C–C Bond Formation between Fischer Carbene Complexes and Allylic Alcohols by a [3,4] Sigmatropic Rearrangement Promoted by a [1,2] $M(CO)_5$ Shift**

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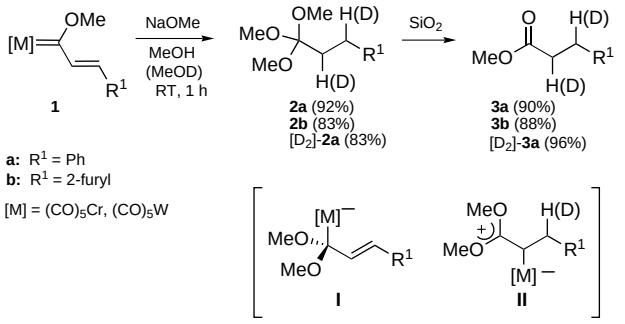
Dedicated to Professor José Elguero on the occasion of his 65th birthday

In the last few years Fischer carbene complexes have been developed into useful reagents for selective synthesis of organic molecules.[1] For instance, the importance of Michael additions of carbon nucleophiles and various cyclization reactions with unsaturated substrates in carbon–carbon bond formation is widely recognized.[2] However, studies of the reactivity of Fischer carbene complexes towards nucleophiles with heteroatoms, such as alcohols, have mainly focused on physical organic chemistry[3] or structural modification of the carbene complex.[4] Moreover, no practical applications of the reactions of alkenylcarbene complexes with oxygen nucleophiles are known, in spite of their superior versatility compared to simple carbenes and even alkynylcarbenes.[5, 6] We report herein preliminary studies on the reaction of Fischer alkenylcarbene complexes with unsaturated alcohols such as allyl and propargyl derivatives, as well as with simple alcohols such as methanol. These lead to unexpected C–H and C–C bond-forming reactions and might be regarded as a further surprise from Fischer carbene complexes.[7] Moreover, all reactions were equally effective for both chromium and tungsten carbene complexes.[8]

Alkenyl(methoxy)carbene complexes **1** (1 mmol) were dissolved in MeOH (5 mL) containing sodium methoxide (0.1 mmol) and stirred for 1 h at room temperature. Conventional chromatographic purification afforded saturated esters **3** in high yields (88–90%). Careful column chromatography of the crude reaction mixture on deactivated silica gel allowed orthoesters **2** to be isolated (83–92%). The reaction of **1a** with NaOMe/MeOD gave the corresponding deuterated methyl ester $[D_2]$**3a** (96%, 1:1 mixture of diastereoisomers) and the not readily accessible orthoester $[D_2]$**2a** (83%) (Scheme 1).

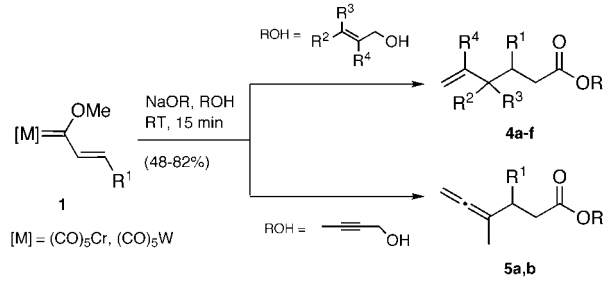
This simple transformation of alkenyl(methoxy)carbene complexes into saturated methyl esters implies the transfer of oxygen (oxidation) and hydrogen (reduction) to the carbene; the sole transfer agent is methanol. Species of types **I** and **II** are likely involved as active intermediates. Intermediate **I**, which arises from 1,2-addition of methoxide ion, was characterized for simple carbene complexes by Bernasconi et al.,[9]



Scheme 1. Reaction of sodium methoxide/methanol with Fischer alkenylcarbene complexes. Formation of saturated orthoesters **2** and their hydrolysis products **3**.

while species **II** would result from protonation at C-3 promoted by a [1,2] $M(CO)_5$ shift, a process well known from recent work by us and others.[10] Formation of **2** would require addition of methanol to **II**, protonation, and reductive elimination of the metal fragment.

On the basis of this mechanistic assumption, we tried to trap **I** with allylic alcohols. The reaction of **1** with allyl alcohol and derivatives thereof in the presence of the corresponding alkoxide ion (0.1 equiv, 20 °C, 15 min) resulted in the transfer of the allyl moiety to the carbene group by selective C–C coupling to give the ester adducts **4** (Scheme 2, Table 1). In



Scheme 2. Reaction of allyl and propargyl alcohols with Fischer alkenylcarbene complexes.

general, the reaction gives satisfactory yields, particularly for unsubstituted (R^2, R^3, $R^4 = H$; entries 1 and 2) and 3-substituted ($R^2 = Pr$; R^3, $R^4 = H$; entry 6) alcohols. Even the prenyl alcohol furnished quite efficiently the adducts **4c**, **d** ($R^2 = R^3 = Me$, $R^4 = H$; entries 3 and 4), in which a quaternary carbon center has been created. The C–C coupling occurs with low stereoselectivity (entry 6), but with complete regioselectivity between the γ-C atom of the allyl alcohol and the β-C atom of the carbene complex (entries 3, 4, and 6).[11] Moreover, the applicability of the method to propargylic alcohols was proven by the reaction of **1** with 2-butynol, which gave the cumulene derivatives **5** in acceptable yields (entries 7 and 8).

