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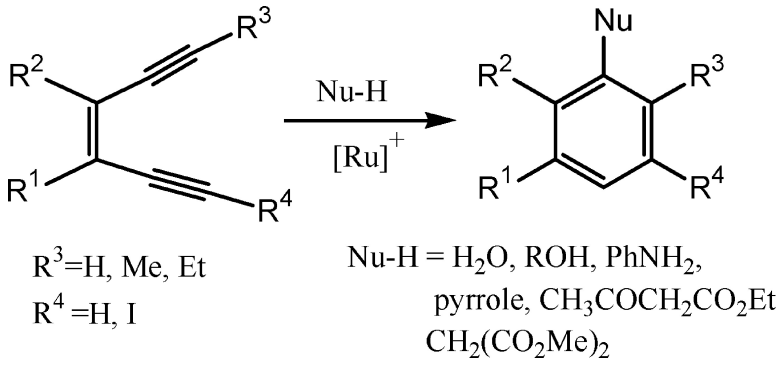

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Ruthenium-Catalyzed Aromatization of Enediynes via Highly Regioselective Nucleophilic Additions on a π-Alkyne Functionality. A Useful Method for the Synthesis of Functionalized Benzene Derivatives

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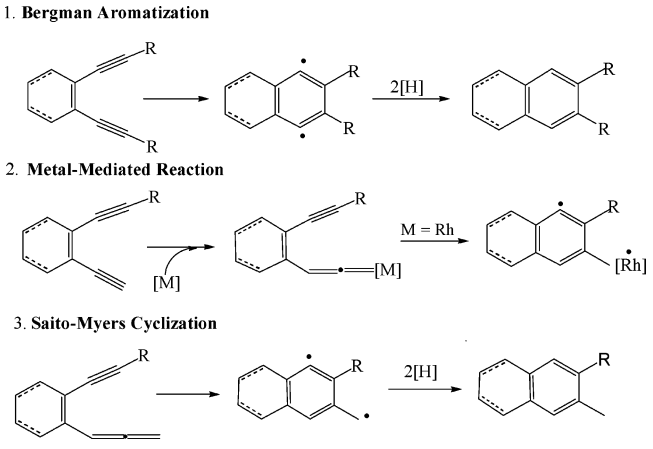
Abstract: $TpRu(PPh_3)(CH_3CN)_2PF_6$ (10 mol %) catalyst effected the nucleophilic addition of water, alcohols, aniline, acetylacetone, pyrroles, and dimethyl malonate to unfunctionalized enediynes under suitable conditions (100 °C, 12−24 h) and gave functionalized benzene products in good yields. In this novel cyclization, nucleophiles very regioselectively attack the internal C1′ alkyne carbon of enediynes to give benzene derivatives as a single regioisomer. Experiments with methoxy substituents exclude the possible involvement of naphthyl cations as reaction intermediates in the cyclization of (*o*-ethynylphenyl) alkynes. Deuterium-labeling experiments indicate that the catalytically active species is ruthenium−π-alkyne rather than ruthenium−vinylidene species. This hypothesis is further confirmed by the aromatization of *o*-(2′-iodoethynyl)phenyl alkynes with alcohols. We propose a nucleophilic addition/insertion mechanism for this nucleophilic aromatization on the basis of a series of experiments.

Introductions

Bergman aromatization of enediynes[1] has attracted considerable attention because of its potential applications in medicinal and materials chemistry (Scheme 1, eq 1).[2,3] The Bergman reaction of unstrained enediynes can be implemented by an excess (>1.0 equiv) of metal complexes under mild conditions via metal−vinylidene intermediates[4a,b] (eq 2) or through a metal-chelated effect.[4c−f] The metal−vinylidene process mimics the cyclization of 5-allene-3-en-1-ynes (Saito−Myers cyclization)[5] occurring at 50−100 °C (eq 3).[4−6] Uemura et al. recently reported[6] rhodium-catalyzed Bergman reactions via this protocol,

Scheme 1



which led to dehydrogenation or C−H bond insertion of an tethered alkane (eq 2). In all examples reported to date, the cyclization of enediynes via metal−vinylidene intermediates has followed the traditional diradical mechanism, and these reactions have very limited applications in organic synthesis because they cannot give functionalized benzenes from unstrained and unfunctionalized enediynes.[1−5]

In contrast, the aromatization of enediynes via nucleophilic addition (anionic Bergman cyclization) is more useful because organic functionality can be introduced onto aromatic products via suitable nucleophiles.[7,8] Although anionic Bergman cyclization was first reported by Magnus in the early 1990s,[7c] such reactions have never been implemented by metal catalysts. The

(1) (a) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. (b) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082.
(2) Reviews: (a) *Enediyne Antibiotics as Antitumor Agents*; Borders, D. B., Doyle, T. W. Eds.; Marcel Dekker: New York, 1995. (b) Xi, Z.; Goldberg, I. H. In *Comprehensive Natural Product Chemistry*; Barton, D. H. R., Nakanishi, K. Eds.; Pergamon: Oxford, 1999; Vol. 7, p 553.
(3) Recent reviews: (a) Basak, A.; Mandal, S.; Bag, S. S. *Chem. Rev.* **2003**, *103*, 4077. (b) Rawat, D. S.; Zaleski, J. M. *Synlett*. **2004**, 393. (c) Bowles, D. M.; Palmer, G. J.; Landis, C. A.; Scott, J. L.; Anthony J. E. *Tetrahedron* **2001**, 57, 3753. (d) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453. (e) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207.
(4) For selected examples of stoichiometric metal-mediated Bergman cyclization, see: (a) Wang, Y. S.; Finn, M. G. *J. Am. Chem. Soc*. **1995**, *117*, 8045. (b) O'Connor, J. M.; Friese, S. J.; Tichenor, M. *J. Am. Chem. Soc*. **2002**, *124*, 3506. (c) Zaleski, J. M.; Rawat, D. S. *J. Am. Chem. Soc*. **2001**, *123*, 9675. (d) Warner, B. P.; Millar, S. P.; Broene, R. D.; Buchwald, S. L. *Science* **1995**, *269*, 814. (e) Konig, B.; Hollnagel, H.; Ahrens, B.; Jones, P. G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2538. (f) Landis, C. A.; Payne, M. M.; Eaton, D. L.; Anthony, J. E. *J. Am. Chem. Soc.* **2004**, *126*, 1338.
(5) (a) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057. (b) Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 4995.
(6) (a) Ohe, K.; Kojima, M.-a; Yohehara, K.; Uemura, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1823. (b) Manabe, T.; Yanagi, S.-I.; Ohe, K.; Uemura, S. *Organometallics* **1998**, *17*, 2942.

