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Applications of carbene complexes toward organic synthesis

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Contents

Abstract

The article highlights advances in the discovery and development of reaction processes utilizing metal–carbene complexes which are useful in the field of synthetic organic chemistry. Emphasis is on reaction processes which result in the formation of carbon–carbon

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bonds in a reliable and efficient manner. Examples utilizing these reaction processes for the synthesis of biologically-important molecules has been noted wherever appropriate.

Keywords: Carbene complexes; Organic synthesis; Reactivity patterns

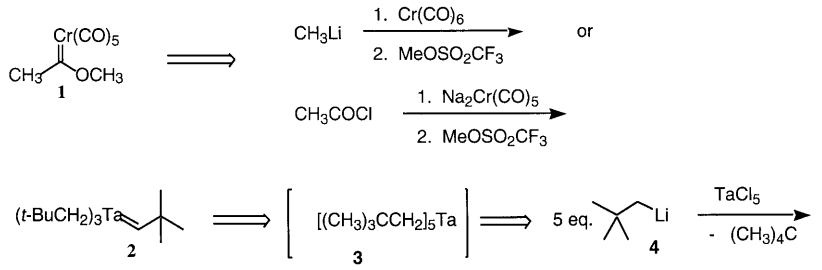
1. General overview

The first stable transition metal carbene complex was reported by Fischer in 1964 [1], however prior to that time, complexes of carbenes with transition metals had been proposed as intermediates in metal-catalyzed reactions of diazo compounds and in other carbene transfer reactions [2]. Since the first report by Fischer, studies of the synthesis and reactivity of metal–carbene complexes has been a very active area of research. This review will focus on the use of carbene complexes in organic synthesis. This review will highlight reaction processes that have been well studied and can reliably lead to the production of a single class of compounds, and where possible will note applications of these reaction processes for the synthesis of biologically important molecules. Although not all of the reactions discussed have culminated in successful total syntheses, these reaction processes offer advantages for the synthesis of important structural features often present in numerous pharmaceutically-important molecules.

This review is not comprehensive and in most cases offers a sample reaction equation to represent a class of reactions. In most cases, references to the latest article, or a review, or an article of special significance has been included. Numerous reviews of carbene complexes in organic synthesis have appeared [3], and wherever possible, review articles will be referenced. The reaction of diazo compounds with transition metal salts is not covered in this review, although strong evidence suggests that metal–carbene complexes are intermediates in this process; several reviews of this area have recently appeared [4–7].

2. Classification of reactivity patterns

Transition-metal carbene complexes are generally divided into two classes, 'Fischer-type' carbene complexes and 'Schrock-type' carbene complexes. Fischer carbene complexes (exemplified by structure **1** of Scheme 1) exhibit the following features: (1) the carbene carbon is electrophilic; (2) the metal is in a relatively low oxidation state; and (3) the metal is typically toward the right side of the transition block. Schrock carbenes (exemplified by complex **2** of Scheme 1) exhibit the following features: (1) the carbene carbon is nucleophilic; (2) the metal is in a relatively high oxidation state; and (3) the metal is typically toward the left side of the transition block. There are some carbene complexes that do not fit comfortably into either class (e.g. amphiphilic [8]) and show features common to both classes.

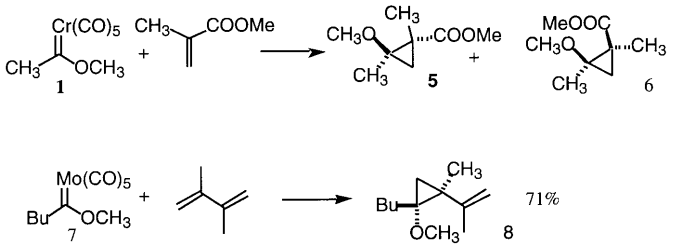


Scheme 1.

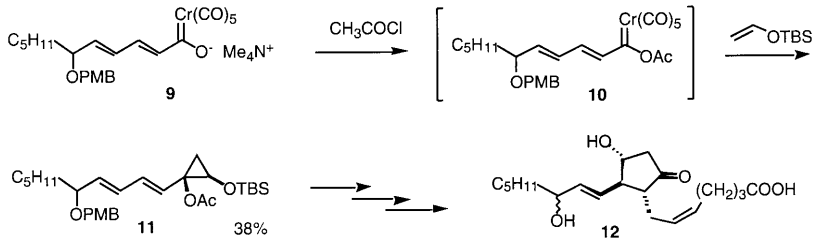
Common synthetic routes to complexes **1** and **2** are also depicted in Scheme 1. The most common routes to Fischer carbene complexes are through treatment of organolithium reagents with metal carbonyls followed by alkylation or through treatment of acyl halides with nucleophilic transition metal complexes followed by alkylation. Schrock carbene complexes are commonly generated through α-hydride elimination/alkane extrusion processes; for example, the formation of **3** is accompanied by rapid loss of neopentane and formation of carbene complex **2**.

3. Cyclopropanation

One of the early goals after the discovery of carbene complexes was to effect the most common transformation of carbenes, cyclopropanation [9] (Scheme 2). The heteroatom-stabilized Fischer carbene complexes can only cyclopropanate electron-poor alkenes [10,11] and 1,3-dienes [12,13] (Scheme 2), or electron-rich alkenes under CO pressure [14]. Intramolecular cyclopropanation reactions appear to be more facile [15]. Unstable acetoxycarbene analogs (e.g. **10**, Scheme 3) appear to undergo cyclopropanation of electron-rich alkenes more readily [16,17], while Group VI metal–carbene complexes lacking heteroatom substitution proved to be a more general cyclopropanating agent [18,19]. This reaction process is the cornerstone for the synthesis of prostaglandin derivatives **12** (Scheme 3). For the metals of Group VI, the molybdenum carbene complexes appear to be more reactive than the chromium carbene complexes; tungsten carbene complexes are not generally useful cyclopropanating agents except when lacking heteroatom substitution [20].



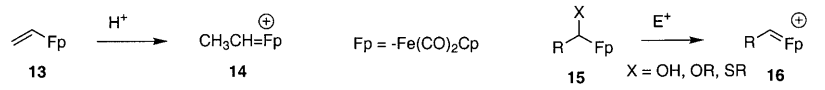
Scheme 2.



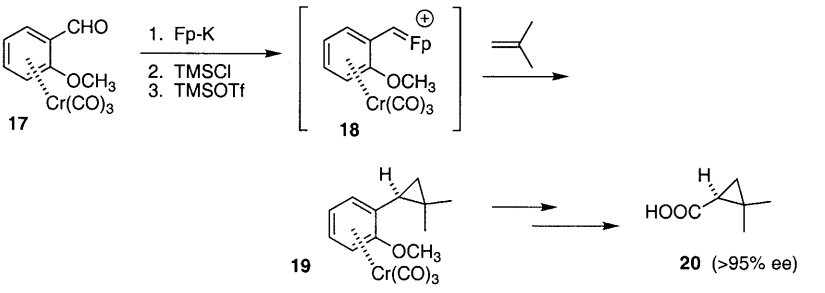
Scheme 3.

Cationic iron–carbene complexes, which are typically unstable but generated in situ, appear to be excellent reagents for cyclopropanation of unactivated alkenes (Scheme 4). These iron–carbene complexes can be generated via a variety of methods, including protonation of vinyliron species, alkylation of thioalkyliron species, or protonation or silylation of alkoxyiron (or hydroxyiron) species. The thiomethyliron complexes appear to be the most convenient starting materials for carbene transfer [21]. Some degree of asymmetric induction has been observed in the reaction of chiral-at-iron phosphine-substituted iron carbene complexes [22] and in iron carbene complexes featuring chiral auxiliaries [23]; this method has been used as the cornerstone for a recent synthesis of optically-pure cyclopropanecarboxylate derivatives (e.g. **20**, Scheme 5).

