Stoichiometric applications of organotransition metal complexes in organic synthesis

TIMOTHY J. DONOHOE

Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK

Reviewing the literature published between 1 September 1994 and 30 April 1995
Continuing the coverage in *Contemporary Organic Synthesis*, 1995, **2**, 43

1 Introduction

This article is a review of the literature published between 1 September 1994 and 30 April 1995. It is designed to be a selective account of recent developments in the field of stoichiometric organotransition metals in organic synthesis, and to augment two earlier reviews of the same field, which have already been published in *Contemporary Organic Synthesis*.[1]

The manner in which the field has been subdivided is similar to the earlier articles, with an emphasis being placed upon methods which will be of use to the practising organic chemist. The final section in this review is one which, although not technically under the purview of this article, covers the use of stoichiometric titanium reagents in organic synthesis, and should be of interest despite the fact that few transition metal–carbon bonds are involved!

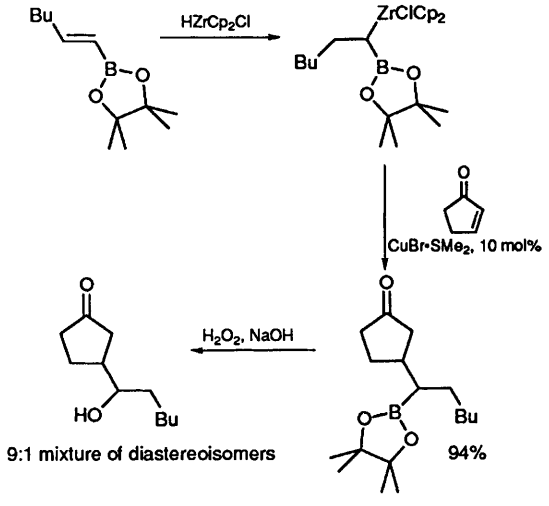
2 Transition metal alkyl, allyl, alkenyl, alkynyl and acyl complexes in organic synthesis

2.1 Organozirconium based methodology

The area of organozirconium chemistry has continued to abound, as witnessed by the publication of a substantial body of work from a number of research groups: the opportunities for the controlled synthesis of complex organic molecules using this methodology should not be underestimated. For a more in-depth survey, the reader is directed to an issue of *Tetrahedron*, which has been entirely devoted to the organic chemistry of this element,[2] and to a review of carbon–carbon bond formation using the zirconocene butene complex.[3]

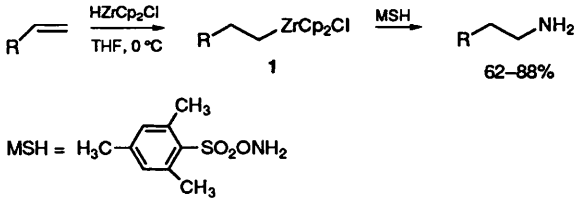
2.1.1 Hydrozirconation methodology

The addition of the H–Zr fragment across a double or triple bond has continued to yield opportunities for the synthesis of multifunctional compounds. The primary advances in this area have been made by Srebnik, who has published work on the regioselective hydrozirconation of allyl boronates and on subsequent transformations of the bimetallic complexes thus formed (**Scheme 1**).[4] The main advantage of this chemistry lies in the fact that it is possible to transmetallate the carbon–zirconium bond selectively, whilst leaving the carbon–boron fragment untouched. Indeed, the reaction shown in Scheme 1 involves a hydrozirconation reaction, followed by a transmetallation with copper, and subsequent 1,4-addition to an enone; this can be performed in a 'one-pot' sequence. The boronate that is formed from this reaction can be transformed into a hydroxyl group under standard conditions, and so the sequence becomes equivalent to the 1,4-addition of an α-hydroxy anion to an enone.



Scheme 1

Related work from the same group has also demonstrated that the product of hydrozirconation of an alkene **1** can be selectively converted into an amine upon treatment with *o*-(mesitylsulfonyl)-hydroxylamine [MSH], so providing an interesting alternative to hydroboration methodology (**Scheme 2**).[5] With the exception of styrene, each of the alkenes examined under these conditions exhibited excellent regiochemistry during the hydrozirconation step.



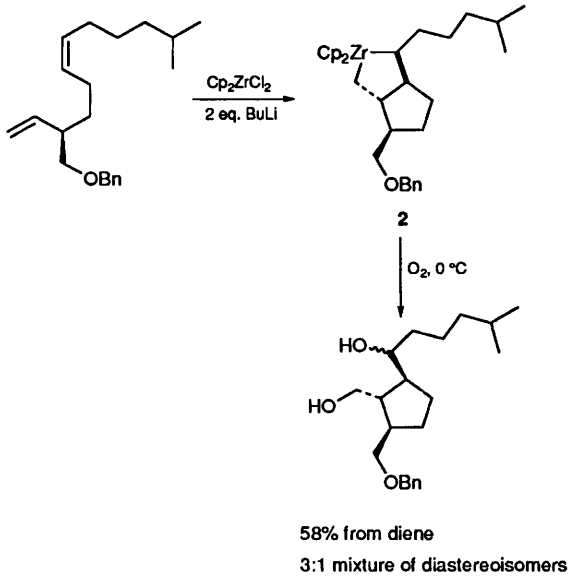
Scheme 2

It has also been demonstrated that the vinyl zirconium complex derived from the addition of Schwartz's reagent to an alkyne can be transformed into a vinyl telluride (with retention of configuration) upon reaction with PhTeI.[6]

2.1.2 Alkyl and alkenyl zirconium and titanium chemistry

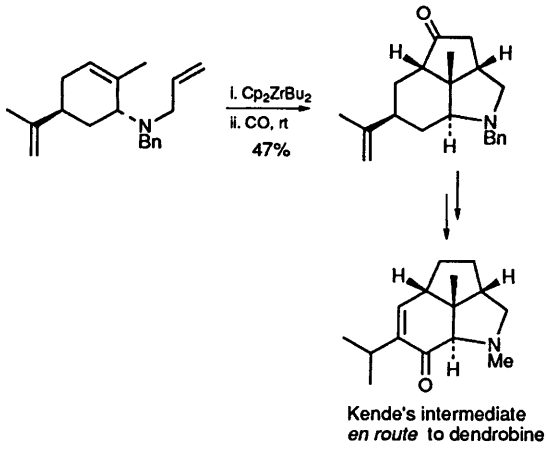
This section is related to the one above, except that the organozirconium complexes which are utilised do not originate from a hydrozirconation reaction. The majority of work in this area is concerned with the use of 'zirconocene' as an agent for the cyclisation of alkenes and alkynes. This putative, carbene-like, intermediate is formed when Cp_2ZrCl_2 is treated with an organolithium or Grignard reagent.[3] Functionalisation of the carbon–zirconium bond is fundamental to the success of this methodology, and a variety of techniques for accomplishing this goal are illustrated below.

Taber's group have studied the cyclisation of various dienes with zirconocene, and found that the stereochemistry created during ring formation is not always transferred to the products after functionalisation of the carbon–metal bond (**Scheme 3**).[7,8] For example, cyclisation of the diene illustrated gave a single zirconacycle **2**. However, oxidation of the organometallic bonds with gaseous oxygen was not a stereoselective reaction and a mixture of diols was observed: the intermediacy of free radicals was suspected and those species are possibly to blame for the epimerisation that is encountered.[7]



Scheme 3

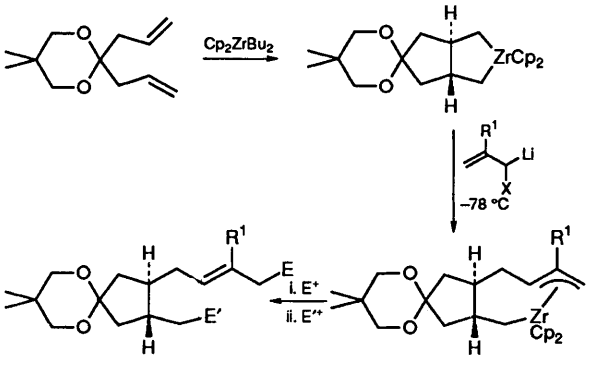
Conversion of zironacycles into cyclic ketones can be readily accomplished by the use of carbon monoxide, and this is nicely illustrated in the latest (formal) synthesis of dendrobine by Mori and co-workers, who successfully achieved a synthesis of Kende's intermediate (**Scheme 4**).[9]



Kende's intermediate
en route to dendrobine

Scheme 4

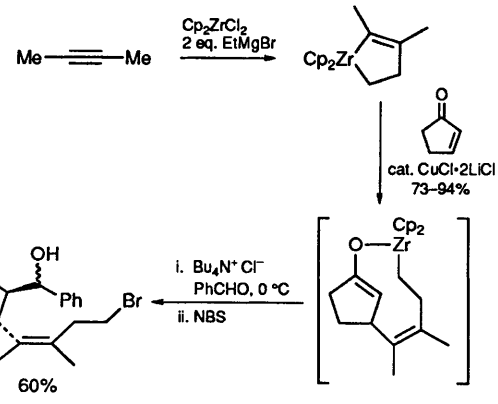
Whitby has published some elegant work in which he explores the scope of zirconacycle functionalisation with allylic metal reagents (formally carbenoids), to furnish an array of substituted cyclopentanes (**Scheme 5**).[10] The allyl metal fragment can be varied in many ways without compromising the efficiency of the substitution reaction, and the geometry of the olefin that is derived from reaction of the intermediate η^3-zirconium complex can be altered by changing the electrophilic conditions. Moreover, it has proven possible to functionalise both carbon–zirconium bonds of the intermediate by judicious choice of electrophile; the result is a spectacular cyclisation/functionalisation sequence.



