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Chelation-Assisted Palladium-Catalyzed Direct Cyanation of 2-Arylpyridine C−H Bonds

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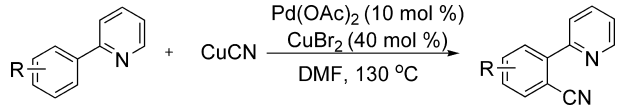
ABSTRACT



A chelation-assisted palladium-catalyzed *ortho*-cyanation of the sp^2 C−H bond by CuCN provided aromatic nitriles in moderate to good yields. Notably, the reaction could be conducted on a 10 mmol scale. The key intermediate of the natural product of *Menispermum dauricum* DC was concisely synthesized by the procedure. This new approach represents an exceedingly practical method for the synthesis of aromatic nitriles and offers an attractive alternative to the traditional Sandmeyer reaction.

Aromatic nitriles are not only key components of numerous commercial compounds, including pharmaceuticals, agrochemicals, pigments, and dyes,[1] but also valuable in the installation of functional groups, such as aldehydes, amines, amidines, tetrazoles, carboxylic acids, and carboxylic acid derivatives.[2] The Sandmeyer reaction is a powerful method for the synthesis of aromatic nitriles, but the multiple-step procedure limits its application (Path a, Scheme 1). Alternative transformations involve the palladium-catalyzed cyanation of aryl halides with cyanating reagents, such as KCN, $Zn(CN)_2$, TMSCN, and $K_3Fe(CN)_6$[3] (Path b, Scheme 1). However, prefunctionalization, mostly bromination, is required in this cyanation reaction.

Over the past several decades, extensive efforts have been directed toward a transition-metal-catalyzed C−H functionalization.[4] The combination of transition metals and directing groups has been a useful strategy to facilitate the transformation of C−H bonds into C−C[5] and C−hetero bonds,[6] which suffered from the limited scope of reaction partners. From the synthetic point of view, the direct and catalytic cyanation via C−H bond cleavage is attractive in organic chemistry (Path c, Scheme 1); nevertheless, to the best of our knowledge, few examples have been reported to access

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(1) (a) Uehling, D. E.; Nanthakumar, S. S.; Croom, D.; Emerson, D. L.; Leitner, P. P.; Luzzio, M. J.; McIntyre, G.; Morton, B.; Profeta, S.; Sisco, J.; Sternbach, D. D.; Tong, W.-Q.; Vuong, A.; Besterman, J. M. *J. Med. Chem.* **1995**, *38*, 1106. (b) Nagamura, S.; Kobayashi, E.; Gomi, K.; Saito, H. *Bioorg. Med. Chem.* **1996**, *4*, 1379. (c) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substance: Synthesis, Patents, Applications*, 4th ed., Georg Thieme: Stuttgart, 2001. (d) Sundermeier, M.; Zapf, A.; Beller, M.; Sans, S. *Tetrahedron Lett.* **2001**, *42*, 6707.

(2) (a) Rappoport, Z. *The Chemistry of the Cyano Group*; Interscience Publishers: London, 1970. (b) Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1988.

(3) (a) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388. (b) Cristau, H.-J.; Ouali, A.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2005**, *11*, 2483. (c) Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem.—Eur. J.* **2003**, *9*, 1828. (d) Zhu, Y.-Z.; Cai, C. *Eur. J. Org. Chem.* **2007**, 2401. (e) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508. (f) Marcantonio, K. M.; Frey, L. F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D. J.; Chen, C. *Org. Lett.* **2004**, *6*, 3723. (g) Yang, C.; Williams, J. M. *Org. Lett.* **2004**, *6*, 2867. (h) Littke, A.; Soumeillant, M.; Kaltenbach, R. F., III; Cherney, R. J.; Tarby, C. M.; Kiau, S. *Org. Lett.* **2007**, *9*, 1711. (i) Chidambaram, R. *Tetrahedron Lett.* **2004**, *45*, 1441. (j) Srivastava, R. R.; Collibee, S. E. *Tetrahedron Lett.* **2004**, *45*, 8895. (k) Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271. (l) Schareina, T.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 4576. (m) Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003**, *684*, 50. (n) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 1087. (o) Okano, T.; Iwahara, M.; Kiji, J. *Synlett* **1998**, 243.

