Stereoselective Synthesis of Functionalized Pyrrolidines via Intramolecular 1,3-Dipolar Silyl Nitronate Cycloaddition[†,1]

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Michael addition products of secondary allylamines to nitroalkenes were captured as the *O*-silyl α-allylaminoalkylnitronates. These undergo stereoselective intramolecular silyl nitronate–olefin 1,3-dipolar cycloaddition to provide highly functionalized pyrrolidines.

Introduction

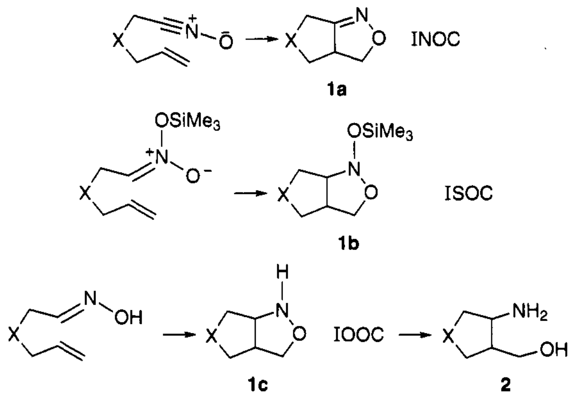
Intramolecular 1,3-dipolar cycloadditions have been shown to have considerable synthetic utility.[2] Among these, intramolecular nitrile oxide-olefin cycloadditions (INOC),[2,3] intramolecular silyl nitronate–olefin cycloadditions (ISOC),[4,5] and intramolecular oxime–olefin cycloadditions (IOOC)[6] give a [*n*.3.0] bicyclic system **1** with a cleavable N–O bond. Reduction of this bond results in a functionalized carbocycle or heterocycle **2** (Scheme 1).

For the synthesis of nitrogen heterocycles via the INOC reaction two routes were developed for the precursor nitrile oxide olefins, (a) via aldoximes or (b) via primary nitroalkanes.

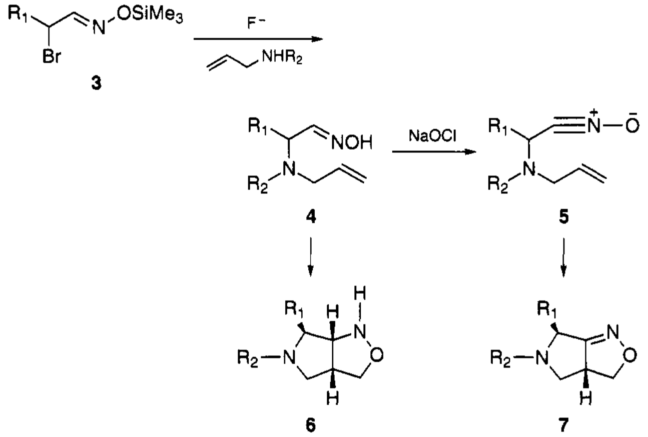
(a) α-Bromo-*O*-silyl aldoxime ethers **3** are treated with fluoride ion to generate unstable nitrosoalkenes which are trapped by an unsaturated nitrogen nucleophile affording allylaminoaldoxime **4**. Chlorination with NaOCl and elimination leads directly to cycloadduct **7** via the nitrile oxide **5** (Scheme 2).

The α-bromo-O-silylaldoxime ethers **3** were generated by NBS treatment of the *O*-silyl oxime ethers.[7] α-Allylaminoaldoxime **4** can also cycloadd to form **6** thermally via an NH nitrone, formed by O to N migration of the oxime proton (IOOC).[6]

Scheme 1



Scheme 2



(b) Monodisplacement on dihaloalkanes by the nitrogen of an *N*-allylamide and treatment of the ω-haloalkylamide with nitrite anion yields the unsaturated nitroalkylamide.[8,9] The monoalkylation does not work well with allylamines. Conversion of the nitro group to a nitrile oxide is usually accomplished with phenyl isocyanate–triethylamine[10] and leads to a dipolar cycloaddition product.

