Chromium arene complexes in organic synthesis

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The complexation of an arene to a chromium tricarbonyl unit changes its chemical behavior, giving rise to unprecedented transformations. The electron-withdrawing effect of the unit allows efficient nucleophilic attack (S_NAr and dearomatization reactions), stabilizes negative charges in benzylic positions and activates C_{Ar}–halogen bonds for cross-coupling reactions. In addition, the $Cr(CO)_3$ moiety exerts great facial control so it can be used as an auxiliary that can easily be removed. The 1,2- and 1,3-unsymmetrically disubstituted complexes are planar chiral and there are various ways to prepare them in enantiomerically pure form. Planar chiral chromium complexes are becoming useful intermediates and ligands for asymmetric catalysis. This mature field of organometallic chemistry has given rise to several synthetic applications of chromium arene complexes in the synthesis of natural products. This chemistry is overviewed in this *tutorial review*, giving special attention to the most recent and outstanding contributions in the area.

1. Introduction

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

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Gema Domínguez

de-coordinate chromium are exposure to light or treatment with I_2, ceric ammonium nitrate, CO, PPh_3, or pyridine.

Chromium arene complexes are synthesized mostly by thermolysis of $Cr(CO)_6$ under an inert atmosphere in a high-boiling solvent, for a long period (up to 4 days). The main problem is the sublimation of the $Cr(CO)_6$. This is minimized using a mixture of the arene, dibutyl ether, and THF as solvent. The use of special apparatus or other homemade tricks is also frequent. Alternatively, they may be prepared by arene exchange from naphthalene chromium tricarbonyl or with $Cr(CO)_3L_3$, L being a two-electron ligand (ammonia, pyridine, acetonitrile or propionitrile) (Scheme 1).[1]

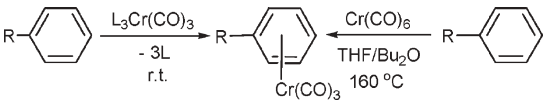
With regard to generality of the synthesis, the direct access to vinyl-, alkynyl-, aryl- and electron-withdrawing group-(EWG) substituted complexes is not general. The low electron density of aromatics bearing EWGs makes complexation of the metal difficult, whereas complexation of phenyl-substituted alkynes, alkenes or arenes generally proceeds with low yields and with poor chemo- and regioselectivity.[2]

Complexation to metals gives arenes unprecedented reactivity that has been extensively studied by many groups. Fig. 1 summarizes the main reactions. Due to the electron-withdrawing properties of the $Cr(CO)_3$ unit, the ring can be deprotonated. Benzylic anions are readily formed and, despite the electrophilic character of the $Cr(CO)_3$ group, benzylic carbocations are also stabilized, which is explained in terms of the neighbouring group effect. In addition, the $Cr(CO)_3$ moiety blocks one side of the molecule and has found widespread use as a 'stereodirecting' group in reactions at side chains.

1.1. Stereochemical aspects of chromium arene complexes

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

Thus, compounds such as **1** cannot be superimposed on their mirror images ***ent*-1** because they are planar chiral. Although the names of these chiral compounds have been addressed using two different approaches (that give opposite



Scheme 1

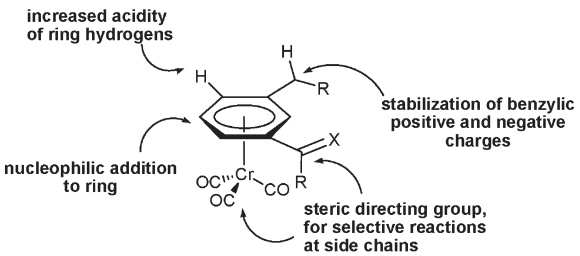


Fig. 1

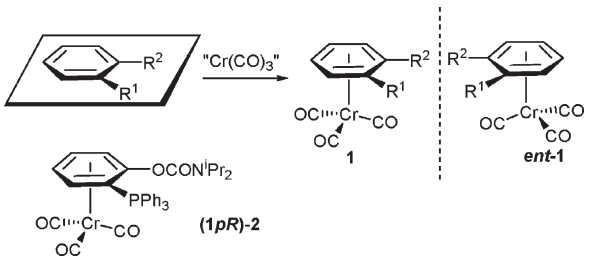


Fig. 2

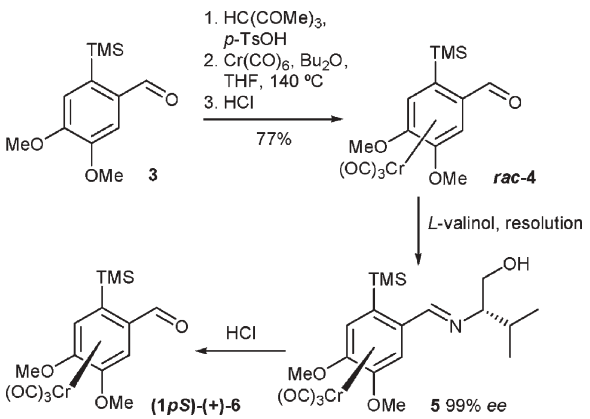
descriptors), namely, the rules introduced by Schlög and the extended Cahn–Ingold–Prelog rules, the latter have found more acceptance.[3] Following this approach, all carbons of the coordinated arene ring may be named as if they were tetrahedral, the chromium atom being one of the substituents. For practical reasons, in most cases it is sufficient to classify only the stereogenic centre with the highest priority substituent. To specify the element of chirality, a (*p*) for planar is frequently put in front of, or after, the assignment attributed to the planar chirality. Thus, a complex such as **2** would be named **(1*pR*)-2**.

2. Preparation of enantiomerically pure chromium arene complexes

Enantiomerically pure planar chiral complexes can be obtained by resolution, *via* diastereoselective synthesis and by enantioselective methods.

2.1. Racemate resolution

Racemic mixtures of chiral chromium complexes can be separated by means of interaction with chiral molecules or by chiral chromatography. These methods are the most classical but still used by many groups as they are experimentally easy to perform. Thus L-valinol is an efficient agent to resolve racemic planar chromium arylaldehyde complexes. One recent example is the synthesis of **(1*pS*)-(+)-6**, an intermediate in the synthesis of (−)-lasubine (*vide infra*), by resolution of chiral racemic complex ***rac*-4** with L-valinol (Scheme 2).[4]



Scheme 2

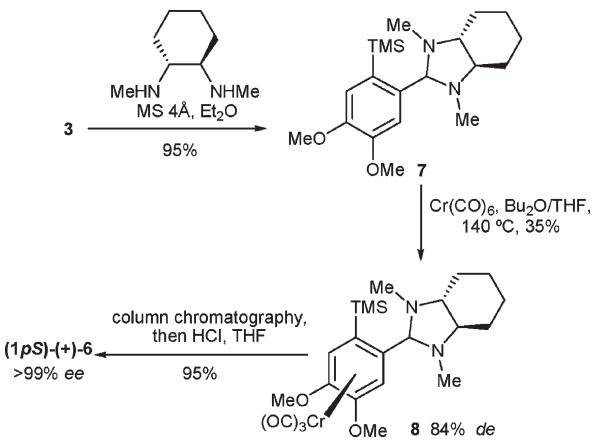
2.2 Renewable chiral auxiliaries

The selective complexation of the $Cr(CO)_3$ fragment to one of the diastereotopic faces of enantiomerically pure arene substrates is commonly carried out through the use of chiral auxiliaries, mainly chiral acetals or aminals.[5]

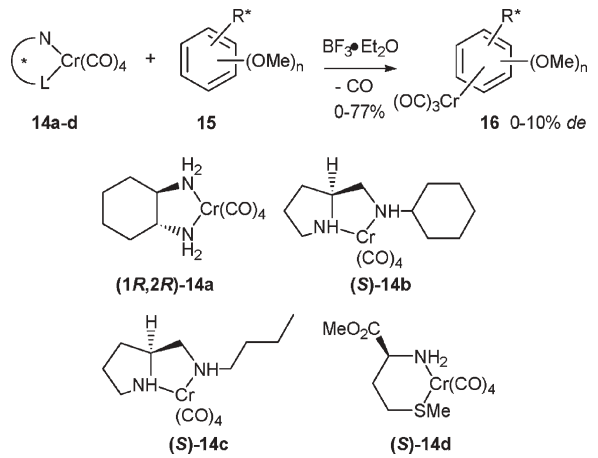
This strategy has two variants, that is, complexation to a prochiral 1,2- or 1,3-disubstituted arene that previously is transformed into a chiral acetal or aminal, or diastereoselective lithiation of the complexed benzaldehyde derivative.

One example of the first possibility is an alternative synthesis of fragment **(1*pS*)-(+)-6** in the above-mentioned total synthesis of (−)-lasubine.[4] The authors performed the alternative synthesis of **(1*pS*)-(+)-6** by diastereoselective complexation of aminal **7** and hydrolysis of complex **8** (Scheme 3).

