J|A|C|S
A R T I C L E S

Thermal and Metal-Catalyzed Cyclization of 1-Substituted 3,5-Dien-1-ynes via a [1,7]-Hydrogen Shift: Development of a Tandem Aldol Condensation−Dehydration and Aromatization Catalysis between 3-En-1-yn-5-al Units and Cyclic Ketones

Jian-Jou Lian, Chung-Chang Lin, Hsu-Kai Chang, Po-Chiang Chen, and
Rai-Shung Liu*

Contribution from the Department of Chemistry, National Tsing-Hua University, Hsinchu 30043, Taiwan, Republic of China

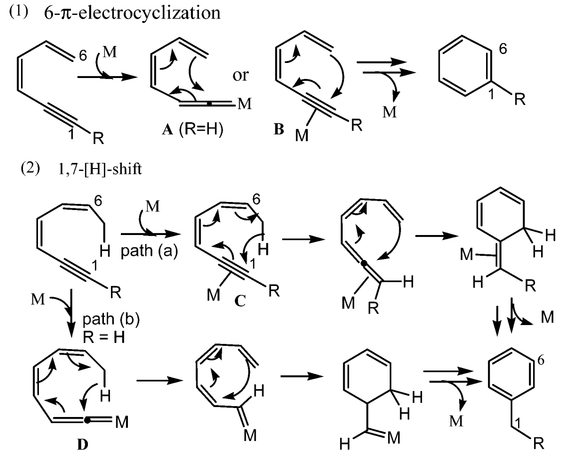
Received February 20, 2006; E-mail: rsliu@mx.nthu.edu.tw

Abstract: This work investigates the feasibility of thermal and catalytic cyclization of 6,6-disubstituted 3,5-dien-1-ynes via a 1,7-hydrogen shift. Our strategy began with an understanding of a structural correlation of 3,5-dien-1-ynes with their thermal cyclization efficiency. Thermal cyclization proceeded only with 3,5-dien-1-ynes bearing an electron-withdrawing C(1)-phenyl or C(6)-carbonyl substituent, but the efficiencies were generally low (20−40% yields). On the basis of this structure−activity relationship, we conclude that such a [1,7]-hydrogen shift is characterized by a "protonic" hydrogen shift, which should be catalyzed by π-alkyne activators. We prepared various 6,6-disubstituted 3,5-dien-1-ynes bearing either a phenyl or a carbonyl group, and we found their thermal cyclizations to be greatly enhanced by $RuCl_3$, $PtCl_2$, and $TpRuPPh_3(CH_3CN)_2PF_6$ catalysts to confirm our hypothesis: the C(7)−H acidity of 3,5-dien-1-ynes is crucial for thermal cyclization. To achieve the atom economy, we have developed a tandem aldol condensation−dehydration and aromatization catalysis between cycloalkanones and special 3-en-1-yn-5-als using the weakly acidic catalyst $CpRu(PPh_3)_2Cl$, which provided complex 1-indanones and α-tetralones with yields exceeding 65% in most cases. The deuterium-labeling experiments reveal two operable pathways for the metal-catalyzed [1,7]-hydrogen shift of 3,5-dien-1-ynes. Formation of α-tetralones *d*$_4$-**56** arises from a concerted [1,7]-hydrogen shift, whereas benzene derivative *d*$_4$-**9** proceeds through a proton dissociation and reprotonation process.

Introduction

Thermal cyclization of 3,5-dien-1-ynes to benzene derivatives normally proceeds above 200 °C, and this reaction has attracted considerable theoretical and experimental interest.[1] In the presence of suitable metal catalysts, cyclization of 3,5-dien-1-ynes occurs under mild conditions via exclusive formation of either a metal-vinylidene (**A**)[2,3] or a π-alkyne intermediate (**B**)[4] as depicted in Scheme 1. There is no report of metal-catalyzed aromatization of 3,5-dien-1-ynes via other mechanisms in the literature.[5] Here, we report a new metal-catalyzed cyclization of 3,5-dien-1-ynes via a [1,7]-hydrogen shift of π-alkyne intermediate **C** (path a, eq 2).

Scheme 1



---

[1] Thermal cyclization and theoretical calculations of 3,5-dien-1-ynes, see: (a) Zimmermann, G. *Eur. J. Org. Chem.* **2004**, 457 (a review). (b) Litovitz, A. E.; Carpenter, B. K.; Hopf, H. *Org. Lett.* **2005**, *7*, 507. (c) Christl, M.; Braun, H.; Muller, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 473. (d) Hopf, H.; Berger, H.; Zimmerman, G.; Nuchter, U.; Jones, P. G.; Dix, I. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1187. (e) Bettinger, H. F.; Schreiner, P. R.; Schaefer, H. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1998**, *120*, 5741.

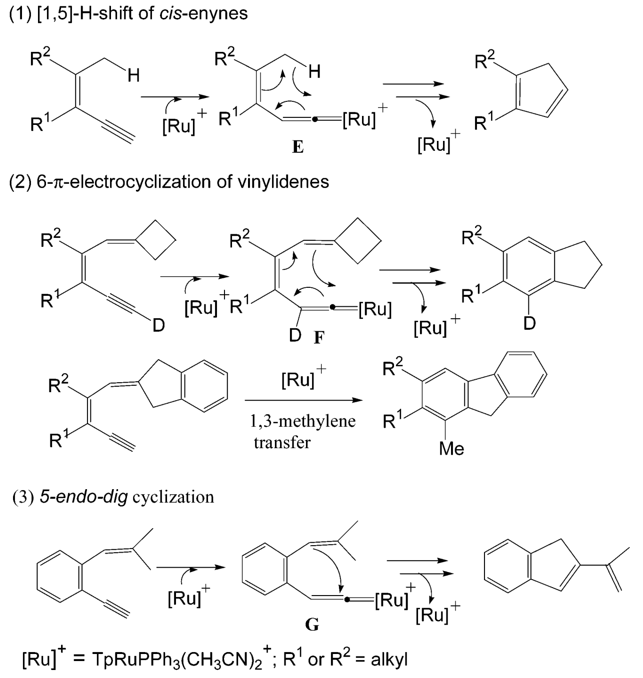
[2] Review for metal-vinyldene catalysis, see: (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (b) Bruneau, C.; Dixneuf, P. *Acc. Chem. Res.* **1999**, *32*, 311. (c) Puerta, M. C.; Valerga, P. *Coord. Chem. Rev.* **1999**, *193*−*195*, 977. (d) Bruneau, C. *Top. Organomet. Chem.* **2004**, *11*, 125.