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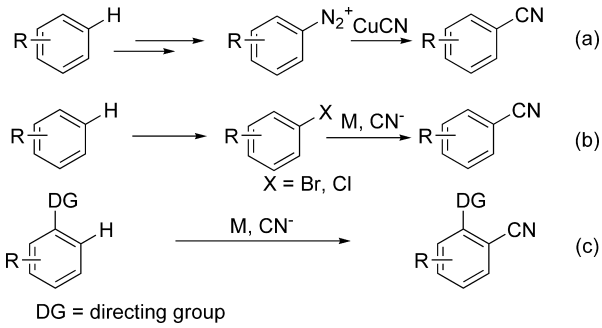
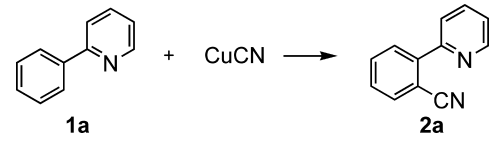
Scheme 1. Three Pathways to Access Aromatic Nitrile



aromatic nitriles via C−H bond cleavage employing TMSCN as the cyanating reagent.[7] The general problem of these cyanation reactions is the deactivation of the transition-metal catalyst by formation of highly stable cyano complexes.[8] Thus, the concentration of dissolved cyanide ions is crucial for the direct cyanation of C−H bonds. Herein, we report the palladium-catalyzed *ortho*-cyanation of aromatic C−H bonds employing CuCN as a cyanating reagent.

We first tested the cyanation of 2-phenylpyridine with CuCN. To our delight, cyanation took place in the presence of $Pd(OAc)_2$ (10 mol %) with $Cu(OAc)_2$ (0.4 equiv) in DMF under air (Table 1, entry 1). Among the Cu(II) catalysts tested, $CuBr_2$ was the best, and the yield was sharply increased to 81% by employing 0.4 equiv of $CuBr_2$ at 130 °C in DMF for 24 h (entry 3). In the case of employing 5 mol % of $Pd(OAc)_2$, the cyanation product was isolated in 85% yield with elongated reaction time (36 h). Other oxidants, such as $K_2S_2O_8$ and $PhI(OAc)_2$, were totally ineffective for this transformation. The use of toluene, xylene, and 1,4-dioxane as solvents resulted in lower yields or no reaction (entries 11−13, Table 1). Gratifyingly, the mono-cyanated product was obtained as a major product, probably because the electron-withdrawing cyanogen group attached to the aryl ring inhibited further reaction. Under an O_2 atmosphere, a comparable result was obtained, providing the cyanation products in 75% yield. Under N_2, only 27% of the desired product was isolated, indicating that air may serve as a terminal oxidant in the procedure. Further studies revealed that $Pd(OAc)_2$ was superior to other Pd(II) catalysts and Pd(0) was totally ineffective. No product was formed in the absence of Pd(II). Importantly, this transformation is very practical as it does not require the use of strong bases or expensive ligands, and the rigorous exclusion of air/moisture is not required.

Table 1. Selected Results of Screening the Optimal Conditions[a]



1a 2a

entry	palladium	oxidant (equiv)	solvent	yield (%)[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2$ (0.4)	DMF	34
2	$Pd(OAc)_2$	$CuCl_2$ (0.4)	DMF	25
3	$Pd(OAc)_2$	$CuBr_2$ (0.4)	DMF	81(85)[c]
4	$Pd(OAc)_2$	$CuSO_4$ (0.4)	DMF	20
5	$Pd(OAc)_2$	$Cu(OTf)_2$ (0.4)	DMF	16
6	$Pd(OAc)_2$	$Cu(acac)_2$ (0.4)	DMF	42
7	$Pd(OAc)_2$	$CuBr_2$ (0.2)	DMF	60
8	$Pd(OAc)_2$	$K_2S_2O_8$ (1.0)	DMF	<5
9	$Pd(OAc)_2$	$PhI(OAc)_2$ (1.0)	DMF	<5
10	$Pd(OAc)_2$	Oxone (1.0)	DMF	<5
11	$Pd(OAc)_2$	$CuBr_2$ (0.4)	toluene	8
12	$Pd(OAc)_2$	$CuBr_2$ (0.4)	xylene	11
13	$Pd(OAc)_2$	$CuBr_2$ (0.4)	1,4-dioxane	<5
14	$Pd(OAc)_2$	$CuBr_2$ (0.4)	DMSO	32
15	$PdCl_2$	$CuBr_2$ (0.4)	DMF	47
16	Pd(dba)[2]	$CuBr_2$ (0.4)	DMF	<5
17	$Pd(OCOCF_3)_2$	$CuBr_2$ (0.4)	DMF	13
18		$CuBr_2$ (0.4)	DMF	<5

[a] 2-Phenylpyridine (0.2 mmol), CuCN (0.24 mmol), Pd (10 mol %), indicated oxidant, dry solvent (1 mL), 130 °C, under air, 24 h. [b] Isolated yield. [c] $Pd(OAc)_2$ (5 mol %), 36 h.