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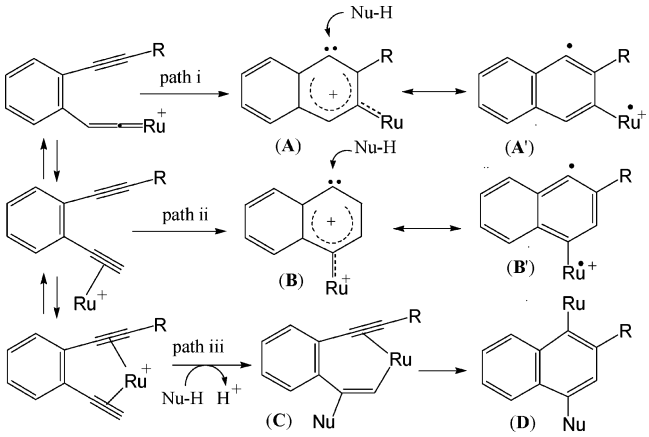
widespread use of this protocol has been restricted by its limited scope: the reactions required either anionic nucleophiles, such as sodium methoxide and thiophenoxide,[7] or strained cyclic enediynes.[8] Techniques for the cyclization of unstrained enediynes using mild nucleophiles and metal catalysts are currently unavailable and thus provide a challenge in synthetic chemistry. This report describes a novel ruthenium-catalyzed aromatization of unstrained enediynes with mild nucleophiles. This new pathway is mechanistically interesting because it does not follow the traditional Saito−Myers protocol; the active intermediate is metal−alkyne rather than metal−vinylidene species.[4a,b,6]

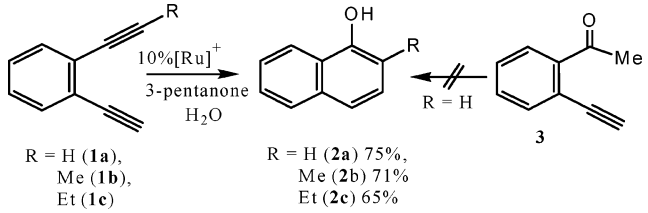
Results and Discussions

Although cyclization of unfunctionalized enediynes has been performed with different approaches, including diradical pathways,[1b,9] eletrophilic additions,[10a−c] and radical cation,[10d] these reactions only gave benzene[1b,9] or fulvene products[10] of special types. We seek to find a new method to realize the aromatization of functionalized enediynes with various nucleophiles. We selected $TpRuPPh_3(CH_3CN)_2PF_6$ [Tp = tris(1-pyrazolyl)borate][11,12] as the catalyst because it reacts with terminal alkyne to form a cationic ruthenium−π-alkyne complex that equilibrates with ruthenium−vinylidene species.[13] Scheme 2 shows the catalytic protocols that we design to realize this nucleophilic aromatization with high regioselectivity: (1) electrocyclic cyclization of these ruthenium−π-alkyne or −vinylidene intermediates to generate reactive naphthyl carbocations **A** (path i) and **B** (path ii) that can be trapped by suitable nucleophiles and (2) nucleophilic attack at ruthenium−π-alkyne species to give vinylruthenium species (path iii), followed by a 6-endo-dig insertion reaction. We envisage that nucleophilic additions preferably occur at the internal alkynyl C′(1) carbon for species **A** and **B** and at the terminal alkynyl C′(1) carbon

Scheme 2



Scheme 3



for species **C** because of its electron-deficient character. For paths (i) or (ii), the success of this nucleophilic cyclization relies on the hypothesis that the resonance structures are best represented by singlet state species **A** and **B** rather than the diradical resonance forms **A′** and **B′**.

As shown in Scheme 3, treatment of *o*-ethynylphenyl alkyne **1a** (1.50 M) in a solvent mixture of water and 3-pentanone (1:1 volume ratio, 100 °C, 24 h) using 10 mol % $TpRuPPh_3(CH_3CN)_2PF_6$ catalyst gave 1-naphthol **2a** in 75% yield. The yield was decreased to 51% for a 5% loading of catalyst. Similar cyclizations were also observed for enediynes bearing prop-1-ynyl and but-1-ynyl substituents **1b** and **1c**, which gave 2-substituted 1-naphthol **2b** and **2c** in respective yields of 71 and 65%. The reaction was inhibited by basic additives, including Et_3N (10 mol %) or DBU (10 mol %).[14] Such a nucleophilic aromatization is novel and surprising because many electrophilic metals catalyze the hydration of terminal alkynes to give methyl ketones very efficiently.[15] The value of this cyclization is shown by the regioselectivity of the addition of water, which occurs only at the internal C5 alkyne carbon. The structure of **2a** was easily determined by its ^1H NMR spectra.[16] Ketone **3** was unlikely to be a reaction intermediate because it failed to give 1-naphthol **2a** under similar catalytic conditions. We examined the cyclization of **1a** using various ruthenium

(7) For anionic Bergman cyclization, see: (a) Wu, M.-J.; Lin, C.-F.; Lu, E.-D. *J. Org. Chem.* **2002**, *67*, 5907. (b) Wu, M.-J.; Lee, C.-Y.; Lin, C.-F. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4077. (c) Magnus, P.; Eisenbeis, S. A.; Rose, W. C.; Zein, N.; Solmon, W. *J. Am. Chem. Soc.* **1993**, *115*, 12627. (d) Sugiyama, H.; Yamashita, K.; Nishi, M.; Saito, I. *Tetrahedron Lett.* **1992**, *33*, 515.

(8) For the cyclization of strained enediynes with anionic nucleophiles, the enediynes actually underwent traditional Bergman or Saito−Myers diradical processes after attack of anionic nucleophiles. For examples, see: (a) Nicolaou, K. C.; Dai, W. M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387 and references therein. (b) Hirama, M.; Fujiwara, K.; Shigematsu, K.; Fukazara, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4120. (c) Wender, P. A.; Hartmata, M.; Jefferey, D.; Mukai, C.; Suffert, J. *Tetrahedron Lett.* **1988**, *29*, 909. (d) Bekele, T.; Brunette, S. R.; Lipton, M. A. *J. Org. Chem.* **2003**, *68*, 8741.

(9) For cyclization of enediynes via diradical pathways, see: ref 1b and (a) Jones, L. H.; Hartwig, C. W.; Wentworth, P., Jr.; Simeonov, A.; Wentworth, A. D.; Py, S.; Ashley, J. A.; Lerner, R. A.; Janda, K. D. *J. Am. Chem. Soc.* **2001**, *123*, 3607. (b) Grissom, J. W.; Gunawardena, G. U. *Tetrahedron Lett.* **1995**, *36*, 4951. (c) Schottelius, M.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 4896. (d) Dai, W.-M. *Curr. Med. Chem.* **2003**, *10*, 2265.

(10) For cyclization of enediynes with electrophile addition[a−c] and radical cation,[d] see: (a) Whitlock, H. W., Jr.; Sandvick, P. E.; Overman, L. E.; Reichardt, P. B. *J. Org. Chem. Soc.* **1969**, *34*, 879. (b) Whitlock, H. W., Jr.; Sandvick, P. E. *J. Am. Chem. Soc.* **1966**, *88*, 4525. (c) Schreiner, P. R.; Prall, M.; Lutz, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5757. (d) Schmittel, M.; Kiau, S. *Liebigs Ann./Recl.* **1997**, 1391.

