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Palladium(0)-Catalyzed Cyclization of Electron-Deficient Enynes and Enediynes

Yoshihiko Yamamoto,*,† Shoji Kuwabara,† Yoji Ando,‡ Hitomi Nagata,‡ Hisao Nishiyama,† and Kenji Itoh‡

Department of Applied Chemistry, and Department of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University, Chikusa, Nagoya 464-8603, Japan

yamamoto@apchem.nagoya-u.ac.jp

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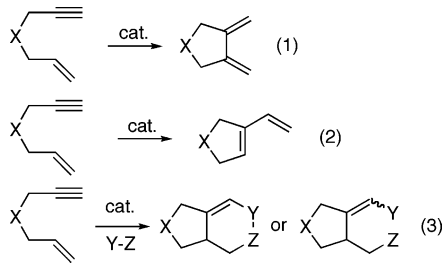
In the presence of a Pd(0) precatalyst, $Pd_2(bq)_2(nbe)_2$ or $Pd_2(dba)_3$, 1,6-enyne esters were heated in refluxing benzene to give cyclodimers as single regioisomers. On the other hand, the combination of the Pd(0) precatalyst and triphenyl phosphite gave rise to various cycloisomerization products depending on the substitution pattern of the enyne esters. Six-membered ring cycloisomerization products were predominantly obtained from enyne esters bearing methallyl or 2-phenyl-2-propenyl moieties, while other enyne esters afforded normal five-membered ring cycloisomerization products. Intramolecular [2 + 2 + 2] cyclocotrimerization of enediyne esters also proceeded in the presence of the Pd(0) precatalyst and triphenylphosphine to give fused cyclohexadienes.

Introduction

Transition-metal-catalyzed carbocyclizations are powerful tools for the assembly of carbo- and heterocyclic frameworks.[1] In particular, growing attention is currently devoted to the environmentally benign catalytic cycloisomerizations of α,ω-enynes.[2] For example, the intramolecular alkyne−alkene coupling reaction converts enyne substrates into 1,3-dienes (eq 1),[3] and enyne metathesis or skeletal reorganization reactions produce vinylcyclopentene derivatives via the carbon−carbon bond fission (eq 2).[4,5] α,ω-Enynes are also attractive substrates for the catalytic cyclo-coupling with other unsaturated organic molecules such as alkynes,[6] alkenes,[7] and CO (the Pauson−Khand reaction)[8] or with organosilicon and tin compounds (eq 3).[9]



Previously, we have developed the palladium(0)-catalyzed intramolecular cyclotrimerizations of diyne diesters or triyne diesters in which electron-deficient 1,6-diyne moieties are essential for the formation of key

† Department of Applied Chemistry.
‡ Department of Molecular Design and Engineering.

(1) (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92. (b) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635−662. (c) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523−596.
(2) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834.
(3) (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34−42. (b) Trost, B. M.; Kirsche, M. J. *Synlett* **1998**, 1−16.
(4) (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636−1638. (b) Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850−1852. (c) Trost, B. M.; Trost, M. K. *Tetrahedron Lett.* **1991**, *32*, 3647−3650. (d) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049−6050. (e) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901−903. (f) Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* **2001**, *66*, 4433−4436. (g) Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294−10295. (h) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863−11869. (i) Oi, S.; Tsukamoto, I.; Miyano, S.; Inoue, Y. *Organometallics* **2001**, *20*, 3704−3709. (j) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402−2406. (k) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509−1511.
(5) (a) Mori, M. In *Alkene Metathesis in Organic Synthesis*; Fürstner, A., Ed.; Springer-Verlag: Berlin, 1998; pp 133−154. (b) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1−18.
(6) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1987**, *109*, 4753−4755.
(7) Mori, M.; Saito, N.; Tanaka, D.; Takimoto, M.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 5606−5607.
(8) (a) Shore, N. E. In *Comprehensive Organic Synthesis*; Paquette, L. A., Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol 5. pp 1037−1064. (b) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263−3283. (c) Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800−1810. (d) Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32−42.
(9) (a) Ojima, I.; Donovan, R. J.; Shay, W. R. *J. Am. Chem. Soc.* **1992**, *114*, 6580−6582. (b) Ojima, I.; Vu, A. T.; Lee, S.-Y.; McCullagh, J. V.; Moralee, A. C.; Fujiwara, M.; Hoang, T. H. *J. Am. Chem. Soc.* **2002**, *124*, 9164−9174. (c) Molander, G. A.; Retsch, W. H. *J. Am. Chem. Soc.* **1997**, *119*, 8817−8825. (d) Fukuta, Y.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* **1999**, *40*, 4703−4706. (e) Chakrapani, H.; Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2003**, *5*, 157−159. (f) Park, K. H.; Kim, S. Y.; Son, S. U.; Chung, Y. K. *Eur. J. Org. Chem.* **2003**, 4341−4345. (g) Park, K. H.; Jung, I. G.; Kim, S. Y.; Chung, Y. K. *Org. Lett.* **2003**, *5*, 4967−4970. (h) Onozawa, S.; Hatanaka, Y.; Tanaka, M. *Chem. Commun.* **1997**, 1229−1230. (i) Onozawa, S.; Hatanaka, Y.; Choi, N.; Tanaka, M. *Organometallics* **1997**, *16*, 5389−5391. (j) Lautens, M.; Mancuso, J. *Org. Lett.* **2000**, *2*, 671−673. (k) Lautens, M.; Mancuso, J. *Synlett* **2002**, 394−398. (l) Mori, M.; Hirose, T.; Wakamatsu, H.; Imakuni, N.; Sato, Y. *Organometallics* **2001**, *20*, 1907−1909. (m) Sato, Y.; Imakuni, N.; Mori, M. *Adv. Synth. Catal.* **2003**, *345*, 488−491.

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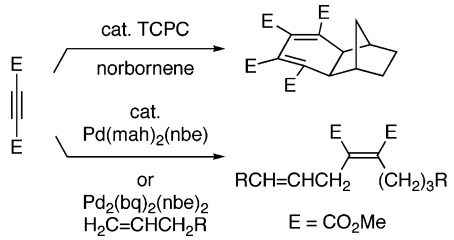
SCHEME 1



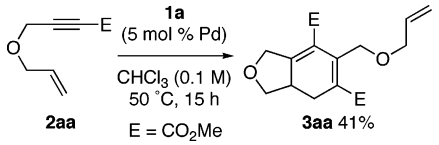
intermediates, palladacyclopentadienes.[10] As a continuation of our studies on palladium(0)-catalyzed cyclization, we turned our attention to 1,6-enynes having an ester group on the alkyne terminal because such enyne esters might be attractive precursors for palladacyclopentenes. The oxidative cyclization giving rise to palladacyclopentenes has been proposed as the key step in the previously reported linear couplings of highly electron-deficient dimethyl acetylenedicarboxylate (DMAD) and electronically neutral terminal alkenes,[11a] or the three-component linear coupling of DMAD, terminal alkenes, and allyl alcohol.[11b] In this context, we envisaged that the enyne esters might be entropically more suitable for the oxidative cyclization leading to palladacyclopentenes. Here we report the palladium(0)-catalyzed cyclodimerization and cycloisomerizations of enyne esters. As an extension of the cyclodimerization reaction, we also present the cyclization of some enediyne esters.

