Decomposition of *N*-Sulfonylhydrazones to Diazoalkanes Goes to Room Temperature and Application to [2+1] Cyclopropenation with Alkynes

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It is well known that diazo compounds are outstanding building blocks in organic synthesis. Since their discovery over 100 years ago, these reagents have been frequently employed in a variety of processes, starting from homologation reactions to metal-catalyzed C–H insertions. However, due to their toxic and explosive nature, direct use of diazo compounds in many of these chemically interesting reactions and their utilization in large-scale production has been very difficult. To avoid these difficulties, chemists have developed a range of diazo surrogates as an alternative diazo source in numerous organic transformations. Thus, the organic chemistry community has devoted a lot of effort and interest in developing efficient protocols where these reagents could be generated in situ. To date, *N*-tosylhydrazones have proved to be some of the most useful diazo surrogates, because of their rapidly expanding repertoires of organic transformations. However, high dissociation temperature (≥70 °C) remains an inherent drawback of *N*-tosylhydrazones, and severely limits their use in synthetic areas where low reaction temperatures are generally employed, such as reactions of highly strained small rings, asymmetric and natural product synthesis. Great efforts have been devoted towards solving this challenging issue, but room-temperature decomposable *N*-sulfonylhydrazones remain unknown thus far.

Recently, this challenging issue has been addressed by the research group of Professor Xihe Bi at the Northeast Normal University (P. R. of China), who discovered for the first time the room-temperature decomposable property of *N*-nosylhydrazones. "We initially investigated the NaH-promoted dissociation of *N*-nosylhydrazone **1a** and *N*-tosylhydrazone **1a**′ at 25 °C and observed that the former smoothly released 4-chlorophenyl diazomethane, whereas the latter remained

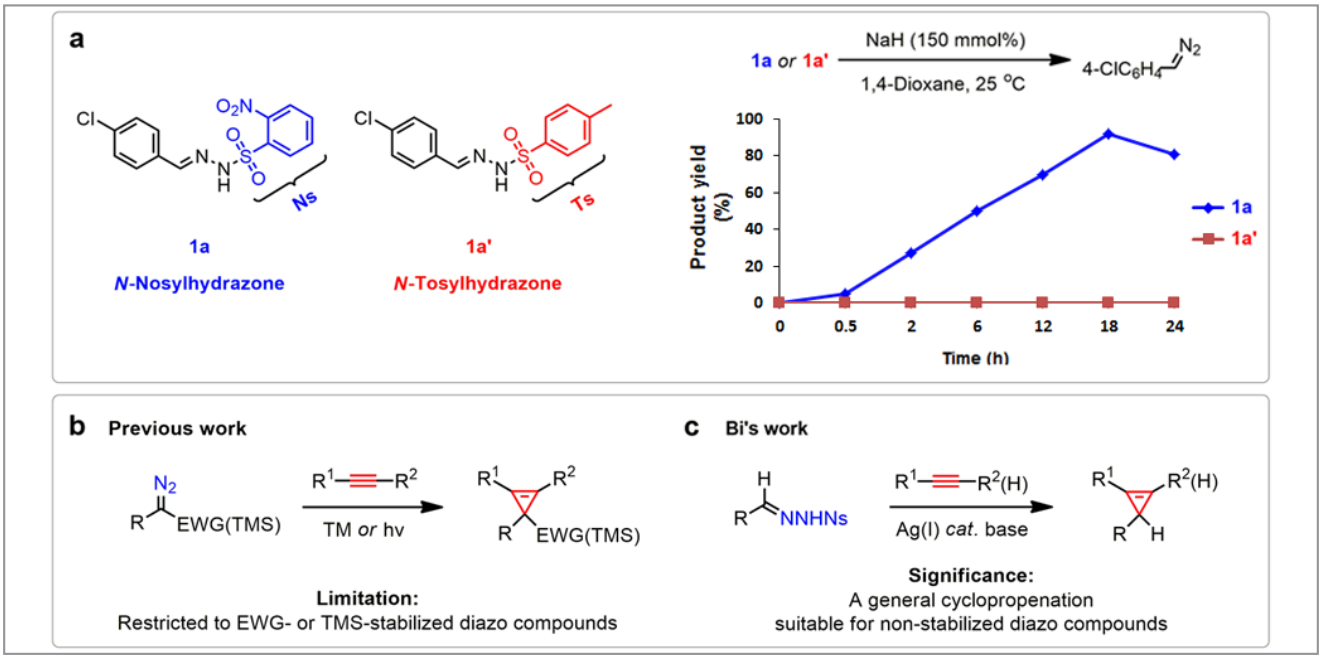

Figure 1 Comparison discovery of *N*-nosylhydrazones as room-temperature diazo surrogates, and cyclopropenation with alkynes; a: of the base-promoted dissociation of *N*-nosylhydrazones and *N*-tosylhydrazones at 25 °C, b,c: cyclopropenation of alkynes with diazo compounds

