Ruthenium-Catalyzed Cyclizations of Dienylalkynes Via Vinylidene Intermediates

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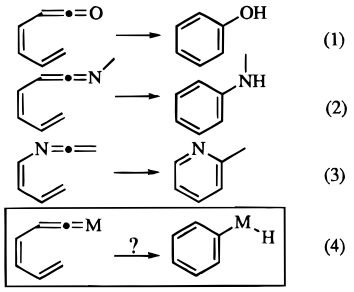
α,β-γ,δ-Unsaturated heterocumulenes have become versatile intermediates for the synthesis of complex aromatic compounds via 6π-electrocyclization and aromatization reactions as illustrated by eqs 1−3.[1] The challenge, though, has been convenient and efficient generation of the dienylheterocumulene intermediate. Dienylketenes (eq 1) are generated from thermal reactions of vinyl chromium carbene complexes with alkynes,[2] photochemical reactions of dienyl chromium carbene complexes,[3] thermal reactions of vinyl cyclobutenones,[4] and photochemical reactions of vinyl diazoketones and alkynes.[5] Dienylketenimines (eq 2) can be generated from thermal reactions of dienyl chromium carbene complexes with isonitriles[6] and condensation reactions of dienylphosphoranes with isocyanates.[7] *N*-Dienylketenimines (eq 3) are generated from thermal reactions of chromium carbene complexes with dienyl isonitriles[8] and condensation reactions of dienyliminophosphoranes with ketenes.[9]



(1)

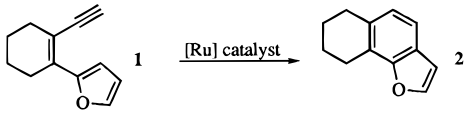
(2)

(3)

(4)

Recognizing the value of heterocumulene intermediates, we postulated that substituted arenes could be synthesized through electrocyclization of dienylvinylidene intermediates (eq 4) and subsequent reductive elimination. Vinylidenes are readily formed through reaction of terminal alkynes with a variety of metal complexes.[10] Furthermore, recent work has shown that ruthenium vinylidenes, in analogy with ketenes and ketenimines, react with nucleophiles, primarily heteroatoms, at the electrophilic α-carbon of the complex.[10] We now report the first examples of 6π-electrocyclization reactions involving vinylidene intermediates.[11]

Table 1. Catalyst Optimization



entry	catalyst[a]	time (h)	yield (%)
1	1% $RuClCp(PPh_3)_2$	24[b]	9[c]
2	none	24[b]	0
3	10% $RuClCp(PPh_3)_2$	22	51
4	5% $RuClCp(PPh_3)_2$	30	44[c]
5	5% RuClCp(dppe)	24	56
6	5% RuClCp(dppm)	∼24	19[c]
7	6% $RuClCp[P(OEt)_3]_2$	40	66[c]
8	4% $[RuCl_2(CO)_3]_2$/CO	48[b]	58
9	5% $RuCl_2(C_6H_6)AsPh_3$	43	42
10	7% $RuCl_2(C_6H_6)PPh_3$	24	80[c]
11	5% $RuCl_2(C_6H_6)[P(OEt)_3]$	45	79[c]
12	4% $RuCl_2$(p-cymene)PPh_3	10	89

[a] Reaction performed in the presence of 5−14% NH_4PF_6 in refluxing CH_2Cl_2 unless otherwise noted. [b] THF solvent. [c] Yield calculated from ^1H NMR integration.

In the initial test reaction, dienylalkyne **1** cyclized in 9% yield with 1% $RuClCp(PPh_3)_2$ and 12% NH_4PF_6, demonstrating a successful cyclization catalytic in ruthenium (Table 1, entry 1). In the absence of the ruthenium catalyst, only starting furan **1** was recovered, establishing that the reaction is not catalyzed by the acidic counterion NH_4PF_6. With a 10-fold increase in catalyst, the turnover number decreased; therefore, 5% catalyst was used in further reactions (Table 1, entries 3 and 4). The ruthenium catalyst was then optimized through several test reactions (Table 1).[12] Since vinylidenes are electrophilic species, modification with less electron-rich ligands was expected to lead to more electrophilic, more reactive species,[10,13] thereby promoting the cyclization reaction. For example, replacement of the triphenylphosphine ligand with triethyl phosphite increased the cyclization yield to 66% (Table 1, entry 7). After further ligand substitutions, $RuCl_2(C_6H_6)PPh_3$ and $RuCl_2$(*p*-cymene)PPh_3, particularly electron-deficient complexes,[14] were determined to be the most efficient catalysts for cyclization of substrate **1** and were used in all other cyclization reactions.

Under the optimized conditions, benzofuran product **2** could be obtained in 89% yield (Table 2, entry 1). Several other dienylalkyne substrates underwent the electrocyclization reaction equally well. Thiophene **3** cyclized to give **4** in 74% yield, and benzofuran **7** cyclized to give **8** in 87% yield. Surprisingly, indole **5** decomposed readily instead of undergoing the electrocyclization reaction efficiently.

