was heated to reflux for 2.5 h, concentrated by distillation to ca. 20 mL, and then cooled to afford 1.82 g (67% based on ammonium chloride) of 5-cyanouracil-^{15}N (95 atom % ^{15}N). The compound was heated to reflux in 50 mL of 6 N hydrochloric acid for 20 h with a bath temperature of 140 °C, and then concentrated in vacuo. The residue was recrystallized from water to give 1.32 g (60% based on ammonium chloride) of the title compound. The ^{15}N chemical shifts were determined at 30.41 MHz on a Bruker WM-300 with formamide as an internal standard as follows: **1c** (Me_2SO-d_6), N_1 = −22.9 ppm, N_3 = 32.6 ppm; **6c** (Me_2SO-d_6), 57.1 ppm; **21c** ($CDCl_3$), N_1 = 0.97 ppm, N_3 = 35.8 ppm. We thank Dr. Charles Cottrell for these measurements.

General Procedure for Kinetics. For all kinetic runs, the solutions of **6c** and **21c** were prepared in volumetric flasks at room temperature. Base solutions were prepared immediately prior to use by dissolving freshly cut potassium in *tert*-butyl alcohol distilled from sodium. This standard solution was titrated with 1.004 M sulfuric acid by using phenolphthalein as an indicator. The required amount of each solution was transferred via syringe to a stoppered flask and diluted to the desired concentration with the appropriate amount of *tert*-butyl alcohol. Aliquots from this stock solution were then sealed into ampules and placed in a constant temperature bath. The ampules were pulled from the bath at appropriate time intervals so that most points would be recorded within the first 3 half-lives of the reaction. The ampules were labeled and placed in a dry ice/2-propanol bath to quench the reaction. The ampules were then warmed to room temperature in a water bath and analyzed by removing an aliquot (40 μL) and diluting it in 2.5 mL of 0.5 N sulfuric acid. Spectrophotometric analysis at 268 nm gave the concentration of the product pyridone.

The data for all kinetics are summarized in Figures 1 and 2. The correlation coefficients for the slopes in Figure 1 are 0.999, 0.996, and 0.999, respectively. Likewise, the correlation coefficients for the slopes in Figure 2 are 0.995, 0.998, and 0.988, respectively.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Registry No. **1a**, 66-22-8; **1f**, 65-71-4; **1h**, 51-21-8; **1k**, 59523-07-8; **2a**, 74-99-7; **2b**, 627-19-0; **2c**, 628-71-7; **2d**, 503-17-3; **2e**, 928-49-4; **2i**, 693-02-7; **3a**, 72323-49-0; **3b**, 72323-51-4; **3c**, 72323-52-5; **3d**, 72323-50-3; **3e**, 85995-55-7; **3f**, 85995-56-8; **3g**, 72323-55-8; **3h**, 72323-53-6; **3i**, 85995-59-1; **3j**, 72323-54-7; **3k**, 85995-57-9; **3l**, 85995-58-0; **4**, 85995-62-6; **5**, 86023-36-1; **6a**, 1003-68-5; **6b**, 72323-57-0; **6c**, 72323-58-1; **6d**, 72323-56-9; **6e**, 85995-60-4; **6f**, 36330-90-2; **6g**, 72323-61-6; **6h**, 72323-59-2; **6j**, 72323-60-5; **6k**, 85995-61-5; **7h**, 72323-62-7; **7j**, 72323-63-8; **21c**, 85995-63-7; **21i**, 85995-64-8; **21k**, 85995-65-9; uracil-$^{13}C_2$, 35803-45-3; uracil-^{15}N, 85995-66-0.

Ruthenium Tetroxide Catalyzed Oxidations of Aromatic and Heteroaromatic Rings

Masaji Kasai[1] and Herman Ziffer*

Laboratory of Chemical Physics, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20205

Received November 9, 1982

In order to determine the absolute stereochemistry of several aromatic and heterocyclic alcohols, it was necessary to oxidize protected derivatives to mono- and dicarboxylic acids of established configuration. A recently improved procedure utilizing aqueous sodium periodate in the presence of catalytic quantities of ruthenium tetroxide has been used to oxidize a number of compounds to the desired acids in satisfactory yield. The oxidations of (−)-α-(2-thienyl)ethyl acetate, (−)-α-(2-furyl)ethyl acetate, and several substituted α-phenylethyl acetates to (*S*)-*O*-acetyllactic acid have been used to confirm their absolute stereochemistries. However, α-(2-pyridyl)ethyl acetate was inert, and α-(3-phenanthryl)ethyl acetate yielded a complex reaction mixture. Prior conversion of the pyridine derivative to its *N*-oxide and of the substituted phenanthrene to the 9,10-dibromo derivative permitted each compound to be degraded to *O*-acetyllactic acid.

