REVIEW
PERKIN 1

Applications of stoichiometric organotransition metal complexes in organic synthesis

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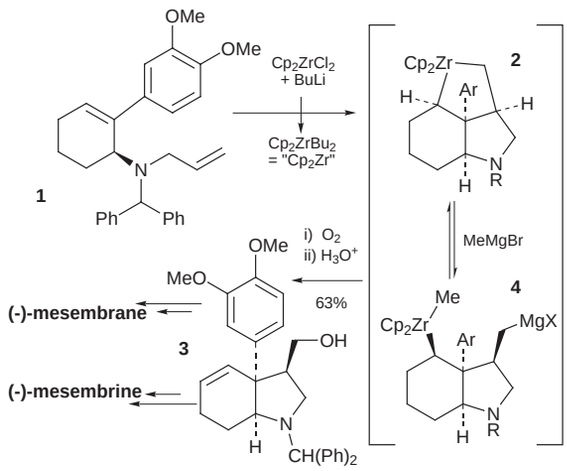
1 Introduction

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

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

2.1 Organozirconium-based methodology

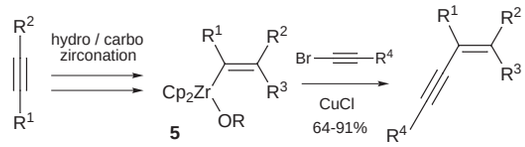
The field of organozirconium chemistry offers diverse opportunity in the synthesis of complex organic molecules. Of no surprise, then, is the flourishing research into novel applications and methodology this year. Two natural product syntheses are of note. Mori describes the total synthesis of both (−)-mesembrane and (−)-mesembrine[2] possessing the *cis*-3a-aryloctahydroindole skeleton of their common precursor **3** (Scheme 1). The chiral amine **1**, obtained by palladium-catalysed asymmetric amination, interacts with the zirconocene equivalent, Cp_2ZrBu_2, prepared *in situ* from Cp_2ZrCl_2 and BuLi. Zirconocene, "Cp_2Zr", mediates intramolecular stereoselective cyclisation of the two alkene units of **1** to form an



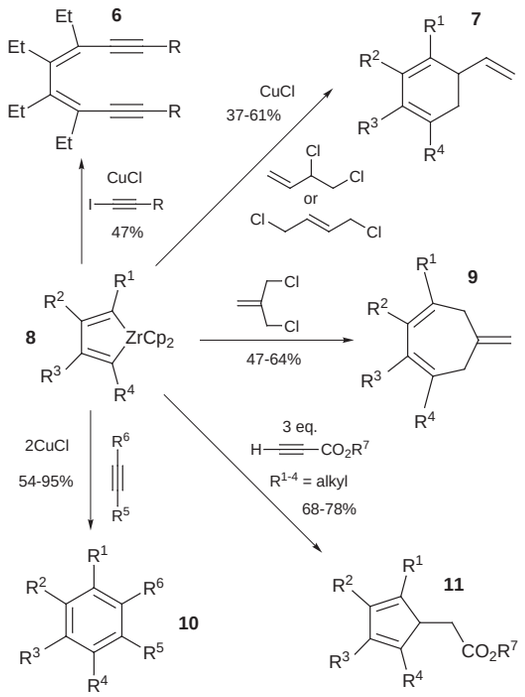
Scheme 1

intermediate zirconacycle **2**. Subsequent ring opening with the Grignard reagent delivers a bimetallic species such as **4** which undergoes oxidative decomplexation to **3** after hydrolysis. Whitby has described a synthesis of (±)-tecomanine.[3] Known not to undergo reaction with the usual zirconocene equivalent, an alkene/*terminal* alkyne system was successfully cyclised with the ethyl Grignard-induced (*ethylene*)zirconocene reagent developed for this purpose by Takahashi. Carbonylation effects demetallation to deliver the desired products.

In a series of papers relating the coupling of alkenylzirconium compounds with a variety of allyl and alkynyl species, Takahashi does much to expand the scope of zirconium chemistry. An initial communication relates the efficient one-pot preparation of highly substituted 1-en-3-ynes and dienynes[4] from zirconium species **5** and an alkynyl bromide in the presence of CuCl (Scheme 2). The system was also applied to zirconacyclopentadiene **8** (Scheme 3) to afford diene–diyne compounds **6**. The yield is only moderate but the product is unique to this system: Pd-coupling of the equivalent diiododiene and hex-1-yne delivers not **6** but a fulvene derivative. Sequential coupling of **8** with an aryl iodide and alkynyl iodide proceeds in excellent yield to deliver extended unsymmetrically-substituted conjugated compounds. Analogous chemistry results in the formation of vinylcyclohexadienes **7**.[5] Various monocyclic, bicyclic and indenyl zirconacyclopentadienes, following transmetallation of their Zr–C bonds to the more reactive Cu–C bonds, react through an inter-intramolecular series of S_N2/S_N2' substitutions. Methylenecycloheptadienes **9** are delivered similarly. An unprecedented inter- and intramolecular Michael addition reactivity of **8** is revealed in its reaction with propynoates.[6] Cyclopentadienes **11** are formed in very good yield when **8** undergoes direct conjugate addition (without transmetallation) to the alkyne terminal carbon atom. Protonolysis of the resulting oxazirconacycle with a second equivalent of propynoate sets the stage for the *intra*molecular



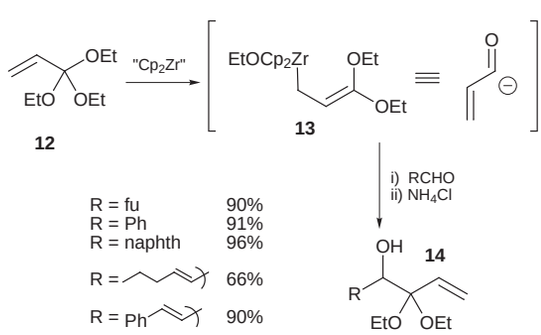
Scheme 2



Scheme 3

conjugate addition to afford **11** after hydrolysis. Takahashi has also described the highly selective formation of benzene derivatives **10** involving copper-mediated cycloaddition of electron poor alkynes with mono- and bicyclic zirconacyclopentadiene **8**.[7] In addition, the one-pot coupling of three different alkynes is reported where sequential addition of the first two alkynes to "Cp_2Zr" constitutes formation of the zirconacyclopentadiene which reacts, again, with the third alkyne in excellent yield.

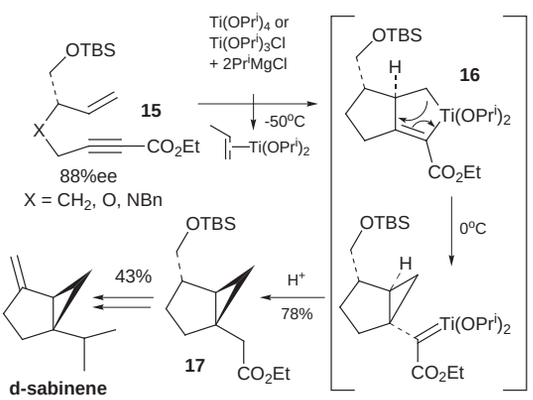
Given the ubiquity of the α,β-unsaturated carbonyl moiety in organic synthesis, a very attractive process is reported by Taguchi who describes a γ,γ-bis-alkoxyallylic zirconium species **13** which behaves as an α,β-unsaturated acyl anion synthon (Scheme 4).[8] Prepared from triethyl orthoacrylate **12** and the standard zirconocene equivalent, **13** reacts with a variety of (α,β-unsaturated) aldehydes to deliver the hydroxy acetal derivatives **14**; treatment with acid, of course, affords the keto forms.



Scheme 4

2.2 Organotitanium-based methodology

Research into this area continues to abound and, in particular, into the reactivity of alkene and alkyne complexes of $Ti(OPr^i)_2$. Although their behaviour is evocative of organozirconium species, the titanium complexes display certain interesting differences to systems described in the previous section. Prolific as ever is the output of Sato who describes in a full paper the versatile and stereospecific intramolecular cyclisation of 2,7- and 2,8-bis-olefinic esters:[9] much in the same way as the zirconocene equivalent, (η^2-propene)$Ti(OPr^i)_2$ is shown to mediate an efficient cyclisation to afford a titanabicycle. Successive inter- and intramolecular electrophilic attack at the C–Ti bonds delivers various bicyclopentanones in good yield circumventing the need for carbon monoxide. The reaction of α,β-acetylenic esters can proceed differently; a synthesis of d-sabinene[9] is representative of the chemistry (Scheme 5). Treatment of enyne **15** with the *in situ* prepared "$Ti(OPr^i)_2$" reagent forms the titanabicycle **16** which, at −50 °C, undergoes the expected electrophilic attack at both alkyl– and alkenyl–Ti bonds. When warmed to 0 °C, however, rearrangement occurs to an intermediate titanium carbene complex. Subsequent hydrolysis delivers compounds of type **17**, generally in good yield as single diastereoisomers. Alternatively, treatment with a ketone effects smooth alkylidenation. A heteroatomic moiety in substrate **15** is also tolerated to generate various heterocyclic products. Further structural manipulation of **17** completes the synthesis of the natural product.

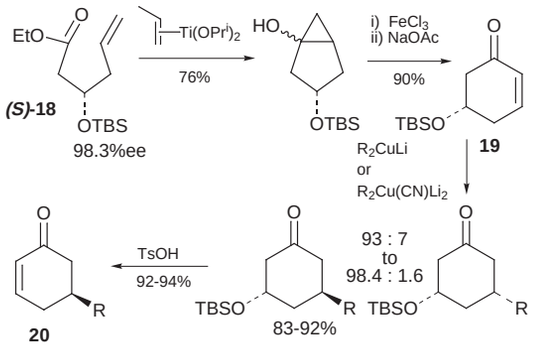


Scheme 5

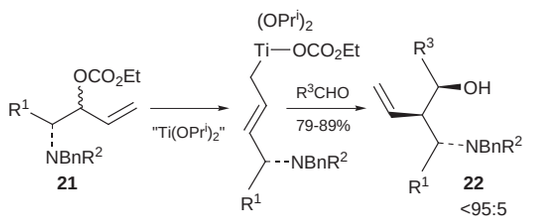
A different "$Ti(OPr^i)_2$"-mediated cyclopropanation of carboxylic esters, originally developed by Kulinkovich, and indeed recently applied by him to the synthesis of a cockroach sex pheromone component,[10] has been exploited by Sato.[11] Described is a convenient synthesis of a versatile chiral cyclohexa-2,5-dienone synthon **19** (Scheme 6). Reaction of **18** with the (η^2-propene)-$Ti(OPr^i)_2$ reagent, prepared *in situ* as before, results in a tandem intramolecular nucleophilic acyl substitution/carbonyl addition reaction to afford the hydroxycyclopropane. Ring-opening with $FeCl_3$ and treatment with sodium acetate delivers enone (*S*)-**19**: (*R*)-**19** is also accessible since both enantiomers of the chiral precursor to **18** are commercially available in high optical purity. Synthon (*S*)-**19** reacted with Bu_2CuLi or $Bu_2Cu(CN)Li_2$ to give the 1,4-addition products with excellent diastereoselectivity. Subsequent elimination affords the optically pure cyclohexenone **20**. The methodology has also achieved the equivalent cyclohepta-2,6-diene synthon.

Such formal double alkylation reactivity of an (alkene)Ti-$(OPr^i)_2$ complex with other carboxylic acid derivatives such as carbonates or amides (to form the corresponding heteroatom-substituted cyclopropanes) is documented. Kun Cha, however, describes a divergence from this outcome when applied to imide functionality.[12] Hence, the titanium-mediated coupling of ω-vinylimides represents a new approach to mitomycin antibiotics and pyrrolizidine and indolizidine alkaloids.

