Applications of stoichiometric organotransition metal complexes in organic synthesis

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1 Introduction

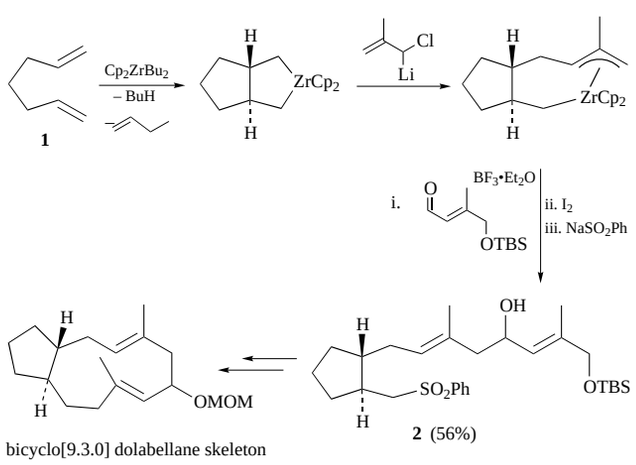
This article is a review of the literature published between May 1996 and April 1997, and is designed to be a selective account of developments in the field of stoichiometric organotransition metals in organic synthesis. The survey supplements two previous reviews, already published in *Contemporary Organic Synthesis*.[1]

The manner in which the field has been subdivided follows earlier precedent,[1] with preference being given to methods which will be useful to the practising organic chemist.

2 Transition metal alkyl, alkenyl, alkynyl and acyl complexes in organic synthesis

2.1 Alkyl and alkenyl organozirconium based methodology

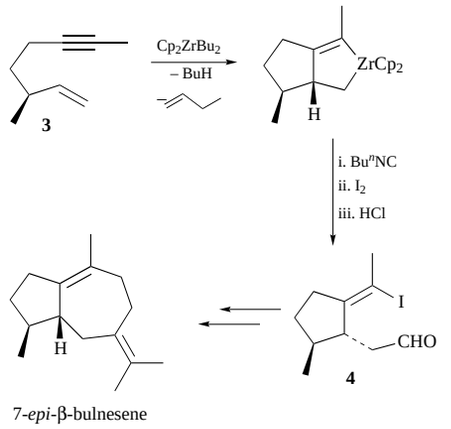
Whitby and his group have continued to expand on the scope of their organozirconium based methodology.[2] An efficient construction of the dolabellane skeleton was reported by treatment of diene **1** with the reactive 'Cp_2Zr' fragment: this gave a *trans*-fused zirconacycle which was subsequently treated with an α-chloro allyllithium reagent (**Scheme 1**). The resulting η^3-zirconium species was then functionalised twice: firstly by reaction with an aldehyde in the presence of BF_3–diethyl ether, and secondly upon reaction of the remaining carbon–zirconium bond with iodine. After sulfone formation, the diene **2** was isolated as a 1.2:1 mixture of diastereoisomers; these were efficiently transformed into the requisite skeleton in five steps.



Scheme 1

Use of an enyne precursor to cyclisation enabled Negishi to undertake a similar sequence which resulted in the synthesis of (±)-7-*epi*-β-bulnesene (**Scheme 2**).[3] Compound **3** was cyclised in a manner analogous to reaction of **1**, and the resulting zirconacycle was functionalised with an isocyanide and then iodine to produce (after acid hydroysis) vinyl iodide **4**. This was subsequently transformed into the target molecule in four steps. Negishi has also used related chemistry to prepare a series of substituted cyclobutenes by reacting an alkene–zirconium complex with an alkyne to produce a zirconacycle which was subsequently reacted with BuLi.[4]

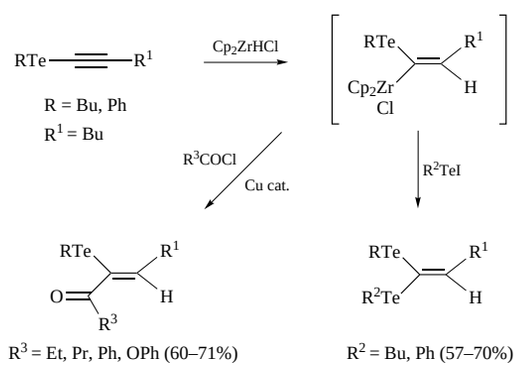
Further functionalisation of the zirconacycles that result from carbometallation of alkenes is the key to making organozirconium chemistry useful to synthetic chemists. Takahashi



Scheme 2

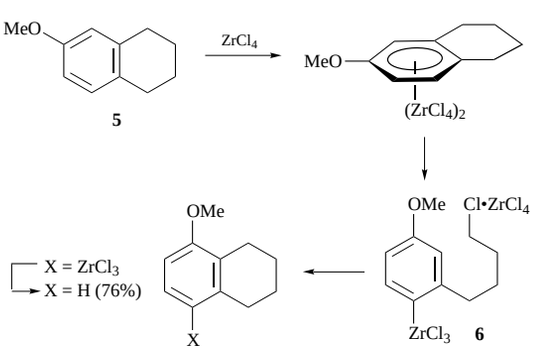
has shown that reaction of zirconacycles with acid chlorides (catalysed with copper) can lead to the formation of substituted cyclopentadienes and vinylcyclopropanes.[5] An unusual and potentially useful method of cyclopropane formation by the zirconium promoted rearrangment of allylic alcohols was reported by Taguchi and Hanzawa.[6]

Some interesting methodology describing the hydrozirconation of acetylenic tellurides has been reported recently (**Scheme 3**). Reaction of the resulting vinylzirconium species with acid chlorides[7] or tellurenyl iodides[8] gave substituted vinyl tellurides and ketene telluroacetals respectively. A nice synthesis of 1,4-dienes *via* the hydrozirconation of an allene, followed by carbometallation of the resulting allylzirconium complex onto an acetylene has been published by Suzuki's group.[9]



Scheme 3

Zirconium tetrachloride has been shown to promote a curious rearrangement of tetralins (**Scheme 4**).[10] Thus, reaction of **5** with the aforementioned Lewis acid gave an isomeric compound in good yield: the mechanism is formulated as proceeding through an η^6-arene complex which fragments to the corresponding alkylzirconium species **6**; recombination then yields the rearranged compound.



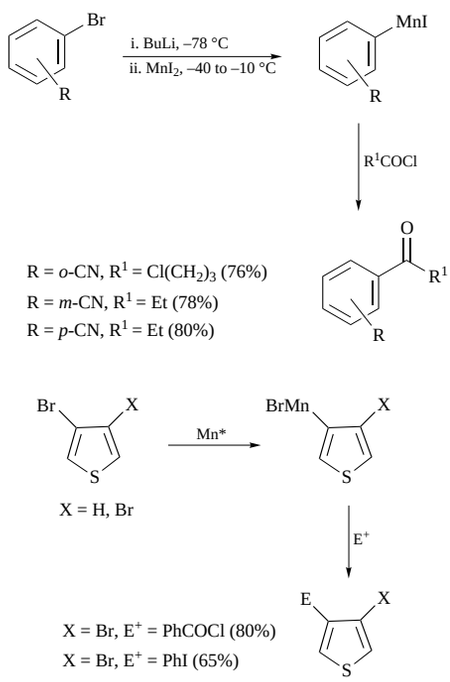
Scheme 4

Finally, although not strictly under the purview of this article, the reduction of secondary amides to imines by reaction with Cp_2ZrHCl, as reported by Ganem, is certainly a worthwhile new reduction that is sure to find application in the field of organic synthesis.[11]

2.2 Alkylmanganese reagents in organic synthesis

A significant amount of new work has been published in the area of organomanganese chemistry and these species look set to rival more traditional organometallic compounds such as organomagnesium or organozinc complexes as tools for synthesis.

Knochel has described the preparation of a range of functionalised aryl- and alkenyl-manganese halides from the corresponding organolithium compounds (**Scheme 5**).[12] These reagents react selectively with acid chlorides (to yield ketones) in the presence of esters, nitriles and alkyl chlorides. Knochel also illustrated that these reagents were capable of selective conjugate addition to α,β-unsaturated esters and ketones.



Scheme 5

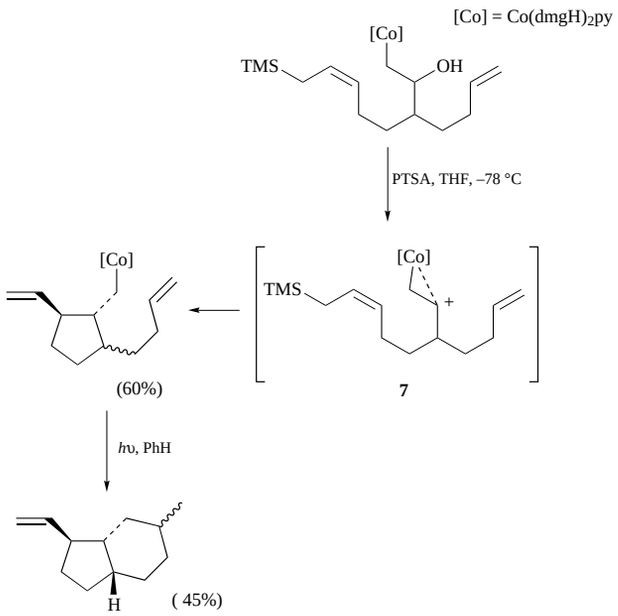
In a continuation of his earlier work, Rieke has shown that Rieke manganese is the metal of choice for direct oxidative addition to bromothiophenes (Scheme 5).[13] The resulting thiophene manganese reagents were coupled (palladium catalysed) with acid chlorides and aryl iodides. Moreover, the thiophenes which contained two bromine atoms (X = Br, Scheme 5) could be treated with a second portion of Rieke manganese and then a second electrophile to generate 3,4-disubstituted thiophenes in good yields.

There have also been some interesting developments regarding the formation and reactivity of allylmanganese reagents,[14] and also the use of organomanganese reagents to allow the preparation of substituted cyclopropanes and vinylsilanes.[15]

2.3 Alkylcobalt reagents in organic synthesis

The homolytic cleavage of a carbon–cobalt bond to generate radicals has been a productive area of organometallic chemistry.[16] It is less well known however, that the carbon–cobalt bond is also capable of providing anchimeric assistance to aid in the ionisation of a leaving group that is β to the metal. Branchaud has published some nice work concerning the outcome from ionisation of chiral secondary alcohols positioned β to an alkyl cobalt bond—this process results in the formation

of a cobaloxime π-cation which is attacked by a nucleophile.[17] In a confirmation of earlier work by Golding, this process was shown to proceed with overall retention (presumably *via* double inversion). Pattenden has demonstrated the electrophilc nature of cobaloxime π-cations in cyclisations, together with the potential of organocobalt complexes as radical precursors (**Scheme 6**).[18] Cyclisation of the allylsilane moiety onto cation **7** (which was generated *in situ* under acidic conditions) gave a heavily substituted cyclopentane. Homolytic cleavage of the weak C–Co bond was achieved by irradiation at room temperature and the resulting radical underwent a 6-*exo*-*trig* cyclisation: the low yield for this step is probably a consequence of the cyclisation of only one epimer of the radical precursor; the reductive termination of the radical cyclisation is rather unusual and deserving of note.



