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A New Electron-Poor Fischer Carbene Complex: Unusually Efficient and General Benzannulation of Amino-Stabilized Alkenyl Fischer Carbene Complexes

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In recent years, Fischer carbene complexes have been developed into useful reagents for selective carbon−carbon bond formation.[1] Probably the formal $[3 + 2 + 1]$ cycloaddition of alkoxycarbene complexes with alkynes (Dötz benzannulation reaction) represents the most striking example.[2] Significantly, one can realize that the carbene ligand of all Fischer carbene complexes hitherto employed contains electron-donating substituents (alkyl, aryl, heteroaryl, alkoxy, amino, etc). Recently, the participation of the [[β-(methoxycarbonyl)ethenyl](*tert*-butyldimethylsiloxy)methylene]pentacarbonylchromium(0) complex **I** (Figure 1) has been postulated as a reactive intermediate in the $[3 + 2]$ cyclization of Fischer alkenyl carbene complexes and captodative olefins.[3] Therefore, we thought it of interest to synthesize alkenyl Fischer carbene complexes having electron-withdrawing substituents and to study their reactivity, particularly their ability to participate in the benzannulation reaction. We first focused on the alkenyl(amino)carbene complex **1** since the benzannulation reaction of conventional aryl- and alkenyl(amino)carbene complexes remains severely limited in comparison with that of the corresponding alkoxy counterparts. This is clear in terms of (i) much lower reactivity (reaction temperature: $>$90 °C vs 50−60 °C) and (ii) competitive, or exclusive, cyclopentannulation (cyclization without CO incorporation).[4] Significantly, Wulff et al.[5] showed for the first time that alkenyl(dimethylamino)carbene complexes **II** (R^1, R^2 = alkyl, H) react with 1-pentyne, but not with internal alkynes, to give selectively the benzannulation product with moderate yield (up to 65% optimized yield).

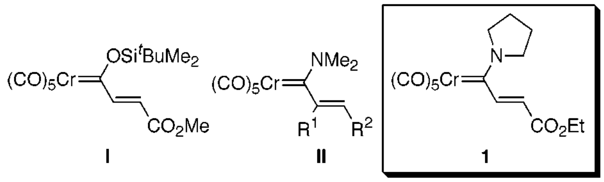
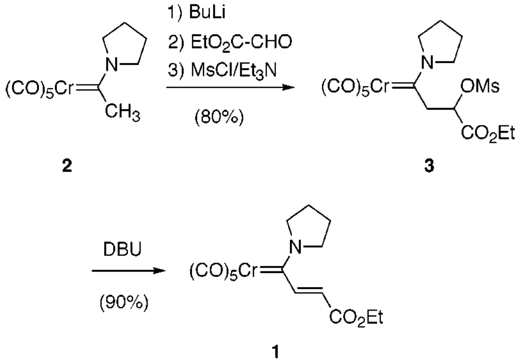


Figure 1.

Scheme 1



The preliminary results of this study are disclosed herein and show that chromium complex **1** is readily prepared and smoothly undergoes the benzannulation reaction with various types of alkynes.[6]

The synthesis of the target complex is accomplished by a standard procedure (Scheme 1).[7] Thus, the sequential treatment of pentacarbonyl(methylpyrrolidinocarbene)chromium (0) **2** with butyllithium, ethyl glyoxylate (5 equiv), and methanesulfonyl chloride yielded the aldol derivative **3**, which was further converted into β-(ethoxycarbonyl)alkenylpyrrolidino complex **1** upon DBU promoted elimination. This procedure allowed us to isolate **1** (72% overall yield from **2**) solely as the *E*-isomer ($J_{\mathrm{H-H}}$ = 16 Hz).[8]

The benzannulation reaction of chromium carbene complex **1** was accomplished efficiently in THF at 60 °C using an excess of the alkyne (1.5−4.0 equiv). The resulting phenol derivatives **5** and **6** were isolated and purified by column chromatography (Scheme 2, Table 1).[8] Thus, terminal alkynes such as phenylacetylene and 1-hexyne gave **5a** and **5b** in $>$88% yield (entries 1 and 2) while electron-rich and functionalized alkynes (entries 3 and 4, respectively) also worked fine, affording **5c,d**. It was delight to

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(8) **Experimental Procedure for the Synthesis of Carbene Complex 1**. Complex **2** (10 mmol) in THF (30 mL) was deprotonated (−78 °C, 30 min) with *n*-BuLi (11 mmol). Ethyl glyoxylate (50 mmol) was added, and the resulting mixture was allowed to reach rt. After aqueous workup, the resulting aldol was treated with MsCl (20 mmol) and Et_3N (22 mmol) in CH_2Cl_2 (30 mL) at 0 °C for 2 h to give, after quenching with methanol (20 mL) and chromatography on silica gel, the mesylate derivative **3**. A solution of compound **3** (8 mmol) in diethyl ether (30 mL) was treated with DBU (12 mmol) and the resulting mixture stirred at room temperature overnight. Aqueous workup and chromatographic purification on silica gel furnished the carbene complex **1** as a yellow solid in 72% overall yield. **Experimental Procedure for the Benzannulation Reaction:** To a solution of complex **1** (0.2 mmol) in THF (7 mL) was added an excess of the appropriate alkyne at room temperature. The mixture was heated (16 h for **5a**−**d**,**g**, 48 h for **5e**−**f**, and **6a**−**c**) at 60 °C. The solvent was then removed, and the resulting residue was subjected to flash chromatography on silica gel using mixtures of hexane/ethyl acetate (**5a**−**b**,**d**−**g** and **6a,b**) and hexane/dichloromethane (**5c** and **6c**) as eluents.