(11) For catalytic reactions that use this ruthenium catalyst, see the following selected examples: (a) Yeh, K.-L.; Liu, B.; Lo, C.-Y.; Liu, R.-S. *J. Am. Chem. Soc.* **2002**, *124*, 6510. (b) Datta, S.; Chang, C.-L.; Yeh, K.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 9294. (c) Shen, H.-C.; Pal, S.; Lian, J.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 15762. (d) Madhushaw, R. J.; Lin, M.-Y.; Abu Sohel, S. M.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 6895. (e) Madhushaw, R.-J.; Lo, C.-Y.; Huang, C.-W.; Su, M.-D.; Shen, H.-C.; Pal, S.; Shaikh, I. R.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 15560.

(12) Chan, W.-C.; Lau, C.-P.; Chan, Y.-Z.; Fang, Y.-Q.; Ng, S.-M.; Jia, G. *Organometallics* **1997**, *16*, 34.

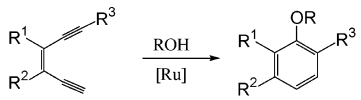
(13) (a) Trost, B. M. *Acc. Chem. Res.* **2002,** *35*, 695. (b) Bruneau, C.; Dixneuf, P. *Acc. Chem. Res.* **1999**, *32*, 311. (c) Puerta, M. C.; Valerga, P. *Coord. Chem. Rev.* **1999**, *193*−*195*, 977.

(14) In the presence of aliphatic amine base, cationic ruthenium complex tends to react with terminal alkyne to give alkynyl ruthenium species. See: (a) Bustelo, E.; Carbo, J. J.; Lledos, A.; Mereiter, K.; Puerta, M. C.; Valerga, P. *J. Am. Chem. Soc.* **2003**, *125*, 3311. (b) Bruce, M. I.; Wallis, R. C. *Aust. J. Chem.* **1979**, *32*, 1471. (c) Haquette, D. T.; Pirio, N.; Touchard, L.; Toupet, P. H.; Dixneuf, J. *J. Chem. Soc., Chem. Commun.* **1993**, 163. (d) Yang, S.-M.; Chan, M. C.-W.; Cheung, K.-K.; Che, C.-M.; Peng, S.-M. *Organometallics* **1997**, *16*, 2819.

(15) (a) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4563. (b) Tokunaga, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2867. (c) Damiano, J. P.; Postel, M. *J. Organomet. Chem.* **1996**, *522*, 303. (d) Uemura, S.; Miyoshi, H.; Okano, M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1098. (e) Baidossi, W.; Lahav, M.; Blum, J. *J. Org. Chem.* **1997**, *62*, 669.

(16) The structures of the addition products in Tables 1−4 were assigned on the basis of two new doublets (J = 7.8−8.0 Hz) in the aromatic regions.

Table 1. Regioselective Alkoxylation and Hydration in the Aromatization Reactions



[Ru] = 10 mol% $TpRuPPh_3(CH_3CN)_2^+$

enediynes	ROH [a,b]	arene[c]	enediynes	ROH	arene[c]
R^1, R^2 = 			(7) R^3 = Me (**1e**)	R = H	**2**j (71%)
(1) R^3 = H (**1a**)	R = ^{i}Bu	**2d** (81%)	(8) **1e**	R = ^{t}Bu	**2**k (81%)
(2) R^3 = Me (**1b**)	R = ^{i}Bu	**2e** (65%)	R^1, R^2 = $-(CH_2)_4-$		
(3) **1b**	R = ^{n}Bu	**2**f (66%)	(9) R^3 = H (**1f**)	R = H	**2**l (74%)
(4) **1b**	R = *sec*-Bu	**2**g (62%)	(10) R^3 = Me (**1g**)	R = H	**2**m (70%)
(5) R^3 = Et (**1c**)	R = ^{i}Bu	**2h** (60%)	(11) R^1= H, R^2= $^nC_6H_{13}$ R^3 = Me (**1h**)	R = H	**2**n (78%)
R^1, R^2 = $-(CH_2)_3-$					
(6) R^3 = H (**1d**)	R = H	**2**i (77%)	(12) **1h**	R = ^{t}Bu	**2o** (70%)

[a] 10 mol % catalyst, 100 °C, 12 h for alcohols (6.0 equiv) and 24 h for water. [b] Water and 3-pentanone (vol. 1:1) were used as a mixing solvent. [c] Yields were reported after separation from a silica column.

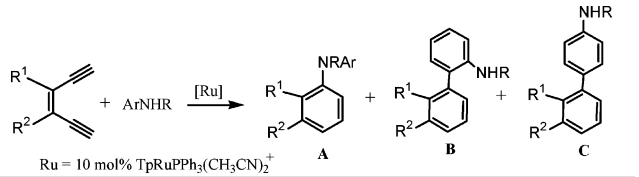
catalysts, including $CpRuL(CH_3CN)_2PF_6$ [L = PPh_3, P(t-Bu)$_3$, and P(n-Bu)$_3$] and $C_5Me_5RuPPh_3(CH_3CN)_2PF_6$,[17] which failed to show any catalytic activity. One possible reason is that these complexes may react with benzene to give stable XRu(π-benzene)PF_6 (X = Cp, C_5Me_5) species.[4b]

We used this new method for the synthesis of substituted aromatic compounds containing hydroxy and alkoxy functionalities via treatment of various unfunctionalized enediynes with water and alcohols. As shown in Table 1, entries 1−5 show examples of the regioselective alkoxylation of *o*-ethynylphenyl alkynes **1a**−**1c** with *n*-butanol, *i*-butanol, and *sec*-butanol; the corresponding 1-alkoxynaphthalenes **2d**−**2h** were obtained in good yields (60−81%). We further established the reliability of this method by conducting similar alkoxylation and hydroxylation reactions using the enediynes **1d**−**1h**, which gave highly substituted benzene derivatives **2i**−**2o** (entries 6−12) in good yields (70−81%), each as a single regioisomer.

We extended this method to the synthesis of diphenylamine derivatives via nucleophilic carbon−nitrogen bond formation (Table 2). In a typical operation, enediynes and neat aniline (6.0 equiv) were heated with 10% ruthenium catalyst (100 °C, 15 h). For enediynes **1a**, **1d**, and **1f**, nucleophilic cyclization worked for anilines but not for aliphatic amines.[14] Although the same regiochemistry was observed for these enediynes, we obtained both *N*-aryl (A) and *ortho*-*C*-aryl (B) products in most cases. The amounts of the corresponding *para*-*C*-aryl products were too low for isolation except for entry 2, where (4b-C) was obtained in 32% yield. For enediyne **1a**, the *N*-aryl and *ortho*-C-aryl products were obtained in equal proportions (entries 1 and 2), whereas the analogues **1d** and **1f** preferably gave *N*-aryl products (4c-A)−(4f-A) in 52−63% (entries 3−6). Notably, such an aniline addition failed to work with enediynes **1b**, **1c**, and **1e**, which have an internal alkyne. Compared to enediyne **1a**, species **1b** and **1c** bearing an internal alkyne were also less

(17) $CpRuL(CH_3CN)_2PF_6$ [L = PPh_3, P(t-Bu)$_3$, and P(n-Bu)$_3$] and C_5Me_5-$RuPPh_3(CH_3CN)_2PF_6$ complexes were prepared in situ by treatment of $CpRu(CH_3CN)_3PF_6$ and $C_5Me_5Ru(CH_3CN)_3PF_6$ with an equimolar amount of phosphine ligand.

