# Transition-Metal-Mediated Dearomatization Reactions

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## Contents



## I. Introduction

The quest to discover new synthetic transformations which enable the syntheses of complex organic molecules in a highly selective fashion remains an exciting challenge. An integral part of modern day synthetic organic chemistry is the design of novel reactions that proceed with high atom economy and a minimal protection strategy and that enable multiple transformations in a one-pot reaction sequence. In addition, the ability to deliver methodology which is chemo- and regioselective while offering a high degree of stereocontrol is essential. These goals are addressed in a number of elegant procedures that allow the transformation of aromatic systems into functionalized alicyclic systems.

Arenes and aromatic heterocycles are widely available, often at low cost, highly stable, and readily derivatized through electrophilic substitution or via *ortho*-lithiation followed by reaction with electrophiles. Routes to differentially substituted aromatic products are thus well established. However, this is not the case for substitutive dearomatization reactions, primarily because this requires disruption of the aromatic $\pi$ system. Benzene and its derivatives are attractive starting materials because they have the potential to provide a rapid entry into complex alicyclic synthetic building blocks containing unmasked functionality, new carbon−carbon bonds, and new stereogenic centers.[1]

The synthesis of complex organic molecules via elegant dearomatization chemistry has undergone intensive investigation. Indeed, there are a number of efficient synthetic methods available that enable dearomatization. Immediately one thinks of the Birch reduction which achieves dearomatization via single electron transfer.[2] In addition, the photocycloaddition of arenes to alkenes has recently received much attention.[3,4] Closer to the topic of this review are methods which rely on nucleophilic addition to an electron-deficient arene.[5] In this area, Meyers has reported extensively on chemistry with naphthyloxazolines[6,7] while Tomioka and Koga's work has focused on dearomatization via conjugate addition of organolithium reagents to bulky naphthylesters.[8,9] Both approaches are limited to fused aromatics and to pyridine because these molecules are easier to dearomatize than benzene and its derivatives. However, Yamamoto has succeeded in dearomatization of benzaldehydes and acetophenone via conjugate addition of carbanions in the presence of ATPH.[10] Barluenga has also shown the potential for dearomatization reactions via conjugate addition to arenes bearing a Fischer carbene appendage.[11] In a conceptually different approach, Hudlicky and Ley have developed access to synthetically important *cis*-cyclohexadienediols by microbial oxidation of benzene derivatives with *Pseudomonas putida*.[12−14]

Arene dearomatization reactions can also be induced by temporary complexation of its $\pi$-system to

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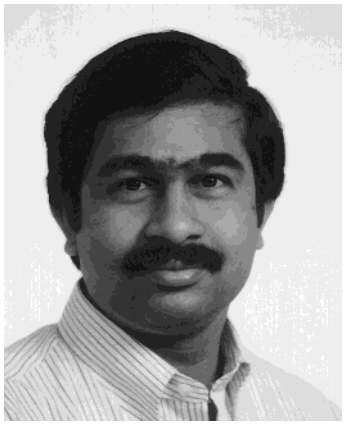
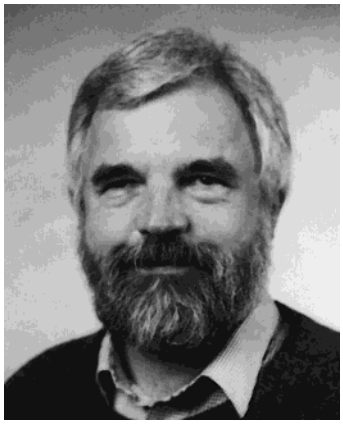


Krishna P. Kaliappan was born in Kallidaikurichi (T.N.), India, and obtained his B.Sc. and M.Sc. degrees from Madurai Kamaraj University. He received his Ph.D. degree (1997) working at the Indian Institute of Science, Bangalore, with Professor G. S. R. Subba Rao. Following two years at the University of Geneva working with Professor E. P. Kündig as a postdoctoral fellow, he joined Professor. M. C. Pirrung's group at Duke University in April 1999, where he is currently working on combinatorial chemistry. He was awarded the Professor B. H. Iyer medal for his Ph.D. work. He was also awarded a merit certificate from C.S.I.R. for his outstanding performance. His research interests are mainly directed toward the total synthesis of complex natural products and on the development of new asymmetric catalysts.



E. Peter Kündig was born in Weinfelden, Switzerland. He graduated from the Federal Institute of Technology (ETH) in Zurich in 1971 and in the same year moved to the University of Toronto, where he carried out research on transition-metal carbonyl and dinitrogen complex fragments by matrix isolation techniques (Ph.D. degree in 1975) under the guidance of G. A. S. Ozin. Following a postdoctoral stay at the University of Bristol with P. L. Timms on organometallic synthesis via metal vapor/ligand cocondensation, he moved to the University of Geneva, Switzerland, where he started his own research in 1978 and where he is now Professor of Organic Chemistry. His current research interests focus on the development of new asymmetric methodology via transition metals and their application in synthesis and on the design of new chiral ligands and asymmetric catalysts.

a transition-metal complex. Specifically, this review will cover the synthesis of alicyclic molecules from arene metal complexes of $Cr(CO)_3$, $Mn(CO)_3^+$, and $Os(NH_3)_5^{2+}$. New synthetic methodology will be the prime subject, and particular attention is focused on asymmetric methodologies. The development of dearomatization methodology via $\pi$-arene complexes of these complex fragments is at different stages of development; however, a diverse array of activity is observed and they have been successfully employed in organic synthesis. The tricarbonyl chromium and tricarbonyl manganese groups form $\eta^6$-arene complexes.[15−18] The electrophilic nature of the complex fragments make the arene electron deficient and renders it susceptible to nucleophilic attack. This characteristic is also shared by ($\eta^6$-arene)$FeCp^+$ and ($\eta^6$-arene)$RuCp^+$ analogues.[19−23] The arene complexes of $CpFe^+$ and $CpRu^+$ have been investigated intensively and very successfully in their applications in aromatic substitution reactions, but they have seen little use in dearomatization chemistry. For this reason they are not included in this review. An alternative activation is operative in ($\eta^2$-arene)$Os(NH_3)_5^{2+}$ complexes.[24] Here, the nature of the binding results in an increase in electron density and the bound aromatic systems are now open to initial reactions with electrophiles.

Diverse chemistry has been developed, often with novel and interesting selectivity, enabling elegant and efficient access to complex organic molecules. Metal-mediated dearomatizations are accompanied by the introduction of one, two, or three carbon units to the arene ring systems in highly stereoselective reactions. While the fundamental reactions have been established, new reactions and in particular asymmetric methodologies continue to be found and applications in this area flourish. The present review aims to present the scope and limitations of the methodologies currently available which enable the dearomatization of ($\eta^6$-arene)$Cr(CO)_3$, ($\eta^6$-arene)$Mn(CO)_3^+$, and ($\eta^2$-arene)$Os(NH_3)_5^{2+}$ complexes. The latter was the subject of an extensive review[24] in 1997, and we aim to report only the literature which has appeared since then. Following a brief description of the methods available for the synthesis of each species, the general approaches toward dearomatization will be outlined. Later sections will contain specific examples from the current literature and will be used to demonstrate the highly effective use of this methodology in organic synthesis. The review covers the literature up to June 1999.

## II. Complexation Methods

### A. ($\eta^6$-Arene)$Cr(CO)_3$ Complexes

The arene tricarbonyl complexes of chromium are yellow to red, often crystalline compounds that are stable to air in the solid state and can be stored for long periods provided they are kept away from light. In solution they are moderately air sensitive. The preferred method for the synthesis of (arene)$Cr(CO)_3$ complexes is thermolysis of $Cr(CO)_6$ under an inert atmosphere ($N_2$ or Ar) in the presence of an excess of the arene in a high-boiling solvent. This can be the arene itself or a variety of solvent mixtures,[25−32] the most frequently adopted procedure is a mixture of the arene, dibutyl ether, and THF.[33] This procedure is suited for the preparation of a wide range of complexes, often in high yields (80−95%) with reaction times typically in the 1−4 day range. Milder complexation conditions and shorter reaction times are possible with suitable $Cr(CO)_3L_3$ (L = $CH_3CN$, Py, $NH_3$) precursors, which allow higher compatibility with arenes bearing functional groups and higher chemo- and diastereoselectivity.[34] Room-temperature complexation of arenes is accomplished by reaction of $Cr(CO)_3(NH_3)_3$ with $BF_3{\cdot}OEt_2$ in the presence of an arene, a method particularly well suited for condensed aromatics.[35,36] Finally, complexation can also be carried out by arene exchange in (naphthalene)$Cr(CO)_3$.[37] This method has found widespread usage due to highly facile arene exchange and the ease with which this complex can be handled.[37−44]

### B. [($\eta^6$-Arene)$Mn(CO)_3$]$^+$ Complexes

Similar to chromium analogues, the manganese complexes are stable, yellow, and usually crystalline solids. The preferred method for the formation of (arene)$Mn(CO)_3^+$ complexes involves treating $Mn(CO)_5Br$ with a stoichiometric amount of $AgBF_4$ in $CH_2Cl_2$, stirring for 1 h, filtering, and then adding the arene and heating at reflux for 1 h.[17] This method enables attachment of the arene unit to the $Mn(CO)_3^+$ moiety under conditions which are mild enough to preclude any reaction or isomerization of arene ring substituents. Similarly, arene complexes are accessible from the reaction of the arene with $Mn(CO)_5OClO_3$ or $Mn(CO)_3(acetone)_3^+$ in dichloromethane at reflux.[45] An older method involves heating $Mn(CO)_5Br$ and the arene in the presence of $AlCl_3$, although this is restrictive when using arenes with more sensitive functionality.[46]

### C. [($\eta^2$-Arene)$Os(NH_3)_5$]$^{2+}$ Complexes

Complexes of pentaammineosmium(II) are most commonly prepared by reducing the $Os^{III}$ precursor $[Os(NH_3)_5(OTf)][(OTf)_2]$ in the presence of the desired ligand under $N_2$ atmosphere with magnesium in DMAc or a DMAc/DME mixture. Alternatively, $Zn^0$/$Hg^0$ amalgam may be used as the reducing agent if the reaction is carried out in methanol. Using this procedure a wide array of complexes have been formed in excellent yield (typically >90%). The complexes are generally yellow to red crystalline solids.[24] The requirement of the $Os^{2+}$ species to bind $\eta^2$ limits the arenes to those that do not contain functional groups capable of donor interactions with the $Os^{2+}$ fragment. Arenes which contain nitrile, aldehyde, some ketones, alkenes, and alkynes as substituents result in coordination of the $Os^{2+}$ outside the arene ring. This is driven by formation of the most thermodynamically stable complex, which results from minimal disruption to the aromatic $\pi$ system, hence osmium coordinates outside the ring. Monosubstituted arenes bind the metal preferentially at C(5) and C(6) because this allows linear conjugation of the substituent and unbound portion of the aromatic ring. This is true for both electron-rich (e.g. anisole, aniline, phenol) and electron-deficient (e.g. diphenylacetylene, benzophenone) arenes, although the effect is most pronounced in the former. Only in cases where steric factors disfavor the 5,6-$\eta^2$ isomer does the 4,5-$\eta^2$ isomer dominate. While the $\eta^2$-arene Os complexes are sensitive to air, they are reasonably robust and the arene ligand is displaced only slowly by other ligands, and this does not constitute a problem with regard to the chemistry described herein.

## III. General Reactivity Patterns

### A. ($\eta^6$-Arene)$Cr(CO)_3$ Complexes

(Arene)$Cr(CO)_3$ complexes deliver unprecedented reactivity to the complexed arene system. The chemistry of these complexes is extensive (Figure 1). The $\eta^6$-coordinated arene ring is susceptible to a number of synthetic manipulations due to the electron-withdrawing properties of the $Cr(CO)_3$ unit. The ring hydrogens have increased acidity and are therefore prone to deprotonation with lithium amides or organolithium reagents.[47] Benzylic anions are readily formed by deprotonation, but despite the predominantly electrophilic character of the $Cr(CO)_3$ unit, benzylic carbocations are also readily stabilized.[48−50] In addition to this, the $Cr(CO)_3$ moiety has found widespread use as a 'stereodirecting' group in reactions of side chains attached to the arene ring.[48]

However, in the context of this review, it is the susceptibility of the arene ring to undergo nucleophilic addition reactions which is of most importance. The electron-withdrawing properties of the $Cr(CO)_3$ group enable direct attack by nucleophiles (generated

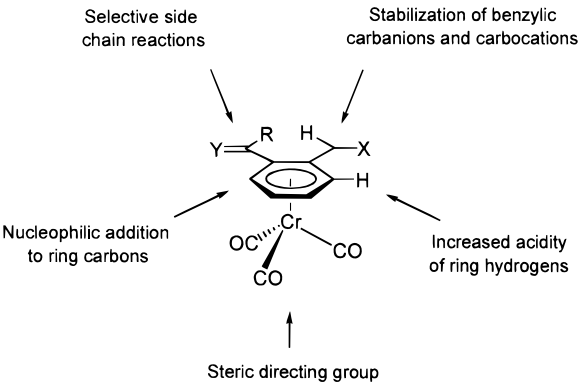



**Figure 1.** Changes in arene reactivity after complexation with chromium tricarbonyl.

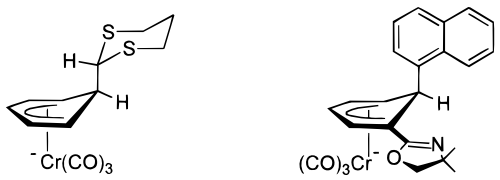


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**Figure 2.** Single-crystal X-ray determination of two $\eta^5$-cyclohexadienyl intermediates to confirm that nucleophilic attack is *exo* to the chromium tricarbonyl moiety.

**Table 1. Reactivity of Carbanions in the Nucleophilic Addition Process to Benzene**

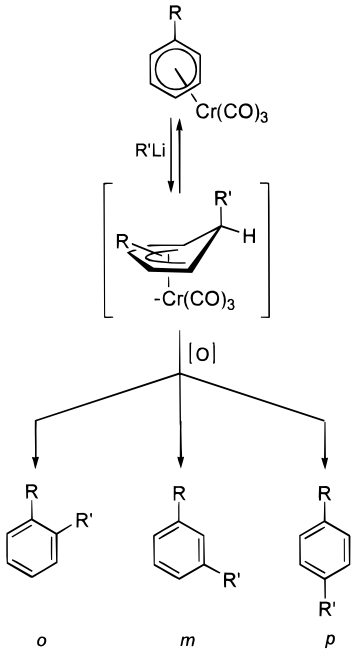
| unreactive | successful | metalation |
|---|---|---|
| $LiCH(CO_2R)_2$ | $LiCH_2CO_2R$ | $^nBuLi$ |
| $LiCH_2COR$ | $LiCH_2CN$ | $LiCH_3$ |
| $CH_3MgBr$ | $KCH_2COC(CH_3)_3$ | $^sBuLi$ |
| $(CH_3)_3CMgBr$ | LiCH(CN)(OR) | |
| $(CH_3)_2CuLi$ | $LiCH_2SPh$ | |
| LiC(OR)(CN)Ph | 2-Li-1,3-dithianyl | |
| | $LiCH{=}CH_2$ | |
| | LiPh | |
| | $LiC{\equiv}CR$ | |
| | $LiCH_2CH{=}CH_2$ | |
| | tBuLi | |

from C−H acids of p$K_a$ > 22) on the arene ring *exo* to the $Cr(CO)_3$ moiety. The anionic cyclohexadienyl complex formed can be isolated or, more convenient for organic transformations, transformed in situ into other products. Two X-ray structures, **1** and **2**, have confirmed the *exo*-addition of the nucleophile, and their crystallization from warm dioxane attests to the stability of these complexes (Figure 2).[44,51]

In general, the types of nucleophile which can be used are those listed in Table 1. This list was established by Semmelhack at a very early stage and holds true for nucleophilic additions to (benzene)$Cr(CO)_3$ in THF as solvent. Extensions to other nucleophiles have been reported, and with different aromatic systems, deviations of this pattern have become apparent. Hydride ($LiBHEt_3$) has been shown to add to (benzene)$Cr(CO)_3$ and also to the closely related (benzene)$Cr(PF_3)_3$ complex.[52,53] When an imine, oxazoline, or hydrazone substituent is attached to the aromatic ring, hard organolithium reagents (e.g. n-BuLi, MeLi) will act as nucleophiles rather than as bases as is the case in reactions with (benzene)-$Cr(CO)_3$.[54,55] Limitations to the scope of nucleophilic additions to (arene)$Cr(CO)_3$ complexes result from the moderate electrophilicity imparted by the $Cr(CO)_3$ group (comparable to an arene nitro substituent), the activation of the arene hydrogens toward deprotonation, and the potential attack by the nucleophile at CO.

