 824-826; also, Vol. II, 1969, p 316.

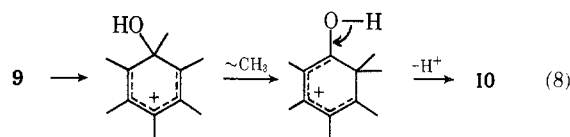
(12) H. Hart and C. A. Buehler, *J. Org. Chem.*, **29**, 2397 (1964).



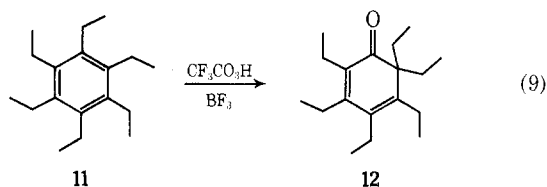
The yields of **7** and **8** represented only 9% of the prehnitene oxidation products, but the formation of these products, particularly **8**, led us to try a substrate in which *only* attack at a substituted position was possible. The result was rewarding. Hexamethylbenzene (**9**) gave the corresponding 2,4-cyclohexadienone **10** in over 90% yield.^{16,17} The pentadienyl cation intermediate has no competition from alternative stabilization paths and leads to **10**, by methyl migration



and proton loss, in high yield.

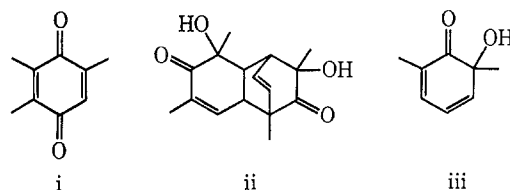


The reaction is quite general, as the following examples will illustrate. Hexaethylbenzene gives a hexaethylidienone (eq 9).¹⁶ Halopentamethylbenzenes



give halocyclohexadienones (eq 10).¹⁸ The strained

(13) Actually there were two earlier reports which indicated oxidative electrophilic attack at already substituted positions. Musgrave⁸ obtained small amounts of the trimethylquinone **i** from mesitylene and $\text{CF}_3\text{CO}_2\text{H}$; the structure requires a methyl migra-



tion. McClure¹⁴ obtained **ii**, the Diels-Alder dimer of **iii**, from the oxidation of 2,6-xyleneol. In this case (and in the related Wessely acetoxylation of phenols¹⁵) the carbonyl oxygen of the dienone is derived from the phenolic hydroxyl group, whereas in **8** it is derived from the oxidant.

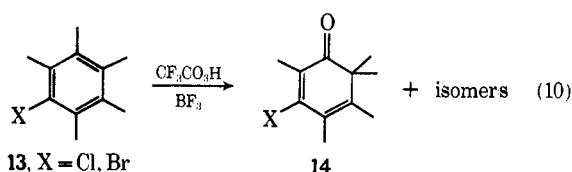
(14) J. D. McClure, *J. Org. Chem.*, **28**, 69 (1963).

(15) For a review, see A. J. Waring, *Advan. Alicyclic Chem.*, **1**, 129-256 (1966), especially pp 162-167.

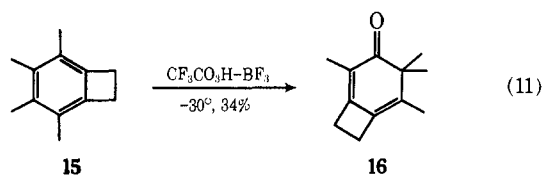
(16) A. J. Waring and H. Hart, *J. Amer. Chem. Soc.*, **86**, 1454 (1964); H. Hart, P. M. Collins, and A. J. Waring, *ibid.*, **88**, 1005 (1966).

(17) H. Hart, R. M. Lange, and P. M. Collins, *Org. Syn.*, **48**, 87 (1968).

(18) Unpublished results with D. Shapiro.

