Hydrogenation

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$B(C_6F_5)_3$-Catalyzed Hydrogenation of Oxime Ethers without Cleavage of the N–O Bond**

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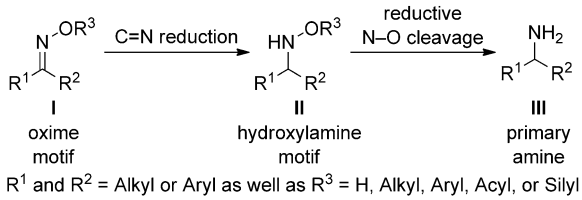
Abstract: *The hydrogenation of oximes and oxime ethers is usually hampered by N–O bond cleavage, hence affording amines rather than hydroxylamines. The boron Lewis acid $B(C_6F_5)_3$ is found to catalyze the chemoselective hydrogenation of oxime ethers at elevated or even room temperature under 100 bar dihydrogen pressure. The use of the triisopropylsilyl group as a protecting group allows for facile liberation of the free hydroxylamines.*

The catalytic reduction of oximes and its congeners to the hydroxylamine oxidation level without cleavage of the weak N–O bond is still a challenge (**I**→**II**, Scheme 1). The hydroxylamine motif is particularly prevalent among molecules with a biological function,[1] and its formation from



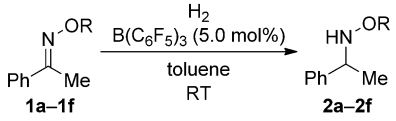
Scheme 1. Reduction of oximes and its congeners: How to stop at the hydroxylamine oxidation level?

readily available oxime precursors is desirable. A literature survey revealed that the heterogeneous hydrogenation of oximes had been described nearly a century ago,[2] but there were issues with reproducing this work.[3] The homogeneous, transition-metal-catalyzed hydrogenation of oximes is commonly plagued by deoxygenation to yield primary amines (**I**→**III**, Scheme 1).[4] However, there is a single patent where the hydrogenation of oxime ethers is reported to stop at the corresponding hydroxylamine derivative (**I**→**II**, Scheme 1).[5]

The majority of methods that allow reliable reduction of the oxime functional group to hydroxylamines with or without substitution at the oxygen atom is based on the stoichiometric use of borohydrides as reducing agents.[1,3,6–8] We reasoned that reactions involving catalytic borohydride generation would be perfectly suited to address the problem of catalytic oxime reduction while leaving the N–O bond intact. Borohydrides are key intermediates in reduction processes catalyzed by $B(C_6F_5)_3$ and related Lewis acids with either hydrosilanes or dihydrogen used as reductants.[9] Activation of the Si–H bond was established by Piers and coworkers, and successfully applied to catalytic imine hydrosilylation.[10] Heterolytic splitting of the H–H bond is accomplished in a similar way by making use of the unique reactivity of frustrated Lewis pairs (FLPs),[11] and several systems for the hydrogenation[12] of imines have been reported to date.[13] Electron-deficient boranes alone also bring about H–H bond activation in the presence of the Lewis basic imine.[14] With regard to potential applications of these catalytic systems to oxime reduction, hydrosilylation will be hampered by the oxophilicity of the silicon atom, and our own experimental findings support this assumption.[15] The hydrogenation approach looked more promising, and we disclose here the $B(C_6F_5)_3$-catalyzed hydrogenation of oxime ethers to furnish *O*-alkylated or *O*-silylated *N*-monosubstituted hydroxylamines with no overreduction.

We began our studies by attempting to hydrogenate the acetophenone-derived oxime **1a** by using catalytic amounts of $B(C_6F_5)_3$, but did not detect any conversion even at high dihydrogen pressures (Table 1, entry 1). We reasoned that its free hydroxy group intervenes, and we therefore prepared

Table 1: Hydrogenation of oximes to hydroxylamines: Effect of the substituent at the oxygen atom.[a]



Entry	Oxime	R	Hydroxylamine	Pressure [bar]	*t* [h]	Conv. [%][b]	Yield [%][c]
1	**1a**	H	**2a**	100	16	0	–
2	**1b**	Me	**2b**	100	16	5	n.d.
3[d]	**1b**	Me	**2b**	100	16	0	–
4	**1c**	*t*Bu	**2c**	60	16	95	n.d.
5	**1c**	*t*Bu	**2c**	100	18	>99	88
6	**1d**	$SiEt_3$	**2d**	100	18	5	n.d.
7	**1e**	$SitBuMe_2$	**2e**	100	18	27	n.d.
8[e]	**1f**	$SiiPr_3$	**2f**	60	16	>99	99

[a] Reactions were performed on a 90–145 μmol scale. [b] Determined by GLC analysis. [c] Determined after purification by filtering through a small plug of silica gel. [d] Reaction performed with addition of Mes_3P (5 mol%). [e] Reaction successfully performed on a 1.5 g scale. n.d. = not determined.