Scheme 6

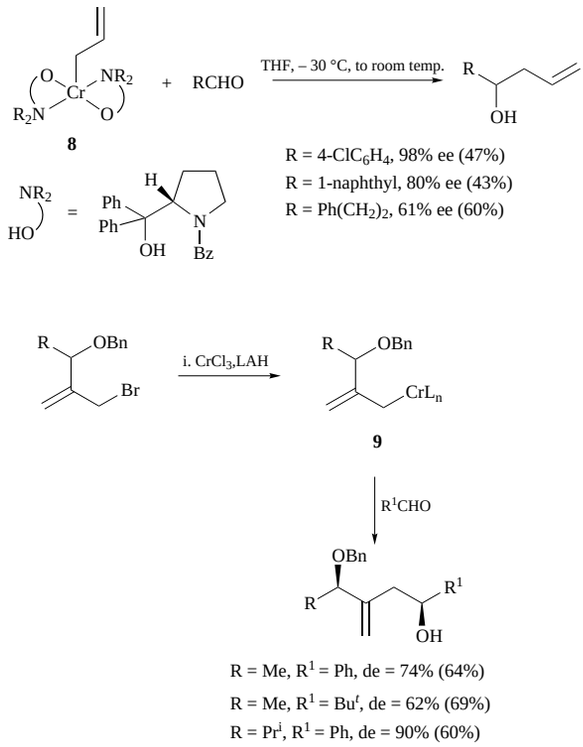
2.4 Miscellaneous alkyl and allyl transition metal reagents in organic synthesis

The large number of papers in this field means, inevitably, that there is insufficient space to describe all of the work that falls into this area.

Two papers have been published recently which describe the issues of stereochemistry that arise from the reaction of allylchromium reagents with aldehydes. One way of controlling the absolute stereochemistry of the products is to employ an enantiopure ligand on the metal in the hope that it will influence the course of the reaction. In this regard, Kibayashi's group have studied a range of chiral diols and amino alcohols as ligands for allylchromium reagents (**Scheme 7**).[19] Some impressive ees (up to 98%) were obtained by using (dialkoxyallyl)chromium(III) compounds **8**, modified by the addition of prolinol derivatives.

Of course, addition of a chiral allylchromium reagent to an aldehyde would be expected to result in the formation of an unequal mixture of diastereoisomers. Mulzer has done just this and has prepared chiral allylchromium reagents of this type **9** (Scheme 7).[20] Upon addition to an aldehyde one observes an excess of the *syn* diastereoisomer, with selectivities for the 1,4 asymmetric induction ranging up to 95:5 (90% de). In some conceptually related work, there has been some useful methodology published which examines the stereoselectivity obtained when chiral allyltitanium anions react with aldehydes; in this case the stereoinduction originated from a sulfoximine.[21]

The chemistry of organotitanium complexes continues to provide useful routes to valuable organic molecules. Petasis has



Scheme 7

expanded on his earlier work and introduced an alkenyltitanium reagent capable of transforming aldehydes into allenes.[22] Moreover, Schwartz has described an efficient route to a variety of glycals by treatment of 3-acetoxy glycosyl bromides with Cp_2TiCl.[23]

2.5 Acyl transition metal complexes

In the period to be covered, this area was confined to the chemistry of iron–acyl complexes.

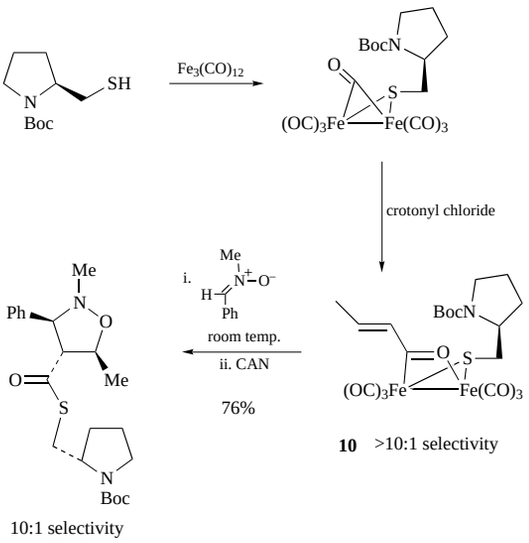
Enolates derived from $Fe(CO)(\eta^5\text{-}C_5H_5)(PPh_3)COCH_3$ have been thoroughly investigated, and are powerful tools for asymmetric synthesis:[24] a study of the reactions of the enolate of $Fe(CO)(\eta^5\text{-}C_5H_5)(PPh_3)COCH_2Ph$ has been reported in an attempt to prepare stereochemically defined aryl acetic acids.[25]

Gilbertson has continued his work on the cycloaddition reaction of diiron–acyl complexes and nitrones (**Scheme 8**).[26] The use of iron–acyl complexes as partners for nitrone cycloadditions has been previously shown to improve the low *endo*/*exo* ratio that is commonly observed with cycloaddition to α,β-unsaturated esters. However, in this case, additional control of absolute stereochemistry is made possible by the synthesis of enantiopure diiron–acyl complex **10** (Scheme 8). Use of the thiol derived from *N*-Boc proline enabled the complex **10** to be formed with >10:1 diastereoselectivity: this complex then underwent diastereoselective cycloaddition with nitrones and the resulting complexes were transformed into the corresponding (enantiopure) thioesters by oxidation of the iron with Ce^{IV}. The issue of stereochemistry here is quite complicated and the reader is urged to consult the primary literature for a more detailed account.

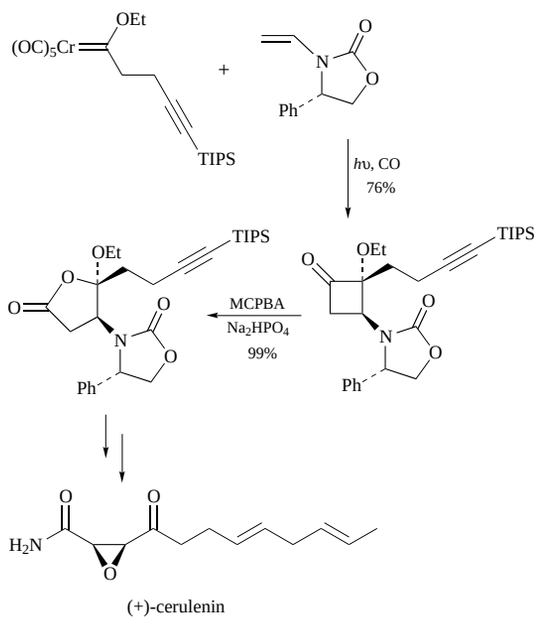
3 Transition metal carbene and vinylidene complexes in synthesis

3.1 Annulations

Hegedus has continued to publish some stimulating work in the area of carbene photochemistry. Recent endeavours have reported the synthesis of (+)-cerulenin utilising the (diastereoselective) photochemical reaction of a chromium alkoxycarbene with an enantiopure ene carbamate (**Scheme 9**).[27] The resulting



Scheme 8



Scheme 9

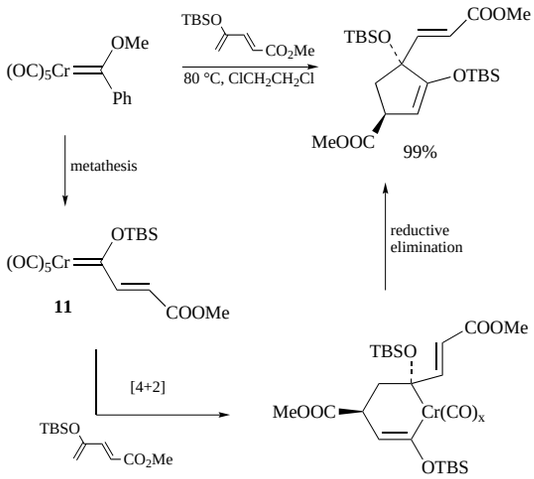
cyclobutanone was expanded to a δ-lactone *via* a regioselective Baeyer–Villiger oxidation; the target molecule was then prepared efficiently in a further seven steps.

An unusual synthesis of cyclopentenes has been published which involves the reaction of a diene with a chromium alkoxycarbene in a formal [3 + 2] cycloaddition (**Scheme 10**).[28] The reaction was presumed to proceed *via* an initial ligand carbene metathesis to generate a new unsaturated carbene species **11**: remarkably, this complex acted as a 4π component in a subsequent [4 + 2] cycloaddition and reductive elimination of the metal generated the cyclopentene in excellent yields and with high diastereoselectivities.

The annulation of alkynylcarbenes has continued to provide interesting routes to unsaturated carbocyclic ring systems: work by Aumann has described a method of preparing substituted cyclopentadienes by reacting alkynylcarbenes with enamines.[29]

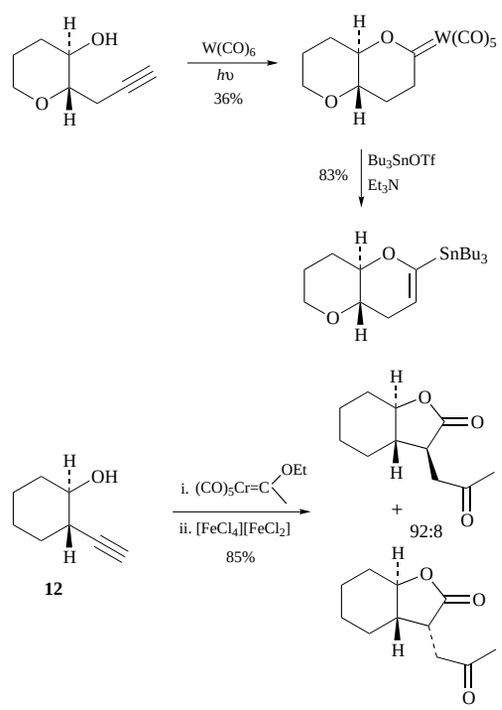
3.2 Spirocycle formation

The reaction of but-3-ynyl alcohols with chromium, tungsten and molybdenum carbonyls is known to furnish cyclic carbene complexes. This useful reaction has been studied further, and McDonald has recently shown that bis-homoacetylenic



Scheme 10

alcohols undergo cyclisation when treated with tungsten hexacarbonyl: the products are six-membered ethers containing an exocyclic carbene functionality and, moreover, the transition metal can be easily removed from the substrate to give a vinyltin species (**Scheme 11**).[30]

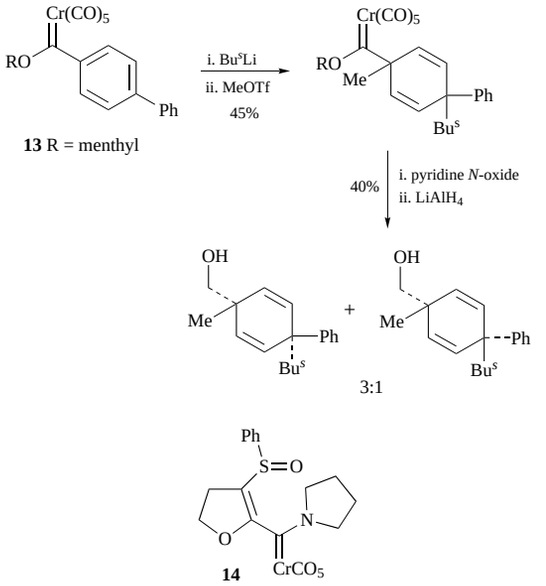


Scheme 11

Compare the above cyclisation with that accomplished by treatment of acetylenic alcohols with alkoxycarbene complexes (Scheme 11).[31] Reaction of **12** with an alkoxy chromium carbene proceeded to give the cyclised products in good yields and alteration of the number of carbon atoms between the acetylene and the hydroxy group facilitated the synthesis of a variety of ring sizes.

