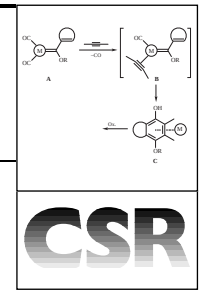
Annulation reactions of chromium carbene complexes: scope, selectivity and recent developments



K. H. Dötz* and P. Tomuschat

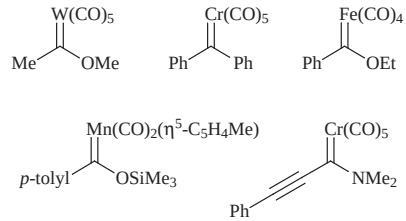
Kekulé-Institut für Organischen Chemie und Biochemie der Universität Bonn, Gerhardt-Domagk-Straße 1, D-53121 Bonn, Germany

Received 19th February 1998

Over the past three decades Fischer-type carbene complexes have received increasing interest as selective reagents in organic synthesis. Apart from its electron-acceptor properties exploited in carbene ligand centered reactions, the metal carbonyl fragment provides a template for non-classical cycloaddition reactions. The most useful among them is the chromium-mediated benzannulation which allows a one-pot access to densely functionalized oxygenated arenes coordinated to a $Cr(CO)_3$ fragment. It is compatible with a variety of functional groups, occurs under mild conditions with remarkable chemo-, regio- and diastereoselectivity, and thus has considerable potential in the synthesis of complex targets and natural products.

1 Introduction

Metal carbenes $(CO)_nM{=}C(OR')R$, introduced by E. O. Fischer in 1964 as a novel class of compounds bearing a carbene stabilized by coordination to a metal carbonyl fragment have been developed to provide valuable reagents in selective carbon–carbon bond formation over the last 2 decades.[1] They have been applied to either ligand-centered or metal-centered processes.[2] Representative examples of Fischer carbene complexes are shown in Scheme 1. The central carbene carbon is connected *via* a formal metal–carbon double bond to a low-valent Group VI to VIII transition metal. Typically, one carbene



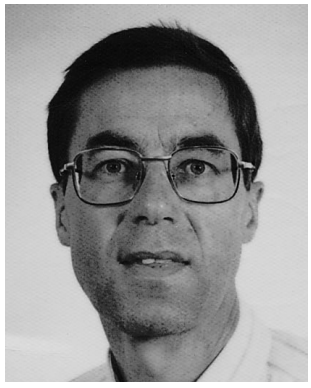
Scheme 1 Representative Fischer-type metal carbenes.

substituent acts as a π-donor which allows for an electronic stabilization of the electron-deficient carbene carbon atom, whereas the other carbene substituent may be either a saturated or an unsaturated group. The low-valent metal center is stabilized by π-acceptors such as carbon monoxide, phosphine or cyclopentadienyl ligands. The electrophilic nature of the metal coordinated carbene carbon, illustrated by remarkable downfield shifts of 250–400 ppm in the ^{13}C NMR spectra, reflects the isolobal nature of Fischer type metal carbenes and carboxylic acid derivatives and is exploited in both nucleophilic addition reactions and α-C–H acidity of alkyl side chains.

2 Synthesis of carbene complexes

The most general synthetic route to Fischer-type metal carbenes is based on the addition of an organolithium nucleophile to a

Karl Heinz Dötz was born in 1943 and received his PhD from the Technical University of Munich with Professor E. O. Fischer. He then moved towards the borderline between Inorganic and Organic Chemistry, focusing during his habilitation on the organic chemistry of metal carbenes which he applied to novel metal-assisted cycloaddition patterns. In 1986 he became Professor of Organometallic Chemistry at the University of Marburg. In 1992 he joined the University of Bonn where he was appointed Professor of Organic Chemistry and Co-Director of the Kekulé Institute. He held visiting appointments in Princeton and Paris, and is a recipient of the Victor Grignard–Georg Wittig Lectureship. His research interests concentrate on organometallic template reactions, stereoselective synthesis, asymmetric catalysis and on carbohydrate chemistry.

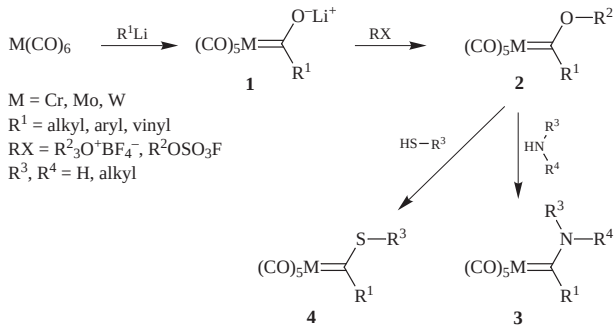


K. H. Dötz

Philipp Tomuschat, born in 1968, studied chemistry at the University of Bonn. He joined Professor Dötz's group and completed his Diploma Degree in 1995 with a research project on axial-chiral chromium biscarbenes. Currently, he is finishing his PhD Thesis. His research interests focus on synthetic challenges of chiral organometallic and organic compounds as well as their application in chiroptics, electrochemistry and asymmetric catalysis.

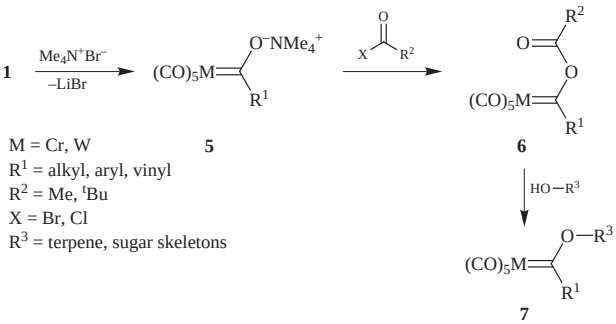
P. Tomuschat

metal carbonyl to give an acyl metalate **1** which undergoes subsequent *O*-alkylation by strong alkylating reagents such as trialkyloxonium salts, alkyl fluorosulfonates or alkyl trifluoromethanesulfonates to form alkoxycarbene complexes **2**. This strategy provides direct access to a great variety of carbene complexes and is only limited by the availibility of the organolithium compound. Treatment of alkoxycarbene complexes **2** with amine or thiol nucleophiles affords amino and thiol complexes **3** or **4** (Scheme 2).



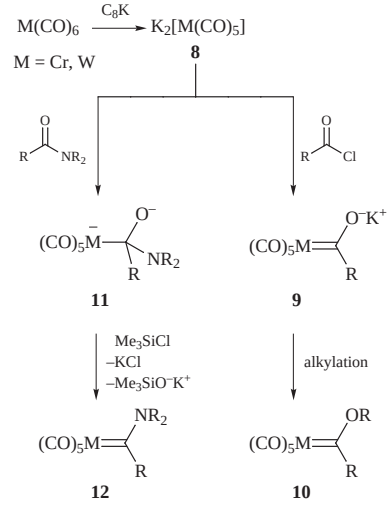
Scheme 2 Standard Fischer route to metal carbenes.

The addition of alcohols requires even more electrophilic acyloxycarbene complexes **6** accessible *via* acylation of ion-separated tetraalkylammonium acyl metalates **5**. This strategy allows the synthesis of more complex chiral metal carbenes **7** bearing terpene and sugar auxiliaries (Scheme 3).

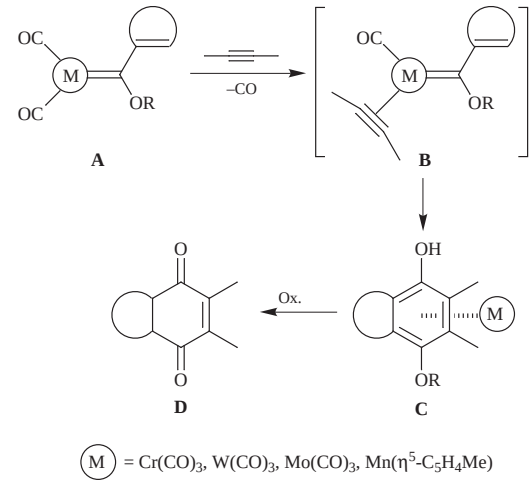


Scheme 3 Alcoholysis of acyloxy metal carbenes.

An alternative approach combining an organoelectrophile and a metal nucleophile has been developed by Hegedus and Semmelhack.[2] Reduction of the hexacarbonyl metal by the intercalation compound C_8K affords the pentacarbonyl dianion **8** which undergoes low-temperature addition to acid chlorides or carboxylic amides. Alkylation of acyl metalate **9** as described above generates alkoxycarbene complex **10** whereas TMSCl-assisted deoxygenation of the tetrahedral intermediate **11** affords aminocarbene complex **12** (Scheme 4).



Scheme 4 Hegedus–Semmelhack approach to alkoxy- and aminocarbene complexes.



Scheme 5 Benzannulation of carbene complexes.

