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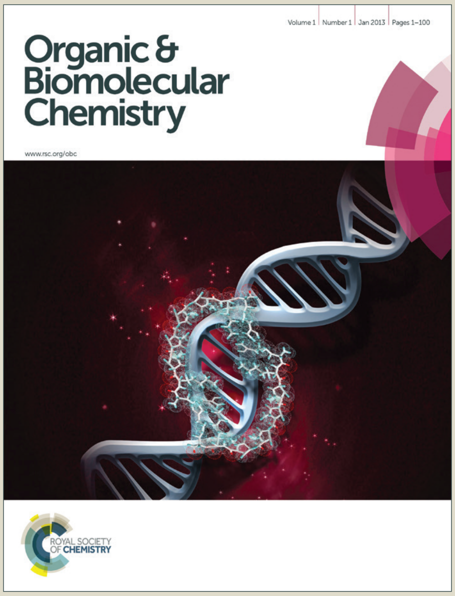

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Cu-Mediated Nitrogen Atom Transfer via C≡N Bond Cleavage

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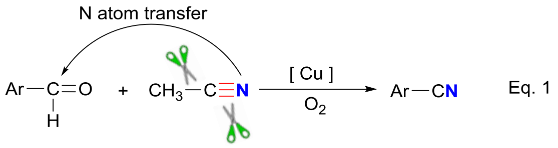
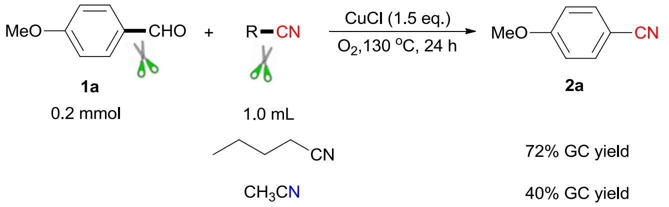
A nitrogen atom transfer to organic molecules via Cu-mediated C-N triple bond cleavage is firstly developed, which provides a variety of functionalized aryl nitriles from the readily accessible acetonitrile and aryl aldehydes.

Comparable to carbon atom, nitrogen atom is the fundamental unit in organic compounds. Nitrogen atom transfer from simple nitrogen sources to organic molecules is a topic of significant importance in organic chemistry, biochemistry and industrial chemistry.[1] Acetonitrile is one of the simplest N-containing organic compounds, which is easily available and often used as solvent in organic synthesis. Given that C≡N bond of acetonitrile contains a *sp* hybridized nitrogen atom, cleavage of C≡N bond is regarded as an analogue of N≡N bond activation of molecular nitrogen. Therefore, the transfer of nitrogen atom to organic molecules via C≡N bond cleavage presents a potential model for N_2 transformation.[2,3]

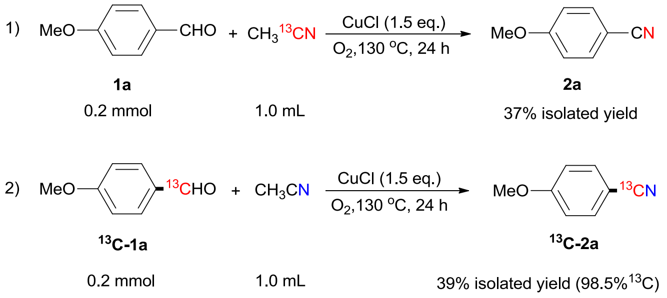
Complete C≡N bond scission has attracted much attention in the past decades.[4-8] In this context, transition metals such as W,[4] Mo,[5] Ru,[6] and Os,[7] have been used for the formation of metal nitrides, which are frequently produced in fixation of molecular nitrogen.[9] However, *in-situ* transfer of the nitrogen atom to organic molecule via C≡N bond cleavage has not been successfully achieved.[10] Herein, we report a nitrogen atom transfer to aldehyeds via copper-mediated C≡N bond cleavage affording aryl nitriles (Eq. 1). It is noted that the hydration of nitriles catalyzed by acids or bases,[11] enzymes,[12] and transition metals[13] is well known as an efficient way for complete C≡N bond cleavage, but it produces ketones, carboxylic acid and their derivatives etc. and the nitrogen atom transfer is not involved.



