

MECHANISM, STEREOSELECTIVITY AND SYNTHETIC APPLICATIONS OF THE NITroso ENE REACTION

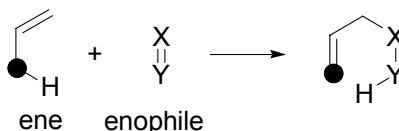
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INTRODUCTION

The ene reaction is a pericyclic reaction that proceeds with activation of an allylic C-H bond throughout an array of continuously bonded atoms and results in allylic transposition of the carbon-carbon double bond with functionalization (Scheme 1). This process involves an alkene with an allylic hydrogen (the 'ene') and a compound with electron-deficient multiple bond (the 'enophile'). As a result of this rearrangement, the ene π -bond migrates and two σ -bonds are formed. The ene reaction gives acyclic products, unlike the related Diels-Alder (DA) reaction, that furnishes cyclic adducts. Although the two processes are mechanistically related, the stereoselectivity of the ene reaction is much less obvious.

Scheme 1. Ene reaction



Several variations of the ene reaction are known. Diversity mostly arises from the enophile used in the reaction. Ene reactions involving alkenes (Alder ene reaction), singlet oxygen ($^1\text{O}_2$),¹ azo compounds,² carbonyl functionalities (carbonyl-ene reaction),³ and nitroso groups⁴ have been used in carbon-carbon and carbon-heteroatom transformations with olefins. The reactivity of the enophile is closely associated with its electronic properties and depends on the HOMO-LUMO energy difference. In the case of the Alder and carbonyl-ene reactions, elevated temperatures or Lewis acid activation are often required.

One distinguishing property of the nitroso compounds is high reactivity, a consequence of the low excitation energy due to a very small HOMO-LUMO energy gap. High reactivity leads to complications in handling, as most of nitroso compounds tend to form dimers.⁵ In the case of nitroso compounds bearing electron-withdrawing substituents on the nitrogen, they are generated in situ. Dimerization, however, is reversible process, and upon thermolysis it is possible to shift the equilibrium towards the monomeric nitroso compound. Since nitroso compounds are susceptible to air oxidation, an inert atmosphere is required to avoid this complication. One drawback of the nitroso ene reaction is the instability of the products of the reaction. The hydroxylamines formed tend to undergo further transformations, and often several side products are observed as a result of disproportionation. These include nitrones, amines, azoxy compounds, and nitroxides. The instability of nitrosyls makes analysis of products and byproducts rather challenging and only limited spectroscopic characteristics are available. Nevertheless, the nitroso ene reaction potentially can be an atom-efficient method for carbon-

nitrogen bond formation. Understanding the mechanism and overcoming troublesome aspects of this reaction is currently of interest. The first portion of this review will discuss synthesis and properties of nitrosyl compounds. Mechanistic considerations of the nitroso ene reaction, including deuterium labeling, directing effects of the hydroxyl group, and computational experiments will be presented in the second part. The third section will cover applications of the nitroso-ene reaction in synthesis.