Nucleophilic additions to substituted arene complexes are often highly regioselective. This and the mild reaction conditions are major advantages of this methodology. Resonance donor substituents on the ring direct attack to the *meta* position, [56−58] while bulky substituents and acceptor substituents direct preferentially *para*.[59] Functional groups that can efficiently coordinate the incoming organolithium reagent direct *ortho*.[54,55] A number of investigations have described the regioselectivity obtained with various (arene)$Cr(CO)_3$ complexes and different nucleophiles. The results obtained have been related to electronic and steric effects, to the questions of kinetic or thermodynamic control, and to the presence of substituents which coordinate the incoming nucleophile and direct it to a specific position on the arene ring.[55,56,60−63] Scheme 1 lists the preferred position of

**Scheme 1. Regioselective Addition to Arene Chromium Tricarbonyl Complexes**



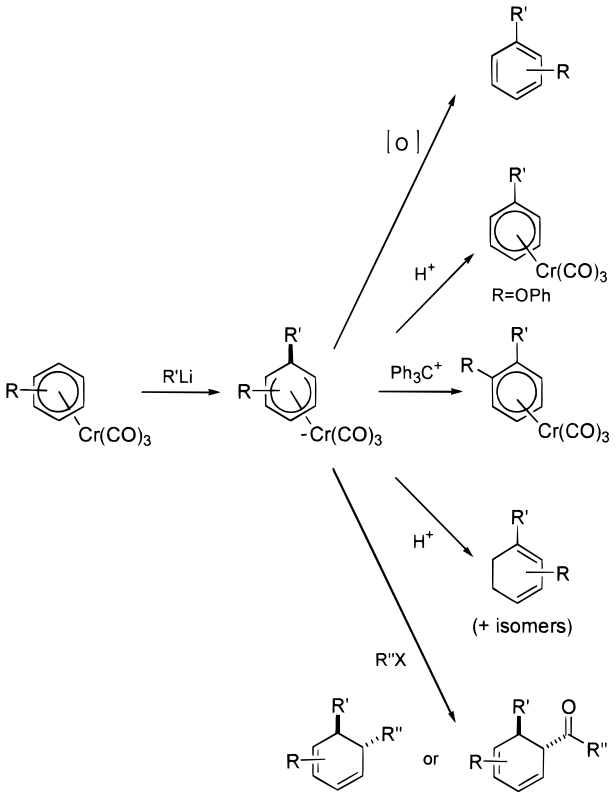

| R | Product |
|---|---|
| MeO | meta |
| $NMe_2$ | meta |
| Me, Et | meta/ortho |
| Cl | ortho/meta |
| Hydrazone | ortho |
| Imine | ortho |
| Oxazoline | ortho |
| $SiMe_3$ | para |
| $CMe_3$ | para |
| $CF_3$ | para |

attack under kinetic control of the reaction for a number of substituents. Regioselectivity may vary however, and with nucleophiles that add reversibly (in THF), large differences in regioselectivity may be observed depending on the reaction conditions. A thorough discussion of regioselectivity in these reactions is beyond the scope of this review, and the literature should be consulted for specific cases.[16,62,63]

As shown in Scheme 1, oxidation ($I_2$, Ce(IV), Fe(III), $O_2$) releases a modified arene, the overall reaction being a substitution of a $C_{Ar}$−H by a carbanion. This reaction pattern has been thoroughly investigated and applied in the pioneering and elegant work of Semmelhack.[16,64] Alternatively, the intermediate anionic cyclohexadienyl complex can be reacted with other electrophiles and, depending on their nature and the starting complex, results in different reaction pathways and products (Scheme 2).

Whereas oxidation leads invariably to arene−metal bond cleavage, it has recently been shown that in some cases trityl cation can be used to abstract the *syn*-hydride at the cyclohexadienyl $sp^3$ carbon center

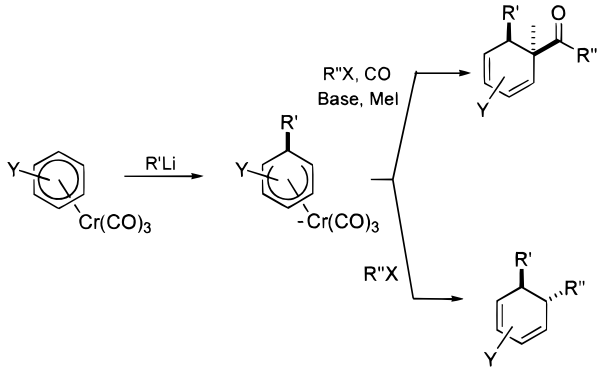
**Scheme 2. Range of Products Resulting from the Sequential Reactions of Nucleophiles and Electrophiles with (arene)Cr(CO)$_3$ Complexes**




to yield the substituted product with an intact arene−metal bond.[44,65] This has opened a new asymmetric route to planar chiral complexes.[66] Another sequence that allows the conservation of the metal−arene bond are *ipso*-, *cine*-, and *tele*-substitution reactions. Though outside the scope of this review, we note that the latter two of these involve a nucleophile addition/protonation sequence that gives a cyclohexadiene complex which then, following a series of isomerizations, aromatizes via an elimination reaction.[47,67−69] The prerequisite for rearomatization via this method is the presence of a leaving group. In its absence, or as competing reaction pathway, reaction of the cyclohexadienyl intermediate with a strong acid results in a dearomatization reaction, the product being a cyclohexadiene.

Carbon electrophiles react with the anionic cyclohexadienyl chromium tricarbonyl complexes by addition to the metal center or by regeneration of the original arene complex. This second pathway is operative in cases where nucleophilic addition is reversible. In THF this is the case with stabilized carbanions (e.g., ester enolates, α-nitrile carbanions). Double-crossover experiments have provided evidence for this reversibility, and it has also been shown that the initial regiochemistry of the nucleophilic attack is subject to change upon warming the reaction mixture.[62,63] Conditions that slow the back-reaction have been developed; the use of K rather than the Li carbon nucleophile, addition of additives such as HMPA or DMPU that complex the Li cation and increase nucleophilicity of the cyclohexadienyl complex, or the use of the more reactive dithiane lithium and alkyl-, vinyl-, and aryllithium reagents that add irreversibly. Under these conditions a dearomatization reaction is achieved by sequential nucleophile/electrophile addition across an arene double bond. The stereochemical relationship is strictly trans and is the result of nucleophilic attack on the arene *exo* to the Cr(CO)$_3$ moiety, followed by electrophilic attack at the metal center and *endo* migration to the cyclohexadienyl ring.[70] The nature of the electrophile and the presence of substituents on the arene determines whether migratory CO insertion precedes the reductive elimination. Where CO insertion does take place, a third carbon unit can be introduced to form a new quaternary center (Scheme 3).

**Scheme 3. Sequential Addition of a *C*-nucleophile and a *C*-electrophile Across an Arene Double Bond**




## B. [($\eta^6$-Arene)Mn(CO)$_3$]$^+$ Complexes

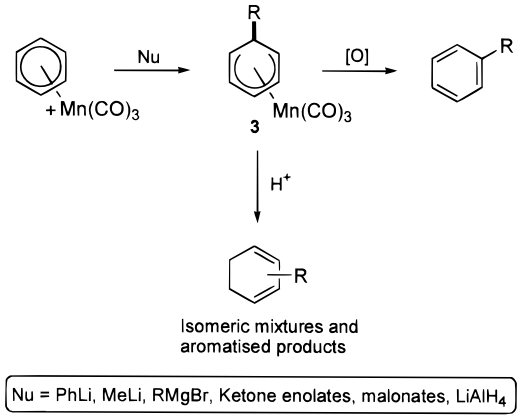
When an arene is bound to the cationic Mn(CO)$_3^+$ fragment it becomes substantially more electrophilic than in the neutral (arene)Cr(CO)$_3$ complexes (Table 2).[17] This means that a wider range of nucleophiles can be used, but the reaction conditions available become limited with compatibility proving problematic.

Nucleophiles that can be used include Grignard reagents, ketone enolates, malonates, and hydride (LiAlH$_4$). Others include hydroxyl, cyano, and azido anions, but these have not been studied extensively.[20] Phosphines also add rapidly to the arene which delivers phosphorus-substituted complexes, but this initial reaction is readily reversible and subsequently leads to a substitution of one of the carbonyl ligands under both thermal and photolytic conditions.[71] As with the complexes of chromium, nucleophilic addition occurs *exo* to the Mn(CO)$_3^+$ unit and the reaction results in the neutral stable cyclohexadienyl complex **3** (Scheme 4). The position of attack is dependent on the nature of the arene substituents, although the effects are not as marked as with arene chromium tricarbonyl complexes and the studies available are

**Table 2. Relative Reactivity of Arene−Metal Complexes toward Nucleophilic Addition**

| arene complex | relative reactivity |
|---|---|
| $(C_6H_6)Fe(C_6H_6)^{+2}$ | $2 \times 10^8$ |
| $(C_6H_6)Ru(C_6H_6)^{+2}$ | $6 \times 10^6$ |
| $(C_6H_6)Mn(CO)_3^+$ | $1.1 \times 10^4$ |
| $(C_6H_6)Mn(CO)_2PPh_3^+$ | 160 |
| $(C_6H_6)FeCp^+$ | 1 |
| $(C_6H_6)Cr(CO)_3$ | very low |

**Scheme 4. Addition of Nucleophiles to [(Benzene)Mn(CO)$_3$]$^+$**



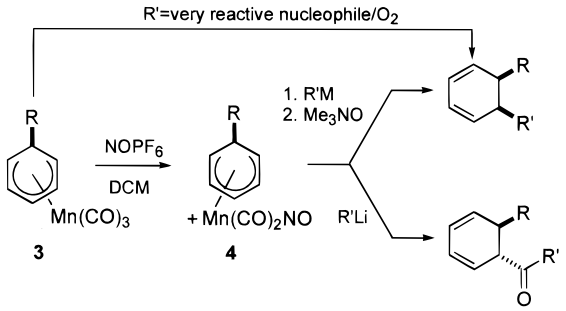

not as extensive. In general, anisole and aniline complexes react with Grignard reagents to give the *meta*-addition products. Addition to (chlorobenzene)-Mn(CO)$_3^+$ gives similar amounts of *ortho* and *meta* product, while (toluene)Mn(CO)$_3^+$ gives addition to all three positions.[15,17,72]

The addition of a single C-nucleophile to an arene manganese tricarbonyl species, followed by decomplexation under oxidative conditions (stoichiometric amount of Jones reagent—$CrO_3/H_2SO_4$/acetone), generally leads to rearomatization. Where the dearomatized product is isolated, a complex mixture of diene isomers is obtained, separation of which has proved problematic. Therefore, this method has not found wide application in dearomatization chemistry. Routes to products resulting from the overall single addition of C-nucleophiles are available, however, and these will be discussed below.[73,74]

The area of (arene)Mn(CO)$_3^+$ chemistry, which has received the most attention, involves the sequential addition of two nucleophiles. Through this chemistry a number of dearomatized products have been synthesized with interesting selectivities. The reactivity of the cyclohexadienyl Mn(CO)$_3$ complex **3**, which results after the addition of a nucleophile, differs markedly from the Cr(CO)$_3$ analogue. Due to the decreased nucleophilicity of the neutral Mn(CO)$_3$ species, reactions with C-electrophiles are not possible. However, in stark contrast to the chromium species, **3** can react with a second nucleophile. The nature of the product, either a cis or trans disubstituted cyclohexadiene, depends very much on the nature of the nucleophiles involved. There are two general strategies available, which are shown in Scheme 5.

The first and more direct method requires treatment of **3** with a second nucleophile. Addition again occurs *exo* to the manganese unit at a cyclohexadienyl terminus, and this affords a *cis*-substituted cyclohexadiene.[75] The reaction appears to be limited to very reactive nucleophiles (see Scheme 36). When the first nucleophile is $LiAlH_4$ and therefore R = H, the overall transformation leads to a dearomatized product resulting from the addition of a single carbon unit. This method can also be applied to the addition of two carbon units, although at this time the first nucleophilic addition is restricted to MeLi (R = Me).

**Scheme 5. Double Addition to Arene Manganese Tricarbonyl Complexes**



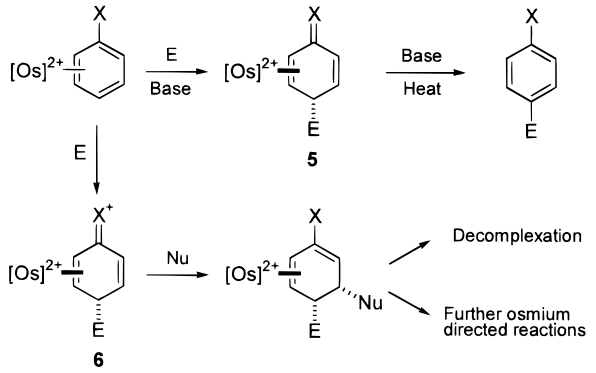

The second method available for double nucleophilic addition to an arene manganese tricarbonyl complex requires 'reactivation' of the cyclohexadienyl species **3**. Treatment of **3** with $NOPF_6$ in DCM results in substitution of a CO ligand by $NO^+$ to give complex **4**. This complex can now react with less reactive nucleophiles.[76−78] The cationic cyclohexadienyl Mn-(CO)$_2$NO$^+$ complex is in fact more electrophilic than the original (arene)Mn(CO)$_3^+$ complex, which leads to complications with some nucleophiles. Useful carbon donors, such as Grignard reagents, react with **4** in what appears to be single-electron transfer to give none of the desired diene. This problem has been somewhat circumvented by further replacement of a CO ligand with $PMe_3$, although it can be argued that this renders the procedure rather cumbersome.[17,79] Phosphorus and nitrogen nucleophiles have been shown to add, but perhaps the most useful conversions are those resulting from either hydride or carbon nucleophile addition.[76,79−81] Hydride and stabilized enolates add directly to the unsaturated ligand. The addition of hydride has been shown to be *endo*, while stabilized carbon nucleophiles add *exo* to the manganese unit.[82,83] The methods described above yield, after oxidative decomplexation of the manganese unit, mono- and *cis*-disubstituted cyclohexadienes, respectively.

