

## Acceleration of Conjugated Dienyne Cycloaromatization

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## CONTENTS

1. Introduction	7904
2. Photochemical	7904
3. Alkyne–Allene Isomerization	7907
4. Nucleophilic Attack by the Alkyne	7909
5. Umpolung Activation of the Alkyne	7910
6. Alkyne–Vinylidene Isomerization	7916
7. $\eta^6$ -Coordination of the $\pi$ System	7918
8. Metal Carbene Induced	7919
9. Conclusions and Future Outlook	7920
Author Information	7920
Biographies	7920
Acknowledgment	7921
References	7921

## 1. INTRODUCTION

The thermal cycloaromatization of conjugated 1,3-dien-5-yne has long been an area of intense interest among physical organic and computational chemists.<sup>1</sup> Hopf and Musso initially reported that heating (*Z*)-1,3-hexadien-5-yne (**1**) at temperatures in excess of 274 °C resulted in conversion to benzene (**2**, Scheme 1).<sup>2</sup> At temperatures greater than 550 °C, several mechanisms may be active; however, computational and experimental studies provide strong support for the mechanism shown in Scheme 1 as the most dominate one at lower temperatures.<sup>3</sup> From **1**, electrocyclization leads to cyclic allene intermediate **3** that then proceeds through an initial [1,2]-H shift to afford intermediate **4** which can be represented as either carbene **4-A** or diradical **4-B**. A final [1,2]-H shift leads to the aromatized product **2**.

While the electrocyclization pathway shown in Scheme 1 represents the most well studied thermal dienyne cycloaromatization, a lesser-known variant initiates via a [1,7]-H shift from a *cis*-allylic substituted dienyne **5** to give allene intermediate **6** (Scheme 2).  $6\pi$ -Electrocyclization of **6** gives **7**, which in turn isomerizes to **8** via a [1,3]-H shift. Although thermal [1,7]-H shifts are well-known for 1,3,5-hexatrienes,<sup>4</sup> examples with dienynes are rare and generally occur at high temperature (>200 °C).<sup>5,6</sup>

Synthetically, dienyne cycloaromatization provides a reliable way to construct highly substituted aromatic systems from readily available starting materials as depicted in Scheme 3. A major drawback of the thermal mode of cyclization is the exceedingly high temperatures required to effect cyclization, thus limiting the substrate scope.

The motive of this review is to highlight the discovery, mechanism, and synthetic utility of methodologies that use either catalytic or stoichiometric activators to promote dienyne cycloaromatizations at temperatures below 200 °C. The review is

organized by mechanism of activation and covers cyclizations resulting in carbon-based aromatic systems (e.g., benzenoid, naphthalenoid). Heterocyclic aromatic systems are not reviewed unless a mechanistic discussion is warranted. In order to decrease redundancy throughout the discussion, dienyne substrates have been classified according to the presence and location of aromatic alkene subunits as shown in Figure 1.

## 2. PHOTOCHEMICAL

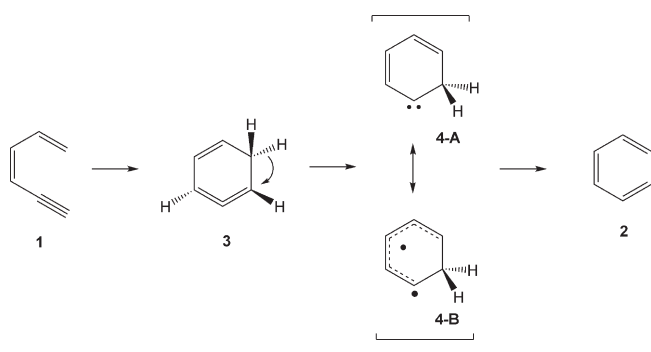
The earliest observation of photolytic dienyne cycloaromatization was demonstrated by Kaplan and co-workers who showed that irradiation of dienyne **1** at 254 nm resulted in slow ( $\Phi = \sim 0.01$ ) but quantitative conversion to a 2:1 mixture of benzene and fulvene.<sup>7</sup> This single example actually predates the thermal cycloaromatization, but no mechanistic rationale was provided for the reaction. In later studies, Laarhoven and co-workers demonstrated the utility of photolyzing substituted enynyl-naphthalenes (e.g., **9**, Scheme 4) and phenanthrenes to form cycloaromatized polyaromatic systems in good to moderate yields.<sup>8</sup> Although alternative mechanisms were proposed in earlier papers, these researchers now favor a mechanism proceeding through cycloallene intermediate **10**, similar to the thermal reaction.<sup>8d</sup> Intermediate **10** was proposed to convert to product **11** by a variety of pathways depending on the reaction conditions. In protic solvents, **10** acquires a proton from solvent to form cation **12**, which subsequently aromatizes to **11**. This mechanism is consistent with the observation that in the presence of CH<sub>3</sub>OD product **11** had >95% deuterium incorporation at the C-2 position. In general, use of protic solvents led to higher quantum yields when compared to nonpolar aprotic solvents because protonation of **10** represents the lowest energy pathway to product.

Rate acceleration in the presence of air was also observed, particularly in aprotic solvents. On the basis of this observation, oxygen was proposed to trigger the conversion of **10** by hydrogen abstraction resulting in the formation of intermediate **13**. In the absence of oxygen, the predominate mechanism results from **10** abstracting a hydrogen atom from solvent to form **14**. This was supported by faster rates in hexanes versus benzene (weaker C-H bonds for the former), formation of small amounts of biphenyl when the reaction was conducted in benzene (presumably from attack of the resulting phenyl radical on another molecule of benzene) and incorporation of iodine at the C-2 position of the product **11** when the reaction was conducted in the presence of I<sub>2</sub>. Reaction of **9**, labeled with deuterium at the C-2 position, gave, albeit diminished, incorporation of D at the C-2 position of **11** suggesting a formal intramolecular [1,5]-H shift may also be operative under air-free conditions.

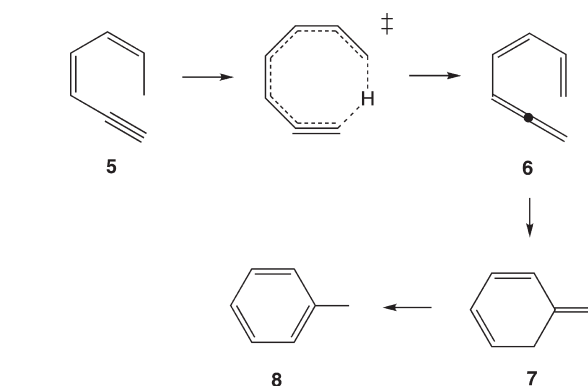
Received: May 4, 2011

Published: October 06, 2011

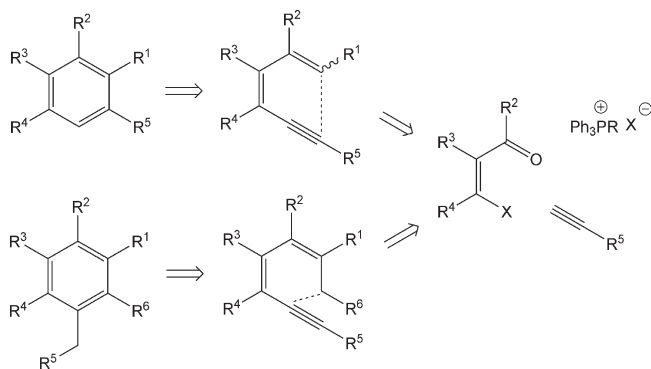
Scheme 1. Intermediates Believed to Be Involved in the Thermal Cycloaromatization of Dienes<sup>3</sup>



Scheme 2. General Mechanism for a Thermal Diene [1,7]-H Shift/Cycloaromatization



Scheme 3. Retrosynthesis of Aromatic Products Deriving from Dienes



The most surprising observation was the high degree of rate acceleration in the presence of amine bases, which was determined to be an order of magnitude higher than molecular oxygen acceleration and 4 orders of magnitude higher than hydrogen abstraction from solvent. Use of C-2 deuterium enriched **9** with amine showed high levels of D incorporation in the C-2 position of **11** under all conditions. Furthermore, in the absence of amine under identical open-air conditions, negligible deuterium incorporation in **11** was observed, ruling out an intramolecular

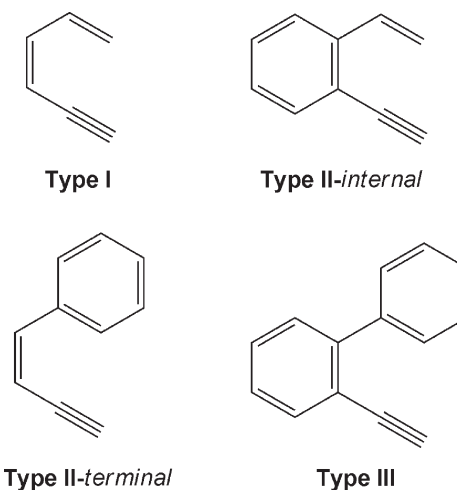
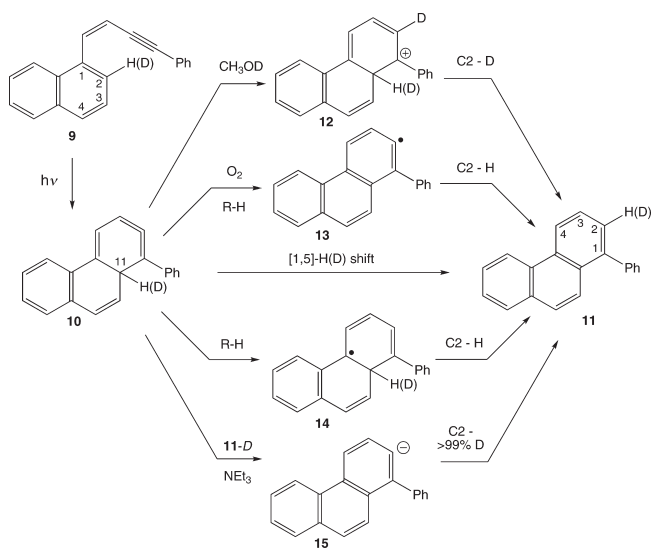


Figure 1. Classification of diene substrates.

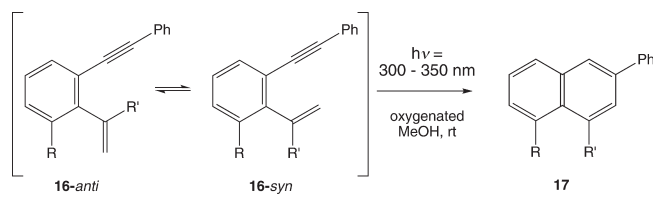
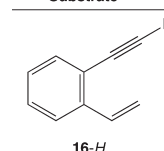
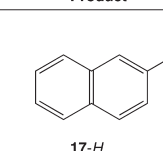
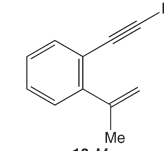
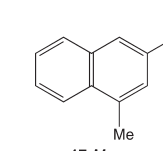
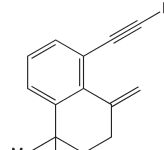
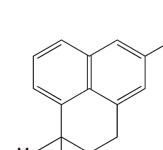
Scheme 4. Mechanistic Pathways of Conversion for Photochemically Generated Cyclic Allene **10**<sup>8</sup>

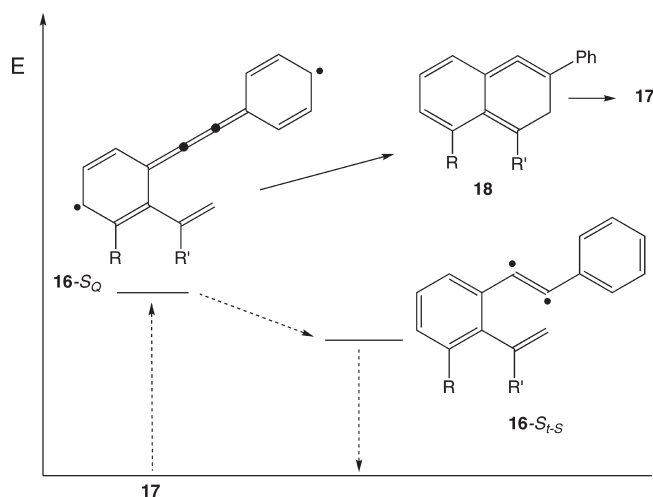


[1,5]-H transfer. On the basis of these results, a deprotonation/reprotonation mechanism was proposed to proceed through aryl anion **15**. Laarhoven and co-workers have also obtained similar findings for the photocycloaromatizations of **Type II-internal** dienes.<sup>9</sup>

Key insight into the reactive excited state of the photocycloaromatization came through the work of Lewis and Sajimon who studied the reactivity of various **Type II-internal** dienes with varying substitution at the terminal alkene.<sup>10</sup> These researchers hypothesized that the efficiency of the cyclization would increase if a higher proportion of the terminal alkene existed in the less stable *syn* conformation, **16-syn**, versus the *anti* conformation, **16-anti** (Table 1). To test this prediction, dienes **16-Me** and **16-cy** were prepared with the expectation that **16-Me** would increase the concentration of rotamer **16-syn** and **16-cy** would lock the diene in the *syn* conformation. As expected, the quantum yield for the formation of **17** ( $\Phi_{rxn}$ ) increased along the series **16-cy** > **16-Me** > **16-H**, but with an unexpected identical trend in

**Table 1.** Comparison of Fluorescent Singlet State Lifetime ( $\tau_s$ ), Quantum Yield of Fluorescence ( $\Phi_f$ ) and Reaction ( $\Phi_{rxn}$ ) for Diynes of Differing Terminal Alkene Substitution<sup>10</sup>

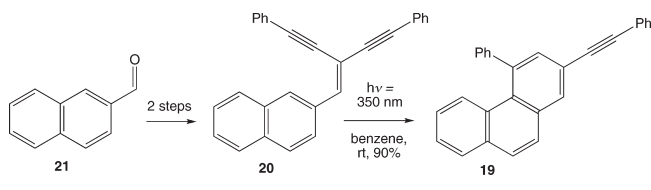
				
Substrate	Product	$\Phi_f$	$\tau_s$ (ns)	$\Phi_{rxn}$
		0.1	< 0.1	< 0.02
		0.17	5.9	0.21
		0.21	6.8	0.47