The other strategy, that is, the diastereoselective *ortho*-lithiation of chiral acetal and aminal complexes, has found great use recently. Uemura *et al*. reported the synthesis of *ortho*-brominated 3,4,5-trialkoxybenzaldehyde complex **(+)-11** using a chiral acetal complex of benzaldehyde. The diastereoselective bromination of 3,4,5-trialkoxy-substituted benzaldehyde acetal complex **10** gave **(+)-11** with excellent ee and moderate chemical yield. The authors explained the preference



Scheme 3



Scheme 5

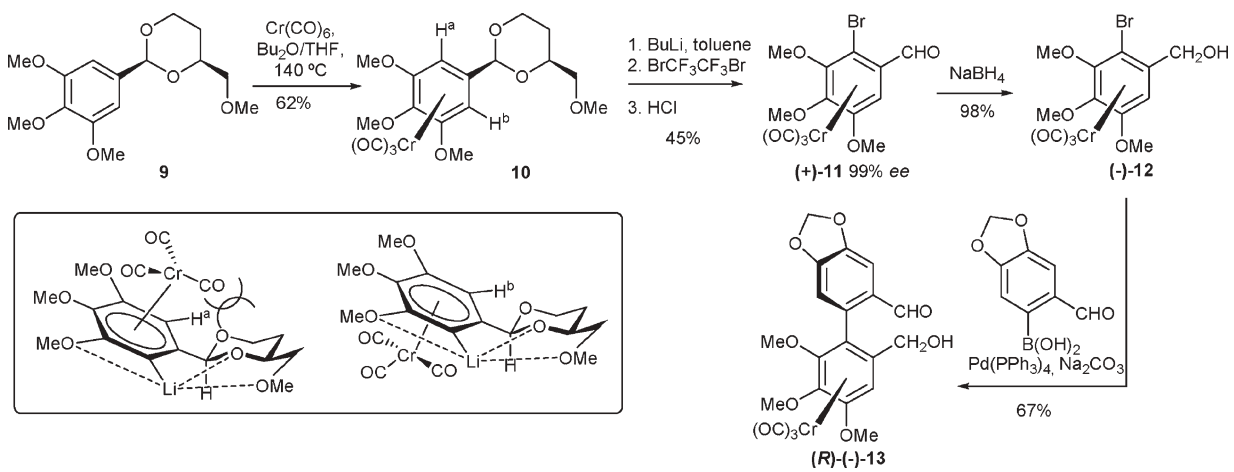
for hydrogen H^a as due to a directive effect of the 1,2,4-butanetriol. This type of acetal was much more effective than traditional tartrate derived chiral acetals, used thoroughly in the literature. The brominated planar chiral complex **(−)-12** was used as the coupling partner in diastereoselective Suzuki–Miyaura cross-couplings with arylboronic acids *en route* to the synthesis of (−)-steganone (Scheme 4).[6]

An interesting attempt by Butenschön and Strotmann, devoted to obtaining chiral complexes, consisted of situating chiral auxiliaries in the metal moiety to be delivered. They used chiral bidentate amines coordinated to $Cr(CO)_4$ as transfer agents. Unfortunately, they achieved negligible de in the reactions with a number of chiral arenes (Scheme 5).[7]

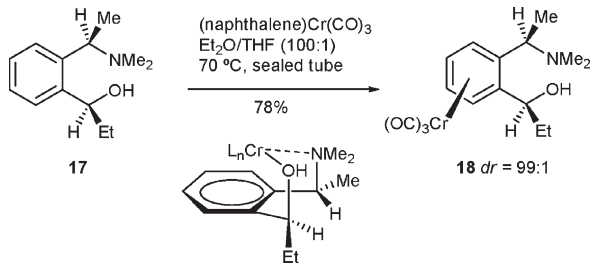
2.3. Complexation to enantiopure arenes

Simple discrimination of the two faces of unsymmetrically substituted rings works partially with fused arenes and has been used in a number of early works only.[8]

It is more efficient to deliver the $Cr(CO)_3$ fragment to one diastereotopic face with the aid of a heteroatom, which is generally attached to a chiral centre situated at benzylic position.



Scheme 4



Scheme 6

Uemura *et al*. used heteroatom delivery to prepare complex **18** with 99 : 1 facial selectivity. Success of this approach relied on the complexation of aryl amino alcohol **17**, bearing two directing heteroatoms (Scheme 6).[9]

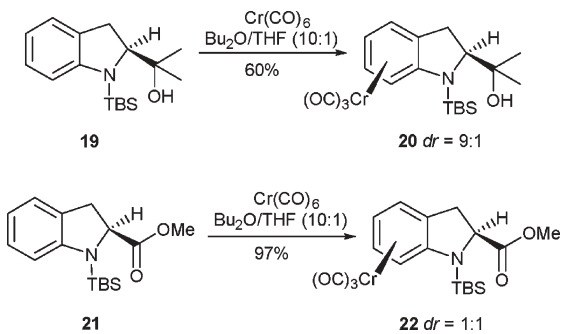
More recently, Jones reported the selective complexation (9 : 1) of indoline **19** by heteroatom delivery. The related carbomethoxy indoline **21** was complexed without selectivity, which is a proof of the participation of the heteroatom in the facial discrimination (Scheme 7).[10]

2.4. Intramolecular transfer of central chirality

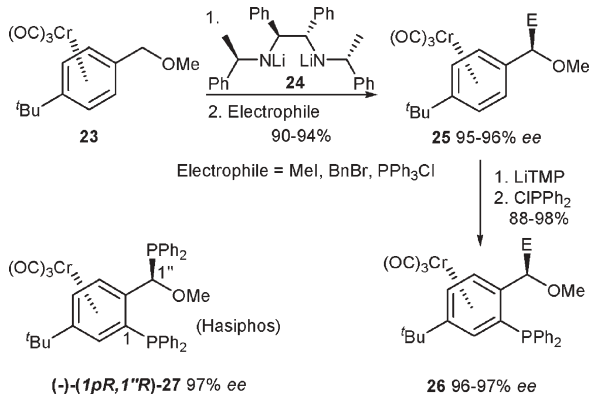
Another strategy closely related to the previous one is the use of heteroatoms attached to chiral centres in benzylic positions to direct *ortho*-lithiation, thus creating planar chirality. The increased acidity of aromatic hydrogens of complexed arenes facilitates deprotonation with lithium alkyls and amides.

Some of the most used starting materials are those derived from enantiopure α-methylbenzylamines. Recently, several groups have improved the scope of this approach introducing different heteroatoms and substituents at the benzylic position.

Gibson *et al*. reported a highly chemo- and diastereoselective OMe group-directed *ortho*-lithiation–electrophilic quench sequence starting from complex **23**. An enantioselective lithiation mediated by chiral bis(amide) **24**, followed by an electrophilic quench, gave complexes **25** in high enantiomeric purity. Reaction of **25** with lithium tetramethylpiperidide (LiTMP), followed by electrophilic quench with $ClPPh_2$, gave complexes **26** (Scheme 8).[11] The *tert*-butyl at the *para*-position avoided substitution at the *meta*- and *para*-positions. The electrophiles used were not only carbonated but also phosphorus electrophiles. In this way, they obtained a useful ligand for asymmetric catalysis named ''Hasiphos'', **27**, *via* a second phosphination at the *ortho*-position of **25**.



Scheme 7



Scheme 8

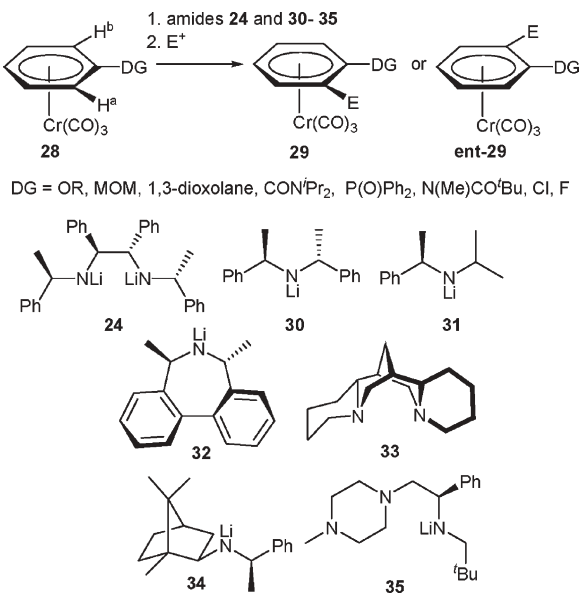
2.5. Enantioselective lithiation

Complexes carrying heteroatom-containing substituents can be *ortho*-deprotonated by chiral lithium amides to give desymmetrized lithiated arenes that may be quenched with appropriate electrophiles. This strategy has been developed by several groups and reviewed recently.[12]

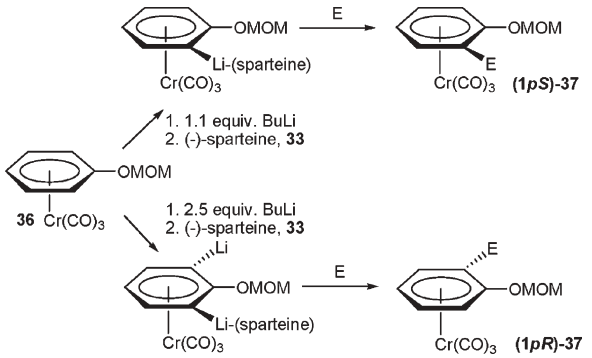
Scheme 9 shows the amides that have reached popularity in this field. Amides **24** and **30** are widely used with several directing groups as an entry to many chiral functionalized complexes.

One spectacular example of this methodology is the use of (−)-sparteine **33**, as the base. This amide allows the synthesis of both enantiomers of the chiral chromium complex **37** just by altering the equivalents of base used. When 1 equivalent of diamine **33** and *n*-BuLi is used, it gives, after electrophilic quench with $(CH_2O)_n$, the planar chiral complex **(1*pS*)-37** in 58% yield and 92% ee. On the other hand, using 2.5 equivalents of diamine **33** and *n*-BuLi, complex **(1*pR*)-37** was obtained in 95% ee and in 30% yield (Scheme 10).[13]

The differentiation of enantiotopic *ortho*-hydrogens by chiral non-racemic amides can be extended to enantiotopic



Scheme 9



Scheme 10

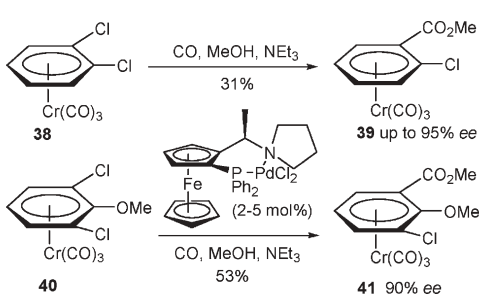
benzylic hydrogens. This variant is based on the stabilization of benzylic charges by chromium and will be outlined below.

