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Alkynyl *N*-Nosylhydrazones: Easy Decomposition to Alknynl Diazomethanes and Application for Allene Synthesis

Yang Yang,[§] Zhaohong Liu,[§] Alessio Porta, Giuseppe Zanoni* and Xihe Bi*

Abstract: The dissociation of *N*-tosylhydrazones is a safe and convenient method for the generation of donor carbenes. However, alkynyl carbenes cannot be isolated by this route because they readily undergo intramolecular cyclization to pyrazoles as soon as formed from alkynyl *N*-tosylhydrazones. Herein we report the use of alkynyl *N*-nosylhydrazones for the in situ generation of alkynyl carbenes and their coupling reaction with boronic acids under metal-free conditions, giving rise to a wide array of di- and trisubstituted allenes. Preliminary mechanistic investigations demonstrated that γ-protodeboration of propargyl boric acid was responsible for the initial allene formation. This methodology based on the nosyl group allows for novel transformations that involve an alkynylcarbene transient species.

Acetylenic carbenes, first obtained by Skell and Klebe in 1960,[1] are found in extreme chemical environments such as in interstellar space and in the atmosphere of Titan.[2] In addition, acetylenic carbenes and their derivatives are frequently used as versatile synthetic intermediates in organometallic chemistry and organic synthesis.[3-6] These carbene species are most commonly generated from Fischer carbene complexes,[4] from diynes by ring-closing and cross metathesis,[5] and from oligoynes possessing propargyl ester moieties by isomerization.[6] The preferred prevalent methods for the generation of free- or metal carbene species are photolytic, thermal or through metal-induced extrusion of nitrogen from diazo compounds.[7] Over the past decades, considerable efforts have also been put into the in situ generation of alkynyl carbenes from diazo precursors. Established synthetic methods include (1) the base treatment of sulfonylhydrazones[8] and *N*-nitroso-alkynylamines,[9] (2) the thermolysis of aziridinylimines,[10] (3) the dehydrogenation c hydrazones,[11] and (4) the decomposition c alkynyldiazoacetates.[12] However, investigations into th synthetically useful alkynyl carbenes generated in situ from diaz precursors have lagged behind the established knowledge c carbene chemistry. For example, *N*-tosylhydrazones are widel used as diazo surrogates of alkyl-, alkenyl-, or aryldiazomethane and have significantly contributed to the development of carben chemistry.[13] In contrast, despite their long history,[14] alkynyl *N* tosylhydrazones have been scantily used as precursors c alkynyldiazomethanes, because of the preferred intramolecula cyclization to pyrazoles (Figure 1a).[8e-8g] Hence, alkynyl *N* tosylhydrazones, first pioneered by McMahon, were restricted t work as triplet carbene precursors.[8] Notably, Thomson an Schaus reported the synthesis of allenes from alkynyl *N* nosylhydrazones by catalytic Traceless Petasis reactions, whic not involves carbene intermediates.[14c] Myers,[15a] Thomson[15b- and We[15d] have previously reported the readily decomposition c *o*-nosylhydrazides to allenes at room temperature. More recentl we have for the first time discovered the decomposition capabilit of *N*-nosylhydrazones at room-temperature, as opposed to th higher temperatures required for the dissociation of *N* tosylhydrazones.[16] As continued interest in the syntheti potential of such kind of compounds, we propose the use c alkynyl *N*-nosylhydrazones, instead of alkynyl *N*-tosylhydrazone for the expeditious in situ generation of alkynyl carbenes. Wit this nosyl based strategy, the pyrazole formation was suppressec thus opening new opportunities for alkynylcarbene-base transformations (Figure 1b). Herein, we report the new couplin with boric acids to from allenes.

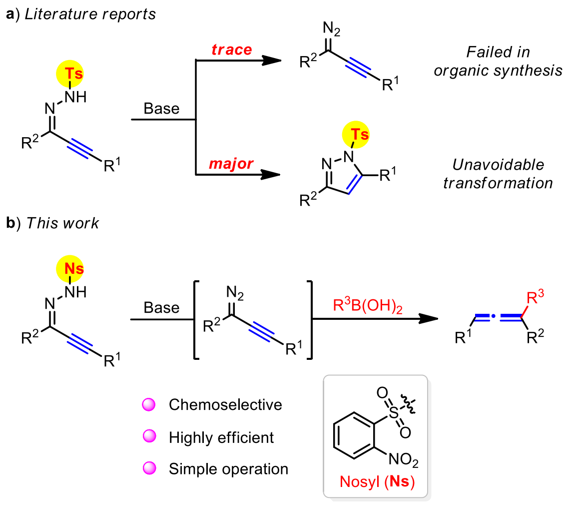

Figure 1. [2+1] Cylopropenation of alkynes with diazo surrogates.

