ORGANIC LETTERS

2013
Vol. 15, No. 13
3354–3357

Copper-Mediated Direct Aryl C−H Cyanation with Azobisisobutyronitrile via a Free-Radical Pathway

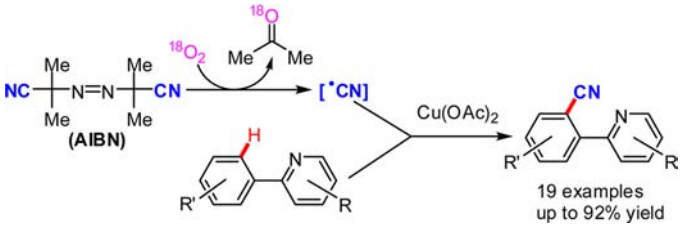
Hao Xu,[†] Peng-Tang Liu,[‡] Yun-Hui Li,[‡] and Fu-She Han*[,§]

Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, 5625 Renmin Street, Changchun, Jilin 130022, Changchun University of Science and Technology, Changchun, Jilin 130022, China, and State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116024, China

fshan@ciac.jl.cn

Received May 17, 2013

ABSTRACT



An unprecedented protocol for the copper-mediated direct cyanation of aryl C−H by employing 2,2′-azobisisobutyronitrile (AIBN) as a free radical "CN" source is presented. The protocol not only provides a more efficient pathway for the synthesis of aryl nitriles in terms of the yields and the loading amount of copper salts but also, more importantly, represents a novel strategy for aryl C−H cyanation *via* a CN free-radical mechanism as compared to the CN anion-participating protocols often reported.

Owing to the great importance of aryl nitriles either as the key building blocks in natural products and designed molecules[1] or as a versatile latent group for facile conversion into a diverse class of functionalities,[2] the development of efficient methods for the synthesis of aryl nitriles constitutes a continuing focus in synthetic organic chemistry. The transition-metal-catalyzed cyanation of aryl (pseudo)halides has been comprehensively investigated with various cyanation reagents[3] including MCN (M = Na, K, Cu, Zn, Me_3Si, etc.) and a few organic sources such as acetone cyanohydrin,[4] malononitrile,[5] benzyl cyanide,[6] and formamide.[7] In addition, cyanation of organometallics such as organoboron compounds[8] and Grignard reagents[9] has also been intensively investigated.

Recently, with the pioneering work of Yu,[10] rapidly growing interest has been observed in direct cyanation of

[†] Changchun Institute of Applied Chemistry.
[‡] Changchun University of Science and Technology.
[§] State Key Laboratory of Fine Chemicals.

(1) (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH: Weinheim, 1989; p 819. (b) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical, Substance: Synthesis, Patents, Applications*, 4th ed.; Georg Thieme: Stuttgart, 2001.

(2) Rappoport, Z. *The Chemistry of the Cyano Group*; Interscience Publishers: London, 1970.

(3) For selected recent publications, see: (a) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4879. (b) Klinkenberg, J. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5758.

(4) For selected examples, see: (a) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661. (b) Park, E. J.; Lee, S.; Chang, S. *J. Org. Chem.* **2010**, *75*, 2760. (c) Schareina, T.; Zapf, A.; Cott, A.; Gotta, M.; Beller, M. *Adv. Synth. Catal.* **2011**, *353*, 777.

(5) Jiang, Z.; Huang, Q.; Chen, S.; Long, L.; Zhou, X. *Adv. Synth. Catal.* **2012**, *354*, 589.

(6) Wen, Q.; Jin, J.; Hu, B.; Lu, P.; Wang, Y. *RSC Adv.* **2012**, *2*, 6167.

(7) Sawant, D. N.; Wagh, Y. S.; Tambade, P. J.; Bhatte, K. D.; Bhanage, B. M. *Adv. Synth. Catal.* **2011**, *353*, 781.

