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Intramolecular Cycloaddition of *O-tert*-Butyldimethylsilyloximes in the Presence of $BF_3 \cdot OEt_2$

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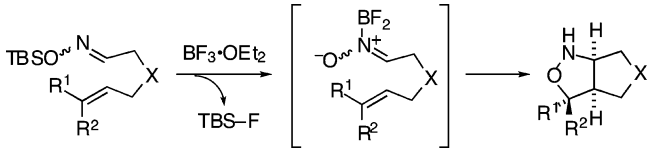
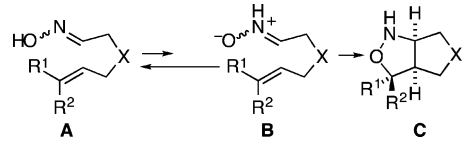


Intramolecular cycloaddition of novel 1,3-dipoles, *N*-boranonitrones, was examined. Treatment of *O-tert*-butyldimethylsilyloximes **9**−**12** having olefin moieties with 2 equiv of $BF_3 \cdot OEt_2$ generated *N*-boranonitrones, which underwent intramolecular cycloaddition to afford *N*-nonsubstituted cycloadducts **16** (and/or **18**) after extractive workup. Despite the Lewis-acidic conditions, the olefin geometry of the substrates was retained in the cycloadducts in the present cycloaddition. The electronic nature of the *N*-boranonitrones appeared to be electrophilic. In the case of substrate **11c**, having an electron-donating methyl group at an internal position of the olefin moiety, the cycloaddition gave the bridged cycloadduct **18b**. The cycloaddition proceeded at relatively low temperature, and the diastereoselectivity was high.

Introduction

Intramolecular cycloaddition of nitrones (NR instead of NH in **B** in Scheme 1) bearing an olefin moiety has been widely recognized as a very powerful method for stereoselective construction of nitrogen-containing carbon frameworks.[1] The cycloaddition features high regioselectivity and stereospecificity that reflects the geometry of the olefin moiety. In this category of reactions, intramolecular oxime−olefin cycloaddition (IOOC) occupies a unique position. Thus, an oxime **A** having an olefin moiety, on heating, undergoes intramolecular cycloaddition to give an *N*-nonsubstituted isoxazolidine **C** via tautomerization of the oxime to an *N*-nonsubstituted nitrone **B** (Scheme 1).[2−13] IOOC seems to be an attractive reaction compared with the corresponding usual nitrone−olefin cycloaddition because an oxime functionality is readily available and is more stable than a nitrone.

SCHEME 1



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† Showa Pharmaceutical University.
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(1) For general reviews on cycloaddition of nitrones, see: (a) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1−173. (b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Gazz. Chim. Ital.* **1989**, *119*, 253−269. (c) Frederickson, M. *Tetrahedron* **1997**, *53*, 403−425. (d) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909. (e) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun*. **2000**, 1449−1458. (f) Adams, J. P.; Paterson, J. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3695−3705. (g) Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957−5978. (h) Adams, J. P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2586−2597.

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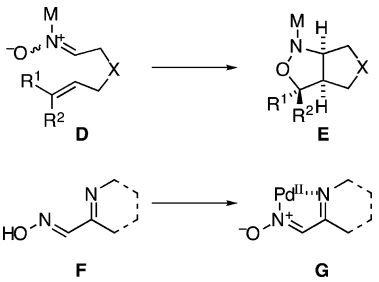
SCHEME 2



However, most IOOCs proceed only under high-temperature conditions because the essential tautomerization from oxime **A** to nitrone **B** is a thermodynamically unfavorable process.[14]

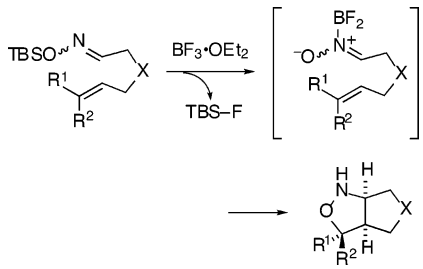
It is expected that treatment of an oxime derivative **A** with a Lewis acid having a high affinity for the nitrogen atom may yield a *N*-metallonitrone **D**, which, in turn, could undergo intramolecular cycloaddition to provide the cycloadduct **E** under mild conditions, and the *N*-nonsubstituted cycloadduct **C** might be obtained after workup (Scheme 2). Indeed, Grigg and co-workers reported intermolecular cycloaddition of Pd(II)-based *N*-metallonitrones.[15] The reaction is, however, strictly limited to the reaction of (*E*)-α-iminoaldoximes **F** with *N*-methylmaleimide because Pd(II) requires a bidentate structure to form the complex **G**.

