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The palladium-catalyzed cyanation of indole C–H bonds with the combination of NH_4HCO_3 and DMSO as a safe cyanide source†

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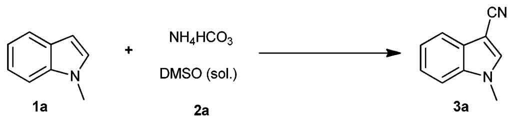
A palladium-catalyzed cyanation of the 3-position of indole sp^2 C–H bonds by the combination of NH_4HCO_3 and DMSO as the "CN" source was achieved to provide aromatic nitriles in moderate to good yields with excellent regioselectivity. It represents a practical and safe cyanation method.

Aryl nitriles are not only key components of pharmaceuticals and natural products but also basic constituents of dyes and herbicides.[1] In addition, they are valuable in the installation of functional groups, such as aldehydes, amines, amidines, tetrazoles, carboxylic acids and their derivatives.[2] The Sandmeyer[3] and Rosenmund–von Braun reactions[4] are traditional methods for the synthesis of organo nitriles, but suffer from multiple-step procedures. The cyanation of aryl halides catalyzed by Pd,[5] Cu[6] and Ni[7] is a common and useful transformation in organic synthesis. However, pre-halogenation is required in these cyanation reactions.

The direct conversion of C–H bonds into carbon–carbon, carbon–halogen, carbon-oxygen, carbon–nitrogen and carbon–sulfur bonds is a very powerful methodology for building complex molecules.[8] Recently, chelation-assisted C–H bond cyanation using metal-bound precursors of MCN (M = Cu, K, Na, Zn, TMS) or $K_3Fe(CN)_6$ has been reported.[9] However, except for $K_3Fe(CN)_6$, the toxicity of the MCN would greatly decrease the practicality of this transformation. Thus, the development of a safe cyanide source in the cyanation reaction still remains a highly desired goal. Very recently, Chang demonstrated the palladium-catalyzed chelation-assisted cyanation of 2-arylpyridine C–H bonds using the combination of ammonia and DMF as a safe cyanide source.[10] Our interest in C–H functionalization and cyanation led us to explore the possibility of a safe "CN" source for such transformations.[9b,c,11] Herein, we report our study in the direct cyanation reaction of indole C–H bonds using a combination of NH_4HCO_3 and DMSO as a safe "CN" source.

We first tested the cyanation of 1-methyl-1*H*-indole as the model reaction. To our delight, cyanation took place in the presence of $Pd(OAc)_2$ (10 mol%) and $Cu(OAc)_2$ (1.1 equiv.) in DMSO under O_2 (entry 1, Table 1). Both palladium and copper species were required for the cyanation (entry 2 and 7, Table 1). Among the Pd sources tested, $PdCl_2$ was the best and the yield sharply increased to 85% (entries 3–6, Table 1). Using $[Pd(cod)Cl]_2$ and $Pd(dppe)Cl_2$, or without palladium, no cyanation product was isolated. As for Cu sources tested, $Cu(OAc)_2$ was superior to others, such as CuO, $Cu(OTf)_2$, $CuCl_2$ and CuCl (entries 8–11, Table 1). Other oxidants such as $K_2S_2O_8$ were totally ineffective for this transformation. The use of NMP, toluene and xylene as solvents resulted in no reaction. The combination of DMF and NH_4HCO_3 delivered the cyano product in 35% yield. Employing NH_4F or $(NH_4)_2C_2O_4$ as nitrogen source inhibited the reaction, while $NH_3{\cdot}H_2O$ or $(NH_4)_2SO_4$ provided the product in poor yields (entries 19 and 20, Table 1). Under

Table 1 Selected results of screening the optimal conditions[a]