[3] For catalytic aromatization of 3,5-dien-1-ynes via metal-vinylidene intermediates, see selected examples: (a) Merlic, C. A.; Pauly, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 11319. (b) Maeyama, K.; Iwasawa, N. *J. Org. Chem.* **1999**, *64*, 1344. (c) Iwasawa, N.; Shido, M.; Kusawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 5815. (d) O'Connor, J. M.; Friese, S. J.; Tichenor, M. *J. Am. Chem. Soc.* **2002**, *124*, 3506. (e) Martin-Matute, B.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757. (f) Shen, H.-C.; Pal, S.; Lian, J.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 15762.

[4] For catalytic aromatization of 3,5-dien-1-ynes via metal-π-alkyne intermediates, see: (a) Mamane, V.; Hannen, P.; Fürstner, A. *Chem.-Eur. J.* **2004**, *10*, 4556 and references therein. (b) Dankwardt, J. W. *Tetrahedron Lett.* **2001**, *42*, 5809.

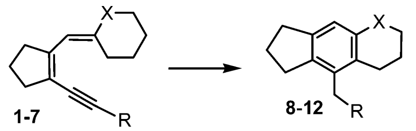
10.1021/ja061203b CCC: $33.50 © 2006 American Chemical Society

Scheme 2



Recently, we reported[6] a catalytic cyclization of *cis*-3-en-1-ynes using $TpRuPPh_3(CH_3CN)_2PF_6$ catalyst, and this process actually mimics the thermal [1,5]-hydrogen shift of *cis*-1-allen-4-enes because the terminal alkyne of substrate was transformed into ruthenium-vinylidene species **E** (eq 1, Scheme 2). We thought that this catalytic process was extensible to the aromatization of 6,6-disubstituted 3,5-dien-1-yne through an analogous [1,7]-hydrogen shift as represented by intermediate **D** (path **b**, eq 2, Scheme 1); instead, we observed a competitive 6-π-electrocyclization of intermediate **F** to give highly structurally reorganized products with two selected instances shown in Scheme 2 (eq 2). The mechanism was supported by deuterium-labeling experiments.[7] We applied this catalytic cyclization to 2′,2′-disubstituted *o*-(ethynyl)styrenes, but the ruthenium-vinylidene intermediate **G** underwent 5-*endo-dig* cyclization to give indene products with a considerable skeletal rearrangement (eq 3).[8] After unsuccessful efforts with metal-vinylidene approaches, we seek an alternative solution using π-alkyne activators, which ultimately lead to aromatization of 3,5-dien-1-ynes via a [1,7]-hydrogen shift.

Table 1. Cyclization of 1-Substituted 3,5-Dien-1-ynes by a Thermal and Ruthenium-Catalyzed Process ([TpRu] = $TpRuPPh_3(CH_3CN)_2PF_6$)



1-7 → **8-12**

dienynes	products	thermal[a] time (yields)[c]	catalyst[b] time (yields)[c]	
X = CH_2			$RuCl_3$	[TpRu]
(1) R = TMS (**1**)		72 h (N.R.[d])	dec.[e]	dec.[e]
(2) R = ^{n}Pr (**2**)		72 h (N.R.[d])	dec.[e]	dec.[e]
(3) R = Ph (**3**)	**8**	48 h (26%)	24 h (71%)	24 h (75%)
X = $(CH_2)_0$				
(4) R = Ph (**4**)	**9**	36 h (31%)	24 h (78%)	24 h (83%)
X = CO				
(5) R = TMS (**5**)	**10**	36 h (58%)	12 h (92%)	12 h (86%)
(6) R = ^{n}Pr (**6**)	**11**	72 h (12%)	dec.[e]	30 h (74%)
(7) R = Ph (**7**)	**12**	72 h (33%)	18 h (81%)	18 h (61%)

[a] Xylene, 120 °C, [substrate] = 0.5 M. [b] 5 mol % catalyst, [substrate] = 0.5 M, xylene, 120 °C. [c] Yields are given after separation from a silica column. [d] Starting **1** and **2** were recovered in 58% and 62% yields, respectively. [e] No starting substrates were recovered with the same reaction period as the thermal process.

Results and Discussion

Structure−Activity Correlation in the [1,7]-Hydrogen Shift. Although a [1,7]-hydrogen shift is well documented for 1-substituted 1,3,5-trienes,[9] little is known about the thermal cyclization of 3,5-dien-1-ynes via a 1,7-hydrogen shift.[10] To the best of our knowledge, such a process was proposed only as a possible route for flash vacuum pyrolysis (500 °C) of 2-methylstyrylalkynes to 2-alkenylnaphthalenes,[10] and acid-catalyzed thermal cyclization of acetylenic enones to benzene products (200−250 °C).[11] Both reactions proceeded sluggishly at elevated temperatures.[10,11] We first investigated the thermal feasibility of this process, with an emphasis on the structural correlation of substrates with their thermal activities. Table 1 summarizes the results for thermal cyclization (xylene, 120 °C, 36−72 h) of model molecules **1**−**7** via alternation of their C(1)-alkynyl and C(6)-alkenyl substituents; species **5**−**7** have *E*-configuration. Entries 1−3 show the C(1)-phenyl effect of 3,5-dien-1-yne **3**, which was the only active species in thermal cyclization. The C(6)-carbonyl groups of dienynes **5**−**7** also show a significant improvement in both thermal and catalytic cyclizations as compared to their cycloalkyl analogues **1**−**4**. These results indicate the importance of the C(7)−H acidity of 3,5-dien-1-ynes, which is crucial for both thermal and catalytic cyclization. Accordingly, we selected electrophilic π-alkyne

---

(5) Very recently, O'Connor and co-workers reported an unusual aromatization of 3,5-dien-1-ynes via a η^6-coordinated mode in a stoichiometric reaction. See: O'Connor, J. M.; Friese, S. J.; Rodgers, B. L.; Rheingold, A. L.; Zakharov, L. *J. Am. Chem. Soc.* **2005**, *127*, 9346.