(8) For selected recent publications, see: (a) Zhang, Z.; Liebeskind, L. S. *Org. Lett.* **2006**, *8*, 4331. (b) Liskey, C. W.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11389. (c) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 519. (d) Zhang, G.; Zhang, L.; Hu, M.; Cheng, J. *Adv. Synth. Catal.* **2011**, *353*, 291. (e) Kim, J.; Choi, J.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 2528. (f) Ye, Y.; Wang, Y.-H.; Liu, P.-T.; Han, F.-S. *Chin. J. Org. Chem.* **2013**, *31*, 27.

(9) For an example, see: Anbarasan, P.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2010**, *16*, 4725.

(10) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.

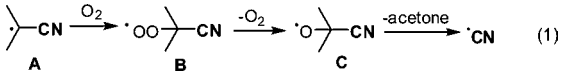
(11) For selected examples, see: (a) Jia, X.; Yang, D.; Zhang, S.; Cheng, J. *Org. Lett.* **2009**, *11*, 4716. (b) Jia, X.; Yang, D.; Wang, W.; Luo, F.; Cheng, J. *J. Org. Chem.* **2009**, *74*, 9470. (c) Do, H.-Q.; Daugulis, O. *Org. Lett.* **2010**, *12*, 2517. (d) Yan, G.; Kuang, C.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 1052. (e) Liskey, C. W.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11389.

10.1021/ol401404y
Published on Web 06/14/2013

aryl C−H with MCN,[11] or organic CN surrogates such as the combination of ammonium salts and DMF or DMSO,[12] or the independent use of DMF[13] and benzyl nitrile.[14] Effective reactions typically required the use of a noble transition metal catalyst associated with the assistance of stoichiometric amounts of copper salts, although a few methods have realized the transformation only by using stoichiometric amounts of copper metals.

Despite these significant advances, a general problem for the CN anion-participating cyanation is the fast deactivation of the catalysts owing to the strong bonding affinity of the CN anion to metals. This resulted in a demand for a high catalyst loading, and/or a decreased yield of the products. Deliberations on the shortcomings of the extant methods led us to initiate a study aimed at achieving the direct aryl C−H cyanation *via* a radical pathway. To the best of our knowledge, such a novel strategy has never been investigated and would provide an alternative option for more efficient synthesis of aryl nitriles. Herein, we present the design, implementation, and mechanistic elucidation of the new protocol.

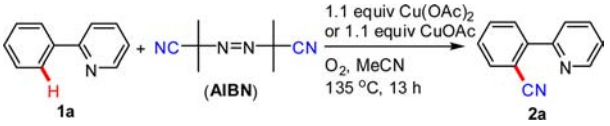
Conceptually, we conceived that the reactivity as well as the affinity property of a CN radical to a metal ion differs from its anion form. Moreover, to compare with the CN anion, the CN radical possesses oxidation ability. Therefore, the formation of the M−CN bond would be accompanied by an oxidation of the metals to a higher valent state. Such a high-valent metal is catalytically more active for C−H activation and swiftly undergoes reductive elimination, thereby, leading to an improved catalytic efficiency. For the CN radical source, the relatively safe and readily available 2,2′-azobisisobutyronitrile (AIBN) is assumed to be suitable. Although AIBN has been popularly used as a radical initiator in a myriad of chemical transformations by extruding a molecule of N_2 to form the 2-cyanoprop-2-yl radical **A** (eq 1), it has never been studied as a CN source for cyanation. However, with the early reports[15] showing that **A** could be trapped by oxygen to form the radical **C** whose thermolysis might further release a CN radical, we reasoned that AIBN might be a suitable CN radical source for cyanation if the reaction conditions could be properly controlled.



(1)

To examine the feasibility of the new protocol, we chose the cyanation of 2-phenylpyridine **1a** (Table 1) as a model reaction. After an exhaustive screening of various combinations of an array of copper salts[16] and solvents,[17] we were pleased to find that $Cu(OAc)_2$ or CuOAc coupled with the use of acetonitrile as solvent was a promising combination. The desired *ortho*-cyanated product **2a** could be obtained in 60% and 51% yields, respectively, under O_2 with the presence of 5.0 equiv of AIBN (Table 1, entry 2). The reaction did not occur in the absence of copper salts or under N_2. Only 12% of **2a** was obtained under air. These results imply that both copper and O_2 are of crucial importance for the cyanation. The control experiment by replacing AIBN with CuCN did not afford any product, indicating that CuCN, a possible intermediate formed *in situ* from $Cu(OAc)_2$ and AIBN, is not the latent CN source. In addition, the reaction also did not occur in the absence of AIBN, implying that MeCN solvent is not the provider of the CN source.

