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Cu-catalyzed aerobic oxidative C–CN bond cleavage of benzyl cyanide for the synthesis of primary amides†

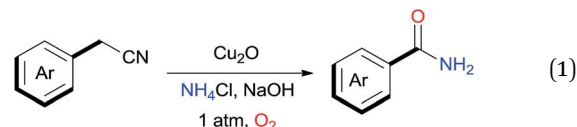
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An efficient method *via* copper-catalyzed aerobic oxidative amidation of benzyl cyanide for primary amides is successfully developed. Using readily available NH₄Cl as a nitrogen source and Cu/O₂ as a catalytic oxidation system offers new opportunities for C–CN bond cleavage and primary amide bond formation.

Primary amides are prevalent organic motifs in peptide, protein synthesis, intensifiers of perfume, anti-block reagents, color pigments for inks, detergents, and lubricants.¹ Generally, the synthetic procedures for the preparation of primary amides are rely on the reaction of carboxylic acid,² or its derivatives with ammonia or ammonium salt.³ However, toxic and corrosive, materials, low functional groups tolerance and complex operation are generally required in conventional synthetic procedures. To overcome these problems, alternative methods for primary amide synthesis have been developed. The direct amidation of aldehydes,⁴ alcohols,⁵ or methylarenes⁶ to primary amides represents an interesting topic in this area, however, hazardous peroxides (TBHP), the toxic halogens, or an excess amount of molecular sieves were required. Other attractive approaches include the hydration of nitriles,⁷ oxidative amidation of terminal alkynes,⁸ transition-metal-catalyzed C–H activation and amidation⁹ and catalytic oxidation C–C bond cleavage of ketones into benzamides.¹⁰ Although great progress has been achieved in this field, there still remains significant challenges for synthetic organic chemists in reactivity, efficiencies, and high functional group tolerance.

Recently, C–C bond cleavage has become an attractive topic because of its potential usage in new chemical bond formation *via* inert starting materials.¹¹ Also molecular oxygen has been considered as an ideal oxidant due to its atom-economical, environmentally benign, and abundance.¹² However, few reactions are compatible with aerobic oxidation¹³ and C–C bond cleavage in one transformation.¹⁴ Therefore, the development of an efficient catalytic system towards aerobic oxidative unstrained C–C bonds cleavage is always highly desired. As our

continued interest in Cu or Fe-catalyzed aerobic oxidative C–C bond cleavage reaction,¹⁵ we developed a Cu-catalyzed aerobic oxidative C–C bond cleavage of benzyl cyanide for the synthesis of primary amides. Using readily available NH₄Cl as a nitrogen source and a Cu/O₂ catalytic oxidation system offers new opportunities for primary amide bond formation. The developed methodology tolerated a wide range of functional groups and produced high yields for the synthesis of primary amides.



We carried out experiments to test the reactivity of benzyl cyanide **1a** with ammonium salts in the presence of a metal catalyst under an oxygen atmosphere and the obtained results are compiled in Table 1. First, our studies started with the reaction between benzyl cyanide **1a** and 5.0 equiv. of ammonia (25% aqueous) in CH₃CN at 120 °C (Table 1, entries 1–5). When 5 mol% of CuCl was used as catalyst, the benzamide **2a** was obtained in 38% yield along with the hydration of nitrile products **2b** (Table 1, entry 1). We then screened the types of catalysts, and discovered that CuCl₂ or Cu₂O produces higher yields (Table 1, entries 4–5). However the products **2b** was always by a product. Then, optimization studies were performed to improve the yield of **2a**. To our surprise, when ammonia was replaced with NH₄Cl, **2a** was obtained in 50% yield, and only trace amounts **2b** was observed (Table 1, entry 6). Four bases were tested using Cu₂O as the catalyst in CH₃CN, and NaOH showed the highest yield (Table 1, entries 6–9). Several copper salts and amine salts were screened (Table 1, entries 10–16), and the best result was obtained under Cu₂O/NH₄Cl/NaOH system (Table 1, entry 9). Noteworthy, NaOH is essential for this reaction. In the absence of NaOH, **2a** could not be obtained at all (Table 1, entry 17). The reaction did not proceed in the

