Synthesis of 4-Alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-ones and 5-Alkyl-5-phenyl-1,3-cyclohexadienes from Bis(tricarbonylchromium)-Coordinated Biphenyls

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Abstract: (η^6:η^6-Biphenyl)$[Cr(CO)_3]_2$ and (η^6:η^6-4,4′-dimethoxybiphenyl)$[Cr(CO)_3]_2$ were chemically reduced with lithium anthracenide or lithium naphthalenide in THF to generate stable dianions having a (η^5-cyclohexadienylidene)$_2[Cr(CO)_3]_2$ structure. The (η^5-cyclohexadienylidene)$_2[Cr(CO)_3]_2$ dianion reacted cleanly with electrophiles such as H_2O, D_2O, benzyl tosylate, allyl tosylate, methyl iodide, and primary alkyl bromides, tosylates, and sulfates in a highly stereoselective and regioselective manner to form [μ-6-substituted-6-(η^6-phenyl)(1-5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anions. Direct oxidation of the [μ-6-alkyl-6-(η^6-phenyl)(1-5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anions with iodine yielded 2-alkylbiphenyls, whereas protonation with trifluoroacetic acid (TFAA) generated [5-alkyl-5-(η^6-phenyl)-1,3-cyclohexadiene]tricarbonylchromiums. The [5-alkyl-5-(η^6-phenyl)-1,3-cyclohexadiene]tricarbonylchromiums were oxidized by I_2 or air to generate the free 5-alkyl-5-phenyl-1,3-cyclohexadienes without rearrangement and in excellent yields. Chemical reduction of (η^6:η^6-4,4′-dimethoxybiphenyl)$[Cr(CO)_3]_2$ at −78 °C with lithium naphthalenide yielded a dianion which reacted with methyl triflate, ethyl triflate, or allyl tosylate. Workup with TFAA and I_2 resulted in the formation of 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one products in fair yields. Isolation of 4-allyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one represents a formal synthesis of the synthetically important Sceletium alkaloid, *O*-methyljoubertiamine.

Introduction

(η^6-Arene)tricarbonylchromium complexes have been widely studied due to the relative ease of formation and cleavage of the metal π complex, along with the remarkable reactivity exhibited by these complexes toward a large variety of reagents. Hundreds of (η^6-arene)tricarbonylchromium complexes have been synthesized and characterized, and many have found significant applications in organic synthesis methodology.[2] The majority of work described in the literature involves the facile generation of anionic species from (η^6-arene)tricarbonylchromium complexes by nucleophilic addition,[3,4] metalation of the aromatic ring[5] or deprotonation of benzylic sites.[6]

The methodology of reaction of (η^6-arene)tricarbonylchromium complexes with nucleophiles was largely developed by Semmelhack and co-workers.[3] They observed anions of carbon acids with pK_a's between 20 and 29; such as acetylenes, arenes, olefins, allyls, dithianes, thianes, esters, and nitriles, reacted with the starting arene complexes to give good conversion to (η^5-cyclohexadienyl)tricarbonylchromium anions. Semmelhack has characterized several of the (η^5-cyclohexadienyl)tricarbonylchromium anions by ^1H and ^{13}C NMR and isolated the intermediate generated by attack of the 1,3-dithiane anion on (η^6-benzene)tricarbonylchromium as a crystal suitable for X-ray diffraction analysis. The X-ray data for this species and NMR data for a host of others indicate that nucleophilic attack is specifically exo with respect to the metal.[3a] Cooper has since reported a complementary manner of forming (η^5-cyclohexadienyl)tricarbonylchromium anions by electrophilic addition to the dianionic reduction product of (η^6-benzene)tricarbonylchromium.[7]

Semmelhack[3] and others[4] observed that most nucleophilic attacks were reversible processes. Reaction of carbon electrophiles, such as iodomethane, with the substituted (η^5-cyclohexadienyl)-tricarbonylchromium anions resulted in formation of a bond between the electrophile and the original nucleophile, and regeneration of the starting (η^6-arene)tricarbonylchromium. Similar results arose from addition of weak protic acids such as water. The (η^5-cyclohexadienyl)tricarbonylchromium anions were decomposed by two general methods. Oxidative workup with iodine or Ce(IV) cleaved the $Cr(CO)_3$ group with loss of the endo proton, generating the free arene substituted with the nucleophile. In effect, this reaction is a nucleophilic substitution for hydride under mild conditions. Acid workup with excess trifluoroacetic acid prior to oxidation, resulted in a mixture of isomers of conjugated cyclohexadienes substituted with the nucleophile.

Kundig and co-workers[4] extended the work of Semmelhack by studying the kinetic and thermodynamic factors of these reactions. They noted nucleophiles having a pK_a larger than 29, such as 1,3-dithianes resulted in irreversible nucleophilic addition. Conditions favoring nucleophilic attack of hard carbanions like BuLi were explored by Kundig and Trahanovsky,[8] allowing some success with these substrates. (η^5-Cyclohexadienyl)tricarbonylchromium anions generated from nucleophilic attack using the more reactive anions were able to undergo a second alkylation with carbon electrophiles. In all cases where dialkylation could be induced, generating the trans-5,6-disubstituted-cyclohexadiene,

(1) Los Alamos National Laboratory, LA-UR-89-3428.
(2) (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987. (b) Semmelhack, M. F. *N.Y. Acad. Sci.* **1977**, *295*, 36. (c) Mutterties, E. L.; Bleeke, J. R.; Wucherer, E. J.; Albright, T. A. *Chem. Rev.* **1982**, *82*, 499–525. (d) Kane-Maguire, L. A. P.; Honig, E. D.; Sweigart, D. A. *Chem. Rev.* **1984**, *84*, 525–543.
(3) (a) Semmelhack, M. F.; Hall, H. T.; Farina, R.; Yoshifuji, M.; Clark, G.; Bargar, T.; Hirotsu, J.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 3535. (b) Semmelhack, M. F.; Seufert, W.; Keller, L. *J. Am. Chem. Soc.* **1980**, *102*, 6584. (c) Semmelhack, M. F.; Garcia, J. L.; Cortes, G. D.; Farina, R.; Hong, R.; Carpenter, B. K. *Organometallics* **1983**, *2*, 467. (d) Semmelhack, M. F.; Hall, H. T. *J. Am. Chem. Soc.* **1979**, *96*, 7091–7094. (e) Semmelhack, M. F.; Yamashita, A. *J. Am. Chem. Soc.* **1980**, *102*, 5924. (f) Semmelhack, M. F.; Bisaha, J.; Czarny, M. *J. Am. Chem. Soc.* **1979**, *101*, 768. (g) Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034. (h) Semmelhack, M. F.; Seufert, W.; Keller, L. *J. Am. Chem. Soc.* **1980**, *102*, 6584.
(4) (a) Kundig, E. P. *Pure Appl. Chem.* **1985**, *57*, 1855. (b) Kundig, E. P. *J. Am. Chem. Soc.* **1989**, *111*, 1804.
(5) (a) Nesmeyanov, A. N.; Kolobova, N. E.; Anisimov, K. N.; Markarov, Y. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1969**, 2665. (b) Semmelhack, M. F.; Bisaha, J.; Czarny, M. *J. Am. Chem. Soc.* **1979**, *101*, 768. (c) Ghavshou, M.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 3065.
(6) (a) Ceccon, A.; Catelani, G. *J. Organomet. Chem.* **1974**, *72*, 179. (b) Ceccon, A. *J. Organomet. Chem.* **1974**, *72*, 189. (c) Gracey, D. E. F.; Jackson, W. R.; Jennings, W. B.; Rennison, S. C.; Spratt, R. J. *Chem. Soc. B* **1969**, 1210. (d) Jaouen, G.; Top, S.; Laconi, A.; Couturier, D.; Brocard, J. *J. Am. Chem. Soc.* **1984**, *106*, 2207. (e) Top, S.; Vessieres, A.; Abjean, J. P.; Jaouen, G. *J. Chem. Soc., Chem. Commun.* **1984**, 428.
(7) Leong, V. S.; Cooper, N. J. *J. Am. Chem. Soc.* **1988**, *110*, 2644.
(8) (a) Card, R. J.; Trahanovsky, W. S. *J. Org. Chem.* **1980**, *45*, 2554. (b) Card, R. J.; Trahanovsky, W. S. *J. Org. Chem.* **1980**, *45*, 2560.

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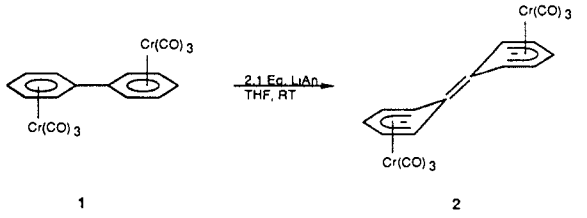
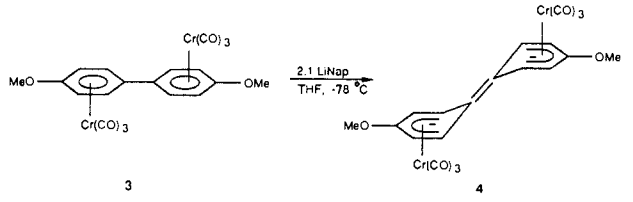
Scheme I



1 2

Scheme II



3 4

the carbon electrophile was observed to have undergone CO incorporation.

Since our initial report in 1975,[9] we have been actively studying arenecarbonylmetal complexes which undergo reductive rearrangements. One of our recent studies involved conjugated bisarene complexes. These systems, when coordinated by two $Cr(CO)_3$ groups, show unique electrochemical behavior in being reduced to dianions which are stable under anhydrous, oxygen-free conditions.[10] The electrochemical behavior of these conjugated bis complexes is in marked contrast to the mono $Cr(CO)_3$ complexes of the conjugated diphenyl compounds, and other substituted (η^6-benzene)$Cr(CO)_3$ complexes, which undergo a highly irreversible two-electron electrochemical reduction. This unusual stability was credited to a haptotropic rearrangement to a (η^5:η^5-biphenyl)$[Cr(CO)_3]_2$ or (η^5-cyclohexadienylidene)$_2[Cr(CO)_3]_2$ structure, in which the η^5-cyclohexadienyl rings maintain considerable conjugation through the connecting π-system.

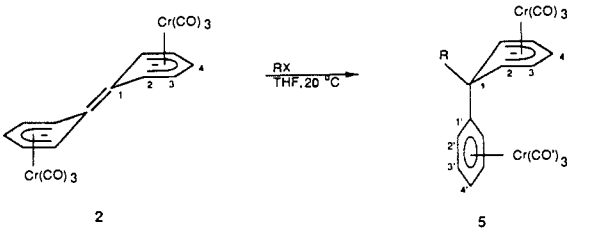
In this paper we wish to report the intermediates and products obtained by reaction of a wide variety of electrophiles with the dianions generated from the chemical reduction of (η^6:η^6-biphenyl)$[Cr(CO)_3]_2$ and (η^6:η^6-4,4′-dimethoxybiphenyl)$[Cr(CO)_3]_2$. The products formed by reaction of these dianions with carbon electrophiles are unique in the literature, as they are the first (η^5-cyclohexadienyl)tricarbonylchromium anions that have a quaternary center on the carbon bent out of the η^5-cyclohexadienyl ring plane. Further reaction of these (η^5-cyclohexadienyl)tricarbonylchromium anions has resulted in a facile synthesis of 2-alkylbiphenyls, 5-alkyl-5-phenyl-1,3-cyclohexadienes, 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-ones, and the Sceletium alkaloid *O*-methyljoubertiamine.

Results

Preparation and Reduction of the Bis Complexes. (η^6:η^6-Biphenyl)$[Cr(CO)_3]_2$ (**1**) and (η^6:η^6-4,4′-dimethoxybiphenyl)$[Cr(CO)_3]_2$ (**3**) were readily prepared by reacting the corresponding arenes with $Cr(CO)_6$ in refluxing butyl ether and THF under an argon atmosphere. The bis complexes were separated from the corresponding mono complexes by recrystallization.

Chemical reduction of **1** under an argon atmosphere to the corresponding (η^5:η^5-biphenyl)bis(tricarbonylchromium) dianion (**2**) was carried out by several methods. THF solutions of **1** were reduced to the dianion with sodium amalgam, lithium biphenylide, lithium naphthalenide, or lithium anthracenide, all of which resulted in a color change from a bright orange to a dark brown. Lithium anthracenide promoted cleaner reduction and subsequent

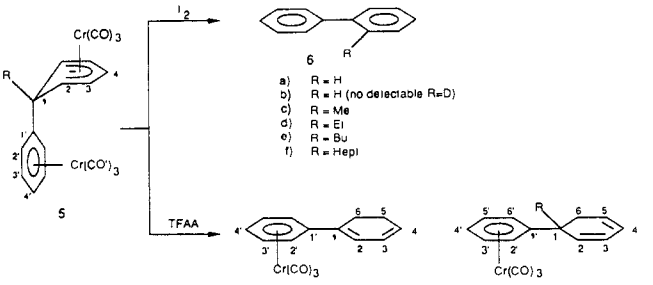
Scheme III



2 5

RX = Entries a-q in Table I

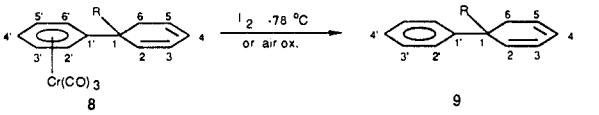
Scheme IV



5 6 7 8

R = H R = Entries c-q in Table I

Scheme V



8 9

R = Entries c-q in Table I

reaction than either lithium naphthalenide or lithium biphenylide and was thus used for the experiments involving **1** (Scheme I).[11] A large portion of **2** precipitated from the THF solution under the described concentrations and could be isolated on a Schlenk-ware frit and stored in an argon or nitrogen drybox.[12] Electrophiles were reacted either with **2** generated in situ or from the isolated dianion. Slow exposure of **2** to air oxidized the dianion to the neutral complex **1**. Rapid exposure of **2** to air resulted in a spontaneous pyrophoric ignition.