Other carbene complexes have been reported to undergo cyclopropanation reactions with alkenes. Reaction of alkenes with titanium alkylidenes followed by iodine leads to cyclopropanation products [24]. Iron-porphyrin-carbene complexes also effect the cyclopropanation of alkenes [25,26].



Scheme 4.

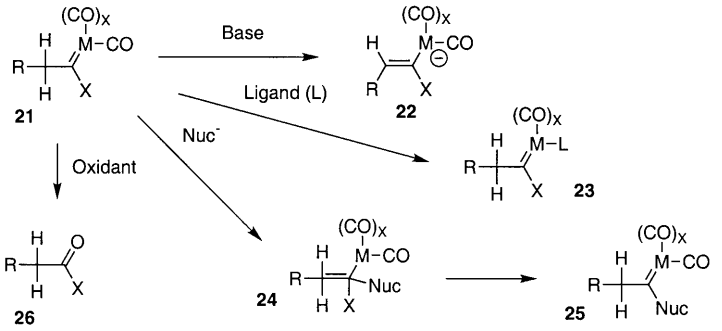


Scheme 5.

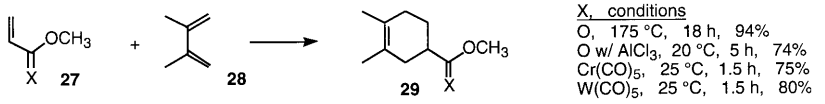
4. Fischer carbenes as ester surrogates

In many ways, the heteroatom-stabilized Fischer carbene complex can be regarded as an activated ester. The general reactivity profile for Fischer carbene complexes is depicted in Scheme 6. The Fischer carbene functionality is easily transformed to an ester using a variety of oxidants (**21** → **26**) [27,28]. Some reaction processes resemble esters, including deprotononation of the protons α to a carbene complex (**21** → **22**) ($pK_a \approx 12$ for complex **21**, R = alkyl, M = Cr, X = OMe [29]), and replacement of the alkoxy group by thiol and amino groups (**21** → **25**) [30,31]. Other reaction processes which do not resemble esters (e.g. ligand replacement, **21** → **23**) are the basis of additional reaction processes, and are discussed in depth in other sections of this review.

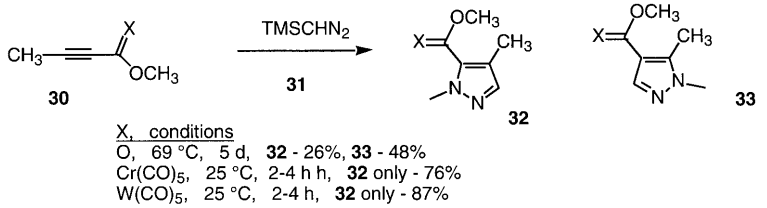
One of the major synthetic uses of carbene complexes is the Diels–Alder reaction of α,β-unsaturated carbene complexes and dienes [32] (Scheme 7). These complexes are extremely reactive dienophiles; their reactivity resembles that of α,β-unsaturated esters in the presence of Lewis acids, and offer superior regio- and stereoselectivity in reactions with unsymmetrical dienes. This reaction can also be conducted asymmetrically if a chiral auxiliary is present on the heteroatom substituent [33]. Successful oxidation of the carbene complex adducts to the corresponding esters or amides has been demonstrated in most examples. Other reactions reminiscent of α,β-unsaturated esters have also been reported, including 1,3-dipolar cycloadditions with diazo compounds (Scheme 8) [34,35], nitrones [36], and nitrile ylides [37], and Michael addition reactions [38], [2 + 2]-cycloadditions [39], and cyclopropanation [40]. In nearly all of these cases, numerous advantages relative to α,β-esters have been noted. In most of these cases, the reaction can be accomplished asymmetrically using a chiral heteroatom substituent [33].



Scheme 6.



Scheme 7.

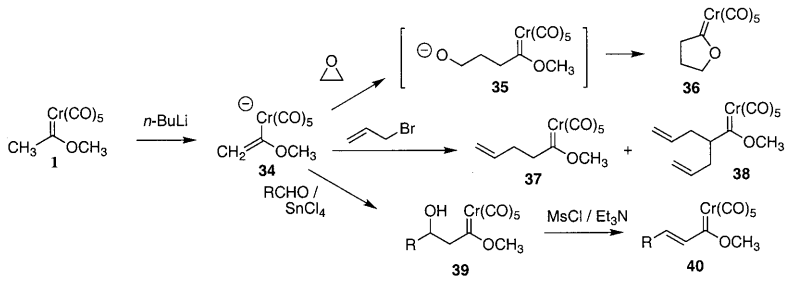


Scheme 8.

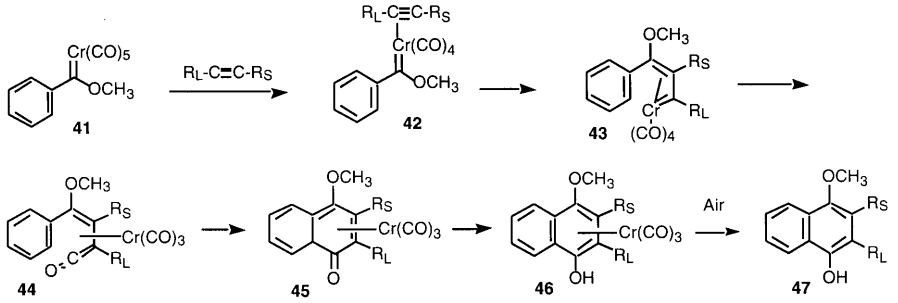
Imitation of other reaction processes of esters have also been demonstrated. The anion derived from carbene complexes (e.g. **34**, Scheme 9) is only weakly nucleophilic, however it does couple efficiently with epoxides (**34** → **36**) [41] or aldehydes (**34** → **39**, **40**) [42,43] in the presence of Lewis acids. Alkylation of the anion derived from Fischer carbene complexes is somewhat sluggish [44], however good yields of alkylation product have been reported for the coupling of phosphine-substituted carbene complexes with primary alkyl halides [44], and for the coupling of allylic, benzylic, and α-carbonyl halides with the pentacarbonyl derivatives (**34** → **37**, **38**) [45,46], however dialkylation is sometimes a problem in these reactions.

5. Coupling of carbene complexes with alkynes

The coupling of carbene complexes with alkynes has been a very important reaction in organic synthesis. The major reaction of interest in this section is the Dötz benzannulation reaction (Scheme 10) [47], which involves the coupling of an α,β-unsaturated carbene complex with an alkyne (the phenylcarbene complex depicted in Scheme 10 can be replaced by an alkenylcarbene complex). The normal product of this coupling is the *p*-methoxyphenol derivative. The generally accepted mechanism of the Dötz reaction is depicted in Scheme 10. The scope and limit of this reaction has been studied widely, and both inter- and intramolecular versions of this reaction have been reported for a diverse array of highly functionalized alkynes and carbene complexes.



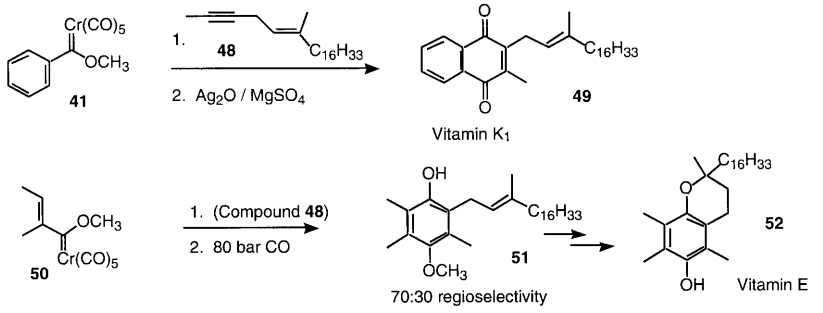
Scheme 9.