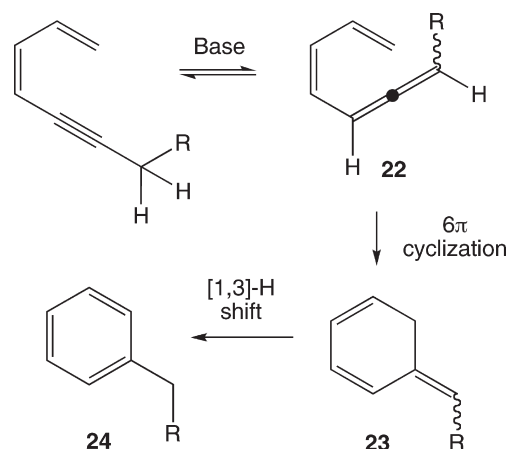
**Figure 2.** Pictorial representation of fluorescent linear singlet state  $16-S_Q$  and nonfluorescent *trans*-stilbene “like” singlet state  $16-S_{L-S}$ .<sup>10</sup>

quantum yield of fluorescence ( $\Phi_f$ ) and lifetime of the excited fluorescent singlet state ( $\tau_s$ ). The  $\Phi_f$  and  $\tau_s$  trend was rationalized by a slower decay of the fluorescent linear singlet state  $16-S_Q$  to a nonfluorescent *trans*-stilbene “like” singlet state  $16-S_{L-S}$  for **16-Me/16-cy** compared to **16-H** which exhibited decay similar to the well-studied diphenylacetylene (Figure 2). This explanation was consistent with calculations that showed the activation for

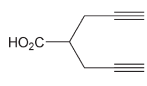
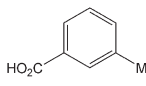





**Scheme 5.** High Yielding Photocycloaromatization of 2,4-Substituted Phenanthrene **19** from Readily Available 2-Naphthylcarboxaldehyde (**21**)<sup>13</sup>



**Scheme 6.** General Mechanism for Diene Cycloaromatization through Base-Catalyzed Allene Formation



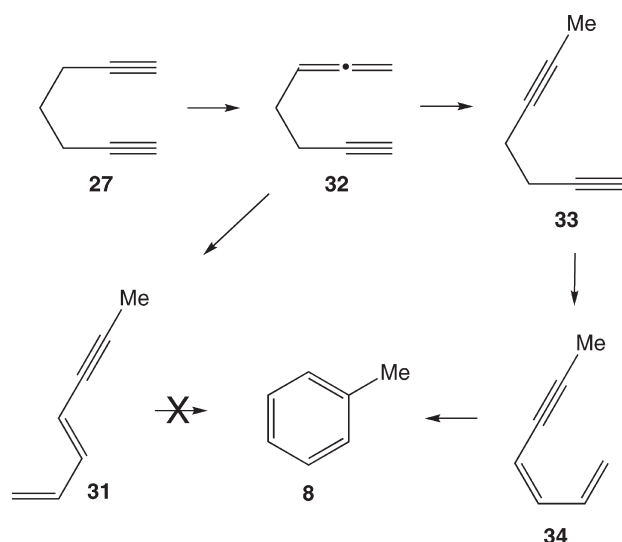
**Table 2.** Cycloaromatization Resulting from Base-Catalyzed Diene Isomerization<sup>a</sup>

Entry	Condition	Substrate	Product(s)
1	A		
2	B		
3	B		 

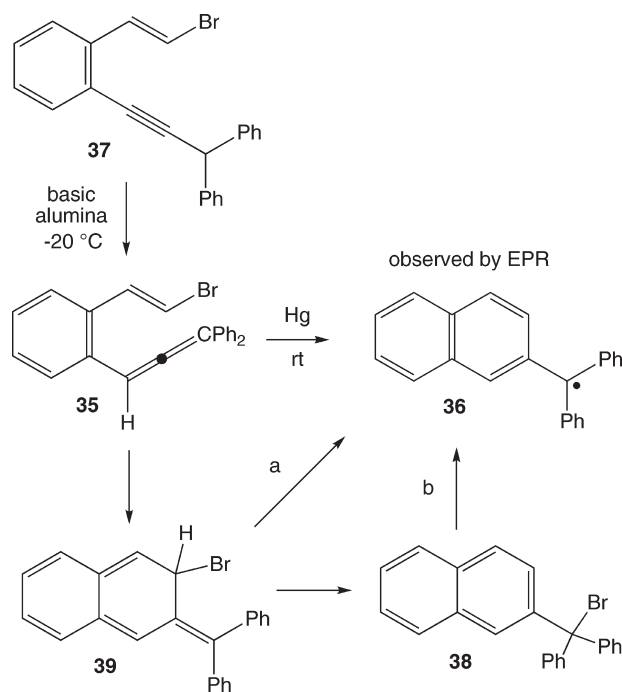
<sup>a</sup> Conditions: (A) KOH, H<sub>2</sub>O, reflux, 4 h. (B) KO<sup>t</sup>Bu, diglyme, reflux, >4 h.<sup>16</sup>

$16-S_Q$  to  $16-S_{L-S}$  conversion was  $6.0 \text{ kcal} \cdot \text{mol}^{-1}$  higher for the respective states of **16-Me/16-cy** compared to **16-H**. Furthermore, a temperature dependence on the  $\tau_s$  was observed for **16-Me/16-cy** that allowed for measurement of the radiation-less decay Arrhenius parameters. While the  $E_a$  for **16-Me/16-cy** was similar to the decay of diphenylacetylene (model for **16-H**), the pre-exponential term ( $\log A$ ) was lower. These authors correlate the decrease in  $A$  to the ordered transition state leading to cyclic allene **18** and therefore, at least for **16-Me/16-cy**, the reactive excited state appears to be the lowest

**Scheme 7. Intermediates Identified by Hopf Involved in the Isomerization of Diyne 27 to Toluene**<sup>18</sup>



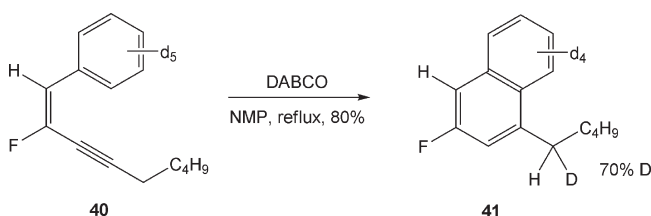
**Scheme 8. Allene Isomerization for the Formation of a Naphtyldiphenylmethyl Radical**<sup>19</sup>



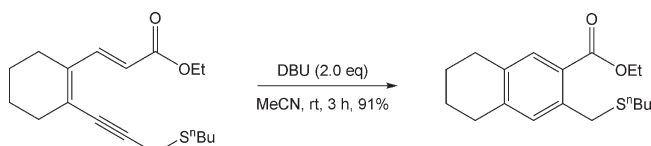
energy fluorescent state of 16-SQ. Similar conclusions were made in latter studies from **Type III** dienyne although  $\Phi_{\text{rxn}}$  was lower in these cases.<sup>11</sup>

The applicability of the photocycloaromatization for synthesis may be limited. While reactions conditions are mild, isolated yields are, in many cases, low and byproduct formation stemming from radical processes can be problematic.<sup>8c,12</sup> Despite these difficulties some photocycloaromatization successes have been reported. Neckers and co-workers were able to prepare 2,4-disubstituted phenanthrene **19** in excellent yield from

**Scheme 9. Labeling Study Demonstrating a Competition between Concerted and Base-Assisted Transfer of Deuterium**<sup>20a</sup>



**Scheme 10. Use of Propargyl Sulfides for Ambient Temperature Cycloaromatization**<sup>22</sup>



diendiyne **20** for use in the synthesis of polyaromatic compounds for optical applications (Scheme 5).<sup>13</sup>

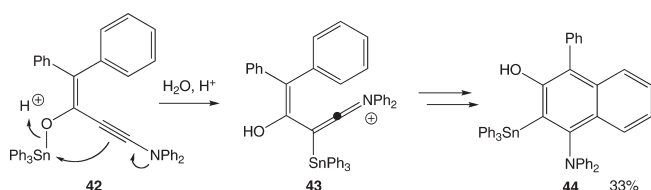
### 3. ALKYNE–ALLENE ISOMERIZATION

Depending on the electronic nature of the dienyne, it may be possible to thermally isomerize the alkyne to an allene (e.g., **22**) under basic conditions (Scheme 6). From **22**,  $6\pi$ -electrocyclization to afford **23** followed by a formal [1,3]-H shift provides a reasonable pathway for production of aromatic product **24**.<sup>14</sup>

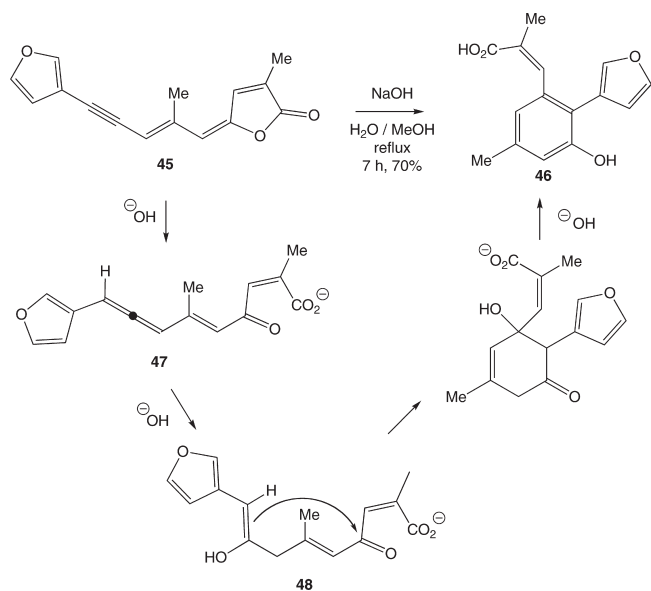
Possibly the first report of this mode of cyclization involving a dienyne intermediate can be dated to 1907 when Perkin and Simonsen showed that *m*-toluic acid (**25**, Table 2) was formed from treatment of 2-(prop-2-yn-1-yl)pent-4-ynoic acid (**26**) with hydrobromic acid or boiling water.<sup>15</sup> These researchers proposed an unlikely mechanism involving hydration of both alkynes and an intramolecular Aldol reaction as key isomerization events. Much later, Eglinton and co-workers independently synthesized **26** from a known route and reinvestigated this transformation.<sup>16</sup> No cyclization was observed under Perkin and Simonsen's conditions, but near quantitative formation of **25** was obtained by refluxing **26** in the presence of aqueous KOH (entry 1). These researchers were able to rule out an Aldol mechanism for the base catalyzed process, by hydrolyzing **26** to the diketone and subjecting the resulting product to refluxing aqueous KOH, which only resulted in the formation of the expected Aldol condensation product (3-methyl-5-oxocyclohex-3-ene-carboxylic acid) with no observation of **25**. It was also found that the reaction was more general. For example, treating simple diynes **27** and **28** with KO<sup>t</sup>Bu in refluxing diglyme resulted in the formation of toluene (**8**) and a mixture of *o*-xylene (**29**)/ethylbenzene (**30**), respectively (entries 2 and 3). Although a dienyne intermediate was not proposed, Eglinton suggested a  $6\pi$ -electrocyclization from an allene structure as the key carbon bond-forming step (see **22**–**23**, Scheme 6).

Ben-Efraim and Sondheimer were the first to provide support of dienyne intermediates in the diyne isomerization/cyclization.<sup>17</sup> By running the reaction of **27** at lower temperatures in refluxing

**Scheme 11.**  $6\pi$ -Electrocyclization from a 1,3-Stannane Shift<sup>23</sup>



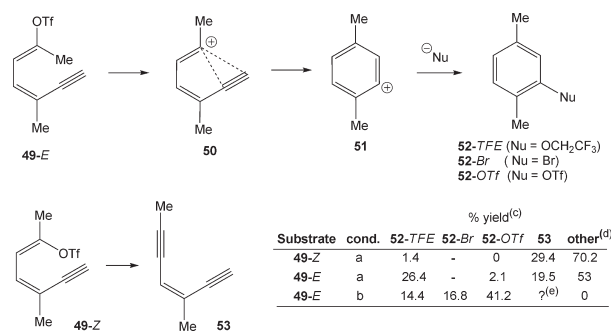
**Scheme 12.** Base-Induced Cycloaromatization of Freilinyne (45) Proceeding through an Allene Intermediate<sup>24</sup>



<sup>t</sup>BuOH, a 1:1 mixture of **8** and *trans*-1,3-heptadien-5-yne (**31**, Scheme 7) was obtained as the sole products, thus demonstrating that **27** was capable of isomerization to a dienyne structure. It was also shown that pure **31** did not convert to **8** when subjected to the reaction conditions, verifying the former as a stable byproduct. In further mechanistic studies, Hopf was able to identify allene **32**, diyne **33**, and the *cis*-dienyne **34** as potential intermediates by carrying out the reaction of **27** at lower temperatures and shorter reaction times.<sup>18</sup> More importantly, subjecting pure **34** to similar reaction conditions resulted in clean formation of **8** with none of the *trans*-isomer **31**, thereby suggesting that only the *cis*-dienyne **34** is able to convert to product. While no mechanistic rationale was provided, the most reasonable pathway would involve isomerization to the allene as shown in Scheme 6. A direct thermal cycloaromatization (Scheme 1) would be unlikely because of the lower temperatures needed and indeed, when 1,5-hexadiyne was subjected to similar conditions to those used for **27**, the only observable products were *cis*- and *trans*-1,3-hexadien-5-yne, which lack the ability to isomerize to an allene.<sup>17</sup>

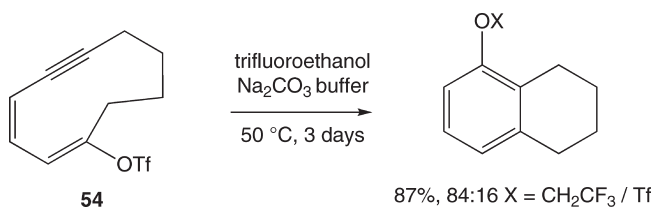
Porter and co-workers provided key mechanistic insight into the allene isomerization induced cycloaromatization by providing evidence for allene **35** during their studies toward the preparation of naphthylidiphenylmethyl radical **36** (Scheme 8).<sup>19</sup> The reactive allene **35** was prepared at low temperature by treatment of dienyne **37** with activated basic alumina. When **35**

**Scheme 13.** Use of Vinyl Triflate Dienynes to Trigger Cycloaromatization via Nucleophilic Attack of the Alkyne<sup>a</sup>



<sup>a</sup> Conditions: (a) trifluoroethanol, Na<sub>2</sub>CO<sub>3</sub> buffer, 100 °C, 5 days; (b) trifluoroethanol/water/dioxane, Na<sub>2</sub>CO<sub>3</sub> buffer, LiBr (excess), 100 °C, 5 days. (c) determined by capillary gas-liquid chromatography. (d) mostly polymer (e) undetermined because of overlap with solvent peak.<sup>25b</sup>

