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An Insight into Silver-Catalyzed Hydroazidation for a General Synthesis of Vinyl Azides

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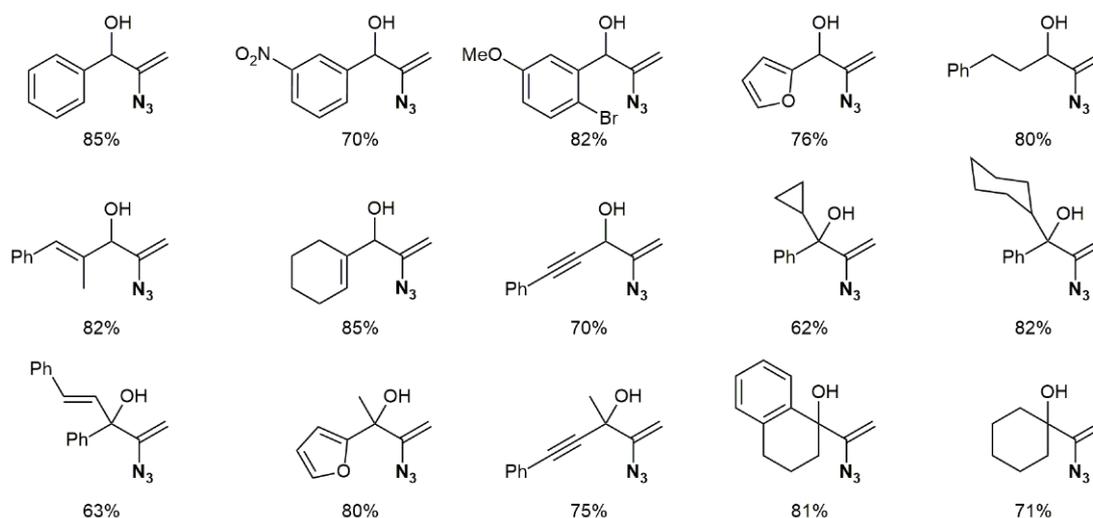
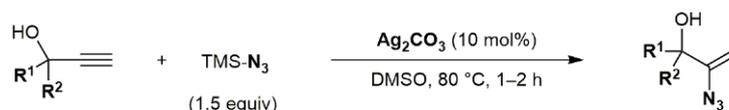
■ Nitrogen-containing heterocycles are ubiquitous in natural products as well as among pharmaceutical substances. Consequently, the development of methods for the introduction of nitrogen in simple organic compounds is an intense focus of modern research. In particular, vinyl azides show unique reactivity in organic synthesis due to the concomitant

presence of the C=C double bond and the azide functionality. In earlier research, much attention was paid to the study of the reactivity of vinyl azides, especially the control of their selectivity and the potential synthetic utilities. However, the synthetic scope of vinyl azides remains largely unexplored because of the intrinsic high reactivity and limited available methods for their preparation. Meanwhile, vinyl azides have drawn much interest for their growing applications in the synthesis of various heterocycles, as well as polysubstituted pyrroles, owing to their remarkably important applications in both medicinal and materials fields. Great efforts have focused on developing simple synthetic approaches for the construction of these privileged structures.

Hydroazidation is one of the most suitable and viable methods for the generation of nitrogen-containing reactive



