CHAPTER - 1

Stereoselective Synthesis Using Arene Chromium Tricarbonyl Complexes:
A Review
The complexation of an arene to a Cr(CO)$_3$ fragment alters its chemistry in a number of ways (Scheme 1):

Scheme 1

The aromatic ring, contrary to its usual reactivity to electrophiles, becomes susceptible to nucleophilic addition$^1$. Both the rate of solvolysis$^2$ and acidity$^3$ of the protons attached to benzylic or homobenzylic site are enhanced. In addition to such modification of reactivity the stereochemical aspect received considerable attention over the recent years. It is possible to carry out stereospecific anti addition of reagents with respect to the Cr(CO)$_3$ moiety and accomplish efficient diastereoselective synthesis of a large number of complex molecular structures.

The most efficient stereocontrol has been obtained at the $\alpha$ carbon attached to the aromatic ring complexed with chromium tricarbonyl. Reactions at the $\beta$ carbon have also been found to proceed with high diastereoselectivity. We present in the following pages a representative survey of current results concerning such diastereoselective synthesis using arene Cr(CO)$_3$ as a stereoselective template.
We recognize that an unsymmetrically substituted aromatic ring complexed with a Cr(CO)₃ moiety would constitute a di pair⁴ (Scheme 2).

Scheme 2

\[
\begin{align*}
&\text{I} \\
&\text{II}
\end{align*}
\]

The chiral element is introduced by destroying the plane of symmetry of the benzene ring. Therefore, if we begin with one optical antipode of such a complex, subsequent diastereoselective transformation would result in an enantioselective synthesis leading to optically pure products.

There are several methods to obtain arene Cr(CO)₃ complexes in optically pure form. Many of the standard resolution procedures can be readily adopted. For instance, the racemic acids can be readily resolved using optically active amines⁵. Complexed aromatic amines are too weak bases to provide diastereomeric salts with optically pure acids commonly employed in resolution. The complexes bearing aliphatic alkoxy function can be resolved via their hemi succinates⁶.

Resolution of racemic aldehydes can be achieved by the use of \(\text{S(-)-5-\alpha\text{-phenylethyl semioxamazide}}\)⁷ (Scheme 3).

The diastereomeric derivatives were separated using column chromatography and the optically active complexed aldehydes were obtained on acid hydrolysis.
Davies et al. have standardised a very useful resolution method for ortho substituted aldehydes. Treatment of racemic complex with L-Valinol in diethyl ether containing 4A molecular sieves afforded a diastereomeric mixture of imines which could be separated by column chromatography. Subsequent hydrolysis gives optically active products (Scheme 4).

Scheme 3

Rest of the text is not visible due to the image limitations.
Microbial and enzymatic resolutions have also been attempted on arene Cr(CO)$_3$ substrates. Characteristic of such processes, high enantiomeric excesses were obtained with a limited number of structures. For example acetophenone Cr(CO)$_3$ complex was completely reduced by baker’s yeast in 24h, the chemical yield of the process was 96% with ee of 99%. But 1-indanone Cr(CO)$_3$ complex was reduced by baker’s yeast much less efficiently$^9$(Scheme 5).

Scheme 5

(±)

\[
\begin{align*}
\text{Baker's Yeast} \\
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{Cr(CO)$_3$} & \quad \text{Cr(CO)$_3$} \\
(-)S & \quad (-)S \quad 71\% \\
\text{ee} & \quad \text{ee} \\
51\% & \quad 71\% \\
\end{align*}
\]

\[
\begin{align*}
\text{Cr(CO)$_3$} & \quad \text{Cr(CO)$_3$} \\
(+)_R & \quad \text{ee} \\
25\% & \\
\end{align*}
\]

On the other hand the tetralone Cr(CO)$_3$ complex was reduced with baker’s yeast with 92% ee$^{10}$ (Scheme 6).