2.6. Desymmetrization of prochiral complexes

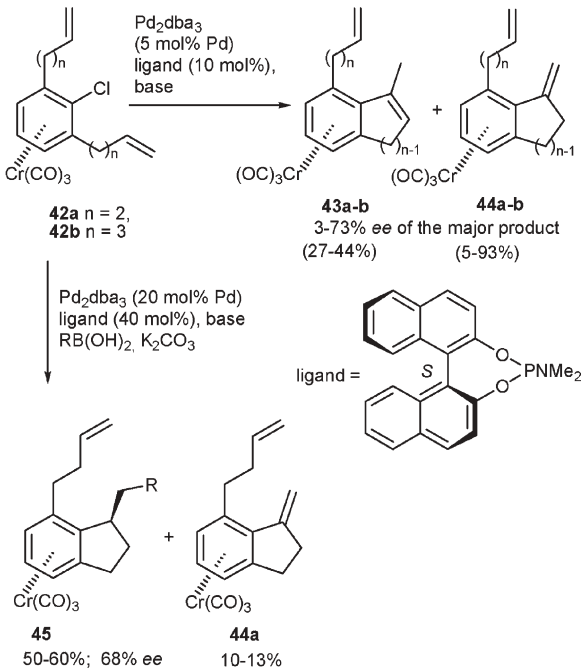
Desymmetrization of prochiral arene–$Cr(CO)_3$ complexes is becoming an important entry into planar chiral bifunctional chromium complexes. Generally, palladium-catalyzed monofunctionalization of 1,2-dichlorobenzene chromium(0) tricarbonyl is used, following initial reports by Uemura *et al.* in 1994. In a recent study, Gotov and Schmalz achieved up to 95% ee in the methoxycarbonylation of complex **38**, albeit that the yield was 31%. Several chiral Pd-catalysts were allowed to react with **38** in a 2 : 1 mixture of MeOH and NEt_3, under 1 atm of CO and in the presence of a chiral ferrocene ligand (*R*,*S*)-PPF-pyrrolidine (PPF = diphenylphosphinoferrocenyl). It was found that the enantioselectivity strongly depends on the reaction time. The initial enantioselectivity is enhanced by a subsequent kinetic resolution connected to the formation of the bis(methoxycarbonylated) by-product (Scheme 11).[14]

More recently, this methodology has been used with 1,3-dichloroarene chromium tricarbonyl complexes. In a reaction of 2-methoxy-substituted substrate **40** with the same ferrocenyl complex, the authors achieved **41** with a high ee, in moderate chemical yield (Scheme 11).[15]

Uemura *et al.* have recently performed an asymmetric intramolecular Mizoroki–Heck reaction of prochiral tricarbonyl(2,6-dibutenylchlorobenzene)chromium **42** in the presence of a chiral phosphine–palladium catalyst, which gave the corresponding bicyclic chromium complex. After surveying chiral ligands for the asymmetric intramolecular Mizoroki–Heck reaction, they selected a chiral phosphine and optimized the reaction, reaching 73% ee. They finally developed an



Scheme 11



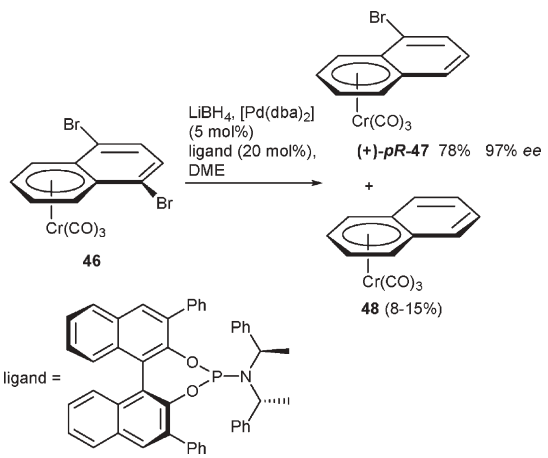
Scheme 12

asymmetric cascade Mizoroki–Heck reaction/Suzuki–Miyaura cross-coupling reaction that gave the desired *exo*-benzyl substituted indan derivative **45** as a single diastereomer in 50–60% yield with 68% ee (Scheme 12).[16]

Desymmetrization of *meso*-dihalides by asymmetric hydrogenolysis has been reported recently. Hydrogenolysis of **46** using a phosphoramidite ligand afforded complex **(1*pR*)-(+)-47** in good yield and high ee. The chiral induction in the reaction arises entirely from the recognition of one of the enantiotopic C–Br units in complex **46** (Scheme 13).[17]

2.7. Dötz reaction

The Dötz benzannulation is an alternative approach towards the synthesis of chromium *para*-dioxygenated arene complexes. This approach consists of the construction of the complexed arene ring from an alkyne and an unsaturated



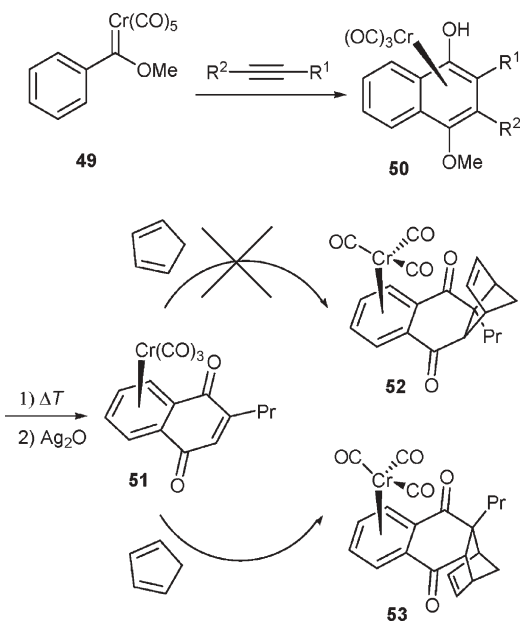
Scheme 13

alkoxy pentacarbonyl chromium carbene complex. Thus, the complexation reaction does not take place and some chromium complexes that are not accessible by other routes can be obtained this way. Recently, Dötz performed an efficient synthesis of tricarbonyl(naphthoquinone)chromium complex **51**, through a sequence based on the benzannulation of phenyl(methoxy) carbene complex **49** by alkynes, haptotropic metal migration of the kinetic benzannulated products, and a final oxidation to naphthoquinone complexes **51** (Scheme 14).[18] Complex **51** stereoselectively adds cyclic and acyclic dienes to its sterically less hindered face to give *endo* [4 + 2] cycloaddition products in good to excellent yields.

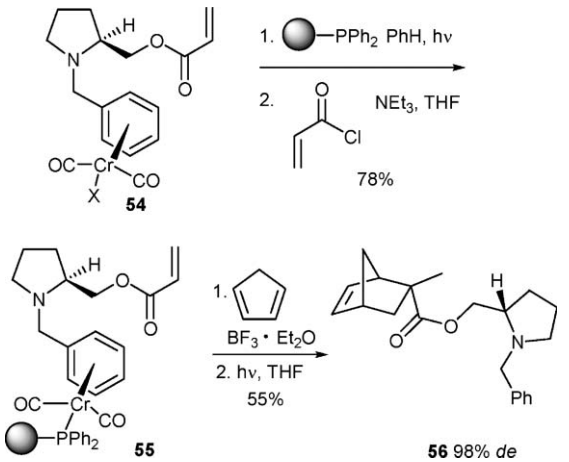
3. General reactivity of chromium arene complexes

Arene chromium tricarbonyl complexes are powerful reagents in stereoselective organic synthesis, and are compatible with many reaction conditions. The electron-withdrawing properties of the metal fragment (they are compared with nitrobenzene) result in nucleophilic additions to the arene, and nucleophilic substitution at benzylic and homobenzylic positions. Moreover, the steric bulk of the metal carbonyl moiety effectively shields one face of the arene and this has been widely exploited in diastereoselective synthesis. Finally, chiral arene complexes have been used as ligands or substrates in efficient enantioselective reactions.

The ability of the chromium tricarbonyl moiety to block one π face of the arene has been used to direct [4 + 2] cycloaddition reactions of (hetero)dienophiles and dienes. In one recent example, Jones described the design and synthesis of a chiral auxiliary template, designed on the basis of the π-shielding capability of L-proline.[19] Cycloaddition to an acrylate derivative gave high *endo* preference, and diastereoselectivities as high as 99%. The electronic factors contributing to the selectivity were probed, and the technology successfully applied to a polymer supported variant (Scheme 15).



Scheme 14



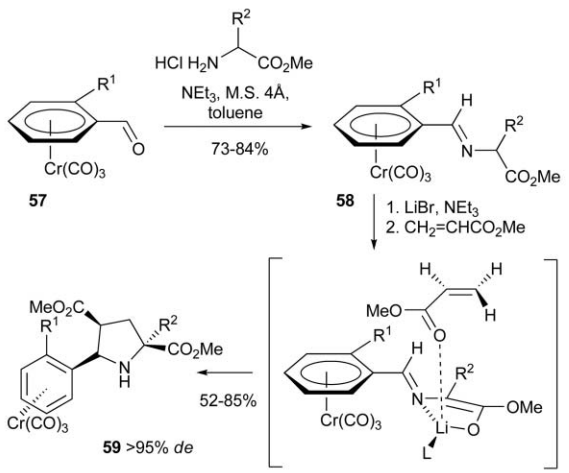
Scheme 15

Dipolar [3 + 2] cycloadditions with planar chiral arene tricarbonyl complexes allowed the synthesis of enantiopure trisubstituted pyrrolidines. The regioselectivity of the cycloaddition could be controlled by the choice of the Lewis acid used (Scheme 16).[20]

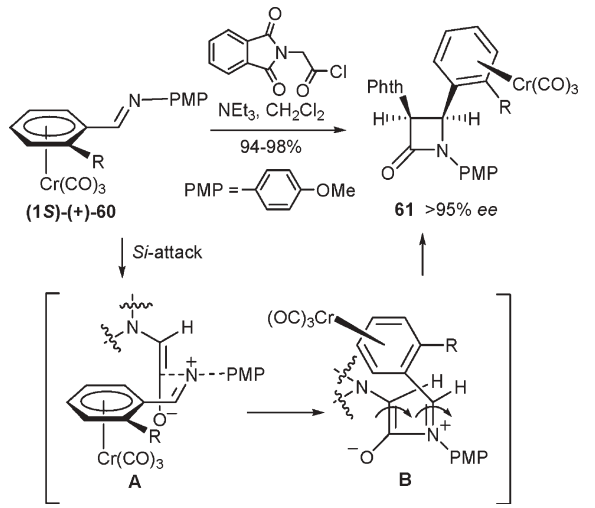
The facial discrimination of these compounds has also given rise to highly diastereoselective [2 + 2] cycloadditions of complexed imines used for the synthesis of 2-azetidinones (Scheme 17).[21]

Compatibility of arene chromium complexes with reactions in which other metals are present is exemplified in several reports regarding the chemistry of Fischer carbene complexes. Reaction of chiral homobinuclear Fischer chromium and tungsten carbene complexes with allyl alkoxide, NaH and the following oxidative demetalation gave α-allyl esters and α-allyl-β-hydroxy esters respectively, in up to 97% ee. The reaction involved a [3,3]-sigmatropic rearrangement promoted by the metal 1,3-shift (Scheme 18).[22]

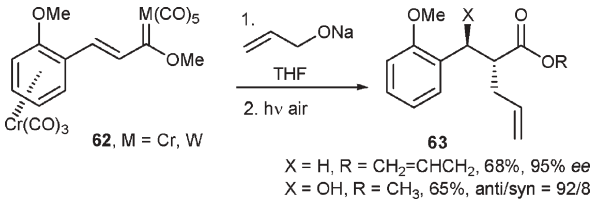
As a continuation of these studies, the same group examined the asymmetric version of the [3 + 2 + 2] cycloaddition reaction developed by Barluenga utilizing chiral binuclear Fischer carbene complexes.



