Carbene Complexes

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# Formal Alkyne Insertion into Alkoxycarbene Complexes: Simple Access to Enantiopure Group 6 Alkynyl(alkoxy)carbene Complexes**

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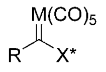
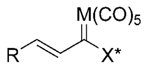
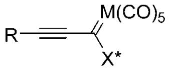
*Dedicated to Professor Heinz Hoberg*
*on the occasion of his 80th birthday*

Since their discovery in 1964, Fischer carbene complexes have been developed into efficient carbene-transfer agents.[1] The successful implementation of enantioselective processes through chiral nonracemic carbene complexes of chromium and tungsten has greatly increased their potential in selective synthesis.[2] In particular, chiral alkoxy carbenes **A** and **B**

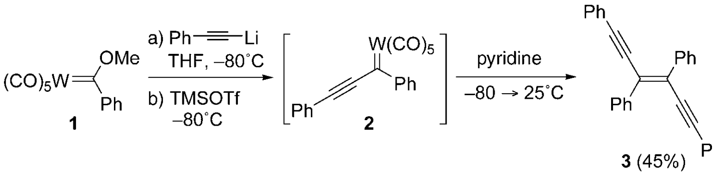

**A**


**B**


**C**

derived from enantiopure alcohols (X* = OR) are efficient systems in a wide array of reactions,[3] while the less reactive chiral amino carbene complexes **A** and **B** (X* = $NR_2$) have proved to be useful when the metal carbene function is not involved, for example, in aldol, Michael, and Diels–Alder reactions.[4] It is remarkable that there was previously no methodology to access chiral alkynyl(alkoxy)carbenes of type **C** (X* = OR).[5]

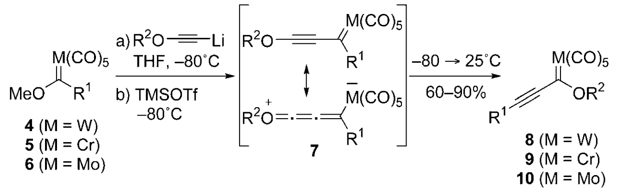
We report herein that group 6 enantiopure alkynylcarbene complexes derived from chiral alcohols, as well as related polyalkynyl(alkoxy)carbenes, can be readily prepared from ordinary alkoxy carbenes via non-heteroatom-stabilized carbene complexes. First, the tungsten phenyl(methoxy)carbene complex **1** was treated in THF at −80 °C with lithium phenylacetylide (Scheme 1). Once the addition was completed the color of the solution changed from orange to yellow. Trimethylsilyl triflate (TMSOTf) was added, and the mixture was stirred for a few minutes until the solution became deep blue. The nonstabilized carbene complex **2**, which is presumed to be formed by elimination of methyl trimethylsilyl ether from the tetrahedral addition species,[6] were not isolated, but allowed to dimerize in the presence of pyridine (5 equiv) to (*E*)-1,3,4,6-tetraphenyl-3-hexen-1,5-diyne (**3**; 45 % yield).[7]



***Scheme 1.*** Generation and dimerization of non-heteroatom-stabilized alkynyl carbene complex **2**.

Unlike some previous reports regarding alkynylcarbene complexes of rhodium,[8] rhenium,[9] and manganese,[10] neither 1,3-migration of the metal center nor products derived thereof were observed in the case of intermediates of type **2**. Focused on this point, we checked whether the rearrangement is an electronically controlled process by using appropriate lithium reagents such as alkoxyacetylides. Gratifyingly, phenylethynyl(ethoxy)carbene complex **8a** was obtained in 90 % yield from carbene complex **4a** and ethoxyethynyl lithium (Table 1, entry 1). We observed that the initially formed nonstabilized carbene **7** undergoes rapid rearrangement, even at low temperatures (below −50 °C), to the more stable alkoxy carbene **8a**. Since alkynyl carbenes were also found to react readily, the reaction was extended to the preparation of elusive Fischer carbene complexes such as

