Palladium Catalysis

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Palladium-Catalyzed Cyanation of Carbon–Carbon Triple Bonds Under Aerobic Conditions**

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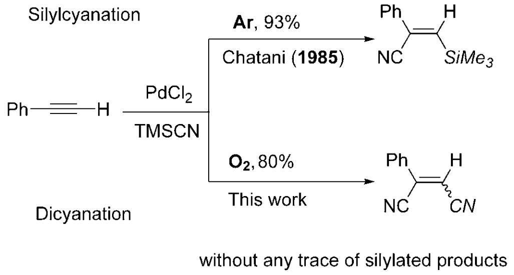
The cyano group has been recognized as a useful functional group that is equivalent to carbonyl, amino-, and hydroxymethyl groups: Its efficient introduction into organic molecules has been explored in synthetic organic chemistry mainly using simple substitution reactions. Although nucleophilic cyanation of carbonyl-type groups such as C=O, C=N, and conjugated C=C bonds[1] has been widely investigated, cyanation of simple and nonconjugated carbon–carbon multiple bonds by transition-metal catalysis is of current interest.[2–6] Since the first report of the hydrocyanation of alkynes,[2] many examples of the addition of X–CN (X = Si,[3a–c] Ge,[3d] Sn,[4a] S,[4b] C,[5] and B[6]) to alkynes by using palladium or nickel catalysis have been reported.

Trimethylsilylcyanide (TMSCN) is one of the most widely used cyanating agents because of its ready availability. Chatani and Hanafusa were the first to use it in the silylcyanation of terminal alkynes under an argon atmosphere.[3a] We discovered that this silylcyanation process can be completely inhibited under an oxygen atmosphere, while 1,2-dicyanation proceeded quite effectively (Scheme 1). Although Chatani et al. isolated a 1,2-dicyanated product from diphenylacetylene with TMSCN under oxygen-free conditions,[3b] no further investigation of its mechanism or reaction scope was reported. We report herein our preliminary results of palladium-catalyzed 1,2-dicyanation of alkynes as well as cyanative cyclization of 1,6-diyne and enyne derivatives.



Scheme 1. Palladium catalyzed cyanation using TMSCN.

When terminal alkynes (**1a**–**e**) and TMSCN (2.5 equiv) were heated in the presence of PdCl$_2$ (2 mol%) with O$_2$ (1 atm) in toluene (0.5 M) at 100 °C, the corresponding *syn*- and *anti*-dicyano alkenes **2a**–**e** were obtained in good yield (Table 1, entries 1–5).[7] Since steric factors seemed to play an important role in the stereoselectivity of the reaction (compare Table 1, entries 3 and 4), substrates bearing a tetrasubstituted carbon center at the propargylic position (**1f**–**k**) were investigated. As expected, *syn* selectivity was dramatically improved (Table 1, entries 6–10) and tritylacetylene **1k** was exclusively converted into *syn*-**2k** in 72 % yield (Table 1, entry 11). Although these reaction conditions were not suitable for internal alkynes, the addition of TMSOTf[8] (50 mol%) with Pd(CN)$_2$ (5 mol%), which would generate a more Lewis acidic palladium(II) species, was found to be most effective after a careful survey of the conditions. For example, *syn*-**2m** and **2n** were obtained as the sole products in 67 % and 45 % yield, respectively (Table 1, entries 12 and 13). However, for terminal alkynes, TMSOTf did not affect the yield or diastereoselectivity of **2**. Meanwhile, simple alkenes did not react under the reaction conditions described.

In palladium-catalyzed cyanation of alkynes[5] or cross-coupling reactions[9] between aryl halides with cyanide, a CN group is installed by reductive elimination from C–Pd–CN. As this simple mechanistic proposal is not sufficient to explain our 1,2-dicyanation, we therefore propose two different modes of cyanation, nucleophilic cyanation and reductive elimination, as the key steps in this catalytic reaction. In general, a CN group on Pd acts as a pseudo halide (less nucleophilic) therefore introduction of the CN group through reductive elimination is favored under palladium catalysis. Herein we propose that an external cyano source and palladium(II) promote nucleophilic cyanation of alkynes.

