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# Catalytic Dicyanative [4 + 2] Cycloaddition Triggered by Cyanopalladation Using Ene−Enynes and Cyclic Enynes with Methyl Acrylate

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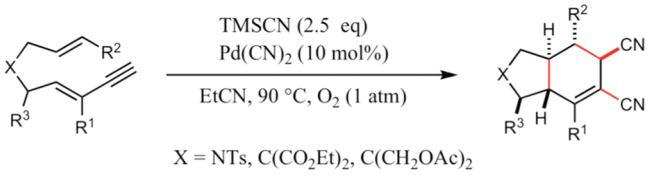


Palladium-catalyzed dicyanative [4 + 2] cycloaddition using various ene−enynes was investigated. The key species in this process is a cyanoallene intermediate that is obtained by the cyanopalladation of conjugated enynes followed by 5-*exo*-cyclization. To achieve an efficient [4 + 2] cycloaddition reaction, both the smooth generation of this species and critical control of regioselectivity in the 6-*endo*-cyclization step are quite important. A study of the substrate scope revealed that the reaction is strongly affected by the steric bulk of the substituents on the enyne and alkene units and prefers to give *trans*-fused cycloadducts. The stereochemistry of olefins was reasonably transferred to the corresponding products. Further study proved that this transformation includes not a thermal [4 + 2] cycloaddition process via 1,2-dicyanoalkenes generated in situ but rather a palladium-mediated stepwise cyclization sequence to control a maximum of five contiguous stereogenic centers in a single operation. An intermolecular version using methyl acrylate with conjugated cyclic enynes and TMSCN also gave the corresponding [4 + 2] cycloadducts in a regioselective manner.

## Introduction

Since the first report of cyanation using simple alkynes with HCN under transition-metal catalysis,[1] the introduction of a cyano function into simple and nonactivated carbon−carbon multiple bonds has been one of the most significant issues in synthetic organic chemistry, and the above cyanation protocol by nickel and palladium catalysis has been recently applied to the introduction of various elements[2−8] together with a CN group. In general, a cyano function on a transition metal acts as a pseudo halide (due to its lower nucleophilicity) and is unlikely to be transferred to C−C triple bonds as a nucleophile. Therefore, the reported

(1) For hydrocyanation, see: (a) Funabiki, T.; Yamazaki, Y.; Tarama, K. *J. Chem. Soc., Chem. Commun.* **1978**, 63. (b) Fallon, G. D.; Fitzmaurice, N. J.; Jackson, W. R.; Perlmutter, P. *J. Chem. Soc., Chem. Commun.* **1985**, 4. (c) Fitzmaurice, N. J.; Jackson, W. R.; Perlmutter, P. *J. Organomet. Chem.* **1985**, *285*, 375.

(2) For silylcyanation, see: (a) Chatani, N.; Hanafusa, T. *J. Chem. Soc., Chem. Commun.* **1985**, 838. (b) Chatani, N.; Takeyasu, T.; Horiuchi, N.; Hanafusa, T. *J. Org. Chem.* **1988**, *53*, 3539. (c) Chatani, N.; Hanafusa, T. *Tetrahedron Lett.* **1986**, *27*, 4201. (d) Suginome, M.; Kinugasa, H.; Ito, Y. *Tetrahedron Lett.* **1994**, *35*, 8635.

(3) For germylcyanation, see: (a) Chatani, N.; Horiuchi, N.; Hanafusa, T. *J. Org. Chem.* **1990**, *55*, 3393. (b) Chatani, N.; Morimoto, T.; Toyoshige, M.; Murai, S. *J. Organomet. Chem.* **1994**, *473*, 335.

(4) For stannylcyanation, see: Obora, Y.; Baleta, A. S.; Tokunaga, M.; Tsuji, Y. *J. Organomet. Chem.* **2002**, *660*, 173.

(5) For thiocyanation, see: Kamiya, I.; Kawakami, J.; Yano, S.; Nomoto, A.; Ogawa, A. *Organometallics* **2006**, *25*, 3562.

(6) For a review of transition-metal-catalyzed carbocyanation of carbon−carbon multiple bonds, see: (a) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2009**, *45*, 2452. (b) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904. (c) Nakao, Y.; Kanyiva, K.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146. (d) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874. (e) Cheng, Y.; Duan, Z.; Yu, L.; Li, Z.; Zhu, Y.; Wu, Y. *Org. Lett.* **2008**, *10*, 901.

(7) For acylcyanation, see: (a) Nozaki, K.; Sato, N.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 2679. (b) Kobayashi, Y.; Kamisaki, H.; Yanada, R.; Takemoto, Y. *Org. Lett.* **2006**, *8*, 2711. (c) Nishihara, Y; Inoue, Y.; Izawa, S.; Miyasaka, M.; Tanemura, K.; Nakajima, K.; Takagi, K. *Tetrahedron* **2006**, *62*, 9872.

