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Book by Prof. A. J. Elias

Chromium Arene Complexes
Complexation of Cr(CO)₃ with ARENES
Chromium arene complexes

- Metal complexation is appealing in organic transformations because it changes the chemical behavior of organic molecules and allows unprecedented transformations that are not possible in simple organic substrates.

- The complexes can be made with numerous organic compounds bearing different functional groups and may solve problems of selectivity.

- Several metals are able to complex aromatic systems, the chromium tricarbonyl compounds being the most recognized as synthetic intermediates.

- The complexation of an arene to a chromium tricarbonyl unit changes its chemical behavior.

- The Cr(CO)₃ moiety exerts great facial control so it can be used as an auxiliary that can easily be removed.


The electron-withdrawing effect of the unit allows efficient nucleophilic attack (SNAr and dearomatization reactions)

- Increased acidity of ring hydrogens
- Nucleophilic addition to the ring
- Stabilization of benzylic positive and negative charges
- Steric directing group for selective reactions on ring and side chain

Stabilizes negative charges in benzylic positions and activates CAr–halogen bonds for cross-coupling reactions
Exerts great facial control so it can be used as an auxiliary that can easily be removed.

The 1,2- and 1,3-unsymmetrically disubstituted complexes are planar chiral and there are various ways to prepare them in enantiomerically pure form. Can serve as ligands for asymmetric catalysis.

**Increased acidity of ring hydrogens**

**stabilization of benzylic positive and negative charges**

**Nucleophilic addition to the ring**

**steric directing group for selective reactions on ring and side chain**

Benzylic anions are readily formed and, despite the electrophilic character of the Cr(CO)$_3$ group, benzylic carbocations are also stabilized, which is explained in terms of the neighbouring group effect. In addition, the Cr(CO)$_3$ moiety blocks one side of the molecule and has found widespread use as a ‘stereodirecting’ group in reactions at side chains.

**Stereochemical Aspects of CAC**

If a non-symmetrically 1,2- or 1,3-disubstituted arene ring is complexed to chromium, the resulting molecule lacks symmetry elements. The result is a chiral compound with a plane as the origin of chirality.
Preparation of enantiomerically pure chromium arene complexes

- Resolution
- Diastereoselective synthesis
- Enantioselective methods

Resolution

Interaction with another chiral molecule chromatography

These are classical and easier methods

Thus L-valinol is an efficient agent to resolve racemic planar chromium arylaldehyde complexes. One recent example is the synthesis of (1pS)-(+)\textsuperscript{6}, an intermediate in the synthesis of (2)-lasubine (vide infra), by resolution of chiral racemic complex rac-4 with L-valinol.

![Chemical reaction diagram](image-url)
2. Renewable chiral auxiliaries

This strategy has two variants, that is, complexation to a prochiral 1,2- or 1,3-disubstituted arene that previously is transformed into a chiral acetal or aminal, or diastereoselective lithiation of the complexed benzaldehyde derivative.

(1pS)-(+)6

>99% ee

Diastereoselective lithiation of the complexed benzaldehyde derivative.
Use of chiral auxiliary delivering the Cr(CO)\textsubscript{3} moiety

Complexation to enantiopure arenes

Heteroatom directed complexation

Uemura et al. used heteroatom delivery to prepare complex 18 with 99:1 facial selectivity. Success of this approach relied on the complexation of aryl amino alcohol 17, bearing two directing heteroatoms.
Intramolecular transfer of central chirality

Enantioselective lithiation:

Complexes carrying heteroatom-containing substituents can be ortho-deprotonated by chiral lithium amides to give desymmetrized lithiated arenes that may be quenched with appropriate electrophiles.
Desymmetrization of prochiral complexes:

\[
\text{Cr(CO)}_3\text{Cl} \xrightarrow{\text{CO, MeOH, NEt}_3} \text{Cr(CO)}_3\text{Cl} \quad 31\%
\]

38

\[
\text{Cr(CO)}_3\text{Cl} \xrightarrow{\text{CO, MeOH, NEt}_3} \text{Cr(CO)}_3\text{Cl} \quad 53\%
\]

39 up to 95% ee

\[
\text{Cr(CO)}_3\text{Cl} \xrightarrow{\text{CO, MeOH, NEt}_3} \text{Cr(CO)}_3\text{Cl} \quad 90\% \text{ ee}
\]

40

\[
\begin{align*}
\text{Pd}_2\text{dba}_3 \\
(5 \text{ mol\% Pd}) \\
ligand (10 \text{ mol\%}), \\
\text{base}
\end{align*}
\]

42a \( n = 2 \)