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Table 1 Optimization of the reaction conditions^a

Entry	Cat	[N] source	Base	2a ^b %	2b ^b %
1	CuCl	NH ₃ ·H ₂ O	—	35	20
2	Cu(OAc) ₂	NH ₃ ·H ₂ O	—	25	30
3	CuO	NH ₃ ·H ₂ O	—	40	41
4	CuCl ₂	NH ₃ ·H ₂ O	—	50	25
5	Cu ₂ O	NH ₃ ·H ₂ O	—	50	31
6	Cu ₂ O	NH ₄ Cl	Ba(OH) ₂	50	<1
7	Cu ₂ O	NH ₄ Cl	KOH	58	<1
8	Cu ₂ O	NH ₄ Cl	Ca(OH) ₂	20	<1
9	Cu ₂ O	NH ₄ Cl	NaOH	88	<1
10	CuCl	NH ₄ Cl	NaOH	71	<1
11	CuCl ₂	NH ₄ Cl	NaOH	65	<1
12	Cu(OAc) ₂	NH ₄ Cl	NaOH	58	<1
13	Cu ₂ O	NH ₄ OAc	NaOH	63	<1
14	Cu ₂ O	(NH ₄) ₂ SO ₄	NaOH	50	<1
15	Cu ₂ O	(NH ₄) ₂ CO ₃	NaOH	71	<1
16	Cu ₂ O	Urea	NaOH	<1	<1
17	Cu ₂ O	NH ₄ Cl	—	—	<1
18	—	NH ₄ Cl	NaOH	—	<1
19 ^c	Cu ₂ O	NH ₄ Cl	NaOH	Trace	Trace
20 ^d	Cu ₂ O	NH ₄ Cl	NaOH	20	<1
21 ^e	Cu ₂ O	NH ₄ Cl	NaOH	13	<1

^a Reaction conditions: 2-benzyl cyanide **1a** (0.2 mmol), cat (5 mol%), N source (0.3 mmol), base (0.4 mmol), CH₃CN (2 mL), in 25 mL Schlenk tube, 120 °C, O₂ (1 atm), 30 h. ^b Yields were determined by GC using *n*-hexadecane as an internal standard. ^c Air was used as oxidant. ^d Toluene as solvent. ^e DMF as solvent.

absence of copper catalyst (Table 1, entry 18). The reaction was also dependent on dioxygen; when air was used as the oxidant, only trace of **2a** was obtained (Table 1, entry 19). Other solvents such as, toluene and DMF gave lower yields (Table 1, entries 20–21).

With the optimal conditions in hand, the scope of copper-catalyzed aerobic oxidative amidation of substituted 2-benzyl cyanides with “NH₂” producing primary amides was investigated, the results were compiled in Table 2. A variety of 2-benzyl cyanide with either an electron-donating or an electron-withdrawing group, were all converted readily to the corresponding primary amides efficiently. Thus, in addition to 2-benzyl cyanide, benzyl cyanide with electron-donating substituents methyl (–CH₃), methoxy (–OCH₃) reacted smoothly with NH₄Cl/NaOH to provide the corresponding primary amides **2a–2c** (Table 2, entries 1–3). However, when hydroxyl (–OH) substituted 2-benzyl cyanide was used as a substrate, none of the expected products were detected. This may have been due to the interaction between the hydroxyl and base or oxidizing agent, which would hinder the C–CN bond activation (Table 2, entry 4). Benzyl cyanide with fluoro (–F), chloro (–Cl), bromo (–Br), iodo (–I), trifluoromethyl (–CF₃) or phenyl (–Ph) electron-withdrawing groups served as good substrates to produce the corresponding primary amides **2e–2j** in excellent yields (Table 2,

Table 2 Cu-catalysed aerobic oxidative amidation of benzyl cyanide with NH₄Cl producing primary amides^a

Entry	Benzonitriles	Products	Yield ^b
1	1a		2a , 82%
2	1b		2b , 81%
3	1c		2c , 79%
4	1d		2d , trace
5	1e		2e , 81%
6	1f		2f , 78%
7	1g		2g , 83%
8	1h		2h , 69%
9	1i		2i , 78%
10	1j		2j , 73%
11 ^c	1k		2k , 92%



Table 2 (Contd.)

