Further Studies of Intramolecular Michael Reactions of Nitrosoalkenes for Construction of Functionalized Bridged Ring Systems

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Further Studies of Intramolecular Michael Reactions of Nitrosoalkenes for Construction of Functionalized Bridged Ring Systems

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Ⓢ *Supporting Information*

ABSTRACT: A wide variety of stabilized carbanions have been found to participate as nucleophiles in intramolecular Michael-type conjugate additions to in situ generated nitrosoalkenes to form bridged carbocyclic systems. The vinylnitroso platforms for these cyclizations have been prepared via two key steps involving ring-closing metathesis of vinyl chlorides and regioselective conversion of vinyl chlorides to α-chloroketones with sodium hypochlorite in glacial acetic acid/acetone. An alternative approach to preparation of some cyclization substrates has involved use of more reactive enol ethers as precursors to the requisite α-chloroketones. A sulfonamide anion has also been found to be an effective nucleophile in this type of reaction, leading to formation of a 6-azabicyclo[3.2.1]octane.

X, Y = CO$_2$R, COAr, NO$_2$, SO$_2$Ph, CN, PO(OEt)$_2$, etc
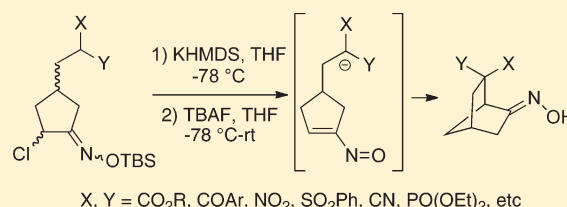
■ INTRODUCTION AND BACKGROUND

Although vinylnitroso compounds **3** were first postulated as transient, highly reactive intermediates over 100 years ago,[1,2] the first isolable member of this class of unstable electron-deficient alkenes was not reported until 1960.[3] Two primary modes of reactivity have been described for nitrosoalkenes over the years. It has been observed that species such as **3** can act as a heterodiene in [4 + 2]-cycloadditions with electron-rich alkenes to form 5,6-dihydro-4*H*-1,2-oxazines. Both inter- and intramolecular versions of this process have been effected.[2b] Vinylnitroso compounds **3** are also known to act as Michael acceptors in conjugate addition reactions with a variety of carbon and heteroatom nucleophiles to afford adducts **4**, but little in the way of systematic study of this type of transformation currently exists (Scheme 1).[2,4]

The two most commonly used methods for producing nitrosoalkenes utilize oximes of α-chloro aldehydes and ketones. The large preponderance of examples in the literature of generation of vinylnitroso compounds has involved base-promoted dehydrohalogenation of α-halooximes **1**.[2] However, for effecting conjugate additions, this process usually involves the use of 2 equiv of a nucleophile, one of which acts as a base. In the 1980s, Denmark and co-workers developed a useful and more efficient alternative procedure based on the fluoride-induced cleavage of easily prepared α-chloro-*O*-silyloximes **2** to give a nitrosoalkene **3**.[5]

We have recently been engaged in expanding the utility of nitrosoalkenes as enolonium ion equivalents and in applying this chemistry to total syntheses of some natural product targets.[4,6] During the course of these studies, we decided to explore the feasibility of effecting intramolecular conjugate additions of nitrosoalkenes to produce bridged and fused ring systems since such methodology had not previously been reported.[7] In a brief preliminary communication,[8] we have demonstrated that such cyclizations are indeed easily effected. This initial work was done primarily with a series of substrates using malonate anions as the nucleophile. For example, malonate **5** was first deprotonated, followed by exposure of the α-chloro-*O*-silyloxime moiety to tetrabutylammonium fluoride in THF to generate the vinylnitroso intermediate **6**, which then cyclized to afford bicyclo-[2.2.2]octane **7** as a single (*E*)-oxime isomer (Scheme 2). Cyclization substrates such as **5** were easily prepared via two reactions developed in these laboratories: ring-closing metathesis of vinyl chlorides[9] and regioselective conversion of vinyl chlorides to α-chloroketones with sodium hypochlorite/glacial acetic acid (vide infra).[10] In view of our success in carrying out these cyclizations, we became interested in exploring the possibility of effecting related transformations using a range of soft nucleophiles other than malonates, and these recent studies are the subject of this paper.
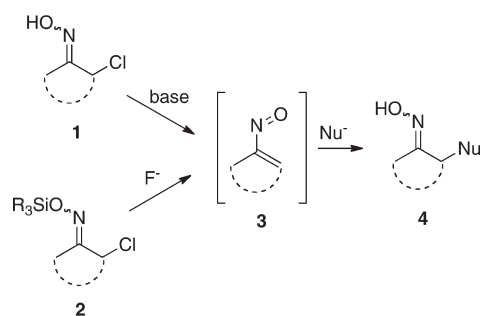
■ RESULTS AND DISCUSSION

Our initial experiments were directed toward synthesis of the requisite cyclization substrates for these expanded studies. It was decided to first explore a platform leading to various bicyclo-[2.2.1]heptane ring systems, and thus readily prepared iodide **8** was chosen as a precursor (see the Supporting Information). Alkylation of malononitrile anion in DMSO with this iodide led to vinyl chloride **9**, which upon treatment with sodium hypochlorite in acetone/glacial acetic acid[10] afforded α-chloroketone **10** as a mixture of diastereomers (Scheme 3). The *O*-silyloxime **11** was then prepared (complex mixture of diastereomers and geometrical isomers) from ketone **10** using commercially available *O*-TBS-hydroxylamine. Using a similar protocol as for the malonate systems,[8] malononitrile **11** was deprotonated with potassium hexamethyldisilazide in THF at −78 °C, followed
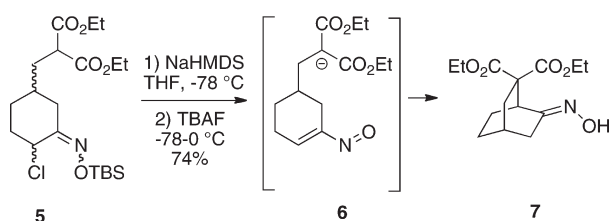
Scheme 1. Formation and Conjugate Additions of Nitrosoalkenes

