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Synthesis of α-Alkynylnitrones via Hydromagnesiation of 1,3-Enynes with Magnesium Hydride

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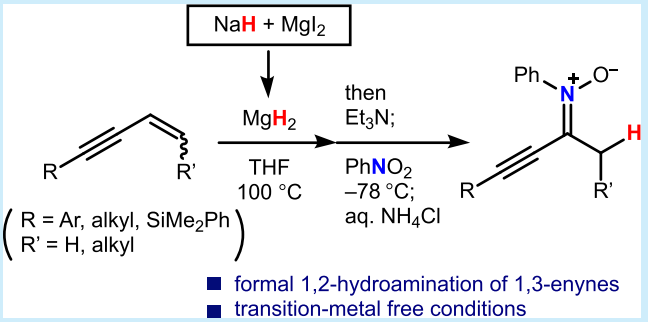
ABSTRACT: A protocol for the synthesis of α-alkynylnitrones from 1,3-enynes has been developed. The process is triggered by hydromagnesiation of 1,3-enynes with magnesium hydride (MgH_2), which is prepared *in situ* through solvothermal treatment of magnesium iodide (MgI_2) with sodium hydride (NaH) in tetrahydrofuran. 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.



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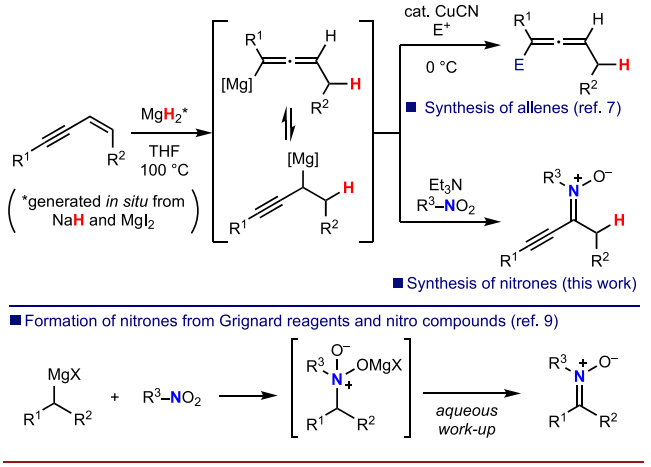
Among carbon−carbon unsaturated π-conjugated systems, readily accessible 1,3-enynes[1] exhibit versatile reactivity toward a series of molecular transformations.[2] As the current state-of-the-art methods, transition-metal-catalyzed hydrofunctionalization of 1,3-enynes has been performed typically in a 1,2/1,4-hydrometalation mode, which 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 multisubstituted allenes. In the search for different electrophiles for selective downstream functionalization of the organomagnesium intermediates derived from 1,3-enynes and MgH_2, our attention was directed at Bartoli's reports about 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.

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 organo-

Scheme 1. Hydromagnesiation of 1,3-Enynes and Downstream Functionalization



magnesium 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 workup with an aqueous ammonium chloride (NH_4Cl) solution provided the desired α-alkynylnitrone **3aa** in 68% NMR yield (63% isolated yield) along with *N*-propargylhydroxylamine **4aa** in 9% NMR

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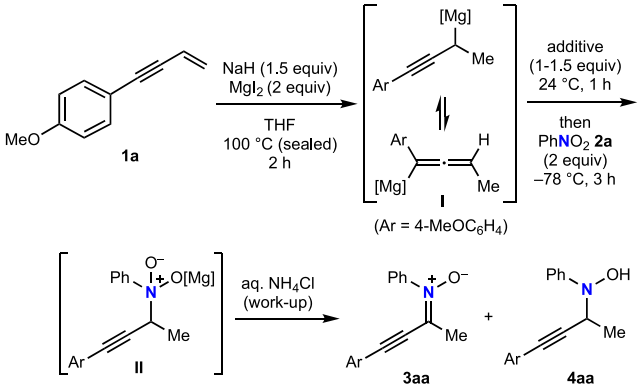
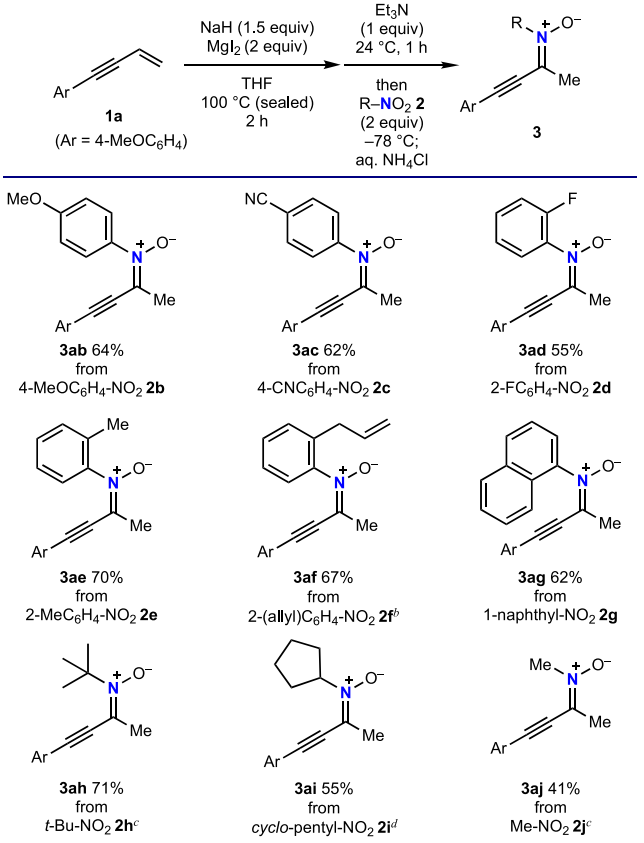
Table 1. Optimization of the Reaction Conditions[a]