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Allenes are crucial structural motifs in a variety of bioactive molecules and natural products,[17] and useful building blocks or intermediates in organic synthesis.[18] Despite great achievements in the allene synthesis by metal-mediated direct coupling of two fragments,[19] an analogous metal-free reactions remain extremely limited to date.[14c, 20] Taking cue from the carbon-carbon bond-forming reaction between boronic acids and diazo compounds under metal-free conditions,[21] we envisaged that a base could promote the coupling of alkynyl *N*-nosylhydrazones with boronic acids to afford allenes. In an initial experiment, alkynyl *N*-nosylhydrazone **1a** was reacted with phenylboronic acid **2a**, in the presence of K_2CO_3 in 1,4-dioxane at 110 °C, to afford an inseparable mixture of propyne 3a and allene **4a** in 64% yield (measured by ^{1}H-NMR; for experimental details see supporting information). Product 3a was conveniently converted to allene 4a by stirring the crude reaction mixture at room temperature in the presence of KOH and *tert*-butylammoiunm bromide (TBAB). After screening of a variety of bases, solvents, and reaction temperatures, the best yield of the expected allene was achieved with sodium hydride (NaH) as base in toluene at 60 °C (Figure 2a). Notably, the reaction between alkynyl *N*-tosylhydrazones **1a'** and phenylboronic acid **2a**, performed under identical conditions, afforded pyrazole **5a'** in 90% yield with a trace amount of alkyne **3a** (Figure 2b). Therefore, the type of sulphonyl group in the hydrazone plays a decisive role on the reactivity of the alkynyl *N*-sulphonylhydrazones.

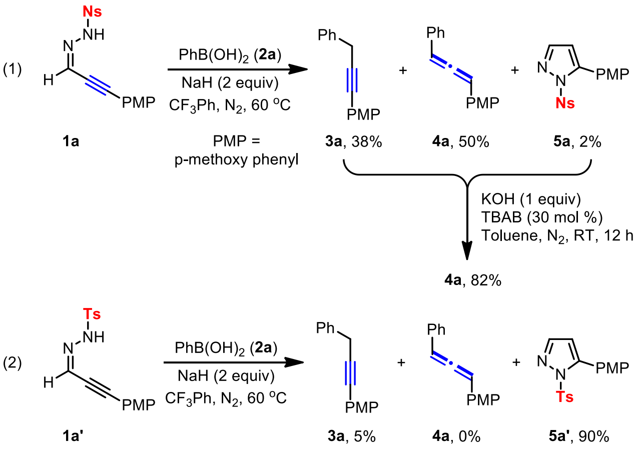
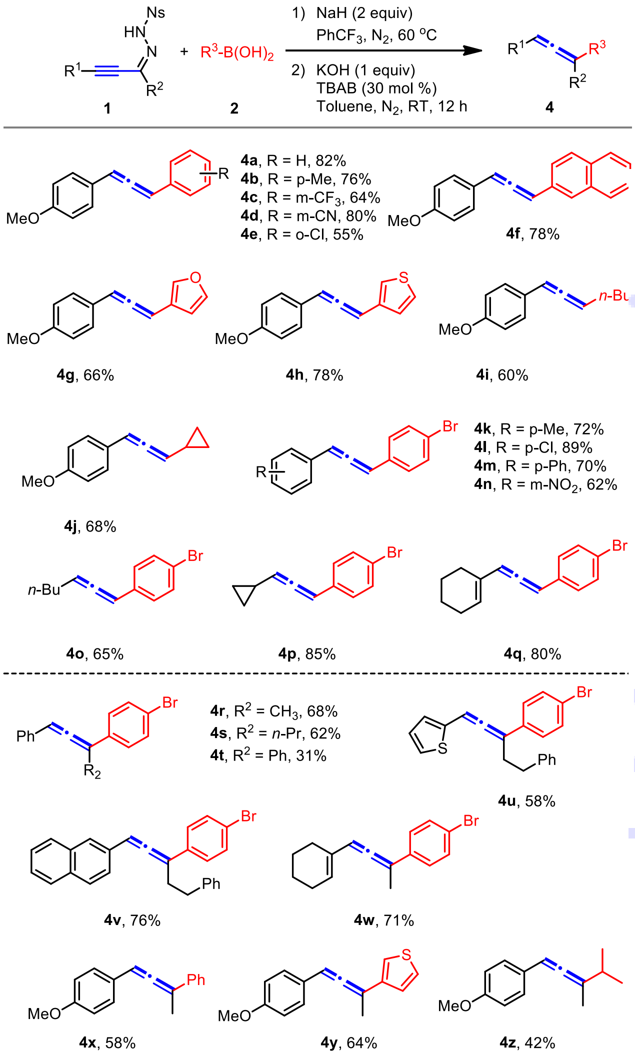


Figure 2. Different reactivity of *N*-tosyl and *N*-nosylhydrazones.

