

Nickel-Catalyzed C-Alkylation of Nitroalkanes with Unactivated Alkyl Iodides

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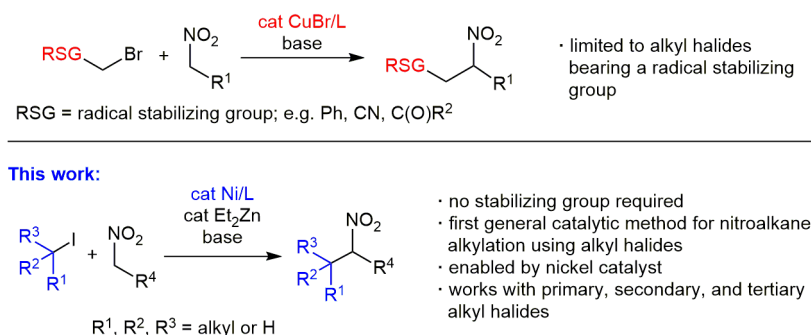
Nitroalkanes are widely used functional groups in organic synthesis. There are many methods known to convert them into useful functionalities, such as amines, carbonyls, and alkanes. In addition, they have been successfully used in many C–C bond forming reactions such as conjugate addition, Henry reaction, arylation, allylation, etc. However, despite this rich chemistry, the simple C-alkylation of nitroalkanes with common alkyl electrophiles (such as alkyl halides) has remained a highly challenging task due to competing O-alkylation. Using transition-metal catalysis, the group of Professor Donald A. Watson at the University of Delaware (USA) has begun to address this century-old problem. Professor Watson said: “Over the past few years we have shown that with the use of appropriate ligand and reaction conditions, simple in situ formed copper complexes can catalyze the C-alkylation of nitroalkanes with benzyl bromides, α -bromocarbonyls, and α -bromonitriles. However, the usable alkyl halides were limited to those bearing adjacent radical stabilizing functional groups, whereas alkyl halides lacking such stabilization groups (i.e. unactivated alkyl halides) failed to show reactivity. We believed a method that could expand the scope of alkyl halides to unactivated ones, could greatly broaden the utility of nitroalkanes.”

The group started testing this hypothesis by using copper catalysis under different conditions. “Unfortunately, our efforts to obtain the desired reactivity with copper catalysts were futile,” explained Professor Watson. He continued: “From

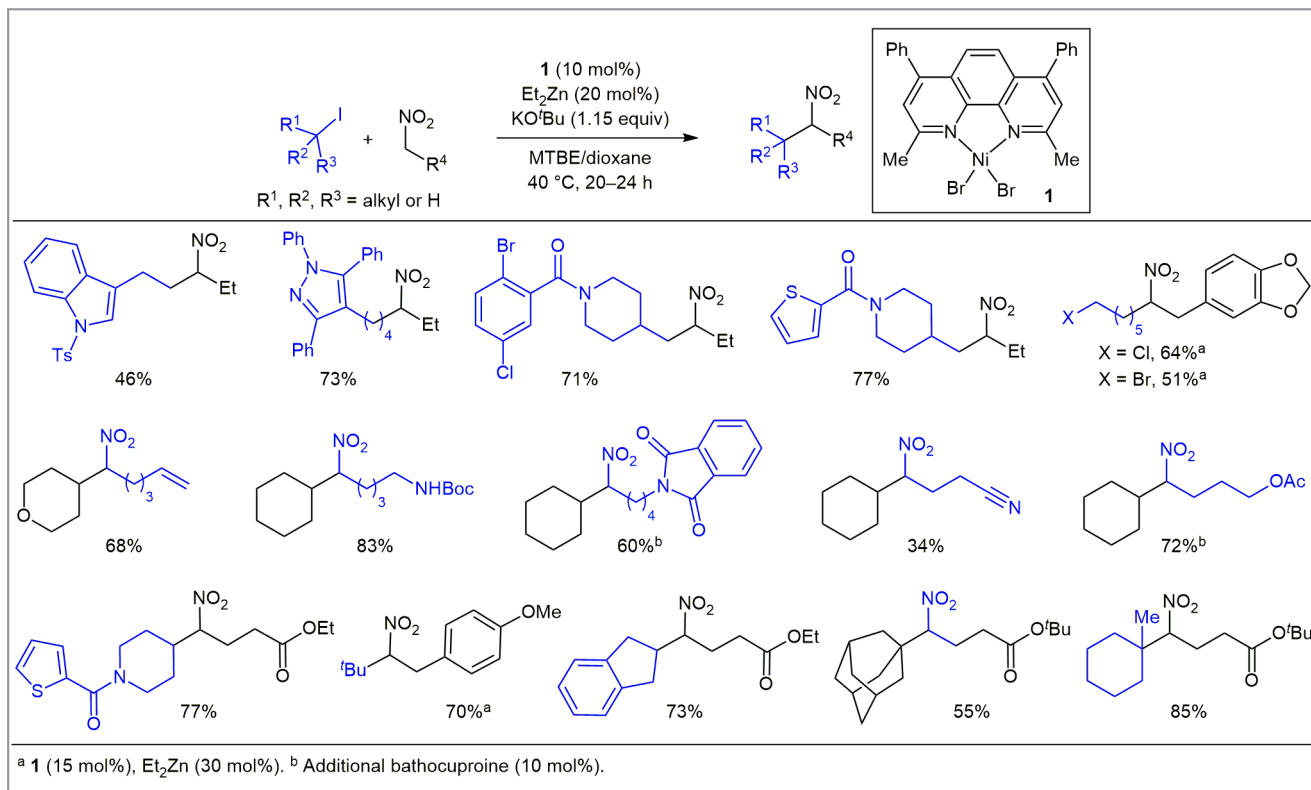
our preliminary results of benzylation chemistry, we were aware that catalysts derived from nickel were able to furnish the benzylated products, albeit in very low yield. Considering the success of nickel in catalyzing reactions of diverse nucleophiles with unactivated alkyl halides, we turned our attention to nickel catalysis. After extensive investigation of different ligands and conditions, we found the optimum ligand to be bathocuproine. The use of ethereal solvents was important, since the insolubility of the nitronate anion in these solvents precludes the competing O-alkylation reaction. Finally, suitable conditions were developed for a nickel(II) source and external reductant to make the reaction more user-friendly, considering the instability of Ni(0) sources such as Ni(cod)₂.”

