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# ADDITION OF CARBON NUCLEOPHILES TO ARENE-CHROMIUM COMPLEXES

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**Abstract**—The electrophilic reactivity of arenes coordinated to the chromium tricarbonyl unit has been developed into several distinct methods for coupling carbon nucleophiles with aromatic rings. Addition of the nucleophile produces stable $\eta^5$-cyclohexadienyl chromium complexes which can be oxidized to induce loss of the *endo* hydrogen and the metal, overall nucleophilic substitution for hydrogen. Alternatively, the intermediate can be protonated and the resulting cyclohexa-1,3-diene can be detached from the chromium, effecting nucleophilic addition with reduction of one double bond. If a halogen (F, Cl) is present as a ring substituent, and if the nucleophile can migrate about the arene ligand, then loss of halide can occur parallel with classical nucleophilic aromatic substitution for halogen in electron-deficient haloarenes.

With substituted arenes, the regioselectivity of addition becomes important and is often very high. Particularly useful are strong resonance donor substituents (RO–, $R_2N$–, F–) where selectivity for meta attack is high. Indole provides an excellent example of selective activation, as the six-membered ring complexes selectively and is then susceptible to nucleophilic substitution, predominantly at the 4 and 7 positions.

Substitution for halogen is a somewhat limited process and depends upon the nature of the nucleophile. Very reactive nucleophiles add to unsubstituted positions and are often slow to isomerize to the *ipso* position from which loss of halide can occur.

It is the purpose of this article to survey the established and potential role of arene–metal complexes as electrophiles in organic synthesis. While aromatic rings are known to form stable complexes with almost every transition metal,[1] the arene–chromium tricarbonyl species in particular have been carried furthest toward practical applications. After a survey of the general preparation and reactivity of coordinated arenes, the scope and limitations of three distinct reaction types involving arene–chromium tricarbonyl complexes will be presented, followed by detailed experimental procedures for prototype examples.

There are two general methods for formation of arene-metal complexes on practical scale. Simplest is direct thermal replacement of other ligands on the metal, a process which can be efficient and mild, requiring reaction temperatures from below 25° (for the formation of $\eta^6$ - benzene - $\eta^4$ - norbornadienerhodium(I)[2] to over 100° (for conversion of chromium hexacarbonyl to $\eta^6$-benzenetricarbonylchromium(0)[3]). This process has been particularly useful for preparation of many $\eta^6$ - arene-$Cr(CO)_3$ complexes, with a variety of substituents on the arene. Direct thermal reaction may be particularly useful with polyfunctional arenes of interest in natural product synthesis. For example, the $\eta^6$-indolechromium tricarbonyl complex is obtained in good yield,[4] but indole is rare in combination with any other metal–ligand system.

Lewis acid-promoted attachment of arene rings to metals is a general method for preparation of cationic arene–metal complexes.[1] The original Fisher–Hafner method employs a Lewis acid such as aluminum chloride with a reducing agent such as aluminum metal, and involves reduction of the transition metal during the process.[5] For example, a Cr(III) salt leads to bis($\eta^6$-benzene)chromium(I). A powerful method for preparation of $\eta^6$ - benzene - $\eta^5$ - cyclopentadienyliron(II) proceeds by a Lewis acid-promoted exchange of a cyclopentadienyl unit for an arene starting from ferrocene.[6] A difficulty with these methods is that many useful or necessary functional groups will undergo serious side reactions: few functionalized arenes have been converted to $\eta^6$-arene complexes by this general method. However, some interconversions of $\eta^6$-(haloarene) manganese tricarbonyl cations have been worked out which point to a general indirect approach for preparation of substitued versions of this type of complex.[7] The virtue of the cationic complexes compared to the arene-$Cr(CO)_3$ species is higher electrophilic reactivity, and several systematic studies of reactions with carbon nucleophiles have appeared.[8]

*Reactivity of $\eta^6$-arene ligands.* Figure 1 summarizes the five general changes in arene reactivity that have been observed when $Cr(CO)_3$ is coordinated with the arene $\pi$-system: (1) steric effects of the metal-ligand system,[9] (2) stabilization of side chain cationic sites (benzyl and phenethyl cations),[10] (3) stabilization of side chain anion sites (benzyl anion),[11] (4) enhanced acidity of the arene ring hydrogens,[12] and (5) addition of nucleophiles to the arene $\pi$-system leading to nucleophilic aromatic substitution.[13]

A most dramatic effect of metal coordination with an arene is the powerful withdrawal of electron density

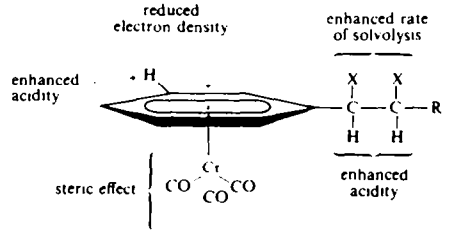


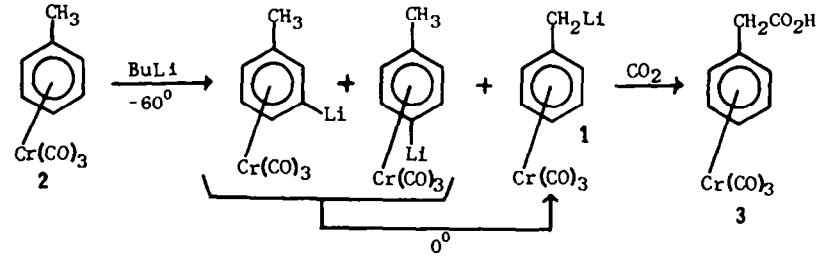

Fig. 1. Effects on arene reactivity of metal coordination.