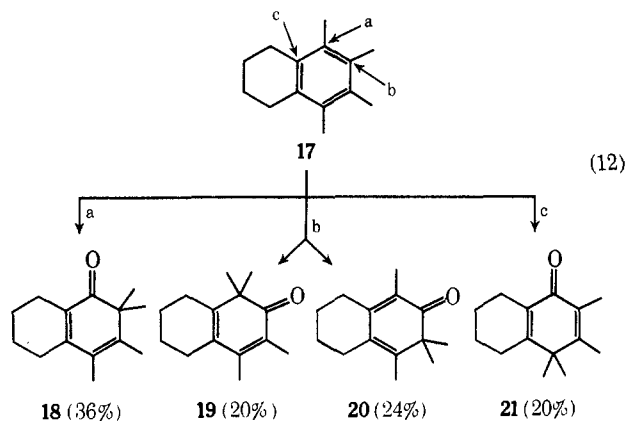


fused ring system in **15** survived the oxidation,¹⁹ though **16** was obtained in only modest yield. Benzo-

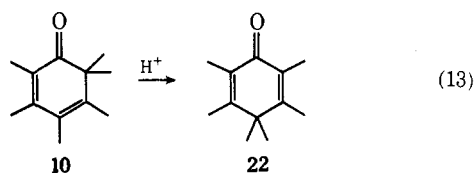


cyclobutenes may undergo considerable ring opening and polymerization in the presence of electrophiles,²⁰ and this may account for the low yield in eq 11.

With a larger fused ring (**17**) the reaction is cleaner, and products from electrophilic attack at all three possible positions were isolated.²¹ The mechanism for the formation of **18-20** is unexceptional, but the isolation of **21**, a cross-conjugated rather than linearly

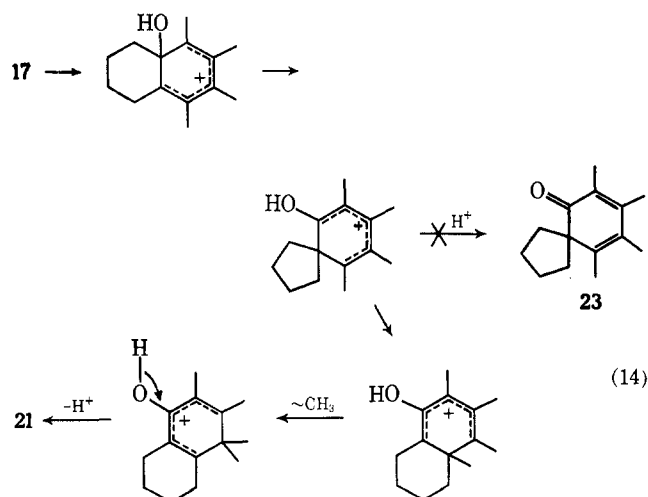


conjugated dienone, requires special comment. This compound could arise from **18** via protonation, two methyl migrations, and deprotonation. However, **18** is stable under the oxidation conditions. Though such rearrangements are known (eq 13),^{22,23} they usually

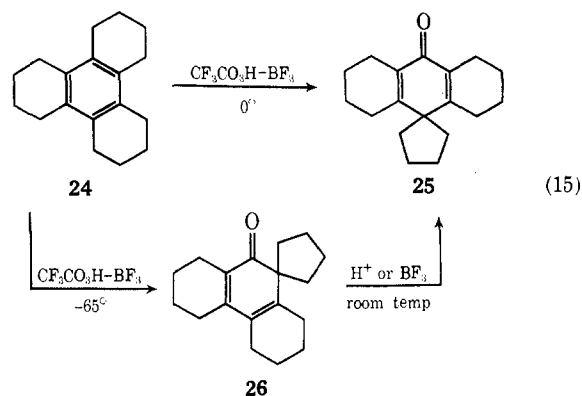


require considerably stronger acid to proceed at a rapid

rate. The most likely route to **21** therefore seems to be attack at position c of **17**, followed by three successive Wagner-Meerwein 1,2 shifts (eq 14).



The conjugated spirodienone **23** was not isolated, and evidence from other experiments indicates that such compounds isomerize extremely rapidly in acid to their cross-conjugated isomers. For example, **24** (the trimeric dehydration product of cyclohexanone) gave only the cross-conjugated product **25** when oxidized at 0°, though when the reaction was carried out at -65° the linearly conjugated dienone **26** was obtained.²⁴ The reason why spirodienones such as **23** or **26** rearrange much more rapidly than dialkyl dienones such as **10**



is not yet known.

