REVIEW

# Applications of stoichiometric organotransition metal complexes in organic synthesis

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## 1 Introduction

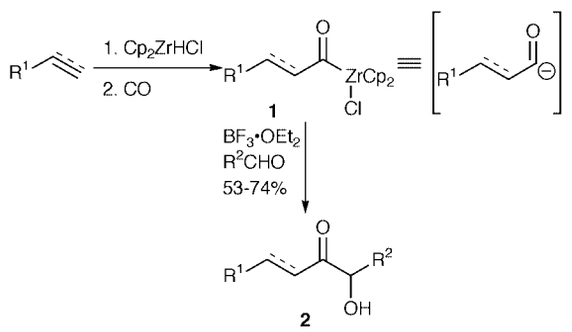
This article describes selected developments in the field of stoichiometric organotransition metals in organic synthesis. Emphasis will be placed on new reactivity and methods of use to the practising organic chemist. The chemistry is subdivided according to the precedent of four previous reviews.[1]

## 2 Transition metal alkyl, alkenyl and allyl complexes in organic synthesis

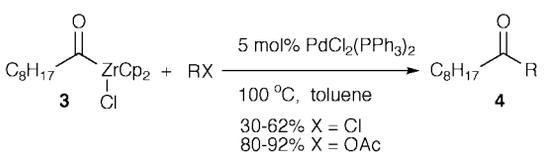
### 2.1 Organozirconium-based methodology

Research into organozirconium chemistry continues to reveal interesting and novel applications. The remarkable reactivity of acyl zirconocene chlorides as "unmasked" acyl anions has been reported.[2] The relative instability of acyl metal reagents is a cause for their limited use in organic synthesis. Acyl zirconocenes **1**, however, were easily synthesised by the reaction of alkenes or alkynes with zirconocene hydrochloride in the presence of carbon monoxide; they reacted smoothly with aldehydes under boron trifluoride catalysis to yield ketols **2** (Scheme 1).

Also investigated is the reaction of these "unmasked" acyl anions with organic halides under palladium catalysis (Scheme 2).[3] Reaction of **3** with simple halides gave fair yields of the coupling product **4**. The yields improved dramatically when



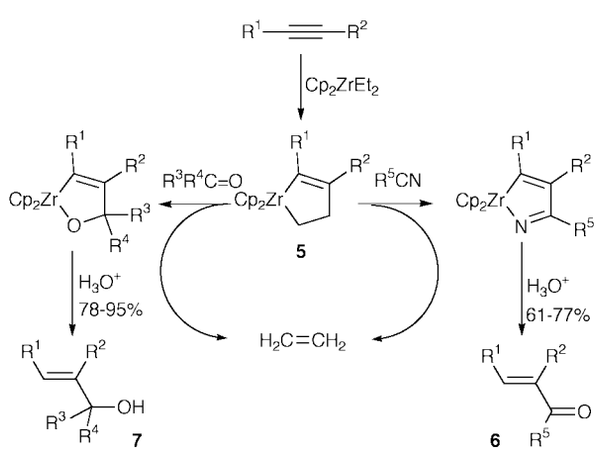

**Scheme 1**




**Scheme 2**

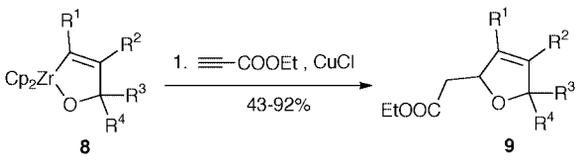
allylic acetates were used in place of the halides. Unsaturated acyl zirconocenes also reacted but with considerably lower yields.

In another report, Takahashi *et al.* describe a selective intermolecular coupling of alkynes with nitriles and ketones *via* zirconacyclopentene **5**. Extrusion of ethene and insertion of a ketone or nitrile gives the corresponding zirconaheterocycle which, on hydrolysis, gives α,β-unsaturated ketones **6** and allylic alcohols **7** respectively, in excellent yields (Scheme 3).[4]




**Scheme 3**

Takahashi and co-workers also report the reaction of oxazirconacyclopentenes **8** with ethyl propynoate,[5] where it was observed that copper(I) chloride mediated the formation of 2,5-dihydrofurans **9** (Scheme 4). A variety of monocyclic and

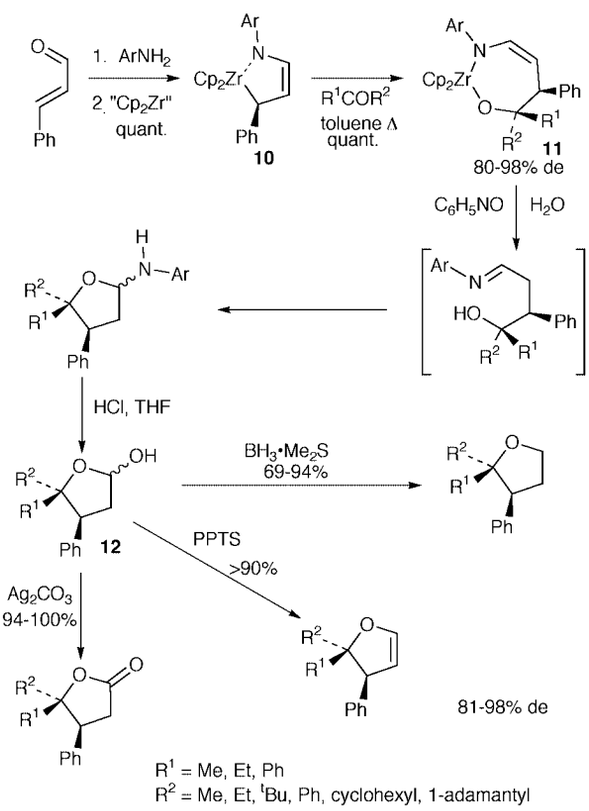



**8** **9**

**Scheme 4**

spirocyclic oxazirconacyclopentenes were found to react in excellent yields. The proposed mechanism involves the transmetallation of the Zr–C bond with copper to generate an intermediate which reacts with ethyl propynoate to yield an enolate which is protonated by the acidic hydrogen of another molecule of the alkyne. An intramolecular Michael addition follows to afford the 2,5-dihydrofuran.

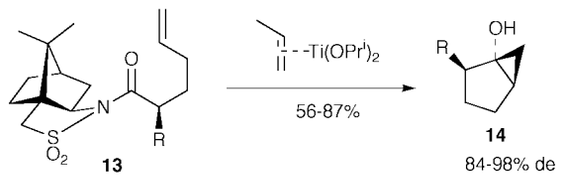
Zirconocene–1-aza-1,3-diene complexes **10**, (Scheme 5) have been used in stereoselective synthesis as homoenolate equivalents for the first time.[6] Starting from α,β-unsaturated imines and the zirconocene equivalent "$Cp_2Zr$", the corresponding azazirconacyclopentenes **10** were prepared. Insertion of sterically demanding ketones generated the seven membered zirconaheterocycle **11** which, on hydrolysis, yielded α-anilinotetrahydrofurans. These were converted into the corresponding γ-butyrolactols **12** on treatment with hydrochloric acid in 84–98% de. γ-Butyrolactol **12** could then be chemically manipulated to generate a series of five-membered oxygen heterocycles (γ-butyrolactones, dihydrofurans and tetrahydrofurans) in good to excellent yields and de.




**Scheme 5**

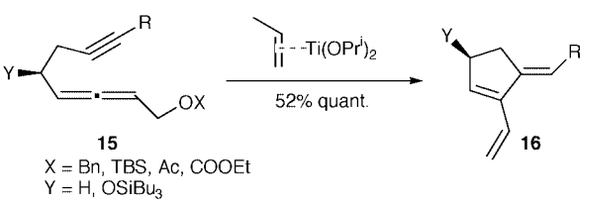
## 2.2 Organotitanium-based methodology

The use of organotitaniums in organic synthesis also continues to grow. Extending his titanium-mediated cyclisation strategy, Sato and co-workers have reported an asymmetric synthesis of bicyclic cyclopropanols.[7] The α-branched *N*-acyl camphor sultams **13** bearing a pendant alkene cyclised stereoselectively in the presence of the titanium reagent, $Ti(O^iPr)_2(\eta^2$-propene) (generated *in situ* from tetraisopropoxytitanium and isopropylmagnesium chloride) to afford the desired cyclopropanols **14** in high yields and excellent des (Scheme 6). The chiral auxiliary was recovered and could be recycled.




**Scheme 6**

The titanium-promoted cyclisation reaction could also be used to generate cyclic cross-conjugated trienes stereoselectively from allenynol derivatives.[8] Treatment of allenynol derivatives **15** bearing a leaving group with the titanium reagent ($Ti(O^iPr_2)$-($\eta^2$-propene)) resulted in the cyclised product **16** (Scheme 7). Poor recovery of the product from flash chromatography, however, reduced the isolated yield considerably from the quantitative conversion observed by $^1$H NMR spectroscopy. The tributylsilyl ether derivative of the optically active allenediol was also cyclised successfully without loss of stereochemical purity. In a related report, it was observed that titanium-mediated cyclisations of enynols and allenynols are efficiently controlled by a remote hydroxy group and lead to diastereoselectivities as high as 98.5:1.5.[9] Notably, the unprotected alcohol was found to lead to higher selectivities than the corresponding tributylsilyl protected ethers.

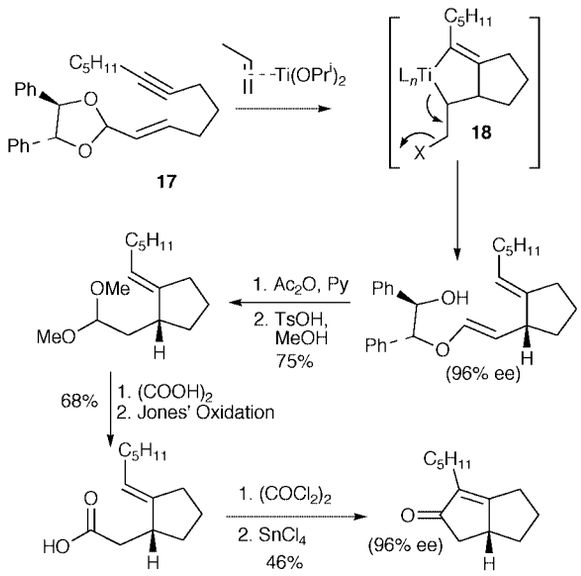



**Scheme 7**

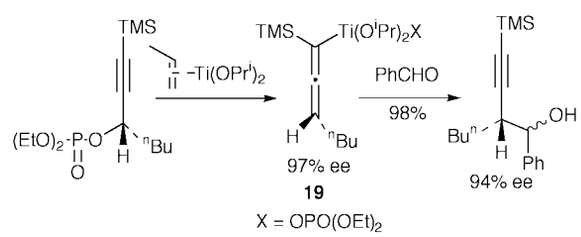
In another remarkable report, an asymmetric intramolecular cyclisation of 2,7- and 2,8-enynyl chiral acetals has been discussed.[10] The reaction, which is a synthetic equivalent of the metallo-ene reaction, uses $C_2$-symmetric chiral acetals to induce a high degree of asymmetry. The enol ether resulting from the cyclisation of 2,7-enynyl acetals **17**, *via* the intermediary bicyclic titanocyclopentene **18**, was then transformed into a variety of non-racemic cyclopentane derivatives (Scheme 8). An oxygen atom could also be successfully accommodated in the chain. The same methodology also yielded optically active cyclohexane derivatives by cyclisation of 2,8-enynyl acetals. In the absence of a suitable leaving group such as the acetal described above, the bicyclic titanacyclopentene has been shown to react with aldehydes to afford allylic alcohols as single diastereoisomers in good yields.[11]

The reaction of the titanium reagent ($Ti(O^iPr_2)(\eta^2$-propene)) with optically active secondary propargyl phosphates (prop-2-ynyl phosphates) (Scheme 9) gave di- and trisubstituted allenyl titaniums such as **19** with more than 97% chirality transfer.[12] Subsequent treatment of these attractive intermediates with benzaldehyde afforded homopropargylic alcohols as a mixture of diastereoisomers. Interestingly, while the reaction with phosphates resulted in inversion, carbonates were observed to react with retention of configuration.

