Chelation-Controlled Bergman Cyclization: Synthesis and Reactivity of Enediynyl Ligands

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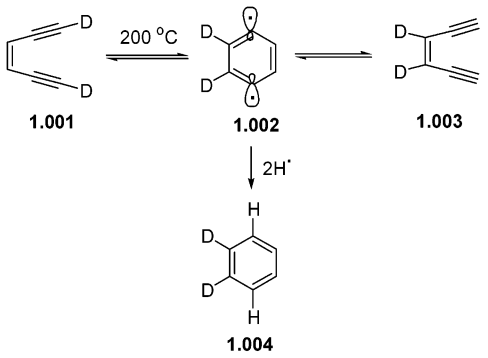
I. Introduction

The discovery of naturally occurring enediynes[1−7] in the late 1980s prompted an unprecedented flurry of activity which is still continuing unabated in various domains of chemical and biological research. Much of these studies were aimed toward understanding the various parameters controlling the kinetics of Bergman cyclization (BC),[8−10] the process that leads to the formation of an aromatic 1,4-diradical system (Scheme 1). The BC, also referred to as cycloaromatization, is at the heart of the chemistry of enediynes and is primarily responsible for their biological activities. Understanding the parameters that control the kinetics of this reaction is of paramount importance for the design of any new enediyne. It is interesting to note that although the chemistry of this class of molecules including the eneyne allenes and related compounds began to unfold in the mid 1960s by Sondheimer,[11,12] Masamune,[13] and Bergman,[8−10] it was only after the discovery of the structures and mode of action of the naturally occurring enediynes as antitumor agents[14] that scientists were stimulated to explore this area of chemistry. Their efforts have culminated in generating a vast knowledge base about the chemistry and biology of enediynes. Apart from the total synthesis[15−25] and elucidation of the mechanism of biological action,[26] due to unacceptable toxicity levels of the natural products, considerable effort has gone into the design and synthesis of model enediynes and related molecules with the ultimate aim of finding a good anticancer drug.

Scheme 1. Bergman Cyclization or Cycloaromatization



1.001 1.002 1.003 1.004

The BC is perhaps one of the few reactions that was applied to synthetic molecules before the discovery of their counterpart in Nature. The reason for the nonexploitation is probably due to the necessity of high temperature to induce the rearrangement. No one could foresee that the same reaction would be possible under ambient conditions until Mother Nature showed the way to do it through the chemistry of the natural enediynes. The natural products undergo BC under ambient conditions after being activated by a triggering reaction. For example, the strain imposed by the double bond in calicheamicin **1.005**[27−32] or by the epoxide in dynemicin **1.006**[33−37] imparts stability to the system; as soon as these are removed, the molecule becomes activated to show their cytotoxicity through generation of diradicals via BC (Schemes 2 and 3).

Thus, in every design of novel enediynes, two basic aspects need to be considered. One is the incorporation of structural features that make the molecule stable at room temperature, which is otherwise unstable under ambient conditions. The other point addresses the question of activation or the so-called triggering of the molecule toward BC at the biological

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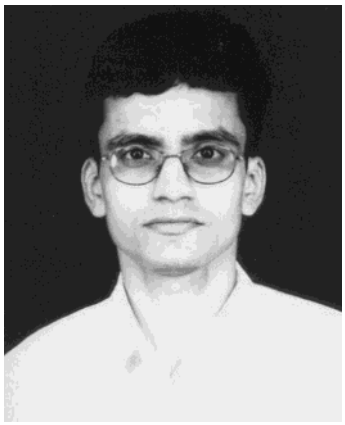
Amit Basak obtained his Ph.D. degree from Calcutta University under Professor S. K. Talapatra in 1982 and his D.Phil. degree in 1986 from Oxford University under the supervision of Professor Sir Jack E. Baldwin. After his postdoctoral research with Professor Craig Townsend at Johns Hopkins University, Baltimore, MD, he joined the Indian Institute of Technology, Kharagpur, in 1991 and is currently an Associate Professor in the Department of Chemistry. Dr. Basak's research involves designing of artificial enediynes as DNA-cleaving agents, role of weak interactions and strained rings on the kinetics of Bergman cyclization, asymmetric synthesis, and biotransformations. He has been a visiting faculty member at The Johns Hopkins University and the University of Basque Country, San Sebastian, Spain. He is a recipient of the CRSI bronze medal, State Scholarship for higher study at Oxford, and University gold medal.



Subrata Mandal was born in 1974 at Suri (Birbhum), West Bengal, India. He received his B.Sc. degree from the University of Burdwan, India, in 1995 and his M.Sc. degree, both in Chemistry, from Visva Bharati University, Santiniketan, India, in 1998. Subsequently, he joined the research group of Professor Amit Basak to obtain his Ph.D. degree in the Department of Chemistry, Indian Institute of Technology, Kharagpur, as a CSIR (Government of India) Fellow. His research covers the field of design and synthesis of novel endiynyl anticancer agents, their metal complexes, and evaluation of their biological activity. He is a recipient of University fellowship for his outstanding performance in M.Sc.

temperature. Once these are achieved, additional structural features can be incorporated to give selectivity to its biological action.

Research in the past decade or so has enabled us to understand some of the controlling parameters for BC kinetics. As already mentioned, from the very inception of its discovery, BC has been known to have high activation barriers for acyclic enediynes. Cyclic enediynes, on the other hand, generally have much lower activation energy, so that the same reaction can take place at a lower temperature. For example, a 10-membered carbocyclic enediyne (structure **1.015**)[38] or a heterocyclic enediyne (N- or O-analogue, structure **1.017** or **1.019**)[39,40] undergoes cyclization

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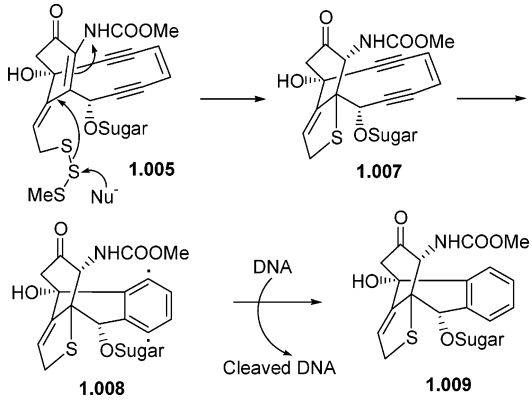
Scheme 2. Mechanism of DNA Cleavage by Calicheamicin (1.005)

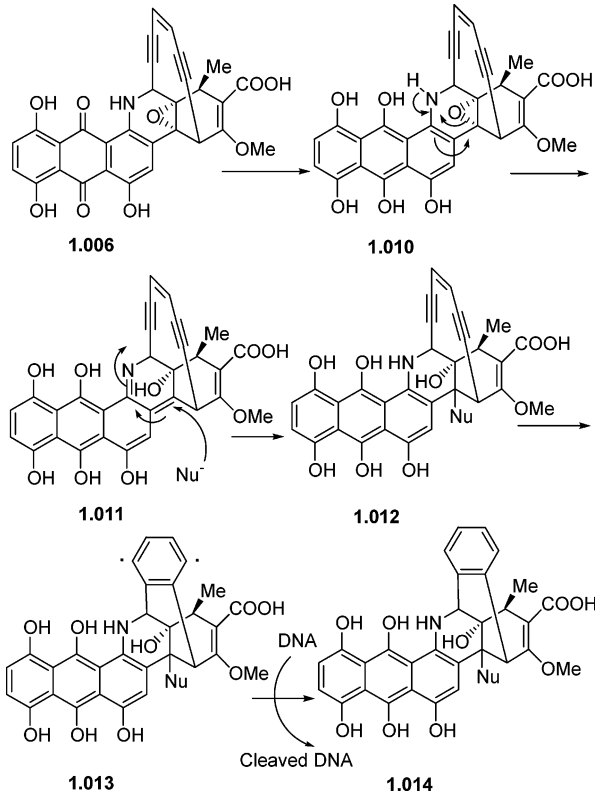


at ambient temperature with fairly decent half-lives (except the sulfur analogue **1.021**, which is stable at room temperature[41]). Fusion of strained rings on to the cyclic enediynes (examples **1.023**−**1.025**) brings back the stability (Scheme 4).[42−45] Incorporation of strain raises the energy of the transition state more than that of the ground state, thus elevating the activation barrier for BC.

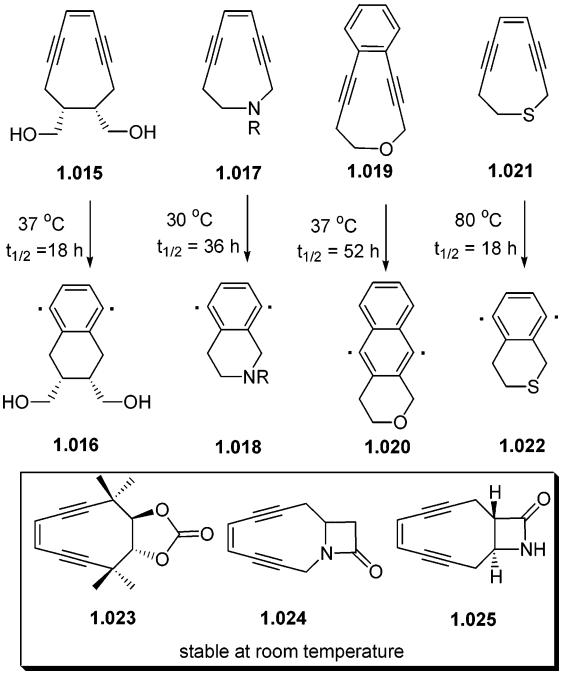
Similar to BC, which is the reaction involving the enediynes, cyclization leading to aromatic systems is also possible with an eneyne allene system via the formation of diradicals. The reaction, known as Myers−Saito cyclization (MSC),[46−49] is depicted in Scheme 5. Neocarzinostatin **1.029**[50−54] shows its biological activity through the involvement of such a reaction (Scheme 6). Contrary to BC, acyclic eneyne allene systems undergo MSC under ambient conditions. Cyclic eneyne allenes are also extremely reactive like their acyclic counterparts.

