NUCLEOPHILIC ADDITION TO DIENE AND ARENE-METAL COMPLEXES
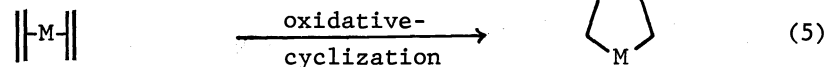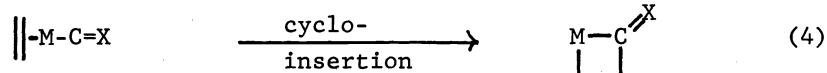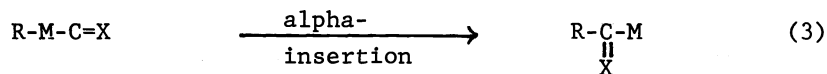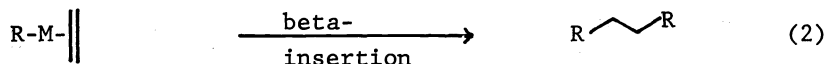
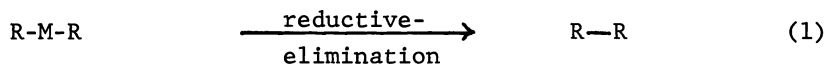M.F. Semmelhack

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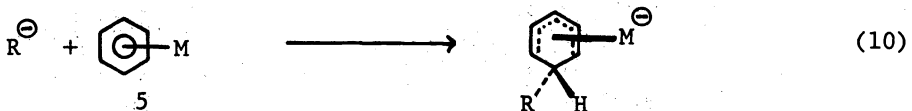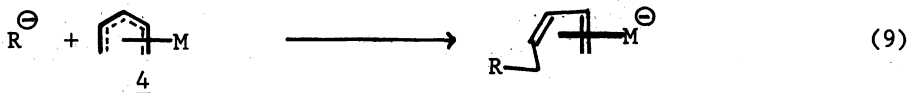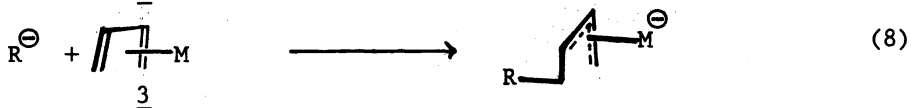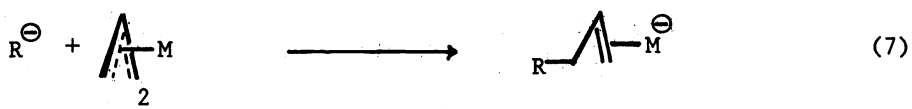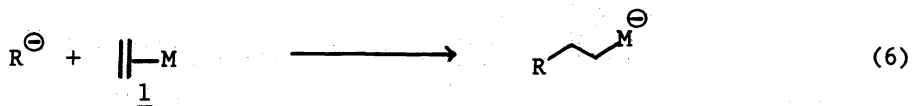Abstract - Attachment of a $M(CO)_3$ unit to a diene (M = Fe) or an arene (M = Cr) induces a strong polarizability in the carbon pi bond systems. Nucleophilic addition occurs to give anionic intermediates which can be manipulated into useful organic products. A series of examples with η^4-(1,3-cyclohexadiene)$Fe(CO)_3$ shows that reactive anions are needed to obtain successful addition and then protonation leads to monosubstituted cyclohexenes. Alternatively, CO insertion can be induced which allows formation of 1,4-disubstituted cyclohexenes. With arene-$Cr(CO)_3$ complexes, addition to the ring is strongly directed meta to resonance electron donor substituents. This selectivity is the basis for three natural product syntheses, of acorenone, aklavinone, and frenolicin. Special selectivity in additions to η^6-indole-$Cr(CO)_3$ opens a new approach to the ergot alkaloids.

INTRODUCTION

Transition metal-promoted reactions are of increasing value in complex organic synthesis because of new power and selectivity in the formation of carbon-carbon bonds. The types of new methods can be divided into two groups: first, the methods based on reactions which are unique to transition metals and second, the methods based on a polarizing effect of the metal-ligand system. In the first series, eq. 1-5, the reactions have no

$$R\text{-}M\text{-}R \quad \xrightarrow{\text{reductive-elimination}} \quad R\text{---}R \qquad (1)$$

$$R\text{-}M\text{-}\| \quad \xrightarrow{\text{beta-insertion}} \quad R\diagup\!\!\!\diagdown\!\!\!\diagup^R \qquad (2)$$

$$R\text{-}M\text{-}C\text{=}X \quad \xrightarrow{\text{alpha-insertion}} \quad \underset{X}{\overset{\|}{R\text{-}C\text{-}M}} \qquad (3)$$

$$\|\text{-}M\text{-}C\text{=}X \quad \xrightarrow{\text{cyclo-insertion}} \quad M\text{---}C\diagup^X \qquad (4)$$

$$\|\text{-}M\text{-}\| \quad \xrightarrow{\text{oxidative-cyclization}} \quad \text{(ring)}M \qquad (5)$$

