be obtained very quickly. Since different conformers often have rather different rotational constants (see Table I), this provides a way for very easily detecting the presence of more than one conformer. Furthermore, with reasonable structural assumptions the approximate rotational constants obtained from the low-resolution spectra can usually be definitive in establishing the identity of the conformers present. Thus it appears that low-resolution microwave spectroscopy may be very useful in the study of molecular conformation.

Conclusion

From the wealth of detailed information already obtained from microwave spectral studies, our knowledge of the factors involved in determining molecular conformation has been greatly increased. Also a substantive beginning has been made toward understanding the nature of the intramolecular forces involved in nonbonded interactions. The area of molecular internal motions and conformation is an active one in microwave spectroscopy, and further advances in our understanding can be expected. Recent improvements in microwave intensity measuring techniques and overall technology should substantially aid in this endeavor by making it much easier to obtain accurate relative energies for different conformations and for vibrational spacings.

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Thallium in Organic Synthesis

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Thallium was discovered in 1861 almost simultaneously by Sir William Crookes and by the French chemist Lamy. It is a soft white metal, slowly oxidized by air or water at room temperature, but rapidly at 100°. It is unique among the group IIIb metals in possessing a stable 1+ oxidation state; interplay between the 1+ and 3+ states forms the basis for much of the chemistry to be described in this review.

Although inorganic thallium salts are generally more stable in the lower oxidation state, organothallium compounds are usually stable only in the 3+ oxidation state; cyclopentadienylthallium appears to be the only stable organothallium compound with an oxidation state of 1+.

For an element relatively unknown to organic chemists, thallium is surprisingly abundant. Recent estimates, in fact, place its abundance in the earth's crust at about 1 g/metric ton, a figure somewhat higher than that for several more commonly known metals such as mercury, antimony, bismuth, cadmium, and silver.[1] The metal is prepared commercially as a by-product from the smelting of lead and zinc ores, and is also found in "flue dust" along with cadmium, indium, selenium, and tellurium. It is supplied commercially in a wide variety of thallium(I) salts, a few thallium(III) salts, and, in rod form, as the metal itself.

(1) C. A. Hampel, "The Encyclopedia of the Chemical Elements," Reinhold, New York, N. Y., 1968.

Some physical properties of thallium metal are summarized in Table I.

Table I
Thallium[1]

Atomic weight	204.37
Atomic number	81
Electronic configuration	(Xe) $6s^2 5d^{10} 4f^{14} 6p^1$
Density at 20°, g/cm³	11.85
Mp, °C	303
Bp, °C	1437
Isotopes	^{203}Tl (spin 1/2), 29.5%
	^{205}Tl (spin 1/2), 70.5%
Oxidation potentials[2]	$Tl \rightarrow Tl^+ + e^-$; $E^\circ = 0.3363$
	$Tl^+ \rightarrow Tl^{3+} + 2e^-$; $E^\circ = -1.25$

Thallium is also unique in group IIIb as the only soft acid on the hard acid–soft base classification of Pearson.[3,4] Both thallium(I) and thallium(III) are soft acids, with thallium(III) definitely softer than thallium(I). Thus, thallium(I) would be expected to show properties characteristic of both silver(I) (soft acid) and potassium(I) (hard acid), which is found to be the case. By contrast, thallium(III) resembles mercury(II) and lead(IV) (soft acids) rather than aluminum(III) (hard acid).

(2) W. M. Latimer, "Oxidation Potentials," Prentice-Hall, Englewood Cliffs, N. J., 1964.
(3) R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963).
(4) R. G. Pearson, *Science*, **151**, 172 (1966).

Toxicity

Thallium and its compounds are extremely toxic[5,6] and must be handled with care. Rubber gloves should be worn at all times, operations conducted in a hood, and good housekeeping rules enforced (scrubbed bench tops, clean laboratory coats, etc.). There is extensive medical literature[7] on thallotoxicosis because of the former widespread availability of thallium-containing rodenticides and insecticides (now illegal in the United States), and antidotes for acute thallium poisoning have been described.[8] Although thallium is classed as a cumulative poison, as are lead and mercury, it is gradually excreted from the body as a result of soft-tissue turnover; persons showing signs of thallium intoxication should avoid further contact with the metal or its compounds until urine tests[9-11] for the presence of thallium are negative.

Applications to Organic Synthesis

There is an extensive literature dealing with inorganic,[12] analytical,[13] and organometallic[14] aspects of thallium, but little work has been done which is of interest to the organic chemist, and there have been few applications of thallium chemistry to organic synthesis. The utility of thallium(III) acetate as a specific oxidant has only recently been assessed;[15] no other thallium reagents have found widespread use. This is surprising in view of the ready accessibility of thallium and the existence in the literature of a number of intriguing reports of unusual and unexpected chemical reactions involving thallium intermediates.[12,14]

We propose in this review to summarize some of the applications of thallium and thallium compounds to organic synthesis which we have investigated in our laboratories in Princeton and the University of East Anglia during the past 3 years.

Thallium(0)

Synthesis of Azoxy Compounds. The literature is virtually devoid of descriptions of direct applications of thallium metal to organic synthesis. Some years ago McHatton and Soulal[16] reported that several aromatic nitro compounds could be converted to azoxy compounds by treatment with thallium foil or pyrophoric thallium in ethanol for prolonged periods (usually 14–28 days). In the course of investigations of the interaction of thallium reagents with nitro compounds, we reinvestigated the reaction between aromatic nitro compounds and metallic thallium. In contrast to the report of McHatton and Soulal, we found[17] that commercial thallium selectively, rapidly, and efficiently reduces nitro compounds to azoxy compounds in refluxing ethanol (eq 1) (see Table II). This is a

Table II
Representative Conversions of Nitrobenzenes to Azoxybenzenes

Nitro compd	Azoxy compd	Yield, %
Nitrobenzene	Azoxybenzene	76
4-Nitrotoluene	4,4′-Dimethylazoxybenzene	77
2-Nitrobiphenyl	2,2′-Diphenylazoxybenzene	84
3-Chloronitrobenzene	3,3′-Dichloroazoxybenzene	84
2-Nitroanisole	2,2′-Dimethoxyazoxybenzene	80

$$2ArNO_2 + 6Tl + 6C_2H_5OH \longrightarrow Ar{-}\overset{+}{N}(O^-){=}N{-}Ar + 6TlOC_2H_5 + 3H_2O \quad (1)$$

remarkable reaction, for thallium does not react with ethanol in the absence of an oxidizing agent. Furthermore, thallium(I) ethoxide does not reduce either nitro or azoxy compounds. We suggest on the basis of these results that further investigation of thallium metal as a reducing agent is warranted.