Recently, we reported that treatment of *O*-*tert*-butyldimethylsilyloximes (*O*-TBS oximes) having olefin moieties with BF_3·OEt_2 resulted in efficient generation of *N*-boranonitrones, which underwent intramolecular cycloaddition at room temperature to afford *N*-nonsubstituted cycloadducts after workup (Scheme 3).[16] Herein, we describe the details of this reaction.

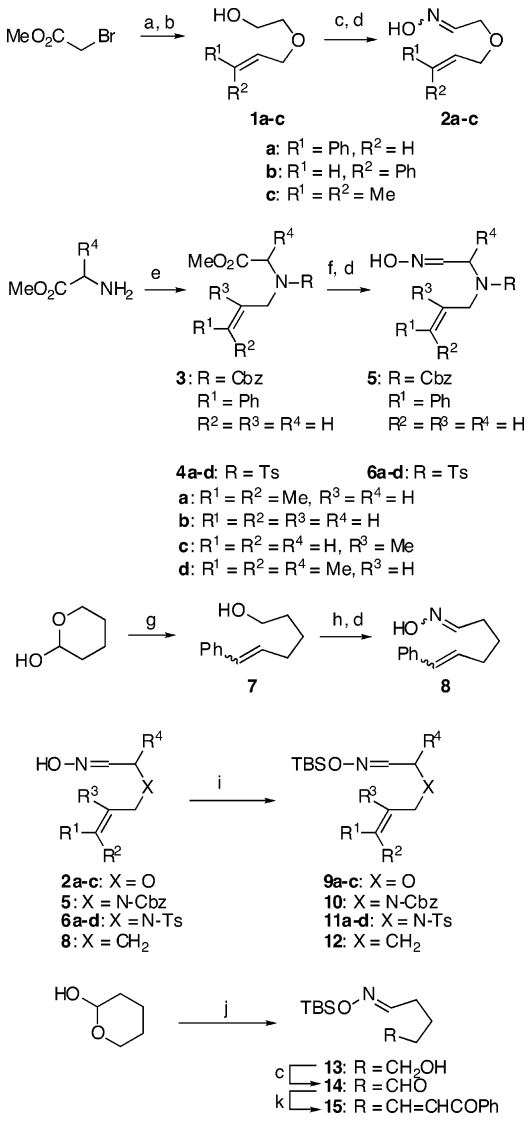
Results and Discussion

Our investigation began with the preparation of the oximes **2**, **5**, **6**, and **8** and *O*-TBS oximes **9**−**12** and **15**. The methods are outlined in Scheme 4.

SCHEME 3



SCHEME 4[a]



[a] Reagent and conditions: (a) allyl alcohol, NaH, benzene; (b) $LiAlH_4$, Et_2O; (c) Swern oxidation; (d) NH_2OH·HCl, $NaHCO_3$, EtOH; (e) *trans*-cinnamyl alcohol, Et_3N, $CHCl_3$, then Et_3N, CbzCl, and CH_2Cl_2 for **3**, TsCl, 10% Na_2CO_3, THF, then allyl bromide, $CsCO_3$, and acetone for **4**; (f) DIBAL-H, Et_2O; (g) $Ph_3P^+CH_2PhCl^-$, *t*-BuOK, *t*-BuOH; (h) PCC, CH_2Cl_2; (i) TBSCl, imidazole, DMF; (j) $TBSONH_2$, $MgSO_4$, Et_2O; (k) $(MeO)_2P(O)CH_2COPh$, NaH, THF.

We first investigated cycloaddition of the oxime **2a** and *O*-TBS oxime **9a** having *trans*-cinnamyl moieties in the presence of a Lewis acid. From the viewpoint of the affinity for nitrogen, $Cu(OTf)_2$ and BF_3·OEt_2 were chosen as the Lewis acids (Table 1). The oxime **2a**, on treatment

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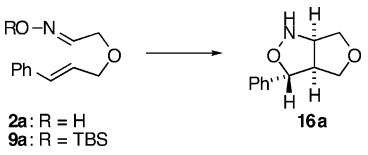
(14) Formaldehyde oxime ($HO-N=CH_2$) was estimated to be 11.1 kcal/mol more stable than the corresponding nitrone [$^-O-N^+(H)=CH_2$] by theoretical analysis. See: Long, J. A.; Harris, N. J.; Lammertsma, K. *J. Org. Chem.* **2001**, *66*, 6762−6767.

(15) Frederickson, M.; Grigg, R.; Thornton-Pett, M.; Redpath, J. *Tetrahedron Lett.* **1997**, *38*, 7777−7780.

