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Mini-Account

Carbon nucleophile addition to sp^2-unsaturated Fischer carbene complexes

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Abstract

The reactions of group 6 (alkoxy)(aryl)- and (alkoxy)(alkenyl)carbene complexes with organolithium compounds, metal enolates, and enamines are summarized. (Alkoxy)(aryl)carbene complexes underwent mainly nucleophilic addition to the carbene carbon atom, but either 1,4- or 1,6-addition products have been observed with derivatives bearing a bulky alkoxy group and phenyl- or alkyllithiums. The more widely studied (alkoxy)(alkenyl)carbene complexes react with carbon nucleophiles to give 1,2- or 1,4-addition products depending on the steric surroundings of both the metal carbene complex and the nucleophile as well as the nature of the latter. These reactions have been employed for several useful carbon–carbon bond-forming processes taking place with high diastereoselectivity.

Keywords: Fischer carbene complexes; Carbon nucleophilic addition; Asymmetric synthesis

1. Introduction

Group 6 heteroatom stabilized Fischer carbene complexes, prepared for the first time in 1964 [1], have attracted broad interest and are becoming increasingly important for organic synthesis [2]. The reactivity of these carbene complexes is mainly controlled by the electronic properties of their substituents. The strong electron-withdrawing character of the pentacarbonyl metal fragment to which the carbene ligand is bound leads to an electrophilic carbene carbon atom which is the target of nucleophilic reagents. When the carbene carbon atom is directly bound to an sp^2 unsaturated moiety, aryl or alkenyl group, the electron deficiency introduced by the metallic group is extended to other positions of the unsaturated carbene ligand, C4 or C6 in structures **I** and **II** of Fig. 1, which will also be prone to undergo nucleophilic attack. The regioselectivity of the reactions of carbene complexes **I** and **II** with nucleophilic reagents is dependent on the choice of nucleophile as well as the nature and steric surroundings of the metal carbene complex.

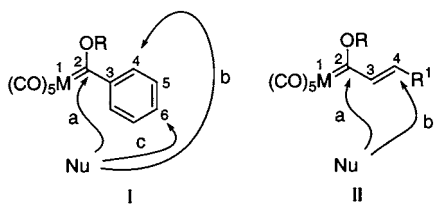

Fig. 1.

In this review, we present the addition reactions of carbon nucleophiles (organolithium compounds, lithium enolates, and enamines) to arylcarbene complexes **I** and alkenylcarbene complexes **II** which lead to formation of new carbon–carbon bonds (Fig. 1). The reactions of these complexes with ylides and ylide-like derivatives have been excluded from the present discussion given that this topic has recently been reviewed [3].

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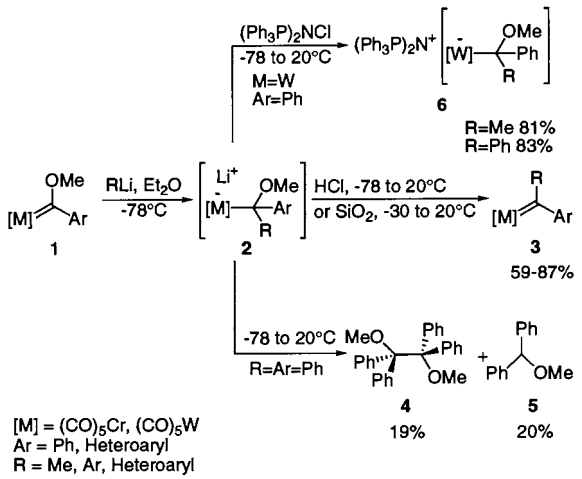
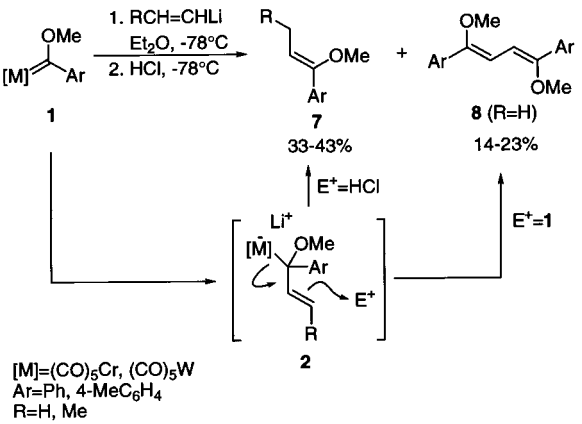
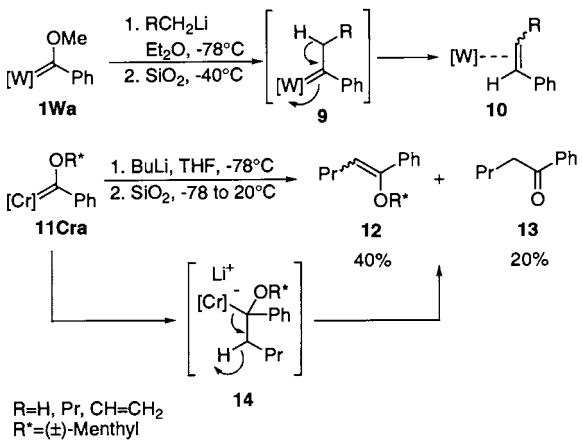


Scheme 1.



Scheme 2.



Scheme 3.

2. Reactions of arylcarbene complexes with organolithium compounds

(Alkoxy)(aryl)carbene complexes bearing a small alkoxy group attached to the carbene carbon react with organolithiums in a 1,2-fashion, whereas the presence of a bulky alkoxy derivative in that position directs the nucleophilic attack to the aromatic ring leading to either 1,4- or 1,6-addition products.

2.1. 1,2-Addition reactions

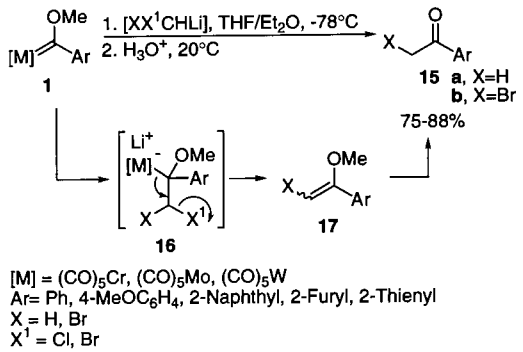
Organolithium reagents add to the carbene carbon atom (1,2-addition) of Fischer (alkoxy)(aryl)carbene complexes giving rise to different reaction products depending on the nature of the organolithium, reaction temperature or work-up conditions.

As shown in Scheme 1, the reaction of pentacarbonylaryl- or heteroaryl(methoxy)carbene complexes **1** with aryl- or heteroaryllithium compounds gave non-heteroatom stabilized Fischer diarylcarbene complexes **3** when the reaction was carried out at low temperature [4]. Generation of the complexes **3** involved addition of the aryllithium at the carbene carbon atom to give tetrahedral intermediates **2**, which on treatment with acid or silica gel at low temperature underwent methoxide elimination. In contrast, when the above reaction was warmed to room temperature a mixture of 1,2-dimethoxy-1,1,2,2-tetraphenylethane (**4**) and diphenylmethyl methyl ether (**5**) was isolated from the reaction of **1** (Ar = Ph) and phenyllithium [4a,5]. The formation of these products can be rationalized in terms of decomposition of the corresponding tetrahedral adduct **2** presumably generating free radical intermediates. Lithium metallate adducts **2** are stable at -78°C and have been isolated as the corresponding bis(triphenylphosphine)imminium salts **6**, which have been shown to be more stable than the lithium adducts [6].