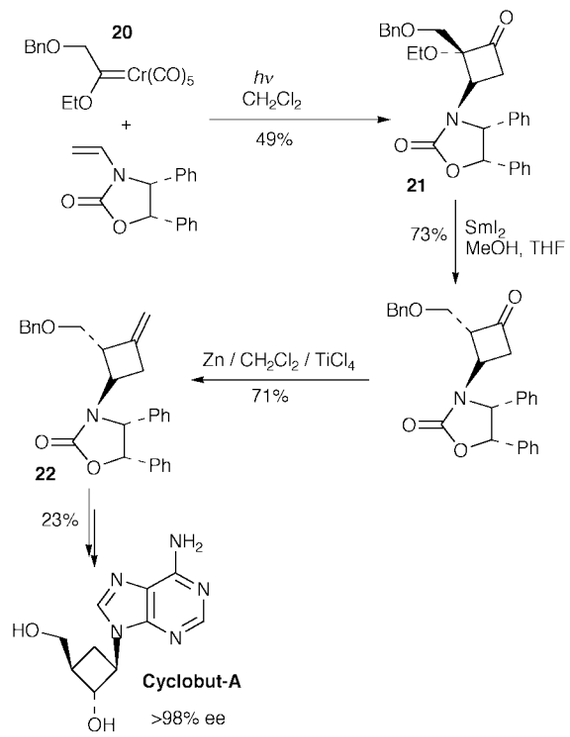
The same group has also developed a method for the conversion of allylic carbonates to alk-1-enes and 3-chloroalk-1-enes.[13] The formation of allyltitanium intermediates and subsequent hydrolysis or halogenolysis occurred with high regioselectivity favouring electrophile addition at the γ-carbon.



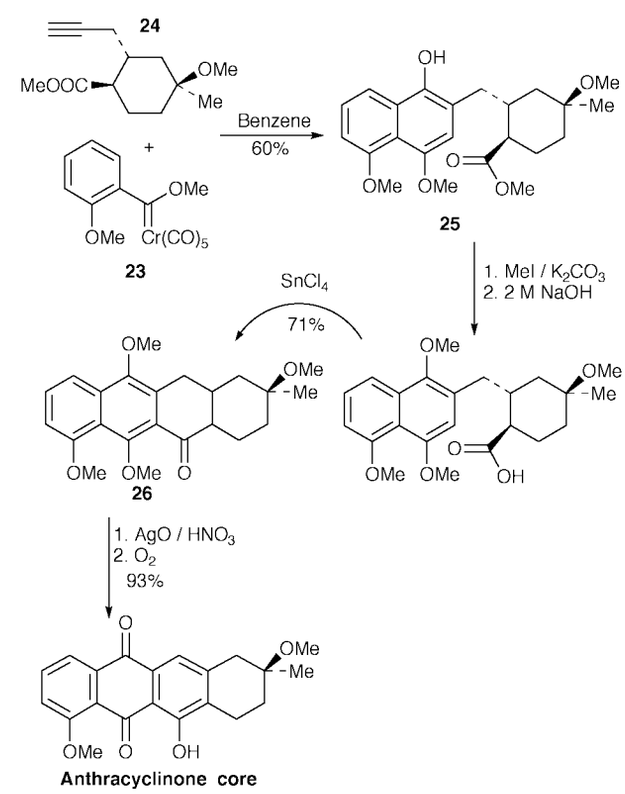
Scheme 8



Scheme 9



Scheme 10



Scheme 11

## 3 Group VI transition metal carbenes in organic synthesis

### 3.1 Carbene photochemistry

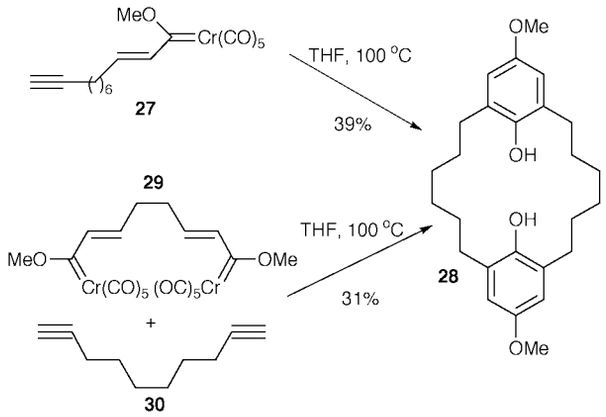
Brown and Hegedus, this year, have applied the photochemical generation of optically active cyclobutanones to the synthesis of the antiviral carbocyclic nucleoside analogue (−)-cyclobut-A (Scheme 10).[14] The key step involves photolysis of carbene **20** with the optically active ene-carbamate to give **21** with the required scaffold in moderate yield. $SmI_2$-mediated α-deoxygenation of **21** was followed by methylenation using the Takai reagent to afford **22**. Further elaboration resulted in the target (−)-cyclobut-A in >98% ee. The same group have also carried out a wide variety of organic transformations on chiral (racemic) cyclobutanones similar to **21**.[15]

### 3.2 Carbene annulations

The importance of the Dötz benzannulation of metal carbenes and alkynes in the formation of complex cyclic systems is reflected by continued research this year. Wulff *et al*. have successfully realised a synthetic strategy to access the tetracyclic anthracyclinone core of the orally active, antitumour antibiotic, menorgil:[16] benzannulation constitutes the key step in accessing this structure (Scheme 11). The reaction of carbene complex **23** with alkyne **24** in benzene afforded the phenol **25** in good yield. After protecting the phenolic group as the methyl ether, the ester was hydrolysed to the carboxylic acid. Ring closure induced by tin tetrachloride furnished the tetracyclic core **26** in 71% yield. Successful oxidation of the dioxygenated aromatic ring to the quinone followed by oxidative aromatisation of the adjacent ring by molecular oxygen in the absence of solvent occurred in excellent yield to give the target tetracycle. Using the same methodology, the group also describes the first steps towards another natural product.[17]

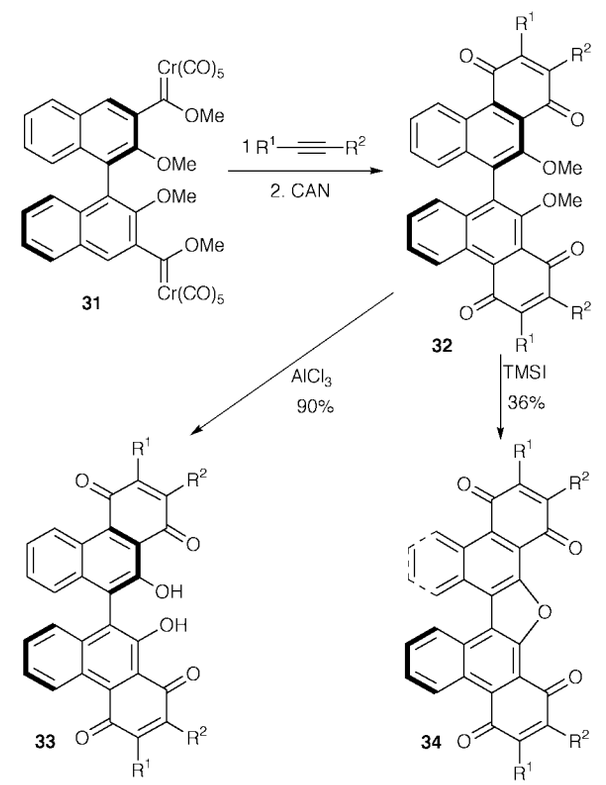
The benzannulation reaction has also been applied to the synthesis of cyclophanes.[18] In the first of two approaches to the same target, a vinylidene alkyne **27**, containing a tether of six methylenes, reacted with another unit of itself to give the 18-membered metacyclophane **28** in moderate yield (Scheme 12). The second route accesses the same target in similar yield using a biscarbene **29** with a diyne **30** in a double benzannulation sequence. A comprehensive review, also by Wulff, documents the development of imidazoline and oxazoline carbene complexes as templates for asymmetric synthesis in, amongst other transformations, the benzannulation process.[19]

Dötz and co-workers use the benzannulation strategy in a




**Scheme 12**

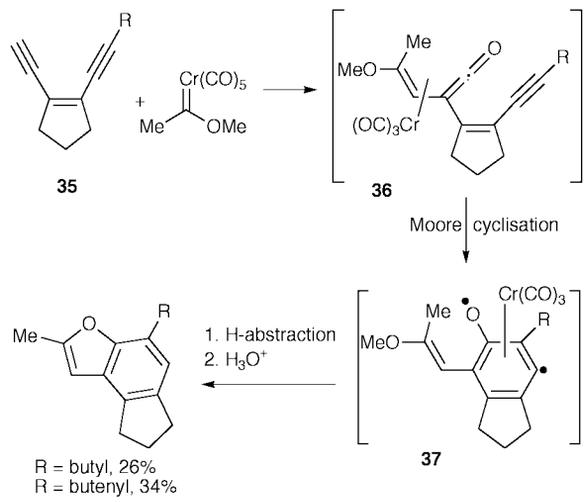
unique manner to generate $C_2$-symmetric axially chiral bi-(phenanthrenequinones) and derivatives which have potential as catalysts for numerous asymmetric reactions (Scheme 13).[20] The biscarbene chromium complex **31** derived from binaphthol underwent facile reaction with hex-1-yne and hex-3-yne to afford the tricarbonylchromium-complexed $\eta^6$-biphenanthrenes. Oxidative workup released the axially chiral $C_2$-symmetric bi(phenanthrenequinones) **32**. The corresponding binaphthol skeletons **33** could be accessed from these by deprotection using $AlCl_3$ and treatment of **32** with iodotrimethylsilane resulted in an unusual reaction to yield a helicene **34**.




**Scheme 13**

A significant development in the benzannulation reaction is described by Barluenga *et al.*[21] An *amino* carbene bearing an *electron withdrawing* conjugated ester substituent was found to undergo smooth benzannulation even with electron poor alkynes.

Herndon and Wang detail the coupling of chromium carbenes with conjugated ene-diynes to form benzofuran derivatives (Scheme 14).[22] Selective coupling of the less hindered alkyne of **35** with the carbene complex affords the

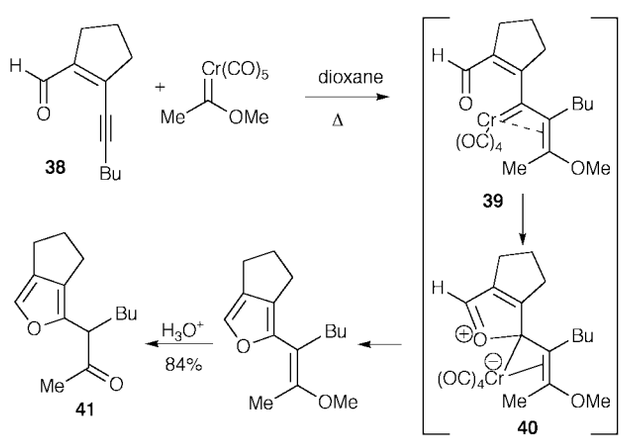



**Scheme 14**

enyne ketene **36** which undergoes Moore cyclisation to generate a chromium-complexed diradical **37**. Hydrogen abstraction from the solvent affords the phenol which, on treatment with acid, gives the butylbenzofuran. A *butenyl* benzofuran derivative, the result of an intramolecular H-abstraction process, was also isolated from the reaction mixture in 34% yield.