Results and Discussion

Cyclodimerization of Enyne Esters. Itoh and coworkers have previously reported that DMAD reacted with norbornene in the presence of a tetramethoxycarbonyl palladacyclopentadiene to afford a cyclocotrimerization product (Scheme 1).[12] On the other hand, a palladium(0) complex, $Pd(mah)_2(nbe)$ (mah = maleic anhydride, nbe = norbornene), selectively catalyzed the 2:1 linear coupling of terminal alkenes with DMAD (Scheme 1).[11a] In the latter case, the electron-deficient olefin ligand, maleic anhydride, was considered to be essential for the selective oxidative cyclization of DMAD and an alkene leading to a putative palladacyclopentene intermediate. Recently, we also reported a new dinuclear palladium(0) complex, $Pd_2(bq)_2(nbe)_2$ **1a** (bq = *p*-benzoquinone), that catalyzed a similar linear coupling.[13]

To extend the Pd(0)-catalyzed coupling methodology through palladacyclopentene intermediates, we attempted the cyclocoupling of an enyne ester **2aa** with excess 1-octene. In a similar manner with the reported linear coupling,[11a] a $CHCl_3$ solution of **2aa** was added to 10 equiv of 1-octene containing $Pd_2(bq)_2(nbe)_2$ (5 mol % Pd) via a syringe pump over 12 h at 50 °C, and the reaction

SCHEME 2



mixture was further stirred at this temperature for 4 h. As a result, a complex mixture including a trace amount of cyclodimer **3aa** was obtained instead of the expected 1:1 coupling product of **2aa** with 1-octene. Such an enyne cyclodimerization is very rare, and to the best of our knowledge, it has been confined to the Rh(I)-catalyzed reactions of electronically neutral 1,6-enynes.[14] Thus, we tried to optimize the new cyclodimerization of the electron-deficient enyne **2aa**. In the absence of the terminal alkene, **3aa** was obtained as the sole product in 41% yield (Scheme 2). The yield was improved to 60% by carrying out the reaction in refluxing benzene. A commercially available precatalyst, $Pd_2(dba)_3$ **1b** (5 mol % Pd), also gave **3aa** in a slightly higher yield (64%) under the same conditions (Table 1, run 1).

To examine the generality of the Pd(0)-catalyzed cyclodimerization, other enyne esters were allowed to react under the same reaction conditions (Table 1). A methallyl derivative **2ab** was similarly converted to **3ab** in 69% yield (Table 1, run 2), whereas cinnamyl and prenyl derivatives **2ac** and **2ad** afforded intractable product mixtures (Figure 1). The ester terminal group on the alkyne moiety plays an important role. Enyne substrates bearing a ketone, an amide, or a phenyl terminal group hardly afforded cyclodimerization products (Figure 1). In addition to the ether derivatives, tosylamides **2ba** and **2bb** also furnished the corresponding products **3ba** and **3bb** in 68 and 58% respective yields (Table 1, runs 3 and 4). It is noteworthy that a much longer reaction time of 18 h was required for the complete conversion of **2bb**, and a small amount of byproduct **4bb** was also obtained (see below).

The cyclodimerization of the enyne esters selectively gave rise to the single regioisomers. The regiochemistry of the cyclodimers was unambiguously confirmed by the X-ray analysis of **3ba** (see the Supporting Information, Figure S1). In its six-membered ring, only the C1−C2 and C7−C8 bonds exhibit typical C=C double bond lengths of 1.3389(19) and 1.3448(18) Å, respectively. The C1−C8 bond length of 1.4801(17) Å is very similar with that of a typical Csp^2-Csp^2 single bond. The two methoxycarbonyl groups are located at a meta position to each other. This regioselectivity is opposite to those reported for the Rh(I)-catalyzed cyclodimerization of enynes.[14] The observed regiochemistry was reasonably explained by the plausible mechanism outlined in Scheme 3. Dibenzylidenacetone ligands might be initially substituted by the two enyne esters to form a trigonal planar complex **I**. Contrary to our assumption, the oxidative cyclization takes place with the two alkyne terminals to produce a palladacyclopentadiene **II** because the electron-deficient alkynoate moiety is a superior electron acceptor to unactivated alkenes. In this stage, the palladacycle must

(10) (a) Yamamoto, Y.; Nagata, A.; Itoh, K. *Tetrahedron Lett.* **1999**, *40*, 5035−5038. (b) Yamamoto, Y.; Nagata, A.; Arikawa, Y.; Tatsumi, K.; Itoh, K. *Organometallics* **2000**, *19*, 2403−2405. (c) Yamamoto, Y.; Nagata, A.; Nagata, H.; Ando, Y.; Arikawa, Y.; Tatsumi, K.; Itoh, K. *Chem. Eur. J.* **2003**, *9*, 2469−2483.

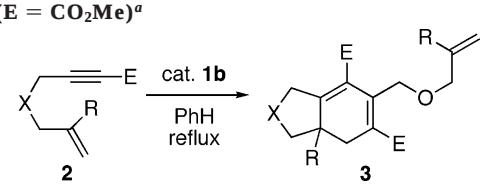
(11) (a) Itoh, K.; Hirai, K.; Sasaki, M.; Nakamura, Y.; Nishiyama, H. *Chem. Lett.* **1981**, 865−868. (b) Munz, C.; Stephan, C.; tom Dieck, H. *J. Organomet. Chem.* **1991**, *407*, 413−420.

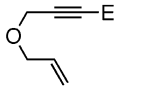
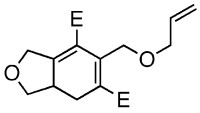
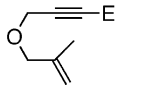
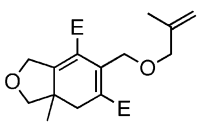
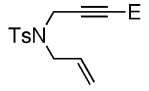
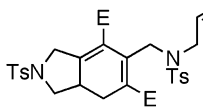
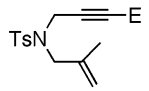
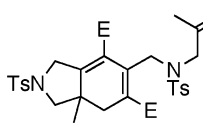
(12) (a) Suzuki, H.; Itoh, K.; Ishii, Y.; Simon, K.; Ibers, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 8494−8500. (b) Brown, L. D.; Itoh, K.; Suzuki, H.; Hirai, K.; Ibers, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 8232−8238.

(13) Yamamoto, Y.; Ohno, T.; Itoh, K. *Organometallics* **2003**, *22*, 2267−2272.

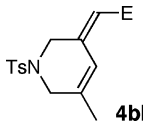
(14) (a) Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1365−1369. (b) Oh, C. H.; Sung, H. R.; Jung, S. H.; Lim, Y. M. *Tetrahedron Lett.* **2001**, *42*, 5493−5495.

TABLE 1. Pd(0)-Catalyzed Cyclodimerizations of Enyne Esters (E = CO_2Me)[a]



run	enynes, (time,h)	cyclodimers, (yield, %)
1	 **2aa** (4)	 **3aa** (64)
2	 **2ab** (4)	 **3ab** (69)
3	 **2ba** (4)	 **3ba** (68)
4	 **2bb** (18)	 **3bb** (58)[b]

[a] A 0.1 M solution of **2** in degassed benzene containing **1b** (5 mol % Pd) was refluxed under Ar for the above specified time.[b] A cycloisomerization product **4bb** was formed in 9% yield.



be formed in such a way that minimizes the steric repulsion between the alkenyl side chains. Subsequently, the pendant alkene is inserted into the Pd−Csp^2 bond to form a palladacycloheptadiene **III**, which undergoes reductive elimination to give rise to the final cyclodimer.

