

## Unexpected Regiochemistry in the Benzannulation Reaction of Fischer Carbene Complexes in the Synthesis of Cyclophanes

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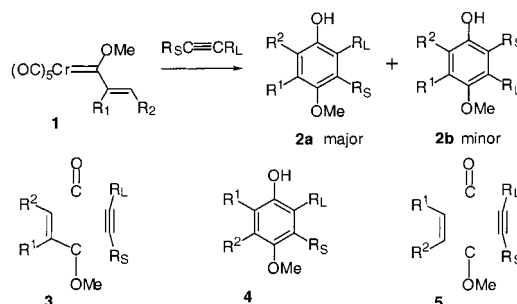
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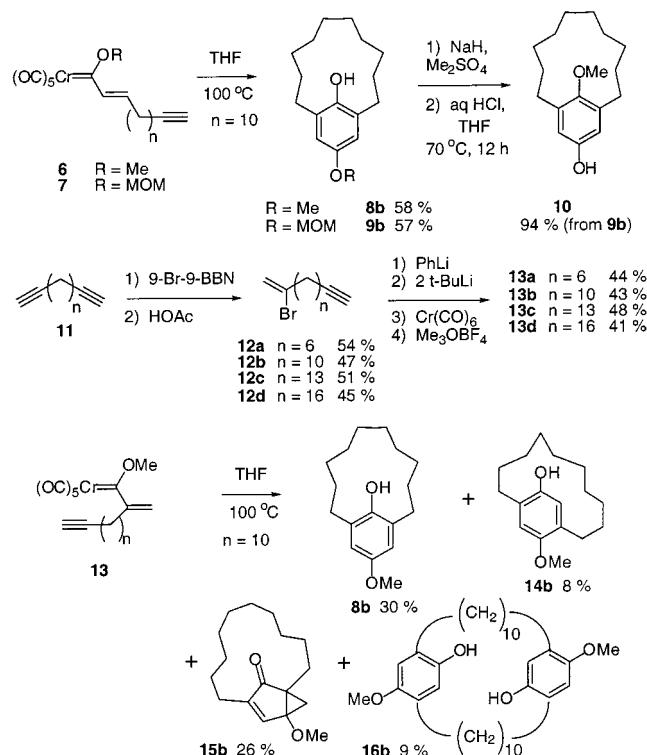
The benzannulation reaction of Fischer carbene complexes with alkynes is one of the most versatile methods for the construction of substituted phenols.<sup>1</sup> The two possible regiochemical outcomes that have previously been observed are illustrated in 4-methoxyphenols **2a** and **2b** which differ in the direction of alkyne incorporation. The regiochemistry of alkyne incorporation is normally controlled by the steric differential between the two substituents of the alkyne<sup>2,3</sup> and the largest substituent is preferentially introduced adjacent to the phenol function, as illustrated in **2a**. The disconnection for the overall process is indicated in the assembly of the three subunits in **3**. We report here the observation of phenol **4**, a new regioisomer for this reaction which was unanticipated since its formation would formally require the breaking of the carbon–carbon bond between the carbene–carbon and the carbon-bearing substituent R<sub>1</sub> in complex **1**. The overall assembly of the pieces in the formation of phenol **4** is indicated in **5** where the vinyl group of the starting carbene complex is incorporated in a fashion that is reversed from normal phenols **2a** and **2b**. We recently reported that  $\beta$ -tethered vinyl chromium carbene complex **6** would undergo an intramolecular benzannulation with incorporation of the tethered terminal alkyne to give *m*-cyclophane **8b** in 58% yield.<sup>4,5</sup> This method gives synthetically useful yields of *m*-cyclophanes and has been examined for tether lengths up to 17 methylenes with no drop-off in yield (60% yield for  $n = 17$ ). The *m*-cyclophane **8b** was expected from this reaction on the basis of the regiochemistry observed for intermolecular reactions, which give phenol **2a** as the major isomer with the larger substituent of the alkyne incorporated adjacent to the phenol function. The same analysis leads to the expectation that  $\alpha$ -tethered complexes of the type **13** would lead to the formation of *p*-cyclophanes **14**.