(6) Datta, S.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 11606.

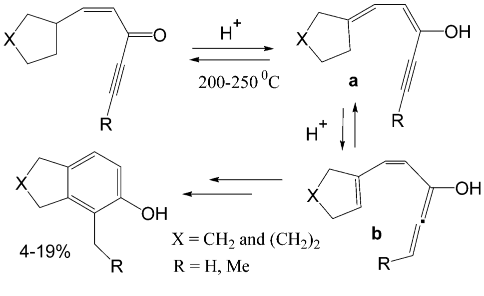
(7) Lian, J.-J.; Odedra, A.; Wu, C.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 4186.

(8) Madhushaw, R. J.; Lo, C.-Y.; Su, M.-D.; Shen, H.-C.; Pal, S.; Shaikh, I. R.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 15560.

(9) Selected examples for a thermal 1,7-hydrogen shift of 1,3,5-trienes: (a) Hess, B. A., Jr. *J. Org. Chem.* **2001**, *66*, 5897. (b) Baldwin, J. E.; Reddy, V. P. *J. Am. Chem. Soc.* **1987**, *109*, 8051. (c) Okamura, W. H.; Hoeger, K. J.; Miller, K. J.; Reischl, W. *J. Am. Chem. Soc.* **1988**, *110*, 973. (d) Steuhl, H.-M.; Bornemann, C.; Klessinger, M. *Chem.-Eur. J.* **1999**, *5*, 2404.

(10) Aitken, R. A.; Boeters, C.; Morrison, J. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2625.

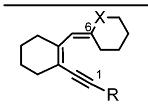
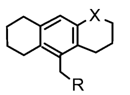
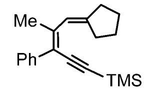
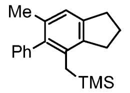
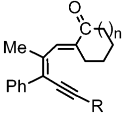
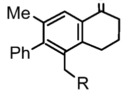
(11) Collindine *p*-toluenesulfonate (CPTS) was attempted to catalyze the cyclization of acetylenic enones to benzene products, but the efficiencies were very low (4−19%) under drastic temperatures of 200−250 °C. This cyclization is thought to proceed via initial formation of 3,5-dien-1-ynes (a) by tautomerization, followed by a second acid-catalyzed rearrangement to 3,5-diene-1-allene. The low yields of products were attributed to the kinetically instability of enol intermediates a,b caused by enol−ketone tautomerization. See: Jacobi, P. A.; Kravitz, J. I. *Tetrahedron Lett.* **1988**, *29*, 6873.



activators[12−14] to enhance their C(7)−H acidity and aromatization efficiencies. Among substrates **1**−**7**, thermal cyclization performs most efficiently with compound **5** bearing a trimethylsilyl (TMS) and a carbonyl group at its C(1)- and C(6)-carbons, respectively. The yield of benzene derivative **10** was 58% (entry 5), but was increased significantly using RuCl$_3$[15] (92%) and TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$[16] (89%) at 5 mol % catalyst loading. The retention of the trimethysilyl functionality of benzene derivative **10** precludes the participation of proton in the catalytic transformation. In entry 5, PtCl$_2$[12] gave benzene **10** (xylene/DMF = 2/1, 120 °C, 16 h) equally efficiently with 86% yield but at a 10% loading; AuCl$_3$ (5 mol %)[13] produced the desilylated derivative of benzene **10** in 78% yield (DMF, 120 °C, 18 h). Although thermal cyclization of internal alkynes **3**, **4**, **6**, and **7** proceeded unsatisfactorily (12−33%), their efficiencies can be significantly improved with RuCl$_3$[15] and TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$,[16] which gave desired benzenes **8**, **9**, **11**, and **12** with yields up to 75−92%. The molecular structure of benzene **10** was confirmed by ^{1}H NOE spectra.

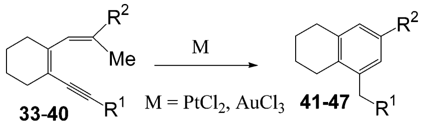
The Scope of a Catalytic [1,7]-Hydrogen Shift. To test our hypothesis that the cyclization efficiency is determined by the C(7)−H acidity of substrates, we prepared additional 3,5-dien-1-ynes **13**−**22** in Table 2, which contained exclusively either a C(1)-phenyl or C(6)-carbonyl substituent. Similar to the preceding examples, 3,5-dien-1-ynes **16** and **22** are more active than other substrates in thermal cyclization because of their activating C(1)-TMS and C(6)-carbonyl groups. Again, we observed an obvious enhancement of cyclization using RuCl$_3$ and TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$ catalysts (5 mol %) when substrates **13**, **14**, and **18** performed inefficiently in the thermal process. The resulting products **23**, **24**, and **28** were obtained in 26−42% yields in hot xylene, but were greatly increased to 81−91% using either RuCl$_3$ or TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$ (entries 1, 2, and 6). For the remaining substrates **15**−**17** and **19**−**22** bearing a cycloketone group, the two ruthenium species showed a similar catalytic improvement, and gave the observed benzenes **25**−**27** and **29**−**32** with yields up to 77−93%, much higher than their thermal yields (entries 3−5, 7−10) in most instances. Although the structure−activity relationship follows the same trend as in Table 1, we notice that dienynes **4**, **13**, and **19** bearing a five-membered carbocyclic ring performed better in catalytic aromatization than did their six-membered analogues **3**, **14**, and **20**.