3.3 Miscellaneous reactions of carbene and vinylidene complexes

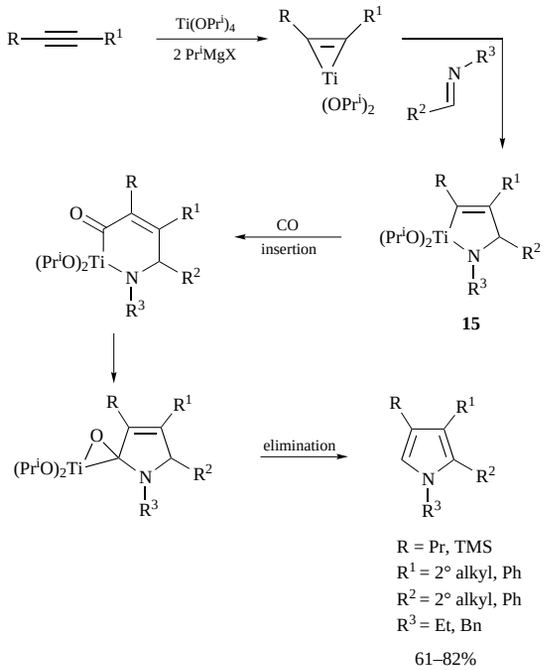
Barluenga's group have published an interesting new method of synthesising functionalised dihydrobenzenes *via* reaction of an aryl alkoxy chromium carbene complex. Apparently, the electron deficient transition metal moiety suffices to activate the aromatic ring of **13** to *nucleophilic* attack (**Scheme 12**).[32] Moreover, the resulting enolate may be quenched, in a diastereoselective fashion, by addition of an electrophile. The metal was



13 R = menthyl

14

Scheme 12



15

Scheme 13

removed under standard oxidative conditions to furnish a carboxylic ester in good yield and removal of the auxiliary was achieved with a reductive step. Once optimised, this chemistry promises to become an interesting alternative to the Birch reduction.

Quayle has reported the formation of the rather unusual carbene complex **14** (Scheme 12).[33] Oxidation of the corresponding thioether carbene complex with hydrogen peroxide (activated with methyltrioxorhenium) gave **14** in good yield: the authors point out that the stability of this complex is remarkable given that sulfoxides are commonly used to decomplex aminocarbenes into amides! Indeed, this paper is one of a series which have appeared recently showing that organotransition metal complexes can be used in conjunction with a judiciously chosen oxidant without oxidation of the metal.[1]

While the Wittig olefination is well known to work with metal carbenes as substrates, a recent report has shown that carbonyl stabilised sulfur ylides also react with chromium alkoxy carbenes, so providing an unusual route to 2-acylvinyl ethers.[34]

The reaction of alkoxycarbenes with alkynes and isocyanates has been reported. Use of these two reagents results in a nice synthesis of the 2-butene-4-lactam skeleton.[35] Indeed, the viability of this chemistry was demonstrated in an efficient synthesis of (−)-PI-091 which is an interesting platelet aggregation inhibitor.

4 η^2-Complexes in organic synthesis

4.1 η^2-Complexes with titanium

Sato and co-workers have again had a productive year! A large amount of useful chemistry involving the synthesis and reactivity of olefin and alkyne titanium complexes has been published recently. These complexes can be formed by reacting a suitable π-system with titanium tetraisopropoxide and isopropylmagnesium chloride and they behave in a manner reminiscent of alkene- and alkyne-zirconium complexes which have been described earlier in this review.

Reaction of alkyne–$Ti(OPr^i)_2$ complexes with imines and then subsequent reaction with CO gas (1 atm pressure) provided a neat synthesis of a variety of substituted pyrroles (**Scheme 13**).[36] The reaction is believed to proceed *via* the azatitanacyclopentene **15** which undergoes CO insertion, migration and elimination to yield the requisite pyrrole in good yield.

The '$Ti(OPr^i)_2$' fragment is responsible for initiating the cyclisation of dienes, diynes and enynes. Moreover, as the product of cyclisation contains two carbon–titanium bonds, further functionalisation of the products can be accomplished by reaction with suitable electrophiles. The cyclisation of the diynes shown in **Scheme 14** illustrates this point admirably.[37] Indeed, the use of silicon as a substituent on one of the alkyne units means that, after cyclisation, a regiochemically controlled electrophilic quench (with an aldehyde) can be performed. Clearly, this methodology will prove to be an important method of carbon–carbon bond formation in the future.

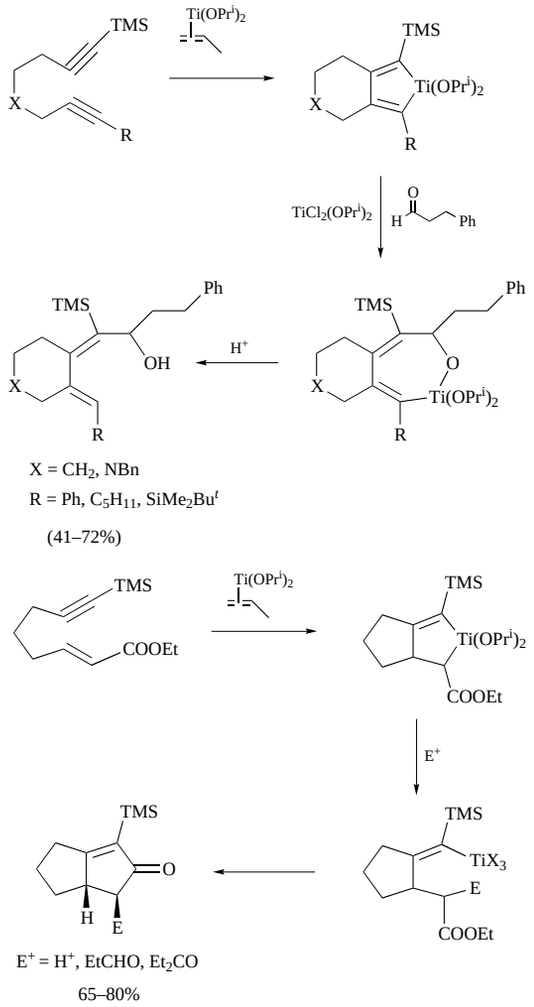
The situation can become even more interesting if one of the olefinic partners for a cyclisation is activated by an ester group (Scheme 14).[38] In this case the titanium intermediate undergoes regioselective reaction at the *alkyl*–titanium bond (this result should be compared to the results described above) and subsequent intramolecular attack at the ester group ensues to yield a series of bicyclic enones.

Cha has recently reported a simple and elegant procedure for the cleavage of allyl ethers and esters; this threatens to become the method of choice for such a transformation (**Scheme 15**).[39] Once more, this reaction relies on the intermediacy of an η^2-alkene complex formed from reaction of $Ti(OPr^i)_4$ and c-$C_6H_{11}MgCl$: this reagent transfers '$Ti(OPr^i)_2$' to the alkene functionality of an allyl ether and the resulting complex **16** is unstable with respect to rearrangement to the allyl metal. Hydrolysis of the oxygen–titanium bond occurs upon work-up to generate the free alcohol or acid in excellent yield. This chemistry appears to be rather general and will tolerate other protecting groups (esters are an obvious exception) as illustrated by the selective deprotection of **17** and **18**.

4.2 η^2-Complexes with cobalt

Derivatisation of alkynes with dicobalt hexacarbonyl has seen widespread use in synthesis, particularly in the area of the enediyne antitumor agents as pioneered by Magnus. Recently, Caddick has used the intramolecular aldol reaction of cobalt complex **19** to good effect in a stereoselective synthesis of the kedarcidin core enediyne **20** (**Scheme 16**).[40] The advantage that cobalt complexation gives to the process revolves around the deviation from linearity that the transition metal enforces upon the alkyne: naturally this makes the synthesis of strained cyclic compounds easier.

Recent work by Nicholas has illustrated how dicobalt



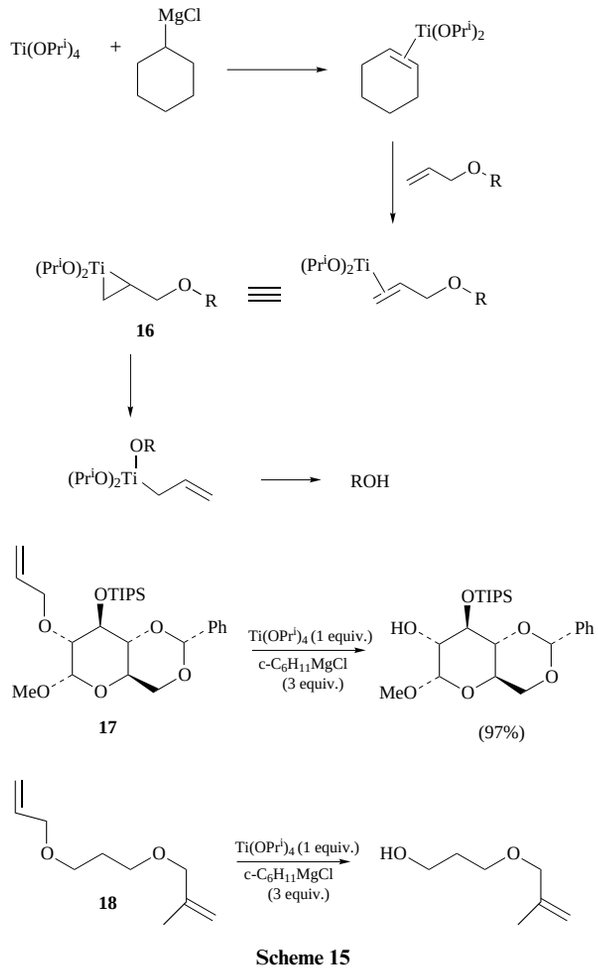
Scheme 14

hexacarbonyl complexed aldehydes may be used as substrates for reaction with (*Z*)- and (*E*)-γ-alkoxy diisopinocampheylboranes.[41] Apparently, the transition metal serves to ensure these reactions proceed with high levels of regio-, diastereo- and enantio-selectivity.

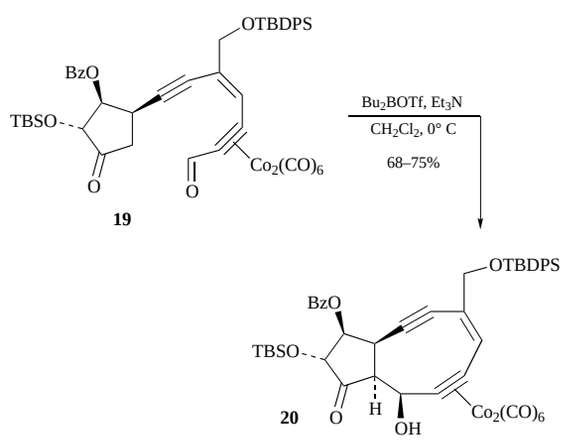
Of course, it is the expeditious formation of carbocations adjacent to a dicobalt complexed alkyne and subsequent reaction with a nucleophile (the Nicholas reaction) that garners most interest in this area. Krafft has succesfully utilised 1,1-disubstituted alkenes as nucleophilic partners in this reaction.[42] Moreover, Jacobi has used both boron enolates and silylenol ethers to facilitate the construction of stereochemically defined γ-acetylenic carboxylic acid derivatives. For example, reaction of oxazolidinone enolate **21** with the dicobalt acetylene complex in **Scheme 17** enabled an addition reaction to occur (presumably *via* the intermediacy of a cobalt stabilised carbocation).[43] Ceric ammonium nitrate facilitated decomplexation of the transition metal and removal of the chiral auxiliary was achieved (with lithium hydroperoxide) in good yield to furnish **22**; this material was then converted into (−)-phaseolinic acid.