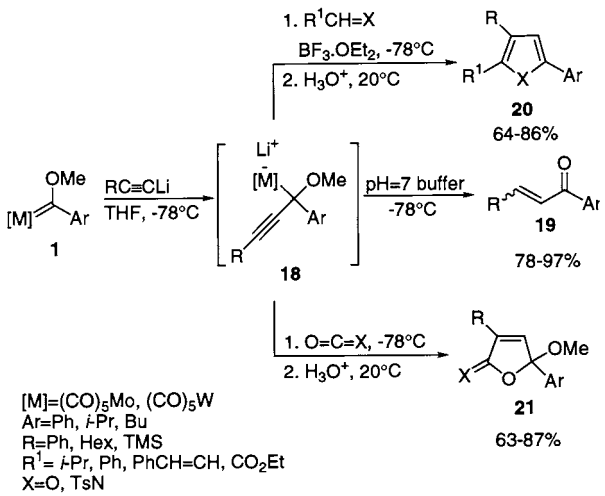
On the other hand, the reaction of the same type of carbene complexes with alkenyllithiums at -78°C followed by treatment with dry hydrogen chloride at the same temperature afforded diastereoselectively either a mixture of vinyl ethers **7** (R = H) and **8** or only vinyl ether **7** (R = Me) [7]. The formation of enol ethers **7** and 1,4-dimethoxybutadienes **8** can be understood in terms of electrophilic attack at the terminal end of the σ-allyl moiety of anionic 1,2-adduct **2**. Terminal protonation of **2** leads selectively to *Z* vinyl ether **7**, whereas analogous reaction with the electrophilic carbene carbon atom of another molecule of complex **1** gives rise to dimethoxybutadienes **8** (Scheme 2).

Addition to the carbene carbon atom of chromium and tungsten (alkoxy)(aryl)carbene complexes has also been observed with primary alkyllithium reagents. When tungsten (methoxy)(phenyl)carbene complex **1Wa** was treated with different alkyllithiums at -78°C and then silica gel at -40°C the corresponding pentacarbonyl(η^2-olefin)tungsten complex **10** was isolated [8]. Presumably, these products arise from the initially formed non-heteroatom stabilized (alkyl)(aryl)carbene complexes **9**, which undergo a 1,3-hydrogen shift followed by reductive elimination (Scheme 3). Even the

chromium (menthyloxy)(phenyl)carbene complex **11Cra**, whose carbene carbon atom is less sterically accessible, reacts with butyllithium at −78°C to give the 1,2-adduct **14** which goes through a β-hydrogen elimination to provide, after silica gel addition at −78°C, a mixture of enol ether **12** and its corresponding hydrolysis product, ketone **13** [9] (Scheme 3). In addition, (methoxy)(aryl)carbene complexes **1** can be transformed to the corresponding aryl methyl ketones **15a** or aryl bromomethyl ketones **15b** by successive treatment



Scheme 4.



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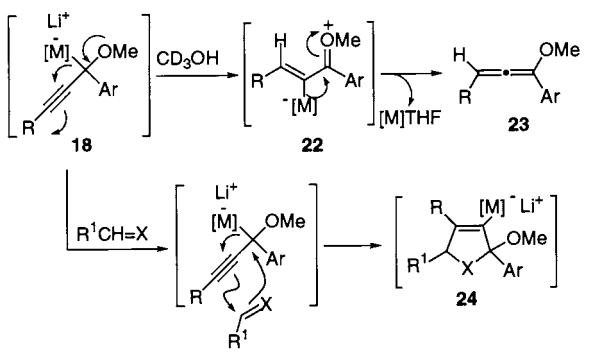
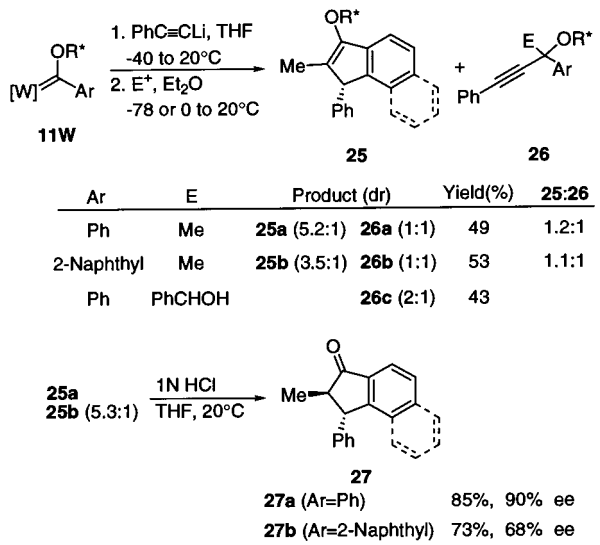


Scheme 6.

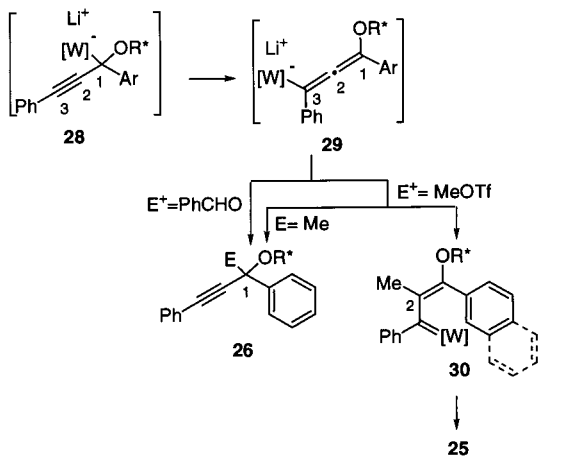
at −78°C with in situ generated chloromethyllithium, from chloroiodomethane and methyllithium, or dibromomethyllithium, from dibromomethane and lithium diisopropylamide (LDA), respectively, and then acid hydrolysis at 20°C. Likewise, these reactions can be viewed as proceeding by nucleophilic addition of either chloromethyllithium or dibromomethyllithium to the electron-deficient carbene carbon atom of **1** to form intermediates **16** which subsequently undergo spontaneous β-elimination yielding enol ethers **17**, whose hydrolyses under the reaction conditions afford products **15a** [10a] or **15b** [10b] (Scheme 4).

In the case of alkynyllithiums all the reactions reported with Group 6 arylcarbene complexes showed addition to the carbene carbon atom. Initially Iwasawa group described the reactions of various alkynyllithiums with (methoxy)(phenyl) and also with (methoxy)(alkyl)carbene complexes **1** [11]. The anionic propargyl metallic species **18** thus generated react regioselectively at low temperature with different electrophiles to give on either γ-protonation or γ-alkylation the products **19**–**21** shown in Scheme 5. Neutral aqueous work-up with phosphate buffer at −78°C followed by mild acid treatment gave enones **19** arising from hydrolysis of initially formed allenyl ethers (**23** in Scheme 6). Treatment of intermediates **18** with aldehydes, sulfonylimines, carbon dioxide and tosyl isocyanate provides furans **20** (X = O), pyrroles **20** (X = NSO_2Ph), butenolides **21** (X = O) and heterocyclic products **21** (X = NTs), respectively. These latter reactions have been proposed to occur with 1,2-migration of the metal group to generate a vinylmetal species **22** or **24**, which were detected by NMR studies of the protonation reaction with methanol-d^3 [11c] and of the reaction with benzaldehyde [11d] (Scheme 6).

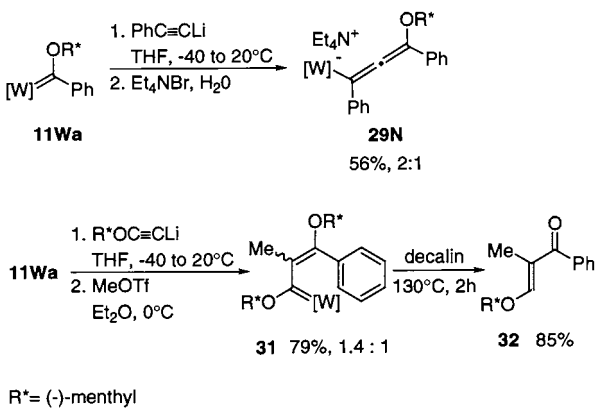
We have found that lithium acetylides also add to the more sterically hindered carbene carbon atom of tungsten (menthyloxy)(aryl)carbene complexes **11W** [12]. These reactions were carried out between −40°C and room temperature and, after addition of methyl triflate, a nearly equimolar mixture of a five-membered ring benzannulated product **25** and a propargylic ether **26** was formed (Scheme 7). The latter **26a**,**b** were isolated as a 1:1 diastereoisomeric mixture, while indenyl ethers **25a**,**b** were formed with acceptable diastereoselection (only the major isomer is shown). When benzaldehyde in the presence of boron trifluoride diethyl ether complex was used as the electrophile, only the corresponding propargylic ether **26c** was generated. Compounds **25** and **26** were separated by column chromatography on silica gel. Further acid hydrolysis of enol ethers **25a** (single diastereoisomer) and **25b** (5.3:1 mixture of diastereoisomers) furnished selectively the corresponding *trans*-2,3-disubstituted benzocyclopentanones **27a**,**b** as enantiomerically-enriched compounds. The absolute configuration of compounds **25** and **27** was established



Scheme 7.



