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BF_3·OEt_2-mediated cycloaddition of *O-tert*-butyldimethylsilyloximes having olefin moieties: intramolecular cycloaddition of *N*-borano-nitrones†

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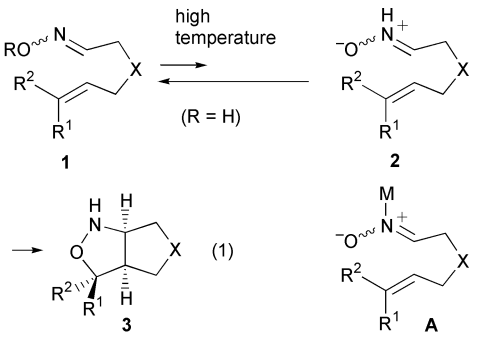
Treatment of *O-tert*-butyldimethylsilyloximes having olefin moieties in the molecules with BF_3·OEt_2 results in efficient generation of *N*-borano-nitrones, which undergo intramolecular cycloaddition at room temperature to afford *N*-nonsubstituted cycloadducts after work-up.

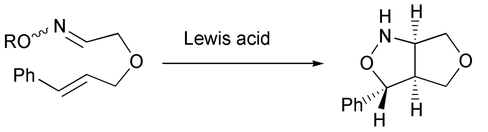
Cycloaddition of an oxime **1** (R = H) having an olefin moiety, so-called intramolecular oxime-olefin cycloaddition (IOOC), gives an *N*-nonsubstituted isoxazolidine **3** *via* tautomerization of the oxime to an *N*-nonsubstituted nitrone **2** (eqn. (1)).[1–9]



IOOC seems to be a more attractive reaction than the corresponding usual nitrone-olefin cycloaddition because an oxime functionality is more readily available and stable than a nitrone one. In general, most IOOCs, however, proceed only under high temperature conditions, since the essential tautomerization from oxime **1** (R = H) to nitrone **2** is a thermodynamically unfavourable process.‡ It is expected that treatment of an oxime derivative **1** (R = H or an alternative group) with a Lewis acid having high affinity to nitrogen might induce an *N*-metallo-nitrone **A**, which, in turn, could undergo intramolecular cycloaddition to provide the cycloadduct **3** under mild conditions. Indeed, Grigg and co-workers reported intermolecular cycloaddition of Pd(II)-based *N*-metallo-nitrones.[10] The reaction is, however, strictly limited to the reaction of (*E*)-α-iminoaldoximes (RN=CR′–CH=NOH) with *N*-methylmaleimide, since Pd(II) requires bidentate structures for its efficient coordination. We report here BF_3·OEt_2-mediated intramolecular cycloaddition of **1** (R = TBS) leading to **3** at rt probably *via* *N*-borano-nitrone **A** (M = BF_2).[11]

We initiated our investigation by the reaction of oxime **1a** having a *trans*-cinnamyl moiety in the presence of $Cu(OTf)_2$ or BF_3·OEt_2 (Table 1) taking into account their affinities to nitrogen. Treatment of oxime **1a** (R = H) with $Cu(OTf)_2$ in acetonitrile at rt gave **3a** in 16% yield (entry 1). When **1a** (R = H) was treated with $Cu(OTf)_2$ in the presence of *i*-Pr_2NEt, dehydration occurred to provide nitrile **4** (entry 2). This suggests that $Cu(OTf)_2$ may coordinate with the oxygen atom of the oxime group in place of the nitrogen atom of **1a**, and that the hydroxy group of **1a** had better be blocked. Thus, *O-tert*-butyldimethylsilyloxime **1a** (R = TBS) was treated with $Cu(OTf)_2$ to give a slightly improved yield of **3a** (entry 3). Although the desired cycloadduct **3a** was obtained, compound **3a** appeared to be unstable in the presence of $Cu(OTf)_2$.§ We then turned our attention to the use of BF_3·OEt_2 as a Lewis acid considering the strong affinities of Si–F as well as B–N.[12] Treatment of **1a** (R = TBS) with BF_3·OEt_2 (2.1 equiv.) caused intramolecular cycloaddition at rt to afford **3a** in 97% yield (entry 4). Since a diminished amount of BF_3·OEt_2 (1.1 equiv.) gave half of the yield (50%) of **3a** (entry 5), the use of two equivalents of BF_3·OEt_2 appears to be essential for efficient cycloaddition. In contrast, treatment of **1a** (R = H) with BF_3·OEt gave a complex mixture, and standing the solution of **1a** (R = H) in CH_2Cl_2 at room temperature for 24 h, of course, resulted in recovery of the starting oxime.

Table 1 Reactions of oximes **1a** with $Cu(OTf)_2$ or BF_3·OEt_2



1a: R = H or TBS **3a**

Entry	R	Conditions	Yield (%)
1	R = H	$Cu(OTf)_2$ (1.0 eq.), MeCN, rt, 2 h	16
2	R = H	$Cu(OTf)_2$ (1.0 eq.), *i*-Pr_2NEt (1.0 eq.), MeCN, rt, 2 h	24[a]
3	R = TBS	$Cu(OTf)_2$ (1.0 eq.), MeCN, rt, 2 h	27
4	R = TBS	BF_3·OEt_2 (2.1 eq.), CH_2Cl_2, 0 °C to rt, 1 h	97
5	R = TBS	BF_3·OEt_2 (1.1 eq.), CH_2Cl_2, 0 °C to rt, 1 h	50

[a] Nitrile $PhCH{=}CHCH_2OCH_2CN$ **4** was obtained.

