ORGANOMETALLICS IN SYNTHESIS: CHROMIUM, IRON & COBALT REAGENTS

Introduction to Metal-Carbon Bonding

Organometallic chemistry involves the interaction of an organic compound with a transition metal unit to form an intermediate complex. These may or may not be stable, but often have properties and undergo reactions that are quite different to the parent organic compound.

Before we consider the properties of such complexes, think about the bonding involved between a metal and an organic ligand.

The 18 electron rule:
- Derives from a desire to achieve a stable configuration – all bonding orbitals full.
- In order to assess the number of electrons contained within a complex, count electrons on the free metal, add the electrons from the ligands, and consider the charges (see **Inorganic Organometallics Notes** for details).

Details of M-C Bonding

CO Bonding

Chatt-Dewar-Duncanson Model: Carbon donates a lone pair of electrons to an empty orbital on the metal, while the metal donates electrons from a filled orbital into antibonding CO orbitals. See **Inorganic Organometallics Notes** for pictures. The result of this is that CO is very electron withdrawing.

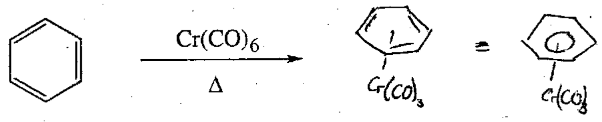
Bonding to π Ligands

A similar situation to the above occurs with these, e.g. alkenes (again, **Inorganic Organometallics Notes** for pictures).

Arene-Chromium Tricarbonyl Chemistry

Formation of ArCr(CO)$_3$ Complexes

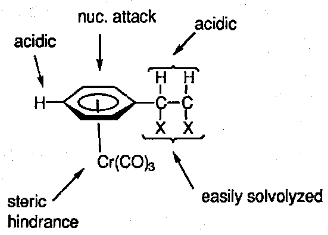
Heating an aromatic complex with chromium hexacarbonyl in dibutyl ether results in the formation of a complex between the aromatic ring and the transition metal. Electron-rich arenes complex the best and strong electron-withdrawing groups (e.g. nitro, keto) are incompatible. Schlenk lines should be used.



Moderately air stable

Decomplexation occurs with an oxidant (O_2 or CAN – $(NH_4)_2Ce(NO_3)_6$.

The key features of these complexes are:
1) Inductive – e-withdrawing.
2) Steric – size of tricarbonyl groups.
3) Stereochemistry – can be chiral – can influence stereoselectivity.
4) Neighbouring Group Participation – stability of benzylic cations.

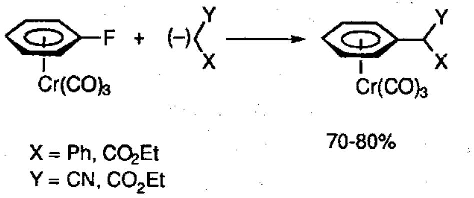


This diagram sums up all chromium-arene chemistry, and is brought about by the electron-withdrawing nature of the Cr(CO)$_3$ group.

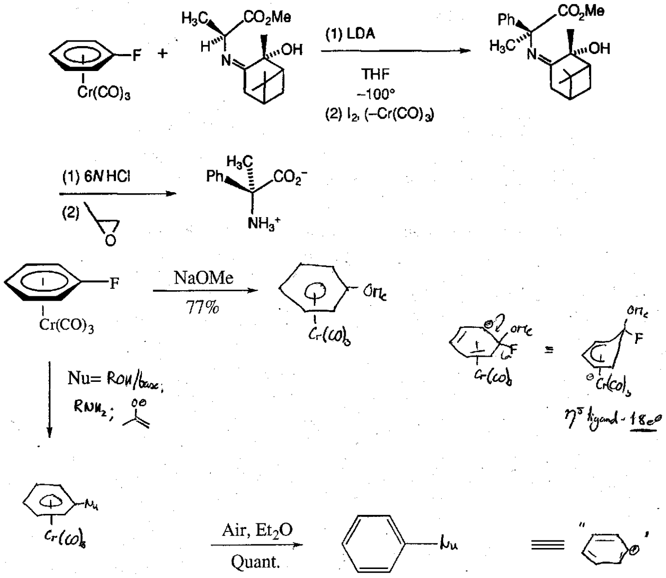
Reactivity

Nucleophilic Aromatic Substitution of Aryl Halides

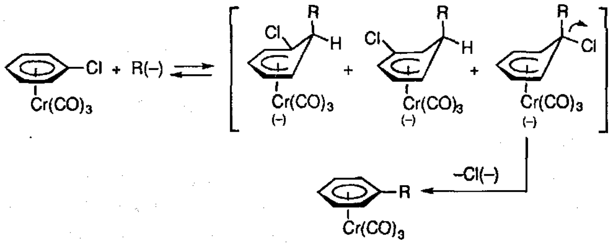
Although simple aryl halides are relatively inert to nucleophilic aromatic substitution, when complexed to chromium, this reaction is greatly facilitated.



X = Ph, CO_2Et
Y = CN, CO_2Et



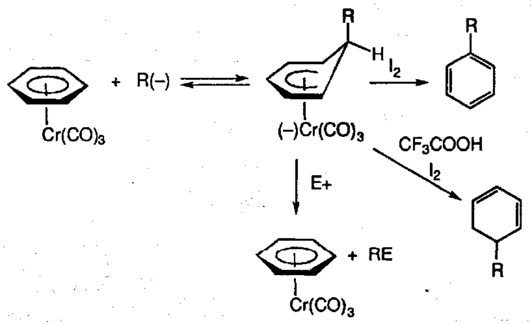
These substitution reactions all proceed by a two step process, involving nucleophilic attack of the arene ring from the face opposite the metal, forming an anionic η^5-cyclohexadienyl complex, followed by rate-limiting loss of the halide from the endo side of the ring.



The displacement of halide by carbanions is limited to stabilised carbanions capable of adding reversibly to the complexed arene. More reactive carbanions, such as 2-lithio-1,3-dithiane, attack the complexed arene ortho and meta to the halide, producing η^5-cyclohexadienyl complexes which cannot directly lose chloride, and furthermore, cannot rearrange to the η^5-cyclohexadienyl complex (which can). Stabilised carbanions also initially attack ortho and meta to chloride, but the addition is reversible such that eventually attack at the halide-bearing position occurs, followed by loss of halide (substitution).

Addition of Carbon Nucleophiles to Arenechromium Complexes

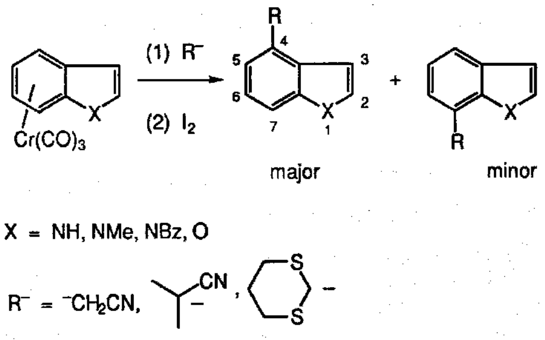
A range of stabilised carbanions attack from the face opposite the metal, producing anionic η^5-cyclohexadienyl complexes.



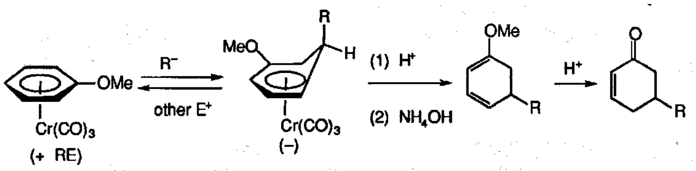
With substituted aromatics, under conditions of kinetic control, the regioselectivity is that expected for nucleophilic aromatic substitution (meta to e-donating groups, para to acceptor groups) and predicted by the assumption that the frontier MOs are arene-centred. Ortho addition occurs with groups capable of coordinating the incoming nucleophile (e.g. imines). In contrast to benzene-$Cr(CO)_3$ complexes, for which MeLi and n-BuLi react by deprotonation, these reagents add to phenylmethaneimine or similar. Note also that replacement of an electron-withdrawing CO ligand with a ligand such as phosphine (e-donating) decreases the reactivity of arene complexes towards nucleophilic attack.

Very reactive carbanions, such as dithiane lithium or phenyllithium, add irreversibly to the complexed arene. The resulting anionic η^5-cyclohexadienyl complexes are relatively stable and can sometimes be isolated. Oxidation of these complexes generates the alkylated arene, protonolysis generates mixtures of isomeric cyclohexadienes, and reaction with carbon electrophiles produces trans disubstituted species. In contrast, stabilised carbanions add to complexed arenes reversibly, and are always in equilibrium with the starting compounds. Reaction with carbon electrophiles results in regeneration of the starting arene complex and alkylation of the electrophile by the stabilised carbanion, as shown in the equation above.