A reaction pathway in which a [3,4] sigmatropic rearrangement is promoted by a [1,2] shift of $M(CO)_5$ is consistent with these results (Scheme 3). The first step involves consecutive methoxy exchange and nucleophilic addition of alkoxide ion to give the tetrahedral intermediate **III**. Probably, **III** then undergoes a [1,2] $M(CO)_5$ shift followed by an anionic [3,4]

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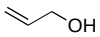
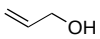
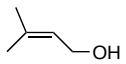
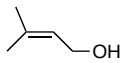
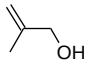
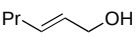
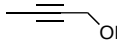
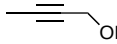
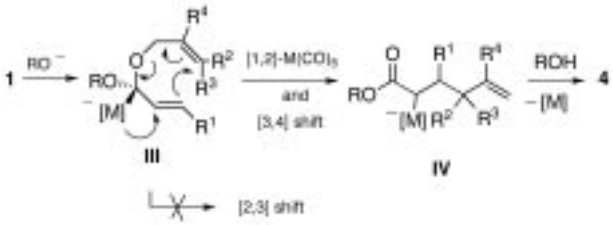
Table 1. Reaction of carbene complexes with allylic and propargylic alcohols.

Entry	ROH	R^1	R^2	R^3	R^4	Product	Yield [%][a]
1		Ph	H	H	H	**4a**	82
2		2-Furyl	H	H	H	**4b**	76
3		Ph	Me	Me	H	**4c**	48
4		2-Furyl	Me	Me	H	**4d**	55
5		Ph	H	H	Me	**4e**	50
6		2-Furyl	Pr	H	H	**4f**[b]	71
7		Ph	–	–	–	**5a**	62
8		2-Furyl	–	–	–	**5b**	58

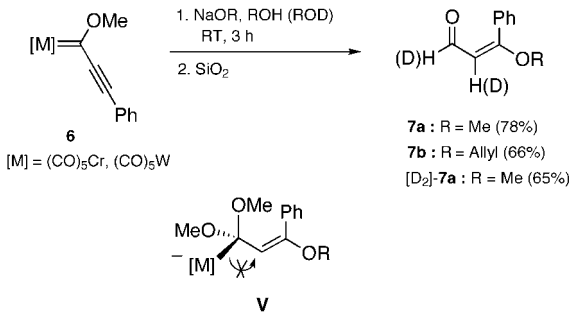
[a] Nonoptimized yields of purified isolated products. All yields refer to reactions with tungsten complexes. [b] Isolated as a 3:2 mixture of diastereoisomers.



Scheme 3. Mechanism proposed for the rearrangement observed in the formation of **4**.

sigmatropic rearrangement to form **IV**, which gives **4** upon protonation and reductive elimination of the metal moiety. The transition metal plays a crucial role in the *peri* selectivity of the process, since diallyl ether lithium species analogous to **III** do not undergo a [3,4] shift, but only a [2,3] sigmatropic rearrangement.[12]

Support for the above reaction pathways, specifically the 1,2-addition and [1,2] $M(CO)_5$ shift steps, was gained by studying the alcoholysis of alkynylcarbene complexes (Scheme 4). The reaction of **6** with NaOMe/MeOH and $NaOC_3H_5/C_3H_5OH$ (20°C, 3 h) furnished, after chromatographic purification, **7a** (78%) and **7b** (66%), respectively. Using deuteriated methanol gave $[D_2]$**7a** (65%). In this case,



Scheme 4. Reaction of alcohols with Fischer alkynylcarbene complexes.

the facile 1,4-addition of the alcohol precedes the 1,2-addition of alkoxide to give intermediate **V**. The electron-releasing nature of the alkoxy group at C-3 of **V** prevents 1,2 migration of the anionic metal complex fragment, and the process continues by conventional reductive metal elimination and hydrolysis.