R^1 = H, Me, CH_2TMS, CH_2Cl, OR^2
X = Cl, Br, OTs, $OCON(Pr^i)_2$
E^+ = R^3CHO, $R^4{}_2CO$
E'^+= I_2, O_2, MeOH
yields 72–80%

Scheme 5

Another impressive Scheme which involves the sequential functionalisation of a zirconacycle species has been reported by Lipshutz (**Scheme 6**).[11] Transmetallation of the zirconacycle that is formed from carbometallation of an alkyne, can be achieved with catalytic amounts of copper(I) salts. The resulting organometallic then adds its vinyl carbon to the β-position of an enone, generating a



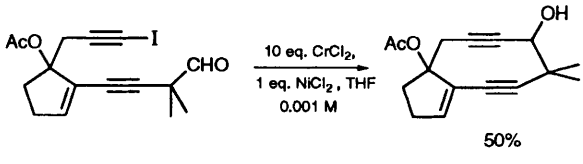
Scheme 6

zirconium enolate. This rather unreactive enolate can be treated with a quaternary ammonium salt to provide an enolate which is capable of reacting with aldehydes in the normal manner. However, the reaction is not finished, because an alkyl–zirconium bonded complex still remains; this is subsequently treated with NBS to generate an alkyl halide. This remarkable one-pot, seven-step sequence is capable of proceeding in good to excellent yields.

Deviation from zirconium in this section is in order to publicise a powerful methylating agent, Cp_2TiMe_2, which has recently been utilised in organic synthesis by Petasis.[12] It was found that this reagent, which is conveniently prepared from Cp_2TiCl_2, and methyl-lithium, is capable of olefinating the carbonyl group of lactones, esters, amides, thio-esters and seleno-esters in remarkably high yields: this organometallic compound will undoubtedly find manifold uses in synthesis.

2.2 Alkynyl chromium species in organic coupling reactions

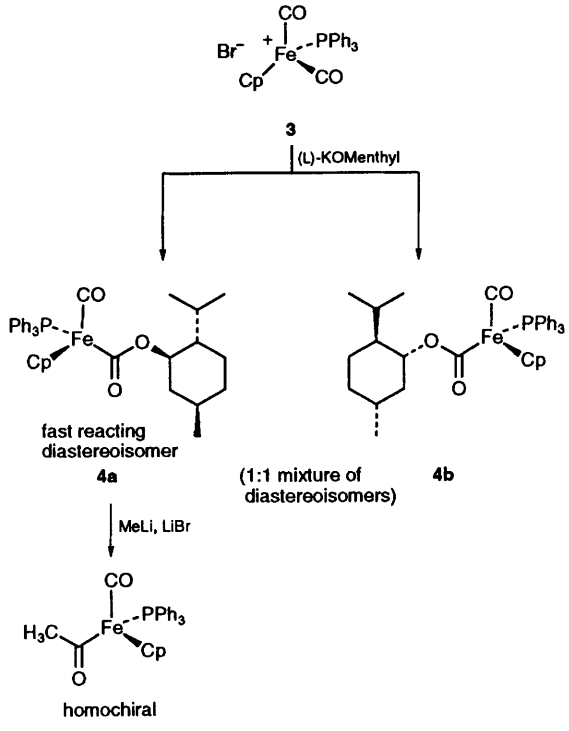
The chromium–nickel mediated coupling reaction between an alkynyl iodide and a carbonyl group provides a mild and effective carbon–carbon bond forming reaction for synthetic organic chemists. The intramolecular variant of this reaction was first introduced by Kishi during the synthesis of ophiobolin,[13] and continues to prove its usefulness in organic synthesis. Buszek's group have managed to close a nine-membered ring in this manner, *en route* to the neocarzinostatin chromophore, and comment that high dilution conditions are necessary for this unfavourable cyclisation to proceed with even moderate efficiency (**Scheme 7**).[14] Similar methodology has been used in the preparation of an oxabicyclo [7.3.1] analogue of esperamycin.[15]



Scheme 7

2.3 Acyl transition metal complexes

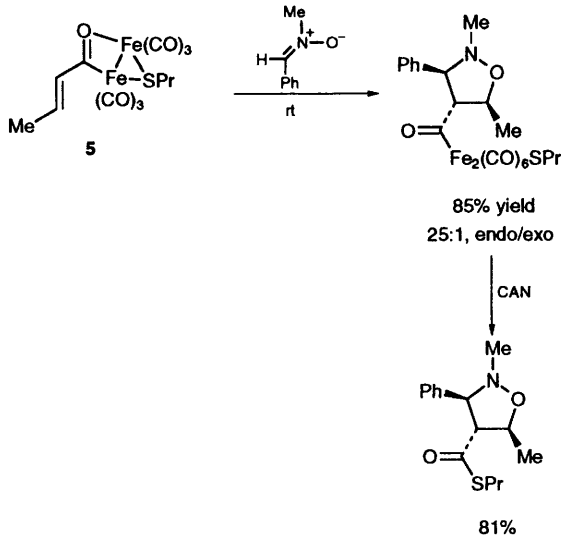
Iron acyl complexes dominate this area of organotransition metal methodology, as illustrated by research from the group of S. G. Davies at Oxford. A 'commercial preparation' of homochiral (*S*)-(+)-Fe(CO)(η^5-C_5H_5)(PPh_3)$COCH_3$ from [Fe(CO)$_2$(η^5-C_5H_5)(PPh_3)]$^+Br^-$ **3** utilising L-menthol is described (**Scheme 8**).[16] Reaction of this salt with potassium L-menthyl proceeds to give the addition product **4** with no stereoselection. However, treatment of the diastereoisomeric mixture **4a**+**b** that is formed with MeLi and LiBr empowers one of the two diastereoisomers (**4a**) to proceed to the requisite iron acyl complex, whilst the other proves unreactive. This transformation was shown to occur with inversion of configuration at iron, thus implicating nucleophilic attack at the carbon monoxide ligand of **4a** and not at the carbonyl group.



Scheme 8

The reactivity of enolates derived from Fe(CO)(η^5-C_5H_5)(PPh_3)$COCH_3$ has been thoroughly investigated and they have been shown to be powerful tools for asymmetric synthesis.[17] A study of the reactions of such enolates with chiral sugar-derived aldehydes has been reported, with particular attention being paid to the matching and mismatching stereodirecting effects that occur when two chiral reagents combine.[18]

Iron acyl complexes have also been used as a device to improve the poor *endo*/*exo* selectivity that is observed upon the cycloaddition of acyclic nitrones to α,β-unsaturated esters (**Scheme 9**).[19] Apparently, low diastereoisomeric ratios are



Scheme 9

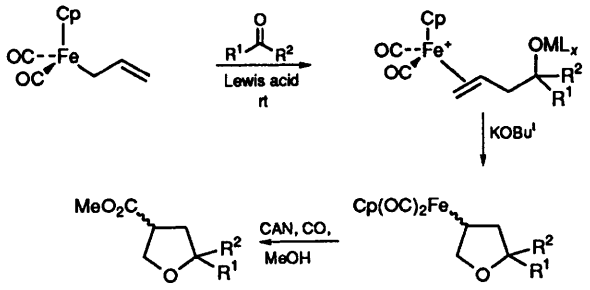
commonly observed when electron deficient olefins are employed as the dipolarophile. This situation can, however, be remedied via the use of a suitable di-iron acyl complex **5**. Not only does the cycloaddition of nitrones now proceed with excellent regiochemistry and stereoselectivity, but the corresponding thioesters can be liberated in good yield upon treatment with cerium(IV) ammonium nitrate (CAN).

Potassium tetracarbonylferrate, $K_2[Fe(CO)_4]$, has recently been introduced as a non-pyrophoric and practicable alternative to Collman's reagent.[20] Reaction with alkyl halides gave the corresponding iron acyl complexes, which could be manipulated to yield carboxylic acids (using oxygen gas) and ketones (utilising an alkyl halide or ethylene gas).[20]

2.4 Allyl transition metal complexes

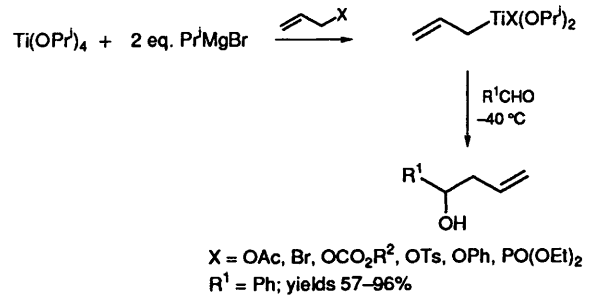
The allyl complexes of iron and titanium figure strongly in the recent literature, with work from the group of Turos illustrating how allylic iron compounds can be used in the preparation of substituted tetrahydrofurans.[21] An extension of his previously described methodology focuses on an improved procedure for reactions of allylic iron compounds with aldehydes and ketones under Lewis acidic conditions ($ZnCl_2$ or $TiCl_4$) (**Scheme 10**). After potassium *tert*-butoxide mediated cyclisation to form the tetrahydrofuran, the resulting carbon–iron σ bond can be converted to an ester upon reaction with CAN, under an atmosphere of carbon monoxide.

The allylic compounds of titanium have been championed as useful synthetic reagents, capable of exhibiting high levels of regio-, diastereo-, and enantioselectivity in their reactions with organic substrates.[22] A recent paper by Sato has described an efficient method of preparing these compounds from allylic halides, by reaction with titanium tetraisopropoxide and isopropyl magnesium bromide (**Scheme 11**).[22] Allylic carbonates,



R^1 = *p*-$NO_2C_6H_4$; R^2 = H; 15 mol% $ZnCl_2$; 71% yield
R^1R^2 = $(CH_2)_6$; 200 mol% $TiCl_4$; 37% yield

Scheme 10



X = OAc, Br, OCO_2R^2, OTs, OPh, $PO(OEt)_2$
R^1 = Ph; yields 57–96%

Scheme 11

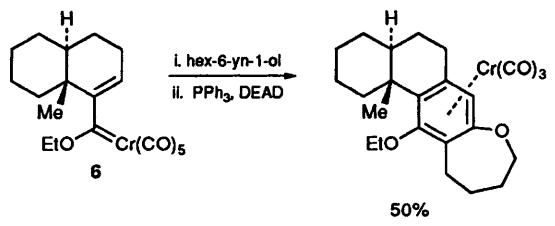
phosphonates, sulfonates and ethers are also shown to be viable precursors to the organometallic species. The exact structure and composition of the organometallic compound thus formed remains to be delineated. However, these species display similar reactivity to those generated by the addition of $ClTi(Pr^iO)_3$ to allyl-lithium derivatives, which includes smooth addition to aldehydes and ketones and 1,2-addition to α,β-unsaturated carbonyl compounds.

3 Group 6 transition metal carbene complexes in synthesis

3.1 Annulation reactions

The use of group VI carbenes (notably chromium based) in the construction of aromatic systems has proven to be a productive area of organometallic chemistry over recent years, and the period under review is no exception.