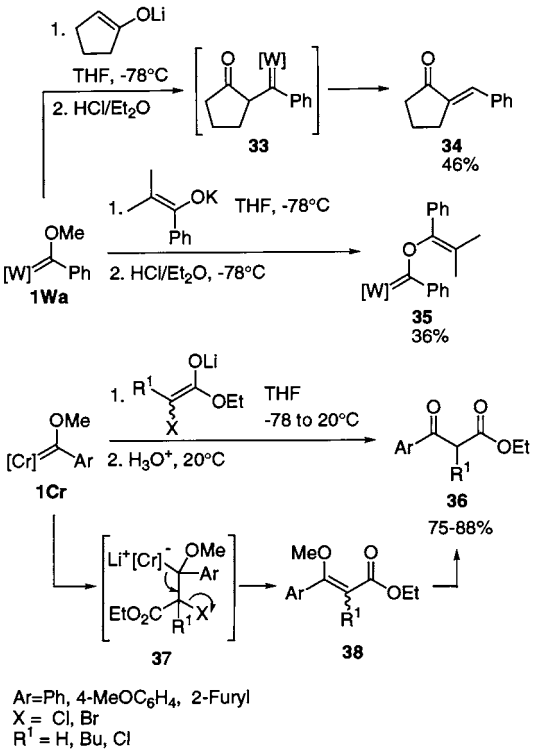
Scheme 8.



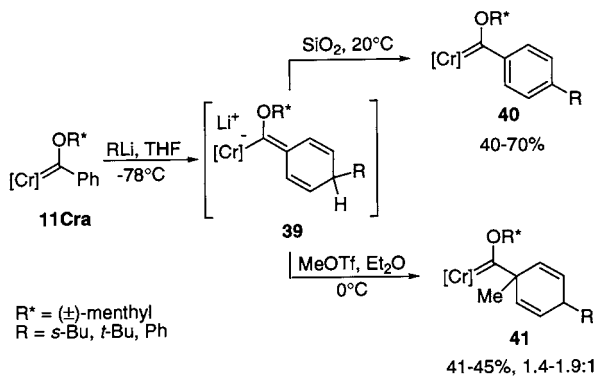
Scheme 9.

on the grounds of an X-ray analysis carried out with the tricarbonyltungsten complex of **25a** derived from (−)-menthol and prepared by an alternative method. The above results can be explained by the reaction pathway outlined in Scheme 8. The anionic propargyltungsten 1,2-adduct **28** is selectively formed and is stable at −40°C, but on warming to room temperature, it undergoes a 1,3-propargylic rearrangement to afford anionic allenyltungsten intermediate **29**. A variable-temperature NMR study showed direct evidence of this thermal 1,3-migration of the $(CO)_5W$ moiety. The reaction of intermediate **29** with electrophiles takes place regioselectively at C1 in the case of benzaldehyde, while a small and more reactive electrophile (MeOTf) reacts with **29** both at C1 and C2. The attack of MeOTf at the central allenic carbon atom furnishes initially the non-heteroatom stabilized 2-arylvinylcarbene complex **30**, an undetected intermediate analogous to that accepted in the Dötz benzannulation reaction, which subsequently would undergo cyclization according to one of the previously proposed mechanisms [13] to give indene-derived products **25**. This mechanism is supported by the successful isolation and characterization of intermediates analogous to **29** and **30** as shown in Scheme 9. Compound **29N**, obtained by cation exchange with an aqueous solution of tetraethylammonium bromide, is a yellow solid characterized by single X-ray structural analysis. In addition, ((−)-menthyloxy)(2-phenylvinyl)carbene complex **31**, which is a heteroatom-stabilized derivative, was isolated as a 1.4:1 mixture of diastereoisomers in the reaction of **11Wa** with in situ generated enantiomerically pure lithium 2-(−)-menthyloxyacetylide. Although further thermolysis of this complex did not yield the corresponding indene product and instead 2-alkoxyvinyl ketone **32** was formed as a single diastereoisomer [12] (Scheme 9).

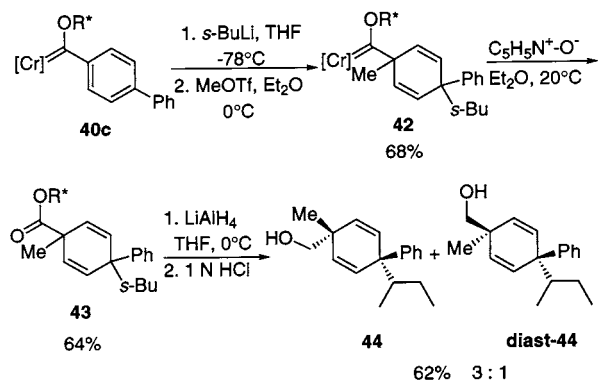
Finally, the reaction of metal enolate anions with arylcarbene complexes has been briefly tested. The two initial experiments were performed by the Casey group and the results are presented on the top of Scheme 10 [14]. The reaction of tungsten (methoxy)(phenyl)-carbene complex **1Wa** with the lithium enolate of cyclopentanone at −78°C followed by addition of HCl in diethyl ether at this same temperature, gave 2-benzylidenecyclopentanone (**34**). This product was thought to arise via acid-catalyzed conversion of the initial anionic 1,2-adduct to a non-heteroatom stabilized carbene complex **33** which then undergoes formal 1,2-proton shift decomposition by way of successive carbon-to-metal hydrogen migration and metal reductive elimination. In contrast, the potassium enolate of isobutyrophenone reacted with **1Wa** to give alkenyloxycarbene complex **35**. This latter enolate is so sterically crowded that 1,2-addition to carbene complex **1Wa** occurs only via the less hindered oxygen atom of the enolate. In addition, the 1,2-nucleophilic addition of α-haloester lithium enolates to chromium (methoxy)(aryl)carbene



Scheme 10.



Scheme 11.



Scheme 12.

complexes **1Cr** has been reported [10b] (Scheme 10). The initially formed anionic intermediate **37** undergoes a β-elimination process providing enol ethers **38**, as a mixture of Z/E isomers, which can be isolated (73–95%) after quenching with silica gel, and converted to β-ketoesters **36** upon acid hydrolysis.

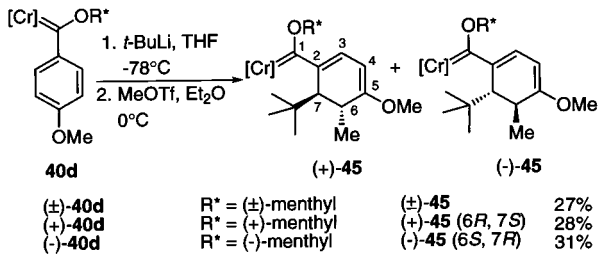
2.2. 1,6-Addition reactions

Sterically demanding (alkoxy)(aryl)carbene complexes derived from menthol underwent regioselective nucleophilic conjugate addition of either secondary or tertiary alkyllithiums or aryllithiums to the aromatic nucleus [9]. Thus, treatment of carbene complex **11Cra** with *sec*-butyl-, *tert*-butyl-, or phenyllithium at -78°C provided, on warming to room temperature overnight and after chromatographic purification, the corresponding aromatic *p*-substituted carbene complex **40**. On the other hand, quenching the reaction with methyl triflate at 0°C, after a short reaction time, afforded the dearomatized 1,4-dialkylated carbene complexes **41** as a mixture of Z/E isomers. In the former conditions, the initially generated 1,6 adducts **39** went through a spontaneous aromatization while in the latter ones they were regioselectively trapped at the α position to the carbene carbon atom. (Scheme 11). *p*-Phenyl-substituted carbene complex **40c** reacted analogously with *sec*-BuLi and MeOTf to give tetrasubstituted 2,5-cyclohexadienylcarbene complex **42** as a 3:1 mixture of Z/E diastereoisomers, determined after oxidation of the metal carbene group to the carboxylic ester **43** [9] (Scheme 12). The stereochemistry of the major isomer, which corresponds to a *trans* addition of the nucleophile and electrophile, was deduced from a 2D NOESY experiment performed on the 3:1 mixture of primary alcohols **44**/**diast-44** obtained after $LiAlH_4$ reduction of esters **43**.