4.3 η^2-Complexes with osmium

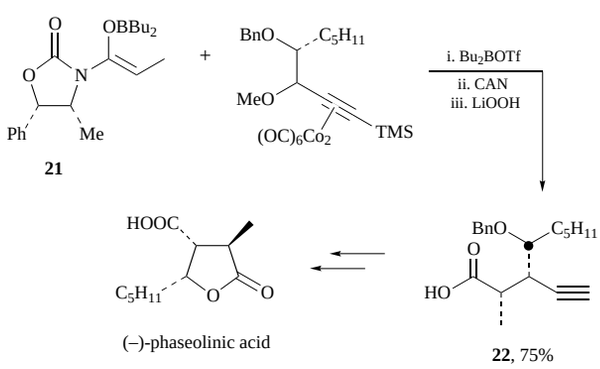
The use of pentaammineosmium(II) as a π-base to coordinate aromatic rings continues to be explored. Harman has shown that this metal will essentially dearomatise a variety of aromatic compounds by complexing in an η^2 mode, rendering the remaining π-system partially localised. In the case of anisole complex **23** (**Scheme 18**), the π-system is capable of adding to α,β-unsaturated ketones in a high yielding and regioselective process: aromatisation and decomplexation of the transition metal can be achieved by reaction with base and acetonitrile



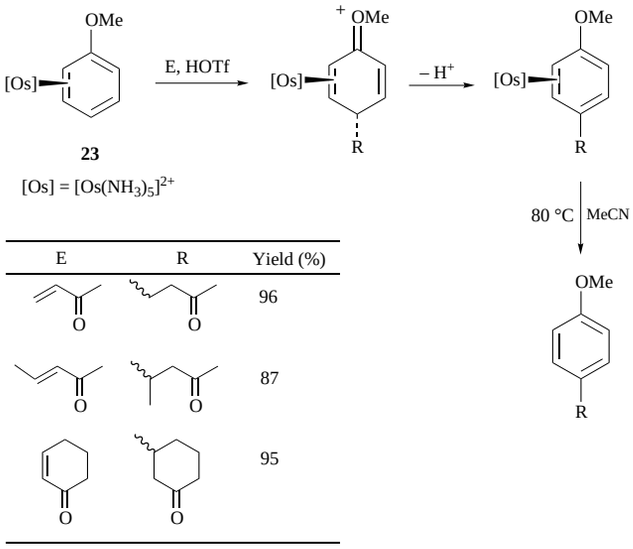
Scheme 15



Scheme 16



Scheme 17

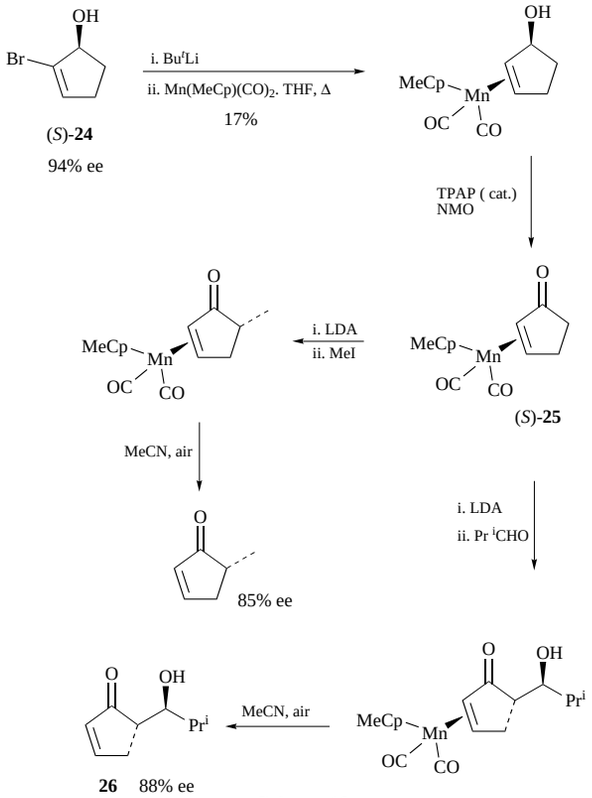


Scheme 18

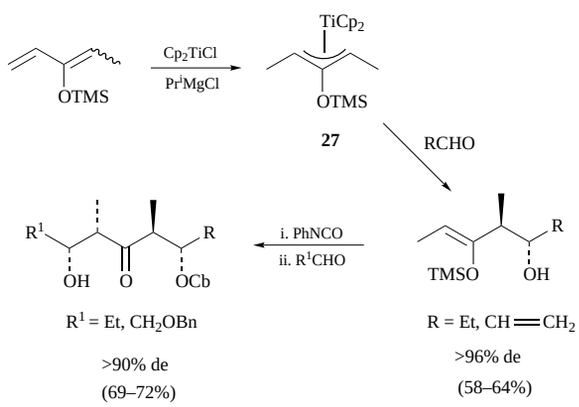
respectively.[44] As such, this chemistry represents an interesting and selective alternative to classical Friedel–Crafts alkylation. Harman has also used similar organometallic chemistry to derivatise pyrrole, cyclopentadiene and simple acyclic enol ethers.[44]

4.4 η^2-Complexes with manganese

The complexes of α,β-unsaturated ketones with $Mn(CO)_2$-MeCp have proven to be useful tools for organic synthesis; the transition metal influences the stereoselectivity observed upon subsequent reaction of the ketone enolate. Recently, these complexes were prepared in enantiomerically pure form by the sequence illustrated in **Scheme 19**.[45] Bromo alcohol **24** was obtained in 94% enantiomeric excess by resolution of the racemate with lipase and, after removal of bromine, this compound was complexed diastereoselectively with the manganese fragment as shown. The original chiral centre was then removed *via* an oxidative procedure (TPAP) which, remarkably, left the transition metal untouched. Alkylation of the enolate of **25** took place exclusively from the *exo* face as a consequence of the large steric bulk of the manganese fragment. Removal of the transition metal gave ketones with high enantiomeric excesses. Aldol reaction of the aforementioned enolate was also diastereoselective and this chemistry gave compound **26** in 88% ee and as a single diastereoisomer (Scheme 19).



Scheme 19



Scheme 20

5 η^3-Complexes in organic synthesis

5.1 η^3-Complexes of titanium

η^3-Complexes of titanium have been used to good effect in the synthesis of stereochemically defined acyclic 1,3-diols using the aldol reaction (**Scheme 20**).[46] The allyltitanium species **27** was prepared from the corresponding diene and then treated with a series of aldehydes. The addition reaction proceeds with excellent levels of (*anti*) diastereoselectivity and moreover, the products still contain a silyl enol ether moiety which may be readily subjected to another aldol reaction after a suitable protection sequence: in contrast, this aldol reaction proceeds with high levels of *syn* diastereoselectivity (Scheme 20). Subsequent studies on the second aldol reaction revealed the crucial role of the protecting group (PhNHCO) introduced after the first addition.

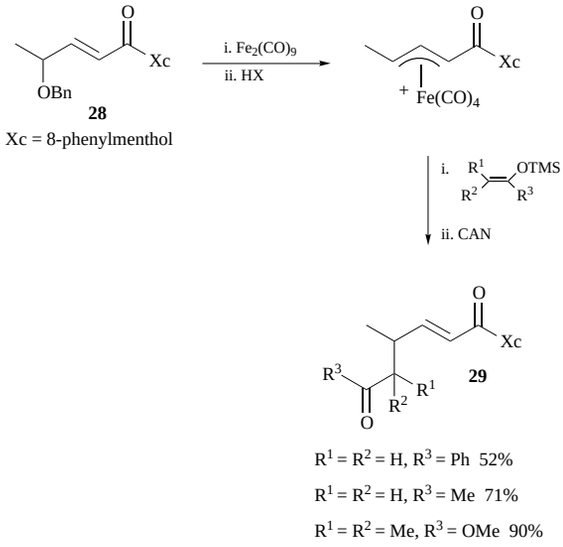
5.2 η^3-Complexes of iron

Enders and co-workers have recently published some nice work concerning the formation and reactivity of η^3-allyl iron complexes.[47] The allylic ether **28** was prepared from lactic acid in either enantiomeric form (**Scheme 21**). This compound then underwent substitution upon reaction with $Fe_2(CO)_9$ and acid: the allylic iron complexes were formed with excellent levels of diastereoselectivity. Subsequent displacement of the iron with silyl enol ethers was achieved to give (after removal of the transition metal with CAN) the corresponding oxo enoates **29** in good yield. The stereochemical outcome of this sequence was studied with interest, especially with regard to a chiral auxiliary (8-phenylmenthol) at the ester group; in keeping with earlier studies a double inversion mechanism which leads to overall retention was operative.

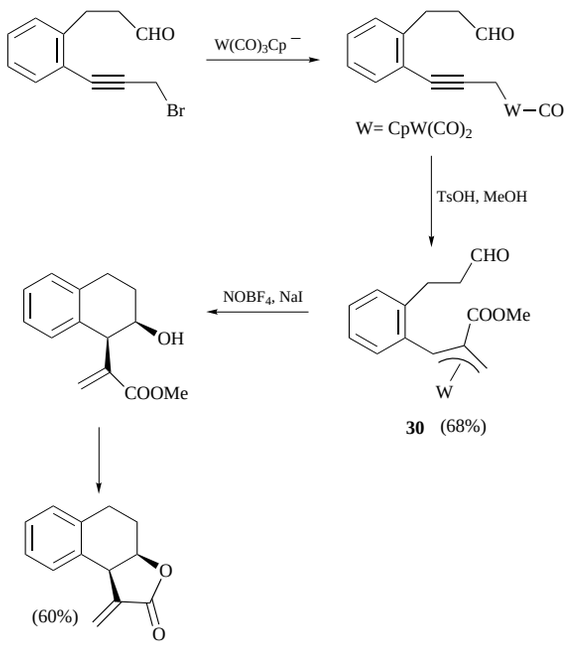
Enders has also examined the effect of using chiral nucleophiles to attack prochiral iron–allyl complexes.[48] Enantiomeric excesses of up to 92% were obtained in a study which utilised chiral enamines, metallated imines and metallated ketones as the nucleophilic partners.

5.3 η^3-Complexes of tungsten

An interesting synthesis of *exo*-methylene γ-lactones has been reported recently.[49] This chemistry uses the alkoxycarbonylation of a η^1 prop-2-ynyltungsten species to the corresponding η^3-complex **30** under the action of PTSA in methanol (**Scheme 22**).[50] This organometallic complex reacts as an allyl anion



Scheme 21



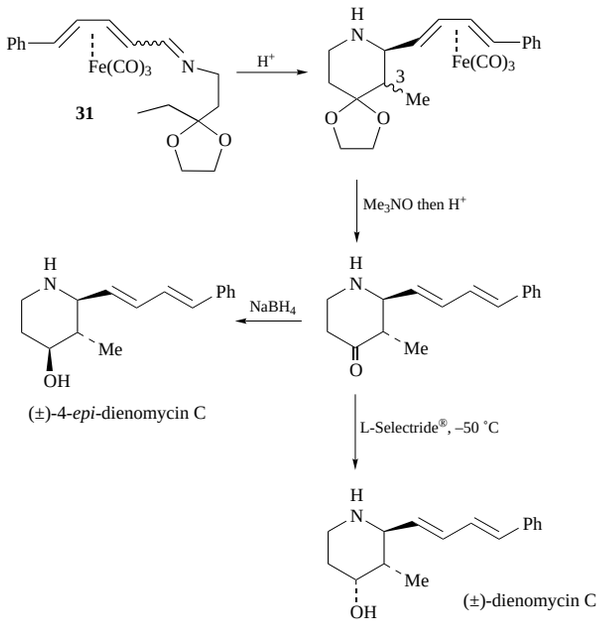
Scheme 22

when treated with $NOBF_4$ and NaI and attacks the aldehyde group in an intramolecular fashion. The preparation of a variety of *exo*-methylene γ-lactones, fused with five-, six- and seven-membered carbocycles was reported.