In the course of a series of studies on the use of microbially mediated reductions[2] and hydrolyses[3] to prepare chiral alcohols of a predictable absolute stereochemistry, it was necessary to employ chemical methods to unambiguously establish the configuration of some of the resulting alcohols. In most cases this was done by protecting the alcohol through esterification or conversion to an ether, followed by exhaustive ozonolysis of the aromatic and heteroaromatic groups present. While the approach is simple in principle, we and others[2a,4,5] have encountered a number of experimental problems. The first of these was the need to separate a number of related mono- and dicarboxylic acid derivatives formed during the ozonolysis; e.g., α-acetoxyglutaric and α-acetoxyadipic acids are obtained together in the ozonolysis of α-tetralyl acetate.[2a,4]

Table I. Oxidation of Benzocycloalkenyl Acetates

	reaction conditions		products	
starting materials	$NaIO_4$, equiv	reaction time, h	yields as esters, %	configurations
(±)-**1a**	15	20	62	(±)-**3a**
(*S*)-**1b**	15	18	47	(*S*)-**3b**
(*S*)-**2a**	18	45	51	(*S*)-**3c**
(*S*)-**2b**	18	69	49	(*S*)-**3d**

(1) On leave from Kyowa Hakko Kogyo Co., Ltd., Tokyo Research Laboratory, 3-6-6, Asahi-machi, Machida-shi, Tokyo, 194, Japan.

(2) (a) Kabuto, K.; Imuta, M.; Kempner, E. S.; Ziffer, H. *J. Org. Chem.* **1978**, *43*, 2357. (b) Imuta, M.; Ziffer, H. *Ibid.* **1978**, *43*, 3530. (c) Kasai, M.; Ziffer, H. *Ibid.* **1983**, *48*, 712.

(3) Kawai, K.; Imuta, M.; Ziffer, H. *Tetrahedron Lett.* **1981**, *22* (no. 27), 2527.

(4) Briaucourt, P.; Guettê, J. P.; Horeau, A. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1972**, *274*, 1203.

(5) Koreeda, M.; Akhtar, M. N.; Boyd, D. R.; Neill, J. D.; Gibson, D. T.; Jerina, D. M. *J. Org. Chem.* **1978**, *43*, 1023.

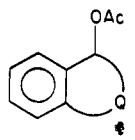
0022-3263/83/1948-2346$01.50/0

Table II. Oxidation of Substituted Aromatic, Heteroaromatic, and Polycyclic Aromatic Acetates

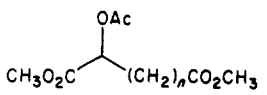
starting materials	reaction conditions: $NaIO_4$, equiv	reaction conditions: reaction time, h	products: yields as esters, %	products: configurations
(*R*)-**4a**	18	39	42	(*R*)-**7**
(*S*)-**4b**	18	63	34	(*S*)-**7**
(±)-**4c**	18	41	recovered	
(±)-**4d**	18	54	recovered	
(*S*)-**4e**	15	44	31	(*S*)-**7**
(*S*)-**4f**	15	40	79	(*S*)-**7**
(±)-**4g**	15	64	recovered	
(±)-**5**	18	64	10	(±)-**7**
(±)-**4h**	30	69	44	(±)-**7**
(±)-**4i**	45	65	~5	(±)-**7**
(±)-**4j**	30	113	~40	(±)-**7**
(±)-**6**	30	72	75	(±)-**8**