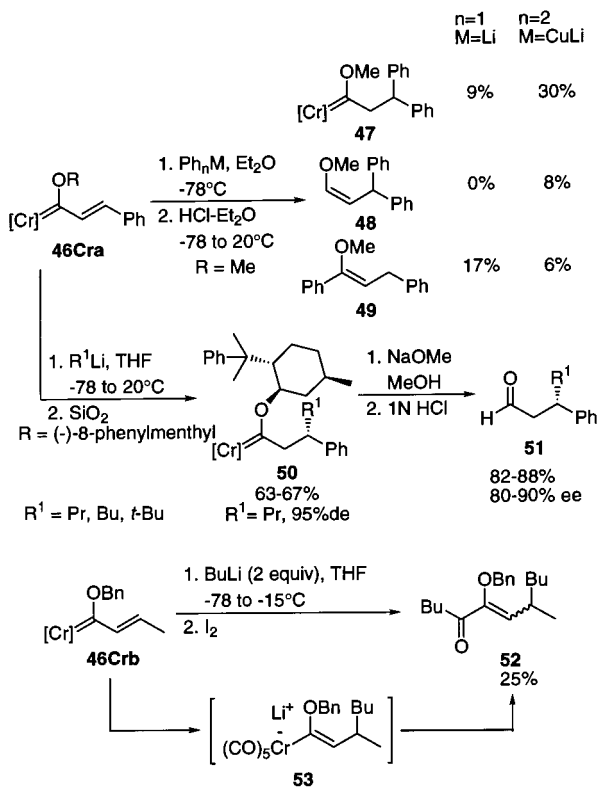
2.3. 1,4-Addition reactions

The reaction of *p*-methoxy-substituted racemic (±)-**40d** or optically active (+)-**40d** and (−)-**40d** carbene complexes, which hold a more electron-rich aromatic ring, with *tert*-butyllithium occurred in a 1,4-fashion leading, after addition of methyl triflate, to conjugated but non-aromatic carbene complexes **45** (Scheme 13). These tetra-substituted 1,3-cyclohexadienylcarbene complexes were generated with low chemical yields, but exclusively as a single diastereoisomer enantiomerically pure (+)-**45** or (−)-**45** when the starting carbenex complex **40d** was either the (+)- or (−)-menthol derivative, respectively [9]. The absolute configuration of compounds **45** was assigned on the basis of a single-crystal X-ray structure analysis performed on compound (+)-**45**.

These regio- and stereoselective nucleophilic aromatic 1,6- or 1,4-additions of organolithium reagents to (menthyloxy)(aryl)carbene complexes of chromium represent a new dearomatization reaction [15].



Scheme 13.



Scheme 14.

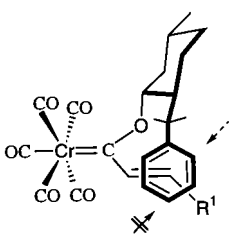


Fig. 2.

3. Reactions of alkenylcarbene complexes with organolithium compounds

In the reactions of (alkoxy)(alkenyl)carbene complexes with organolithiums, the steric factors in addition to the nature of the organometallic reagent play an important role in determining whether attack occurs on the carbene carbon atom or via conjugate addition at the olefinic double bond.

3.1. Simple organolithium compounds

The Casey group reported the first experiments carried out with alkenylcarbene complexes and either organolithium or organocopper reagents [7]. The reaction of chromium (methoxy)(styryl)carbene complex **46Cra** with phenyllithium at −78°C afforded after treatment with hydrogen chloride in ether a mixture of carbene complex **47** and enol ether **49** (Scheme 14). The minor product **47** is formed by protonation at the α-position of the anionic 1,4-adduct while the major one **49** results on protonation at the σ-allyl unit of the corresponding 1,2-adduct. Otherwise, when lithium diphenylcuprate is employed in the initial reaction with **46Cra** (R = Me) an increased ratio of conjugate addition products **47** and **48** to carbene carbon atom addition product **49** is obtained. The new enol ether **48** arises from the Michael adduct by elimination of the metallic fragment.

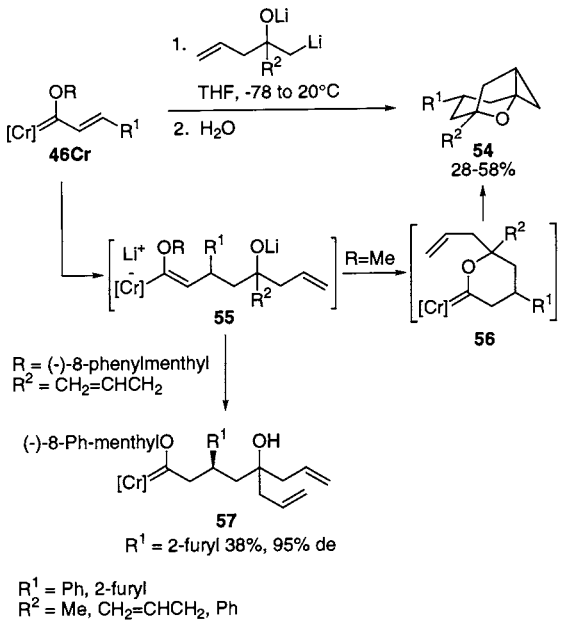
Optically active Fischer vinylcarbene complexes derived from (−)-8-phenylmenthol **46Cra** (R = (−)-8-phenylmenthyl) react with alkyllithium reagents to give diastereoselectively the corresponding Michael adducts **50**, after treatment with silica gel (Scheme 14). The regioselective formation of carbene complexes **50** is favored by the presence of a bulky alkoxy group bonded to the carbene carbon atom. Successive removal of the pentacarbonylchromium fragment by basic treatment and of the chiral auxiliary group by acid hydrolysis, led to optically active β-substituted aldehydes **51** with high enantiomeric excesses [16]. The absolute configuration of the newly formed stereogenic center was determined by a single-crystal X-ray structure analysis of compound **50** (R^1 = Pr). The sense of facial diastereoselectivity can be explained in terms of the model shown in Fig. 2 of the most stable conformation of ((−)-8-phenylmenthyloxy)(alkenyl)carbene complexes, which is favored by the alkene–arene π-stacking effect [17]. Nucleophilic attack on these Michael acceptors occurs selectively from the opposite side of the phenyl group. These results represent the first examples of asymmetric Michael additions of organolithiums to chiral Fischer alkenylcarbene complexes.

Conjugate addition of butyllithium to **46Crb** has been observed in an isolated example where this (benzyloxy)(1-propenyl)carbene complex was treated with two equivalents of butyllithium and then with iodine. In these conditions the initially formed 1,4-adduct **53** underwent alkylation of a carbonyl ligand producing a dianionic (σ-acyl)(σ-vinyl)chromium complex. Iodine oxidation of this intermediate led to coupling of the two organic fragments providing α-alkoxy enone **52** as a single stereoisomer about the double bond but whose stereochemistry could not be assigned [18] (Scheme 14).

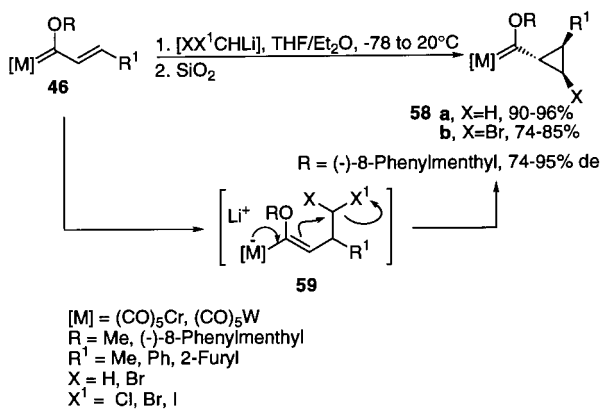
Recently, the 1,4-addition of alkylcerium reagents to tungsten (methoxy)(alkenyl)carbene complexes has been reported [19]. In the presence of cerium trichloride, butyl- and *s*-butyllithium undergo almost quantitative conjugate addition, whereas in the case of the in situ formed *t*-butylcerium reagent, the yield was only 10%.

