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Copper-Catalyzed Decarboxylative $C\equiv N$ Triple Bond Formation: Direct Synthesis of Benzonitriles from Phenylacetic Acids Under O_2 Atmosphere

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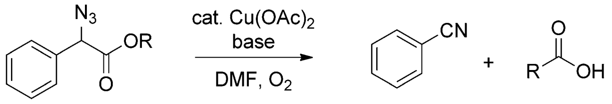
Abstract: A copper-catalyzed reaction of phenylacetic acids with urea was found to afford benzonitriles under an oxygen atmosphere. This reaction proceeds smoothly by a sequence of decarboxylation, dioxygen activation, C–H bond functionalization, and nitrile formation with urea as the nitrogen source. Molecular oxygen was found to play a crucial role in this transformation. This reaction represents a novel protocol for the formation of benzonitriles in an environmental friendly way and with good functional group tolerability.

Keywords: copper; decarboxylation; nitriles; oxygen; phenylacetic acids

Transition metal-catalyzed decarboxylative couplings have attracted much attention in light of the readily accessible starting materials, simple operation and gaseous by-product (CO_2 as the only by-product). Among all of the decarboxylative coupling reactions, copper-catalyzed coupling reactions have lots of advantages over the prevailing palladium ones due to the ready availability, low price, less toxicity and eco-friendly properties of the metal;[1–3] yet copper-catalyzed decarboxylative coupling reactions[4,5] are relatively rare compared to the well-developed Pd-catalyzed decarboxylative coupling reactions. And transition metal-catalyzed decarboxylation at *sp*^{3}-hybridized carbon atoms for the introduction of functional groups remains a significant challenge.

Aromatic nitriles are prevalent scaffolds in organic synthesis, and as important intermediates, they can be easily transformed into other functional groups, including amides, amines, acids, aldehydes and heterocycles,[6–8] thus aromatic nitriles have been widely implemented in pharmaceuticals, natural products and agricultural chemicals synthesis.[8,9] The Sandmeyer reaction[6–8,10] is the traditional method for the synthesis of aromatic nitriles, yet toxic CuCN is required as the cyanating agent; later on, dehydration approaches, for example, oxidation of alcohols with ammonia,[11–13] dehydration of amides[12,14] or aldoximes[13,15] were developed as alternative methods for aromatic nitriles. More recently, transition metal-catalyzed cross-coupling reactions between aromatic halides and a cyano source have emerged as an attractive approach to aromatic nitriles,[16–18] and non-metallic cyano sources are especially attractive. Since the pioneer works of Meyers[19,20] and Gooßen,[21,23] aromatic carboxylic acids have emerged as a surrogate of aromatic halides, but transition metal-catalyzed syntheses of aromatic nitriles directly from carboxylic acids are still rare.[23–26] The existing methods either need explosive chemicals or toxic cyano sources or strong acidic conditions, thus the development of neutral, greener and environment-friendly methods for aromatic nitrile formation with molecular oxygen as oxidant and reagent from readily available carboxylic acids is still a big challenge in synthetic organic chemistry.

Molecular oxygen is the ideal terminal oxidant for oxygenation, because of its abundance, inexpensiveness, and high atom efficiency. Recently, Chiba and co-workers reported one reaction for benzonitrile formation with a copper catalyst under an O_2 atmosphere (Scheme 1).[27] This reaction needs preinstallation of an azido group at the benzylic position. To the best of our knowledge, there is no example describing a direct decarboxylation of C(*sp*^{3}) atoms and formation of $C\equiv N$ triple bonds simultaneously *via* a copper-only-catalyzed decarboxylative coupling yet; herein we present a novel aerobic decarboxylative reaction to afford aromatic nitriles[11–14,28–30] from readily available phenylacetic acids and with urea as nitrogen source in DMSO. This transformation proceeds smoothly by a sequence of decarboxylation, dioxygen

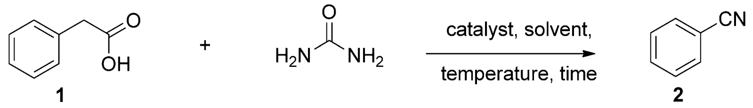


Scheme 1. Chiba's method for benzonitrile formation.

activation, C–H bond activation and ammoxidation of phenylacetic acids to benzonitriles in good to excellent yields. This reaction represents a novel protocol for the formation of benzonitriles in an environmental friendly way. Furthermore, the ready availability of phenylacetic acids, urea and copper(II) salts makes this reaction very practical and the scope of the tolerated substrates very wide.