Novel results published by Quayle have demonstrated how the Dötz reaction can be applied to the diastereoselective synthesis of arene chromium tricarbonyl compounds (which are themselves of use to the synthetic organic chemist –see Section 8.1). The two coupling partners in the Dötz reaction are a vinyl carbene and an acetylene; Quayle's group have been the first to utilise a chiral vinyl carbene in this benzannulation reaction, which leads to the preparation of complex, fused heterocyclic ring systems (**Scheme 12**).[23] Reaction of the chiral racemic carbene **6**, with hex-6-yn-1-ol at



Scheme 12

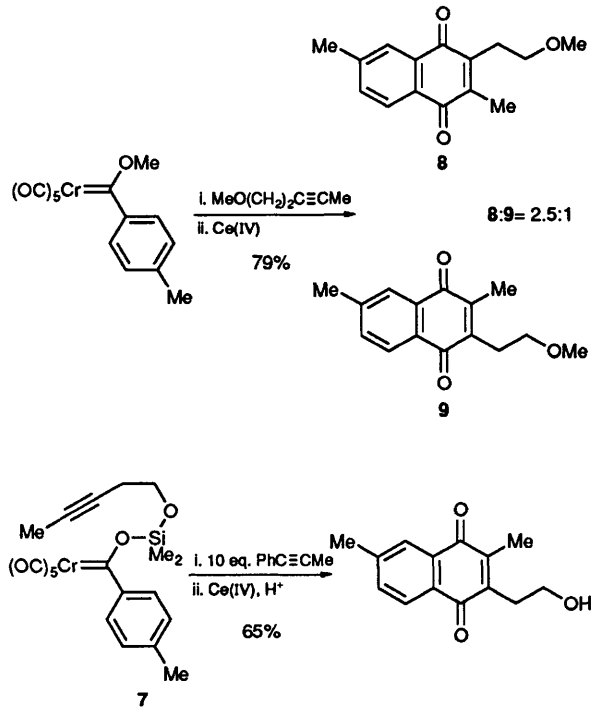
reflux in THF furnished the corresponding arene chromium tricarbonyl compound in good yield: moreover, this complex was subsequently shown to be a single diastereoisomer. This work may be compared with that of Wulff, who has utilised a chiral non-racemic acetylene-containing compound as the asymmetric partner in his diastereoselective synthesis of arene chromium tricarbonyl compounds via the Dötz reaction.[24]

Although the Dötz reaction has been utilised in synthesis many times, the mechanism of this process is not fully understood. A paper by Barluenga has described isolation of the proposed first intermediate in the mechanistic pathway, namely a vinyl carbene complex which has undergone photodissociation of a carbon monoxide ligand: an eighteen electron arrangement at the metal is maintained by coordination of the vinyl group to chromium.[25] Another development in this area relates to an improvement in experimental procedure: irradiation of the reaction mixture with a 300 W xenon lamp has been shown to improve yields of the Dötz reaction.[26]

When an intermolecular coupling between a vinyl carbene complex and an unsymmetrical alkyne is performed, the main problem that is often encountered is one of regiochemistry. M. G. Finn has gone some way to overcoming this difficulty by using a temporary silicon-based tether to connect the two reacting species. In an approach that is reminiscent of the elegant intramolecular Diels–Alder reactions recently introduced by Stork, the α-methoxy aryl carbene **7** was treated with diphenyl acetylene to furnish the annulated product in high yield and with complete control of regiochemistry (**Scheme 13**).[27] It is instructive to compare this result to that obtained without the temporary tether where the ratio of the products obtained (**8**:**9**) is 2.5:1 (**Scheme 13**). Addition of diphenyl acetylene, in order to improve the yields and reduce the presence of by-products, is noteworthy, and the reader is directed to this paper's discussion of the possible role of the symmetrical alkyne, which is not incorporated into the products of the benzannulation reaction.[27]

3.2 Spirocycle formation

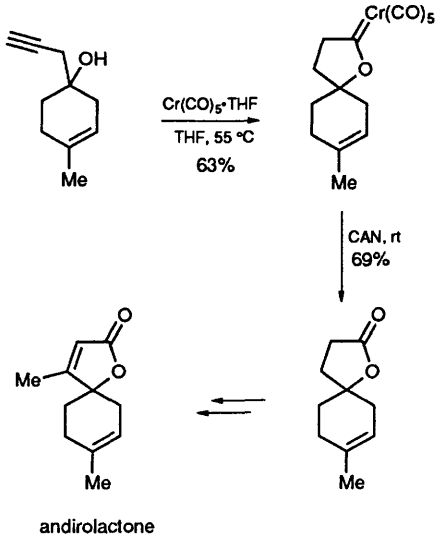
The cyclisation of homoprop-2-ynylic alcohols, when treated with transition metal carbonyl complexes, to give heterocycles holds much promise for the preparation of complex synthetic targets. After initial reports set the stage for this methodology, it



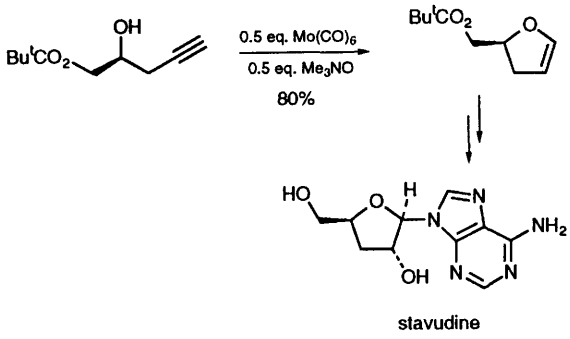
Scheme 13

appears that the scope and generality of the cyclisations are to be explored in the arena of total synthesis. Two groups have been active in this area: Quayle and co-workers have used methodology which they developed themselves, based upon a chromium pentacarbonyl tetrahydrofuran complex, in a concise synthesis of andirolactone (**Scheme 14**).[28]

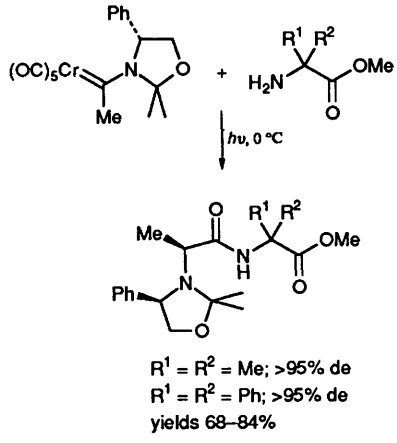
Similarly, McDonald has used his molybdenum derived chemistry to prepare stavudine, which exhibits antiviral activity (**Scheme 15**).[29]



Scheme 14



Scheme 15



Scheme 16

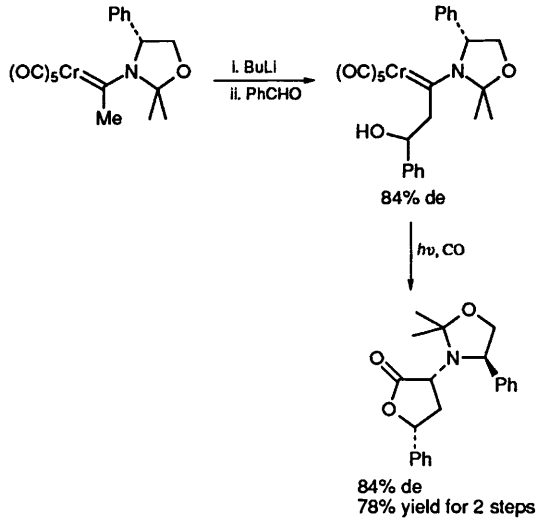
3.3 α-Amino and hydroxy acid synthesis using carbenes

Hegedus and co-workers have continued to publish some useful methodology in which amino–carbene complexes are photoirradiated and the resulting metal-bound ketenes used as electrophilic fragments for peptide coupling. Particular attention has been paid to the use of chiral auxiliaries, attached to the carbene participant, as a method for controlling both the relative and absolute stereochemistry of the products so formed (**Scheme 16**).[30] As such, this represents an unusual method of peptide synthesis, as the incipient stereogenic centre is formed at the same time as the peptide bond, under relatively mild conditions. One of the advantages of this approach stems from the fact that the activated ester fragment manifests itself in the form of a ketene intermediate that is both reactive and (of course) sterically unhindered. Therefore, this methodology proved ideal for the preparation of some hindered dipeptides containing α,α-disubstituted amino acids (**Scheme 16**).[30] The good yields and high diastereoisomeric selectivities that are observed at the newly formed stereogenic centre are worthy of comment.

In a related study, irradiation of bis-alkoxy carbene complexes in the presence of imidazolines led to the formation of azapenams, which dimerised

to furnish bis-dioxocyclams upon treatment with acid.[31] The dimerisation process, which involves initial fragmentation of the azapenams, raises a number of stereochemical issues, and these are fully addressed in the paper.

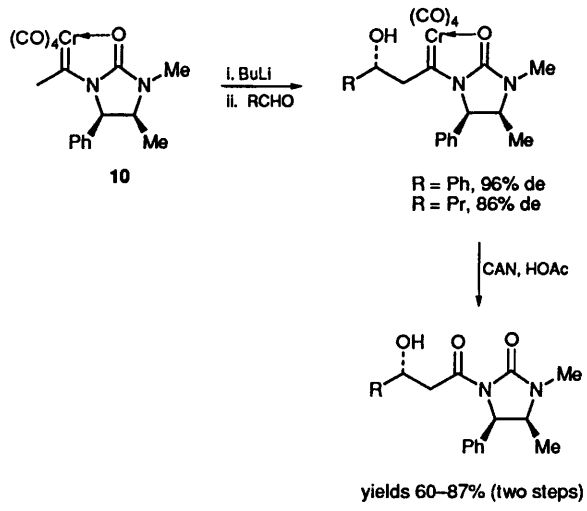
Hegedus has also shown how the aldol adduct arising from reaction of the enolate of an α-amino-carbene with an aldehyde can be photocyclised to provide α-amino-γ-lactones in a diastereoisomerically and enantiomerically pure form (**Scheme 17**).[32] As illustrated earlier, it is a chiral auxiliary positioned on the amino-carbene fragment[30] that is responsible for the stereocontrol during the initial aldol reaction, and also during intramolecular attack of the alcohol nucleophile onto a metal bound amino ketene intermediate.



