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Efficient and Stereoselective Nitration of Mono- and Disubstituted Olefins with $AgNO_2$ and TEMPO

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Supporting Information

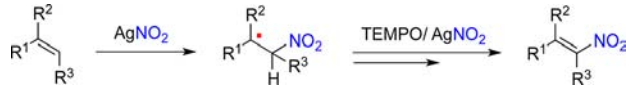
ABSTRACT: Nitroolefin is a common and versatile reagent. Its synthesis from olefin is generally limited by the formation of mixture of *cis* and *trans* compounds. Here we report that silver nitrite ($AgNO_2$) along with TEMPO can promote the regio- and stereoselective nitration of a broad range of olefins. This work discloses a new and efficient approach wherein starting from olefin, nitroalkane radical formation and subsequent transformations lead to the desired nitroolefin in a stereoselective manner.

Nitroolefins are building blocks for generating molecules of biological and pharmaceutical relevance.[1] These are widely used in different carbon−carbon bond-forming reactions like Michael reaction,[2] cycloaddition,[3] and Morita−Baylis−Hillman reaction,[4] and for the generation of oximes,[5] hydroxylamines, nitroalkanes,[6] aliphatic amines, and nitroso compounds.[3a,b] Nitroolefins are conventionally synthesized by the Henry reaction,[7] which relies upon base-mediated condensation of an aldehyde or ketone with a nitroalkane. However, synthesis of nitroolefin via incorporation of a nitro group directly into the olefin is a powerful and preferred class of reactions.[8] In this context, development of an efficient and practical method of regio- and stereoselective nitration of olefin is highly desirable.[9]

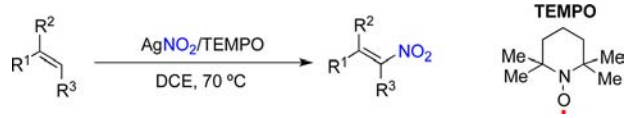
Despite significant developments, nitroolefin synthesis is elusive due to severe limitations.[8] Most importantly, an undesirable mixture of *E*/*Z* isomers is obtained.[8a,b] In addition, prior methods employed harsh or complex reaction conditions[8c,d] and/or suffered from poor substrate scope.[8e,f] Olefins attached with heterocycles and in complex settings have not been explored.[8] One approach to solve these problems lies in discovering a nitration protocol that is highly reactive yet selective enough for a broad range of olefins.

Recently, we reported an *ipso*-nitration reaction in which nitro radical is generated from bench-stable nitrate salt.[10] Following this concept, it was envisioned that if an olefin is reacted under these conditions, nitro radical would generate a carbon-centered radical that can be further oxidized to give the corresponding nitroolefin (Scheme 1). Herein, we report efficient and user-friendly reaction conditions using silver nitrite ($AgNO_2$) in combination with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)[11] to effect highly selective nitration of olefins (Scheme 2). The site of nitration can be predicted in complex settings with multiple olefins on the basis of the electronic and steric environment of the olefin.

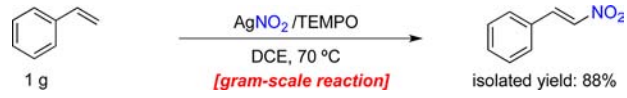
Scheme 1. Proposed Pathway for Nitroolefin Synthesis



Scheme 2. Synthesis of Nitroolefin by $AgNO_2$/TEMPO



Scheme 3. Gram-Scale Reaction with Styrene



Use of TEMPO in combination with $AgNO_2$ gave 99% yield of (*E*)-*β*-nitrostyrene in dichloroethane.[12] Under the optimized condition, a gram-scale reaction resulted in 88% isolated yield of the desired nitro product (Scheme 3).

