Controlled Cycloadditions

[3+2] and [4+1] Cycloaddition Reactions of Fischer Alkoxy(alkenyl)carbene Complexes with Electronically Neutral 1,3-Dienes**

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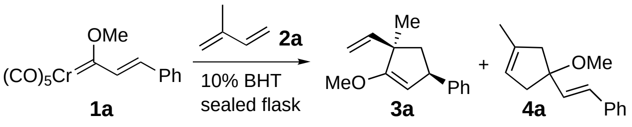
Dedicated to Professor Julio D. Martín
on the occasion of his 60th birthday

Reactions of the heteroatom-stabilized carbene complexes of group 6 metals with conjugated carbodienes allow for the construction of cyclic products with different ring sizes[1] that depend upon both the nature of the reaction partners and the reaction conditions.[2] Electron-deficient 1,3-dienes are known to react when heated with alkoxy(aryl/alkyl)carbene complexes to afford $[2_D+1_C]$[3] cycloadducts with high selectivity.[4] While analogous reactions with aminocarbene complexes provide a $[4_D+1_C]$ cycloadduct with pentacarbonyl-[(*N*,*N*-dimethylamino)methylene]chromium[5] or $[4_D+3_C]$ cycloadducts with molybdenum–amino(alkenyl)carbene complexes.[6] Electron-rich 1,3-dienes also react with alkoxy(alkenyl)carbene complexes, which undergo a $[4_D+3_C]$ cycloaddition reaction in the case of the chromium derivatives,[7] and a $[4_D+2_C]$ cycloaddition process when tungsten–carbene complexes are involved.[8,9] Nevertheless, the corresponding $[4_D+1_C]$ adduct was isolated when a Cr complex was mixed at room temperature with 2-methyl-1,3-dimorpholino-1,3-butadiene.[7c] In addition, the reaction of alkenylcarbene derivatives with a 1-acceptor-3-donor-substituted 1,3-diene furnished cyclopentenes, which are the $[3_C+2_D]$ adducts of the corresponding carbene ligand to the electron-rich terminal double bond of the silyloxydiene.[7d,10] Simple 1,3-dienes have been shown to undergo either a thermally selective monocyclopropanation reaction ($[2_D+1_C]$ cycloaddition) with alkoxy(alkyl/aryl)carbene complexes of Mo and Cr,[11] or a room-temperature Diels–Alder reaction ($[4_D+2_C]$ annulation) with alkoxy(alkenyl)carbene complexes of Cr and W.[8a,c,12] On the other hand, the photolytic reaction of chromium–alkoxy(alkyl/aryl)carbene complexes with simple cyclic 1,3-dienes produced bicyclic cyclobutanones ($[2_D+1_C+1_{CO}]$ annulation products) with a high degree of selectivity.[13]

Herein, we report the first examples of $[3_C+2_D]$ or $[4_D+1_C]$ cycloaddition reactions between alkoxy(alkenyl)carbene complexes and electronically neutral 1,3-dienes. The transfer reaction of the carbene ligand as a three-carbon-atom synthon, which seems to be more general than that in which it acts as a one-carbon-atom synthon, took place with total regio- and diastereoselectivity, and high asymmetric induction can be observed when alkenylcarbene complexes derived from (−)-8-phenylmenthol are used.[14]

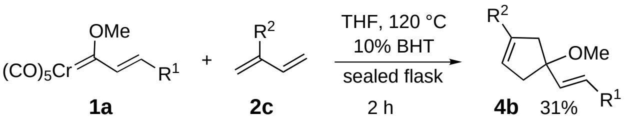
In the initial experiment, the standard protocol previously established for the intermolecular cyclopropanation of simple alkenes with alkenylcarbene complexes[15] was utilized to evaluate the reaction of methoxycarbene complex **1a** with isoprene (**2a**). Accordingly, this reaction was conducted in THF with five equivalents of diene **2a** in the presence of a catalytic quantity (10 mol% with respect to the diene) of 2,6-di-*tert*-butyl-4-methylphenol (BHT).[16] After heating for 9 h at 80 °C, a nearly equimolar mixture of tetrasubstituted cyclopentene enol ether **3a** and trisubstituted cyclopentene **4a** was obtained (Scheme 1). These structural isomers were easily separated by column chromatography. Compound **3a** was formed as a single diastereoisomer. We observed that performing the reaction in toluene led exclusively to the [3+2] cycloadduct **3a** in high yield, whereas heating the reaction in THF at 120 °C in a sealed flask gave only the [4+1] cycloadduct **4a**, although only in moderate yield. The reactions of other alkenylcarbene complexes with different 1,3-dienes were carried out under both of the above-mentioned reaction conditions to produce the corresponding [3+2] or [4+1] cycloadducts; the results are summarized in both Table 1 and Scheme 2.