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Scheme 2

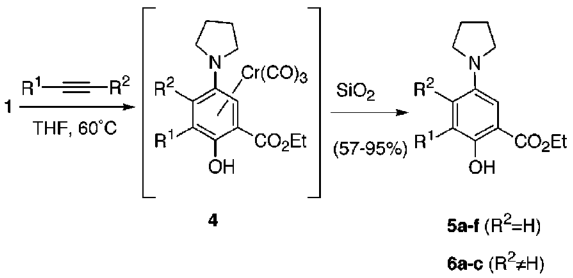

Table 1. Benzannulation of Carbene Complex 1a[a]

entry	compd	R^1	R^2	yield[b] (%)
1	**5a**	Ph	H	95
2	**5b**	Bu	H	88
3	**5c**	ferrocenyl	H	85
4	**5d**	1-cyclopentenyl	H	82
5	**5e**	COOEt	H	94
6	**5f**	COMe	H	63
7	**5g**[c]	$(CH_2)_2$−OTs	H	68
8	**6a**	Et	Pr	75
9	**6b**	Ph	Ph	57
10	**6c**	Ph	Me	70

[a] All the reactions were carried out in THF at 60 °C with 4 equiv of alkyne, except for entries 5, 6, and 9 (1.5 equiv), at 0.03 M in carbene complex. [b] Isolated, nonoptimized yields of purified products. [c] See Figure 2 for the structure of **5g**.

find out that electron-poor alkynes behaved in the same way and with very high yield as shown in entries 5 and 6 for ethyl propynoate and 3-butyn-2-one. We have also found that the benzannulation of carbene complex **1** with internal alkynes such as 3-hexyne, diphenylacetylene, and 1-phenyl-1-propyne takes place with acceptable yields (57−75%, entries 8−10).

Regardless of the electronic nature of the alkyne the regiochemistry found in all cases was that expected on the basis of steric control[9] and was unambiguously confirmed in two cases. First, the reaction of **1** with 3-butynyl tosylate afforded the benzannulation/cyclization product **5g** (Table 1, entry 7, and Figure 2), and second, the benzannulation of **1** with ethyl propynoate led to the symmetrical adduct **5e** (Table 1, entry 5).

Finally, the $(CO)_3Cr$-arene intermediate **4** could be easily isolated as the O-silylated complex.[10] Thus, complex **7** (Figure 2) was obtained in 70% yield when the reaction of **1** with phenylacetylene was run in toluene (60 °C, 16 h) and was followed by treatment with $ClSi^tBuMe_2/Et_3N$ and column chromatography.

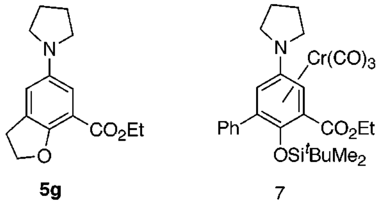

Figure 2.

In summary, a new alkenyl(amino)carbene chromium complex bearing an electron-withdrawing group at the C_β-position was prepared for first time and found to display a remarkable reactivity toward different types of alkynes. Specifically, the benzannulation of aminocarbene complexes with carbonyl-conjugated alkynes[11] as well as the intermolecular benzannulation of alkenyl(amino)carbene complexes with internal alkynes[4] are reported for the first time. The benzannulation products, polysubstituted salicylic acid esters,[12] were cleanly formed under reaction conditions that are comparable to those required in the case of alkoxycarbene complexes. Finally, further studies are being directed to investigate the reasons for the particular behavior of this type of carbene complexes in the benzannulation reaction as well as their potential in asymmetric processes.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**, **5a**−**g**, **6a**−**d,** and **7** (6 pages).

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[9] In the case of terminal alkynes (R^2 = H) the coupling constant $^4J_{H-H}$ for the aromatic hydrogens of **5** was 2−3 Hz. The regiochemistry of **6c** was determined by 2D NOESY experiments.

[10] For the preparation of protected hydroquinone chromium(tricarbonyl) complexes from alkenyl(alkoxy)carbene complexes, see: Chamberlin, S.; Wulff, W. D.; Bax, B. *Tetrahedron* **1993**, *49*, 5531.

[11] Even in the case of Fischer alkoxycarbene complexes, the presence of carbonyl groups conjugated with the alkyne is a major limitation for the benzannulation reaction. Specifically, alkenyl(alkoxy)carbene derivatives lead to phenol derivatives in <22% yield; see, for instance: Wulff, W. D.; Chang, K.-S.; Tang, P.-C. *J. Org. Chem.* **1984**, *49*, 2293.

[12] Compounds of type **5e** seem to be attractive as ligands in transition-metal catalysis after appropriate derivatization of both ester functions. For recent preparation and coordination chemistry of related ligands, see: (a) Fharni, C. J.; Pfalz, A. *Helv. Chim. Acta* **1998**, *81*, 491. (b) Fharni, C. J.; Pfalz, A.; Neuburger, M.; Zehnder, M. *Helv. Chim. Acta* **1998**, *81*, 507.