obvious polar characteristics and are potentially compatible with most functional groups. In the second series, eq. 6-10, increased polarizability of the pi ligand allows addition of nucleophiles, invariably from the face of pi system opposite the metal (anti addition). Complexes with a pi ligand having an odd number of carbons (i.e., **2**, **4**) are prepared indirectly (insertion reactions, Grignard additions) and nucleophilic addition produces alkenes and dienes directly. For ligands with an even number of atoms (**1**, **3**, **5**), the complexes are prepared directly by ligand substitution; nucleophilic addition leads to organometallic intermediates which must be further manipulated to give simple organic molecules. We have been interested in the arene-$Cr(CO)_3$ system (i.e., **5**) for ten years (Ref. 1) and have recently begun a consideration of the diene-$Fe(CO)_3$ species.

$$R^{\ominus} + \underset{\underline{1}}{\|{-}M} \longrightarrow R\underset{}{\diagdown}\underset{}{\diagup}M^{\ominus} \qquad (6)$$

$$R^{\ominus} + \underset{\underline{2}}{\triangle{-}M} \longrightarrow R\underset{}{\diagdown}\underset{}{\diagup}M^{\ominus} \qquad (7)$$

$$R^{\ominus} + \underset{\underline{3}}{\#{-}M} \longrightarrow R\underset{}{\diagdown}\underset{}{\diagup}M^{\ominus} \qquad (8)$$

$$R^{\ominus} + \underset{\underline{4}}{\diagup{-}M} \longrightarrow R\underset{}{\diagdown}\underset{}{\diagup}M^{\ominus} \qquad (9)$$

$$R^{\ominus} + \underset{\underline{5}}{\hexagon{-}M} \longrightarrow \underset{R\quad H}{\hexagon}{-}M^{\ominus} \qquad (10)$$

ADDITION OF CARBANIONS TO 1,3-CYCLOHEXADIENE-Fe(CO)$_3$

Addition of carbon nucleophiles to the diene ligand in η^4-(1,3-cyclohexa-diene)-Fe(CO)$_3$, 6, would give the η^3-allyl anionic complex $\underline{7}$. Addition to the carbonyl ligand is also possible (Ref. 2). Anion $\underline{7}$ is also expected from addition of tetracarbonylferrate dianion to an allylic halide (Ref. 3) but the author is aware of no examples of this process; no close analogs of $\underline{7}$ are characterized. We find that reactive anions combine with $\underline{6}$ to
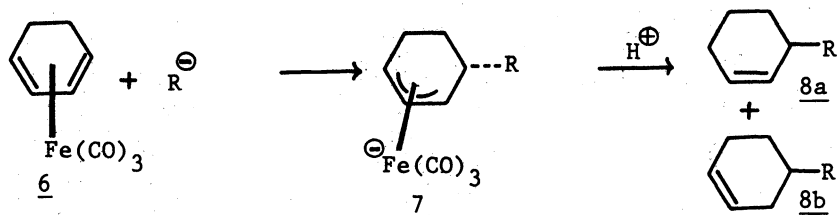

give an intermediate, perhaps $\underline{7}$, which reacts with acid to produce the cyclo-hexenes $\underline{8}$ in a relatively invarient ratio of 1:1. Table 1 presents the re-sults with a series of anions.

TABLE 1. Addition to Complex $\underline{6}$

Anion[a]	Products (8a,8b)	Yield[c]
1. 2-lithio-2-methylpropionitrile	R = C(CH$_3$)$_2$CN	87
2. t-butyl 2-lithio-2-methylpro-pionate	R = C(CH$_3$)$_2$CO$_2$tBu	95
3. 2-lithiopropionitrile	R = CH(CH$_3$)CN	47
4. potassium enolate of pinacolone	R = CH$_2$COC(CH$_3$)$_2$	25[b]
5. 2-lithio-1,3-dithiane	R = 2-(1,3-dithianyl)	59
6. lithiodiphenylmethane	R = CHPh$_2$	80
7. lithio(thiophenyl)methane	R = CH$_2$SPh	58
8. lithio butylacetylide	R = C≡C(CH$_2$)$_3$CH$_3$	20

(a) The anion reacts with complex 6 at $-78°$ for 0.5 hr followed
by quenching with trifluoroacetic acid.   (b) A crown ether (18-
crown-6) was added.   (c) The yield is based on the isolated mix-
ture of 8a and 8b, in each case ca 1:1.