Allyltitanium chemistry has also been explored by Sato this year, and some highly diastereoselective addition reactions with aldehydes are reported (Scheme 7).[13] The optically active substrates **21**, prepared in high yield from primary allylic alcohols



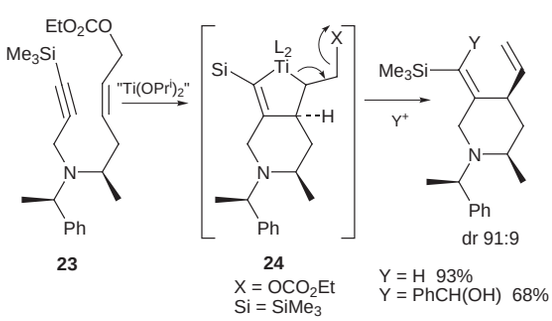
Scheme 6



Scheme 7

using a Sharpless asymmetric epoxidation, deliver the allyltitanium reagent when treated with $Ti(OPr^i)_4$–$2Pr^iMgX$. In the following reaction with aldehydes, asymmetric induction from the amino group at C_4 results in a highly diastereoselective formation of the γ-addition products **22** (with the exception of aryl substitution at R^1 or R^3 when the diastereofacial selectivity is very low; an observation explained by steric considerations around a six-membered chair-like transition state).

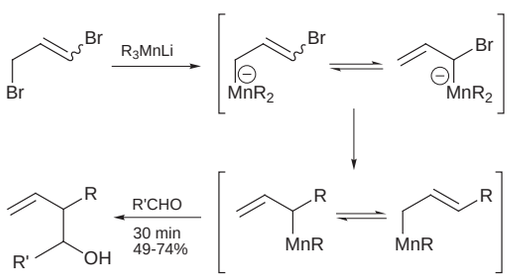
Analogous allyl hydroxy derivatives with appended alkyne functionality are shown to undergo "$Ti(OPr^i)_2$"-mediated intramolecular cyclisation in a variant of the chemistry described at the beginning of this section. In a preliminary paper, Sato reports cyclisation of 2,7- and 2,8-bis-unsaturated carbonates and acetates in a synthesis of carbocycles.[14] In part synthetically equivalent to the intramolecular metallo-ene reactions of Li and Mg, several functionalities not tolerant of these metals are left unaffected by titanium. The same methodology was later applied to the formation of optically active piperidines and pyrrolidines[15] (Scheme 8) from substrates such as **23** whose precursors are readily available α- or β-amino acid derivatives. In the presence of both alkenyl and alkynyl groups in **23** the titanocene equivalent initially forms not the allyltitanium species but an (η^2-alkyne)$Ti(OPr^i)_2$ complex which inserts the olefin to form titanabicycle **24**. Subsequent elimination of the carbonate and hydrolysis or electrophilic attack at the remaining C–Ti bond delivers the products in 55–93% yield with high diastereoselectivity (up to 95 : 5): the olefinic substituents are well placed for further structural manipulation.



Scheme 8

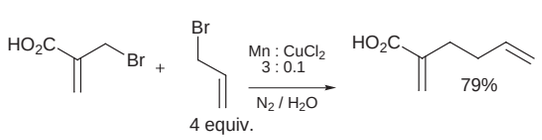
2.3 Organomanganese-based methodology

Interesting new transformations have emerged from the field of organomanganese chemistry: research into the use of trialkylmanganate reagents has been particularly rewarding. When treated with this metal species and an electrophilic trap, 1,3-dihalopropene undergoes a three-component coupling reaction to provide homoallylic alcohols in good yield.[16] Oshima proposes a mechanism which is detailed in Scheme 9 and includes a 1,2-alkyl group migration from manganese to the adjacent carbon with bromide displacement. A not dissimilar mechanism accompanies the formation of a manganese enolate in the reaction of R_3MnLi with a dibromoacetate or dibromoacetamide.[17] This enolate is quenched efficiently with a range of electrophiles to furnish in excellent yield α,α-disubstituted carboxylic acid derivatives (where one substituent is an alkyl unit from the manganese reagent and the other is the result of electrophilic addition). Hosomi also describes electrophilic addition to manganese enolates[18] derived from carbonyl compounds bearing a leaving group at the α-carbon.



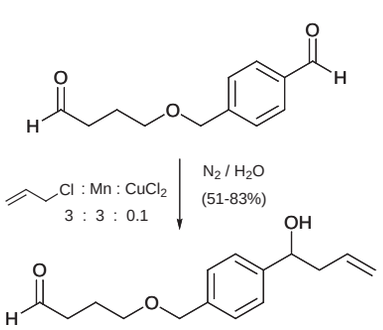
Scheme 9

The ability to perform chemistry in aqueous media is an attractive concept and one which Chan promotes persuasively during the period under review. Homo-coupling of primary and secondary alkyl halides can be mediated by manganese [under copper(II) catalysis] to give the dimerisation products in excellent yield.[19] Cross-coupling is also controllable to give the desired product. The coupling of 2-iodoethylbenzene did not suffer the elimination of styrene. Remarkable, too, is the successful coupling of α-bromomethylacrylic acid (Scheme 10) which illustrates that reactive functionality is tolerant of the conditions, a clear advantage of such organometallic reactions in aqueous media.



Scheme 10

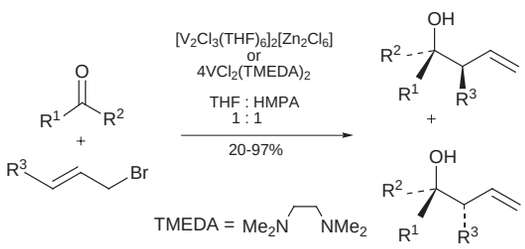
Also reported is a striking chemoselectivity for the allylation of aryl aldehydes (Scheme 11):[20] aliphatic aldehydes are inert under the conditions. Aqueous allylation systems mediated by other metals (Zn, Sn, In) are indiscriminate. Both allylation and pinacol coupling, which is subject to the same unique selectivity, proceed in good yield without affecting sensitive functional groups.



Scheme 11

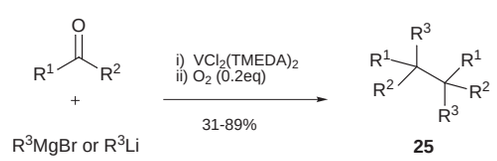
2.4 Organovanadium-based methodology

Kataoka and co-workers have published results concerning vanadium-mediated carbon–carbon bond formation. In the presence of the binuclear vanadium(II) complex shown in Scheme 12 the allylation of aldehydes and ketones[21] is shown to proceed smoothly and largely in excellent yield. Stereoselectivities are generally low, however. The alkylation of ketones and Reformatsky-type reactions are also successful under these conditions. The novel allylvanadium reagent is stabilised by HMPA thereby preventing the previously-reported allyl dimerisation and β-elimination processes. A related communication describes the activation of dialkylzinc reagents with VCl_4 or $VCl_3(THF)_3$ and their application to the alkylation, pinacol coupling and deoxygenative coupling of carbonyl compounds:[22] the chemical outcome is controlled efficiently by varying the reaction conditions.



Scheme 12

A remarkable one-pot process, also reported by the Japanese group, effects C–C single bond formation and C–O bond cleavage with concomitant inclusion of components from the alkylating agent to give products of type **25** (Scheme 13).[23] A catalytic amount of oxygen is essential for the formation of a higher valent vanadium species which, in collaboration with the low valent vanadium(II) reagent, effects oxygen abstraction and reductive coupling.



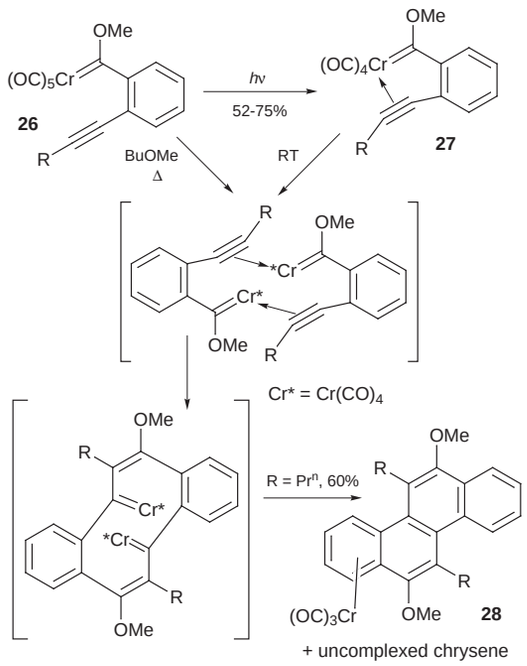
Scheme 13

3 Group VI transition metal carbenes in organic synthesis

3.1 Annulations

The construction of densely substituted cyclic systems from transition metal carbenes and alkynes, namely the well-established Dötz reaction, has attracted undiminished interest this year. Dötz, in fact, reported the preparation of highly-functionalised centrosymmetric chrysenes (Scheme 14).[24] Low temperature photodecarbonylation of Fischer carbene complex **26** results in intramolecular substitution to deliver the isolable alkyne–carbene chelates **27**. These complexes may be considered arrested intermediates in the chromium-mediated benzannulation process; the alkyne is only weakly bound and the complexes undergo a novel decomposition at ambient temperature to afford the (chrysene)tricarbonylchromium complex **28**. Thermal decarbonylation of the pentacarbonyl precursor results in identical dimerisation.

The diastereoselective synthesis of (arene)tricarbonylchromium complexes *via* the annulation process receives attention due, not least, to the inherent synthetic potential of these compounds. Previous studies have focussed on chiral unsaturated carbene substituents or on sterically demanding propargyl (prop-2-ynyl) ethers by way of asymmetric induction. Dötz has now described a more general approach[25] which exploits readily available chiral alcohol auxiliaries at the carbene heteroatom



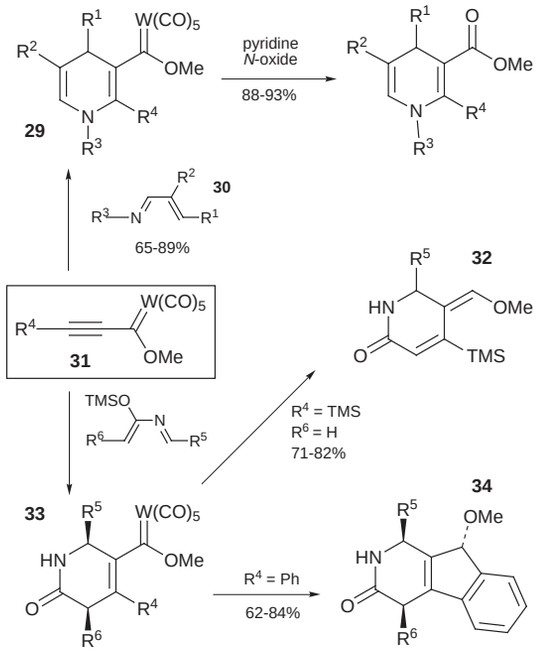
Scheme 14

site: use of (+)- or (−)-menthol is seen to induce a dr of 10 : 1 in the subsequent benzannulation. In a similar vein, Wulff reports the cyclohexadienone annulation of an indol-2-ylchromium carbene complex bearing an imidazolidinone chiral auxiliary.[26] The 4*H*-carbazol-4-one products were obtained in good yields as single diastereoisomers.