Based on the findings that 1) molecular oxygen is essential, 2) the reaction using Pd(CN)$_2$ (100 mol%) alone without TMSCN under an oxygen atmosphere gave no dicyano adducts, 3) other cyanating agents such as n-Bu$_3$SnCN or Me$_2$C(OH)CN did not work at all, 4) no interconversion was observed between *syn* and *anti* adducts under the reaction conditions, and 5) the separately prepared (Ph$_3$P)$_2$PdO$_2$[10] (50 mol%) with TMSCN (2.5 equiv) promoted the reaction even under an argon atmosphere (36 % yield of **2e**), a plausible mechanism can be suggested and is shown in Scheme 2.

In the initial stage of this reaction, palladium(II) could activate the alkyne substrates. The resulting π complex acts as a Lewis base to activate the Si–CN bond (path A) and cleavage of the Pd–X bond is caused by the initial nucleo-

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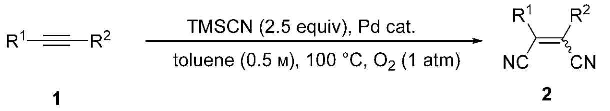
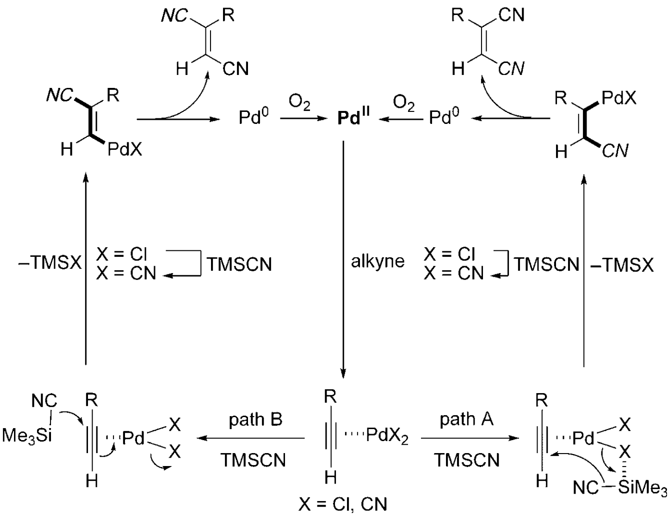
Table 1: 1,2-Dicyanation of various alkynes.



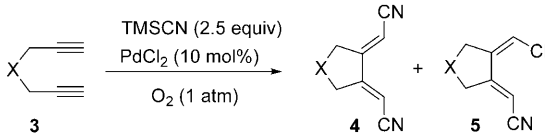
Entry	Pd (mol%)	1	Substrate R^1	R^2	*t* [h]	Product (yield [%])	*Syn*/*anti*
1	$PdCl_2$ (2)	**1a**	$AcO(CH_2)_3$	H	16	**2a** (80)	2:1
2	$PdCl_2$ (2)	**1b**	$Ts(Ph)NCH_2$	H	16	**2b** (78)	1:1
3	$PdCl_2$ (2)	**1c**	*n*-Hex	H	16	**2c** (79)	1:1
4	$PdCl_2$ (2)	**1d**	*c*-Hex	H	16	**2d** (51)	3:1
5	$PdCl_2$ (2)	**1e**	Ph	H	14	**2e** (80)	2.5:1
6	$PdCl_2$ (5)	**1f**	TMSOC(Ph)Me	H	19	**2f** (77)	11:1
7	$PdCl_2$ (5)	**1g**	TMSOC(Ph)Et	H	19	**2g** (86)	13:1
8	$PdCl_2$ (5)	**1h**	$TMSOCPh_2$	H	19	**2h** (79)	12:1
9	$PdCl_2$ (5)	**1i**	$TMSOC(CH_2)_5$	H	14	**2i** (52)	25:1
10	$PdCl_2$ (5)	**1j**	PhCMe(*n*Pr)	H	15	**2j** (63)	12:1
11	$PdCl_2$ (10)	**1k**	Ph_3C	H	15	**2k** (72)	syn only
12[a]	$Pd(CN)_2$ (5)	**1m**	*n*-Pent	Me	15	**2m** (67)	syn only
13[a]	$Pd(CN)_2$ (5)	**1n**	$PivO(CH_2)_2$	Me	15	**2n** (45)	syn only

[a] TMSOTf (50 mol%) was added. Hex = hexyl, Pent = pentyl, Piv = pivaloyl, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

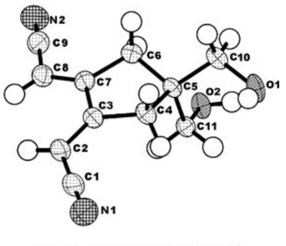


Scheme 2. Proposed mechanism.

