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Synthesis of [*m.n*]Cyclophanes: Regiochemistry Transfer from Vinyl Halides to Cyclophanes via Fischer Carbene Complexes

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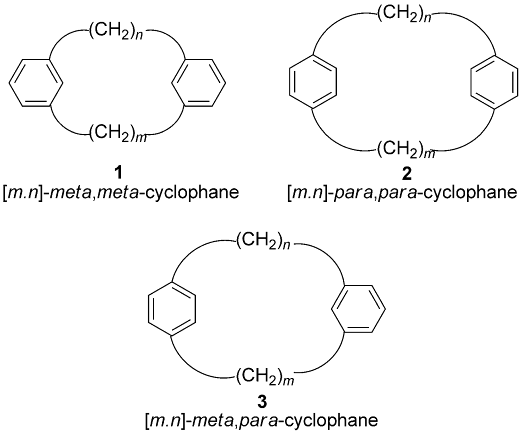
Abstract: The double benzannulation of bis-carbene complexes of chromium with α,ω-diynes generates [*m.n*]cyclophanes in which all three rings are generated in a single reaction. This triple annulation process is very flexible allowing for the construction of symmetrical [*n.n*]cyclophanes and unsymmetrical [*m.n*]cyclophanes as well as isomers in which the two benzene rings are both *meta* bridged or both *para* bridged, and isomers that contain both *meta* and *para* bridges. The connectivity patterns of the bridges in the cyclophanes can be controlled by regioselectivity transfer from the bis-vinyl carbene complexes in which the substitution pattern of the vinyl groups in the carbene complexes dictate the connectivity pattern in the [*m.n*]cyclophanes. This synthesis of [*n.n*]cyclophanes is quite flexible with regard to ring size and can be used with tether lengths ranging from $n=2$ to $n=16$ and thus to ring sizes with up to 40 member rings. The only limitation to regioselectivity transfer from the carbene complexes to the [*m.n*]cyclophanes was found in the synthesis of *para*,*para*-cyclophanes with four carbon tethers for which the loss of fidelity occurred with the unexpected formation of *meta*,*para*-cyclophanes.

Keywords: chromium · cyclophanes · Fischer carbene complexes · regioselectivity · triple annulation

Introduction

The family of compounds known as [*m.n*]cyclophanes has permeated the interests and creative thinking of a diverse array of chemists and as a result their chemistry can be found in polymer science, molecular recognition and materials chemistry as well as in asymmetric catalysis.[1–3] Naturally occurring [*m.n*]cyclophanes have also served to inspire those who are practitioners of the total synthesis of natural products.[3j] The chemistry of [*m.n*]cyclophanes dates to the synthesis of [2.2]-*meta*-cyclophane by Pellegrin in 1899.[3a] The most common connectivity patterns are those represented in [*m,n*]-*meta*,*meta*-cyclophanes **1** and [*m.n*]-*para*,*para*-cyclophanes **2** (Scheme 1), and these are more commonly referred to as simply [*m.n*]-*meta*-cyclophanes and [*m.n*]-*para*-cyclophanes, respectively. Although [*m.n*]-*meta*,*para*-cyclophanes are known,[3d,q] they have been rarely studied compared to other [*m.n*]cyclophanes of which the most popular have been the [2.2]-*para*-cyclophanes.[2,3c] Numerous methods have been developed for the synthesis of [*m.n*]cyclophanes.[1–3] Most of these methods involve multiple identical reaction sites, and therefore, are limited to the generation of symmetric dimers. Several other protocols, on the other hand, can only generate tethers of specific lengths. We describe in this work a general approach to the synthesis of [*m.n*]cyclophanes, in which both tethers can either be of the same or different lengths, and—with one exception—can be used with all tether lengths examined and is applicable to *meta*,*meta*-, *para*,*para*- and *para*,*meta*-cyclophanes. This approach is based on the benzannulation reaction of Fischer carbene complexes and features a triple annulation in which all three rings of the [*m.n*]cyclophanes are generated in a single step.[4]



Scheme 1. Common connectivity patterns in [*m.n*]cyclophanes.

