

BF₃·OEt₂-mediated cycloaddition of *O*-*tert*-butyldimethylsilyloximes having olefin moieties: intramolecular cycloaddition of *N*-borano-nitrones†

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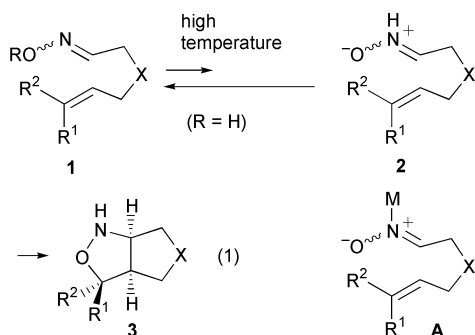
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Treatment of *O*-*tert*-butyldimethylsilyloximes having olefin moieties in the molecules with BF₃·OEt₂ results in efficient generation of *N*-borano-nitrones, which undergo intramolecular cycloaddition at room temperature to afford *N*-nonsubstituted 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 nitronone **2** (eqn. (1)).^{1–9}



IOOC seems to be a more attractive reaction than the corresponding usual nitronone-olefin cycloaddition because an oxime functionality is more readily available and stable than a nitronone one. In general, most IOOCs, however, proceed only under high temperature conditions, since the essential tautomerization from oxime **1** (R = H) to nitronone **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-nitronone **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-nitronones.¹⁰ The reaction is, however, strictly limited to the reaction of (*E*)- α -iminoaloximes (RN=CR'-CH=NOH) with *N*-methylmaleimide, since Pd(II) requires bidentate structures for its efficient coordination. We report here BF₃·OEt₂-mediated intramolecular cycloaddition of **1** (R = TBS) leading to **3** at rt probably via *N*-borano-nitronone **A** (M = BF₂).¹¹

We initiated our investigation by the reaction of oxime **1a** having a *trans*-cinnamyl moiety in the presence of Cu(OTf)₂ or BF₃·OEt₂ (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*-Pr₂NEt, 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

Table 1 Reactions of oximes **1a** with Cu(OTf)₂ or BF₃·OEt₂

Entry	R	Conditions	Yield (%)
1	R = H	Cu(OTf) ₂ (1.0 eq.), MeCN, rt, 2 h Cu(OTf) ₂ (1.0 eq.), <i>i</i> -Pr ₂ NEt (1.0 eq.), MeCN, rt, 2 h	16 24 ^a
2	R = H	Cu(OTf) ₂ (1.0 eq.), MeCN, rt, 2 h	27
3	R = TBS	BF ₃ ·OEt ₂ (2.1 eq.), CH ₂ Cl ₂ , 0 °C to rt, 1 h	97
4	R = TBS	BF ₃ ·OEt ₂ (1.1 eq.), CH ₂ Cl ₂ , 0 °C to rt, 1 h	50

^a Nitrile PhCH=CHCH₂OCH₂CN **4** was obtained.

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 BF₃·OEt₂ as a Lewis acid considering the strong affinities of Si–F as well as B–N.¹² Treatment of **1a** (R = TBS) with BF₃·OEt₂ (2.1 equiv.) caused intramolecular cycloaddition at rt to afford **3a** in 97% yield (entry 4). Since a diminished amount of BF₃·OEt₂ (1.1 equiv.) gave half of the yield (50%) of **3a** (entry 5), the use of two equivalents of BF₃·OEt₂ appears to be essential for efficient cycloaddition. In contrast, treatment of **1a** (R = H) with BF₃·OEt gave a complex mixture, and standing the solution of **1a** (R = H) in CH₂Cl₂ at room temperature for 24 h, of course, resulted in recovery of the starting oxime.

Next, the BF₃·OEt₂-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 BF₃·OEt₂ (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 BF₃·OEt₂ gave cyclic nitronone **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

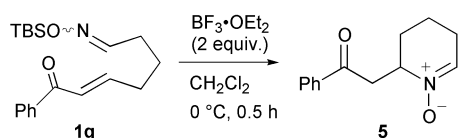
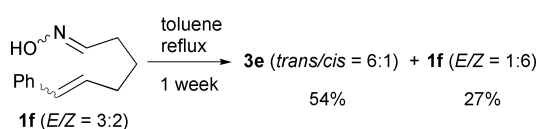
Although the exact mechanism is still obscure, the plausible mechanism is shown in Scheme 2. Since the geometry of the

