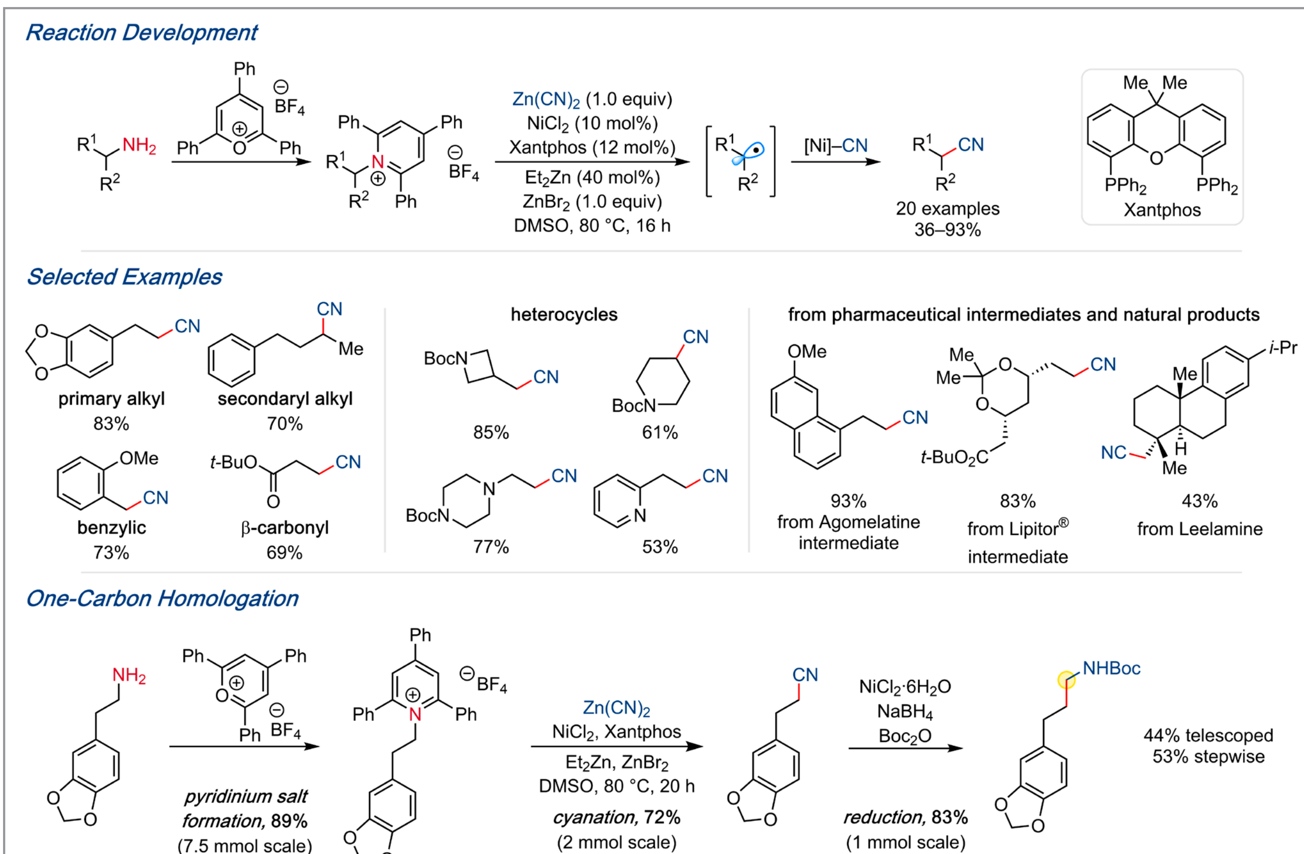
Nickel-Catalyzed Deaminative Cyanation: Nitriles and One-Carbon Homologation from Alkyl Amines

Org. Lett. **2021**, *23*, 6242–6245

A wide range of methods for achieving the cyanation of alkyl halides – which delivers useful alkyl nitrile products – are well established, including several metal-catalyzed cross-coupling reactions.[1–3] However, the use of low-toxicity sources of cyanide as well as the expansion of the pool of viable substrates to compounds other than alkyl halides (and related molecules) are among the issues that still need to be solved in this fundamental reaction. In particular, nickel-catalyzed cross-couplings of alkyl halides with less toxic cyanide sources formed much of the inspiration for the methodology developed in this paper from Professor Mary Watson at the University of Delaware (Newark, USA).[4] Professor Watson explained: "This new method offers an alternative class of starting materials, alkyl amines, to access highly valuable nitrile products. The ability to use an amine precursor can be advantageous when the alkyl amine is commercial or less expensive than an alkyl halide, or when the amine is more easily synthesized than an alkyl halide. The use of alkyl amines also offers opportunities for late-stage functionalization, because a protected amine can be carried through multiple synthetic steps, revealed, and converted into the pyridinium salt at the appropriate point in the synthetic sequence. The use of pharmaceuticals, pharmaceutical intermediates, and natural products containing alkyl amines offers another opportunity for late-stage deaminative reactions."