Entry	Pd source	Cu source	N source	Solvent	Yield (%)
1	$Pd(OAc)_2$	$Cu(OAc)_2$	NH_4HCO_3	DMSO	36
2	—	$Cu(OAc)_2$	NH_4HCO_3	DMSO	0
3	$[Pd(cod)Cl]_2$	$Cu(OAc)_2$	NH_4HCO_3	DMSO	0
4	$Pd(dppe)Cl_2$	$Cu(OAc)_2$	NH_4HCO_3	DMSO	0
5	**$PdCl_2$**	**$Cu(OAc)_2$**	**NH_4HCO_3**	**DMSO**	**85 (43^b)**
6	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$	NH_4HCO_3	DMSO	0
7	$PdCl_2$	—	NH_4HCO_3	DMSO	0
8	$PdCl_2$	CuO	NH_4HCO_3	DMSO	0
9	$PdCl_2$	$Cu(Otf)_2$	NH_4HCO_3	DMSO	0
10	$PdCl_2$	$CuCl_2$	NH_4HCO_3	DMSO	40
11	$PdCl_2$	CuCl	NH_4HCO_3	DMSO	0
12	$PdCl_2$	$K_2S_2O_8$	NH_4HCO_3	DMSO	0
13	$PdCl_2$	$Cu(OAc)_2$	NH_4HCO_3	NMP	0
14	$PdCl_2$	$Cu(OAc)_2$	NH_4HCO_3	Toluene	0
15	$PdCl_2$	$Cu(OAc)_2$	NH_4HCO_3	DMF	35
16	$PdCl_2$	$Cu(OAc)_2$	NH_4HCO_3	xylene	0
17	$PdCl_2$	$Cu(OAc)_2$	NH_4F	DMSO	0
18	$PdCl_2$	$Cu(OAc)_2$	$(NH_4)_2C_2O_4$	DMSO	0
19	$PdCl_2$	$Cu(OAc)_2$	NH_3H_2O	DMSO	50
20	$PdCl_2$	$Cu(OAc)_2$	$(NH_4)_2SO_4$	DMSO	38

[a] *Reaction conditions*: *N*-methyl-1*H*-indole (0.2 mmol), NH_4HCO_3 (0.3 mmol, 1.5 equiv.), Pd source (10 mol%), Cu source or other oxidant (1.1 equiv.), and DMSO (1.5 mL), under O_2, 140 °C, 6 h. [b] Under air.

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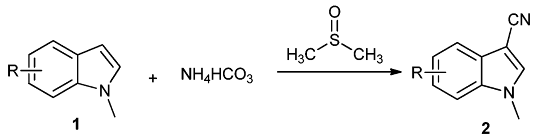
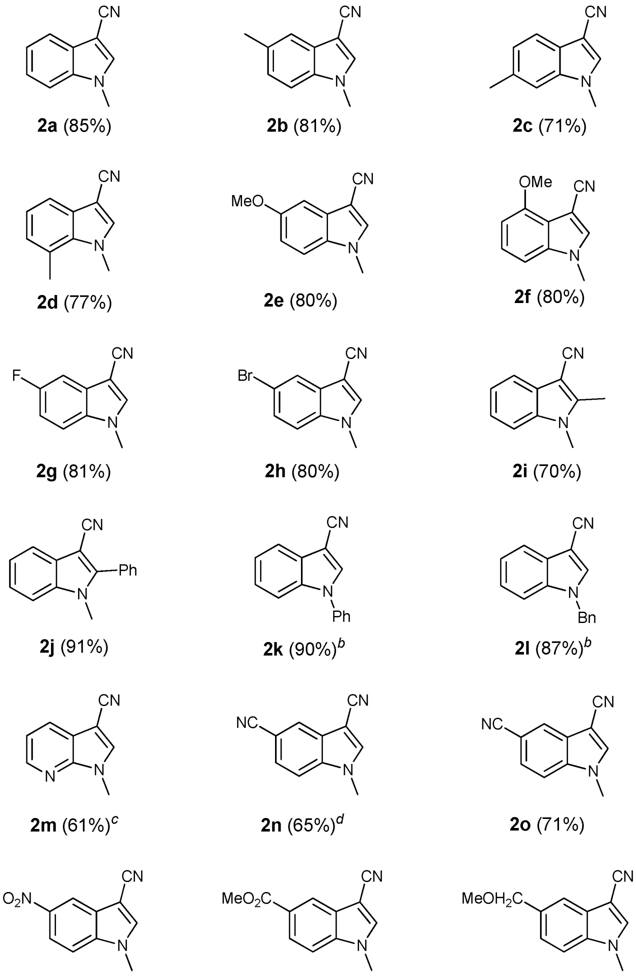
Table 2 Palladium-catalyzed cyanation of 3-indole C–H bonds[a]





