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Lewis acid-promoted electron transfer deoxygenation of epoxides, sulfoxides, and amine *N*-oxides: the role of low-valent niobium complexes from $NbCl_5$ and Zn

Kyungsoo Oh *, William Eric Knabe

Department of Chemistry and Chemical Biology, Indiana University–Purdue University Indianapolis, Indianapolis, IN 46202, USA

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ABSTRACT

A mild and operationally simple deoxygenation of epoxides, sulfoxides, and amine *N*-oxides is described using a sub-stoichiometric amount of low-valent niobium complexes generated in situ from commercially available $NbCl_5$ and zinc dust. The deoxygenation proceeds by a reductive cleavage of polarized O–C/O–N/O–S bonds through a single electron transfer from zinc metal to the niobium–substrate complex due to the high oxophilic nature of the niobium species. The presence of adjacent radical-stabilizing groups is beneficial to epoxide substrates; however the similar prerequisite does not apply to sulfoxides and amine *N*-oxides, where a broad range of substrates are efficiently deoxygenated in excellent yields.

1. Introduction

Radical reactions have become one of the most powerful synthetic tools in modern organic chemistry.[1] Numerous methods are known to generate reactive radical species from various physical (i.e., photochemical or thermal) and chemical means. Generally, the radicals generated from chemical means, reagent-controlled, provide a high predictability of behaviors.[2] In particular, tremendous progress has been made in the area of metal-induced radical chemistry over the last three decades.[3] While a variety of functional groups are known to participate in radical generation through metal-induced single electron transfer (SET) reactions, oxygen-containing radical species present a high potential in the context of synthetic method development as well as its application to the synthesis of complex molecules.[4] One of the most obvious pathways of radicals generated from oxygen-containing substrates is deoxygenation. Among various functional moieties epoxides and amine *N*-oxides can be deoxygenated to the corresponding alkenes and amines, where the oxygenated form serves as a protecting group for the parent functionality. Furthermore, the deoxygenation of sulfoxides, an important functional group in asymmetric synthesis, provides a useful synthetic utility of organosulfur reagents in various synthetic transformations.

Although the detailed mechanism of deoxygenation reactions might differ among functional groups, in our simplistic overview of deoxygenation reactions, as shown in Scheme 1, the activation of the substrates requires the following: (1) a covalent bond formation between the oxygen atom of the substrates and various electrophilic reagents, (2) Lewis acids or oxophilic transition metal complexes to activate the oxygen atom of less nucleophilic substrates. The subsequent reaction pathways are guided either by an intra- or intermolecular nucleophile-mediated reductive route (path *a*) or a single electron transfer (SET) route mediated by metal complexes with low ionization potentials to the low-lying $\sigma*$ orbital of the C–O/N–O/S–O bonds (path *b*). Alternatively, selected transition metal complexes can induce a concerted reductive deoxygenation, where a stoichiometric amount of co-reducing agents renders a unique opportunity for the catalytic deoxygenation protocol (path *c*).

The concept depicted in path *a* has been frequently utilized in the deoxygenation of sulfoxides, where halides,[5] hydrides,[6] heteroatom-based (phosphorus,[7] selenium,[8] and sulfur[9]) nucleophiles facilitate reductive deoxygenation. Recent studies also suggest that path *a* can be extended to epoxides using $ZrCl_4/NaI$[10] and to amine *N*-oxides with LiCl[11] or $ZrCl_4$[12] in the presence of $NaBH_4$.[13] Path *b* is more common for amine *N*-oxides and sulfoxides; where reactive transition metal complexes promote deoxygenation in the presence of co-reducing species such as indium,[14] chromium,[15] and zinc metals.[16] Non-transition metal activators, pivalyl chloride[17] and dimethyl silyl chloride,[18] are also known to effect deoxygenation of sulfoxides in the presence of indium and zinc, respectively. Some known dissolving metal reduction protocols[19] should fall into this path *b* as well as some cases of Lewis acid-promoted deoxygenation of amine *N*-oxides.[20] The deoxygenation of epoxides using path *b* typically requires electron-acceptors other than epoxides such as carbonyl moieties as evidenced in InCl/In,[21] SmI_2,[22] and $CrCl_2$ systems.[23] The radical intermediate generated from a SET to epoxides

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* Corresponding author. Tel.: +1 317 278 7531; fax: +1 317 274 4701.
E-mail address: ohk@iupui.edu (K. Oh).

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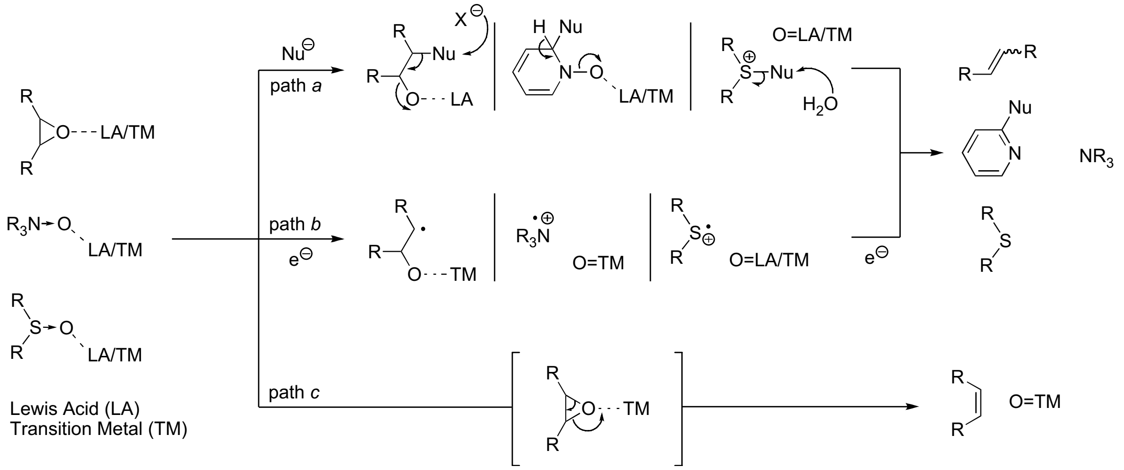