Scheme 1 The new Ni-catalyzed deaminative cyanation: scope and applications

According to Professor Watson, in addition to offering another substrate class for nickel-catalyzed cyanations, a key innovation presented by this method is the one-carbon homologation of alkyl amines. “There were no previous methods that allow one-carbon homologations of these important molecules. Typically, adding a carbon to a lead structure would require a complete re-synthesis. This method allows scientists to study the optimal position of the amino group without going back to square one synthetically,” remarked Professor Watson.

“With respect to other cross-couplings of alkylpyridinium salts, most deaminative cross-couplings of alkylpyridinium salts will deliver final products equipped with aryl, vinyl, or alkyl groups,” explained Professor Watson, who added: “This method is one of the few that transforms the amino group into another functional group (the nitrile) with as many or even more possibilities for derivatization as the original amine.”

Professor Watson continued: “There are still several open mechanistic questions though. In particular, the conditions that were empirically identified include multiple zinc reagents, opening the possibility for the involvement of several different zinc species in the process. At present, it is especially unclear how $ZnBr_2$ assists in this reaction. The use of Xantphos as ligand is also somewhat unique in nickel-catalyzed deaminative reactions. Understanding how this ligand enables the desired reaction may offer opportunities to develop other, challenging deaminative or cyanation reactions.”

One of the major applications of this nickel-catalyzed deaminative cyanation is the one-carbon homologation of alkyl amines. Co-author Cameron Twitty extensively optimized a telescoped procedure for this one-carbon homologation sequence. “Although solvent-switching was necessary, column chromatography could be avoided until the last step, and the product can be isolated in comparable yield to the sequence with careful purification after each step,” commented Professor Watson.

Dr. Jianyu Xu, the first author, also demonstrated that the cyanation works well on pharmaceutical intermediates and natural products. The group anticipates this method may be particularly useful to discovery efforts in medicinal chemistry.

Professor Watson remarked: “When I first started giving talks about our deaminative cross-couplings of alkylpyridinium salts, many academics thought it was nuts. “Why would you take out the amine that is driving the bioactivity?” they would ask. I believe that the adoption of deaminative methods by the pharmaceutical industry has changed most people’s minds, but this idea stuck with us: Why delete a nitrogen? Perhaps we could just move its position. Dr. Jianyu Xu decided to invent a method to allow such a one-carbon homologation, and that’s how this method came to be.” She concluded: “It’s exciting that this cyanation method not only provides a one-carbon homologation approach, but also delivers nitrile intermediates, which are highly useful in their own right.”

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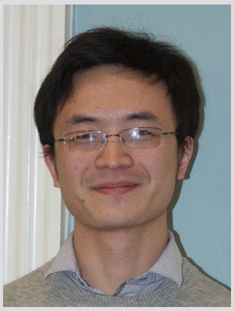

Dr. J. Xu

Dr. Jianyu Xu is from Zhejiang, P. R. of China. He earned his B.E. in Pharmaceutical Engineering from East China University of Science and Technology (P. R. of China) in 2014, where he performed research with Profs. Feng Ren and Jin Zhu. He then pursued PhD studies at the University of Delaware (USA), where he worked with Prof. Mary Watson. His graduate work includes a range of nickel-catalyzed reactions spanning deaminative cross-couplings of alkylpyridinium salts to stereospecific cross-couplings of benzylic carboxylates to set all-carbon quaternary stereocenters. He completed his PhD in 2020, and is currently a Senior Scientist at Insilico Medicine in Shanghai, P. R. of China.

J. C. Twitty

J. Cameron Twitty is from Gilbert, South Carolina, USA. He earned his B.S. from the College of Charleston (USA) in 2017, where he performed research with Prof. Tim Barker. He began his PhD studies at the University of Delaware (USA) in 2018, where he is developing new deaminative reactions of alkylpyridinium salts under the mentorship of Prof. Mary Watson.

Prof. M. P. Watson

Professor Mary P. Watson is a Professor of Chemistry at the University of Delaware (USA). She grew up in Tampa, Florida, USA, and then earned her A.B. from Harvard University (USA) in 2000. As an undergraduate, she performed research with Prof. David Evans, as well as Prof. Kenneth Wagener at the University of Florida (USA). She earned her PhD in 2006 from the University of California, Irvine (USA), where she pursued methodology and mechanistic studies of the palladium-catalyzed allylic imidate rearrangement under the mentorship of Prof. Larry Overman and in collaboration with Prof. Robert Bergman. She then worked with Prof. Eric Jacobsen at Harvard University as an NIH NRSA postdoctoral fellow (2006–2009), where she developed nickel-catalyzed arylcyanation reactions. In 2009, she began her independent career at the University of Delaware, where she leads a talented team in the development of new methods for organic synthesis, enjoys helping to organize the annual Empowering Women in Organic Chemistry conference, and is the proud mom of twin daughters.