3 Annulation reactions

3.1 Metal-centered annulation reactions—scope and limitations

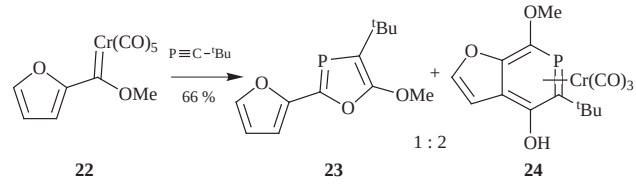
The most unique type of metal carbene reactions is the benzannulation of complexes **A** bearing unsaturated (aryl or vinyl) alkoxycarbene ligands by an alkyne and a carbon monoxide.[3] This process is most efficiently mediated by a $Cr(CO)_3$ template (**B**) and provides a one-pot access to densely substituted oxygenated arenes **C** which remain coordinated to the metal fragment (Scheme 5). Subsequent oxidative demetalation may be applied to generate the corresponding quinones **D**. Chromium is the metal template of choice for the benzannulation; it allows excellent chemo- and regioselectivity under mild conditions (*tert*-butyl methyl ether, 50 °C). Other transition metal templates (Mo, W, Mn) have been used in isolated cases but generally suffer from modest chemoselectivity and harsher reaction conditions. For instance, molybdenum carbenes favour the cocyclization of carbene, carbonyl and alkyne ligands to give furans in moderate yields;[4] the increased thermostability of the tungsten homologues results in the formation of relevant amounts of formal [3+2]cycloaddition products without incorporation of the carbonyl ligand. Application of a η^5-cyclopentadienylmanganese template requires additional electrophilic activation in terms of a titaniumoxycarbene ligand under more drastic thermal (or photochemical) conditions to give only poor annulation yields.[5]

The chromium-mediated benzannulation is compatible with a broad substitution pattern both in the alkyne and in the unsaturated carbene side chain.[6] Aryl carbene complexes with methoxy, methyl or trifluoromethyl substituents in the *ortho*-, *para*-, or *meta*-position work as well as naphthyl and heteroaryl carbene complexes derived from furans, thiophenes, pyrroles, pyrazoles and indoles. Vinyl carbene complexes have been studied extensively bearing alkyl substituents (and in a few cases oxygen and silicon substituents) in a variety of cyclic and acyclic systems.

The benzannulation has been reported to give moderate to excellent yields with alkynes bearing aryls, esters, lactones,

ketones, amides, acetals, α-ethers, enol ethers, sulfides, tosylates and nitrile groups. However, only moderate yields are observed with alkynes bearing electron withdrawing groups such as conjugated carbonyl groups as pointed out in the reaction of carbene complex **13** with the alkynyl ketone to give **14** in 42% or with the alkynyl ether to give **15** in 54% (Scheme 6).[7] The even more electron-deficient hexafluorobutyne is inert towards chromium carbene **13**. The bifunctionality of alkynols results in a competition of benzannulation and lactonization. For instance, the reaction of **16** with but-3-yn-1-ol affords the ketene intermediate **17** which either may undergo 6π electrocyclization to the benzannulation product **18** or addition of the alcohol nucleophile to the ketene to give lactone **19**.[8] Direct substitution of the alkyne with oxygen increases the nucleophilicity of the C≡C bond and reduces the yield of the annulation product; the more nucleophilic enamines undergo insertion into the metal–carbon bond to give C_2-homologous aminocarbene complexes.[9] Sterically overcrowded alkynes such as bis-(trimethylsilyl)acetylene prevent the final electrocyclization step, and stable vinyl ketenes, *e.g.* **20** and **21**, result from the benzannulation attempt[10] (Scheme 6).

The extension from alkynes to "heteroalkynes" is limited; as a rare example, the kinetically stabilized *tert*-butylphosphaethyne which exhibits an alkyne-like coordination chemistry has been incorporated into furanophosphahydroquinone **24** along the reaction with 2-furylcarbene complex **22**; a side-reaction based on a competing ligand coupling process results in the formation of the 1,3-oxaphosphole **23** as the minor product[11] (Scheme 7).

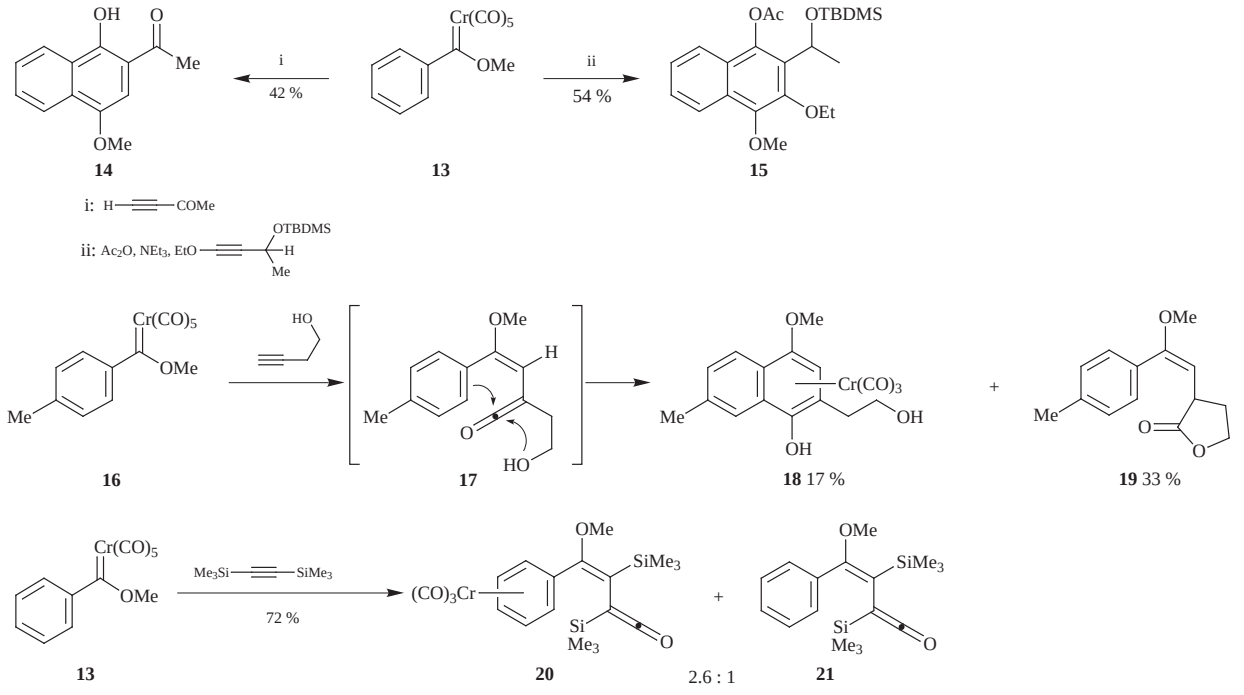


Scheme 7 Hetero-benzannulation with phosphaalkynes.

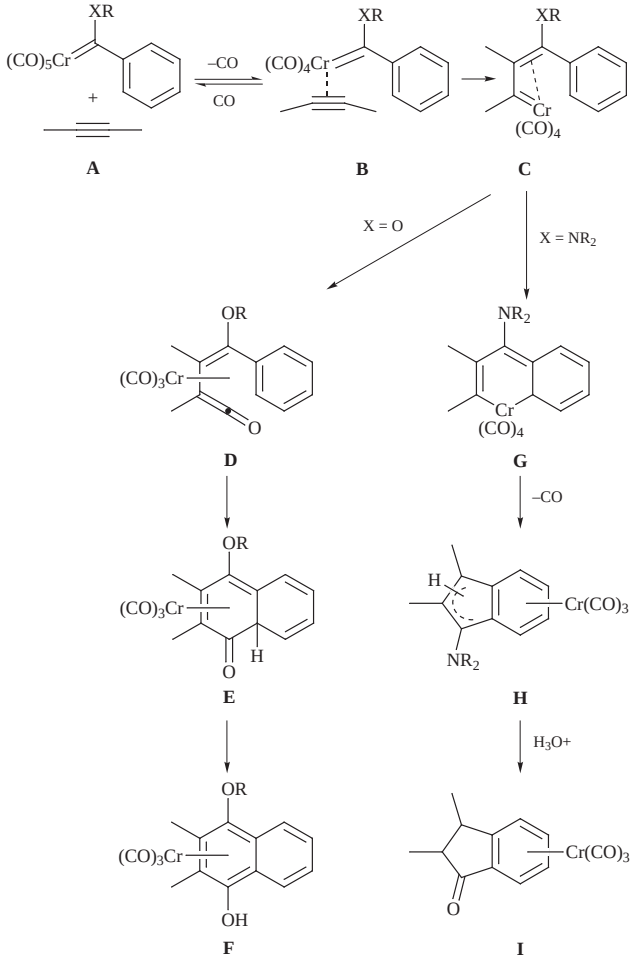
3.2 Mechanism of the benzannulation

The benzannulation is supposed to involve a stepwise alkyne–carbene–carbon monoxide coupling sequence occurring at the $Cr(CO)_3$ template (Scheme 8). The mechanism has been supported both by kinetic studies and the isolation of presumed model intermediates.[12] An early kinetic investigation[13] and the observation that the reaction of the metal carbene with the alkyne is suppressed in the presence of external carbon monoxide demonstrated that the rate-determining step is a reversible decarbonylation of carbene complex **A** followed by coordination of the alkyne to form the η^2-alkyne–carbene complex intermediate **B**. Extended Hückel calculations[14] together with structural studies on η^2-alkyne carbene complex analogues[15] indicate only a weak metal–alkyne interaction. Subsequent insertion of the alkyne into the metal–carbene bond generates η^3-allylidene complex **C**. A stable analogue of this type of complex has been isolated as the decarbonylation product of a chromium pentacarbonyl aminovinylcarbene complex precursor and characterized by NMR and X-ray analysis. Depending on the electron-donation ability of the α-heteroatom the reaction may follow two different pathways. In the alkoxycarbene series the subsequent insertion of carbon monoxide results in the formation of the η^4-vinyl ketene complex intermediate **D**, a stable analogue of which has been characterized in the case of enaminoketene complexes. Electrocyclic ring closure affords the cyclohexadienone complex **E** which tautomerizes to give the $Cr(CO)_3$-coordinated hydroquinone **F**. An arrested cyclohexadienone complex has been isolated in the molybdenum series. In accordance with the experimental results the mechanism has been supported by DFT calculations.[16]

Due to the superior donor properties of amino groups over alkoxy substituents aminocarbene complexes require harsher conditions for the primary decarbonylation step. Similarly, the CO insertion to give the vinyl ketene intermediate **D** is hampered and cannot compete successfully with an electrocyclization of amino-substituted η^3-allylidene complex intermediate **C** which results in the formation of chromacyclohexadiene intermediate **G**. Reductive elimination and metal migration afford aminoindene complex **H** which may be hydrolized upon chromatographic workup to give indanone complex **I** as the final cyclopentannulation product.