The reaction of 3-aryl/heteroaryl- or 3-alkyl-substituted alkenylcarbene–chromium complexes **1a–d** with 1,3-dienes **2a–c** in toluene proceeded smoothly to afford the cyclopentenes **3a–f** diastereoselectively and with high efficiency (Table 1, entries 1–6). The reaction with the structurally analogous molybdenum–carbene complex **1e**, which was conducted at 45 °C, was less efficient (entry 7), while treatment with the corresponding tungsten complex **1f** gave compound **3a** with comparable yield, but required a much longer reaction time (entry 8).[17] Acid hydrolysis of enol ethers **3a–d** and **f** (where R^2 is not H) furnished cyclo-



			3a	4a
THF	80 °C	9 h	42%	36%
$PhCH_3$	80 °C	9 h	94%	–
THF	120 °C	1 h	–	47%

Scheme 1. Illustration of [3+2] and [4+1] cycloaddition reactions.



1a	**2c**	2 h	**4b**	31%
1b	**2a**	1 h	**4c**	30%

4b R^1 = Ph, R^2 = $(CH_2)_2CH=CMe_2$
4c R^1 = 2-furyl, R^2 = Me

Scheme 2. [4+1] Cycloaddition reactions.

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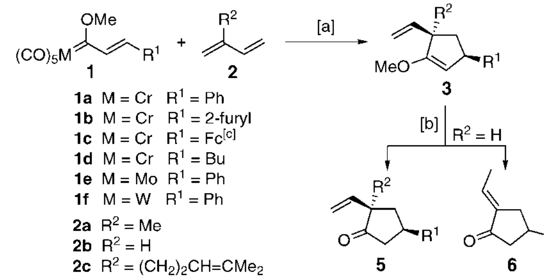
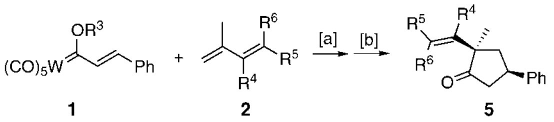
Table 1: [3+2] Cycloaddition reactions of alkenylcarbene complexes with simple 1,3-dienes and their subsequent hydrolysis reactions.



Entry	**1**	**2**	*t* [h][d]	**3**	Yield [%][e]	**5** or **6**	Yield [%][f]
1	**1a**	**2a**	9	**3a**	94	**5a**	70
2	**1b**	**2a**	10.5	**3b**	91	**5b**	85
3	**1c**	**2a**	24	**3c**	94	**5c**	90
4	**1d**	**2a**	5.5	**3d**	75[g]	**5d**	90
5	**1a**	**2b**	5	**3e**	95	**6a**	86
6	**1a**	**2c**	11	**3f**	86	**5e**	78
7	**1e**	**2a**	24[h]	**3a**	50[i]		
8	**1f**	**2a**	72	**3a**	80[i]		

[a] $PhCH_3$, 5 equiv of **2**, 10% BHT (with respect to the diene), 80 °C (bath temperature), sealed flask. [b] 2 N HCl, THF, room temperature, 10–15 min. [c] Fc = ferrocenyl. [d] Reaction time required for complete disappearance of starting carbene complex **1**. [e] Yield obtained from the cycloaddition reaction. [f] Yield obtained after hydrolysis. [g] Crude yield of impure product, which was submitted to hydrolysis without characterization. [h] Reaction temperature = 45 °C. [i] Crude yield.

Table 2: [3+2] Cycloadditions of tungsten–carbene complexes **1f** and **g** with 1,3-dienes **2d–f**.

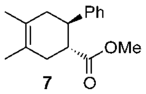


Entry	**1**	R3	**2**	R4	R5	R6	*t* [d][c]	**5**	Yield [%]
1	**1f**	Me	**2d**	Me	H	H	2.5	**5f**	50[d]
2	**1g**	menthyl[e]	**2d**	Me	H	H	8	**5f**	60
3	**1g**	menthyl[e]	**2e**	H	Me	H	2	**5g**	80
4	**1f**	Me	**2f**	H	Me	Me	4	**5h**	65

[a] $PhCH_3$, 5 equiv of **2**, 10% BHT (with respect to the 1,3-diene), 80 °C (bath temperature), sealed flask. [b] The crude product was treated with 2 N HCl, THF, room temperature, 10–15 min (for R^3 = Me) or 1 h (for R^3 = menthyl). [c] Reaction time required for complete disappearance of starting carbene complex **1** at 80 °C. [d] In this experiment compound **7** was also isolated in 25% yield. [e] (−)-Menthol was used to prepare the starting carbene complex **1g**.

pentanones **5a–e** (entries 1–4, 6), while the same hydrolysis reaction of enol ether **3e** (R^2 = H) occurred with concomitant isomerization of the terminal C=C bond to form 2-ethylidenecyclopentanone **6a** (entry 5). Both compounds **5** and **6** were isolated as unique diastereoisomers.

