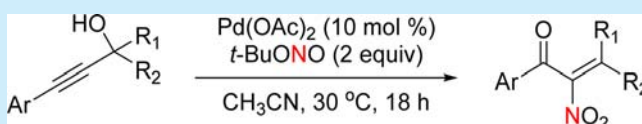


Palladium-Catalyzed Nitration of Meyer–Schuster Intermediates with *t*BuONO as Nitrogen Source at Ambient TemperatureYuanguang Lin,[†] Weiguang Kong,[†] and Qiuling Song^{*,†,‡}[†]Institute of Next Generation Matter Transformation, College of Chemical Engineering and College of Material Sciences Engineering at Huaqiao University, 668 Jimei Boulevard, Xiamen, Fujian 361021, P. R. China[‡]National Laboratory for Molecular Sciences, Institute of Chemistry, CAS, Beijing, 100190, P. R. China

S Supporting Information

ABSTRACT: A novel domino palladium-catalyzed nitration of Meyer–Schuster intermediates which were generated in situ from propargylic alcohols was developed, by the use of *t*-BuONO, leading to α -nitro enones in good to excellent yields at room temperature with a broad functional group tolerance.



Nitro compounds are widely used as building blocks¹ and key intermediates in synthetic chemistry, the pharmaceutical industry, and material sciences.² The conventional nitration, which proceeds via an electrophilic substitution pathway, usually requires nitric acid as the nitrating reagent with another strong acid as the catalyst at high temperature, causing poor selectivities and severe strong acid waste.² Therefore, the development of new nitrating reagents and new approaches to synthesize nitro compounds under mild conditions with high selectivities is highly desirable. Radical chemistry has boomed in the past decade. Synthesis of nitro compounds through the radical process attracted great attention, and great effort has been devoted to this topic. In 2011, Beller and his co-workers reported a metal-free nitration of arylboronic acids under mild conditions, by the use of *tert*-butyl nitrite as a nitro reagent.³ Recently, Maiti discovered that AgNO₂ along with TEMPO can serve a nitrating reagent to lead to nitro olefins with good regio- and stereoselectivities.^{4a,b} And later on, the same group reported a pretty similar reaction with Fe(NO₃)₂ as the NO₂ source.^{4c} In 2014, Li reported a cascade nitration/cyclization reaction to synthesize pyrrolo-[4,3,2-*de*]quinolinones.⁵ In 2015, Liang developed a metal-free nitro-carbocyclization of 1,6-enynes.⁶ However, all of the above-mentioned nitration reactions were limited to alkynes and alkenes, and the addition of nitro radicals to allenes has not yet been reported.

It is well documented that the propargylic alcohols or propargyl esters could generate allenols via Meyer–Schuster rearrangement.⁷ As part of our continuous interest in radical chemistry, we envisioned that nitro radicals, which could be generated from a NO source under oxidative conditions, might attack the allene intermediate A which comes from the rearrangement of propargylic alcohols, rendering α -NO₂ enones via a cascade reaction (Figure 1). To the best of our knowledge, the efficient methods for preparation of complex polysubstituted α -NO₂ enones have not yet been explored despite the fact that enones are valuable building blocks in many reactions.⁸ Herein, we reported a radical involved Pd-

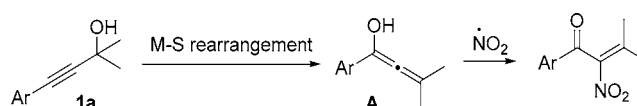


Figure 1. Proposed nitration of propargylic alcohols.

catalyzed nitration of allene intermediates which were generated via Meyer–Schuster rearrangement, leading to α -nitro enones in good to excellent yields at ambient temperature.

To verify our hypothesis, we chose 2-methyl-4-phenylbut-3-yn-2-ol (**1a**) as model substrates (Table 1). To our delight, when 10 mol % of Pd(OAc)₂ was employed, the nitration

Table 1. Optimization of Reaction Conditions^a

entry	cat. (10 mol %)	solvent (1 mL)	temp (°C)	yield ^b (%)
1	Pd(OAc) ₂	THF	60	73
2	—	THF	60	0
3	PdCl ₂	THF	60	49
4	Pd(PPh ₃) ₂ Cl ₂	THF	60	0
5	Pd(PPh ₃) ₄	THF	60	15
6	Pd(OAc) ₂	1,4-dioxane	60	74
7	Pd(OAc) ₂	CH ₃ CN	60	84
8	Pd(OAc) ₂	CH ₃ CN	50	89
9	Pd(OAc) ₂	CH ₃ CN	40	84
10	Pd(OAc) ₂	CH ₃ CN	30	92(86) ^c

^aReaction conditions (unless otherwise mentioned): **1a** (0.25 mmol), *t*-BuONO (2 equiv), catalyst (10 mol %), solvent (1 mL), 18 h, under air. ^bDetermined by GC yield. ^cIsolated yield (THF = tetrahydrofuran, CH₃CN = acetonitrile).

