Synthesis of Heterocycles via Group VI Fischer Carbene Complexes

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1. Introduction

Since the discovery of the pentacarbonyl[methoxybenzylidene]tungsten(0) complex by Fischer and Maasböl[1] in 1964, a rich chemistry of transition metal carbene complexes has evolved. Most of this work has dealt with heteroatom-stabilized carbene complexes, particularly with group 6 alkoxy and amino carbene complexes. Although two relevant reactions, namely cyclopropanation and Dötz benzannulation reactions, were thoroughly studied in the beginning, a plethora of novel stoichiometric carbon−carbon coupling and carbocyclization processes have been nicely delineated in the past two decades. Accordingly, this chemistry has been the subject of a number of reviews and accounts.[2] It came to us that no specific reports focused on the utility of these organometal reagents in the synthesis of heterocyclic compounds have actually been released. Therefore, the purpose of this review is to call the attention of people involved in organic synthesis mediated or catalyzed by organometallic reagents to the potential of Fischer-type carbene complexes for accessing different types of heterocycles. The report will be centered basically on synthetic processes wherein either a carbon−heteroatom bond is formed or a heteroatom functionality is directly involved, though examples of intramolecular reactions involving substrates with the heteroatom in a tether chain are also displayed.

The general structure of the metal carbene complexes that are reviewed is shown in Figure 1. In most cases R applies for alkyl, aryl, or heteroaryl, X for OR or NR_2, and M for Cr, Mo, W (structure A) or Cr, W (structures B and C). Among them, pentacarbonyl[alkenyl(methoxy)carbene]chromium(0) and tungsten(0) complexes (type B, M = Cr, W; X = OMe) have certainly become the most powerful systems, at least in terms of reactivity.

This report is divided into four main parts according to the specific ring heteroatom. Therefore, the first and largest part (section 2) compiles different ways to produce nitrogen heterocycles starting from either nitrogen-containing carbene complexes or nitrogen-containing organic substrates. In the following part (section 3), some methodologies leading to oxygen heterocycles are shown; in these cases, special emphasis will be put on those where at least one carbonyl ligand participates in the process and is incorporated in the final heterocyclic framework. Finally, a few examples illustrate the synthesis of phosphorus-containing heterocycles (section 4), and isolated examples are given of heterocycles with two different heteroatoms, such as oxygen−nitrogen or oxygen−phosphorus heterocycles (section 5).

2. Synthesis of Nitrogen Heterocycles

This part is divided into two sections according to the role of the metal carbene functionality in the formation of the ring system (Figure 2). The heterocyclization reactions wherein the carbene carbon of an α,β-unsaturated carbene complex is not directly involved, but the C_α- and C_β-carbon atoms participate, are covered first (section 2.1). Methods for the formation of nitrogen heterocycles based on the particular reactivity of the carbene carbon are collected in section 2.2.

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José Barluenga studied chemistry at the University of Zaragoza and received his doctorate in 1966. He spent three and a half years as a postdoctoral research fellow of the Max Planck Gesellschaft at the Max Planck Institut für Kohlenforschung (Mülheim a.d. Ruhr, Germany) in the group of Professor H. Hoberg. In 1970, he become Research Associate at the University of Zaragoza, where he was promoted to Associate Professor in 1972. In 1975, he moved to the University of Oviedo as Professor in Organic Chemistry, where he is currently Director of the Instituto Universitario de Química Organometálica "Enrique Moles". His major research interest is focused on developing new synthetic methodologies in organic chemistry by means of organometallic reagents as well as iodine-based systems.

Javier Santamaría was born in Villaviciosa (Asturias, Spain). He received his B.S. degree (1992) and his Ph.D. (1997) from the University of Oviedo. He spent a two-year postdoctoral stay (1997–1999) at the Skaggs Institute for Chemical Biology at the Scripps Research Institute (La Jolla, CA) with Professor Julius Rebek, Jr., working on supramolecular chemistry. He then returned to the University of Oviedo, where he was appointed as Profesor Asociado in 2000. Currently, he is involved in selective solution- and solid-phase syntheses of carbocycles and heterocycles promoted by transition metal carbene complexes.

Miguel Tomás received his B.A. degree in chemistry from the University of Zaragoza in 1974 and his Ph.D. degree from the University of Oviedo in 1979. He was a postdoctoral fellow (1981–1983) in the research group of Professor A. Padwa at Emory University (Atlanta, GA), working on 1,3-dipolar cycloadditions. He then returned to the University of Oviedo, where he was appointed Profesor Titular in 1985 and promoted to Professor of Organic Chemistry in 1996. His major research encompasses the use of transition metal reagents, particularly metal carbene complexes, as flexible intermediates in organic synthesis and the design of new metal-catalyzed processes.

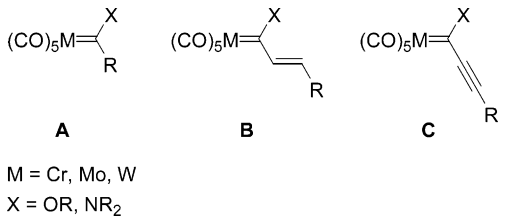


Figure 1.

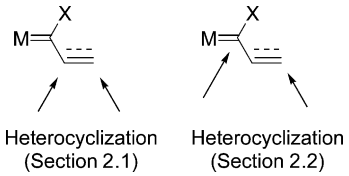


Figure 2.

2.1. Heterocyclizations Involving the C–C π-Bond of Unsaturated Carbene Complexes

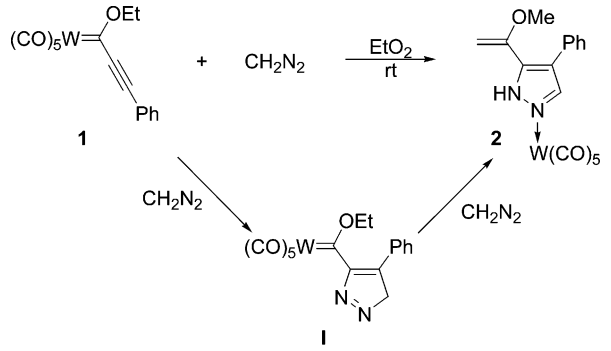
2.1.1. Five-Membered Heterocycles

The pentacarbonylmetal fragment is a powerful electron-withdrawing group that makes the conjugated π-system highly electron-poor. An additional point of real interest relies on the fact that, after the appropriate reaction takes place, the reaction product still contains the metal carbene functionality suitable for consecutive processes. In this general context, the Michael-type addition of carbo- and heteronucleophiles has been extensively studied. Moreover, there have been shown many examples of [4+2] cycloadditions between classical carbodienes and alkenyl or alkynyl carbene complexes of group 6. In contrast, there are much fewer reports on 1,3-dipolar cyclaodditions involving α,β-unsaturated carbene complexes as dipolarophiles.[21] In this sense, diazomethane derivatives, nitrilimines, and nitrones have successfully been employed as dipoles toward unsaturated carbene complexes. The cycloaddition reactions of diazomethane and nitrilimine dipoles leading to nitrogen heterocycles are covered in this section, while the analogous cycloaddition with nitrones leading to heterocycles containing nitrogen and oxygen is studied in section 5.

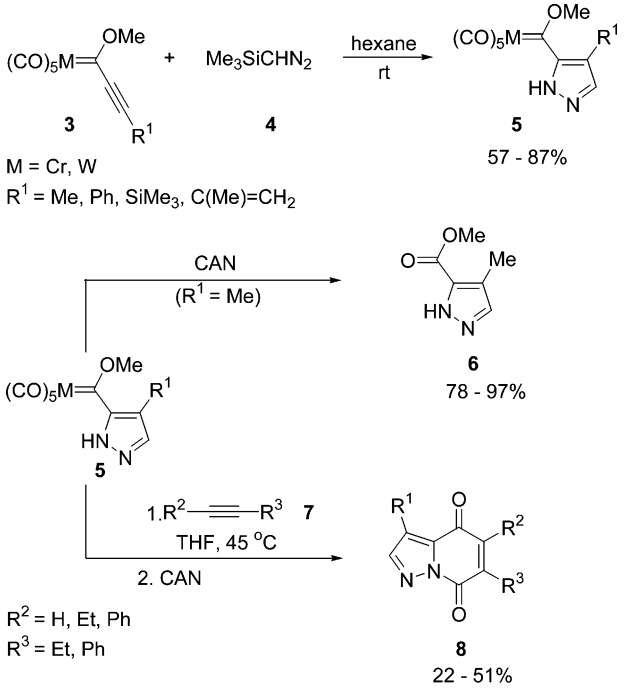
As early as 1973, Fischer published the cycloaddition of the tungsten phenylethynyl(ethoxy)carbene complex **1** to diazomethane, leading to the substituted pyrazole **2** (Scheme 1).[3] This two-step process very likely involves the 1,3-dipolar cycloaddition of **1** to diazomethane to produce the intermediate **I** (not isolated), which then goes to the observed pyrazole by metathesis of the carbene functionality with a second equivalent of diazomethane.

Thirteen years later, Chan and Wulff carried out a more detailed study of this reaction (Scheme 2).[4]

Scheme 1



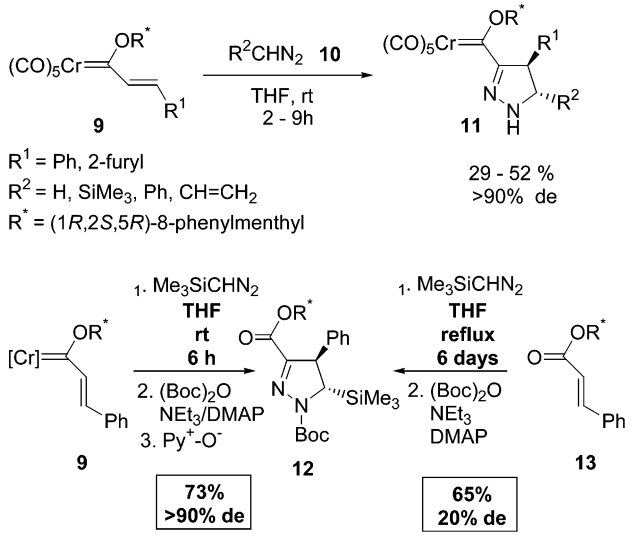
Scheme 2



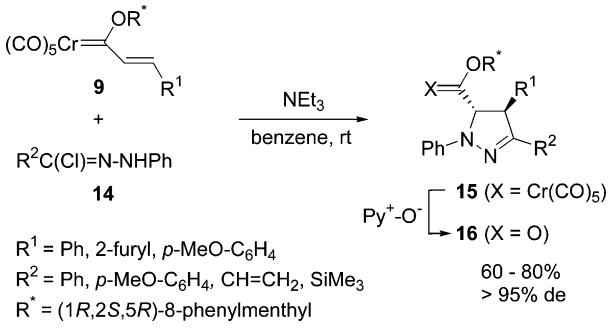
Thus, alkynylcarbene complexes **3** cycloadd to trimethylsilyldiazomethane **4** at room temperature to generate the pyrazole complexes **5** with high yields and complete regioselectivity. The metal carbene group (M = Cr, W) can be efficiently oxidized with cerium ammonium nitrate (CAN) to the pyrazole ester **6**. In addition, the new alkenylcarbene complexes **5** undergo the benzannulation reaction with alkynes **7** to give fused pyrazoles **8** in moderate yields. Interestingly, the conjugated carbon−nitrogen double bond of the tautomer of **5**, rather than the carbon−carbon double bond, takes part in the annulation reaction.

Some years later, Maiorana et al. demonstrated that alkenyl(alkoxy)carbene chromium complexes also effect the 1,3-dipolar cycloaddition with diazomethane and trimethylsilyldiazomethane, giving pyrazoline derivatives.[5] Because of our interest in the chemistry of Fischer carbene complexes, particularly in their potential for effecting enantioselective transformations,[6] we focused our attention on the dipolar cycloaddition reaction (Scheme 3).[7] Thus, chromium carbene complexes derived from (−)-8-phenylmenthol **9** were treated with various diazo derivatives **10** at room temperature to afford new pyrazolylcarbene

Scheme 3



Scheme 4



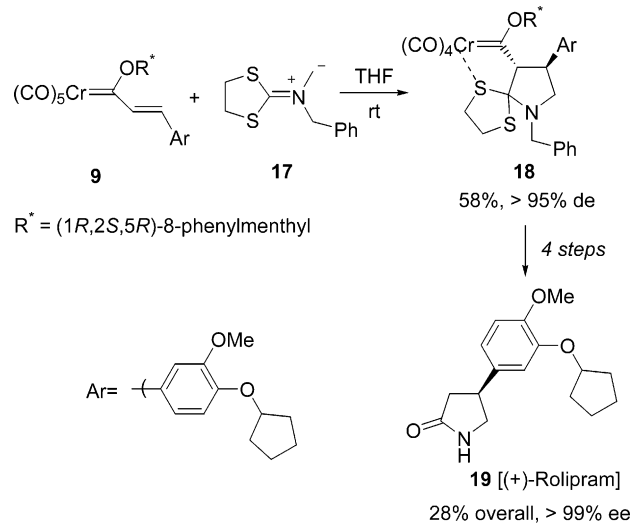
complexes **11** in acceptable yields and with very high diastereoselectivity. The dipolar cycloaddition methodology to prepare pyrazolines **12** using metal alkenylcarbenes **9** or alkenyl esters **13** is compared and the results are outlined in the scheme. Although the synthesis of pyrazolines **12** from complexes **9** requires one step more than that from esters **13** (pyridine oxide oxidation of metal carbene to carbonyl), the efficiency in terms of chemical yield, reactivity, and diastereoselectivity doubtless is much higher in the former case.

In a similar way, a number of nitrilimines, formed from chlorohydrazones **14** and NEt_3, smoothly reacted with chromium carbene complexes **9** to form the *N*-phenylpyrazoline complexes **15**, which were further oxidized with pyridine oxide to metal-free pyrazolines **16** (Scheme 4). The overall yields were high, and the diastereoselectivity was excellent.[8]

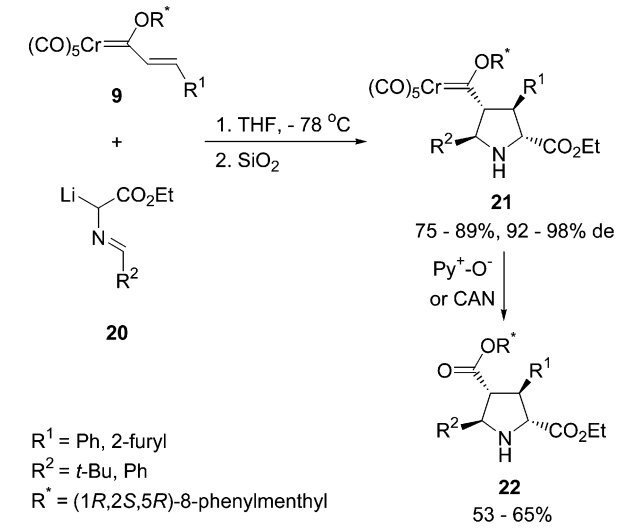
On the basis of this strategy, a short, high-yielding, and diastereoselective synthesis of the anti-inflammatory and antidepressant drug (+)-rolipram has been recently executed (Scheme 5).[9] The key step consisted of the dipolar cycloaddition of enantiopure chromium carbene complex **9** with imine ylide dipole **17** to provide the pyrazoline complex **18** with complete face selectivity. This adduct was readily converted into rolipram **19** as the sole enantiomer, the overall yield being 28%.

The pyrrolidine ring can also be constructed by reaction of carbene complexes **9** with the lithium salt of various glycine imines **20** (Scheme 6).[10] This

Scheme 5



Scheme 6



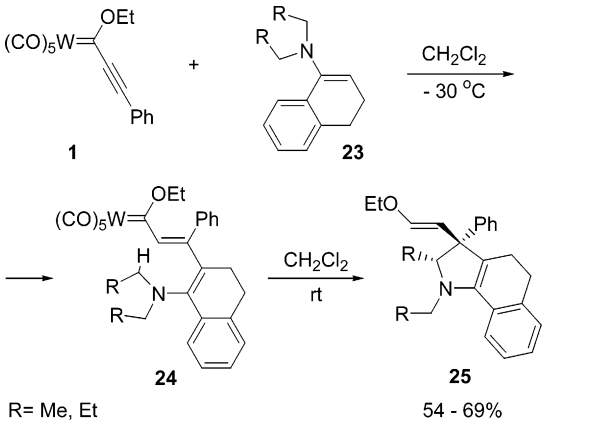
protocol involves the conjugated addition of the iminoenolate **20** to carbene **9**, followed by ring closure to furnish pyrrolidine complexes **21** in up to 89% yield. The formation of **21** takes place with complete regioselectivity, and the four stereogenic centers are created with nearly total diastereoselectivity. The oxidative demetalation of the complex **21** to the ester **22** requires treatment with either pyridine oxide or CAN.