Background: The benzannulation reaction of Fischer carbene complexes with alkynes is one of the most versatile methods for the synthesis of aromatic compounds (Scheme 2).[5] The alkenyl Fischer carbene complexes **5** are

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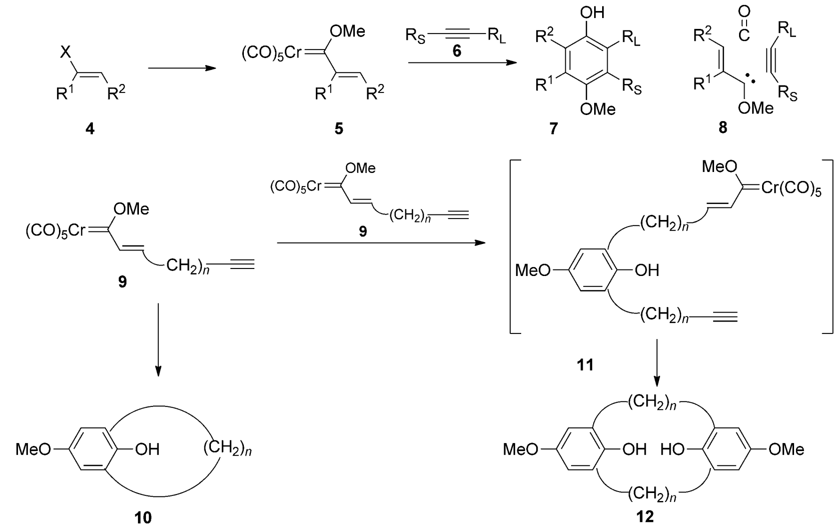
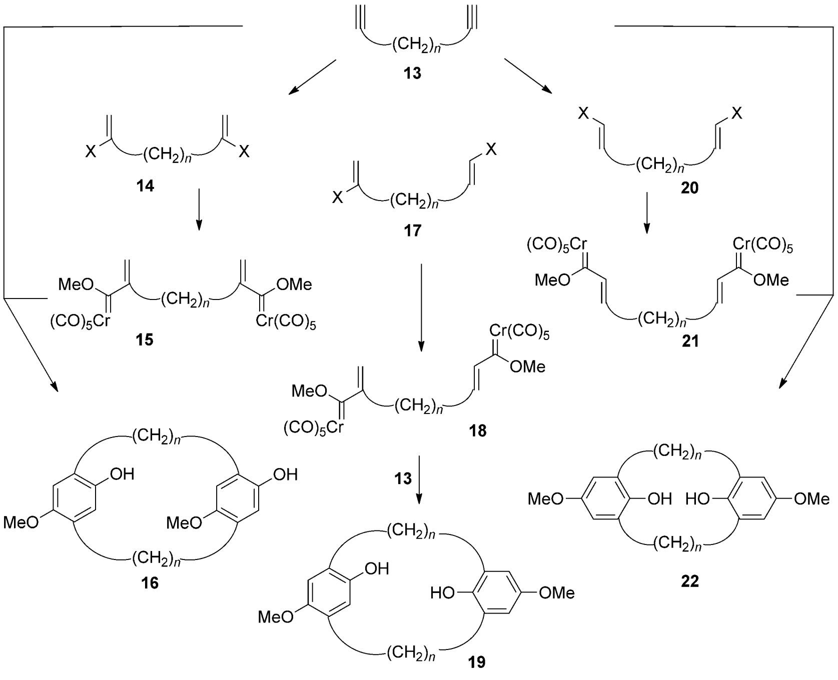


Scheme 2. Benzannulation reaction of Fischer carbene complexes with alkynes.

