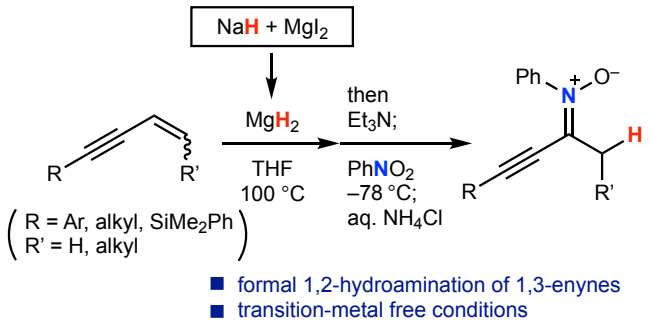
Synthesis of α-alkynylnitrones via hydromagnesiation of 1,3-enynes with magnesium hydride

Yihang Li,[a] Jia Sheng Ng,[a] Bin Wang,[a] and Shunsuke Chiba*[a]

[a]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore.

Supporting Information Placeholder

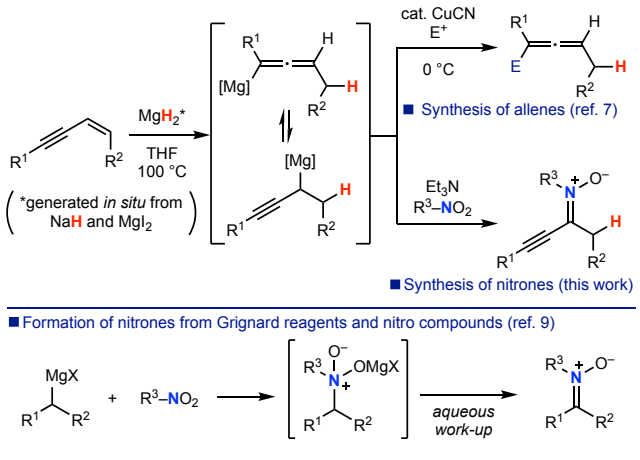


ABSTRACT: A protocol for the synthesis of α-alkynylnitrones from 1,3-enynes has been developed. The process is triggered by hydromagnesiation of 1,3-enynes with magnesium hydride (MgH_2), which is prepared *in situ* through solvothermal treatment of magnesium iodide (MgI_2) with sodium hydride (NaH) in THF. Downstream functionalization of the resulting propargylmagnesium intermediates with organo nitro compounds affords α-alkynylnitrones, which could be used as versatile precursors for the construction of various nitrogen-containing compounds.

Among carbon-carbon unsaturated π-conjugated systems, readily accessible 1,3-enynes[1] exhibit versatile reactivity toward a series of molecular transformations.[2] As the current state-of-the-art methods, transition-metal-catalyzed hydrofunctionalization of 1,3-enynes has been performed typically in a 1,2/1,4-hydrometallation mode, that is followed by downstream functionalization with various electrophiles to form substituted allenes[3] or alkynes.[4]

We have recently disclosed that magnesium hydride (MgH_2),[5] generated *in situ* by the solvothermal treatment of magnesium iodide (MgI_2) with sodium hydride (NaH) in tetrahydrofuran (THF),[6] exhibited unique hydridic reactivity to induce 1,2/1,4-hydromagnesiation of 1,3-enynes without the aid of transition-metal catalysts (Scheme 1).[7,8] The resulting organomagnesium intermediates as an equilibrium mixture of allenyl- and propargylmagnesium species could be functionalized with electrophiles (E^+) such as alkyl and silyl halides in the presence of copper(I) cyanide (CuCN) as a catalyst, affording multi-substituted allenes. In seeking for different electrophiles for selective downstream functionalization of the organomagnesium intermediates derived from 1,3-enynes and MgH_2, our attention was directed at the Bartoli's reports on the synthesis of nitrones by the treatment of Grignard reagents with nitro compounds.[9] We surmised if the downstream treatment of the organomagnesium intermediates derived from 1,3-enynes and MgH_2 with nitro compounds enables selective propargylic functionalization, thus affording synthetically useful α-alkynylnitrones. The reaction optimization, substrate scope and synthetic applications of the method are described herein.