In contrast to the ether and tosylamide substrates, dimethyl malonate analogues bearing an allyl or a methallyl terminal failed to undergo cyclodimerization under the same reaction conditions. At higher temperature in refluxing toluene, **2cb** was completely consumed for 24 h, and the inseparable mixture of a cyclohexene **4cb** and a cyclopentene **5** was obtained in 21% combined yield instead of the expected cyclodimer (Scheme 4). The latter product **5** was probably formed via enyne metathesis, and the following ^{1}H NMR data were consistent with those reported in the literature.[4a] The absorption of the vinyl protons were observed at δ 5.54 and 6.26 (each 1 H, d, J = 1.7 Hz). The two methylenes of the cyclopentene ring appeared at δ 3.22 and 3.07 as broad peaks, and the singlet signal corresponding to the allylic methyl protons was observed at δ 1.66. The methoxy protons resonated at δ 3.75 and 3.74 with the 1:2 integral ratio.

The cycloisomerization converting 1,6-enynes into six-membered ring products such as **4bb** and **4cb** has hardly been explored, although a similar result has been encountered by Trost,[4c,15] Mikami,[16] and co-workers in their study on the Pd(II)-catalyzed reactions of enynes. In the following section, we disclose the selective transformation of enyne esters into the six-membered ring carbo- and heterocycles.

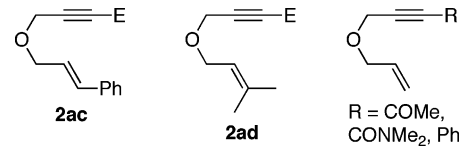
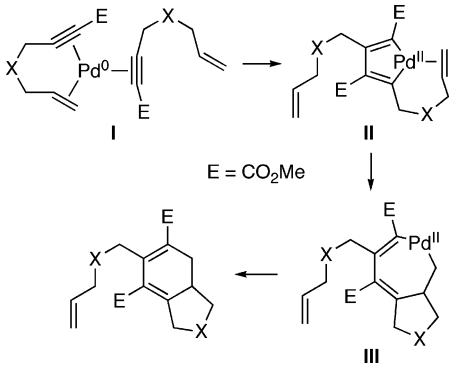
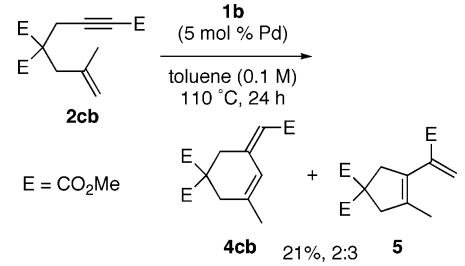


FIGURE 1. Enyne substrates which failed to undergo cyclodimerization.

SCHEME 3



SCHEME 4

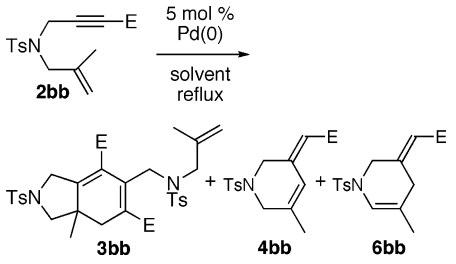


Six-Membered-Ring Formations from 1,6-Enyne Esters. We next examined the effect of ligands and solvents on the product selectivity with respect to **2bb**, and the results are summarized in Table 2. In our previous study on the cycloaddition of the diyne diesters, triphenylphosphine turned out to be an optimal ligand.[10] On the contrary, the phosphine suppressed the cyclodimerization leading to **3bb** but, instead, promoted the six-membered ring formation yielding **4bb** and its isomer **6bb** (run 1). In an aprotic polar solvent, 1,2-dichloroethane (DCE), the cyclodimerization was completely inhibited to afford **4bb** and **6bb** in 57 and 14% respective yields (run 2). The replacement of triphenylphosphine by less electron-donating triphenyl phosphite improved the selectivity of **4bb** over **6bb** (run 3), and 2 equiv of $P(OPh)_3$ retarded the reaction (run 4). The combination of the *p*-quinone complex **1a** and $P(OPh)_3$ gave a similar selectivity albeit with somewhat lower yield (run 5). More electron-accepting ligands, tri(pentafluorophenyl)phosphine or xylyl isocyanide, afforded considerable amounts

(15) Trost, B. M.; Zhi, L.; Imi, K. *Tetrahedron Lett.* **1994**, *35*, 1361−1364.

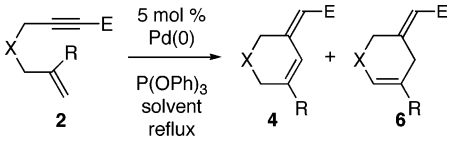
(16) Mikami, K.; Hatano, M *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5767−5769.

TABLE 2. Effects of Additives and Solvents on Pd(0)-Catalyzed Reaction of Enyne Ester 2bb (E = CO_2Me)



run	catalyst	solvent/time (h)	yield (%) 3bb	4bb	6bb
1	**1b** + $2PPh_3$	PhH/12	30	34	8
2	**1b** + $2PPh_3$	DCE/12	0	57	14
3	**1b** + $2P(OPh)_3$	DCE/12	0	64	9
4	**1b** + $4P(OPh)_3$	DCE/32	0	60	7
5	**1a** + $2P(OPh)_3$	DCE/12	0	54	4
6	**1b** + $2P(C_6F_5)_3$	DCE/6	40	20	2
7	**1b** + 2CN(xylyl)	DCE/24	25	34	0

TABLE 3. Pd(0)/$P(OPh)_3$-Catalyzed Reaction of Enyne Esters 2 (E = CO_2Me)



run	enynes	Pd(0)	solvent/time (h)	products (yield, %)
	X = O, R = Me			
1	**2ab**	**1a**	DCE/12	**4ab** (57)
	X = NTs, R = Me			
2	**2bb**	**1a**	DCE/12	**4bb** (54) + **6bb** (4)
3	**2bb**	**1b**	DCE/12	**4bb** (64) + **6bb** (9)
	X = $C(CO_2Me)_2$, R = Me			
4	**2cb**	**1a**[a]	PhCl[b]/1	**4cb** (59)
5	**2cb**	**1b**[a]	PhCl[b]/1	**4cb** (64)
	X = NTs, R = Ph			
6	**2be**	**1a**	PhCl[b]/8	**4be**/**6be** (53)[c]

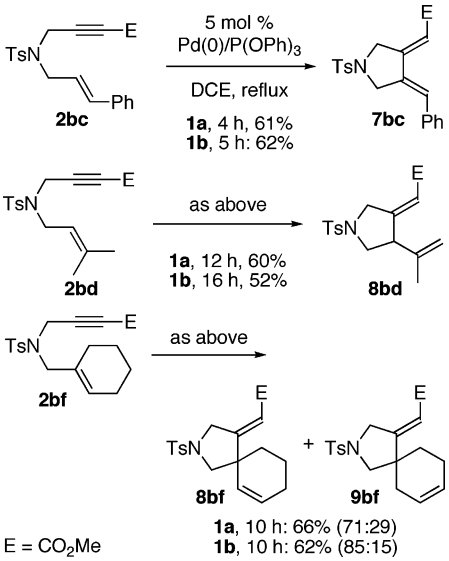
[a] 5 mol % Pd(0) complexes (10 mol % Pd) were employed. [b] Reactions were carried out at 110 °C. [c] Inseparable 1:1 mixture.

of the cyclodimer **3bb** (runs 6 and 7). Other ligands such as triethylphosphine and triethyl phosphite proved to be entirely inefficient. Therefore, triphenyl phosphite appeared to be the optimal ligand for the six-membered ring formation.