Initially, phenylacetic acid (**1a**) was chosen to react with urea under the Cu(OAc)$_2$/O$_2$ system as a model reaction (Table 1). To our delight, benzonitrile was obtained in 55% isolated yield (Table 1, entry 1) at 130 °C in the presence of 20 mol% Cu(OAc)$_2$ under 1 atm of O$_2$. Other copper salts and transition metal catalysts, such as Cu(OTf)$_2$, Cu(TFA)$_2$, Cu$_2$O, CuBr$_2$, CuSO$_4$, CuCl$_2$, FeCl$_2$, FeCl$_3$ and Pd(OAc)$_2$ were investigated subsequently at 130 °C (Table 1, entries 2–10), among them, Cu(TFA)$_2$ showed the highest efficiency in this transformation (Table 1, entry 3). Further sol-

Table 1. Optimization of the reaction parameters.[a]



Entry	Catalyst		Solvent	Temperature [°C]	Time [h]	Yield [%][b]
1	Cu(OAc)$_2$ (20 mol%)	O$_2$	DMSO (1mL)	130	20	71 (55)[c]
2	Cu(OTf)$_2$ (20 mol%)	O$_2$	DMSO	130	20	69
3	Cu(TFA)$_2$ (20 mol%)	O$_2$	DMSO	130	20	84
4	CuBr$_2$ (20 mol%)	O$_2$	DMSO	130	20	33
5	CuSO$_4$ (20 mol%)	O$_2$	DMSO	130	20	81
6	Cu$_2$O (20 mol%)	O$_2$	DMSO	130	20	75
7	CuCl$_2$ (20 mol%)	O$_2$	DMSO	130	20	23
8	FeCl$_2$ (20 mol%)	O$_2$	DMSO	130	20	17
9	FeCl$_3$ (20 mol%)	O$_2$	DMSO	130	20	36
10	Pd(OAc)$_2$ (20 m%)	O$_2$	DMSO	130	20	11
11	Cu(TFA)$_2$ (10 mol%)	O$_2$	DMSO	130	21	76
12	Cu(TFA)$_2$ (10 mol%)	O$_2$	DMSO	100	24	24
13	Cu(TFA)$_2$ (10 mol%)	O$_2$	DMSO	120	24	60
14	Cu(TFA)$_2$ (20 mol%)	O$_2$	DMSO	100	24	68
15	Cu(TFA)$_2$ (20 mol%)	O$_2$	DMSO	120	24	98 (80)[c]
16	Cu(TFA)$_2$ (20 mol%)	O$_2$	DMF	120	23	32
17	Cu(TFA)$_2$ (20 mol%)	O$_2$	toluene	120	23	45
18	Cu(TFA)$_2$ (20 mol%)	O$_2$	H$_2$O	130	24	39^{c}
19	Cu(TFA)$_2$ (20 mol%)	air	DMSO	120	24	56
20	Cu(TFA)$_2$ (20 mol%)	N$_2$	DMSO	120	24	2
21		O$_2$	DMSO	120	24	10
22	Cu(TFA)$_2$ (20 mol%)	O$_2$	DMSO	120	24	52[d]
23	Cu(TFA)$_2$ (20 mol%)	O$_2$	DMSO	120	24	4[e]

[a] *Reaction conditions:* phenylacetic acid (**1a**) (0.5 mmol), urea (3 equiv., 1.5 mmol), catalyst, solvent (1 mL) in a sealed tube under the corresponding atmosphere.

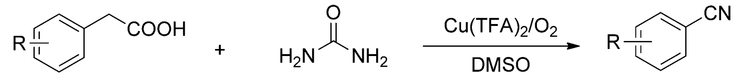
[b] GC yields.