Scheme 6 Limitations of the benzannulation reaction.



Scheme 8 Suggested mechanism for the chromium-mediated benzannulation and cyclopentannulation.

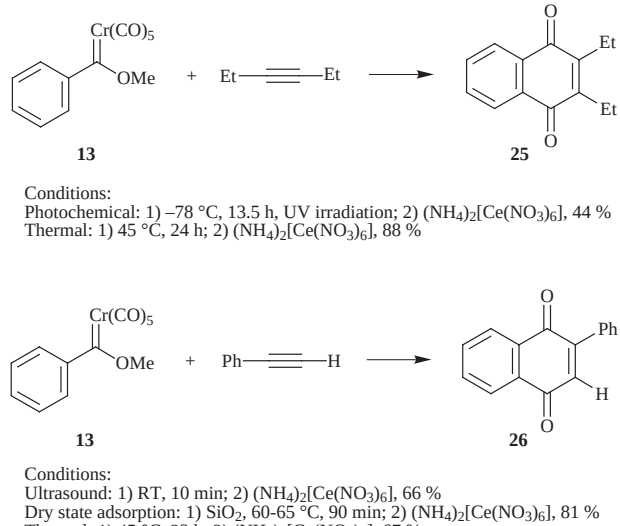
3.3 Experimental methodology

The standard protocol for the benzannulation involves a thermal decarbonylation carried out in an ethereal solvent, *e.g. tert*-butyl methyl ether or tetrahydrofuran, at 45–65 °C. Reflux conditions favour the removal of evolved carbon monoxide and speed up the reaction. An alternative photodecarbonylation allows low-temperature conditions; however, as a consequence of the photosensitive intermediates photoinduced benzannulations generally proceed less cleanly and selectively[17] and, thus, have gained synthetic importance only in cases where the thermal protocol fails.[18] A few examples have been reported in which the benzannulation has been promoted by high intensity ultrasound or carried out by dry state adsorption conditions.[19] These techniques may allow comparable yields within shorter reaction times as observed with the thermal protocol; however, they did not allow the isolation of $Cr(CO)_3$-coordinated hydroquinone annulation products (which—due to their inherent plane of chirality—are promising reagents for stereoselective synthesis, *vide infra*) and, instead, led to quinones after oxidative workup as shown for the benzannulation of complex **13** to give **25** and **26** (Scheme 9).

4 Selectivity

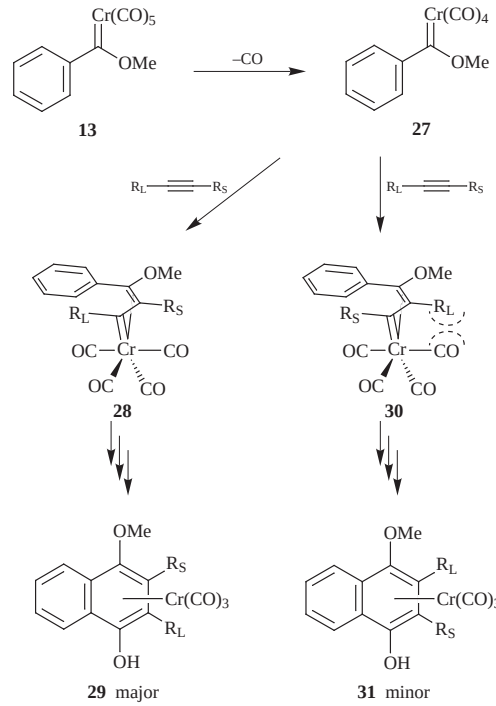
4.1 Regiochemistry

When the benzannulation is carried out with unsymmetrical alkynes the major regioisomer generally bears the larger alkyne substituent next to the phenolic group suggesting that the



Scheme 9 Comparison of benzannulation protocols.

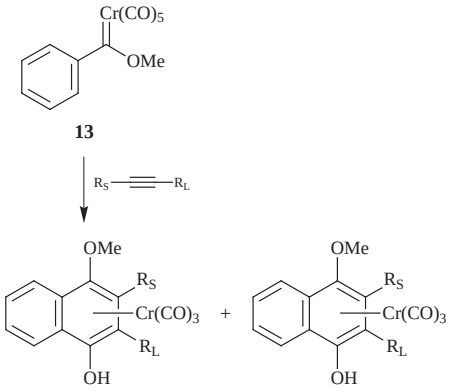
regioselectivity is mainly governed by the different steric demands of both alkyne substituents (Scheme 10).[3] This result



Scheme 10 Regioselective alkyne incorporation.

can be rationalized in terms of the minimization of the repulsive steric interaction between the alkyne substituents and the carbonyl ligands of the metal fragment in the insertion product **28** compared with its regioisomer **30**. This argument takes into account the fact that the smaller alkyne substituent R_S is closer to the apical CO ligand than the larger R_L is to the equatorial CO ligand.[14] Subsequent CO insertion of the η^3-allylidene complexes, electrocyclization and tautomerization afford naphthol **29** as the major and naphthol **31** as the minor annulation product.

Synthetically useful regioselectivities are encountered with terminal alkynes which give a single regioisomer whereas unsymmetrical internal alkynes generally afford regioisomeric mixtures. The regioselectivity is lost with diarylalkynes bearing two differerent *para*-substituents.[20] Scheme 11 demonstrates the distribution of both regioisomers **32** and **33** resulting from the benzannulation of **13** with some unsymmetrical alkynes.



32 a–d **33 a–d**

Entry	R_S, R_L	Ratio **32** : **33**
a	H, C_3H_7	100 : 0
b	CH_3, ^tBu	90 : 10
c	CH_3, C_2H_5	70 : 30
d	C_6H_5, *p*-$CH_3C_6H_4$	54 : 46

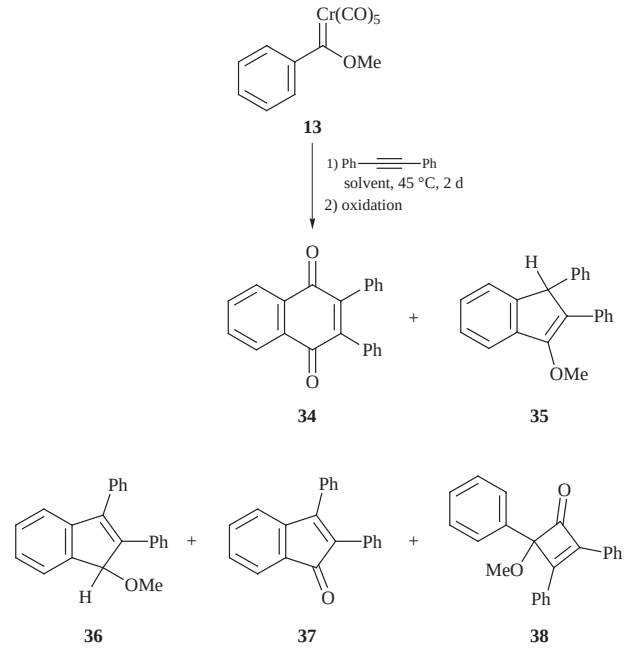
Scheme 11 Alkyne-dependent regioselectivity.

A complementary regiochemistry can be achieved exploiting a stannyl acetylene incorporation–deprotection strategy.[21]

4.2 Chemoselectivity

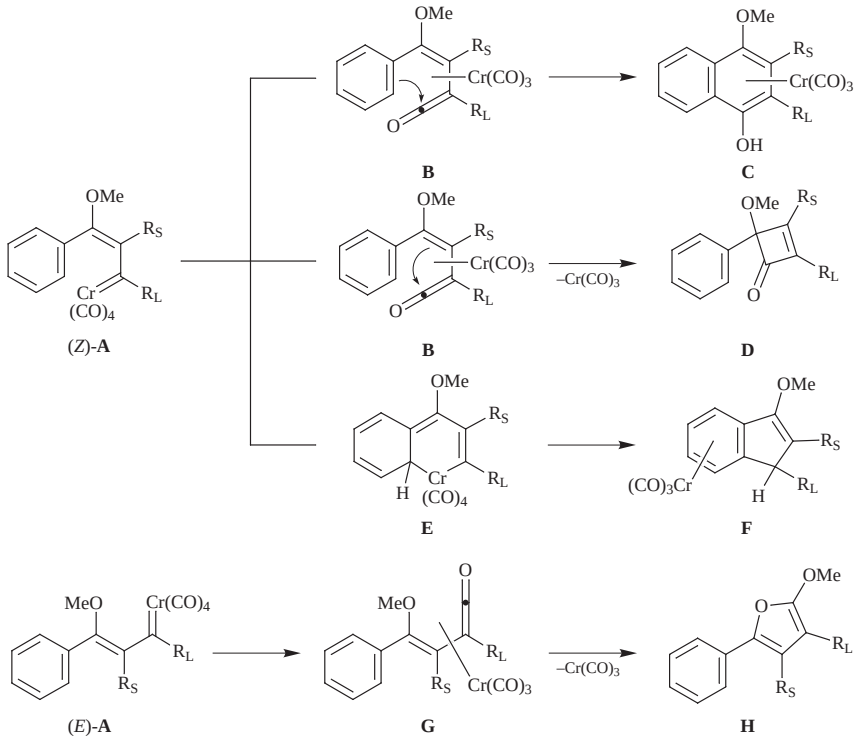
The η^3-allylidene intermediate (*Z*)-**A** formed upon alkyne insertion may give rise to the formation of various types of cyclization products. The benzannulation affords the most valuable product but has to compete with the formation of indenes and cyclobutenones. The competing pathways are outlined in Scheme 12. Insertion of CO generates the vinyl ketene complex **B** which—instead of 6π-benzannulation to **C**—may undergo a 4π-electrocyclization to give cyclobutenone **D**. Direct electrocyclic ring closure of **A** generates chromacyclohexadiene **E** which is regarded to afford the indene **F** after reductive elimination and tautomerization. A less obvious cyclization/alkyl migration sequence, starting from the (*E*)-isomer of **A**, is believed to be responsible for the formation of the furan skeleton **H**.[22]

The chemoselectivity depends on the nature of the metal template, the carbene substitution pattern and the reaction conditions. The role of the solvent and the alkyne concentration has been addressed[17] but no consistent results are available so far. The trends outlined in Scheme 13 indicate that donor solvents like ethers favour selective benzannulation whereas a



Solvent	**34**	**35** + **36** + **37**	**38**
THF	59	—	—
Hexane	41	38	—
CH_3CN	—	19	51
DMF	—	83	—

Scheme 13 Solvent-dependent chemoselectivity.