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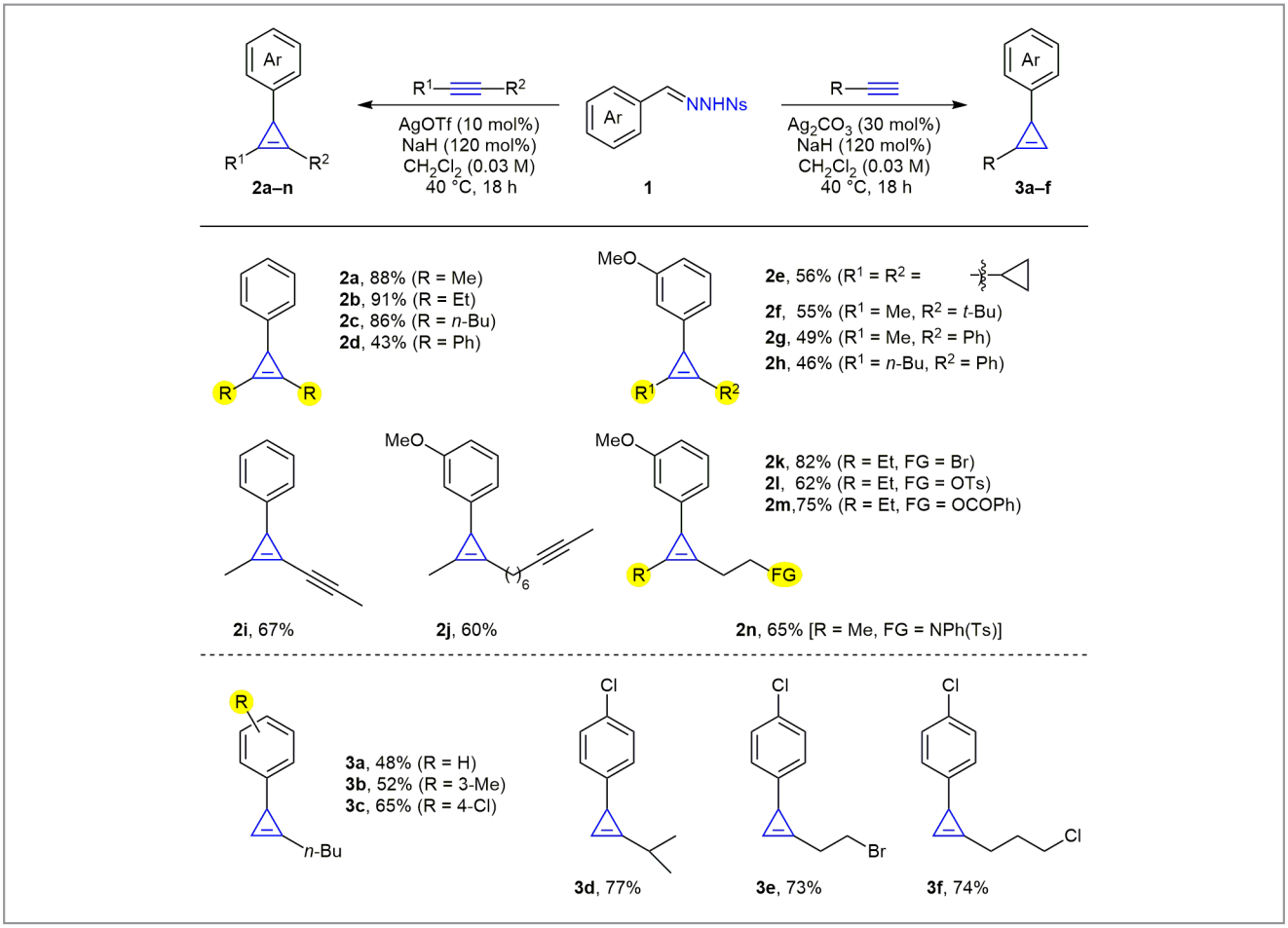
intact (Figure 1a)," said Professor Bi. "The significance of this discovery was demonstrated by overcoming the long-standing challenge in cyclopropene chemistry of non-stabilized diazo compounds not being suitable partners in the cyclopropenation of alkynes (Figure 1b,c)."

