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Nickel/Lewis Acid-Catalyzed Cyanoesterification and Cyanocarbamoylation of Alkynes

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Abstract: Cyanoformates and cyanoformamides are found to add across alkynes by nickel/Lewis acid (LA) cooperative catalysis to give β-cyano-substituted acrylates and acrylamides, respectively, in highly stereoselective and regioselective manners. The resulting adducts serve as versatile synthetic building blocks through chemoselective transformations of the ester, amide, and cyano groups as demonstrated by the synthesis of typical structures of β-cyano ester, β-amino nitrile, γ-lactam, disubstituted maleic anhydride, and γ-aminobutyric acid. The related reactions of cyanoformate thioester and benzoyl cyanide, on the other hand, are found to add across alkynes with decarbonylation in the presence of a palladium/LA catalyst.

Introduction

The vicinal difunctionalization of alkynes with carbonaceous groups has gained much interest in organic synthesis, mainly because the transformation allows simultaneous construction of two different C−C bonds. In particular, transition-metal-catalyzed cleavage of C−C bonds followed by insertion of unsaturated bonds should be of great synthetic potential because there is no need for prefunctionalization and no formation of byproduct.[1−3] Whereas the initial developments of this class of transformations depend heavily on the release of ring-strain in three-[1] or four-membered[2] compounds, much attention has been paid to reactions involving the cleavage of strain-free C−C bonds.[3] In this regard, we and others have been interested in the cleavage of C−CN bonds by transition metals through oxidative addition[4] or the formation of silylisonitrile complexes,[5] which is relatively feasible due presumably to a kinetically favorable interaction of a cyano group with a

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transition metal through η^1- or η^2-coordination[6] and a resultant highly stable metal−CN bond[7] as a thermodynamic driving force. These elemental reactions have been applied to catalytic transformations of nitriles including isomerization,[8] decarbonylation,[9] decyanation,[10] silylation,[11] and cross-coupling[12] reactions. Taking advantage of the particular ability of nickel to activate various C−CN bonds, we, on the other hand, reported the nickel-catalyzed addition reaction of nitriles across alkynes, namely the carbocyanation reaction, as a new entry in the class of transformations.[13] More recently, we disclosed that the use of Lewis acid (LA) cocatalysts allowed the scope of nitriles to expand significantly to include even alkyl cyanides to give a wide variety of (*Z*)-alkyl-substituted acrylonitriles highly stereo- and regioselectively[14] probably through the promotion of both oxidative addition[15] and reductive elimination[16] of C−CN bonds.

Cyanoketones, cyanoformates, and cyanoformamides are attractive substrates for the carbocyanation reactions, in view that the transformation with these particular nitriles allows simultaneous installation of both carbonyl and cyanofunctionalities. The intermolecular addition reaction of benzoyl cyanide across arylacetylenes was first reported using a palladium catalyst.[17] Unfortunately, the scope of this reaction is severely limited, since its mechanism involves benzoylation of the terminal alkyne followed by hydrocyanation of the resulting alkynyl ketones and isomerization of the double bond. More recently, palladium catalysis has been found to be effective for the activation of C−CN bonds of cyanoformates and cyanoformamides, allowing the intermolecular cyanoesterification of norbornene[18] and the intramolecular cyanocarbamoylation of alkynes and alkenes,[19] respectively. Independently, we have also been interested in such difunctionalization by the nickel catalysis and have developed the intermolecular cyanoesterification of 1,2-dienes.[20] Nevertheless, a general scope of these transformations has remained unexplored, and its successful realization is highly desired as a new synthetic tool for introducing two different functional groups at a vicinal position with defined stereochemistry. We report herein nickel/LA-catalyzed regio- and stereoselective cyanoesterification and cyanocarbamoylation reactions of alkynes to give β-cyano-substituted acrylate esters and acrylamides. Subsequent transformations of the two functional groups thus introduced are demonstrated to readily afford a range of useful building blocks such as β-cyano ester, β-amino nitrile, γ-lactam, disubstituted maleic anhydride, and γ-aminobutyric acid. Also described briefly is that related reactions of cyanoformate thioesters and cyanoketones with alkynes are accompanied by decarbonylation and are more efficiently catalyzed by palladium/LA.

Results and Discussion

Nickel/BAr_3-Catalyzed Cyanoesterification of Alkynes. We first examined the reaction of ethyl cyanoformate (**1a**) with 4-octyne (**2a**) at 100 °C in the presence of a nickel catalyst along with various ligands (Table 1). Two ligands PMe_2Ph and PMe_3, effective for the cyanoesterification of 1,2-dienes[20] and arylcyanation of alkynes,[13] were completely ineffective (entries 1 and 2). On the other hand, electron-deficient triarylphosphine ligands such as $P(4\text{-}CF_3{-}C_6H_4)_3$ and $P[3,5\text{-}(CF_3)_2{-}C_6H_3]_3$ gave a small amount of desired adduct **3aa** (entries 3 and 4), whereas neutral PPh_3 and electron-donating $P(4\text{-}MeO{-}C_6H_4)_3$ showed no trace amount of **3aa**. These observations prompted us to examine the effect of LA cocatalysts in assisting the activation of the C−CN bond of **1a** by a nickel(0) species coordinated by the less electron-donating phosphines. Of organoboron LA compounds examined with $P[3,5\text{-}(CF_3)_2{-}C_6H_3]_3$ as a ligand (entries 7 and 8), $B(C_6F_5)_3$ was found to be dramatically effective, giving **3aa** in 64% yield as estimated by GC (entry 8). The reaction proceeded even at 35 °C giving a higher yield of **3aa** (entry 9). A further increase in yield was observed using 20 mol % of the ligand, and the reaction with a 1 mmol scale