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

[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) for 1 h; then $PhNO_2$ **2a** (2 equiv), −78 °C (dry ice/acetone bath) for 3 h before workup with a saturated aqueous NH_4Cl solution. Abbreviations: TMEDA, tetramethylethylenediamine; DMAP, 4-dimethylaminopyridine. [b]^1H NMR yields based on the internal standard were recorded. [c]Isolated yields in parentheses. [d]The amination step was conducted using 1.2 equiv of **2a** for 4.5 h. [e]The reaction was performed using 7 mmol of **1a**.

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) for 1 h; then nitro compounds **2** (2 equiv) at −78 °C (dry ice/acetone bath) for 1.5−3 h before workup with a saturated aqueous 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.

yield, which was formed probably via over-reduction of 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 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 the sole product in good yields (entries 5 and 6). The reaction of **1a** on a 7 mmol scale did not diminish the isolated yield of **3aa**, proving the scalability of the process (entry 7).

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 (for **2e**−**2g**) forms, 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 the smooth introduction of a cyclo-pentyl group (for **3ai**), while the reaction with nitromethane (**2j**) resulted in the formation of *N*-methylnitrone **3aj** in moderate yield.

Next, the substituent compatibility on the 1,3-enynes **1** was investigated using nitrobenzene (**2a**) for the downstream functionalization (Scheme 3). As for substituent R^1 (Scheme 3A), the method was amenable to efficient installation of a series of aryl (for **3ba**−**3ga**) and heteroaryl (for **3ha** and **3ia**) groups. Alkyl-substituted alkynylnitrone **3ja** could be synthesized in 59% yield. It should also be noted that the protocol was compatible with employment of 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).

Having developed the method for the construction of α-alkynylnitrones **3**, we next directed our attention to demonstrating 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)