Complexes **13** were prepared in two steps from the  $\alpha,\omega$ -diynes **11** as outlined in Scheme 2. Bromoboration with 1 equiv of 9-bromo-9-BBN and subsequent hydrolysis gave a statistical mixture of products from which the bromoenyne **12** could be

Scheme 1



Scheme 2



readily separated.<sup>6</sup> Attempts to generate the dianion of **12** by reaction with 2 equiv of butyllithium or 3 equiv of *tert*-butyllithium failed to give any significant yield of the desired carbene complex.<sup>7–9</sup> This problem was solved by deprotonation of **12** with phenyllithium and then subsequent metal halogen exchange with *tert*-butyllithium to give the dianion of **12**, which underwent selective reaction with chromium hexacarbonyl by the vinyl anion.

As anticipated, *p*-cyclophane **14b** was isolated from the intramolecular benzannulation of complex **13b** accompanied by a nearly equal amount of [10,10]-*p,p*-cyclophane **16b**. However, the major products of the reaction were [10]-*m*-cyclophane **8b** and bicyclo[3.1.0]hexenone **15b**. The formation of *m*-cyclophane **8b** from this reaction was particularly surprising since this is the

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(7) Reaction of **12a** with 1 equiv of NaH or EtMgBr and then 2 equiv of *tert*-butyllithium failed to give more than 2% of **13a**.

(8) For successful related transformations, see: (a) Barluenga, J.; Sanz, R.; Fananas, F. J. *Chem. Eur. J.* **1997**, 3, 1324. (b) Henniges, H.; Meyer, F. E.; Schick, U.; Funke, F.; Parson, P. J.; de Meijere, A. *Tetrahedron* **1996**, 52, 11545. (c) Furber, M.; Taylor, R. J. K. *J. Organomet. Chem.* **1986**, 311, C35.

(9) This failure may be related to observations made with haloaryl acids: Beak, P.; Musick, T.; Chen, C.-W. *J. Am. Chem. Soc.* **1988**, 110, 3538.

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(1) For recent reviews on carbene complexes in organic chemistry, see: (a) Wulff, W. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, R. G. A., Wilkinson, G., Eds.; Pergamon Press: New York, 1995; Vol. 12, p 469. (b) Bernasconi, C. F. *Chem. Soc. Rev.* **1997**, 26, 299. (c) Hegedus, L. S. *Tetrahedron* **1997**, 53, 4105. (d) Wulff, W. D. *Organometallics* **1998**, 17, 3116. (e) Dötz, K. H.; Tomuschatt, P. *Chem. Soc. Rev.* **1999**, 28, 187. (f) Herndon, J. W. *Coord. Chem. Rev.* **1999**, 181, 177. (g) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: New York, 1999.

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(3) (a) Chamberlin, S.; Waters, M. L.; Wulff, W. D. *J. Am. Chem. Soc.* **1994**, 116, 3113. (b) Brandvold, T. A.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1991**, 113, 5459. (c) Brandvold, T. A.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1990**, 112, 1645.

(4) Wang, H.; Wulff, W. D. *J. Am. Chem. Soc.* **1998**, 120, 10573.

(5) For an additional example, see: Dötz, K. H.; Gerhardt, A. *J. Organomet. Chem.* **1999**, 578, 223.