Previously, 1-methoxy-4-(2-nitrovinyl)benzene[8e] was obtained as a mixture of *E*/*Z* isomers in ∼1:1 ratio from 4-methoxystyrene and nitric oxide. Using an alternative approach with $AgNO_3$/CH_3COCl, nitrostyrene was synthesized as a 1:1 *E*/*Z* mixture.[8h] Notably, only (*E*)-product was obtained under the present $AgNO_2$/TEMPO protocol (Schemes 3 and 4). Encouraged by these results, we investigated nitration of electronically and sterically demanding styrene derivatives. Different halogen-substituted styrenes were nitrated with equal ease (**4e**, **4f**, and **4k**, 92−97% yield). A number of functional moieties were tolerated under these reaction conditions, such as alkyl (**4b**), naphthyl (**4l**), methoxy (**4a**, **4j**), carbonyl (**4h**), nitro (**4g**, **4p**), ester (**4d**), and amide (**4i**), as well as cyano (**4c**). It was evident that the electronic and steric properties of the substituents had little or no effect on the yield of the desired product. Specifically, all these reactions exclusively formed (*E*)-nitro product in preparatively useful yield. Given the broad utility of nitrostyrenes in bulk/fine chemical and pharmaceutical industries, direct stereoselective nitration of styrene derivatives is of great importance.[13]

Substituents on the *α*-position of styrene (**4m**, **4o**) had little or no effect on the yield; however, a 7:1 *E*/*Z* mixture was

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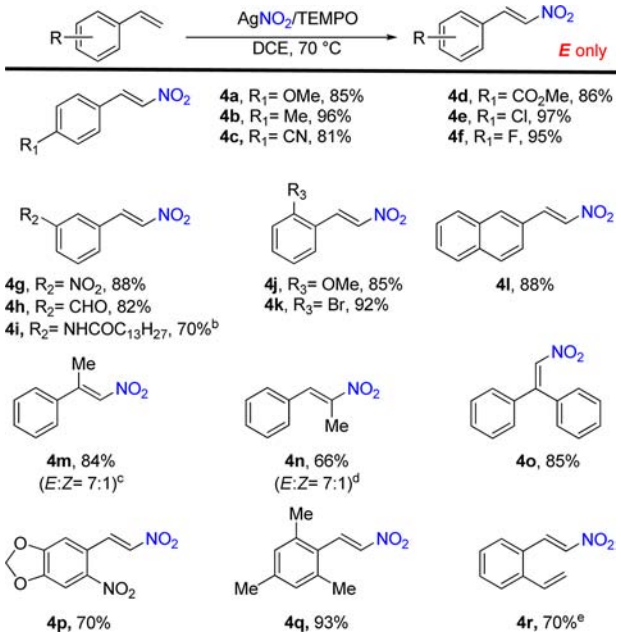
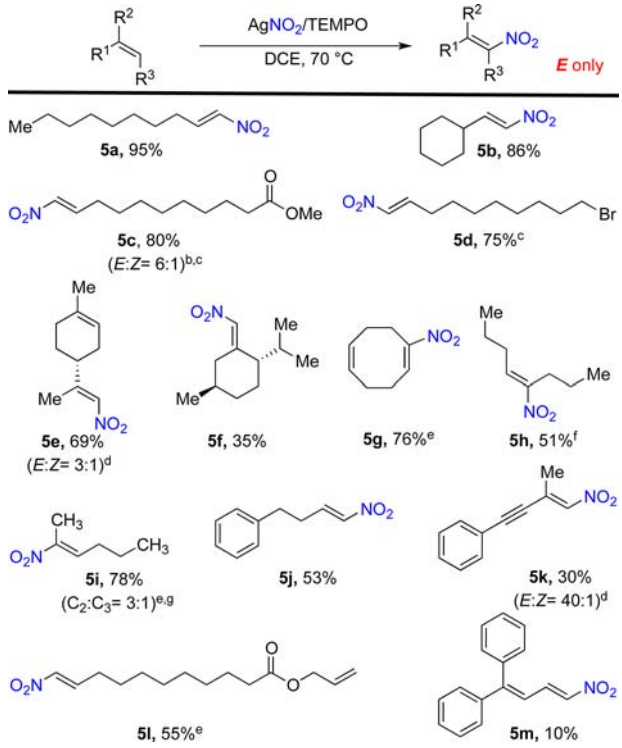
Scheme 4. Stereoselective Synthesis of Nitrostyrenes[a]