generally prepared from the vinyl halides **4** via the corresponding vinyl lithiums according to the standard Fischer method.[5] Treatment of carbene complex **5** with the alkyne **6** will give the phenol **7**, which arises from the incorporation of the alkyne, the carbene ligand and a carbon monoxide ligand according to the construct **8**. The regiochemistry of incorporation of the alkyne is driven mainly by the steric differential between the two substituents on the alkyne.[6] The larger group on the alkyne (R_L) is selectivity incorporated adjacent to the hydroxyl of the phenol as indicated in phenol **7**. In the case of terminal alkynes ($R_S = H$, $R_L \neq H$), the regioselectivity is usually greater than 100:1. The intramolecular version of this reaction has been described for the synthesis of cyclophanes,[7] and an example with the alkyne tethered to the β-carbon of the vinyl carbene complex is illustrated by carbene complex **9** (Scheme 2).[7a] The thermolysis of **9** leads to mixtures of [*n*]-*meta*-cyclophanes **10** and/or [*n.n*]-*meta*,*meta*-cyclophanes **12** and to a much lesser extent [*n.n.n*]-*meta*,*meta*,*meta*-cyclophanes (data not shown). The distribution between cyclophanes **10** and **12** was found to be dependent on the tether length. When $n=6$ the [6]-*meta*-cyclophane **10** was not observed and the [6.6]-*meta*,*meta*-cyclophane **12** was the major product.[7a] With tether lengths of $n=8$ or larger, the cyclophane **10** is the major product with the yield rising to 58% at $n=10$ and this yield was maintained out to $n=17$.[7c] These results have been interpreted to involve a bimolecular reaction of the carbene unit in carbene complex **9** reacting with the alkyne function in a second molecule of carbene complex **9** to give the intermediate carbene complex **11**, which undergoes an intramolecular benzannulation to give the [*n.n*]-*meta*,-*meta*-cyclophane **12**. This bimolecular reaction is apparently competitive when the unimolecular reaction of carbene complex **9** to give **10** is disfavored by the strain associated with the shorter tethers in **10**.

A more efficient approach to the [*m.n*]cyclophanes was envisioned to result from the reactions of bis-carbene complexes with α,ω-diynes (Scheme 3).[8] We have also utilized the reaction of bis-carbene complexes with diynes in the synthesis of calixarenes.[9] There are several advantages of this approach. First, it eliminates the formation of [*n*]cyclophanes or any odd-numbered cyclic or non-cyclic oligomers, leaving the formation of even-numbered oligomers as the only possibility. Cyclization to [*n.n*]cyclophanes thus becomes the first viable intramolecular pathway (via intermediate **11**, Scheme 2) and should be favored. Secondly, it allows for the preparation of unsymmetrical [*m.n*]cyclophanes by treating diynes and bis-car-



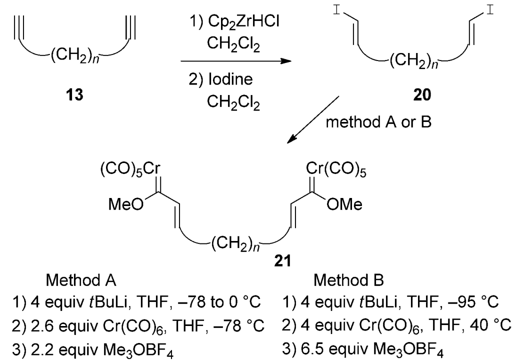
Scheme 3. The reactions of bis-carbene complexes with α,ω-diynes.

bene complexes with different tether lengths. A library of [*m.n*]cyclophanes could potentially be obtained from these two sets of compounds using a combinatorial approach. Third, convergence in the synthesis results from the fact that the bis-carbene complexes would be derived from the same set of α,ω-diynes. Hydrohalogenation of diyne **13** could be used to generate the bis-vinyl halides **14** and **20**, which in turn could be converted to the bis-carbene complexes **15** and **21** through the standard Fischer procedure. Finally, the regiochemistry of the dihalides can be established in the hydrohalogenation step and then transferred to the cyclophanes through the benzannulation reaction of carbene complexes **15** and **21** since high regioselectivity is observed with both α- and β-substituted vinyl carbene complexes with terminal alkynes.[5,6] The dihalide **14**, obtained from Markovnikov addition, would thus eventually lead to *para,para*-cyclophanes **16**, whereas dihalide **20**, resulting from anti-Markovnikov addition, would lead to the *meta,meta* isomers **22**. Access to the *meta,para*-cyclophanes **19** should be possible via a dihalide of the type **17** that has both a 1,1-disubstituted olefin and a 1,2-disubstituted olefin.