The structures of **4bb** and **6bb** were clearly determined by X-ray analyses (see the Supporting Information, Figures S2 and S3). They are inner-ring double-bond isomers. While a conjugated s-trans diene is found in **4bb**, the exocyclic olefin is isolated from the inner-ring double bond in **6bb**. The vinyl protons of **4bb** resonated at δ 5.48 and 7.24, while those of **6bb** were observed at δ 5.57 and 6.45. It is noteworthy that the exocyclic alkenes have an *E* geometry as a result of the net *trans*-addition of the alkene C−H bond onto the electron-deficient alkyne. This observation is inconsistent with the *cis*-addition mechanism proposed by Trost and co-workers (see below).[4c]

Table 3 summarizes the results of the cycloisomerization of various methallyl enyne esters. In a similar manner using **1a** as a precatalyst, the ether enyne **2ab** (X = O) was selectively converted to the expected **4ab** in 57% yield (run 1). In this case, **1a** is a preferable catalyst precursor because of the difficulty in the separation of **4ab** from dibenzylideneacetone. In contrast to enyne esters bearing ether or tosylamide tethers (runs 1−3), the malonate analogue **2cb** failed to undergo cycloisomerization in refluxing DCE. The smooth conversion of **2cb** was observed at 110 °C in chlorobenzene to afford **4cb** in 59−64% yields (runs 4 and 5). In the cases of **2ab** and **2cb**, **6ab** or **6cb** were hardly formed. Furthermore, the cycloisomerization of a 2-phenylallyl analogue **2be** was attempted under the same conditions with **2bb**, but no reaction occurred. Thus, the reaction was conducted at higher temperature in refluxing chlorobenzene for 8 h to give rise to equal amounts of **4be** and **6be** as an inseparable mixture in 53% combined yield (run 6).

SCHEME 5

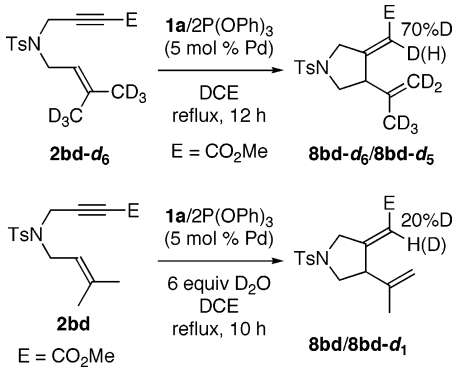


Cycloisomerization of Other Enyne Esters. We further explored the reactivity of other enyne esters bearing a tosylamide tether under the cycloisomerization conditions. The allyl analogue **2ba** resulted in intractable products, although it gave the cyclodimer under the ligand-free conditions (Table 1, run 3). On the other hand, a cinnamyl derivative **2bc** gave rise to a pyrrolidine **7bc** possessing a *exo*-1,3-diene moiety as a result of the normal cycloisomerization (Scheme 5).[3] The *Z*,*Z*-geometry of the *exo*-diene moiety was confirmed by X-ray analysis (see the Supporting Information, Figure S6). Similarly, a prenyl derivative **2bd** underwent the cycloisomerization to afford an Alder−ene product **8bd** selectively in 52−60% yields (Scheme 5). Only five-membered ring cyclization was also observed for **2bf** (Scheme 5). The obtained products were a spirocyclic Alder−ene product **8bf** and its isomerized byproduct **9bf**.[17] A slightly higher isomer selectivity was obtained with the precatalyst **1b**, while the total yields were similar in either case.

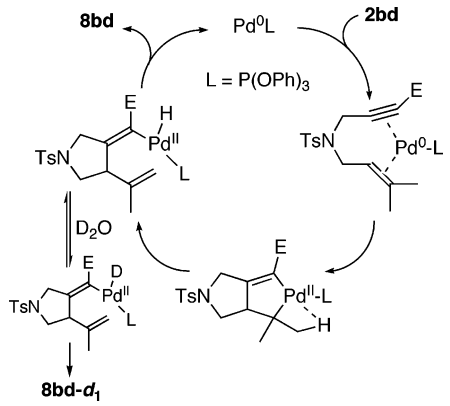
Cycloisomerization Mechanisms. The five-membered ring cycloisomerization catalyzed by a low-valent transition metal is expected to proceed via oxidative cyclization followed by β-H elimination of the resultant palladacyclopentene intermediate. On the other hand, a

(17) Asymmetric Alder−ene cycloisomerization of **2bf** has been reported; see: Hatano, M.; Mikami, K. *Org. Biomol. Chem.* **2003**, *1*, 3871−3873.

SCHEME 6



SCHEME 7

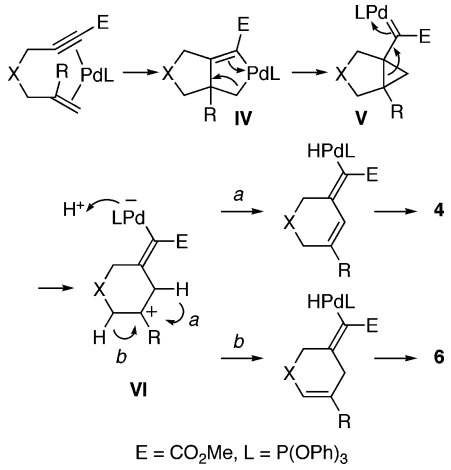


palladium(II) hydride might be a catalytically active species, when Pd(II) catalyst is used with a hydride donor such as carboxylic acids or hydrosilanes. In this case, the catalytic cycle starts with hydropalladation of an alkyne, and subsequent insertion of a pendant alkene into the resultant Pd−Csp^2 bond is followed by the β-H elimination, which affords the final product as well as Pd−H species. To obtain further information with respect to the mechanism, we carried out some D-labeling studies. As depicted in Scheme 6, **2bd**-d_6 was subjected to the cycloisomerization under identical conditions with **2bd** to afford **8bd** in 55% yield with ca. 70% D content (**8bd**-d_6/**8bd**-d_5 = 7:3). The D content was slightly reduced to 63% in the presence of 600 mol % H_2O, while the deuterated ligand, $P(OC_6D_6)_3$, never affected the D content. Similarly, **2bd** underwent cycloisomerization with 600 mol % D_2O to obtain **8bd** in 58% yield with ca. 20% D content (**8bd**/**8bd**-d_1 = 80:20). On the other hand, no deuterium incorporation was detected when the same cycloisomerization was carried out in benzene-d_6 or DCE-d_4. These data suggest that most of the D-labels were transferred in an intramolecular fashion via a palladacyclopentene intermediate, but some of them were lost probably via D−H exchange with water from the solvent. The 20% deuterium incorporation from excess D_2O supports such a D−H exchange (Scheme 7), which is, however, less pronounced than that of the recently reported Pd(II)-catalyzed asymmetric cycloisomerization of a related enyne ester.[18]

The six-membered ring cyclization might proceed via a polarized η^1-alkyne complex as proposed in the skeletal

(18) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249−253.