In a totally different approach, Aumann has reported the formation of the pyrroline ring **25** from the tungsten alkynylcarbene **1** and enamines **23** (Scheme 7).[11] The reaction can be regarded as a [4+1] cyclization ($C_\beta-C_\alpha-N-C_{\alpha'}$ of the enamine + C_β of the carbene ligand) initiated by a Michael-type addition to generate the adduct **24**. At this point the authors invoke an intramolecular C_α−hydride addition followed by ring-closing to explain the formation of **25**.

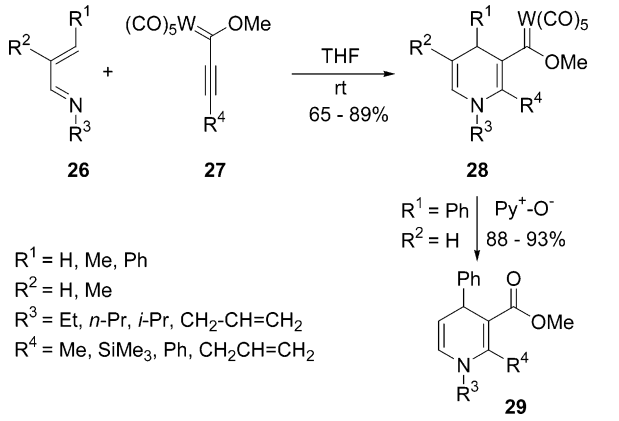
2.1.2. Six-Membered Heterocycles

The [4+2] heterocyclization reaction of metal carbenes represents a facile access to six-membered nitrogen heterocycles. Thus, 1-aza-1,3-dienes **26** smoothly cycloadd to tungsten alkynylcarbenes **27**,

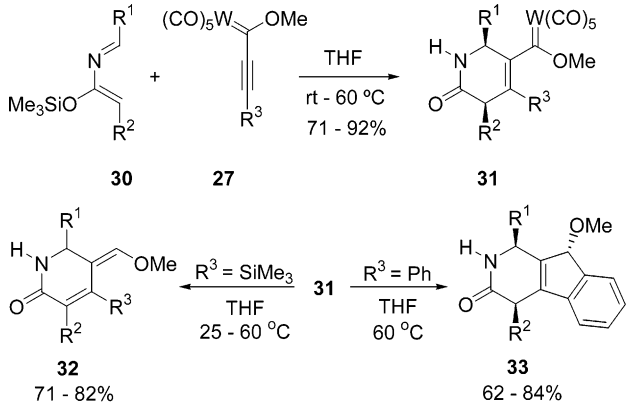
Scheme 7



Scheme 8



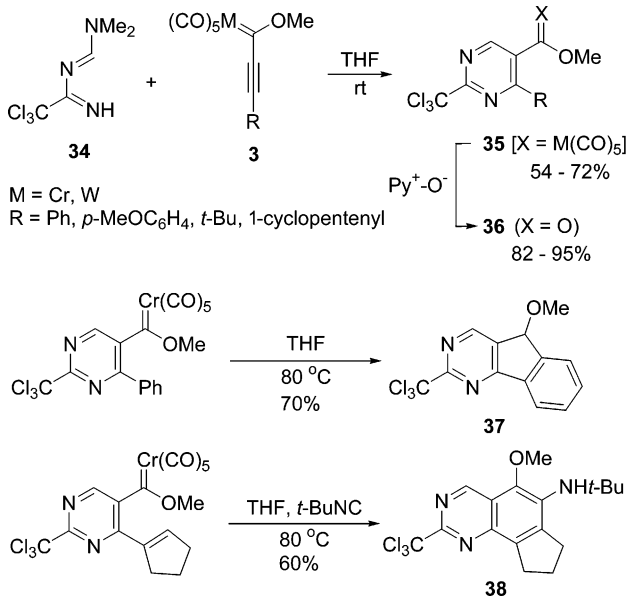
Scheme 9



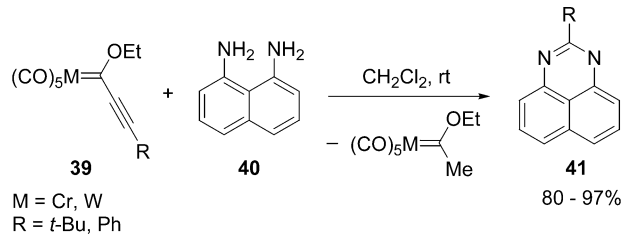
providing 1,4-dihydropyridine complexes **28** in high yields (Scheme 8). Representative examples for the oxidation of **28** to the corresponding esters **29** using pyridine oxide were also reported.[12]

In a similar way, the well-known heterodienes 3-trimethylsiloxy-2-azadienes **30** are easily converted into the dihydropyridone skeleton (Scheme 9).[13] Thus, the cycloaddition of alkynyl carbenes **27** and 2-azadienes **30** occurs at room temperature (for R^1 = 2-furyl) or at 60 °C (for $R^1 \neq$ 2-furyl) to yield the pyridone complexes **31**, which can be isolated in the case of $R^1 = t$-Bu and allowed to thermally transform into metal-free heterocycles **32** and **33**. Pyridones **32** result from [1,5]-H shift/reductive metal elimination of **31** (for $R^3 = SiMe_3$), while a metallaelectrocyclic

Scheme 10



Scheme 11



ring closure/reductive metal elimination of **31** (for R^3 = Ph) accounts well for the formation of 2-azafluorenones **33**.

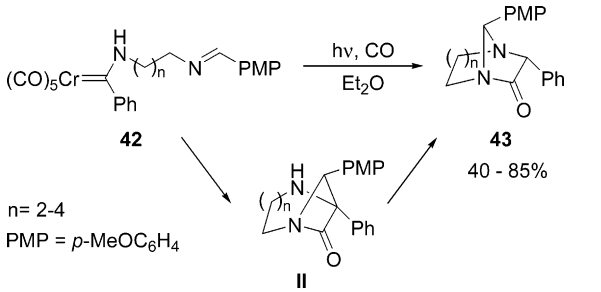
The [4+2] heterocycloaddition strategy has also been applied for the synthesis of the pyrimidine ring (Scheme 10).[14] Thus, the treatment of complexes **3** with diazadienes of the type **34** results in the formation of pyrimidine carbene complexes **35**, which in turn are oxidized to the pyrimidine esters **36**. The chromium carbene adducts can be thermally transformed into the polyheterocycle **37** (see the formation of **33**, Scheme 9) or elaborated into **38** by heating in the presence of *tert*-butylisocyanide via ketenimine formation followed by electrocyclic ring closure.

Substituted perimidines **41** are obtained in high yields by room-temperature reaction of alkynylcarbenes **39** with the proton sponge 1,8-diaminonaphthalene **40** (Scheme 11).[15] This transformation is explained in terms of an initial double conjugate addition which is probably followed by a retroaldol-type reaction. Actually, the major interest of this process concerns the unexpectedly facile fragmentation of the carbon−carbon π-bond of the alkynylcarbene complex.

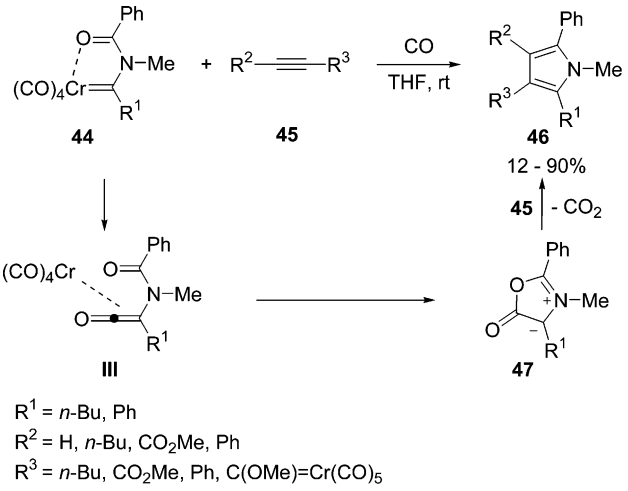
2.2. Heterocyclizations Involving the Metal–Carbon Double Bond

This section covers the most important and versatile methods for the synthesis of nitrogen heterocycles by means of Fischer carbene complexes. Moreover, all of the examples that follow are based on the particular and varied reactivity of the metal carbene functionality. This section is divided into two subsections in order to separate the heterocyclizations wherein the nitrogen appears initially installed either in the carbene ligand of the metal complex (subsection 2.2.1) or in the organic substrate (subsection 2.2.2). An early interesting revision showing the potential of Fischer carbene complexes for the synthesis of four- and five-membered heterocycles via ketenimine complexes was reported by Aumann.[2c]

Scheme 12



Scheme 13



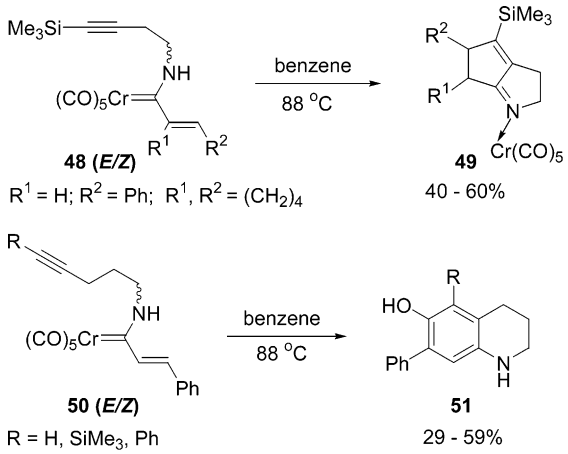
2.2.1. From Nitrogen-Containing Carbene Complexes

Three basic strategies that employ amino-, imino-, and β-amino/β-imino-carbene complexes as the source of the nitrogen reactant are shown.

2.2.1.1. From Aminocarbene Complexes. The ability of chromium aminocarbene complexes to undergo carbonyl insertion under photochemical reaction conditions is well documented.[2k,16] On the basis of this process, Sierra et al. studied the photochemical reaction of chromium complexes having a suitably placed *p*-methoxyphenylimine tether (Scheme 12).[17] In this case, the irradiation of complexes **42** under CO pressure does not permit isolation of the expected bicyclic β-lactams **II** via CO insertion/[2+2] cycloaddition (see section 3.1, Scheme 55), but bicyclic "anti-Bredt" γ-lactams **43**, very likely derived therefrom, were obtained in moderate to good yields.

Recently, Merlic has observed that acylaminocarbene complexes of chromium suffer non-photochemical insertion of carbon monoxide at room temperature, a fact that is the basis for a new synthesis of substituted pyrroles (Scheme 13).[18] Thus, benzoylaminocarbene complexes **44** react with neutral and

Scheme 14

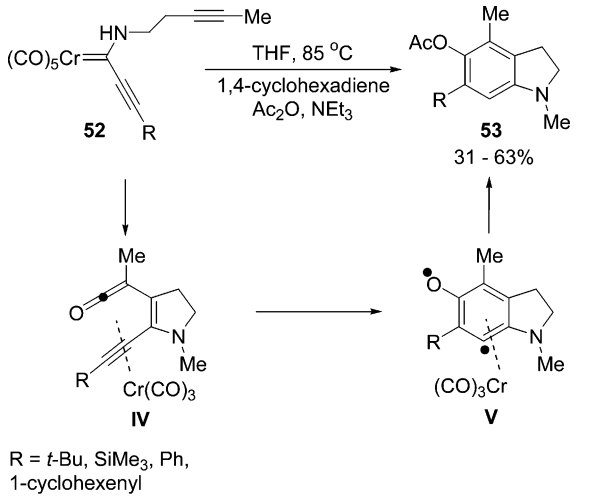


electron-poor alkynes **45** under CO pressure to afford pyrroles **46** in variable yields. The formation of the pyrrole ring is outlined in the scheme and basically involves three major steps: (i) the tetracarbonyl complex **44** undergoes insertion of carbon monoxide to form the ketene complex intermediate **III**; (ii) this ketene complex cyclizes to the free-metal munchnone **47**, which could be isolated and characterized; and (iii) finally, the dipolar cycloaddition of **47** toward alkyne dipolarophiles **45** and carbon dioxide cycloreversion complete the sequence.

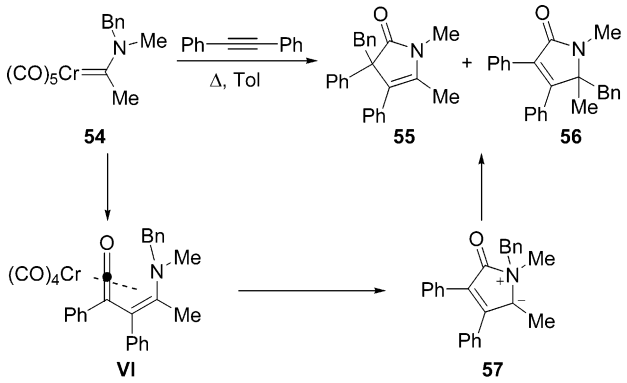
By far, most heterocyclizations gathered in this section are based on, or initiated by, the facile carbon−carbon triple-bond insertion reaction into the metal carbene functionality. Thus, simple approaches, like the intramolecular cyclopentannulation and benzannulation reactions of alkenyl aminocarbene complexes with alkyne groups tethered through the nitrogen atom, are outlined (Scheme 14).[19] First, heating *Z*/*E* mixtures of complexes **48** in benzene at 80 °C yielded bicyclic pyrrolines **49**. These cycloadducts arise from intramolecular alkyne insertion into the metal carbene functionality, followed by cyclization of the resulting chromium dienylcarbene system. In contrast, starting with the carbene complexes **50**, the tetrahydroquinoline ring **51** is exclusively formed in moderate yields. In this case, the intermediate metal dienylcarbene complex undergoes CO insertion to generate a metal ketene species which cyclizes to the final phenol system (Dötz reaction). The difference in terms of chemoselectivity for **48** and **50**, cyclopentannulation vs benzannulation, is a consequence of the tether length between nitrogen and alkyne (two-carbon vs three-carbon spacers, respectively).[20]

Because of the biological interest of the 5-hydroxyindoline unit and the failure to synthesize it by the intramolecular benzannulation of alkenyl complexes **48** (vide supra), Wulff et al. envisioned an elegant alternative based on the radical benzannulation of the alkynylcarbene complexes **52** (Scheme 15).[21] Thus, several complexes **52** were heated in the presence of 1,4-cyclohexadiene, as the hydrogen source, to afford regioselectively substituted indolines **53**. The key step of the process lies in the cyclization of the enynyl ketene complex intermediate **IV**, formed by consecutive alkyne and CO insertion reactions.

Scheme 15



Scheme 16

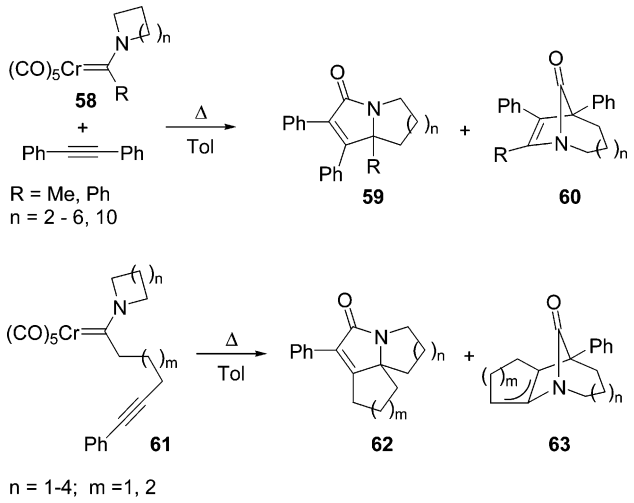


The radical benzannulation of **IV** then produces the 1,4-diradical species **V**, which leads to **53** by hydrogen abstraction and *O*-acetylation.

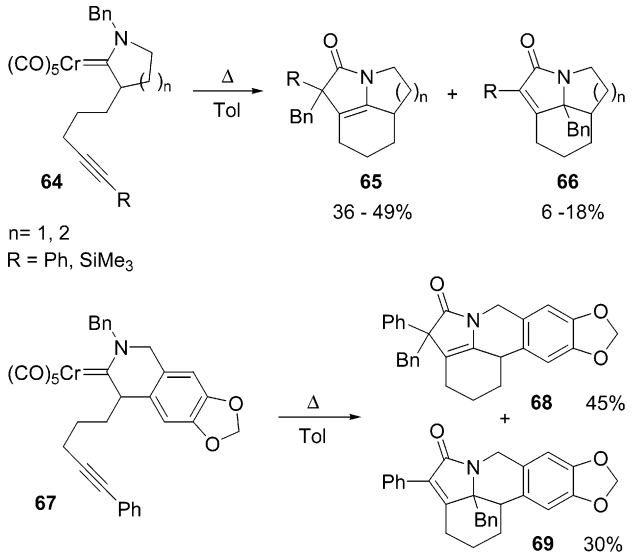
Some years ago, Rudler et al. introduced a conceptually new strategy for the synthesis of nitrogen heterocycles that begins with the inter- or intramolecular alkyne insertion into aminocarbene complexes, followed by rearrangement. A general view for this reaction model is displayed in Scheme 16. Thus, heating a toluene solution of *N*-benzyl-*N*-methylaminocarbene complex **54** and diphenylacetylene results in the formation of the pyrrolidone cycloadducts **55** and **56**. Their formation is rationalized by double insertion of alkyne and CO to form the intermediate **VI**, followed by cyclization to the nitrogen ylide **57** (characterized by X-ray analysis) and final 1,4- or 1,2-benzyl-migration, respectively.[22] Bicyclic lactams are readily available by the intramolecular protocol starting from *N*-benzyl-*N*-methylaminocarbene complexes with an alkyne tether.[23] This procedure has been developed to a wide scope by the same group in recent years (vide infra).