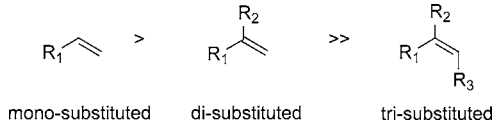


[a]Isolated yield of *E* isomer; reaction mixtures analyzed by GC-MS and/or ^{1}H NMR to determine *E*/*Z* ratio. Olefin (0.5 mmol, 1 equiv), $AgNO_2$ (3 equiv), TEMPO (0.4 equiv), molecular sieves 4 Å (MS, 150 mg), 70 °C, DCE (2 mL), 12 h. [b]Olefin (0.25 mmol), 4.8 equiv $AgNO_2$, and 0.6 equiv TEMPO. [c]Yield of *E* only. [d]Isolated as *E*/*Z* mixture. [e]Olefin (0.25 mmol), 3 equiv $AgNO_2$ and 0.4 equiv TEMPO, MS (80 mg), DCE (1 mL).

Scheme 5. Scope of Nitration with Aliphatic Olefin[a]



[a]Isolated yield of *E* isomer; reaction mixtures analyzed by GC-MS and/or ^{1}H NMR to determine *E*/*Z* ratio. Olefin (0.5 mmol, 1 equiv), $AgNO_2$ (3 equiv), TEMPO (0.4 equiv), molecular sieves 4 Å (MS, 150 mg), 70 °C, DCE (2 mL), 12 h. Recovered olefin: **5c**, 12%; **5e**, 20%; **5h**, 10% and 20% side product (m/z = 128); **5l**, 30%. [b]Yield of *E* only. [c]4 equiv $AgNO_2$ used. [d]Isolated as *E*/*Z* mixture. [e]$CHCl_3$ used as solvent. [f]From *trans*-4-octene; stereochemistry of the product determined by COSY/NOESY analysis. [g]Isolated as a mixture of regioisomers.



obtained for **4m**. A sterically demanding substrate like 2,4,6-trimethylstyrene (**4q**) was nitrated in 93% yield. A substituent on the β-position further increased the steric demand; therefore, β-methylstyrene produced the desired product (**4n**) in slightly lower yield. 1,2-Divinylbenzene was selectively mono-nitrated in 70% yield (**4r**).

Having demonstrated the protocol on styrene derivatives, we next investigated aliphatic olefins of different complexity (Scheme 5). A non-activated monosubstituted olefin was nitrated in excellent yield (**5a**, 95%). Nitration of terminal olefins with either ester (**5c**) or halide (**5d**) on a distal position proceeded smoothly. Homoallylbenzene also gave the desired nitro product (**5j**). When monosubstituted olefins were absent, nitration occurred at the disubstituted olefins (**5g**–**5i**). A natural product such as (+)-limonene (**5e**) was nitrated in acceptable yield with high regio- and stereoselectivity. An internal olefin, (*E*)-4-octene, produced thermodynamically stable (*E*)-4-nitrooctene (**5h**) via rotation of the C_4–C_5 bond upon formation of the TEMPO adduct (*vide infra*).

Next, we sought to investigate whether the site selectivity of olefin nitration is sensitive to the steric and electronic environment. When a competition experiment with 1-decene and (*E*)-4-octene was carried out, nitration of the former olefin was observed exclusively.[12] Consistent with this observation, terminal olefin was selectively nitrated in the presence of cyclic internal olefin in the case of (+)-limonene (**5e**). From these observations and competition experiments, we were able to outline the order of reactivity of olefins as follows:

An olefin such as *cis*-2-hexene is without any electronic bias; therefore two regioisomeric nitroolefin products were obtained in 3:1 ratio (**5i**, 78%). In cases with unequal electronic environments at two olefinic carbon centers, such as in **5l**, nitration occurred at the site farther from the electron-withdrawing group.