### 3.3 Miscellaneous carbenes

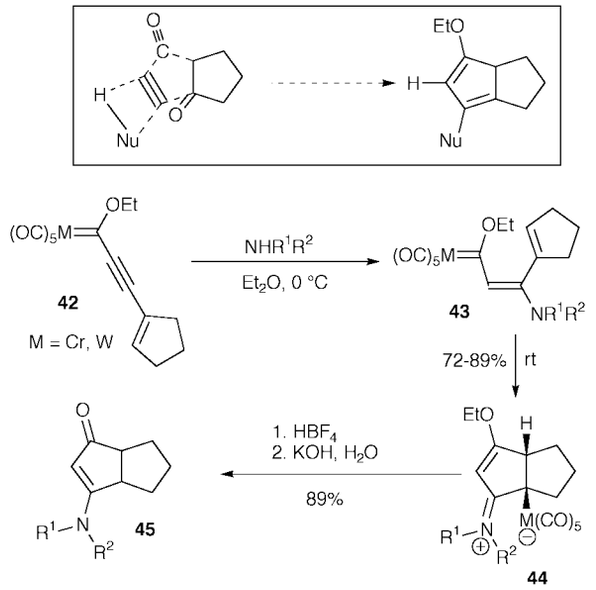
Resulting from a variety of interrupted and modified benzannulation processes, some interesting chemistries have been described this year. The coupling of conjugated enyne aldehydes and ketones such as **38** with methyl methoxy carbene complexes is shown to constitute a novel synthetic route to oxygen heterocycles (Scheme 15).[23] Herndon and Wang propose a mechanism involving regio- and stereoselective alkyne insertion to afford vinyl carbene complex **39**, then nucleophilic attack by oxygen to generate ylide **40**. Following metal loss a variety of furan derivatives such as **41** were obtained in very good yield.




**Scheme 15**

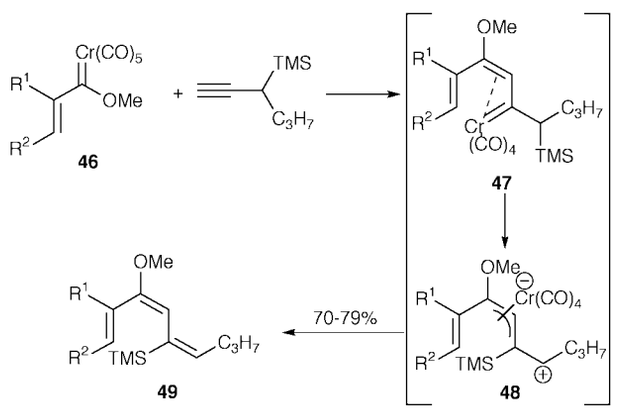
An interesting metal-mediated cyclopentadiene annelation onto enolisable cycloalkanones is reported by Aumann *et al.*[24] The final product is formally constructed from ethyne, carbon monoxide, a cycloalkanone and a protic nucleophile (Scheme 16). Thus, the treatment of carbene complex **42** with secondary amines resulted in amino-substituted dienes **43**. These underwent ring closure at ambient temperature to $\eta^1$-complexes **44**. The displacement of the metal from this zwitterionic species led to the product cycloalkenone **45**.

An unprecedented reaction between vinyl carbenes **46** and propargylsilanes (prop-2-ynylsilanes) resulting in the formation of 1,3,5-trienes **49** has been reported by Herndon and Zhu



Scheme 16

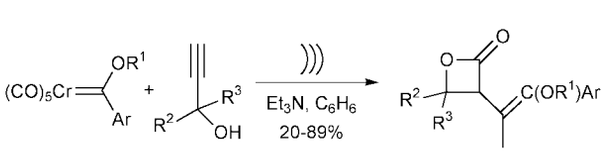
(Scheme 17).[25] The mechanism entails the formation of the zwitterionic complex **48** *via* a 1,2-migration of the silyl group in the initially produced vinyl carbene **47**. Demetallation resulted in good yields of the trienes. Significantly, benzannulation was not a competing process.



Scheme 17

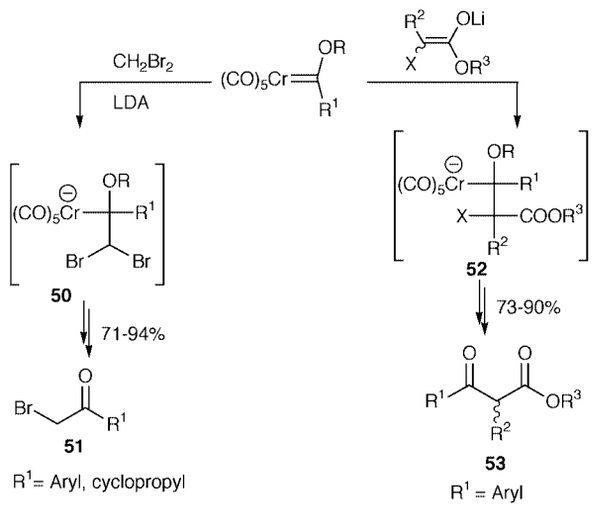
An ultrasound technique developed by Kerr and co-workers presents a viable alternative to thermal activation of Fischer carbene complexes to reaction with alkynes (Scheme 18).[26] Generation of heavily functionalised β-lactones results from nucleophilic attack of the hydroxy group onto the carbonyl of the common benzannulation vinyl ketene intermediate. Using optimised ultrasound conditions (3 equivalents of triethylamine in benzene) a variety of substituted propargyl alcohols were converted into the corresponding β-lactones in poor to high yield. In a related report, results from the newly developed sonication technique were compared with the thermal reaction of the generally less stable alkoxy*alkyl* chromium carbene complexes.[27] The results indicate that sonication is a more effective protocol for gaining access to less heavily substituted β-lactones.

Some fundamentally different carbene chemistry has also



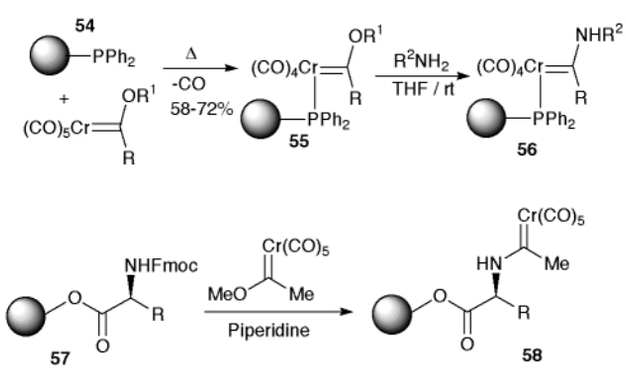
Scheme 18

been described. Two comparable one-pot transformations involving Fischer carbene complexes have been reported (Scheme 19).[28] Treatment of various carbenes with dibromomethyllithium proceeded smoothly *via* nucleophilic attack on the carbene; the resulting intermediate **50** underwent spontaneous β-elimination to afford an enol ether which hydrolysed to a bromomethyl ketone **51** in good to excellent yield. The nucleophilic addition of haloester lithium enolates, on the other hand, gave intermediate **52**; β-elimination resulted in enol ethers which were hydrolysed to β-diketones **53** with equal efficiency.



Scheme 19

In a striking new development, the first synthesis of polymer-bound Fischer carbenes has been reported by Maiorana *et al.*[29] Alkoxy chromium carbenes were appended to diphenylphosphine-substituted polystyrene **54** by the thermal exchange of a CO ligand to generate complexes of type **55** in moderate to good yields (Scheme 20); amination afforded the amino carbenes **56**. The use of a leucine or phenylalanine-grafted polystyrene support **57** allows for immobilisation *via* amination of an alkoxycarbene resulting in amino carbene **58**.

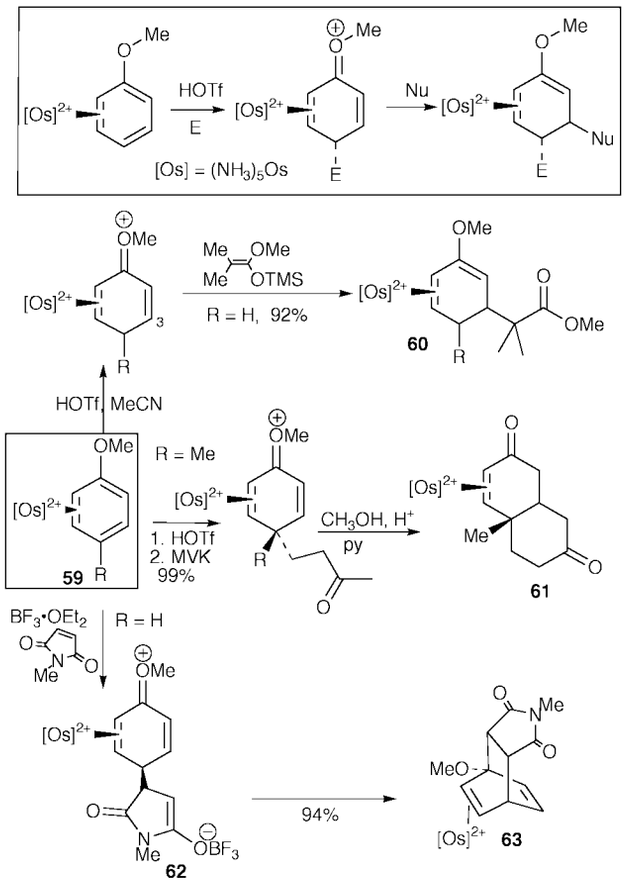


Scheme 20

## 4 $\eta^2$-Complexes in organic synthesis

### 4.1 $\eta^2$-Complexes of osmium

The chemistry of ($\eta^2$-arene) osmium complexes continues to be dominated by Harman. Amongst the salient developments in this area is a tandem addition to pentaamine osmium complexes of anisole **59**.[30] These complexes are versatile synthons in a diverse array of reactions (Scheme 21); the chemistry is characterised by electrophilic addition at the *para* position and subsequent nucleophilic attack on the resulting cationic substrate. The 4*H*-anisolium complex formed on addition of triflic acid to **59** undergoes nucleophilic addition with ketene silyl acetal at




**Scheme 21**

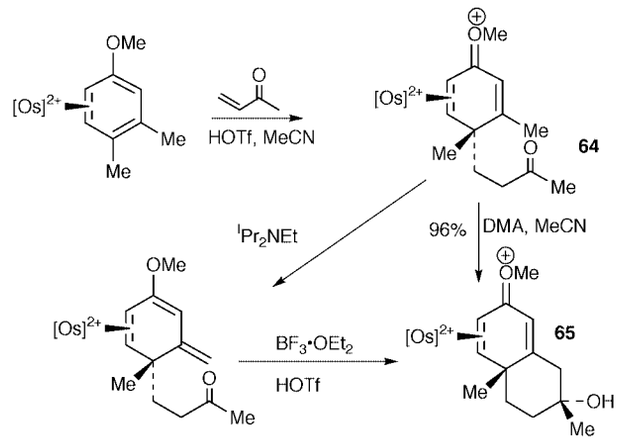
C3 to yield **60**. The Michael addition product of **59** and methyl vinyl ketone underwent Michael ring closure resulting in the decalin core **61**. Addition of *N*-methyl maleimide mediated by boron trifluoride resulted in a boron enolate **62** which reacted with the highly electrophilic C1 to furnish a formal Diels–Alder adduct **63**. A similar sequence of reactions was used to carry out the dearomatisation of naphthalene.[31] The pentaamine osmium complex of naphthalene reacted smoothly with a variety of carbon-based electrophiles to generate naphthalenium complexes which, in turn, when treated with non-basic nucleophiles, reacted stereospecifically to afford *cis*-1,4-dihydronaphthalene complexes. The desired organic compounds were readily obtained by oxidative decomplexation.

The introduction of asymmetry into $\eta^2$-osmium complexes is also described.[32] A single diastereoisomer was observed upon complexation of aromatic ligands bearing a chiral alkoxy substituent. Excellent stereocontrol was observed on addition of a ketene silyl acetal at C3 to the face opposite to that of the metal moiety.