We accidently discovered this N-atom transfer reaction during our studies aiming at direct cyanation of aryl aldehyde via the inert Ar-C(O)H bond cleavage. By treatment of 4-anisic aldehyde **1a** with 1.5 equiv of CuCl in valeronitrile under O_2 at 130 °C for 24 h, anisonitrile **2a** was observed in 72% yield. Replacement of valeronitrile with acetonitrile resulted in a 40% yield of **2a** (Scheme 1). It seemed that a novel cross-decarbonylative coupling via Ar-C(O)H and C-CN bond cleavage was successfully achieved. To confirm this expectation, the ^{13}C isotope labeling $CH_3{}^{13}CN$ was subjected to this reaction system, to our surprise, ^{13}C was not incorporated into the product and the cleavage of Ar-C(O)H bond did not take place. It was further confirmed by the use of *p*-MeOPh^{13}CHO (Scheme 2).



Scheme 1 The expected cross-decarbonylative coupling.



Scheme 2 Isotope labeling experiments.

The above results suggested that a novel nitrogen atom transfer reaction via C≡N bond cleavage was achieved, producing aryl nitriles from the available starting materials.[14]

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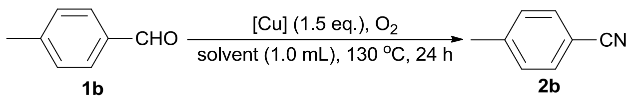
†Electronic Supplementary Information (ESI) available: General information, experimental procedures, copies of ^{1}H and ^{13}C NMR spectra for products. See DOI: 10.1039/x0xx00000x

Aromatic nitriles are key structural motifs in various natural products, pharmaceuticals and fine chemicals,[15] and also are versatile precursors for numerous functional groups,[16] such as amines, imidazoles, amides, tetrazoles.

Encouraged by the initial finding, we then investigated the optimum reaction conditions. Reaction of 4-methylbenzaldehyde **1b** with 1.5 equiv of CuCl in CH_3CN at 130 °C for 24 h under O_2 produced *p*-tolunitrile **2b** in 40% yield (Table 1, entry 1). Addition of an appropriate amount of *N*,*N*-dimethylacetamide (DMAc) could remarkably increase the reaction efficiency (entries 2-5), and the ratio of CH_3CN to DMAc at 2 : 1 gave the best yield (90%, entry 4), whereas, the desired product **2b** was not observed in the absence of acetonitrile (entry 6). Screening of the copper salts revealed that CuCl had the unique reactivity toward this reaction, whereas, other copper salts, such as Cu powder, CuBr, CuI, and $CuCl_2$ were not effective for the present N-atom transfer reaction (entries 7-10). To confirm the unique ability of CuCl, the 99.999% ultrahigh purity CuCl was examined, which gave a comparable yield of **2b** (91%, entry 11). Molecular oxygen was also crucial for the current reaction and only a negligible amount of **2b** was produced under air (entries 12-13; for details, see ESI).

Table 1 Optimization of the reaction conditions[a]