3.2 Carbene cycloadditions

Cycloaddition reactions onto appended unsaturated carbene functionality are well represented over the review period and Frühauf has published an exhaustive review of transition metal-assisted cycloaddition reactions in general covering the past forty years.[27] Precedent for the [4 + 2] cycloaddition of 1-azadienes is scant; indeed Barluenga,[28] and later Aumann,[29] describe the first known reactions between an *unactivated* 1-azadiene and an electron poor dienophile (Scheme 15).[28] Barluenga reports the regioselective cycloaddition of heterodienes **30** and alkynyltungsten carbene complexes **31** which proceeds in very good yield to deliver the cycloadducts **29**. NMR experiments point to an initial Michael addition of the nitrogen lone pair to the conjugated triple bond. Noteworthy also is the 1,3-induction of chirality during reaction of the azadiene derived from (*S*)-(−)-perillaldehyde: a 2 : 1 diastereomeric mixture of products is obtained. Demetallation with pyridine *N*-oxide affords the 1,4-dihydropyridine ester derivatives, compounds of relevance for their multiple biological activities. For the less sterically-demanding chromium analogues of tungsten carbene **31**, Aumann reports a different outcome:[29] the azadiene nitrogen undergoes direct 1,2-addition to the carbene centre resulting, ultimately, in *N*-heterocyclic cycloheptatrienyl compounds. Also described is the reaction of 2-ethoxy activated 1-azadienes[30] which participate in a domino [4 + 2] and subsequent [2 + 2] cycloaddition with a second equivalent of the alkynyltungsten carbene. Isomerisation of the resulting (cyclobutenyl)carbenes *via* ring opening and a 1,3-hydrogen shift generates 1-tungstahexa-1,3,5-triene derivatives of **29** in excellent yield.

2-Azabuta-1,3-dienes are also investigated as the [4 + 2] dienophile partner[31] and are shown to deliver pyridone derivatives **33** (Scheme 15). Further heating in THF effects demetallation to afford the conjugated system **32**. For the (phenylethynyl)carbene complex a second cyclisation results in the stereoselective formation of 2-azafluorenones **34**. Various



Scheme 15

[4 + 1] and [4 + 3] cycloadditions are also demonstrated with the 2-azabuta-1,3-diene component and deliver pyrrolidone and 7-membered azepinone derivatives respectively; these processes, too, occur in good yield.

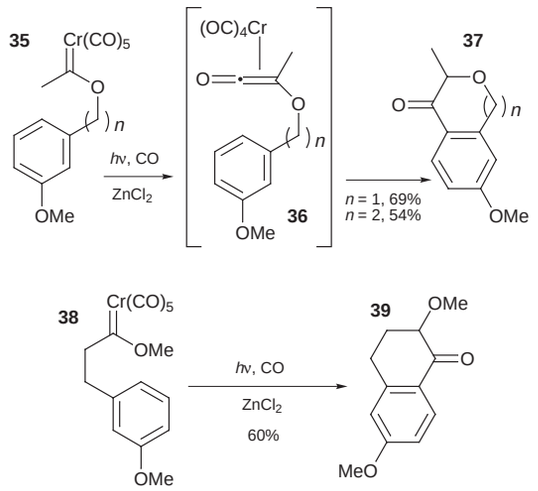
Further studies from the same group detail a series of enantioselective Diels–Alder reactions between alkenylcarbenes and various 2-aminobuta-1,3-dienes in the preparation of spirocyclic lactones,[32] α,α-branched β-amino acids[33] or cyclohexanone derivatives.[34] Similarly, the asymmetric *exo*-selective [4 + 2] reaction of chiral imidazolidinone carbene complexes is described by Wulff.[35] Finally, the first diastereoselective [3 + 2] cycloaddition of chiral menthol-derived carbenes with diazomethane derivatives[36] represents an expeditious route to 4,5-dihydro-1*H*-pyrazole esters.

3.3 Carbene photochemistry

Hegedus continues to dominate this field. Recent applications of the metal-bound ketenes resulting from photoirradiation of a carbene complex include the preparation of optically active spiroketals[37] by Baeyer–Villiger ring expansion of cyclobutanones derived from the formal [2 + 2] cycloaddition reaction between a chiral ene-carbamate and the intermediate ketene species. Similar methodology affords an enantiomerically pure template with potential for further manipulation into 4′-substituted nucleoside analogues.[38] Hegedus and co-workers also offer an interesting variant on the Friedel–Crafts acylation of aromatic systems (Scheme 16).[39] Heteroatom-tethered complexes such as **35** are prepared in fair to good yield by the exchange between aryl alcohols and *in situ* generated (acyloxy)-carbene complexes. Reaction of the chromium pentacarbonyl dianion with an acid chloride and Me_3OBF_4 delivers carbenes of type **38**. Photolysis in the presence of carbon monoxide and a Lewis acid catalyst proceeds in moderate yield *via* a metal-bound ketene intermediate such as **36** to give benzopyranones **37** and α-alkoxytetralones **39**. The system succeeds where at least one aromatic activating group is present and with high regioselectivity: electrophilic attack at the *para*-position was the sole outcome.

3.4 Miscellaneous carbenes

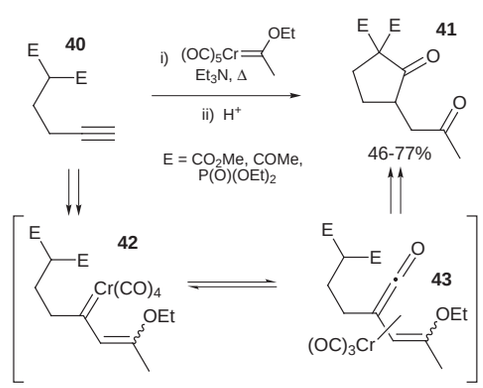
A considerable body of work has also been developed, primarily by Dötz, on carbene-modified sugars. By means of incorporation into an electrophilic metal carbene moiety, the



Scheme 16

anomeric position should become susceptible to nucleophiles: such reactivity may offer a novel approach to *C*- and heteroatom glycosides. A variety of transition metals (Fe, Cr, Mo, W) are applied in the synthesis of glucal carbene complexes, cyclic α,β-unsaturated glycosylidene complexes[40,41] and acyclic sugar carbene complexes.[42] Within the fundamental carbene chemistry investigated, the benzannulation reaction of glucal carbene complexes is shown to provide functionalised benzopyrans.[43]

Mori continues to elaborate on his interesting cyclisation chemistry between acetylenic alcohols and alkoxycarbene complexes.[44] The formation of numerous medium ring lactones is described: 8-, 9- and 10-membered lactones are prepared in 81, 25 and 43% yield respectively. Analogous reactivity has been extended to the formation of cyclic ketones (Scheme 17).[45] Under thermal conditions the alkyne group of **40** inserts into the carbene–chromium bond to give a carbene species **42** which is in equilibrium with the vinyl ketene species **43**. This ketene undergoes nucleophilic attack from the base-activated methine tether (or, for the lactones described above, from a suitably tethered hydroxy group). Cyclopentanones **41** are afforded in moderate to good yield in this three C–C bond forming process.

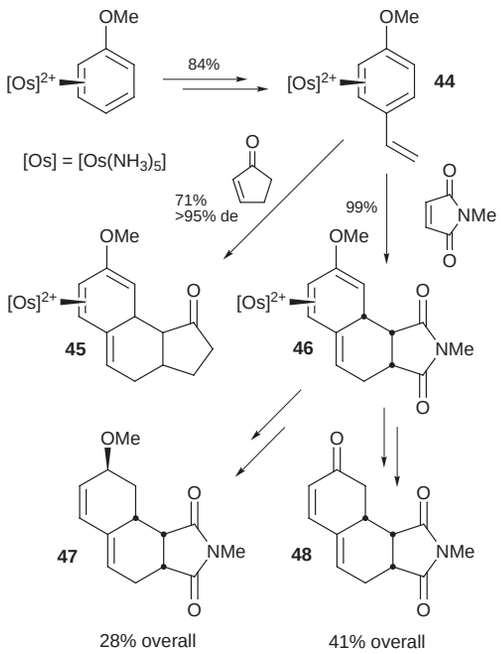


Scheme 17

4 η^2-Complexes in organic synthesis

4.1 η^2-Complexes of osmium

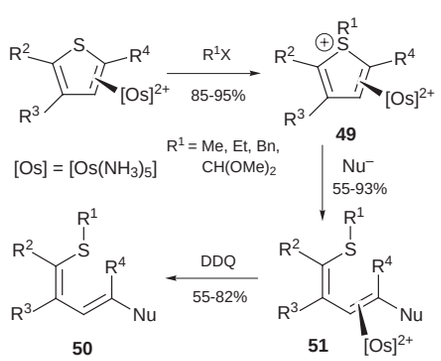
Still championed by Harman, the use of pentaammineosmium(II) in the activation of aromatic molecules has been comprehensively reviewed[46] and further elaborated this year. An elegant solution to the notoriously problematic Diels–Alder cycloaddition of a styrene and olefin is reported in the synthesis of stereodefined decalin ring systems (Scheme 18).[47] Styrene complex **44**, prepared by a previously reported aldol condensation–elimination process, is shown to undergo a highly regio-



Scheme 18

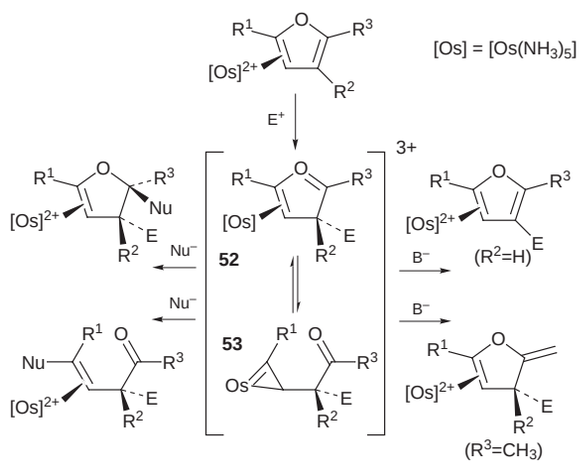
and stereoselective cycloaddition with a diverse range of dienophiles to form only the *external* cycloadduct in excellent yield; **45** and **46**, for example. The relatively unreactive cyclopentenone and such sensitive reagents as α,β-unsaturated aldehydes react cleanly under the very mild reaction conditions, unprecedented for the uncoordinated styrenes. A cyclopentenyl anisole complex (*cf.* **44**) reacts similarly. Not only responsible for stabilising the resulting cycloadduct, thus preventing further reaction between the methoxytriene fragment and the dienophile, the osmium(II) metal centre also mediates further transformation *via* its activating and stereodirecting properties. Hence, subsequent to the cycloaddition, further ligand-centred elaboration and decomplexation generates numerous highly functionalised decalin or tetralin systems such as **47** or **48**.

Also reported by Harman is the electrophile-promoted carbon–sulfur bond cleavage of thiophenes mediated by pentaammineosmium(II).[48] In contrast to the free heterocycle, the thiophene and benzothiophene complexes readily alkylate at sulfur to form *S*-thiophenium species **49** (Scheme 19), stable even in aqueous solution. Complex **49**, in equilibrium with its ring-opened metallacyclopropane vinyl cation isomer, undergoes attack at C5 by such nucleophiles as hydride, cyanide, acetate, phenoxide, phosphine and carboxylate to give thiobutadiene complex **51**. Despite a susceptibility to polymerisation, the intact ligand **50** may be removed oxidatively in good yield.



Scheme 19

Another recent paper describes the dearomatisation of furans[49] wherein the complexed ligands readily undergo a wide variety of electrophilic addition reactions featuring two reactive species **52** and **53** (Scheme 20). Complex **52** is prone to attack at C2 or deprotonation at C3 to deliver a variety of η^2-furan and η^2-2,3-dihydrofuran derivatives whereas **53** undergoes nucleophilic addition at C5 resulting in acyclic or cyclic η^2-complexes. Again, the free ligands are released with a one electron oxidising agent. All transformations occur in very good yield and the reader is urged to refer to the primary publication for further details of this extensive chemistry.