Scheme 2. Intramolecular Nitrosoalkene Conjugate Addition

Scheme 3. Formation of a Dicyanobicyclo[2.2.1]heptane

Scheme 4. Synthesis of Various Cyclization Substrates

15a X = Y = COPh	16a X = Y = COPh 63%
15b X = Y = SO₂Ph	16b X = Y = SO₂Ph 51%
15c X = CO₂Et; Y = COPMP	16c X = CO₂Et; Y = COPMP 78%
15d X = CO₂Me; Y = SO₂Ph	16d X = CO₂Me; Y = SO₂Ph 74%
15e X = CO₂Et; Y = NO₂	16e X = CO₂Et; Y = NO₂ 59%
15f X = CO₂Et ; Y = PO(OEt)₂	16f X = CO₂Et ; Y = PO(OEt)₂ 55%
15g X = CN; Y = SO₂Ph	16g X = CN; Y = SO₂Ph 38%

| 17a X = Y = COPh 40% | 18a X = Y = COPh 61% |
17b X = Y = SO₂Ph 40%	18b X = Y = SO₂Ph 61%
17c X = CO₂Et; Y = COPMP 57%	18c X = CO₂Et; Y = COPMP 50%
17d X = CO₂Me; Y = SO₂Ph 75%	18d X = CO₂Me; Y = SO₂Ph 68%
17e X = CO₂Et; Y = NO₂ 41%	18e X = CO₂Et; Y = NO₂ 70%
17f X = CO₂Et ; Y = PO(OEt)₂ 43%	18f X = CO₂Et ; Y = PO(OEt)₂ 75%
17g X = CN; Y = SO₂Ph 56%	18g X = CN; Y = SO₂Ph 42%

by addition of TBAF and slow warming to room temperature to generate the transient nitrosoalkene intermediate **12**, which then cyclized to bicyclic dinitrile **13** in good yield. Compound **13** is a single oxime isomer we have tentatively assigned the (*E*)-geometry as shown. It might also be noted that with several of the substrates described in this paper, it was found that yields of cyclization products were slightly improved by using potassium hexamethyldisilazide rather the corresponding sodium base (cf. Scheme 2).

Since iodide **8** proved rather difficult to manipulate due to its volatility, we therefore opted to prepare other substrates via a modified strategy. Thus, the sequence shown in Scheme 4 was used to synthesize a diverse array of cyclization precursors bearing various groups to be tested as nucleophiles (yields unoptimized; see the Supporting Information for detailed experimental procedures). Diene iodide **14**, which we have previously described,[8] is more easily handled than **8** and could be combined with a number of active methylene compounds to produce alkylated products **15a–g**. These dienes all underwent successful ring-closing metathesis using the second-generation Grubbs catalyst to afford cyclic vinyl chlorides **16a–g**.[9] Using our sodium hypochlorite methodology,[10] vinyl chlorides **16a–g** were then converted to the corresponding α-chloroketones **17a–g**, respectively, in moderate yields. Finally, these α-chloroketones were transformed into the requisite α-chloro-*O*-TBS-oxime cyclization substrates **18a–g**.

Cyclization studies were then conducted on the 1,3-diketone **18a** and the bis-phenylsulfone **18b** (Scheme 5). Using our standard protocol, *O*-silyloxime substrates **18a** and **18b** were first deprotonated using potassium hexamethyldisilazide, followed by treatment with TBAF to generate the vinylnitroso intermediate, leading to bicyclo[2.2.1]heptanes **19** and **20**, respectively. Both of these compounds were found to be single oxime geometric isomers, once again presumed to have the (*E*)-stereochemistry.
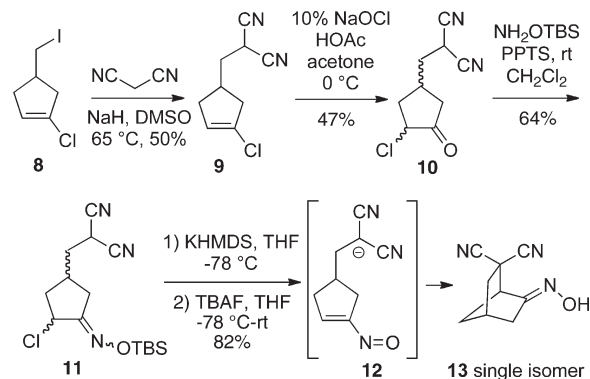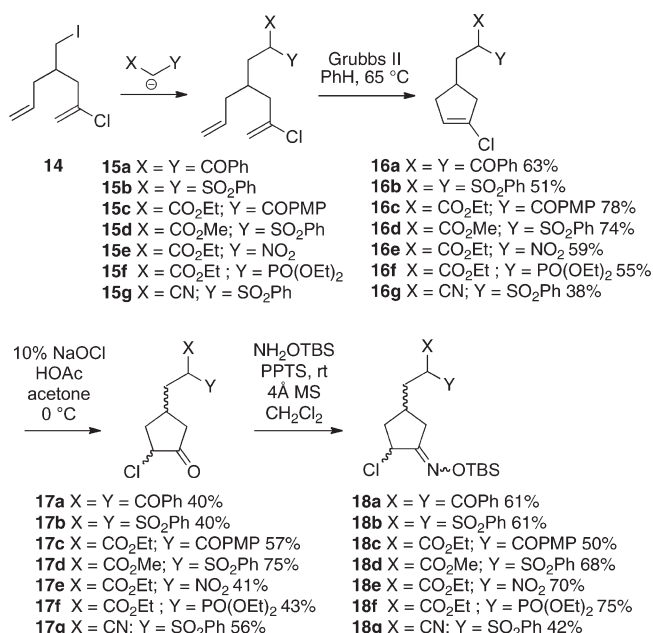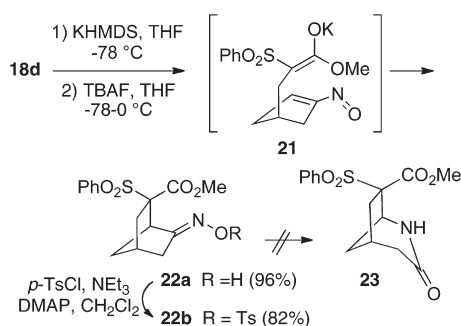
Another system to be examined was the phenylsulfone methyl ester **18d**, which upon cyclization under the usual reaction conditions led to a single stereoisomeric product **22a** in high yield (Scheme 6). Since we could not establish the configuration of **22a** directly by NMR methods due to peak overlap, we attempted to effect a Beckmann rearrangement to afford the azabicyclo[3.2.1]octane **23** which we hoped might be more easily analyzed. However, treatment of **22a** with tosyl chloride/triethylamine/DMAP[11] instead led to the stable crystalline oxime tosylate **22b**. 2D NMR studies on tosylate **22b** established its configuration to be as shown, primarily due to an NOE enhancement between the methyl group of the ester and an aromatic proton *ortho* to the sulfonyl group of the tosyl moiety. In addition, we observe an upfield shift for the ¹H NMR resonances of the *O*-methyl group of **22a** and **22b** (0.17 and 0.49 ppm, respectively) relative to the corresponding uncyclized precursors **15d–18d**. Further confirmation of this structure, along with the (*E*)-geometry of the oxime, came from an X-ray analysis of **22b** (see the Supporting Information). In the crystal, the methyl ester moiety of **22b** is disposed above the face of the aromatic ring of

Scheme 5. Formation of Bicyclo[2.2.1]heptanes
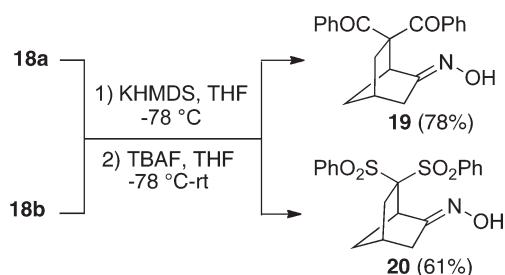
Scheme 6. Stereoselective Formation of Oxime 22a

Scheme 7. Cyclizations of Additional Unsymmetrical Substrates

Scheme 8. Substrate Preparation via an Enol Ether and Stereoselective Cyclization to a Bicyclo[3.2.1]octane


the tosyl group, thus lending support to the NMR upfield shift argument. Thus, the cyclization apparently occurs via an ester enolate conformation like **21**. At this point, it is not clear if the preference for formation of the product having the ester group *syn* to the oxime is a result of steric factors, or if there is some type of dipole effect controlling the stereochemical outcome.