Table 1. Optimization of the Reaction Conditions[a]



entry	$Cu(OAc)_2$ (equiv)	AIBN (equiv)	time (h)	temp (°C)	yield (%)[b]
1	–	5.0	13	135	n.r.[c]
2	1.1	5.0	13	135	60 (51)[d]
3	1.5	5.0	13	135	65
4	1.8	5.0	13	135	75
5	2.0	5.0	13	135	75
6	1.1	5.0	13	145	40
7	1.1	5.0	13	125	39
8	1.1	5.0	13	115	24
9	1.1	3.0	13	135	50
10	**1.1**	**5.0**	**24**	**135**	**80**
11	1.1	5.0	48	135	54
12	**0.55**	**5.0**	**48**	**135**	**74**
13	0.30	5.0	48	135	11

[a] Reaction conditions: **1a** (0.4 mmol), AIBN (2.0 mmol), additives (1.1 equiv), $Cu(OAc)_2$ (amount showed in table), MeCN (4.0 mL) under an O_2 atmosphere in a sealed tube. [b] Isolated yield. [c] No reaction. [d] 1.1 equiv of CuOAc was used for the yield in parentheses.

With these preliminary conditions established, we further optimized the reaction parameters (Table 1). A gradual increase of $Cu(OAc)_2$ from 1.1 to 2.0 equiv resulted in a complete conversion of **1a** and an increased yield of **2a** to 75% (entries 2−5). However, the formation of a small amount of dicyanated byproduct made the purification of the desired monocyanated **2a** laborious. Therefore, 1.1 equiv of $Cu(OAc)_2$ was used in our following optimization. The suitable reaction temperature is *ca.* 135 °C. Either elevating or lowering the temperature led to a decreased yield (entries 5−8). The yield was also somewhat decreased when 3.0 equiv of AIBN was used (entry 9). In addition, an appropriate reaction time is also crucial. For instance, by elongating the reaction time from 13 to 24 h, **2a** was

(12) (a) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272. (b) Ren, X.; Chen, J.; Chen, F.; Chen, J. *Chem. Commun.* **2011**, *47*, 6725. (c) Kim, J.; Choi, J.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 2528.

(13) Ding, S.; Jiao, N. *J. Am. Chem. Soc.* **2011**, *133*, 12374.

(14) Jin, J.; Wen, Q.; Lu, P.; Wang, Y. *Chem. Commun.* **2012**, *48*, 9933.

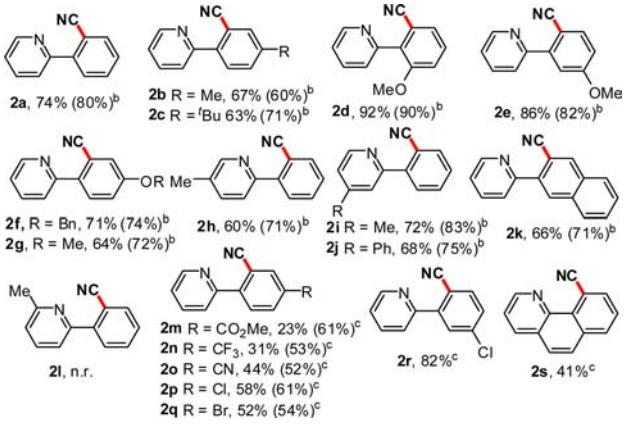
(15) (a) Janzen, E. G.; Krygsman, P. H.; Lindsay, D. A.; Haire, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 8279. (b) Sick, H.; Kim, K. *B. Korean Chem. Soc.* **1985**, *6*, 284.