Next, the BF_3·OEt_2-mediated cycloaddition of several *O*-silyloximes was examined (Table 2). The cycloaddition of oxime **1b**, (*Z*)-isomer of **1a** (R = TBS), also proceeded under similar conditions to those for **1a** to provide **3b**, 4,5-*cis* isomer of **3a**, stereospecifically (entry 1; compare with Table 1, entry 4). Dimethyl-substituted oxime **1c** underwent clean cycloaddition to give **3c** (entry 2). Reaction of nitrogen-tethered substrate **1d** also afforded **3d** in a high yield (entry 3). Carbon-tethered oxime **1e** (a 1 : 1 olefin-geometrical mixture) gave **3e** as a 1 : 1 mixture of diastereomers, although the reaction of **1e** took a long time (entry 4). It should be noted that oxime **1e** having no heteroatom in the tether also required two equiv. of BF_3·OEt_2 (entry 5). In contrast, the reaction of **1f**, the desilylated congener of **1e**, under usual high temperature conditions was not completed even after one week to give **3e** in 54% yield along with the starting oxime **1f** (27%). Finally, the effect of the electron-withdrawing group was examined. Treatment of benzoyl-substituted oxime **1g** with BF_3·OEt_2 gave cyclic nitrone **5** in 56% yield, instead of the corresponding cycloadduct, probably *via* intramolecular Michael addition of the nitrogen atom of the oxime onto α,β-unsaturated ketone (Scheme 1).[13]

Although the exact mechanism is still obscure, the plausible mechanism is shown in Scheme 2. Since the geometry of the

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b2/b201423h/

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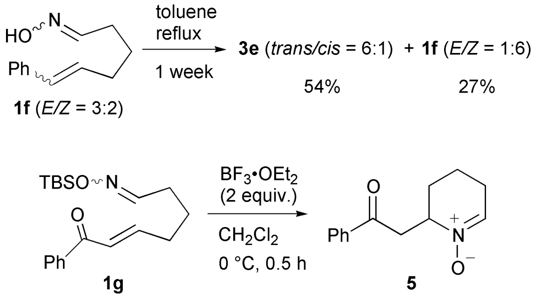
Table 2 Cycloaddition of *O*-silyloximes **1** with $BF_3{\cdot}OEt_2$[a]

1b: R^1 = Ph, R^2 = H; X = O
1c: R^1 = R^2 = Me; X = O
1d: R^1 = H, R^2 = Ph; X = CbzN
1e: R^1, R^2 = H, Ph; X = CH_2

3b: R^1 = Ph, R^2 = H; X = O
3c: R^1 = R^2 = Me; X = O
3d: R^1 = H, R^2 = Ph; X = CbzN
3e: R^1, R^2 = H, Ph; X = CH_2

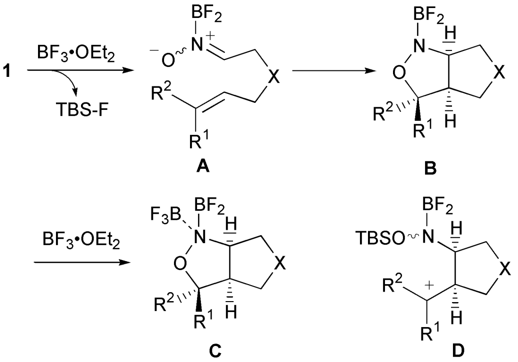
Entry	Oxime	Time	Product	Yield (%)
1	**1b**	1 h	**3b**	87
2	**1c**	1 h	**3c**	80
3	**1d**	1 h	**3d**	92
4	**1e**[b]	5 d	**3e**[c]	73
5	**1e**[b]	5 d[d]	**3e**[c]	38

[a] Unless otherwise noted, all reactions were carried out with 2.1 equiv. of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at rt. [b] *E*/*Z* = 1 : 1. [c] *Trans*/*cis* = 1 : 1. [d] One equiv. of $BF_3{\cdot}OEt_2$ was used.



Scheme 1

olefin moiety reflected into the product (Table 1, entry 4; Table 2, entry 1), the present reaction seems not to be a stepwise process *via* cation **D** but to be a concerted reaction *via* *N*-borano-nitrone **A**. The second equivalent of $BF_3{\cdot}OEt_2$ might be consumed by the formation of complex **C** from the initial cycloadduct **B**.[14] The possibility of further coordination of $BF_3{\cdot}OEt_2$ with nitrone-oxygen of **A** cannot be ruled out.[15]



Scheme 2

We have developed the first intramolecular cycloaddition of *N*-metallo-nitrones. Extension of this reaction to its intermolecular counterpart and application of the concept to a novel asymmetric cycloaddition using a chiral Lewis acid are currently under investigation.

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Notes and references

‡ For facile equilibration between **1** and **2**, use of $ZnCl_2$[3a,8] and reactions in polar solvents[6c,7] have been examined.

§ Indeed, treatment of **3a** with $Cu(OTf)_2$ in acetonitrile afforded a complex mixture.

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