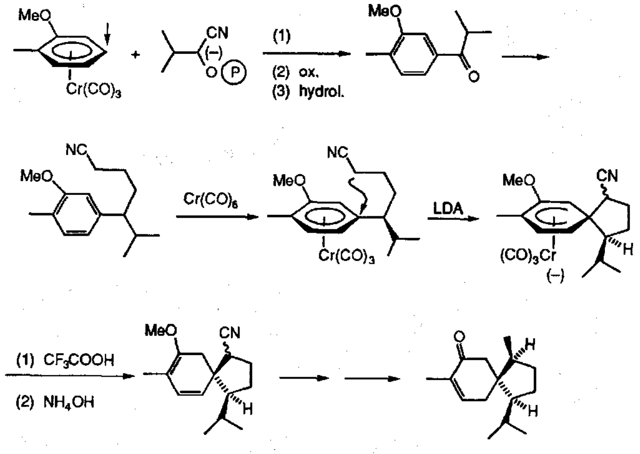
Both the activating and the directing effects of complexation to chromium are synthetically useful. For example, allows nucleophilic substitution at indoles, and permits reaction to occur at the usually inaccessible C4 (or indeed C7 with a bulky substituent at C3).



Protolytic cleavage of the η^5-cyclohexadienyl complexes resulting from alkylation of η^6-arenechromium tricarbonyl complexes produces cyclohexadienes rather than arenes.



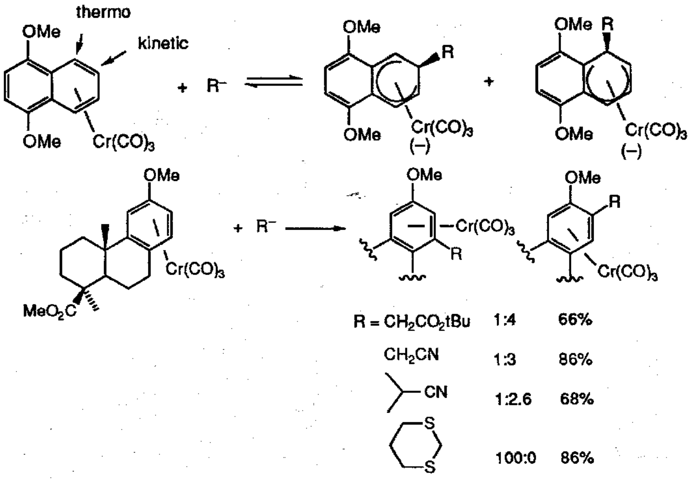
The ability of chromium to activate arenes, direct the attack, and to permit protolytic cleavage of the η^5 complex to produce cyclohexenones has been used below:



(±)-Acorenone B

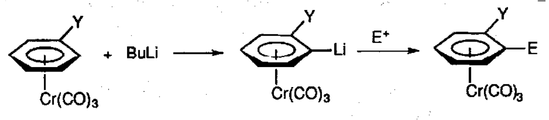
Again, protons are the only electrophile that cleaves the η^5 complex. Since most alkylations are reversible, other electrophiles react preferentially with the free carbanion.

More Examples:



Lithiation of Arenechromium Tricarbonyl Complexes

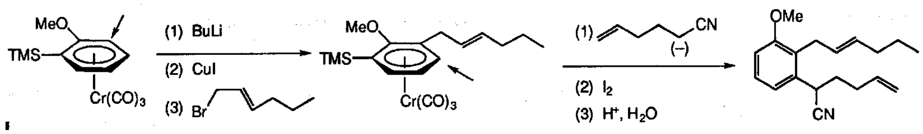
Chromium activates the ring to lithiation too.



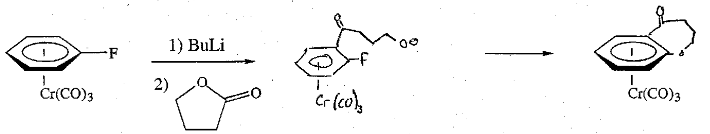
Y = H, OMe, F, Cl

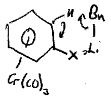
E⁺ = CO_2, MeI, PhCHO, TMSCl,

Arenes with substituents with lone pairs (MeO, Cl, etc) gives lithiation always ortho to the substituent. Complexed indoles are lithiated in the normally unreactive 4-position, provided a large protecting group is present on the nitrogen to suppress lithiation at the 2-position.

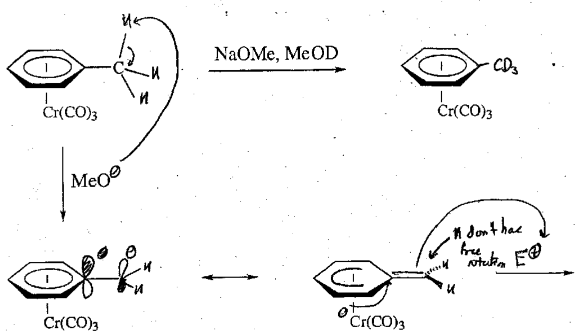


Also,





Chelation is essential here; explains regiochemistry



All things being equal; benzylic protons removed first

exocyclic alkene character

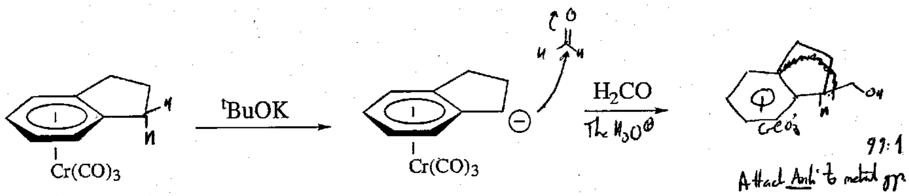
η^5 18e⊖

E⊕ approaches from top - no chance from bottom.

Benzylic protons more acidic than aromatic protons in this system

with DOM grp - Ar H tend to be removed 1st.
BuLi

Combine with the large size of the chromium tricarbonyl unit and:



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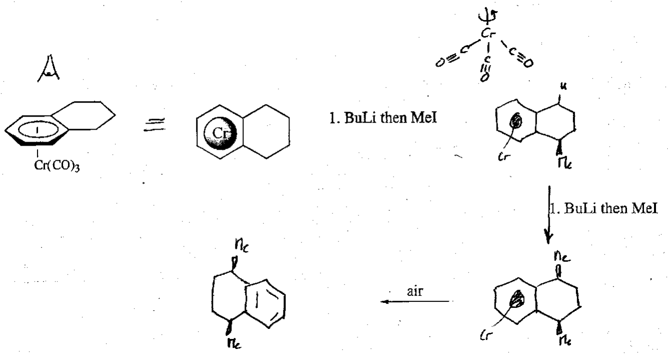
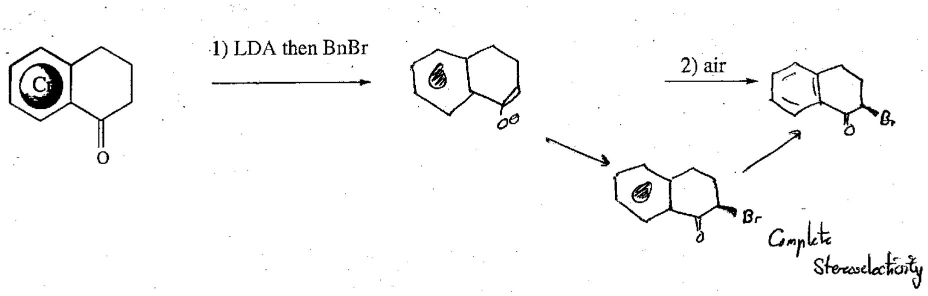
Attack Anti to metal grp

Electrophiles approach anti to it:

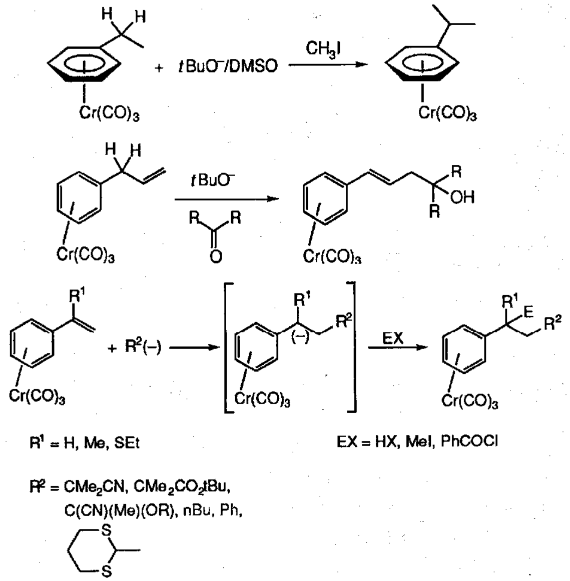


In fact this effect is noticeable at centres that are doubly removed from the ring.