2a (85%) **2b** (81%) **2c** (71%)

2d (77%) **2e** (80%) **2f** (80%)

2g (81%) **2h** (80%) **2i** (70%)

2j (91%) **2k** (90%)[b] **2l** (87%)[b]

2m (61%)[c] **2n** (65%)[d] **2o** (71%)

2p (75%) **2q** (72%) **2r** (73%)

[a] *Reaction conditions*: 1-methyl-1*H*-indole (0.2 mmol), NH$_4$HCO$_3$ (0.3 mmol), PdCl$_2$(10 mol%), Cu(OAc)$_2$ (1.1 equiv.) in DMSO (1.5 mL), O$_2$, 140 °C, 6 h. [b] 12 h. [c] Under air. [d] **1n** = 1-methyl-1*H*-indole-5-carbaldehyde.

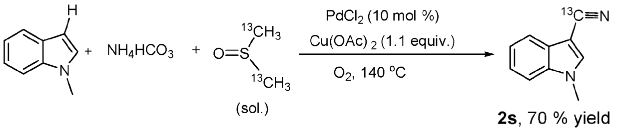
air atmosphere, only 43% of the product was isolated. Importantly, this transformation is very practical since it does not require the use of expensive ligands.

Further investigation showed that *N*-substituent groups such as *N*-phenyl and *N*-benzyl analogues did not cause any difficulties for this transformation though long reaction times were required (**2k** and **2l**, Table 2). *N*-Methyl indoles possessing electron-withdrawing groups on the phenyl, such as formyl, cyano, nitro, bromo and methoxycarbonyl groups, reacted smoothly under the standard conditions (**2h**, **2o**, **2p** and **2q**, Table 2). Interestingly, *N*-methyl-1*H*-indole-5-carbaldehyde produced *N*-methyl-1*H*-indole-3,5-dicarbonitrile in 65% yield, and synchronously, the aldehydic carbonyl was converted to a cyano group (**2n**, Table 2).[12] Notably, the cyanation of *N*-methyl-1*H*-pyrrolo[2,3-*b*]pyridine led to nitrile product (**2m**) in an acceptable 61% yield. Particularly, the bromo group survived well under the procedure and the bromo product could be easily further modifiable (**2h**, Table 2). In Wang's protocol, the C2 position should be blocked to ensure the reaction efficiency.[13] However, under this procedure, whether the C2 positions of indoles were blocked or not, the cyanation of indoles furnished the corresponding products in good yields (**2a**, **2i** and **2j**, Table 2). Disappointingly, methyl 1-methyl-1*H*-indole-3-carboxylate, benzofuran and benzimidazole did not work under the standard condition. Evidently, the cyanation predominantly took place on the 3-position of indole. No regioisomeric products were observed by GC-MS and ^{1}H NMR spectroscopy. In comparison with Chang's procedure,[10] the reaction time was dramatically shortened to 6 h and avoided ammonia. Disappointingly, free indole failed to deliver the cyano product. Methylsulfinylbenzene and ethylsulfinylethane were subjected to the procedure instead of DMSO and a trace of the cyano product was detected by GC-MS in each case.

