Enyne Synthesis

DOI: 10.1002/anie.200704095

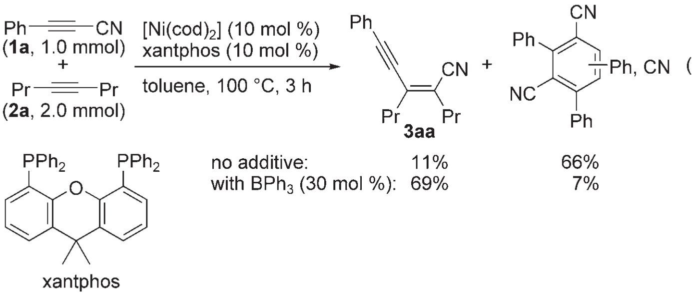
Nickel/BPh$_3$-Catalyzed Alkynylcyanation of Alkynes and 1,2-Dienes: An Efficient Route to Highly Functionalized Conjugated Enynes**

Yoshiaki Nakao, Yasuhiro Hirata, Masaaki Tanaka, and Tamejiro Hiyama**

In memory of Makoto Kumada

Highly substituted conjugated enynes with functional groups have gained significant importance as versatile synthetic intermediates.[1] However, conventional approaches to these structures have relied on tedious multistep sequences involving the Sonogashira coupling reaction. Transition-metal-catalyzed alkynylmetalation reactions have emerged recently as novel protocols for the construction of conjugated enyne frameworks through cleavage of a C(sp)–m bond (m = SnBu$_3$[2] and B(pinacol)[3] followed by addition of the resulting alkynyl and metallic moieties across alkynes; the latter is then converted further to an organic group by subsequent cross-coupling reactions. On the other hand, to our knowledge, catalytic direct insertion of alkynes into a C(sp)–C bond has never been achieved. Herein, we report nickel/BPh$_3$-catalyzed alkynylcyanation of alkynes and 1,2-dienes as an atom-economical and stereoselective method to access functionalized conjugated enyne structures.

At the onset, we anticipated the reaction mode of alkynyl cyanides in the presence of a nickel catalyst, because electron-deficient alkynes are prone to undergo homo- and/or cross-cyclotrimerization reactions under nickel catalysis.[4] Indeed, the reaction of 3-phenylpropynenitrile (**1a**) with 4-octyne (**2a**) in the presence of [Ni(cod)$_2$] (10 mol%) (cod = cyclooctadiene) and xantphos (10 mol%) in toluene at 100°C for 3 h gave the expected *cis*-alkynylcyanation product (**3aa**) in only 11% yield and a mixture of substituted benzenes in 66% yield which arose by trimerization of **1a** [Eq. (1)]. On the other hand, the presence of BPh$_3$ (30 mol%) as a Lewis acid (LA) cocatalyst[5] dramatically shifted the reaction path,[6] affording **3aa** in 69% yield with a small amount of the benzene derivatives.



(1)

We then further tested the catalysis on the reactions of various alkynyl cyanides and found that aryl-, alkenyl-, alkyl-, and silyl-substituted ethynyl cyanides underwent the alkynylcyation reaction across **2a** (entries 1–6, Table 1). In particular, the addition of silylethynyl cyanides gave the corresponding enynes in excellent yields even with a diminished amount of the catalysts, presumably because the bulky silyl group protects the triple bond and, thus, suppresses cyclotrimerization and/or oligomerization of the nitriles (entries 5 and 6, Table 1). It is worth noting that diynyl cyanide **1h** also added across **2a** to afford functionalized conjugated endiyne **3ha** in 72% yield (entry 7, Table 1). The scope of terminal alkynes in reactions with **1g** as the nitrile substrate was also studied (entries 8–12, Table 1). The present reaction displayed excellent chemoselectivity in the presence of a variety of functional groups (entries 9–12, Table 1). An alkyl–CN bond, which is cleavable under nickel/LA catalysis,[5] is compatible (entry 10, Table 1). The observed regioselectivities were fair to excellent and identical to what had been observed for the carbocyanation reaction of alkynes with other nitriles;[5,7] the major product was always the isomer having the larger substituent at the cyano-substituted carbon.

Alkynyl cyanides were also found to add across 1,2-dienes in the presence of the same catalyst (Table 2). The reaction with alkyl-substituted allenes took place mainly at the internal double bond, giving conjugated enynes **5** (entries 1–4, Table 2).[8] On the other hand, silylallene **4e** showed opposite regioselectivity, giving exclusively the *Z* vinylsilane having a conjugated enyne structure (entry 5, Table 2).