(16) Copper salts being screened: $Cu(OAc)_2$, Cu(OAc), $Cu(OTf)_2$, $CuSO_4$, $CuSO_4 \cdot 5H_2O$, $Cu(NO_3)_2 \cdot 3H_2O$, $CuCl_2$, CuF_2, CuO, CuI, CuCN, CuBr, CuCl, Cu_2O.

(17) Solvents being screened: DMSO, DMF, DME, DCE, dioxane, toluene, MeCN, PhCN, AcOH, and H_2O.

obtained in 80% yield (entry 10). In contrast, the yield was lowered remarkably to 54% when the time was elongated to 48 h (entry 10 vs 11). Control experiments revealed that the product **2a** may participate in some side reactions such as hydrodecyanation in the presence of copper. Attempted suppression of the side reactions by adding various *N*- or *O*-containing additives, which is assumed to weaken the interaction between copper and **2a** through a coordination effect, proved to be futile. The *O*-containing additives such as 1,2-dimethoxyethane, ethylene glycol, HOAc, and NaOAc exhibited only a slight influence on the yields (data not shown). Surprisingly, the presence of *N*-containing additives such as L-proline, DMEDA, TMEDA, and 2,2′-bipyridine completely suppressed the reaction. Efforts toward lowering the loading amount of $Cu(OAc)_2$ showed that the reaction also proceeded smoothly in the presence of 0.55 equiv of $Cu(OAc)_2$ for 48 h (entry 12). However, the yield was lowered markedly when the amount of $Cu(OAc)_2$ was further decreased (entry 13).

Scheme 1. Products for Cu-Mediated C−H Cyanation of Various Substrates[a]

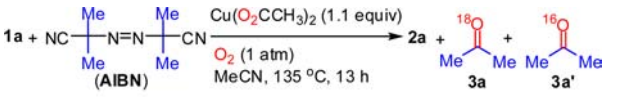


[a] Reaction conditions: **1** (0.4 mmol), AIBN (2.0 mmol), $Cu(OAc)_2$ (0.55 equiv) in MeCN (4.0 mL) under an O_2 atmosphere at 135 °C for 48 h; isolated yields. [b] The reaction was carried out with 1.1 equiv of $Cu(OAc)_2$ for 24 h; isolated yields. [c] The reaction was carried out with 1.1 equiv of $Cu(OAc)_2$ for 48 h; isolated yields.

With the suitable conditions for the direct aryl C−H cyanation using AIBN as the CN source established, we next examined the scope and limitation of the protocol under two different conditions as shown in entries 10 and 12 in Table 1. The results are summarized in Scheme 1. Either in the presence of 0.55 or 1.1 equiv of $Cu(OAc)_2$, comparably good yields were obtained under both conditions for 2-aryl pyridines whose aryl ring was modified by weak alkyl (**2b** and **2c**) or strong alkyloxy electron-donating groups (**2d**−**2g**). Moreover, substrates bearing a substituent at the 5- and 4-position of the pyridyl ring were also well tolerated (**2h**−**2j**). In addition, a fused aromatic derivative was also a competent substrate (**2k**). These extensive results clearly exemplify that AIBN is a powerful CN source for efficient cyanation of relatively electron-rich aryl substrates in the presence of a substoichiometric amount of copper. However, the reaction was sluggish when a Me group is present at the carbon adjacent to the *N*-atom (**2l**). The poor reactivity results from the steric effect of the Me group which prevents the coordination of copper and the pyridyl ring.[10,14]

We also inspected the efficacy of the protocol for electron-deficient substrates. According to the reported methods,[12a,14] such substrates are often less reactive in the direct cynation reaction. We also found that, in comparison with the relatively electron-rich substrates, the reaction of the electron-deficient derivatives was somewhat less reactive in the presence of 0.55 equiv of $Cu(OAc)_2$. Only low to moderate yields were observed under the standard conditions. However, the yield was improved substantially when $Cu(OAc)_2$ was increased to 1.1 equiv. Under the slightly modified conditions, various electron-deficient 2-aryl pyridines were demonstrated to be viable substrates. The cyanation of an array of compounds proceeded uneventfully to afford the corresponding products in moderately high to high yields (**2m**−**2s**).