A more direct route for construction of the required β-(allylamino)nitroalkanes **8** would be the Michael addition of a secondary amine to a conjugated nitroalkene. However, such a method suffers from a competitive retro-

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[†] This paper is dedicated to the memory of Prof. Dov Ben Ishai (Israel Institute of Technology).

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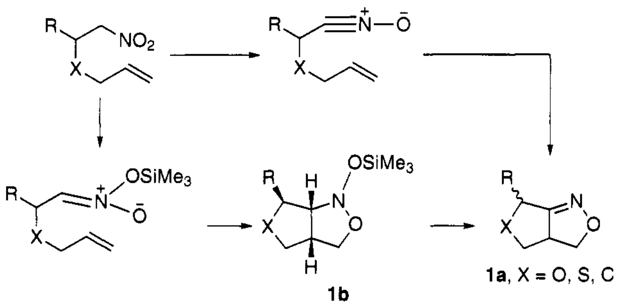
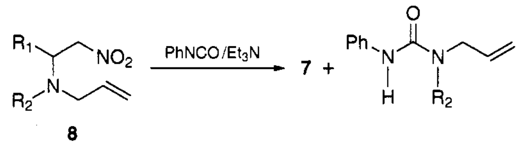
Scheme 3



Michael reaction.[11] For instance, treatment of a β-(allylamino)nitroalkane **8** with phenyl isocyanate and triethylamine gave two isomeric cycloadducts **7** together with the phenylurea **9** formed in 50% yield. Urea **9** had formed from the retro-Michael[8] regenerated amine which added to phenyl isocyanate.



8 **9**

Other simple methods for construction of β-aminonitroalkanes also suffer from limitations. For instance, nitromethane and nitroethane were reported to add only to benzaldehyde *N*-benzyl imine,[12] but the reaction is not general. Mannich type reaction between an aldehyde, an amine, and nitro compounds was unsuccessful with nitromethane, and only its higher homologs can be condensed[13] to give β-aminonitroalkanes. Unfortunately, secondary nitroalkanes cannot be converted into nitrile oxides.

Oxygen[14] and sulfur[15] nucleophiles, on the other hand, are readily added to conjugated nitroalkenes, and the resulting Michael adducts can be used effectively in 1,3-dipolar cycloadditions.

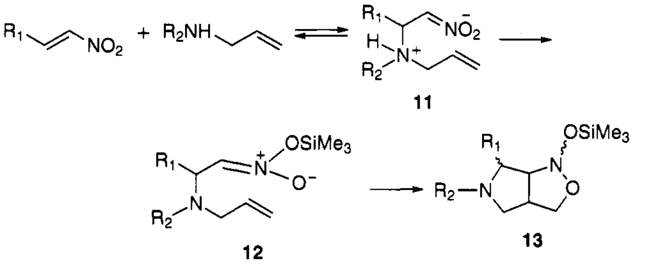
Nitrile oxide–olefin cycloaddition (INOC) often leads to a mixture of stereoisomeric fused isoxazolines.[3] Intramolecular silyl nitronate–olefin cycloaddition (ISOC) was shown to be a stereoselective alternative to the nitrile oxide–olefin cycloaddition.[5b] Indeed, ISOC was applied to the synthesis of oxygen, sulfur, and carbon but not N-containing bicyclic isoxazolines **1a**[5] (Scheme 3).

The somewhat cumbersome methods of preparation of β-aminonitroalkanes or of α-allylaminoaldoximes required for the INOC reaction coupled with its low stereoselectivity motivated us to look for simpler methods of preparation of precursors which will undergo stereoselective cycloadditions.

Results and Discussion

Michael addition of amines to nitroalkenes is the most rapid method to prepare β-aminonitroalkanes but because of the retro-Michael reaction it results in low yields of addition products.[8] Trapping of such an allylamine