**Table 1.** Macrocyclizations of Complexes **13**<sup>a</sup>

entry	series	<i>n</i>	temp (°C)	time (h)	yield <b>8</b>	yield <b>14</b>	yield <b>15</b>	yield <b>16</b>
1	a	6	100	2				36 <sup>b</sup>
2	b	10	100	10	30	7	26	9
3	b	10	100	1	13	6	42	11
4	b	10	70	19	30	8	31	10
5	c	13	100	20	16	3	38	10
6	c	13	65 <sup>c</sup>	22	20	1	40	6
7	d	16	100	12	1	56	2	10

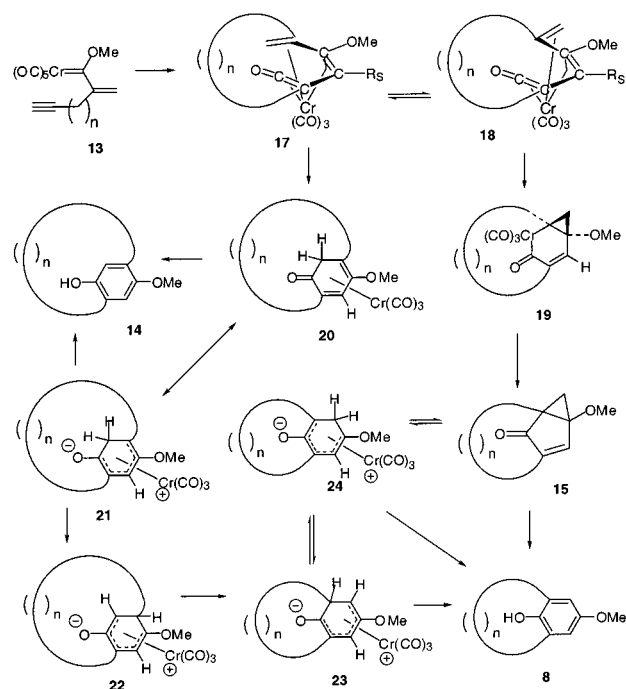
<sup>a</sup> Reaction performed at 0.002 M. <sup>b</sup> A 13% yield of trimer was also isolated. <sup>c</sup> Reaction performed with 3 equiv of Et<sub>3</sub>N.

same product produced from the thermolysis of  $\beta$ -tethered carbene complex **6**. The isolation of **8b** from the thermolysis of **13b** corresponds to the regiochemistry indicated in phenol **4** (Scheme 1) and is unprecedented from the reaction of a carbene complex and an alkyne. The formation of bicyclo[3.1.0]hexenone **15b** from the thermolysis of **13b** was equally a surprise and is a product type that has never before been reported from the reaction of a carbene complex and an alkyne. The structure of **15b** was assigned by a series of NMR experiments and confirmed by an X-ray analysis of a single crystal.<sup>10</sup> The carbon-carbon bond connectivity in **15b** is related to that of the unexpected *m*-cyclophane **8b** by the cleavage of a cyclopropane bond. It was thus anticipated that **15b** might be a precursor to **8b** and it was found that this interconversion occurs both thermally and under acid catalysis. The thermolysis of a 44:56 mixture of **8b**:**15b** for 45 h in THF at 100 °C resulted in conversion to an 86:14 mixture in 96% yield. Treatment of this mixture with trifluoroacetic acid in chloroform at room temperature led to complete conversion to **8b** in 98% yield within 2 h.

The *m*-cyclophane that would have been possible from the thermolysis of **13b** is **10**, which corresponds to an intramolecular cyclization with inverted regiochemical incorporation of the alkyne as indicated by the substitution pattern in phenol **2b**. It was shown that **10** is not the product of this reaction by an independent synthesis from carbene complex **7**. Thermolysis of **7** gave *m*-cyclophane **9b** and then **10** upon methylation and deprotection. *m*-Cyclophane **10** was found to have spectral data nonidentical with **8b**. The structure of **10** prepared in this manner was confirmed by X-ray diffraction analysis of a single crystal.<sup>11</sup>

The effect of the tether link on the macrocyclization of complex **13** was examined for tethers ranging from *n* = 6 to 16 and the results are presented in Table 1. The results show that the chemoselectivity of these reactions falls into three distinct regions. The thermolysis of complex **13a** (*n* = 6) produces predominantly dimeric cyclophane **16a** (36% yield) and also a 13% yield of the trimeric cyclophane. Complexes **13b** and **13c**, with *n* = 10 and 13, respectively, give predominantly *m*-cyclophane **8** and bicyclo[3.1.0]hexenone **15**. The ratio of these two products varies, but the combined yield is constant (55–63%). The reaction in entry 6 in the table was performed in the presence of 3 equiv of triethylamine but did not have any clear effect on the product. The thermolysis of complex **13d** (*n* = 16) is the only intramolecular benzannulation that is chemoselective for the formation of *p*-cyclophanes, giving **14d** in 56% isolated yield.