6 η^4-Complexes

6.1 η^4-Iron–diene complexes

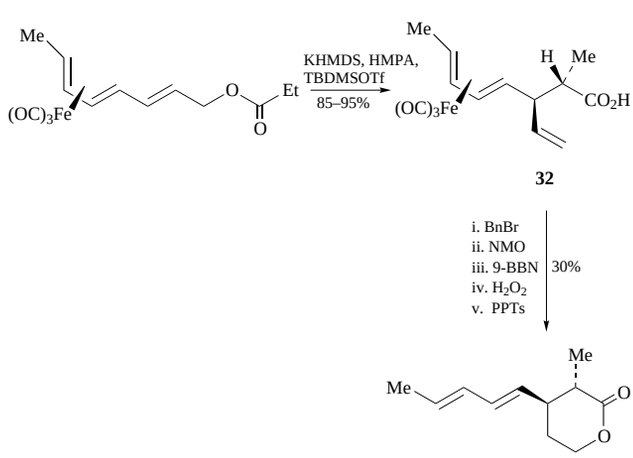
Interest in the application of iron–diene chemistry in organic synthesis has continued unabated over the last twelve-month period.[51] Recent work has served to highlight their use in the stereoselective synthesis of naturally occurring alkaloids. Troin has extended the use of iron tricarbonyls for intramolecular Mannich-type cyclisations,[1] utilising the diene complex **31** as a key intermediate in the total synthesis of (±)-dienomycin C and its corresponding epimer **(Scheme 23)**.[52] Acid induced cyclisation of complex **31** proceeded in a diastereoselective fashion, providing the *endo*-piperidone as the major product (mixture of epimers at C3). Demetallation, followed by equilibration under acidic conditions gave the more stable *trans*-disubstituted 4-piperidone, which could in turn be reduced to the target alkaloid. This extension of iron–diene chemistry offers concise



Scheme 23

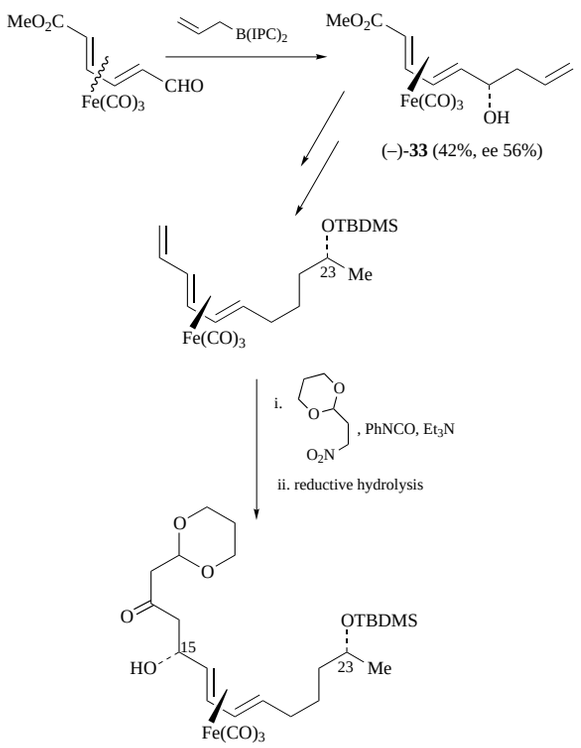
access to piperidines bearing a number of contiguous stereocentres.

Iron–diene complexes have provided key intermediates in the stereocontrolled formation of lactones.[53] Of particular note is the work of Roush,[54] who employed the $Fe(CO)_3$ unit as a template for controlling the stereoselective Claisen rearrangement of allylic esters (**Scheme 24**). The rearrangement of a number of iron complexed allylic esters was found to proceed with moderate to excellent diastereofacial selectivity; in each case the developing C–C bond was *anti* to the existing $Fe(CO)_3$ unit. In the example illustrated, the stereochemistry of the major product **32** (resulting from rearrangement of the propionate ester) was assigned on the basis of its conversion to the corresponding lactone. The authors have interpreted these results in terms of the adoption of a chair-like transition state during the rearrangement process.



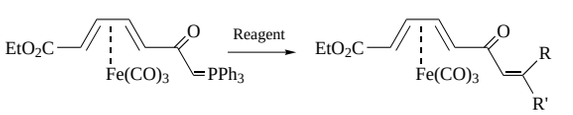
Scheme 24

Two groups have used the planar chirality exhibited by iron–diene complexes in approaches towards the stereoselective synthesis of macrolactin A.[55,56] One approach completed the synthesis of the C11–C24 segment of this important antiviral agent using the complexed metal to control introduction of two remote asymmetric centres (**Scheme 25**).[56] The sequence commences with the enantiomerically enriched alcohol **33**, which was obtained in 56% ee through the use of Brown's chiral allylborane. Subsequent steps employed the (diene)$Fe(CO)_3$ unit in a *chirality relay strategy* to install the C23 stereogenic centre. Finally, nitrile oxide cycloaddition took place, as predicted, from the face opposite to the metal centre, establishing the required stereochemistry at C15. This economical use of organoiron compounds to introduce remote stereogenic centres should provide a versatile method for the preparation of other polyene macrolides.



Scheme 25

Other current areas of interest include the alkylation[57] and Friedel–Crafts acylation of tricarbonyl(diene)iron complexes,[58] whilst Grée has investigated the reactivity of a novel class of organometallic cross-conjugated polyenones (**Scheme 26**).[59] These polyenones are readily available through Wittig reaction between the appropriate carbonyl compound and the optically pure metal complexed phosphorane. The resulting organoiron complexes have been shown to undergo cycloadditions with 2,3-dimethylbutadiene and azomethine ylides with moderate levels of stereocontrol. As expected, addition of nucleophiles occurs *anti* to the large $Fe(CO)_3$ unit.

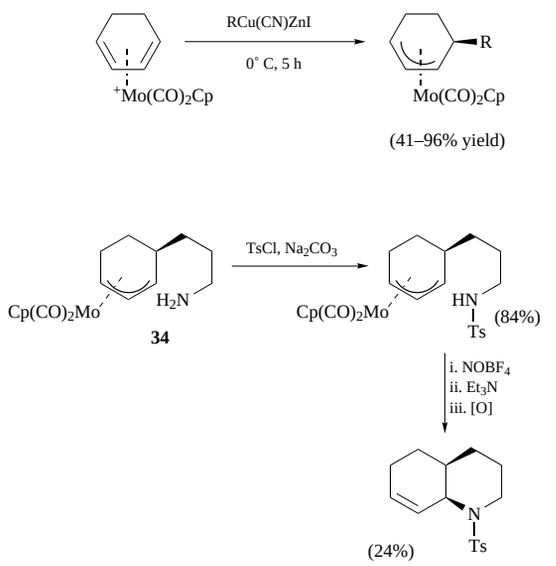


Scheme 26

Reagent	R	R′	Yield (%)
$(EtO_2C)_2CO$	CO_2Et	CO_2Et	98
PhCOCHO	H	COPh	83
PhCOCDO	D	COPh	90
MeO_2CCHO	H	CO_2Me	54

6.2 η^4-Molybdenum–diene complexes

The addition of highly functionalised organocuprates to molybdenum–diene cationic complexes takes place in a regio- and stereo-controlled manner, providing access to various 4-substituted (π-allyl)molybdenum species in moderate to excellent yield (**Scheme 27**).[60] These complexes can undergo intramolecular cyclisation to provide 2-heterobicyclo[4.4.0]decene derivatives stereoselectively. In one example, amine **34** was converted to the less reactive tosylate before cyclisation which was induced through generation of the nitrosyl cation followed by treatment with triethylamine.[61] Similar cyclisations have been achieved with acids, alcohols and thiols.



Scheme 27

7 η^5-Complexes

7.1 Stoichiometric ferrocene complexes

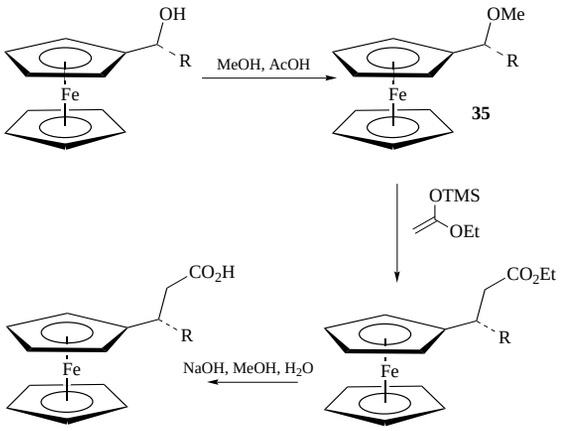
The search for novel ferrocene-derived ligands for use in asymmetric catalysis has continued to be the focus of much synthetic effort. Numerous publications over the period since the last literature review[1] serve to emphasise the importance of this organometallic complex. A small selection of examples should illustrate current interest.

The preparation of enantiomerically pure ferrocenyl amines by reduction of chiral ferrocenyl imines[62] or by enantioselective addition of dialkylzincs to ferrocenyl diphenylphosphinylimines[63] has proved a very successful approach, whilst chiral alcohols have been prepared *via* the ethylation of ferrocenyl aldehydes:[64] interestingly, this alkylation process proceeds efficiently without addition of an external catalyst, probably proceeding by way of an *asymmetric intramolecular autoactivation*.

Ferrocenepropanoic acids have been prepared in excellent yield and enantioselectivity by Richards (**Scheme 28**).[65] Initial methanolysis of the chiral ferrocenyl alcohols (obtained by reduction with Corey's oxazaborolidine catalyst) proceeded in all cases with retention of stereochemistry (presumably through double inversion). Subsequent generation of the corresponding ethyl esters and basic hydrolysis gave the target acids. The enantioselectivity of the overall process was determined by esterification of these acids with (*S*)-(+)-methyl mandelate and comparison of their ^1H NMR spectra with those of previously prepared racemic samples. The authors ascribe the success of this approach to the known configurational stability of the α-ferrocenyl carbenium ion, which is generated during the addition of the silyl ketene acetal to methyl ethers **35**.