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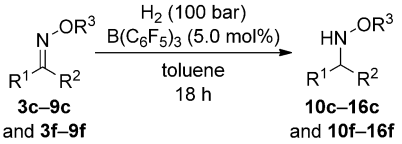
methyl-substituted oxime **1b**. Reduction to hydroxylamine **2b** indeed occurred, but no catalytic turnover was achieved (entry 2). This result is in agreement with a similar observation by Stephan and co-workers during the hydrogenation of sterically less-demanding imines.[13a] According to Pápai and co-workers, the formation of stable Lewis pairs with sterically unhindered amines that accumulate over the course of the reaction inhibits the catalysis.[14c] As the catalyst system $B(C_6F_5)_3$/Mes_3P (Mes = mesityl), known to be superior to $B(C_6F_5)_3$ in the reduction of imines,[14a] showed no improvement (entry 3), we decided to test oxime ether **1c**, which bears a *tert*-butyl group at the oxygen atom. Gratifyingly, **1c** showed 95% conversion at a dihydrogen pressure of 60 bar at room temperature (entry 4). The reaction proved to be highly chemoselective. Neither N–O bond fission nor other side reactions were observed, with only hydroxylamine **2c** and remaining **1c** detected. Increasing the dihydrogen pressure to 100 bar resulted in full conversion, and enabled the isolation of **2c** in excellent yield (entry 5).[16] We then turned our attention to *O*-silylated oximes, which would allow us to subsequently liberate the unprotected hydroxylamine by facile Si–O bond cleavage. Again, the steric demand of the substituent was the key to success. Oxime ethers **1d** (entry 6) and **1e** (entry 7) were not fully converted into the corresponding hydroxylamines, but hydrogenation of triisopropylsilyl-substituted oxime **1f** (entry 8) afforded hydroxylamine **2f** in quantitative yield at a dihydrogen pressure of 60 bar at room temperature. It is noteworthy that neither **1e** and **1f** nor *tert*-butyl-substituted **1c** showed adduct formation with $B(C_6F_5)_3$ at room temperature, as verified by ^{11}B and ^{19}F NMR spectroscopy.

To our surprise, related benzaldehyde-derived oxime ethers were completely inert under these reaction conditions. Lewis acid/base pairing was again excluded by means of NMR spectroscopy. We think that aldehyde-based oxime ethers are not sufficiently Lewis basic at the nitrogen atom to participate in the cooperative dihydrogen activation.

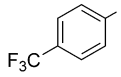
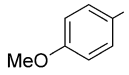
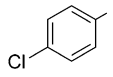
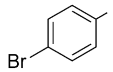
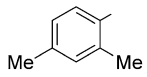
With the optimal substituents at the oxygen atom identified, we set out to explore the substrate scope of the hydrogenation. Representative *O*-*tert*-butyl (**3c**–**9c**) and *O*-triisopropylsilyl oxime ethers (**3f**–**9f**) were treated with $B(C_6F_5)_3$ at 100 bar dihydrogen pressure (Table 2). Oxime ethers bearing electron-withdrawing (entries 1 and 2) or electron-donating substituents (entries 3 and 4) were converted into the corresponding hydroxylamines, with the *O*-silyl oximes requiring elevated temperatures to reach full conversion. Prolonged reaction times at room temperature generally had little or no effect on the conversion. Even the Lewis basic methoxy substituent in oxime ethers **4c** and **4f** is tolerated under these reaction conditions. Likewise, halogenated (entries 5–8) and *ortho*-substituted substrates (entries 9 and 10) were successfully hydrogenated. No dehalogenation was observed for chloro-substituted **5c**/**5f** and bromo-substituted **6c**/**6f**. Benzophenone-derived oxime ethers were far less reactive (entries 11 and 12), not exceeding 50% conversion in the case of *O*-silyl-substituted oxime **8f** even at elevated temperature and higher catalyst loading. Aliphatic oxime ethers **9c** and **9f** reacted poorly at room temperature, but showed complete conversion at 60 °C (entries 13 and 14).