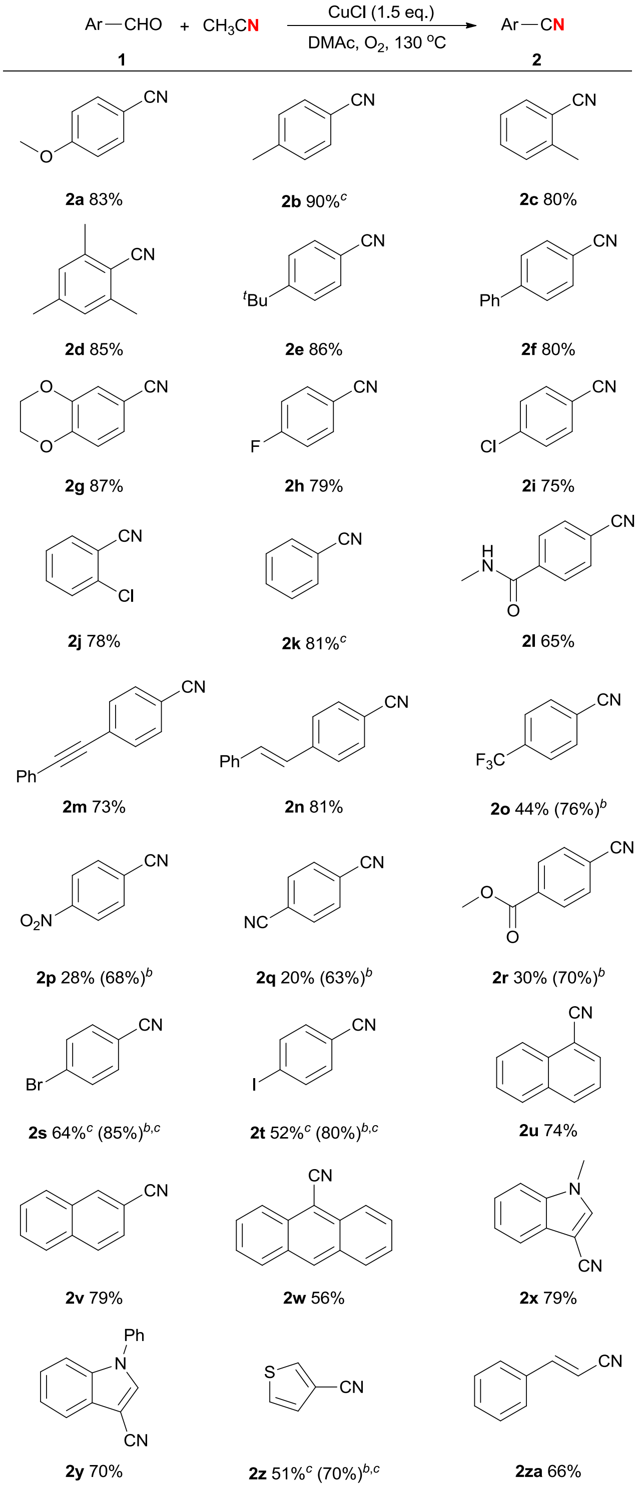


Entry	[Cu]	Solvent	Yield %
1	CuCl	CH_3CN	40
2	CuCl	CH_3CN:DMAc(9:1)	56
3	CuCl	CH_3CN:DMAc(3:1)	80
4	$CuCl_2$	CH_3CN:DMAc(2:1)	90
5	$CuCl_2$	CH_3CN:DMAc(1:1)	86
6	CuCl	DMAc	0
7	Cu	CH_3CN:DMAc(2:1)	0
8	CuBr	CH_3CN:DMAc(2:1)	38
9	CuI	CH_3CN:DMAc(2:1)	0
10	$CuCl_2$	CH_3CN:DMAc(2:1)	10
11[b]	CuCl	CH_3CN:DMAc(2:1)	91
12[c]	CuCl	CH_3CN:DMAc(2:1)	0
13[d]	CuCl	CH_3CN:DMAc(2:1)	trace

[a] Reaction conditions: **1b** (0.2 mmol), [Cu] (0.3 mmol), solvent (1.0 mL), GC yield using dodecane as an internal standard. [b] 99.999% CuCl. [c] under N_2. [d] under air.

As shown in Table 2, aryl aldehydes, with a broad range of functional groups, are tolerable to this N-atom transfer reaction, giving the corresponding aryl nitriles in good to excellent yields. Despite being liable to be oxidized to inactive benzoic acids, benzaldehydes bearing electron-donating groups, such as alkyl, alkoxyl, phenyl, and halogen, worked well, giving the corresponding benzonitriles in high to excellent yields, regardless of their positions on the phenyl rings (Table 2, **2a**-**2k**). Notably, the versatile functional groups acetyl amino (**2l**), alkynyl (**2m**) and alkenyl (**2n**) were well tolerable in this oxidation system, and the desired products **2l**-**2n** were produced in satisfactory yields (65-81%). Although low yields (20-44%) of aryl nitriles were observed by the treatment of

Table 2 N-atom transfer to aryl aldehydes from CH_3CN[a]