Thallium(I)

Alkylation of 1,3-Dicarbonyl Compounds. Thallium(I) hydroxide and ethoxide have been used sporadically as bases for alkylations of phenols[18,19] and some 1,3-dicarbonyl compounds,[18] for the preparation of carboxylic acid esters,[18] and for methylations of polyhydroxy compounds, particularly sugars and polysaccharides.[20] In connection with other studies, we reexamined the utility of thallium(I) salts of β-dicarbonyl compounds in alkylation reactions and found that these salts possess unique properties as alkylation substrates. The salts themselves are prepared by addition of thallium(I) ethoxide to an ethanol or heptane solution of the β-dicarbonyl compounds and are obtained in quantitative yield as colorless, crystalline, light-insensitive, indefinitely stable, sharp-melting solids.[21]

We have found that heating these thallium(I) salts with alkyl iodides results in regiospecific C-alkylation in virtually quantitative yield.[22] Some representative alkylations are summarized in Table III. It is striking

(5) E. C. Browning, "Toxicity of Industrial Metals," Butterworths, London, 1961.
(6) A. Christie, "The Pale Horse," William Collins and Sons, Ltd., London, 1961.
(7) O. Grunfeld and G. Hinostroza, *Arch. Int. Med.*, **114**, 132 (1964).
(8) H. Heydlaug, *Eur. J. Pharm.*, **6**, 340 (1969).
(9) W. J. Wilson, Jr., and R. Hausman, *J. Lab. Clin. Med.*, **64**, 154 (1964).
(10) G. D. Christian and W. C. Purdy, *Amer. J. Clin. Path.*, **46**, 185 (1966).
(11) F. M. Farhan, J. Eyvani, and J. Atabakhsh, *Toxicol. Appl. Pharmacol.*, **15**, 493 (1969).
(12) J. W. Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Vol. V, Longmans, Green and Co., Ltd., London, 1924.
(13) I. M. Korenman, "Analytical Chemistry of Thallium," Oldbourne Press, London, 1963.
(14) A. N. Nesmeyanov and A. Sokolik, "Methods of Elemento-Organic Chemistry. Vol. 1. The Organic Compounds of Boron, Aluminum, Gallium, Indium and Thallium," North Holland Publishing Co., Amsterdam, 1967.
(15) For leading references, see (a) A. South, Jr., and R. J. Ouellette, *J. Amer. Chem. Soc.*, **90**, 7064 (1968); (b) W. Kitching, *Organometal. Chem. Rev., Sect. A*, **3**, 61 (1968).
(16) L. P. McHatton and M. J. Soulal, *J. Chem. Soc.*, 4095 (1953).
(17) A. McKillop, R. A. Raphael, and E. C. Taylor, *J. Org. Chem.*, **35**, 1670 (1970).
(18) C. M. Fear and R. C. Menzies, *J. Chem. Soc.*, 937 (1926).
(19) G. H. Christie and R. C. Menzies, *ibid.*, 2369 (1925).
(20) R. C. Menzies, *ibid.*, 1378 (1947).

Table III
Mono-C-alkylation of Thallium(I) Salts of β-Dicarbonyl Compounds

Tl(I) salt of	Yield, %, with CH_3I	CH_3CH_2I	$(CH_3)_2CHI$
Ethyl acetoacetate	100	100	91
Acetylacetone	100	93	90
2-Carbethoxycyclopentanone	100	100	96
Ethyl benzoylacetate	100	100	99
Ethyl 2-methylbenzoylacetate	100	92	93

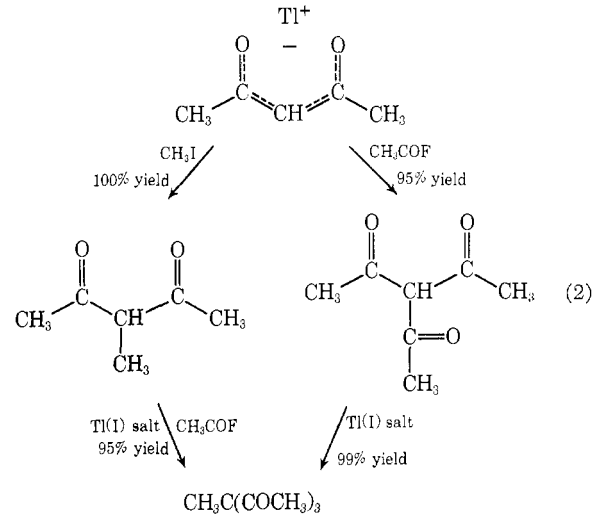
that *none* of the usual side reactions accompanying alkylation of alkali metal salts of ambident anions is observed (dialkylation, O-alkylation, β-keto cleavage, oxidative coupling, Claisen condensations, etc.).

The crystal structure of a representative thallium(I) salt (acetylacetonatothallium(I)) has been determined;[22] the oxygen and thallium atoms are located within the interior of the crystal with a consequent exposure of the carbon backbone of acetylacetone units at the crystal surface. It is thus attractive to postulate that the extraordinary specificity observed in the above alkylations may be directly related to the crystal structure of the thallium complexes and to the rigid geometry imposed on the transition states for alkylation as a consequence of the tetragonal-pyramidal structure of the tetracoordinate thallium complex. Clearly heterogeneity is a critical requirement for specificity; alkylations *in solution* give complex product mixtures analogous to those normally observed with alkali metal salts.

Acylation of 1,3-Dicarbonyl Compounds. The thallium(I) salts of β-dicarbonyl compounds may be acylated as well as alkylated, and this reaction can be controlled to give O- or C-acylation (see Table IV).[22] For example, treatment of an ethereal suspension of the thallium(I) salt of acetylacetone with acetyl chloride at −78° gives the enol acetate in >90% yield, while treatment with acetyl fluoride at room temperature gives triacetylmethane in >95% yield. Conversion of the latter compound to its thallium(I) salt followed by alkylation with methyl iodide gives 1,1,1-triacetylethane in an overall yield of >95%. The same compound

Table IV
Acetylation of Thallium(I) Salts of β-Dicarbonyl Compounds

Thallium(I) salt of	Yield, %, of *O*-Acetyl derivative	*C*-Acetyl derivative
Ethyl acetoacetate	90	95
Acetylacetone	90	95
2-Carbethoxycyclopentanone	90	95
Ethyl benzoylacetate	90	98
3-Methylpentane-2,4-dione	95	95



(2)

may alternately be prepared by alkylation of the thallium(I) salt of acetylacetone to give 3-methylpentane-2,4-dione, which, as its thallium(I) salt, is C-acetylated with acetyl fluoride (eq 2). The flexibility of these procedures for the preparation of previously inaccessible, highly reactive but simple molecules is illustrated by the C-acetylation of the thallium(I) salt of triacetylmethane to give tetraacetylmethane.