from the aromatic ring, much like the effect of a nitro substituent in the sigma bond framework. This factor appears to be responsible for the significant enhancement of acidity of benzylic hydrogens in $\eta^6$-(alkylarene) metal complexes, observed for both the chromium tricarbonyl series[11] and the bis ($\eta^6$-arene) iron(II) species.[14] The earliest applications of this effect in synthesis involved slightly easier generation of the enolate anion of methyl phenylacetate through complexation of the phenyl group.[11b] However, generation of significant concentrations of the simple benzyl anion attached to $Cr(CO)_3$ (in **1**) was observed only recently.[12] Reaction of n-butyllithium with $\eta^6$-(toluene)chromium tricarbonyl (**2**) gives proton abstraction predominantly from the ring position at first, but after equilibration at 0° for a few hours, exchange to give **1** is complete; quenching with $CO_2$ gives only $\eta^6$-(phenylacetic acid)chromium tricarbonyl (**3**, 61% yield).[12] The generation of anions such as **1** by direct deprotonation has not been developed as a synthesis method, but formation of related anions by addition to styrene complexes has allowed a study of their reactivity with electrophiles.[15]

this early work, no systematic studies with carbon nucleophiles were reported, nor were the anticipated $\eta^5$-cyclohexadienyltricarbonyl-chromium (0) complexes detected. A report in 1973 demonstrated direct substitution for hydrogen by organo-lithium reagents,[18] but this suggestive observation was, and remains, mechanistically obscure. We set out initially to determine the scope and limitations for halide substitution by carbon nucleophiles and discovered that the $\eta^5$-cyclohexadienyl anionic complexes were indeed intermediates, can be generated with high efficiency in solution, and can be manipulated into useful organic products.

## RESULTS

Reactive carbon nucleophiles add to $\eta^6$-benzene-$Cr(CO)_3$ and produce $\eta^5$-cyclohexadienyl anionic complexes such as **4** (Scheme I).[19] A number of examples have now been characterized by $^1$HNMR spectroscopy and the adduct from 2 - lithio - 1,3 - dithiane has been subjected to X-ray diffraction analysis, as shown in the ORTEP drawing in Fig. 2.[19] The structure is unexceptional with regard to earlier examples of $\eta^5$-cyclohexa-




Coordination of metals has been known for many years to reverse the normal reactivity of carbon $\pi$-bonds, from nucleophilic to electrophilic.[16] Arene ligands show particularly dramatic effects of the reversed polarization and this effect opens new concepts in aromatic substitution. The possibilities were recognized at the time of the first preparation of $\eta^6$-chlorobenzene-$Cr(CO)_3$, when it was shown that the complex undergoes nucleophilic substitution by methoxide anion at roughly the same rate as *p*-nitrochlorobenzene.[17] However, in

dienyl complexes, but is the first example with chromium. In **4** a new carbon–carbon bond has been formed in a special way, and it remains to develop efficient ways of converting **4** into useful products. Three general reactions are now well-defined and will be the focus of this presentation (Scheme 1). First, oxidation of **4** by a wide variety of oxidizing agents leads to loss of the hydrogen as a proton and loss of chromium as chromium(III), step **a**.[19] The result is formal replacement of hydride by a carbanion, referred to as the ad-

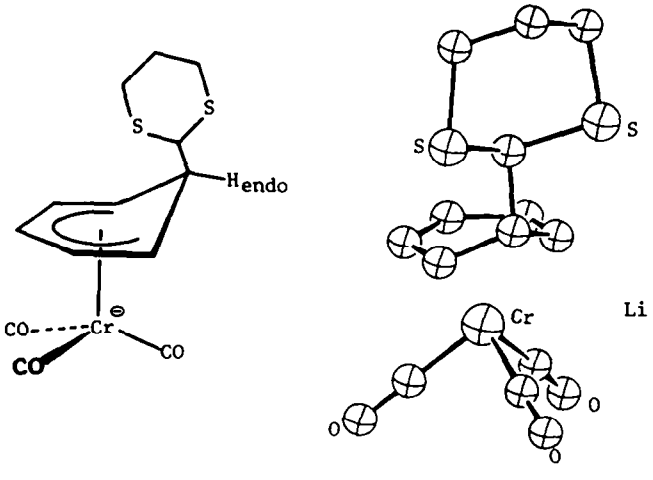
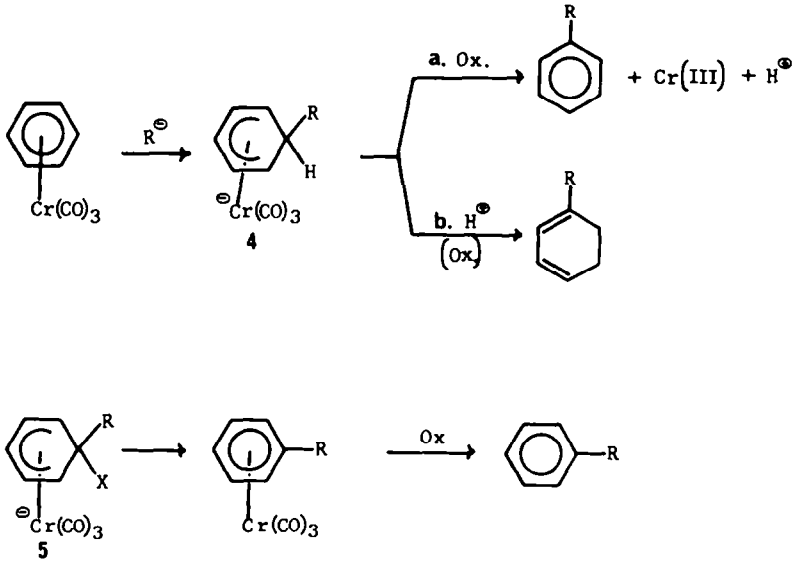



Fig. 2. The structure of the adduct with 2-lithio-1,3-dithiane.

dition/oxidation process. Alternatively, **4** can be protonated by strong acid to give unstable diene–chromium intermediates from which the alkylcyclohexa-1,3-diene is freed by oxidation or displacement by ammonia.[20] The overall conversion amounts to the addition of R-H across a $\pi$-bond of the arene, referred to as the addition/protonation process, step **b**. A quite separate process occurs spontaneously from intermediates such as **5** where a fluoride or chloride atom can reside *endo* to the incoming nucleophile. The result is replacement of halogen by the nucleophile and *maintains* the arene-chromium bond, a process referred to as direct substitution.[21]