An important side reaction, especially prevalent with simple alkyl-lithium
and Grignard reagents is the incorporation of CO to give unsymmetrical ke-
tones and carbonylation of the nucleophile, as exemplified with PhLi in eq.
11.   Direct attack at coordinated CO followed by protonation could lead to
an intermediate (9) and then to the observed products.

$$ 6 \xrightarrow[\text{b. } H^+]{\text{a.PhLi}} \left[\text{9} \right] \longrightarrow + RCHO \quad (11) $$
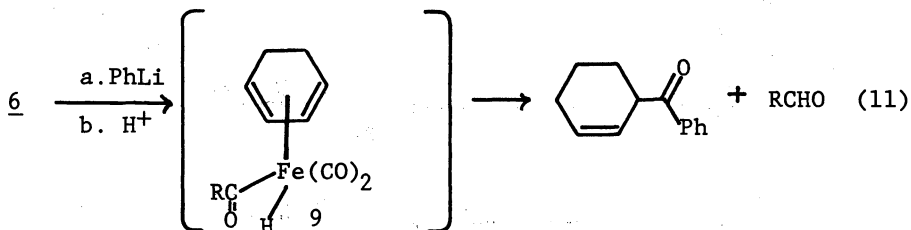
When CO is added to the reaction mixture from 6 and $LiC(CH_3)_2CN$, protonation
produces the products 8a/8b in good yield; CO is not incorporated. However,
if 6 is added to the anion under an atmosphere of CO, a new intermediate
appears (perhaps 10) which reacts with acid to give aldehyde 11 and with
methyl iodide to give 12 (eq. 12). The stereochemistry of 11 and 12 has
not been rigorously established; a single isomer is obtained in both cases.

$$ 6 \xrightarrow[\text{CO}]{LiC(CH_3)_2CN} \left[\text{10} \right] \xrightarrow{E^{\oplus}} $$

11: E=H
12: E=CH_3
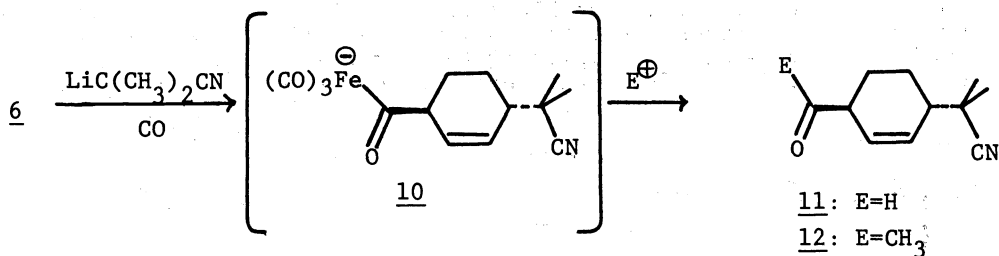
ADDITION OF CARBANIONS TO ARENE-Cr(CO)$_3$ COMPLEXES

Arene-metal complexes are known for most of the transition metals (Ref. 4).
Examples of addition of nucleophiles are known for almost every type of
arene-metal complex; in a few cases, the resulting η^5-(cyclohexadienyl)-
metal species have been manipulated into useful organic products (Ref. 5).
We have worked with arene-Cr(CO)$_3$ species, the most abundant and easily
handled examples, and observed that reactive anions will produce stable
cyclohexadienyl anionic intermediates (Ref. 6). Addition of acid provides
substituted 1,3-cyclohexadienes (the addition/protonation method) while
oxidizing agents give the substituted arene (the addition/oxidation method).
If a Cl or F substituent is present, stabilized anions can give direct sub-
stitution for halide, but more reactive carbanions fail (Ref. 7). Questions
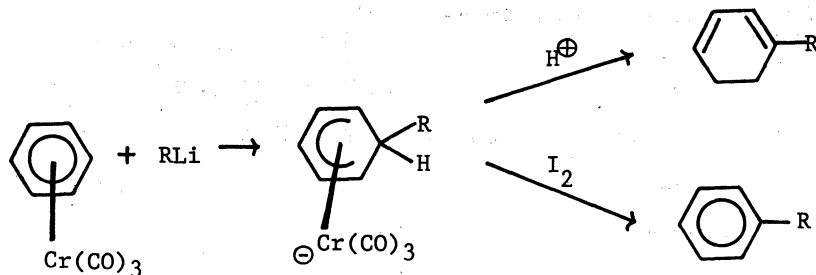
of regiochemistry arise, particularly intriguing because the activating group [Cr(CO)$_3$] is more or less equally bound to each of the arene ring atoms and can give no obvious directing effect. We find that a most useful selectivity derives from the meta directing influence of powerful resonance donor substituents, such as methoxy, amino, and fluoro (eq. 12, Ref. 7). A significant steric effect is generally observed, so that (o-


$$\text{(12)}$$

greater than 95% meta for
X = OR, NR$_2$, and F.
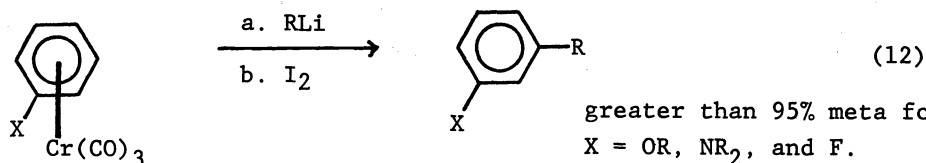
methylanisole)Cr(CO)$_3$, with two meta positions activated by methoxy, reacts with good selectivity at the less hindered meta position, especially with tertiary carbanions (Ref. 8).