Alkylation, Acylation, Aroylation, and Tosylation of Phenols. We have examined the reaction of thallium(I) ethoxide with a wide diversity of acidic compounds and have found, as expected, that salts are formed with compounds with $pK_a < 20$. These salts may generally be alkylated, acylated, aroylated, or tosylated by treatment of a suspension of the salt in ether or chloroform with the appropriate reagent at room temperature. Thus, treatment of thallium(I) salts of phenols with acid chlorides leads to quantitative yields of acylated or aroylated phenols; we believe this to be the method of choice for their preparation.[23] Tosylation may also be effected in virtually quantitative yield by addition of tosyl chloride to a suspension of the thallium(I) salt of the phenol in dimethylformamide.[23]

Synthesis of Anhydrides. An extremely efficient and mild synthesis of symmetrical and unsymmetrical acid anhydrides consists of treatment of thallium(I) carboxylates with 1 equiv of an acid halide. Filtration of thallium(I) halide and evaporation of the solvent give the anhydride in quantitative yield. This method, which employs stoichiometric amounts of both reactants and proceeds quantitatively at room temperature (or below), probably utilizes the minimal conditions requisite for mixed anhydride formation and preservation.[23] An alternate and even simpler synthesis of symmetrical anhydrides consists of addition of 1 equiv of thionyl chloride to a suspension of the thallium(I) carboxylate in ether; the intermediate diacyl or diaroyl sulfite spontaneously loses sulfur dioxide, and evaporation of the ether gives the anhydride in 96–98% yield (eq 3).[23]

$$2RCO_2^-Tl^+ + SOCl_2 \longrightarrow [RCOOSOOCOR] \longrightarrow (RCO)_2O + SO_2 + 2TlCl \quad (3)$$

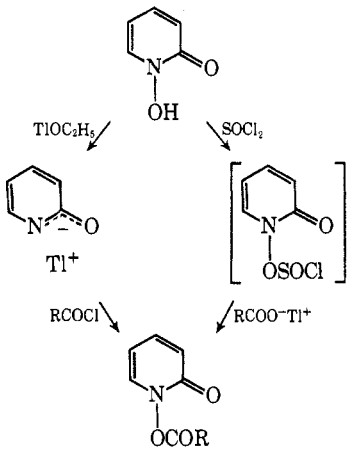
(21) Thallium(I) ethoxide is readily prepared by reaction of thallium sponge with ethanol in the presence of oxygen (G. Brauer, Ed., "Handbook of Preparative Inorganic Chemistry," Vol. 1, 2nd ed, Academic, New York, N. Y., 1963, p 877). It is a dense, colorless liquid at room temperature (mp about 3°) which decomposes above 100° and, as a consequence of its covalent tetrameric structure (L. F. Dahl, G. L. Davis, D. L. Wampler, and R. West, *J. Inorg. Nucl. Chem.*, **24**, 357 (1962)), is soluble in a wide range of polar and nonpolar organic solvents including benzene and heptane. It is thus an extremely useful reagent for effecting base-catalyzed reactions in homogeneous solution in nonpolar solvents. Thallium(I) ethoxide is now commercially available from a number of suppliers.

(22) E. C. Taylor, G. H. Hawks, III, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2421 (1968).

(23) E. C. Taylor, G. W. McLay, and A. McKillop, *ibid.*, **90**, 2422 (1968).

Acylation and Alkylation of Heterocyclic Amides. Synthesis of Active Esters. 1-Acyloxy-2(1*H*)-pyridones have been shown by Paquette to be useful, extremely reactive active esters which he has successfully applied to the synthesis of a number of peptides.[24] We have devised an alternate synthesis of these active esters which proceeds quantitatively at room temperature and consists of treatment of the thallium(I) salt of 1-hydroxy-2(1*H*)-pyridone in ether suspension with an acid chloride. An alternate synthesis which permits the direct conversion of a carboxylic acid to the active ester without the intermediacy of the acid chloride consists of treatment of the thallium(I) carboxylate with 1-chlorosulfonyloxy-2(1*H*)-pyridone (prepared *in situ* by treatment of a chloroform solution of 1-hydroxy-2-(1*H*)-pyridone with thionyl chloride; Scheme I).[25]

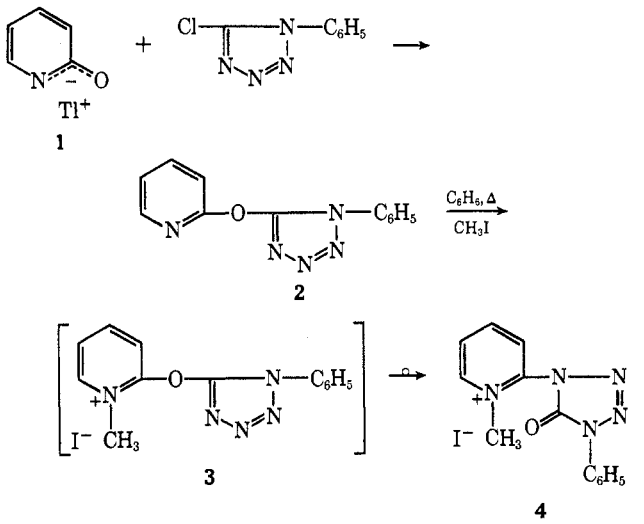
Scheme I



The thallium(I) salts of heterocyclic amides (*e.g.*, 2(1*H*)-pyridone) may likewise be regiospecifically acylated, aroylated, tosylated, or alkylated. For example, 2-acyloxy- and 2-aroyloxypyridines are readily prepared in quantitative yield at room temperature by treatment of the thallium(I) salt of 2(1*H*)-pyridone with acyl or aroyl chlorides.[26,27]

A major problem in heterocyclic chemistry which has yet to find a satisfactory general solution is a method for the direct conversion of heterocyclic amides (*e.g.*, 2(1*H*)-pyridone) to heterocyclic amidines (*e.g.*, 2-aminopyridine). During the course of our studies on the acylation of the thallium(I) salt of 2(1*H*)-pyridone (**1**), we discovered a new reaction which may provide a solution to this problem.[27] Treatment of **1** with 1-phenyl-5-chlorotetrazole gave the ether **2**. Treatment of this latter compound with methyl iodide in refluxing benzene gave the pyridinium salt **4**, in which the original carbon–oxygen bond present in 2(1*H*)-pyridone has been replaced by a carbon–nitrogen bond. The overall reaction is thus a Chapman rearrangement[28] of the initially formed quaternary salt **3**, but effected under the mildest conditions yet reported for such an isomerization (see Scheme II). We are now

Scheme II



investigating the generality of such Chapman rearrangements in heterocyclic systems and their application to the solution of the above synthetic problem.

