Fischer Carbene Complexes in Organic Synthesis: Metal-Assisted and Metal-Templated Reactions

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Contents

1. Introduction: Synthesis and Reactivity of Fischer Carbene Complexes

The formal combination of a carbene and an organometallic fragment yields carbene complexes. They are commonly classified as *Fischer*- and *Schrock*-type complexes. While Schrock-type compounds (first described in the early 1970s) play an important role in olefin metathesis (acknowledged by the Nobel Prize 2005[1]), Fischer carbene complexes, which were first reported in 1964[2a] and 1965,[2b] have been developed into powerful reagents for organic synthesis.[3] This review concentrates on group 6 metal carbene complexes with a special focus on chromium complexes since, because of their balance of reactivity and stability combined with easy accessibility (see below), they are the most prominent members of the Fischer carbenes and have found the broadest application. While most of the recent chemistry of Fischer carbene complexes has been periodically summarized during the last 5−10 years,[4] this review, apart from the basic characteristics of Fischer carbene complexes in the introductory part, will focus on the developments since the mid-1990s. The literature is covered up to April 2009.

1.1. Synthesis

The original and still most general entry into Fischer-type metal carbenes ("Fischer route") involves the se-

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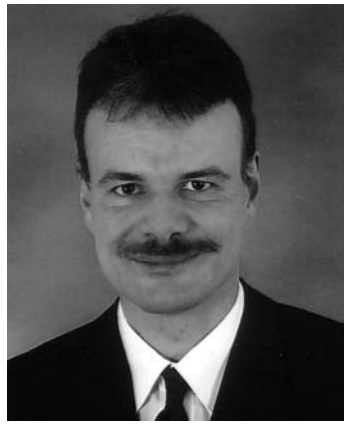
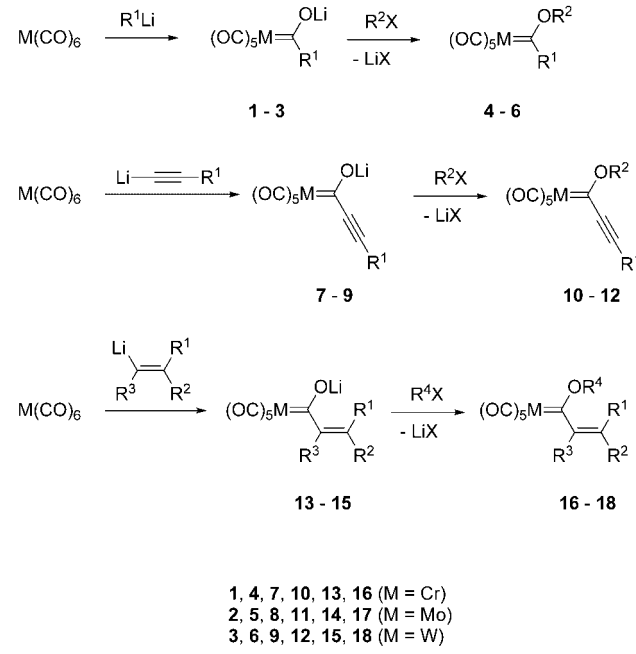
Karl Heinz Dötz received his Ph.D. in Inorganic Chemistry from the Technical University in Munich with Prof. E. O. Fischer. He then focused on the organic chemistry of metal carbenes, which he applied to novel metal-templated cycloaddition reaction patterns. In 1986 he moved to the Philipps-University of Marburg, where he became Professor of Organometallic Chemistry. In 1992 he was appointed Professor of Organic Chemistry at the Rheinische Friedrich-Wilhelms-University and Co-Director of the Kekulé-Institute. He is a recipient of the Victor Grignard−Georg Wittig Lectureship and chaired the Bonn-based Collaborative Research Center SFB 624 "Templates—From chemical matrices to reaction control" from 2002−2007. He was a member of the Review Board of the German Research Foundation from 2005−2008. His present research interests concentrate on organometallic template reactions, stereoselective synthesis and catalysis, haptotropic metal migration, and low-molecular-mass gelators.



Joachim Stendel was born and raised in Bruehl and Huerth, two towns located in the Rhineland between the cities of Cologne and Bonn. After graduation from the Gymnasium (High School), he studied chemistry at the Rheinische Friedrich-Wilhelms-University at Bonn. He stayed in Bonn and joined the group of Prof. Dr. K. H. Dötz at the Organic Chemistry Department in 1999. In his Diploma Thesis, which he completed in 2000, he started to work on the synthesis and haptotropic metal migration of phenanthrene chromium tricarbonyl complexes. He continued and expanded this work on phenanthrene and triphenylene chromium tricarbonyl derivatives during his Ph.D. Thesis, which was finished in 2004. Since then, he is a postdoctoral researcher in the Dötz group. His research interests include the organometallic chemistry of Fischer carbene and arene chromium tricarbonyl complexes.

quential addition of a carbon nucleophile and a carbon electrophile across a metal-coordinated carbon monoxide ligand (Scheme 1).[5] Addition of an organolithium reagent (alkyl-, aryl-, alkenyl-, or alkynyllithium derivative) to hexacarbonyl chromium affords acyl metalates **1**−**3**, **7**−**9**, and **13**−**15**, respectively, that undergo an in situ O-alkylation by hard alkylating reagents such as trialkyloxonium tetrafluoroborates[6a,b] or alkyl fluorosulfonates[6c−e] to give alkoxycarbene complexes **4**−**6**, **10**−**12**, and **16**−**18**, respectively, in typical yields of 60−90%. Alkylation of the acyl

Scheme 1. Fischer Route to Group 6 Metal Alkoxycarbene Complexes

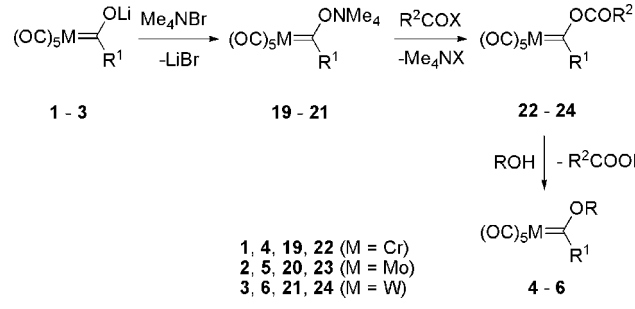


metalate has been also performed with methyl iodide using phase-transfer catalysis.[7] Very recent work includes the synthesis of fully alkylated pyranylidene Fischer carbene complexes by addition of 1-lithio-1,3-butadienes to $Cr(CO)_6$ bearing a terminally attached leaving group, which allows for the intramolecular alkylation of the acyl metalate intermediate.[8] For applications in combinatorial chemistry, Fischer carbene complexes attached to solid supports have been prepared.[9]

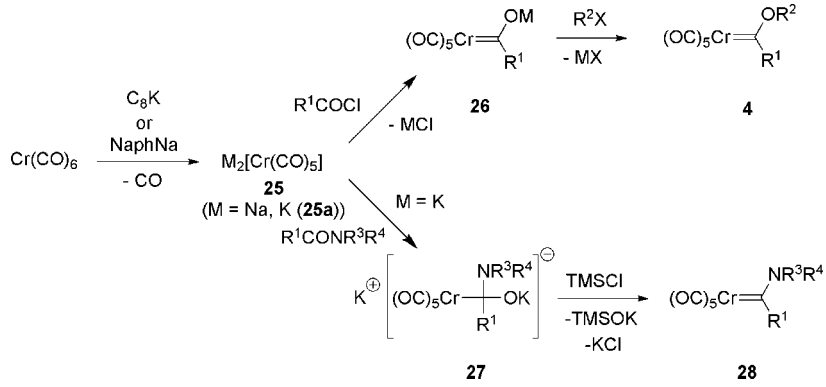
A slight modification of the Fischer route is necessary to obtain diazophenylcarbene complexes; here, the transmetalation of the aryllithium to an organozinc intermediate[10] was found to suppress the undesired attack of the alkyllithium reagent on the diazo functionality (causing reduction to hydrazines).

Highly functionalized alkoxycarbene complexes are formed upon alcoholysis of strongly electrophilic acyloxycarbene complexes **22**−**24**[11] generated via in situ acylation starting from the storable tetraalkylammonium acyl metalates **19**−**21**, which are obtained from the lithium precursors **1**−**3**. This is the method of choice for the synthesis of metal carbenes **4**−**6** that bear chiral terpene or sugar auxiliaries or functionalized alkyl moieties in the alkoxy substituent (Scheme 2). Functionalized carbene complexes have been also prepared via diphenylsulfonium salts.[12]

Scheme 2. Preparation of Fischer Carbene Complexes Bearing Functionalized or Optically Active Alkoxy Substituents



Scheme 3. Semmelhack−Hegedus Route to Group 6 Metal Alkoxy- and Aminocarbene Complexes

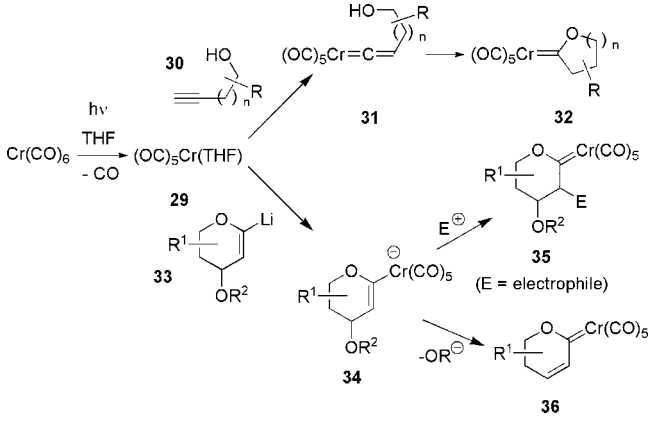


A factor limiting the versatile Fischer route may be the availability of the organolithium compound. Here, a complementary access to alkoxy- and aminocarbene complexes (Semmelhack-Hegedus route) offers an alternative. That approach involves the addition of the pentacarbonylchromate dianion **25** (obtained from the reduction of hexacarbonyl chromium with sodium naphthalenide (NaphNa)[14a,b] or—more conveniently—C_8K[14c] (**25a**)) to acyl chlorides and amides (Scheme 3).[13,14] While alkylation of acyl chromate **26** leads to alkoxycarbene complexes **4**, addition of chromate dianion **25** to carboxylic amides generates the tetrahedral intermediates **27**, which are deoxygenated by trimethylsilyl chloride to give aminocarbene complexes **28**.

Both the Fischer and Semmelhack−Hegedus routes have been applied for the synthesis[15] of biscarbene[16a] and polymetallic carbene complexes.[16b]

Finally, a special synthetic entry into vinylidene and cyclic carbene complexes has been developed (Scheme 4). Photochemical cleavage of one carbonyl ligand in hexacarbonyl chromium in the presence of a weakly coordinated ligand like tetrahydrofuran[17a] or triethylamine[17b] yields a pentacarbonyl chromium σ-complex $(OC)_5CrL$ **29**, which is reacted with either ω-alkynols **30** or with lithioglycals **33**.[18,19] In the former case, vinylidene complexes **31** (that may be generated with[18a−f] or without[18g] irradiation) are formed first, which transform into metal oxacycloalkylidenes **32**. Using lithioglycals **33**, the tetrahydrofuran (THF) complex **29** produces vinyl chromates **34**, which may add an electrophile to yield **35** or undergo OR^--elimination resulting in α,β-unsaturated chromium carbene complexes **36**. Medium-sized chromium oxacycloalkylidenes have been prepared by ring-closing metathesis of chromium alkenyl(alkenyloxy)carbene complexes,[20a] while bis(alkenyl)carbene chromium complexes afford carbocylic carbene complexes.[20b] The use of diphenylcarbene complexes $(OC)_5Cr{=}C(Ph)_2$ (see section 2.1.1 for their preparation) offers a complementary metathesis-based access to cyclic (sugar-type) Fischer carbene complexes.[21]

Scheme 4. Preparation of Furanylidene and Pyranylidene Fischer Carbene Complexes



Alkenyl- and alkynylcarbene complexes have found the broadest application in synthetic organic chemistry (see below). These derivatives have been exclusively prepared by the Fischer route using alkenyl- and alkynyllithium compounds as organolithium sources. An alternative access to alkenylcarbene complexes is based on aldol reactions starting from alkylcarbene precursors or on Michael-type addition of carbon and heteroatom nucleophiles to alkynylcarbene complexes (see section 2.1.1).

For a better overview, the carbene complexes discussed in this review are compiled in Figures 1−3 and 7.

1.2. General Reactivity

Fischer-type metal carbenes usually contain a late transition metal (groups 6−8) in a low oxidation state in the organometallic fragment generally bearing ligands with good π-acceptor properties (typically carbon monoxide) in the coligand coordination sphere. The carbene carbon atom represents a strongly electrophilic center as evident from low-field ^{13}C NMR shifts of up to 400 ppm[22] resembling those of carbenium ions (see mesomeric structure **II** in Figure 4), which is usually stabilized by π-donation from heteroatoms (oxygen or nitrogen, as depicted in mesomeric structure **III** in Figure 4). Thus, the metal carbonyl fragment plays the role of a functional group that activates the carbene ligand for subsequent reactions (as discussed in section 2). The characteristic reactivity pattern of carbonyl alkylcarbene complexes is illustrated in Figure 5.

The electrophilicity of the carbene carbon atom favors the attack of carbon and heteroatom nucleophiles (**A**). Electrophiles may add to the heteroatom carbene substituent (**B**), which represents the first step in the transformation of metal carbenes to metal carbynes.[23,24]

As a consequence of the electrophilicity of the carbene carbon, the acidity of α-CH groups is significantly enhanced, for instance, the methoxy(methyl)carbene chromium complex **4a** features a pK_a value of ~8.[25] Therefore, deprotonation by strong bases generates metal carbene anions that may be applied as C-nucleophiles to alkylation, aldol-, and *Michael*-type reactions (**C**). Finally, carbonyl ligands undergo thermal or photochemical substitution for other types of ligands (e.g., phosphines, alkenes, alkynes), which allows for a modifica-

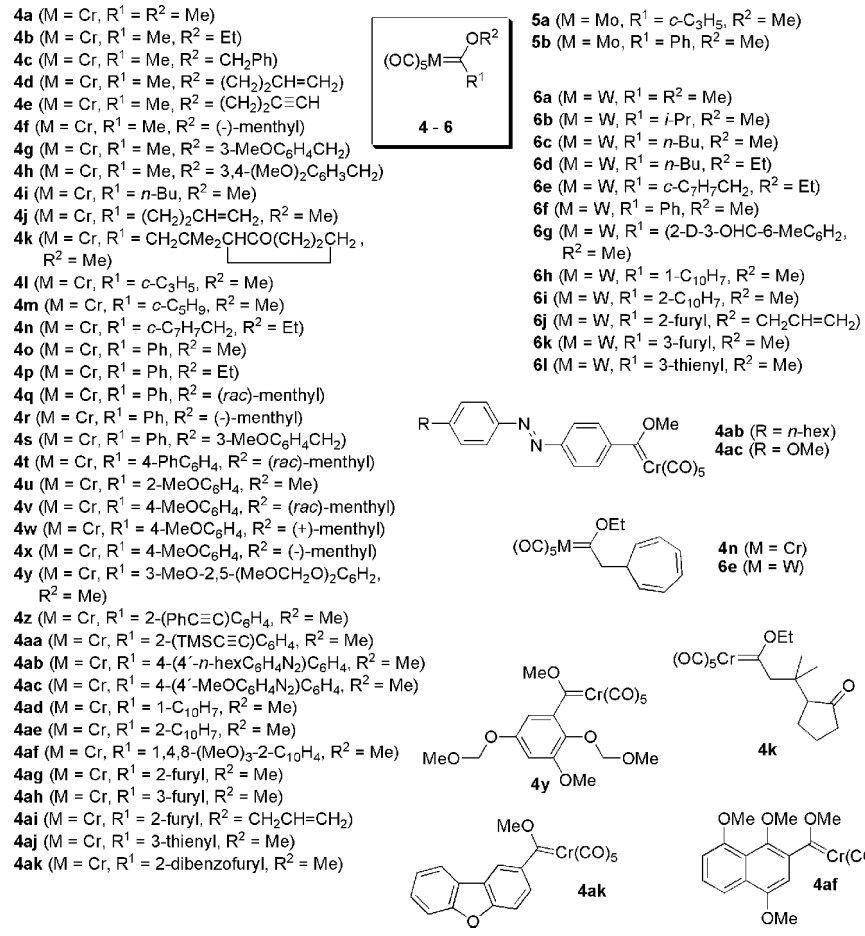
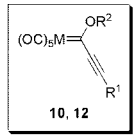


Figure 1. Compilation of individual group 6 metal *Fischer* alkyl- and aryl(alkoxy)carbene complexes discussed in this review.



10a (M = Cr, $R^1 = R^2$ = Me)
10b (M = Cr, R^1 = *n*-Bu, R^2 = Me)
10c (M = Cr, R^1 = *t*-Bu, R^2 = Me)
10d (M = Cr, R^1 = TMS, R^2 = Me)
10e (M = Cr, R^1 = CH=CH(*E*-Ph), R^2 = Me)
10f (M = Cr, R^1 = CH_2CH=CH(*E*-CH=C(*E*-Me), R^2 = Me)
10g (M = Cr, R^1 = C(Me)=CH(*E*-Ph), R^2 = Me)
10h (M = Cr, R^1 = C(Me)=CH(*E*-CH_2OCH_2CH=CH_2), R^2 = Me)
10i (M = Cr, R^1 = 1-cyclopentenyl, R^2 = Me)
10j (M = Cr, R^1 = 1-cyclohexenyl, R^2 = Me)
10k (M = Cr, R^1 = Ph, R^2 = Me)
10l (M = Cr, R^1 = Ph, R^2 = Et)
10m (M = Cr, R^1 = 4-MeC_6H_4, R^2 = Et)
10o (M = Cr, R^1 = 4-$MeOC_6H_4$, R^2 = Et)
10p (M = Cr, R^1 = 2-(CH_2=CH)C_6H_4, R^2 = Me)
10q (M = Cr, R^1 = 2-(PhHC=CH)C_6H_4, R^2 = Me)
10q (M = Cr, R^1 = 2-(HC≡C)C_6H_4, R^2 = Me)
10r (M = Cr, R^1 = 3-(HC≡C)C_6H_4, R^2 = Et)
10s (M = Cr, R^1 = 3-(TMSC≡C)C_6H_4, R^2 = Et)
10t (M = Cr, R^1 = 2-(PhC≡C)C_6H_4, R^2 = Me)

12a (M = W, $R^1 = R^2$ = Me)
12b (M = W, R^1 = *n*-Bu, R^2 = Me)
12c (M = W, R^1 = *i*-Bu, R^2 = Me)
12d (M = W, R^1 = *t*-Bu, R^2 = Me)
12e (M = W, R^1 = TMS, R^2 = Me)
12f (M = W, R^1 = C(Me)=CH_2, R^2 = Me)
12g (M = W, R^1 = C(Me)=CH(*E*-Ph), R^2 = Me)
12h (M = W, R^1 = 1-cyclopentenyl, R^2 = Me)
12i (M = W, R^1 = 1-cyclohexenyl, R^2 = Me)
12j (M = W, R^1 = Ph, R^2 = Me)
12k (M = W, R^1 = Ph, R^2 = Et)
12l (M = W, R^1 = 4-$MeOC_6H_4$, R^2 = Me)
12m (M = W, R^1 = 4-ClC_6H_4, R^2 = Me)

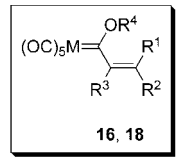
Figure 2. Compilation of individual chromium and tungsten Fischer alkynyl(alkoxy)carbene complexes discussed in this review.

tion of the coligand sphere (**D**). This reactivity pattern demonstrates that the organometallic functionality may induce either ligand-centered or metal-centered reactions. Another typical reaction pattern of carbene complexes in general, the (intramolecular) insertion of the metal−carbene bond into C−H bonds, has been applied to the synthesis of heterocycles: Chromium *o*-phenyl(dialkylamino)carbene complexes have been transformed into indoles at room temperature in 70−80% yield.[26]

Decarbonylation in the coligand sphere creates a vacant coordination site at the metal, which may act as a template (template effect)[27] and provide a suitable geometry for subsequent interligand coupling, thus allowing for C−C bond formation to proceed within the coordination sphere of the metal (see section 3).

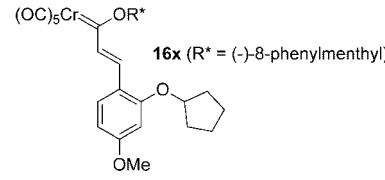
Generally, carbon nucleophiles (organolithium compounds, enolates, and amides) can add in a 1,2- or 1,4-fashion to α,β-alkenyl- (**I**) and also in a 1,6-fashion to arylcarbene complexes (**II**) (Figure 6).[28] While 1,2- and 1,4-addition to alkenyl- and alkynylcarbene complexes will be disclosed in various examples throughout this review, 1,4- and 1,6-addition reactions are discussed here.

The 1,4- and 1,6-addition to arylcarbene complexes has been investigated with phenylcarbene complexes **4q**, **4t**, and **4v**−**4x** bearing a bulky menthyloxy substituent at the carbene carbon atom that blocks the 1,2-addition pathway.[29a] Instead, 1,4-addition of alkyllithium compounds to electron-rich *para*-methoxyphenylcarbene complexes leads to 1,3-cyclohexadienylcarbene complexes **37**, while 1,6-addition affords 1,4-cyclohexadienylcarbene complexes **38**. Starting from unsubstituted phenyl(menthyloxy)carbene complexes, substituted phenylcarbene complexes **39** were isolated after 1,6-addition and treatment with silica gel (Scheme 5). The 1,4-addition to chromium furyl(menthyloxy)carbene complexes has been exploited for the regio- and diastereoselective dearomatization of furans.[29b]



16a (M = Cr, R^4 = Me, R^1 = R^2 = R^3 = H)
16b (M = Cr, R^2 = R^4 = Me, R^1 = R^3 = H)
16c (M = Cr, R^1 = Me, R^2 = NMe_2, R^4 = Et, R^3 = H)
16d (M = Cr, R^1 = $(CH_2)_3$OTBDMS, R^2 = NMe_2, R^4 = Et, R^3 = H) (TBDMS = $SiMe_2t$-Bu)
16e (M = Cr, R^1 = $(CH_2)_2C(Br)=CH_2$, R^2 = NMe_2, R^4 = Et, R^3 = H)
16f (M = Cr, R^1 = *n*-Pr, R^2 = NMe_2, R^4 = Et, R^3 = H)
16g (M = Cr, R^2 = *i*-Pr, R^4 = Me, R^1 = R^3 = H)
16h (M = Cr, R^1 = R^2 = R^4 = Me, R^3 = H)
16i (M = Cr, R^1 = *c*-C_3H_5, R^2 = NMe_2, R^4 = Et, R^3 = H)
16j (M = Cr, R^2 = R^3 = -$(CH_2)_3$-, R^4 = Me, R^1 = H)
16k (M = Cr, R^2 = R^3 = -$(CH_2)_4$-, R^4 = Me, R^1 = H)
16l (M = Cr, R^2 = R^3 = -$O(CH_2)_3$-, R^4 = Me, R^1 = H)
16m (M = Cr, R^2 = Ph, R^4 = Me, R^1 = R^3 = H)
16n (M = Cr, R^2 = Ph, R^4 = Et, R^1 = R^3 = H)
16o (M = Cr, R^2 = Ph, R^4 = $(CH_2)_2I$, R^1 = R^3 = H)
16p (M = Cr, R^2 = Ph, R^4 = (-)-menthyl, R^1 = R^3 = H)
16q (M = Cr, R^2 = Ph, R^4 = (+)-menthyl, R^1 = R^3 = H)
16r (M = Cr, R^2 = Ph, R^4 = (-)-8-phenylmenthyl, R^1 = R^3 = H)
16s (M = Cr, R^2 = Ph, R^4 = Me, R^1 = R^3 = H)
16t (M = Cr, R^1 = Ph, R^2 = NMe_2, R^4 = Et, R^3 = H)
16u (M = Cr, R^2 = 4-MeC_6H_4, R^4 = Me, R^1 = R^3 = H)
16v (M = Cr, R^2 = 4-$MeOC_6H_4$, R^4 = Me, R^1 = R^3 = H)
16w (M = Cr, R^2 = 4-$MeOC_6H_4$, R^4 = (-)-8-phenylmenthyl, R^1 = R^3 = H)
16x (M = Cr, R^2 = 4-MeO-3-[(*c*-C_5H_9)O]C_6H_3, R^4 = (-)-8-phenylmenthyl, R^1 = R^3 = H)
16y (M = Cr, R^2 = 2-furyl, R^4 = Me, R^1 = R^3 = H)
16z (M = Cr, R^2 = 2-furyl, R^4 = (-)-menthyl, R^1 = R^3 = H)
16aa (M = Cr, R^2 = 2-furyl, R^4 = (-)-8-phenylmenthyl, R^1 = R^3 = H)
16ab (M = Cr, R^2 = 2-thienyl, R^4 = Me, R^1 = R^3 = H)
16ac (M = Cr, R^2 = 2-thienyl, R^4 = $(CH_2)_2I$, R^1 = R^3 = H)

18a (M = W, R^2 = R^4 = Me, R^1 = R^3 = H)
18b (M = W, R^1 = R^4 = Me, R^2 = R^3 = H)
18c (M = W, R^2 = *n*-Pr, R^4 = Me, R^1 = R^3 = H)
18d (M = W, R^2 = *i*-Pr, R^4 = Me, R^1 = R^3 = H)
18e (M = W, R^1 = CH=CH(*Z*-$(CH_2)_3CH$=CH(*E*-$CH=CH_2$)), R^4 = Me, R^2 = R^3 = H)
18f (M = W, R^3 = $C(Me)=CH_2$, R^1 = OEt, R^2 = D, R^4 = Me)
18g (M = W, R^2 / R^3 = -$(CH_2)_3$-, R^4 = Me, R^1 = H)
18h (M = W, R^2 / R^3 = -$O(CH_2)_3$-, R^4 = Me, R^4 = H)
18i (M = W, R^2 = Ph, R^4 = Me, R^1 = R^3 = H)
18j (M = W, R^2 = Ph, R^4 = Et, R^1 = R^3 = H)
18k (M = W, R^1 = Ph, R^2 = NMe_2, R^4 = Et, R^3 = H)
18l (M = W, R^2 = 4-$MeOC_6H_4$, R^4 = Me, R^1 = R^3 = H)
18m (M = W, R^2 = 2-furyl, R^4 = Me, R^1 = R^3 = H)



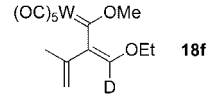


Figure 3. Compilation of individual chromium and tungsten Fischer alkenyl(alkoxy)carbene complexes discussed in this review.

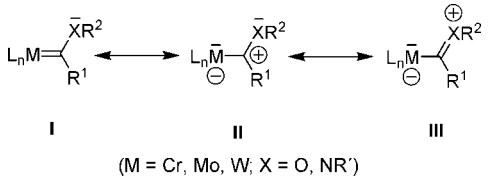


Figure 4. Mesomeric structures of Fischer carbene complexes.

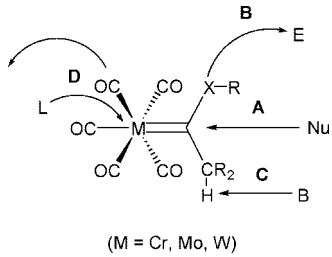


Figure 5. Reaction pattern of group 6 Fischer alkylcarbene complexes (B = base, E = electrophile, L = ligand, and Nu = nucleophile).

A similar approach was used to generate some chromium *para*-acylphenyl(isobutyloxy)carbene complexes by dehalolithiation of the corresponding *para*-bromophenylcarbene complex and trapping the lithiated phenylcarbene complex intermediate with an appropiate electrophile.[30] Here, the

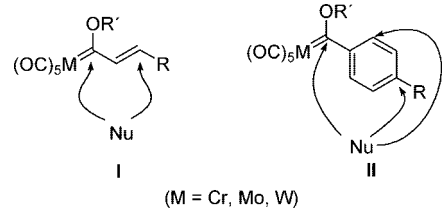


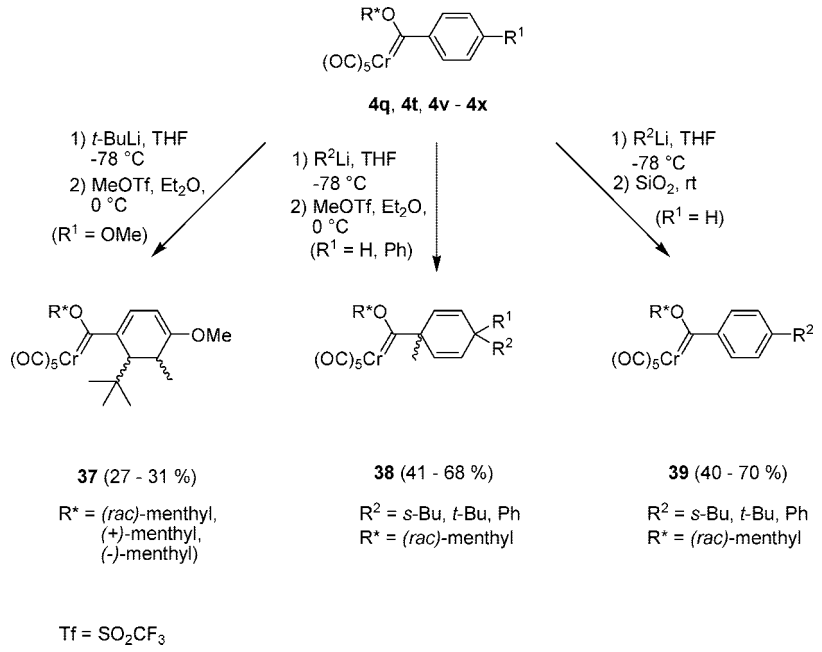
Figure 6. 1,2-, 1,4-, and 1,6-addition patterns of carbon nucleophiles (Nu) to α,β-alkenyl- and arylcarbene complexes.

sterically demanding alkoxy substituent at the carbene carbon atom was essential for the dehalolithiation to occur in the *para* position, albeit in only up to 49% yield.

2. Metal-Assisted Modification of Fischer Carbene Complexes

The metal−carbonyl fragment in Fischer carbene complexes renders the carbene carbon atom the electrophilic center of the molecule and enhances the α-C−H acidity of adjacent alkyl substituents. This can be exploited in carbon−carbon- and carbon−heteroatom-forming reactions. Both transformations include processes in which the carbene complex acts as electrophile or nucleophile and in which cycloaddition reactions of an α,β-unsaturated carbene complex take place. The combination of these fundamental

Scheme 5. 1,4- and 1,6-Addition of Alkyllithium Compounds to Chromium Phenyl(menthyloxy)carbene Complexes



reactions may be employed in the construction of multicomponent and multistep methodologies that lead to complex carbo- and heterocyclic target molecules (section 4).

2.1. Reactions with Carbon and Heteroatom Electrophiles and Nucleophiles

2.1.1. Addition of Carbon Electrophiles and Nucleophiles

Applications of Fischer carbene complexes according to reaction paths **A** and **C** (Figure 5) are discussed in this chapter. Carbene complexes may be used as both electrophilic and nucleophilic reagents in carbon−carbon bond-forming reactions. The intrinsic electrophilic nature of the carbene carbon atom allows for the addition of *C*-nucleophiles and is also evident in Michael reactions in which an α,β-unsaturated carbene complex acts as an organometallic acceptor.