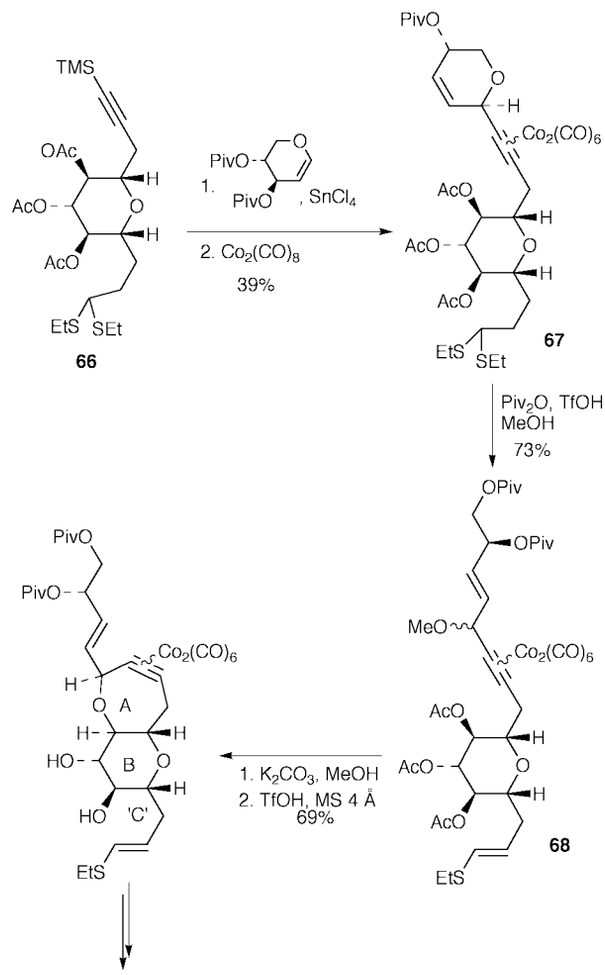
A novel and efficient synthesis of functionalised decalins is also detailed (Scheme 22).[33] Complementary to the reactivity of ($\eta^6$-arene)tricarbonylchromium complexes, the $\eta^2$-coordinated pentaamine osmium 4*H*-anisolium complex **64** was found to be activated at the benzylic position and undergoes an intramolecular aldol reaction with a carbonyl, appended as previously described, to afford the decalin core **65**.

### 4.2 $\eta^2$-Complexes of cobalt

As part of his continued efforts towards ciguatoxin,[34] Isobe reports an elegant enantioselective synthesis of the (5*R*)-ABC fragment *via* the Nicholas reaction (Scheme 23).[35] Constructed in 12 steps in good overall yield from a D-glucoside, silylacetylene **66** underwent *C*-glycosidation and complexation with $Co_2(CO)_8$ to afford hexacarbonyldicobalt complex **67**. Opening of the dihydropyran ring resulted in a mixture of diastereo-




**Scheme 22**



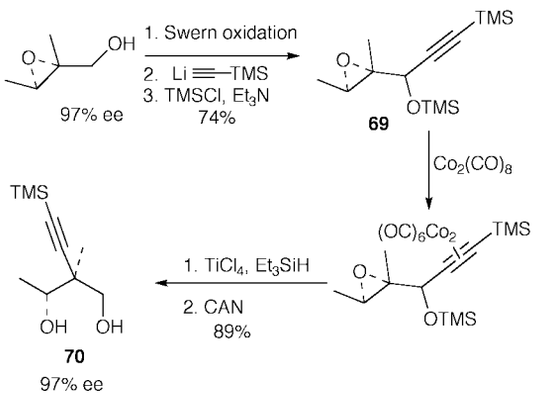

**Scheme 23**

isomers **68** and hydrolysis gave the corresponding triol. Nicholas cyclisation, *via* trapping of a stabilised propargyl cation by the adjacent hydroxy group, was effected with triflic acid to provide the seven-membered ring. Concomitant decomplexation and hydrogenation of the alkyne unit by tributyltin hydride delivered the product with the A and B rings possessing the correct stereochemistry; the vinyl thioether group is poised for extension towards the C and D rings.

A new approach to the asymmetric Nicholas reaction is reported by Martín and co-workers whereby a camphoric acid-derived chiral auxiliary induces moderate to high (<80%) ees from a centre remote from cation formation.[36] The system has been effectively applied to the synthesis of enantiomerically

pure α-hydroxy esters. Also based on the Nicholas effect is a new access to unstable homopropargylic ketones.[37]

The formation of a key fragment in the challenging total synthesis of the furaquinocines is shown to proceed *via* an interesting alkynyl migration (Scheme 24).[38] Alkyne substrate **69**, prepared from an optically active epoxy alcohol, was converted into the cobalt complex and treated with $TiCl_4$. Despite the poor migratory aptitude of an alkynyl group, the complexation-facilitated 1,2-migration occurred smoothly to afford an aldolate, reduced *in situ* with triethylsilane. Oxidative decomplexation gave diol **70** with no overall loss of stereochemical integrity. Desilylation provided the fragment key to the success of the natural product synthesis.



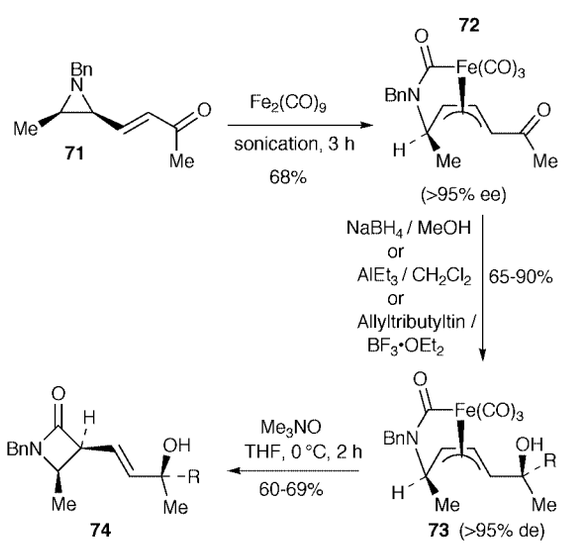

**Scheme 24**

## 5 $\eta^3$-Complexes in organic synthesis

### 5.1 $\eta^3$-Complexes of iron

The chemistry of ($\eta^3$-allyl)tricarbonyliron complexes continues to attract attention and the applications of (π-allyl) tricarbonyliron complexes in acyclic stereocontrol have been reviewed this year.[39]

A stereoselective synthesis of functionalised β-lactams has been reported by Ley and Middleton (Scheme 25).[40] The (π-allyl)tricarbonyliron lactam complexes **72** were generated from appropriately functionalised alkenylaziridines **71**. Nucleophilic addition on the methyl ketone sidechain occurred completely stereoselectively from the *anti* face to yield secondary and tertiary alcohol functionalities **73**. An improved decomplexation technique (trimethylamine *N*-oxide) allowed generation of β-lactams **74**, bearing stereodefined secondary and tertiary alcohol centres, in attractive yields.

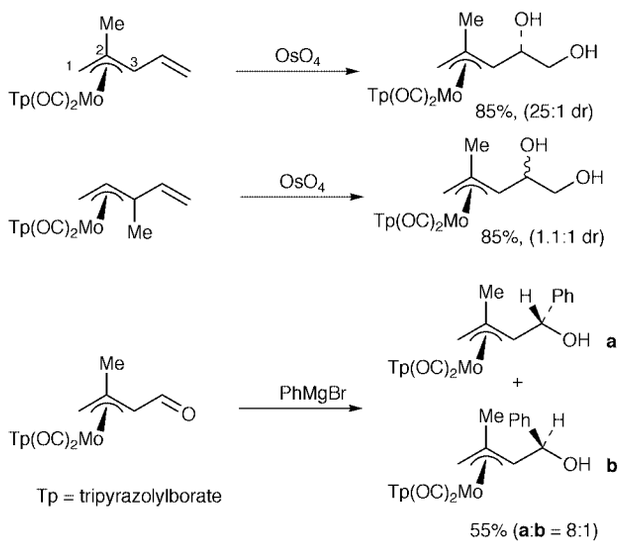



**Scheme 25**

The remarkable 1,7-induction observed in the Mukaiyama aldol reaction of a trimethylsilyl enol ether appended to a (π-allyl)tricarbonyliron scaffold has been investigated in detail.[41] It was observed that in boron trifluoride-mediated reactions simple aliphatic and aromatic aldehydes reacted with a higher degree of diastereoselection compared to those bearing an α-benzyloxy substituent. The observed diastereoselectivity was in accordance with Cram's chelation model. Oxidative demetallation afforded stereodefined β- and γ-lactones, (*E*,*E*)-dienes and enediols.

### 5.2 $\eta^3$-Complexes of molybdenum

Pearson and Neagu have shown that the presence of an alkyl group at C2 of an alkene-substituted (π-allyl)molybdenum complex leads to notable improvement in lateral stereocontrol (Scheme 26).[42] One of the competing conformers of the substrate is destabilised (due to severe non-bonded interaction between the alkyl group and the pendant alkene) resulting in a marked increase in the diastereoisomeric ratio obtained in osmium tetraoxide-mediated dihydroxylation of the alkene sidechain. Similar improvement was observed in nucleophilic addition of a Grignard reagent to the corresponding aldehyde complex. Alkyl substitution at C3, however, affected the diastereoisomeric ratio only marginally.

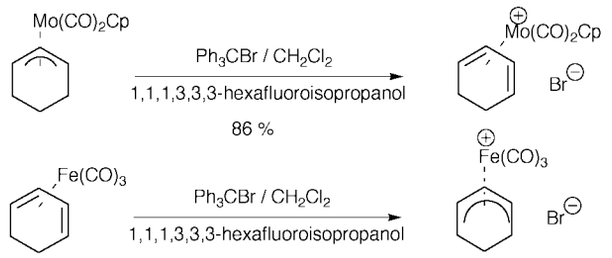



**Scheme 26**

A useful preparative procedure for the cationic $\eta^4$-diene complexes of tricarbonyl molybdenum has been reported (Scheme 27).[43] The routine preparative procedure for these cationic dienes, *via* hydride abstraction from an $\eta^3$-allyl species using trityl tetrafluoroborate, usually does not yield satisfactory results for substituted precursors. The method was successfully modified to generate the trityl cation *in situ* using 1,1,1,3,3,3-hexafluoroisopropanol to promote the dissociation of trityl bromide. The yields were good to excellent and a control experiment confirmed the critical role of 1,1,1,3,3,3-hexafluoroisopropanol in the procedure. A preliminary experiment also demonstrated conversion of tricarbonyl($\eta^4$-cyclohexadiene)iron into the corresponding cationic tricarbonyl($\eta^5$-cyclohexadienyl)iron bromide complex suggesting the general applicability of this protocol for the generation of cationic π-complexes.

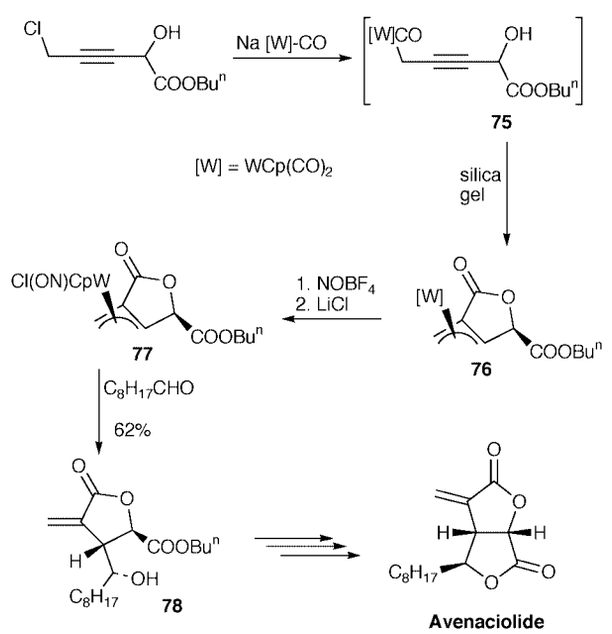
### 5.3 $\eta^3$-Complexes of tungsten

Since the application of ($\eta^3$-allyl)tungsten complexes to natural product syntheses is rare, it is of particular note that Narkunan and Liu have highlighted the utility of these intermediates to access several challenging target molecules. The total syntheses




**Scheme 27**

of the bis-lactones avenaciolide and isoavenaciolide were achieved in six and three steps respectively starting from chloropropargyl derivatives (Scheme 28).[44] Formed by intramolecular alkoxycarbonylation of the unstable tungsten-$\eta^1$-propargyl complex **75**, key intermediate **76** was treated with nitrosyl tetrafluoroborate then lithium chloride to generate the allyl anion equivalent **77**. This reacted with nonanal to give α-methylene butyrolactone **78** in good overall yield. Four further steps to correct the *trans* configuration of **78** and create the bicycle gave the desired avenaciolide. Isoavenaciolide was prepared from a different chloropropargyl species using the same strategy in only three steps. The versatile process has also been applied to the total synthesis of four other bioactive γ-lactones.[45,46]