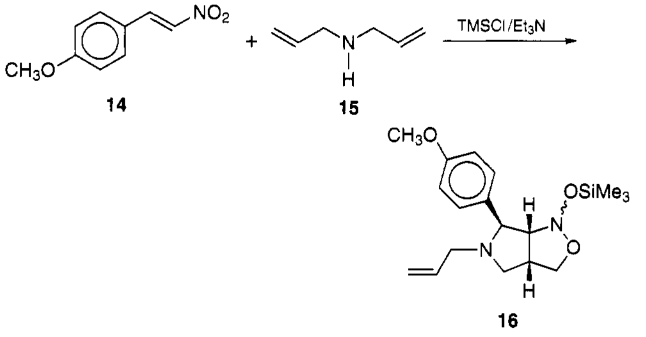
Scheme 4



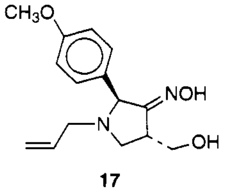
addition product would be an attractive entry to an unsaturated amino silyl nitronate which is an efficient precursor to the highly selective ISOC[5b] reaction. In such a process an allylamine would reversibly add to the α,β-unsaturated nitro olefin;[11] the nitronate **11** formed would be trapped by a silylating agent. A base would be necessary for liberating the α-allylamino *O*-silyl nitronate **12** which can undergo cycloaddition to the *N*-(silyloxy)-isoxazolidine **13** (Scheme 4).

When this Scheme 4 was tested with diallyltrimethylsilylamine (prepared *in situ* from diallylamine **15**, n-BuLi, TMSCl), serving as a nucleophile as well as a silylating agent, and *p*-methoxy-β-nitrostyrene **14** as the Michael acceptor, no reaction occurred and dialyllamine and **14** were recovered. Apparently diallyltrimethylsilylamine is a poor nucleophile or a poor silylating agent.[5]

However, success was realized when a toluene solution of *p*-methoxy-β-nitrostyrene **14** was treated with diallylamine **15** (2.2 equiv), triethylamine (2.2 equiv) and TMSCl (2.2 equiv) under nitrogen at ambient temp for 14–24 h. N-Trimethylsiloxyisoxazolidine **16** was isolated by rapid filtration of triethylamine hydrochloride and removal of solvents. The ^{1}H-NMR spectrum of **16** showed it to be a1:1 mixture of conformers most likely due to the



high energy barrier of inversion in the isoxazolidine ring.[16a] High energy barriers between conformers in *N*-siloxyisoxazolidines have been observed.[16b] Whereas, the C, O, and S-analogs of **16** on treatment with acid gave exclusively the isoxazoline **1a**,[5b] exposure of **16** to aqueous HCl or anhydrous CF_3CO_2H followed by liberation of the salt resulted in a 3:1 mixture of the hydroxy oxime **17** and isoxazoline **18** in 60% overall yield.



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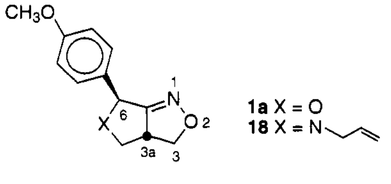

Pyrrolidine **17** and isoxazoline **18** were easily separable using silica gel chromatography (10% Et_3N in ethyl acetate). Only a single isomer was observed for both **17**

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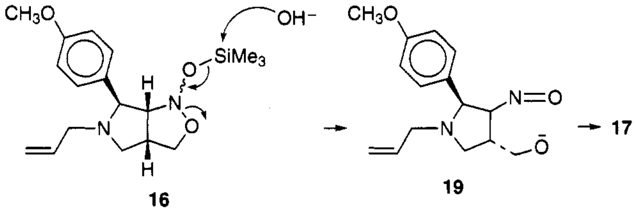
and **18**. By contrast, **1a**, the oxygen analog of **18**, was formed in an INOC reaction as a 4:1 *trans*:*cis* mixture of separable isomers.[14] **18** is the result of acid-catalyzed elimination of Me_3SiOH from **16**. Apparently, treatment with base to liberate the amine after reaction of **16** with acids led partially to ring cleavage with formation of oxime **17**. Formation of an oxime:isoxazoline mixture can be avoided by treating the crude *N*-(silyloxy)isoxazolidine **16** with fluoride ion in THF[5b] or more conveniently with methanolic KOH[4a] which gave exclusively the oxime **17** in 60% overall yield. This basic N–O bond cleavage probably proceeds through an alkoxy nitroso intermediate **19** as is evident from the blue-green color which appears during the reaction.