Reaction of **2** at room temperature with many electrophiles produced a color change within 1 to ca. 30 min from the dark brown dianion to a translucent orange or yellow. Electrophiles such as H_2O, D_2O, benzyl tosylate, allyl tosylate, methyl iodide, and primary alkyl bromides, tosylates and sulfates reacted cleanly with **2** to form the [μ-6-substituted-6-(η^6-phenyl)(1-5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anions (**5a–q**) (Scheme III) in a highly stereo- and regioselective manner.[13] The ipso-attack to generate a quaternary center was unexpected and provided a facile entry into a complex molecular system.

Anions **5a–q** were reacted further by either oxidation, protonation followed by oxidation, or strong electrophiles such as triflates followed by oxidation. Direct oxidation of **5c–f** with iodine at −78 °C, followed by warming to room temperature, cleanly

(9) Rieke, R. D.; Arney, J. R.; Rich, W. E.; Willeford, B. R.; Poliner, B. S. *J. Am. Chem. Soc.* **1975**, *97*, 5951.

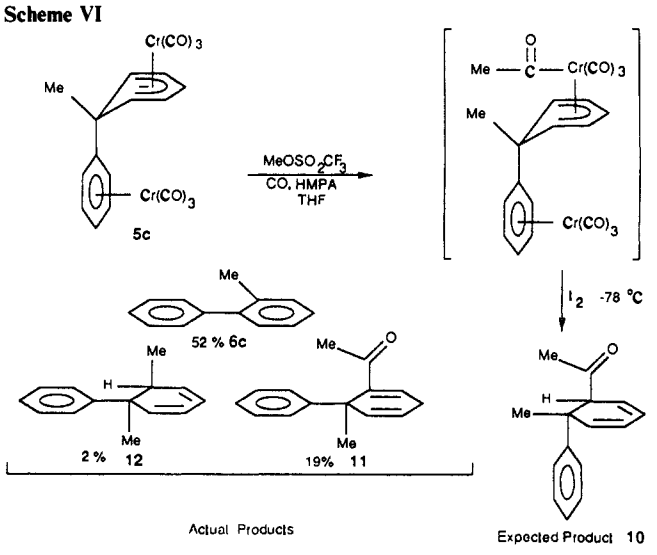
(10) (a) Rieke, R. D.; Milligan, S. N.; Schulte, L. D. *Organometallics* **1987**, *6*, 699 and references therein. (b) Schulte, L. D.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 4827. (c) Schulte, L. D.; Rieke, R. D. *Tetrahedron Lett.* **1988**, *29*, 5483. (d) Milligan, S. N.; Rieke, R. D. *Organometallics* **1983**, *2*, 171. (e) Rieke, R. D.; Henry, W. P.; Arney, J. R. *Inorg. Chem.* **1987**, *26*, 420. (f) Rieke, R. D.; Henry, W. P. *J. Am. Chem. Soc.* **1983**, *105*, 6314.

(11) One likely explanation for this observation is the probability of overreducing the (η^6:η^6-biphenyl)$[Cr(CO)_3]_2$ (reduction potential ca. −1.61 V) with the more negative potential of lithium naphthalenide (ca. −2.60 V) or lithium biphenylide (ca. −2.80 V), as opposed to the less harsh anthracenide (reduction potential ca. −1.98 V). Reduction potentials for the radical anions taken from Bank, S.; Juckett, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 7742. Reduction potentials for (η^6:η^6-biphenyl)$[Cr(CO)_3]_2$ and related complexes were obtained in our laboratory (see ref 10a).

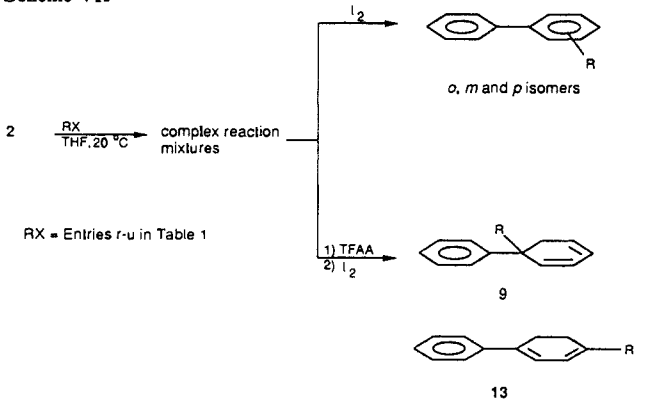
(12) The dianion **2** was best stored wet with THF solvent in a −35 °C freezer inside the drybox. **Note:** The dianion solid was pyrophoric with rapid exposure to air.

(13) The numbering system used for the structures shown in Scheme III was selected for easy comparison of the various structures and signals in the schemes and tables. This numbering system is not that recommended by IUPAC and is not used in the nomenclature of the isolated products.

Scheme VI



Scheme VII



generated 2-alkylbiphenyls (**6c–f**) (Scheme IV)[14] in near quantitative yields. Similar oxidative treatment of the analogous anions produced by protonation or deuteration of **2** led to formation of biphenyl. Mass spectral analysis of the biphenyl product obtained from **5b** did not show deuterium incorporation, indicating that the endo deuterium was lost as the complex was oxidized to the aromatic product.

Acidic workup of **5a** with TFAA generated [(η^6-phenyl)-1,3-cyclohexadiene]tricarbonylchromium (**7**). Similar protonations of **5c–q** with TFAA produced [5-alkyl-5-(η^6-phenyl)-1,3-cyclohexadiene]tricarbonylchromiums (**8c–q**). This protonation proved to be regioselective as no other diene isomers were observed.

Compounds **8c–q** were oxidized by either I_2 or air to generate the free 5-alkyl-5-phenyl-1,3-cyclohexadienes (**9c–q**) without rearrangement and in good yields (Scheme V). This approach provides a unique method to form a phenyl-substituted quaternary center on a six-membered ring in excellent yields.

Reaction of **5c** with methyl triflate, followed by iodine oxidation, resulted in the formation of three products (Scheme VI): 2-methylbiphenyl (**6c**) (52% isolated), 2-acetyl-3-methyl-3-phenyl-1,4-cyclohexadiene (**11**) (19% isolated), and 5,6-dimethyl-5-phenyl-1,3-cyclohexadiene (**12**) (2% isolated), along with traces of biphenyl. Product **11** is postulated to arise from a double bond isomerization of the expected 1,3-cyclohexadiene (**10**). A COSY experiment indicated that the methyl groups of **12** were trans.

Reaction of **2** with secondary, tertiary, allylic, and benzylic halides did not yield clean ipso-attack. Instead, a mixture of ipso ortho, meta and para attack was observed (Scheme VII). Oxidation of these reaction mixtures with iodine led to mixtures of the 2-, 3- and 4-substituted alkylbiphenyls (Table II). For secondary and tertiary halides, protic workup of the reaction mixtures with TFAA followed by I_2 oxidation led to the isolation of two diene products, 5-alkyl-5-phenyl-1,3-cyclohexadiene (**9**) and 4-alkyl-1-phenyl-1,3-cyclohexadiene (**13**), in ratios which varied with the electrophile. The amount of the latter product was minor in the 2-bromopropane case, but was clearly the major isomer in the *tert*-butyl bromide case (Table I). The secondary and tertiary halides appeared to react more slowly than the primary halides, requiring in the tertiary case reaction times on the order of 12 h to undergo the expected color change to orange. The benzyl bromide and allyl bromide reacted very quickly with the dianion, but gave mixtures of products unlike the corresponding tosylates.

The reaction of **2** with electrophiles at room temperature to form the [μ-6-substituted-6-(η^6-phenyl)(1-5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anion was unexpected. D_2O or H_2O caused a nearly instantaneous color change from the dark brown of the dianion to a yellow orange solution. Most carbon electrophiles reacted somewhat more slowly to give similar color changes over the course of one to several minutes. Temperature studies with primary alkyl bromides indicated reaction with **2** initiated approximately between −20 °C and 0 °C. The simple primary electrophiles such as bromoethane appeared to react faster than primary electrophiles which had more β substituents, such as 1-bromo-2-methylpropane. The carbon–electrophile bond formation was both highly regioselective and stereoselective for the electrophiles **5a–q** in Table I, as only one isomer was observed in the ^{13}C and ^1H NMR spectra. Intermediates for reaction of several of the electrophiles in the lower part of Table I (entries **5r–u**) were also studied by NMR. These spectra were very complex, consistent with the proposal that a mixture of anionic intermediates were formed and could not be fully interpreted.

The ^{13}C NMR data for the products **5a–l** shown in Scheme III are listed in Table IV along with **1** and **2**. NMR shift as-

Table I. Protonation of Anions **5a–u** with TFAA and Subsequent Oxidation with I_2

entry	X	R	yield, %	ratio of **9**/**13**
a	OH	H		
b	OD	D		
c	I	CH_3	95[a]	1.0/0
d	Br	CH_2CH_3	97[a]	1.0/0
e	Br	$(CH_2)_3CH_3$	63[a]	1.0/0
g	Br	$(CH_2)_3CO_2Et$	77[b]	1.0/0
h	Br	$(CH_2)_3CN$	93[b]	1.0/0
i	Br	$(CH_2)_2CN$	67[b]	1.0/0
j	Br	$CH_2CH(CH_3)_2$	67[b]	1.0/0
k	Br	CH_2CH_2Ph	62[a]	1.0/0
l	Br	$(CH_2)_4CH{=}CH_2$	68[a]	1.0/0
m	Br	CH_2-cyclopropyl	80[a]	1.0/0
n	OTs	$CH_2CH{=}CH_2$	50[a]	1.0/0
o	OTs	CH_2Ph	55[b]	1.0/0
p	SO_4Me	CH_3	61[a]	1.0/0
q	SO_4Et	CH_2CH_3	59[b]	1.0/0
r	Br	$CH(CH_3)_2$	35[b]	20/1
s	Br	$C(CH_3)_3$	10[b]	1/4
t	Br	CH_2Ph	*c*	
u	Br	$CH_2CH{=}CH_2$	*c*	

[a] Yields obtained by GC analysis. [b] Isolated yields. [c] Reliable yield data and product ratios were not obtained due to the complexity of the reaction mixture.

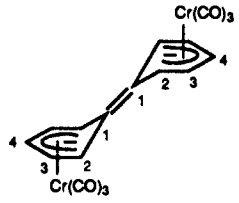
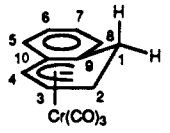
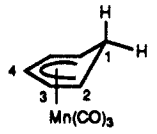
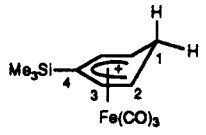
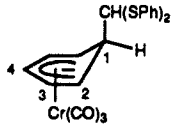
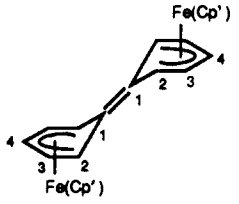
Table II. Direct Oxidation of Anions **5c–t** with I_2

entry	X	R	yield, %	ratio of *o*-/*m*-/*p*-biphenyl
c	I	CH_3	96[a]	1.0/0/0
d	Br	CH_2CH_3	97[a]	1.0/0/0
f	Br	$(CH_2)_6CH_3$	85[a]	1.0/0/0
r	Br	$CH(CH_3)_2$	29[b]	31/1/4
s	Br	$C(CH_3)_3$	45[b]	2/1/5
t	Br	CH_2Ph	24[b]	5/2/1

[a] Yields obtained by GC analysis. [b] Isolated yields.

(14) The regiosubstitution of the 2-alkylbiphenyls was proven in the case of 2-methylbiphenyl by comparison with the 3- and 4-substituted isomers and in the 2-heptylbiphenyl case by independent synthesis from 2-biphenylcarboxylic acid.

Table III. Spectroscopic Data for Isoelectronic (η^5-Cyclohexadienyl)metal Complexes (η^5:η^5-Biphenyl)bis(tricarbonylchromium) Dianion (**2**), (η^5-Naphthalene)tricarbonylchromuim Anion, (η^5-Cyclohexadienyl)tricarbonylmanganese, [η^5-2-(Trimethylsilyl)-1,3-cyclohexadienyl]-tricarbonyliron Cation, [η^5-6-(Bis(phenylthio)methyl)cyclohexadienyl]tricarbonylchromium Anion, and (η^5:η^5-Biphenyl)bis(pentamethylcyclopentadieneiron)

compound	CO region of IR: ν_{CO}, cm^{-1}	^1H NMR shifts for η^5-cyclohexadienyl ring, ppm			^{13}C NMR shifts for η^5-cyclohexadienyl ring, ppm [$^1J_{CH}$, Hz]			
		H_2	H_3	H_4	C_1	C_2	C_3	C_4
	1828 1805 1730	2.88	4.29	4.67	102.17 [s]	67.19 [d,154]	98.02 [d,158]	69.58 [d,167]
	1895 1800 1745	2.37	4.57	5.42	32.0 [dd,118–128]	44.8 [d,162]	97.8 [d,168]	–
	2020 1942	2.35	4.16	5.20	24.2 [dd,135]	50.1 [d,168]	98.0 [d,168]	79.7 [d,177]
	2100 2050	4.17	5.45	–	23.93	68.36	104.71	98.87
	1901 1802 1712	2.80	4.41	4.92	–	–	–	–
	–	2.6	4.1	5.6	102.7	53.1	81.9	77.4

signments were made by comparison with isoelectronic (η^5-cyclohexadienyl)metalcarbonyl complexes for which ^{13}C NMR and ^1H NMR data have been reported (some listed in Table III).

