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Published on Web 07/16/2009

Nickel-Catalyzed Carbocyanation of Alkynes with Allyl Cyanides

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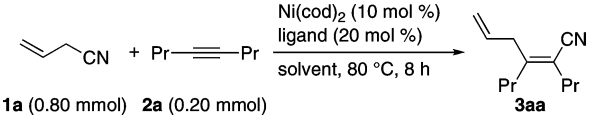
Abstract: Allyl cyanides are found to add across alkynes in the presence of a nickel/P(4-CF_3−C_6H_4)$_3$ catalyst to give polysubstituted 2,5-hexadienenitriles with defined stereo- and regiochemistry. Use of $AlMe_2Cl$ or $AlMe_3$ as a Lewis acid cocatalyst accelerates the reaction and expands the substrate scope significantly. The cyano group in the allylcyanation products can be transformed to a hydroxymethyl or aminomethyl group to afford highly substituted allylic alcohols or amines. α-Siloxyallyl cyanides also add across alkynes selectively at the less hindered γ-carbon to allow introduction of 3-oxo-propyl functionality after hydrolysis of the resulting silyl enol ethers. This particular carbocyanation reaction has been applied to the stereoselective construction of the trisubstituted double bond of plaunotol, an antibacterial natural product active against *Helicobacter pylori*.

Introduction

Development of regio- and stereoselective construction of polysubstituted ethenes is an important issue in synthetic organic chemistry.[1] Of many synthetic methods, transition metal-catalyzed regio- and stereoselective addition reactions across alkynes have advanced significantly to a level of particularly useful protocols.[2] For example, allyl-functionalization reactions such as allyl-metalation,[3] allyl-halogenation,[4] and allyl-chalcogenation[5] followed by C−C bond-forming reactions are powerful and straightforward methods to access synthetically versatile highly substituted 1,4-diene structures. Ultimately, however, direct insertion of alkynes into an allylic C−C bond should be of great synthetic potential to construct such structures efficiently. Carbocyanation reactions of alkynes have appeared recently as new efficient methods for stereo- and regioselective construction of polysubstituted ethenes.[6,7] While various nitriles have been demonstrated to participate in the carbocyanation reaction through oxidative addition of C−CN bonds to palladium(0) or nickel(0), allyl cyanides have been expected to be a promising substrate for the transformation because their C−CN bonds have also been known to undergo the oxidative addition readily to nickel(0).[8] A representative example is seen in the DuPont adiponitrile process, which utilizes nickel-catalyzed isomerization of 2-methyl-3-butenenitrile to 3- and 4-pentenenitriles through oxidative addition of the C−CN bond to nickel(0).[9] A π-allylnickel intermediate generated by the oxidative addition is suggested to undergo reductive elimination at the less hindered carbon to give linear 3-pentenenitrile, which is subjected to hydrocyanation to give finally adiponitrile. Accordingly, we envisaged that insertion of alkynes into the allyl-Ni bond of the π-allyl nickel intermediate[10] followed by reductive elimination could lead to catalytic allylcyanation reaction of alkynes. Herein we describe nickel- or nickel/Lewis acid-catalyzed regio- and stereoselective carbocyanation of alkynes with allyl cyanides to afford highly functionalized polysubstituted acrylonitriles with a variety of functional groups.[11] We also demonstrate the synthetic utility of the carbocyanation reaction by efficient synthesis of a trisubstituted ethene moiety of plaunotol, an antibacterial particularly effective against *Helicobacter pylori*.

Table 1. Nickel-Catalyzed Allylcyanation of 4-Octyne (**2a**)[a]



entry	ligand	solvent	yield of **3aa** (%)[b]
1[c]	P(4-CF_3−C_6H_4)$_3$	CH_3CN	98 (78)[d]
2[e]	P(4-CF_3−C_6H_4)$_3$	CH_3CN	35
3	P(4-CF_3−C_6H_4)$_3$	DMF	70
4	P(4-CF_3−C_6H_4)$_3$	1,4-dioxane	39
5	P(4-CF_3−C_6H_4)$_3$	toluene	22
6	PPh_3	CH_3CN	61
7	P(4-MeO−C_6H_4)$_3$	CH_3CN	8
8	PMe_3	CH_3CN	0
9	P(OPh)$_3$	CH_3CN	2

[a] All reactions were carried out using **1a** (0.80 mmol), **2a** (0.20 mmol), Ni(cod)$_2$ (20 μmol), and ligand (40 μmol) in a solvent (0.40 mL) at 80 °C for 8 h. [b] Estimated by GC using $C_{14}H_{30}$ as an internal standard. [c] The reaction was carried out using **1a** (4.0 mmol) and **2a** (1.00 mmol). [d] Isolated yield based on **2a**. [e] The reaction was carried out using **1a** (0.20 mmol) and **2a** (0.20 mmol).

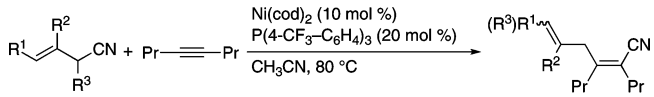
Results and Discussion

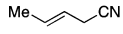
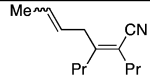
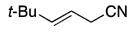
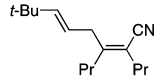
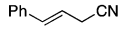
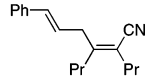
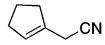
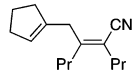
Nickel-Catalyzed Allylcyanation of Alkynes. We first examined the reaction of allyl cyanide (**1a**, 4.0 mmol) with 4-octyne

(1) (a) Faulkner, J. *Synthesis* **1971**, 175–189. (b) Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698–4745.
(2) *Comprehensive Organometallic Chemistry III*; Crabtree, R. H.; Mingos, D. M. P.; Ojima, I., Eds.; Elsevier: Oxford, 2007, Vol. 10.