In 1988, Nicolaou et al.[55] put forward a theory (popularly known as the distance theory) according

Scheme 3. Mechanism of Biological Action of Dynemicin (1.006)

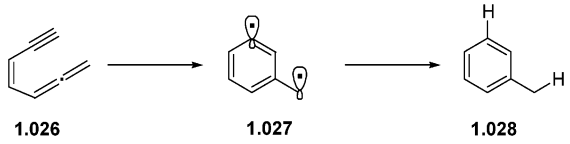


Scheme 4. Some Examples of Stable and Unstable Endiynes

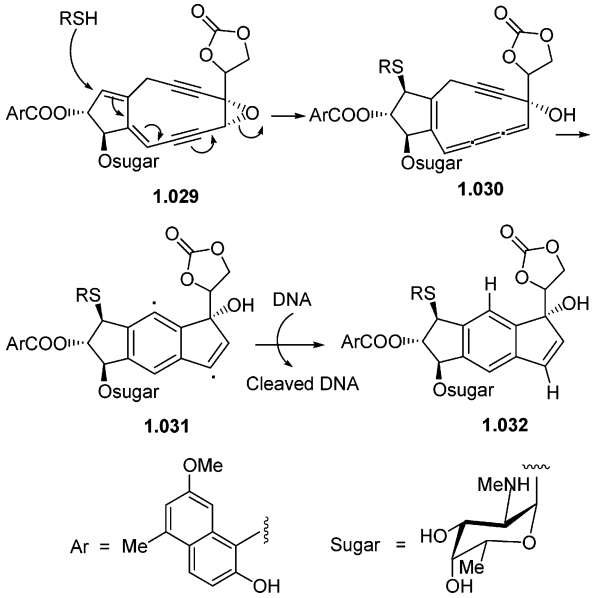


to which the distance between the acetylenic carbon atoms undergoing covalent connection (commonly referred to as the *c,d* distance) governs the rate of cyclization. The critical *c,d* distance proposed for an enediyne to have a modest half-life at room temperature is 3.31−3.20 Å. An alternate theory based on differential molecular strain between the GS and TS as proposed by Magnus and Snyder[56,57] appears to be more precise and is of general applicability,

Scheme 5. Myers−Saito Cyclization



Scheme 6. Mechanism of DNA Cleavage by Neocarzinostatin (1.029)



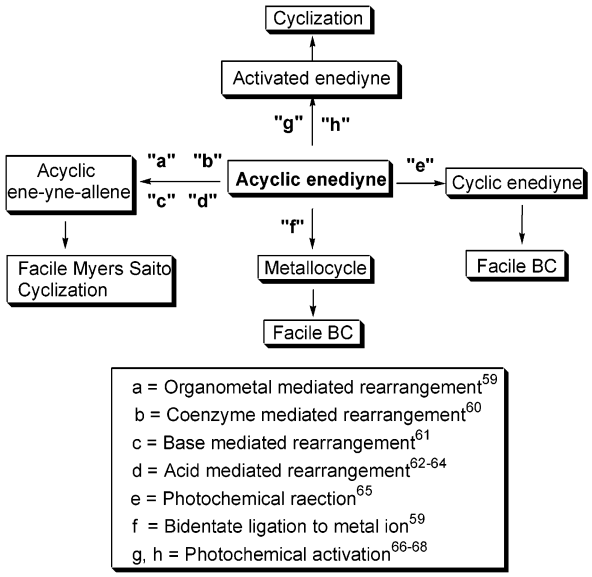
especially for strained cyclic systems. However, the distance theory has gained popularity and is more exploited because of its simplicity and user-friendliness. Moreover, a recent DFT-based calculation[58] suggests a correlation between the spontaneity of BC and the *c,d* distance. It has been shown that if structural perturbation could be done to reduce the *c,d* distance to the range 2.9−3.4 Å, cyclization should occur spontaneously except for systems with large olefin strain.[58]

II. Strategies for Design of Enediynes

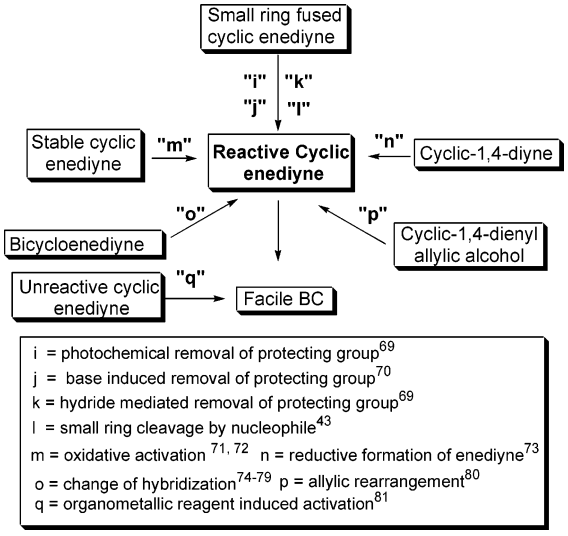
In the past 15 years or so, various enediyne models have been designed with the objective of enhancing their reactivity toward BC under suitable triggering conditions. The rationales for these designs are shown in Schemes 7 and 8, while the structural representations of all the approaches with appropriate examples are shown in Schemes 9−22.

This review will describe only those cases where the rate of BC is perturbed by the presence of metal ions or organometallic reagents. It is interesting to note that there has been no precedence of metal-ion triggering of enediynes in Nature so far, and hence, this idea is quite novel in the true sense. The basic principle behind such metal-ion-mediated BC is quite simple. The enediyne having ligating systems in the two acetylenic arms chelates a metal ion, thus forming a cyclic network or a metallocycle. This, in turn, is expected to lower the activation barrier for BC. The situation may, however, be much more complex, and in many cases, metal-ion complexation has a detrimental effect on the cyclization kinetics

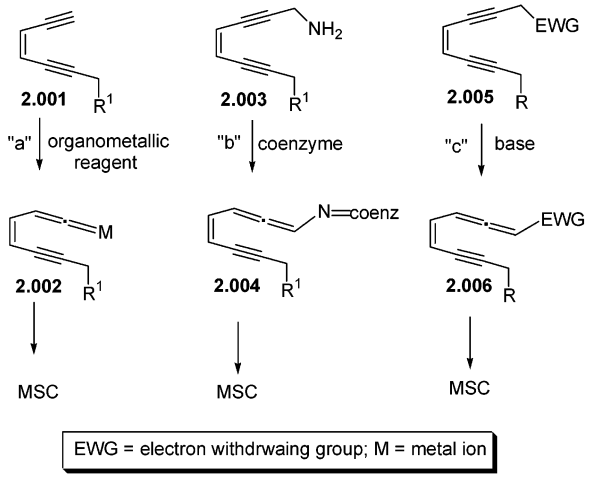
Scheme 7. Design Involving Acyclic Enediynes



Scheme 8. Design Involving Cyclic Enediynes

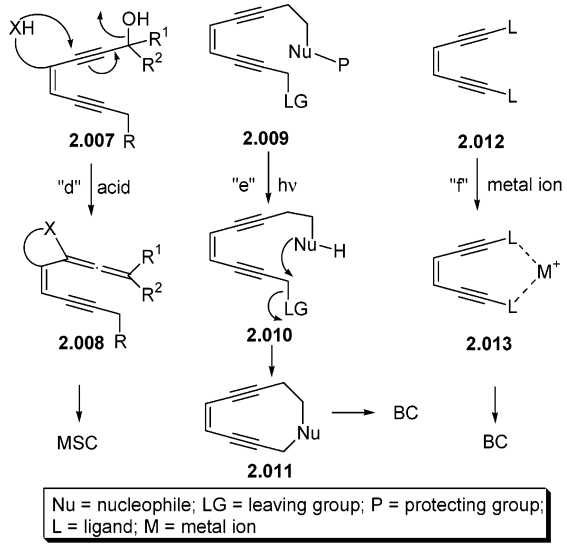


Scheme 9. Structural Representations of Various Designs of Acyclic Enediynes

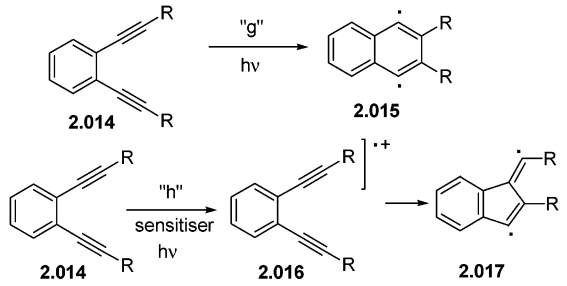


because of certain configurational restrictions. Nevertheless, many interesting results have been obtained using this approach, which will be summarized here followed by some logical conclusions.

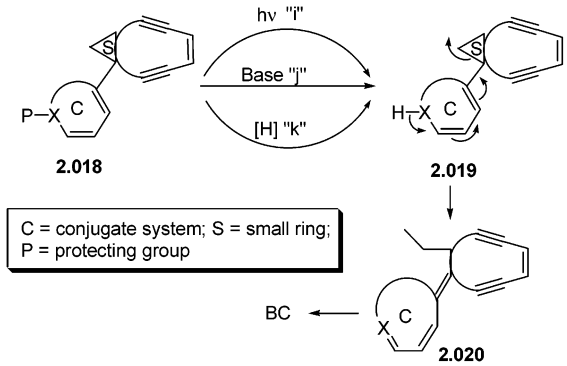
Scheme 10. Structural Representations of Various Designs of Acyclic Enediynes



Scheme 11. Structural Representations of Various Designs of Acyclic Enediynes



Scheme 12. Structural Representations of Various Designs of Cyclic Enediynes

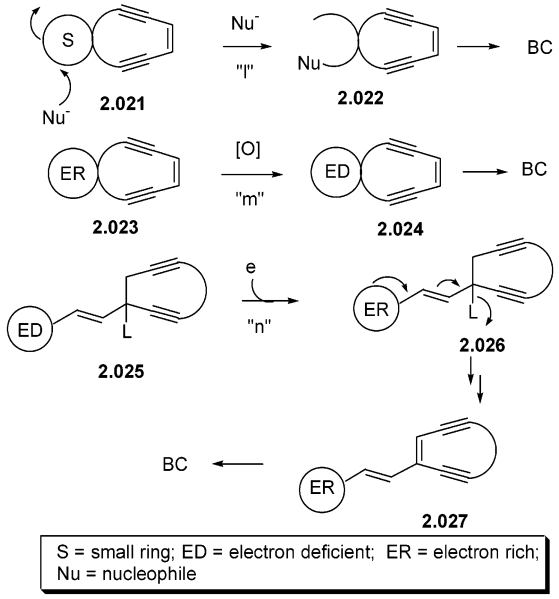


III. Metal-Ion-Induced Bergman Cyclization

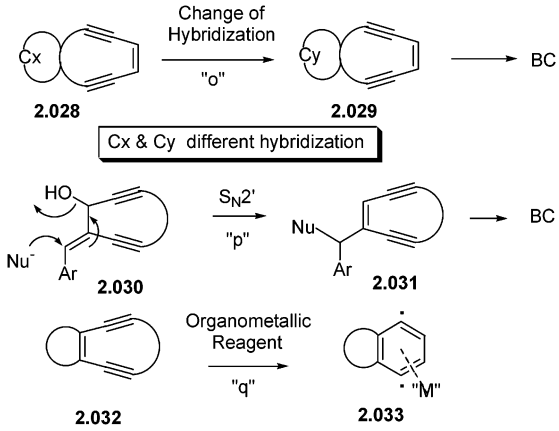
A. Enediyne Crown Ethers

The use of metal ions to control the kinetics of BC was first demonstrated by Konig et al.[82,83] to be followed by Buchwald and co-workers.[84] The former studied the effect of complexation of adjacent crown ether moieties in an acyclic enediyne with different metal ions. The starting acyclic enediyne **3.001**, containing crown ether in the two acetylenic arms, was synthesized by a Pd(0)-catalyzed coupling of 1,5-hexadiyn-3-ene (**3.002**) with 2 equiv of 3′-iodo benzo-15-crown-5 (**3.003**) under standard Sonogashira conditions[85−89] (Scheme 23). Upon treatment with

