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# Iminonitroso ene reactions: experimental studies on reactivity, regioselectivity, and enantioselectivity

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ABSTRACT

Ene reactions of iminonitroso agents with olefins were investigated in both solution and solid phase. Reactions afforded allyl hydroxylamine products in up to 99% yield and with high regioselectivity. A Cu(I)-mediated enantioselective nitroso ene reaction gave an ene product with up to 40% ee.

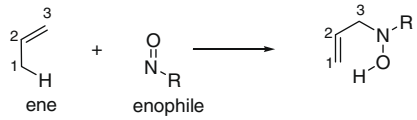


The nitroso ene reaction with alkenes constitutes a mild, valuable method for generation of allylamines, versatile and fundamental building blocks in organic synthesis, in an atom economical fashion (Scheme 1).[1] However, this method has received relatively little attention compared to ene reactions with other enophiles such as singlet oxygen ($^1O_2$),[2] azo compounds,[3] and carbonyl functionalities[4] presumably due to the labile nature of the resulting hydroxylamine products.[5] To minimize such problems, a frequently employed strategy involves the introduction of electron-withdrawing groups at the nitroso functionality to not only increase the enophilic reactivity, but also afford relatively stable hydroxylamine products that are useful for further transformation. In this regard, electron-poor enophiles, such as pentafluoronitrosobenzene,[6] α-chloronitroso agents,[7] acylnitroso agents,[8] and *p*-nitronitrosobenzene[9] are often used.

Enantioselective nitroso ene reactions would offer an attractive pathway to valuable, optically active amines from readily available olefins. However, only limited examples of asymmetric nitroso ene reactions have been reported, by either using a chiral auxiliary for stereo control[10] or using *a*-chloronitroso sugar derivatives as chiral nitrosyl reagents.[7] Recently, iminonitroso agents have attracted a great deal of interest. Unlike the transient acylnitroso species, most iminonitroso agents, in particular, pyridinylnitroso derivatives, can be synthesized from commercially available amine precursors and stored in pure form.[11] Their successful application in Diels–Alder reactions, including enantioselective versions,[12] encouraged us to examine their reactivity in ene chemistry, which surprisingly has not been disclosed. Herein, we report studies of the reactivity and regioselectivity of iminonitroso agents with various olefins in ene reactions. We also describe preliminary results from solid phase-supported nitroso ene reactions as well as enantioselective nitroso ene reactions.

To begin our investigation, a panel of iminonitroso agents **1a–e** were synthesized based on a literature-reported procedure.[11] The unsymmetrical alkene, 2-methyl-2-butene **2a**, was used as a model olefin substrate to examine the reactivity of enophiles **1a–e** in the ene reaction. The results are summarized in Table 1.[13] While low yields were observed when 6-methyl-2-nitrosopyridine **1a** and 2-nitrosopyridine **1b** were used (entries 1 and 2), the introduction of a bromo substituent on the pyridine ring increased the reactivity of nitroso species **1c–d**. Thus, ene products **3c** and **3d** were generated in 64% and 53% yields, respectively (entries 3 and 4). Clearly, use of electron-poorer enophiles increased the reactivity. On the other hand, we were pleased to find that reaction of **1e**, 5-methyl-3-nitrosoisoxazole, afforded ene product **3e** in 94% yield within 10 min (entry 5). In all foregoing ene reactions, single regio-isomeric ene adducts **3a–e** derived from abstraction of the allylic hydrogen on the more substituted side of olefin **2a** were observed and isolated.

Geraniol (**4**) was also used as a substrate to test the relative reactivity of allylically functionalized olefins versus simple alkenes. The results are summarized in Table 2.[14] In general, reactions of nitroso agents **1a–e** with 2.0 equiv of geraniol gave both regioisomeric ene products, 6,7-adducts **5a–e** and 2,3-adducts **6a–e**, in moderate to good yields, with compounds **5a–e** as the major products (entries 1–5). The regioselective preference for adducts **5a–e** is consistent with ene reactions of simple olefin **2a**. The formation of compounds **6a–e** can be rationalized by steric effects in the transition state of the ene reaction (Fig. 1).[15] The best yield and highest intramolecular double bond regioselectivity were observed when 5-methyl-3-nitrosoisoxazole **1e** was employed,