A different pathway is followed in the reaction of the cationic (cyclohexadienyl)Mn(CO)$_2$NO species **4** with phenyl- and methyllithium reagents. Reaction now occurs at one of the CO ligands, which is followed by rapid reductive elimination of the resulting cyclohexadienyl/acyl moieties and decomplexation to yield a *trans*-disubstituted 1,3-cyclohexadiene.[17]

## C. [($\eta^2$-Arene)Os(NH$_3$)$_5$]$^{2+}$ Complexes

The complexation of an arene to pentaammineosmium(II) provides a species which has an arene ring coordinated $\eta^2$ to an $Os^{2+}$ species. The distinct difference between the organometallic species mentioned above and (arene)$Os^{2+}$ complexes is that the arene is now activated toward attack by electrophiles (Scheme 6). Through $\pi$ back-bonding the aromatic $\pi$ system becomes more electron rich. In addition, the $\eta^2$ coordination causes distortions in the bond lengths of the ring, consistent with localization of $\pi$ electron density. This results in the activation of the arene toward electrophilic rather than nucleophilic addition. One distinct advantage of the Os complexes is that the $\eta^2$ binding mode extends this chemistry to

**Scheme 6. Modes of Reactivity for Arene Osmium Complexes**




heteroaromatics, and successful dearomatization reactions of furan, pyrrole, and thiophene have been reported. These interesting transformations are not within the scope of this article, and the reader is referred to the recent literature.[24,84]

Osmium complexes of phenols, anilines, acetanilides, and anisoles undergo electrophilic addition with a high regiochemical preference for *para* addition. As with chromium and manganese complexes, the initial addition to the arene is always *exo* to the metal moiety. The osmium complex **5** can be rearomatized after electrophile addition by treatment with base followed by heat. However, the stable 4*H*-arenium species **6** which result after electrophilic addition are now activated toward nucleophilic addition, and it is perhaps this which is the most exciting feature of this chemistry. The sequential electrophile/nucleophile addition sequence provides, after decomplexation (CAN or AgOTf), a dearomatized product in which a *cis*-1,2-disubstituted cyclohexadiene results. Another salient feature of this approach is that as long as an $\eta^2$-donor is present, the $Os(NH_3)_5^{2+}$ can remain bound and therefore influence and direct further reactions (Scheme 6).

## *IV. Chromium-Mediated Dearomatization Reactions*

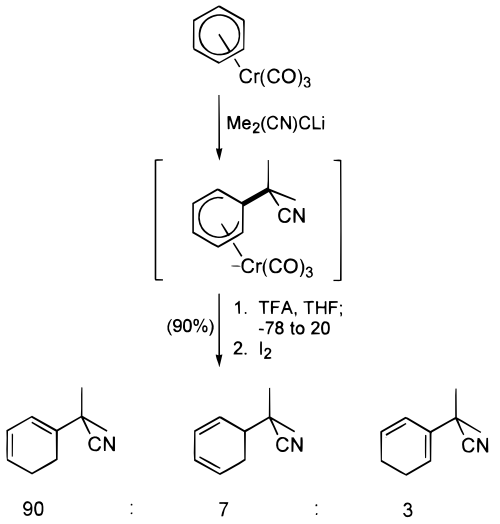
### A. Racemic Products

#### *1. Nucleophilic Addition/Protonation Reactions*

In the course of investigations into the mechanism of nucleophilic addition reactions to (chlorobenzene)$Cr(CO)_3$ it became evident that *ipso*-nucleophilic substitution was preceded by fast and often reversible addition, primarily to the *ortho*-position of complexed chlorobenzene.[85,86] This suggested that the intermediate cyclohexadienyl complex might be trapped with electrophiles to give dearomatized products. The first successful reaction of this type was protonation with a strong acid.[87,88] Unfortunately the reaction yields mixtures of isomeric cyclohexadienes, whose distribution depends on reaction conditions and in general the reaction tends to converge to the most stable diene (Scheme 7).[64]

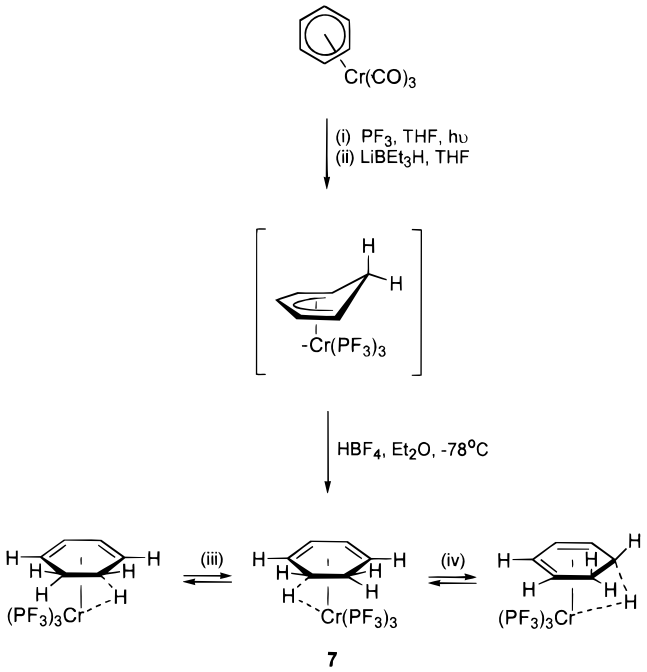
The mechanism of this isomerization has recently been probed in the analogous (benzene)$Cr(PF_3)_3$ complex. Hydride addition followed by protonation

**Scheme 7. Semmelhack's Nucleophilic Addition with Dearomatization of Benzene Chromium Tricarbonyl Complexes**




yielded complex **7**. Kinetic investigations show 1,5-hydride migration (which involves C−H bond breaking) and 1,2-hydride (which involves M−H bond breaking) exchange processes in the agostic complex to be so rapid that only cooling to −130 °C stopped the processes which interconvert the complexed isomeric dienes (Scheme 8).[53]

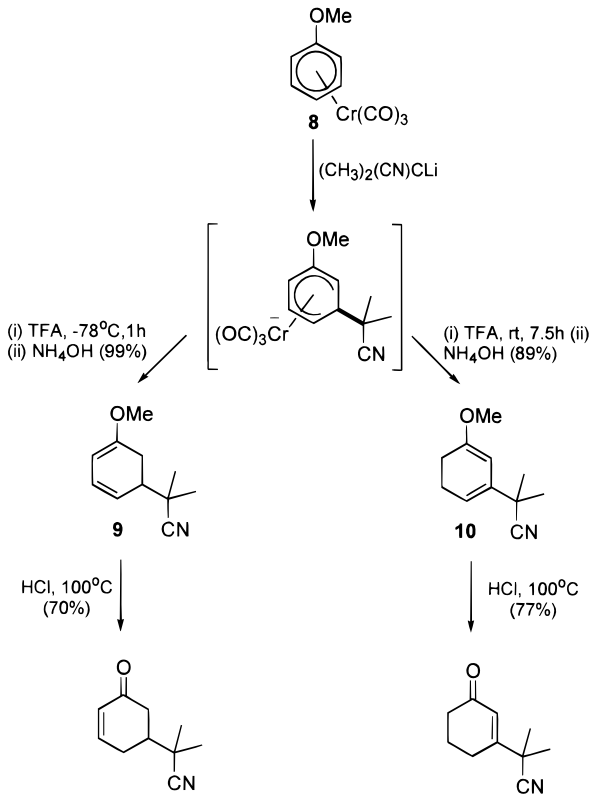
**Scheme 8. Addition of Hydride Followed by Protonation Leads to a Highly Fluxional Agostic System: (iii) 1,2-H-Exchange; (iv) 1,5-H-Migration**




**7**

Careful choice of temperature and reaction time allows diene regiocontrol and the obtention of single products in the reaction with (anisole)$Cr(CO)_3$ **(8)**. Low temperatures and short reaction times provide isomer **9**, whereas higher temperatures and longer reaction times give **10**. The substituted dienol ethers can be readily converted into 3-substituted cyclohexenones (Scheme 9).[64,89] It has also been reported that

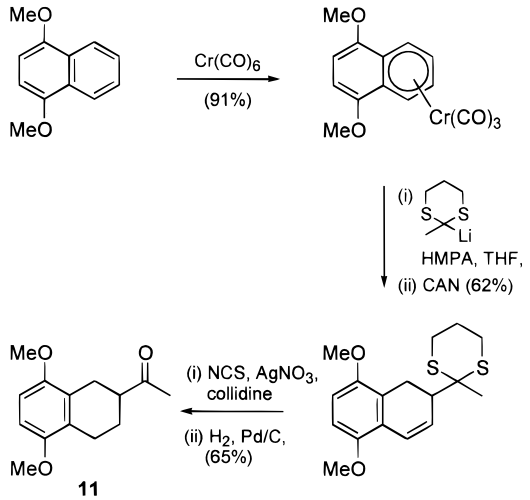
**Scheme 9. Nucleophilic Addition To Give Dienol Ethers and Cyclohexenones**




protonation under a CO atmosphere allows advantageous recycling of $Cr(CO)_6$.[90]

Studies in these laboratories have resulted in regioselective transformation of 1,4-dimethoxynaphthalene to the daunomycinone precursor **11** shown in Scheme 10.[60] Nucleophilic attack follows expected

**Scheme 10. Dearomatization of 1,4-Dimethoxynaphthalene to a Daunomycinone Precursor**

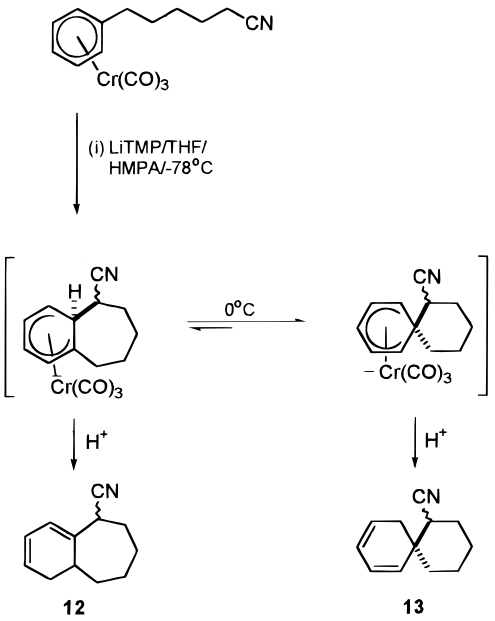



trends and occurs irreversibly at the $\beta$-position. Protonation/decomplexation in this case was effected with cerium ammonium nitrate in $THF/H_2O$ (9:1) (Scheme 10).

This methodology was extended at an early stage to intramolecular reactions, although to this date there are but a few reports. The examples available elegantly illustrate the potential for rapid synthesis of complex organic compounds with high selectivity.

Semmelhack reported the intramolecular nitrile-stabilized carbanion addition shown in Scheme 11.

**Scheme 11. Intramolecular Nucleophilic Addition**




| Time, h | Temp, °C | 12 | 13 | Yield, % |
|---|---|---|---|---|
| 0.5 | -78 | 72 | 28 | 72 |
| 0.25 | 0 | 37 | 63 | 79 |
| 4.0 | 0 | 25 | 75 | 81 |
| 24 | 0 | 3 | 97 | 70 |

Products from this reaction are the bicyclic system **12** as a mixture of diene isomers and the spirocyclic system **13**.[91] The product ratio is dependent on the length of the chain and on the reaction conditions. Kinetic conditions very much favor the bicyclic product, whereas thermodynamic conditions deliver the spirocyclic system. This approach was subsequently applied in a rapid synthesis of acorenone and acorenone B.[92]

Wulff reported an elegant route to more functionalized compounds of this type. A sequential benzannulation/nucleophilic addition from the Fischer carbene complex **14** gives direct access to either the spirocycles **15** or the fused bicycles **16** described below (Scheme 12 and Table 3). Depending on the conditions used, the synthesis can be directed toward the spirocycle product. The approach provides products of higher complexity, a matter that caused complications in the Semmelhack approach.[93−95]

Schmalz recently reported on the intramolecular radical cyclization of (arene)$Cr(CO)_3$ complexes (Scheme 13). In this work tricyclic systems such as **17** are readily synthesized.[96−98] While most of the products from these investigations were transformed into aromatics, dearomatized products can potentially be accessed via this new and very appealing approach.

**Scheme 12. Benzannulation Followed by Intramolecular Nucleophilic Addition**

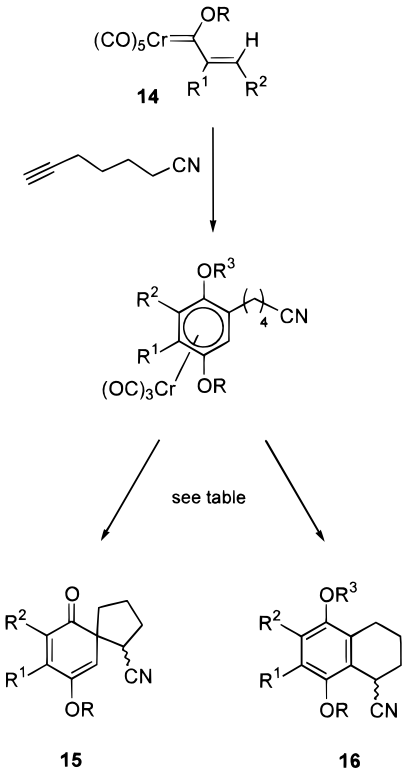
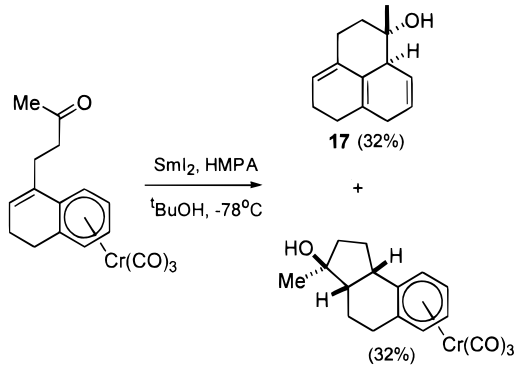



**Table 3. Substituents for the Benzannulation of Fischer Carbene Complexes Followed by Nucleophilic Addition**

| entry | R | $R_1$ | $R_2$ | $R_3$ | method[a] | product | yield, % |
|---|---|---|---|---|---|---|---|
| 1 | Me | H | H | TBS | A | 15 | 73 |
| | | | | | B | 16 | 67 |
| 2 | Me | Me | H | TBS | A | 16 | 62 |
| | | | | | B | 16 | 52 |
| 3 | Cy | Me | H | TBS | A | 16 | 18 |
| 4 | Me | H | Me | TBS | A | 15 | 73 |
| | | | | | B | 16 | 13 |
| 5 | Me | H | Me | TIPS | A | 15 | 48 |

[a] Method of cyclization: (A) 1.2 equiv of LDA, −78 °C for 1.5 h, then 7−8 equiv of $I_2$, −78 °C for 1 h then 25 °C 1−3 h; (B) 1.2 equiv of LDA, −78 °C for 10 min, then O°C for 1 h, 7−8 equiv of $I_2$ at O °C and then 25 °C for 2−4 h.

**Scheme 13. Schmalz's Intramolecular Radical Cyclization Strategy**




A highly diastereoselective addition/protonation reaction with a nonracemic planar chiral complex will be detailed in section IV.B.2.