Reduction of aryl alkyl ketone complexes also proceeded with considerable success in terms of enantioselectivity depending on the substitution pattern on the aromatic ring$^{10}$. 
Scheme 6

Baker's yeast reduction of racemic ortho-anisaldehyde Cr(CO)₃ complex resulted in partial formation of the corresponding alcohol. The selectivities were moderate to good¹¹ (Scheme 7).

Scheme 7

Racemic Mixture

<table>
<thead>
<tr>
<th>Compound</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr(CO)₃</td>
<td>99%</td>
</tr>
</tbody>
</table>

Baker's Yeast Reduction of Racemic Ortho-Anisaldehyde Cr(CO)₃ Complex

Reactions:

1. Baker's Yeast reduction of Cr(CO)₃-ortho-anisaldehyde resulted in partial formation of the corresponding alcohol.
2. The selectivities were moderate to good.

Racemic Mixture of Ortho-Anisaldehydes

<table>
<thead>
<tr>
<th>Compound</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr(CO)₃-CHO</td>
<td>66%</td>
</tr>
<tr>
<td>Cr(CO)₃-OMe</td>
<td>81%</td>
</tr>
</tbody>
</table>

Conditions:

- 22°C
- H₂O
- Baker's Yeast
- D-Glucose
- 99% yield
The enantioselective hydrolysis using lipases to obtain optically enriched products have met with considerable success with ortho substituted benzyl alcohol Cr(CO)\(_3\) complexes\(^{12}\) (Scheme 8).

Scheme 8

\[
\text{Lipase} \quad \text{Isoprenylacetate} \\
\text{Cr(CO)}_3 \quad \text{(R, S)} \quad \text{Me} \quad \text{OMe} \quad \text{SiMe}_3
\]

<table>
<thead>
<tr>
<th>X</th>
<th>Lipase</th>
<th>(R) Yield %</th>
<th>ee %</th>
<th>(S) Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Amano-P</td>
<td>47</td>
<td>100</td>
<td>48</td>
<td>98</td>
</tr>
<tr>
<td>OMe</td>
<td>Amano-AK</td>
<td>46</td>
<td>95</td>
<td>47</td>
<td>97</td>
</tr>
<tr>
<td>SiMe(_3)</td>
<td>Toyobo Type A</td>
<td>48</td>
<td>85</td>
<td>45</td>
<td>84</td>
</tr>
</tbody>
</table>

Diastereoselective modification on aldehyde function:

A variety of nucleophiles add to substituted benzaldehydes complexed with Cr(CO)\(_3\) with high diastereoselectivity. A perusal of such reactions indicate that the presence of an ortho substituent is a necessary condition to achieve such high stereocontrol.

When fluoroalkyllithium reagents were used as nucleophiles variable diastereoselectivity were observed\(^{13}\) (Scheme 9). Perfluoroalkyl iodides in the presence of zinc would add to ortho tolualdehyde Cr(CO)\(_3\) complex in good to excellent yield. But the diastereoselectivity was less satisfactory\(^{14}\) (Scheme 10).
Scheme 9

\[
\begin{align*}
\text{R}^1 &= \text{Me} / \text{OMe} \\
\text{R}^2 &= \text{H} / \text{OMe} \\
\text{R}^F &= \text{C}_2\text{H}_5 / \text{i-C}_3\text{F}_7
\end{align*}
\]

Scheme 10

<table>
<thead>
<tr>
<th>R_f</th>
<th>Yield (%)</th>
<th>Diastereomer Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_2F_5</td>
<td>85</td>
<td>72 / 28</td>
</tr>
<tr>
<td>C_6F_13</td>
<td>80</td>
<td>65 / 35</td>
</tr>
<tr>
<td>C_3F_7</td>
<td>100</td>
<td>83 / 17</td>
</tr>
</tbody>
</table>
With enantiomerically pure alcohols obtained in this manner chiral induction in Prelog type synthesis was also studied. Fluoroalkyllithium and various Grignard reagents were used\textsuperscript{15} (Scheme 11).