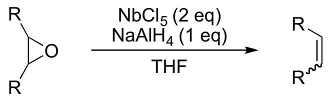
Scheme 1. A simplistic overview of deoxygenation reactions.

also presents ample opportunities for further synthetic utility in intra- and intermolecular C–C bond forming reactions.[4] Deoxygenation via path *c* represents a rare, but practical approach to catalytic deoxygenation protocols; however they often require elaborate synthesis of the molybdenum[24] or rhenium[25] complexes as reactive deoxygenating reagents at the expense of co-reducing reagents such as PPh_3 or $P(OPh)_3$.

While numerous methods are available to effect deoxygenation of a specific functional moiety, the development of a general deoxygenating reagent across multiple functional moieties is yet to be achieved. Some progress in deoxygenation via path *a* includes Tebbe reagent by which sulfoxides and selenoxides as well as pyridine *N*-oxides are efficiently deoxygenated, although the concomitant methyl addition was accompanied in cases of pyridine *N*-oxides.[26] It is evident that path *b* holds great promise in the development of a general deoxygenating reagent across multiple functional moieties. Previously, Gladysz and co-workers demonstrated that a variety of oxygen- and sulfur-containing organic compounds could be deoxygenated upon condensation with chromium metal.[15] Titanium(III) complexes, i.e., Cp_2TiCl, are also known to effect deoxygenation of epoxides[27] and amine *N*-oxides,[14e] although sulfoxide deoxygenation has not been studied. Moreover, Ti(II) porphyrin complex has been also employed for deoxygenation of epoxides and sulfoxides,[28] while molybdenum complex[24] and pivalyl chloride[17] are used in deoxygenation of sulfoxides and amine *N*-oxides in the presence of co-reducing agents.

In the pursuit of a general deoxygenation protocol across multiple functional moieties, we became interested in path *b* using transition metal complexes.[29] From the inception of our program we were mindful of major drawbacks of current deoxygenation protocols, i.e., isolation of active deoxygenating reagents, employment of high temperature, and use of stoichiometric amounts of reagents. The deoxygenation via path *b* was envisioned to offer multiple advantageous solutions for the aforementioned drawbacks, and recent success in the Ti(III)-mediated radical epoxide-opening[30] led us to examine other d^1 transition metal complexes.[31] In addition, we postulated that the in situ generation of reactive deoxygenating reagent, MX_n, from the corresponding MX_{n+m} would present a possibility of regeneration of the reagent from the oxidized form, MOX_n, either in the form of MX_n or MOX_{n-2} in the presence of metals with low oxidation potentials.

Among the various transition metal halides, we initially focused on the readily available $NbCl_5$.[32] Oshima has previously demonstrated the preparation of low-valent Nb complexes[33] and its use in the deoxygenation of epoxides, although high temperature and 2 equiv of niobium reagent were used with only four epoxide substrates (Scheme 2).[34] The exact nature of the deoxygenating agent produced in Oshima's seminal publication was not known; however the loss of stereochemical integrity of the olefins as well as the slow reaction rate of mono-alkylsubstituted epoxide toward deoxygenation led us to favor path *b* as the most likely deoxygenation pathway.



1 2

1	temp (°C)	time (h)	2	yield (GC %)	*E/Z*
E-Cyclododecene oxide	80	1	Cyclododecene	53	87/13
Z-Cyclododecene oxide	80	1	Cyclododecene	50	71/29
E-Stilbene oxide	25	1	Stilbene	75	*E* only
1-Dodecene oxide	80	15	1-Dodecene	50	—

Scheme 2. Deoxygenation of epoxides by Oshima using $NbCl_5/NaAlH_4$.

Furthermore, Utimoto and co-workers have shown that the generation of low-valent Nb complexes from the $NbCl_5$-Zn system is superior to $NbCl_3(DME)$ upon cross coupling of carbonyl compounds leading to multi-substituted 1,3-diene derivatives through a facile deoxygenation of (*Z*)-but-2-ene-1,4-diol intermediates.[35]

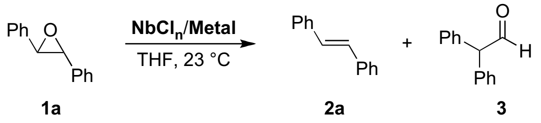
2. Results and discussion

2.1. Reaction design and optimization

Deoxygenation of epoxides is a synthetically useful method for liberating alkenes from epoxides, a temporary protecting group for the parent alkenes.[36] This strategy utilizes the orthogonal reactivity of alkenes; selective epoxidation of electron-deficient alkenes with nucleophilic oxidants or epoxidation of electron-rich alkenes with electrophilic oxidants. With this high potential of synthetic utility of epoxide deoxygenation in mind, we initially investigated the deoxygenation of *trans*-stilbene oxide **1a** with low-valent Nb complexes generated from $NbCl_5$ in the presence of various metals with low ionization potentials (Table 1).[37] First, the generation of low-valent niobium species was examined at room temperature with a small excess of metal. The appearance of a black color (or deep purple in a diluted concentration) was judged as the formation of low-valent Nb complexes. As shown in Table 1, aluminum took