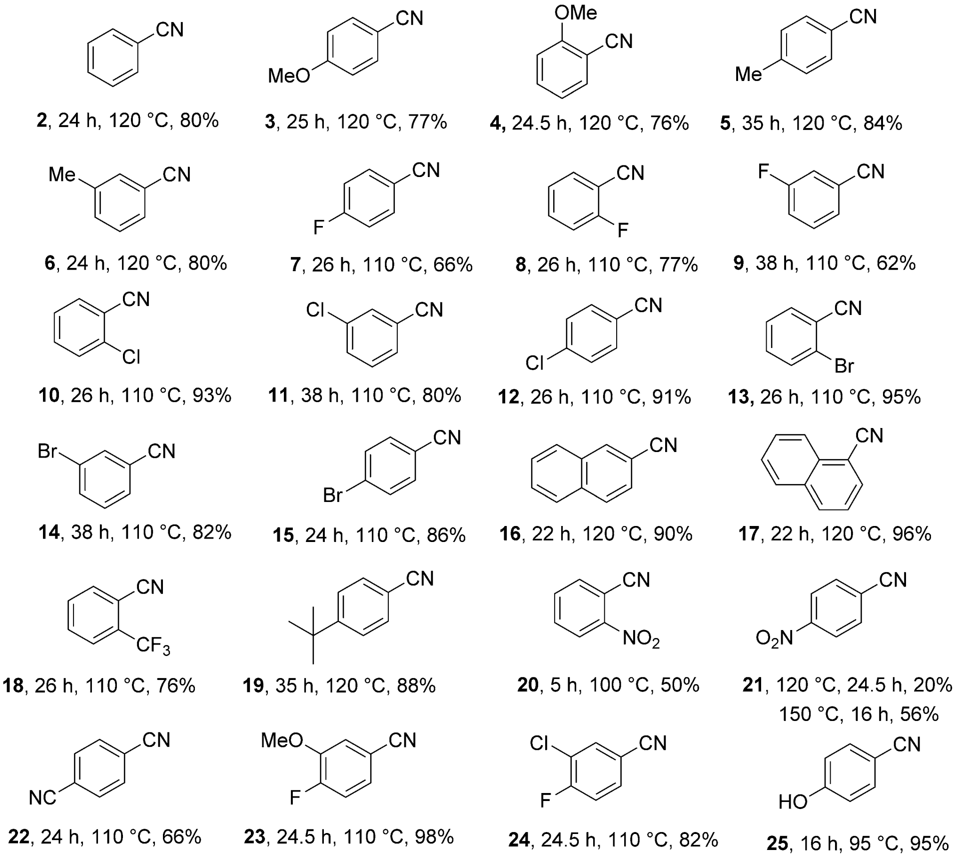
[c] Isolated yields.

[d] NH$_4$OH as ammonia source.

[e] NH$_4$Cl as ammonia source with 6% benzaldehyde formation.

Table 2. Copper-catalyzed aerobic decarboxylative ammoxidation of phenylacetic acids to benzonitriles.[a]





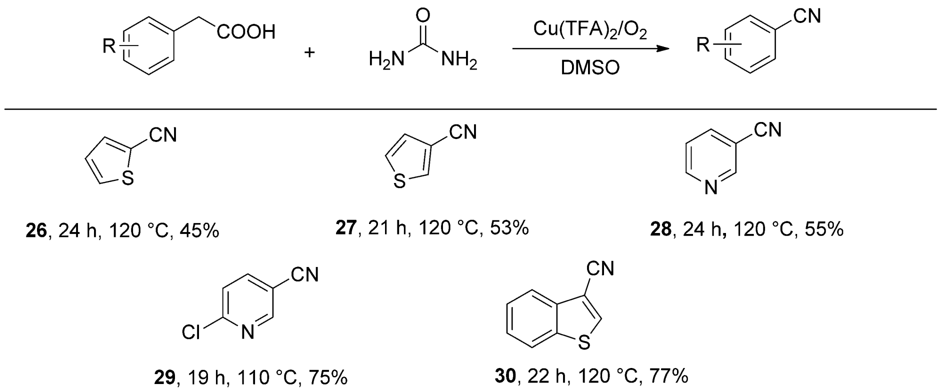
2, 24 h, 120 °C, 80%
3, 25 h, 120 °C, 77%
4, 24.5 h, 120 °C, 76%
5, 35 h, 120 °C, 84%
6, 24 h, 120 °C, 80%
7, 26 h, 110 °C, 66%
8, 26 h, 110 °C, 77%
9, 38 h, 110 °C, 62%
10, 26 h, 110 °C, 93%
11, 38 h, 110 °C, 80%
12, 26 h, 110 °C, 91%
13, 26 h, 110 °C, 95%
14, 38 h, 110 °C, 82%
15, 24 h, 110 °C, 86%
16, 22 h, 120 °C, 90%
17, 22 h, 120 °C, 96%
18, 26 h, 110 °C, 76%
19, 35 h, 120 °C, 88%
20, 5 h, 100 °C, 50%
21, 120 °C, 24.5 h, 20%
150 °C, 16 h, 56%
22, 24 h, 110 °C, 66%
23, 24.5 h, 110 °C, 98%
24, 24.5 h, 110 °C, 82%
25, 16 h, 95 °C, 95%