(8) For cyanoboration, see: (a) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358. (b) Suginome, M.; Yamamoto, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2380. (c) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Organomet. Chem.* **2005**, *690*, 5300.

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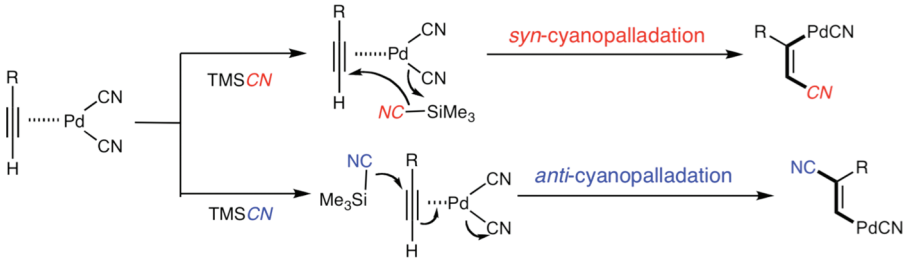
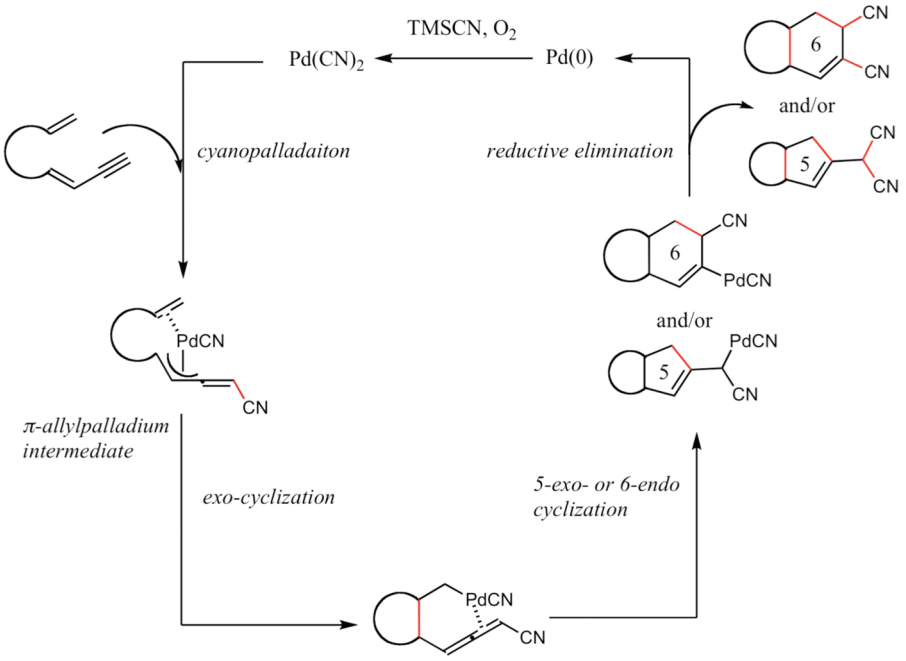
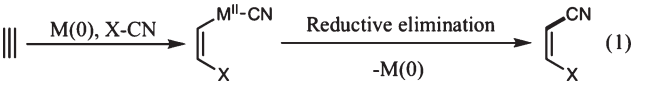
**SCHEME 1.** ***syn*- and *anti*-Cyanopalladation of Alkynes**




**SCHEME 2.** **Proposed Catalytic Cycloaddition Using Ene−Enynes**




methods for the introduction of a cyano functionality by Ni and Pd catalysis usually involve reductive elimination from an alkenyl−$M^{II}$−CN species (M = metal) that is generated through X−C bond formation, and alkenyl−CN is obtained together with M(0) (eq 1). On the other hand, we previously reported that the nucleophilic addition of cyanide by the use of TMSCN was effectively promoted under Pd(II) catalysis in the presence of oxygen,[9] and these results are, to the best of our knowledge, the first example of the cyanometalation of simple and nonactivated alkynes.[10a] According to our protocol, a catalytic cyanation of internal alkynes was also applicable[10] and the substrate-controlled 5-*exo*- and 6-*endo*-cyclizations of various enynes triggered by *syn*-cyanopalladation have been established.[10a,c] In this paper, we present a new application based on the above findings to establish a new protocol for dicyanative [4 + 2] cycloaddition triggered by cyanopalladation.[10d]




(1)

