

Metal-Free Oxidation of Primary Amines to Nitriles via Coupled Catalytic Cycles

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Although the oxidation of primary amines would be, in principle, a straightforward and atom-economical entry to nitriles, the reaction is not conventionally used because of the difficulties connected with controlling the many different oxidation pathways that can originate from amines. Recently, the group of Professor William F. Bailey at the University of Connecticut (USA) has described a novel efficient strategy for accomplishing this challenging transformation.

“For the past ten years or so, my research group has been collaborating with my close friend and colleague, Professor Emeritus Dr. James M. Bobbitt, exploring the oxidation chemistry of 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (**1**). The salt, which we and others colloquially refer to as ‘Bobbitt’s salt’ (the systematic name is quite a mouthful), as well as its nitroxide precursor (**2**) were developed by Jim (Professor Bobbitt) in the 1990s,” said Professor Bailey (Figure 1). He continued: “While both the nitroxide (4-acetamido-TEMPO, ACT, **2**) and Bobbitt’s salt (**1**) are commercially available, it is far more cost-effective to prepare the salt from 4-amino-2,2,6,6-tetramethylpiperidine, via the nitroxide, than it is to purchase it: **1** may be prepared in a few simple steps, on a multi-mole scale in water, for < US\$ 1 per gram; the nitroxide precursor, **2**, is significantly less expensive to prepare.”

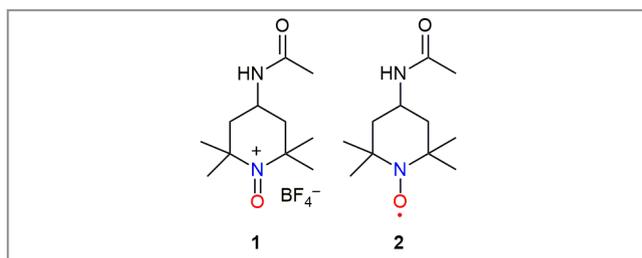
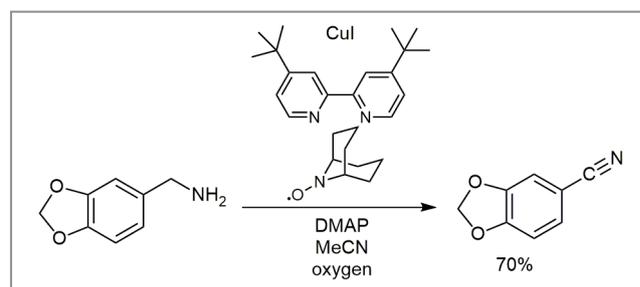


Figure 1

The group’s initial ventures in oxoammonium chemistry involved exploration of the mechanism of alcohol oxidation and the reactions of Bobbitt’s salt with alcohols, aldehydes, ethers, and alkenes.² “More recently, prompted by Jim’s prescient suggestion that we consider the implications of a 1983 report by Martin Semmelhack,³ we became interested in the

potential of oxoammonium cations to provide a selective and mild method for oxidation of amines to nitriles,” explained Professor Bailey. The seminal Semmelhack–Schmid publication disclosed that generation of the oxoammonium cation by electrochemical oxidation of TEMPO in the presence of a primary amine afforded a mixture of nitriles, imines, and aldehydes in variable proportions. Professor Bailey said: “At the time we began our investigations in 2013, the conversion of an amine into a nitrile (formally a double dehydrogenation) was a non-trivial transformation. Amines are, of course, quite easy to oxidize with a host of reagents: the difficulty is controlling the process to give only the desired product.”

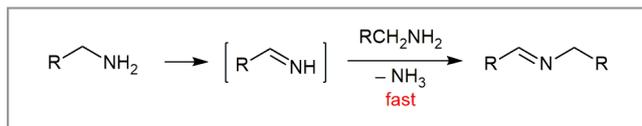
He continued: “Shannon Stahl beat us to the punch with his mid-2013 report of a catalytic method to accomplish the $RCH_2NH_2 \rightarrow RCN$ conversion (Scheme 1).⁴ This beautiful piece of chemistry, which, the authors noted, involved ‘extensive screening of ligands and bases’, set a high bar for us.”



Scheme 1 Catalytic approach by Kim and Stahl (2013)

Professor Bailey explained that the major difficulty identified by Stahl in the oxidation of RCH_2NH_2 to a nitrile is the unexpectedly rapid formation of homocoupled imines by condensation of the amine starting material with the aldimine generated in the first oxidation step (Scheme 2). Professor Bailey’s group had also already encountered this difficulty.