Several other cyclizations involving unsymmetrical substrates are shown in Scheme 7. The nitro ester **18e** also was stereoselective and provided a single cyclization product **24**. Surprisingly, treatment of oxime **24** with tosyl choride, as was done with oxime **22a**, gave no reaction even upon heating. However, based upon the fact that the −OCH₂− group of the ethyl ester of **24** is not shifted upfield relative to precursors **15e**−**18e**, we have tentatively assigned the configuration of this compound as having the oxime and ester *anti* as shown.

The β-ketoester substrate **18c** also could be successfully cyclized, but in this case an inseparable 2.2:1 mixture of epimeric products **25** was produced. Similarly, phosphonate ester **18f** also cyclized in good yield, but with this system an inseparable 1:1 mixture of epimers **26** was obtained. Finally, with phenylsulfone nitrile substrate **18g** a 10:1 epimeric mixture of bicycloheptanes **27** was generated, which again was inseparable by chromatography. In each of the above three examples, the products all appeared to be single oxime geometric isomers assumed to be (*E*), although the configuration of the products at the quaternary carbon was not determined due to our inability to obtain pure compounds. At present, it is unclear why there is so much variation in the stereochemical outcomes of these cyclizations with different functional groups.

One difficulty encountered during the course of these studies is that the hypochlorite-induced halogenation of vinyl chlorides often leads to a variety of undesired side products, including competitive chlorination of the active methine portion of the substrate, thereby lowering the yield of the desired α-chloroketones (Cf Scheme 4).[10b] It is believed that some of these problems
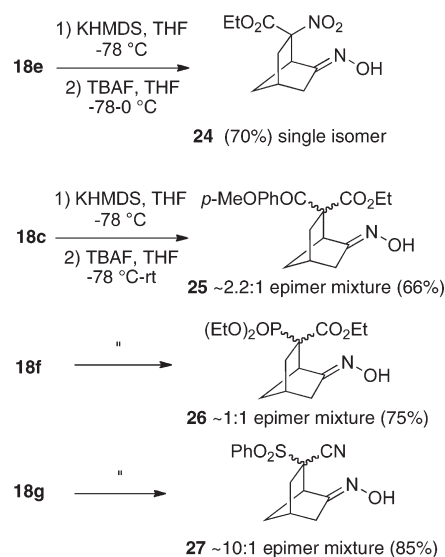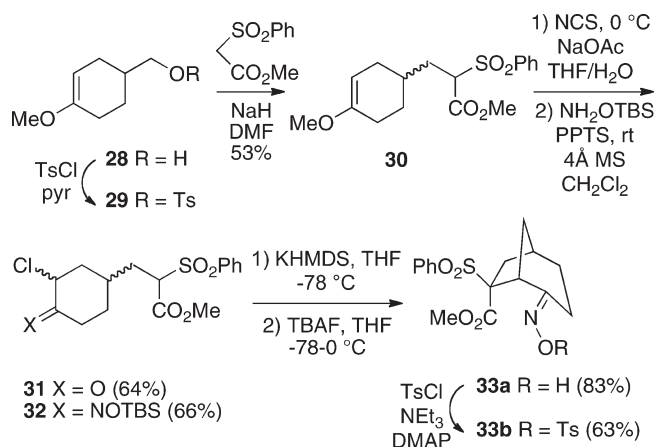
are probably due in part to the electron-deficient nature of the olefinic double bond of vinyl chlorides, thus leading to relatively slow conversion to the respective α-chloroketones. We therefore considered the possibility of using more electron rich enol ethers as alternative precursors to α-chloroketones in order to accelerate the halogenation and possibly obviate some of these problems. Moreover, we anticipated that such a strategy should provide greater flexibility in preparation of various precursors for the nitrosoalkene conjugate addition methodology.

To test this idea, the known enol ether alcohol **28**, prepared via the Diels−Alder reaction of 2-methoxybutadiene[12] with ethyl acrylate followed by ester reduction with lithium aluminum hydride,[13] was converted to tosylate **29** (Scheme 8). Alkylation of methyl α-phenylsulfonylacetate with this tosylate then led to **30** as a mixture of diastereomers in 53% yield based on alcohol **28**. Using the halogenation conditions described by Cha et al.,[14] enol ether **30** was transformed to α-chloroketone **31** with N-chlorosuccinimide in 64% yield. Conversion of this α-chloroketone to *O*-TBS-oxime **32**, followed by cyclization under the usual

Scheme 9. Cyclization with a Sulfonamide Nucleophile
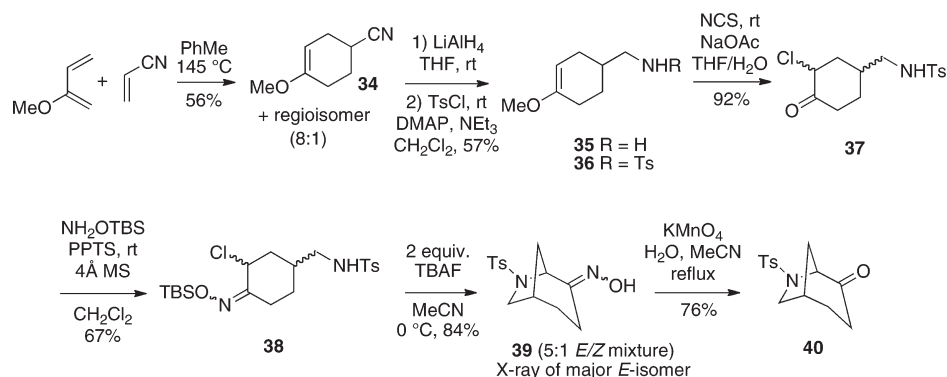
conditions afforded the bicyclo[3.2.1]octane **33a** as a single diastereomer. The configuration and (*E*)-oxime geometry of this product was established by conversion to the oxime tosylate **33b**, which was analyzed by X-ray crystallography. Therefore, the outcome of this cyclization is the same as that observed in the bicyclo[2.2.1]heptane series **22** where the ester group is *syn* to the oxime in the product (cf. Scheme 6).