Although the reduction of unprotected oximes had failed (see Table 1, entry 1), the deprotection of *O*-silylated hydroxylamines was considered to be a way to liberate the hydroxylamine functionality. To illustrate its feasibility, we investigated the removal of the silyl protecting group of *O*-silylated **2f**. Cleavage of the Si–O bond was observed under acidic as

Table 2: Substrate scope of the hydrogenation of oxime ethers to *O*-protected hydroxylamines.[a]

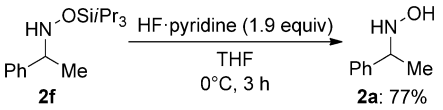


3c–9c and **3f–9f** → **10c–16c** and **10f–16f**

Entry	Oxime ether	R^1	R^2	R^3	Hydroxylamine	*T* [°C]	Conv. [%][b]	Yield [%][c]
1	**3c**		Me	*t*Bu	**10c**	25	>99	80
2	**3f**		Me	Si*i*Pr$_3$	**10f**	60	>99	99
3	**4c**		Me	*t*Bu	**11c**	25	>99	96
4[d]	**4f**		Me	Si*i*Pr$_3$	**11f**	60	>99	97
5	**5c**		Et	*t*Bu	**12c**	25	>99	99
6[d]	**5f**		Et	Si*i*Pr$_3$	**12f**	60	>99	99
7	**6c**		Me	*t*Bu	**13c**	25	>99	96
8	**6f**		Me	Si*i*Pr$_3$	**13f**	25	>99	95
9[e]	**7c**		Me	*t*Bu	**14c**	60	95	94[f]
10	**7f**		Me	Si*i*Pr$_3$	**14f**	25	>99	99
11[d]	**8c**			*t*Bu	**15c**	60	90	66[f]
12[d]	**8f**			Si*i*Pr$_3$	**15f**	60	50	n.d.
13	**9c**			*t*Bu	**16c**	60	>99	n.d.[g]
14	**9f**				Si*i*Pr$_3$**16f**	60	>99	99

[a] Reactions were performed on a 0.12–0.14 mmol scale. [b] Determined by GLC analysis. [c] Determined after purification by filtering through a small plug of silica gel. [d] Reaction was performed with 10 mol% $B(C_6F_5)_3$. [e] Reaction was performed with 8.2 mol% $B(C_6F_5)_3$. [f] Calculated yield, contains starting material. [g] Not isolated because of its volatility. n.d. = not determined.

well as basic conditions (**2f**→**2a**). However, depending on the solvent, decomposition or in situ oxidation[17] to the free oxime (**2a**→**1a**, not shown) thwarted the isolation of **2a**. Likewise, the use of tetra-*n*-butylammonium fluoride (TBAF) in THF yielded a complex mixture. Finally, unprotected **2a** was obtained after treatment of **2f** with HF·pyridine in THF at 0 °C (Scheme 2).



Scheme 2. Removal of the silyl group to liberate the free hydroxylamine.

In summary, we presented herein a catalytic method for the reduction of *O*-alkyl and *O*-silyl oxime ethers to their corresponding *N*-monosubstituted hydroxylamines. The simple setup which employs dihydrogen as a reducing agent and commercially available Lewis acid $B(C_6F_5)_3$ as the catalyst results in exceptionally clean reactions. These assets distinguish the present approach from traditional ones[1] that require stoichiometric amounts of boron hydrides.[6,7] It was shown that desilylation of the resulting *O*-silylhydroxylamines furnishes unprotected hydroxylamines, thereby adding a new reaction to synthetic chemists' repertoire.

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Keywords: boron · homogeneous catalysis · hydrogenation · Lewis acids · reduction

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[15] The $B(C_6F_5)_3$-catalyzed hydrosilylation of various acetophenone-derived oxime ethers produced a complex mixture, clearly indicating that deoxygenation occurred. Moreover, *N*-ethylaniline was detected in variable quantities as a result of a reductive rearrangement that is related to the Beckmann rearrangment: M. Ortiz-Marciales, L. D. Rivera, M. De Jesús, S. Espinosa, J. A. Benjamin, O. E. Casanova, I. G. Figueroa, S. Rodríguez, W. Correa, *J. Org. Chem.* **2005**, *70*, 10132 – 10134.

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