“At the outset of our investigation of amine oxidations we were interested in the development of a method for oxidation of amines to nitriles that would not involve a metal and associated ligand for the process,” said Professor Bailey. They began by first exploring the use of a stoichiometric quantity of Bobbitt’s salt (**1**) as the oxidant. The solution to the rapid



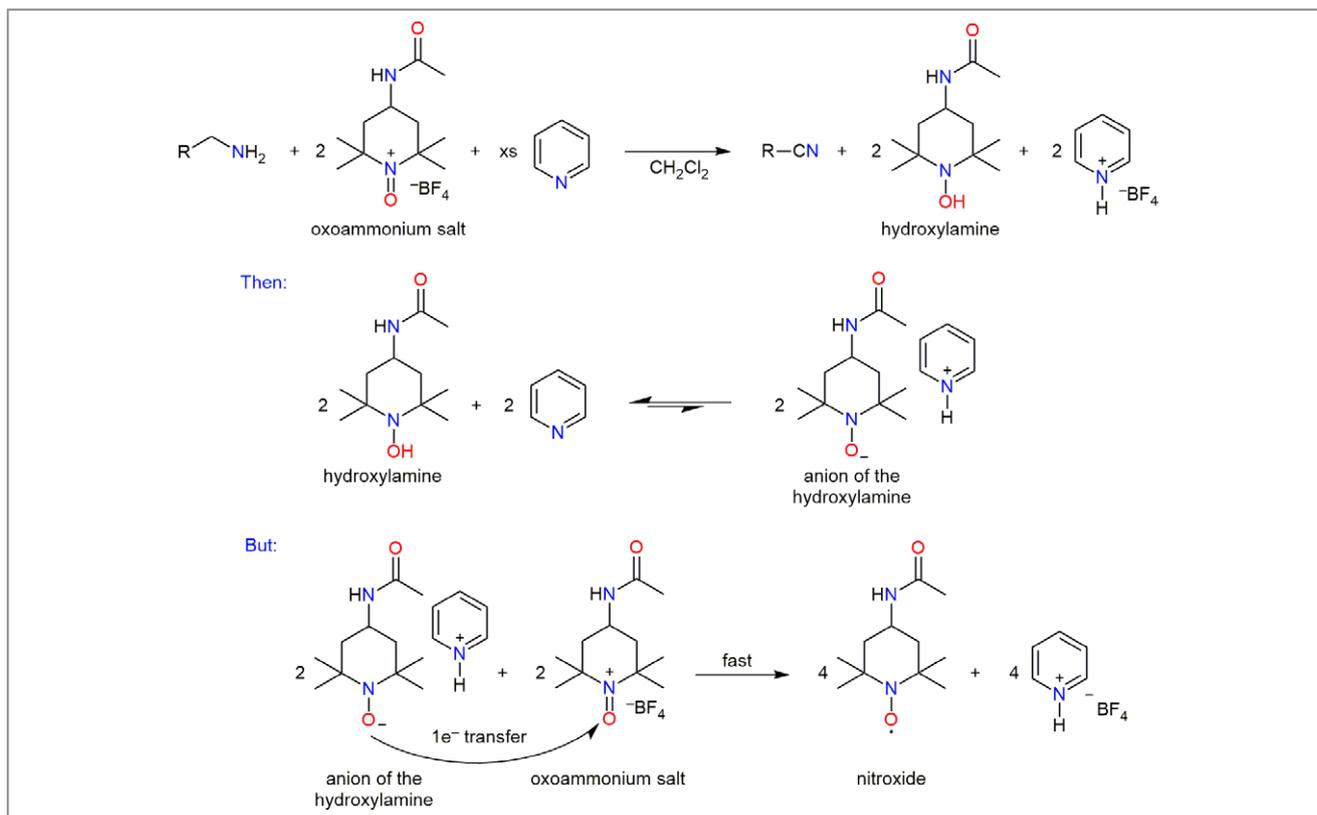
Scheme 2 Homocoupled imine formation

formation of imine in the oxidation of primary amines was a simple, operational one: they slowly added a 0.5 M solution of the amine in dichloromethane (15–20 mL/h using a syringe pump) to a stirred slurry of slightly more than the stoichiometric quantity of oxoammonium salt and an excess of pyridine as base in dichloromethane at room temperature. Professor Bailey explained: “We reasoned that the slow addition of amine allowed the oxidation of the aldimine intermediate to proceed to completion before excess amine could react to give unwanted imine. It worked. Reaction mixtures were stirred at room temperature overnight, and a simple extractive workup afforded pure nitriles in good yield (85–95%.)” The report of this chemistry was submitted in November of 2014 and published in December of that year.⁵ The paper also demonstrated that the mechanism of the oxidation involves a hydride trans-

fer from the amine to the oxygen atom of **1** as the rate-limiting step.