Scheme 17

3.4 Stereoselective reactions of enolates derived from carbene complexes

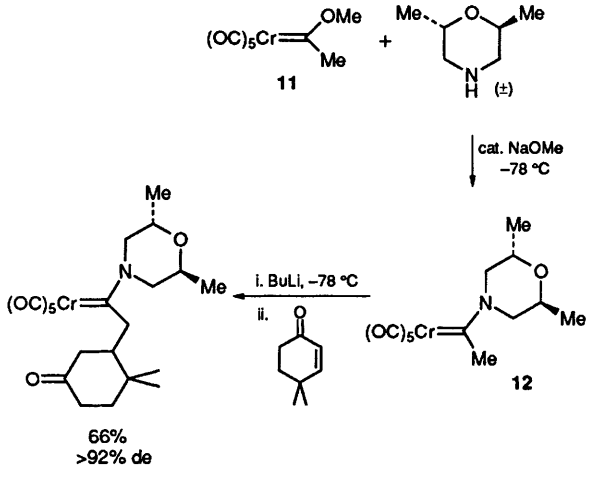
The theme introduced in the above paragraph is continued in the work of Wulff, who has reported on the use of chiral, urea derived, chromium carbenes as acetate equivalents in the aldol reaction (historically this is an area that has proven problematic for most, but not all, chiral enolate equivalents).[33] Deprotonation of carbene **10** (**Scheme 18**) with butyl-lithium generates the corresponding enolate, which is capable of reacting with aldehydes in a highly stereoselective and high yielding manner. The stereoselectivity that is observed in this reaction is presumed to derive from an 'open' transition state, with coordination from the urea carbonyl being crucial to the facial selectivity that is displayed by the organometallic enolate.[33] Finally, removal of the transition metal and liberation of a carbonyl group can be accomplished in good yield upon exposure to cerium (IV) ammonium nitrate (CAN): the resulting *N*-acyl urea can, of course, be readily converted into the



Scheme 18

corresponding β-hydroxy acid (enantiomerically enriched).

In another exciting development to this area, the group of E. Licando have introduced a chiral, amino substituted chromium carbene, the enolate of which shows promise in asymmetric Michael reactions (**Scheme 19**).[34] The problem with utilising such chiral amino carbene complexes is one of preparing the organometallic compound from the requisite methoxy carbene complex. For example, it appears that *trans*-2,5-dimethylpyrrolidine is incapable of displacing the methoxy group of complex **11**, and so the ideal candidate for a chiral auxiliary had to be abandoned in favour of a morpholine derivative with stereogenic centres further removed from the amine, so as to increase its nucleophilicity.[34] Nevertheless, the enolate derived from compound **12** is capable of reacting with cyclic enones in a stereoselective manner and so this methodology has potential in the field of asymmetric synthesis, which only awaits a synthesis of non-racemic *trans*-2,6-dimethylmorpholine.

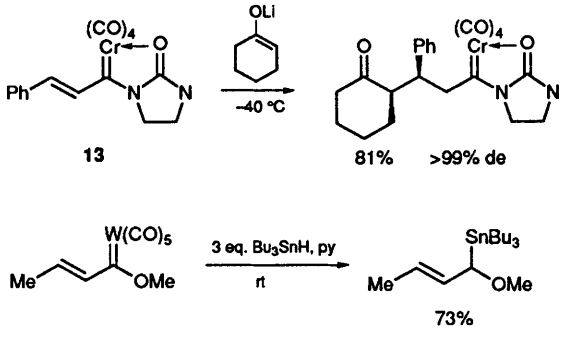


Scheme 19

3.5 Vinyl carbene complexes

Wulff has recently expanded upon the work of Nakamura, who had reported that the addition of ketone enolates to vinyl alkoxy chromium carbene complexes proceeded with good diastereoselectivity. However, the *syn* selectivity that was observed in this chemistry can be improved upon if unsaturated imidazolidone carbene complexes **13** are used in the role of Michael acceptor (**Scheme 20**).[35] If the addition product is subsequently treated with an oxidising agent to liberate the transition metal, followed by sodium methoxide, the imidazoline carbene becomes a carboxylic ester. This reaction scheme is now equivalent to the addition of a ketone enolate to an α,β-unsaturated ester, normally an energetically unfavourable reaction.

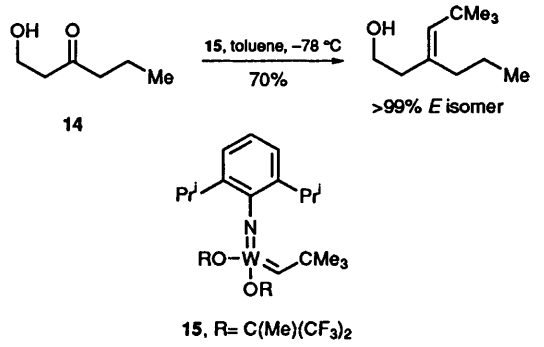
Merlic has also reported on the use of vinyl carbene complexes, and discovered that tributyl tin hydride can insert into the carbon–metal bond of an unsaturated tungsten or chromium methoxy carbene to furnish substituted allylic tin reagents which will be useful in organic synthesis (**Scheme 20**).[36]



Scheme 20

3.6 Olefination reactions

Grubbs and co-workers have described some ingenious methodology which outlines the concept of a hydroxy group directed olefination as a means of controlling the geometry of trisubstituted olefins (**Scheme 21**).[37] When the β-hydroxy ketone **14** is treated with the tungsten alkylidene **15** selective formation of one double bond isomer is observed.



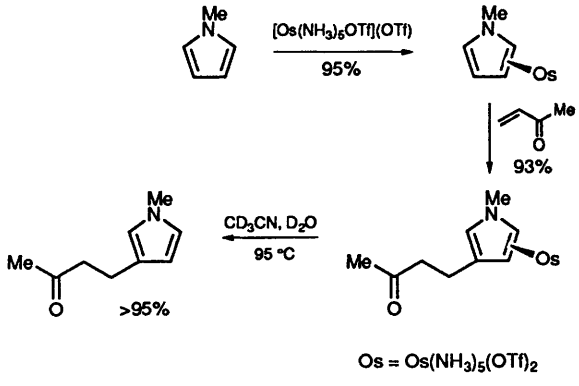
Scheme 21

The success of this chemistry relies on the fact that the metal complex is coordinatively unsaturated and welcomes complexation with the oxygen lone pairs. In fact, utilisation of the corresponding molybdenum alkylidene complex $[Mo(CHCMe_2Ph)(NAr)(OCMe(CF_3)_2)_2]$ reveals that there is a substantial rate acceleration for the olefination reaction of **14** as the oxygen coordinates to the transition metal. The nature of the alkylidene group that is transferred is not restricted, and can be altered by first performing a metathesis reaction upon the above molybdenum compound, prior to the olefination.[37]

4 η^2-Complexes in organic synthesis

4.1 η^2-Complexes of osmium(II)

In a recent series of papers, W. D. Harman has investigated a range of η^2-osmium(II) complexes of aromatic systems, with the purpose of examining their uses in synthetic organic chemistry.[38–41] In effect, formation of the complexes of pyrroles with osmium(II) dearomatises the heterocycle into what is the equivalent of a complexed olefin and an enamine which will react with electrophiles at the C-3 position.[38] Decomplexation of the transition metal unit is normally achieved by moderate heating, under anaerobic conditions, to liberate the free pyrrole (**Scheme 22**). Overall, this technique is useful for selective electrophile substitution at the β-position of pyrroles.



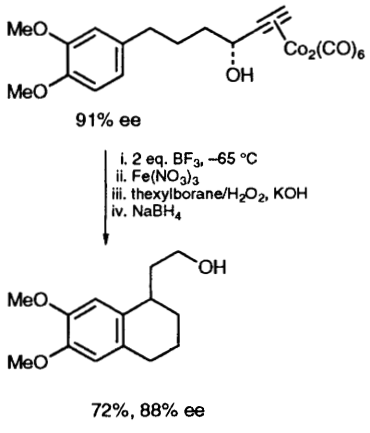
Scheme 22

The same group have also reported that similar osmium(II) pyrrole complexes undergo 1,3-dipolar cycloadditions with electron deficient alkenes.[39] This chemistry has considerable potential, as the end result is the same as accomplishing the Diels–Alder reaction of pyrroles with alkenes (normally an unfavourable reaction which requires high pressures) under mild conditions.

4.2 η^2-Complexes of cobalt

Formation of cobalt complexes of acetylenes as a device to alter the reactivity and steric environment

of the organic group has many varied and elegant uses in synthesis. The Nicholas reaction (namely the formation and trapping of a carbocation α to a complexed alkyne) has been continually expanded in scope, as synthetic chemists have illustrated how all manner of organic molecules may be constructed via this chemistry. Recent papers have revealed successful attempts to generate the core of the enediynes,[42] and a host of medium-ring ethers[43] via the intramolecular variant of the Nicholas reaction. A particularly intriguing study has concentrated upon the stereochemical issues that are raised when the position adjacent to the complexed acetylene is substituted with a leaving group and is the sole source of stereochemistry in the molecule to be subjected to the Nicholas reaction (**Scheme 23**).[44] It was found that, under certain conditions, there was a complete transfer of stereochemical information from the leaving group to the nucleophile. Unfortunately, at this time it is not possible to determine whether the substitution reaction has proceeded with retention or inversion, and so any comment on mechanism must await further experimental evidence.[44]

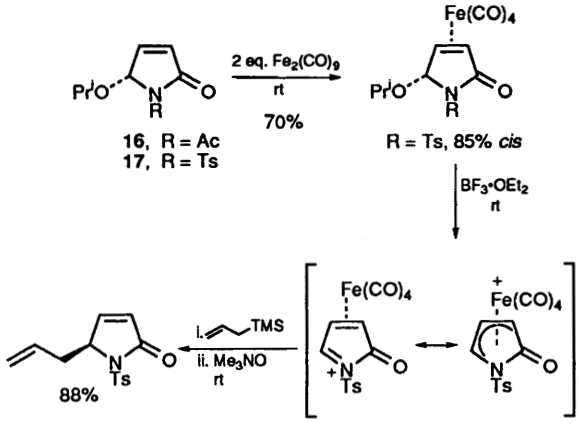


Scheme 23

Other developments in this area relate to use of the cobalt complex as a protecting group for an acetylene,[45] or alternatively, use of the steric bulk of the transition metal to influence stereoselectivity during aldol reactions of (complexed) acetylenic aldehydes.[46]

4.3 η^2-Complexes of iron

Hiemstra and Speckamp have published two papers which describe the role of η^2-iron complexes in the formation and reactivity of *N*-acyl iminium ions.[47] Complexation of the unsaturated lactam **16** (**Scheme 24**) with di-iron nonacarbonyl yields predominantly the *cis* isomer (presumably as a result of the complex induced proximity effect). Unfortunately, upon treatment with a Lewis acid, this complex cannot easily form the *N*-acyl iminium ion, as the transition metal is unable to donate electrons into the σ^* orbital of the alkoxy group and so form a stabilised cation. However, by altering the

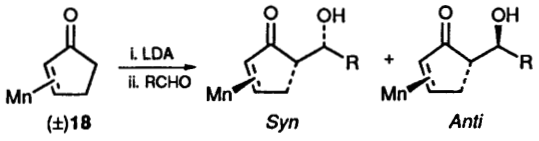


Scheme 24

protecting group on the lactam nitrogen to a tosyl group **17**, the nitrogen lone pair is more available for assisting the ionisation process and the iminium ion is accessible. Of course, once the iminium ion is formed, the transition metal satiates the positive charge on the α-carbon, and also influences the reactivity of the aforementioned ion by blocking one π face to the approach of nucleophiles. A corollary of this situation is that an enantiopure lactam can be converted into the substituted product with stereochemical fidelity (overall inversion).