Scheme 13. Structural Representations of Various Designs of Cyclic Enediynes

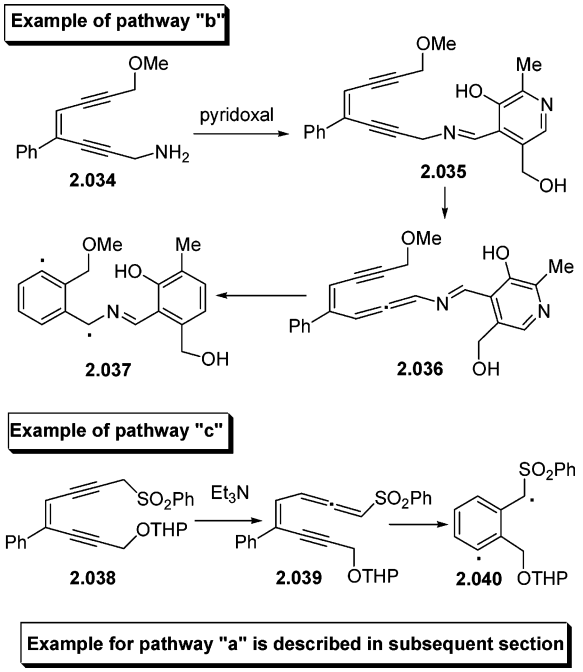


Scheme 14. Structural Representations of Various Designs of Cyclic Enediynes

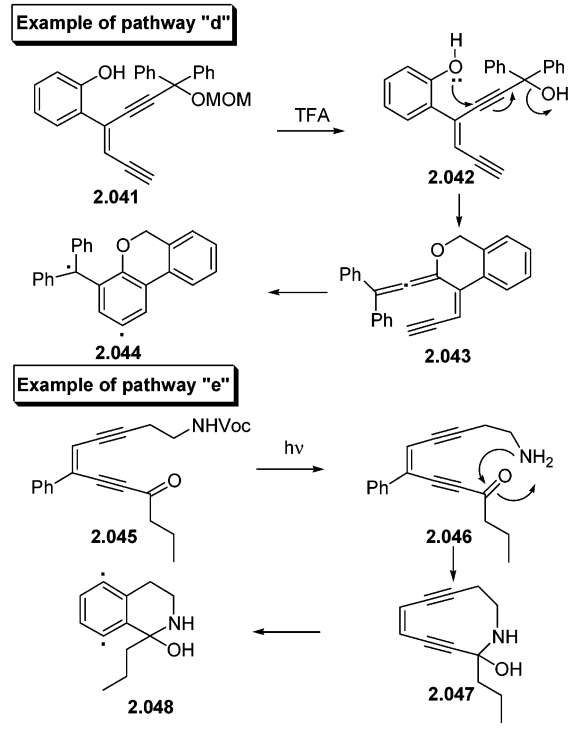


excess of $NaPF_6$ or $NaClO_4$ in acetonitrile at room temperature, the corresponding bissodium complex (**3.004**) was obtained while reaction with KPF_6 gave a potassium sandwich complex (**3.005**) (Scheme 24).The thermal properties of the bisbenzo crown ether and its complexes were investigated by differential scanning calorimetry (DSC).[90,91] Thus, when the enediynes are heated in the neat state, beyond a certain temperature cycloaromatization sets in, generating the diradicals. Because of the absence of any donor atoms, these radicals begin to polymerize, resulting in the evolution of thermal energy. This is manifested by the appearance of an exothermic peak in the DSC curve. The temperature at which the exothermic peak started to appear is regarded as the onset temperature of BC. Apart from polymerization via BC, other polymerization pathways such as alkyne oligomerization in the presence of metal ions can be ruled out, as then one would not expect wide variation of onset temperature for polymerization. For the three compounds, the crown ether enediyne **3.001** and its complexes **3.004** and **3.005**, the onset temperatures for BC were found to be 142, 157, and 169 °C, respectively. Thermolysis experiments in

Scheme 15. Representative Examples of Various Designs



Scheme 16. Representative Examples of Various Designs

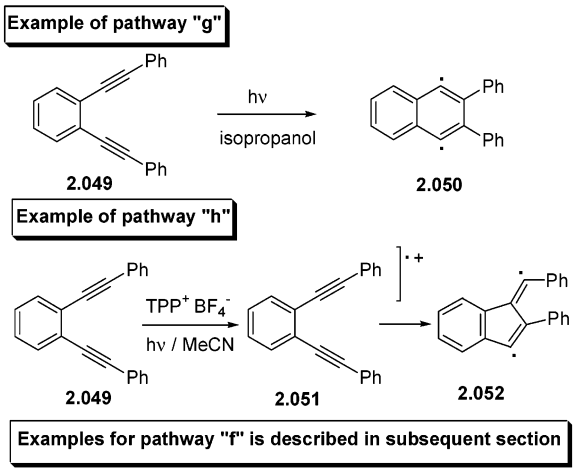


solution in the presence of H-donors confirm the formation of aromatic products from BC, *albeit* in poor yield. Judging from the various onset temperatures for BC, the effect by metal-ion complexation appears to be marginal. However, this work did set the tune for one of the future directions the enediyne chemistry was going to take.

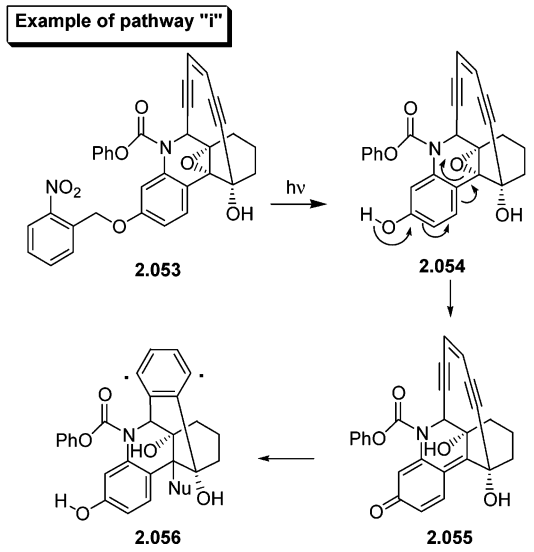
B. Bisphosphino Enediyne

Buchwald et al.[84] in his seminal paper in 1995 reported a dramatic change of BC kinetics upon

Scheme 17. Representative Examples of Various Designs



Scheme 18. Representative Examples of Various Designs

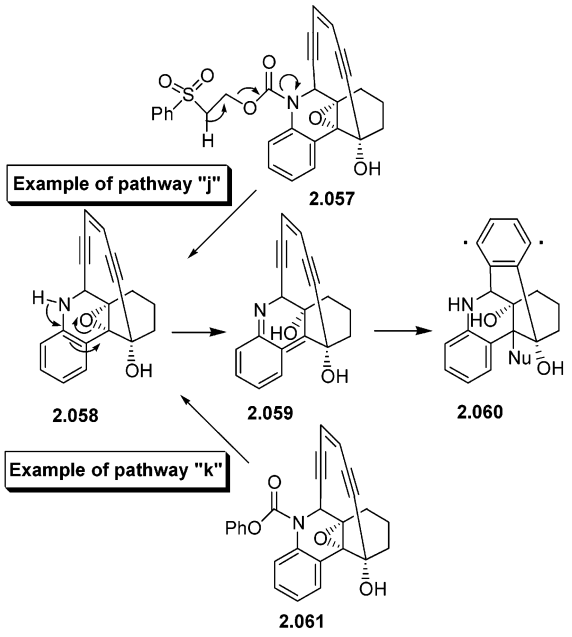


metal-ion chelation to an acyclic enediyne. They used a bisphosphane-1,2-diaryl diyne **3.006** for coordination to metal ions in order to change the cyclization temperature. The enediyne was synthesized (Scheme 25) from the known[92] bistrimethylsilyl ethynyl benzene **3.009** by a desilylative phosphorylation in the presence of potassium *tert*-butoxide and diphenyl phosphoryl chloride.

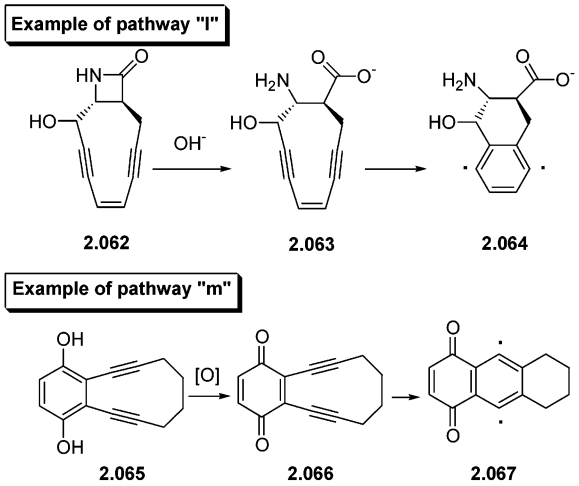
The enediyne **3.006** itself undergoes cyclization at 243 °C; with Pd^{2+} and Pt^{2+} ions, a dramatic increase in reactivity was observed whereby the compound cyclizes at a significantly lower temperature (Scheme 26). The effect is, however, dependent upon the nature of metal ions. For example, Hg^{2+} ion stabilizes the enediyne moiety, and no cyclization was observed even heating to 450 °C. Both conformational and electronic effects have been implicated to contribute to the change of reactivity of the enediyne in these systems.

From the above examples, it is clear that the currently available theories are inadequate to definitely predict the nature of perturbation of kinetics of BC upon complexation to metal ions. This is primarily due to the lack of knowledge about the *c,d* distance and also about the relative difference in strain energy between the ground state and the transition state for BC in the neat and in the complexed state.

Scheme 19. Representative Examples of Various Designs



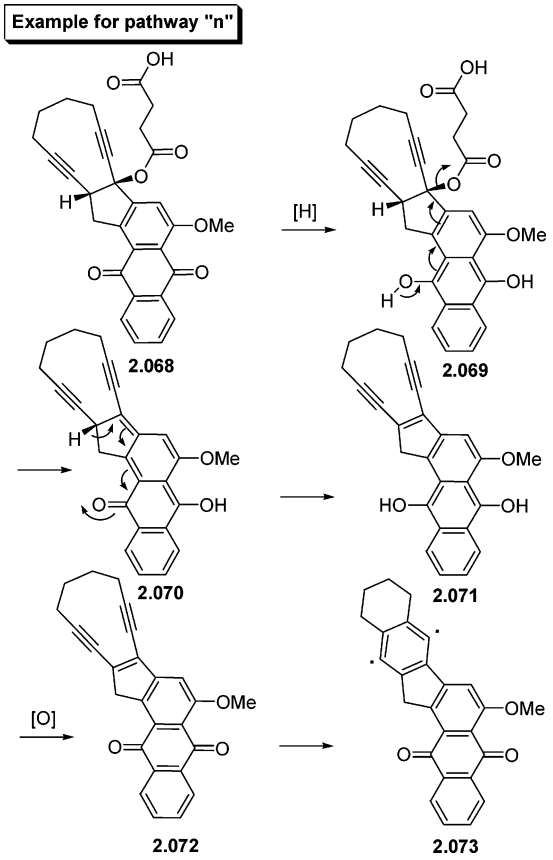
Scheme 20. Representative Examples of Various Designs



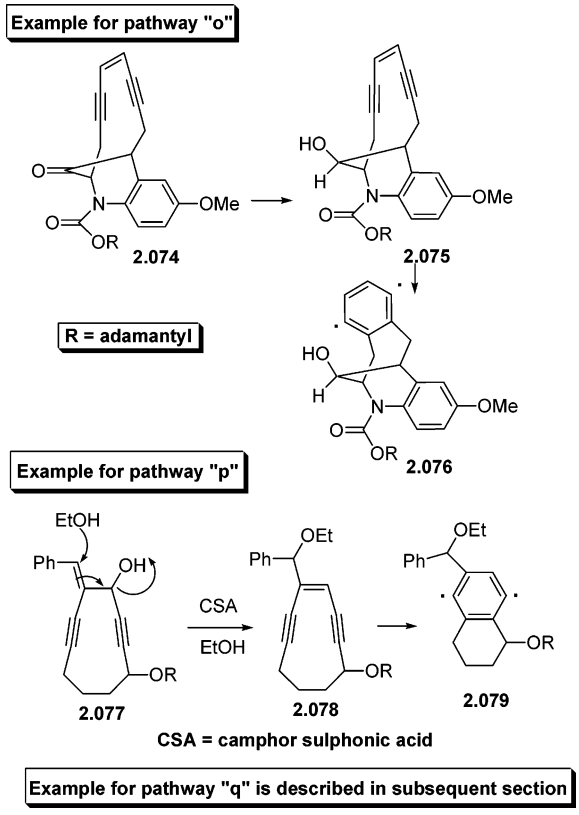
C. Bipyridyl Enediyne

Although formation of a cyclic network upon complexation is expected to bring down the *c,d* distance between the reacting acetylenic carbon atoms, a change in conformation is also critical at the same time in deciding the activation barrier for BC. Konig et al.[93] elegantly demonstrated a significant lowering of the activation barrier for BC by a subtle change in conformation. They synthesized a bipyridyl-based macrocyclic enediyne **3.012** (Scheme 27). The starting bromide **3.016** was synthesized in two steps and found to be a very useful synthon for a diverse array of enediynyl ligands.[94,95] For example, the ligand **3.012** was obtained by a base-induced macrocyclization of **3.016** with 3,3′-dihydroxy-6,6′-dimethyl-2,2′-dipyridyl.