Scheme 20

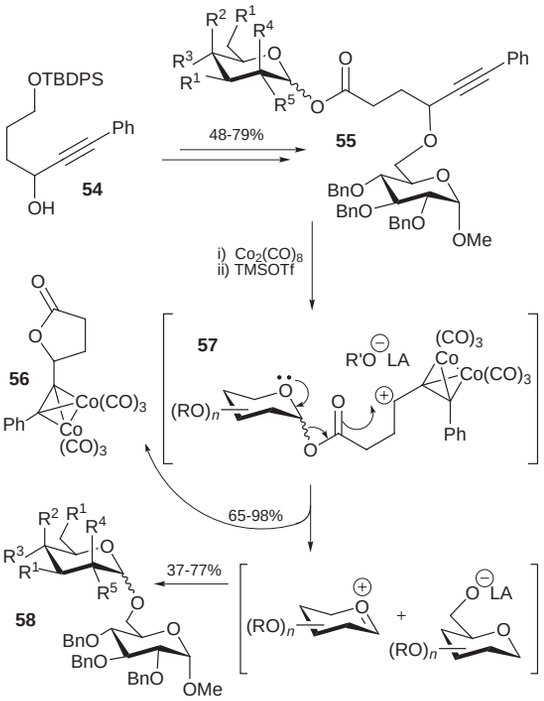
4.2 η^2-Complexes of cobalt

The Nicholas reaction, namely the nucleophilic trapping of a carbocation formed α- to a hexacarbonyldicobalt complexed alkyne, is now well established and among examples of its application this year[50] is a methodology suitable for construction of the Ingenol scaffold.[51] Facilitated by the deviation from linearity of the complexed alkyne, electrophilic addition of the propargyl cation to the ethylidene carbon of the key precursor substrate effects cyclisation; subsequent rearrangement affords the ingenane skeleton in good yield.

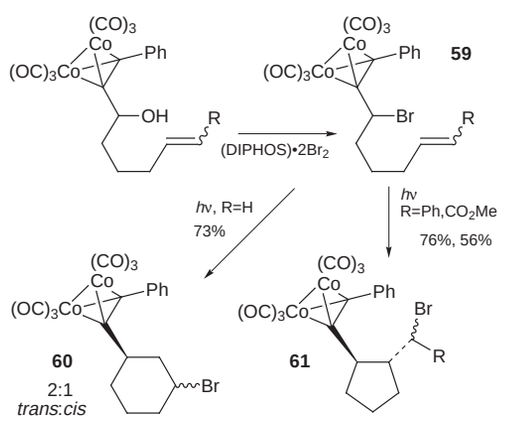
A Nicholas cationic intermediate is also seen to facilitate a novel internal glycosylation process described by Mukai *et al.*[52] The key reaction substrates **55** were prepared in four steps in good yield from **54** and complexed with $Co_2(CO)_8$ (Scheme 21). Propionyl cation **57**, formed under Lewis acid conditions, will spontaneously extrude the cobalt complexed γ-lactone **56** to afford an oxonium cation captured intermolecularly by its counter alkoxy anion species: in essence an alkoxy group migration from the propionyl to the anomeric position. High α- or β-selectivity is observed in the glucoside derivatives **58** dependent on the glucosyl substitution pattern, in particular that of the C2 position.

Also involving activation of the α-position to a complexed alkyne, $Co_2(CO)_6$ is seen to mediate a novel regio- and stereoselective *radical* cyclisation (Scheme 22).[53] Nicholas demonstrates that propargyl bromide complexes **59**, prepared from the corresponding alcohol, undergo facile photo-cyclisation to cycloisomerised products **60** and **61**. The extent to which ring size depends on the alkene substituent is striking, ranging from exclusively *6-endo* (R = H) to exclusively *5-exo* (R = Ph, CO_2Me); the exclusive *trans*-stereoselectivity of the latter stands in contrast to the slight *cis*-preference seen in the cyclisation of uncomplexed 1-substituted hex-5-enyl radicals.

A new use of alkyne–$Co_2(CO)_6$ complexes is reported by Iwasawa (Scheme 23).[54] 1-(Alk-1-ynyl)cyclopropanols **62** with a wide range of alkyne substituents are shown to undergo a novel rearrangement to 3-substituted cyclopent-2-en-1-ones **63** with octacarbonyldicobalt. Depending on which bond of the cyclopropane is cleaved, alkynylcyclopropanols with a substituent on the 2-position of the cyclopropane ring **64** can deliver either the



Scheme 21



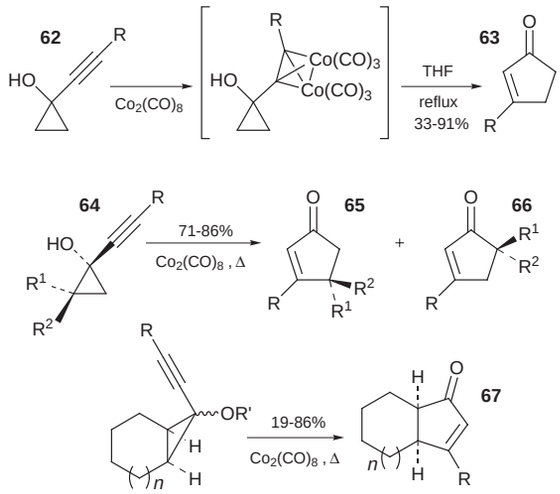
Scheme 22

4- or 5-substituted cyclopentenones **65** and **66** respectively with excellent stereoselectivity. The difference is attributed to steric interactions during formation of a metallacyclic intermediate. Cyclopentenone annulation onto cycloalkenes is also carried out successfully to furnish products of type **67** and has been applied to the steroidal scaffold. It should be noted that the process can also be promoted by catalytic $Co_2(CO)_8$ in the presence of triaryl phosphite.

5 η^3-Complexes in organic synthesis

5.1 η^3-Complexes of iron

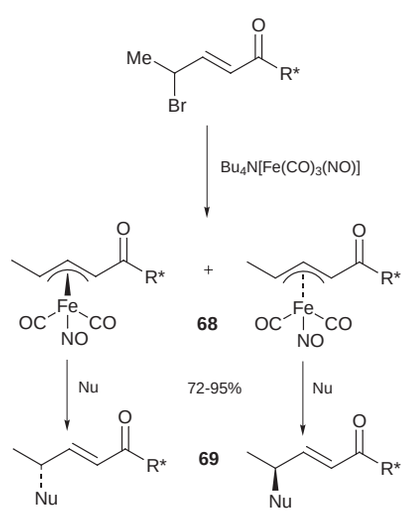
The use of (η^3-allyl)tetracarbonyliron complexes to mediate the stereoselective allylic substitution reaction has been extensively explored by Enders who has this year published a comprehensive account of his work to date.[55] Means of chiral induction (chiral nucleophile approach, auxiliary-controlled complexation, and "chirality transfer") are described and applied to numerous natural product syntheses. Analogous methodology has been elaborated by Jackson who reports stereospecific allylation with his serine-derived zinc–copper



Scheme 23

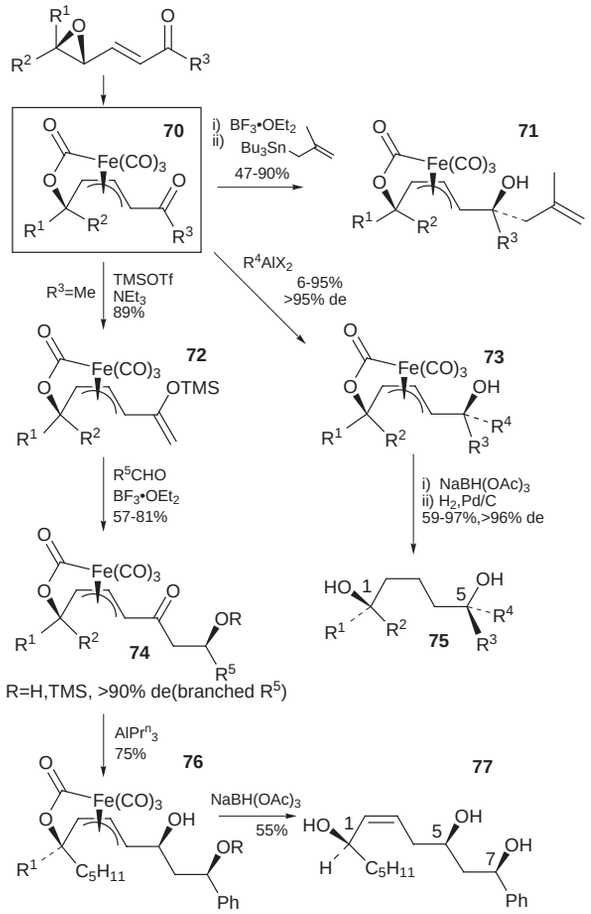
reagent.[56] The substitution product is cyclised to deliver pipecolic acid derivatives in good yield.

Similarly, the nucleophilic addition to neutral (η^3-allyl)-dicarbonylnitrosyliron complexes is reported by Nakanishi (Scheme 24)[57] who has recently described their ambiphilic reactivity towards both nucleophiles and electrophiles. The allyl bromide, bearing an ester or amide chiral auxiliary, reacts with the iron source to yield a diastereoisomeric mixture of complexes **68**, separated by chromatography. The reaction of these planar chiral complexes with amines proceeded regio- and stereospecifically to give γ-amino α,β-unsaturated carboxylic acid derivatives **69** as single (*E*)-isomers in high yield. The addition of carbanions such as sodium malonate, however, occurs with somewhat lower diastereoselectivity. The allylic ester and amide functionality is seen to confer a remarkable improvement in reaction rate and regioselectivity over the analogous unsubstituted complexes.



Scheme 24

The utility of (π-allyl)tricarbonyliron lactone complexes as tools for 1,5-asymmetric induction of chirality has been fully illustrated in recent years by Ley who, this year, has published three full papers on the previously-reviewed[1] addition of various organoaluminium/allylstannanes to side-chain aldehydes[58] and ketones[59,60] of this complex (Scheme 25). High yields and levels of diastereoselectivity are observed in the transformation of complex **70** to **71** and **73** where the lactone tether imparts



Scheme 25

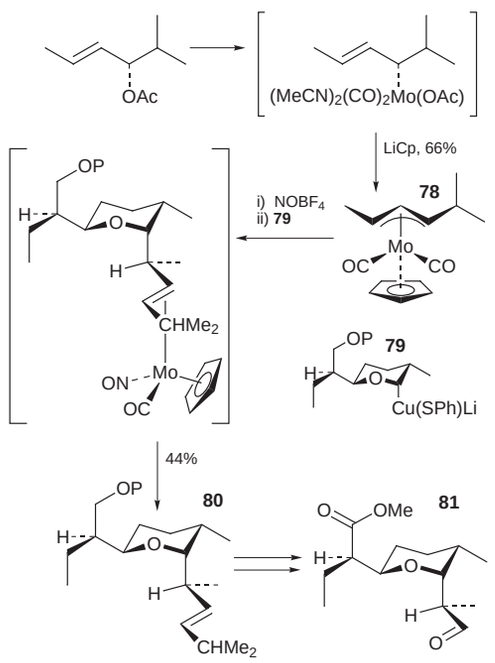
chiral induction *via* the tricarbonyliron moiety. In general, asymmetric induction is somewhat lower for aldehydes than their ketone congeners; excellent levels of stereocontrol can be achieved, though, through careful choice of nucleophile and reaction conditions. Without loss of diastereo- or enantiopurity, these complexes can be converted into the corresponding (*E*,*E*)-(η^4-diene)tricarbonyliron complexes upon treatment with barium hydroxide solution.