Scheme 3 summarizes the approach. The scheme also illustrates a major limitation of this method for the preparation of larger quantities of nitriles: a stoichiometric quantity of oxoammonium salt is a full 4 molar equivalents of the reagent. This is a consequence of the fact that, in the presence of base, **1** and the hydroxylamine syn-proportionate to give 4 molar equivalents of nitroxide **2**.

“Clearly, as all the reviewers of our *Org. Lett.* article properly noted, a catalytic method for the oxidation of amines to nitriles would be far superior to this stoichiometric process for the preparation of nitriles on scale,” commented Professor Bailey. At first, the group estimated that development of a catalytic procedure for the transformation of an amine to a nitrile would take no more than a few weeks, reasoning that there are any number of ways to oxidize alcohols to aldehydes and ketones using a catalytic quantity of TEMPO and a terminal oxidant. “We should have remembered Robert Burns’ admonition: ‘The best laid schemes o’ mice an’ men/Gang aft a-gley,’”⁶ laughed Professor Bailey. Indeed; it took almost a year to reduce the chemistry to practice.



Scheme 3 Stoichiometric oxidation of amines to nitriles using Bobbitt's salt

Professor Bailey continued: “The credit belongs to my co-author, Kyle Lambert. An exceptionally talented chemist and one of the most technically accomplished graduate students that I have had in my long career, Kyle finally cracked the problem.” The difficulty was in identifying a suitable terminal oxidant to generate the active oxoammonium salt without negatively impacting the sensitive amine substrate. “Kyle tried many approaches; the solution, detailed in the *Chem. Eur. J.* account, involved adaptation of several, pH-dependent catalytic cycles to create a catalytic cascade using a catalytic amount of Bobbitt’s nitroxide (ACT, **2**), pyridinium bromide, oxone as a terminal oxidant, and an excess of pyridine as base in dichloromethane solution at room temperature,” explained Professor Bailey, continuing: “Once again, slow addition of the amine was required to prevent formation of the imine. Simple filtration of the product mixture through a small bed of silica gel, and removal of the solvent, afforded pure nitrile products; no chromatography needed. The procedure is a robust one. All manner of primary amines are converted into nitriles in good to excellent yield.” Scheme 4 provides an overview of the process and a few representative yields of isolated products.

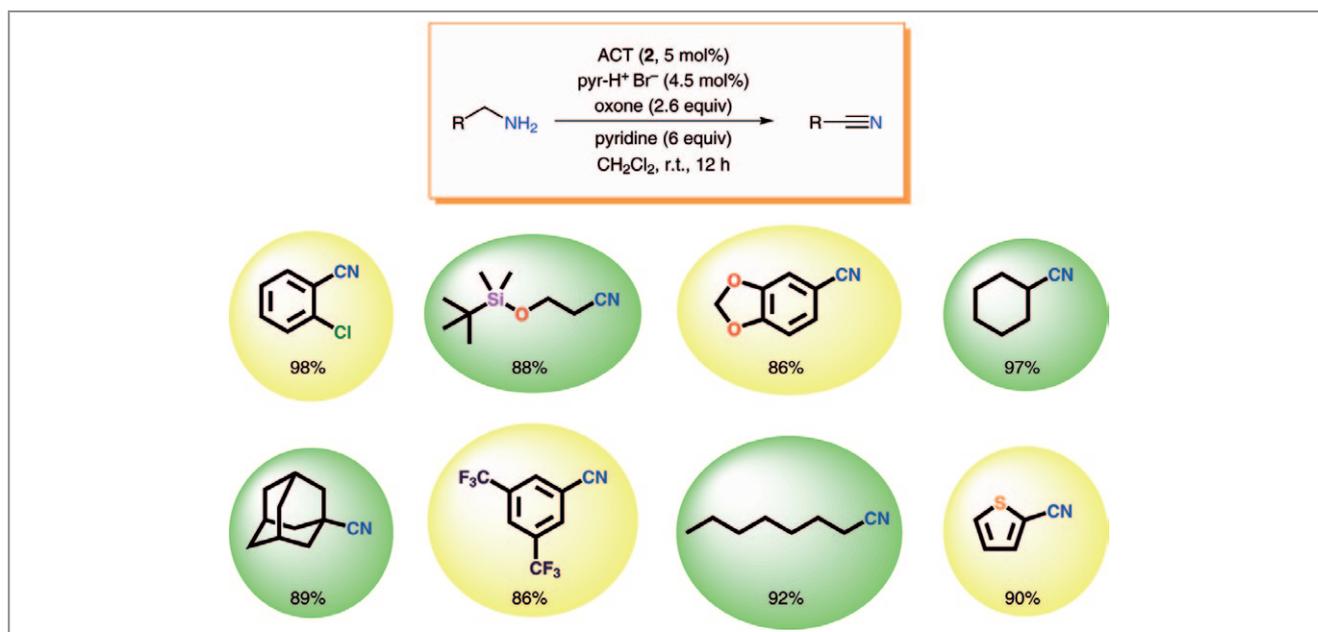
Professor Bailey acknowledged that the undergraduate co-authors, Sherif A. Eldirany, Liam E. Kissane, Rose K. Sheridan, Zachary D. Stempel, and Francis H. Sternberg, participated materially in the development of the chemistry presented in the account. “They prepared, purified, and characterized many of the amine substrates used in the study and checked the ox-