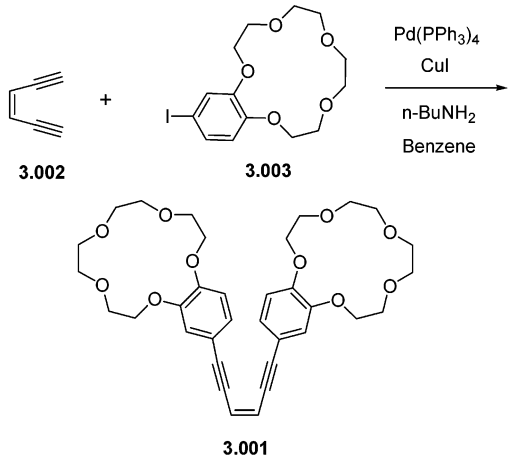
Scheme 21. Representative Examples of Various Designs



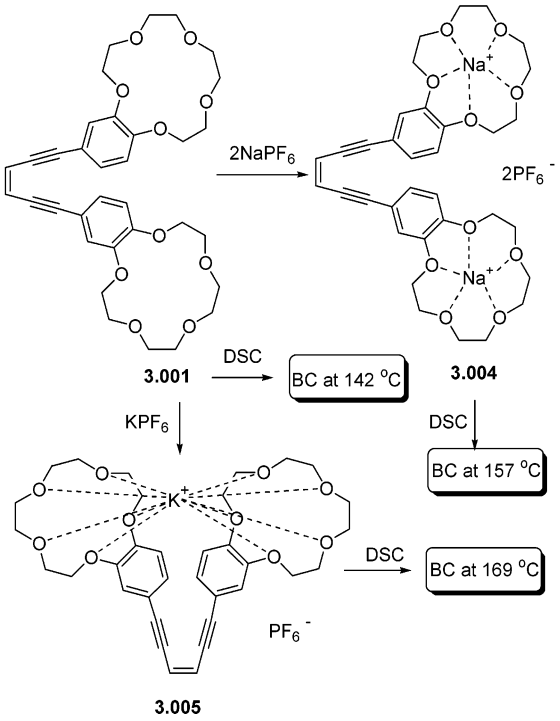
Scheme 22. Representative Examples of Various Designs



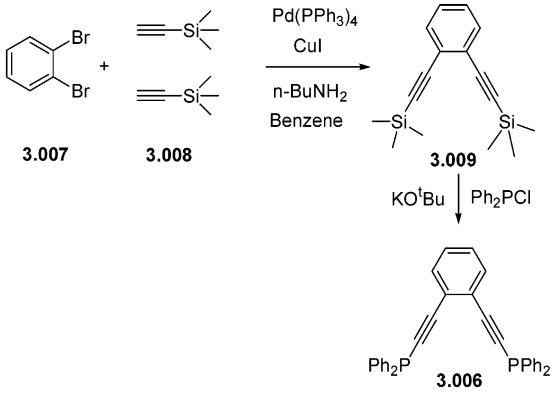
Scheme 23. Synthesis of Biscrown Ether



Scheme 24. BC of Biscrown Ether and Its Metal Complexes

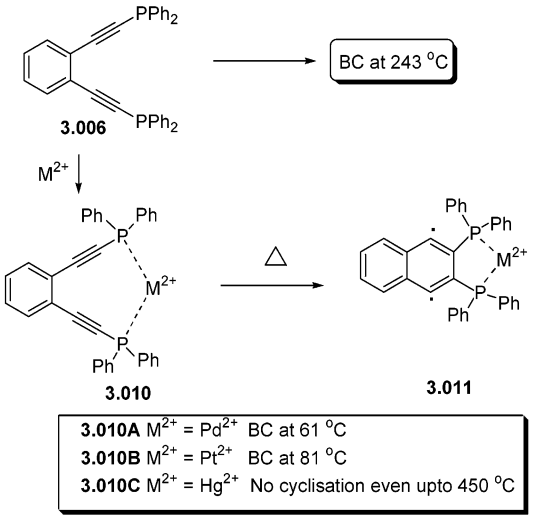


Scheme 25. Synthesis of Bisphosphino Enediyne

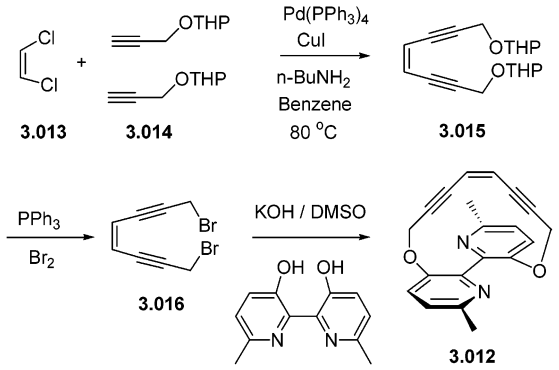


Without metal-ion complexation, the bipyridyl unit in **3.012** exists in the transoid conformation, which forces the terminal acetylenic carbon atoms to be far apart. Upon metal-ion binding, the 2,2′-bipyridyl unit changes into a cisoid conformation that allows the bidentate ligands to coordinate to the metal ion. In

Scheme 26. BC of Bisphosphino Enediyne and Its Metal Complexes



Scheme 27. Synthesis of Bipyridyl Enediyne

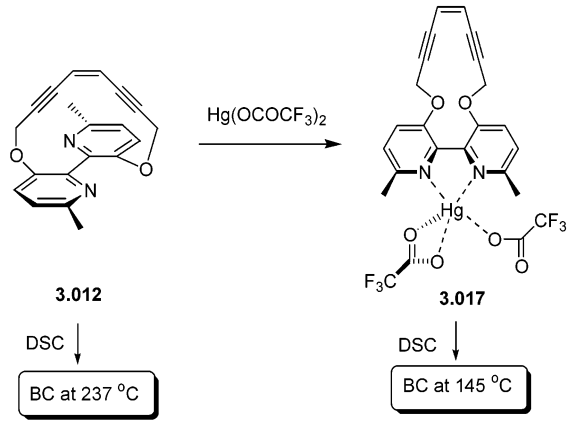


the process, the *c,d* distance decreases and one expects an increase in thermal reactivity. This was indeed found to be so. The thermal stability of compound **3.012** and its Hg^{2+} complex **3.017**, as investigated by DSC, showed significant difference. While a temperature around 237 °C is necessary to induce irreversible thermal cyclization of **3.012**, the Hg^{2+} complex **3.017** reacts at around 145 °C. Solution studies and H-trapping experiments revealed that the observed exothermic reaction corresponds to radical polymerization initiated by enediyne cyclization to 1,4-diradicals. It was therefore concluded that the induced conformational change of **3.012** brought about by metal-ion coordination results in a drop of the cyclization temperature by about 100 °C.

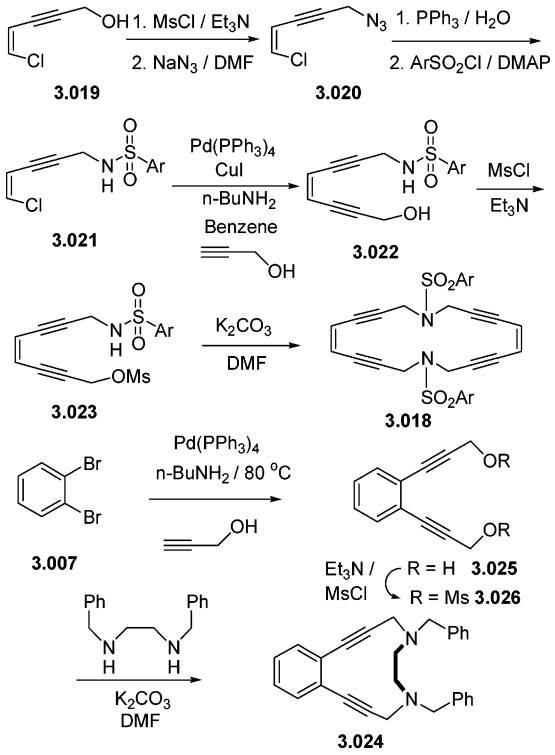
D. Amino and Sulfonamido Enediynes

Our group, over the past few years, has also been involved in studying the metal-ion-affected thermal BC of various enediynyl ligands.[96−98] For that, we chose macrocyclic enediynes as a template with nitrogen atoms as suitable coordinating sites. These systems should, in principle, give a much larger effect upon metal-ion coordination because of their more rigid structure. With this idea in mind, we synthesized three macrocyclic enediynes, two of them, namely, **3.018** and **3.024**, having two N-atoms and the other **3.032** with four N-atoms. The enediyne **3.018** was prepared from the mesylate **3.023** by an

Scheme 28. BC of Bipyridyl Enediyne and Its Hg Complex



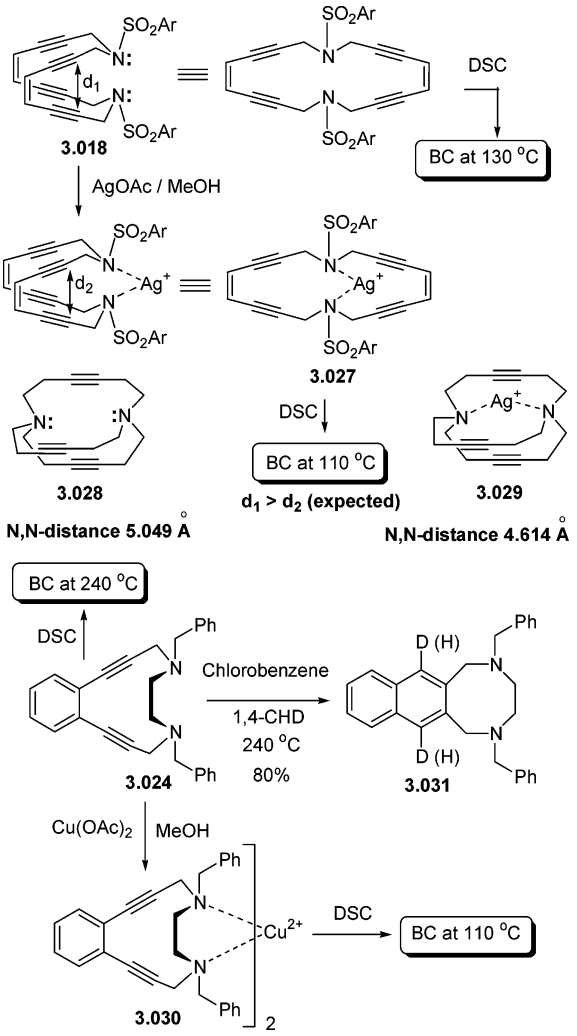
Scheme 29. Synthesis of Bissulfonamido and Bisamino Enediynes



initial intermolecular N-alkylation followed by intramolecular macrocyclization (Scheme 29).[96] No evidence was found for the formation of nine-membered enediyne. The other bis-N-substituted enediyne **3.024** was synthesized in a single step by a double N-alkylation with *N,N′*-dibenzyl ethylenediamine.[97] Interestingly, only the 1:1 adduct was obtained in this reaction.