In summary, we have demonstrated simple, novel applications of chromium and tungsten Fischer carbene complexes based on the [1,2] migration of the pentacarbonylmetal group. For instance, methanol readily transfers hydrogen to the carbon–carbon double bond of alkenylcarbene complexes by double protonation. More importantly, we discovered a new facet of Fischer carbene complexes: C–C bond formation by transfer of an allyl or propargyl group in a novel [3,4] sigmatropic shift.[13] This rearrangement, which is very rare in aliphatic compounds[14] and unkown for diallyl ethers,[12] is facilitated by the above-mentioned [1,2] $M(CO)_5$ shift.[15]

Experimental Section

General procedure for the preparation of **4** and **5**: The carbene complex (1 mM) was added to a solution (0.02 M) of the sodium alkoxide in the corresponding alcohol (5 mL). After stirring at room temperature until complete disappearance of the carbene complex (monitored by IR spectroscopy), the solvent was removed at reduced pressure and the crude product subjected to column chromatography (silica gel, hexane/ethyl acetate 40/1). All compounds gave satisfactory analytical data, including elemental analysis and mass and NMR spectra.

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[1] Recent reviews: a) W. D. Wulff in *Comprehensive Organic Synthesis*, *Vol. 5* (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon, New York, **1991**, p. 1065; b) W. D. Wulff in *Comprehensive Organometallic Chemistry II*, *Vol. 12* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, New York, **1995**, p. 469; c) M. P. Doyle in *Comprehensive Organometallic Chemistry II*, *Vol. 12* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, New York, **1995**, p. 387; d) D. F. Harvey, D. M. Sigano, *Chem. Rev.* **1996**, *96*, 271.

[2] A recent review on important applications of Fischer carbene complexes in asymmetric synthesis: W. D. Wulff, *Organometallics* **1998**, *17*, 3116.

[3] C. F. Bernasconi, *Chem. Soc. Rev.* **1997**, *26*, 299.

[4] a) R. Aumann, H. Nienaber, *Adv. Organomet. Chem.* **1997**, *41*, 163; b) A. de Meijere, *Pure Appl. Chem.* **1996**, *68*, 61.

[5] Alkenyl-, aryl- and, alkylcarbene complexes undergo base-catalyzed hydrolysis to give aldehydes: a) C. F. Bernasconi, F. X. Flores, K. W. Kittredge, *J. Am. Chem. Soc.* **1997**, *119*, 2103; b) R. Aumann, P. Hinterding, C. Krüger, R. Goddard, *J. Organomet. Chem.* **1993**, *459*, 145.

[6] The formation of multicomponent mixtures from simple carbene complexes and methoxide ion: E. O. Fischer, U. Schubert, W. Kalbfus, C. G. Kreiter, *Z. Anorg. Allg. Chem.* **1975**, *416*, 135. For the CH_3O^-/CD_3O^- exchange reaction, see U. Schubert, E. O. Fischer, *Liebigs Ann. Chem.* **1975**, 393.

[7] In accordance with the thinking of H.-U. Reissig in a recent paper: M. Hoffmann, M. Buchert, H.-U. Reissig, *Angew. Chem.* **1997**, *109*, 281; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 283.

[8] Throughout the text and schemes the yields refer to the reactions of tungsten carbene complexes.

[9] C. F. Bernasconi, F. X. Flores, J. R. Gandler, A. E. Leyes, *Organometallics* **1994**, *13*, 2186.

  1433-7851/99/3808-1092 $ 17.50+.50/0

[10] a) N. Iwasawa, T. Ochiai, K. Maeyama, *Organometallics* **1997**, *16*, 5137; b) J. Barluenga, M. Tomás, A. Ballesteros, J. Santamaría, R. J. Carbajo, F. López-Ortiz, S. García-Granda, P. Pertierra, *Chem. Eur. J.* **1996**, *2*, 88. This migration was previously suggested: c) H. Fischer, T. Meisner, J. Hofmann, *Chem. Ber.* **1990**, *123*, 1799; d) K. Dötz, C. Christoffers, P. Knochel, *J. Organomet. Chem.* **1995**, *489*, C84.

[11] Alternatively, the regioselective formation of compounds of type **4** by addition of allyl metal reagents to α,β-unsaturated carbonyl compounds has not been definitively addressed. For elegant work on this subject, see T. Ooi, T. Kondo, K. Maruoka, *Angew. Chem.* **1997**, *109*, 1231; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1183.

[12] a) Review: J. A. Marshall in *Comprehensive Organic Synthesis*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming, G. Pattenden), Pergamon, New York, **1991**, p. 975; b) V. Rautenstrauch *Chem. Commun.* **1970**, 4.

[13] An interesting case of C–C bond formation by sequential addition of propargyl alcohol to [ethoxy(phenylethynyl)carbene]pentacarbonylchromium(0) and Claisen rearrangement: A. Segundo, J. M. Moretó, J. P. Viñas, S. Ricart, *Organometallics* **1994**, *13*, 2467.

[14] I. Erden, F.-P. Xu, W.-G. Cao, *Angew. Chem.* **1997**, *109*, 1557; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1516.