It can be realized that more complex molecules would be readily accessible if aminocarbene complexes derived from cyclic secondary amines are employed (Scheme 17). In fact, heating carbene complexes **58** in the presence of diphenylacetylene leads to [*n*+2.3.0] and [*n*+2.2.1] lactam structures **59** and **60**, which arise from 1,2- and 1,4-rearrangement, respectively, of the corresponding nitrogen ylide intermediate.[22a,24] The intramolecular version, using

Scheme 17



Scheme 18



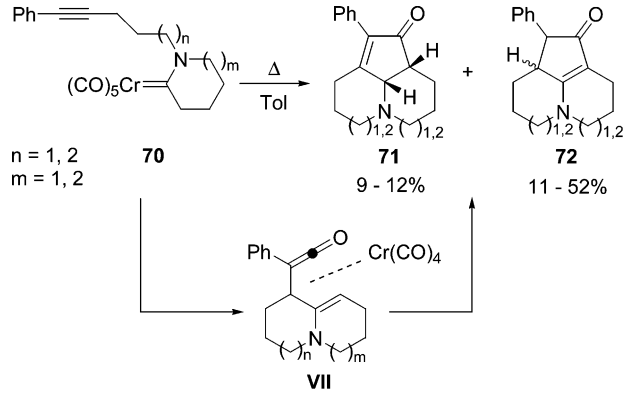
complexes **61**, wherein the alkyne group is tethered through the alkyl chain, has been demonstrated to be also useful for yielding tricyclic lactams **62** and **63**.[23]

The use of cyclic aminocarbene complexes with an alkynyl chain provides rapid access to pyrroloindole and pyrrolochinoline structures (Scheme 18).[25] Thus, *N*-benzylaminocarbene complexes **64** afford mixtures of cycloadducts **65** and **66** in fair yields. Moreover, application of this protocol to the synthesis of substituted lycorane alkaloids **68** and **69** from carbene complex **67** has been found to work equally well.

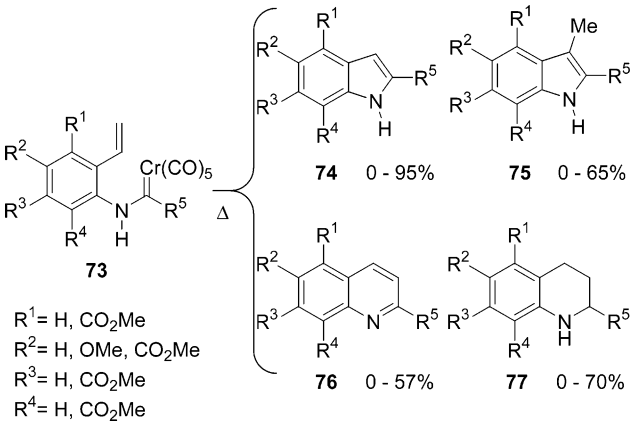
The behavior of aminocarbene complexes **70** having the alkyne chain attached to nitrogen has also been tested by the Rudler group (Scheme 19).[26] In this particular case, the insertion of both alkyne and CO effectively occurs to give the ketene complex intermediate **VII**. At this stage, it cannot evolve via nitrogen ylide unlike previous examples, but C_β−H enamine addition to the complexed ketene takes place, providing mixtures of tricyclic isomers **71** and **72**.

A synthesis of indoles and quinolines in a thermally induced intramolecular cyclization of arylamino-

Scheme 19



Scheme 20

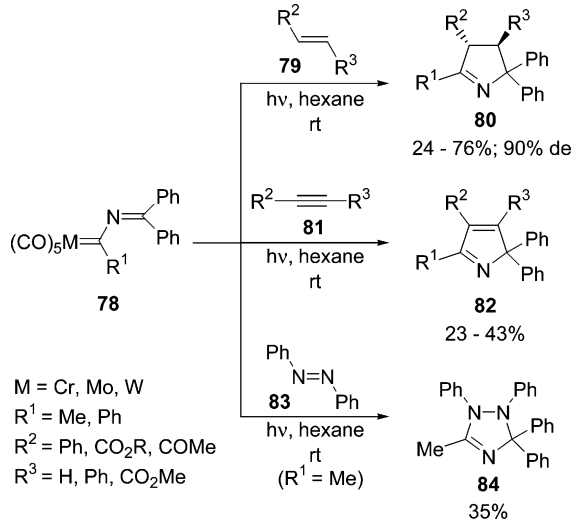


substituted carbene complexes (Scheme 20) was reported by Söderberg et al.[27] Mixtures of indoles **74** and **75**, quinolines **76**, and tetrahydroquinolines **77** were obtained from complexes **73** in a ratio that is highly dependent on the carbene substitution and the solvent choice. Formation of indoles **74** can be envisaged through a methatesis process, while indoles **75** and quinolines **76** and **77** are apparently formed by intramolecular vinylic C−H insertion reactions into the metal−carbon double bond, followed by reductive metal elimination.

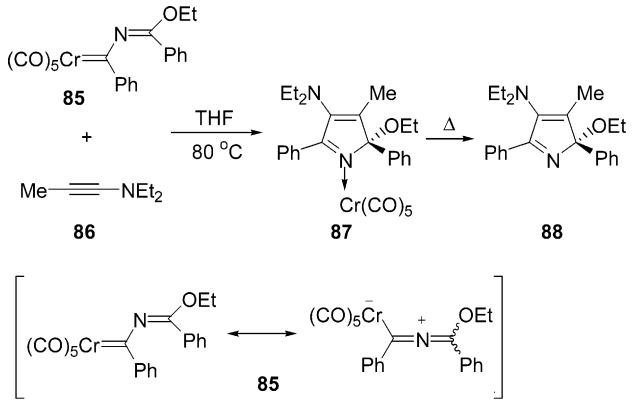
Finally, minor amounts of dihydroazepines have been reported by the Rudler group in the reaction of chromium *N*-allylaminocarbene complexes and diphenylacetylene via alkyne insertion and cyclization.[28]

2.2.1.2. From Iminocarbene Complexes. Iminocarbene complexes of group 6 transition metals are readily available from the corresponding alkoxy analogues and have been shown to be useful precursors of nitrogen heterocycles, particularly five-membered rings. The photochemical behavior of these systems toward various unsaturated organic substrates has been studied in detail by the research group of Campos (Scheme 21). Thus, complexes **78** are able to react with styrene and electron-poor alkenes **79** under photochemical conditions, providing 1-pyrrolines **80** in moderate to good yields.[29] On the other hand, a theoretical and experimental study was done which focused on the formation of substituted 2*H*-pyrroles **82** by irradiation of **78** in the presence of unactivated as well as electron-poor alkynes

Scheme 21



Scheme 22

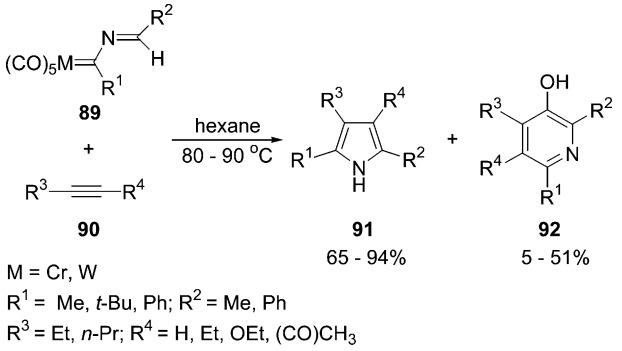


81.[29a,30] Similarly, the methyl(imino)carbene complex of chromium **78** leads to the substituted triazol **84** upon irradiation in the presence of azobenzene **83**.[31]

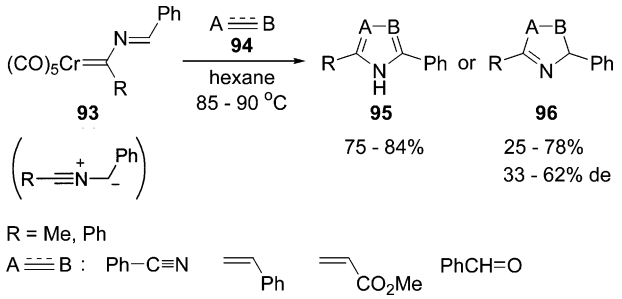
Aumann et al. reached similar results by thermal treatment of the iminocarbene complex **85** with the ynamine **86** (Scheme 22).[32] The mechanistic proposal involves a dipolar cycloaddition of the ynamine **86** with the polarized structure of the carbene complex **85**, followed by chromium-to-nitrogen complexation to produce compound **87**. This complex decomposes thermally to the corresponding metal-free 2*H*-pyrrole **88**.

Detailed studies carried out by the groups of Wulff and Aumann revealed that iminocarbene complexes thermally cyclize to different types of alkynes, yielding variable mixtures of pyrrols and 3-hydroxypyridines (Scheme 23).[33] Thus, heating iminocarbene complexes **89** and alkynes **90** in hexane results in the formation of a mixture of pyrroles **91** ([3+2] cyclization) and 3-hydroxypyridines **92** ([3+2+1] cyclization). Minor amounts of the regioisomeric pyrrole were eventually observed for unsymmetrical alkynes. Additionally, the pyrrole ratio increases on going from chromium to tungsten carbene complexes. These observations, along with the high regioselectivity toward the described pyrrole cycloadduct **91**, led Wulff et al.[33b] to consider the iminocarbenes **89** as nitrile ylide synthons for the [3+2] dipolar cycloaddition with alkynes.

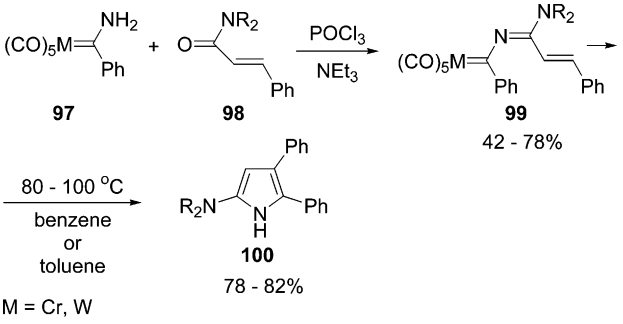
Scheme 23



Scheme 24



Scheme 25

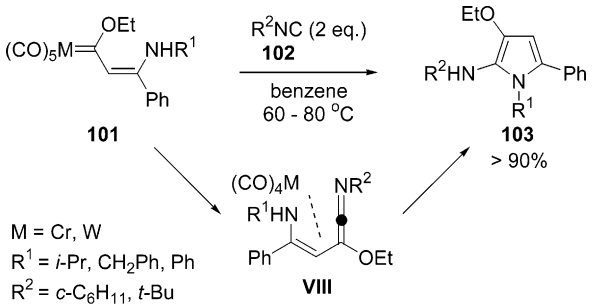


This [3+2] cyclization reaction of iminocarbenes was extended later by Wulff et al. to other carbo- and heterodipolarophiles **94** (Scheme 24).[33b] Thus, the reaction of chromium iminocarbene complexes **93** (represented as a dipolar synthon in parentheses) with benzonitrile gives rise to substituted imidazoles **95**, while the heterocyclization of **93** to styrene, methyl acrylate, and benzaldehyde gives the corresponding imidazoline or oxazoline rings **96**, though with low diastereoselectivity.

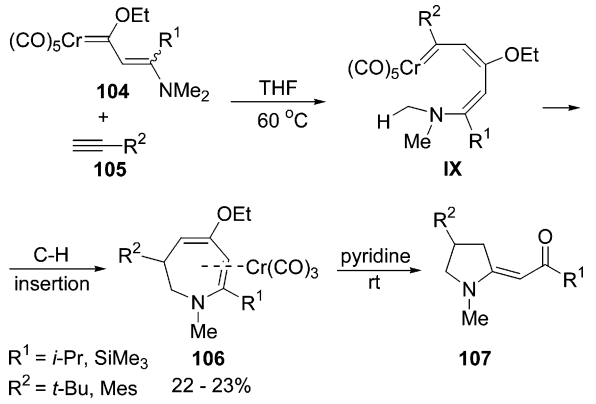
Recently, the synthesis of a new type of iminocarbene complexes, amenable to be used in heterocyclic synthesis, was reported (Scheme 25).[34] Thus, alkenyliminocarbene complexes of chromium and tungsten **99** are readily synthesized by condensation of aminocarbenes **97** and α,β-unsaturated amides **98**. The newly formed carbenes **99** undergo thermal cyclization to the pyrroles **100** in high yields.

2.2.1.3. From β-Amino and β-Imino Alkenylcarbene Complexes. β-Amino and β-imino alkenylcarbene complexes appear to be appropriate organometal reagents for heterocyclic synthesis. They are easily prepared by Michael-type addition of amines and imines to the corresponding alkynylcarbenes, according to the report by Fischer et al. in 1972.[35,36]

Scheme 26



Scheme 27

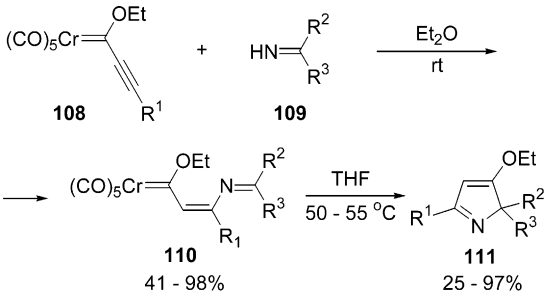


Thus, heating the β-amino complex **101** at 60−80 °C with 2 equiv of isocyanide **102** affords substituted pyrroles **103** in high yields (Scheme 26).[37] The mechanistic proposal consists of the insertion reaction of isocyanide into the carbon−metal bond to form the intermediate **VIII**, which undergoes cyclization to the pyrrole **103**, facilitated by isocyanide-mediated removal of the metal carbonyl fragment.

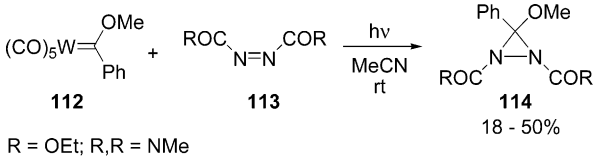
In a different approach, the dihydroazepine ring has been reported by de Meijere et al. to be formed from β-aminocarbene complexes and alkynes via [5+2] cycloaddition (Scheme 27).[38] Thus, the treatment of pentacarbonyl(3-dimethylamino-1-ethoxyalkenylidene)chromium complexes **104** with alkynes **105** leads to the chromium-complexed dihydroazepines **106** in low isolated yields. The proccess is expected to begin with the regioselective insertion of the alkyne into the chromiun−carbon bond to form the 6-dimethylaminometallahexatriene intermediate **IX**. The final step implies intramolecular insertion of the new carbene ligand into the amino C_α−H bond. Further treatment of complexes **106** with pyridine results in metal decomplexation and ring-opening/ring-reclosing, yielding pyrrolidine derivatives **107**.

Pentacarbonyl(3-imino-1-ethoxyalkenylidene)chromium complexes **110** were first synthesized by de Meijere et al. by Michael-type addition of imines **109** to alkynyl(alkoxy)carbenes **108** (Scheme 28).[39] These complexes smoothly undergo thermal cyclization to 2*H*-3-ethoxypyrroles **111**. Aumann et al. reported that analogous pentacarbonyl(3-imino-1-diethylaminoalkenylidene)chromium complexes, prepared by insertion of ynamines into phenyl(imino)carbene complexes, behave similarly, giving rise to the corresponding 3-diethylaminopyrroles.[40]

Scheme 28



Scheme 29



2.2.2. From Nitrogen-Containing Organic Substrates

This section deals with heterocyclic syntheses involving nitrogen-containing organic substrates and conventional metal carbene complexes; in other words, the cyclic nitrogen atom now comes from the nonmetallic reagent. Due to the broad range of organic substrates able to participate in this type of reactions, this section is not divided according to the organic substrate, but it is based on the size of the heterocycle formed.