(4) For representative reviews on C−H functionalization, see: (a) Dyker, G. *Handbook of C-H Transformations. Applications in Organic Synthesis*; Wiley-VCH: Weinheim, 2005. (b) Murai, S. *Activation of Unreactive Bonds and Organic Synthesis*; Springer: Berlin, 1999; pp 48−78. (c) Crabtree, R. H. *J. Organomet. Chem.* **2004**, *689*, 4083. (d) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (e) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (f) Kakiuchi, F. *Top. Organomet. Chem.* **2008**, *24*, 1. (g) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (h) Goj, L. A.; Gunnoe, T. B. *Curr. Org. Chem.* **2005**, *9*, 671. (i) Park, Y. J.; Park, J. W.; Jun, C. H. *Acc. Chem. Res.* **2008**, *41*, 222. (j) Li, B.; Yang, S.; Shi, Z. *Synlett* **2008**, 949. (k) Mori, C. A.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548. (l) Diaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379.

(5) (a) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (b) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858. (c) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449. (d) Wen, J.; Zhang, J.; Chen, S.-Y.; Li, J.; Yu, X.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 8897. (e) Wakui, H.; Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2004**, *126*, 8658. (f) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084. (g) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411. (h) Deng, G. J.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278. (i) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. (j) Kuninobu, Y.; Fujii, Y.; Matsuki, T.; Nishina, Y.; Takai, K. *Org. Lett.* **2009**, *11*, 2711. (k) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (l) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (m) Jin, W.-W.; Yu, Z.-K.; He, W.; Ye, W.-J.; Xiao, W.-J. *Org. Lett.* **2009**, *11*, 1317.

(6) (a) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416. (b) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (c) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (d) Zhao, X.; Dimitrijeviæ, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466. (e) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (f) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (g) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (h) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285. (i) Thu, H. Y.; Yu, W. Y.; Che, C. M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (j) Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058. (k) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (l) Ihara, H.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 7502. (m) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058.

(7) (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. For the ruthenium-catalyzed cyanation employing NaCN, see: (b) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005.

(8) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661, and references cited therein.

With the optimized conditions in hand, the scope of substrates was further explored as shown in Figure 1. As

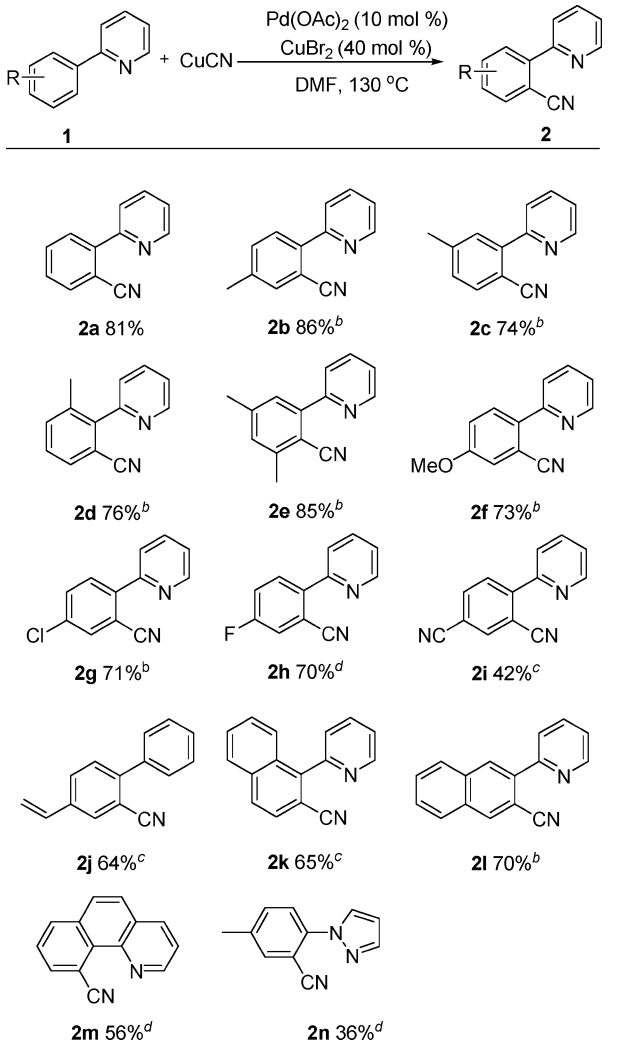
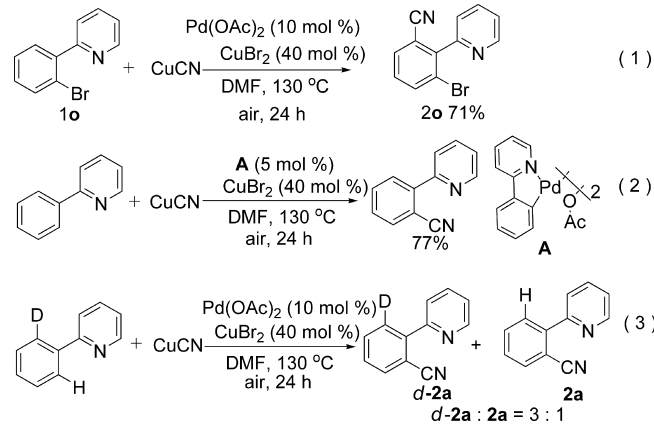