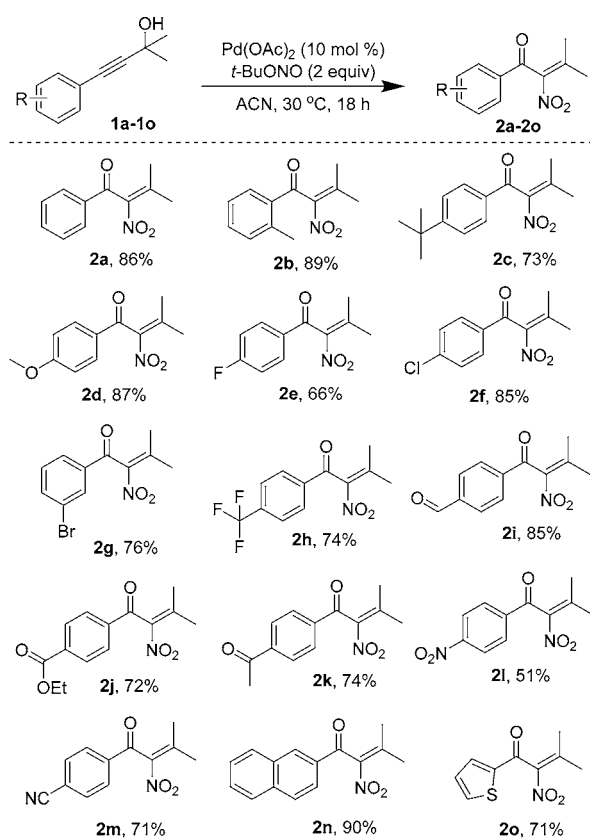
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product **2a** was obtained in 73% yield by GC (entry 1); however, the desired product could not be obtained without a metal catalyst (entry 2). We next investigated other palladium catalysts, such as PdCl_2 , $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, and $\text{Pd}(\text{PPh}_3)_4$, and no better results were obtained (entries 3–5). Subsequent solvent optimization suggested that CH_3CN was the best choice (entries 6–7). In addition, we found that decreasing the reaction temperature to 30°C could increase the yield from 84% to 92% (entries 8–10). Thus, based on the above experiments, we determined the optimized conditions to be *t*-BuONO (2 equiv), $\text{Pd}(\text{OAc})_2$ (10 mol %), and CH_3CN (1 mL) at 30°C under air for 18 h.

Under the optimal reaction conditions, the nitration of propargylic alcohols via Meyer–Schuster rearrangement to generate α -nitro enones was performed. We first applied the reaction to a range of propargylic alcohols which were prepared from corresponding aryl bromides and 2-methylbut-3-yn-2-ol (Scheme 1). Electron-donating substituents such as 2-methyl,

Scheme 1. Nitration of γ,γ -Dimethyl Propargylic Alcohols^a



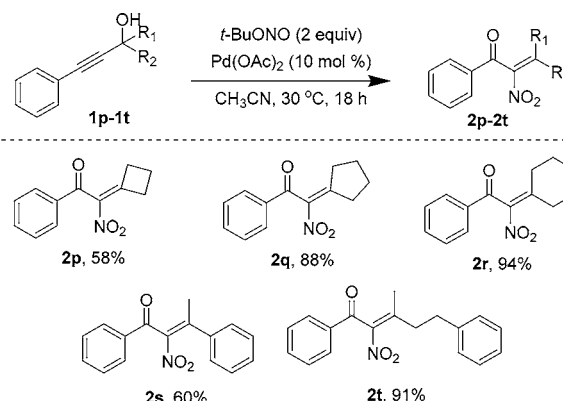
^aReaction conditions: **1** (0.25 mmol), *t*-BuONO (0.5 mmol), 10 mol % of $\text{Pd}(\text{OAc})_2$, CH_3CN (1 mL), stirred at 30°C under air for 18 h. Isolated yield.

4-*tert*-butyl, 4-methoxy gave the expected products in 89%, 73%, 87% yields respectively (**2b**, **2c**, **2d**). Halo substituents were also well tolerable under the standard conditions, giving corresponding desired products which could be employed for further structural manipulations in good yields (**2e–2g**). Moreover, various electron-deficient groups, including trifluoromethyl, aldehyde, esters, ketone, nitro and cyano were compatible in the method as well (**2h–2m**). Polyphenylene compound 2-ethynyl-naphthalene and a heteroaromatic one,

such as thiophene, were also good substrates for this transformation, and corresponding desired products were formed in 90% and 71% yields respectively (**2n–2o**).