16 **19**

The stereochemistry of **18** was deduced from ^1H NMR and NOE experiments by comparison with **1a**. Irradiation of the benzylic singlet at 5.52 ppm of **1a** caused a 2.5% enhancement of the bridgehead multiplet at 4.30 ppm only in the *cis* isomer of **1a**. Irradiation of the benzylic single in **18** at 4.31 ppm caused a 2% enhancement of the pseudoaxial C-4 proton at 2.40 ppm and had no influence on the pseudoaxial C-3a bridgehead proton at 4.03 ppm. This indicates a *trans* relationship between positions 3a and 6.

The coupling constant between the pseudoaxial C-4 proton and the vicinal pseudoaxial C-3a proton is 7.5 Hz indicating a dihedral angle of ca. 160° as expected from the *trans* isomer. For the *cis* isomer a dihedral angle of ca. 110° for H_{3a} and H_{4ax} could be expected, which would result in a much smaller (about 2 Hz) coupling constant.

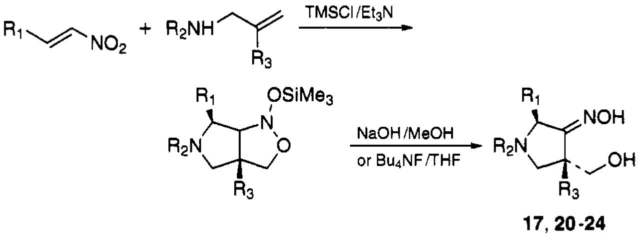
The stereochemistry of the pyrrolidone oxime **17** could not be determined unambiguously by NOE. For instance, irradiation of the C-3a proton did not show NOE enhancement of the ortho protons on the *p*-methoxyphenyl moiety.

Since the stereochemistry in the isoxazolidine **16** is determined during the cycloaddition step, the stereochemistry of the isoxazoline **18** and of the oxime **17** must be identical. Hence, we assign the *trans* stereochemistry to **17**. The fact that oxime **17** is isomerically pure implies that only one oxime geometry is present, probably because of intramolecular hydrogen bonding, but the actual oxime geometry could not be determined unambiguously.

The generality of the reaction was demonstrated by the isolation of several functionalized pyrrolidines **20–24**. Diallylamine, cyclohexylallylamine and *N*-ethyl-2-methallylamine were smoothly added to *β*-nitrostyrenes giving after basic or fluoride work-up, hydroxymethyl pyrrolidone oximes (Scheme 5) in 50–60% overall yields (Table 1). In all cases a single isomer was isolated.

Pyrrolidone oxime **22** provided further evidence regarding the stereochemistry of these products as assigned above on the basis of coupling constants and analogy with the oxygen analog. Irradiation of the ortho protons on the *p*-methoxyphenyl moiety at 7.25 ppm caused an 8% enhancement of the singlet methyl protons at 1.40 ppm indicating these substituents to be on the same face of the ring.

Scheme 5



17, 20-24

Table 1. 4-(Hydroxymethyl)-3-pyrrolidone oximes 17, 20–24 Prepared by Tandem Michael Addition–Silylation–Cycloaddition (Scheme 5)

R_1	R_2	R_3	workup	yield, %	product
4-MeO-C_6H_4	allyl	H	F^-/OH^-	60	**17**
C_6H_5	allyl	H	OH^-	63	**20**
4-MeO-C_6H_4	cyclohexyl	H	OH^-	52[a]	**21**
4-MeO-C_6H_4	Et	Me	F^-	66	**22**
4-MeO-C_6H_4	$C_6H_5CH_2$[b]	H	OH^-	66	**23**
Me	allyl	H	OH^-	10–20	**24**[c]

[a] Only 1 equiv of allylcyclohexylamine was used. [b] Footnote 18c. [c] The main product is the bicyclic isoxazoline **27**.

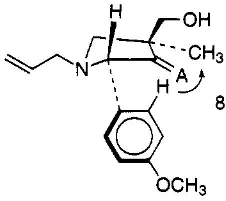
The N-allylated compounds may serve as precursors to the N-unsubstituted pyrrolidines by a mild Pd(0) catalyzed deallylation procedure reported recently.[17] The deallylation may be more straightforward than hydrogenolysis of the N-benzylated product, in which complications due to the presence of the oxime and the other benzyl moiety (1,2 bond in the pyrrolidine ring) may arise during reduction.