Figure 1. Palladium-catalyzed cyanation of C−H bonds.[a] [a]2-Arylpyridine (0.2 mmol), CuCN (0.24 mmol), $Pd(OAc)_2$ (10 mol %), $CuBr_2$ (40 mol %), dry DMF (1 mL), air, 130 °C, 24 h. Isolated yield. [b]18 h. [c]36 h. [d]48 h.

expected, a variety of functional groups, including methoxy, chloro, fluoro, vinyl, and cyanogen, were well tolerated. Compared with electron-deficient analogues (Figure 1, **2a**−**2f** vs **2i**), electron-rich arenes exhibited high reactivity in the procedure. Notably, the regioselectivity of *meta*-substituted substrate was dominated by steric effects, and only the less hindered *ortho*-cyanated 2-arylpyridine (**2c**) was produced. Regioisomeric products were not observed by GC−MS and ^{1}H NMR spectroscopy. The observed selectivity is at least partly linked to the regioselectivity of the cyclopalladation step[9] which is known to be sterically sensitive.[10] The hindrance of the aryl group of 2-arylpyridine had a limited effect on the reaction. For example, the *ortho*-substituted substrate delivered a 76% yield of **2d**. When 2-(naphthalen-1-yl)pyridine was subjected to the procedure, the cyanation product **2k** was isolated in 65% yield. Interestingly, 2-(naphthalen-2-yl)pyridine produced the β-cyanation product **2l** in 70% yield. Benzo[*h*]quinoline and 1-*p*-tolyl-1*H*-pyrazole were good reaction partners, delivering the corresponding cyanation product in 56% and 36% yields along with the recovered substrates, respectively (Figure 1, **2m** and **2n**).

Experiments to gain a preliminary understanding of the mechanism revealed that 2-(2-bromophenyl)pyridine **1o** did not appear to be an intermediate in the reaction since the product **2o** was isolated in 71% yield under the standard reaction condition (Scheme 2, eq 1). This result ruled out

Scheme 2. Preliminary Studies on the Mechanism



the possibility of a tandem C−H bond halogenation/cyanation pathway. Palladacycle **A** was prepared (see Supporting Information).[11] and **A** could catalyze the formation of **2a** in 77% isolated yield. Moreover, **A** reacted with CuCN cleanly forming the cyanated pyridine in 83% yield, indicating that palladacycle **A** may be an intermediate during this catalytic cycle (Scheme 2, eq 2). Additionally, the reaction exhibited a kinetic isotope effect ($k_H/k_D = 3.0$), indicating slow C−H bond activation (Scheme 2, eq 3).

