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Contingency and Serendipity in the Reactions of Fischer Carbene Complexes with Conjugated Triynes

May Xiao-Wu Jiang, Manish Rawat, and William D. Wulff*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

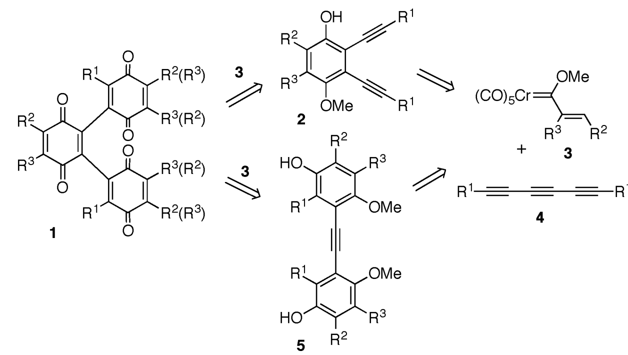
Received January 10, 2004; E-mail: wulff@cem.msu.edu

The reaction of Fischer carbene complexes with alkynes is one of the most flexible methods for the synthesis of phenols and quinones.[1] The reaction has been extended to conjugated diynes, and it was found to proceed as expected in a stepwise fashion with 2 equiv of the carbene complexes to give biaryl compounds in which the bond connecting the two newly formed aryl rings is the bond connecting the two alkyne units in the starting diyne.[2] With this as a precedent, we were encouraged to consider an approach to the biologically active trisquinone family of natural products[3] that unfolds from the sequential reaction of conjugated triynes with 3 equiv of a Fischer carbene complex. We report herein the first examples of reactions of triynes **4** with Fischer carbene complexes, the unexpected regioselectivity of the two different alkynes in **4**, and the serendipitous solution for regioselective control.

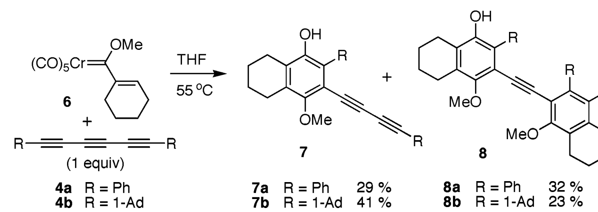
The regioselectivity of the reactions of Fischer carbene complexes with unsymmetrical alkynes has been extensively examined, and the summation of the findings is that the regioselectivity is much more sensitive to the steric difference between the two substituents of the alkyne than any electronic perturbation these substituents may have.[1,4] On the basis of the importance of sterics in control of the regiochemistry in mono-alkynes, it was expected that the reaction of the first equivalent of carbene complex would react at the central alkyne of **4** to give the dialkynyl phenol **2** (Scheme 1). The alternative is that the carbene complex would preferentially react at the end alkynes in **4** and give the diaryl acetylene **5**.[5] The intermediacy of **5** on the pathway to trisquinones was considered much less desirable than **2** because it is generally the case that the benzannulation of highly sterically congested alkynes tends to give increasing amounts of side products.[1,2] Again, for the reasons mentioned above, the reaction of the carbene complex **3** with the end alkynes in **4** to give **5** would be considered the least likely outcome.

We were thus taken unaware to find that the reaction of the cyclohexenyl complex **6** with 1,6-diphenylhexatriyne **4a** gave a mixture of the products **7a** and **8a** which both resulted from the reaction of the carbene complex at the end alkynes of the triyne (Scheme 2). The reaction could be driven to give only the double-benzannulation product **8a** in 69% yield with 5 equiv of the carbene complex, and the formation of **8a** could be prevented if 5 equiv of the triyne was used in which case **7a** was obtained in 43% yield. The use of the larger adamantyl groups on the triyne did not result in the formation of any detectable amount of the product resulting from reaction of the central alkyne unit. The structure of **7b** and **8a** (via its quinone) was confirmed by X-ray diffraction. As was anticipated, the diaryl alkyne **8** cannot be used as an entry point to trisquinones. The reaction of **8a** with carbene complex **6** in THF led to complete consumption of the starting carbene complex and the formation of only trace amounts of silica gel mobile compounds which were not characterized. This is undoubtedly due to the steric hindrance around the alkyne in **8** and not to the presence of phenol hydroxyls.[2]

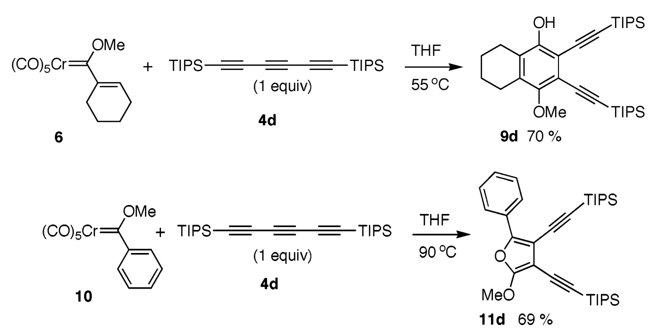
Scheme 1



Scheme 2



Scheme 3



As the investigation was further pursued, the reaction of triynes with Fischer carbene complexes continued to offer up surprises. The reaction of carbene complex **6** with silyl-substituted triyne **4d** gives the mono-benzannulated product **9d** in which the reaction has occurred at the central alkyne unit (Scheme 3). The regioselectivity of this reaction was assigned by symmetry in the ^{1}H and ^{13}C NMR spectra after methylation of the phenol and desilylation to give **15a**. The yield of **9d** could be improved to 81% in toluene. The reaction of the phenyl complex **10** with the bis-(triisopropylsilyl)triyne **4d** also occurred at the central alkyne unit, but in this case the reaction did not produce the phenol product but instead gave the furan **11d** in 69% yield. The regioselectivity in this case was confirmed by removal of the silyl groups which produced a compound with two terminal alkynes. The formation of furan products has been reported from the reaction of carbene complexes