Results and Discussion

The bis-carbene complex **21** with *trans*-vinyl substituents tethered to both β-positions were prepared as indicated in Table 1. Anti-Markovnikov hydrohalogenation was effected by the hydrozirconation of the diyne **13** and then treatment of the bis-vinylzirconium species with iodine.[10] It has been our experience that the yields of the diiodides **20** are dependent on the solvent and the purity of Schwartz's reagent. The yields are 10–20 % higher if the Schwartz's reagent is newly purchased or freshly prepared[11] even if it is stored under argon in a freezer wrapped in aluminum foil. Higher yields are also observed if methylene chloride is used as solvent instead of either benzene or THF.[12] In addition, in two cases, the diiodides were prepared using dibromoborane dimethyl sulfide complex[13] to compare with their preparation by hydrozirconation with Schwartz's reagent, and as can be seen in Table 1 (entries 1 and 2), hydrozirconation generally gives higher yields. The conversion of the diiodides **20** to the bis-carbene complexes **21** was investigated with two different protocols. Method A involves a more traditional procedure in which the vinyl halide (in this case a bis-vinyl halide) is treated with four equivalents of *tert*-butyl lithium in THF at −78 °C to generate organolithium intermediates, which are added to $Cr(CO)_6$ at −78 °C. Method B involves the addition of four equivalents of *tert*-butyl lithium at −95 °C and then immediate addition of the bis-vinyl lithium to a solution of $Cr(CO)_6$ at 40 °C. Method B gives significantly higher yields (Table 1) and, in addition, gives crude reaction mixtures from which the product is much more easily separated by chromatography on silica gel.

Table 1. Preparation of bis-carbene complexes **21**.

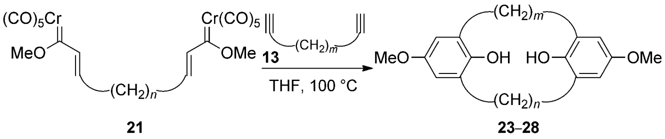


Entry	*n*	Series	Yield **20** [%][a]	Method	Yield **21** [%][a]
1	2	a	90[b] (40)[c]	B (A)	65 (33)
2	3	b	86 (46)[c]	B	71
3	4	c	68[d]	A	61
4	5	d	79	B	75
5	6	e	74[e]	A	46
6	10	f	72[e]	A	42
7	11	g	90	B	67

[a] Isolated yield after chromatography on silica gel. [b] The yield of **20a** was 61 % when the hydrozirconation solvent was THF. [c] Reaction performed with $HBBr_2{\cdot}SMe_2$ and then iodine and NaOH in water. [d] The hydrozirconation solvent was THF. [e] The hydrozirconation solvent was benzene.

The results of a test of the triple annulation of carbene complexes **21** with α,ω-diynes **13** in the synthesis of [*m.n*]-*meta,meta*-cyclophanes are shown in Table 2 and the size of

Table 2. Triple annulation in the synthesis of [*m.n*]-*meta,meta*-cyclophanes.[a]



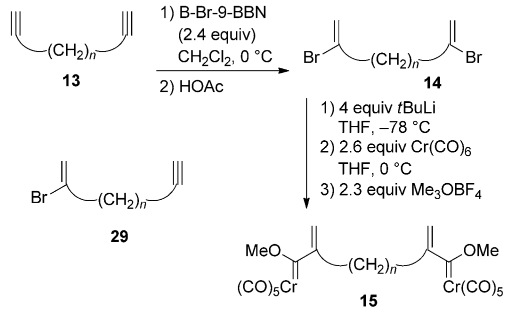
Entry	Carbene complex	*n*	Diyne	*m*	Cyclophane	Yield cyclophane [%][b]
1[c]	**21a**	2	**13a**	2	**23**	21
2	**21c**	4	**13c**	4	**24**	28
3[d]	**21c**	4	**13c**	4	**24**	30
4	**21e**	6	**13e**	6	**25**	31
5[e]	**21e**	6	**13e**	6	**25**	7
6	**21f**	10	**13f**	10	**26**	31
7	**21c**	4	**13a**	2	**27**	44
8	**21c**	4	**13e**	6	**28**	27
9[f]	**21c**	4	**13e**	6	**28**	27
10[g]	**21c**	4	**13e**	6	**28**	33
11[g,h]	**21c**	4	**13e**	6	**28**	30