The present method is not without limitations. A conjugated olefin such as buta-1,3-diene-1,1-diyldibenzene (**5m**) was scarcely reactive, and the attempted nitration gave the desired nitro product in only 10% yield. Another conjugated olefin, (3-methylbut-3-en-1-yn-1-yl)benzene, gave the nitro product in 30% yield (**5k**).

The scarcity of protocols for nitration of heteroaromatic olefins emphasizes that reactions with such substrates are difficult to carry out. We hypothesized that a highly reactive protocol might be effective. Consistent with this expectation, pyrazole (**6a**), oxazole (**6b**) furan (**6c**), and thiophene (**6d**, **6e**)-based olefins were nitrated efficiently (Scheme 6).

Having established nitration of olefins with relatively simple molecules, we applied it to compounds derived from complex natural products. Substrate derived from cholestan-3-one was selected for nitration (**7a**, Scheme 7). Though nitration at the

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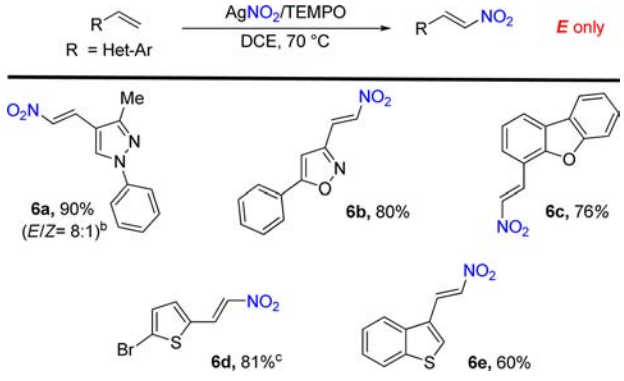
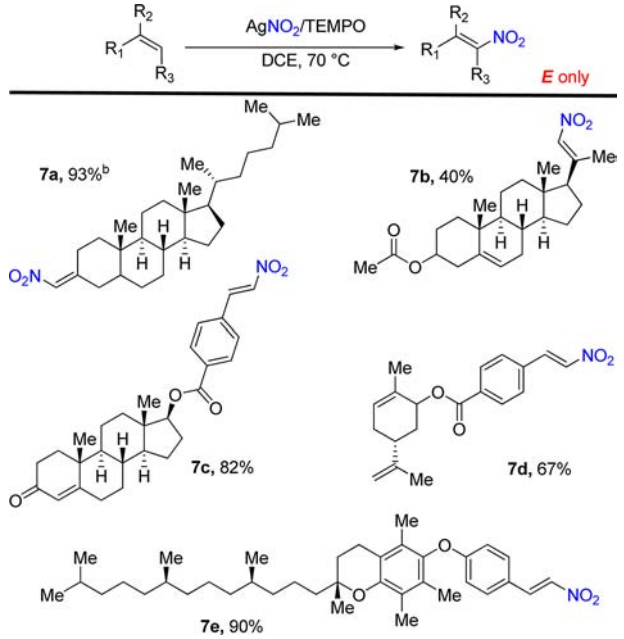
Scheme 6. Scope of Heterocyclic Olefin[a]



[a]Isolated yield of *E* isomer; reaction mixtures analyzed by GC-MS and/or ^{1}H NMR to determine *E*/*Z* ratio. Olefin (0.5 mmol, 1 equiv), $AgNO_2$ (3 equiv), TEMPO (0.4 equiv), molecular sieves 4 Å (MS, 150 mg), 70 °C, DCE (2 mL), 12 h. [b]Yields of *E* only. [c]Olefin (0.16 mmol), 3.75 equiv $AgNO_2$, and 0.625 equiv TEMPO, MS (80 mg).