Table 1

Deoxygenation of *trans*-stilbene oxide with low-valent niobium complexes generated from metal reduction[a]



Entry	NbCl$_n$/metal	Generation of low-valent Nb complex (min)	Reaction time (h)	Yield[b] (%)
1	$NbCl_5$/Al	60	1.5	0[c]
2	$NbCl_5$/Cu	15	0.5	0[c]
3	$NbCl_5$/In	<5	0.5	25[c]
4	$NbCl_5$/Mg	10	2.0	4[c]
5	$NbCl_5$/Sn	15	0.5	24
6	$NbCl_5$/Zn	<5	2.0	63
7	$NbCl_3$(DME)	n/a	1.0	33[c]
8	$NbCl_4(THF)_2$	n/a	3.0	12[c]
9	$NbCl_4(THF)_2$/Zn	n/a	1.0	68
10	$NbCl_3$(DME)/Zn	n/a	1.0	54

[a] Unless stated otherwise, reaction performed with $NbCl_5$ (1 mmol) and metal (1.5 mmol) in THF (10 mL) at 23 °C.

[b] Isolated (*E*)-**2a** after flash column chromatography.

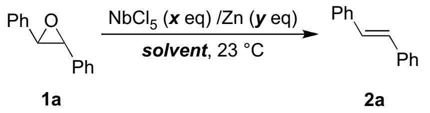
[c] 2,2-Diphenylacetaldehyde **3** was isolated as a major compound.

a considerably longer time for the formation of low-valent Nb complexes, where the color of the solution progresses from yellow to brown, finally to a black solution in 60 min (entry 1).[38] Other metals took less time, while instantaneous color changes were observed for indium and zinc (entries 3 and 6). Upon formation of the black colored solution, *trans*-stilbene oxide **1a** was added and the reaction was monitored by GC as well as TLC. Complete consumption of **1a** was achieved in less than 2 h; however Lewis acid-promoted rearrangement product, 2,2-diphenylacetaldehyde **3**, was isolated as a major product (entries 1–4).[39] Clearly, the Lewis acid by-products ($AlCl_n$, $CuCl_n$, $InCl_n$, $MgCl_n$) interfered with the desired deoxygenation pathway. As noted by Utimoto, the presence of zinc is indispensable for promoting deoxygenation of epoxides (entry 6).[35] Further attempts were made to elucidate the nature of low-valent niobium in the absence of zinc metal using commercially available Pedersen catalysts (entries 7–10). It was revealed that the deoxygenation of *trans*-stilbene oxide **1a** could be effected using Nb(III) complexes in 33% yield (entry 7), while the deoxygenation was significantly slower using Nb(IV) complexes to give 12% yield (entry 8). Thus, it is likely that Nb(III)/Nb(IV) complexes alone are not an efficient deoxygenation reagent due to their obvious Lewis acidity in the absence of zinc metal (entries 7 and 8). It is not clear at this moment if the further reduction of Nb(III) and Nb(IV) complexes can be achieved in the presence of zinc metal. Nevertheless, the deoxygenation of *trans*-stilbene oxide **1a** was effected by Nb(III)/Nb(IV) complexes in the presence of zinc metal with modest to good yields (entries 9 and 10). Although the previous observation by Pedersen on the reductive coupling of imines using Nb(IV) complexes suggests a similar Nb(IV)-promoted radical transfer reaction,[40] given the fact that Nb(III)/Zn equally deoxygenates (entry 10) we believe that niobium complexes simply act as complexing agents (or Lewis acids) to lower the potential energy of the C–O $\sigma*$ orbital, thus promoting a SET reaction by zinc metal. Zinc's low toxicity and high compatibility with other functional moieties is an advantageous aspect of the current mild reducing condition.

Encouraged by the convenient generation of low-valent Nb complexes from reduction of $NbCl_5$ with zinc metal, we next examined solvents as well as catalytic use of low-valent Nb complexes (Table 2). The choice of solvent has been shown to have a profound effect upon deoxygenation. The reactions under non-coordinating solvents were either low yielding or completely inert to deoxygenation (entries 1–3). Coordinating solvents were found to be a more effective medium for the deoxygenation of epoxides, although the reaction in diethyl ether significantly reduced reactivity (entry 4). It is noteworthy that the protic solvent, MeOH, gave an acceptable yield of 50% and in this case the major by-product was derived from epoxide-opening by MeOH,[41] probably due to the presence of multiple Lewis acidic components, including $ZnCl_2$ (entry 8).[42] We then examined a dual solvent system between THF and other non-coordinating solvents (1:1), and found that further improvement on yields can be achieved (entries 9–16). A 1:1 mixture of THF and benzene was found to be an optimal condition, resulting in a 72% yield of the product in 2.5 h at ambient temperature (entry 12). To further optimize the reaction conditions, the amount of niobium and zinc were varied (entries 17–23). Reducing the amount of zinc from 1.5 equiv to 1.0 equiv produced a lower yield of 55% compared to 72% (entry 12 vs 17). A further increase in the amount of zinc to 5 equiv did not improve the yield (entry 18). In the case of niobium, increasing $NbCl_5$ to 1.5 equiv had no effect on yield (entry 12 vs 19). To understand the catalytic use of low-valent niobium complexes, we lowered catalyst loadings to 50, 25, 18, and 10 mol % in the presence of excess zinc metal and found that deoxygenation with 50 mol % of $NbCl_5$ occurred with a comparable yield to the case of 1.0 equiv of $NbCl_5$ (entry 12 vs 20). Use of less than 50 mol % of $NbCl_5$ led to a prolonged reaction time and required higher temperature with diminished yields of alkene (entries 21–23). Furthermore, a control experiment confirmed that no deoxygenation of epoxide occurs with zinc metal in the absence of $NbCl_5$ (entry 24). Given the observations noted above and driven by the attractiveness of sub-stoichiometric use of $NbCl_5$, we decided to pursue deoxygenation conditions with the low-valent