Alkylation of thallium(I) salts of heterocyclic amides takes place exclusively on nitrogen, at least in the ring systems thus far examined. Although the nature of the product therefore may not differ from that produced by alkylation of alkali metal salts, the experimental simplicity of the thallium(I) salt procedure frequently recommends it as the method of choice. For example, alkylation of phenanthridone previously required formation of the potassium salt by fusion with solid potassium hydroxide, followed by treatment in a sealed tube at elevated temperatures with alkyl halides.[29] By contrast, the thallium(I) salt of phenanthridone is smoothly alkylated with alkyl halides at room temperature.[30]

Alkylation of Purines. Thallium(I) salts of purines are readily obtained on addition of thallium(I) ethoxide to a solution of the purine in ethanol or DMF, and have been found to undergo alkylation exclusively at position 9. Several nucleosides have already been prepared in this way, and we have suggested that the ease of formation, stability, high purity, solubility, and reactivity of purine thallium(I) salts, coupled with the observed regiospecific alkylation at position 9, may make them attractive intermediates for the synthesis of nucleosides[31] (see Scheme III).

Synthesis of Primary Alkyl Bromides. Thallium(I) carboxylates are useful substrates for the Hunsdiecker reaction; typical yields of primary alkyl bromides prepared in this way from *n*-alkanoic acids are given in Table V.[32] This modification of the Hunsdiecker re-

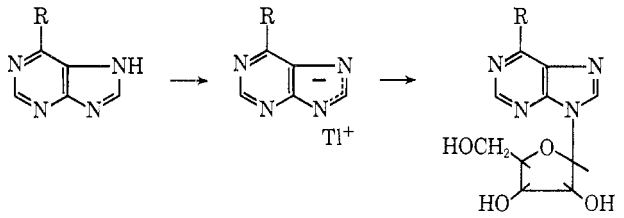
(24) L. A. Paquette, *J. Amer. Chem.*, **87**, 5186 (1965).
(25) E. C. Taylor, F. Kienzle, and A. McKillop, *J. Org. Chem.*, **35**, 1672 (1970).
(26) A. McKillop, M. J. Zelesko, and E. C. Taylor, *Tetrahedron Lett.*, 4945 (1968).
(27) M. J. Zelesko, Ph.D. Thesis, Princeton University, 1969.
(28) J. W. Schulenberg and S. Archer, *Org. Reactions*, **14**, 1 (1965).
(29) C. Graebe and C. A. Wander, *Justus Liebigs Ann. Chem.*, **276**, 245 (1893).
(30) E. C. Taylor, M. J. Zelesko, R. H. Danforth, and A. McKillop, manuscript in preparation.
(31) E. C. Taylor, Y. Maki, and A. McKillop, *J. Org. Chem.*, **34**, 1170 (1969).
(32) A. McKillop, D. Bromley, and E. C. Taylor, *ibid.*, **34**, 1172 (1969).

Table V
Hunsdiecker Reaction of Thallium(I) Carboxylates with Bromine

$$2RCO_2^-Tl^+ + 3Br_2 \longrightarrow 2RBr + 2CO_2 + Tl_2Br_4$$

Tl(I) salt of	Product	Yield, %
$CH_3(CH_2)_6COOH$	$CH_3(CH_2)_6Br$	98
$CH_3(CH_2)_8COOH$	$CH_3(CH_2)_8Br$	89
$CH_3(CH_2)_{12}COOH$	$CH_3(CH_2)_{12}Br$	92
$CH_3OOCCH_2CH_2COOH$	$CH_3OOCCH_2CH_2Br$	86

Scheme III



R = H, Cl, NH_2

reaction has as its major advantage the ease of formation, purity, and stability of the intermediate thallium(I) carboxylates.

Coupling of Grignard Reagents. Synthesis of Biphenyls. By-products of many of the above reactions are thallium(I) halides; thallium(I) bromide has been found to be an extremely effective reagent for the preparation of biaryls from aromatic Grignard reagents (see Table VI).[33] This deceptively simple reaction

Table VI
Representative Couplings of Aromatic Grignard Reagents with TlBr

Grignard reagent from	Biaryl	Yield, %
Bromobenzene	Biphenyl	92
3-Bromotoluene	3,3′-Dimethylbiphenyl	97
4-Bromofluorobenzene	4,4′-Difluorobiphenyl	77
4-Bromoanisole	4,4′-Dimethoxybiphenyl	99
2-Bromonaphthalene	2,2′-Binaphthyl	84

actually consists of a complex series of redox reactions involving all three of the stable oxidation states of thallium (Scheme IV). This was our first introduction to thallium(III) chemistry.

Scheme IV

$$ArMgBr + TlBr \longrightarrow ArTl + MgBr_2$$
$$ArTl + 2TlBr \longrightarrow ArTlBr_2 + 2Tl$$
$$ArTlBr_2 + ArTl \longrightarrow ArAr + 2TlBr$$
$$ArTlBr_2 + ArMgBr \longrightarrow ArAr + TlBr + MgBr_2$$
$$2ArTlBr_2 \longrightarrow Ar_2TlBr + TlBr_3$$
$$Ar_2TlBr + ArMgBr \longrightarrow ArAr + ArTl + MgBr_2$$

Thallium(III)

Selective Bromination of Aromatic Compounds. Catalysis of Friedel–Crafts Reactions. The Lewis acid properties of thallium(III) compounds have not been extensively investigated. Thallium(III) halides are known to catalyze Friedel–Crafts reactions[34] and electrophilic aromatic chlorination[35a–c] and bromination.[34b,35d] These reactions, however, proceeded in low yield, almost certainly as a consequence of the inherent instability of the thallium(III) halides employed.

We have found that thallium(III) acetate is a superb catalyst for the controlled bromination of a wide diversity of aromatic substrates (see Table VII).[36]

Table VII
Representative Aromatic Brominations with $Tl(OOCCH_3)_3$–Br_2

Aromatic substrate	Product	Yield, %
Anisole	4-Bromoanisole	91
Fluorobenzene	4-Bromofluorobenzene	70
Biphenyl	4-Bromobiphenyl	93
Fluorene	2-Bromofluorene	96
Biphenylene	2-Bromobiphenylene	88

Bromination is effected by slow addition of a solution of bromine in carbon tetrachloride to a stirred suspension of thallium(III) acetate in carbon tetrachloride containing the aromatic substrate. In contrast to the majority of electrophilic aromatic bromination procedures, this technique results in the formation of a single, pure monobromo isomer. Moreover, only para bromination of monosubstituted benzenes is observed.