The reaction scope is quite broad (Scheme 1). "All the internal alkynes that we tested underwent the cyclopropenation with *N*-nosylhydrazones to afford the corresponding cyclopropenes (**2a–n**) with useful efficiencies (43–91% yield)," added Professor Bi. He continued: "A remarkable steric hindrance effect of alkyne substrates on the cyclopropenation reaction was observed. For example, the linear alkynes generally gave high yields (**2a–c**, 86–91%), whereas those with branched chains or a bulky phenyl ring led to gradually decreased product yields (**2d–h**, 43–56%). Notably, the most bulky 1,2-diphenylethyne also proved to be reactive, albeit with AgOTFA as catalyst. Diverse functionalities, including alkynyl, halogen, ester, and amino groups, were well tolerated, thus affording a range of functionalized cyclopropenes (**2i–n**, 60–82%)." The tolerance of the bromo group in the presence of a halophilic silver catalyst was especially noteworthy. Furthermore, under slightly modified conditions (Ag_2CO_3 as catalyst, highly diluted reaction solution), terminal alkynes also proved to be suitable reaction partners in this silver-catalyzed protocol, and afforded a group of difficult to synthesize 1-alkyl-3-arylcyclopropenes in good yields (**3a–f**, 48–77%).

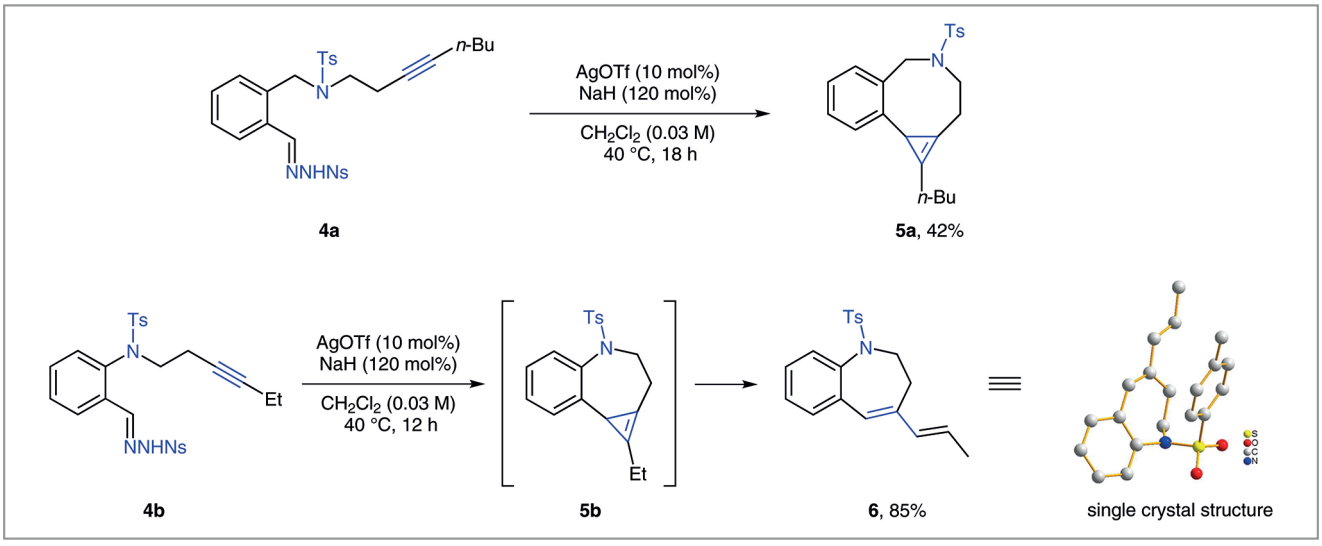
Subsequently, Bi and co-workers applied this silver-catalyzed protocol to the synthesis and isolation of more strained cyclopropenes that are otherwise difficult to obtain by other methods. As shown in Scheme 2, they eventually isolated the eight-member-fused cyclopropene **5a** in moderate yield (42%) starting from *N*-nosylhydrazone **4a**, in a diluted solution (0.03 M). In contrast, the reaction of substrate **4b**, which has one less carbon atom in the side-chain, progressed beyond the step of



