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Chromium-Templated Benzannulation Reactions

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Abstract Since its discovery the chromium-mediated benzannulation reaction has been developed into a unique and useful tool in organic synthesis. In this review, topical aspects of this reaction concerning its mechanism and the chemo-, regio- and stereoselectivity are summerised and discussed in detail. Special attention is paid to the asymmetric benzannulation reaction and, finally, the importance of this reaction as a key step in the total synthesis of natural products is outlined.

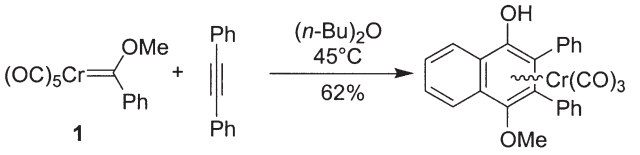
Keywords Fischer carbene complex · [3+2+1]-benzannulation reaction · Asymmetric benzannulation · Linear benzannulation

Abbreviations

Ac	Acetyl
Bn	Benzyl
n-Bu	*n*-Butyl
t-Bu	*t*-Butyl
CAN	Ceric ammonium nitrate
cod	Cyclooctadiene
Cp	Cyclopentadienyl
de	Diastereomer excess
DEAD	Diethyl azodicarboxylate
dr	Diastereomer ratio
ee	Enantiomer excess
Et	Ethyl
h	Hour(s)
kcal	Kilocalories
mol	Mole
NMR	Nuclear magnetic resonance
Me	Methyl
Ph	Phenyl
i-Pr	*iso*-Propyl
n-Pr	*n*-Propyl
rac	Racemic
rt	Room temperature
S	Solvent
TBDMSCl	*tert*-Butyldimethylsilyl
TBME	*tert*-Butyl methyl ether
Tf	Trifluoromethanesulphonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl

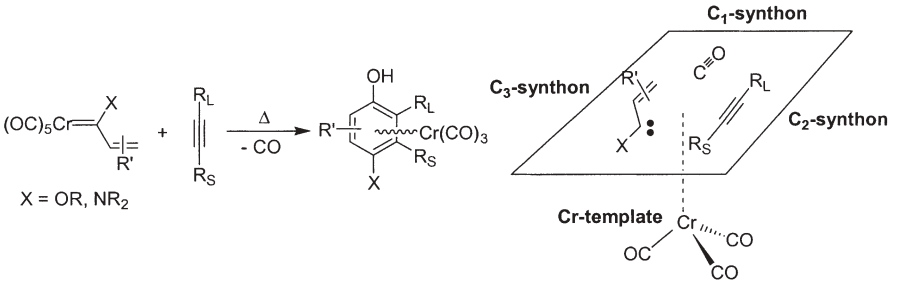
1 Introduction

The thermal [3+2+1]-benzannulation reaction of α,β-unsaturated Fischer carbene complexes with alkynes was discovered in 1975 in our laboratory along with the reaction of methoxy(phenyl)carbene chromium complex **1** upon gentle warming with tolane [1] (Scheme 1). It established the potential of an organometallic template in the stereocontrolled assembly of different ligands and their activation for C–C bond formation at a low-valent metal centre. This unique type of metal carbene reaction provides one of the most powerful tools to generate densely substituted benzenoid compounds. Within the [3+2+1]-benzannulation the concept of atom economy is convincingly preserved as this type of reaction represents a highly efficient one-pot procedure.



Scheme 1 [3+2+1]-Benzannulation reaction as the first example of a metal-templated coupling of three different ligands

The formal [3+2+1]-cycloaddition involves an α,β-unsaturated carbene ligand (C3-synthon), an alkyne (C2-synthon) and a carbonyl ligand (C1-synthon) and takes place within the coordination sphere of the chromium(0), which acts as a metal template (Scheme 2).



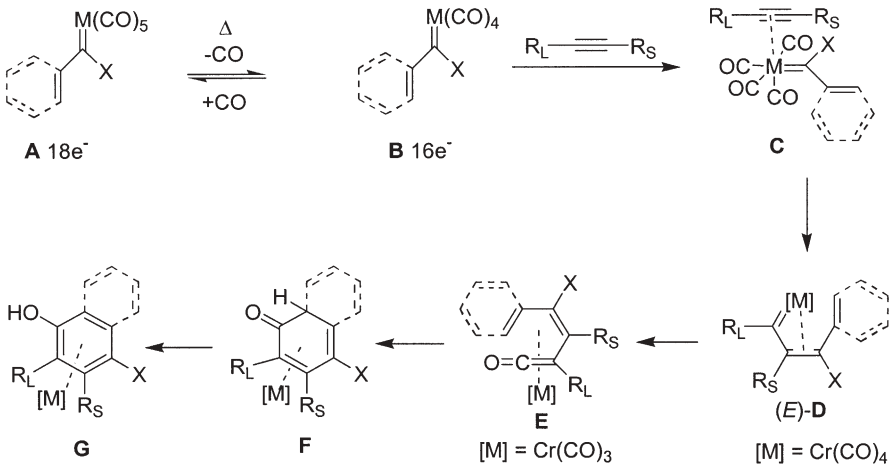
Scheme 2 Atom connectivity in the [3+2+1]-benzannulation reaction

2 Mechanism

2.1 Phenol Formation

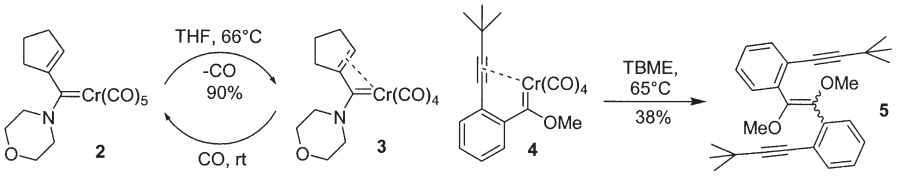
Nearly 25 years after its discovery the mechanism of the benzannulation reaction has been theoretically and experimentally elucidated in detail. The most predominant outcome of this reaction is the formation of the 4-methoxyphenol or 4-methoxy-1-naphthol skeleton coordinated to a $Cr(CO)_3$ fragment. Therefore the mechanism leading to this type of product will be discussed first.

The first and rate-determining step involves carbon monoxide dissociation from the initial pentacarbonyl carbene complex **A** to yield the coordinatively unsaturated tetracarbonyl carbene complex **B** (Scheme 3). The decarbonylation and consequently the benzannulation reaction may be induced thermally, photochemically [2], sonochemically [3], or even under microwave-assisted conditions [4]. A detailed kinetic study by Dötz et al. proved that the initial reaction step proceeds via a reversible dissociative mechanism [5]. More recently, density functional studies on the preactivation scenario by Solà et al. tried to propose alkyne addition as the first step [6], but it was shown that this



Scheme 3 Mechanism of the benzannulation reaction

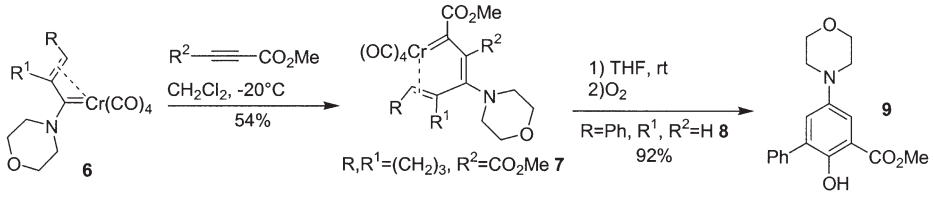
associative sequence does not agree with the available experimental data [7]. A (η^1:η^3)-vinylcarbene complex analogue **3**, corresponding to the first reaction intermediate **B** of the benzannulation reaction, has been isolated and characterised [8]. The tetracarbonyl carbene complex **3** was generated upon heating **2** under reflux in tetrahydrofuran in the absence of any alkyne, and the reversibility of this dissociative process was proven by reisolating the starting compound after bubbling CO into the solution at room temperature (Scheme 4). The subsequent step in the benzannulation reaction involves the trapping of the coordinatively unsaturated 16e complex by the alkyne present in the solution to yield **C**. A structural analogue **4** displaying an intramolecular alkyne coordination has been characterised by X-ray analysis [9]. In spite of this promising isolation of an intramolecular alkyne carbene chromium chelate **4**, the expected benzannulation reaction did not take place after heating this formal intermediate. Instead, a formal dimerisation of the carbene complex yielding **5** was observed (Scheme 4).



Scheme 4 Isolated intermediates

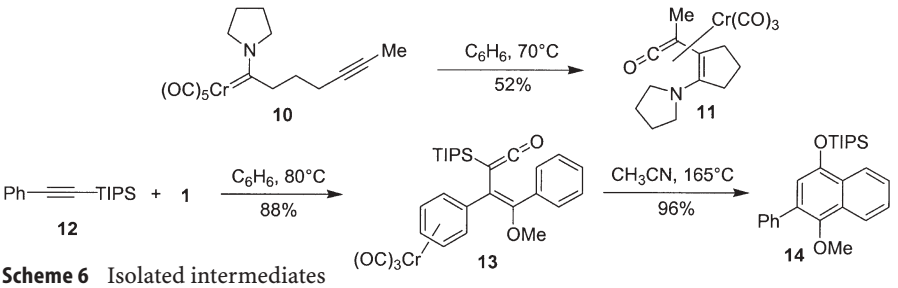
The subsequent insertion of the alkyne into the metal–carbene bond affords the (η^1:η^3)-vinylcarbene complex **D**, which may exist either as a (*Z*)- or an (*E*)-metallatriene. This intermediate may be considered as a branching point in the benzannulation reaction as three diverging routes starting from this point have been explored.

According to Dötz the η^3-vinylcarbene complex **D** forms a η^4-vinylketene **E** by CO insertion into the chromium–carbene bond, followed by electrocyclic ring closure to yield the η^4-cyclohexadienone **F** [10]. Extended Hückel molecular orbital and recent quantum chemical calculations support the Dötz route [11]. A modification of this theory was proposed by Solà, as recent DFT studies showed that an η^1-coordination of the vinylcarbene **D** is energetically favoured, which subsequently allows formation of a chromahexatriene intermediate through structural rearrangement involving a π-coordination of the terminal C=C bond. This intermediate can be regarded as a five-membered chelate ring if the midpoint of the coordinated double bond is taken as one ring member. A subsequent insertion of a CO ligand was proposed to give the η^4-cyclohexadienone **F** mentioned before [12]. It should be noted that the formation of the η^4-cyclohexadienone **F** via a chromacycloheptadienone was suggested by Casey, but this hypothesis was rejected due to thermodynamic arguments [13]. An exact validation of these mechanistic suggestions requires a benzannulation reaction along which all individual steps can be established by characterisation of the relevant intermediates. Although this goal has not been reached yet, Barluenga succeeded in realising a very similar project referred to as the "first stepwise benzannulation reaction" [14]. The reaction of tetracarbonyl carbene complex **6** with dimethyl acetylene dicarboxylate takes place at –20 °C and after 22 h yields the metallahexatriene **7** (Scheme 5). The coordination of the external double bond to the metal was proven by NMR spectroscopy. Although the decomposition of this compound **7** at room temperature did not lead to the expected phenol product, the metallahexatriene **8** yielded the phenol **9** in a completely selective fashion.