*The addition/oxidation process.* Both steps **a** and **b** in Scheme 1 require complete conversion of the arene-$Cr(CO)_3$ complex to intermediate **4**. For benzene-$Cr(CO)_3$ itself, an extensive series of carbanions have been tested and generally fall into one of three groups (Table 1).[22] The unreactive anions fail to give significant conversion to **4**; also included in this group are heteroatom anions such as alkoxide and amines. The successful anions are formed from carbon acids with $pK_a > 20$, and conversion to **4** is favored by potassium counter ions, crown ethers, etc. Ketone enolates are borderline cases, while cyano-stabilized anions are nearly ideal. Proton abstraction is the primary reaction with anions in Group C, and there are borderline cases such as sec-butyllithium which gives similar amounts of metalation and nucleophilic addition. Remarkably, t-butyllithium adds as a nucleophile, perhaps suggesting an important electron transfer component in the addition step. In general, more highly substituted versions of the anions in Group B are also successful.[22]

Since the overall process results in substitution for hydrogen, in any simple arene several sites of substitution are possible, parallel with electrophilic aromatic substitution. An important difference between the transition metal system and classical arene chemistry is that the activating substituent $[Cr(CO)_3]$ is more-or-less symmetrically bound to the arene ring carbons and in a first approximation will show no directing effect. Then the substituents attached by $\sigma$-bonds to the arene ligand



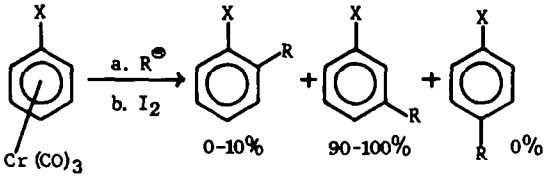

Scheme 1. The three general processes.

Table 1. Reactivity of carbanions in the addition process

| A. Unreactive | B. Successful | C. Metalation |
|---|---|---|
| 1. $LiCH(CO_2R)_2$ | 1. $LiCH_2CO_2R$ | 1. nBuLi |
| 2. $LiCH_2COR$ | 2. $LiCH_2CN$ | 2. $LiCH_3$ |
| 3. $CH_3MgBr$ | 3. $KCH_2COC(CH_3)_3$ | 3. sBuLi |
| 4. $(CH_3)_3CMgBr$ | 4. LiCH(CN)(OR) | |
| 5. $(CH_3)_2CuLi$ | 5. $LiCH_2SPh$ | |
| 6. LiC(OR)(CN)Ph | 6. 2-Li-1,3-dithianyl | |
| | 7. $LiCH{=}CH_2$ | |
| | 8. LiPh | |
| | 9. LiC≡CR | |
| | 10. $LiCH_2CH{=}CH_2$ | |
| | 11. $LiC(CH_3)_3$ | |

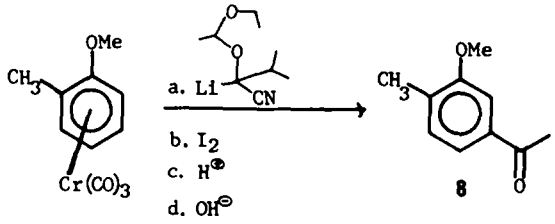
may be the primary influence on site selectivity, and in a simple view, one might expect the reverse of the well-known selectivity pattern of electrophilic aromatic substitution. The simple view is useful for substituents which give strong perturbations (powerful donors or acceptors) but more subtle arguments are required in many cases.

With strong resonance donors such as alkoxy, amino, and fluoro, *meta* substitution is always preferred, usually 95% selectivity and the remainder ending up *ortho*.[23] A

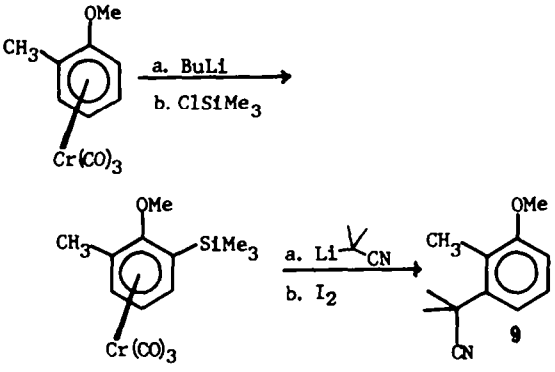



X = -OR, $-NR_2$, -F

small steric effect appears, so that 2 - lithio - 2 - methylpropionitrile gives >99% *meta* addition to $\eta^6$-(anisole)$Cr(CO)_3$ while lithioacetonitrile gives a 90:10 mixture of *o*:*m*. The reactivity of the arene is retarded somewhat by these substituents, so that simple lithium enolates of esters are not efficient, and the more reactive potassium enolates are used. In addition, ortho-metalation is enhanced, so that 2 - lithio - 1,3 - dithiane reacts with $\eta^6$-anisole-$Cr(CO)_3$ to give the products from addition (30%) and metalation (70%). The substitution process is exemplified by the reaction of the cyanohydrin acetal of pentanal with $\eta^6$-(1,3-dimethoxybenzene)$Cr(CO)_3$, (**6**). A single isomer is produced, isolated as **7** in 84% yield after hydrolytic manipulation of the cyanohydrin acetal unit. This efficient nucleophilic acylation *meta* to an alkoxy group has no classical alternative. An early step in a synthesis of acorenone involved an addition of a cyanohydrin acetal anion to $\eta^6$-(*o*-methylanisole)-$Cr(CO)_3$, where the less hindered position *meta* to the OMe group is attacked with greater than 98% selectivity, to give **8**.[24] That selectivity can be




altered through metalation, silylation, and then addition. With proto-desilylation occurring spontaneously during the oxidation step, isomer **9** is obtained in 45% yield and high purity, resulting from the *para*-directing effect of the silyl substituent.[12]




The steric effect is often comparable in influence to the electronic effects. For example, with the series of differently substituted cyano-stabilized anions in Scheme