Scheme 11

\[ \text{R}_2 - \text{M}_3 - 70^\circ \text{C} \]
\[ \text{Et}_2\text{O} \]
\[ 64 - 99\% \]

\[ \text{OH} \]
\[ \text{O} \]
\[ \text{C} \]
\[ \text{C} \]
\[ \text{OH} \]
\[ \text{C} \]
\[ \text{R} \]
\[ \text{R}^2 \]

\[ \text{Cr(CO)}_3 \]
\[ \text{Me} \]

\[ \text{Me} \]
\[ \text{R} \]

\[ \text{PhH / Py} \]
\[ 20^\circ \text{C} \]
\[ 90\% \]

\[ \text{Cl} \]
\[ \text{C} \]
\[ \text{C} \]
\[ \text{R} \]

\[ \text{Cr(CO)}_3 \]

\[ \text{KOH 5\%} \]
\[ \text{EtOH 20^\circ C} \]
\[ 95\% \]

\[ \text{99\%} \]

\[ \text{OH} \]
\[ \text{HOOC} - \text{C} \]
\[ \text{R}^2 \]
\[ \text{R'} \]

\[ 84 - 100\% \text{ ee} \]
Reformatsky reaction on ortho anisaldehyde Cr(CO)$_3$ complex took place in high yield and excellent diastereoselectivity. For the tolualdehyde complex the diastereoselectivity was less. Though the chemical yield was comparable$^{16}$ (Scheme 12).

Scheme 12

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>A</th>
<th>Yield (%)</th>
<th>d.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>OMe</td>
<td>70-80</td>
<td>100</td>
</tr>
</tbody>
</table>

Excellent diastereoselectivity was also obtained in the Darzen's condensation with ortho substituted benzaldehyde Cr(CO)$_3$ complex$^{17}$ (Scheme 13).
Scheme 13

R
CHO
Cr (CO)₃
Optically pure

+ ClCH₂CO₂Bu⁺
Bu⁺OH/Bu⁺OK
r.t.

R
CH=CH-CO₂Bu⁺
Cr(CO)₃

30% H₂O₂
TOAB
CH₂Cl₂, r.t.

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>76</td>
<td>97</td>
</tr>
<tr>
<td>Cl</td>
<td>70</td>
<td>96</td>
</tr>
<tr>
<td>Me</td>
<td>70</td>
<td>45</td>
</tr>
</tbody>
</table>

In an interesting variation the Schiff's base derived from ortho substituted benzaaldehydes and substituted aryl amine complexed with Cr(CO)₃ reacted with Grignard reagents to provide highly stereoselective C-C bond formation. With benzylmagnesium bromide the asymmetric induction was as high as 100%¹⁶ (Scheme 14).

Scheme 14
Stabilised anion like nitromethane react with ortho tolualdehyde Cr(CO)_3 complex in a manner similar to aldol reaction. The diastereoselectivity has been shown to be temperature dependant^9 (Scheme 15).

\[
\begin{align*}
&\text{Scheme 15} \\
&\begin{array}{c}
\text{Cr(CO)}_3 \\
\text{Me} \\
(\pm)
\end{array} \\
\xrightarrow{\text{CH}_3\text{NO}_2, \ NaOH (10\%), EtOH} \\
&\begin{array}{c}
\text{Cr(CO)}_3 \\
\text{H} \\
\text{H} \\
\text{OH} \\
\text{Me}
\end{array} \\
+ \text{II}
\end{align*}
\]

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>Diast ratio (I/II)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>r.t.</td>
<td>64/36</td>
<td>~100</td>
</tr>
<tr>
<td>-20</td>
<td>92/8</td>
<td>95</td>
</tr>
<tr>
<td>-40</td>
<td>97/3</td>
<td>90</td>
</tr>
</tbody>
</table>
In a subsequent paper it was demonstrated that an ortho fluoro substituent, despite its small size, could effect a high degree of diastereoselection in similar reaction\textsuperscript{20} (Scheme 16).