**Scheme 1.** Nitroso ene reaction with olefins.

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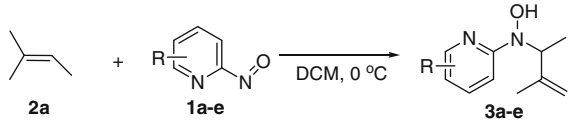
**Table 1**
Ene Reactions of 2-methyl-2-butene **2a** with iminonitroso agents




| Entry[a] | Nitroso | Time[b] | Product | Yield[c] (%) |
|---|---|---|---|---|
| 1 | **1a** | 20 min | **3a** | 38 |
| 2 | **1b** | 15 min | **3b** | 48 |
| 3 | **1c** | 10 min | **3c** | 64 |
| 4 | **1d** | 10 min | **3d** | 53 |
| 5 | **1e** | 10 min | **3e** | 94 |

[a] 2.0 equiv of **2a** used.
[b] Time recorded based on the consumption of nitroso enophile.
[c] Isolated yields reported.

affording an 80:20 ratio of ene adducts **5e** and **6e** in 80% total yield (entry 5).

We next explored the ene reactions of 5-methyl-3-nitrosoisoxazole **1e** with five different alkenes of varying structures (Table 3).[16] Interestingly, reaction with 2,3-dimethyl-2-butene **2b** generated ene adduct **3f** in quantitative yield in less than 1 min (entry 1)! Two isomeric ene products **3g** and **3h** were isolated in an 80:20 ratio and 31% yield, when 1-methylcyclohexene **2c** was used (entry 2). Reaction with cyclohexene **2d**, itself, afforded <10% yield of product **3i** based on LC/MS analysis (entry 3). Compared to alkenes **2a**–**c**, **2d** represented a relatively electron-poor olefin, which corresponded to low reactivity in the ene reaction. When *a*-methylstyrene **2e** was employed, ene product **3j** was isolated in 23% yield (entry 4). Reactions with functionalized alkene **2f** gave ene products **3k** as a single regioisomer in 89% yield (entry 5).

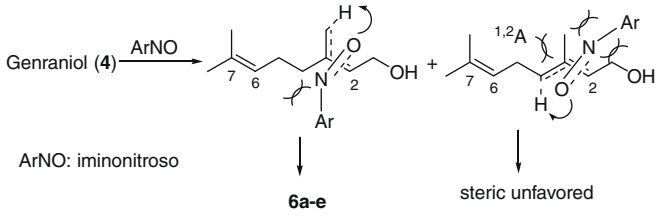
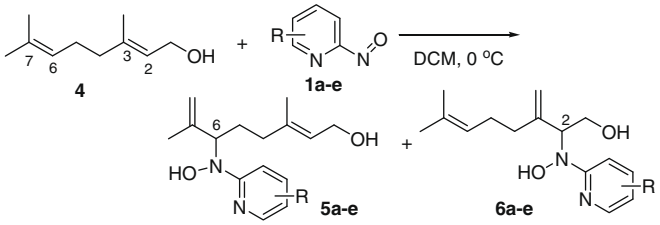



**Figure 1.** Steric encounters in the formation of geraniol 2,3-adducts **6a**–**e**.

A close look at the low yielding ene reactions revealed that, in those cases, a competing decomposition of the initially formed hydroxylamine product in the presence of the nitroso species occurred. As a result, an azoxy compound[5] was generated as the major byproduct, which was not active in the ene reaction. In order to potentially minimize these problems, a solid phase-supported pyridinylnitroso ene reaction strategy was proposed and conducted.[17] As depicted in Scheme 2, a commercially available resin **7** was treated with piperidine to give resin-bound free amine **8**, which was further coupled with 2-fluoro-5-pyridinecarboxylic acid to afford resin **9**. A subsequent nucleophilic substitution with hydroxylamine under basic conditions gave resin-bound pyridyl

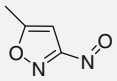
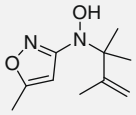
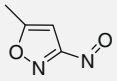
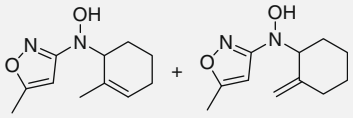
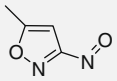
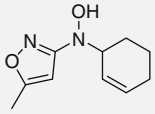
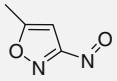
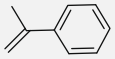
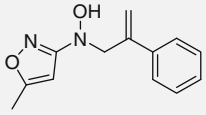
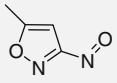
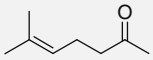
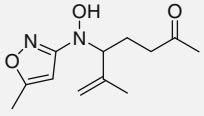
**Table 2**
Ene reactions of geraniol **4** with iminonitroso agents



