REVIEW

Applications of stoichiometric transition metal complexes in organic synthesis

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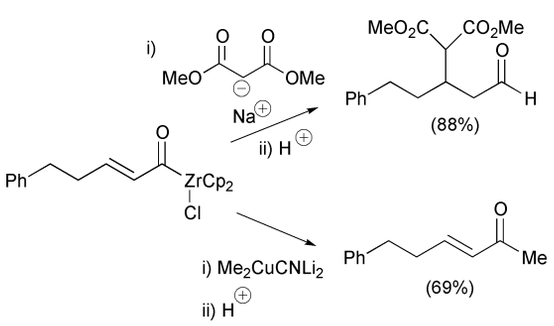
1 Introduction

This review continues in the series describing developments in stoichiometric transition metals applied to organic synthesis. The subdivision of the material is as outlined above, and is in common with the previous reviews.[1] As always, the main aim of this article is to highlight novel or interesting organometallic mediated reactions that have particular relevance to organic synthesis.

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

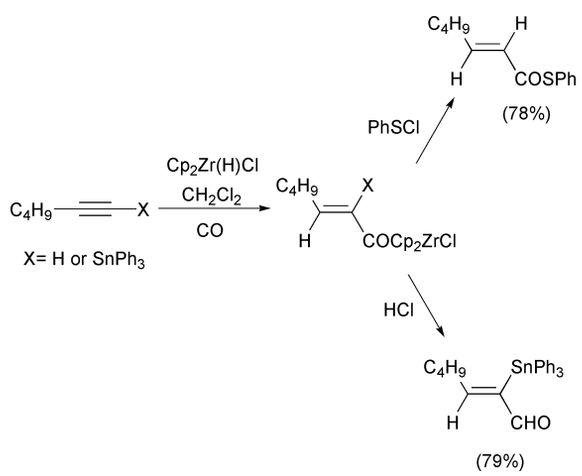
2.1 Organozirconium-based methodology

Organozirconium chemistry remains as popular as ever, with many notable contributions to the field in the last year. Taguchi and co-workers have utilised acylzirconocene intermediates with different substrates. Reaction with enones produces a curious "bimodal" reactivity. As shown in Scheme 1, stabilised



Scheme 1

carbon nucleophiles react in a Michael fashion to produce the expected product aldehyde after protonation and loss of the zirconocene. However, reaction with cyanocuprates leads to direct attack at the carbonyl group and loss of the zirconocene to give the ketone product.[2] Related to this, a palladium-mediated coupling of acylzirconocenes with ynones produces a relatively mild approach to highly substituted cyclopentenones, with good control of regioselectivity.[3] Use of hydrozirconation of alkynes for the formation of highly substituted organic fragments has been very popular this year. Huang has published several papers relating to the functionalisation of alkynes to produce α,β-unsaturated alkenes,[4] unsaturated thioesters[5] and stannyl substituted unsaturated aldehydes (Scheme 2).[6] A



Scheme 2

related reaction concerning the insertion of alkylzirconocene species into alkynes, followed by a second insertion into an alkene has been reported by Takahashi (Scheme 3).[7] In a second paper, the same group has also shown that zirconacycles can be converted to bimetallic zirconium–copper reagents, and the two metal species used to react sequentially to differentially substitute the ends of the molecule.[8] Kasatkin and Whitby have continued to expand the field of zirconium chemistry relating to carbenoid additions. This year, they have inserted metallated epoxy nitriles into organozirconocene chlorides (Scheme 4).[9] Related to this, the reaction of metallated epoxides produces highly functionalised products from the convergence of four different reacting partners (Scheme 5).[10] Other papers have shown that carbenoid insertion into alkenylzirconocenes provides a convergent synthesis of functionalised allylmetallates,[11] and produced a short total synthesis of galbulin and isogalbulin.[12] The reaction of zirconocene complexes with enol ethers has been used as a way to access vinylzirconium derivatives in a stereocontrolled manner.[13] The reaction occurs irrespective of the geometry of the starting material, and the carbon–zirconium bond can be quenched with a large range of electrophiles. The copper assisted quenching of Zr–C bonds has also been illustrated,

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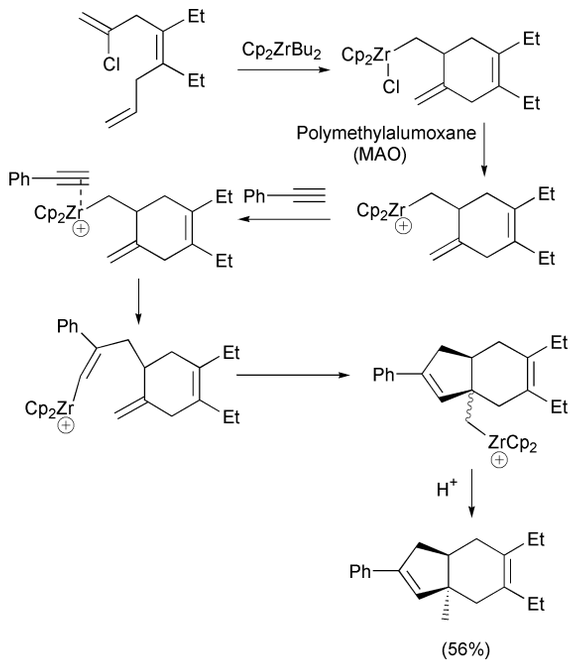
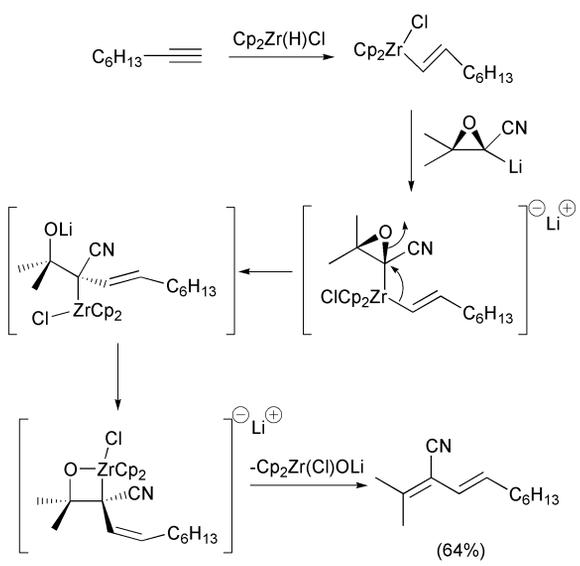
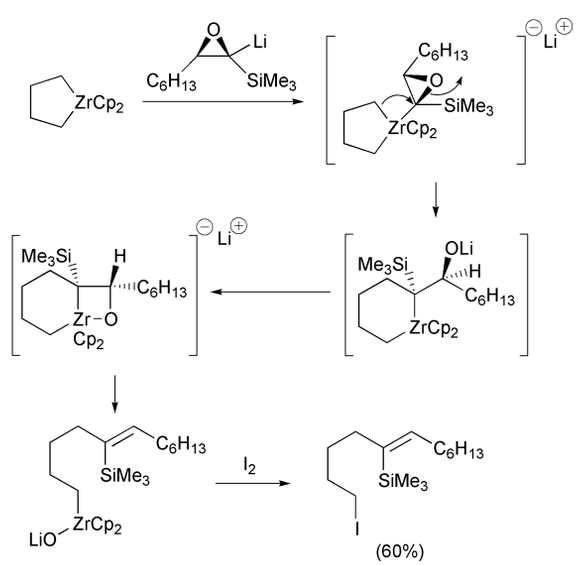