SCHEME 8



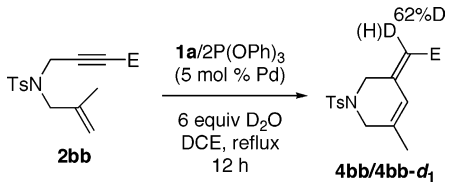
reorganization and related reactions.[4d−k,19] The *palladium(0)*-catalyzed skeletal reorganization, however, is unprecedented, whereas pallada(II)cyclopentadiene complexes have been reported as efficient catalysts for enyne skeletal reorganization.[4a−c] Oi, Inoue, and their coworkers have found that highly electrophilic dicationic species, $[Pd(dppp)(PhCN)_2](BF_4)_2$ and $[Pd(PPh_3)(PhCN)_2](BF_4)_2$, were totally ineffective toward this type of cyclization.[4i] In addition, almost exclusive formation of the cyclohexene derivatives **4** under the present palladium(0) catalysis is inconsistent with the typical examples using $[RuCl_2(CO)_3]_2$,[4d] $PtCl_2$,[4e] and $[IrCl(CO)_3]_n$,[4f] which uniformly produced five-membered ring products. With these facts in mind, we postulated another mechanism, which involves a palladacyclopentene intermediate (Scheme 8). The new mechanism starts with the oxidative cyclization of an enyne ester leading to the palladacyclopentene intermediate **IV**. Its subsequent isomerization would afford the cyclopropyl carbene species **V**. This type of isomerization was proposed for the palladacycle-catalyzed reactions of enynes[4a−c,20] and the titanium(II)-mediated cyclization of enyne esters.[21] If the fused bond in **V** is cleaved, a zwitterionic intermediate **VI** would be produced. In this stage, the coordinated palladium carbene moiety must be oriented to minimize the unfavorable steric interaction between the $P(OPh)_3$-coordinated palladium center and the cyclopropane ring moiety, resulting in the *E* geometry of the exocyclic alkene. Subsequent proton transfer and reductive elimi-

(19) (a) Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104−9105. (b) Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132−2135. (c) Martín-Matute, B.; Ceardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4754−4757. (d) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511−10520. (e) Fernández-Rivas, C.; Meendez, M.; Nieto-Oberhuber, C.; Echavarren, A. M. *J. Org. Chem.* **2002**, *67*, 5197−5201. (f) Nevado, C.; Charruault, L.; Michelet, V.; Nieto-Oberhuber, C.; Munoz, M. P.; Méndez, M.; Rager, M.-N.; Genêt, J.-P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, 706−713. (g) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627−2635. (h) Martin-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757−5766.

(20) (a) Trost, B. M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1085−1087. (b) Trost, B. M.; Hashmi, A. S. K. *J. Am. Chem. Soc.* **1994**, *116*, 2183-2184. (c) Trost, B. M.; Hashmi, A. S. K.; Ball, R. G. *Adv. Synth. Catal.* **2001**, *343*, 490−494.

(21) (a) Suzuki, K.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 8729−8730. (b) Urabe, H.; Suzuki, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 10014−10027.

SCHEME 9



nation give rise to **4** and **6** from the common intermediate **VI**. The cyclization of **2bb** was reexamined in the presence of excess D_2O (Scheme 9). Unfortunately, the reaction was deteriorated by D_2O addition, resulting in the low-yield formation of **4bb**/**4bb-*d*$_1$** (40%). In contrast to the Alder-ene type cycloisomerization of **2bd**, significant deuterium incorporation was observed (62%), indicative of the hydrogen-atom transfer taking place in an intermolecular fashion as outlined in Scheme 8.

The observed deuterium incorporation and the *E* geometry of the exocyclic alkene moiety can also be explained by an alternative mechanism proposed by Mikami and Hatano.[16] They considered that the hydropalladation of the alkyne followed by subsequent two alkene insertions might produce a cyclopropane intermediate, and its ring opening via the fused C−C bond fission finally gives rise to the six-membered ring product. To confirm the palladacycle mechanism, we further carried out the PD(0)-catalyzed reaction of **2bb** in the presence of DMAD, in which the palladacyclopentene intermediate such as **IV** might be trapped as the cycloadduct with DMAD. As outlined in Scheme 10, **2bb** and 2 equiv of DMAD were heated in a DCE solution containing a catalyst (10 mol % Pd) for 24 h. When **1a** was used as a precatalyst, two new products **10** and **11** were formed in 15 and 25% respective yields together with **4bb**. The structure of **10** was deduced from the ^{1}H NMR analysis as follows. The methylene protons on its five-membered pyrroline ring appeared as two multiplets at lower field (δ 4.08 and 4.27) than those of the six-membered ring compound **4bb** (δ 3.69 and 3.78).[22] The vinyl protons were observed as a couple of doublets with a small coupling constant (δ 5.55 and 6.32, J = 1.4 Hz). These data allowed us to assign **10** as an enyne metathesis product similar to **5**. The other product **11** is the 1:1 cycloadduct of **2bb** and DMAD. Its ^{1}H NMR showed the absorptions of the methoxy groups as three singlets with an equal intensity (δ 3.74, 3.75, and 3.79) and the methylene protons as three sets of doublets (δ 2.36 and 2.59, J = 16.8 Hz; δ 2.79 and 3.62, J = 9.2 Hz; δ 4.08 and 4.64, J = 19.8 Hz).

During the reaction, a palladacyclopentadiene **1c** must be generated from **1a** and DMAD.[12] In fact, hexamethyl mellitate **12**, which was formed via **1c**, was obtained in 40% yields based on DMAD. With this fact in mind, the reaction was also conducted using **1c** as a precatalyst. As a result, a similar product distribution was observed, although the sluggish reaction reduced the total isolated yield (Scheme 10, run 2). On the contrary, **1c**/$P(OPh)_3$ gave rise to only the six-membered ring products **4bb** and **6bb** in the absence of DMAD (Scheme 10, run 3). These results indicate that the formation of **10** and **11** requires a [Pd(0)−$P(OPh)_3$] species and DMAD.

(22) It was reported for the related enyne metathesis that the methylene protons of five-membered ring products generally appeared at lower fields than those of six-membered ring products (Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678−693.).

Previously, Trost and Tanoury reported the palladacycle-catalyzed reaction of a 1,6-enyne and DMAD affording the corresponding 1:1 cycloadduct and metathesis product.[6] In this paper, they proposed a pallada(IV)-cyclopentene as a common intermediate. For our case, it might be reasonable to consider that the metathesis product **10** and the cycloadduct **11** were formed from a pallada(II)cyclopentene−DMAD complex **13** because the palladacycle **1c** itself never gave **10** and **11** in the absence of DMAD (Scheme 11). In addition, the in-situ-formed palladacyclopentadiene species was readily trapped with DMAD to form considerable amounts of hexamethyl mellitate. The reductive elimination from **13** would give rise to an elusive cyclobutene intermediate **14**, which undergoes electrocyclic ring opening to afford **10**. DMAD is considered to facilitate the reductive elimination of **14** as a highly electron-accepting ligand. Alternatively, the insertion of the coordinated DMAD into the Pd−Csp^2 bond is followed by reductive elimination to furnish **11**. On the basis of these results, we can conclude that the Pd(0)-catalyzed cycloisomerizations of the enyne esters proceed via the palladacycle mechanism.[23]

Cycloisomerization of Arene−Yne Ester. Recently, the cyclizations of a variety of arene−ynes have been accomplished by means of ruthenium, platinum, and gallium catalyses.[24] With our catalytic system, a *N*-benzyltosylamide **2bg** failed to undergo cycloisomerization even at 110 °C in chlorobenzene for 24 h (Scheme 12). This indicates that the arene−yne ester cannot undergo oxidative cyclization. In contrast, a furan derivative **2bh** was cyclized in the presence of **1a**/2P(OPh)$_3$ (30 mol % Pd) in refluxing DCE to give a furopiperidine **16bh** albeit in low yield (Scheme 12). With reduced catalyst loadings, the longer reaction gave rise to intractable product mixture, probably due to the decomposition of the starting material or the product. The structure of **16bh** was confirmed by X-ray analysis (see the Supporting Information, Figure S7). The *exo*-alkylidenepiperidine core is very similar to that of **4bb** except for the exocyclic alkene geometry.

