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Catalytic Dicyanative [4+2] Cycloaddition Triggered by Cyanopalladation of Conjugated Enynes under Aerobic Conditions

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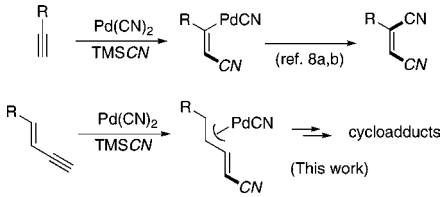
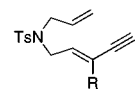
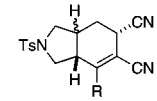
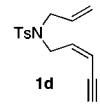
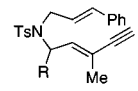
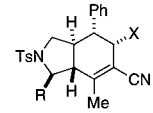
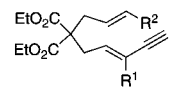
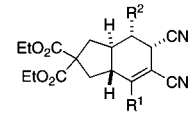
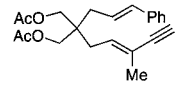
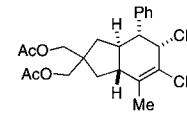
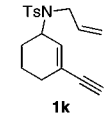
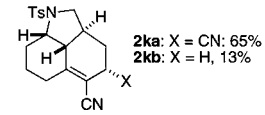
Ever since a cyano group was recognized as a useful functionality, its introduction, in particular to carbon−carbon triple bonds by Ni(0)- or Pd(0) complexes with X−CN (X = H,[1] Si,[2] Ge,[3] Sn,[4] S,[5] C,[6] B[7]), has been a major topic in synthetic organic chemistry. Recently, we developed a catalytic 1,2-dicyanation of alkynes by Pd(II) under aerobic conditions and revealed that this reaction involves direct *nucleophilic cyanation* to C−C triple bonds (*anti*- and *syn*-cyanopalladation).[8a,b] Since a cyano group on palladium(II) acts as a pseudo halide and is not likely to be transferred due to lower nucleophilicity, the above findings are quite interesting. In this communication, we focused on the unique reactivity of π-allyl palladium species generated by the cyanopalladation of conjugated enynes and investigated its application to the construction of highly functionalized fused cyclohexenes in a stereoselective manner by a new protocol (Scheme 1).

Scheme 1. Cyanopalladation of Alkynes and Enynes



Initially, treatment of **1a** under the optimized conditions (2.5 equiv of TMSCN in propionitrile under an O_2 atmosphere (1 atm) at 80 °C) gave the *cis*- and *trans*-fused cyclohexene derivatives **2a** in 55% yield as a separable mixture, and their stereochemistry was determined by X-ray crystallographic analysis.[9] The reaction rate was influenced by a bulky substituent on R; for example, the reaction of **1a,b** was completed within 5 and 3 h, respectively, and a longer reaction time and higher concentration were required when R was a phenyl group. On the other hand, the steric bulk of R obviously improved the diastereoselectivity with a cis:trans ratio of from 1:1.1 (R = H) to 1:3.6 (R = Ph) (entries 1−3). The stereochemistry of the conjugated enyne was critically important because **1d** gave no reaction and was recovered quantitatively (entry 4). This result suggests that the stereochemistry of the enyne would be important for activation by Pd(II), and the fact that no 1,2-dicyano adducts were obtained at all indicates that the terminal C−C triple bond of **1d** could not be activated effectively. In the case of **1e** bearing a cinnamyl moiety, both *trans*-fused cycloadducts **2ea** and **2eb** were obtained in respective yields of 59% and 5%, while **1f** gave the *trans*-adduct of **2f** in 60% yield, exclusively. These findings indicate that our protocol could effectively control four or five contiguous stereogenic centers through one operation (entries 5 and 6). As shown in entries 7 and 8, the malonate derivatives **1g,h** gave the corresponding *trans*-fused cycloadducts as sole products, in respective yields of 78% and 56%. With a substrate having a crotyl group instead of an allyl group, **2i** was obtained in 41% yield as inseparable diastereomers (entry 9). When **1j** with a bisacetoxymethyl functionality was examined, the cycloadduct **2j** was successfully obtained in a stereoselective fashion (entry 10). Finally, treatment of **1m** gave the tricyclic compound **2ka** in 65% yield together with **2kb** in 13% yield (entry 11). These results are summarized in Table 1.

Table 1. Dicyanative [4+2] Cycloaddition of **1**[a]

entry	substrates	conditions	products
			
1	**1a**: R = Me	5 h	**2a**: 55% (cis:trans = 1:2.4)[2)]
2	**1b**: R = H	3 h	**2b**: 60% (cis:trans = 1:1.1)
3[3)]	**1c**: R = Ph	8 h	**2c**: 55% (cis:trans = 1:3.6)
4	 **1d**	7 h	no reaction[4)]
			
5	**1e**: R = H	6 h	**2ea**: X = CN: 59%, **2eb**: X = H: 5%
6[3)]	**1f**: R = Me	3 h	**2f**: X = CN: 60%
			
