Communication

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An Efficient and Stereoselective Nitration of Mono- and Di-Substituted Olefins with $AgNO_2$ and TEMPO

Soham Maity,[a] Srimanta Manna,[a] Sujoy Rana,[a] Togati Naveen,[a] Arijit Mallick,[b] and Debabrata Maiti[a]*

[a]Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India

[b]Physical/Materials Chemistry Division, National Chemical Laboratory, Dr. Homi Bhaba Road, Pune 411008, India

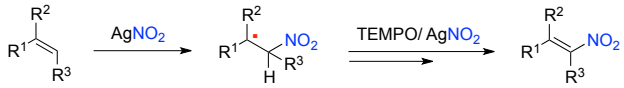
RECEIVED DATE (automatically inserted by publisher); E–mail: *dmaiti@chem.iitb.ac.in*

Abstract: Nitroolefin is a common and versatile reagent, synthesis of which 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] 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 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]

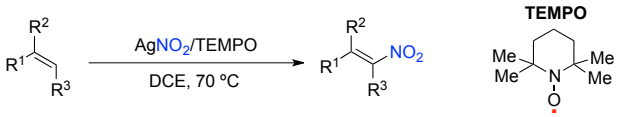
Despite significant developments, nitroolefin synthesis is eluded by severe limitations.[8] Most importantly, an undesirable mixture of *E*/*Z* isomers was obtained.[8a, 8b] In addition, prior methods either employ harsh or complex reaction condition[8c, 8d] and/or suffer from poor substrate scope.[8e,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

Scheme 1. Proposed pathway for nitroolefin synthesis



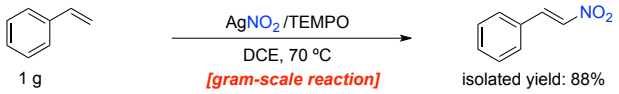
Recently, we reported an *ipso*-nitration reaction in which nitro radical is generated from bench stable nitrate salt.[10] Following this concept, it was envisioned that if an olefin is reacted under these conditions, nitro radical would generate a carbon centered radical which can be further oxidized to give the corresponding nitroolefin (Scheme 1). Herein an efficient and user-friendly reaction conditions have been discovered 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). Site of nitration can be predicted in complex settings with multiple olefins on the basis of electronic and steric environment of the olefin.

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

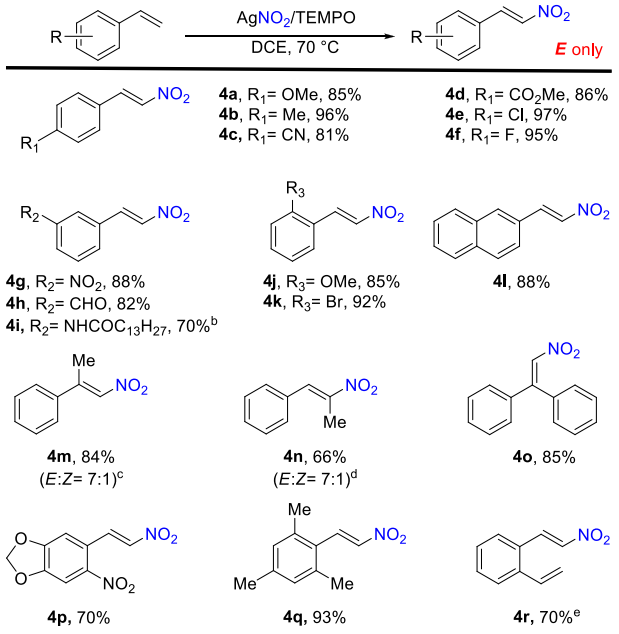


Use of TEMPO in combination with $AgNO_2$ gave 99% yield of (*E*)-*β*-nitro styrene in dichloroethane.[12] Under the optimized condition, a gram scale reaction resulted in 88% isolated yield of the desired nitro product (Scheme 3).

Scheme 3. Gram scale reaction with styrene



Scheme 4. Stereoselective synthesis of nitrostyrenes[a]

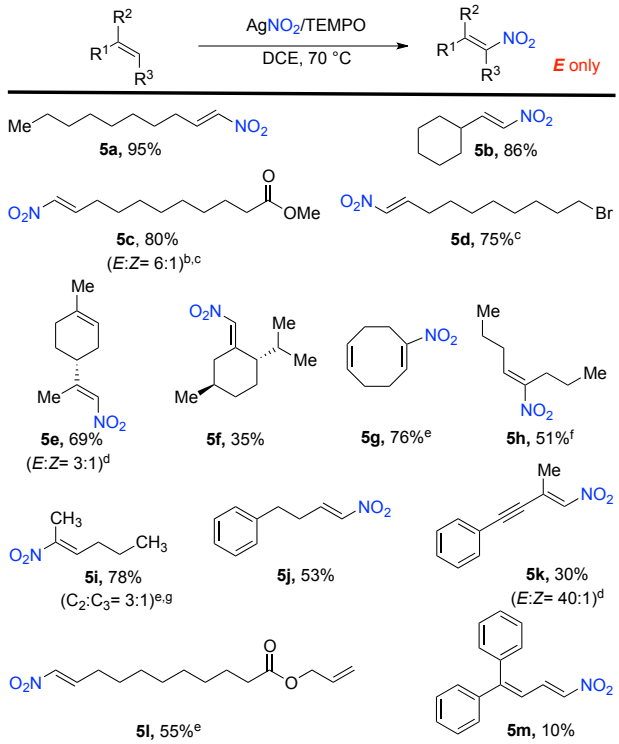


[a]Isolated yield of the *E* isomer. Reaction mixtures were analyzed by GC-MS and/or ^{1}H-NMR to determine *E*/*Z* ratio. olefin (0.5 mmol, 1 equiv.), $AgNO_2$ (3 equiv.), TEMPO (0.4 equiv.), molecular sieves 4 Å (MS, 150 mg), 70 °C, DCE (2 mL), 12 h; [b]olefin (0.25 mmol), 4.8 equiv $AgNO_2$ and 0.6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

Previously, 1-methoxy-4-(2-nitrovinyl)benzene[8e] was obtained as a mixture of *E*/*Z* isomers in a ~1:1-ratio from 4-methoxy styrene and nitric oxide (NO). Using an alternate

approach with $AgNO_3/CH_3COCl$, nitrostyrene was synthesized in 1:1 *E*/*Z* mixture.[8h] Notably, only (*E*)-product was obtained under present $AgNO_2$/TEMPO protocol (Schemes 3 and 4). Encouraged by these results, nitration of electronically and sterically demanding styrene derivatives was investigated. 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** and **4j**), carbonyl (**4h**), nitro (**4g** and **4p**), ester (**4d**), amide (**4i**), as well as cyano (**4c**). It was evident that electronic and steric effect of the substituents had little/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, the direct stereoselective nitration of styrene derivatives is of great importance.[13]

Scheme 5. Scope of nitration with aliphatic olefin[a]

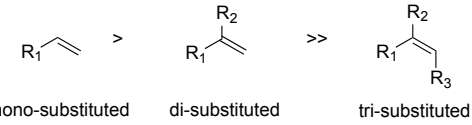


[a]Isolated yield of the *E* isomer. Reaction mixtures were analyzed by GC-MS and/or ^{1}H-NMR to determine *E*/*Z* ratio. olefin (0.5 mmol, 1 equiv.), $AgNO_2$ (3 equiv.), TEMPO (0.4 equiv.), molecular sieves 4 Å (MS, 150 mg), 70 ºC, DCE (2 mL), 12 h. Recovered olefin: **5c**, 12%; **5e,** 20%; **5h**, 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]$CHCl_3$ is used as solvent; [f]from *trans*-4-octene, stereochemistry of the product was determined by COSY/NOESY analysis; [g]isolated as a mixture of regioisomers.

Substituents on the α–position of styrene (**4m** and **4o**) had little or no effect on the yield, however, 7:1 *E*/*Z* mixture was obtained in **4m**. Sterically demanding substrates like 2,4,6-trimethylstyrene (**4q**) was nitrated in 93% yield. Substituent on the β-position further increased the steric demand; therefore β-methyl styrene produced the desired product (**4n**) in slightly lower yield. 1,2-divinylbenzene was selectively mono-nitrated in 70% yield (**4r**).

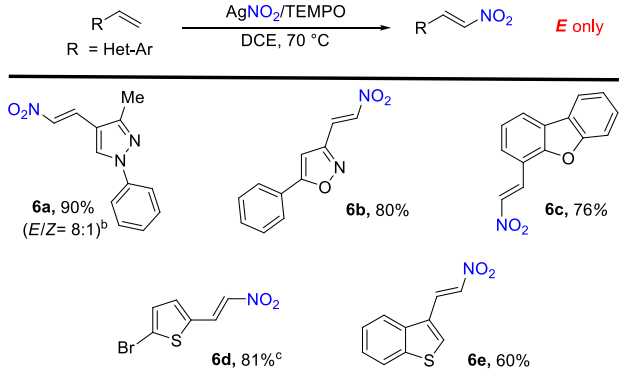
Having demonstrated the protocol on styrene derivatives, aliphatic olefins of different complexity were investigated. A non-activated monosubstituted olefin was nitrated in an excellent yield (**5a**, 95%). Nitration of terminal olefins with either ester (**5c**) or halide (**5d**) on a distal position proceeded smoothly. Homoallyl benzene also gave the desired nitro product (**5j**). In cases where monosubstituted olefins were absent, nitration occurred at the di-substituted olefins (**5g-5i**). 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 case of (+)-limonene (**5e**). From these observations and competition experiments, we were able to outline the order of reactivity of olefins as follows:



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

Scheme 6. Scope of heterocyclic olefin[a]



[a]Isolated yield of the *E* isomer. Reaction mixtures were 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 ºC, 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).

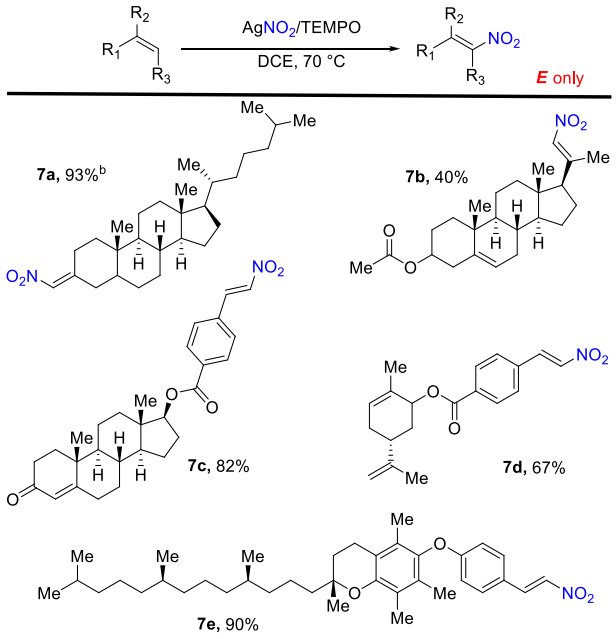
The present method is not without limitations. Conjugated olefins such as buta-1,3-diene-1,1-diyldibenzene (**5m**) was scarcely reactive and the attempted nitration resulted the desired nitro product in 10% yield only. Another conjugated olefin, (3-methylbut-3-en-1-yn-1-yl)benzene gave the nitro product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

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

Having established nitration of olefins with relatively simple molecules, it was applied to complex natural product derived compounds. Substrate derived from cholestan-3-one was selected for nitration (**7a**). Though nitration at the terminal site could have produced two diastereomers, incorporation of nitro group toward *endo* cavity leading to (*Z*) product would be sterically disfavoured. Thereby, as anticipated, *exo*-cyclic double bond was nitrated with complete (*E*)–selectivity and 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*-nitro styrene product was observed exclusively (**7d**). This example highlights the selectivity factors that can be implemented to produce nitroolefins in a complex molecule setting. A diarylether analogue of vitamin E was also nitrated efficiently (**7e**).

Scheme 7. Nitration of complex molecular scaffolds[a]

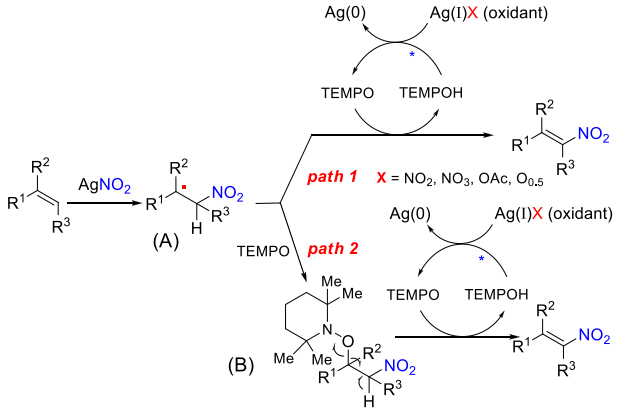


[a]Isolated yield of the *E* isomer. Reaction mixtures are analyzed by GC-MS and/or ^{1}H-NMR to determine *E*/*Z* ratio. olefin: $AgNO_2$: TEMPO (in mmol) **7a** 0.4 mmol olefin, 3 equiv $AgNO_2$, 0.5 equiv TEMPO; **7b** 0.14 mmol olefin, 3.2 equiv $AgNO_2$, 0.7 equiv TEMPO; **7c** 0.3 mmol olefin,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

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 presence of cyclic internal olefin (**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 beneficial aspects of the current method and indicate that it can be applied in synthesis of large molecules of pharmacological significance and for SAR studies.