4.4 η^2-Complexes of manganese

The complexes of α,β-unsaturated ketones with $Mn(CO)_2MeCp$ have proven to be useful tools for organic synthesis, as the transition metal has been shown to influence the reactivity of cyclic *Z*-enolates formed upon treatment with LDA (**Scheme 25**).[48] For example, reaction of cyclopentenone complex **18** with LDA and subsequent treatment with a series of aldehydes leads to the formation of the *anti* aldol adducts with high stereoselectivity. Moreover, the electrophile is directed to a single face of the enolate, that which is opposite the transition metal, presumably as a consequence of steric effects. Decomplexation of the transition metal unit was accomplished by mild heating, and yielded the free cyclopentenones in high yields. This methodology should be compared with that described by Panek, who had previously shown that the corresponding



Mn= $Mn(CO)_2MeCp$

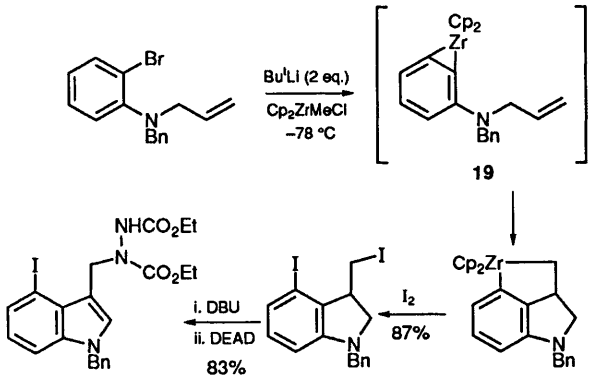
R	*Syn*	*Anti*	Yield
Bu	25	75	54%
Pr^i	5	95	59%
Ph	<5	>95	41%

Scheme 25

lithium enolate of cyclopentenone reacted in an essentially non-selective manner with aldehydes to give mixtures of *syn* and *anti* products, and that the transmetallated zirconium enolate was only moderately *syn* selective.[49]

4.5 η^2-Complexes of zirconium

This section, which is clearly related to Section 2, concentrates upon the reactivity and scope of η^2-complexes of zirconium with aromatic systems, as reported by Buchwald.[50,51] Treatment of an *N*-allyl bromoaniline derivative with *tert*-butyl-lithium and $Cp_2ZrMeCl$, leads to an intermediate η^2-benzyne complex **19** (**Scheme 26**).[51] However, this putative intermediate is not isolated, and undergoes an intramolecular insertion reaction with the pendant alkene to furnish an indolene containing zirconacycle. Quenching with iodine replaces each of the carbon–metal bonds to yield the di-iodo substiuted indolene in good yield: the primary iodide functionality can be subjected to nucleophilic attack, or the molecule may be transformed into a substituted indole by an elimination–ene reaction sequence.[51] In summary, this methodology becomes a useful method of constructing some highly substituted heterocycles when more elaborate bromo-aniline derivatives are subjected to an analogous sequence of reactions.

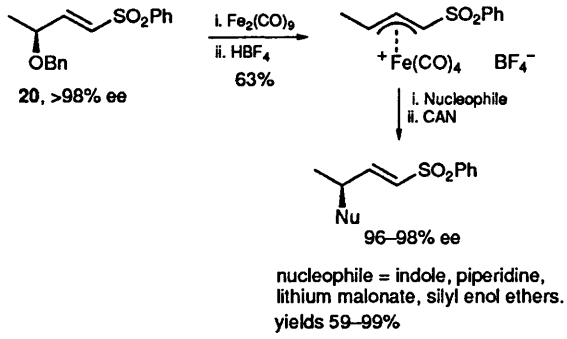


Scheme 26

5 η^3-Complexes in organic synthesis

5.1 η^3-Complexes of iron

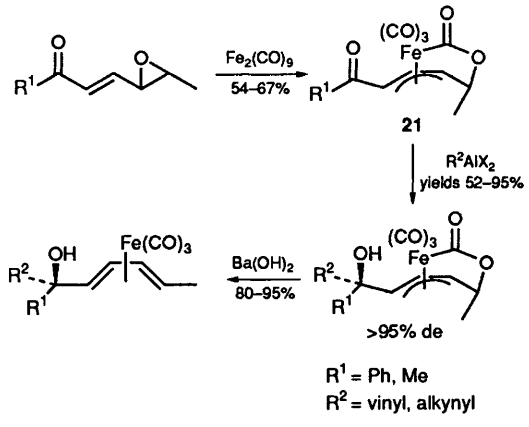
Enders has recently published two papers which detail the use of cationic η^3-iron complexes as a means of controlling stereochemistry during allylic substitution reactions (**Scheme 27**).[52] Reaction of the allylic ether **20** with di-iron nonacarbonyl gave a single iron olefin complex, which was subsequently ionised with HBF_4 to the cationic species shown. This complex reacts with nucleophiles in a highly regio- and stereoselective manner to furnish the substituted products with retention of configuration (via double inversion). Enders has subsequently



Scheme 27

proven the utility of this methodology in a synthesis of (−)-myoporone.[52]

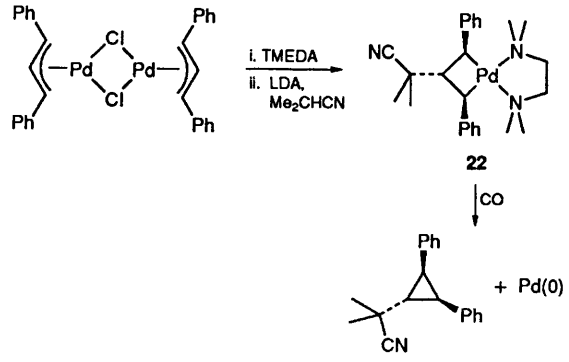
The utility of π-allyl tricarbonyl iron lactone complexes as tools for organic synthesis has been demonstrated many times, and recent work by Ley has illustrated how they may be applied to a preparation of iron diene complexes (**Scheme 28**).[53] Nucleophilic attack of various organo-aluminiums upon the carbonyl group of the π-allyl tricarbonyl iron compound **21** occurs in a highly stereoselective fashion; the resulting lactone may be decarboxylated with barium hydroxide to give one diastereoisomer of the corresponding diene complex in good yield. This particular approach to these valuable diene complexes has the advantage that the precursors may be synthesised in enantiomerically enriched form via Sharpless epoxidation chemistry, and so constitutes an asymmetric synthesis of the iron diene complexes.



Scheme 28

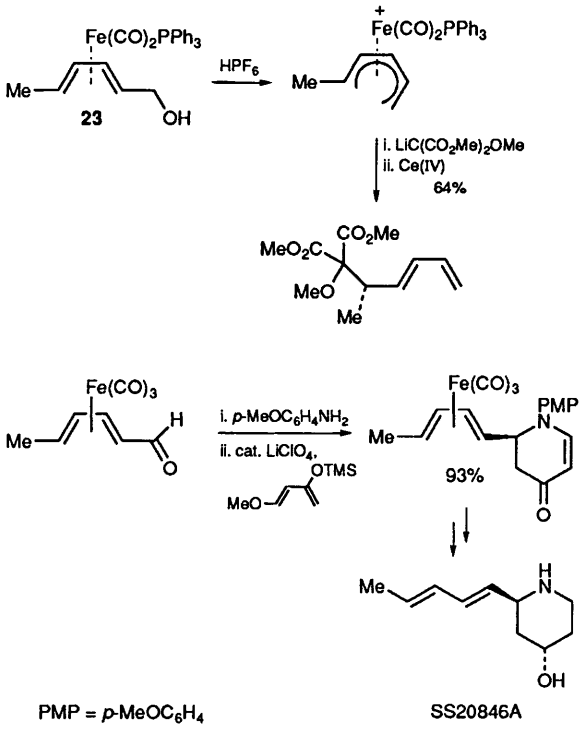
5.2 η^3-Complexes of palladium

Hoffmann has recently described some mechanistic studies on the reaction of η^3-palladium(II) compounds with an enolate and carbon monoxide gas (**Scheme 29**): normally this reaction results in formation of a trisubstituted cyclopropane.[54] However, by judicious choice of the substituents on the allyl system, the mechanistic pathway that leads to the cyclopropane can be interrupted and an intermediate 16-electron species **22** can be isolated



Scheme 29

and characterised by X-ray crystallography. It appears that this complex has arisen through nucleophilic attack at the central carbon of the allyl ligand, and owes its unusual stability to unfavourable steric interactions between the two phenyl groups in the three-membered ring that is formed upon completion of the reaction. However, attack on the metal by carbon monoxide leads to an 18-electron species, and presumably this then collapses to form the cyclopropane.[54]



