



Cite this: DOI: 10.1039/c6ob00184j

Received 22nd January 2016,
Accepted 7th March 2016

DOI: 10.1039/c6ob00184j

www.rsc.org/obc

Synthesis of nitriles from amines using nanoscale Co_3O_4 -based catalysts *via* sustainable aerobic oxidation†

Kishore Natte, Rajenahally V. Jagadeesh, Muhammad Sharif, Helfried Neumann and Matthias Beller*

The selective oxidation of amines for the benign synthesis of nitriles under mild conditions is described. Key to success for this transformation is the application of reusable cobalt oxide-based nanocatalysts. The resulting nitriles constitute key precursors and central intermediates in organic synthesis.

The development of selective oxidation processes continues to be a major challenge for sustainable organic synthesis. In this regard, the development of novel catalysts is crucial, which should be based on abundant bio-relevant metals.¹ Generally for industrial processes, heterogeneous catalysts are preferred due to their stability, separation and re-usability. In order to achieve high activity and selectivity for redox reactions, nano-structured metal oxides attracted significant interest.^{2,3} As an example, recently we developed specific nano-scaled Fe- and Co-oxides, which are modified with nitrogen-doped carbon layers.³ Based on their high activity and remarkable selectivity, we became interested to apply them in the dehydrogenation of amines.

Amines constitute key precursors and central intermediates for many fine and bulk chemicals.⁴ Importantly, the amino group is a versatile motif presented in numerous industrial chemicals including agrochemicals and pharmaceuticals.⁴ Among the various chemical transformations of amines,⁵ the selective oxidation to nitriles is of special interest.^{6,7} In general, nitriles are synthesized by traditional cyanation processes using toxic HCN and metal cyanides.⁸ On industrial scale, gas-phase ammoxidations are often used for the synthesis of simple benzonitriles.⁹ Alternatively, such nitriles have been prepared by the oxidation of primary amines using ruthenium,¹⁰ copper¹¹ and manganese¹² based catalysts. However, most of these catalyst systems are restricted to structurally simple substrates and exhibit poor activities towards more challenging and structurally diverse amines. More recently,

we demonstrated that iron oxides activated by pyrolyzed N-ligands allow for a broad substrate scope.¹³ Based on that work, here we report a most general oxidation process for the synthesis of nitriles from aliphatic and benzylic amines with oxygen in the presence of a re-usable cobalt oxide nanocatalyst ($\text{Co}_3\text{O}_4/\text{NGr@C}$).

As previously described this $\text{Co}_3\text{O}_4/\text{NGr@C}$ -catalyst was prepared by pyrolysis of *in situ*-generated phenanthroline-cobalt acetate complexes on commercial carbon support at 800 °C for 2 h under argon atmosphere.^{3b,c} The resulting material was systematically characterized by transmission electron microscopy (TEM), X-ray photoelectron spectroscopy (XPS), electron paramagnetic resonance (EPR) and X-ray diffraction spectroscopy (XRD) (see ESI†). All these characterization data reveals the formation of predominately nanoscale Co_3O_4 of size 2–10 nm (Fig. 1(a)) along with small quantities of CoO. All these metal oxide particles are surrounded by nitrogen-doped graphene layers (see ESI†).^{3b,c} The XPS analysis (Fig. 1(b); see ESI†) showed three distinct peaks in the N 1s spectra with an electron binding energy of 399.0 eV, 400.8 eV, and 402.3 eV attributed to pyridine-type nitrogen, pyrrole-type nitrogen and quaternary amine species (NR_4^+), respectively.

In exploratory catalytic experiments the reaction of benzyl amine with molecular oxygen as a green oxidant was used as a

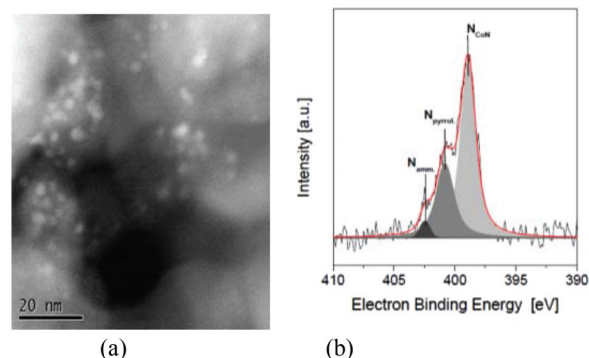


Fig. 1 STEM-HAADF (a) and XPS spectra of $\text{Co}_3\text{O}_4/\text{NGr@C}$ -catalyst.