Entry	Benzonitriles	Products	Yield ^b
12	1l		2l , 57%
13	1m		2m , 71%
14	1n		2n , 63%
15	1o		2o , 72%
16	1p		2p , 71%
17 ^d	1q		2q , 35%

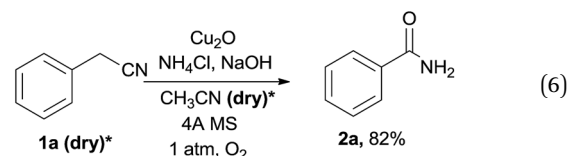
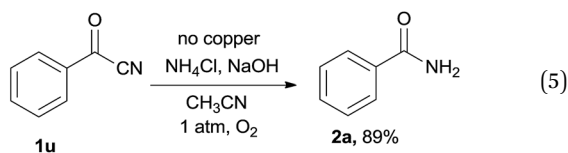
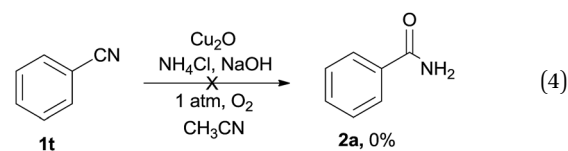
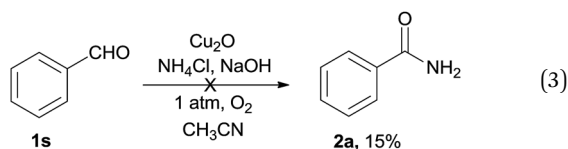
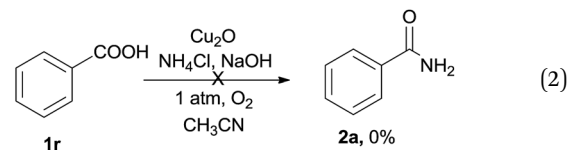
^a Reaction conditions: substrate **1a–1q** (0.2 mmol), Cu₂O (5 mol%), NH₄Cl (0.3 mmol), NaOH (0.4 mmol), CH₃CN (2 mL), O₂ in 25 mL Schlenk tube, 120 °C, 24 h. ^b Isolated yield. ^c 16 h. ^d 48 h.

entries 5–10), and there is no sharp difference. Interestingly, when nitro (–NO₂) substituted 2-benzyl cyanide were used, the corresponding 4-nitrobenzamide was obtained in high yield and with short time (Table 2, entry 11).

Even the 1-(naphthalen-2-yl)acetonitrile and 2-(naphthalen-2-yl)acetonitrile furnished the corresponding primary amide **2l** and **2m** in 57% and 71% yield respectively. The heteroaryl-substituted primary amide **2n** and **2o** were obtained from the corresponding 2-(thiophen-2-yl)acetonitrile or 2-(pyridin-2-yl)acetonitrile under the present Cu₂O/NH₄Cl/NaOH system. While, the reaction was influenced by the substituent steric effects. For example, the yield of **2q** was decreased for *ortho*-substituted 2-benzyl cyanide contrast to *para*-substituted and *meta*-substituted 2-benzyl cyanide (Table 2, entry 2, entries 16–17).

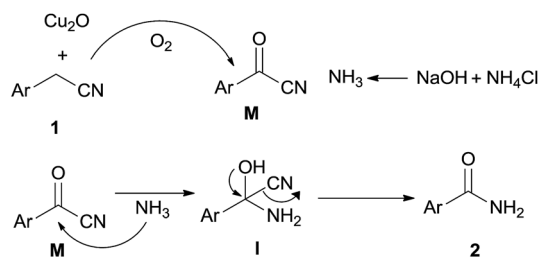
To get more information of the reaction mechanism, a few potential intermediates were subjected to the reaction under standard conditions. As shown below, phenylacetic acid **1r** was