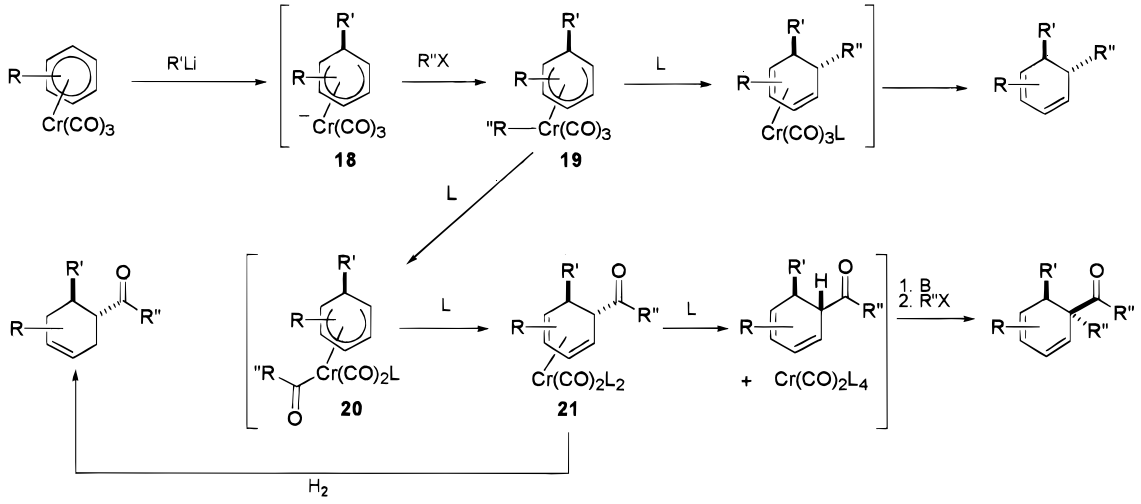
### *2. Nucleophile Addition/C-Electrophile Addition Reactions*

The sequential addition of a carbon nucleophile and a carbon electrophile across an arene double bond in (arene)$Cr(CO)_3$ was first reported in 1983.[99] Since then this methodology has undergone extensive development, with recent efforts mainly directed toward enantioenriched products. Given the modest nucleophilicity of anionic (cyclohexadienyl)$Cr(CO)_3$ complexes, reactions with carbon electrophiles are subject to more limitations than simple protonations but have the advantage of being highly regioselective. Specifically, these reactions are successful when carbanion dissociation from intermediate **18** is slow compared to the reaction with the carbon electrophile. The sequential addition is usually carried out as a one-pot reaction, and the proposed reaction sequence is that shown in Scheme 14.

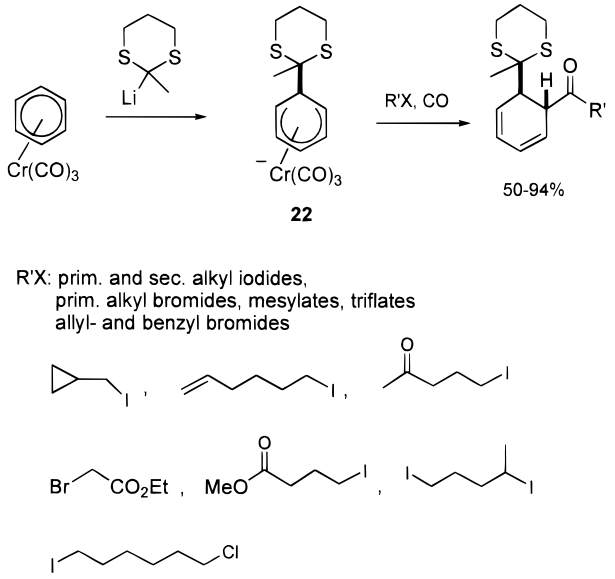
Thus, treatment of **18** with an electrophile results in alkylation, allylation, or propargylation at the Cr center to give **19**. This is followed by CO insertion to give **20** and *endo* migration to the $\eta^5$-cyclohexadienyl ring system to give **21**. The diene−Cr(0) bond in **21** is labile, and decomplexation results in a *trans*-1,2-disubstituted cyclohexadiene. Intermediates other than **18** have not been isolated in this sequence, but three X-ray structures of the products of interception of anionic cyclohexadienyl chromium complexes with $ClSnPh_3$ provide indirect evidence for the proposed mechanism.[52,70,100] Electrophile selectivity was established with **22** (R′ = methyldithiane) (Scheme 15).

Reactive or soft electrophiles work best in this reaction with leaving group preferences following the sequence OTf ≈ OMs ≈ I > Br ≫ Cl, and yields are often better when polar cosolvents such as HMPA or DMPU are added.[70,101] Conservation of the three-membered ring in the reaction with cyclopropylmethyl iodide and lack of cyclization in reactions with 6-iodo-hex-1-ene argue for an $S_N2$ mechanism rather than an electron-transfer reaction. Ketones, esters, alkenes, primary alkyl chlorides, and secondary alkyl iodides are conserved when present in the same molecule as a primary alkyl iodide. Substituted allyl bromides react to give the product without allylic rearrangement. Migratory CO insertion depends very much on the nature of the electrophile and the presence or absence of electron-withdrawing substituents on the arene ring. In the case of benzene, all groups R″ (Scheme 14), with the exception of propargyl, undergo carbonylation prior to reductive elimination and reactions are cleaner and yields higher when carried out under CO (up to 4 bar) or in the presence of an added ligand ($PR_3$, $P(OPh)_3$, $NEt_3$). When CO is used, $Cr(CO)_6$ can be partly recovered.[101] Carbonylation follows the expected order based on migratory aptitude of R″ to an adjacent CO group: ethyl > methyl > benzyl,allyl ≫ propargyl. When either oxazoline or imine groups are present, carbonylation takes place with alkyl groups but is a very minor pathway with allyl (<15%) and does not occur at all with propargyl. This result is attributed to the electron-withdrawing properties of the ring substituents and also the use of electrophiles which show low migratory aptitude toward CO.

**Scheme 14. Cr-Mediated Transformation of Arenes into Functionalized Substituted Cyclohexadienes**



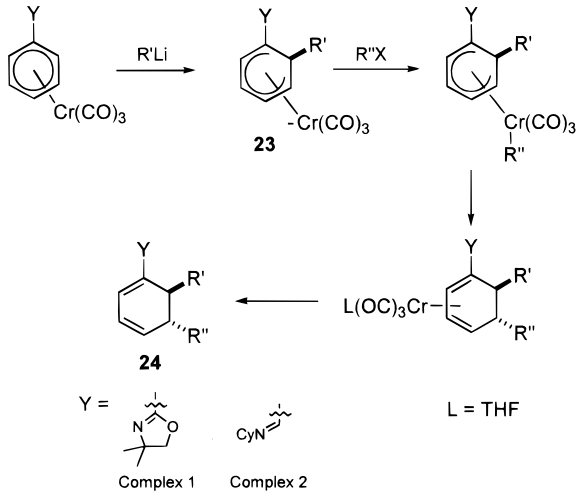

**Scheme 15. Trans Addition of Methyldithiane and an Acylated Electrophile Across a Benzene Double Bond**




Another salient feature of the imine and oxazoline systems is the regioselectivity of the nucleophilic attack. Through an intermediate which is believed to involve coordination of the RLi reagent to the nitrogen of either the imine or the oxazoline, nucleophilic addition is directed to the *ortho* position to give **23** with all but *tert*-organolithium compounds in reactions of phenyl oxazolines (Scheme 16).[55,102,103] This regioselectivity is also observed with hydrazones.[44,66] Reductive elimination is highly regioselective and always occurs at a terminus of the cyclohexadienyl ligand to result in **24**, a product of formal trans addition of a nucleophile and an electrophile across an arene double bond.

For benzene, the above procedure has been extended to include an in situ hydrogenation of the Cr-coordinated diene product to give predominantly the cyclohexene resulting from 1,4-hydrogen addition. This procedure is based on an analogy between the postulated diene intermediate **21** (Scheme 14), and that advanced for the catalytic '$Cr(CO)_3$' hydrogenation of conjugated dienes.[104] Thus, adding either

**Scheme 16. Sequential Addition of Organolithium Reagents and Allyl/Benzyl/Propargyl Bromides to Arene Chromium Tricarbonyls Substituted with an Oxazoline or Cyclohexylamine Appendage**

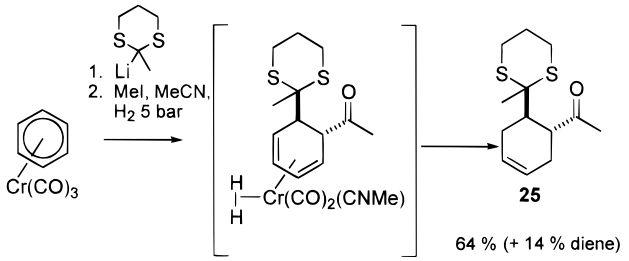



| Complex | R'Li | R"X | Yield, % |
|---|---|---|---|
| 1/2 | MeLi | $CH_2CHCH_2Br$ | 68/57[a] |
| 1 | | $CH_2CH(Me)CH_2Br$ | 61 |
| 1 | | $PhCH_2Br$ | 52 |
| 1 | | $HC{\equiv}CCH_2Br$ | 71[b]/76[a] |
| 1/2 | | $Me_3SiC{\equiv}CCH_2Br$ | 72[b] |
| 1 | n-BuLi | $CH_2CHCH_2Br$ | 63 |
| 1 | | $HC{\equiv}CCH_2Br$ | 87[b] |
| 1 | PhLi | $CH_2CHCH_2Br$ | 67 |
| 1 | | $HC{\equiv}CCH_2Br$ | 77[b] |
| 1 | $CH_2CHLi$ | $CH_2CHCH_2Br$ | 54 |
| 1 | | $HC{\equiv}CCH_2Br$ | 82[b] |
| 1 | | $Me_3SiC{\equiv}CCH_2Br$ | 88[b] |
| 1 | $NCCH_2Li$ | $CH_2CHCH_2Br$ | 48[b] |

[a] reaction proceeds with hydrolysis of the imine to give the aldehyde. [b] use of HMPA as co-solvant

acetonitrile or benzonitrile with the electrophile (to make up for the consummation of one carbonyl ligand) and placing the reaction under 5 bar of hydrogen provides **25** as the major isomer (Scheme

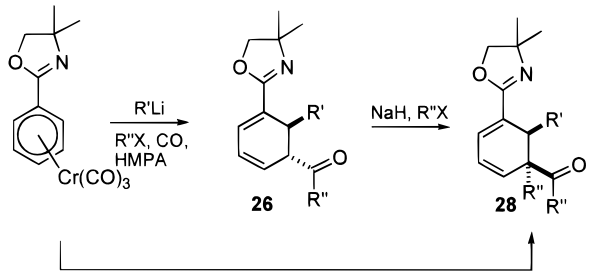
**Scheme 17. Sequential One-Pot Nucleophile/ Electrophile/Hydrogenation**




17).[105] The synthetic potential of this reaction sequence is evident, but it has not yet been explored.

With acyl products, there is also potential for the addition of a third carbon unit via enolate formation. This is particularly facile if an oxazoline or imine substituent is present. Thus, treatment of compounds **26** and **27** with a base followed by an electrophile results in products **28** and **29** in which the diastereoselectivity is governed by the adjacent stereogenic center.[102,103] Remarkably, protonation in the imine intermediate takes place at the (harder) nitrogen center whereas alkylation is at the (softer) carbon adjacent to the carbonyl function (Schemes 18 and 19).[103]

**Scheme 18. Triple Addition to Arene Chromium Tricarbonyl Complexes with Carbonylation**



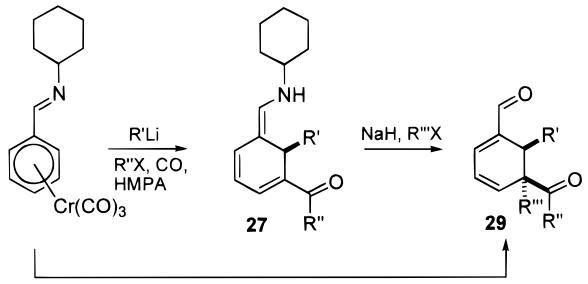

| R'Li | R''X | Yield,% |
|---|---|---|
| MeLi | MeI | 52 |
| | EtI | 62 |

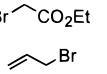
Careful selection of the relative nucleophile and electrophile can lead to organic intermediates from which more complex organic systems can be built. This has been demonstrated by selective 5-*exo*-trig radical cyclizations to give the bicyclic and bridged systems shown below (Scheme 20).[106]

This chemistry can also be applied to the dearomatization of naphthalene and derivatives. Treatment of 1,4-dimethoxynaphthalene complex **30** with sulfur-stabilized anions followed by methyl iodide results in the formation of **31** and **32**.[99,101] The chemistry has also been extended to include the dearomatization of **30** by attack of α-nitrile anions to give **33**. HMPA is essential in this case to enable the use of MeI as the electrophile and favors alkylation as opposed to anion dissociation (Scheme 21).[101]

(1-Methoxynaphthalene)$Cr(CO)_3$ **(34)**, prepared in 91% yield as a single regioisomer, served as the starting complex in a route to the AB ring system of

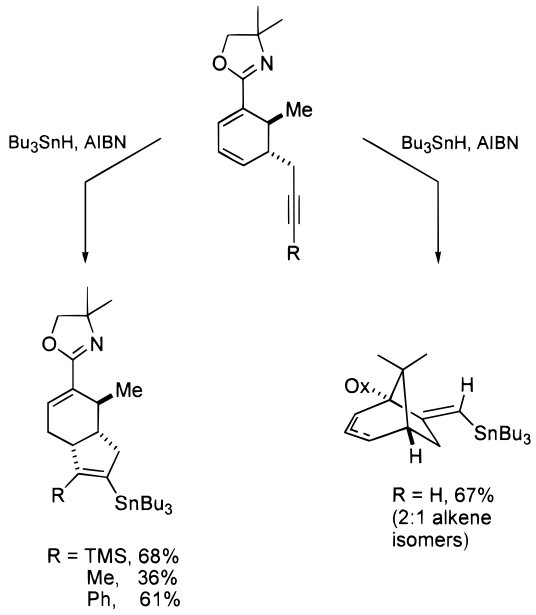
**Scheme 19. Addition of Three Different Carbon Substituents**




| R'Li | R''X | R'''X | Yield, % |
|---|---|---|---|
| MeLi | MeI | MeI | 90 |
| PhLi | MeI | MeI | 80 |
|  | MeI | MeI | 56 |
| MeLi | MeI | MeI | 63[a] |
| MeLi | MeI | EtI | 43[b] |
| MeLi | MeI |  | 58[c] |
| MeLi | MeI |  | 37[d] |
| MeLi | MeI |  | 36[e] |

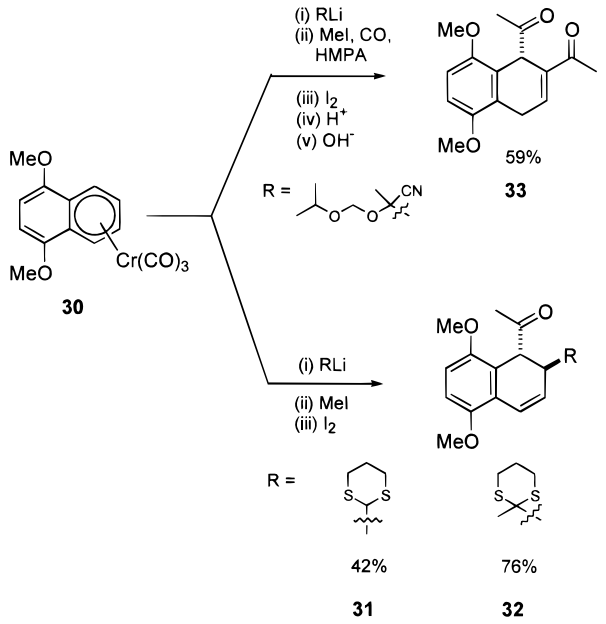
Note: when R''=R''' the one-pot reaction sequence was followed. Yield of **27** when R''=Me=73%; Et=45%. Yield for conversion from **27**:-[a] 86; [b] 59; [c] 79; [d] 50 (KOH used as base); [e] 79.