Carbanions (lithioarenes, lithioalkanes) can act as *C*-nucleophiles in reaction with aryl(alkoxy)carbene complexes but only lithioarenes give rise to other carbene complexes in which the alkoxy group in the starting complexes **40**−**42** is replaced for another aryl substituent yielding diarylcarbene complexes of the type $(OC)_5M{=}C(Ar^1)(Ar^2)$ **46**−**48** (M = Cr, Mo, W)[31] (Scheme 6). The reaction involves the treatment of aryl(alkoxy)carbene complexes **40**−**42** with aryllithium derivatives (attack at the carbene carbon atom generating tetrahedral anionic intermediate **43**−**45**) followed by addition of a strong Brønsted acid (e.g., HCl), which triggers the elimination of the alkoxy group.

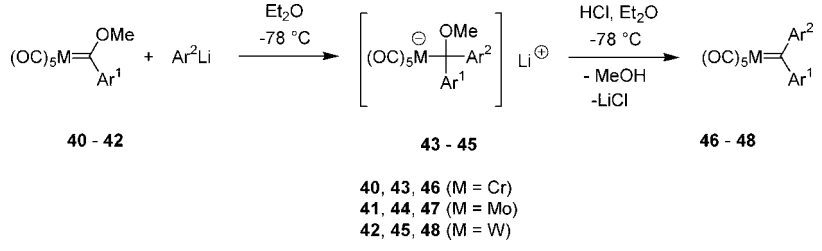
A novel procedure for the preparation of dieneynes and dienediynes is based on the addition of alkynyllithium compounds to the carbene carbon atom of Fischer arylcarbene chromium complexes. This reaction yields reactive, nonstabilized alkynylcarbene complex intermediates that subsequently add to 2-methoxyfuran to yield the target molecules.[32] Using achiral and chiral alkoxyalkynyllithium compounds, this approach has also been applied in an access to group 6 alkynyl(alkoxy)carbene complexes.[33]

The deprotonation of carbene complexes in α-position to the carbene carbon atom provides metal carbene anions representing *C*-nucleophiles, which can take part in alkylation,[34] aldol-, and Michael-type reactions (Schemes 7 and 8). For aldol reactions, the best results are obtained if the reaction is run under nonequilibrating conditions[35a,b] using triethylamine as a base, e.g., in the reaction of chromium methyl(ethoxy)carbene complex **4b** and benzaldehyde, providing aldol condensation product **16n** in good yields (Scheme 7). Clean aldol reactions generally require nonenolizable aldehydes, but if catalytic amounts of base are present, even enolizable aldehydes can be used.[35c,d]

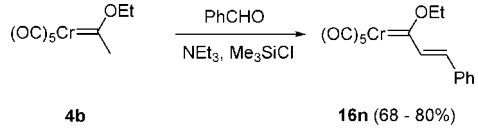
Anions of alkyl(amino)carbene complexes (e.g., **28b**) have been reported to undergo Michael addition to α,β-unsaturated carbonyl compounds (e.g., (β-styryl)methylketone), leading to 1,4-adducts (e.g., **28d**) (Scheme 8).[36]

The addition of carbon nucleophiles to the carbene carbon atom generates a new C—C bond. As described previously, the reaction of organolithium reagents with alkoxycarbene complexes serves as an entry to nonheteroatom-stabilized diarylcarbene complexes. In alkenyl- and alkynylcarbene complexes, the addition of nucleophiles to the carbene carbon atom competes with the addition to the β-carbon of the conjugated

Scheme 6. Synthesis of Group 6 Diarylcarbene Complexes

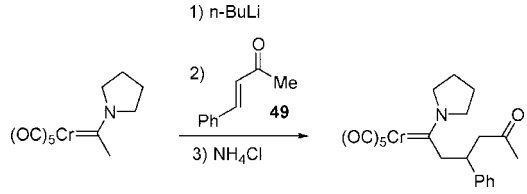


Scheme 7. Aldol Reaction of an Alkyl(alkoxy)carbene Chromium Complex



4b **16n** (68 - 80%)

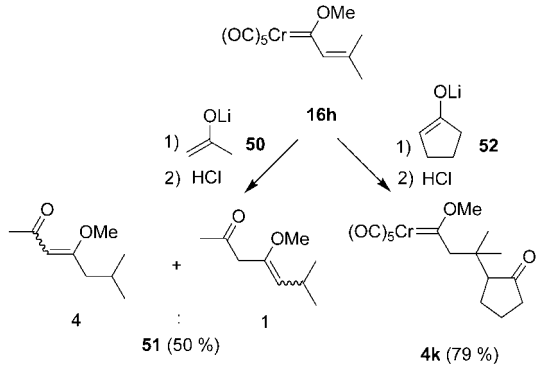
Scheme 8. Michael Reaction of an Aminocarbene Complex Anion to an Enone



28b **28d** (88 %)

C—C multiple bond.[37] The regioselectivity of the addition of amines to alkynylcarbene complexes depends on the temperature; 1,2-addition is favored by lower temperatures.[37c] Enolates turned out to be efficient *C*-nucleophiles for Michael addition reactions with α,β-unsaturated metal carbenes. However, the product distribution may be influenced by steric factors as shown in Scheme 9[37d] for the addition of different enolates to alkenylcarbene complex **16h**. The less bulky acetone enolate **50** adds to the carbene carbon; protonation of the primary addition product results in demetalation and in the formation of a mixture of isomeric enones **51**. In contrast, the more bulky cyclopentanone enolate **52** adds to the less shielded vinylic position, affording the Michael adduct **4k**. The Michael-type addition has also been applied to reactions in which Fischer carbene complexes represent both the Michael donor and acceptor, providing biscarbene complexes.[38]

Scheme 9. 1,2- and 1,4-Addition Reactions of Enolates to an Chromium Alkenylcarbene Complex



51 (50 %) **4k** (79 %)

Michael addition reactions employing carbene complexes as the acceptor allow for the bifunctionalization of the α,β-unsaturated carbene complex by a consecutive addition of nucleophile and electrophile across the carbene complex. While in most cases the electrophile reacts intermolecularly, intramolecular examples are also known. Two applications of this strategy include α-chloroethyloxazoline and a substituted oxirane as electrophile to form a cyclopropane ring.[39] The styrylcarbene complexes **18i** and **18l** undergo conjugative addition of lithiated oxazoline **53** to give, after treatment with silica gel, the tungsten cyclopropylcarbene complexes **54a** and **54b** in high chemical yield and excellent diastereoselectivity.[39a] Alternatively, after lithiation with *s*-BuLi, oxirane **55** reacts with **18i** and **18l** to form cyclopropylcarbene complexes **56a** and **56b** in similar high chemical yields (Scheme 10).[39b]

An *umpoled* variation of a Michael reaction with an alkenylcarbene complex has been recently described.[40] The enolate generated from silyl enolether **57** with *n*-butyllithium under normal Michael conditions reacted with carbene complex **16v** to give—after oxidative removal of the organometallic moiety—the α,β-disubstituted ester **58** in 95% de (diasteromeric excess). However, after the addition of copper(I) iodide and workup with aqueous NH_4Cl, the same reactants afforded ketone **59** (95% de), originating from the attack of the electrophile (allyl bromide) at the former carbene carbon atom followed by hydrolysis of the intermediate enol ether (Scheme 11).

Nucleophilic multiple bond systems primarily insert into the metal—carbene bond[41,42] via metathesis at the metal. Enamines (e.g., **61**), ynamines **62**, and cyanamides **64** react with alkoxycarbene complex **4o** (M = Cr, X = OMe) to give amino(alkenyl)carbene complexes **28g** (in low yield), **28f**, and iminocarbene complex **28j**, respectively (Scheme 12). The less nucleophilic ynether **63**, however, requires metal carbenes with enhanced electrophilic properties such as the thermolabile tungsten benzylidene complex **60** (M = W, X = H)—which is even more reactive than the diarylcarbene complexes of type $(OC)_5Cr{=}C(Ar^1)(Ar^2)$[31]—to push the alkyne insertion to completion (giving **18j** in low yield) (Scheme 12).[43]

Ynamines (like **62**) also insert into the metal—carbene bond of alkynyl(alkoxy)carbene complexes (e.g., **12k**) to give ynenyl(amino)carbene complexes (e.g., **30b**) (Scheme 13).[42,44] In contrast to this finding, the less nucleophilic ("softer") β-acyl enamine **65** rather adds to the ("softer") β-carbon of the alkynylcarbene ligand in **12k** to give 1-metala-1,3,5-hexatriene **66**, which, upon thermolysis in nonpolar solvents, undergoes cyclization and demetalation to homopyrrole **67** (Scheme 14).[45]

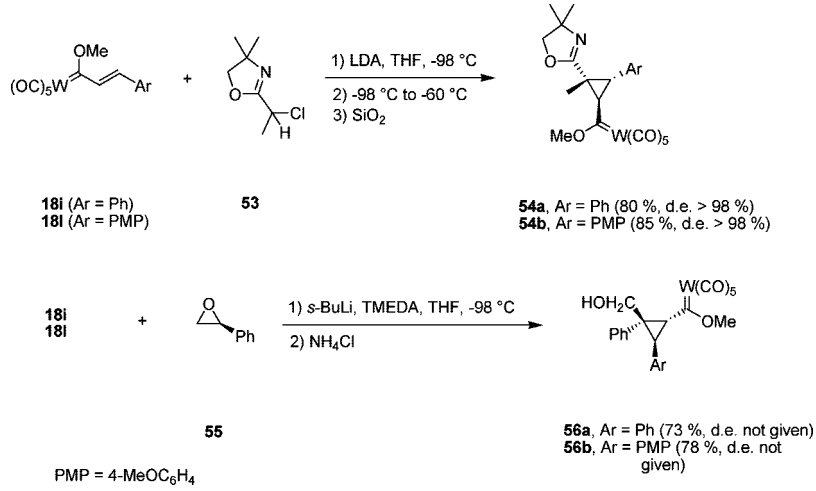
2.1.2. Addition of Heteroatom Nucleophiles

The simplest addition mode of heteroatom nucleophiles to alkoxycarbene complexes **4**—**6** involves the formation of thio- and aminocarbene complexes. Treatment of **4**—**6** with (primary or secondary) amines and (alkyl- or aryl-)thiols gives aminocarbene (**28**—**30**)[46a,b] and thiocarbene complexes (**68**—**70**),[46a,c] respectively (Scheme 15). Nonracemic chiral amines yield optically active aminocarbene complexes.[47] The incorporation of more bulky amines or of chiral alcohol auxiliaries into the carbene ligand requires a more electrophilic metal carbene center such as in acyloxycarbene complexes. Amino- and thiocarbene complexes are provided by the reaction of acyloxycarbene complexes (Scheme 2) with amines or amides and thiols, respectively.[48] Figure 7 summarizes the chromium and tungsten aminocarbene complexes discussed in this review.

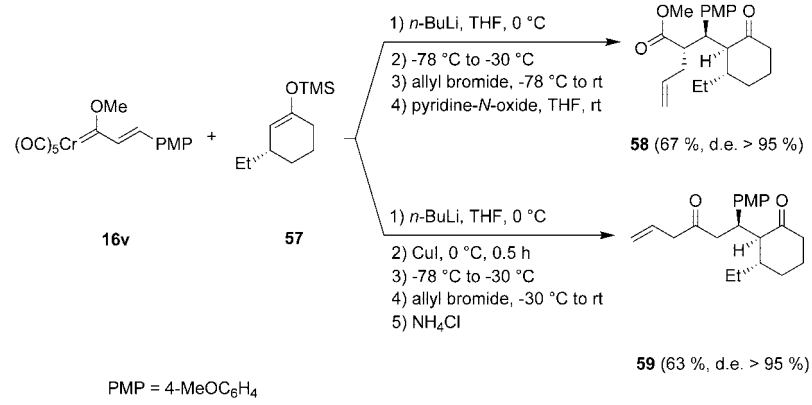
Carbene complex anions (e.g., that generated from **4a**) are suitable *C*-nucleophiles for the ring-opening of oxiranes (e.g., **71**). The resulting alkoxide intermediates (e.g., **72**) undergo a subsequent cyclization to give 2-oxacyclopentylidene complexes (e.g., **73**) (Scheme 16).[49] Unsymmetrically substituted epoxides are attacked by the carbene complex anion at the less-hindered carbon atom, following a S_N2-like mechanism.

α,β-Unsaturated carbene complexes are able to react with nucleophiles at the carbene carbon in a 1,2-addition fashion or by attack at the β-carbon in a 1,4-addition mode. Thus,

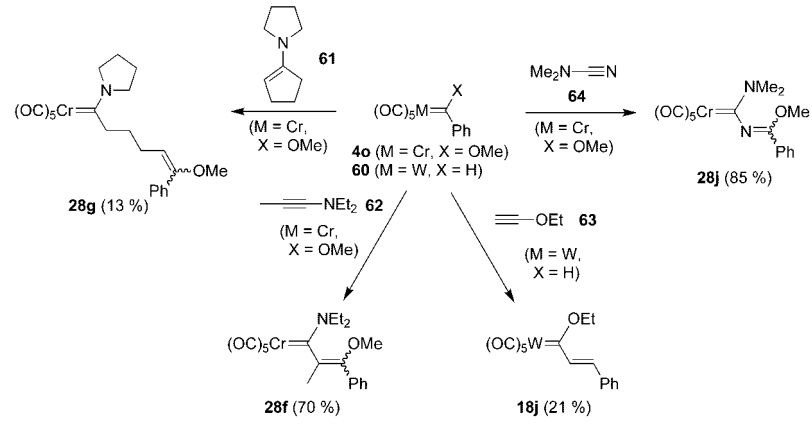
Scheme 10. Synthesis of Tungsten Cyclopropylcarbene Complexes via Michael Addition



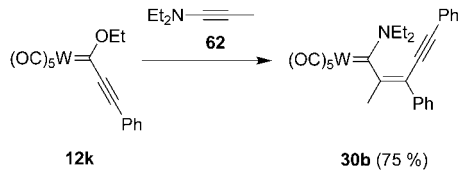
Scheme 11. Normal and Reversed Michael Addition with α,β-Unsaturated Carbene Complexes



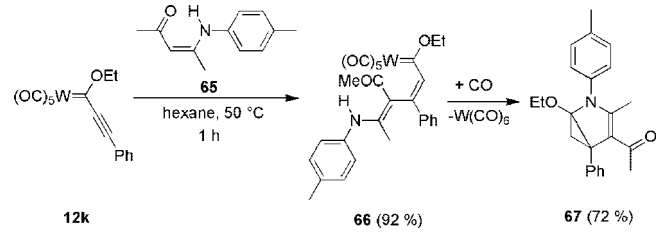
Scheme 12. Reaction of Enamines, Ynamines, Ynethers, and Cyanamides with Carbene Complexes



Scheme 13. Reaction of Ynamines with Fischer Alkynylcarbene Complexes



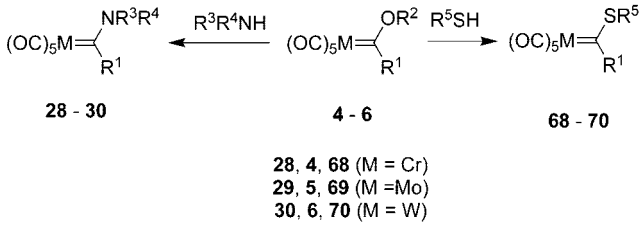
Scheme 14. Michael Addition of an Acyl Enamine to a Tungsten Alkynylcarbene Complex



hydrazines **74** can add to alkynylcarbene complexes **10l** or **12k** to give the pyrazoles **75** originating from a combined 1,2- and 1,4-addition process.[50] Similarly, acetylhydrazine or phenylhydrazine affords the corresponding pyrazole derivatives in high yields (Scheme 17).

In a similar way, nucleophiles containing a 1,3-dinitrogen system such as diamines, hydrazines,[51a] amidines, guanidines, aminothiazoles, aminopyridines, ureas, and

Scheme 15. Synthesis of Fischer Amino- and Thiocarbene Complexes from Alkoxycarbene Complexes



thioureas[51a,c,d] add to alkynylcarbene complexes **10l** and **12k**, generating the corresponding heterocyclic metal carbenes. Of particular interest is the reaction with urea **76** or thiourea **77**, which provides an easy access to pyrimidine derivatives **78** or **79**, respectively (Scheme 18).[51b]

2.1.3. Successive Addition of Heteroatom and Carbon Nucleophiles

The sequential 1,4- and 1,2-addition of dianions such as β-oxygen-functionalized dilithium species **80** to alkenylcarbene complexes has been reported. The carbanion adds to the vinylcarbene complex **16y** via a combined *C*-1,4 and *O*-1,2-addition, affording the 2-oxacyclohexylidene complex **81** as a 1:1 mixture of *cis*/*trans*-isomers (Scheme 19).[52]

Similarly, alkynylcarbene complexes **10a**, **10c**, **10k**, and **12a** react with β-dicarbonyl compounds **82** and in the presence of substoichiometric amounts of a base to generate pyranylidene derivatives **83**.[53] The reaction is initiated by 1,4-addition of the enolate to the β-position, leading to an intermediate that evolves through an intramolecular exchange of the alkoxy group by 1,2-addition (Scheme 20). The pyranylidene complexes **83** may serve as a diene component in a reverse-electron-demand Diels−Alder reaction.

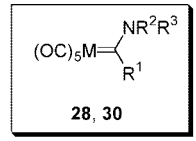
Radical-based coupling of alkenylcarbene complexes **18a**, **18d**, and **18i** and 1,2-cyclohexene oxide **84** affords 2-oxycyclohexylidene derivatives **85** utilizing "Cp_2TiCl" as the radical source. The use of cyclic epoxides is rewarded by good diastereoselectivities (Scheme 21).[54]

2.2. Cycloaddition Reactions

The cycloaddition of alkenyl and alkynyl units adjacent to electron-withdrawing functional groups (e.g., COR) with alkenes and alkynes is a powerful tool in synthetic organic chemistry. Following the isolobal principle, the metal carbene moiety activates alkenyl and alkynyl building blocks in α,β-unsaturated carbene complexes toward cycloaddition reactions as represented in the following chapters.

2.2.1. [2 + 2]-Cycloaddition

The [2 + 2]-cycloaddition reaction is the most versatile method to generate four-membered rings. Fischer alkynylcarbene complexes of type **10a**, **10e**, **10h**−**10j**, **10k**, and **12c**−**12h** as ester surrogates have been most often applied to these cycloadditions that run efficiently under thermal conditions, giving the corresponding cyclobutene derivatives **87** under relatively mild experimental conditions (Scheme 22). The reaction partners of Fischer carbene complexes include oxygen-containing alkenes (like enol and silyl enol ethers **86**, vinyl acetates, and ketene acetals)[55] and nitrogen-substituted olefins (such as lactims and alkenyl imidates), affording cyclobutenylcarbene complexes.[56] For instance, reaction of chromium alkynylcarbene **10a** with electron-rich butadiene **88** gave the [2 + 2]-cycloadduct **89** instead of the expected Diels−Alder product.[55j] Cycloadducts of type **89**

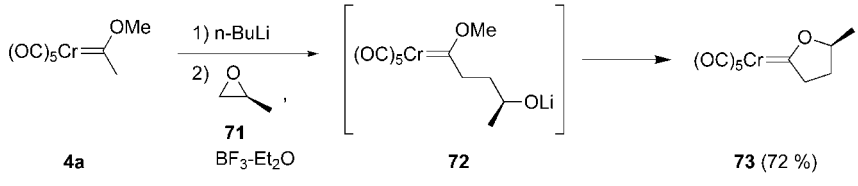


28a (M = Cr, R^1 = H, R^2 = R^3 = Me)
28b (M = Cr, R^1 = Me, R^2 = R^3 = -$(CH_2)_4$-)
28c (M = Cr, R^1 = CH(*n*-Pr)CH_2CN, R^2 = R^3 = Me)
28d (M = Cr, R^1 = CH_2CH(Ph)CH_2COMe, R^2 = R^3 = -$(CH_2)_4$-)
28e (M = Cr, R^1 = CH=CH(*E*-Ph), R^2 = R^3 = Me)
28f (M = Cr, R^1 = C(Me)=C(OMe)Ph, R^2 = R^3 = Et)
28g (M = Cr, R^1 = $(CH_2)_3$CH=C(OMe)Ph, R^2 = R^3 = -$(CH_2)_4$-)
28h (M = Cr, R^1 = CH=C(*E*-CO_2Et), R^2 = R^3 = -$(CH_2)_4$-)
28i (M = Cr, R^1 = C≡CH, R^2 = R^3 = Me)
28j (M = Cr, R^1 = N=C(OMe)Ph, R^2 = R^3 = Me)

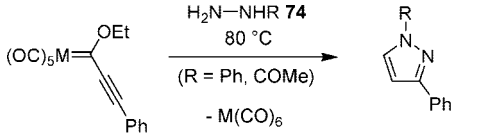
30a (M = W, R^1 = C≡CH, R^2 = R^3 = Me)
30b (M = W, R^1 = CMe=C(*Z*-C≡CPh)Ph, R^2 = R^3 = Et)

Figure 7. Compilation of individual Fischer chromium and tungsten aminocarbene complexes discussed in this review.

Scheme 16. Synthesis of 2-Oxacyclopentylcarbene Complexes via (Intramolecular) Nucleophilic Attack of an Alkoxide



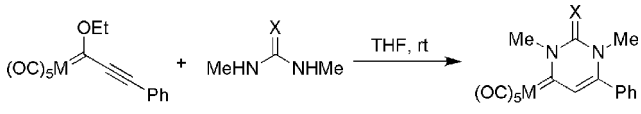
Scheme 17. Pyrazole Derivatives via 1,2- and 1,4-Addition of Hydrazines to Alkynylcarbene Complexes



10l (M = Cr)
12k (M = W)

75 (75 - 90 %)

Scheme 18. Synthesis of 2-Pyrimidinone Derivatives via Addition of (Thio)Ureas at Alkynylcarbene Complexes

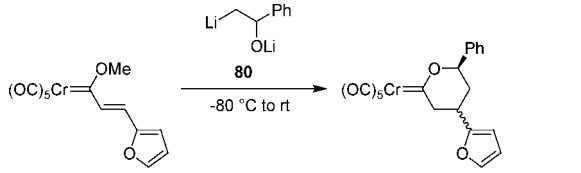


10l (M = Cr)
12k (M = W)

76 (X = O)
77 (X = S)

78 (X = O, 90 %)
79 (X = S, 52 %)

Scheme 19. 2-Oxacyclohexylidene Complexes via Reaction of 2-Lithioalkoxides with Alkenylcarbene Complexes



16y

81 (50 %, *cis* : *trans* = 1 : 1)

may undergo ring-opening into 1,3-butadienyl derivatives and have been utilized in multicomponent reaction sequences (see section 4).

Contrasting the number of alkynylcarbene complexes, only a few alkenylcarbene complexes have been applied to [2 + 2]-cycloaddition reactions. One example is the transformation of chromium and tungsten α-*exo*-methylene-2-oxacyclopentylidene complexes **90** in the [2 + 2]-cycloaddition reaction with enol ethers **91**, yielding diastereomerically pure spirocyclobutanes **92** in good yields (Scheme 23).[57]

The potential of the [2 + 2]-cycloaddition reaction with Fischer carbene complexes is extended by ring-opening of cyclobutenylcarbene complexes of type **87** and **89** to generate butadienylcarbene complexes that may serve as dienes in Diels−Alder reactions (see compound **18f** in Scheme 40 for an example).

2.2.2. [3 + 2]-Cycloaddition

α,β-Unsaturated Fischer carbene complexes represent C_2-building blocks for the [3 + 2]-cycloaddition reaction. They react with 1,3-dipoles to afford five-membered heterocyclic systems. Metal alkynylcarbenes are appropriate C_2-building blocks for reactions with dipoles including nitrones, nitrilimines, and diazomethane(s). Diazomethane has been used as the 1,3-dipole in the first [3 + 2]-cycloaddition reaction with tungsten phenylethynylcarbene **12k** (Scheme 24).[58] The fact that N-coordinated pentacarbonyltungsten derivative **94** was isolated as the final product is rationalized by nucleophilic addition of a second equivalent of diazomethane at the carbene carbon atom of [3 + 2]-cycloadduct **93** followed by a 1,4-metal shift from carbon to one of the heterocyclic nitrogen atoms.

The [3 + 2]-cycloaddition reaction with trimethylsilyl diazomethane **95a** as the 1,3-dipole has been proven to be advantageous. As shown in Scheme 25for Fischer alkynylcarbene complexes **10a**, **10d**, **10k**, **12a**, and **12f**, the respective pyrazolylcarbene complexes **96** have been obtained in >50% yield.[59]

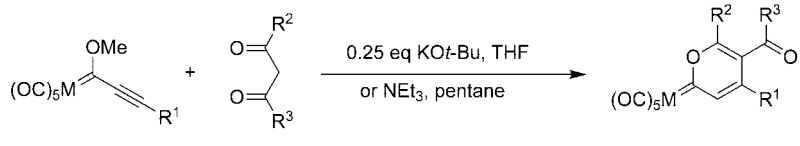
Incorporation of a chiral auxiliary into the carbene ligand allows for a diastereoselective cycloaddition as demonstrated for the reaction of (−)-8-phenylmenthyloxycarbene complexes **16r** and **16aa** with diazomethanes **95**. Moderate chemical yields but high diastereomeric excesses were observed for the preparation of pyrazolinylcarbene complexes **97** (Scheme 26)[60,61]

Like in the Diels−Alder reaction (see section 2.2.3), the presence of the metal carbene fragments speeds up the [3 + 2]-cycloaddition reaction and increases both the chemical yield and the diastereomeric excess (Scheme 27).[61] This has been shown by comparing chiral chromium styrylcarbene complexes (e.g., **16r**) with chiral cinnamoyl esters (e.g., **98**) in the reaction with $TMSCHN_2$ **95a** to give chiral pyrazolinyl ester **99**, despite the fact that an additional step for the demetalation is involved. Thus, the carbene complex **16r** gave pyrazoline **99** in 73% chemical yield and >90% diastereomeric excess after reaction at room temperature for 6 h, while only 65% chemical yield and 20% diastereomeric excess were observed for the cycloaddition with carboxylic ester **98**. The latter diastereoselectivity might reflect the more severe reaction conditions that had to be applied for the ester.

The regioselectivity of the [3 + 2]-cycloaddition reaction of nitrones to chromium alkynylcarbene complexes[62] has been studied by density functional theory (DFT) calculations.[63] They also confirm the role of the carbene complex fragment as enhancing the electrophilicity at the alkyne moiety in the dipolarophile that equals Lewis-acid activated alkyl propiolates. Nitrones **100** have been used as 1,3-dipoles in the reaction of chromium *tert*-butylethynylcarbene complex **10c** to afford β-enamino ketoaldehydes **102** in rather moderate yields by the light-promoted ring-opening of the corresponding [3 + 2]-cycloadduct **101** (Scheme 28).[62c]

The 1,3-cycloaddition of sodium azide to chromium α,β-alkynylcarbene complexes[64a] as well as to carbene complexes

Scheme 20. Base-Promoted Reaction of 1,3-Dicarbonyl Derivatives with Alkynylcarbene Complexes

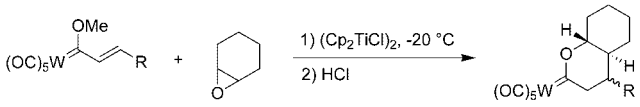


10a, **c**, **k** (M = Cr),
12a (M = W)
(R^1 = Me, *t*-Bu, Ph,
R^2 = Me, OMe,
R^3 = Me)

82

83 (62 - 87 %)

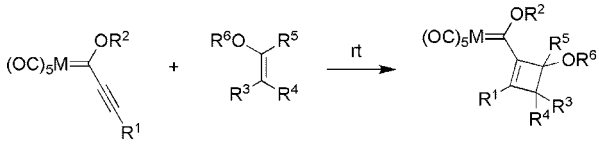
Scheme 21. Radical-Based Synthesis of Fischer 2-Oxacyclohexylidene Complexes



18a, **18d**, **18i** **84** **85** (36 - 74 %)

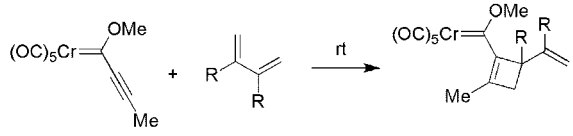
(R = Me, *i*-Pr, Ph)

Scheme 22. [2 + 2]-Cycloaddition Reactions of Alkynylcarbene Complexes



10a, **10e**, **10h - 10j**,**10k** (M = Cr)
12c - 12h (M = W)
86
87 (46 - 93 %)

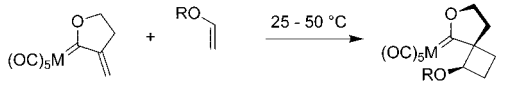
(R^1 = Me, *i*-Bu, *t*-Bu, TMS, CH=CH(*E*-Ph), C(Me)=CH_2, C(Me)=CH(*E*-Ph), C(Me)=CH(*E*-$CH_2OCH_2CH=CH_2$), 1-cyclopentenyl, 1-cyclohexenyl, Ph)
(R^2 = Me, Et)
(R^3 = H, Me)
(R^4 = H, Me)
(R^5 = H, Me, Ph, 4-MeC_6H_4)
(R^6 = H, Me, Et, TMS, TES, TBDMS)
(R^3 / R^6 = -$(CH_2)_2$-, -$(CH_2)_3$-)
TES = $SiEt_3$
TBDMS = $SiMe_2$*t*-Bu



10a **88** **89** (45 %)

R = $OSiMe_2$*t*-Bu

Scheme 23. [2 + 2]-Cycloaddition Reaction of Enol Ethers to an *exo*-Methylene 2-Oxacyclopentylidene Complex



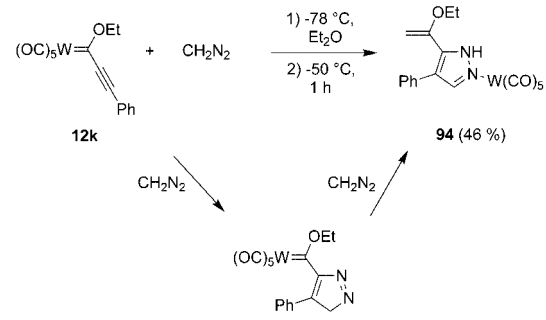
90 (M = Cr, W) **91** **92** (26 - 81 %)

(R = Et (**91a**), *n*-Bu, *t*-Bu, $CH_2CH=CH_2$)

bearing a remote carbon carbon triple bond[64b] has been reported to provide carbene complexes bearing 1,2,3-triazol entities. While in the latter case copper(I) halides were needed, the former reaction could be carried out in the absence of such an additive (for transmetalation reactions, see section 6). The reaction of aryl and alkyl azides with tungsten alkynylcarbene complexes afforded β-aminoalkenylcarbene complexes instead of [3 + 2]-cycloaddition products.[64c]

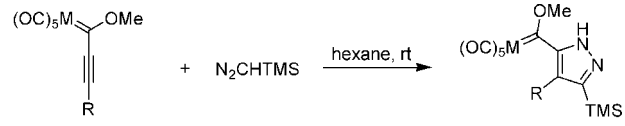
Employing azomethine ylides in the [3 + 2]-cycloaddition reaction with α,β-unsaturated carbene complexes provides an entry into 2-pyrrolidinone derivatives. This has been exploited in the total synthesis of the anti-inflammatory and antidepressant (+)-rolipram **105** (Scheme 29).[65] The cycloaddition product **104** has been synthesized from styrylcarbene complex **16x** and azomethine ylide precursor **103**

Scheme 24. First [3 + 2]-Cycloaddition Reaction of a Fischer Carbene Complex



12k **94** (46 %) **93**

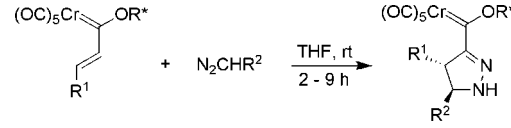
Scheme 25. Trimethylsilyl Diazomethane as the 1,3-Dipole in [3 + 2]-Cycloaddition Reactions with Alkynylcarbene Complexes



10a, **10d**, **10k** (M = Cr)
12a, **12f** (M = W)
95a
96 (57 - 87 %)

R = Me, C(Me)=CH_2, TMS, Ph

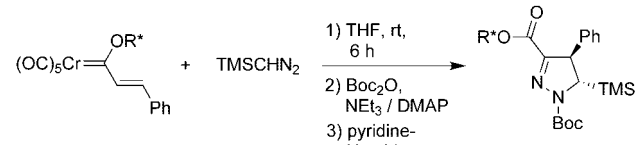
Scheme 26. Diazomethanes as 1,3-Dipoles in [3 + 2]-Cycloaddition Reactions with Alkenylcarbene Complexes



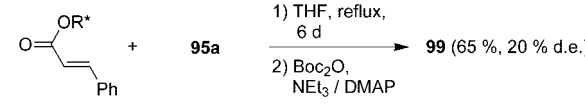
16r, **16aa** **95** **97** (29 - 52 %, d.e. > 90 %)

R^1 = Ph, 2-furyl
R^2 = H, $CH=CH_2$, Ph, TMS (**95a**)
R* = (-)-8-phenylmenthyl

Scheme 27. Comparison of [3 + 2]-Cycloaddition Reactions of Chiral Alkenyl(alkoxy)carbene Complexes and Cinnamates as Their Isolobal Analogues with Trimethylsilyl Diazomethane



16r **95a** **99** (73 %, >90 % d.e.)