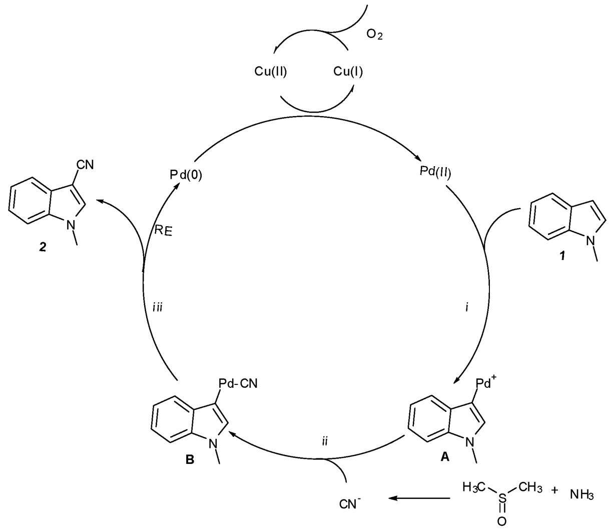
In order to validate the source of the "CN" in this unique cyanation procedure, a series of experiments were performed (entries 13–16, Table 1). We found that CuCl$_2$ instead of Cu(OAc)$_2$ as the oxidant also led to the cyanide product under the same reaction conditions, which eliminated the possibility of the carbon atom in the cyano group deriving from Cu(OAc)$_2$. Moreover, when NH$_3$·H$_2$O or (NH$_4$)$_2$SO$_4$ replaced NH$_4$HCO$_3$ as the nitrogen source, the nitrile product was also isolated. The results proved that the carbon atom could not derive from NH$_4$HCO$_3$. Furthermore, the ^{13}C-DMSO labelled experiment confirmed the carbon in the cyano group came from DMSO (Scheme 1).

A plausible mechanism for the cyanation of indoles is proposed in Scheme 2. Step (i) involves the C–H activation of *N*-methyl indole to afford a palladated intermediate **A**. Step (ii) of the proposed catalytic cycle involves ligand exchange of CN$^-$ to form Pd(II) species **B**. In the presence of Cu(OAc)$_2$, the combination of DMSO and NH$_3$, which was derived from the decomposition of NH$_4$HCO$_3$, released the CN$^-$.[14] Finally, the reductive elimination of intermediate **B** delivers the cyanation product and Pd(0), which is oxidized to Pd(II) by Cu(II) to regenerate the catalyst. However, the detailed mechanism on the formation of CN$^-$ from the combination of DMSO and NH$_3$ remains unclear at the current stage.

In conclusion, we have demonstrated a new protocol for the generation of a cyano unit from two readily available precursors. The reaction represents a convenient and safe method for the cyanation of the 3-position of indole C–H bonds. This new developed safe cyanide source may have potential utility in other cyanation reaction.



Scheme 1 ^{13}C-DMSO labelled experiment.



Scheme 2 Plausible mechanism.

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Notes and references

1 (*a*) D. E. Uehling, S. S. Nanthakumar, D. Croom, D. L. Emerson, P. P. Leitner, M. J. Luzzio, G. McIntyre, B. Morton, S. Profeta, J. Sisco, D. D. Sternbach, W.-Q. Tong, A. Vuong and J. M. Besterman, *J. Med. Chem.*, 1995, **38**, 1106; (*b*) S. Nagamura, E. Kobayashi, K. Gomi and H. Saito, *Bioorg. Med. Chem.*, 1996, **4**, 1379; (*c*) A. Kleemann, J. Engel, B. Kutscher and D. Reichert, *Pharmaceutical Substances: Syntheses, Patents, Applications*, Georg Thieme, Stuttgart, 4th edn, 2001; (*d*) D. Murdoch and S. Keam, *Drugs*, 2005, **65**, 2379; (*e*) V. C. O. Njar and A. M. H. Brodie, *Drugs*, 1999, **58**, 233.

2 (*a*) *The Chemistry of the Cyano Group*, ed. Z. Rappoport, Wiley, London, 1970; (*b*) R. C. Larock, *Comprehensive Organic Transformations*., Wiley-VCH, New York, 1989, pp. 819–995; (*c*) Y. Ju, F. Liu and C. Li, *Org. Lett.*, 2009, **11**, 3582; (*d*) J. X. Qiao, X. Cheng, D. P. Modi, K. A. Rossi, J. M. Luettgen, R. M. Knabb, P. K. Jadhav and R. R. Wexler, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 29.