3.2. Functionalized organolithium compounds

Conjugate addition to Fischer (alkoxy)(alkenyl)-carbene complexes is also observed with β-oxygen-functionalized sp^3 organolithium compounds [20]. When these dilithium dianions are properly substituted by an allyl group, the reaction with (methoxy)(vinyl)carbene complexes **46Cr** led directly, after addition of water, to tricyclic ethers **54** as single diastereoisomers (Scheme 15). The formation of these strained cyclopropane-containing tricyclic structures involves initial Michael addition of the β-alkoxide organolithium reagent to complex **46Cr** (R = Me) to give anionic adduct **55** (R = Me) which subsequently undergoes a spontaneous intramolecular alkoxide exchange, furnishing neutral cyclic alkoxycarbene complex **56**, and finally an intramolecular cyclopropanation reaction [21]. The same reactions carried out with carbene complexes **46Cr** (R = (−)-8-phenylmenthyl) afforded the acyclic 1,4-addition products **57** with high diastereoselectivity [16]. But in these cases the intramolecular alkoxide exchange and cyclopropanation reactions did not take place from intermediates **55** (R = (−)-8-phenylmenthyl), probably due to the bulkiness of the 8-phenylmenthyl group, which prevented the enantioselective synthesis of unusual tricyclic ring systems **54** (Scheme 15).



Scheme 15.



Scheme 16.

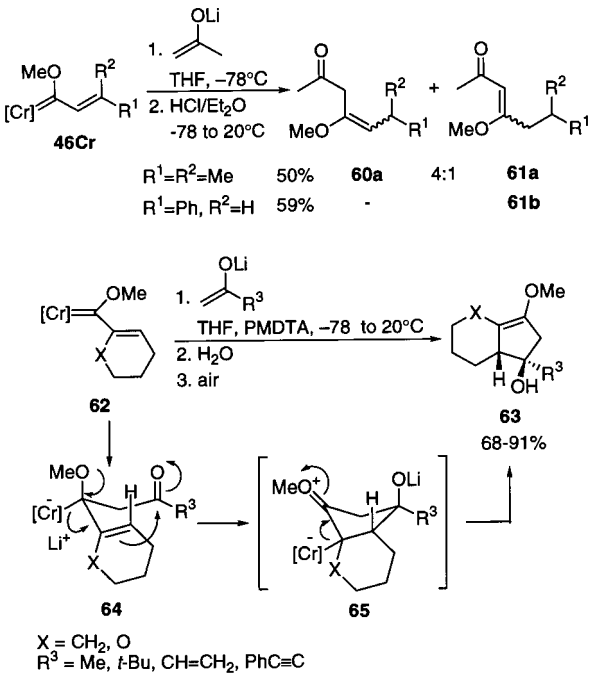
α-Halogen-functionalized sp^3 organolithium compounds have also been added in a 1,4-fashion to (alkoxy)(alkenyl)carbene complexes [22]. As depicted in Scheme 16 the reaction of complexes **46** with in situ generated chloro- or iodomethyllithium or dibromomethyllithium gave diastereoselectively *trans*-disubstituted cyclopropylcarbene complexes **58a** (X = H) or 1,2,3-trisubstituted cyclopropylcarbene derivatives **58b** (X = Br), respectively. In addition, these compounds are also obtained with high diastereoselectivity when chiral carbene complexes **46** (R = (−)-8-phenylmenthyl) were used [22b]. This chemical transformation begins with 1,4-addition of the corresponding halomethyllithium to vinylcarbene complex **46** affording anionic intermediate **59**, which suffers a spontaneous γ-elimination to produce compounds **58**. The sense of asymmetric induction is in agreement with our earlier results [16].

4. Reactions of alkenylcarbene complexes with lithium enolates

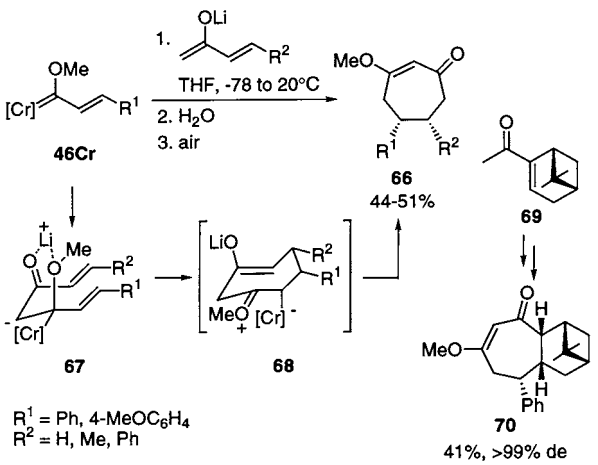
It is known that lithium enolates, which are softer nucleophiles than alkyllithiums, are more prone to undergo conjugate addition to Michael acceptors [23]. Nevertheless, the course of nucleophilic addition to alkenylcarbene complexes is different depending mainly on the steric requirements of the enolate. Thus, bulky enolates are added to the more accessible β vinylic position, while less bulky enolates attack the carbene carbon atom.

4.1. 1,2-Addition reactions

Unsubstituted lithium enolates derived from methyl ketones react with (methoxy)(alkenyl)carbene complexes to give different products, which arise via initial nucleophilic attack of the enolate at the carbene carbon atom. Two preliminary results achieved with the lithium enolate of acetone and carbene complexes **46Cr** are summarized in Scheme 17. These reactions, carried



Scheme 17.



Scheme 18.

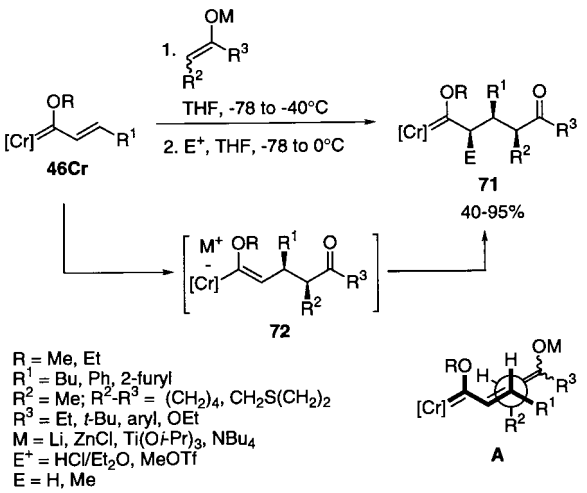
out and quenched at low temperature (− 78°C), provided a mixture of β,γ- and α,β-unsaturated ketones **60a** and **61a** when starting with complex **46Cr** ($R^1 = R^2 = Me$) and only α,β-unsaturated ketone **61b** when complex **46Cr** ($R^1 = Ph$, $R^2 = H$) was involved [14]. The initial 1,2-adduct, formed in the first step, is a σ-allylchromium anion which can react with acid at the remote allylic position to produce vinyl ether **60** and/or its double bond regioisomer **61**.

