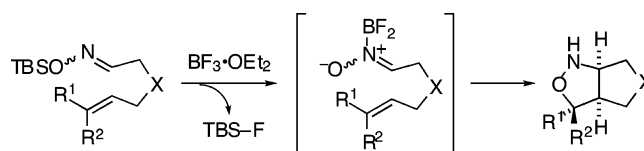


Intramolecular Cycloaddition of *O*-*tert*-Butyldimethylsilyloximes in the Presence of  $\text{BF}_3 \cdot \text{OEt}_2$ Osamu Tamura,<sup>\*,†</sup> Takahiro Mitsuya,<sup>‡</sup> Xin Huang,<sup>‡</sup> Yoshiyuki Tsutsumi,<sup>‡</sup> Sanae Hattori,<sup>‡</sup> and Hiroyuki Ishibashi<sup>\*,‡</sup>*Showa Pharmaceutical University, Higashi-tamagawagakuen, Machida, Tokyo 194-8543, Japan, and Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kanazawa 920-1192, Japan*

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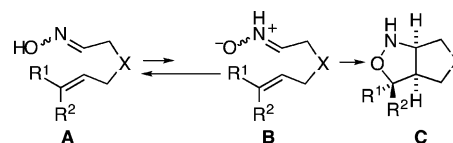


Intramolecular cycloaddition of novel 1,3-dipoles, *N*-boranonitrones, was examined. Treatment of *O*-*tert*-butyldimethylsilyloximes **9–12** having olefin moieties with 2 equiv of  $\text{BF}_3 \cdot \text{OEt}_2$  generated *N*-boranonitrones, which underwent intramolecular cycloaddition to afford *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.<sup>1</sup> 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 nitron **B** (Scheme 1).<sup>2–13</sup> IOOC seems to be an attractive

## SCHEME 1



reaction compared with the corresponding usual nitron–olefin cycloaddition because an oxime functionality is readily available and is more stable than a nitron.

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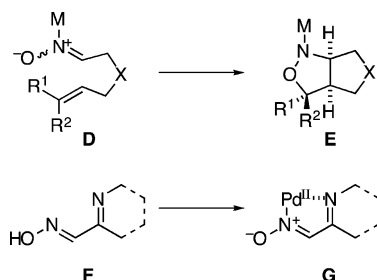
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## SCHEME 2



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

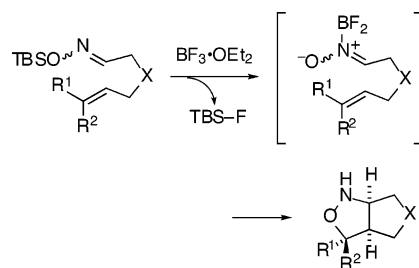
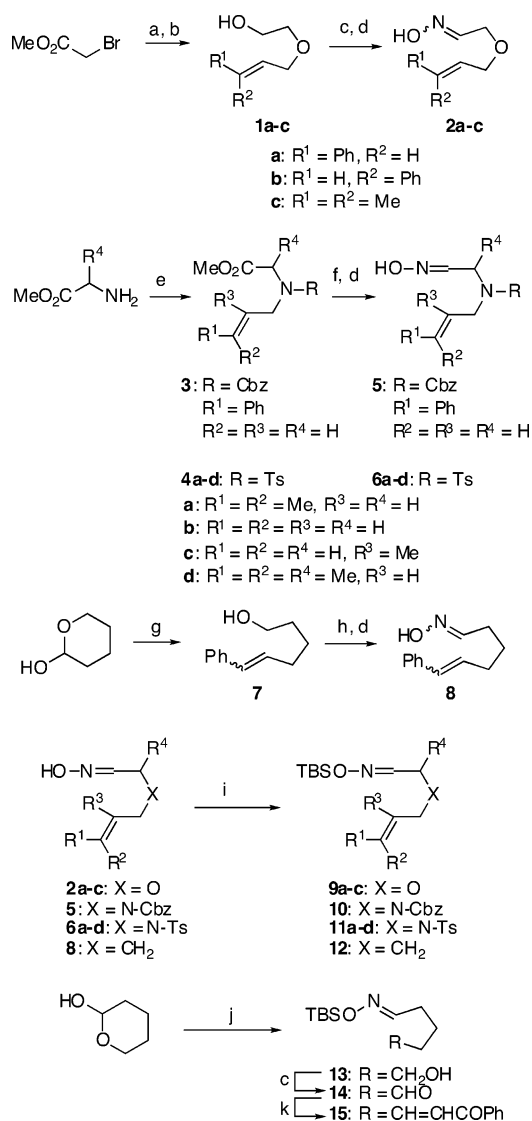
It is expected that treatment of an oxime derivative **A** with a Lewis acid having a high affinity for the nitrogen atom may yield a *N*-metalloniitrone **D**, which, in turn, could undergo intramolecular cycloaddition to provide the cycloadduct **E** under mild conditions, and the *N*-nonsubstituted cycloadduct **C** might be obtained after workup (Scheme 2). Indeed, Grigg and co-workers reported intermolecular cycloaddition of Pd(II)-based *N*-metalloniitrone.<sup>15</sup> The reaction is, however, strictly limited to the reaction of (*E*)- $\alpha$ -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  $\text{BF}_3 \cdot \text{OEt}_2$  resulted in efficient generation of *N*-boranonitrone, which underwent intramolecular cycloaddition at room temperature to afford *N*-nonsubstituted cycloadducts after workup (Scheme 3).<sup>16</sup> 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<sup>a</sup>