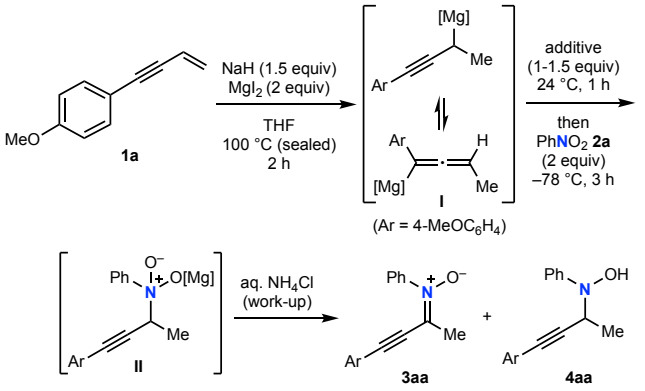
Scheme 1. Hydromagnesiation of 1,3-enynes and downstream functionalization



At the outset of the project, we optimized the reaction conditions using 1,3-enyne **1a** and nitrobenzene ($PhNO_2$, **2a**) as the model substrates (Table 1). Treatment of organomagnesium intermediates **I**, generated by the reaction of **1a** with sodium hydride (NaH, 1.5 equiv) and magnesium iodide (MgI_2, 2 equiv)

at 100 °C for 2 h, with nitrobenzene (**2a**) (2 equiv) at –78 °C followed by aqueous work-up with aqueous ammonium chloride (NH_4Cl) solution provided desired α-alkynylnitrone **3aa** in 68% NMR yield (63% isolated yield) along with *N*-propargylhydroxylamine **4aa** in 9% NMR yield, which was formed probably via over-reduction of the tetrahedral intermediate **II** by the remaining magnesium hydride (entry 1).[9b] Reduction of the amount of nitrobenzene (**2a**) to 1.2 equiv diminished the yield of **3aa** (entry 2). We observed that addition of tertiary amines (1-1.5 equiv) to a solution of the organomagnesium intermediates in prior to the treatment with nitrobenzene (**2a**) could suppress the over-reduction (entries 3-6), where tertiary amines might serve as a chelating ligand to the magnesium cations.[10] Among the tertiary amine additives screened, use of triethylamine (Et_3N) was found to be optimal to provide nitrone **3aa** as a sole product in good yields (entries 5 and 6). The reaction of **1a** in 7 mmol scale did not diminish the isolated yield of **3aa**, proving the scalability of the process (entry 7).

Table 1. Optimization of the reaction conditions[a]

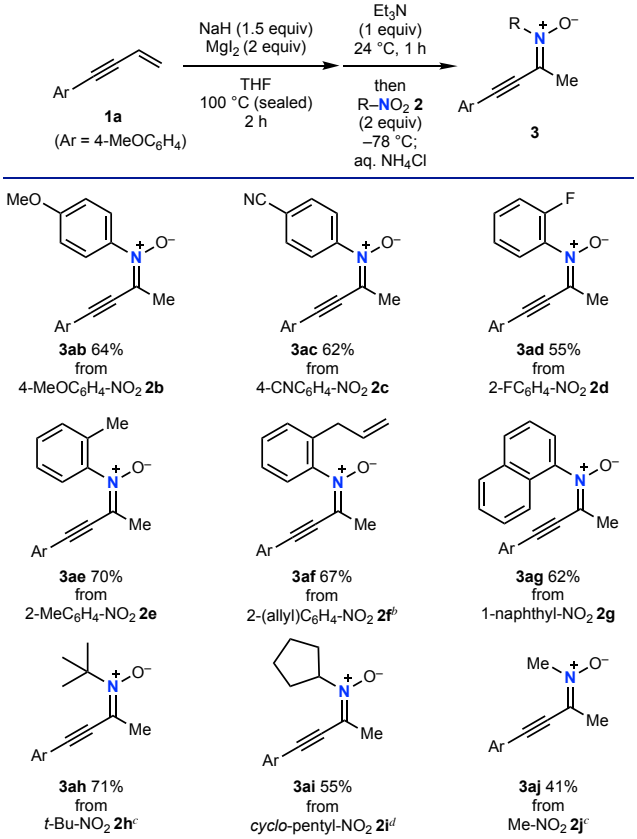


Entry	Additive (equiv)	Yield of **3aa** [%][b]	Yield of **4** [%][b]
1	none	68 (63)[c]	9
2[c]	none	61	10
3	TMEDA (1.5)	66	–
4	DMAP (1.5)	70	–
5	Et_3N (1.5)	76 (73)[d]	–
6	Et_3N (1)	76 (72)[d]	–
7[e]	Et_3N (1)	(78)[d]	–