***Table 1:*** Synthesis of achiral (1–3) and enantiopure (4–8) Group 6 alkynyl(alkoxy)carbene complexes **8**–**10**.



| Entry | $R^1$ | $R^2$ | **8** [%][a] | **9** [%][a] | **10** [%][a] |
|---|---|---|---|---|---|
| 1 | Ph | Et | **8a** (90) | | |
| 2 | PhC≡C | Et | **8b** (81) | **9b** (89) | |
| 3 | Ph(C≡C)$_2$[b] | Et | **8c** (60) | | |
| 4 | Ph | menthyl[c] | **8d** (90) | **9d** (77) | **10d** (85) |
| 5 | Ph | 8-PhMenth[d] | **8e** (90) | **9e** (85) | **10e** (85) |
| 6 | Ph | 2-PhCy[e] | **8f** (87) | **9f** (84) | |
| 7 | PhC≡C | 8-PhMenth[d] | **8g** (75) | **9g** (80) | |
| 8 | *i*Pr | 2-PhCy[e] | **8h** (65) | | |

[a] Yields of pure, isolated products. [b] Complex **8b** is used as starting carbene. [c] Menthyl = (1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyloxy. [d] 8-PhMenth = (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)-cyclohexyloxy. [e] 2-PhCy = (1*R*,2*S*/1*S*,2*R*)-2-phenylcyclohexyloxy.

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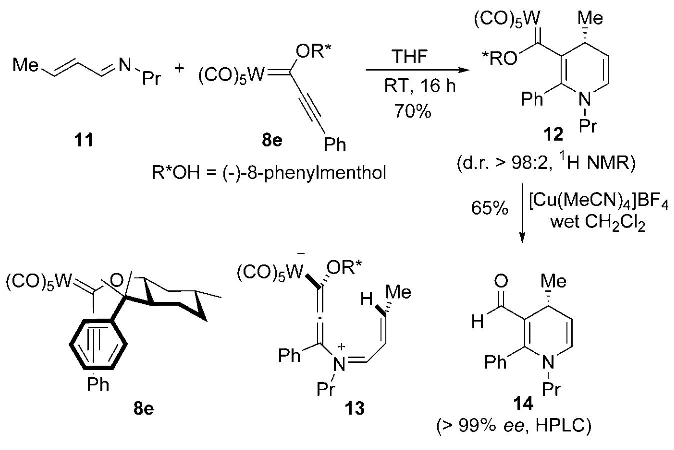
Supporting information for this article (characterization data and $^{13}$C NMR spectra of **8, 9, 10, 12, 14**) is available on the WWW under http://www.angewandte.org or from the author.

diynyl(alkoxy)carbenes.[11] This is exemplified for 4-phenyl-1,3-butadiynyl carbenes of tungsten **8b** (81 %) and chromium **9b** (89 %) (Table 1, entry 2). Moreover, (6-phenyl-1,3,5-hexatriynyl)carbene complex **8c** (Table 1, entry 3) was synthesized in 60 % yield from the tungsten diynylcarbene complex **8b** as starting material.

This finding prompted us to investigate whether it was feasible to access group 6 alkynylcarbenes with a chiral alkoxy group, as the preparation of such compounds had hitherto been unsuccessful. Importantly, a number of alkynyl carbenes derived from chiral alcohols were readily synthesized in high yields by following the routine protocol (Table 1, entries 4–8). The process seems to be of wide scope on the basis of the following observations: 1) common chiral bulky alkoxy groups are efficiently assembled into the carbene structure (menthyloxy, 8-phenylmenthyloxy, *trans*-2-phenylcyclohexyloxy); 2) the process is applicable not only to tungsten and chromium metals (compounds **8** and **9**), but also to the much more elusive molybdenum metal (compounds **10**);[12] 3) besides aryl-substituted complexes, enolizable carbenes ($R^1 = i$Pr; Table 1, entry 8) can also be employed successfully.