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<sup>a</sup> Reagent and conditions: (a) allyl alcohol, NaH, benzene; (b)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ; (c) Swern oxidation; (d)  $\text{NH}_2\text{OH}\cdot\text{HCl}$ ,  $\text{NaHCO}_3$ ,  $\text{EtOH}$ ; (e) *trans*-cinnamyl alcohol,  $\text{Et}_3\text{N}$ ,  $\text{CHCl}_3$ , then  $\text{Et}_3\text{N}$ ,  $\text{CbzCl}$ , and  $\text{CH}_2\text{Cl}_2$  for **3**,  $\text{TsCl}$ , 10%  $\text{Na}_2\text{CO}_3$ , THF, then allyl bromide,  $\text{CsCO}_3$ , and acetone for **4**; (f) DIBAL-H,  $\text{Et}_2\text{O}$ ; (g)  $\text{Ph}_3\text{P}^+\text{CH}_2\text{PhCl}^-$ , *t*-BuOK, *t*-BuOH; (h) PCC,  $\text{CH}_2\text{Cl}_2$ ; (i) TBSCl, imidazole, DMF; (j)  $\text{TBSONH}_2$ ,  $\text{MgSO}_4$ ,  $\text{Et}_2\text{O}$ ; (k)  $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{COPh}$ , 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,  $\text{Cu}(\text{OTf})_2$  and  $\text{BF}_3 \cdot \text{OEt}_2$  were chosen as the Lewis acids (Table 1). The oxime **2a**, on treatment

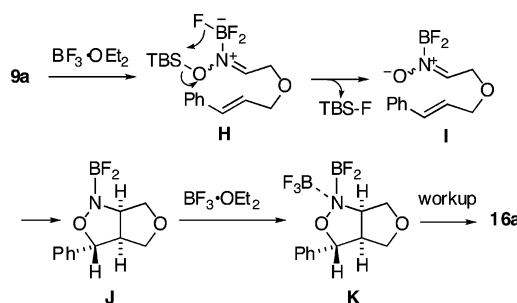
**TABLE 1.** Reactions of Oximes **2a** and **9a** with Cu(OTf)<sub>2</sub> or BF<sub>3</sub>·OEt<sub>2</sub>

<b>2a:</b> R = H <b>9a:</b> R = TBS				
entry	oxime	conditions <sup>a</sup>	% yield	
1	<b>2a</b>	Cu(OTf) <sub>2</sub> (1.0 equiv), MeCN, rt, 2 h	16	
2	<b>2a</b>	Cu(OTf) <sub>2</sub> (1.0 equiv), <i>i</i> -Pr <sub>2</sub> NEt (1.0 equiv), MeCN, rt, 2 h	24 <sup>a</sup>	
3	<b>9a</b>	Cu(OTf) <sub>2</sub> (1.0 equiv), MeCN, rt, 2 h	27	
4	<b>9a</b>	BF <sub>3</sub> ·OEt <sub>2</sub> (1.1 equiv), CH <sub>2</sub> Cl <sub>2</sub> , 0 °C to rt, 1 h	50	
5	<b>9a</b>	BF <sub>3</sub> ·OEt <sub>2</sub> (2.1 equiv), CH <sub>2</sub> Cl <sub>2</sub> , 0 °C to rt, 1 h	97	