The present alkynylcyanation reaction should be initiated by the oxidative addition of a C(*sp*)-CN bond to nickel(0) by the aid of BPh$_3$ (Scheme 1).[5,9,10] An alkyne coordinates to the nickel center, and the alkynyl group migrates to the less hindered carbon of the coordinating alkyne to give an alkenylnickel intermediate, which then produces conjugated enyne **3** upon reductive elimination. On the other hand,

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[**] This work has been supported financially by a Grant-in-Aid for Creative Scientific Research (No. 16GS0209) and the Priority Area "Molecular Theory for Real Systems" (No. 19029024) from MEXT. Y.N. also acknowledges Japan Chemical Innovation Institute, Showa Shell Sekiyu Foundation for Promotion of Environmental Research, and The Sumitomo Foundation for support. Y.H. acknowledges the JSPS for a predoctoral fellowship.

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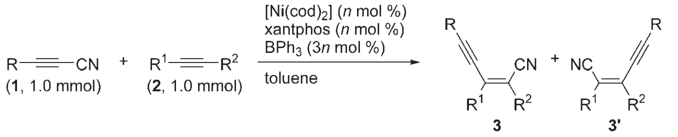
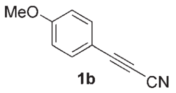
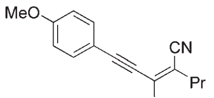
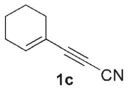
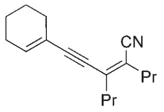
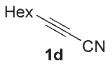
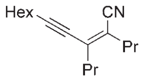
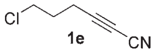
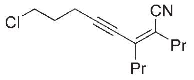
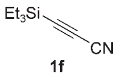
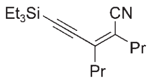
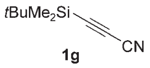
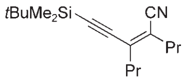
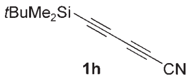
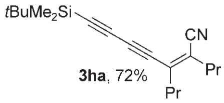
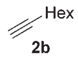
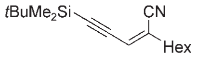
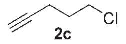
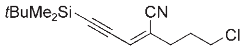
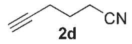
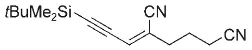
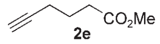
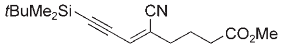
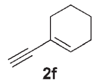
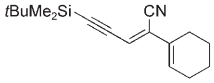
Table 1: Nickel/BPh$_3$-catalyzed alkynylcyanation of alkynes.



Entry	1	2	*n*	*T* [°C]	*t* [h]	Major product yield,[a] **3**/**3'**[b]
1[c]	 **1b**	**2a**	10	100	2	 **3ba**, 68%
2[c]	 **1c**	**2a**	10	80	2	 **3ca**, 67%
3[c]	 **1d**	**2a**	10	100	3	 **3da**, 72%
4[c]	 **1e**	**2a**	10	100	3	 **3ea**, 54%
5	 **1f**	**2a**	1	80	24	 **3fa**, 95%
6	 **1g**	**2a**	1	80	21	 **3ga**, 95%
7	 **1h**	**2a**	3	80	21	 **3ha**, 72%
8	**1g**	 **2b**	1	40	15	 **3gb** + **3'gb**, 96%, 83:17
9	**1g**	 **2c**	1	40	15	 **3gc**, 79%, **3'gc**, 17%, 82:18[d]
10	**1g**	 **2d**	1	40	15	 **3gd** + **3'gd**, 99%, 82:18
11[e]	**1g**	 **2e**	1	40	17	 **3ge** + **3'ge**, 93%, 83:17
12	**1g**	 **2f**	1	40	15	 **3gf** + **3'gf**, 86%, 95:5

[a] Yield of isolated product based on **1**. [b] Estimated by ^{1}H NMR analysis of the crude product or an isolated mixture of **3** and **3'**. [c] 2.0 mmol of **2a** was used. [d] Calculated based on yield of isolated product. [e] 1.1 mmol of **2e** was used.

coordination of a 1,2-diene takes place at its terminal double bond, and the alkynyl group is transferred to the cumulative carbon of the 1,2-diene, giving a π-allylnickel species.[8] Reductive elimination with the allyl and the cyano group would give another type of conjugated enyne **5**, although it remains elusive how the R^3 group controls the regiochemistry of the reductive elimination.