**Scheme 20. Application of the Triple Addition to Ring Systems**

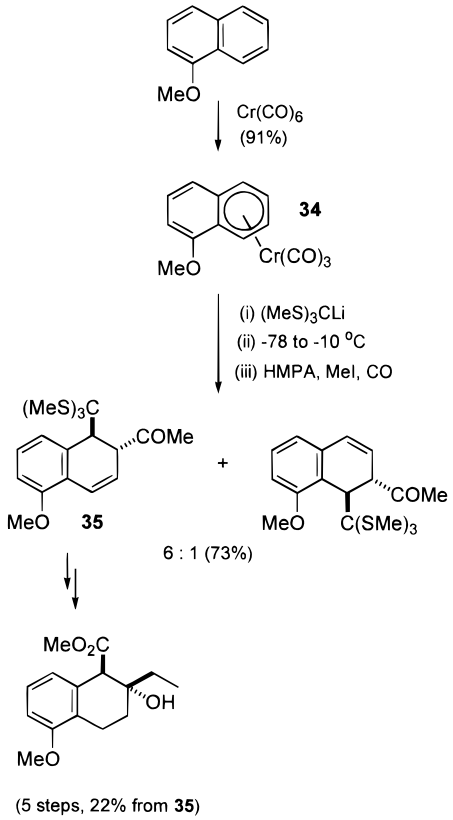



Aklavinone.[63] Nucleophilic attack on **34** under kinetic conditions is nonselective, and all four regioisomers are formed. However, on warming the reaction mixture to −10 °C, equilibration of the less stable anionic *β*-addition products to the more stable α-addition products takes place, with addition to C(5) being favored over addition to C(8) for steric reasons. Treatment with a cosolvent to suppress anion dissociation, followed by alkylation/migratory CO insertion and reductive elimination, gives a mixture of two isomers from which the key intermediate **35** can be isolated by a single crystallization (Scheme 22).

**Scheme 21. Sequential Nucleophile/Electrophile Addition to 1,4-Dimethoxynaphthalene**



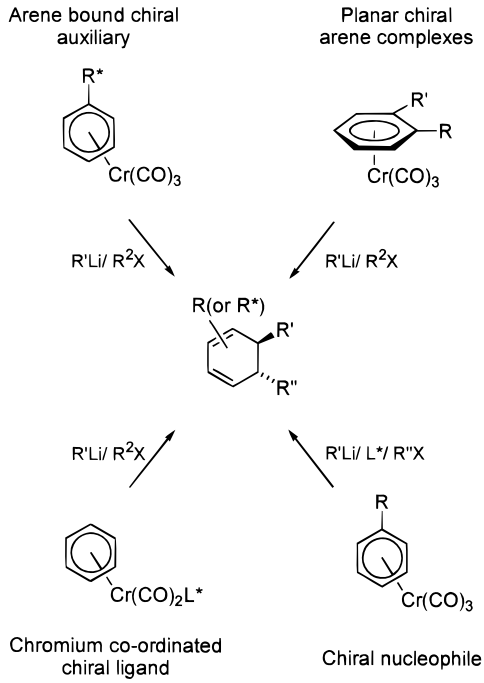

**Scheme 22. Synthesis of the Aklavinone AB Ring System**




## B. Asymmetric Induction

The methodology available in this area covers four different approaches (Scheme 23). These are asymmetric induction (1) with complexes of arenes bearing chiral auxiliaries as substituents, (2) with arene complexes of planar chirality, (3) of prochiral complexes with chiral nucleophiles, and (4) with complexes containing a chiral ligand at the metal center. In all but the last method, asymmetric induction

**Scheme 23. Asymmetric Versions of Transition-Metal-Mediated Dearomatization Reactions**




takes place in the nucleophilic addition step. The third method offers an enantioselective variant in that chirality can be centered on an external ligand rather than on the nucleophile itself. These approaches will be detailed in the following sections.

### *1. Chiral Auxiliary Control*

**i. Chiral Groups That Direct Nucleophilic Addition to the *ortho* Position.** As described in section IV.A.2, oxazoline and imine substituents direct nucleophilic addition to the *ortho* position in the corresponding (arene)$Cr(CO)_3$ complexes. The use of chiral oxazolines **36**, derived from L-valinol and L-*tert*-butylglycinol, result in nonracemic, highly diastereomerically enriched cyclohexadienes. The methodology is available to a number of reactive nucleophiles (Scheme 24),[107] and the method leads to products of high synthetic potential, given that oxazolines are readily cleaved by N-alkylation and $NaBH_4$ reduction to give the corresponding aldehydes.[7]

Asymmetric induction is thought to stem from the coordination-controlled nucleophile addition as shown in Figure 3. Steric interactions between the bulky

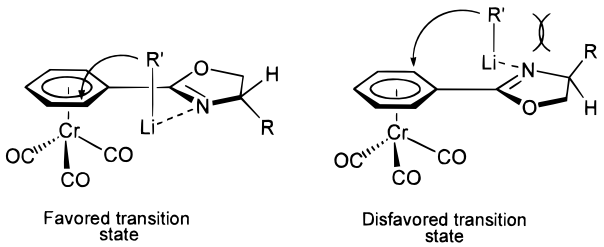
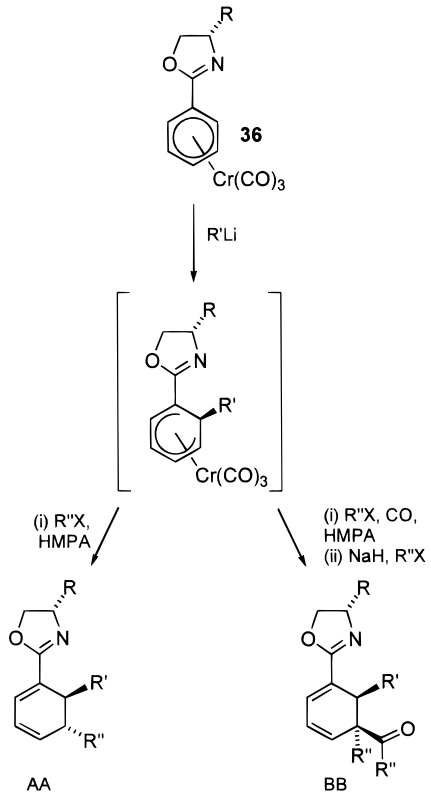



**Figure 3.** Origin of diastereoselectivity.

oxazoline R group and the nucleophile are avoided in the favored *endo* conformation. While there is no

**Scheme 24. Diastereoselective Additions to Arene Chromium Complexes Bearing Chiral Oxazoline Auxiliaries**



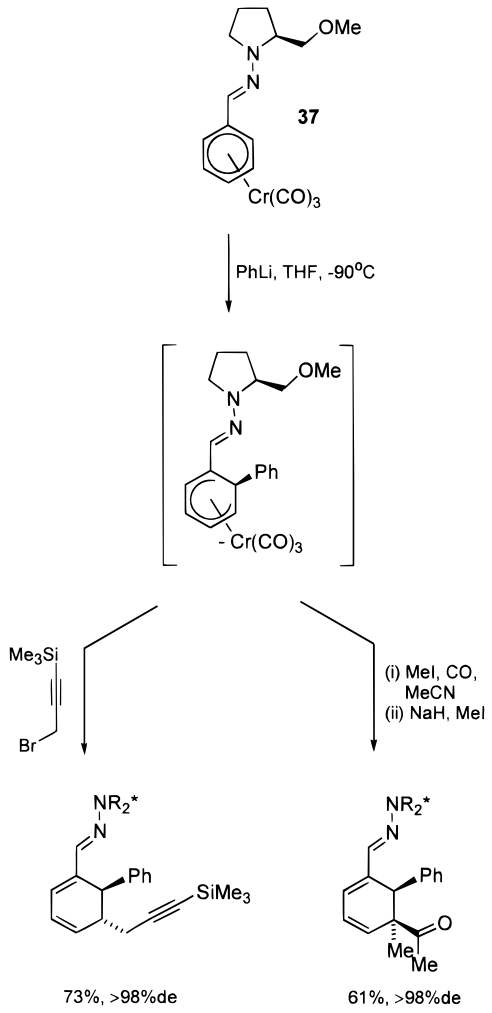

| R | R'Li | R"X | Yield, % | Diastereomeric ratio |
|---|---|---|---|---|
| $^{i}$Pr | MeLi |  | 61[a] | 96:4 |
| | BuLi |  | 54[a] | 95.5:4.5 |
| | PhLi |  | 60[a] | 81:19 |
| |  |  | 48[a] | 95.5:4.5 |
| |  | $Me_3Si$—≡—$CH_2Br$ | 86[a] | 85:15 |
| | MeLi | $Me_3Si$—≡—$CH_2Br$ | 77[a] | 93:7 |
| | MeLi | $PhCH_2Br$ | 51[a] | 95:5 |
| | MeLi | MeI | 54[b] | 95:5 |
| $^{t}$Bu | MeLi |  | 69[a] | >99:1 |
| | BuLi |  | 62[a] | >99:1 |
| | PhLi |  | 51[a] | 95.5:4.5 |
| | MeLi | MeI | 58[b] | >99:1 |

[a] double addition to give AA. [b] triple addition to give BB

hard mechanistic evidence for this proposal, an X-ray structure of the starting complex (R = $^{i}$Pr) shows that the R group in the oxazoline is pseudoequatorial and hence does not interact with the $Cr(CO)_3$ group in the *endo*-conformation.[107] The model shown (Figure 3) is in accord with the observed diastereoselectivity, with the observation of better induction by R = *t*-Bu than *i*-Pr and with the subsequent finding of the same mode of action in chiral oxazoline-mediated diastereoselective *ortho* deprotonations of ferrocenes.[108,109]

In addition to chiral oxazolines, SAMP-hydrazone has also been utilized. In this case, addition to the enantiopure complex **37** results in the production of a single diastereoisomer, thus providing efficient access to enantioenriched substituted cyclohexadienes (Scheme 25).[110]

**Scheme 25. Diastereoselective Additions to Arene Chromium Complexes Bearing a SAMP Hydrazone**

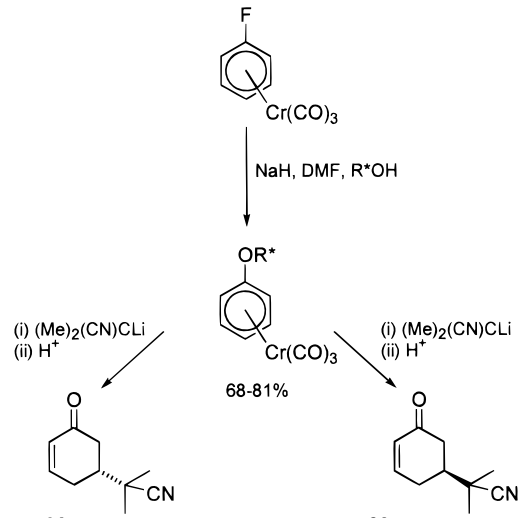


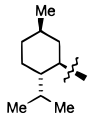
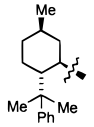
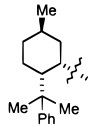
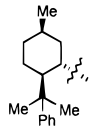

**ii. Chiral Groups That Direct Nucleophilic Addition to the *meta* Position.** The potential of asymmetric syntheses of 5-substituted cyclohexenones via this methodology has attracted attention from two research groups. Semmelhack's results in this area are shown in Scheme 26 where menthol-derived chiral auxiliaries were investigated.[58] The starting complexes are accessible by an efficient $Cr(CO)_3$-mediated nucleophilic substitution, and good yields of products **38** and **39** are obtained. Enantiomeric excesses in these reactions are however modest (<48% ee).

Interestingly, higher enantiomeric excesses are obtained at elevated temperatures (0 °C as opposed to −78 °C), and this suggests a change in the reaction from kinetic control at low temperature to thermodynamic control at the higher temperature. This is in keeping with the ready reversibility of nucleophilic addition of nitrile-stabilized carbanions at temperatures above −70 °C[62,111] (Scheme 27). The approach suffers from modest enantiomeric excesses, but this preliminary work benefits from ready accessibility of chiral complexes, efficient recycling of the auxiliary, and the potential for highly asymmetric routes to compounds useful in organic synthesis.

Pearson has taken a similar approach with the same target molecules but using terpenoid-derived

**Scheme 26. Semmelhack's Synthesis of Enantioenriched Cyclohexenones**




| R* | Product | Temp. °C | Yield, % | ee, % |
|---|---|---|---|---|
|  | 38 | -78<br>0 | 80<br>65 | 15<br>22 |
|  | 38 | -78<br>0<br>0-10 | 76<br>73<br>70 | 14<br>48<br>42 |
|  | 38<br>39 | -78<br>0 | 62<br>63 | 10<br>13 |
|  | 39 | -78<br>0 | 45<br>76 | <2<br>32 |

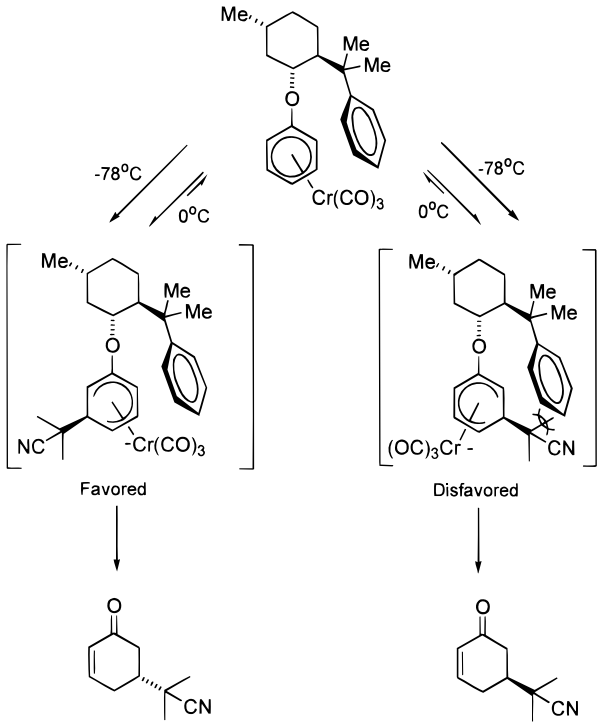
chiral auxiliaries. Higher diastereoselectivities are found with these auxiliaries as shown in Scheme 28 and Table 4, and the presence of a *para* Me group very much enhances induction.[57,112] In contrast to Semmelhack's results, diastereoselectivity varies little with temperature. Interestingly, regioselectivity changes from *meta* to *ortho* on warm-up when a *para* alkyl group is present (Scheme 29).

Overall Pearson's approach provides diastereoselective access to 5- and 4,5-substituted enones Scheme 30, where steric approach control appears to be the dominant factor in determining the stereochemical outcome of the nucleophilic addition. The substrates are readily synthesized, and the chiral auxiliaries can easily be recycled.