To further investigate the scope and limitations of this reaction, we next turned our attention toward the propargylic alcohols prepared from phenylacetylene and various ketones (Scheme 2). The desired products were obtained in good to

Scheme 2. Propargylic Alcohols Scope with Various γ -Substituents^a

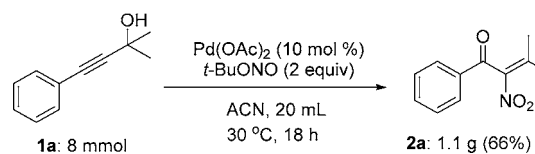


^aReaction conditions: **1** (0.25 mmol), *t*-BuONO (0.5 mmol), $\text{Pd}(\text{OAc})_2$ (10 mol %), CH_3CN (1 mL), stirred at 30°C under air for 18 h. Isolated yield.

excellent yields from the substrates started from different cyclic ketones (**2p–2r**). Other propargylic alcohols prepared from aryl aliphatic ketones or aliphatic aliphatic ketones also gave excellent outcomes (**2s–2t**). It should be pointed out that the desired product was obtained in low yields when we employed the present reaction conditions with propargylic alcohols with only one substituent on the γ -position.

Gratifyingly, the reaction could be readily scaled up without loss of its efficiency: 1.1 g (66%) of α -nitro enone **2a** was obtained in 8 mmol scale (Scheme 3), implying its potential synthetic utility in industry.

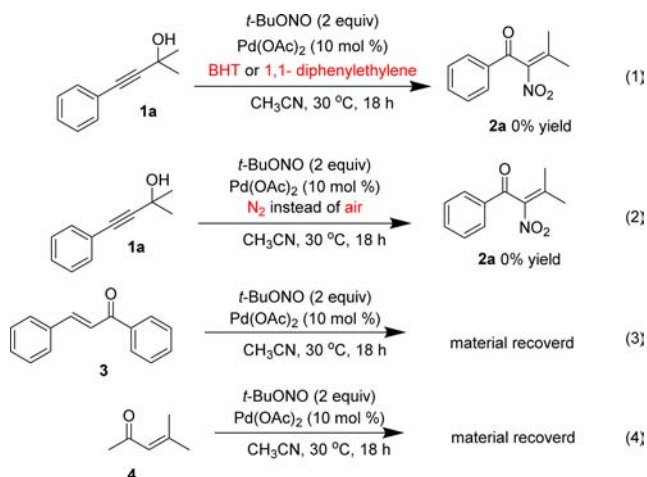
Scheme 3. Scaled-up Reaction



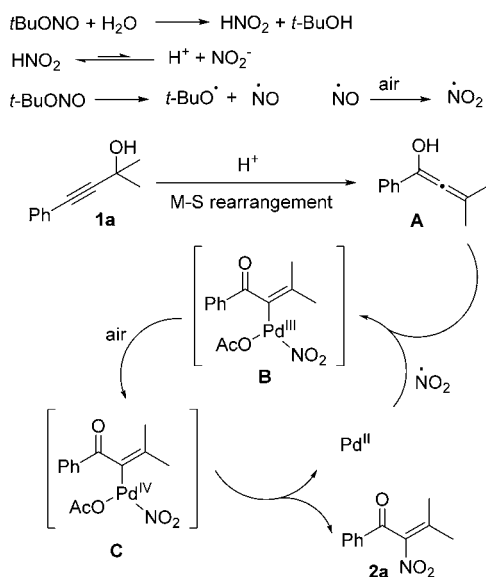
In order to understand the reaction mechanism, various control experiments were carried out as described in Scheme 4. In the presence of radical quencher 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 1,1-diphenylethylene, the reaction were completely suppressed (eq 1). It also showed that, in the absence of oxygen, the reaction did not perform at all (eq 2). Moreover, when enones **3** and **4** were subjected to the standard conditions, no corresponding desired α -nitro enones were ever detected by GC, which implied that the reaction should not proceed through direct nitration of enones.

On the basis of the above-mentioned control experiments, a tentative reaction mechanism was proposed in Scheme 5: Initially, the combination of *t*-BuONO and H_2O leads to the formation of HNO_2 , which promotes the M-S rearrangement to

Scheme 4. Experiments for Mechanistic Studies



Scheme 5. Plausible Mechanism



generate intermediate A. Subsequently, the NO_2 radical is formed from the NO radical which is directly generated from $t\text{-BuONO}$ under aerobic conditions.⁹ In the presence of a Pd catalyst and NO_2 radical, intermediate A is converted into intermediate B, which is further oxidized into intermediate C.¹⁰ The desired product 2a is formed with reductive elimination along with the recovery of the Pd catalyst, thus completing the catalytic cycle.

In conclusion, we have developed an efficient protocol for Meyer–Schuster/nitration of propargylic alcohols into α -nitro enones with a Pd-catalyzed aerobic oxidative system. The α -nitro enones have been widely used as synthetic building blocks in organic chemistry and material sciences. The significant features of this method are (1) mild reaction conditions avoiding use of any ligand; (2) very good functional group tolerance; (3) high efficiency with good to excellent isolated yields. We think this method will merit the synthetic organic field, and further studies on its scope, mechanism, and application will be reported in due course in our laboratory.

■ ASSOCIATED CONTENT

§ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01740.

Information regarding materials and methods, and all characterization data of compounds from this study (PDF)

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Notes

The authors declare no competing financial interest.

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