Scheme 16

\begin{equation*}
\begin{array}{c}
\text{CHO} \\
\text{Cr(CO)}_3
\end{array}
\xrightarrow{\text{CH}_3\text{NO}_2, \text{KF}}
\begin{array}{c}
\text{CHO} \\
\text{Cr(CO)}_3
\end{array}
\xrightarrow{\text{THF, O}^\circ \text{C}}
\begin{array}{c}
\text{NO}_2 \\
\text{Cr(CO)}_3
\end{array}
\end{equation*}

Diastereomer ratio 93/7

\begin{equation*}
\begin{array}{c}
\text{CHO} \\
\text{Cr(CO)}_3
\end{array}
\xrightarrow{\text{Me}_3\text{SiCN}}
\begin{array}{c}
\text{CN} \\
\text{TMS}
\end{array}
\end{equation*}

Diast. ratio 100/0

Similar nucleophilic additions have been used to prepare optically pure analogs of ephedrine\textsuperscript{21}.

Enolate addition to substituted benzaldehyde Cr(CO)\textsubscript{3} complexes were also shown to proceed with excellent stereoselectivity. Use of ortho trimethylsilyl group was shown to provide very high erythro selectivity\textsuperscript{22} (Scheme 17).

Addition of chiral allyl boronate to benzaldehyde Cr(CO)\textsubscript{3} complex resulted in a chiral benzyl alcohol after decomplexation with an ee of 83% while only moderate enantioselectivity (55-72% ee) could be obtained with uncomplexed aldehydes\textsuperscript{23} (Scheme 18).
Scheme 17

\[
\begin{align*}
&\text{Erythro: Threo} & \text{Yield} \\
&\text{X = H, n = 3} & > 98:2 & 75 \\
&\text{X = OMe, n = 3} & > 98:2 & 86 
\end{align*}
\]

Scheme 18

\[
\begin{align*}
R^1 & \quad R^2 \\
H & \quad H & 83 \\
\text{Me} & \quad H & 92 
\end{align*}
\]
More than 98% asymmetric induction was obtained during addition of TosMic with chiral complexes. Similar selectivity was also observed with ethyl cyano acetate with chiral complexes\textsuperscript{24} (Scheme 19).

Scheme 19
The addition of nucleophiles to tricarbonyl(η⁸-ω-trialkylsilylbenzaldehyde)chromium (0) complexes proceeds with complementary diastereoselectivities in the presence or absence of strong Lewis acids (Scheme 20).

Scheme 20

Diastereoselective addition on complexed aromatic ketones:

Addition of Grignard reagents to ortho substituted aromatic ketones complexed with Cr(CO)₃ have been reported to produce tertiary alcohols with high diastereoselectivity (Scheme 21).

In the case of α substituted 1-tetralone Cr(CO)₃ complex Grignard reagents produce a single diastereomer of tertiary alcohol thereby generating two contiguous chiral centre with predictable stereochemical relationship. With optically pure substrate optically pure products can be conveniently obtained (Scheme 22).

Efficient strategies to prepare optically pure indanol derivatives have been explored by Jaouen as shown below (Scheme 23)
Scheme 21

\[
\begin{align*}
\text{OH} & \quad \text{PhMgBr} & \quad \text{OH} \\
\text{C─CH}_3 & \quad \text{Cr(CO)}_3 & \quad \text{C─CH}_3 \\
\text{Cr(CO)}_3 & & \quad \text{(CO)}_3\text{Cr}
\end{align*}
\]

Single diastereomer

\[
\begin{align*}
\text{OH} & \quad \text{H} & \quad \text{OH} \\
\text{C─CH}_3 & \quad \text{C─CH}_3 & \quad \text{C─CH}_3 \\
\text{Cr(CO)}_3 & \quad \text{Cr(CO)}_3 & \quad \text{Cr(CO)}_3
\end{align*}
\]

85% 15%

Scheme 22

\[
\begin{align*}
\text{Optically pure} & \quad \text{MeMgI} & \quad \text{Optically pure}
\end{align*}
\]
In spite of the small size of the hydride reagents high diastereoselectivity is observed in the reaction of indanone complexes. However with acyclic ketones the selectivity is reduced\textsuperscript{28}.