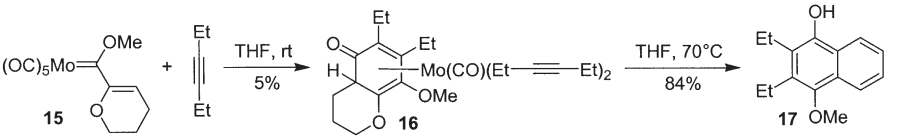
Scheme 5 Isolated intermediates

Structural analogues of the η^4-vinylketene **E** were isolated by Wulff, Rudler and Moser [15]. The enaminoketene complex **11** was obtained from an intramolecular reaction of the chromium pentacarbonyl carbene complex **10.** The silyl vinylketene **13** was isolated from the reaction of the methoxy(phenyl)-carbene chromium complex **1** and a silyl-substituted phenylacetylene **12,** and – in contrast to alkene carbene complex **7** – gave the benzannulation product **14** after heating to 165 °C in acetonitrile (Scheme 6). The last step of the benzannulation reaction is the tautomerisation of the η^4-cyclohexadienone **F** to afford the phenol product **G.** The existence of such an intermediate and its capacity to undergo a subsequent step was validated by Wulff, who synthesised an



Scheme 6 Isolated intermediates

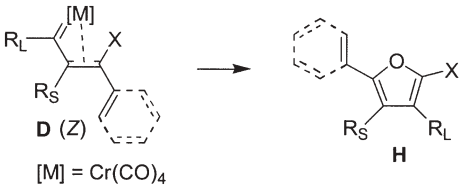
η^4-cyclohexadienone analogue **16** starting from the molybdenum carbene complex **15** and 3-hexyne. This complex tautomerises in tetrahydrofuran at 70 °C to yield the phenol product **17** [16] (Scheme 7).



Scheme 7 Isolated intermediates

2.2 Furan and Indene Formation

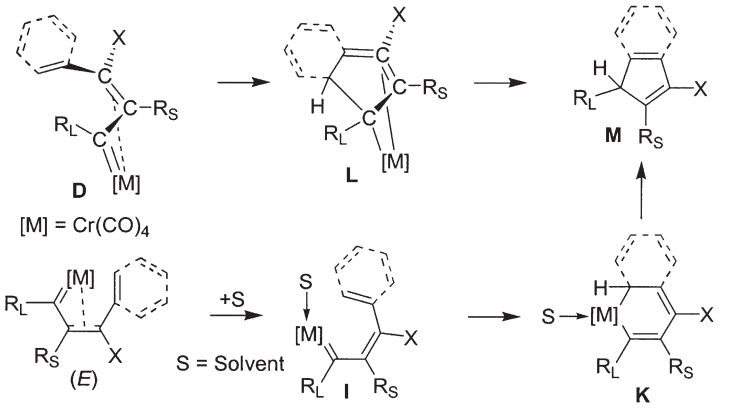
Chemoselectivity plays an important role in the benzannulation reaction as five-membered rings such as indene or furan derivatives are potential side products. The branching point is again the η^3-vinylcarbene complex **D** intermediate which may be formed either as a (*Z*)- or an (*E*)-metallatriene; the (*E*)-configuration is required for the cyclisation with the terminal double bond. (*Z*)-Metallatriene **D**, however, leads to the formation of furan derivatives **H** (Scheme 8). Studies on the formation of (*E*)- and (*Z*)-isomers discussing stereoelectronic effects have been undertaken by Wulff [17].



Scheme 8 Formation of furan products

For the indene derivatives **M** two different reaction pathways have been discussed so far, starting from the (*E*)-metallatriene **D**. A strongly coordinating solvent may induce an electrocyclic ring closure yielding the metallacyclohexadiene **K**, and the indene product is obtained after tautomerisation and reductive

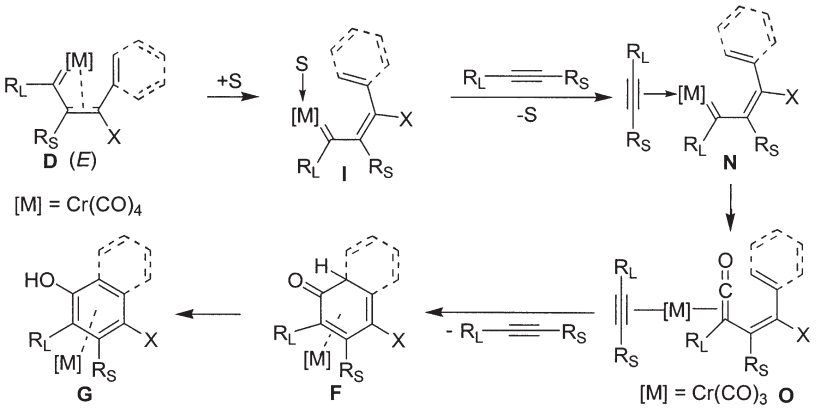
elimination of the metal centre [14]. The decisive point is the strong coordinating ability of the solvent molecule; non-coordinating solvents are unable to cleave the η^1- or η^3-coordination of the metal centre to the double bond in complex **D**. On the other hand, a direct electrocyclic ring closure may afford the cyclopentadiene **L** which tautomerises to the indene product [16] (Scheme 9).



Scheme 9 Formation of indene products

2.3 Allochemical Effect

The distribution of products obtained from the benzannulation reaction may be influenced by the concentration of alkyne substrate [18]. In strongly coordinating solvents the ratio of the phenolic benzannulation product over five-membered cyclisation products increases with the concentration of the alkyne (Scheme 10).



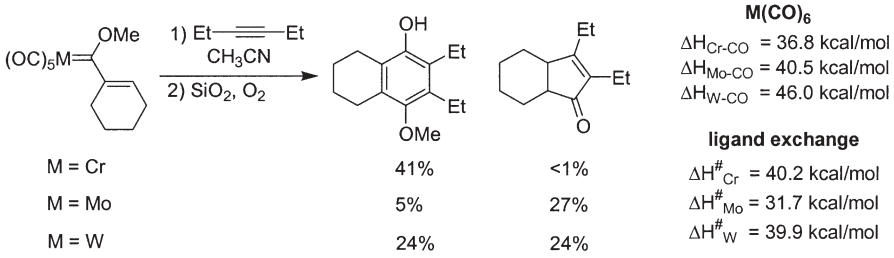
Scheme 10 The allochemical effect

This "allochemical effect" has been explained in terms of an accelerated CO insertion resulting from the coordination of the alkyne [19]. During the insertion of CO, the alkyne can switch from a 2e donor to a 4e donor, resulting in electronic saturation of the metal centre in the intermediate. The effect is distinctly reduced or even non-existent when the reaction is carried out in a non-coordinating solvent.

3 Trends in Chemoselectivity

The chemoselectivity of the [3+2+1]-benzannulation reaction is governed by four general trends:

1. A greatly enhanced chemoselective formation of phenol is observed for alkoxy(alkenyl)carbene complexes compared to alkoxy(aryl)carbene complexes. This behaviour reflects the ease of formation of the η^6-vinylketene complex intermediate **E** starting from alkenylcarbene complexes; for aryl complexes this transformation would require dearomatisation.
2. Phenol over indene formation is favoured in the order chromium>tungsten>molybdenum. The ability for CO insertion during the benzannulation reaction is expected to correlate with the strength of the metal–CO bond [20]. However, this correlation does not hold for molybdenum which is known for the kinetic lability of the Mo–CO bond, indicated by the well-established propensity of molybdenum carbonyl complexes to undergo ligand substitution at higher rates than their homologues [21]. In a coordinating solvent such as acetonitrile, molybdenum is very susceptible to the displacement of the double bond in complex **D** by a solvent molecule, which results in increased amounts of the indene product (Scheme 11).

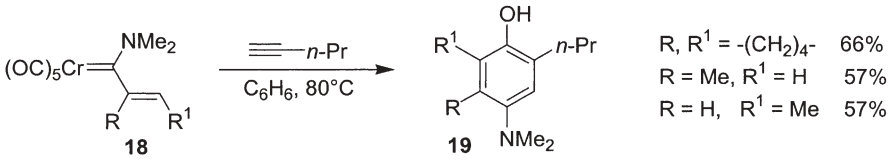


Scheme 11 Phenol versus indene formation. (ΔH_{M-CO}=metal–CO bond strength; $\Delta H^{\#}_{M}$ refers to substitution of CO for PR_3)

3. Phenol formation is favoured in less coordinating and/or less polar solvents; however, for clean reactions affording the $Cr(CO)_3$-coordinated benzannulation products, ethereal solvents are the solvents of choice.
4. Amino(aryl)carbene complexes prefer cyclopentannulation over benzannulation. Amino(alkenyl)carbene complexes may react in a benzannulation reaction.

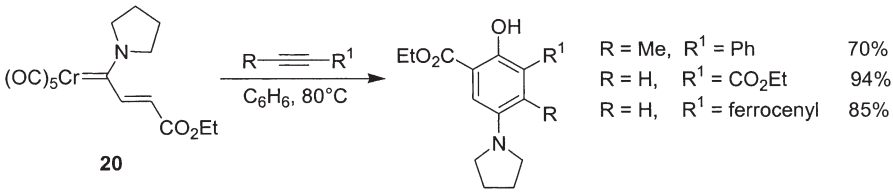
The superior donor properties of amino groups over alkoxy substituents causes a higher electron density at the metal centre resulting in an increased M–CO bond strength in aminocarbene complexes. Therefore, the primary decarbonylation step requires harsher conditions; moreover, the CO insertion generating the ketene intermediate cannot compete successfully with a direct electrocyclisation of the alkyne insertion product, as shown in Scheme 9 for the formation of indenes. Due to that experience amino(aryl)carbene complexes are prone to undergo cyclopentannulation. If, however, the donor capacity of the aminocarbene ligand is reduced by *N*-acylation, benzannulation becomes feasible [22].

Wulff et al. examined the necessary reaction conditions for α,β-unsaturated aminocarbene complexes to react in a benzannulation reaction [23]. The reaction of dimethylamino(alkenyl)carbene complexes **18** with terminal alkynes in non-coordinating and non-polar solvents afforded phenol products in acceptable yields (Scheme 12).



Scheme 12 Benzannulation of alkenyl(dimethylamino)carbene complexes

If the dimethylamino group is exchanged for a pyrrolidino **20** or a morpholino moiety the choice of alkyne is not restricted any more, and both electron-rich and electron-poor terminal and internal alkynes may be applied to the benzannulation [24, 42b] (Scheme 13).