Scheme 2. Isotopic Labeling Experiments



Conditions: a) $^{18}O_2$ and $Cu(^{16}O_2CCH_3)_2$: **3a:3a'** = *ca.* 2.5:1
b) $^{16}O_2$ and $Cu(^{18}O_2CCH_3)_2$: **3a:3a'** = *ca.* 1:4.8
c) $^{18}O_2$ and $Cu(^{18}O_2CCH_3)_2$: **3a:3a'** = *ca.* 7.3:1

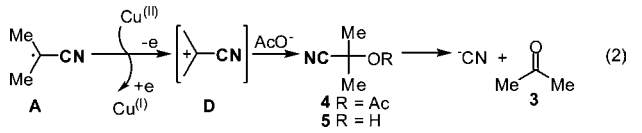
Having examined the generality of the protocol, we became interested in exploring the reaction mechanism. GC-mass analysis revealed that acetone was really formed in the reaction system (Figure S2).[18] Isotopic labeling experiments under $^{18}O_2$ (95 atom % ^{18}O) generated the ^{18}O acetone **3a** paired with the formation of a minor amount of unlabeled **3a′** (Scheme 2, conditions a). The abundance ratio of **3a:3a′** was *ca.* 2.5:1, indicative of the fact that *ca.* 71% of oxygen atom in acetone originates from O_2 (Figure S3). Alternatively, when the reaction was performed with ^{18}O-labeled $Cu(^{18}O_2CCH_3)_2$ (95 atom % ^{18}O)[19] under unlabeled O_2, the ^{18}O-labeled **3a** could also be detected with an abundance ratio of **3a:3a′** = *ca.* 1:4.8; *ca.* 17% of ^{18}O acetone was formed (conditions b; Figure S4). Finally, by carrying out the reaction with $Cu(^{18}O_2CCH_3)_2$ under $^{18}O_2$, the component of ^{18}O acetone was increased remarkably to 7.3:1; *ca.* 88% of ^{18}O acetone was formed (conditions c; Figure S5). The overall content of the ^{18}O acetone equals exactly the sum of that generated from $^{18}O_2$ (71%) and the $^{18}O_2CCH_3$ anion (17%), respectively.

Thus, the generation of acetone mainly from the combination of O_2 and AIBN is in good agreement with our proposed working hypothesis in eq 1. However, the formation of a minor amount of acetone from AcO^- raised

(18) See Supporting Information for detailed GC-Mass, ESI-MS, and XPS analyses.

(19) See Supporting Information for the preparation of anhydrous $Cu(^{18}O_2CCH_3)_2$.

two interesting questions of how is it formed and what is the relatiohship between this forming process and the cyanation reaction. Through extensive spectroscopic studies, we found that acetyl acetone cyanohydrin **4** could be detected from the reaction mixture by ESI-MS analysis (eq 2). Correlated with this observation, X-ray photoelectron spectroscopic (XPS) analyses revealed that $Cu(OAc)_2$ was almost completely reduced to the $Cu^{(I)}$ species by AIBN either in the presence or in the absence of 2-phenylpyridine **1a** (Figure S6). On the basis of these results, we proposed a plausible pathway to explain the formation of **4** and $Cu^{(I)}$ species. Namely, the redox reaction of radical **A** and $Cu^{(II)}$ through single electron transfer (SET) generates the $Cu^{(I)}$ ion and the cation species **D**. Then, the highly reactive species **D** is readily trapped by AcO^- to form **4**. Conversion of **4** into acetone **3** should readily occur in various ways, e.g., through the nucleophilic attack of AcO^- to **4**. However, extensive control experiments clearly demonstrated that **4** or the deacetylated **5** was not, or at most just a very minor, supplier of the CN source for the cyanation (see Scheme S1 in the Supporting Information for details). Consequently, the real reactive CN must be generated predominantly from the combination of O_2 and AIBN.