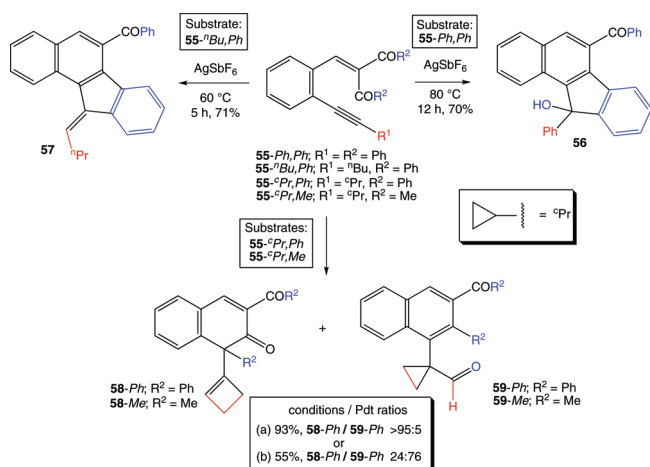
**Scheme 14.** Improved Cyclization Yields by Use of a Strained Cyclic Dienyne<sup>27a</sup>



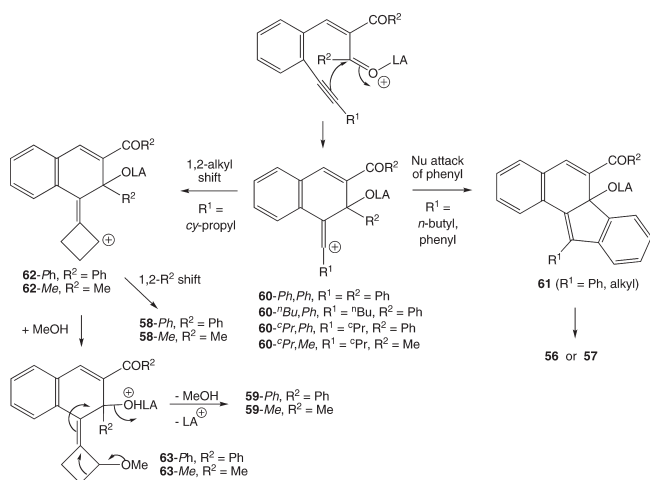
was warmed to ambient temperature, the benzylic halide **38** was cleanly formed, presumably through initial formation of *ortho*-quinodimethane **39**. The reduction of **35** to **36** with Hg was confirmed by EPR, although it was unclear if the pathway to **36** was directly from **39** (path a) or via **38** (path b).

Burton and co-workers have developed conditions to prepare a variety of 1,3-disubstituted naphthalenes using the alkyne isomerization approach.<sup>20</sup> Under optimized conditions, allowing dienyne to react with a nitrogen base such as DABCO or DBU in refluxing *N*-methyl-2-pyrrolidone (NMP) gave arenes in yields ranging from 60 to 95%. In line with the base-catalyzed isomerization to **22** (Scheme 6), only use of **Type II-terminal** dienyne containing a central alkene with an electron-withdrawing substituent (e.g., F, CO<sub>2</sub>R, CHO) or **Type III** dienyne were effective for the cyclization due to the increased acidity of the propargyl proton.<sup>21</sup> Another interesting observation came when *d*<sub>5</sub>-dienyne **40** was treated under optimized conditions to give the cyclized naphthalene **41** with partial incorporation of deuterium into the benzylic position (Scheme 9). This result was rationalized by hypothesizing that a base-assisted conversion may compete with an intramolecular [1,3]-H shift for this step in the mechanism (see **23–24**, Scheme 6). A deprotonation/reprotonation would require acquisition of protons from the solvent and this explains the loss of deuterium at the benzylic position.

More recent work by Zhou and co-workers has shown much milder cyclization conditions can be effected by use of **Type I** and **Type II-internal** dienyne containing propargyl sulfides with an ester or amide at the terminal alkene position (Scheme 10).<sup>22</sup>

Scheme 15. Activation of Dienynyl Ketones under Lewis Acidic Conditions<sup>a</sup>

<sup>a</sup> Conditions: (a) AgOTf (5 mol %), 1,2-dichloroethane, 80 °C, 12 h (b) In(OTf)<sub>3</sub> (5 mol %), 1,2-dichloroethane, MeOH (4 equiv), 50 °C, 48 h.<sup>28</sup>

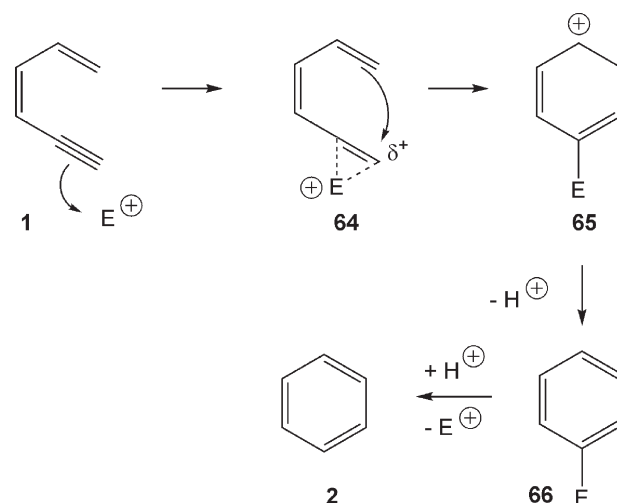
Scheme 16. Proposed Intramolecular Bond Rearrangements for the Formation of 56–59<sup>28</sup>

Although the authors did not provide an exact explanation, the decreased  $pK_a$  of the propargylic hydrogen atoms resulting from the combined resonance and inductive effects of the carbonyl and sulfide may rationalize the rate acceleration compared to dienyne lacking those substituents.

While the base-induced isomerization pathway represents the most common way to bring about a  $6\pi$ -electrocyclization, it is not the only possible route. Himbert and co-workers have used alkoxytannane dienyynes, **42**, with a highly nucleophilic amino alkyne substituent to induce a [1,3]-shift of the tin moiety resulting in the formation of the iminiumene **43** (Scheme 11). Compound **43** then follows cyclization and tautomerization to give product **44**.<sup>23</sup>

Finally, although not a  $6\pi$ -electrocyclization, treatment of the dienyne natural product, Freelingyne (**45**), with base was observed to proceed through a cycloaromatization to give the trisubstituted phenol **46** (Scheme 12).<sup>24</sup> The proposed

Scheme 17. General Mechanism for Umpolung Activation of Alkynes



mechanism involves hydrolysis of the lactone to allene **47**. Conjugate addition of hydroxide to **47** gives enol/enolate **48** that subsequently cyclizes and aromatizes to form **46**.

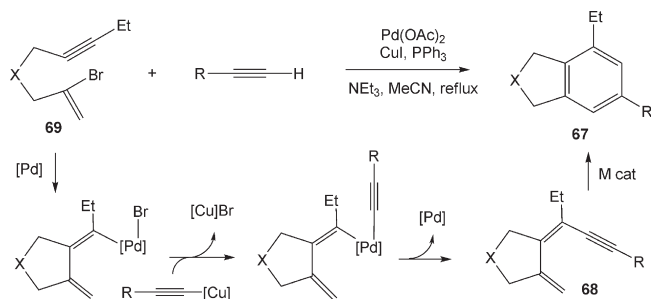
#### 4. NUCLEOPHILIC ATTACK BY THE ALKYNE

In some instances, the  $\pi$  system of the alkyne can act as a nucleophile if the terminal alkene is sufficiently activated. The most fundamental example of this type of reactivity is demonstrated by the work of Hanack and co-workers who have studied the cycloaromatization of vinyl triflate dienyne **49** (Scheme 13).<sup>25</sup> Upon heating in a basic buffered media, **49** was proposed to ionize to alkyne-stabilized vinyl cation **50**. Attack of the alkyne to give aryl cation **51**, followed by trapping with a nucleophile gave cycloaromatized product **52**. It is unclear whether **50** is an actual intermediate or transition state to **51**, but the alkyne is thought to assist in the departure of the leaving group based on the higher proportion of **52** formed when the *E*-stereoisomer (**49-E**) was employed versus the *Z*-stereoisomer (**49-Z**). The latter favors formation of the elimination product **53**. The anti relationship of the triflate and alkyne in **49-E** was postulated to provide anchimeric assistance of the  $\pi$  electrons. The reaction performs well in weakly nucleophilic polar solvents supporting the formation of ionic intermediates. Although a large proportion of the starting material was observed to polymerize, this problem was minimized by added bromide nucleophile (entry 3). Formation of **52-Br** also suggests that **49** proceeds through intermediate aryl cation **51** during conversion to product, thus ruling out other cyclization mechanisms. In later studies, Hanack in collaboration with Schwarz was able to observe a species consistent with **51** by collisional activation mass spectrometry.<sup>26</sup>

Yields of the substitution products were greatly improved by use of the cyclic dienyne **54** (Scheme 14).<sup>27</sup> The strained-ring system raises the ground state energy of **54** as compared to **49** and favors the cyclization pathway over elimination.

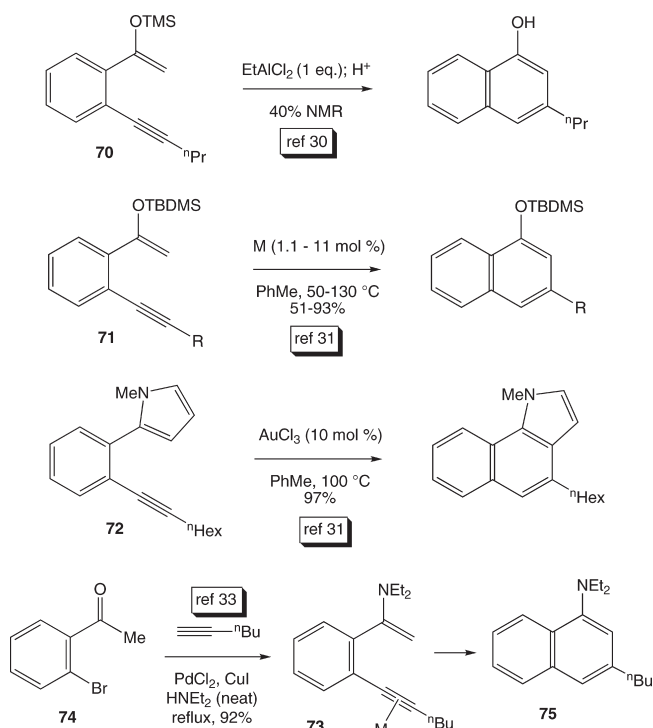
Zhang and Liu have utilized Lewis acids to activate dienynyl ketones, **55**, for intramolecular nucleophilic attack to form several cyclized products depending on the alkyne substituent (Scheme 15).<sup>28</sup> Reaction of **55-Ph, Ph** or **55-*n*Bu, Ph** in the presence

**Scheme 18. In Situ Generation of Dienyne Resulting in Cycloaromatized Product<sup>a</sup>**



<sup>a</sup> X = C(CO<sub>2</sub>Me)<sub>2</sub>, NBn; R = C(OH)Me<sub>2</sub>, 1-hydroxycyclohexyl, CH<sub>2</sub>O-THP, C<sub>6</sub>H<sub>13</sub>.<sup>29</sup>

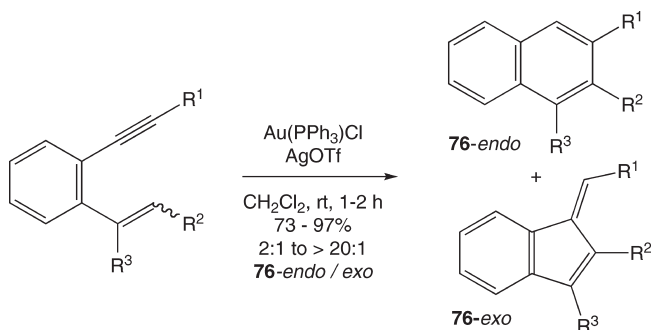
**Scheme 19. Metal-Catalyzed Cycloaromatization of Diynes Possessing Nucleophilic Terminal Alkene Components<sup>a</sup>**



<sup>a</sup> M = [Rh(CO)<sub>2</sub>Cl]<sub>2</sub>, PtCl<sub>2</sub>, PdCl<sub>2</sub>, Pd(PhCN)<sub>2</sub>Cl<sub>2</sub>, [RuCl<sub>2</sub>(CO)<sub>3</sub>]<sub>2</sub>; R = H, Me, <sup>n</sup>Hex, CH<sub>2</sub>Bn, Ph, <sup>t</sup>Bu.<sup>30,31,33</sup>

of a catalytic amount of AgSbF<sub>6</sub> resulted in the formation cycloaromatized products **56** and **57**, respectively, in good yields. Use of cyclopropyl substituted alkyne **55-<sup>c</sup>Pr,Ph** afforded a mixture of naphthalen-2(1*H*)-one (**58-Ph**) and naphthalene derivative **59-Ph** with the ratio depending upon the conditions. In general, it was found to be more difficult to obtain higher ratios of the aromatized product, but **59-Ph** was favored by use of excess methanol under optimized conditions with an In(III) catalyst. Formation of **59-Ph** was limited to use of unsubstituted cyclopropyl substituents in substrate **55-<sup>c</sup>Pr,Ph**. Any substitution on the cyclopropyl ring resulted in exclusive formation of **58** derivatives.

