An Enzyme-Mimic Single Fe-N_3 Atom Catalyst for the Oxidative Synthesis of Nitriles via C–C Bond Cleavage Strategy

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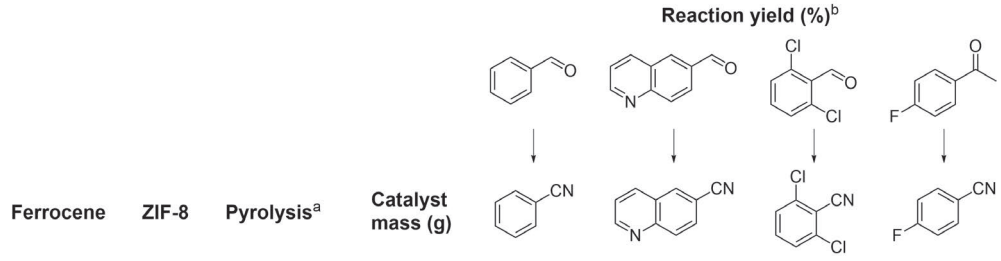
Nitriles constitute a ubiquitous class of compounds, present in natural products, agrochemicals, and pharmaceuticals and widely utilized as versatile intermediates in organic synthesis. Cyanide-free, one-step direct construction of aryl nitriles – which occupy a particularly prominent position in terms of their applications – is often challenging under heterogeneous catalytic conditions. Professor Zehui Zhang's research group at South-Central University for Nationalities (P. R. of China) has been focusing on the development of green and sustainable catalytic systems for the one-pot synthesis of various value-added compounds and recently achieved a breakthrough in this area of research. "We aim to develop general, efficient, and practical synthesis methods for value-added nitrile compounds from simple and readily available feedstock molecules, such as alcohols, ketones, and aldehydes," said Professor Zhang, continuing, "Single-atom catalysts (SACs) are emerging as a rapidly developing and attractive catalytic system, with the exact properties we want in a catalyst, so our research strategy stems from this consideration." Professor Wen Dai at the Chinese Academy of Sciences (P. R. of China), co-corresponding author of the *Sci. Adv.* article, added: "The synthesis of nitriles from ketones and secondary alcohols via inert C–C bond cleavage is very challenging and requires high catalyst activity. This novel route can avoid the use of toxic cyano-organic compounds and has huge potential in practical applications."

"Previous literature reported the excellent catalytic activity of the P450 enzyme for O_2 activation at room temperature, therefore we thought we could design a catalyst with a structure inspired by this enzyme," said Jingzhong Qin, the first author of the title article. He and other authors designed two types of SACs bearing atomically dispersed Fe sites with different coordinating nitrogen atoms (FeN_3-SAC and FeN_4-SAC) by pyrolysis of ZIF-8 (ZIF = Zeolite Imidazolate Framework) and ferrocene, following methods reported in the literature. The FeN_3-SAC showed a high enzyme-like activity and was capable of activating O_2 to superoxide radical anion at room temperature, while the commonly reported FeN_4-SAC is inactive. "Inspiringly, this FeN_3-SAC proved to be highly active for the oxidative nitrification of alcohols (primary alcohols and secondary alcohols), ketones, and aldehydes to nitriles, where the oxidative nitrification of ketones and secondary alcohols is via a C–C bond cleavage route. This newly developed FeN_3-SAC enzyme-mimic can serve as a bridge between enzymatic catalysis and heterogeneous catalysis," said Mr. Qin.

Professor Bo Han at China University of Geosciences (P. R. of China) and second author on the article added: "Density functional theory (DFT) calculations revealed that the activa-



Ferrocene	ZIF-8	Pyrolysis[a]	Catalyst mass (g)				
56 mg	4 g	1100 °C, 2 h	1.46	97	92	99	85[c]
112 mg	8 g	1100 °C, 2 h	3.28	99	89	99	88[c]
168 mg	12 g	1100 °C, 2 h	5.12	95	90	99	86[c]

Scheme 1 Preparation and catalytic activity of 1–5 g of Fe-N_3/NC-1100. [a] *Pyrolysis conditions*: ramp. 5 °C/min. [b] *Reaction conditions*: substrate (0.20 mmol), catalyst (20 mg), $NH_3{\cdot}H_2O$ (26.5 wt%, 400 µL), toluene (1.5 mL), O_2 (1 bar), 25 °C, 24 h. [c] O_2 (10 bar), 150 °C, 10 h.