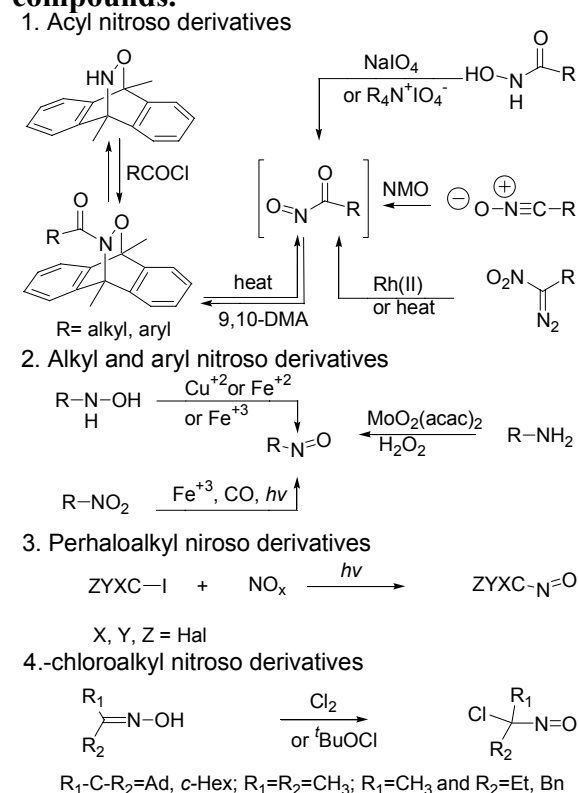
BACKGROUND

Methods of Synthesis of nitroso compounds

Several strategies for synthesis of acyl, alkyl, α -chloroalkyl, perhaloalkyl, and aryl nitrosyls are summarized below (Scheme 2). Acyl nitroso compounds are highly reactive and virtually impossible to isolate in pure form. They rapidly form dimers or disproportionate in polar and non polar solvents. Most of the known approaches generate these reactive intermediates in situ. The most commonly used methods include oxidation of hydroxamic acids by sodium or tetraalkylammonium periodates,⁶ oxidation of nitrile *N*-oxides with morpholine *N*-oxide,⁷ and decomposition of nitrodiazoalkanes under catalysis of rhodium diacetate or upon gentle heating.⁸ Regardless of the synthetic method, acyl nitroso compounds are often isolated and purified as Diels-Alder adducts. 9,10-Dimethylantracene (9,10-DMA) is commonly used for this purpose. Another method resulting in acyl nitroso compounds is direct acylation of the H-N=O/DA adduct with acid chlorides. Yields of nitroso adducts are generally high, ranging between 50-99%.⁹ Thermal decomposition of 9, 10-DMA-acyl nitroso adducts proceeds by retro DA reaction to generate 9,10-DMA and acylnitroso compound in situ. Although chiral acylnitrosyls have been successfully applied in the DA reaction, they have not been yet investigated in the ene reaction.

Several approaches to alkyl and aryl nitroso derivatives are based on oxidation of the corresponding hydroxylamines and amines. Johansen,¹⁰ Srivatsava,¹¹ and others have utilized Fe(II)-Fe(III) reagents to generate nitrosobenzene from *N*-phenylhydroxylamine. In addition, various copper complexes were used by Chi-Ming.¹² Synthesis of different *C*-nitroso compounds by H₂O₂ oxidation of the corresponding amines under MoO₂(acac)₂ catalysis was recently reported by Porta and Prati.¹³

Scheme 2. Synthesis of nitrosyl compounds.

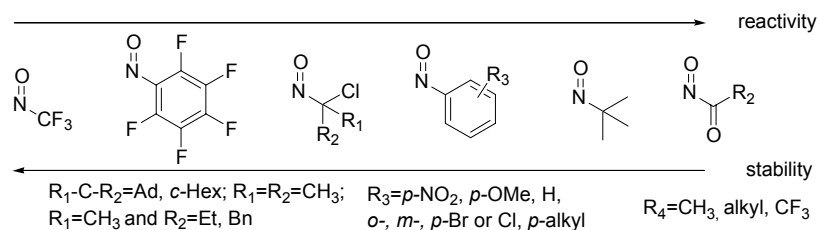


Another approach is based on readily available nitroarenes. Photochemical reactions of nitroarenes with olefins under an atmosphere of carbon monoxide and with iron or ruthenium catalysis at elevated temperatures presumably proceed via nitrosoarene intermediates.¹⁴ Perfluoroalkylnitrosyls were synthesized by photolysis in the presence of nitric oxide or pyrolysis of the corresponding nitrites.¹⁵ α -Chloro-*C*-nitroso alkanes can be easily obtained by reaction of corresponding oximes with Cl₂ or *t*-butyl hypochlorite.¹⁶ They are stable and can be purified by conventional methods, like crystallization.¹⁷

Trends in stability and reactivity of nitroso compounds

Organic nitroso compounds produce blue or blue-green solutions, as a result of absorption in the visible region at $\lambda_{max} \approx 700$ nm. In the crystalline state, the color disappears due to dimerization, a characteristic of many nitrosyls. Currently there is no systematic study on the stability of nitroso compounds, but it is accepted that substitution with halogens (e.g. ordinarily F and Cl) in α position to the NO group increases stability (Scheme 3). Reactivity of R-NO is inversely correlated with stability as acylnitrosyls tend to dimerize and disproportionate much faster than α -halonitroso compounds. Chemical properties of nitrosobenzene are summarized in a review by Zuman and Shah.¹⁸

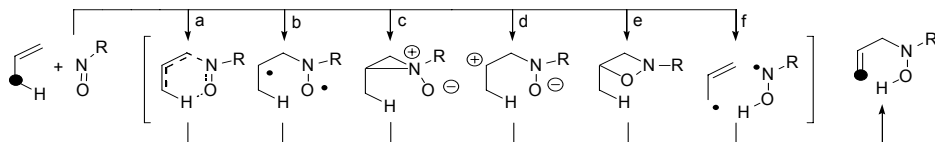
Scheme 3. Stability of nitroso compounds.