[a] Reaction conditions: **1a** (0.5 mmol), NaH (1.5 equiv), MgI_2 (2 equiv), THF (2.5 mL, 0.2 M), 100 °C (sealed, oil bath) for 2 h; then additive (1-1.5 equiv) at room temperature (24 °C), 1 h; then $PhNO_2$ **2a** (2 equiv), –78 °C (dry ice-acetone bath) for 3 h before work-up with saturated aq. NH_4Cl solution. [b] ^1H NMR yields based on the internal standard were recorded. [c] The amination step was conducted using **2a** in 1.2 equiv for 4.5 h. [d] Isolated yields in parenthesis. [d] The reaction was performed using 7 mmol of **1a**. TMEDA = tetramethylethylenediamine. DMAP = 4-dimethylaminopyridine.

The synthesis of α-alkynylnitrones has been underdeveloped and successful examples are limited to the oxidative cross-coupling between aldonitrones and alkynyl Grignard reagents reported by Studer.[11,12] Therefore, we next examined the substrate scope with respect to the nitro compounds for the synthesis of α-alkynylnitrones **3** from 1,3-enyne **1a** (Scheme 2). Various nitroarenes including electron-rich (for **2b**), electron-deficient (for **2c** and **2d**), and sterically hindered ones (for **2e**-**2g**) were found to be compatible for the downstream functionalization to give the corresponding *N*-arylnitrones **3ab**-**3ag** generally in good yields.[13] As for nitroalkanes, use of 2-methyl-2-nitropropane (**2h**) allowed for installation of a removable *tert*-butyl group on the nitrogen of nitrone **3ah**. Similarly, employment of nitrocyclopentane (**2i**) resulted in smooth introduction of a *cyclo*-pentyl group (for **3ai**), while the reaction with nitromethane (**2j**) resulted in formation of *N*-methylnitrone **3aj** in moderate yield.

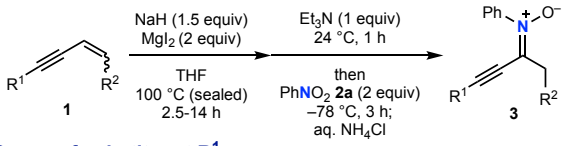
Scheme 2. Scope of organo nitro compounds 2[a]



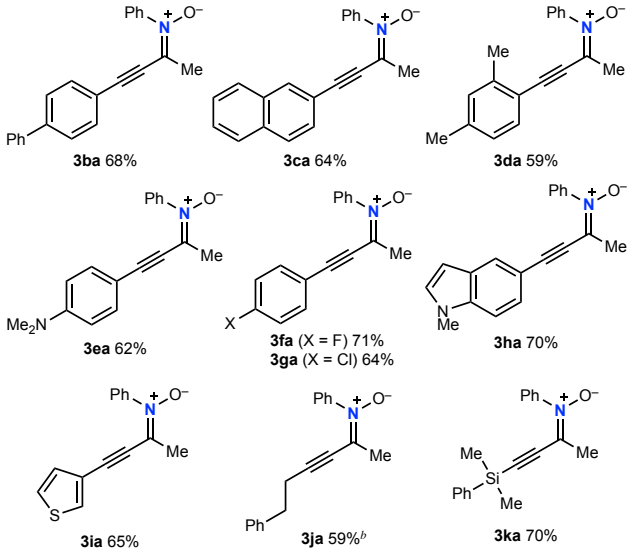
[a] Reaction conditions: **1a** (0.5 mmol), NaH (1.5 equiv), MgI_2 (2 equiv), THF (2.5 mL, 0.2 M), 100 °C (sealed, oil bath) for 2 h; then Et_3N (1 equiv) at room temperature (24 °C), 1 h; then nitro compounds **2** (2 equiv), –78 °C (dry ice-acetone bath) for 1.5 – 3 h before work-up with saturated aq. NH_4Cl solution. (see the Supporting Information for details). Isolated yields of **3** were recorded. [b] The reaction was conducted using 1 mmol of **1a**. [c] Nitroalkane **2h** or **2j** was added at 0 °C (ice-water bath) and the reaction mixture was stirred at the same temperature for 20 h. [d] Nitrocyclopentane (**2i**) was added at 24 °C and the reaction mixture was stirred at the same temperature for 20 h.