A key signal in identifying structure **5** was observed at approximately 40 ppm in the ^{13}C NMR spectrum for the newly formed quaternary center carbon (labeled as C_1 in Table IV and the drawing of **5** in Scheme III). The observed signal was a doublet ($^1J_{CH}$ = 135 Hz) for the protonated product **5a**, a 1:1:1 triplet ($^1J_{CD}$ = 20 Hz) for the deuterated product **5b**, and a singlet for the alkylated products **5c–l**. The $^1J_{CD}$ coupling observed for **5b** was unchanged in both decoupled and coupled spectra. The size of the deuterated carbon signal for C_1 was much smaller than that observed for this signal in the other products.[15] Other signals are consistent with the proposed structure, including the presence of characteristic signals for the ortho and para carbons of the (η^5-cyclohexadienyl)$Cr(CO)_3$ ring at 50–55 ppm and 76 ppm, respectively. Two separate CO signals were observed at approximately 241 and 235 ppm for the $Cr(CO)_3$ groups of the anionic and neutral rings.

The ^1H NMR data for products **5a–l** shown in Scheme III are listed in Table V along with signals for **1** and **2**. NMR shift assignments were made by comparison with isoelectronic (η^5-cyclohexadienyl)metalcarbonyl complexes for which ^1H NMR data have been reported (some listed in Table III).[16] A close examination of the ^1H NMR coupling constant for the protons on positions 1 and 2 for **5a** ($^3J_{HH}$ = 5.7 Hz) reveals strong evidence that the new proton (or deuterium in **5b**) is endo substituted on the η^5-cyclohexadienyl ring with respect to the coordinating $Cr(CO)_3$ group. Endo protons in η^5-cyclohexadienyl complexes have a larger $^3J_{HH}$ coupling (5–6 Hz) with vicinal protons than do exo protons (<2 Hz) in several cases of unambiguous structure assignments.[17] The $^3J_{HH}$ larger coupling for endo protons in η^5-cyclohexadienyl complexes has been attributed by one author to

(15) This is a commonly observed phenomenon due to the longer T_1 observed for ^{13}C–D than for ^{13}C–H, due to the decreased dipole–dipole relaxation and the loss of the nuclear Overhauser effect. Silverstein, R. M.; Bassler, G. C.; Morill, T. C. *Spectrometric Identification of Organic Compounds, 4th ed.*; John Wiley and Sons: New York, NY, 1981; pp 257–258. *Organic Chemistry*; Academic Press: New York, NY, 1972; Vol. 24 (*Carbon-13 NMR Spectroscopy*) pp 313–321.

(16) The data shown in Table III was obtained from the following sources: (η^5-naphthalene)tricarbonylchromium anion, ref 10f. (η^5-Cyclohexadienyl)-tricarbonylmanganese, Whitesides, T. H.; Budnik, R. A. *Inorg. Chem.* **1976**, *15*, 874. [η^5-(2-Trimethylsilyl-1,3-cyclohexadienyl)]tricarbonyliron cation, Paquette, L. A.; Daniels, R. G.; Gleiter, R. *Organometallics* **1984**, *3*, 560. (η^5-[6-(Bis(phenylthio)methyl)cyclohexadienyl]tricarbonylchromium anion, Semmelhack, M. F.; Hall, H. T.; Yoshifuji, M. *J. Am. Chem. Soc.* **1976**, *98*, 6387. (η^5:η^5-Biphenyl)[$FeCp]_2$, Lacoste, M.; Varret, F.; Toupet, L.; Astruc, D. *J. Am. Chem. Soc.* **1987**, *109*, 6504.

(17) See: (a) Pearson, A. J. *J. Chem. Soc., Perkin 1* **1977**, 2069. (b) Connelly, N. G.; Kelly, R. L. *J. Chem. Soc., Dalton Trans.* **1974**, 2334. (c) Bae, H. K.; Jung, I. N.; Chung, Y. K. *J. Organomet. Chem.* **1986**, *317*, C1. (d) Faller, J. W. *Inorg. Chem.* **1980**, *19*, 2857. (e) Ceccon, A.; Gambaro, A.; Romanin, A. M. *J. Organomet. Chem.* **1983**, *254*, 199.

Table IV. ^{13}C NMR Shifts (ppm) and $^{1}J_{CH}$ Coupling Constants (Hz) Where Obtained for **1**, **2**, **5a–d**, **5g**, **5h**, and **5l**[a] (The Position Assignments Correspond with the Structure Shown in Scheme III)

compd	CO	CO′	C_1	C_2	C_3	C_4	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$
1	233.4 (s)	CO	106.2 (s)	94.5 (d,174)	93.3 (d,174)	94.8 (d,177)	C_1	C_2	C_3	C_4
2	243.0 (s)	CO	102.2 (s)	67.2 (d,158)	98.0 (d,159)	69.6 (d,168)	C_1	C_2	C_3	C_4
5a	242.1 (s)	234.8 (s)	41.7 (d,135)	51.1 (d,160)	*b* *b*	75.9 (d,169)	122.8 (s)	*b* *b*	*b* *b*	92.9 (d,164)
5b	242.1 (s)	234.8 (s)	41.3 (t,20)[c]	51.1 (d,160)	*b* *b*	75.9 (d,169)	122.8 (s)	*b* *b*	*b* *b*	92.9 (d,164)
5c	241.4 (s)	235.6 (s)	40.7 (s)	57.2 (d,163)	*d* *d*	75.9 (d,173)	125.2 (s)	*d* *d*	*d* *d*	96.5 (d,176)
5d	241.0 (s)	235.3 (s)	44.3 (s)	56.4 (d,162)	*e* *e*	76.0 (d,172)	124.3 (s)	*e* *e*	*e* *e*	97.4 (d,176)
5g	241.2	235.5	44.0	56.5	*f*	76.1	124.9	*f*	*f*	97.5
5h	241.2	235.6	43.9	56.1	*g*	76.4	124.2	*g*	*g*	97.9
5l	241.4	235.8	44.2	57.0	*h*	76.1	127.4	*h*	*h*	*h*

[a] All spectra were obtained in and referenced to DMF-d_7 (30.10 ppm). All samples listed, with the exception of **1**, showed signals for residual THF at 67.7 and 25.8 ppm. Entries under the "prime" columns such as C_1 under $C_{1'}$ imply that the two signals are identical due to symmetry. [b] Three signals for **5a** and **5b** are ambiguously assigned at present. The signals are observed at 95.9 (d, 170 Hz), 95.8 (d, 171 Hz), and 93.3 (d, 168 Hz) and correspond to C_3, $C_{2'}$, and $C_{3'}$. [c] Coupling constant reported is for $^{1}J_{CD}$ which is observed in both decoupled and gated decoupled spectra. The size of the deuterated carbon signal for C_1 was much smaller than that observed for C_1 in the other products. [d] Three signals for **5c** are ambiguously assigned at present. The signals are observed at 98.4 (d, 172 Hz), 96.1 (d, 162 Hz), and 92.1 (d, 175 Hz) correspond to C_3, $C_{2'}$, and $C_{3'}$. The signal for the methyl group is tentatively assigned to a peak observed at 34.9 ppm which is partially obscured by solvent. [e] Three signals for **5d** are ambiguously assigned at present. The signals are observed at 99.2 (d, 171 Hz), 96.3 (d, 161 Hz), and 91.0 (d, 168 Hz) correspond to C_3, $C_{2'}$, and $C_{3'}$. The ethyl group is also visible in **5d** at 40.1 (t, 126 Hz) and 8.2 (q, 125 Hz). [f] Three signals for **5g** are ambiguously assigned at present. The signals are observed at 99.1, 96.4, and 91.1 correspond to C_3, $C_{2'}$, and $C_{3'}$. Signals for the alkyl chain are observed at 173.4, 60.8, 47.8, 35.0 (overlapping with the DMF signal), 19.5, and 14.3. [g] Three signals for **5h** are ambiguously assigned at present. The signals are observed at 99.4, 96.5, and 91.2 correspond to C_3, $C_{2'}$, and $C_{3'}$. Signals for the alkyl chain are observed at 120.7, 47.2, 20.2, and 17.1. [h] Several signals for **5l** are ambiguously assigned at present. The signals are observed at 139.0, 114.3, 99.4, 97.6, 96.4, 91.1, 48.4, 32.8, 27.7, and 23.0 correspond to C_3, $C_{2'}$, and $C_{3'}$, and the alkyl chain.

Table V. ^{1}H NMR Shifts (ppm, δ), $^{3}J_{HH}$ Splitting Patterns, Integration, and Coupling Constants (Hz) for **1**, **2**, **5a–d**, **5g**, **5h**, and **5l**[a] (The Position Assignments Correspond with the Structure Shown in Scheme V)

compd	H_1	H_2	H_3	H_4	$H_{2'}$	$H_{3'}$	$H_{4'}$
1	–	6.27	5.91	5.81	6.27	5.91	5.81
	–	(d, 4 H, 7.1)	(t, 4 H, 6.3)	(t, 2 H, 6.2)	(d, 4 H, 7.1)	(t, 4 H, 6.3)	(t, 2 H, 6.2)
2	–	2.88	4.29	4.67	2.88	4.29	4.67
	–	(d, 4 H, 7.0)	(dd, 4 H, 7.0 and 5.5)	(t, 2 H, 5.2)	(d, 4 H, 7.0)	(dd, 4 H, 7.0 and 5.5)	(t, 2 H, 5.2)
5a	3.30	2.70	4.58	4.98	5.27	5.57	5.40
	(t, 1 H, 5.7)	(t, 2 H, 6.3)	(t, 2 H, 6.3)	(dt, 1 H, 5.4)	(d, 2 H, 5.7)	(t, 2 H, 6.4)	(t, 1 H, 6.3)
5b	–	2.69	4.59	4.99	5.31	5.56	5.41
	–	(d, 2 H, 6.1)	(t, 2 H, 6.3)	(t, 1 H, 5.6)	(d, 2 H, 7.1)	(t, 2 H, 6.4)	(t, 1 H, 6.7)
5c[b]	–	2.29	4.55	5.09	6.28	5.60	5.78
	–	(d, 2 H, 6.2)	(t, 2 H, 6.1)	(t, 1 H, 5.2)	(d, 2 H, 5.9)	(t, 2 H, 5.9)	(t, 1 H, 6.0)
5d[c]	–	2.26	4.56	5.00	6.21	5.51	5.82
	–	(d, 2 H, 6.9)	(t, 2 H, 5.9)	(t, 1 H, 5.2)	(d, 2 H, 6.3)	(t, 2 H, 6.3)	(t, 1 H, 5.9)
5g[d]	–	2.27	4.57	5.01	6.25	5.54	5.85
	–	(d, 2 H, 6.3)	(t, 2 H, 5.3)	(t, 1 H, 5.4)	(d, 2 H, 6.2)	(t, 2 H, 6.0)	(t, 1 H, 5.4)
5h[e]	–	*e*	4.60	5.05	6.28	5.57	5.90
	–		(t, 2 H, 5.5)	(t, 1 H, 4.4)	(d, 2 H, 5.8)	(t, 2 H, 5.5)	(t, 1 H, 5.8)
5l[f]	–	*f*	4.56	5.05–4.83	6.26	5.54	5.95–5.70
	–		(t, 2 H, 6.2)	(m, 3 H)[f]	(d, 2 H, 6.5)	(t, 2 H, 6.8)	(m, 2 H)[f]

[a] All spectra were obtained in DMF-d_7 and referenced to DMF-d_7 at 2.74 ppm δ. All samples listed, with the exception of **2**, showed signals for residual THF at 3.61 and 1.76 ppm δ. The signals for H_3 in compounds **5a–d**, **5g**, **5h**, and **5l** are probably not true triplets, but doublets of doublets which are not resolved. This was verified by selective decoupling experiments for **5c**. [b] A signal was observed for the methyl group at 0.71 (s, 3 H). [c] Signals were observed for the ethyl group at 1.13 (q, 2 H, 7.5 Hz) and 0.76 (t, 3 H, 7.4 Hz). [d] Signals were observed for the ester ethyl group at 4.03 (q, 2 H, 6.5 Hz) and 1.17 (t, 3 H, 7.1 Hz). Signals for the methylene protons were observed at 2.11 (t, 2 H, 6.5 Hz), 1.7 (m, overlapping with large THF peak), and 1.1 (m, overlapping with methyl of ester function). [e] Signals were observed for the alkyl substituent at 2.4–2.2 (m, overlapping signals for H_2 and one of the methylenes), 1.3 (m, overlapping with large THF peak), and 1.3–1.1 (m, 2 H). [f] Signals were observed for the alkyl substituent at 2.294 (d, 2 H, 6.6 Hz), 2.12–1.05 (m, 8 H, overlapping with THF signal). In addition, the signals at 5.05–4.83 and 5.95–5.70 are observed to be overlapping signals of the terminal olefin and the assigned coordinated neutral arene protons.

differences in the dihedral angle between the exo or endo protons and the vicinal ring protons, caused by the deformation of the η^5 ring from planarity.[18] Decoupling experiments performed on the [μ-6-methyl-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anion (**5c**) support the shift assignments of the (η^5-cyclohexadienyl)Cr(CO)$_3$ ring.

The [μ-6-alkyl-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anions (**5c–l**) have not been identified as exo or endo substituted. The reaction appears to be as stereospecific as the formation of the protonated intermediates **5a** and **b**, with no other isomers visible in either the ^{1}H or ^{13}C NMR. Attempts to isolate a crystal of the methyl derivative **5c** for X-ray diffraction studies, by solvent reduction and cation exchange, have not been successful.

Addition of 1 equiv of the appropriate electrophile was sufficient to convert **2** to **5**. An excess of iodomethane or bromoethane failed to give further reaction with **5c** over several days in an NMR tube. A similar experiment involving excess H_2O with **5a** also failed to promote further reaction. A crossover experiment involving the deuterated adduct **5b** in the presence of excess H_2O did not undergo exchange. The formation of the [μ-6-(η^6-phenyl)(1–5-

(18) Hoffmann, R.; Hofman, P. *J. Am. Chem. Soc.* **1976**, *98*, 598 and references therein.