Scheme 16

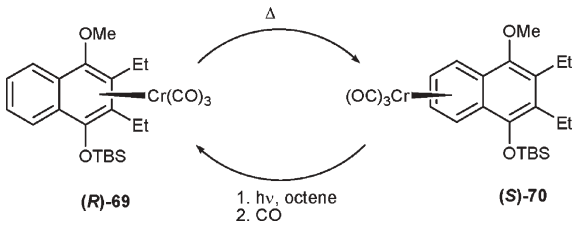


Scheme 17



Scheme 18

The reaction of binuclear Fischer carbene complex **62** with 1-pentyne in the presence of a stoichiometric amount of $Ni(cod)_2$ gave the bis(tricarbonylchromium)-coordinated 7-aryl cycloheptatriene derivative **66** *via* the [3 + 2 + 2] cycloaddition in 47% yield with high diastereoselectivity (dr >98 : 2). This binuclear chromium complex with two planar chiralities was submitted to several transformations. Thus, nucleophilic addition–dearomatization gave enyne **67**, which, upon an intramolecular Pauson–Khand reaction, gave tricyclic diketone **68** as a single diastereomer. The chromium



Scheme 20

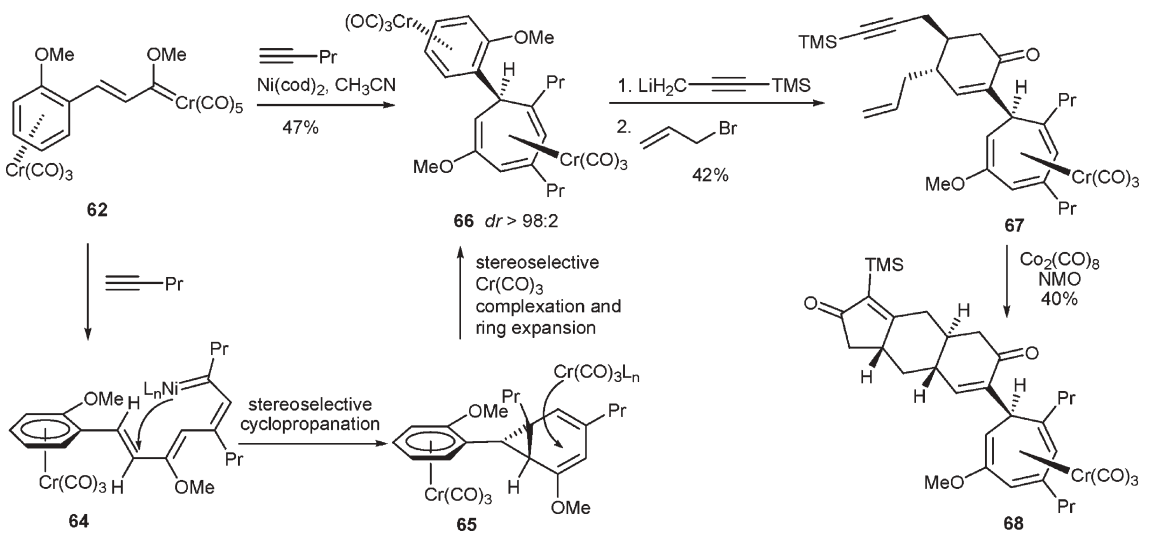
tricarbonyl fragment of the cycloheptatriene ring binds to the heptatriene ring without influence in a series of these reactions. (Scheme 19).[23]

Coordinated metals can undergo haptotropic migrations between the rings of certain polycyclic arene–metal complexes. The best studied systems are anionic chromium tricarbonyl complexes in which the $Cr(CO)_3$ group migrates from a neutral to an anionic ring. Haptotropic migrations are also well-known for neutral systems in which the $Cr(CO)_3$ group equilibrates between two rings, Recently, Dötz reported a haptotropic $Cr(CO)_3$ migration in a naphthalene complex that can be used as a molecular switch (Scheme 20).[24]

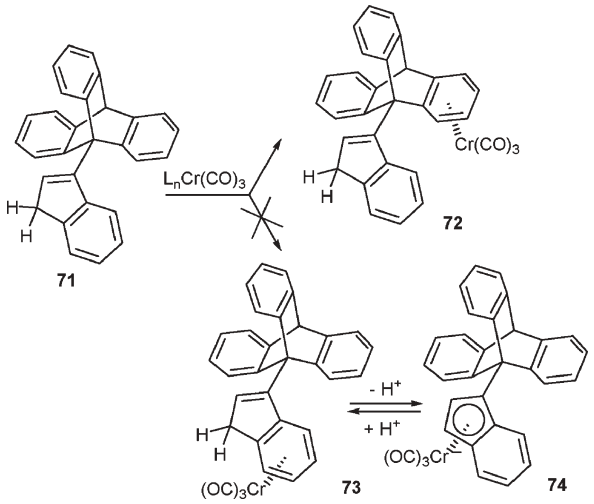
The potential use of haptotropic shifts to control rotational barriers has been shown by the synthesis of (9-indenyl)triptycene **71** and its chromium tricarbonyl derivative, **72**. These complexes revealed barriers to rotation of 12 and 13 kcal mol^{-1}, respectively, as shown by variable-temperature NMR spectroscopy. The chromium carbonyl moiety coordinates to one of the blades of the triptycene unit rather than to the more crowded indenyl group (Scheme 21).[25]

3.1 Stereoselective chromium-mediated transformations of arenes *via* nucleophilic attack

The strong electron-withdrawing ability of the $Cr(CO)_3$ group makes haloarene chromium complexes prone to suffer nucleophilic attack. The scope of reactive nucleophiles for the addition reaction ranges from sulfur-stabilized carbanions to alkyl, vinyl, and aryl lithium reagents, with the exception of



Scheme 19



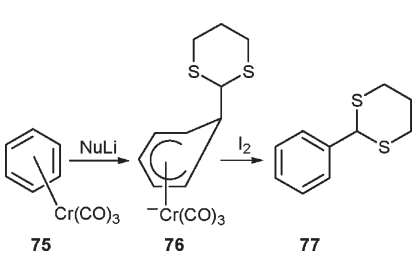
Scheme 21

n-BuLi and MeLi, which generally act as bases except if an imine is attached to the aromatic ring. The addition of the nucleophile occurs *ipso*, *ortho*, *meta*, or *para* to pre-existing substituents. The regioselectivity of this reaction is hard to predict as it depends on a plethora of factors, from the nature and the relative positions of the substituents on the arene ring, to the conformation of the $Cr(CO)_3$ tripod and the nucleophile. There are a couple of excellent reviews that cover this chemistry comprehensively so we will summarize the main aspects and give an account of the most recent work.[26]

In a typical reaction, 2-lithio-1,3-dithiane reacts with benzene chromium tricarbonyl to give an anionic η^5-cyclohexadienyl complex **76**. This intermediate has been characterized by X-ray diffraction analysis by Semmelhack *et al*.[27] Oxidation of **76** with of I_2 gives the substituted arene **77** (Scheme 22).

Semmelhack *et al*. established a list of nucleophiles that can be used for these reactions, and, although it was published long time ago, it is still useful for simple aromatic complexes (Table 1).[27]

Some nucleophiles, such as certain hydrides, have joined the list of successful reagents. Carbon nucleophile addition to a substituted complex gives four possible products. The nucleophile can react at the *ipso*-carbon atom, bearing the X group, or at the positions *ortho*, *meta*, or *para* to the X group. The regioselectivity of the nucleophilic addition under kinetic control is influenced by substituents on the arene and by the conformation of the $Cr(CO)_3$ group. Under thermodynamic control, the equilibrium depends on steric and electronic interactions in the intermediate anions. The problem of kinetic



Scheme 22

Table 1 Representative sample of carbanions tested with benzene chromium tricarbonyl

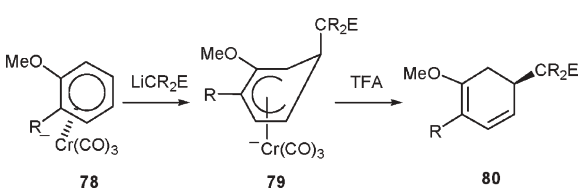
Unreactive carbanions	Successful carbanions	Ring metalating reagents
$LiCH(CO_2{}^tBu)_2$	$LiCH_2CO_2{}^tBu$	BuLi
MeMgBr	$LiCH_2CN$	MeLi
Me_2CuLi	$LiCH_2SPh$	^{s}BuLi
	2-Li-1,3-dithiane	
	LiCH=CHR	
	LiPh	
	$LiCMe_3$	

vs. thermodynamic control is rather difficult in this reaction because the difference between both is generally small. Adequate choice of the solvent can slow down the rate of equilibration (mixtures of THF and HMPA or HMPT are best used for this purpose). Arenes with donor acceptors are usually attacked at a *meta*-position, while bulky groups direct to *para*. Groups that can coordinate the attacking reagent direct to *ortho*.