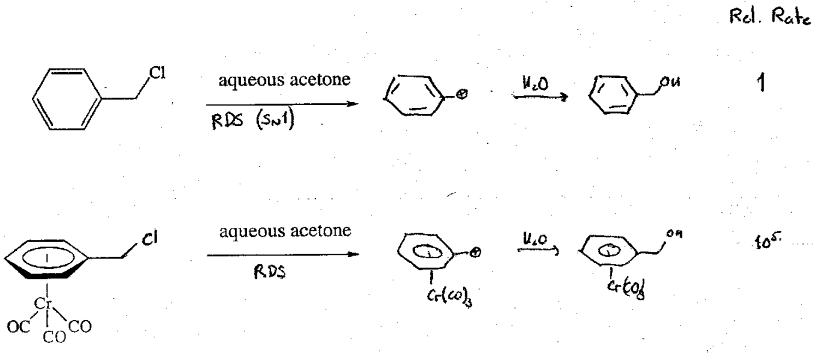


Activation of the Benzylic Position

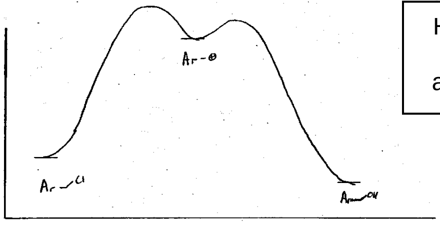
This is another manifestation of the electron-withdrawing properties of the $Cr(CO)_3$ group – stabilises negative charge at the benzylic position.



Unusually, however, chromium also stabilises positive charge in the benzylic position. This is thought to be due to stabilisation by a "through-space" interaction with the metal-bound carbonyl groups and/or filled metal d-orbitals. First discovered when:

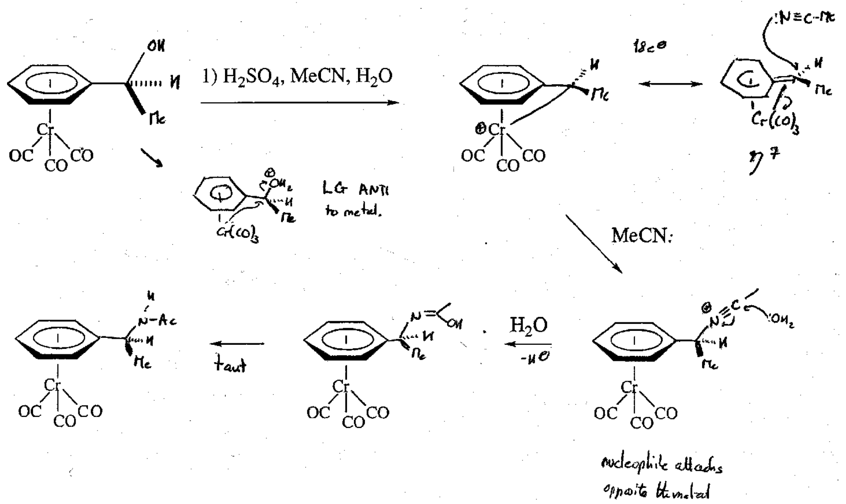


Consider an energy diagram for the reaction: a fast S_N1 reaction implies that the cation is stable.

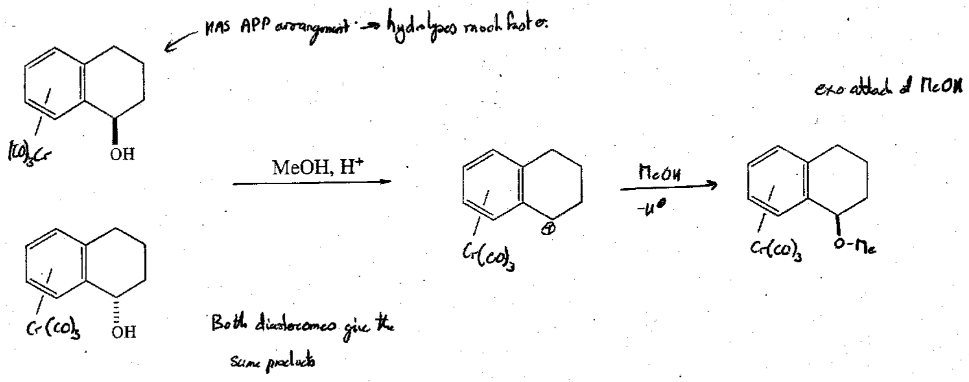


Hammond Postulate – a low energy cation has a low activation energy ➔ fast S_N1

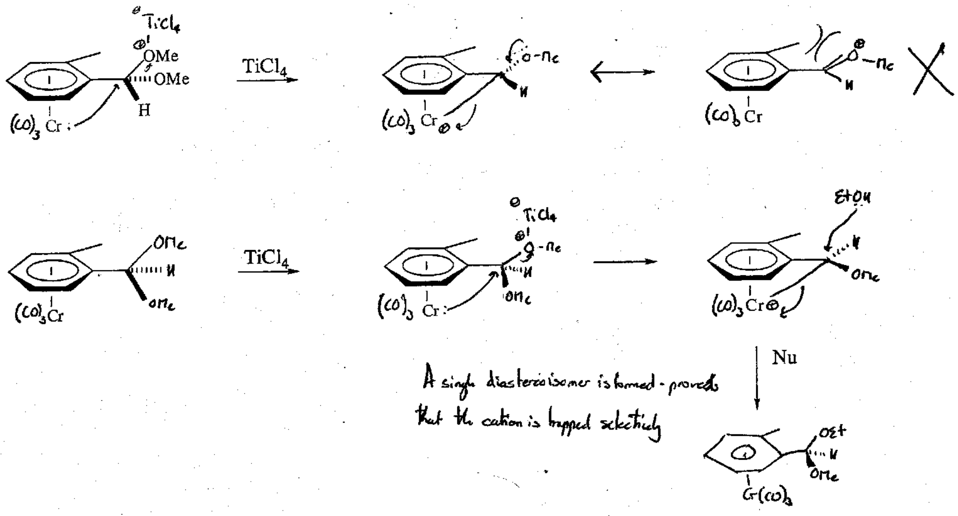
There are stereochemical implications for this process. Consider the Ritter Reaction:



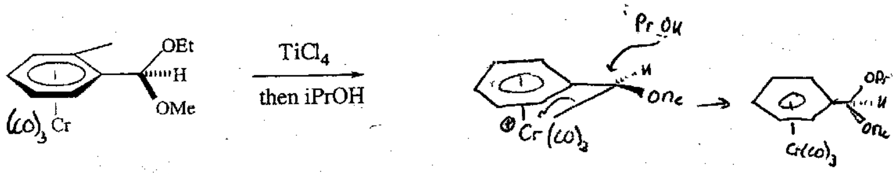
So double inversion leads to retention:



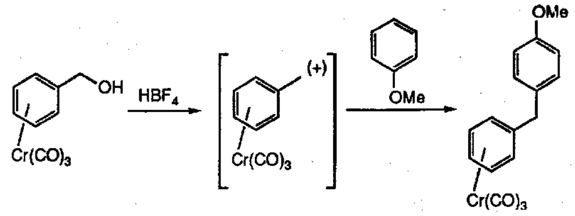
Now consider the ionisation of this acetal:

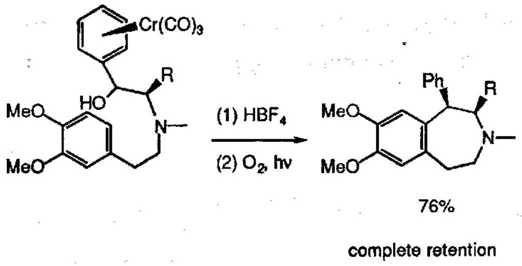


The following experiment shows 2 things – 1) only OEt is hydrolysed, which validates the mechanism, and 2) it is stereoselective.



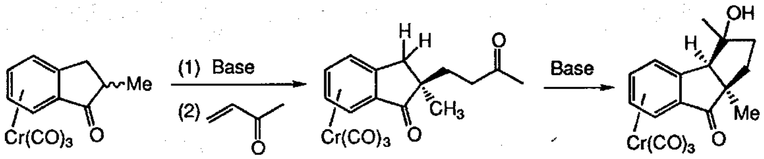
This allows useful synthetic transformations:





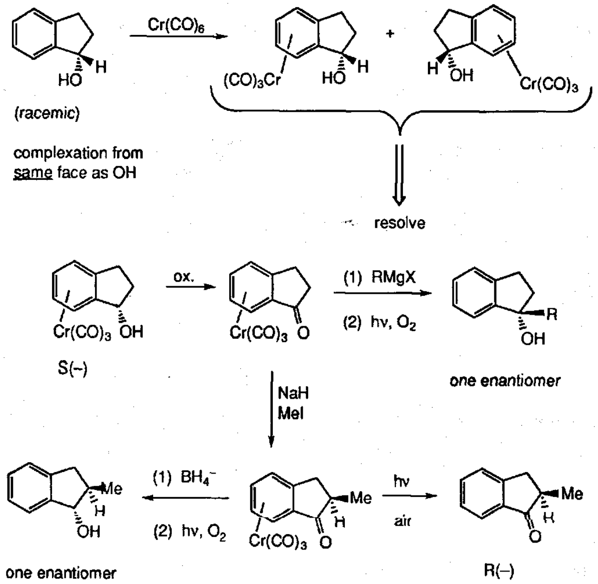
Steric Effects

The chromium tricarbonyl fragment completely blocks one face of the arene, so that reactions occur from the face opposite the metal. This can result in a very high degree of stereocontrol, and hence the use in organic synthesis. For example:

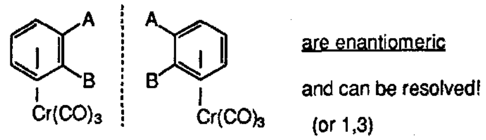


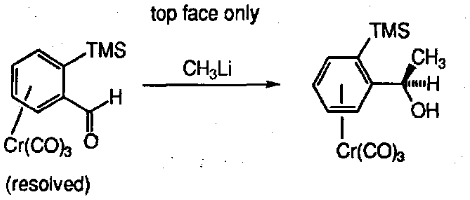
Removal of an activated benzylic proton permitted intramolecular alkylation of the keto group, resulting in clean cis-stereochemistry from the opposite face of the metal.