10.1021/ja901374v CCC: $40.75 © 2009 American Chemical Society

Table 2. Allylcyanation of 4-Octyne (**2a**) Using Substituted Allyl Cyanides Catalyzed by Nickel[a]



entry	1	time (h)	product(s)	yield (%)[b] (5*E*/5*Z*)[c]
1	 **1b**	17	 **3ba**	69 (85:15)
2	**1c**	17	**3ba**	55 (83:17)
3[d]	 **1d**	18	 **3da**	49 (>99:1)
4[d]	 **1e**	18	 **3ea**	86 (>99:1)
5	 **1f**	106	 **3fa**	21 (—)

[a] All reactions were carried out using a nitrile (4.0 mmol), **2a** (1.00 mmol), $Ni(cod)_2$ (0.100 mmol), and $P(4\text{-}CF_3{-}C_6H_4)_3$ (0.20 mmol) in CH_3CN (2.0 mL) at 80 °C. [b] Isolated yields based on **2a**. [c] Estimated by ^1H NMR and/or GC analysis of a crude and/or purified product. [d] The reaction was carried out in CH_3CN (1.0 mL).

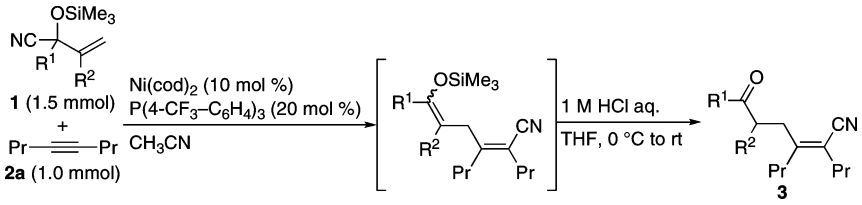
(**2a**, 1.0 mmol) in acetonitrile at 80 °C in the presence of $Ni(cod)_2$ (10 mol %) and various phosphine ligands (Table 1). Of ligands examined, $P(4\text{-}CF_3{-}C_6H_4)_3$ (20 mol %) was found to be the most effective to give (*Z*)-2,3-dipropylhexa-2,5-dienenitrile (**3aa**) in 78% yield after isolation (entry 1). The stereochemistry was unambiguously assigned by NOE experiments irradiating the allylic methylenes in ^1H NMR analyses. An equimolar reaction resulted in a low yield of **3aa** due presumably to formation of unidentified side products derived from side reactions of allyl cyanide (entry 2). Phosphorus ligands having electron-donating substituents and phosphites as well as use of less polar solvents all retarded the reaction (entries 3−9).

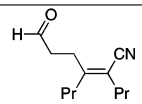
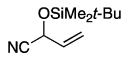
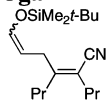
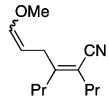
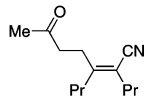
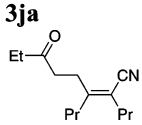
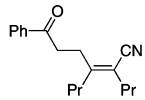
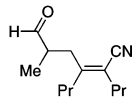
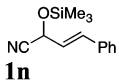
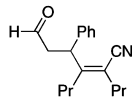
With the optimized conditions in hand, we next examined the scope of the reaction (Table 2 and eq 1). Carbocyanation of **2a** with both 3-pentenenitrile (**1b**) and 2-methyl-3-butenenitrile (**1c**) gave the same crotylcyanation product (**3ba**) as a mixture of stereoisomers in similar yields with similar stereoselectivity (entries 1 and 2). No trace amount of an α-adduct was obtained with **1c**, suggesting a catalytic cycle involving a π-crotylnickel intermediate (*vide infra*). The reactions of (*E*)-5,5-dimethyl-3-hexenenitrile (**1d**) and (*E*)-4-phenyl-3-butenenitrile (**1e**) gave the corresponding α-adducts as single stereoisomers possibly through a *syn*-π-allylnickel species (entries 3 and 4). The addition of cyclopenten-1-ylacetonitrile (**1f**) was sluggish (entry 5). The allylcyanation of 1-phenyl-1-propyne (**2b**) with **1a** gave a mixture of two regioisomers (**3ab/3′ab** = 94:6) in 43% yield (eq 1). An isomer having a phenyl group at the cyano-substituted carbon was obtained as a major product. The regiochemistry