Communicated this year is the unprecedented 1,7-asymmetric induction of chirality in a Mukaiyama aldol reaction with the silyl enol ether of complex **70** (Scheme 25).[61] With a range of achiral aldehydes this complex **72** affords β-hydroxy ketone products **74** in good yield and with excellent levels of stereocontrol. Quantitative conversion of the silyl ether/free alcohol mixture to the free alcohol was achieved with HF–pyridine. Reduction of the ketone group in **74** (R = $SiMe_3$) with $AlPr^n_3$ produces only one diastereoisomer **76**.

A novel decomplexation of these (π-allyl)tricarbonyl iron lactone complexes has also been developed.[62] Treatment with sodium triacetoxyborohydride induces highly stereoselective decomplexation in high yield to deliver the fully saturated 1,5-diols **75** after hydrogenation. For the *syn*-5,7-diol **76**, hydrogenation was seen to cleave the C7 hydroxy group; the unsaturated 1,5,7-triol **77** could, however, be isolated. Taken in conjunction with the numerous decomplexation possibilities afforded by these π-allyl lactone complexes (affording β-, γ- and δ-lactones, (*E*,*E*)-dienes or alkenols), the systems depicted in Scheme 25 represent a considerable arsenal at the disposal of the organic chemist.

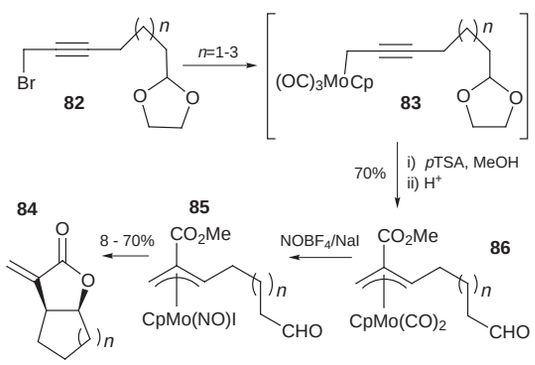
5.2 η^3-Complexes of molybdenum

Applied to the total synthesis of salinomycin[63] by Kocienski is a new methodology for the alkylation of α- and β-glucosylcopper(I) reagents **79** with diastereoisomeric (η^3-allyl)molybdenum cationic complexes.[64] Easily derived from homochiral allylic acetates with $Mo(CO)_3(MeCN)_3$ (Scheme 26), the neutral complex **78** (in which enantiofacial discrimination of the allyl ligand is achieved due to retention of configuration in the initial oxidative addition step) undergoes carbonyl ligand replacement by nitrosyl with $NOBF_4$ to give a cationic complex as a mixture of isomers. The *exo*- and *endo*-isomers are in equilibrium under the reaction conditions thereby allowing kinetic selection of the faster-reacting *exo*-isomer. Hence, subsequent alkylation occurred with high regio- and facial-selectivity to afford the adduct **80**, with two contiguous stereogenic centres, after oxidative demetallation. This system clearly complements that of the (η^3-allyl)iron complexes of Enders and Nakanishi (Scheme 24). Further elaboration of **80** affords **81**, a key fragment in the synthesis of the natural product.



Scheme 26

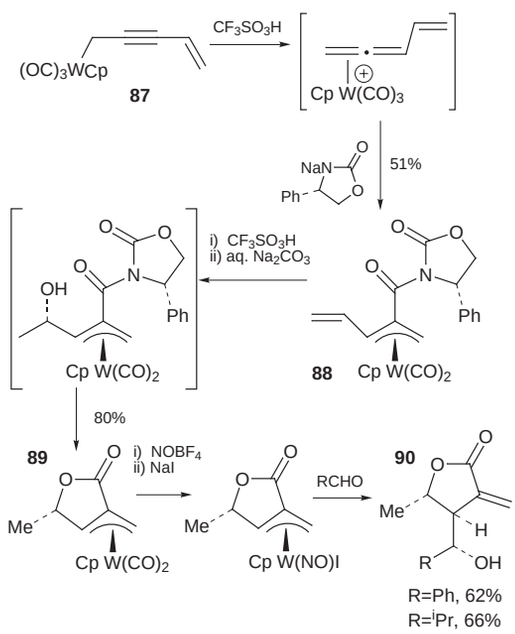
Liu describes a (π-allyl)molybdenum-mediated synthesis of various bicyclic α-methylene butyrolactones (Scheme 27).[65] The η^1-propargyl molybdenum complex **83**, formed by treatment of bromopropargyl **82** with $CpMo(CO)_3Na$, undergoes alkoxycarbonylation in the presence of methanol and catalytic *p*-TSA to deliver the π-allyl species **86** in high yield after hydrolysis. Subsequent carbonyl substitution with $NOBF_4$ and NaI affords the aldehyde complex **85** which behaves as an allyl anion to induce intramolecular cyclisation delivering *cis*-fused **84**. Indeed α-methylene butyrolactone products fused with various carbocyclic rings are reported, although *trans*-fused products dominate where *n* = 2 or 3.



Scheme 27

5.3 η^3-Complexes of tungsten

A second stereoselective synthesis of α-methylene butyrolactones **90** reported by Liu involves a π-γ-lactone tungsten complex (Scheme 28).[66] The enantioselective aminocarbonylation of vinylprop-2-ynyl tungsten complex **87** proceeds through an η^2-vinylallene cation formed in the presence of acid. Nucleophilic attack of an oxazolidinone at a carbonyl ligand is followed by insertion of the aminocarbonyl group into the central allene carbon to deliver complex **88**, the major of two diastereoisomers separated by chromatography. Subsequent acidification gave a cationic diene complex which, on hydrolysis, affords the optically pure π-allyl-γ-lactone complex **89**. The allyl anion equivalent, again formed through treatment with $NOBF_4$ and NaI, reacts *in situ* with an aldehyde in good yield and stereoselectivity.

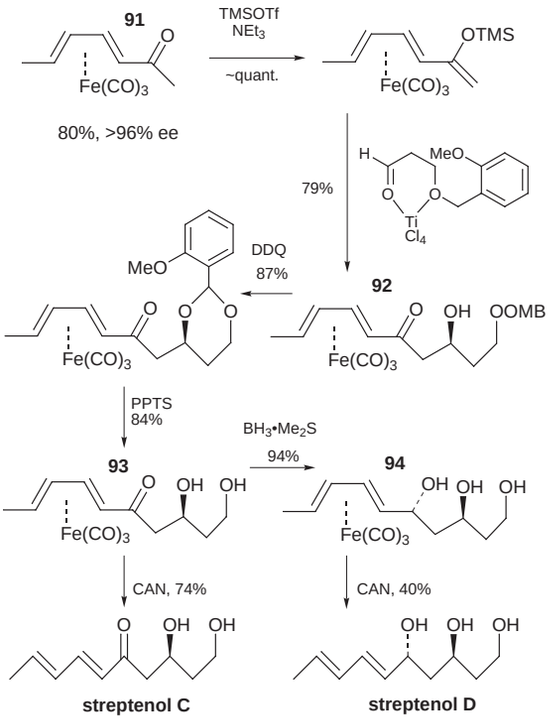


Scheme 28

6 η^4-Iron–diene complexes in organic synthesis

The field of iron–diene chemistry still attracts much attention. Recent communications from Franck–Neumann illustrate the stereoselective synthesis of 1,3-diols[67,68,69] *via* an aldol condensation reaction where the optical activity is introduced by three distinct means. An efficient synthesis of two metabolites, streptenols C and D, Scheme 29, is representative of the methodology.[67] Optical activity is introduced by the resolution of the starting material, the (1-acetyldiene)tricarbonyliron complex **91**. Reaction of the silyl enol ether, formed almost quantitatively from **91**, with the protected β-hydroxypropanal under Mukaiyama conditions formed the ketol **92** in high yield, easily separable by chromatography from 8% of the other diastereoisomer. Intermediate formation of the acetal of **92** followed by acidic cleavage gave the deprotected keto diol **93** in high yield. Prone to oxidative decomplexation, the tricarbonyliron complex showed remarkable tolerance to the oxidant DDQ. From complex **93** streptenols C and D were obtained by CAN decomplexation, directly in the case of the former, and after metal-induced stereoselective reduction to the triol complex **94** for the latter.

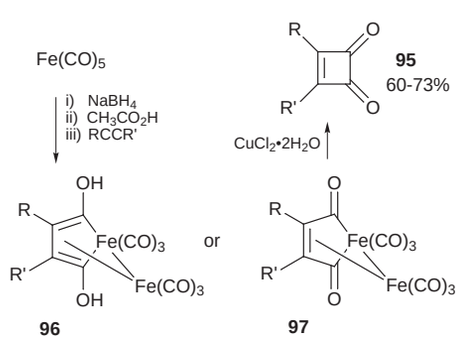
Reported by the same group, using similar aldol methodology, is a total synthesis of protected 3,6-dideoxyhexoses.[68] The chirality in this case is introduced in the reaction between an optically active α-hydroxy aldehyde and a *racemic* diene complex. The diastereoisomeric products are, again, readily separable. Following further manipulation and ozonolysis of the decomplexed diene the protected natural products are



Scheme 29

delivered in 21 and 20% overall yield. Optical activity introduced *via* stereoselective complexation of a chiral ligand is also relayed to two 3-deoxypentoses,[69] again through an aldol process. A strategy for the diastereoselective preparation of dienol complexes whose alcohol centre is 2, 3 or 4 carbons removed from the $Fe(CO)_3$ group has been detailed by Donaldson.[70]

A novel synthesis of cyclobutenediones *via* an interesting double carbonylation of alkynes using the $[HFe_3(CO)_{11}]^-$ reagent, Scheme 30, is described by Periasamy.[71] The iron reagent is selective for alkyne over alkene functionality and is tolerant of unmasked hydroxy groups, but the exact nature of the intermediate is not clear: neither **96** nor **97** can be discounted. Copper(II) chloride oxidation of the iron complex affords the cyclobutenediones **95** in a simple one-pot process.

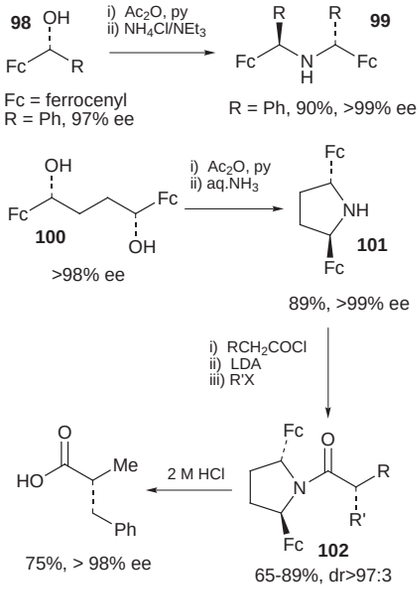


Scheme 30

7 η^5-Complexes in organic synthesis

7.1 Stoichiometric ferrocene complexes

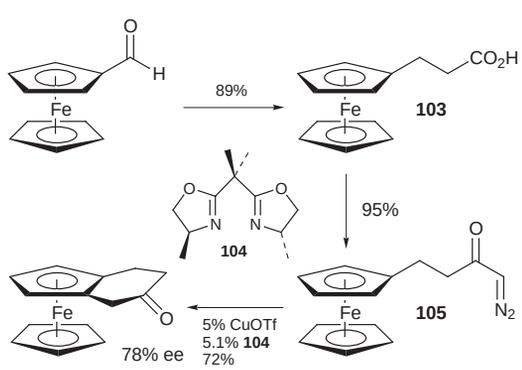
Ferrocene derivatives are still exciting considerable interest as tools in asymmetric synthesis. Two new C_2-symmetric ferrocenyl amines **99** and **101**, successfully applied as a chiral base and chiral auxiliary respectively, are reported by Knochel[72] (Scheme 31). α-Chiral ferrocene alcohols **98** and **100** are readily prepared with high enantioselectivity by the established CBS reduction of the corresponding ketones. Quantitative conversion to the acetates and treatment with NH_4Cl–NH_3 furnishes the diastereomerically pure amine and pyrrolidine after chromatography. The efficient conversion of **101** to the amide pre-



Scheme 31

cedes highly diastereoselective alkylation to afford the alkylated amides **102** in good yield. Removal of the auxiliary occurs without epimerisation to deliver α-chiral carboxylic acids with excellent enantiomeric purity. In a similar role, amine **99** exhibited only moderate chiral induction, but was used with some success as a chiral lithium amide base (on treatment with BuLi) in the enantioselective deprotonation of 4-*tert*-butylcyclohexanone. The resulting silyl enol ether was obtained with up to 62% ee.