42b \( n = 3 \)

\[
\begin{align*}
\text{Cr(CO)}_3\text{Cl} \xrightarrow{\text{Pd}_2\text{dba}_3 \\
(20 \text{ mol\% Pd}) \\
ligand (40 \text{ mol\%}), \\
\text{base} \\
\text{RB(OH)}_2, \text{K}_2\text{CO}_3}
\end{align*}
\]

43a-b 3-73% ee of the major product (27-44%)

44a-b (5-93%)

ligand =

\[
\begin{align*}
\text{Cr(CO)}_3\text{Cl} + \text{Cr(CO)}_3\text{Cl}
\end{align*}
\]

45 50-80%; 68% ee

44a 10-13%
Dötz reaction

The Dötz benzannulation is an alternative approach towards the synthesis of chromium para-dioxygenated arene complexes.

General reactivity of chromium arene complexes

Arene chromium tricarbonyl complexes are powerful reagents in stereoselective organic synthesis, and are compatible with many reaction conditions.

The electron-withdrawing properties of the metal fragment (they are compared with nitrobenzene) result in nucleophilic additions to the arene, and nucleophilic substitution at benzylic and homobenzylic positions.

Moreover, the steric bulk of the metal carbonyl moiety effectively shields one face of the arene and this has been widely exploited in diastereoselective synthesis.

Finally, chiral arene complexes have been used as ligands or substrates in efficient enantioselective reactions.

Dipolar [3 + 2] cycloadditions with planar chiral arene tricarbonyl complexes allowed the synthesis of enantiopure trisubstituted pyrrolidines. The regioselectivity of the cycloaddition could be controlled by the choice of the Lewis acid used.
Coordinated metals can undergo haptotropic migrations between the rings of certain polycyclic arene–metal complexes. Dotz reported a haptotropic Cr(CO)$_3$ migration in a naphthalene complex that can be used as a molecular switch.
The potential use of haptotropic shifts to control rotational barriers has been shown by the synthesis of 71 and 72. These complexes revealed barriers to rotation of 12 and 13 kcal mol\(^{-1}\), respectively (variable-temp. NMR spectroscopy).

The chromium carbonyl moiety coordinates to one of the blades of the triptycene unit rather than to the more crowded indenyl group.
The strong EW-ability of the Cr(CO)$_3$ group makes haloarene chromium complexes prone to suffer nucleophilic attack.

**Nu:**  
S-stabilized carbanions  
alkyl, vinyl, and aryl lithium reagents  
exception of $n$-BuLi and MeLi (act as bases except if an imine is attached to the aromatic ring)

**Nu addition occurs** *ipso, ortho, meta, or para* to pre-existing substituents.

Regioselectivity? hard to predict  
Depends: nature and the relative positions of the substituents on the arene ring  
conformation of the Cr(CO)$_3$ tripod nucleophile

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In a typical reaction, 2-lithio-1,3-dithiane reacts with benzene chromium tricarbonyl to give an anionic $\eta^5$-cyclohexadienyl complex **76**. This intermediate has been characterized by X-ray diffraction analysis by Semmelhack et al. Oxidation of **76** with I$_2$ gives the substituted arene **77**.
**Table 1** Representative sample of carbanions tested with benzene chromium tricarbonyl

<table>
<thead>
<tr>
<th>Unreactive carbanions</th>
<th>Successful carbanions</th>
<th>Ring metalating reagents</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiCH(CO$_2$'Bu)$_2$</td>
<td>LiCH$_2$CO$_2$'Bu</td>
<td>BuLi</td>
</tr>
<tr>
<td>MeMgBr</td>
<td>LiCH$_2$CN</td>
<td>MeLi</td>
</tr>
<tr>
<td>Me$_2$CuLi</td>
<td>LiCH$_2$SPh</td>
<td>$^5$BuLi</td>
</tr>
<tr>
<td></td>
<td>2-Li-1,3-dithiane</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LiCH=CHR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LiPh</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LiCMe$_3$</td>
<td></td>
</tr>
</tbody>
</table>

**Certain Hydrides can also serve as nucleophiles**

**C-nucleophile**

**Four possible products: ipso, ortho, meta, or para to the X group.**

The regioselectivity of the Nu addition under kinetic control is influenced by substituents on the arene and by the conformation of the Cr(CO)$_3$ group.

Under thermodynamic control, the equilibrium depends on steric and electronic interactions in the intermediate anions.

**Donor/acceptors are usually attacked at a meta-position**
**Bulky groups direct to para.**
**Coordinating groups direct to ortho.**
In particular, nucleophilic addition to methoxy-substituted arene–Cr(CO)$_3$ complexes give meta-substitution.

This has been investigated by theoretical methods using density functional calculations employing the hybrid-DFT approach. It was demonstrated that the preferred reaction pathway proceeds via the most stable intermediate.