[a] *Reaction conditions:* **1** (0.5 mmol), Cu(TFA)$_2$ (20 mol%), urea (1.5 mmol), DMSO (1.0 mL), O_2, the reaction was monitored by TLC. All yields shown above are isolated yields.

vent screening showed that DMSO is the best one for this reaction (Table 1, entries 15–18). When O_2 was replaced by air or N_2, only 56% and 2% of the desired product was formed, respectively (Table 1, entries 19 and 20), and without a copper catalyst, only 10% of the product was obtained (Table 1, entry 21). These results suggested that O_2 is essential for the success of this transformation and Cu(TFA)$_2$ and DMSO also play crucial roles in this transformation. When NH_4OH and NH_4Cl were used as ammonia source (Table 1, entries 22 and 23), only 52% and 4%, of benzonitrile were formed in the presence of 20 mol% Cu(TFA)$_2$, which is much lower than the urea case (Table 1, entry 15). Eventually, the reaction temperature and catalyst loading screenings suggested that Cu(TFA)$_2$ (20 mol%) at 120 °C in DMSO (1 mL) under an O_2 atmosphere could give the optimal result (Table 1, entry 15).

Having the optimized reaction conditions in hand, the substrate scope of phenylacetic acids was explored (Table 2). We found that the reaction yield was not affected by the electronic nature of the phenylacetic acids. Substrates with both electron-releasing groups and electron-withdrawing groups gave the desired products in good to excellent yields. The position of the substituents on the aromatic ring of the phenylacetic acids had no effect on the reaction efficiency (Table 2, products **3**/**4**, **5**/**6**, **7**–**9**, **10**–**12** and **13**–**15**). It is noteworthy that halo-substituted aryl groups survived well, leading to halo-substituted aromatic nitriles which could be used for further transformations (Table 2, products **7**–**15**). In addition, 1-naphthylacetic acid and 2-naphthylacetic acid also reacted excellently to give the corresponding naphthyl nitriles in 90% and 96% yields (Table 2, products **16** and **17**). Trifluoromethyl, *tert*-butyl, nitro and cyano groups are

Table 3. Copper-catalyzed aerobic decarboxylative ammoxidation of heteroaromatic acetic acids to the corresponding nitriles.[a]



26, 24 h, 120 °C, 45%

27, 21 h, 120 °C, 53%

28, 24 h, 120 °C, 55%

29, 19 h, 110 °C, 75%

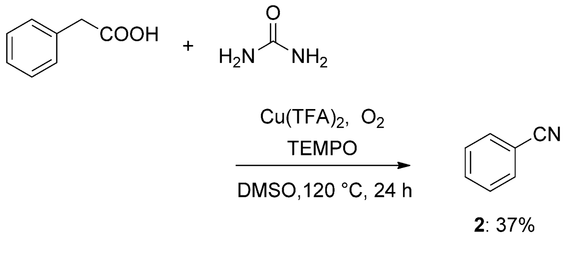
30, 22 h, 120 °C, 77%

[a] *Reaction conditions:* **1** (0.5 mmol), $Cu(TFA)_2$ (20 mol%), urea (1.5 mmol), DMSO (1.0 mL), O_2; the reaction was monitored by TLC. All yields shown above are isolated yields.

also tolerable under the standard conditions (Table 2, products **18–22**), and the temperature played a key role in the reaction to afford 4-nitrobenzonitrile. When the reaction was conducted under the standard conditions, the desired product was obtained in only 20% yield after 24 h heating, yet when the reaction temperature was increased to 150 °C, the yield was increased to 56% after 16 h (Table 2, products **21**). Significantly, a free hydroxy group on the aromatic ring of phenylacetic acid also survived under the standard conditions and gave a 95% of the desired product. (Table 2, **25**) which is hard to synthesize by other methods.