(16) Tamura, O.; Mitsuya, T.; Ishibashi, H. *Chem. Commun.* **2002**, 1128−1129.

TABLE 1. Reactions of Oximes 2a and 9a with $Cu(OTf)_2$ or BF_3·OEt_2



entry	oxime	conditions[a]	% yield
1	**2a**	$Cu(OTf)_2$ (1.0 equiv), MeCN, rt, 2 h	16
2	**2a**	$Cu(OTf)_2$ (1.0 equiv), *i*-Pr_2NEt (1.0 equiv), MeCN, rt, 2 h	24[a]
3	**9a**	$Cu(OTf)_2$ (1.0 equiv), MeCN, rt, 2 h	27
4	**9a**	BF_3·OEt_2 (1.1 equiv), CH_2Cl_2, 0 °C to rt, 1 h	50
5	**9a**	BF_3·OEt_2 (2.1 equiv), CH_2Cl_2, 0 °C to rt, 1 h	97

[a] rt = room temperature. [b] The nitrile **17** (PhCH=$CHCH_2$-OCH_2CN) was obtained.

with $Cu(OTf)_2$ (1 equiv) in MeCN at room temperature, gave the intramolecular cycloadduct **16a** in 16% yield (entry 1). When the reaction was carried out in the presence of *i*-$PrNEt_2$, a small amount of nitrile **17** was obtained (entry 2). The formation of the nitrile **17** indicated the coordination of Cu(II) with the oxygen atom of the oxime functionality in place of the nitrogen atom, and hence, the *O*-protected dervative **9a** of **2a** was next used as the substrate. When the *O*-TBS oxime **9a** was exposed to $Cu(OTf)_2$ under conditions similar to those for entry 1, the yield of **16a** was slightly improved (entry 3). Taking into account the strong affinities of both N–B and Si–F, we next examined BF_3·OEt_2 as a Lewis acid.[17–22] Treatment of **9a** with BF_3·OEt_2 (1.1 equiv) gave the cycloadduct **16a** in 50% yield (entry 4). The oxime **9a** smoothly reacted with 2.1 equiv of BF_3·OEt_2 to give **16a** in almost quantitative yield after workup (entry 5). In contrast, reaction of **2a** with BF_3·OEt gave a complex mixture.[23]

Formation of the cycloadduct **16a** from the *O*-TBS oxime **9a** with BF_3·OEt_2 may involve *N*-boranonitrone **I** (Scheme 5). Boron trifluoride coordinates with the nitrogen of the oxime functionality to give complex **H**, which generates *N*-boranonitrone **I** accompanied with the release of TBS–F due to the strong Si–F affinity. The nitrone **I** undergoes intramolecular cycloaddition to afford the cycloadduct **J**. The second equivalent of BF_3 may react with the initial cycloadduct **J** to form complex **K**.[24] This would be the reason that 2 equiv of BF_3·OEt_2 are essential for efficient cycloaddition. The BF_3 and BF_2 groups in **K** are removed by the extractive workup. The possibility of further coordination of BF_3 with the nitrone–oxygen of **I** cannot be ruled out.[25]

SCHEME 5

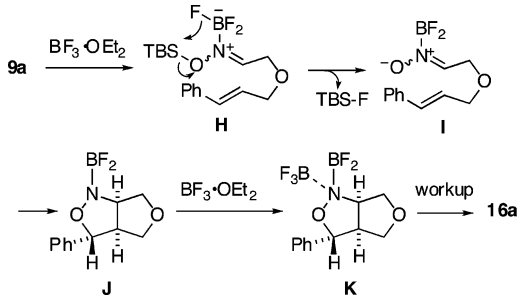
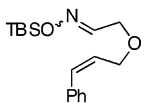
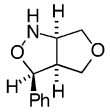
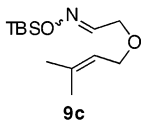
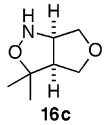
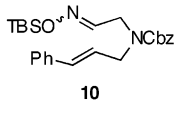
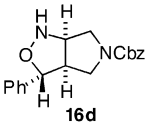
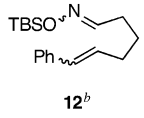
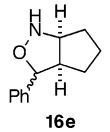


TABLE 2. Cycloaddition of *O*-TBS Oximes 9a,b, 10, and 12 with BF_3·OEt_2[a]

entry	oxime	time	product	% yield
1	 **9b**	1 h	 **16b**	87
2	 **9c**	1 h	 **16c**	80
3	 **10**	1 h	 **16d**	92
4	 **12**[b]	5 d	 **16e**	73

[a] All reactions were carried out with 2.1 equiv of BF_3·OEt_2 in CH_2Cl_2 at room temperature. [b] E/Z = 1:1.