MECHANISM OF NITROSO ENE REACTION

The ability of nitroso compounds to undergo the ene reaction was reported as early as 1910 by Alesandri,¹⁹ and by Banks in 1965,¹⁵ but a more systematic study was accomplished by Knight.²⁰ Despite this background, experimental work on the mechanism of the nitroso ene reaction is limited. Several mechanistic pathways have been proposed. As depicted in Scheme 4, the reaction might proceed via a concerted synchronous or asynchronous transition state (pathway **a**), which is allowed by the Woodward-Hoffman selection rules as a $[2\pi_s+2\sigma_s+2\pi_s]$ process. Other possible pathways could involve intermediate diradicals (**b**), aziridine *N*-oxides (**c**), or zwitterions (**d**). Pathways **e**²¹ and **f**, involving highly strained oxazetidine and two radical species, were also proposed, but they are believed to be most unlikely.

Scheme 4. Possible mechanistic pathways of the nitroso ene reaction.



Computational methods have been used to support intermediacy of aziridine *N*-oxide (ANO) by several groups. In an early PM3 computational study of H-N=O reaction with propene, Davies and Schiesser located several transition structures on the potential energy surface. According to their

calculations, concerted pathway (a) is highly asynchronous, and the carbon-nitrogen bond is almost fully formed during hydrogen transfer. In the case of an ANO intermediate (pathway c), the authors found an energy barrier of 8 kcal mol⁻¹ lower than that of the concerted reaction. Based on this fact and the experimental results of Baldwin, they proposed that the nitroso ene reaction proceeds via an aziridine *N*-oxide.^{22,23} Adam and coworkers, using B3LYP/6-31+g* basis in their DFT calculations, identified ANO as the sole intermediate along the reaction pathway. They argued that formation of the ANO is the rate-determining step and proposed a skew trajectory for the incoming enophile as the most energetically favored approach.^{24,25} Leach and Houk applied B3LYP/6-31g* basis calculations to investigate the ene reaction of H-N=O and propene.^{26,27} They suggested that a polarized diradical intermediate (pathway b) is initially formed based on several computational methods, and proposed a unified stepwise process for the nitroso ene reaction. Initial approach of H-N=O to a propene molecule results in formation of a polarized diradical, characterized by relatively high rotation barriers of C-N and C-C bonds (4-5 kcal/mol), which can abstract an allylic hydrogen to form the corresponding hydroxylamine or can equilibrate to the aziridine *N*-oxide. Formation of the polarized diradical is proposed to be the rate-limiting step, which is in agreement with KIE data.³⁸ Computational data for *p*-nitro-nitrosobenzene, an experimentally benign enophile, is in good agreement with the experimental results.

In the case of monosubstituted olefins (e.g. propene) hydrogen can be transferred from the only allylic position. However, with di-, tri- and tetra substituted olefins, when several allylic hydrogens from different substituents are available for transfer, the regioselectivity issue becomes apparent. Unfortunately no systematic study was attempted to determine the regioselectivity of the nitroso ene reaction of disubstituted alkenes. Scarce data indicate that the rates of the reaction of nonequivalently substituted (*Z*)-alkenes is much faster compared to (*E*)-isomers and cyclic alkenes react at an approximately equal rates.²⁸ An investigation of Adam and Bottke addressed issues of regioselectivity for trisubstituted alkenes. Reaction of trisubstituted olefins with *p*-nitro-nitrosobenzene afforded mixtures of hydroxylamines in moderate to good yields. Using a CD₃ group to differentiate geminal substituents in several acyclic trisubstituted olefins, the investigators found a remarkable preference for allylic H-abstraction from the cis alkyl group (Figure 1).²⁹ Transfer of hydrogen from the lone substituent was not observed and the amount of hydroxylamine, originating from trans abstraction, ranged between 5 and 17%. (*E*)- and (*Z*)-2-Methyl-2-butene-2-d₃ also showed a preference for the cis abstraction. Bulky lone substituents improve selectivity for transfer of allylic hydrogen from the cis