Heteroaromatic acetic acids were also transformed well under the standard conditions, for example, thiophene-2-carbonitrile (**26**), thiophene-3-carbonitrile (**27**), nicotinonitrile (**28**), 6-chloronicotinonitrile (**29**), and benzothiophene-3-carbonitrile (**30**) were obtained from the corresponding acetic acids in 45%, 53%, 55%, 75% and 77% yields, respectively (Table 3, products **26–30**).

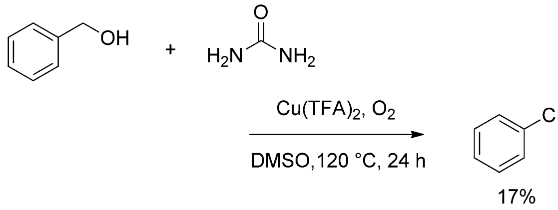
Control experiments have been investigated to probe the mechanism of this copper-catalyzed aerobic decarboxylative nitrile formation reaction. In the presence of TEMPO, still 37% of benzonitrile (**2**) was obtained, suggesting that this transformation might not proceed by a radical pathway, but this still could not be totally ruled out as the pathway [Eq. (1)].



2: 37%

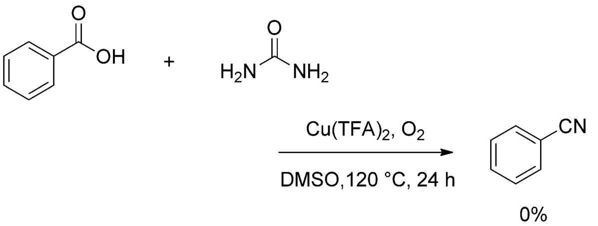
(1)

Furthermore, the reactions of benzyl alcohol, 2-oxo-2-phenylacetic acid, benzaldehyde and benzoic acid with urea under the standard conditions were explored. In the case of benzyl alcohol, although the desired product was detected, the yield was only 17% [Eq. (2)], this is much lower compared to the result under optimized conditions (80%, Table 1, entry 15), so this result indicated that benzyl alcohol might be involved in this process, but it is not a major intermediate in this transformation.



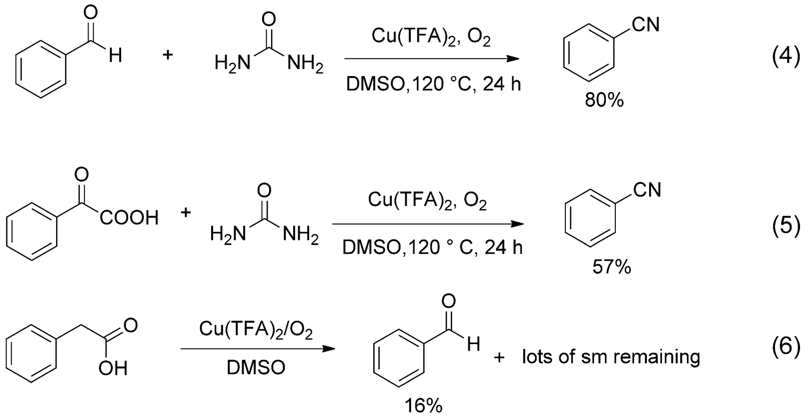
(2)

For benzoic acid, no desired benzamide was formed at all, showing that benzoic acid is not an intermediate for this reaction [Eq. (3)].

