Organic LETTERS

Letter

pubs.acs.org/OrgLett

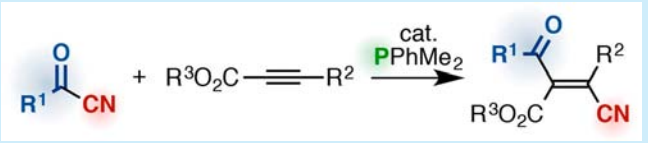
Phosphine-Catalyzed Vicinal Acylcyanation of Alkynoates

Hiroaki Murayama, Kazunori Nagao, Hirohisa Ohmiya,* and Masaya Sawamura*

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

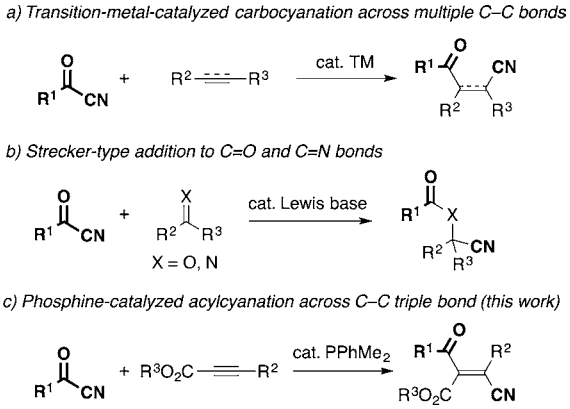
Supporting Information

ABSTRACT: Phosphine organocatalysis enabled vicinal acylcyanation of alkynoates with acyl cyanides to form acrylonitrile derivatives with a tetrasubstituted alkene moiety. The acyl and cyano groups were introduced at the α and β carbon atoms, respectively, of the C−C triple bond in the alkynoates with complete regioselectivity and high *anti* stereoselectivity. A variety of functional groups in the acyl cyanides and alkynoates were tolerated.



Nitrile structures are found in many pharmaceuticals, agrochemicals, natural products, and biologically active compounds.[1] Accordingly, the development of versatile and efficient methods for the introduction of a cyano group into organic molecules presents an important synthetic challenge. Cyanocarbonyl compounds have been used as reagents for introducing carbonyl and cyano groups into molecules through addition of the C−CN bond across unsaturated bonds of the substrate. To date, several transition-metal-catalyzed carbocyanations of unsaturated C−C bonds, which result in simultaneous formation of two C−C bonds, have been reported (Scheme 1a).[2]

Scheme 1. Catalytic Carbocyanation of Unsaturated Compounds



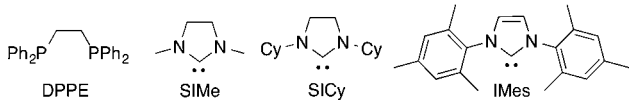
Lewis base catalyzed reactions of cyanocarbonyl compounds have also been reported, but the scope has been limited to addition reactions across carbon−heteroatom double bonds (C═O, C═N) (Strecker-type reactions) (Scheme 1b).[3,4]

Herein, we report phosphine-catalyzed vicinal acylcyanation of alkynoates with acyl cyanides (Scheme 1c).[5] The acyl and cyano groups were introduced at the α and β carbon atoms of the C−C triple bond in the alkynoates, respectively, with complete regioselectivity and high *anti* stereoselectivity. Various functional groups were tolerated in both the acyl cyanides and alkynoates. Thus, this protocol provides a versatile and efficient approach to functionalized acrylonitrile derivatives with a tetrasubstituted alkene moiety. The simple and transition-metal-free reaction conditions are attractive features of this method.