3 (*a*) T. Sandmeyer, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 2650; (*b*) H. H. Hodgson, *Chem. Rev.*, 1947, **40**, 251; (*c*) C. Galli, *Chem. Rev.*, 1988, **88**, 765; (*d*) R. Bohlmann, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, UK, 1991, vol. 6, p. 203.

4 (*a*) K. W. Rosenmund and E. Struck, *Ber. Dtsch. Chem. Ges.*, 1919, **2**, 1749; (*b*) J. Lindley, *Tetrahedron*, 1984, **40**, 1433.

5 (*a*) S. A. Weissman, D. Zewge and C. Chen, *J. Org. Chem.*, 2005, **70**, 1508; (*b*) C. Yang and J. M. Williams, *Org. Lett.*, 2004, **6**, 2837; (*c*) K. M. Marcantonio, L. F. Frey, Y. Liu, Y. Chen, J. Strine, B. Phenix, D. J. Wallace and C. Chen, *Org. Lett.*, 2004, **6**, 3723; (*d*) A. Zhang and J. L. Neumeyer, *Org. Lett.*, 2003, **5**, 201; (*e*) T. Schareina, A. Zapf and M. Beller, *Chem. Commun.*, 2004, 1388; (*f*) D. Gelmana and O. Grossman, *Org. Lett.*, 2006, **8**, 1189; (*g*) T. Schareina, A. Zapf, W. Magerlein, N. Muller and M. Beller, *Tetrahedron Lett.*, 2007, **48**, 1087; (*h*) Y.-Z. Zhu and C. Cai, *Eur. J. Org. Chem.*, 2007, 2401; (*i*) P. Ryberg, *Org. Process Res. Dev.*, 2008, **12**, 540; (*j*) F. G. Buono, R. Chidambaram, R. H. Mueller and R. E. Waltermire, *Org. Lett.*, 2008, **10**, 5325; (*k*) S. Erhardt, V. V. Grushin, A. H. Kilpatrick, S. A. Macgregor, W. J. Marshall and D. C. Roe, *J. Am. Chem. Soc.*, 2008, **130**, 4828.

6 (*a*) J. Zanon, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 2890; (*b*) M. Sundermeier, A. Zapf and M. Beller, *Angew. Chem., Int. Ed.*, 2003, **42**, 1661; (*c*) C. Yang and J. M. Williams, *Org. Lett.*, 2004, **6**, 2837; (*d*) S. A. Weissman, D. Zewge and C. Chen, *J. Org. Chem.*, 2005, **70**, 1508; (*e*) Z. Zhang and L. S. Liebeskind, *Org. Lett.*, 2006, **8**, 4331; (*f*) T. Schareina, A. Zapf, W. Mägerlein, N. Müller and M. Beller, *Tetrahedron Lett.*, 2007, **48**, 1087; (*g*) Y. Ren, W. Wang, S. Zhao, X. Tian, J. Wang, W. Yin and L. Cheng, *Tetrahedron Lett.*, 2009, **50**, 4595; (*h*) Y. Ren, Z. Liu, S. Zhao, X. Tian, W. Yin, S. He and J. Wang, *Catal. Commun.*, 2009, **10**, 768; (*i*) C. DeBlase and N. E. Leadbeater, *Tetrahedron*, 2010, **66**, 1098.

7 (*a*) L. Cassar, S. Ferrara and M. Foa, *Homogeneous Catalysis—II*, Gould. RF. Ed., American Chemical Society, Washington, 1974, ch. 17, pp. 252–273; (*b*) L. Cassar, *J. Organomet. Chem.*, 1973, **54**, C57; (*c*) Y. Sakaibara, F. Okuda, A. Shimoyabashi, K. Kirino, M. Sakai, N. Uchino and K. Takagi, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1985; (*d*) V. Percec, J.-Y. Bae and D. H. Hill, *J. Org. Chem.*, 1995, **60**, 6895; (*e*) N. E. Leadbeater and R. K. Arvela, *J. Org. Chem.*, 2003, **68**, 9122.