Scheme 3

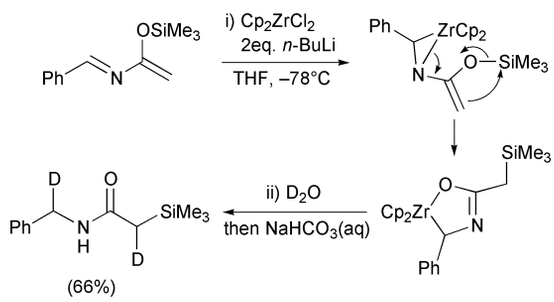


Scheme 4

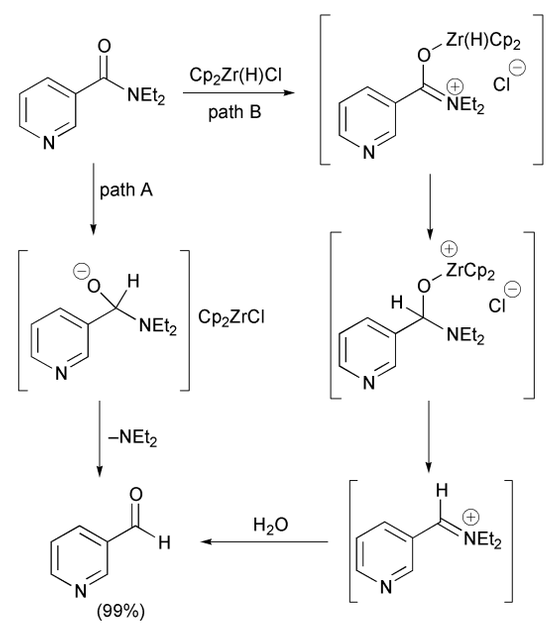


Scheme 5

producing, in this case, a homoenolate equivalent from a dialkoxy allylic zirconium complex.[14] The reaction of zirconocyclopentadienes with appropriately substituted benzene rings has given rise to a synthesis of benzocycloheptenes.[15] Azadienes have been shown to react with zirconocenes *via* a retro-Brook rearrangement.[16] Subsequent reaction of the intermediate with electrophiles produces the organic products, as illustrated in Scheme 6. The reduction of tertiary amides to aldehydes has been achieved using Schwartz's reagent (Scheme 7).[17] The reaction is thought to proceed *via* one of



Scheme 6

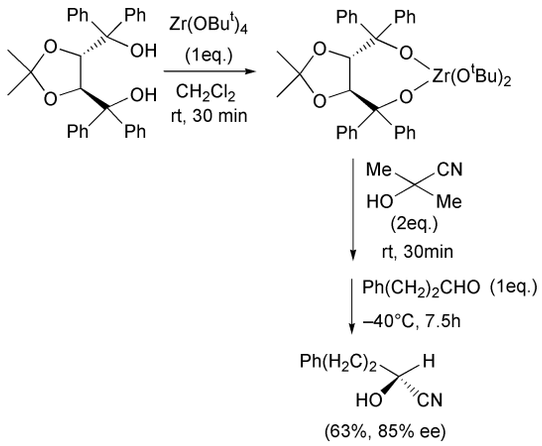


Scheme 7

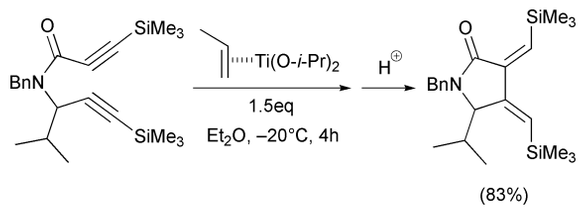
the two pathways illustrated. Pentadienylzirconium complexes have been reported and used for the production of substituted dienes.[18] The well-documented zirconium-mediated coupling of alkenes is reported to be promoted by a solubilised, substituted zirconium hydride source.[19] Finally, chiral zirconium alkoxide complexes have been shown to mediate asymmetric Meerwein–Pondorf–Verley cyanation of aldehydes (Scheme 8).[20]

2.2 Organotitanium-based methodology

Organotitanium reagents have been employed extensively in synthesis in the last year, with Sato continuing his extensive use of titanium alkoxides as organometallic precursors. Using ester or amide linkers, the coupling of two alkyne units in an intermolecular fashion using titanium alkoxides has provided a route to exocyclic dienes (Scheme 9).[21] Reaction of these with dienophiles has allowed the rapid construction of a series of bicyclic lactone and lactam structures with a high degree of regiocontrol. Intramolecular coupling of alkenes has been used by the same group to access carbacyclin in a highly stereocontrolled manner.[22] Related reactions have also been carried

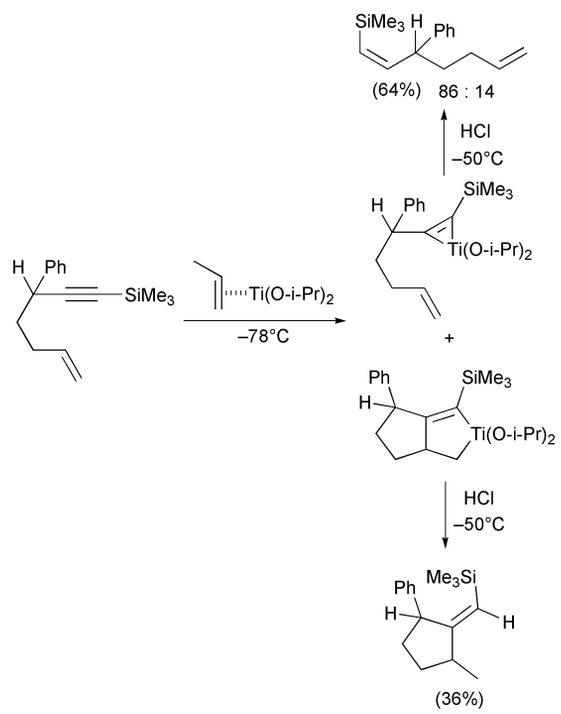


Scheme 8



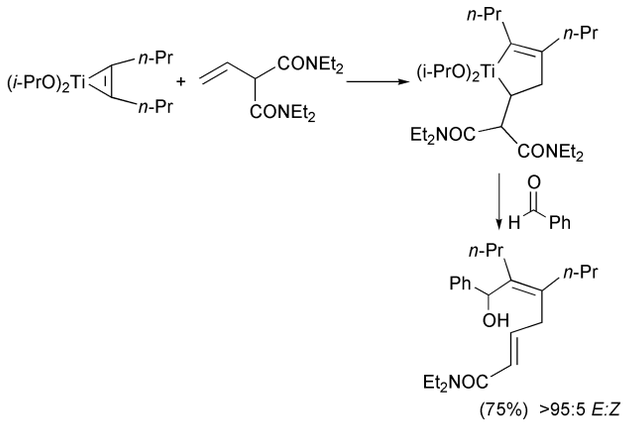
Scheme 9

out to assess the level of diastereocontrol achieved during the synthesis of bicyclic titanacyclopentenes from chiral enynes (Scheme 10).[23] Production of multiple stereocentres in an



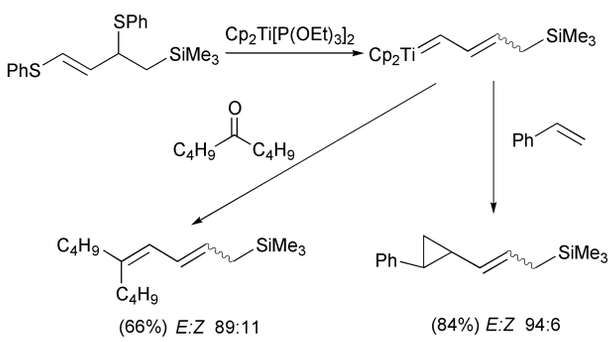
Scheme 10

acyclic system has been achieved by the addition of the nucleophilic titanium intermediate to aldehydes, ketones and imines.[24] Even more impressively, since the titanium–alkyne complex has two metal–carbon bonds, sequential addition of two electrophiles allows differential substitution at the ends of the complex. The same principle of coupling unsaturated units using titanium can also be applied to alkenes and alkynes, in an intermolecular fashion. As illustrated in Scheme 11, this allows a series of diene and trienes to be assembled in one-pot.[25]



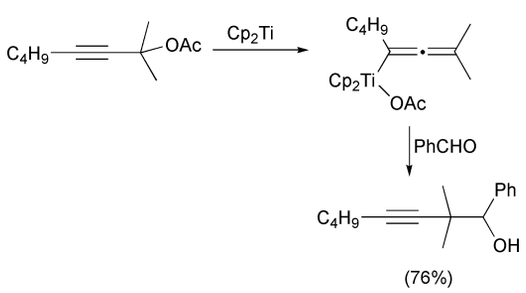
Scheme 11

Closely related to this is the use of silylethylene–titanium complexes which allows the silylethylation of unsaturated compounds.[26] Unsymmetrically substituted acetylenes have been prepared from chloroalkynes.[27] Takeda has continued using vinyl sulfides as precursors to organotitanium species.[28] The resultant titanium carbene species can then be used to react with carbonyl compounds, or to form cyclopropanes by reactions with alkenes (Scheme 12). A closely related reaction has