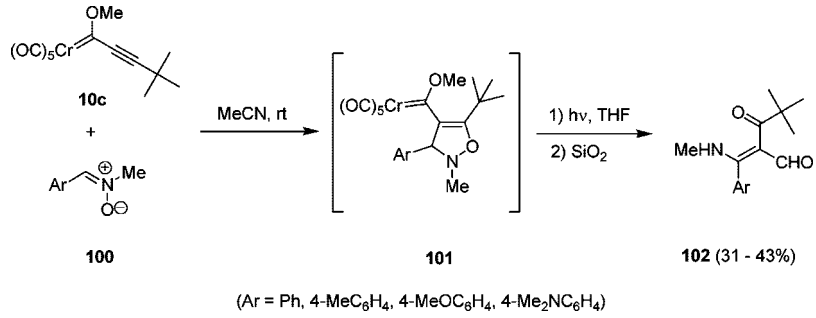
98

R* = (-)-8-phenylmenthyl

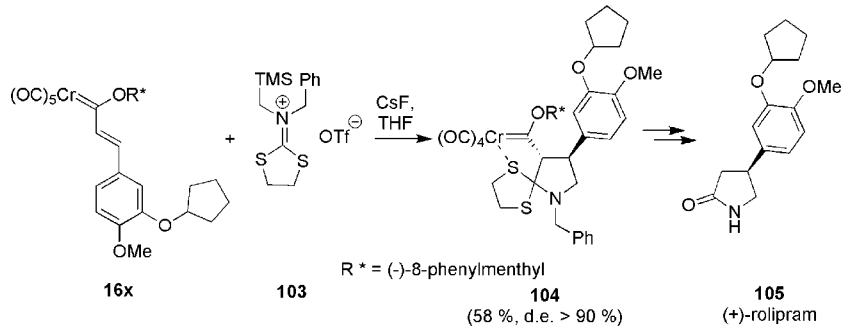
in 58% yield and high diastereoselectivity and elaborated into (+)-rolipram **105** in three consecutive steps.

Nitrilimines (generated from their precursors **106** by dehydrochlorination) react with chiral alkenylcarbene complexes **16r**, **16w**, and **16aa** (Scheme 30)[62c,66] to give fairly

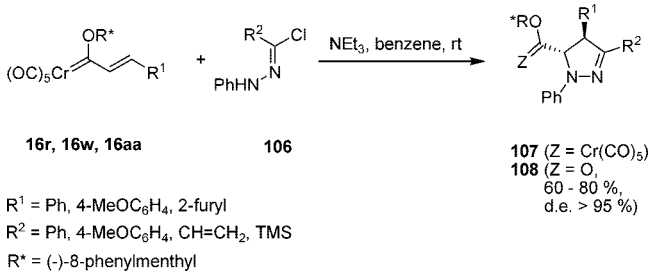
Scheme 28. [3 + 2]-Cycloaddition Reaction of Nitrones in the Preparation of Acyclic Enamino 1,3-Dicarbonyl Compounds



Scheme 29. Application of the [3 + 2]-Cycloaddition Reaction of Azomethine Ylides with Chiral Chromium Alkenylcarbene in the Total Synthesis of (+)-Rolipram



Scheme 30. [3 + 2]-Cycloaddition Reaction of Nitrilimines and Alkenylcarbene Complexes



unstable tetrasubstituted 4,5-dihydropyrazolylcarbene complexes **107**, which were oxidatively demetalated to give pyrazolinyl esters **108** in up to 80% chemical and >95% optical yield.

Another class of (masked) dipoles is represented by heterocyclic mesoionic compounds such as **109** and **110** that provide access to pyrazolyl- and pyrrolylcarbene complexes **111** and **112**, respectively (Scheme 31).[67a] The reaction proceeds via elimination of carbon dioxide from the cycloaddition products that are initially formed by addition of 1,3-dipoles **109** and **110** to alkynylcarbene complexes **10b**, **10k**, **12b**, and **12j**, respectively. Whereas **109** adds to both the chromium and tungsten carbene, the reaction of **110** was efficient only with the tungsten complex. Another entry into heterocycles (thiophenes and pyridinones) utilizing heterocyclic mesoionic compounds has been reported for 1,3-thiazolium-4-olates.[67b]

2.2.3. [4 + 2]-Cycloaddition

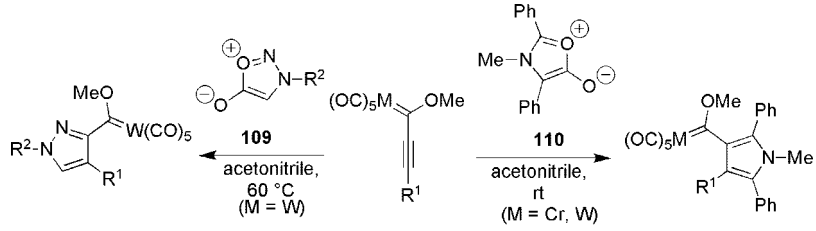
The Diels−Alder reaction of activated olefins is considered as one of the most useful reactions in organic synthesis. Like in the [3 + 2]-cycloaddition reaction, the electron-accepting pentacarbonylmetal fragment is a powerful activator of the alkyne or alkene functionality in α,β-unsaturated carbene complexes toward the [4 + 2]-cycloaddition reaction with dienes.

2.2.3.1. Intermolecular [4 + 2]-Cycloaddition. *2.2.3.1.1. Alkenylcarbene Complexes as Dienophiles.* Alkenyl(alkoxy)- and alkenyl(amino)carbene complexes are highly efficient dienophiles in Diels−Alder reactions exhibiting not only higher reaction rates but also higher regio- and stereoselectivities than the corresponding esters and amides,[68] as illustrated in Scheme 32 for the reaction of alkenyl(methoxy)carbene complex **16a** with isoprene to give regioisomeric cyclohexenylcarbene complexes **113a** and **113b** in a ratio of 11.5:1. The reaction of the carbene complex is complete after 3 h at 25 °C, whereas methyl acrylate **114** requires several months to yield the regioisomeric cyclohexene carboxylic esters **115a** and **115b** (ratio 2.3:1). The rate enhancement observed for this complex is comparable to that observed for the $AlCl_3$-assisted reactions of methyl acrylate and isoprene (Scheme 32).[68a]

Moreover, as observed for the [3 + 2]-cycloaddition reaction, the presence of the metal auxiliary may increase the stereoselectivity in the Diels−Alder reaction. The reaction of the isomeric tungsten propenylcarbene complexes **18a** (*E*-isomer) and **18b** (*Z*-isomer) with cyclopentadiene afforded good chemical yields (>85%) combined with an *endo*/*exo* selectivity of 90:10 for the *trans* complex **116** and of 89:11 for the *cis* isomer **119** (Scheme 33).[68b] For comparison, the isolobal *E*-methyl crotonate **117** gave an *endo*/*exo* ratio of 54:46 for the carboxylic esters **118** under thermal conditions, which could be improved to 93:7 in the presence of aluminum trichloride.

The Diels−Alder reaction of simple alkenyl(alkoxy)carbene complexes leads to mixtures of *endo* and *exo* cycloadducts with, in general, the *endo*-isomer prevailing.[69] A DFT study on the *endo*/*exo*-selectivity of thermal Diels−Alder reaction between alkenylcarbene complexes and an open-chain (isoprene) and a cyclic 1,3-diene (cyclopentadiene)[70] revealed for the reaction with isoprene an exclusive 1,4-

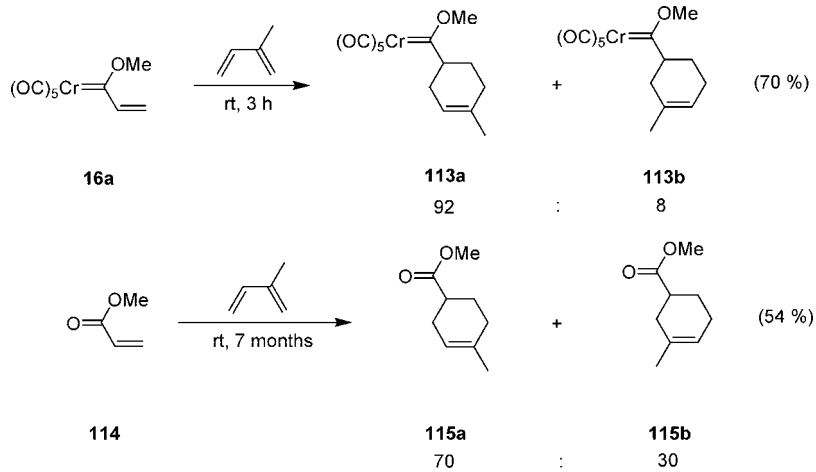
Scheme 31. Mesoionic Heterocycles as 1,3-Dipoles in [3 + 2]-Cycloaddition Reactions with Alkynylcarbene Complexes



111 (42 - 85 %) **10b**, **10k** **12b**, **12j** **112** (40 -60 %)

M = Cr, W;
R^1 = *n*-Bu, Ph; R^2 = Ph, 4-ClC_6H_4

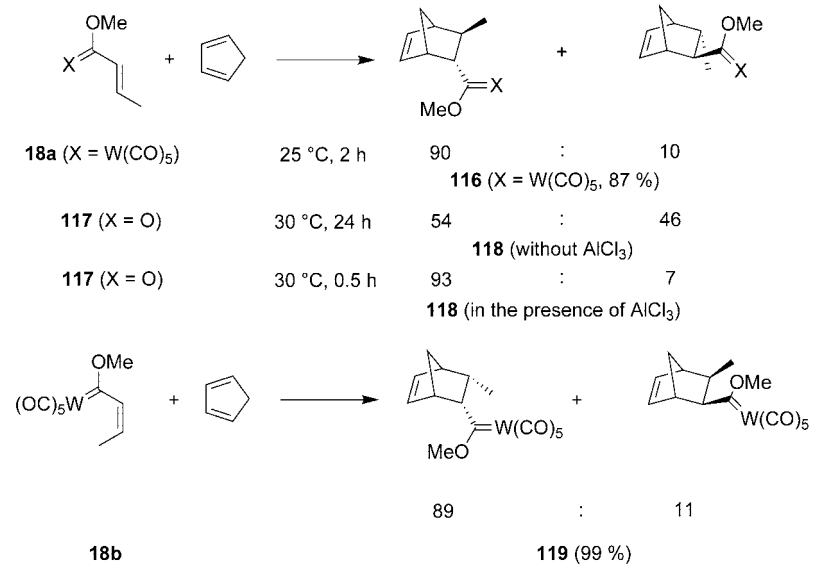
Scheme 32. Comparison of the Alkenyl(methoxy)carbene Complex and Methyl Acrylate in the Diels−Alder Reaction with Isoprene



16a **113a** : **113b**
92 : 8

114 **115a** : **115b**
70 : 30

Scheme 33. (*E*)- and (*Z*)-Alkenylcarbene Complexes in the Diels−Alder Reaction with Cyclopentadiene



18a (X = $W(CO)_5$) 25 °C, 2 h 90 : 10 **116** (X = $W(CO)_5$, 87 %)

117 (X = O) 30 °C, 24 h 54 : 46 **118** (without $AlCl_3$)

117 (X = O) 30 °C, 0.5 h 93 : 7 **118** (in the presence of $AlCl_3$)

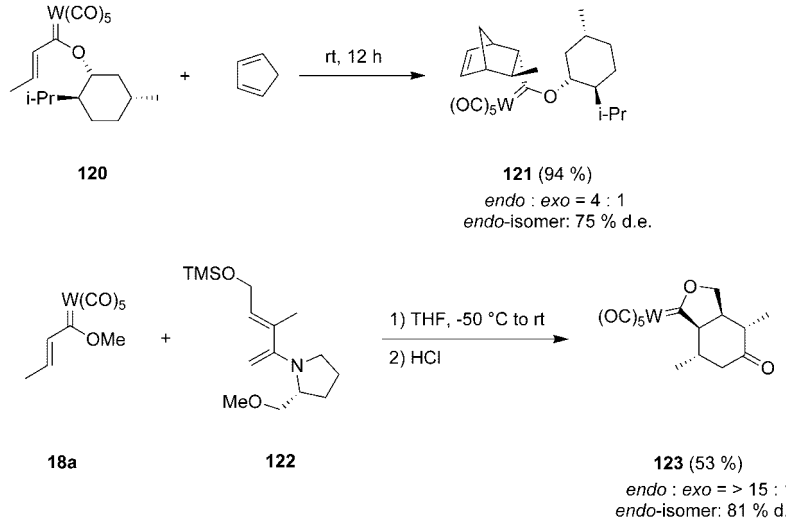
18b 89 : 11 **119** (99 %)

regioselectivity of the carbene and the methyl substituents in the cycloadduct. The high *endo*-selectivity in the reaction with cyclopentadiene has partially contributed to stabilizing secondary orbital interactions.

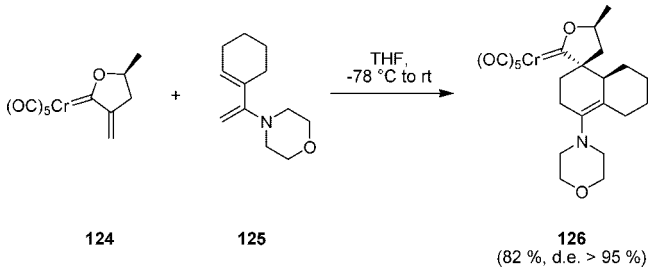
Asymmetric examples of *endo*-Diels−Alder reactions have also been reported, incorporating a chiral auxiliary both into the carbene complex and into the diene. The reaction of cyclopentadiene with the (−)-menthyloxy(alkenyl)carbene complex **120** afforded a 4:1 *endo*/*exo* mixture. A 75% diastereomeric excess was found for the major *endo* isomer **121** (Scheme 34).[69d] On the other hand, chiral 2-amino-1,3-diene **122** derived from (*S*)-methoxymethylpyrrolidine reacted with tungsten alkenyl(alkoxy)carbene complex **18a** to give the *endo*-cycloadduct **123** as the major product in high diastereoselectivity.[71]

Exocyclic α,*β*-unsaturated carbene complex dieonophiles such as **124** undergo *exo*-selective Diels−Alder reactions probably due to the fixed *s-cis* conformation of the vinylcarbene moiety. Moreover, the reaction of optically active carbene complexes with 2-morpholino-1,3-butadienes **125**

Scheme 34. Diastereoselective Diels−Alder Reactions of an Alkenylcarbene Complex



Scheme 35. *Exo*-Selective Diels−Alder Reaction of an *exo*-Methylene 2-Oxacyclopentylcarbene Complex



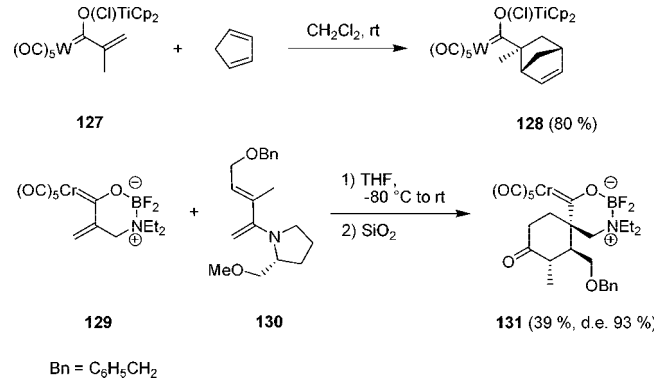
allows the asymmetric synthesis of spiro-compounds **126** (Scheme 35).[72]

The alkenyl(titanoxy)carbene complex **127** has been used as dienophile toward cyclopentadiene to give predominantly the *exo*-cycloadduct **128** in high yield. The unexpected formation of the *exo*-isomer is attributed to the steric environment of the dienophile, contrasting the stereoelectronic factors usually identified with *endo* selectivity (Scheme 36).[73]

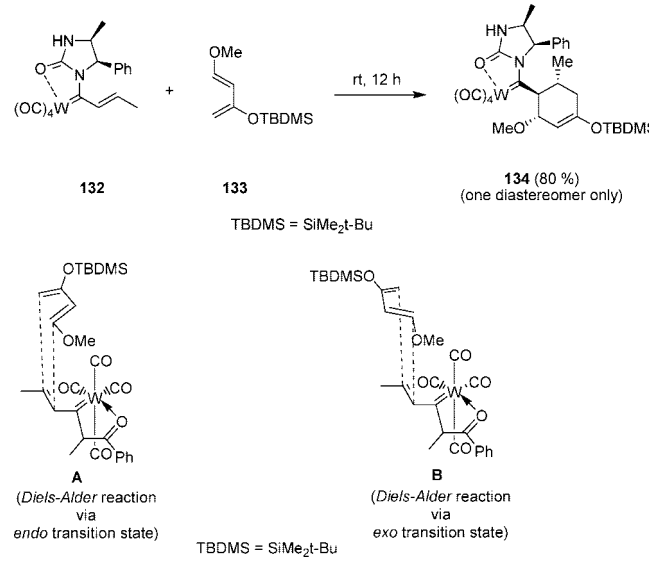
In vinylcarbene complexes containing a BF_2-chelate structure (e.g., **129**), the *s-cis* conformation of the exocyclic C═C and chromium carbene bonds is temporary locked. These boroxycarbene complexes serve as dienophiles toward 2-amino-1,3-butadienes (e.g., **130**), affording the cycloadducts, such as **131**, with remarkable regio- and *exo*-selectivity. In addition, high degrees of enantioselectivity have been obtained with chiral 2-aminodienes derived from (*S*)-methoxymethylpyrrolidine (Scheme 36).[74]

The reactivity of α,β-unsaturated aminocarbene complexes in Diels−Alder reactions is distinctly lower than that of analogous alkoxycarbene complexes (Scheme 37). Thus, the attempted conversion of [2-butenylidene(methylamino)]pentacarbonylchromium with Danishefsky's diene failed to give any cycloadduct. However, the reactivity of aminocarbene complexes can be increased by *N*-acylation.[69d,75a] The reaction results in a high *exo*-selectivity typical for the reaction of aminocarbene complexes and acyclic dienes. The best results were observed for diene **133** and tetracarbonyl complexes such as **132** in which the urea-type carbonyl oxygen is chelated to the metal. The high degree of *exo*-selectivity in **134** has been explained as a consequence of close contacts between the apical CO ligands and the diene in the *endo* transition state **A** favoring the *exo* transition state **B**.[75b]

Scheme 36. Alkenyl(metaloxy)carbene Complexes as Dienophiles in Diels−Alder Reactions

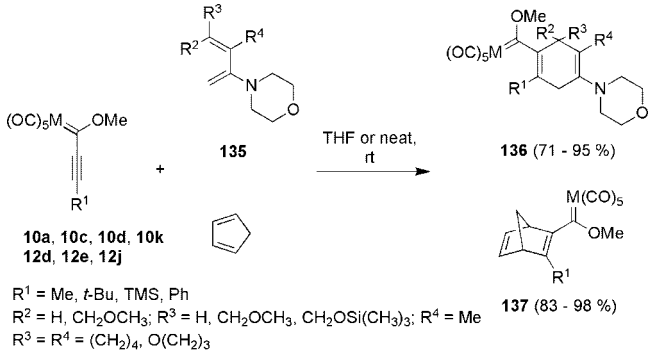


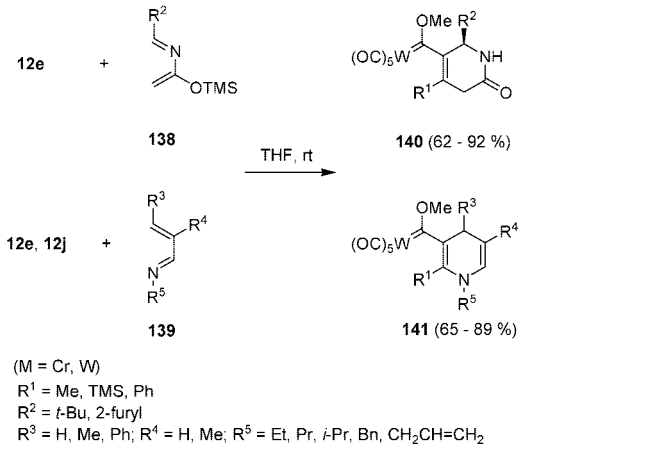
Scheme 37. *exo*-Selective Diels−Alder Reaction between an Alkenyl(amino)carbene Complex and Danishefsky's Diene



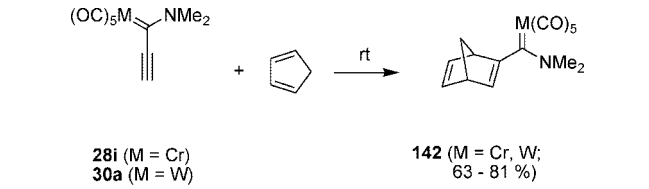
2.2.3.1.2. Alkynylcarbene Complexes as Dienophiles. An additional feature of alkynylcarbene complexes is the acceleration of the reaction with 1,3-dienes by the metal carbene moiety compared to their organic isolobal analogues.[76] Chromium and tungsten alkynyl(alkoxy)carbene complexes **10a**, **10c**, **10d**, **10k**, **12d**, **12e**, and **12j** undergo Diels−Alder reactions with neutral (e.g., cyclopentadiene)

Scheme 38. [4 + 2]-Cycloaddition Reaction of Electronically Tuned Dienes to Group 6 Metal Alkynylcarbenes





Scheme 39. Alkynyl(amino)carbene Complexes as Dienophiles

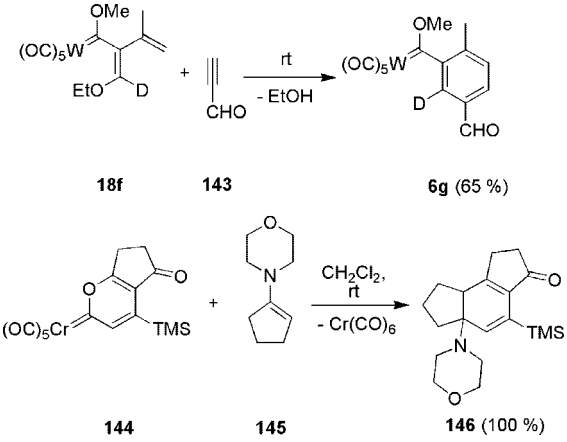


and electron-rich dienes (**135**)[76a,c,77] to give **136** and **137**, respectively (Scheme 38). Moreover, the reaction has been extended to electron-poor 2-aza- and 1-aza-1,3-butadienes **138** and **139**, respectively,[33,78] to afford unsaturated *N*-heterocyclic metal carbenes **140** and **141**. In contrast to 2-aza-1,3-butadienes 1-aza-1,3-butadienes undergo Michael addition to the alkynylcarbene complex.

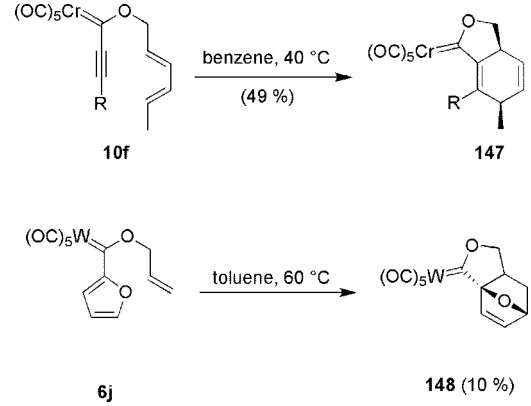
Compared with alkenylcarbene complexes, the addition of 1,3-dienes to amino(alkenyl)carbene derivatives is slowed down significantly.[75a,76c] Substitution at the alkyne terminus further decreases the reactivity. Whereas amino(ethynyl)carbene complexes **28i** and **30a** react with cyclopentadiene to give [4 + 2]-cycloadducts **142**, their C-substituted homologues are unreactive under these conditions (Scheme 39).[79a] Asymmetric induction in the cycloaddition is generated in the reaction of amino(alkynyl)carbene complexes bearing chiral pyrrolidines. The diastereoselectivity, however, is very sensitive to the substituents of the diene; the highest diastereoselectivities have been found in the reaction with 2-triisopropylsiloxy-1,3-pentadiene, and modest selectivities are observed with cyclopentadiene.[79b]

Intermolecular [4 + 2]-cycloaddition reactions where the diene moiety is part of the carbene complex are less frequent. Ethoxy-substituted 2-butadienylcarbene complex **18f**, generated

Scheme 40. Alkoxycarbene Complexes as Dienes



Scheme 41. Intramolecular [4 + 2]-Cycloaddition Reactions of Fischer Carbenes under Cyclization of Both Carbene Substituents



by a [2 + 2]-cycloaddition/cyclobutene ring-opening sequence, undergoes a reversed Diels−Alder reaction with typical dienophiles (like **143**) followed by elimination of ethanol to yield arylcarbene complex **6g** (Scheme 40).[55d,j] Expanding this strategy, pyranylidene complexes like **144** have been applied to a quantitative inverse-electron-demand Diels−Alder reaction with enol ethers and enamines (such as **145**); cyclohexadiene **146** has been obtained after extrusion of $Cr(CO)_6$ from the cycloadduct intermediate (Scheme 40).[53]

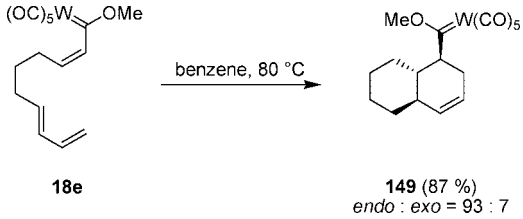
2.2.3.2. Intramolecular [4 + 2]-Cycloaddition. Fischer carbenes bearing both the dienophile and the diene functionality undergo intramolecular [4 + 2]-cycloaddition reactions under mild conditions,[76b,80] affording moderate yields of the cycloadducts. It is advantageous to incorporate the diene moiety into the alkoxy substituent (e.g., complex **10f** affording Diels−Alder adduct **147**); the reverse approach (e.g., using furylcarbene complex **6j**) is hampered by poor yields (e.g., 10% for product **148**) (Scheme 41).

A third variant includes complexes such as **18e** bearing the diene and the dienophile in the nonheteroatom carbene substituent. Bicarbocyclic carbene complexes (e.g., **149**) are obtained via intramolecular Diels−Alder reaction with stereoselectivities comparable to those observed for Lewis acid-catalyzed reactions of the corresponding methyl esters; an additional benefit is the high *endo*-selectivity (Scheme 42).[81]

2.2.4. Higher-Order Cycloaddition

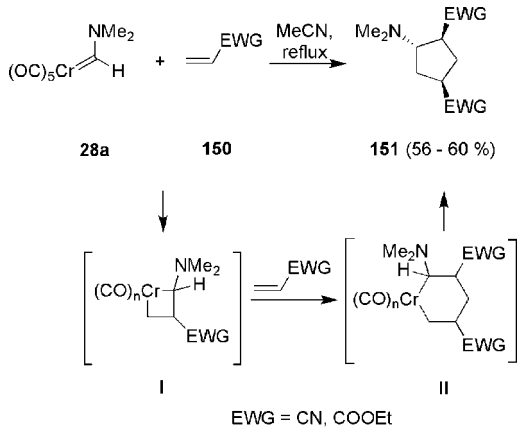
Higher-order cycloaddition reactions include three- and four-component processes. The former can be classified as

Scheme 42. Intramolecular [4 + 2]-Cycloaddition Reaction of Fischer Carbenes Occurring in a Single Carbene Substituent



18e **149** (87 %) *endo* : *exo* = 93 : 7

Scheme 43. Synthesis of Cyclopentanes via Formal [2 + 2 + 1]-Cycloaddition Reaction of Fischer Carbene Complexes



28a **150** **151** (56 - 60 %)

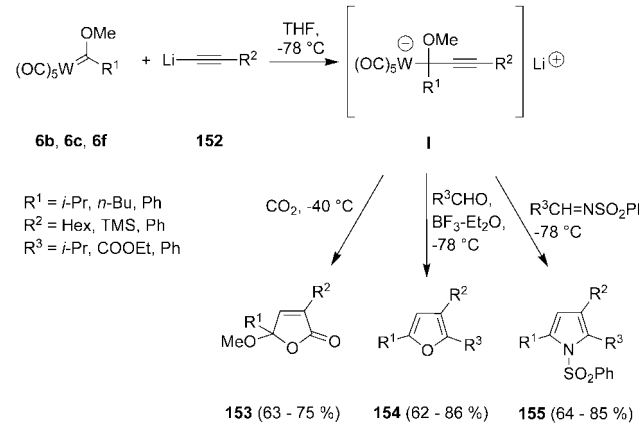
formal [2 + 2 + 1]-, [3 + 2 + 2]-, [4 + 2 + 1]-, and [5 + 2 + 1]-cycloaddition reactions, while the latter represents a formal [2 + 2 + 1 + 1]-cycloaddition reaction. Although mechanistic details of these complex reaction sequences have not been elucidated so far, a combination of mostly nucleophilic addition processes upon carbene carbon atoms or Michael-type addition reactions at β-carbon atoms of alkenyl- or alkynylcarbene complexes has been invoked to rationalize the overall schemes.

2.2.4.1. Formal [2 + 2 + 1]-Cycloaddition Reaction. The reaction of alkenes bearing electron-withdrawing groups (EWGs) **150** like methyl acrylate and acrylonitrile with pentacarbonyl[(*N*,*N*-dimethylamino)methylene]chromium **28a** generates trisubstituted cyclopentanes **151** via formal [2 + 2 + 1]-cycloaddition reaction. Two molecules of the alkene and one carbene ligand are incorporated into the cyclopentane ring (Scheme 43).[82] A mechanism suggested for this reaction implies a double insertion of the alkene into the metal carbene bond, e.g., via intermediates **I** and **II**, followed by reductive elimination.