As enantioselective cycloaddtition reactions with chiral alkynes are very rare,[13–15] the chiral induction by the alkoxy group was then examined in the [4+2]-cycloaddition with 1-azadienes (Scheme 2).[16] Thus, the reaction of 1-azadiene **11** with phenylethynyl(8-phenylmenthyloxy)carbene complex **8e** in THF at room temperature furnished, after chromatographic purification, the dihydropyridine complex **12** in 70 % yield as a sole regio- and diastereoisomer (by NMR spectroscopic analyis). The structure of the cycloadduct was determined by a X-ray crystallographic analysis.[16] According to our previous reports[17,18] we propose a working model that involves, 1) diastereoselective conjugate addition of the nitrogen atom of **11** to the more accessible face of alkyne (probably due to a π-stacking effect as shown) to form the intermediate **13** with central and axial chirality; and 2) cyclization of **13** through the *Re* face of the C=C bond to afford the observed cycloadduct **12**.[19] The latter was demetalated, and the chiral auxiliary removed by treatment with $[Cu(MeCN)_4]BF_4$ in wet $CH_2Cl_2$ to provide the aldehyde **14** (65 %, > 99.5 % *ee*).[20]



***Scheme 2.*** Diastereoselective [4+2] cycloaddition of 1-azadiene **11** and carbene **8e**. Synthesis of enantiopure 1,4-dihydropyridine **14**.

In conclusion, new aspects that enhance the synthetic utility of Fischer carbene complexes are featured in this report: 1) 1,3-alkynyl carbene ligand rearrangement is a very easy process for non-heteroatom-stabilized alkynyl carbenes and seems to be thermodynamically controlled; 2) based on this finding a facile and general access to novel chiral alkynyl(alkoxy)carbene complexes was undertaken; 3) their efficient chiral induction was proved and allowed the first enantioselective synthesis of 1,4-dihydropyridines through [4+2]-cycloaddition;[21] 4) this procedure should find application in the extensive chemistry already reported for achiral alkynyl(alkoxy)carbene complexes of various transition metals;[1c] 5) this methodology might provide access to different achiral and chiral heteroatom-susbstituted carbene complexes of metals and heteroatom substituents other than Group 6 and alkoxy or amino groups.

## Experimental Section

General procedure (**8**, **9**, **10**): The appropriate Fischer carbene complex **4–6** (1 mmol) was added to a solution of lithium alkoxyacetylide (1.5 mmol) in THF (10 mL) at −80 °C. After stirring for 15 minutes at this temperature, the mixture was transferred with a cannula into a solution of trimethylsilyl triflate (1.6 mmol, 290 μL) in THF (5 mL) at −80 °C. The deep coloured solution was allowed to reach room temperature. Removal of the solvents and chromatographic purification of the residue on silica gel (hexanes) gave the corresponding Fischer carbene complexes **8–10**.

**12** and **14**: 1-Azadiene **11** (0.122 g, 1.1 mmol) was added to a solution of the complex **8e** (0.484 g, 1 mmol) in THF (20 mL), and the mixture was stirred at room temperature for 16 h. Removal of solvents followed by chromatographic purification on silica gel (10 % ethyl acetate in hexanes, $R_f = 0.55$) yielded pure dihydropyridine complex **12** as a sole regio- and diastereoisomer (0.55 g, 70 %). Further crystallization from pentane gave crystals suitable for X-ray crystallographic analysis. A solution of cycloadduct **12** (0.4 g, 0.5 mmol) in $CH_2Cl_2/H_2O$ (49:1 v/v; 50 mL) was stirred at room temperature with $[Cu(CH_3CN)_4]BF_4$ (0.15 g,0,5 mmol) for 48 h. The mixture was quenched with water (10 mL) and extracted with dichloromethane (3 × 20 mL). The organic layer was washed with water (2 × 20 mL) and dried over $Na_2SO_4$. The solvents were removed, and the residue purified by chromatography on silica gel (hexanes/EtOAc/$Et_3N$ 5:1:1; $R_f = 0.45$) to afford the metal-free cycloadduct **14** (79 mg, 65 %).

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