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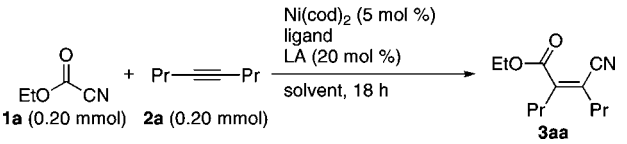
Table 1. Cyanoesterification of 4-Octyne (**2a**) with Ethyl Cyanoformate (**1a**)[a]



entry	ligand (mol %)	LA	solvent	temp (°C)	yield (%)[b]
1	PMe_3 (10)	none	toluene	100	0
2	PMe_2Ph (10)	none	toluene	100	0
3	$P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$ (10)	none	toluene	100	4
4	$P(4\text{-}CF_3\text{-}C_6H_4)_3$ (10)	none	toluene	100	4
5	PPh_3 (10)	none	toluene	100	0
6	$P(4\text{-}MeO\text{-}C_6H_4)_3$ (10)	none	toluene	100	0
7	$P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$ (10)	BPh_3	toluene	100	35
8	$P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$ (10)	$B(C_6F_5)_3$	toluene	100	64
9	$P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$ (10)	$B(C_6F_5)_3$	toluene	35	74
10	$P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$ (20)	$B(C_6F_5)_3$	toluene	35	83 (80)[c]
11	$P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$ (20)	$B(C_6F_5)_3$	1,4-dioxane	35	42
12	$P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$ (20)	$B(C_6F_5)_3$	DMF	35	0
13	$P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$ (10)	$AlMe_3$	toluene	100	0
14	$P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$ (10)	$AlMe_2Cl$	toluene	100	0

[a] All the reactions were carried out using **1a** (0.20 mmol), **2a** (0.20 mmol), $Ni(cod)_2$ (10.0 μmol), a ligand (20 or 40 μmol), and a LA (40 μmol) in toluene (0.133 mL). [b] GC yields as determined using tridecane as an internal standard. [c] Isolated yield with a 1.00 mmol scale.

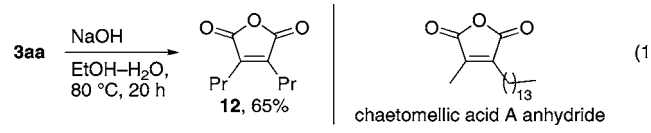
for 24 h gave **3aa** in 80% yield after isolation (entry 10). The use of more polar solvents such as 1,4-dioxane and DMF was not effective, because they could act as a Lewis base to coordinate to highly Lewis acidic $B(C_6F_5)_3$ to retard the LA cocatalysis (entries 11 and 12). Organoaluminum LAs were ineffective (entries 13 and 14).

With the optimized conditions in hand, we next studied the scope of alkynes using nitrile **1a** (Table 2). The reaction with 1,4-bis(trimethylsilyl)-2-butyne (**2b**) yielded highly functionalized allylsilane **3ab** stereoselectively in 75% yield (entry 1). The stereochemistry of **3ab** was confirmed by NOE observed between the two allylic methylenes in **3ab**. Whereas 4-methyl-2-pentyne (**2c**) gave a mixture of regioisomers (entry 2), 4,4-dimethyl-2-pentyne (**2d**) gave single adduct **3ad** with complete regioselectivity (entry 3). This regioselectivity is identical to that observed for the carbocyanation reactions of alkynes with other nitriles:[13,14] isomers having a larger substituent at the cyano-substituted carbon were produced preferentially. On the other hand, alkynes with a silyl terminus **2e**−**2j** proceeded highly stereoselectively but with opposite regioselectivity using BPh_3 as a LA in 1,4-dioxane instead of $B(C_6F_5)_3$ in toluene (entries 4−10). It is worth noting that internal double bond, silylether, ester, and imide functionalities were tolerated under the present Ni/LA catalysis (entries 7−10). The use of $B(C_6F_5)_3$ for the reaction of **1a** with **2e** in toluene resulted in 17% yield of **3ae**. Methyl cyanoformate (**1b**) also added across **2f** in a moderate yield under similar conditions (entry 6). The reactions with other alkynes such as 1-phenylpropyne (<30% of adducts), methyl 2-butynoate, and terminal alkynes (trimerization and/or oligiomerization of the alkynes) as well as simple 1-alkenes (no reaction) were all futile.

The cyanoesterification reaction likely proceeds through a plausible catalytic cycle shown in Scheme 1. The cycle should be initiated by the oxidative addition of C−CN bonds of cyanoformate esters,[21] whose CN group coordinates to BAr_3 to give **4**. After the phosphine ligand in **4** is replaced by an alkyne to give **5** or **6**, the alkoxycarbonyl group migrates to the coordinating alkyne to give rise to **7** or **8**, which then undergoes reductive elimination followed by transfer of BAr_3 to **1**, giving adduct **3** or **3′**, respectively, and regenerating nickel(0) and a BAr_3 adduct of **1**. The cyano group rather than the ester carbonyl is considered to coordinate to the borane LAs throughout the catalytic cycle, making the cyano group less nucleophilic and reluctant to undergo the migratory insertion step. The borane LA could also interact with the triarylphosphine ligand to assist the ligand exchange step (e.q. **4** to **6** in Scheme 1).[22] However, the stoichiometric reaction of the triarylboranes with $P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$ monitored by ^{31}P NMR showed no significant shift of the original signal of the free triarylphosphine due presumably to the steric bulk and/or the electron-withdrawing nature of the aryl group that makes the phosphorus atom less Lewis basic, whereas that with PPh_3 showed formation of white precipitates ascribed probably to a $Ar_3B\text{−}PPh_3$ complex.[23] On the basis of these observations, we conclude that such effect of the borane LA may not be operative in our system especially in the presence of Lewis basic cyano and alkoxycarbonyl functionalities in a higher amount.