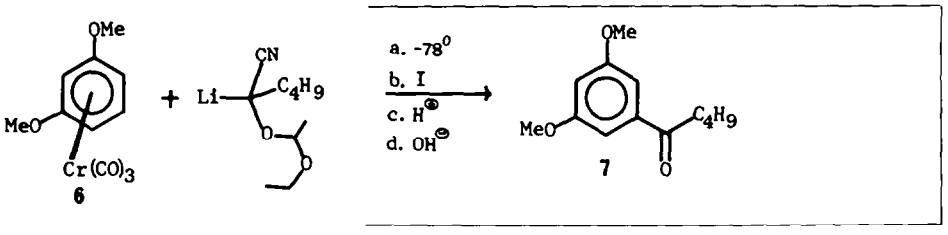
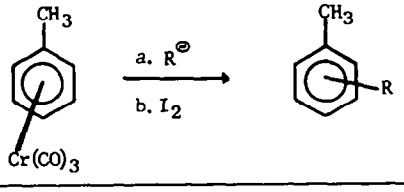



Table 2. Selectivity in additions to $\eta^6$-toluene-$Cr(CO)_3$




| Carbanion | ortho/meta[a] | yield(combined) |
|---|---|---|
| 1. $LiCH_2CN$ | 35/65 | 88% |
| 2. $LiCH(CH_3)CN$ | 15/85 | 82% |
| 3. $LiC(CH_3)_2CN$ | 1/99 | 95% |
| 4. 2-Li-1,3-dithianyl | 52/48 | 94% |
| 5. $LiCH_2CO_2tBu$ | 28/72 | 89% |
| 6. $LiC(CH_3)_2CO_2tBu$ | 3/97 | 96% |

(a) Para substitution varied from 0-2%

2, the selectivity ranges from 70:30 meta: ortho to > 95% *meta*, a trend interpreted in terms of steric repulsion between the incoming anion and the *ortho* substituent. With reactive anions such as 2-lithio-1,3-dithiane, the tendency toward *ortho* substitution is still higher (Table 2). More interesting than the steric effect disfavoring ortho addition is the electronic factor which can make *ortho* and *meta* substitution *equally probable*, disfavoring para. A correlation with the frontier orbitals of the reactants (LUMO for the arene complex) has been noted,[25] and the effect of the $Cr(CO)_3$ conformation on site selectivity has been used to explain the influence of certain substituents.[26,27] However, neither picture correlates the selectivity in certain cases, such as $\eta^6$ - indole - $Cr(CO)_3$, **10**, and good predictive understanding of the selectivity is yet to be reported.

The reaction of indole with $Cr(CO)_3$ produces a single product (**10**) from coordination of the 6-membered ring. In this complex and the corresponding benzofuran complex (**11**), there is a strong preference for addition at the 4-position. Minor amounts of addition at C-7 are also detected, except with reactive anions such as 2-lithio-1,3-dithiane where addition to C-7 is preferred (Table 3). The combination of steric and electronic effects contrive to direct addition to C-7 in N-methyl-3-alkylindole complexes such as **12**, but choosing a bulky protecting group at nitrogen such as diphenyl-t-butylsilyl returns the selectivity to favor C-4 (in **13**).[28]

*Formation of cyclohexa-1,3-dienes by addition/protonation.*

The cyclohexadienyl anionic intermediates generally react with electophiles (alkyl halides, acyl halides, ketones, trityl cation, etc) by cleavage of the *exo* bond and transfer of the nucleophile to the new electrophile.[19,20] However, strong acid ($CF_3CO_2H$) leads to protonation of the ligand, presumably to give an unstable diene-$Cr(CO)_3$ complex, and detachment of the diene can be accomplished easily.[20] With benzene-$Cr(CO)_3$, rapid H-shifts occur in the intermediate diene-$Cr(CO)_3$

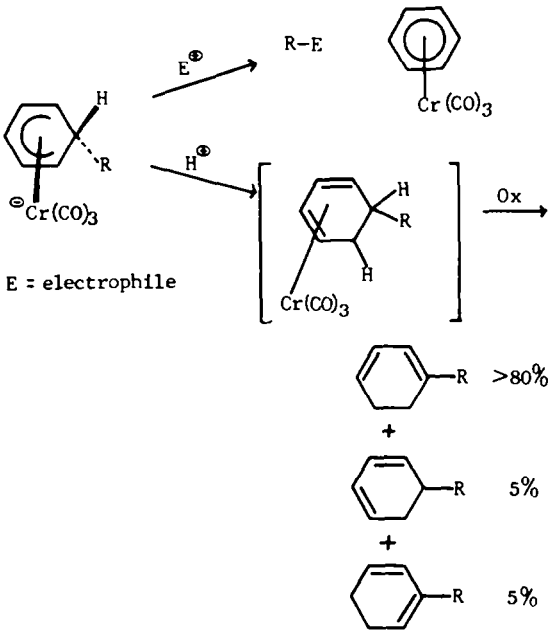
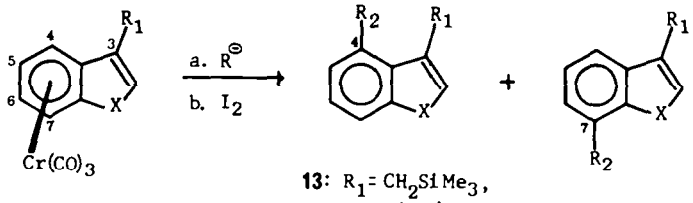