[a] Unless otherwise specified, all reactions were performed at 0.0025 M in **21** in THF with 1.0 equiv diyne **13** at 100 °C for 30–45 min under argon in a solution that had been deoxygenated by the freeze-thaw method. [b] Isolated yield after chromatography on silica gel. [c] Reaction time was 12 h. [d] Syringe pump addition (0.35 mL min^{-1}) of both reactants (0.01 M) to dioxane at 98 °C. Addition complete in 20 min (final concentration was 0.0022 M) and the mixture was heated at reflux for an additional 10 min. [e] Syringe pump addition (0.67 mL min^{-1}) of **13e** to **21e** in dioxane (0.0025 M) at 95 °C. Addition complete in 15 min (final concentration was 0.0021 M) and the mixture was heated at reflux for an additional 5 min. [f] Reaction performed in the presence of 10 equiv of diphenyl-acetylene. [g] Reaction performed at 0.001 M. [h] Solvent was deoxygenated by an argon purge rather than by the freeze-thaw method.

the cyclophane ranges from [2.2] to [10.10] and the actual ring size varies from 10 to 26 carbons. It was surprising to find that the efficiency of the triple annulation is relatively insensitive to the tether length. The [2.2]cyclophane **23** is formed in almost the same yield as the [10.10]cyclophane **26** despite the fact that the formation of the former is a much slower process (12 h vs. 30–45 min). Dissymmetry can be easily introduced into the system by treating bis-carbene complexes with diynes with different tethers. As shown in entries 7–11, [4.2]- and [6.4]cyclophanes can be obtained in yields similar to their symmetric counterparts. Attempts to optimize the annulation process met with little success. The intramolecular reactions of carbene complexes with alkynes are sensitive to concentration, and all the reactions shown in Table 2 were performed at 0.0025 M since this has proved optimal for other intramolecular reactions.[7,8] However, slow addition of both reactants to dioxane did not result in a significant improvement in yield (entry 3). Perhaps this was due to some inadvertent introduction of air during the process. Slow addition of the diyne to the bis-carbene complex in dioxane caused a sharp decrease in yield (entry 5) and this may be due to the instability of the bis-carbene complexes at this temperature. No affect was observed upon performing the reaction in the presence of 10 equiv of diphenylacetylene (Table 2, entries 8 and 9), and thus this reaction is not subject to the xenochemical effect even though other intramolecular reactions of Fischer carbene complexes with alkynes are.[14] In line with these previous observations,[7,9] a slight increase in the yield is observed upon lowering the concentration to 0.001 M (entry 10). Although Fischer carbene complexes can be prepared, handled and chromatographed in the presence of air, they become much more sensitive to air at elevated temperatures and thus the standard protocol for the triple annulations (Table 2) involves deoxygenating the reaction mixture by the freeze-thaw method before heating. This was found not to be necessary as indicated by the data in entry 10 of Table 2 in which it was shown that simply purging the solution with argon for a few minutes was sufficient.

The Markovnikov hydrohalogenation of the diynes **13** was accomplished by the method of Suzuki with B-bromo-9-borabicyclononane.[15] The yields of this reaction are quite high (Table 3, entries 1 and 4). The dibromo-diynes **14f**, **14h** and **14i** were obtained as side-products in the monohydrobromination of the corresponding diynes where the use of one equivalent of 9-bromo-9-borabicyclononane gave a nearly statistical mixture of the monobromo adduct **29**, the bis-bromo adduct **14** and the starting material. In these reactions the monobromo adduct **29** was desired for another purpose. The preparation of the bis-carbene complexes **15** was accomplished by treating the bis-vinyl bromide **14** with 4 equiv of *tert*-butyl lithium and then treating the resulting bis-vinyl lithium with chromium hexacarbonyl in THF at 0 °C. Finally, treatment of the resulting bis-metal acylate with Meerwein's reagent provided the bis-carbene complexes **15** in moderate yields except for the complex **15a** with $n=2$ where only traces of the desired bis-carbene complex was observed. The alternative procedure for the preparation of bis-carbene complexes indicated as Method B in Table 1 has not been investigated for complexes **15**.