Alkenylnickel intermediate **8** seems to be favored kinetically since migration of the alkoxycarbonyl group to a less hindered carbon of the coordinating alkyne in **6** would proceed in a manner similar to the arylcyanation of alkynes.[24] With silyl-substituted alkynes, on the other hand, the alkoxycarbonyl group could interact with the silyl group through the carbonyl oxygen to direct coordination of the silylalkynes as depicted in **5′** to result in the exclusive formation of **3′** The ratios of **3**:**3′** were constant during the course of the reaction with silyl-substituted alkynes, suggesting both that **3′** should be a kinetic product and irreversibility of the reductive elimination step.

The synthetic versatility of the cyanoesterification products is demonstrated by the transformations shown in Scheme 2. Protodesilylation of **3′ae** followed by reduction of the remaining double bond gave β-cyano ester **9**. Upon treatment of **9** with $NaBH_4$ in the presence of $CoCl_2$,[25] γ-lactam **10** was obtained, whereas hydrolysis of the ester group[26] in **9** and the subsequent Curtius rearrangement[27] afforded N-Boc-protected β-cyano amide **11**, a potential precursor for β-amino acid derivatives. Treatment of **3aa** with a base gave **12** (eq 1). Because disubstituted maleic anhydrides such as **12** are found in some biologically active natural products such as chaetomellic acid A anhydride,[28] the present synthetic scheme would be applicable to access this class of compounds,[29] starting with readily available cyanoformate esters and internal alkynes.

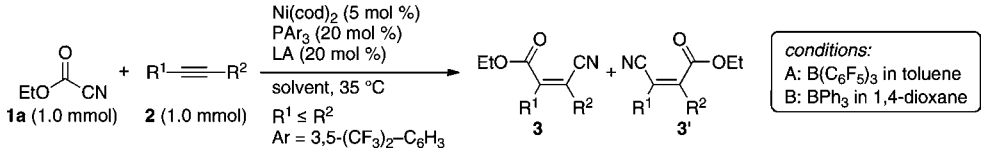


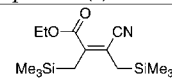
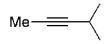
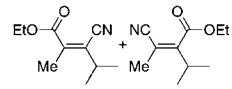
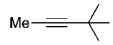
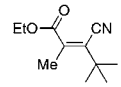
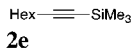
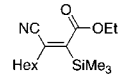
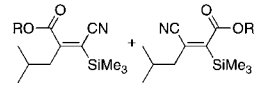
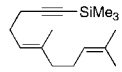
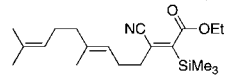
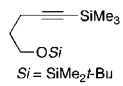
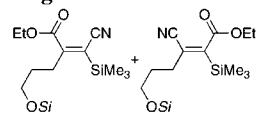
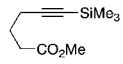
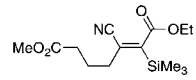
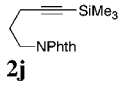
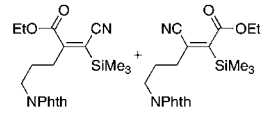
(1)

The synthetic potential of the cyanoesterification is also demonstrated by the formal synthesis of pregabalin, an anticonvulsant drug used for the treatment of neuropathic pain (Scheme 3).[30,31] Protodesilylation of **3′bf** followed by enantioselective conjugate reduction of the α,β-unsaturated ester moiety with polymethylhydrosiloxane (PMHS) in the presence of a chiral Cu/(*R*)-binap catalyst[32] afforded β-cyano ester **14** of 80% ee, which was hydrolyzed without loss of the %ee to give synthetic precursor **15** for pregabalin.[31a]

Nickel/BPh_3-Catalyzed Cyanocarbamoylation of Alkynes. We next turned our attention to the reactions of cyanoformamides with alkynes. We again surveyed nickel/LA catalysts for the reaction of *N*,*N*-dimethylcyanoformamide (**16a**) with 4-octyne (**2a**) (Table 3). Of various combinations of $Ni(cod)_2$, a ligand,

Table 2. Nickel/BAr_3-Catalyzed Cyanoesterification of Alkynes[a]



entry	alkyne	cond.	time (h)	product(s)	yield (%),[b] **3**:**3'**[c]
1	 **2b**	A	21	 **3ab**	75
2	 **2c**	A	46	 **3ac** **3'ac**	35 (55:45)
3	 **2d**	A	46	 **3ad**	49 (>95:5)
4	 **2e**	B	22	 **3'ae**	75 (5:>95)
5	 **2f**	B	16	 **3af** (R = Et) **3'af** (R = Et)	85 (6:94)
6[d]		B	24	**3bf** (R = Me) **3'bf** (R = Me)	59 (9:91)
7	 **2g**	B	22	 **3'ag**	64 (5:>95)
8	 **2h**	B	46	 **3ah** **3'ah**	67 [5:>95 (1:99)[e]]
9	 **2i**	B	41	 **3'ai**	62 (5:>95)
10	 **2j**	B	51	 **3aj** **3'aj**	67 [5:>95 (3:97)[e]]