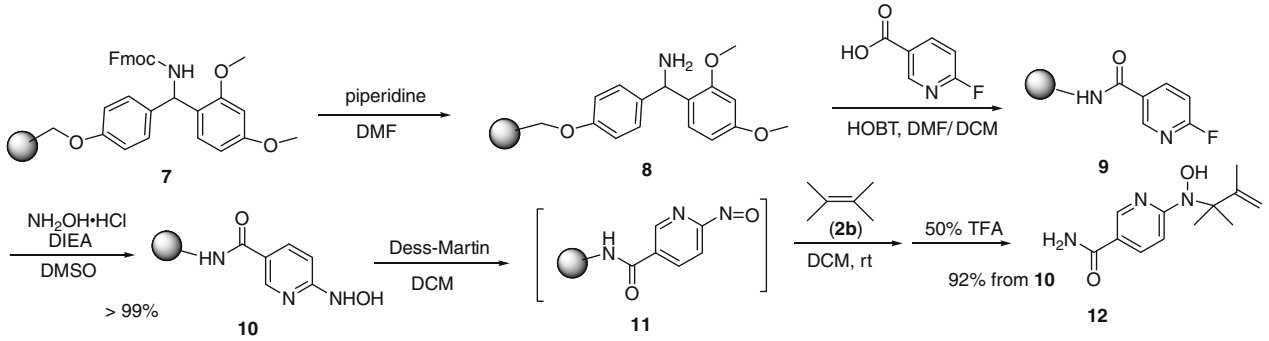

| Entry[a] | Nitroso | Time[b] (min) | Product | Yield[c] (%) | Ratio[d] **5**:**6** |
|---|---|---|---|---|---|
| 1 | **1a** | 30 | **5a** + **6a** | 46 | 68:32 |
| 2 | **1b** | 25 | **5b** + **6b** | 71 | 72:28 |
| 3 | **1c** | 20 | **5c** + **6c** | 70 | 70:30 |
| 4 | **1d** | 20 | **5d** + **6d** | 60 | 66:34 |
| 5 | **1e** | 10 | **5e** + **6e** | 80 | 80:20 |

[a] 2.0 equiv of **4** used.
[b] Time recorded based on the consumption of nitroso enophile.
[c] Isolated yields reported.
[d] Ratio determined by $^1$H NMR of the crude product mixture.

**Table 3**
Iminonitroso ene reactions of 5-methyl-3-nitrosoisoxazole **1e** with various olefins

| Entry[a] | Nitroso **1e** | Olefin | Time[b] | Product | Yield[c] (%) |
|---|---|---|---|---|---|
| 1 |  | **2b**  | 1 min | **3f**  | 99 |
| 2 |  | **2c**  | 2 h | **3g + 3h**  | 31[d] |
| 3 |  | **2d**  | 12 h | **3i**  | <10[e] |
| 4 |  | **2e**  | 20 min | **3j**  | 23 |
| 5 |  | **2f**  | 5 min | **3k**  | 89 |

[a] 2.0 equiv of **2a–f** used.
[b] Time recorded based on the consumption of nitroso enophile.
[c] Isolated yields reported.
[d] Ratio of **3g**:**3h** = 80:20, determined by $^1$H NMR of the crude mixture.
[e] Based on LC/MS analysis.



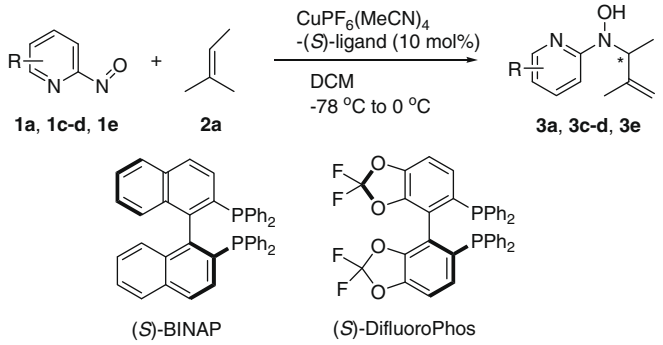

**Scheme 2.** Resin-bound pyridinylnitroso ene reaction with **2b**.

hydroxylamine **11** in excellent yield. In situ oxidation of **11** in the presence of a representative olefin, **2b**, afforded ene product **12** in 92% yield after acid cleavage from the resin. On the other hand, the solution ene reactions of nitroso agents **1a** and **1c** with **2b** gave the corresponding ene products in 78% and 85% yields, respectively. These preliminary results showed that solid phase-supported ene reactions might afford an alternative method for efficient nitroso ene chemistry.