## Results and Discussion

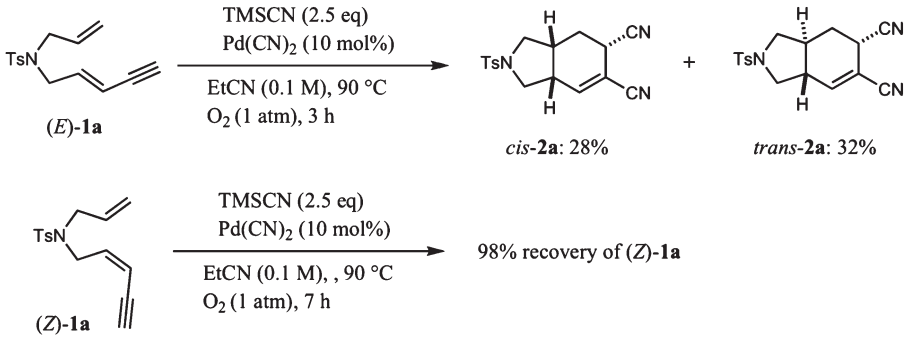
We recently developed a catalytic 1,2-dicyanation of various alkynes through the use of TMSCN with Pd(II) under aerobic conditions and proposed that both *syn*- and *anti*-cyanopalladation to C−C triple bonds are key reactions (Scheme 1).[10a,b] In addition, we revealed that the former transformation plays an important role in the 5-*exo*- and 6-*endo*-cyclization sequences that give the functionalized heterocycles.[10a,c]

For a further application of this approach, we next investigated a new cycloaddition protocol using ene-enynes. If a cyanoallene species[10c] could be generated as a key intermediate in a catalytic cycle and react with an organopalladium species to promote ring formation, this strategy

(9) For reviews on palladium catalysis with oxidants, see: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. Pd-catalyzed enantioselective oxidative [2 + 1] cycloadditions have been reported; see: (c) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836. (d) Tsujihara, T.; Takenaka, K.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Am. Chem. Soc.* **2009**, *131*, 3452.

(10) For dicyanation, see: (a) Arai, S.; Sato, T.; Koike, Y.; Hayashi, M.; Nishida, A. *Angew. Chem.* **2009**, *121*, 4598. *Angew. Chem., Int. Ed.* **2009**, *48*, 4528. (b) Arai, S.; Sato, T.; Nishida, A. *Adv. Synth. Catal.* **2009**, *351*, 1897. (c) Arai, S.; Koike, Y.; Nishida, A. *Adv. Synth. Catal.* **2010**, *352*, 893. (d) Arai, S.; Koike, Y.; Hada, H.; Nishida, A. *J. Am. Chem. Soc.* **2010**, *132*, 4522.

**SCHEME 3. Reaction of 1a**




would enable easy access to functionalized cycloalkenes (Scheme 2). To realize the above transformation, we initially designed ene-enyne **1** having a conjugated enyne: nucleophilic cyanation (cyanopalladation) would occur at the terminal *sp*-carbon of the conjugated enynes and subsequent *exo*-cyclization via an allylpalladium intermediate would give the corresponding alkylpalladium species that would react with the C−C double bonds of the cyanoallene to afford cyclized products. The features of this reaction include (1) four C−C bond-forming reactions in a single operation, (2) regiocontrol of C−C double bonds of cyanoallene in a second cyclization, (3) stereocontrol at the ring juncture, and (4) facile synthesis of highly functionalized cycloalkenes.

To realize our expectation, we initially examined the reaction using **1a** to evaluate their reactivity (Scheme 3). Interestingly, the stereochemistry of the conjugated enyne was found to be critical in this reaction. For example, the reaction of (*E*)-**1a** proceeded smoothly to give the *cis*- and *trans*-fused cyclohexene derivatives (**2a**) in respective yields of 28% and 32%. On the other hand, (*Z*)-**1a** was recovered quantitatively even after 7 h under similar conditions without any trace of the 1,2-dicyanated products, which means that the terminal C−C triple bond in the latter substrate was not effectively activated by Pd(II). These results suggest that the terminal C−C triple bond in (*E*)-**1a** is more suitable for activation by Pd(II) and the diene moiety of the *Z*-isomer could act as a bidentate ligand to Pd(II) and significantly prevent the activation of a terminal C−C triple bond.