[a] All the reactions were carried out using **1a** (1.00 mmol), an alkyne (1.00 mmol), $Ni(cod)_2$ (50 μmol), a ligand (0.100 or 0.20 mmol), and a LA (0.20 mmol) in toluene or dioxane (0.67 mL). [b] Isolated yield. [c] Estimated by ^{1}H NMR analysis of a crude product. [d] Methyl cyanoformate (**1b**) was used instead of **1a**. [e] Estimated by ^{1}H NMR analysis of an isolated product.

and a LA examined, electron-donating and sterically bulky ligands with BPh_3 as a LA catalyst gave β-cyano-substituted acrylamide **17aa** with yields better than those including triarylphosphines (entries 1−5 vs entries 11−13). A catalyst derived from $Ni(cod)_2$ (5 mol %), $PCyPh_2$ (10 mol %), and BPh_3 (15 mol %) was found indeed optimum to give **17aa** in 93% isolated yield (entry 5). The use of other LAs such as $B(C_6F_5)_3$ and $AlMe_3$ completely retarded the reaction (entries 6 and 7), whereas only a trace amount of **17aa** was obtained in the absence of a LA catalyst (entry 8). A less polar solvent such as 1,4-dioxane did not affect the reaction, while highly Lewis basic DMF retarded the reaction (entries 9 and 10). The catalysts suitable for cyanoesterification were not effective (entries 12 and 13). No trace amount of the adduct was obtained with $Pd(PPh_3)_4$, a catalyst of choice for the intramolecular cyanocarbamoylation of alkynes.[19]

Cyanoformamides derived from *N*-methylbenzylamine (**16b**) and morpholine (**16c**) also added across **2a** in good yields under the optimized conditions (entries 1 and 2 of Table 4). The reaction of **16a** with 4-methyl-2-pentyne (**2c**) gave **17ac** in a

(21) (a) Bianchini, C.; Masi, D.; Meli, A.; Sabat, M. *Organometallics* **1986**, *5*, 1670. (b) Nishihara, Y.; Miyasaka, M.; Inoue, Y.; Yamaguchi, T.; Kojima, M.; Takagi, K. *Organometallics* **2007**, *26*, 4054.
(22) Stapleton, R. L.; Chai, J.; Taylor, N. J.; Collins, S. *Organometallics* **2006**, *25*, 2514.
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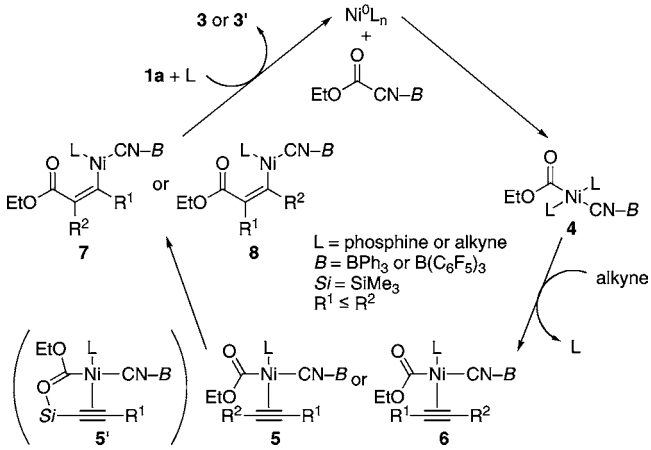
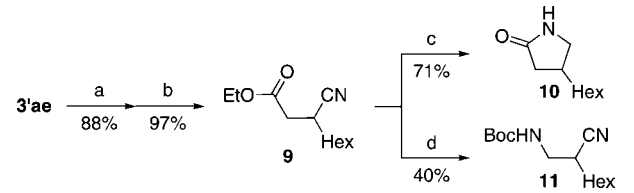
(24) Ohnishi, Y.-y.; Nakao, Y.; Sato, H.; Sakaki, S.; Nakao, Y.; Hiyama, T. *Organometallic* **2009**, *28*, 2583.

Scheme 1. Plausible Mechanism of Cyanoesterification of Alkynes by Nickel/LA Catalysis



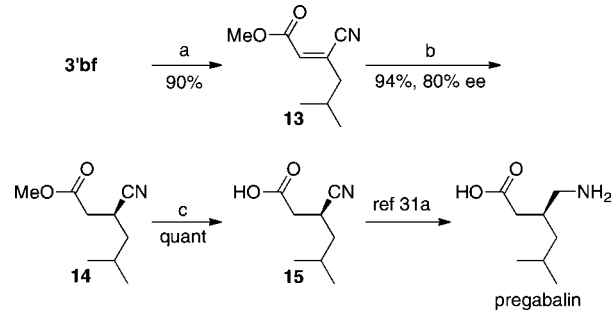
Scheme 2. Transformations of **3′ae**[a]



[a] Reagents and Conditions: (a) TBAF, CF_3CO_2H, THF, 0 °C, 1.5 h; (b) H_2, Pd/C (10 mol %), dioxane, rt, 2.5 h; (c) $CoCl_2$, $NaBH_4$, EtOH, 0 °C to rt, 11 h; (d) $Ba(OH)_2 \cdot H_2O$, MeOH, rt, 4 h, then $Ph_2P(O)N_3$, NEt_3, *t*-BuOH, 75 °C, 11 h.