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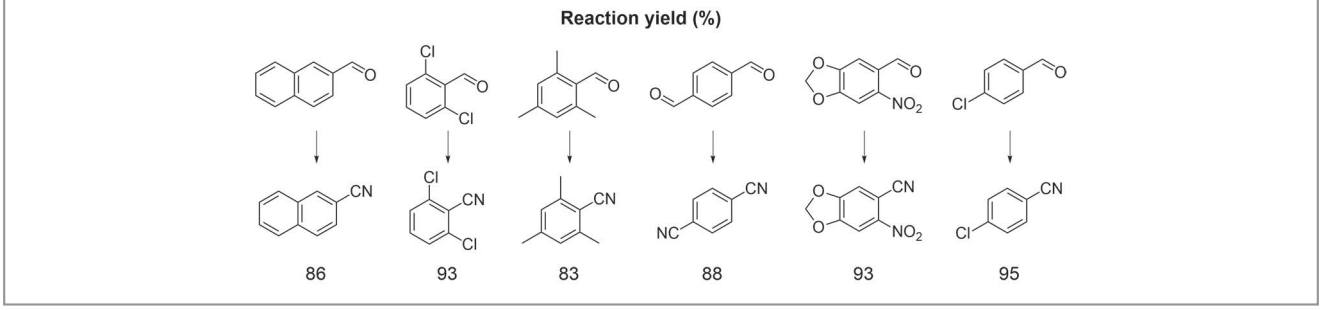


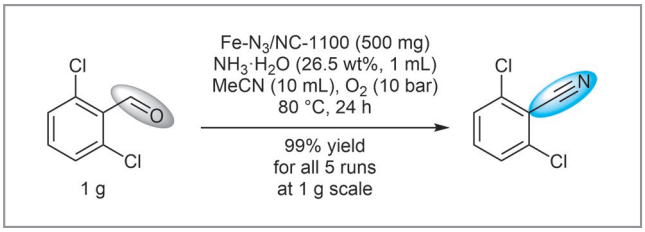
Scheme 2 Large-scale applications in the synthesis of nitriles. *Reaction conditions*: substrate (2 g), catalyst (500 mg), $NH_3{\cdot}H_2O$ (26.5 wt%, 1 mL), MeCN (10 mL), O_2 (10 bar), 80 °C, 24 h.

tion energies for O_2 activation, and the rate-determining step of nitrile formation are much lower over FeN_3-SAC than FeN_4-SAC."

According to the authors, the FeN_3-SAC catalyst preparation procedure is very simple and can be scaled up to 5.12 g. In addition, the catalytic activity of the FeN_3-SAC remains stable across the scaling-up (Scheme 1), thus validating the practical application of this catalytic method.

Large-scale synthesis of the nitrile products was also performed. "As shown in Scheme 2, some representative substrates including 2-naphthaldehyde, 2,6-dichlorobenzaldehyde, mesitaldehyde, 1,4-phthalaldehyde, 6-nitrobenzo[*d*][1,3]dioxole-5-carbaldehyde, and 4-chlorobenzaldehyde were performed with a loading of 2 g," explained Professor Zhang, adding: "The corresponding products of 2-naphthonitrile, 2,6-dichlorobenzonitrile, mesitonitrile, 1,4-dicyanobenzene, 6-nitrobenzo[*d*][1,3]dioxole-5-carbonitrile, and 4-chlorobenzonitrile were obtained in isolated yields from 83 to 95% (Scheme 2). Furthermore, the catalytic activity did not decrease after five large-scale cycle experiments (Scheme 3), indicating that Fe-N_3/NC-1100 exhibits high stability."

Professor Zhang concluded: "We are convinced that this work will expedite the synthesis of nitrile compounds. The developed method has several attractive features: (1) readily available substrates, as it uses easily accessible alcohol, ketone, and aldehyde feedstock molecules; (2) avoidance of toxic cyano-organic compounds; (3) sustainable reaction conditions, as it takes advantage of O_2 and NH_3 as oxidant and nitrogen source, respectively, with H_2O as the only by-product; and (4) excellent substrate scope and stability. This catalytic system can serve as a bridge between enzymatic catalysis and heterogeneous catalysis and is promising in industrial applications too."



Scheme 3 Large-scale cycle experiments in the synthesis of nitriles.

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Jingzhong Qin was born in Hunan, P. R. China. He completed his B.Sc. from South-Central University for Nationalities. He joined Professor Zehui Zhang's group as a Master's student at the Key Laboratory of Catalysis and Materials Sciences of the Ministry of Education at the same university. His recent research interests are finding green and sustainable catalytic systems for the synthesis of high value-added chemicals.

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Zehui Zhang obtained his Ph.D. from Dalian Institute of Chemical Physics (DICP) in 2011, Chinese Academy of Science (P. R. of China). After that, he joined South Central University for Nationalities (SCUEC, P. R. of China), and started his independent research. His current research interest is the design of novel catalytic systems for sustainable chemistry, particularly in biomass conversion. He is the director of the catalysis and green chemistry research group at SCUEC. He has published more than 120 papers with an H-Index of 51 and has applied for 20 patents.

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