The onset temperature for BC in the case of the 18-membered macrocyclic enediyne **3.018** was 130 °C, as determined by DSC. However, the compound, complexed to Ag (I) ion, showed cyclization at 110 °C, a modest decrease of cyclization temperature of 20 °C from its parent enediyne. Complexation leads to the removal of transannular repulsion between the lone pair of electrons on the nitrogens, thus bringing them closer together to form the metallocycle. As a result, the distance between the reacting acetylenic carbons is reduced, thereby lowering the activation

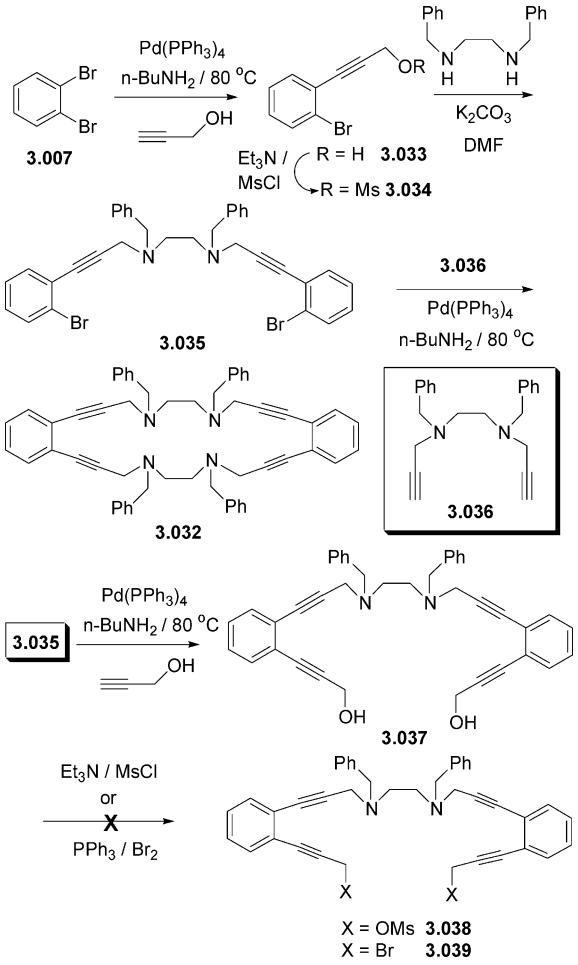
Scheme 30. BC of Bissulfonamido and Bisamino Enediynes



barrier to BC. Such shortening of the N−N distance upon complexation has been observed recently by Gleiter et al.[99] in 1,8-diazabicyclotriyne system (vide structures **3.028** and **3.029**). The bis-N-substituted enediyne **3.024** forms a brown Cu(II) complex **3.030** when treated with Cu(II) acetate in methanol. The complex has significantly lower stability than the free ligand. Thus, while **3.024** is stable up to a temperature of 240 °C, a thermal reaction of the complex **3.030** takes place at 110 °C (Scheme 30). Thus, a reduction of about 130 °C in cyclization temperature upon complexation was observed. The cycloaromatization of enediynes **3.024** to the bisazacyclooctene derivative **3.031** could be followed by heating a degassed solution of **3.024** in the presence of a large excess (100-fold) of cyclohexa-1,4-diene (1,4-CHD) to 240 °C for 24 h. The presence of an equivalent amount of copper acetate enhanced the rate of disappearance of starting enediyne, demonstrating the effect of metal-ion complexation.

-The tetra-N-substituted enediyne **3.032** was synthesized in a single step from the dibromodiyne **3.035** by a double Pd(0)-catalyzed eneyne coupling leading to the macrocycle[98] as shown in Scheme 31. The alternate route involving Pd(0) coupling between the dibromodiyne **3.035** and propargyl alcohol to form the bisalcohol **3.037** followed by mesylation and bisalkylation with N,N′-dibenzyl ethylenediamine was not successful. The attempted preparation of mesylate **3.038** or dibromide **3.039** failed, probably because of the complication created by the 3° nitrogens.

Scheme 31. Synthesis of Tetraamino Enediyne

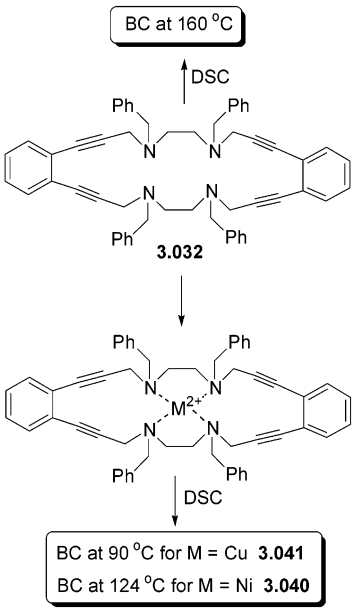


The onset temperature for BC for the tetra-N-substituted enediyne **3.032** changed from 160 (neat state) to 90 °C upon complexation to Cu(II), as indicated by the appearance of exothermic peak during recordings of DSC (Scheme 32). Similar observation was made[96,98] upon Ni(II)-ion complexation also (from 160 to 124 °C), although the extent of lowering is different. Solution-based experiments revealed the formation of BC-like products as indicated by the appearance of new aromatic peaks. However, no well-defined products could be isolated in this case. Our results, however, reemphasized the fact that significant lowering of the cyclization temperature could be achieved by metal-ion complexation and the extent of lowering depends on the nature of the metal ion.

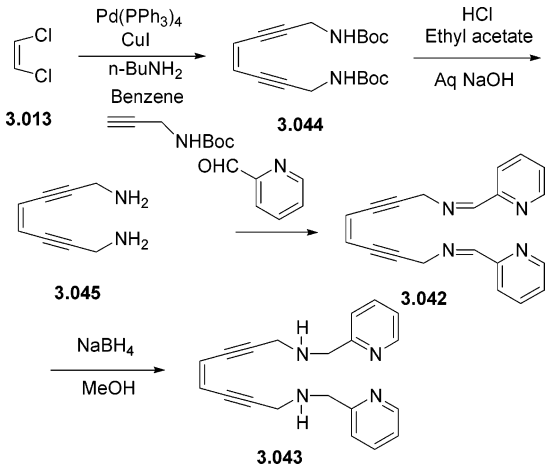
E. Aldimino Enediynes

Since the aromatic enediynes are thermally quite stable to start with, cyclization temperature could not be brought down to the level of ambient conditions despite significant lowering upon metal-ion complexation. Perhaps starting with an aliphatic system might provide such an example. As a matter of fact,

Scheme 32. BC of Tetraamino Enediynes and Its Metal Complexes

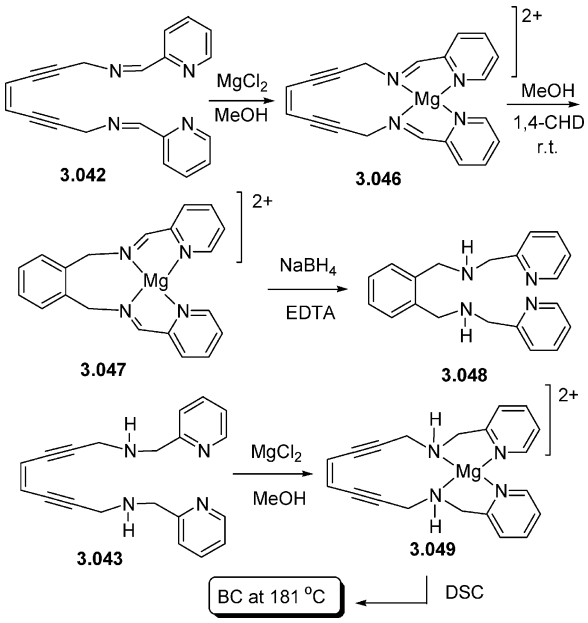


Scheme 33. Synthesis of Pyridyl Aldimino Enediynes

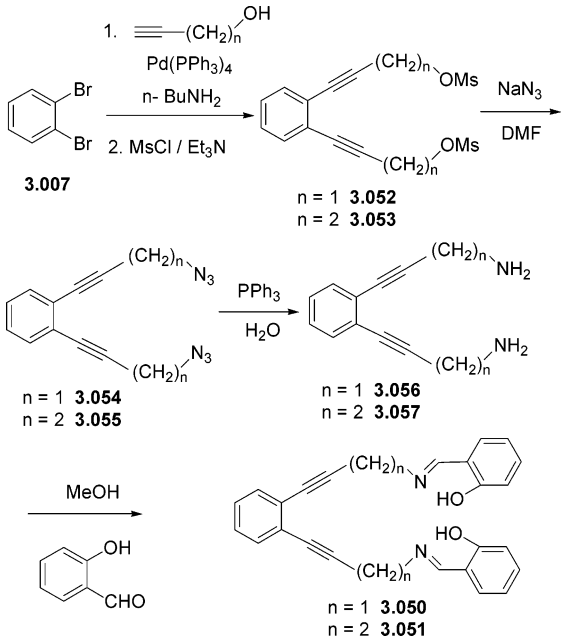


Zaleski et al.[100] reported an excellent example of a pyridine-based nonaromatic fused enediyne **3.042**, prepared from *Z*-diamine **3.045** (Scheme 33). While in the neat state, **3.042** cyclizes at 100 °C as revealed by DSC, its Mg^{2+} complex **3.046** underwent cyclization at room temperature in methanol in the presence of 1,4-CHD. The result is quite remarkable; for the first time, a nontoxic biorelevant metal ion like Mg^{2+} has been able to lower the activation barrier of an acyclic enediyne to such an extent that the reaction takes place at room temperature. It is also interesting to note that the Mg^{2+} complex **3.049** of the amino enediyne **3.043** undergoes cyclization at a temperature as high as 181 °C in the neat condition (Scheme 34). This large difference in reactivity upon metal-ion complexation has been explained by the authors in terms of the basicity of the coordinating amino and the imino nitrogens. Since the imino nitrogen is less basic than that of an amino, additional ligation, probably by solvent or by the counterion, is necessary to satisfy the Lewis acidity of Mg^{2+}. Computational studies have shown that greater coordination leads to higher lowering of *c*,*d* distance and hence also of the activation barrier for cyclization.

Scheme 34. BC of Pyridyl Aldimino Enediynes

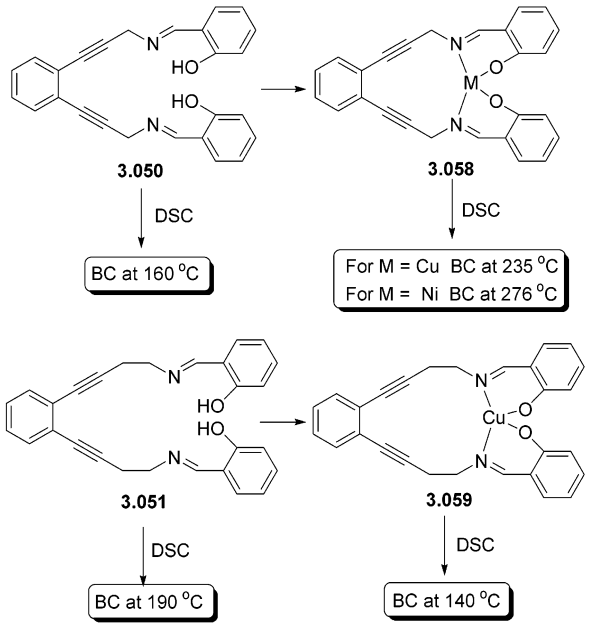


Scheme 35. Synthesis of Bissalicylaldimino Enediynes

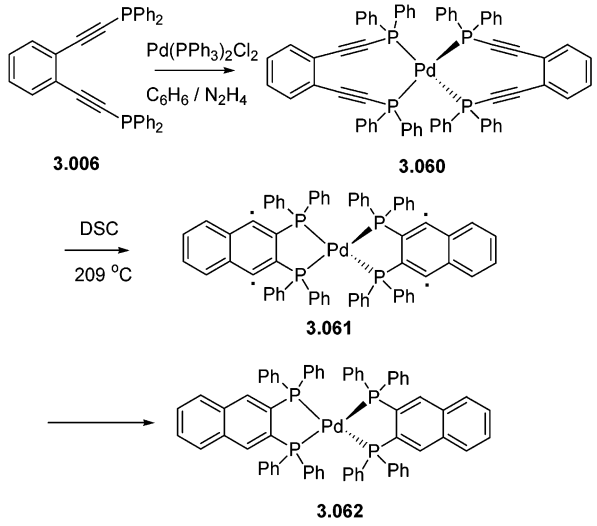


Recently[101] our group reported the synthesis of aromatic fused bis-salicylaldimino enediynes with different spacers separating the ligating center and the enediyne and observed some interesting results. The enediynes were synthesized from the corresponding diamines (Scheme 35). While the reactivity of the enediyne **3.050** upon complexation with metal ions such as Cu^{2+} decreased as revealed by the elevation of cyclization temperature,[96] the other enediyne **3.051** with two methylenes separating the ligand and the enediyne showed an opposite effect (Scheme 36).[102] The reason for this differential behavior is not known at present; the strain imposed upon complexation for the shorter enediyne **3.050** could be a reason for such behavior.