Table VI. ^{13}C NMR Shifts (ppm) and $^{1}J_{CH}$ Coupling Constants (Hz) Where Obtained for Complexed Dienes **8c,d,g,** and **h** and **7**[a] (The Position Assignments Correspond with the Structures Shown in Scheme IV)

compd	CO	C_1	C_2	C_3	C_4	C_5	C_6	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	$C_{6'}$
8c[b]	234.7	39.8	133.6	125.5	124.4	123.5	37.8	122.0	95.9	95.8	94.5	93.7	93.6
8d[c]	233.2	40.4	130.3	125.04	124.98	123.1	35.5	118.9	94.0	93.8	92.8	90.3	90.2
8g[d]	234.5	40.5	131.1	125.8	124.8	123.4	35.5	120.7	96.1	95.7	95.2	93.1	92.9
8h[e]	234.6	40.5	130.8	125.9	125.1	123.5	39.8	120.5	96.2	95.7	95.2	93.2	93.1
7[f]	233.0	132.1	128.5	124.1	122.7	22.9	24.6	111.0	92.9	89.4	91.0	$C_{3'}$	$C_{2'}$
	(s)	(s)	(d,163)	(d,162)	(d,161)	(t,128)	(t,128)	(s)	(d,174)	(d,172)	(d,175)		
7[b]	234.6	132.8	128.7	124.7	123.1	24.6	23.1	112.3	95.5	93.7	91.8	$C_{3'}$	$C_{2'}$

[a] Spectra were obtained in and referenced to DMF-d_7 (30.10 ppm), except where noted. Carbons 3–5 and 2′–6′ were ambiguously assigned for **8** and are listed in descending order. Carbons 2–4 and 5–6 were likewise ambiguously assigned for **7** and are listed in descending order. [b] The signal for the methyl group was not observed, very likely due to problems of overlap with the DMF-d_7 multiplet at 30.10 ppm. [c] Signals for the ethyl alkyl chain were observed at 32.8 and 9.8. [d] Signals for the ester alkyl chain were observed at 173.1, 60.3 40.1, 35.5, 34.5, 21.1, and 14.3. [e] Signals for the nitrile alkyl chain were observed at 120.7, 30.3, 21.9, and 17.2. [f] Obtained in and referenced to DMF-d_7 (30.10 ppm), following generation with TFAA. [g] Obtained in and referenced to $CDCl_3$ (77.00 ppm) following isolation from the benchtop reaction in THF.

η^5)-cyclohexadienyl]bis(tricarbonylchromium) anions appears to be irreversible under the conditions described.

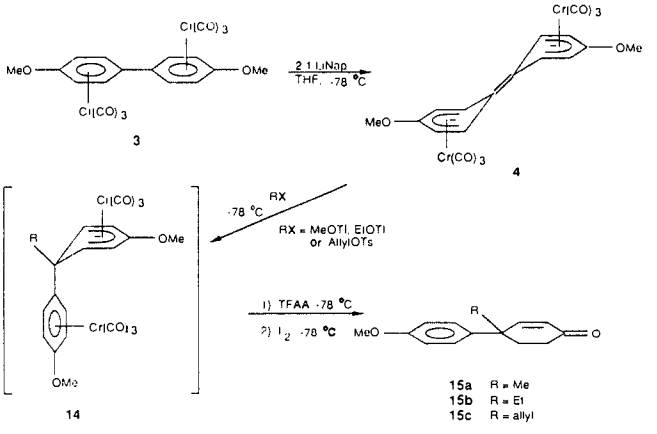
Following the spectroscopic characterization of the alkyl-substituted anionic intermediates (**5c–l** in Scheme III), it became apparent that it was the oxidative decomposition of this complex with iodine that resulted in the exclusive formation of 2-alkylbiphenyls (**6c–l**).[19] As **5c–l** were oxidized, a rearrangement occurred in which either the alkyl substituent or the arene ring underwent a 1,2 shift. The decomposition of deuterium substituted **5b** did not result in a measurable amount of deuterium incorporation (by mass spectral analysis) in the biphenyl product, indicating that the endo deuterium is lost as the complex is oxidized and the ring aromatizes. The mechanism and other aspects of the alkyl rearrangement will be addressed in a manuscript which is being prepared for publication.

Anions **5c–h**, generated in DMF-d_7,[20] were protonated with TFAA to produce **8c–h** (Scheme IV) with the loss of one $Cr(CO)_3$ group. The protonation occurred regioselectively, vicinal to the previously formed quaternary center, without rearrangement of the type observed with direct I_2 addition. The ^{13}C NMR data obtained for **8c,d,g,** and **h** are listed in Table VI.

Chemistry of the Dianion Generated from (η^6:η^6-4,4′-Dimethoxybiphenyl)[$Cr(CO)_3$]$_2$. A large number of synthetically interesting compounds, including several classes of alkaloids, are related by a number of structural similarities. Many alkaloids have a quaternary center on a six-membered ring system, which has an arene ring and a basic nitrogen (often separated from the ring by an ethylene group) attached to the quaternary center.[21] It became apparent that this complex ring system could be synthesized in one step by using the novel reaction reported in this manuscript. Starting with the commercially available 4,4′-dimethoxybiphenyl, one could generate the 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one system of some of the Sceletium alkaloids by ipso-alkylation followed by hydrolysis of the vinyl ether.

Chemical reduction of **3** with lithium naphthalenide, lithium anthracenide or sodium amalgam at room temperature, under conditions similar to those used for **1**, did not lead to clean generation of the (η^5:η^5-4,4′-dimethoxybiphenyl)[$Cr(CO)_3$]$_2$ dianion (**4**). Reoxidation of the solution with iodine generated large amounts of 4-methoxybiphenyl. Apparently the dianion had undergone a reductive cleavage of a methoxyl group at room temperature. Electrochemical studies also indicated that **4** was

Scheme VIII



unstable at room temperature but became more stable as the temperature in the electrochemical cell was lowered.[22] Chemical reduction at −78 °C greatly slowed the decomposition of **4** (Scheme II). Lithium naphthalenide proved to be the reagent of choice for the reduction of **3**, as lithium anthracenide generally gave lower yields. This dianion was never isolated but was freshly generated in situ at low temperatures immediately prior to the addition of electrophiles.

Reductions with lithium anthracenide at −78 °C, followed by reaction with primary alkyl bromides in the presence of HMPA, resulted in the isolation of a product in good yield which had incorporated the alkyl group. Surprisingly, it was determined by MS, ^1H NMR, COSY ^1H NMR, ^{13}C NMR, and DEPT ^{13}C NMR that the alkylated product had also incorporated a molecule of anthracene.[23] Anthracene has been noted to react with alkyl lithiums, apparently via a nucleophilic type attack.[24] Anthracene did not react with **2** but interfered with the more reactive (η^6:η^6-4,4′-dimethoxybiphenyl)[$Cr(CO)_3$]$_2$ analogue. Subsequent reductions were attempted with lithium naphthalenide at −78 °C to avoid side reactions with the anthracene.

Attempted reactions of primary alkyl bromides with **4** at −78 °C, followed by reaction with TFAA and I_2, did not result in the desired alkylations but did generate 4-(4-methoxyphenyl)cyclohex-3-en-4-one. Although this reaction did not result in successful

(19) Yields over 95% have been observed via GC analysis based on **2**. Satisfactory ^1H NMR and ^{13}C NMR data have been obtained for all products from the dianion. Mass spectral data has been obtained for all products following loss of $Cr(CO)_3$ groups and several of the [5-alkyl-5-(η^6-phenyl)-1,3-cyclohexadiene]tricarbonylchromiums.

(20) The dianion was not sufficiently soluble in THF-d_8 for NMR experiments. While DMF-d_7 was used for the NMR work described, THF was routinely used for the benchtop chemistry of **2**. Addition of an electrophile to the partially dissolved dianion in THF-d_8 resulted in the usual color changes and in generation of a soluble complex. Data for **5c** and **5d** in THF-d_8 were nearly identical with those obtained in DMF-d_7, with slight solvent shifts.

(21) Jeffs, P. W. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press, Inc.: New York, 1981; Vol. XIX, pp 1–80 and references therein.

(22) Cyclic voltammetry of (η^6:η^6-4,4′-dimethoxybiphenyl)bis(tricarbonylchromium) in THF (0.2 M TBAP, 22 °C, 200 mV/s, HMDE) generates a chemically irreversible wave at −1.95 V, i_{pc}/i_{pa} = 7.3 (vs the Ag/AgCl, saturated NaCl(aq) reference electrode) indicating that an unstable dianion was formed. Lowering the temperature in the electrochemical cell to −35 °C results in a much more chemically reversible wave in the cyclic (i_{pc}/i_{pa} = 2.2). This situation is very different from that observed for other (conjugated arene)bis(tricarbonylchromium) complexes, which have been observed to form stable dianions. See ref 10 for a full discussion of the electrochemistry of these complexes.

(23) For a full discussion, see: Schulte, L. D.; Ph.D. Dissertation, University of Nebraska—Lincoln, 1988.

(24) Zieger, H.; Perri, C.; Bharucha, K. *Tetrahedron Lett.* **1987**, *28*, 5989 and references therein.

alkylation, it was seen as an indicator of the presence of the dianion. The 4-(4-methoxyphenyl)cyclohex-3-en-4-one could have been formed by diprotonation of **4** with TFAA, followed by hydrolysis to the enone. Careful temperature studies showed that **4** did not react with primary alkyl bromides from −78 °C up to room temperature at which point **4** began to decompose.

Reactions of **4** under identical conditions with methyl or ethyl triflate and allyl tosylate, followed by workup with TFAA and I_2, resulted in the formation of the desired 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one products (**15a–c**) in fair yields (Scheme VIII).[25] The initial alkylation of **4** apparently occurs at the phenyl-substituted ring position to generate the anion **14**. This species is presumed structurally similar to the intermediate generated in reactions of **1** which was characterized by ^1H and ^{13}C NMR. Protonation of **14** with excess TFAA is postulated to generate a dienol ether, which hydrolyzed under the acidic conditions to the 4-alkyl-4-[(η^6-4-methoxyphenyl)tricarbonylchromium]cyclohex-2-en-1-ones.[26] Cleavage of the remaining $Cr(CO)_3$ group with iodine generated the free 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one products (**15a–c**). Isolated yields of **15a–c** have been modest under the conditions described (**15a**, 30%; **15b**, 23%; **15c**, 17%). Addition of HMPA to reactions with allyl tosylate did not increase the yield.

Isolation of 4-allyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one (**15c**) represents a formal synthesis of *O*-methyljoubertiamine as Martin and co-workers[27] have converted **15c** to *O*-methyljoubertiamine in one pot in 75% yield by an ozonolysis, followed by a reductive amination using $NaBH_3CN$ in the presence of Me_2NH_2Cl. The (η^6:η^6-4,4′-dimethoxybiphenyl)$[Cr(CO)_3]_2$ system represents a short and direct route to the synthetically important 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-ones.

Discussion

The remarkable regioselectivity and stereoselectivity shown in the exclusive formation of the [μ-6-substituted-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anions from the addition of a variety of electrophiles to **2** represents a facile route to a complex molecular system containing a quaternary center. Electrophiles such as H_2O, D_2O, benzyl tosylate, allyl tosylate, methyl iodide, primary alkyl bromides, most primary alkyl iodides, and alkyl sulfates gave exclusive attack at the 1-position. However, secondary and tertiary bromides and iodides as well as allylic and benzylic bromides gave mixtures of 2-, 3-, and 4-substituted biphenyls after I_2 oxidation.

Semmelhack has reported that (η^5-cyclohexadienyl)$Cr(CO)_3$ anions, generated by exo attack of nucleophiles, could be protonated with TFAA to form mixtures of cyclohexadienes.[28] The [μ-6-alkyl-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anions were observed to protonate regioselectively with TFAA to form only one diene product. The [μ-6-alkyl-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anions are the only (η^5-cyclohexadienyl)$Cr(CO)_3$ anions, of which we are aware, that have a quaternary center on the carbon bent out of the η^5-cyclohexadienyl ring plane. Most other (η^5-cyclohexadienyl)$Cr(CO)_3$ anions discussed in the literature were formed by exo attack of nucleophiles and have an endo proton on the newly substituted position. These species appear to be more prone to rearrangement with TFAA protonation than the anions containing a quaternary center. A similar observation was made in our work for the [μ-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anion, which rearranged to the fully conjugated **7** upon protonation.

Kundig[29] was able to introduce an acyl group in reactions of certain (η^5-cyclohexadienyl)$Cr(CO)_3$ anions, obtaining highest yields when triflates in the presence of HMPA and under CO pressure were used. The *trans*-5-acyl-6-alkyl-1,3-cyclohexadiene product was obtained specifically due to the stereospecificity of the two alkylation steps with the nucleophilic attack occurring exo and acyl insertion endo. We hoped to obtain similar results in the reaction of the [μ-6-alkyl-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anions (**5**) with reactive electrophiles such as triflates. The stereochemical relationship of the two groups added to the ring could, by analogy with Kundig's results, give information regarding the stereochemistry of the initial alkylation, as the acyl incorporation would occur only from the face of the ring coordinating the $Cr(CO)_3$ group. Unfortunately, none of the expected product could be isolated from the reaction as the only acylated product obtained was **11**. While an interesting and significant product, the 2-acetyl-3-methyl-3-phenyl-1,4-cyclohexadiene, has lost the relative stereochemical information which was sought. The low yield of **12** isolated from this reaction was also unexpected. This is the first reaction of which we are aware in which such an alkylation has occurred without CO incorporation. An NOE experiment indicated that the two methyl groups are trans. The stereochemical significance of this finding is uncertain as the stereospecificity of the addition of the second methyl group without CO incorporation is without precedent. The second alkylation may have occurred directly on the ring in an exo fashion to generate the trans product.

We postulated that alkylation of dianion **4** occurs at the phenyl-substituted ring position to generate anion **14**. This species is structurally similar to the intermediate generated in reactions of **1** which has been characterized by ^1H and ^{13}C NMR. Protonation of **14** with excess TFAA is postulated to generate a dienol ether, which hydrolyzed under acidic conditions to the [4-alkyl-4-(η^6-4-methoxyphenyl)cyclohex-2-en-1-one]tricarbonylchromium. Cleavage of the remaining $Cr(CO)_3$ group with iodine generates the free 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one products (**15a–c**). The reasons for the relative low yields of the desired products from the reaction of **3** are not fully understood at this time.