Various five-membered heterocycles have been prepared in a reaction involving another three-component coupling process. This sequence starts with a nucleophilic attack of an alkynyllithium derivative **152** at the carbene carbon atom of Fischer carbene complexes **6b**, **6c**, and **6f** at −78 °C, generating alkynylmetalate **I**, which reacts either with carbon dioxide, with aldehydes under Lewis-acid catalysis, or with sulfonylimines. Thus, either unsaturated γ-butyrolactones **153**, furans **154** or pyrroles **155** have been prepared (Scheme 44).[83]

Highly substituted cyclopentanols **158** have been obtained diastereoselectively from the reaction of α,β-disubstituted lithium enolates **156** ($R^3 \neq H$) with chromium carbene complexes **4m**, **4o**, **4ae**, and **4ag** followed by addition of allylmagnesium bromide **157**.[84] A mechanistic rationale for

Scheme 44. Formal Three-Component [2 + 2 + 1]-Cycloaddition Reaction of Fischer Carbene Complexes with Alkynyllithium Derivatives To Give Five-Membered Heterocycles



6b, **6c**, **6f** **152** **I**

153 (63 - 75 %) **154** (62 - 86 %) **155** (64 - 85 %)

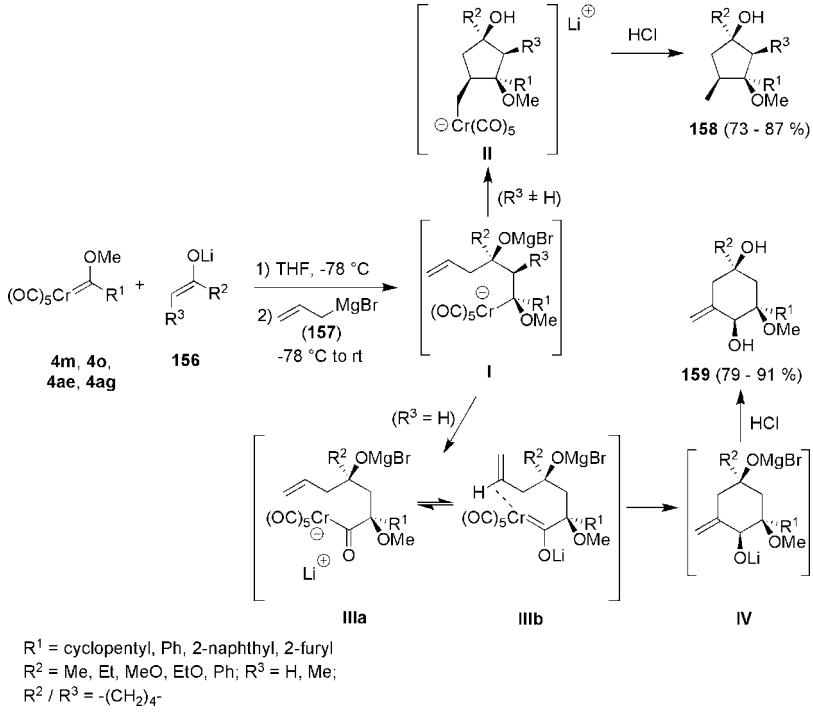
this formal [2 + 2 + 1]-cycloaddition reaction involves initial nucleophilic 1,2-addition of the lithium enolate to the starting carbene complexes **4**, generating a new ketone functionality (arising from the enolate), which undergoes addition of the organomagnesium reagent to afford 5-hexenylchromate **I** as the key intermediate. Intramolecular carbometalation affords **II**, which is hydrolyzed to the final cyclopentanol derivatives **158** (upper part of Scheme 45).

α-Unsubstituted lithium enolates **156** ($R^3 = H$), however, finally afford tetrasubstituted cyclohexane-1,4-diols **159** (lower part of Scheme 45)[84a] in a process that may be considered a formal [2 + 2 + 1 + 1]-cycloaddition reaction. The chemoselectivity of the reaction is determined by the substitution pattern of key intermediate **I**. An unsubstituted α-carbon atom in **156** favors a migratory insertion of carbon monoxide to generate lithium acyl tetracarbonylchromate **IIIa**/**IIIb**. Demetalative intramolecular insertion of the carbene carbon atom into the secondary vinylic C−H bond (**IV**) and subsequent protonation afford diol **159**. The attack of lithium enolates on alkenylcarbene complexes depends on the metal. While the reaction with chromium carbene complexes leads to the formation of cyclopentanediols, oxabicyclo[3.2.1]nonanols are obtained from tungsten carbene complexes. The addition of 3-lithoxy-1,3-butadienes to chromium and tungsten carbene complexes yields cycloheptenones.[84b]

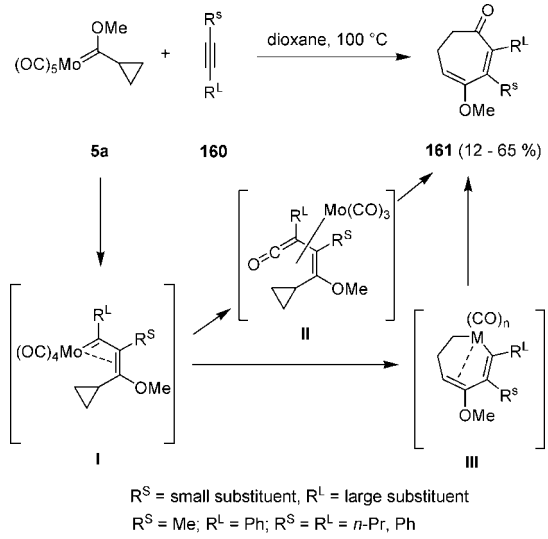
The reaction of aminocarbene complexes with diphenylethyne in refluxing benzene triggers a formal [2 + 2 + 1]-cycloaddition reaction. The successive insertion of the alkyne into the carbene complex followed by insertion of a carbonyl ligand finally produces $Cr(CO)_3$-coordinated ylidic pyrrolidinone derivatives in yields up to 80%.[85] Oxidation of these ylide complexes with dimethyldioxirane leads to lactones, and at elevated temperatures, neutral pyrrolidinones are obtained via a nitrogen-to-carbon migration of an alkyl group.

2.2.4.2. Formal [4 + 2 + 1]-Cycloaddition Reaction. Tungsten and molybdenum cyclopropylcarbene complexes, e.g., **5a**, react (in contrast to the chromium analogue that affords cyclopentenones in a formal [2 + 2 + 1]-cycloaddition reaction)[86] with alkynes **160** to afford cycloheptadienone derivatives **161** (Scheme 46).[87] The mechanism of this reaction is expected to involve a primary insertion of the alkyne into the metal−carbene bond to give metal vinylcarbene **I**. Subsequent CO insertion to the vinylketene inter-

Scheme 45. Synthesis of Cyclopentanols and Cyclohexanols from Carbene Complexes, Enolates, and Allyl Magnesium Bromide



Scheme 46. Molybdenum-Mediated Formal [4 + 2 + 1]-Cycloaddition Reaction of a Cyclopropylcarbene Complex and Alkynes Affording Cycloheptadienones



mediate **II** followed by oxidative addition into one of the cyclopropane C—C bonds may ultimately afford cycloheptadienone **161**. Alternatively, a metal-induced opening of the cyclopropyl ring in **I** may generate intermediate **III**, which may undergo final CO insertion.

2.3. Decomplexation

The synthetic potential of the modification of the carbene complex moiety is enhanced by cleavage of the organometallic moiety. The carbene ligand can be released by oxidative, reductive, or ligand exchange-based demetalation (Figure 8). None of these protocols has been shown so far to proceed via free carbenes.

The thermal decomposition of carbene complexes generally results in a dimerization of the carbene ligand to give alkenes. The replacement of the carbene ligand by carbon monoxide, tertiary phosphines, or amines is a less drastic method to cleave the metal—carbene bond and, in principle, allows for a recovery of a defined low-valent metal species. Hydrogenation, treatment with hydrobromic acid or triflic acid, and pyridine as a ligand for the stabilization of the metal fragment leads to the reductive cleavage of the carbene bond to give ethers and aldehydes,[36,68a,88] and enol ethers,[68a,89] respectively. Metathesis of the metal—carbene bond can be achieved with diazomethane,[68a,90] also yielding enol ethers.

Reductive cleavage by hydrogenolysis provides saturated hydrocarbons but requires harsh conditions.[91] Metal hydrides have been used for the reduction of amino- and alkoxycarbene complexes to amines and alcohols.[92]

The more common protocols are based on the oxidative cleavage of the metal—carbene bond, formally replacing the metal pentacarbonyl fragment by the isolobal oxygen atom. The oxidation is easy to carry out and results in high chemical yields but is accompanied by oxidized metal waste. Among various oxidizing agents, cerium(IV) compounds have found the widest application.[93] Other protocols are based on dimethyl sulfoxide,[94] pyridine *N*-oxide,[95] dimethyldioxirane,[96] PhIO,[95a] iodine, hypochlorites, or molecular oxygen,[97] also in combination with silica gel.[98c] Recently, both stoichiometric and catalytic quantities of KF or Bu_4NF were reported to promote the oxidative cleavage

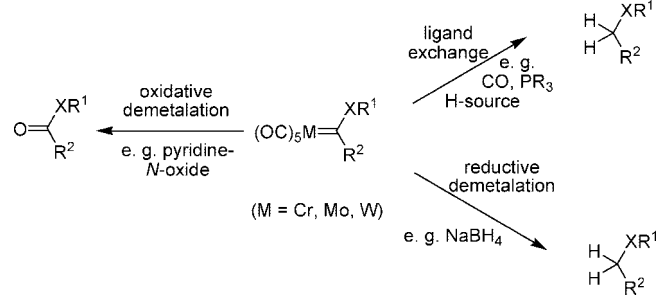
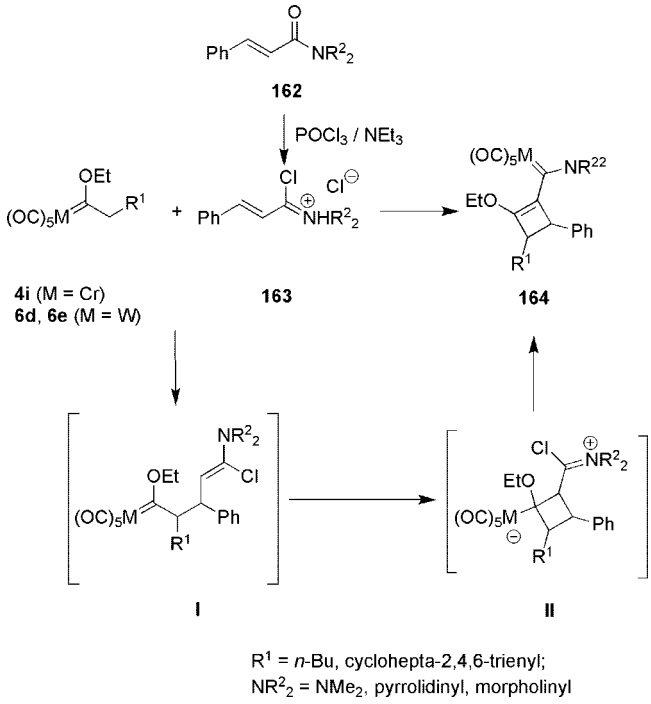


Figure 8. General methodologies for demetalation of Fischer carbene complexes.

Scheme 47. Synthesis of Cyclobutenylcarbene Complexes by Michael-type Addition of Alkylcarbene Complexes to Tertiary Acrylamides



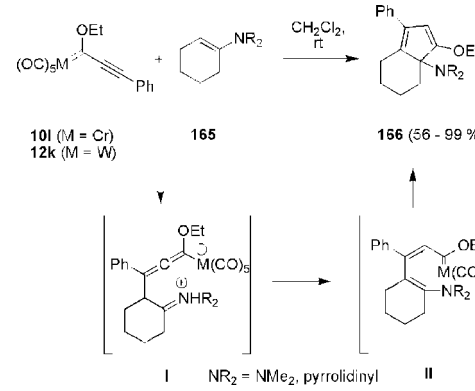
of alkoxycarbene complexes on air.[99] Chromium carbene complexes bearing less bulky carbene ligands undergo demetalation in the presence of catalytic amounts of Bu_4NF ($\leq$0.5 mol %).[99] This methodology was also applied to demetalate tungsten carbene complexes of uracil derivatives; morpholine *N*-oxide and *t*-butyl hydroperoxide turned out to be efficient in this case.[100] Both reductive and oxidative demetalation using sodium borohydride (for aminocarbene complexes) and pyridine *N*-oxide, respectively, have been recently reported in the presence of sulfur and selenium.[101a] The use of S=C=O or Se=C=O (in situ generated by the reaction of sulfur and selenium with carbon monoxide, respectively) provides an entry into S- and Se-carboxylates.[101b] Both reductive and oxidative demetalation protocols have been applied for the enantioselective and diastereoselective synthesis of cyclopropane derivatives, for instance.[102]

2.4. Stepwise Processes Leading to Formal Cycloaddition Products

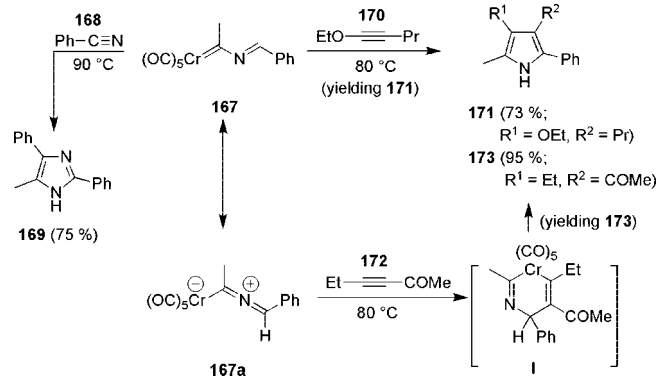
2.4.1. Formal [2 + 2]-Cycloaddition Products

An unusual example of a formal [2 + 2]-cycloaddition has been reported for the formation of cyclobutenyl(amino)carbene complexes **164** from alkyl(alkoxy)carbene complexes **4i**, **6d**, and **6e** and tertiary acrylic amides **162** in the presence of $POCl_3/Et_3N$ (Scheme 47).[103] The reaction involves a Michael addition of the conjugated base of the carbene complex to the iminium chloride **163** formed from acrylic amide **162** to generate the ω-alkenylcarbene complex **I**. Subsequent ring-closure to the cyclobutyl metalate **II**, dehydrochlorination, and [1,3]-migration of the metal fragment have been suggested to explain the formation of **164**.

Scheme 48. Synthesis of Fused Cyclopentadienes by Reaction of Cyclic Enamines and Alkynylcarbene Complexes



Scheme 49. Synthesis of Five-Membered *N*-Heterocycles from Iminocarbene Complexes



2.4.2. Formal [3 + 2]-Cycloaddition Products

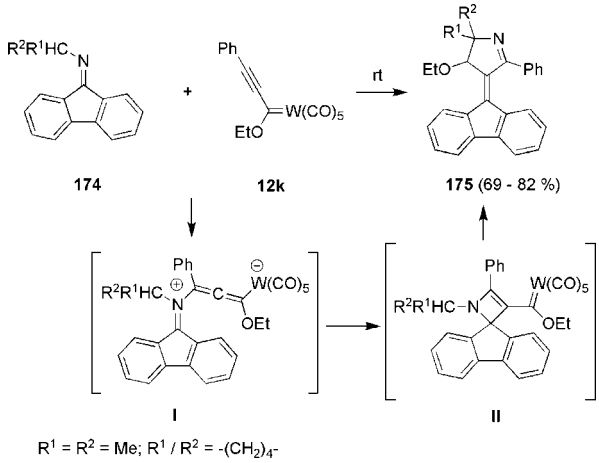
Fused cyclopentadienes **166** can be obtained from the reaction of alkynylcarbene complexes **10l** and **12k** and secondary cyclopentyl or cyclohexyl enamines (**165**) at ambient temperature (Scheme 48).[104] This regioselective formal [3 + 2]-cycloaddition reaction is initiated by a Michael-type addition of the enamine **165** to the alkynylcarbene complex. Intramolecular hydrogen transfer from **I** to 1,3,5-metalatriene **II** followed by ring-closure and demetalation results in the cyclopentadiene annulation product **166**. A recent asymmetric cyclopentannulation of indoles has been reported in which indoles react as the enamines with chiral tungsten alkynylcarbene complexes.[104d]

Chromium (and tungsten) iminocarbene complexes (e.g., **167**) react with electron-acceptor (for instance benzonitrile **168** and 3-hexyn-2-one **172**), electronically neutral, and electron-rich (such as 1-ethoxypentyne **170**) carbon-carbon or carbon-heteroatom triple-bond systems (Scheme 49)[105] to give imidazoles **169** and pyrroles **171** and **173**, respectively. The regioselectivity observed for the reaction of **167** with the ynone **172** can be correlated with the resonance structure **167a**. Addition of the ynone provides the metalacyclic intermediate **I**, which undergoes reductive elimination to give pyrrole **173**.

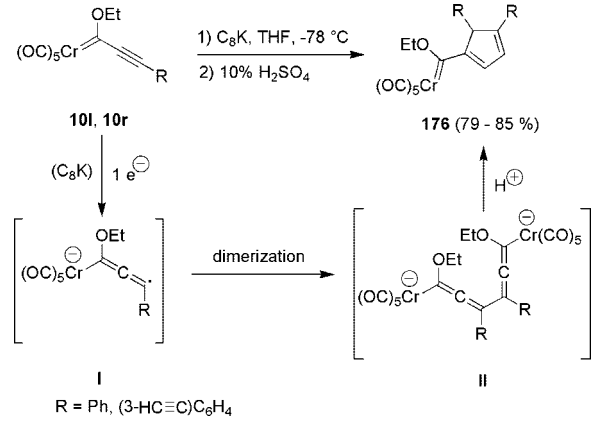
Under photochemical conditions, iminocarbene complexes[106] react with alkynes,[107a−c] alkenes[107b,d] and heteroatom-containing double bonds to give 2*H*-pyrrole, 1-pyrroline, and triazoline derivatives, respectively.[107e]

Nonenolizable imines such as 9-fluorene imines **174** react with alkynylcarbene complex **12k** to afford dihydropyrrol derivatives **175** (along with mesoionic pyrrolium carbonyltungstates as side products) (Scheme 50).[108] Both types of

Scheme 50. Reaction of Tungsten Alkynylcarbene Complexes with Azafulvenes



Scheme 51. SET-Reductive Dimerization of Chromium Alkynylcarbene Complexes



compounds have been considered as evolved from competing intramolecular [2 + 2]- and [3 + 2]-cycloaddition reactions of a common intermediate **I** formed by 1,4-conjugated addition of imine **174** to alkynylcarbene complex **12k**; dihydropyrrol **175** has been suggested to form from spiroazacyclobutene intermediate **II**.

Recently, this kind of reaction has been extended to alkenylcarbene complexes and 8-azafulvenes.[108b] Formal [8 + 2]- or [8 + 3]-reaction pathways afford cycloheptapyridinone or tetrahydroazaannulene skeletons, respectively, depending on the substitution pattern at the C_β-carbon atom of the alkenylcarbene complex.

A formal [3 + 2]-cycloaddition reaction between two molecules of alkynylcarbene complexes **10l** and **10r** is observed upon one-electron reduction,[109] e.g., by potassium graphite (C_8K) at low temperature (Scheme 51).[109a] The tail-to-tail dimerization of the resulting radical anions **I** is suggested to afford biscarbene dianion **II**, which may rearrange upon protonation with a strong acid to give chromium cyclopentadienylcarbene **176** after partial demetalation.

Although alkenylcarbene complexes typically react with alkynes to give [3 + 2 + 1]-benzannulation products (see section 3.2.1), some isolated examples of formation of five-membered rings via a [3 + 2]-cycloaddition process have been reported.[3l,110] β-Donor substituted alkenylcarbene complexes react with alkynes to give cyclopentene derivatives,[3l] which also have been reported to result from the coupling of β-pyrrolyl-substituted carbene complexes as exclusive products.[111] Moreover, alkenylcarbene complexes react with siloxy-substituted 1,3-dienes to afford vinylcyclopentene derivatives through a formal [3 + 2]-cycloaddition process.[112]

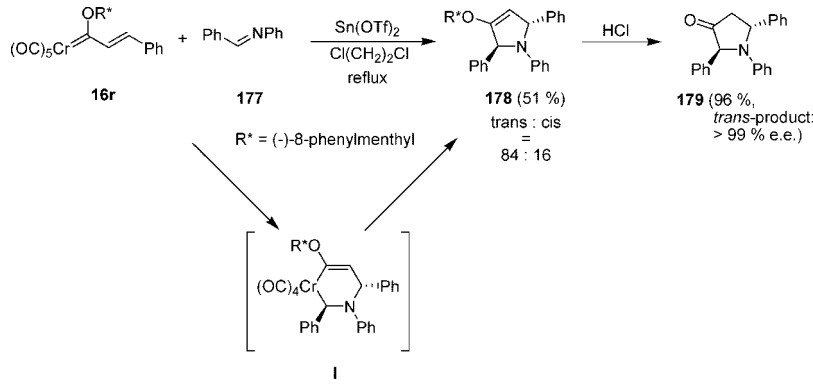
The intermolecular reaction of electronically neutral 1,3-dienes with alkenylcarbene complexes results in the formation of mixtures of [3 + 2]- and [4 + 1]-cycloadducts;[113a] the course of the reaction is highly dependent on the solvent[113b] and reaction temperature used. Selective cyclopentene formation via formal [3 + 2]-cycloaddition reaction was observed in toluene at 80 °C along with high asymmetric induction (up to 99% de) when chiral alkenylcarbene complexes derived from (−)-8-phenylmenthol were applied. Similar high diastereoselectivities but only moderate chemical yields were obtained for the reaction of alkenylcarbene complexes with 1-amino-1-aza-1,3-dienes to give substituted cyclopentenes.[114] The reaction of alkenylcarbene complexes **16r** with imines **177** in the presence of a Lewis acid generates pyrroline derivatives (e.g., **178**) as a result of a formal [3 + 2]-cyclization process that is rationalized in terms of a metalaheterocyclic intermediate **I** (Scheme 52).[115] High asymmetric induction has been observed with the (−)-8-phenylmenthol auxiliary and catalytic amounts of $Sn(OTf)_2$. 2,5-Dihydropyrroles **178** were obtained with high *trans*/*cis* selectivity and hydrolysis of the major *trans* diastereoisomer led to optically pure 2,5-disubstituted-3-pyrrolidinone derivatives **179**.

Further diastereoselective and enantioselective formal [3 + 2]-carbocyclizations include the reaction of tungsten alkenylcarbene complexes **18c**, **18d**, **18i**, and **18m** and enamines **180** derived from chiral amines to give chiral substituted cyclopentanone and cyclopentenone derivatives **182** and **184** via enol ethers **181** and **183**, respectively. Interestingly, the regiochemistry of the final products differs for enamines derived from aldehydes and those derived from ketones (Scheme 53).[116] The mechanism for aldehyde-derived enamines (affording **181**/**182**) involves a Michael-type 1,4-addition of the enamine to the alkenylcarbene complex, whereas ketone-derived enamines (yielding **183**/**184**) react through an initial 1,2-addition to the carbene carbon atom.

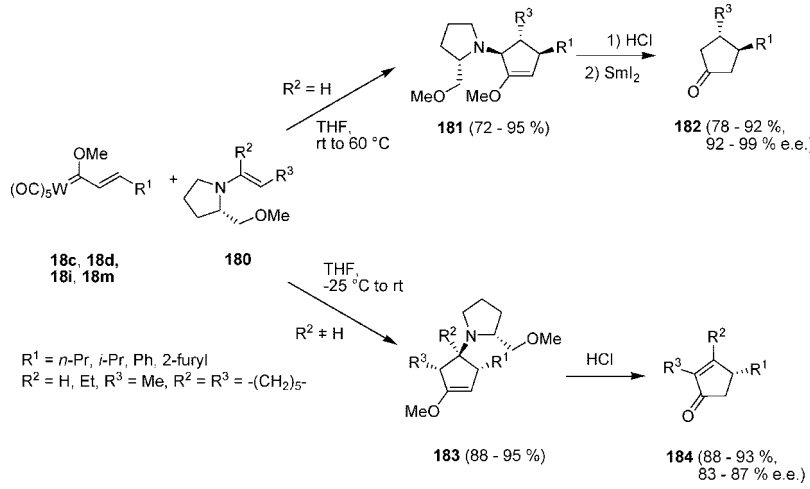
Another strategy for the diastereoselective synthesis of five-membered carbocycles involves α-substituted alkenylcarbene complexes (e.g., **16l** and **18h**) and lithium methyl ketone enolates **185** (Scheme 54)[117a,b] or ketene acetals.[117c] In the reaction with enolates, the use of a coordinating solvent (THF or Et_2O) or the presence of a chelating additive such as pentamethyldiethylenetriamine (PMDTA) allows to switch between one (**186**) or the other diastereoisomer (**187**) of the final cyclopentene derivative. The influence of the solvent/additive on the diastereoselectivity is rationalized in terms of the capability of lithium to coordinate to the oxygen atoms of the 1,2-addition intermediates favoring the orientation of the carbonyl group in a particular conformation.

The formal [3 + 2]-cycloaddition of chromium alkenyl(ethoxy)carbene complexes of type **16c**, **16d**, **16f**, **16i**, or **16t** with alkynes **160** has been utilized to construct 5-dialkylamino-3-ethoxycyclopentadienes **188** in which the sterically less demanding substituent (R^S) has been incorporated next to the carbon atom bearing the ethoxy group.[118] Hydrolysis of the enol ether affords cyclopentenones **189** (Scheme 55); alternatively, densely substituted cyclopentenones **192** are also accessible by transformation of standard carbene complexes **4b** and **4p** with alkylidenecyclopropanes **190** (representing a formal [4 + 1]-cycloaddition) (Scheme 56).[119] The cyclopentane derivatives **191** can serve as starting

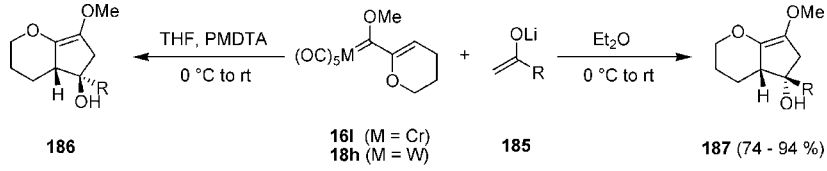
Scheme 52. Enantioselective Synthesis of Pyrrolidinones by Reaction of Imines and an Optically Active Chromium Alkenyl(alkoxy)carbene Complex



Scheme 53. Enantioselective Synthesis of Cyclopentanones and Cyclopentenones from Tungsten Alkenylcarbene Complexes and Optically Active Enamines



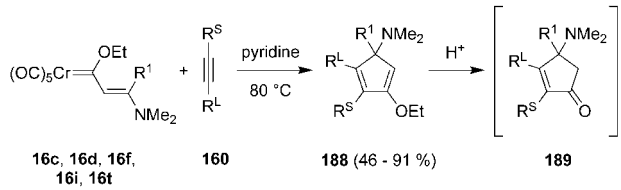
Scheme 54. Solvent-Induced Control of Diastereoselectivity in the Reaction of Enolates with Tetrahydropyranylcarbene Complexes



R = Me, *i*-Pr, *i*-Bu, *t*-Bu, Ph, 4-MeOC$_6$H$_4$, 2-furyl, (*E*)-PhCH=CH, (*E*)-(4-MeOC$_6$H$_4$)CH=CH, (*E*)-PrCH=CH, Me$_2$C=CH, 1-cyclohexenyl, PhC≡C, BuC≡C, TMSC≡C, DHP

DHP = 4,5-dihydro-4*H*-pyran-2-yl

Scheme 55. Synthesis of Cyclopentadienes via Formal [3 + 2]-Cycloaddition of Chromium *β*-Aminoalkenyl(ethoxy)carbene Complexes with Alkynes



R^1 = Me, *n*-Pr, (CH$_2$)$_3$OTBDMS, *c*-C$_3$H$_5$, Ph
R^S = H, Me, *c*-C$_3$H$_5$, Ph
R^L = Me, *n*-Pr, CH$_2$TMS, CH$_2$OTBDMS, TMS, *c*-C$_3$H$_5$, Ph

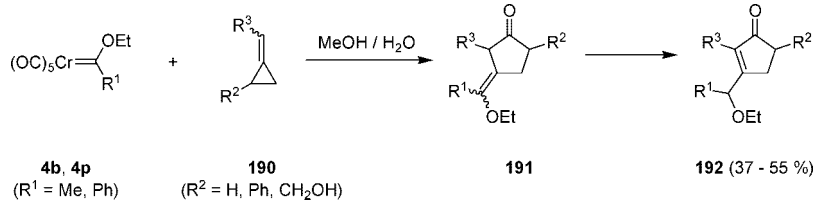
point toward oligocyclic hydrocarbons like triquinanes, steroid-like ring skeletons, and more extended carbocyclic systems.

2.4.3. Formal [3 + 3]-Cycloaddition Products

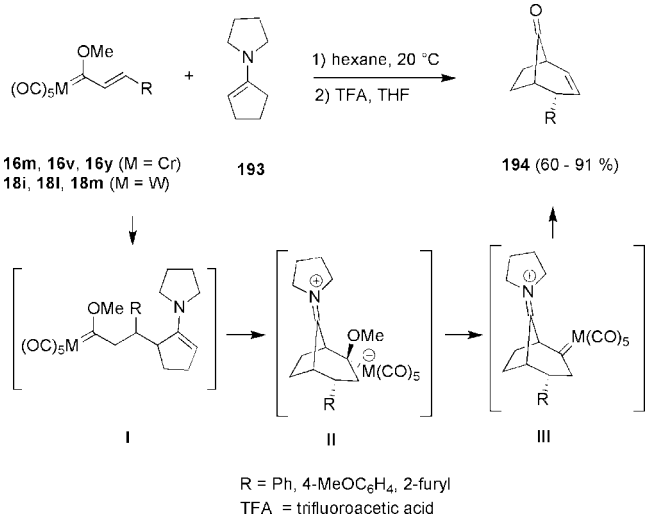
[3 + 3]-Cyclization reactions[120] supported by transition metals are scarce. α,*β*-Unsaturated Fischer carbene complexes mimic a C$_3$-synthon bearing two terminal electrophilic carbon atoms that may be connected with molecules that include two nucleophilic positions. Combined with the capability of alkenyl- and alkynylcarbene complexes to undergo a [1,2]-migration of the pentacarbonylmetal fragment, an electrophilic-to-nucleophilic *umpolung* of the *β*-carbon atom of the carbene ligand is feasible.