Scheme 36. BC of Bissalicylaldimino Enediynes and Their Metal Complexes



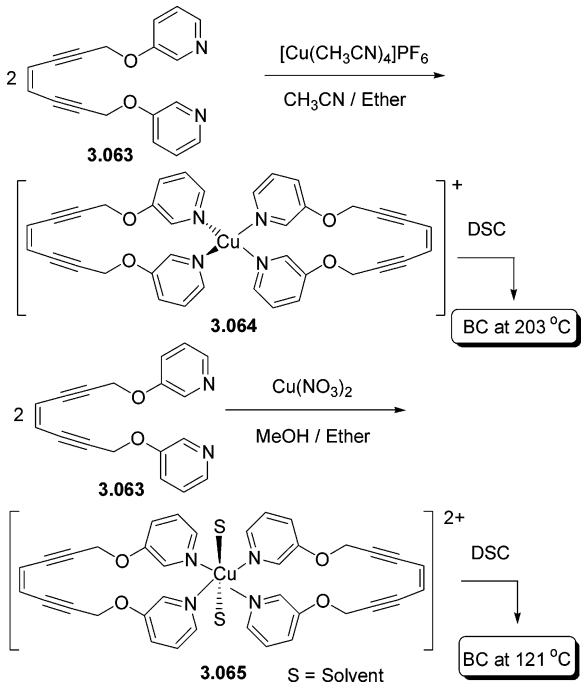
Scheme 37. BC of Tetrahedral Pd Complex



F. Copper- and Palladium-Based Metallocylic Enediynes

Metal-ion binding can impose structural consequences upon the enediyne ligand, which is governed by the ligand-field-mandated geometry of the metal center.[103−106] The thermal reactivity of such systems can thus be modulated by judicious choice of metal ligand geometry. Zaleski and his group[103] prepared (Scheme 37) a Pd(0) metallocycle, namely, bis[1,2-bis(diphenylphosphinoethynyl)benzene] palladium(0) (**3.060**). Its X-ray crystal structure showed that the ligands are arranged in a tetrahedral fashion around the palladium as expected for a d^{10} center. The complex is thermally stable, cyclizing only at a temperature of 209 °C (DSC). This is in sharp contrast to the reactivity of complex **3.010** reported by Buchwald et al.[84] (refer to Scheme 26). It has been speculated that the square planar geometry of d^8 with P−Pd−P angle close to 90° in **3.010** is facilitating the cyclization.

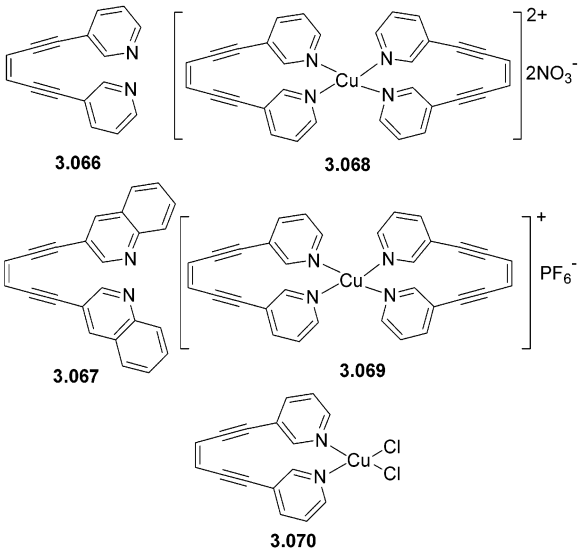
Scheme 38. BC of Cu(I) and Cu(II) Complexes



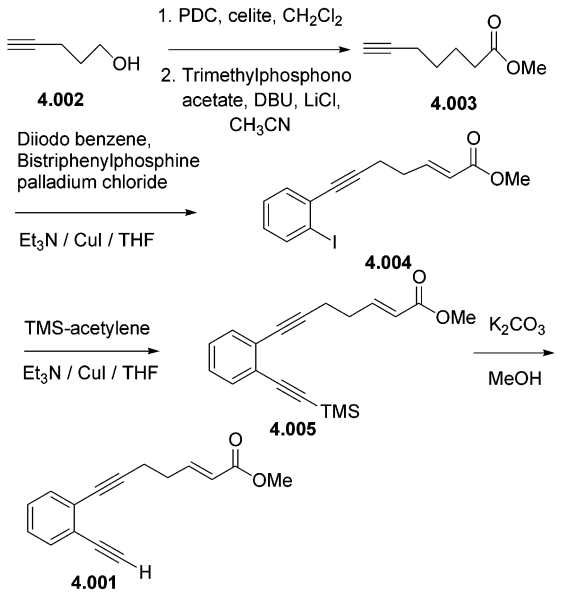
The same group in a separate set of examples[104] also demonstrated the importance of ligand-field geometry. The thermal reactivities of Cu(I) and Cu(II) complexes, **3.064** and **3.065** respectively, of the flexible ligand 1,8-bis(pyridine-3-oxy)oct-4-ene-2,6-diyne (bpod) (**3.063**) have been studied and shown to be dependent upon the oxidation state of the metal ion (Scheme 38). While the Cu(I) complex **3.064** undergoes BC at 203 °C, the Cu(II) complex **3.065** is substantially more reactive, undergoing cyclization at 121 °C. The Cu(II) complex being a d^9 system adapts a tetragonal configuration (as derived from EPR studies), while the Cu(I) complex (a d^{10} system) has a tetrahedral geometry (similar to the X-ray structure of $Cu(Py)_4^+$). The adoption of a tetrahedral geometry for the complex increases the distance between the alkyne termini, thereby decreasing the reactivity. Similar results were also obtained for mixed-ligand systems $[Cu(bpod)(pyridine)_2]^{+/2+}$.

Zaleski et al.[105] also studied the thermal behavior of Cu(I) and Cu(II) complexes of 1,6-bis(pridine-3)-hex-3-ene-1,5-diyne (PyED) (**3.066**) and 1,6-bis-(quinoline-3)hex-3-ene-1,5-diyne (QnED) (**3.067**). DSC measurements demonstrated that the complex $[Cu^{II}(PyED)_2](NO_3)_2$ (**3.068**) exhibited a BC temperature of 156 °C, which is substantially lower from that of the corresponding cuprous complex, namely, $[Cu^{I}(PyED)_2]PF_6$ (**3.069**); the latter underwent cyclization at 326 °C (Scheme 39).[105] This again demonstrated the importance of the oxidation state of metal ions. The distorted 4-coordinated dichloride compound $Cu^{II}(PyED)_2Cl_2$ **(3.070**) showed a cyclization temperature of 265 °C, which is between those of **3.068** and **3.069,** thus demonstrating the way of manipulating the activity of enediyne complexes by a judicious variation of geometry of the metal-ion center. Similar variation of cyclization temperature was also observed for the QnED complexes.

Scheme 39. Structures of Enediynyl Ligands PyEDand QnED and Their Metal Complexes



Scheme 40. Synthesis of Precursor Enediynes for Metal−Vinylidene Complexes

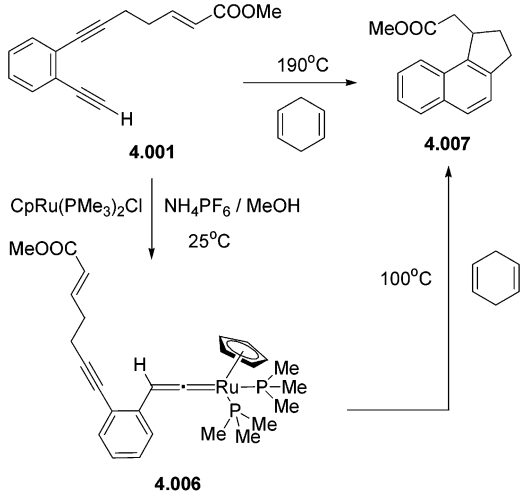


IV. Bergman Cyclization Mediated by Organometallic Reagents

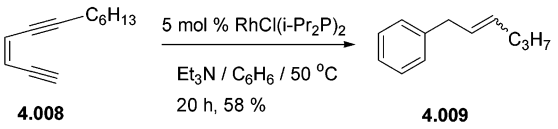
A. Involvement of Metal-Centered Radicals

Apart from the effect of metal ions on the kinetics of BC, organometallic reagents have also been employed for activation of enediyne without any ligating heteroatom. As it has already been pointed out that MSC occurs at a much lower temperature as compared to enediynes of similar structure, attempts have been made to rearrange an acyclic enediyne with a terminal alkyne to the more reactive eneyne allene. Finn et al.[81] first achieved this objective via the formation of a vinylidene complex,[107−110] which is formed when 1,2-benzodiyne (synthesis shown in Scheme 40) is treated with $CpRu(PMe_3)_2Cl$ and NH_4PF_6 (Scheme 41). Thermolysis of complex **4.006** required only a temperature of 100 °C, whereas the uncomplexed enediyne **4.001** needs to be heated to

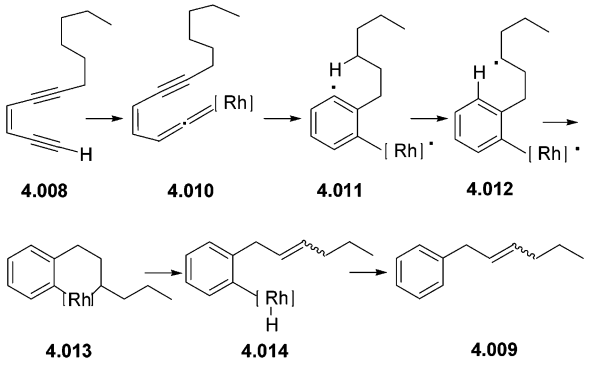
Scheme 41. MSC Mediated by Formation of Organometallic Compound



Scheme 42. BC of Acyclic Aliphatic Enediynes Mediated by Rh Complex



Scheme 43. Mechanism of BC Mediated by Rh Complex at Room Temperature



190 °C for cyclization to occur. This clearly illustrates increased thermal reactivity of the vinylidene complex toward MSC.