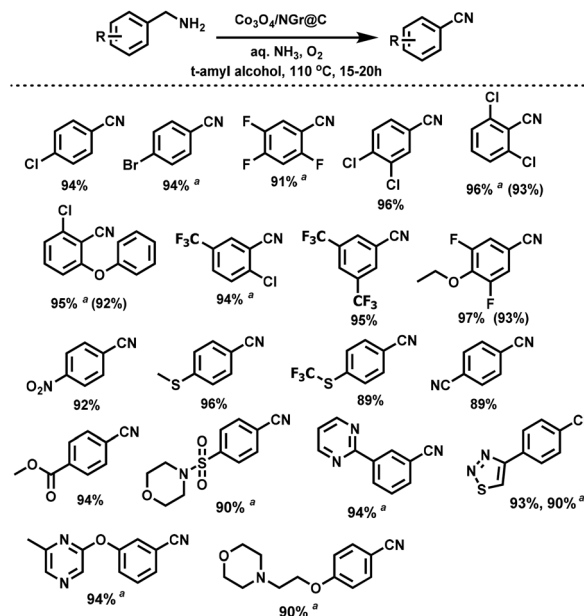
Leibniz-Institut für Katalyse an der Universität Rostock, Albert-Einstein-Straße 29a, 18059 Rostock, Germany. E-mail: matthias.beller@catalysis.de

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ob00184j

bench mark (Table 1). Expectedly, the homogeneous Co-phenanthroline complex, the non-pyrolyzed Co-phenanthroline/C as well as the pyrolyzed cobalt acetate on carbon are all not active for the model reaction. However, to our delight, significant conversion was observed in the presence of $\text{Co}_3\text{O}_4/\text{NGr}@C > 60^\circ\text{C}$ demonstrating the high activity of the nanostructured catalyst for C–N activation. Unfortunately, in addition to the desired product (benzonitrile), we observed mainly the formation of the corresponding secondary imine and small amounts of additional benzaldehyde. In order to suppress the formation of this secondary imine and allow for further oxidation, aqueous ammonia was added to the reaction mixture, which indeed led to a highly selective formation of benzonitrile (96% yield). Hence, all further catalytic tests were performed in the presence of aq. ammonia.

With respect to the mechanism, we propose an initial cobalt oxide-catalyzed oxidation of the primary amine to the corresponding imine.¹⁴ Interestingly, this reactive intermediate undergoes fast dehydrogenation under optimized conditions to give the desired nitrile. In the absence of aqueous ammonia alternatively mainly the secondary imine is formed by addition of benzyl amine and subsequent elimination of ammonia. Notably, the formed NGr's are crucial for the activity of the cobalt oxide. This might be explained by the improved interaction with the substrate provided by N-doped graphitic matrix.

Next, we were interested to demonstrate the general applicability of the $\text{Co}_3\text{O}_4/\text{NGr}@C$ -catalyst for the synthesis of structurally diverse and challenging benzonitriles. As shown in Scheme 1, substituted and functionalized aromatic nitriles, which constitute sub-units of pharmaceuticals and agrochemicals, were obtained in good to excellent yields. Noteworthy, halogenated benzonitriles, which are precursors for agrochemicals,



Scheme 1 $\text{Co}_3\text{O}_4/\text{NGr}@C$ -catalyzed synthesis of substituted and functionalized benzonitriles. Reaction conditions: 0.5 mmol amine, 40 mg catalyst (4 mol% Co), 200 μL aq. NH_3 (28–30% NH_3 basis), 2 bar O_2 , 4 mL *t*-amyl alcohol, 110 $^\circ\text{C}$, 15–20 h, yields were determined by GC using 100 μL *n*-hexadecane standard. ^a For 24 h. Yields in parenthesis refer to isolated yields.

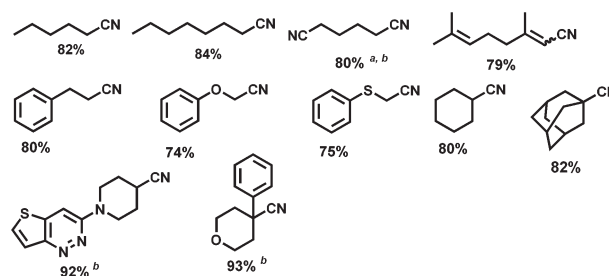
pesticides and engineering materials, were prepared in 91–97% yields. In addition, numerous functionalized benzonitriles, which are difficult to prepare by classical ammoxidation, have been successfully synthesized in up to 96% yield.