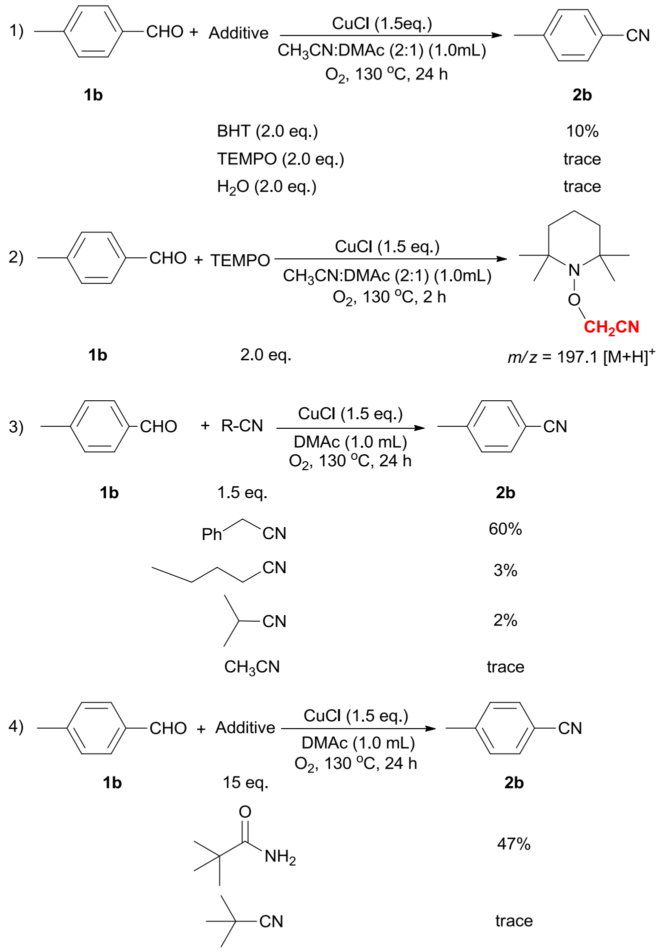


[a] Reaction conditions: aldehyde **1** (0.2 mmol), CuCl (0.3 mmol), CH_3CN (0.67 mL), DMAc (0.33 mL) in 25 mL tube under O_2, 130 °C, 24 h, isolated yields. [b] benzeneacetonitrile (0.3 mmol), CH_3CN (1.0 mL). [c] GC yields.

electron-deficient aryl aldehydes with acetonitrile (**2o**-**2r**), the reaction was accelerated by the replacement of DMAc with stoichiometric benzeneacetonitrile, and electron-withdrawing groups, such as CF_3-, NO_2-, CN-, and $CH_3OC(O)$-, were successfully introduced to aryl nitriles (63-76% yields). When 4-bromobenzaldehyde and 4-iodobenzaldehyde were employed as the substrates, the side product 4-chlorobenzonitrile **2i** was detected in 17% and 23% yields, respectively. Whereas, the side reactions were suppressed by the use of benzeneacetonitrile (**2s**-**2t**, for details, see ESI).

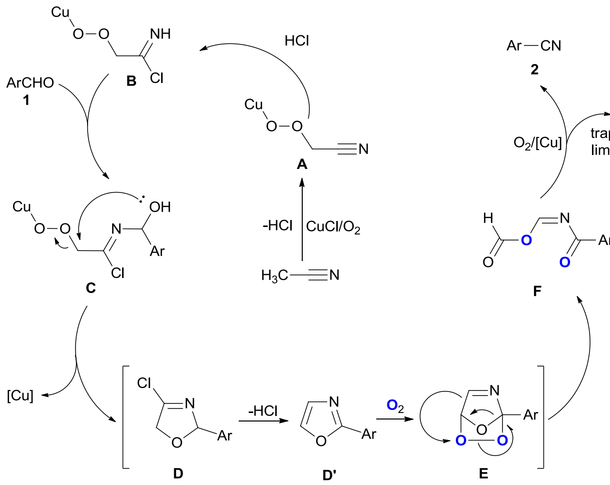
In addition to substituted benzaldehydes, other aryl aldehydes were also good substrates for this reaction. Treatment of 1-naphthaldehyde and 2-naphthaldehyde with acetonitrile mediated by CuCl gave the corresponding products in high yields (**2u**-**2v**), in the case of anthracene-9-carbaldehyde, moderate yield was observed (**2w**). 1-methyl-1*H*-indole-3-carbaldehyde and 1-phenyl-1*H*-indole-3-carbaldehyde were well applicable to the present transformation, and the corresponding heteroaryl nitriles **2x** and **2y** were obtained in 79% and 70% yields, respectively. Other heteroaryl aldehydes such as thiophene-3-carbaldehyde also worked well, giving the corresponding product **2z** in moderate yield. In addition, cinnamaldehyde reacted with acetonitrile smoothly to produce the α,β-unsaturated nitrile **2za** in 66% yield.