Table 1. Catalyst Effects in Reactions between 1a and 2a[a]

entry	catalyst	yield[b] (%)	*anti*/*syn*[c]
1	$PPhMe_2$ (eq 1)	97 (97)	87:13
2	$PPhEt_2$	82	85:15
3	PPh_2Me	74	82:18
4	PMe_3	0	
5	PBu_3	48	84:16
6	PPh_3	0	
7	PCy_3	0	
8	P^tBu_3	0	
9	DPPE	25	85:15
10	SIMe	0	
11	SICy	0	
12	IMes	0	
13	DABCO	0	
14	DBU	0	
15	DMAP	0	
16	Bu_4NCN	0	

[a]Conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), $PPhMe_2$ (10 mol %), toluene (1.2 mL), 60 °C, 12 h. [b]^{1}H NMR yield. Yield of isolated product is in parentheses. [c]Determined by ^{1}H NMR analysis of the crude product.



We previously developed phosphine-catalyzed *anti*-selective vicinal carboboration, silaboration, and diboration across the C−C triple bond in alkynoates.[6] This prompted us to explore the vicinal carbocyanation of alkynoates using the C−CN bond in place of the C−B, Si−B, and B−B bonds.

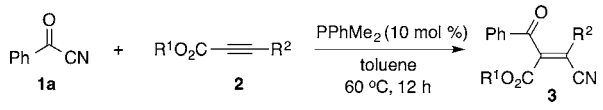
Screening of Lewis base catalysts for the reaction between **1a** and **2a** identified $PPhMe_2$ to be the most effective. Thus,

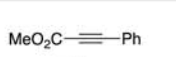
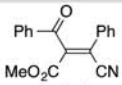
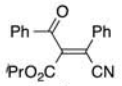
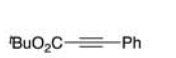
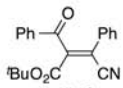
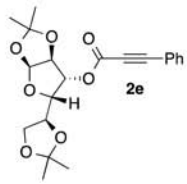
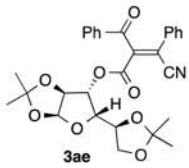
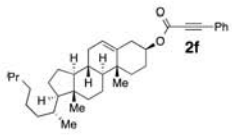
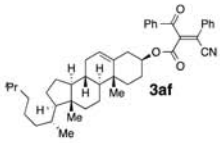
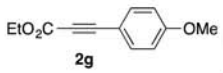
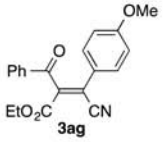
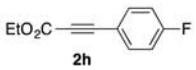
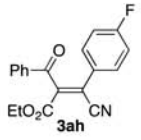
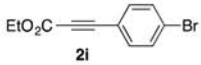
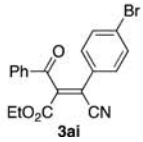
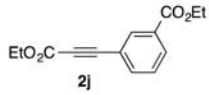
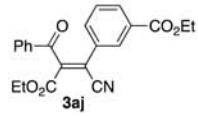
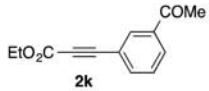
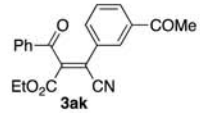
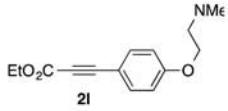
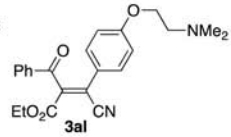
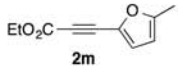
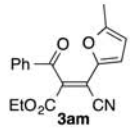
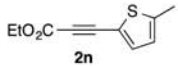
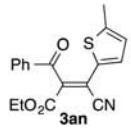
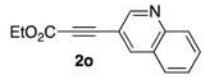
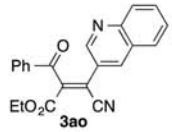
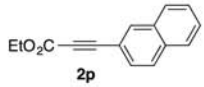
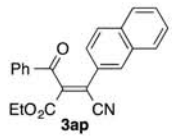
Received: March 9, 2016
Published: March 24, 2016