Conclusions

Lithium anthracenide has proved to be an excellent reagent for chemical reduction of (η^6:η^6-biphenyl)bis(tricarbonylchromium) to the (η^5:η^5-biphenyl)bis(tricarbonylchromium) dianion. The (η^5:η^5-biphenyl)bis(tricarbonylchromium) dianion (**2**) has been isolated and characterized by IR, ^1H NMR, and ^{13}C NMR spectroscopy. The dianion reacts with electrophiles such as H_2O, D_2O, methyl iodide, and primary alkyl bromides, tosylates, and sulfates in a highly stereoselective and regioselective manner to form the [μ-6-substituted-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anion (**5**). Appropriate workup of the alkyl derivatives which cleanly form **5**, yields 2-alkylbiphenyls (**6**) or [5-alkyl-5-(η^6-phenyl)-1,3-cyclohexadiene]tricarbonylchromiums (**8**) in excellent yields. The $Cr(CO)_3$ group can be readily removed to provide high yields of 5-alkyl-5-phenyl-1,3-cyclohexadienes. [μ-6-Methyl-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anion (**5c**) reacted with methyl triflate to undergo a second alkylation, eventually producing 2-acetyl-3-methyl-3-phenyl-1,4-cyclohexadiene (**11**) in fair yield. Reaction of the (η^5:η^5-biphenyl)bis(tricarbonylchromium) dianion (**2**) with halides which are more prone to electron transfer or steric problems, such as *tert*-butyl bromide, benzyl bromide, allyl bromide, and isopropyl bromide, resulted in the competitive formation of 4-substituted products following workup with either I_2 or TFAA followed by I_2.

(η^6:η^6-4,4′-Dimethoxybiphenyl)$[Cr(CO)_3]_2$ (**3**) was reduced to a similar dianion with lithium naphthalenide, which was stable

(25) All compounds discussed have been fully characterized by ^1H NMR, ^{13}C NMR, IR, and mass spectral analysis. IR and NMR data for **15c** are in agreement with those reported in the literature (see ref 27a).

(26) (η^6-Anisole)tricarbonylchromium has been reacted with nucleophiles to generate anionic intermediates similar to **5**. Protonation of these species with excess TFAA also resulted in the production of conjugated cyclohexenones (see Semmelhack, M. F.; Harrison, J. J.; Thebtaranonth, Y. *J. Org. Chem.* **1979**, *44*, 3275).

(27) (a) Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391. (b) Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (c) Sanchez, I. H.; Tallabs, F. R. *Chem. Let.* **1981**, 891.

(28) Semmelhack, M. F.; Hall, H. T. *J. Am. Chem. Soc.* **1974**, *96*, 7092.

(29) (a) Kundig, E. P.; Simmons, D. P. *Chem. Commun.* **1983**, 1320. (b) Kundig, E. P.; Desobry, V.; Simmons, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 6962. (c) Desobry, V.; Kundig, E. P. *Helv. Chim. Acta* **1981**, *64*, 1288.

only at low temperatures, and could be reacted with certain primary electrophiles such as tosylates under altered reaction conditions to give synthetically important 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-ones. Isolation of 4-allyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one (**15c**) completed a formal synthesis of the synthetically important Sceletium alkaloid, *O*-methyljoubertiamine. This approach represents a new and short entry into a number of biologically active alkaloids. While the yields are modest, the route is extremely short and direct when compared to current literature approaches.[27]

Experimental Section

Manipulations of air-sensitive materials were conducted in a VAC argon or nitrogen drybox. Additional manipulations involved Schlenk apparatus connected to a double manifold providing vacuum and dry argon. THF and Bu_2O were freshly distilled from Na/K alloy under argon immediately before use. HMPA was dried over molecular sieves and purged with argon. Deuterated solvents were stored in the drybox. DMF-d_7 was dried over activated Al_2O_3. THF-d_8 was dried over Na/K alloy, subjected to three freeze–pump–thaw cycles and distilled.

(Arene)metalcarbonyl anion solutions were dissolved or generated in anhydrous deuterated solvents with use of 5-mm Wilmad NMR tubes attached to Teflon plug valves[30] in the nitrogen drybox. ^{1}H NMR spectra were typically obtained on a Nicolet NT-360 or Varian VXR-200. ^{13}C NMR spectra were obtained on the Varian VXR-200. Chemical shifts are reported in parts per million in reference to TMS or deuterated solvent where appropriate.

Infrared spectra were recorded on a Perkin-Elmer 283 IR spectrophotometer. Air-sensitive samples were dissolved in THF by using standard Schlenk techniques. NaCl IR solution cells were capped with septa, flushed with argon, and loaded by transferring the prepared solution via cannula. The sample was placed in the spectrophotometer. The 2000–1600 cm^{-1} region was scanned immediately.

Analytical GC was performed on a Hewlett-Packard 5890A gas chromatograph equipped with 10–15 ft lengths of $^1/_8$ in. stainless steel tubing packed with 5% SP 2100 on a Supelco support[31] and interfaced with a Perkin-Elmer LCI-100 integrator. GC yields were quantitated by determining response factors for pure samples and calculating the yield relative to an internal standard. Preparative GC was performed on a Varian 920 GC equipped with 6–12 ft lengths of $^1/_4$ in. stainless steel tubing packed with the same Supelco SP 2100 material.

Product purification was typically performed by column chromatography with use of Merck flash silica gel 60 (230–400 mesh). Similar results were obtained from Analtech preparative thick-layer Uniplates. Eluents such as hexane and $CHCl_3$ were distilled prior to use. Whatman reverse-phase TLC plates provided a useful alternative in some instances.

Elemental analyses were performed by Galbraith Labs, Knoxville, TN. High-resolution mass spectra were obtained from the Midwest Regional Center for Mass Spectrometry, University of Nebraska—Lincoln.

Synthesis of (η^6:η^6-Biarene)bis(tricarbonylchromium) Complexes. The bis(tricarbonylchromium) complex of biphenyl (**1**) was prepared by a method described elsewhere.[32] In a similar method, **(η^6:η^6-4,4′-dimethoxybiphenyl)bis(tricarbonylchromium)** (**3**) was prepared from 4,4′-dimethoxybiphenyl (22.4 mmol) and $Cr(CO)_6$ (63.6 mmol) by refluxing in 300 mL of Bu_2O and 35 mL of THF for 6 days. The reaction mixture was cooled to room temperature and vacuum filtered. The filtrate was washed with hexane. Unreacted $Cr(CO)_6$ was sublimed at 40 °C, 0.5 Torr to leave **3** (60%). IR (THF) 1963, 1895 cm^{-1}. ^{1}H NMR ($CDCl_3$, 360 MHz): 5.79 (d, 4 H, J = 6.96 Hz), 5.16 (d, 4 H, J = 6.96 Hz), 3.73 (s, 6 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 232.1, 142.9, 98.8, 76.8, 55.8.

(η^5:η^5-Biphenyl)bis(tricarbonylchromium) Dianion (2). Preparation of **2** ($C_{34}H_{42}O_{10}Cr_2Li_2$, FW = 728.58) is reported in a previous paper.[10a] The dilithium salt can be isolated and stored in a drybox.

Generation of [μ-6-Substituted-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) Anions. Anions were generated in situ in the NMR tube. In a general procedure, **2** was reacted with the electrophile in 1.5 mL of DMF-d_7 in the drybox. The reaction mixture was stirred with a pipet for a few seconds until it became clear. The solution was then filtered through a pipet packed with fine glass wool into a Young valve equipped 5-mm NMR tube.

[μ-6-(η^6-Phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anion (5a) was produced from **2** (0.275 mmol) and water (0.100 mmol). ^{1}H NMR (DMF-d_7, 200 MHz): 5.58 (t, 2 H, J = 6.3 Hz), 5.40 (t, 1 H, J = 6.3 Hz), 5.27 (d, 2 H, J = 5.7 Hz), 4.98 (dt, 1 H, J = 5.4 Hz), 4.58 (t, 2 H, J = 6.3 Hz), 3.30 (t, 1 H, J = 5.7 Hz), 2.70 (t, 2 H, J = 6.3 Hz), THF peaks were observed at 3.62 and 1.78 ppm. ^{13}C NMR (DMF-d_7, 50 MHz): 242.1, 234.8, 122.8, 95.9, 95.8, 93.3, 92.9, 75.9, 51.5, 41.7.

[μ-6-Deuterio-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anion (5b) was produced from **2** (0.192 mmol) and D_2O (0.19 mmol). ^{1}H NMR (DMF-d_7, 200 MHz): 5.59 (t, 2 H, J = 6.57 Hz), 5.41 (t, 1 H, J = 6.73 Hz), 5.31 (d, 2 H, J = 7.07 Hz), 4.99 (t, 1 H, J = 5.56 Hz), 2.67 (d, 2 H, J = 6.12 Hz). ^{13}C NMR (DMF-d_7, 50 MHz): 242.1, 234.8, 122.8, 95.9, 95.8, 92.9, 75.9, 51.1, 41.3.

[μ-6-Methyl-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) Anion (5c). **2** (0.146 mmol) was reacted with CH_3I (0.159 mmol) in the drybox. ^{1}H NMR (DMF-d_7, 200 MHz): 6.28 (d, 2 H, J = 5.9 Hz), 5.78 (t, 1 H, J = 6.0 Hz), 5.60 (t, 2 H, J = 5.9 Hz), 5.09 (t, 1 H, J = 5.2 Hz), 4.55 (t, 2 H, J = 6.1 Hz), 2.29 (d, 2 H, J = 6.2 Hz), 0.71 (s, 3 H). ^{13}C NMR (DMF-d_7, 50 MHz): 241.1, 235.6, 125.2, 98.4, 96.5, 96.1, 92.1, 75.9, 57.2, 40.7, 34.9.

[μ-6-Ethyl-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anion (5d) was produced from the reaction of **2** (0.190 mmol) with 1-BrC_2H_5 (0.202 mmol). ^{1}H NMR (DMF-d_7, 200 MHz): 6.21 (s, 2 H, J = 6.3 Hz), 5.82 (t, 1 H, J = 5.9 Hz), 5.51 (t, 2 H, J = 6.3 Hz), 5.00 (t, 1 H, J = 5.2 Hz), 4.56 (t, 2 H, J = 5.9 Hz), 2.26 (d, 2 H, J = 6.9 Hz), 1.11 (q, 2 H, J = 7.5 Hz), 0.76 (t, 3 H, J = 7.4 Hz). ^{13}C NMR (DMF-d_7, 50 MHz): 241.1, 235.3, 124.3, 99.2, 97.4, 96.3, 91.0, 76.0, 56.3, 44.3, 40.1, 8.0.

[μ-6-(3-Carbethoxypropyl)-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anion (5g) was produced from the reaction of **2** (0.172 mmol) with ethyl 4-bromobutanoate (0.174 mmol). ^{1}H NMR (DMF-d_7, 200 MHz): 6.25 (d, 2 H, J = 6.2 Hz), 5.85 (t, 1 H, J = 5.4 Hz), 5.54 (t, 2 H, J = 6.0 Hz), 5.01 (t, 1 H, J = 5.4 Hz), 4.57 (t, 2 H, J = 5.3 Hz), 4.03 (q, 2 H, J = 6.5 Hz), 2.27 (d, 2 H, J = 6.3 Hz), 2.11 (t, 2 H, J = 6.5 Hz), 1.7 (m, 2 H), 1.17 (t, 3 H), 1.1 (m, 2 H). ^{13}C NMR (DMF-d_7, 50 MHz): 241.1, 135.5, 173.4, 124.9, 99.2, 97.5, 96.4, 91.1, 76.1, 56.5, 47.8, 44.0, 35.0, 19.5, 14.3.

[μ-6-(3-Cyanopropyl)-6-(η^6-phenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anion (5h) was produced from the reaction of **2** (0.119 mmol) with 4-bromobutyronitrile (0.119 mmol). ^{1}H NMR (DMF-d_7, 200 MHz): 6.28 (d, 2 H, J = 5.8), 5.90 (t, 1 H, J = 5.8 Hz), 5.57 (t, 2 H, J = 5.5 Hz), 5.05 (t, 1 H, J = 4.4 Hz), 4.60 (t, 2 H, J = 5.5 Hz), 2.4–2.2 (m, 6 H), 1.3–1.1 (m, 2 H). ^{13}C NMR (DMF-d_7, 50 MHz): 241.2, 235.6, 124.2, 120.7, 99.4, 97.9, 96.5, 91.2, 76.4, 56.1, 47.2, 43.9, 20.2, 17.1.

[μ-6-(η^6-Phenyl)-6-(5-hexenyl)(1–5-η^5)-cyclohexadienyl]bis(tricarbonylchromium) anion (5l) was produced from the reaction of **2** (0.143 mmol) with 6-bromo-1-hexene (0.133 mmol). ^{1}H NMR (DMF-d_7, 200 MHz): 6.26 (d, 2 H, J = 6.5 Hz), 5.95–5.70 (m, 2 H), 5.54 (t, 2 H, J = 6.8 Hz), 5.05–4.83 (m, 3 H), 4.56 (t, 2 H, J = 6.3 Hz), 2.29 (d, 2 H, J = 6.6 Hz), 2.12–1.05 (m, 8 H). ^{13}C NMR (DMF-d_7, 50 MHz): 241.4, 235.8, 139.0, 127.4, 114.3, 99.4, 97.6, 96.4, 91.9, 76.1, 57.0, 48.4, 44.2, 32.8, 27.7, 23.0.