To gain an insight into the reaction mechanism, several control experiments were carried out under standard conditions (Scheme 3). Firstly, radical inhibitors, such as 2,6-di-tert-butyl-4-methylphenol (BHT) and 2,2,6,6-tetramethylpiperidine N-oxide (TEMPO) could block this reaction, suggesting that free-radical mechanism involved in this N-atom transfer reaction (Eq. 1, Scheme 3). Indeed, the radical adduct 2-(2,2,6,6-tetramethylpiperidin-1-yloxy)acetonitrile was detected by the treatment of 2.0 equiv of TEMPO with CH_3CN for 2 h (Eq. 2, Scheme 3).[14d,17] Compared with pentanenitrile, acetonitrile and isobutyronitrile, benzeneacetonitrile showed the highest reactivity (Eq. 3, Scheme 3), attributing to its excellent ability to form the cyanomethyl radical. Whereas, no desired product was detected even by the use of a large amount of pivalonitrile, without sp^3 C-H bond adjacent to CN. In a sharp contrast, reaction of pivalamide with 4-methylbenzaldehyde gave **2b** in 47% yield (Eq. 4, Scheme 3). These results suggested that the reaction did not proceed via the hydration of nitrile. It was further confirmed by the detrimental effect on this reaction of water. When 2.0 equiv of water was added, only a trace amount of **2b** was observed (Eq. 1, Scheme 3).



Scheme 3 The control experiments.

On the basis of the above experimental results, a reaction mechanism was proposed as shown in Scheme 4. Initially, similar to the reaction of TMEPO with acetonitrile, the oxidation of sp^3 C-H bond adjacent to CN forms a cyanomethyl radical adduct **A** with the deliverance of HCl.[18] The addition reaction of **A** with HCl produces the iminochloride **B**, then **B** was converted into the aldehydecyanohydrin **C** with aryl aldehydes **1** through nucleophilic reaction. The formation of the oxazole peroxide **E** from **C** involves series of reactions, including an analogous Fischer oxazole synthesis[19] (**C** to **D'**) and subsequent O_2 insertion reaction.[20] Next, rearrangement of **E** results in **F**, which is further oxidized to benzonitrile **2**[20] with concomitant generation of CO_2.



Scheme 4 The possible reaction pathway

Conclusions

In summary, we have discovered the first copper promoted aerobic oxidative N-atom transfer via simultaneous cleavage of C-N triple bond and C-CN bond of acetonitrile to produce aryl nitriles in high yields. It provides not only a new approach for complete C-N triple bond cleavage, but also an alternative way for the synthesis of aryl nitriles. Further studies toward the elucidation of the exact reaction mechanism and the synthetic utility of this novel protocol are currently underway.

Acknowledgements

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Notes and references

1 For reviews on nitrogen atom transfer, see: (a) T. Wang, N. Jiao, *Acc. Chem. Res.*, 2014, **47**, 1137; (b) J. Roizen, M. E. Harvey, J. D. Bois, *Acc. Chem. Res.*, 2012, **45**, 911; (c) K. S. Williamson, D. J. Michaelis, T. P. Yoon, *Chem. Rev.*, 2014, **114**, 8016; (d) T. G. Driver, *Org. Biomol. Chem.*, 2010, **8**, 3831; (e) J. D. Bois, C. S. Tomooka, J. Hong, E. M. Carreira, *Acc. Chem. Res.*, 1997, **30**, 364.

2 Fixations of molecular nitrogen and subsequently transferring it to organic compounds are known in the biochemical processes with the aid of nitrogenase and transaminase, see: (a) J. B. Howard, D. C. Rees, *Chem. Rev.*, 1996, **96**, 2965; (b) B. M. Hoffman, D. Lukoyanov, Z.-Y. Yang, D. Dean, L. C. Seefeldt, *Chem. Rev.*, 2014, **114**, 4041; (c) B. M. Hoffman, D. R. Dean, L. C. Seefeldt, *Acc. Chem. Res.*, 2009, **42**, 609-619; (d) K. Drauz, H. Gröger, O. May, *Enzyme Catalysis in Organic Synthesis*, 3rd ed., Wiley-VCH, Weinheim, 2012, 779.