Table 3. Preparation of bis-carbene complexes **15**.

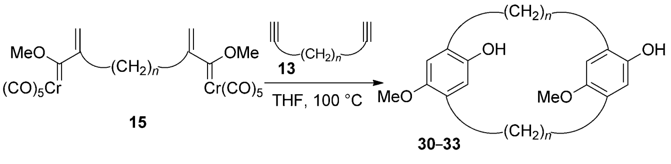


Entry	n	Series	Yield **14** [%][a]	Yield **15** [%][a]
1	2	a	88	<2
2	3	b	–	25[b]
3	4	c	–	35[b]
4	6	e	80	60
5	10	f	25[c]	36
6	13	h	19[d]	38
7	16	i	19[e]	47

[a] Isolated yield after chromatography on silica gel. [b] Yield for the two-step process; [c] **14f** obtained as minor product along with **29f** (47 %) in a reaction with 1.03 equiv B-Br-9-BBN; [d] **14h** obtained as minor product along with **29h** (46 %) in a reaction with 1.03 equiv B-Br-9-BBN; [e] **14i** obtained as minor product along with **29i** (45 %) in a reaction with 1.03 equiv B-Br-9-BBN.

The triple annulation of bis-carbene complexes with α,ω-diynes is just as efficient for the synthesis of *para*,*para*-cyclophanes (Table 4) as it is for *meta*,*meta*-cyclophanes (Table 2) giving yields in the 30–40 % range. The concentration effect seen for the *meta*,*meta*-cyclophanes is also observed for the *para*,*para*-cyclophanes with a doubling of the yield noted when the concentration is lowered from 5 to 1 millimolar (Table 4, entry 1 vs. 3). The cyclization of the bis-carbene complex **15b** connected by three methylenes (Table 3) was

Table 4. Triple annulation in the synthesis of [*n.n*]-*para*,*para*-cyclophanes.[a]

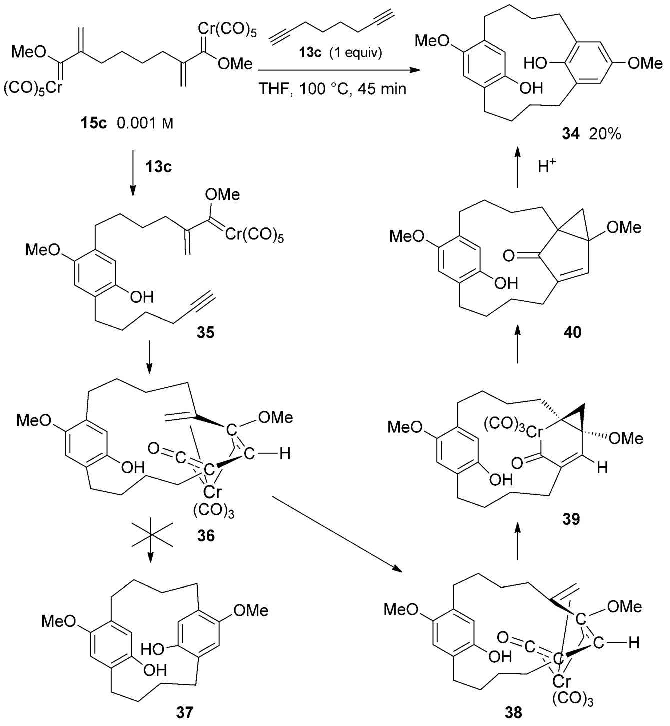


Entry	Carbene complex	Diyne	n	**15** [M]	Cyclophane	Yield cyclophane [%][b]
1	**15e**	**13e**	6	0.005	**30**	19
2	**15e**	**13e**	6	0.0025	**30**	30
3	**15e**	**13e**	6	0.001	**30**	42
4	**15f**	**13f**	10	0.001	**31**	35
5	**15h**	**13h**	13	0.001	**32**	28
6	**15i**	**13i**	16	0.001	**33**	31

[a] Unless otherwise specified, all reactions were performed in THF with 1.0 equiv of diyne **13** at 100 °C for 30 min under argon in a solution that had been deoxygenated by the freeze-thaw method. [b] Isolated yield after chromatography on silica gel.