Table 2

Optimization of epoxide deoxygenation: solvents and reagents loadings[a]



Entry	Solvent	$NbCl_5$/Zn	Yield[b] (%)
1	PhH	1:1.5	25[c]
2	$PhCH_3$	1:1.5	20[c]
3	DCE	1:1.5	0[c]
4	Et_2O	1:1.5	3
5	DME	1:1.5	41
6	THF	1:1.5	63
7	1,4-Dioxane	1:1.5	69
8	MeOH	1:1.5	50[d]
9	DME/PhH	1:1.5	63
10	DME/$PhCH_3$	1:1.5	13
11	THF/$PhCH_3$	1:1.5	68
12	THF/PhH (1:1)	1:1.5	72
13	THF/PhH (1:4)	1:1.5	57
14	THF/PhH (4:1)	1:1.5	57
15	1,4-Dioxane/PhH	1:1.5	45
16	MeOH/PhH	1:1.5	55[d]
17	THF/PhH (1:1)	1:1.0	55
18	THF/PhH (1:1)	1:5.0	64
19	THF/PhH (1:1)	1.5:1.5	72
20	THF/PhH (1:1)	0.5:5.0	68
21	THF/PhH (1:1)	0.25:5.0	56[e]
22	THF/PhH (1:1)	0.18:5.0	58[e]
23	THF/PhH (1:1)	0.1:5.0	46[c,e]
24	THF/PhH (1:1)	0:1.5	0[f]

[a] Reaction performed in 5 mL of solvent at 23 °C until starting material is consumed (1–6 h).

[b] Isolated after flash column chromatography.

[c] Reaction did not go to completion after 48 h.

[d] Epoxide-opening by MeOH was observed.

[e] Reaction performed at 80 °C.

[f] Recovery of 97% of *trans*-stilbene epoxide after 24 h.

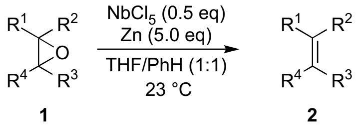
niobium complexes generated from 0.5 equiv of $NbCl_5$ and 5.0 equiv of zinc metal in a 1:1 mixture of THF/PhH (0.2 M) at ambient temperature (entry 20).

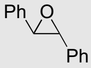
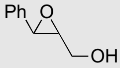
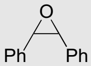
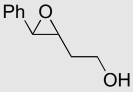
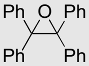
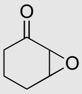
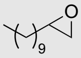
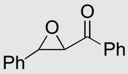
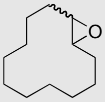
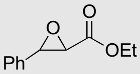
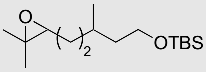
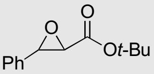
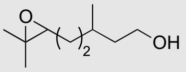
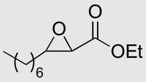
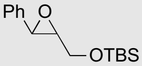
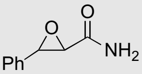
2.2. Epoxide substrate scope and limitation

With our optimized deoxygenation conditions in hand, we next turned our attention to expand the substrate scope of our deoxygenation of epoxides (Table 3). As opposed to *trans*-stilbene oxide **1a**, *cis*-stilbene oxide **1b** was deoxygenated with a much improved reaction rate and yield; however the stereochemical integrity was compromised to give rise to *trans*-stilbene **2a** as a sole product (entry 2). Conducting the reaction at low temperature as well as monitoring the unfinished reaction mixture with a crude ^1H NMR did not show any detectable amount of *cis*-stilbene product. In the case of tetraphenyl oxirane **1c**, an elevated temperature with 1 equiv of $NbCl_5$ was required due to the sluggish reaction rate (entry 3). The deoxygenation of alkyl epoxides was not as effective as aryl epoxides and was plagued with the formation of by-products depending on substrates, although complete consumption of the starting materials was observed (entries 4–7). Generally, the deoxygenation of alkyl epoxides was significantly slower than that of aryl epoxides. In addition, excess use of deoxygenating reagent had a minimal effect on the deoxygenation efficiency. In the case of mono-substituted alkyl epoxide **1d**, chlorohydrins and dodecan-1-ol balanced out the loss of the product mass (entry 4).[43] A mixture of

Table 3

Scope of deoxygenation of epoxides[a]