Mono(tricarbonylchromium)-Complexed Intermediates. [4-(η^6-Phenyl)-1,3-cyclohexadiene]tricarbonylchromium (7). **2** (0.869 mmol) was loaded in the drybox into a 50-mL round-bottom flask and dissolved in 35 mL of THF. Water (0.869 mmol) was added neat from a microsyringe, and mixture was stirred for 10 min. After 1 min, the color changed to a clear orange solution. TFAA (0.87 mmol) was added neat from a microsyringe, producing a color change within seconds. The reaction was poured onto silica gel and quickly stripped to dryness on a rotary evaporator before purifying the product on a silica gel column under argon. **7** was isolated as a viscous orange oil (0.83 mmol) for 96% yield. IR (CH_2Cl_2): 1972, 1894 cm^{-1}. ^{13}C NMR ($CDCl_3$, 50 MHz): 233.0, 132.2, 128.5, 124.1, 122.7, 111.0, 92.9, 91.0, 89.4, 24.6, 22.9. Mass spectrum, calcd for $C_{15}H_{12}CrO_3$ 292.0192, found 292.0192.

[5-Methyl-5-(η^6-phenyl)-1,3-cyclohexadiene]tricarbonylchromium (8c). **5c**, from the above NMR experiment, was protonated with TFAA (0.138 mmol) in the drybox. ^{13}C NMR (DMF-d_7, 50 MHz): 234.7, 133.5, 125.5, 124.4, 123.5, 122.0, 96.0, 95.7, 94.5, 93.7, 93.6, 39.8, 37.8. The ^{13}C signal for the methyl group was obscured by the DMF-d_7 multiplet at 30.1 ppm.

[5-Ethyl-5-(η^6-phenyl)-1,3-cyclohexadiene]tricarbonylchromium (8d) was generated from the analogous NMR experiment with the addition of TFAA (0.19 mmol). IR ($CHCl_3$): 1970, 1894 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): 7.64–7.14 (m, 5 H), 6.04 (ddd, 1 H, J = 9.77, 4.88, 0.70 Hz), 5.93 (d, 1 H, J = 9.73 Hz), 5.88–5.83 (m, 1 H), 5.79–5.70 (m, 1 H), 2.58 (ddd, 1 H, J = 17.55, 4.72, 1.33 Hz), 2.43 (ddd, 1 H, J = 17.55, 3.93, 2.22 Hz), 1.89 (dq, 1 H, J = 13.70, 7.4 Hz), 1.78 (dq, 1 H, J = 13.70, 7.40 Hz), 0.73 (t, 3 H, J = 7.40 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 233.2, 130.3, 125.0, 123.1, 118.9, 94.0, 93.8, 92.8, 90.3, 90.2, 40.4, 35.5.

(30) These NMR tubes are available from R. J. Brunfeldt Glass Co., Bartlesville, OK.

(31) This packing material was purchased from Supelco with liquid-phase precoating on the Supelco support.

(32) Top, S.; Jaouen, G. *J. Organomet. Chem.* **1979**, *182*, 381.

[5-(3-Carbethoxypropyl)-5-(η^6-phenyl)-1,3-cyclohexadiene]tricarbonylchromium (8g) was generated with the addition of TFAA (0.173 mmol). ^{13}C NMR (DMF-d_7, 50 MHz): 234.5, 173.1, 131.1, 125.8, 124.8, 123.4, 120.7, 96.2, 95.7, 95.2, 93.1, 92.9, 60.3, 40.5, 40.0, 35.6, 34.5, 21.1, 14.3.

[5-(3-Cyanopropyl)-5-(η^6-phenyl)-1,3-cyclohexadiene]tricarbonylchromium (8h). TFAA (0.12 mmol) was added to the anion produced in the respective NMR experiment. ^{13}C NMR (DMF-d_7, 50 MHz): 234.6, 130.8, 125.9, 125.1, 123.5, 120.7, 120.5, 96.2, 95.7, 93.2, 93.1, 40.5, 39.8, 30.3, 21.9, 17.2. The product was purified by column chromatography under argon. Mass spectrum, calcd for $C_{19}H_{17}CrNO_3$ 359.0614, found 359.0612.

General Procedure for Reaction of 2 with Electrophiles. The dilithium salt of **2** was dried of residual THF[12] for constant weight in the drybox (0.55 mmol) and loaded into a two-neck round-bottom flask. The flask was brought to the double manifold by utilizing standard Schlenk techniques to exclude air. THF (15 mL) was syringed into the flask. An electrophile (0.61 mmol) was syringed neat at room temperature. Time allowed for reaction ranged from 30 min to 12 h depending on electrophile. Oftentimes, the initial dark brown reaction mixture turned to a translucent yellow or orange solution.

(A) I_2. Substituted biphenyl products were produced from I_2 oxidation. I_2 (8 equiv) was dissolved in 20 mL of THF in a separate two-neck flask. The reaction flask was cooled to −78 °C and the I_2 was transferred to the reaction flask via a cannula. After 3 h, the reaction was allowed to warm to room temperature. After an additional 3 h, the reaction mixture was added to an equal volume of ether which in turn was extracted twice with aqueous saturated $Na_2S_2O_3$, 1 M HCl, and saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, and reduced in volume for product purification.

2-Methylbiphenyl (6c). Reaction of **2** with CH_3I resulted in 96% GC yield with naphthalene as the internal standard. ^1H NMR ($CDCl_3$, 200 MHz): 7.54–7.19 (m, 9 H), 2.24 (s, 3 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 141.95, 141.91, 135.3, 130.3, 129.8, 129.1, 128.0, 127.2, 126.7, 125.7, 20.4. Mass spectrum, calcd for $C_{13}H_{12}$ 168.0939, found 168.0935.

2-Ethylbiphenyl (6d). The electrophile for the reaction was 1-BrC_2H_5. GC analysis indicated 97% yield. Vacuum sublimation (3 mTorr) at ambient temperature for 36 h removed biphenyl and naphthalene, leaving **6d** as a clear liquid in 63% yield. ^1H NMR ($CDCl_3$, 200 MHz): 7.39–7.18 (m, 9 H), 2.59 (q, 2 H, J = 7.5 Hz), 1.09 (t, 3 H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 142.1, 141.7, 141.6, 130.0, 129.2, 128.6, 128.0, 127.5, 126.7, 125.5, 26.2, 15.6. Mass spectrum, calcd for $C_{14}H_{14}$ 182.1096, found 182.1093.

2-Heptylbiphenyl (6f). Use of 1-BrC_7H_{15} as the electrophile resulted in 85% GC yield of **6f**. ^1H NMR ($CDCl_3$, 200 MHz): 7.4–7.1 (m, 9 H), 2.56 (t, 2 H, J = 7.9 Hz), 1.45 (m, 2 H), 1.16 (m, 8 H), 0.83 (t, 3 H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 142.1, 141.9, 140.4, 130.0, 129.3, 129.2, 128.0, 127.3, 126.7, 125.5, 33.0, 31.7, 31.4, 29.4, 29.0, 22.7, 14.1.

Isopropyl-Substituted Biphenyls. Use of 2-BrC_3H_7 as the electrophile resulted in an isolated yield of 29% for three isomers after separation by prepatative GC. **2-Isopropylbiphenyl (6r).** 25% yield. ^1H NMR ($CDCl_3$, 360 MHz): 7.5–7.2 (m, 9 H), 3.05 (m, 1 H), 1.15 (d, 6 H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 146.4, 142.1, 141.1, 130.0, 129.3, 128.0, 127.6, 126.7, 125.5, 125.3, 29.4, 24.3. Mass spectrum, calcd for $C_{15}H_{16}$ 196.1252, found 196.1257. **3-Isopropylbiphenyl.** 0.8% yield. ^1H NMR ($CDCl_3$, 360 MHz): 7.6–7.3 (m, 9 H), 3.0 (m, 1 H, J = 6.8 Hz), 1.31 (d, 6 H, J = 6.8 Hz). Mass spectrum, found 196.1250. **4-Isopropylbiphenyl.** 3.2% yield. ^1H NMR ($CDCl_3$, 360 MHz): 7.6 (d, 2 H), 7.5 (d, 2 H), 7.44 (t, 2 H), 7.32 (t, 3 H), 2.95 (m, 1 H), 1.3 (d, 6 H, J = 6.9 Hz). Mass spectrum, found 196.1247.

***tert*-Butyl-Substituted Biphenyls.** Use of *tert*-butyl bromide as the electrophile produced a 44.5% yield of isomers after separation by preparative GC. Biphenyl was isolated in 30.0% yield. **2-*tert*-Butylbiphenyl (6s).** 11.0% yield. ^1H NMR ($CDCl_3$, 360 MHz): 7.54 (d, 2 H), 7.32–7.25 (m, 6 H), 7.18 (t, 1 H), 1.20 (s, 9 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 147.7, 145.4, 142.1, 132.6, 130.1, 127.2, 126.7, 126.5, 124.9, 36.6, 32.7. Mass spectrum, calcd for $C_{16}H_{18}$ 210.1409, found 210.1401. **3-*tert*-Butylbiphenyl.** 5.8% yield. ^1H NMR ($CDCl_3$, 360 MHz): 7.6 (d, 2 H), 7.5–7.3 (m, 7 H), 1.40 (s, 9 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 151.6, 141.9, 141.1, 128.7, 128.5, 127.4, 127.1, 124.5, 124.4, 124.3, 34.9, 31.5. Mass spectrum, found 210.1410. **4-*tert*-Butylbiphenyl.** 27.7% yield. ^1H NMR ($CDCl_3$, 360 MHz): 7.6–7.5 (m, 4 H), 7.5–7.4 (m, 4 H), 7.32 (t, 3 H), 1.38 (s, 9 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 150.3, 141.1, 138.4, 128.7, 127.1, 127.0, 126.8, 125.8, 34.6, 31.4. Mass spectrum, found 210.1407.

Benzyl-Substituted Biphenyls. Benzyl bromide, when reacted with **2**, resulted in 2-, 3- and 4-benzyl-substituted biphenyls in a ratio of 5.5, 2.3, and 1.0, respectively. A total yield of isomers equaled 24% after separation by preparative GC. **2-Benzylbiphenyl (6t).** ^1H NMR ($CDCl_3$, 360 MHz): 7.33–7.19 (m, 14 H), 3.95 (s, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 142.5, 141.9, 141.7, 138.5, 130.6, 130.4, 129.6, 129.1, 128.5, 128.3, 127.7, 127.1, 126.4, 126.0, 39.3. Mass spectrum, calcd for $C_{19}H_{16}$ 244.1252, found 244.1248. **3-Benzylbiphenyl.** ^1H NMR ($CDCl_3$, 360 MHz): 7.55–7.23 (m, 14 H), 4.05 (s, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 141.6, 141.5, 141.3, 141.0, 129.0, 128.9, 128.7, 128.5, 127.92, 127.87, 127.3, 127.2, 126.2, 125.0, 119.9, 42.1. Mass spectrum, found 244.1252. **4-Benzylbiphenyl.** ^1H NMR ($CDCl_3$, 360 MHz): 7.27–7.24 (m, 14 H), 4.0 (s, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 141.0, 140.3, 139.0, 138.3, 129.0, 128.7, 128.5, 127.2, 127.1, 127.0, 126.1, 41.6. Mass spectrum, found 244.1242.

(B) TFAA/I_2. 5-Alkyl-5-phenyl-1,3-cyclohexadiene and 4-alkyl-1-phenyl-1,3-cyclohexadiene products were obtained when 4 equiv of TFAA were injected neat into the reaction mixture at room temperature prior to I_2 oxidation.

5-Methyl-5-phenyl-1,3-cyclohexadiene (9c). ^1H NMR ($CDCl_3$, 360 MHz): 7.63–7.17 (m, 5 H), 6.00 (ddd, 1 H, J = 9.96, 4.94, 0.73 Hz), 5.94–5.87 (m, 1 H), 5.81 (d, 1 H, J = 9.70 Hz), 5.76–5.70 (m, 1 H), 2.62 (ddd, 1 H, J = 17.58, 4.16, 1.89 Hz), 2.37 (ddd, 1 H, J = 17.58, 4.54, 1.77 Hz), 1.42 (s, 3 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 149.3, 135.8, 128.1, 126.1, 125.9, 125.1, 123.1, 122.9, 38.9, 38.4, 26.6. Mass spectrum, calcd for $C_{13}H_{14}$ 170.1096, found 170.1099.

5-Butyl-5-phenyl-1,3-cyclohexadiene (9e). Use of 1-BrC_4H_9 as the electrophile resulted in 63% GC yield of **9e**. Biphenyl GC yield equaled 35%. A spectroscopically pure sample was isolated by preparative GC. ^1H NMR ($CDCl_3$, 200 MHz): 7.4–7.1 (m, 5 H), 6.03 (ddd, 1 H, J = 9.70, 4.76, 1.10 Hz), 5.93 (dt, 1 H, J = 9.67, 2.18 Hz), 5.89–5.82 (m, 1 H), 5.79–5.69 (m, 1 H), 2.59 (ddd, 1 H, J = 17.70, 4.44, 1.28 Hz), 2.43 (ddd, 1 H, J = 17.36, 4.03, 1.97 Hz), 1.93–1.62 (m, 2 H), 1.30–1.00 (m, 4 H), 0.83 (t, 3 H, J = 7.06 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 147.5, 134.3, 128.0, 126.4, 125.7, 125.5, 123.6, 123.5, 41.5, 40.5, 36.7, 26.8, 23.4, 13.9. Mass spectrum, calcd for $C_{16}H_{20}$ 212.1565, found 212.1568.