In general, the oxidation of aliphatic amines is more challenging compared to benzyl amines and most of the known catalytic systems applied for this transformation are less active towards aliphatic substrates.^{10–12} Notably, our cobalt oxide-based catalyst is effective and selective for the oxidation of such substrates. Thus, a variety of aliphatic nitriles, which constitute precursors and key intermediates for polymeric and electronic materials, were prepared (Scheme 2).

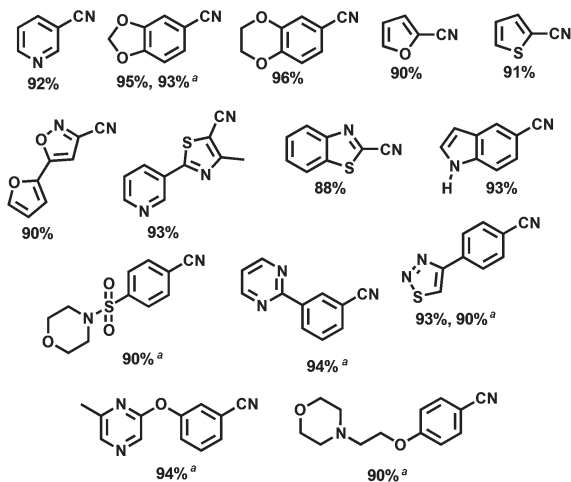
Table 1 Oxidation of benzyl amine with cobalt catalysts^{a,b}

Entry	Catalyst	Yield of benzonitrile [%]
2 ^a	$\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	<2
3 ^a	$\text{Co}(\text{OAc})_2$ -Phen	<3
4 ^b	$\text{Co}(\text{OAc})_2@C$	4
5 ^b	$\text{Co}(\text{OAc})_2$ -Phen@C	4
6 ^b	$\text{Co}(\text{OAc})_2@C$ -800	5
7 ^b	$\text{Co}(\text{OAc})_2$ -Phen@C-800	96
8 ^{b,c}	$\text{Co}(\text{OAc})_2$ -Phen@C-800	10

Materials are pyrolyzed at 800 $^\circ\text{C}$ for 2 h under argon. C = carbon support (Vulcan XC 72R). Phen = phenanthroline. ^a Homogeneous catalysis reaction conditions: 0.5 mmol benzylamine, 0.02 mmol $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$, 0.06 mmol ligand, 200 μL aq. NH_3 (28–30% NH_3 basis), 2 bar O_2 , 4 mL *t*-amyl alcohol. ^b Heterogeneous catalysis reaction conditions: 0.5 mmol benzylamine 40 mg catalyst (4 mol% Co), 200 μL aq. NH_3 (28–30% NH_3 basis), 3 bar O_2 , 4 mL *t*-amyl alcohol. ^c Same as footnote ^b without aq. NH_3 . Yields were determined by GC.



Scheme 2 $\text{Co}_3\text{O}_4/\text{NGr}@C$ -catalyzed synthesis of aliphatic nitriles. Reaction conditions: 0.5 mmol amine, 40 mg catalyst (4 mol% Co), 200 μL aq. NH_3 (28–30% NH_3 basis), 2 bar O_2 , 4 mL *n*-heptane or *t*-amyl alcohol, 110 $^\circ\text{C}$, 20–24 h, yields were determined by GC 100 μL using *n*-hexadecane as standard. ^a 60 mg catalyst, 300–400 μL aq. NH_3 , 4 mL *n*-heptane or *t*-amyl alcohol. ^b Isolated yields.



Scheme 3 $\text{Co}_3\text{O}_4/\text{NGr}@C$ -catalyzed synthesis of heterocyclic nitriles. Reaction conditions: 0.5 mmol amine, 40 mg catalyst (4 mol% Co), 200 μL aq. NH_3 (28–30% NH_3 basis), 2 bar O_2 , 4 mL *t*-amyl alcohol, 110 $^\circ\text{C}$, 15 h, yields were determined by GC using *n*-hexadecane standard. ^a Isolated yields.