Scheme 30

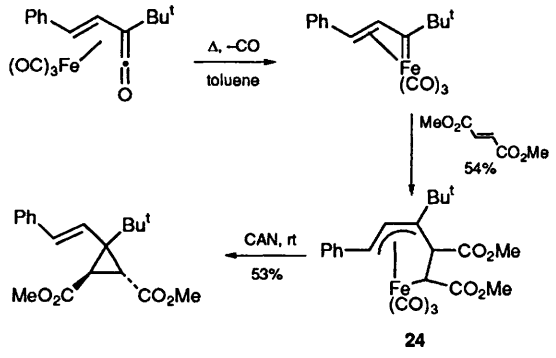
6 η^4-Iron complexes in organic synthesis

6.1 η^4-Iron diene complexes

Examples of the stereocontrolled synthesis of organic molecules using iron diene complexes continue to abound in the literature, as this methodology is rapidly assimilated by the synthetic community.[55] Donaldson has reported on the use of pentadienyl cations as a device for achieving the stereoselective synthesis of the C_{21}–C_{24} segment of discodermolide (an unusual immunosuppresent).[56] Ionisation of the hydroxy substituted iron-complexed diene **23** with HPF_6 gives the corresponding pentadienyl cation, which is susceptible to nucleophilic attack on the *exo* face at either end of the pentadienyl ligand (**Scheme 30**). Donaldson found that the regiochemistry of attack is crucially dependant upon the ligands placed on the transition metal (for example $Fe(CO)_3$ was less regioselective than $FePPh_3(CO)_2$, which promoted attack at the more hindered end of the cationic pentadiene). After nucleophilic addition by a malonate anion had been accomplished, decomplexation of the iron fragment with Ce(IV) was sufficient to reveal the desired portion of the target molecule.[56]

An iron diene substituted imine has been subjected to a cycloaddition reaction with Danishefsky's diene, in the key step of a recent synthesis of SS20846A; this synthesis also determined the absolute configuration of the natural product (isolated from Streptomyces sp. S20846, **Scheme 30**).[57] High diastereoselectivity was observed in what is a fairly unusual combination of cycloaddition partners, presumably as a consequence of the steric bulk of the transition metal moiety.

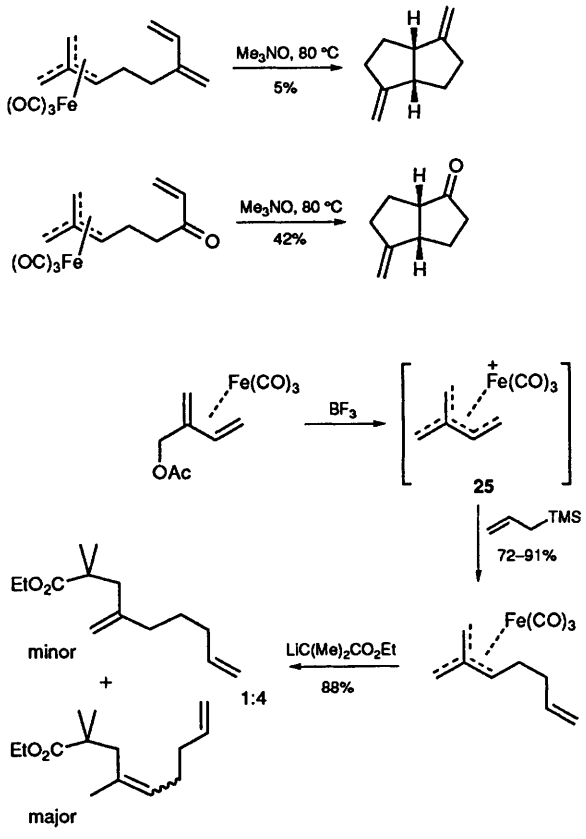
Gibson (née Thomas) has continued to publish useful results in the field of tricarbonyl(vinylketene)iron(0) complexes, which outline their utility in organic synthesis. Recent studies have shown that these vinylketene complexes are capable of combining with a range of electron poor olefins to provide [after oxidation with cerium(IV)] the corresponding, vinyl-substituted cyclopropanes [methyl fumarate is illustrated as an example (**Scheme 31**)].[58] Mechanistically, the reactions are presumed to proceed via a decarbonylation/[2+2]-addition sequence which leads to an intermediate η^3-iron complex **24**: upon oxidation of the iron, a vinyl cyclopropane is produced in good yield.[58]



Scheme 31

6.2 η^4-Iron trimethylene methane complexes

The iron complexes of trimethylene methane derivatives have not witnessed widespread use in organic synthesis, with other transition metals being preferred partners for this unusual (and unstable!) organic fragment. The major problem that is encountered when attempting to use the iron complexes as synthetic reagents occurs upon decomplexation of the transition metal to liberate the organic ligand, when poor yields are frequently reported. However, a recent solution to this problem has been published, which utilises reaction with an olefin in an *intramolecular* cycloaddition reaction as a method for improving the yields of oxidative decomplexation (**Scheme 32**).[59] A series of iron-complexed trimethylene methane compounds (which were obtained from η^4-diene complexes) were decomplexed with trimethylamine *N*-oxide, and a cycloaddition ensued: moderate yields could be observed, depending upon the electronic nature of the olefin employed as the trap.[59]



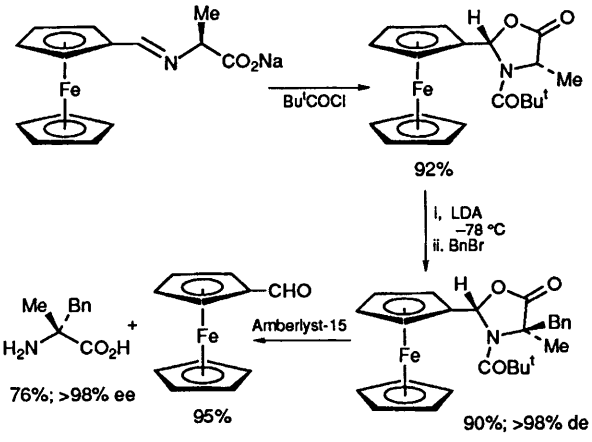
Scheme 32

Donaldson has also reported on studies in this area, and has made some progress in the trapping of cations that are adjacent to the *internal* carbon of an η^4-iron diene complex **25** (**Scheme 32**).[60] Reaction of this cationic species with a nucleophile (allylsilane) takes place at the terminus of the diene system to produce an iron-bound trimethylene methane complex: decomplexation of the transition metal occurs upon treatment with an enolate and furnishes a regioisomeric mixture of substituted olefins.[60]

7 η^5-Complexes in organic synthesis

7.1 Stoichiometric ferrocene complexes in organic synthesis

Davies has published an account of a practical ferrocene containing chiral auxiliary for the preparation of α,α-disubstituted amino acids in enantiopure form (**Scheme 33**).[61] This approach is related to work on the self-regeneration of chirality published by Seebach; however, the presence of the transition metal confers some particularly desirable properties onto the auxiliary. Firstly, formation of the *N*-acyl oxazolidone is completely *cis* selective (probably as a consequence of the large steric bulk of the transition metal complex). Deprotonation with LDA then yields an enolate which is capable of reacting with electrophiles in a highly stereoselective manner (>98% de). The desired amino acid can then be liberated under particularly mild conditions to give enantiomerically pure products, coupled with a good yield of recovered auxiliary. Presumably, it is the ability of the ferrocence moiety to stabilise α-carbocations that is responsible for the expeditious and non-destructive removal of the auxiliary under acidic conditions.[62]

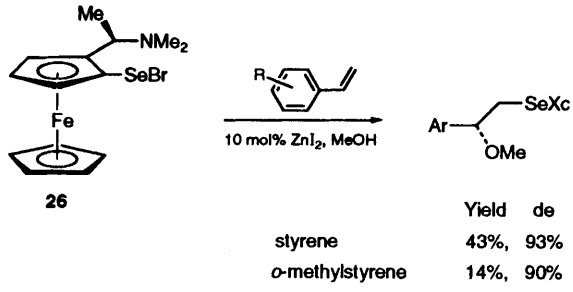


Scheme 33

Fukuzawa has described an approach to the selenation of olefins using a chiral (non-racemic) selenating agent, which is based on ferrocene (**Scheme 34**).[63] When a selenyl bromide **26** is added to olefins in the presence of methanol, a highly diastereoselective selenation ensues: although this approach to enantiopure compounds has undoubted value, its utility is presently hampered by the low yields of product that are obtained.

7.2 η^5-Ruthenium and rhenium complexes as chiral auxiliaries

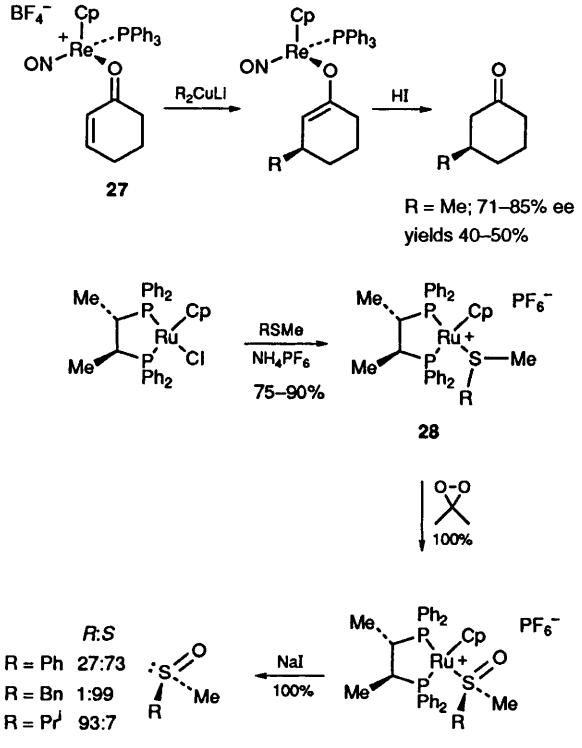
Gladysz has extended earlier work on the use of chiral rhenium complexes as Lewis acids for



Scheme 34

promoting asymmetric transformations, by examination of the complex **27** as a precursor to enantiomerically enriched 3-substituted cyclohexanones (**Scheme 35**).[64] The asymmetry present at the transition metal is sufficient to influence the π facial approach of an organocuprate and, after decomplexation of the transition metal with HI, the requisite cyclohexanones are provided in good enantiomeric excesses.