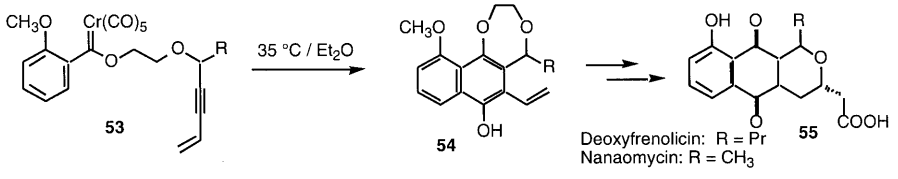
Scheme 10.

The Dötz reaction has been employed as a key step in the total synthesis of a variety of natural products, including vitamins E (**52**, Scheme 11) [48] and K_1 (**49**) [49], nanaomycin (**55**, Scheme 12), deoxyfrenolicin [50], angelicin, sphondin, thiosphondin (**59**, Scheme 13) [51], daunomycinone, 11-deoxydaunomycinone (**63**, Scheme 14) [52,53], khellin (**67**, Fig. 1) [54] and 7-ethoxyprecocene (**68**) [55].

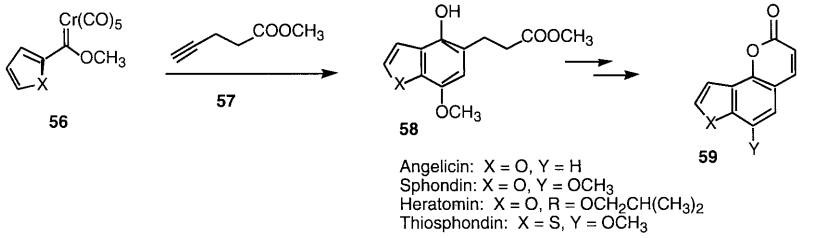
The Dötz benzannulation appears to be a general reaction process only for alkoxy-substituted chromium carbene complexes. Nitrogen analogs usually afford five-membered ring annulation products (e.g. **69**→**70**, Scheme 15) unless the nitrogen is acylated [56], however there are cases where benzannulation [57,58] and other ketene-derived products [59] are observed. Molybdenum- and tungsten carbene complexes also typically afford cyclopentannulation products (e.g. **71**→**72**, **73**)



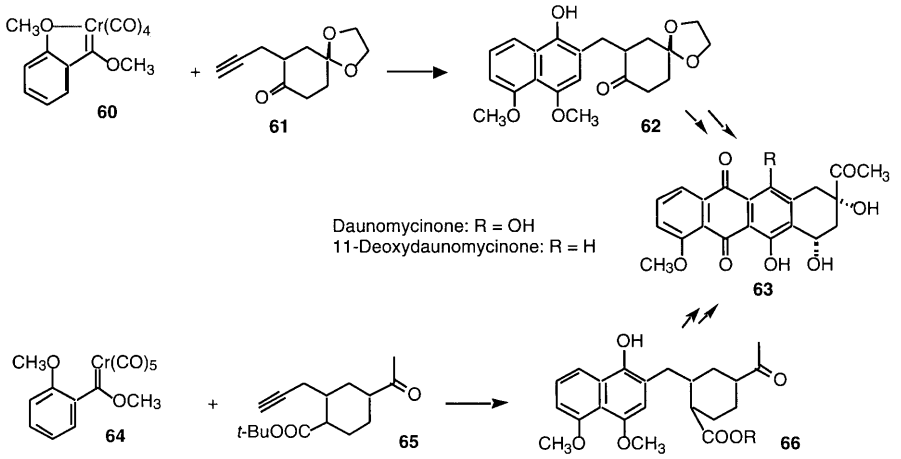
Scheme 11.



Scheme 12.



Scheme 13.



Scheme 14.

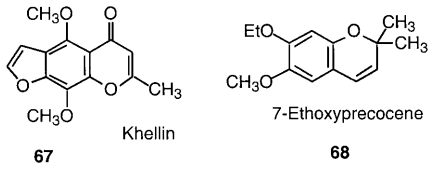
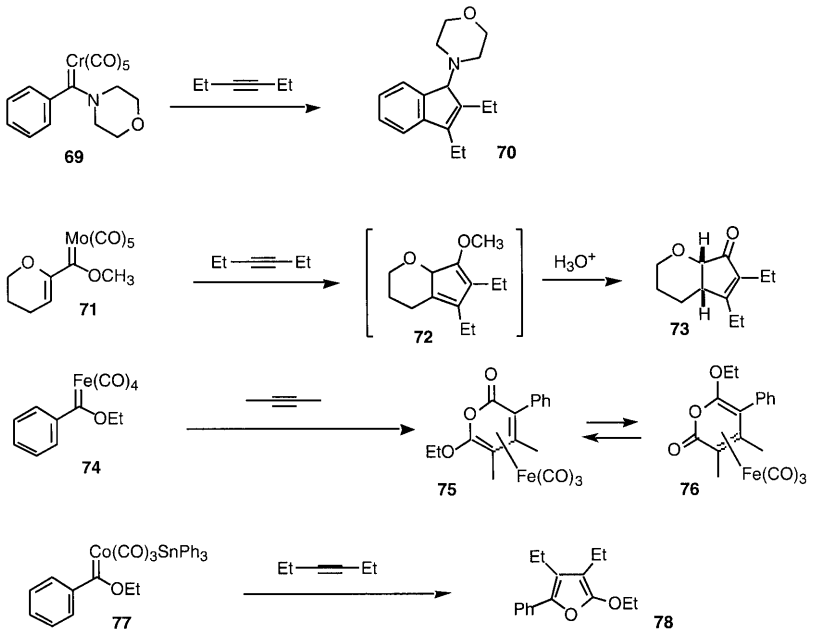


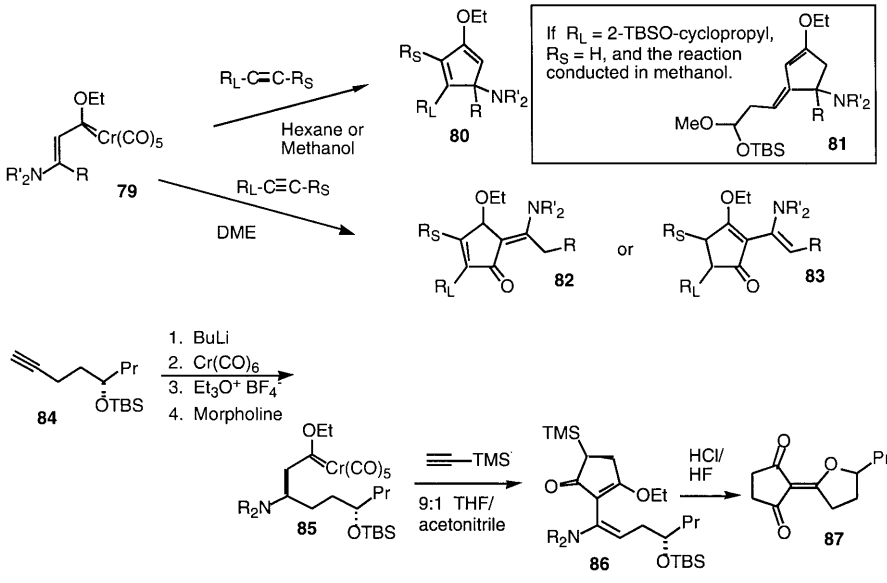
Fig. 1. Other compounds prepared using the Dötz reaction.

[60–62]. Iron carbene complexes afford pyrones (e.g. **74**→**75** or **76**) [63] or furans [64,65], while cobalt carbene complexes afford furans (e.g. **77**→**78**) [66].

