

Coupling of Fischer Carbene Complexes with Conjugated Enyne–Aldehydes and Ketones: A Novel Synthesis of Furan Derivatives

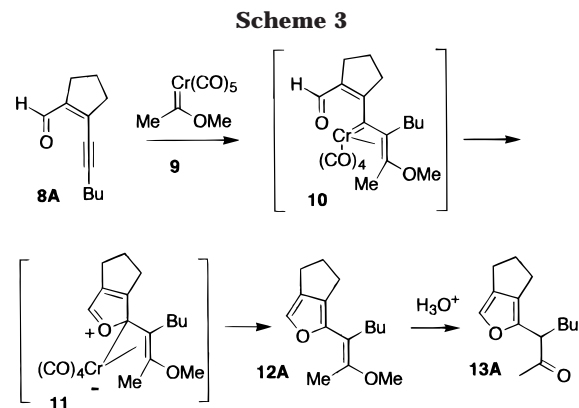
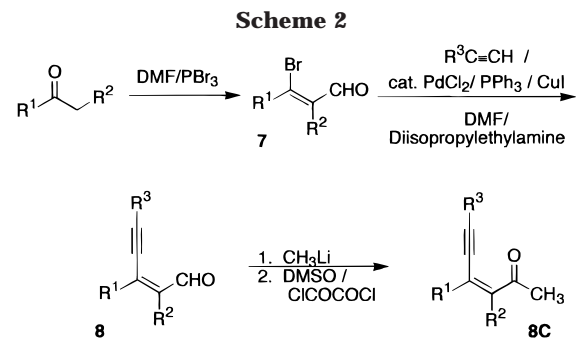
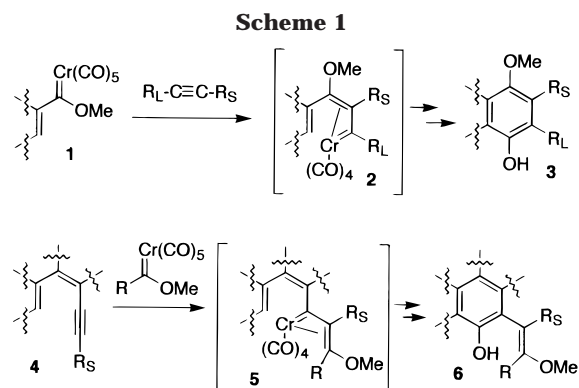
James W. Herndon^{*1a} and Haixia Wang^{1b}

Department of Chemistry and Biochemistry, New Mexico State University, Las Cruces, New Mexico 88003, and Department of Chemistry & Biochemistry, University of Maryland, College Park, Maryland 20742-2021

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The synthesis of highly-substituted aromatic rings (e.g., **3**, Scheme 1) via the coupling of alkynes with α,β -unsaturated Fischer carbene complexes (Dötz reaction) is a reliable and high-yielding process and has been used frequently in complex natural products synthesis.² A key intermediate in this reaction is the $\alpha,\beta,\gamma,\delta$ -unsaturated carbene complex **2**, which forms via a regio- and stereoselective alkyne insertion reaction. Alternative reaction processes that generate similar intermediates can serve as mechanism-based alternatives to the Dötz reaction.³ For example, conjugated *Z*-vinylacetylenes of general structure **4** couple with simple carbene complexes to afford $\alpha,\beta,\gamma,\delta$ -unsaturated carbene complex **5**, which ultimately affords benzannulation products derived from phenol **6**.^{3b} A new synthetic route to oxygen heterocycles might be realized if a C–O π -bond could replace the γ,δ -C–C π -bond of reactive intermediates **2** or **5**. For the expeditious evaluation of this idea,⁴ the reaction of enyne–carbonyl compounds with Fischer carbene complexes has been examined. Herein, the initial studies of this reaction, which leads to vinylfuran derivatives, are reported.