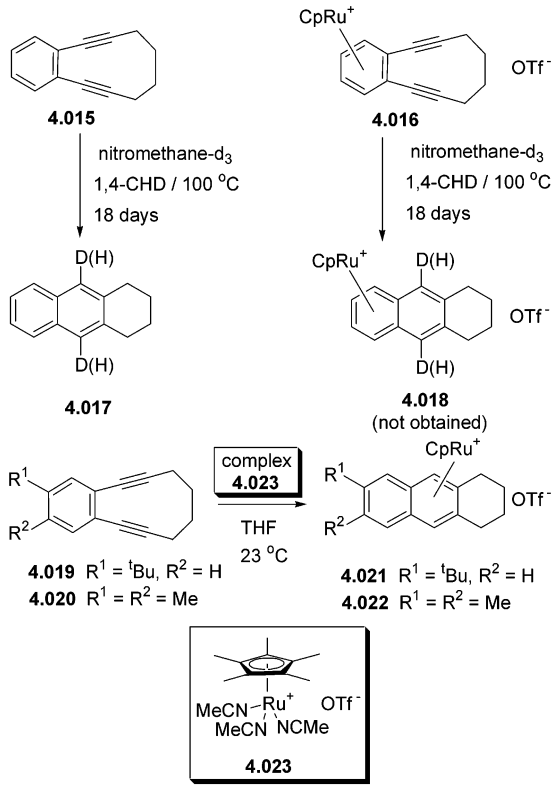
A somewhat similar but catalytic process has been reported[111,112] with a rhodium complex. Treatment of enediyne **4.008** with 5 mol % of $RhCl(i\text{-}Pr_3P)_2$ and triethylamine in benzene at 50 °C resulted in the formation of **4.009** in 58% via MSC of an in-situ-formed vinylidene complex (Scheme 42).

The proposed mechanism for the formation of **4.009** is shown in Scheme 43. The benzenoid radical **4.011** formed via MSC abstracts the γ-H in the hexyl arm followed by the formation of an intermediate metallocycle **4.013**. Reductive elimination of rhodium produces the final product **4.009**.

B. Effect of Ligation to the Ene Function

Another approach to perturb the kinetics of BC is by the ligation to the ene function in aromatic fused enediynes. This coordination actually retards the kinetics, presumably because of lesser aromaticity of

Scheme 44. BC Mediated by Pentamethyl Cyclopentadienyl Ruthenium Cation (4.023)

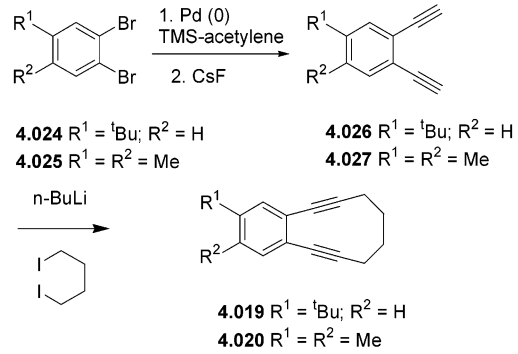


the resulting diradical after BC. Semmelhack et al.[71] previously reported that heating a benzene solution of 3,4-benzcyclodec-3-ene-1,5-diyne **4.015** and 1,4-CHD at 84 °C gave tetrahydroanthracene with a half-life of 24 h. O'Connor et al.[113] also found complete cycloaromatization when the same compound **4.015** was heated to 100 °C in nitromethane-d_3 in the presence of 1,4-CHD for 18 days. In marked contrast, the ruthenium complex **4.016** was stable under essentially identical conditions (Scheme 44). A similar result was also obtained under photochemical conditions.

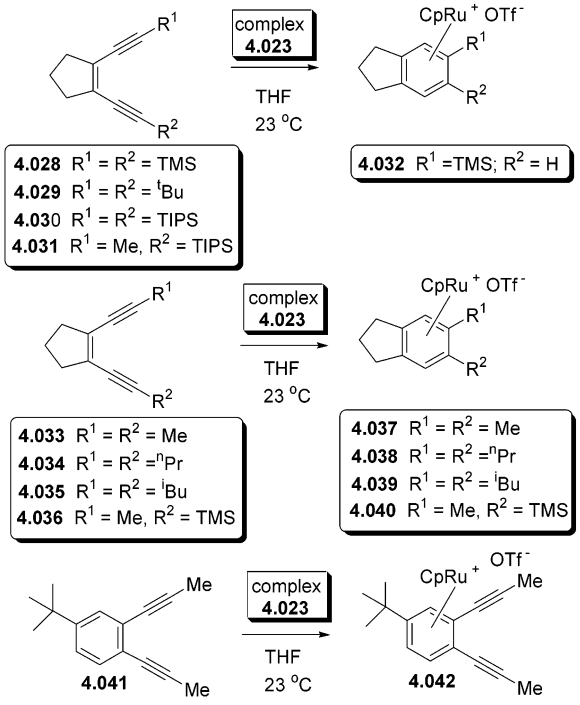
The situation is, however, somewhat different if one does not start with an enediyne with a preformed arene complex. Apart from forming a complex with the arene part of enediyne, addition of ruthenium complex **4.023** to the arene enediyne can also increase the rate of BC in benzene-fused cyclic enediynes via a ruthenium−alkyne interaction. Thus, in the presence of catalyst **4.023**, the otherwise stable enediynes **4.019** and **4.020** have been shown[113] to undergo cyclization at 23 °C in THF to form the cyclized naphthalene ruthenium complexes **4.021** and **4.022,** respectively, in good yields (Scheme 44). The synthesis of the starting cyclic enediynes as originally devoloped by Semmelhack et al.[71] is shown in Scheme 45.

The same group, in a more recent paper,[114] has shown that even acyclic enediynes can be made to undergo cyclization at room temperature. In the case of the bis-TMS enediyne **4.028**, at first sight, the cyclization appeared to involve the loss of a TMS under the reaction conditions to provide a terminal alkyne which then cycloaromatizes via a vinyledine

Scheme 45. Synthesis of Enediynes for Studying the Ligation to Ene Function

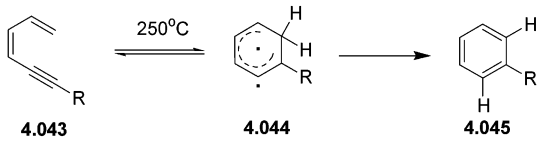


Scheme 46. BC of Acyclic Enediynes in Presence of the Complex 4.023

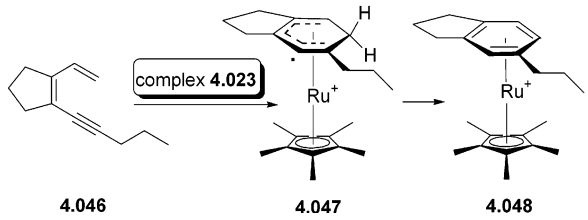


mechanism similar to that proposed by Finn et al.[81] However, isotope labeling studies with enediynes unsubstituted in one acetylenic arm indicated that that these compounds cyclize via a *p*-benzyne intermediate and not via the vinylidene mechanism. Encouraged by this result, the authors also studied the cyclization of enediynes **4.033**−**4.036**, disubstituted at both alkyne termini, in the presence of complex **4.023**. Interestingly, these enediynes also undergo rapid cyclization at 23 °C in THF. Thus, the catalyst provides an enormous driving force toward BC in these systems (Scheme 46). Too much steric crowding, however, prevents the enediynes **4.029**−**4.031** from undergoing the cyclization. Also, enediynes with an electron-rich aromatic system like **4.041** failed to show BC; it is very likely that the compound readily forms the arene metal complex **4.042,** thereby preventing the cyclization to occur. Although the mechanism of this metal-accelerated BC remains to be established, the above results indicate that 1,4-diradicals are certainly involved and point to ruthenium−alkyne interactions as a key

Scheme 47. Hopf Cyclization of Acyclic Enediynes



Scheme 48. Acceleration of Hopf Cyclization in the Presence of Complex 4.023



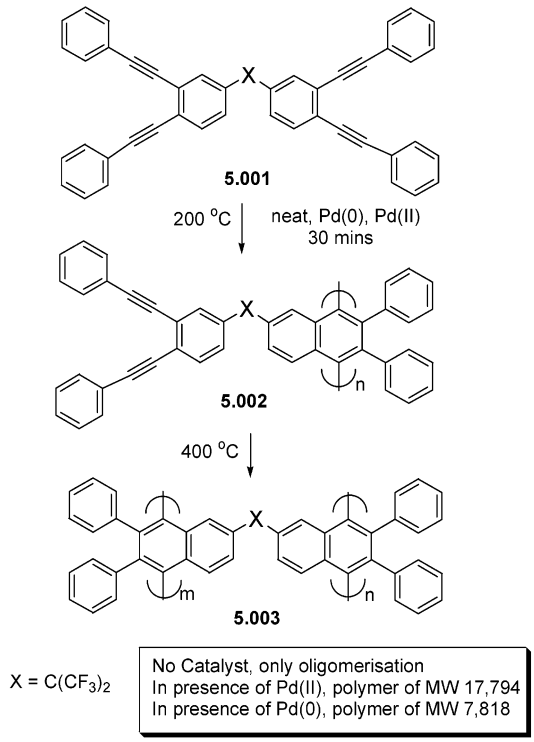
feature of the triggering process for cycloaromatization.

One interesting aspect of the above work is its extension to the Hopf cyclization (HC)[115,116] of dieneynes which is worth mentioning. As shown in Scheme 47, the HC is the high-temperature conversion of hexadieneynes to benzene derivatives, and like BC, it also proceeds via a cyclic intermediate of diradical character. O'Connor et al.[114] successfully demonstrated that in the presence of the ruthenium complex **4.023**, the dieneyne **4.046** underwent Hopf cyclization even at 23 °C in THF or $CHCl_3$ as solvent (Scheme 48). In this case, unlike in BC, no hydrogen abstraction takes place from the solvent because of fast intramolecular H-atom transfer.

V. Metal-Ion-Mediated Polymerization via Bergman Cyclization

Apart from the interaction of diradicals generated via BC with biological molecules such as DNA, these radicals have also been successfully demonstrated as a tool for the synthesis of linear[117] and branched polyarylenes.[118] John and Tour[117] first demonstrated that thermally initiated BC could be used as a synthetic methodology for linear polyarylenes. Thus, the diradicals, in the absence of any radical donor, undergo exothermic polymerization, which is also the basis of differential calorimetric studies in these systems. Smith et al.[119] very recently demonstrated that the metal catalysts have a significant effect upon the rate of polymerization of bis-*ortho*-diynyl arene **5.001** (abbreviated as BODA) monomers via thermally induced BC. The rate of polymerization was dramatically increased in the presence of Pd(0) and Pd(II). The polymerization was monitored by dynamic DSC measurements. Both Pd catalysts significantly enhanced the reactivity over neat polymerization. Increasing the catalyst concentration also accelerated BODA polymerization. The activation energies were calculated to be 29.7, 19.2, and 25.3 kcal/mol for neat-, Pd(0)-, and Pd(II)-catalyzed processes. Although the intermediate metal complex is not known, it is plausible that monodentate or bidentate enediyne metal π-complexation decreases the *trans*-alkyne distance and overall activation barrier to cyclization. Isothermal conversion of neat and catalyst-

Scheme 49. BC-mediated Polymerization of Enediynes

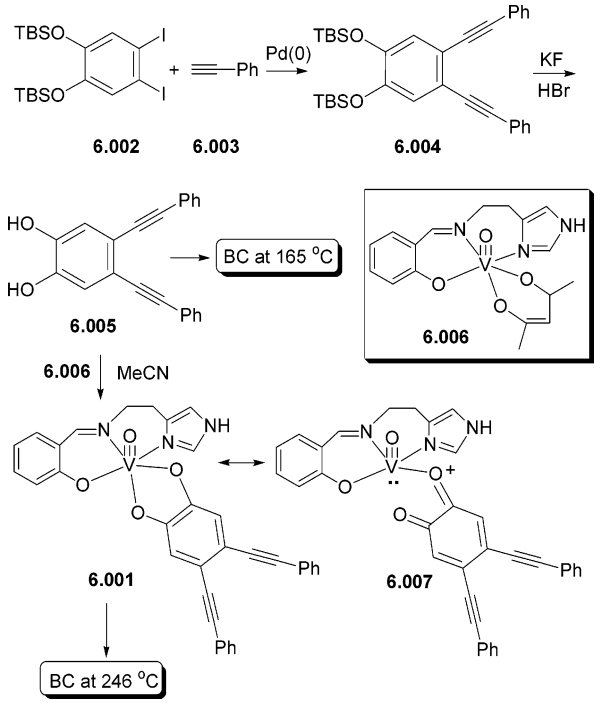


assisted melt polymerizations were studied. While the neat monomer on being heated to 200 °C gave only oligomers, both Pd(II)- and Pd(0)-catalyzed processes exhibited a significant molecular weight increase when heated to the same temperature for a brief period. In addition, the Pd(II)-catalyzed polymer exhibited much higher polydispersity over Pd(0)-processes, which demonstrated the dependence of diradical production on metals in the free and oxidized states, (Scheme 49).