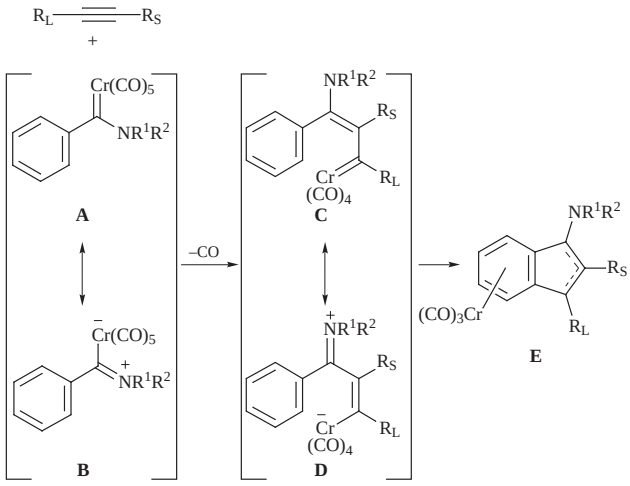


Scheme 12 Competitive benzannulation, cyclopentannulation, cyclobutenone and furan formation.

non-cordinating solvent (hexane) increases the amount of cyclopentannulation products for which a more polar solvent such as DMF is the medium of choice. Cyclobutenone **38** is the major product when the reaction of alkoxycarbene complex **13** with diphenylacetylene is carried out in strongly coordinating acetonitrile.

The competition of benzannulation and cyclopentannulation depends further on the concentration of metal carbene and alkyne as well as on the temperature.[17] An increase of the concentration and a decrease of the temperature favour benzannulation (which is best carried out at 45–65 °C) over cyclopentannulation.

The most striking influence on the competition between benzannulation and cyclopentannulation results from the donor ability of the heteroatom carbene side chain. The substitution of the alkoxy group for a better electron donor such as a dialkylamino group results in exclusive cyclopentannulation. Amino(aryl)carbene complexes of chromium react with alkynes at 125 °C to give indene derivatives **E** as formal [3+2] cycloaddition products without incorporation of CO (Scheme 14).[23] The increased temperatures required for the primary



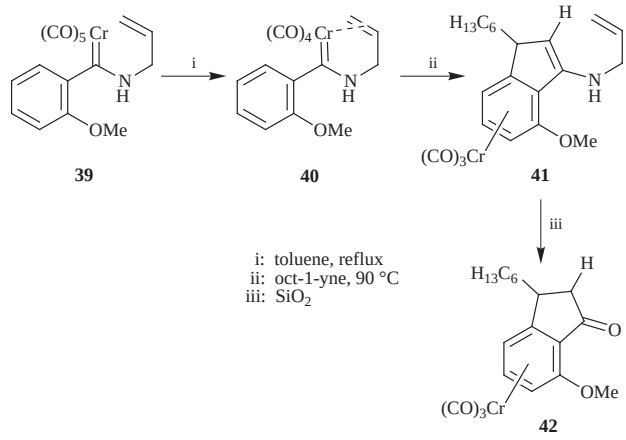
Scheme 14 Cyclopentannulation of aminocarbene complexes.

decarbonylation as well as the absence of CO incorporation reflect the increased back-donation from the metal to the carbonyl ligands as indicated by the resonance forms **A**–**D** describing the aminocarbene starting materials and the alkyne insertion intermediates.

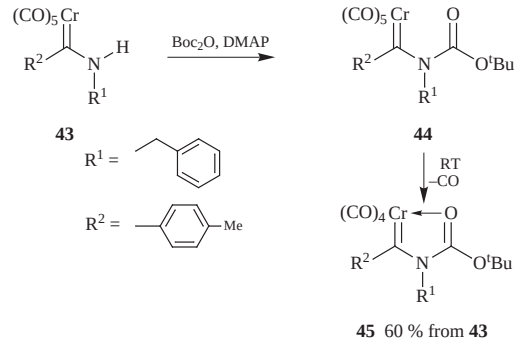
The cyclopentannulation reaction of aminocarbene complexes proceeds with similar high regioselectivity as observed for the benzannulation of chromium alkoxycarbenes. The aminocarbene chelate **40** accessible by decarbonylation from **39** in refluxing toluene reacts with oct-1-yne at 90 °C to give indene complex **41** as a single regioisomer; hydrolysis of the enamine upon chromatography on silica gel affords the indanone complex **42** as a single diastereomer bearing the alkyl substituent and the chromium fragment on the same face of the bicyclic skeleton. Obviously, ring-opening of the chelate **40** occurs under milder conditions than the decarbonylation of its pentacarbonyl precursor **39** (Scheme 15).[24]

The electron donating capability of the amino substituent can be reduced by *N*-acylation. Introduction of the Boc-group into carbene complex **43** generates the 'activated' aminocarbene **44**, the reactivity of which rather ressembles that of alkoxycarbene complexes. Decarbonylation occurs at room temperature to form the tetracarbonyl chelate complex **45** (Scheme 16).[24]

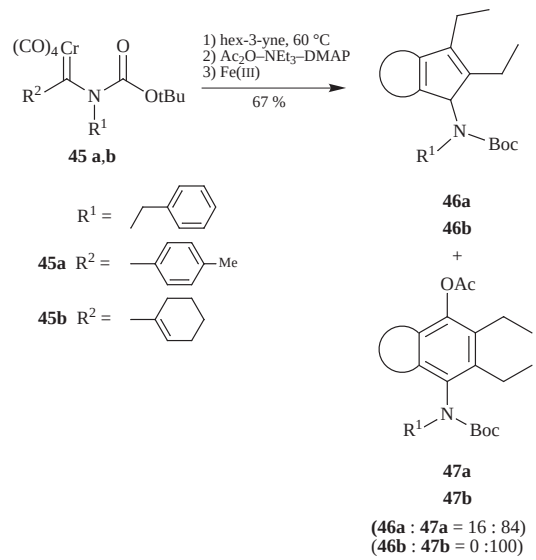
The annulation of tetracarbonyl acylaminocarbene complexes **45a,b** as demonstrated for hex-3-yne requires only moderate warming (60 °C) and reveals a competition between benzannulation and cyclopentannulation. Generally, the formation of six-membered rings prevails (**46a**/**47a** = 1:5) or is observed exclusively (**47b**) (Scheme 17).[24]



Scheme 15 Cyclopentannulation *via* allylaminocarbene chelate **40**.



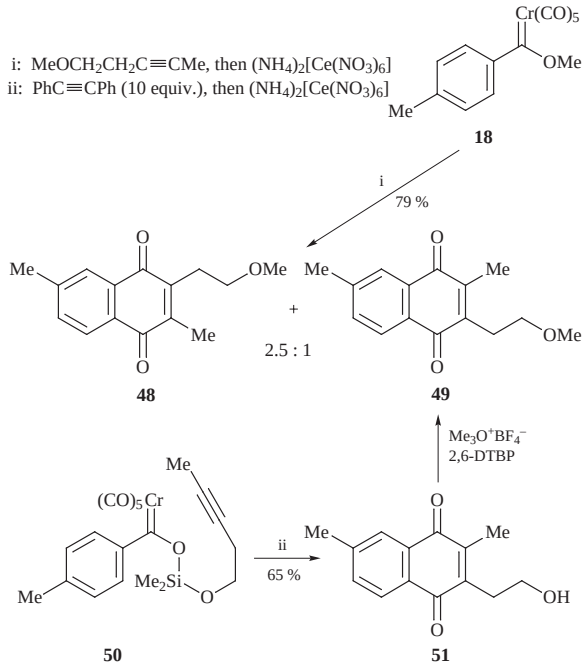
Scheme 16 Boc-activation of aminocarbene complexes.



Scheme 17 Control over competition between benzannulation and cyclopentannulation.

