Synthetic Methods

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Construction of Morphan Derivatives by Nitroso–Ene Cyclization: Mechanistic Insight and Total Synthesis of (±)-Kopsone

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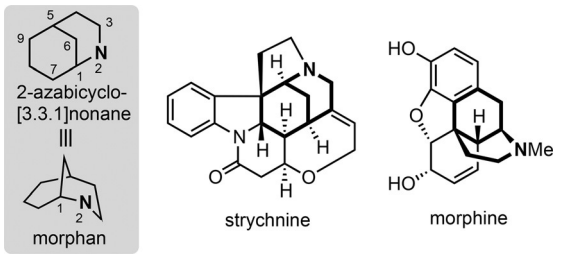
Abstract: *A type II nitroso–ene cyclization was developed for the construction of morphan derivatives with good functional-group tolerance. DFT calculations revealed that the nitroso–ene reaction proceeds in a stepwise manner involving diradical or zwitterionic intermediates. The rate-determining step is C–N bond formation, followed by a rapid hydrogen-transfer step with a chair-conformation transition state. The current approach was also successfully applied in the first total synthesis of (±)-kopsone, a highly strained yet simple morphan-type alkaloid isolated from Kopsia macrophylla.*

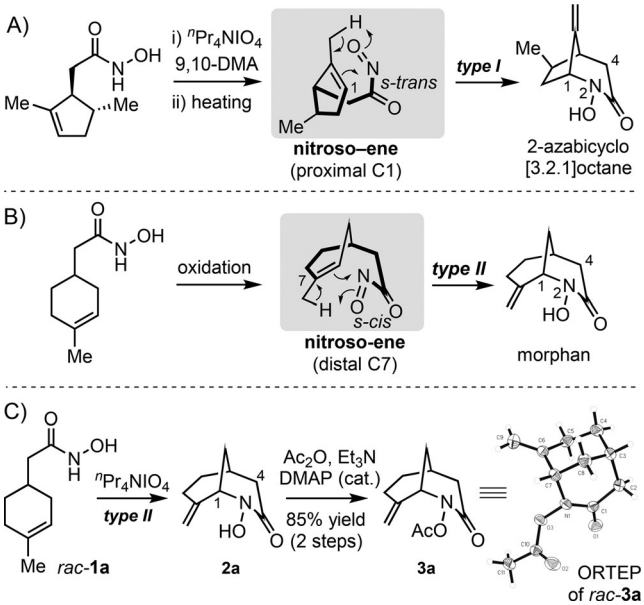
Morphan, also named 2-azabicyclo[3.3.1]nonane, is abundant in complex bioactive alkaloids and a privileged structure in drug discovery.[1] Strychnine and morphine are arguably the best-known molecules in this category (Scheme 1) because of their broad biological profile, their clinical use for the treatment of human diseases, and their intriguing structures that inspire the development of novel synthetic methods.[2]



Scheme 1. The morphan core, morphine, and strychnine.

For example, the practical synthesis of morphine remains an intriguing objective for the synthetic community although more than 30 syntheses have emerged since the masterpiece by Gates and Tschudi in 1956.[3] Continuing efforts in this field have led to state-of-the-art synthetic methods and tactics to access medicinally significant alkaloids.

The recent application of the nitroso–ene reaction motivated us,[4] with synthetic applications in mind, to further explore the unique reactivity of *N*-acyl nitroso compounds to construct a new cyclic skeleton.[5] According to the classification of the intramolecular ene reaction by Oppolzer and Snieckus,[6] reaction at the proximal end of the tethered alkene to the nitroso group would result in a type I ene product, such as 2-azabicyclo[3.2.1]octane[4] and other ring systems[5] (Scheme 2 A). We envisioned that the morphan skeleton could be constructed by an alternative type II mode, in which the tether is attached to the distal end of the alkene (Scheme 2 B). However, this type of intramolecular nitroso–ene reaction remains underdeveloped since a pioneering study by Kirby et al. in 1985.[7] As shown in the illustrative transition state, the *N*-acyl nitroso compound would adopt an



Scheme 2. Reaction design. A) Type I nitroso–ene cyclization. B) Type II nitroso–ene cyclization developed in this study. The term "tether" refers to the longest unbranched carbon chain and is highlighted in bold in the proposed transition state. C) Initial attempt to construct the morphan ring by the nitroso–ene reaction. 9,10-DMA = 9,10-dimethylanthracene, DMAP = 4-(*N*,*N*-dimethylamino)pyridine.