VI. Oxo–Vanadium Enediyne: Photoinitiation of Bergman Cyclization

In a very recent paper, Zaleski et al.[120] reported a unique approach for photoinitiating BC. This is quite different from the method of photochemically promoting cyclization via UV-mediated electronic transition. The authors synthesized a novel vanadium(V) metalloenediyne **6.001** from the ligand 4,5-bis(penylethynyl)benzene-1,2-diol (CatED) (**6.005**). The metalloenediyne exhibited a strong ligand to metal charge transfer (LMCT) transition in the near-IR spectral region. This is due to the low redox potential of the high-valent vanadium center and the easily oxidizable catechol binding motif. These LMCT transitions have been used to photochemically activate the complex **6.001** toward BC upon laser excitation at 785 or 1064 nm. The cyclization was monitored by DSC as well as by resonance Raman spectroscopy. The enediyne was shown to be inert to photo-BC[66] upon electronic excitation in the UV spectral region. Incidentally, this is the first example where an enediyne has been activated with near-IR photons. The ability to employ longer excitation wavelengths to activate the enediyne offers a distinct advantage for biomedical applications such as photodynamic

Scheme 50. Thermal and Photochemical Reactivity of Catechol Enediyne and Its Oxo−Vanadium Complex

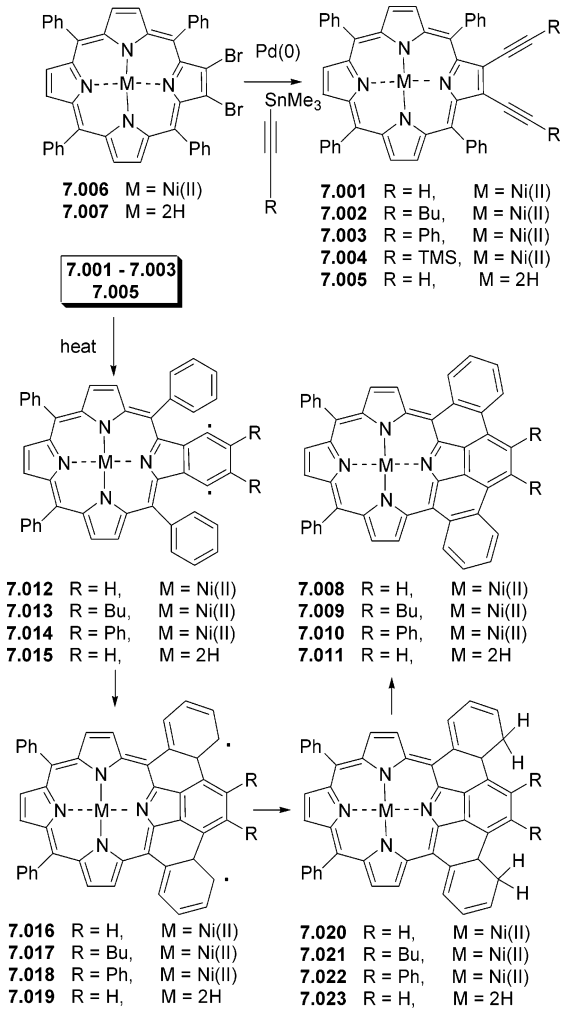


therapy due to enhanced tissue penetration by near-IR photons. Another interesting feature of complex **6.001** is its higher thermal barrier to BC as compared to the free ligand. The free ligand **6.005** showed an exothermic rise in DSC at 165 °C as compared to 246 °C for complex **6.001**. This was partly due to the different physical states of the ligand (an oil, which represents an ensemble of various configurations) and the complex (a solid). However, electronic contribution to the cyclization temperature could not be ruled out. Relative to the diprotonated enediyne **6.005**, the long V−O bond of the catechol enediyne trans to the oxo ligand may permit a small electronic contribution to the cyclization temperature arising from an allyl quinonoid resonance form **6.007**, which should stabilize the formal enediyne motif with respect to BC. The oxo−vanadium complex **6.001** has been prepared via a ligand-exchange reaction as shown in Scheme 50.

VII. Porphyrinic Enediyne: Formation of Picenoporphyrins via BC

Smith et al.[121] reported the synthesis and unusual reactivity of a series of nickel(II)−porphyrinic enediynes **7.001**−**7.004**. These compounds were prepared by palladium(0)-catalyzed cross-coupling reactions[122] of nickel(II) 2,3-dibromo-5,10,15,20-tetraphenylporphyrin with the corresponding alkynyl trimethylstannanes. Except for the TMS-substituted enediyne, the enediynes when heated in the presence of 1,4-CHD in chlorobenzene solution produced picenoporphyrins in good yields. The formation of these unusual cyclized products has been postulated to arise from the 1,4-diradical, which then adds on to the aromatic system. The resulting tetrahydro intermediate loses two molecules of hydrogen to promote

Scheme 51. Synthesis and Thermal Reactivity of Porphyrinic Enediynes

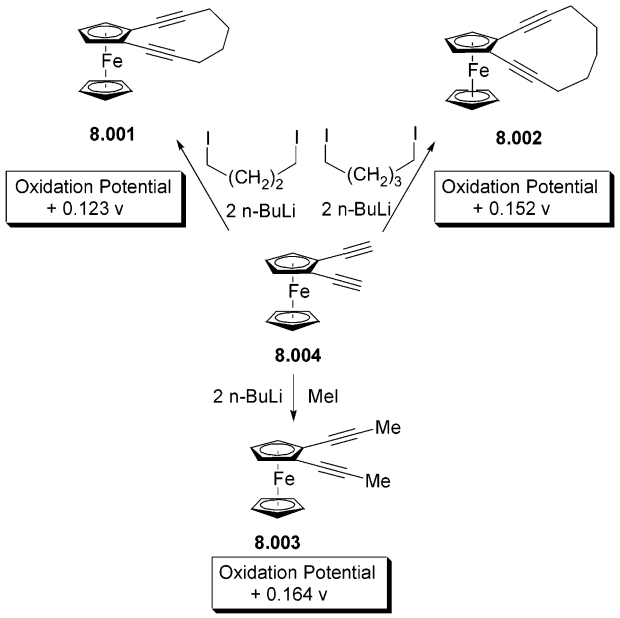


the aromatization of the picenoporphyrin products. In a later communication, Zaleski et al.[123] showed that addition of hydrogen-atom acceptors such as DDQ greatly enhances the product formation, thus proving that the loss of hydrogen is the rate-determining step. In addition to the Ni(II) complex, Zaleski et al.[123] also prepared the free base. From X-ray studies the *c,d* distances were 4.44 and 4.09 Å for the Ni(II) complex and the free base, respectively. DSC measurements revealed a small difference in reactivity; the complex cyclized at a temperature of 172 °C, while the free base cyclized at 160 °C. Thus, there is only a small degree of lowering of reactivity upon metal-ion complexation in these systems, Scheme 51.

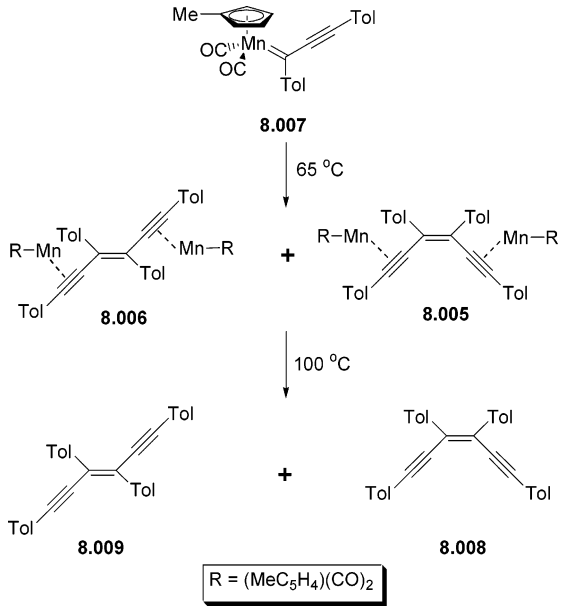
VIII. Ferrocene and Manganese Enediyne Complexes

The ferrocene−enediyne complexes **8.001**−**8.003**, reported[124] only this year, were prepared from 1,2-diethynylferrocene (**8.004**) via double C-alkylation (Scheme 52). A correlation was observed between ring strain and increased ease of electrochemical oxidation along the series **8.003** (+0.164 V) to **8.002** (+0.152 V) to **8.001** (+0.123 V). A similar trend in ionization potentials was identified in both the gas phase and

Scheme 52. Variation of Oxidation Potential in Ferrocene Enediynes



Scheme 53. Formation of Manganese Endiyne Complexes and Their Demetalation



in solution by computational methods. The correlation between ring strain and the increased ease of oxidation along the series, **8.003** < **8.002** < **8.001**, is not due to any difference in metal−enediyne interactions, as then one would not expect to see a similar effect in the metal-free systems. It has been suggested by the authors that the observed trend is primarily due to enhanced in plane π-π repulsion as increased ring strain brings the alkynes into closer proximity. The reactivity of these enediynes toward BC has not been reported, and hence, no correlation between oxidation potential and the rate of BC cannot be drawn at this stage.

The formation of manganese enediyne complexes **8.005** and **8.006** by dimerization of the corresponding alkyne complex **8.007** has just been reported.[125] The metal-free enediynes **8.008** and **8.009** could be isolated by thermolysis of the complex at 100 °C, thus showing the thermal stability of the metal−enediyne complexes (Scheme 53).

IX. Concluding Remarks

Since the first demonstration of the dependence of kinetics of BC on metal ions by Konig et al.,[82] significant advances have been made in this area of chelation control of BC. New ligands, which show BC even at room temperature in the presence of metal ions or organometallic reagents, have been designed. However, better understanding based on ligand-field theory is needed to help in the design of proper ligands to promote BC under ambient conditions. In the future what one would like to see is the interaction of these ligands with their biological targets, namely, DNA and proteins, in the presence of metal ions or organometallic reagents. The selectivity in terms of BC kinetics shown by different ligands may also open up a new application of enediynes as sensors for metal ions. Besides, the role of weak interactions such as the H-bond[126] may also play a role in influencing BC kinetics. Advancement is also expected in that direction. The importance of metal-ion-mediated BC is reflected by the recent issuance of a U.S. patent to Zaleski et al.[127] for possible use of enediyne metal complexes as antitumor and antiviral agents. Two more papers, both from Zaleski's laboratory, have just appeared. One[128] addressed the cause of variation of cyclization temperature upon ligation to different metal ions by a conformationally restricted enediynyl ligand similar to the one, **3.024,** prepared in our laboratory.[97] It has been shown that the reactivity difference is independent of metal center geometry; it is the electron donation from the ancillary chloride ligand which has a dramatic influence on cyclization kinetics. The other one[129] studied the photoelectronic BC of copper metalloenediynes promoted by metal−ligand charge transfer. The photolysis has resulted in DNA cleavage via H-atom abstraction from the 4′-position of the deoxyribose.

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XI. References

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