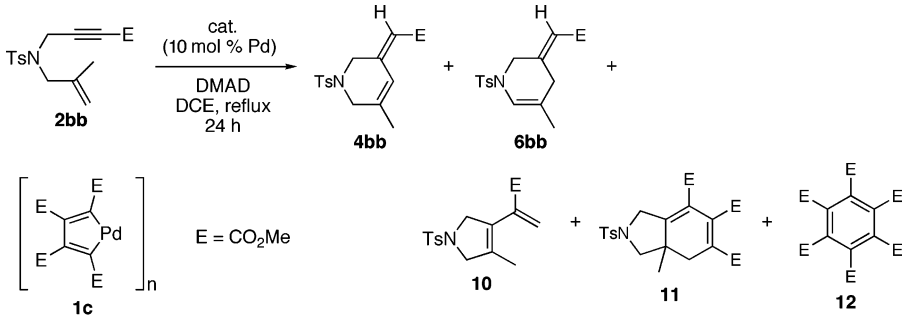
Cyclization of Enediyne Esters. We have previously found that a triyne diester **17** was cyclized upon treatment with a catalytic amounts of **1b**/2PPh_3 in refluxing toluene to afford a tricyclic product **18** via intramolecular [2 + 2 + 2] cyclotrimerization (Figure 2).[10] A palladium(0) trialkyne complex **19** was also obtained from the stoichiometric reaction of **1b** with **17** at ambient temperature and fully characterized by NMR spectroscopy and X-ray diffraction study.[10b,c]

As a part of the present palladium(0)-catalyzed cyclization of enyne esters, we briefly explored the cyclization of enediyne diesters **20** and **21** and enediyne esters **22**. First, the *cis*-enediyne diester **20** was subjected to the reaction under the same conditions as with that for **17**. However, an intractable product mixture was ob-

(23) The alternative palladium(II) hydride mechanism was proposed; see ref 16.

(24) (a) Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913−4918. (b) Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2002**, *67*, 1414−1417. (c) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264−6267. (d) Fürstner, A.; Mamane, V. *Chem. Commun.* **2003**, 2112−2113. (e) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055−1058. (f) Pastine, S. J.; Sames, D. *Org. Lett.* **2003**, *5*, 4053−4055. (g) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859−8868.

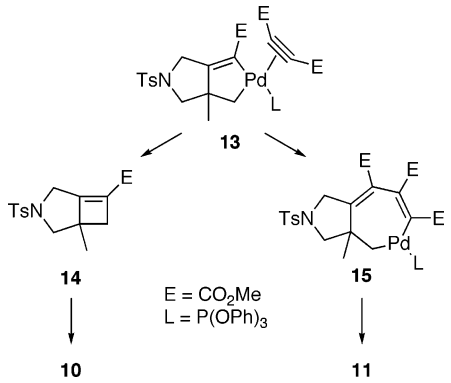
SCHEME 10



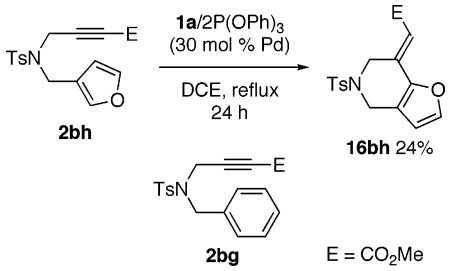
run	catalyst	DMAD/equiv	**4bb**/%	**6bb**/%	**10**/%	**11**/%	**12**/%[a]
1	**1a**/2P(OPh)$_3$	2	19	0	15	25	40
2	**1c**/P(OPh)$_3$	2	3	0	11	16	29
3	**1c**/P(OPh)$_3$	0	54	8	0	0	0

[a]Isolated yield based on DMAD.

SCHEME 11



SCHEME 12



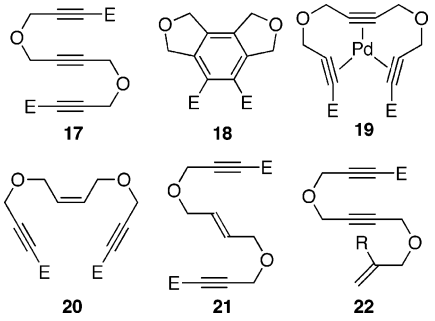
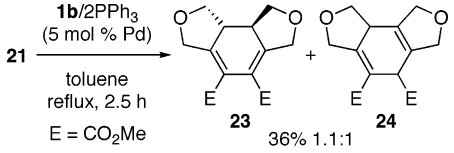
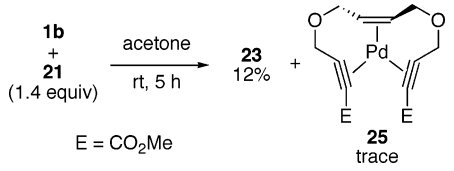


FIGURE 2. Triyne diester **17** and its Pd(0) complex **19**, cyclization product **18**, and enediyne esters **20**−**22** (E = CO_2Me).

SCHEME 13



SCHEME 14



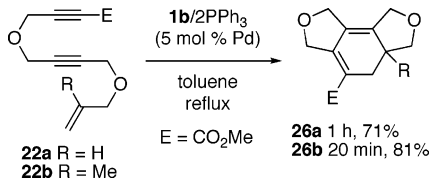
tained. In contrast, the *trans*-isomer **21** was similarly heated in the refluxing toluene containing **1b**/2PPh$_3$ (5 mol % Pd) for 2.5 h to give nearly equal amounts of cyclized products **23** and **24** as an inseparable mixture in 36% combined yield (Scheme 13). The stoichiometric reaction of **1b** with 1.4 equiv of **21** was also carried out in acetone at room temperature to obtain **23** in 12% yield together with trace amounts of white solid (Scheme 14).

The cyclization products were characterized as follows. The ^{1}H NMR spectrum of **23** shows only one singlet peak of the methoxy group as well as a pair of doublets and three broad multiplet peaks, indicative of its highly symmetrical structure. This was also supported by its ^{13}C NMR data. One carbonyl (δ 165.20) and two olefinic (δ 155.58 and 120.34) signals are observed with four upfield peaks (δ 45.34, 51.81, 70.20, and 72.73). These data allows us to assign **23** to the symmetrical 1,3-cyclohexadiene, which is directly formed via [2 + 2 + 2] cyclization of **21**. Although the spectral data of the pure **24** were not available, its unsymmetrical structure is deduced from the ^{13}C NMR measurement of the mixture of **23** and **24**. Total fourteen signals were observed for **24**. The conjugated and nonconjugated carbonyl signals appeared at δ 165.54 and 171.10, respectively. The olefinic carbons conjugated with the methoxycarbonyl group were observed at δ 117.14 and 156.10, while the isolated alkene carbons resonated at δ 129.47 and 129.50. These data suggested that **24** has a 1,4-cyclohexadiene ring with one enoate moiety.