ACS Publications © 2016 American Chemical Society

DOI: 10.1021/acs.orglett.6b00677
Org. Lett. 2016, 18, 1706−1709

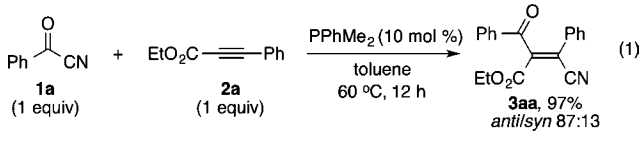
Table 2. Scope of Alkynoates[a]



entry	alkynoate	product	yield (%)[b]	*anti*/*syn*[c]
1	 2b	 3ab	97	89:11
2	 2c	 3ac	85	87:13
3	 2d	 3ad	79	85:15
4	 2e	 3ae	77	88:12
5	 2f	 3af	89	89:11
6	 2g	 3ag	90	90:10
7	 2h	 3ah	83	87:13
8[d]	 2i	 3ai	76	84:16
9	 2j	 3aj	85	82:18
10	 2k	 3ak	83	85:15
11	 2l	 3al	90	84:16
12	 2m	 3am	60	95:5
13	 2n	 3an	82	92:8
14[d]	 2o	 3ao	67	84:16
15[d]	 2p	 3ap	80	89:11

[a]Conditions: **1a** (0.3 mmol), **2** (0.3 mmol), $PPhMe_2$ (10 mol %), toluene (1.2 mL), 60 °C, 12 h. [b]Yield of isolated product. [c]Determined by ^1H NMR analysis of the crude product. [d]$PPhMe_2$ (20 mol %) was used.

the reaction between benzoyl cyanide (**1a**) (0.3 mmol) and ethyl 3-phenylpropiolate (**2a**) (0.3 mmol) in the presence of $PPhMe_2$ (10 mol %) in toluene (1.2 mL) at 60 °C over 12 h afforded acrylonitrile **3aa** in 97% isolated yield (based on **2a**; 97% NMR yield; complete conversion of **2a**) (eq 1). The NMR analysis of the crude product indicated that the *anti*/*syn* ratio for the addition stereochemistry was 87:13. The reaction was readily scalable: a gram-scale reaction with 1.74 g (10 mmol) of **2a** afforded **3aa** in 95% isolated yield.



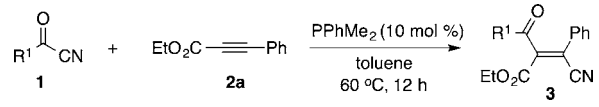
(1)

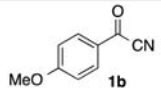
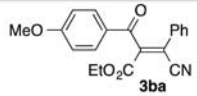
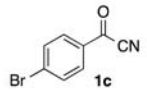
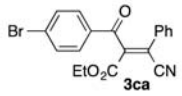
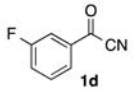
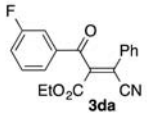
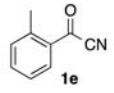
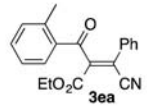
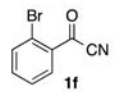
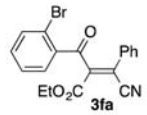
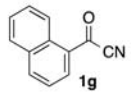
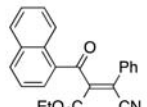
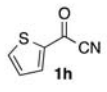
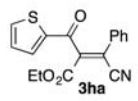
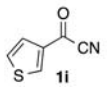
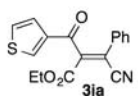
The effect of Lewis base catalysts on the reaction between **1a** and **2a** are shown in Table 1.[7] The use of $PPhEt_2$ or PPh_2Me instead of $PPhMe_2$ under otherwise identical conditions resulted in slightly decreased product yields and *anti* selectivities (entries 1−3). Sterically less demanding PMe_3 was ineffective (entry 4). The more strongly electron-donating PBu_3 gave a moderate product yield with a slightly decreased *anti* selectivity (entry 5). The bulkier phosphines such as PPh_3, PCy_3, and P^tBu_3 resulted in no reaction (entries 6−8). DPPE bisphosphine gave a significantly decreased product yield (entry 9). No reaction occurred with *N*-heterocyclic carbenes or amines (DABCO, DBU, and DMAP) with different steric and electronic natures (entries 10−15). The use of Bu_4NCN also resulted in no reaction (entry 16).