The potential of Fischer carbene complexes in the construction of complex structures from simple starting materials is illustrated in the reaction of chromium and tungsten alkenylcarbene complexes **16** and **18** with cycloalkanone enamines (e.g., **193**). A diastereo- and enantioselective synthesis of bicyclo[3.2.1]octanone (e.g., **194**) and bicyclo-

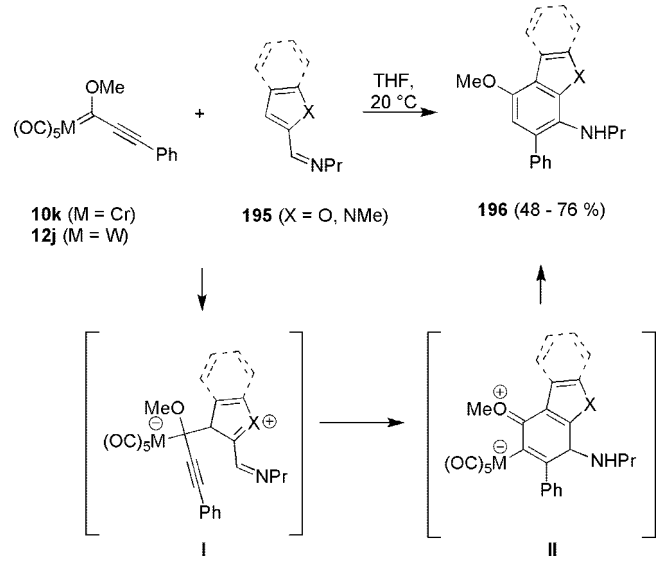
Scheme 56. Access to Cyclopentenones by Reaction of Alkoxycarbene Complexes with Alkylidenecyclopropanes



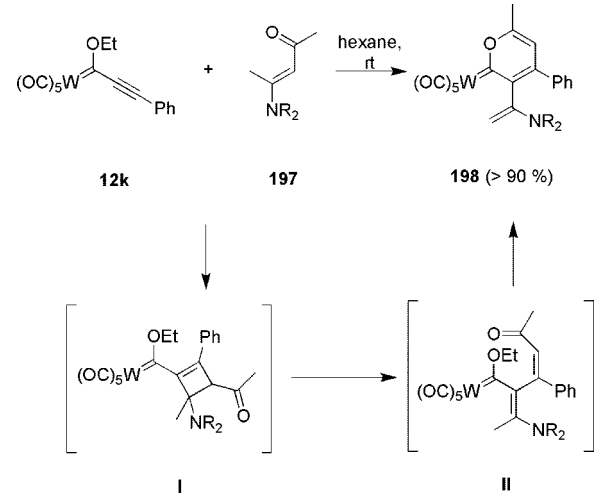
Scheme 57. Bicyclo[3.2.1]octenone Derivatives from the Reaction of Cyclopentyl Enamines with Alkenylcarbene Complexes



Scheme 58. Benzannulation of Imines by Alkynylcarbene Complexes



Scheme 59. Synthesis of 2-Pyranylidene Complexes from Tungsten Alkynylcarbene Complexes and β-Acyl Enamines



[3.3.1]nonanone derivatives (Scheme 57)[121] is based on a 1,4-addition of the C_β-enamine to the alkenylcarbene complex (**I**) and a 1,2-addition of the C_β-enamine to the carbene carbon atom leading to the isolable metalate intermediate **II**. Acid-induced elimination of methanol gives **III**, and hydrolysis affords the unsaturated bicycloketone **194** via β-hydrogen elimination.

Alkynylcarbene complexes **10k** and **12j** react with imines derived from furan-, benzofuran-, *N*-substituted pyrrole-, and *N*-substituted indole-2-carboxaldehydes **195** to give the formal [3 + 3]-cycloaddition products **196** (Scheme 58).[122] This carbocyclization process is thought to involve an initial 1,2-addition to generate zwitterionic intermediate **I**. [1,2]-Migration of the pentacarbonyl metal fragment, cyclization (to intermediate **II**), aromatization, and demetalation lead to **196**.

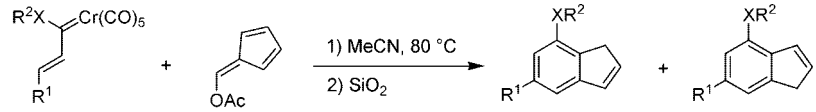
Another formal [3 + 3]-cycloaddition results from a [2 + 2]-cycloaddition reaction followed by cyclobutene ring-opening. A typical example is the reaction of ethyl 2,2-diethoxyacrylate with alkynyl(alkoxy)carbene complexes to afford ethoxy-substituted metal 2-pyranylidenes.[55e,123] Similarly, tertiary β-ketoenamines **197** react with alkynylcarbene complex **12k** to give pyranylidene complexes **198** in high yields (Scheme 59). The [2 + 2]-cycloaddition reaction between the alkynyl moiety of the carbene complex and the C═C double bond of the enamine generates cyclobutene **I**, which undergoes a conrotatory cyclobutene ring-opening to enamino carbene complex **II** followed by cyclization to **198**.[45c,124]

The unique C═C bond conjugation in fulvenes allows for unusual cycloaddition reactions with other unsaturated systems. For example, alkenylcarbene complexes **16** and **28** react with fulvene **199** to give two indene isomers (**200**) in a formal [3 + 3]-cycloaddition process.[125a] The reaction is suggested to proceed via an initial 1,2-addition of the fulvene to the carbene carbon followed by a [1,2]-[$Cr(CO)_5$]-shift-triggered ring-closure (Scheme 60).[125b]

2.4.4. Formal [4 + 3]-Cycloaddition Products

Upon reaction with electron-rich 1,3-butadienes such as Danishefsky's diene, chromium alkenylcarbene complexes afford seven-membered rings in low yields in a formal [4 + 3]-cycloaddition process; in contrast, analogous tungsten carbene complexes undergo Diels−Alder reaction, reflecting the enhanced acceptor character of the tungsten fragment.[68b,112a] The formation of the seven-membered ring is explained by an initial cyclopropanation of the most electron-rich double bond of the diene followed by a Cope rearrangement of

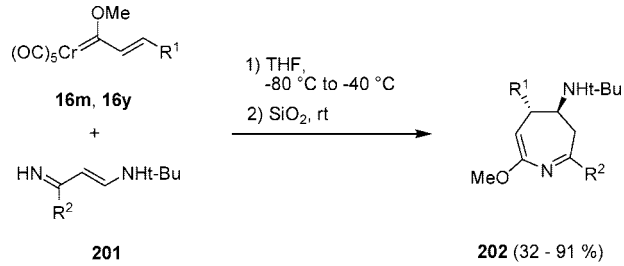
Scheme 60. Synthesis of Indenes by Reaction of Acetoxyfulvene with Chromium Alkenylcarbene Complexes



16m, **16o**, **16y**, **28e**, **28h** **199** **200** (65 - 75 %)

R^1 = CH=CH(*E*-CO_2Et), CH=CH(*E*-Ph), Ph, 2-furyl
(XR^2 = OMe, $O(CH_2)_2I$, NMe_2, pyrrolidinyl)

Scheme 61. Synthesis of Dihydroazepines Starting from Alkenylcarbene Complexes and Aminoazadienes



R^1 = Ph, 2-furyl
R^2 = Et, *c*-C_3H_5, Ph, 4-MeC_6H_4, 4-ClC_6H_4

the resulting divinylcyclopropane. Increased yields were obtained with amino-substituted 1,3-butadienes and chromium alkenylcarbene complexes to produce racemic and chiral 1,3-cycloheptadiones.[126]

Seven-membered carbocycles are also accessible from the reaction of chromium alkenylcarbene complexes and methyl vinyl ketone enolates.[117b] In addition, formal [4 + 3]-heterocyclization results from 4-amino-1-azadienes. The cycloaddition of reactive 4-amino-1-aza-1,3-butadienes **201** to chromium or tungsten alkenyl(methoxy)carbene complexes **16m** and **16y** affords substituted 4,5-dihydro-3*H*-azepines **202** in 52−91% yield (Scheme 61).[127] NMR monitoring suggests a 1,2-addition of the imine functionality in **201** to the starting carbene complex at −78 °C followed by a [1,2]-$W(CO)_5$ shift and ring-closure as the key steps of the reaction.

A chiral version of this [4 + 3]-heterocyclization is based on chiral, nonracemic carbene complexes **16p**, **16q**, and **16z** derived from menthol and oximes **203** as imine surrogates (Scheme 62).[128] One equivalent of an alkyl(alkoxy)carbene complex (**4a**) is used for the transformation of the oxime into the imine. The ready crystallization of the major diastereomer from methanol allows the isolation of dihydroazepine **204** and **205** in enantiomerically pure form.

While tungsten alkynylcarbene complexes represent excellent dienophiles in the classical Diels−Alder reaction with 1-azadienes, the chromium analogues behave differently, providing an entry into azepine derivatives.[128]

In a related process, zwitterionic pyrrolodiazepine derivatives have been obtained from alkynylcarbene complexes and imines derived from *N*-unsubstituted-pyrrole-2-carboxaldehyde via a formal [4 + 3]-heterocyclization reaction.[122]

The cyclopropanation of fulvenes **206** by alkynylcarbene complexes **12i** and **12j** can be inhibited in the presence of CO; under these conditions, formal [4 + 3]-cycloadducts **207** are obtained in moderate to good yields (Scheme 63).[129] Again, the reaction features a sequence of 1,2-addition of fulvene to the carbene carbon atom, 1,2-[$W(CO)_5$] shift and cyclization.

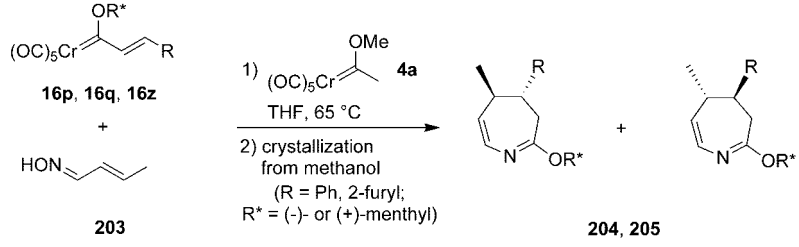
Deprotonation of hydroxybenzocyclobutene **208** with *n*-butyllithium generates an equivalent of vinylogous enolate **209**, which adds to tungsten alkynylcarbene complexes **12** to afford either benzocycloheptene ketals **210** or benzocycloheptenones **211** depending on the solvent used. While diethyl ether affords exclusively **210**, THF leads to increased formation of **211** (accompanied by 5−30% of **210**) (Scheme 64).[130] The formation of **210** and **211** is rationalized in terms of a 1,2-addition at the carbene complex, followed by 1,2-migration of the organometallic fragment.

3. Metal-Templated Cycloaddition Reactions of Fischer Carbene Complexes

3.1. Cyclopropanation

The carbene ligand in metal carbenes **4o**, **5b**, and **6f** may be transferred to alkenes to give cyclopropanes. Early [2 + 1]-

Scheme 62. Diastereoselective Synthesis of Dihydroazepines from Alkenylcarbene Complexes and Oximes



	total yield	ratio **204** : **205**	isolated major isomer (yield)	isolated major isomer (d.e.)
		204a - b : **205a - b**		
R* = (-)-menthyl, R = Ph	87 %	70 : 30	**204a** (50 %)	> 97 %
R* = (+)-menthyl, R = Ph	80 %	30 : 70	**205b** (46 %)	> 97 %

cycloaddition reactions of this type with electron-poor alkenes **212** revealed that the isomeric ratio of the cyclopropanes **213a**/**213b** formed depends on the metal used. These results indicate that the metal is involved in the product-forming step and consequently exclude the intermediacy of free carbenes (Scheme 65).[21a,131] This idea was further supported by an (even low) transfer of chirality from a chromium carbene—bearing an optically active phosphine ligand—to the resulting cyclopropane.[132] Moreover, an efficient cyclopropanation of electron-rich and electron-deficient alkenes requires different reaction conditions, suggesting that different mechanisms are operative in these transformations, as discussed below. The cyclopropanation with carbene complexes is stereospecific; the configuration of the alkene is retained in the cycloadduct.

The cyclopropanation of α,β-unsaturated esters with group 6 phenyl(methoxy)carbene complexes to give **213a**/**213b** requires elevated temperatures (≥90 °C), allowing a rapid CO exchange in the carbonyl(carbene) complex. Thus, a reasonable mechanism involves a decarbonylation pre-equilibrium of carbene complex **214** followed by coordination of the alkene to the coordinatively unsaturated tetracarbonyl intermediate **I**. The resulting alkene(carbene) complex **II** may rearrange to a metalacyclobutane **III**, which undergoes reductive elimination to give the cyclopropane **215** (Scheme 66).[133]

3.1.1. Cyclopropanation of Electron-Rich Alkenes

The cyclopropanation of electron-rich alkenes with Fischer carbene complexes requires modified reaction conditions. Warming a solution of a metal carbene **214** and an enol ether **91** at atmospheric pressure results in the formation of an alkene **216**, which apparently is formed via the tetracarbonyl carbene complex **I**, alkene carbene complex **II**, and metalacyclobutane **III** intermediates in an olefin metathesis reaction. However, good yields of cyclopropanation products are obtained under CO pressure. Under these conditions, the metal does not act as a template; instead, the enol ether is supposed to add as a nucleophile at the carbene carbon atom to generate zwitterion **IV** in which the metal-coordinated carbon atom undergoes an either front—side or back—side attack at the former α-enol ether carbon atom to give the cyclopropane **217** (Scheme 67).[134]

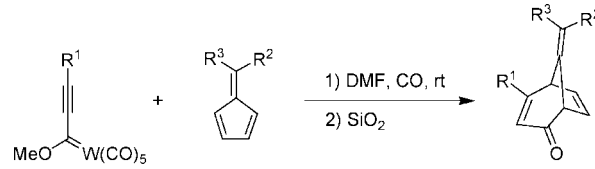
Again the isomeric ratios of the cyclopropanes **218a** and **218b** formed from carbene complexes **4o**, **5b**, and **6f** and ethyl vinyl ether **91a** reflect the role of the metal used (Scheme 68).[134a]

Ketene acetals as (electron-rich) alkene derivatives have also been demonstrated to undergo a [2 + 1]-cycloaddition reaction. Whereas simple methoxycarbene complexes give cyclic *ortho*-esters,[135a] isopropoxy- or cyclopropoxycarbene complexes afford the cyclopropanation products when the reaction is carried out under carbon monoxide atmosphere.[135b] The reaction of acyloxycarbene complexes with β-unsubstituted enol ethers at low temperature afforded mixtures of diastereomeric cyclopropanols.[136]

3.1.2. Cyclopropanation of Nonfunctionalized Alkenes

Nonfunctionalized alkenes **220** undergo cyclopropanation by stronger electrophilic metal carbenes as provided by nonheteroatom-stabilized group 6 (e.g., **219**)[137a] or cationic iron carbenes;[137b] the reaction is highly *syn*-selective (see **221**, Scheme 69). Iron carbenes bearing optically active phosphine ligands allowed for an efficient enantioselective cyclopropanation.[137b] Nonfunctionalized alkenes have been also cyclopropanated by ferrocenyl-substituted group 6 metal carbene complexes.[137c,d]

Scheme 63. Synthesis of 8-Methylenebicyclo[3.2.1]hexadienones from Fulvenes and Tungsten Alkynylcarbene Complexes



12i, **12j** **206** **207** (50 - 88 %)

R^1 = 1-cyclohexenyl, Ph
R^2 = Me, *t*-Bu, 4-$MeOC_6H_4$, OAc
R^3 = H, Me

The cyclopropanation protocol can be applied to 1,3-dienes as well.[138] Electron-deficient 1,3-dienes yield vinyl-substituted cyclopropanes upon [2 + 1]-cycloaddition reaction with Fischer carbene complexes.[139]

3.1.3. Cyclopropanation of Electron-Poor Alkenes

The reaction of alkenylcarbene complexes and electron-poor alkenes normally leads to mixtures of vinylcyclopropane and cyclopentene derivatives reflecting a [2 + 1]-cycloaddition—ring-expansion sequence; the product distribution can be controlled by choosing the appropriate reaction conditions.[111,140] Donor—acceptor-substituted alkynylcyclopropanes are accessible from alkynyl(alkoxy)carbene complexes and methyl acrylate or acrylonitrile.[141] Thus, methoxy-substituted alkynylcyclopropyl carboxylic esters and nitriles could be obtained in moderate to high chemical yields and up to high diastereoselectivities. If the reaction is run in the presence of acetonitrile, the organometallic fragment can be recovered; microwave conditions at room temperature may speed up the reaction to completion within a few minutes.

The thermal reaction between chromium alkenylcarbene complexes (e.g., **16m**) and enals (e.g., **222**) or enones provides an entry into dihydrofurans (e.g., **223**) and furans (Scheme 70).[142] This process has been found to proceed via a [2 + 1]-cycloaddition reaction to form formyl- and acylcyclopropanes, respectively, which undergo a subsequent ring enlargement to furans.

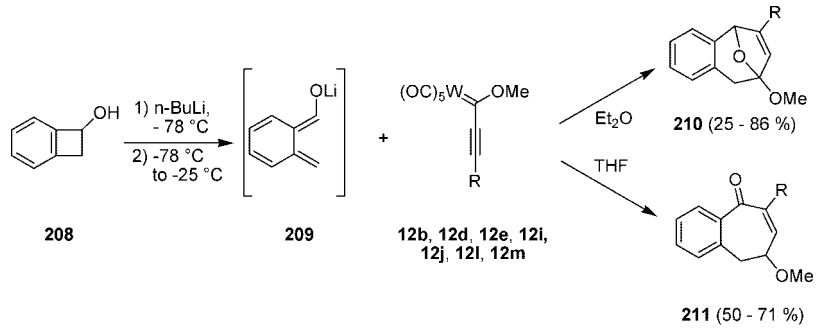
Methyl crotonate and γ-crotonolactone have been applied in the diastereoselective cyclopropanation of *O*-protected chromium glucal carbene complexes.[143,144] The [2 + 1]-cycloaddition reaction affords glycals attached to a rigid cyclopropyl or bicyclo[3.1.0]hexane skeleton, although in only moderate diastereoselectivity.

3.2. Benzannulation and Cyclopentannulation

3.2.1. Benzannulation

3.2.1.1. Mechanism and Selectivity. Probably the most important stoichiometric application of metal carbenes in organic synthesis is the construction of hydroquinoid benzenoid arenes in the presence of alkynes. Pentacarbonylchromium complexes bearing aryl- or alkenyl(alkoxy)carbene ligands react with alkynes to give densely substituted arenes that remain coordinated to a $Cr(CO)_3$ fragment.[145,146] Scheme 71 illustrates the reaction of phenyl(methoxy)carbene complex **4o** with tolan, which yields naphthohydroquinoid chromium tricarbonyl **224**. This type of cycloaddition

Scheme 64. Formation of Benzoheptenones and Benzocycloheptene Ketals



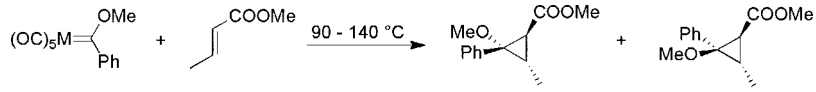
208 209 12b, 12d, 12e, 12i, 12j, 12l, 12m

210 (25 - 86 %)

211 (50 - 71 %)

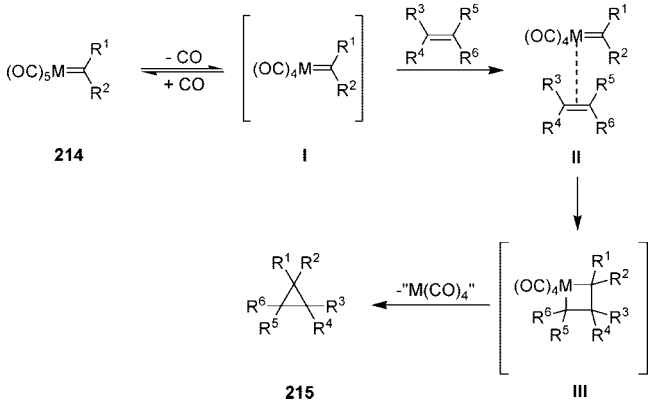
R = *n*-Bu, *t*-Bu, TMS, 1-cyclohexenyl, Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$

Scheme 65. [2 + 1]-Cycloaddition Reaction of Electron-Poor Alkenes with Fischer Carbene Complexes



4o (M = Cr) **5b** (M = Mo) **6f** (M = W)	**212**		**213a** 70 85 68	**213b** 30 15 32

Scheme 66. Metal-Templated Cyclopropanation of Alkenes by Fischer Carbene Complexes



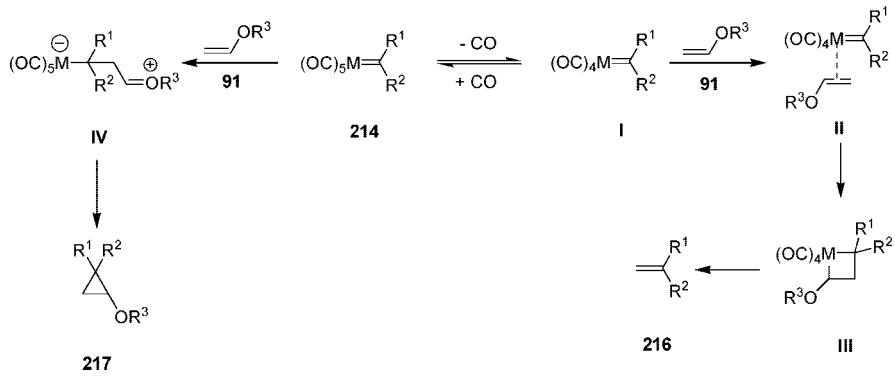
214 I II III 215

reaction assembles the α,β-unsaturated carbene ligand (C_3-synthon), the alkyne (C_2-synthon), and a carbonyl ligand (C_1-synthon) at the $Cr(CO)_3$ fragment, which serves as a template for a stepwise interligand coupling. Chromium is the metal of choice for this type of annulation, which occurs with considerable chemo-, regio-, and stereoselectivity.

The product distribution depends on the nature of the metal, the heteroatom substitution in the carbene ligand, the solvent used, and the workup conditions. Along with the predominating benzannulation, competing paths may lead to cyclopentannulation; the formation of furans and cyclobutenones has also been observed to occur in varying extents. The reaction of phenyl(methoxy)carbene complexes of chromium, molybdenum, and tungsten with 3-hexyne in benzene affords—after demetalative workup—hydroquinone, indene, and furan skeletons.[110a] The greatest extent of chemoselectivity was found for the chromium complex, which produced the hydroquinone almost exclusively. The molybdenum and tungsten analogues led to indenes as the major products along with varying amounts of furan. Apart from group 6 metal carbenes, manganese[147a,b] and ruthenium[147c] complexes have been reported to undergo a similar, but less efficient benzannulation under either more drastic thermal or photochemical conditions.

The solvent may also influence the product distribution.[148] The reaction of chromium carbenes with alkynes in donor solvents like ethers or in benzene reveals a strong preference for benzannulation; the allochemical effect[110a] has been invoked for strongly coordinating solvents to explain the increase of the phenolic benzannulation product over five-membered cyclization products with increasing alkyne concentrations. Noncoordinating solvents such as hexane or polar solvents such as dimethylformamide (DMF) favor the formation of cyclopentannulation products. A strongly coordinating solvent like acetonitrile leads to the formation of cyclobutenones in moderate yields.

Scheme 67. Cyclopropanation of Electron-Rich Alkenes by Fischer Carbene Complexes



IV 214 I II 216 III 217

On the basis of experimental and kinetic studies, a mechanism for the benzannulation has been proposed that is consistent with more recent theoretical calculations[149,150] (Scheme 72). The initial and rate-determining step is a reversible decarbonylation of the pentacarbonylchromium carbene complex **I** affording the coordinatively unsaturated tetracarbonyl complex **II**. This is in accordance with the observation that the reaction is suppressed in the presence of external carbon monoxide,[151a] and the decarbonylation equilibrium was later supported by a kinetic study.[151b] Subsequent coordination of the alkyne gives an η^2-alkyne complex **III**; structural intramolecular analogues have been characterized by X-ray crystallography as alkyne−carbene chromium chelates in which the alkyne and carbene moieties are linked by a rigid C_2-*ortho*-phenylene moiety.[152]

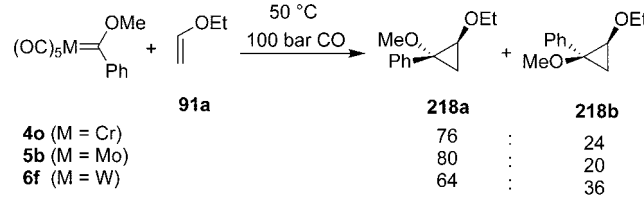
The subsequent steps are too fast for further kinetic investigation. A previously proposed 16-electron chromacyclobutene intermediate arising from a formal [2 + 2]-cycloaddition reaction of the alkyne ligand across the metal−carbene bond was later discarded on the basis of theoretical studies that support a direct insertion of the alkyne into the metal−carbene bond to generate the η^1:η^2-vinylcarbene complex **IV** as an 18-electron valence isomer.[149a,b] A related species has been isolated from the reaction of an alkenyl(amino)carbene complex.[153] Subsequent insertion of a carbonyl ligand leads to η^6-vinylketene complex **V**, structural analogues of which have been synthesized as an enaminoketene complex.[153b,154] Electrocyclic ring-closure affords the cyclohexadienone complex **VI**,[155] which tautomerizes to give the naphthol complex **VII**. If the alkyne incorporates two trimethylsilyl groups[156a] or one bulky trialkylsilyl group and one phenyl substituent[156b] at the carbon−carbon triple bond, the generated ketenes cannot adopt the appropriate *s-cis* geometry for ring-closure and are stable enough for isolation. Depending on the substitution pattern and the solvent, on irradiation or heating they afford either benzannulation products[156b] or cyclobutenones[156c] while addition of diazomethanes yields cyclopentenones.[156d]

The energy profile of the benzannulation reaction of an arylcarbene complex with an alkyne is shown in Figure 9[149c] and reveals that the individual C−C bond-forming steps of the reaction proceed with low energy barriers (~20 kJ/mol). The thermodynamic driving force of the overall process results from the final aromatization, providing ~170 kJ/mol.

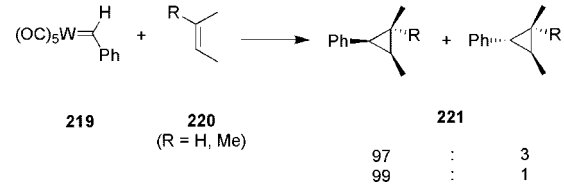
The benzannulation is typically performed under mild thermal conditions in the temperature range of 45−60 °C and gives yields up to 90%. Mildly coordinating solvents are used for this transformation; *tert*-butyl methyl ether is a typical example. Alternative reaction procedures include a photoinduced decarbonylation as the initial step, which allows benzannulation under low-temperature conditions. However, the lower selectivity of this protocol, due to the presence of other photosensitive intermediates, has restricted its synthetic application to cases where the thermal protocol fails.[157] On the basis of earlier observations of photodecarbonylation processes (see section 5), a photobenzannulation was performed starting from a preassembled α,*β*,*γ*,*δ*-dienyl(alkoxy)carbene complex. By reacting the alkoxycarbene complex with carbon monoxide, *ortho*-methoxyphenols[76b,158a] were obtained, thus complementing the thermal benzannulation route to *para*-methoxy phenols. This approach has been extended to the generation of *ortho*-aminophenols from the reaction of dienyl alkoxycarbene complexes with isonitriles,[158a,b] and of dienyl(amino)carbene complexes with carbon monoxide[158a,c] Finally, *meta*-benzannulation products have been obtained from the intramolecular reaction of some α,(*ω*−1)-enynylcarbene complexes to produce *meta*-cyclophanes.[159]

In a few examples, other synthetic techniques were applied to the benzannulation reaction. High-intensity ultrasound, microwave, or dry-state absorption conditions have been reported to accelerate the benzannulation.[160] Dichloroethane has been used for an intermolecular benzannulation reaction to be performed under mild reaction conditions close to room temperature;[161] however, extended reaction times (18 h) are required for high yields. These alternative protocols may lead

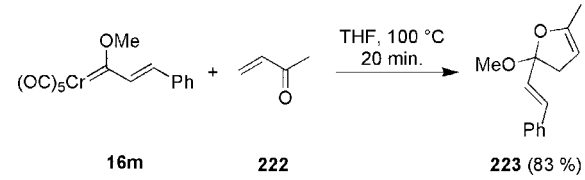
Scheme 68. Cyclopropanation of Electron-Rich Alkenes by Group 6 Phenyl(methoxy)carbene Complexes



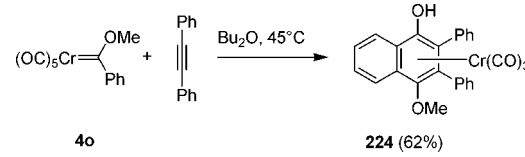
Scheme 69. Cyclopropanation of a Nonfunctionalized Alkene by a Strongly Electrophilic Tungsten Carbene Complex



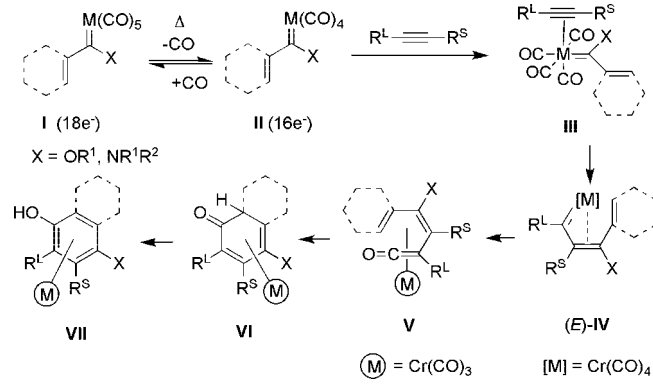
Scheme 70. Synthesis of Dihydrofurans via a [2 + 1]-Cyclopropanation-Ring Enlargement Sequence Starting from Alkenylcarbene Complexes



Scheme 71. Chromium-Templated Benzannulation of Arylcarbene Complexes



Scheme 72. Generally Accepted Mechanism of the [3 + 2 + 1]-Benzannulation



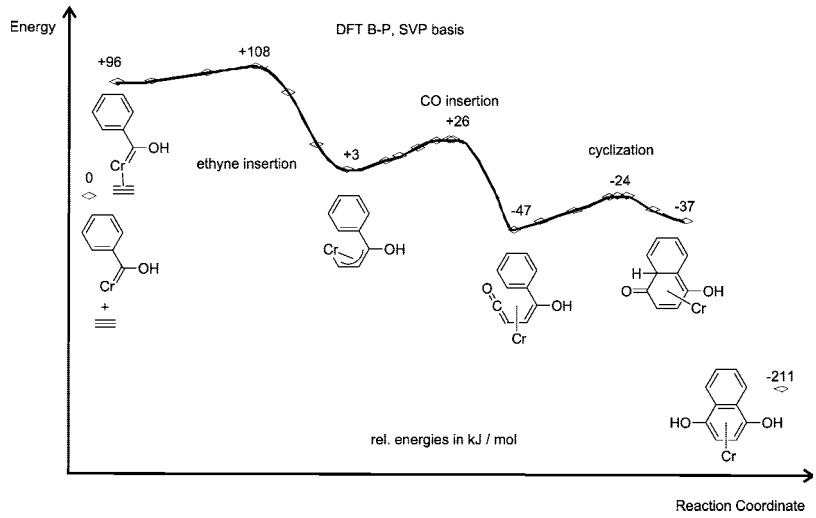
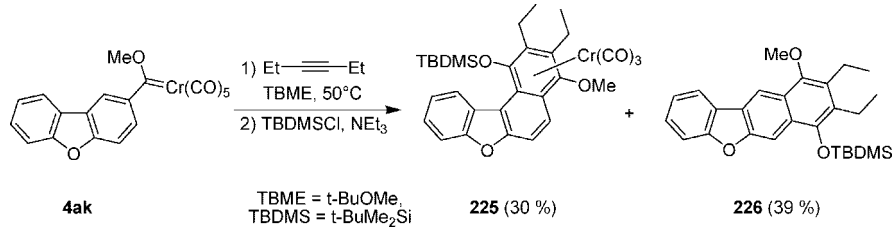


Figure 9. Energy profile and intermediates of the benzannulation reaction of chromium arylcarbene complexes with alkynes (CO ligands omitted for clarity).