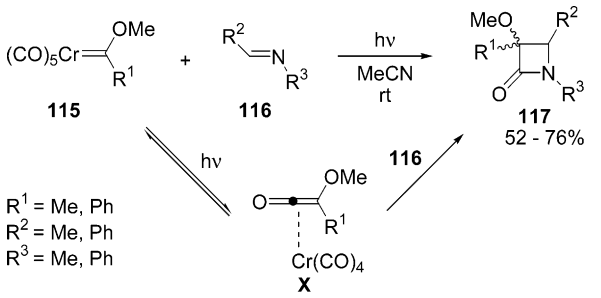
2.2.2.1. Three-Membered Heterocycles. Fischer carbene complexes have not been successfully used for the synthesis of three-membered heterocyclic rings. For instance, attempts to obtain aziridines by [2+1] cyclization of imines and Fischer carbene complexes were unsuccessful.[41] An example of this type of heterocyclization involving azo compounds has been reported by McElwee-White et al. (Scheme 29).[42] Accordingly, diaziridines of type **114** are available in low to moderate yields by thermal or photochemical [2+1] cyclization of the tungsten carbene **112** and azocompounds **113**, e.g., diethylazodicarboxylate and 4-methyl-1,2,4-triazoline-3,5-dione.

2.2.2.2. Four-Membered Heterocycles. Since its discovery by the Hegedus group in 1982,[16a] the photochemical reaction of heteroatom-stabilized carbene complexes has emerged as a powerful tool for the selective synthesis of both α-amino acid derivatives and four-membered rings.[2k]

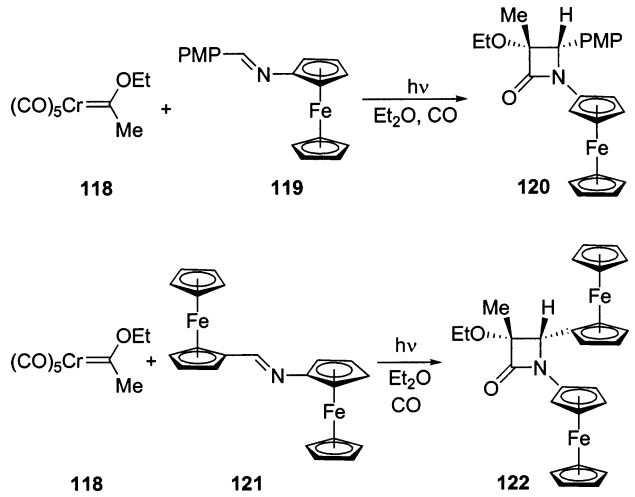
This procedure has been particularly useful for accessing the β-lactam and β-lactone skeletons. At this point, some selected examples are given, focused on the synthesis of four-membered nitrogen heterocycles.

The pioneering work in this field[16a] is shown in Scheme 30, which describes the [2+1+1] cyclization of chromiun carbene complexes **115** with imines **116** to provide substituted β-lactams **117**. The mechanism involves the photochemical insertion of CO into the metal carbon double bond to give the metal ketene intermediate **X**. This species undergoes [2+2] cy-

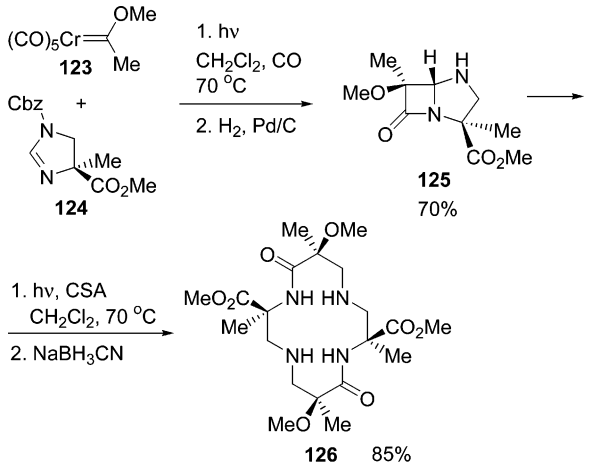
Scheme 30



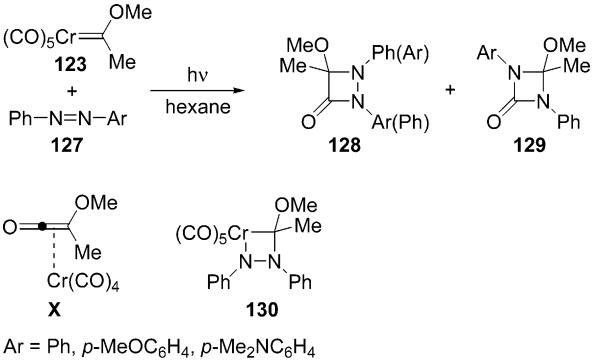
Scheme 31



Scheme 32



Scheme 33



cloaddition to the corresponding imine **116**, affording a diastereoisomeric mixture of the *β*-lactams **117**.

Following that work, a large number of *β*-lactam syntheses based on this procedure have been reported. For instance, Sierra et al. have been able to accomplish the synthesis of 2-azetidinones having organometallic moieties attached to the ring, e.g., one or two ferrocenyl groups (Scheme 31).[43] Thus, the photochemical treatment of the chromium complex **118** with the monoferrocenyl- and diferrocenylimines **119** and **121** results in the diastereoselective formation of the lactams **120** and **122**, respectively.

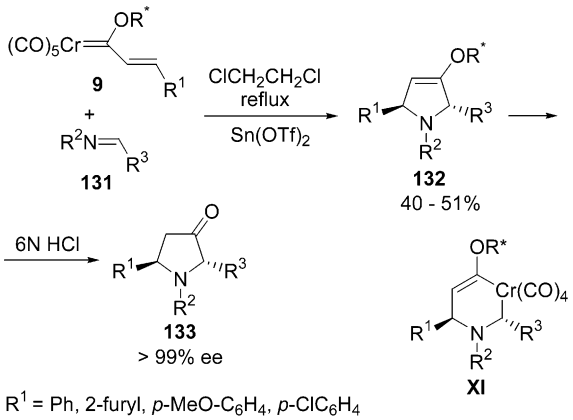
Enantiopure imine derivatives have been successfully employed by Hegedus et al. for the synthesis of optically active azapenams and dioxocyclams. Thus, photolysis of the chiral imidazoline **124** with the chromium complex **123** produces the azapenan **125** as a single diastereoisomer (Scheme 32).[44] This azapenan **125** undergoes acid-catalyzed dimerization followed by reduction, affording the optically active dioxocyclam **126** as a single diastereoisomer. Moreover, this process has been utilized as the key step in the synthesis of several natural products, thus enhancing greatly its synthetic potential.[45]

When azobenzene derivatives are used in this reaction instead of imine derivatives, a more complex reaction pathway is observed. Specifically, mixtures of 1,2-diazetidinones **128** and 1,3-diazetidinones **129** are formed in modest yields by photochemical treatment of azobenzene derivatives **127** and chromiun carbene complex **123** (Scheme 33).[46] Further NMR studies allowed the course of the reaction to be clarified.[47] The formation of the 1,2-diazetidinone **128** takes place via [2+2] cycloaddition of *cis*-azobenzene and the ketene chromium complex intermediate **X**. In contrast, the 1,3-diazetidinone **129** is reported to arise from the chromacycloadduct **130** via retro [2+2] cycloaddition, CO insertion into the Cr=N bond, and [2+2] cycloaddition between the resulting metal ketenimine complex and imidate systems. The intermediate **130** was characterized in solution and transformed independently into the 1,3-diazetidinone **129**.

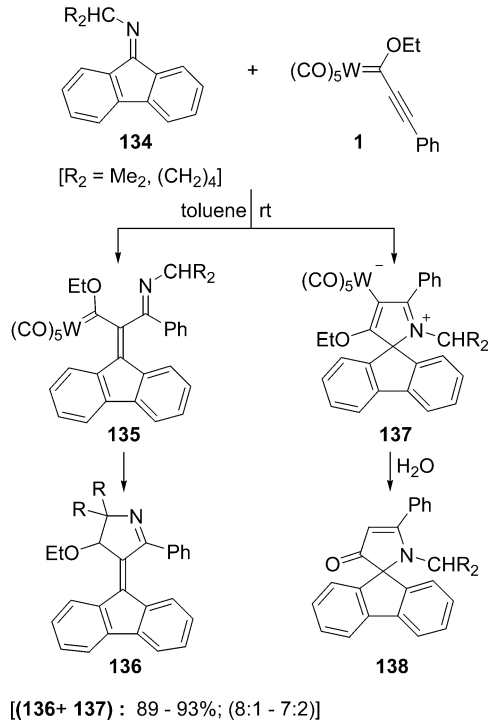
2.2.2.3. Five-Membered Heterocycles. This section deals basically with the cyclization of Fischer carbene complexes with various types of substrates containing the carbon−nitrogen double bond, e.g., imines, isocyanates, and azadienes, as well as with saturated nitrogen substrates such as hydrazines and amines.

2.2.2.3.1. [3+2] Cyclization with Imine Derivatives. The first useful example of the reactivity of Fischer carbene complexes toward simple imines was recently reported by Akiyama et al. (Scheme 34).[48] First, they found that achiral carbene complexes **9** (R* = Me) diastereoselectively produce dihydropyrroles **132** (R* = Me) when heated with aldimines in the presence of some Lewis acids.[48a] Importantly, the use of carbene complexes **9**, having the chiral auxiliary 8-phenylmenthyloxy group, makes it possible to obtain dihydropyrroles **132** as a sole diastereoisomer. The acid hydrolysis of **132** nicely completes the asymmetric synthesis of optically pure pyrrolidinones **133**.[48b] The mechanism invoked by the authors[48a] implies the [4+2] cycloaddition of the chromadiene

Scheme 34



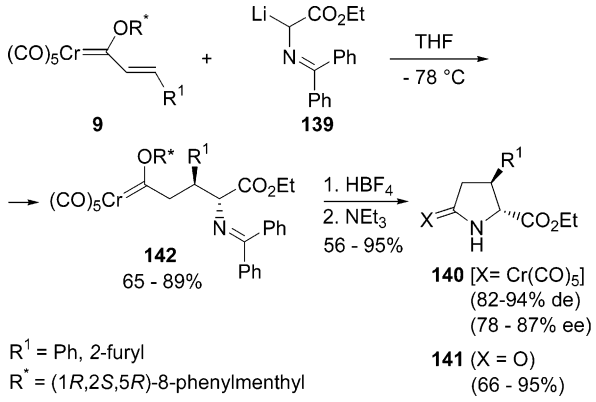
Scheme 35



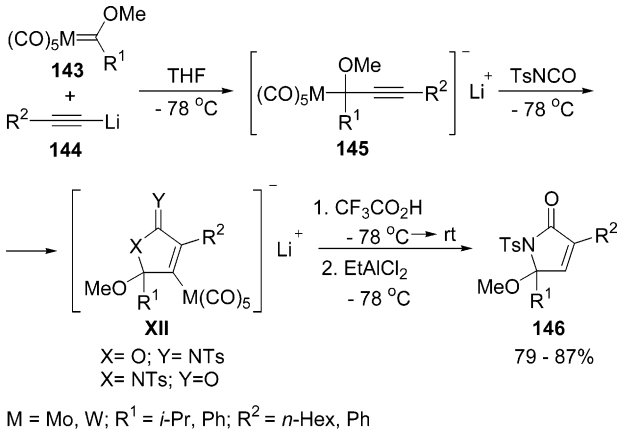
9 to the imine dienophile **131** to generate the metallacycloadduct **XI**, followed by reductive elimination of the metal fragment.

Aumann et al. have reported that pyrrole derivatives are also available starting from non-enolizable imines and tungsten alkynyl(alkoxy)carbene complexes (Scheme 35).[49] Thus, the reaction of the alkynyl carbene **1** with fluorenone imines **134** affords mixtures of dihydropyrroles **136** and mesoionic pyrrolium complexes **137** (ratio from 8:1 to 7:2), the latter being readily hydrolyzed to spiropyrrolinones **138**. The formation of the dihydropyrrole **136** is rationalized in terms of insertion of the alkyne function into the carbon−nitrogen double bond to form the new complex **135**, which suffers subsequent intramolecular C−H insertion into the metal carbene bond and reductive metal elimination. Compounds **137** may result from conjugate imine addition to the

Scheme 36



Scheme 37



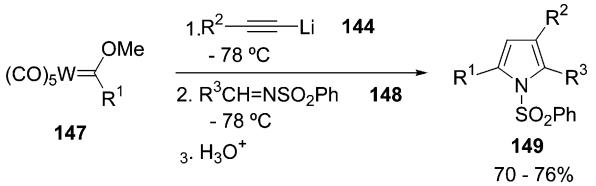
alkynyl carbene, followed by cyclization promoted by a 1,2-[$(CO)_5W$] shift.

Our group was highly interested in the synthesis of the pyrrolidine framework in an enantioselective fashion. To this end, we started with metalated imines derived from amino acid esters and chiral nonracemic carbene complexes (Scheme 36).[50] Thus, the lithium salt **139** undergoes conjugate addition to alkenyl carbenes **9**, derived from (−)-phenylmenthol, to produce the coupling products **142** in high yield and with high anti diastereoselectivity (82−94% de). The acyclic adducts **142** lead to aminocarbenes **140**, after imine hydrolysis and cyclization. Aminocarbenes **140** were also synthesized in a one-pot procedure (84−88% de; 78−87% ee for the anti isomer). Oxidation of the carbene complexes **140** following standard procedures gives rise to the pyrrolidones **141**.

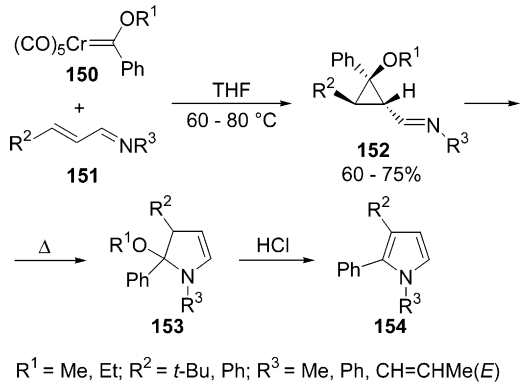
In a different approach, Iwasawa et al.[51] used metal anion complexes **145**, generated by addition of lithium acetylides **144** to metal alkoxycarbenes **143** and characterized by NMR ^{13}C-labeled experiments,[52] as a reactive metal carbene-derived species (Scheme 37). These lithium salts **145** readily cyclize with tosylisocyanates, leading to the formation of the pyrrolinones **146** in good yields via the metalate intermediates **XII** (mixture of regioisomers). Most likely, **XII** is formed by nucleophilic addition of **145** to the imine, followed by cyclization promoted by 1,2-migration of the $M(CO)_5$ fragment.

Taking advantage of this protocol, *N*-sulfonylpyrroles **149** were also synthesized via addition of

Scheme 38



Scheme 39

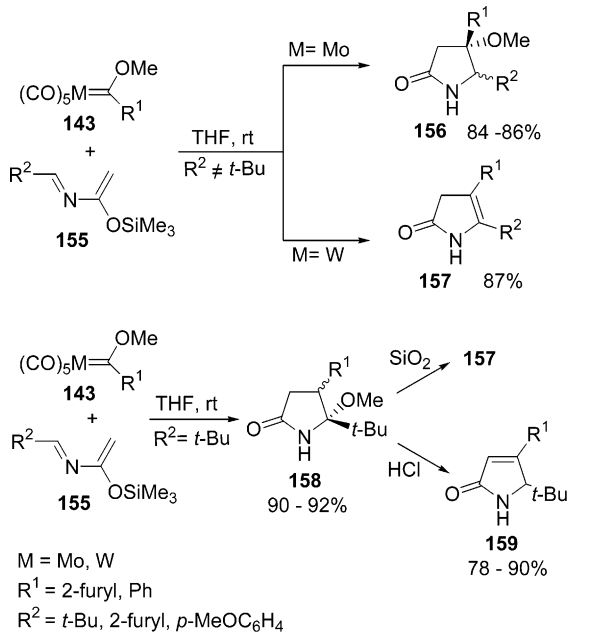


lithium acetylides **144** to the carbene complex **147**.The resulting species are able to cycloadd to sulfonylimines **148** to produce *N*-sulfonylpyrroles **149** in good overall yields (Scheme 38).[52,53]

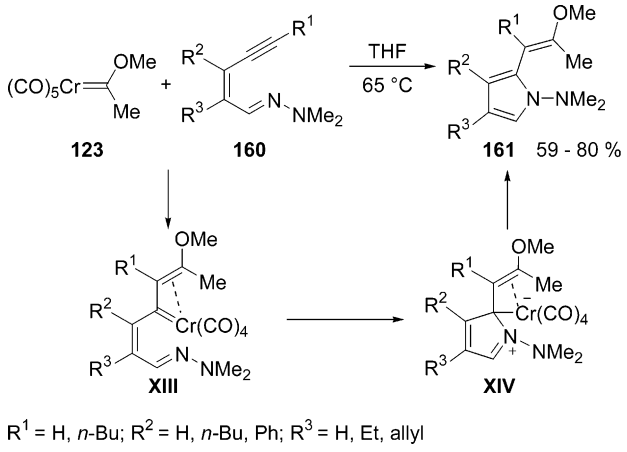
2.2.2.3.2. From Azadienes. Azadienes have been well recognized as potential building blocks in the synthesis of nitrogen heterocycles.[54] Once we initiated our adventure in the chemistry of transition metal carbene complexes some years ago,[55] we realized that combining these nitrogen systems and the organometal reagents might open new routes to heterocycles. In this context, we found that simple metal carbene complexes **150** smoothly cycloadd to 1-azadienes **151** to produce pyrrole derivatives **154** (Scheme 39).[56] Use of short reaction times made it possible to stop the reaction at the cyclopropanation step and to isolate iminocyclopropanes **152** in good yields. Therefore, the mechanism of this [4+1] heterocyclization could be established as a cyclopropanation of the activated carbon−carbon double bond, followed by rearrangement of the resulting iminocyclopropane to pyrrolines **153** and heteroaromatization. The direct formation of pyrroles **154** from carbene complexes **150** and azadienes **151** was also reported by Danks and Velo-Rego.[57]