The homologous amines *N*-benzyl-(3-butenyl)amine (**25**) and *N*-benzyl-N-(4-pentenyl)amine (**26**) were prepared[18] in order to test this method for the synthesis of piperidine and azepine systems.

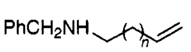
Unfortunately **25** gave a complex mixture of products and **26** did not react at all. Allylamine itself gave under the described conditions a complex mixture of products. Other allylamine derivatives like(methoxycarbonyl)-allylamine and *N*-tosylallylamine did not react when treated with sodium hydride, TMSCl, and *β*-nitrostyrene.

2-Methyl-4-(hydroxymethyl)-3-pyrrolidone oxime (**24**) was obtained in only 10–20% yield when diallylamine was added to nitropropene; the major product was the isoxazoline **27**.

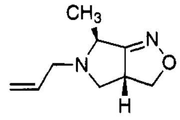
In conclusion, the one pot Michael addition–silylation–cycloaddition procedure (Scheme 5) represents a convenient stereospecific route to a functionalized pyrrolidine ring in particular one containing an aromatic C-2 substituent.



22 A = NOH



25 *n* = 1
26 *n* = 2



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Experimental Section

Procedure for Synthesis of Pyrrolidone Oxime 17 and Isoxazoline 18 Mixture (acidic workup). To a toluene (50 mL) solution of 4-methoxy-β-nitrostyrene (**14**) (935 mg, 5.22 mmol) were added under N_2 diallylamine (**15**) (1.43 mL, 11.6 mmol), TEA (1.6 mL, 11.4 mmol), and TMSCl (1.46 mL, 11.4 mmol). The mixture was stirred for 24 h. At this stage *N*-[(trimethylsilyl)oxy]isoxazolidine **16** could be isolated by rapid filtration over Celite and concentration. When **16** was not isolated, concentrated HCl was added to pH 1 and the biphasic mixture was stirred for 1 h. Water was added, the aqueous phase was washed several times with ether and the solution was basified with KOH to pH 13. The organic material was extracted with ether, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (10% TEA in EtOAc) to yield 210 mg (16%) of isoxazoline **18** and 640 mg (44%) of the more polar pyrrolidone oxime **17** (spectral data for **17** appears in the next section).

7-Allyl-8-(4-methoxyphenyl)-2-[(trimethylsilyl)oxy]-3-oxa-2,7-diazabicyclo[3.3.0]octane (16): oil, ^{1}H NMR (200 M Hz, $CDCl_3$) δ [−0.05 (s, 9H), 0.00 (s, 9H)],[19] 1.90−2.05 (m, 1H), 2.30−2.52 (m, 1H), 2.90−3.00 (m, 1H), 3.10−3.33 (m, 2H), 3.52−3.63 (m, 1H), 3.72−3.87 (m, 2H), [3.79 (s, 3H); 3.83 (s, 3H)],[19] 4.22−4.33 (m, 1H), 5.00−5.22 (m, 2H), 5.63−5.91 (m, 1H), 6.87 (d, J = 7.5 Hz, 2H), 7.26 (d, J = 7.5 Hz, 2H).

5-Allyl-6-(4-methoxyphenyl)-3,3a,4,6-tetrahydropyrrolo[3,4-*c*]isoxazole (18): oil, IR ($CHCl_3$) 1640, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (dd, J = 9.5, 8.5 Hz, 1H), 3.13 (dd, J = 13.5, 7.5, 1H), 3.39 (ddt, J = 13.5, 5, 1.5 Hz, 1H), 3.50 (dd, J = 9.5, 8.5 Hz, 1H), 3.79 (s, 3H), 3.92 (dd, J = 12.5, 7.5 Hz, 1H), 3.96−4.10 (m, 1H), 4.31 (s, br, 1H), 4.53 (dd, J = 8.5, 7.5 Hz, 1H), 5.12 (d, J = 10 Hz, 1H), 5.20 (d, J = 17 Hz, 1H), 5.81 (dddd, J = 19, 17, 7.5, 5 Hz, 1H), 6.88 (d, J = 9 Hz, 2H), 7.36 (d, J = 9 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 52.9, 54.8, 55.3, 56.1, 61.5, 73.0, 114.0, 117.9, 128.5, 131.1, 134.2, 159.4, 170.9; MS *m/z* EI 258 (27 M$^+$), 227 (100, M − HNO). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C 69.74, H 7.02. Found: C 69.53, H 6.95.