The cycloadditions of various *O*-TBS oximes were examined next (Table 2). Reaction of the oxime **9b** having a *cis*-cinnamyl group with BF_3·OEt_2 afforded the cycloadduct **16b** in 87% yield (entry 1). The stereospecific formation of **16b** from **9b** suggests that this reaction is a concerted reaction of nitrone. The dimethyl-substituted *O*-TBS oxime **9c** also underwent smooth cycloaddition to give adduct **16c** (entry 2). Reaction of the *N*-Cbz-tethered

(17) For excellent reviews on *N*-metalloazomethine ylides, see: (a) Kanemasa, S. *Synlett* **2002**, 1371–1387. (b) Husineca, S.; Savic, V. *Tetrahedron: Asymmetry* **2005**, *16,* 2047–2061.

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(21) For activation of oxime ethers by BF_3 for radical addition, see: (a) Miyabe, H.; Fujii, K.; Naito, T. *Org. Lett.* **1999**, *1*, 569–572. (b) Miyabe, H.; Fujii, K.; Naito, T. *Org. Biomol. Chem.* **2003**, *1*, 381–390.

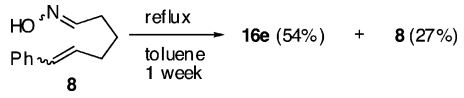
(22) For addition reactions of crotylboronates to oximes, see: (a) Hoffmann, R. W.; Eichler, G.; Endesfelder, A. *Liebigs Ann. Chem.* **1983**, 2000–2007. (b) Hoffmann, R. W.; Endesfelder, A. *Liebigs Ann. Chem.* **1986**, 1823–1836. (c) Hoffmann, R. W.; Endesfelder, A. *Liebigs Ann. Chem.* **1987**, 215–219.

(23) BF_3 is known to be an efficient catalyst for Beckmann rearrangement of oximes. See: (a) Hauser, C. R.; Hoffenberg, D. S. *J. Org. Chem.* **1955**, *20*, 1482–1490. (b) Hoffenberg, D. S.; Hauser, C. R. *J. Org. Chem.* **1955**, *20*, 1496–1500. (c) Cainelli, G.; Morrocchi, S.; Quilico, A. *Tetrahedron Lett.* **1963**, *4*, 1959–1964.

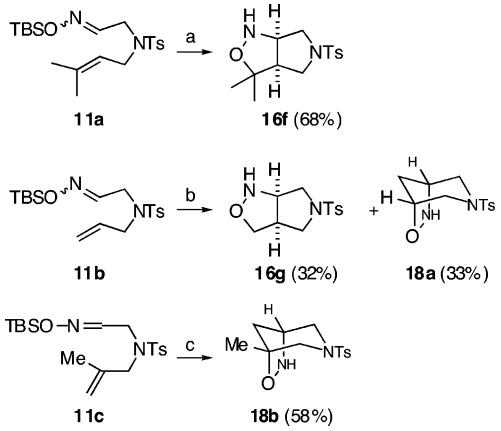
(24) Hall, D. G.; Laplante, C.; Mansuku, S.; Nagendran, J. *J. Org. Chem.* **1999**, *64*, 698–699.

(25) Katagiri, N.; Okada, M.; Morishita, Y.; Kaneko, C. *Tetrahedron* **1997**, *53*, 5725–5746.

SCHEME 6



SCHEME 7[a]



[a] Reagent and conditions: (a) $(CH_2Cl)_2$, 0 °C to room temperature, 21 h; (b) $(CH_2Cl)_2$, 50 °C, 40 h; (c) $(CH_2Cl)_2$, room temperature, 18 h.

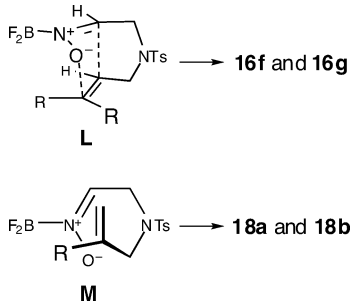
oxime **10** proceeded without difficulty to provide the corresponding adduct **16d** in a high yield (92%) (entry 3). On the other hand, reaction of the carbon-tethered substrate **12** (*E*/*Z*, 1:1) required a prolonged reaction time and gave the cycloadduct **16e** as a 1:1 mixture of diastereomers in a reasonable yield (73%) (entry 4). Reaction of **12** with 1 equiv of BF_3·OEt_2 gave **16e** in half the yield (38%). In contrast to the BF_3-mediated cycloaddition of **12** (Table 2, entry 4), the reaction of the oxime **8** under usual conditions (reflux in toluene) did not reach completion even after one week, giving **16e** in 54% yield along with recovery of the starting oxime **8** (27%) (Scheme 6).