Based on these observations, we further studied the scope and limitations of this reaction (Table 1). As shown in entries 1 and 2, the stereoselectivity at the ring juncture is strongly influenced by $R^1$, and a bulkier substituent gave a higher *trans* selectivity. The stereochemistry of both *cis*- and *trans*-**2b** was determined by X-ray crystallographic analysis.[11] To investigate the influence of the olefin geometry, both **1d** and **1e** were examined under similar conditions. As a result, the former gave a separable mixture of *cis*- and *trans*-**2d** in 15% yield (entry 3), and the latter was smoothly transformed to **2e** with a shorter reaction time and in better yield (entry 4). A careful investigation of the NMR results revealed that the stereochemistry of the methyl group in **1d**,**e** was successfully transferred to the corresponding products. We next examined the effect of $R^2$ using **1f**−**h**. A substrate with a phenyl group as $R^2$, such as **1f**, gave the corresponding *trans* adducts (**2fa**) in 59% yield together with **2fb** in 5% yield (entry 5). In the case of **1g**, the reaction was completely prohibited; however a substrate with a cyclopropyl group (**1h**) gave the *trans* adduct in 27% yield (entries 6 and 7). When the reaction using **1i** was performed under similar conditions, the formation of five contiguous stereogenic centers was completely controlled in a single operation to give **2i** as a sole cycloadduct in 60% yield (entry 8). The reactivity of a substrate with alkylidene cyclopropane (**1j, k**) also depended on the steric bulk of $R^1$ and **1j** gave a separable mixture of *cis*- and *trans*-fused cycloadducts in 60% yield (entry 9). However, **1k** was completely inert for this cycloaddition reaction (entry 10). In the case of malonate derivatives, $R^1$ had a significant effect, and bulkier substituents gave *trans* selectivity. For example, **1j** gave an inseparable 1:1 mixture of *cis* and *trans* adducts in 60% yield (entry 11), and both **1k** and **1l** were exclusively transformed to the corresponding *trans* adducts in respective yields of 78% and 56% (entries 12 and 13). As described in entries 14 and 15, the steric bulk of $R^2$ dramatically decreased the reactivity of **1o** and **1p** even when $R^1$ was H, and the latter gave an inseparable mixture of cycloadducts *cis*- and *trans*-**2p** in 41% yield. The substituents at both the $R^1$ and $R^2$ positions in **1q** and **1r** completely prevented the reaction (entries 16 and 17). Bisacetoxymethyl instead of an ethoxycarbonyl group gave *trans*-**2s** in 59% yield exclusively when $R^2$ was phenyl group (entry 18).

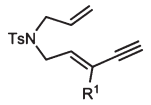
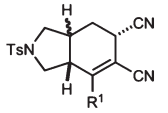
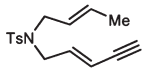
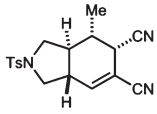
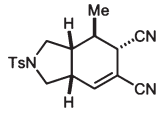
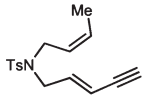
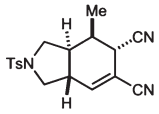
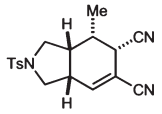
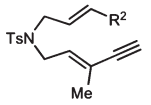
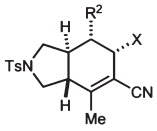
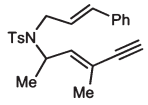
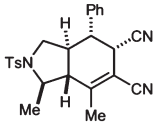
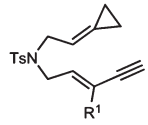
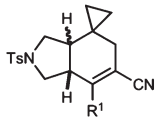
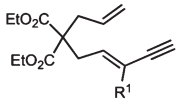
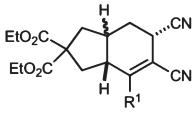
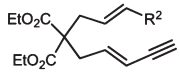
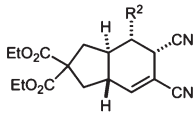
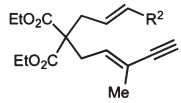
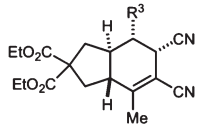
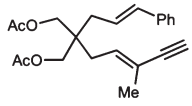
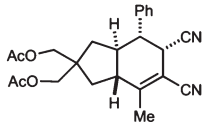
Next, we sought to prepare a tricyclic skeleton using this protocol (Scheme 4). Both substrates (**3a**,**b**) were successfully converted to the corresponding nitrogen heterocycles in a stereoselective manner. The stereochemistry of all of the products was fully assigned by NMR analysis.

To confirm the reaction pathways and catalytic cycle, **5a** was examined for the formation of the third ring by the insertion of terminal carbon−carbon double bonds if organopalladium species could be generated as key intermediates and were sufficiently reactive (Scheme 5). We realized that both the [4 + 2] cycloadducts (**6aa**) and the expected tricyclic product were obtained. The latter product (**6ab**) was fully characterized, and its stereochemistry was assigned based on the results of an NOE experiment between $CH_2CN$ and C*H*CN. This result constitutes direct evidence for the generation of an alkenylpalladium species that reacts with a cyanoallene intermediate before reductive elimination.

Other substrates **5b**−**d** revealed the reactivity of cyanoallene intermediates. When alkenyl chains were introduced at the *ortho* position in a phenyl group, the [4 + 2] cycloaddition reaction was favored and terminal C−C double bonds were

(11) Supplemental crystallographic data is available free of charge from the Cambridge Crystallographic Data Centre (nos. 746745 and 748867 for *cis*- and *trans*-**2b**, respectively).