**Scheme 20. Ambient Temperature Gold Catalyzed Cycloaromatization of Geminal and Tri-Substituted Terminal Alkene Type II-Internal Diynes<sup>a</sup>**

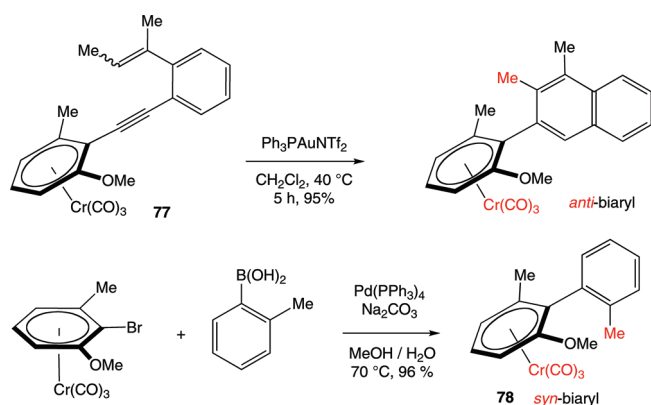


<sup>a</sup> R<sup>1</sup> = Ph, CH<sub>2</sub>OMe, CH<sub>2</sub>OSiR<sub>3</sub>, CH<sub>2</sub>OH, CH<sub>2</sub>NMeTs, <sup>n</sup>Bu, I; R<sub>2</sub> = H, Me; R<sub>3</sub> = Me, Ph.<sup>34</sup>

The proposed mechanisms for these transformations begin with Lewis acid coordination of the carbonyl that induces attack of the internal alkyne carbon to give **60** (Scheme 16). Intermediate **60** can then proceed through several pathways depending upon the alkyne substituent. For simple aryl or alkyl substitution at R<sup>1</sup> and R<sup>2</sup> = Ph, nucleophilic attack of the phenyl gives intermediate **61** that subsequently isomerizes to aromatized products **56** and **57**, respectively. For cyclopropyl substitution at the alkyne, (e.g. **60-<sup>c</sup>Pr,Ph**; R<sup>1</sup> = *cy*-propyl, R<sup>2</sup> = Ph) the reaction proceeds through a 1,2-alkyl shift (ring expansion) resulting in the formation of cyclobutyl cation **62-Ph**. Two pathways were proposed for the conversion of **62-Ph** to **58-Ph** and **59-Ph**. One pathway involves a pinacol rearrangement where the carbinol substituent undergoes a 1,2-shift to form cyclobutenyl product **58-Ph**. In the other pathway, cation **62-Ph** was trapped by an oxygen nucleophile (Nu = MeOH), before the pinacol rearrangement can occur, to form **63-Ph**. Intermediate **63-Ph** was then proposed to proceed through a cascade of bond rearrangements to give the cyclopropyl-substituted aromatized product **59-Ph**. The latter pathway was supported by the observation that **59-Ph** was favored by using methanol, which would be expected to accelerate the formation of **63-Ph**. There appears to be a very interesting trend for the migratory ability of the migrating substituent (R<sup>2</sup> in Scheme 16) for conversion of **62** to **58**. For example, reaction of methyl ketone **55-<sup>c</sup>Pr,Me** (R<sup>1</sup> = <sup>c</sup>Pr, R<sup>2</sup> = Me) under the In(III) optimized conditions resulted in a > 20:1 ratio of **59-Me**/**58-Me**. The methyl group apparently has a lower ability to undergo the 1,2-shift therefore shifting the partitioning of **62-Me** to favor formation of intermediate **63-Me** and product **59-Me**.

## 5. UMPOLUNG ACTIVATION OF THE ALKYNE

The higher energy  $\pi$ -system of the alkyne makes an easy target for metal and nonmetal Lewis and Brønsted acids and represents a well-studied mode of initiation for cycloaromatization of conjugated diynes. The most general form of activation begins with formation of an alkyne complex **64** from reaction of diyne **1** and an electrophile (Scheme 17). Formation of **64** results in a deficiency of electrons on the sp-hybridized carbon atoms and induces a 6-*endo-dig* attack of the terminal alkene leading to the cyclized product **65**. Subsequent aromatization by loss of a proton gives **66**. If the electrophile is a metal (e.g., Pd, Pt, Au, In), proton

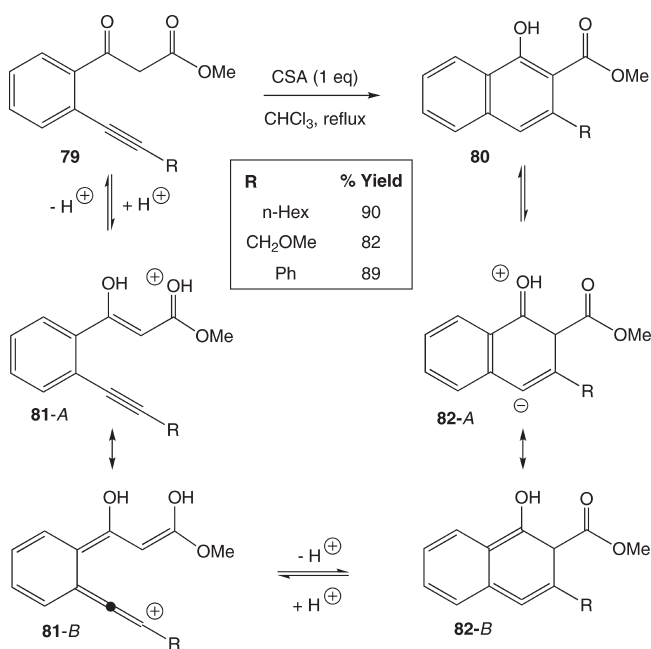
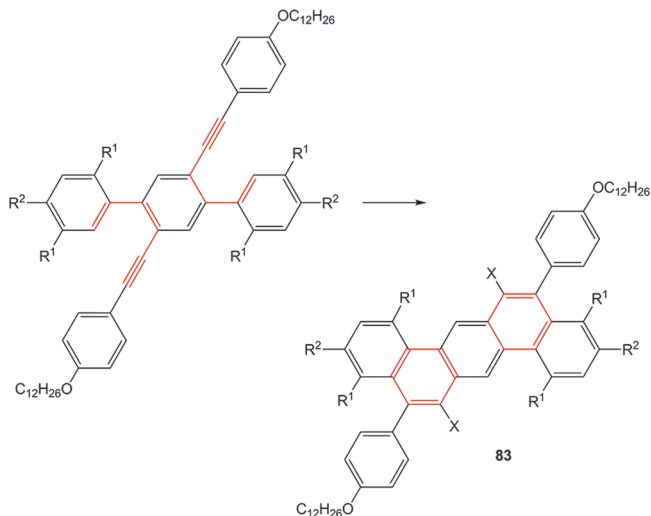
Scheme 21. Complementary Methods for Synthesis of Stereoisomeric Pairs of Biaryl Complexes<sup>35</sup>

exchange usually follows to give the formal Hopf product **2**. In line with the nucleophilic role of the terminal alkene, most reactions proceeding through this mechanism utilize electron-donating terminal alkene substituents to facilitate the cyclization.

The presumed first example of umpolung activation was reported by Torii and co-workers who were able to obtain cycloaromatized product **67** in moderate to high yield by in situ generation of diyne **68** under a Sonogashira coupling platform (Scheme 18).<sup>29</sup> In support of a mechanism involving **68**, the reaction was slowed at room temperature with **69** ( $X = C(CO_2Me)_2$ ,  $R = C(OH)Me_2$ ) thereby permitting isolation of diyne intermediate **68**. Subjecting the intermediate to the same reaction conditions resulted in the formation of **67**. Although the  $[Pd]/[Cu]$  catalytic cycle was hypothesized as the mechanism for formation of **68**, the pathway responsible for conversion of **68** to **67** was not discussed.

Yamamoto and co-workers reported a single example utilizing a **Type II**—internal diyne (**70**) toward the synthesis of a naphthalene derivative (Scheme 19).<sup>30</sup> This was done in extension of their enyne cyclization methodology promoted by ethylaluminum dichloride. Dankwardt later published an extensive screen of metal catalysts for the thermal cyclization of various silyl enol ethers **71**.<sup>31</sup> Among many significant findings, he found that the cyclization could be conducted at room temperature using stoichiometric silver(I) trifluoroacetate ( $AgOC(O)CF_3$ ) in nitromethane. The methodology was also applied to a series of pyrrole containing diynes (e.g., **72**), giving cyclized product in excellent yield. Belmont and co-workers have used a similar procedure for the synthesis of acridine derivatives.<sup>32</sup> Herndon and co-workers have also made progress toward the use of diynes for synthesis of nitrogen substituted naphthalenes by in situ generation of an enamine **73** from Sonogashira coupling of bromide **74**.<sup>33</sup> The transient **73** was proposed to proceed through a 6-*endo* cyclization to give the 1-naphthalenamine **75**. While **75** was formed in high yield, the methodology seems to be limited in scope as use of nonalkyl substituted alkynes (e.g., phenylacetylene, trimethylsilylacetylene) or increasing the alkyl substitution at the ketone  $\alpha$ -carbon only resulted in isolation of the *ortho*-alkynyl arene product.

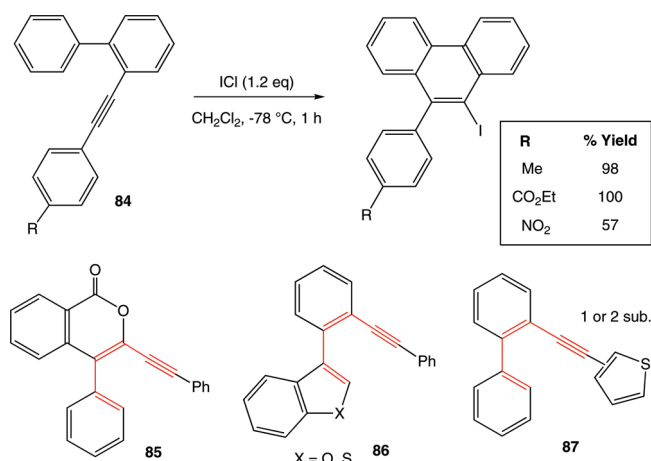
A major improvement for the synthesis of substituted naphthalenes was made by Shibata and co-workers who discovered that in situ generated  $Ph_3PAu^+$  resulted in the high yield formation of products **76** at ambient temperature (Scheme 20).<sup>34</sup> Generally, the 6-*endo* product **76-endo** was favored >20:1, yet in some cases,

Scheme 22. Acid-Catalyzed Tautomeric Dienyne **81-A** Cycloaromatization<sup>36</sup>Scheme 23. TFA and  $I(py)_2BF_4$  Triggered Cycloaromatizations in the Formation of Extended Polyaromatic Platforms<sup>a</sup>

<sup>a</sup> Conditions:  $CF_3CO_2H$  ( $X = H$ ) or  $I(py)_2BF_4$  ( $X = I$ );  $R^1 = OMe, Me, H$ ;  $R^2 = H, OMe$ .<sup>38</sup>

significant amounts of **76-exo** were formed ( $R^1 = CH_2N(Me)Ts, I$ ). Only geminally substituted nucleophilic alkene substrates were reported ( $R^3 = Me, Ph$ ), presumably because of the stability of the carbocation intermediates. Uemura and co-workers have applied the gold cyclization methodology to diynes possessing a planar chiral ( $\eta^6$ -arene) $CrCO_3$  auxiliary (e.g., **77**) for stereoselective formation of axial chiral biaryl complexes (Scheme 21).<sup>35a,b</sup> The major stereoisomeric product from these reactions has an anti relationship between the metal fragment

**Scheme 24. Expanded Alkyne Substituent Scope via Use of ICl as the Cyclization Triggering Reagent**<sup>39</sup>



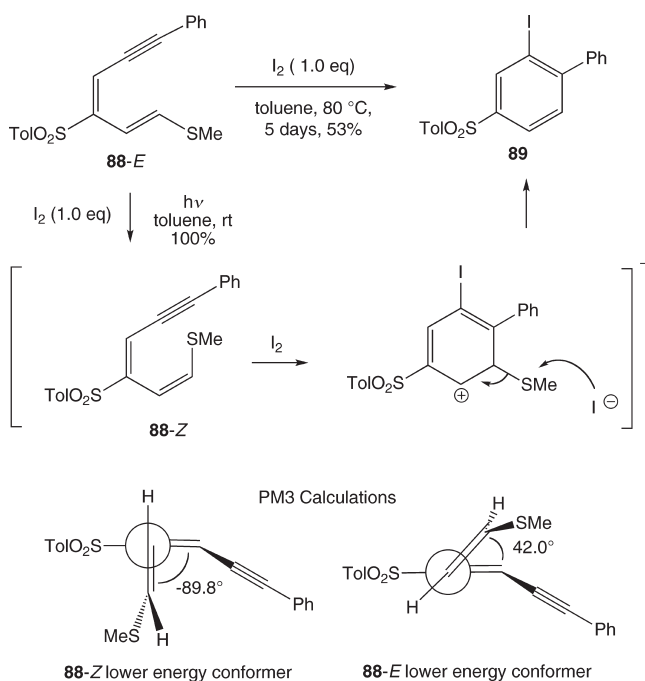
and the ortho substituent of the biaryl junction. This route is a nice complement to the palladium-catalyzed coupling of these complexes that, in most cases, gives predominately the syn isomer (e.g., **78**).<sup>35c</sup>

Toward a metal-free route to naphthalenes, Ciufolini and Weiss have described the use of camphorsulfonic acid (CSA) as a trigger for cyclization of *ortho*-alkynylphenyl- $\beta$ -ketoesters **79** (Scheme 22).<sup>36</sup> A variety of alkyne substitution was tolerated to give 1,2,3-substituted naphthalenes **80** in high yield. The reaction is thought to proceed through charged intermediates due to the inability of thoroughly purified samples of **79** to give any product under photolytic or thermal conditions. The proposed mechanism initiates by protonation of the tautomeric dienyne form of **79** giving cationic intermediate **81**. This structure has significant positive charge build-up on the terminal alkyne carbon due to resonance delocalization. Intramolecular nucleophilic attack of the enol and deprotonation gives allenic intermediate **82-B** that can be represented as a resonance hybrid with zwitterionic **82-A**. Proton exchange would then lead to the naphthalene product **80**. In support of this mechanism, calculations performed at the MNDO level of theory show the reaction from a structurally simplified enol form of **79** to the zwitterionic intermediate **82-B** is exothermic by  $-3.7 \text{ kcal} \cdot \text{mol}^{-1}$ .

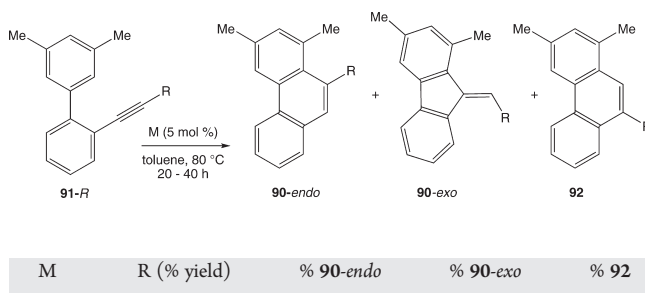
A significant amount of research has been directed toward triggering a Friedel–Crafts type cyclization of **Type III** dienyne to give substituted phenanthrenes which are useful building blocks for polycyclic aromatics.<sup>37</sup> Swager and co-workers first demonstrated the utility of such a transformation in the preparation of compound **83** with the ultimate goal of making fused polycyclic aromatic polymers (Scheme 23).<sup>38</sup> The reactions were extremely high yielding (>90%) but required an alkyne substituted with an electron-donating group (i.e., OC<sub>12</sub>H<sub>26</sub>) for cyclization to occur. When a cyclohexyl or phenyl substituted alkyne was used, the reaction failed. Also interesting was the observation that the reaction only proceeded in polar non-nucleophilic solvents (i.e., CH<sub>2</sub>Cl<sub>2</sub>) and not in nonpolar or ethereal solvents. The solvent dependence suggested formation of carbocation intermediates.

