Macrocyclization of Fischer Carbene Complexes as an Approach to Cyclophanes

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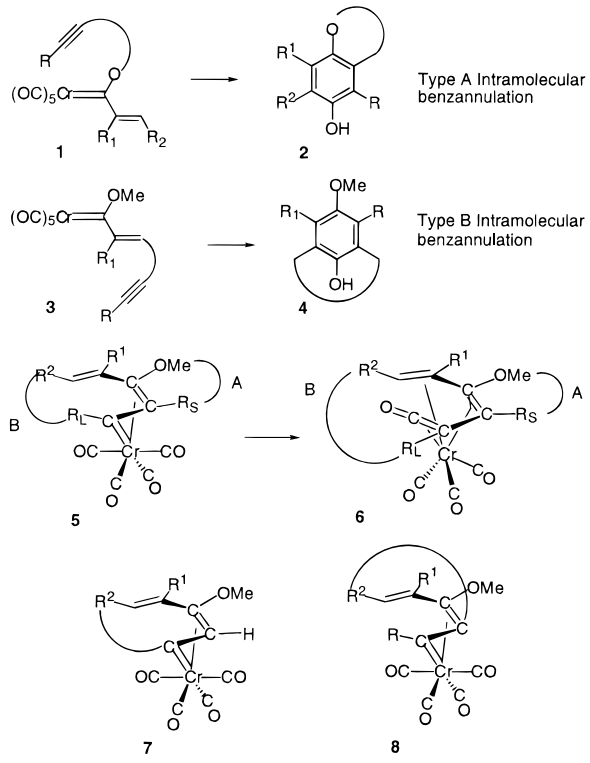
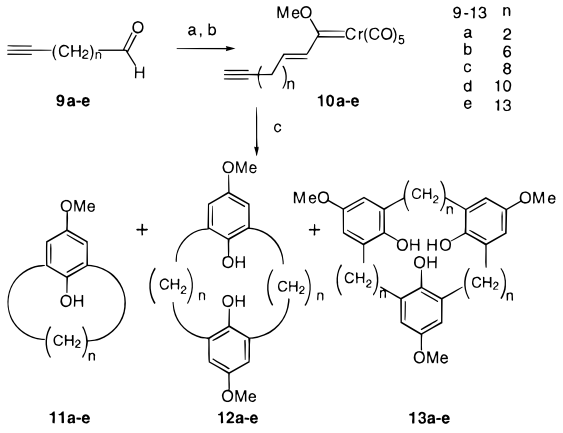
The benzannulation reaction of Fischer carbene complexes with alkynes provides an extremely versatile method for the synthesis of oxygen-substituted benzene derivatives.[1] Intramolecular versions of this reaction have been reported in which the alkyne was tethered through the oxygen heteroatom substituent giving rise to benzofurans, benzopyrans, and benzoxepins via a type A cyclization indicated in Scheme 1.[2,3] An alternate mode of intramolecular benzannulation involves tethering the alkyne to the β-carbon of an alkenyl carbene complex. This type B cyclization should lead to the formation of cyclophanes if ring strain in key reaction intermediates (vinyl carbene intermediate **5** or vinyl ketene complex **6**) does not change the product distribution and/or render intermolecular reactions competitive. We report herein the first examples of an intramolecular benzannulation of the type B shown in Scheme 1 and illustrate that the regioselectivity of the benzannulation can be used in the controlled formation of either para- or metacyclophanes.

The smallest [*n*]-metacyclophane that has been isolated has five methylenes bridging the benzene ring.[4,5] Thus, this should represent the minimum spacer that could span R^2 and R_L in the vinyl carbene and vinyl ketene complexed intermediates **5** and **6**, which are thought to be the key intermediates in the benzannulation reaction.[1] Of the two, it is suggested by mechanical models that bridging in the vinyl ketene complex **6** would be the most difficult, requiring approximately eight methylenes in the bridge to avoid distortion of normal bond angles. With the realization that eight or more atoms may be required in the tether, the probability for success was tempered by the fact that there may be competition not only from intermolecular benzannulation but also from alkyne polymerization which is well-known to compete with intermolecular benzannulations.[6,7]