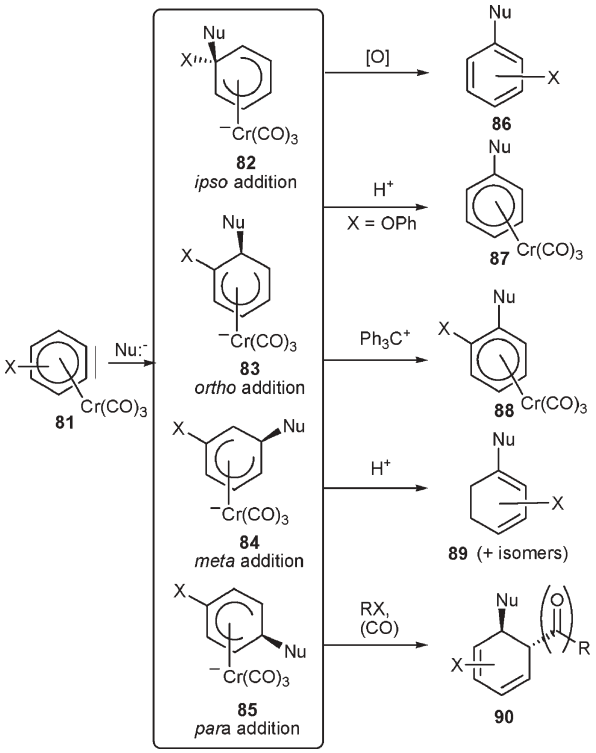
In particular, nucleophilic addition to methoxy-substituted arene–$Cr(CO)_3$ complexes is known to give *meta*-substitution. This has been investigated by theoretical methods using density functional calculations employing the hybrid-DFT approach. It was demonstrated that the preferred reaction pathway proceeds *via* the most stable intermediate. (Scheme 23).[28]

After the nucleophilic attack, several pathways are possible. Oxidation (I_2, Ce(IV), Fe(III), O_2) gives an arene with a new substituent (substitution of C–H). Reaction of the intermediate with other electrophiles traps the intermediate only when the nucleophilic addition is irreversible (if it is reversible the original arene complex is recovered upon electrophilic attack). If there is no leaving group, the reaction of the cyclohexadienyl intermediate with strong acids or carbon electrophiles is a dearomatization, resulting in a cyclohexadiene. Carbon electrophiles react with the anionic intermediate by coordination to the metal center and further *endo*-migration to the cyclohexadienyl ring. Thus, the stereochemical relationship in the product is *trans*. With certain electrophiles, migratory CO insertion precedes the reductive elimination (Scheme 24).

Sequences that conserve the metal group, thus allowing further transformations, are highly desirable. This goal is achieved, provided a leaving group is present, by treatment of the anionic intermediate with acids. The complete sequence implied is nucleophilic addition–protonation–possible isomerizations of the cyclohexadiene intermediate–elimination to aromatize the product. The incoming group can attack in four possible orientations with respect to the leaving group, thus giving *ipso*-, *cine*-, and *tele*-substitutions (the latter with two possibilities, *tele–meta* and *tele–para*).



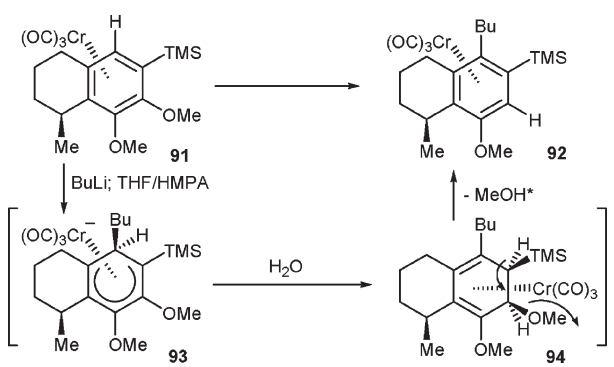
Scheme 23



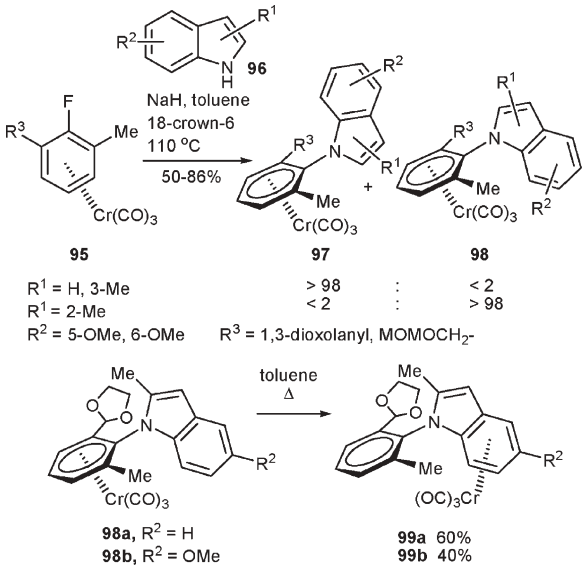
Scheme 24

Recent examples of these approaches follow. Schmalz *et al.* have shown that *tele*-substitution is the major pathway in S_NAr reactions of *ortho*-alkylated η^6-anisoles complexed to $Cr(CO)_3$. In this context they have also reported that addition of *n*-BuLi to tetralin derivative complex **91** in THF–HMPA gives a high yield of complex **92**. These reactions are *tele–meta*-substitutions with methoxide as the leaving group (Scheme 25).[29]

Kamikawa *et al.* obtained recently *N*-aryl indoles with axially chiral bonds by stereoselective nucleophilic aromatic substitution reactions of planar chiral arene chromium complexes. The nucleophilic substitution reaction took place between an indolyl anion and optically active dioxolanyl-methylfluorobenzene chromium tricarbonyl, **95**, in the presence of 18-crown-6 in refluxing toluene. The authors also found that when sterically hindered *N*-aryl indole chromium complexes **98a**,**b** were refluxed in toluene, a stereoselective



Scheme 25

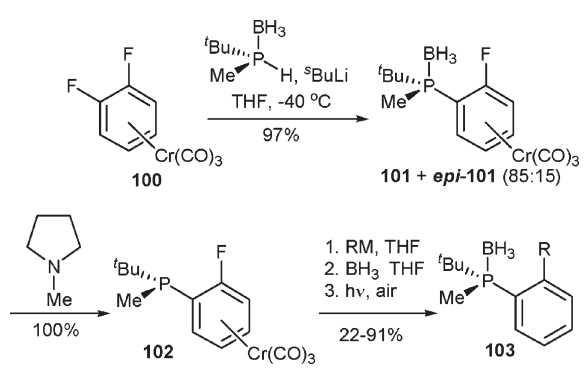


Scheme 26

migration of the chromium tricarbonyl group to the arene ring of the indole occurred, giving **99**. The 1,3-dioxolane group was crucial for this reaction (Scheme 26).[30]

Optically pure, P-chiral (dialkyl)arylphosphine boranes **101** were prepared by two component coupling of fluorobenzene chromium tricarbonyl complexes and P-chiral secondary phosphine boranes. The stereochemical integrity at the P-stereogenic center was completely retained during the S_NAr process when the reaction was carried out in THF, at low temperature. These products could be further elaborated *via* nucleophilic substitution to provide P-chiral arylphosphine borane derivatives **103** bearing a functional group at the *ortho*-position (Scheme 27).[31]

The one-pot dearomatization procedure consisting of nucleophilic addition, electrophilic addition, and decomplexation of η^6-anisole chromium tricarbonyl has been extended recently to prochiral nucleophiles in the dearomatization procedure, which leads to the formation of two new adjacent stereocenters. Anisole chromium tricarbonyl complexes **104**, with a bulky group at the 4-position, were chosen for the study. The nucleophile selected was *tert*-butyl lithiopropionate with HMPA as additive. The addition was, as expected, *meta* to the methoxy substituent, although with some substrates,



Scheme 27

considerable *ortho*-attack was observed. The addition of *tert*-butyl lithiopropionate to 4-trimethylsilylanisole chromium tricarbonyl **104**, followed by protonation gave diene **106** not only with excellent regioselectivity but also vicinal stereocontrol (>99 : 1). These results were applied to a formal synthesis of (±)-*erythro*-juvabione (Scheme 28).[32]

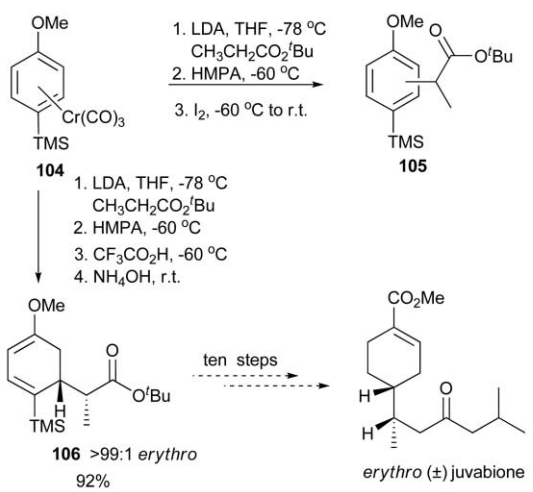
3.2. Metalated chromium arene complexes

3.2.1. Synthesis of heterobimetallic arene complexes. There is a wide experience in the synthesis of bimetallic complexes derived from arene–$Cr(CO)_3$ complexes.[33] The routes to heterobimetallic complexes start with the classical deprotonation–lithiation reactions that have been outlined above. In this context, even triple simultaneous lithiations are possible, so trisubstitution can be performed in a one-pot procedure.