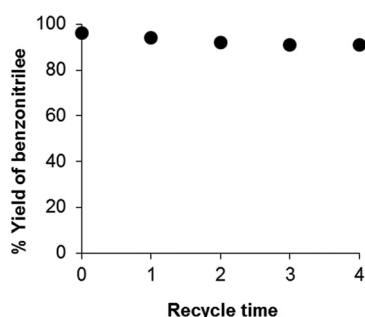


Fig. 2 Synthesis of benzonitrile: recycling of $\text{Co}_3\text{O}_4/\text{NGr}@C$ -catalysts. Reaction conditions: 1 mmol benzylamine, 80 mg catalyst (4 mol% Co), 400 μL aq. NH_3 (28–30% NH_3 basis), 2 bar O_2 , 4 mL *t*-amyl alcohol, 110 $^\circ\text{C}$, 15–20 h, yields were determined by GC using *n*-hexadecane standard.

Finally, we showed the broad applicability of this methodology by synthesizing a number of heterocyclic nitriles. Heterocycles including pyridines, oxazoles, thiazoles, indoles, pyrazines and others were well tolerated and the corresponding products are obtained in good to excellent yield (Scheme 3). Several of these heterocyclic nitriles are valuable precursors and intermediates for active life science products.

From a practical point of view the stability and recyclability of our Co-based catalyst is noteworthy. Such recycling is an important aspect for industry. Indeed, the catalyst is highly stable in the bench mark reaction and can be conveniently re-used up to 4 times (Fig. 2).

Conclusions

In summary, we developed a highly selective and general oxidation process for the synthesis of nitriles from amines. This

green methodology makes use of molecular oxygen and aqueous ammonia and does not need any toxic cyanides. Key to success for this reaction is the use of a nanostructured cobalt oxide material, which is activated by nitrogen-doped graphene layers. The general applicability of this methodology is demonstrated by the synthesis of >40 structurally diverse and interesting nitriles in good to excellent yields. Notably, the heterogeneous catalyst is stable, easily recycled and can be conveniently re-used.

Acknowledgements

The Federal Ministry of Education and Research (BMBF) and the State of Mecklenburg-Vorpommern are gratefully acknowledged for their general support. We are grateful to Prof. A. Brückner, Dr J. Radnik and Dr M.-M. Pohl for catalyst characterization.

Notes and references

- (a) Price of metals. <http://www.metalprices.com/>; (b) S. M. Holzwarth and B. Plietker, *ChemCatChem*, 2013, 5, 1650; (c) M. R. Bullock, *Science*, 2013, 342, 1054; (d) L. Que Jr. and B. W. Tolman, *Nature*, 2008, 455, 333.
- L. Kesavan, R. Tiruvalam, M. H. Ab Rahim, M. I. bin Saiman, D. I. Enache, R. L. Jenkins, N. Dimitratos, J. A. Lopez-Sanchez, S. H. Taylor, D. W. Knight, C. J. Kiely and G. J. Hutchings, *Science*, 2011, 331, 195.
- (a) R. V. Jagadeesh, A.-E. Surkus, H. Junge, M.-M. Pohl, J. Radnik, J. Rabeah, H. Huan, V. Schünemann, A. Brückner and M. Beller, *Science*, 2013, 342, 1073; (b) F. A. Westerhaus, R. V. Jagadeesh, G. Wienhöfer, M.-M. Pohl, J. Radnik, A.-E. Surkus, J. Rabeah, K. Junge, H. Junge, M. Nielsen, A. Brückner and M. Beller, *Nat. Chem.*, 2013, 5, 537; (c) R. V. Jagadeesh, H. Junge, M.-M. Pohl, J. Radnik, A. Brückner and M. Beller, *J. Am. Chem. Soc.*, 2013, 135, 10776; (d) R. V. Jagadeesh, H. Junge and M. Beller, *Nat. Commun.*, 2014, 5, 4123; (e) R. V. Jagadeesh, K. Natte, H. Junge and M. Beller, *ACS Catal.*, 2015, 5, 1526.
- (a) S. A. Lawrence, in *Amines: Synthesis, Properties, and Application*, Cambridge University Press, Cambridge, 2004; (b) M. Johannsen and K. A. Jørgensen, *Chem. Rev.*, 1998, 98, 1689.
- For transformation of amine, see: (a) D. Koszelewski, B. Grischek, S. M. Glueck, W. Kroutil and K. Faber, *Chem. – Eur. J.*, 2011, 17, 378; (b) S. Bahn, S. Imm, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, 3, 1853; (c) C. Gunanathan and D. Milstein, *Science*, 2013, 341, 249.
- For oxidation of amines, see: (a) A. E. Wendlandt and S. S. Stahl, *J. Am. Chem. Soc.*, 2014, 136, 506; (b) K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2003, 42, 1480; (c) M. L. Deb, S. S. Dey, I. Bento,