Highly substituted naphthalenes can be oxidized by $\text{CF}_3\text{CO}_2\text{H}-\text{BF}_3$ to benzocyclohexadienones. With 1,2,3,4-tetramethylnaphthalene (**27**), oxidation occurred almost exclusively in the substituted ring and, as expected with electrophilic reactions of naphthalenes, attack at C-1 (to give **28** and **30**) was favored over attack at C-2 (to give **29**), by 4:1.²⁵ The diketone **30** arises solely from further oxidation of **28**, not **29**, as shown by the separate quantitative oxidation of **28** → **30** and by the fact that treatment of **27** with excess oxidant gave only **29** and **30**.

An unusual result was obtained with octamethylnaphthalene (**31**).²⁶ This molecule is quite strained,

(24) H. Hart and D. C. Lankin, *J. Org. Chem.*, **33**, 4398 (1968).

(25) H. Hart and R. K. Murray, Jr., *ibid.*, **32**, 2448 (1967).

(26) Unpublished results with A. Oku.

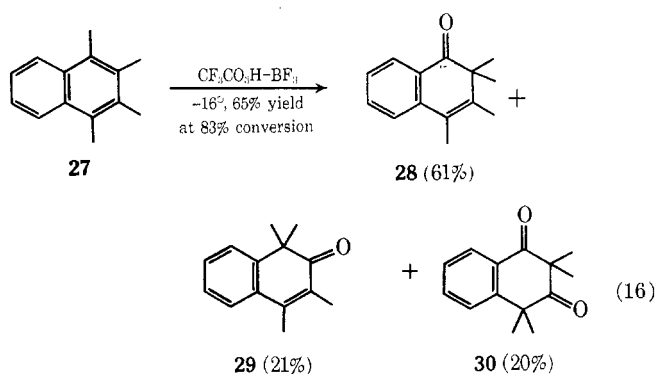
(19) R. J. Bastiani, D. J. Hart, and H. Hart, *Tetrahedron Lett.*, 4841 (1969).

(20) J. B. F. Lloyd and P. A. Ongley, *Tetrahedron*, **20**, 2185 (1964).

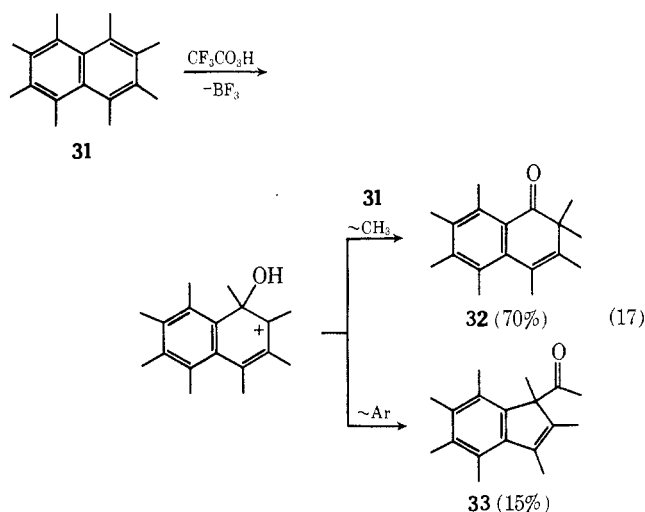
(21) R. J. Bastiani, Ph.D. Thesis, Michigan State University, 1970.

(22) H. Hart and D. W. Swatton, *J. Amer. Chem. Soc.*, **89**, 1874 (1967).

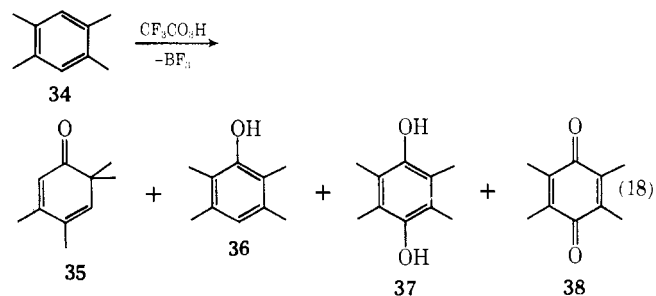
(23) V. G. Shubin, V. P. Chzhu, A. I. Rezvukhim, and V. A. Koptuyug, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1999 (1966); V. G. Shubin, V. P. Chzhu, A. I. Rezvukhim, A. A. Tabatskaya, and V. A. Koptuyug, *ibid.*, 2264 (1967); R. F. Childs, *Chem. Commun.*, 946 (1969).