8 For selected reviews on C–H functionalization, please see: (*a*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*b*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293; (*c*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*d*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215. For selected reports on C–H functionalization, please see: (*e*) Y. Lu, D. Leow, X. Wang, K. M. Engle and J.-Q. Yu, *Chem. Sci.*, 2011, **2**, 967; (*f*) B.-J. Li and Z.-J. Shi, *Chem. Sci.*, 2011, **2**, 488; (*g*) B. Haffemayer, M. Gulias and M. J. Gaunt, *Chem. Sci.*, 2011, **2**, 312; (*h*) C. S. Yeung, X. Zhao, N. Borduas and V. M. Dong, *Chem. Sci.*, 2010, **1**, 331.

9 (*a*) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790; (*b*) X. Jia, D. Yang, S. Zhang and J. Cheng, *Org. Lett.*, 2009, **11**, 4716; (*c*) X. Jia, D. Yang, W. Wang, F. Luo and J. Cheng, *J. Org. Chem.*, 2009, **74**, 9470; (*d*) P. Yeung, C. So, C. Lau and F. Kwong, *Angew. Chem., Int. Ed.*, 2010, **49**, 8918; (*e*) B. Reddy, Z. Begum, Y. Reddy and J. Yadav, *Tetrahedron Lett.*, 2010, **51**, 3334; (*f*) C. Liskey, X. Liao and J. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 11389; (*g*) Y. Ren, Z. Liu, S. He, S. Zhao, J. Wang, R. Niu and W. Yin, *Org. Process Res. Dev.*, 2009, **13**, 764; (*h*) H. Do and O. Daugulis, *Org. Lett.*, 2010, **12**, 2517; (*i*) T. Tajima and A. Nakajima, *J. Am. Chem. Soc.*, 2008, **130**, 10496; (*j*) T. Dohi, K. Morimoto, N. Takenaga, A. Goto, A. Maruyama, Y. Kiyono, H. Tohma and Y. Kita, *J. Org. Chem.*, 2007, **72**, 109.

10 J. Kim and S. Chang, *J. Am. Chem. Soc.*, 2010, **132**, 10272.

11 (*a*) X. Jia, S. Zhang, W. Wang, F. Luo and J. Cheng, *Org. Lett.*, 2009, **11**, 3120; (*b*) S. Zhang, F. Luo, W. Wang, M. Hu, X. Jia and J. Cheng, *Tetrahedron Lett.*, 2010, **51**, 3317; (*c*) S. Zhang, P. Qian, M. Zhang, M. Hu and J. Cheng, *J. Org. Chem.*, 2010, **75**, 6732; (*d*) Z. Ye, W. Wang, F. Luo, S. Zhang and J. Cheng, *Org. Lett.*, 2009, **11**, 3974; (*e*) W. Wang, F. Luo, S. Zhang and J. Cheng, *J. Org. Chem.*, 2010, **75**, 2415; (*f*) W. Wang, C. Pan, F. Chen and J. Cheng, *Chem. Commun.*, 2011, **47**, 3978; (*g*) G. Zhang, L. Zhang, M. Hu and J. Cheng, *Adv. Synth. Catal.*, 2011, **353**, 291.

12 For transformation of aldehydic carbonyl to cyano group in the presence of ammonia, please see: (*a*) C. Zhu, L. Ji and Y. Wei, *Synthesis*, 2010, 3121; (*b*) J. R. Hwu and F. F. Wong, *Eur. J. Org. Chem.*, 2006, 2513; (*c*) P. Capdevielle, A. Lavigne and M. Maumy, *Synth. Commun.*, 1989, 451.

13 G. Yan, C. Kuang, Y. Zhang and J. Wang, *Org. Lett.*, 2010, **12**, 1052.

14 CN^- was detected by indicator paper when the combination of NH_4HCO_3, DMSO and $Cu(OAc)_2$ was heated at 140 °C under O_2 for 3 h. However, heating of NH_4HCO_3, DMSO and $Pd(OAc)_2$ at 140 °C under O_2 for 3 h did not produce any detectable CN^-. These results indicated the $Cu(OAc)_2$ played an important role in the *in situ* formation of CN^-. See ESI†.