7.2 η^5-Iron cationic complexes

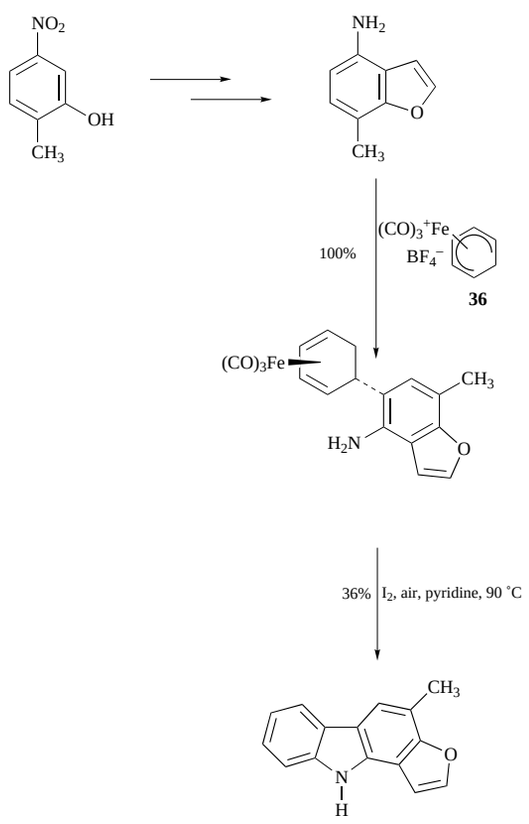
This field has continued to be dominated by Knölker, who



Scheme 28

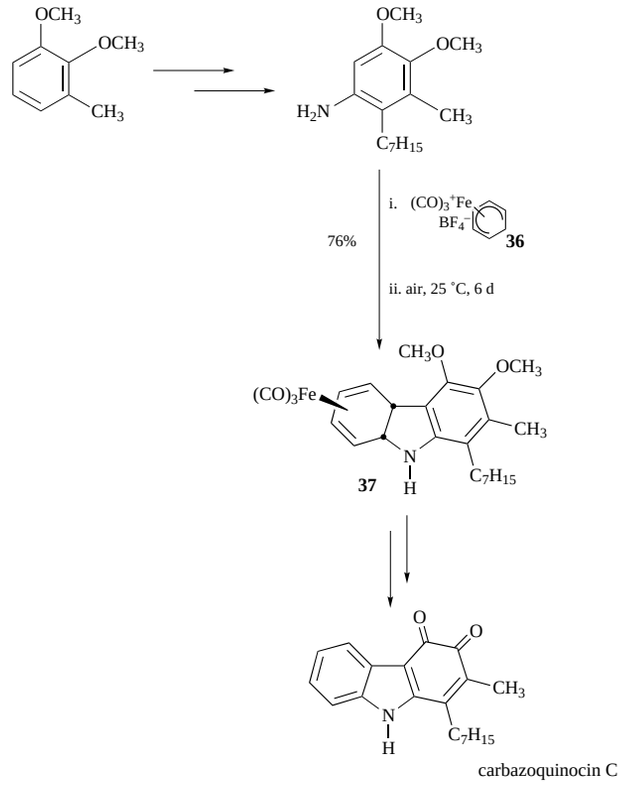
R	Overall yield (%)	Ee (%)
Me	61	92
Ph	83	96
p-$C_6H_4OCH_2Ph$	27	92
p-C_6H_4Br	58	96

routinely applies iron complexes in electrophilic aromatic substitution and oxidative cyclisation processes.[66] The general strategy may be illustrated using the total synthesis of two carbazole alkaloids. In the first example (**Scheme 29**),[67] electrophilic substitution of the benzofuran with the complex salt **36** occurs both regio- and diastereo-selectively to provide the iron–diene complex in quantitative yield. Oxidative cyclisation with concomitant aromatisation afforded the target alkaloid furostifoline.



Scheme 29

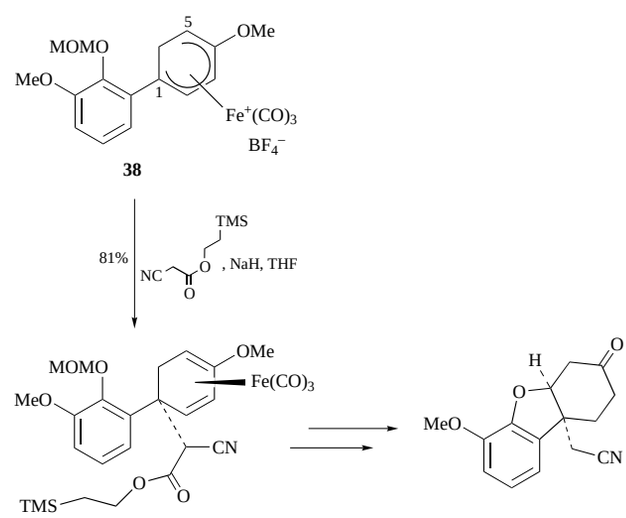
A similar strategy was used for the total synthesis of the potent antioxidant carbazoquinocin C (**Scheme 30**).[68] In this case, iron salt **36** reacts with a polysubstituted aniline, in the presence of air, to give the cyclised product **37** directly. Demetallation, aromatisation and removal of the methyl ether functionality then afforded the required tricyclic natural product.



carbazoquinocin C

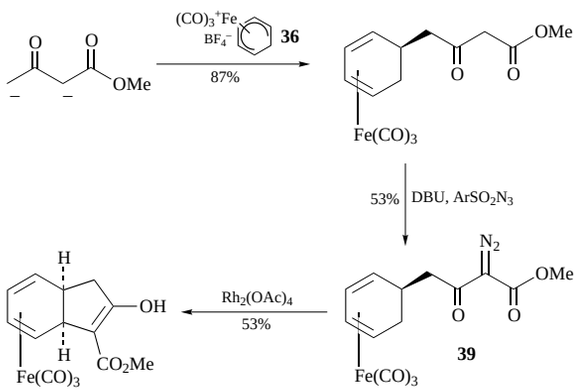
Scheme 30

Other areas of natural product synthesis have also relied on cationic iron complexes. Lycoramine is a member of the galanthamine family of alkaloids, which possess an ether bridge between two carbocyclic rings as a common structural motif. Stephenson[69] has developed iron complexes **38** that allow for the formal total synthesis of this type of alkaloid (**Scheme 31**). The key structural feature of these complexes is an *ortho*-substituted aromatic ring possessing electron donating substituents. Increased π-overlap between the arene and dienyl regions causes the complex to adopt a more planar conformation, allowing nucleophiles to add at the less sterically blocked C1 position (as opposed to C5). This simple modification should provide ready access to compounds containing an otherwise restrictive quaternary centre, such as the *Amaryllidaceae* alkaloids.



Scheme 31

Amongst other recent applications of cationic iron complexes[70] has been their combination with metallocarbenoid chemistry in a coherent synthetic strategy (**Scheme 32**).[71] This appealing concept was realised through the generation and subsequent cyclisation of the α-diazo carbonyl tethered complex **39**. Initial nucleophilic attack on cation **36** with the dianion of methyl acetoacetate followed by diazotisation provided the required cyclohexadienyl–iron complex **39**. The key role played by the tether is revealed upon addition of rhodium(II) acetate, which induced the regio- and stereo-selective formation of the bicyclic product *via* a metallocarbenoid intermediate. Future investigations into metal complex, ring size and diazo tether length should reveal the applicability of this method to the synthesis of other bicyclic systems.



Scheme 32

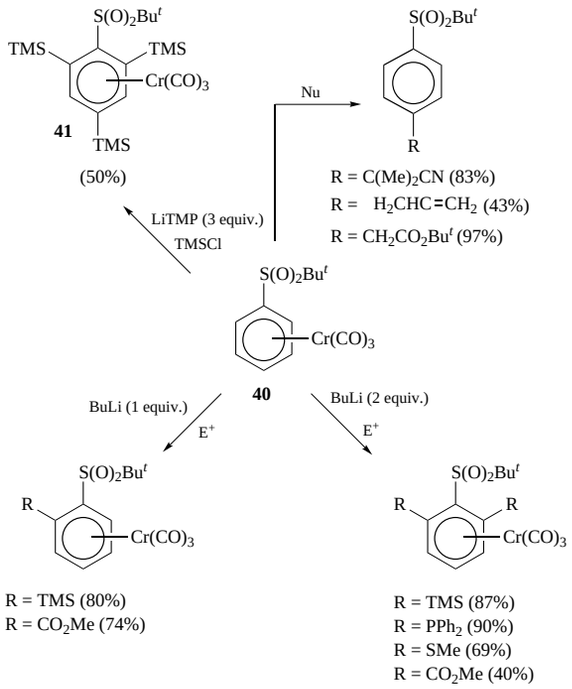
8 η^6-Complexes

8.1 η^6-Complexes of chromium

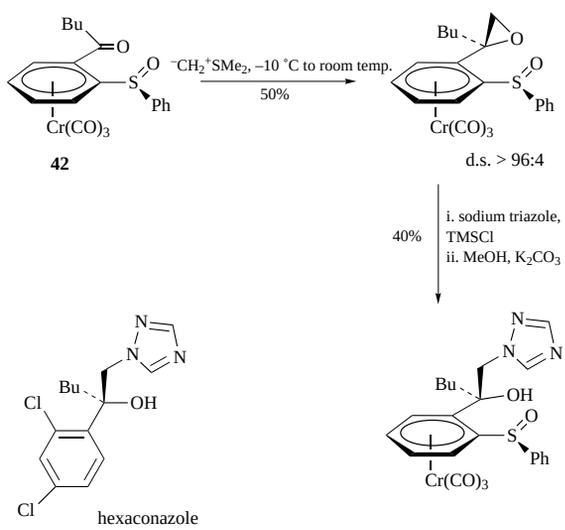
η^6-Tricarbonylchromium complexes are extremely versatile synthetic intermediates. Some examples of particular note include the stereoselective preparation of pinacols and 1,2-diamines by the samarium diiodide promoted reductive coupling of chromium complexed benzaldehydes and imines.[72] Diels–Alder reactions have been used to generate tetralins in excellent enantiomeric excess,[73] whilst lithiated (arene)tricarbonylchromium complexes react with a host of electrophiles to yield functionalised benzyl ether complexes.[74]

Gibson[75] has performed extensive studies into the reactivity of the sulfonyl-substituted complex **40** (**Scheme 33**). The presence of an electron withdrawing group on the ring leads to reactivity that is complementary to that exhibited by the corresponding complexes bearing donor substituents. Thus, addition of nucleophiles such as $Li(Me)_2CN$ or $BrMgCH_2CH{=}CH_2$ followed by demetallation with iodine provides the *para*-substituted product only [X-ray analysis has suggested that the site of attack is controlled by the conformational preference of the tricarbonylchromium unit]. *ortho*-Monosubstituted arenes were obtained *via* initial deprotonation of the complex with butyllithium (1 equiv.) followed by an electrophilic quench, whilst the use of 2 equiv. of base provided the 2,6-disubstituted species. Interestingly, deprotonation of complex **40** with 3 equiv. of a relatively hindered base (LiTMP) gave the novel tetrasubstituted complex **41**.

Chiral epoxides have assumed a major role in the field of asymmetric synthesis and the development of methods for their generation continues to be of great importance.[76] As part of a programme towards the synthesis of hexaconazole and analogues, Davies has reported the stereoselective epoxidation of a sulfinyl-substituted chromium complex **42** (**Scheme 34**).[77] The key step in this scheme uses the bulky $Cr(CO)_3$ unit to direct Corey's ylide to the *Re* face of the carbonyl group. Epoxide ring opening with triazole anion was best achieved in the presence of chlorotrimethylsilane: omission of this trapping agent results in fragmentation of the incipient alkoxide anion.