These results are best accommodated by assuming the intermediacy of a highly ordered aromatic substrate–bromine–thallium(III) acetate complex where the orientation of substitution is determined by the steric bulk of the complexed electrophile. Furthermore, preliminary kinetic investigations of this reaction suggest that the complexed electrophile is only slightly more reactive than molecular bromine. Consequently, dibromination under the reaction conditions is not observed.

Research in progress indicates that thallium(III) acetate is also a useful Friedel–Crafts catalyst. For example, anisole is smoothly converted to *p*-acetylanisole in 80% yield at room temperature in carbon tetrachloride by a mixture of thallium(III) acetate and acetyl chloride. An intermediate complex analogous to that suggested in the bromination above may be involved, since only para substitution has thus far been observed with monosubstituted benzenes.

Electrophilic Thallation of Aromatic Compounds. Our early speculations on the mechanism of the thallium(III) acetate catalyzed aromatic bromination discussed above included the possibility that thallation (analogous to the well-known mercuration reaction) might have been involved, as suggested in eq 4. Sub-

$$ArH \overset{?}{\dashrightarrow} ArTl(OOCCH_3)_2 \overset{?}{\dashrightarrow} ArBr \qquad (4)$$

sequent investigations disproved this possibility but led

(33) A. McKillop, L. F. Elsom, and E. C. Taylor, *J. Amer. Chem. Soc.*, **90**, 2423 (1968).

(34) (a) L. I. Kashtanov, *J. Gen. Chem. USSR*, **2**, 515 (1932); (b) G. A. Olah in "Friedel-Crafts and Related Reactions," Vol. 1, G. A. Olah, Ed., Interscience, New York, N. Y., 1963, p 255.

(35) (a) V. Thomas, *C. R. Acad. Sci.*, **144**, 32 (1907); (b) A. G. Page, *Justus Liebigs Ann. Chem.*, **225**, 196 (1884); (c) C. Willgerodt, *J. Prakt. Chem.*, **34**, 264 (1886); (d) L. Bruner, *Bull. Acad. Sci. Cracow*, 22 (1901); *J. Chem. Soc. Abstr.*, **80**, 441 (1901).

(36) A. McKillop, D. Bromley, and E. C. Taylor, *Tetrahedron Lett.*, 1623 (1969).

us to examine both the process of thallation itself and the potential utility of the resulting organothallium compounds as synthetic intermediates.

The first successful thallation of an aromatic substrate was described by Gilman and Abbott, who prepared bis(4-dibenzofuryl)thallium chloride in 9% yield by treatment of dibenzofuran with thallium(III) chloride at 165°.[37] The only other previously described thallation procedure involved the use of thallium(III) triisobutyrate, which was heated at elevated temperatures in an excess of benzene or an activated aromatic substrate to yield arylthallium diisobutyrates in moderate yield.[38]

Mercury(II) trifluoroacetate is a much more reactive electrophilic species than mercury(II) acetate,[39] and we reasoned that an analogous potentiation of the electrophilic properties of thallium(III) might be observed with thallium(III) trifluoroacetate, as compared with thallium(III) triisobutyrate. Not only have these expectations been fully realized, but the organothallium derivatives prepared using this reagent promise to be important new intermediates in aromatic substitution reactions.

Thallium(III) trifluoroacetate (hereafter referred to as TTFA) is conveniently prepared by heating under reflux a suspension of thallium(III) oxide in trifluoroacetic acid (TFA). The resulting solution of TTFA in TFA constitutes a powerful reaction mixture for the direct thallation of organic compounds. Reaction with substrates which are activated toward electrophilic substitution is generally complete within a few minutes at room temperature. Thallation of mildly deactivated substrates such as the halobenzenes requires longer reaction times at room temperature or short heating, while deactivated substrates such as benzoic acid require heating under reflux for several hours.[40]

The products obtained from the above thallations (see Table VIII) are arylthallium ditrifluoroacetates, which often crystallize directly from the reaction mixture. They are stable, colorless, crystalline solids which in general are soluble in methanol, ethanol, glyme, acetonitrile, tetrahydrofuran, and DMSO. The orientation of the thallium substituent in these arylthallium ditrifluoroacetates can readily be determined by examination of their well-defined nmr spectra. In benzene and substituted benzenes, Tl–H coupling constants are approximately 130 times greater than the corresponding H–H coupling constants.[41] Figure 1 is representative; the very large differences in the coupling constants for Tl–*o*-H (~1000 Hz), Tl–*m*-H (~400 Hz), and (where applicable) Tl–*p*-H (~115 Hz) make possible the unambiguous determination of the orientation of the carbon–thallium bond.

(37) H. Gilman and R. K. Abbott, Jr., *J. Amer. Chem. Soc.*, **65**, 122 (1943).
(38) (a) V. P. Glushkova and K. A. Kocheshkov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1211 (1957); (b) see ref 14, pp 571–574.
(39) H. C. Brown and R. A. Wirkkala, *J. Amer. Chem. Soc.*, **88**, 1447, 1453 (1966).
(40) A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2423 (1969).
(41) M. P. Maher and D. F. Evans, *J. Chem. Soc.*, 637 (1965).

Table VIII
Representative Aromatic Thallations with TTFA

$$ArH + Tl(OOCCF_3)_3 \longrightarrow ArTl(OOCCF_3)_2 + 2CF_3COOH$$

Ar	Yield, %
C_6H_5	96
4-$CH_3C_6H_4$	75
4-ClC_6H_4	80
2,4-$(CH_3)_2C_6H_3$	100
2-$COOHC_6H_4$	79

Synthesis of Aromatic Iodides. The stability of $ArTlX_2$ compounds appears to be a direct function of the nature of the X^- ligand. Although arylthallium ditrifluoroacetates are stable, exchange of the trifluoroacetate groups by other X^- groups may lead to unstable species which decompose to give substituted aromatic compounds by cleavage of the carbon–thallium bond. For example, treatment of arylthallium ditrifluoroacetates with aqueous potassium iodide at room temperature results in the instantaneous precipitation of thallium(I) iodide and formation of the corresponding aromatic iodides in high yield. The overall process of thallation followed by treatment with aqueous iodide thus constitutes an extremely simple synthesis of aromatic iodides (see Table IX).[42]