Table 2. Cyclization of Various 3,5-Dien-1-ynes by a Thermal and Ruthenium-Catalyzed Process ([TpRu] = TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$)

dienynes	products	thermal[a]	RuCl$_3$	[TpRu][b]	time[c]
					
(1) R = Ph, X = (CH$_2$)$_0$ (**13**)	**23**	24 h (42%)[d]	83%	91%	13h
(2) R = Ph, X = (CH$_2$) (**14**)	**24**	48 h (26%)	55%	81%	24 h
(3) R = Ph, X = CO (**15**)	**25**	16 h (46%)	82%	70%	9 h
(4) R = TMS, X = CO (**16**)	**26**	12 h (74%)	90%	91%	7 h
(5) R = ^{n}Pr, X = CO (**17**)	**27**	24 h (47%)	88%	93%	13 h
					
(6) **18**	**28**	10 h (30%)	87%	73%	2 h
					
(7) R = ^{n}Bu, n = 0 (**19**)	**29**	6 h (51%)	77%	70%	4 h
(8) R = ^{n}Bu, n = 1 (**20**)	**30**	24 h (41%)	78%	67%	16 h
(9) R = Ph, n = 1 (**21**)	**31**	24 h (47%)	82%	70%	13 h
(10) R = TMS, n = 1 (**22**)	**32**	5 h (61%)	81%	86%	3 h

[a] Xylene, 120 °C, [substrate] = 0.5 M. [b] 5 mol % catalyst, [substrate] = 0.5 M, xylene, 120 °C. [c] Reaction time for RuCl$_3$ (5%) and TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$ (5%). [d] Yields were given after separation from a silica column.

Table 3. Thermal and Catalyzed Cyclization of 3,5-Dien-1-ynes Bearing Acyclic Substituents



33-40 **41-47**

dienynes	products	thermal[a]	AuCl$_3$[b]	PtCl$_2$[c]
(1) R^1 = ^{n}Bu, R^2 = CO$_2$Et (**33**)		N.R.	N.R.	N.R.
(2) R^1 = ^{n}Bu, R^2 = COPh (**34**)	**41**	26%	68%	66%[d]
(3) R^1 = Ph, R^2 = CO$_2$Et (**35**)	**42**	30%	74%	61%
(4) R^1 = Ph, R^2 = COPh (**36**)	**43**	37%	76%	80%
(5) R^1 = H, R^2 = CO$_2$Et (**37**)	**44**	41%	88%	78%
(6) R^1 = H, R^2 = COPh (**38**)	**45**	45%	89%	82%
(7) R^1 = TMS, R^2 = CO$_2$Et (**39**)	**46**	27%	d.s.[e]	76%
(8) R^1 = TMS, R^2 = COPh (**40**)	**47**	25%	d.s.	71%

[a] [substrates] = 0.5 M, DMF, 140 °C, 72 h. [b] 5 mol % AuCl$_3$, [substrate] = 0.5 M, DMF, 24−32 h, 140 °C. [c] 10 mol % PtCl$_2$, [substrate] = 0.5 M, 140 °C, 30−36 h. [d] Product yields are reported after separation from a silica column. [e] Desilylation occurred with formation of products **44** and **45** in 80% and 81% yields, respectively.

We further extended this catalytic cyclization to 3,5-dien-1-ynes **33**−**40** bearing two acyclic substituents (Table 3); their cyclizations require higher temperature (140 °C) probably due to the conformational flexibility of acyclic substituents. AuCl$_3$[16] (5 mol %, DMF, 18−30 h) and PtCl$_2$ (10 mol %, DMF/xylene = 1, 24−46 h) are far superior to RuCl$_3$ and TpRuPPh$_3$(CH$_3$CN)$_2$PF, which gave approximately the same yields as those in thermal activation. DMF solvent serves to prevent AuCl$_3$ from a rapid formation of a gold mirror as observed in hot 1,2-

---

(12) Selected reviews for π-alkyne activators including various platinum and gold catalysts: (a) Hashimi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990. (b) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (c) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200.

(13) For recent catalytic reactions, using PtCl$_2$ salts as π-alkyne activators, see: (a) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244. (b) Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536. (c) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (d) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901. (e) Mendez, M.; Munoz, M. P.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511. (f) Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Chem.-Eur. J.* **2003**, *9*, 2627. (g) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. (h) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (i) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509.

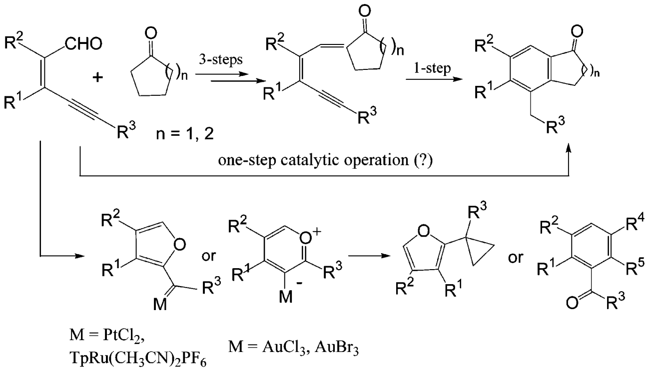
(14) For recent catalytic reactions using Au(I) and Au(III) as π-alkyne activators, see selected examples: (a) Kennedy-Smith, J. J.; Staben, S.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (b) Gorin, D. J.; Davies, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (c) Nieto-Oberhuber, C.; Munoz, M. P.; Bunuel, E.; Nevedo, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. (d) Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178. (e) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. (f) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (g) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180. (h) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596.

(15) We selected RuCl$_3$ as an activator because it was reported to be the best catalyst in the literature for aldol condensation and dehydration between aldehydes and cycloalkanones, see: Iranpoor, N.; Kazemi, F. *Tetrahedron* **1998**, *54*, 9475.

dichloroethane, toluene, and xylene, which gave products in a messy mixture.[17,18] AuCl$_3$ and PtCl$_2$ efficiently catalyzed cyclization of dienynes **34**−**40** bearing a C(6)-carbonyl substituent and gave good yields (68−89%) of benzene products **41**−**47** even though their thermal yields were generally low (25−45%). Notably, species **33** bearing a C(6)-ester substituent is totally inactive; this observation emphasizes the importance of a functional group (R^1 = TMS, H, and Ph) at the C(1)-carbon as in species **35**, **37**, and **39**. A drawback in the AuCl$_3$-catalyzed reaction is the occurrence of desilylation as shown in entries 7 and 8; this reaction is caused probably by partial hydrolysis of AuCl$_3$ with residual water to generate a small amount of HCl, which catalyzed the cleavage of the reactive C−Si bond of benzenes **46** and **47**. To understand the role of HCl, in separate experiments, we heated 3,5-dien-1-yne **36** and **39** with HCl (10 mol %) that led to a serious polymerization.[19]