<sup>a</sup> rt = room temperature. <sup>b</sup> The nitrile **17** (PhCH=CHCH<sub>2</sub>-OCH<sub>2</sub>CN) was obtained.

with Cu(OTf)<sub>2</sub> (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*-Pr<sub>2</sub>NEt<sub>2</sub>, 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 derivative **9a** of **2a** was next used as the substrate. When the *O*-TBS oxime **9a** was exposed to Cu(OTf)<sub>2</sub> 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<sub>3</sub>·OEt<sub>2</sub> as a Lewis acid.<sup>17–22</sup> Treatment of **9a** with BF<sub>3</sub>·OEt<sub>2</sub> (1.1 equiv) gave the cycloadduct **16a** in 50% yield (entry 4). The oxime **9a** smoothly reacted with 2.1 equiv of BF<sub>3</sub>·OEt<sub>2</sub> to give **16a** in almost quantitative yield after workup (entry 5). In contrast, reaction of **2a** with BF<sub>3</sub>·OEt gave a complex mixture.<sup>23</sup>

Formation of the cycloadduct **16a** from the *O*-TBS oxime **9a** with BF<sub>3</sub>·OEt<sub>2</sub> 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 re-

**SCHEME 5****TABLE 2.** Cycloaddition of *O*-TBS Oximes **9a,b**, **10**, and **12** with BF<sub>3</sub>·OEt<sub>2</sub><sup>a</sup>

entry	oxime	time	product	% yield
1	 <b>9b</b>	1 h	 <b>16b</b>	87
2	 <b>9c</b>	1 h	 <b>16c</b>	80
3	 <b>10</b>	1 h	 <b>16d</b>	92
4	 <b>12<sup>b</sup></b>	5 d	 <b>16e</b>	73

<sup>a</sup> All reactions were carried out with 2.1 equiv of BF<sub>3</sub>·OEt<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> at room temperature. <sup>b</sup> E/Z = 1:1.

lease of TBS–F due to the strong Si–F affinity. The nitron **I** undergoes intramolecular cycloaddition to afford the cycloadduct **J**. The second equivalent of BF<sub>3</sub> may react with the initial cycloadduct **J** to form complex **K**.<sup>24</sup> This would be the reason that 2 equiv of BF<sub>3</sub>·OEt<sub>2</sub> are essential for efficient cycloaddition. The BF<sub>3</sub> and BF<sub>2</sub> groups in **K** are removed by the extractive workup. The possibility of further coordination of BF<sub>3</sub> with the nitron–oxygen of **I** cannot be ruled out.<sup>25</sup>

The cycloadditions of various *O*-TBS oximes were examined next (Table 2). Reaction of the oxime **9b** having a *cis*-cinnamyl group with BF<sub>3</sub>·OEt<sub>2</sub> 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 nitron. The dimethyl-substituted *O*-TBS oxime **9c** also underwent smooth cycloaddition to give adduct **16c** (entry 2). Reaction of the *N*-Cbz-tethered

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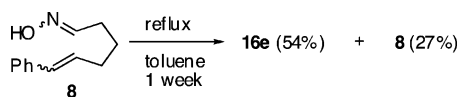
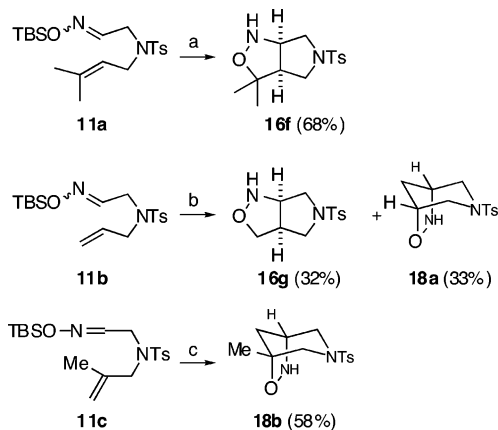
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## SCHEME 6

SCHEME 7<sup>a</sup>

<sup>a</sup> Reagent and conditions: (a)  $(\text{CH}_2\text{Cl})_2$ , 0 °C to room temperature, 21 h; (b)  $(\text{CH}_2\text{Cl})_2$ , 50 °C, 40 h; (c)  $(\text{CH}_2\text{Cl})_2$ , room temperature, 18 h.