This selectivity allows the formulation of strategies for synthesis of a number of aromatic natural products. We have focussed on three targets, examples of important structural types. The synthesis of acorenone (13) has been published in preliminary form (Ref. 9) and will be outlined here. An approach to aklavinone (14) is underway at the stage of simple models, while the formal synthesis of the naphthoquinone derivative frenolicin (15) has been completed. The bonds labeled a in each of these molecules can be

13 acorenone B   14 aklavinone   15 frenolicin
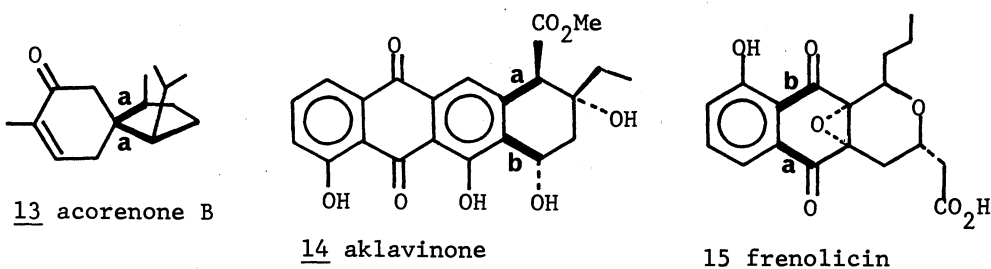
imagined to be meta to an alkoxy group in a coordinated arene, while the bonds labeled b are ortho to the same alkoxy. The ortho positions can be activated through metalation by n-butyllithium, either with the free or complexed arene (Ref. 10).

In the plan for acorenone, both bonds a can be made by direct addition to (o-methylanisole)Cr(CO)$_3$, consistent with the natural selectivity for the less hindered meta position. The synthesis begins by addition of an isobutyroyl anion equivalent (Ref. 11) to give the trisubstituted arene 16. A series of six conventional steps produces the key intermediate 17. Complexation with the Cr(CO)$_3$ group affords a separable mixture of diastereomers (18a, 18b; diastereotopic faces of the arene). Consistent with the exclusive anti addition of nucleophiles observed in intermolecular examples (Ref. 6), intramolecular addition (followed by protonation) from 18a leads exclusively to the acorenone β series (19a) while 18b leads only to the acorenone configuration (19b). Conventional methods allow stereospecific introduction of the final stereocenter. The second crucial carbon-carbon bond (to give 19) requires spirocyclization rather than formation of fused rings, and the methoxy unit is clearly important in favoring 19 (Ref. 12).

(one enantiomer shown)
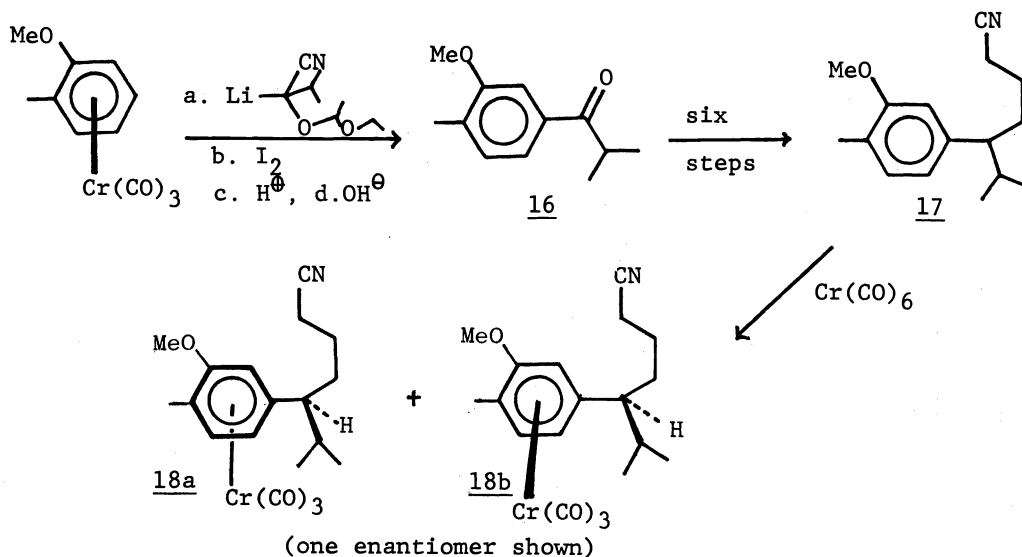
The natural selectivity is not appropriate for a direct route to aklavinone, so intramolecular reaction, this time directed to a fused ring by the alkoxy group, is planned. Starting from anisole-Cr(CO)₃ as a simple model for a 3-ring synthon (20) for aklavinone, we add on ortho side chain by metalation followed by reaction with cyano-aldehyde 21. The intermediate benzyl alcohol complex, 22, (mixture of diastereomers, ca 60:40) is stabilized as the methyl ether and then treated with lithium diisopropylamide to induce cyclization. Addition of excess iodine allows isolation of the free arene 23 as a mixture of four diastereoisomers. The mixture of epimers at C-1 and C-2 in 23 is not a significant problem since the plan for elaboration to the aklavinone ring D pattern includes introducing a double bond between C-1 and C-2 (Ref. 13). The strategy has the advantage that the C-4 hydroxyl group is introduced simply as part of a carbon-carbon bond forming step.