The second problem is related to the low yields occasionally obtained; for instance, Koreeda et al.[5] reported that the ozonolysis of 2-methoxy-1,2,3,4-tetrahydrophenanthrene yielded only about 0.5% of the desired β-methoxy dicarboxylic acid. These difficulties prompted us to reexamine the problem and to investigate the suitability, for our purpose, of an improved procedure recently reported by Sharpless et al.,[6] who utilized periodate oxidations catalyzed by ruthenium tetroxide for the conversion of olefins and phenyl groups to carboxyl groups. Although these authors showed that a biphasic mixture of aqueous sodium periodate and carbon tetrachloride containing acetonitrile could be used to oxidize phenylcyclohexane to cyclohexane carboxylic acid in high yield (94%), they did not investigate the oxidation of more complex aromatic systems. Caspi et al.[7] had previously oxidized some aromatic steroids to dicarboxylic acids (with ruthenium tetroxide and sodium periodate) and in addition observed formation of an allylic oxidation product from estradiol diacetate (the steroidal 6-keto aromatic acetate). Further oxidation of the latter could yield a mixture of homologous dicarboxylic acids similar to those obtained from ozonolyses of the aromatic esters.

In an effort to determine whether the Sharpless procedure could be used to oxidize benzocycloalkenyl acetates to the corresponding dicarboxylic acids, the oxidation of **1** and **2** was studied. The results are summarized in Table



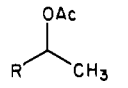
1, Q = $-(CH_2)_n-$
a, $n = 4$
b, $n = 5$
2, Q = $-(CH_2)_nO-$
a, $n = 2$
b, $n = 3$



3
a, $n = 4$
b, $n = 5$
c, $n = 1$
d, $n = 2$

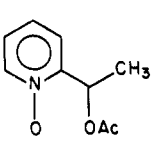
I; they show that the reaction proceeds to give the appropriate α-acetoxy dicarboxylic acid in satisfactory yield. The dicarboxylic acids were not contaminated with the lower homologous compounds as occurs during the ozonolysis of 1-tetralyl acetate. If allylic oxidation occurs, the resulting aromatic ketones are probably not oxidized further (see discussion below on the oxidation of phenanthrene).

We were interested in determining whether heteroaromatic systems could also be oxidized by this reagent. The study was now extended to the oxidation of chiral samples of α-(2-furyl)ethyl acetate, **4e**, and α-(2-thienyl)ethyl acetate, **4f**.[8] Červinka et al.[9] had assigned *S* configurations to (−)-α-(2-furyl)ethyl alcohol and (−)-α-(2-thienyl)ethyl alcohol. They had prepared the (+) enantiomers by asymmetric reduction of the corresponding ketones with $LiAlH_4$ and (−)-quinine and had assigned them *R* configurations by analogy to the products formed in other reductions. Oxidation of the (−) enantiomers by ruthenium tetroxide confirmed these assignments; see Table II.

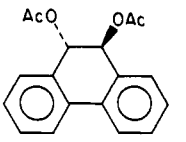


4

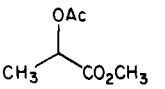
a, R = 4-methylphenyl
b, R = 2,4,6-trimethylphenyl
c, R = 4-nitrophenyl
d, R = 4-(carbomethoxy)phenyl
e, R = 2-furyl
f, R = 2-thienyl
g, R = 2-pyridyl
h, R = 2-naphthyl
i, R = 3-phenanthrenyl
j, R = 9,10-dibromo-9,10-dihydrophenanthren-3-yl



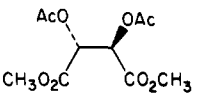
5



6



7



8

In addition to the compounds described above, we also had prepared a chiral sample of 4-acetoxybenzopyran, **2a**, by a microbially mediated reduction[2] followed by acetylation. The absolute stereochemistry of this compound had not been previously assigned, and a ruthenium tetroxide catalyzed oxidation appeared suitable to degrade this compound to α-acetoxysuccinic acid, simultaneously oxidizing the aromatic ring and the methylene group bearing the ether oxygen to carboxyl groups. The oxidation proceeded in good yield to 2(*S*)-acetoxysuccinic acid, establishing the configuration of the microbial reduction product as *S*. When we attempted to oxidize α-(2-pyridyl)ethyl acetate, the color change associated with oxidation—i.e., formation of black ruthenium dioxide that is then slowly reoxidized to the tetroxide—did not occur. This was surprising, since Ayres[10] had reported that the corresponding benzo derivatives, quinoline and isoquinoline, were oxidized in the absence of acetonitrile. In discussing their improved procedure, Sharpless et al.[6] had suggested that inconsistencies in reports on ruthenium tetroxide oxidations may result from complexes of lower valent ruthenium formed during the reaction. They therefore introduced acetonitrile into the reaction mixture to disrupt such complexes and/or to increase their solubility. We