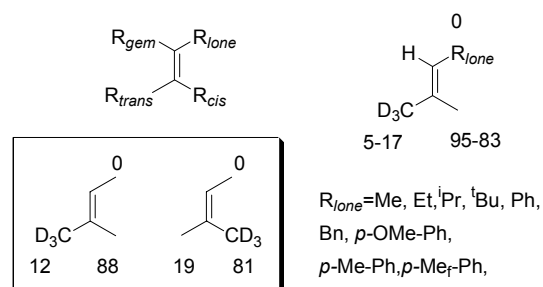


Figure 1. Differentiation of alkene substituents.

position. In a series $R_{lone} = \text{Me, Et, } ^i\text{Pr, and } ^t\text{Bu}$, the cis regioselectivity increased from 83 to 95 %. Cyclic trisubstituted olefins behave similarly, but conformational constraints come into play. For example, reaction of (*E*)-1-methylcyclooctene with $p\text{-NO}_2\text{C}_6\text{H}_4\text{NO}$ resulted in more than 95:5 regioselective cis abstraction, while in case of (*Z*)-1-methylcyclooctene, regioselection between cis and trans was reversed (31:69). Regioselective reactions of tetrasubstituted olefins (all R unequal) have not been reported and the case of tetrasubstituted allylic alcohols will be presented next.

A steric argument was proposed to rationalize the selectivity of the nitroso ene reaction of trisubstituted alkenes.³⁰ Two different modes of approach of the incoming enophile towards the ene molecule were postulated regardless of possible intermediates (Figure 2). In the first geometrical arrangement, the aryl group of the enophile is positioned between the lone and cis substituents of the ene molecule. As a consequence, transfer of the allylic hydrogen from R_{trans} must occur. In this scenario, steric repulsions of both R_{lone} and R_{cis} with the incoming enophile would be expected. When the ene is approached from the opposite direction, steric encounter of the trans alkyl group and aryl substituents of the enophile would be the only steric interaction. In order to minimize unfavorable strain, the aryl substituent would be forced towards an unsubstituted quadrant of the ene, which would result in closer alignment of the nitrosyl oxygen with R_{cis} compared to R_{lone} . Therefore, H-transfer from the cis position would predominate. A similar rationale would explain the regioselectivity observed for cyclic olefins as well.³⁰

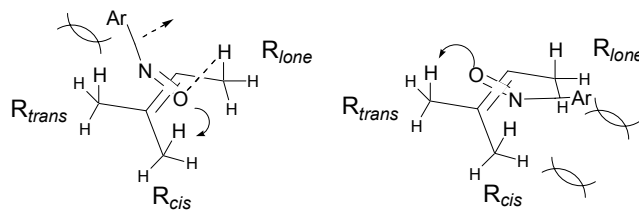
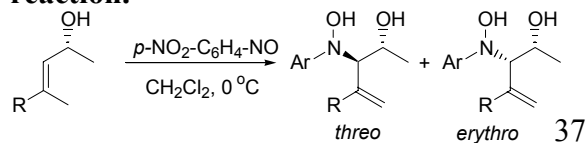


Figure 2. Steric encounters of ene and enophile.

HYDROXY-GROUP DIRECTING EFFECT

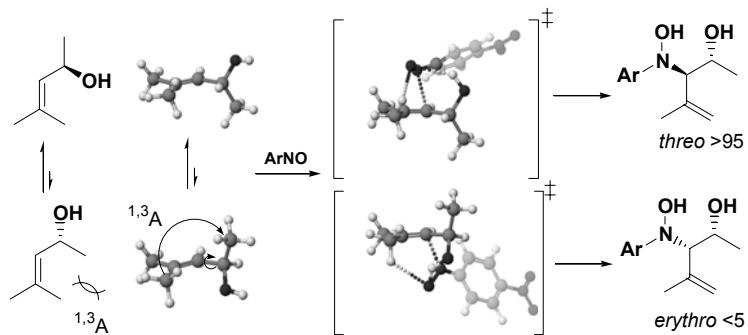
Adam and Bottke investigated the nitroso ene reaction of secondary chiral allylic alcohols.^{31,32} The authors observed a strong directing effect of the hydroxyl group (Scheme 5). As a consequence, high diastereoselectivity was observed for tri- and tetrasubstituted substrates. By analogy with trisubstituted olefins, abstraction of hydrogen from the cis position of chiral allylic alcohols was predominant compared to the trans isomers ($R_{lone} = (R)\text{-CH(OH)CH}_3$ in Figure 1; >99:1 for $R = \text{CH}_3$). In each case two diastereomers can be formed. Using a deuterium-labeled methyl in the cis position, the authors determined the ratios of diastereomers. Remarkable diastereoselectivity was achieved in the reaction of 4-methyl-3-penten-2-ol with $p\text{-NO}_2\text{-PhNO}$ (threo:erythro = >95:5) and its deuterated analogs. This virtually exclusive preference for the threo diastereomer was rationalized by a combined effect of $A^{1,3}$ strain of the starting allylic alcohol and hydrogen bonding of the incoming enophile with the hydroxyl group. Similar to the case depicted above, approach of