In a similar vein, Schenk has used ruthenium complexes containing a chiral phosphine ligand (CHIRAPHOS) as auxiliaries for the oxidation of sulfides to sulfoxides (**Scheme 35**).[65] Complexation of one of the lone pairs on the sulfide to the metal (**28**) ensures that oxidation of the other will occur when dimethyl dioxirane is added; removal of the auxiliary proceeds with retention of configuration at sulfur. An interesting reversal of enantioselectivity can be observed when comparing the oxidation of methyl benzyl sulfide.

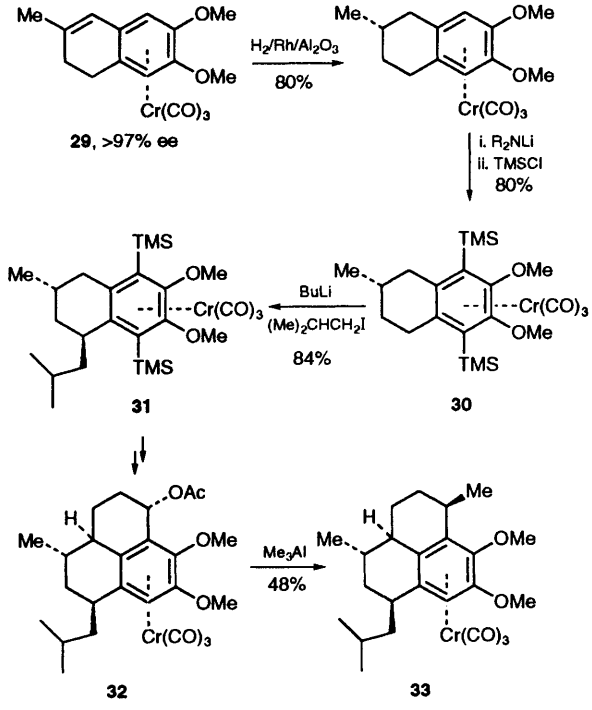


Scheme 35

8 η^6-Complexes in organic synthesis

8.1 η^6-Arene chromium tricarbonyl complexes

Arene chromium tricarbonyl complexes are particularly useful for the asymmetric synthesis of a variety of organic molecules, as the transition metal imparts several useful properties onto the associated aromatic ligand.[66] It is pleasing to see these complexes being used in synthesis, and a recent approach to the aglycone of pseudopterosin G by Schmalz nicely illustrates most of the advantageous properties to be gained upon complexation of an arene to this transition metal (**Scheme 36**).[67] The first step, which utilises the large steric bulk of the transition metal moiety, involves the diastereoselective reduction of **29** by hydrogenation over rhodium: approach of the catalyst from the *exo* face, away from the chromium, leads to the desired stereoselectivity. Subsequently, facile deprotonation at a position benzylic to the complexed arene **30** (made possible by the electron-withdrawing property of the chromium tricarbonyl group), is followed by quenching with an electrophile which proceeds in a diastereoselective manner to give **31**.[67] Several steps later in the synthesis, the transition metal's ability to stabilise benzylic carbocations is illustrated by the ionisation of complex **32**. The stabilised carbocation is trapped by trimethylaluminium, again from the *exo* face of the molecule to avoid destabilising steric interactions, and gives the *exo* methyl compound **33**. Removal of the transition metal was high-yielding, easy to accomplish, and the free arene could be readily transformed into a compound which is very close indeed to the naturally occurring product.

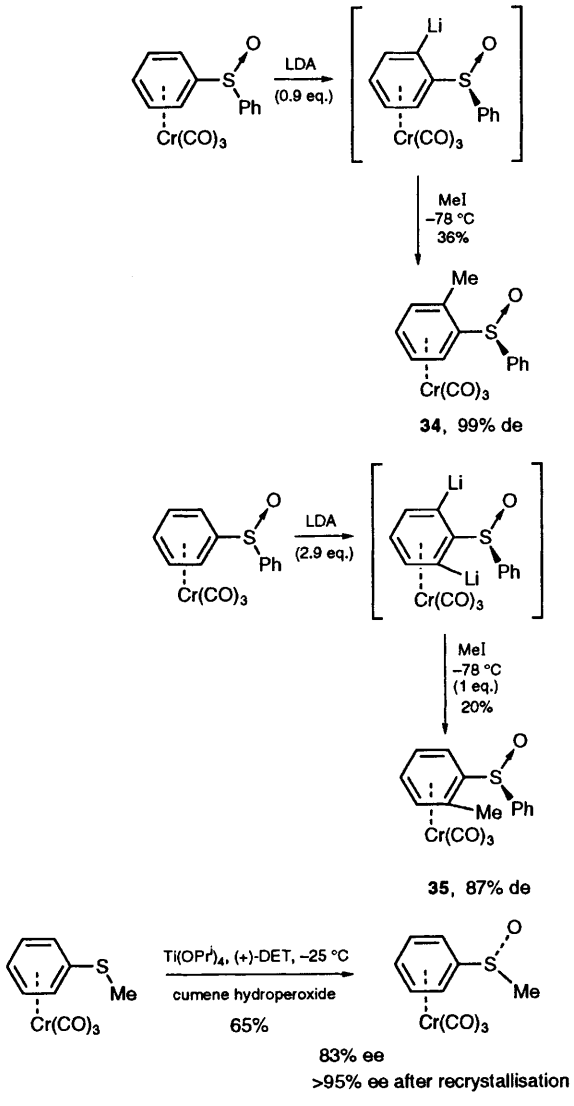


Scheme 36

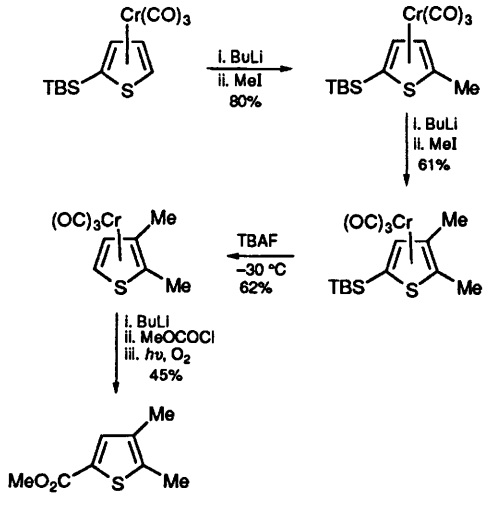
A nice study on the deprotonation reactions of complexed aromatic sulfoxides has been reported by Davies, who has shown that either mono- or di-anions may be formed upon treatment with the suitable number of equivalents of base (**Scheme 37**).[68] These anions are formed in a highly stereoselective manner, as the two *ortho* protons on the complexed arene are rendered diastereotopic by the transition metal. Indeed, upon reaction of such anions with electrophiles, the resulting disubstituted complexes are formed with very high diastereoselectivity; if a dianionic species is reacted with one equivalent of an electrophile then complementary stereoselectivity is observed (compare **34** and **35**). This observation may be significant in explaining the inconsistent results (in terms of stereoselectivity) that are sometimes obtained when quenching similar anions with a range of electrophiles. Bearing in mind that deprotonation is the stereochemical determining step in such reaction, the nature of the electrophile should not affect the stereoselectivity of the quench. However, this is not always the case, and the presence of dianionic species inadvertantly formed in the reaction medium may explain such discrepancies.[68]

Gibson (née Thomas) has also published work in this area, but with the emphasis on oxidation of phenyl thioether chromium tricarbonyl derivatives.[69] Enantiomerically enriched phenyl methyl sulfoxide may be obtained by the asymmetric oxidation of the chromium tricarbonyl complex of phenyl methyl sulfide with a diethyl tartrate modified oxidising agent (**Scheme 37**). (The very fact that arene chromium tricarbonyl complexes have been shown to be compatible with this and other oxidising systems is one of the reasons that this work is significant). A range of substituents were introduced onto the phenyl ring, and their effect upon the asymmetric oxidation scrutinised.[69]

Heteroaromatic ligands are also known to form η^6-complexes with chromium tricarbonyl, with pyridine, indole and thiophene being the most widely publicised examples. However, the chemistry of these compounds is still a relatively unexplored area, with many interesting possibilities for synthesis awaiting discovery. Two recent papers from Widdowson's group have defined an account of the lithiation chemistry of thiophene chromium tricarbonyl, with the aim of expediting the synthesis of polysubstituted thiophenes (**Scheme 38**).[70] Complexation of the thiophene nucleus to chromium tricarbonyl proceeds more efficiently if the C-2 position is substituted with a trialkyl silyl group (this strategy was first introduced by Davies in his preparation of pyridine chromium tricarbonyl:[71] the increased steric hindrance at the sulfur atom prevents σ-coordination of the thiophene to the metal). Once formed, these compounds can be deprotonated (and therefore substituted) at C-5, and then subsequently functionalised at the C-4 position using iterative methodology.[70] Removal of the silyl group and further deprotonation/ electrophilic quenching at C-2 is also possible; this leads to some nice examples of the synthesis of trisubstituted thiophenes.