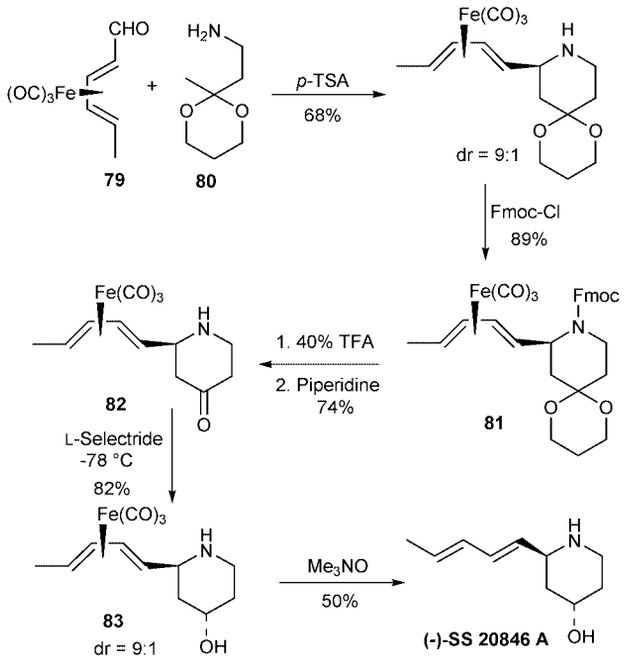



**Scheme 28**

## 6 $\eta^4$-Complexes in organic synthesis

### 6.1 $\eta^4$-Complexes of iron

Research continues into the use of planar chiral iron diene complexes in organic synthesis. An asymmetric synthesis of the alkaloid (−)-SS 20846, a proposed intermediate in the biosynthesis of the potent antimicrobial agent streptazolin, has been achieved using a tricarbonyliron dienal complex (Scheme 29).[47] A stereoselective cyclisation was observed when the planar chiral tricarbonyl($\eta^4$-dienal)iron complex **79**, (resolved as the sorbic acid derivative), was treated with amine **80** resulting in the formation of a 2-substituted piperidine ring. The tricarbonyliron moiety served as a protecting and directing group for the formation of the stereogenic centre with a dr of 9:1. The amine was then protected with Fmoc-Cl to afford **81**. Cleavage of the ketal was realised with trifluoroacetic acid and was followed by regeneration of the amine in **82**. The ketone was then stereoselectively reduced with L-Selectride at low temperature to furnish, after chromatography, the piperidinol **83** in good overall yield. The desired target was obtained upon decomplexation of the metal fragment with trimethylamine *N*-oxide.



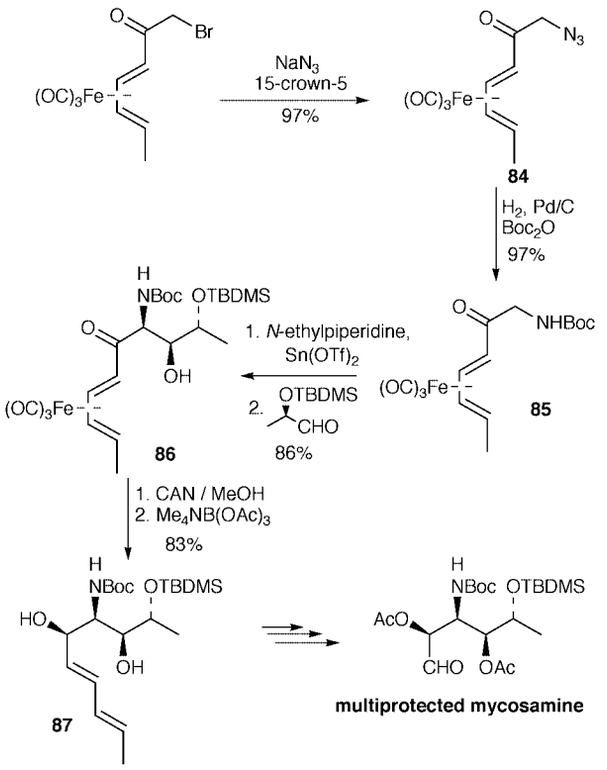

**Scheme 29**

Franck-Neumann *et al.* have reported the synthesis of mycosamine, the nitrogen containing moiety of polyene antifungal antibiotics.[48] A highly stereoselective crossed aldol reaction of the amino ketone **85** was the key step in this short synthesis (Scheme 30). Treatment of the bromo enone with sodium azide gave the azide complex **84** which underwent catalytic reduction in the presence of Boc-anhydride to afford **85**. The divalent tin enol ether of **85** participates in a highly diastereoselective crossed aldol reaction with protected (*R*)-lactaldehyde to afford **86** in excellent yield. Oxidative decomplexation and stereoselective ketone reduction generates the *anti*-1,3-diol **87**. A short sequence then delivers the multiprotected product.

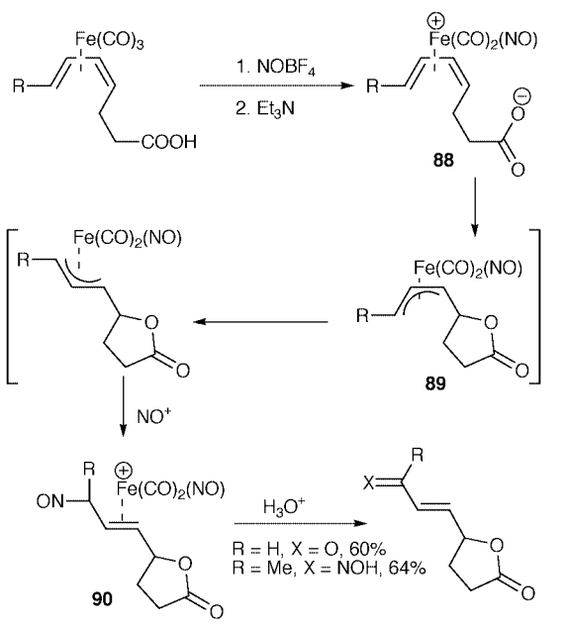
An intramolecular nucleophilic conjugate addition of appended carboxylic acids to an iron-diene scaffold has been used to prepare γ- and δ-lactones bearing an unsaturated aldehyde or oxime functionality (Scheme 31).[49] The proposed mechanism invokes the generation of zwitterionic complex **88** on treatment of the irontricarbonyl complex with nitrosyl tetrafluoroborate; the pendant carboxylate then attacks at the terminal position of the diene to produce the π-allyl species **89** which undergoes *syn*/*anti* isomerism. Insertion of another nitrosyl unit into the carbon scaffold results in **90** which, on hydrolysis, affords the products. Cyclic dienes reacted similarly to generate *cis*-fused lactones.

A novel intramolecular cycloaddition of (cyclobutadiene)-tricarbonyliron complexes and various tethered dienes has been reported by Limanto and Snapper:[50] [2 + 2] and [4 + 2] cycloadditions generated cyclobutene-containing products in moderate to very good yield. The [2 + 2] cycloadduct was found to undergo a facile Cope rearrangement to formal [4 + 2] adducts.

Directed towards a catalytic asymmetric complexation of methoxycyclohexadiene with pentacarbonyliron, a new catalyst derived from L-amino acid esters and cinnamaldehyde has been investigated (Scheme 32).[51] The complexation of prochiral diene **91** in the presence of 0.25 equivalents of catalyst **92** afforded the product in excellent yield and up to 24% ee.




Scheme 30




Scheme 31

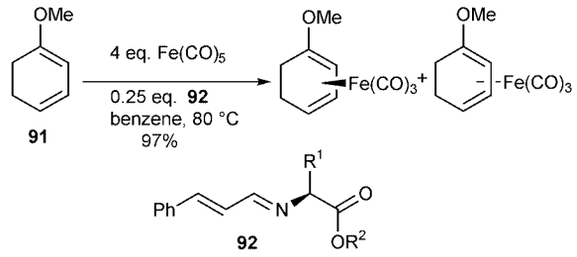
### 6.2 $\eta^4$-Complexes of molybdenum

In an extension of his previous work, Pearson has investigated the addition of carbon nucleophiles to $Mo(CO)_2Tp$-complexed isoprene (Tp = tripyrazolylborate) (Scheme 33).[52] The addition of various Grignard reagents proceeded with excellent regiocontrol. A preference of the nucleophiles to attack the less hindered diene terminus was observed, a preference which could be further enhanced to levels of 95:5 by addition of a complexing agent such as TMEDA.

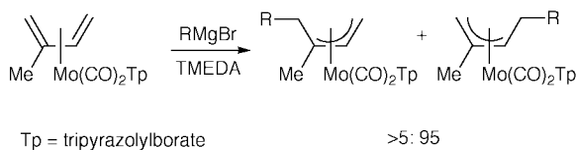
## 7 $\eta^5$-Complexes in organic synthesis

### 7.1 Cationic $\eta^5$-complexes of iron

The efficient use of $\eta^5$-iron complexes in organic synthesis is



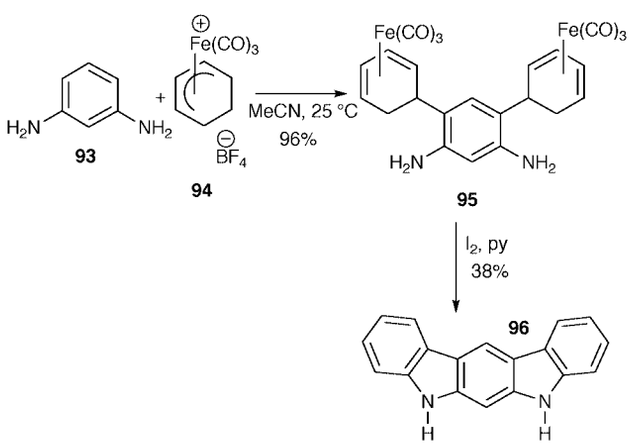

Scheme 32




Scheme 33

demonstrated by Knölker *et al.* who report the first total synthesis of the free radical scavenger (±)-neocarazostatin B, a carbazole alkaloid, using his established coupling of a cationic iron complex and an aniline derivative.[53]

The same group has also reported the simple 2-step synthesis of indolo[2,3-*b*]carbazole (Scheme 34).[54] An *ortho*-selective double electrophilic substitution of *m*-phenylenediamine **93** by the cationic ($\eta^5$-cyclohexadienyl)tricarbonyliron complex **94** afforded the dinuclear iron complex **95**. Oxidative cyclisation with iodine in pyridine formed the desired carbazole **96**.



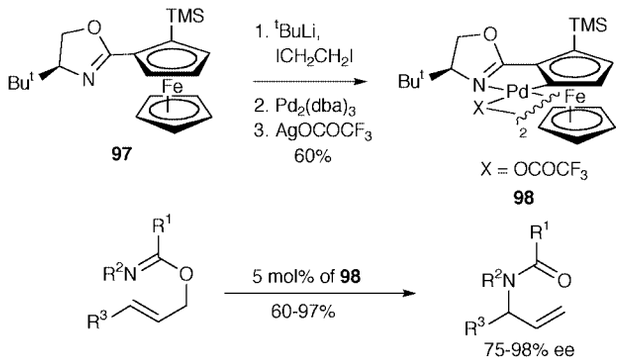

Scheme 34

### 7.2 Stoichiometric ferrocene complexes

The use of ferrocene-derived ligands in organic catalysis still continues to grow. Though strictly not within the purview of this article, a brief summary of new developments in this area, with emphasis on new ferrocene chemistry, should be of interest.

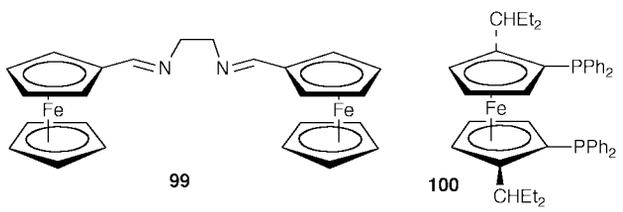
Donde and Overman have developed a new family of chiral ferrocenyl palladacycles such as **98**, (Scheme 35).[55] *ortho*-Lithiation and diiodoethane quench of enantioenriched oxazoline **97** gave the iodide as a single diastereoisomer. Oxidative addition of Pd(0) and conversion to the trifluoroacetate gave catalyst **98** which was found to promote the rearrangement of allylic imidates to allylic imides with up to 98% ee.