Various alkynoates were subjected to acylcyanation with **1a** using the $PPhMe_2$ catalyst (Table 2).[8,9] The ethoxycarbonyl

DOI: 10.1021/acs.orglett.6b00677
Org. Lett. 2016, 18, 1706−1709

Table 3. Scope of Acyl Cyanides[a]



entry	acyl cyanide	product	yield (%)[b]	*anti*/*syn*[c]
1	 **1b**	 **3ba**	58	85:15
2	 **1c**	 **3ca**	70	89:11
3[d]	 **1d**	 **3da**	93	84:16
4	 **1e**	 **3ea**	86	80:20
5	 **1f**	 **3fa**	56	77:23
6	 **1g**	 **3ga**	94	80:20
7	 **1h**	 **3ha**	78	83:17
8	 **1i**	 **3ia**	75	83:17

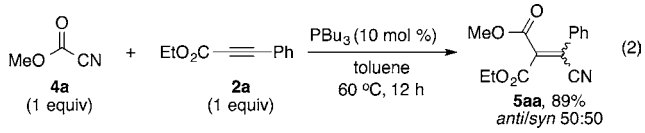
[a]Conditions: **1** (0.3 mmol), **2a** (0.3 mmol), $PPhMe_2$ (10 mol %), toluene (1.2 mL), 60 °C, 12 h. [b]Yield of isolated product. [c]Determined by ^1H NMR analysis of the crude product. [d]The reaction was carried out at 80 °C.

group of 2a could be replaced with methoxy-, isopropoxy-, and tert-butoxycarbonyl groups without a significant change in the *anti* selectivity (entries 1−3). Sugar (**2e**) and cholesterol (**2f**) derivatives underwent acylcyanation (entries 4 and 5).

Alkynoates **2g−l** bearing functional groups such as methoxy, fluoro, bromo, ester, ketone, and 2-(dimethylamino)ethoxy moieties at the *meta*- or *para*-positions of aromatic rings of the *β*-substituent reacted to afford the corresponding acrylonitrile products with high *anti* selectivities (82−90% *anti*) (entries 6−11). However, the substitution with a CN group at the *para* position of aromatic ring inhibited the reaction (data not shown). The 2-furyl-, 2-thienyl-, and 3-quinolinyl-substituted alkynoates were compatible with the acylcyanation and gave high *anti* selectivities (entries 12−14). 2-Naphthyl-conjugated alkynoate also underwent acylcyanation (entry 15). *o*-Tolyl-substituted alkynoate did not react at all (data not shown).

Various acyl cyanides were used in the reaction with **2a** (Table 3).[9] The methoxy, bromo and fluoro groups were tolerated as *para*- or *meta*-substituents of the aromatic rings in the acyl cyanides (entries 1−3). The sterically more demanding aroyl cyanides bearing *ortho*-substituents such as methyl and bromo on the aromatic ring underwent the acylcyanation without a significant reduction in the *anti* selectivity (entries 4 and 5). 1-Naphthoyl cyanide **1g** also reacted with high *anti* selectivity (entry 6). Thiophene derivatives (**1h,i**) served as suitable substrates (entries 7 and 8). However, alkanoyl cyanides resulted in no reaction (data not shown).

The cyanoesterification of alkynoate with cyanoformate also proceeded in high yield, but a significant reduction in stereoselectivity was observed. In this case, PBu_3 was a more appropriate catalyst than $PPhMe_2$. The reaction between methyl cyanoformate (**4a**) and **2a** provided the corresponding acrylonitrile **5aa** in 89% yield with a 50:50 *anti*/*syn* ratio (eq 2).[10]



As shown in Table 1, entry 16, the reaction with Bu_4NCN catalyst as a cyanide ion source did not give the acylcyanation product. Based on this observation, the addition of $PPhMe_2$ to benzoyl cyanide to form a cyanide ion was ruled out as a reaction pathway for the phosphine-catalyzed acylcyanation. Thus, the phosphine catalysis is likely initiated by conjugate addition of the phosphine to the alkynoate **2** (Figure 1).[6]