Development of Tandem Catalytic Aldol Condensation−Dehydration and Aromatization Reactions. In this study, the synthesis of final 1-indanones and α-tetralones requires four-step operations beginning with 3-en-1-yn-5-als and cycloalkanones; three-step operations served to prepare 3,5-dien-1-yn-7-ones through enol silane formation, Mukaiyama aldol condensation, and a dehydration protocol[20] (Scheme 3). To achieve an atom economy, development of a tandem aldol condensation−dehydration and aromatization catalysis between 3,5-dien-1-als and certain ketones is highly desired, but this approach seems formidable because of an eminent problem: electrophilic π-alkyne activators such as AuCl$_3$,[18b,c] PtCl$_2$,[21] and TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$[16c] were reported be very active in self-cyclization of 3-en-1-yn-5-als to form undesired benzo[*c*]-pyrylium or 2-(furyl)carbenoid species (Scheme 3), which were catalytic intermediates for syntheses of special aromatic and furyl derivatives. To accomplish this process, we focused on 3-en-1-yn-5-als bearing a C(1)-TMS group because their resulting 3,5-dien-1-yn-7-ones gave thermal cyclization in moderate yields (ca. 50−60%), which could be equally improved by weak π-alkyne activators. Furthermore, weakly acidic catalysts are expected to be less active in the self-cyclization of 3-en-1-yn-5-al, but more active in aldol condensation.[22−25]

Scheme 3



Although catalytic aldol reaction and its subsequent dehydration have attracted considerable attention,[22,23] many studies focused on Mukaiyama aldol−dehydration reactions using enol ethers.[21] RuCl$_3$ was reported to be the most active catalyst using starting cycloketones,[15] but it only gave moderate yields of benzene products in our targeted tandem reactions because of its strong acidity to induce side reactions as described in Scheme 4 (eq 2). Similarly, other strong π-alkyne activators including PtCl$_2$, AuCl, AuCl$_3$, and TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$ gave a complicated mixture of products. On screening weakly acidic ruthenium catalysts[24] (5 mol %) including RuCl$_2$(PPh$_3$)$_3$, H$_2$-Ru(CO)(PPh$_3$)$_3$, [RuCl$_2$(p-cymene)]$_2$, CpRu(PPh$_3$)$_2$Cl, and TpRu-(PPh$_3$)$_2$Cl, we found that the only active CpRu(PPh$_3$)$_2$Cl shows greater efficiency than RuCl$_3$ in the aldol condensation−dehydration as depicted in a test in Scheme 4 (eq 1). In the cyclization of 3-en-1-yn-5-al **49** with cyclohexanone (5 equiv, eq 2), we found that the two ruthenium species not only catalyzed the aldol reaction−dehydration sequence, but also the subsequent aromatization with CpRu(PPh$_3$)$_2$Cl (78%) being more efficient than RuCl$_3$ (48%) in production of α-tetralone **10**. The thermal cyclization of unsaturated ketone **5** into α-tetralone **10** proceeds with 58% yield (Table 1, entry 5), less than the tandem reaction yield (78%) using the CpRu(PPh$_3$)$_2$Cl catalyst; this result is indicative of its catalytic activity in the final aromatization reaction. Actually, treatment of ketone **5** with CpRu(PPh$_3$)$_2$Cl (5 mol %) in hot xylene (120 °C, 12 h) gave α-tetralone **10** in 89% yield. Equation 3 shows a one-step CpRu-

---

(16) TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$ is active in catalytic reactions via generation of not only ruthenium-π-alkyne intermediates[15a−c] but also ruthenium-vinylidene species;[6−8] see examples for the former case: (a) Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 3406. (b) Lin, M.-Y.; Maddirala, S. J.; Liu, R.-S. *Org. Lett.* **2005**, *7*, 1745. (c) Shen, H.-C.; Liu, R.-S. *Tetrahedron Lett.* **2004**, *45*, 9245. (d) Yeh, K.-L.; Liu, B.; Lo, C.-Y.; Liu, R.-S. *J. Am. Chem. Soc.* **2002**, *124*, 6510. (e) Datta, S.; Chang, C.-L.; Yeh, K.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 9294. (f) Madhushaw, R. J.; Lin, M.-Y.; Abu Sohel, S. M.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 6895.

(17) In Table 3, when AuCl$_3$ catalyst was heated with 3,5-dien-1-ynes in dry toluene, benzene, and 1,2-dichloroethane at 100 °C, a gold mirror was gradually deposited from solution after several hours, and no catalytic activity was observed in these solvents. The resulting solution was black because polymerization of substrates occurred, presumably caused by HCl during formation of gold mirror. We found that DMF seemed to stabilize gold complexes, so that the metallic gold mirror formed more slowly even at 140 °C; this dark brown DMF solution showed a cyclization activity. Laguna[17a] reported that Au(III) complexes are stabilized by acid to avoid decomposition to Au(0) in catalytic hydration of terminal alkyne with water or alcohol. We believed that residual water in DMF reacted with AuCl$_3$ to give HCl in small amount, which might stabilize Au(III) species in the course of catalytic reactions.

(18) We noticed that several catalytic reactions were performed at high temperatures[4b,13h,17] using AuX$_3$ (X = Cl, Br) and other Au(I) complexes; see selected examples: (a) Casado, R.; Contel, M.; Laguna, M.; Romero, P.; Sanz, S. *J. Am. Chem. Soc.* **2003**, *125*, 11925. (b) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650. (c) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458. (d) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563. (e) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729.

(19) In these experiments, 3,5-dien-1-yne **36** and **39** (0.42 M) were heated with concentrated HCl (10 mol %) in hot xylene (140 °C, 24 h) to give a black solution of a complicated mixture of products in addition to polymer formation, from which the desired benzene derivative **43** and desilylated benzene product **44** were isolated in only 15% and 7% yields, respectively. These data, however, cannot exclude the possibility of using a proton source to catalyze this [1,7]-hydrogen shift.