Entry	Epoxide	Reaction time (h)	Yield[b] (%)	Entry	Epoxide	Reaction time (h)	Yield[b] (%)
1	 **1a**	12	**2a**, 68	9	 **1i**	3	**2i**, 50
2	 **1b**	0.5	**2a**, 95	10	 **1j**	1.5	**2j**, 43
3	 **1c**	48	**2c**, 69[c]	11	 **1k**	17	**2k**, 36[g]
4	 **1d**	24 2 0.5	**2d**, 25 **2d**, 41[d] **2d**, 33[e]	12	 **1l**	2	**2l**, 0[g]
5	 **1e** **(1:1)**	24 8 1	**2e**, 45[f] **2e**, 13[d] **2e**, 27[e]	13	 **1m**	24 3	**2m**, 67 **2m**, 48[d]
6	 **1f**	24 5 0.5	**2f**, 30 **2f**, 32[d] **2f**, 45[e]	14	 **1n**	30	**2n**, 61
7	 **1g**	30 24 3	**2g**, 21 **2g**, 42[d] **2g**, 36[e]	15	 **1o**	96	**2o**, 35[h]
8	 **1h**	6	**2h**, 55	16	 **1p**	24	**2p**, 65[i]

[a] Unless stated otherwise, the reaction was performed with epoxide (1 mmol) and Nb complexes, generated from $NbCl_5$ (0.5 mmol) and zinc (5.0 mmol), in a 1:1 mixture of THF/PhH (5 mL) at ambient temperature until starting material is consumed.

[b] Isolated after column chromatography.

[c] Reaction performed at 80 °C.

[d] 1 mmol of $NbCl_5$ was employed.

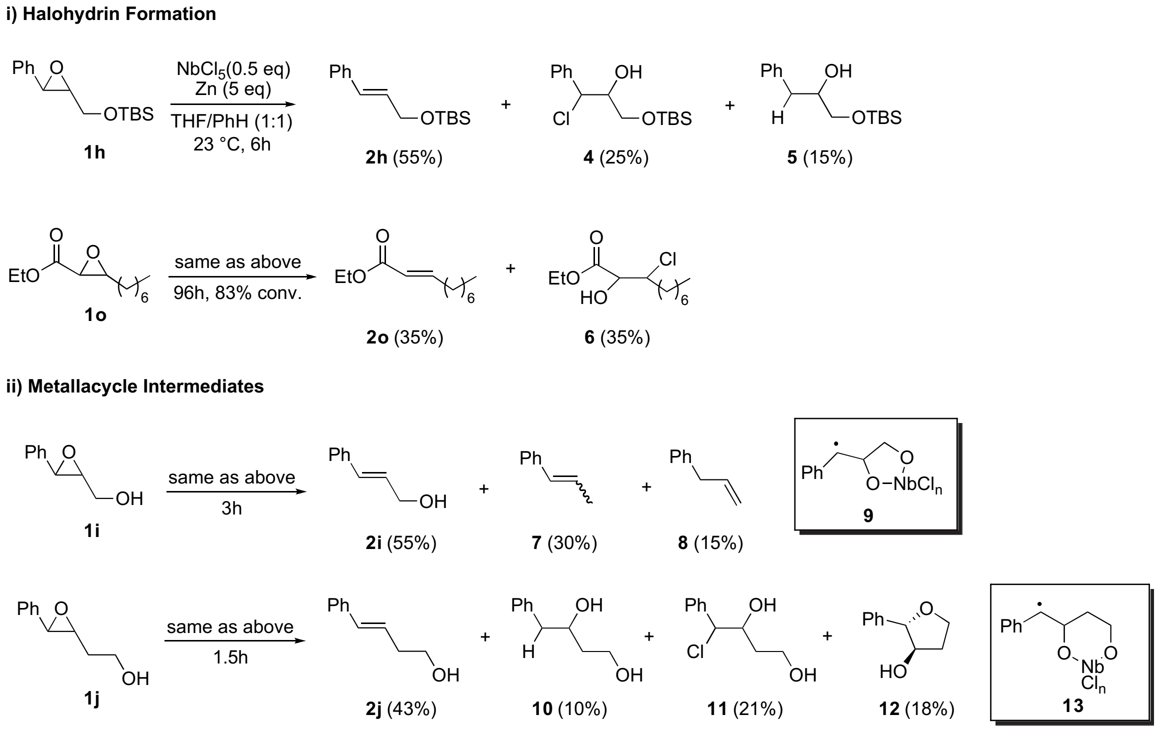
[e] 3 mmol of $NbCl_5$ was employed.

[f] A mixture of *cis*/*trans* isomers (1:2) was isolated.

[g] Reaction performed at −10 °C (GC yield).

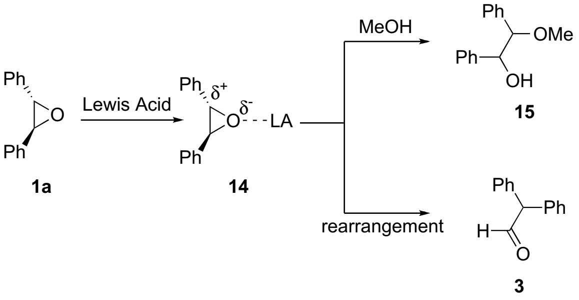
[h] Starting material was recovered (27%).

[i] ^1H NMR yield determined with internal standard (2,5-dimethylfuran).