(3) (a) Allylboration: Mikhailov, B. M. *Pure Appl. Chem.* **1974**, *39*, 505–523. (b) Bubnov, Y. N.; Kuznetsov, N. Y.; Pastukhov, F. V.; Kublitsky, V. V. *Eur. J. Org. Chem.* **2005**, 4633–4639. (c) Allylmagnesiation: von Rein, F. W.; Richey, H. G., Jr. *Tetrahedron Lett.* **1971**, *12*, 3777–3780. (d) Okada, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1996**, *118*, 6076–6077. (e) Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* **1997**, *53*, 5061–5072. (f) Anastasia, L.; Dumond, Y. R.; Negishi, E.-i. *Eur. J. Org. Chem.* **2001**, 3039–3043. Allylalumination: Miller, J. A.; Negishi, E.-I. *Tetrahedron Lett.* **1984**, *25*, 5863–5866. (g) Allylsilylation: Yeon, S. H.; Han, J. H.; Hong, E.; Do, Y.; Jung, I. N. *J. Organomet. Chem.* **1995**, *499*, 159–165. (h) Asao, N.; Yoshikawa, E.; Yamamoto, Y. *J. Org. Chem.* **1996**, *61*, 4874–4875. (i) Yoshikawa, E.; Gevorgyan, V.; Asao, N.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 6781–6786. (j) Imamura, K.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5339–5340. (k) Asao, N.; Tomeba, H.; Yamamoto, Y. *Tetrahedron Lett.* **2005**, *46*, 27–30. (l) Park, S.; Lee, D. *J. Am. Chem. Soc.* **2006**, *128*, 10664–10665. (m) Horino, Y.; Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 11364–11365. (n) Matsuda, T.; Kadowaki, S.; Yamaguchi, Y.; Murakami, M. *Chem. Commun.* **2008**, 2744–2746. (o) Allylzincation: Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 1475–1478. (p) Nishikwa, T.; Yorimitsu, H.; Oshima, K. *Synlett* **2004**, 1573–1574. (q) Allylindation: Araki, S.; Imai, A.; Shimizu, K.; Butsugan, Y. *Tetrahedron Lett.* **1992**, *33*, 2581–2582. (r) Araki, S.; Imai, A.; Shimizu, K.; Yamada, M.; Mori, A.; Butsugan, Y. *J. Org. Chem.* **1995**, *60*, 1841–1847. (s) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2318–2319. (t) Allylstannylation: Asao, N.; Matsukawa, Y.; Yamamoto, Y. *Chem. Commun.* **1996**, 1513–1514. (u) Miura, K.; Itoh, D.; Hondo, T.; Saito, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1996**, *37*, 8539–8542. (v) Matsukawa, Y.; Asao, N.; Kitahara, H.; Yamamoto, Y. *Tetrahedron* **1999**, *55*, 3779–3790. (w) Shirakawa, E.; Yamasaki, K.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 10221–10222. (x) Shirakawa, E.; Yoshida, H.; Nakao, Y.; Hiyama, T. *Org. Lett.* **2000**, *2*, 2209–2211.

(4) (a) Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55–63. (b) Camps, F.; Coll, J.; Llebaria, A.; Moretó, J. M. *Tetrahedron Lett.* **1988**, *29*, 5811–5814. (c) Llebaria, A.; Camps, F.; Moretó, J. M. *Tetrahedron* **1993**, *49*, 1283–1296. (d) Bäckvall, J.-E.; Nilsson, Y. I. M.; Gatti, R. G. P. *Organometallics* **1995**, *14*, 4242–4246. (e) Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4317–4320. (f) Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4321–4323. (g) Tong, X.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 6370–6371. (h) Hoye, T. R.; Wang, J. *J. Am. Chem. Soc.* **2005**, *127*, 6950–6951. (i) Huang, J.; Zhou, L.; Jiang, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 1945–1949.

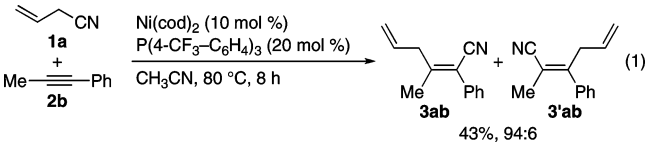
Table 3. Carbocyanation of 4-Octyne (**2a**) Using α-Siloxyallyl Cyanides Catalyzed by Nickel[a]



entry	1	temp (°C)	time (h)	product	yield (%)[b]
1	**1g**	80	1	 **3ga**	81
2	 **1h**	80	5	 **3ha**	87[c]
3	**1i**	80	5	 **3ia**	82[d]
4	**1j**	120	2	 **3ja**	79
5	**1k**	120	3	 **3ka**	81
6	**1l**	120	2	 **3la**	54
7	**1m**	80	12	 **3ma**	69
8	 **1n**	120	12	 **3na**	<5

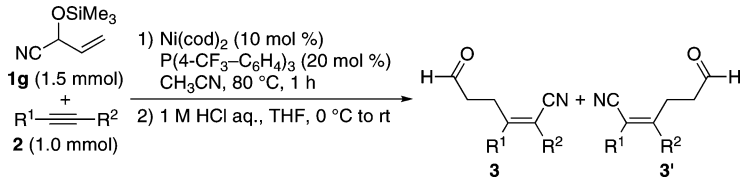
[a] All reactions were carried out using a nitrile (1.50 mmol), **2a** (1.0 mmol), $Ni(cod)_2$ (0.100 mmol), and $P(4\text{-}CF_3{-}C_6H_4)_3$ (0.20 mmol) in CH_3CN (1.0 mL), and crude products were treated with 1 M HCl aq in THF at 0 °C to rt. [b] Isolated yields based on **2a**. [c] 5*E*/5*Z* = 52:48. [d] 5*E*/5*Z* = 22:78.

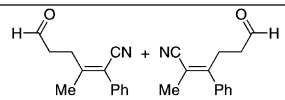
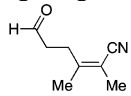
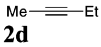
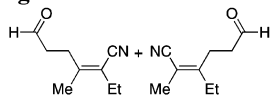
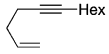
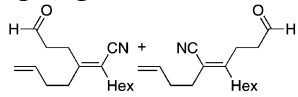
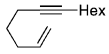
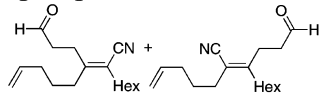
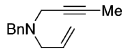
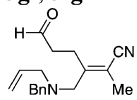
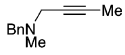
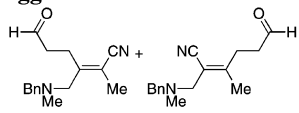
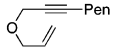
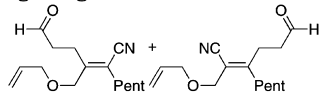
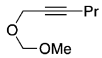
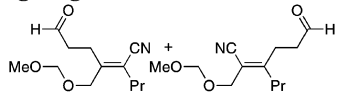
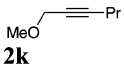
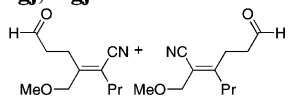
was unambiguously assigned by ^{1}H NMR NOE experiments. On the other hand, reactions with terminal alkynes such as 1-octyne gave no detectable amount of allylcyanation products due to rapid trimerization and/or oligomerization of the alkynes.