idation procedure to ensure reproducibility. Significantly, this was the first taste of independent chemical research for many of the undergraduate students,” concluded Professor Bailey.

Mattes Fank

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- (6) ‘Gang aft a-gley’ can be translated from Scottish as ‘often go awry’.



Scheme 4 Catalytic oxidation of amines to nitriles

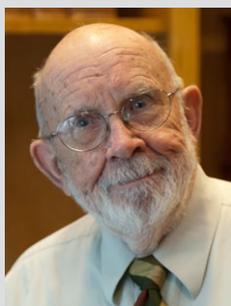
About the authors



Prof. W. F. Bailey

Bill Bailey was born and raised in Jersey City, NJ (USA), and received his B.S. degree in chemistry in 1968. He worked with Ernest Eliel at the University of Notre Dame (IN, USA) investigating conformations of saturated heterocycles and the stereochemical dependence of C-13 shifts and obtained his Ph.D. in 1973. After a two-year postdoc with Kenneth Wiberg at Yale (USA), Bill joined the faculty at the University of Connecticut (USA)

where he is currently Professor of Chemistry. A major focus of Bill's research is development of new synthetic methodology using novel main-group organometallic chemistry.



Prof. J. M. Bobbitt

Jim Bobbitt was born in Charleston, WV (USA) in 1930. He received his B.S. degree in chemistry at the University of West Virginia (USA) and then obtained his Ph.D. at Ohio State University (USA) where he worked on natural products and periodate oxidation of sugar derivatives with M. L. Wolfrom. Following postdoctoral studies with Carl Djerassi at Wayne State University (USA) on alkaloid structure determination, Jim was appointed

in 1956 to an instructorship in chemistry at the University of Connecticut in Storrs (USA). He rose through the ranks at the University of Connecticut (USA) and served as department head from 1976–1982. His research included structure elucidation of natural products, heterocyclic chemistry, and electrooxidation of alkaloids and similar materials. In 1985, he encountered oxoammonium chemistry in his electrochemical work and has worked in that field since. He formally retired in 1992, but has continued to do bench chemistry himself and with a number of colleagues and their graduate students.



K. M. Lambert

Kyle Lambert graduated summa cum laude from the University of New Haven (USA) in 2012 with dual B.S. degrees in chemistry and forensic science. He is currently a fourth-year graduate student working with Bill Bailey at the University of Connecticut (USA). Kyle's doctoral research involves exploration of oxoammonium salts as selective oxidants as well as conformational studies of saturated

heterocycles. In his spare time he enjoys coaching track and field at a local high school and plans to pursue an academic position upon completion of his graduate studies.



Undergraduates in the Bailey lab from left to right: Z. D. Stempel, L. E. Kissane, S. A. Eldirany, F. H. Sternberg

Zachary Stempel and **Frank Sternberg** are currently sophomores majoring in chemistry while **Liam Kissane** is a freshman undecided major at the University of Connecticut (USA). **Sherif Eldirany** is a senior graduating from the UCONN honors program this spring with a degree in chemistry and will be attending medical school in the fall of 2016.