Mak and co-workers report the synthesis of a dimeric chloro-bridged cyclopalladated ferrocene.[56] Acetylferrocene was condensed with enantiomerically pure 1-amino-2-(methoxymethyl)-pyrrolidine to generate the chiral derivative for which asymmetric cyclopalladation using sodium tetrachloropalladate was achieved in 92.5% de. Compound **99** is reported to be an efficient ligand for copper-mediated transfer of carbenes and



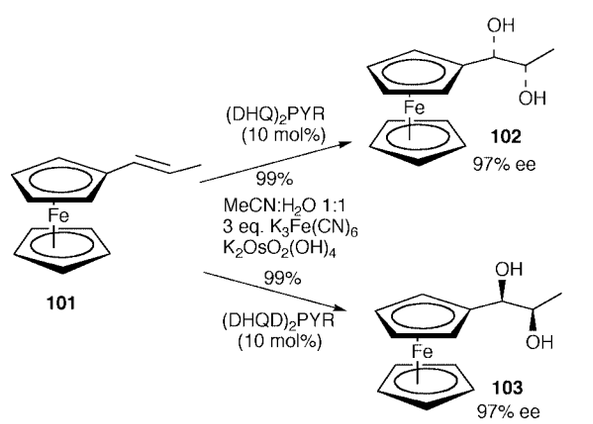

**Scheme 35**

nitrenes to olefins.[57] Cyclopropanes and aziridines were synthesised in good to excellent yield from various olefins using the copper(I) complex of **99**. Kang *et al*. describe a novel tetra-



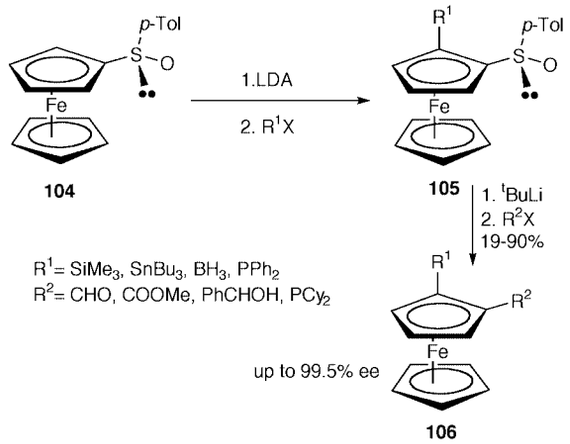

substituted ferrocenyl diphosphine ligand **100**[58] which induces extremely high enantiomeric excess in the rhodium-catalysed asymmetric hydrogenation of various dehydroamino acid derivatives. The synthesis of this novel ligand was accomplished with 99.9% ee from 1,1′-ferrocenedicarbaldehyde in 6 steps.

Amongst the new methodology developed for the generation of chiral ferrocene derivatives, two reports show especial potential. The synthesis of chiral ferrocenyl diols **102** and **103** from their alkene precursors has been accomplished (Scheme 36).[59] The vinyl ferrocene **101** was found to be totally unreactive under standard Sharpless dihydroxylation conditions but improvements were achieved by a systematic variation of conditions. Although each derivative behaved differently, a solvent mixture of 1:1 acetonitrile–water and three equivalents of additive [$K_3Fe(CN)_6$ and $K_2CO_3$] yielded the desired diols with ees as high as 97% (>99% after recrystallisation) and in excellent yields. Homoallyl substrates were also treated with some success.




**Scheme 36**

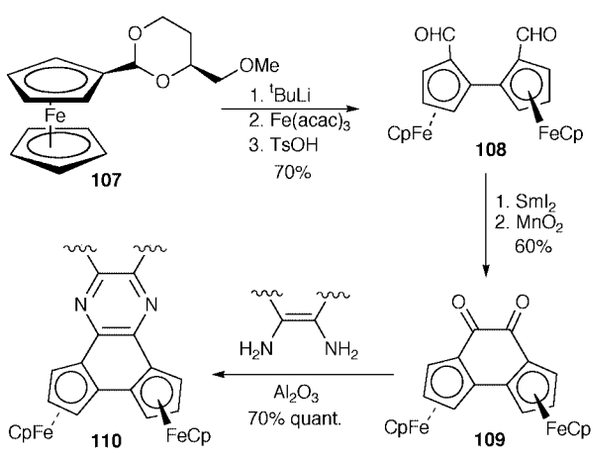
Kagan and co-workers report a short and flexible asymmetric synthesis of enantiopure 1,2-disubstituted ferrocenes (Scheme 37).[60] The strategy involves the enantiopure *p*-tolyl sulfoxide **104**, prepared with >99.8% ee by a previously-developed method from metallated ferrocene and commercially available




**Scheme 37**

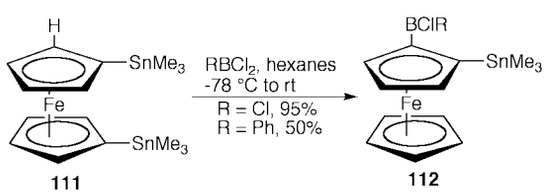
($R_s$) or ($S_s$)-menthyl *p*-tolyl sulfinate. A highly diastereoselective (>98% de) *ortho*-functionalisation of sulfoxide **104** was then achieved by treatment with LDA; a subsequent electrophilic quench afforded complex **105**. A second functionalisation was accomplished by treatment with *tert*-butyllithium followed by various electrophiles to generate chiral ferrocene derivatives **106** with total stereocontrol.

A novel $C_2$-symmetric chiral bisferrocenyl derivative has been described (Scheme 38).[61] The enantiomerically pure acetal **107** was diastereoselectively *ortho*-lithiated and Fe(III)-mediated coupling followed by deprotection afforded the chiral bisferrocenyl bisaldehyde **108** in high yield. Only the $C_2$-symmetric isomer was formed; no *meso* isomer was detected. Pinacolisation by samarium iodide followed by oxidation of the diol led to the *o*-quinone **109**. Condensation with various aromatic 1,2-diamines led to quinoxaline derivatives **110** in good to excellent yield.



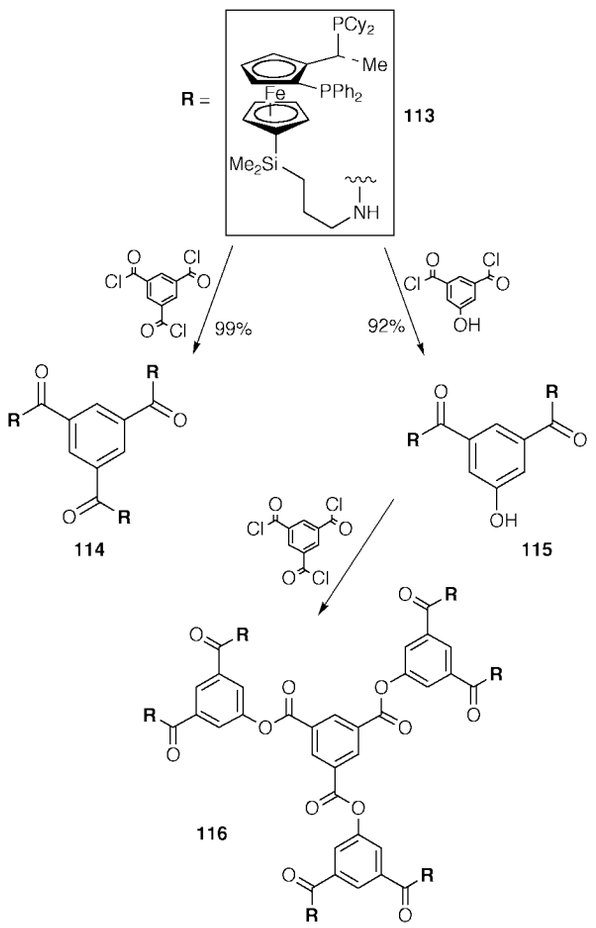

**Scheme 38**

The one-step synthesis of Lewis acids based on the ferrocenyl skeleton has been reported by Manners and co-workers (Scheme 39).[62] Treatment of 1,1′-bis(trimethylstannyl)ferrocene **111** with haloboranes led to 1-stannyl-2-boryl ferrocenes **112**. An unusual substituent rearrangement between cyclopentadienyl rings was observed during this process.



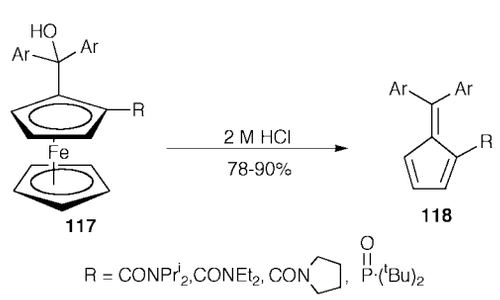

**Scheme 39**

Ferrocene-based dendrimers are interesting as a potential solution to the problem of catalyst recovery by means of nanofiltration or precipitation. Chiral ferrocenyl amine **113**, whose tether length appears sufficient to ensure conformational flexibility at the dendrimer periphery, reacted smoothly with benzene-1,3,5-tricarboxylic acid trichloride to afford the first generation dendrimer **114** (Scheme 40).[63] A second generation dendritic system **116** was synthesised from intermediate **115**. Dendrimer yields are excellent. Asymmetric hydrogenation with these dendritic complexes afforded high enantioselectivities (>98%). Togni and co-workers report the complete retention of **116** (with an estimated molecular size of 3 nm), by a commercial nanofiltration membrane.




**Scheme 40**

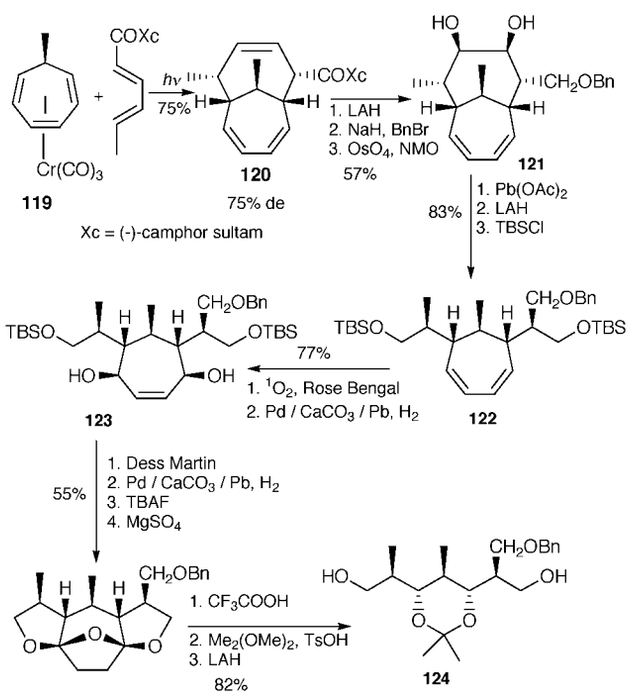
Previously only accessible by a Friedel–Crafts protocol, a novel preparation of *ring-functionalised* fulvene derivatives is reported by Snieckus and co-workers (Scheme 41).[64] Directed *ortho*-metallation on a ferrocenyl amide affords **117** which undergoes acid-catalysed Nesmeyanov fragmentation to deliver a variety of the ring substituted 6-aryl and 6,6-diaryl fulvenes **118** in high yield; a variety of amide and phosphinyl directed metallation groups were employed.