Schmalz describes an interesting enantioselective catalytic entry to planar chiral ferrocenes *via* a novel intramolecular insertion of carbenoids into the Cp–H bond (Scheme 32).[73] Formylferrocene, first transformed by decarboxylative Knoevenagel condensation and catalytic hydrogenation into acid **103**, was further converted into diazoketone **105** in high yield. Cyclisation with the catalyst prepared *in situ* from copper(I) trifluoromethanesulfonate and chiral ligand **104** proceeded with significant enantioselectivity and, remarkably, in higher yield than under achiral catalysis.

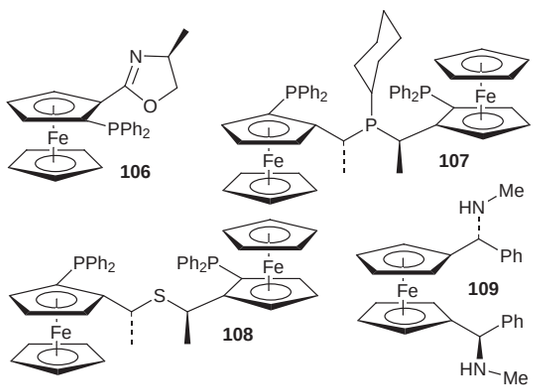


Scheme 32

Ferrocene-derived ligands for use in asymmetric catalysis arouse continued interest. Although not strictly within the purview of this article, a brief summary of ligand types in the context of catalysis undertaken this year should be of interest. Asymmetric transfer hydrogenation has been effected using the ligands depicted below with the results collated in Table 1. The planar chiral ligand **106** is prepared from the parent ferrocenyloxazoline with excellent diastereoselectivity and yield *via* the diastereotopic group selective metallation with *sec*-BuLi and Ph_2PCl.[74] Only 0.2% of the catalyst system is shown to effect the asymmetric transfer hydrogenation of various aryl

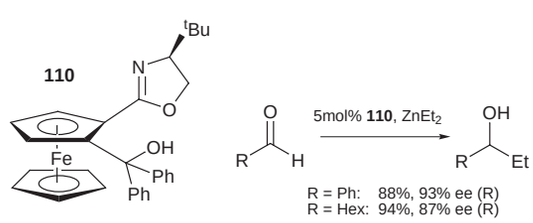
Table 1

Ligand (mol%)	R	R′	Yield (%)	Ee (%)	Ref.
106 (0.26)	Ph	Me	93	94	74
	^{t}Bu	Me	51	94	
107 (1)	Ph	Me	99.1	71.7	75
108 (1)	Ph	Me	24.2	20.1	
109 (2)	Ph	Me	95	80	76



alkyl ketones in excellent yield and enantioselectivity. Several new chiral tridentate ligands of type **107** have been synthesised from cyclohexylphosphine with different chiral ferrocenylaminophosphines in hot acetic acid.[75] The thioether ligand **108** is similarly prepared from the ferrocenylethyl acetate and a ferrocenylethyl mercaptan sodium salt. Hydrogenation enantioselectivity, however, is somewhat lower than that achieved with other ruthenium(II) chiral catalysts. Although their preparation is previously reviewed,[1] diamines of type **109**, prepared *via* a highly flexible synthetic route, have also been applied with success achieving a maximum of 88% ee.[76]

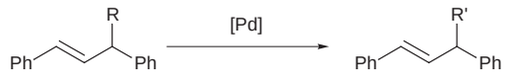
Asymmetric ethylation, with enantioselectivity of up to 95% ee, is catalysed by ligand **110** (Scheme 33).[77] Selective *ortho*-deprotonation of the parent oxazoline and subsequent addition of benzophenone proceeded in 87% yield. Unlike many other systems, ferrocene ligand **110** catalyses the ethylation of aliphatic aldehydes.



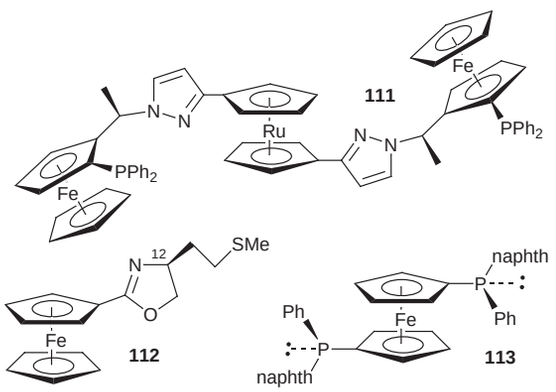
Scheme 33

The third transformation to receive attention is palladium-catalysed allylic substitution (Table 2). In a step towards dendritic asymmetric catalysts which, by virtue of low solubility, should facilitate catalyst recovery and re-use, Togni reports the preparation of ligand **111** containing two independent *P*,*N*-chelating moieties.[78] The bis(pyrazolyl)ruthenocene, formed in two steps from 1,1′-diacetylruthenocene, is coupled with the appropriate ferrocenylphosphine to afford **111**. The yield and enantioselectivity in the substitution reaction are excellent and significantly, following recovery by crystallisation, a second catalytic run showed no loss in activity and only a slight loss of enantioselectivity. Chiral ferrocenyloxazoline **112**, prepared in four steps and 55% overall yield from ferrocenecarbonyl chloride and L-methionine, effects substitution with very good yield

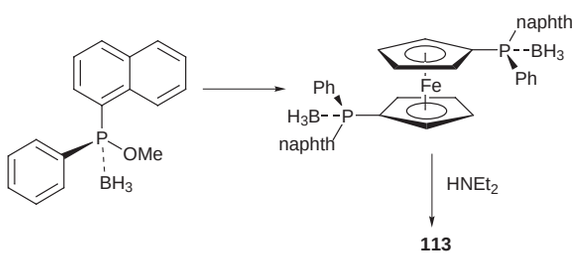
Table 2



Ligand (mol%)	R	R′	Mol% Pd	Yield (%)	Ee (%)	Ref.
111 (1.5)	OCO_2Et	$PhCH_2NH$	3	100	99.3 (*S*)	78
112 (10)	OAc	$(MeO_2C)_2CH$	2.5	98	93 (*R*)	79
113 (1)	OAc	$(MeO_2C)_2CH$	0.5	84	73 (*R*)	80



and enantioselectivity.[79] The C_2-symmetric *P*-chiral bidentate diphosphine ligand **113**, formed *via* the stereocontrolled nucleophilic substitution sequence of Scheme 34,[80] also performs well in the model system shown. Extended to aliphatic substrates, however, the enantioselectivity is considerably lower, an observation ascribed to the absence of aromatic π-stacking interactions.



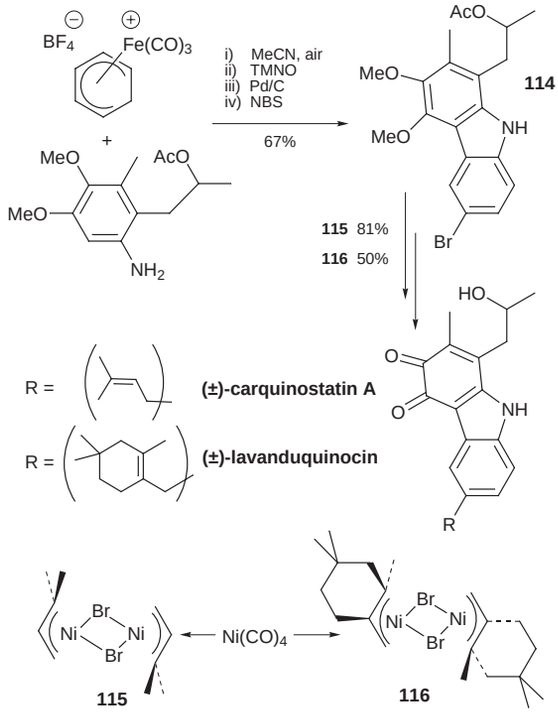
Scheme 34

7.2 η^5-Iron cationic complexes

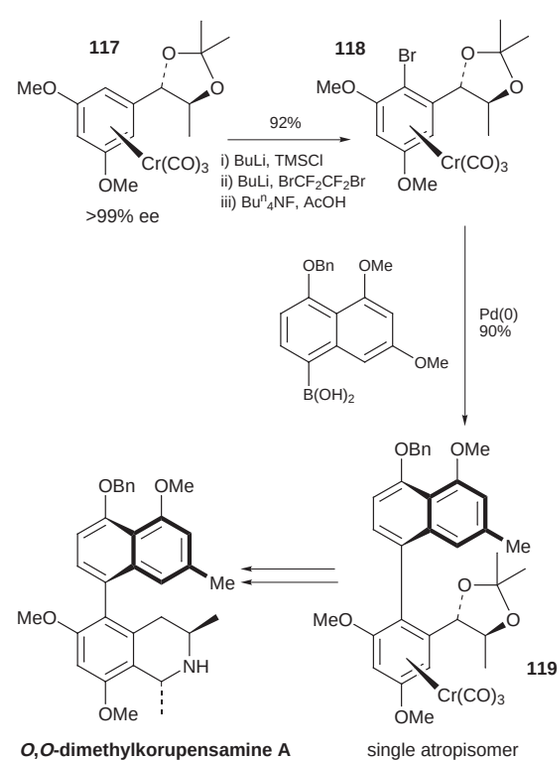
Knölker continues to elaborate on his well-established electrophilic aromatic substitution and oxidative cyclisation processes. An iron- and nickel-mediated coupling process has delivered the alkaloids (±)-lavanduquinocin[81] and (±)-carquinostatin A[82] from a common intermediate **114** (Scheme 35). Coupling of the aniline and iron complex salt, demetallation using trimethylamine *N*-oxide, aromatisation with Pd–C and subsequent regioselective bromination with *N*-bromosuccinimide provided **114** in good overall yield. The dimeric π-allylnickel bromide complexes **115** and **116**, prepared from the corresponding allyl bromide and tetracarbonylnickel, are highly sensitive to oxidation and were thus used crude in the cross-coupling with **114**. Further elaboration affords the natural products, both in seven steps overall.

8 η^6-Complexes of chromium in organic synthesis

η^6-Tricarbonylchromium(0) complexes continue to show their value in the total synthesis of natural products and their derivatives. The stereoselective synthesis of *O*,*O*-dimethylkorupensamine A, one of a series of alkaloids with remarkable antiviral activity against HIV-1 and -2, is reported by Uemura (Scheme 36).[83] The key step is an asymmetric palladium(0)-catalysed cross-coupling with naphthylboronic acid of the planar chiral 3,5-dimethoxy-2-bromobenzene complex **118**. Regioselective bromination of **117** *via* lithiation and a 1,2-dibromo-1,1,2,2-tetrafluoroethane quench at the *ortho*-position to the C1 side chain group was effected by protection and subsequent deprotection of the C4 position with the easily removable $SiMe_3$ group. The enantiomerically pure complex **118** was afforded in 92% overall yield. The single atropisomeric coupling product **119** was decomplexed and taken through to the product alkaloid in good yield.