In the case of reacting 3-trimethylsilyloxy-2-azadienes **155** with complexes **143**, a new family of pyrrole derivatives **156**−**159** is obtained according to a formal [4+1] heterocyclization (Scheme 40).[13] The reaction course is highly dependent on the azadiene substitution pattern. Thus, azadienes **155** lacking a *tert*-butyl group (R^2 = aryl, heteroaryl) give high yields of the expected pyrrolidinones **156** or their elimination products **157** upon treatment with carbene complexes **143** of molybdenum or tungsten, respectively. In contrast, the 1-*tert*-butyl-2-azadiene **155** (R^2 = *t*-Bu) leads unexpectedly to the rearranged pyrrolidinone **158** upon reaction with tungsten complexes **143**. Further controlled elimination of methanol under SiO_2 and aqueous acid conditions affords

Scheme 40



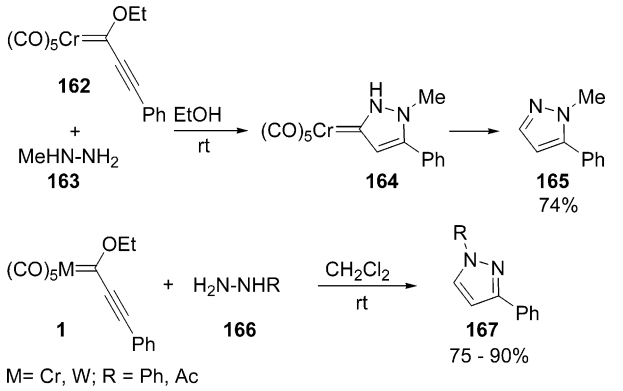
Scheme 41



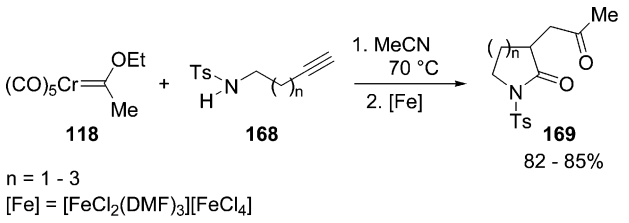
isomeric pyrrolidones **157** and **159**, respectively. A reaction course implying cyclopropanation of the C=C of the azadiene and iminocyclopropane−pyrroline rearrangement accounts well for the formation of **156**, while a multistep sequence is invoked in the case of compounds **158**, consisting of (i) nucleophilic nitrogen addition, (ii) [1,3]-OMe migration, (iii) intramolecular C−H insertion into the M=C bond, and (iv) *N*-vinylaziridine-to-pyrroline rearrangement.

More sophisticated azadienes, like enyne-hydrazones **160**, have been reported by Herndon et al. to produce variable yields of *N*-aminoalkenylpyrrole derivatives **161** when reacted with chromiun methyl(methoxy)carbene complexes **123** (Scheme 41).[58] The mechanistic proposal begins with the alkyne insertion into the carbon−metal bond to form the metal carbene intermediate **XIII**, followed by cyclization to the intermediate **XIV** via nucleophilic nitrogen attack to the newly formed metal carbene. The last step requires simply aromatization to the pyrrole ring **161** by loss of the $(CO)_4Cr$ fragment. Alkenylpyrroles are also formed as minor reaction products from the [4+1] heterocyclization of alkenylhydrazones and alkenyl(methoxy)carbene complexes of chromium.[59]

Scheme 42



Scheme 43



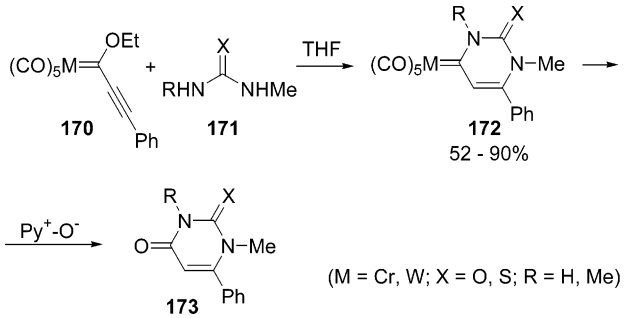
2.2.2.3.3. From Hydrazines. Aumann et al. have studied the reaction of alkynylcarbene complexes with hydrazines as a simple entry into the pyrazole ring (Scheme 42).[60] Thus, treatment of the carbene **162** with methylhydrazine leads to the cyclic aminocarbene complex **164**, which can be demetalated to the *N*-methyl-2-substituted pyrazole **165**. The formation of **164** implies a Michael-type addition of the methyl-substituted nitrogen, followed by intramolecular methoxy desplacement. In the case of hydrazine **166** and carbenes **1**, the opposite regioisomer, the 3-substituted pyrazole **167**, is solely isolated, which is most probably due to the decreased nucleophilic character of the substituted nitrogen.

2.2.2.3.4. From Alkynylamines. More interestingly, Mori et al. have reported the synthesis of five- to seven-membered lactams **169** by reaction of alkynylamines **168** with the carbene complex **118** (Scheme 43).[61] The process is invoked to begin with an alkyne insertion and evolves through a CO insertion followed by intramolecular nucleophilic nitrogen attack to the ketene intermediate.

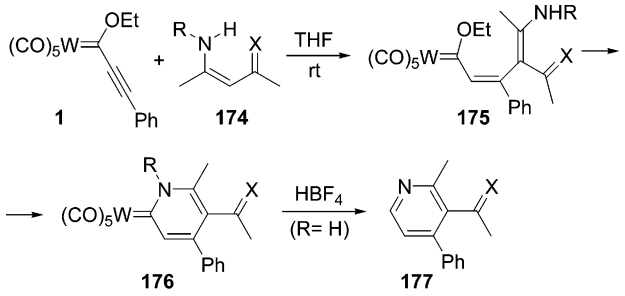
Several pyrrolidine derivatives also have been synthesized by the Mori group using alkenylalkynylamines. The process is initiated by an alkyne insertion reaction and is followed by cyclopropanation, CO insertion−cyclization, or metathesis to form cyclopropyl, cyclobutanone-fused, or alkenyl pyrrolidines, respectively.[62] The use of identical substitution on the carbene and olefin allows implementation of a catalytic metathesis process.[62d,e]

2.2.2.4. Six-Membered Heterocycles. In the past decade, some examples of synthesis of six-membered *N*-heterocyclic rings from alkynyl- and alkenyl(alkoxy)carbene complexes have been published. Thus, the formal [3+3] cyclization of alkynyl carbene complexes **170** with ureas and thioureas **171**, reported by Ricart et al., appears to be a practical method for the preparation of new cyclic carbene

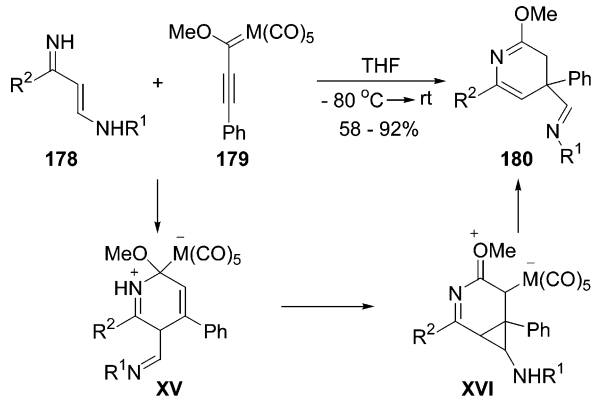
Scheme 44



Scheme 45



Scheme 46

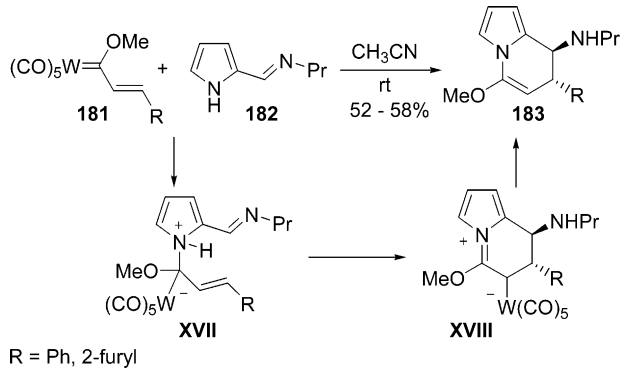


complexes **172** and of the metal-free pyrimidinone derivatives **173** (Scheme 44).[63]

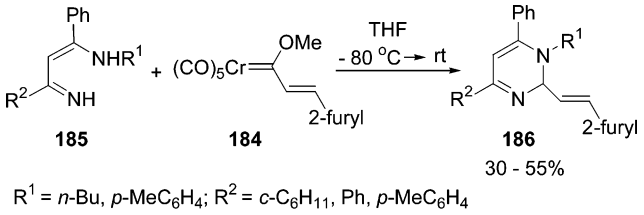
On the other hand, Aumann et al. used enaminoketones and enaminoimines **174** as the N−C−C synthon toward alkynyl carbenes (Scheme 45).[64] In this case, 1,2-dihydropyridin-2-ylene complexes **176** are isolated from tungsten alkynylcarbene complexes **1** and nitrogen substrates **174**. The initial Michael adduct **175** could be characterized by NMR. On the other hand, complexes **176** (R = H) can be demetalated to pyridines **177** by acid treatment.

Surprisingly, we have found that *N*-substituted enaminoimines also undergo [3+3] cyclization but accompanied with rearrangement of the imidoyl group (Scheme 46).[65] Thus, complexes **179** smoothly cycloadd to imine derivatives **178** to furnish dihydropyridines **180** in moderate to high yields. The reaction is thought to proceed via the primary cycloadduct intermediate **XV**, followed by 1,2-metal migration-promoted formation of the cyclopropane **XVI** and cylopropane ring-reopening.

Scheme 47



Scheme 48



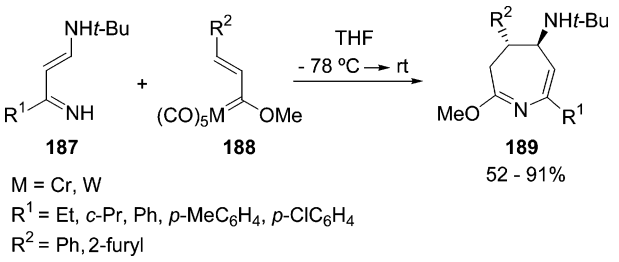
An example of a [3+3] heterocyclization involving alkenyl(methoxy)carbene complexes, instead of alkynyl carbenes, was observed in our group.[66] The reaction of alkenyl Fischer carbene complexes **181** and pyrrolecarbaldehyde imine **182** produces substituted indolizines **183** in a chemo-, regio-, and diastereoselective way (Scheme 47). The mechanism is based on previous results from this laboratory and involves a 1,2-addition of the pyrrole nitrogen to form the zwitterionic intermediate **XVII**. The cyclization of this intermediate to **XVIII**, facilitated by the [1,2]-metal migration, and the reductive metal elimination may reasonably explain the formation of **183**.

Finally, a facile synthesis of dihydropyrimidines using Fischer carbene complexes has been accomplished in our group (Scheme 48).[67] Thus, the alkenylcarbene complex **184** cycloadds to enaminoimines **185** in a [5+1] fashion, rather than in a [3+3] way as found for alkynyl complexes (see Schemes 45 and 46), yielding 2-alkenyl-1,2-dihydropyrimidines **186**. These heterocycles are not accessible by condensation of aminoazadienes **185** and acrolein derivatives.[68]

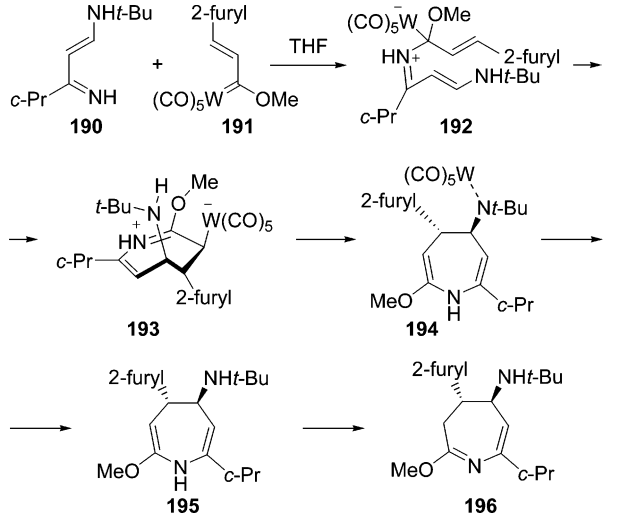
2.2.2.5. Seven-Membered Heterocycles. The potential of α,β-unsaturated carbene complexes as C-3 units in cyclization reactions leading to five- and six-membered heterocycles has been widely outlined (sections 2.2.2.3 and 2.2.2.4). In contrast, no alternative synthetic ways to seven-membered heterocycles were known until recently. We realized that, using appropriate nitrogen substrates, new [4+3] cyclization reactions might be achieved.[69] Those studies have crystallized into various azepine syntheses and have additionally made it possible to get a better understanding of a number of cyclization reactions involving Fischer carbene complexes.

Thus, the first successful example deals with the formation of 4,5-dihydro-3*H*-azepines **189** from 4-amino-1-azadienes **187** and alkenylcarbene complexes **188** under unusually mild reaction conditions (Scheme 49).[70] This novel [4+3] cycloaddition takes place with

Scheme 49



Scheme 50

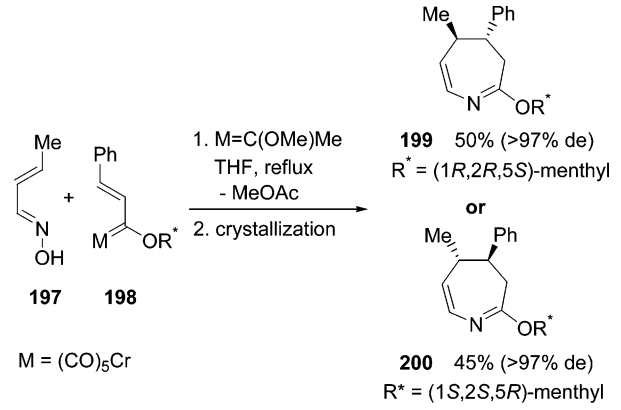


moderate to high yields and with complete regio- and diastereoselectivity.

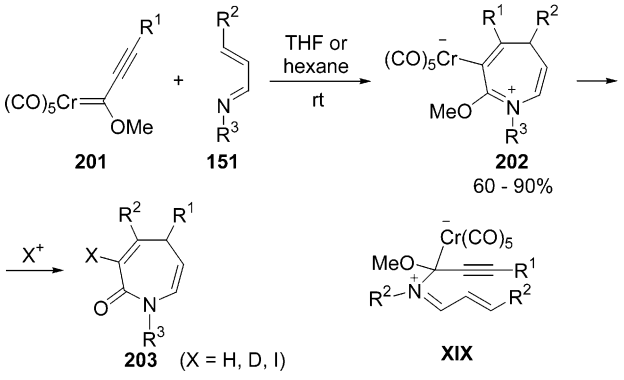
The proposed mechanism of this process is outlined in Scheme 50 and has been well established by means of ^{1}H, ^{13}C, ^{15}N, and ^{183}W NMR studies at low temperature.[70b] These NMR experiments led us to fully characterize the intermediates **192**−**195** and establish an unambiguous mechanistic reaction pathway. The reaction begins at a temperature as low as −60 °C and involves the 1,2-nucleophilic attack of the imine nitrogen to the carbene carbon to form compound **192**. This compound evolves at −40 °C to the metal azepine ring **193** via a cyclization promoted by a [1,2]-migration of the metal fragment. As the temperature increases, **193** demetalates, leading to the nitrogen-coordinated azepine **194**. Last, the decomplexation of the latter occurs at −20 °C, affording the 4,5-dihydro-1*H*-azepine **195**, which tautomerizes to the 4,5-dihydro-3*H*-azepine **196** on silica gel.