Recently, we have reported that the treatment of cyclic alkenylcarbene complexes **62** with lithium enolates of either methyl ketones, methyl enones, or methyl ynones in the presence of an excess of *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) and between − 78°C and room temperature led, after hydrolysis and oxidative metal decoordination, to bicyclic cyclopentenol derivatives **63**, which were isolated as single diastereoisomers [24]. The formation of these products involves 1,2-addition of the lithium enolates to carbene complexes **62** to form intermediates **64**. These ketone functionalized σ-allylchromium derivatives presumably undergo a cyclization by intramolecular addition to the carbonyl group induced by a 1,2-migration [11c,d,25] of the pentacarbonylchromium fragment leading to five-membered ring intermediates **65**. Subsequent elimination of the metallic group and hydrolysis of the lithium alkoxide finally furnishes compounds **63**. When the reaction of complex **62** (X = O) with the lithium enolate of *t*-butyl methyl ketone was hydrolyzed at low temperature the corresponding β,γ-unsaturated ketone analogous to compound **60** was isolated, which confirms that the initial addition occurs at the carbene carbon atom. Additionally, we found that performing the reaction of alkenylcarbene complexes **46Cr**, which do not contain the carbon–carbon double bond inside a six-membered ring, with lithium enolates of methyl enones and in the absence of PMDTA, gave rise to *cis*-3,5,6-trisubstituted-2-cycloheptenones **66** as single diastereoisomers as well [24] (Scheme 18). In these experiments intermediate **67**, generated by nucleophilic addition at the carbene carbon atom, goes through a similar cyclization induced by the 1,2-migration of the pentacarbonylchromium group, but with intramolecular conjugated addition to the enone moiety, to give seven-membered ring intermediates **68**. An analogous elimination of the metal fragment and hydrolysis of the lithium enolate moiety followed by double bond isomerization led to **66**. The *cis* diastereoselectivity can be explained by invoking a chair-like transition state, derived from **67**, presumably favored by internal coordination of the oxygen atoms to the lithium atom. Finally, the reaction of the lithium enolate derived from homochiral ketone **69**, easily prepared from (−)-myrtenal, with carbene complex **46Cr** ($R^1 = Ph$), carried out under similar conditions, yielded tricyclic enone **70** as an enantiomerically pure compound (Scheme 18).

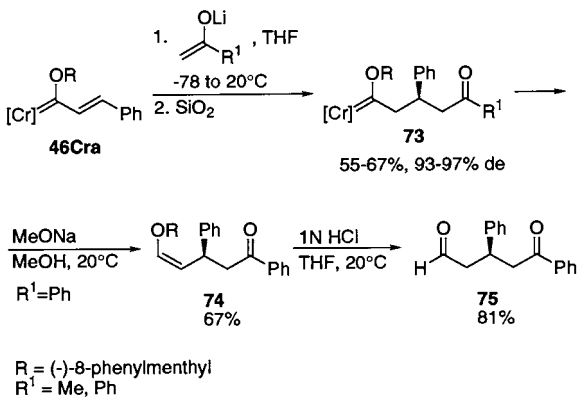
4.2. 1,4-Addition reactions

Substituted enolate anions add to alkenylcarbene complexes in a 1,4-fashion to produce new functionalized Fischer carbene complexes. The pioneering work by Casey and co-workers revealed that the lithium enolate of cyclopentanone, potassium enolate of isobutyrophenone, and sodium enolate of dimethyl malonate conjugately add to pentacarbonyl[(isobutenyl)-(methoxy)carbene]chromium and pentacarbonyl-[(methoxy)(styryl)carbene]chromium to form new δ-oxo-substituted carbene complexes [14]. More recent studies in the Nakamura group have demonstrated that Michael addition of β-*C*-substituted metal enolates derived either from cyclic or open chain ketones or esters to (alkoxy)(alkenyl)carbene complexes of

chromium occurs with *syn* diastereoselectivity irrespective of the enolate geometry or the nature of the counterion [26]. The anionic 1,4-adduct **72**, generated by addition of the corresponding metal enolate to **46Cr**, can be stereoselectively trapped with methyl triflate to afford carbene complexes **71** (E = Me) with stereocontrol of three contiguous stereogenic centers (Scheme 19). The *syn* diastereoselectivity of the Michael addition is particularly high for the lithium enolates of cyclohexanones (up to > 94% de) or for those enolates with a bulky R^3 group (99% de as the best result). Approach topology A depicted in Scheme 19 has been proposed to explain the observed *syn* diastereoselectivity. This open chain model assumes an *s-trans* conformation for the vinylcarbene complex and that the Michael addition occurs with an *anti* relationship of the donor and acceptor π-systems, placing the bulkiest substituent of the enolate (R^2) away from the [Cr] = C(OR) grouping to avoid steric interactions [27].

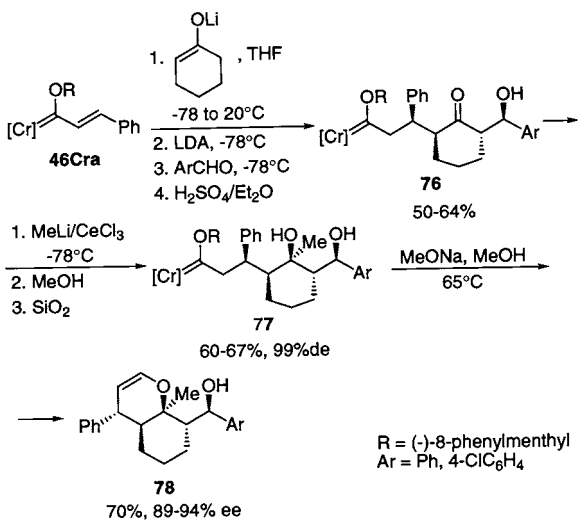


Scheme 19.



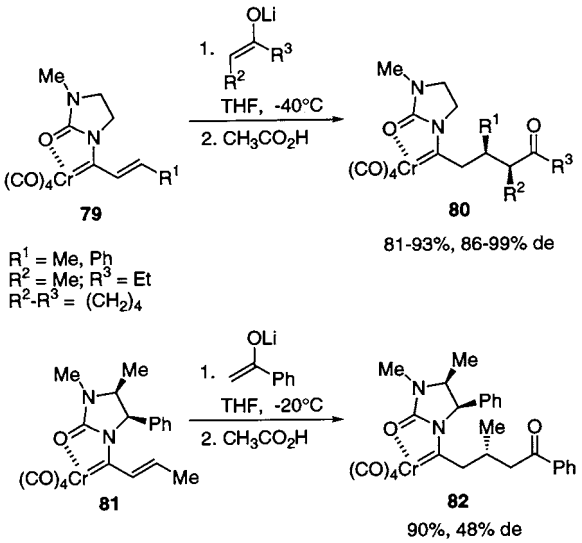
Scheme 20.

Furthermore, we have ascertained that the Michael addition reactions of ketone and ester lithium enolates to enantiomerically pure ((−)-8-phenylmenthyloxy)(alkenyl)carbene complexes of chromium proceed with uniformly high levels of asymmetric induction and high *syn* diastereoselectivity when substituted lithium enolates are involved [16,28]. These alkenylcarbene complexes **46Cra** bearing a chiral and more sterically demanding alkoxy group undergo conjugate addition even with lithium enolates derived from methyl ketones [16]. As indicated in Scheme 20, lithium enolates of acetone and acetophenone reacted with complex **46Cra** to yield 1,4-adducts **73** with high diastereoisomeric excesses. Metal and chiral auxiliary-free products are accessible in high enantiomeric purity by basic treatment followed by acid hydrolysis, which transforms carbene complex **73** (R^1 = Ph) into *Z*-enol ether **74** and finally 1,5-dicarbonyl compound **75**. The initial Michael adducts generated in these reactions can be further elaborated through diastereoselective addition of organometallic reagents to ketones and aldol reactions. A synthetic sequence which leads to cyclic enol ethers with five contiguous stereogenic centers and of high enantiomeric purity is summarized in Scheme 21 [28]. Anionic 1,2-adduct, obtained by reaction of complex **46Cra** with cyclohexanone lithium enolate, was treated with lithium diisopropylamide (LDA) and then with the corresponding aromatic aldehyde to give, after acid hydrolysis, a single aldol product **76**. Addition of methyllithium in the presence of $CeCl_3$ to β-hydroxyketones **76** afforded 1,3-diols **77** as single diastereoisomers. Final treatment of carbene complexes **77** with a sodium methoxide solution in methanol at reflux furnished bicyclic enol ethers **78**. This last transformation presumably involves intramolecular alkoxide exchange followed by elimination of the $(CO)_5Cr$ moiety. Likewise, the sense of facial selectivity is in agreement with the precedents [16,22b,29].