Table 2: Cyclization of **3a–c** and X-ray structure of **4d**.



Entry	Substrate (X)	Reaction conditions	Products (yield [%])
1	**3a** (CH_2)	CH_3CN, RT, 16 h	**4a** (48), **5a** (13)
2	**3b** ($C(CH_2OAc)_2$)	CH_3CN, RT, 12 h	**4b** (55), **5b** (14)
3	**3c** (NTs)	toluene, 60 °C, 18 h	**4c** (33), **5c** (20)



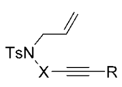
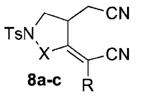
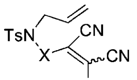
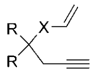
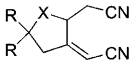
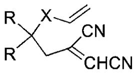
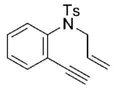
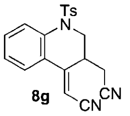
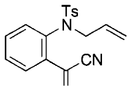
(*E*,*E*)-**4d**: X = $C(CH_2OH)_2$

philic cyanation at the less hindered terminal carbon atom (*syn* cyanopalladation). Another cyanation mode would be *anti* cyanopalladation (path B), which proceeds by direct nucleophilic cyanation of an internal carbon atom. The regioselectivity observed in path B can be controlled according to the Markovnikov rule when electrophilic activation of the alkyne by palladium(II) takes place. The resulting alkenylpalladium species are both converted into the corresponding palladium cyanides followed by reductive elimination, which gives the dicyano adducts and palladiun(0) that is quickly oxidized to palladium(II).[11] When **1f–k** were used, path B (direct cyanation to internal carbon atoms) was effectively prohibited because of steric bulk at the propargylic position, and thus increased *syn* selectivity. In particular, internal alkynes (**1m**, **n**) were activated by cationic palladium species or $Pd(OTf)_2$ prepared in situ,[8] thus leading to *syn* rather than *anti* cyanopalladation because of the steric bulk of R^1 and R^2 (Table 1).

For 1,6-diynes, three carbon–carbon bonds were formed smoothly in a single operation at room temperature, and the cyclized products were obtained in a stereoselective fashion (Table 2). For example, **3a** was converted into **4a** and **5a** in 48% and 13% yield, respectively (Table 2, entry 1). The configuration of the major symmetric product was assigned as *E*,*E* based on X-ray analysis of **4d**, which was derived from **4b** by deacetylation (aq HCl, RT, 4 h, 74%). Although the precise cyanation mode is still unclear, we propose two different intermediates through *anti* cyanopalladation.[12]

Furthermore, enyne **7a** was found to be suitable for dicyanative cyclization to give **8a** in 62% yield (Table 3, entry 1). This result shows that **7a** can act as a bidentate template to be electrophilically activated by palladium(II), and that an olefin functionality is effectively cyanated. The following findings: 1) **8a** being assigned with an *E* configuration,[13] and 2) the corresponding 1,6-diene not reacting under similar conditions, suggest that to give an alkylpalladium species the enyne cyclization could be initialized by *syn* cyanopalladation at an alkynyl carbon center rather than an olefinic carbon center and subsequent 5-*exo* cyclization. Various enynes were applicable, for example the substrates