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

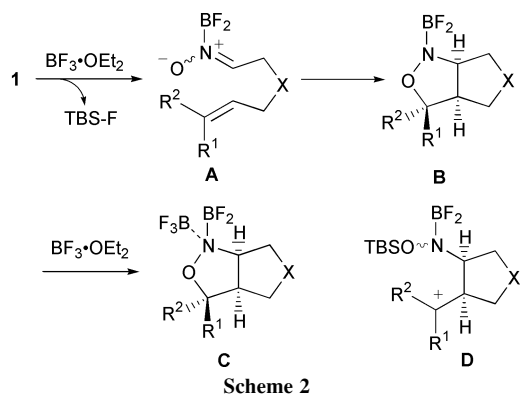
Table 2 Cycloaddition of *O*-silyloximes **1** with BF₃·OEt₂^a

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 BF₃·OEt₂ in CH₂Cl₂ at rt. ^b E/Z = 1:1. ^c Trans/cis = 1:1. ^d One equiv. of BF₃·OEt₂ 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 BF₃·OEt₂ might be

**Scheme 2**

consumed by the formation of complex **C** from the initial cycloadduct **B**.¹⁴ The possibility of further coordination of BF₃·OEt₂ with nitrone-oxygen of **A** cannot be ruled out.¹⁵

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 ZnCl₂^{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.

- R. Grigg, F. Heaney, J. Markandu, S. Surendrakumar, M. Thornton-Pett and W. J. Warnock, *Tetrahedron*, 1991, **47**, 4007.
- N. P. Peet, E. W. Huber and R. A. Farr, *Tetrahedron*, 1991, **47**, 7537.
- (a) A. Hassner, R. Maurya and E. Mesko, *Tetrahedron Lett.*, 1988, **41**, 5313; (b) A. Hassner and R. Maurya, *Tetrahedron Lett.*, 1989, **30**, 2289; (c) A. Hassner, R. Maurya, A. Padwa and W. H. Bullock, *J. Org. Chem.*, 1991, **56**, 2775; (d) A. Hassner, S. Singh, R. Sharma and R. Maurya, *Tetrahedron*, 1993, **49**, 2317; (e) A. Hassner, R. Maurya, O. Friedman, H. E. Gottlieb, A. Padwa and D. Austin, *J. Org. Chem.*, 1993, **58**, 4539.
- A. Arnone, M. Cavicchioli, A. Donadelli and G. Resnati, *Tetrahedron: Asymmetry*, 1994, **5**, 1019.
- J. E. Bishop, K. A. Flaxman, B. S. Orlek, P. G. Sammes and D. J. Weller, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2551.
- (a) M. Gotoh, T. Mizui, B. Sun, K. Hirayama and M. Noguchi, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1857; (b) M. Gotoh, B. Sun, K. Hirayama and M. Noguchi, *Tetrahedron*, 1996, **52**, 887; (c) M. Noguchi, H. Okada, S. Nishimura, Y. Yamagata, S. Takamura, M. Tanaka, A. Kakehi and H. Yamamoto, *J. Chem. Soc., Perkin Trans. 1*, 1999, 185; (d) M. Noguchi, H. Okada, M. Tanaka, S. Matsumoto, A. Kakehi and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 917.
- U. Chiacchio, A. Corsaro, V. Pistara, A. Rescifina, G. Romeo and R. Romeo, *Tetrahedron*, 1996, **52**, 7875.
- A. Abiko, J.-F. Liu, G. Wang and S. Masamune, *Tetrahedron Lett.*, 1997, **38**, 3261.
- S. Moutel and M. Shipman, *Synlett*, 1998, 1333; P. J. Dransfield, S. Moutel, M. Shipman and V. Sik, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3349.
- M. Frederickson, R. Grigg, M. Thornton-Pett and J. Redpath, *Tetrahedron Lett.*, 1997, **38**, 7777.
- For related *N*-silylazomethine ylides, see: K.-I. Washizuka, S. Minakata, I. Ryu and M. Komatsu, *Tetrahedron*, 1999, **55**, 12969.
- For related deprotection of *O*-trimethylsilylethyl group with BF₃·OEt₂, see: K. Jansson, T. Frejd, J. Kihlberg and G. Magnusson, *Tetrahedron Lett.*, 1986, **27**, 753.
- For Lewis acid-mediated Michael addition of oximes to α,β-unsaturated ketones, see: I. S. Saba, M. Frederickson, R. Girigg, P. J. Dunn and P. C. Levett, *Tetrahedron Lett.*, 1997, **38**, 6099; K. Nakama, S. Seki and S. Kanemasa, *Tetrahedron Lett.*, 2001, **42**, 6719.
- D. G. Hall, C. Laplante, S. Manku and J. Nagendran, *J. Org. Chem.*, 1999, **64**, 698.
- N. Katagiri, M. Okada, Y. Morishita and C. Kaneko, *Chem. Commun.*, 1996, 2137; N. Katagiri, M. Okada, Y. Morishita and C. Kaneko, *Tetrahedron*, 1997, **53**, 5725.