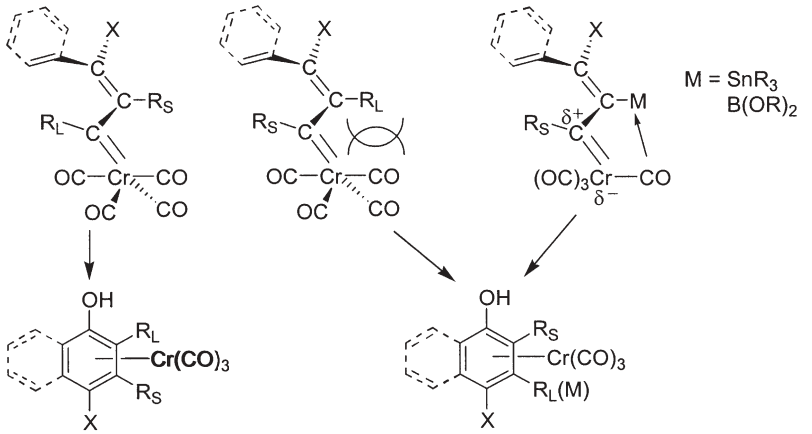


Scheme 13 Benzannulation of pyrrolidino(alkenyl)carbene complexes

4 Regioselectivity

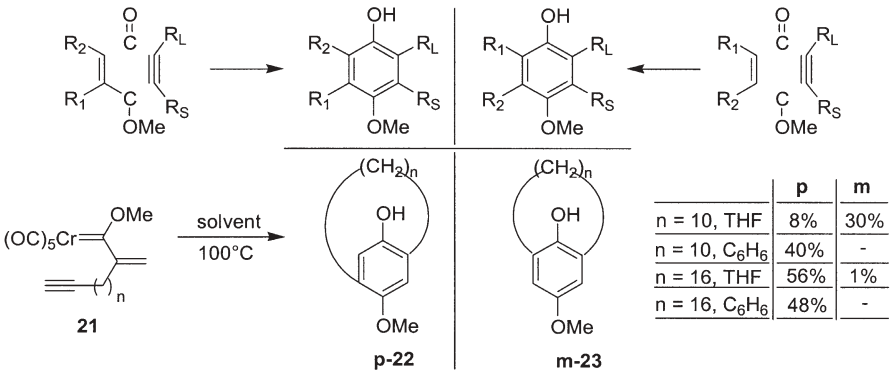
When the benzannulation is carried out with unsymmetrical alkynes the major regioisomer generally bears the larger alkyne substituent (R_L) next to the phenolic group, suggesting that the regioselectivity is mainly governed by the difference in steric demands of the two alkyne substituents. A reversal of this regiochemistry may be achieved either by an intramolecular version of the benzannulation, where the alkyne is incorporated in the alkoxy chain [25], or

by the use of stannyl acetylenes [26] and alkynyl boronates [27] (Scheme 14). There are two possible explanations for the inversion of the regioselectivity for the last two alkynes: (1) the installation of the electron-withdrawing metal centres far away from the electrophilic carbene carbon centre and (2) Lewis acid/base interactions [CO→M] in the η^3-metallatriene intermediate.



Scheme 14 Normal and inverse regioselectivity

An unexpected varying regiochemistry in intramolecular benzannulation has also been observed in the synthesis of cyclophanes. As mentioned above, there are only two possible regiochemical outcomes in the benzannulation reaction, which differ in the direction of alkyne incorporation. β-Tethered vinylcarbene chromium complexes undergo an intramolecular benzannulation reaction with incorporation of the tethered alkyne with normal regioselectivity to give *meta*-cyclophanes [28].



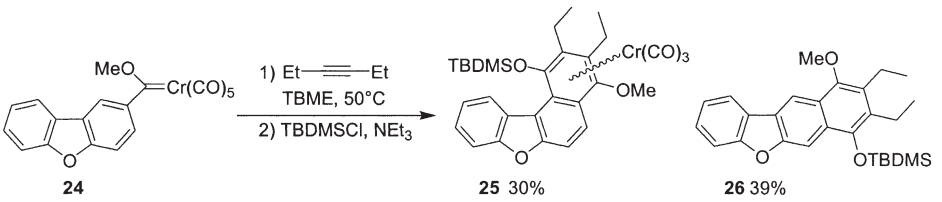
	p	m
n = 10, THF	8%	30%
n = 10, C_6H_6	40%	-
n = 16, THF	56%	1%
n = 16, C_6H_6	48%	-

Scheme 15 Inverse regioselectivity via bond cleavage

The formation of a new unanticipated regioisomer was observed in the intramolecular benzannulation reaction of the α-tethered vinylcarbene chromium complex **21** (Scheme 15). The *para*-cyclophane **22** was expected for this reaction on the basis of normal regiochemistry; however, upon warming a carbene complex bearing a bridge of ten methylene units between the alkene and alkyne moieties in tetrahydrofuran, *meta*-cyclophane **23** was obtained in 30% isolated yield [29a]. Its formation requires the cleavage of the carbon–carbon bond between the carbene carbon and the carbon-bearing substituent R_1, which may be consequence of conformational strain within the intermediates. Further studies revealed that the choice of the solvent and the tether length had a strong influence on the outcome of the reaction [29b]. In coordinating solvents macrocycles which are most sensitive to ring strain (n=10) yield *meta*-cyclophanes **23**, whereas non-coordinating solvents facilitate the formation of the expected *para*-cyclophane **22**. Strainless macrocycles (n=16) do not reveal any solvent dependence.

5 Annulation Pattern

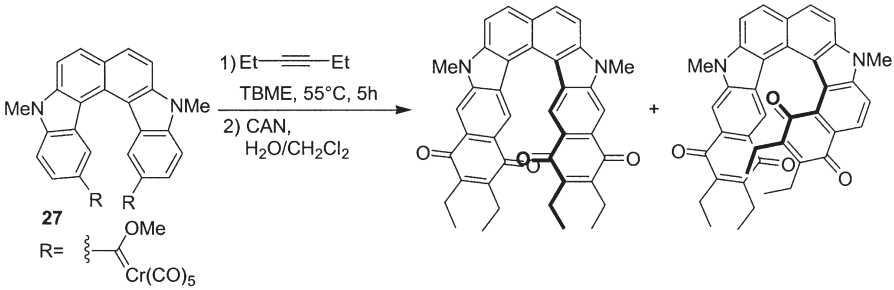
Benzannulation of fused arenes raises the question of angular versus linear annulation. The benzannulation of naphthylcarbene ligands generally leads to the phenanthrene skeleton in which both terminal rings obtain an optimum aromaticity [30]; a similar preference was observed even in cases where an *ortho* substitution was applied in order to force the annulation into a linear pathway [31]. However, recent studies indicate that linear benzannulation may become a major competition as observed for carbene complexes derived from dibenzo-substituted five-membered heteroarenes [32] or from helicenes [33]. A surprising linear benzannulation was observed for the dibenzofurylcarbene complex **24** [32a]. The uncoordinated benzo[*b*]naphthol[2,3-*d*]furan **26** was isolated along with the expected angular $Cr(CO)_3$-coordinated benzonaphthofuran **25** (Scheme 16). The formation of a linear $Cr(CO)_3$-coordinated benzannulation



Scheme 16 Angular versus linear benzannulation of (dibenzo)heteroarenes

product was achieved when the central furan ring in the carbene complex was substituted for a thiophene system [32b]. Both types of molecular structures have been widely established by X-ray analysis.

A double linear annulation was observed in the benzannulation reaction of the helical biscarbene complex **27** with 3-hexyne along with a product bearing

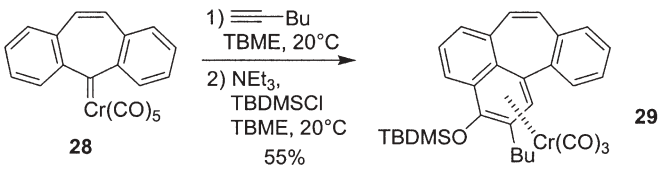


Scheme 17 Angular versus linear benzannulation of helicenes

a mixed annulation pattern (Scheme 17). The two products could be separated by column chromatography [33].

6
Benzannulation with Diarylcarbene Complexes

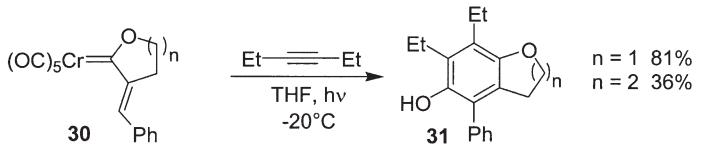
The electrophilic carbene carbon atom of Fischer carbene complexes is usually stabilised through π-donation of an alkoxy or amino substituent. This type of electronic stabilisation renders carbene complexes thermostable; nevertheless, they have to be stored and handled under inert gas in order to avoid oxidative decomposition. In a typical benzannulation protocol, the carbene complex is reacted with a 10% excess of the alkyne at a temperature between 45 and 60 °C in an ethereal solvent. On the other hand, the non-stabilised and highly electrophilic diphenylcarbene pentacarbonylchromium complex needs to be stored and handled at temperatures below –20 °C, which allows one to carry out benzannulation reactions at room temperature [34]. Recently, the first syntheses of tricyclic carbene complexes derived from diazo precursors have been performed and applied to benzannulation [35a,b]. The reaction of the non-planar dibenzocycloheptenylidene complex **28** with 1-hexyne afforded the $Cr(CO)_3$-coordinated tetracyclic benzannulation product **29** in a completely regio- and diastereoselective way [35c] (Scheme 18).



Scheme 18 Benzannulation of diarylcarbene-type complexes

Exo-alkylidene oxacycloalkylidene complexes such as chromium 2-oxacyclopentylidene **30** are reluctant to react thermally with alkynes. Nevertheless, benzannulation can be achieved under photochemical conditions (for a detailed

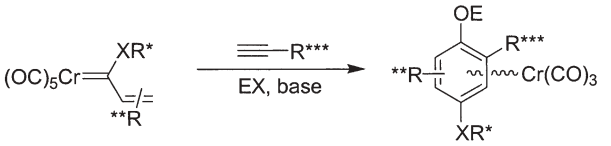
discussion of photochemical reactions of carbene complexes, see Chap. of L. S. Hegedus, page 157). Exploiting this approach, 2,3-dihydro-5-benzofuranol **31** and 2,3-dihydro-6-benzopyranol skeletons, which are encountered as a structural part in a variety of natural products and biologically active compounds, are accessible in moderate to good yields [36] (Scheme 19).