We have also explored the possibility of effecting intramolecular nitrosoalkene conjugate additions using nitrogen nucleophiles to form bridged azaheterocycles. Thus, Diels–Alder cycloaddition of 2-methoxybutadiene[12] with acrylonitrile as reported by Katritzky and co-workers[15] gave an 8:1 mixture of the desired adduct **34** along with its regioisomer, which was not easily separated (Scheme 9). Therefore, the mixture was reduced to the corresponding amine **35**,[16] followed by treatment of the crude material with tosyl chloride to afford sulfonamide **36**, which could be purified by chromatography. We were pleased to find that under the Cha reaction conditions[14] enol ether **36** was cleanly transformed to α-chloroketone **37** in high yield. It should be added that we have observed that halogenation of some vinyl chloride systems related to enol ether **36** using our sodium hypochlorite method led to significantly lower yields of the respective α-chloroketones and also produced varying amounts of products resulting from *N*-chlorination of the sulfonamide.[17]

Subsequent reaction of compound **37** with *O*-TBS-hydroxylamine produced the required α-chloro-*O*-silyloxime **38**. Interestingly, it was discovered that TBAF is a sufficiently strong base to deprotonate the sulfonamide for the cyclization onto the derived nitrosoalkene. Thus, exposure of substrate **38** to 2 equiv of TBAF in acetonitrile at 0 °C led directly to formation of the desired 6-azabicyclo[3.2.1]octane in good total yield as a 5:1 oxime geometric isomer mixture. The major isomer of **39** was determined by X-ray crystallography to have the (*E*)-geometry as shown. For further characterization, the oxime mixture could be oxidatively cleaved to afford the bridged ketone **40** in 76% yield.[18]

■ CONCLUSION

In summary, we have found that intramolecular conjugate additions of nitrosoalkenes, generated in situ via the Denmark α-chloro-*O*-silyloxime methodology,[5] can be effected using a wide variety of soft carbon nucleophiles to produce bridged ring systems.[19] Some of these cyclizations were found to proceed with high stereoselectivity, although the factors controlling the product configurations are not yet well understood. Similarly, use of a sulfonamide nucleophile leads to the formation of a bridged

aza-heterocyclic ring system.[20] We are currently investigating further extensions and variations of this methodology, along with applications to the synthesis of some natural products.

■ EXPERIMENTAL SECTION

2-(3-Chlorocyclopent-3-enylmethyl)malononitrile (9). A suspension of NaH (60% dispersion in mineral oil, 180 mg, 4.5 mmol) in DMSO (2 mL) was heated at 70 °C for 1 h and cooled to rt. To the resulting mixture was added a solution of malononitrile (298 mg, 4.5 mmol) in DMSO (2 mL) at rt. After the mixture was stirred for 5 min, a solution of iodide **8** (545 mg, 2.25 mmol) in DMSO (1 mL) was added, and the mixture was stirred for 12 h at 65 °C. Saturated aqueous NH_4Cl and ether were added. The organic layer was separated, and the aqueous layer was extracted with ether. The combined ether layer was washed with water and brine. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (30% ether/pentane) to afford the vinyl chloride **6** as a colorless oil (203 mg, 50%): ^{1}H NMR (300 MHz, CDCl₃) δ 5.47–5.46 (m, 1H), 3.59 (t, *J* = 7.4 Hz, 1H), 2.67–2.46 (m, 3H), 2.17–2.09 (m, 1H), 2.03–1.91 (m, 3H); ^{13}C NMR (75 MHz, CDCl₃) δ 130.2, 124.5, 112.1, 42.1, 36.5, 35.8, 34.4, 20.9; no molecular ion was detected by HRMS.

2-(3-Chloro-4-oxocyclopentylmethyl)malononitrile (10). To a solution of vinyl chloride **9** (39 mg, 0.22 mmol), acetone (2.1 mL), and glacial acetic acid (0.9 mL) at 0 °C was added dropwise sodium hypochlorite (0.18 mL of 10% solution, 0.22 mmol) via syringe. The reaction mixture was stirred at 0 °C for 30 min and quenched by addition of saturated aqueous $NaHCO_3$ solution. The mixture was then extracted with dichloromethane. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (80% ether/pentane) affording the α-chloroketone **10** as a clear oil (20 mg, 47%): ^{1}H NMR (300 MHz, CDCl₃, diastereomer mixture) δ 4.21–4.11 (m, 1H), 3.79–3.72 (m, 1H), 2.88–2.66 (m, 2H), 2.48–2.40 (m, 1H), 2.23–2.15 (m, 2H), 2.12–1.89 (m, 2H); ^{13}C NMR (75 MHz, CDCl₃) δ 207.3, 207.1, 112.3, 112.2, 58.3, 56.6, 41.4, 41.3, 39.5, 39.2, 36.3, 36.1, 31.9, 31.0, 21.8, 21.6; HRMS-AP [M + NH_4]⁺ calcd for $C_9H_{13}ClN_3O$ 214.0747, found 214.0748.

2-(3-Chloro-4-*tert*-butyldimethylsilyloxyiminocyclopentylmethyl)malononitrile (11). To a solution of α-chloroketone **10** (17 mg, 0.086 mmol) in dichloromethane (3 mL) were added *O*-(*tert*-butyldimethylsilyl)hydroxylamine (16.5 mg, 0.11 mmol), 4 Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 24 h and then filtered through a pad of Celite. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (30% ether/hexanes) to afford the

α-chloro-*O*-silylketoxime **10** as a colorless oil (18 mg, 64%): ^{1}H NMR (300 MHz, CDCl$_3$, complex mixture of diastereomers including oxime geometric isomers) δ 4.88−4.54 (m, 1H), 3.63−3.57 (m, 1H), 2.86− 2.42 (m, 2H), 2.24−1.89 (m, 4H), 1.76−1.61 (m, 1H), 0.77−0.70 (m, 9H), 0.01−0.00 (m, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 165.5, 165.0, 164.5, 164.1, 112.6, 112.5, 58.4, 56.0, 50.7, 42.3, 41.2, 36.7, 36.1, 35.8, 33.4, 32.1, 31.9, 26.4, 26.3, 26.3, 22.0, 21.9, 18.5, 18.5, −4.8, − 4.8; HRMS-AP [M + H]$^+$ calcd for C$_{15}$H$_{25}$ClN$_3$OSi 326.1455, found 326.1459.

Typical Intramolecular Nitrosoalkene Cyclization: 6-Hydr-oxyiminobicyclo[2.2.1]heptane-2,2-dicarbonitrile (13). To a stirred solution of *O*-silyloxime **11** (16.3 mg, 0.05 mmol) in THF (3 mL) at −78 °C was added dropwise KHMDS (0.5 M in toluene, 0.12 mL, 0.06 mmol) via syringe, and the reaction mixture was stirred at −78 °C for 1 h. TBAF (1 M in THF, 0.05 mL, 0.05 mmol) was added dropwise via syringe, and the mixture was warmed to rt over 3 h. Saturated aqueous NH$_4$Cl was then added. The mixture was extracted with ether, and the combined extracts were dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (75% ether/pentane) to afford the bridged bicyclic oxime **13** as a single geometric isomer (7.1 mg, 82%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.94 (br s, 1H), 3.37 (d, *J* = 1.2 Hz, 1H), 2.70−2.66 (m, 1H), 2.47−2.31 (m, 2H), 2.14 (dd, *J* = 3.3, 17.9 Hz, 1H), 2.02 (dd, *J* = 2.5, 13.4 Hz, 1H), 1.90−1.84 (m, 1H), 1.79−1.67 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 156.7, 114.5, 113.5, 50.9, 42.2, 36.9, 34.4, 32.8, 32.5; HRMS-EI [M]$^+$ calcd for C$_9$H$_9$N$_3$O 175.0746, found 175.0759.