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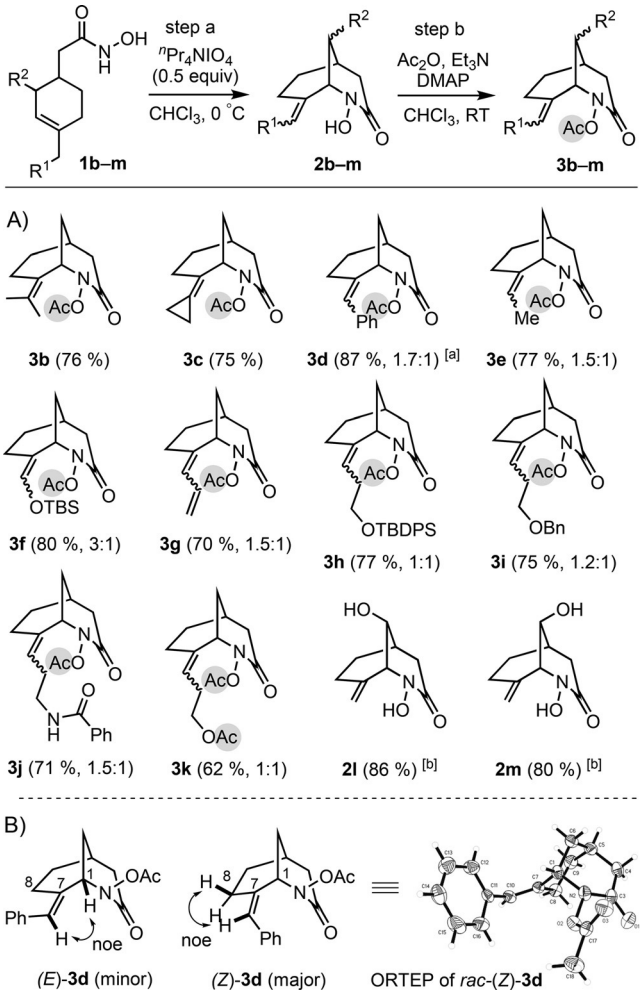
electronically demanding *s-cis* rotamer of the acyl nitroso group in the possible pericyclic reaction. To prove this concept, we designed a simple cyclohexene-derived hydroxamic acid **1a**, readily prepared on a gram scale from 1,4-cyclohexanedione,[8] for the cyclization. After treatment with tetrapropylammonium periodate (^{n}Pr$_4$NIO$_4$), the proposed transient *N*-acyl nitroso species rapidly underwent the subsequent ene reaction to deliver a cyclized product **2a**, the structure of which was unambiguously confirmed by X-ray crystallographic analysis of its acetate derivative **3a** (Scheme 2C).[9]

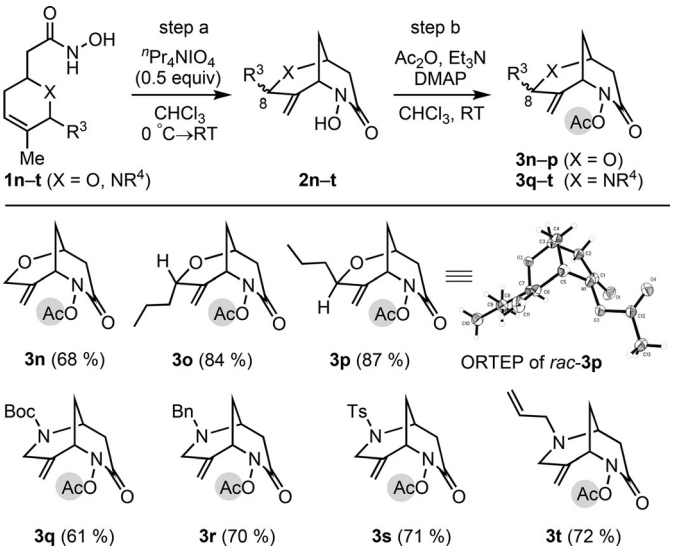
The excellent regioselectivity of the nitroso–ene cyclization promoted us to explore the functional-group tolerance of the reaction. The cyclization was efficient for substrates **1b–j** bearing a variety of functional groups, such as various alkyl and secondary amide groups (Scheme 3). The resulting secondary hydroxamic acids were found to be highly polar and difficult to elute from silica gel.[10] Therefore, acetylation was immediately performed for easy purification and characterization of the corresponding products. Generally, the stereoselectivity of the formation of the *exo* alkene was low, even when bulky substituents were introduced (**3d** versus **3e**; the structure was assigned as shown in Scheme 3B).[8] Nevertheless, the overall yields of the cyclized products were good to excellent. It is known that acyl nitroso compounds readily react with oxa, thio, and aza nucleophiles to release nitrioxyl (HNO).[11] To our surprise, for substrates **1k–m** bearing free hydroxy groups at the side chain and the bridging carbon atom, the ene cyclization remained kinetically favorable and delivered the morphan derivatives in high yields.