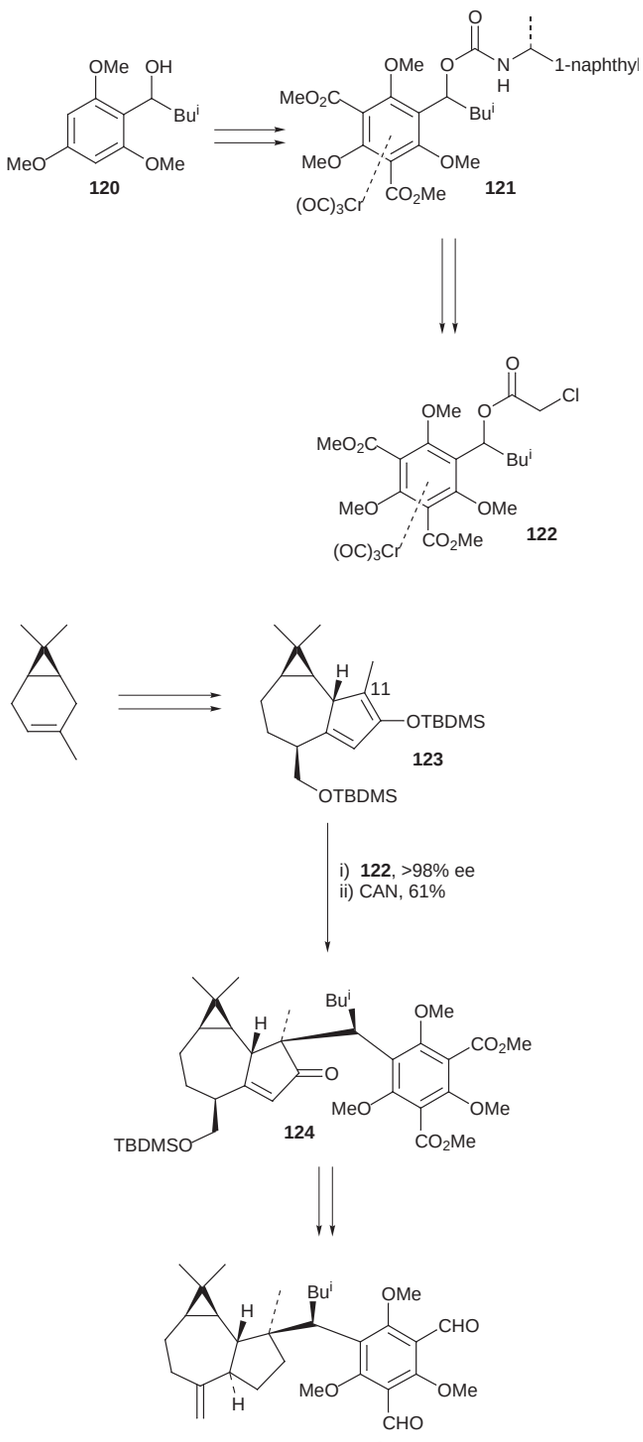


Scheme 35



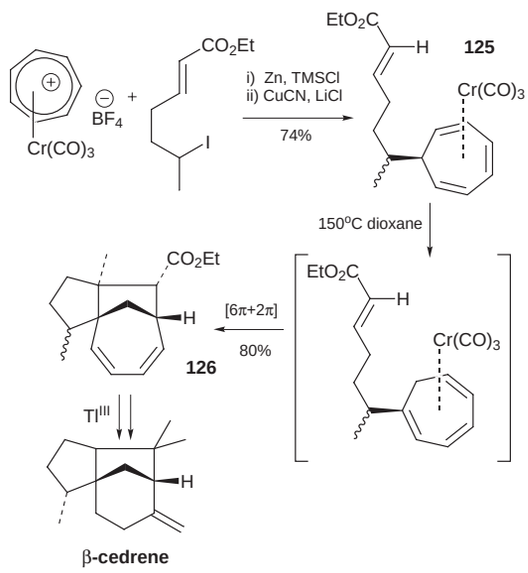
Scheme 36

The first enantioselective synthesis of macrocarpal C is reported by Iwata (Scheme 37).[84] Requiring high stereoselectivity at both the benzylic and C11 positions, the crucial step is a Lewis acid mediated coupling of silyl dienol ether **123** with chromium complex **122**. It is known that, with some nucleophiles, S_N1-type C–C bond formation *via* a $Cr(CO)_3$-stabilised carbonium ion proceeds with stereochemical retention at the benzylic position, and also from previous work of Iwata, that electrophilic attack at C11 of **123** occurs stereoselectively from the less hindered β-side. Hence, the racemic complex of **120**, following bis-methoxycarbonylation, chromatographic resolution of its diastereomeric carbamates **121**, hydrolysis and conversion to the chloroacetate gave **122**. As an optically active benzyl cation equivalent, **122** couples stereoselectively to deliver **124** and only 2% of the benzylic epimer.



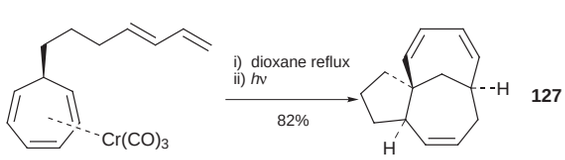
Scheme 37

Rigby continues to expand on his higher order [6π + 4π] and [6π + 2π] cycloadditions of tricarbonyl(cycloheptatriene)-chromium(0). In a total synthesis of β-cedrene[85] the *endo*-selective intramolecular [6π + 2π] cycloaddition with the pendant activated alkene of **125** delivers the tricyclic system **126** (Scheme 38). The cycloaddition proceeds through the preferred 1-substituted isomer resulting from thermal isomerisation of **125** *via* a series of chromium(0)-facilitated 1,5-hydrogen shifts; subsequent thallium(III)-mediated oxidative ring contraction provides the product.



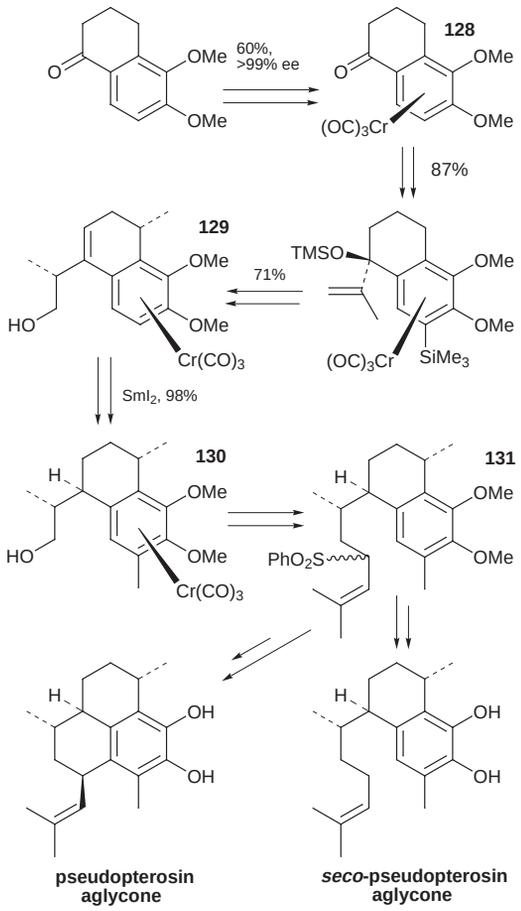
Scheme 38

The [6 + 2] cycloadditions of complexed cycloheptatrienes and tropone systems bearing pendant alkynes of various tether length have also been successful.[86] Similar [6π + 4π] methodology from the same group has efficiently given the ingenol scaffold **127** with a substrate bearing a diene tether.[87] This process rises elegantly to the formidable challenge of delivering the highly strained *trans*-intrabridgehead stereochemical relationship, the cycloaddition again occuring through the requisite 1-substituted isomer to afford a single diastereoisomer (Scheme 39). Also developed is a novel chromium(0)-promoted intermolecular [6π + 4π] cycloaddition–pinacol rearrangement strategy[88] which delivers the 9-membered carbocycles possessed by numerous natural products.



Scheme 39

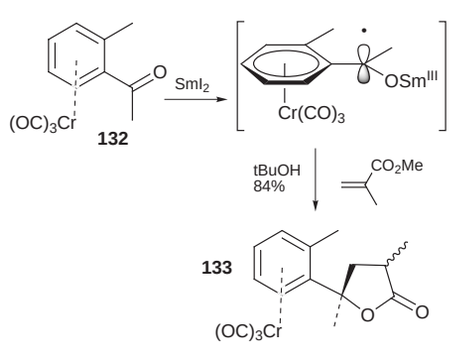
Schmalz reports the successful realisation of work started some years ago with a refined enantioselective entry to the aglycone of seco-pseudopterosin.[89,90] The unique stereochemical opportunities offered by the (η^6-arene)$Cr(CO)_3$ are used to beautiful effect (Scheme 40).[89] Complex **128**, obtained by diastereoselective complexation of the temporarily chirally modified ligand, undergoes simultaneously both *ortho*-lithiation and *exo*-nucleophilic attack with isopropenyllithium (TMSCl quench). Regio- and diastereoselective deprotonation–methylation at the free benzylic position is followed by diastereoselective hydroboration of the isopropenyl side-chain, desilylation (TBAF) and selective elimination of the benzylic OH group to deliver complex **129**. Following deprotonation–methylation of this complex, hydrogenation was effected with SmI_2 in THF–HMPT–H_2O to afford complex **130**. The relative



Scheme 40

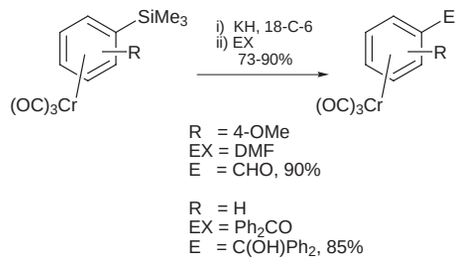
stereochemistry at the new chiral centre of **130** is controlled by diastereoselective protonation of an intermediate benzylic anion as described in a complementary communication.[90] Decomplexation and further elaboration affords the key intermediate **131** from which both aglycones are easily accessible in only two steps. Comparable methodology has achieved the first enantioselective synthesis of helioporin D.[91]

Still relatively new to tricarbonylchromium(0) complexes, radical chemistry has enjoyed further elaboration this year. Two almost identical communications from Merlic[92] and Uemura[93] report the stereoselective reaction of complexed aryl aldehydes and ketones with samarium(II) iodide and methyl (meth)acrylate (Scheme 41).[93] The preference for the carbonyl of **132** to adopt a *syn*-conformation is well documented and the author suggests initial Lewis acid coordination of samarium to oxygen such that **132** isomerises to an *anti*-conformer prior to one electron reduction. The resulting ketyl radical possesses substantial *exo*-double bond character and thus restricted bond rotation. Acrylate traps the complex radical from the *exo*-side to generate the optically pure γ-butyrolactone **133** in good yield.



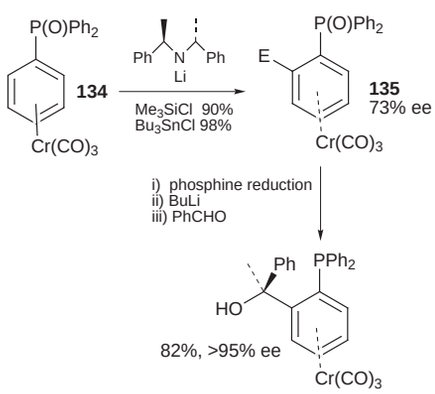
Scheme 41

Described by Sarkar[94] is a useful synthetic method for the preparation of complexes not readily obtainable by direct complexation such as those bearing elecron-withdrawing functionality or more than one aromatic ring (where mixtures are produced). Facile cleavage of a $Cr(CO)_3$ complexed Ar–$SiMe_3$ bond with nucleophilic potassium hydride furnishes an anionic intermediate which is readily trapped by various electrophiles (Scheme 42).