Scheme 7. Nitration of Complex Molecular Scaffolds[a]



[a]Isolated yield of *E* isomer; reaction mixtures analyzed by GC-MS and/or ^{1}H NMR to determine *E*/*Z* ratio. Olefin:$AgNO_2$:TEMPO (in mmol): **7a**, 0.4 mmol olefin:3 equiv $AgNO_2$:0.5 equiv TEMPO; **7b**, 0.14 mmol olefin:3.2 equiv $AgNO_2$:0.7 equiv TEMPO; **7c**, 0.3 mmol olefin:3.3 equiv $AgNO_2$:0.5 equiv TEMPO; **7d**, 0.25 mmol olefin:3 equiv $AgNO_2$:0.4 equiv TEMPO; **7e**, 0.2 mmol olefin:5 equiv $AgNO_2$:1 equiv TEMPO. [b]Stereochemistry of the product determined by COSY/NOESY analysis.

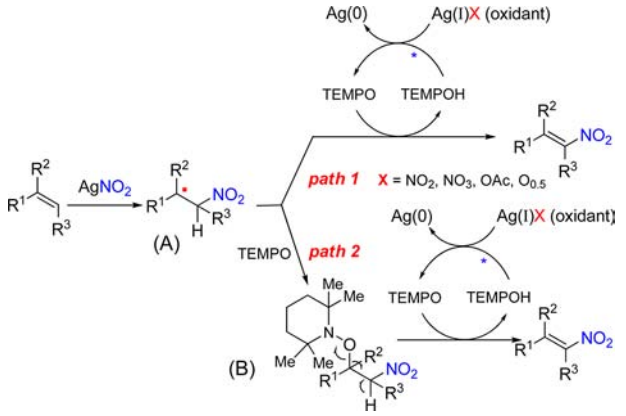
terminal site could have produced two diastereomers, incorporation of the nitro group toward the *endo* cavity, leading to (*Z*)-product, would be sterically disfavored. Thereby, as anticipated, the *exo*-cyclic double bond was nitrated with complete (*E*)-selectivity in excellent yield (**7a**, 93%).[14]

Selective nitration can be achieved at styrene by covalently attaching substituted aliphatic olefins in an electronically unbiased natural product skeleton. Thus, despite having four putative sites of nitration with a possibility of forming six isomers at three different olefins, (*E*)-*β*-nitrostyrene product was observed exclusively (**7d**). This example highlights the selectivity factors that can be implemented to produce nitroolefins in a complex molecule setting. A diaryl ether analogue of vitamin E was also nitrated efficiently (**7e**).

Derivatives of naturally occurring pregnenolone (**7b**) and testosterone (**7c**) were converted to the desired nitro product in good to excellent yields. Disubstituted olefins were selectively nitrated in the presence of cyclic internal olefin in **7b**, as was also observed in **5e**. Unlike **5e**, the cyclic internal olefin in **7b** is buried and is inaccessible for nitration. In all cases examined in which stereogenic centers were involved, nitration occurred with retention of stereochemistry. These examples clearly exhibit the benefits of the current method and indicate that it can be applied in synthesis of large molecules of pharmacological significance and for SAR studies.

A plausible mechanism for nitration of olefin is outlined in Scheme 8. Nitro radical may be generated from $AgNO_2$ under

Scheme 8. Proposed Mechanism for Nitration of Olefins



the applied reaction conditions. A carbon-centered radical (**A**) can then be generated at the more substituted (or benzylic) position, determining regioselectivity of the reaction solely in terms of stability of the radical. From **A**, nitroolefin can be formed via path 1 or 2. TEMPOH is generated upon abstraction of H-atom either directly from intermediate **A** (path 1) or from **B** (path 2). Excess $AgNO_2$ likely oxidizes TEMPOH back to TEMPO. This is further supported by the fact that nitration of olefin proceeds smoothly even with 1 equiv of $AgNO_2$ while using another equivalent of AgX (X = NO_2, OAc, NO_3, $O_{0.5}$) or Ag_2CO_3.[12] Thus, $AgNO_2$ plays a dual role, as source of nitro radical and stoichiometric oxidant. X-ray photoelectron spectroscopy indicated formation of Ag(0) under these reaction conditions.[12]