A versatile synthesis of various classes of cyclopentanoid derivatives can be achieved through coupling of β-amino-α,β-unsaturated carbene complexes **79** (Scheme 16) and alkynes [67]. The starting carbene complexes are readily available from the addition of alkynyllithium reagents to chromium hexacarbonyl, followed by alkylation and amine addition. The two different reaction processes depicted in Scheme 16 are commonly observed in the coupling of complex **79** with alkynes, depending primarily upon the structure of the alkyne, the identity of R, and the



Scheme 15.

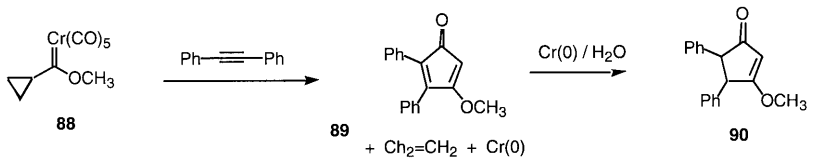


Scheme 16.

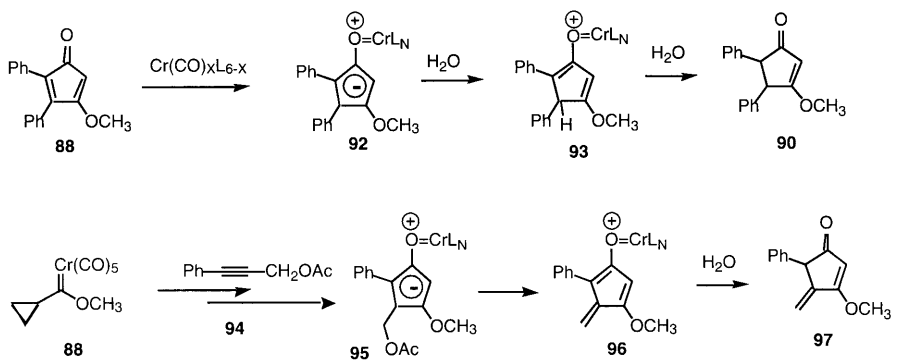
reaction conditions. The reaction affords predominantly aminocyclopentadiene derivatives **80** under two circumstances: (1) coupling with terminal alkynes; and (2) coupling with internal alkynes using either pyridine or acetonitrile as solvent [68,69]. The major products are 5-alkylidene-2-cyclopentenones (**82**) or 2-alkenyl-2-cyclopentenones (**83**) if **79** is coupled with either terminal or internal alkynes in ethereal solvents. This reaction process is the basis of a synthesis of the antihypertentisive oudenone **87** [70].

Coupling of alkylcarbene complexes and alkynes can lead to a variety of products, including cyclobutenones, cyclopentenones, furans, and dienes, and numerous products resulting from multiple alkyne incorporation. Only a few selective processes have been developed in these systems.

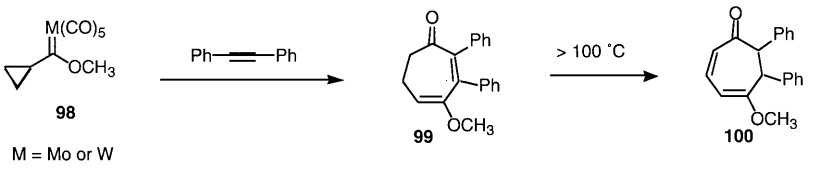
The coupling of alkynes with cyclopropylcarbene–chromium complexes affords cyclopentenone derivatives (e.g. **88** → **89** or **90**, Scheme 17); both intermolecular [71] and intramolecular [72] versions of this reaction have been demonstrated. The reaction produces a cyclopentadienone intermediate **89** through a complex mechanistic process, which is reduced by the chromium byproduct of the cycloaddition process. The reduction process involves cyclopentadienide intermediates (e.g. **92**, Scheme 18), which can be intercepted if the starting alkyne features leaving groups in the propargyl position, resulting in alkylidenecyclopentenone derivatives (**88** + **94** → **97**) [73]. The intramolecular reaction featuring chiral propargyl groups proceeds stereoselectively to afford five-membered rings with a high degree of stereocontrol [74]. This process has been used as cornerstone for the preparation of vitamin D synthetic intermediates. The coupling of alkynes with the molybdenum



Scheme 17.



Scheme 18.



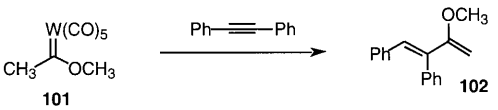
Scheme 19.

and tungsten analogs of complex **88** afford cycloheptadienone derivatives (Scheme 19) [75], however the scope of this reaction is highly limited.

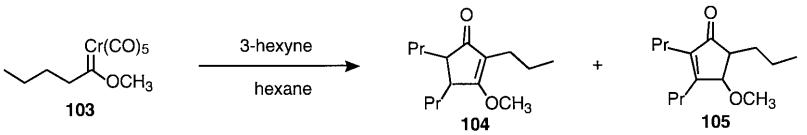
Other processes of alkylcarbene–metal complexes and alkynes lead to reliable reaction pathways, many of which will be discussed in Section 11. In certain cases, the reaction of carbene complexes and alkynes leads to diene derivatives (e.g. **101** → **102**, Scheme 20) by either H-shift [76,77] or silicon shift [78] processes. Reaction of alkylchromium–carbene complexes with alkynes affords cyclopentenones (e.g. **103** → **104**, **105**, Scheme 21) as the predominant products when the reaction was conducted in hexane solvent [79], accompanied by varying amounts of products derived from multiple alkyne insertions.

6. Conversion of carbene complexes to ketene and ketimine complexes

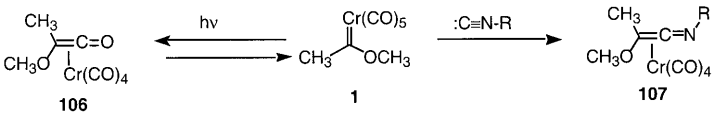
Photolyses of chromium carbene complexes generates ketene complexes (e.g. **1** → **106**, Scheme 22), and this has been the basis for the design of numerous



Scheme 20.



Scheme 21.

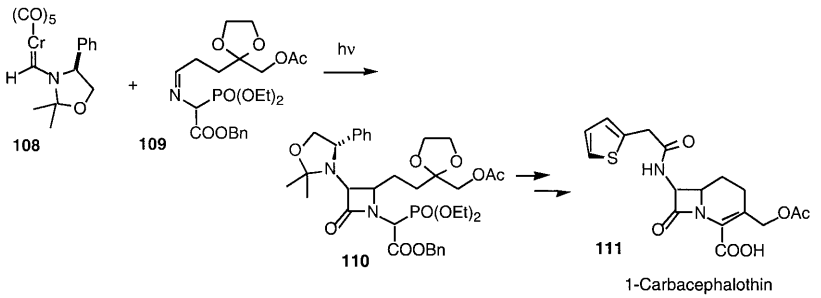


Scheme 22.

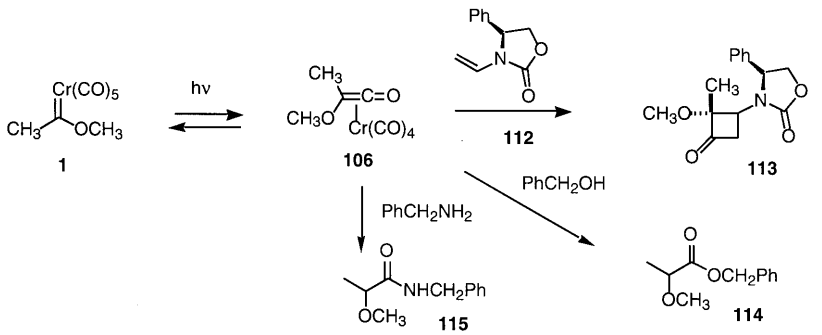
transformations [80]. The coupling of carbene complexes with isocyanides leads to the analogous ketimine complexes (e.g. **1** → **107**) [81]. The reaction of imines and chromium carbene complexes in the presence of light leads to β-lactam derivatives (e.g. **108** + **109** → **110**, Scheme 23), and this reaction has been used as the basis of the synthesis of biologically active β-lactam derivative 1-carbacephalothin (**111**) [82]. Photolysis in the presence of amines or alcohols affords the expected amine and ester derivatives (e.g. **1** → **114** or **115**, Scheme 24). Photolysis in the presence of alkenes affords cyclobutanone derivatives (**1** → **113**) [83]. Amino acid derivatives can be prepared through photolysis of aminocarbene complexes in the presence of alcohols [84]. The coupling of aminocarbene complexes with amines under these conditions provides access to oligopeptide derivatives [85].