Scheme 73. Angular vs Linear Benzannulation of Chromium (Dibenzo)heteroarylcarbene Complexes



in some cases to comparable yields in shorter reaction times, affording the corresponding quinones after oxidative workup. Thus, they do not allow for the isolation of tricarbonylchromium complexes of the hydroquinoid benzannulation products that provide a plane of chirality as a stereogenic element, which may be exploited in stereoselective synthesis.[162]

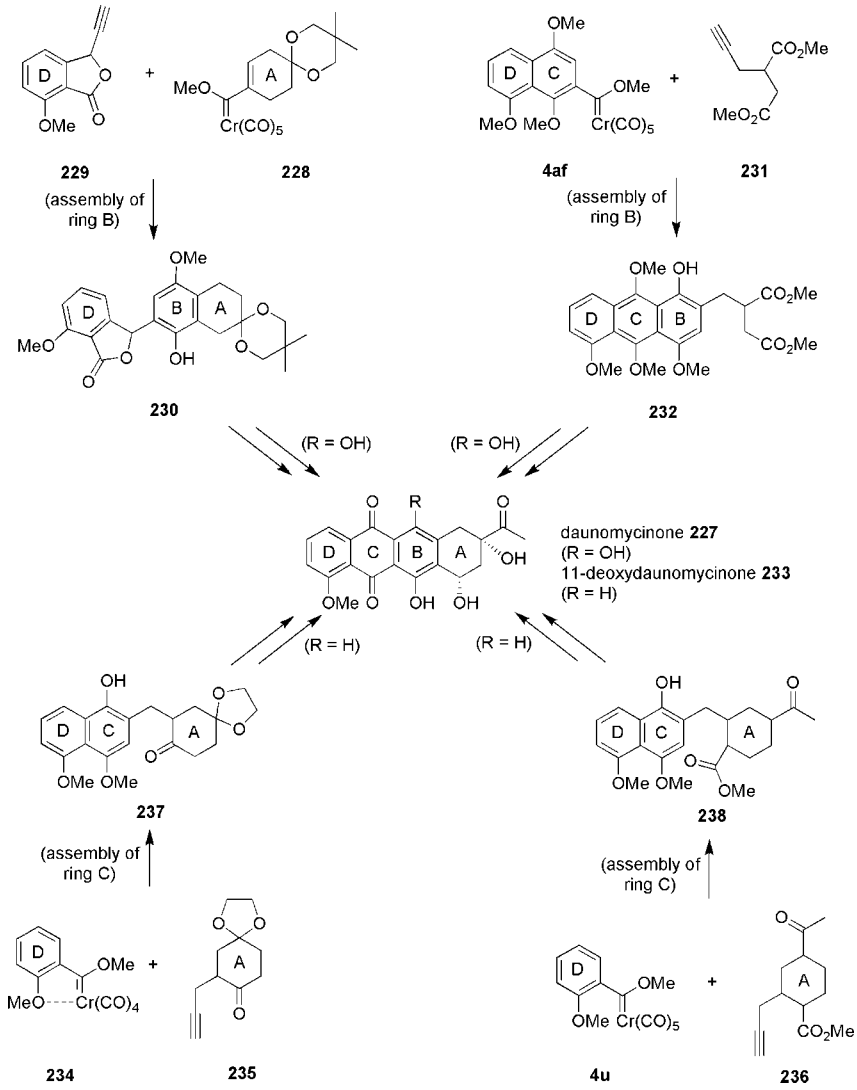
Besides chemoselectivity, the regioselectivity of the alkyne incorporation is another important criterion for the synthetic value of the benzannulation. The regiocontrol mainly arises from steric factors, which favor a coupling of the alkyne carbon atom bearing the less bulky alkyne substituent with the carbene carbon atom. Therefore, the regioselection is virtually complete for terminal alkynes that lead to benzannulation products bearing the alkyne substituent exclusively next to the phenolic group. Unsymmetrical dialkylalkynes afford regioisomeric mixtures; the ratio of regioisomers depends on the relative steric bulk of the alkyl substituents.[163] This regiochemistry can be reversed with stannyl-[164a,b] or borylalkynes[164c] and in intramolecular benzannulation reactions, e.g., using carbene complexes in which the alkyne is incorporated into the alkoxy substituent.[164d]

Benzannulation of fused arenes may afford angular and linear annulation products. The benzannulation of naphthylcarbene ligands generally leads to the phenanthrene skeleton in which both terminal rings obtain a maximum of aromaticity;[151a,165] a similar preference has been observed even in cases where an *ortho*-substitution has been applied to enforce a linear benzannulation.[164b,165] Apart from the construction of phenanthrenes, carbene complexes have also been used for the synthesis of more extended polycyclic arenes.

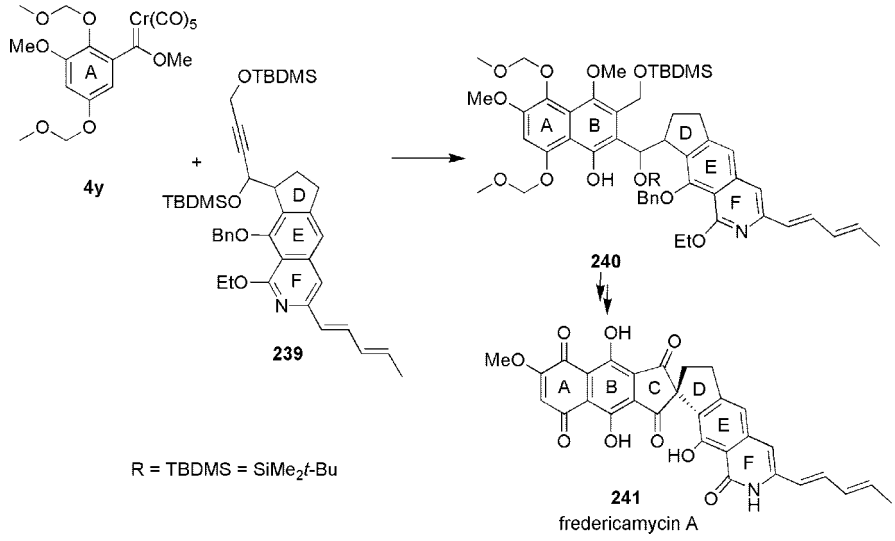
Recent studies indicate that linear benzannulation may become a major competition as observed for carbene complexes derived from dibenzo-substituted five-membered heteroarenes[166] or from helicenes.[167,168] The linear benzannulation for dibenzofurylcarbene complex **4ak**[167] in the presence of 3-hexyne is illustrated in Scheme 73. The uncoordinated benzo[*b*]naphthol[2,3-*d*]furan **226** has been isolated along with the expected angular $Cr(CO)_3$-coordinated benzonaphthofuran **225**. The formation of a linear $Cr(CO)_3$-coordinated benzannulation product was observed when the central furan ring in the carbene complex was substituted for the thiophene system.

3.2.1.2. Application to Bioactive Target Molecules. The benzannulation provides a straightforward access to densely functionalized oxygenated arenes and, as such, has been applied to the synthesis of more complex arene skeletons. Earlier applications to natural product synthesis concentrated on vitamins,[169] steroids[170] and antibiotics.[171] The versatility of the chromium-templated benzannulation is demonstrated in Scheme 74[76b,166,172] by complementary approaches to the daunomycinone (**227**) and 11-deoxydaunomycinone (**233**) skeleton, the former of which is the aglycon of the established antitumor agent daunomycin. For **227,** two benzannulation approaches were used to assemble ring B of the anthraquinone moiety as key steps. The first strategy is based on the benzannulation of cyclohexenyl(ketal)carbene complex **228** by ethynyl lactone **229**, providing tetrahydronaphthol **230**. For the alternative ring B construction, naphthohydroquinonylcarbene complex **4af** (which readily decarbonylates to give the tetracarbonylchromium chelate) and methyl 3-methoxycarbonyl-5-hexynoate **231**, were applied to give intermediate **232**. For the approach toward 11-deoxydaunomycinone **233**, both syntheses use a phenyl(methoxy)carbene complex (**234**/**4u**) that reacts with a propargylic cyclohexane derivative (**235**/**236**) to give naphthols **237** and **238**, respectively.

Scheme 74. Chromium-Templated Benzannulation Approaches to Daunomycinone



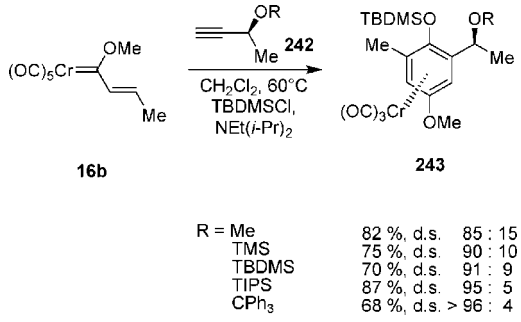
Scheme 75. Benzannulation Approach to Fredericamycin A



A more recent strategy to the antibiotic and antitumor agent fredericamycin A incorporated the benzannulation as the key step of the total synthesis.[173] Benzannulation of the oxygenated arylcarbene complex **4y** with the properly functionalized alkyne **239** gave a 35% yield of a single regioisomer **240**, which was subjected to a final spirocyclization to give the target molecule **241** after chromatographic separation of the racemic mixture (Scheme 75).

3.2.1.3. Asymmetric and Multiple Benzannulation. The chromium-templated coupling of alkenyl- or arylcarbene, alkyne, and carbonyl ligands generates arene tricarbonylchromium complexes as primary benzannulation prod-

Scheme 76. Diastereoselective Benzannulation with α-Chiral Propargylic Ethers



ucts, which—based on their unsymmetric substitution pattern—bear a plane of chirality. Complexes of this type are powerful reagents in stereoselective synthesis.[162] Since the preparation of pure enantiomers is a lengthy and often tedious procedure, a diastereoselective modification of the benzannulation appears to be an attractive alternative. In order to lure the chromium fragment to one or the other face of the arene formed, chiral information has to be incorporated into the carbene complex or into the alkyne.

Benzannulation of the chromium 1-propenyl(methoxy)-carbene complex **16b** with α-chiral propargylic ethers, such as **242**, resulted in diastereofacial selection in the formation of benzohydroquinonoid chromium tricarbonyl derivatives **243**. The degree of the diastereofacial selection was strongly dependent on the substitution pattern of the carbene ligand and, in particular, of the steric bulk of the ether oxygen substituent (Scheme 76).[174]

A more general approach concentrates on the chiral modification of the carbene ligand. Some target molecules for which this modification is based on a chiral carbene carbon side chain are depicted in Figure 10.[15c,175]

The reaction of chiral cyclohexenyl(alkoxy)- (e.g., **244a**) and (amino)carbene complexes (e.g., **244b**) with 1-pentyne afforded diastereomeric tetralin complexes **245** in moderate yields (Scheme 77).[176] The sense of stereoselection was found to depend on the substitution pattern of the cyclohexenyl substituent. Whereas 5-methyltetralin derivatives were obtained in low preference for the *syn* complex, a higher preference for the *anti* diastereomer was observed in the synthesis of 8-methyltetralin complexes **245**.

The most versatile and promising approach to pure enantiomers is based on chiral alcohol auxiliaries incorporated into the carbene ligand via the acylation−alcoholeysis sequence. Several chiral secondary alcohols have been screened for their ability of diastereoinduction.[177] The best performance (de = 80%) within a series of terpenoid alcohol auxiliaries was observed for (+)- and (−)-menthol as applied in the benzannulation of carbene complex **4r** with 3,3-dimethyl-1-butyne, affording the naphthohydroquinoid complex **246** (Scheme 78). The diastereomeric excess depends on the solvent and decreases

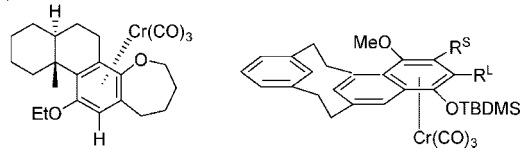
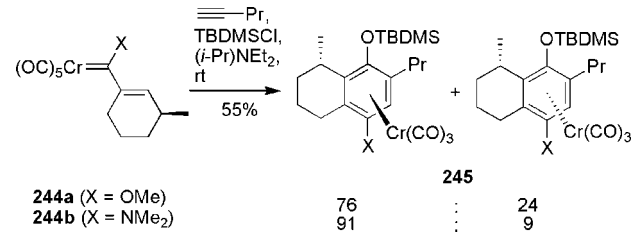


Figure 10. Asymmetric benzannulation products obtained from carbene complexes with chiral carbene carbon substituents.

Scheme 77. Diastereoselective Benzannulation of Chiral Methylcyclohexenylcarbene Complexes



when *tert*-butyl methyl ether is substituted for less polar hydrocarbon solvents. Compared with arylcarbene complexes, the menthol auxiliary is much less efficient with alkenylcarbene complexes, which only gave de values below 20%. Attempts to improve the diastereoselection by means of chiral amine auxiliaries met with similar little success.[178]

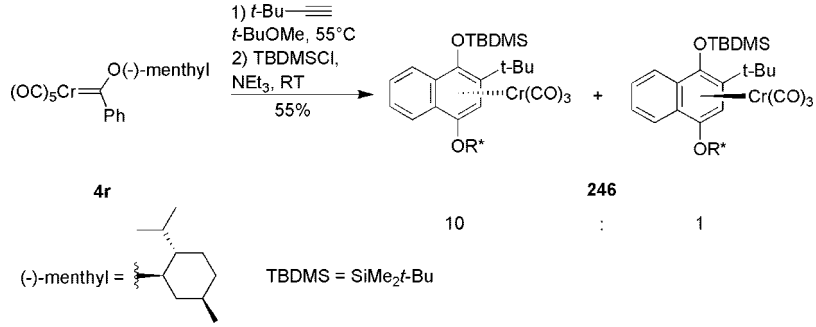
The benzannulation of carbene complexes bearing either multiple metal carbene or alkyne functionalities allows for the construction of extended aromatic frameworks. Scheme 79 presenting two double and two quadruple benzannulations illustrates the scope of this strategy. The exhaustive cycloaddition of biphenyl biscarbene complex **247** with tolan affords binaphthyl bis-$Cr(CO)_3$ complex **248** as a diastereomeric mixture in 51%.[179a] The bidirectional benzannulation of the axial−chiral biscarbene complex **249** yields bis-$Cr(CO)_3$-coordinated biphenanthrene derivative **250**, which combines elements of axial and planar chirality.[165c,179b] A quadruple benzannulation has been realized from either tetrakis−carbene complexes or a skeleton bearing four alkyne functionalities. The reaction of dendritic carbene complex **251** with 4 equiv of 3-hexyne followed by *O*-silylation and decomplexation affords naphthohydroquinone **252** in remarkably good yield.[179c] Finally, the benzannulation of the porphyrine **253** with phenylcarbene complex **4o** leads to the tetranaphthoquinone **254** after oxidative workup.[179d]

3.2.2. Cyclopentannulation

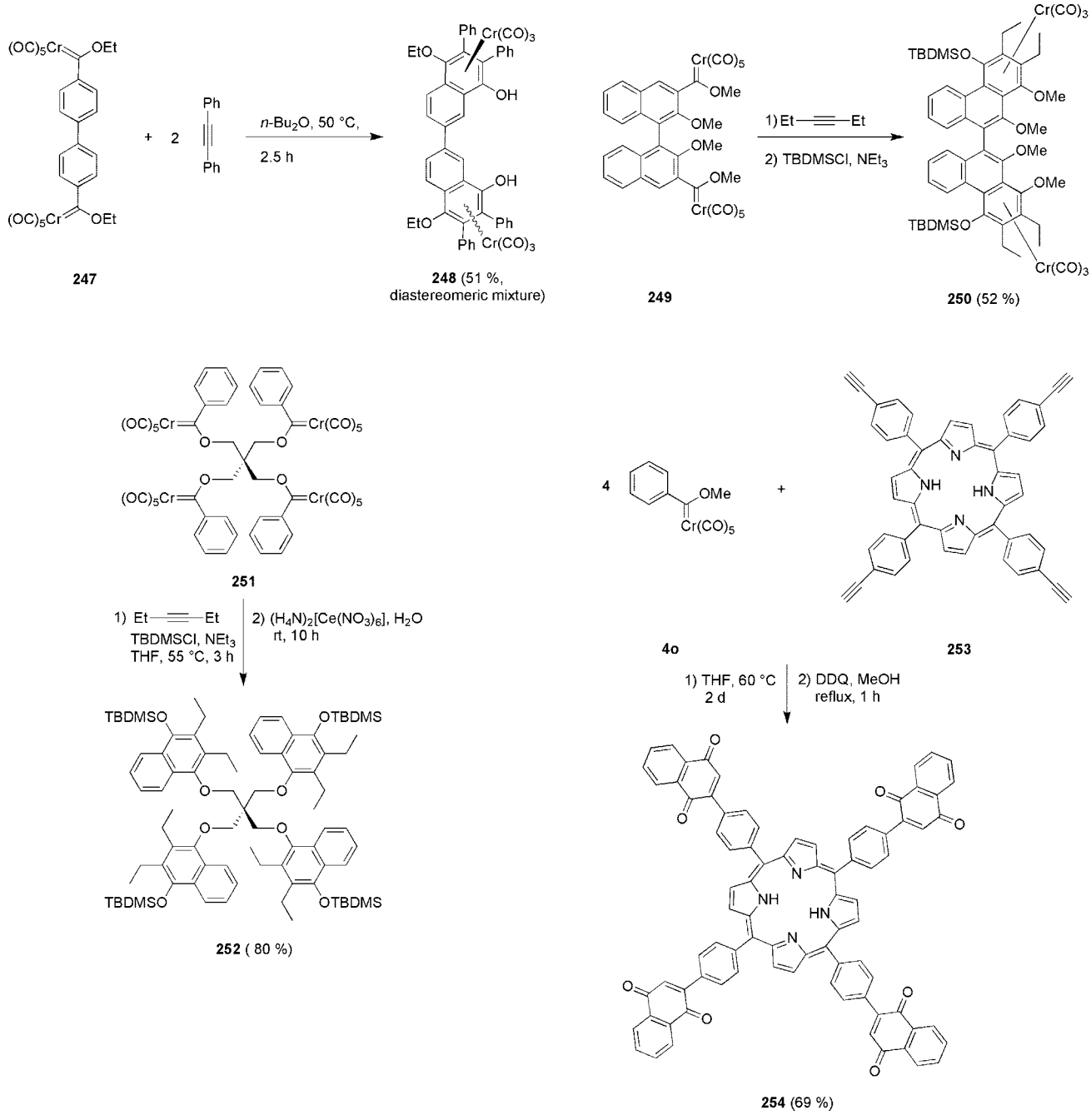
The competition of benzannulation and pentannulation significantly depends on the donor ability of the carbene ligand. Substitution of alkoxy for amino groups in the carbene ligand (leading to **255**) increases the thermal stability of the metal−carbonyl bond, which hampers both the primary decarbonylation and the CO incorporation into the final product (step from **IV** to **V** in Scheme 72).[43d,180] As a consequence, annulation of chromium aryl(amino)carbenes requires elevated temperatures (≥90 °C) and affords cyclopentannulation products (indenes). *N*-Acylation (e.g., with the *tert*-butyloxycarbonyl (BOC) group) reduces the donor properties of the amino substituent and thus favors again the benzannulation.[181] The competition of benzannulation versus cyclopentannulation also depends on the concentration and the temperatures applied;[148] dilute solutions and high temperatures favor cyclopentannulation over benzannulation. The cyclopentannulation of aminocarbene complexes **255** is supposed to occur via chromacyclohexadiene **II**, leading to the isomeric aminoindenes **III**, which readily hydrolyze to give indanones **256** (Scheme 80).

Both electron-rich and electron-poor alkynes do not undergo benzannulation. While strongly electron-deficient alkynes cannot compete with carbon monoxide in the

Scheme 78. Diastereoselective Benzannulation of an Aryl((−)-menthyloxy)carbene Complex

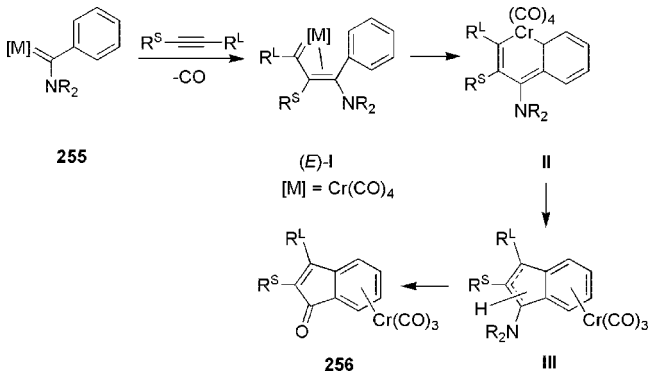


Scheme 79. Multiple Benzannulations in the Construction of Benzenoid Frameworks



initial ligand-exchange process, electron-rich alkynes (with a polarized C≡C bond such as in ynamines) generally prefer addition to the carbene carbon atom and subsequent insertion into the metal−carbene bond. The insertion products may undergo cyclopentannulation at elevated temperature.[43d,182]

Scheme 80. Cyclopentannulation of (Amino)carbene Complexes

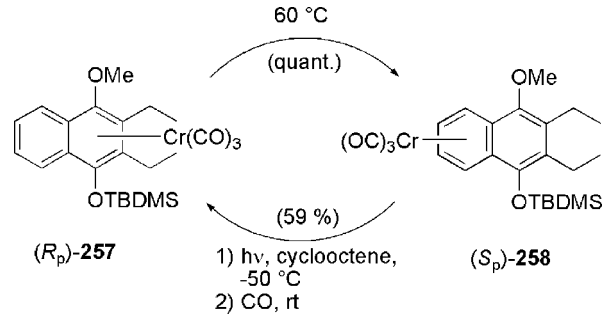


3.3. Regiospecific Labeling of Arene Rings by Haptotropic Metal Migration

Arene chromium tricarbonyl complexes are valuable building blocks in synthetic organic chemistry.[162,183] While thermal complexation of arenes with $Cr(CO)_3L_3$ precursors is hampered by low regioselectivity of the coordination of the $Cr(CO)_3$ fragment reflecting the thermodynamic equilibrium of regioisomers, the benzannulation of α,β-unsaturated chromium carbene complexes with alkynes can be carried out under distinctly milder conditions; thus, it directly affords coordinated oligocyclic arenes in which the organometallic moiety is exclusively attached to the hydroquinoid ring as the kinetically stable regioisomers. On further warming a solution of the "kinetic" benzannulation products in solvents with poor coordinating abilities (selected ethers such as dibutyl ether or fluorinated aromatic compounds), the metal fragment is shifted along the same π-face of the hydrocarbon ligand, and an intramolecular metal migration to the less-substituted terminal ring is observed to give the "thermodynamic" isomer. This process is termed haptotropic metal migration,[184] and from a synthetic perspective, it makes the $Cr(CO)_3$ fragment a moveable and tunable label suited to activate a specific aromatic ring. The activation of benzenoid rings by coordination to a $Cr(CO)_3$ fragment is an established strategy for an *umpolung* of the arene and has been widely exploited in the addition of nucleophiles and in nucleophilic substitution reactions.[162b,183b−d] It further allows for enhancement of the C−H acidity of both the arene[183d,e] and benzylic hydrogen atoms.[183f]

In the primary benzannulation product obtained under kinetic conditions ($\leq$55 °C), the organometallic moiety is attached exclusively to the higher substituted (hydroquinoid) terminal ring. Above 60 °C (typically between 60 and 90 °C), this "kinetic" complex rearranges to its "thermodynamic" haptotropomer in which the chromium tricarbonyl moiety is coordinated to the less-substituted terminal ring. This metal shift can be monitored by IR and NMR spectroscopy, and NMR spectroscopy has been used for kinetic studies of the migration of $Cr(CO)_3$ and $Cr(CO)_2L$ fragments (L = phosphines, phosphites) along naphthalene and more extended aromatic skeletons. Substituted naphthalenes,[177b,185] phenanthrenes,[186] triphenylenes,[186] and extended heterocyclic platforms (benzonaphthofurans, benzonaphthothiophenes)[167] have been submitted to haptotropic metal migration. According to theoretical studies for naphthalene and phenanthrene platforms,[187] a metal migration along the periphery of the arene ligand with a η^4-coordinated trimethylenemethane complex as transition state is favored

Scheme 81. Stereospecific Naphthalene Chromium Tricarbonyl Switch



over the least motion pathway across the carbon−carbon bond(s) common to the adjacent six-membered rings. This work has recently been extended to a $Cr(CO)_3$ shift in both directions by a proper adjustment of the metal coligand sphere. The quantitative thermal rearrangement of naphthalene $Cr(CO)_3$ complex (R_p)-**257** at 60 °C to give the thermodynamic haptotropomer (S_p)-**258** can be combined with a photoinduced low-temperature substitution of one carbonyl ligand for the weakly coordinated cyclooctene. When allowed to warm to room temperature, the starting "kinetic" $Cr(CO)_3$ complex is regenerated in a CO atmosphere in 59% yield. Stereochemical and X-ray analyses demonstrated that the metal migration occurred intramolecularly along the π-arene face via transfer of the planar chirality and, thus, established the first stereospecific organometallic switch (Scheme 81).[184g,185g,188]

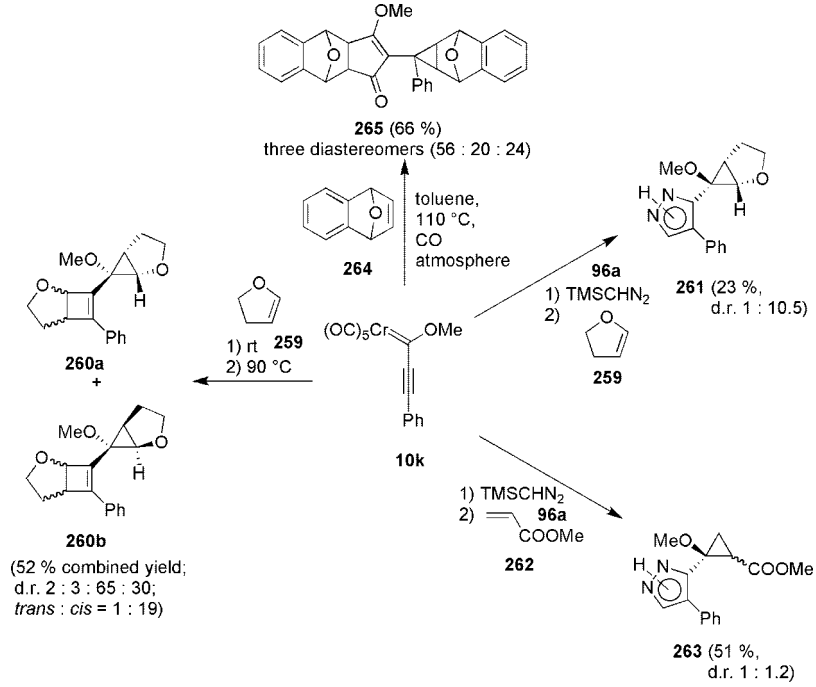
Phenanthrene ligands[186,187d] offer two alternative peripheral pathways along the inner or the outer bay area. DFT calculations suggest a preference for the inner π-periphery pathway occurring along the central biphenyl axis. These metal shifts are characterized by a η^2-coordinated complex intermediate or a "central ring complex" intermediate, respectively, and also proceed via η^4-trimethylenemethane-like complex transition states. The haptotropic rearrangement is also compatible with other helical distorted aromatic platforms as demonstrated for $Cr(CO)_3$ complexes of distorted hydroquinoid naphthobenzofurans, -thiophenes,[167] and extended heterohelicenes.[189] The fused five-membered heteroaromatic π-systems do not act as a stopper for the migration of the chromium tricarbonyl fragment, and the metal shift proceeds from the hydroquinoid ring across the central heterocycle to the other terminal benzene ring.

For a closer investigation of the influence of the helical distortion on the rearrangement, substituted phenanthrenes as the simplest hydrocarbons with a helical distortion represent a particularly attracting target. The rate of the metal shift has been demonstrated to depend on the arene substitution pattern; bromo and methoxy substituents at the central and the less-substituted terminal ring slow down the rearrangement while increasing helical distortion of the phenanthrene platform favors decomplexation.[186]

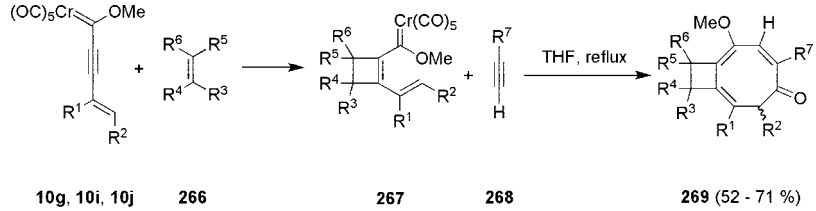
4. Multistep and Multicomponent Reactions

This chapter covers reaction sequences that start from simple carbene complexes using multistep sequences and multicomponent strategies[190] that afford either complex polycyclic target molecules or less-complex molecules with a substitution pattern not accessible by standard functionalization methodologies. These approaches often reveal high stereoselectivities.