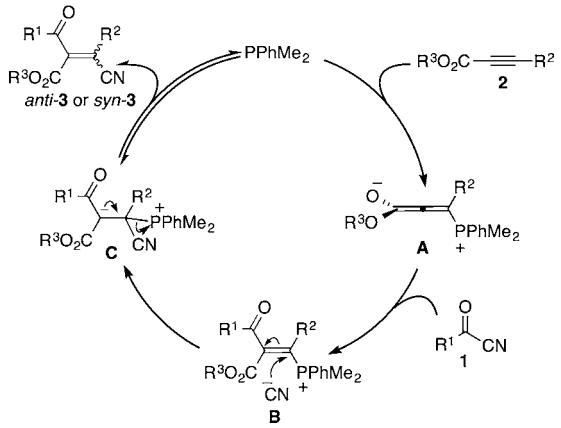
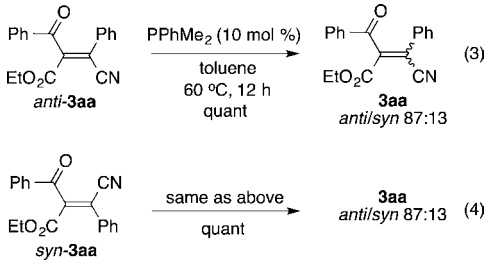


Figure 1. Possible catalytic cycle.

The conjugate addition forms a zwitterionic allenolate intermediate **A**. The acyl cyanide **1** then undergoes a nucleophilic acyl substitution with **A** to form phosphonium cyanide **B**. Conjugate addition of the cyanide ion to the *β*-phosphonium acrylate counterpart in **B** followed by the elimination of phosphine gives **3**.

Alkene isomerization experiments were carried out to clarify how *syn*-acylcyanation products formed (eqs 3 and 4). The subjection of isomerically pure *anti*-**3aa** or *syn*-**3aa** to the standard reaction conditions gave identical 87:13 *anti*/*syn* ratios for **3aa**. This result indicated that the zwitterionic intermediate **C** is in equilibrium with **3** through addition−elimination of the phosphine catalyst. Thus, the phosphine-catalyzed acylcyanation affords the thermodynamically favored product.

DOI: 10.1021/acs.orglett.6b00677
Org. Lett. 2016, 18, 1706−1709



In summary, we have developed a phosphine-catalyzed vicinal acylcyanation of alkynoates with acyl cyanides as a versatile and efficient route to acrylonitrile derivatives with a tetrasubstituted alkene moiety. The acylcyanation across the C−C triple bond in alkynoates occurred with complete regioselectivity and with high *anti* selectivity. Various functional groups were tolerated in both the acyl cyanides and alkynoates. This metal-free phosphine-catalyzed protocol provides a new strategy for the carbocyanation of unsaturated C−C bonds.[2]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00677.

Experimental details; characterization data for all new compounds (PDF)

Crystallographic data for **3an** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ohmiya@sci.hokudai.ac.jp.

*E-mail: sawamura@sci.hokudai.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research (B) (No. 15H03803), JSPS, to H.O. and by CREST, JST, to M.S. Additionally, K.N. thanks JSPS for scholarship support. We thank Prof. Tomohiro Iwai (Hokkaido University) for the X-ray crystal structure analysis.

■ REFERENCES

(1) (a) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Synthesis, Patents, Applications, 4th ed.*; George Thieme: Stuttgart, 2001. (b) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.

(2) For transition-metal-catalyzed intermolecular carbocyanation of unsaturated C−C bonds with cyanocarbonyl compounds, see: (a) Nozaki, K.; Sato, N.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 2679. (b) Nozaki, K.; Sato, N.; Takaya, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1629. (c) Nishihara, Y.; Inoue, Y.; Itazaki, M.; Takagi, K. *Org. Lett.* **2005**, *7*, 2639. (d) Nishihara, Y.; Inoue, Y.; Izawa, S.; Miyasaka, M.; Tanemura, K.; Nakajima, K.; Takagi, K. *Tetrahedron* **2006**, *62*, 9872. (e) Nakao, Y.; Hirata, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7420. (f) Hirata, Y.; Inui, T.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 6624. (g) Hirata, Y.; Yada, A.; Morita, E.; Nakao, Y.; Hiyama, T.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2010**, *132*, 10070. For transition-metal-catalyzed intramolecular carbocyanation of unsaturated C−C bonds with cyanocarbonyl compounds, see: (h) Kobayashi, Y.; Kamisaki, H.; Yanada, R.; Takemoto, Y. *Org. Lett.* **2006**, *8*, 2711. (i) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303. (j) Rondla, N. R.; Levi, S. M.; Ryss, J. M.; Vanden Berg, R. A.; Douglas, C. J. *Org. Lett.* **2011**, *13*, 1940.