Table 2. Aromatization via Addition of Anilines to Enediynes

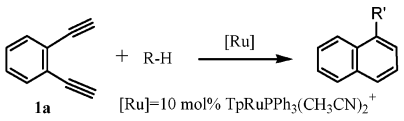


Ru = 10 mol% $TpRuPPh_3(CH_3CN)_2^+$

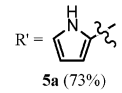
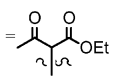
enediynes	ArNHR[a]	products (yields)[b]	enediynes	ArNHR	products (yields)
(1) R^1, R^2=  **1a**	$PhNH_2$	**4a-A** (42%), **4a-B** (35%)	(4) **1d**	PhNHMe	**4d-A** (63%) **4d-B** (14%)
(2) **1a**	PhNHMe	**4b-A** (29%), **4b-C** (32%)	(5) R^1, R^2= $-(CH_2)_4-$ **1f**	$PhNH_2$	**4e-A** (63%) **4c-B** (18%)
(3) R^1, R^2= $-(CH_2)_3-$ **1d**	$PhNH_2$	**4c-A** (57%), **4c-B** (21%)	(6) **1f**	PhNHMe	**4f-A** (52%) **4f-B** (16%)

[a] 10 mol % catalyst, aniline (6.0 equiv), 100 °C, 15 h. [b] Yields were reported after purification from a silica column.

Table 3. Aromatization via Carbon Nucleophiles to Enediyne **1a**



[Ru]=10 mol% $TpRuPPh_3(CH_3CN)_2^+$

R-H[a]	product[b]	R-H	product
(1) 	R' =  **5a** (73%)	(3) 	R' =  **5c** (62%)
(2) 	R' = CH_2COPh **5b** (28%)	(4) $CH_2(CO_2Me)_2$	R' = CH_2CO_2Me **5d** (64%)
		(5) Et_3SiH	N.R.

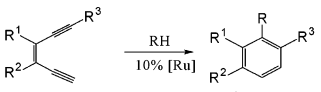
[a] 10 mol % catalyst, nucleophiles (6.0 equiv), 100 °C, 15 h. [b] Yields were reported after separation from a silica column.

effective in the water and alcohol addition reactions (Scheme 3 and Table 1).

The synthetic potential of this method is further enhanced by its compatibility with carbon-centered nucleophiles, as is evidenced by the range of examples in Table 3. These reactions were performed by heating enediyne **1a** with neat carbon-centered nucleophiles (6.0 equiv) at 100 °C for 15 h. The method worked well for pyrrole, which gave 2-aryl pyrrole **5a** in 73% yield. The efficiency of cyclization for silyl enol ether was low (entry 2), and the corresponding product **5b** was obtained in 28% yield. Ethyl acetoacetonate (EA) was active in cyclization, and gave *C*-aryl product **5c** (62%), whereas dimethyl malonate (DMA) gave 1-naphthalene species **5d** in 64% yield through decarboxylation reaction. Heating **1a** with neat Et_3SiH (6.0 equiv) and catalyst (10 mol %, 100 °C, 15 h) only led to a 66% recovery yield of starting **1a**.

Table 4 summarizes the results for the generality of this cyclization with suitable carbon-centered nucleophiles. Enediynes **1b**, **1e**, and **1h** bearing an internal alkyne were compatible with this new method. EA, DMA, and pyrrole were added very regioselectively to these enediynes and gave aromatic products **5e**−**5p** as a single regioisomer; except for entry 3, the yields exceeded 60%. Notably, the reaction with methyl-substituted ethyl acetoacetate (entry 2) gave 1-naphthalene **5f** (60% yield), which contains a tertiary acetoacetate substituent.

Table 4. Regioselective Aromatizations of Enediynes with Carbon Nucleophiles

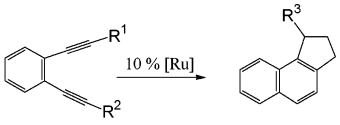


[Ru] = $TpRuPPh_3(CH_3CN)_2^+$

enediynes	RH [a]	arene[b]	enediynes	RH	arene
R^1, R^2 =  (1) R^3 = Me (**1b**)	EA[c]	R =  **5e** (67%)	(7) **1e** R^1, R^2 = $-(CH_2)_4-$	DMA	R = CH_2CO_2Me **5k** (75%)
(2) **1b**		R =  **5f** (60%)	(8) R^3 = H (**1f**)	EA	R =  **5l** (76%)
(3) **1b**	DMA.[c]	R = CH_2CO_2Me **5g** (50%)	(9) **1f**	DMA	R = CH_2CO_2Me **5m** (73%)
R^1, R^2 = $-(CH_2)_3-$ (4) R^3 = H (**1d**)	EA	R =  **5h** (60%)	(10) **1f**		R =  **5n** (81%)
(5) **1d**		R =  **5i** (78%)	R^1= H, R^2= $^nC_6H_{13}$ (11) R^3 = Me (**1h**)	EA	R =  **5o** (73%)
(6) R^3 = Me(**1e**)	EA	R =  **5j** (62%)	(12) **1h**	DMA	R = CH_2CO_2Me **5p** (65%)

[a] 10 mol % catalyst, nucleophiles (6.0 equiv), 15 h. [b] Yields were reported after separation from a silica column. [c] EA = ethyl acetoacetate. DMA = dimethyl malonate.

Scheme 4



[Ru]= $TpRuPPh_3(CH_3CN)_2^+$ R^3=H(**6a**), Me(**6b**), ^{n}Pr(**6c**)

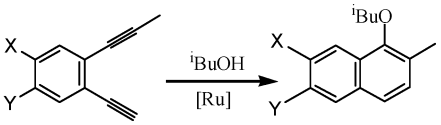
enediynes	Nu-H	products[c]
(1) R^1=^{n}Pr, R^2=H (**1i**)	^{n}BuOH[a]	**6a** (27%)
(2) **1i**	——[b]	**6a** (35%)
(3) R^1=^{n}Bu, R^2=H (**1j**)	——	**6b** (54%)
(4) R^1=$^nC_6H_{13}$, R^2=H (**1k**)	——	**6c** (61%)
(5) R^1= R^2=Me (**1l**)	^{n}BuOH	N.R

[a] 10 mol % catalyst, ^{n}butanol (6.0 equiv) 100 °C, 15 h. [b]Toluene solvent. [c]Yields were separated from a silica column.