Scheme 19 Photo-induced benzannulation of *exo*-alkylidene oxacycloalkylidene complexes

7
Diastereoselective Benzannulation

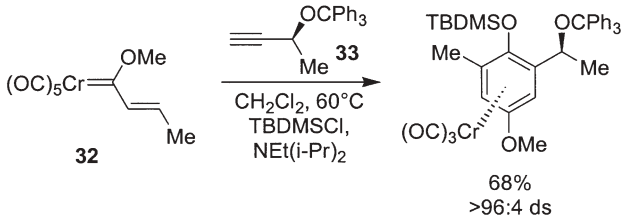
Due to the inherent unsymmetric arene substitution pattern the benzannulation reaction creates a plane of chirality in the resulting tricarbonyl chromium complex, and – under achiral conditions – produces a racemic mixture of arene $Cr(CO)_3$ complexes. Since the resolution of planar chiral arene chromium complexes can be rather tedious, diastereoselective benzannulation approaches towards optically pure planar chiral products appear highly attractive. This strategy requires the incorporation of chiral information into the starting materials which may be based on one of three options: a stereogenic element can be introduced in the alkyne side chain, in the carbene carbon side chain or – most general and most attractive – in the heteroatom carbene side chain (Scheme 20).



Scheme 20 Strategies towards diastereoselective benzannulation: incorporation of chiral information

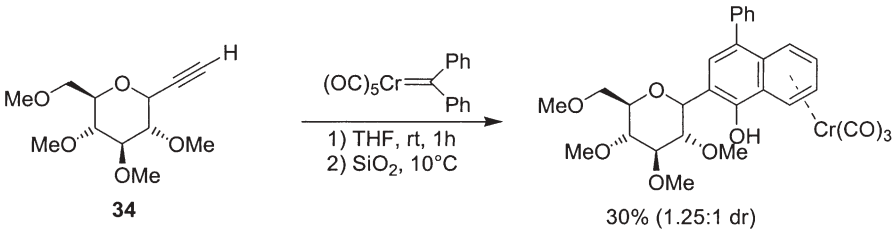
7.1
Chiral Alkynes

Chiral alkynes (R***) bearing a chiral propargylic ether functionality show high asymmetric induction, as observed in the benzannulation of the propenyl complex **32** with alkyne **33** [37] (Scheme 21). The degree of optical induction in this reaction depends on the steric bulk of the acetylenic oxygen substituent, and is not the result of chelation of the propargylic oxygen to the metal. Therefore, the propargylic oxygen plays a stereoelectronic role in determining the stereoselectivity, which underlines (and dominates) the steric effects of the propargylic ether protecting group.



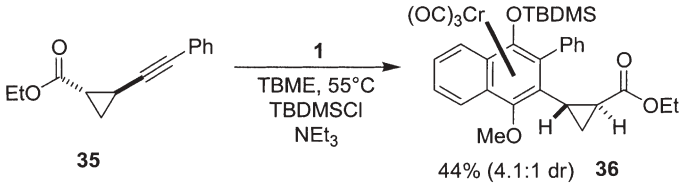
Scheme 21 Diastereoselective benzannulation of chiral propargylic ethers

Benzannulation of the diphenylcarbene ligand by 2-ethynylglucose derivative **34** results in only low diastereoselection, albeit it represents a rather rare example of a low-temperature protocol [38] (Scheme 22).



Scheme 22 Room-temperature benzannulation with a 2-ethynylglucose derivative

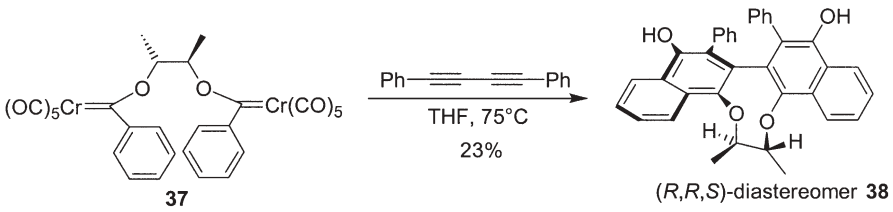
Attempts to increase the diastereoselectivity by a more rigid cyclopropane backbone were not successful. However, the incorporation of racemic *trans*-cyclopropane carboxylate **35** is completely regioselective, and both diastereomeric products **36** were isolated in a ratio of 4.1:1 [39] (Scheme 23).



Scheme 23 Benzannulation with a racemic cyclopropane carboxylate

7.2 Chiral Alkoxy or Amino Auxiliaries

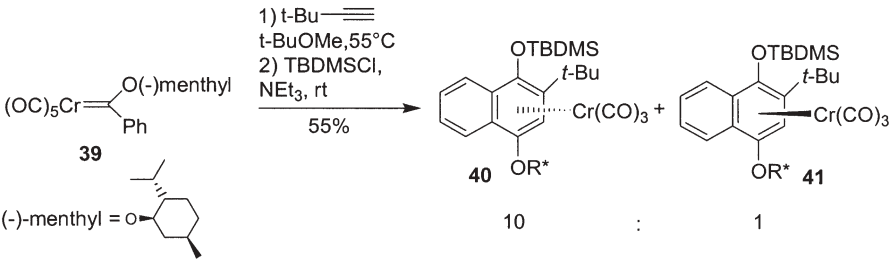
The second option involves the incorporation of either chiral amines or chiral alcohols into the heteroatom–carbene side chain (R*), which represents the most versatile approach to diastereoselective benzannulation. The optically pure (2*R*,3*R*)-butane-2,3-diol was used to tether the biscarbene complex **37**. The double intramolecular benzannulation reaction with diphenylbutadiyne allowed introduction of an additional stereogenic element in terms of an axis



Scheme 24 Diastereoselective biaryl synthesis via double benzannulation

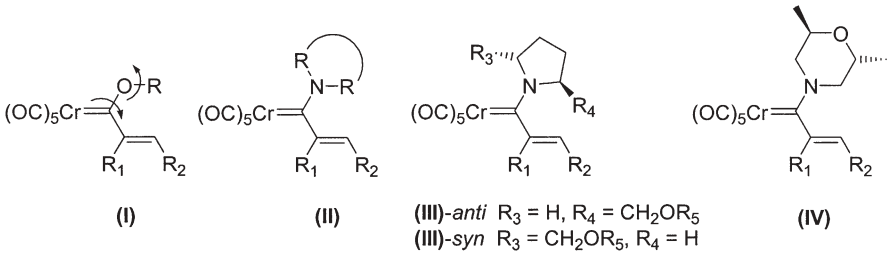
of chirality; a single diastereomer of 2,2′-binaphthol **38** was formed in moderate yield [40] (Scheme 24).

Excellent diastereomeric ratios were achieved with terpene-derived auxiliaries. The pentacarbonyl[(–)-menthyloxycarbene]chromium complex **39** reacted with the sterically hindered 3,3-dimethylbut-1-yne to give tricarbonyl chromium naphthohydroquinone complex **40** in 81% de as the major diastereomer which was also characterised by X-ray analysis [41] (Scheme 25). Surprisingly, the application of other even more sterically demanding terpene auxiliaries or a variation of the alkyne did not improve the diastereomeric ratio [42].



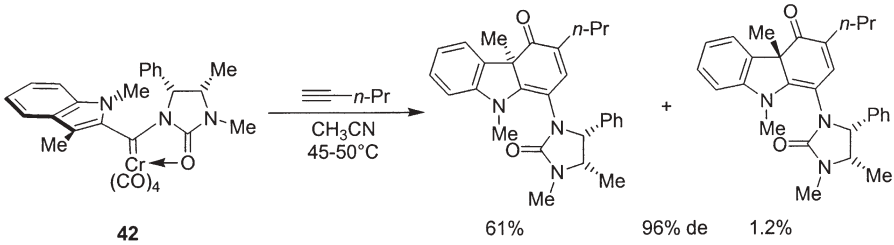
Scheme 25 Diastereoselective benzannulation with chiral terpene alcohols

One explanation for the low induction observed in the benzannulation of alkoxy carbene complexes (**I**) is the fact that there are actually two degrees of freedom that separate the chiral centre in a chiral alkoxy substituent and the metal centre. The rotation about the heteroatom–carbene carbon bond can be inhibited by switching to aminocarbene complexes (**II**) as the rotational barrier is increased from 15 to 25–30 kcal/mol due to the resonance delocalisation from nitrogen to the carbene carbon [43]. The other degree of freedom can be removed by using cyclic amino complexes (**III**) and (**IV**) (Scheme 26). α,β-Unsaturated carbene complexes derived from (*S*)-prolinol (**III**) exist as (**III**)-*syn* and (**III**)-*anti* isomers. The synthesis and isolation of a single isomer are hampered by α-deprotonation from the aminocarbene complex which is to be expected at different stages of the synthesis, resulting in an equilibration of the rotamers [44]. Due to this uncontrollable isomerisation, which occurs under the benzannulation conditions, these complexes failed to give even modest



Scheme 26 Carbene complexes with chiral amino substituents

asymmetric induction. Incorporation of a C_2-symmetric chiral amine such as in complex (**IV**), avoiding the problem of *syn* and *anti* isomers, however, does not improve the diastereoselectivity since the chiral information in the amine is too remote from the metal centre which assists the C–C bond formation to effect any facial selectivity. An exceptionally high asymmetric induction is observed for the heterocyclic carbene complex **42** bearing a (4*R*,5*S*)-5-phenyl-4-methylimidazolidinone auxiliary; in this carbene complex chelate the free rotation around the carbon–carbon bond that connects the imidazole ring to the carbene carbon is blocked as a result of chelation (Scheme 27).