7. Insertion reactions

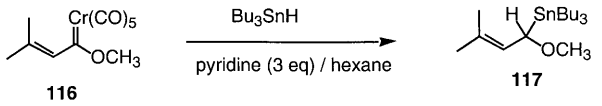
In some cases, the direct insertion of carbene complexes into σ-bonds can be a general process. The most well known example of this is the insertion into the H–ER_3 (E = Si, Ge, Sn) bond. Synthetically important allyl- and propargylmetal species are readily prepared using this method (e.g. **116** → **117**, Scheme 25) [86–88].



Scheme 23.



Scheme 24.



Scheme 25.

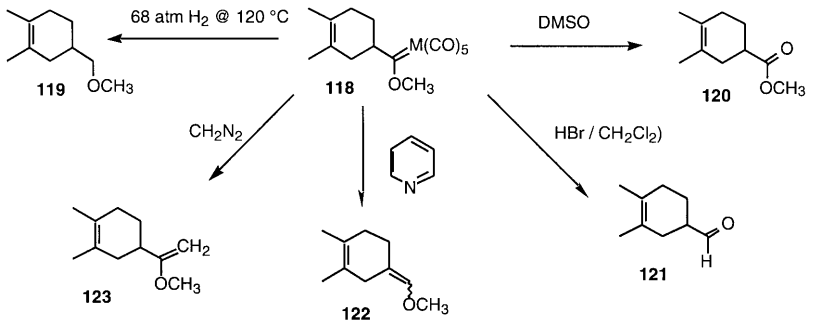
In special circumstances, electrophilic carbene complexes can undergo facile intramolecular C–H insertion reactions [89,90]. Fischer carbene complexes also undergo selective C–C bond insertion reactions with cyclobutenediones [91] and cyclopropenones [92].

8. Other transformations of the metal carbene functionality to nonorganometallic compounds

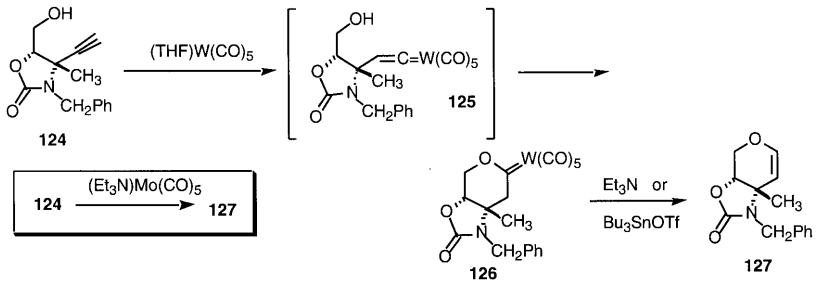
The metal carbene complex functionality is quite readily transformed into a variety of different functional groups (Scheme 26). As noted previously, carbene complexes are easily oxidized to the corresponding carbonyl group using a variety of oxidants (e.g. **118**→**120**) [27,28,32]. Other processes include conversion to enol ethers (e.g. **122**) [93] and reduction to alkoxyalkyl groups (e.g. **119**) [94]. The carbene complex functionality can also be olefinated by reaction with diazo compounds (e.g. **118**→**123**) [95] and a variety of ylide-type reagents [96,97], most notably stabilized sulfur ylides. Acetoxycarbene complexes decompose to enol acetate derivatives with a very high degree of selectivity for the *Z*-isomer [98]. Carbene complexes are also known to dimerize upon thermolysis [99,100].

9. Metal vinylidene complexes

Coupling of terminal alkynes with a variety of transition metal complexes leads to vinylidene-metal complexes (e.g. **124**→**125**, Scheme 27) [101]. In many cases, the



Scheme 26.



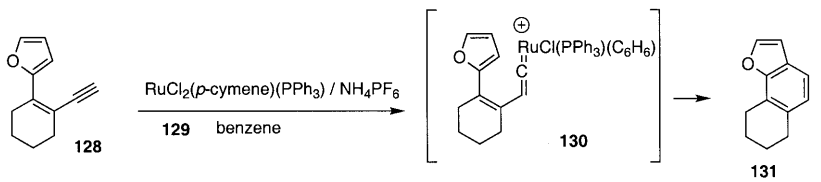
Scheme 27.

generation of metal vinylidene complexes followed by designed reaction processes is a highly useful process for organic synthesis. Reaction of sources of tungsten and chromium–pentacarbonyl with terminal alkynols results in cyclic carbene complexes which are subsequently transformed to cyclic enol ethers (e.g. **124** → **126** → **127**). In the case of molybdenum derivatives, the carbene complexes are not stable and result in the direct formation of the enol ether derivatives [102]. In many cases, the metal–vinylidene is a more suitable partner for an electrocyclic process, and enediynes [103,104] and dienynes (e.g. **128**, Scheme 28) [105] spontaneously rearrange to the six-membered ring systems upon conversion of the alkyne to a terminal vinylidene intermediate (e.g. **128** → **129**).

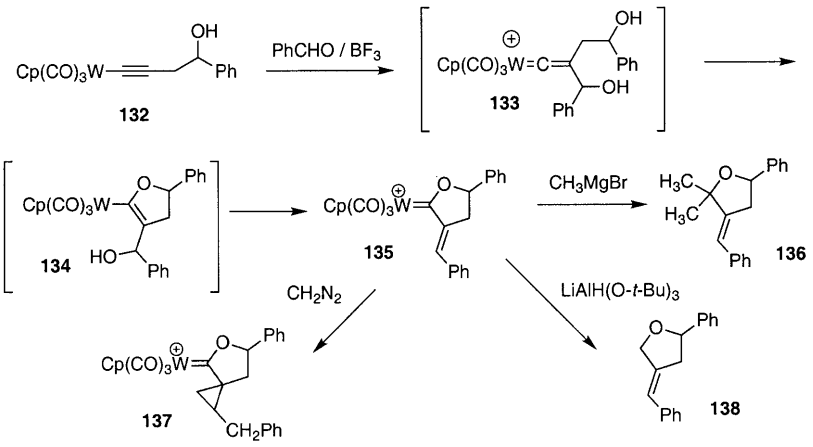
Metal–vinylidene complexes can also be generated from the coupling of alkynylmetal systems with electrophiles. Treatment of alkynyltungsten complexes (e.g. **132**, Scheme 29) with aldehydes and Lewis acids leads to cyclic carbene complexes which undergo a versatile array of demetallation processes [106]. Other synthetic routes to metal vinylidene complexes include treatment of alkoxycarbene complexes with strong electrophiles [107].

10. Carbonyl olefination processes/Schrock carbene complexes

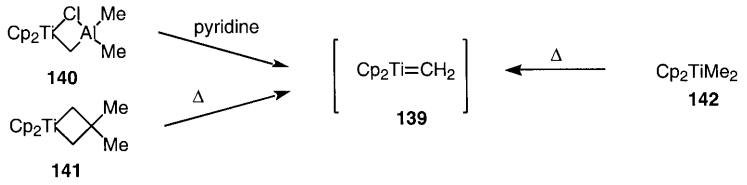
The major uses of Schrock carbene complexes in synthetic organic chemistry are as substitutes for phosphorus ylides in the Wittig reaction [108] and for olefin metathesis (see Section 12). Titanium methylene complexes (e.g. **139**, Scheme 30) are the most utilized class of reagents; titanium alkylidene **139** is generated in situ



Scheme 28.