Larock and co-workers demonstrated that through the use of ICl as an electrophilic trigger even a para-substituted nitrophenyl substituted alkyne **84** (R = NO<sub>2</sub>) would proceed to product albeit in moderate yield (Scheme 24).<sup>39a</sup> These researchers also showed an expanded substrate scope by using several alternative alkene and alkyne components (i.e., **85**–**87**). In later studies, it

**Scheme 25. Photolytic Activation of Cycloaromatization with Iodine Electrophilic Triggering**<sup>40</sup>



**Table 3. Metal Catalyzed Formation of Phenanthrenes from Dienyne Cycloaromatization**<sup>a</sup>

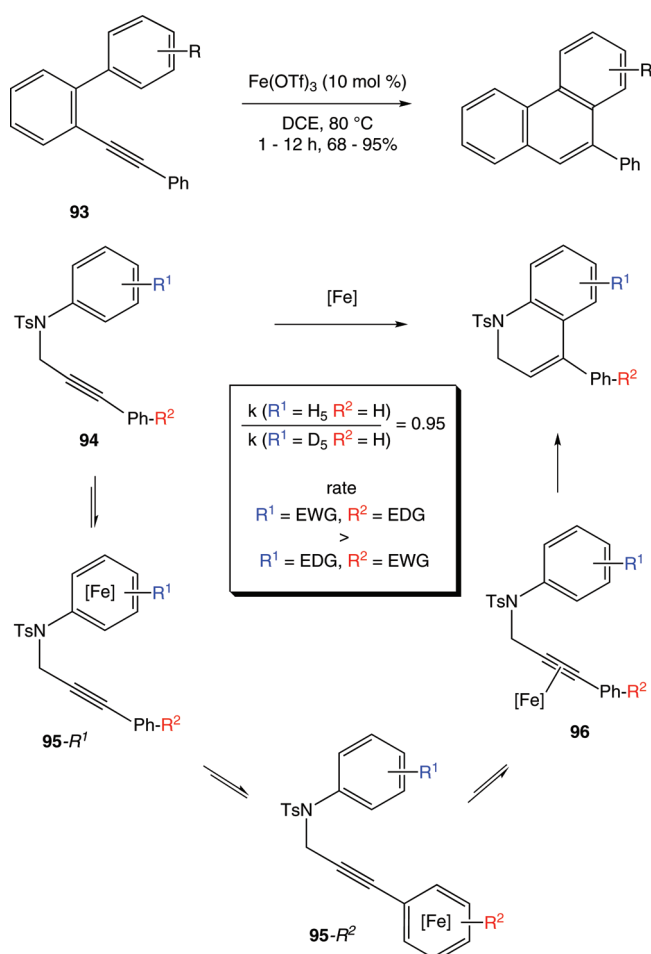


M	R (% yield)	% 90-endo	% 90-exo	% 92
PtCl <sub>2</sub>	H (64)	97	3	0
	Me (89)	100	0	0
	CO <sub>2</sub> Me (a)	5	95	0
InCl <sub>3</sub>	Br (77)	100	0	0
	Cl (90)	100	0	0
AuCl	Br (77)	0	0	100
	I (76)	0	0	100

<sup>a</sup>Yield not reported.<sup>41</sup>

was also shown that other stoichiometric electrophiles could also affect the cyclization.<sup>39b</sup>

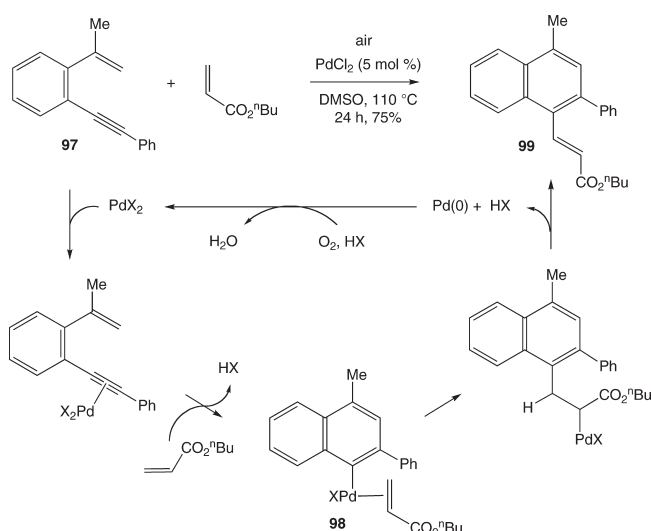
Ogura and co-workers have discovered an interesting photolytic dienyne cycloaromatization involving I<sub>2</sub> as an electrophilic trigger (Scheme 25).<sup>40</sup> Reaction of the *E*-vinyl methyl sulfide **88-E** with I<sub>2</sub> under thermal conditions proceeds very slowly, yet, photolyzing the reaction mixture gives quantitative yield of product **89** within 1 h. It is believed the photolytic acceleration is due to an initial isomerization of **88-E** to **88-Z** as the latter is believed to cyclize faster. Support for **88-Z** as an intermediate

Scheme 26. Use of Iron Catalysis for Dienyne Cycloaromatization<sup>a</sup>

<sup>a</sup> R = 4-CN, 4-CO<sub>2</sub>Me, 4-NO<sub>2</sub>, 4-CF<sub>3</sub>, 3,5-F<sub>2</sub>, H, 4-OMe.<sup>43</sup>

comes from isolation of the species from the reaction mixture followed by independent cyclization with I<sub>2</sub> in the dark. The reason for the enhanced rate of cyclization of **88-Z** compared to **88-E** was not clear. Energy minimization calculations using PM3 level of theory showed the distance between the terminal alkene and alkyne carbons is larger for **88-Z** than **88-E**, which does not correlate with the reactivity. One major difference observed from the computational study was a significant difference in the central diene dihedral angle, calculated to be +42.0° for **88-E** and -89.8° for **88-Z**. From the discussion of this parameter, the authors seemed to suggest that better orbital alignment between the terminal alkene and alkyne  $\pi$  systems may be responsible for the increased reactivity.

The earliest in-depth look at metal catalysis for the formation of phenanthrenes via diene cyclization was performed by Fürstner and co-workers over several publications.<sup>41</sup> Fürstner's work has been applied to many different systems.<sup>42</sup> Summarized in Table 3, were some key findings from their study. For cyclization of terminal and simple alkyl substituted alkynes, PtCl<sub>2</sub> was determined to be the most general high yielding catalyst although AuCl<sub>3</sub> and GaCl<sub>3</sub> also proved effective.<sup>41a</sup> In general the reaction proceeds to the 6-*endo* product **90-endo** although use of an electron-withdrawing alkyne substituent **91-CO<sub>2</sub>Me** gave almost exclusively the *exo* product **90-exo**. Reactions of alkynyl halides

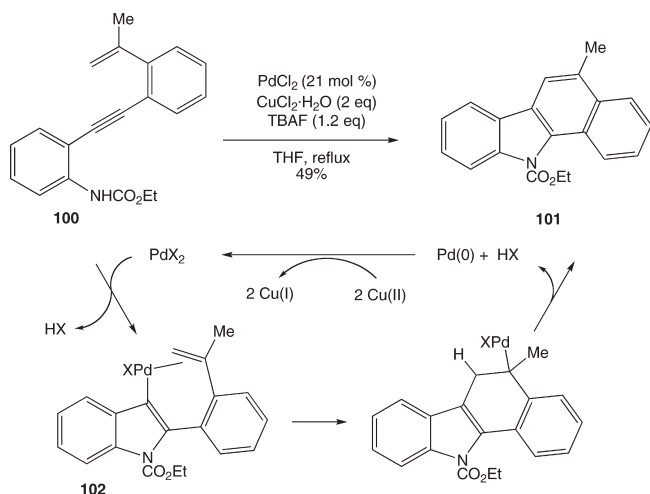
Scheme 27. One-Pot 6-*endo*-Cycloaromatization/Heck Coupling<sup>44</sup>

failed under PtCl<sub>2</sub> catalysis, but use of InCl<sub>3</sub> gave the halogenated **90-endo** in high yield with no detectable amount of the other regioisomer.<sup>41b</sup> As an extension of the InCl<sub>3</sub> catalysis, these researchers used the methodology to prepare a biaryl natural product, *O*-methyldehydroisopiline. A surprising find came while testing halogenated alkynes **91-Br(I)** with gold(I) chloride that resulted in the rearranged product **92**.<sup>41c</sup> These researchers explain this unexpected reactivity by the formation of a gold vinylidene complex that then presumably proceeds to product through an initial 6 $\pi$ -electrocyclization (vide infra).

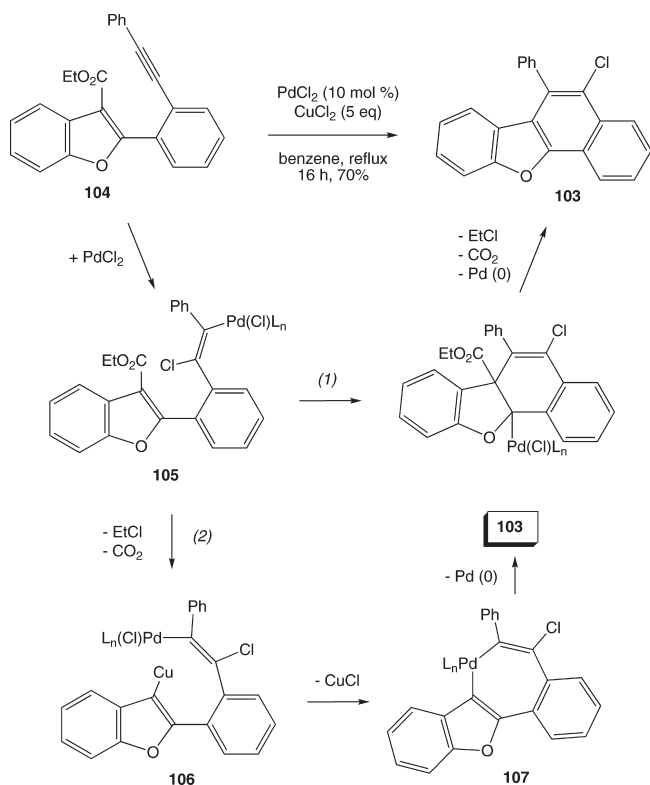
More recently, Takaki and co-workers have reported iron(III) triflate catalysis of *ortho*-alkynyl substituted biphenyl arenes **93** (Scheme 26).<sup>43</sup> These studies were done in parallel with cyclization of arene-tethered alkynes **94**. The kinetic isotope effect (KIE) for the nucleophilic arene of **94** (R<sup>1</sup> = H(D)<sub>5</sub>/R<sub>2</sub> = H<sub>5</sub>) was calculated to be 0.95 suggesting a Friedel–Crafts mechanism. Contrary to the KIE mechanistic implications, the rate of the reaction was observed to increase when the nucleophilic arene was substituted with an electron-withdrawing group (EWG) while the alkyne phenyl substituent possessed an electron-donating group (EDG). To explain this, a pre-emptive determining step equilibrium between Fe-arene complexes **95-R<sup>1</sup>** and **95-R<sup>2</sup>** was invoked where only **95-R<sup>2</sup>** could deliver the metal to the alkyne to form the activated electrophilic complex **96**. Despite these interesting mechanistic studies, the diene substrates **93** do not seem to follow the arene electronic trend. Use of an EWG on the nucleophilic arene **93** (R = NO<sub>2</sub>, CN, CF<sub>3</sub>) increased the reaction time to >6 h, where an unsubstituted arene (R = H) went to completion within 1 h.

Although in most cases, the metal-vinyl species **66** (E = Pt, Pd, Au, etc., Scheme 17) is lost by protonation, Loh and Feng were able to intercept this species with an alkene demonstrating the multicomponent potential of the diene 6-*endo*-cyclization (Scheme 27).<sup>44</sup> Using PdCl<sub>2</sub> to catalyze the cyclization of **97** allowed for metalated adduct **98** to enter into the Heck catalytic cycle to give the trisubstituted naphthalene **99**. Many oxidants were screened, however none substantially increased the yield compared to that obtained by the simple use of atmospheric oxygen. Although most examples utilized geminal-substituted

**Scheme 28. Capture of Activated Alkyne by Tethered Nucleophile Coupled with Heck Coupling to Give Cycloaromatized Product**<sup>45a</sup>



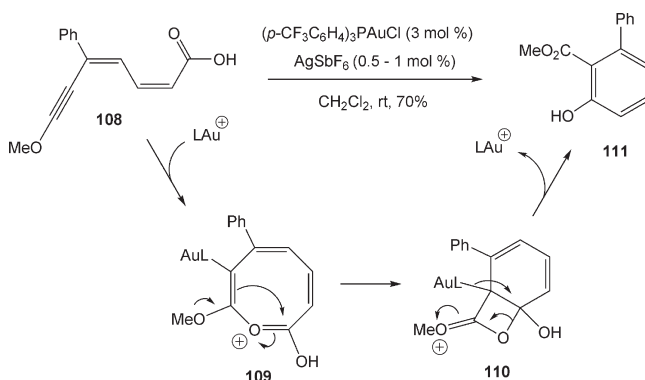
**Scheme 29. Intermolecular Capture of Coordinated Alkyne Leading to Aromatized Product**<sup>46</sup>



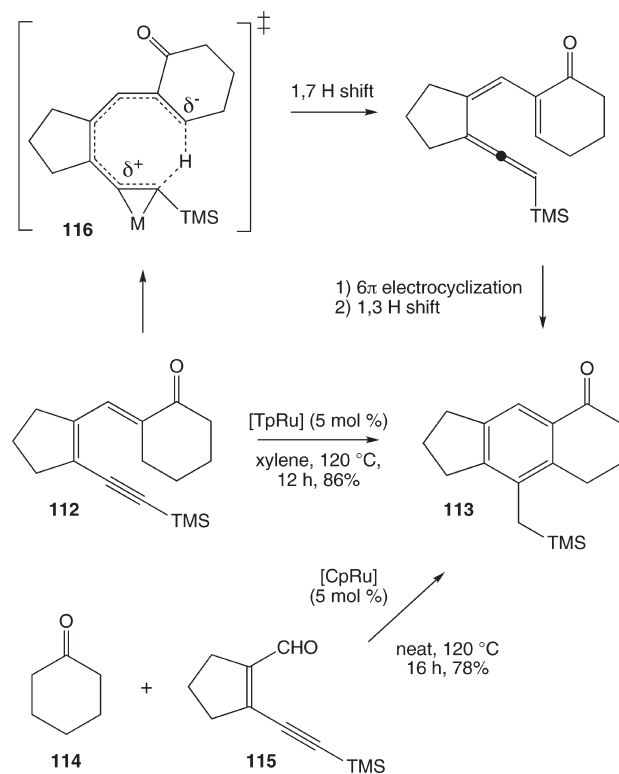
alkenes, one case employed the use of a trisubstituted alkene that gave rise to a tetrasubstituted naphthalene in 61% yield.