A mechanism is presented in Scheme 3 to account for the formation of *p*-cyclophane **8** as well as for bicyclo[3.1.0]hexenone **15**. In the normal course of events, the  $\alpha$ -tethered vinyl carbene complex **13** would be expected to undergo an intramolecular

**Scheme 3**

insertion of the alkyne and then carbon monoxide insertion to give the  $\eta^4$ -vinyl ketene complex **17**. In this intermediate the substituted alkyne carbon is incorporated into the C-1 position of the ketene function. Electrocyclic ring-closure to the cyclohexadienone **20** and subsequent tautomerization would give the phenol **14** which is the expected product from the reaction of carbene complexes with alkynes. However, in the case of tethers less than 16 methylenes, the *p*-cyclophane **14** is a minor product of the reaction. One possible explanation for this may result from the strain in the conformation of the  $\eta^4$ -vinyl ketene complex **17** that is necessary for the electrocyclic ring-closure to give the normal product **14**. As a result it is possible that the vinyl ketene complex may isomerize to the *s*-*cis*,*s*-*trans* conformation **18**<sup>3c</sup> and then undergo a cyclization to the metallabicyclo[4.1.0]heptenone **19**. This cyclization could be driven by the release in strain accompanied by the change in hybridization of the cyclopropyl carbon attached to the chromium in **19**. Reductive elimination from **19** would give the bicyclo[3.1.0]hexenone **15** that is isolated from the thermolysis of **13**. Another explanation for the shift in product distribution from **14** for shorter tethers is that a 1,2-hydride shift in **21** (perhaps via a chromium hydride species) to give **22** followed by a 1,2-alkyl shift to give the meta-bridged species **23** would upon tautomerization give the observed phenol **8**.<sup>12</sup> Further rearrangement of **23** to **24** and then electrocyclic ring closure could then account for the formation of **15**. At this point we do not have any experimental evidence to distinguish between these two mechanisms.

The initial results from the present and other recent studies<sup>4,5</sup> on the intramolecular benzannulation of alkyne tethered carbene complexes have revealed that while this reaction is useful for the synthesis of a number of different types of macrocyclic cyclophanes, it produces a few surprises as well. Further studies on the scope of macrocyclic synthesis with carbene complexes are planned as well as applications to molecules of biological and structural interest.

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**Supporting Information Available:** Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) We would like to thank a reviewer for suggesting this mechanism.

(10) Crystal data for **15b**: C<sub>17</sub>H<sub>26</sub>O<sub>2</sub>, fw = 262.38, monoclinic, *P*2<sub>1</sub>/*c*, *a* = 9.785(2) Å, *b* = 14.622(2) Å, *c* = 11.357(2) Å,  $\beta$  = 109.897(3)°, *V* = 1527.8(7) Å<sup>3</sup>, *Z* = 4, *D*<sub>c</sub> = 1.141 g cm<sup>-3</sup>, *T* = 173 K, *R* = 7.76, w*R*2 = 24.74%.

(11) Crystal data for **10**: C<sub>17</sub>H<sub>26</sub>O<sub>2</sub>, fw = 262.38, monoclinic, *P*2<sub>1</sub>/*c*, *a* = 12.3276(9) Å, *b* = 28.236(2) Å, *c* = 11.9241(7) Å,  $\beta$  = 99.169(3)°, *V* = 3066.6(4) Å<sup>3</sup>, *Z* = 8, *D*<sub>c</sub> = 1.137 g cm<sup>-3</sup>, *T* = 173 K, *R* = 9.18, w*R*2 = 26.49%. The asymmetric unit contains two crystallographically independent, chemically similar, molecules.