Table 3. Additions to indole and benzofuran complexes




**10**: $R_1$ = H, X = NH

**11**: $R_1$ = H, X = O

**12a**: $R_1$ = $CH_2SiMe_3$, X = NMe

**12b**: $R_1$ = $CH_2SiMe_3$, X = NSi($Ph_2tBu$)

**13**: $R_1$ = $CH_2SiMe_3$, $R_2$ = $C(CH_3)_2CN$, X = NSi($Ph_2tBu$)

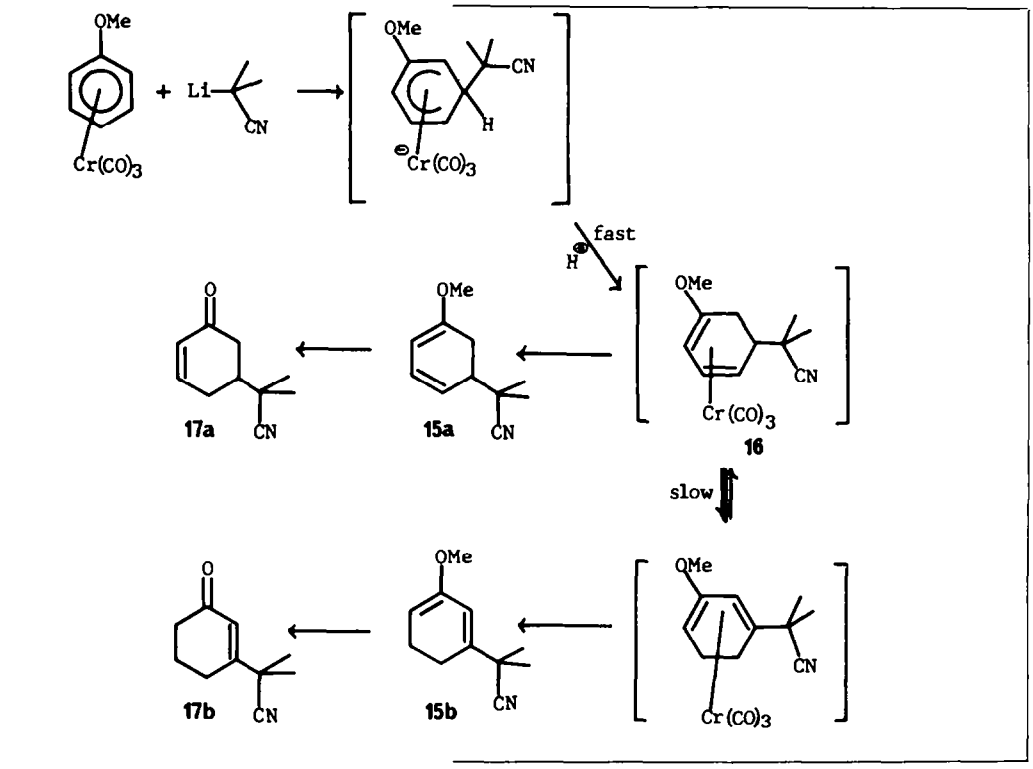
| | Complex | Anion | Ratio of Substitution at C-4/C-7 | (yield) |
|---|---|---|---|---|
| 1. | 10 | $LiCH_2CN$ | 75/25 | (43%) |
| 2. | 10 | $LiC(CH_3)_2CN$ | 97/3 | (73%) |
| 3. | 10 | $LiC(CH_3)_2CO_2tBu$ | 99/1 | (92%) |
| 4. | 10 | 2-Li-1,3-dithianyl | 14/86 | (68%) |
| 5. | 11 | 2-Li-1,3-dithianyl | 86/14 | (42%) |
| 6. | 11 | $LiC(CH_3)_2CN$ | 73/27 | (71%) |
| 7. | 12a | $LiC(CH_3)_2CN$ | 17/83 | (82%) |
| 8. | 12a | $LiCH(CH_3)CN$ | 33/67 | (64%) |
| 9. | 12b | $LiC(CH_3)_2CN$ | 95/* | (73%) |

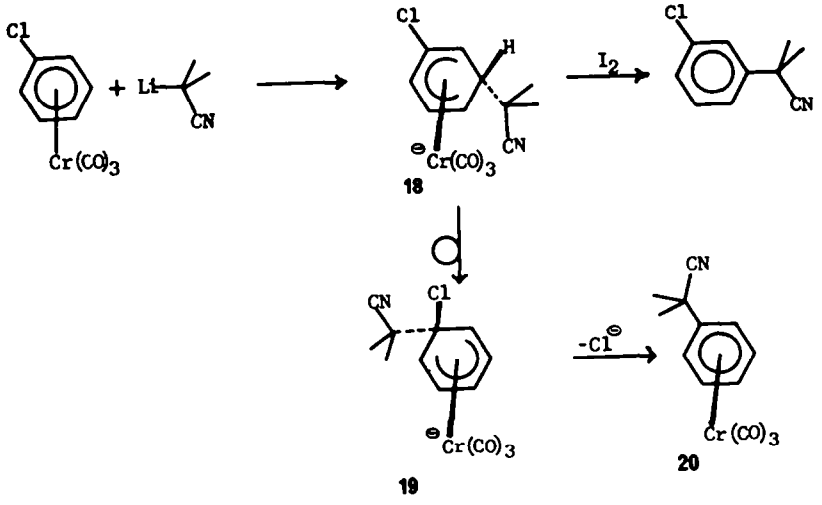
*The minor isomer is tentatively identified as the C-6 substitution product, <5% of the mixture.

complex, and the 1-substituted cyclohexa - 1,3 - diene invariably predominates.

A particularly useful example is the addition/protonation of $\eta^6$-anisole-$Cr(CO)_3$, where dienol ethers (e.g. **15**) are produced.[20b] It is observed that H-shifts in the intermediate (e.g. from **16**) are now slow relative to formation of **16** so that by careful attention to experimental conditions, either isomer (**15a** or **15b**) can be made to predominate. Standard hydrolysis produced cyclohexenones **17a** and **17b** in overall yields of 70–75%.[20b] The intramolecular version of this process was a key step in forming the spirocyclohexenone system of the acorenones.[24]

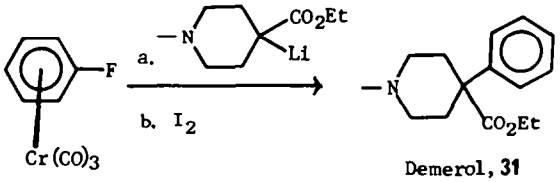
*Direct substitution for halogen.* Conceptually, the simplest process is direct nucleophilic *ipso* addition followed by elimination of halide, parallel with classical nucleophilic aromatic substitutions. But, also parallel with the classical examples,[29] the reaction is considerably more complicated than the overall conversion suggests. A prototype is the reaction of 2 - lithio - 2 - methylpropionitrile with $\eta^6$-chlorobenzene $Cr(CO)_3$.[21] At −78°, the arene complex is consumed and oxidation of the intermediate with excess iodine gives mainly substitution for hydrogen at the *meta* position, following the addition/oxidation pathway. However, at 25°, the intermediate (**18**) slowly isomerizes to the isomer (**19**) which