20
P = protecting group
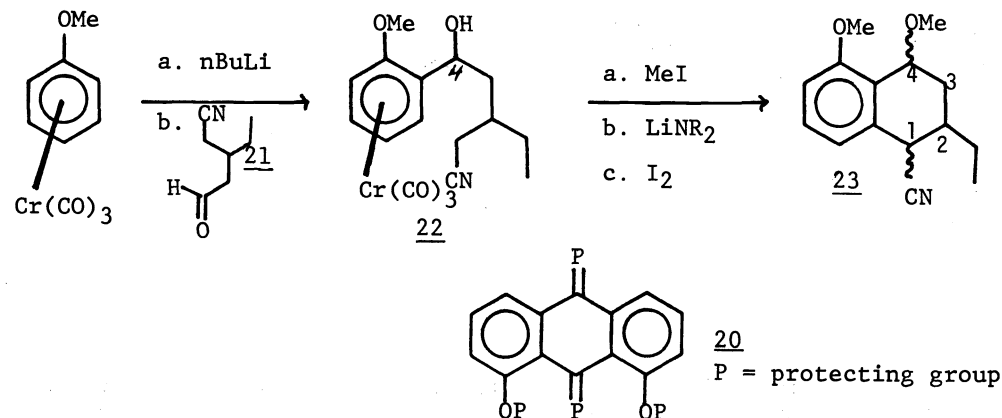
Frenolicin (15) is a member of a large class of naphthoquinone antibiotics which have seen considerable synthesis activity lately, including the first synthesis of 15 itself (Ref. 14). We propose two general strategies, one involving addition of two side chains to anisole (in 24) and subsequent ring closure to give a key intermediate, 25. The second involves a naphthalene-Cr(CO)₃ complex (eg. 26) to give the same intermediate (25). Conversion of 25 to the tricyclic system of frenolicin is based on alkoxy-carbonylation of alkenes, promoted by palladium (Ref. 15). While intramolecular addition of alkoxide to alkenes is well known (Ref. 16), trapping of the intermediate