Scheme 3. Identification of by-products.

cyclododecane epoxide isomers **1e** marginally improved deoxygenation, although no further analysis on by-products was investigated (entry 5). Deoxygenation of tri-substituted alkyl epoxide **1f** also suffered with a diminished yield (entry 6). Further decrease in yield was observed in the case of hydroxyl-bearing tri-substituted alkyl epoxide **1g**, although employment of 1 equiv of deoxygenating reagent seemed to improve yield marginally (entry 7). In order to further examine the substitution pattern as well as the hydroxyl compatibility, other 1,2-disubstituted epoxides were tested (entries 8–10). It was revealed that the presence of an aryl substitution is highly beneficial to the reaction rate as well as the preferential radical formation at the carbon adjacent to phenyl group (entry 8 and Scheme 3).[44] The presence of hydroxyl group in **1i** led to formation of a 2:1 mixture of *cis*/*trans*-prop-1-enylbenzene **7** and allylbenzene **8** (~50%) as by-products, possibly through the intermediacy of a five-membered metallacycle **9** (entry 9 and Scheme 3).[39] The six-membered metallacycle **13**, a presumable intermediate from the deoxygenation of β-epoxy alcohol **1j**, does not lead to the similar elimination to give alkenes; instead, reductive and Lewis acid-promoted epoxide-opened products, 4-phenylbutane-1,3-diol **10** (~10%)[45] and 4-chloro-4-phenylbutane-1,3-diol **11** (~21%), were isolated as by-products (entry 10).[46] Furthermore, we examined the compatibility of other functional moieties such as α,β-epoxy carbonyl substrates (entries 11–16). While the ketones are not compatible with our deoxygenation conditions[47]—either low yielding or unsuccessful deoxygenation (entries 11 and 12)—the deoxygenation of α,β-epoxy ester and amide was achieved with good yields (entries 13–16). As expected, the deoxygenation of α,β-epoxy ester **1o** without a radical-stabilizing group was significantly slow and led to formation of chlorohydrin **6** as a by-product (entry 15 and Scheme 3).[48]



Scheme 4. Lewis acid-promoted epoxide-opening and rearrangement.

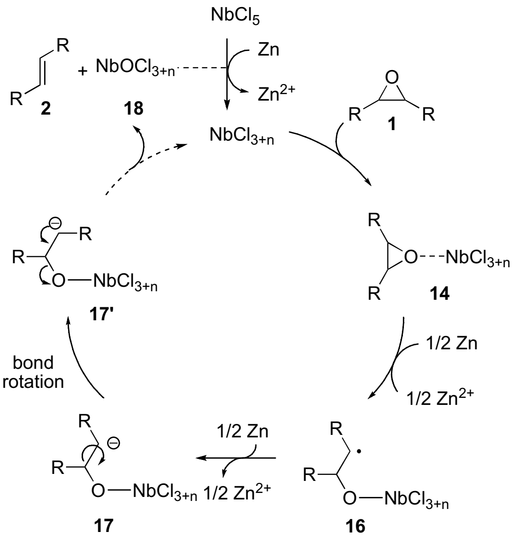
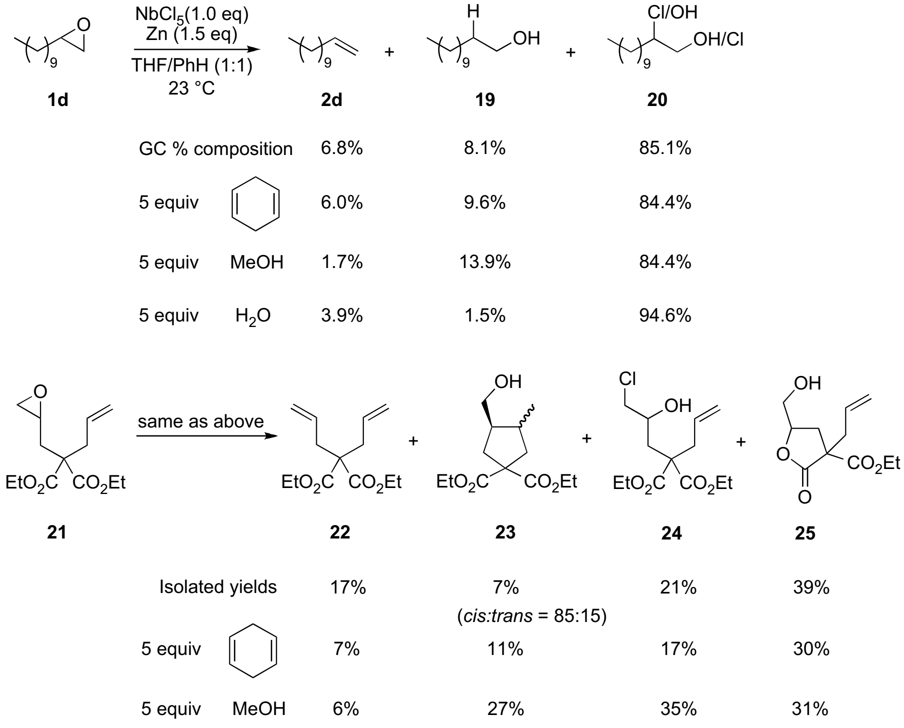


Figure 1. A proposed mechanism.



Scheme 5. Niobium-catalyzed reductive epoxide opening.