4.3 Intramolecular benzannulation

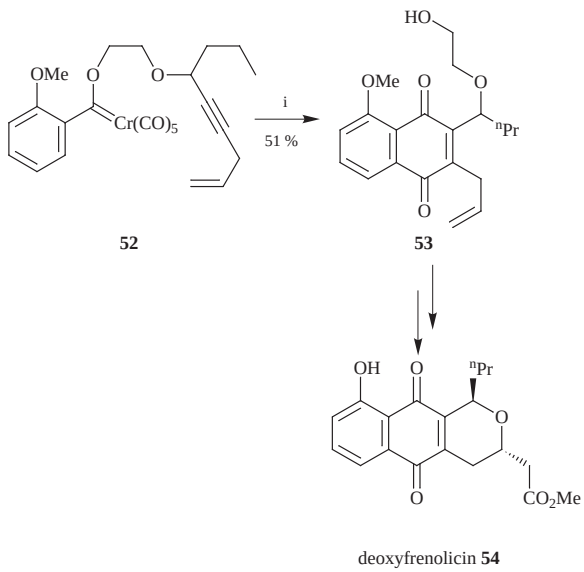
Carbene complexes bearing an alkyne side chain may undergo intramolecular benzannulation. This strategy may be exploited in a reversal of regioselectivity as demonstrated for unsymmetric dialkylalkynes (Scheme 18). Whereas upon reaction with 5-methoxypent-2-yne and oxidative workup benzannulation of



Scheme 18 Reversal of regiochemistry *via* intramolecular benzannulation.

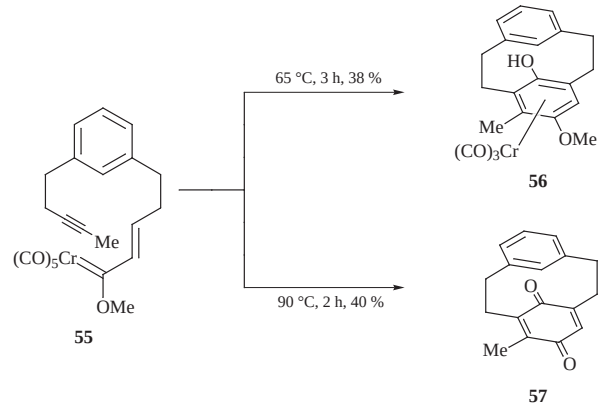
methoxycarbene complex **18** gives a 2.5:1 mixture of regioisomers in favour of the 2,6-dimethylnaphthoquinone **48**, the intramolecular variant based on a pent-2-ynyloxysilyloxycarbene complex bearing a silyl linker affords after methylation the 3,6-dimethylnaphthoquinone **49** as a single isomer.[25]

A similar linker-assisted intramolecular benzannulation has been applied to the synthesis of the naphthoquinone antibiotic deoxyfrenolicin **54**. The quinone ring is formed from the enyne carbene complex precursor **52** in perfect regiochemistry under mild conditions in refluxing ether. The final pyranoannulation was achieved by a palladium-promoted cyclization–carbonylation sequence (Scheme 19).[26]



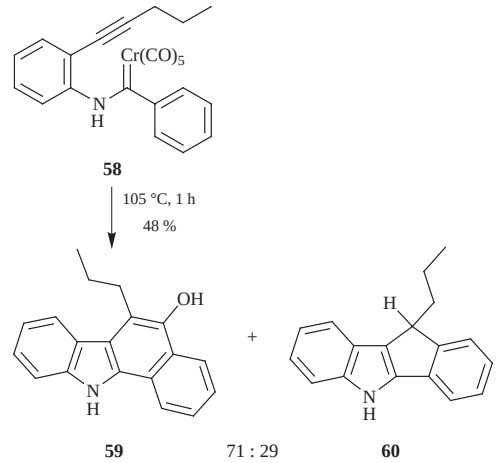
Scheme 19 Synthesis of deoxyfrenolicin *via* intramolecular benzannulation and palladium-assisted cyclization–carbonylation.

The intramolecular benzannulation may be also applied to the synthesis of strained aromatic systems such as [2.2]metacyclophanes. Cyclization of the alkyne–vinylcarbene complex **55** affords the $Cr(CO)_3$-coordinated [2.2]metacyclophane hydroquinone **56** (in which the chromium fragment is bound to the hydroquinone from the face opposite to the other benzene deck) which undergoes *in situ* or stepwise oxidation to give the planar-chiral cyclophane quinone **57** (Scheme 20).[27]



Scheme 20 Synthesis of planar-chiral [2.2]metacyclophane quinones *via* intramolecular benzannulation.

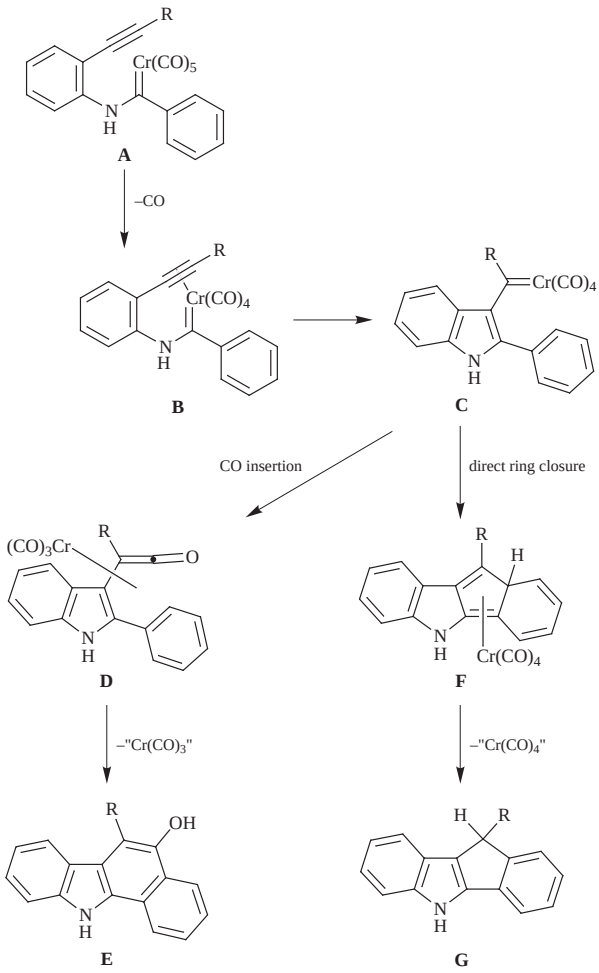
The (alkynylanilino)carbene chromium complex **58** bearing a rigid three atom spacer between the alkyne and the carbene moiety can react in an insertion–cyclization sequence to give a mixture of the benzo[*a*]carbazole **59** and the indeno[1,2-*b*]-indole **60**[28] (Scheme 21).



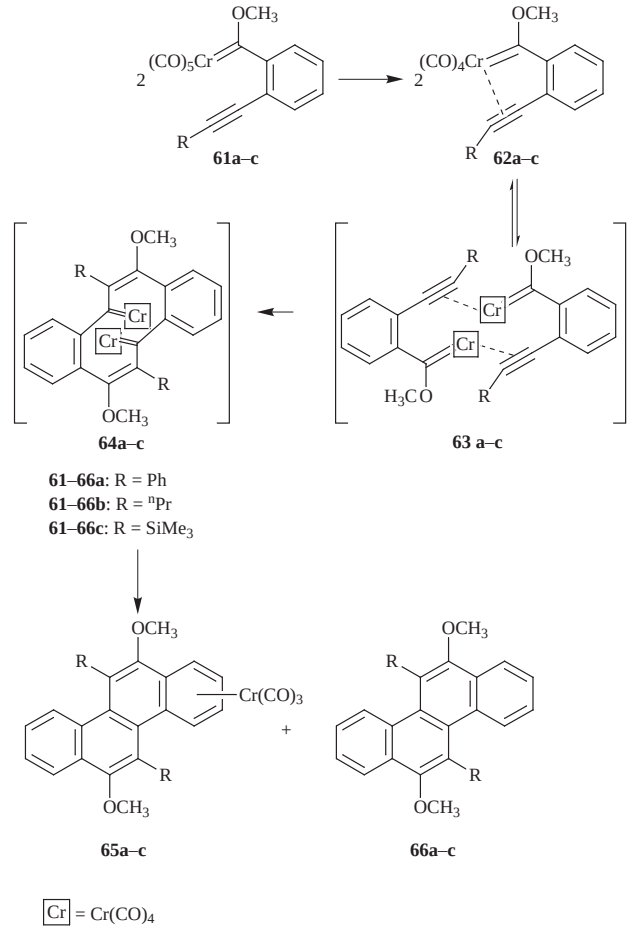
Scheme 21 Competitive formation of benzo[*a*]carbazole **59** and indeno-[1,2-*b*]indole **60**.

The two different reaction products are caused by two different reaction pathways as outlined in Scheme 22. Decarbonylation of the (alkynylanilino)carbene complex **A** affords the η^2-alkyne carbene complex intermediate **B** which undergoes subsequent alkyne insertion generating the pyrrole ring in carbene complex **C** intermediate; insertion of carbon monoxide results in the formation of the vinyl ketene intermediate **D** which cyclizes to the benzannulation product **E**. In contrast, direct ring closure of **C** affords the cyclopentannulation product **F** which finally gives **G** after tautomerization and loss of the metal fragment. The product distribution is governed by the steric demand of the alkyne substituent R. In the presence of the bulky mesitylene group as alkyne substituent exclusive benzannulation is observed.[29]

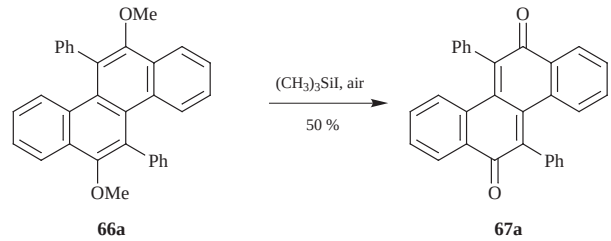
If, however, the linker between the alkyne and carbene functionalities is reduced to a rigid C_2-arene fragment the intramolecular insertion of the alkyne into the chromium carbene bond is kinetically blocked. Instead, an intermolecular reaction may occur resulting in a formal alkyne carbene dimerization to give densely oxygenated chrysene derivatives (Scheme 23).[15] The tetracarbonyl alkyne carbene chelates **62** accessible by low-temperature photodecarbonylation from their



Scheme 22 Suggested mechanism for the formation of benzo[*a*]carbazoles and indeno[1,2-*b*]indoles.