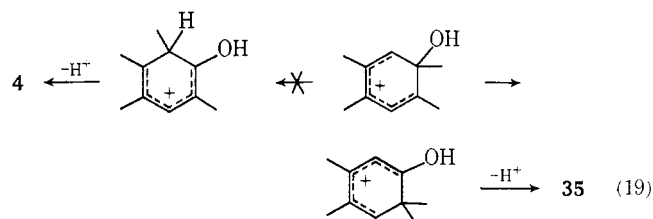
due to interactions between the methyl groups in the peri positions.²⁷ Attack occurred almost exclusively at C-1 and, interestingly, the carbonium ion intermediate underwent not only the expected methyl migration to give **32** but aryl migration to give the acetylidene **33**. Analogous ring contraction in simpler systems has not yet been observed.



In all the oxidations described above (eq 7-12, 14-17) at least one of the aromatic rings in the substrate was fully substituted, and the reagent had essentially no alternative but to attack a substituted position. But this condition has turned out *not* to be an essential requirement for obtaining high yields of dienone. Durene (**34**) provides a particularly striking example.²⁸ Although some phenols (**36**, **37**) and duroquinone (**38**) were produced, the principal product, obtained in yields as high as 75%; was the dienone **35**. Attack at

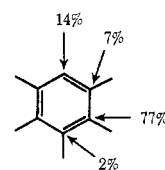


an already substituted position is favored 2:1 statistically, and the methyl substitution pattern is nearly identical for attack at either position, although it is our experience that methyl groups are usually somewhat more effective at stabilizing pentadienyl cations when located at the central carbon atom (as one of them would be, for attack at a substituted position). Methyl migration occurs preferentially toward the adjacent substituted position, giving **35**; no isodureneol (**4**) was

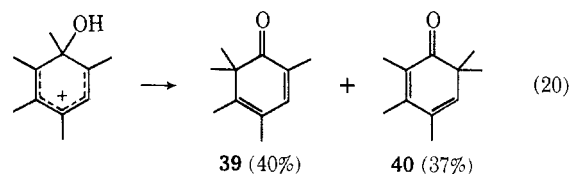


observed among the products.

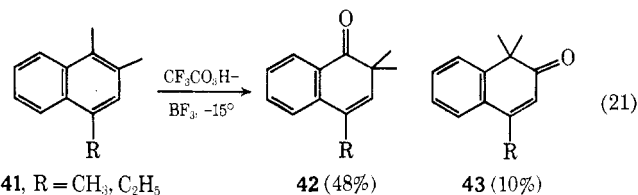
In sharp contrast with mesitylene, pentamethylbenzene gave very little phenolic product; 86% was converted to dienones as a result of attack at substituted positions.²⁹ The preferred intermediate underwent



methyl migration in either direction with nearly equal facility (eq 20).



It was recently shown³⁰ that naphthalenes with incomplete substitution in either ring give respectable yields of benzodienones (eq 21).



Oxidations Involving 1,2 Hydrogen Shifts

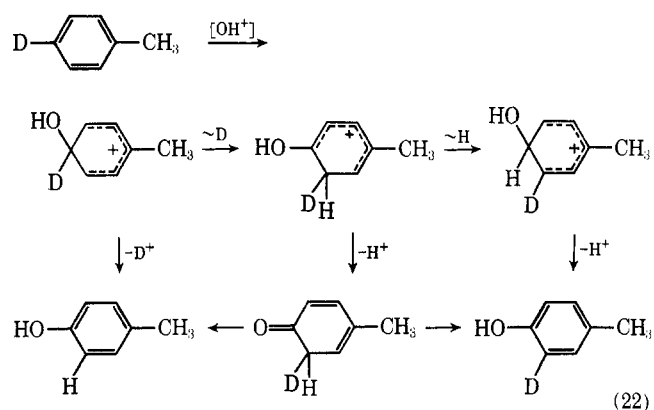
The observation of 1,2 alkyl shifts such as those described above in electrophilic oxidations naturally raised the question of whether analogous 1,2 hydride shifts are also possible. For example, one could imagine the electrophilic oxidation of toluene to *p*-cresol occurring through a scheme such as that outlined in eq 22. Indeed, in their fundamental studies of enzymatic

(27) V. Balasubramanian, *Chem. Rev.*, **66**, 567 (1966).