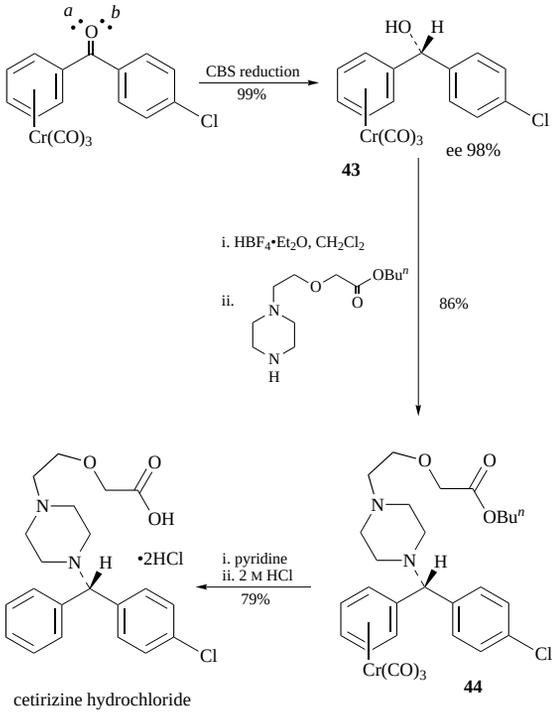
Scheme 33



Scheme 34

The first enantioselective synthesis of the histamine H_1 antagonist cetirizine hydrochloride using an η^6-chromium complex has been reported by Corey (**Scheme 35**).[78] The approach is based on previous observations regarding the stereoselectivity of the oxazaborolidine (CBS) reduction of π-conjugated ketones having remote substituents. Complexation of a single aromatic ring in benzophenone **43** has the effect of making this the larger of the two carbonyl substituents, and reduction then occurs by complexation of the catalyst to lone pair *b*, providing the optically active alcohol. The known configurational stability of $Cr(CO)_3$ stabilised cations is then used to great effect in the formation of the piperazine **44**, which proceeds with complete retention of stereochemistry. Demetallation and ester hydrolysis then provided the target cetirizine: previous synthetic attempts had relied on the resolution of a racemic mixture of 4-chlorobenzhydrylamines.

Nucleophilic addition of organolithium species and Grignard reagents to the activated arene unit in η^6-chromium complexes is of great synthetic potential.[79] This protocol has been



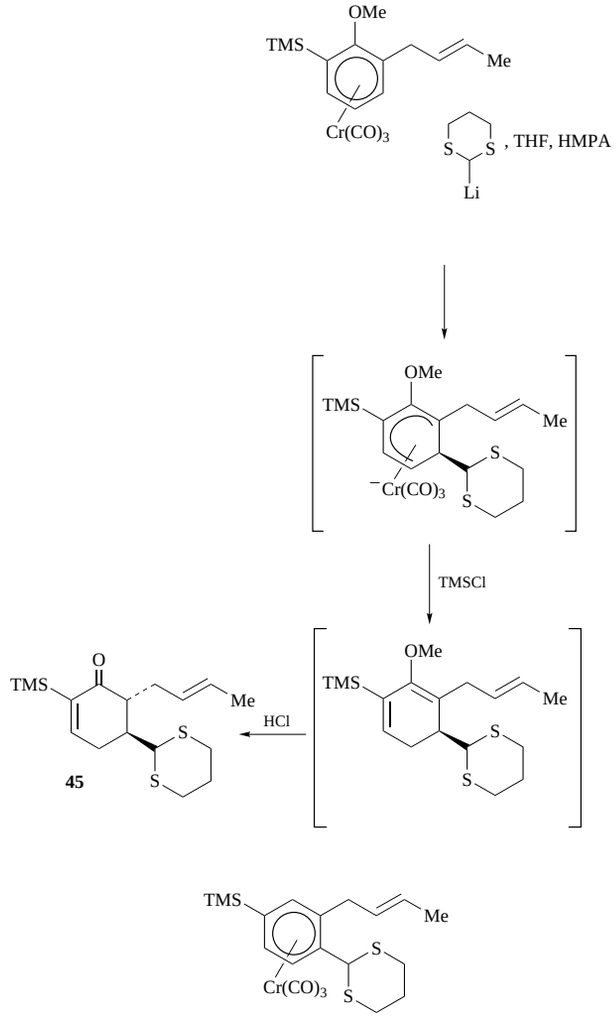
Scheme 35

used in the synthesis of enone **45** (**Scheme 36**), a key synthon in the projected synthesis of the marine natural product (+)-ptilocaulin.[80] Addition of lithiated dithiane to the *ortho*-substituted arene complex, followed by acidification (TFA), gave the unexpected tele-substituted product **46**. However, the use of HMPA as cosolvent and addition of (acid free) chlorotrimethylsilane gave the required dienol ether, which was then converted to the diastereomerically pure enone **45**. The authors interpreted these results in terms of protonation of the chromium atom in the anionic η^5-complex by TFA, subsequent elimination of methanol giving the undesired tele-substituted product.

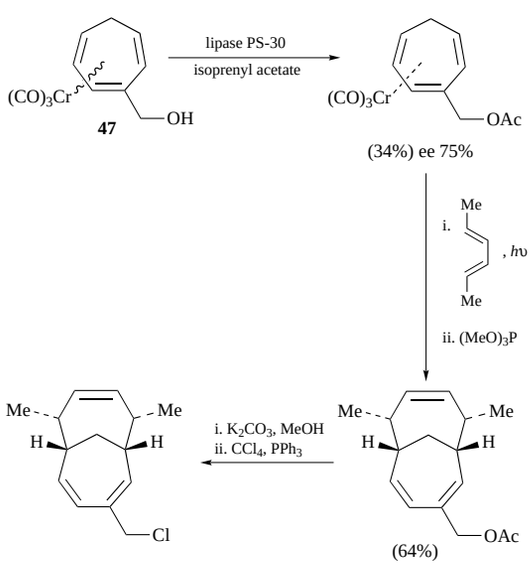
Higher-order cycloadditions of chromium(0) complexed trienes can provide polycyclic systems in a stereochemically defined manner. Rigby[81] has continued to develop this methodology: one recent example involved the first enzymatic resolution of a (η^6-cycloheptatriene)chromium(0) complex (**Scheme 37**).[82] Treatment of a racemic mixture of alcohols **47** with lipase PS-30 gave the enantiomerically enriched acetate. The absolute configuration of this acetate was established by cycloaddition with hexa-2,4-diene followed by preparation of the corresponding chloride. This chloride was found to be identical with a sample of known absolute configuration previously prepared by Rigby's group.

8.2 η^6-Complexes of manganese

As with the analogous chromium species, nucleophilic addition to cationic manganese arene complexes is an important and versatile process.[83] However, the preparation of 1,2-disubstituted dienes, by addition of a second nucleophile to these activated arenes, has achieved only limited success. Astley[84] has approached this problem using an *intramolecular* nucleophile in a second addition step (**Scheme 38**). Thus, Grignard addition to the activated arene gave the expected cyclohexadienyl product bearing an *ortho*-functionalised aromatic ring. Oxidation of the metal centre with NO^+ regenerated the activated cationic species, which underwent a smooth nucleophilic addition by the recently incorporated oxazoline to provide the desired polycyclic cation **48**. Alkaloids and other natural products should become viable targets using this novel approach for the introduction of nitrogen nucleophiles onto a six-membered ring.



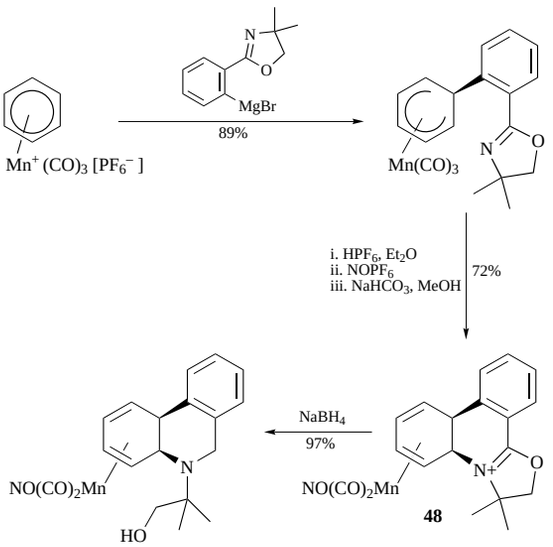
Scheme 36



Scheme 37

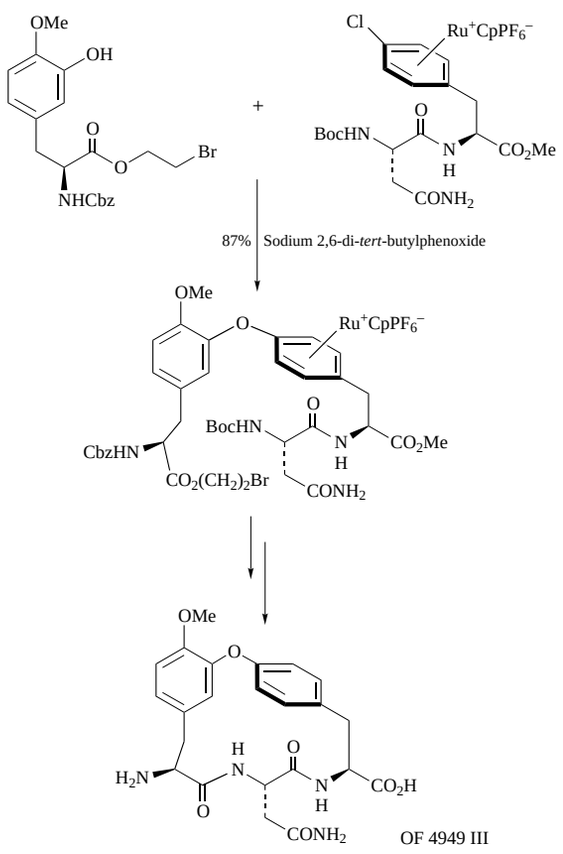
8.3 η^6-Complexes of ruthenium

The use of ruthenium complexes in peptide synthesis was mentioned in our previous review.[1] The key step in this type of strategy generally involves formation of a diaryl ether linkage by intramolecular S_NAr reaction between a ruthenium activated π-complex and a substituted phenol. Pearson's recent formal total synthesis of the biologically active diaryl ether OF 4949



Scheme 38

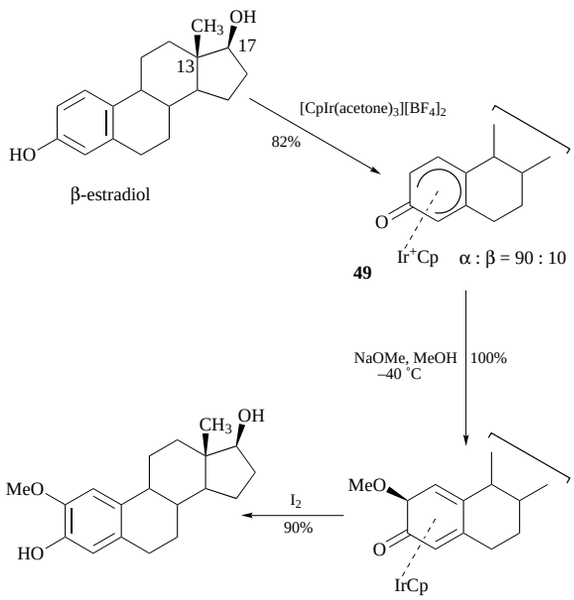
III (isolated from *Penicillium rugulosum*) illustrates one application of this chemistry (**Scheme 39**).[85] The success of such an approach rests with the ability of ruthenium (as opposed to iron or manganese) to form the required chloroarene complex under conditions that do not cause racemisation of the labile amino acid functionalities.