used as a substrate under the standard reaction conditions, while **2a** was not detected at all (eqn (2)). Benzaldehyde **1s** was treated under the optimized conditions, **2a** was obtained in 15% yield (eqn (3)), indicating that an aldehyde or acid was not the efficient intermediate. The reaction of benzonitrile **1t** with NH₄Cl/NaOH under standard conditions was also explored, and the desired benzamide **2a** was not detected at all, showing that benzyl cyanide was not converted to benzonitrile *via* hydration of nitriles to primary amides (eqn (4)). The reaction of benzoyl cyanide **1u** and NH₄Cl/NaOH was performed in the absence of Cu₂O, the corresponding primary amide **2a** was obtained in 89% yield (eqn (5)). The results indicated that benzoyl cyanide **1u** was the efficient intermediate for this transformation, at first benzyl cyanide was converted to benzoyl cyanide *via* sp³ C–H bond oxygenation. Under dry conditions and in the absence of air, the desired product **2a** was also generated in 82% yield under the optimal conditions, thus the oxygen atoms of the product amides should originate from molecular dioxygen (eqn (6)).



*The solvent CH₃CN and **1a** were dried, degassed by standard methods before use, and stored under nitrogen using standard Schlenk techniques.





Scheme 1 Plausible reaction pathway for the synthesis of primary amides 2.

Based on the above results and the reported literature,^{15a} a possible mechanism for the copper-catalyzed aerobic oxidative amidation of benzyl cyanide to the synthesis of primary amides is suggested in Scheme 1. The catalytic cycle reaction involved sp^3 C–H bond oxygenation of benzyl cyanide to the intermediate benzoyl cyanide **M** and with the Cu catalyst being regenerated, NH_3 was generated from the heating of NH_4Cl and $NaOH$. Then intermediate benzoyl cyanide **M** was attacked by NH_3 to generate **I**, followed by C–CN bond cleavage affording the desired primary amide **2**.

Conclusions

In summary, we have developed a simple and highly efficient method for the synthesis of primary amides *via* C–CN bond cleavage under copper-catalyzed aerobic oxidative conditions. Using readily available NH_4Cl as a nitrogen source, conversion of benzyl cyanides to primary amides provides an opportunity to utilize inert starting materials to construct amides bond. The present method is practical and economical, and the starting materials are readily available.