alkyl-Pd species with CO is not well developed. We find that the model 27 is cyclized efficiently (eq. 14), producing a 6:1 mixture of cis:trans in high yield. Diverging from the specific problem of frenolicin briefly, it is of general significance to find that the 1,2-disubstituted alkenes (28, 29) also undergo cyclization in good yield. The stereoselectivity also
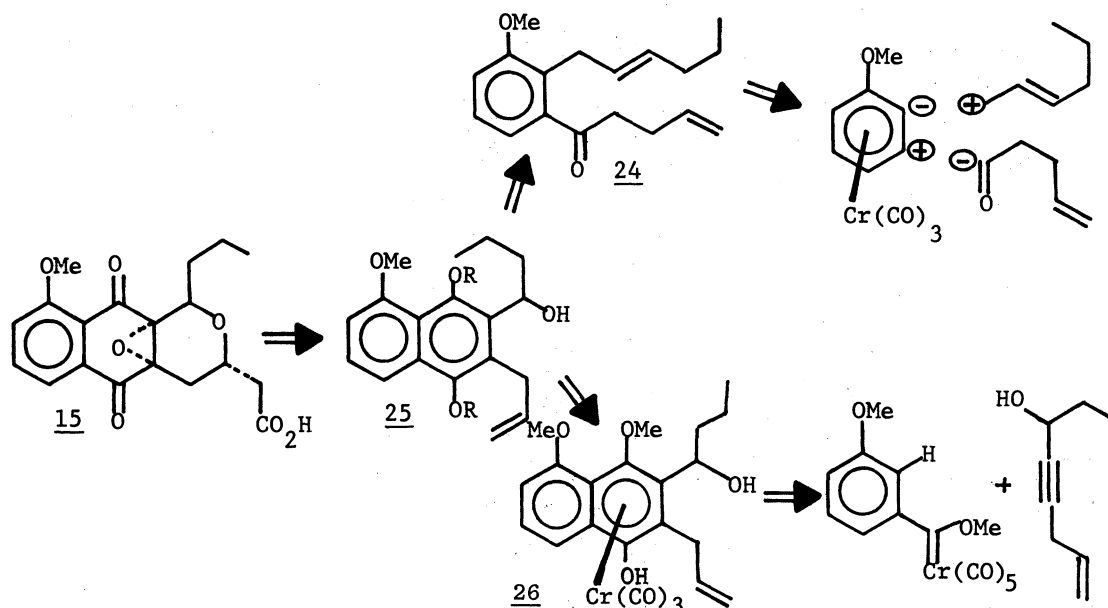
appears high since different diastereomers are produced from each olefin isomer. The structures have not been proven; the drawings 30 and 31 are based on the mechanistic expectation of anti addition by alkoxide and retention in the CO incorporation.
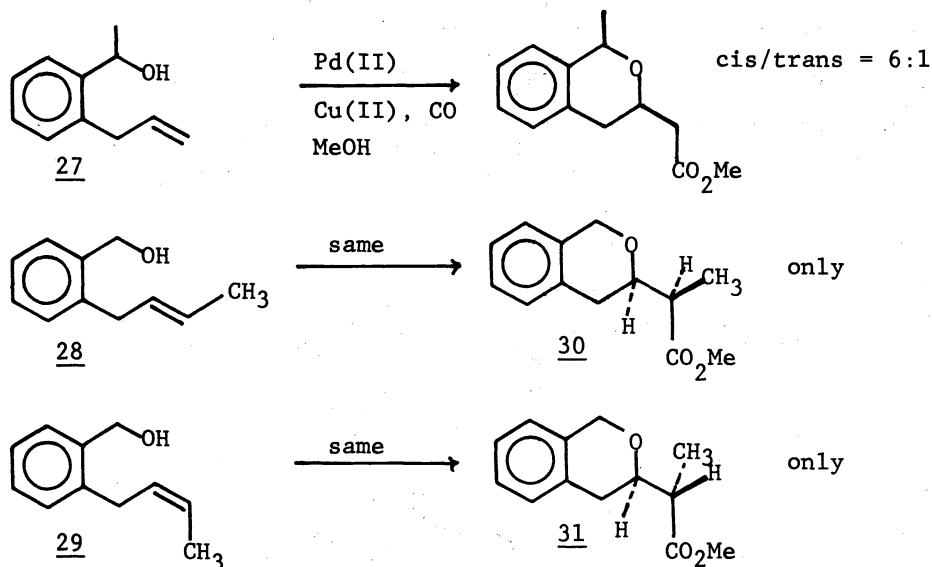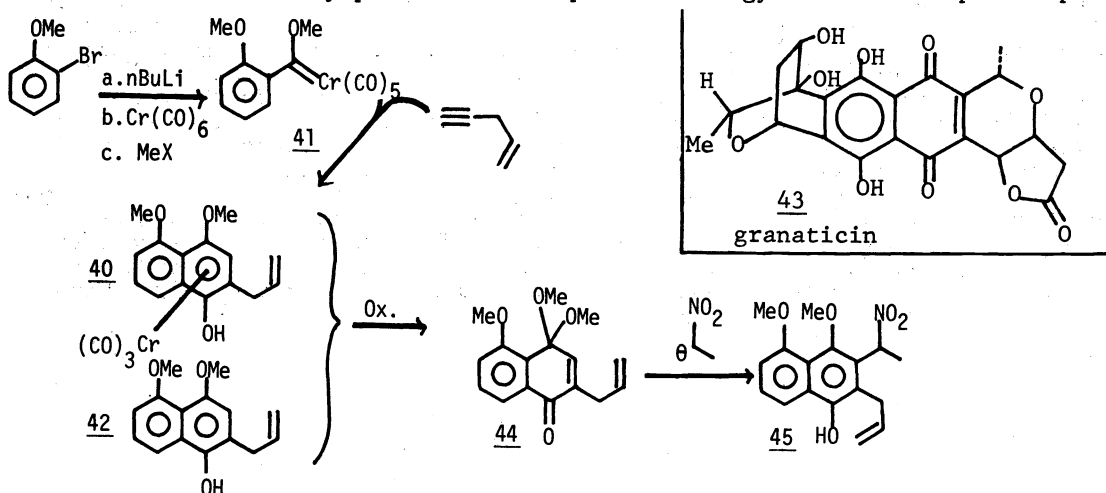