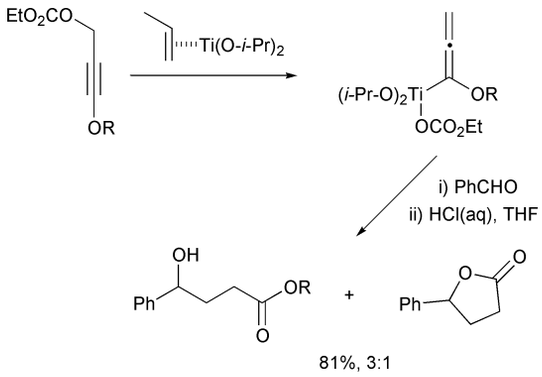
Scheme 12

been achieved in an intramolecular sense using bis(phenylthio)alkanoates.[29] The reaction of titanocene with propargylic (prop-2-ynyl) acetates has provided a route towards homopropargylic alcohols.[30] The intermediate titanium species is proposed to be an allene type structure, which then rearranges back to the alkyne on reaction with the electrophile (Scheme 13). Extension of this to alkynyl ethers has produced a route to



Scheme 13

γ-hydroxy esters and γ-lactones.[31] The initial alkyne product is hydrolysed on work-up to produce the product (Scheme 14). Titanium allyl derivatives have been employed in stereoselective additions to alkynyl aldehydes.[32] A cyclopentadienyl titanium complexed tartrate derivative was used as the source of chirality. An allyl–titanium intermediate has been used in the regioselective formation of alkenes from allylic alcohols and ethers.[33] Cyclisation reactions using radical methodology mediated by a Ti(III) species has been employed in a total synthesis of



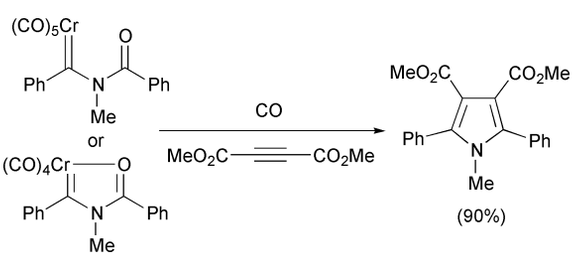
Scheme 14

sesamin.[34] Cyclopropanation of carboxylic acids using titanium alkoxides has been studied in some detail.[35] The Tebbe reagent is well-known for the methylenation of carbonyl derivatives. Recently this has been extended to the methylenation of β-lactams.[36] An alternative titanium source has been used for the deoxygenation of sulfoxides to produce sulfides.[37] Titanium tetraiodide chemoselectively reduces the sulfoxide quickly at room temperature in very high yields. Finally, the use of titanium tetraisopropoxide as an activating group in the organozinc-mediated reduction of aldehydes has been reported.[38]

3 Group VI transition metal carbenes in organic synthesis

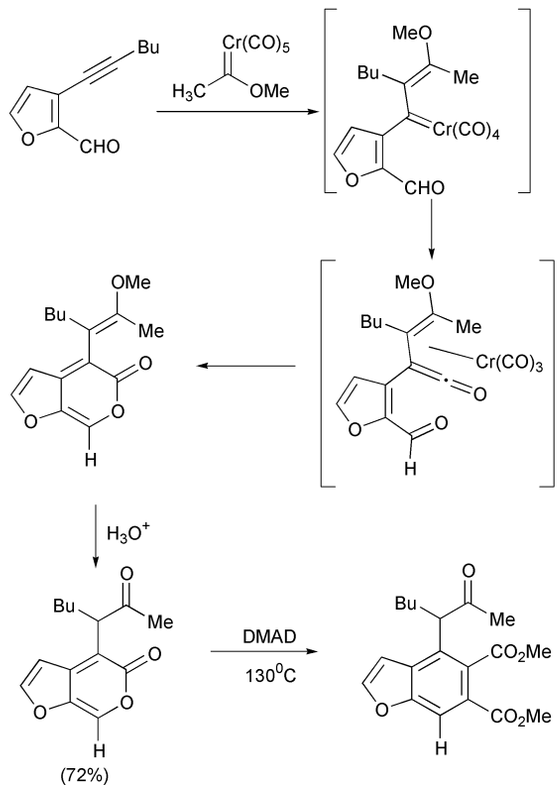
Metal carbene chemistry has seen some intense interest this year. As usual the most popular types of complex come from the chromium, molybdenum, tungsten group.

The Dötz annulation reaction is one of the best-known reactions of chromium carbenes. This year, two groups have used modified chromium carbenes where one of the carbon monoxide ligands is replaced by an intramolecularly coordinated methoxy group.[39,40] Related complexes have been used by Merlic in reactions with dipolarophiles, producing a route to münchnones (Scheme 15).[41] Cyclophanes have been synthesised

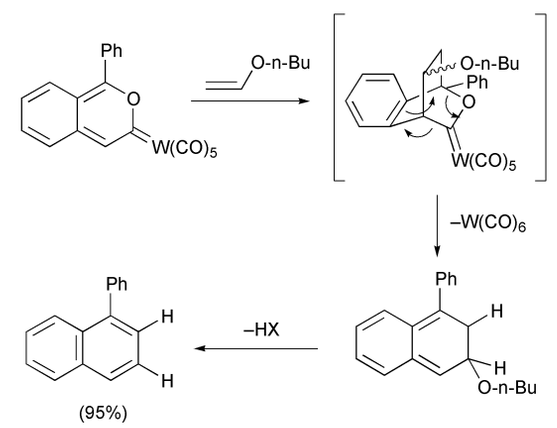


Scheme 15

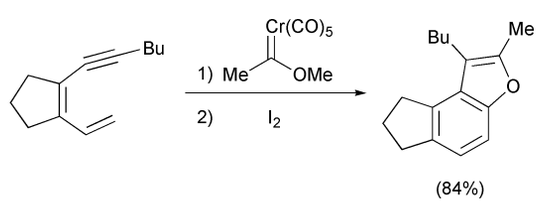
by this type of annulation, although some unexpected regiochemistry was noted.[42] Zhang and Herndon have reported on some related chemistry. Reaction of heteroaromatic substrates provides access to pyranone derivatives after reaction with a carbene.[43] The alkyne inserts into the carbene and produces the pyranone, which can undergo a cycloaddition reaction to give a benzofuran (Scheme 16). A related use of a tungsten carbene has been reported in a two part Diels–Alder reaction (Scheme 17).[44] Firstly, reaction of an electron-rich alkene gives a Diels–Alder adduct, which can be isolated. However, further reaction of this expels tungsten hexacarbonyl in a retro Diels–Alder reaction producing the organic product. Related to Scheme 16, dienynes produce benzofuran derivatives, presumably through a similar mechanism (Scheme 18).[45] Another use of chromium carbene complexes in dipolar cycloaddition reactions for the formation of cyclopentanones has been published by Barluenga.[46] A related reaction with imines allows access to pyrroles in a regio- and stereo-controlled manner.[47] An alkenyl carbene complex reacted in good yield when $GaCl_3$ was added, although the role