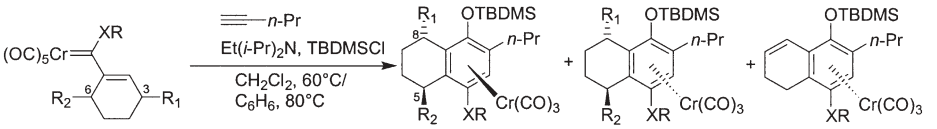


Scheme 27 Rigid chiral carbene complex chelates in diastereoselective benzannulation

7.3
Chiral Carbene Carbon Side Chains

Chiral alkoxy and amino cyclohexenylcarbene complexes substituted in the 3- or 6-position (R**), respectively, were examined in the benzannulation reaction [45] (Scheme 28). Tetralin $Cr(CO)_3$ complexes with substituents in the 5- or 8-position, respectively, are formed with different degrees of stereoselectivity and even reversed stereoselection depending on the substitution pattern of the chiral carbene complex. While 5-methyltetralin derivatives (entry 1) are formed with low diastereoselectivity, but with a consistent preference for the *syn*-isomer, the 8-methyltetralin complexes (entries 2–5) show a reversal of the sense of stereoselection and are formed with higher stereoselectivity. Interestingly, the diastereomeric ratio is increased on switching from methoxycarbene

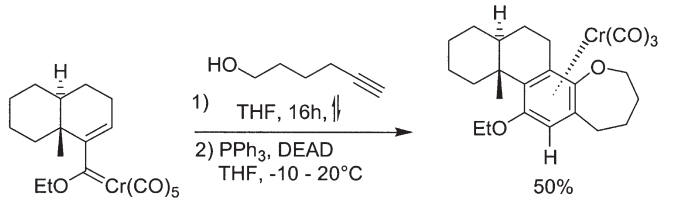
complexes (entries 2, 4) to aminocarbene complexes (entries 3, 5). An additional improvement of the stereoselectivity is achieved in the benzannulation reaction of the 3-methoxycyclohexenylcarbene complex with 1-pentyne; the didehydrotetralin $Cr(CO)_3$ complex is also obtained as a result of elimination of methanol.



entry 1 X = OMe, R_1 = H, R_2 = Me	(65%)	60(*syn*)	:	40(*anti*)	
entry 2 X = OMe, R_1 = Me, R_2 = H	(50%)	76(*anti*)	:	24(*syn*)	
entry 3 X = NMe_2, R_1 = Me, R_2 = H	(39%)	91(*anti*)	:	9(*syn*)	
entry 4 X = OMe, R_1 = OMe, R_2 = H	(48%)	94(*anti*)	:	6(*syn*)	16%
entry 5 X = NMe_2, R_1 = OMe, R_2 = H	(34%)	94(*anti*)	:	6(*syn*)	9%

Scheme 28 Benzannulation of chiral cyclohexenylcarbene complexes

The stereoselectivity observed in these reactions is assumed to result from steric interactions in the η^3-vinylcarbene complex intermediate **D**. In the first case (entry 1) an eclipsed interaction between the methyl group in the 6-position of the cyclohexene ring and the methoxy group of the vinylcarbene ligand has to be avoided, favouring the formation of the *syn*-tetralin complex. The minimisation of the steric interaction between the methyl group in the 3-position of the cyclohexene ring and a carbon monoxide ligand favours the formation of the *anti*-isomer in the other cases. The key step in the synthesis of the oxepin derivative **44** is a tandem Dötz–Mitsunobu reaction starting from the enantiomerically pure decalin-derived carbene complex **43** [46] (Scheme 29). The benzannulation reaction with hex-5-yn-1-ol proceeds with a high level of induction, as the complex **43** is isolated as a single diastereomer after ring closure via the Mitsunobu reaction.

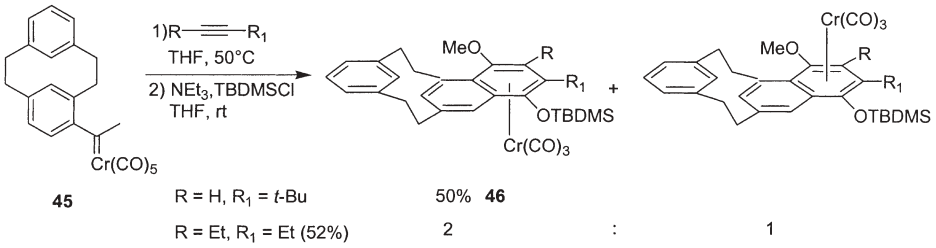


43 **44**

Scheme 29 Tandem benzannulation–Mitsunobu reaction of a chiral decalin-derived carbene complex

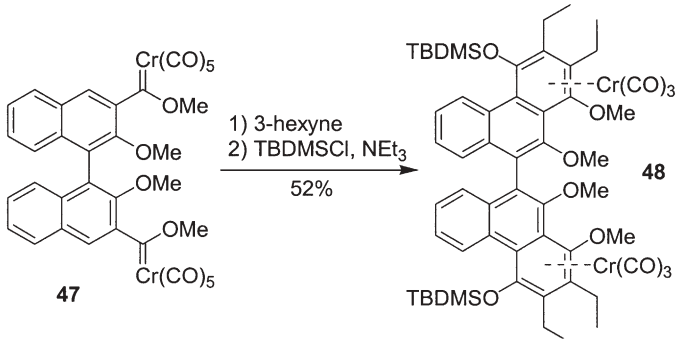
A similar tandem Dötz–Mitsunobu reaction has been reported starting from a 1,6-methano[10]annulene carbene complex, but no conclusion could be reached on the influence of the chiral information regarding the stereoselective course of the reaction since the chromium fragment could not be kept coordinated to the benzannulation product [47].

The inherent plane of chirality in the metal carbene-modified cyclophane **45** was also tested in the benzannulation reaction as a source for stereoselectivity [48]. The racemic pentacarbonyl(4-[2.2]metacyclophanyl(methoxy)carbene)-chromium **45** reacts with 3,3-dimethyl-1-butyne to give a single diastereomer of naphthalenophane complex **46** in 50% yield; the sterically less demanding 3-hexyne affords a 2:1 mixture of two diastereomers (Scheme 30). These moderate diastereomeric ratios indicate that [2.2]metacyclophanes do not serve as efficient chiral tools in the benzannulation reaction.



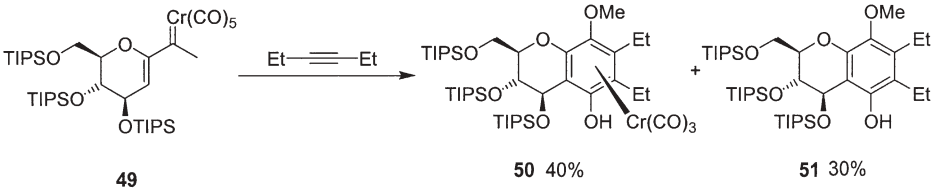
Scheme 30 A chiral [2.2]metacyclophane carbene complex in a benzannulation reaction

A bidirectional benzannulation of the axial–chiral biscarbene complex **47** affords a bis-$Cr(CO)_3$-coordinated biphenanthrene derivative **48**, which combines elements of axial and planar chirality [49] (Scheme 31). Four diastereomers are formed in moderate diastereoselectivity, two of which have been isolated as the major isomers.



Scheme 31 Bidirectional benzannulation with an axial–chiral biscarbene complex

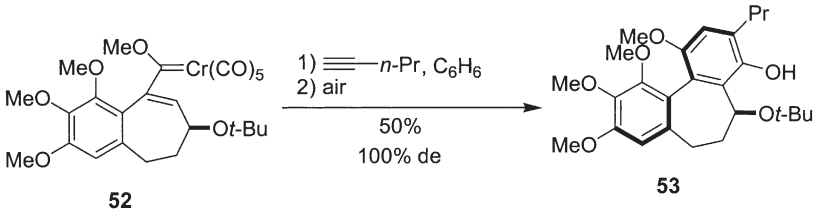
Upon reaction with 3-hexyne glucal-derived chromium, carbenes undergo benzannulation to afford highly oxygenated chromans coordinated to the chromium tricarbonyl fragment [50]. The diastereoselectivity depends on the nature of the protective groups. Best results were obtained with the TIPS-protected complex **49**, which produced benzochroman **50** as a single isomer along with demetalated hydroquinone **51** (Scheme 32).



49 **50** 40% **51** 30%

Scheme 32 Benzannulation with glucal-derived chromium carbenes

The use of a stereogenic carbon centre allowed an efficient asymmetric induction in the benzannulation reaction towards axial–chiral intermediates in the synthesis of configurationally stable ring-C-functionalised derivatives of allocolchicinoids [51]. The benzannulation of carbene complex **52** with 1-pentyne followed by oxidative demetalation afforded a single diastereomer **53** (Scheme 33).



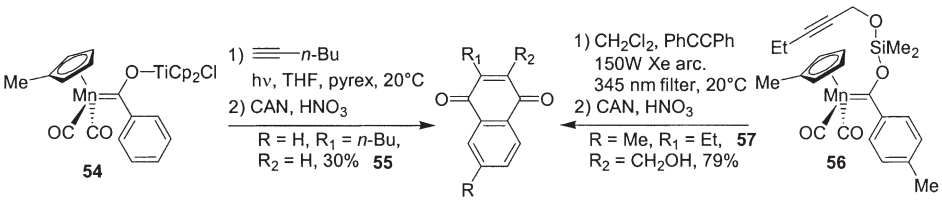
52 **53**

Scheme 33 Diastereoselective benzannulation towards allocolchinoids

8
Carbene Complexes with Different Metal Centres

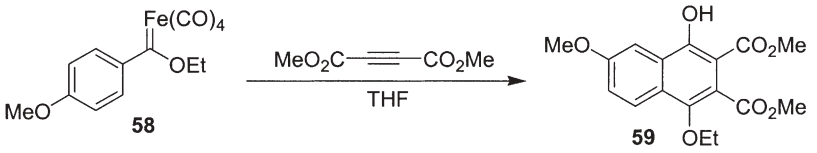
For a long time the benzannulation reaction has been restricted to metals of group 6, primarily complexes of the pentacarbonylchromium moiety. Carbene complexes of manganese do not undergo benzannulation reaction with alkynes unless the carbene system is activated by introducing a second, electron-deficient metal bound through oxygen to the carbene carbon atom. The carbene complex **54** with an electron-withdrawing titanium(IV)oxy substituent reacts with 1-hexyne under photochemical conditions, or in refluxing toluene, affording the naphthoquinone derivative **55** after oxidative workup [52]. Crystallographic data show that upon Ti(IV) substitution the manganese increases π-donation to the carbonyl ligands and therefore decreases π-donation to the carbene centre. The silyloxycarbene manganese complex **56** bears a tethered alkyne and therefore reacts in an intramolecular benzannulation reaction, yielding the functionalised naphthoquinone **57** [53] (Scheme 34).

Alkoxy(carbene)iron(0) and amino(carbene)iron(0) complexes usually react with alkynes to give η^4-pyrone iron complexes and furans, respectively [54]. Nevertheless the chemoselective formation of naphthols was reported for alkoxy(carbene)iron(0) complexes with the electron-poor alkyne dimethyl



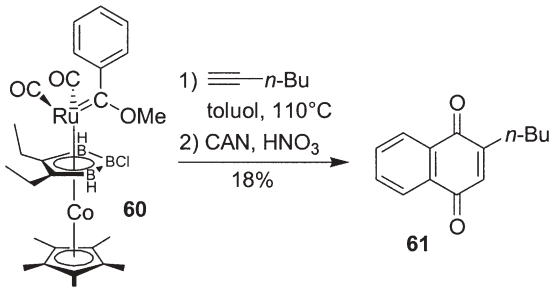
Scheme 34 Manganese carbene complexes in benzannulation reactions

acetylene dicarboxylate [55]. The electron-rich iron(0) carbene complex **58** gave excellent yields of naphthol **59** (Scheme 35). Further studies revealed that the formation of naphthols is restricted to the use of this specific acetylene, as alkyne monoesters give furans.