The analogous oxime derivatives (1-hydroxy-1-azabutadienes) **197** have also been found to efficiently produce *trans*-4,5-disubstituted-4,5-dihydro-3*H*-azepines with complete regio- and diastereoselectivity.[70b] Importantly, this protocol allowed us to obtain enantiopure azepines using chiral nonracemic Fischer carbene complexes (Scheme 51).[70b] Thus, the reaction of oximes **197** with carbene complexes **198**, derived from either (+)- or (−)-menthol, affords high yields of diastereomeric mixtures where azepines **199** and **200**, respectively, are prevailing. Fortunately, these mixtures can be readily separated by crystallization, allowing the isolation of diastereomerically pure (>97% de) azepines **199**

Scheme 51



Scheme 52



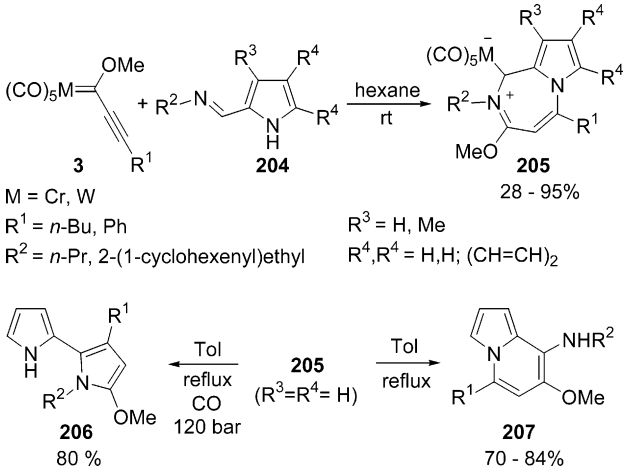
R^1 = $SiMe_3$, Ph; R^2 = Me, Ph; R^3 = *n*-Pr, *i*-Pr, Bn

(from (−)-menthol-derived metal carbenes) and **200** (from (+)-menthol-derived metal carbenes) in overall yields higher than 45%. Adding of 1 equiv of chromium methyl(methoxy)carbene is required; otherwise, the chiral carbene **198** would be sacrified, since the hydroxyazepine that is presumably formed oxidizes the carbene functionality.

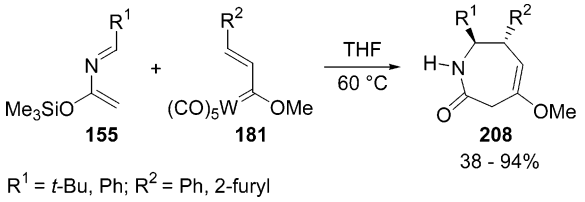
Not only 4-amino- or 1-hydroxy-1-azadienes are suitable substrates for metal carbenes-mediated heterocycloheptannulation reactions, but also simple 1-azadienes have been reported to cycloadd to alkynyl carbene complexes in a similar way. In this particular case, chromium alkynylcarbenes **201** give rise to azepine chromium complexes **202** when reacted with 1-azadienes **151** at room temperature (Scheme 52).[71] Interestingly, an X-ray analysis of the intermediate directly resulting from the [1,2]-metalpentacarbonyl migration could be performed, and therefore this key step is fully confirmed. Such a reaction pathway is not restricted to particular cases, but it has been observed in a number of carbo- and heterocyclization reactions. Complexes **202** should arise from the 1,2-addition intermediate **XIX** and can be further elaborated into azepinones **203**.

The 1,4-diazepine framework is accessible by using imines derived from pyrrole- and indole-2-carbaldehydes (Scheme 53).[66] The room-temperature reaction of iminopyrroles or indoles **204** and alkynylcarbenes **3** results in the formation of 1,4-diazepine complexes **205** in moderate to very high yields. This [4+3] heterocyclization takes place through a reaction pathway different from that observed previously (see

Scheme 53



Scheme 54



R^1 = *t*-Bu, Ph; R^2 = Ph, 2-furyl

above) and may involve Michael-type addition of the amine group, followed by intramolecular 1,2-imine addition to the M=C and finally [1,3]-metalpentacarbonyl migration. The zwitterionic pyrrolodiazepines **205** thermally rearrange, under CO or N_2 atmosphere, to the substituted bispyrroles **206** or indolizines **207**, respectively.

The well-established [4+3] cyclization of 1-azadiene derivatives has been successfully extended to 2-azadienes (Scheme 54).[13] In this case, 2-azepinones **208** are readily synthesized by heating of 3-trimethylsilyloxy-2-azadienes **155** and tungsten alkenylcarbene complexes **181**. Whereas a nearly equimolecular mixture of cis/trans diastereoisomers is formed in the case of R^1 = Ph, the *trans*-2-azepinone isomer was solely isolated when R^1 = *t*-Bu.

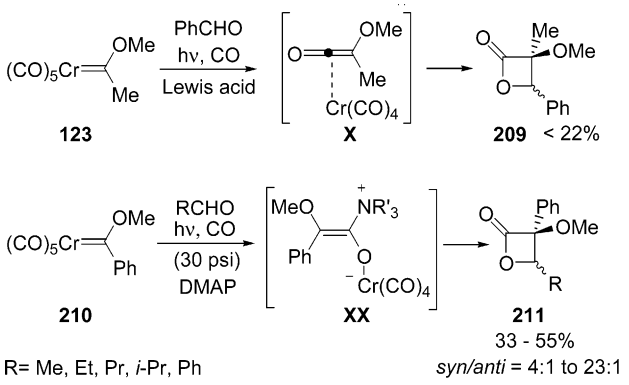
3. Synthesis of Oxygen Heterocycles

Regarding the synthesis of oxygen heterocycles, a large number of varied processes have been reported in recent years. Taking into account the different mechanistic proposals that have been delineated, this section has been written accordingly and deals with the following subsections: photochemical cyclizations (3.1), cyclizations initiated by alkyne insertion (3.2), cyclizations involving C−H insertion (3.3), and cyclizations initiated by nucleophilic attack (3.4).

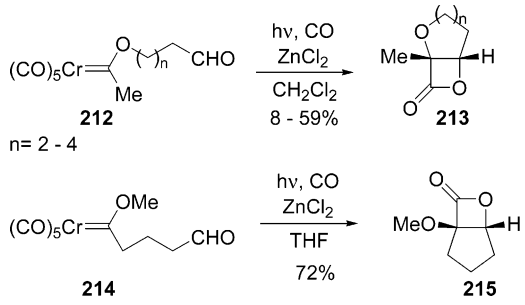
3.1. Photochemical Cyclizations

The ability of Fischer carbene complexes to undergo a photochemical decomplexation of a carbonyl ligand allows for the formation of a ketene intermediate (see Scheme 30), which would be amenable to produce lactones when reacted with suitable oxygen substrates, such as aldehydes.[2k] This reactivity has been widely explored by the Hegedus group and has

Scheme 55



Scheme 56

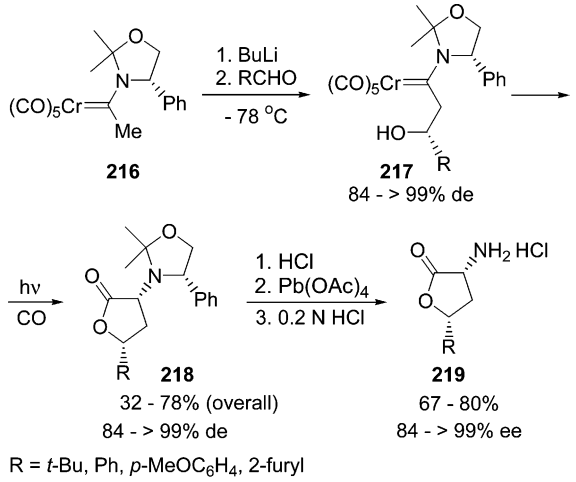


received a great deal of attention due to the mild reaction conditions and wide versatility. However, the first examples reported were not as successful as expected, due to the low yields and lack of selectivity. Thus, synthesis of the β-lactone **209** by photochemical decomposition of carbene **123** to the metal ketene intermediate **X** and cycloaddition to benzaldehyde takes place in very low yield (Scheme 55).[72] Recently, Merlic has found that, with the use of amine additives, the [2+2] cycloaddition reaction is significantly improved in terms of both yield and diastereoselectivity (Scheme 55).[73] When the benzylidene(methoxy)-chromium complex **210** and aliphatic and aromatic aldehydes were irradiated under CO atmosphere in the presence of DMAP, the expected lactones **211** were obtained with moderate yields and high diastereoselectivity in favor of the syn isomer. A zwitterion intermediate **XX,** arising from addition of DMAP to the primary ketene complex, is proposed to explain the selectivity of the reaction. In the case of electron-rich aldehydes the lactones are not isolated, but they decarboxylate to the corresponding enol ethers.

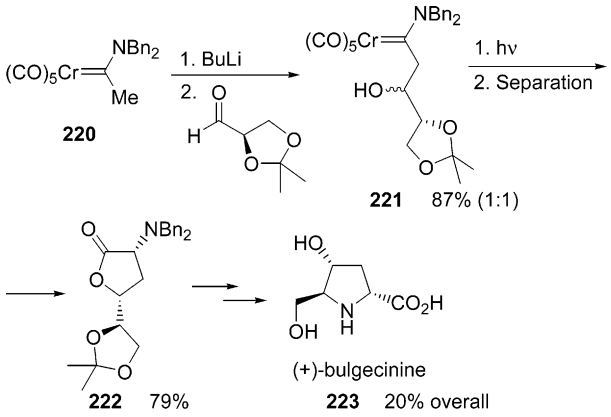
Much more efficiency was found when the aldehyde functionality is incorporated into either side chain of the starting metal carbene (Scheme 56). Thus, fused β-lactones **213** and **215** are diastereoselectively formed by photolysis of chromium carbene complexes **212** and **214**, respectively, in the presence of Lewis acids.[72]

Another synthetically useful entry into lactones consists of intramolecular trapping of the metal ketene intermediate with a remote hydroxy functionality. Moreover, this strategy has been found to work nicely in the synthesis of enantiopure γ-lactones (Scheme 57).[74] For this purpose, the required chromium β-hydroxycarbene complex **217** is available by the stereoselective aldol reaction of chiral aminocarbene **216** and the corresponding aldehyde. Photolysis of complexes **217** then gives rise, with total face selectivity, to lactones **218** by nucleophilic hydroxy addition to the initially generated chromium ketene species. Finally, the hydrolytic removal of the chiral auxiliary affords lactones **219** with very high optical purity.

Scheme 57



Scheme 58



The utility of this strategy has been demonstrated in a short and enantioselective synthesis of (+)-bulgecinine **223** (Scheme 58).[74] In this case, the aldol reaction of the carbene **220** with glyceraldehyde acetonide gives a mixture of diastereoisomers **221**, which is then photolyzed and the key stereoisomer **222** separated and elaborated in five steps to **223**. We agree with the final statement made by the authors: "Although this is not an asymmetric synthesis, the low number of steps and good overall yield make it attractive".

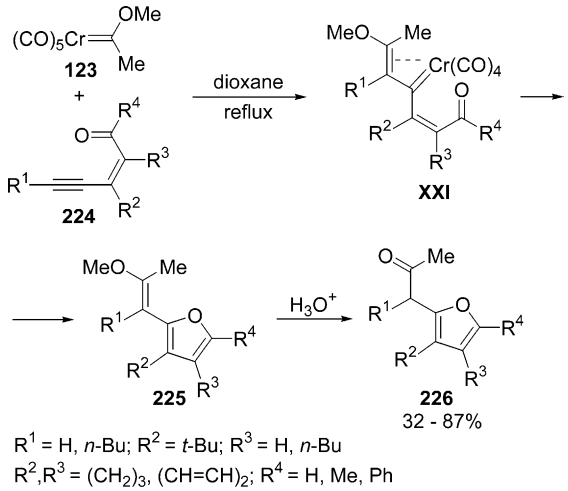
3.2. Cyclizations Initiated by Alkyne Insertion

This section covers different approaches to oxygenated heterocycles that begin with alkyne insertion into the metal carbene functionality. After the initiation step, the cyclization may occur spontaneously or may be preceded by insertion of carbon monoxide.

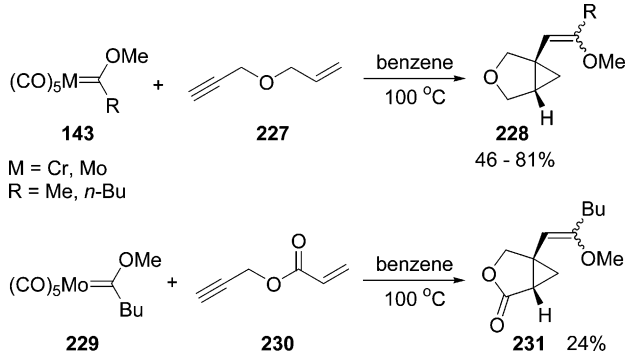
3.2.1. Cyclizations without Incorporation of CO

The reaction of insertion of an alkyne into a carbene−metal bond is a well-known process for

Scheme 59



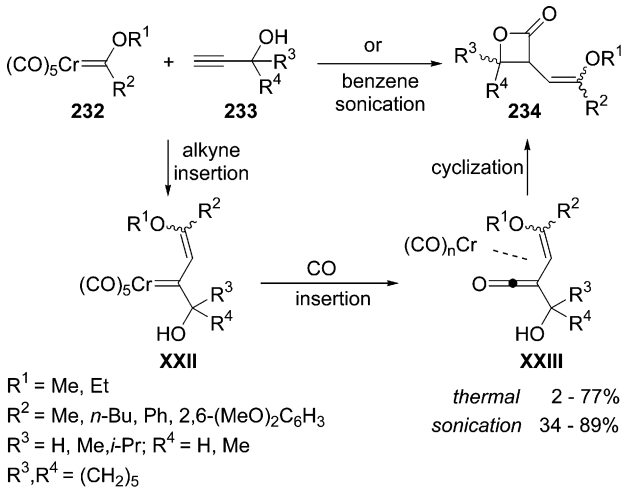
Scheme 60



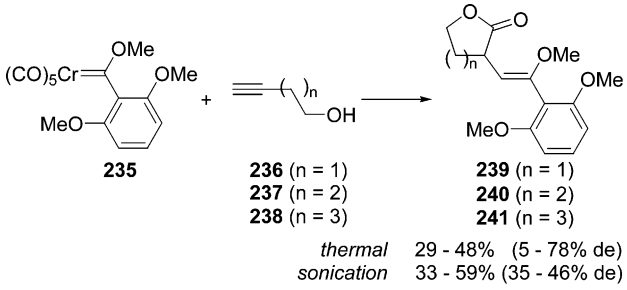
Fischer carbene complexes. Taking advantage of this reactivity, Herndon et al. have reported the cyclization of conjugated enyne-aldehydes and -ketones to the furan ring (Scheme 59).[75] Thus, refluxing the chromium carbene complex **123** and enynes **224** in dioxane results in the formation of alkenylfurans **225**, which yield methyl ketones **226** on acid treatment. Mechanistically, the authors propose the formation of the insertion intermediate **XXI**, followed by oxygen attack into the new carbene carbon and metal elimination/aromatization. The furan ring of the isobenzofurans **225** undergoes "in situ" a Diels−Alder reaction with different dienophiles.[75b−d] Following this methodology, steroid derivatives have been synthesized involving an intramolecular Diels−Alder reaction as the last step.[76,77]

The usefulness of the reaction of Fischer carbene complexes with enynes has been exploited by Harvey as a facile entry into bicyclic cyclopropanes. On the basis of this finding, Harvey et al. have used oxygen-containing enynes to access the oxabicyclo[3.1.0]-hexane framework (Scheme 60).[78] Thus, allyl propargyl ether **227** reacts with carbene complexes **143** to form the bicyclic tetrahydrofuran **228** in moderate to high yield. On the other hand, when propargyl acrylate **230** is employed the bicyclic γ-lactone **231** is obtained in rather low yield. This two-step process involves just alkyne−metal carbene insertion followed by intramolecular alkene cyclopropanation. Katz et al. reported similar results employing Fischer carbene complexes adsorbed on solid supports.[79]

Scheme 61



Scheme 62



3.2.2. Cyclizations with Incorporation of One Equivalent of CO

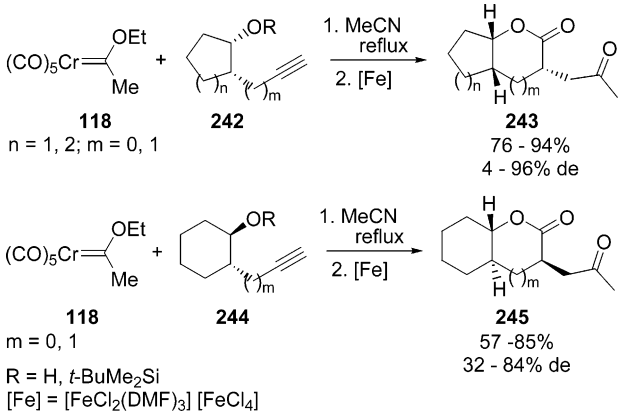
Incorporation of carbon monoxide into the organic skeleton is a common event when working with Fischer (pentacarbonyl)carbene complexes. In general, but not always, the CO incorporation takes place by insertion into the metal carbene bond. For instance, the reaction of propargylic alcohols **233** with carbene complexes **232** has been reported by Kerr et al. under thermal and sonication conditions and represents a facile entry into substituted β-lactones **234** (Scheme 61).[80] The whole sequence involves consecutive insertion of alkyne to generate **XXII**, CO insertion to form the metal ketene **XXIII**, and intramolecular nucleophilic oxygen attack onto the ketene function.