3 Nitrogen atom transfer to organic molecules via N≡N bond cleavage is a long-standing challenge in chemistry, which has been reported in harsh conditions in lab. For review, see: (a) M. Mori, *J. Organomet. Chem.*, 2004, **689**, 4210; For selected examples, see: (b) J. J. Curley, E. L. Sceats, C. C. Cummins, *J. Am. Chem. Soc.*, 2006, **128**, 14036; (c) K. Ueda, Y. Sato, M. Mori, *J. Am. Chem. Soc.*, 2000, **122**, 10722; (d) J. G. Andino, S. Mazumder, K. Pal, K. G. Caulton, *Angew. Chem. Int. Ed.*, 2013, **52**, 4726.

4 (a) R. R. Schrock, M. L. Listemann, L. G. Sturgeoff, *J. Am. Chem. Soc.*, 1982, **104**, 4291; (b) J. H. Freudenberger, R. R. Schrock, *Organometallics*, 1986, **5**, 398; (c) M. H. Chisholm, K. Folting, M. L. Lynn, D. B. Tiedtke, F. Lemoigno, O. Eisentein, *Chem. Eur. J.*, 1999, **5**, 2318; (d) M. H. Chisholm, K. Folting-Streib, D. B. Tiedtke, F. Lemoigno, O. Eisenstein, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 110.

5 (a) H. Seino, Y. Ishii, Y. Tanabe, M. Hidai, *Inorg. Chim. Acta*, 1998, **280**, 163; (b) Y. Tanabe, H. Seino, Y. Ishii, M. Hidai, *J. Am. Chem. Soc.*, 2000, **122**, 1690; (c) B. Li, S. Xu, H. Song, B. Wang, *J. Organomet. Chem.*, 2008, **693**, 87; (d) H. Seino, Y. Mizobe, M. Hidai, *Chem. Rec.*, 2001, **1**, 349.

6 T. Kawashima, T. Takao, H. Suzuki, *Angew. Chem. Int. Ed.*, 2006, **45**, 485.

7 B. K. Bennett, S. Lovell, J. M. Mayer, *J. Am. Chem. Soc.*, 2001, **123**, 4336.

8 (a) W.-X. Zhang, S. Zhang, X. Sun, M. Nishiura, Z. Hou, Z. Xi, *Angew. Chem. Int. Ed.*, 2009, **48**, 7227; (b) X. Sun, C. Wang, Z. Li, Z. Xi, *J. Am. Chem. Soc.*, 2004, **126**, 7172.

9 Activation of dinitrogen to form metal nitrides, see: (a) C. E. Laplaza, C. C. Cummins, *Science*, 1995, **268**, 861; (b) M. D. Fryzuk, J. B. Love, S. J. Rettig, V. G. Young, *Science*, 1997, **275**, 1445; (c) D. V. Yandulov, R. R. Schrock, *Science*, 2003, **301**, 76; (d) F. Akagi, T. Matsuo, H. Kawaguchi, *Angew. Chem. Int. Ed.*, 2007, **46**, 8778; (e) T. Shima, S. Hu, G. Luo, X. Kang, Y. Luo, Z. Hou, *Science*, 2013, **340**, 1549.

10 Metal nitrides mediated nitriles metathesis have been reported, see: (a) M. H. Chisholm, E. E. Delbridge, A. R. Kidwell, K. B. Quinlanb, *Chem. Commun.*, 2003, **2**, 126; (b) A. M. Geyer, R. L. Gdula, E. S. Wiedner, M. J. A. Johnson, *J. Am. Chem. Soc.*, 2007, **129**, 3800; (c) A. M. Geyer, E. S. Wiedner, J. B. Gary, R. L. Gdula, N. C. Kuhlmann, M. J. A. Johnson, B. D. Dunietz, J. W. Kampf, *J. Am. Chem. Soc.*, 2008, **130**, 8984; (d) B. A. Burroughs, B. E. Bursten, S. Chen, M. H. Chisholm, A. R. Kidwell, *Inorg. Chem.*, 2008, **47**, 5377; (e) E. S. Wiedner, K. J. Gallagher, M. J. A. Johnson, J. W. Kampf, *Inorg. Chem.*, 2011, **50**, 5936.

11 (a) H. R. Sydner, C. T. Elston, *J. Am. Chem. Soc.*, 1954, **76**, 3039; (b) C. R. Hauser, C. J. Eby, *J. Am. Chem. Soc.*, 1957, **79**, 725; (c) N. Kornblum; S. Singaram, *J. Org. Chem.*, 1979, **44**, 4727; (d) J. N. Moorthy, N. Singhal, *J. Org. Chem.*, 2005, **70**, 1926; (e) G. C. Midya, A. Kapat, S. Maiti, J. Dash, *J. Org. Chem.*, 2015, **80**, 4148.