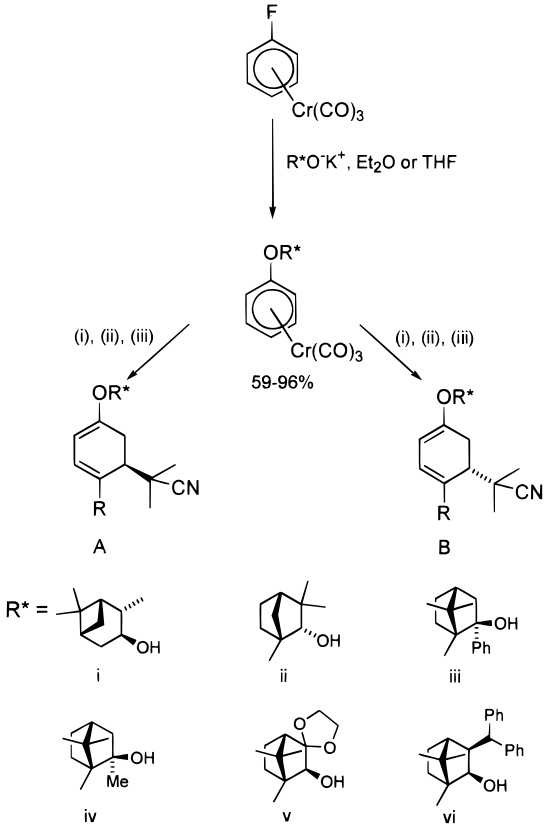
## 2. Planar Chiral Arene Chromium Complexes

Arene complexes with different *ortho* or *meta* substituents are chiral. Enantiopure planar chiral complexes can be obtained by resolution via diastereoselective synthesis and by enantioselective methods. The vast bulk of literature reports on this topic concerns planar chiral ferrocenes[113,114] and planar chiral (arene)$Cr(CO)_3$ complexes.[115] The treatment of this subject is beyond the scope of this article, and

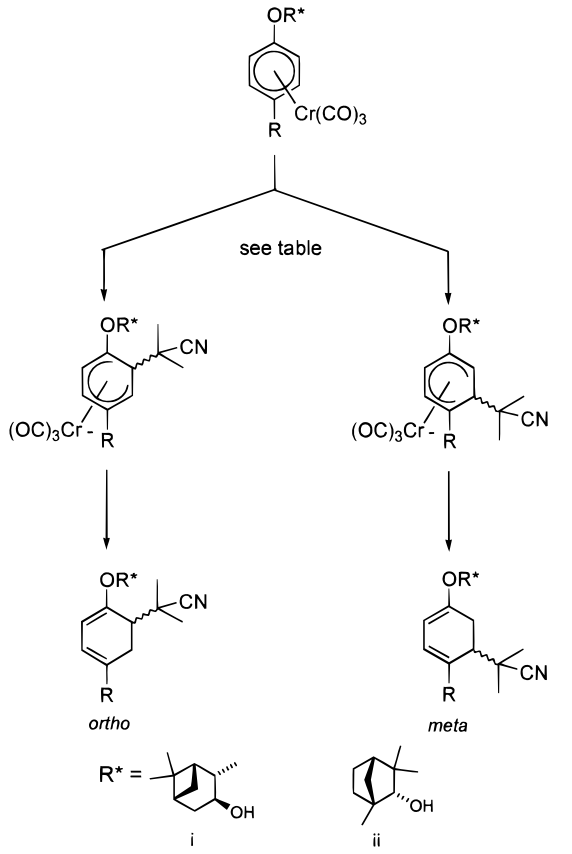
**Scheme 27. Proposed Intermediates and Temperature Dependence**




**Scheme 28. Pearson's Diastereoselective Route to Dienol Ethers: (i) $Me_2(CN)CLi$; (ii) TFA, −78°C; (iii) $NH_3$ (aq)**



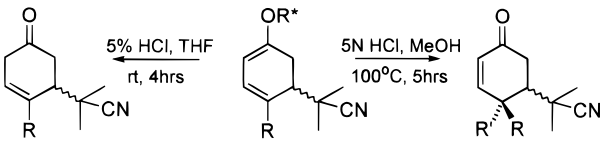
**Scheme 29. Effect of Temperature on Regioselectivity**




| R | R* | Reaction[a] conditions | ortho/meta ratio | Yield, % |
|---|---|---|---|---|
| Me | Me | THF/HMPA, -5°C | 62:38 | 54 |
| Me | Me | THF/HMPA, -78°C | 14:86 | 55 |
| Me | (i) | THF, 0°C | 72:28 | 84 |
| Me | (i) | THF/HMPA, -5°C | 80:20 | 70 |
| Me | (i) | THF/HMPA, -30°C | 19:81 | 78 |
| Me | (i) | THF/HMPA, -78°C | 11:89 | 90 |
| Me | (ii) | THF, -5°C | 78:22 | 68 |
| Me | (ii) | THF, -30°C | 14:86 | 73 |
| Me | (ii) | THF/HMPA, -78°C | 5:95 | 76 |
| TMS | (ii) | THF, -5°C | 77:23 | 79 |
| TMS | (ii) | THF, -5°C, 22h | 92:8 | 92 |

[a] all reactions run for 2-2.5h, unless stated.

**Scheme 30. Pearson's Conversion to Enantioenriched Cyclohexenones**



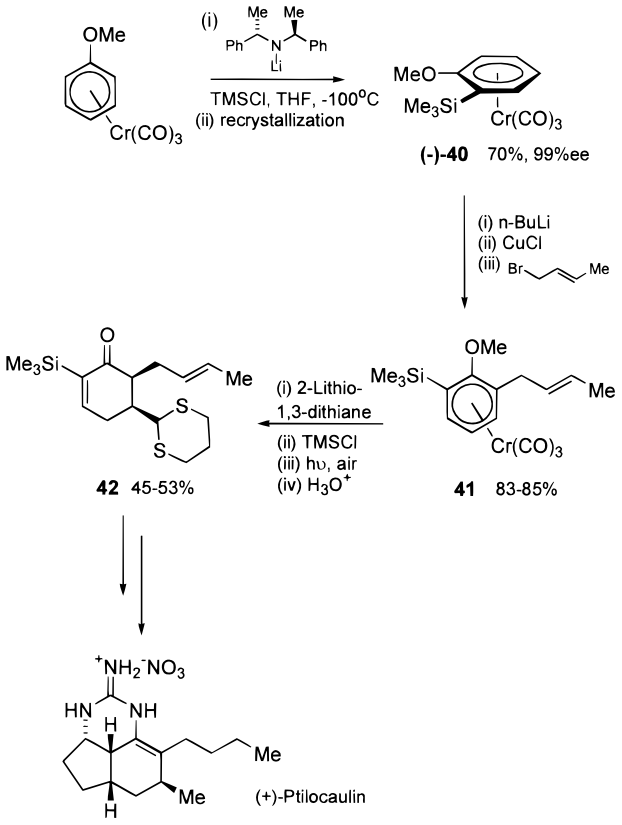

the reader is referred to the above cited reviews. While asymmetric variants of manganese and osmium complexes have yet to be realized, planar chiral (arene)$Cr(CO)_3$ complexes have been applied successfully to asymmetric dearomatization reactions by two groups. In both cases, the requisite enantioenriched planar chiral starting complex was obtained via an enantioselective lithiation reaction of a prochiral arene complex with a chiral base[116−121]

Schmaltz recently described an application to the synthesis of (+)-ptilocaulin, a marine natural product

**Table 4. Proportion of A:B with Differing Auxiliaries − Scheme 28**

| auxiliary | R | A:B | yield |
|---|---|---|---|
| i | H | 70:30 | 80 |
| | Me | 73:27 | 90 |
| ii | H | 78:22 | 67 |
| | Me | 88:12 | 76 |
| iii | H | 80:20 | 95 |
| | Me | 96:4 | 63 |
| iv | H | 36:64 | 89 |
| | Me | 10:90 | 81 |
| v | H | 12:88 | 86 |
| | Me | 6:94 | 65 |
| vi | Me | 8:92 | 76 |

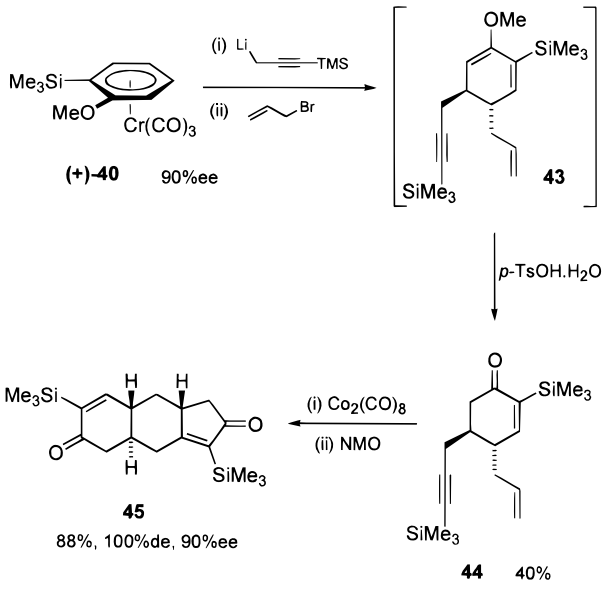
**Scheme 31. Schmalz's Use of Planar Chiral Arene Chromium Tricarbonyl Complexes in the Total Synthesis of (+)-Ptilocaulin**




which shows high antimicrobial and cytotoxic activity (Scheme 31).[122] Synthesis of the enantiomerically enriched complex (−)-**40** by Simpkin's protocol[116] is followed by Cu-mediated *ortho* substitution to give **41**. A highly diastereoselective nucleophilic addition of 2-lithio-1,3-dithiane, treatment with acid-free chlorotrimethylsilane, and then acidic work up provides **42** in good yield and exceptional enantiomeric excess (99%).[68,123] This synthesis elegantly demonstrates the power and competitiveness of the underlying strategy.

The anisole complex (+)-**40** is the starting material in the synthesis of the fused alicyclic ring system shown in Scheme 32. Propargyllithium addition is followed by reaction with allyl bromide, both reactions occurring with complete regio- and diastereoselectivity. The cyclohexadiene **43** was readily manipulated to the enone **44**, and the subsequent

**Scheme 32. Double Addition with Planar Arene Chromium Complexes and Synthesis of *trans*-Fused Ring Systems**




Pauson−Khand cyclization afforded the tricyclic product **45** containing a 6,6-*trans*-fused ring system in 90% ee and 100% de. This corresponds to the quantitative transfer of chiral information and illustrates the strength of this approach.[124]

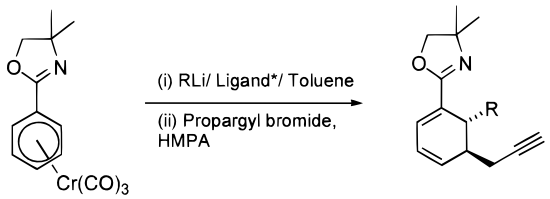
### *3. External Chiral Ligands*

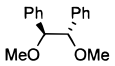
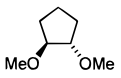
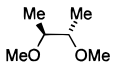
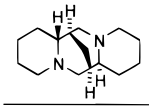
In this approach external chiral ligands were used in combination with organolithium nucleophiles to induce asymmetry in the sequential nucleophile/electrophile addition to a prochiral arene complex (Schemes 33 and 34). This chiral modification of the nucleophile enables high levels of enantioselectivity to be achieved.[125] Work in these laboratories has highlighted ligand **46**[126] as the most efficient chiral ligand. This transformation is open to a broad range of nucleophiles and electrophiles. However, the distinct advantage of this method compared to section IV.B.1.i is the potential for the catalytic use of chiral information.

### *4. Chiral Ligands at Chromium*

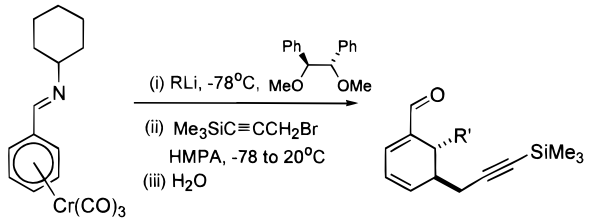
Yet another approach is the use of a chiral chromium species (Scheme 35). In contrast to the methods described above, here asymmetric induction does not occur in the nucleophilic addition step but in either the CO insertion step or the reductive elimination step or both. Work in this area is not at an advanced stage, and thus far, enantioselectivities are modest and the requirement for the use of a chiral phosphorus ligand in a stoichiometric reaction is unlikely to become a method of synthetic utility. Mechanistically, the approach is highly interesting as it poses the question of the influence of the chiral ligand L* on the migratory CO insertion step and on the reductive elimination—both being diastereomeric processes.[100,105]

**Scheme 33. Nucleophilic Additions to Arene Chromium in the Presence of a Chiral Ligand**




| Ligand* | RLi | Yield,% | ee, % |
|---|---|---|---|
|  **46** | PhLi | 66 | 93 |
| | VinylLi | 53 | 87 |
| | MeLi | 51 | 87 |
| | N-BuLi | 67 | 65 |
|  | PhLi | 66 | 81 |
| | VinylLi | 60 | 61 |
| | MeLi | 50 | 84 |
| | N-BuLi | 75 | 61 |
|  | PhLi | 72 | 81 |
| | VinylLi | 85 | 50 |
| | MeLi | 60 | 47 |
| | N-BuLi | 68 | 45 |
|  | PhLi | 72 | 54 |
| | VinylLi | 87 | 34 |
| | MeLi | 70 | 47 |
| | N-BuLi | 65 | 36 |

**Scheme 34. Addition of a Chiral Nucleophile**




| RLi | Yield, % | ee, % |
|---|---|---|
| MeLi | 62 | 91 |
| PhLi | 64 | 93 |
|  | 77 | 75 |

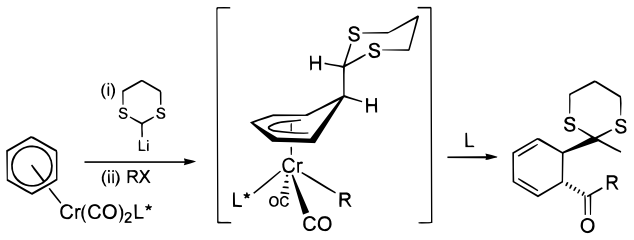
## *V. Manganese-Mediated Dearomatization Reactions*

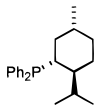
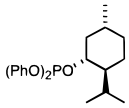
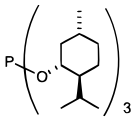
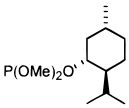
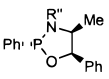
## A. Racemic Products

Arene tricarbonyl manganese complexes are open to attack by a broad range of nucleophiles because of their increased electrophilic character when compared to arene chromium tricarbonyl complexes. However, the simple addition of a nucleophile followed by cleavage under acidic, oxidative conditions generally leads to either the rearomatized product or, where the dearomatized product is isolated, a number of diene isomers. Therefore, routes to dearomatized products rely upon the methods below, which require treatment with two nucleophiles.

The most direct route to dearomatized products from arene manganese complexes involves the use of very reactive nucleophiles. The first nucleophile can be either hydride or a C-nucleophile, but the

**Scheme 35. Nucleophilic Addition to Arene Chromium Complexes Bearing a Chiral Ligand**



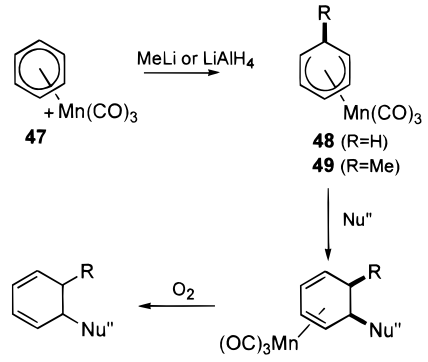

| L* | R'X | L | Yield, % | ee, % (config.) |
|---|---|---|---|---|
|  | MeI | CO | 60 | 8(SS) |
| | EtI | CO | 44 | 19(SS) |
|  | MeI | CO | 55 | 14(RR) |
| | MeI | $P(OPh)_3$ | 91 | 16(RR) |
| | EtI | CO | 67 | 28(RR) |
|  | MeI | CO | 54 | 40(SS) |
| | MeI | $P(OPh)_3$ | 70 | 31(SS) |
| | EtI | $P(OPh)_3$ | 57 | 21(SS) |
|  | EtI | CO | 82 | 26(RR) |
|  | MeI | CO | 71 (R"=Me) | 41(SS) |
| | | | 60 (R"=Cy) | 56(SS) |
| | | | 50 (R"=$^i$Pr) | 69(SS) |

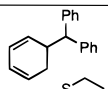
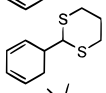
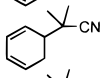
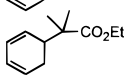
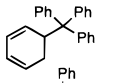
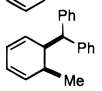
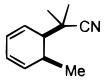
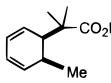
second is always a C-nucleophile. Thus, products resulting from the addition of one or two carbon units can be isolated. Treatment of **47** with either $LiAlH_4$ or MeLi provides **48** and **49**, respectively, which have low electrophilic character. A reactive nucleophile must be used for the second nucleophilic addition to be successful. This sequential nucleophile/nucleophile addition sequence has been used to some success, and a number of examples have been described as outlined in Scheme 36. Decomplexation to the dearomatized product is simply achieved by stirring in the presence of oxygen.[75]

The most extensive work in this area of dearomatization chemistry involves reactivation of the manganese complex that results from the first nucleophilic addition. As described earlier, replacement of a CO ligand with $NO^+$ reactivates the manganese complex toward addition from less reactive nucleophiles. A number of carbon nucleophiles have been used in the second nucleophilic addition, although the first is restricted to methyl and phenyl Grignard reagents. In general, the replacement of CO with a phosphorus ligand provides an increase in yield which is due to the less reactive nature (see Table 2) of this species compared to arene$(Mn(CO)_3)^+$. Oxidative decomplexation of **50** provides the dearomatized compound in 50−60% yield and depending on the nature of the substituents on the aromatic ring delivers either a diene or an enone as indicated in Scheme 37 and Table 5.