Morphan rings with additional embedded heteroatoms have also been documented as intriguing platforms for derivatization.[12] Tetrahydropyran- and tetrahydropyridine-derived hydroxamic acids **1n–t** were therefore prepared and subjected to the optimal conditions (Scheme 4). The desired cyclization proceeded smoothly to give the corresponding bicyclic products in good yields. Inherent stereogenic centers (C8 with R^3 in **1o** and **1p**) and protecting groups at N (in **1q–t**) did not negatively affect the reaction, which suggests its potential application for late-stage modification of complex substrates. This novel ring construction could also be used to access interesting lead compounds for medicinal chemistry.

The cyclopropyl group of **1c** remained intact in the ene reaction, which was rather striking to us owing to the sensitivity of adjacent cyclopropyl groups[13] towards radical or cationic reaction pathways. To gain more insight into the mechanism, we examined a variety of solvents (see Table S1 in the Supporting Information). Although the reaction rate attenuated with a decrease in the solvent polarity, the ene

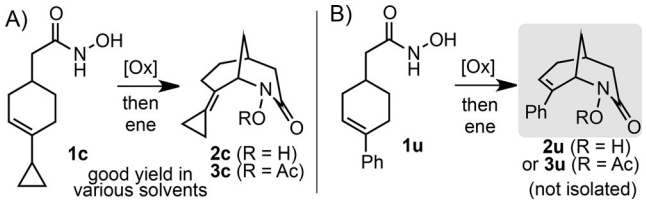


Scheme 3. Ene cyclization of carbocyclic substrates. A) Substrate scope and B) stereochemical determination of **3d**. Reaction conditions: hydroxamic acid (1 mmol), ^{n}Pr$_4$NIO$_4$ (0.5 mmol), CHCl$_3$ (40 mL), 0 °C, 10 min; then Ac$_2$O (1.2 mmol), Et$_3$N (1.3 mmol), DMAP (0.1 mmol), room temperature, 10–30 min. The acetyl group introduced in step b is highlighted in gray. The yield for the two steps is shown in parentheses. The *Z*/*E* isomer was tentatively assigned on the basis of the characterization of **3d**, and the ratio (shown in parentheses) was determined by ^{1}H NMR spectroscopy (400 MHz, [D$_6$]acetone). [a] See the Supporting Information for details. [b] Yield of the isolated ene product. TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, Bn = benzyl.



Scheme 4. Ene cyclization of heterocyclic substrates. The yield of the isolated product after the two steps is shown in parentheses. The acetyl group introduced in step b is highlighted in gray. Boc = *tert*-butoxycarbonyl, Ts = *p*-toluenesulfonyl.

product **3c** (the acetate form) remained prominent, and the ring opening of the cyclopropane product was not detected (Scheme 5A). Moreover, when the phenyl-substituted hydroxamic acid **1u** was tested in the ene reaction, none of the potential product **2u** or **3u** was formed, thus suggesting that the double bond could not be located within the cyclohexane ring of the product (Scheme 5B).



Scheme 5. Experimental results with substrates **1c** and **1u**.