TABLE 4. Comparison of Spectral Data for 17, 19, 21, and 25

	17	19	21	22
IR (cm^{-1})	2239 (C≡C)	1977 (C≡C)	2251 (C≡C)	1970 (C≡C)
^{13}C NMR δ (ppm)	78.03 (C≡C)	72.90 (C≡C)	77.74 (C≡C)	77.21 (C≡C)
	82.02 (C≡C)	75.75 (C≡C)	83.36 (C≡C)	88.22 (C≡C)
	82.45 (C≡C)	89.69 (C≡C)	129.06 (C═C)	94.08 (C═C)
	153.13 (C═O)	160.80 (C═O)	153.24 (C═O)	160.66 (C═O)

SCHEME 15



Whereas no single-crystal suitable for X-ray diffraction study was obtained, the white solid obtained from the stoichiometric reaction was assigned to a palladium(0) enediyne complex **25** by comparison of its spectral data with those of the triyne complex **19** as well as the parent triyne diester **17** and the enediyne diester **21** (Table 4). In the IR spectra of **17** and **21**, the C≡C stretching vibration appeared at around 2000 cm^{-1}, which was shifted to around 1970 cm^{-1} in **19** and **25**. In the ^{13}C NMR spectrum of **17**, three Csp signals were observed at δ 78.03, 82.02, and 82.45. Upon formation of **19**, two of them moved upfield to δ 72.90 and 75.75, and one shifted downfield to δ 89.69. A similar correlation in the ^{13}C chemical shifts was observed for **21** and **25**. The alkyne and alkene carbons were observed at δ 77.74 and 83.36 (C≡C) and 129.06 (C═C) in **21**, while they moved to δ 77.21 and 88.22 (C≡C) and 94.08 (C═C) in **25**. The downfield shifts were observed for the carbonyl carbons from **17** and **21** (δ ~153) to **19** and **25** (δ ~160). The structural assignment of **25** as the enediyne complex was also supported by FAB mass measurement (M^+ *m*/*z* 386) and elemental analysis.

The enediyne esters involving a 1,6-diyne unit were also explored as substrates for the intramolecular [2 + 2 + 2] cyclocotrimerization. In the presence of **1b**/2PPh_3 (5 mol % Pd), **22a** was heated in refluxing toluene for 1 h to afford the expected cyclohexadienecarboxylate **26a** in 71% yield as a sole product (Scheme 15). The cyclization of the corresponding methallyl derivative **22b** completed within 20 min to give a similar product **26b** in 81% yield. The higher efficiencies of **22a**,**b** than **21** are attributed to their 1,6-diyne moieties, which undergo facile oxidative cyclization.

Conclusions

We have explored the palladium(0)-catalyzed reactions of 1,6-enyne esters. In the absence of an extra ligand, $Pd_2(dba)_3$ or $Pd_2(bq)_2(nbe)_2$ catalyzed the cyclodimerization of enyne esters. On the other hand, the enyne esters underwent cycloisomerizations with triphenyl phosphite to give rise to various products depending on the substitution pattern of the olefin termini. When enyne esters bearing a methallyl moiety were used, uncommon six-membered ring products were predominantly formed with concomitant enyne metathesis products. In contrast, other enyne esters having a cinnamyl, a prenyl, or a cyclohexenylmethyl moiety selectively underwent normal cycloisomerizations to furnish five-membered ring products. As an extension of these enyne ester cyclizations, we also examined the palladium(0)-catalyzed reactions of some enediyne esters to obtain intramolecular [2 + 2 + 2] cyclocotrimerization products.

Experimental Section

Typical Procedure for Cyclodimerization of Enyne Esters: Cyclodimerization of 2aa Using $Pd_2(dba)_3$ as Precatalyst. A solution of **2aa** (77 mg, 0.50 mmol) and $Pd_2(dba)_3$·$CHCl_3$ (13 mg, 0.013 mmol) in dry degassed benzene (5 mL) was refluxed under Ar for 4 h. The solvent was then evaporated, and the crude product was purified by silica gel flash column chromatography (hexane/AcOEt = 9:1) to give **3aa** (48 mg, 64%) as colorless oil: IR ($CHCl_3$) 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.92−2.05 (m, 1 H), 2.91 (dd, *J* = 15.3, 6.6 Hz, 1 H), 2.95−3.07 (m, 1 H), 3.41 (dd, *J* = 9.6, 8.7 Hz, 1 H), 3.75 (s, 3 H), 3.77 (s, 3 H), 3.79−3.83 (m, 1 H), 3.87 (dtq, *J* = 12.3, 5.4, 1.5 Hz, 1 H), 4.35 (t, *J* = 8.4 Hz, 1 H), 4.50 (dd, *J* = 17.4, 2.4 Hz, 1 H), 4.53 (dd, *J* = 13.8, 3.9 Hz, 1 H), 4.94 (dd, *J* = 13.8, 1.5 Hz, 1 H), 4.93 (d, *J* = 17.4 Hz, 1 H), 5.13 (dq, *J* = 10.5, 1.5 Hz, 1 H), 5.21 (dq, *J* = 17.1, 1.5 Hz, 1 H), 5.83 (ddt, *J* = 17.4, 10.5, 5.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 41.3, 51.7, 51.9, 67.8, 70.7, 71.6, 73.6, 116.9, 121.6, 124.2, 134.2, 144.4, 158.5, 165.9, 167.2; MS (FAB) *m*/*z* 309 (24) [MH^+], 277 (41) [M^+ − OMe], 251 (100) [M^+ − OCH_2-CH═CH_2]. Anal. Calcd for $C_{16}H_{20}O_6$ (308.33): C, 62.33; H, 6.54. Found: C, 62.29; H, 6.58.

Other cycloadducts were obtained similarly. The yields and the reaction conditions are summarized in Table 1.

Typical Procedure for Cycloisomerizations of Enyne Esters: Cycloisomerization of 2ab Using $Pd_2(bq)_2(nbe)_2$ and $P(OPh)_3$. A solution of **2ab** (84 mg, 0.50 mmol), $Pd_2(bq)_2$-$(nbe)_2$ (8 mg, 0.013 mmol), and $P(OPh)_3$ (8 mg, 0.026 mmol) in dry degassed 1,2-dichloroethane (5 mL) was refluxed under Ar for 12 h. The solvent was then evaporated, and the crude product was purified by silica gel flash column chromatography (hexane/AcOEt = 10:1) to give **4ab** (48 mg, 57%) as a colorless solid (mp 56.9−57.7 °C): IR ($CHCl_3$) 1708, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.83 (s, 3 H), 3.70 (s, 3 H), 4.13−4.16 (m, 2 H), 4.19−4.21 (m, 2 H), 5.37 (br s, 1 H), 7.35−7.37 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2, 46.7, 64.3, 65.0, 104.5, 114.5, 141.2, 143.0, 162.3; MS (FAB): *m*/*z* 167 (100) [M^+ − H]. Anal. Calcd for $C_9H_{12}O_3$ (168.19): C, 64.27; H, 7.19. Found: C, 63.98; H, 6.91.