(6) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(7) Piatak, D. M.; Herbst, G.; Wicha, J.; Caspi, E. *J. Org. Chem.* **1969**, *34*, 116.
(8) Ziffer, H.; Kawai, K.; Kasai, M.; Imuta, M.; Froussios, C. *J. Org. Chem.*, in press.
(9) Červinka, O.; Belovský, O.; Korálová, L. *Z. Chem.* **1969**, *9*, 448.
(10) Ayres, D. C.; Hossain, A. M. M. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 707.

speculated that the 2- and 3-substituted pyridines were not oxidized because of similar complexes and therefore prepared the *N*-oxide of the 2-substituted compound, **5**, to decrease the ability of the nitrogen to complex with ruthenium. The *N*-oxide was oxidized to *O*-acetyllactic acid, albeit in low yield (Table II).

Oxidation of α-(3-phenanthryl)ethyl acetate by ruthenium tetroxide yielded the corresponding 9,10-quinone and a derivative of diphenic acid along with small quantities of a host of other products. Djerassi and Engle[11] had previously shown that the major product from the ruthenium tetroxide oxidation of phenanthrene was the 9,10-quinone. Ayres[10] had also reported earlier that phenols were readily oxidized but that the presence of halogens, nitro groups, and other electron-withdrawing substituents markedly reduced their reactivity. A simple extension of Ayres' observations, consistent with the available experimental data, is that the 9,10 double bond of phenanthrene (or the 3-substituted derivative) is readily oxidized to the quinone or to the dicarboxylic acid. The carboxylic acid formed either complexes with the reagent or deactivates the aromatic ring so that it reacts very slowly. In order to provide more data on the effects of substituents, we examined the reactivity of the substituted α-phenylethyl acetates shown in Table II. While substituents such as methyl groups did not appear to affect the yields of *O*-acetyllactic acid, the presence of a nitro group slowed or stopped oxidation with no detectible formation of **7**. The presence of a *p*-carbomethoxy substituent slowed down the oxidation so that after 54 h 65% of the starting material was recovered and **7** formed in approximately 35% yield. Presumably other electron-withdrawing substituents would also slow oxidation of the aromatic ring. It thus appears that if one could prevent formation of an intermediate quinone, the desired oxidation of the 3-substituted phenanthrene could occur. To test this we examined the oxidation of *trans*-9,10-diacetoxy-9,10-dihydrophenanthrene, **6**, which was smoothly oxidized to diacetyltartaric acid in good yield. Several attempts at selective reduction of the 9,10 double bond of α-(3-phenanthryl)ethyl acetate were unsuccessful, as extensive hydrogenolysis of the acetoxyl group occurred. It was possible, however, to prepare a 9,10-dibromo derivative, which was oxidized to *O*-acetyllactic acid in modest yield (Table II). It is thus feasible to oxidize rings A and C of phenanthrene, if oxidation of the 9,10 double bond is prevented.

The absolute stereochemistry of several substituted α-phenylethanols had previously been assigned by using general methods, e.g., Horeau's.[12] The present study provided an opportunity to verify these assignments, since we had prepared chiral samples of some of these compounds in the course of a study of microbially mediated enantioselective hydrolyses.[8] The results of these oxidations (Table III and the Experimental Section) confirm the assignments made by using Horeau's method.