Scheme 23 Alkynylcarbene dimerization to chrysene derivatives.



Scheme 24 Synthesis of phenanthrenedione **67a**.

pentacarbonyl precursors **61** contain a weak metal–alkyne bond as suggested by their X-ray and ^{13}C NMR data. They are supposed to form metal-bridged dimers **63** which may undergo a double alkyne insertion to generate central ten-membered ring intermediates **64** bearing two opposite metal carbene fragments. The formation of chrysene derivatives **65** and **66** may be rationalized in terms of a final carbene dimerization and subsequent partial or complete demetalation.

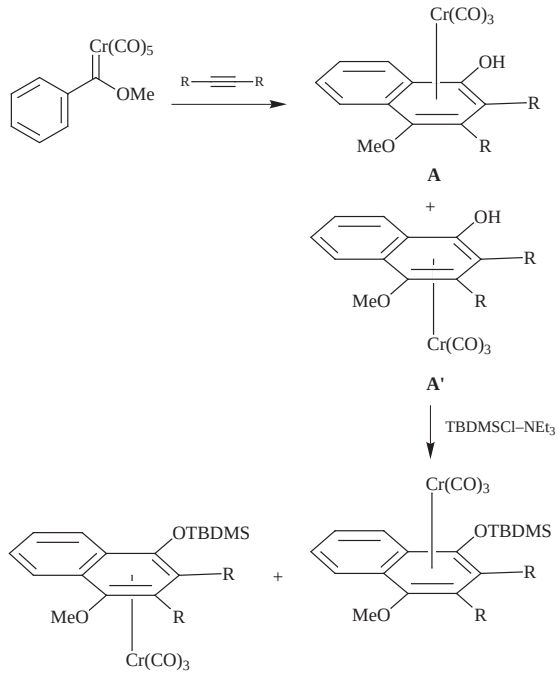
The *peri*-interaction between the substituents in positions 4,5 and 10,11 results in a steric repulsion which forces the aromatic skeleton to adopt a conformation twisted across the central arene C4b–C10b bond. As indicated by a comparative X-ray study the dihedral angle θ (C5–C4b–C10b–C11) gradually increases with a decrease of the aromatic character of the two central rings; the twisting increases in the order of **66a** (R = Ph, θ = 15°), **66b** (R = ^{n}Pr, θ = 22°), **65b** (R = ^{n}Pr, θ = 24°) and culminates for the chrysene-6,12-dione **67a** (R = Ph, θ = 33°) obtained from **66a** after cleavage of the aryl methyl ether with $(CH_3)_3SiI$ followed by oxidation on air (Scheme 24).

4.4 Diastereoselectivity

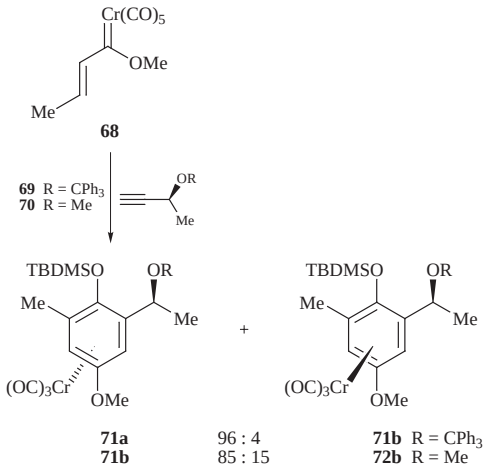
The benzannulation affords racemic mixtures of arene $Cr(CO)_3$ complexes (**A**/**A′**) which—due to the unsymmetric arene substitution pattern of monoprotected hydroquinones—possess a plane of chirality. The chiral plane is maintained after silylation of the remaining phenol functionality (**B**/**B́**) (in order to increase the stability of the annulation products towards oxidation) and is also compatible with the use of symmetric alkynes (Scheme 25). Enantiopure arene $Cr(CO)_3$ complexes[30] are powerful reagents in asymmetric synthesis; however, their availability is widely hampered by tedious protocols for the separation of the racemates.

Three different strategies have been envisaged for the benzannulation to lure the $Cr(CO)_3$ fragment selectively to one or the other face of the arene skeleton formed. The chiral information can be incorporated into α-alkoxyalkynes which allow good to excellent diastereoselectivities increasing markedly with the steric bulk of the alkynol protective group and depending on the type of the carbene ligand used. A very successful example is outlined in Scheme 26 combining a trityl-protected chiral alkynol with a propenylcarbene complex.[31] Alternatively, a chiral *C*-carbene side chain has been exploited in diastereoselective benzannulation. The methoxycyclohexenylcarbene complex **73** gave an 88% de in favour of the *anti* annulation product **74** upon reaction with pent-1-yne (Scheme 27).[32] An *anti* annulation product was isolated as a single diastereomer from the reaction of carbene complex **75**, obtained from optically pure 8a-methyl decalone, with hex-5-yn-1-ol upon a tandem benzannulation–Mitsunobu reaction to give the benzoxepine complex **76** (Scheme 28).[33]

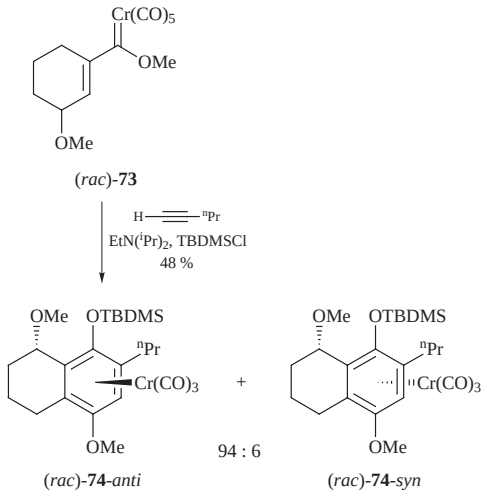
The most general approach to diastereoselective benzannulation aims at the incorporation of the chiral information into the



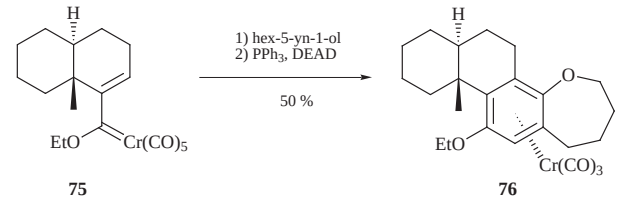
Scheme 25 Benzannulation approach to planar chiral arene complexes.



Scheme 26 Diastereoselective benzannulation with α-chiral alkynes.

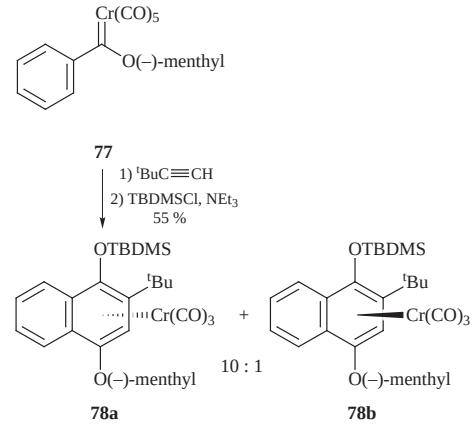


Scheme 27 Diastereoselective benzannulation of (*rac*)-**73**.



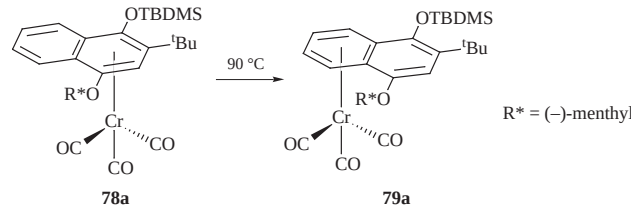
Scheme 28 Stereoselective synthesis of metal modified benzoxepine derivative **76**.

heteroatom carbene side chain which avoids any limitation in the substitution pattern of either the alkyne or the carbon skeleton of the carbene synthon. Chiral alcohol auxiliaries are readily available from the terpene or carbohydrate pool and can be attached to the carbene carbon atom *via* alcoholysis of acyloxycarbene complex precursors. Diastereoselectivities up to 82% de have been achieved in the annulation of menthyloxy carbene complex **77** with *tert*-butylacetylene to result in a 10:1 preference of diastereoisomer **78a** over **78b** (Scheme 29).[34]



Scheme 29 Diastereoselective benzannulation of (−)-menthyloxycarbene complex **77**.