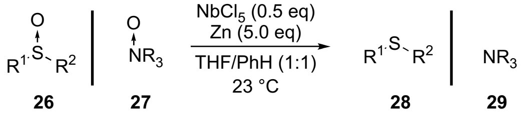
2.3. Reaction mechanism

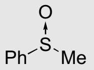
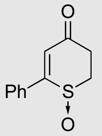
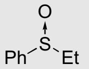
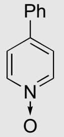
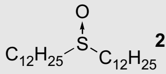
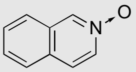
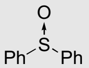
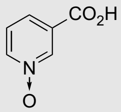
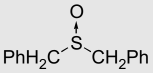
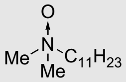
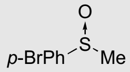
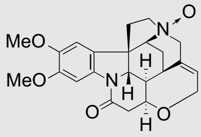
In order to shed light on the reaction mechanism it was necessary to piece together the findings from our experimental observations. A key mechanistic implication was derived from the erosion of stereochemical integrity of stilbene oxides, which led us to believe that the concomitant deoxygenation via path *c* (in Scheme 1) can be ruled out. Although a possibility of nucleophile-promoted reductive deoxygenation (path *a*) could not be completely dismissed, the absence of appreciable amounts of chlorohydrin intermediates along the course of the reaction[49] together with the fact that the faster deoxygenation reaction of *cis*-stilbene oxide **1b** as opposed to *trans*-stilbene oxide **1a** appears to indicate that nucleophile-promoted deoxygenation is less likely a major pathway under our reaction conditions. Furthermore, the low reaction rate with sterically demanding substrates suggested that the interaction of niobium complexes with the epoxide substrate might be a prerequisite for the desired reaction pathway. This proposed complexation between niobium and epoxide substrate would certainly experience a stiff competition with other Lewis acid-promoted reaction pathways (Scheme 4). According to our deoxygenation of *trans*-stilbene oxide **1a** using Pedersen's reagent, the niobium species preferentially acts as a Lewis acid in the absence of zinc metal to promote rearrangement to give 2,2-diphenylacetaldehyde **3** as a major product, although this rearrangement could not be substantiated with other alkyl epoxides. Furthermore, the reluctant deoxygenation of alkyl epoxides led to the successful isolation of chlorohydrins, which indicates the Lewis acid-promoted epoxide-opening as an identifiable side reaction. In addition, the complexation of Lewis acid to substrates also explains our observation about an epoxide-opened product **15** in protic solvents (entries 8 and 16 in Table 2) and somewhat low yields of hydroxy-containing substrates (entries 7, 9, and 10 in Table 3).

Given the fact that zinc metal plays a vital role in deoxygenation and supported by our observation on the different reaction results from Pedersen's reagents and low-valent Nb complexes generated by $NbCl_5$/Zn system, the electron transfer deoxygenation via path *b* was proposed (Fig. 1). Obviously, there are potentially multiple stages, where zinc metal could participate in a single electron transfer (SET) during the proposed reaction cycle. The first role of zinc metal can be found in the reduction of $NbCl_5$ to low-valent Nb complexes. Although the exact nature of the resulting niobium species cannot be certain, we believe that Nb(III)/Nb(IV) species are both involved in complexation with the substrates, where zinc metal induces reductive opening of Nb–epoxide complex **14** to give β-nioboxy radical **16** through a SET process. In order to proceed with the deoxygenation pathway, further SET to β-nioboxy radical **16** should take place quickly to form anionic species **17**, which in turn collapses to give the alkene **2** after a single bond rotation. The redundant $Nb(O)Cl_{3+n}$ **18** can be recycled upon reduction with zinc to $Nb(O)Cl_{1+n}$,[50] and our sub-stoichiometric use of $NbCl_5$ somewhat supports the strong possibility of such catalyst regeneration. Nevertheless, the inefficiency of such reagents upon epoxide deoxygenation led to our optimal use of 0.5 equiv of $NbCl_5$.

The involvement of β-nioboxy radical **16** in our proposed reaction mechanism was further supported by the deoxygenation of dodecane epoxide **1d**, which led to the formation of dodecan-1-ol **19** as a by-product, possibly through hydrogen abstraction from solvent, THF (Scheme 5).[51] In order to obtain further information about our reaction mechanism, we examined several radical trapping agents for β-nioboxy radical **16** as described by RajanBabu and Nugent.[52] Inverse addition of low-valent niobium reagents to epoxides was carried out in the presence of excess *tert*-butyl acrylate or cyclohexa-1,4-diene. Although the radical capture of aryl epoxides was not successful due to a facile deoxygenation reaction, the alkyl epoxide **1d** gave rise to the improved formation of the corresponding alcohol **19** in the presence of the hydrogen atom donor, cyclohexa-1,4-diene (Scheme 5). Other hydrogen atom donors, water[30b] and methanol,[53] were also tested; however, no further improvement on reductive radical epoxide-opening was obtained beyond 14%.[54] In the light of the above observations with our intermolecular radical trapping experiments, the 5-*exo-trig* radical

Table 4
Deoxygenation of sulfoxides and amine *N*-oxides[a]



Entry	26	Reaction time (h)	Yield (%)[b]	Entry	26/27	Reaction time (h)	Yield[b] (%)
1	 **26a**	<1	90	7	 **26g**	0.5	78
2	 **26b**	2.0	90	8	 **27a**	5.0	72
3	 **26c**	2.5	97	9	 **27b**	24	90[c]
4	 **26d**	4.5	97	10	 **27c**	24	58[c]
5	 **26e**	24	99	11	 **27d**	1.0	77
6	 **26f**	3.5	95	12	 **27e**	24	95

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[a] Unless stated otherwise, the reaction was performed with sulfoxide/amine *N*-oxide (1 mmol) and Nb complexes, generated from $NbCl_5$ (0.5 mmol) and zinc (5.0 mmol), in a 1:1 mixture of THF/PhH (5 mL) at ambient temperature until starting material is consumed.