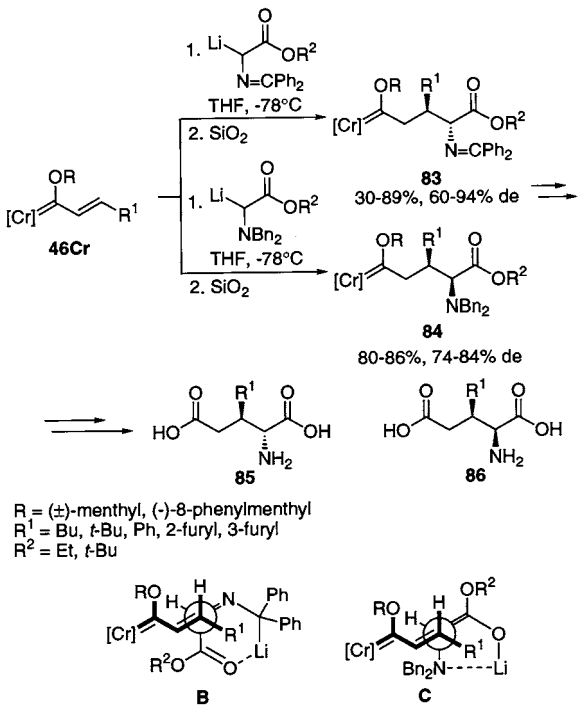


Scheme 21.

High *syn* selectivity in the addition of ketone *E* lithium enolates to nitrogen-stabilized (*O*-chelated imidazolidinone) chromium vinylcarbene complexes has been reported by Wulff and coworkers [30]. The reac-



Scheme 22.



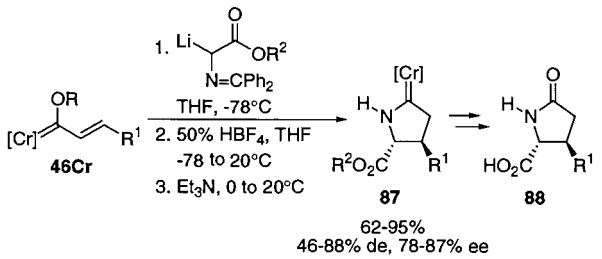
Scheme 23.

tions of imidazolidinone carbene complexes **79** with the *E* enolates shown in Scheme 22 led after quenching with acetic acid to *syn* Michael adducts **80** with high diastereoisomeric excesses. However, the analogous reaction of chiral imidazolidinone carbene complex **81**, which possesses a sterically encumbered carbene carbon atom, with acetophenone lithium enolate took place also in a 1,4-fashion, providing Michael adduct **82** but with a low asymmetric induction [31].

In this context, we have additionally reported the reaction of lithium enolates of achiral *N*-protected glycine esters with chiral alkoxyalkenylcarbene complexes of chromium, which provided the corresponding Michael adducts with either high *anti* or *syn* selectivity depending on the nature of the nitrogen protecting group, and high diastereofacial selectivity when carbene complexes containing the (−)-8-phenylmenthyloxy group were employed [32] (Scheme 23). Treatment of carbene complexes **46Cr** with lithium enolates of benzophenone Schiff base derivatives of glycine alkyl esters afforded, after silica gel column chromatography, the corresponding and unexpected *anti* 1,4-adduct **83**. The *anti*/*syn* diastereoselectivity of this conjugate addition was good with 3-aryl-substituted carbene complexes **46Cr** (R^1 = Ph, 2-furyl, 3-furyl), while with the aliphatic derivatives **46Cr** (R^1 = Bu, *t*-Bu), no selectivity was observed and the chemical yield was lower. Racemic complexes derived from (±)-menthol **46Cr** (R = (±)-menthyl) did not show any facial selectivity, but chiral carbene complexes derived from (−)-8-phenylmenthol **46Cr** (R = (−)-8-phenylmenthyl) yielded adducts **83** as very major isomers (almost a single diastereoisomer by ^{1}H- and ^{13}C-NMR). On the other hand, the reactions of lithium enolates of *N*,*N*-dibenzylglycinate esters with the same Michael acceptors **46Cr** and under identical experimental conditions, led with high selectivity to the expected *syn* 1,4-adducts **84**. Further elaboration of functionalized carbene complexes **83** and **84** through sequential oxidation of the metal–carbene moiety, deprotection of the amine group and hydrolysis of both carboxylic esters, allowed the preparation of enantiomerically-enriched β-substituted glutamic acids of natural **86** as well as unnatural stereochemistry **85**. The *anti*/*syn* diastereoselectivity of these conjugate additions, which proved to be strongly dependent on the nature of the protective group on the glycine nitrogen atom, can be rationalized in terms of the model mentioned above, which was initially proposed by Nakamura el al. [26b]. According to that, the formation of *syn* Michael adducts **84** can be explained by the sterically favorable approach C of the lithium anion of *N*,*N*-dibenzylglycinate alkyl esters as a *Z*-enolate (1-oxaallylanion five-membered ring derivative) in which the dibenzylamino group is placed away from the metal–carbene moiety. The diastereoselective formation of *anti* Michael adducts **83** can be explained likewise by this mechanistic model but assuming that lithium enolates of *N*-(diphenylmethylidene)glycinate alkyl esters interact with the vinylcarbene complex as a 2-azaallylanion six-membered ring structure, presumably favored by a greater stability, giving rise to approach topology B, in which the alkoxycarbonyl group is placed away from the metal–carbene moiety (Scheme 23). The absolute configuration of the newly created stereogenic centers, established from a single-crystal X-ray analysis of **83** (R = (−)-8-phenylmenthyl, R^1 = 2-furyl, R^2 = Et), is once more in agreement with the sense of facial selectivity previously observed in other conjugate additions to

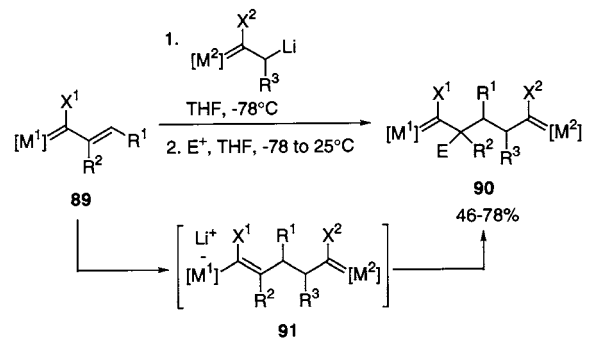
((−)-8-phenylmenthyloxy)(alkenyl)carbene complexes of chromium [16,22b,28] and to analogous enoates [29].

Alternatively, we observed that treatment of the anionic 1,4-adduct formed in the reaction of **46Cr** with lithium enolates derived from benzophenone imine of glycine alkyl esters, with 50% aqueous solution of HBF_4 and then with triethylamine led directly and more efficiently to cyclic *trans*-disubstituted aminocarbene complexes **87** with good diastereoselectivity and high enantiomeric purity when chiral complexes **46Cr** (R = (−)-8-phenylmenthyl) were used [32] (Scheme 24). This methodology represents a novel synthetic approach to optically enriched β-substituted pyroglutamic acids **88**, which are formed after sequential oxidative removal of the metal fragment and hydrolysis of the ester group of compounds **87**.



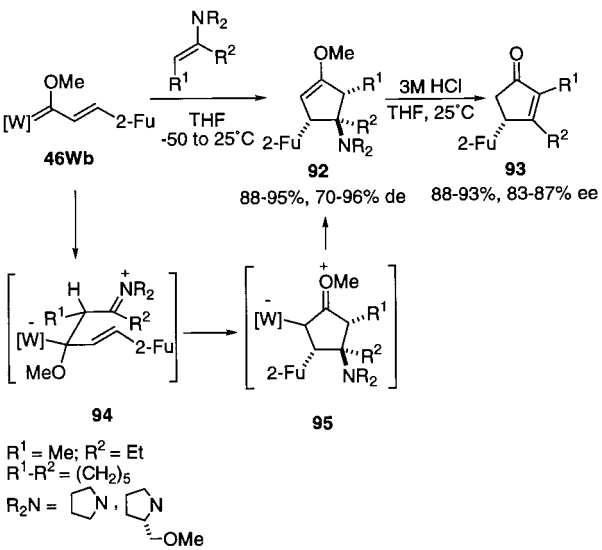
R = (±)-menthyl, (-)-8-phenylmenthyl
R^1 = Ph, 2-furyl
R^2 = Et, *t*-Bu

Scheme 24.