Scheme 4 shows the structural effects of the substrates on the catalytic activity. Enediyne **1i**, which bears a pent-1-ynyl group, failed to react with *n*-butanol, but cyclized itself to give cyclopentyl species **6a** (27%) via a C−H bond insertion. The yield of compound **6a** was increased to 35% by heating species **1i** in toluene (100 °C, 15 h). Interestingly, enediynes **1j** and **1k** bearing a long hex-1-ynyl and oct-1-ynyl group gave improved yields of cyclopentyl products **6b** (54%) and **6c** (61%). The enhancing effect of the longer alkynyl alkyl group of enediynes is opposite to the results observed in preceding nucleophilic cyclizations. Furthermore, the structures of products **6a**−**6c** are distinct from those using rhodium catalysts, which gave a cyclopentyl ring fused at the naphthyl C(2) and C(3) carbons.[6b] These results suggest that this C−H bond insertion does not proceed via a diradical mechanism (Scheme 1, eq 2). The ^{n}BuOH addition failed to work with enediyne **1l**, which has two internal alkyne substituents.

We are uncertain whether the mechanism of nucleophilic aromatization of enediynes is the same as that for intramolecular

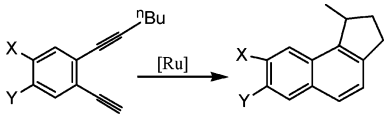
Scheme 5



enediynes[a]	products[b] (yields)
(1) X=OMe, Y=H (**1m**)	**7a** (61%)
(2) X=H, Y=OMe (**1n**)	**7b** (60%)
(3) X, Y= -OCH_2O- (**1o**)	**7c** (58%)

[a] 10 mol % catalyst, [substrate] = 1.2 M, isobutanol 95 °C, 12 h. [b]Yields were isolated from a silica column.

Scheme 6

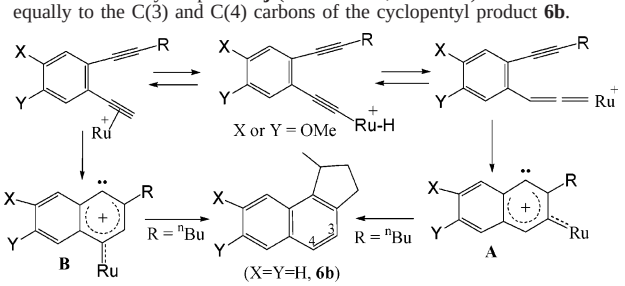


enediynes[a]	products[b] (yields)
(1) X=OMe, Y=H (**1p**)	**8a** (76%)
(2) X=H, Y=OMe (**1q**)	**8b** (80%)
(3) X, Y= -OCH_2O- (**1r**)	**8c** (84%)

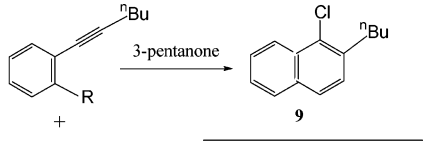
[a] 10 mol % catalyst, [substrate] = 0.75 M, toluene 100 °C, 15 h. [b]Yields were isolated from a silica column.

aromatization via the C−H bond insertion. We prepared substrates **1m**−**1o** and **1p**−**1r** bearing a methoxy group at the phenyl C(4) and C(5) carbons, respectively, to clarify the role of the cationic nature of the reaction intermediates. As shown in Scheme 5, (1-isobutoxy)naphthalene derivatives **7a**−**7c** were obtained in 58−61% yields, which were slightly lower than that (65%) of the parent compound **2e** (X = Y = H, Table 2), whereas cyclopentane derivatives **8a**−**8c** were obtained in 78−85% yields (Scheme 6), which are much higher than that (54%) of the unsubstituted analogue **6b** (Scheme 4). This information suggests that the key intermediates for nucleophilic aromatization are likely to be neutral species, whereas those in intramolecular C−H bond insertion may be cationic naphthyl carbene intermediates **A** and **B** (Scheme 2).[18] The notation that cationic naphthyl carbene intermediates are involved in nucleophilic cyclization is contradicted by the inactivity of the enediyne **1a** toward Et_3SiH[19] (Table 3, entry 5).

(18) These methoxy experiments suggest that the intermediates for the C−H bond insertion likely involve the following two cationic naphthyl carbenes **A** and **B** via electrocyclization of ruthenium−π-alkyne and ruthenium−vinylidene species, respectively (see Scheme 2). The methoxy groups will stabilize these carbenium species and give better yields of insertion products. In our preliminary results, we found that the alkynyl deuterium of starting ruthenium−π-alkyne species **1j** (X = Y = H, R = ^{n}Bu) was transferred equally to the C(3) and C(4) carbons of the cyclopentyl product **6b**.

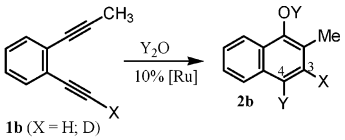


Scheme 7



alkyne	products
(1) R = (1j)	**9** (76%)
(2) R = H (**1s**)	**N.R.**

Scheme 8



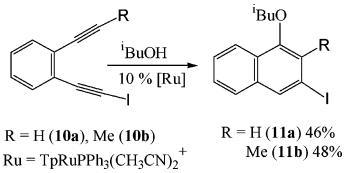
1b	Y_2O	**2b**	**1b**[c]
(1) X = H	D_2O[a]	X = 0.46D Y = 1.0 D	X = 0.50D
(2) X = H	D_2O[b]	X = 0.70D Y = 1.0 D,	X = 0.71D
(3) X = 0.97D	H_2O[a]	X = 0.60D Y = 1.0 H,	X = 0.45H

[a] 10.0 equiv of D_2O. [b] 22 equiv of D_2O. [c] Unreacted **1a** after catalytic reaction.

The mechanism for nucleophilic aromatization has been elucidated on the basis of a series of experiments. As shown in Scheme 7, we found that $TpRuPPh_3(CH_3CN)Cl$[12] (1.0 equiv) reacted with enediyne **1j** (2.5 equiv) in hot 3-pentanone (100 °C, 12 h) and gave 1-chloronaphthalene **9** in 76% yield on the basis of ruthenium reagent. This cyclization followed the same regiochemistry as preceding examples, and C−H bond insertion did not occur in this case although a *n*-butyl group is tethered with **1j**. We did not observe a similar chloride insertion for internal alkyne **1s**. This phenomenon suggests that a diyne functionality is required for this chloride insertion. The terminal alkyne of species **ij** is thought to serve as an entering group to facilitate the chloride insertion via intramolecular coordination.[20]

Scheme 8 shows deuterium labeling experiments. Treatment of enediyne **1b** with D_2O (10.0 equiv) in 3-pentanone gave naphthalene **d-2b** with deuterium contents of 100 and 46%, respectively, at the C4 and C3 carbons (entry 1). Notably, the alkynyl proton of unreacted **1b** was also deuterated (50%), which indicated that proton exchange with D_2O occurred.[21] This exchange process accounts for the lower proton content (30%) at the C3 carbon of **d-2b** in the presence of D_2O in 22-fold proportions (entry 2). The alkynyl deuterium of **1b** was transferred mainly to the C3 carbon of the product **d-2b** (entry 3) with a 40% loss of deuterium content. This labeling experiment indicates that the catalytic cycle is achieved by

Scheme 9



π-alkyne species rather than ruthenium−vinylidene because there is no 1,2-hydrogen shift in the cyclization.