With the optimized conditions in hand, the group then set out to examine the substrate scope and functional group tolerance of the reaction. “Gratifyingly, primary, secondary, and tertiary alkyl iodides were all reactive and gave the complex C-alkylated nitroalkane products in moderate to good yields,” said Professor Watson. “We particularly focused on examining relevant and important bioactive functional groups and heterocycles, and in most cases, they did not interfere with the reaction. A variety of functionalized nitroalkanes were also tested and they worked well too. Significantly, an anti-viral drug, adapromine, could be synthesized in two steps with good yields using this method.”

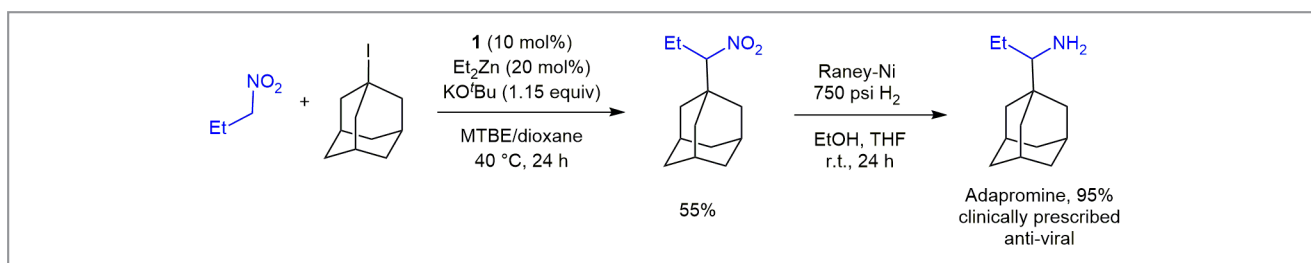
“While we believe that this newly reported method makes a major advance in nitroalkane alkylation, there is still



Scheme 1 Comparison between prior art and present method



Scheme 2 Selected examples



Scheme 3 Synthesis of adapromine

work to be done. For example, the new conditions still show limitations with respect to steric bulk of the nitroalkane and diastereoselectivity,” said Professor Watson. He concluded: “Current and future studies are aimed at continuing to improve and expand the scope of transition-metal-catalyzed nitroalkane alkylation.”

Matthew Farnish

About the authors



Prof. D. A. Watson

Donald A. Watson was born in California (USA) in 1976. He received his BS in chemistry from UC San Diego (USA) in 1998. During his undergraduate years, he studied in the laboratories of Professors K. C. Nicolaou and Emmanuel Theodorakis, working on natural products synthesis. He completed his PhD in organic chemistry at UC Irvine (USA) in 2004, working under the direction of Professor Larry E. Overman. His dissertation work

focused on stereochemical problems in palladium-catalyzed transformations. From 2004 to 2006 he was an NIH Postdoctoral Fellow in the laboratories of Professor Robert G. Bergman at UC Berkeley (USA). During this time he developed zirconium-based catalysts for asymmetric intramolecular hydroaminations. He then moved to the Massachusetts Institute of Technology (USA) to take a position as a Postdoctoral Associate in Professor Stephen L. Buchwald's laboratory, where he studied metal-catalyzed processes for C–F bond formation.

He joined the Chemistry and Biochemistry faculty at the University of Delaware (USA) as an Assistant Professor in July 2009. His research focuses on the development of new chemical methods for preparing organic molecules and structures, with a particular interest in the development transition-metal-based catalytic reactions and in the construction of carbon–heteroatom bonds. In 2013, he received a CAREER Award from the National Science Foundation and a Cottrell Scholar Award from the Research Cooperation. In 2015, he was promoted to Associate Professor with tenure. In addition, he currently serves as Associate Chair for Graduate Studies in the Department of Chemistry and Biochemistry.



S. Rezazadeh

Sina Rezazadeh was born in Ramsar (Iran). He obtained his Pharm. D. from Tehran University of Medical Sciences (Iran) in 2013. He joined Donald A. Watson's lab at the University of Delaware (USA) in 2014 as a graduate student and has been working on developing transition-metal-catalyzed reactions to make complex nitroalkanes.



V. Devannah

Vijayarajan Devannah was born in Chennai, Tamil Nadu (India). He received his MSc in organic chemistry from the University of Madras (India) in 2009. He is currently pursuing doctoral studies under the guidance of Professor Donald A. Watson at the University of Delaware (USA). His research work focuses on developing transition-metal-catalyzed reactions to make complex nitroalkanes.