Using different ω-alkynols **236**−**238**, having variable tether length between the alkyne and the hydroxy functions, makes it possible to obtain γ-, δ-, and ϵ-lactones **239**−**241** in variable yields (Scheme 62).[81] The presence of two substituents at the 2,6-positions of the phenyl group inhibits the competitive benzannulation reaction.

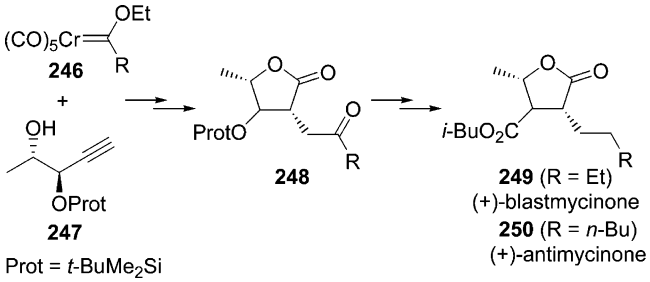
Mori et al. observed a similar reaction pathway in the reaction of Fischer carbene complexes **118** with rigid alkynols or silyl-protected alkynols **242** and **244** (Scheme 63).[82] The lack of flexibility allows in some cases a diastereoselective synthesis of bicyclic δ-lactones **243** and **245**. The diastereoselectivity of the reaction is highly dependent on the ring size and on the protecting group.

Based on this protocol, a short synthesis of the natural products (+)-blastmycinone **249** and (+)-

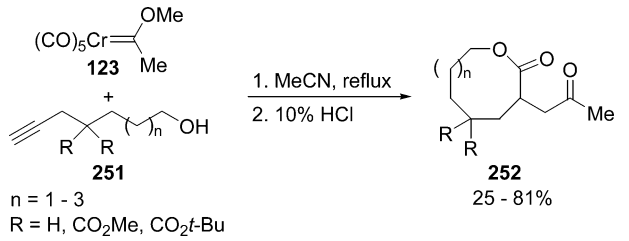
Scheme 63



Scheme 64



Scheme 65

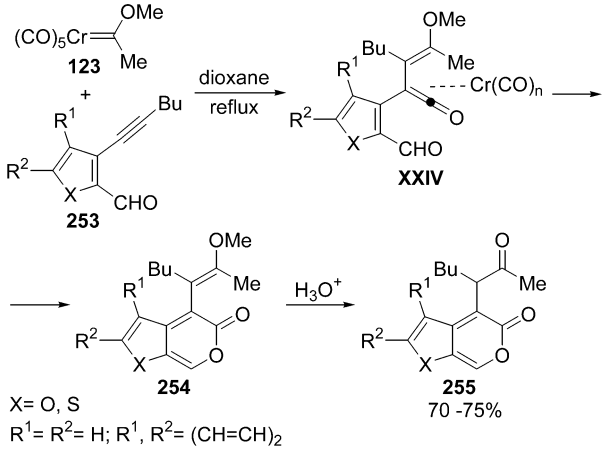


antimycinone **250** has been published by the same group (Scheme 64).[82] The synthesis of the key lactones **248** is easily accomplished from the carbene **246** and the chiral nonracemic alkynol **247**. γ-Lactones **248** were further elaborated into (+)-blastmycinone **249** and (+)-antimycinone **250** in three steps.

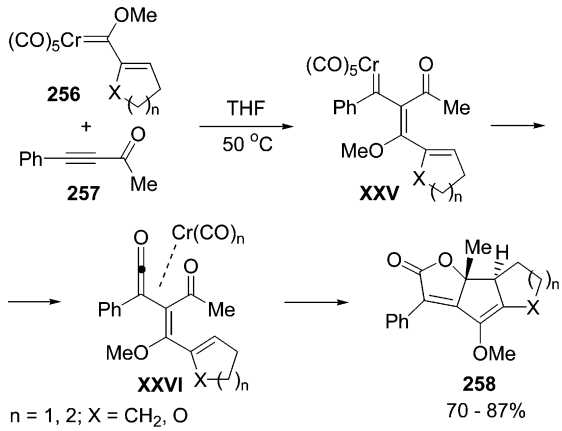
The same strategy is also adequate for the synthesis of medium-size lactones (Scheme 65).[83] Thus, chromium complex **123** and alkynols **251** afford eight-, nine-, and ten-membered lactones **252** in more than satisfactory yields.

The reaction of *o*-alkynylbenzaldehydes **224** [R^2,R^3 = (CH=CH)$_2$] and carbene complexes **123** has been shown to provide isobenzofurans **225** via alkyne insertion and cyclization (see Scheme 59).[75−77] However, the use of heteroaromatic enyne-aldehydes of the type **253** with carbene **123** does not result in the formation of furans, but rather the incorporation of CO occurs, leading to pyrone derivatives (Scheme 66).[84] In this case, the initial alkyne insertion step is followed by CO insertion, giving rise to the ketene intermediate **XXIV**. Finally, nucleophilic oxygen attack results in the formation of alkenylpyrone derivatives **254** or their hydrolysis products **255** in good overall yields. The subsequent intramolecular Diels−Alder reaction between the pyrone moiety and a remote alkene substituent has been demonstrated

Scheme 66



Scheme 67



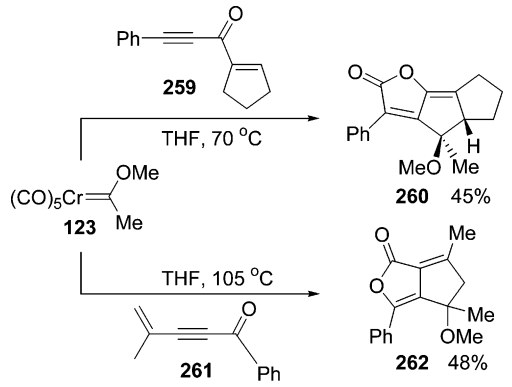
and enhances the synthetic potential of the basic process.[84,85]

On the other hand, alkynyl ketones show a peculiar behavior toward alkenylcarbene complexes, leading to fused lactones, as reported some years ago by Wulff et al. (Scheme 67).[86] For instance, the thermal treatment of cyclopentenyl and dihydropyranylcarbene complexes **256** toward phenylbutynone **257** produces good yields of tricyclic lactones **258** in a diastereoselective manner. The mechanism is claimed to initiate by consecutive alkyne and CO insertion reactions (intermediates **XXV** and **XXVI**, respectively). The geometry of the resulting intermediate **XXVI** precludes the benzannulation reaction, thus forcing the reaction to proceed to the final lactone derivatives by a Halban−White double cyclization.[87]

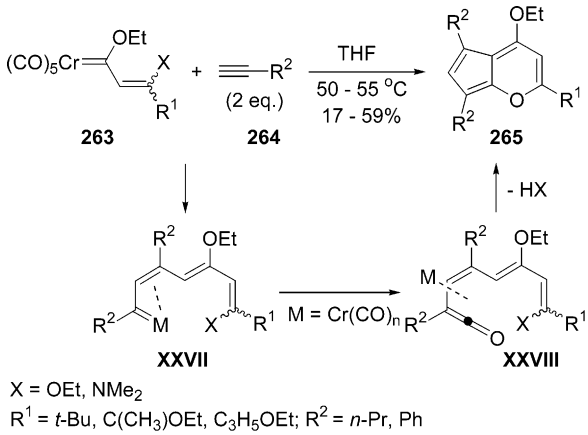
Simple chromium carbene complexes, such as **123**, can also participate in this process if an additional alkene functionality is incorporated into the alkyne substrate in conjugation with either alkyne or ketone functionalities (Scheme 68).[88] Thus, the reaction of **123** with the alkynyl alkenyl ketone **259** yields the tricyclic lactone **260** as a single diastereoisomer, while the bycyclic lactone **262** results from the conjugated enyne ketone **261**.

A relevant example of double alkyne insertion, along with CO insertion, has been described by de Meijere et al. This one-pot process allows an expeditious entry into the cyclopenta[*b*]pyran skeleton from alkenyl carbenes and alkynes (Scheme 69).[89] In this

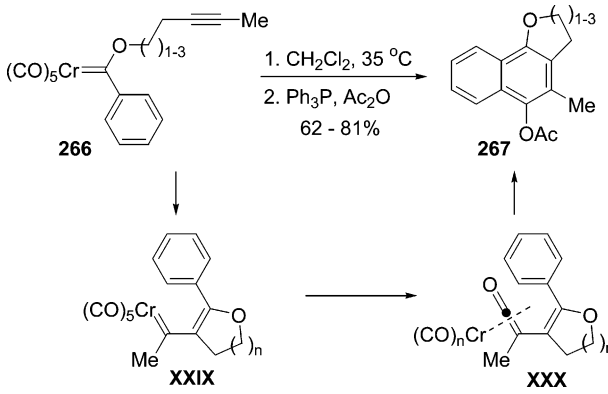
Scheme 68



Scheme 69



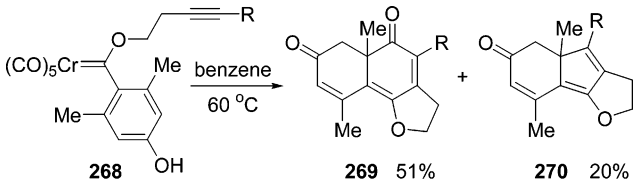
Scheme 70



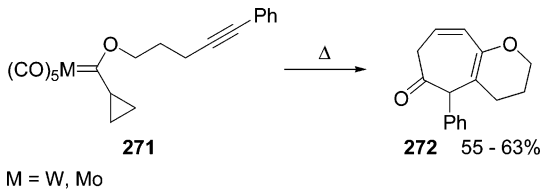
case, the starting β-amino- or β-ethoxyalkenylcarbene complexes **263** are able to consecutively and regioselectively insert 2 equiv of alkyne **264** to form the intermediate **XXVII**. This newly formed metal carbene undergoes CO insertion to generate the metal ketene **XXVIII**, which cyclizes to cyclopenta[*b*]pyrans **265** after amine or ethanol elimination.

Since its discovery by Dötz et al.,[90] the benzannulation reaction has been an excellent method to assemble an alkenyl(aryl) carbene, an alkyne, and CO to give substituted phenols (naphthols). The intramolecular version of this procedure, using carbenes with the alkyne tethered to the oxygen, would give rise to different benzofused oxygen heterocycles, depending on the tether length (Scheme 70).[91] Thus, carbene complexes **266** have been efficiently transformed into naphthofuran, naphthopyran, and naphthooxepine derivatives **267**, via the insertion intermediates **XXIX** and **XXX**.

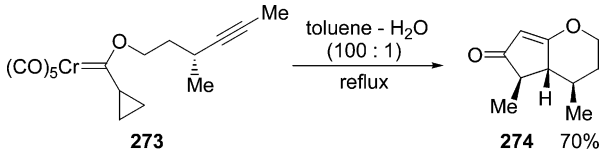
Scheme 71



Scheme 72



Scheme 73



The use of 2,6-dibustituted aryl carbene complexes **268** prevents the final aromatization step, thus leading to the cyclohexadienone moiety **269** (Scheme 71).[92] Along with the cyclohexadienone **269**, the cyclopentannulation compound (alkyne insertion and cyclization) **270** is obtained as a side product.

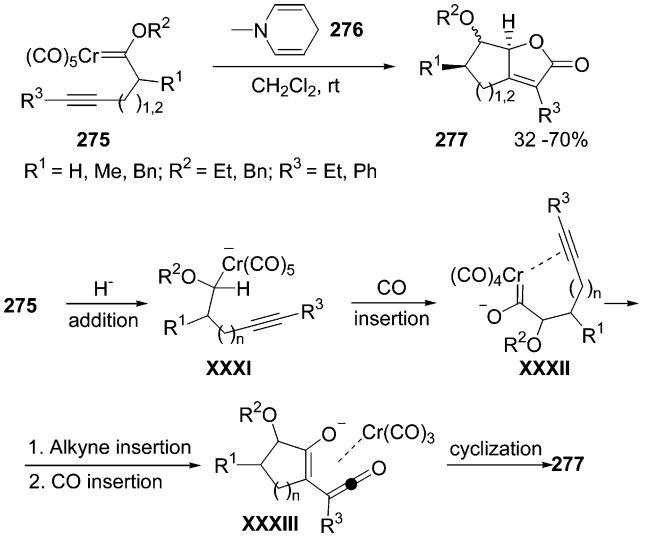
Cyclopropyl carbene complexes of tungsten and molybdenum can follow a similar reaction pattern, wherein the cyclopropane ring behaves in the cyclization step as does the conjugated C=C in the model benzannulation reaction. In this way, Herndon et al. have reported the synthesis of the cycloheptadienone **272** in moderate yield by heating cyclopropylalkoxycarbene complexes **271** (Scheme 72).[93]

Herndon et al. discovered that, contrary to the behavior of tungsten and molybdenum carbenes **271**, chromium cyclopropylcarbene complexes follow a different reaction pathway toward alkynes in the sense that no cycloheptadienone ring is formed, but cyclopentenones and ethene are instead the real reaction products.[94] The intramolecular version provides another route to oxygen heterocycles fused to the cyclopentenone ring.[95] Such a strategy is exemplified in Scheme 73 for the diastereoselective transformation of the cyclopropylcarbene **273** into the cycloadduct **274**.[96] Moreover, cyclopentenone **274** has been demonstrated to be a useful precursor of vitamin D_3.

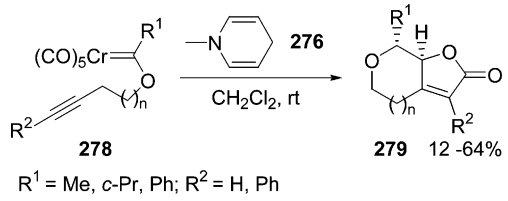
3.2.3. Cyclizations with Incorporation of Two Equivalents of CO

From a mechanistic point of view, the reactions collected in this section are not alkyne insertion-initiated processes, but the insertion reactions of CO (2 equiv) and alkyne take place in an alternate manner. The work described here has been performed by the Rudler group and provides a new and elegant aspect of the synthetic utility of Fischer carbene complexes.

Scheme 74



Scheme 75



A representative example using carbene complexes having an alkyne group tethered to the carbene alkyl chain is depicted in Scheme 74. Thus, different bicyclic butenolides **277** are readily formed in a single step by stirring a mixture of carbene complexes **275** in the presence of *N*-methyl-1,4-dihydropyridine **276**.[97] This apparently complex transformation is explained as follows: (i) dihydropyridine reduction of the M=C forms the metalate **XXXI**; (ii) insertion of CO generates **XXXII**; (iii) consecutive intramolecular insertion reactions of alkyne and CO provide **XXXIII**; and (iv) finally cyclization and metal decoordination give the observed butenolides.

Similarly, butenolides fused to oxygen-containing rings **279** result by starting with carbenes **278** having the alkyne tethered to the alkoxy chain (Scheme 75).[97b,c] Nucleophiles other than the hydride (MeO^-, Me^-, Bu^-, $Me_3SiCH_2^-$) have also been employed to initiate the process, yielding butenolides with an additional carbon or heteroatom substituent.[98]

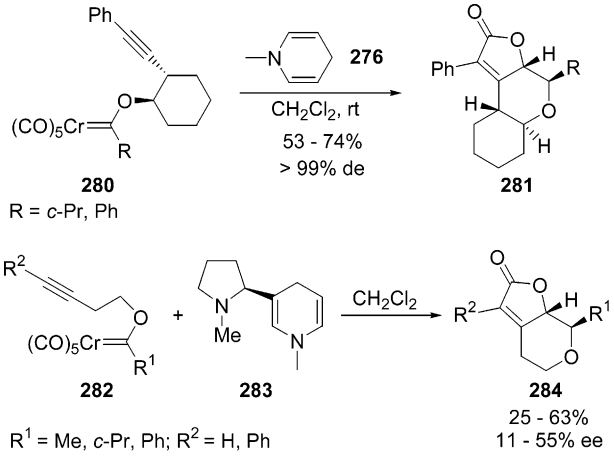
Some efforts have also been devoted to the enantioselective version of this reaction.[99] For instance, the use of chiral nonracemic carbene complexes **280** results in the formation of the tricyclic butenolide **281** as the sole isomer (Scheme 76). Unfortunately, attempts to achieve the asymmetric cyclization of carbenes **282** using enantiopure dihydropyridines **283** were not so satisfactory, as enantiomeric excesses up to 55% were reached.