**Scheme 41**

## 8 η⁶-Complexes of chromium

Rigby has further extended his elegant methodology of higher order (6π + 4π) cycloadditions to construct the C5–C11 segment of the ansa bridge found in the ansamycin antibiotics streptovaricin C and D and damavaricin D (Scheme 42).[65] The key step involved the irradiation of the 7-*exo*-methylcycloheptatriene complex **119** in the presence of the *N*-sorbate derivative of (−)-camphorsultam to yield the cycloadduct **120** in good yield and 75% de. The major diastereoisomer was chromatographically separated and carried through the remaining sequence: reduction, benzyl protection and subsequent *cis*-dihydroxylation gave **121**. Oxidative cleavage of the diol, reduction of the resultant aldehydes and protection as TBS ethers yielded the highly substituted cycloheptadiene **122**. Face selective cycloaddition of $^1O_2$ across the diene was followed by reductive cleavage of the peroxide to provide the *syn* diol **123** in excellent overall yield. This was then carried through, *via* a bisacetal, to the protected diol bearing the entire substitution pattern of the target **124** in six steps.

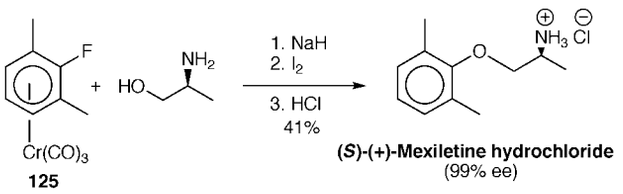



**Scheme 42**

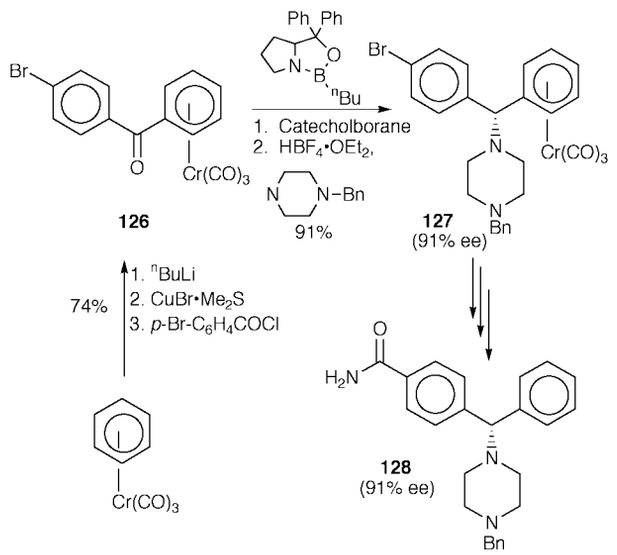
Due to their unique chemical and stereochemical properties, (η⁶-arene)tricarbonylchromium complexes continue to enjoy increasing application in synthetic organic chemistry. A variety of transformations have been carried out leading to various natural products and their derivatives.

An attractive application of these complexes is a novel stereospecific synthesis of both enantiomers of Mexiletine (Scheme 43).[66] (The (*R*)-isomer of Mexiletine, a class I-B antiarrhythmic agent, could previously be synthesised in only 7.2% yield in a stereospecific four-step procedure.) Loughhead *et al.* describe a smooth displacement of fluoride from the parent chromium complex **125** using a variety of primary and secondary alkoxides bearing unprotected primary, secondary and tertiary amino functionalities. Application of commercially available enantiopure 2-aminopropan-1-ol in the $S_NAr$ coupling process afforded the Mexiletine complex in moderate yield (after decomplexation and hydrochloride salt formation) but with excellent ee.

Dolorme *et al.* have described an efficient asymmetric synthesis of diarylmethylamines, which form an integral part of many pharmacologically active compounds including the delta receptor agonist (+)-BW373U86 (Scheme 44).[67] The (4-bromo-




**Scheme 43**

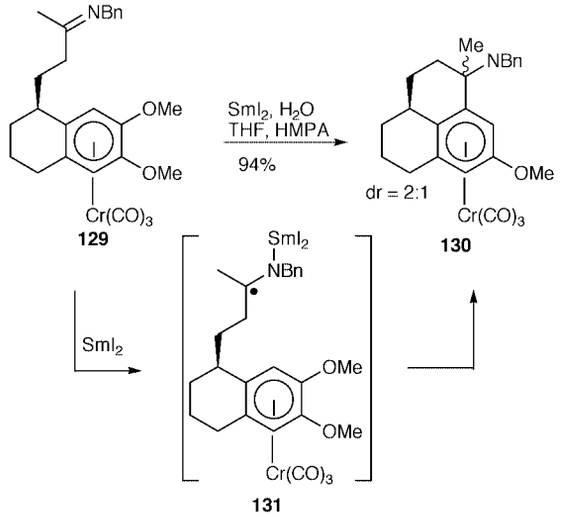



**Scheme 44**

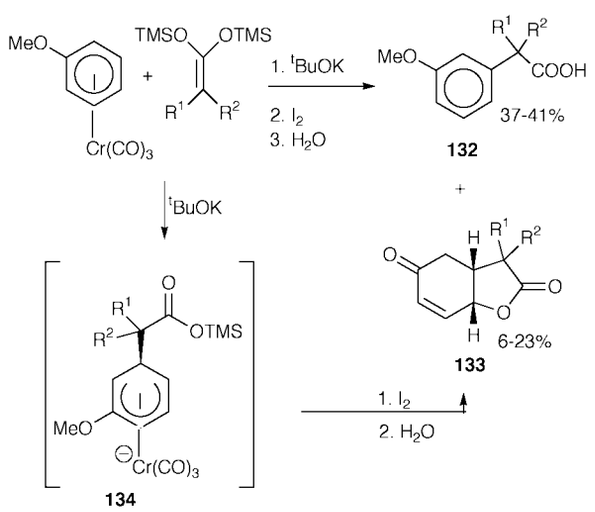
benzophenone) tricarbonylchromium complex **126**, formed from (benzene)tricarbonylchromium in good yield, was asymmetrically reduced using Corey's oxazaborolidine catalyst in 91% ee. *N*-Benzyl piperazine was then introduced to afford methanol **127** which was decomplexed and carried through to the desired delta receptor ligand **128** without any loss of enantiomeric purity in moderate yield.

In continuation of his use of chiral ($\eta^6$-arene)tricarbonylchromium complexes as building blocks, Schmalz reports the first ketimine cyclisation on the complexed arene mediated by $SmI_2$ (Scheme 45).[68] The model imine **129**, on treatment with excess $SmI_2$ in the presence of water, cyclised to yield a diastereoisomeric mixture of the product **130** in a 2:1 ratio and in excellent yield. The cyclisation is believed to involve the azaketyl radical **131** which adds to the activated ring from the face opposite to that of the metal. Single electron reduction of the resulting 17 valence electron species and chromium-guided *endo*-protonation gives an $\eta^4$-intermediate from which **130** is formed by the elimination of methanol. In a related $SmI_2$ single electron-driven transformation, Schmalz effects the hydrogenation of styrene complexes of tricarbonylchromium using water as a proton source.[69] A chromium stabilised benzylic anion, formed on trapping a benzylic radical by electron transfer, undergoes regio- and stereoselective protonation from the less hindered *exo* face.

An unexpected, double *exo* nucleophilic addition has been reported by Bellasoued *et al.* (Scheme 46).[70] In exploring the previously unknown, direct introduction of carboxylic acid groups into ($\eta^6$-arene)tricarbonylchromium complexes, a variety of bis(trimethylsilyl)ketene acetals were reacted with mono-substituted substrates in the presence of *t*-BuOK. The desired *meta*-substituted carboxylic acids **132** were obtained in good to excellent yields. However, a double nucleophilic addition resulted in the concomitant formation of tetrahydrobenzofurandiones **133** when anisole complexes were used. Although the mechanism of this apparent [3 + 2] cycloaddition is a matter of speculation, experiments suggest the intra-




**Scheme 45**

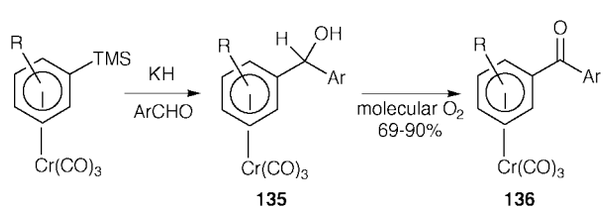



**Scheme 46**

molecular trapping of intermediate **134** during the oxidative demetallation step.

Exploiting his previously reported facile cleavage of an Ar–Si bond (where the arene ring is complexed to a tricarbonylchromium moiety) by commonly used bases at room temperature, Mandal and Sarkar now describe a convenient and general synthesis of biarylketones **136** (Scheme 47).[71] Following desilylation with KH the complexed phenyl anion is trapped by various aromatic and heteroaromatic aldehydes. The resultant methanol **135** undergoes autoxidation in the presence of molecular oxygen to afford the biarylketones in very good yield. The novelty of this one-pot sequence is the function of KH first as a nucleophile in the desilylation step and then base during autoxidation; also of note is the remarkable stability of the tricarbonylchromium moiety to these oxidising conditions.

Gibson has demonstrated the introduction of nitrogen, usually an inefficient process, into α-oxygenated arene tri-

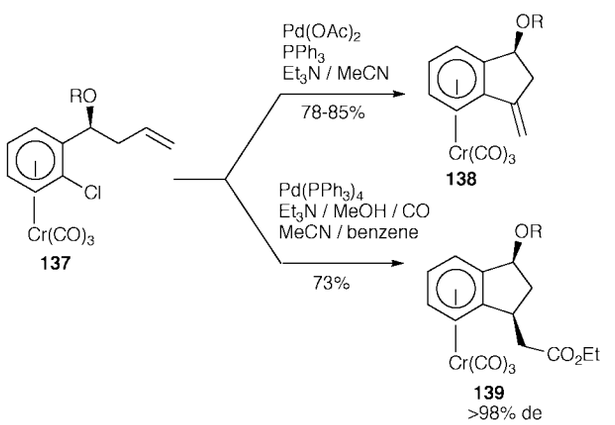



Ar = Ph, 4-Me-Ph, 2-thienyl, 2-pyridyl, ferrocenyl

**Scheme 47**

carbonylchromium complexes.[72] Complexed benzyl methyl ethers underwent methoxy substitution in the presence of $HBF_4{\cdot}OMe_2$ for the *N*-nucleophilic *tert*-butyl *N*-hydroxycarbamate. The defined stereochemistry (introduced beforehand by her previously reported functionalisation of the benzylic position using a chiral base) is retained thus providing, after reduction, decomplexation and Boc deprotection, a variety of non-racemic chiral amines in good yield and ee.

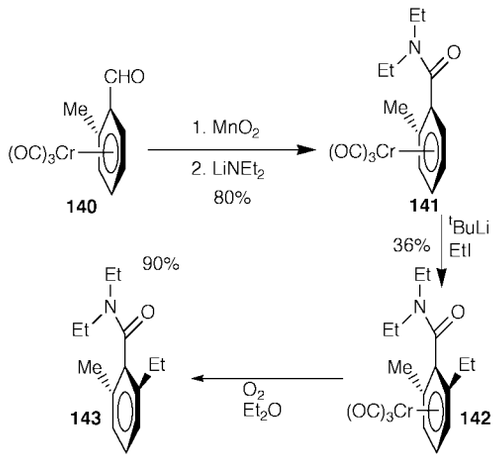
A hitherto unknown palladium-catalysed cyclisation reaction has been reported by Kündig and co-workers (Scheme 48).[73] The tricarbonylchromium group effectively activates the $C_{Ar}$–X bond of a complexed haloarene to intramolecular aryl alkenation. The planar chirality of the alkenyl chlorobenzene complex **137** was found to exert a powerful influence on the diastereoselectivity of the intramolecular Heck reaction: methylene indane complexes **138** could be formed in 75–85% de. However, the β-elimination which terminates the sequence destroys the stereogenic centre created in the carbopalladation step. In the presence of carbon monoxide and methanol, though, the termination step is modified to yield esters **139** with excellent diastereoselectivity.