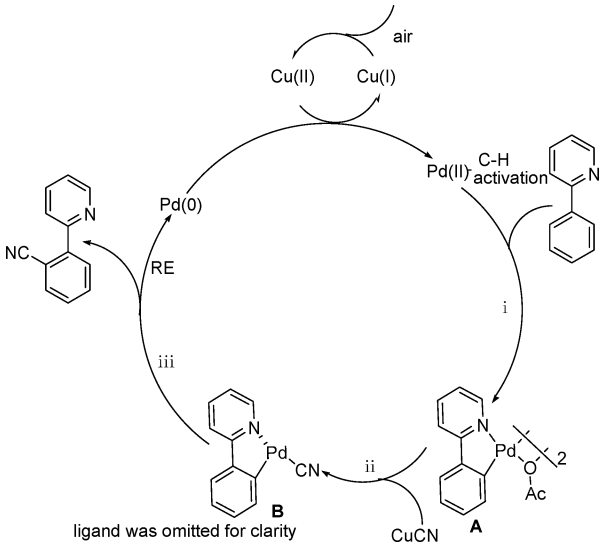
Upon the basis of these experimental results, a plausible mechanism is outlined in Scheme 3. Step (i) involves the chelate-directed C−H activation of 2-phenylpyridine to afford a cyclopalladated intermediate **A**. The high *ortho*-selectivity as well as preliminary mechanistic experiments (Scheme 2, eq 2) have provided strong evidence to support this step. Step (ii) of the proposed catalytic cycle involves ligand exchange of CN^- to form Pd(II) species **B**. In the final step (iii), intermediate **B** undergoes carbon−carbon bond-forming reductive elimination to deliver the product along with a Pd(0) species, which is oxidized to Pd(II) by Cu(II) and/or air.

(9) (a) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149. (b) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523.

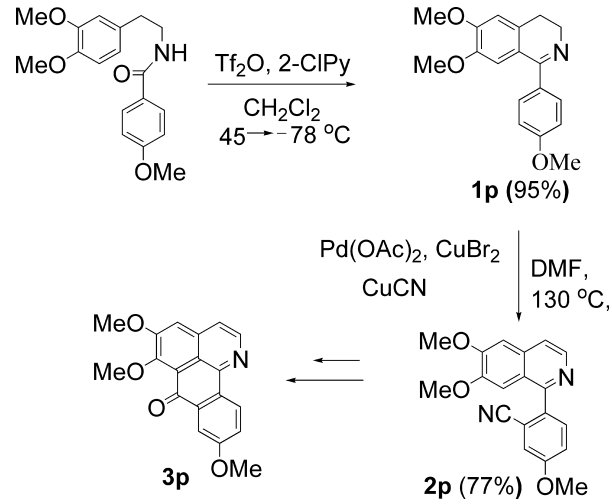
(10) (a) Dupont, J.; Consorti, C. S.; Spenser, J. *Chem. Rev.* **2005**, *105*, 2527. (b) Ryabov, A. D. *Synthesis* **1985**, 233.

(11) Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304.

Scheme 3. Plausible Mechanism



Scheme 4. Concise Pathway to a Key Intermediate of **3p**



We next turned our efforts toward investigation of the practicality of the direct cyanation reaction of the C−H bond. The reaction conducted on a 10 mmol scale formed the cyanation product **2a** in an acceptable 61% yield.

5,6,9-Trimethoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one (**3p**) is a known base from *Menispermum dauricum* DC (Menispermaceae). Some alkaloids possessing the 7*H*-dibenzo-[*de*,*h*]quinoline skeleton isolated from *Menispermum dauricum* DC have exhibited cytotoxic activities against a small panel of cancer cell lines.[12] The key intermediate (**2p**) for the synthesis of **3p** was concisely synthesized under the standard procedure (Scheme 4). Importantly, under the present cyanating procedure, the cyclic imine motif in **1p** was directly converted to the pyridine ring.

In conclusion, we have demonstrated an efficient palladium-catalyzed direct cyanation of arene C−H bonds. The reaction represents a convenient and atom economic method for the synthesis of aromatic nitriles. Ongoing work seeks to gain further insights into the mechanism of this reaction and to expand the scope of the cyanation of unactivated sp^3 C−H bonds.

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Supporting Information Available: Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Kunitomo, J.-I.; Satoh, M. *Chem. Pharm. Bull.* **1982**, *30*, 2659. (b) Kunitomo, J.-I.; Satoh, M.; Shingu, T. *Tetrahedron* **1983**, *39*, 3261. (c) Takani, M.; Takasu, Y.; Takahashi, K. *Chem. Pharm. Bull.* **1983**, *31*, 3091. (d) Kunitomo, J.-I.; Kaede, S.; Satoh, M. *Chem. Pharm. Bull.* **1985**, *33*, 2778. (e) Hu, S.-M.; Xu, S.-X.; Yao, X.-S.; Cui, C.-B.; Tezuka, Y.; Kikuchi, T. *Chem. Pharm. Bull.* **1993**, *41*, 1866. (f) Yu, B.-W.; Meng, L.-H.; Chen, J.-Y.; Zhou, T.-X.; Cheng, K.-F.; Ding, J.; Qin, G.-W. *J. Nat. Prod.* **2001**, *64*, 968.