Nickel-Catalyzed Carbocyanation of Alkynes Using α-Siloxyallyl Cyanides. α-Siloxyallyl cyanide (**1g**), readily available from acrolein and trimethylsilyl cyanide, also underwent the carbocyanation reaction (Table 3).[12] Worth noting is that **1g** (1.5 mmol) reacted with **2a** exclusively at the γ-carbon of **1g** to give aldehyde **3ga** in 81% yield after hydrolysis of the resulting silyl enol ether (entry 1). The reactions of α-*tert*-butyldimethylsiloxyallyl cyanide (**1h**) and α-methoxyallyl cyanide (**1i**) with **2a** gave the corresponding enol ether products, which were successfully isolated by silica gel column chromatography as a mixture of stereoisomers (entries 2 and 3). Silyl ethers of enone cyanohydrins also reacted similarly at 120 °C to give the corresponding cyanoketones (entries 4−6). Whereas a β-substituent in **1m** did not affect the reaction to give aldehyde **3ma** in good yield at 80 °C (entry 7), γ-substituted α-siloxyallyl cyanide **1n** did not participate in the reaction (entry 8).

Table 4. Carbocyanation of Internal Alkynes Using **1g** Catalyzed by Nickel[a]

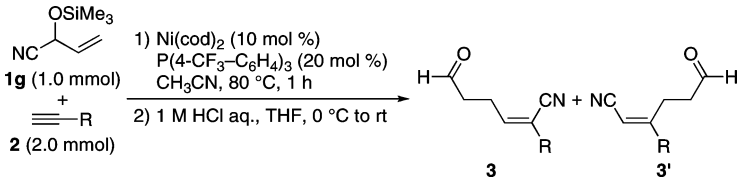


entry	2	product(s)	yield (%)[b] (3/3')[c]
1	**2b**	 **3gb, 3'gb**	70 (93:7)
2	**2c**	 **3gc**	58 (—)
3	 **2d**	 **3gd, 3'gd**	58 (61:39)
4	 **2e**	 **3ge, 3'ge**	69 (50:50)
5	 **2f**	 **3gf, 3'gf**	51 (50:50)
6	 **2g**	 **3gg**	48 (>95:5)
7	 **2h**	 **3gh, 3'gh**	51 (73:27)
8	 **2i**	 **3gi, 3'gi**	57 (94:6)
9	 **2j**	 **3gj, 3'gj**	53 (85:15)
10	 **2k**	 **3gk, 3'gk**	66 (83:17)

[a] All reactions were carried out using **1g** (1.50 mmol), an alkyne (1.0 mmol), $Ni(cod)_2$ (0.100 mmol), and $P(4\text{-}CF_3{-}C_6H_4)_3$ (0.20 mmol) in CH_3CN (1.0 mL) at 80 °C for 1 h, and crude products were treated with 1 M HCl aq in THF at 0 °C to rt. [b] Isolated yields of an inseparable mixture of two regioisomers based on **2**. [c] Determined by ^1H NMR and/or GC analysis of a crude and/or purified product.

Various internal alkynes were examined next for the reaction with **1g** (Table 4). The addition of **1g** across **2b** proceeded in good yield with high regioselectivity (entry 1). Moderate yield of **3gc** was obtained with 2-butyne (**2c**) due presumably to competitive trimerization and/or oligomerization of **2c** under the reaction conditions (entry 2). Poor or no regioselection was observed with alkynes having sterically similar substituents **2d**−**2f** (entries 3−5) even with a tethered olefin moiety (entries 4 and 5).[13] Alternatively, heteroatoms such as oxygen and nitrogen at a propargylic position of alkynes were found to effect regioselection of the carbocyanation (entries 6−9). Remarkably, the effect was further intensified by introducing an allyl group on the propargylic heteroatoms (entry 6 vs entry 7 and entry 8 vs entry 10),

Table 5. Allylcyanation of Terminal Alkynes Using **1g** Catalyzed by Nickel[a]



entry	alkyne (**2**)	product(s)	yield (%)[b](**3**:**3'**)[c]
1[d]	**2l**	**3gl**, **3'gl**	74 (92:8)
2	**2m**	**3gm**, **3'gm**	48 (95:5)
3	**2n**	**3gn**	61 (>99:1)
4	**2o**	**3go**	36 (>99:1)
5	**2p**	**3gp**	70 (>99:1)
6	**2q**	**3gq**, **3'gq**	78 (95:5)
7	**2r**	**3gr**, **3'gr**	62 (95:5)
8	**2s**	**3gs**, **3'gs**	60 (90:10)

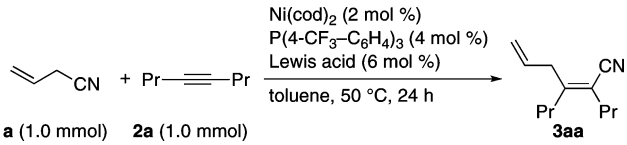
[a] All reactions were carried out using **1g** (1.00 mmol), an alkyne (2.0 mmol), $Ni(cod)_2$ (0.100 mmol), and $P(4\text{-}CF_3{-}C_6H_4)_3$ (0.20 mmol) in CH_3CN (1.0 mL) at 80 °C for 1 h, and crude products were treated with 1 M HCl aq in THF at 0 °C to rt. [b] Isolated yields of an inseparable mixture of two regioisomers based on **1g**. [c] Determined by ^1H NMR and/or GC analysis of a crude and/or purified product. [d] The reaction was carried out using **1g** (15 mmol) and **2l** (30 mmol).

whereas a possibly chelating methoxymethyl ether moiety gave no significant improvement of the regioselectivity compared with the methyl ether (entry 9 vs entry 10).