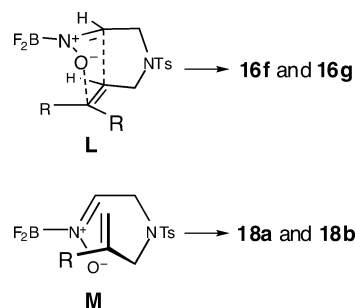
oxime **10** proceeded without difficulty to provide the corresponding adduct **16d** in a high yield (92%) (entry 3). On the other hand, reaction of the carbon-tethered substrate **12** (*E/Z*, 1:1) required a prolonged reaction time and gave the cycloadduct **16e** as a 1:1 mixture of diastereomers in a reasonable yield (73%) (entry 4). Reaction of **12** with 1 equiv of  $\text{BF}_3 \cdot \text{OEt}_2$  gave **16e** in half the yield (38%). In contrast to the  $\text{BF}_3$ -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  $\text{BF}_3 \cdot \text{OEt}_2$  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  $\text{BF}_3 \cdot \text{OEt}_2$  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*- $\beta$ -methallyl group resulted in exclusive formation of the bicyclo[3.2.1] cycloadduct **18b** in 58% yield.

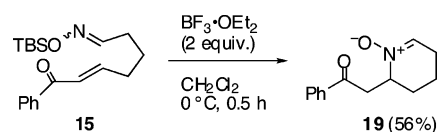
Adducts **16f** and **16g** may be formed via transition state (TS) **L**, whereas **18a** and **18b** may be formed via TS **M** (Scheme 8). This consideration suggests that the carbon atoms of *N*-boranonitrone should exhibit highly electrophilic character because of the empty orbitals of the borane 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).<sup>26</sup>

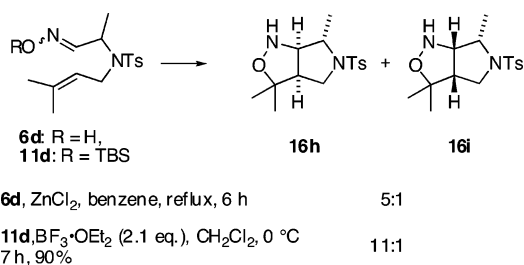
## SCHEME 8



## 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**.<sup>9</sup> In contrast,  $\text{BF}_3 \cdot \text{OEt}_2$ -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  $\text{BF}_3 \cdot \text{OEt}_2$ -promoted cycloaddition of *O*-*tert*-butyldimethylsilyloximes, which probably occurs via the *N*-boranonitrone. 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*\*,3*aS*\*,6*aR*\*)-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  $\text{NH}_3$ , and the whole was extracted with  $\text{Et}_2\text{O}$ , washed successively with water and brine, dried ( $\text{MgSO}_4$ ), 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  $\alpha,\beta$ -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<sub>3</sub>) 2968, 3013 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) 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; <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>) δ 58 (br), 68.8 (br), 72.5 (br), 92 (br), 127.0, 128.8, 129.2, 138.7; HRMS calcd for C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub> 191.0946, found 191.0936.

**Table 1, Entry 5: General Procedure for the BF<sub>3</sub>·OEt<sub>2</sub>-Mediated Cycloaddition of *O*-TBS Oximes **16**.** To a stirred solution of **9a** (61 mg, 0.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added BF<sub>3</sub>·OEt<sub>2</sub> (53 μL, 0.42 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. Saturated aqueous NaHCO<sub>3</sub> was added, and the whole was extracted with CHCl<sub>3</sub>, washed successively with water and brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–AcOEt, 4:1–1:1) to give **16a** (37 mg, 97%).