(20) The procedure for the synthesis of 3,5-dien-1-yn-7-one **5** using 3-en-1-yn-5-al and cyclohexanone is provided in the Supporting Information.

(21) Miki, K.; Nishino, F.; Ohe, K.; Uemura. *J. Am. Chem. Soc.* **2002**, *124*, 5260.

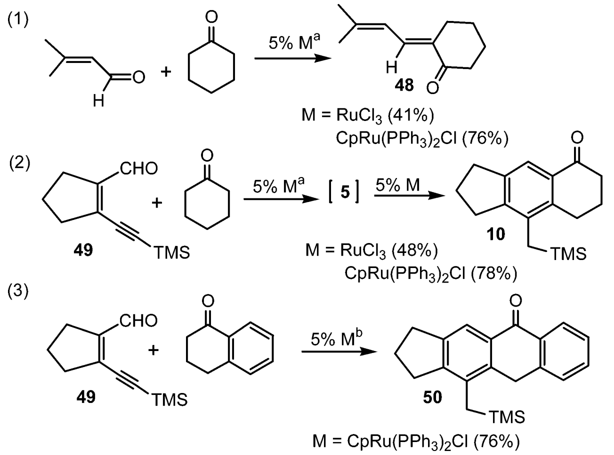
(22) For the catalytic Mukaiyama aldol−dehydration sequence, see selected examples: (a) Yanagisawa, A.; Coudu, R.; Arai, T. *Org. Lett.* **2004**, *6*, 4281. (b) Ishihara, K.; Kurihara, H.; Yamamoto, H. S. *Synlett* **1997**, 597.

(23) (a) Wang, W.; Mei, Y.; Hao, L.; Wang, J. *Org. Lett.* **2005**, *7*, 601. (b) Kreher, U. P.; Rosamilia, A. E.; Raston, C. L.; Scott, J. L.; Strauss, C. R. *Org. Lett.* **2003**, *5*, 3107. (c) Abelló, S.; Medina, F.; Rodríguez, X.; Cesteros, Y.; Salagre, P.; Sueiras, J. E.; Tichit, D.; Coq, B. *Chem. Commun.* **2004**, 1096.

(24) Formation of a metal enolate requires a base, whereas an acid favors dehydration of the aldol product. We envisage that CpRu(PPh$_3$)$_2$Cl undergoes dissociation in solution to form CpRu(PPh$_3$)Cl and free PPh$_3$, which are actually Lewis acid and base, respectively. We use this guideline to screen weakly acidic ruthenium catalysts containing a phosphine ligand. A catalyst with an acid−base pair is reported to be very active in the aldol reaction−dehydration sequence; see the examples in refs 26a−c.

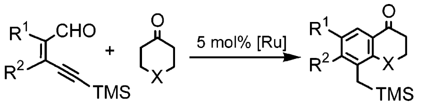
(25) The X-ray crystallographic data of anthrone **50** are provided in the Supporting Information.

Scheme 4 [a]



[a] Conditions: (a) cyclohexanone (5.0 equiv), aldehyde (1.0 equiv), neat, 120 °C, 16 h; (b) tetralone (2.0 equiv), aldehyde (1.0 equiv, 0.5 M), xylene, 120 °C, 96 h.

Table 4. Ruthenium-Catalyzed Cyclization of 3-En-1-yn-5-als with Cyclic Ketones



aldehyde	ketone[a,b]	products (yields)[c]
(1) $R^1 = R^2 = -(CH_2)_3-$ (**49**)	$X = (CH_2)_0$	**53** (72%)
(2) **49**	X = CHMe	**54** (68%)
(3) **49**	X = CH(ᵗBu)	**55** (65%)
(4) **49**	X = CO	**56** (38%)
(5) $R^1 = R^2 = -(CH_2)_4-$ (**51**)	$X = (CH_2)_0$	**57** (78%)
(6) **51**	$X = CH_2$	**16** (72%)
(7) **51**	X = CHMe	**58** (68%)
(8) R^1 = Me, R^2 = Ph (**52**)	$X = (CH_2)_0$	**59** (75%)
(9) **52**	$X = CH_2$	**31** (82%)
(10) **52**	X = CHMe	**60** (72%)

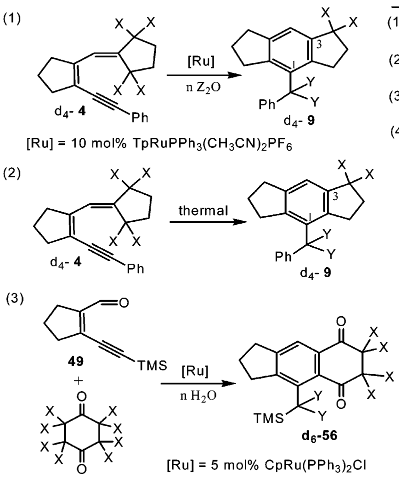
[a] [Ru] = $CpRu(PPh_3)_2Cl$, conditions for entries 1, 2, and 5−10: aldehyde (1 equiv), ketone (5 equiv), neat, 120 °C, 16 h for entries 1 and 2, 24 h for entries 5−10. [b] For entries 3 and 4, aldehyde (1 equiv), ketone (2 equiv, 0.60 M), xylene, 140 °C, 36 h for entry 3 and 96 h for entry 4. [c] Yields are given after separation from a silica column.

$(PPh_3)_2Cl$-catalyzed synthesis of complex anthrone **50** (76% yield) according to our tandem catalytic protocol; its molecular structure has been characterized by X-ray diffraction study.[25]

Table 4 shows the generalization of this tandem process through annulation of 3-en-1-yn-5-als **49**, **51**, and **52** with various cycloketones using $CpRu(PPh_3)_2Cl$ (5 mol %) catalyst. Entries 1−3 provide additional examples for aldehyde **49**, which reacted smoothly with cyclopentanone, 4-methylcyclohexanone, and 4-(*tert*-butyl)cyclohexanone to give cyclized ketone products **53**−**55** in 65−72% yields. Its reaction with 1,4-cyclohexanedione was less efficient, giving the corresponding benzene **56** in 38% yield (entry 4). The same cyclizations also worked satisfactorily for 3-en-1-yn-5-al **51** bearing a cyclohexyl ring, which provided cyclized products **57**, **16**, and **58** in 68−78% yields following the same protocol (entries 5−7). Acyclic 3-en-1-yn-5-als **52** maintained the same catalytic efficiency and produced cyclized benzenes **59**, **31**, and **60** with yields exceeding 72% (entries 8−10).