General Procedure for Synthesis of Trans-2-Substituted-4-(hydroxymethyl)-*N*-alkyl-3-pyrrolidone Oximes (17, 20−24). To a toluene solution of nitroolefin (1 equiv) was added a secondary allyl amine (1−2.2 equiv), TEA (1.2−2.2 equiv) and TMSCl (1.1−2.2 equiv) under N_2. The mixture was stirred for 14−24 h, the solid TEA was removed by filtration through Celite, and the filtrate was washed with pentane. The solvents were evaporated, and the residue was worked up either with base or with tetrabutylammonium fluoride.

a. Basic Workup. The residue was dissolved in methanol, and solid sodium hydroxide (10% w/w of nitroolefin used) was added. The mixture was stirred at rt for 1 h. The methanol was evaporated, water added, and the product extracted with CH_2Cl_2. The organic solution was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel (SG) chromatography.

b. Fluoride Workup. The residue was dissolved in THF and treated with Bu_4NF (solution or hydrated solid, 1.4 equiv). Usually the color changed from light yellow to dark green-blue. The mixture was kept at rt for 1 h. Water was added until the color changed back to pale yellow and the THF was evaporated. The product was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by SG chromatography.

1-Allyl-*trans*-4-(hydroxymethyl)-2-(4-methoxyphenyl)-3-pyrrolidone oxime (17) was obtained from 4-methoxy-β-nitrostyrene **(14)** (432 mg, 2.41 mmol) with diallylamine (**15**) (0.6 mL, 4.86 mmol), TEA (0.72 mL, 5.12 mmol), and TMSCl (0.64 mL, 5.00 mmol) in 20 mL toluene. Basic workup and chromatography over SG (10% TEA EtOAc) gave 400 mg (60%) of pure product; IR ($CHCl_3$) 3570, 3320, 1610 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 2.31 (dd, J = 10.5, 9 Hz, 1H), 2.87 (ddtd, J = 14, 8, 1, 0.5 Hz, 1H), 3.11−3.25 (m, 2H), 3.40 (ddd, J = 10.5, 9, 1 Hz, 1H), 3.61 (dd, J = 11, 7.5 Hz, 1H), 3.76 (s, 3H), 3.89 (dd, J = 11, 5.5 Hz, 1H), 4.23 (d, J = 0.5 Hz, 1H), 5.04 (dddd, J = 10, 2, 1.5, 1 Hz, 1H), 5.16 (dtd, J = 17, 2, 1 Hz, 1H), 5.77 (dddd, J = 17, 10, 8, 5 Hz, 1H), 6.83 (d, J = 9 Hz, 2H), 7.31 (dd, J = 9, 0.5 Hz, 2H), 9.75 (broad s, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 44.33, 53.0, 55.2, 55.5, 61.9, 67.4, 113.5, 117.8, 123.0, 130.0, 131.5, 134.6, 158.9, 165.4; MS *m/z* EI 276 (14.7 M$^+$), 259 (100, M−OH); *m/z* (CI, isobutane) 336 (66, M + C_4H_9), 277 (100, M + 1). Anal. Calcd for $C_{15}H_{20}N_2O_3$: C 65.19 H 7.30. Found: C 65.22, H 7.38.