Plausible mechanism for nitration of olefin is outlined in Scheme 8. Nitro radical may be generated from $AgNO_2$ under the applied reaction condition. Subsequently a carbon-centered radical (**A**) can be generated at the more substituted (or benzylic position), thereby determining regioselectivity of the reaction solely in terms of stability of the radical. From **A**, nitroolefin can be formed *via* path 1 and/or path 2. TEMPOH will be generated upon abstraction of H-atom either directly from intermediate **A** (path 1) or from **B** (path 2). Excess silver nitrite ($AgNO_2$) is likely oxidizing TEMPOH back to TEMPO. This is further supported by the fact that nitration of olefin proceeds smoothly even with 1 equivalent $AgNO_2$ while using another equivalent of AgX (X = NO_2, OAc, NO_3, $O_{0.5}$) or Ag_2CO_3.[12] Therefore, silver nitrite is playing a dual role, as source of nitro radical and stoichiometric oxidant. X-ray photoelectron spectroscopy (XPS) indicated formation of Ag(0) under the present reaction condition.[12]

Scheme 8. Proposed mechanism for nitration of olefins



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 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 nitro-norbornene compound. Although such an 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. Using steady state analysis, it can be shown that both 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 undergoing in our laboratory.

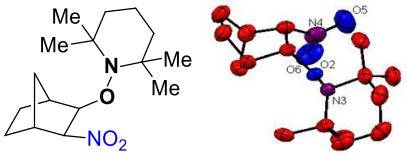


Figure 1. ORTEP diagram of plausible intermediate[16]

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

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See Supporting Information for detailed description.

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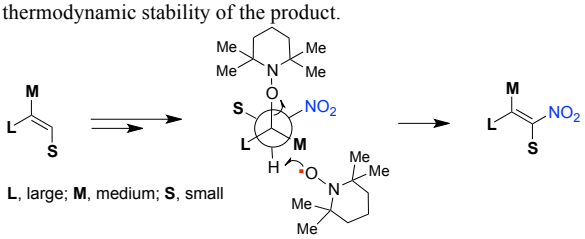
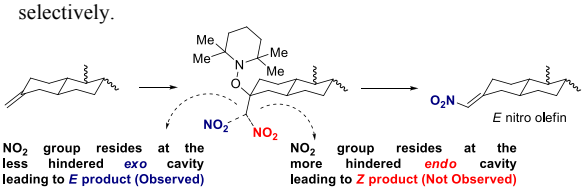
(14) Intermediate **A** contains a sp^2-radical center (Scheme 8). Formation of **B** is likely stereo-determining and may depend on the substituents present in **A**. The (*E*)-*β*-nitro olefins were generated exclusively possibly due to the stereo electronic requirement of H-atom abstraction by TEMPO (*trans*-elimination) and/or thermodynamic stability of the product.



Notably, nitration reactions were found to be stereo-convergent *e.g.* (*E*)-4-octene produced thermodynamically stable (*E*)-4-nitrooctene (**5h**) and (*Z*)-2-hexene produced (*E*)-2-nitrohexene (**5i**).

Observed stereo chemical outcome of nitration leading to product **7a** can be rationalized as follows: orientation of the incorporated nitro group at the terminal site should be preferentially *exo* rather than *endo* to the sterically encumbered cavity of fused *trans*-decalin system. 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.

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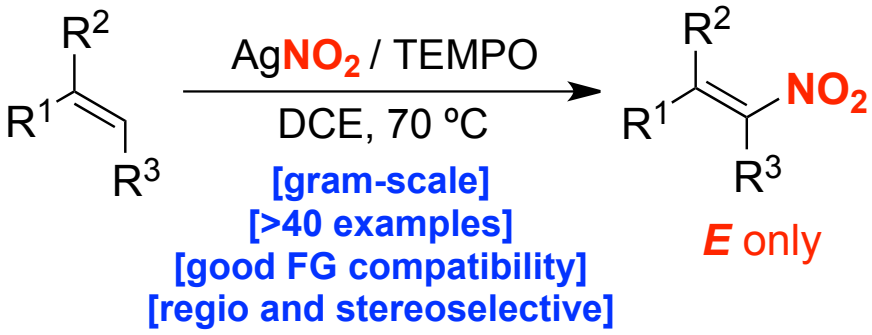
R2
R1
R3
AgNO2 / TEMPO
DCE, 70 ºC
[gram-scale]
[>40 examples]
[good FG compatibility]
[regio and stereoselective]
R2
R1
NO2
R3
E only