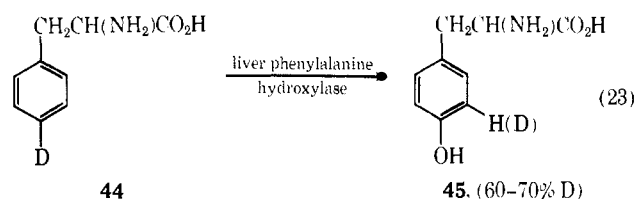
(28) H. Hart and R. M. Lange, *J. Org. Chem.*, **31**, 3776 (1966).

(29) P. M. Collins and H. Hart, *J. Chem. Soc.*, 895 (1967); also unpublished results with S. Ramaswami.

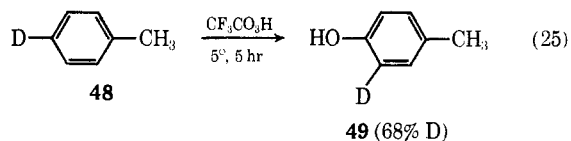
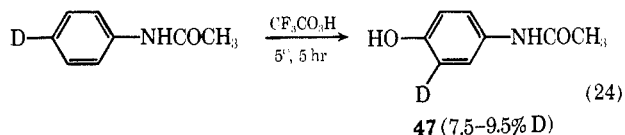
(30) H. Hart and R. K. Murray, Jr., *J. Org. Chem.*, **35**, 1535 (1970).



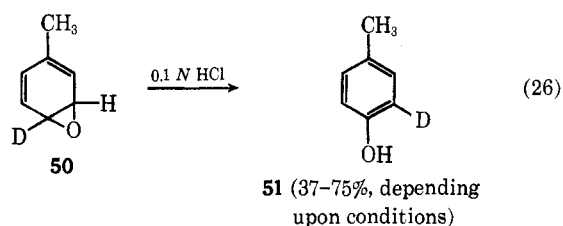
hydroxylations of aromatic compounds (such as phenylalanine or tryptophan) Witkop and coworkers showed that such migrations are common.³¹ For example, oxidation of labeled phenylalanine **44** gave the hydroxylated product **45** with considerable label retention.



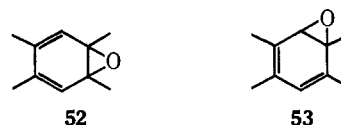
Similar retentions of label have been observed in non-enzymatic systems. 4-Deuterioacetanilide and 4-deuteriotoluene, oxidized with $\text{CF}_3\text{CO}_3\text{H}$ (no BF_3 used), gave appreciable D-retained product. Other electrophilic substitutions (bromination, nitration, alkylation)



on the same substrates gave products devoid of deuterium, which suggested that perhaps there was something unique about the oxidation mechanism. A benzene oxide intermediate was suggested, and this hypothesis was made tenable by the demonstration of label retention in the acid-catalyzed rearrangement of the toluene oxide **50**.



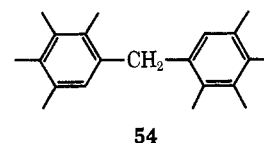
The possibility that arene oxides may also be intermediates in the alkyl migrations observed in $\text{CF}_3\text{CO}_3\text{H}-\text{BF}_3$ oxidations has not been adequately explored. One might speculate, for example, that the high yield of dienone from durene (eq 18) arises out of the preferred intermediacy of the most substituted oxide (**52** >



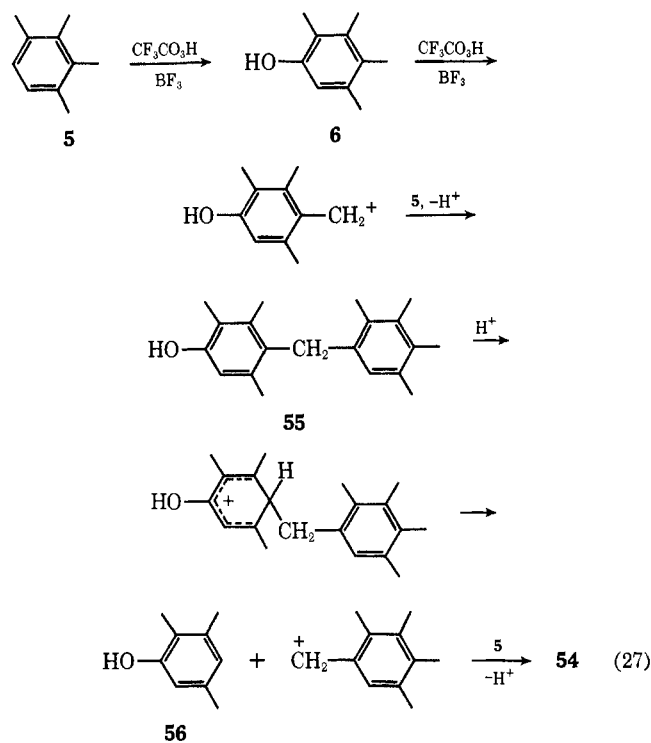
53), rearrangement of which can only lead to dienone **35**.