Starting from [o-(trimethylsilyl)anisole]Cr(CO)$_3$, metalation, formation of the aryl-copper species, and coupling with E-1-bromo-2-hexene produces the trisubstituted arene complex 32 in high yield. The silyl substituent is crucial because nucleophile addition is desired at C-4 in 32. Silicon is known to be a strong para directing group and also provides steric hindrance to attack at C-6. Addition of anion 33 proceeds to give a single regioisomer. Proto-desilylation is induced by treatment with acid and then 34 can be obtained in 74% yield. Following the procedure of Watt, oxidative-decyanation gives ketone 35. Selective epoxidation prepares the molecule for ring closure which is best accomplished by formation of the enol-silyl ether and Lewis acid promoted attack on the epoxide to give 36. The cis product (shown) appears to predominate. The heterocyclic ring formation proceeds as smoothly as with the model, giving the cis isomer (37) only. Aromatization of 37 leads to the naphthol 38 which is oxidized (Jones Reagent) to the quinone, 39. At this point, our strategy essentially parallels the published synthesis and we are in the process of developing optimum conditions for the final steps. Key reactions include equilibration of the side chains to

the more stable, natural trans arrangement and selective epoxidation directed by the carboxyl group.
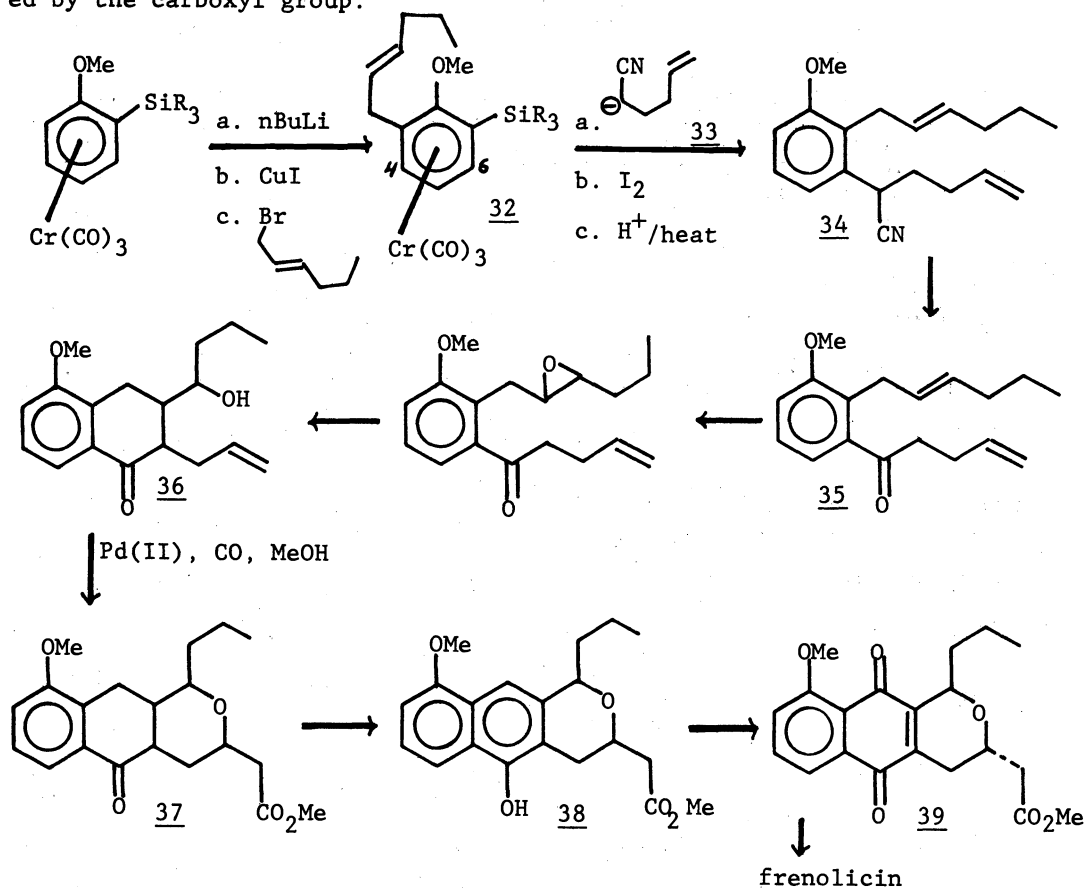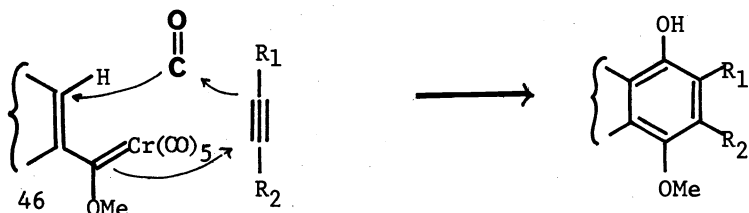

The alternate strategy for frenolicin requires a substituted naphthalene complex with the Cr(CO)$_3$ unit attached to the more substituted ring. While naphthalene complexes are well known, the standard synthesis method (heating the arene with a Cr(CO)$_3$L$_3$ species) often results in low yields and the metal invariably attaches to the less substituted ring. In pursuing the preparation of a naphthalene complex such as 40, we tested the reaction of Dötz (Ref. 17). In this process, a carbene-chromium complex (eg. 41) reacts with an alkyne to produce 40, with incorporation of one CO ligand. However, for our specific application, with allylacetylene, the method fails because we cannot avoid detachment of the naphthalene ligand. Nevertheless, the reaction does provide a simple entry into substituted juglone derivatives with high regioselectivity. We have carried out development work on the Dötz reaction because it may provide the simplest strategy for more complex naph-
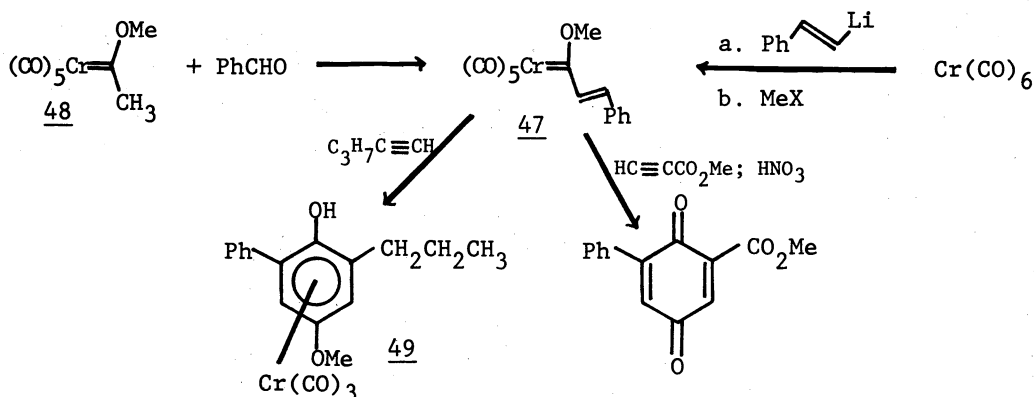
thoquinones such as granaticin (43). In the frenolicin pathway, the mixture of complexed and free naphthol is oxidized according to the method of Wulff (Ref. 18) to give the monoketal 44. Conversion to frenolicin is underway via conjugate addition of units such as nitroethane (in 45).