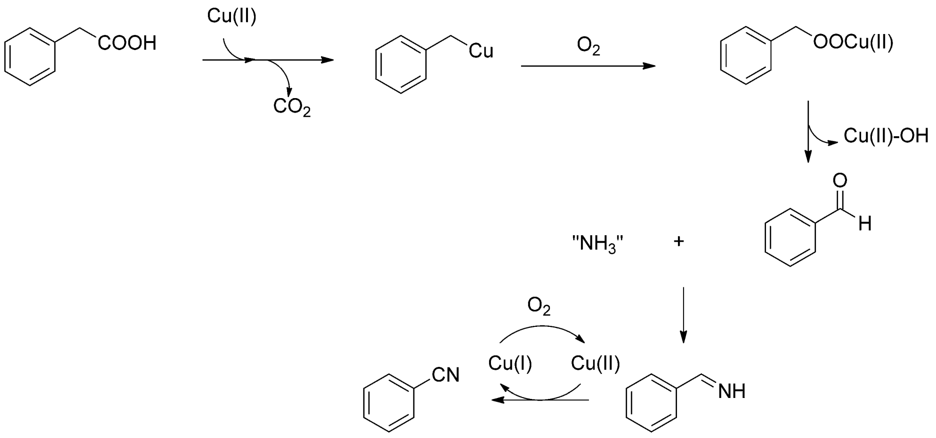


(3)

Yet benzaldehyde and 2-oxo-2-phenylacetic acid gave 80% and 57% of benzamide, respectively [Scheme 2, Eq. (4) and Eq. (5)]; and when phenylacetic acid was treated under the standard conditions without urea, 16% of benzaldehyde was formed with



Scheme 2. Control experiments under standard conditions with urea.



Scheme 3. Plausible reaction mechanism.

lots of starting material remaining [Scheme 2, Eq. (6)]. Even though benzaldehyde was formed in low yield under standard conditions, combining Eq. (4) and Eq. (6), we can hypothesize that once benzaldehyde is formed, it will react with urea to afford benzonitrile, thus pushing the whole reaction in the direction of the product. Based on previous reports and the above results, a proposed reaction mechanism is depicted in Scheme 3: phenylacetic acid was decarboxylated and oxidized into aldehyde in the presence of copper(II) and O_2, the ammonia surrogate reacted with aldehyde with the help of molecular oxygen, and after oxidative condensation, benzonitrile was obtained (Scheme 3).

In conclusion, a Cu(II)/O_2 system that catalyzes the oxidative decarboxylative ammoxidation of phenylacetic acids and urea has been developed. This reaction proceeds smoothly by a sequence of decarboxylation, dioxygen activation, C–H bond functionalization, and nitrile formation with urea as the nitrogen source. Molecular oxygen was found to play a crucial role in this transformation. This reaction represents a novel protocol for the formation of benzonitriles in an environmental friendly way and with good functional groups tolerability. Further studies to elucidate the reaction mechanism and the applications are currently underway in our laboratory.

Experimental Section

General Procedure for Benzonitrile Formation

A sealed pressure vessel was charged with phenylacetic acid **1** (68.0 mg, 0.5 mmol), $Cu(TFA)_2$ (29 mg, 0.1 mmol), urea (90 mg, 1.5 mmol), and DMSO (0.75 mL). The resulting solution was stirred at 120 °C under O_2 monitored by TLC and GC) for 24 h. Upon completion of the reaction, ethyl acetate (20 mL) was added, the organic layer was washed with saturate $NaHCO_3$ (20 mL) solution twice, brine (20 mL) once, the combined aqueous layers was extracted with ethyl acetate (20 mL) twice. The combine organic layers were dried over anhydrous Na_2SO_4. The solvents were removed *via* a rotary evaporator and the residue was purified with flash chromatography (silica gel, ethyl acetate: petroleum ether = 50:1) to give benzonitrile **2** as a colorless liquid; yield: 41.2 mg (80%). ^1H NMR: (400 MHz, $CDCl_3$): $\delta =$

7.64–7.56 (3H, m), 7.47–7.43 (2H, m); ^{13}C NMR: (100 MHz, $CDCl_3$): $\delta = 132.6, 131.9, 129.0, 118.6, 112.2$.