Scheme 29.



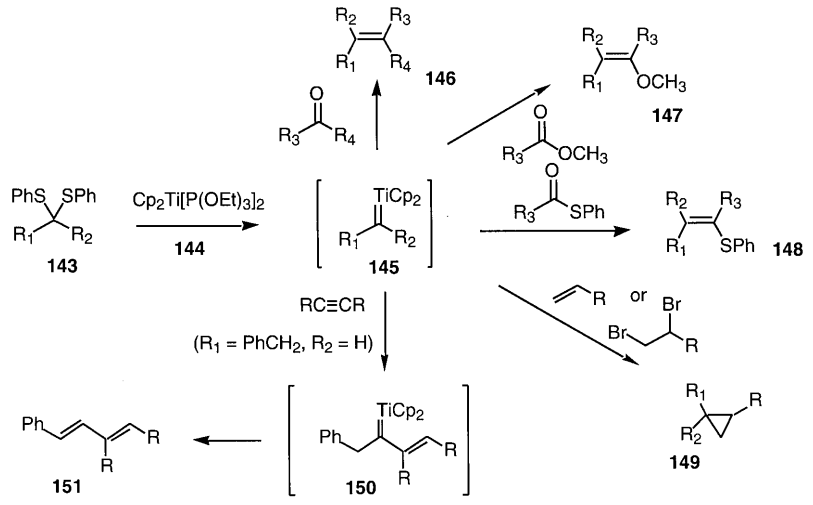
Scheme 30.

from the Tebbe reagent **140**, titanacyclobutanes **141** [109] or dialkyltitanium species **142** [110]. The dimethyltitanium systems are more conveniently generated, and this procedure has been extended to a variety of alkyl groups that have no β-hydrogens. A wide variety of alkyltitanium species can be generated from the reaction of thioacetals with titanium (II) species (Scheme 31) [111]. The Schrock carbene complexes offer several advantages over Wittig reagents, including: (1) the ability to olefinate esters and amides; (2) a tendency to avoid acid–base side reactions; and (3) less sensitivity to steric effects.

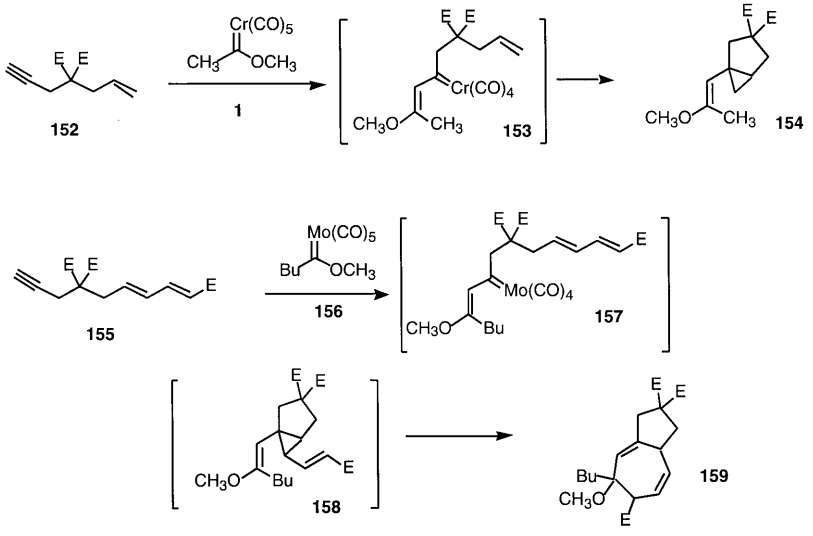
11. Tandem reaction processes

Numerous tandem reaction processes have been cleverly developed using carbene complexes. In most cases, the reactions presented are one-pot processes, however in some cases one carbene reaction generates a special synthetic route to another type of complex.

A number of investigators have designed serial reaction processes for the vinylcarbene intermediates obtained from the reaction of carbene complexes with alkynes [112]. The intermediate vinylcarbene complex (e.g. **153**, Scheme 32) can be



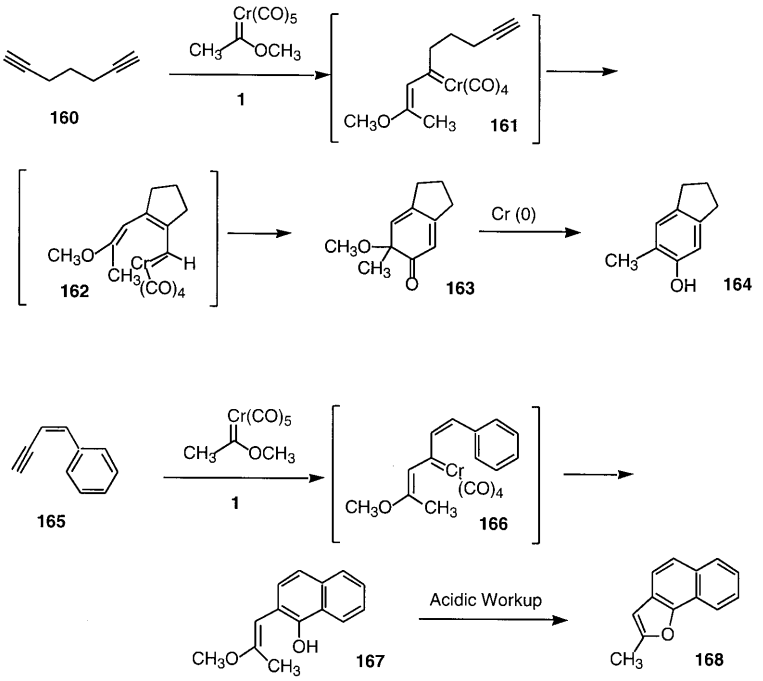
Scheme 31.



Scheme 32.

intercepted via intramolecular cyclopropanation reactions with pendant alkenes (i.e. **152** → **154**) [113–116]. The reaction of the dienyne **155** with a simple carbene complex affords the 5,7-fused ring system after intramolecular cyclopropanation followed by divinylcyclopropane rearrangement (**155** → **159**) [117].

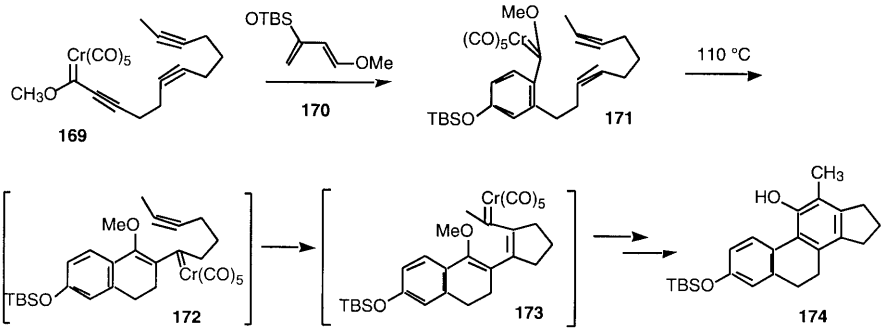
The intermediate vinylcarbene complex can also be intercepted by other alkynes to effect alternative strategies for benzannulation (Scheme 33). Thus the treatment of 1,6-heptadiyne with carbene complexes affords the benzannulation products (e.g.



Scheme 33.

163 or **164**) in high yield [118]; a secondary reduction process affords phenol derivative **164**. If the alkyne is conjugated with a functionalized alkene, the intermediate vinylcarbene complex can mimic other reaction processes such as the Dötz reaction (e.g. **165** + **1** → **168**) or the cyclopentannulation reaction mentioned previously in Scheme 17 [119,120].