12 (a) K. Ingvosersen, J. Kamphuis, *In Enzyme Catalysis in Organic Synthesis*; K. Drauz, H. Waldmann, Eds.; VCH: Weinheim, Germany, 1995, **1**, 365; (b) S. Prasad, T. Bhalla, *Biotechnol. Adv.*, 2010, **28**, 725.

13 For reviews, see: (a) S. I. Murahashi, H. Takaya, *Acc. Chem. Res.*, 2000, **33**, 225; (b) V. Yu. Kukushkin, A. J. L. Pombeiro, *Chem. Rev.*, 2002, **102**, 1771; (c) V. Yu. Kukushkin, A. J. L. Pombeiro, *Inorg. Chim. Acta*, 2005, **358**, 1; (d) T. J. Ahmed, S. M. M. Knapp, D. R. Tyler, *Coord. Chem. Rev.*, 2011, **255**, 949; (e) R. G. Álvarez, P. Crochet, V. Cadierno, *Green Chem.*, 2013, **15**, 46; (f) L. Yang, H. Huang, *Chem. Rev.*, 2015, **115**, 3468.

14 The use of acetonitrile as a simple CN source via C-CN bond cleavage has been recognized, see: (a) R.-J. Song, J.-C. Wu, G.-B. Deng, Y. Liu, C.-Y. Wu, W.-T. Wei, J.-H. Li, *Synlett*, 2012, **23**, 2491; (b) X. Kou, M. Zhao, X. Qiao, Y. Zhu, X. Tong, Z. Shen, *Chem. Eur. J.*, 2013, **19**, 16880; (c) C. Pan, H. Jin, P. Xu, X. Liu, Y. Cheng, C. Zhu, *J. Org. Chem.*, 2013, **78**, 9494; (d) Y. Zhu, M. Zhao, W. Lu, L. Li, Z. Shen, *Org. Lett.*, 2015, **17**, 2602; (e) F.-H. Luo, C.-I. Chu, C.-H. Cheng, *Organometallics*, 1998, **17**, 1025.

15 A. Kleemann, J. Engel, B. Kutscher, D. Reichert, *Pharmaceutical Substance: Synthesis, Patents, Applications*, 4th ed., Georg Thieme, Stuttgart, 2001.

16 (a) *The Chemistry of the Cyano Group*; Z. Rappoport, Ed.; Interscience: London, 1970; (b) R. C. Larock, *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, Weinheim, 1999.

17 For selected examples, see: (a) J. Shen, D. Yang, Y. Liu, S. Qin, J. Zhang, J. Sun, C. Liu, C. Liu, X. Zhao, C. Chu, R. Liu, *Org. Lett.*, 2014, **16**, 350; (b) A. Bunescu, Q. Wang, J. Zhu, *Chem. Eur. J.*, 2014, **20**, 14633; (c) A. Bunescu, Q. Wang, J. Zhu, *Org. Lett.*, 2015, **17**, 1890; (d) C. C. Sazepin, Q. Wang, G. M. Sammis, J. Zhu, *Angew. Chem. Int. Ed.*, 2015, **54**, 5443; (e) D. Zhou, Z.-H. Li, J. Li, S.-H. Li, M.-W. Wang, X.-L. Luo, G.-L. Ding, R.-L. Sheng, M.-J. Fu, S. Tang, *Eur. J. Org. Chem.*, **2015**, 1606.

18 At the beginning of the reaction, a white fog was formed. Finally, the reaction system became acidic.

19 (a) E. Fischer, *Ber.*, 1896, **29**, 205; (b) B. H. Ingham, *J. Chem. Soc.*, **1927**, 692.

20 (a) H. H. Wasserman, F. J. Vinick, Y. C. Chang, *J. Am. Chem. Soc.*, 1972, **94**, 7180; (b) M. L. Graziano, M. R. Lesce, A. Carotenuto, R. Scarpati, *J. Heterocycl. Chem.*, 1977, **14**, 261; (c) M. L. Graziano, M. R. Lesce, R. Scarpati, *J. Heterocycl. Chem.*, 1979, **16**, 129; (d) D. Cantillo, C. O. Kappe, *J. Org. Chem.*, 2013, **78**, 10567.