Using the favoured direction of reagent approach from the face opposite to that of the metal, \textalpha\textbeta\textgamma\textdelta tetralone Cr(CO)\textgamma complex could be converted to \textalpha\textgamma-1-methyl or \textbeta\textgamma-1-methyl tetralin derivative (Scheme 24).

High selectivity is also achieved on acyclic substrates for similar transformations\textsuperscript{29}. A useful variation of this approach resulted in stereoselective synthesis of Acorenone A and Acorenone B\textsuperscript{30} (Scheme 25).
Scheme 24

\[
\text{MeLi} \quad \text{MeLi} \quad \text{Et}_3\text{SiH} \quad \text{CF}_3\text{COOH}
\]

Scheme 25

\[
\text{LiAlH}_4, \text{Ac}_2\text{O} \quad \text{Me}_3\text{Al}, 99\%
\]

d.e. \approx 100\%
Diastereoselectivity in alkylation and rearrangement:

Carbanions at the benzylic position are stabilised by the Cr(CO)$_3$ group complexed to the aromatic ring. Alkylation of such anions particularly rigid indane molecule can lead to highly stereoselective C-C bond formation$^{31}$ (Scheme 26).

Scheme 26

![Chemical structure](image)

Presence of an electron withdrawing group at the benzylic position renders such alkylation even more facile$^{32}$ (Scheme 27).

Scheme 27

![Chemical structure](image)

<table>
<thead>
<tr>
<th>RX</th>
<th>Yield %</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeI</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>≡Br</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>PhCH Br</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Only diastereomer
(2)-3-Butenyl pyridine Cr(CO)_3 complex can be deprotonated at the benzylic position and alkylated at low temperature. The reaction is highly stereoselective. A planar lithiated derivative where the lithium might be complexed with nitrogen of the pyridine ring could provide the rigidity necessary to effect the observed stereoselective reaction\(^{33}\) (Scheme 28).

Scheme 28

\[
\begin{align*}
\text{Cr(CO)_3} & \quad \text{Me} \\
\text{1: LDA, } -40^\circ\text{C} & \quad \text{Me} \\
\text{2: MeI, 79\%} & \quad \text{H}
\end{align*}
\]

One diastereomer

A three step reaction sequence starting from optically pure orthotolualdehyde Cr(CO)_3 complex resulted in the transfer of a nitrogen atom from a trivial reactant (benzylamine) to yield highly enantiomerically enriched chiral benzylamine\(^{34}\) (Scheme 29).

Scheme 29

\[
\begin{align*}
\text{PhCH_2NH_2} & \quad \text{Me} \\
\text{PhH, PTSA, } \Delta & \quad \text{Me} \\
\text{Cr(CO)_3} & \quad \text{CH=NM-CH_2-Ph}
\end{align*}
\]

THF/HMPT 20 \%, LDA, RX

\[
\begin{align*}
\text{Me} & \quad \text{R} \\
\text{Cr(CO)_3} & \quad \text{N=CH-Ph}
\end{align*}
\]
The 2,3 Wittig rearrangement of ortho substituted benzylallyl ether complexed with Cr(CO)$_3$ can occur with variable stereoselectivity depending on the configuration of the olefin. As shown below, the benzyl(\(E\)) crotyl ether gave the erythro isomer while the \(Z\) crotyl ether gave a stereoisomeric mixture$^9$ (Scheme 30).