The direct support of ruthenium−π-alkyne intermediates in this nucleophilic aromatization is shown in Scheme 9. Treatment of enediynes **10a**,**10b** with $TpRuPPh_3(CH_3CN)_2PF_6$ catalyst (10 mol %) in hot isobutanol gave addition products **11a** and **11b** in respective yields of 56 and 59%. The absence of a 1,2-iodo shift in this aromatization is indicative of a ruthenium−π-alkyne species as an active intermediate. Ruthenium−vinylidene intermediates are expected to lead to a 1,2-shift of alkynyl iodide.[22] Formation of naphthalene products **11a** and **11b** may arise from the attack of ^{i}BuOH at the more electron-rich alkyne substituent (R = H, Me), and this regiochemistry is identical to that in the preceding examples in considering this electronic effect. The structures of **11a** and **11b** were characterized on the basis of the ^{1}H NOE effect.[23]

The stoichiometric reaction described in Scheme 7 is very informative and leads us to propose a plausible mechanism based on the observation that the Ru−Cl bond of $TpRuPPh_3(CH_3CN)Cl$[12] is inserted into the internal alkyne group of enediyne **1j** to trigger aromatization. The proposed mechanism in Scheme 10 is consistent with our observations (see Schemes 6, 8, and 9), which preclude the involvement of cationic naphthyl species **A** (or **B**) and ruthenium−vinylidene intermediates. We propose that $TpRuPPh_3(CH_3CN)_2^+$ species, after the loss of a CH_3CN ligand, selectively binds to the more electron-rich internal alkyne (R = H, alkyl) of enediyne and gives ruthenium−π-alkyne species (I). This π-alkyne selectivity is attributed to the cationic ruthenium nature of species (I). A possible route involves the ligand exchange of nucleophiles with CH_3CN at the ruthenium center, followed by insertion of the Ru−NuH σ-bond of species (II) into the alkyne group to form vinylruthenium species (III). An intramolecular 6-endo-dig cyclization of species (III) gave naphthylruthenium intermediate (IV) and ultimately led to the observed aromatization products via protonation.

An alternative route involves a direct nucleophilic addition at species (I) to form vinylruthenium species (III), with ruthenium coordinated to a remaining alkynyl group (X = H, I). This pathway is applicable to pyrrole nucleophiles because they cannot undergo ligand exchange with ruthenium center since the pyrrole nitrogen is not a good ligating atom. The nucleophilic attack at ruthenium−di-π-alkyne species depicted in Scheme 2 (path iii) is unlikely to occur because the expected regiochemistry is not consistent with our observations.

The insertion process (I) → (II) → (III) is proposed on the basis of stoichiometric cyclization of enediyne **1j** using $TpRuPPh_3(CH_3CN)Cl$ complex (see Scheme 7), which apparently coordinates to the more electron-rich alkyne group (R = H, Me, Et) before delivery of the chloride ligand. According to the literature,[12] the structure of intermediate (II) is proposed to

(19) Et_3SiH will add to carbene intermediate via a Si−H bond insertion. See: (a) Alder, R. W. In *Carbene Chemistry*; Bertrand, G., Ed.; Marcel Dekker: New York, 2002; p 153. (b) Bertrand G. In *Carbene Chemistry*; Bertrand, G., Ed.; Marcel Dekker: New York, 2002; pp 177−203.

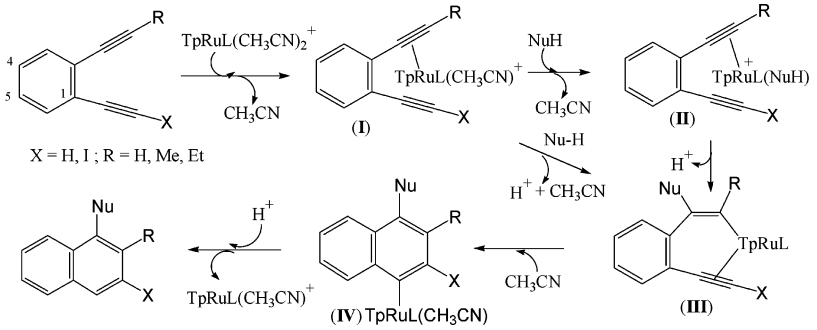
(20) Although our proposed mechanism suggests the feasibility of the catalytic addition of HCl to enediyne **1j**, the yield was only 15% using 10 mol % $TpRuPPh_3(CH_3CN)_2PF_6$ (3-pentanone, 100 °C, 72 h) and HCl (aq, 2.0 equiv). Under this condition, unreacted enediyne **1j** was only recovered in 15% with formation of a black heavy oil. This information suggests that this catalytic reaction is slower than the decomposition of enediynes **1j** by ruthenium catalyst alone.

(21) The exchange between D_2O and alkynyl proton can proceed via an alkynyl ruthenium hydride species, which was responsible for the ruthenium−π-alkyne and ruthenium−vinylidene equilibrium. See refs 12 and 16.

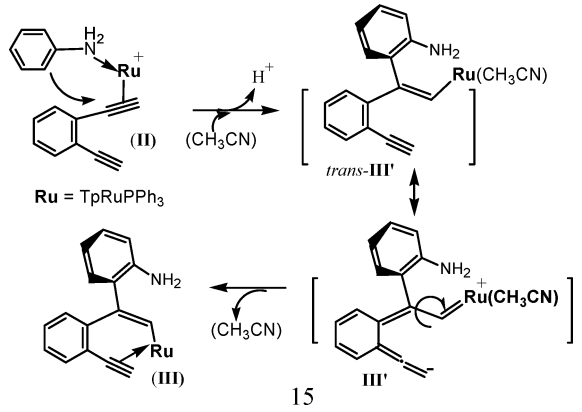
(22) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518.

(23) The ^{1}H NOE map of naphthalenes **11a** and **11b** is shown in the Supporting Information.

Scheme 10



Scheme 11



be a TpRuL(NuH)(π-alkyne)$^+$ cation rather than a neutral species, TpRuL(Nu)(π-alkyne). This insertion step also provides a good rationale for the aniline-addition regiochemistry, which gives *ortho*-C-aryl products B (Table 2), whereas the *para*-C-aryl products are not seen in most cases. The preference for *ortho*-C-aryl product is thought to arise from the intramolecular cyclization of species (II), depicted in Scheme 11. The resulting cis-insertion species *cis*-III′ can be transformed into the vinylruthenium π-alkyne III via isomerization of *cis*-vinylmetal to its *trans*-vinylmetal species.[24,25] The feasibility of this process is likely to occur by rotation of the σ-carbon−carbon bond of the resonance structure (**III′**).