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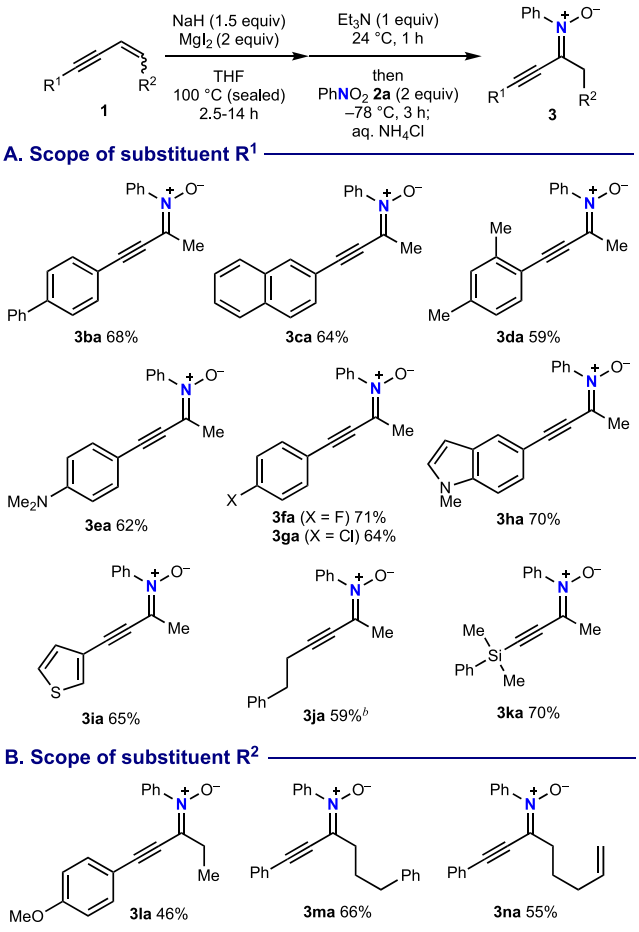
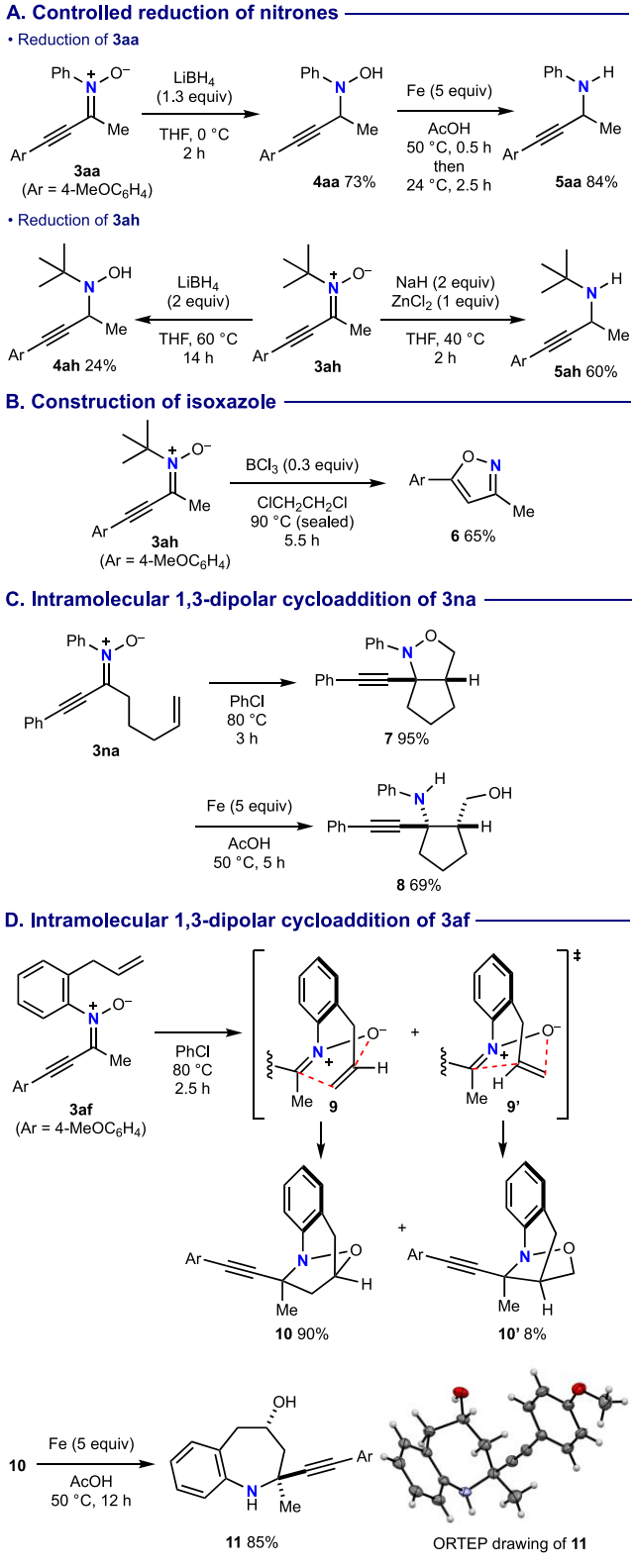
Scheme 3. Scope of 1,3-Enynes 1[a]



[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) for 1 h; then $PhNO_2$ **2a** (2 equiv) at −78 °C (dry ice/acetone bath) for 3 h before workup with a saturated aqueous NH_4Cl solution. Isolated yields of **3** were recorded. [b]Hydromagnesiation was conducted using NaH (1.5 equiv) and MgI_2 (1.5 equiv).

Scheme 4. Derivatization of α-Alkynylnitrones 3



powder in acetic acid (AcOH) induced deoxygenation to form propargylamine **5aa** while keeping the alkynyl moiety intact. On the contrary, 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 the 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 Studer's protocol[11] that employs boron trichloride (BCl_3) in 1,2-dichloroethane (Scheme 4B). One of the features of the method presented here is its ability in the 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 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**

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

This work has demonstrated the 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 concise access to synthetically valuable α-alkynylnitrones. Given the broad substrate scope of this protocol and the synthetic potentials of α-alkynylnitrones, we view our method to be viable in various synthetic endeavors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01583.

Experimental procedures and spectral data (PDF)
FAIR data, including the primary NMR FID files, for compounds **1a**−**1n**, **3aa**−**3aj**, **3ba**−**3na**, **4aa**, **4ah**, **5aa**, **5ah**, **6**−**8**, **10**, **10′**, and **11** (ZIP)

Accession Codes

CCDC 2080264−2080265 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(18) The structure of **11** was confirmed by X-ray crystallographic analysis. See the Supporting Information for details.

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