[15] This study was also prompted by the fact that undesired oxidation of the carbene to a carbonyl group frequently took place when working with Fischer carbene complexes. The current results suggest that nucleophilic addition/demetalation/hydrolysis processes might be responsible rather than the routinely invoked accidental oxidation by atmospheric oxygen.

treatment of arthritis.[2] The equally potent β-lactone **2** acts by selective acylation of the N-terminal threonine residue of a protein subunit of the cylindrical 20*S* proteasome,[3] a result confirmed by X-ray crystallographic studies at 2.4 Å resolution of the lactacystin inactivated proteasome.[4] Recent mechanistic studies have shown that lactacystin hydrolyzes to the inactive dihydroxy acid through its β-lactone **2**. It is the β-lactone species that subsequently acylates the proteasome and results in its inactivation (Figure 1).[3b] The presence of intracellular levels of glutathione (GSH) converts **2** into lactathione, which is believed to act as a "lactone reservoir".[3c]

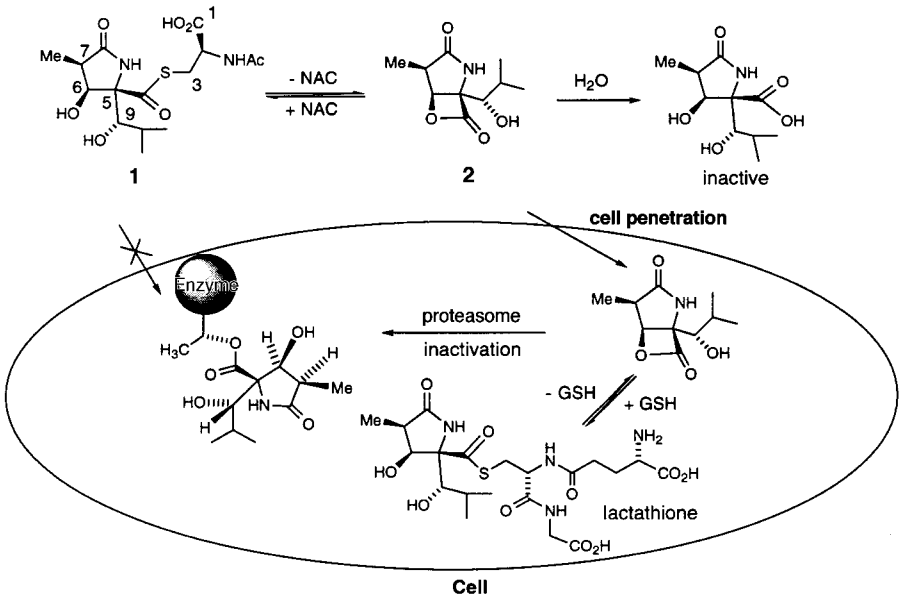

Figure 1. Mechanism of proteasome inhibition by (+)-lactacystin.

Total Synthesis of (+)-Lactacystin**

James S. Panek* and Craig E. Masse

(+)-Lactacystin (**1**) is a metabolite isolated from *Streptomyces sp.* OM-6519 that exhibits significant neurotrophic activity.[1a] The relative and absolute stereochemistry of (+)-lactacystin has been elucidated by ^{1}H and ^{13}C NMR spectroscopy, and single-crystal X-ray analysis.[1b] (+)-Lactacystin has been shown to be a potent proteasome inhibitor, and has led to speculation that it may be therapeutically useful in the treatment of arthritis.

(+)-Lactacystin (**1**) is a unique member of a class of neurotrophic factors since it consists of a nonprotein γ-lactam thioester. Its compact array of five resident stereogenic centers renders (+)-lactacystin a significant target for synthesis; a number of other syntheses of **1** have been reported.[5] A critical issue relative to the synthesis of lactacystin is the fact that most of the structural features of **1** are essential to maintain its unique biological profile. The C4-carboxylic moiety and the C6-hydroxyl group must be *cis* because of the necessity for β-lactone formation to achieve proteasome inactivation.[4] The absolute configuration of the C9-hydroxyl and the isopropyl substituents are also essential for biological activity.[5c] The C7-methyl group is critical to the activity and stability of **1**, although replacement of this group with either ethyl or isopropyl groups does lead to a two- to threefold increase in activity.[5c]

As a consequence of these strict structural and stereochemical requirements any synthesis of **1** must not only be efficient, but also highly selective for the introduction of each of the stereogenic centers. Our approach to lactacystin nicely compliments the synthesis by Smith and co-workers[5e] through the use of the hydroxyleucine-derived oxazoline **5** to set the stage for the critical *anti*-crotylation reaction for the installation of the C6 and C7 stereocenters.

Retrosynthetic analysis of the lactacystin skeleton (Scheme 1) reveals two key operations: a) stereoselective

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

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