Vinylcarbene complexes are also produced by the Diels–Alder reaction with alkynylcarbene complexes. The Diels–Alder reaction of carbene complex **169** (Scheme 34) and diene **170** affords arylcarbene complex **171**, which undergoes an

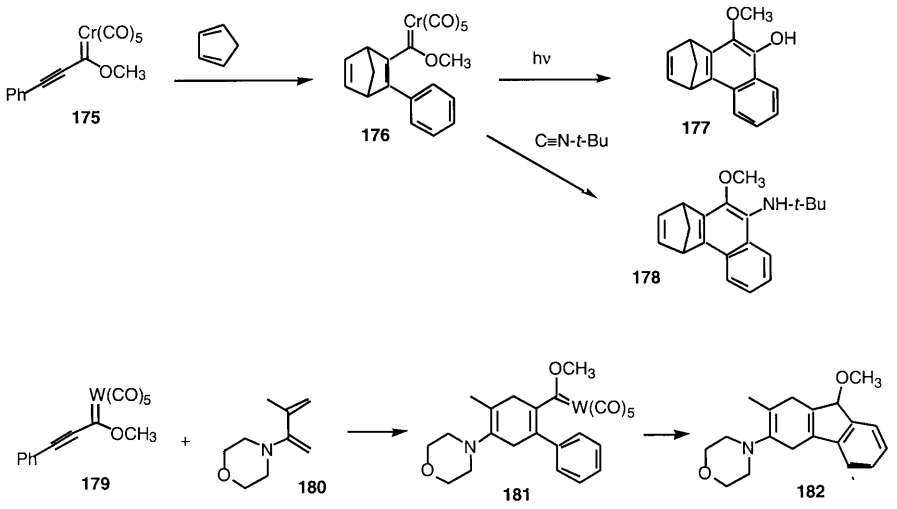


Scheme 34.

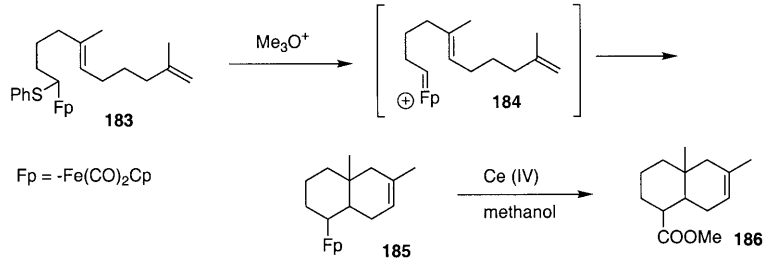
intramolecular two-alkyne coupling to afford the steroid derivative **174** [121]. The Diels–Alder reaction of arylalkynylcarbene complexes followed by photolysis generates the same ketene intermediate as the Dötz reaction, which ultimately affords the benzannulation product (e.g. **176** → **177**, Scheme 35) [122]. Simple treatment of the Diels–Alder adducts with isonitriles affords the aminated aromatic rings (e.g. **176** → **178**) [123]. Mild thermolysis of these adducts affords cyclopentannulated products (e.g. **181** → **182**) [124].

Cation-olefin cascade cyclization processes can be initiated by the generation of iron–carbene complexes in polyene systems (Scheme 36) [125]. In the reaction process depicted, the iron–carbene complex functions as a carbocation equivalent.

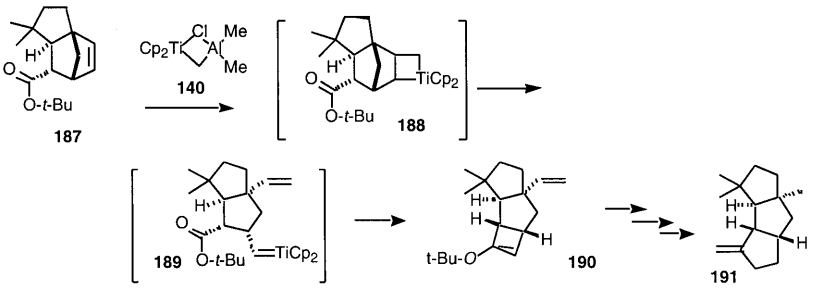
Tandem reaction processes have also been designed for Schrock carbene complexes. Treatment of norbornene derivatives (e.g. **187**, Scheme 37) functionalized by hindered esters proceeds via [2 + 2]-cycloaddition between the alkene and titanium alkylidene complex, followed by ring opening and carbonyl olefination, ultimately



Scheme 35.



Scheme 36.



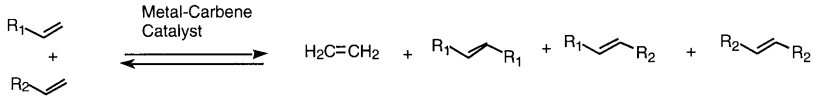
Scheme 37.

affording cyclobutene derivative **190** [126]. This reaction process was used as the cornerstone for a total synthesis of capnellene (**191**).

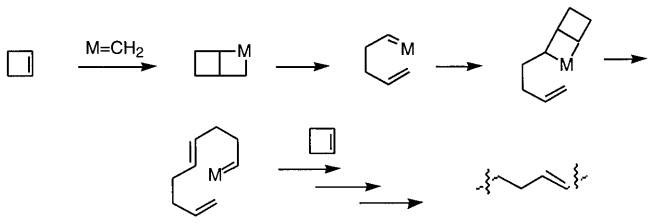
12. Olefin metathesis

The basic equation for the olefin metathesis reaction is displayed below in Scheme 38. Historically, the most utilized aspect of olefin metathesis is the ring opening metathesis polymerization (ROMP) of strained cycloalkenes, depicted in Scheme 39 for cyclobutene. Until recently, olefin metathesis reactions were sparsely utilized in organic synthesis. This review will highlight reactions that do not result in the formation of polymers. The primary problems associated with use of olefin metathesis for complex molecule synthesis are: (1) the difficulty controlling the equilibrium; and (2) the lack of functional group compatibility of most olefin metathesis catalyst systems.

Most of the successful developments in olefin metathesis for organic synthesis have occurred in the last decade of the millennium [127], primarily due the



Scheme 38.



Scheme 39.

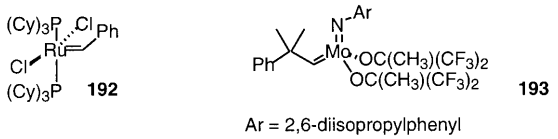


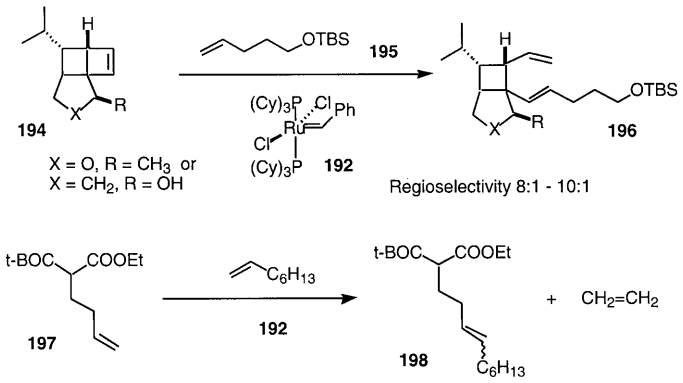
Fig. 2. Functional group tolerant olefin metathesis catalysts.

discovery of well-defined ruthenium- (**192**, Fig. 2, 'Grubbs catalyst') and molybdenum (**193**, 'Schrock catalyst') catalysts which tolerate a variety of functional groups. Prior to that, reports of olefin metathesis for the selective preparation of nonpolymeric organic compounds were very limited.