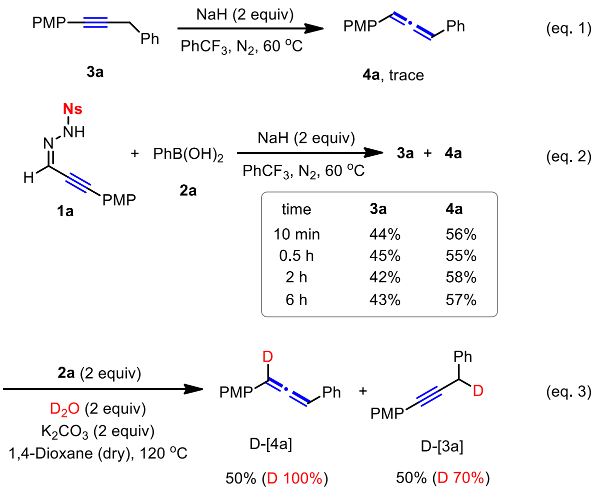
With these optimized conditions in hand, we investigated the scope of this novel transformation (Scheme 1). Using alkynyl *N*-nosylhydrazone **1a**, a productive conversion to allenes was achieved with a variety of aryl, heteroaryl, and alkyl boronic acids. Aryl boronic acids with different electron-donating (Me) and electron-withdrawing groups (CF_3, CN, Cl) at the *para*, *meta*, or *ortho* positions efficiently provided 1,3-diarylallenes (**4b-4e**) in good yield (55% to 82%). Gratifyingly, the reactions with naphthyl (**1f**) and two heteroaryl boronic acids (**1g** and **1h**) also proceeded smoothly, producing the corresponding allenes in good yields. The reaction performed well with aliphatic boronic acids (**1i** and **1j**), too. We then investigated the reaction scope for *N*-nosylhydrazones with a variety of substituents on the phenyl ring, obtained from a variety of alkynals, with *p*-bromo-phenylboronic acid. Aryl substituents such as methyl, chloro, and nitro groups did not negatively impact on the reaction, affording the target allenes in good yields (**4k-4n**, 62% to 89%, Scheme 1). In addition, we found that alkynyl *N*-nosylhydrazones with an alkyl or alkenyl moiety smoothly converted to the corresponding disubstituted allenes in synthetically useful yields (**4o-4q**, 65% to 85%, Scheme 1). Of note, the conjugated alkenyl allene **4q** is an important synthon in organic synthesis.[22]



Scheme 1. Substrate scope. Reaction conditions: Step 1: *N*-nosyhydrazone **1** (0. mmol), boronic acid **2** (0.6 mmol), NaH (0.6 mmol) and $PhCF_3$ (3 mL) were stirre at 60 °C for 2 h under inert atmosphere. Step 2: KOH (1.0 equiv) and TBAB (3 mol %) in toluene at RT under inert atmosphere for 12 h.

Encouraged by these results, we attempted to expand th scope of this metal-free synthetic methodology to the synthesis o trisubstituted allenes. A wide range of *N*-nosylhydrazones o alkynones reacted smoothly with *p*-bromo-phenylboronic acid, providing various trisubstituted allenes in moderate to good yield (**4r-4w**, 31% to 76%, Scheme 1). A diaryl-substituted alkynyl *N*-nosylhydrazone gave the triaryl allene **4t** in somehow reduced yield, presumably because of steric hindrance that would result in an increased proclivity to undergo the intramolecular cyclization to pyrazole. Phenyl, 3-thiophenyl, and isopropyl boronic acid participated in the coupling reaction efficiently, to give the corresponding trisubstituted allenes in synthetically meaningful yields (**4x-4z**, 42% to 58%). The overall excellent scope of reactivity and the broad tolerance of functional groups make this metal-free reaction amenable to routine chemical synthesis. We have therefore devised a novel approach to di- and trisubstituted allenes by the coupling under metal-free conditions of readily available alkynyl *N*-nosylhydrazones with commercially available boronic acids.