Side-Chain Oxidation; a Diarylmethane Synthesis

Among the "other products" in eq 5 was a 24% yield of the octamethyldiphenylmethane **54** and, as will be seen, other aromatic substrates than prehnitene have produced similar products. Compound **54** must be derived from two prehnitene fragments with an addi-



tional carbon needed for the methylene group. A plausible sequence which accounts for the formation of **54** is given in eq 27. An entirely analogous scheme,

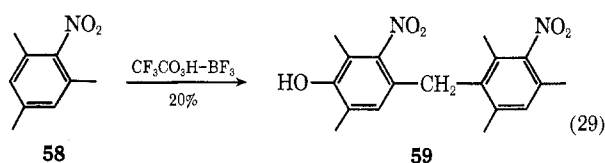
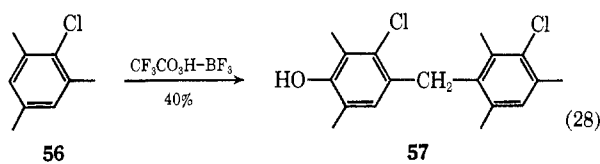


but involving further oxidation of **7** rather than **6**, can be constructed which would lead to 2,3,6-trimethylphenol as the other product corresponding to **56**. In full accord with this proposal, both expected trimethylphenols were isolated as reaction products.

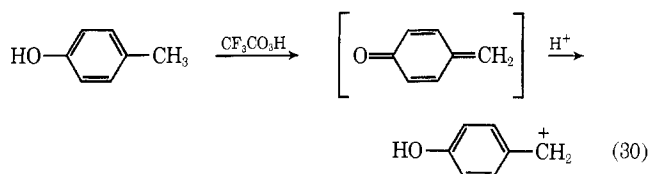
Proposed intermediate **55** was not isolated from the prehnitene oxidation, but analogous compounds (**57**, **59**)

(31) For a brief review of what is termed the NIH shift, see G. Guroff, J. W. Daly, D. M. Jerina, J. Renson, B. Witkop, and S. Udenfriend, *Science*, **157**, 1524 (1967).

have been obtained in modest yield from the oxidation of chloro- and nitrobenzylene.³²

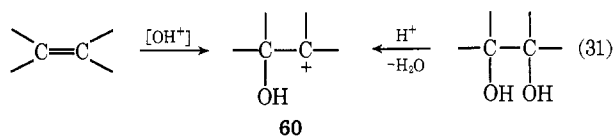


Since no diarylmethanes were obtained which might have been derived from direct oxidation of a methyl group of the original substrate (for example, a heptamethyldiphenylmethane from prehnitene), it seems most likely that this reaction path is due to attack at a phenolic hydroxyl group, possibly as in eq 30.



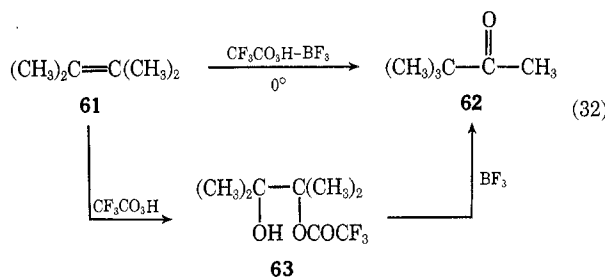
Oxidation of Alkenes

Organic peracids have long been used to epoxidize alkenes,³³ and boron fluoride has been used³⁴ to rearrange epoxides to carbonyl compounds. It seemed possible, therefore, that the combined $\text{CF}_3\text{CO}_3\text{H}-\text{BF}_3$ reagent might directly convert alkenes to carbonyl compounds. Regarded another way, one could imagine generating the pinacol-pinacolone rearrangement intermediate **60** by direct hydroxylation of an alkene (eq 31). Accordingly we studied the oxidation of highly