The idea of limiting the number of possible oxidation products and of avoiding formation of intermediates that are only slowly oxidized was also employed by Nakagawa et al.[13] in their study of the absolute stereochemistry of (+)-*tert*-butyl-α-naphthylacetic acid. They limited the number of oxidation products of naphthalene by initially reducing one of the aromatic rings. In this regard it is interesting to note that the 2-substituted naphthalene, **4h**, was oxidized to *O*-acetyllactic acid in satisfactory yield without prior partial reduction of the naphthalene system (Table II). However, our attempts to oxidize the naphthalene moiety of 1,2-diacetoxy-1,2-dihydroacenaphthene to diacetyltartaric acid were unsuccessful. Complex reaction mixtures were obtained from which we were unable to isolate the desired compound. Some of the acetates we used in these oxidations were not optically pure, and values for specific rotations of pure material were not known. We have therefore compared estimates of the optical purity of these compounds made from data based on their behavior on a chiral Pirkle HPLC column and from reports of specific rotations of the chiral alcohols with estimates of the optical purities deduced from the methyl *O*-acetyllactate obtained in these oxidations. The data indicate no significant amounts of racemization occurs during the oxidations. Sharpless et al.[6] estimated that there was a maximum of 2% racemization in their examples. That estimate is consistent with our data.

Table III. Chiroptical Properties of Starting Materials and Products in Ruthenium Tetraoxide Oxidations

starting materials	$[\alpha]^{25}_D$	products	$[\alpha]^{25}_D$
(*S*)-**1b**[a]	−51.4° (*c* 4.5, $CHCl_3$)	(*S*)-**3b**	−17.4° (*c* 3.0, $CHCl_3$)
(*S*)-**2a**[a]	−209° (*c* 2.2, $CHCl_3$)	(*S*)-**3c**	−22.5° (*c* 3.5, EtOH)
(*S*)-**2b**[a]	−89.1° (*c* 3.44, $CHCl_3$)	(*S*)-**3d**	−25.0° (*c* 2.3, $CHCl_3$)
(*R*)-**4a**[b]	+94.6° (*c* 5.2, $CHCl_3$)	(*R*)-**7**	+38.0° (*c* 2.5, $CHCl_3$)
(*S*)-**4b**[c]	−5.1° (*c* 5.4, $CHCl_3$)	(*S*)-**7**	−2.0° (*c* 4.5, $CHCl_3$)
(*S*)-**4e**[c]	−25.6° (*c* 5.1, $CHCl_3$)	(*S*)-**7**	−6.0° (*c* 3.5, $CHCl_3$)
(*S*)-**4f**[c]	−155.0° (*c* 3.6, $CHCl_3$)	(*S*)-**7**	−31.2° (*c* 6.0, $CHCl_3$)

[a] Prepared from the alcohol formed by microbial reduction using *C. macerans*. [b] Prepared from the alcohol formed by the enantioselective hydrolysis using *R. nigricans*. [c] Acetate recovered from the enantioselective hydrolysis by *R. nigricans* was used.

In summary, the improved ruthenium tetroxide procedure of Sharpless et al. can be used as a superior replacement for ozonolysis of a number of aromatic and heteroaromatic esters. In select cases it is first necessary to modify the substrate in order to prevent formation of stable complexes or to otherwise limit and direct the course of the oxidation. These strategies should enhance the value and use of ruthenium tetroxide as an oxidizing agent.

Experimental Section

Proton magnetic resonance spectra were recorded on a Varian HR-220 MHz instrument. Optical rotations were recorded on a Perkin-Elmer 241MC polarimeter. Mass spectra were obtained on a LKB spectrometer. Preparative and analytical TLC work was performed on plates coated with silica gel F-254.

Optically active substrates used in this study were prepared by microbially mediated reduction using *Cryptococcus macerans*[2] and hydrolysis using *Rhizopus nigricans*.[8]

General Procedure for RuO_4 Oxidations.[6] A biphasic mixture of 1 mmol of substrate in 4 mL of CCl_4, 4 mL of CH_3CN, and 6 mL of H_2O containing $NaIO_4$ (see Tables I and II), and 0.02 mL of a RuO_4–CCl_4 solution (100 mg/mL) was vigorously stirred at room temperature. When more than 30 equiv of $NaIO_4$ was used, the volumes of solvents were doubled. After the reaction was completed, the mixture was poured into a 2 N HCl solution saturated with NaCl and extracted several times with ethyl acetate. The ethyl acetate solution was washed with 2 N HCl saturated with NaCl and then dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was treated with freshly

(11) Djerassi, C.; Engle, R. R. *J. Am. Chem. Soc.* **1953**, *75*, 3838.
(12) Horeau, A. "Stereochemistry Fundamentals and Methods"; George Thieme: Stuttgart, Federal Republic of Germany, 1977; Vol. 2, pp 52–94.
(13) Imajo, S.; Kuritani, H.; Shingu, K.; Nakagawa, M. *J. Org. Chem.* **1979**, *44*, 3587.

prepared diazomethane in ether. The reaction mixture was concentrated and chromatographed on silica gel to yield the desired methyl carboxylate.