Through DFT calculations at the (U)B3LYP/6-31G(d) level, we found that these ene reactions proceed in a stepwise manner involving zwitterionic or diradical intermediates (Figure 1).[14,15] The first step of the ene reaction of **1d′**, derived from **1d** by oxidation, is the addition of the nitroso group to the alkene moiety of the substrate, thus generating **IN1-Z** via **TS1-Z** or **IN1-E** via **TS1-E** (Figure 1a). **TS1-Z** and **TS1-E** are closed-shell species, with computed activation Gibbs free energies of about 10.6 kcal mol^{-1} in chloroform solution. Intermediate **IN1-Z** is a diradical species, but **IN1-E** is a zwitterionic species.[16] Intermediate **IN1-E** can directly give **2d-E** through a hydrogen-transfer transition state with an activation free energy of 0.3 kcal mol^{-1}. Intermediate **IN1-Z** can also directly give **2d-Z** through a hydrogen-transfer process (via **TS2-Z** with an activation free energy of 6.9 kcal mol^{-1}). Interestingly, **IN1-Z** could undergo C–C bond rotation via transition state **TS-rot** (with a computed activation free energy of 5.3 kcal mol^{-1}) to give **IN1-E**, which would then give **2d-E**. From these calculations, we can conclude that the ene reaction has two parallel pathways: **1d′**→**TS1-Z**→**IN1-Z**→**2d-Z** and **1d′**→**TS1-E**→**IN1-E**→**2d-E**, together with a bifurcation from **IN1-Z**→**TS-rot**→**IN1-E**→**TS2-E**→**2d-E**. The above whole potential-energy surface indicates that the first step of the ene reaction is irreversible. Because **TS1-Z** and **TS1-E** are close in energy, and **TS-rot** and **TS2-Z** are also close in energy, **2d-E** and **2d-Z** should have similar reaction yields, which is consistent with the experimental results (*Z*/*E* 1.7:1 for **3d** in Scheme 3).

In the case of **1c′** bearing a cyclopropyl group, the ene reaction is also stepwise process with a singlet diradical **IN2** (Figure 1b). It is suggested that **IN2** can undergo cyclopropane-ring opening via **TS5**, but this reaction is disfavored as compared to rapid hydrogen transfer via **TS4** to give the final ene product **2c** (acetate form **3c**). The calculation results also agree with the experimental observations shown in Scheme 3 and Table S1. For the conjugated substrate **1u′** (Figure 1c), derived from the oxidation of **1u**, DFT calculations revealed the hydrogen-transfer step to be very difficult with an activation free energy of 28.0 kcal mol^{-1}. Consequently, other side reactions could become favored, and no target ene product **2u** (or **3u**) would be formed. The difficulty of hydrogen transfer is mainly due to the boatlike transition structure of the forming six-membered ring in **TS7**, whereas for substrate **1d′**, this hydrogen-transfer transition state has a favorable chair conformation (see the Supporting Information).

Having established a method to access the morphan skeleton, we embarked on the synthesis of kopsone, the