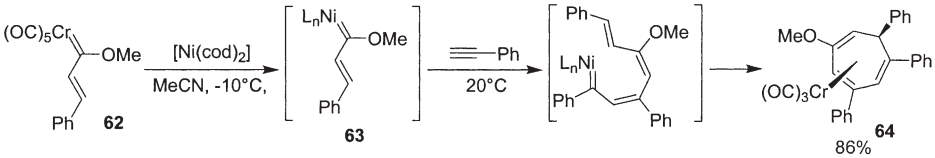
Scheme 35 Iron-mediated benzannulation

A benzannulation reaction yielding the naphthoquinone **61** could also be performed with the ruthenium carborane-stabilised carbene **60** and 1-hexyne [56] (Scheme 36). The ruthenium carbene unit can be regarded as an 18-electron fragment containing a formal Ru(II) centre coordinated to a dianionic six-electron-donor cobaltacarborane ligand.



Scheme 36 Ruthenium-mediated benzannulation

A transmetalation of the styrylcarbene chromium complex **62** in the presence of stoichiometric amounts of $[Ni(cod)_2]$ to give the nickel carbene intermediate **63** was applied to the synthesis of $Cr(CO)_3$-coordinated cycloheptatriene **64** upon reaction with terminal alkynes [57] (Scheme 37). The formation of pentacarbonyl(acetonitrile)chromium is expected to facilitate the metal exchange.



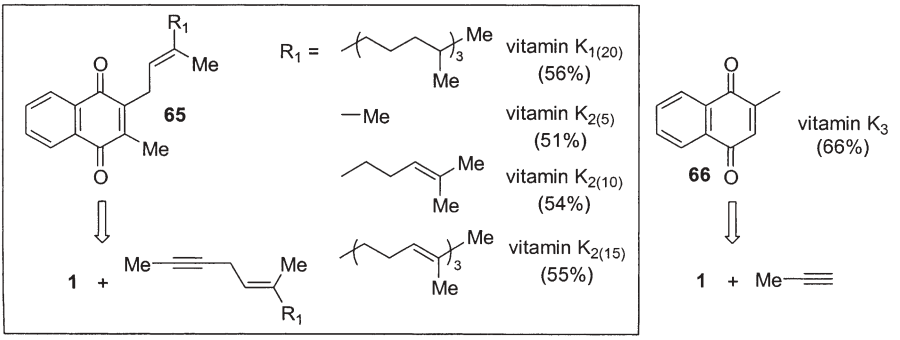
Scheme 37 Transmetalation of chromium to nickel in a metal carbene-mediated cyclisation reaction (L=cod, MeCN, alkyne)

A pathway may be considered which involves a double regioselective alkyne insertion followed by a stereoselective cyclisation to undergo a novel [3+2+2]-cyclisation. These examples illustrate the scope in which the reactivity of Fischer carbene complexes can be tuned in a qualitative manner by transmetalation.

9
Total Synthesis

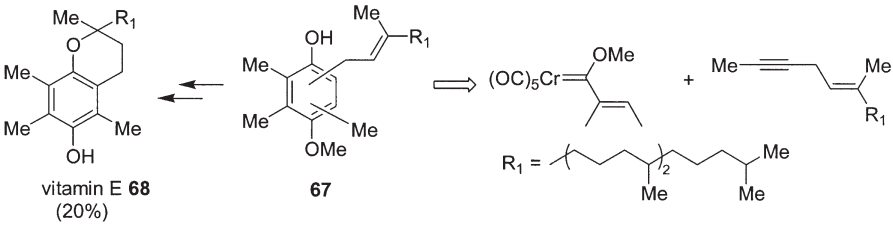
9.1
Vitamins

The fact that pentacarbonyl carbene complexes react with enynes in a chemoselective and regiospecific way at the alkyne functionality was successfully applied in the total synthesis of vitamins of the K_1 and K_2 series [58]. Oxidation of the intermediate tricarbonyl(dihydrovitamin K) chromium complexes with silver(I) oxide afforded the desired naphthoquinone-based vitamin K compounds **65**. Compared to customary strategies, the benzannulation reaction proved to be superior as it avoids conditions favouring (*E*)/(*Z*)-isomerisation within the allylic side chain. The basic representative vitamin K_3 (menadione) **66** was synthesised in a straightforward manner from pentacarbonyl carbene complex **1** and propyne (Scheme 38).



Scheme 38 Metal carbene approach to vitamins K_1, K_2 and K_3

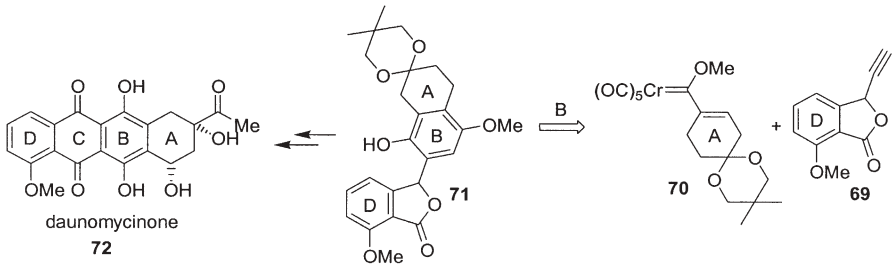
Encouraged by the short synthesis of K vitamins, the chromium-mediated benzannulation was extended to the synthesis of vitamin E **68** [59]. The problem of imperfect regioselectivity of alkyne incorporation – which did not hamper the approach to vitamin K due to the final oxidation to the quinone – was tackled by demethylation of both regioisomeric hydroquinone monomethyl ethers **67** to give the unprotected hydroquinone. Subsequent ring closure yielded α-tocopherol (vitamin E) **68** (Scheme 39).



Scheme 39 Metal carbene approach to vitamin E

9.2 Antibiotics

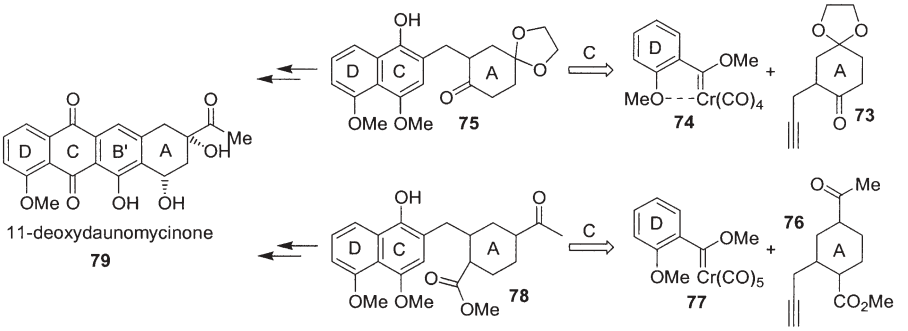
Daunomycinone **72**, one of the clinically important agents in cancer chemotherapy, is a member of the anthracycline familiy of antitumour antibiotics. The 11-deoxy analogue **79** is of current interest due to an improved therapeutic index. The common structure of this family of antibiotics is a linear tetracyclic skeleton containing a quinone C ring attached to a hydroquinone B ring (for daunomycinone) or a phenol B′ ring (for 11-deoxydaunomycinone). Both ring B and ring C can be constructed via benzannulation [60a,b]. The key step of the ring B approach involves the reaction of the ethynyl lactone **69** and the cyclohexenyl(ketal)carbene complex **70** which provides the tetrahydronaphthol **71** in 72–76% yield [60a,b] (Scheme 40).



Scheme 40 Benzannulation towards daunomycinone based on ring B formation

Replacing a hydroxy group in daunomycinone by a hydrogen atom leads to 11-deoxydaunomycinone **79**. However, this formally simple transformation affords a fundamental change of the synthetic strategy. Two very similar syn-

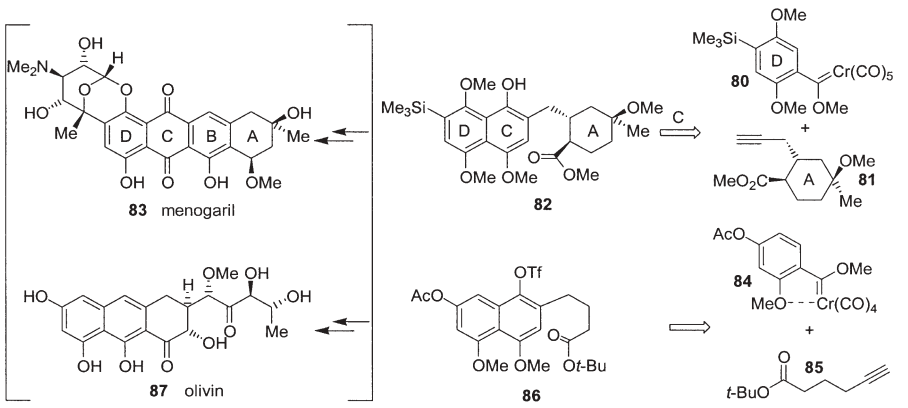
theses with the benzannulation reaction as the key step were developed by Dötz and Wulff [60c–f]. In both cases the carbene complex **77** reacts with a propargylic cyclohexane derivative **73** or **76** to give naphthol **75** and **78**, respectively (Scheme 41). The metal carbene chelate **74** generated by decarbonylation of pentacarbonyl complex **77** readily undergoes opening of the chelate ring and, thus, allows the formation of the alkyne complex intermediate under mild conditions resulting in improved yields. The final B ring closure was effected by Friedel–Crafts cyclisation in an acidic medium.



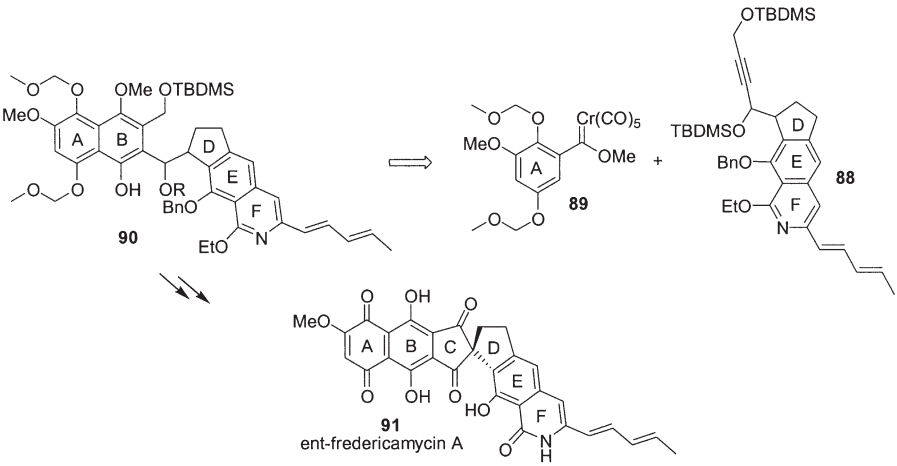
Scheme 41 Ring C benzannulation strategy to 11-deoxydaunomycinone

A similar synthetic strategy was applied in the synthesis of menogaril **83**, another important anthracycline antitumour antibiotic, and to the synthesis of the tricyclic core of olivin **87**, the aglycon of the antitumour antibiotic olivomycin [61, 62]. In both cases a tandem benzannulation/Friedel–Crafts cyclisation sequence yielded the tetracyclic and tricyclic carbon core, respectively (Scheme 42).