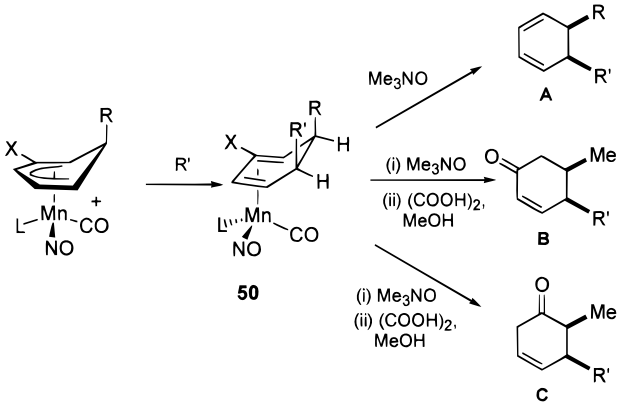
The situation with methyl- and phenyllithium is more intriguing. Treatment of the reactivated species

**Scheme 36. Sequential Double Nucleophilic Addition to Arene Manganese Tricarbonyl Complexes**




| Complex | Nu" | Product | Yield, % |
|---|---|---|---|
| **48** |  |  | 77 |
| |  |  | 65 |
| |  |  | 88 |
| |  |  | 91 |
| |  |  | 90 |
| **49** |  |  | 73 |
| |  |  | 58 |
| |  |  | 43 |

**Scheme 37. Double Addition To Give *trans*-1,2-Disubstituted Products**




**51** results in transformation to the diene **52**. Thus, attack of the nucleophile at CO is followed by *endo* migration of the acyl group to give the *trans*-1,2-disubstituted system. Unfortunately this chemistry has not yet been extended beyond phenyl- or methyllithium (Scheme 38).[17,82,127]

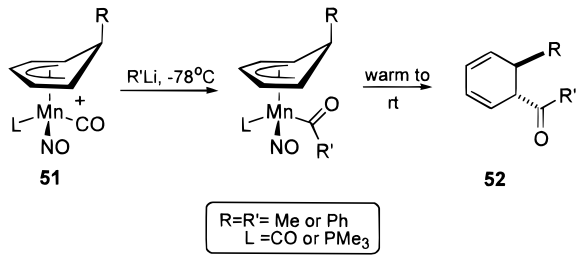
The double nucleophilic addition to arene$Mn(CO)_3^+$ complexes provides elegant methodology which is open to a number of nucleophiles and offers the

**Table 5. Carbon and Hydride Nucleophiles Active in the Nucleophilic Addition/Ligand Exchange/ Nucleophilic Addition Sequence with Arene Manganese Complexes Following Reactivation**

| X | R | L | nucleophile | yield,[a] % | product |
|---|---|---|---|---|---|
| H | Me | CO | $NaCH(CO_2Et)(COMe)$ | 67 | A |
| | | | $NaCH(CO_2Et)CN$ | 59 | A |
| | | | $NaCH(CO_2Me)(SO_2Ph)$ | 67 | A |
| | | | $NaSCH_2CH_2OH$ | 60 | A |
| H | Me | $P(OPh)_3$ | $NaCH(CO_2Et)(COMe)$ | 79 | A |
| | | | $NaCH(CO_2Et)CN$ | 82 | A |
| | | | $NaCH(CO_2Me)(SO_2Ph)$ | 83 | A |
| | | | $NaSCH_2CH_2OH$ | 83 | A |
| OMe | Me | CO | $NaCH(CO_2Et)(COMe)$ | 18 | C |
| | | | $NaCH(CO_2Et)CN$ | 27 | B |
| | | | $NaCH(CO_2Me)(SO_2Ph)$ | 28 | B |
| | | | $NaSCH_2CH_2OH$ | 50 | B |
| OMe | Me | $P(OPh)_3$ | $NaCH(CO_2Et)(COMe)$ | 62 | – |
| | | | $NaCH(CO_2Et)CN$ | 80 | – |
| | | | $NaCH(CO_2Me)(SO_2Ph)$ | 82 | – |
| H | Ph | CO | $NaCH(CO_2Et)(COMe)$ | 66 | A |
| | | | $NaCH(CO_2Et)CN$ | 59 | A |
| | | | $NaCH(CO_2Me)(SO_2Ph)$ | 62 | A |
| | | | $NaSCH_2CH_2OH$ | 87 | A |
| | | | $NaBH_4$ | 85 | – |
| | | | $NaCH(CN)_2$ | – | – |
| | | | NaCp | – | |
| H | Ph | $PMe_3$ | $NaBH_4$ | 85 | A |
| | | | $NaCH(CN)_2$ | 94 | – |
| | | | NaCp | 62 | – |
| | | | $NaCH(CO_2Me)_2$ | 80 | – |

[a] Please note, yield given is for the complex 50.

**Scheme 38. Addition of Organolithiums to Reactivated Manganese Complexes**




potential for asymmetry.[83] However, while very reactive nucleophiles enable rapid access to dearomatized products, the use of soft nucleophiles becomes more complicated with the requirement for reactivation and ligand exchange.

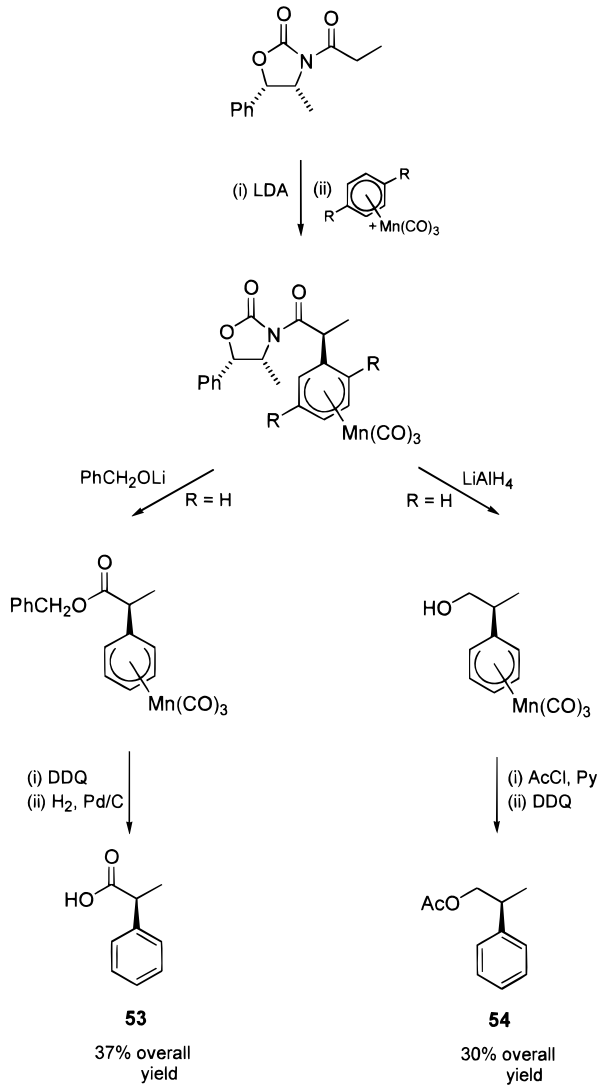
## B. Asymmetric Reactions

### *1. Chiral Nucleophile*

Initial work in this area was developed by Miles. A chiral nucleophile was used in reactions with an achiral organomanganese complex, an approach based on Pearson's earlier work with dienyliron and dienemolybdenum complexes.[128−130] Thus, chiral enolates derived from *N*-acyloxazolidinones were reacted with organomanganese complexes to give chiral $\eta^5$-dienylmanganese complexes (Scheme 39).[131,132]

Cleavage of the chiral auxiliary and oxidation of the $\eta^5$-dienylmanganese moiety leads to chiral 2-arylpropionic acids **53** and their derivatives **54**. High diastereoselectivity (d.r. > 9:1 in the attack and diastereoisomerically pure after recrystallization) was achieved with the benzene complex (R = H), whereas substituted arenes (where R = OMe, or OPh)

**Scheme 39. Miles' Addition of a Chiral Nucleophile to an Arene Manganese Complex**



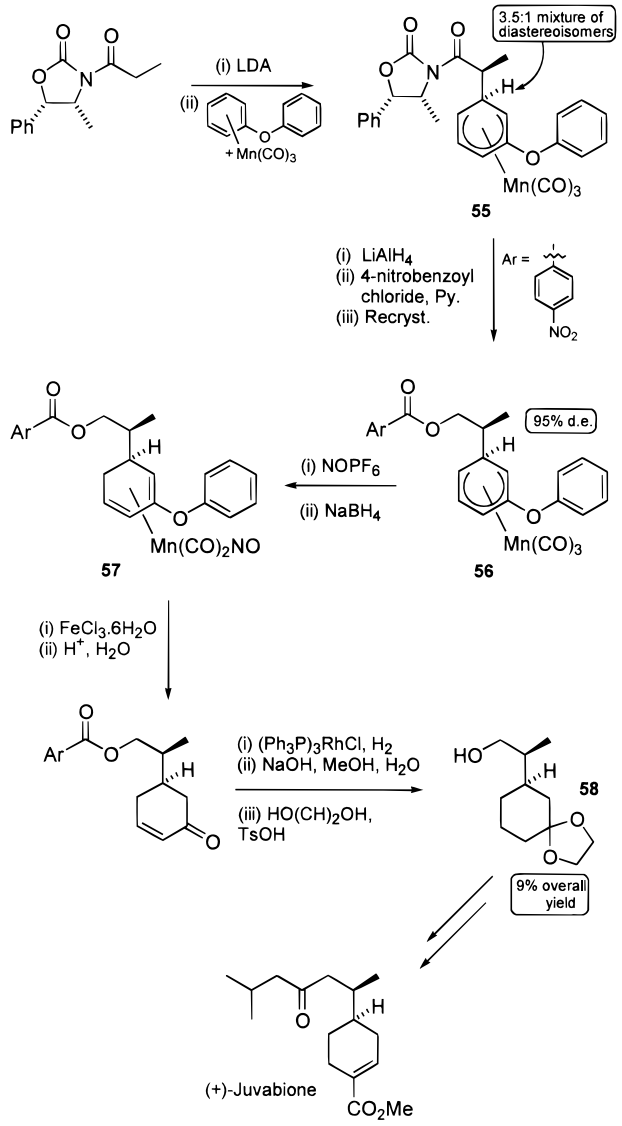

provided relatively low diastereoselectivity at the ring chiral center. The low diastereoselectivity is of no consequence when followed by decomplexation to give aromatic products, but a sequence leading to dearomatized products would obviously result in poor asymmetric induction. Nevertheless, Miles applied this approach to the formal asymmetric synthesis of (+)-juvabione,[133−137] a highly active juvenile hormone (Scheme 40).

Attack of the chiral nucleophile, generated from the reaction of LDA and an oxazolidinone, on the manganese phenoxyphenyl complex provides **55**. This manipulation proceeds with high diastereoselectivity at the enolate center, and also modest diastereoselectivity (3.5:1) is realized at the ring carbon. Conversion to the 4-nitrobenzoate esters enables diastereomeric enrichment by recrystallization to give **56** in 95% de. Reactivation of the $\eta^5$-dienylmanganese moiety (vide infra) afforded the dearomatized product **57**, which was advanced after a number of manipulations to the ketal **58**, an intermediate in the total synthesis of (+)-juvabione.[138]

### *2. Chiral Auxiliary Control*

Pearson's approach in this area centers on a $C_2$ chiral pyrrolidine auxiliary whose mode of asym-

**Scheme 40. Miles' Formal Synthesis of (+)-Juvabione**




metric induction is predicted as shown in Figure 4.[139] It is postulated that the arene complex would undergo nucleophilic attack at the *meta* position of the arene ring, furthest away from the methyl group that projects toward the angle of trajectory of the incoming nucleophile.

Treatment of the chiral (arene)$Mn(CO)_3^+$ complex with a number of nucleophiles has provided access to $\eta^5$-cyclohexadienyl complexes with modest to excellent diastereoselectivity (Scheme 41). Where selectivity is achieved, the complex obtained is a product of 1,5-asymmetric induction. In general, most nucleophiles deliver the major diastereoisomer **59**

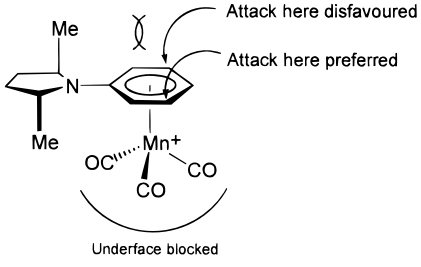
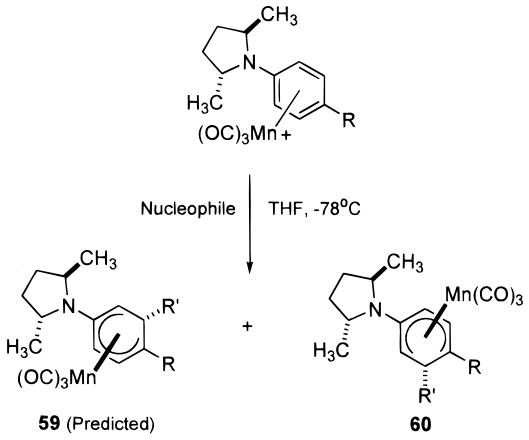



**Figure 4.** Pearson's model for diastereoselectivity.

**Scheme 41. Nucleophilic Addition to Arene Manganese Complexes Bearing a $C_2$-Symmetric Substituent**



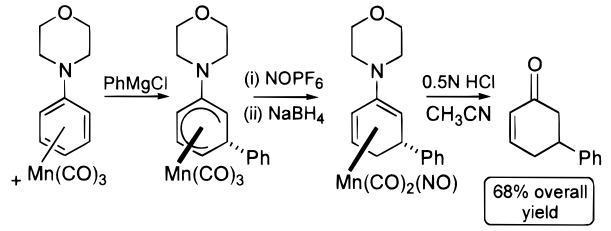

| Entry | R | Nucleophile | Ratio 59:60 | Yield, % |
|---|---|---|---|---|
| 1 | H | PhLi | 66:33 | 52 |
| 2 | Me | PhLi | 87:13 | 78 |
| 3 | H | PhMgBr | 95:5 | 60 |
| 4 | Me | PhMgCl | 98:2 | 93 |
| 5 | H | VinylMgBr | 62:38 | 50 |
| 6 | Me | VinylMgBr | 78:22 | 36[a] |
| 7 | Me | AllylMgBr | 80:20 | 65 |
| 8 | H | LS-Selectride | 92:8 | 84 |
| 9 | Me | LS-Selectride | | no reaction[b] |
| 10 | H | L-Selectride | 84:16 | 77 |
| 11 | Me | L-Selectride | 85:15 | 30[b] |
| 12 | H | Superhydride | 74:26 | 75 |
| 13 | Me | Superhydride | 63:37 | 37[b] |
| 14 | H | $LiAlH_4$ | 68:32 | 81 |
| 15 | Me | $LiAlH_4$ | 42:58 | 83 |
| 16 | H | $LiAl(t\text{-}OBu)_3H$ | 58:42 | 70 |
| 17 | Me | $LiAl(t\text{-}OBu)_3H$ | 50:50 | trace[a] |
| 18 | H | $NaBH_4$ | 19:81 | 80 |
| 19 | Me | $NaBH_4$ | 25:75 | 93 |
| 20 | H | $LiBH_4$ | 21:79 | 85 |
| 21 | Me | $LiBH_4$ | 11:89 | 73 |
| 22 | H | MeLi[c] | 25:75 | 60 |
| 23 | Me | MeLi | 22:78 | 67 |
| 24 | Me | VinylLi | 29:71 | 62 |
| 25 | Me | $LiCH_2CO_2Bu^t$ | 36:64 | 65 |

[a] unreacted starting material recovered; [b] substantial decomplexation of arene observed; [c] reaction in DCM at -95 to -85°C.