The carbene + alkyne + CO reaction is potentially a powerful new method for assembling aromatic rings. It has been shown to succeed with aryl, 2-cyclopentenyl and 2-furyl carbene complexes, leading to bicyclic systems (Ref. 17). In principle, the process can be applied to any vinyl-carbene complex bearing a β-hydrogen substituent (i.e., 46). We find that the simple sty-


rene complex 47, obtainable either from 2-lithiostyrene or from aldol-like condensations between complex 48 and benzaldehyde (Ref. 19), reacts with a variety of alkynes in moderate efficiency to give tetra- or pentasubstituted hydroquinone complexes. The regioselectivity is excellent with mono-substi-


tuted alkynes and apparently independent of electronic effects. Alkyl, aryl, and carboalkoxy alkynes give isomers corresponding to 49, where the substituent ends up nearer the hydroxyl unit.

The selectivity observed in nucleophilic addition to anisole ligands is powerful and easily rationalized using the same resonance effect arguments applied to electrophilic aromatic substitution. However, other substituted arene ligands give rise to equally striking selectivity which is not easily rationalized parallel with classical electrophilic reactions. A correlation with frontier orbital interactions has been noted (Ref. 20) and conformational effects of the $Cr(CO)_3$ unit have been used to correlate a limited set of selectivity results (Ref. 21). A particularly dramatic example is η^6-(indole)$Cr(CO)_3$ (50), where the metal selectively coordinates to the 6-membered ring. Of course, electrophiles invariably attack the pyrrole ring of free indole derivatives, but with 50, nucleophilic addition occurs at C-4 and C-7 with high selectivity. The balance between positions 4 and 7 appears to depend on the nature of the anion and especially on steric parameters at the anion and at the indole positions. With N-methylindole, several highly reactive anions such as 2-lithio-1,3-dithiane and α-lithio allyltrimethyl silane strongly prefer to add at C-7 (at least 85:15 for C-7:C-4) while cyano- and ester-stabilized anions add at C-4 (at least 80:10 for C-4:C-7). With
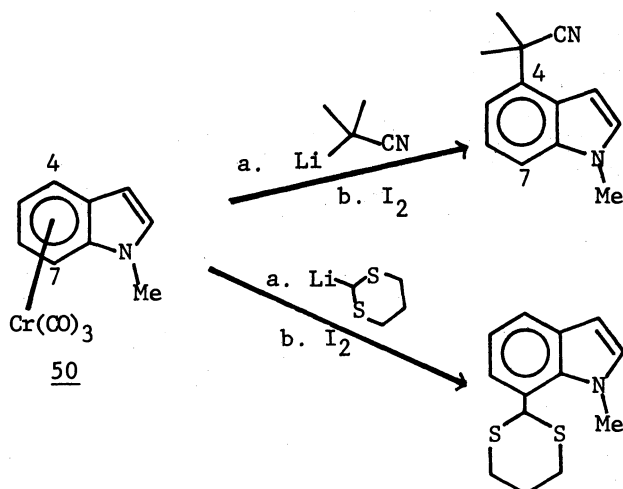
N-benzylindole, the tendency toward C-4 is still stronger, but with a substituent at C-3, as in 51, all anions react preferentially at C-7. With the
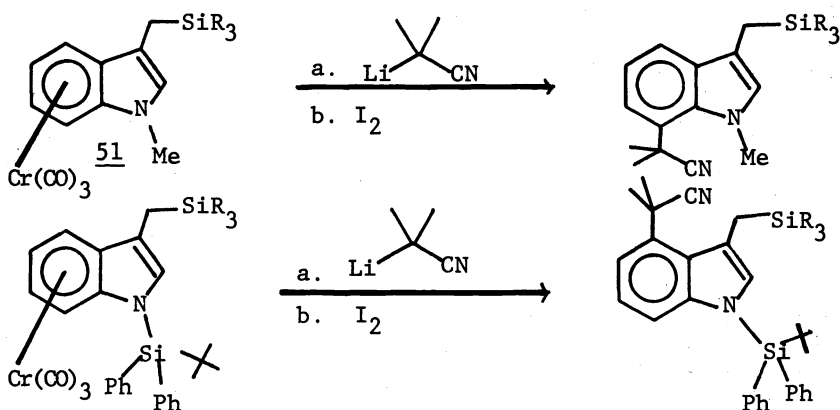
same substituent at C-3, but with the large diphenyl-t-butylsilyl group at the nitrogen, C-4 is again selected. While this sensitivity to steric effects leads to widely different results with the same nucleophile, the selectivity is reasonably easy to predict and manipulate. The ability to directly add carbon units to C-4 opens up new strategy for synthesis in the ergot alkaloid area.

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