7	**1g**: R^1 = Me, R^2 = H	19 h	**2g**: 78 %
8[3)]	**1h**: R^1 = Ph, R^2 = H	24 h	**2h**: 56%
9[3)]	**1i**: R^1 = H, R^2 = Me	30 h	**2i**: 41 %[5)]
			
10[3)]	**1j**	3 h	**2j**: 59%
			
11[3)]	**1k**	3 h	**2ka**: X = CN: 65% **2kb**: X = H, 13%

[a] All reactions were carried out in the presence of TMSCN (2.5 equiv), $Pd(CN)_2$ (10 mol %)in EtCN (0.1 M) under O_2 atmosphere (1 atm) at 80 °C. [b] The stereochemistry for *cis*- and *trans*-**2a** was assigned by X-ray analysis; see Supporting Information. [c] Reaction concn was 0.5 M. [d] Starting material was recovered in quantitative yield. [e] Inseparable mixture of two diastereomers (3:1); see Supporting Information.

Next, we examined the intermolecular reaction between **3a** and methyl acrylate (MA), as shown in Scheme 2. The reaction proceeded smoothly under the optimized conditions to give the

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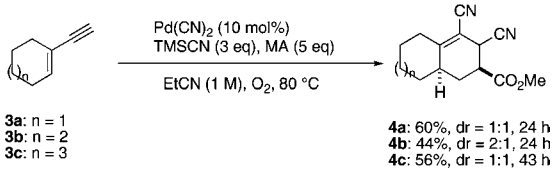
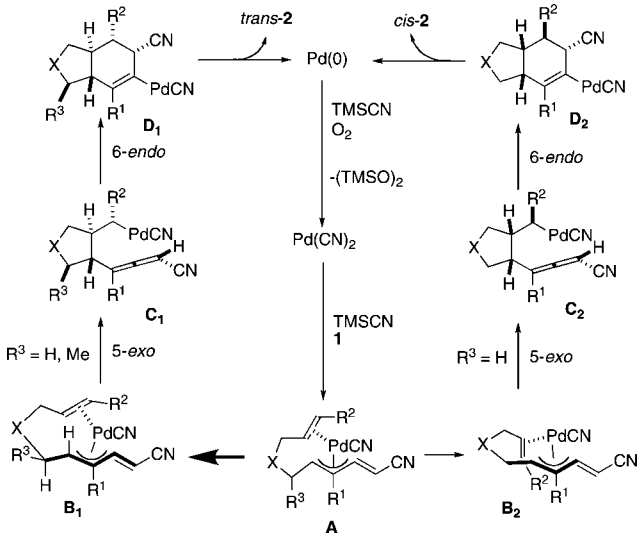
bicyclic products **4a** in 60% yield as a 1:1 diastereomixture in a regioselective fashion. This system was applicable for seven- and eight-membered cyclic enynes to give the corresponding [4+2] cycloadducts (**4b,c**) in moderate yield (Scheme 2). Further investigation showed that simple alkenes and internal alkynes instead of MA were all inert in cycloaddition and the reaction with separately prepared 1,2-dicyano-1,3-diene from **3a** with MA under the optimized conditions did *not* give **4a** at all. These preliminary results suggest the cycloaddition reaction does not include the thermal [4+2] cycloaddition between 1,2-dicyano-1,3-diene derivatives from **3** and MA but rather involves a Pd-mediated stepwise cycloaddition sequence.

Scheme 2. Reaction of **3** with MA



Based on the experimental findings observed in the reaction of **1** [(1) bulky substituents R^1 decreased the reaction rate, (2) the *trans*-selectivity is strongly influenced by the steric bulk of R^1 or R^2, and (3) no trace of the 1,2-dicyanoadducts were not observed at all during the reactions], we propose the reaction pathway shown in Scheme 3.

Scheme 3. Plausible Reaction Pathways



Dienyne **1** activated by Pd(II) is converted to π-allyl palladium complex **A** by cyanopalladation. When R^2 is not H or when bulkier substituents are introduced to R^1, steric repulsion between R^1 and CHR^2 would prevent the formation of $\mathbf{B_2}$ and R^3 at an equatorial position is more favored to avoid steric repulsion against R^1 due to A^{13} strain. Thus, $\mathbf{B_1}$ would act as a favored intermediate to give *trans*-fused alkylpalladium species $\mathbf{C_1}$. The resulting intermediate reacts with a cyanoallene functionality *via* 6-*endo* cyclization to give $\mathbf{D_1}$, and the subsequent reductive elimination gives *trans*-**2** together with Pd(0), which may be oxidized to Pd(II) under aerobic conditions.

In summary, we have demonstrated the dicyanative [4+2] cycloaddition of the dienyne derivatives that is triggered by cyanopalladation. This new protocol includes the formation of four carbon−carbon bond formations and gives highly functionalized cyclohexenes in only one operation. These transformations may provide a new insight into palladium chemistry, and further investigations are currently underway.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) ORTEP figures for both *trans*- and *cis*-**2a** and additional details of X-ray analysis are in the Supporting Information.
(10) Substrates having allene, internal alkyne, and diene moieties instead of alkenes were all unsuccessful in catalytic dicyanative [4+2] cycloaddition, see: Supporting Information.

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