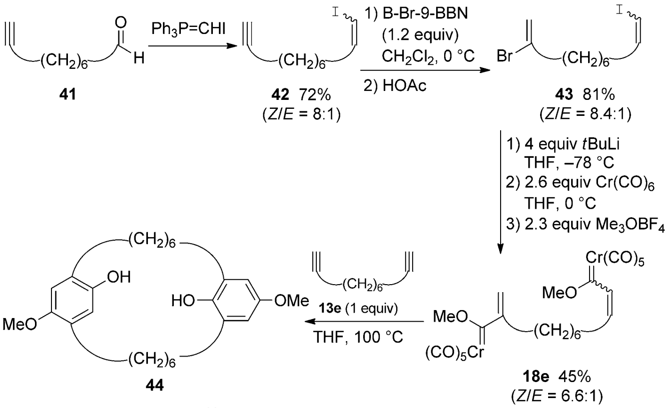
also examined with diyne **13b** under the conditions indicated in Table 4, however, this reaction produced a formidably complex mixture of products and no attempt was made to separate and identify any of the components of this mixture.

The triple annulation of the bis-carbene complex **15c** with a tether length of four methylenes with the corresponding diyne **13c** produced an interesting surprise (Scheme 4) and represents the only exception to the rule that the regiochemistry is transferred intact from the vinyl halide to the cyclophanes. Instead of the expected [4.4]-*para*,*para*-cyclophane **37**, this reaction produced the [4.4]-*meta*,*para*-cyclopane **34**! This type of switch in regiochemistry has been observed before in the synthesis of [*n*]-*para*-cyclophanes from the intramolecular benzannulation of Fischer carbene complexes containing an alkyne tethered to the carbene complex.[7c,e] In this previous work, a bicycle-[3.1.0]-hexenone of the type **40** was isolated and characterized by X-ray diffraction, and was shown to undergo an acid catalyzed isomerization to a *meta*-substituted phenol of the type **34**.[7c] In the present case, the formation of the *meta*,*para*-cyclophane **34** can be envisioned to occur by the mechanism outlined in Scheme 4. The first ring to form in the triple benzannulation is undoubtedly the *para*-bridged phenol ring. This expectation is borne out of consideration of the nearly universal rule that the regioselectivity with terminal alkynes in intermolecular reactions occurs with incorporation of the larger group on the alkyne adjacent to the phenol group in the product as indicated in structure **7** (Scheme 2).[5,6] Thus, the first benzannulation reaction between bis-carbene complex **15c** and diyne **13c** would be expected to generate the carbene complex **35**. A key intermediate that is thought to be involved in the formation of phenols in the benzannulation reaction is the η^6-dienylketene complex of the type **36** in which a chromium tricarbonyl group is coordinated to three carbon–carbon double bonds.[6] The normal transition state that intermediate **36** would be expected to traverse is a 6e^- electrocyclization leading to a cyclohexadienone and, after tautomerization, to the phenol **37**. Although this did occur for the same intermediate with six methylene tethers (Table 4, entries 1–3), it did not occur in this case with four methylene tethers, presumably due to strain associated with this transition state. In analogy with previous mechanistic analyses, we propose that the endocyclic η^6-dienylketene complex **36** undergoes an isomerization to the presumably less strained exocyclic η^6-dienylketene complex **38** and then this species undergoes a reductive cyclization to the complex **39** in which a cyclopropane ring is generated and finally a reductive elimination of the chromium to generate the bicycle-[3.1.0]-hexenone **40**. Since compound **40** was not isolated from this reaction, it may be that the isomerization of **40** to the phenol **34** is promoted by the close proximity of the phenol function in **40** to the carbonyl group. In previous work on [*n*]-*para*-cyclophanes it was found that the "abnormal" product related to **40** and/or **34** did not disappear until the tether length was increased to 16 carbon atoms. It is interesting to note that in the triple annulation of carbene complexes of the type **15** with diynes **13**, the "abnormal" product does not disappear until the tether length in both **15** and **13** is increased to six methylenes, which, incidentally, would involve a carbene complex related to **35** and which has 16 carbons in the tether. The reactions summarized in Table 4 produced at most trace amounts of a *meta*,*para*-cyclophane.