Scheme 16

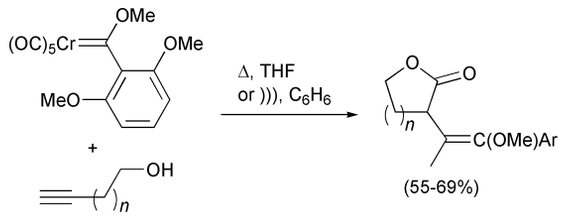


Scheme 17



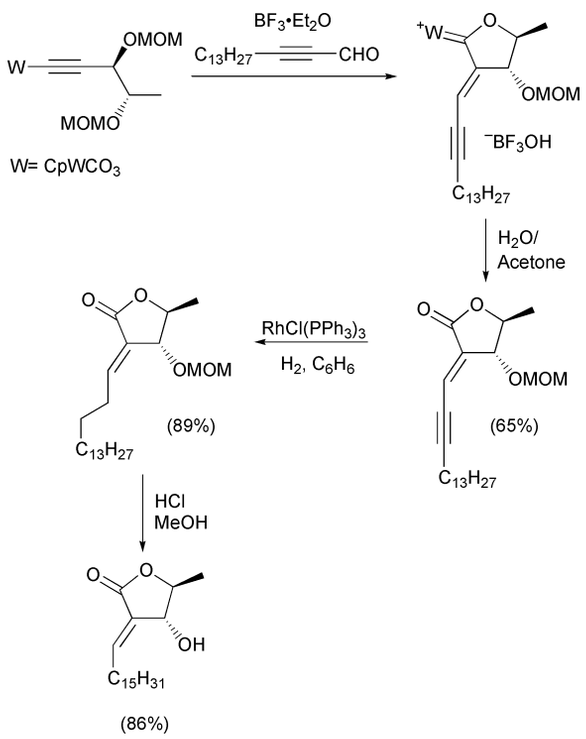
Scheme 18

of the additive was unclear since other Lewis acid sources were less effective. The reaction of carbene complexes with samarium diiodide allows the addition of the carbene function to a Michael acceptor.[48] A one electron reduction is proposed to give rise to an acyl chromate complex, which adds to electron deficient olefins in a 1,4-manner. The formation of lactones from chromium carbenes has been extended to 5- to 7-membered rings.[49] The reaction proceeds with alkynyl alcohols under either thermal or ultrasound conditions (Scheme 19). A more conventional reaction for a carbene source has been reported: the diastereoselective cyclopropanation of simple alkenes by Fischer carbenes.[50] A range of simple alkenes have



Scheme 19

been shown to work in the reaction. The only, perhaps predictable, drawback occurred using enynes when the alkyne reacted to produce an aromatic ring *via* a Dötz annulation. The use of diphenyl sulfonium salts as alkyl transfer reagents in the preparation of Fischer carbene complexes has been reported.[51] The scheme works for chromium, molybdenum and tungsten complexes. Liu has continued his extensive investigation of tungsten carbene complexes as intermediates in natural product synthesis. As shown in Scheme 20, the initial organometallic is a

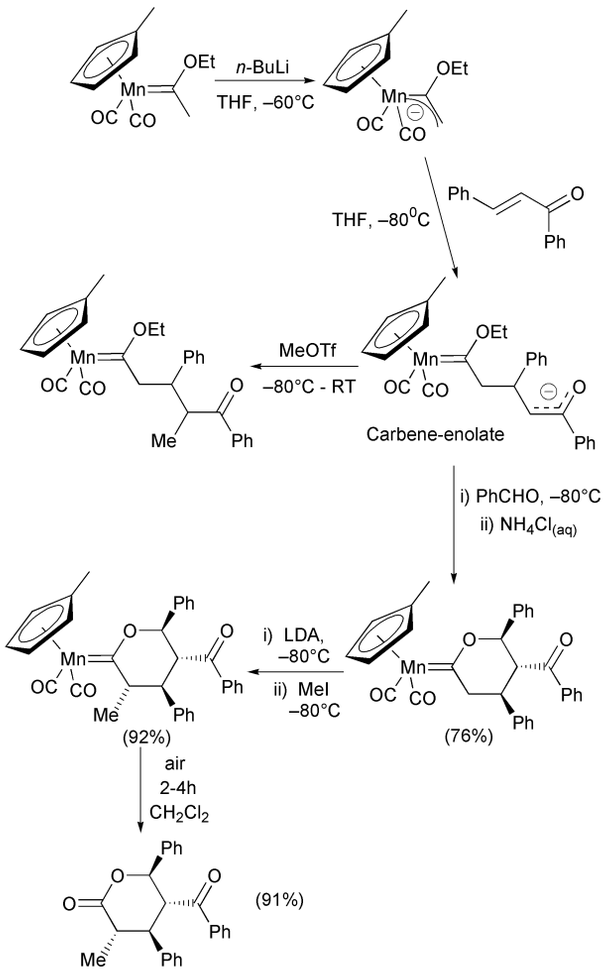


Scheme 20

tungsten alkyne moiety, but the key transformation is the generation of the carbene. This scheme provides access to (+)-blasmycinone and other trisubstituted lactones.[52] Related chemistry has also been used as a means of accessing other lactone and furan natural products.[53,54] Barluenga and coworkers have published the reaction of enamines with alkenyl Fischer carbenes.[55] Depending on the mode of cyclisation, access to bicyclo or tricyclo systems can be achieved. Finally, a manganese carbene has been used in a tandem reaction.[56] As shown in Scheme 21, deprotonation of the carbene is followed by reaction with an α,β-unsaturated carbonyl compound. The enolate thus formed can be quenched, or reacted further in an aldol reaction. Cyclisation onto the carbene then occurs. It is then possible to further functionalise by another deprotonation, before finally oxidising to reveal a lactone.

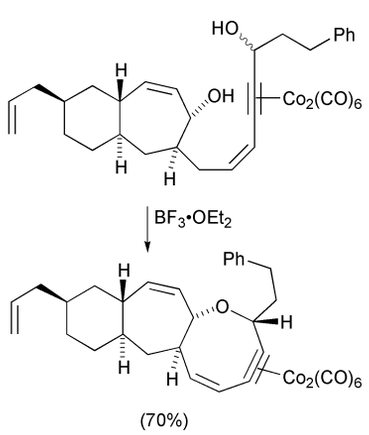
4 η^2-Complexes in organic synthesis

One of the main areas under study continues to be the use of cobalt-complexed propargylic, or Nicholas carbocations. Kira



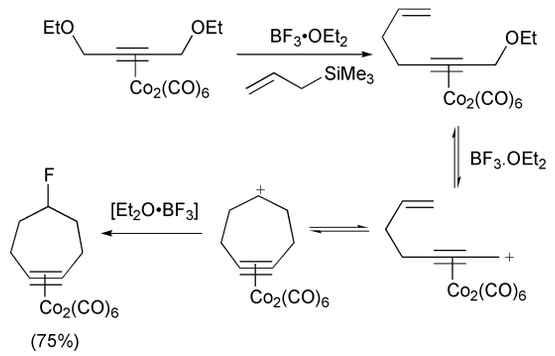
Scheme 21

and Isobe have continued their efforts towards the preparation of medium sized ring ethers, such as those in the ciguatoxin skeleton, *via* this methodology.[57] As illustrated in Scheme 22,



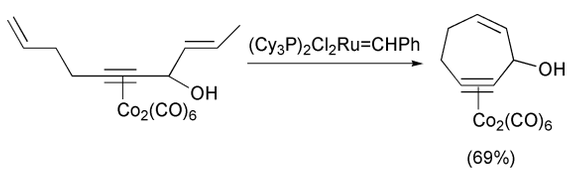
Scheme 22

the Lewis acid mediates formation of the stabilised cation, and ring closure through the pendant oxygen. Mukai has extended studies relating to the *endo* cyclisation of epoxy alcohols, again mediated by appropriately positioned metal–alkyne complexes.[58] The preparation of unsymmetrical propargylic ethers has been controlled using the Nicholas reaction.[59] The unique geometry of these metal complexes has allowed the formation of seven-membered rings that contain an alkyne unit. Lu and Green have utilised the Nicholas methodology in an intramolecular fashion (Scheme 23).[60] Firstly, reaction of the first carbocation with an allylsilane produces a complexed enyne.