6,6-Dibenzoylbicyclo[2.2.1]heptan-2-one oxime (19): 78% (8 mg, prepared from 15 mg (0.031 mmol) of **18a**); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.80−7.76 (m, 2H), 7.71−7.68 (m, 2H), 7.35−7.28 (m, 2H), 7.23−7.17 (m, 4H), 6.60 (br s, 1H), 3.89 (d, *J* = 0.9 Hz, 1H), 3.08 (dd, *J* = 2.6, 12.8 Hz, 1H), 2.53 (s, 1H), 2.33−2.16 (m, 2H), 1.93−1.85 (m, 2H), 1.64−1.60 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 197.9, 197.2, 163.4, 137.2, 135.3, 133.7, 133.5, 129.7, 129.5, 129.0, 128.9, 70.1, 51.2, 40.5, 38.6, 35.8, 33.6; HRMS-ES [M + H]$^+$ calcd for C$_{21}$H$_{20}$NO$_3$ 334.1443, found 334.1447.

6,6-Bis-benzenesulfonylbicyclo[2.2.1]heptan-2-one oxime (20): 61% (5.7 mg, prepared from 13 mg (0.023 mmol) of **18b**); ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.03−8.00 (m, 2H), 7.64−7.61 (m, 2H), 7.56−7.49 (m, 2H), 7.44−7.34 (m, 4H), 6.98 (br s, 1H), 3.25 (s, 1H), 2.66−2.60 (m, 2H), 2.45−2.34 (m, 3H), 2.24 (dd, *J* = 3.5, 17.3 Hz, 1H), 1.47−1.34 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.3, 139.6, 137.1, 135.0, 134.6, 131.0, 131.0, 129.3, 129.0, 95.5, 50.8, 40.8, 35.9, 35.1, 33.5; HRMS-ES [M + H]$^+$ calcd for C$_{19}$H$_{20}$NO$_5$S$_2$ 406.0783, found 406.0774.

2-Benzenesulfonyl-6-hydroxyiminobicyclo[2.2.1]heptane2-carboxylic acid methyl ester (22a): 96% (17 mg, prepared from 26 mg (0.055 mmol) of **18d**); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.71 (d, *J* = 7.4 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 3.41 (s, 3H), 3.26 (s, 1H), 2.76−2.65 (m, 2H), 2.46−2.41 (m, 1H), 2.33−2.15 (m, 2H), 1.98 (dd, *J* = 3.4, 17.8 Hz, 1H), 1.44 (d, *J* = 10.7 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.7, 161.9, 137.7, 134.7, 130.1, 129.3, 79.2, 53.3, 50.4, 38.2, 36.0, 34.0, 34.0; HRMS-ES [M + H]$^+$ calcd for C$_{15}$H$_{18}$NO$_5$S 324.0906, found 324.0901.

6-Hydroxyimino-2-nitrobicyclo[2.2.1]heptane-2-carboxylic Acid Ethyl Ester (24). In this case, the reaction mixture was warmed to 0 °C after the TBAF addition: 70% (6.4 mg, prepared from 15 mg (0.038 mmol) of **18e**); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.22 (br s, 1H), 4.38−4.22 (m, 2H), 3.74 (d, *J* = 1.0 Hz, 1H), 2.80−2.71 (m, 2H), 2.55−2.47 (m, 1H), 2.37 (dd, *J* = 3.3, 17.8 Hz, 1H), 2.27−2.17 (m, 1H), 2.00−1.95 (m, 1H), 1.86−1.81 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.2, 159.8, 97.3, 63.1, 51.4, 40.0, 38.3, 34.8, 33.2, 13.8; HRMS-ES [M + H]$^+$ calcd for C$_{10}$H$_{15}$N$_2$O$_5$ 243.0981, found 243.0979.

6-Hydroxyimino-2-(4-methoxybenzoyl)bicyclo[2.2.1]hep-tane-2-carboxylic acid ethyl ester (25): 66% (16.2 mg, prepared from 39 mg (0.081 mmol) of **18c**); ^{1}H NMR (300 MHz, CDCl$_3$, inseparable ∼2.2:1 mixture of isomers) δ 7.96−7.92 (m, 2H, *major*), 7.88−7.84 (m, 2H, *minor*), 7.04 (br s, 1H, *minor*), 6.91 (d, *J* = 6.6 Hz, 2H, *major and minor*), 6.71 (br s, 1H, *major*), 4.12−4.04 (m, 2H, *major and minor*), 3.87 (s, 3H, *major and minor*), 3.70 (s, 1H, *major*), 3.66 (s, 1H, *minor*), 2.88 (dd, *J* = 2.1, 9.8 Hz, 1H, *major*), 2.71 (dd, *J* = 1.8, 9.7 Hz, 1H, *minor*), 2.59 (s, 1H, *major and minor*), 2.43−2.30 (m, 1H, *major and minor*), 2.19−2.11 (m, 1H, *major and minor*), 1.92−1.86 (m, 1H, *major and minor*), 1.75−1.64 (m, 2H, *major and minor*), 1.07−1.01 (m, 3H, *major and minor*); ^{13}C NMR (75 MHz, CDCl$_3$) δ 193.4, 192.5, 173.6, 172.3, 163.8, 163.8, 163.7, 162.8, 131.6, 131.3, 129.2, 127.4, 114.2, 64.1, 63.5, 62.4, 61.9, 55.8, 55.8, 50.5, 50.1, 40.5, 40.2, 38.7, 37.8, 36.1, 34.9, 34.0, 33.3, 14.2, 14.1; HRMS-ES [M + H]$^+$ calcd for C$_{18}$H$_{22}$NO$_5$ 332.1498, found 332.1512.

2-(Diethoxyphosphoryl)-6-hydroxyiminobicyclo[2.2.1]-heptane-2-carboxylic acid ethyl ester (26): 75% (5.4 mg, prepared from 10.5 mg (0.022 mmol) of **18f**); ^{1}H NMR (300 MHz, CDCl$_3$, inseparable ∼1:1 mixture of isomers) δ 7.83 (br s, 1H), 4.26−4.00 (m, 6H), 3.40−3.34 (m, 1H), 2.60 (s, 1H), 2.46−1.95 (m, 6H), 1.39−1.23 (m, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.9, 169.9, 163.1, 162.9, 63.1, 63.0, 63.0, 62.9, 61.8, 55.3, 53.5, 48.8, 38.4, 35.5, 35.4, 33.7, 33.6, 33.5, 16.4, 16.4, 16.3, 16.3, 13.9; HRMS-ES [M + H]$^+$ calcd for C$_{14}$H$_{25}$NO$_6$P 334.1420, found 334.1426.