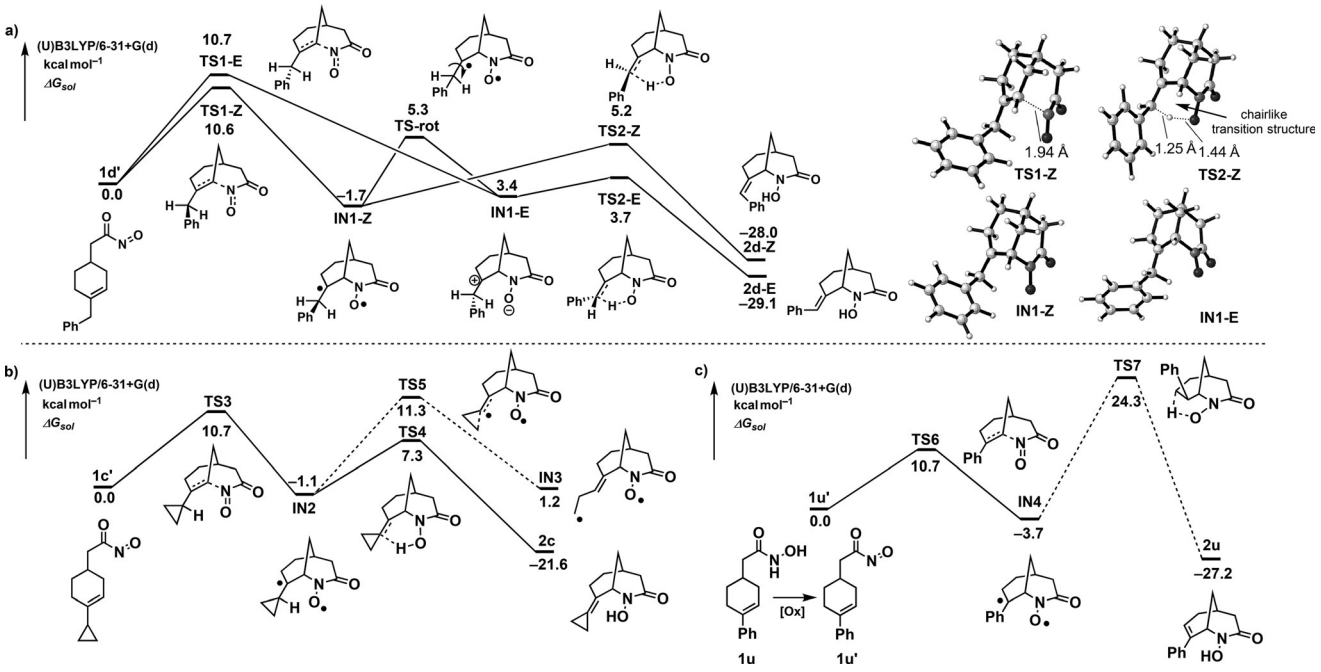
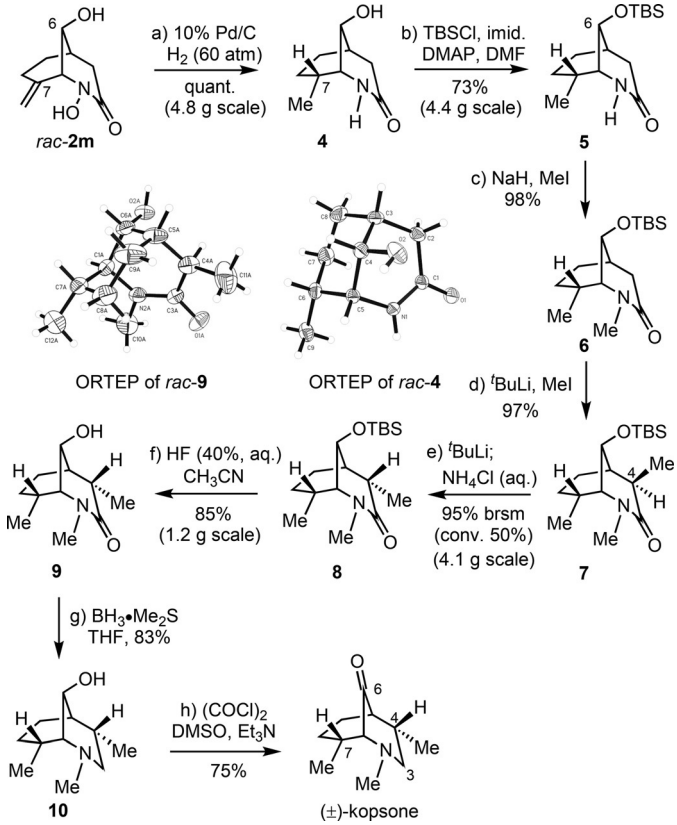


Figure 1. Mechanistic study with DFT calculations at the PCM($CHCl_3$)/(U)B3LYP/6-31G(d)//(U)B3LYP/6-31G(d) level. IN = intermediate, TS = transition state, rot = rotation.

simplest morphan-type monoterpene alkaloid known.[17] The structure features three methyl groups with the same orientation and a carbonyl functionality at the bridging carbon atom. Although the biogenetic origin and bioactivity of kopsone remain unknown, the intriguing strained architecture was anticipated as an ideal testing ground for the derivatization of **2m** with a preinstalled hydroxy group at C6.