Scheme 5. Diastereoselective nitroso ene reaction.



the incoming enophile is preferred from less congested side (Scheme 6). A conformationally preferred orientation of the hydroxyl group avoids the allylic strain and determines facial orientation of the enophile. The combination of both factors in a polarized transition state, stabilized by hydrogen bonding, leads to high diastereoselectivity. Solvent effects are consistent with this

Scheme 6. A^{1,3} strain effect on diastereoselectivity.

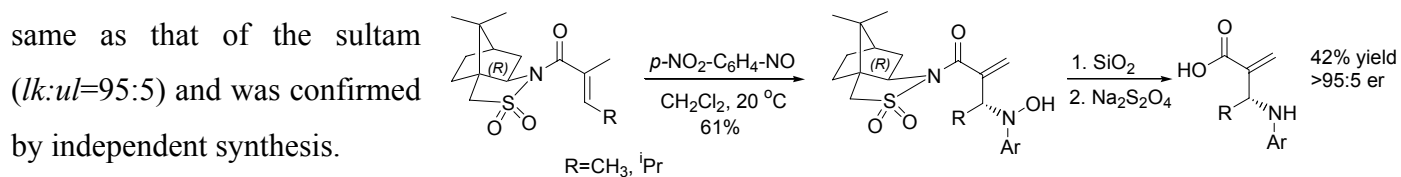


hypothesis. In polar protic and aprotic solvents (CD₃OD, CH₃OH, and DMSO) diastereoselectivity was diminished by hydrogen bonding with the solvent. Substitution of the hydroxyl group with ester or ether functionality also resulted in diminution of the diastereomeric ratio. Tetrasubstituted allylic alcohols (Figure 1, R_{gem} = alkyl) also were tested under similar conditions. The possibility of forming six diastereomers arises in this case (both erythro and threo for gem, trans and cis abstraction). The authors observed exclusive hydrogen transfer from the cis position in non-polar aprotic solvents; at 50% conversion ratio of the cis/trans abstraction was >95:5 and the major regioisomer was threo (threo:erythro = >95:5).

ASYMMETRIC NITROSO ENE REACTIONS

Asymmetric nitroso ene reactions have not been as extensively investigated as their DA counterparts, and only two approaches have been reported. The first approach, reported by Adam,³³ is based on a chiral auxiliary for stereo control (Scheme 7). Reaction of tiglic acid derivatives of a chiral bornane-derived sultam with *p*-nitro-nitrosobenzene in CH₂Cl₂ at 20 °C afforded chiral hydroxylamines in 55-61% isolated yield as single diastereomers. Cleavage of the chiral auxiliary and reduction of hydroxylamine group with Na₂S₂O₄ in wet ethanol gave chiral β-amino acid products in about 42% isolated yield. The configuration of the newly formed chiral center was the

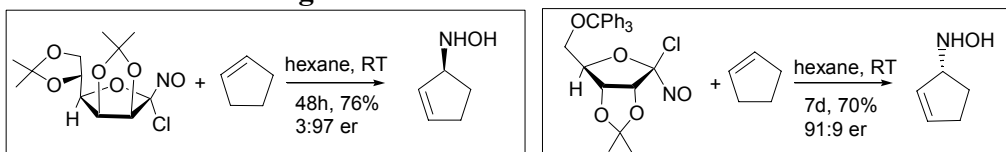
Scheme 7. Chiral auxiliary controlled nitroso ene reaction.



same as that of the sultam (*lk:ul*=95:5) and was confirmed by independent synthesis. Another approach is based on chiral nitrosyl reagents.²⁸ Sugar-derived α-chloronitrosyls, when subjected to a reaction with cyclopentene at room temperature, produced chiral hydroxylamines in good yield and enantioselectivity (Scheme 8). Both enantiomers of the product were accessible by the choice

of the chiral reagent. Several examples of reactions of cyclic and acyclic olefins were

Scheme 8. Chiral reagent controlled ene reaction.