The examples covered thus far have all used the terminal alkene as the nucleophile for attack on the activated alkyne. It is also possible to intercept the alkyne with an external or tethered nucleophile creating a species that can cyclize by other mechanisms. Yasuhara and co-workers were the first to implement this strategy for dienyne with the cyclization of *ortho*-alkynyl

**Scheme 30. Gold-Catalyzed Cycloaromatization of the *Z,Z*-Dienyne 108**<sup>47</sup>



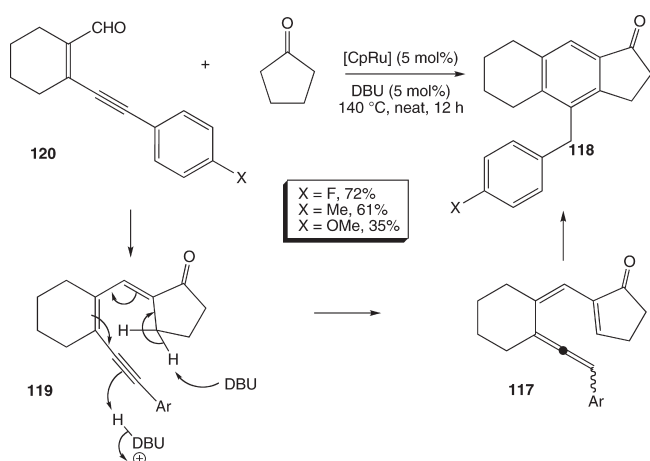
**Scheme 31. [1,7]-H Shift Facilitated by  $\eta^2$ -Complexation<sup>a</sup>**



<sup>a</sup> [TpRu] = [TpRu(PPh<sub>3</sub>)(NCMe)<sub>2</sub>]PF<sub>6</sub>, [CpRu] = ( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>)Ru(PPh<sub>3</sub>)<sub>2</sub>Cl.<sup>5b</sup>

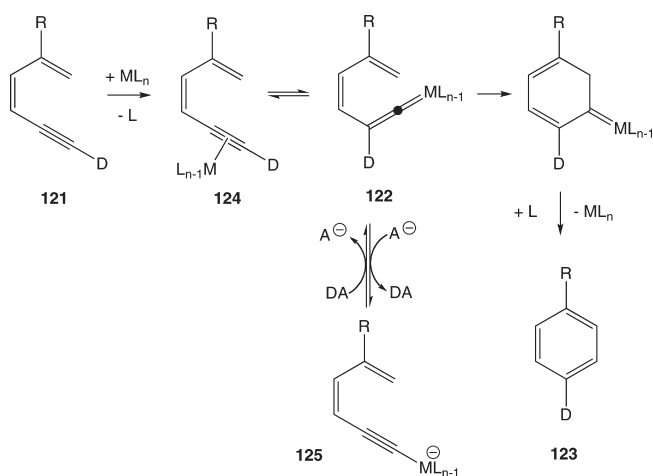
carbamates **100** to the substituted indole **101** under PdCl<sub>2</sub> catalysis (Scheme 28).<sup>45a</sup> Initial attack of the carbamate gives vinyl palladium species **102** that proceeds through a successive 1,2-insertion and  $\beta$ -hydride elimination to proceed to **101**. The role of TBAF (tetrabutylammonium fluoride) appears to be that of a mild base.<sup>45b</sup>

A related transformation reported by Li and co-workers toward the synthesis of polycyclic aromatic furan **103**, involved initial *trans* 1,2-insertion across the alkyne of the substrate **104** to give **105** (Scheme 29).<sup>46</sup> The authors do not comment on how the insertion occurred, but it may be reasonable to propose a nucleophilic attack of the chloride on the palladium alkyne

Scheme 32. Formal [1,7]-H Shift Cycloaromatization Pathway Catalyzed by Base<sup>a</sup>

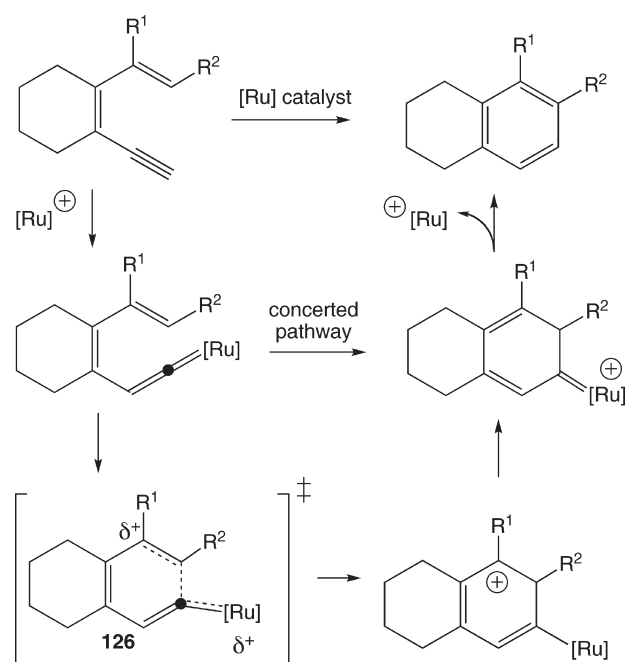
<sup>a</sup> [CpRu] =  $(\eta^5\text{-C}_5\text{H}_5)\text{Ru}(\text{PPh}_3)_2\text{Cl}$ .<sup>49</sup>

Scheme 33. General Mechanism of Diene-yne Cycloaromatization via Metal Vinylidene Intermediates



complex. From **105**, two possible pathways to **103** were proposed: (1) 1,2-insertion into the furan ring followed by decarboxylation with elimination of ethyl chloride and palladium to give the product **103** and (2) decarboxylation with elimination of ethyl chloride to form a vinyl copper species **106** that can transmetallate with palladium to proceed to product through metallacycle **107**. CuCl<sub>2</sub> has multiple roles in the reaction by providing a source of chloride, oxidizing the Pd(0) back to the active Pd(II), and potentially inducing decarboxylation. Use of LiCl in place of CuCl<sub>2</sub> resulted in no observation of product thus confirming at least one of the latter two roles of the reagent.

Aguiar and co-workers recently reported an impressive use of gold catalysis to induce an aromatization initiated by intramolecular nucleophilic attack of a pendent carboxylic acid.<sup>47</sup> The unusual *Z,Z*-dienyne substrate **108** can be prepared in a single step from the coupling of a dialkynyl chromium carbene species and 2-methoxyfuran (Scheme 30).<sup>48</sup> Activation of the alkyne by the in situ generated cationic gold catalyst was proposed to induce an intramolecular nucleophilic attack of the carboxylate to give **109** which then ring closes to form bicyclic compound **110**. Regeneration of the AuL<sup>+</sup>

Scheme 34. First Example of Metal Vinylidene Diene-yne Cycloaromatization<sup>a</sup>

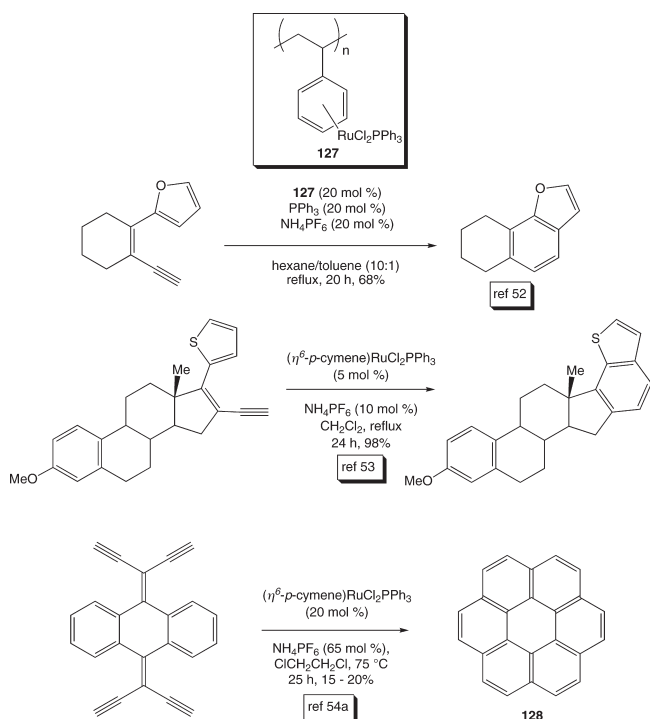
R <sup>1</sup> , R <sup>2</sup>	Temp / Time / Yield
	40 °C / 10 h / 89%
H, CH <sub>2</sub> OH	70 °C / 30 h / 23%
H, CO <sub>2</sub> Me	70 °C / 68 h / 12%

<sup>a</sup> Conditions:  $(\eta^6\text{-}p\text{-cymene})\text{Ru}(\text{Cl})_2(\text{PPh}_3)_2$  (5 mol %), NH<sub>4</sub>PF<sub>6</sub> (5–15 mol %), CH<sub>2</sub>Cl<sub>2</sub> or ClCH<sub>2</sub>CH<sub>2</sub>Cl.<sup>51</sup>

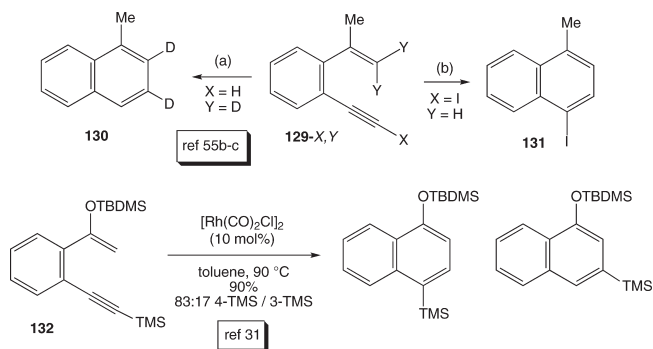
species gives a 1,2,3-trisubstituted arene **111**. The reaction was dependent on the alkoxyalkyne substrate and the use of aryl-substituted alkynes resulted in a 6 $\pi$ -electrocyclization from an intermediate analogous to **109** that ultimately led to meta-substituted arenes after loss of CO<sub>2</sub>.

Liu and co-workers have demonstrated the use of ruthenium complexes to activate the alkyne for a [1,7]-H shift that ultimately leads to cycloaromatized product.<sup>5b</sup> Diene-yne structure activity studies show the reaction was most efficient with substrates containing an electron-donating alkyne substituent and an electron-withdrawing terminal alkene substituent. Substrates without this substitution showed little enhancement with metal complexes over the noncatalyzed thermal reaction. A particularly successful diene-yne, **112**, possess both of these characteristics and gives the aromatized product **113** in high yield (Scheme 31). The observation that diene-yne containing an  $\alpha,\beta$ -unsaturated ketone work well for the reaction, led these researchers to consider developing a one-pot Aldol condensation/cycloaromatization methodology as demonstrated by the reaction of cyclohexanone **114** with aldehyde **115**. The mechanism of this reaction is believed to proceed through an asynchronous transition state **116** for the [1,7]-H shift followed by a 6 $\pi$ -electrocyclization and

**Scheme 35. Applications of Metal Vinylidene Dienyne Cycloaromatizations**<sup>52–54</sup>



**Scheme 36. Vinylidene Cycloaromatizations Resulting in 1,2-Shift of Non-hydrogen Substituents**<sup>a</sup>

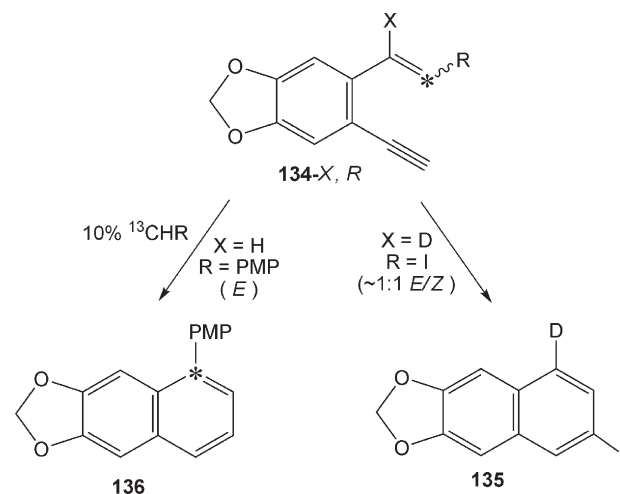


<sup>a</sup> (a) (CO)<sub>5</sub>W·THF (1 equiv), THF, 1 day, rt. (b) (CO)<sub>5</sub>W·THF (1 equiv), THF, 15 h, rt.<sup>31,55b,55c</sup>

[1,3]-H shift to give **113**. Consistent with the nonsymmetrical nature of **116** are the observed structure activity relationships that are hypothesized to stabilize the developing charge in the transition state. The role of  $\eta^2$ -complexation is 2-fold: (1) distorting the geometry of the alkyne away from linearity thus facilitating the shift by proximity and (2) polarizing the  $\pi$  system to stabilize the positive charge build-up in **116**.