**(Scheme 30)**

\[
\begin{align*}
\text{BuLi} & \quad \text{Et}_2\text{O} \\
\text{(Z)} & \quad \text{Me} \quad \text{CH}_2\text{O} \quad \text{CH}_3 \quad \text{H} \\
\text{Cr(CO)}_3 & \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{H} & \quad \text{C} \quad \text{OH} \quad \text{H} \\
\text{Me} & \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{Cr(CO)}_3 & \quad \text{Cr(CO)}_3 \\
\text{Threeo (59\%)} & \quad + \quad \text{Erythro (41\%)}
\end{align*}
\]

\[
\begin{align*}
\text{BuLi} & \quad \text{Et}_2\text{O} \\
\text{(E)} & \quad \text{H} \quad \text{CH}_2\text{O} \quad \text{CH}_3 \quad \text{H} \\
\text{Cr(CO)}_3 & \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{H} & \quad \text{C} \quad \text{OH} \quad \text{H} \\
\text{Me} & \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{Cr(CO)}_3 & \quad \text{Cr(CO)}_3 \\
\text{Erythro 100\%}
\end{align*}
\]

Highly diastereoselective C-C bond formation is possible at the homobenzylic position of the tetralin derivative enroute the synthesis of 11 deoxy daunomycinone$^9$ (Scheme 31).
Similar nucleophilic addition to imines derived from an arylamineCr(CO)_3 complex can be highly diastereoselective at the β position from the aromatic ring\textsuperscript{37} (Scheme 32).

<table>
<thead>
<tr>
<th>R</th>
<th>Nu</th>
<th>Yield (%)</th>
<th>Diast. Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>MeLi</td>
<td>42</td>
<td>90:10</td>
</tr>
<tr>
<td>Ph</td>
<td>NaBD\textsubscript{4}</td>
<td>50</td>
<td>95:5</td>
</tr>
<tr>
<td>tBu</td>
<td>NaBD\textsubscript{4}</td>
<td>78</td>
<td>95:5</td>
</tr>
</tbody>
</table>
Diastereoccontrol can be achieved even at a centre 3 atoms removed from the chromium complexed aromatic ring by a suitably designed aldol condensation (Scheme 33).

Scheme 33

\[
\begin{align*}
    \text{R} & \quad \text{R} \\
    \text{n-Bu} & \quad \text{Ph} \\
\end{align*}
\]

\[\text{Yield \%} \quad 92:8 \quad 75\]

Reaction of silyl enol ethers with secondary benzyl acetate \(\text{Cr(CO)}_3\) complex in the presence of Lewis acid afforded highly stereoselective \(\alpha\)-alkylation reaction. Both cyclic and acyclic substrates have been studied (Scheme 34).

Scheme 34

Optically pure

Optically pure
Such stereoselective C-C bond formation is also possible with allyl silanes\textsuperscript{40} (Scheme 35).

**Scheme 35**

\[
\begin{align*}
&\text{R}^1 = \text{H} \\
&\text{R}^2 = \text{Ac}
\end{align*}
\]

Benzyllic carbocations are stabilised by metal complexation in indane or tetralin systems such carbocations can be stereoselectively trapped by nucleophilic reagents\textsuperscript{41} (Scheme 36).

**Scheme 36**

\[
\begin{align*}
&\text{H} \\
&\text{R}
\end{align*}
\]

100 % inversion

100 % retention
Scheme 36

(contd.)

\[ (\text{CO})_3\text{Cr} \rightarrow \text{HBF}_4 \cdot \text{OMe}_2 \rightarrow \]

\[ (\text{CO})_3\text{Cr} \quad 74\% \]

\[ \begin{array}{c}
\text{Me} \\
\text{OH}
\end{array} \rightarrow \text{HBF}_4 \cdot \text{OMe}_2 \rightarrow \]

\[ \begin{array}{c}
\text{Me} \\
\text{OMe}
\end{array} \quad 77\%
\]

\[ \begin{array}{c}
\text{CH}_2(\text{COMe})_2, 73\%
\end{array} \]
Summary:

Current research has clearly established the viability of using Cr(CO)$_3$ moiety as an effective stereodirecting group in a wide variety of transformations. This constitutes the background of the present work which strives to extend and explore the efficacy of stereoselection at remote sites on a arene-Cr(CO)$_3$ template.
References:


