In Situ Generation of N-Unsubstituted Imines from Alkyl Azides and Their Applications for Imine Transfer via Copper Catalysis

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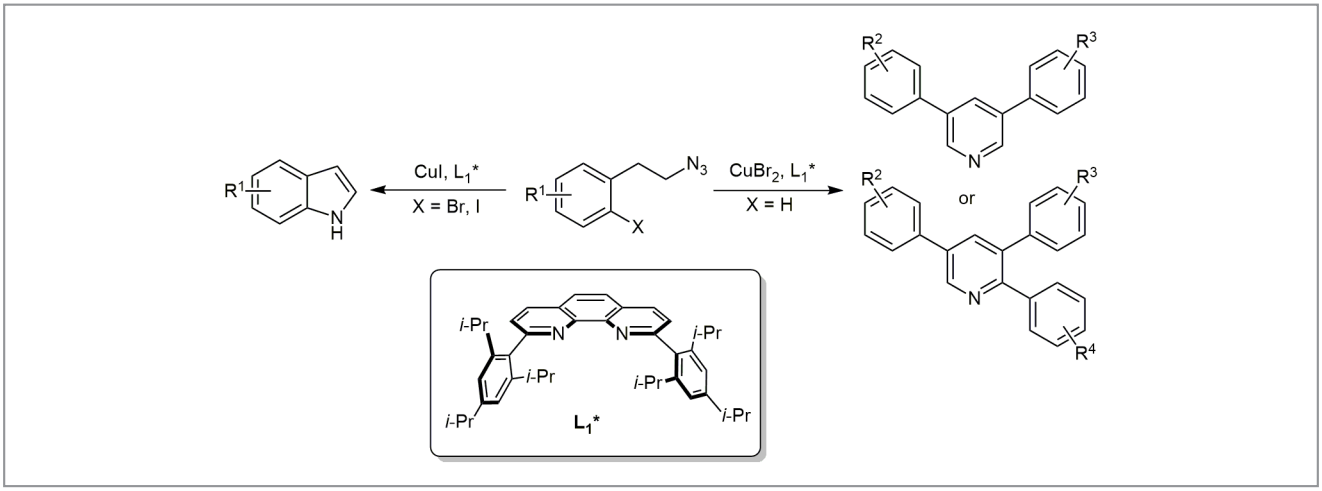


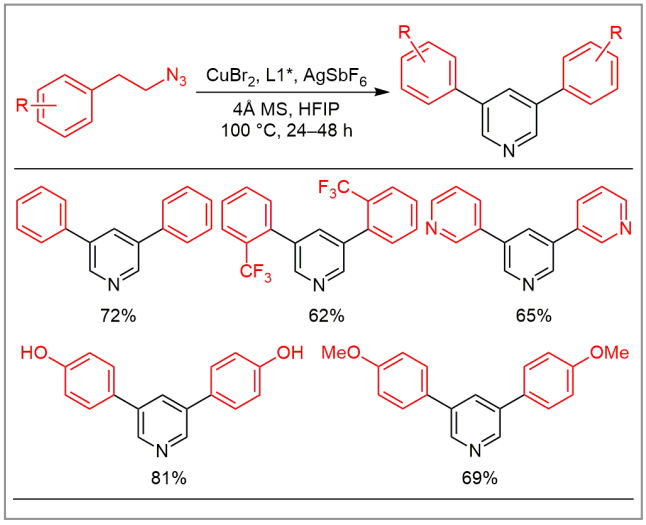
Scheme 1 Novel methodology to synthesize multi-substituted pyridines or indole derivatives

N-Unsubstituted aliphatic imines have rarely been used in synthetic organic chemistry since this chemistry is affected by several drawbacks, especially the necessity of pre-forming protected imines and subsequently removing the N-protecting group. To solve this problem, the group of Professor Xuebin Liao at Tsinghua University (Beijing, P. R. of China) developed a method to produce in situ N–H imines generated from alkyl azides. In addition, they also explored the reactivity of aliphatic N–H imines and their application in the unusual construction of multi-substituted pyridines or indole derivatives (Scheme 1).

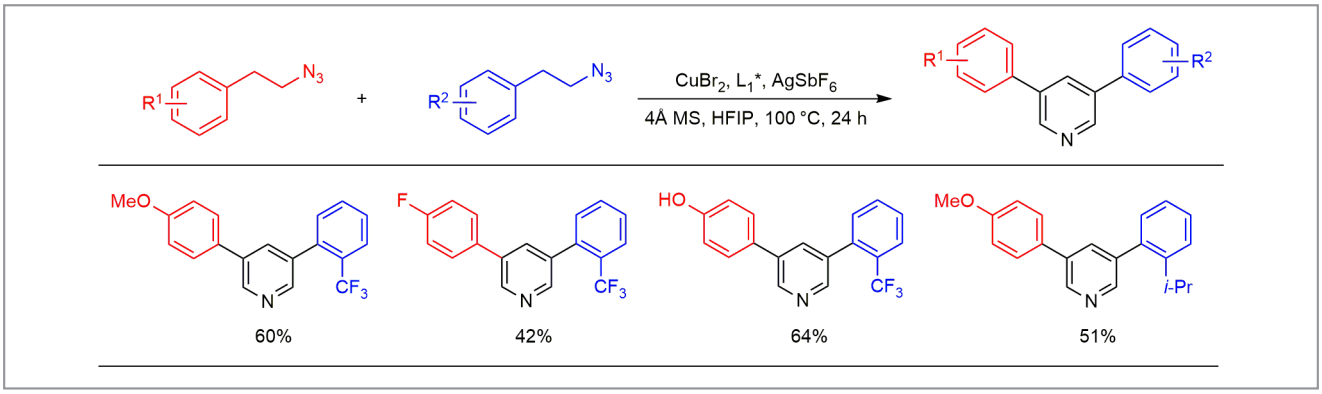
"It is believed that alkyl azides could be ideal precursors for in situ generation of N–H imines, because of their notable features such as: (i) facile accessibility and (ii) environmental friendliness (in fact they only release an equivalent of nitrogen as byproduct)," explained Professor Liao. He continued: "Inspired by the seminal work of Albertin, Park, and Rhee, among others (see the original article for references), we strived to develop a method to produce N–H imines using an earth-abundant copper catalyst. With the in situ generated N–H imine methodology, we have successfully constructed multi-substituted pyridines (Scheme 2) and indoles."

Besides that, the group was also pleased to discover that either unsymmetrical 3,5-diaryl pyridines (Scheme 3) or 2,3,5-triaryl pyridines (Scheme 4) could be obtained using this method.

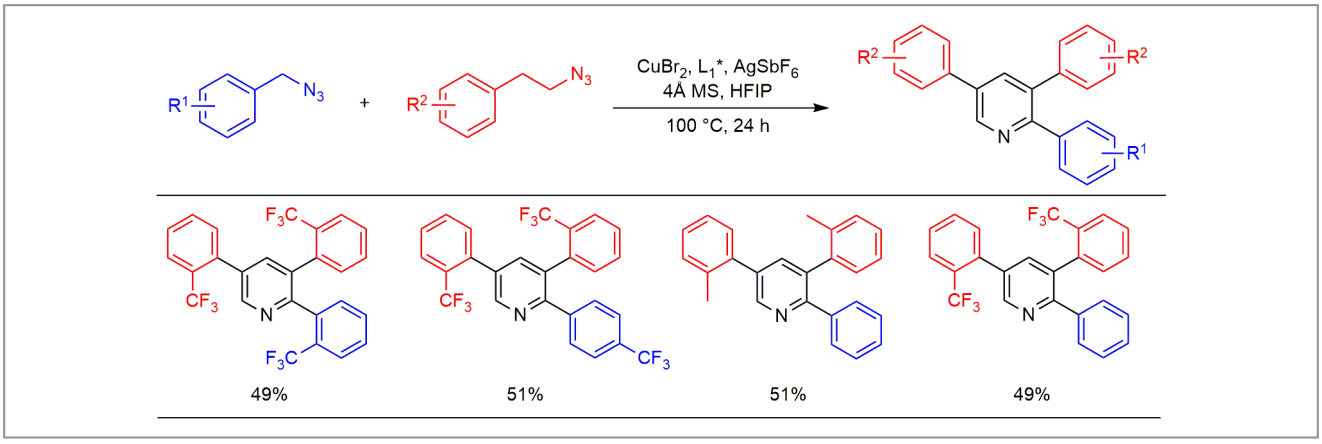
"To the best of our knowledge, this is the first reported transformation of alkyl azides into multi-substituted pyridines or N–H indoles (Scheme 5)," remarked Professor Liao.



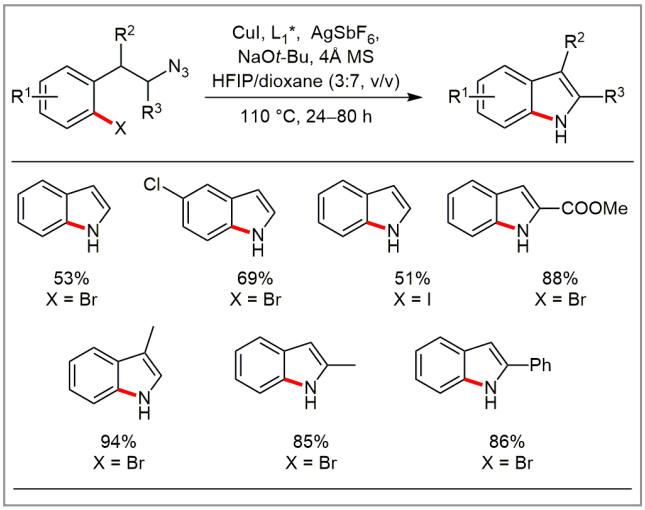
Scheme 2 Construction of 3,5-diaryl pyridines



Scheme 3 Construction of unsymmetrical 3,5-diaryl pyridines



Scheme 4 Construction of 2,3,5-triaryl pyridines



Scheme 5 Construction of indoles

"We believe our chemistry has a lot of potential for further strengthening the role of imine chemistry and will be widely applied by the synthetic community. This work was completed by a junior student in my group, Lu Hu, and I very much appreciate his hard work and dedication."

"Further work is still ongoing in our laboratory," concluded Professor Liao. "Firstly, we are continuing to develop other potential applications of imine chemistry. Our attention will mainly focus on exploring chiral catalysis for the application of N–H imines on their downstream transformations. Secondly, we will investigate the details of the mechanism involved in this transformation, through which we hope to achieve chemoselective catalytic transformations of azides to engage them in either nitrene transfer or imine chemistry."

About the authors

L. Hu

Lu Hu was born in 1991 in Wuhan (P. R. of China). He received his B.S. degree in chinese medicine from the Huazhong University of Science and Technology (P. R. of China) in 2014. Afterwards, he joined Professor Liao's group at the School of Pharmaceutical Sciences, Tsinghua University (P. R. of China) as a graduate student. His main research interests include the development of new synthetic reactions using late-transition-metal catalysts and natural product synthesis.

Dr. Y. A. Liu

Yahu A. Liu received his PhD degree in organic chemistry from Case Western Reserve University (Canada) under the guidance of late Professor Lawrance M. Sayre in 2000. Afterwards, he worked in medicinal chemistry teams at Pharmacia/Pfizer, Vertex, and ChemBridge. In 2007, he joined the Genomics Institute of Novartis Research Foundation (USA), where he is currently an Investigator III and chemistry outsourcing lead. He has co-authored 68 publications and serves on two biochemistry journal editorial boards. His main research interests include drug discovery, natural product synthesis, synthetic methodology and supramolecular chemistry. He had also served as President of Sino-American Biotechnology and Pharmaceutical Professional Association from 2015 to 2017.

Prof. X. Liao

Xuebin Liao obtained his B.S. degree from Peking University (P. R. of China) in 1995, and carried out his PhD work on natural product synthesis with Professor James M. Cook at the University of Wisconsin at Milwaukee (USA) from 1998–2004. From 2005–2008, he was a postdoctoral associate with Professor John F. Hartwig at Yale University (USA) and later at the University of Illinois at Urbana-Champaign (USA). In 2009, he held a position of Research Investigator I at the Genomics Institute of the Novartis Research Foundation (GNF, USA). At GNF, his research was centered on discovering new drug candidates for pharmaceutical optimization. In September of 2012, he joined the Department of Pharmacology and Pharmaceutical Science, School of Medicine, Tsinghua University (P. R. of China). Currently Professor Liao's research focuses on three major areas: 1) bioactive natural product oriented synthesis and new synthetic method development; 2) immuno-oncology projects related to T cell exhaustion and innate immunity; and 3) structure-based drug discovery.

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