Intensive studies towards the total synthesis of fredericamycin A **91** culminated in the enantioselective synthesis of this potent antitumour antibiotic [63].

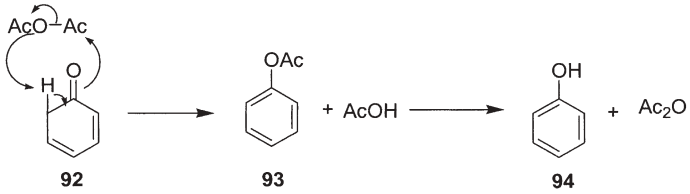


Scheme 42 Studies towards the synthesis of menogaril and olivin



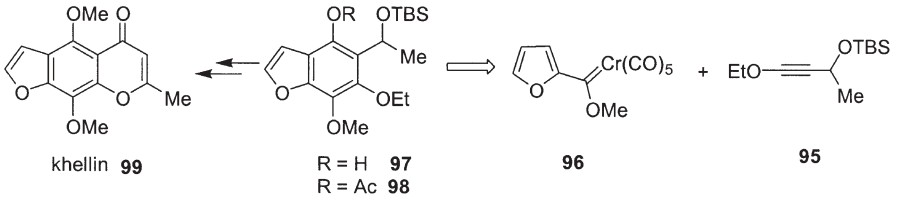
Scheme 43 Total synthesis of fredericamycin A (R=TBDMS)

The convergent approach comprises, among other reaction steps, a regiospecific intermolecular benzannulation reaction between the alkyne **88** and the chromium carbene complex **89** for AB ring construction (Scheme 43). It is noteworthy that the regioselectivity of this reaction is attributed to the bulky TBDMS ether in the alkyne α-substituent, that dictates the incorporation of the large substituent *ortho* to the phenol. Another curiosity is the fact that the reaction failed to provide **90** in the absence of acetic anhydride.



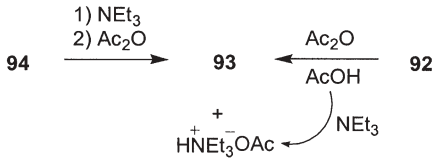
Scheme 44 The role of acetic anhydride in the aromatisation of cyclohexadienone

A plausible pathway is that the aromatisation of the cyclohexadienone **92** by a proton shift is accelerated in the presence of Ac_2O under formation of acetate **93**. The simultaneously generated acetic acid then cleaves the acetate to form the free phenol **94** (Scheme 44). This effect was observed for the first time during studies towards the total synthesis of the lipid-alternating and anti-atherosclerotic furochromone khellin **99** [64]. The furanyl carbene chromium complex **96** was supposed to react with alkoxyalkyne **95** in a benzannulation reaction to give the densely substituted benzofuran derivative **97** (Scheme 45). Upon warming the reaction mixture in tetrahydrofuran to 65 °C the reaction was completed in 4 h, but only a dimerisation product could be isolated. This



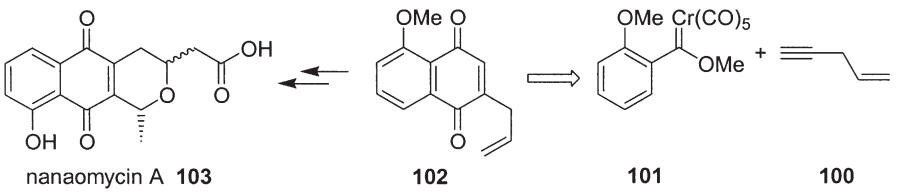
Scheme 45 Total synthesis of khellin

dimer formation was suppressed by in situ protection. When the benzannulation reaction was carried out in the presence of acetic anhydride and triethylamine, the benzofuran acetate **98** was formed in 43% isolated yield; in the absence of triethylamine the unprotected benzofuran **97** was isolated in 36% yield. Triethylamine is not only supposed to deprotonate the phenol intermediate **94**, but also to neutralise the acetic acid formed in an alternative pathway in order to avoid the cleavage of the acetate-protected phenol **93** (Scheme 46).



Scheme 46 The role of triethylamine in acetylation and aromatisation

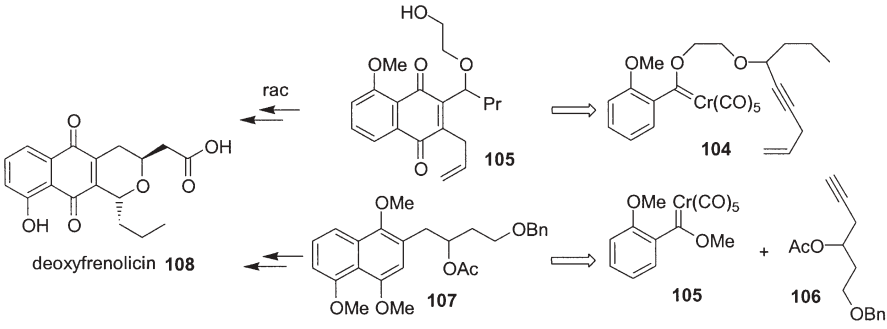
Nanaomycin A **103** and deoxyfrenolicin **108** are members of a group of naphthoquinone antibiotics based on the isochroman skeleton. The therapeutic potential of these natural products has attracted considerable attention, and different approaches towards their synthesis have been reported [65, 66]. The key step in the total synthesis of racemic nanaomycin A **103** is the chemo-and regioselective benzannulation reaction of carbene complex **101** and allylacetylene **100** to give allyl-substituted naphthoquinone **102** after oxidative workup in 52% yield [65] (Scheme 47). The allyl functionality is crucial for a subsequent intramolecular alkoxycarbonylation to build up the isochroman structure. However, modest yields and the long sequence required to introduce the



Scheme 47 Benzannulation approach to nanaomycin A

hydroxy group in the C3 position, which is the other component in the alkoxycarbonylation, reduces the attractiveness of this benzannulation approach.

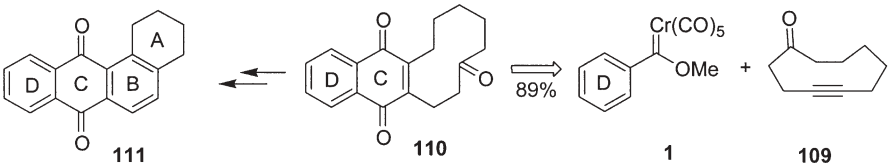
For that reason an intramolecular benzannulation was developed, which incorporates all components for the intramolecular alkoxycarbonylation into the naphthoquinone **105** [65]. Based on that strategy a short and convergent pathway for the synthesis of racemic deoxyfrenolicin **108** was accomplished. Xu et al. replaced the allylacetylene **100** in the reaction sequence for nanaomycin A by alkynoate **106.** The benzannulation product **107** was an appropriate precursor for a subsequent tandem oxa-Pictet–Spengler cyclisation/DDQ-induced coupling reaction [66]. Following this strategy the total synthesis of enantiomerically pure deoxyfrenolicin could be accomplished (Scheme 48).



Scheme 48 Benzannulation approach to deoxyfrenolicin

The synthesis of the naphthalene rings found in the gilvocarcin group and in the rubromycin class of natural products via benzannulation was also reported. Both classes show promising antitumour activity [67, 68].

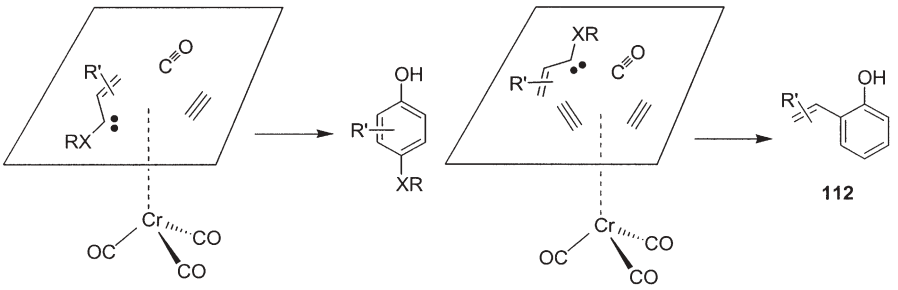
Danishefsky et al. succeeded in preparing the benz[*a*]anthracene core structure **111** of angucycline antibiotics by performing a benzannulation reaction with the cycloalkynone **109** [69]. Deprotonation of the naphthoquinone **110** with DBU yields the desired anthraquinone **111** (Scheme 49).



Scheme 49 Synthesis of the benz[*a*]anthracene core structure

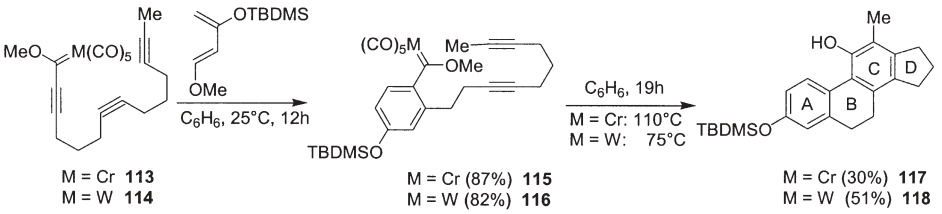
9.3 Steroids

The benzannulation reaction with small alkynes such as 1-pentyne may generate a two-alkyne annulation product. In this case the original [3+2+1]-benzannulation is changed to a [2+2+1+1]-benzannulation. After CO dissociation and insertion of the first alkyne, the coordinated α,β-unsaturated moiety in the vinylcarbene complex is supposed to be replaced by the second alkyne. The subsequent reaction steps give the phenol **112** (Scheme 50).



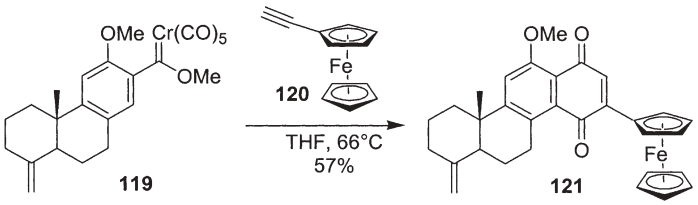
Scheme 50 [3+2+1]- and [2+2+1+1]-benzannulation

The selectivity for two-alkyne annulation can be increased by involving an intramolecular tethering of the carbene complex to both alkynes. This was accomplished by the synthesis of aryl-diynecarbene complexes **115** and **116** from the triynylcarbene complexes **113** and **114**, respectively, and Danishefsky's diene in a Diels–Alder reaction [70a]. The diene adds chemoselectively to the triple bond next to the electrophilic carbene carbon. The thermally induced two-alkyne annulation of the complexes **115** and **116** was performed in benzene and yielded the steroid ring systems **117** and **118** (Scheme 51). This tandem Diels–Alder/two-alkyne annulation, which could also be applied in a one-pot procedure, offers new strategies for steroid synthesis in the class O→ABCD.