5-(3-Carbethoxypropyl)-5-phenyl-1,3-cyclohexadiene (9g) was isolated as a colorless oil in 77% yield from the reaction of **2** with ethyl 4-bromobutanoate. ^1H NMR ($CDCl_3$, 200 MHz): 7.37–7.15 (m, 5 H), 6.04 (dd, 1 H, J = 9.74, 4.88 Hz), 5.94 (d, 1 H, J = 9.70 Hz), 5.90–5.86 (m, 1 H), 5.78–5.71 (m, 1 H), 4.09 (q, 2 H, J = 7.13 Hz), 2.58 (ddd, 1 H, J = 17.45, 4.49, 1.51 Hz), 2.43 (ddd, 1 H, J = 17.50, 4.09, 2.00 Hz), 2.22 (t, 2 H, J = 7.38 Hz), 1.94–1.84 (m, 1 H), 1.80–1.70 (m, 1 H), 1.51–1.40 (m, 2 H), 1.23 (t, 3 H, J = 7.16 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 173.4, 147.0, 133.7, 128.1, 126.3, 125.9, 125.4, 123.9, 123.5, 60.1, 41.5, 39.8, 36.7, 34.8, 20.2, 14.2. Mass spectrum, calcd for $C_{18}H_{22}O_2$ 270.1620, found 270.1614.

5-(3-Cyanopropyl)-5-phenyl-1,3-cyclohexadiene (9h). 93% GC yield. ^1H NMR ($CDCl_3$, 360 MHz): 7.61–7.19 (m, 5 H), 6.08 (dd, 1 H, J = 9.8, 4.8 Hz), 5.95–5.87 (m, 1 H), 5.92 (d, 1 H, J = 9.5 Hz), 5.80–5.72 (m, 1 H), 2.60 (ddd, 1 H, J = 17.51, 4.30, 1.80 Hz), 2.42 (ddd, 1 H, J = 17.50, 4.34, 1.86 Hz), 2.25 (t, 2 H, J = 12.61 Hz), 1.99–1.96 (m, 1 H), 1.94–1.91 (m, 1 H), 1.57–1.45 (m, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 147.0, 132.8, 128.3, 126.2, 125.4, 124.5, 123.6, 39.3, 37.0, 29.7, 20.9, 17.7.

5-(2-Cyanoethyl)-5-phenyl-1,3-cyclohexadiene (9i). 3-Bromopropionitrile reacted with **2** to yield 67% **9i**, a colorless oil. ^1H NMR ($CDCl_3$, 200 MHz): 7.45–7.20 (m, 5 H), 6.13 (ddd, 1 H, J = 9.56, 5.13, 1.10 Hz), 5.98–5.88 (m, 1 H), 5.88 (dt, 1 H, J = 9.54, 0.94 Hz), 5.83–5.72 (m, 1 H), 2.61 (ddd, 1 H, J = 17.57, 4.00, 1.88 Hz), 2.41 (ddd, 1 H, J = 17.73, 4.53, 1.61 Hz), 2.20–2.09 (m, 4 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 145.1, 131.1, 128.5, 126.6, 126.1, 125.2, 123.5, 120.0, 41.1, 36.6, 35.2, 12.7. Mass spectrum, calcd for $C_{15}H_{15}N$ 209.1205, found 209.1206.

5-Isobutyl-5-phenyl-1,3-cyclohexadiene (9j). 62% isolated yield resulted from reaction of **2** with isobutyl bromide. ^1H NMR ($CDCl_3$, 360 MHz): 7.60–7.14 (m, 5 H), 6.04–5.97 (m, 2 H), 5.88–5.83 (m, 1 H), 5.76 (m, 1 H), 2.58 (ddd, 1 H, J = 17.39, 4.59, 1.57 Hz), 2.44 (ddd, 1 H, J = 17.36, 4.07, 1.96 Hz), 1.84 (dd, 1 H, J = 13.90, 5.72 Hz), 1.68 (dd, 1 H, J = 13.92, 5.70 Hz), 1.62–1.53 (m, 1 H), 0.76 (d, 3 H, J = 6.60 Hz), 0.74 (d, 3 H, J = 6.65 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 147.6, 135.0, 128.7, 127.9, 127.2, 126.4, 125.7, 125.6, 123.6, 123.4, 49.6, 41.8, 36.8, 24.9, 24.7, 24.6. Mass spectrum, calcd for $C_{16}H_{20}$ 212.1565, found 212.1568.

5-Phenyl-5-(2-phenylethyl)-1,3-cyclohexadiene (9k) was produced from the reaction of **2** with the corresponding primary bromide. 62% GC yield. 33% Biphenyl GC yield. ^1H NMR ($CDCl_3$, 360 MHz): 7.42–7.09 (m, 10 H), 6.09 (dd, 1 H, J = 9.72, 4.90 Hz), 6.01 (dd, 1 H, J = 9.73, 0.72 Hz), 5.90 (m, 1 H), 5.79–5.73 (m, 1 H), 2.63 (ddd, 1 H, J = 17.60, 4.48, 1.41 Hz), 2.53–2.36 (m, 3 H), 2.25–2.16 (m, 1 H), 2.08–1.99 (m, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 147.0, 142.9, 133.6, 128.3, 128.25, 128.2, 126.4, 126.0, 125.6, 125.5, 124.0, 123.5, 42.5, 41.7, 36.9, 31.1. Mass spectrum, calcd for $C_{20}H_{20}$ 260.1565, found 260.1553.

5-(5-Hexenyl)-5-phenyl-1,3-cyclohexadiene (9l). 68% GC yield. ^{1}H NMR ($CDCl_3$, 200 MHz): 7.62–7.17 (m, 5 H), 6.04 (ddd, 1 H, J = 9.60, 4.60, 1.20 Hz), 5.92 (dt, 1 H, J = 9.60, 2.20 Hz), 5.87–5.82 (m, 2 H), 5.79–5.68 (m, 1 H), 5.00–4.86 (m, 2 H), 2.58 (ddd, 1 H, J = 17.40, 4.40, 1.40 Hz), 2.42 (ddd, 1 H, J = 17.40, 4.00, 2.00 Hz), 2.10–1.10 (m, 8 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 147.4, 139.0, 134.3, 128.0, 126.4, 125.8, 125.5, 123.6, 123.5, 114.2, 41.6, 40.5, 36.7, 33.6, 30.0, 24.1. Mass spectrum, calcd for $C_{18}H_{22}$ 238.1721, found 238.1714.

5-(Cyclopropylmethyl)-5-phenyl-1,3-cyclohexadiene (9m). Cyclopropylmethyl bromide produced 80% GC yield of **9m** when reacted with **2**. A spectroscopically pure sample was isolated by preparative GC. ^{1}H NMR ($CDCl_3$, 200 MHz): 7.39–7.18 (m, 5 H), 6.13 (dt, 1 H, J = 9.73, 1.92 Hz), 6.00 (ddd, 1 H, J = 9.70, 4.75, 1.35 Hz), 5.86–5.75 (m, 2 H), 2.62–2.60 (m, 2 H), 1.77 (dd, 1 H, J = 13.79, 6.02 Hz), 1.64 (dd, 1 H, J = 13.86, 6.93 Hz), 0.47–0.39 (m, 1 H), 0.32–0.28 (m, 2 H), –0.01–0.09 (app dd, 2 H, J = 4.94, 1.70 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 148.2, 135.9, 127.3, 126.5, 124.4, 124.2, 46.8, 43.1, 36.1, 7.6, 5.7, 4.9. Mass spectrum, calcd for $C_{16}H_{18}$ 210.1409, found 210.1409.

5-Phenyl-5-(2-propenyl)-1,3-cyclohexadiene (9n). Allyl tosylate addition to **2** resulted in an instantaneous color change to orange. GC analysis indicated a 50% yield. Further attempt to isolate **9n** by preparative GC resulted in decomposition of product to several unknowns. ^{1}H NMR ($CDCl_3$, 200 MHz): 7.62–7.15 (m, 5 H), 6.06 (ddd, 1 H, J = 9.78, 4.84, 1.21 Hz), 5.91 (dt, 1 H, J = 9.78, 1.08 Hz), 5.93–5.85 (m, 1 H), 5.79–5.72 (m, 1 H), 5.55 (m, 1 H), 4.95 (m, 1 H), 2.58–2.50 (m, 4 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 146.5, 135.0, 133.8, 128.0, 126.4, 126.0, 125.6, 123.9, 123.6, 117.4, 44.9, 36.0.

5-Benzyl-5-phenyl-1,3-cyclohexadiene (9o). Benzyl tosylate reacted with **2** to yield **9o** in 55% isolated yield.[33] ^{1}H NMR ($CDCl_3$, 200 MHz): 7.30–7.08 (m, 8 H), 6.74 (m, 2 H), 6.05 (m, 2 H), 5.99–5.81 (m, 2 H), 3.06 (s, 2 H), 2.55 (m, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 146.0, 137.7, 134.5, 130.5, 127.8, 127.4, 126.7, 126.0, 125.9, 125.8, 123.9, 46.7, 42.4, 34.6. Mass spectrum, calcd for $C_{19}H_{18}$ 246.1409, found 246.1399.

5-Methyl-5-phenyl-1,3-cyclohexadiene (9p). Use of $(MeO)_2SO_2$ as the electrophile resulted in 61% GC yield. ^{1}H NMR ($CDCl_3$, 360 MHz): 7.63–7.17 (m, 5 H), 6.00 (ddd, 1 H, J = 9.69, 4.94, 0.73 Hz), 5.94–5.87 (m, 1 H), 5.81 (d, 1 H, J = 9.70 Hz), 5.76–5.70 (m, 1 H), 2.62 (ddd, 1 H, J = 17.58, 4.16, 1.89 Hz), 2.37 (ddd, 1 H, J = 17.58, 4.54, 1.77 Hz), 1.42 (s, 3 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 149.3, 135.8, 128.1, 126.1, 125.9, 125.1, 123.1, 122.9, 38.9, 38.4, 26.6.

5-Ethyl-5-phenyl-1,3-cyclohexadiene (9q). Use of $(EtO)_2SO_2$ as the electrophile and subsequent isolation with RPTLC, resulted in 59% yield of **9q**. ^{1}H NMR ($CDCl_3$, 360 MHz): 7.64–7.14 (m, 5 H), 6.04 (ddd, 1 H, J = 9.77, 4.88, 0.70 Hz), 5.93 (d, 1 H, J = 9.73 Hz), 5.88–5.83 (m, 1 H), 5.79–5.70 (m, 1 H), 2.58 (ddd, 1 H, J = 17.55, 4.17, 1.33 Hz), 2.43 (ddd, 1 H, J = 17.55, 3.93, 2.22 Hz), 1.89 (dq, 1 H, J = 13.70, 7.40 Hz), 1.78 (dq, 1 H, J = 13.70, 7.40 Hz), 0.73 (t, 3 H, J = 7.40 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 147.1, 134.0, 128.0, 126.5, 125.8, 125.5, 123.8, 123.5, 41.8, 36.2, 33.2, 8.9.

5-Isopropyl-5-phenyl-1,3-cyclohexadiene (9r). 2-BrC_3H_7 reacted with **2** to yield 35% **9r** after isolation by preparative GC. ^{1}H NMR ($CDCl_3$, 360 MHz): 7.32 (d, 2 H), 7.28 (t, 2 H), 7.15 (t, 1 H), 6.05–5.90 (m, 2 H), 5.82 (dd, 2 H, J = 3.3, 1.0 Hz), 2.61–2.55 (m, 2 H), 2.10 (m, 1 H), 0.84 (d, 3 H, J = 6.8 Hz), 0.79 (d, 3 H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 146.9, 132.9, 127.7, 126.6, 126.0, 125.8, 124.0, 44.8, 37.6, 30.2, 18.7, 18.1. Mass spectrum, calcd for $C_{15}H_{18}$ 198.1408, found 198.1408. **4-Isopropyl-1-phenyl-1,3-cyclohexadiene (13r)** was a second isomer purified for a 1% isolated yield. ^{1}H NMR ($CDCl_3$, 360 MHz): 7.45 (d, 2 H), 7.40 (t, 2 H), 7.21 (t, 1 H), 6.34 (d, 1 H, J = 5.74 Hz), 5.84 (d, 1 H, J = 5.76 Hz), 2.60 (t, 2 H, J = 9.61 Hz), 2.40 (m, 1 H), 2.28 (t, 2 H, J = 9.74 Hz), 1.1 (d, 6 H, J = 6.81 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 146.0, 141.3, 133.9, 128.3, 126.5, 124.7, 121.5, 117.1, 34.6, 26.2, 25.6, 21.1. Mass spectrum, found 198.1407.

5-*tert*-Butyl-5-phenyl-1,3-cyclohexadiene (9s). Use of *tert*-butyl bromide yielded 9.5% **9s** after isolation on preparative GC. Biphenyl was isolated in 30% yield. ^{1}H NMR ($CDCl_3$, 360 MHz): 7.35 (d, 2 H), 7.2–7.1 (m, 3 H), 6.39 (dd, 1 H, J = 9.99, 0.93 Hz), 6.05 (dd, 1 H, J = 9.96, 9.21 Hz), 5.84–5.70 (m, 2 H), 2.75 (dd, 1 H, J = 17.00, 6.7 Hz), 2.60 (d, 1 H, J = 17.00 Hz), 0.90 (s, 9 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 143.2, 134.2, 128.9, 126.7, 126.3, 125.8, 124.2, 123.9, 46.8, 35.8, 28.6, 26.7. Mass spectrum, calcd for $C_{16}H_{20}$ 212.1565, found 212.1562. **4-*tert*-Butyl-1-phenyl-1,3-cyclohexadiene (13s)** was isolated as the major product in 38.9% yield. ^{1}H NMR ($CDCl_3$, 360 MHz): 7.45 (d, 2 H), 7.23 (t, 2 H), 7.21 (t, 1 H), 6.37 (d, 1 H, J = 5.85 Hz), 5.90 (d, 1 H, J = 5.85 Hz), 2.59 (t, 2 H, J = 9.72 Hz), 2.32 (t, 2 H, J = 9.72 Hz), 1.12 (s, 9 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 148.5, 141.2, 143.1, 128.4, 126.6, 124.8, 121.7, 116.2, 35.5, 28.7, 26.7, 24.2. Mass spectrum, found 212.1558.