**TABLE 1. Substrate Scope of [4 + 2] Cycloaddition**[a]

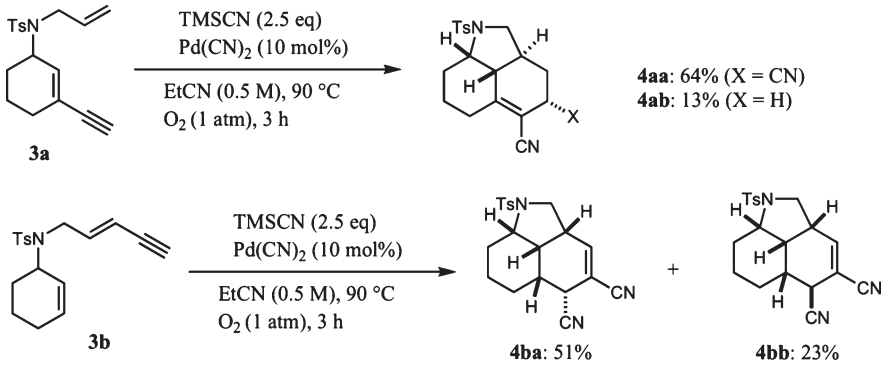
| entry | substrate | | time, conc | products (%) | |
|---|---|---|---|---|---|
| 1 |  | **1b**: $R^1$ = Me | 5 h, 0.1 M |  | **2b**: 55% (cis:trans = 1:2.4) |
| 2 | | **1c**: $R^1$ = Ph | 8 h, 0.5 M | | **2c**: 55% (cis:trans = 1:3.6) |
| 3 |  | **1d** | 6 h, 0.5 M |  | *trans*-**2d**:10% |
| | | | |  | *cis*-**2d**:5% |
| 4 |  | **1e** | 4 h, 0.5 M |  | *trans*-**2e**:14% |
| | | | |  | *cis*-**2e**:35% |
| 5 |  | **1f**: $R^2$ = Ph | 6 h, 0.1 M |  | **2fa**: X = CN, 59% **2fb**: X = H, 5% |
| 6 | | **1g**: $R^2$ = Me | 24 h, 0.5 M | | **2g**: 0% |
| 7 | | **1h**: $R^2$ = cyclopropyl | 1 h, 0.5 M | | **2h**: 27% |
| 8 |  | **1i** | 3 h, 0.5 M |  | **2i**: 60% |
| 9 |  | **1j**: $R^1$ = H | 10 h, 0.1 M |  | **2j**: 60% (cis:trans = 1:0.7) |
| 10 | | **1k**: $R^1$ = Me | 24 h, 0.5 M | | **2k**: 0 |
| 11 |  | **1l**: $R^1$ = H | 10 h, 0.1 M |  | **2l** 60% (cis:trans = 1:1) |
| 12 | | **1m**: $R^1$ = Me | 19 h, 0.1 M | | **2m**78% (trans only) |
| 13 | | **1n**: $R^1$ = Ph | 24 h. 0.5 M | | **2n**: 56% (trans only) |
| 14 |  | **1o**: $R^2$ = Ph | 5 h, 0.5 M |  | *trans*- and cis-**2o**: trace |
| 15 | | **1p**: $R^2$ = Me | 30 h, 0.5 M | | trans- and cis-**2p**: 41% (*dr* = 3:1) |
| 16 |  | **1q**: $R^2$ = Ph | 12 h, 0.1 M |  | **2q**: 0% |
| 17 | | **1r**: $R^2$ = Me | 12 h, 0.1 M | | **2r**: 0% |
| 18 |  | **1s** | 3 h, 0.5 M |  | **2s:** 59% |

[a]All reactions were carried out in the prepsence of $Pd(CN)_2$ (10 mol %) with TMSCN (2.5 equiv) in EtCN at 90 °C under $O_2$ atmosphere (1 atm).

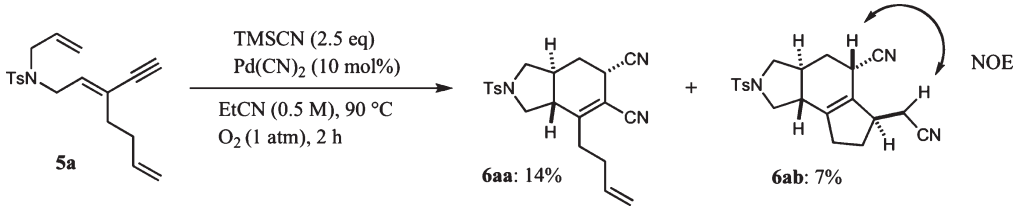
intact during the reactions (Scheme 6). For example, **5b** was successfully transformed to **6b** in 48% yield as a single stereoisomer. Compounds **5c** and **5d** showed similar reactivity to give **6c** and **6d** without any trapping by the terminal C−C double bonds, with respective yields of 34% and 52%. Finally, we concluded that alkyl- or benzylpalladium species would quickly react with cyanoallene intermediates via *a* 6-*endo* mode rather than 5- or 6-*exo*-cyclization with terminal C−C double bonds in **5b**−**d**.