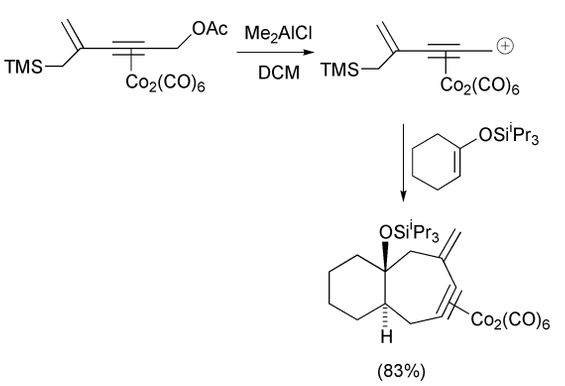


Scheme 23

Then generation of the second carbocation induces electrophilic capture of the alkene. The resultant carbocation is then captured by a halide. Related to this is the selective Nicholas reaction on 1,4-diyne complexes.[61] Here, enol ethers, allylsilanes and aromatic groups are used as nucleophiles and coupled onto metal–alkyne complexes. Another method for the formation of rings is through ring closing metathesis. Using Grubbs' first generation catalyst, reactions proceed smoothly in the seven- and eight-membered ring cases, but not surprisingly fail in the six-ring case, the strain in the ring presumably being just too great (Scheme 24).[62] Another method for the formation of metal complexed cycloalkynes has appeared (Scheme 25).[63] In a

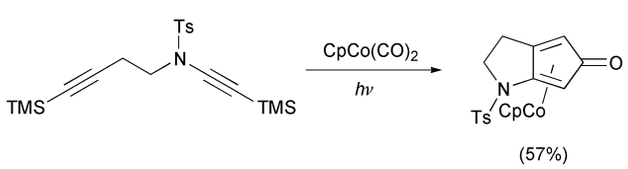


Scheme 24



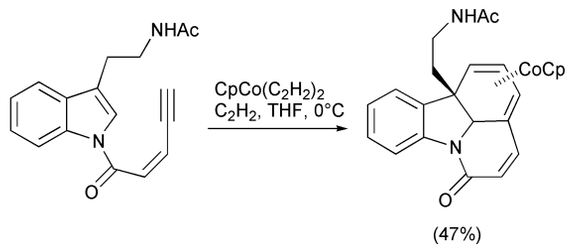
Scheme 25

formal [5 + 2] cycloaddition process, the Nicholas reaction is used to form the carbon–carbon bond at one end of the alkyne. Activation of the allylsilane then allows an intramolecular trap to close the ring onto the ketone. The other main use of η^2 complexes is the cycloaddition of diynes and enynes to form cyclopentadienones and cyclopentenones. In this manner, Rainier and Imbriglio have used $CpCo(CO)_2$ to form aminocyclopentadienes from dialkynyl amines (Scheme 26).[64] Malacria has reported on the diastereoselective [2 + 2 + 2] cyclisation of allene diynes using $CpCo(CO)_2$.[65] Using a chiral



Scheme 26

allene allows complete transfer of the chiral information to the product. Vollhardt has pioneered the use of this cyclisation in natural product chemistry. Continuing this work, a formal total synthesis of strychnine has been presented, which assembles that tetracyclic core in the key organometallic step (Scheme 27).[66] Finally, Knölker and Cämmerer have used a

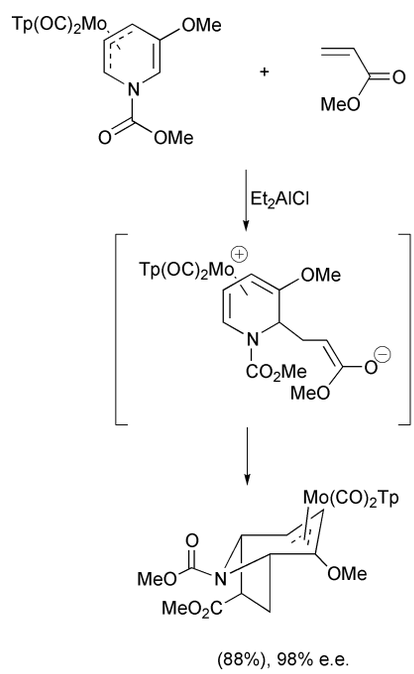


Scheme 27

related iron-mediated cyclisation and used it in the preparation of two alkaloid natural products.[67]

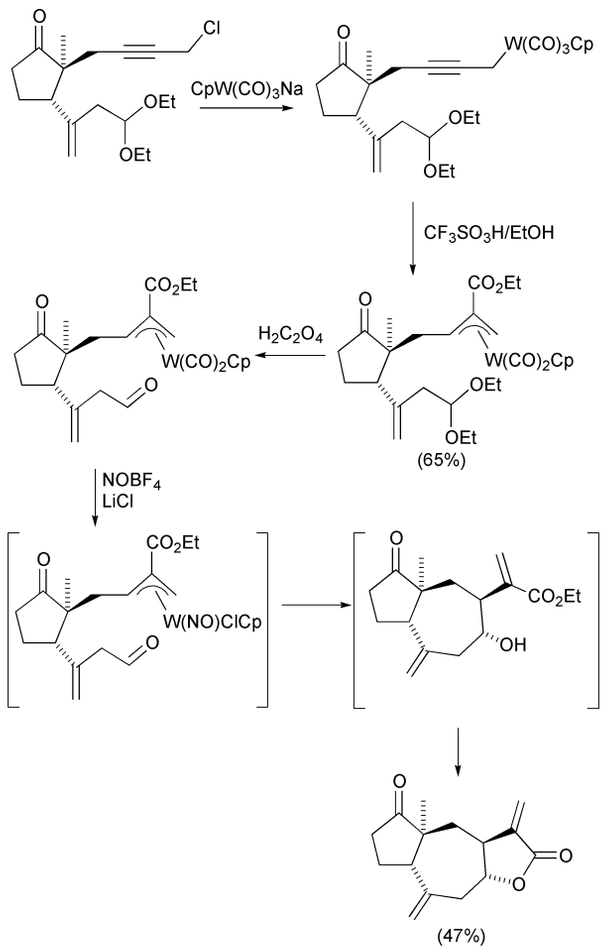
5 η^3-Complexes in organic synthesis

Allyl complexes have seen limited use this year. Among the more novel reactions in this area, Liebeskind reports on the preparation of η^3-allylmolybdenum complexes and their use in multiple carbon–carbon bond forming reactions.[68] The stereo- and regio-control in the reactions is controlled by the molybdenum unit. Further enhancement of this chemistry has allowed a formal [5 + 2] cycloaddition to take place (Scheme 28).[69] The mechanism involves formation of a cationic



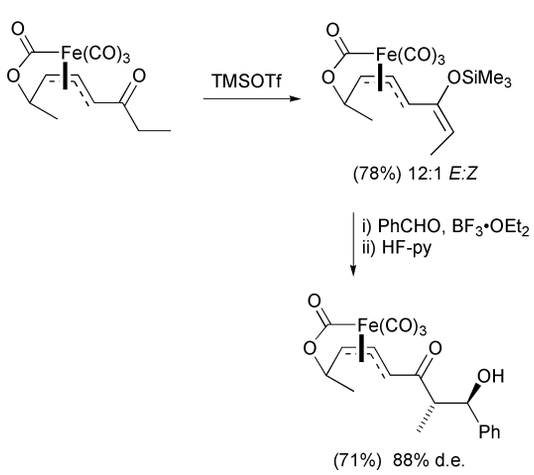
Scheme 28

η^4-complex after attack on the enone. The enolate thus formed then attacks the other end of the complex to re-install an η^3 system. As mentioned above, Liu has used alkynyl tungsten complexes to great effect. The corresponding propargylic complexes are also of use, but the key intermediate is the η^3-allyl system produced after reaction with acid.[70] This intermediate acts as a nucleophile, attacking a pendant aldehyde, as shown in Scheme 29. Ley and Burckhardt have continued the use of ferrilactone complexes as a way to natural products. Reported this year is a route towards the macrolides α- and β-zearalenol.[71] In addition, Mukaiyama aldol reaction with



Scheme 29

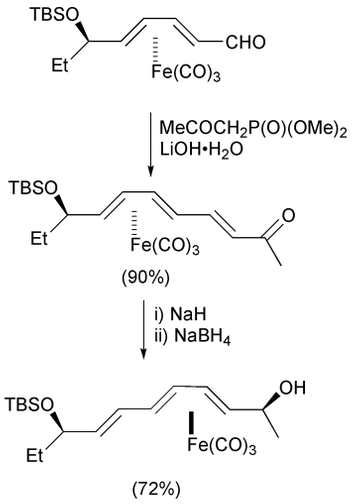
ferrilactone complexes has been shown to produce a diastereoselective reaction equivalent to a 1,7-asymmetric induction from the metal chiral centre (Scheme 30).[72]