The cyano group of the alkynylcyanation products was readily converted to a formyl and then to a hydroxyalkyl group by conventional ways with their conjugated enyne moieties completely intact (Scheme 2).[11] The resulting aldehydes[1c,g] and allylic alcohols[1e–h] have been reported to serve as versatile synthetic intermediates for a wide range of highly substituted cyclic compounds. On the other hand, 1,2-diene-alkynylcyanation product **5b** was desilylated and then underwent the stannylative cross-cycloaddition reaction with ethyl (*Z*)-2-undecen-4-ynoate in the presence of a palladium-iminophosphine catalyst[1d] to give highly substituted phenylstannane **9**.

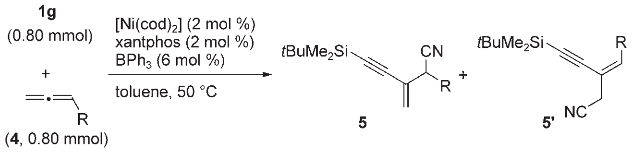
In conclusion, we have demonstrated the alkynylcyanation of alkynes and 1,2-dienes as a novel and convenient protocol for the atom-economical synthesis of highly functionalized conjugated enynes, which are suitable for further inter- and intramolecular transformations to elaborate a range of carbon frameworks. Current efforts are directed to the enantioselective alkynylcyanation of 1,2-dienes as well as simple olefins by the aid of nickel/LA catalysis.

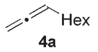
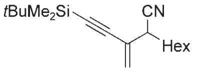
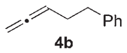
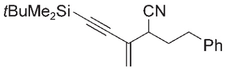
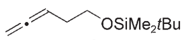
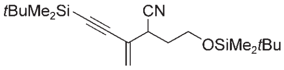
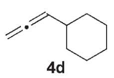
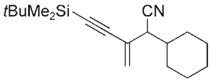
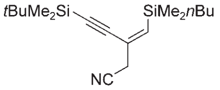
Experimental Section

General procedure for nickel/BPh$_3$-catalyzed alkynylcyanation of alkynes: An alkynyl cyanide (1.00 mmol), an alkyne (1.00–2.0 mmol), and C$_{14}$H$_{29}$ (internal standard, 99 mg, 0.50 mmol) were added sequentially to a solution of [Ni(cod)$_2$] (2.8–28 mg, 0.010–0.10 mmol), BPh$_3$ (7.3–73 mg, 0.030–0.30 mmol), and xantphos (5.8–58 mg, 0.010–0.10 mmol) in toluene (1.5 mL) in a dry box. The vial was taken outside the dry box and heated at the temperature and for the time specified in Equation (1) and Table 1. The resulting mixture was filtered through a silica gel pad, concentrated in vacuo, and purified by flash column chromatography on silica gel to give the corresponding alkynylcyanation products in the yields listed in Equation (1) and Table 1. A mixture of regioisomers was further purified by preparative recycling silica gel chromatography to give an isomerically pure product.

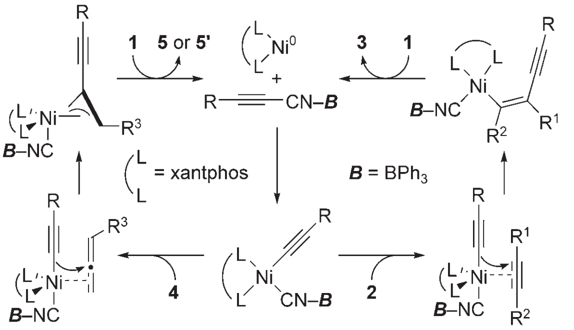
Received: September 5, 2007

Table 2: Nickel/BPh$_3$-catalyzed alkynylcyanation of 1,2-dienes.



Entry	1.2-Diene	t [h]	Major product, yield,[a] **5**/**5′**[b]
1	 **4a**	19	 **5a** + **5'a**, 73%, 93:7[c]
2	 **4b**	24	 **5b**, 75%, **5'b**, 7%, 91:9
3	 **4c**	17	 **5c**, 69%, **5'c**, 6%,[d] 92:8
4	 **4d**	59	 **5d**, 74%, **5'd**, <5%, >95:5[c]
5	 **4e**	66	 **5e**, <5%, **5'e**, 55%, 5:>95

[a] Yield of isolated product. [b] Calculated based on yields of isolated products. [c] Estimated by ^{1}H NMR analysis of the isolated mixture of **5a** and **5′a**. [d] E/Z = 11:89.