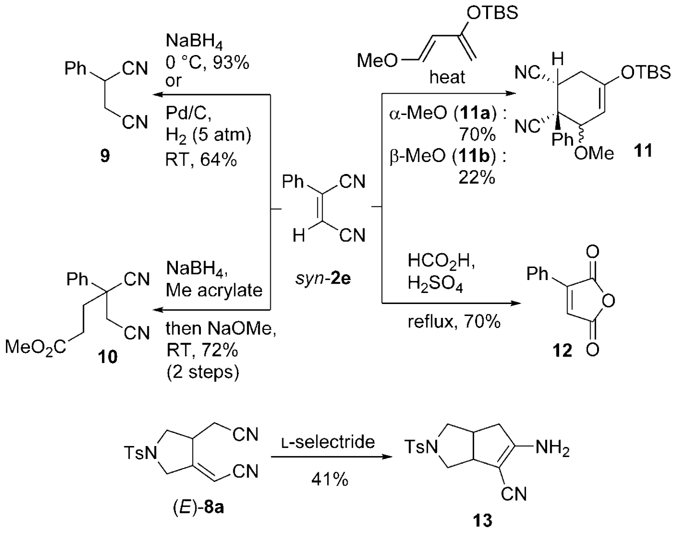
Table 3: Dicyanative cyclization of **7**.[a]

Entry	Substrate				*t* [h]	Product (yield [%])[b]		
		7	X	R				
1		**7a**	CH_2	H	5	 **8a-c**	 **8aa-cc**	**8a** (62) **8aa** (27)
2		**7b**	$(CH_2)_5$	H	23			**8b** (75) **8bb** (6)
3		**7a**	CH_2	Me	48			**8c** (20)
4		**7d**	CH_2	CO_2Et	2	 **8d-f**	 **8dd-ff**	**8d** (80) **8dd** (11)
5		**7e**	CH_2	CH_2OAc	23			**8e** (45) **8ee** (18)
6		**7f**	$(CH_2)_2$	CO_2Et	9			**8f** (30) **8ff** (60)
7		**7g**	–	–	18[c]	 **8g**	 **8gg**	**8g** (67) **8gg** (trace)

[a] All reactions were carried out in EtCN (0.1 м) at 90 °C in the presence of $Pd(CN)_2$ (10 mol%) with TMSCN (2.5 equiv) under an oxygen atmosphere (1 atm). [b] Concentration was 0.5 м.

bearing a bulky substituent or an internal alkyne gave the corresponding cycloadducts (Table 3, entries 2 and 3). This operation was applicable to carbocycles and an ethoxycarbonyl group dramatically accelerated the cyclization (Table 3, entries 4 and 5). Also, six-membered rings were successfully constructed (Table 3, entries 6 and 7).

Finally, another important conversion of the dicyano adducts is shown in Scheme 3. Reduction of *syn*-**2e** by $NaBH_4$ or Pd/C with H_2 proceeded smoothly to give **9**. Michael addition using methyl acrylate with a base created the quaternary carbon center of **10** (72 % yield, over 2 steps). In the Diels–Alder reaction using siloxydiene, cycloadducts **11** were obtained in 92 % yield in a regio- and steroselective fashion, and acidic treatment of *syn*-**2e** gave the corresponding anhydride **12**. Two different cyano functions of (*E*)-**8a** were easily discriminated by 1,4-reduction. When L-selectride was used, reductive cyclization proceeded to give **13** in 41 % yield.



Scheme 3. Synthetic application of dicyanated products. TBS = *tert*-butyldimethylsilyl.

In summary, we have demonstrated a novel dicyanation of simple alkynes that proceeds by *syn* and *anti* cyanopalladation. Also, dicyanative cyclization of 1,6-diynes and enynes has enabled the formation of three carbon–carbon bonds in single operation to construct carbo- and heterocycles. We believe that these simple and basic methods may provide a new approach to palladium chemistry, and further investigation of this transformation is currently underway.

Experimental Section

Typical procedure for palladium-catalyzed 1,2-dicyanation of terminal alkynes: To a solution of alkyne (1.0 mmol) in toluene (2.0 mL) were added palladium chloride (3.5 mg, 0.02 mmol, 2 mol%) and TMSCN (0.34 mL, 2.5 mmol) at room temperature. The mixture was stirred for 14–19 h at 100 °C under an oxygen atmosphere (1 atm). Once the reaction was complete (as evident by TLC), purification of the crude reaction mixture by column chromatography on silica gel (*n*-hexane/AcOEt 1:1) gave the desired 1,2-dicyano adducts.