With these encouraging results in hand, the regiochemistry of the present cycloaddition was examined by using *N*-Ts tethered substrates **11a**−**c** (Scheme 7). When the *O*-TBS oxime **11a** having dimethyl groups at the olefin terminus was treated with BF_3·OEt_2 at room temperature, cycloadduct **16f** bearing a bicyclo[3.3.0] skeleton was obtained in 68% yield. Exposure of the *N*-allyl substrate **11b** to BF_3·OEt_2 gave the bicyclo[3.3.0] cycloadduct **16g** and the bicyclo[3.2.1] cycloadduct **18a** in 32 and 33% yields, respectively. Reaction of the oxime **11c** having a *N*-β-methallyl group resulted in exclusive formation of the bicyclo[3.2.1] cycloadduct **18b** in 58% yield.

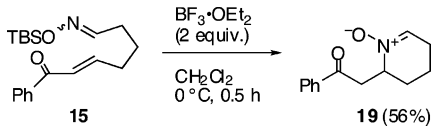
Adducts **16f** and **16g** may be formed via transition state (TS) **L**, whereas **18a** and **18b** may be formed via TS **M** (Scheme 8). This consideration suggests that the carbon atoms of *N*-boranonitrones should exhibit highly electrophilic character because of the empty orbitals of the borane atoms, and hence, the more electron-rich carbon atoms in the olefins would attack the electrophilic nitrone−carbons.

Probably because of the electrophilic nature of *N*-boranonitrone, reaction of the oxime **15** having an electron-deficient alkene moiety did not result in cycloaddition but gave the cyclic nitrone **19** via Michael addition of the nitrogen atom of the oxime (Scheme 9).[26]

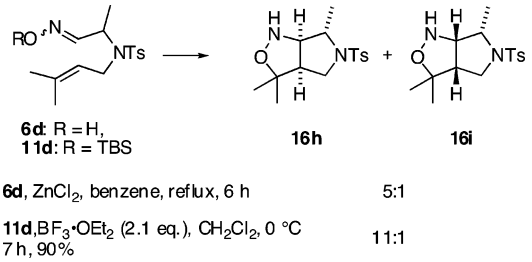
SCHEME 8



SCHEME 9



SCHEME 10



Finally, the diastereoselectivity of the present cycloaddition was examined. Cycloaddition of **6d** catalyzed by zinc chloride in refluxing benzene was reported to give a 5:1 mixture of **16h** and **16i**.[9] In contrast, BF_3·OEt_2-promoted cycloaddition of **11d** proceeded with high stereoselectivity to afford an 11:1 mixture of **16h** and **16i**, probably because of the low reaction temperature (Scheme 10).

In conclusion, we have explored BF_3·OEt_2-promoted cycloaddition of *O*-*tert*-butyldimethylsilyloximes, which probably occurs via the *N*-boranonitrones. The electronic nature of *N*-boranonitrone is highly electrophilic, and this characteristic made possible the synthesis of unique bicyclic systems, such as cycloadduct **18b**. Extension of the present intramolecular cycloaddition to the intermolecular counterpart is currently under study.

Experimental Section

(3*R,3a*S**,6a*R**)-Hexahydro-3-phenylfuro[3,4-*c*]isoxazole (16a) (Table 1, Entry 1).** Copper(II) trifluoromethanesulfonate (72 mg, 0.2 mmol) was added to a stirred solution of **2a** (38 mg, 0.2 mmol) in MeCN (2 mL) at room temperature, and the mixture was additionally stirred for 2 h. The mixture was poured into 10% aqueous NH_3, and the whole was extracted with Et_2O, washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude material was chromatographed on silica gel (hexane−AcOEt, 1:1) to give **16a** (6 mg, 16%) as an oil: IR

(26) For Lewis-acid-mediated conjugate addition of oximes to α,β-unsaturated carbonyl compounds, see: (a) Saba, I.; Frederickson, M.; Grigg, R.; Dunn, P.; Levett, P. C. *Tetrahedron Lett.* **1997**, *38*, 6099−6102. (b) Nakama, K.; Seki, S.; Kanemasa, S. *Tetrahedron Lett.* **2001**, *42*, 6719−6722. (c) Nakama, K.; Seki, S.; Kanemasa, S. *Tetrahedron Lett.* **2002**, *43*, 829−832.