**(3*R*\*,3*aR*\*,6*aS*\*)-Hexahydro-3-phenylfuro[3,4-*c*]isoxazole (**16b**) (Table 2, Entry 1).** Oxime **9b** (61 mg, 0.2 mmol) was treated with BF<sub>3</sub>·OEt<sub>2</sub> (53 μL, 0.42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>) 3013, 2862 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>) δ 53.0, 67.3, 69.9, 75.1, 88.0, 126.8, 128.1, 128.8, 136.4; HRMS calcd for C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub> 191.0946, found 191.0939.

**(3*aR*\*,6*aS*\*)-Hexahydro-3,3-dimethylfuro[3,4-*c*]isoxazole (**16c**) (Table 2, Entry 2).** Oxime **9c** (51 mg, 0.2 mmol) was treated with BF<sub>3</sub>·OEt<sub>2</sub> (53 μL, 0.42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>) 3013, 2980, 2866 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) 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; <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>) δ 21.0, 26.2, 57.1, 67.4, 69.6, 73.0, 84.7; HRMS calcd for C<sub>7</sub>H<sub>13</sub>NO<sub>2</sub> 143.0946, found 143.0933.

**(3*R*\*,3*aR*\*,6*aR*\*)-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<sub>3</sub>·OEt<sub>2</sub> (53 μL, 0.42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>) 3013, 1697 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>) 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<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub> 324.1474, found 324.1476.

**(3*aR*\*,6*aS*\*)-Hexahydro-3-phenyl-1*H*-cyclopenta[*c*]isoxazole (**16e**) (Table 2, Entry 4).** Oxime **12** (60 mg, 0.2 mmol) was treated with BF<sub>3</sub>·OEt<sub>2</sub> (53 μL, 0.42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>) 3011, 2961, 2870 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>) 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<sub>12</sub>H<sub>15</sub>NO 189.1154, found 189.1155.

**(3*aR*\*,6*aR*\*)-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<sub>3</sub>·OEt<sub>2</sub> (0.45 mL, 5.3 mmol) in (CH<sub>2</sub>Cl<sub>2</sub>)<sub>2</sub> (5 mL) at room temperature for 21 h. After workup, the crude material was chromatographed on silica gel (AcOEt–CHCl<sub>3</sub>, 1:10) to give **16f** (278 mg, 68%): mp 172–175 °C (hexane–AcOEt); IR (CHCl<sub>3</sub>) 1348 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>) 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<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S: C, 56.73; H, 6.80; N, 9.45. Found: C, 56.59; H, 6.95; N, 9.38.

**(3*aR*\*,6*aR*\*)-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<sub>3</sub>·OEt<sub>2</sub> (53 μL, 0.42 mmol) in (CH<sub>2</sub>Cl<sub>2</sub>)<sub>2</sub> (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<sub>3</sub>) 1348 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>) δ 21.6, 47.6, 52.8, 64.8, 77.2, 128.1, 129.8, 131.4, 144.1. Anal. Calcd for C<sub>12</sub>H<sub>16</sub>O<sub>3</sub>N<sub>2</sub>S: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.77; H, 6.25; N, 10.05. **18a**: IR (CHCl<sub>3</sub>) 1336 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) 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; <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>) 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<sub>12</sub>H<sub>16</sub>O<sub>3</sub>N<sub>2</sub>S 268.0882, found 268.0886. Anal. Calcd for C<sub>12</sub>H<sub>16</sub>O<sub>3</sub>N<sub>2</sub>S: 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<sub>3</sub>·OEt<sub>2</sub> (43 μL, 0.32 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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 (CHCl<sub>3</sub>) 1340 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>) 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<sub>13</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub>S (MH<sup>+</sup>) 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<sub>3</sub>·OEt<sub>2</sub> (53 μL, 0.42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) at 0 °C for 30 min. After workup, the crude material was triturated with Et<sub>2</sub>O, 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<sub>3</sub>) 2361, 1686 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>) 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<sub>13</sub>H<sub>15</sub>NO<sub>2</sub> 217.1103, found 217.1103.

**(3*aR*,6*S*,6*aR*\*)-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<sub>3</sub>·OEt<sub>2</sub> (53 μL, 0.42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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 silica gel (hexane–AcOEt, 2:3): IR (CHCl<sub>3</sub>) 2980, 1344 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, C<sub>6</sub>D<sub>6</sub>) 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,  $CDCl_3$ )  $\delta$  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**;  $^1H$  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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