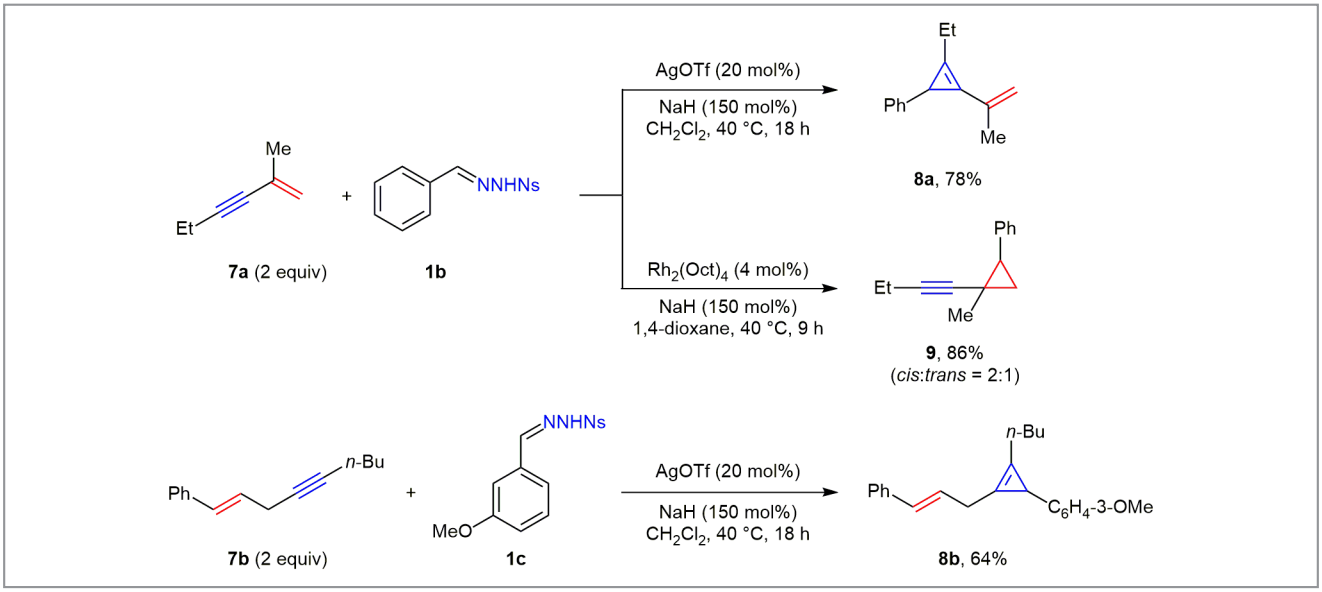
Scheme 1 Reaction scope

forming fused cyclopropene **5b**, giving the pharmacologically interesting benzo[*b*]azepine **6** in 85% yield by a regioselective ring-opening reaction. The structure of **6** was confirmed by X-ray crystallographic analysis.

"Interestingly, we found that the present silver-catalyzed protocol was applicable for the chemoselective cyclopropenation of enyne systems **7a** and **7b** with *N*-nosylhydrazones, thus providing the corresponding cyclopropenes **8a** and **8b** in good yields," said Professor Bi. However, the same reaction was carried out with rhodium catalysts, affording the alkynyl cyclopropanes **9** in 86% yield as a 2:1 mixture of *cis* and *trans* isomers. "Normally, silver catalysts do not favor the cyclopropenation selectivity in an enyne system, as reported by Davies and co-workers, who observed complete cyclopropanation of enyne **7a** with α-diazocarbonyl compounds under silver catalysis," said Professor Bi, who remarked: "These results clearly indicate the difference in the reactivity between *N*-nosylhydrazone and α-diazocarbonyl compounds. It is noteworthy



Scheme 2 Intramolecular reaction

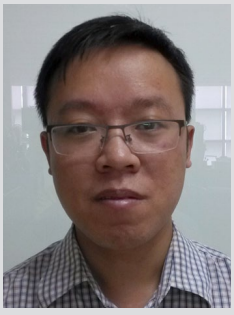


Scheme 3 Switchable chemoselectivity of cyclopropenation vs cyclopropanation

that the chemoselectivity, i.e. cylopropenation vs cyclopropanation, of the enyne system can be altered by choosing the appropriate diazo species and metal catalysts."

Finally, Professor Bi concluded: "*N*-Nosylhydrazones have been found for the first time as a room-temperature-decomposable diazo surrogate, and its synthetic application was demonstrated in the cyclopropenation of alkynes with donor-diazo compounds by silver catalysis. We have no doubt that this *N*-nosylhydrazone strategy will have a broad impact across diazo chemistry, especially for applications in asymmetric synthesis."

About the authors



Z. Liu

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Prof. X. Bi

Xihe Bi obtained his Ph.D. in 2006 from Northeast Normal University (P. R. of China). He then joined the group of Professor Michael Famulok at University of Bonn (Germany) as an Alexander von Humboldt Research Fellow. At the end of 2008, he started his independent research at Northeast Normal University. Professor Bi's research team mainly focuses on silver catalysis in organic synthesis. He has received honors and awards including the Young Scholar of the Changjiang Scholars Program of China (2016), the NSFC Foundation for Excellent Young Scientist (2015), the Thieme Chemistry Journals Award (2014), and the Alexander von Humboldt Research Fellowship (2006).

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