2-Benzenesulfonyl-6-hydroxyiminobicyclo[2.2.1]hept-ane-2-carbonitrile (27). 85% (7 mg, prepared from 12.5 mg (0.028 mmol) of **18g**); ^{1}H NMR (300 MHz, CDCl$_3$, inseparable ∼10:1 mixture of isomers) δ 7.98 (d, *J* = 7.5 Hz, 2H, *minor*), 7.89 (d, *J* = 7.5 Hz, 2H, *major*), 7.62 (t, *J* = 7.3 Hz, 1H, *major and minor*), 7.49 (t, *J* = 7.7 Hz, 2H, *major and minor*), 7.33 (br s, 1H, *minor*), 7.22 (br s, 1H, *major*), 3.21 (s, 1H, *major*), 2.99 (s, 1H, *minor*), 2.67−2.60 (m, 2H, *major and minor*), 2.40−2.26 (m, 2H, *major and minor*), 2.06 (dd, *J* = 3.5, 18.1 Hz, 1H, *major and minor*), 1.90 (dd, *J* = 2.6, 13.1 Hz, 1H, *major and minor*), 1.51 (d, *J* = 10.4 Hz, 1H, *major and minor*); ^{13}C NMR (75 MHz, CDCl$_3$) δ 160.3, 159.8, 135.8, 135.6, 135.0, 130.9, 129.9, 129.7, 118.5, 117.7, 67.1, 65.7, 50.1, 40.6, 39.3, 37.6, 37.2, 36.0, 35.6, 33.6, 33.5; HRMS-ES [M + H]$^+$ calcd for C$_{14}$H$_{15}$N$_2$O$_3$S, 291.0803; found, 291.0800.

2-Benzenesulfonyl-6-(*p*-toluenesulfonyloxyimino)bicy-clo[2.2.1]heptane-2-carboxylic Acid Methyl Ester (22b). To a stirred mixture of *p*-toluenesulfonyl chloride (23.4 mg, 0.123 mmol), triethylamine (0.017 mL, 0.123 mmol), and a catalytic amount of 4-dimethylaminopyridine in dichloromethane (1 mL) was added a solution of oxime **22a** (15.7 mg, 0.049 mmol) in dichloromethane (2 mL) at rt. The resulting mixture was stirred for 2 h at rt. Dichloromethane was then added, and the organic layer was washed with water and brine. The organic layer was dried over MgSO$_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (30% ethyl acetate/ hexanes) to afford the bicyclic *O*-tosyl oxime **22b** as a white solid (19.0 mg, 82%). A sample of **22b** was recrystallized for X-ray analysis from CH$_2$Cl$_2$/EtOAc: mp 121−125 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.77−7.69 (m, 4H), 7.65−7.59 (m, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 3.46 (s, 1H), 3.14 (s, 3H), 2.78− 2.69 (m, 2H), 2.54−2.49 (m, 1H), 2.42−2.30 (m, 5H), 2.15 (dd, *J* = 3.8, 18.4 Hz, 1H), 1.50 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.7, 167.0, 145.4, 137.4, 134.9, 133.0, 130.1, 130.0, 129.4, 129.2, 78.5, 53.1, 50.8, 38.3, 35.9, 35.8, 33.9, 22.0; HRMS-ES [M + H]$^+$ calcd for C$_{22}$H$_{24}$NO$_7$S$_2$ 478.0994, found 478.0989.

Methyl 3-(4-Methoxycyclohex-3-enyl)-2-(phenylsulfonyl)-propanoate (30). To a solution of alcohol **28** (230 mg, 1.62 mmol) in pyridine (10 mL) was added tosyl chloride (617 mg, 3.24 mmol). The mixture was stirred at rt for 18 h and washed with saturated NaHCO$_3$. The

organic layer was removed, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure to give the tosylate **29** as a yellow oil. The compound was used for the next step without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 4.434 (br s, 1H), 3.84 (d, J = 6.8 Hz, 2H), 3.40 (s, 3H), 2.34 (s, 3H), 2.11–1.66 (m, 7H).

Methyl phenylsulfonylacetate (0.29 mL, 1.62 mmol) was added to a stirred solution of sodium hydride (77 mg, 1.94 mmol, 60% dispersion in mineral oil) in DMF (8 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 1 h. A solution of crude tosylate **29** in DMF (2 mL) and NaI (98 mg, 0.65 mmol) was added at rt. The resulting mixture was heated at 65 °C for 18 h and then cooled to rt. The mixture was washed with brine, the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure to give a residue purified by flash column chromatography on silica gel (1:3:0.01 EtOAc/hexanes/triethylamine) to afford the title compound **30** as a clear oil containing a mixture of diastereomers in an 1:1 ratio (290 mg, 53% for two steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.81 (m, 2H), 7.68–7.62 (m, 1H), 7.60–7.51 (m, 2H), 4.47 (br s, 1H), 4.08–3.98 (m, 1H), 3.61–3.61 (m, 3H), 3.46–3.42 (m, 3H), 2.12–1.95 (m, 6H), 1.94–1.66 (m, 4H), 1.661.21 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 165.9, 154.4, 154.2, 136.3. 136.2, 133.6, 128.6, 128.4, 90.9, 90.5, 68.6, 68.4. 53.3, 52.3, 52.3, 32.0, 31.2, 30.8, 30.2, 29.3, 28.6, 28.2, 27.0, 26.4, 26.2; HRMS-ES $[M + H]^+$ calcd for $C_{17}H_{23}O_5S$ 339.1266, found 339.1259.

Methyl 3-(3-Chloro-4-oxocyclohexyl)-2-(phenylsulfonyl)-propanoate (31). To a solution of enol ether **30** (110 mg, 0.33 mmol) in THF/H_2O (4:3, 3 mL) were added NaOAc (29 mg, 0.36 mmol) and N-chlorosuccinimide (48 mg, 0.36 mmol). The reaction mixture was stirred at 0 °C for 5 h and then extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure to give a residue purified by flash column chromatography on silica gel (1:3 EtOAc/hexanes) to afford the title compound **31** as a clear oil (74 mg, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) (complex diastereomer mixture) δ 7.89–7.82 (m. 2H), 7.71–7.66 (m, 1H), 7.58–7.54 (m, 2H), 4.16 (br s, 1H), 3.98 (dd, J = 11.0, 4.2 Hz, 1H), 3.65–5.60 (m, 3H), 3.13–2.84 (m, 1H), 2.29–2.12 (m, 3H), 2.07–1.97 (m, 3H), 1.89–1.75 (m, 1H), 1.48–1.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 204.0, 203.9, 166.7, 166.6, 137.2, 137.1, 135.0, 129.7, 129.7, 129.6, 69.3, 69.2, 59.6, 59.3, 53.9, 53.7, 53.6, 41.3, 40.1, 35.7, 35.5, 32.9, 31.8, 31.7, 31.7, 31.3, 29.2, 29.1.

O-Silyloximes 32. To a solution of α-chloroketones **31** (19 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) were added O-(tert-butyldimethylsilyl)hydroxylamine (16 mg, 0.11 mmol), 4 Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 84 h and then filtered through a pad of Celite which was washed with EtOAc. The filtrate was evaporated under reduced pressure to give a residue purified by flash column chromatography on silica gel (1:3 EtOAc/hexanes) to afford compound **32** as a clear oil containing a complex mixture of diastereomers including oxime geometric isomers (17 mg, 66%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.82 (m, 2H), 7.73–7.64 (m, 1H), 7.62–7.52 (m, 2H), 5.60–4.70 (m, 1H), 4.07–3.97 (m, 1H), 3.63–3.60 (m, 3H), 3.28–1.83 (m, 7H), 1.84–1.03 (m, 2H), 0.92–0.87 (m, 9H), 0.13–0.03 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ166.9, 166.8, 161.0, 159.7, 137.2, 134.8, 129.8, 129.7, 129.5, 69.3, 69.1, 59.0, 58.9, 53.6, 53.5, 47.0, 46.8, 41.9, 40.7, 32.7, 32.7, 32.6, 31.8, 30.8, 30.0, 29.7, 27.1, 26.4, 20.0, 19.8, 18.6, −4.9; HRMS-ES $[M + H]^+$ calcd for $C_{22}H_{35}ClNO_5SSi$ 488.1694, found 488.1691.

Methyl 4-(Hydroxyimino)-6-(phenylsulfonyl)bicyclo[3.2.1]-octane-6-carboxylate (33a). To a stirred solution of oxime **32** (40 mg, 0.08 mmol) in THF (2 mL) at −78 °C was added KHMDS (0.5 M in toluene, 0.24 mL, 0.12 mmol) dropwise. After the mixture was

stirred for 1 h at −78 °C, TBAF (1 M in THF, 0.13 mL, 0.12 mmol) was added, and the reaction mixture was stirred at 0 °C for 3 h. Saturated NH_4Cl was added, and the mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (2:1 EtOAc/hexanes) to afford the title compound **33a** as a white solid (23 mg, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.67 (m, 2H), 7.56–7.50 (m, 1H), 7.43–7.38 (m, 2H), 3.40 (s, 3H), 3.38–3.29 (m, 1H), 2.97–2.87 (m, 2H), 2.58–2.39 (m, 3H), 1.63–1.42 (m, 4H), 1.21–1.04 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ168.0, 158.8, 137.0, 134.7, 130.4, 129.3, 83.0, 53.3, 49.6, 37.5, 35.0, 33.4, 30.5, 18.5; HRMS-ES $[M + H]^+$ calcd for $C_{16}H_{20}NO_5S$ 338.1062, found 338.1061.

Synthesis of Oxime Tosylate 33b. To a stirred mixture of triethylamine (0.02 mL, 0.11 mmol), tosyl chloride (20 mg, 0.11 mmol), and a catalytic amount of 4-dimethylaminopyridine in CH_2Cl_2 (1 mL) was added a solution of oxime **33a** (12 mg, 0.036 mmol) in CH_2Cl_2 (2 mL) at rt. The resulting mixture was stirred at rt for 2 h and washed with saturated $NaHCO_3$. The organic layer was removed, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure to give a residue purified by flash column chromatography on silica gel (1:2 EtOAc/hexanes) to afford compound **33b** as a white solid (11 mg, 63%). A sample was crystallized from $MeOH/CH_2Cl_2$ for X-ray analysis: mp 120–124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77–7.71 (m, 4H), 7.71–7.65 (m, 1H), 7.60–7.47 (m, 2H), 7.28–2.25 (m, 2H), 3.61 (d, J = 4.8 Hz, 1H), 3.19 (s, 3H), 3.06–2.92 (m, 2H), 2.70–2.58 (m, 2H), 2.42 (s, 3H), 1.76–1.51 (m, 4H), 1.55–1.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 166.2, 143.8, 135.5, 133.4, 131.6, 128.8, 128.4, 128.0, 81.1, 51.8, 47.2, 36.3, 33.0, 32.6, 29.2, 20.66, 19.3; HRMS-ES $[M + H]^+$ calcd for $C_{23}H_{26}NO_7S_2$ 492.1151, found 492.1134.

4-Methoxycyclohex-3-ene Carbonitrile (34) and 3-Methoxycyclohex-3-ene Carbonitrile.[15] To a pressure flask containing 2-methoxy-1,3-butadiene[12] (3.21 g, 38.2 mmol) in toluene (12 mL) was added acrylonitrile (2.75 mL, 42.0 mmol). The flask was sealed tightly, and the mixture was stirred for 16 h at 145 °C. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (1:1 EtOAc/hexanes) to afford the adducts as a clear oil containing a mixture of regioisomers in an 8:1 ratio (2.93 g, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (t, J = 3.9 Hz, 0.11H), 4.49 (t, J = 12.9 Hz, 0.88H), 3.44 (s, 3H), 2.72–2.69 (m, 0.88H), 2.38–2.35 (m, 0.11H), 2.35–2.18 (m, 2H), 2.18–2.11 (m, 1H), 2.11–1.96 (m, 1H), 1.96–1.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 152.0, 122.7, 93.2, 90.2, 54.5, 30.9, 27.3, 26.0, 25.9, 25.7, 25.3, 21.6; HRMS-EI $[M + H]^+$ calcd for $C_8H_{12}NO$ 138.0919, found 138.0921.

N-(4-Methoxycyclohex-3-enylmethyl)-4-methylbenzene-sulfonamide (36). To a stirred suspension of $LiAlH_4$ (276 mg, 7.29 mmol) in THF (10 mL) at 0 °C was added the mixture of the above nitriles (500 mg, 3.64 mmol) in THF (2 mL) dropwise, and the mixture was stirred at rt for 2 h. The reaction was quenched by slow addition of a 5:1 mixture of THF/H_2O at 0 °C, followed by addition of 1 M NaOH with stirring. The solids were filtered off and washed with EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organics were dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford a yellow oil. The mixture of amines was used for the next step without purification. Data for major regioisomer **35**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.51 (br s, 1H), 3.44 (s, 3H), 2.56 (d, J = 6.5 Hz, 2H), 2.15–1.92 (m, 5H), 1.76–1.64 (m, 2H), 1.64–1.36 (m, 1H), 1.36–1.06 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 92.3, 54.4, 47.8, 37.6, 28.1, 27.7, 26.9; HRMS-EI $[M + H]^+$ calcd for $C_8H_{16}NO$ 142.1232, found 142.1240.

To a solution of the above crude amines (513 mg, 3.64 mmol) in CH_2Cl_2 (12 mL) were added triethylamine (0.5 mL, 3.59 mmol), tosyl

chloride (2 g, 10.5 mmol), and a catalytic amount of 4-(dimethyl-amino)pyridine. The mixture was stirred at rt for 18 h and washed with saturated $NaHCO_3$. The organic layer was removed, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:4 EtOAc/hexanes) to afford the title compound **36** as a white solid (617 mg, 57% for two steps): ^1H NMR (300 MHz, CDCl$_3$) δ 7.68 (d, J = 8.3 Hz, 2H) 7.23 (d, J = 8.0 Hz, 2H), 4.90 (t, J = 10.7 Hz, 1H), 4.42 (br s, 1H), 3.40 (s, 3H), 2.77 (t, J = 6.0 Hz, 2H), 2.35 (s, 3H), 2.07−1.90 (m, 3H), 1.73−1.55 (m, 3 H), 1.25−1.16 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.4, 143.8, 137.4, 130.1, 127.5, 112.1, 109.6, 91.8, 54.4, 48.5, 34.4, 27.8, 27.2, 26.6, 22.0; HRMS-EI [M + H]$^+$ calcd for C$_{15}$H$_{22}$NO$_3$S 296.1320, found 296.1316.