Scheme 30

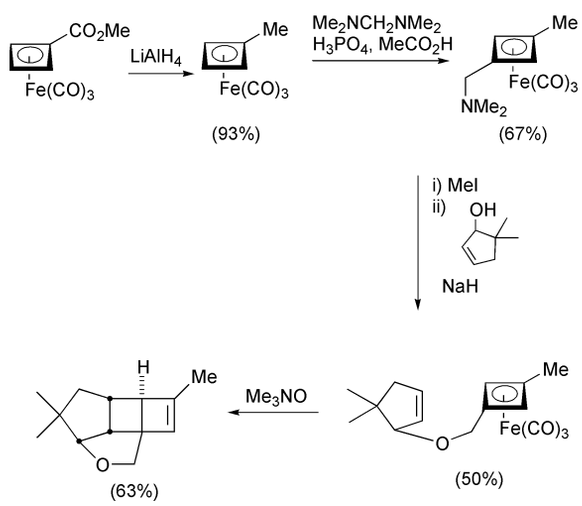
6 η^4-Complexes in organic synthesis

Two noteworthy reviews of iron–diene chemistry have been published this year.[73,74] The diastereoselective synthesis of remote stereocentres up to nine carbons apart using iron–diene chemistry has been used in the preparation of some macrolide antibiotics (Scheme 31).[75] Complexation of the iron carbonyl is followed by chain extension of the aldehyde. A stereospecific migration of the iron then allows a selective reduction of the ketone. The completely diastereoselective complexation of iron tricarbonyl to a diene bearing a ketopinoxy group has been



Scheme 31

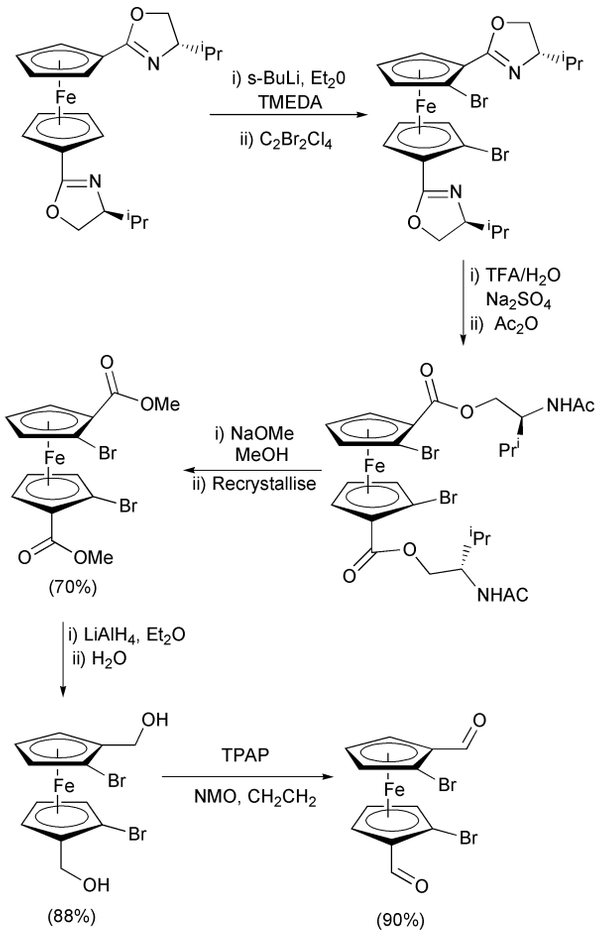
reported.[76] Cyclobutadiene iron complexes have also seen some use this year. Limanto and Snapper have functionalised an iron-stabilised cyclobutadiene before decomplexing it to provide an adduct for an intramolecular cycloaddition (Scheme 32). This was then carried on to complete the synthesis of asteriscanolide.[77]



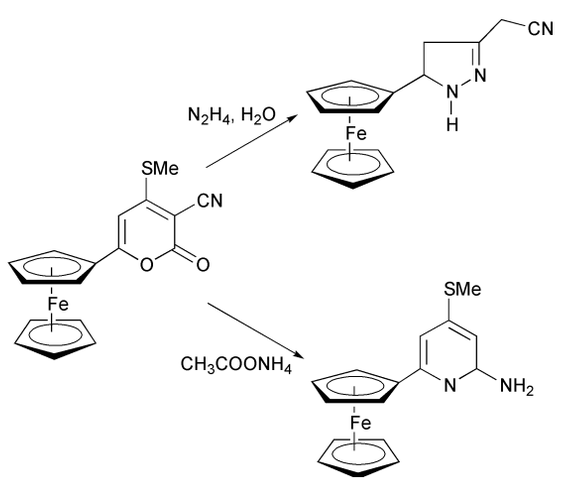
Scheme 32

7 η^5-Complexes in organic synthesis

η^5-Complexes are as usual dominated by ferrocene derivatives. The planar chirality of ferrocene continues to attract interest. Richards and co-workers have produced a diastereoselective route to C_2 symmetric dihaloferrocenes.[78] As shown in Scheme 33, a directed double deprotonation puts the two bromides in place on the separate rings of the ferrocene. After this, standard manipulation of the side chains produces various substituted ferrocene derivatives. Fu has described the preparation of a new type of P,N-bidentate ligand.[79] This new phosphaferrocene has been employed as a new type of chiral catalyst. New syntheses of a diverse range of ferrocenyl substituted arenes and heteroarenes has been reported.[80] As shown in Scheme 34, the starting point is the ferrocenyl lactone, which can be derivatised in a number of ways. The unique electronic properties of ferrocene have been exploited in conjunction with squaric acid to produce a novel series of near infrared dyes.[81] The synthetically useful ferrocenyl formyl complex has been produced in a new, convenient manner by using triethyl orthoformate and aluminium trichloride.[82] This complex has been used in the preparation of ethynylferrocene,[82] and in the synthesis of β-amino alcohols

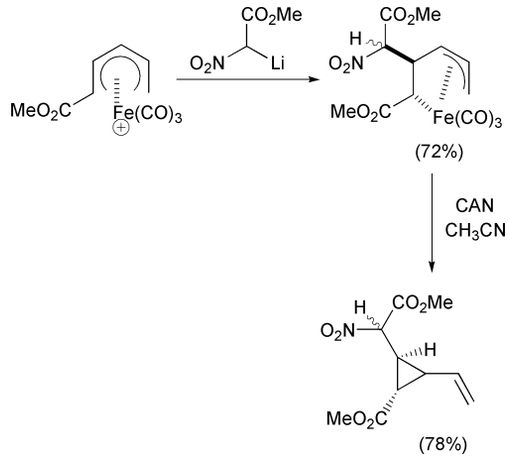


Scheme 33

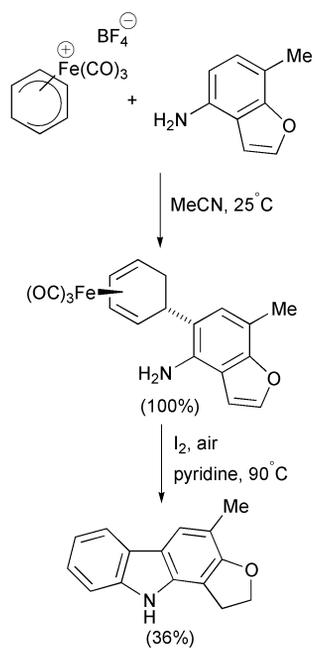


Scheme 34

containing planar chiral ferrocene substituents.[83] The reductive coupling of cinnamyl substituted ferrocenes has given rise to a synthesis of [3]ferrocenophanes.[84] The anti-malarial activity and electrochemical studies of ferrocenyl derived quinolines has been reported.[85] Moving away from ferrocene complexes, η^5-dienyl systems have also seen some use this year. Godula and Donaldson have provided a synthesis of cyclopropanes (Scheme 35).[86] Attack on the electrophilic dienyl system allows a diverse range of substituents to be added before removal of the metal and cyclisation to produce the ring. In a related vein, Knölker and Fröhner have used dienyl–iron methodology in a route to the carbazole alkaloid, 1-furostifoline (Scheme 36).[87] Finally, cyclopentadienyltungsten tricarbonyl units have been appended to dendrimeric compounds to provide complexes of use as organometallic