After the nucleophilic attack, several pathways are possible.

Oxidation ($I_2$, Ce(IV), Fe(III), O$_2$) gives an arene with a new substituent (substitution of C–H). Reaction of the intermediate with other electrophiles traps the intermediate only when the nucleophilic addition is irreversible (if it is reversible the original arene complex is recovered upon electrophilic attack).

If there is no leaving group, the reaction of the cyclohexadienyl intermediate with strong acids or carbon electrophiles is a dearomatization, resulting in a cyclohexadiene.

Carbon electrophiles react with the anionic intermediate by coordination to the metal center and further *endo-migration* to the cyclohexadienyl ring. Thus, the stereochemical relationship in the product is *trans*.

With certain electrophiles, migratory CO insertion precedes the reductive elimination.
C-E⁺ react with the anionic intermediate by coordination to the metal center and further endo-migration to the cyclohexadienyl ring. Thus, the stereochemical relationship in the product is trans.

Sequences that conserve the metal group, thus allowing further transformations, are highly desirable.

This goal is achieved, provided a leaving group is present, by treatment of the anionic intermediate with acids.

The complete sequence implied is nucleophilic addition–protonation–possible isomerizations of the cyclohexadiene intermediate–elimination to aromatize the product.

The incoming group can attack in four possible orientations with respect to the leaving group, thus giving ipso-, cine-, and tele-substitutions (the latter with two possibilities, tele-meta and tele-para).
N-aryl indoles with axially chiral bonds by stereoselective nucleophilic aromatic substitution reactions of planar chiral arene chromium complexes. The nucleophilic substitution reaction took place between an indolyl anion and optically active dioxolanylmethylfluorobenzene chromium tricarbonyl, 95, in the presence of 18-crown-6 in refluxing toluene.
When sterically hindered N-aryl indole chromium complexes 98a,b were refluxed in toluene, a stereoselective migration of the chromium tricarbonyl group to the arene ring of the indole occurred, giving 99. The 1,3-dioxolane group was crucial for this reaction.

Nucleophilic addition to the aromatic ring (ipso-substitution):
The ability of the Cr(CO)$_3$ moiety to strongly stabilize positive charges in the benzylic position is explained by a neighbouring group effect arising from an overlap of occupied d orbitals of the metal and the empty orbital of the carbenium centre.

This anchimeric effect allows SN$_1$ reactions with conservation of the stereochemical information.

Transformation of planar chiral complex 130 into a chloro derivative 133 by treatment with chloroethyl chloroformate. The configuration of the benzylic chiral centre is retained. The chloro substituent can be displaced by P, N and O in high yield.
Electrophilic addition to the benzylic position: Stabilization of negative charge

Planar/atrop/central chirality

Application in catalysis

Josiphos: 88% ee. Daniphos: 95% ee
Indane diphosphines: 88% ee
Chromium-Mediated Dearomatization Reactions


Dearomatization strategy/ synthesis of Enantioenriched Cyclohexenones


* R = chiral auxiliaries
Diastereoselective Dearomatization strategy/ Dienol Ethers


Application of chromium arene complexes in total synthesis of Natural Products

Chromium arene complexes in organic synthesis

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The complexation of an arene to a chromium tricarbonyl unit changes its chemical behavior, giving rise to unprecedented transformations. The electron-withdrawing effect of the unit allows efficient nucleophilic attack (Stille and deuteromethylation reactions), stabilizes negative charges in benzylic positions and activates C–H bonds for cross-coupling reactions. In addition, the Cr(CO)3 moiety exerts great facial control so it can be used as an auxiliary that can easily be removed. The 1,2- and 1,3-asymmetrically disubstituted complexes are planar chiral and there are various ways to prepare them in enantiomerically pure form. Planar chiral chromium complexes are becoming useful intermediates and ligands for asymmetric catalysis. This mature field of organometallic chemistry has given rise to several synthetic applications of chromium arene complexes in the synthesis of natural products. This chemistry is overviewed in this tutorial review, giving special attention to the most recent and outstanding contributions in the area.

1. Introduction

Transition metal complexation is attractive in organic synthesis because it changes the chemical behavior of organic molecules, allowing transformations that are not possible in uncomplexed substrates. In addition, the complexes are usually compatible with numerous functional groups and may solve problems of selectivity. Several metals are able to complex aromatic rings, the chromium tricarbonyl complexes being the most recognized as synthetic intermediates. The reasons that account for this popularity are: the arene chromium tricarbonyl complexes are stable to air, often crystalline and only sensitive to oxidizing reagents and to light. In solution they are moderately air sensitive. In addition, after being transformed, the chromium fragment is easily removed, releasing the modified arene. The usual ways to

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