In this catalytic reaction, enediyne **1l** bearing two internal alkynes (Scheme 4, entry 5) is not catalytically active in the ^{n}BuOH addition. We believe that this is caused by the congested environment of intermediate III, in which the two methyl groups exert steric hindrance with the bulkyl $TpRuPPh_3$ fragment. Such a hindrance inhibits the formation of intermediate III. The adverse effects of a long internal alkynyl on the aromatization have been observed in our results. For example, the endiyne bearing a R′ = ^{n}Pr group is inactive in the ^{n}BuOH addition, whereas its analogues R′ = H(**1a**), Me(**1b**), and Et (**1c**) show catalytic activities with product yields following the trend **1a** > **1b** > **1c**. Similarly, aniline and pyrrole addition reactions work only for enediynes **1a**, **1d**, and **1f** (Table 3), but not for those enediynes **1b**, **1c**, **1e**, and **1h** bearing an internal alkyne.[26]

Conclusions

In summary, we have reported a new nucleophilic aromatization of unstrained enediynes catalyzed by $TpRu(PPh_3)(CH_3CN)_2PF_6$ catalyst. The value of this cyclization is indicated by the regioselectivity of nucleophilic addition, which occurs only at the more electron-rich alkyne carbon. The cyclization is compatible with various mild nucleophiles including water, alcohols, aniline, pyrrole, ethyl acetylacetonate, and dimethyl malonate, which reflects nucleophilic C−X (X = O, N, C) bond formation. This method is very useful because it provides easy access to functionalized aromatic compounds from readily available unfunctionalized enediynes. We propose a nucleophilic addition/insertion mechanism[27] based on the results of a series of experiments, which preclude the involvement of ruthenium−vinylidene and cationic naphthyl species in the reaction mechanism. In the case of enediynes bearing a long alkyl substituent, we observed the aromatization of these enediynes accompanied by a C−H bond insertion, and the mechanism likely involves a naphthyl cation[18] according to the methoxy substituent effects. We will expand the scope of this C−H bond insertion and characterize its mechanism in future studies.

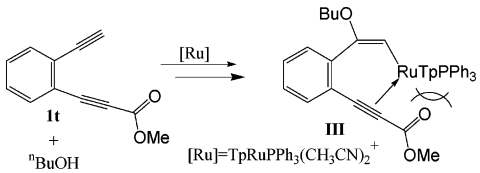
Experiment Section

(1) General Sections. Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere in oven-dried glassware using standard syringe, cannula, and septa apparatus. Benzene, diethyl ether, tetrahydrofuran, and hexane were dried with sodium benzophenone and distilled before use. $TpRuPPh_3(CH_3CN)_2PF_6$ (**1**) catalyst was prepared by heating $TpRu(PPh_3)_2Cl$ with $LiPF_6$ in CH_3CN.[12] Enediyne **1a** was prepared according to the literature procedure.[4b] Synthesis of representative enediynes is given in the Supporting Information.

(24) For a mechanistic study of the *cis*-vinylmetal and *trans*-vinylmetal isomerization reaction, see: Bodner, G. S.; Smith, D. E.; Hatton, W. G.; Heah, P. C.; Georgiou, S.; Reingold, A. L.; Geib, S. J.; Hutchinson, J. P.; Gladysz, J. A. *J. Am. Chem. Soc.* **1987**, *109*, 7688.

(25) For the trans-insertion of alkyne into metal−hydride and −chloride bonds, see: (a) Huggins, J. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 3002. (b) Vessey, J. D.; Mawby, R. J. *J. Chem. Soc., Dalton Trans.* **1993**, 51.

(26) Enediyne **1t** bearing a CO_2Me group is not active in the ^{n}BuOH addition. We envisage that this enediyne will give the intermediate **III** according to our proposed mechanism. We believe that the ester group of species **III** exerts steric hindrance with the $TpRuPPh_3$ fragment to destabilize this species in accordance with our proposal in the text. This observation strengthens our views about the steric effects of enediynes on the catalytic activity.



(27) As suggested by one reviewer, this nucleophilic aromatization should be effected by other π-alkyne activators such as $PtCl_2$ and $AuCl_3$ according to the propose mechanism. In the reaction of enediyne **1a** and **1b** with water/3-pentanone, $PtCl_2$ (10 mol %) gave 1-naphthnols **2a** and **2b** in 30 and 35% yields, respectively, whereas $AuCl_3$ was catalytically inactive. In the Pt case, water preferably attacks the propynyl C(1) carbon, following the same regiochemistry as ruthenium catalyst. The mild activity of $PtCl_2$ gives additional support for the proposed π-alkyne intermediate.

(2) Standard Procedure for Ruthenium-Catalyzed Aromatization of Enediynes by Water. To a 3-pentanone/water mixture (vol 1:1, 0.60 mL) of enediyne **1a** (100 mg, 0.79 mmol) was added $TpRuPPh_3(CH_3CN)_2PF_6$ (60 mg, 0.079 mmol), and the mixture was heated at 100 °C for 24 h. The solution was concentrated and eluted through a silica column (hexane/EA = 5:1) to give 1-naphthol **2a** (86 mg, 0.60 mmol, 75%) as a white solid.

(3) Standard Procedure for Ruthenium-Catalyzed Aromatization of Enediynes by Alcohols. To an isobutanol solution (0.60 mL, 6.48 mmol) of enediyne **1a** (100 mg, 0.79 mmol) was added $TpRuPPh_3(CH_3CN)_2PF_6$ (60 mg, 0.079 mmol), and the mixture was heated at 100 °C for 12 h. The solution was concentrated and eluted through a silica column (hexane) to give (1-isobutanoxy)naphthelene **2d** (128 mg, 0.64 mmol, 81%).

(4) Standard Procedure for Ruthenium-Catalyzed Aromatization of Enediynes by Anilines. To an aniline solution (0.50 mL, 5.48 mmol) of enediyne **1a** (100 mg, 0.79 mmol) was added $TpRuPPh_3(CH_3CN)_2PF_6$ (60 mg, 0.079 mmol), and the mixture was heated at 100 °C for 15 h. The solution was eluted through a short silica column with hexane to remove catalyst and excess aniline. The hexane eluent was concentrated and eluted through a silica column to give naphthalene **4aA** (73 mg, 0.33 mmol) and **4aB** (61 mg, 0.28 mmol) in 42 and 35% yields, respectively.

(5) Standard Procedure for Ruthenium-Catalyzed Aromatization of Enediynes Carbon-Centered Nucleophile. To an ethyl acetonate solution (0.5 mL, 3.94 mmol) of enediyne **1a** (100 mg, 0.79 mmol) was added $TpRuPPh_3(CH_3CN)_2PF_6$ (60 mg, 0.079 mmol), and the mixture was heated at 100 °C for 15 h. The solution was eluted through a short silica column with hexane to remove catalyst and excess ethyl acetonate. The hexane eluent was concentrated and eluted through a silica column to give naphthalene **5c** (126 mg, 0.49 mmol, 62%).