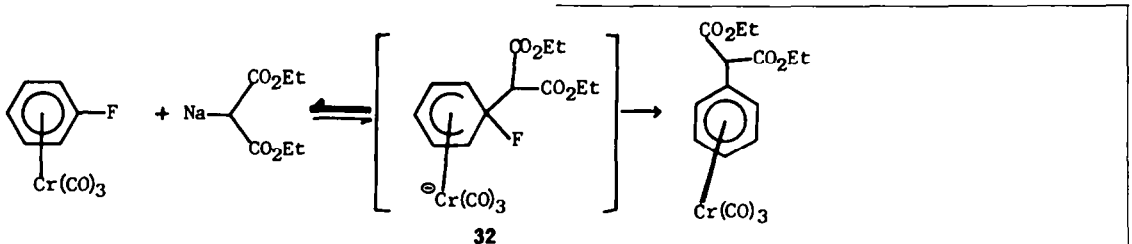

**21**: $LiC(CH_3)_2CN$
**22**: $LiC(CH_3)_2CO_2tBu$
**23**: $LiC(CN)(OR)CH_3$
**24**: $LiC(CH_3)_2CO_2Li$
**25**: LiC(CN)(OR)Ph
**26**: 2-Li-1,3-dithianyl
**27**: $LiCH_2SPh$
**28**: $LiCH_2CO_2tBu$
**29**: $LiCH_2CN$
**30**: $LiCH_2COC(CH_3)_3$

can lose chloride and produce the substituted product, **20**. Complex **20** has been isolated in 80% yield from this reaction.[21] The isomerization steps are fairly rapid (24 hr at 25° in THF) when tertiary carbon nucleophiles (anions **21–25**) are employed, but much slower with very reactive (anions **26, 27**) or less substituted (anions **28–30**) nucleophiles. With **26–30**, efficient substitution for *hydrogen* can be achieved by addition/oxidation, but direct substitution for *halide* is inefficient. The process is exemplified by direct phenylation of the enolate anion of N - methyl - 4 - carboethoxypiperidine to give Demerol (**31**) in 85% yield.[30]




Demerol, **31**

More stabilized anions (e.g. diethyl sodiomalonate) do not form detectable concentrations of the $\eta^5$-cyclohexadienyl intermediates (e.g. **32**) and therefore the substitution for hydrogen via addition/oxidation cannot be achieved. However, substitution for chloride and fluoride is observed,[21] and tertiary anions are not required for efficient substitution. This reaction is interpreted in terms of unfavorable, reversible formation of **32** followed by irreversible loss of halide, and is a simple extension of the original observations of Whiting.[17]




**32**

Representative experimental procedures are presented below for each of the processes discussed here, specifically for formation of **7**, **8**, **13**, **17a**, and **31**. The arene–chromium complexes can be handled as air-stable solids, soluble in organic solvents, and readily purified by crystallization or solid/liquid chromatography. In solution, the complexes slowly decompose through oxidation, but are stable toward acid and base hydrolysis, metal hydride reductions, etc. The $\eta^5$-cyclohexadienyl anionic complexes are stable at 25° but are exceedingly air sensitive, and are generated and used *in situ*.

## EXPERIMENTAL

Standard experimental and spectroscopic techniques were employed. Tetrahydrofuran and dioxane were distilled from sodium benzophenone ketyl immediately before use. For a system containing no volatile material, "under argon" means that the apparatus was alternately evacuated with an oil pump and filled with argon at least three times. For systems containing volatile reactants, "under argon" means carrying out the standard freeze-pump-thaw cycle several times.[31]

*Preparation of* 1 - (3,5 - *dimethoxyphenyl*) - 1 - *pentanone* (**7**).[23] To a soln of the Li salt of 2 - [(1 - ethoxy)ethoxy]hexylnitrile (16.5 mmol, prepared from the cyanohydrin of valeraldehyde[32]) under argon in THF (70 ml) and hexamethylphosphoric triamide (15 ml, HMPA) at −78° was added a soln in 15 ml of THF of $\eta^6$ - (*m* - dimethoxybenzene)$Cr(CO)_3$ (10 mmol, prepared from $Cr(CO)_6$ and *m*-dimethoxybenzene by heating in dioxane for 5 days, m.p. 124–127°; lit[33] m.p. 122°). The mixture was allowed to warm to 0° for 30 min and was then cooled at −78°. A soln of $I_2$ (20 g, 79 mg-at) in THF (20 ml) was added rapidly. After 7 hr at 24°, the dark soln was diluted with ether (100 ml) and shaken with sat $NaHSO_3$aq to remove excess $I_2$. The two-phase system was filtered to separate a red solid and the organic layer in the filtrate was washed with three 70-ml portions of 1M HCl, then stirred for 3 hr with each of one 50-ml portion of 6M HCl and one 50-ml portion of 15% NaOHaq. The ether layer was dried ($MgSO_4$) and concentrated by rotary evaporation. The residue was purified by chromatography (25 g silica gel, 8% ether in hexane) to afford a pale yellow low m.p. solid, 2.08 g, 96% yield. The $^1$H NMR spectrum was identical to the published spectrum of 1 - (3,5 - dimethoxyphenyl) - 1 - pentanone (**7**).[34] Analytical tlc indicated a single component. The structure was confirmed by conversion into olivetol.

*Preparation of* $\eta^6$ - (*o* - *methylanisole*)*tricarbonylchromium*.[24] A 300 ml one-neck flask equipped with a magnetic stirring bar and 1-m air condenser,[19] and containing *o*-methylanisole (10 g, 82 mmol), chromium hexacarbonyl (Pressure Chem. Co., 22 g, 100 mmol), and 200 ml dioxane was placed under argon. After being heated at reflux for 10 days, the mixture was cooled and unreacted $Cr(CO)_6$ was removed by filtration. The filtrate was concentrated by rotary evaporation with gentle heating to leave a dark residue which was dissolved in ether (partial dissolution) and transferred to a short column of Florisil The column was flushed with ether and the total eluate was concentrated to leave a yellow solid. One crystallization from ether/hexane afforded yellow crystals, 20.0 g, 94% yield, m.p. 74–76°. IR ($CHCl_3$): 1960 (br, s, CO), 1880 (br, s, CO) $cm^{-1}$. $^1$H NMR ($CHCl_3$): $\delta$ 5.60–4.77 (m, 4H, aryl-H), 3.75 (s, 3H, $OCH_3$), 2.17 (s, 3H, $CH_3$). (Found: C, 51.33; H, 3.96. Calc. for $C_{11}H_{10}O_4Cr$: C, 51.17; H, 3.90).