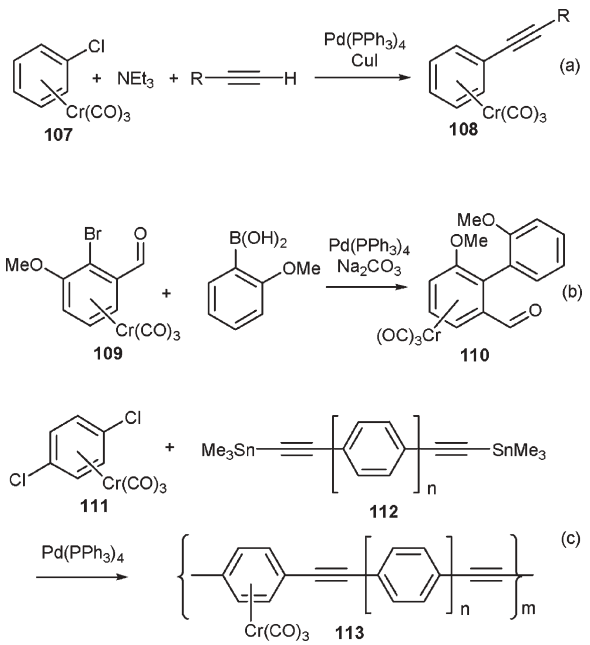
Other routes include transmetalation, ligand exchange, aromatic nucleophilic and electrophilic additions of anionic and cationic metal complexes, and oxidative addition for cross-coupling reactions in aromatic carbon–halogen bonds. For the purpose of this review we will focus on those bimetallic complexes that are obtained to produce synthetic organic transformations.

3.2.2. Reactions and applications of metalated chromium arene complexes. The carbon–halogen bond of aryl halide chromium tricarbonyl complexes is electron-deficient, which facilitates the oxidative addition step of the carbon–carbon coupling reactions. This fact, jointly with the efficient blockage of one face of the aryl halide, make chromium arene complexes especially attractive for palladium catalyzed cross-coupling reactions.

In situ formed Cu(I), Zn(II), Cr(0) bimetallic species have been studied in palladium-mediated cross-coupling reactions with haloarenes, vinyl chlorides, acyl chlorides and allylic halides. Moreover, the palladium-catalyzed carbonylation of η^6-chloroarene–$Cr(CO)_3$ complexes has been described, although not always with good yields, using Pd(II) pre-catalysts. The products were the corresponding esters, amides, oxoamides and aldehydes in various ratios. In addition, a wide



Scheme 28

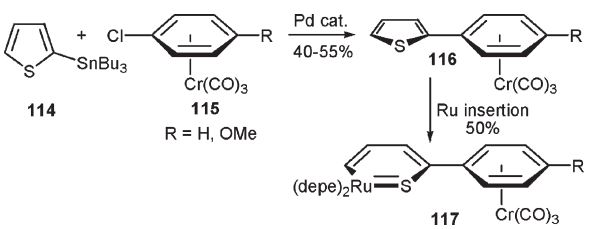


Scheme 29

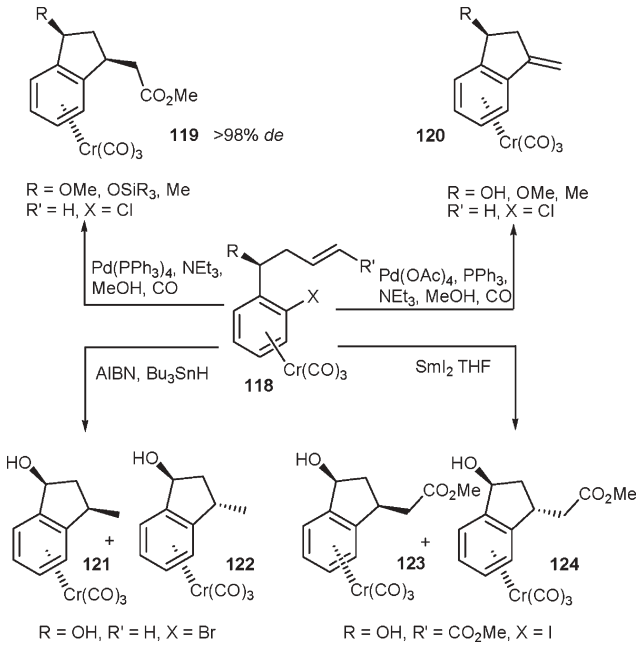
variety of cross-coupling reactions such as the Sonogashira (a), Suzuki–Miyaura (b) or Stille (c) types, as well as the catalytic Heck olefination, have been developed (Scheme 29). Recent reviews account for this chemistry.[33] In general, Br or I derivatives are preferred due to their better reactivity but fluoroarene chromium tricarbonyl complexes have been used in Suzuki reactions with arylboronic acids. Common side reactions in all these couplings are carbonylation and decomplexation. Several authors have shown that the CO is supplied by the $Cr(CO)_3$.

Rose-Munch *et al.* have synthesised thienylanisole chromium tricarbonyl complexes using an efficient Stille coupling reaction. In a recent work they have shown the further insertion of ruthenium into a thienyl bond, giving **117** in 50% yield (Scheme 30; depe = 1,2-bis(diethylphosphino)ethane).[34]

Recent work by Kündig *et al.* describes the synthesis of indane complexes *via* intramolecular Pd-catalyzed carbocyclization Heck-type reactions with *ortho*-substituted planar chiral butenylhalobenzene–$Cr(CO)_3$ complexes. In the Heck reactions involving complexes **118** with a stereogenic benzylic center, the stereochemistry of the alkene carbopalladation was governed by the planar chirality of the substrate. Alternatively, the indanes were obtained by radical-mediated cyclizations initiated by tin hydride or carried out with stoichiometric amounts of samarium iodide (Scheme 31).[35]



Scheme 30

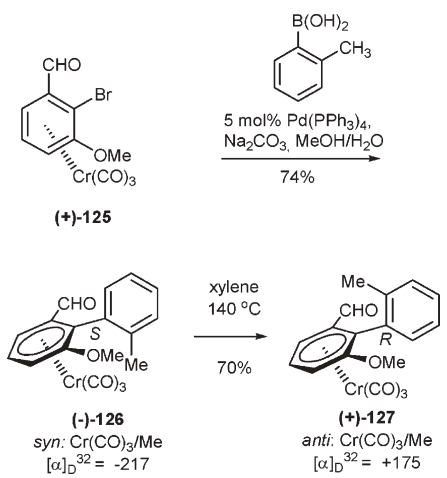


Scheme 31

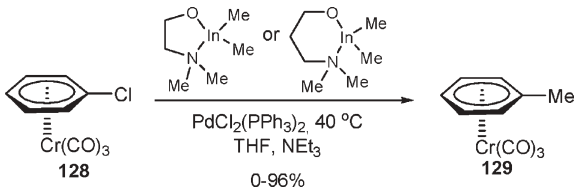
The Suzuki coupling of a chiral arene chromium tricarbonyl complex with a boronic acid, first developed by Uemura *et al*., is widely used for the synthesis of axially chiral biaryls. The axial chirality of biaryls arises from their atropisomerism, a phenomenon occurring in the presence of at least two bulky substituents in the *ortho*-position to this bond. Axially chiral biaryls are present in a number of natural products and also have been used as ligands for asymmetric catalysis.[36]

One recent example of this methodology is the reaction of complex **(+)-125** with *o*-tolylboronic acid in refluxing methanol. The kinetically favoured *syn*-chromium complex **(−)-126** was exclusively formed, while in refluxing xylene this complex underwent isomerization to the thermodynamically favoured *anti*-diastereoisomer **(+)-127** (Scheme 32).[37]

Coupling of alkyl groups onto arenes using palladium catalysis is also possible. Several contributions account for this possibility following the work by Jackson *et al.*, who described



Scheme 32



Scheme 33

the alkylation of haloarene chromium tricarbonyl complexes by zinc-activated amino acid residues. The most recent contribution is by Schmalz, who reported methyl *ipso*-substitutions of the chloroaryl chromium tricarbonyl complex **128** using methylindium derivatives and affording complexes **129**. The reactions took place in variable yields (Scheme 33).[38]

3.3. Reactions at side chains

The $Cr(CO)_3$ moiety has been described as ''hermaphroditic'' because of its ability to stabilize *both* benzylic cations *and* anions. Some computational studies showed that, also, radicals would be stabilized in the benzylic position, although this effect has been less exploited.[39] The chromium tricarbonyl moiety in arene systems is highly polarizable and thus inductively electron withdrawing, but directly electron donating. Whereas cationic carbon centers preferentially interact directly with the metal, anionic centers do not (Fig. 3).

3.3.1. Stabilization of positive charges. The ability of the $Cr(CO)_3$ moiety to strongly stabilize positive charges in the benzylic position is explained by a neighbouring group effect arising from an overlap of occupied d orbitals of the metal and the empty orbital of the carbenium centre. This anchimeric effect allows S_N1 reactions with conservation of the stereochemical information. Salzer *et al*. described the transformation of planar chiral complex **130** into a chloro derivative by treatment with chloroethyl chloroformate. The configuration of the benzylic chiral centre is retained in this transformation. The chloro substituent is displaced easily by different nucleophiles, giving P, N and O planar chiral complexes in high yield (Scheme 34).[40]

Müller *et al*. have studied planar chiral (*ortho*-substituted aryl) chromium tricarbonyl propargyl cations in their reaction with nucleophiles. In their most recent contribution, they described the reaction of **135** with silyl enol ether derivatives with poor, and with enamines with good facial diastereoselectivity to give rise to the corresponding arene chromium tricarbonyl-substituted propargylated derivatives **137** and **138**. The origin of facial diastereoselectivity in this case lay in steric and stereoelectronic biases rather than in purely electronic nucleophilicity (Scheme 35).[41]