Mechanism of the Thermal and Catalytic [1,7]-Hydrogen Shift. Scheme 5 (eq 1) depicts our deuterium-labeling results

Scheme 5

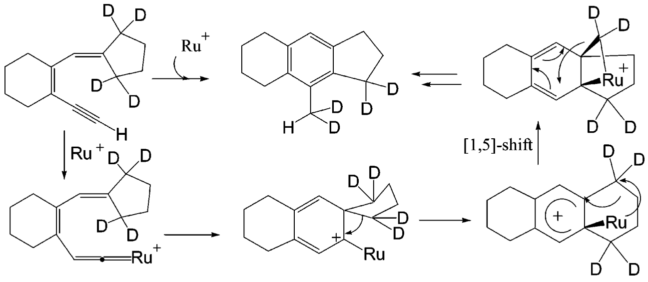


d_4-**4**	n Z_2O	d_4-9
(1) X = 0.94 D	n = 0	X = 0.94 D Y = 0.73 D
(2) X = 0.94 D	n = 1 Z = D	X = 0.94 D Y = 0.87 D
(3) X = 0.94 D	n = 1 Z = H	X = 0.94 D Y = 0.60 D
(4) X = 0.94 D	n = 5 Z = H	X = 0.94 D Y = 0.50 D

d_4-**4**	n H_2O	d_4-9
(1) X = 0.96 D	n = 0	X = 0.96 D Y = 0.91 D
(2 X = 0.96 D	n = 1	Y = 0.91 D

d_8-ketone	n H_2O	d_6-56
(1) X = 0.94 D	n = 0	X = 0.94 D Y = 0.93 D
(2) X = 0.94 D	n = 5	X = 0.94 D Y = 0.91 D

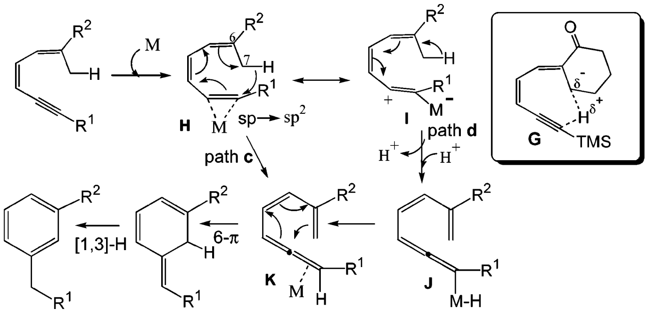
Scheme 6



to elucidate the mechanism of the 1,7-hydrogen shift catalyzed by $TpRuPPh_3(CH_3CN)_2PF_6$. We prepared deuterated d_4-**4** containing 94% deuterium contents at the two allylic methylene protons; this species was catalytically transformed into benzene d_4-**9** with deuterium contents located at the two methylene carbons (X = 0.94 D; Y = 0.73 D) adjacent to the C(3)- and C(1)-carbons, respectively. The loss of 20% deuterium at the CY_2 group of species d_4-**9** is attributed to the proton exchange with residual water during the cyclization process. Because of the isotope effect, a longer period (xylene, 120 °C, 48 h) is required to complete this catalytic reaction relative to its undeuterated d_0-**4** (24 h). For species d_4-**9**, its benzyl CY_2 deuterium content was increased to 87% (Y = 0.87 D) in the presence of D_2O (1.0 equiv), but was decreased to 60% in the case of H_2O (1.0 equiv). The CY_2 deuterium value remained at 50% for a large excess of H_2O (5.0 equiv). In the absence of catalyst, we did not observe a loss of deuterium content at the CY_2 of species d_4-**9** in thermal activation, even though water was present. In the ruthenium-catalyzed transformation depicted in eq 3, the methylene CX_2 proton of d_6-**56** was unaffected by the presence of H_2O or D_2O in various proportions, indicative of a direct [1,7]-hydrogen shift. We observed negligible loss of the benzyl deuterium contents of d_6-**56** upon heating the 3-en-1-yn-5-al **49** with d_8-1,4-cyclohexanedione in the presence of $CpRu(PPh_3)_2Cl$. This benzyl deuterium content remained the same even though excess water (5 equiv) was present.

The labeling experiment shown in Scheme 5 has deuterium distributions that are different from those observed in ruthenium-catalyzed cyclization of 3,5-dien-1-yne bearing a terminal alkyne as depicted in Scheme 6. In the latter case, the two benzylic protons of the product arise primarily from the remote allylic

Scheme 7



protons of starting 3,5-dien-1-ynes. These deuterium-labeling results reveal a methylene transfer process, consistent with the example shown in Scheme 2 (eq 2). Such a cyclization is thought to proceed through a 6-π-electrocyclization of initial metal-vinylidene intermediate with key steps shown in Scheme 6.[6]

Scheme 7 rationalizes the mechanistic nature of the thermal aromatization of 3,5-dien-1-ynes bearing internal alkynes. As species **5**, **16**, and **22** are more intrinsically active than other analogues in thermal cyclization, we proposed that their alkynyl C(1)-TMS carbon is reactive toward electrophiles[26] and that their C(6)-ketone group increases the adjacent C−H acidity to facilitate a "protonic" hydrogen shift as represented by species **G**. Such a "protonic" hydrogen shift is also favored by the presence of an electron-withdrawing C(1)-phenyl and C(6)-carbonyl group as reflected by the substituent-activity trends in Tables 1−3. This model also rationalizes the superior cyclization efficiencies of dienynes **4**, **13**, and **19** bearing a five-membered carbocyclic ring relative to their six-membered ring analogues **3**, **14**, and **20** as the C−H acidity is higher for a smaller ring because of a greater s-character.[27] The [1,5]-hydrogen shift of 3-en-1-ynes represented by intermediate **E** (Scheme 2, eq 1) has been characterized as a "hydridic" hydrogen shift according to our recent findings.[28]