Dialkylation Reaction of the (η^5:η^5-Biphenyl)bis(tricarbonylchromium) Dianion (2). The dilithium salt of **2** (0.347 mmol) was loaded in the drybox and dissolved in 15 mL of THF. CH_3I (0.355 mmol) was injected neat into the reaction and stirred for 25 min. Methyl triflate (0.352 mmol) was added from a microsyringe and the reaction placed under CO atmosphere by bubbling for 15 min. HMPA (2.5 mL) was added neat. After 3 h, the reaction was quenched with I_2 and subjected to the previously mentioned workup procedures.

2-Methylbiphenyl (6c). Isolated for 52% yield (0.184 mmol).

2-Acetyl-3-methyl-3-phenyl-1,4-cyclohexadiene (11). 19% isolated yield (0.072 mmol, $C_{14}H_{13}O$, FW = 212.29). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.38–7.11 (m, 5 H), 7.03 (td, 1 H, J = 3.63, 1.46 Hz), 5.59 (dtd, 1 H, J = 9.97, 3.10, 1.42 Hz), 5.45 (dt, 1 H, J = 9.96, 1.81 Hz), 3.07–3.01 (m, 2 H), 2.19 (s, 3 H), 1.70 (s, 3 H). A COSY experiment provided data consistent with the assigned structure. ^{13}C NMR ($CDCl_3$, 50 MHz): 198.1, 147.6, 144.6, 137.5, 137.4, 127.9, 126.6, 125.6, 116.8, 41.6, 27.4, 27.1, 25.5. Mass spectrum, calcd for $C_{17}H_{17}O$ 212.1201, found 212.1203.

5,6-Dimethyl-5-phenyl-1,3-cyclohexadiene (12). 2.0% isolated yield (0.033 mmol, $C_{14}H_{16}$, FW = 184.28). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.38–7.15 (m, 5 H), 6.01 (ddd, 1 H, J = 9.54, 5.27, 1.06 Hz), 5.98–5.85 (m, 1 H), 5.84 (dt, 1 H, J = 9.54, 0.90 Hz), 5.63 (ddt, 1 H, J = 9.43, 4.57, 0.90 Hz), 2.49–2.41 (m, 1 H), 1.49 (s, 3 H), 0.58 (d, 3 H, J = 7.26 Hz). An NOE experiment provided evidence for a trans relationship between methyl groups. Mass spectrum, calcd for $C_{14}H_{16}$ 184.1252, found 184.1250.

General Reaction of (η^6:η^6-4,4′-Dimethoxybiphenyl)bis(tricarbonylchromium) (3) with Electrophiles. A solution of lithium naphthalenide was formed by stirring naphthalene (2.17 mmol) with lithium (1.95 mmol) in 25 mL of THF for 2.5 h. **3** (0.93 mmol) was dissolved in 40 mL of THF. Both solutions were cooled in an acetone/CO_2 bath, and then the dark green lithium naphthalenide solution was transferred via a cannula to the cold stirring solution containing the bis complex. A color change to reddish brown was observed. Electrophile (0.94 mmol) was immediately added neat from a microsyringe and stirred at –78 °C for 20 min. TFAA (0.87 mmol) was added neat from a microsyringe and stirred at –78 °C for 15 min. The solution turned red and transparent. I_2 (6.61 mmol) oxidation preceded usual extractions and isolation procedures.

4-Methyl-4-(4-methoxyphenyl)cyclohexanone (15a). When the electrophile equaled methyl triflate in the above procedure, 4,4′-dimethoxybiphenyl (0.27 mmol) was recovered in 29% yield. **15a** (0.26 mmol) was isolated as a colorless oil in 28% yield. IR (CCl_4): 3050–2900, 2835, 1690 (s, br), 1610 (s), 1510 (s), 1460 (br), 1414, 1385, 1370, 1300, 1200 (s, br), 1045, 860, 825 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$, 360 MHz): 7.25 (m, 2 H), 6.88 (m, 2 H), 6.91 (ddd, 1 H, J = 10.17, 1.19, 0.56 Hz), 6.10 (dd, 1 H, J = 10.17, 0.50 Hz), 3.80 (s, 3 H), 2.40 (dddd, 1 H, J = 16.91, 6.64, 4.80, 0.60 Hz), 2.29 (ddd, 1 H, J = 16.88, 10.15, 4.59 Hz), 2.21 (dddd, 1 H, J = 13.22, 6.66, 4.60, 1.26 Hz), 2.12 (ddd, 1 H, J = 13.25, 10.03, 4.82 Hz), 1.54 (s, 3 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 199.4, 158.3, 157.3, 137.1, 128.3, 127.2, 113.9, 55.2, 39.9, 38.1, 34.6, 27.7. Mass spectrum, calcd for $C_{14}H_{16}O_2$ 216.1150, found 216.1154.

4-Ethyl-4-(4-methoxyphenyl)-2-cyclohexenone (15b). Ethyl triflate (1.03 mmol) was added neat from a microsyringe as the electrophile in the above procedure. **15b** (0.24 mmol) was isolated as a colorless oil by preparative TLC in 23% yield. ^{1}H NMR ($CDCl_3$, 360 MHz): 7.08 (m, 2 H), 6.97 (d, 1 H, J = 10.30 Hz), 6.76 (m, 2 H), 6.04 (dd, 1 H, J = 10.24, 0.69 Hz), 3.69 (s, 3 H), 2.24–2.04 (m, 4 H), 1.83–1.67 (m, 2 H), 0.70 (t, 3 H, J = 7.42 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 199.8, 158.1, 155.8, 135.2, 129.3, 127.8, 113.9, 55.2, 43.6, 35.6, 34.5, 34.3, 8.7. Mass spectrum, calcd for $C_{15}H_{18}O_2$ 230.1307, found 230.1313.

4-Allyl-4-(4-methoxyphenyl)-2-cyclohexenone (15c). Optimum yield of **15c** was achieved from the following procedure. A solution of lithium naphthalenide was formed by stirring naphthalene (0.82 mmol) with lithium (0.74 mmol) in 15 mL of THF for 2.5 h. **3** (0.355 mmol) was dissolved in 15 mL of THF. Both solutions were cooled in an acetone/CO_2 bath. The dark green lithium naphthalenide solution was transferred via a cannula to the cold stirring solution containing **3**. A color change to reddish brown was observed. Allyl tosylate (0.368 mmol) was added neat from a microsyringe and stirred at –78 °C for 5 min. The reaction mixture was warmed in a CH_3CN/CO_2 bath for 2 h. TFAA (1.41 mmol) was added neat from a microsyringe and stirred at –41 °C for 30 min. The solution became red and transparent. I_2 (2.48 mmol) was added. The reaction was allowed to warm to room temperature overnight before usual extractions with aqueous solutions of $Na_2S_2O_3$, 1 M HCl, and NaCl. The organic layer was dried over $MgSO_4$. 4,4′-Dimethoxybiphenyl (0.257 mmol) was recovered for a 72% yield. **15c** (0.060 mmol) was isolated as a colorless oil in 17% yield. IR (CCl_4):

(33) Elemental analysis for $C_{19}H_{18}$. Calcd for C 92.64, found 92.20. Calcd for H 7.36, found 7.08.

3100-2890, 2830, 1691 (s, br), 1611, 1513 (s), 1470-1435, 1415, 1385, 1280, 1250, 1182 (s, br), 1113, 1040, 1000, 918, 828 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 360 MHz): 7.21 (m, 2 H), 7.07 (dd, 1 H, J = 10.29, 1.06 Hz), 6.88 (m, 2 H), 6.16 (dd, 1 H, J = 10.27, 0.62 Hz), 5.61-5.49 (m, 1 H), 5.09 (dm, 1 H, J = 17.44 Hz), 5.07 (dm, 1 H, J = 9.81 Hz), 3.80 (s, 3 H), 2.68 (ddt, 1 H, J = 13.98, 5.95, 1.41 Hz), 2.47 (ddt, 1 H, J = 14.03, 8.44, 0.80 Hz), 2.36-2.18 (m, 4 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 199.5, 158.3, 155.4, 134.8, 133.5, 129.3, 127.8, 118.8, 113.9, 55.3, 46.3, 43.2, 35.9, 34.4. Mass spectrum, calcd for $C_{16}H_{18}O_2$ 242.1307, found 242.1307. IR and ^1H NMR data show good agreement with literature values.

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Dependence of Transition-State Structure on Acyl Chain Length for Cholesterol Esterase Catalyzed Hydrolysis of Lipid *p*-Nitrophenyl Esters

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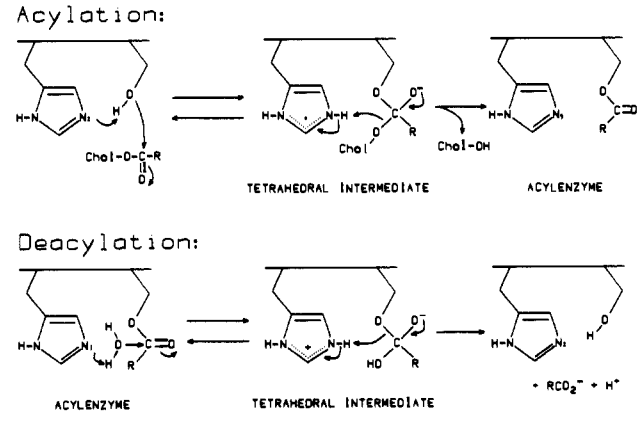
Abstract: Cholesterol esterase (CEase) catalyzes hydrolysis of lipid substrates via a serine esterase mechanism. A variety of reaction kinetic probes has been used to characterize features of the mechanistic anatomy of porcine pancreatic CEase-catalyzed hydrolysis of lipid *p*-nitrophenyl esters that have acyl chain lengths from C_2 to C_{12}. Nucleophilic trapping experiments demonstrate that k_{cat} is rate-limited by deacylation across the homologous series of substrates. The dependence of k_{cat}/K_m on acyl chain length displays a maximum for the C_6 ester. Both the ascending and descending limbs of the structure–reactivity profile give linear free energy plots of ln (k_{cat}/K_m) versus the number of acyl carbons of substrate, with slopes that yield $\Delta\Delta G^{\ddagger} = -430$ and 470 cal/mol per methylene, respectively. Solvent isotope effects ($^{D_2O}k_{cat}/K_m$) decrease from ~2 for short esters to ~1.2 for long esters. Except for the C_2 and C_3 esters, proton inventories of k_{cat}/K_m are linear. These results indicate that the phenomenological transition state for the acylation stage of CEase catalysis is highly variable: For short substrates (C_2 and C_3), serial microscopic transition states contribute to rate determination. For the C_4 substrate, a single transition state that is stabilized by a single general-acid–base proton transfer is rate-determining, while with increasing acyl chain length rate determination shifts between parallel reaction pathways. The deacylation rate constant k_{cat} is nearly invariant for C_4–C_8 substrates but drops off sharply for C_{10} and C_{12} substrates. However, solvent isotope effects ($^{D_2O}k_{cat}$) are ~2, and proton inventories are linear for all substrates. Therefore, both the acylation and deacylation stages of CEase-catalyzed hydrolysis of lipid *p*-nitrophenyl esters have chemical transition states that are stabilized by single proton transfers.

Introduction

Pancreatic cholesterol esterase (CEase[1]) is secreted into the duodenum in response to an oral fat load, where it catalyzes the hydrolysis of cholesteryl esters, phospholipids, and acylglycerols.[2-4] The enzyme is necessary for full absorption of dietary fats, including cholesterol, across the intestinal mucosa into the bloodstream.[5,6] Because of this physiological role and since CEase efficiently catalyzes the hydrolysis of structurally diverse substrates, studies of CEase catalysis are of great interest.

It is believed that CEase belongs to the serine hydrolase class of enzymes[7,8] whose reactions proceed via the acylenzyme mechanism depicted in Scheme I.[9] This mechanism involves nucleophilic attack by serine, aided by general-base catalysis by histidine, on the scissile carbonyl carbon of the substrate, eventually leading to the acylenzyme intermediate. Water attacks the acylenzyme, again aided by general-base catalysis by histidine. This mechanism has received powerful support from the recent report by Kissel et al.[10] of the primary sequence of rat pancreatic CEase, deduced from the corresponding cDNA sequence. The mature enzyme contains 592 amino acids, of which a 63 amino acid domain (residues 159-221) shows high similarity to the active-site regions of *Torpedo californica* acetylcholinesterase[11] and human serum butyrylcholinesterase.[12] In particular, the sequence that contains the active-site serines (starred) of the cholinesterases, V-T-I/L-F-G-E-S*-A-G-G/A-A-S-V, is nearly identical with the corresponding sequences that contains S194 in CEase. Despite the sequence information, many features of the chemical mechanism of CEase catalysis are undefined.

Scheme I. Cholesterol Esterase Mechanism



This study was designed to answer several questions concerning

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(1) Abbreviations: CEase, cholesterol esterase; AChE, acetylcholinesterase; BuChE, butyrylcholinesterase; PNPA, *p*-nitrophenyl acetate, the C_2 ester; PNPP, *p*-nitrophenyl propanoate, the C_3 ester; PNPB, *p*-nitrophenyl butyrate, the C_4 ester; PNPV, *p*-nitrophenyl valerate, the C_5 ester; PNPC, *p*-nitrophenyl caproate, the C_6 ester; PNPO, *p*-nitrophenyl octanoate, the C_8 ester; PNPD, *p*-nitrophenyl decanoate, the C_{10} ester; PNPL, *p*-nitrophenyl laurate, the C_{12} ester; MeCN, acetonitrile; TX100, Triton X-100; LpL, lipoprotein lipase; $[S]_0$, initial substrate concentration; $[E]_T$, analytical enzyme concentration; V, maximal velocity, $V_{max} = k_{cat}[E]_T$; K, Michaelis constant, K_m; V/K, first-order rate constant when $[S]_0 \leq K/10$; k_{cat}/K, second-order acylation rate constant, sometimes called k_E; $^{D_2O}k_{cat}$ and $^{D_2O}k_{cat}/K$, observed solvent isotope effects for $k_{cat}(V)$ and $k_{cat}/K(V/K)$, respectively; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; BCA, bicinchoninic acid.

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