Preparation and Oxidation of (±)-5. A sample of (±)-**5** was prepared from (±)-**4g** (1.14 g) by treatment with *m*-chloroperbenzoic acid (1.65 g excess) in $CHCl_3$ (50 mL) at 0–5 °C over the weekend. The $CHCl_3$ solution was washed with $NaHCO_3$, dried, and concentrated. The *N*-oxide was purified by chromatography on silica gel; NMR ($CDCl_3$, 220 MHz) δ 1.59 (d, 3 H), 2.14 (s, 3 H), 6.39 (q, 1 H), 7.14–7.43 (m, 3 H), 8.18 (d, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 181 (12, M^+), 138 (66), 122 (100), 104 (23).

The oxidation of (±)-**5** (362 mg) was carried out as described above to give (±)-**7** (29 mg) in 10% yield.

Preparation and Oxidation of (±)-4j. To a solution of (±)-**4i** (123 mg) in 25 mL of CCl_4 was added an excess of bromine (ca. 150 mg) at room temperature, and the reaction mixture was stirred overnight. The solvent was removed in vacuo, and the residue was chromatographed on silica gel with *n*-hexane–AcOEt (92:8) to give (±)-**4j** (65 mg) as a colorless solid (33% yield): mass spectrum (70 eV), *m/e* (relative intensity) 422, 424, and 426 (M^+, 1, 2, 1), 342 and 344 (17, 18), 264 (90), 222 (81), 205 (100); ^1H NMR ($CDCl_3$) δ 1.58 (d, 3 H), 2.11 (s, 3 H), 5.68 (s, 2 H), 5.96 (q, 1 H), 7.3–7.9 (m, 7 H).

The oxidation of (±)-**4j** (65 mg) was run to give crude (±)-**7** in ca. 40% yield.

Registry No. (±)-**1a**, 79416-46-9; (*S*)-**1b**, 84499-99-0; (*S*)-**2a**, 85828-06-4; (*S*)-**2b**, 84499-97-8; (±)-**3a**, 85880-65-5; (*S*)-**3b**, 84500-01-6; (*S*)-**3c**, 85828-07-5; (*S*)-**3d**, 55095-00-6; (*R*)-**4a**, 84194-74-1; (*S*)-**4b**, 84194-77-4; (±)-**4c**, 73104-87-7; (±)-**4d**, 85828-08-6; (*S*)-**4e**, 85828-09-7; (*S*)-**4f**, 84194-85-4; (±)-**4g**, 85880-66-6; (±)-**4h**, 85880-67-7; (±)-**4i**, 85880-68-8; **4j**, 85828-10-0; (±)-**5**, 85828-11-1; (±)-*trans*-**6**, 85880-69-9; (*R*)-**7**, 60426-97-3; (*S*)-**7**, 14031-88-0; (±)-**7**, 85880-70-2; (±)-(*R**,*R**)-**8**, 36065-08-4; RuO_4, 20427-56-9; $NaIO_4$, 7790-28-5.

Arene–Metal Complex in Organic Synthesis: Directed Regioselective Lithiation of (π-Substituted benzene)chromium Tricarbonyl Complexes[1]

Motokazu Uemura,* Naomi Nishikawa, Kazuhiko Take, Masato Ohnishi, Ken Hirotsu, Taiichi Higuchi, and Yuji Hayashi

Faculty of Science, Osaka City University, Sugimoto 3-3-138, Sumiyoshi-ku, Osaka 558, Japan

Received October 20, 1982

(3-Methoxybenzyl alcohol)chromium tricarbonyl complex (**8**) and (2-substituted 7-methoxy-1-tetralol)chromium complexes **14–17** are selectively lithiated at the 4-position and 6-position, respectively, by treatment with *n*-BuLi/TMEDA. The regioselectivity of this lithiation is improved with increasing bulk of the butyllithium reagent employed. Since the direct lithiation of the corresponding chromium-free arenes normally proceeds at the 2- and 8-positions, complementarily substituted arenes can be prepared by using chromium tricarbonyl complexes. The different lithiation is explained by the relative configuration of the chromium tricarbonyl group in the (π-arene)$Cr(CO)_3$ complexes and the electrostatic factor. This rationalization is supported, at least in part, by X-ray crystallography of the complex **16**. On the other hand, the chromium complexes of arenes without a free hydroxyl group, such as benzyl methyl ether or ethylene acetals of benzaldehydes, are lithiated at the 2-position preferentially.