Next, the substituent compatibility on the 1,3-enynes **1** was investigated using nitrobenzene (**2a**) for the downstream functionalization (Scheme 3). As for the substituent R^1 (Scheme 3A), the method was amenable to install a series of aryl (for **3ba**-**3ga**) and heteroaryl (for **3ha** and **3ia**) group efficiently. Alkyl-substituted alkynylnitrone (**3ja**) could be synthesized in 59% yield. It should also be noted that the protocol was compatible to employ silyl-substituted enyne **1k**, affording **3ka** in 70% yield. We found that the method can engage internal alkenes having alkyl substituents as the R^2 to provide nitrones **3la**-**3na** in good to moderate yields (Scheme 3B).

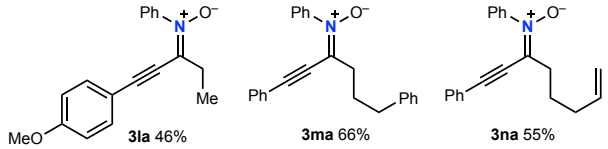
Scheme 3. Scope of 1,3-enynes 1[a]



A. Scope of substituent R^1



B. Scope of substituent R^2

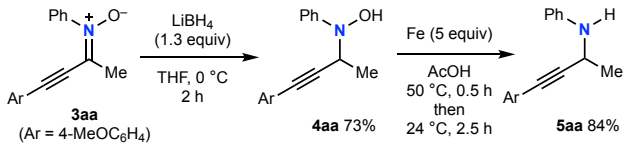


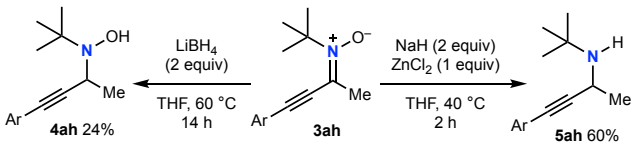
[a] Reaction conditions: **1** (0.5 mmol), NaH (1.5 equiv), MgI_2 (2 equiv), THF (2.5 mL, 0.2 M), 100 °C (sealed, oil bath) for 2.5-14 h; then Et_3N (1 equiv) at room temperature (24 °C), 1 h; then $PhNO_2$ **2a** (2 equiv), –78 °C (dry ice-acetone bath) for 3 h before work-up with saturated aq. NH_4Cl solution. Isolated yields of **3** were recorded. [b] Hydromagnesiation was conducted using NaH (1.5 equiv) and MgI_2 (1.5 equiv).

Having developed the method for the construction of α-alkynylnitrones **3**, our next attention was directed to demonstrate their derivatization (Scheme 4). Hydride reduction of *N*-phenyl nitrone **3aa** with lithium borohydride ($LiBH_4$) afforded *N*-propargylhydroxylamine **4aa** in good yield (Scheme 4A).[14] Subsequent treatment of **4aa** with iron (Fe) powder in acetic acid (AcOH) induced deoxygenation to form propargylamine **5aa** with keeping the alkynyl moiety intact. On the other hand, reduction of *N*-*tert*-butyl nitrone **3ah** with $LiBH_4$ became sluggish, affording the corresponding hydroxylamine **4ah** in 24% yield. In turn, we found that reduction of **3ah** by the NaH-$ZnCl_2$ system, which was recently developed for controlled reduction of carboxamides and carbonitriles by our group,[15] directly provides propargylamine **5ah** in 60% yield. Conversion of *N*-*tert*-butyl nitrone **3ah** into isoxazole **6** was successfully implemented by following the Studer's protocol[11] that employs boron trichloride (BCl_3) in 1,2-dichloroethane (Scheme 4B). One of the features of the present method is its ability in facile installation of an alkene tether on the α-alkynylnitrone scaffolds (e.g. synthesis of **3af** and **3na**), which could be utilized for the ensuing intramolecular 1,3-dipolar [3+2]-cycloaddition.[16,17] Thus, solvothermal treatment of **3na** in chlorobenzene (PhCl) at 80 °C resulted in smooth cycloaddition to form diastereomerically