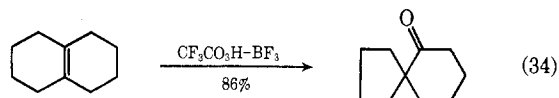
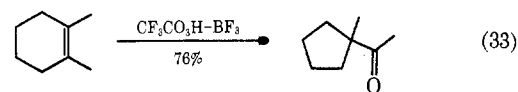


substituted alkenes with peroxytrifluoroacetic acid-boron fluoride.³⁵

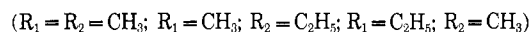
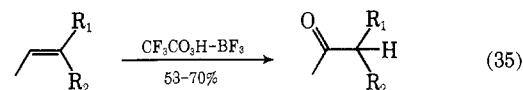
Pinacolone (**62**) was obtained in 75–100% yield directly from tetramethylethylene (eq 32). When the BF_3 was omitted, the major product was the hydroxy-



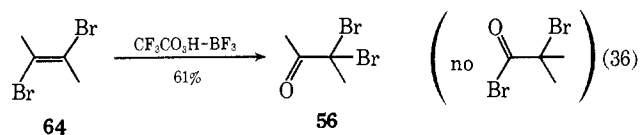
trifluoroacetate **63** which, with BF_3 , rearranged quantitatively to **62**. Other tetrasubstituted alkenes reacted similarly (eq 33, 34), whereas trisubstituted alkenes



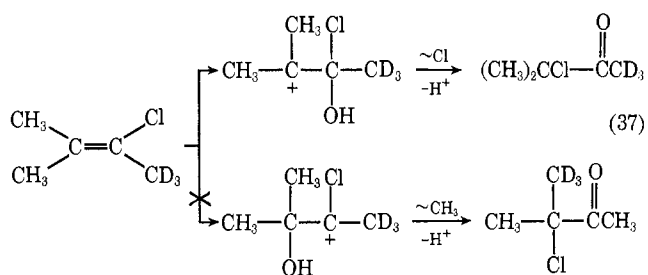
gave mainly hydrogen (rather than alkyl) migration products (eq 35).



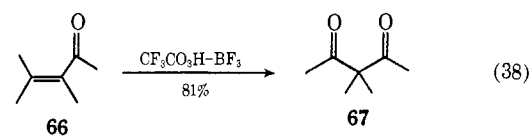
One tremendous advantage of the $\text{CF}_3\text{CO}_3\text{H}-\text{BF}_3$ reagent in such oxidations (aside from the shortening of a two-step sequence to one step, often with a yield improvement) is that it is sufficiently "hot" to attack alkenes with electron-withdrawing substituents, and this can lead to rare or previously unobserved rearrangements. For example, halogen (Cl, Br) migration takes precedence over alkyl migration. Oxidation of **64** gave the dibromo ketone **65**; no 2-bromobutyl bromide, the methyl migration product, was observed.



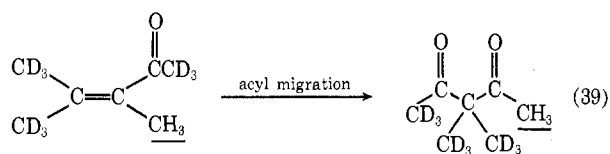
With 2-chloro-3-methyl-2-butene a similar reaction path was established by deuterium labeling (eq 37).



With α,β -unsaturated ketones, attack occurs at the carbon-carbon rather than the carbon-oxygen double bond, since no Baeyer-Villiger type product was observed (eq 38). Furthermore acyl, *not* alkyl migration



occurs, as was demonstrated using labeled **66** (eq 39).



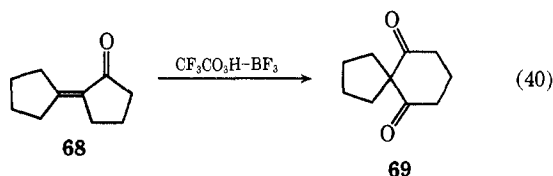
(32) H. Hart, C. A. Buehler, A. J. Waring, and S. Meyerson, *J. Org. Chem.*, **30**, 331 (1965).

(33) D. Swern, *Org. React.*, **7**, 378 (1953).