Gratifyingly, **1g** underwent the carbocyanation reaction across terminal alkynes in modest to good yields (Table 5). To push the reaction effectively as compared with rapid cyclotrimerization and/or oligomerization of terminal alkynes, use of 2 mol equiv of terminal alkynes is preferred. The reactions were smooth and regioselective like the ones with internal alkynes; adducts having substituents at a cyano-substituted carbon were major products. The reaction tolerated a gram-scale synthesis (entry 1). Excellent regioselectivity was observed with alkynes having a bulky substituent such as *t*-Bu and $SiMe_3$ (entries 3 and 4). Highly substituted allylsilane **3gp** was obtained from propargylsilane **2p** in good yield (entry 5). Terminal alkynes having various functional groups including chloro, ester, and *N*-phthalimidoyl underwent the reaction to give the corresponding substituted acrylonitriles in good yields (entries 6−8), whereas methyl or *tert*-butyldimethylsilyl propargyl ethers gave rise to no trace amount of the corresponding adducts but trimers of the alkynes.

Allylcyanation of Alkynes Catalyzed by Nickel/Lewis Acid. It has recently been reported that the arylcyanation of alkynes is significantly accelerated by a Lewis acid cocatalyst.[6f] The

Table 6. Effect of Lewis Acid Cocatalysts on the Reaction of **1a** with **2a**[a]



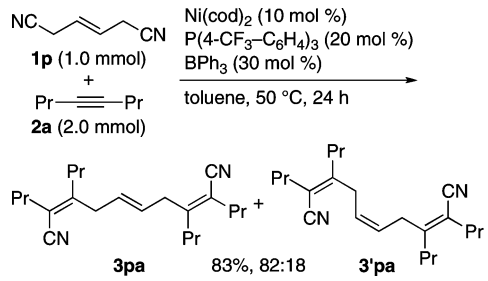
entry	Lewis acid	yield (%)[b]
1	$AlMe_3$	6
2	$AlMe_2Cl$	96[c]
3	$AlMeCl_2$	51
4	BPh_3	39
5	none	2

[a] All reactions were carried out using **1a** (1.00 mmol), **2a** (1.00 mmol), $Ni(cod)_2$ (20 μmol), $P(4\text{-}CF_3{-}C_6H_4)_3$ (40 μmol), and Lewis acid (60 μmol) in toluene (1.00 mL) at 50 °C for 24 h. [b] Determined by GC using $C_{14}H_{30}$ as an internal standard. [c] Isolated yield.

effect of BPh_3 as a Lewis acid on the oxidative addition of allyl cyanides to a nickel(0)/bisphosphine complex has also been revealed in detail by Jones, making the elemental reaction preferable kinetically and thermodynamically compared with competitive oxidative addition of the allylic C−H bond.[8b] Because unidentified side reactions of allyl cyanide **1a** could be ascribed to this competitive pathway and thus use of **1a** in excess was essential to obtain allylcyanation products in good yields, we anticipated that use of a Lewis acid cocatalyst would be beneficial for the allylcyanation reaction especially with **1a**. Of Lewis acid cocatalysts examined for the reaction of **1a** with **2a**, $AlMe_2Cl$ (6 mol %) was found to be optimum to give **3aa** in 96% yield even using allyl cyanide (**1a**) and 4-octyne (**2a**) in stoichiometric amounts and the nickel catalyst in a small amount (2 mol %) (entry 2 of Table 6). $AlMe_3$, $AlMeCl_2$, and BPh_3 were not as effective as $AlMe_2Cl$ (entries 1, 3, and 4), whereas the absence of Lewis acid gave only a trace amount of **3aa** under the modified conditions (entry 5). Use of polar solvents such as acetonitrile, 1,4-dioxane, and DMF was futile with this binary catalyst system.

With the nickel/$AlMe_2Cl$ catalyst in hand, we reexamined the scope of the allylcyanation reaction (Table 7). Substituted allyl cyanides **1e** and **1f** underwent the equimolar reaction with **2a** with 2 mol % of the nickel catalyst at 50 °C (entries 1 and 2). γ,γ-Disubstituted allyl cyanide such as prenyl cyanide (**1o**), which was inert under the conditions without a Lewis acid cocatalyst, participated in the reaction (entry 3). The scope of alkynes with **1a** as a nitrile substrate was significantly expanded to include various terminal alkynes (entries 4−10). Complete regioselectivity observed with terminal alkynes is particularly useful for synthesis of trisubstituted ethenes (entries 5−10). Functional groups such as chloro, cyano, and siloxy did not affect the Lewis acid cocatalysis (entries 8−10).

The reaction of **1p** having two allylic cyanide moieties with 2 mol equiv of **2a** gave double allylcyanation products **3pa** and **3′pa** with BPh_3 as a Lewis acid cocatalyst (eq 2). Use of optimal $AlMe_2Cl$, on the other hand, resulted in a low conversion of **2a** (∼20%). Isomerization of the double bond geometry in **1p** under the reaction conditions was observed and would be responsible for the formation of **3′pa**.