Hydrogenation of the terminal alkene in **2m** was possible under a high pressure of hydrogen when the reaction was carried out on a 4.8 g scale (Scheme 6). Interestingly, both the alkene and the *N*-hydroxy group were reduced to deliver amide **4** in excellent yield. The requisite chirality at C7 was unambiguously verified by X-ray crystallographic analysis of **4**.[9] To prevent undesired O-methylation and to enable the late-stage introduction of a methyl group at C4 with the proper facial selectivity, protection with a silyl group was undertaken prior to N-methylation of the amide to deliver compound **6**. The following methylation at C4 proved to be challenging owing to the steric hindrance. We screened various sets of basic conditions and found that *tert*-butyllithium[18] effectively enabled methylation at the α position to the amide, albeit with the opposite stereochemistry to that desired. The resulting stereogenic center was then epimerized by repeated exposure to basic conditions. Although the conversion was moderate (50% on a 4 g), **8** was isolated 83% total yield after three runs. After removal of the silyl group, the free hydroxy group greatly facilitated the borane reduction of the amide to deliver tertiary amine **10**, whereas amide **8** was obstinate to even harsh reduction conditions (e.g., $LiAlH_4$). The subsequent Swern oxidation with freshly distilled oxalyl dichloride[19] proceeded smoothly to afford (±)-kopsone, whose spectral data were consistent with those reported.[17]

In summary, a carbon-tethered type II nitroso–ene cyclization was developed to construct morphan derivatives. Substrates bearing free hydroxy and amide groups as well as heteroatoms embedded in the second ring are of particular interest for future medicinal applications. The current approach was also successfully applied to the first synthesis of (±)-kopsone. Quantum-chemical calculations indicated that the present nitroso–ene reactions proceed in a stepwise manner, in which the first step to form the C–N bond and generate a diradical or zwitterionic intermediate is rate-determining, and the second step is a facile hydrogen-transfer reaction with a chairlike transition structure. These mechanistic studies revealed the unique reactivity of the *N*-acyl nitroso group for the ene reaction, thus laying the groundwork for the future development of novel reaction modes in the context of complex-alkaloid synthesis.



Scheme 6. Total synthesis of (±)-kopsone. Reaction conditions: a) 10% Pd/C (25 wt%), H_2 (60 atm), MeOH, 40 °C, 24 h, quant; b) TBSCl (1.5 equiv), imidazole (1.5 equiv), DMAP (0.15 equiv), DMF, 0→80 °C, 2 h, 73%; c) NaH (2.5 equiv), MeI (2.5 equiv), THF, 0 °C→RT, 2 h, 98%; d) ^{t}BuLi (1.6 M in heptane, 3 equiv), MeI (5 equiv), THF, −78 °C, 2 h, 97%; e) ^{t}BuLi (1.6 M in heptane, 6 equiv), THF, −78 °C; then saturated, aqueous NH_4Cl, 1 h, 95% (brsm); f) aqueous HF (10 equiv), CH_3CN, 0 °C→RT, 4 h, 85%; g) $BH_3{\cdot}Me_2S$ (2 M in THF, 25 equiv), THF, 0→80 °C, 4 h, 83%; h) $(COCl)_2$ (1.3 equiv), DMSO (2.4 equiv), Et_3N (6 equiv), CH_2Cl_2, −78 °C, 2 h, 75%. DMF = *N*,*N*-dimethylformamide, imid. = imidazole, brsm = based on the recovered starting material, DMSO = dimethyl sulfoxide.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · cyclization · diradicals · morphan core · nitroso–ene reactions

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[1] a) D. C. Palmer, M. J. Strauss, *Chem. Rev.* **1977**, *77*, 1; b) J. Bosch, J. Bonjoch, *Heterocycles* **1980**, *14*, 505; c) J. Bonjoch, F. Diaba, B.

Bradshaw, *Synthesis* **2011**, 993; d) B. Kang, P. Jakubec, D. J. Dixon, *Nat. Prod. Rep.* **2014**, *31*, 550; for selected recent methods toward morphan synthesis, see: e) B. Bradshaw, C. Parra, J. Bonjoch, *Org. Lett.* **2013**, *15*, 2458; f) A. D. Gammack Yamagata, S. Datta, K. E. Jackson, L. Stegbauer, R. S. Paton, D. J. Dixon, *Angew. Chem. Int. Ed.* **2015**, *54*, 4899; *Angew. Chem.* **2015**, *127*, 4981; g) R. Manzano, S. Datta, R. S. Paton, D. J. Dixon, *Angew. Chem. Int. Ed.* **2017**, *56*, 5834; *Angew. Chem.* **2017**, *129*, 5928; h) B. Li, R. Liu, R. Liang, Y.-X. Jia, *Acta Chim. Sin. (Chin. Ed.)* **2017**, *75*, 448.