According to the experimental details described above, we propose a plausible catalytic cycle for this [4 + 2] cycloaddition (Scheme 7). A terminal C−C triple bond of the conjugated enyne is initially activated by Pd(II) and nucleophilic cyanation with TMSCN at a terminal sp carbon (cyanopalladation) gives allylpalladium species **A** that promotes 5-*exo*-cyclization by the insertion of olefin. This first cyclization step obviously determines the stereochemistry of the ring juncture, and the results in Table 1 suggest that the steric

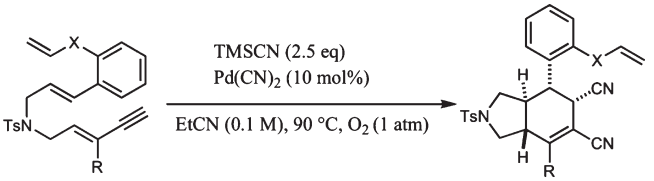
**SCHEME 4. Application to the Synthesis of a Tricyclic Core**




**SCHEME 5. Sequential Ring Formation Using 5a**




**SCHEME 6. Cycloaddition Using 5b−d**

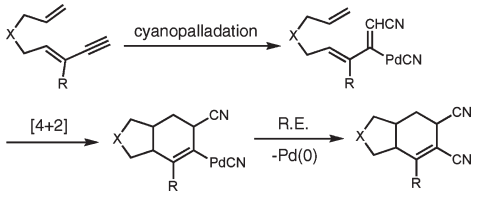



bulk of $R^1$ and $R^2$ is quite important for both the reactivity and selectivity in this cyclization. On the basis of the results of **1b** vs **1g**, **1j** vs **1k**, and **1m** vs **1r**, the steric repulsion between $R^1$ and $R^2$ would prevent *exo*-cyclization. On the other hand, higher *trans* selectivity was observed when bulky substituents were introduced. These results explain why intermediate **B1** from **A** is preferred to **B2**, so that cycle I could proceed predominantly when the reaction proceeds trans-selectively. These schemes reasonably explain the results in entries 3 and 4. The reactivity is dependent on the stereochemistry of the olefin because an *E*-methyl group rather than *Z*- would cause more critical steric repulsion against $R^1$ to prevent the first cyclization. The stereogenic center on $R^3$ is completely controlled because the $A^{13}$ strain in the transition state in the first cyclization step would cause $R^3$ to be at a pseudo-equatorial position. When 5-*exo*-cyclization successfully occurred, the corresponding alkyl palladium(II) species **C1** and **C2** could be generated. In the case of **1d**, **1g** and **1q**, the reactions proceeded smoothly against the steric bulk of the phenyl group. This could be explained by the notion that the corresponding benzylpalladium species ($R^2$ = Ph) could be stabilized due to $\eta^1-\eta^3$ equilibrium and subsequent insertion of the double bond of cyanoallene would complete 6-*endo*-cyclization to give alkenyl palladium species **D1** and **D2**. Finally, the dicyanated bicyclic products **2** are obtained by reductive elimination from **D** together with Pd(0), which could be smoothly converted to $Pd(CN)_2$ by oxygen with TMSCN via $PdO_2$. When a butenyl side chain is introduced to a conjugated enyne such as **5d**, **D1** could be trapped by insertion for the third cyclization before reductive elimination, and would give **6ab** with Pd(0). The above results can explain why this cycloaddition proceeds *via* a palladium-mediated sequence that includes organopalladium intermediates **A**−**D**.[12]

Next, we applied this protocol to an intermolecular version. When a conjugated enyne **7a** was examined, methyl acrylate (MA) gave [4 + 2] cycloadducts **8a** as an exclusive product with a 1:1 mixture of diastereomers in 60% yield (entry 1). Substrates with a seven- and eight-membered ring were also applicable to give **8b**,**c** in respective yields of 44 and 56% (entries 2 and 3). Compound **7d** was also converted to the corresponding cycloadducts in moderate yield. These results are summarized in Table 2.

When the *syn*-1,2-dicyano adduct from **7a** with methyl acrylate was employed under similar thermal conditions, traces of the cycloadducts were obtained as a mixture of regioisomers. Even in the presence of TMSCN and/or Pd(II)

(12) As the one of the reviewers indicates, another reaction pathway is also possible. If the alkenylpalladium species by initial cyanopalladation could be directly converted to cyclohexenylpalladium species via [4 + 2] cycloaddition, the following reductive elimination would give the same products, as shown below. Further investigation to evaluate this possibility is currently underway.