*Preparation of* 1 - *acetyl* - 3 - *methoxy* - 4 - *methylbenzene from addition/oxidation on* (o - *methylanisole*)$Cr(CO)_3$. The Li salt of the cyanohydrin acetal of isobutyraldehyde was prepared according to the method of Stork and Maldonado.[32] To a soln of the anion (generated from 18.8 g, 0.11 mmol of the cyanohydrin acetal of isobutyraldehyde and lithium diisopropylamide) in 200 ml THF containing 38 ml HMPA at −78° was added dropwise over 10 min a soln of the complex (above, 25.8 g, 0.1 mol) in 50 ml of THF under argon. The mixture was stirred at −78° for 1 hr and then at −20° for 4 hr. It was then cooled to −78° for 0.5 hr and a soln of 70 g of $I_2$ in 100 ml THF was added rapidly via syringe. After being stirred at −78° for 1 hr, then at 25° for 4 hr, it was poured into a mixture of 400 ml of $NaHSO_3$aq and 400 ml ether. The mixture was stirred for 1 hr, and the clear organic layer was decanted. Celite and an additional 200 ml of ether were stirred with the residue, the mixture was filtered, and the ether layer was separated. The combined ether layers were concentrated by rotary evaporation and to the residue was added 100 ml 10% $H_2SO_4$ at 25°. After being stirred for 2 hr, the mixture was neutralized with powdered $NaHCO_3$ and 100 ml 15% NaOHaq was added. The mixture was extracted with ether 3X and the combined ether soln was washed sequentially with 15% NaOHaq and sat NaClaq, dried over $MgSO_4$, and concentrated to leave a yellow oil. Fractional distillation gave **8** in a center cut of b.p. 92–110°/0.04 torr, 16.3 g, 83% yield, homogeneous by glpc. IR($CHCl_3$): 1680(s, CO), 1600(s), 1590(s), $cm^{-1}$. $^1$HNMR ($CDCl_3$): $\delta$ 1.16 and 1.23 (d, 6H, $CH(CH_3)_2$), 2.23(s, 3H, $ArCH_3$), 3.25–3.70(m, 1H), 3.80 (s, 3H, $OCH_3$), 7.06–7.50 (m, 3H, aryl-H).

(Found: C, 74.85; H, 8.35. Calc. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%).

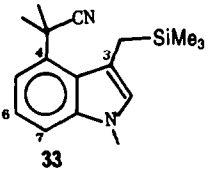
*Addition of 2 - lithio - 2 - methylpropionitrile to $\eta^6$ - anisole - $Cr(CO)_3$ followed by protonation to give cyclohexenone* **17a**.[20b] Into a 3-necked flask equipped with an argon/vacuum inlet, rubber septum, and magnetic stirrer under argon and containing 2 - lithio - 2 - methyl - propionitrile (above, 10 mmol) in 50 ml THF at −78° was added solid $\eta^6$-anisole-$Cr(CO)_3$ (2.45 g, 10 mmol). After being stirred at 0° for 1 hr, the mixture was cooled to −78° and trifluoroacetic acid (1.85 ml, 25 mmol) was added dropwise over a few min (dark red soln). After the mixture warmed to 0°, it was poured into cold $NH_4OH$ and the suspension was extracted several times with ether. The combined ether soln was washed with sat NaClaq by rotary evaporation. The residue was treated with a mixture of THF and 5N HCl (equivolume) at 100° for 20 hr. The mixture was washed with ether several times and the combined ether soln was dried ($MgSO_4$) and concentrated to give a yellow oil which slowly solidified. Recrystallization from ether gave m.p. 54.5–55°, 1.13 g, 70% yield of **17a**. $^1$HNMR ($CDCl_3$): $\delta$ 7.05 (ddd, 1H, $J_{AB}$ = 10 Hz, $J_{AC}$ = 5 Hz, and $J_{AD}$ = 3 Hz), 6.10 (dt, 1H, $J_{AB} \simeq 10$ Hz), $J_{BC} \simeq J_{BD} \simeq$ 1 Hz), 2.0–2.8 (m, 5H), 1.40 (s, 6H, $-CH_3$). IR($CHCl_3$): 2240(w), 1680(s) cm$^{-1}$. (Found: C, 73.72; H, 8.12; N, 8.66. Calc. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58%).

*Preparation of 4 - carboethoxy - 4 - phenyl - N - methylpiperidine*(**31**), *demerol.* To a 3-necked flask equipped with a magnetic stirring bar, a 2-way stopcock, and a serum cap under argon was added via syringe THF (25 ml) and N,N-diisopropylamine (0.130 ml, 2.0 mmol). The mixture was cooled to −78° and a soln of n-BuLi (1.97 M in hexane, 1.15 ml, 2.10 mmol) was added rapidly. After being stirred for 2 hr at 25°, the mixture was cooled to −78° and HMPA (10 ml) was added followed by a soln of $\eta^6$-fluorobenzene-$Cr(CO)_3$[35] in THF (5 ml). After the mixture was stirred at 25° for 2 hr, a soln of $I_2$ (2.0 g) in THF (5 ml) was added slowly with the mixture at −78°. The mixture was stirred at 25° for 4 hr, then poured into a cold soln of 30% $K_2CO_3$aq (25 ml). The mixture was extracted several times with ether and the combined ether soln was washed sequentially with 10% $Na_2S_2O_3$aq and water (5X). After the ether soln was dried ($MgSO_4$) and concentrated by rotary evaporation, the yellow solid residue (crude Demerol) was converted to the hydrochloride salt by passing HCl gas through an ether soln. The colorless crystals were recrystallized from EtOH/ether yielding Demerol hydrochloride, 82% yield, m.p. 186.5–188°. Lit[36] 187–188°. The neutral amine showed the following spectral data: $^1$H NMR ($CDCl_3$): $\delta$ 1.18 (t, 3H, J = 7Hz), 1.80–2.95 (m, 8H), 2.24 (s, 3H, N-$CH_3$), 4.08 (q, 2H, J = 7Hz), 7.31 (s, 5H, aryl H). IR(mull): 2900(br), 1765, 1235, 765, 700 cm$^{-1}$.