(6) Standard Procedure for Ruthenium-Catalyzed Cyclization via C−H Bond Insertion. To a toluene solution (0.60 mL) of enediyne **1i** (100 mg, 0.59 mmol) was added $TpRuPPh_3(CH_3CN)_2PF_6$ (45 mg, 0.059 mmol), and the mixture was heated at 100 °C for 15 h. The solution was concentrated and eluted through a short silica column with hexane to give cyclopentane derivative **6a** (35 mg, 0.21 mmol, 35%).

(7) Spectral Data for Naphthalen-1-ol (2a): IR (neat, cm^{-1}): 3300 (br, vs), 3066 (w), 1600 (m), 1085 (m); ^1H NMR (400 MHz, $CDCl_3$): δ ~8.18−8.15 (m, 1 H), ~7.82−7.79 (m, 1 H), ~7.49−7.42 (m, 3 H), 7.29 (t, 1 H, J = 8.0 Hz), 6.80 (d, 1 H, J = 8.0 Hz), 5.20 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 134.7, 127.6, 126.4, 125.8, 125.3, 124.3, 121.4, 120.7, 108.7; HRMS calcd. for $C_{10}H_8O$ 144.0575. Found 144.0585.

(8) Spectral Data for 1-Isobutoxynaphthalene (2d): IR (neat, cm^{-1}): 3056 (w), 1610 (w), 1582 (s), 1245 (s), 1130 (s); ^1H NMR (400 MHz, $CDCl_3$): δ ~8.34−8.31 (m, 1 H), ~7.82−7.79 (m, 1 H), ~7.52−7.45 (m, 2 H), ~7.43−7.35 (m, 2 H), 6.79 (d, 1 H, J = 7.2 Hz), 3.91 (d, 2 H, J = 6.4 Hz), ~2.31−2.21 (m, 1 H), 1.12 (d, 6 H, J = 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 134.5, 127.4, 126.3, 125.9, 125.8, 125.0, 122.1, 119.9, 104.5, 74.4, 28.4, 19.4; HRMS calcd. for $C_{14}H_{16}O$ 200.1201. Found 200.1205.

(9) Spectral Data for Naphthalen-1-yl-phenylamine (4a-A): IR (neat, cm^{-1}): 3411 (vs), 3022 (w), 1622 (w), 1308 (m); ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, 1 H, J = 8.8 Hz), 7.85 (d, 1 H, J = 8.8 Hz), 7.56 (d, 1 H, J = 7.6 Hz), ~7.51−7.44 (m, 2 H), ~7.43−7.35 (m, 2 H), 7.25 (t, 2 H, J = 7.6 Hz), 6.98 (d, 2 H, J = 7.6, Hz), 6.90 (t, 1 H, J = 7.6 Hz), 5.86 (br, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.7, 138.7, 134.7, 129.3 (×2), 128.5, 127.7, 126.1, 126.0, 125.7, 123.0, 121.8, 120.5, 117.4 (×2), 115.9; HRMS calcd. for $C_{16}H_{13}N$ 219.1048. Found 219.1040.

(10) Spectral Data for 2-Naphthalen-1-yl-phenylamine (4a-B): IR (neat, cm^{-1}): 3401 (vs), 3022 (w), 1628 (w), 1265 (m); ^1H NMR (600 MHz, $CDCl_3$): δ 7.82 (d, 1 H, J = 8.1 Hz), 7.81 (d, 1 H, J = 8.2 Hz), 7.57 (d, 1 H, J = 8.4 Hz), 7.47 (t, 1 H, J = 7.7 Hz), 7.42 (t, 1 H, J = 7.0 Hz), 7.37 (d, 1 H, J = 7.0 Hz), 7.34 (t, 1 H, J = 7.2 Hz), 7.18 (td, 1 H, J = 8.0, 1.5 Hz), 7.01 (dd, 1 H, J = 8.0, 1.5 Hz), 6.80 (td, 1 H, J = 6.8, 1.5 Hz), 6.75 (d, 1 H, J = 8.0 Hz), 3.38 (br, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.3, 136.9, 133.8, 131.6, 131.1, 128.7, 128.2, 127.9, 127.5, 126.2, 126.0, 125.9, 125.8, 125.7, 118.2, 115.2; HRMS calcd. for $C_{16}H_{13}N$ 219.1048. Found 219.1040.

(11) Spectral Data for 2-Naphthalen-1-yl-3-oxo-butyric Acid Ethyl Ester (5c): IR (neat, cm^{-1}): 3054 (w), 2982 (w), 1709 (s), 1637 (s), 1127 (s); ^1H NMR (400 MHz, $CDCl_3$): δ ~7.88−7.85 (m, 1 H), ~7.82−7.80 (m, 1 H), 7.72 (d, 1 H, J = 8.4 Hz), ~7.52−7.48 (m, 2 H), 7.44 (t, 1 H, J = 8.4 Hz), 7.13 (d, 1 H, J = 8.4 Hz), 4.78 (s, 1 H) 4.02 (q, 2 H, J = 6.8 Hz), 2.63 (s, 3 H), 1.14 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.6, 167.6, 149.1, 134.9, 128.0, 126.7 (×2), 126.5, 125.8, 125.7, 121.5, 117.9, 96.3, 59.5, 18.2, 14.2; HRMS calcd. for $C_{16}H_{16}O_3$ 256.1099. Found 256.1150.

(12) Spectral Data for 2,3-Dihydro-1*H*-cyclopenta[α]naphthalene (6a): IR (neat, cm^{-1}): 3028 (w), 2986 (w), 1717 (s), 1618 (w); ^1H NMR (400 MHz,$CDCl_3$): δ 7.86 (d, 1 H, J = 7.6 Hz), 7.81 (d, 1 H, J = 8.4 Hz), 7.69 (d, 1 H, J = 8.4 Hz), 7.50 (t, 1 H, J = 6.8 Hz), 7.43 (t, 2 H, J = 9.2 Hz), 3.27 (t, 2 H, J = 7.2 Hz), 3.13 (t, 2 H, J = 7.2 Hz), 2.31−2.25 (m, 2 H); ^{13}C NMR (150 MHz): δ 140.9, 139.4, 132.5, 130.4, 128.3, 126.6, 125.8, 124.6, 124.3, 123.3, 33.8, 31.0, 24.5; HRMS calcd. for $C_{13}H_{12}$ 168.0939. Found 168.0934.

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Supporting Information Available: Synthetic procedures for enediynes, NMR spectra, spectral data of compounds **1a**−**1r**, **2a**−**2o**, **3**, **4a(A)**−**4f(B)**, **5a**−**5p**, **6a**−**6c**, **7a**−**7c**, **8a**−**8c**, **9**, **10a**,**10b**, **11a**,**11b**, and ^1H NMR spectra of deuterium-labeled **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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