($CHCl_3$) 2968, 3013 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.24 (1H, br dtd, J = 2.7, 6.0, 8.5 Hz), 3.75 (1H, dd, J = 5.1, 10.0 Hz), 3.83 (1H, dd, J = 6.5, 9.2 Hz), 3.87 (1H, dd, J = 2.2, 10.0 Hz), 3.97 (1H, dd, J = 2.7, 9.2 Hz), 4.27 (1H, m), 4.65 (1H, d, J = 5.3 Hz), 7.37 (5H, br s); the NH was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 58 (br), 68.8 (br), 72.5 (br), 92 (br), 127.0, 128.8, 129.2, 138.7; HRMS calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0936.

Table 1, Entry 5: General Procedure for the BF_3·OEt_2-Mediated Cycloaddition of *O*-TBS Oximes 16. To a stirred solution of **9a** (61 mg, 0.2 mmol) in CH_2Cl_2 was added BF_3·OEt_2 (53 μL, 0.42 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. Saturated aqueous $NaHCO_3$ was added, and the whole was extracted with $CHCl_3$, washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane−AcOEt, 4:1−1:1) to give **16a** (37 mg, 97%).

(3a*R,3a*R**,6a*S**)-Hexahydro-3-phenylfuro[3,4-*c*]isoxazole (16b) (Table 2, Entry 1).** Oxime **9b** (61 mg, 0.2 mmol) was treated with BF_3·OEt_2 (53 μL, 0.42 mmol) in CH_2Cl_2 (2 mL) at room temperature for 1 h. After workup, the crude material was chromatographed on silica gel (hexane−AcOEt, 1:1) to give **16b** (33 mg, 87%): IR ($CHCl_3$) 3013, 2862 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.27−3.42 (2H, m), 3.51 (1H, dd, J = 6.9, 9.2 Hz), 3.79 (1H, dd, J = 4.4, 9.6 Hz), 4.01 (1H, dd, J = 6.9, 9.6 Hz), 4.30 (1H, dt, J = 4.4, 8.2 Hz), 4.88 (1H, d, J = 6.3 Hz), 5.64 (1H, br s), 7.24−7.39 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 53.0, 67.3, 69.9, 75.1, 88.0, 126.8, 128.1, 128.8, 136.4; HRMS calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0939.

(3a*R,6a*S**)-Hexahydro-3,3-dimethylfuro[3,4-*c*]isoxazole (16c) (Table 2, Entry 2).** Oxime **9c** (51 mg, 0.2 mmol) was treated with BF_3·OEt_2 (53 μL, 0.42 mmol) in CH_2Cl_2 (2 mL) at room temperature for 1 h. After workup, the crude material was chromatographed on silica gel (hexane−AcOEt, 1:4) to give **16c** (23 mg, 80%) as an oil: IR ($CHCl_3$) 3013, 2980, 2866 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.28 (3H, s), 1.32 (3H, s), 2.74 (1H, dt, J = 4.0, 7.6 Hz), 3.64 (1H, dd, J = 7.6, 9.5 Hz), 3.75 (1H, dd, J = 4.1, 9.5 Hz), 3.79 (1H, dd, J = 5.6, 9.5 Hz), 3.88 (1H, dd, J = 4.0, 7.6 Hz), 4.16 (1H, br td, J = 4.5, 7.6 Hz); the NH was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.0, 26.2, 57.1, 67.4, 69.6, 73.0, 84.7; HRMS calcd for $C_7H_{13}NO_2$ 143.0946, found 143.0933.

(3a*R,3a*R**,6a*R**)-Benzyl Tetrahydro-3-phenyl-1*H*-pyrrolo[3,4-*c*]isoxazole-5-(3*H*)-carboxylate (16d) (Table 2, Entry 3).** Oxime **10** (88 mg, 0.2 mmol) was treated with BF_3·OEt_2 (53 μL, 0.42 mmol) in CH_2Cl_2 (2 mL) at room temperature for 1 h. After workup, the crude material was chromatographed on silica gel (hexane−AcOEt, 1:1) to give **16d** (60 mg, 92%) as an oil: IR ($CHCl_3$) 3013, 1697 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.24 (1H, br s), 3.54 (2H, br s), 3.72 (2H, br s), 4.22 (1H, td, J = 4.8, 7.9 Hz), 4.74 (1H, br s), 5.42 (1H, br s), 7.27−7.44 (10H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 50.5, 55 (br), 66 (br), 67.5, 91 (br), 126.6, 128.4, 128.5, 128.7, 128.9, 129.2, 136.9, 138.9, 155.2; HRMS calcd for $C_{19}H_{20}N_2O_3$ 324.1474, found 324.1476.