Table IX
Representative Aromatic Iodinations

$$ArTl(OOCCF_3)_2 + 2KI \longrightarrow [ArTlI_2] + 2K^+{}^-OOCCF_3 \longrightarrow ArI + TlI$$

Substrate	Product	Yield, %
Benzene	Iodobenzene	96
tert-Butylbenzene	4-Iodo-*tert*-butylbenzene	93
o-Xylene	4-Iodo-*o*-xylene	98
Mesitylene	Iodomesitylene	94
Benzoic acid	*o*-Iodobenzoic acid	79

Synthesis of Aromatic Nitriles. We have also found that treatment of arylthallium ditrifluoroacetates with excess aqueous potassium cyanide gives the complex ions $[ArTl(CN)_3]^-K^+$, which decompose upon irradiation to give aromatic nitriles (see Table X).[43]

Table X
Representative Syntheses of Aromatic Nitriles

$$ArTl(OOCCF_3)_2 \xrightarrow{\text{aq KCN}} [ArTl(CN)_3]^-K^+ + 2K^+{}^-OOCCF_3 \xrightarrow[h\nu]{} ArCN + TlCN$$

Substrate	Product	Yield, %
Benzene	Benzonitrile	41
Ethylbenzene	4-Cyanoethylbenzene	80
o-Xylene	4-Cyano-*o*-xylene	53
Benzyl methyl ether	2-Cyanobenzyl methyl ether	55
Phenylacetic acid	2-Toluonitrile	33

Synthesis of Thiophenols. In a more complex reac-

(42) A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2427 (1969).
(43) E. C. Taylor, H. W. Altland, R. H. Danforth, G. McGillivray, and A. McKillop, *J. Amer. Chem. Soc.*, **92**, 3520 (1970).

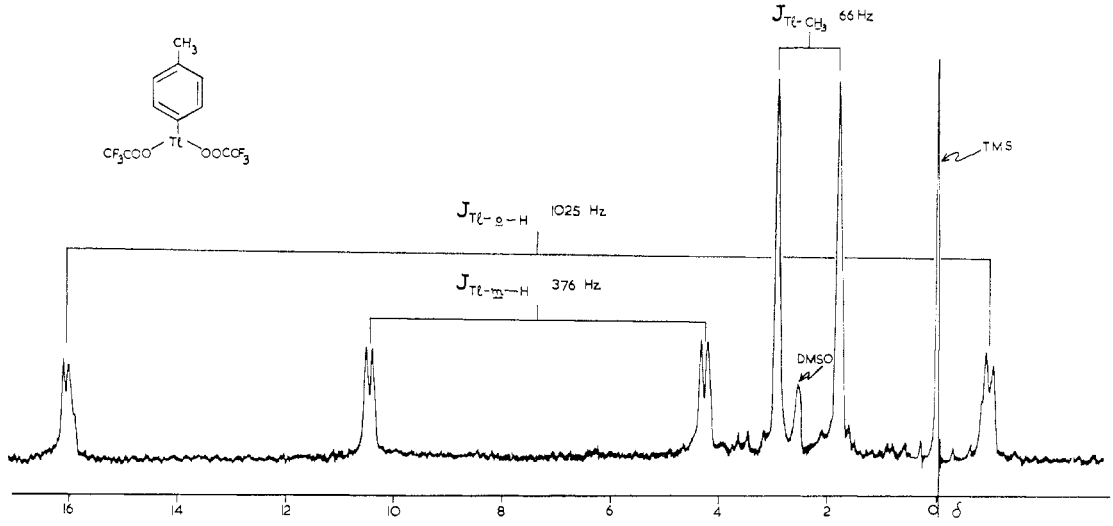
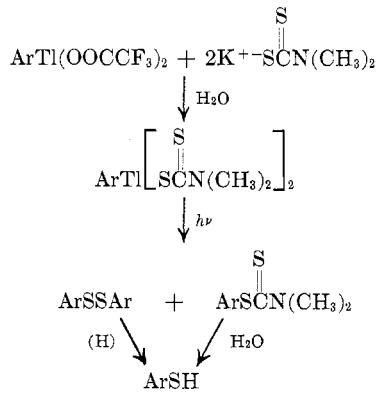


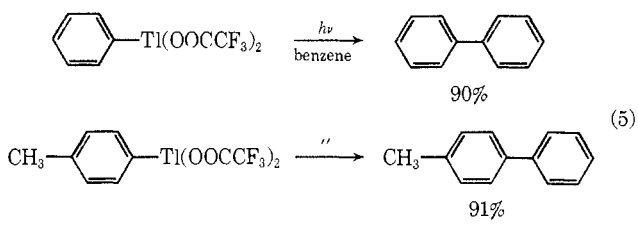
Figure 1. Nmr spectrum of *p*-tolylthallium ditrifluoroacetate in DMSO-d_6 solution at 60 MHz.

Scheme V



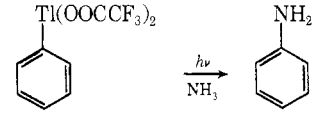
tion sequence, arylthallium ditrifluoroacetates may be converted to thiophenols (Scheme V).[44]

Controlled Synthesis of Symmetrical and Unsymmetrical Biphenyls. The above examples of aromatic nitrile and thiophenol syntheses suggest a photochemical fragility to the carbon–thallium bond in arylthallium ditrifluoroacetates and a consequent wide range of new aromatic substitution reactions. Initial explorations of these possibilities have been extremely promising. Thus, we have found that photolysis of arylthallium ditrifluoroacetates in benzene solution (3000-Å lamps, Rayonet reactor) gives biphenyls in extremely high yields. For example, biphenyl itself is formed by irradiation of phenylthallium ditrifluoroacetate in benzene solution, and 4-methylbiphenyl in analogous fashion from *p*-tolylthallium ditrifluoroacetate (eq 5).[45] This simple reaction is thus a versatile complement to the Kharasch photochemical biphenyl synthesis from aryl iodides,[46] and yields are apparently substantially higher.



(5)

Furthermore, photolysis of phenylthallium ditrifluoroacetate in the presence of ammonia gives aniline (eq 6).[45] We are actively pursuing extensions



(6)

of this reaction with alkyl, aryl, and heterocyclic amines as a new and general synthesis of arylamines.