(entry 1−14 and 16) as predicted by the model; however, in certain cases the reactivity trend is reversed and the other diastereoisomer **60** (entry 15 and 18−25) is dominant.[140,141] Sterically demanding, very reactive nucleophiles give the best results, and they can be rationalized by a steric approach model. Nucleophiles of lower reactivity give reduced or even reversed selectivity which appears to be consistent with a late transition state model, although the reason for the reversal in reactivity is not clearly understood. The selectivity has also been shown to be both solvent and temperature dependent.[142]

Manipulation through to the dearomatized products has, however, proved impossible with this system. To address this problem, Pearson recently described (albeit racemic) methodology which enables the nucleophilic addition to arene manganese complexes (bearing an amino linkage) and transformation to substituted cyclohexenones (Scheme 42).[143]

**Scheme 42. Pearson's Cyclohexenone Synthesis**

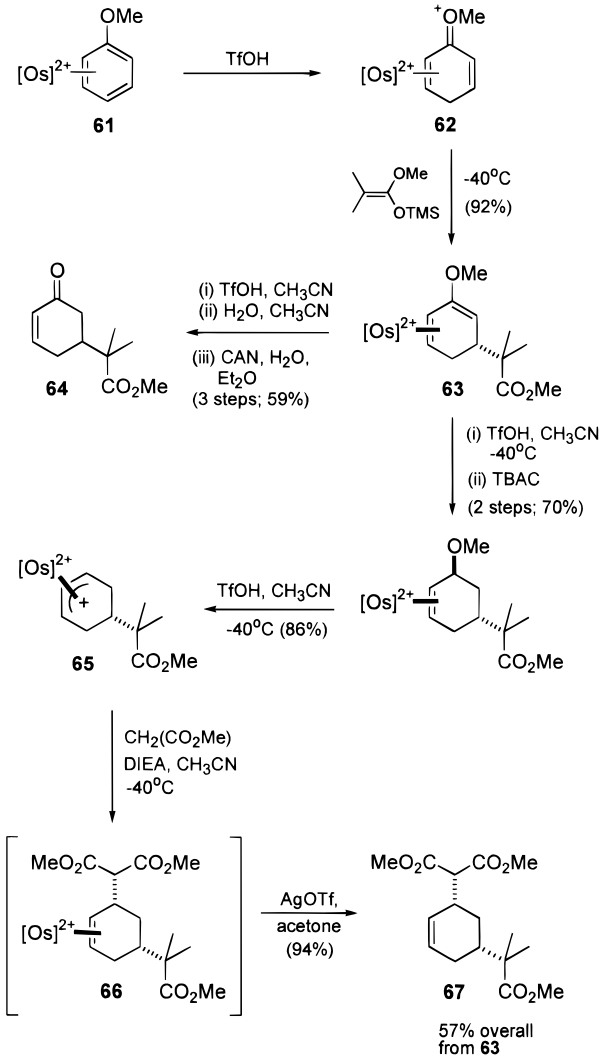



## VI. Osmium-Mediated Dearomatization Reactions

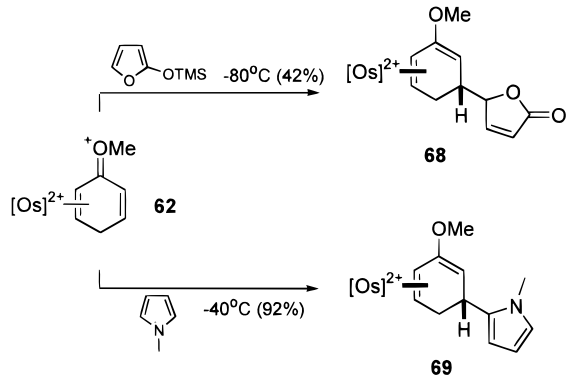
### A. Racemic Products

A review by Harman in 1997 details Os(II)-mediated transformations of the $\eta^2$-bound arenes.[24] Recent work by this group has focused on sequential electrophile/nucleophile addition reactions to these complexes (Scheme 43).[144] The anisole complex **61** is readily protonated to give the arenium species **62**, which is followed by Mukaiyama type-1,4-addition with a silyl enol ether to give diene **63**. At this stage a single carbon unit has been added to an arene with high regio- and stereocontrol, the attack of the nucleophile being *exo* to the osmium unit. The diene

**Scheme 43. Sequential Electrophile/Nucleophile Addition to Anisole Pentaamineosmium Complexes**




**Scheme 44. Nucleophilic Addition to Anisolium Pentaamineosmium**

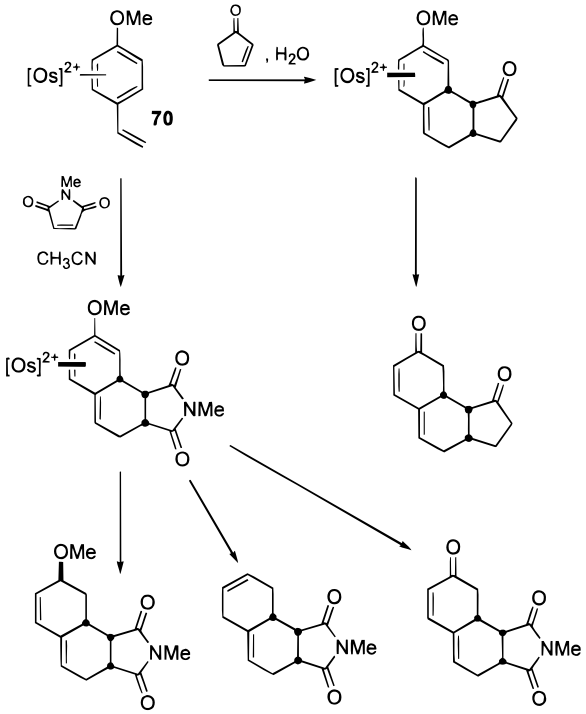



**63** can be manipulated to the 5-substituted enone **64.** Synthesis of the $\pi$-allyl osmium species **65** enables attack by malonate, thus introducing a second carbon unit to give **66**. Decomplexation with silver triflate delivers the *cis*-3,5-disubstituted cyclohexene **67** in an overall yield of 57%. This example shows the ability of the Os(II) group to be used repeatedly as an activating and stereodirecting group in an extended reaction sequence.

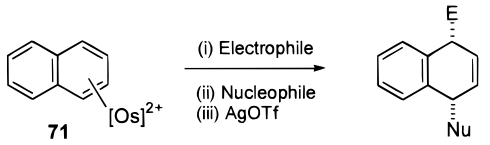
Reaction of the arenium complex **62** with 2-trimethylsilyloxy furan and *N*-methyl pyrrole has enabled the efficient syntheses of **68** and **69**, respectively. These compounds have not been manipulated further, and decomplexation to provide the pure organic products has not yet been reported (Scheme 44).[144]

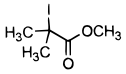
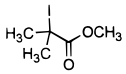
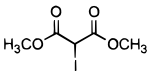
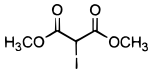
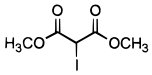
In a further extension of this work, Harman developed the use of pentaammineosmium(II) styrene complexes in Diels−Alder chemistry (Scheme 45). A number of tricyclic ring systems have been synthesized using this approach. The chemistry is highly selective and open to a number of dienophiles, where the styrene complex **70** serves as the diene.[145]

**Scheme 45. Diels−Alder Reactions with Osmium Styrene Complexes**



**Scheme 46. Osmium-Mediated Dearomatization of Naphthalene**




| Electrophile | Nucleophile | Yield, % |
|---|---|---|
| H | H | 56 |
| H |  | 77 |
|  |  | 65 |
|  |  | 54 |
|  |  | 69 |
|  | H | 45 |
|  | $CH_3I$ | 40 |
|  | PhI | 40 |
|  |  | 41 |
|  |  | 25 |

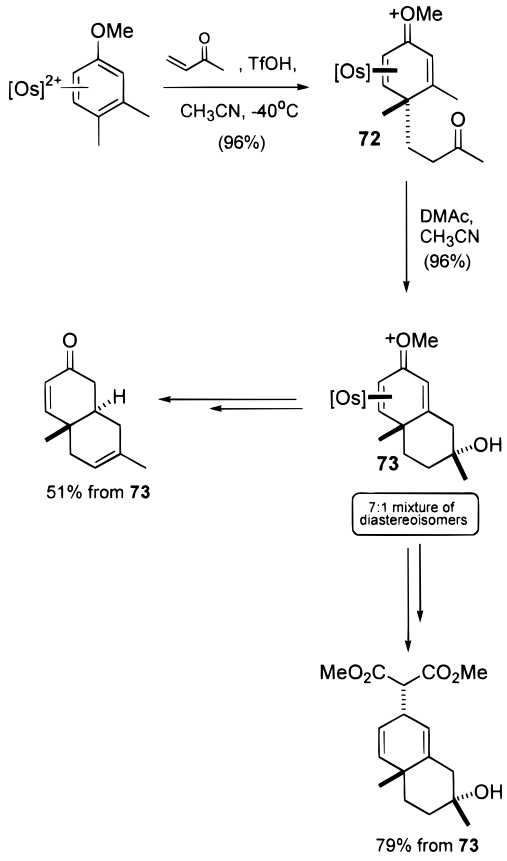
The double addition of an electrophile followed by a nucleophile to the naphthalene osmium complex **71** above gives access to a number of 1,4-*cis*-disubstituted 1,4-dihydronaphthalenes in moderate yields (Scheme 46). The chemistry here has the advantage of being performed in a one-pot sequence; however, the products from the reaction are generally very unstable under ambient conditions.[146]

In an approach which utilizes the activity of the bound osmium after the dearomatization event, Harman also described intramolecular methodology for the synthesis of fused ring systems (Scheme 47).[147] In this research a standard electrophile/nucleophile addition sequence, where methyl vinyl ketone in the presence of triflic acid serves as the electrophile, gives complex **72**. Deprotonation of **72** at the benzylic position with DMAc is followed by intramolecular cyclization to give **73**. The chemistry can lead directly to the dearomatized ring system or the osmium can be used for further synthetic manipulations.

## B. Asymmetric Reactions–Chiral Auxiliary Control

An approach which provides the *potential* for access to enantioenriched 5-substituted cyclohexenones is centered on the diasteroselective complexation of a phenol derivative.[148,149] When R′ (Scheme 48) is an ester or amide group, diastereoisomer **74** is formed with high preference over its diastereoisomer **75**. Hydrogen bonding between the amide or ester moiety and the ammonia ligands attached to osmium is advanced as being at the origin of this diastereoselectivity. **74** is preferred over **75** due to unfavorable steric interactions in the latter (Figure 5).

**Scheme 47. Intramolecular Cyclization with Osmium Arene Complexes**




The major isomer **74** is readily subjected to the known electrophile/nucleophile addition sequence to give **76** as a single diastereoisomer (>90% de). Removal of the auxiliary followed by decomplexation of the metal provides the dearomatized product **77** bearing a new stereogenic center.

A range of complexes have been synthesized in excellent diastereoisomeric excess. However, so far, only one of these complexes has been carried through to the dearomatized product, which is in fact racemic. The approach here provides excellent diastereoisomeric selectivity, but one can only *assume* that this will relate to highly enantioenriched products should enantiopure chiral auxiliaries be employed.[149]

## *VII. Concluding Remarks*

This review describes a wealth of literature covering transition-metal-mediated dearomatization chemistry. The use of chromium, manganese, and osmium has been shown to provide rapid access to compounds which otherwise require long and tedious manipulations. Efficient use of the described methodology can lead to the synthesis of complex organic products with high regio-, chemo-, stereo-, and often enantioselectivity. The chemistry covering intermolecular manipulations is extensive, and there is a broad understanding of the respective limitations for application of each approach. Research within the asymmetric arena is still at the development stage, although numerous methods which deliver asymmetric induction have been designed and adopted. There is no doubt that development in this area will be pursued vigorously and that, with efficient meth-

**Scheme 48. Harman's Diastereoselective Addition to an Anisole Osmium Complex**

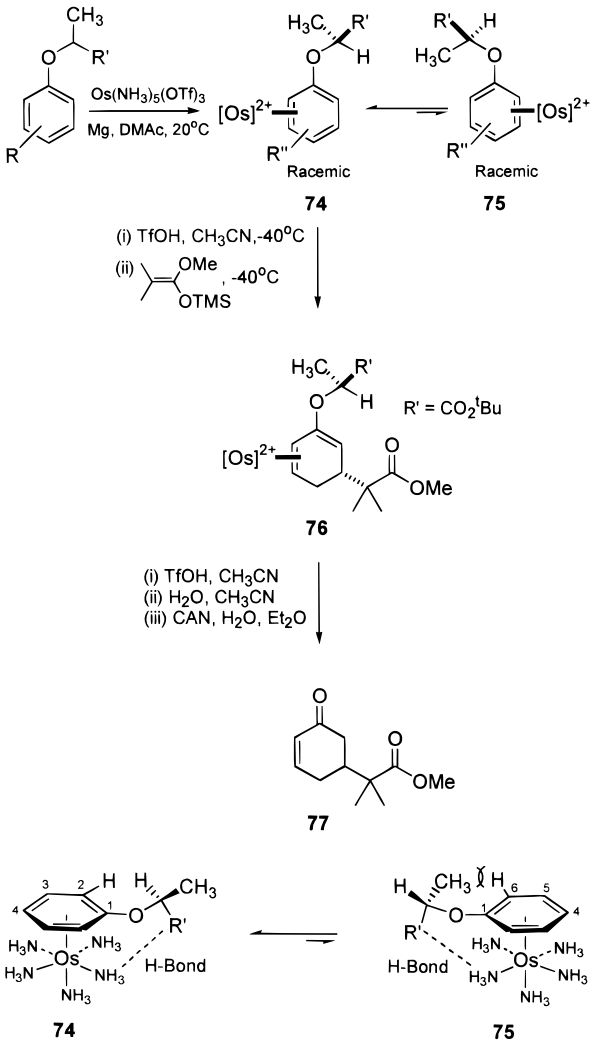



**Figure 5.** Favored and disfavored transition states.

odology established, applications in the synthesis of organic compounds of high complexity will follow.

## VIII. Abbreviations

| | |
|---|---|
| AIBN | 2,2′-azobis(2-methylpropionitrile) |
| ATPH | aluminum tris(2,6-diphenylphenoxide) |
| BHA | 2,6-di-*tert*-butyl-4-methoxyphenyl naphthalene-carboxylate |
| CAN | ceric ammonium nitrate |
| Cy | cyclohexyl |
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyanobenzoquinone |
| DIEA | diisopropylethlyamine |
| DMAc | *N*, *N*-dimethylacetamide |
| DME | 1,2-dimethoxyethane |
| DMPU | 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone |
| HMPA | hexamethylphosphoramide |
| L | ligand |
| LDA | lithiumdiisopropylamide |
| NMO | 4-methylmorpholine *N*-oxide |
| Py | pyridine |
| SAMP | (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine |
| TBAC | tetra-*n*-butylammonium cyanoborohydride |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| Ts | tosyl |

## IX. Acknowledgment

We thank the Swiss National Science Foundation, the 'Fonds Firmenich et Chuit', and Novartis-Pharma for the support of the Geneva laboratory research.

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