[b] Isolated after column chromatography.

[c] ^1H NMR yield determined with internal standard (2,5-dimethylfuran).

clock experiment of epoxyolefin **21** was attempted to further clarify the involvement of β-nioboxy radical **16**.[55] Thus, epoxyolefin **21** was treated with our deoxygenation reaction conditions in the presence and absence of hydrogen atom donors. In this way the formation of cyclopentane derivative **23** was confirmed together with deoxygenated product **22** and chlorohydrin derivative **24** (Scheme 5). The formation of lactone **25** was attributed to a facile cyclization of chlorohydrin **24**, followed by nucleophilic addition of water upon work-up. Furthermore, to illustrate our proposed mechanism regarding niobium species acting as a complexing agent with epoxide substrates, we also investigated the potential role of $ZnCl_2$ as a deoxygenating reagent. To our delight, it was found that $ZnCl_2$ (1.0 equiv) coupled with zinc metal (4.0 equiv) induces deoxygenation of *trans*-stilbene oxide **1a**, although it is less likely to be a major reaction pathway due to the extremely slow reaction rate (92% in 96 h).[56] Nevertheless, it is still possible to speculate on the positive influence of $ZnCl_2$ in our deoxygenation conditions.[57]

2.4. Deoxygenation of sulfoxides and amine *N*-oxides

With the insights into the reaction mechanisms at hand, we next explored deoxygenation of sulfoxides and amine *N*-oxides. As discussed in the Introduction, the deoxygenation of sulfoxides and amine *N*-oxides typically requires a stoichiometric amount of deoxygenating reagent, which proceeds via path *b*, although limited success has been achieved via path *c* with molybdenum and rhenium catalysts in the presence of PPh_3 or $P(OPh)_3$.[58] Utilizing our optimized deoxygenation conditions, generating niobium complexes from 0.5 equiv of $NbCl_5$ and 5.0 equiv of zinc metal, we applied this to a series of sulfoxides and amine *N*-oxides (Table 4). Gratifyingly, the deoxygenation of sulfoxides was highly efficient to give near quantitative yields of the corresponding sulfides (entries 1–7). A few noteworthy aspects of our current method include efficient deoxygenation of dibenzyl sulfoxide **26e** without cleavage of C–S bond (entry 5), halide-containing sulfoxide **26f** (entry 6), and cyclic sulfoxide **26g** (entry 7). The deoxygenation of amine *N*-oxides was equally effective with aromatic and alkyl amine *N*-oxides (entries 8–12). Although the isolated yields of the corresponding amines are somewhat lower than the sulfoxide cases, it is mainly attributed to material loss upon purification on silica gel chromatography.

3. Conclusion

An efficient sub-stoichiometric deoxygenation of epoxides, sulfoxides, and amine *N*-oxides has been developed utilizing the in situ generation of low-valent niobium complexes from $NbCl_5$ and Zn metal at ambient temperature. The deoxygenation works well with aryl epoxides and α,β-epoxy carbonyl compounds, while modest yields are observed with epoxide substrates without an adjacent radical-stabilizing group. The preliminary investigation into the reaction mechanism revealed that the reaction is most likely initiated by a single electron transfer from zinc to Nb–epoxide complexes. Although more detailed mechanistic studies are necessary to confirm our proposed reaction mechanism, the successful application of our deoxygenation method to a variety of sulfoxides and amine *N*-oxides suggests that the low-valent niobium complexes may provide further development of other types of catalytic reductive C–O/N–O/S–O bond cleavage. Our current investigation is directed to the generation of highly functionalized radicals in the presence of chiral ligands around niobium,[59] and our results will be reported in due course.

4. Experimental section

4.1. Typical procedure for the deoxygenation of epoxides, sulfoxides, and *N*-oxides

To $NbCl_5$ (135 mg, 0.5 mmol) under argon atmosphere were added successively benzene (1.5 mL) and THF (1.5 mL) at ambient temperature. Zinc dust (163 mg, 2.5 mmol) was added to the pale yellow solution and stirred for 40 min. The color of the mixture turned to black upon addition of zinc. A solution of the starting material (1.0 mmol) in benzene/THF (1:1, 2 mL) was added to the reaction mixture at ambient temperature and monitored by TLC. After consumption of the starting material was confirmed via TLC, water (2 mL) was added and the mixture was stirred for 1 h. The mixture was filtered over Celite and washed with diethyl ether (3×10 mL), dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give the deoxygenated product. *(E)-Stilbene* ***2a***:[60] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.1 (s, 2H), 7.30–7.24 (m, 2H), 7.35–7.40 (m, 4H), 7.51–7.55 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 126.5, 127.6, 128.7, 128.8, 137.4; *Methyl phenyl sulfide* ***28a***:[61] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (s, 3H), 7.14–7.19 (m, 1H), 7.28–7.34 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 15.9, 125.0, 126.7, 128.8, 138.4; *4-Phenylpyridine* ***29a***:[62] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.55 (m, 5H), 7.63–7.65 (m, 2H), 8.65–8.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 121.6, 127.0, 129.0, 129.1, 138.2, 148.3, 150.3.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.02.013.

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