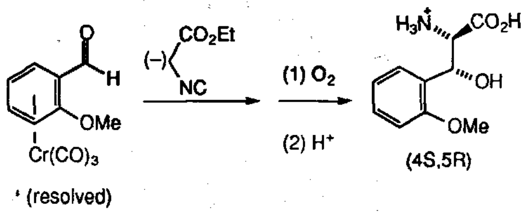
It is also possible to obtain facial selectivity by complexation to e.g. OH groups, e.g.



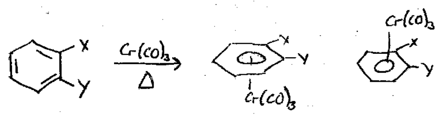
Unsymmetrically 1,2- and 1,3-disubstituted arenechromium tricarbonyl complexes are chiral and are enantiomeric on the basis of which face of the arene the chromium tricarbonyl fragment occupies. Known as planar chirality – chirality resulting from the arrangement of out-of-plane groups with respect to a reference plane (the chiral plane). This allows highly enantioselective reactions:

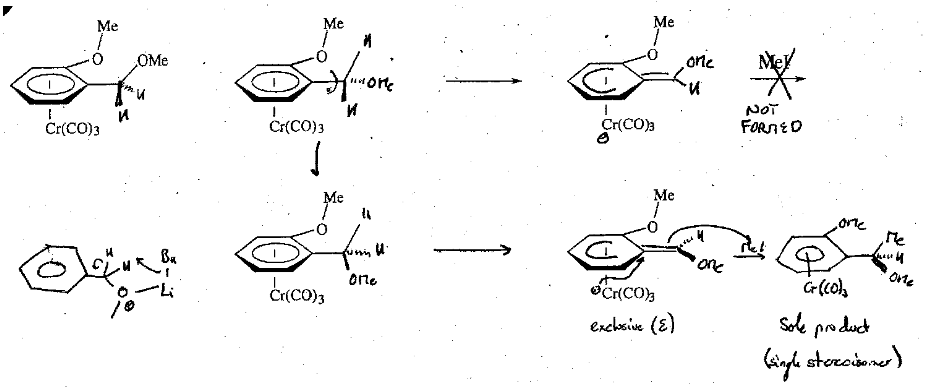




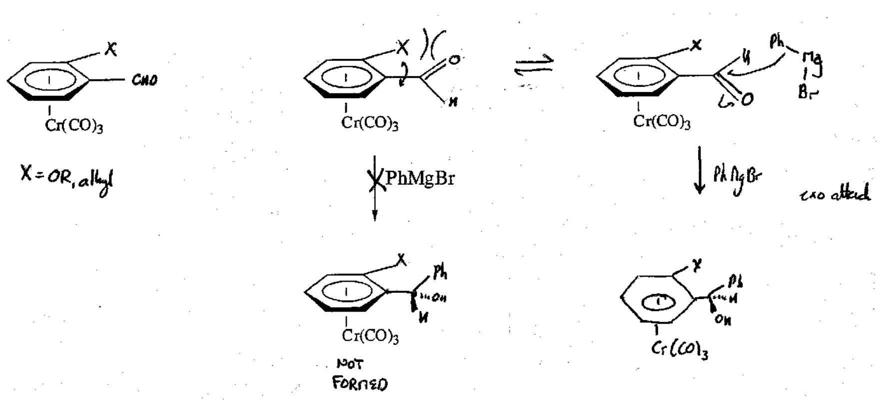


Complexation of XYC_6H_4 will give a racemic mixture (addition to both enantiotopic faces). But, there are a number of methods available for the formation of single enantiomers by resolution or asymmetric synthesis. We can use this chirality to influence the formation of new chiral centres, i.e. stereoselective synthesis.

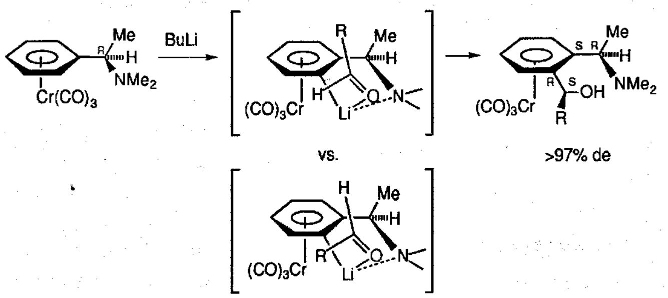




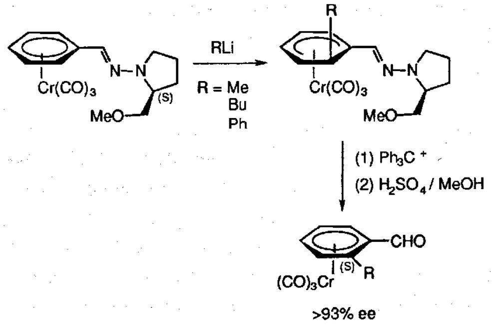
Consider addition to the following aldehyde:



Planar chiral arene-Cr(CO)$_3$ complexes can also be generated by diastereoselective reactions. For example, α-lithiation of the Cr(CO)$_3$ complex below occurs almost exclusively at one of the two diastereotopic ortho positions, and the resulting carbanion alkylates aldehydes almost exclusively from a single face.



Also, diastereoselective nucleophilic addition ortho to a chiral hydrazone group gollowed by hydride abstraction and removal of the chiral auxiliary gives the planar chiral benzaldehyde complexes with high enantiomeric excess:

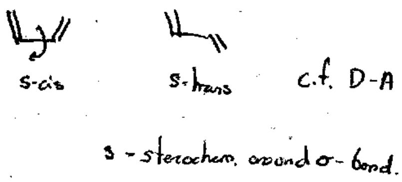


Organo-Iron Reagents

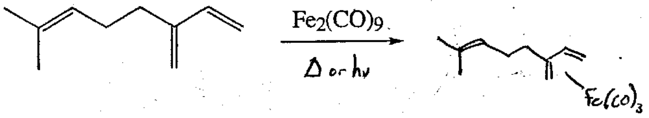
Cationic olefin complexes of iron(II) are easily made by alkene exchange with the stable CpFe(CO)$_2$(isobutene)$^+$ complex which is a stable gold-yellow solid, made by reaction of Fp$^-$ (Fo = CpFe(CO)$_2$) with methallyl bromide, followed by γ-protonation. Once complexed, the olefin becomes reactive to nucleophilic attack, sharing most of the reactivity, regio- and stereochemical features of the neutral olefin Pd(II) complexes. However, the main difference is the stability of the σ-alkyl iron(II) complex, such that the iron must be removed in a separate chemical step, usually oxidation.

Formation / Decomplexation

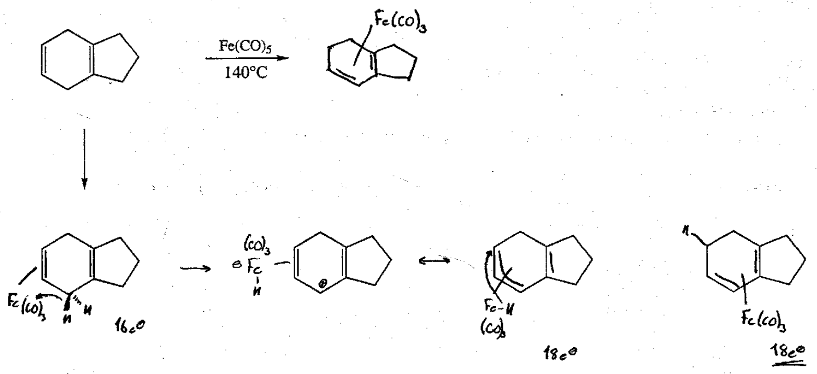
Not surprisingly, iron forms metal tricarbonyl complexes with dienes (Cr d^6, Fe d^8). Reaction of a diene with di-iron nonacarbonyl forms a complex. The diene must be conjugated, and also capable of existing in the s-cis conformation:



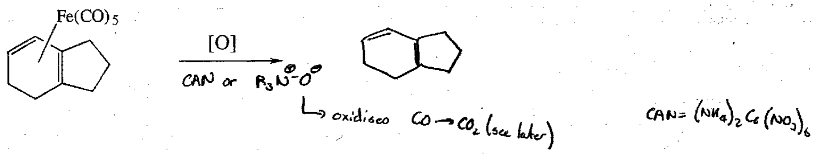
The iron has 8 + (3x2) + 4 = 18 electrons.