Scheme 7 also depicts a plausible mechanism for metal catalysts to accelerate the 1,7-hydrogen shift. These metal complexes may have two roles: (1) an alternation of the alkyne sp-character toward sp^2-character[13c] as in intermediate **H**, and (2) the enhancement of the C(7)−H hydrogen acidity. The π-alkyne bonding is also characterized by the resonance structure **I**, which is thought to be responsible for several reactions catalyzed by PtCl$_2$,[13] AuPPh$_3^+$,[14a,b] AuCl$_3$,[13] and AuCl.[14] The polar nature (**I**) of this π-alkyne moiety is supported by theoretic calculations.[13c] This π-alkyne bonding may facilitate a 1,7-hydrogen shift of 3,5-dien-1-ynes because of a closer C(1)−C(7) distance; this actually mimics the 1,7-hydrogen shift of 1,3,5-trienes. Such a direct [1,7]-shift pathway (path **c**) is compatible with formation of d_6-**56**, of which the benzyl CY$_2$ deuterium contents arise exclusively from d_8-1,4-cyclohexadienone (Scheme 5, eq 2) even though water was present. However, this process is not supported by deuterium-labeling experiments for formation of d_4-**9** (Scheme 5, eq 1), which confirms that external water is also the source for one of its benzyl CY$_2$ protons. Accordingly, we propose that the major role of species **I** is to enhance the dissociation of the C(7)−H proton (path **d**) to form metal-allenyl intermediate **J**, and to give 4,6-dien-1-allene species **K** through subsequent reprotonation and reductive elimination. Species **K** ultimately gives the observed benzene product via 6-π-electrocyclization[30] and a [1,3]-hydrogen shift.

The proposed mechanism in Scheme 7 emphasizes the importance of the methylene C(7)−H acidity of 3,5-dien-1-ynes, and this mechanistic hypothesis is verified by the rate-acceleration effects of added 2,6-lutidine in both thermal and ruthenium-catalyzed cyclization of 3,5-dien-1-yne **4** according to the results in a separate experiment.[30] This phenomenon suggests that dissociation of a proton of intermediate **H** (or **I**) is the rate-determining step in the metal-catalyzed cyclization. It also suggests that base-catalyzed cyclization of 3,5-dien-1-ynes is likely to occur.[31]

Conclusions

Before this study, little information was available on the [1,7]-hydrogen shifts of 3,5-dien-1-ynes. In assessing the feasibility in thermal and metal-catalyzed cyclization of 6,6-disubstituted 3,5-dien-1-ynes via a 1,7-hydrogen shift, we first studied the thermal efficiency of model molecules via alternation of the C(1) and C(9) substituents of substrates; we concluded that the observed 1,7-hydrogen shift is nearly a "protonic" hydrogen shift. This structure−activity relationship indicates that π-alkyne activators can catalyze suitably functionalized 3,5-dien-1-ynes efficiently although their thermal yields were generally low. We prepared various 6,6-disubstituted 3,5-dien-1-ynes containing either a C(1)-phenyl, a TMS, or a C(6)-carbonyl group, and we found their thermal cyclizations to be greatly enhanced with RuCl$_3$, PtCl$_2$, and TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$ catalysts to confirm our hypothesis: the C(7)−H acidity of 3,5-dien-1-ynes determines the cyclization efficiency. To highlight the synthetic utility of this cyclization, we developed a tandem aldol condensation−dehydration and aromatization catalysis between cycloalkanones and special 3-en-1-yn-5-als using weakly acidic CpRu(PPh$_3$)$_2$-Cl catalyst; the yields generally exceeded 65% yield. Deuterium-labeling experiments show two different behaviors for metal-

---

(26) (a) Fleming, I. In *Comprehensive Organic Synthesis: Addition to C−X π-Bonds, Part 1*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 2.2, p 575. (b) Panek, J. S. In *Comprehensive Organic Synthesis: Addition to C−X π-Bonds, Part 1*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 2.2, p 580. (c) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375.

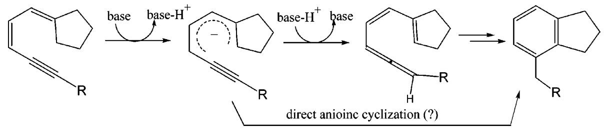
(27) (a) Bordwell, F. G.; Matthews, W. S. *J. Am. Chem. Soc.* **1974**, *96*, 1214. (b) Streitwieser, A., Jr.; Reuben, D. M. E. *J. Am. Chem. Soc.* **1971**, *93*, 1974.

(28) Datta, S.; Odedra, A.; Liu, R.-S., unpublished results.

(29) For 6-π-electrocyclization of 3,5-dien-1-allenes, see selected examples: (a) Bross, H.; Schneider, R.; Hopf, H. *Tetrahedron* **1979**, 2129. (b) Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6115.

(30) The cyclization yields of 3,5-dien-1-yne **4** to benzene derivative **9** in hot xylene (120 °C) were obtained in 31% (36 h) and 83% (24 h), respectively, in thermal and TpRuPPh$_3$(CH$_3$CN)$_2$PF$_6$-catalyzed reactions (see Table 1, entry 4). In the presence of 2,6-lutidine (5 mol %), the yields of these two processes improved to 51% (12 h) and 93% (12 h) with shorter reaction periods. We thank one reviewer for his very helpful suggestion.

(31) The observation that 2,6-lutidine accelerates the thermal cyclization of 3,5-dien-1-yne 4 suggests the feasibility for a cyclization of 3,5-dien-1-ynes using organic bases as depicted below. We will conduct related reactions toward this direction.



catalyzed aromatization of 3,5-dien-1-ynes. Formation of d_4-**56** arises from a direct [1,7]-hydrogen shift mechanism, whereas d_4-**9** proceeds through a proton dissociation and reprotonation process.

Acknowledgment. We wish to thank the National Science Council, Taiwan, for supporting this work.

Supporting Information Available: Experimental procedures for the synthesis of 3,5-dien-1-yne substrates and catalytic operations, NMR spectra, spectral data of compounds **1**−**60**, and X-ray structural data of anthrone **50**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA061203B