(3a*R,6a*S**)-Hexahydro-3-phenyl-1*H*-cyclopenta[*c*]isoxazole (16e) (Table 2, Entry 4).** Oxime **12** (60 mg, 0.2 mmol) was treated with BF_3·OEt_2 (53 μL, 0.42 mmol) in CH_2Cl_2 (2 mL) at room temperature for 5 days. After workup, the crude material was chromatographed on silica gel (hexane−AcOEt, 1:1) to give **16e** (28 mg, 73%) as a 1:1 mixture of diastereomers: IR ($CHCl_3$) 3011, 2961, 2870 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.10−2.01 (6H, m), 3.02 (1H × 1/2, m), 3.12 (1H × 1/2, td, J = 6.6, 8.1 Hz), 4.00−4.13 (1H, m), 4.51 (1H × 1/2, br s), 4.82 (1H, d, J = 6.6 Hz), 4.90−5.90 (1H, br), 7.22−7.42 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.8, 26.5, 28.6, 31.3, 32.1, 35.5, 52.3, 56.6, 67.3, 67.9, 88.8, 91.3, 126.4, 126.7, 127.4, 128.2, 128.4, 128.9, 137.9, 140.1; HRMS calcd for $C_{12}H_{15}NO$ 189.1154, found 189.1155.

(3a*R,6a*R**)-Hexahydro-3,3-dimethyl-5-tosyl-1*H*-pyrrolo[3,4-*c*]isoxazole (16f).** Oxime **11a** (654 mg, 2.61 mmol) was treated with BF_3·OEt_2 (0.45 mL, 5.3 mmol) in $(CH_2Cl)_2$ (5 mL) at room temperature for 21 h. After workup, the crude material was chromatographed on silica gel (AcOEt−$CHCl_3$, 1:10) to give **16f** (278 mg, 68%): mp 172−175 °C (hexane−AcOEt); IR ($CHCl_3$) 1348 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.21 (3H, s), 1.26 (3H, s), 2.44 (3H, s), 2.71 (1H, br q, J = 6.9 Hz), 2.92−3.49 (4H, m), 4.10 (1H, dt, J = 4.6, 7.6 Hz), 7.34 (2H, d, J = 7.9 Hz), 7.69 (2H, d, J = 7.9 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.4, 21.5, 29.7, 43.2, 50.1, 54.9, 53.3, 127.5, 129.6, 134.5, 143.5. Anal. Calcd for $C_{14}H_{20}N_2O_3S$: C, 56.73; H, 6.80; N, 9.45. Found: C, 56.59; H, 6.95; N, 9.38.

(3a*R,6a*R**)-Hexahydro-5-tosyl-1*H*-pyrrolo[3,4-*c*]isoxazole (16g) and (1*R**,5*S**)-3-(Toluene-4-sulfonyl)-3,7-diaza-6-oxabicyclo[3,2,1]octane (18a).** Oxime **11b** (77 mg, 0.2 mmol) was treated with BF_3·OEt_2 (53 μL, 0.42 mmol) in $(CH_2Cl)_2$ (2 mL) at 50 °C for 40 h. After workup, the crude material was chromatographed on silica gel (hexane−AcOEt, 1:2−1:4) to give **16g** (18 mg, 32%) and **18a** (19 mg, 33%). **16g**: IR ($CHCl_3$) 1348 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.44 (3H, s), 2.83 (2H, br), 3.15 (1H, m), 3.26−3.90 (4H, br), 4.08 (1H, m), 5.07 (1H, br), 7.35 (2H, d, J = 7.9 Hz), 7.68 (2H, d, J = 8.2 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.6, 47.6, 52.8, 64.8, 77.2, 128.1, 129.8, 131.4, 144.1. Anal. Calcd for $C_{12}H_{16}O_3N_2S$: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.77; H, 6.25; N, 10.05. **18a**: IR ($CHCl_3$) 1336 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.04 (2H, m), 2.43 (3H, s), 2.85 (1H, br d, J = 11.9 Hz), 3.03 (1H, br d, J = 11.9 Hz), 3.62 (1H, br d, J = 11.9 Hz), 3.77 (1H, br s), 4.48 (1H, br s), 7.31 (2H, d, J = 8.3 Hz), 7.71 (2H, d, J = 8.3 Hz); the NH was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.5, 37.2, 50.7, 51.1, 53.3, 71.3, 127.5, 129.6, 134.5, 143.6; HRMS calcd for $C_{12}H_{16}O_3N_2S$ 268.0882, found 268.0886. Anal. Calcd for $C_{12}H_{16}O_3N_2S$: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.96; H, 6.18; N, 10.06.