Scheme 1 Hydroazidation of terminal alkynes toward the synthesis of vinyl azides

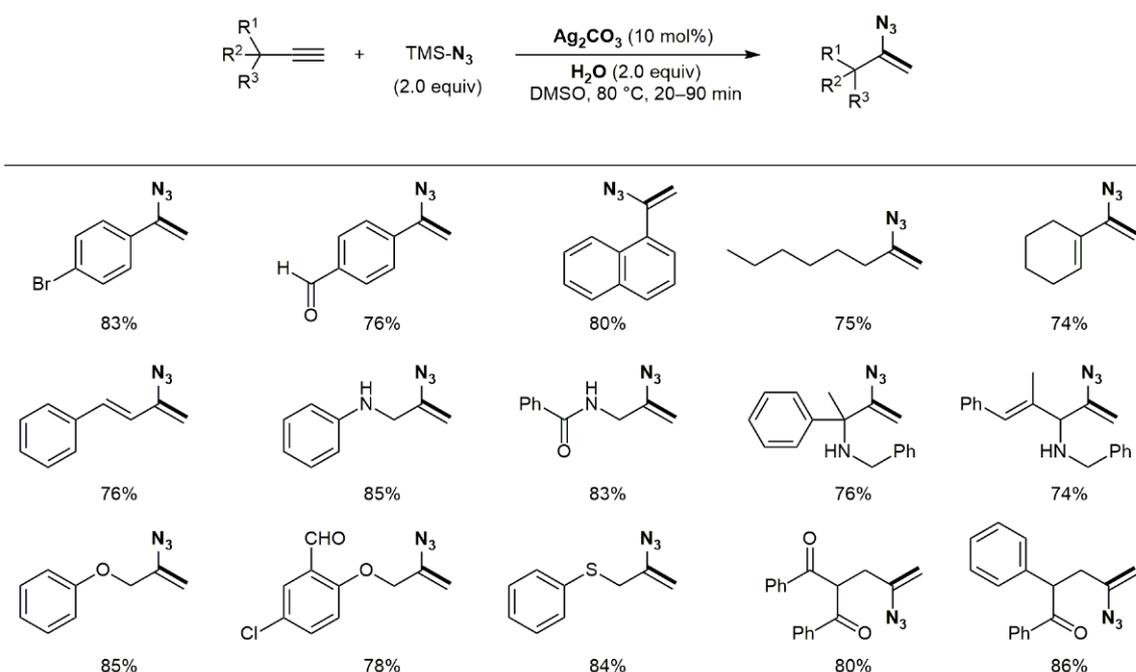


Scheme 2 Hydroxyl-dependent hydroazidation

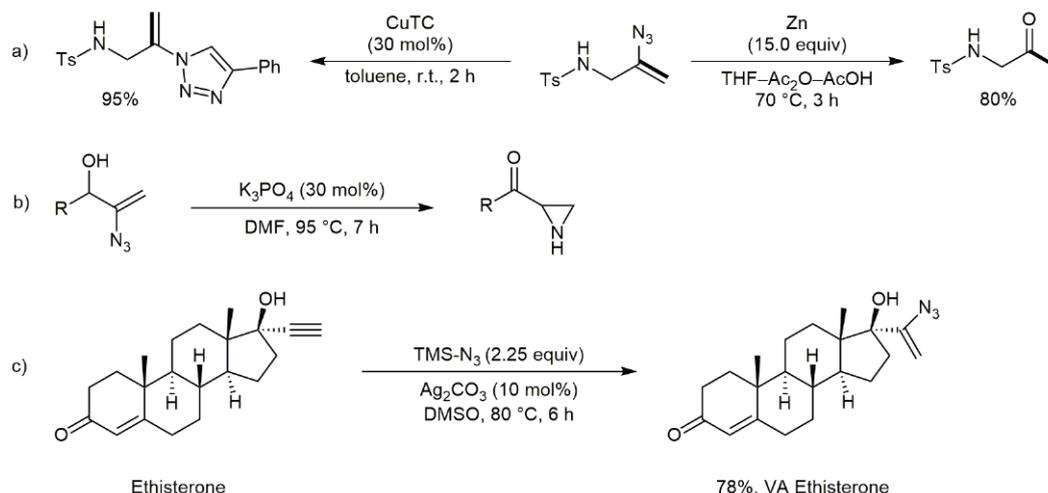
species and useful synthetic intermediates or building blocks. Specifically, hydroazidation of alkynes is an ideal route to obtain vinyl azides (*Angew. Chem. Int. Ed.* **2012**, *51*, 7511) and only a few reports are available for their synthesis. Most recently, Professor Xihe Bi and co-workers at Northeast Normal University (Changchun, P. R. of China) have demonstrated an efficient hydroazidation reaction of unactivated alkynes using silver catalysis and have applied it to the synthesis of structurally diverse vinyl azides from terminal alkynes with trimethylsilyl azide (TMS-N₃) (Scheme 1). In their continuous efforts to develop novel organic reactions using functionalized alkynes, Professor Bi's group subsequently accomplished a chemo- and regioselective silver-catalyzed hydroazidation of ethynyl carbinols with TMS-N₃, which afforded diverse 2-azidoallyl alcohols (Scheme 2) (*Angew. Chem. Int. Ed.* **2014**, *53*, 5305). In general, this alkyne hydroazidation reaction, whose success depends on the presence of a vicinal hydroxyl group, can be applied to a wide variety of secondary and tertiary ethynyl carbinols giving corresponding products within 1–2 hours in good to excellent yields. Professor Bi explained that in this reaction the hydroxyl group of ethynyl carbinols played a critical role as the proton source, and it is assumed that a trace amount of water in DMSO was also necessary to alleviate the need for a hydroxyl