***N*-(3-Chloro-4-oxocyclohexylmethyl)-4-methylbenzene-sulfonamide (37).** To a solution of sulfonamide enol ether **36** (950 mg, 3.22 mmol) in THF/H$_2$O (4:3, 35 mL) were added NaOAc (26 mg, 0.32 mmol) and *N*-chlorosuccinimide (475 mg, 3.54 mmol). The reaction mixture was stirred at rt for 1 h and then extracted with EtOAc. The combined organic extracts were dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (1:2 EtOAc/hexanes) to afford the α-chloroketone **37** as a mixture of two dia-stereomers (935 mg, 92%). A sample of the isomers was separated by chromatography for characterization purposes. Less polar major diastereomer of **37**: ^1H NMR (300 MHz, CDCl$_3$) δ 7.68 (d, J = 8.3 Hz, 2H) 7.25 (d, J = 7.9 Hz, 2H), 5.35 (t, J = 6.6 Hz, 1H), 4.14−4.11 (m, 1H), 2.86−2.76 (m, 3H), 2.36 (s, 3H), 2.25−2.16 (m, 3H), 1.98−1.93 (m, 1H), 1.82−1.74 (m, 1H), 1.35 −1.13 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 204.6, 144.2, 137.1, 130.3, 127.4, 59.7, 47.5, 38.6, 35.5, 31.5, 30.1, 22.0. More polar minor diastereomer of **37**: ^1H NMR (300 MHz, CDCl$_3$) δ 7.68 (d, J = 10 Hz, 2H) 7.26 (d, J = 8.2 Hz, 2H), 5.38 (t, J = 6.6 Hz, 1H), 4.44−4.39 (m, 1H), 2.82−2.77 (m, 2H), 2.51−2.48 (m, 1H), 2.36 (s, 3H), 2.33−2.00 (m, 3H), 2.02−1.98 (m, 1H), 1.60−1.48 (m, 1H), 1.36−1.28 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.3, 144.3, 137.0, 130.3, 127.4, 63.2, 47.6, 42.1, 39.9, 37.8, 30.7, 22.0.

***O*-Silylketoximes 38.** To a solution of α-chloroketones **37** (128 mg, 0.41 mmol) in CH$_2$Cl$_2$ (5 mL) were added *O*-(*tert*-butyldi-methylsilyl)hydroxylamine (66 mg, 0.45 mmol), 4 Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 48 h and then filtered through a pad of Celite which was washed with EtOAc. The filtrate was evaporated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:3 EtOAc/hexanes) to afford compound **38** as a clear oil which was an inseparable complex mixture of diastereomers and silyloxime geometric isomers (121 mg, 67%): ^1H NMR (300 MHz, CDCl$_3$) δ 7.60 (d, J = 8.3 Hz, 2H) 7.16 (d, J = 8 Hz, 2H), 5.55−4.48 (m, 2H), 4.00−3.11, (m, 1H), 2.66−2.29 (m, 2H), 2.21 (s, 3H), 2.08−1.94 (m, 3H), 1.89−1.08 (m, 2H), 0.91−0.78 (m, 1H), 0.78−0.69 (m, 9H), 0.04−0.00 (m, 6H); HRMS-EI [M + H]$^+$ calcd for C$_{20}$H$_{34}$N$_2$O$_3$SSiCl 445.1748, found 445.1751.

6-(Toluene-4-sulfonyl)-6-azabicyclo[3.2.1]octan-4-one Oxime (39). To a solution of *O*-silyloxime **38** (190 mg, 0.43 mmol) in acetonitrile (5 mL) was added TBAF (1 M in THF, 1.07 mL, 1.07 mmol) dropwise at 0 °C, and the mixture was stirred at that temperature for 1 h. Saturated NH$_4$Cl was added, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$, and the solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:1 EtOAc/hexanes) to afford the title compound **39** as a white solid (106 mg, 84%) containing a mix-ture of *E*/*Z* oxime isomers in a 5:1 ratio. The solid was recrystallized from chloroform to afford colorless crystals of the (*E*)-isomer suitable for

X-ray analysis. Data for mixture: ^1H NMR (300 MHz, CDCl$_3$) δ 7.69−7.57 (m, 2H), 7.19 (d, J = 8 Hz, 2H), 5.38 (d, J = 5.8 Hz, 0.17H), 4.42 (d, J = 5.6 Hz, 0.83H), 3.41−3.33 (m, 1H), 3.22 (d, J = 9.5 Hz, 0.17H), 3.06 (d, J = 13.2 Hz, 0.83H), 2.82 (dd, J = 16.5, 6.6 Hz, 1H), 2.45 (br s, 1H), 2.3 (s, 3H), 1.73−1.40 (m, 4H), 1.47−1.13 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ157.1, 142.7, 142.6, 134.8, 134.8, 128.9, 128.8, 128.6,126.9, 126.4, 126.2, 59.6, 51.9, 50.8, 50.4, 49.3, 48.5, 36.7, 36.3, 34.2, 33.4, 29.7, 27.8, 25.6, 24.3, 20.7, 17.0; HRMS-EI [M + H]$^+$ calcd for C$_{14}$H$_{19}$N$_2$O$_3$S 295.1116, found 295.1107.

6-(Toluene-4-sulfonyl)-6-azabicyclo[3.2.1]octan-4-one (40). To a stirred solution of oximes **39** (40 mg, 0.14 mmol) in 2:1 acetonitrile/H$_2$O (4 mL) was added KMnO$_4$ (43 mg, 0.272 mmol). The mixture was refluxed for 2.5 h and then cooled to rt. The mixture was extracted with CH$_2$Cl$_2$, and the aqueous layer was washed with CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$, and the solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (1:1 EtOAc/hexanes) to afford the ketone **40** as a white solid (29 mg, 76%): ^1H NMR (300 MHz, CDCl$_3$) δ 7.63 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 4.07 (d, J = 6.0 Hz, 1H), 3.51−3.46 (m, 1H) 3.39 (d, J = 9.7 Hz, 1H), 2.54 (m, 1H), 2.36 (s, 3H), 2.30−2.21 (m, 1H), 2.13−2.05 (m, 1H), 1.91−1.79 (m, 2H), 1.72−1.51 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 207.3, 144.2, 136.0, 130.3, 127.4, 66.2, 52.3, 37.9, 34.8, 34.7, 30.7, 22.0; HRMS-EI [M + H]$^+$ calcd for C$_{14}$H$_{18}$NO$_3$S 280.1007, found 280.0984.

■ ASSOCIATED CONTENT

ⓢ Supporting Information. Proton and carbon NMR spec-tra of new compounds and experimental procedures for some sequences. X-ray data for compounds **22b**, **33b**, and (*E*)-**39** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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