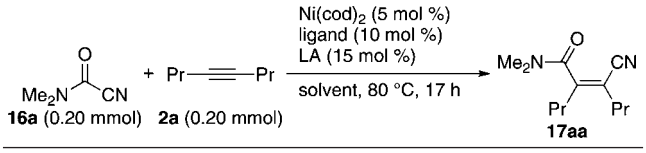
poor yield but as a single isomer with regioselectivity opposite to that of the cyanoesterification (entry 3, cf. entry 2 of Table 2). Reactions with silyl-substituted alkynes also proceeded with excellent stereo-, regio-, and chemoselectivities with P*i*-PrPh_2 as a ligand in a 1,4-dioxane solvent to afford single isomers (entries 4−9). The observed regioselectivity compares well with those for the cyanoesterification reaction of silyl-substituted alkynes. The structure of the adducts was assigned based on NOE experiments of ^{1}H NMR after desilylation of **17ae**.

Scheme 3. Formal Synthesis of Pregabalin[a]



[a] Reagents and Conditions: (a) TBAF, CF_3CO_2H, THF, 0 °C, 2 h; (b) CuCl (5 mol %), NaO*t*-Bu (5 mol %), (*R*)-BINAP (5 mol %), PMHS, *t*-BuOH, toluene, rt, 24 h; (c) $Ba(OH)_2 \cdot H_2O$, MeOH, rt, 4 h.

Table 3. Cyanocarbamoylation of **2a** Using *N*,*N*-Dimethylcyanoformamide (**16a**)[a]



entry	ligand	LA	solvent	yield (%)[b]
1	PMe_3	BPh_3	toluene	17
2	PCy_3	BPh_3	toluene	73
3	PCy_2Ph	BPh_3	toluene	89
4	P*i*-PrPh_2	BPh_3	toluene	91
5	$PCyPh_2$	BPh_3	toluene	100 (93)[c]
6	$PCyPh_2$	$B(C_6F_5)_3$	toluene	0
7	$PCyPh_2$	$AlMe_3$	toluene	0
8	$PCyPh_2$	none	toluene	6
9	$PCyPh_2$	BPh_3	1,4-dioxane	92
10	$PCyPh_2$	BPh_3	DMF	14
11	PPh_3	BPh_3	toluene	60
12	$P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$	BPh_3	toluene	15
13	$P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$	$B(C_6F_5)_3$	toluene	12

[a] All the reactions were carried out using **16a** (0.20 mmol), **2a** (0.20 mmol), $Ni(cod)_2$ (10.0 μmol), a ligand (20 μmol), and a LA (30 μmol) in a solvent (0.40 mL). [b] GC yields as determined using tetradecane as an internal standard. [c] Isolated yield obtained with a 1.00 mmol scale reaction.

The stoichiometric reaction of **16a** (0.50 mmol), $Ni(cod)_2$, $PCyPh_2$ (2 equiv), and BPh_3 in benzene gave a new nickel species showing a signal at δ 32.1 (s) in ^{31}P NMR, which was assigned to be the signal of *trans*-$(Ph_2CyP)_2Ni(CONMe_2)(C{\equiv}N{-}BPh_3)$ (**18**) (Scheme 4). Evaporation of the solvent *in vacuo* followed by washing of the resulting precipitates with hexane gave **18** as a pale yellow powder in 80% yield. Single yellow crystals suitable for X-ray crystallographic analysis were obtained by recrystallization from hexane and tetrahydrofuran. The molecular structure of **18** thus obtained clearly indicates that two equivalent phosphorus ligands coordinate in a *trans* geometry to nickel having a carbamoyl and a BPh_3-bounded cyano groups (Figure 1). As expected for the d^8 Ni(II) complexes, the Ni atom in **18** is a square-planar geometry, with the sum of the angles of L−Ni−L′ (L, L′ = C1, C2, P1, and P2) being 358.38°. The Ni−C−N−B linkage is almost linear, and the Ni−C−N and C−N−B angles (179.7(3) and 172.0(3)°, respectively) are similar to those reported for [(dippe)Ni(η^3-allyl)(C≡N−BPh_3)] (171.05(14) and 175.12(12)°),[15b] [(dppf)Ni(η^3-*1*-$CH_3-C_3H_4$)(C≡N−BEt_3)] (175.8(4) and 177.3(5)°),[33a] and