Scheme 4. Triple annulation of bis-carbene **15c** (tether length of four methylenes) with the corresponding diyne **13c**.

The application of the triple annulation to the synthesis of *meta*,*para*-cyclophanes was explored with bis-carbene complex **18e** with six methylenes in the tether and with diyne **13e**, which has the same tether length (Scheme 5). The



[18e] [M]	Yield [%]
0.005	19
0.001	32

Scheme 5. Triple annulation with bis-carbene **18e** (six methylenes in tether) and diyne **13e** (also six methylenes in tether).

asymmetry in this complex and in the dihalide **43** was introduced by beginning with an orthogonally difunctionalized hydrocarbon in the form of 8-nonynal **41**. The Wittig reaction of 8-nonynal **41** with Stork and Zhao's iodomethylenephosphorane gave the vinyl iodide **42** in 72% yield and as an 8:1 mixture of *E* and *Z* isomers.[16] The bromoboration and protiodeborylation occurred without event to give the dihalide **43** in 81% yield.[15] The mixture of *Z* and *E* isomers of **43** was converted to the bis-carbene complex **18e**, which was isolated in 45% yield and as a 6.6:1 mixture of *Z* and *E* isomers. It was a little surprising that the ratio of isomers was nearly maintained in the bis-carbene complex since it has been our experience that *cis*-substituted alkenyl carbene complexes can undergo isomerization to the more stable *trans* isomers. Nonetheless, this was not an issue to be negatively anticipated for the success of the triple annulation reaction since we have previously shown that in simple intermolecular benzannulation reactions both *cis*- and *trans*-alkenyl complexes undergo reactions with alkynes to give the phenol product.[6c] As expected, the thermolysis of complex **18e** with diyne **13e** gave the *meta*,*para*-cyclophane **44** (Scheme 5) in much the same yield as the *para*,*para*-cyclophanes (Table 4) and the *meta*,*meta*-cyclophanes (Table 2).

Conclusion

The present work serves to validate the universal roadmap for the synthesis of [*m.n*]cyclophanes from the reaction of bis-carbene complexes and α,ω-diynes as outlined in Scheme 3. The α,ω-diynes not only serve as one of the reactants but also as the precursor to the bis-carbene complexes with which the α,ω-diynes react in a triple annulation to give the [*m.n*]cyclophanes. The flexibility in this approach allows for the synthesis of unsymmetrical [*m.n*]cyclophanes by employing bis-carbene complexes and α,ω-diynes with different tethers. Flexibility can also be exercised on a higher order in the control of the regiochemistry of the [*m.n*]cyclophanes. α,ω-Divinyl halides that have the halide in the 1-position can be used to generate bis-carbene complexes that give access to [*m.n*]-*meta*,*meta*-cyclophanes, whereas α,ω-divinyl halides that have the halide in the 2-position can lead to the generation of [*m.n*]-*para*,*para*-cyclophanes. Furthermore, it was shown that [*m.n*]-*meta*,*para*-cyclophanes can be generated from α,ω-divinyl halides in which one olefin has a halide in the 1-position and the other has a halide in the 2-position. The yields of the triple annulation were found to be relatively insensitive to tether length with similar yields observed across a range of tethers from two to sixteen methylenes. The only limitation observed was in the attempt to generate a *para*,*para*-cyclophane with four methylenes in each tether. This reaction surprisingly gave a *meta*,*para*-cyclophane and the reason for this was attributed to the influence of strain in the final benzannulation reaction, which caused the formation of a *meta*-substituted ring rather than the expected *para*-substituted ring.

Acknowledgements

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