(1*R,5*S**)-5-Methyl-3-tosyl-3,7-diaza-6-oxabicyclo[3,2,1]-octane (18b).** Oxime **11c** (62 mg, 0.16 mmol) was treated with BF_3·OEt_2 (43 μL, 0.32 mmol) in CH_2Cl_2 (1.6 mL) at room temperature for 20 h. After workup, the crude material was chromatographed on silica gel (hexane−AcOEt, 1:5) to give **17b** (26 mg, 58%): IR (CHCl3) 1340 cm^{-1}; ^1H NMR (270 Mz, $CDCl_3$) δ 1.35 (3H, s), 1.92 (2H, m), 2.43 (3H, s), 2.71 (1H, d, J = 11.6 Hz), 2.86 (1H, d, J = 11.6 Hz), 3.66−3.77 (2H, m), 7.30 (2H, d, J = 8.3 Hz), 7.72 (2H, d, J = 8.3 Hz); ^{13}C NMR (67.8 Mz, $CDCl_3$) δ 20.4, 21.5, 29.7, 43.2, 50.1, 54.9, 55.3, 127.5, 129.6, 134.4, 143.5; HRMS (FAB) calcd for $C_{13}H_{19}N_2O_3S$ (MH^+) 283.1116, found 283.1127.

2-(Oxo-2-phenylethyl)-1,2,3,4-tetrahydropyridine *N*-Oxide (19). Oxime **15** (77 mg, 0.2 mmol) was treated with BF_3·OEt_2 (53 μL, 0.42 mmol) in CH_2Cl_2 (2 mL) at 0 °C for 30 min. After workup, the crude material was triturated with Et_2O, and the resulting precipitates were collected to give **19** (24 mg, 56%) as colorless powder. This material was too unstable to be recrystallized: IR ($CHCl_3$) 2361, 1686 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.69−2.33 (4H, m), 2.47 (2H, m), 3.19 (1H, dd, J = 9.2, 17.5 Hz), 4.23 (1H, dd, J = 3.3, 17.5 Hz), 4.43 (1H, m), 7.22 (1H, t, J = 3.9 Hz), 7.38−7.66 (3H, m), 7.94−8.05 (2H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 16.3, 26.4, 28.5, 41.7, 64.1, 128.6, 129.1, 129.1, 133.5, 133.8, 180.4; HRMS calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1103.

(3a*R*,6*S*,6a*R*)-Hexahydro-3,3,6-trimethyl-5-tosyl-1*H*-pyrrolo[3,4-*c*]isoxazole (16h). Oxime **11d** (85 mg, 0.2 mmol) was treated with BF_3·OEt_2 (53 μL, 0.42 mmol) in CH_2Cl_2 (2 mL) at 0 °C for 6 h. After workup, the crude material was chromatographed on silica gel (hexane−AcOEt, 1:1) to give an 11:1 mixture of **16h** and **16i** (57 mg, 92%). An analytical sample of **16h** was obtained by preparative TLC on silca gel (hexane−AcOEt, 2:3): IR ($CHCl_3$) 2980, 1344 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 0.67 (3H, s), 0.81 (3H, s), 1.43 (3H, d, J = 6.3 Hz), 1.84 (3H, s), 2.03 (1H, br q, J = 7.5 Hz), 2.92 (1H, dd, J = 6.9, 10.1 Hz), 2.99 (1H, dd, J = 5.5, 7.5 Hz), 3.20 (1H, br quint, J = 6.0 Hz), 3.43 (1H, dd, J = 8.5, 10.1 Hz), 6.78 (2H,

d, J = 8.2 Hz), 7.76 (2H, d, J = 8.2 Hz); the NH was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.8, 21.5, 21.9, 26.3, 49.9, 53.2, 61.5, 74.1, 84.7, 128.2, 130.1, 133.5, 144.2; HRMS calcd for $C_{15}H_{22}N_2O_3S$ 310.1351, found 310.1356.

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Supporting Information Available: Preparation of compounds **1a**−**c**, **2a**−**c**, **3, 4a**−**c**, **5**, **6a**−**c**, **7**, **8**, **9a**−**c**, **10**, **11a**−**d**, and **12**−**15**; ^{1}H NMR spectra of **1a**−**c**, **2a**−**c**, **3**, **4b**,**c**, **5**, **6b**, **7**, **8**, **9a**−**c**, **11b**,**d**, **12**−**15**, **16a**−**e**, **16h**, **18a**,**b**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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