(25) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, *10*, 4555.
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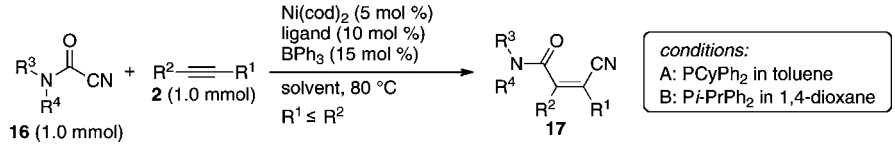
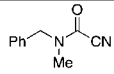
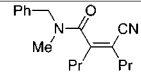
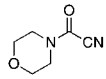
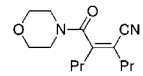
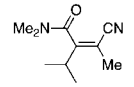
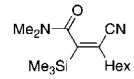
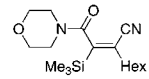
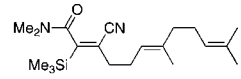
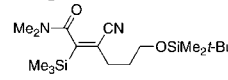
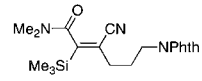
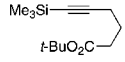
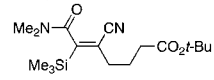
(28) (a) Singh, S. B.; Zink, D. L.; Liesch, J. M.; Goetz, M. A.; Jenkins, R. G.; Nallinomstead, M.; Silverman, K. C.; Bills, G. F.; Mosley, R. T.; Gibbs, J. B.; Albersschonberg, G.; Lingham, R. B. *Tetrahedron* **1993**, *49*, 5917. (b) Lingham, R. B.; et al. *Appl. Microbiol. Biotechnol.* **1993**, *40*, 370. (c) Singh, S. B.; Jayasuriya, H.; Silverman, K. C.; Bonfiglio, C. A.; Williamson, J. M.; Lingham, R. B. *Bioorg. Med. Chem.* **2000**, *8*, 571.
(29) For a review for maleic anhydrides in natural products, see: Chen, X.; Zheng, Y.; Shen, Y. *Chem. Rev.* **2007**, *107*, 1777.
(30) Silverman, R. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 3500.
(31) For examples of catalytic asymmetric synthesis of pregabalin, see: (a) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442. (b) Burk, M. J.; de Koning, P. D.; Grote, T. M.; Hoekstra, M. S.; Hoge, G.; Jennings, R. A.; Kissel, W. S.; Le, T. V.; Lennon, I. C.; Mulhern, T. A.; Ramsden, J. A.; Wade, R. A. *J. Org. Chem.* **2003**, *68*, 5731. (c) Hoge, G. *J. Am. Chem. Soc.* **2003**, *125*, 10219. (d) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126*, 5966. (e) Mita, T.; Sasaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 514. (f) Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 5820. (g) Monge, D.; Martín-Zamora, E.; Vázquez, J.; Alcarazo, M.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2007**, *15*, 2867. (h) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *25*, 5307.
(32) For related copper-catalyzed enantioselective conjugate reduction of α,β-unsaturated esters, see: (a) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. (b) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352.

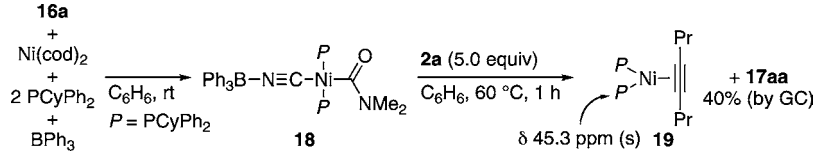
Table 4. Nickel/BPh_3-Catalyzed Cyanocarbamoylation of Alkynes[a]



entry	16	2	cond.	time (h)	product	yield (%)[b]
1	 **16b**	**2a**	A	27	 **17ba**	82
2	 **16c**	**2a**	A	23	 **17ca**	87
3	**16a**	**2c**	A	24	 **17ac**	31
4	**16a**	**2e**	B	22	 **17ae**	66
5	**16c**	**2e**	B	22	 **17ce**	79
6	**16a**	**2g**	B	41	 **17ag**	56
7	**16a**	**2h**	B	39	 **17ah**	66
8	**16a**	**2j**	B	50	 **17aj**	42
9	**16a**	 **2k**	B	41	 **17ak**	62

[a] All the reactions were carried out using **16** (1.00 mmol), an alkyne (1.00 mmol), $Ni(cod)_2$ (50 μmol), a ligand (100 μmol), and BPh_3 (150 μmol) in a solvent (2.0 mL). [b] Isolated yield.

Scheme 4. Synthesis and Reactions of *trans*-$(Ph_2CyP)_2Ni(CONMe_2)(C{\equiv}N\text{-}BPh_3)$ (**18**)



$[Ni(C{\equiv}N{-}B(C_6F_5)_3)_4]^{2-}$ (174.8−178.2 and 174.8−178.2°).[33b] The N−B and C≡N bond lengths of **18**, 1.607(4) and 1.160(3) Å, respectively, fall within the respective ranges reported for well-defined $Tm{-}C{\equiv}N{-}BR_3$ complexes (1.526−1.614 and 1.135−1.163 Å, where Tm represents transition metals, such as Ni,[15b,33] Fe,[34] Ru,[35] Mn,[36] and Rh[37]). The oxidative adduct was consumed upon treatment with five equivalents of **2a** in benzene at 60 °C for 1 h to give a new nickel complex showing a signal at δ 45.3 ppm (s) in ^{31}P NMR, and cyanocarbamoylation product **17aa** was observed in 40% yield as estimated by GC. The new nickel species was assigned to be $(Ph_2CyP)_2Ni$(4-octyne) **19** based on the fact that the same set of peaks was