Entries 5−8 in Table 2 provide insight into the cyclization mechanism. The isopropyl-substituted product **10** was isolated in a 57% yield while the methoxy-substituted dienylalkyne **11** did not cyclize. We propose that π-donation from the alkoxy

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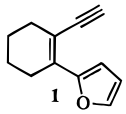
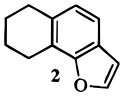
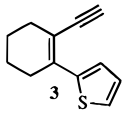
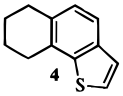
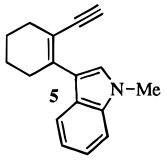
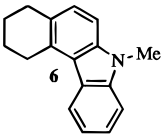
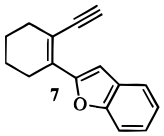
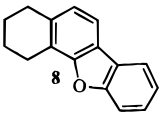
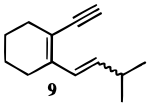
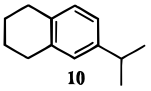
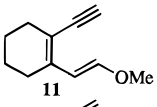
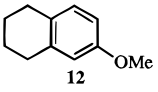
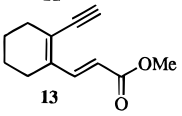
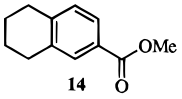
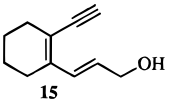
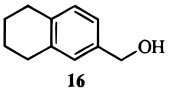
Table 2. Results of Cyclization Reactions

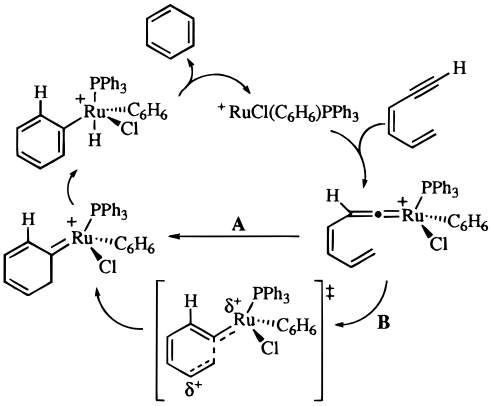
entry	substrate	product	cond.[a]	yield (%)
1			A	89
2			A	74
3			B	18[b]
4			A	86
5			B	57
6			C	0
7			A	12[b]
8			A	23[b]

[a] Conditions: refluxing CH_2Cl_2 or $C_2H_4Cl_2$; (A) 5−15% NH_4PF_6, ~5% $RuCl_2$(*p*-cymene)PPh_3; (B) 6% NH_4PF_6, ~5% $RuCl_2(C_6H_6)PPh_3$; (C) attempted several catalysts. [b] Yield calculated from ^{1}H NMR integration.

substituent of **11** increases the electron density at the C-2 position of the terminal olefin, thereby *deactivating* the C-1 position toward nucleophilic attack on the vinylidene. When the polarity was reversed by replacing the methoxy group with an ester to give **13**, the cyclization yield increased to 12%. When ester **13** was reduced to alcohol **15**, the yield increased further to 23%, supporting the notion that the C-1 position of the terminal olefin must be nucleophilic to promote electrocyclization as in entry 1 of Table 2.

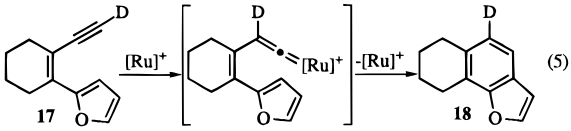
Several of the electrocyclization reactions (Table 2, entries 1, 2, 4, and 5) were quite successful, but a greater understanding of the mechanism of cyclization is necessary. It is well precedented that the terminal alkyne reacts with a cationic ruthenium complex, formed by loss of chloride ion, to yield a vinylidene intermediate.[10] We then envision two different modes of cyclization (Scheme 1): path A, a nonpolar pericyclic reaction where nucleophilicity of the terminal alkene and electrophilicity of the vinylidene complex have little effect on the efficiency of the cyclization reaction, or path B, a polarized transition state formed when the terminal olefin adds to the α-carbon of the vinylidene shifting electron density toward the

Scheme 1. Proposed Reaction Mechanism



metal while cationic charge buildup occurs on C-2 of the alkene. The majority of the cyclization results are consistent with path B; cyclization yields are improved by less electron-rich catalysts and increased nucleophilicity of the terminal olefin. Cyclization is followed by aromatization of the intermediate carbene complex and reductive elimination of the metal hydride complex to form the substituted arene.

Regarding another aspect of the mechanism, we verified the 1,2-hydride shift of the terminal acetylenic hydrogen during formation of the vinylidene. Vinylidene complexes are thought to be formed through η^2-coordination of alkynes to the metal followed by 1,2-hydride shift of the terminal acetylenic hydrogen.[10,15] The cyclization product of deuterium-labeled substrate **17** should then contain a deuterium only at the C-5 position. Indeed, 100% of the cyclized product **18** possessed a deuterium at the C-5 position, presenting strong evidence for the vinylidene intermediate (eq 5). Furthermore, the clean shift of the deuterium negates the possibility of an acid-catalyzed reaction or a radical cyclization, since no exchange or scrambling of the deuterium was observed.



(5)

In conclusion, we have presented the first examples of 6π-electrocyclization reactions involving vinylidene intermediates, readily generated from terminal acetylenes. We found that vinylidene intermediates are much less reactive than ketenes, but have about the same reactivity as ketenimines.[3,8,6] The ruthenium-catalyzed cyclization presented herein may be applicable to the synthesis of biologically relevant molecules containing complex aromatic structures. Further studies are in progress.

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Supporting Information Available: Descriptions of syntheses, experimental details and characterization data for ruthenium-complexes and all substrates (20 pages). See any current masthead page for ordering and Internet access instructions.

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