Scheme 39

8.4 η^6-Complexes of iridium

Group VIII metals such as rhodium and ruthenium are known to coordinate to the A-ring of β-estradiol, providing thermally stable complexes. Amouri has now shown that iridium behaves in the same manner, activating the A-ring of this hormone to subsequent attack by methoxide ion (**Scheme 40**).[86] Initial complexation of the metal generated the cationic iridium complex **49** as a mixture of α and β isomers (relative to the methyl group at C13). Nucleophilic addition of methoxide gave the corresponding neutral dienone system which underwent concomitant oxidative demetallation and aromatisation to yield 2-methoxyestradiol. The synthesis of this important anticancer compound in such a concise manner (60% overall yield, requiring no protection of the C17 hydroxy group), offers a considerable improvement on the previously published method (five synthetic steps, 5% overall yield).



Scheme 40

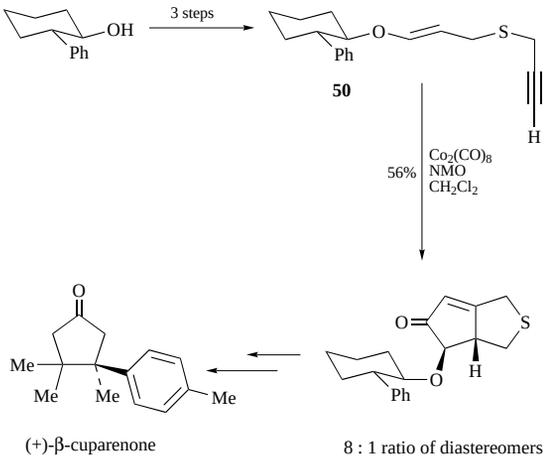
9 Transition metal mediated cycloadditions in organic synthesis

9.1 Pauson–Khand type reactions

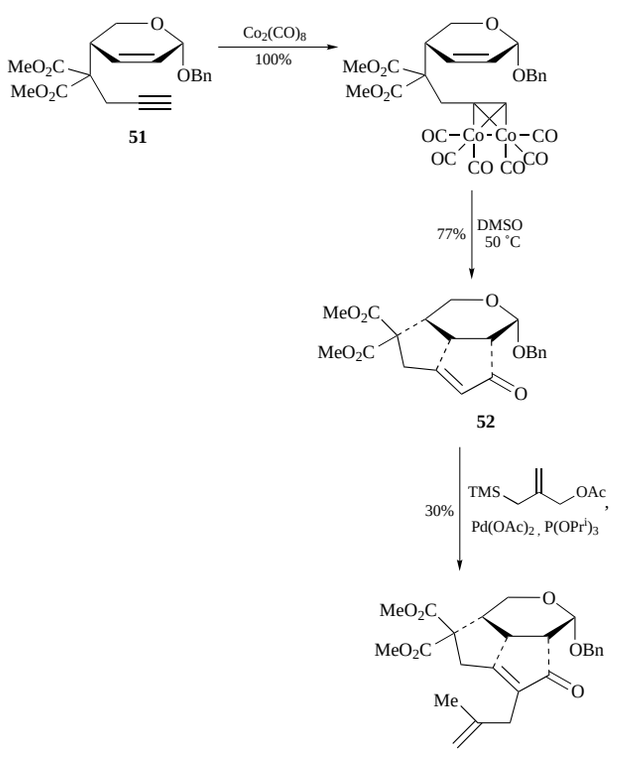
The undiminished popularity of this reaction in the synthetic community is based on its inherent simplicity: the reaction produces cyclopent-2-enones with a number of stereogenic centres, in a single synthetic step. The development of asymmetric variants[87] of this reaction and its application in total synthesis are always of particular interest.[88] In one example,[89] the cyclopentanone (+)-β-cuparenone (an important component of the essential oil of the 'Mayur pankhi' tree) was constructed using a chiral auxiliary-based approach (**Scheme 41**). The success of this method relies upon the use of a chiral alcohol as an auxiliary, which is known to impart predictable stereocontrol over cobalt mediated cyclisation reactions. Thus, Pauson–Khand reaction of the key alkoxythiaheptenyne **50** provided the required bicyclic enone with good (8 : 1) diastereoselectivity. Subsequent organocuprate addition to this enone installed the required quaternary chiral centre.

The rich stereochemistry and functionality of carbohydrates, coupled with their relative abundance, provides an unparalleled natural source of important synthetic intermediates. Their use as templates for the construction of stereochemically defined bicyclic systems *via* the Pauson–Khand reaction has been investigated by Voelter (**Scheme 42**).[90] Treatment of the unsaturated carbohydrate **51** with octacarbonyldicobalt in benzene gave the corresponding cobalt complex as a red oil. Utilisation of an *intramolecular* Pauson–Khand reaction ensured carbonylative insertion from the α-face, and gave the tricyclic product **52** as a single regio- and stereo-isomer. Unfortunately, numerous attempts at installing a further cyclopentane, by palladium assisted annulation of the enone system, only resulted in isolation of the alkylated product.

The emergence of a novel group of tricyclic β-lactam antibiotics that exhibit excellent antibacterial activity has aroused much interest in the development of methods for their syn-



Scheme 41

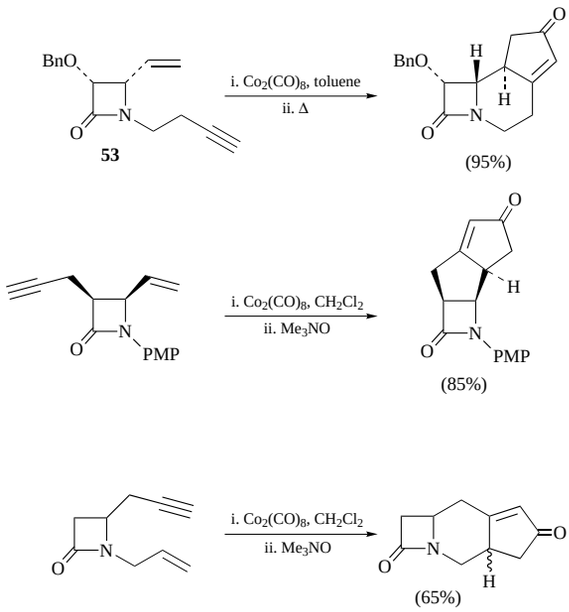


Scheme 42

thesis. These *tribactams* are generally prepared by stepwise elaboration of the readily available β-lactam core. However, the Pauson–Khand reaction offers an extremely efficient alternative to these more established methods, constructing the polycyclic framework in a single synthetic step (**Scheme 43**).[91] A number of key observations have been made regarding the applicability of this method to tribactam synthesis. Firstly, attempts at generating larger central ring systems (seven- or eight-membered) proved unsuccessful. Secondly, formation of five- and six-membered rings proceeded, in all cases, with complete diastereocontrol (cyclisation of homochiral lactam **53** gave the tricyclic product as a single stereoisomer). The generation of tribactams in such a succinct and stereoselective manner should be a major factor in their continued development.

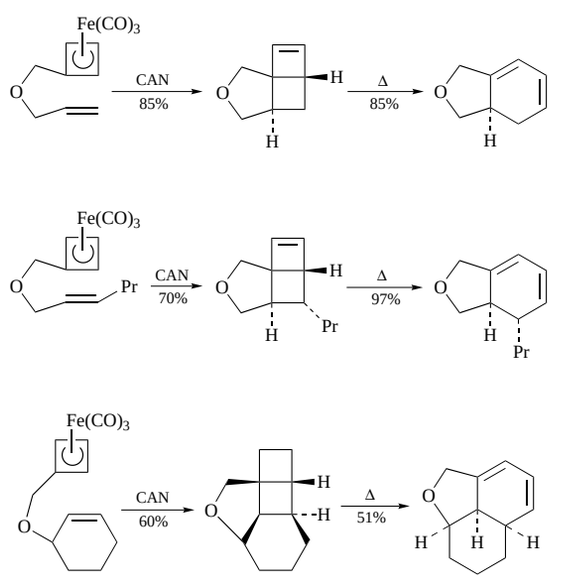
9.2 Iron promoted cycloadditions

Cycloaddition reactions between activated olefins (benzoquinones and norbornadiene) and cyclobutadiene are well established in the literature. However, the corresponding reaction with unactivated olefins is a little known process. This limitation has been overcome by tethering the olefin to an iron complexed cyclobutadiene, so that an intramolecular cyclo-



Scheme 43

addition may ensue under appropriate conditions (**Scheme 44**).[92] Oxidation of the iron complexed species with ceric ammonium nitrate gave the corresponding cycloadducts in good to excellent yield. In all cases the reaction was stereospecific, ruling out any stepwise mechanism that may occur under the reaction conditions. Thermally induced cyclobutane ring-opening was then shown to be capable of generating other useful synthetic intermediates (*i.e.* stereochemically defined cyclohexa-1,3-dienes).



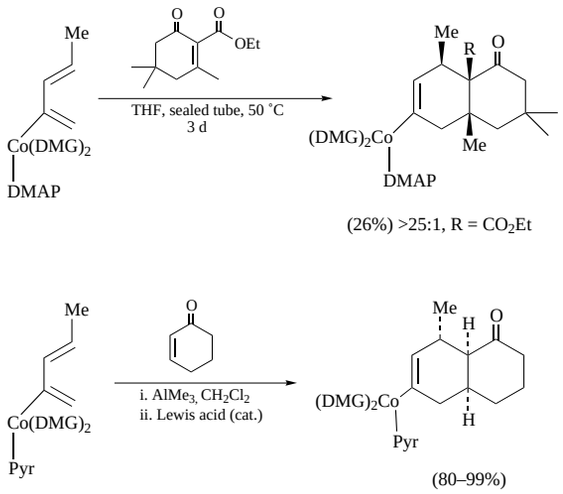
Scheme 44

9.3 Cobalt promoted cycloadditions

The use of alkyl-substituted cyclohexanones in the Diels–Alder reaction with acyclic dienes is beset with problems of poor yield and stereoselectivity. Many of these difficulties have now been overcome through the use of cobaloxime substituted 1,3-dienes (**Scheme 45**).[93] The reactions proceed under conditions (thermal and Lewis acidic) that are notable for their mildness and are unusual in that the major products result from reaction *via* an *exo* transition state. This reversal of stereoselectivity has been rationalised using a model that orientates the bulk of the dienophile away from the metal's equatorial ligands.

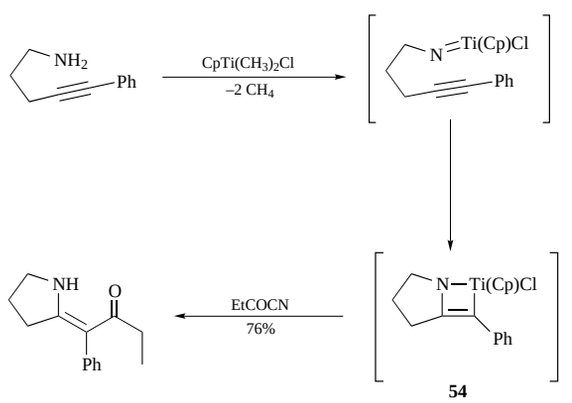
9.4 Titanium promoted cycloadditions

Alkynyl amines have been used to prepare 2-substituted tetra-



Scheme 45

hydropyrroles through the intermediacy of a transient imidotitanium complex (**Scheme 46**).[94] These complexes are prepared by the addition of a solution of $CpTi(CH_3)_2Cl$ (generated *in situ* by the action of MeLi on $CpTiCl_3$) to the appropriate amine. The resulting complexes undergo immediate [2 + 2] cycloaddition with the tethered alkyne, yielding azametalline **54**. Further reaction with acyl cyanides (use of this reagent avoids problems of *N*-acylation) gave the demetallated 2-substituted tetrahydropyrrole in excellent yield.



Scheme 46

Acknowledgements

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