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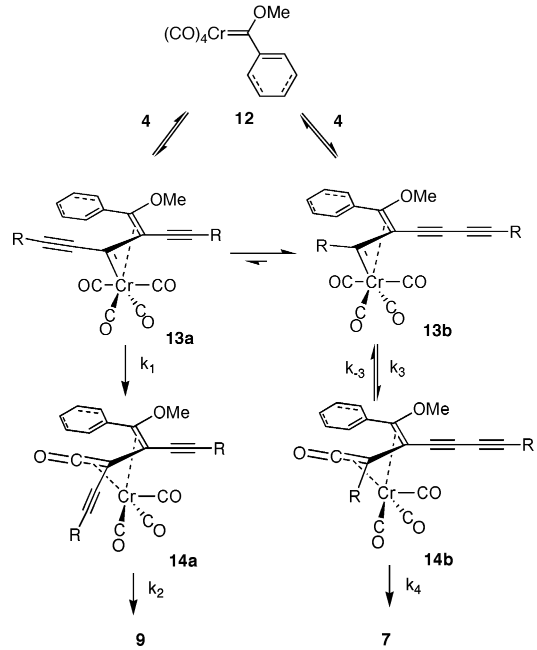
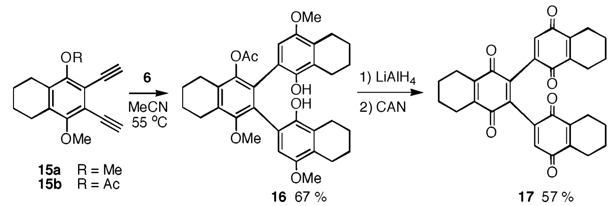
Scheme 4



Scheme 5



with mono-alkynes,[1,6] but not as the major product from the reaction with the phenyl complex **8**.

A mechanism[1,7] to account for the difference in regioselectivity of triynes **4a** and **4b** versus **4d** is shown in Scheme 4. Rate-determining loss of a CO ligand followed by insertion of the central alkyne in **4** gives the η^1,η^3-vinyl carbene complexed intermediate **13a**. Insertion of the end alkyne of **4** would lead to the η^1,η^3-vinyl carbene complexed intermediate **13b**. On the basis of previous studies, it is assumed that these intermediates are in rapid equilibrium with respect to CO insertion which gives the vinyl ketene intermediates **14a** and **14b**.[7d] Previous work has established that cyclization and aromatization of the vinyl ketene intermediate is faster than deinsertion of the carbon monoxide which regenerates the η^1,η^3-vinyl carbene complexed intermediate. This conclusion has been reached in computational studies[7b] and in experiment.[6b] However, these studies did not include alkynes that have silicon substituents. We propose that the cylization of the vinyl ketene intermediate **14b** (but not **14a**) is slow relative to CO deinsertion when the substituent R is a silicon group ($k_{-3} > k_4$). Support for this proposal comes from the known ability of silicon to greatly increase the stability of metal-free ketenes[8] and from observations that stable metal-free silyl-substituted vinyl ketenes can be isolated from the reaction of Fischer carbene complexes and silyl-substituted alkynes.[9] The observation that the silyl-substituted triynes produce **9** from reaction at the central alkyne can then be accounted for by CO deinsertion in **14b** to give **13b**, and then a depletion of the equilibrium between **13a** and **13b** via CO insertion and cyclization of **14a**. The reason that the triynes **4a** and **4b** with carbon substituents produce **7** is not clear, but one explanation is that η^1,η^3-vinyl carbene complexed intermediate **13b** is more stable than **13a** and thus that the equilibrium favors **13b**. It is not possible to rule out another scenario that involves a nonreversible CO insertion and a product determination that is the result of an equilibrium between **13b** and **13a** where **13b** is favored for R as silicon and **13a** is favored for R as a carbon group. The formation of the furan product **11d** suggests that the reaction of the aryl complex **10** with **4d** gives the η^1,η^3-vinyl carbene complexed intermediate **13a** with a Z-double-bond (methoxy and phenyl reversed).[6b] Further studies of this and other mechanistic issues are ongoing.

The serendipitous finding that the silyl-substituted triyne **4d** reacts at the central alkyne has led to the realization of the synthesis of trisquinones. Acetylation and desilylation of **9d** gave the bis-alkyne **15b** in 58% yield (Scheme 5). The reaction of **15b** with 2 equiv of carbene complex **6** in acetonitrile at 55 °C gave **16** in 67% yield. Reduction with $LiAlH_4$ gave the trisphenol which was oxidized with CAN to give the trisquinone **17** in 57% yield. With the viability of this approach established, the scope of this method for the synthesis of trisquinones is being actively pursued.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds and X-ray data for **7b** and the quinone of **8a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) It is anticipated that **7** would preferentially react with carbene complexes to give **5** as long as R was less sterically hindered than a 2,6-substituted aryl group.

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