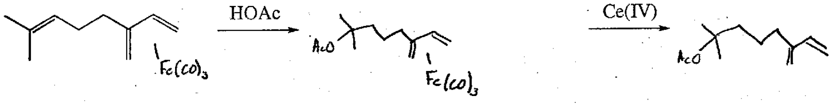
Skipped dienes may also react indirectly:



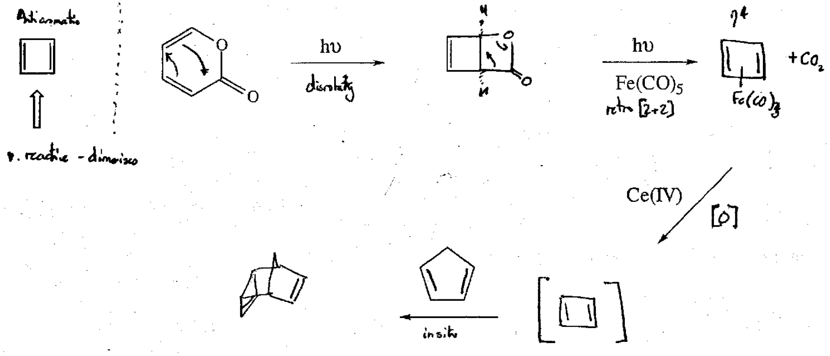
And decomplexation can be effected with an oxidant:



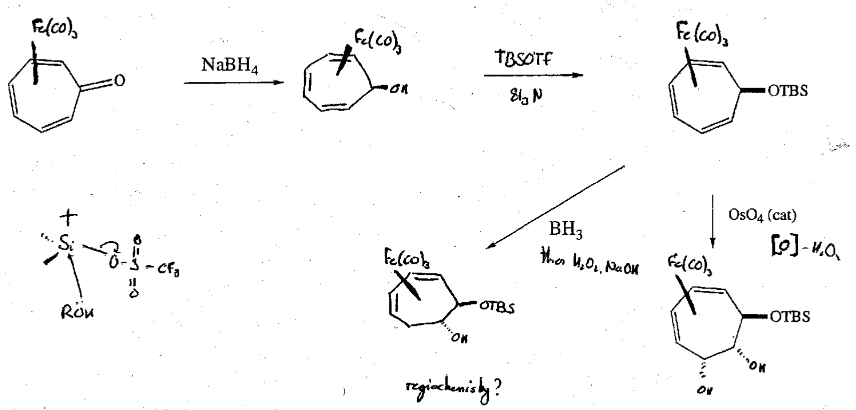
Protecting / Stabilising
Firstly, this derivative can be used as protecting group for a diene.



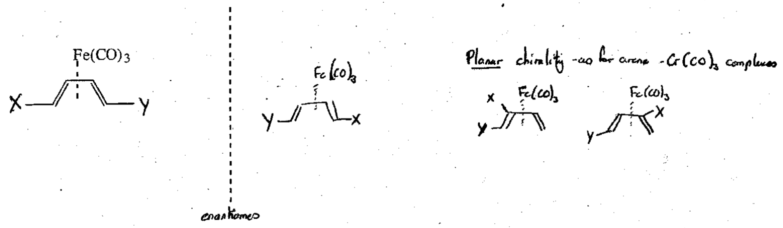
And, in addition, complexation to iron can confer stability on a reactive diene.



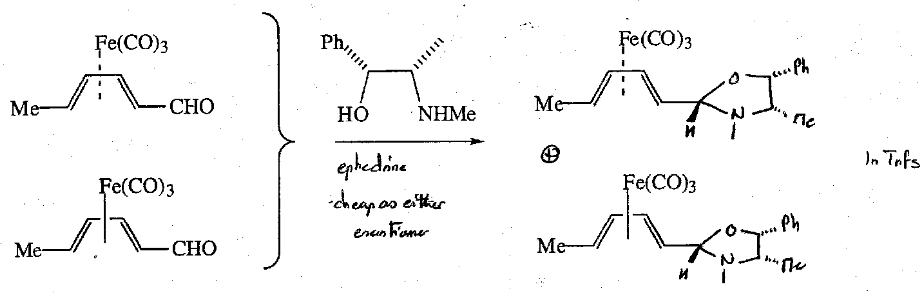
Steric Influence
Also, reagents prefer to add opposite to the bulky Transition Metal.



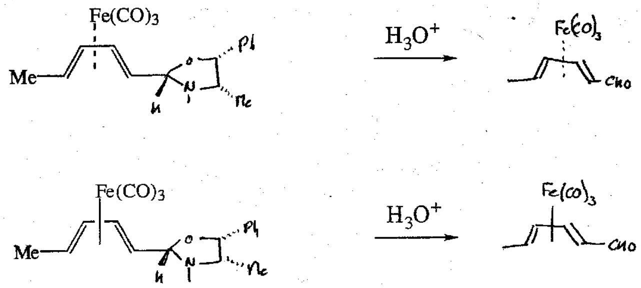
Remember that unsymmetrical substituted diene complexes are chiral:



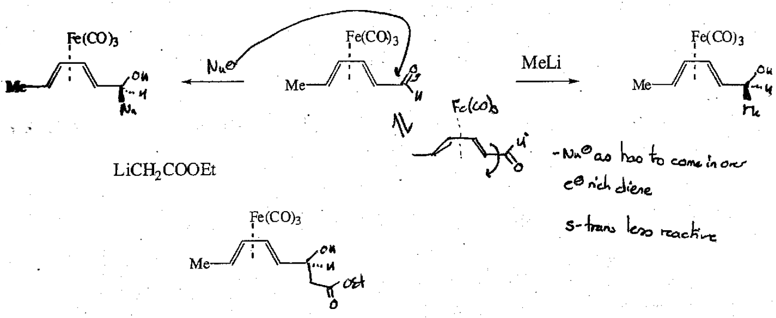
In fact, this complex can be resolved:



These two complexes can then be separated by chromatography:



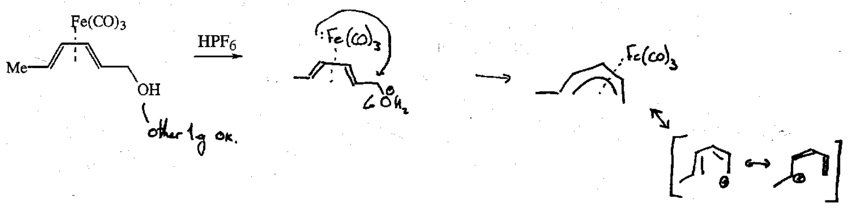
Selective addition can now be performed.



Cyclohexadienyl Cationic Complexes of Iron

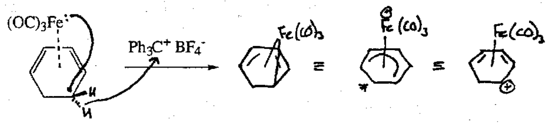
The iron-tricarbonyl diene unit is capable of stabilising adjacent carbocations (cf. Cr). Prepared from the diene complexes by 2 main methods:

1) Adjacent leaving group:

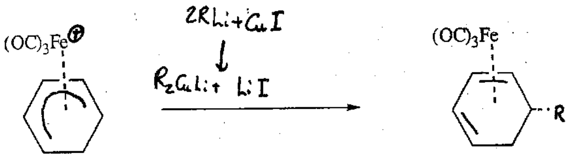


other lg ok.

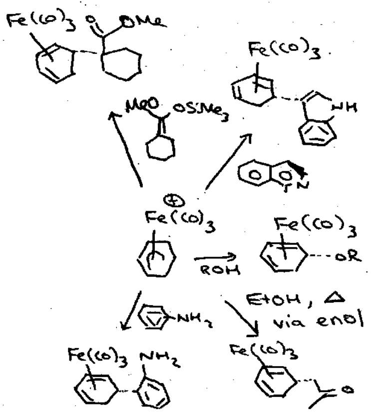
2) Reaction of trityl cation on a diene complex:



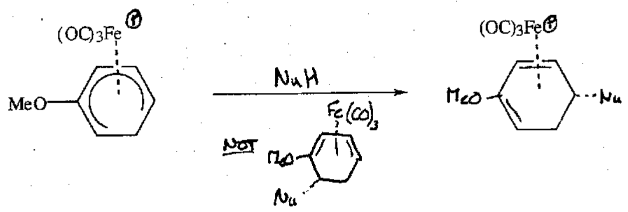
These complexes are capable of reaction with a variety of different nucleophiles. All these attack ANTI to the large Fe(CO)$_3$unit.