Scheme 82. Consecutive One-Pot [2 + 2]/[2 + 1]- and [3 + 2]/[2 + 1]-Cycloaddition Reactions of Alkynylcarbene Complexes



Scheme 83. Synthesis and Electrocyclic Ring-Closure of Alkenylcyclobutenylcarbene Complexes with Terminal Alkynes



R^1 = Me; R^2 = Ph; R^1 / R^2 = -$(CH_2)_3$-, -$(CH_2)_4$-
R^3 = H, OMe; R^4 = Me, OMe; R^5 = H, OMe; R^4 / R^5 = -O$(CH_2)_2$-
R^6 = H, OMe; R^7 = *n*-Bu, CH_2OTBDMS, TMS, Ph

4.1. Starting from Alkynylcarbene Complexes

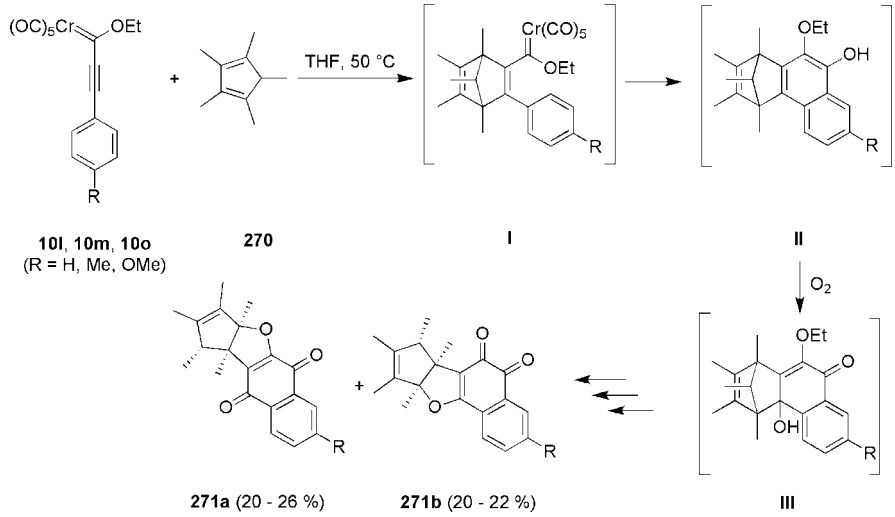
4.1.1. Cycloaddition Reactions

Beyond individual [*n* + 2]-cycloaddition reactions of α,β-unsaturated alkynyl Fischer carbene complexes covered in sections 2.2 and 3.1, two of these transformations can be combined to one-pot [2 + 2]/[2 + 1]- and a [3 + 2]/[2 + 1]-cycloaddition sequences (Scheme 82).[191] Both types of cascades start with a [2 + 2]- or a [3 + 2]-cycloaddition reaction followed by an in situ [2 + 1]-cycloaddition reaction. Alkynylcarbene complex **10k** first adds one 2,3-dihydrofuran **259** to the alkyne functionality followed by cyclopropanation of a second dihydrofuran molecule to give two diastereomeric bis-cycloaddition products **260a** and **260b** in 52% combined yield. Initial addition of trimethylsilyl diazomethane **96a** as 1,3-dipole for the [3 + 2]-cycloaddition reaction to chromium alkynylcarbene complex **10k** followed by cyclopropanation of dihydrofuran **259** afforded desilylated bis-cycloadduct **261** in low yield but with good diastereoselectivity. A similar sequence of cycloaddition reactions using diazomethane **96a** and methyl acrylate **262** resulted in an increased yield for **263**; however, the diastereoselection decreased dramatically. By careful adjustment of the reaction temperatures for the two individual steps (ambient temperature for the cyclopropanation with the diazomethane and 70 °C for the [3 + 2]-cycloaddition reaction), products were obtained from a combined [3 + 2]/[2 + 1]-cycloaddition sequence. These sequences allow for the generation of four carbon−carbon bonds with up to five stereocenters in structurally complex products and, moreover, are characterized by a high diastereoselectivity for the final [2 + 1]-cycloaddition reaction. The bicyclic dihydrofuran **264** reacts with alkynylcarbene complex **10k** in toluene at 110 °C to give oligocyclic cyclopentenone **265** in moderate yield via a [2 + 2 + 1]/[2 + 1]-reaction sequence (Scheme 82).[192]

Considerable effort has been devoted to thermo-induced reactions subsequent to cycloaddition reactions of β-substituted alkynylcarbene complexes. Depending on the substitution pattern, cycloadducts arising from [2 + 2]-, [3 + 2]-, and [4 + 2]-cycloaddition reactions have been shown to undergo electrocyclic ring-closure, rearrangement, cyclopropanation, and C−H insertion reactions.[77c,193−195]

Cyclobutene-containing dienylcarbene complexes **267**, which are readily accessible from enynylcarbene complexes **10g**, **10i**, and **10j** via [2 + 2]-cycloaddition with alkenes **266**, react with terminal alkynes **268** to generate bicyclic cyclooctatrienone derivatives **269** (Scheme 83).[193] The reaction proceeds in a regioselective fashion, leading to a mixture of diastereoisomers. This process is reminiscent of the [3 + 2 + 1]-benzannulation; however, the additional C=C bond present in the starting enynylcarbene complex participates in the subsequent electrocyclic ring-closure to give eight-membered carbocycles. The transformation of the carbon−carbon triple bond in **10g**, **10i**, and **10j** into the

Scheme 84. Diels−Alder Reaction-Electrocyclization-Rearrangement Strategy for the Construction of Fused *ortho*-Naphthoquinones



carbon−carbon double bond in **267** is essential for the success of the following electrocyclization since the all-sp^2 hybridization of the dienylcarbene complex is required for a close proximity of the terminal C═C bond and the metal center.

Similar to this reaction sequence, the Diels−Alder reaction of the alkyne moiety in several Fischer β-aryl alkynylcarbene complexes triggers further cycloaddition reaction, which results in the formation of several benzannulated oligocyclic hydrocarbons. Arylethynylcarbene complexes **10l**, **10m**, and **10o** undergo a Diels−Alder reaction with pentamethylcyclopentadiene **270** to finally give (via intermediate **II** formed after carbonylation and electrocyclic ring-closure of Diels−Alder cycloaddition product **I**) tetracyclic diones **271a** and **271b** after oxidation as a mixture of isomers in low yields. These isomers originate from a rearrangement of the oxidation product **III** within the bicyclo[2.2.1]heptadiene skeleton (Scheme 84).[77c,194]

The versatility of tandem reactions is controlled by the fine-tuning of the substitution pattern of the carbene side chain as illustrated for alkynylcarbene complexes bearing slightly modified aryl substituents at the β-carbon atom (Scheme 85). If an *ortho*-ethenylphenyl group is present in the substrate **10p**, the initial [3 + 2]-cycloaddition reaction with nitrone **272** is followed by intramolecular cyclopropanation to give dihydronaphthalene derivatives **273**.[195a] The introduction of a phenyl group as terminal substituent at the ethenyl group of **10p** (**10q**) combines the initial [4 + 2]-cycloaddition reaction (with Danishefsky's diene **274**) with an olefin metathesis providing phenanthrenes such as **275**. The replacement of the alkene moiety for a phenylethynyl group (**10t**) results in the formation of complex naphthalene **276** from a sequence of a [2 + 2]-cycloaddition reaction with dihydrofuran **259**, an alkyne insertion followed by CO insertion to give a ketene intermediate, which undergoes a final [2 + 2]-cycloaddition reaction with excess dihydrofuran.[195b] Finally, azepinoindole **278** has been isolated from a reaction sequence starting with the [4 + 2]-cycloaddition reaction (with cyclopentadiene) of indolyl-modified alkynylcarbene complex **277**. The formation of **278** can be rationalized in terms of a C−H insertion of the carbene ligand into the α−C−H bond of the *N*-alkyl group in the primary cycloaddition product **279**.[26]

4.1.2. Multifaceted Cycloaddition Reaction Sequences

Chromium alkynylcarbene complexes (e.g., **10k**) react with symmetrical internal alkynes to afford products resulting from consecutive insertions of several alkyne units and carbonyl groups into the metal carbene bond (Scheme 86).[196] Cyclopentene-fused cyclopentenones, spirocyclopentenones, and symmetrical biscyclopentenones (e.g., **280**) have been isolated as the final products in low yields.

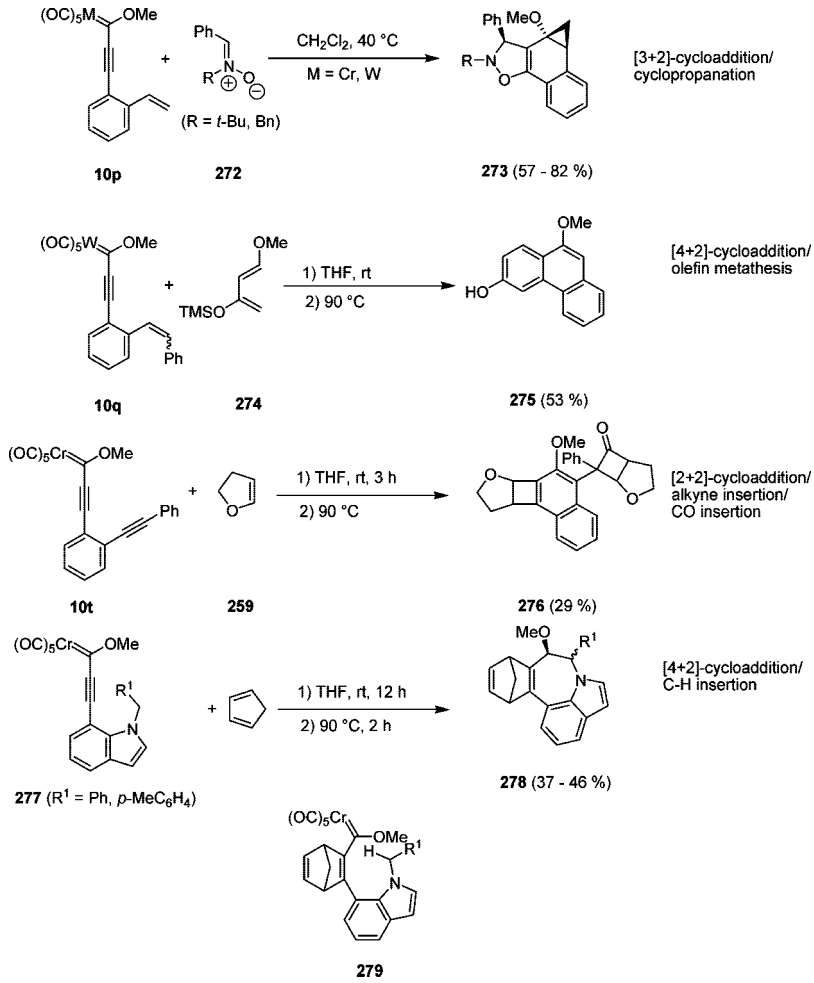
Another concept that has been introduced into multistep reactions of Fischer alkynylcarbene complexes combines a [1,5]-hydride shift of *ortho*-aminophenylalkynylcarbene complexes **281** (as the zwitterionic structure **281a**) with cyclization and subsequent benzannulation. Ring-closure of hydride shift intermediate **I** generates 3-(1,2-dihydroquinolinyl)carbene complex intermediates **II**, which undergo benzannulation with alkynes to afford 5,6-dihydrophenanthridines **282** in overall yields of 42−72% for this three-step reaction sequence (Scheme 87).[197]

4.2. Starting from Alkenylcarbene Complexes

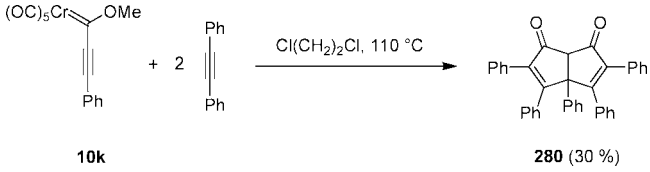
The attempted cyclopropanation reaction of alkenylcarbene complexes **16** with ketene acetal **283** resulted in the unexpected isolation of dihydrocoumarin **284** (Scheme 88).[198] This finding has been rationalized in terms of an isolable alkyne intermediate **I** generated by the reaction of the ketene acetal with the carbene complex. Benzannulation of another equivalent of the carbene complex by the alkyne formed in situ leads to hydroquinone **II**, which via lactonization forms dihydrocoumarin **284**. This reaction can be carried out as a one-pot procedure in air as well.

The discussion of the cyclopropanation of Fischer carbene complexes (section 3.1) referred to stable cycloadducts. In particular cases, however, the three-membered cycloadducts may be unstable and susceptible to a subsequent Cope rearrangement as outlined in Scheme 89 for an electron-rich diene.[78b,199] The carbene transfer from carbene complex **16y** to the more electron-rich C═C bond in diene **285** generates *cis*-divinylcyclopropane intermediate **I**, which undergoes a spontaneous ring-expansion to give cycloheptadiene **286** in a regio- and stereoselective one-pot reaction. A similar reaction sequence has been applied to the synthesis of dihydroazepines starting from aza-1,3-dienes.[78b,200]

Scheme 85. Reaction Sequences Starting from Aryl-Substituted Fischer Ethynylcarbene Complexes



Scheme 86. Synthesis of Fused Biscyclopentenones from Alkynylcarbene Complexes and Alkynes



Group 6 alkenylcarbene complexes offer an elegant entry into tricyclic oxacarbocycles (Scheme 90).[201] Upon reaction with enolate **287**, the alkenylcarbene complexes **16m**, **16v**, **16y**, and **16ab** are transformed into β-cyclohexylethylcarbene complexes **288**. Addition of allyllithium followed by treatment with silica gel affords bicyclic tetrahydropyranylcarbene complex **289** via nucleophilic attack at the carbene carbon atom. Thermal intramolecular cyclopropanation of the alkene leads to the tetracyclic ether **290**, which undergoes an acid-induced ring-opening of the strained cyclopropane to give oxa-tricyclo[7.3.1.$0^{4,9}$]tridecanol **291**. Whereas the stepwise protocol gave an approximately 30−37% total yield, a one-pot procedure starting from optically active silyl enolethers increased the total yield of **291** to 69−82% maintaining the high enantiomeric excess (ee) of >98%.

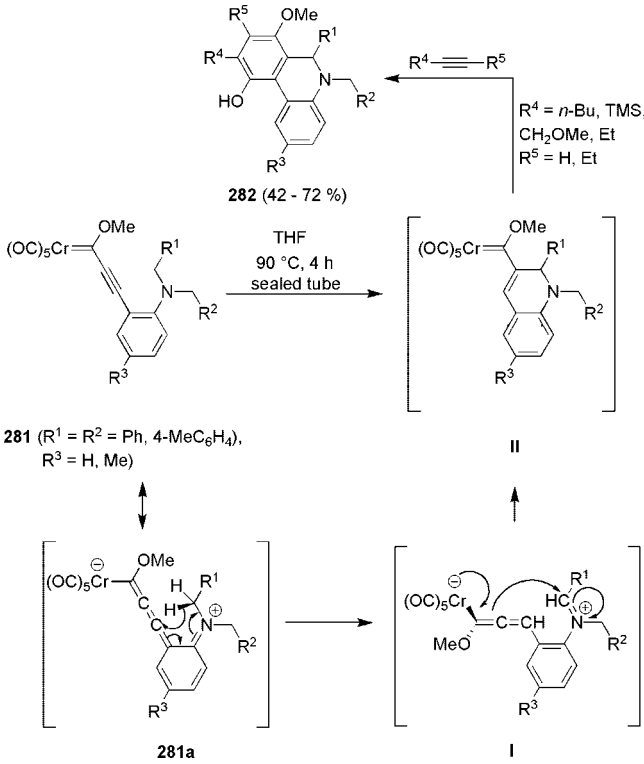
4.3. Starting from Alkylcarbene Complexes

The insertion of alkynes into the metal−carbene bond of alkyl(alkoxy)carbene complexes affords alkenylcarbene complexes. Cyclopropylcarbene complexes like **4l** react with alkynes **160** in a formal [2 + 2 + 1]-cycloaddition reaction to give cyclopentadienones **I**, which upon chromium(0)-induced reduction[202] transform into cyclopentenone derivatives **292** (Scheme 91). This reaction has been widely applied in an intramolecular version;[203] one example is the reaction of methylcarbene complexes (e.g., **4a**) with the phenylacetylene derivative **293**, affording the cyclopentenone derivative **294** in low yields[86b] via a presumed benzylidene complex intermediate **II**.

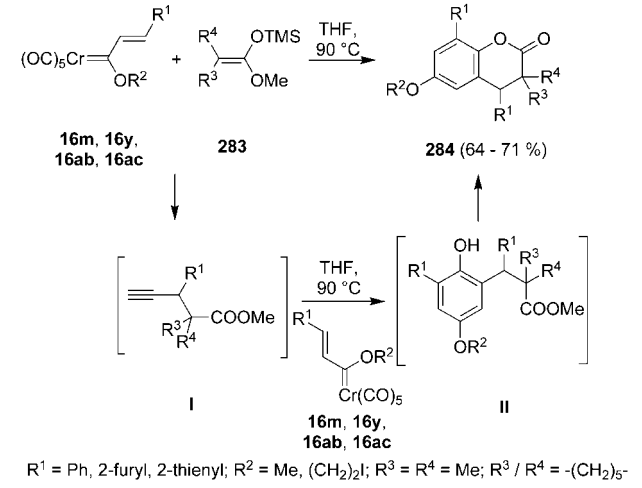
Terminal alkynes have been applied in this approach to construct a variety of oligocyclic carbo- and heterocycles.[86b] This reaction resembles that of simple alkyl-substituted carbene complexes with an excess of alkyne (or diyne) to produce phenol derivatives containing two molecules of alkyne, one carbon monoxide ligand, and the carbene carbon atom in the aromatic core.[204] Whereas the intermolecular version affords the phenols in rather low yields (e.g., **296** from **4a** with terminal alkynes **295**), the intramolecular reaction using diynes (e.g., **297**) results in synthetically useful yields of the oligocyclic phenols (e.g., **298**); even tungsten carbene complex **6a** has been shown to give good yields of benzannulation product **298** (Scheme 92).

Chromium alkoxycarbene complexes react with (*Z*)-eneynes to give benzannulation products in fair to good yields.[204c] This reaction is initiated by decarbonylation and followed by alkyne insertion into the chromium−carbene bond generating α,β-unsaturated carbene complex intermedi-

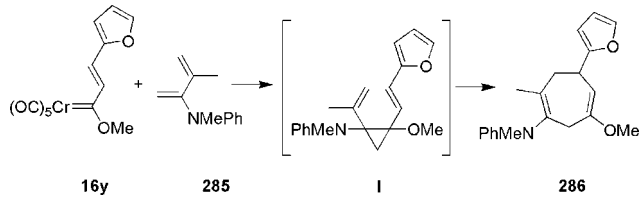
Scheme 87. Hydride Shift−Cyclization−Benzannulation Sequence to Phenanthridines



Scheme 88. Synthesis of Dihydrocoumarins by an Unexpected [3 + 2 + 1]-Benzannulation

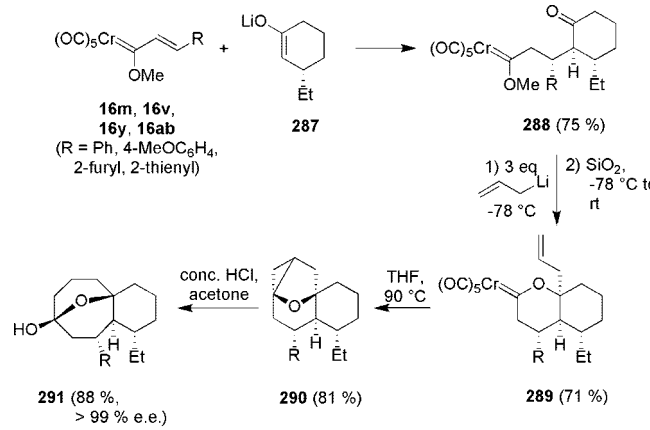


Scheme 89. Cycloheptatrienes via Consecutive Cyclopropanation of 1,3-Dienes and Cope Rearrangement



ates that may form different products depending on the substitution pattern of the eneyne unit. Scheme 93 illustrates the products accessible from the reaction of dieneynes (**300**), enediynes (**302**), or acyl−eneynes/eneyne−hydrazones (**304**) with carbene complex **299**. While dieneynes **300** or enediynes **302** afford phenols **301** and **303**,[204e] eneynes **304** lead

Scheme 90. Tandem Synthesis of Tricyclic Cyclooctanol Ethers from Alkenylcarbene Complexes, Cyclohexanone Enolate, and Allyllithium



to furan[204e,205a] and pyrrole[205b] derivatives **305** that can be applied as dienes in Diels−Alder reactions with dienophiles **306**,[206] providing cyclohexenyl and cyclohexadienyl enol ethers **307**. If the dienophile is connected with the alkyne via a tether, the construction of extended oligocyclic frameworks becomes feasible.[207]

The eneyne metathesis-Diels−Alder strategy has been extended to the synthesis of fused carbocycles, arenes, and *N*-heteroarenes (Scheme 94). The reaction of cyclopentylcarbene complex **308** and *ortho*-ethynylbenzaldehyde **309** affords the steroid-like tetracyclic ketone **310** in good yield.[207a] Upon reaction with *ortho*-hexynylbenzaldehyde **311**, the nitrile aminocarbene complex **28c** has been used in an access to synthesize phenanthridine **312**.[207b] Alkynyl-substituted indolecarbaldehyde **313** undergoes annulation by carbene complex **4j** to give carbazole derivative **314**.[207d]

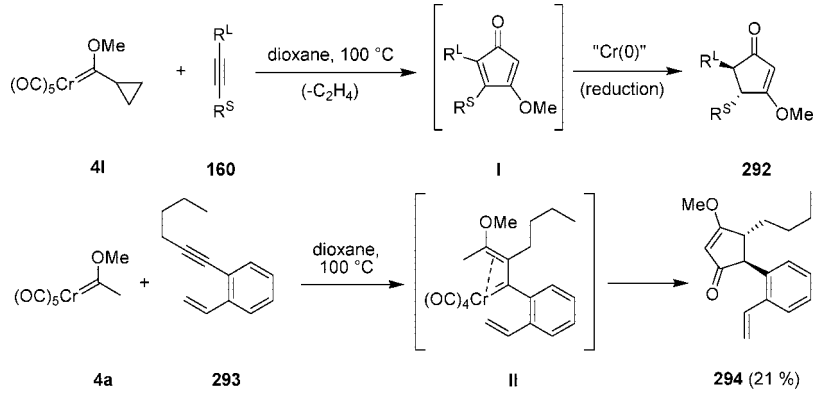
Chrysene derivatives **315** and **317** are accessible from *ortho*-alkynylphenylcarbene complexes **4z** and **4aa**, respectively, either by intermolecular alkyne insertion into the chromium−carbene bonds and subsequent formal carbene dimerization[152b,208] or by reaction with *ortho*-hydrazone alkyne derivative **316** (Scheme 95).[207g] The unusual dimerization is presumably caused by the rigid C_2 bridge that links the carbene and the alkyne moieties; thus, under typical benzannulation conditions, carbene complex **4z** affords an equimolar mixture of chrysene **315b** and its monochromium complex **315a**.

The reaction of carbene complexes with substituted eneynes has been extended to the synthesis of pyrones and subsequent Diels−Alder reactions[209a] as well as indanes accessible from highly electrophilic carbene complexes and styrenes.[209b]

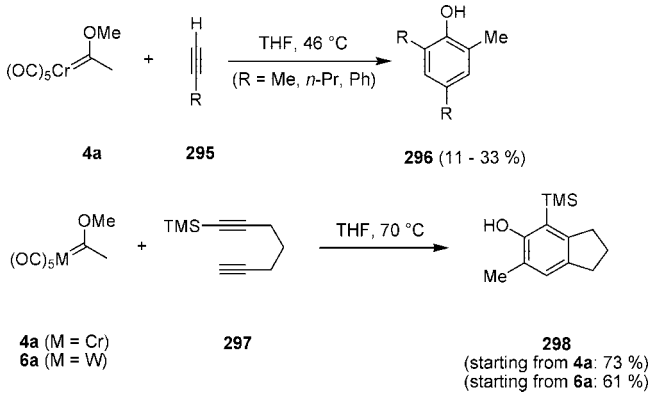
5. Photo-Induced Reactions

UV-irradiation into the metal-to-ligand charge transfer (MLCT) band of chromium carbene complexes[210] leads to insertion of one CO ligand into the metal−carbene bond and generates a species featuring ketene-like reactivity.[211] A similar CO insertion is involved as a (thermally induced) key step in the chromium-templated benzannulation forming metal-coordinated vinylketene intermediates. The structure of the photogenerated ketene intermediate is best described as a

Scheme 91. Synthesis of Cyclopentenones from Chromium Cyclopropyl- and Methylcarbene Complexes and Alkynes



Scheme 92. Inter- and Intramolecular Version of the Two-Alkyne Benzannulation Reaction



metal-coordinated ketene **A** or a metalacyclopropanone **B** (Figure 11).[212]

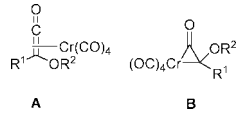


Figure 11. Valence bond structures of pentacarbonyl chromium-coordinated ketene intermediates.

The ketene species can be trapped by nucleophiles or [2 + 2]-cycloaddition reactions with imines, aldehydes, or alkenes. The synthetic photochemistry of Fischer chromium aminocarbenes provides a nonconventional access to a variety of biologically active cyclic and acyclic target molecules.[213] The methodology is more efficient for chromium carbene complexes than for molybdenum[214a] analogues, while no CO insertion has been reported for tungsten carbenes under similar conditions.[214b] The reaction sequences involving the photogenerated ketenes derived from Fischer carbene complexes are considered to occur within the coordination sphere of the metal. Neither free ketenes nor products originating therefrom have been detected along the generation and subsequent reactions of the ketene species.

5.1. Addition of Nucleophiles to Ketene Intermediates

Ketene complex intermediates photogenerated from Fischer carbenes are readily trapped by nucleophiles to give carboxylic acid derivatives. The addition of amine nucleophiles has been exploited in an elegant synthesis of amino acids and peptides,[215] and these protocols have been extended to alcohols, stabilized ylides, benzenes (intramolecular Friedel−Crafts reaction), and tertiary allylic amines (zwitterionic aza-Cope reaction).

5.1.1. Addition of Amines

The addition of amino acids **319** to photogenerated ketene intermediates (generated from oxazolidinylcarbene complexes **318**) has been intensively used in a metal carbene based synthesis of peptides. The general route to dipeptides **320** is shown in Scheme 96.[216]

This methodology is quite general and is efficient for a wide range of amino acids but only a modest selection of carbene complexes. It is compatible with bulky amino acid esters bearing alkyl substituents R^5 and R^6 and *N*-alkyl amino acid esters. The stereoinformation incorporated into the amino carbene substituent allows for a generally high diastereoselectivity of the peptide formation. Merrifield-resin supported systems have been applied in a solid-phase protocol.

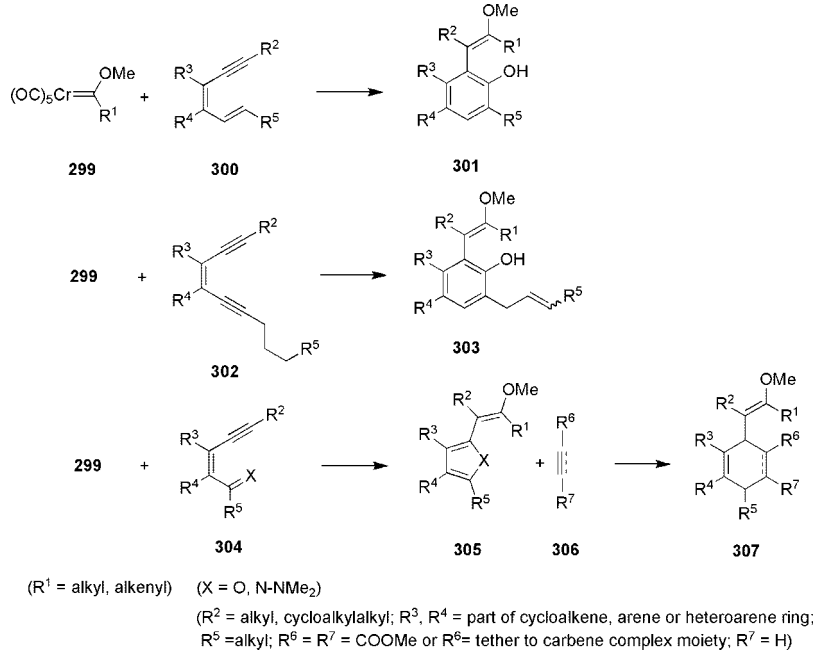
5.1.2. Addition of Alcohols

The reaction of alcohols with the ketene intermediates affords carboxylic esters. The irradiation of the α-alkylation products of chiral chromium oxazolidinylcarbene complexes **321** generated ketenes that were trapped with alcohols to afford homoalanine derivatives **322** (Scheme 97).[215]

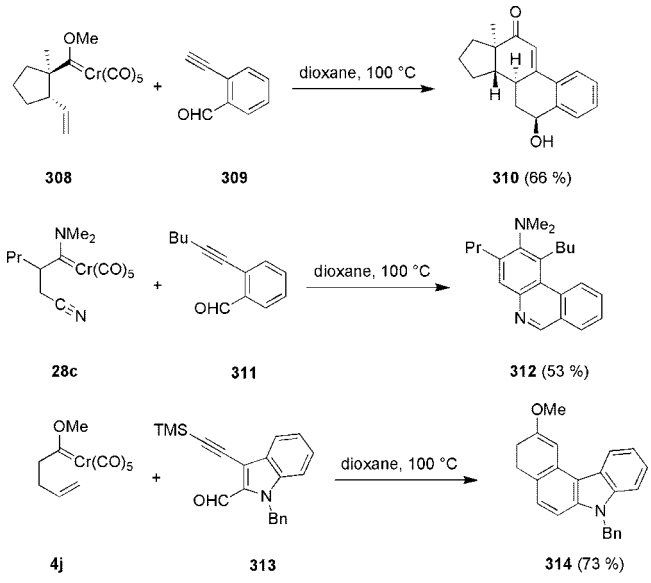
α-Deprotonation of aminocarbene complex **323** followed by α-hydroxyalkylation gave carbene complexes **324**; subsequent photoinduced intramolecular carbonylation generated ketene intermediates **I**, which underwent cyclization to give lactones **325** in 40−80% yield. Subsequent hydrolysis of the lactone and oxazolidine rings afforded homoserines **326** in 60−80% yield (Scheme 98).[217] The diastereoselectivity of the reaction depends on the nature of the aldehyde used. While for R = *p*-$MeOC_6H_4$, 2-furyl, and *t*-Bu the reaction exclusively gave the *cis*,*cis*-diastereomer of **326**, the phenyl analogue (R = Ph) led to a 92:8 mixture of *cis*,*cis*- and *cis*,*trans*-diastereomers. Acetaldehyde and isobutyraldehyde produced a mixture of all three possible diastereomers (*cis*,*cis*; *cis*,*trans*; *trans*,*cis*), which could be separated by chromatography.

The oxazolidine auxiliary allowed for an enantioselective synthesis of amino acids. Since both enantiomers of the auxiliary may be obtained from the corresponding phenylglycine enantiomers, natural (*S*-) and non-natural (*R*-) amino acid esters are accessible via this route.

Scheme 93. Synthesis of Six-Membered Carbocycles from Chromium Carbenes and Structurally Modified Eneynes



Scheme 94. Synthesis of Fused Carbo- and Heterocyclic Skeletons through the Eneyne-Metathesis−Diels−Alder Reaction Methodology of Carbene Complexes with Substituted Eneynes



5.1.3. Addition of Other Nucleophiles

The photoinduced addition of α-alkoxycarbonyl ylides to alkoxycarbene chromium complexes, best carried out in a coordinating solvent under CO atmosphere, yields captodative allenes (4-alkoxy-4-alkyl-substituted alkyl 2,3-butadienoates) in which a donor group (provided by the carbene complex moiety) is attached to the one end of the cumulene system and the acceptor (provided by the ylide) is attached at the other end. Rearrangement under mildly acidic conditions leads to 1,4-disubstituted 2-alkoxy-1,3-butadienes (68−80% yield), while acidic hydrolysis affords enones (60−90%).[218] Electron-rich arenes tethered to chromium carbene complexes (**4g**, **4h**, and **4s**) have been used as nucleophiles in intramolecular Friedel−Crafts reactions. The electrophilic aromatic substitution is highly regioselective, providing the acylation products **327a−c** in which ring-closure has occurred exclusively at the position *para* to the activating group (Scheme 99).[219]

Cyclic (e.g., **328**) and strained (e.g., **330**) tertiary allylic amines have been reported to give the best results if reacted with ketenes generated from **4a** under Lewis acid catalysis, leading to mono- (**329**) and bicyclic (**331**) *N*-heterocycles (Scheme 100).[220] The reaction course involves zwitterionic intermediates that undergo an aza-Cope rearrangement.