1-Allyl-*trans*-4-(hydroxymethyl)-2-phenyl-3-pyrrolidone oxime (20) was obtained from a toluene solution (50 mL) of β-nitrostyrene (977 mg, 6.55 mmol), diallylamine (2.4 mL, 19.44 mmol), TEA (2.8 mL, 19.9 mmol), and TMSCl (2.5 mL, 19.7 mmol). Basic workup and chromatography over SG (EtOAc:hexane:TEA = 6:4:1) gave 1.01 g (67.5%) of pure **20**; IR ($CHCl_3$) 3570, 3320 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (dd, J = 8.5, 7.5 Hz, 1H), 2.86 (dd, J = 13, 8 Hz, 1H), 3.15−3.30 (m, 4H), 3.77 (d, J = 5 Hz, 2H), 4.26 (s, 1H), 5.07 (d, J = 10 Hz, 1H), 5.14 (d, J = 17 Hz, 1H), 5.72 (dddd, J = 17, 10 8, 5 Hz, 1H), 7.25−7.35 (m, 5H), 8.20 (broad s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 44.5, 53.0, 55.5, 62.0, 68.1, 117.8, 127.4, 128.0, 129.0, 134.5, 139.4, 165.5; MS *m/z* EI 247 (81, M + 1), 229 (100, M + 1 − H_2O), 169 (72, M − Ph).

1-Cyclohexyl-*trans*-4-(hydroxymethyl)-2-(4-methoxyphenyl)-3-pyrrolidone Oxime (21). 4-Methoxy-β-nitrostyrene **(14)** (378 mg, 2.11 mmol), cyclohexylallylamine (0.3 mL, 2.07 mmol), TEA (0.36 mL, 2.56 mmol), TMSCl (0.29 mL, 2.28 mmol), stirred for 24 h. Basic workup and chromatography (EtOAc:hexane:Et_3N = 4:5:1) gave 340 mg (51.6%) of **21**; IR ($CHCl_3$) 3570, 3320, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93−1.24 (m, 5H), 1.46−1.68 (m, 3H), 1.68−1.79 (m, 1H), 1.79−1.94 (m, 1H), 2.25−2.45 (m, 1H), 2.51 (dd, J = 9.5, 8 Hz, 1H), 3.12−3.32 (m, 1H), 3.26 (t, J = 7.5 Hz, 1H), 3.79 (s, 3H), 3.80 (broad s, 2H), 4.65 (s, 1H), 6.82 (d, J = 9 Hz, 2H), 7.35 (d, J = 9 Hz, 2H), the acidic OH proton was not observed; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 25.3, 25.6, 26.2, 28.0, 32.1, 43.8, 49.0, 55.2, 58.7, 62.0, 64.0, 113.3, 129.8, 133.2, 158.6, 165.9; MS *m/z* EI 318 (55.9, M$^+$), 275 (100).

1-Ethyl-*trans*-4-(hydroxymethyl)-2-(4-methoxyphenyl)-4-methyl-3-pyrrolidone Oxime (22). From 4-methoxy-β-nitrostyrene (**14**) (685 mg, 3.82 mmol), *N*-ethyl-2-methylallylamine (1 mL, 7.6 mmol), TEA (1.1 mL, 7.83 mmol), and TMSCl (1.0 mL, 7.88 mmol) at rt for 24 h. Fluoride workup (5.2 mL of 1.1 M solution of Bu_4NF in THF) and two recrystallizations from CH_2Cl_2/hexane gave 700 mg (65.9%) of pure **22**, mp 121−122 °C; IR ($CHCl_3$) 3570, 3320, 1610; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 7 Hz, 3H), 1.40 (s, 3H), 2.22 (dt, J = 12, 7 Hz, 1H), 2.51 (m, 2H), 2.91 (d, J = 9 Hz, 1H), 3.58 (d, J = 11 Hz, 1H), 3.61 (d, J = 11 Hz, 1H), 3.78 (s, 3H), 4.23 (s, 1H) 6.83 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 8.08 (broad s, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 12.7, 21.8, 46.2, 46.4, 55.1, 59.6, 68.5, 68.5, 113.4, 130.1, 131.2, 158.7, 168.3, MS *m/z* EI 278 (29, M$^+$), 261 (100). Anal. Calcd for $C_{15}H_{22}N_2O_3$: C 64.72, H 7.97. Found: C 64.11 H 8.08.