In path 2, TEMPO could intercept the carbon-centered radical to form a TEMPO−alkane−NO_2 intermediate (**B**). Anti-elimination from intermediate **B** would generate nitroolefin stereoselectively.[14] Studer's group has recently characterized a series of related adducts wherein exogenous radical added to olefin with subsequent TEMPO trapping.[15] We were able to trap one such proposed intermediate with norbornene as the substrate. Formation of *syn*-adduct across the double bond was confirmed by X-ray crystallography (Figure 1). As is evident from the crystal structure, steric demand of the bicyclic system inhibited further progress of the reaction to form a nitronorbornene compound. Although this observation supports path 2 as the likely mechanism, at present we could not rule out any of the two pathways we have depicted in Scheme 8.

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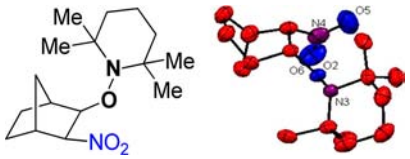

Figure 1. ORTEP diagram of plausible intermediate.[16]

Using steady-state analysis, it can be shown that both of the suggested mechanisms (Scheme 8) are kinetically equivalent and have a partial order (0.4) with respect to TEMPO.[12] Detail mechanistic studies are presently underway in our laboratory.

In summary, a highly selective and efficient protocol for nitration of olefins has been developed employing $AgNO_2$/TEMPO under ambient conditions.[17] The process is practical, and a wide array of substrates, including aromatic, aliphatic, and heteroaromatic olefins, can be nitrated regio- and stereoselectively. This strategy allows olefin nitration as a method for rationalizing complex molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) See Supporting Information for detailed description.

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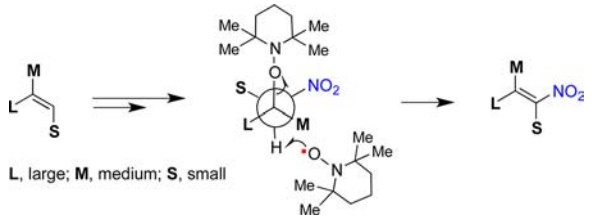
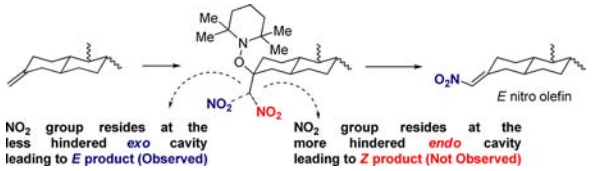
(14) Intermediate **A** has a sp^2-radical center (Scheme 8). Formation of **B** is likely stereodetermining and may depend on the substituents in **A**. (*E*)-*β*-Nitroolefins were generated exclusively, possibly due to the stereoelectronic requirement of H-atom abstraction by TEMPO (*trans*-elimination) and/or thermodynamic stability of the product.



Notably, nitration reactions were found to be stereoconvergent, e.g., (*E*)-4-octene produced thermodynamically stable (*E*)-4-nitrooctene (**5h**) and (*Z*)-2-hexene produced (*E*)-2-nitrohexene (**5i**). The stereochemical outcome of nitration leading to **7a** can be rationalized as follows: orientation of the incorporated nitro group at the terminal site should be *exo* rather than *endo* to the sterically encumbered cavity of fused *trans*-decalin. Subsequent elimination/oxidation of the *exo* intermediate would provide (*E*)-nitroolefin selectively.



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(16) Experimental details of the structure determination can be found in the Supporting Information. CCDC-905717 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

(17) A provisional patent on this work has been filed: IPA 3052/Mum/2012.