**SCHEME 7. Plausible Catalytic Cycle**

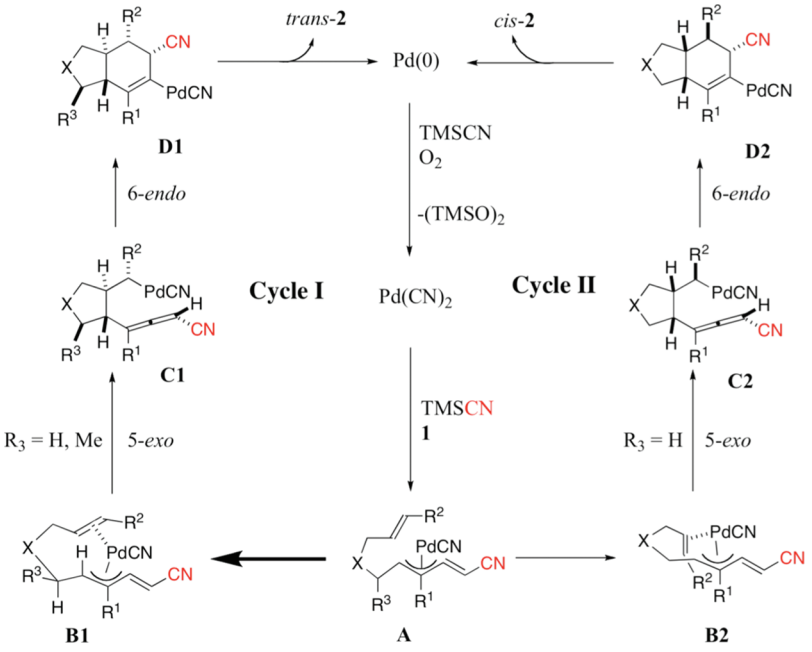
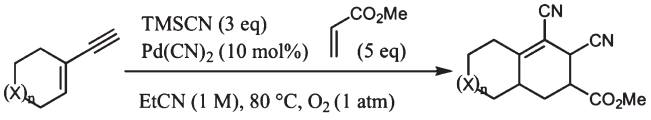



**TABLE 2. Intermolecular Dicyanative [4 + 2] Cycloaddition**




7 8

| entry | substrate **7** | time (h) | yield of **8** (%) | diastereo ratio |
|---|---|---|---|---|
| 1 | **7a**: X = $CH_2$, $n$ = 1 | 24 | **8a**: 60 | 1:1 |
| 2 | **7b**: X = $CH_2$, $n$ = 2 | 24 | **8b**: 44 | 2:1 |
| 3 | **7c**: X = $CH_2$, $n$ = 3 | 43 | **8c**: 56 | 1:1 |
| 4 | **7d**: X = C*t*-Bu, $n$ = 1 | 24 | **8d**: 35 | 1:1 |

and/or oxygen, the results were not improved at all. These results suggest that this cycloaddition reaction includes not a concerted mechanism but a palladium-mediated stepwise cyclization pathway through the reaction (see the Supporting Information).

## Conclusion

We have demonstrated a palladium-catalyzed dicyanative [4 + 2] cycloaddition of various dienynes and propose a catalytic cycle that offers a reasonable explanation for the observed stereoselectivity. This cycloaddition includes (1) the sequential formation of four C−C bonds, (2) easy access to functionalized cyclohexenes, and (3) facile construction of a polycyclic ring system. For example, ene−enynes **1** and **3** were successfully converted to the corresponding dicyano cycloadducts **2** and **4**, respectively. The former reaction was strongly influenced by the substituents on carbon−carbon multiple bonds and their steric repulsion was quite important for achieving higher *trans* selectivity. Furthermore, cycloaddition using **1** can control a maximum of five contiguous stereogenic centers. In the case of **3,** a tricyclic core was easily constructed in a single operation. The reaction using enynes **7** with MA gave the corresponding cycloadducts in a regioselective fashion. These observations could provide a new perspective on palladium chemistry, and further application of this dicyanation of alkynes is currently underway.

## Experimental Section

**Typical Procedure for Pd-Catalyzed Enyne Cyclization of 1d (Table 1, Entry 3).** To a solution of enyne **1d** (0.3 mmol) in EtCN (3.0 mL) were added palladium cyanide (4.8 mg, 0.03 mmol, 10 mol %) and TMSCN (0.1 mL, 0.75 mmol) at room temperature. The mixture was stirred for 3 h at 90 °C under an oxygen atmosphere. After the reaction was monitored by TLC, subsequent direct column chromatography (hexane−AcOEt) gave the cyclized products *cis*-**2d** and *trans*-**2a**, respectively.