(2)

The binary catalysis was found also effective for the carbocyanation reaction using α-siloxyallyl cyanide (Table 8). The reaction of **1g** (1.00 mmol) with **2a** (1.00 mmol) in the presence of $Ni(cod)_2$ (2 mol %), $P(4\text{-}CF_3{-}C_6H_4)_3$ (4 mol %), and $AlMe_3$ (8 mol %) in toluene at 50 °C for 12 h gave

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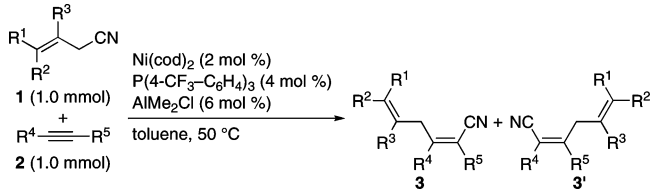
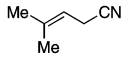
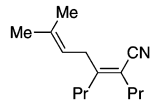
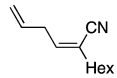
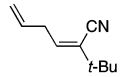
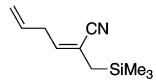
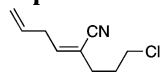
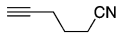
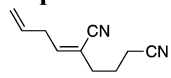
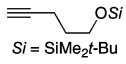
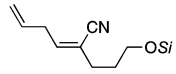
Table 7. Nickel/Lewis Acid-catalyzed Allylcyanation of Alkynes[a]



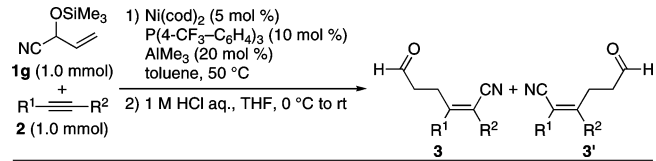
entry	1	2	time (h)	product(s)	yield (%)[b] (3:3')[c]
1	**1e**	**2a**	72	**3ea**	74 (—)
2	**1f**	**2a**	48	**3fa**	82 (—)
3[d]	 **1o**	**2a**	24	 **3oa**	61 (—)
4	**1a**	**2b**	24	**3ab** + **3'ab**	64[e] (92:8)
5	**1a**	**2l**	4	 **3al**	67 (>99:1)
6	**1a**	**2n**	12	 **3an**	52 (>99:1)
7	**1a**	**2p**	4	 **3ap**	34 (>99:1)
8	**1a**	**2q**	4	 **3aq**	60 (>99:1)
9	**1a**	 **2t**	4	 **3at**	46 (>99:1)
10	**1a**	 *Si* = $SiMe_2$*t*-Bu **2u**	4	 **3au**	72 (>99:1)

[a] All reactions were carried out using allyl cyanide (1.00 mmol), an alkyne (1.00 mmol), $Ni(cod)_2$ (20 μmol), $P(4\text{-}CF_3{-}C_6H_4)_3$ (40 μmol), and $AlMe_2Cl$ (60 μmol) in toluene (2.0 mL) at 50 °C. [b] Isolated yields. [c] Determined by ^{1}H NMR analysis. [d] $Ni(cod)_2$ (0.20 mmol), $P(4\text{-}CF_3{-}C_6H_4)_3$ (0.40 mmol), and $AlMe_2Cl$ (0.60 mmol) were used. [e] Isolated yield of an inseparable mixture of **3ab** and **3'ab**.

3ga in 80% yield after acidic hydrolysis of the resulting silyl enol ether (entry 1). Use of $AlMe_2Cl$ was less effective with this particular nitrile substrate. To our regret, no appreciable improvement of the stereoisomeric ratio of silyl enol ethers formed in situ was observed by GC analyses of the reaction mixture. Nevertheless, variously functionalized α,β-disubstituted acrylonitriles were obtained with excellent regioselectivity higher than that observed under the conditions without the LA catalyst (entries 2−5).

Mechanism of Allylcyanation Reaction. Catalytic cycle of the present carbocyanation reaction should be initiated by coordination of the double bond of allyl cyanides to nickel(0) to give **4** or **5** followed by oxidative addition of the C−CN bond to nickel(0) to give π-allylnickel intermediate **6** or **7** (Scheme 1).[8] The intermediacy of the π-allylnickel species **6** and **7** is fully supported by literature precedents as well as the experimental results for the reactions of crotyl and 3-buten-2-yl cyanides (entries 1 and 2 of Table 2). With γ-substituted allyl cyanides, the resulting π-allylnickel **7** would be in equilibrium with **6** through isomerization via a σ-allyl complex and rotation. One of the phosphine ligands in **6** or **7** may be dissociatively substituted by an alkyne to give **8**. Migratory insertion of alkynes into the allyl−Ni bond in **8** would take place to make bonds at the nickel-bound less hindered allyl and alkyne carbons, giving **10** with high regioselectivity as observed especially with alkynes having sterically biased substituents. High regioselectivity attained with substrates containing a propargylic heteroatom (entries 6−10 of Table 4) may be ascribed to the formation of σ-allylnickel **9** by intramolecular coordination of a heteroatom to the nickel center. Facile isomerization of a η^3-allyl ligand to a η^1-allyl one may direct this particular coordination of the alkynes. An allyl substituent on the heteroatom appears to further enhance the directing effect. Reductive elimination of alkenylnickel intermediate **10** gives *cis*-allylcyanation products and regenerates nickel(0). With α-siloxyallyl cya-

Table 8. Nickel/Lewis Acid-Catalyzed Carbocyanation of Alkynes Using **1g**[a]



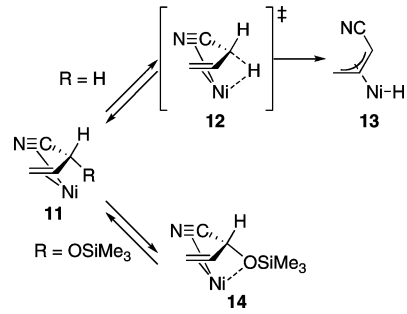
entry	alkyne (**2**)	time (h)	product(s)	yield (%)[b] (**3**:**3′**)[c]
1[d]	**2a**	12	**3ga**	80
2	**2l**	2	**3gl** + **3′gl**	62 (98:2)
3[e]	**2p**	7	**3gp**	58 (>99:1)
4	**2q**	1	**3gq** + **3′gq**	60 (98:2)
5	**2r**	2	**3gr** + **3′gr**	59 (97:3)