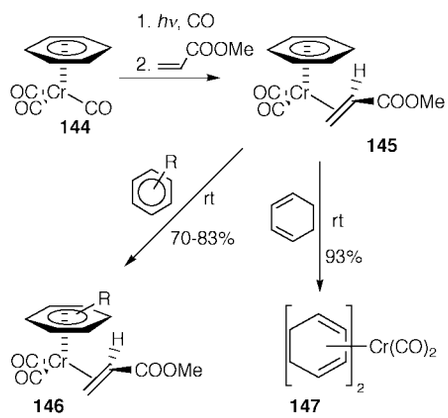

**Scheme 48**

The utility of planar chiral ($\eta^6$-arene)tricarbonylchromium complexes has also been efficiently exploited by Uemura in the remarkable synthesis of axially chiral enantiopure 2,6-disubstituted *N*,*N*-dialkyl benzamides **143** (Scheme 49).[74] Optically pure tricarbonyl(2-methylbenzaldehyde)chromium complex **140** was initially oxidised to the corresponding methyl benzoate with $MnO_2$, NaCN and methanol. Direct *ortho*-lithiation of the corresponding *N*,*N*-diethyl amide **141** followed by electrophilic quench using iodoethane resulted in a moderate yield of enantiomerically pure axially chiral complexes **142**. Oxidative demetallation released the target axially chiral benzamides **143**. To prevent the slow racemisation of these compounds at room temperature, bulkier substituents were efficiently introduced using the same strategy.

The ligand exchange reaction is a key step in catalytic applications of ($\eta^6$-arene)tricarbonylchromium complexes. A report by Kündig *et al*. describes the acrylate-assisted labilisation of the arene–metal bond.[75] Haptotropic slippage is induced in the normally inert (benzene)tricarbonylchromium complex **144** when one carbon monoxide ligand is photolytically replaced by an acrylate (Scheme 50). The resultant dicarbonyl complex **145** was found to be unusually susceptible to arene substitution and displacements. Treatment of the acrylate-substituted complex afforded near quantitative amounts of hexacarbonylchromium when stirred at room temperature under a CO atmosphere. Dissolving the complex in cyclohexadiene resulted in the bis-($\eta^4$-cyclohexadiene) complex **147** in high yield. Arene exchange to afford **146** was also facile: a variety of arenes were introduced at room temperature in 70–83% yield. The labilisation effect is probably due to a smooth $\eta^2$ to $\eta^4$ slippage of the




**Scheme 49**



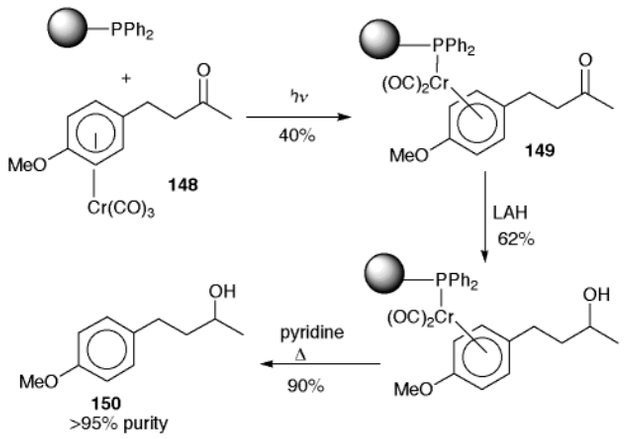

**Scheme 50**

acrylate ligand which induces a corresponding $\eta^6$ to $\eta^4$ slippage of the coordinated arene. Preliminary experiments with this novel chromium complex **145** have realised the catalytic hydrogenation of methyl sorbate to methyl *cis*-hex-3-enoate at ambient temperature in 87% yield.

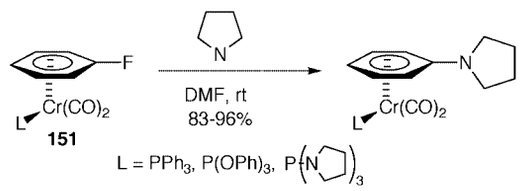
Also in the field of catalysis, Uemura and co-workers have demonstrated an efficient Pd(0)-catalysed amination of aryl bromides using ($\eta^6$-arene)tricarbonylchromium derivatives as accelerating ligands.[76] The chromium ligand sphere is able to modulate the inductive capacity of an $\eta^6$-arylphosphorus atom (thus modifying the complexes' ligating properties) by substitution in the tricarbonylchromium tripod with a phosphine. Thus, monotriphenylphosphine(dicarbonyl)chromium complexes were found to be efficient supporting ligands for the Pd(0)-catalysed amination of both electron-rich and poor aryl bromides.

A new development is the use of a dicarbonylchromium moiety as a means to immobilise arene substrates onto a solid support *via* their $\eta^6$-complexes (Scheme 51).[77] Chemical manipulation and subsequent release into solution allows the filtration of the detached arene, effectively demonstrating the concept of "traceless" linking. Hence, tricarbonyl(4-methoxyphenylbutan-2-one)chromium complex **148** was irradiated in the presence of polymer-supported triphenylphosphine in THF to yield **149**. Reduction on the solid phase gave **150** after liberation from the polymer in good overall yield.

In a related report, Semmelhack *et al*. have carried out model studies of $S_NAr$ reactions on a variety of ($\eta^6$-fluorobenzene) complexes of $Cr(CO)_2L$ **151** (Scheme 52) to evaluate candidates for phosphine linker ligand L.[78] The rapid and highly efficient reaction using the tris(pyrrolyl)phosphine ligand indicates this phosphine to be suitable for development into a solid phase linker.



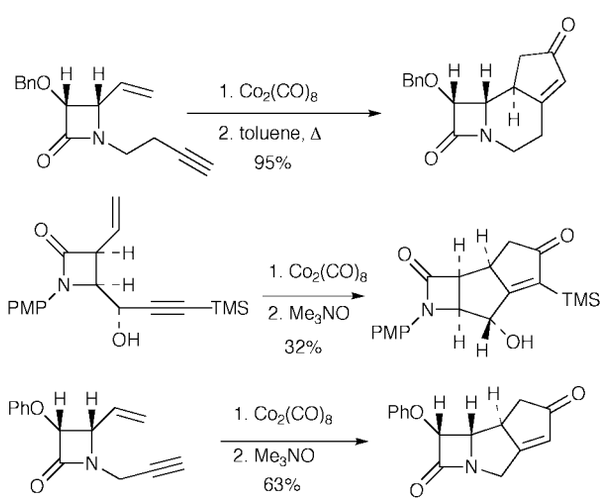

**Scheme 51**




**Scheme 52**

## 9 Pauson–Khand reactions

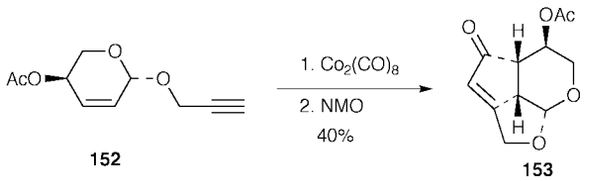
The inherent simplicity of the Pauson–Khand reaction, the carbonylative cyclisation of enynes, makes it a method of choice for the synthesis of selected complex ring systems. A highly diastereoselective synthesis of tribactams *via* a Pauson–Khand reaction on enynes tethered to a strained four membered heterocycle has been reported by Alcaide *et al.* (Scheme 53).[79] This provides an efficient synthetic approach to both racemic and enantiomerically pure fused tricyclic azetidin-2-ones and azetidines by simultaneous construction of two of the three rings of the target. A wide variety of monocyclic enyne β-lactam ring fusions were investigated. Treatment with dicobaltoctacarbonyl afforded the (alkyne)hexacarbonyldicobalt complexes in near quantitative yield; these smoothly cyclised to the corresponding tricyclic systems on treatment with chemical promoters or under thermal conditions.




**Scheme 53**

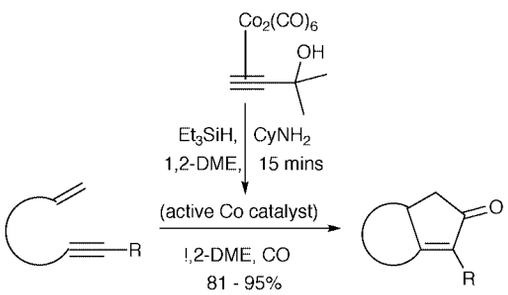
The intramolecular Pauson–Khand reaction of thioether-linked enynes has been employed in the stereoselective synthesis of *cis*-fused perhydroazulenes and perhydrocyclopentacyclooctenes:[80] reductive cleavage of the tetrahydrothiophene component of the resulting tricycles removes the temporary sulfur-bridge to deliver the target bicyclic structures.

The intramolecular Pauson–Khand reaction on a sugar pyranoside has also been successfully used in the synthesis of enantiomerically pure Iridoid aglycones (Scheme 54):[81] reaction of the β-anomer of an enyne **152** derived from 3,4-diacetyl-L-arabinal under chemical activation gave the resulting aglycone **153** possessing the correct absolute configuration required for the Iridoid skeleton.



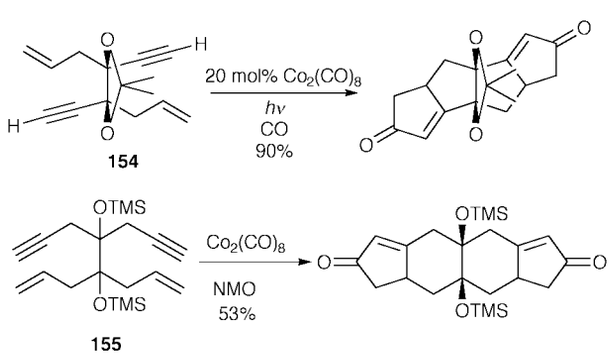

**Scheme 54**

In an exciting development, Livinghouse and co-workers have demonstrated the extraordinary catalytic ability of selected (alkyne)hexacarbonyldicobalt complexes to serve as substitutes for the comparatively unreliable octacarbonyldicobalt-catalysed thermal Pauson–Khand reaction.[82] These "shelf-stable" crystalline complexes, on *in situ* reductive decomplexation with triethylsilane or triethoxysilane, represent an active cobalt catalyst which proved to be exceptionally efficient in catalysing the intramolecular cyclisation of enynes (Scheme 55).[83]



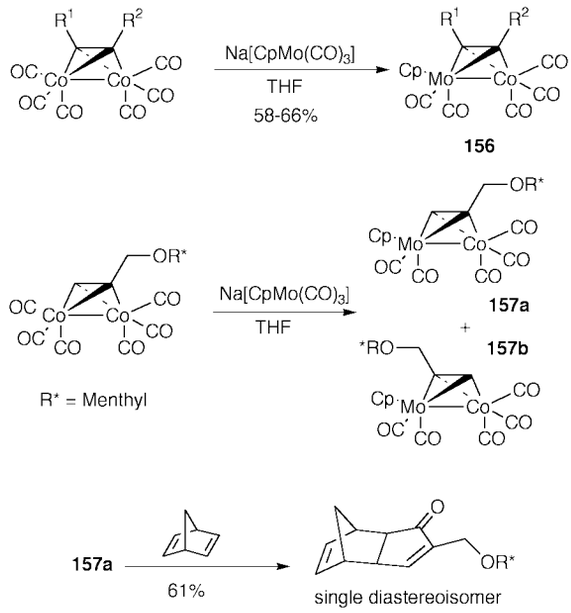

**Scheme 55**

Cook and co-workers report a photochemically-mediated catalytic tandem intramolecular Pauson–Khand reaction. The diynediene **154** was converted in a totally regioselective manner into the product tetracycle upon irradiation in the presence of 20 mol% octacarbonyldicobalt (Scheme 56).[84] The same group also presents the synthesis of *cis* fused decalin systems by a thermally-promoted intramolecular Pauson–Khand reaction of dienediynes **155**.[85]




**Scheme 56**

Another striking new development in this area is the synthesis of a heterobimetallic alkyne complex **156** and its use in the Pauson–Khand reaction (Scheme 57).[86] The novel complex




**Scheme 57**

was synthesised by the reaction of a tricarbonyl(cyclopentadienyl)molybdenum anion with (alkyne)hexacarbonyldicobalt complexes. Simple thermal activation in the presence of alkenes afforded cyclopentenones in yields which compared favourably with the corresponding hexacarbonyldicobalt complex. The inherent asymmetry of the complex was harnessed by the synthesis of complexes bearing a chiral auxiliary **157a** and **b**; impressively, either complex induced 100% diastereoselectivity in the Pauson–Khand product as compared to the marginal diastereoselectivity observed with the corresponding hexacarbonyldicobalt complex.

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