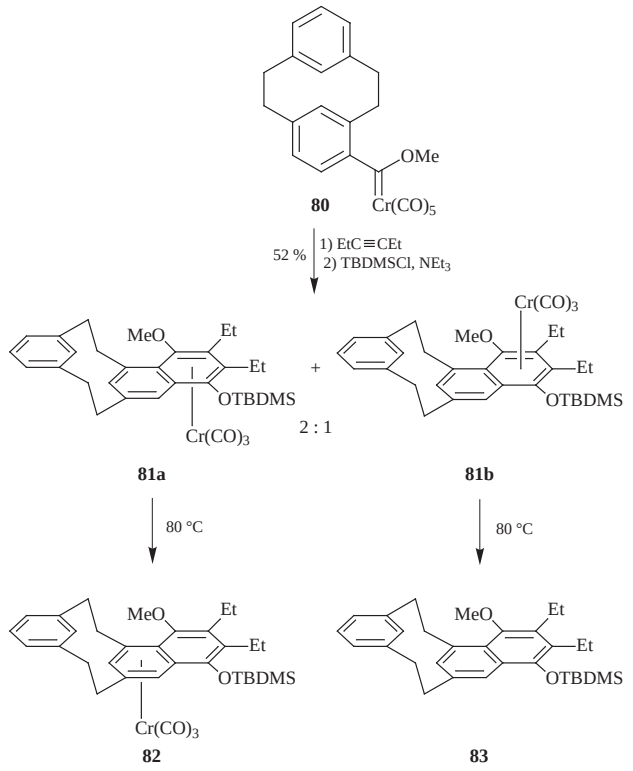
Benzannulation of phenylcarbene complexes carried out below 55 °C generally provides the kinetic product bearing the metal fragment on the oxygenated ring; under more drastic conditions a haptotropic metal migration occurs to give the thermodynamic 5-10-η^6 isomer (Scheme 30). As demonstrated



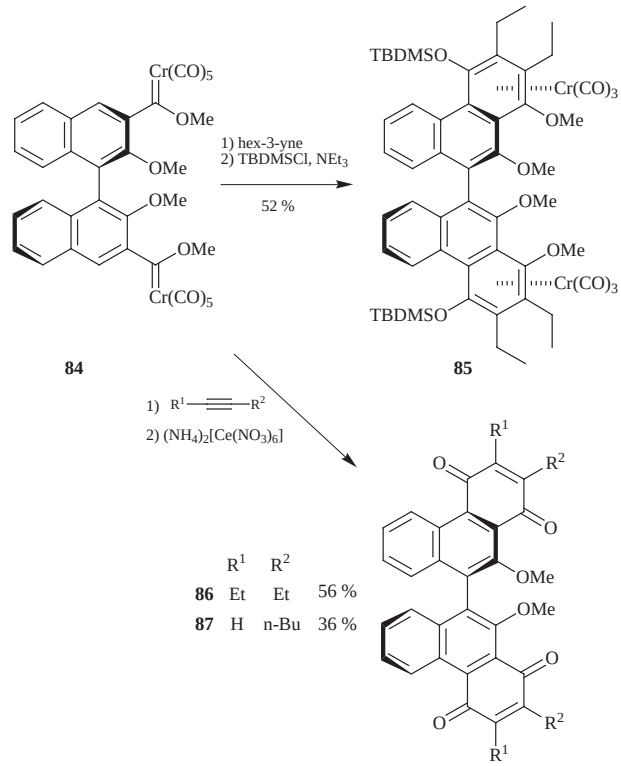
Scheme 30 Stereoselective haptotropic migration of the $Cr(CO)_3$ fragment.

for the pure diastereomer **78a** upon warming in di-*n*-butyl ether to 90 °C the metal migrates intramolecularly along the same face of the naphthalene system to give pure diastereomer **79a** which is in accordance with earlier Extended Hückel-MO calculations.

The arene deck of [2.2]metacyclophanes can be extended *via* the benzannulation reaction to give densely functionalized naphthalenophane $Cr(CO)_3$ complexes (Scheme 31).[35] Annulation of the racemic [2.2]metacyclophane carbene complex **80** results in the formation of diasteroisomeric hydroquinoid naphthalenophanes *anti*-**81a** and *syn*-**81b**; the diastereoselection arising from the chiral plane in the cyclophane is only moderate (2:1). In the major diastereomer *anti*-**81a** the $Cr(CO)_3$ fragment coordinates from the less hindered face of the arene;



Scheme 31 Benzannulation of [2.2]metacyclophane complex **80**.

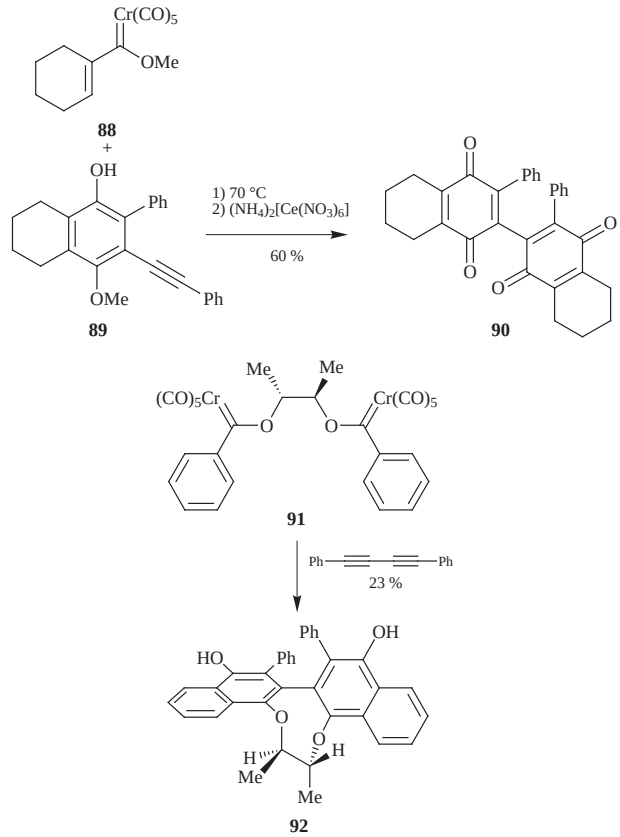


Scheme 32 Double benzannulation of axial chiral biscarbene complex **84**.

warming to 80 °C induces a haptotropic metal migration to the less substituted naphthalene ring to give *anti*-**82**. In the more congested minor benzannulation diastereomer *syn*-**81b**, however, the steric bulk of the uncoordinated cyclophane deck prevents a similar haptotropic migration and demetalation to **83** occurs under the same conditions.

Double benzannulation of the axial chiral enantiopure (*R*)-biscarbene complex **84**, accessible in a two-step sequence from commercially available binaphthol, affords biphenanthrene bischromium derivative **85** combining elements of axial and planar chirality (Scheme 32).[36] Four diastereomers are formed in moderate diastereoselectivity, two of which have been isolated as the major isomers. Oxidative workup of the annulation reaction affords C_2-symmetric bi(phenanthrenequinones) **86** and **87**; their quinone units represent independent reversible redox systems which offer new perspectives as ligands in enantioselective metal-catalyzed oxidation reactions.

Another approach to C_2-symmetric biaryls involves the annulation of carbene complex **88** with the diaryl alkyne **89**; oxidative workup afforded the C_2-symmetric bisquinone **90**. The C_2-symmetry of biscarbene complex **91** has been exploited in a double benzannulation with diphenylbuta-1,3-diyne to give a moderate yield of the bridged biaryl **92** as a single diastereoisomer (Scheme 33).[37]



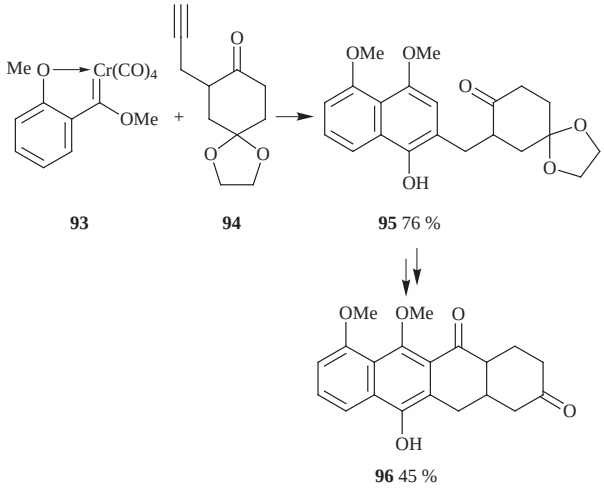
Scheme 33 Benzannulation approach to bridged and non-bridged C_2-symmetric quinones and hydroquinones.

5 Synthesis of natural products

The compatibility with functional groups, the regio- and stereoselectivity have made the benzannulation an attractive methodology for the synthesis of natural products bearing hydroquinoid, quinoid or fused phenolic substructures.

An early formal total synthesis of the antitumor antibiotic aglycon 11-deoxydaunomycinone started from the *ortho*-methoxyphenylcarbene chelate complex **93** which underwent benzannulation with alkyne **94** to form regioselectively the ring C of naphthohydroquinone intermediate **95**. C_1-homologation of the ketone to give the carboxylic acid and subsequent acid-mediated cyclization afforded in 45% overall yield the tetracyclic 6,9-diketone **96** which has been previously modified into the anthracycline aglycon (Scheme 34).[38]

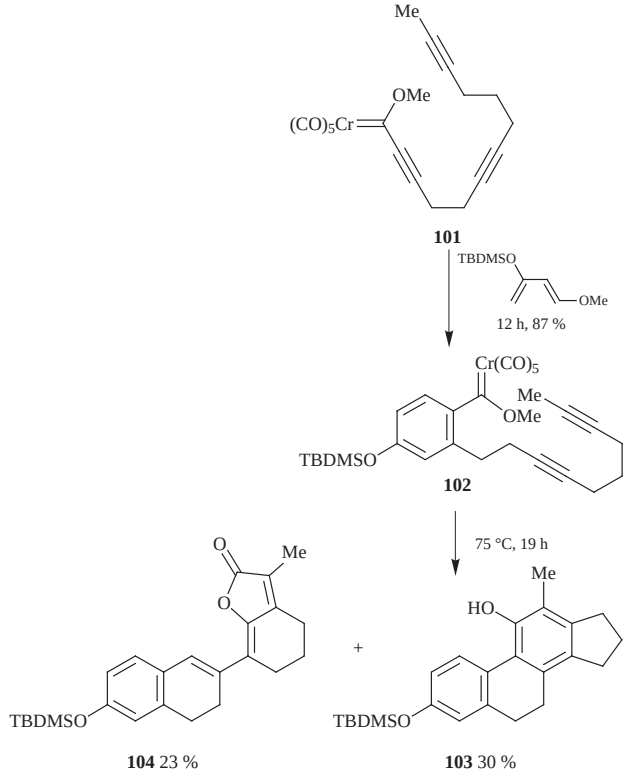
A recent benzannulation approach to fredericamycin A **100**, another potent antitumor antibiotic, has been based on the assembly of an oxygenated arylcarbene ligand in **97** and a



Scheme 34 Synthesis of 11-deoxydaunomycinone precursor **96**.

highly functionalized internal alkyne **98** (Scheme 35).[39] The hydroquinone ring B has been formed as the late key step affording a 35% yield of a single regioisomer **99** which has been subsequently converted to the target spirocycle **100**.