For *cis*-**2d**: colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.15 (d, $J$ = 6.4 Hz, 3H), 1.47−1.56 (m, 1H), 2.00−2.05 (m, 1H), 2.84−2.90 (m, 2H), 3.04 (ddd, $J$ = 2.0, 2.4, 9.2 Hz, 1H), 3.29 (dd, $J$ = 3.6, 11.2 Hz, 1H), 3.53 (dd, $J$ = 6.8, 11.2 Hz, 1H), 3.68 (dd, $J$ = 12.4, 14.0 Hz, 1H), 6.62 (dd, $J$ = 2.8, 4.0 Hz, 1H), 7.38 (d, $J$ = 8.4 Hz, 2H), 7.71 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 18.3, 21.6, 32.0, 35.3, 38.2, 40.9, 50.6, 50.7, 109.5, 115.5, 116.8, 127.5, 130.0, 132.5, 144.6, 145.0; IR (ATR) $\nu$ 2924, 2221, 1341, 1156, 1091, 814, 753 cm$^{-1}$; LRMS (EI) $m/z$ 341 ($M^+$), 275, 238, 186 ($M^+$ − Ts), 155 (Ts), 140, 105, 91, 58; HRMS (EI) calcd for $C_{18}H_{19}N_3O_2S$, 341.1198 ($M^+$), found 341.1186.

For *trans*-**2d**: colorless solid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.22 (d, $J$ = 6.8 Hz, 3H), 1.58−1.69 (m, 1H), 1.99−2.08 (m, 1H), 2.34−2.42 (m, 1H), 2.46 (s, 3H), 2.95 (dd, $J$ = 9.2, 11.6 Hz, 1H), 3.05 (dd, $J$ = 9.6, 11.2 Hz, 1H), 3.53 (m, 1H), 3.60 (dd, $J$ = 7.2, 9.6 Hz, 1H), 3.79 (dd, $J$ = 7.6, 9.2 Hz, 1H), 6.83−6.85 (m, 1H), 7.36 (d, $J$ = 8.4 Hz, 2H), 7.71 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 16.8, 21.6, 33.5, 36.9, 43.2, 43.7, 49.5, 49.7, 110.5, 115.2, 115.8, 127.2, 130.1, 134.2, 144.1, 145.3; IR (ATR) $\nu$ 2969, 2923, 2225, 1322, 1157, 1099, 809, 766 cm$^{-1}$; LRMS (EI) $m/z$ 341 ($M^+$), 277, 198, 186 ($M^+$ − Ts), 155 (Ts), 91, 83, 58; HRMS (EI) calcd for $C_{18}H_{19}N_3O_2S$ 341.1198 ($M^+$), found 341.1201; mp 196−197 °C.

**Typical Procedure for Pd-Catalyzed Intermolecular [4 + 2] Cycloaddition Using Conjugated Enynes 7a with Methyl Acrylate (Table 2, Entry 1).** To a solution of a starting enyne (162 mg,

1.0 mmol) in propionitrile (1.0 mL) were added TMSCN (298 mg, 3.0 mmol), methyl acrylate (400 mg, 5.0 mmol), and $Pd(CN)_2$ (16 mg, 0.1 mmol) at room temperature. The resulting mixture was heated under oxygen atmosphere (1 atm) at 100 °C for 24 h. The following direct flash column chromatography (hexane/AcOEt = 2:1) gave inseparable diastereomixture of the desired [4 + 2] cycloadducts as yellow oil (106.2 mg, 35%).

Major two isomers are assigned: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.85 (s, 9H X 0.5), 0.89 (s, 9H X 0.5), 1.10−1.68 (m, 4H), 1.72−1.85 (m, 1H), 1.95−2.05 (m, 1H), 2.32−2.87 (m, 4H), 3.76 (s, 3H X 0.5), 3.82 (s, 3H X 0.5); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.5, 21.6, 23.8, 26.8, 26.9, 27.4, 27.8, 29.0, 29.2, 30.1, 31.2, 31.6, 32.6, 33.1, 34.6, 35.8, 40.4, 41.3, 41.7, 43.1, 52.1, 52.7, 99.7, 100.9, 115.3, 115.7, 116.8, 117.9, 164.2, 166.4, 170.1, 171.5; IR (ATR) $\nu$ 2953, 2870, 2214, 1735, 1202 cm$^{-1}$; LRMS (EI) $m/z$ 300 ($M^+$), 285 ($M^+$ − Me), 273 ($M^+$ − HCN), 244, 230, 217, 185, 158; HRMS (EI) calcd for $C_{18}H_{24}N_2O_2$ 300.1838 ($M^+$), found 300.1835.

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**Supporting Information Available:** Full characterization of new compounds of cycloadducts and cyclization precursors via $^1$H and $^{13}$C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.