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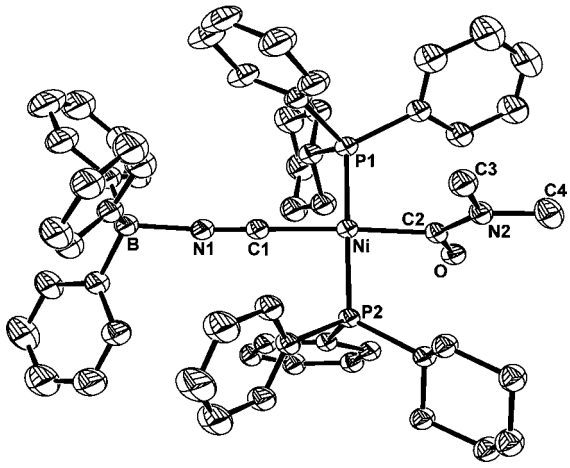
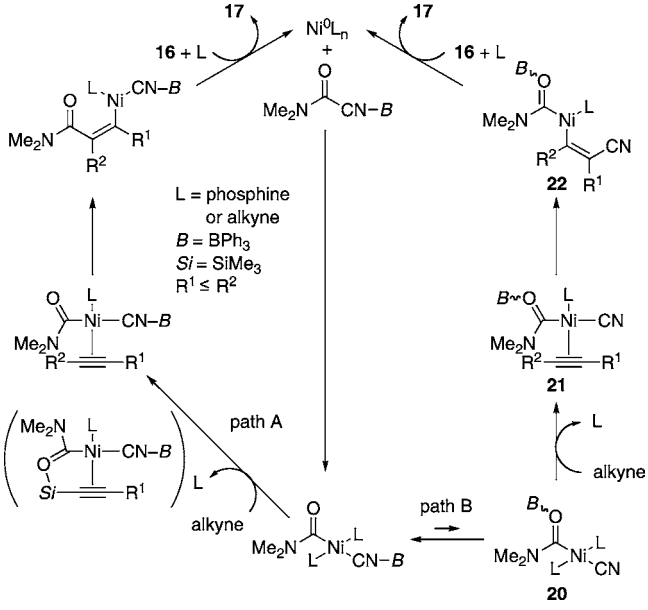
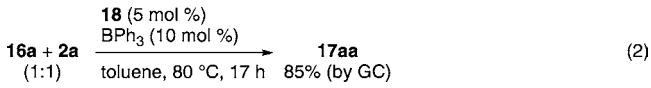


Figure 1. Molecular Structure of **18** with thermal ellipsoids at the 30% probability level. H atoms are omitted for clarity. Selected bond lengths [Å] and angles [deg]: Ni−C1 1.893(3), Ni−P1 2.2208(8), Ni−P2 2.2112(8), Ni−C2 1.898(3), N1−C1 1.160(3), N1−B 1.607(4); C1−Ni−P2 90.60(8), C2−Ni−P2 87.28(8), C1−Ni−P1 90.10(8), C2−Ni−P1 90.94(8), C1−Ni−C2 173.56(12), Ni−C1−N1 179.7(3), C1−N1−B 172.0(3).

Scheme 5. Plausible Mechanism of Cyanocarbamoylation of Alkynes by Nickel/LA Catalysis



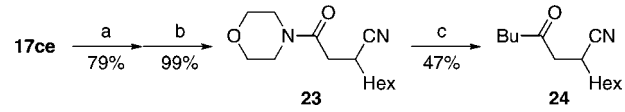
observed in the reaction of $Ni(cod)_2$, $PCyPh_2$, and **2a**. No conversion of **18** was observed when the reaction was run at room temperature for 24 h, suggesting that the coordination of alkynes could be rate-determining. In addition, **18** served as a catalyst for the reaction of **16a** (0.20 mmol) with **2a** (0.20 mmol) in the presence of added BPh_3 (10 mol %) in toluene at 80 °C to give **17aa** in 85% yield after 17 h as estimated by GC (eq 2). These results clearly suggest that **18** is a plausible intermediate for the cyanocarbamoylation.



(2)

On the basis of these results, a catalytic cycle for the cyanocarbamoylation reaction is proposed in path A in Scheme 5, which resembles those for the cyanoesterification. The only difference between these reactions is the regioselectivity observed with **2c** (entry 2 of Table 2 vs entry 3 of Table 4). Though speculative, a carbamoyl group may also coordinate reversibly to the borane LA due to its higher Lewis basicity than an alkoxycarbonyl group to form intermediate **20** in equilibrium, the phosphine ligand being substituted by an alkyne subsequently to give **21** (path B). Migratory insertion into the Ni−CN bond at the less hindered carbon of the alkyne may take place to give alkenylnickel intermediate **22**, which reductively eliminates the adducts. The insertion of alkynes into Ni−CN bonds was also proposed in the nickel-catalyzed silylcyanation of ynones,[38] and is energetically feasible ($\Delta E \leq 10$ kcal/mol) based on our theoretical calculations of the arylcyanation of alkynes.[24] The aminocarbonyl group coordinating to BPh_3 is likely reluctant to undergo the migration in path B due to its plausibly less nucleophilic nature.

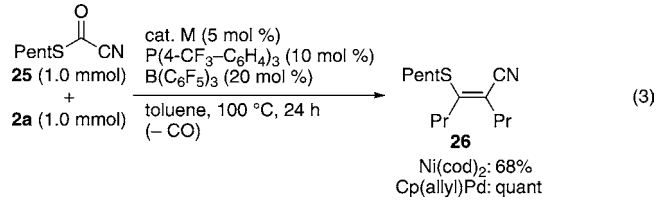
Scheme 6. Transformations of **17ce**[a]



[a] Reagents and Conditions: (a) TBAF, CF_3CO_2H, THF, 0 °C, 3 h; (b) H_2, Pd/C (10 mol %), dioxane, rt, 5 h; (c) BuLi, THF, −78 °C, 30 min.