The steroid skeleton has been formed *via* a tandem Diels–Alder reaction–two alkyne annulation starting from the triple alkyne carbene chromium complex **101**. The Diels–Alder adduct **102** generated from the carbon–carbon triple bond activated by the adjacent metal carbene functionality and Danishefsky's diene undergoes a thermal intramolecular two alkyne annulation to give a 30% yield of the fused tetracyclic skeleton **103** along with the lactone **104** as a minor product (Scheme 36).[40] The yield of **103** could be improved to 63% when the chromium starting material **101** was replaced by its tungsten analogue.



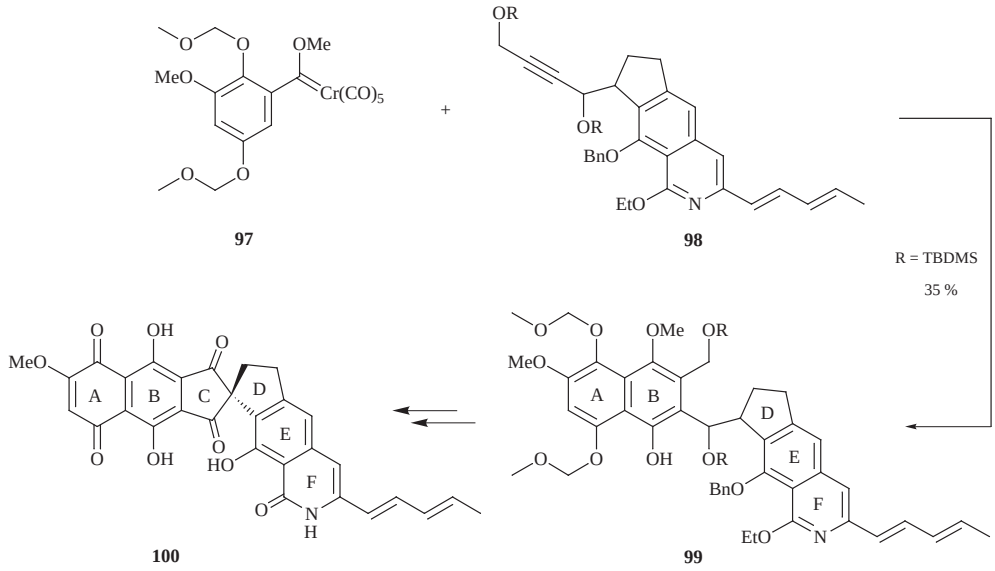
Scheme 36 Formation of the steroid skeleton **103** *via* a tandem Diels–Alder reaction–two alkyne annulation.

6 Conclusion and outlook

During three decades metal carbenes have evolved from organometallic curiosities to valuable tools in stereoselective organic synthesis and catalysis. The metal carbonyl fragment in Fischer-type complexes provides a template for non-classic carbene cycloaddition reactions which can be tuned by the metal and the substitution pattern of the carbene ligand. The chromium-mediated benzannulation with alkynes allows for a regio- and stereoselective one-step formation of $Cr(CO)_3$-coordinated densely functionalized hydroquinones which may be used as building blocks in the synthesis of natural and bioactive compounds or modified into chiral quinone ligands for catalysts in oxidation reactions. Finally, haptotropic metal migration to adjacent arene rings activates them for the addition of nucleophiles which occurs under the stereocontrol by the $Cr(CO)_3$ fragment.

7 Acknowledgements

It is a pleasure to thank the group of students mentioned in the references for their enthousiastic work. We gratefully acknowledge the continuous financial support by the Deutsche For-



Scheme 35 Benzannulation approach to fredericamycin A **100**.

schungsgemeinschaft and the Fonds der Chemischen Industrie.

8 References

1 K. H. Dötz, H. Fischer, P. Hofmann, F. R. Kreissl, U. Schubert and K. Weiss, *Transition Metal Carbene Complexes*, Verlag Chemie, Weinheim, 1983.
2 Recent reviews: W. D. Wulff, in *Comprehensive Organometallic Chemistry II*, ed. A. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon Press, Oxford, 1995, vol. 12, p. 469; L. S. Hegedus, *ibid.*, vol. 12, p. 549.
3 Review: K. H. Dötz, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 587.
4 K. H. Dötz and H. Larbig, *Bull. Soc. Chim. Fr.*, 1992, **129**, 579.
5 B. L. Balzer, M. Cazanoue, M. Sabat and M. G. Finn, *Organometallics*, 1992, **11**, 1759.
6 W. D. Wulff, in *Comprehensive Organic Synthesis*, eds. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon Press, Oxford, 1991, vol. 5, p. 1065.
7 A. Yamashita and A. Toy, *Tetrahedron Lett.*, 1986, **27**, 3471.
8 K. H. Dötz and W. Sturm, *J. Organomet. Chem.*, 1985, **285**, 205.
9 K. H. Dötz and H. Fischer, *Chem. Ber.*, 1980, **113**, 193.
10 K. H. Dötz and B. Fügen-Köster, *Chem. Ber.*, 1980, **113**, 1449.
11 K. H. Dötz, A. Tiriliomis and K. Harms, *Tetrahedron*, 1993, **49**, 5577.
12 The isolated and structurally characterized model intermediates are referred to in ref. 15.
13 H. Fischer, J. Mühlemeier, R. Märkl and K. H. Dötz, *Chem. Ber.*, 1982, **115**, 1355.
14 P. Hofmann, M. Hämmerle and G. Unfried, *New J. Chem.*, 1991, **15**, 769.
15 F. Hohmann, S. Siemoneit, M. Nieger, S. Kotila and K.H. Dötz , *Chem. Eur. J.*, 1997, **3**, 853.
16 M. M. Gleichmann, K. H. Dötz and B. A. Hess, *J. Am. Chem. Soc.*, 1996, **118**, 10551.
17 K. S. Chan, G. A. Peterson, T. A. Brandvold, K. L. Faron, C. A. Challener, C. Hyldahl and W. D. Wulff, *J. Organomet. Chem.*, 1987, **334**, 9.
18 B. Weyershausen and K. H. Dötz, *Eur. J. Org. Chem.*, 1998, 1739.
19 J. P. A. Harrity, W. D. Kerr and D. Middlemiss, *Tetrahedron*, 1993, **49,** 5565.
20 K. H. Dötz, J. Mühlemeier, U. Schubert and O. Orama, *J. Organomet. Chem.*, 1983, **247**, 187.
21 S. Chamberlin, M. L. Waters and W. D. Wulff, *J. Am. Chem. Soc.*, 1994, **116**, 3113.
22 J. S. McCallum, F.-A. Kunng, S. R. Gilbertson and W. D. Wulff, *Organometallics*, 1988, **7**, 2346.
23 A. Yamashita, *Tetrahedron Lett.*, 1986, **27**, 5915.
24 D. B. Grotjahn and K. H. Dötz, *Synlett*, 1991, 381.
25 M. F. Gross and M. G. Finn, *J. Am. Chem. Soc.*, 1994, **116**, 10921.
26 M. F. Semmelhack, J. J. Bozell, L. Keller, T. Sato, E.J. Spiess, W. Wulff and A. Zask, *Tetrahedron*, 1985, **41**, 5803.
27 K. H. Dötz and A. Gerhardt, *J. Organomet. Chem.*, 1999, in press.
28 T. Leese and K. H. Dötz, *Chem. Ber.*, 1996, **129**, 623.
29 K. H. Dötz and T. Leese, *Bull. Soc. Chim. Fr.*, 1997, **134**, 503.
30 G. Schmalz and S. Siegel, in *Transition Metals for Organic Synthesis*, eds. M. Beller, C. Bolm, Wiley-VCH, Weinheim, 1998, vol. 1, p. 550.
31 R. P. Hsung, W. D. Wulff and A. L. Rheingold, *J. Am. Chem. Soc.*, 1994, **116**, 6449.
32 R. P. Hsung, W. D. Wulff and C. A. Challener, *Synthesis*, 1996, 773.
33 R. L. Beddoes, J. D. King and P. Quayle, *Tetrahedron Lett.*, 1995, **36**, 3027.
34 C. Stinner and K. H. Dötz, *Tetrahedron: Asymmetry*, 1997, **8**, 1751.
35 A. Longen, M. Nieger, K. Airola and K. H. Dötz, *Organometallics*, 1998, **17**, 1538.
36 P. Tomuschat, L. Kröner, E. Steckhan, M. Nieger and K. H. Dötz, *Chem. Eur. J.*, 1999, **5**, 700.
37 J. Bao, W. D. Wulff, M. J. Fumo, E. B. Grant, D. P. Heller, M. C. Whitcomb and S.-M. Yeung, *J. Am. Chem. Soc.*, 1996, **118**, 2166.
38 K. H. Dötz and M. Popall, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 1158.
39 D. L. Boger, O. Hüter, K. Mbiya and M. Zhang, *J. Am. Chem. Soc.*, 1995, **117**, 11839.
40 J. Bao, W. D. Wulff, V. Dragisich, S. Wenglowsky and R. G. Ball, *J. Am. Chem. Soc.*, 1994, **116**, 7616.

Review 8/01442F