Encouraged by the previous results, enantioselective ene reactions between iminonitroso agents **1a–e** and unsymmetrical olefin **2a** were investigated using a chiral Cu(I)$PF_6$(MeCN)$_4$-biphosphine catalyst.[12b] The reaction was conducted at −78 °C and gradually warmed to 0 °C.[18] The results are summarized in Table 4. Reaction of **2a** with **1e** in the presence of Cu(I)-(*S*)-DifluoroPhos indeed generated ene adduct **3e** in 81% yield but only with a 12% ee value. Separate use of 6-methyl-2-nitrosopyridine **1a** with (*S*)-BINAP and (*S*)-DifluoroPhos increased the enantioselectivity, generating ene product **3a** with 25% and 40% ee, respectively, although in relatively low chemical yields (entries 2 and 3). The major *R*-enantiomer was proposed based on the relevant mechanistic model.[12b] When nitroso enophile **1c** was used, the yield increased as expected; however, a dramatically decreased ee value was observed (entry 4). The trend of increased enantioselectivity with nitroso enophile having a 6-substitutent close to nitrogen is consistent with the results of asymmetric nitroso Diels–Alder reactions.[12b] 6-Methyl-5-bromo-2-nitrosopyridine **1d**, as a combination of **1a** and **1c**, was also used in ene reaction with (*S*)-DifluoroPhos. Unfortunately, low conversion and ee values were observed.

In summary, we have demonstrated an unprecedented ene reaction using iminonitroso agents. The allyl hydroxylamine ene products were obtained in various yields and with high regioselectivity. A solid phase-supported iminonitroso ene reaction and asymmetric nitroso ene reactions were also attempted for the first time. Despite the low enantioselectivity, the methodology presented here holds promise for the development of potentially valuable preparative methods for useful allylamine compounds.

**Table 4**
Enantioselective ene reactions of **2a** with various iminonitroso agents




| Entry[a] | Nitroso | Ligand | 3[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **1e** | (*S*)-DifluoroPhos | **3e**, 81 | 12 |
| 2 | **1a** | (*S*)-BINAP | **3a**,11 | 25 |
| 3 | **1a** | (*S*)-DifluoroPhos | **3a**, 14 | 40 |
| 4 | **1c** | (*S*)-BINAP | **3c**, 36 | 4 |
| 5 | **1d** | (*S*)-DifluoroPhos | **3d**, 37 | 16 |

[a] 1.2 equiv of **2a** used.
[b] Isolated yields reported.
[c] Determined by Chiralcel OD-H analyses.

Further development of enantioselective nitroso ene reactions are in progress.