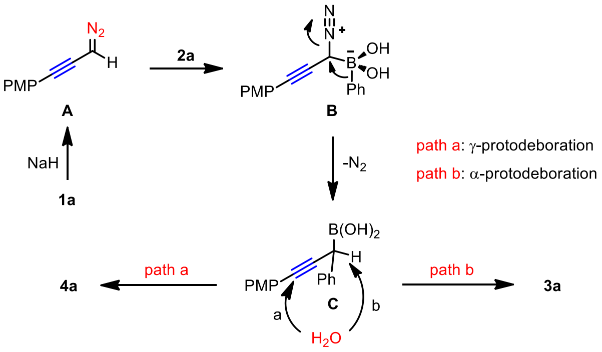
Mechanistic studies were undertaken to unravel the reaction pathway. When alkyne **3a** was independently synthesized and subjected to the standard basic conditions for the known rearrengement to allene,[23] only a trace amount of allene **4a** was observed (Scheme 2, eq. 1). Interestingly, the ratio of allene **4a** and alkyne **3a** did not change with reaction time (Scheme 2, eq. 2). These results seem to refute the notion that allene **4a** would form by rearrangement of alkyne **3a**. Reaction of **1a** with **2a** in anhydrous 1,4-dioxane at 110 °C in the presence of D_2O (2.0 equiv) led to the formation of deuterated allene D-[**4a**] with 100% deuterium content, and of deuterated alkyne D-[**3a**] with 70% deuterium content (Scheme 2, eq. 3). These results clearly indicated that the adventitious water in the reaction solvent was the proton source of the products.



time	3a	4a
10 min	44%	56%
0.5 h	45%	55%
2 h	42%	58%
6 h	43%	57%

Scheme 2. Investigation on the reaction mechanism.

Based on our results and on previous reports,[21] we propose a possible mechanism for this reaction (Scheme 3). The alkynyl *N*-nosylhydrazone (**1a**) would undergo a base-promoted Bamford-Stevens rearrangement, leading to an unstabilized alkynyldiazomethane (**A**). The latter would immediately react with phenylboronic acid (**2a**) to give a propargyl boronic acid (**C**) *via* a 1,2-migration of the phenyl group from boron to carbon in boronate intermediate (**B**). A γ-protodeboration[24] of propargyboronic intermediate (**C**) under the given basic conditions would lead to the major product allene **4a** (Scheme 3, path a). To our knowledge, this would notably be the first example of a γ-protodeboration involving a carbon-carbon triple bond. Intermediate (**C**) could also generate the minor product propyne **3a** by α-protodeboration (Scheme 3, path b).[21]



Scheme 3. Postulated reaction pathway.

In conclusion, with our work the expediency of th dissociation of alkynyl *N*-sulfonylhydrazones into alkyny diazomethanes was realized for the first time by incorporating th nosyl group in the substrate. The synthetic potential alkynyldiazomethanes was demonstrated by their unprecedente coupling with boronic acids in the absence of metals, giving a easy access to a wide range of allenes. Preliminary mechanisti studies implied a γ-protodeboration of the intermediate alkyny propargyl boric acid may be responsible for the formation of th allene product.

Acknowledgements

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Keywords: acetylenic carbene • *N*-nosylhydrazone • boronic acid • allene • coupling reaction

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***N*-Nosylhydrazones**———————

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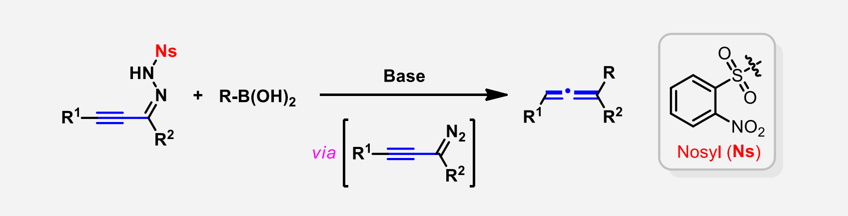
Alkynyl *N*-Nosylhydrazones: Easy Decomposition to Alknynl Diazomethanes and Application for Allene Synthesis



Formation of pyrazole by-product is the frequently encountered side reaction in the dissociation of alkynyl-*N*-sulfonylhydrazones, which represents a long-standing challenge for chemists to generate acetylenic carbenes for thereafter applications. We resolved this by means of introduction of nosyl group in the place of tosyl moiety of alkynyl-*N*-tosylhydrazones, thus generating the required acetylenic carbenes for the coupling/isomerization reactions with aryl/alkyl boronic acids.