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References

[1] S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558–5607; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449.
[2] F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 7088–7105; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971.
[3] G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054–3131.
[4] D. Zhao, C. Gao, X. Su, Y. He, J. You, Y. Xue, *Chem. Commun.* **2010**, *46*, 9049–9051.
[5] R. Shang, Y. Fu, Y. Wang, Q. Xu, H.-Z. Yu, L. Liu, *Angew. Chem.* **2009**, *121*, 9514–9518; *Angew. Chem. Int. Ed.* **2009**, *48*, 9350–9354.
[6] Z. Rappoport, *The Chemistry of the Cyano Group*, Interscience Publisher, New York, **1970**.
[7] R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd edn., Wiley-VCH, New York, **1989**.
[8] A. J. Fatiadi, *Preparation and Synthetic Applications of Cyano Compounds*, Wiley, New York, **1983**.
[9] A. Kleemann, B. Kutschner, D. Reichert, *Pharmaceutical Substances: Syntheses, Patents, Applications*, 4th edn. Georg Thieme Verlag, Stuttgart, **2001**.
[10] M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th edn., Wiley, Hoboken, NJ, **2007**.
[11] T. Oishi, K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2009**, *121*, 6404–6406; *Angew. Chem. Int. Ed.* **2009**, *48*, 6286–6288.
[12] K. Ishihara, Y. Furuya, H. Yamamoto, *Angew. Chem.* **2002**, *114*, 3109–3112; *Angew. Chem. Int. Ed.* **2002**, *41*, 2983–2986.
[13] K. Yamaguchi, H. Fujiwara, Y. Ogasawara, M. Kotani, N. Mizuno, *Angew. Chem.* **2007**, *119*, 3996–3999; *Angew. Chem. Int. Ed.* **2007**, *46*, 3922–3925.
[14] C.-W. Kuo, J.-L. Zhu, J.-D. Wu, C.-M. Chu, C.-F. Yao, K.-S. Shia, *Chem. Commun.* **2007**, 301–303.
[15] E. Choi, C. Lee, Y. Na, S. Chang, *Org. Lett.* **2002**, *4*, 2369–2371.
[16] T. Schareina, A. Zapf, W, Mägerlein, N. Müller, M. Beller, *Chem. Eur. J.* **2007**, *13*, 6249–6254.
[17] F. G. Buono, R. Chidambaram, R. H. Mueller, R. E. Waltermire, *Org. Lett.* **2008**, *10*, 5325–5328.
[18] Y. Ren, W. Wang, S. Zhao, X. Tian, J. Wang, W. Yin, L. Cheng, *Tetrahedron Lett.* **2009**, *50*, 4595–4597.
[19] A. G. Myers, D. Tanaka, M. R. Mannion, *J. Am. Chem. Soc.* **2002**, *124*, 11250–11251.
[20] D. Tanaka, S. P. Romeril, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 10323–10333.
[21] L. J. Gooßen, N. Rodríguez, K. Gooßen, *Angew. Chem.* **2008**, *120*, 3144–3164; *Angew. Chem. Int. Ed.* **2008**, *47*, 3100–3120.
[22] L. J. Gooßen, N. Rodríguez, B. Melzer, C. Linder, G. Deng, L. M. Levy, *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833.
[23] Y. I. Smushkevich, V. Y. Smushkevich, M. I. Usorov, *J. Chem. Res. S* **1999**, 407.
[24] C. O. Kangani, B. W. Day, D. E. Kelley, *Tetrahedron Lett.* **2008**, *49*, 914–918.
[25] K. Mlinarić-Majerski, R. Margeta, J. Veljković, *Synlett* **2005**, 2089–2091.
[26] V. J. Huber, R. A. Bartsch, *Tetrahedron* **1998**, *54*, 9281–9288.
[27] S. Chiba, L. Zhang, G. Y. Ang, B. W.-Q. Hui, *Org. Lett.* **2010**, *12*, 2052–2055.
[28] W. Zhou, L. Zhang, N. Jiao, *Angew. Chem.* **2009**, *121*, 7228–7231; *Angew. Chem. Int. Ed.* **2009**, *48*, 7094–7097.
[29] J. Zanon, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 2890–2891.
[30] Z. Shu, Y. Ye, Y. Deng, Y. Zhang, J. Wang, *Angew. Chem.* **2013**, *125*, 10769–10770; *Angew. Chem. Int. Ed.* **2013**, *52*, 10573–10576.

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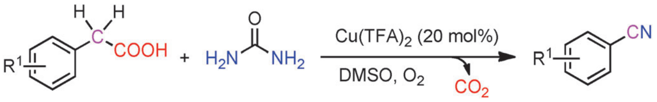

7

Adv. Synth. Catal. **2014**, *356*, 1 – 7

Qiang Feng, Qiuling Song*