group in the substrate and provide an alternative proton source. Further, this assumption was confirmed by experimental results.

In general, the hydroazidation reaction of diverse terminal alkynes with TMS-N₃ in the presence of H₂O has very broad scope and affords the corresponding vinyl azides in excellent yields (Scheme 3) (*Org. Lett.* **2014**, *16*, 3668). Professor Bi said: "Under the optimized reaction conditions, the effect of the stoichiometry of water was investigated at first with a model reaction and we found that in dry DMSO, a mixture of product and starting material was obtained in a ratio of 1:3 (determined by ¹H NMR analysis), whereas two equivalents of water were needed to yield the target vinyl azide as sole product." According to Professor Bi, these findings confirm that an appropriate amount of water is essential to generate HN₃. The effect of time on the reaction was also investigated and it was noticed that a proportional increase of product and consumption of substrate was observed. "This result proved the clean transformation from substrate to product," said Professor Bi. "Also, it must be mentioned that strict control of the reaction time was necessary in order to avoid the further conversion of vinyl azides into nitriles as previously reported by Jiao (*Angew. Chem. Int. Ed.* **2013**, *52*, 6677)." Under the optimized conditions, a library of vinyl azide derivatives was generated. In general, the substrate scope was quite broad and



Scheme 3 A general hydroazidation



Scheme 4 Synthetic utility of vinyl azides

diverse aryl-, alkyl-, and alkenyl-alkynes could be subjected to this silver-catalyzed procedure, thus affording the corresponding vinyl azides chemoselectively and in good to excellent yields within 20–90 min.

Professor Bi remarked: “In addition, the synthetic utility of vinyl azide was further demonstrated by the transformation of various vinyl azides into aziridine, triazole, α -amino ketone, and by the transformation of ethisterone into vinyl azide (VA) ethisterone without any change in their chiral centers and using known synthetic pathways (Scheme 4).”

Professor Bi concluded: “This novel and practical silver-catalyzed hydroazidation reaction has a broad substrate scope, good functional group tolerance, simple operation, and high reaction efficiency, thus providing an easy access to various functionalized vinyl azides. It opens up new prospects in synthetic and pharmaceutical chemistry for further exploiting the synthetic power of vinyl azides.”

Matteo Zanda

About the authors



Prof. X. Bi

Xihe Bi was born in Jilin (P. R. of China) in 1977. He obtained his BSc in 2000 and PhD in 2006 under the guidance of Professor Qun Liu at Northeast Normal University (P. R. of China). He spent two years (2006–2008) as an Alexander von Humboldt postdoctoral fellow with Professor Michael Famulok at Kekulé-Institut für Organische Chemie und Biochemie, University of Bonn (Germany). In 2013, he was promoted to Professor.

His research interests include functionalized alkynes, inert chemical bond transformations, and new organic reagents. He has received several honors and awards, including the Thieme Chemistry Journal Award 2014, the New Century Ex-

cellent Talents in University (2013) from The Ministry of Education of the People's Republic of China, and an Alexander von Humboldt research fellowship (2006) from Alexander von Humboldt-Stiftung.



Z. Liu

Zhenhua Liu was born in Shandong (P. R. of China) in 1986. He received his BSc in chemistry from Linyi University (P. R. of China) in 2010, and then joined the Department of Chemistry in the Northeast Normal University as a PhD candidate in 2011, working under the supervision of Professor Xihe Bi. His research interest concerns functionalized alkynes.