3.3. Cyclizations Involving C–H Insertion

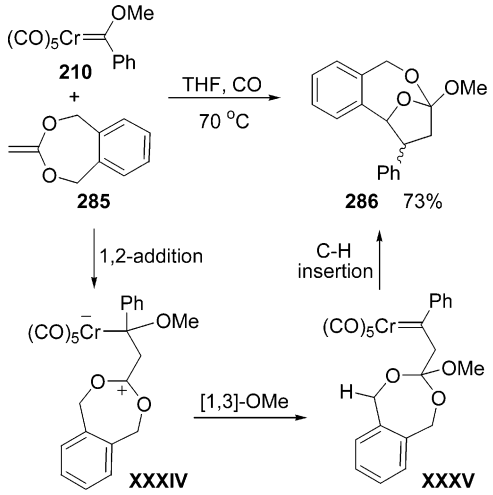
A few examples of C−H insertion reactions into group 6 Fischer carbene complexes have been reported.[100] In some of those cases, the strategy has found application in heterocyclic synthesis. For instance, Scheme 77 illustrates the synthesis of the structurally complex ortho ester **286** from the carbene **210** and the ketene acetal **285** that has been accomplished by Wulff et al.[101] The mechanistic proposal involves an initial 1,2-addition with the formation of the zwitterionic intermediate **XXXIV**, which goes to the nonstabilized carbene intermediate **XXXV** by methoxy migration. This intermediate undergoes intramolecular C−H insertion, leading to the ortho ester **286** in good yield and moderate diastereoselectivity.

An elegant application of this methodology was brought about in the synthesis of the sex pheromone eldanolide **289** (Scheme 78).[101] The procedure takes place with excellent stereoselectivity (trans/cis = 24) and requires only heating of the readily available

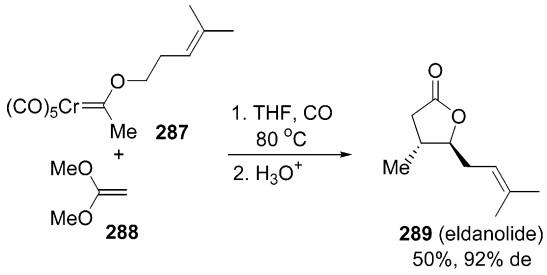
Scheme 76



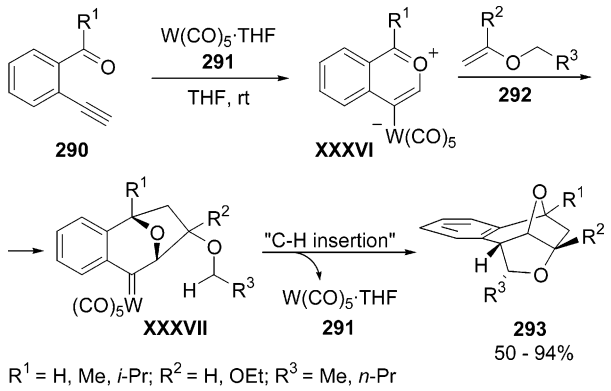
Scheme 77



Scheme 78



Scheme 79



reagents **287** and **288** and hydrolysis of the resulting ortho ester.

Iwasawa et al. have proposed a similar C−H insertion into an "in situ" nonstabilized Fischer carbene complex to rationalize the complex heteropolycyclic synthesis shown in Scheme 79.[102] First, 2-alkynyl phenones **290** are known to cyclize to the dipole **XXXVI** in the presence of $W(CO)_5$·THF **291**. This intermediate undergoes dipolar cycloaddition to electron-rich alkenes **292**, giving rise to the nonstabilized carbene complex **XXXVII**, which in turn is capable of cyclizing to the polycyclic structure **293** by intramolecular C−H insertion.

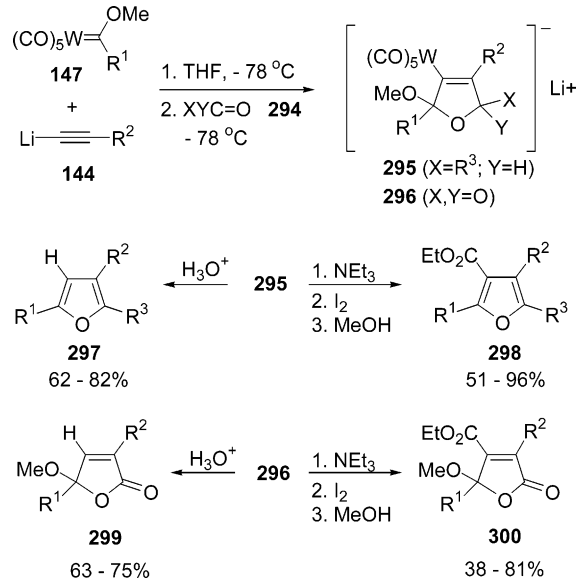
3.4. Cyclizations Initiated by Nucleophilic Attack

The electrophilic nature of the carbene carbon of Fischer carbene complexes makes them appropriate systems for nucleophilic addition-initiated heterocyclization reactions. In this context, it has been shown that the addition of lithium acetylides to structurally simple carbenes, followed by treatment with imine derivatives, leads to γ-lactams and pyrroles (see Schemes 37 and 38). This protocol has been extended to oxygen heterocycles by simply using suitable substrates, e.g., aldehydes and carbon dioxide (Scheme 80).[52,53] Thus, the metal intermediate (not shown) generated from carbenes **147** and acetylide **144** reacts with carbonyl derivatives **294**, affording metal heterocycles **295** (from aldehydes R^3CHO) and **296** (from CO_2). The intermediates **295** give substituted furans **297** and **298** by acid hydrolysis and ethoxycarbonylation, respectively. In turn, complexes **296** yield lactones **299** and **300**.

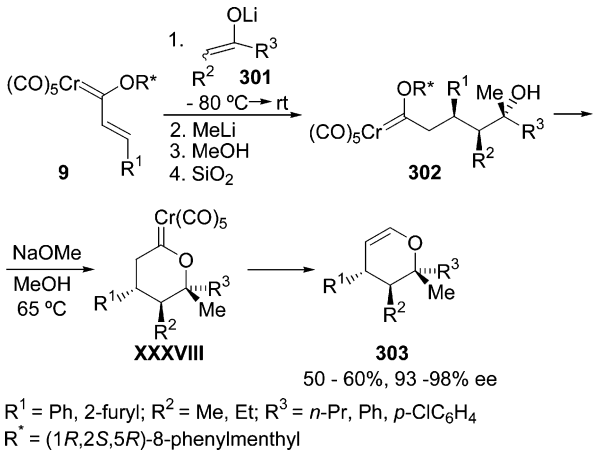
Taking advantage of the efficiency of the enantioselective Michael addition reaction to chiral nonracemic alkenyl Fischer carbene complexes, the asymmetric synthesis of optically active dihydropyrans has been carried out in this laboratory (Scheme 81).[103] The process begins with the diastereoselective conjugate addition of the ketone enolates **301** to the homochiral carbenes **9**, followed by "in situ" addition of methyllithium to the ketone function, to form **302**. The treatment of **302** with base results in 8-phenylmenthol displacement and formation of the carbene intermediate **XXXVIII**, which under the reaction conditions suffers reductive metal elimination, yielding **303** with very high enantiomeric excess.

In another interesting case, the synthesis of the polycyclic ether **307** in an optically pure form is

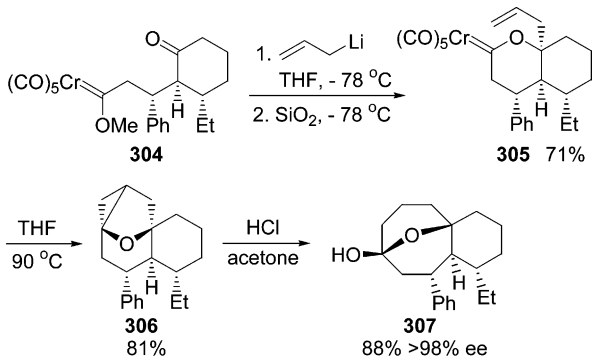
Scheme 80



Scheme 81



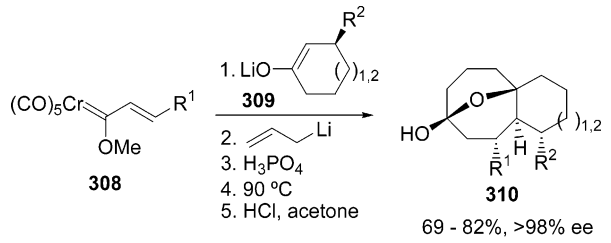
Scheme 82



accomplished from the enantiopure ketocarbene complex **304**, obtained from alkenyl(methoxy)carbenes and chiral nonracemic 3-ethylcyclohexanone enolate[104] (Scheme 82).[105] Carbene **304** is treated with allyllithium, giving the cyclic carbene **305**, which undergoes subsequent thermal cyclopropanation to **306** and acid hydrolysis to the tricyclic hemiketal **307**.

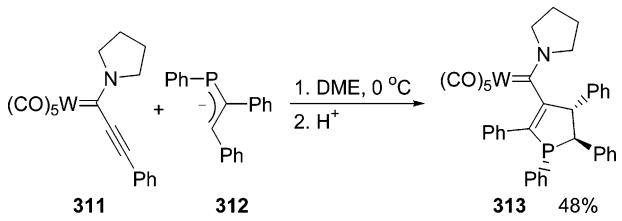
If the whole process is executed in a one-pot fashion, the procedure is greatly improved, not only

Scheme 83

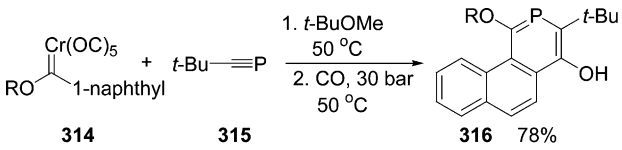


R^1 = Ph, *p*-$MeOC_6H_4$, 2-furyl, 2-thienyl; R^2 = Me, Et

Scheme 84



Scheme 85



R = Me, Et

in terms of operations saving but also because the yield is dramatically improved (Scheme 83).[105] Thus, the one-pot procedure makes it possible to obtain the cycloadducts **310** in more that 69% yield, whereas the overall yield for the stepwise formation of **307** is 37%.

4. Synthesis of Phosphorus Heterocycles

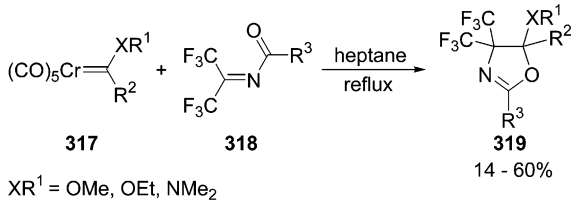
Examples of syntheses of phosphorus-containing heterocycles by means of Fischer carbene complexes are scarcely found in the literature. In this context, the Dötz group has studied some aspects of the reactivity of Fischer carbene complexes with phosphorus substrates. For instance, Scheme 84 illustrates the formation of the dihydrophosphole ring **313** via an anionic [3+2] cycloaddition of the 1-phosphaallyl anion **312** to the alkynyl(amino)carbene complex **311**.[106]

Interestingly, the well-known benzannulation reaction of Fischer carbene complexes with alkynes has been successfully extended by Dötz et al. to phosphaalkynes (Scheme 85).[107] Thus, the reaction of the chromium 2-naphthylcarbene complex **314** with *tert*-butylphosphacetylene **315** gives rise to phosphaphenanthrene **316** in good yields. Other substitution patterns in the carbene complex result in mixtures of products arising from competition between phosphaannulation and oxaphosphole formation (vide infra, Scheme 90).

5. Synthesis of Heterocycles Containing Two Different Heteroatoms

Finally, various processes dealing with the synthesis of heterocyclic compounds containing two different heteroatoms have been developed.

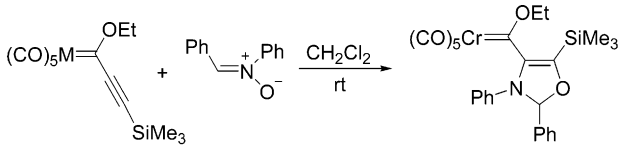
Scheme 86



XR^1 = OMe, OEt, NMe_2

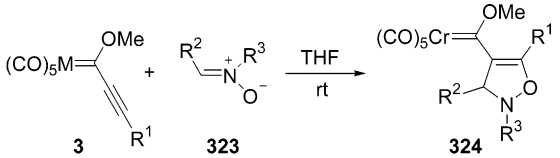
R^2 = Me, Ph; R^3 = *t*-Bu, Ph, *p*-FC_6H_4

Scheme 87



M = Cr, W

Scheme 88



M = Cr, W

R^1 = Ph, *p*-MeC_6H_4

R^2 = Ph, *p*-XC_6H_4, (X= Me, OMe, NMe_2, NO_2, Cl, Br, CN)

R^3 = Me, *t*-Bu, Bn

First of all, an isolated example from simple chromium carbene complexes was reported 30 years ago by Fischer et al. (Scheme 86).[108] Oxazolines **319** were obtained in the reaction of the carbene complexes **317** and the *N*-acylimines of hexafluoroacetone **318**. The cycloadditon was accomplished in poor to good yields.

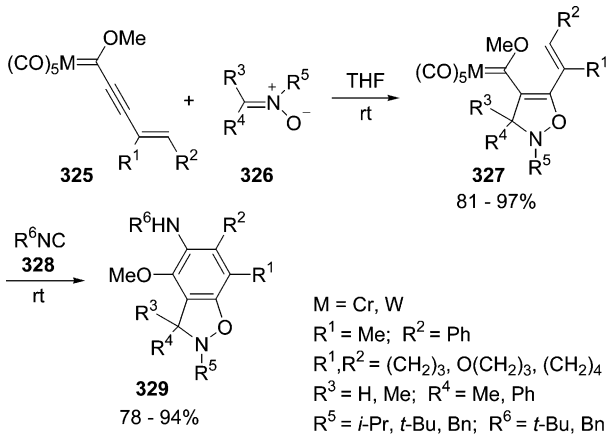
Because of the highly electrophilic character of the carbon−carbon triple bond of alkynyl carbene complexes, the imine oxide **321** reacts with carbenes **320** at room temperature, affording the rearranged metal carbene oxazoline **322**, as reported some years ago by Kalinin et al. (Scheme 87).[109] The authors invoked an isoxazoline−oxazoline rearrangement to occur after the presumed dipolar cycloaddition takes place.

Later on, W. Chan et al. studied this reaction in some detail and reported the chemo- and regioselective preparation of a number of 2,3-dihydroisoxazole carbene complexes **324** from carbenes **3** and imine oxides **323** (Scheme 88).[8b,110]

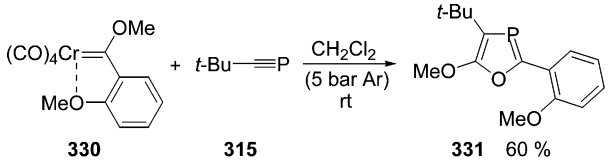
Because of their polyfunctional character, α,β-unsaturated carbene complexes frequently provide polycyclic systems through consecutive reactions. In this way, our group has found that enynecarbene complexes **325** react with imine oxides **326** to produce the expected alkenyldihydroisoxazole carbenes **327**, which in turn undergo a [5+1] cyclization with isonitriles **328**, giving rise to benzoisoxazoles **329** (Scheme 89).[111]

Lastly, an isolated example relative to heterocycles containing phosphorus and oxygen is worth noting (Scheme 90).[107b,c] Dötz et al. have reported the formation of the 1,3-oxaphosphole **331** by reacting the

Scheme 89



Scheme 90



tetracarbonylbenzylidene complex **330** with the phosphaalkyne **315**. The corresponding benzannulation-type reaction may compete, as already mentioned (see Scheme 85).

6. Conclusions

As the examples presented in this review demonstrate, metal carbene complexes of group 6 are reactive toward a wide array of heteroatom-containing substrates, allowing access to a great variety of mono- and polyheterocyclic compounds. In most cases, four- to seven-membered rings are successfully formed in a single step and with high selectivity. Among them, the facile azepine ring formation seems of particular relevance in terms of both mechanistic and synthetic purposes.

On the other hand, and fortunately, much additional work is needed to fully exploit the synthetic utility of transition metal carbene complexes in heterocyclic synthesis. For instance, (i) developing cascade or consecutive processes that resemble those well known in recent syntheses of carbocycles will be welcome; (ii) designing new asymmetric methodologies or strategies is needed to improve the potential of these metal complexes in enantioselective heterocyclic synthesis; and (iii) doubtless the use of stoichiometric amounts of the metal reagent can be considered as the major and general drawback of these carbene complex-based synthetic strategies. Therefore, a conceptually new aspect that requires particular attention and that would qualitatively improve the general potential of these systems lies in the implementation of efficient catalytic processes.

7. Acknowledgments

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