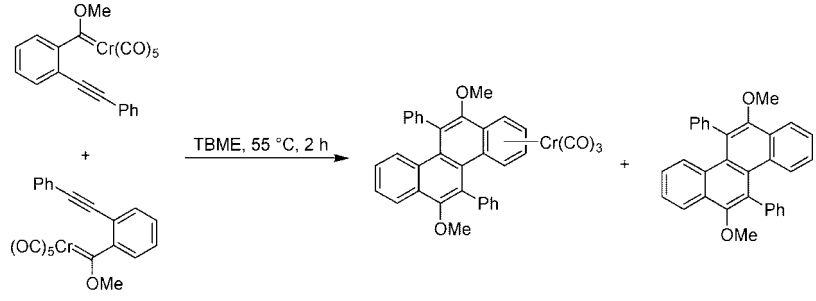
5.2. [2 + 2]-Cycloaddition Reaction with Ketene Intermediates

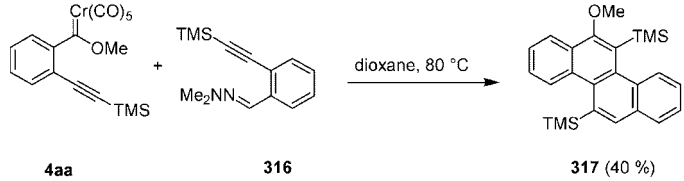
The [2 + 2]-cycloaddition reaction of metal-coordinated ketene intermediates photogenerated from carbene complexes to imines, aldehydes, or alkenes has been used as a convenient access to β-lactames, β-lactones, and cyclobutanones. The analogous reaction with azoarenes turned out to be less efficient.

The irradiation of alkoxycarbene chromium complexes in the presence of imines is a smooth process generally affording β-lactams in high yield and good diastereoselectivity. Chiral auxiliaries incorporated into the aminocarbene side chain allow for excellent diastereoselectivity provided that rigid cyclic imines such as thiazolines[221a] or imidazoles[221b] are used. This photoprotocol has been applied to the synthesis of biologically active β-lactams, which generally bear an amino group and hydrogen at C-3. Photolysis of suitable aminocarbene complexes such as **332**[222a] in the presence of various imines (e.g., **333**) affords lactams (e.g., **334**) in high yield and excellent diastereoselectivity (mostly ≥97% d.e.) (Scheme 101). Group 6 *N*-pyrrolyl carbene complexes undergo a similar photoreaction with amines.[222b]

This method has found application in an efficient synthesis of α-alkyl α-aminoacids, e.g., (−)-(*R*)-α-methylserine **338** (using **337** prepared from carbene complex **335**) applying oxazine **336** as imine component (Scheme 102).[223]

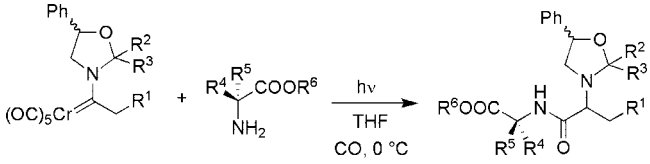
Scheme 95. Chromium-Mediated Dimerization of *ortho*-Alkynylphenylcarbene Ligands to Chrysenes





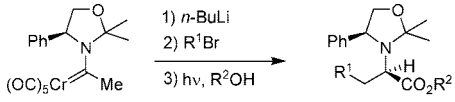
TBME = tert. BuOMe

Scheme 96. Synthesis of Dipeptides from Chromium (Amino)Carbenes and α-Aminoesters



R^1 = H, Bn, CH_2=$CHCH_3$, CH_2COO*t*-Bu; R^2 = H, Me; R^3 = H, Me
R^4 = H, Me, CH_2OH, CH_2SH, $CH(OH)CH_3$, $(CH_2)_2SCH_3$, CH_2COOCH_3, $(CH_2)_2COOCH_3$, Bn, Ph, 4-$HOC_6H_4CH_2$, 2-indolyl
R^5 = H, Me, Pr, Ph; R^6 = Me, *t*-Bu; R^4 / R^5 = -$(CH_2)_3$-

Scheme 97. α-Alkylation/Photolysis Process of a Chiral Oxazolidinyl Carbene Complex



(R¹ = Bn, R² = *t*-Bu: 42 %, at least 93 % de)
R¹ = CH_2CO_2*t*-Bu, R² = Me: 52 %, at least 93 % de)
Bn = CH_2Ph

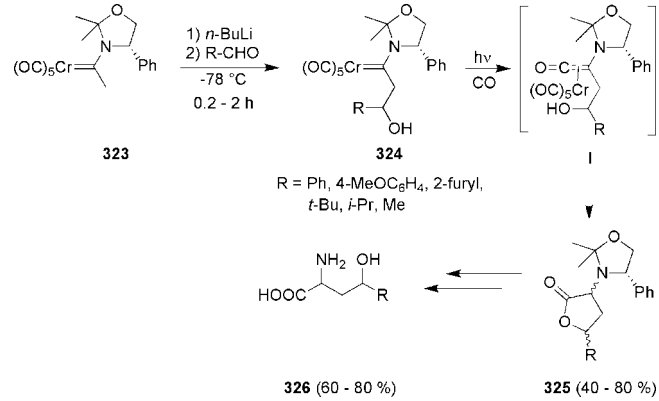
5.3. Non-Carbonylative Reaction

Noncarbonylative photo-induced reactions of the carbene complexes can be classified as (a) nucleophilic addition (or elimination) at the carbene carbon atom, (b) cycloaddition, and (c) acyl migration reactions. The latter type of reaction has only been found in the photolysis of chromium 2-acyloxyethenylcarbene complexes leading to 2-butene-1,4-diones.[224]

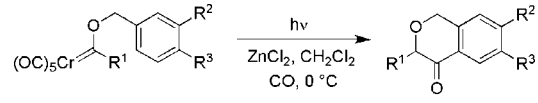
Sulfur-stabilized ylides **339** undergo photo-driven reactions with alkoxycarbene chromium complexes **4** to produce 2-acyl enol ethers **340** as *E*/*Z* mixtures with the *E* isomer predominating (Scheme 103).[225]

Cyclopropanation reactions of electron-poor alkenes with Fischer carbene complexes can be promoted by irradiation.[226]

Scheme 98. Generation of α-Aminobutyrolactones as Precursors of γ-Hydroxyethyl-α-Amino Acids



Scheme 99. Intramolecular Friedel−Crafts Acylation of Electron-Rich Arenes by Photo-Generated Ketene Intermediates



4g (R^1 = Me, R^2 = OMe, R^3 = H)
4s (R^1 = Ph, R^2 = OMe, R^3= H)
4h (R^1 = Me, R^2 = R^3 = OMe)

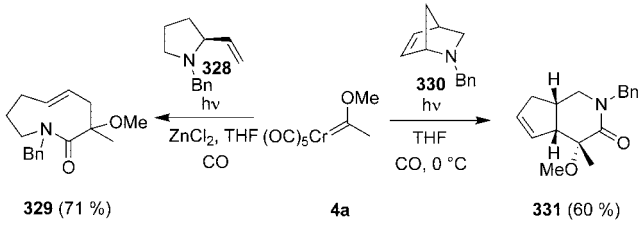
327a (69 %)
327b (15 %)
327c (38 %)

Tetracarbonyl(phosphine)chromium and -tungsten aminocarbene complexes have been recently shown to undergo photo-induced 1,2-dyotropic rearrangements, leading to imino complexes[227a] by noncarbonylative pathways[227b] or triggering α-fragmentation.[227c] So far, however, these processes did not find application in organic synthesis.

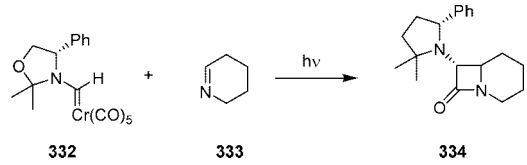
6. Catalytic Carbene Transfer Reactions

The first carbene transfer from a Fischer carbene complex to another metal (e.g., iron or group 10 metals) has been reported already 3 decades ago and has been exploited in the synthesis of organometallic dinuclear and cluster com-

Scheme 100. Photo-Induced Synthesis of *N*-Heterocycles Using Tertiary Allylic Amines and Carbene Complexes



Scheme 101. Photo-Assisted Formation of β-Lactams from Chromium Carbene Complexes



plexes.[228] Applications of carbene transfer reactions in organic synthesis started at the beginning of the new millennium, and—beyond stoichiometric reactions[229]—catalytic transmetalation of carbene complexes, in particular, has become a promising field of research.[230,231] Apart from this synthetic application, the carbene transfer from group 6 metal carbene complexes has been successfully implemented in the preparation of late transition metal *N*-heterocyclic Fischer carbene (NHC) analogues.[232]

6.1. Dimerization Reaction

The dimerization of chromium-coordinated carbene ligands typically requires temperatures above 120 °C. Whereas the addition of catalytic amounts of $Rh_2(OAc)_4$ has only a marginal effect on the activation of the carbene complex and the reaction temperature can be lowered to only 100 °C, palladium catalysis allows one to carry out the carbene dimerization at room temperature.[230a,233] If the reaction of chromium phenyl(methoxy)carbene **4o** was promoted by $Pd(OAc)_2$ (10 mol %) in the presence of NEt_3, an *E*/*Z*-mixture (2:1) of carbene dimers **341** was obtained (Scheme 104). The effects of catalyst loading, phosphine additives, reaction temperature, solvent, and several palladium catalysts have been investigated systematically; however, no significant changes in the reaction outcome were observed.

In contrast, the nature of the catalyst and the reaction conditions have a significant influence on the chemoselectivity of reactions based on alkylcarbene ligands, as demonstrated for chromium methylcarbene **4c** (Scheme 105). Whereas catalytic amounts of $Pd(PPh_3)_4$ give rise to carbene dimerization yielding an *E*/*Z* mixture of enediether **342**, the $Pd(OAc)_2/NEt_3$ system leads to a base-induced hydrogen migration to give enol ether **343**.

The transmetalation strategy was applied to the synthesis of conjugated polyenes and enediyne derivatives from suitable metal carbene precursors. Fischer-type biscarbene complexes intramolecularly dimerize to give cycloalkenes. This was rationalized by a catalytic cycle involving transmetalation and formation of a biscarbene palladium intermediate in the key steps of the reaction.[233]

The cross-coupling of Fischer carbene complexes (e.g., **16y**) with ethyl diazoacetate **346** affords push−pull substituted alkenes such as **347** at ambient temperature using 15 mol % CuBr as a catalyst (Scheme 106).[234] Chromium alkyl-, alkenyl-, and arylcarbenes provided comparable good chemical yields. Whereas no stereocontrol of the configuration of the double bond formed was observed for the formation of dimer **345** from methoxycarbene complex **16y** in the presence of $[Cu(MeCN)_4][PF_6]$ **344**, its menthyloxycarbene analogue afforded exclusively the *E*-isomer. The chemoselectivity of the reaction strongly depends on the nature of the catalyst: in the presence of 15 mol % of **344**, a dimerization of the methoxycarbene ligand was observed, favoring the *E* isomer in a 10:1 ratio.

The intermediacy of new metal carbenes in the catalytic transmetalation is supported by the isolation and structural characterization of a copper carbene **349** obtained from the chromium 2-furylethenyl[(−)-menthyloxy]carbene complex **16z** in the presence of 50 mol % $[Cu(MeCN)_4][PF_6]$ (Scheme 107).[234,235] **349** has been prepared in two steps starting from chromium carbene **16z** via transmetalation with 0.5 equiv $[Cu(MeCN)_4][PF_6]$ **344** to give biscarbene complex **348** (the structure of which has been deduced from NMR data); upon crystallization of the biscarbene complex from a diethylether/dichloromethane mixture, the monocarbene solvate complex **349** was obtained and characterized by X-ray crystallography.[234,235]

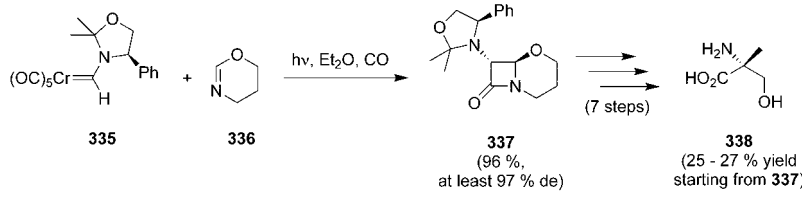
Under the conditions used for the crystallization of copper carbene complex **349**, the carbene ligand is prone to be retransferred to chromium, while the vacant coordination site at copper is occupied by diethyl ether. The X-ray structure of **349** provides a rare example of a tricoordinated metal center. Both copper-containing species, the biscarbene and the monocarbene (**349**), undergo a carbene dimerization in the presence of tributylphosphine to yield (1*E*,3*E*,5*E*)-1,3,5-trienes in a process analogous to the formation of **345**.

6.2. Skeleton-Forming Reaction

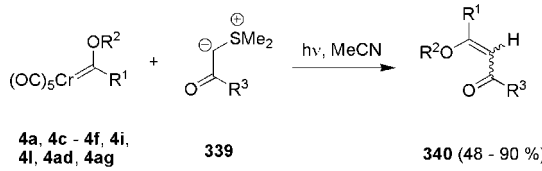
Beyond dimerization, the catalytic carbene transfer process has been applied to skeleton-forming reactions, a strategy that is dominated by Rh-, Ni-, and Cu-precatalysts, so far.[236]

A recent example demonstrates the enhanced reactivity of β-aminovinylcarbene complex **18k** toward eneyne **350** when modified in situ into rhodium intermediate **351**. It is remarkable that even tungsten carbenes, which generally are among the least reactive carbene complexes in metal-centered processes, are activated for C—C bond formation by this procedure. In the presence of catalytic amounts of a rhodium complex, a sequence of eneyne insertion and π-cyclization occurs at ambient temperature to give vinylcyclopentadiene

Scheme 102. Synthesis of Enantiopure Amino Acids via Photolysis of Chromium Carbene Complexes



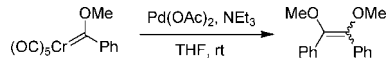
Scheme 103. Photo-Assisted Addition of Sulfur-Stabilized Ylides to Chromium (Alkoxy)carbene Complexes



4a, **4c** - **4f**, **4i**, **4l**, **4ad**, **4ag** **339** **340** (48 - 90 %)

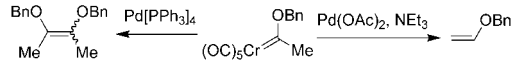
R^1 = Me, *n*-Bu, *c*-C_3H_5, 1-$C_{10}H_7$, 2-furyl
R^2 = Me, CH_2Ph, $(CH_2)_2CH{=}CH_2$, $(CH_2)_2C{\equiv}CH$, (-)-menthyl
R^3 = OMe, O*t*-Bu, Ph

Scheme 104. Palladium-Catalyzed Carbene Dimerization of an Arylcarbene Ligand



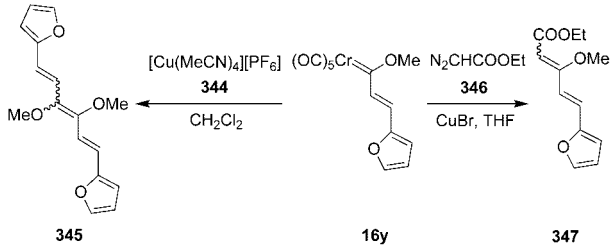
4o **341**

Scheme 105. Chemoselectivity of Palladium Catalysts in Carbene Dimerization and Hydrogen Migration Reactions



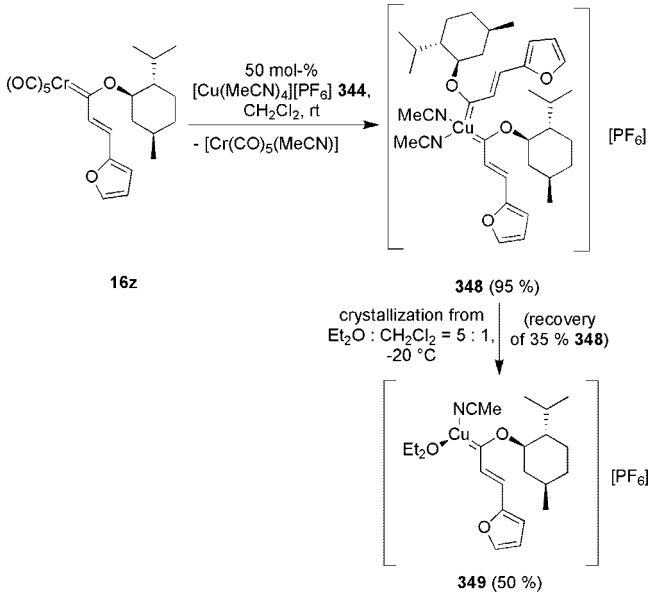
342 **4c** **343**

Scheme 106. Copper-Promoted Carbene Dimerization and Cross-Coupling



345 **16y** **347**

Scheme 107. Stable Copper(I) Carbene Complex Obtained via Transmetalation of a Chromium(0) Percursor



16z **348** (95 %) **349** (50 %)

352 (Scheme 108).[237] $RhCl_3 \cdot 3H_2O$ in methanol, $[(cod)RhCl]_2$, and $[(OC)_2RhCl]_2$ turned out to be similarly efficient precatalysts. A π-cyclization of a rhodiumdienyl(vinyl)carbene (rhodaoctatetraene) intermediate **351**—which could be isolated in one case[237d]—generated by transmetalation of the chromium or tungsten analogue has been suggested as the key to rationalize the reaction.

Apart from palladium and rhodium, copper(I) compounds have been shown to catalyze reactions of Fischer metal carbenes. As an example, the rate of the π-cyclization of tungsten carbene complex **353** to the spirocyclic vinylcyclopentadiene **354** has been found to be strongly enhanced in the presence of CuI and NEt_3 (Scheme 109).[237d] $[(cod)RhCl]_2$ turned out to be a bit less efficient (63%) in this conversion.

Finally, the transmetalation of group 6 metal phenyl and alkenyl(alkoxy)carbene complexes with rhodium(I) in the presence of allenes allows the construction of highly substituted dienyl indenone derivatives[238a] and functionalized alkylidenecyclopentenes.[238b] The transformation of chromium alkyl-,[239a] alkenyl-,[239b] aryl-,[239a] and heteroarylcarbene[239a] complexes with internal alkynes yielding highly substituted cyclopentadienes[239a] and cyclopentenones[239b] has been achieved in the presence of Ni(0)-compounds.

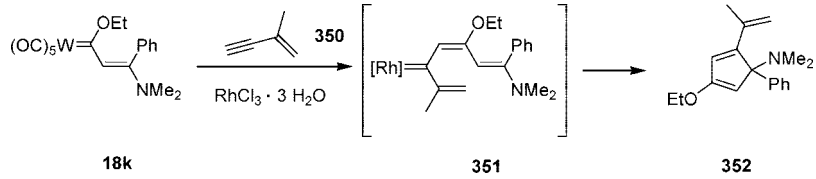
7. Self-Aggregation of Carbene Complexes

This review concentrates on the utilization of Fischer carbene complexes in the construction of more or less complex organic target molecules. Apart from this synthetic aspect, Fischer carbenes also have gained interest as building motifs in the structure of several classes of (natural) compounds (bioorganometallic chemistry) and material science. This includes dithiafulvene carbene complexes as potential precursors of extended thiafulvene architectures,[240] the application in metal-conjugated peptide nucleic acids,[241] and hydrophilic Fischer carbene complexes as organometallic markers[242] and for the immobilization[64a] of proteins. Another material science aspect based on the gelator properties of amphiphilic carbene complexes will be discussed below.

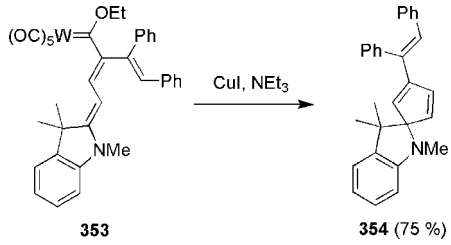
7.1. Amphiphilic Sugar Carbene Complexes

Metal coordination as a concept for metallogelators is an area of increasing interest.[243] Recently, the first examples of organometallics gelators combining soft material aspects with opportunities in organometallic synthesis have been reported.[244] The synthesis of amphiphilic sugar metal carbene gelators is based on the combination of an aldonic acid chloride electrophile and a carbonyl metalate nucleophile as outlined in Scheme 110. Following this strategy, peracylated gluconic acid chloride **355** was modified into chromium sugar methoxycarbene **356**. Low-temperature aminolysis (−78 to −40 °C) followed by exhaustive deprotection afforded the amphiphilic sugar metal aminocarbene **357**. It represents an organometallic isolobal analogue of gluconic amide **358**,[245] the 6-benzoyl derivative of which is an efficient hydrogelator.[246] The formal replacement of the carbonyl group (in **358**) for the chromium carbene fragment makes the chromium aminocarbene **357** a remarkable organogelator immobilizing customary chlorinated (chloroform, dichloromethane) and aromatic solvents (benzene, toluene) at concentrations as low as 0.35−1 wt %.[244a,247]). The configuration of C-2 in the sugar fragment is crucial for the gelation abilities: While *gluco*- and *galacto*-complexes are equally efficient gelators, no solvent immobilization was observed for the *manno*-analogue, indicating that aggregation is controlled by the configuration next to the carbene carbon atom. The gelation ability is independent of the relative

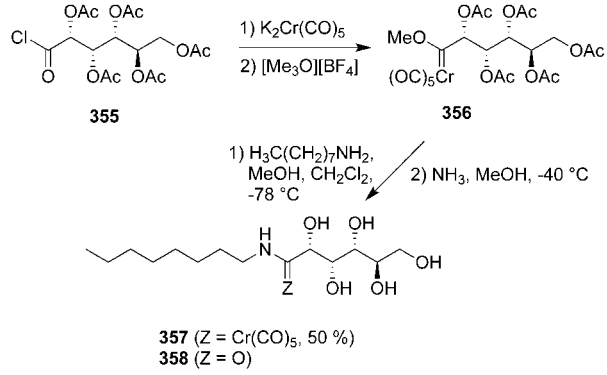
Scheme 108. Rhodium-Catalyzed Formation of Vinylcyclopentadienes from Tungsten Vinylcarbenes and Eneynes



Scheme 109. Copper-Catalyzed Cyclization of a Tungsten Trienylcarbene Complex to a Spirocyclopentadiene



Scheme 110. Synthesis of Amphiphilic Chromium Sugar (Amino)carbene 357: An Organometallic Organogelator and Isolobal Analogue of the Gluconic Amide Hydrogelator 358



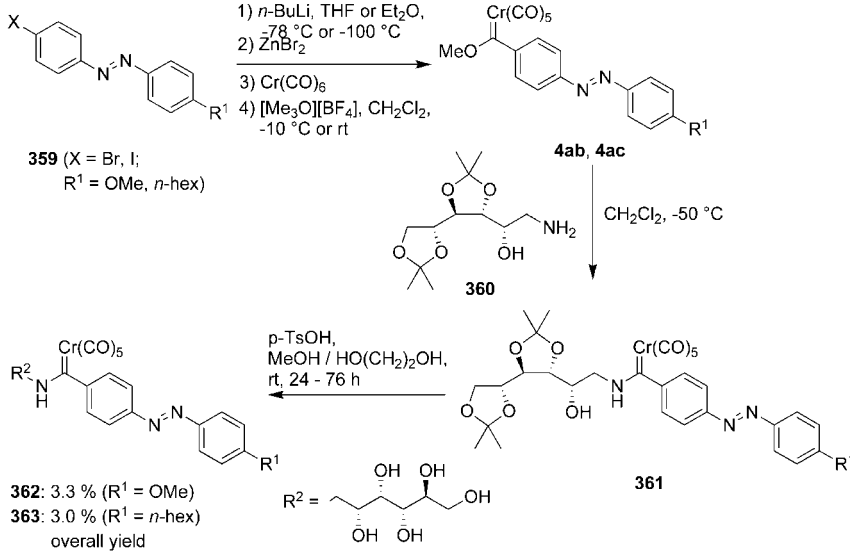
position of the hydrophilic sugar and lipophilic alkyl substituents within the aminocarbene ligand:[248] Chromium complexes bearing unprotected aminosugar (long-chain alkyl)carbene ligands are equally effective as are tungsten homologues. Electrospray ionization−mass spectroscopy (ESI−MS) studies demonstrated an intermolecular aggregation in the gas phase.[249] Temperature-dependent NMR, IR, and circular dichroism (CD) studies support an aggregation model based on a helical motif of inverse micelles with the hydrophilic sugar chains pointing inward and the lipophilic alkyl chains placed at the periphery.[244a]

The structural motifs of chromium sugar aminocarbenes were extended to diazobenzene derivatives **362** and **363** accessible from diazobenzene derivatives **359** and aminosugar **360** via chromium carbenes **4ab**/**4ac** and **361** in similar reaction sequences (Scheme 111)[10] using a different sugar protection/deprotection protocol. The incorporation of the azobenzene spacer kills the gelation ability, suggesting that a well-balanced combination of noncovalent interactions such as hydrogen bonding, van der Waals interactions, and $\pi-\pi$-stacking within the carbene ligand is required for efficient aggregation.

7.2. Pincer-Type *N*-Heterocyclic Carbene (NHC) Complexes as Low-Molecular-Mass Gelators (LMMGs)

Apart from Fischer-type carbene ligands *N*-heterocyclic carbenes (NHCs) have received much attention because of their role both as robust ligands in homogeneous metal catalysis[250] and in organocatalysis.[251] For example, pincer-type metal complexes bearing two NHC moieties bridged by a central pyridine or lutidine ring have been developed to efficient catalysts for C−C and C−N coupling reactions.[252] Palladium pyridine bis(imidazolylidene) pincer complexes **364**, which are readily accessible from commercial starting materials,[253] were found to catalyze cross-coupling reactions. While the poor solubility of the methyl derivative **364a** hampered broader application[254] (Figure 12) its *n*-butyl homologue **364b** has been developed to an efficient catalyst for Heck- and Suzuki-type reactions with catalyst loading as low as ppb amounts.[255] When their π-stacking ability resulting from the coplanar heteroarene ligand was assisted

Scheme 111. Synthesis of Diazobenzene-Containing Chromium (Amino)carbene Complexes



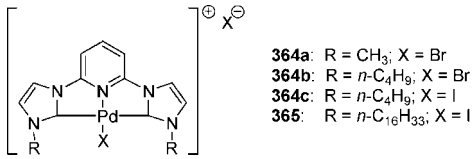


Figure 12. Palladium CNC pincer NHC complexes as air-stable organometallic low-molecular-mass gelators.

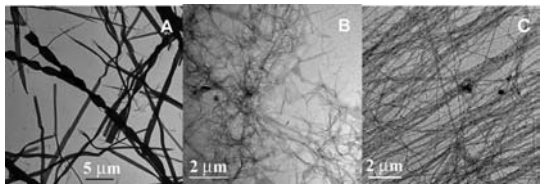


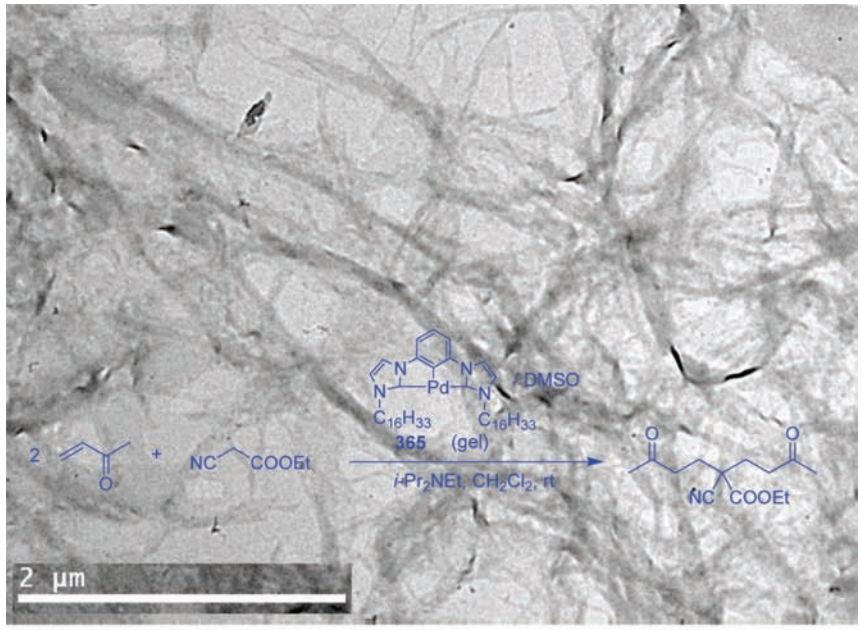
Figure 13. TEM images of gels formed from palladium pincer complex **365**. (Reproduced in part from ref. 244b with permission by Wiley-VCH.)

by a long chain *N*-alkyl substitution such as in **365**, they represent thermoreversible swellable materials that immobilize a broad variety of customary protic, aprotic, polar, and less polar organic solvents in gelator concentrations as low as 1 wt %.[244b] Particularly firm orange-red transparent gels were formed with dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), and dimethyl acetamide (DMA), which are stable under ambient conditions up to 50−60 °C. The morphology of the 3D network present in the xerogels and the dimensions of the individual fibers varied with the solvent used: Large fibers were observed for protic solvents (e.g., MeOH, AcOH), whereas a dense network of smaller fibers resulted from polar nonprotic solvents (e.g., DMSO, DMF, THF) (Figure 13). An X-ray-diffraction study of the gel network of **365**/DMSO revealed a lamellar structure with a mean distance of 15.2 Å, which may reflect the distance of stacked layers of the complex and an additional unit of 3.9 Å, which is assumed to correspond to π-stacking and Pd···Pd-interactions.

The aggregation of the organogelator **365** via noncovalent interactions generates an organometallic gel containing a homogeneous distribution of palladium centers, which reveals a modest but pronounced catalytic activity as demonstrated for the double Michael addition of cyanoacetate to but-1-en-3-one (Figure 14).[244b] The rates observed at room temperature for the homogeneous reaction of complexes **364c** and **365** in solution is doubled if the complex **365** was applied as a 4 wt % gel in DMF. An additional acceleration occurred when **365** was applied as a firmer and more compact DMSO gel.

8. Conclusion

More than four decades after the first report on Fischer carbene complexes has appeared, this class of organometallics has been developed to multifaceted reagents in selective organic synthesis. Metal carbenes are now readily accessible through well-elaborated synthetic methodologies either from noncarbene precursors or via modification of other carbene complexes. The metal carbonyl fragment is known to assist nucleophilic addition or cycloaddition reactions occurring within the carbene ligand that often result in improved yields and selectivities, a feature which may be rationalized by the isolobal analogy of an oxygen atom and the metal carbonyl fragment. Beyond that, the metal itself is able to play a crucial role as a template both in cycloaddition and unprec-



catalyst	k (10^{-6} s^{-1})	$t_{½}$ (h)
364c (solution)	4.3	44.0
365 (solution)	5.5	35.0
gel (**365** / DMF) (4 wt-%)	10.4	18.5
gel (**365** / DMSO) (4 wt-%)	24.1	7.9

Figure 14. Catalytic activity of palladium pincer complexes **365** in the double Michael addition in solution and in the gel state. (Reproduced in part from ref. 244b with permission by Wiley-VCH.)

edented annulation, multistep, and multicomponent reactions, which are characteristic for metal carbenes. This is a predominant role of *chromium* carbenes, which allow for a selective one-pot construction of various, often densely functionalized, frameworks via a balanced sequence of individual bond-forming steps. Additional benefits result from the photochemistry of chromium carbenes and—most recently—from carbene transfer reactions to late transition metals opening new opportunities in homogeneous catalysis. This will not be the end of the story, and beyond application in synthesis, metal carbenes have also started to open new perspectives toward material properties.

9. Acknowledgments

Parts of the research reported from the authors' laboratory focused on chromium-templated benzannulation, haptotropic metal migration, and low-molecular-mass metal carbene organogelators have been generously supported by the Deutsche Forschungsgemeinschaft (SFB 624 *Templates*), which we gratefully acknowledge.

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