In addition, we have found that the more-substituted 1,3-dienes **2d** and **e** led to a complicated mixture of products when they were treated with chromium–carbene complex **1a** (5 equiv of **2**, 10% BHT, $PhCH_3$, 80 °C, 8–21 h). In contrast, tungsten–carbene complexes **1f** and **g** reacted with 1,3-dienes **2d–f** to give the corresponding [3+2] cycloadducts, which after subsequent acid hydrolysis were all isolated as the 2-vinylcyclopentanones **5** as a single diastereoisomer (Table 2). The reaction of methoxycarbene complex **1f** with a disubstituted 1,3-diene, such as 2,3-dimethyl-1,3-butadiene (**2d**), provided a 2:1 mixture of cyclopentanone **5f** and cyclohexene derivative **7**, respectively (Table 2, entry 1), whereas the analogous reaction with the trisubstituted 1,3-diene **2f** afforded only the corresponding [3+2] adduct **5h** (Table 2, entry 4). Formation of the minor compound **7**, which is the formal [4_D+2_C] cycloadduct/oxidation product, was completely suppressed by using the menthyloxycarbene complex **1g**, which on treatment with either of the disubstituted 1,3-dienes **2d** or **2e** afforded cyclopentanones **5f** and **g** (Table 2, entries 2 and 3).[18]



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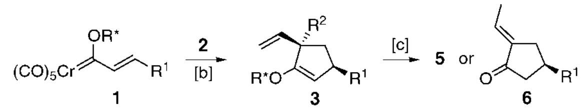
In contrast, the thermal reaction (120 °C in THF) of alkenylcarbene–chromium complexes **1a** and **b** with 1,3-dienes **2a** and **c** led to cyclopentene [4+1] adducts **4b** and **c** with low efficiency. A considerable quantity of unidentified products were obtained in these experiments (Scheme 2).[19,20] The connectivity of the atoms in **3** and **4** and the stereochemistry of **3**, **5**, **6**, and **7** were ascertained by NMR experiments (including HMQC, HMBC, COSY, and NOESY).

Finally, the possibility to prepare enantiomerically enriched cyclopentanones **5** and **6** was examined using 8-phenylmenthyloxy(alkenyl)carbene–chromium complexes **1h** and **i**.[14] These chiral complexes reacted with dienes **2a** and **b** to give the [3+2] adducts **3g–i** with variable diastereomeric excesses (Table 3). The most successful result was achieved in the reaction of **1h** and **2b**, in which **3h** was obtained as a diastereomerically pure material. Acid hydrolysis of **3h** led to the isolation of the enantiomerically pure 2-ethylidene-4-phenylcyclopentanone (+)-**6a**. The geometry of (+)-**5** and (+)-**6** was assumed from X-ray analysis of a single crystal of the major enantiomer (+)-**6b**, which exhibits an absolute configuration *R* for the newly created stereogenic center, and confirmed the *E* configuration of the exocyclic C=C bond.[21]

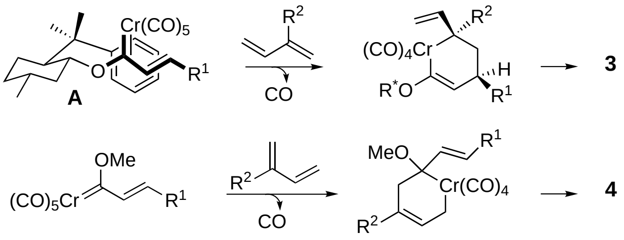
Formation of products **3** and **4** can be rationalized, according to previous models,[5,7d,10,17d] by means of a metalla-Diels–Alder reaction, which presumably occurs after an initial thermally induced dissociation of a CO ligand, followed by reductive elimination of the metal moiety (Scheme 3). The final [3+2] adduct **3** or [4+1] adduct **4** would involve the initial formal addition of the alkenylcarbene complex as a

Table 3: Asymmetric [3+2] cycloaddition reactions.[a]



1	R^1	2	R^2	3	Yield [%][d]	*de* [%][e]	5 or 6	Yield [%]	*ee* [%][f]
1h	Ph	**2a**	Me	**3g**	94	74	(+)-**5a**	73	70
1h	Ph	**2b**	H	**3h**	90	>99	(+)-**6a**	90	>99
1i	Fc	**2b**	H	**3i**	95	80	(+)-**6b**	85	79

[a] R* = 8-Phenylmenthyl; (−)-8-Phenylmenthol was used to prepare carbene complexes **1h** and **i**. [b] PhCH$_3$, 10 mol% BHT, 80 °C (bath temperature), sealed flask, 4–24 h. [c] 2 N HCl, THF, room temperature, 1 h. [d] Crude yield. [e] Determined by integration of ^{1}H NMR spectra of the crude product. [f] Determined by HPLC analysis on a chiral support.



Scheme 3. Proposed models for the [3+2] and [4+1] cycloaddition reactions.

1-chroma-1,3-diene and as a Cr=C dienophile, respectively. The sense of diastereochemical induction, which is in agreement with previous results,[14,17d] involves approach of the dienophile to the less-hindered face (front side in model **A**) of the metalladiene.

In conclusion, a general, selective synthesis of enantiomerically enriched alkenyl-substituted cyclopentanones is reported. The process is based on the new annulation of a three-carbon-atom unit of an alkoxy(alkenyl)carbene complex to a two-carbon-atom unit of a simple 1,3-diene. Studies of the scope of these cycloaddition reactions are currently in progress.

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[18] No asymmetric induction was observed in the cycloaddition reactions with the chiral menthyloxycarbene complex **1g**.

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