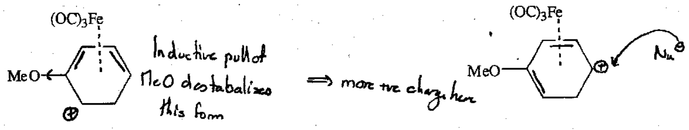


50-90% yield
dimerisation much reduced



The regioselectivity of attack is governed by electronic considerations:



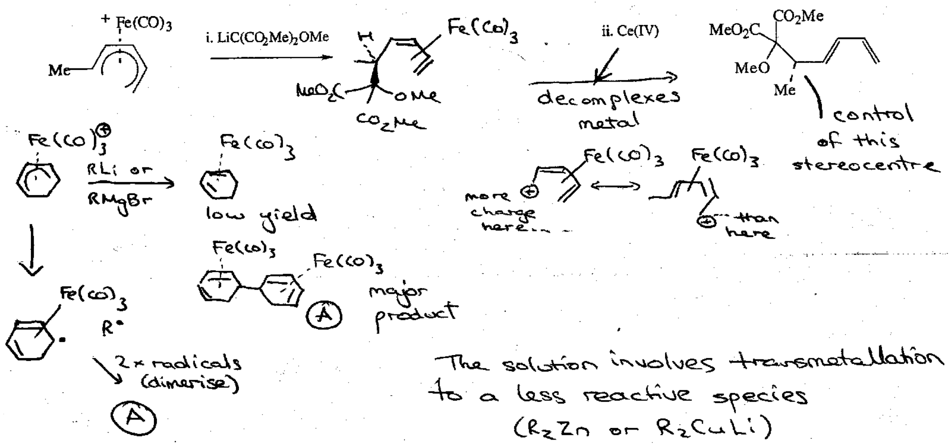


Inductive pull of MeO destabilises this form

⇒ more +ve charge here

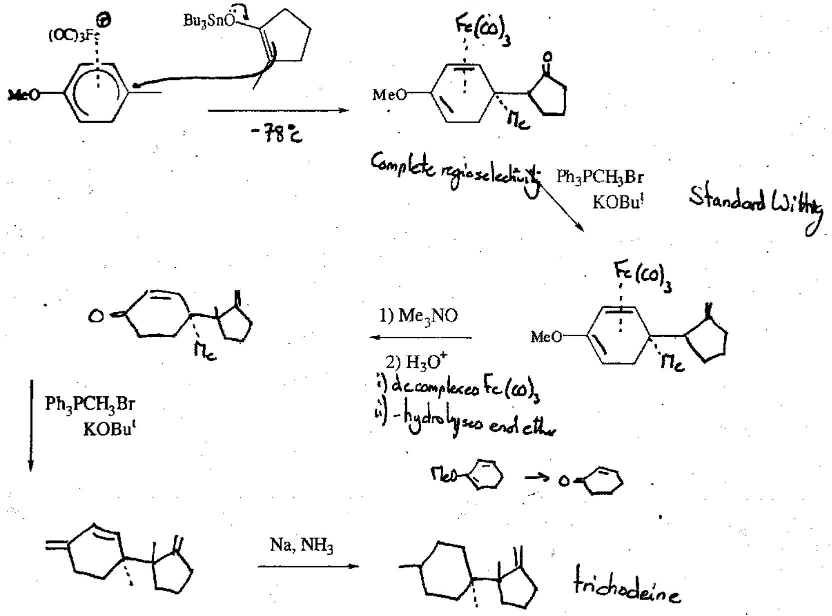
Ref: Organometallics, 1984, p1150. (More detailed – unequal bond lengths in complex).

Similarly for alkyl substituted complexes:



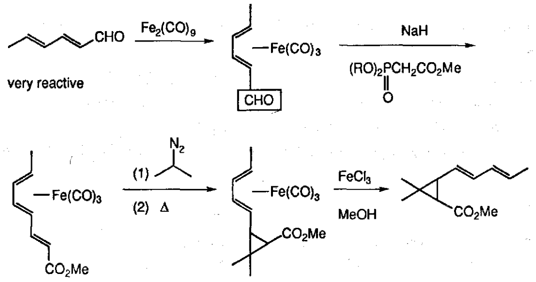
The solution involves transmetallation to a less reactive species (R_2Zn or R_2CuLi)

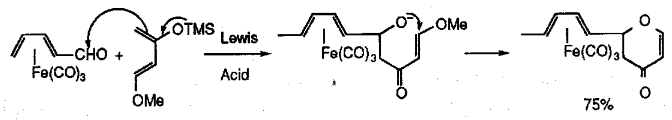
Applications of iron diene complexes in synthesis:

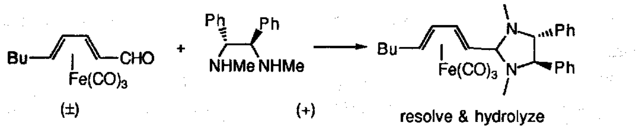


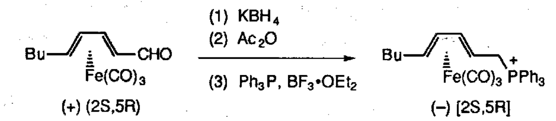
More Reactions

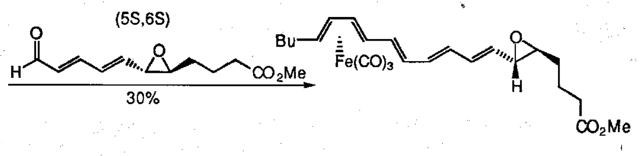
Fe(CO)$_3$ as a 1,3-diene Protecting Group

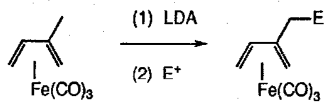


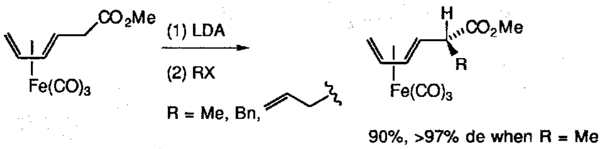




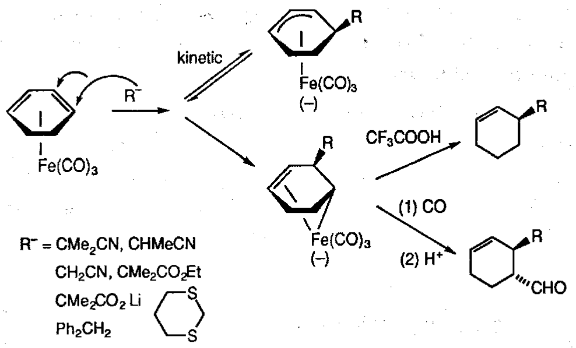


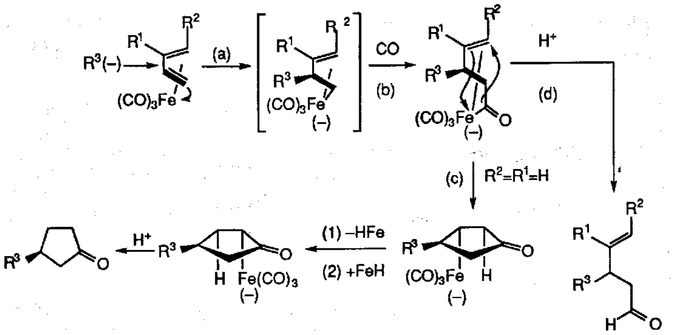


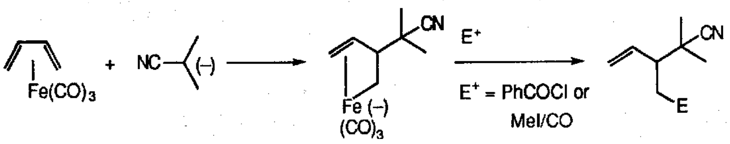




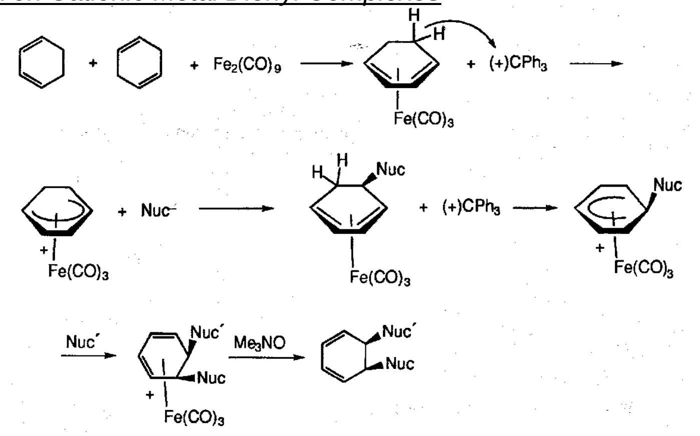
Nucleophilic Attack on Metal-Diene Complexes

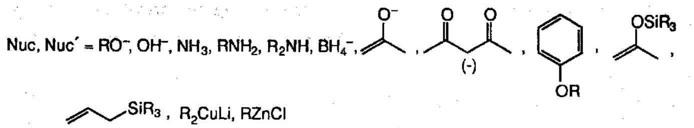






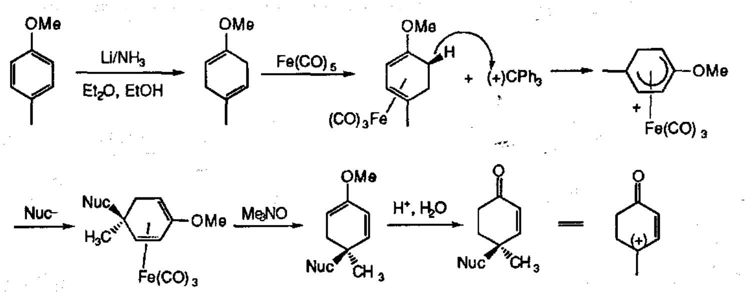
Nucleophilic Attack on Cationic Metal Dienyl Complexes