[a] All reactions were carried out using **1g** (1.00 mmol), an alkyne (1.00 mmol), $Ni(cod)_2$ (50 μmol), $P(4\text{-}CF_3\text{–}C_6H_4)_3$ (0.100 mmol), and $AlMe_3$ (0.20 mmol) in toluene (1.5 mL) at 50 °C. [b] Isolated yields of an inseparable mixture of two regioisomers. [c] Determined by ^{1}H NMR analysis. [d] $Ni(cod)_2$ (20 μmol), $P(4\text{-}CF_3\text{–}C_6H_4)_3$ (40 μmol), and $AlMe_2Cl$ (80 μmol) were used. [e] **2p** (3.0 mmol) was used.

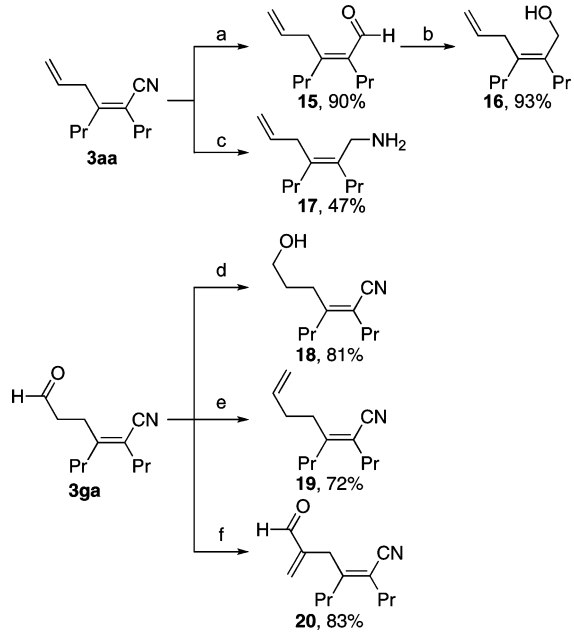
nides, undesired side reactions derived possibly from allylic C−H oxidative addition through transition state **12** (Scheme 2)[8b] are likely suppressed by coordination of the oxygen to the nickel center in **14**. The pronounced effect of phosphine ligands with highly electron-withdrawing aryl groups in the present allylcyanation reaction contrasts sharply with other nickel-catalyzed carbocyanation reactions wherein phosphine ligands with electron-donating alkyl groups are favored in general.[6] The oxidative addition of allyl cyanides to nickel(0) is probably very fast compared with other nitriles, and thus, the turnover-limiting step may lie in other elemental steps. Especially, reductive elimination forming alkenyl−CN bonds would be facilitated by phosphine ligands with a large π-accepting character. Accordingly, Lewis acid cocatalysts may also accelerate the reductive elimination,[14] ligand substitution, and/or migratory insertion of alkynes as well as oxidative addition of allyl cyanides.[8b,15]

Transformations of Allylcyanation Products. Synthetic utility of the allylcyanation products was briefly examined and is summarized in Scheme 3. The cyano group in **3aa** was reduced to give the corresponding enal **15** and then allylic alcohol **16**. Highly substituted allylamine **17** was also available from **3aa**. The formyl group in **3ga** was reduced or methylenated[16] to give

Scheme 2. Oxidative Addition of Allylic C−CN vs C−H Bonds to Nickel(0)[8b]

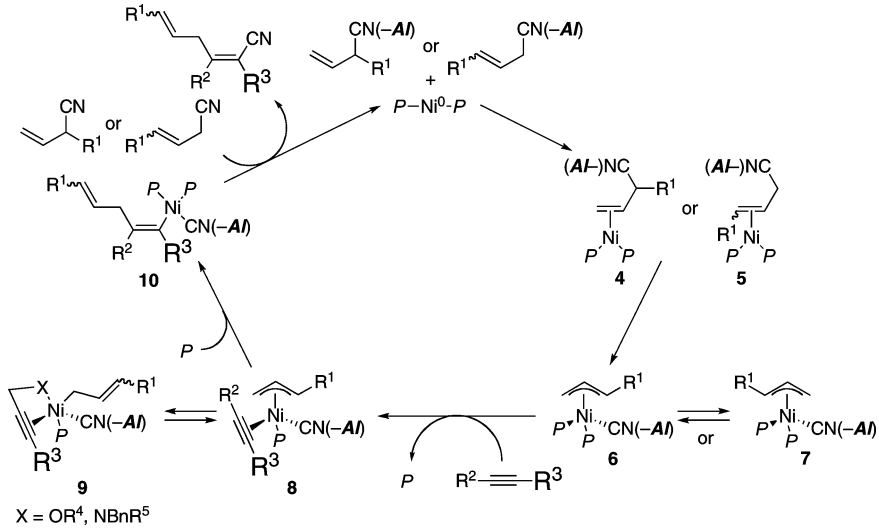


Scheme 3. Transformations of Allylcyanation Products[a]