A variety of enyne–carbonyl derivatives were prepared according to the general synthetic protocol in Scheme 2, involving conversion of a ketone to the β -bromo enal derivative⁵ followed by palladium-catalyzed alkylation. In the case where $R^2 = H$, the reaction was stereoselective for the isomer depicted. Initially, the reaction of enyne–aldehyde **8A** (Scheme 3) with methylcarbene complex **9** in refluxing dioxane was investigated. This coupling reaction afforded vinylfuran derivative **12A**. This compound was not air stable; however, the hydrolysis product, ketone **13A**, was considerably easier to isolate and purify; the yield for conversion of enyne–aldehyde **7A** to ketone **13A** was 84%. The mechanism depicted in Scheme 3 has been proposed for the formation of the furan derivative. Regioselective and stereoselective alkyne insertion affords vinylcarbene complex **10**.² Nucleophilic attack by oxygen affords carbonyl ylide intermediate **11**,⁶ which then loses chromium to afford the furan derivative. A variety of enyne–carbonyl compounds were prepared and tested in their reaction with methylcarbene complex **9**. As noted in Table 1, the coupling of enyne–



aldehydes or ketones and with methylcarbene complex **9** is a general process for the construction of vinylfuran derivatives; the reaction has been tested for a variety of derivatives differing in the degree of substitution within the enyne functionality. The only enyne–carbonyl compound that failed to produce a furan derivative was the enyne ester (Table 1, entry D). Neither starting material was recovered from this reaction; no identifiable compounds could be isolated from this complex reaction mixture.⁷ This failure is presumably due to the lower nucleophilicity of the carbonyl oxygen;⁸ thus, the crucial cyclization to the carbonyl ylide intermediate does not occur.

(1) (a) Address correspondence to this author at New Mexico State University. E-mail: jherndon@nmsu.edu. (b) University of Maryland.

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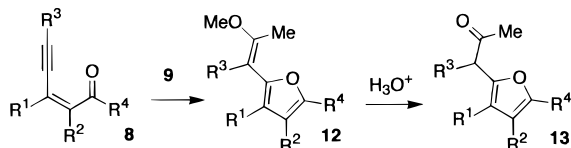
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(6) A similar process has been proposed for rhodium carbenoids derived from diazo compounds. Padwa, A.; Kinder, F. R. *J. Org. Chem.* **1993**, *50*, 21–28.

(7) A variety of compound classes have been reported from the coupling of carbene complex **9** with simple alkynes. (a) For a detailed discussion, see: Challener, C. A.; Wulff, W. D.; Anderson, B. A.; Chamberlin, S. A.; Faron, K. L.; Kim, O. K.; Murray, C. K.; Xu, Y.-C.; Yang, D. C.; Darling, S. D. *J. Am. Chem. Soc.* **1993**, *115*, 1359–1376 and references therein. (b) Polymerization reactions are also possible. Katz, T. J.; Lee, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 422–424.

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Table 1. Synthesis of Furans 12 and 13 from the Coupling on Enyne–Carbonyl Compounds 8 with Carbene Complex 9



entry ^a	R ¹	R ²	R ³	R ⁴	enol ether (yield, %)	ketone (yield, %) ^b
A ^c	R ¹ –R ² = –(CH ₂) ₃ –	Bu	H	H	not isolated	84
B ^c	R ¹ –R ² = –(CH ₂) ₃ –	H	H	H	not isolated	79
C ^c	R ¹ –R ² = –(CH ₂) ₃ –	Bu	CH ₃	H	not isolated	66
D ^d	R ¹ –R ² = –(CH ₂) ₃ –	Bu	OCH ₃	H	0	0
E ^e	<i>t</i> -Bu	H	Bu	H	68	<i>f</i>

^a Entry letters correlate with R¹–R⁴ substituents for compounds **8**, **12**, and **13**. ^b Overall yield from coupling of **8** and **9** followed by hydrolysis. ^c The enyne–carbonyl compound **8** was prepared from bromo aldehyde **7A** (R¹–R² = –(CH₂)₃–). ^d The enyne ester was prepared from the enol triflate derived from methyl 2-oxocyclopentanecarboxylate.⁹ ^e The enyne–carbonyl compound **8E** was prepared from bromo aldehyde **7E** (R¹ = *t*-Bu, R² = H). ^f The hydrolysis was not successful.

In summary, the coupling of carbene complexes with conjugated enyne–carbonyl compounds provides a versatile synthetic route to furan derivatives¹⁰ using readily-synthesized starting materials. Although furan derivatives have

been reported from the coupling of alkynes and Fischer carbene complexes,¹¹ this method is unique in that the carbons of the newly-synthesized furan ring contain no heteroatoms, and the carbon-carbon bonds produced from carbene–alkyne coupling are external to the furan ring. Further investigation of this reaction and of the coupling of carbene complexes with other conjugated enyne–carbonyl derivatives is in progress.

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Supporting Information Available: Experimental procedures for the synthesis of enyne–carbonyl compounds and products in Table 1. Photocopies of ¹H and ¹³C NMR spectra for all new compounds and ¹H NMR spectra for crude enol ethers **12A** and **12C** (24 pages).

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