Acknowledgements

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Notes and references

- (a) J. M. Humphrey and A. R. Chamberlin, *Chem. Rev.*, 1997, **97**, 2243; (b) J. W. Bode, R. M. Fox and K. D. Baucom, *Angew. Chem., Int. Ed.*, 1248, **2006**, 45; (c) B. L. Bray, *Nat. Rev. Drug Discovery*, 2003, **2**, 587.
- E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606.
- (a) M. B. Smith and J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Wiley, Hoboken, NJ, 6th edn, 2007; (b) M. B. Smith, *Organic Synthesis*, Mc-Graw-Hill Companies, New York, 2nd edn, 2002; (c) H. Lundberg, F. Tinnis, J. Zhang, A. G. Algarra, F. Himo and H. Adolfsson, *J. Am. Chem. Soc.*, 2017, **139**, 2286.
- (a) U. B. Patil, A. S. Singh and J. M. Nagarkar, *RSC Adv.*, 2014, **4**, 1102; (b) M. A. Ali and T. Punniyamurthy, *Adv. Synth. Catal.*, 2010, **352**, 288; (c) S. C. Ghosh, J. S. Y. Ngiam, A. M. Seayad, D. T. Tuan, C. L. L. Chai and A. Chen, *J. Org. Chem.*, 2012, **77**, 8007; (d) J. J. Shi and J.-M. Fang, *J. Org. Chem.*, 2003, **68**, 1158; (e) G. Wang, Q. Yu, S. Chen and X. Yu, *Org. Biomol. Chem.*, 2014, **12**, 414.
- (a) T. Zweifel, J.-V. Naubron and H. Grützmacher, *Angew. Chem., Int. Ed.*, 2009, **48**, 559; (b) Y. Wang, D. Zhu, L. Tang, S. Wang and Z. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 8917; (c) J. F. Soulé, H. Miyamura and S. Kobayashi, *J. Am. Chem. Soc.*, 2011, **133**, 18550; (d) K. Yamaguchi, H. Kobayashi, T. Oishi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2012, **51**, 544; (e) R. Nie, J. Shi, S. Xia, L. Shen, P. Chen, Z. Hou and F. S. Xiao, *J. Mater. Chem.*, 2012, **22**, 18115; (f) K. Yamaguchi, H. Kobayashi, Y. Wang, T. Oishi, Y. Ogasawara and N. Mizuno, *Catal. Sci. Technol.*, 2013, **3**, 318; (g) R. Nie, J. Shi, S. Xia, L. Shen, P. Chen, Z. Hou and F. S. Xiao, *J. Mater. Chem.*, 2012, **22**, 18115; X. Q. Li, W. K. Wang, Y. X. Han and C. Zhang, *Adv. Synth. Catal.*, 2010, **352**, 2588. (h) R. Ohmura, M. Takahata and H. Togo, *Tetrahedron Lett.*, 2010, **51**, 4378; (i) R. Das and D. Chakraborty, *Catal. Commun.*, 2012, **26**, 48.
- (a) Y. Wang, K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2012, **51**, 7250; (b) Y. Huang, T. Chen, Q. Li, Y. Zhou and S. F. Yin, *Org. Biomol. Chem.*, 2015, **13**, 7289.
- (a) C. Singh, V. Kumar, U. Sharma, N. Kumar and B. Singh, *Curr. Org. Synth.*, 2013, **10**, 241; (b) T. Tu, Z. Wang, Z. Liu, X. Feng and Q. Wang, *Green Chem.*, 2012, **14**, 921; (c) R. García-Álvarez, P. Crochet and V. Cadierno, *Green Chem.*, 2013, **15**, 46; (d) P. Marcé, J. Lynch, A. J. Blacker and J. M. J. Williams, *Chem. Commun.*, 2016, **52**, 1436; (e) H. Chen, W. Dai, Y. Chen, Q. Xu, J. Chen, L. Yu, Y. Zhao, M. Ye and Y. Pan, *Green Chem.*, 2014, **16**, 2136; (f) Y. Li, H. Chen, J. Liu, X. Wan and Q. Xu, *Green Chem.*, 2016, **18**, 4865.
- S. U. Dighe and S. Batra, *Adv. Synth. Catal.*, 2016, **358**, 500.
- Y. Zhang, K. B. Teuscher and H. Ji, *Chem. Sci.*, 2016, **7**, 2111.
- (a) S. Shimokawa, Y. Kawagoe, K. Moriyama and H. Togo, *Org. Lett.*, 2016, **18**, 784; (b) C. Tang and N. Jiao, *Angew. Chem., Int. Ed.*, 2014, **53**, 6528.
- (a) M. Tobisu and N. Chatani, *Chem. Soc. Rev.*, 2008, **37**, 300; (b) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, *Chem. Rev.*, 2013, **113**, 6234.
- S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, *Chem. Rev.*, 2013, **113**, 6234.
- (a) C. Zhang, P. Feng and N. Jiao, *J. Am. Chem. Soc.*, 2013, **135**, 15257; (b) W. Kong, B. Li, X. Xu and Q. Song, *J. Org. Chem.*, 2016, **81**, 8436; (c) W. Ding and Q. Song, *Org. Chem. Front.*, 2015, **2**, 765; (d) Q. Song, Q. Feng and K. Yang, *Org. Lett.*, 2014, **16**, 624; (e) Q. Feng and Q. Song, *J. Org. Chem.*, 2014, **79**, 1867; (f) Q. Feng and Q. Song, *Adv. Synth. Catal.*, 2014, **356**, 1697.
- (a) H. Liu, C. Dong, Z. Zhang, P. Wu and X. Jiang, *Angew. Chem., Int. Ed.*, 2012, **51**, 12570; (b) C. Hu, X. Yan, X. Zhou and Z. Li, *Org. Biomol. Chem.*, 2013, **11**, 8179; (c) K. Wu, Z. Huang, Y. Ma and A. Lei, *RSC Adv.*, 2016, **6**, 24349.
- (a) X. Chen, T. Chen, Q. Li, Y. Zhou, L. B. Han and S. F. Yin, *Chem.–Eur. J.*, 2014, **20**, 1; (b) X. Chen, T. Chen, F. Ji, Y. Zhou and S. F. Yin, *Catal. Sci. Technol.*, 2015, **5**, 2197.