Synthesis of Phenols. The introduction of a hydroxyl group into benzenoid compounds is, by classical methods, a circuitous sequence of substitution, oxidation, and/or replacement reactions.[47] A new phenol synthesis, utilizing the readily accessible arylthallium ditrifluoroacetates as the key starting materials, and which can be carried out in a single operation, has been developed.[43] Thus, addition of lead tetraacetate to a solution of the thallated compound in TFA, followed by addition of triphenylphosphine and then hydrolytic work-up, gives the phenol (see Table XI). It is not even necessary to isolate the intermediate arylthallium ditrifluoroacetate; the entire operation—thallation, addition of lead tetraacetate and triphenylphosphine, hydrolytic work-up—can be carried out in one reaction vessel, thus making this in effect a one-step phenol synthesis. The presence of activating groups is not required, and the isomer orientation in the resulting phenols is subject to control (*vide infra*).

The direct synthesis of carvacrol from *p*-cymene (eq 7) in >99% isomer purity illustrates not only the synthetic efficiency of this new hydroxylation procedure

(44) E. C. Taylor, M. Ochiai, and A. McKillop, manuscript in preparation.

(45) E. C. Taylor, F. Kienzle, and A. McKillop, *J. Amer. Chem. Soc.*, **92**, 6088 (1970).

(46) W. Wolf and N. Kharasch, *J. Org. Chem.*, **30**, 2493 (1965).

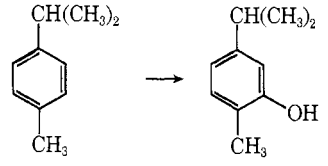
(47) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, New York, N. Y., 1965; direct hydroxylation (with peracids) is possible only with substrates strongly activated toward electrophilic substitution.

Table XI

Representative Phenol Syntheses

$$ArH \xrightarrow{TTFA} [ArTl(OOCCF_3)_2 \xrightarrow[2.\ P(C_6H_5)_3]{1.\ Pb(OOCCH_3)_4} ArOOCCF_3 \xrightarrow[NaOH]{dil}]ArOH$$

Substrate	Product	Yield, %
Benzene	Phenol	39
Toluene	*p*-Cresol	62
o-Xylene	*o*-4-Xylenol	78
m-Xylene	*m*-4-Xylenol	70
p-Xylene	*p*-Xylenol	68
Anisole	4-Hydroxyanisole	41
Chlorobenzene	4-Chlorophenol	56

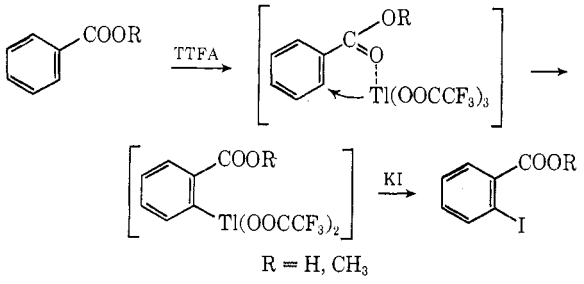


(7)

but also the positional control which can be exercised over electrophilic thallation by steric factors.

Selective Deuteration of Aromatic Compounds. Treatment of arylthallium ditrifluoroacetates with lithium aluminum hydride or aluminum amalgam results in reductive cleavage of the C–Tl bond with regeneration of the aromatic hydrocarbon. Regiospecific introduction of deuterium is thus possible by use of lithium aluminum deuteride or by reduction with aluminum amalgam in D_2O.[48]

Orientation Control. In all of the above syntheses of substituted aromatic compounds from arylthallium ditrifluoroacetates, the new substituent enters the ring at the position previously occupied by thallium. Control over the orientation of thallation, therefore, has as its consequence control over isomer distribution in all of the above aromatic substitution reactions. It is thus of great potential practical significance that thallation can often be controlled, *with the same substrate*, to give selectively ortho, meta, or para substitution.[49] For example, thallation of benzoic acid or methyl benzoate followed by treatment with potassium iodide overwhelmingly leads to *o*-iodo derivatives (eq 8); the



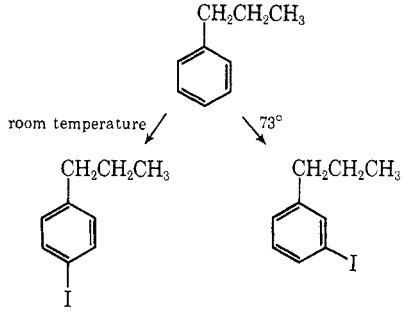
(8)

R = H, CH_3

high ratio of ortho to meta substitution (95:5) is most unusual and is due to the intermediacy of a substrate–electrophile complex which delivers thallium intramolecularly to the ortho position. In a similar manner, benzyl alcohol and benzyl methyl ether give *only* *o*-iodo derivatives. Predominant ortho substitution is also observed with phenylacetic acid and its methyl ester and with 2-phenylethyl methyl ether. In the absence of such complexation between the substrate and the electrophile (TTFA), the kinetically favored reaction is para thallation.

Since thallation,[50] like mercuration,[51] is freely reversible, the orientation of substitution initially dictated by kinetic factors should be susceptible to thermodynamic control, and examination of the reaction pathway for electrophilic substitution predicts that the meta isomer should accumulate in an equilibrium process. Indeed, *n*-propylbenzene, which thallates at room temperature in 91% yield in the para position, gives on heating (refluxing TFA, 73°) 78% of the meta-substituted isomer (see Scheme VI). Similarly,

Scheme VI[a]



[a] Reaction with TTFA–TFA (at temperature indicated), followed by addition of aqueous KI.

cumene gives 94% para substitution at room temperature but 85% meta substitution at 73°.

The potential synthetic utility of these results is illustrated further by the selective conversion of 2-phenylethanol to its *o*-, *m*-, or *p*-iodo isomer. Thallation at room temperature, followed by treatment with aqueous KI, gives predominantly ortho substitution (83%), while thallation at 73° gives predominantly meta substitution (56%). Thallation of the *acetate* of 2-phenylethanol, however (where the distance of the complexed TTFA from the ring has been increased by conversion of OH to $OCOCH_3$), results in predominantly para substitution (84%) (see Scheme VII).

Thus, by appropriate manipulation of conditions, one can control orientation in the initial thallation reaction, and hence isomer distribution in a spectrum of aromatic substitution reactions. Meta substitution is achieved under conditions of thermodynamic control; under conditions of kinetic control, ortho substitution results when chelation of the reagent (TTFA) with the directing substituent permits intramolecular delivery of the electrophile, and para substitution results when such capabilities are absent.