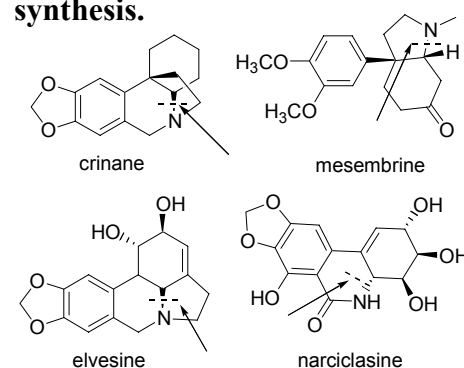


presented. A simple separation of the protected sugar by extraction allows re-cycling of the chiral starting material.

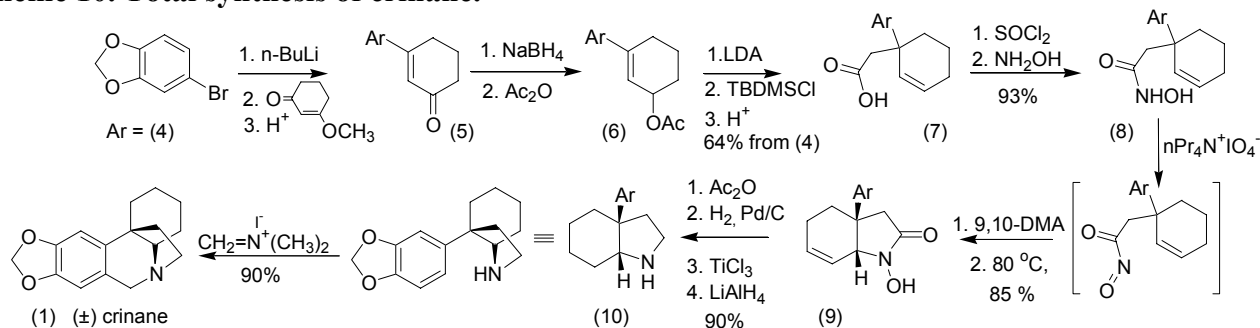
APPLICATION OF NITROSO ENE REACTION IN SYNTHESIS

Nitroso ene reactions were used as key steps in total syntheses of several natural products.³⁴⁻³⁷ Alkaloids crinane, mesembrine, elvesine, and narciclasine are potentially active antitumor agents of synthetic interest (Scheme 9). A total synthesis of (\pm)-crinane (Scheme 10) is presented as an example. The known 4-bromobenzodioxolane underwent metal-halogen exchange and reaction with 3-methoxycyclohexenone rearranged to afford intermediate enone **5** after acidic workup. NaBH_4 reduction in ethanol at 0 °C, followed by acylation, produced allylic acetate **6**, which was transformed into enolsilane. The carboxylic acid **7** was formed after Claisen rearrangement in 64% overall yield after removal of the protecting group. Transformation of **7** to the corresponding acid chloride and reaction with hydroxylamine produced hydroxamic acid **8**, which was oxidized by $n\text{-Pr}_4\text{N}^+\text{IO}_4^-$ and trapped as DA adduct with 9,10-DMA. Heating the DA adduct in toluene for 30 minutes liberated acylnitroso intermediate and resulted in intramolecular nitroso ene reaction to afford cyclic hydroxylactam **9** quantitatively. Acetylation of the hydroxyl group and three-step reduction sequence resulted **10**, which upon heating with 1.5 equivalents of Eschenmoser's salt afforded (\pm) crinane 40% overall yield.

Scheme 9. Nitroso ene in total synthesis.



Scheme 10. Total synthesis of crinane.



CONCLUSIONS

The nitroso ene reaction of C-nitrosyl compounds remains largely unexplored. The transformation is a potentially useful method for the synthesis of allylic amines, hydroxylamines, and cyclic hydroxamic acids. The mechanism is still under debate and further evidence is needed to establish the nature of the intermediates involved in the reaction. While several examples of diastereoselective nitroso ene reactions exist, they are limited to aryl nitrosyls, and asymmetric variants are quite scarce. Despite these drawbacks, two approaches to asymmetric nitroso ene reactions have been developed, and the utility of this method was demonstrated in several total syntheses of alkaloids by Keck and Webb.

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