As alluded to in a footnote in Liu's initial publication, the [1,7]-H shift is facilitated by catalytic use of base (i.e., 2, 6-lutidine, DBU). In later studies conducted by Liu and Yang regarding the tandem Aldol/aromatization reaction, the  $\eta^2$ -complexation mechanism seems to have been abandoned or modified for a protonation/reprotonation sequence resulting in rate enhancement for the formation of allene **117** (Scheme 32).<sup>49</sup>

**Scheme 37. Isotopic Labeling Experiments Probing Mechanism of [TpRu(PPh<sub>3</sub>)(NCMe)<sub>2</sub>]PF<sub>6</sub> (**133**) Catalyzed Cycloaromatization/Formal 1,2-Substituent Shifts<sup>a</sup>**



<sup>a</sup> Conditions: **133** (8–10 mol %), toluene, 110 °C, 6–8 h. \* = <sup>13</sup>C enriched carbon, PMP = *para*-methoxyphenyl.<sup>56a</sup>

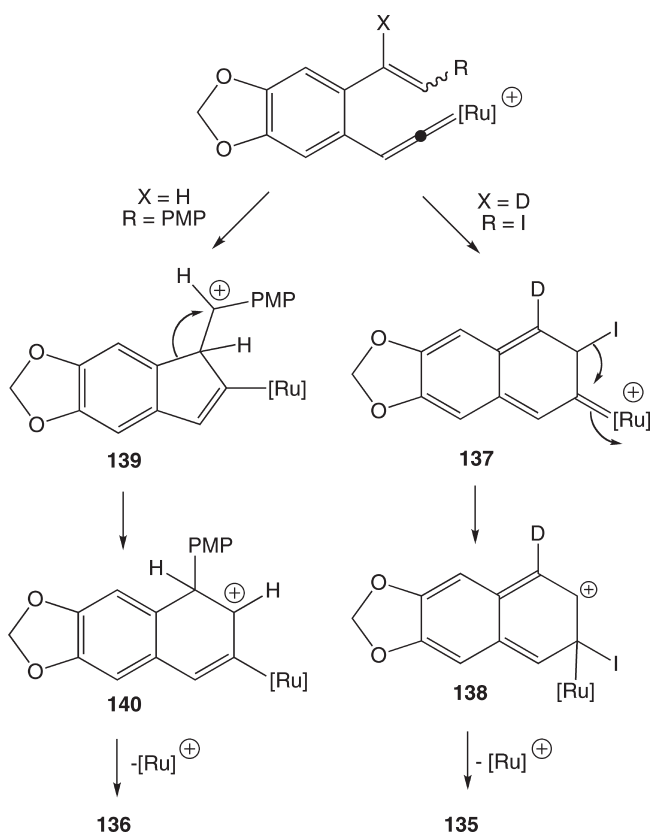
Consistent with this mechanism, the highest yields of product **118** were obtained by use of electron-deficient phenyl substituents on the alkyne as this would be expected to lower the pK<sub>a</sub> of the allylic protons. The primary role of the metal catalyst in this system appears to be facilitating the Aldol reaction as a control experiment from diene **119** (X = H) gave near identical yields when the reaction was conducted with and without the metal (70% and 55%, respectively), whereas removal of the metal from the tandem Aldol reaction with aldehyde **120** resulted in a significantly lower yield (18% vs 65% with metal).

## 6. ALKYNE–VINYLIDENE ISOMERIZATION

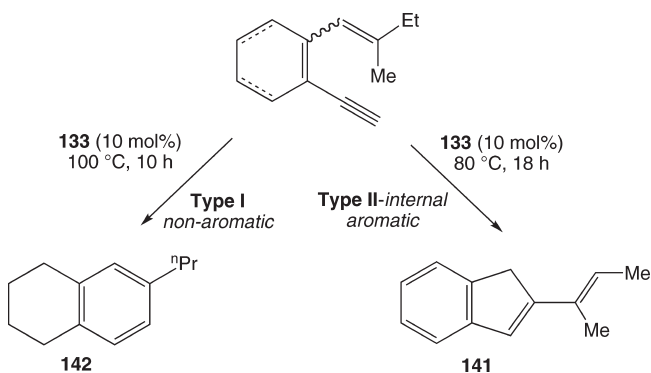
Reaction of a diene possessing a terminal alkyne (i.e., **121**, Scheme 33) with certain transition metal complexes can result in the formation of a metal vinylidene complex **122**.<sup>50</sup> This reactive intermediate provides a common cycloaromatization route for dienes by proceeding through a  $6\pi$ -electrocyclization and formal [1,2]-H transfer/demetallation to provide aromatic product **123**. Complex **122** is in equilibrium with the  $\eta^2$ -alkyne complex **124** and it is often difficult to determine which species is a true intermediate on the direct reaction pathway. As shown in Scheme 33, use of a deuterated terminal alkyne is a commonly employed method of determining if a metal vinylidene forms, as migration of the D-atom from the terminal to internal alkyne carbon should be observed. Depending on the metal and ligand environment, the vinylidene hydrogen can be relatively acidic and deprotonated with weak bases (e.g., basic alumina, for ML<sub>n</sub> = [Ru(PPh<sub>3</sub>)<sub>2</sub>( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>)]<sup>+</sup>) to form a metal acetylide **125**. Thus use of a protic solvent often results in partial loss of the isotopic label in **123**.

Merlic and Pauly were the first to demonstrate the feasibility of the metal vinylidene cycloaromatization pathway for dienes (Scheme 34).<sup>51</sup> A variety of terminal alkene modified dienes were shown to cyclize in relatively high yield under Ru(II) catalysis. It was observed that electron-rich terminal alkene substrates and electron-deficient metal complexes provided the most efficient cyclizations. Because of this substrate and catalyst dependence, these researchers considered both a concerted  $6\pi$ -electrocyclization

**Scheme 38. Proposed Mechanistic Pathways for Formation of the 1,2-Halide and Aryl Shift Products**<sup>56a</sup>



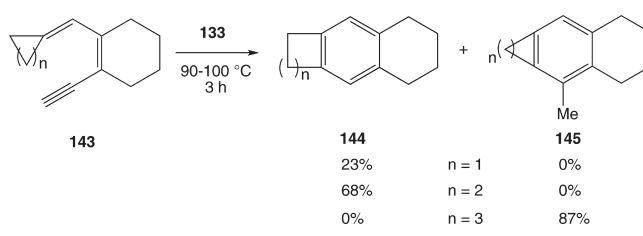
**Scheme 39. Dependence of Electronic Nature of Alkene on Reaction Pathway**<sup>56b,c</sup>



and a stepwise mechanism proceeding through transition state **126** that would be stabilized by nucleophilic alkenes and electron-poor metals.

Merlic and Pauly's pioneering work has sparked many developments and applications with the same or related ruthenium systems. Kobayashi and Akiyama demonstrated use of a polystyrene ruthenium catalyst **127** for diene cycloaromatizations along with many other metal catalyzed reactions (Scheme 35).<sup>52</sup> Thiemann and co-workers have used Merlic's system for synthesis of polyaromatic steroid derivatives.<sup>53</sup> The research group of Scott as well as Liu have also utilized the potential of ruthenium vinylidenes

**Scheme 40. Changing Reactivity of Alkylidenyl Substituted Dienes as the Carbon Tether Size Increases**<sup>56c</sup>



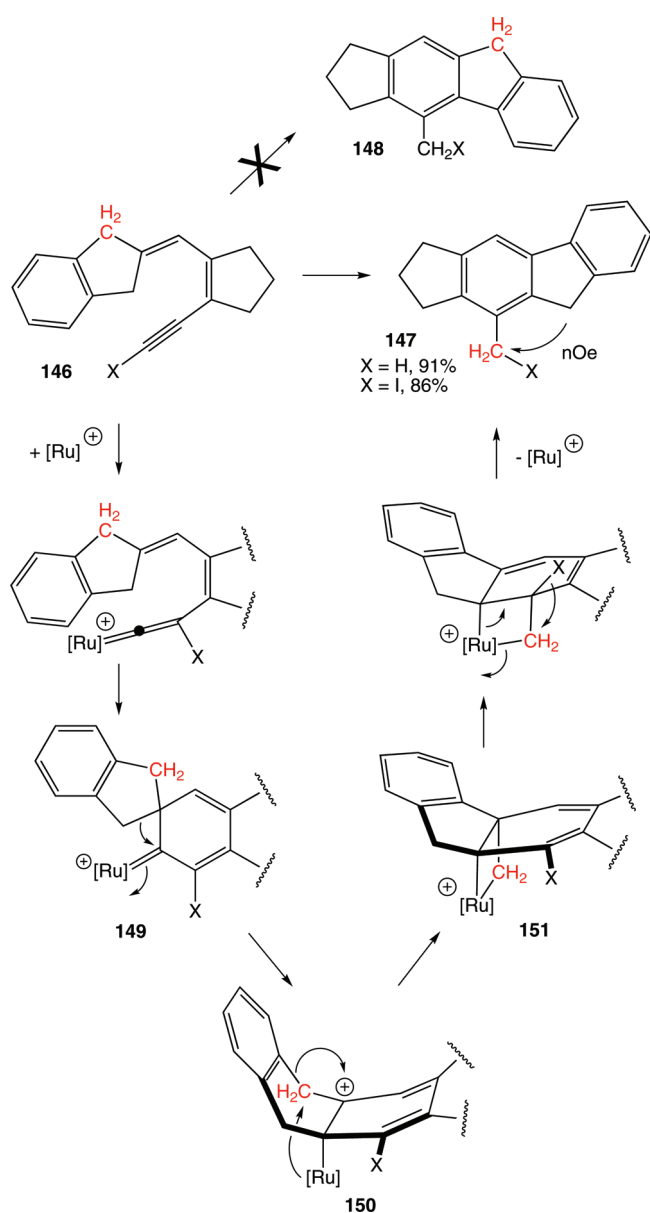
in the synthesis of coronene (**128**) and heteroatom derivatives of coronene.<sup>54</sup>

Iwasawa and co-workers have developed use of  $(\text{CO})_5\text{W} \cdot \text{THF}$  as a cyclization promoter in either stoichiometric or catalytic amounts.<sup>55</sup> In addition to the standard acetylenic deuterium labeling experiment (Scheme 33), it was shown that by allowing the geminal dideuterio diene **129-H,D** to react with  $(\text{CO})_5\text{W} \cdot \text{THF}$  resulted in incorporation of the D label into the 2 and 3 positions of the product naphthalene **130**, thus indicating a 1,2-shift for the alkene hydrogens (Scheme 36).<sup>55b</sup> One of the most impressive features of the tungsten system was the ability to form the intermediate metal vinylidene with an iodoalkyne substrate **129-I,H** thus allowing formation of an aromatic iodide **131**.<sup>55c,d</sup> Dankwardt has also shown and proposed that silyl substituted alkynes (e.g., **132**) undergo 1,2-shifts through a vinylidene mechanism.<sup>31</sup>

Liu and co-workers have uncovered many impressive skeletal rearrangements from studies on the formation of cationic vinylidenes resulting from use of  $[\text{TpRu}(\text{PPh}_3)(\text{NCMe})_2]\text{PF}_6$  (**133**, Tp = tris-pyrazolylborate) and vinyl substituted dienes (Scheme 37).<sup>56</sup> In their initial findings, the reactions of vinyl substituted dienes **134** with **133** were found to undergo formal 1,2-shifts, but in opposite directions depending on the terminal alkene substituent.<sup>56a</sup> Reaction of the vinyl iodide **134-D,I** with catalytic amounts of the metal complex resulted in a 1,2-shift of the iodine to the 7-position of the naphthalene **135** in 80% yield. The reaction also worked with the vinyl bromide, but the yields were substantially lower for most substrates. Use of an electron-rich aryl group as a substituent on the terminal alkene carbon **134-H,PMP** (PMP = *p*-methoxyphenyl) gives a 1,2-shift of the aryl group to the 5-position of the naphthalene to yield **136** as the major product. To provide some mechanistic insight, isotopic labeling experiments with <sup>13</sup>C-enriched aryl substituted **134-H**, PMP were performed and resulted in the incorporation of the label into the 1-position of **136**, ruling out a direct 1,2-aryl shift.

The proposed mechanisms for these transformations are shown in Scheme 38. The halogen-rearranged product **135** is hypothesized to occur through a simple 1,2-halide shift from cyclized intermediate **137** to give **138** followed by regeneration of the catalyst. The aryl shift is postulated to occur by initial *5-endo-dig* cyclization to give carbocation intermediate **139**, the formation of which is facilitated by the strong electron-donating *para*-methoxy aryl group. A 1,2-shift of the ring carbon-carbon bond then gives **140** thus validating the carbon isotopic labeling results. Loss of ruthenium from this species would then give the product **136**.

The reactivity of dienes with geminal disubstituted terminal alkenes with **133** were found to be very sensitive to the electronic and structural environment of the substrate. For example, reaction of a **Type II-internal** diene results in a nonaromatization

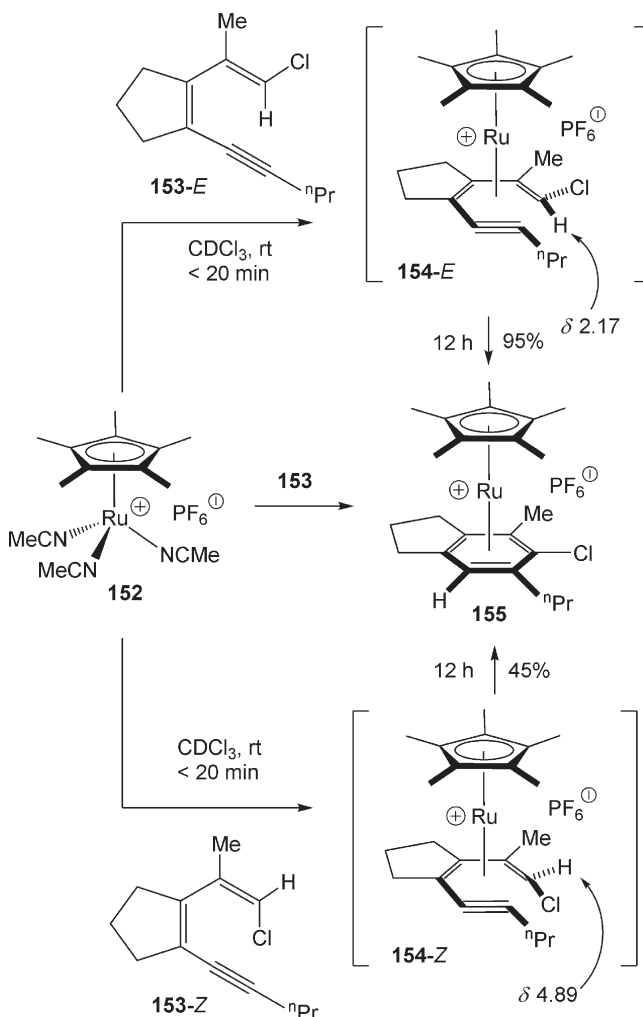
Scheme 41. Proposed Mechanism for 1,3-Methylene Migration<sup>a</sup>

<sup>a</sup> Conditions: 133 (10 mol %), toluene, 100 °C, 1.5 h.<sup>56c</sup>

pathway to indene **141** (Scheme 39).<sup>56b</sup> Simply changing to a **Type I** diyne reverses the reactivity back to a cycloaromatization pathway to give **142**.<sup>56c</sup> The formation of **141** was believed to involve a nonclassical carbocation species and the reader is referred to the cited reference for a full discussion of the mechanism. A mechanistic proposal for the formation of **142** was not given.