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[1] For a recent example of conjugated cyanation of C=C double bonds, see; Y. Tanaka, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 6072, and references therein.

[2] a) T. Funabiki, Y. Yamazaki, K. Tarama, *J. Chem. Soc. Chem. Commun.* **1978**, *63*; b) G. D. Fallon, N. J. Fitzmaurice, W. R. Jackson, P. Perlmutter, *J. Chem. Soc. Chem. Commun.* **1985**, 4.

[3] a) N. Chatani, T. Hanafusa, *J. Chem. Soc. Chem. Commun.* **1985**, 838; b) N. Chatani, T. Takeyasu, N. Horiuchi, T. Hanafusa, *J. Org. Chem.* **1988**, *53*, 3539; c) M. Suginome, H. Kinugasa, Y. Ito,

Tetrahedron Lett. **1994**, *35*, 8635; d) N. Chatani, N. Horiuchi, T. Hanafusa, *J. Org. Chem.* **1990**, *55*, 3393.

[4] a) Y. Obora, A. S. Baleta, M. Tokunaga, Y. Tsuji, *J. Organomet. Chem.* **2002**, *660*, 173; b) I. Kamiya, J. Kawakami, S. Yano, A. Nomoto, A. Ogawa, *Organometallics* **2006**, *25*, 3562.

[5] a) Y. Nakao, S. Oda, T. Hiyama, *J. Am. Chem. Soc.* **2004**, *126*, 13904; b) Y. Nakao, K. Kanyiva, S. Oda, T. Hiyama, *J. Am. Chem. Soc.* **2006**, *128*, 8146; c) Y. Nakao, S. Ebata, A. Yada, T. Hiyama, M. Ikawa, S. Ogoshi, *J. Am. Chem. Soc.* **2008**, *130*, 12874; d) Y. Cheng, Z. Duan, L. Yu, Z. Li, Y. Zhu, Y. Wu, *Org. Lett.* **2008**, *10*, 901; for acylcyanation: see, e) K. Nozaki, N. Sato, H. Takaya, *J. Org. Chem.* **1994**, *59*, 2679; f) Y. Kobayashi, H. Kamisaki, R. Yanada, Y. Takemoto, *Org. Lett.* **2006**, *8*, 2711.

[6] a) M. Suginome, A. Yamamoto, M. Murakami, *J. Am. Chem. Soc.* **2003**, *125*, 6358; b) M. Suginome, A. Yamamoto, M. Murakami, *Angew. Chem.* **2005**, *117*, 2432; *Angew. Chem. Int. Ed.* **2005**, *44*, 2380.

[7] Nickel and platinum catalysis were ineffective. The addition of various ligands (phosphines, phosphites, 1,5-cyclooctadiene, isonitrile, and pyridine derivatives) or Lewis acids (Ag salts and TMSOTf) under palladium catalysis did not improve the chemical yield or stereoselectivity in the 1,2-dicyanation of terminal alkynes.

[8] Palladium(II) with TMSOTf give cationic palladium species: see, S. Ogoshi, S. Tomiyasu, M. Morita, H. Kurosawa, *J. Am. Chem. Soc.* **2002**, *124*, 11598.

[9] a) K. C. Dobbs, W. J. Marshall, V. V. Grushin, *J. Am. Chem. Soc.* **2007**, *129*, 30, and references therein; b) T. Takanami, M. Hayashi, H. Chijimatsu, W. Inoue, K. Suda, *Org. Lett.* **2005**, *7*, 3937.

[10] G. Wilke, H. Schott, P. Heimbach, *Angew. Chem.* **1967**, *79*, 62; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 92.

[11] For a review of palladium with an oxidant in organic synthesis, see: a) S. S. Stahl, *Angew. Chem.* **2004**, *116*, 3480; *Angew. Chem. Int. Ed.* **2004**, *43*, 3400; b) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318; c) C. Adamo, C. Amatore. I. Ciofini, A. Jutand, H. Lakmin, *J. Am. Chem. Soc.* **2006**, *128*, 6829.

[12] See the Supporting Information.

[13] Compound **8a** was determined to have an *E* configuration based on the NOE interactions between allyl and vinyl protons.

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