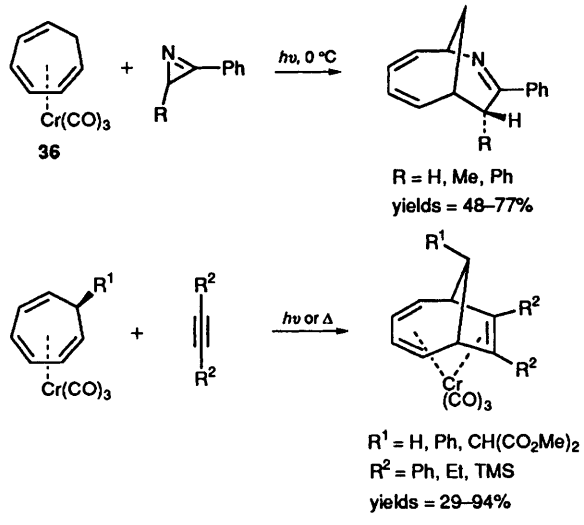
Scheme 37



Scheme 38

8.2 η^6-Chromium complexes in higher order cycloadditions

This is a rapidly expanding field in which the higher order cycloaddition reactions of olefinic systems are seen to be promoted by the chromium tricarbonyl unit. The fact that in some cases sub-stoichiometric amounts of transition metal can be used successfully, should not pass unnoticed. For example, Sheridan's group have recently described their efforts in the chromium tricarbonyl promoted [6+3] cycloaddition of trienes to azirines (**Scheme 39**).[72] Ultraviolet irradiation of toluene solutions containing the chromium tricarbonyl cycloheptatriene complex **36** and a series of azirines furnished the corresponding bicyclo [4.3.1] compounds lacking the transition metal, in good yields. Somewhat surprisingly, this reaction proceeds with addition across the C–N bond of the azirine: azirines normally undergo C–C bond scission during cycloaddition reactions. It was also found that use of distributed azirines (R = Me, Ph) resulted in the formation of a single *endo* diastereoisomer, as indicated in the Scheme.[72]



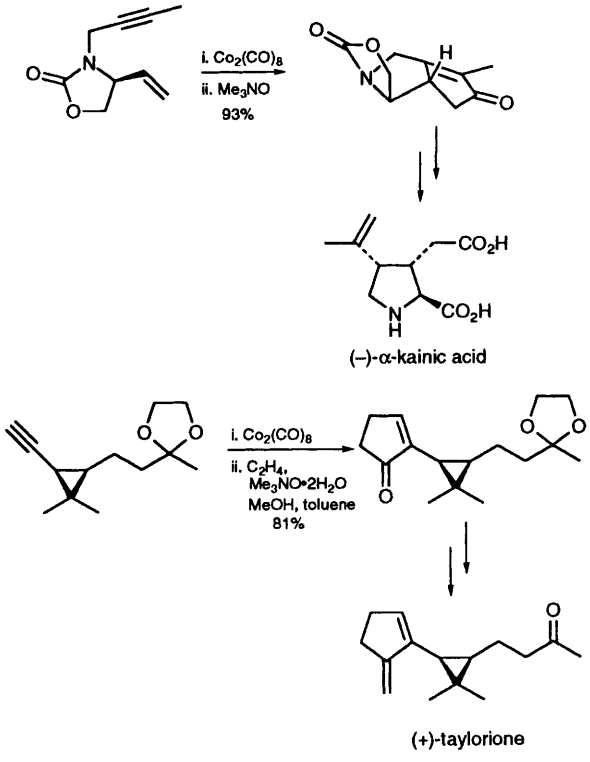
Scheme 39

The same group have also examined a related higher order cycloaddition reaction of complexed cycloheptatrienes with alkynes, to give the [4.2.1] adducts (**Scheme 39**).[73] This reaction can be made to be catalytic in chromium tricarbonyl if it is thermally driven, and the transition metal moiety can be readily removed from the adduct by heating in toluene (to give the free ligand plus toluene chromium tricarbonyl).

9 Transition metal mediated cycloadditions in organic synthesis

9.1 Pauson–Khand type reactions

The Pauson–Khand reaction (that of a dicobalt hexacarbonyl acetylene complex with an olefin, to yield a cyclopentenone) has proven to be of considerable value in organic synthesis. Ever more complex systems are being subjected to the reaction conditions, and it is a measure of the reaction's compatability with a variety of functional groups that it has been utilised in synthesis many times. The development of the intramolecular variant of this reaction realised a method for constructing complex bicyclic organic systems, and also of solving the regiochemical problems that are sometimes associated with the intermolecular Pauson-Khand reaction. Two natural product synthesis have recently been disclosed in which the Pauson–Khand reaction is a key carbon–carbon bond forming step in the synthetic sequence. Sung-eun Yoo has successfully synthesised (−)-α-kainic acid using the intramolecular version of the reaction (**Scheme 40**).[74]



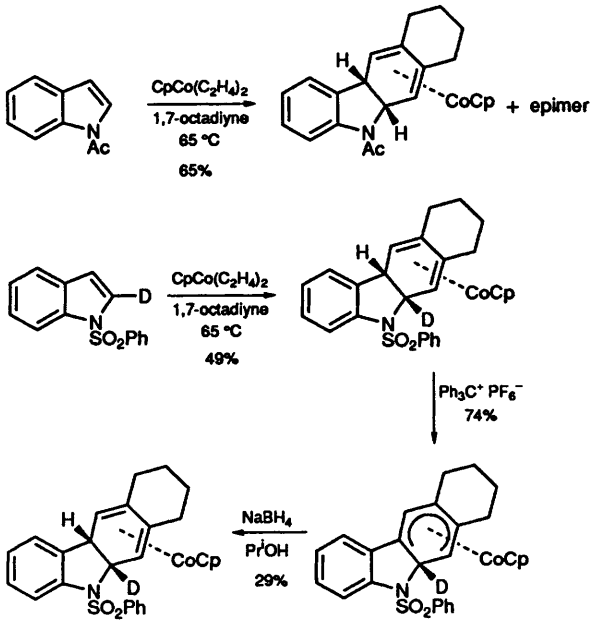
Scheme 40

Kerr has also utilised this reaction in a synthesis of (+)-taylorione, and reports a protocol for improving the yield of the cylisation reaction when ethylene (or any other volatile alkene) is used as the olefinic partner (**Scheme 40**).[75]

Two other reports are relevant to this section. In the first, the scope of the olefin that can be used in the Pauson–Khand reaction is extended to include electron deficient alkenes, by increasing the equivalents of alkene that are used.[76] In a similar vein, it has now been found that allenes are suitable olefinic partners for this reaction, provided that the Pauson–Khand reaction is performed in an intramolecular sense.[77]

9.2 Cobalt mediated [2+2+2] cyclotrimerisations

Two papers, both from Vollhardt's group, illustrate the continuing promise and synthetic utility of these reactions. Studies on reaction of the C2–C3 bond of *N*-acyl indoles with diynes have allowed the construction of a series of functionalised heterocycles, whereby two rings are created in the cycloaddition process (**Scheme 41**).[78] Moreover, hydride abstraction from the cobalt complexed diene product could be promoted upon treatment with trityl cation, and the resulting cation trapped with a range of nucleophiles. Labelling experiments showed neatly that this process had transpired with good regiochemical control (**Scheme 41**).[78]



Scheme 41

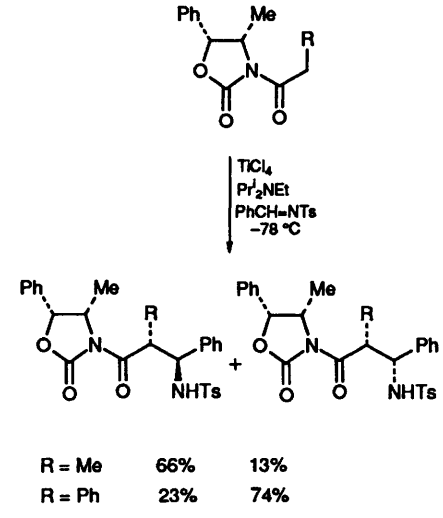
In related work, the cycloaddition of acetylene-substituted furans with other acetylenes was shown to be a viable protocol for the cyclotrimerisation reaction: moreover, the products from this reaction were susceptible to a cobalt induced rearrangement which led to formation of the propellane framework.[79]

10 Miscellaneous uses of stoichiometric titanium reagents in organic synthesis

It was felt that, in view of the manifold uses of stoichiometric titanium reagents in organic synthesis, a Section concerned with recent developments in this area would make a worthwhile addition to this review.

10.1 Titanium enolates

Titanium has proven itself to be an admirable choice of electropositive element for the stabilisation of an enolate anion, as the resulting species are prone to react with electrophiles in a highly stereodefined manner. Recent studies on the reactivity of the titanium enolates of Evans' auxiliary with imines have been reported to yield predominantly *anti* addition adducts (**Scheme 42**).[80] This should be used to balance earlier reports on the use of this metal to furnish *syn* aldol products upon reaction with aldehydes.[81] The addition of enolates to *N*-tosyl imines is presumed to differ from that to aldehydes, in that the predictable six-membered chair transition state tends to be destabilised by 1,3-diaxial interactions, and reaction via open transition states is predicted.[80] However, titanium does have the ability to channel the reaction through the rotamer which has the enolate oxygen chelated to the central oxazolidone carbonyl (compare reaction with the corresponding boron enolates).



Scheme 42

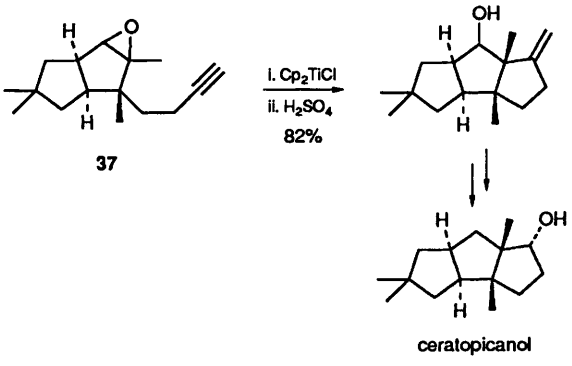
Titanium has also been reported to be useful in promoting the diastereoselective and high yielding hydroxylation of ketone enolates with lithium *tert*-butyl hydroperoxide.[82] This reaction holds much promise if chiral ligands can be placed on the metal, and then optimised so as to influence the course of the hydroxylation reaction. Another group have also utilised a titanium enolate derived from dibenzyl malonate in an intramolecular cyclisation onto an iodonium ion: in this case, the issue of stereochemistry has been addressed, and by using a modified tartrate ligand on the titanium, enantiomeric excesses of up to 85% have been realised.[83]

10.2 Titanium induced radical cyclisations

Several elegant applications of McMurray type (titanium promoted) cyclisations have been reported in the recent literature, and the recent application of this reaction towards construction of the Taxol® nucleus by Nicolaou must be mentioned.[84] This approach to Taxol is related to Kende's earlier

route, and the key cyclisation suffers from being a rather low yielding process. Nevertheless, the cyclised material that is obtained is effectively transformed into the naturally occurring product, which is currently the source of extensive research efforts. In addition, Fürstner has elaborated upon his 'instant' conditions for titanium mediated coupling reactions of amides, by reporting some spectacular and highly selective cyclisation reactions.[85]

Clive has reported on the use of Cp_2TiCl, as first reported by Nugent, for initiating a radical cyclisation reaction in his synthesis of the sesquiterpene ceratopicanol (**Scheme 43**).[86] Treatment of the acetylenic epoxide **37** with this organometallic compound led to the formation of the target skeleton in excellent yield; note that an acid wash is necessary here in order to cleave the carbon–titanium and oxygen–titanium bonds that are formed during the cyclisation process.



Scheme 43

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