(3) For Lewis-base-catalyzed additions of cyanocarbonyl compounds to carbonyl compounds, see: (a) Marvel, C. S.; Brace, N. O.; Miller, F. A.; Johnson, A. R. *J. Am. Chem. Soc.* **1949**, *71*, 34. (b) Hoffmann, H. M. R.; Ismail, Z. M.; Hollweg, R.; Zein, A. R. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1807. (c) Scholl, M.; Lim, C.-K.; Fu, G. C. *J. Org. Chem.* **1995**, *60*, 6229. (d) Okimoto, M.; Chiba, T. *Synthesis* **1996**, *1996*, 1188. (e) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195. (f) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636. (g) Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592. (h) Motokura, K.; Tada, M.; Iwasawa, Y. *J. Am. Chem. Soc.* **2007**, *129*, 9540. (i) Wang, X.; Tian, S.-K. *Synlett* **2007**, 1416. (j) Aoki, S.; Kotani, S.; Sugiura, M.; Nakajima, M. *Tetrahedron Lett.* **2010**, *51*, 3547. (k) Zhang, J.; Du, G.; Xu, Y.; He, L.; Dai, B. *Tetrahedron Lett.* **2011**, *52*, 7153.

(4) For Lewis base catalyzed additions of cyanocarbonyl compounds to imines, see: (a) Pan, S. C.; Zhou, J.; List, B. *Synlett* **2006**, 3275. (b) Pan, S. C.; List, B. *Synlett* **2007**, 318. (c) Pan, S. C.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 612. (d) Pan, S. C.; List, B. *Org. Lett.* **2007**, *9*, 1149. (e) Pan, S. C.; List, B. *Chem. - Asian J.* **2008**, *3*, 430.

(5) Liao and co-workers reported the phosphine- or Bu_4NCN-catalyzed intramolecular acylcyanation across C−C double bonds in highly functionalized acrylates bearing a nitrile moiety: (a) Zhuang, Z.; Chen, J.-M.; Pan, F.; Liao, W.-W. *Org. Lett.* **2012**, *14*, 2354. (b) Chen, J.; Zou, G.; Liao, W.-W. *Angew. Chem., Int. Ed.* **2013**, *52*, 9296. (c) Zhuang, Z.; Hu, Z.-P.; Liao, W.-W. *Org. Lett.* **2014**, *16*, 3380. (d) Chen, J.; Xu, Q.; Liao, W.-W. *Chem. - Eur. J.* **2014**, *20*, 13876. (e) Zhuang, Z.; Liao, W.-W. *Synlett* **2014**, *25*, 905.

(6) (a) Nagao, K.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2014**, *136*, 10605. (b) Nagao, K.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2015**, *17*, 1304. See also: (c) Morinaga, A.; Nagao, K.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 15859.

(7) For reviews on Lewis base catalysis in organic synthesis, see: (a) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (b) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560.

(8) As alkynic substrates, the corresponding conjugated amides, aldehydes, or ketones showed no reactivity under similar conditions.

(9) For Table 2 and Table 3, unreacted acyl cyanide (**1**) and alkynoate (**2**) were detected in the crude materials.

(10) The reaction between **4a** and **2a** with $PPhMe_2$ provided **5aa** in 20% yield with a 50:50 *anti*/*syn* ratio.

DOI: 10.1021/acs.orglett.6b00677
Org. Lett. 2016, 18, 1706−1709