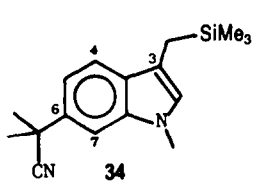
*Preparation of $\eta^6$ - (trimethylsilylmethyl)indole)tricarbonyl - chromium.* Into a 250-ml one-neck flask fitted with a magnetic stirrer and a 1-m air condenser[19] was placed 3 - (trimethylsilylmethyl) - indole[37] (3.16 g, 15.6 mmol), 100 ml of dioxane, and chromium hexacarbonyl (4.4 g, 20.0 mmol). The mixture was placed under argon and then heated at reflux for 4 days. After the mixture was cooled, the excess chromium carbonyl was filtered, and the filtrate was passed through Florisil, washing with ether. Concentration of the eluate by rotary evaporation gave a yellow solid which was recrystallized from ether: hexane to give 4.44 g (84% yield) of yellow crystals, m.p. *ca.* 100° (dec). IR($CHCl_3$): 3450(w, NH), 1940 (s, CO), 1850 (br s, CO)cm$^{-1}$. $^1$HNMR ($CDCl_3$): $\delta$ 7.56 (br s, 1H, NH), 6.82 (br s, 1H, H at C-2), 6.20 (d, 1H, J = 7.2 Hz, H at C-7 or C-4), 6.02 (d, 1H, J = 7.2 Hz, H at C-4 or C-7), 5.36 (t, 1H, J = 7.2 Hz), 5.03 (t, 1H, J = 7.2 Hz), 1.94 (s, 2H, $-CH_2Si$), 0.08 (s, 9H, $-Si(CH_2)$). Mass spectral mole wt: (Found: 339.0381. Calc. for $C_{15}H_{17}NO_3CrSi$: *m/e* 339.0383).

*Preparation of $\eta^6$ - (diphenyl - t - butylsilyl) - 3 - (trimethylsilyl - methyl)indole)tricarbonylchromium* **12b**). In a 50-ml round bottom flask fitted with a two-way stopcock, rubber septum, and a magnetic stirrer under argon was placed a soln of $\eta^6$ - (3 - (trimethylsilylmethyl)indole) - tricarbonylchromium (342 mg, 1.01 mmol) in 15 ml THF via syringe. A septum was removed, and with a positive flow of argon, a suspension of NaH in mineral oil (57 mg, 1.3 mmol of NaH) was dropped in. The mixture was stirred (gas evolution) for 15 min at 25° and then t-butylchlorodimethylsilane (356 mg, 1.3 mmol) was added neat via syringe. After the mixture had been stirred at 25° for 15 min, tlc analysis indicated the absence of starting material ($R_f$ 0.11, ether: $CH_2Cl_2$: hexane at 1:1:5, on silica gel) and a new component at $R_f$ 0.47 appeared. The mixture was poured into 100 ml of ether and the resulting suspension was washed sequentially with 1N HCl, $NaHCO_3$aq (2X), and NaClaq (2X). The organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation. Recrystalization of the solid residue (ether: hexane) gave 530 mg (92%) of an orange solid, m.p. 155–158°. IR ($CHCl_3$): 1938 (s, CO), 1850 (s, CO), 1415 (m), 1290 (w) cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.80–7.15 (m, 10H, PhSi), 7.03 (s, 1H, H at C-2), 6.10–5.89 (m, 1H, complexes aryl-H), 5.12–4.74 (m, 3H, complexed aryl-H), 2.02 (s, 2H, $-CH_2Si$), 1.24 (s, 9H, t-butyl), 0.09 (s, 9H, $Si(CH_3)_3$). Mass spectral mole wt: (Found: 577.1573. Calc. for $C_{31}H_{35}NO_3CrSi_2$: 577.1561.

*Reaction of complex* **12b** *with 2 - lithio - 2 - methylpropionitrile.* In a 50-ml 3-necked flask fitted with a magnetic stirrer, two rubber septa, and a two-way stopcock under argon was placed 15 ml of THF and diisopropylamine (0.28 ml, 2.2 mmol) via syringe. The solution was cooled to −78° and n-BuLi (0.96 ml of a 2.08 M soln in hexane, 2.0 mmol) was added dropwise via syringe. The mixture was warmed to 0° for 15 min and then cooled to −78° at which time 2-methylpropionitrile (0.20 ml, 2.2 mmol) was added dropwise via syringe over 10 min. The mixture was warmed to 0° for 20 min, and then cooled to −78°. A soln of complex **126** (0.58 g, 1.0 mmol) in 15 ml of THF was added rapidly via syringe. The mixture was stirred at −78° for 0.5 hr and then a soln of $I_2$ (2.0 g, 15.7 mg-at) in 10 ml THF was added quickly via syringe. The mixture was stirred at 25° for 14 hr, then diluted with 100 ml ether and washed sequentially with three 100-ml portions sat $NaHSO_3$aq, two 100-ml portions of sat $NaHCO_3$aq, and two portions of sat NaClaq. The organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation. Tlc analysis indicated a major component of $R_f$ 0.50 (ether: hexane = 1.5, silica gel) which was isolated by preparative layer chromatography, 318 mg (72%) of a yellow oil. This material was homogeneous by analytical tlc, and the $^1$H NMR spectral data ($CDCl_3$) were consistent with structure **13**; $\delta$ 7.80–6.40 (m, 14H, aryl H), 2.62 (s, 2H, aryl$CH_2$), 1.85 (s, 6H, $-C(CH_3)_2CN$), 1.20 (s, 9H, $-C(CH_3)_3$), 0.40 (s, 9H, $Si(CH_3)_3$). The structure was established by selective desilylation ($Bu_4NF$) followed by N-methylation to give **33** which has been fully characterized.[28] During isolation of **33**, a minor isomer (< 5%) was detected and tentatively identified as the product from substitution at C-6 (**34**).




**33**

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