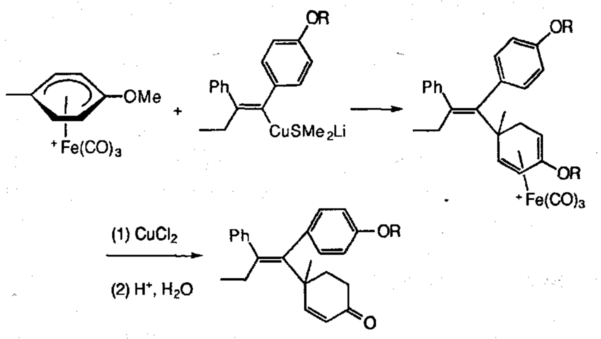


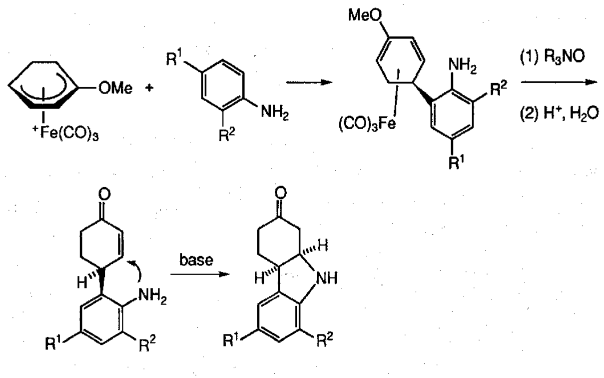


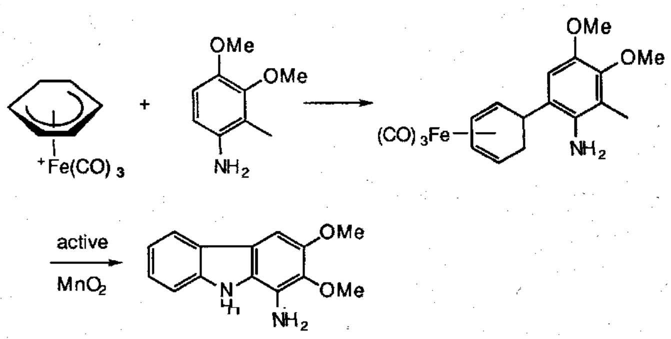
Nuc, Nuc´ = RO^-, OH^-, NH_3, RNH_2, R_2NH, BH_4^-,

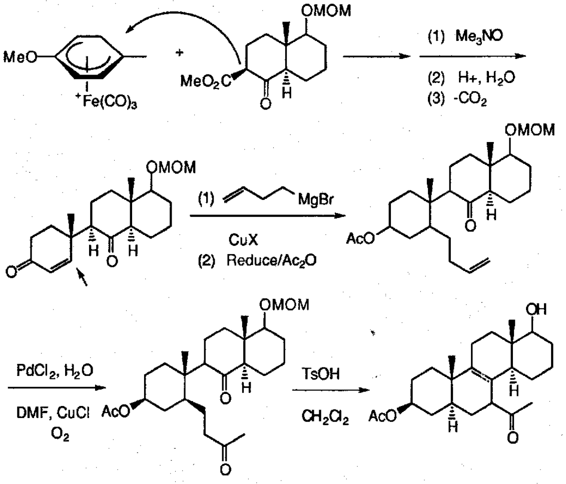
, R_2CuLi, RZnCl

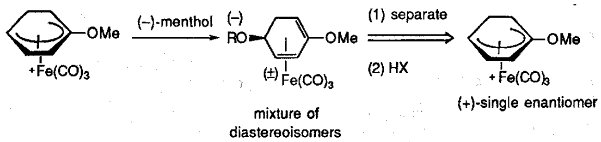






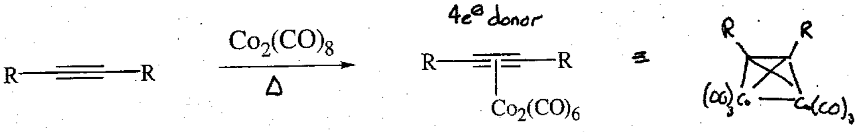


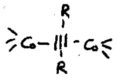




Alkynyl-Cobalt Reagents

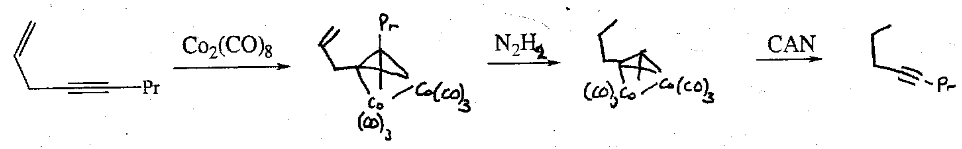
Reaction of an alkyne with $Co_2(CO)_8$ generates an organometallic complex:



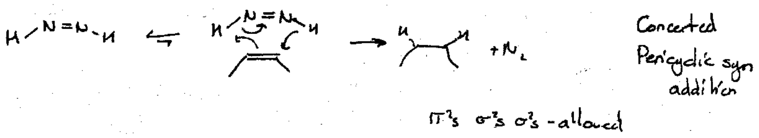


(i) Each cobalt has 9 + (3x2) + 3 = 18 electrons.
(ii) These are air stable (deep red colour).
(iii) The internal angle is reduced from 180^o to 140^o.
(iv) The alkyne unit is much less reactive.
(v) Decomplexation can be accomplished with mild oxidants (CAN, R_3N^+--O^-)

Initial work concentrated on the use of these complexes as protecting groups for alkyne units: they are stable to nucleophiles, hydrogenation and some oxidants. For example:

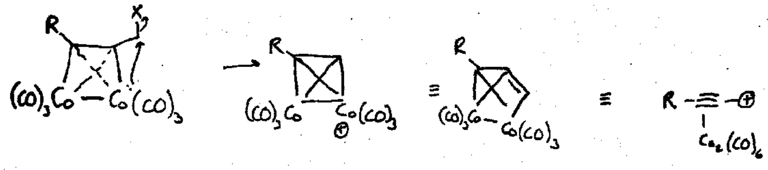


Mechanism for diimide reduction:



The Nicholas Reaction

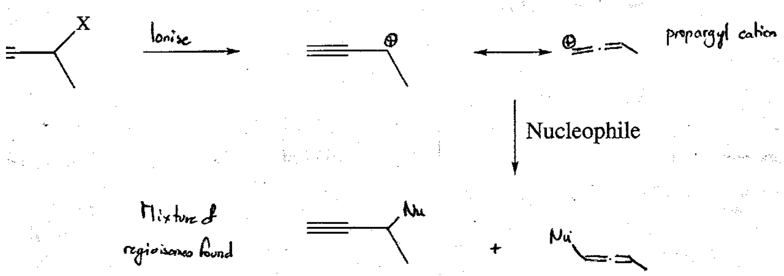
Nicholas discovered that cations α to these complexes were particularly stable. In fact some may be isolated as crystalline solids.



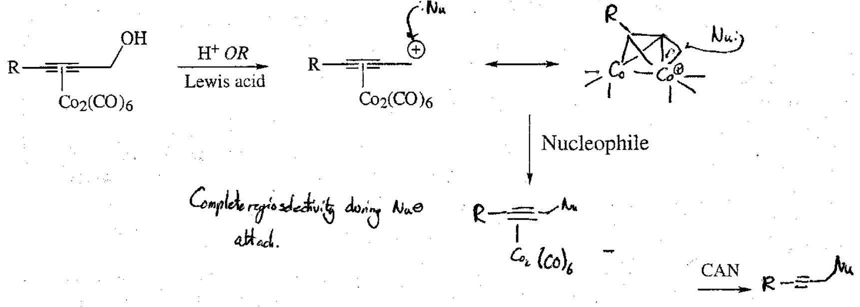
This is due to electron donation from the e-rich cobalt atoms to the cationic centre.

Once formed, these cations undergo smooth reaction with a variety of nucleophiles. The advantages that cobalt confers upon this process are manifold. The reaction can be:

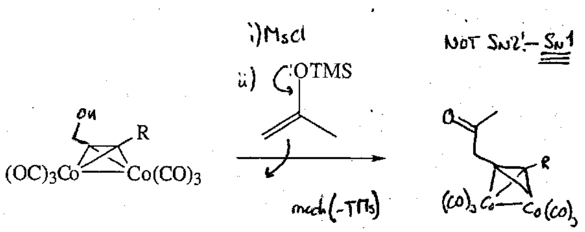
Regioselective –



Now compared the same reaction with the transition metal complex:

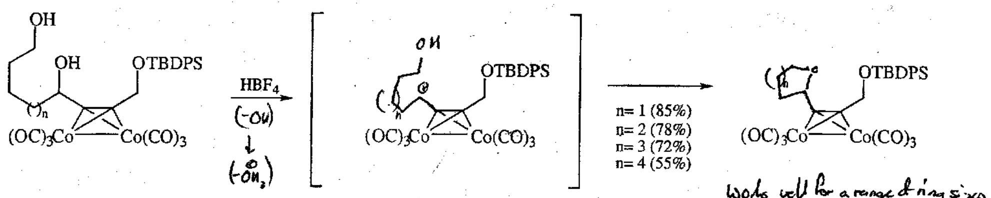


The nucleophile can be an enolate or equivalent:

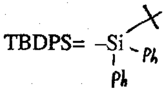


NOT SN2' — SN1

Or the nucleophile can be intramolecular:



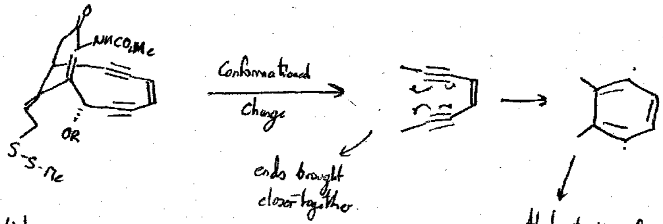
works well for a range of ring sizes



v bulky silyl PG.