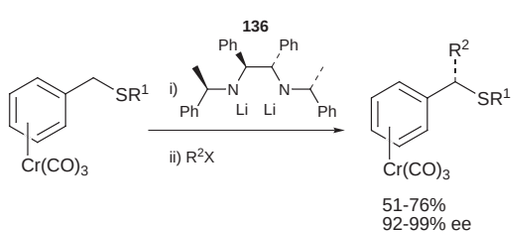
Scheme 42

In the field of asymmetric catalysis, the search for enantiomerically pure ligands is slow to incorporate (η^6-arene)$Cr(CO)_3$ complexes. Simpkins, however, reports the asymmetric synthesis of a range of novel phosphine complexes *via* the enantioselective *ortho*-metallation approach using a chiral lithium amide base (Scheme 43).[95] Initial reaction of a phosphine oxide complex **134** allows the preparation of silyl- or stannyl-substituted products **135** with *ca.* 73% ee. Significantly, the sense of asymmetric induction is opposite to that seen under methoxy direction. Enantiomeric enrichment and phosphine reduction of **135** set the scene for a transmetallation and electrophilic quench sequence from which phosphine derivatives are accessed in good yield and excellent optical purity.

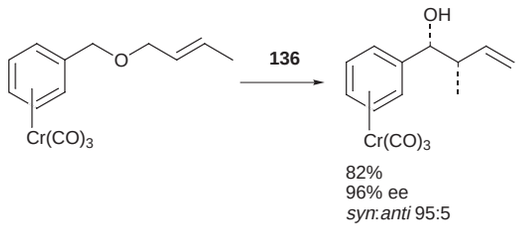


Scheme 43

With a view to using chiral sulfides as ligands in asymmetric synthesis, a chiral base methodology has also been used within the Gibson group for the asymmetric benzylic functionalisation of benzyl sulfide complexes[96] (Scheme 44). Again, an intriguing reversal of stereochemical outcome is observed with respect to analogous oxygen systems. The same chiral base **136** has been employed to mediate a highly enantioselective [2,3]-Wittig rearrangement of allyloxymethylbenzene complexes (Scheme 45).[97]

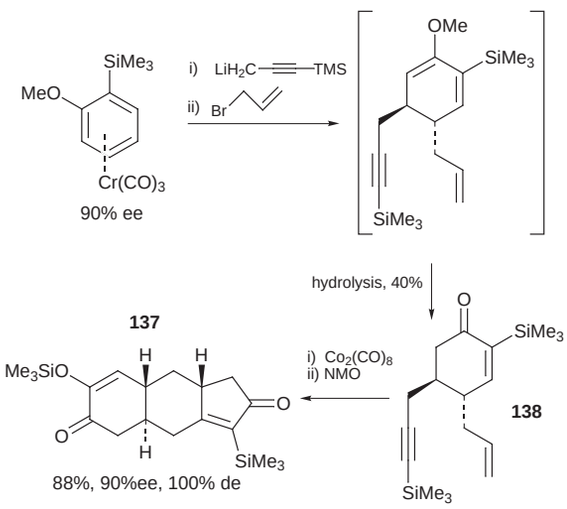


Scheme 44



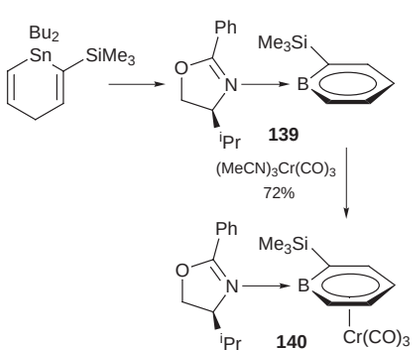
Scheme 45

Kündig has demonstrated the efficient transfer of planar chirality to three new stereogenic centres *via* a propargylation–allylation–Pauson–Khand cyclisation sequence (Scheme 46).[98] Predominantly *meta*-regioselectivity in the nucleophilic addition to the *exo*-face of the anisole complex, followed by *endo* delivery of the allyl electrophile, gave *trans*-disubstituted cyclohexenone **138** as a single regioisomer. Subsequent Pauson–Khand cyclisation, novel with respect to the *trans*-disposition of the pendant substituents, gave the tricyclic ketone **137** as a single diastereoisomer.



Scheme 46

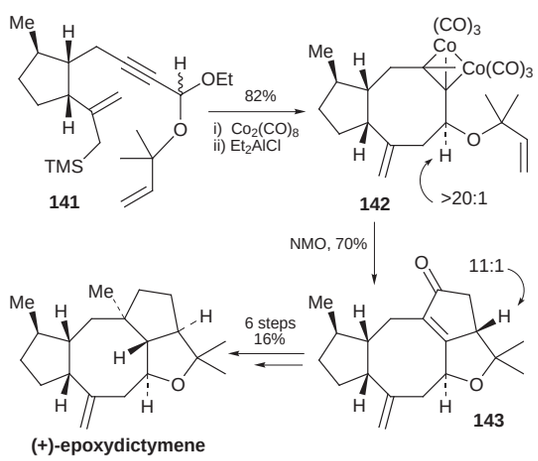
Fu has prepared the first optically pure planar-chiral Lewis acid tricarbonylchromium(0) complex (Scheme 47).[99] Formed from the stannacyclohexadiene, the borabenzene ligand adduct **139**, which exists as a single atropisomer from X-ray crystallography, NOE and *ab-initio* calculations, undergoes highly diastereoselective complexation to give the product **140** as a single diastereoisomer. A new approach to chiral Lewis acid design, an organic carbonyl group should be activated through both σ-symmetry (oxygen lone pair) and π-symmetry (CO π-system) hence defining the reactive conformation of the substrate–Lewis acid complex.



Scheme 47

9 Pauson–Khand reactions

The continuing favour for the Pauson–Khand reaction in the organic community[100] reflects its simplicity, versatility and tolerance of diverse functionality in the construction of cyclopenten-2-ones with numerous stereogenic centres. Of particular interest is the development of the asymmetric process.[101] Among natural product syntheses, that of (+)-epoxydictymene by Schreiber[102] is succinct. Assembling three of four rings in the natural product, an elegant tandem process centred on the reactivity of the alkyne–cobalt complex consists of a Nicholas reaction (as described in Section 4.2) and a subsequent Pauson–Khand cycloaddition (Scheme 48). Hence, dienyne substrate **141**, prepared in good overall yield and possessing asymmetry derived from (*R*)-pulegone, undergoes alkyne complexation with octacarbonyldicobalt followed by a diastereoselective Lewis acid-mediated Nicholas cyclisation to deliver **142**. Pauson–Khand cycloaddition then affords the desired cyclopentenone system of **143** as an 11:1 mixture of diastereoisomers at C12. Further elaboration, incorporating a ring opening–reclosure strategy to reverse the stereochemistry at this centre, gives the natural product with its *trans*-fused 5,5-ring system.

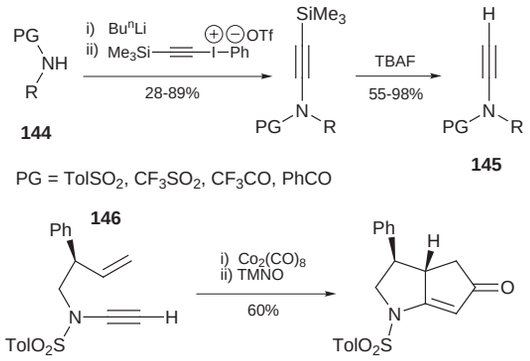


Scheme 48

Witulski outlines the use of alk-1-ynylamines in the Pauson–Khand reaction,[103] a system which represents a fundamental novel strategy for the stereoselective synthesis of nitrogen-containing heterocycles (Scheme 49). In a new process, ethynylation of the amides **144** and desilylation occur in good yields to deliver the alkynylamides **145**, a set of compounds whose protecting group serves both to mask a primary or secondary amine and to tune the electronic density, and hence reactivity, of the pendant triple bond. With norbornadiene, **145** undergoes a highly efficient intermolecular reaction to afford the *exo*-isomer only with high regioselectivity: only the α,β-unsaturated α-amidocyclopentenones were formed. In an intramolecular sense, substrates of type **146** bearing a variety of tethered alkenes undergo the process to form one diastereoisomer only.

Work continues on the allenic Pauson–Khand reaction[104] where the standard alkene moiety is replaced by allene functionality. For the intramolecular process, π-bond regioselectivity can be controlled by means of the allenic substitution pattern to deliver either bicyclic dienones or α-methylenecyclopentenone adducts.

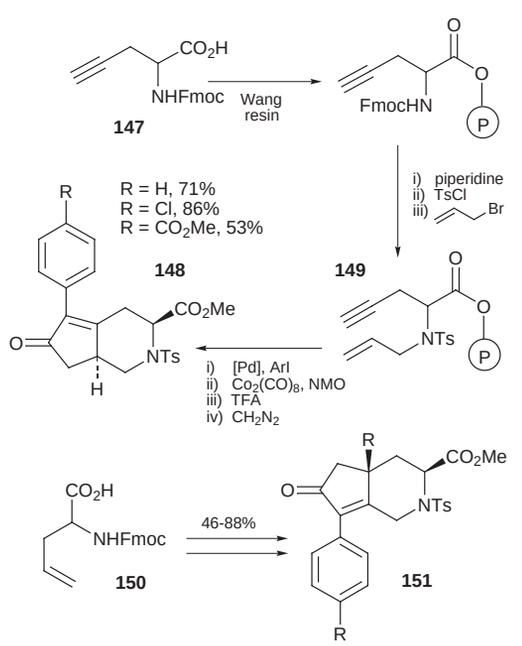
In a more general sense, some very attractive reaction conditions have been developed. Periasamy describes *in situ* preparation of (alkyne)hexacarbonyldicobalt complexes[105] from the benchtop reagents $CoBr_2$–Zn–CO in DCM–Bu^{t}OH. On the basis that primary amines accelerate the reaction due to the labilising effects of these "hard" ligands which facilitate co-ligand substitution, Sugihara and Yamaguchi report almost quantitative cycloaddition[106] in the presence of cyclohexyl-



Scheme 49

amine in 1,2-dichloroethane in only five minutes. Aqueous ammonia is also a very efficient promoter[106] thereby demonstrating the tolerance of this reaction to water.

Also of current interest is the application of the Pauson–Khand reaction to solid phase chemistry. Developed by Bolton[107] is a system which reveals the potential for combinatorial library generation (Scheme 50) where both the Pauson–Khand substrate scaffold design and the introduction of functionality allow for molecular diversity. Coupling of the protected propargyl glycine **147** onto the Wang resin followed by deprotection, tosylation and allylation affords the Pauson–Khand scaffold **149**. The novel highly-functionalised bicyclic amino acids **148** are delivered in good yield by an efficient Pd-catalysed coupling of various aryl iodides with the solid-supported alkyne. Propargylation of the polymer-bound allylglycine **150** gives a different scaffold which undergoes the Pauson–Khand reaction to give products **151**. The insertion of an amino acid resin linker leads also to unusual dipeptide analogues. Bicyclic conformationally constrained lysine derivatives are accessible *via* a solid phase chemoselective 1,4-reduction of the cyclopentenone system with a soluble copper hydride reagent and subsequent reductive amination–acylation. The success of these systems in a combinatorial capacity remains to be demonstrated, however.



Scheme 50

Also reported is a polymer-suppoted *inter*molecular reaction between norbornene-derived substrates and α,ω-alkynols.[108] Compared to equivalent solution chemistry, use of 2% cross-linked resin enhances chemoselectivity significantly in favour of the Pauson–Khand product over side reactions such as trimerisation.

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