[2] a) J. S. Cannon, L. E. Overman, *Angew. Chem. Int. Ed.* **2012**, *51*, 4288; *Angew. Chem.* **2012**, *124*, 4362; b) U. Rinner, T. Hudlicky, *Top. Curr. Chem.* **2012**, *309*, 33.

[3] a) M. Gates, G. Tschudi, *J. Am. Chem. Soc.* **1956**, *78*, 1380; for a recent synthesis of morphine, see: b) H. Umihara, S. Yokoshima, M. Inoue, T. Fukuyama, *Chem. Eur. J.* **2017**, *23*, 6993.

[4] a) J. Ouyang, R. Yan, X. Mi, R. Hong, *Angew. Chem. Int. Ed.* **2015**, *54*, 10940; *Angew. Chem.* **2015**, *127*, 11090; b) S.-H. Huang, X. Tian, X. Mi, Y. Wang, R. Hong, *Tetrahedron Lett.* **2015**, *56*, 6656; c) J. Ouyang, X. Mi, Y. Wang, R. Hong, *Synlett* **2017**, 762.

[5] M. G. Memeo, P. Quadrelli, *Chem. Rev.* **2017**, *117*, 2108.

[6] a) W. Oppolzer, V. Snieckus, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 476; *Angew. Chem.* **1978**, *90*, 506; b) K. Mikami, M. Shimizu, *Chem. Rev.* **1992**, *92*, 1021; c) B. B. Snider in *Comprehensive Organic Synthesis*, *Vol. 2* (Eds.: G. A. Molander, P. Knochel), 2nd ed., Oxford, Elsevier, **2014**, chap. 2.03, pp. 148 – 191.

[7] For a few examples only with *C*-nitrosoformate esters, see: G. W. Kirby, H. McGuigan, D. McLean, *J. Chem. Soc. Perkin Trans. 1* **1985**, 1961.

[8] See the Supporting Information for details.

[9] The crystallographic data of **3a**, (*Z*)-**3d**, **3p**, **3r**, **4**, and **9** are summarized in the Supporting Information and can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[10] a) Y. K. Agrawal, *Russ. Chem. Rev.* **1979**, *48*, 948; b) C. J. Marmion, J. P. Parker, K. B. Nolan in *Comprehensive Inorganic Chemistry II: From Elements to Applications* (Eds.: J. Reedijk, K. Poeppelmeier), Elsevier, Amsterdam, **2014**, chap 3.23, pp. 683 – 708.

[11] F. Doctorovich, P. J. Farmer, M. A. Marti, *The Chemistry and Biology of Nitroxyl (HNO)*, 1st ed., Amsterdam, Elsevier, **2017**.

[12] a) M. Prakesch, S. Srivastava, D. M. Leek, P. Arya, *J. Comb. Chem.* **2006**, *8*, 762; b) K. Wiedemeyer, B. Wünsch, *Carbohydr. Res.* **2012**, *359*, 24; c) S. Hardy, S. F. Martin, *Tetrahedron* **2014**, *70*, 7142.

[13] D. Griller, K. U. Ingold, *Acc. Chem. Res.* **1980**, *13*, 317.

[14] a) A. G. Leach, K. N. Houk, *J. Am. Chem. Soc.* **2002**, *124*, 14820; b) A. G. Leach, K. N. Houk, *Org. Biomol. Chem.* **2003**, *1*, 1389; c) Z.-X. Yu, K. N. Houk, *J. Am. Chem. Soc.* **2003**, *125*, 13825; d) X. Lu, *Org. Lett.* **2004**, *6*, 2813; e) N. C. James, J. M. Um, A. B. Padias, H. K. Hall, Jr., K. N. Houk, *J. Org. Chem.* **2013**, *78*, 6582.

[15] In these calculations, we do not consider in situ generation of the nitroso compound and final elaboration of the ene product by acylation.

[16] The intermediates shown in Figure 1 are either (polarized) diradical or zwitterionic species. The form taken could be determined by the combined effects of substitution, conformation, and solvation (see the Supporting Information for further discussions).

[17] C. Kan-Fan, T. Sevenet, H. A. Hadi, M. Bonin, J.-C. Quirion, H.-P. Husson, *Nat. Prod. Lett.* **1995**, *7*, 283.

[18] A. I. Meyers, K. B. Kunnen, W. C. Still, *J. Am. Chem. Soc.* **1987**, *109*, 4405.

[19] K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651.

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