Scheme 51 Synthesis of the steroid skeleton via [2+2+1+1]-benzannulation

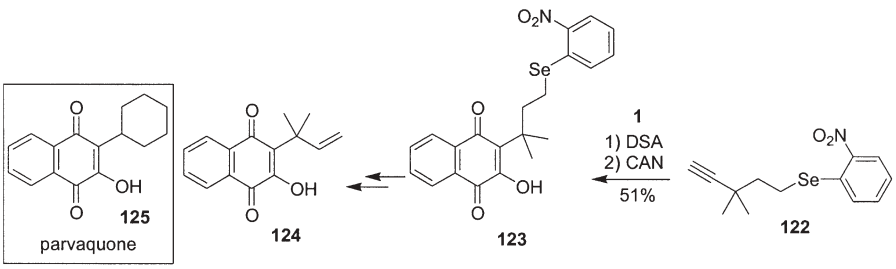
The benzannulation reaction of ethynylferrocene **120** with the diterpenoid chromium alkoxycarbene **119** leads to novel diterpenoid ferrocenyl quinones **121** which, due to their electron-transfer properties, are regarded as potential candidates for non-linear optical materials [71] (Scheme 52).



Scheme 52 Synthesis of fused ferrocenyl quinones

9.4
Insecticides

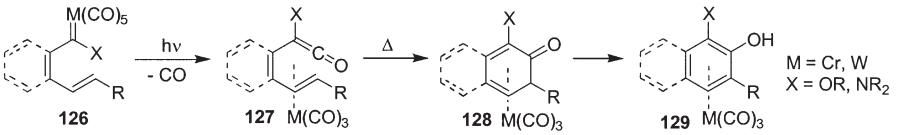
Two very short and elegant syntheses of the antiparasitic agent parvaquone **125** and the insecticide **124** isolated from Scrophulariaceae were developed using the dry-state absorption protocol [72, 73] (Scheme 53).



Scheme 53 Total synthesis of insecticides

10
Various Benzannulation Protocols

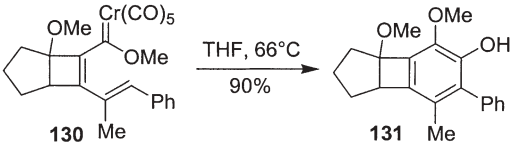
Merlic et al. were the first to predict that exposing a dienylcarbene complex **126** to photolysis would lead to an *ortho*-substituted phenolic product **129** [74a]. This photochemical benzannulation reaction, which provides products complementary to the classical *para*-substituted phenol as benzannulation product, can be applied to (alkoxy- and aminocarbene)pentacarbonyl complexes [74]. A mechanism proposed for this photochemical reaction is shown in Scheme 54. Photoactivation promotes CO insertion resulting in the chromium ketene in-



Scheme 54 Complementary benzannulation via photoactivation of carbonyl ligands

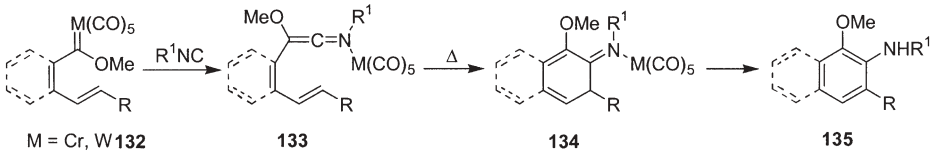
termediate **127**. Subsequent thermal electrocyclisation and keto–enol tautomerisim provides *ortho*-(alkoxy or amino)phenols such as **129**.

A similar substitution pattern can be obtained by applying a thermal protocol as well [75]. *Ortho*-methoxyphenol **131** has been synthesised in good yields by warming the cyclobutene-containing 1,3,5-metallatriene **130** in tetrahydrofuran (Scheme 55).



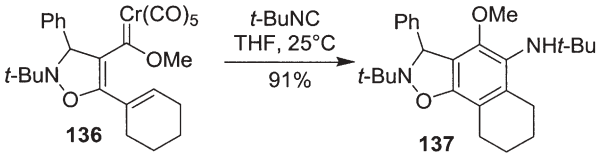
Scheme 55 Thermal benzannulation protocol to *ortho*-alkoxyphenols

Merlic developed a new variation of the thermally induced benzannulation reaction. The dienylcarbene complex **132** was reacted with isonitrile to give an *ortho*-alkoxyaniline derivative **135** [76] (Scheme 56). This annulation product is regiocomplementary to those reported from photochemical reaction of chromium dienyl(amino)carbene complexes. The metathesis of the isocyanide with the dienylcarbene complex **132** generates a chromium-complexed dienylketenimine intermediate **133** which undergoes electrocyclisation. Final tautomerisation and demetalation afford the *ortho*-alkoxyaniline **135**.



Scheme 56 Thermal benzannulation protocol to *ortho*-alkoxyanilines

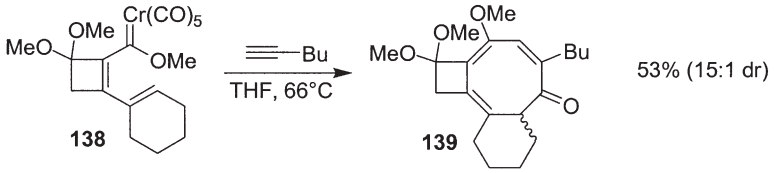
Based on this synthetic strategy an efficient method for the synthesis of 2,3-dihydro-1,2-benzisoxazoles **137** and indazoles was elaborated [77a] (Scheme 57).



Scheme 57 Synthesis of 2,3-dihydro-1,2-benzisoxazoles

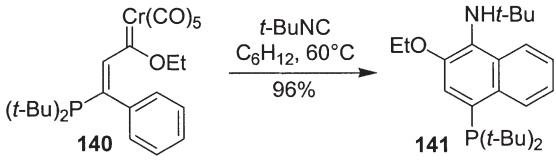
The cyclobutene-containing 1,3,5-metallatriene **130** also reacts with an isocyanide to give the regiocomplementary product [77b], but if the isocyanide is exchanged for a terminal alkyne the course of the reaction is fundamentally changed and a cyclooctatrienone **139** is formed [78] (Scheme 58). The incor-

poration of the alkyne occurs regioselectively, and a new stereogenic centre is formed during the reaction with high diastereoselectivity. This reaction might be considered as a new variant of the [3+2+1]-benzannulation reaction which involves insertion of both the alkyne and a carbon monoxide ligand. The participation of the additional double bond in the electrocyclic ring closure is responsible for the formation of the eight-membered carbocycle formed in an eight-electron cyclisation.



Scheme 58 Formation of eight-membered carbocycles

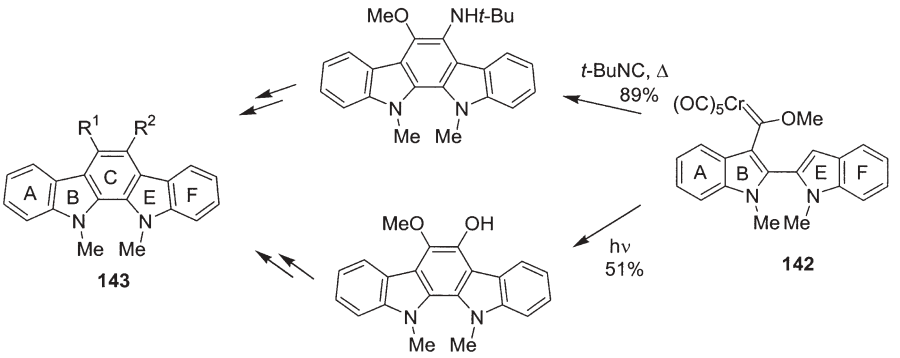
1-Amino-2-ethoxy-4-phosphinonaphthalene **141** is obtained from the (*E*)-arylalkenylcarbene complex **140** and *tert*-butyl isocyanide under mild conditions [79] (Scheme 59). The required substrate **140** is generated from a Michael-type addition of a secondary phosphine to an alkynylcarbene complex.



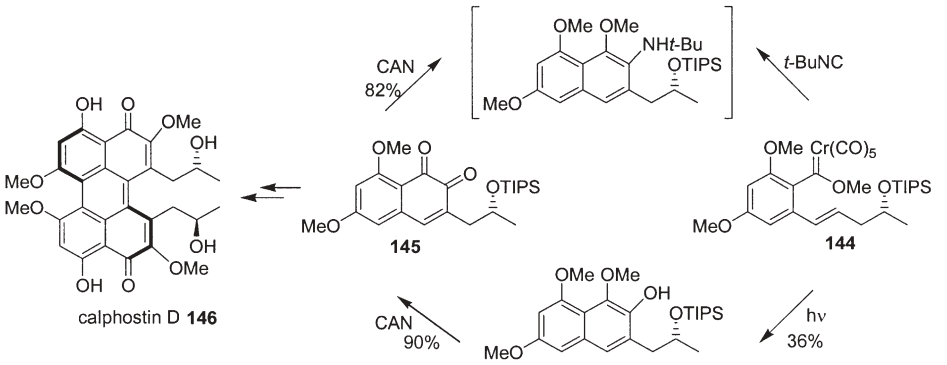
Scheme 59 Synthesis of phosphinonaphthalenes

These two examples of modified benzannulation reactions were successfully applied to the preparation of analogues of indolocarbazole natural products **143** and the total synthesis of calphostins **146.** The indolocarbazoles **143** have emerged as an important structural class revealing considerable biological activity including antitumour properties. Complementary thermal and photochemical protocols were applied to 2,2′-bisindolyl chromium carbene complexes **142** – which may be regarded as aromatic analogues of dienyl carbene complexes – in order to establish the ABCEF ring system which represents the central core of indolocarbazole alkaloids [80] (Scheme 60).

In the total synthesis of the protein kinase C inhibitors calphostins **146**, the *ortho*-substituted intermediates, which are either obtained from photolysis or from reaction of the dienyl carbene complex **144** with *tert*-butyl isocyanide, were oxidised to yield the 1,2-benzoquinone **145** as a common product [81] (Scheme 61).



Scheme 60 Synthesis of indolocarbazole alkaloids



Scheme 61 Complementary thermal and photochemical synthesis of calphostins

11
Final Remarks

The development of the chromium-mediated benzannulation reaction over the past 35 years demonstrates the potential of transition metals in the elaboration of unprecedented reactions. Metals are able to coordinate a variety of organic substrates in a predictable geometry primarily determined by their nature and by their oxidation state. They may act as templates which activate and fix the ligands in an orientation favourable for interligand coupling. The broad and fundamental knowledge of organometallic complexes accumulated over the last half century remains a promising fishing area for the discovery of novel reactions attractive for organic synthesis.

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