In addition, the smaller angle means that strained rings can be formed.

Ene-Diyne antibiotics/anti tumor agents



ends brought closer together

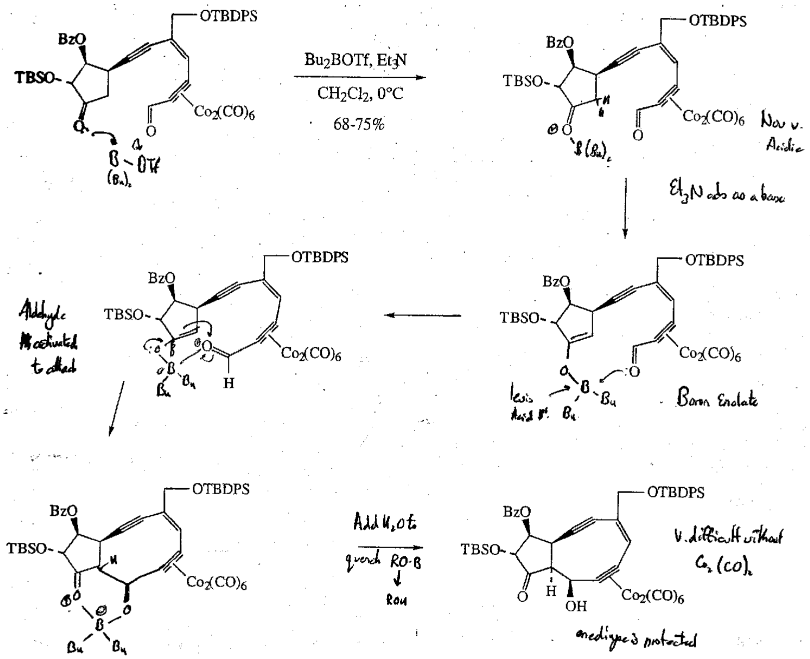
Abstracts H-R from DNA - cuts strands, kills cells.

Calicheamicin

KC Nicholson

Classics in total synthesis

P523



Now v. Acidic

Et_3N acts as a base

Lewis Acid

Boron Enolate

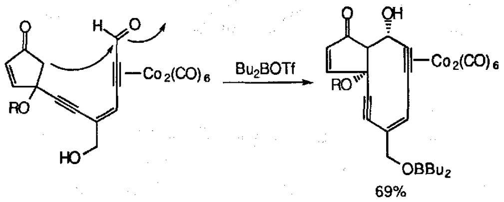
Aldehyde activated to attack

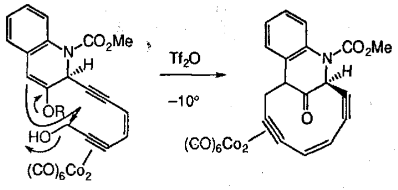
Add H_2O to quench RO-B → ROH

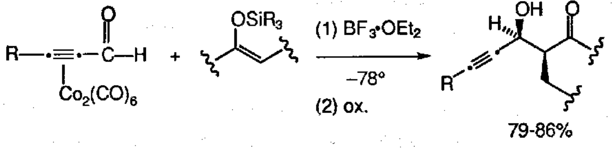
V. difficult without $Co_2(CO)_6$

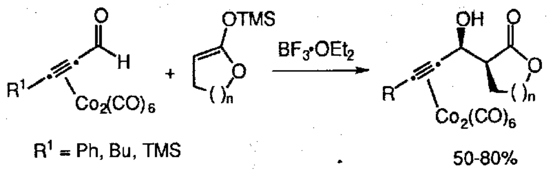
enediynes protected

Examples of this Reaction



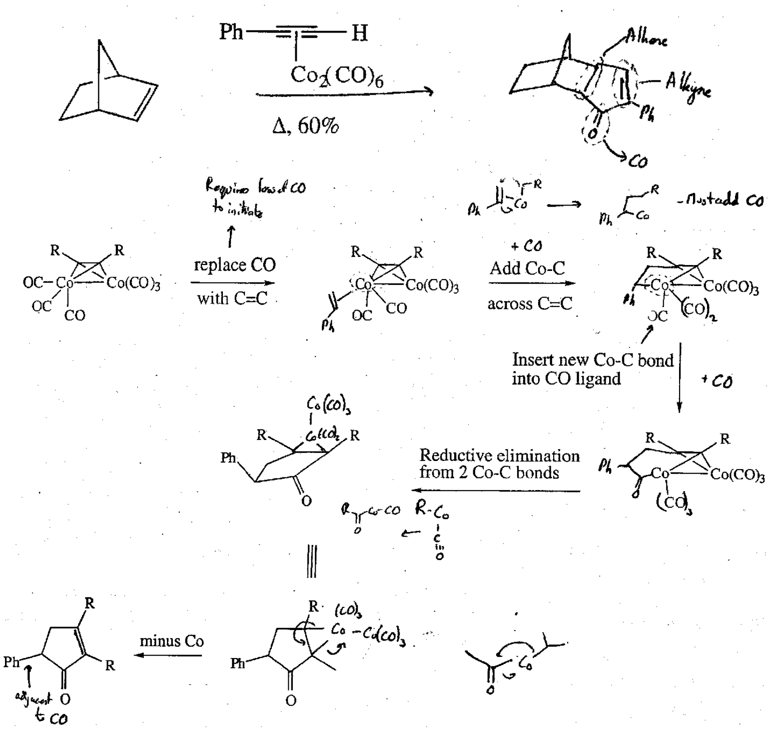




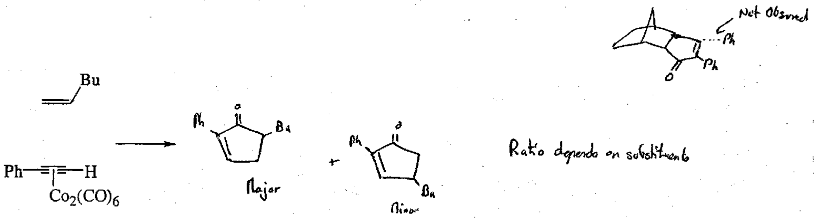


The Pauson-Khand Reaction

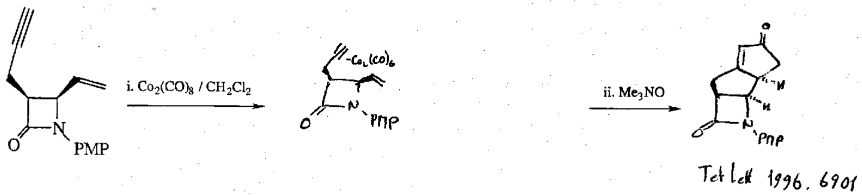
This reaction involves treatment of a cobalt-alkyne complex with an alkene to form a cyclopenteneone (with insertion of a CO group).

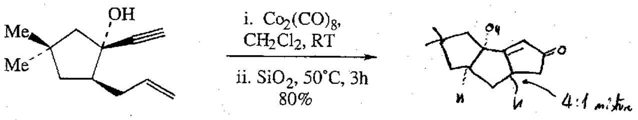


Although the largest group on the alkyne ends up adjacent to the carbonyl in the product, the use of unsymmetrical alkenes gives mixtures.

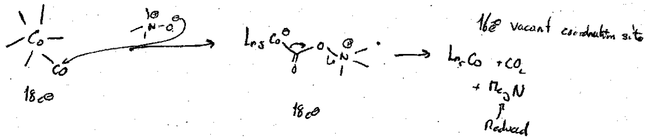


Solutions to this problem usually involve a tether between the alkyne and alkene so only one regioisomers is possible.

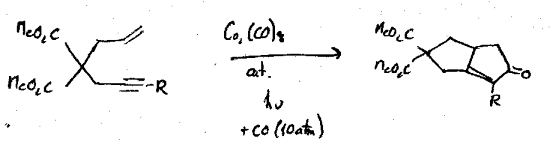




Amine-N-Oxides promote the oxidation of a CO ligand to CO_2. Mechanism:



Recently, the advent of mild conditions which involve Me_3NO or heating on silica mean that the reaction is an extremely useful one for synthesis. There is also some progress on a catalytic Pauson-Khand Reaction using photolysis:



Examples of this Reaction