Cyanocarbamoylation product **17ce** was transformed to β-cyano ketone **24** through protodesilylation, reduction of the double bond, and nucleophilic substitution reaction of the morpholinamide group with an organolithium reagent (Scheme 6).[39]

Palladium/B(C_6F_5)$_3$-Catalyzed Decarbonylative Thiocyanation of 2a. We then examined the nickel/LA catalysis using other nitriles having a carbonyl−CN bond with alkynes. First, thiocyanoformate **25** was prepared and reacted with **2a** in the presence of $Ni(cod)_2$ (5 mol %), P(4-CF_3−C_6H_4)$_3$ (10 mol %), and B(C_6F_5)$_3$ (15 mol %) in toluene at 100 °C. Contrary to our expectation, *cis*-thiocyanation product **26** was isolated in 68% yield after 24 h (eq 3). None of the expected cyanothioesterification product was formed. The stereochemistry of **26** was confirmed by NOE experiments of ^{1}H NMR after reduction of the cyano group to formyl. Use of a palladium catalyst instead of nickel improved the yield significantly, whereas the absence of the LA cocatalyst retarded the reaction with both the palladium and nickel catalysts. Whereas thiocyanation of terminal alkynes has already been achieved with a palladium catalyst solely,[40] this reaction represents the first example of the thiocyanation of internal alkynes.



(3)

The reaction is understood by the initial oxidative addition of either the C−CN bond or S−carbonyl bond[41] to nickel(0) or palladium(0) followed by decarbonylation to give an RS−M−CN

Scheme 7. Plausible Mechanism for Decarbonylative Thiocyanation of **2a**

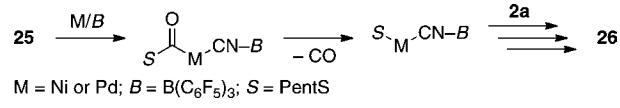
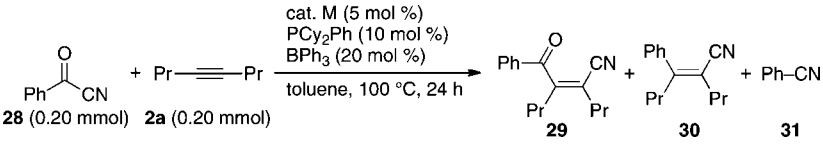


Table 5. Decarbonylative Phenylcyanation of **2a** Using Benzoyl Cyanide (**28**)[a]

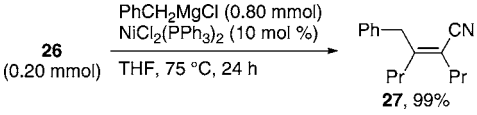


			product(s), yield (%)[b]		
entry	catalyst	conv. of **28**	**29**	**30**	**31**
1[c]	$Ni(cod)_2$	38	3	3	15
2	$Ni(cod)_2$	40	2	3	0
3[c]	$PdCp(\pi\text{-allyl})$	44	0	6	2
4	$PdCp(\pi\text{-allyl})$	75	0	22	0
5[d]	$PdCp(\pi\text{-allyl})$	100	0	57 (58)[e]	21

[a] All the reactions were carried out using **28** (0.20 mmol) and **2a** (0.20 mmol) in toluene (0.40 mL). [b] GC yields as determined using tetradecane as an internal standard. [c] Run in the absence of BPh_3. [d] Run with $PCyPh_2$ as a ligand instead of PCy_2Ph. [e] Isolated yield obtained with a 1.00 mmol scale reaction.

intermediate,[42] which reductively eliminates a thiocyanation product after migratory insertion of an alkyne into either the RS−M[43] or M−CN bond[38] (Scheme 7).

The resulting C−S bond in **26** underwent the Kumada-type cross-coupling reaction with benzylmagnesium chloride in the presence of a nickel catalyst[44] to give formal benzylcyanation product **27** in 99% yield (eq 4).



(4)

Palladium/BAr_3-Catalyzed Decarbonylative Phenylcyanation of 2a. Finally, we attempted the benzoylcyanation of **2a**. In the presence of a nickel catalyst without LA, only a small amount of the expected *cis*-benzoylcyanation product **29** was observed (entry 1 of Table 5), along with phenylcyanation product **30** and benzonitrile (**31**). Products **30** and **31** should be derived from decarbonylation of **28**.[9] Whereas the presence of a LA cocatalyst was not effective (entry 2), palladium/BPh_3 catalysts selectively gave **30** (entries 4 and 5). Of ligands examined, $PCyPh_2$ was the best, giving **30** in 58% yield after isolation (entry 5). The reaction of benzonitrile (**31**) with **2a** under the similar conditions gave **30** in only 20% yield, suggesting that insertion of the alkyne takes place through oxidative addition of **28** to palladium(0) followed by decarbonylation rather than formation of benzonitrile followed by oxidative addition to palladium(0).

Conclusion

In summary, we have demonstrated that the cyanoesterification and cyanocarbamoylation of alkynes proceed by nickel/LA catalysis in highly stereo- and regioselective manners to give a range of β-cyano-substituted acrylates and acrylamides. These highly functionalized nitrile products are shown to be versatile synthetic intermediates for γ-aminobutyric acid, β-amino acid, β-cyano ketone, and 1,2-dicarboxylic acid derivatives. We have also briefly shown that similar reactions of cyanoformate thioesters and cyanoketones with alkynes accompany decarbonylation in the presence of a nickel or palladium/LA catalyst[45] to give thiocyanation and arylcyanation products, respectively.

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Supporting Information Available: Detailed experimental procedures including spectroscopic and analytical data. Complete ref 28b. This material is available free of charge via the Internet at http://pubs.acs.org.

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