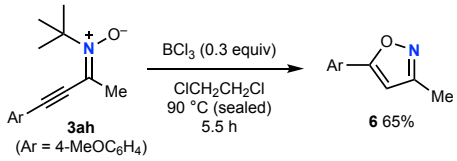
Scheme 4. Derivatization of α-alkynylnitrones 3

A. Controlled reduction of nitrones

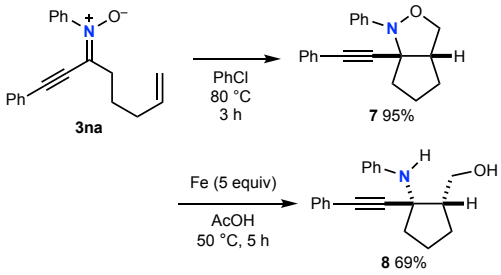




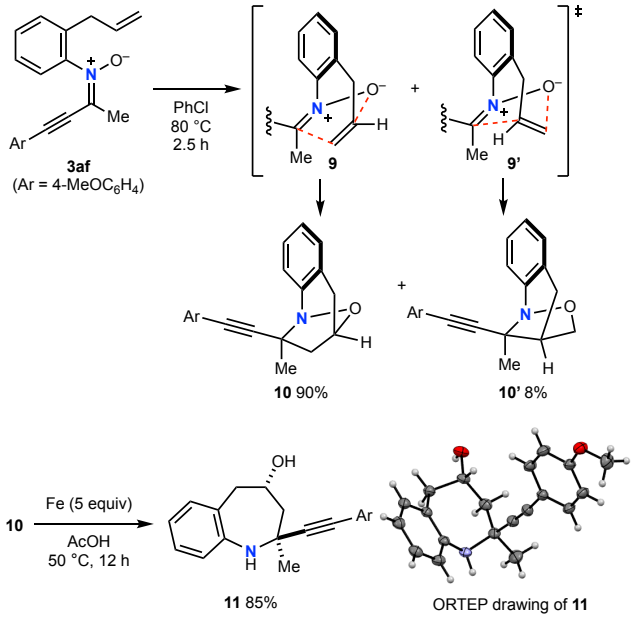
B. Construction of isoxazole



C. Intramolecular 1,3-dipolar cycloaddition of 3na



D. Intramolecular 1,3-dipolar cycloaddition of 3af



pure bicyclic isoxazolidine **7**. The reductive N-O bond fission of **7** with Fe powder in AcOH delivered polysubstituted cyclopentane **8**. Similarly, intramolecular 1,3-diploar [3+2]-cycloaddition of **3af** proceeded selectively via transition state **9** to form tetrahydro-1,4-epoxybenzo[*b*]azepine **10** as the major product, along with the formation of 4,5-dihydro-3*H*-1,4-methanobenzo[*c*][1,2]oxazepane **10'** in 8% yield via another twisted transition state **9'** (Scheme 4D). The reductive N-O bond

cleavage of **10** allowed for assembly of diastereomerically pure tetrahydro-1*H*-benzo[*b*]azepin-4-ol **11**.[18]

This work demonstrated synthesis of α-alkynylnitrones from 1,3-enynes via hydromagnesiation with magnesium hydride followed by downstream treatment with nitro compounds. The process operates under transition-metal free conditions, offering a concise access to synthetically valuable α-alkynylnitrones. Given the broad substrate scope of the present protocol and the synthetic potentials of α-alkynylnitrones, we view the present method to be viable in various synthetic endeavors.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Crystallographic data for compounds **3ab** and **11** (CIF)
Experimental procedures, spectral data (PDF)
FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds **1a-1n**, **3aa-3aj**, **3ba-3na**, **4aa**, **4ah**, **5aa**, **5ah**, **6**, **7**, **8**, **10**, **10'**, and **11**

AUTHOR INFORMATION

Corresponding Author

* E-mail: shunsuke@ntu.edu.sg.

Notes

The authors declare no competing interest.

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