Scheme 35

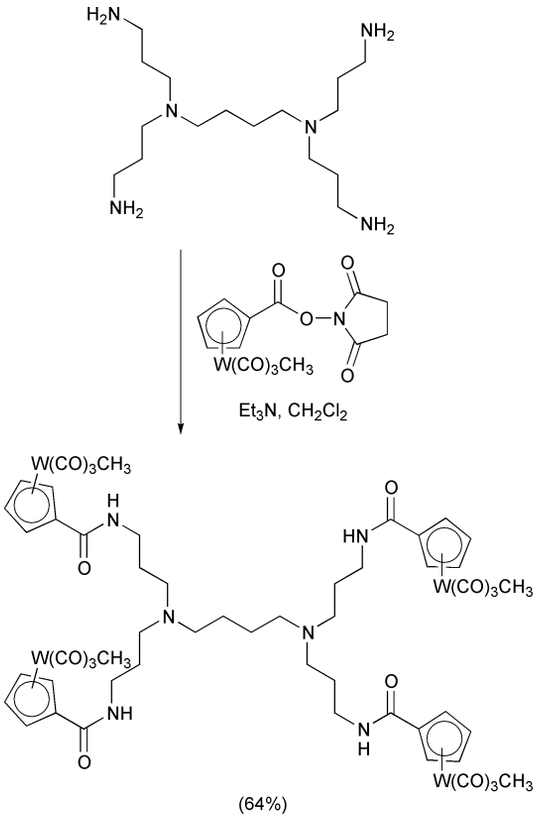


Scheme 36

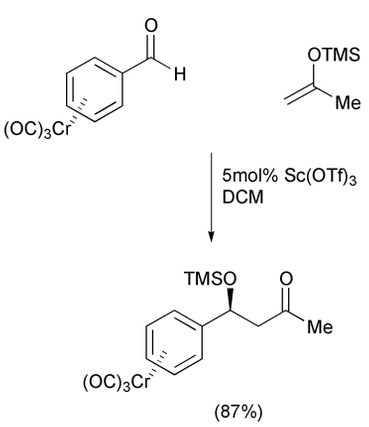
photonucleases (Scheme 37).[88] These have been designed to increase the rate of double strand scission.

8 η^6-Complexes in organic synthesis

The majority of studies of η^6-complexes are, as usual, those of chromium. On this note, Gibson and Reddington have published a review of the application of chiral bases to the deprotonation of chromium–arene complexes.[89] One of the major elements of focus in this area is the planar chirality imparted by complexation of the metal. In this way, Sarkar and co-workers have been successful in the controlled addition of enol silanes to complexed benzaldehydes mediated by scandium triflate (Scheme 38).[90] Semmelhack and Hilt have deprotonated the methyl group of an isodurene complex and functionalised this with an oxygen (Scheme 39).[91] The advantage of their method is that directed bromination of the benzylic position is not viable in this case. Desymmetrisation of a *meso* chromium arene by deprotonation with a chiral base has been used as a route to substituted anilide complexes.[92] Deprotonation directly on the ring has been assessed by Gibson and co-workers.[93,94] Remarkably, multiple substitutions onto the complexed arene have been achieved and a trianion species has been postulated as an intermediate (Scheme 40). Related to these metal–arene complexes are those reported by Simpkins.[95] In this paper,

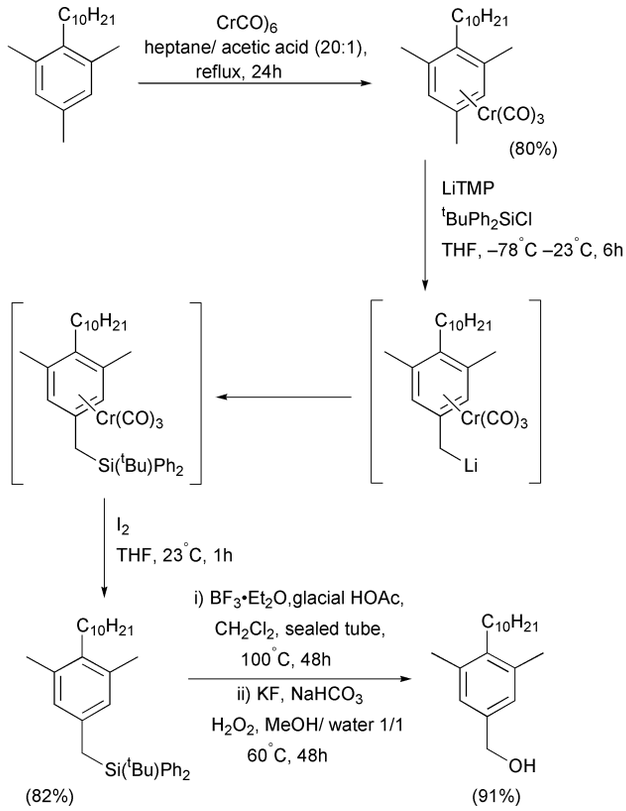


Scheme 37

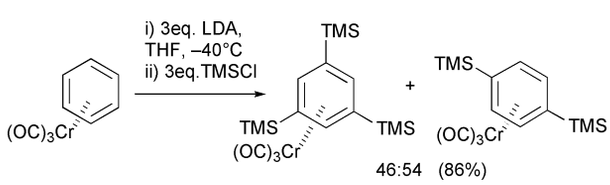


Scheme 38

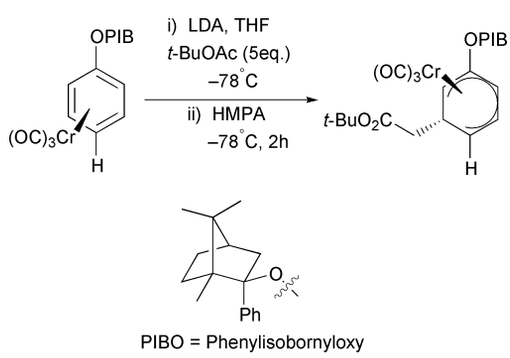
bridged chromium–triene complexes were shown to undergo regioselective addition with a range of nucleophiles. The $Cr(CO)_3$ unit is also known to stabilise benzylic carbocations. A paper this year attempts to quantify this effect, and compare it to the better-known Nicholas carbocation.[96] The chromium–arene unit is also subject to nucleophilic attack, producing an η^5-complex. Dudones and Pearson have shown that this can be extended to ester enolates and that a borneol derived chiral auxiliary can control the stereochemistry of addition (Scheme 41).[97] The other common and useful metal–arene complexes are the cationic species formed by cyclopentadienyliron and benzene derivatives. These are of use since the aromatic ring is now electron deficient, and therefore subject to nucleophilic attack. In this way, replacement of a fluorine substituent by an alkoxy group is possible.[98] A similar reaction has been employed as a means of accessing xanthones and biaryl ethers (Scheme 42).[99,100] A similar reaction has been employed as part of some synthetic studies on the DEF ring of ristocetin A, but this time using the corresponding ruthenium system, as outlined in Scheme 43.[101]