Regioselective ortho lithiation of arenes directed by a heteroatom substituent such as the methoxy group is a useful reaction for the functionalization of aromatic compounds.[2] Ortho lithiation of aromatic compounds by alkyllithiums is facilitated by carboxamides, sulfonamides, and 2-oxazolines which are both electron-withdrawing and can coordinate with the lithium atom. When two substituents of this type are located at the 1,3-positions, lithiation occurs predominantly or exclusively at the 2-position;[3] even if the ortho-directing effect of each of these substituents is not so strong. For example, the lithiation of 3-methoxybenzyl alcohol (**1**), 7-methoxy-1-tetralol (**4**), and the octahydrophenanthrol derivative **5** took place at the 2- or 8-position with high regioselectivity to yield γ-lactone derivatives **2**, **6**, and **7** after quenching with carbon dioxide (Scheme I).[4] On the other hand, proton abstraction from (π-arene)chromium tricarbonyl complexes, easily obtained from 3-methoxybenzyl alcohol derivatives and chromium hexacarbonyl, occurs with different regioselectivity from that of metal-free parent arenes. This effect is attributed to the steric bulk and electron-withdrawing properties of the chromium tricarbonyl group. For example, the chromium complexes **8** and **14** were lithiated predominantly at 4- and 6-positions, respectively.[5] (Lithioarene)chromium tricarbonyl complexes thus formed could be reacted with various electrophiles and converted into the substituted arenes. As the chromium tricarbonyl group is easily removed oxidatively in quantitative yield,

(1) Dedicated to Emeritus Prof. Takeo Sakan on the 70th anniversary of his birth.

(2) For a review, see: Gscjwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.

(3) Meta-oxygenated N-substituted benzamides, piperonal cyclohexylimine, the dimethyl acetal of meta-oxygenated benzaldehyde, oxygenated benzylamine, and 2-(3-methoxyphenyl)-4,4-dimethyl-2-oxazoline are selectively lithiated at 2-position via an intramolecular coordination. Amides: Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823. Baldwin, J. E.; Bair, K. W. *Tetrahedron Lett.* **1978**, 2559. Forbes, I.; Pratt, R. A.; Raphael, R. A. *Ibid.* **1978**, 3965. de Silva, S. O.; Ahmad, I.; Snieckus, V. *Ibid.* **1978**, 5107 and references cited therein. Imine: Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564. Dimethyl acetal: Plaumann, H.; Keay, B. A.; Rodorigo, R. *Tetrahedron Lett.* **1979**, 4921. Benzylamine: Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653. Dean, R. T.; Rapoport, H. *Ibid.* **1978**, *43*, 2115. Oxazoline: Meyers, A. I.; Mihelich, E. D. *Ibid.* **1975**, *40*, 3158. Meyers, A. I.; Avila, W. B. *Tetrahedron Lett.* **1980**, *21*, 3335.

(4) Uemura, M.; Tokuyama, S.; Sakan, T. *Chem. Lett.* **1975**, 1195. Similar selective lithiation of meta-oxygenated benzyl alcohol derivatives was reported several groups: House, H. O.; Strickland, R. C.; Zaiko, E. J. *J. Org. Chem.* **1976**, *41*, 2401. Trost, B. M.; Rivers, G. T.; Gold, J. M. *Ibid.* **1980**, *45*, 1835. Winkle, M. R.; Ronald, R. C. *Ibid.* **1982**, *47*, 2101.

(5) For the preliminary report: Uemura, M.; Nishikawa, N.; Hayashi, Y. *Tetrahedron Lett.* **1980**, *21*, 2069.

0022-3263/83/1948-2349$01.50/0