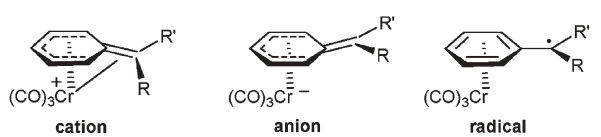
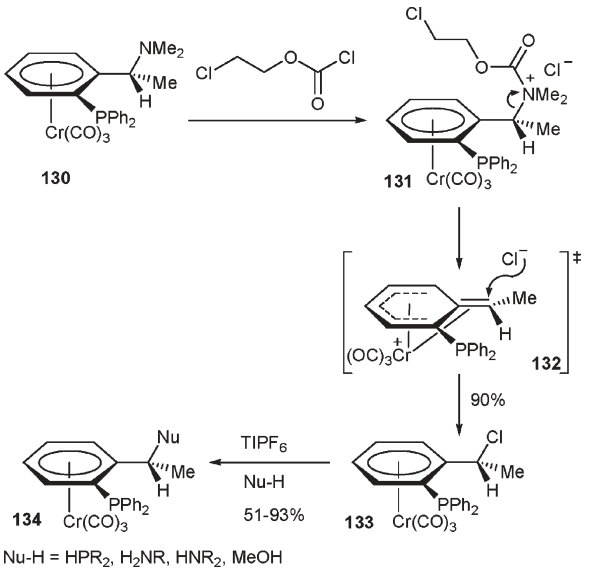
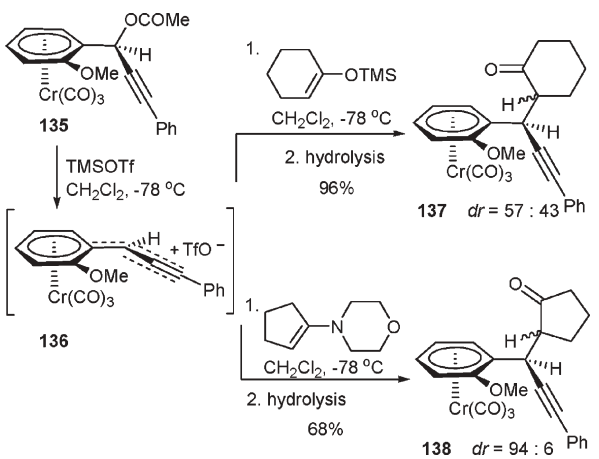


Fig. 3

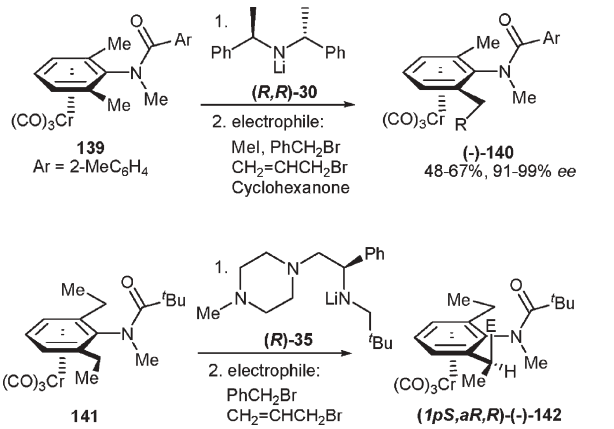


Scheme 34

3.3.2. Stabilization of negative charges. Negative charges at benzylic positions are also stabilized in chromium complexes due to the electron-withdrawing effect of the $Cr(CO)_3$ group. This has allowed efficient functionalizations of bicyclic structures such as complexed tetrahydroquinolines or tetrahydronaphthalenes. More recently, the desymmetrization strategy *en route* to planar chiral chromium complexes by enantioselective deprotonation with chiral bases has been extended to compounds with enantiotopic alkyl groups in *ortho*-positions. Thus, prochiral 2,6-dimethyl substituted amides and anilide chromium complexes **139**, were desymmetrized by Uemura *et al*. using chiral amides. Among the various amides tested, best results were achieved with **(*R*,*R*)-30**. After reaction with several electrophiles, atropisomeric benzamides **140** were obtained in up to 99% ee and moderate chemical yields. Control of the rotation of the amide bond was essential to achieve a high ee (Scheme 36).[42] An interesting extension of this work was the reaction with diethyl complex **141**. Amide **35** was able to deprotonate the *pro*-(*R*) proton of the methylene of only one of the ethyl groups. After reaction



Scheme 35



Scheme 36

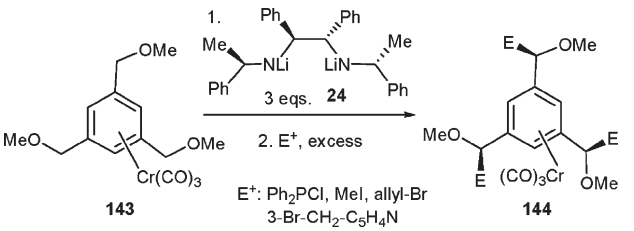
with the electrophiles, a single isomer **(1*pS*,*aR*,*R*)-142** was isolated. This compound bears central, axial and planar elements of chirality (Scheme 36).[42]

Very recently, Gibson *et al*. reported the synthesis of enantiopure C_3-symmetric molecules. A one-pot triple deprotonation, utilizing chiral-base **24**, served to install three stereocenters in the benzylic position of complex **143**. The trilithiated intermediate reacted with iodomethane, allyl bromide, ethylene oxide, chlorodiphenylphosphane and 3-bromomethylpyridine, giving good to excellent yields of enantiopure triderivatives (Scheme 37).[43]

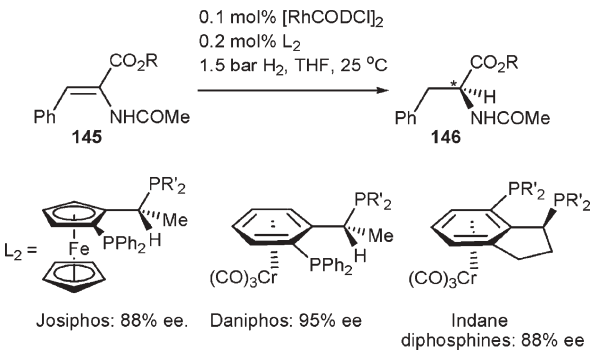
4. Chromium arene complexes in asymmetric catalysis

Chromium arene complexes have been successfully employed as chiral ligands for catalytic enantioselective hydrogenation, carbon–carbon coupling reactions, allylic sulfonation, hydrosilylation and hydroamination.[44] Salzer *et al*. investigated the rhodium-catalyzed enantioselective hydrogenation of double bonds using various diphosphine ligands based on benzene or indane chromium tricarbonyl complexes. The results using the so-called ''Daniphos'' ligand compare well with those obtained with similar ferrocene-based diphosphines such as ''Josiphos'', although the choice of solvent and reaction conditions is sometimes crucial. An example is the hydrogenation of methyl acetamidoacrylate **145** (Scheme 38).[45]

Gibson *et al*. described recently the synthesis of new planar chiral diphosphines and monophosphanes, which were used in two asymmetric catalytic reactions: an asymmetric hydrogenation, and the first asymmetric Heck reaction in which arene chromium(0) tricarbonyl-based ligands are used. The enantioselectivities measured were moderate to good, and lower than



Scheme 37

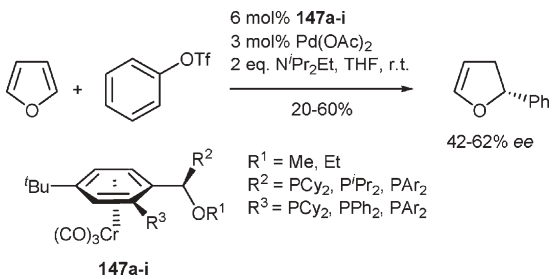


Scheme 38

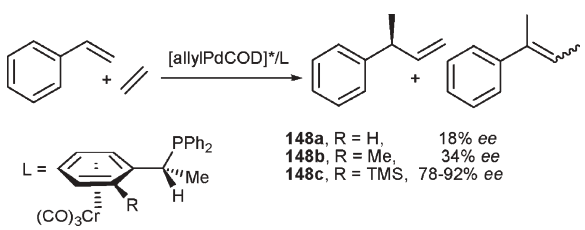
with some planar chiral ferrocene complexes in similar asymmetric catalysis (Scheme 39).[46]

Asymmetric hydrovinylation has been developed. Salzer *et al.* used complexed aryl monophosphines, achieving high activity and selectivity towards the codimers. Chemo- and enantioselectivity were improved with bulky *ortho*-substituents. Thus, the introduction of Me_3Si provided 70% conversion and 78.5% ee with little amount of isomerization products. Longer reaction times improved conversion but dropped selectivity towards 3-phenylbut-1-ene, and, due to a kinetic resolution, the ee of the product was raised to 92% (Scheme 40).[47]

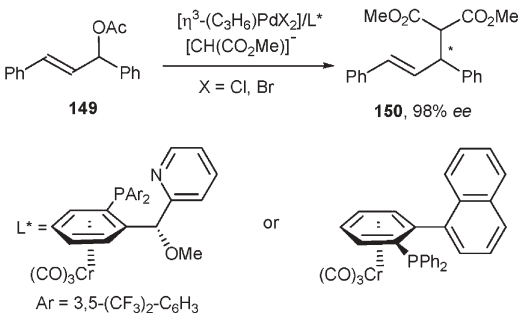
The palladium-catalyzed allylic alkylation reaction of 1,3-diphenyl-1-acetoxypropene **149** with malonate nucleophiles has been studied in detail by several groups. Chiral planar ligands were used, reaching ees of 98% and high yields. Interestingly, only the chiral plane seems to be responsible for induction, as ligands with chiral centres in their structure did not change the sense of the induction as a result of the configuration of the centre. In addition, the opposite configuration in the chiral plane of the chromium arene ligand gave products with opposite configurations (Scheme 41).[48]



Scheme 39



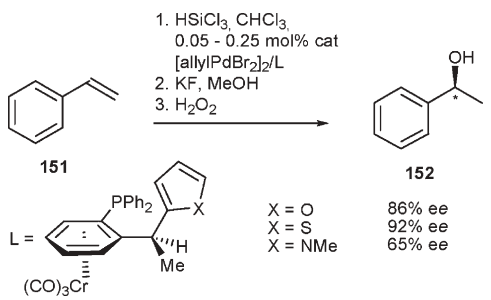
Scheme 40



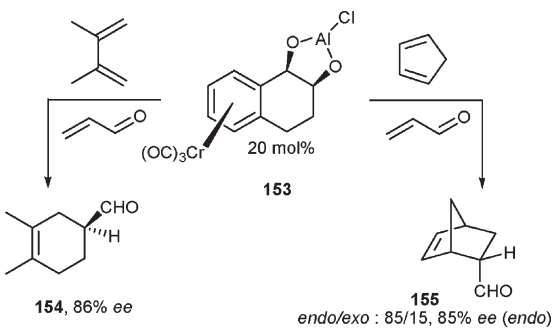
Scheme 41

Other enantioselective addition reactions in which chromium complexes have been used are hydroaminations, hydroborations and hydrosilylation, all of which are covered in previous reviews.[11,44] Both hydroboration and hydrosilylation of alkenes with trichlorosilane provide a powerful method for the conversion of olefins to alcohols. Pd-catalyzed hydrosilylation reactions have the advantage over Rh-catalyzed hydroboration of their lower catalyst loading. Arene chromium ligands have been used in both.[49] In a recent example, a hydrosilylation was carried out in several substituted styrene substrates, followed by *in situ* addition of fluoride and oxidation, which gave the corresponding (*S*)-alcohols **152** with good yields and moderate to high enantioselectivity. The ligands were arene chromium complexes with certain heterocycles at the benzylic position (Scheme 42).