Scheme 1



Scheme 2



[a] $SnCl_4$, $(CO)_5Cr{=}C(OMe)(CH_2^-)$, then H_2O; [b] MsCl / Et_3N, 33-60% (2 steps); [c] see Table I

The preparation of the family of carbene complexes **10** required for the type-B cyclizations was carried out as indicated in Scheme 2. We recently reported a procedure for the aldol-condensation of Fischer carbene complexes with aldehydes that proved pivotal in providing convenient access to the set of substrates **10a**−**e**.[8] Aldehydes **9a**−**e** were obtained by Swern oxidation of the corresponding α,ω-alkynyl alcohols, which are either commercially available or easily prepared by the isomerization of their internal alkyne isomers.[9] The aldol condensation of the methyl carbene complex was found to be optimal when tin tetrachloride

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(7) (a) The largest tether reported for type A cyclization is seven but in this case, vicinal carbons are bridged.[2a] (b) Eight-membered lactone rings have been reported for the reaction of Fischer carbene complexes with 6-heptyn-1-ols: Mori, M.; Norizuki, T.; Ishibashi, T. *Heterocycles* **1998**, *47*, 651.

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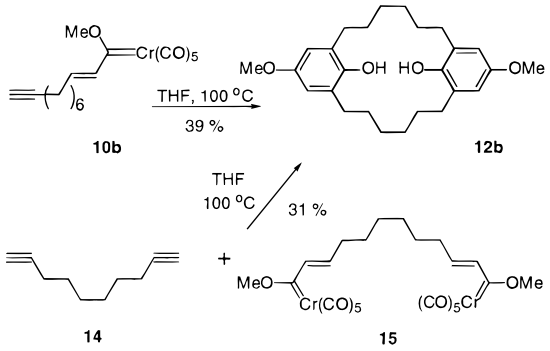
Table 1. Macrocyclization of Complexes **10**[a]

n	% yield **10**[b]	solvent	temp °C	% yield **11**	% yield **12**	% yield **13**
2	42	THF	60[c]			
		THF	100[c]			
6	57	hexane	60		10	4
		benzene	60		14	4
		CH_2Cl_2	60		26	14
		CH_3CN	60		27	19
		THF	60		36	9
		THF	60[d]		19	9
		THF	100		39	18
8	48	THF	100	43	15	2
10	60	THF	100	58	5	
13	33	THF	100	65		

[a] Unless otherwise specified all reactions run at 0.005 M in carbene complexes. Reaction times at 60 °C are 14−18 h and at 100 °C are 0.2 to 4 h. [b] Combined yield for the aldol condensation (steps a and b in Scheme 2), based on the carbene complex. [c] Complex mixture was obtained. [d] Reaction run at 0.025 M in carbene complex.

Scheme 3

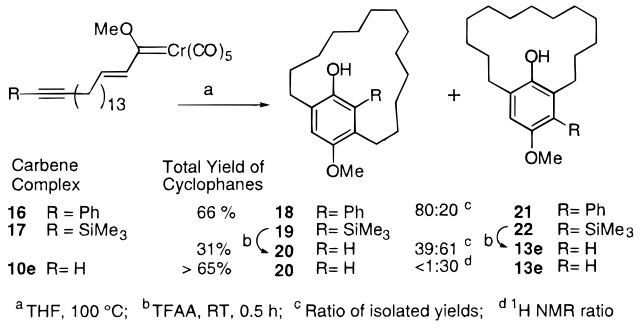


was used to activate the aldehyde and gave complexes **10** in the yields indicated in Table 1 for the two-step process.