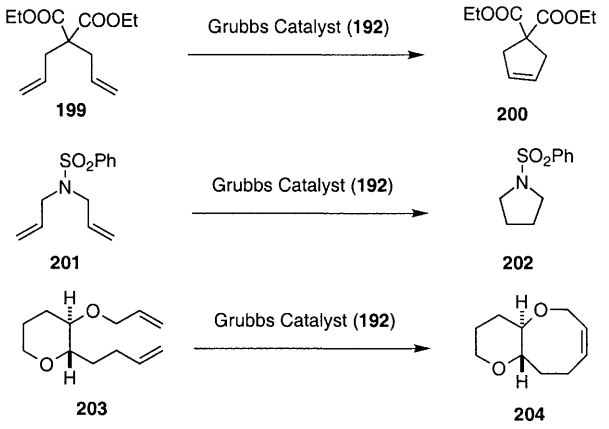
Several examples of the selective preparation of alkenes using cross metathesis of alkenes have been reported [128]. Most of the high-yielding examples feature strained (e.g. **194** → **196**, Scheme 40) [129] or monosubstituted (e.g. **192** → **198**) [130] alkenes coupling with another alkene used in excess. A notable problem in these reactions is that metathesis is an equilibrium-controlled process, thus homocoupling is competitive with heterocoupling. The reactions are selective for one or more of the following reasons: (1) one partner is used in excess; (2) one alkene is strained; or (3) a volatile byproduct is produced. An additional usage of cross metathesis is for the preparation of combinatorial libraries through the total equilibration of mixtures [131,132].

Ring-closing metathesis (RCM) (Scheme 41) has emerged as a very important method for the construction of cyclic compounds; some general reaction equations are depicted in Scheme 41 [133]. Virtually every ring size greater than four has been synthesized using this reaction. The reaction is generally successful for the synthesis of five-, six-, and seven membered ring systems, however larger rings have been synthesized when conformational effects are favorable or under high-dilution conditions.

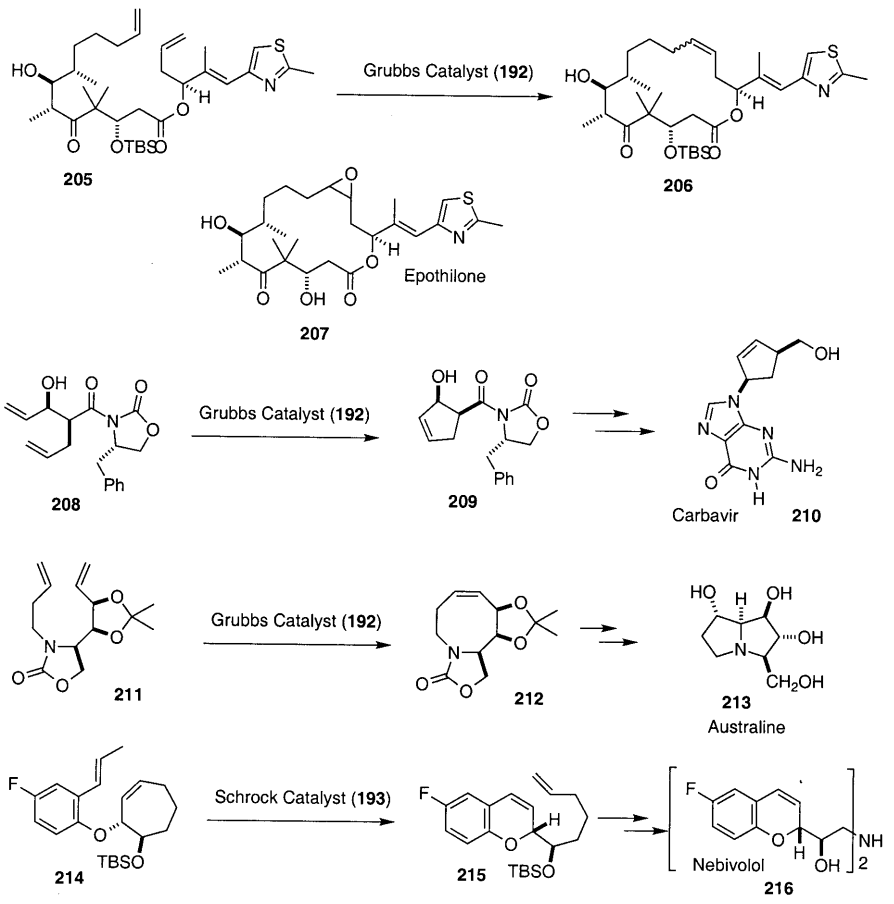
Notable synthetic targets which have utilized alkene metathesis as a key step include: epothilone A (**207**, Scheme 42) [134], carbocyclic nucleosides (e.g. carbavir



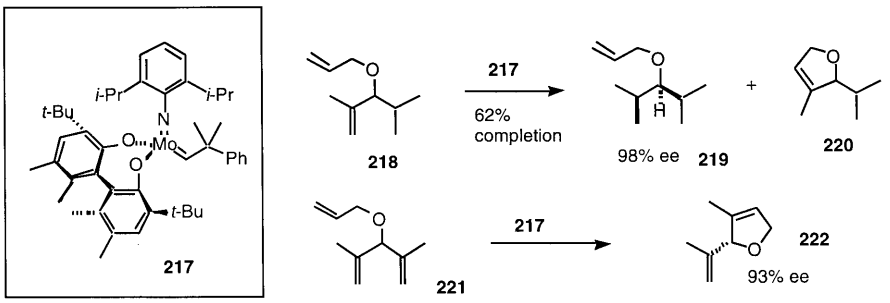
Scheme 40.



Scheme 41.



Scheme 42.



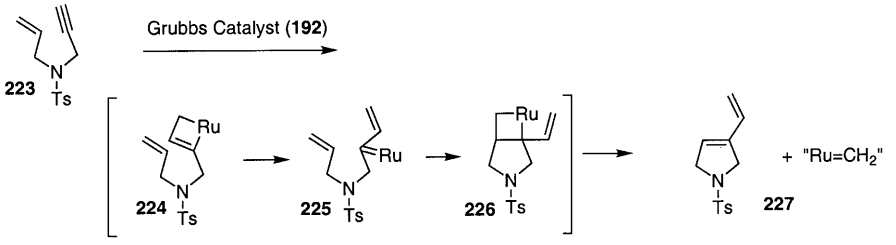
Scheme 43.

(**210**)) [135], australine (**213**) [136], and nebivololol (**216**) [137]. Ring-closing metathesis has been a key step in synthetic approaches to a variety of biologically-important carbon-skeletons, including the macrocyclic ring of roseophilin [138], the medium-size heterocylcic rings of brevitoxin and ciguatoxin [139], the ring closure step for cyclic peptide derivatives [140], geissoschizine [141] and aspidosperma alkaloids [142]. Ring closing metathesis has also been used for the synthesis of trefoil knot compounds [143] and catenanes [144].

Asymmetric versions of the RCM reaction have also been developed (Scheme 43). Kinetic resolution processes can be effected using homochiral catalyst **217** and a diene featuring a chiral ether **218** [145,146]. A compound featuring enantiotopic alkene groups **221** undergoes the RCM reaction with a high degree of enantioselectivity using chiral catalyst **217** [147]. Other catalysts have also been tested in the asymmetric RCM reaction [148].

Metathesis reactions involving alkyne components have also been reported [149]. An example of enyne metathesis is depicted in Scheme 44 [150]. The range of ring sizes prepared using this reaction process rivals that of the RCM reaction.

In summary, carbene complexes have emerged as powerful reagents for synthetic organic chemistry, and have served as the cornerstone for the synthesis of a variety of biologically important molecules. The area remains a very active area of investigation, and the design of new reaction processes using carbene complexes as



Scheme 44.

well as applications in the synthesis of important natural and unnatural compounds continues to be an important area.

Acknowledgements

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