(34) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(35) H. Hart and L. Lerner, *J. Org. Chem.*, **32**, 2669 (1967).

In a useful synthetic application, the cyclopentanone aldol dimer **68** gave the spiro diketone **69** in one step.



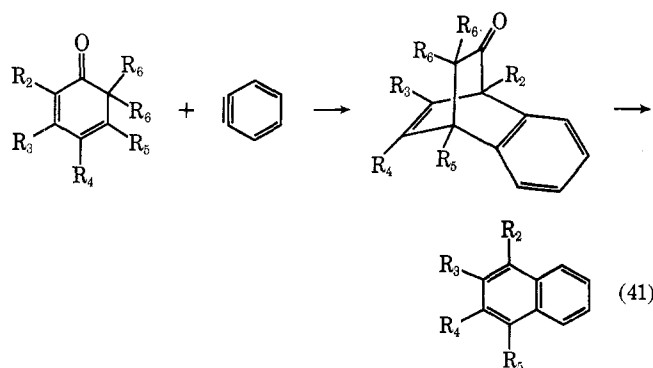
Summary, Spin-off, and the Future

Peroxytrifluoroacetic acid-boron fluoride has been found useful as a potent electrophilic oxidant for a variety of π systems. Not only can one directly hydroxylate aromatic rings, but through attack at already substituted positions one has an efficient, one-step synthesis of cyclohexadienones. Linearly conjugated dienones are usually obtained, but in some cases these rearrange to their cross-conjugated isomers under the reaction conditions (if the latter are desired, and are not obtained directly, they can readily be prepared from the linearly conjugated dienones by treatment with strong acid).

To date by far the greatest synthetic utility for $\text{CF}_3\text{CO}_3\text{H-BF}_3$ has been in the preparation of previously inaccessible, highly substituted cyclohexadienones. These in turn have served as the take-off point for a large number of investigations which would otherwise have been difficult or impossible. A detailed discussion of these would require a separate article, but perhaps the following two examples will illustrate the "spin-off" from these oxidation studies.

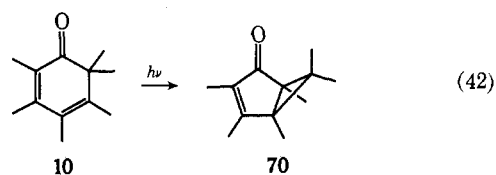
(a) Highly substituted 2,4-cyclohexadienones, unlike less substituted analogs which undergo Diels-Alder dimerization, are stable as monomers. They do, however, react readily with other dienophiles. The reaction with arynes, for example, has been used to develop a new, general naphthalene synthesis (eq 41).³⁶ Elimination of the carbonyl bridge in the last step can be accomplished in several ways. Substituted arynes may be used, and the overall yields are high. It was this route which permitted the synthesis of octamethyl-

(36) A. Oku, T. Kakihana, and H. Hart, *J. Amer. Chem. Soc.*, **89**, 4554 (1967).



naphthalene (**31**) in amounts sufficient for further studies.³⁷

(b) Irradiation of **10** gave the bicyclic ketone **70**,¹⁶ and it was a study of the effect of acid on **70**²² that led to the first example of a 1,4-sigmatropic rearrangement



in carbonium ions and the concept of perimeter walks ("merry-go-round" behavior) in carbonium ions.³⁸

The synthetic utility of $\text{CF}_3\text{CO}_3\text{H-BF}_3$ in aliphatic chemistry has barely been explored. The high reactivity of the reagent and the discovery of 1,2-halogen and acyl migration suggest that the study of other highly substituted alkenes, especially those with electronegative substituents, might be rewarding. Oxidations of non- π systems (for example, sulfides \rightarrow sulfones, etc.) have not been investigated, and such studies may be worthwhile in systems where the substitution pattern may require a vigorous oxidant.

The work described here was supported in part by grants from the National Science Foundation and the National Institutes of Health. I wish to thank especially my students, most of whose names are given in the references, for their diligence, imagination, and friendship throughout these investigations.

(37) Unpublished results with A. Oku.

(38) D. W. Swatton and H. Hart, *J. Amer. Chem. Soc.*, **89**, 5075 (1967); H. Hart, T. R. Rodgers, and J. Griffiths, *ibid.*, **91**, 754 (1969); R. F. Childs and S. Winstein, *ibid.*, **90**, 7146 (1968).