As can be seen from Table 1, metacyclophane derivatives can indeed be obtained from a type-B intramolecular benzannulation of the complexes **10**. The [*n*,*n*]-metacyclophane derivative is predominant with a tether-length of six methylenes, while with eight methylenes and above, [*n*]-metacyclophanes predominate and become the exclusive product with $n = 13$. The conditions for the thermolysis of these complexes were optimized for the complex **10b** which produces predominantly the [*6*,*6*]-metacyclophane derivative **12b** (Scheme 3). The optimal solvent for this reaction was found to be THF and not hexane or benzene as is the case for intermolecular benzannulations.[6c,10] As expected, the total yields are dependent on the concentration, with higher concentrations more detrimental to the total yield of **11**−**13**. The slow addition of complex **10b** to the solvent did not lead to improved yield and in fact led to decreased yield since the addition time is increased (data not listed in Table 1). This is attributed to polymerization of the complex in the concentrated solutions which were used in the additions. Raising the temperature accelerates the reaction by a great deal and also improves the total yields (57% at 100 °C vs 45% at 60 °C).

The symmetrical [*6*,*6*]-cyclophane **12b** is produced from two molecules of complex **10b** in a process that most likely involves the intact formation of one of the phenol rings in an intermolecular benzannulation. The resultant carbene complex then undergoes an intramolecular reaction with the residual alkyne to produce an 18-membered ring. If this is the case, then it should be possible to access the same compound by a double-benzannulation of a bis-carbene complex with a diyne. Indeed, the reaction of the bis-carbene complex **15** with 1,9-decadiyne gave **12b** in roughly the same yield. The significance of the success of this reaction is that unsymmetrical [*n*,*m*]-cyclophanes should be available from the macrocyclization of bis-carbene complexes with diynes.

Scheme 4



[a] THF, 100 °C; [b] TFAA, RT, 0.5 h; [c] Ratio of isolated yields; [d] ^{1}H NMR ratio

The regiochemistry in intermolecular benzannulations is largely controlled by the steric difference between the substituents on the alkyne.[11] The larger substituent R_L on the alkyne is preferentially incorporated into the external position of the vinyl carbene complexed intermediate as is illustrated in **5**, and the smaller substituent R_S is incorporated into the internal position. The macrocyclization of complexes **10** produces metacyclophanes via vinyl carbene intermediate **7**, which has the expected regiochemistry for incorporation of a terminal alkyne. This raises the possibility that a macrocyclization with an internal alkyne bearing a large substituent may occur with a reversal in regiochemistry, as indicated by **8** in Scheme 1, leading to the formation of a paracyclophane.

In an effort to achieve a reversal of the regiochemistry of the cyclization, the complexes **16** and **17** were prepared with phenyl and trimethylsilyl groups on the alkyne function (Scheme 4). The thermolysis of **16** gave the paracyclophane derivative **18** with a 4:1 selectivity over its meta isomer **21**. This can be compared with the >20:1 selectivity observed for the intermolecular benzannulation of phenyl methyl acetylene with aryl carbene complexes.[11] The regiochemistry was assigned by nOe experiments on the phenyl-substituted cyclophanes **18** and **21**. Thermolysis of the silyl-substituted complex **17** also gave a pair of isomers (**19** and **22**), and their regiochemistry was assigned by symmetry after protolytic removal of the trimethylsilyl group to give a 2:3 mixture of the para isomer **20** and the meta isomer **13e**, the latter of which was found to be identical to the product obtained from the macrocyclization of complex **10e**.[12] With authentic samples of the para and meta cyclophanes **20** and **13e** in hand, it was determined that the regioselectivity of the macrocyclization of complex **10e** is > 30:1 in favor of the meta isomer.

It has been generally thought that the intramolecular reactions of Fischer carbene with alkynes would not be useful for the preparation of large ring compounds for a number of reasons.[1,6] The above results clearly suggest that this viewpoint needs to be reconsidered, and further studies on the scope and synthetic applications of these reactions are underway.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (12 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(12) This is to be compared with a 2.6:1.0 regioselectivity in the same direction from the reaction with 1-trimethylsilylpentyne with 1-cyclohexenyl carbene Fischer carbene complex: Wulff, W. D. In *Adv. Metal-Organic Chemistry*; Liebeskind, L., Ed.; JAI Press: Greenwich, CT; 1989; Vol. 1, p 258.