- M. T. Barros and C. D. Maycock, *Angew. Chem., Int. Ed.*, 2013, **52**, 9791; (d) F. Su, S. C. Mathew, M. Möhlmann, M. Antonietti, X. Wang and S. Blechert, *Angew. Chem., Int. Ed.*, 2011, **50**, 657.
- 7 (a) F. Fraser, L. Lihua, P. C. Ravikumar, L. Funk and B. C. Hook, *J. Med. Chem.*, 2010, **53**, 7902; (b) A. Kleemann, V. Engel, B. Kutscher and D. Reichert, in *Pharmaceutical Substances: Syntheses, Patents, Applications of the most relevant APIs*, 4th edn, Georg Thieme, Stuttgart, 2001; (c) F. F. Fleming, *Nat. Prod. Rep.*, 1999, **16**, 597; (d) J. Yang, M. R. Karver, W. Li, S. Sahu and N. K. Devaraj, *Angew. Chem., Int. Ed.*, 2012, **51**, 5222; (e) Z. Rappoport, *Chemistry of the Cyano Group*, Wiley, London, 1970; (f) R. C. Larock, in *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, VCH, New York, 1989.
- 8 For cyanation, see: P. Anbarasan, T. Schareina and M. Beller, *Chem. Soc. Rev.*, 2011, **40**, 5049.
- 9 For ammoxidation, see: A. Martin and V. N. Kalevaru, *ChemCatChem*, 2010, **2**, 1504.
- 10 For ruthenium catalyzed oxidation of amines to nitrile, see: (a) F. Li, J. Chen, Q. Zhang and Y. Wang, *Green Chem.*, 2008, **10**, 553; (b) Y. Zhang, K. Xu, X. Chen, T. Hu, Y. Yu, J. Zhang and V. Huang, *Catal. Commun.*, 2010, **11**, 951; (c) S. Venkatesan, A. S. Kumar, J.-F. Lee, T.-S. Chan and J.-M. Zen, *Chem. – Eur. J.*, 2012, **18**, 6147; (d) L. Cristian, S. Nica, O. D. Pavel, C. Mihailciuc, V. Almasan, S. M. Coman, C. Hardacre and V. I. Parvulescu, *Catal. Sci. Technol.*, 2013, **3**, 2646; (e) K.-N. T. Tseng, A. M. Rizzi and N. K. Szymczak, *J. Am. Chem. Soc.*, 2013, **135**, 16352; (f) E. C. Corker, J. R-Martínez, A. Riisager and R. Fehrmann, *Catal. Sci. Technol.*, 2015, **5**, 5008; (g) L. Claes, J. Verduyck, I. Stassen, B. Lagrain and D. E. D. Vos, *Chem. Commun.*, 2015, **51**, 6528.
- 11 For copper-catalyzed oxidation of primary amines to nitriles, see: (a) J. Kim and S. S. Stahl, *ACS Catal.*, 2013, **3**, 1652; (b) P. Capdevielle, A. Lavigne and M. Maumy, *Synthesis*, 1989, 453; (c) P. Capdevielle, A. Lavigne, D. Sparfel, J. Baranne-Lafont, N. K. Cuong and M. Maumy, *Tetrahedron Lett.*, 1990, **31**, 3305; (d) Y. Maeda, T. Nishimura and S. Uemura, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 2399; (e) D. Damodara, R. Arundhathi and P. R. Likhar, *Adv. Synth. Catal.*, 2014, **356**, 189.
- 12 K. Y. Han, H. S. Kyu, L. Y. Sik and K. J. Won, *Appl. Chem. Eng.*, 2014, **25**, 215.
- 13 R. V. Jagadeesh, H. Junge and M. Beller, *ChemSusChem*, 2015, **8**, 92.
- 14 For recent cobalt oxide-catalyzed aerobic oxidations of N-heterocycles see: (a) A. V. Iosub and S. S. Stahl, *Org. Lett.*, 2015, **17**, 4404; (b) For cobalt-catalyzed oxidations of amines to N-oxides see: S. L. Jain and B. Sain, *Angew. Chem., Int. Ed.*, 2003, **42**, 1265.