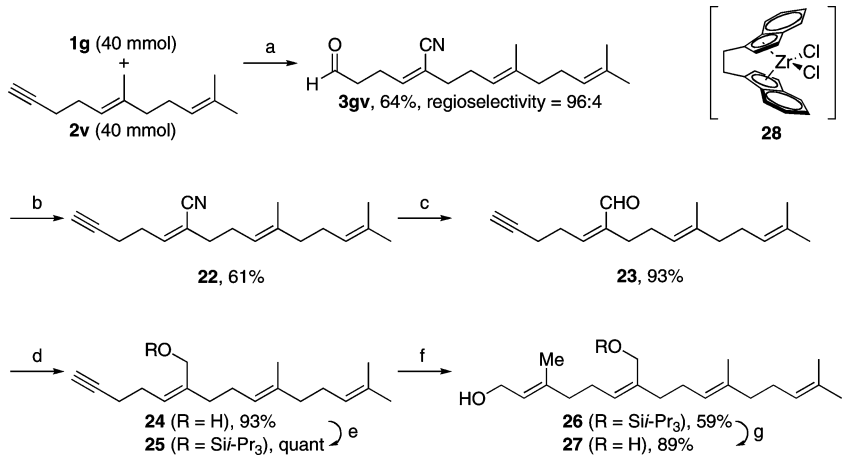


[a] Reagents and conditions: (a) DIBAL-H, toluene, −78 °C, 1.5 h, then SiO_2; (b) $LiAlH_4$, THF, rt, 10 min; (c) DIBAL-H, toluene, −78 °C, 1.5 h, then $NaBH_4$, MeOH, 0 °C, 30 min; (d) $NaBH_4$, MeOH, 0 °C, 1 h; (e) $IZnCH_2ZnI$, THF, rt, 30 min; (f) HCHO aq, pyrrolidine, $EtCO_2H$, *i*-PrOH, 45 °C, 24 h.

Scheme 1. Plausible Mechanism of Allylcyanation of Alkynes



Scheme 4. Total Synthesis of Plaunotol[a]



[a] Reagents and conditions: (a) $Ni(cod)_2$ (2 mol %), $P(4\text{-}CF_3{-}C_6H_4)_3$ (4 mol %), $AlMe_3$ (8 mol %), toluene, 35 °C, 8 h, then 1 M HCl aq, THF, 0 °C to rt; (b) $Me(CO)C(N_2)P(O)(OMe)_2$ (**21**), K_2CO_3, MeOH, 0 °C to rt, 24 h; (c) DIBAL-H, toluene, −78 °C, 1.5 h, then SiO_2; (d) $LiAlH_4$, THF, 0 °C to rt, 20 min; (e) TIPS-Cl, imidazole, DMF, rt, 3 h; (f) $AlMe_3$, **28** (5 mol %), MAO (5 mol %), rt, 48 h, then *n*-BuLi, $(HCHO)_n$, THF, rt, 1.5 h; (g) TBAF, THF, rt, 12 h.

alcohol **18** and 1,5-dienenitrile **19**, the latter serving as a formal homoallycyanation product. α-Methylenation of **3ga** proceeded through aldol-type condensation to give α-substituted propenal **20** without affecting the configuration of the original C=C bond.[17]

The carbocyanation of terminal alkynes with α-siloxyallyl cyanide **1g** was successfully applied to regio- and stereoselective construction of one of the trisubstituted double bonds in plaunotol (**27**), an antibacterial natural product active against *Helicobacter pylori* (Scheme 4).[18,19] Nickel/$AlMe_3$-catalyzed *cis*-carbocyanation of terminal alkyne **2v** with **1g** proceeded at 35 °C with excellent stereo- and regioselectivity to give aldehyde **3gv** upon acidic hydrolysis in 64% yield in a gram scale, two internal double bonds being completely intact under the reaction conditions. The formyl group of **3gv** and its regioisomer **3′gv** (not shown, at most 4%) was transformed to terminal alkyne **22** by the Ohira−Bestmann protocol.[20] The isomer derived from **3′gv** was readily removed at this stage by silica gel column chromatography. The cyano group was reduced to give substituted allylic alcohol **24** through aldehyde **23** with complete retention of its stereochemistry. The hydroxy group was protected with TIPS-Cl, and the terminal alkyne moiety was subjected to the regio- and stereoselective Negishi methylalumination reaction according to a modified protocol reported by Lipshutz using **28** as a catalyst[21,22] to construct another trisubstituted double bond upon treatment of the resulting alkenylaluminum species with paraformaldehyde all in one pot. Deprotection of the TIPS group gave plaunotol (**27**).

Conclusion

In summary, stereo- and regioselective allylcyanation of alkynes has been demonstrated with a $Ni(cod)_2/P(4\text{-}CF_3{-}C_6H_4)_3$ catalyst to give highly substituted and functionalized 1,4-dienenitriles. α-Siloxyallyl cyanides are also shown to participate in the transformation, allowing simultaneous introduction of a cyano and 3-oxo-propyl units. Use of Lewis acid cocatalysts significantly improves the reaction efficiency by reducing catalyst loading, achieving stoichiometric reaction, and expanding substrate scope. The resulting adducts have been shown to undergo various transformations based on cyano, allyl, and carbonyl functionalities. Finally, the reaction was applied to the synthesis of the trisubstituted double bond in plaunotol in a high regio- and stereoselective manner.

Acknowledgment. We thank Prof. Seijiro Matsubara for helpful suggestions and generous donation of $CH_2(ZnI)_2$. We are also grateful to Professor Timothy F. Jamison for fruitful discussion and to Mr. Shinichi Oda and Mr. Jun Satoh for experimental elaboration at the initial stage. This work has been supported financially by a Grant-in-Aid for Creative Scientific Research, COE Research on "Elements Science" and on "United Approach to New Material Science", and Priority Areas "Molecular Theory for Real Systems" from MEXT. Y.H. acknowledges the JSPS for a predoctoral

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fellowship. Y.N. acknowledges the NIPPON SHOKUBAI Award in Synthetic Organic Chemistry, Japan, Mitsubishi Chemical Corporation Fund, NOVARTIS Foundation (Japan) for the Promotion of Science, Japan Chemical Innovation Institute, Showa Shell Sekiyu Foundation for Promotion of Environmental Research, The Sumitomo Foundation, and The Uehara Memorial Foundation for supports.

Supporting Information Available: Detailed experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

JA901374V