A highly selective diol planar chiral chromium arene Diels–Alder catalyst has been described by Jones *et al.* Under optimal conditions, the catalyst gives >85% ee and an 85 : 15 *exo* : *endo* ratio in the cycloaddition of acrolein with various dienes (Scheme 43).[50]



Scheme 42



Scheme 43

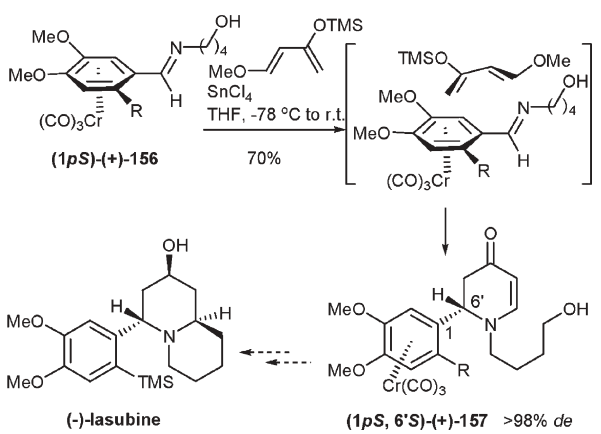
5. Synthesis of natural products

Asymmetric synthesis of natural products *via* arene–$Cr(CO)_3$ complexes has received increasing attention. The use of the metal unit in stoichiometric amounts is a drawback, but the great facial differentiation and "umpolung" of the aromatic ring makes it worth the use of these complexes. One of the first syntheses of a natural product *via* planar chiral η^6-arene chromium complexes was by Kündig and Ratni, who obtained, from highly enantiomerically enriched complex **(1*pS*)-(+)-156** (derived from **(1*pS*)-(+)-6**, *vide supra*), (−)-lasubine I. The key steps were a diastereoselective aza-Diels–Alder reaction of imine **(1*pS*)-(+)-156** and a highly diastereoselective radical cyclization (Scheme 44).[4]

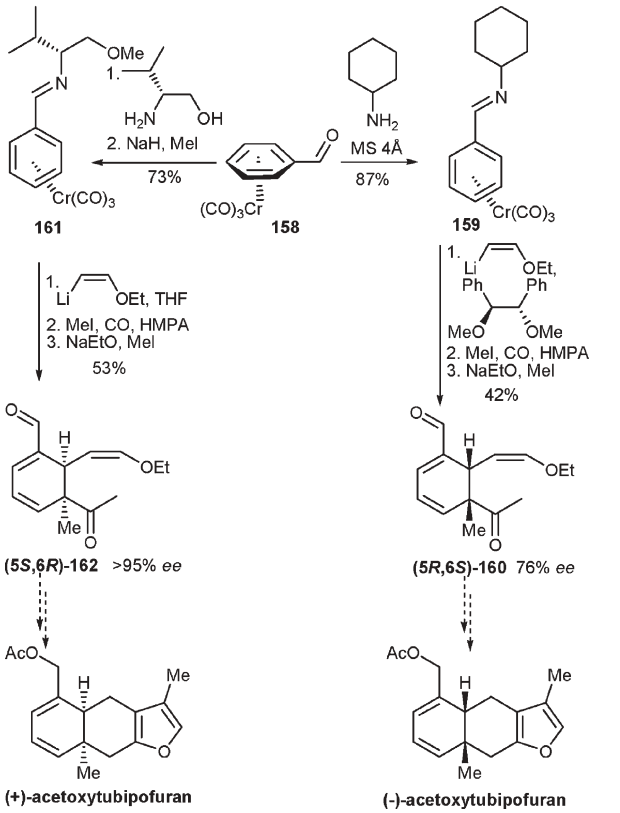
The same group has recently reported the synthesis of both enantiomers of the marine furanosesquiterpene acetoxytubipofuran. The enantiomeric acetoxytubipofurans were obtained *via* an enantioselective or a diastereoselective nucleophilic addition. For the natural (+)-acetoxytubipofuran, the key step is a very efficient Eschenmoser–Claisen rearrangement, while the (−)-*ent*-product was obtained *via* Pd-catalyzed allylic substitution (Scheme 45).[51]

Schmalz *et al*. have carried out the synthesis of an epimer of marine diterpenoid helioporine B. Starting from non-racemic planar chiral arene chromium tricarbonyl complex **(−)-163**, they obtained an unsaturated complex that reacted with 2-lithioacetonitrile. Remarkably, this addition occurs in an *endo* mode, *i.e.*, from the complexed face of the π-ligand. More recently, the same intermediate was used for the synthesis of other serrulatane intermediates (Scheme 46).[52]

Natural axially chiral biaryls are attractive synthetic goals accessible by asymmetric Suzuki couplings with planar chiral complexes. Examples of the efficiency of this method are the formal and total syntheses of (−)-steganone, the synthesis of actinoidinic acid and the total synthesis of korupensamines A and B.[36] The latter synthesis relied on the Suzuki–Miyaura coupling of an aryl bromide chromium complex **167**, which was obtained by enantioselective lithiation and bromination of **166**, with a naphthylboronic acid in refluxing methanol. This reaction gave kinetically-favoured *syn*-complex **168**, which was further elaborated to korupensamine A in sixteen steps (Scheme 47).[53]



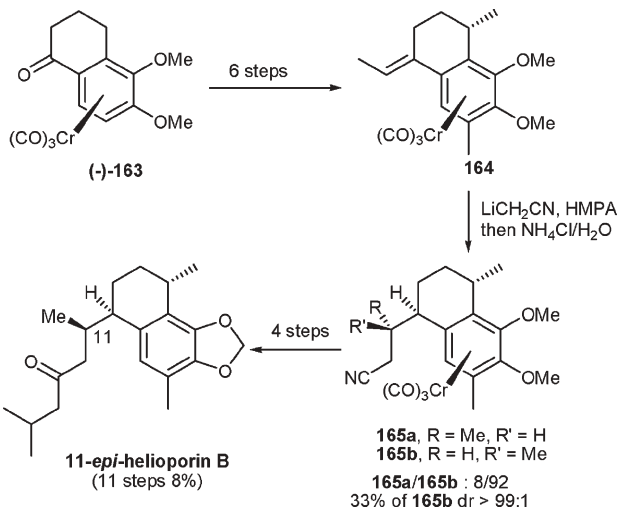
Scheme 44



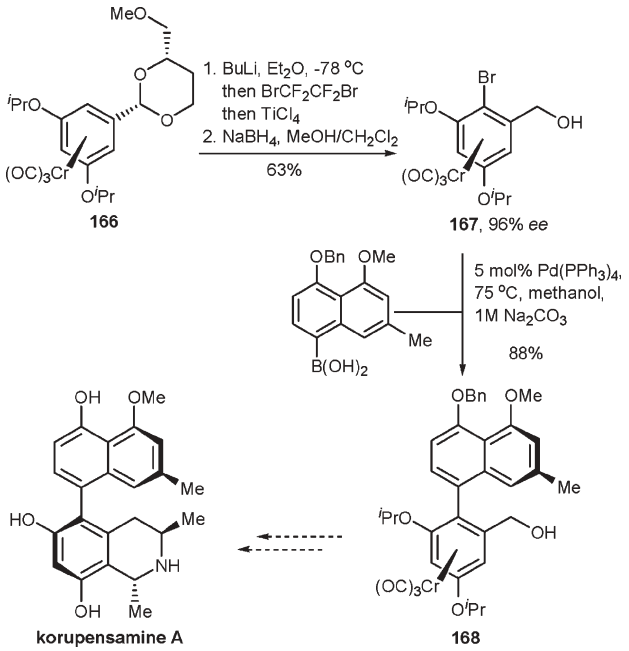
Scheme 45

6. Conclusions and outlook

Chromium complexes can be synthesized easily by direct complexation or derivatization from complexed substrates. In addition, there are a myriad of efficient methods to obtain them in optically active form without any need for resolution. The arene–$Cr(CO)_3$ complexes can suffer a variety of new transformations due to the electron-withdrawing effect and the stereochemical control exerted by the $Cr(CO)_3$ unit. In addition to the numerous transformations of these compounds



Scheme 46



Scheme 47

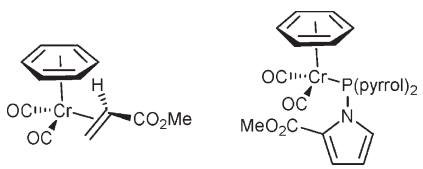


Fig. 4

in more elaborate complexes, three classes of applications are evident: (a) the use of the $Cr(CO)_3$ group as an auxiliary that is easily removed; (b) the synthesis of complex organic molecules (including natural products) based on their unusual chemical behavior; and (c) the use of planar chiral arene chromium-based ligands in catalytic asymmetric transformations.

The first two applications imply stoichiometric $Cr(CO)_3$-mediated arene transformations. This is their main drawback and is due to the robust arene–metal bond these complexes have. There have been a couple of works dedicated to the synthesis of labile complexes that retain electrophilic activation but are able to exchange the arene at low temperatures. The complexation and activation of the arene would be temporary. The complexes depicted in Fig. 4 were designed with this aim, although no catalytic arene functionalizations have been realized.[54] Other approaches involve switching the metal to Mo.

What is evident is that this area is clearly expanding in several aspects and will reveal spectacular applications in the near future, ranging from new uses of chiral planar ligands in asymmetric catalysis to the synthesis of natural compounds and new complex organometallic molecules.

Acknowledgements

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