## Acknowledgments

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13. *General procedure for the nitroso ene reaction*: To a solution of olefin **2a** (0.89 mmol) in 1 mL of DCM at 0 °C was slowly added a solution of iminonitroso **1e** (50 mg, 0.44 mmol) in 0.5 mL of DCM. The resulting reaction mixture was stirred at 0 °C until **1e** was consumed (TLC analysis). The solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography (hexanes/EtOAc = 2:1) to afford nitroso ene adduct **3e** (75 mg, 94% yield) as a white solid. Mp: 80–82 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.95 (s, 1H), 5.94 (m, 1H), 4.90 (br m, 1H), 4.87 (m, 1H), 4.09 (dd, $J$ = 13.2, 6.4 Hz, 1H), 2.28 (s, 3H), 1.75 (s, 3H), 1.19 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 169.6, 168.2, 144.5, 111.9, 94.6, 61.3, 20.7, 12.8, 11.7; HRMS (ESI) [M+H]$^+$ calcd for $C_9H_{15}N_2O_2$ 183.1128, found 183.1131.
14. *Representative spectroscopic data of nitroso ene adducts*: **5b** (white solid): mp: 108–110 °C; $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.81 (s, 1H), 8.10 (ddd, $J$ = 4.7, 1,8, 0.9 Hz, 1H), 7.57 (ddd, $J$ = 9.1, 7.0, 1.7 Hz, 1H), 7.01 (dt, $J$ = 8.2, 0.9 Hz, 1H), 6.66 (ddd, $J$ = 7.0, 4.7, 0.9 Hz, 1H), 5.23 (m, 1H), 4.94 (t, $J$ = 7.3 Hz, 1H), 4.85 (br m, 1H), 4.80 (m, 1H), 4.40 (t, $J$ = 5.3 Hz, 1H), 3.91 (t, $J$ = 5.9 Hz, 2H), 2.00 (m, 1H), 1.90–1.74 (m, 3H), 1.66 (s, 3H), 1.56 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 163.0, 146.9, 144.4, 137.4, 135.6, 125.1, 113.8, 112.6, 107.8, 62.6, 57.5, 36.1, 27.2, 21.4, 16.1; HRMS (ESI) [M+H]$^+$ calcd for $C_{15}H_{23}N_2O_2$ 263.1754, found 263.1768. Compound **5e** (yellow oil): $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 9.04 (s, 1H), 5.91 (s, 1H), 5.25 (m, 1H), 4.87 (m, 1H), 4.84 (m, 1H), 4.43 (br s, 1H), 3.93–3.90 (m, 3H), 2.27 (s, 3H), 2.02 (m, 1H), 1.92 (m, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 1.71 (s, 3H), 1.58 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 169.9, 168.3, 143.4, 135.4, 125.4, 113.8, 94.6, 66.4, 57.5, 35.8, 27.1, 20.9, 16.1, 12.1; HRMS (ESI) [M+Na]$^+$ calcd $C_{14}H_{22}N_2Na\ O_3$ 289.1523, found 289.1538.
15. A rationale for regioselectivity in the ene reaction between 4-nitronitrosobenzene and trisubstituted olefins has been reported, see Ref. 1a, and references therein.
16. An example of solid-supported nitroso hetero Diels–Alder reactions, see: Krchnak, V.; Moellmann, U.; Dahse, H.-M.; Miller, M. J. *J. Comb. Chem.* **2008**, *10*, 104.
17. *Representative spectroscopic data of nitroso ene adducts*: **3f** (white solid): mp: 64–66 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.10 (s, 1H), 5.90 (m, 1H), 4.84 (m, 1H), 4.77 (m, 1H), 2.27 (s, 3H), 1.78 (s, 3H), 1.29 (s, 6H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 169.2, 167.5, 149.9, 110.4, 96.6, 65.6, 23.2, 19.4, 11.9; HRMS (ESI) [M+H]$^+$ calcd for $C_{10}H_{17}N_2O_2$ 197.1285, found 197.1288. Compound **3j** (white glass): $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 9.40 (s, 1H), 7.52 (m, 2H), 7.35 (m, 2H), 7.29 (m, 1H), 5.99 (d, $J$ = 0.9 Hz, 1H), 5.60 (d, $J$ = 1.2 Hz, 1H), 5.35 (d, $J$ = 1.2 Hz, 1H), 4.30 (s, 2H), 2.30 (d, $J$ = 0.9 Hz, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 170.7, 169.0, 142.1, 138.6, 128.2, 127.6, 125.8, 115.7, 94.9, 58.7, 12.1; HRMS (ESI) [M+Na]$^+$ calcd for $C_{13}H_{14}N_2NaO_2$ 253.0947, found 253.0965.
18. *General procedure for enantioselective nitroso ene reaction*: To a flame-dried round-bottomed flask were added Cu(I)$PF_6(CH_3CN)_4$ (9.0 mg, 0.024 mmol) and chiral biphosphine ligand (0.025 mmol). The mixture was dried under vacuum for 10 min. Anhydrous DCM (1.0 mL) was added and the mixture was stirred for 1 h. The reaction mixture was cooled to −78 °C, and then nitroso agent **1a** (30 mg, 0.24 mmol) in anhydrous DCM (0.5 mL) was added dropwise. The resulting dark blue mixture was stirred for 10 min, then olefin **2a** (31 μL, 0.3 mol) in anhydrous DCM (1 mL) was added via a syringe pump over 1 h. The solution was gradually warmed to 0 °C over 3 h, and then the solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography (hexanes/EtOAc = 5:1) to afford nitroso ene adduct **3a** (6.8 mg, 14% yield) as a white solid. Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (95:5 hexanes/2-propanol), 1.0 mL/min, major enantiomer $t_R$ = 5.6 min, minor enantiomer $t_R$ = 6.4 min; mp: 106–108 °C; IR (neat, cm$^{-1}$) 3430, 3074, 2987, 1592, 1421, 1265, 896, 738, 705; $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.64 (s, 1H), 7.47 (dd, $J$ = 8.2, 7.0 Hz, 1H), 6.84 (d, $J$ = 8.2 Hz, 1H), 6.57 (d, $J$ = 7.0 Hz, 1H), 5.09 (dd, $J$ = 13.2, 6.5 Hz, 1H), 4.87 (br m, 1H), 4.84 (m, 1H), 2.32 (s, 3H), 1.72 (s, 3H), 1.15 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 162.6, 155.3, 146.0, 137.8, 113.4, 111.6, 105.5, 58.1, 24.2, 21.5, 13.5; HRMS (ESI) [M+Na]$^+$ calcd for $C_{11}H_{16}N_2NaO$ 215.1155, found 215.1141.