Other cycloisomerization reactions were carried out in a similar manner. **5**,[4a] **8bf**,[17] and **9bf**[17] were known compounds.

Typical Procedure for Reaction of 2bb with DMAD. A solution of **2bb** (151 mg, 0.470 mmol), DMAD (142 mg, 1.00 mmol), $Pd_2(bq)_2(nbe)_2$ (14.6 mg, 0.0237 mmol), and $P(OPh)_3$ (14.6 mg, 0.0470 mmol) in dry degassed 1,2-dichloroethane (5 mL) was refluxed under Ar for 24 h. The solvent was then evaporated, and the crude product was purified by silica gel flash column chromatography (hexane/AcOEt = 30:~3:1) to give **4bb** (28.8 mg, 19%), **10** (23.2 mg, 15%), **11** (54.5 mg, 25%), and **12** (79.9 mg, 40%).

Analytical data for 10: IR ($CHCl_3$) 1721, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60−1.61 (m, 3 H), 2.43 (s, 3 H), 3.74 (s, 3 H), 4.07−4.10 (m, 2 H), 4.25−4.29 (m, 2 H), 5.55 (d, *J* = 1.4 Hz, 1 H), 6.32 (d, *J* = 1.4 Hz, 1 H), 7.33 (d, *J* = 8.1 Hz, 2 H), 7.74 (d, *J* = 8.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

12.6, 21.6, 52.2, 57.3, 59.0, 127.3, 127.4, 128.8, 129.6, 132.6, 133.8, 134.0, 143.3, 166.0; MS (EI) *m/z* 321 (68) [M^+], 306 (11) [M^+ − Me], 246 (68) [M^+ − H − Me − CO_2Me], 166 (100) [M^+ − $SO_2C_6H_4$Me]; This compound is unstable and slowly decomposes even at −15 °C. Thus, satisfactory elemental analytical values were not obtained. Anal. calcd for $C_{16}H_{19}NO_4S$ (321.39): C, 59.79; H, 5.96; N, 4.36. Found: C, 59.42; H, 6.16; N, 3.90.

Analytical data for 11: mp 160.0−161.1 °C; IR ($CHCl_3$) 1724, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 3 H), 2.36 (d, J = 16.8 Hz, 1 H), 2.44 (s, 3 H), 2.59 (d, J = 16.8 Hz, 1 H), 2.79 (d, J = 9.2 Hz, 1 H), 3.62 (d, J = 9.2 Hz, 1 H), 3.74 (s, 3 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 4.08 (d, J = 19.8 Hz, 1 H), 4.64 (d, J = 19.8 Hz, 1 H), 7.36 (d, J = 8.1 Hz, 2 H), 7.73 (d, J = 8.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 21.7, 34.0, 44.0, 52.2, 52.4, 52.5, 60.2, 65.1, 119.0, 127.3, 127.6, 129.8, 132.4, 134.2, 144.0, 161.4, 163.6, 166.4, 167.3; MS (EI) *m/z* 463 (23) [M^+], 431 (58) [M^+ − H − OMe], 404 (46) [M^+ − CO_2Me], 276 (100) [M^+ − H−OMe − $SO_2C_6H_4$Me]. Anal. Calcd for $C_{22}H_{25}NO_8S$ (463.50): C, 57.01; H, 5.44; N, 3.02. Found: C, 56.81; H, 5.49; N, 2.95.

Typical Procedure for Cyclizations of Enediyne Esters: Cyclization of 21 Using $Pd_2(dba)_3$ and PPh_3. A solution of **21** (200 mg, 0.71 mmol), $Pd_2(dba)_3$·$CHCl_3$ (18.5 mg, 0.018 mmol), and PPh_3 (9.4 mg, 0.036 mmol) in dry degassed toluene (7 mL) was refluxed under Ar for 2.5 h. The solvent was then evaporated, and the crude product was purified by silica gel flash column chromatography (hexane/AcOEt = 3:1) to give a mixture of **23** and **24** (73 mg, 36%) as a pale yellow oil: IR ($CHCl_3$) 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) [**23**] δ 2.91−2.98 (m, 2 H), 3.42−3.49 (m, 2 H), 3.76 (s, 6 H), 4.28−4.33 (m, 2 H), 4.52 (d, J = 17.4 Hz, 2 H), 4.98 (d, J = 17.4 Hz, 2 H), [**24**] δ 3.39−3.40 (m, 2 H), 3.72 (s, 3 H), 3.76 (s, 3 H), 4.10−4.15 (m, 1 H), 4.23 (br s, 1 H), 4.46−4.51 (m, 1 H), 4.57−4.61 (m, 1 H), 4.67−4.73 (m, 1 H), 4.80 (dd, J = 10.5, 1.8 Hz, 1 H), 4.90 (dt, J = 10.5, 1.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) [**23**] δ 45.3, 51.8, 70.2, 72.7, 120.3, 155.6, 165.2, [**24**] δ 41.7, 43.8, 52.0, 52.5, 69.3, 70.4, 75.6, 75.7, 117.1, 129.5, 129.5, 156.1, 165.5, 171.1; MS (FAB) *m/z* 277 (67) [M^+ − 3H], 247 (100) [M^+ − 2H − OMe]. Anal. Calcd for $C_{14}H_{16}O_6$ (280.27): C, 59.99; H, 5.75. Found: C, 59.97; H, 5.77.

The cyclization of **22a**,**b** was carried out in a similar manner.

Stoichiometric Reaction of $Pd_2(dba)_3$ with Enediyne Diester 21. A solution of **21** (112 mg, 0.40 mmol) and $Pd_2(dba)_3$·$CHCl_3$ (145 mg, 0.14 mmol) in dry degassed acetone (4 mL) was stirred under Ar for 5 h. The solvent was then evaporated, and the crude product was diluted with ether. Insoluble materials were filtered off through a pad of Celite under reduced pressure, and the residue was rinsed with ether. During the filtration, white solids were precipitated which were separated by filtration to give **25** (4 mg, 3.7% based on **1b**). The filtrate was evaporated in vacuo, and the residue was purified by silica gel flash column chromatography (hexane/AcOEt = 5:1−1:1) to give recovered **21** (11 mg, 10%) and **23** (14 mg, 12%).

Analytical data for 25: mp 145.0−146.0 °C; IR ($CHCl_3$) 1970, 1710, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.03−3.13 (m, 2 H), 3.86 (s, 6 H), 3.99 (d, J = 15.5 Hz, 2 H), 4.19−4.22 (m, 2 H), 4.85 (d, J = 14.4 Hz, 2 H), 5.12 (d, J = 15.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.7, 54.5, 68.0, 77.2, 88.2, 94.1, 160.7; MS (FAB) *m/z* 386 (100) [M^+], 355 (50) [M^+ − OMe]. Anal. Calcd for $C_{14}H_{16}O_6Pd$ (386.69): C, 43.48; H, 4.17. Found: C, 43.22; H, 4.08.

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Supporting Information Available: Analytical data for starting materials and products. X-ray crystallographic analysis data for **3ba**, **4bb**, **6bb**, **4be**, **6be**, **7bc**, and **10bh** and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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