Scheme 1. A plausible mechanism for the nickel/BPh$_3$-catalyzed alkynylcyanation.

Keywords: alkynes · allenes · C–C activation · C–C coupling · nickel

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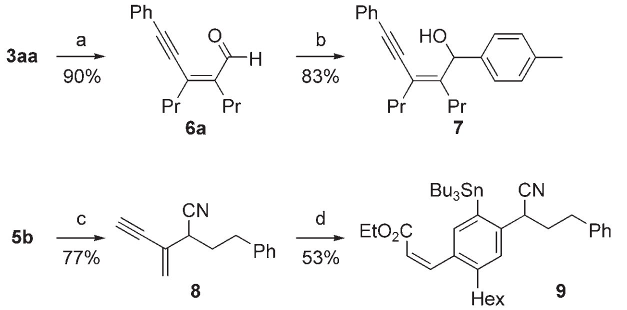

Scheme 2. Transformations of the alkynylcyanation products. a) DIBAL-H, toluene, −78 °C, 2 h, then SiO$_2$; b) p-tolylmagnesium bromide, Et$_2$O, 0 °C, 2 h; c) TBAF, AcOH, THF, RT, 1 h; d) (Z)-Hex-C≡C-CH=CH-CO$_2$Et, (Bu$_3$Sn)$_2$O, [Cp(allyl)Pd] (5 mol%), 2-CyN=CH-C$_6$H$_4$-PPh$_2$ (10 mol%), THF, 50 °C, 24 h. Cp = C$_5$H$_5$, Cy = cyclohexyl, DIBAL-H = diisobutylaluminum hydride, TBAF = tetrabutylammonium fluoride.

[1] For accounts, see : a) M. Rubin, A. W. Sromek, V. Gevorgyan, *Synlett* **2003**, 2265; b) K. Miki, S. Uemura, K. Ohe, *Chem. Lett.* **2005**, *34*, 1068; c) N. Asao, *Synlett* **2006**, 1645. For selected recent examples, see: d) Y. Nakao, Y. Hirata, S. Ishihara, S. Oda, T. Yukawa, E. Shirakawa, T. Hiyama, *J. Am. Chem. Soc.* **2004**, *126*, 15650; e) Y. Liu, F. Song, Z. Song, M. Liu, B. Yan, *Org. Lett.* **2005**, *7*, 5409; f) M. Rubina, M. Conley, V. Gevorgyan, *J. Am. Chem. Soc.* **2006**, *128*, 5818; g) J.-J. Lian, C.-C. Lin, H.-K. Chang, P.-C. Chen, R.-S. Liu, *J. Am. Chem. Soc.* **2006**, *128*, 9661; h) Y. Liu, F. Song, S. Guo, *J. Am. Chem. Soc.* **2006**, *128*, 11332.

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[6] For a related report on controlling the reaction mode of alkynes catalyzed by nickel/Lewis acid, see: N. Mori, S.-i. Ikeda, Y. Sato, *J. Am. Chem. Soc.* **1999**, *121*, 2722.

[7] a) Y. Nakao, S. Oda, A. Yada, T. Hiyama, *Tetrahedron* **2006**, *62*, 7567; b) Y. Nakao, T. Yukawa, Y. Hirata, S. Oda, J. Satoh, T. Hiyama, *J. Am. Chem. Soc.* **2006**, *128*, 7116.

[8] Cyanoesterification of 1,2-dienes also shows the same regioselectivity. See: Y. Nakao, Y. Hirata, T. Hiyama, *J. Am. Chem. Soc.* **2006**, *128*, 7420.

[9] For the effects of Lewis acids on C–CN activation by nickel(0), see: a) C. A. Tolman, W. C. Seidel, J. D. Druliner, P. J. Domaille, *Organometallics* **1984**, *3*, 33; b) N. M. Brunkan, D. M. Brestensky, W. D. Jones, *J. Am. Chem. Soc.* **2004**, *126*, 3627.

[10] Oxidative addition of the C(sp)–CN bond of dicyanoacetylene to platinum(0) has been reported. See: W. H. Baddley, C. Panattoni, G. Bandoli, D. A. Clemente, U. Belluco, *J. Am. Chem. Soc.* **1971**, *93*, 5590.

[11] For more examples, see the Supporting Information.