Cyclic alkylidenyl substrates open up yet another reaction pathway for diynes under catalysis by **133** (Scheme 40).<sup>56c</sup> Use of cyclopropylidenyl ( $n = 1$ ) and cyclobutylidenyl ( $n = 2$ ) diynes **143** resulted in a 1,2-alkyl shift to afford **144** presumably formed by a similar mechanism to **135**. Increasing the cyclic alkylidene chain to a 5-membered ring results in formation of **145**.

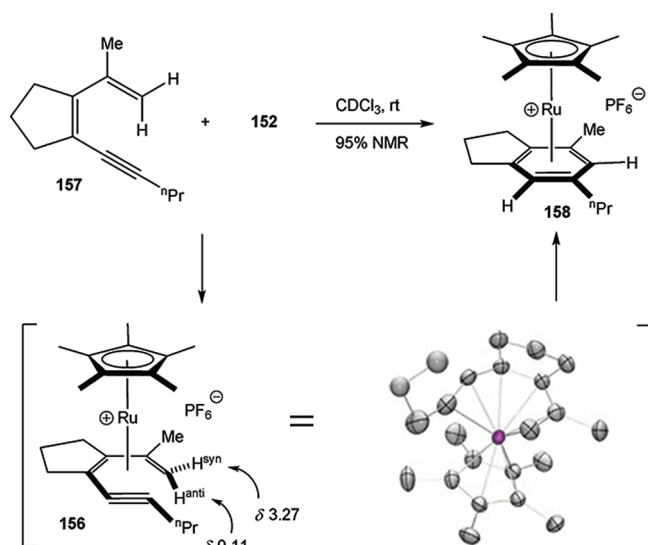
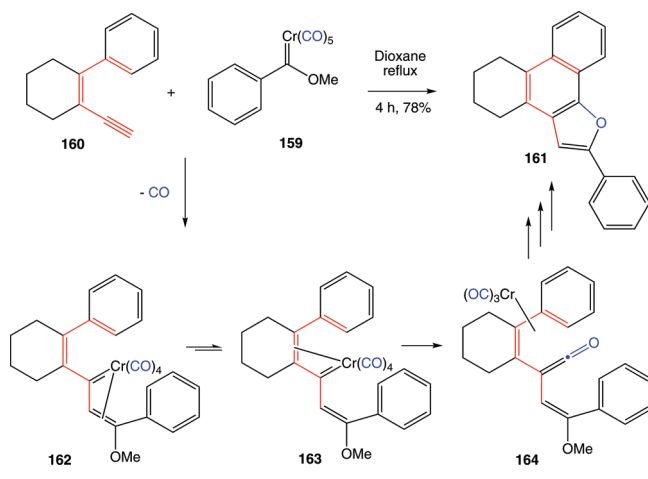
One mechanistic possibility that would lead to **145** would initiate from a [1,7]-H shift of a methylene hydrogen (see

Scheme 42. NMR Observation of Transient Species in  $[(\eta^5\text{-C}_5\text{Me}_5)\text{Ru}(\text{NCMe})_3]\text{PF}_6$  (**152**) Triggered Cycloaromatization of 1-Chlorodienynes<sup>57b</sup>

Scheme 31). This mechanism was ruled out by use of substrates such as **146** that give an alternative product **147** to one originating from a [1,7]-H shift (**148**, Scheme 41). The relative connectivity of the ortho substituents in **147** was verified by nOe of the acyclic benzylic position. Use of the iodo and deuterated alkynyl substrates ( $X = \text{I}$  and  $\text{D}$ , respectively), as well as deuteration of both cyclopentylidenyl methylene positions in **146** confirmed the bond scission of the methylene. To account for this unusual reactivity, Liu has put forth the mechanism shown in Scheme 41. From the vinylidene  $6\pi$ -electrocyclization product **149**, 1,2-alkyl shift gives cationic complex **150**. This species is proposed to undergo a metal-assisted 1,2-phenyl shift to give metallacycle **151**. [1,5]-Alkyl shift of the metallacycle's methylene followed by 1,2-migration of the original alkyne substituent  $X$  and loss of the metal gives **147**.

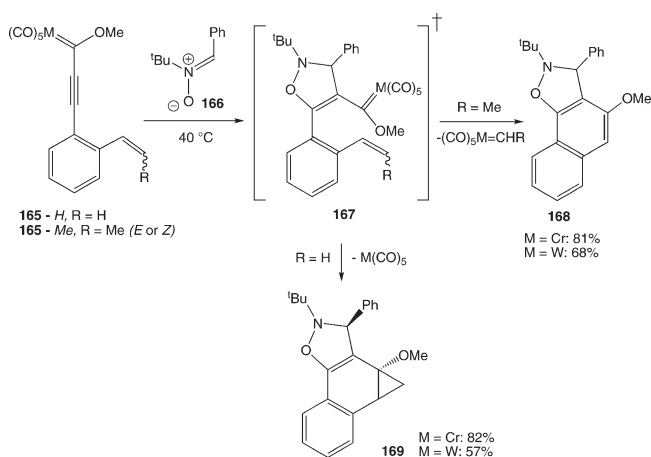
## 7. $\eta^6$ -COORDINATION OF THE $\pi$ SYSTEM

O'Connor and co-workers discovered that use of cationic cyclopentadienyl ruthenium complexes cyclize **Type I** diynes at room temperature in high yield to form  $\eta^6$ -arene complexes.<sup>57</sup> Reaction of

Scheme 43. X-ray Characterization of  $\eta^6$ -Dienyne<sup>57b</sup>Scheme 44. Reaction of a Metal Carbene with the Dienynyl Alkyne Resulting in an Overall Cycloaromatization<sup>58a</sup>

$[(\eta^5\text{-C}_5\text{Me}_5)\text{Ru}(\text{NCMe})_3]\text{PF}_6$  (**152**) with both dienyne **153-E** and **153-Z** led to immediate formation of a different transient metal-dienyne complex **154** as observed by NMR spectroscopy for each isomer (Scheme 42).<sup>57b</sup> This in situ formed complex slowly converted to product **155** over the course of 12 h. These species displayed key  $^1\text{H}$  NMR resonances at  $\delta$  2.17 (s, 1H) for **154-E** and  $\delta$  4.89 (s, 1H) for **154-Z** that provide good correlation by chemical shift to the  $\text{H}^{\text{anti}}$  and  $\text{H}^{\text{syn}}$  of related ruthenium  $\eta^4$ -diene complexes, respectively. Furthermore, integration of the free acetonitrile resonance for the reaction with **153-E** indicated  $\sim 9$  H relative to the **154-E**, providing evidence that the alkyne may be involved in the coordination sphere en route to an  $\eta^6$ -dienyne. As demonstrated by the yields for the reaction of **153-E** and **153-Z**, the trans-stereoisomer gives cleaner formation of the product **155**. Under the reaction conditions **153-Z** was observed by NMR spectroscopy to isomerize to **153-E**, suggesting that **154-Z** may not directly convert to cyclized **155**.

Unequivocal proof for the  $\eta^6$ -coordination mode came from single-crystal X-ray characterization of a crystalline sample

Scheme 45. Use of Pendent Fischer Carbenes for Metathesis Cycloaromatization<sup>61</sup>

obtained at low-temperature of the analogous transient species **156** from the reaction of dienyne **157** with **152** (Scheme 43). Consistent with the structures of **154-E** and **154-Z**, **156** showed both an upfield and downfield vinyl CH resonance corresponding to  $\text{H}^{\text{anti}}$  and  $\text{H}^{\text{syn}}$ , respectively. The solid-state structure of **156** contained some very impressive bond metrics such as a distorted alkyne triple bond ( $\angle \text{C}^{\text{sp}2}-\text{C}\equiv\text{C} = 151.8(4)^\circ$  and  $\angle \text{C}\equiv\text{C}-\text{C}^{\text{sp}3} = 156.8(4)^\circ$ ), a decreased nonbonded distance between the terminal alkyne and alkene carbons of 2.80 Å, and a Ru– $\text{H}^{\text{anti}}$  of 2.20 Å (in range of a metal-agostic interaction).

Although these researchers were not able to definitively show **156** lies on the direct reaction coordinate to **158**, therefore differentiating this mode of activation from other possibilities (i.e.,  $\eta^2$ -alkyne coordination), the proximity of the terminal carbons of the  $\pi$ -system and the short Ru– $\text{H}^{\text{anti}}$  makes **156** an interesting candidate for a reaction intermediate.

## 8. METAL CARBENE INDUCED

Herndon and co-workers have extensively studied the use of chromium Fischer carbene complexes (e.g., **159**) to induce cycloaromatization of dienyne using the Dötz reaction platform (Scheme 44).<sup>58,59</sup> In their initial report, Z-1-aryl-2-alkynyl-alkenes (e.g., **160**) were found to react with metal carbene **159** to give cycloaromatized products of type **161** in high yield.<sup>58a</sup> Although the example shown in Scheme 44 demonstrates use of a **Type II-terminal** dienynyl, **Type I** dienyne were also shown to be effective substrates as well.<sup>58b</sup> One substrate limitation was use of **Type II-internal** dienyne.<sup>58c</sup> This can be explained by analysis of the potential equilibrium between the possible  $\eta^3$ -vinylcarbene intermediates, **162** and **163**, formed during the reaction. It is known that electron-donating substituents in the coordination sphere of the  $\eta^3$ -vinylcarbene inhibit the CO insertion step. Therefore **163** with a less electron-rich alkene should be expected to insert faster to give ketene **164** that proceeds to the observed product **161**. If the central alkene of the dienynyl is inhibited from forming a complex with the Cr metal center, as the case with a **Type II-internal** dienynyl, then only **162** would be able to react further either by cycloaromatization if a  $\gamma$ -vinyl or aryl group is present in the chromium carbene **159** or through other pathways such as CH

**Table 4. Organization of References Covered in This Review for Dienyne Cycloaromatization Activation Methodologies Classified by Dienyne Type (see Figure 1-1) and Promoter/Catalytic Reagent**

dienyne	type I	type II-internal	type II-terminal	type III
photolytic	7	9; 10	8a-d; 13a-b	11
internally activated (e.g., vinyl triflate)	25a-b; 27a-b	25c	23	
acid/electrophile (i.e., TfOH, I <sub>2</sub> )	40	36		38a-c; 39a-b
base	15; 16; 17; 18; 22; 24; 49	19; 20a-c; 22		20b-c
metal (temp <50 °C)	51; 47; 55c-d; 57a-b;	28; 30; 31; 34; 35a-b; 55a-d; 61	51	34; 41a,c; 55b
metal (temp ≥50 °C)	5b; 29; 51; 56c; 58b	28; 31; 32a-b; 33; 44; 45a; 56a-b; 58d; 60	41c; 51; 52; 53; 54a-b; 58a	31; 41a-c; 42a-d; 43; 46; 54b;

insertion. Although **Type II-internal** dienyne were not viable substrates, other heterocyclic aromatic systems were able to perform the cycloaromatization if there is not a competing cyclization component on the Fischer carbene.<sup>58d,60</sup>

Barluenga and co-workers have also found success for dienyne cycloaromatization by incorporating a tungsten or chromium pentacarbonyl carbene moiety pendent to the alkyne (Scheme 45).<sup>61</sup> Fischer carbenes are activating groups for polar cycloaddition reactions because of the metal's electron-withdrawing nature. Treatment of **165** with nitrene **166** initially results in formation of cycloadduct **167**. The carbene is now brought into range of the proximal alkene inducing further reactivity. When either the *E* or *Z* disubstituted alkene **165-Me** was used, the only observed product was cycloaromatized **168** resulting from a metathesis reaction. Reaction of monosubstituted alkene **165-H** resulted in cyclopropane formation to give **169**. These authors postulate that use of the more substituted alkene raises the activation barrier to **169**, presumably because of steric factors, therefore making the pathway to the thermodynamic product **168** favored.

## 9. CONCLUSIONS AND FUTURE OUTLOOK

In summary, the 1,3-dien-5-yne structural unit represents a valuable synthon in the construction of highly substituted benzenoid systems. This review has covered the main mechanisms of activation to achieve both formal cycloaromatization via the two main thermal pathways as well as other pathways providing access to new systems. Table 4 summarizes these methodologies by dienyne structure (see Figure 1) and the activating reagent. From analysis of the references in this table, it is apparent that there is an abundance of systems designed to promote **Type II-internal** over *terminal* dienyne cyclizations. This may be due to a generally easier synthesis of the former substrate thus facilitating a scope study. It may also be reasonable to state that much of the chemistry that was only studied for **Type II-internal** dienyne could also be applicable to **Type II-terminal** dienyne as shown by several of the systems that are able to utilize both types of substrates (e.g., metal-vinylidene induced). While much progress has been made using catalytic and stoichiometric promoters, many of the existing reactions require elevated temperatures and there are relatively few synthetically practical examples of **Type I** dienyne cyclizations. Future development will no doubt lead to new methodologies that overcome these challenges.

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## BIOGRAPHIES



David M. Hitt was born in Pinehurst, North Carolina in 1982. He received a B.S. in Chemistry from North Carolina State University in 2005 with Summa Cum Laude and Valedictorian honors. David's graduate studies were conducted at the University of California, San Diego, under the supervision of Professor Joseph M. O'Connor where he studied metal-mediated and thermal cycloaromatization reactions of conjugated enediynes and dienyne. He received his Ph.D. in Chemistry in 2011 and is currently pursuing postdoctoral studies at the University of Montana, Missoula under the supervision of Professor Charles M. Thompson.



Joe O'Connor is a Professor of Chemistry and Biochemistry at the University of California, San Diego. He grew up in Ohio and received his undergraduate degree in chemistry from John Carroll University. After working for a year at Harshaw Chemical Company, Joe attended St. Louis University, where he carried

out research on organopalladium chemistry and earned a M.S. degree under the direction of Professor Harold A. Dieck. He then moved to the University of Wisconsin, Madison, where his Ph.D. research focused on cyclopentadienyl ligand ring-slippage chemistry under the direction of Professor Charles P. Casey. Following eight months of postdoctoral studies on tricobalt alkyne clusters with Professor K. P. C. Vollhardt at the University of California, Berkeley, Joe joined the faculty at the University of California, San Diego, in 1985. With the exception of a two-year interlude at the University of Nevada, Reno, Joe has remained at UCSD where his research interests have been in the areas of synthetic and mechanistic organometallic chemistry.

## ACKNOWLEDGMENT

Financial support of the National Science Foundation (CHE-0518707 and CHE-0911765) is gratefully acknowledged. The authors thank Prof. Kim Baldrige of the University of Zurich for providing the calculated molecular structure and figure for the  $\eta^6$ -dienyne complex shown in the cover art.

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