1-Benzyl-*trans*-4-(hydroxymethyl)-2-(4-methoxyphenyl)-pyrrolidone Oxime (23). A toluene solution (25 mL) of 4-methoxy-β-nitrostyrene (**14**) (324 mg, 1.81 mmol) was treated with benzylallylamine(18c) (740 mg, 3.6 mmol, 70%, pure), TEA (0.5 mL, 3.6 mmol), and TMSCl (0.46 mL, 3.62 mmol). Basic workup and chromatography (TEA; EtOAc = 1:9) gave 390 mg (66%) of pure **23**; IR ($CHCl_3$) 3560, 3340, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (dd, J = 9.5, 8 Hz, 1H), 3.09 (t, J = 8 Hz, 1H), 3.13−3.21 (m, 1H), 3.24 (d, J = 13 Hz, 1H), 3.71 (d, J = 6 Hz, 2H), 3.77 (d, J = 13 Hz, 1H), 3.79 (s, 2H), 4.31 (d, J = 1.5 Hz, long range coupling can be seen, 1H), 6.86 (d, J = 9 Hz, 2H), 7.14−7.32 (m, 5H), 7.35 (d, J = 9 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 44.4, 52.6, 55.2, 56.6, 62.1, 67.6, 113.5, 127.1, 128.2, 128.9, 130.2, 131.1, 131.6, 138.0, 158.9, 165.9; MS *m/z* EI 326 (70, M$^+$), 309 (100), 235 (27, M$^+$ − Bn), 219 (28, M − PhOMe); *m/z* (CI isobutane) 383 (8.4, M$^+$ + C_4H_9), 327 (100, M$^+$ + 1), 309 (32, M$^+$ + H_2O).

1-Allyl-*trans*-4-(hydroxymethyl)-2-methyl-3-pyrrolidone Oxime (24). Diallylamine (**15**) (2 mL, 16.2 mmol), TEA (2.4 mL, 17.2 mmol), and TMSCl (2.2 mL, 17.3 mmol) were added to nitropropene (699 mg, 7.68 mmol) in toluene (25 mL).

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(19) Data in brackets refer to a mixture of conformers.

Basic workup and chromatography over SG (EtOAc:hexane: TEA = 7:2:1, visualization by burning of the plate) gave 280 mg (20%) of **24** (containing EtOAc). Additional organic material was identified as the isoxazoline **27**.

24: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (d, J = 6.4 Hz, 3H), 2.22 (t, J = 9 Hz, 1H), 2.97 (dd, J = 13.5, 8 Hz, 1H), 3.03 (m, 1H), 3.16 (dd, J = 9, 7 Hz, 1H), 3.39 (dd, J = 13.5, 6 Hz, 1H), 3.51 (q, J = 6.4, 1H), 3.73 (d, J = 6 Jz, 2H), 5.15 (d, J = 10 Hz, 1H), 5.22 (d, J = 17 Hz, 1H), 5.89 (dddd, J = 17, 10, 8, 6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.28, 43.14, 53.64, 56.41, 59.15, 62.30, 117.96, 134.68, 166.46; MS m/z EI 184 (12, M$^+$), 169 (100, M − Me); m/z CI (isobutane) 241 (7.8, M + C_4H_9), 185 (100, M + 1), 167 (14, MH − H_2O).

5-Allyl-6-methyl-3,3a,4,6-tetrahydropyrrolo[3,4-*c*]isoxazole (27): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, J = 6.5 Hz, 3H), 2.27 (dd, J = 10, 8 Hz, 1H), 3.14 (ddt, J = 13.5, 7.5, 1 Hz, 1H), 3.30−3.45 (m, 3H), 3.85 (dd, J = 13, 8 Hz, 1H), 3.86−4.02 (m, 1H), 5.16 (dtd, J = 10, 1, 5, 1 H, 1H), 5.23 (ddd, J = 17, 1.5, 1 Hz, 1H), 5.87 (dddd, J = 17, 10, 1.5, 1Hz, 1H); ^{13}C NMR (50.32 MHz $CDCl_3$) δ 18.58, 52.58, 54.17, 55.76, 56.94, 72.91, 118.05, 134.60, 171.99; MS m/z EI 166 (33, M$^+$), 151 (100).

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Supplementary Material Available: Copies of ^{1}H and ^{13}C NMR spectra **17**, **18**, **20−27** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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