Scheme 39



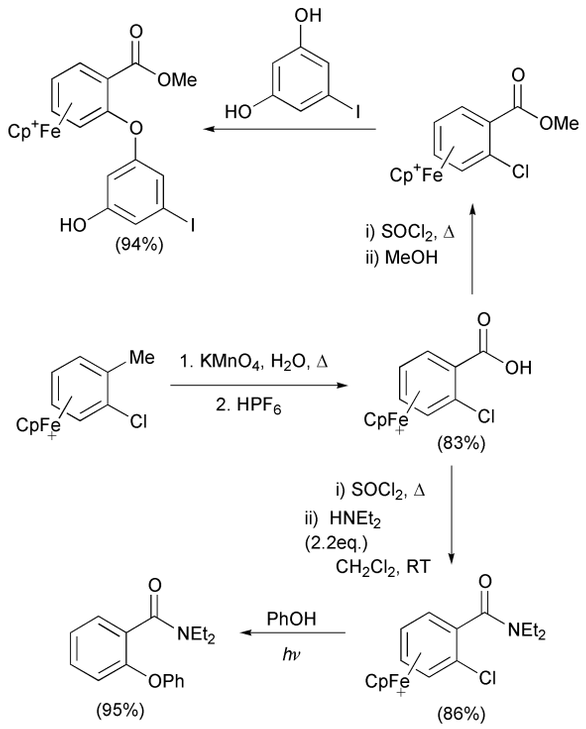
Scheme 40



Scheme 41

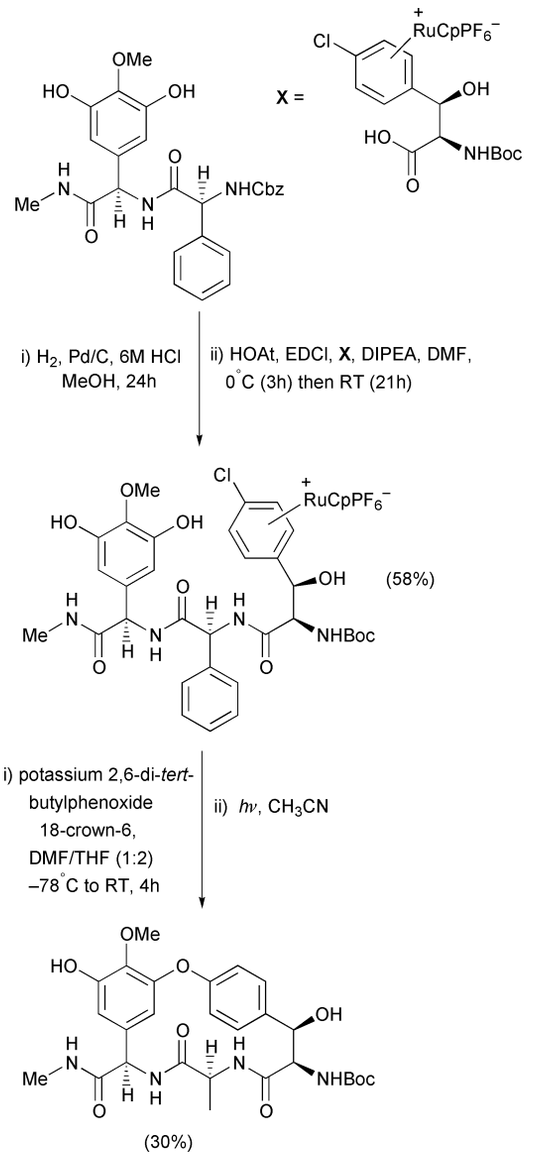
9 Pauson–Khand reaction

The Pauson–Khand reaction remains one of the most popular metal-mediated reactions. Although it is strictly defined as a reaction using a cobalt–alkyne complex to produce a cyclopentenone product, it is now commonly used to encompass all organometallic processes that produce these products. The majority do still employ the original cobalt–alkyne complexes, but there are variations that are useful in certain situations. The first intermolecular Pauson–Khand reaction using 7-azanorbornenes has been reported, and control of regioselectivity has been attributed to the substituents on the alkene.[102] A popular method for promoting reactions is to tie the reacting centres together *via* a temporary tether. A method for achieving this in the Pauson–Khand reaction is to use an N–O linked enyne.[103] Krafft continues to be highly productive in this area.

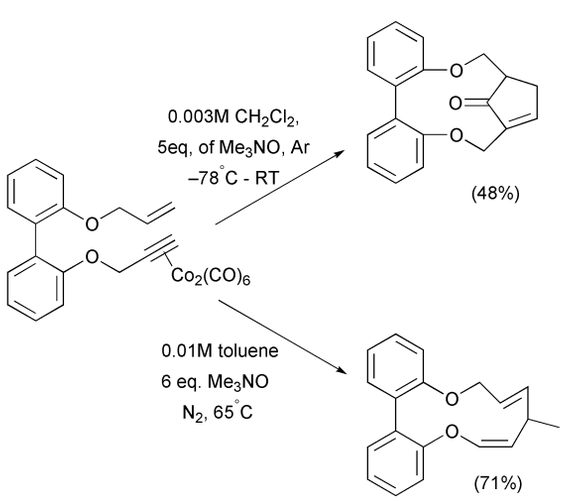


Scheme 42

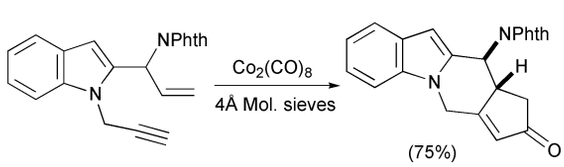
An "inside-out" eight-membered ring has been synthesised by a Pauson–Khand reaction followed by a ring-closing metathesis. This has led to a synthesis of asteriscanolide.[104] The same group has also illustrated a route to medium sized rings using an intramolecular reaction. Interestingly, the conditions for the reaction are critical in determining the product that is formed (Scheme 44).[105] The synthesis of polycycloindoles has been achieved in a stereoselective manner.[106] High stereoselectivity was obtained using the substituents present on the substrate (Scheme 45). Another intramolecular reaction has also shown dependence on the stereochemistry of the substrate in controlling the selectivity of the product. Here, bulky silyl ethers are used and different reaction conditions were studied.[107] Chiral auxiliaries attached to the substrate have remained a popular means for inducing stereochemical control. Among these are the phosphinoxazoline ligands[108] and a chiral bidentate P,S ligand.[109] The same type of cyclisation can also be mediated by molybdenum hexacarbonyl. The most common substrates for this type of reaction are allenes, and this year Hsung and co-workers have used an allenamide to build the precursor and then perform a regioselective Pauson–Khand type reaction (Scheme 46).[110] The stereochemical control of desymmetrised bis-metallic alkyne complexes has been closely studied this year. Kerr and co-workers have identified the source of chiral induction in their phosphine substituted complexes.[111] The formation of the cyclopentenone was found to proceed around the $Co(CO)_3$ vertex of the complex (Scheme 47). Related to this, heterobimetallic complexes where one of the cobalt centres has been replaced with a $CpMo(CO)_3$ unit have also been shown to produce a stereospecific reaction.[112] The enantio-enriched, air-stable Nicholas carbocation can be substituted with a variety of nucleophiles and the complexes then reacted to give the cyclopentenone products (Scheme 48). Other methods for promotion of the reaction have also been introduced. High intensity ultrasound has been shown to improve yields and decrease reaction times in the cyclisation.[113] Methyl sulfides have been shown previously to promote the reaction, but this year a polymer supported variant has been reported.[114] An intramolecular reaction has provided an interestingly alternative cyclisation mode.[115] As shown in Scheme 49, reaction of a trimethylsilyl substituted enyne gives the cyclopentene which does not



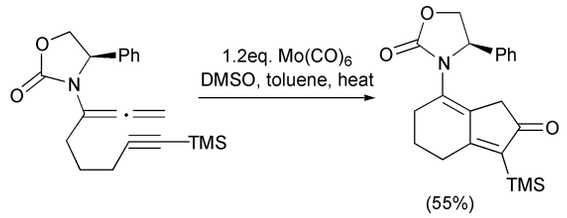
Scheme 43



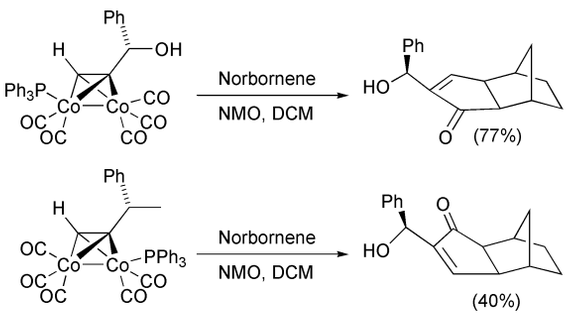
Scheme 44



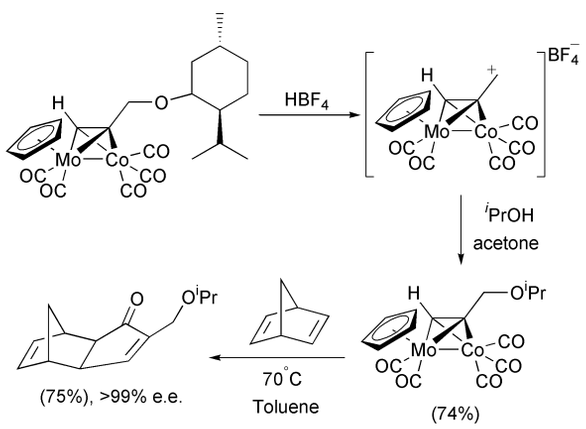
Scheme 45



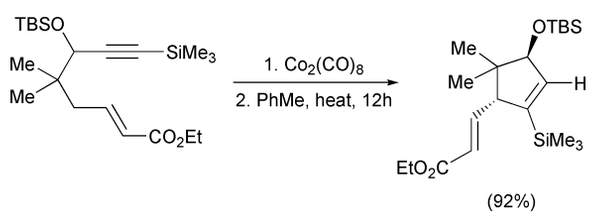
Scheme 46



Scheme 47



Scheme 48



Scheme 49

incorporate carbon monoxide into the ring. The reaction appears to proceed through a C–H allylic activation and a formal 5-*endo-dig* cyclisation. The scope of the reaction is currently under study since some substrates gave the conventional Pauson–Khand product.

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