TTFA as an Oxidizing Agent. Synthesis of *p*-Quin-

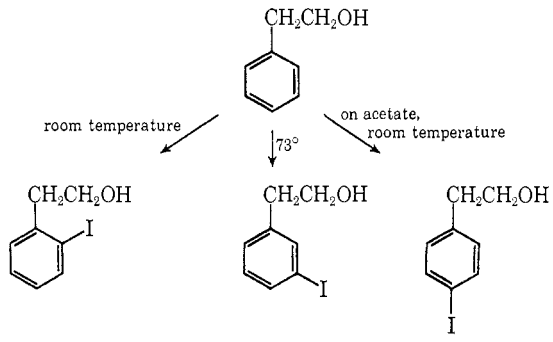
(48) A. McKillop, M. J. Zelesko, J. S. Fowler, and E. C. Taylor, manuscript in preparation.

(49) E. C. Taylor, F. Kienzle, R. L. Robey, and A. McKillop, *J. Amer. Chem. Soc.*, **92**, 2175 (1970).

(50) E. C. Taylor, F. Kienzle, R. L. Robey, A. McKillop, and J. D. Hunt, manuscript in preparation.

(51) M. Malaiyandi, H. Sawatzky, and G. F. Wright, *Can. J. Chem.*, **39**, 1827 (1961).

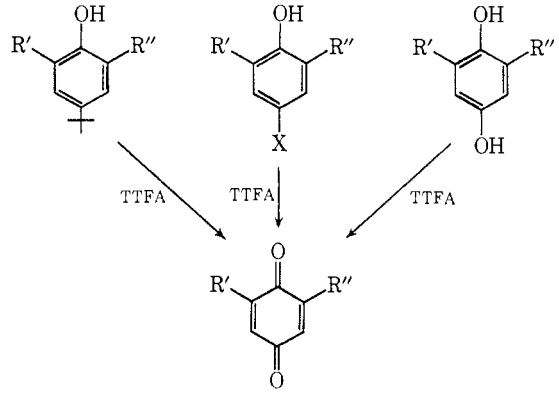
Scheme VII[a]



[a] Reaction with TTFA–TFA (at temperature indicated), followed by addition of aqueous KI.

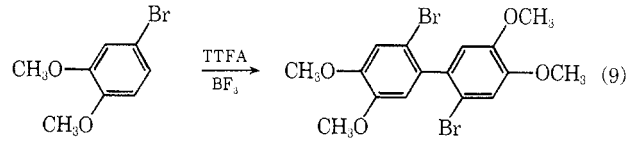
ones and Biphenyls. The utility of TTFA as a reagent is not restricted to thallation. It has been found that TTFA efficiently converts a variety of para-substituted phenols to *p*-quinones (Scheme VIII).[52] Furthermore,

Scheme VIII



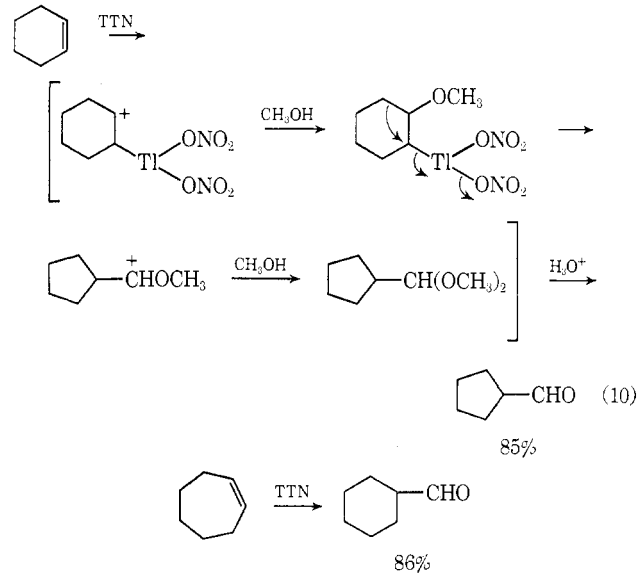
R′ = R″ = alkyl, halogen, etc.
X = halogen, $OOCCH_3$, NR_2, etc.

the reactivity of TTFA as an oxidizing agent can be strongly influenced by the presence of co-reagents. A striking example is found in the reaction of TTFA with aromatic compounds in the presence of boron trifluoride etherate; thallation is inhibited in favor of oxidative coupling. Thus, 4-bromoveratrole is smoothly converted to 2,2′-dibromo-3,3′,4,4′-tetramethoxybiphenyl (eq 9).[53]



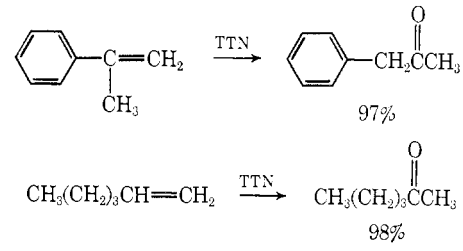
(9)

Oxidative ring contraction of cyclic olefins to aldehydes is remarkably efficient with TTFA in ether or with thallium(III) nitrate (TTN) in methanol; with the latter reagent, the reaction is complete within seconds at room temperature (eq 10).[54] Thallium(III)



(10)

nitrate is also a superior reagent for controlled oxidation of acyclic olefins. Styrenes are converted quantitatively to ketones, with aryl migration; internal olefins are converted to ketones, and terminal olefins to methyl ketones (eq 11). All reactions proceed in-



(11)

stantly at room temperature and in almost quantitative yield.[55]

Investigations thus far of applications of thallium chemistry to organic synthesis would appear to offer some justification for the optimistic predictions expressed more than a century ago by Dumas[56] at the time thallium was first discovered: "Le thallium est destiné à faire époque dans l'histoire de la chimie, par l'etonnant contraste qui se manifeste entre ses caractères chimiques et ses propriétés physiques. Il n'y a pas d'exagération à dire qu'au point de vue de la classification généralement acceptée pour les métaux, le thallium offre une réunion de propriétés contradictoires qui autoriserait à l'appeler le métal paradoxal, l'ornithorrhynque des métaux."

We express our appreciation to our enthusiastic, dedicated, and able coworkers whose efforts contributed so much to the developments described in this review: H. W. Altland, D. Bromley, R. H. Danforth, L. F. Elsom, J. S. Fowler, G. H. Hawks, III, J. D. Hunt, F. Kienzle, J. Klug, Y. Maki, G. McGillivray, G. W. McLay, M. Ochiai, R. A. Raphael, R. L. Robey, B. P. Swann, and M. J. Zelesko.

(52) A. McKillop, B. P. Swann, M. J. Zelesko, and E. C. Taylor, *Angew. Chem., Int. Ed. Engl.*, 9, 74 (1970).
(53) A. McKillop, B. P. Swann, and E. C. Taylor, manuscript in preparation.
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