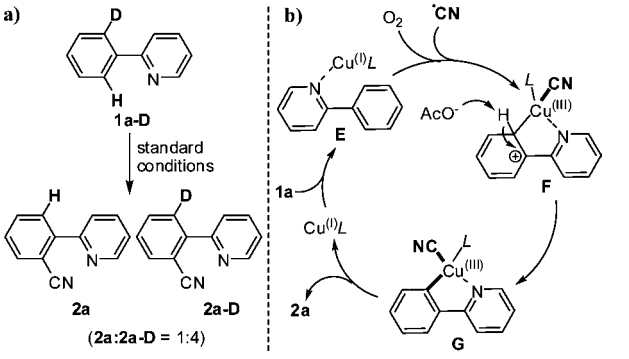


Further ESI-MS spectroscopic studies showed that when the reaction was carried out under N_2 in the presence of $Cu(OAc)_2$, only two signals corresponding to the $Cu^{(I)}$[**1a**]$_2$ and [$Cu^{(I)}$]$_2$[**1a**]$_2$[CN] complexes were detected (Figure S7). This indicates that only simple coordination between $Cu^{(I)}$ and **1a** occurs. In contrast, when the reaction was carried out under O_2, several new strong signals corresponding to $Cu^{(III)}$[**1a-H**]$_2$, $Cu^{(III)}$[**CN**][**1a**][**1a-H**], and $Cu^{(III)}$[**CN**][**1a-H**][**2a**] or $Cu^{(III)}$[**CN**][**1a**][**2a-H**] complexes appeared (Figure S8). However, there was no detection of any possible $Cu^{(II)}$ complexes. The results along with the XPS data strongly suggest that the reaction should proceed via a $Cu^{(I)}$ to $Cu^{(III)}$ cycle, although attempted further clarification of the $Cu^{(III)}$ species was unsuccessful owing to its rather reactive nature.[20] We also investigated the isotopic effect through an intramolecular competition reaction using the deuterated **1a-D** (Scheme 3a). ^{1}H NMR analysis revealed that the ratio between the undeuterated **2a** and the deuterated **2a-D** was 1:4. The large isotopic effect clearly demonstrated that C−H cleavage should be involved in the rate-determining steps. In contrast, no isotopic effect was observed for an anion participating Cu-catalyzed C−H functionalization.[10]

(20) For a review on the high-valent copper in catalysis, see: Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177.

On the basis of the comprehensive control experiments and spectroscopic analyses, we could propose a full mechanism for the newly developed cyanation protocol although a detailed pathway awaits further investigation (Scheme 3b). The real catalytically active copper species should be $Cu^{(I)}L$, which generates *in situ* through the reduction of $Cu^{(II)}$ by AIBN. Coordination of $Cu^{(I)}L$ with **1a** forms the $Cu^{(I)}$ complex **E**. Then oxidation of **E** by the coaction of the CN radical and O_2 generates the high-valent $Cu^{(III)}$ complex **G** *via* **F** through the highly electrophilic $Cu^{(III)}$ promoted dearomatization and rearomatization procedure.[21] Subsequently, reductive elimination of **G** delivers the product **2a** and regenerates $Cu^{(I)}$.

Scheme 3. Isotope Effect (a) and Proposed Mechanism (b) for the Cu-Mediated Cyanation of 2-Aryl Pyridine with AIBN



In summary, we have presented an unprecedented strategy for the direct aryl C−H cyanation *via* a free-radical pathway. The new protocol together with the current CN anion-participating approaches significantly expands the options for the straightforward synthesis of aryl nitriles. Mechanistic study indicates that a $Cu^{(I)}$ to $Cu^{(III)}$ cycle should be rather preferred. The preliminary results would be valuable for the development of new copper catalysts or a CN source for more effective cyanation. Finally, with the extensive experience obtained in this study, a detailed investigation into the reaction mechanism and the development of a more practical cyanation protocol are currently underway.

Acknowledgment. Financial support from Hundred Talent Program of CAS and State Key Lab of Fine Chemicals (KF1201) is acknowledged.

Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR, GC-Mass, ESI-MS, XPS spectra. This material is available free of charge via Internet at http://pubs.acs.org.

(21) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593.

The authors declare no competing financial interest.