$[M^1]$, $[M^2]$ = $(CO)_5Cr$, $(CO)_5W$
X^1, X^2 = OMe, OCH_2Ph, NMe_2
R^1 = H, Me
R^2 = H, Me; R^1-R^2 = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_6$
R^3 = H, Me, Pr, $SiMe_3$
E^+ = HCl, MeOTf, CH_2=$CHCH_2Br$, $PhCH_2Br$, Me_3SiCl
E = H, Me, CH_2=$CHCH_2$, $PhCH_2$

Scheme 25.



R^1 = Me; R^2 = Et
R^1-R^2 = $(CH_2)_5$
R_2N = N, N, OMe

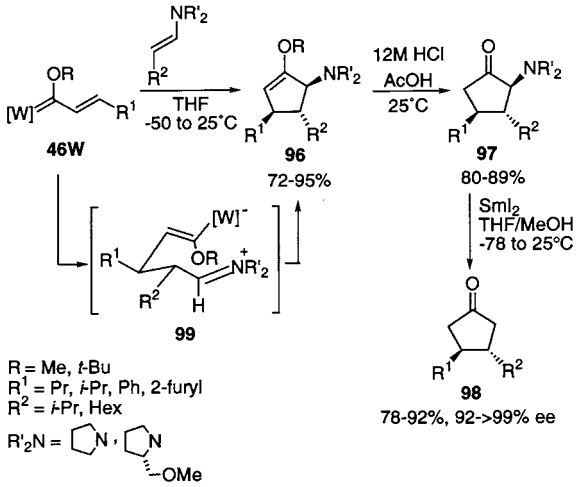
Scheme 26.

Finally, anions generated from Fischer carbene complexes at the α position to the carbene carbon atom can effect a nucleophilic addition to alkenylcarbene complexes to give the corresponding Michael adducts [33,34]. Macomber et al. have developed into a general method the synthesis of binuclear μ-biscarbene complexes of chromium and tungsten **90**, with similar or dissimilar metal fragments, by the conjugate addition reaction of either alkoxy– or amino–alkenylcarbene complexes **89** with α-lithio carbene anions (obtained by treating the corresponding alkoxy– or amino–alkylcarbene complex with butyllithium at −78°C), followed by quenching with various electrophilic reagents (Scheme 25). The process involves the formation of α-lithio μ-biscarbene complex monoanions **91** which subsequently react with the electrophile to give **90**. The reactions described in Scheme 25 which lead to products with two stereogenic carbon centers proceeded in a highly stereoselective manner with formation of the corresponding biscarbene complexes **90** as one major diastereoisomer.

5. Reactions of alkenylcarbene complexes with enamines

5.1. 1,2- and 1,4-Addition reactions of simple enamines

The strong electron-withdrawing character of the $M(CO)_5$ group led us to investigate the reaction of alkenylcarbene complexes with weaker nucleophiles like enamines (Schemes 26 and 27) [25d]. Thus, carbene complex **46Wb** reacts with cycloheptanone and 3-pentanone pyrrolidine enamines under very mild reaction conditions to furnish high yields of racemic cyclopentene derivatives **92**, which are further hydrolyzed to substituted 2-cyclopentenones **93** (Scheme 26). This process brings about a new [3 + 2] cycloaddition that takes place with complete regiocontrol and excellent diastereoselection. The enantioselective version was efficiently accomplished using enamines derived from (*S*)-2-methoxy-methylpyrrolidine leading to diastereomerically enriched 1-methoxycyclopentenes **92** and enantiomerically enriched cyclopentenones **93**. The formation of cycloadducts **92** is readily explained by 1,2-



Scheme 27.

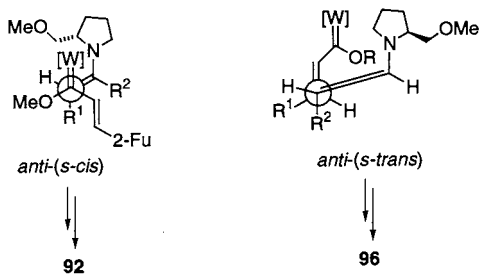
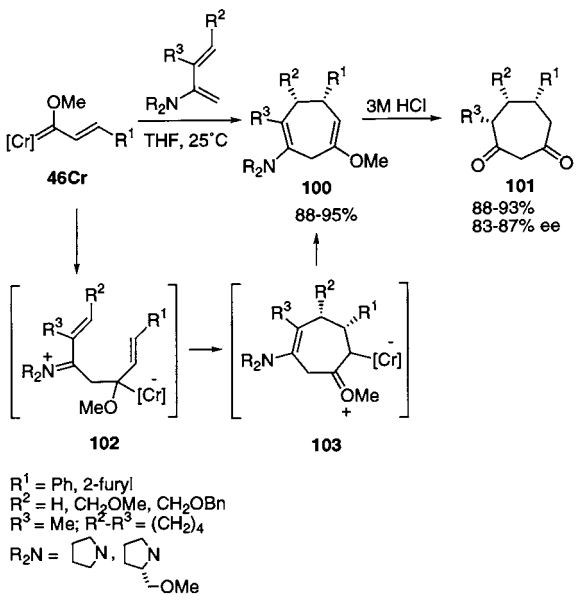


Fig. 3.



Scheme 28.

addition of the enamine to the carbene ligand (intermediate **94**) followed by ring closing promoted by a 1,2-$M(CO)_5$ shift (intermediate **95**). Finally, the carbon-to-metal hydrogen transfer and reductive metal elimination would lead to **92**.

The study of the cyclization reaction of enamines derived from aldehydes reveals that the regioselectivity is dependent on the bulkiness of substituents OR and R^2 (Scheme 27). Thus, the treatment of carbene complexes **46W** (R = Me) with enamines having $R^2 = i$-Pr or, more importantly, complexes **46W** with R = *t*-Bu results in the exclusive formation of regioisomer **96** as a sole diastereoisomer. Cyclopentenes **96** can be elaborated into 3,4-disubstituted cyclopentanones **97** and **98** by enol ether hydrolysis and reductive deamination. Highly enantiopure cyclopentanones **98** (> 92% ee) are produced from (*S*)-2-methoxymethylpyrrolidine enamines. The occurrence of regioisomers **96** reveals that, unlike the case of ketone enamines (Scheme 26), the species **99**, resulting from Michael-type addition of the enamine to the alkenylcarbene complex, is produced first. The cyclization of intermediate **99** and reductive metal elimination accounts well for the diastereoselective formation of **96**. The face selectivity is rationalized in light of Seebach's model for the addition of ketone enamines to nitroalkenes (Fig. 3) [35]. The formation of **92** results from a carbene complex-to-enamine *anti*-(*s*-*cis*) approach, whereas **96** is formed as a consequence of a carbene complex-to-enamine *anti*-(*s*-*trans*) approach.

5.2. 1,2-Addition reactions of 2-amino-1,3-dienes

Finally, we turned our attention to α-vinylenamines, the so-called 2-aminodienes, which have been termed as 'super enamines' on the basis of their enhanced reactivity (Scheme 28) [36]. The treatment of 2-aminodienes derived from pyrrolidine with alkenyl carbene complexes **46Cr** at room temperature results in the regio and diastereoselective formation of substituted cycloheptadienes **100**, which in turn afford cycloheptadiones **101** on hydrolysis. The enantioselective version of the process is efficiently achieved using 2-aminodienes derived from (*S*)-2-methoxymethylpyrrolidine. Although a reaction pathway involving cyclopropanation and Cope rearrangement has been postulated in this and related cycloheptannulations [37], we propose on the basis of the present account that the formation of **100** should actually involve nucleophilic 1,2-addition to generate the zwiterionic intermediate **102** followed by 1,2-metal pentacarbonyl migration/ring closing leading to intermediate **103** and hydrogen transfer–metal elimination.

In conclusion, the reactions presented in this review demonstrate that nucleophilic attack at different positions, besides the carbene carbon atom, of a sp^2-unsaturated carbene ligand is a major feature in the chemistry of Group 6 Fischer aryl- and alkenylcarbene complexes. In addition, several of these reactions have been successfully developed as a method for the diastereoselective and enantioselective synthesis of a number of functionalized organic molecules.

Acknowledgements

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