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Communication

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An Iridium-Catalyzed Reductive Approach to Nitrones from *N*-Hydroxyamides

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Supporting Information Placeholder

ABSTRACT: An iridium-catalyzed reductive formation of functionalized nitrones from *N*-hydroxyamides was reported. The reaction took place through two types of iridium-catalyzed reactions including dehydrosilylation and hydrosilylation. The method showed high chemoselectivity in the presence of sensitive functional groups such as methyl esters, and was successfully applied to the synthesis of cyclic and macrocyclic nitrones, which are known to be challenging compounds to access by conventional methods. ^{1}H NMR studies strongly supported generation of an *N*-siloxyamide and an *N*,*O*-acetel as the actual intermediates.

The development of useful methods to provide nitrones has been extensively investigated, and is still an important topic in organic chemistry.[1] Nitrones can undergo a variety of reactions such as 1,3-dipolar cycloadditions, and are recognized as promising key intermediates for the synthesis of biologically active alkaloids and pharmaceuticals. In this paper, we report an iridium-catalyzed reductive formation of nitrones from *N*-hydroxyamides. The reaction proved to be highly practical not only for the synthesis of acyclic nitrones, but also for cyclic and macrocyclic nitrones, which are known to be difficult to synthesize by conventional methods.

Nucleophilic addition to amide carbonyl groups has received much attention in recent years due to the availability of the amides themselves and a quick supply of multi-substituted amines.[2-4] During our pursuit of practical transformations of amide groups, we envisioned that reduction of *N*-hydroxyamides could be a straightforward method to access functionalized nitrones (Scheme 1).[5] First, *N*-hydroxyamide **1** would be converted to *N*-siloxyamide **2** by dehydrosilylation[6] with a catalytic amount of the Vaska complex [IrCl(CO)(PPh$_3$)$_2$] and (Me$_2$HSi)$_2$O.[7,8] The resulting *N*-siloxyamide **2** would subsequently undergo the hydrosilylation of the amide carbonyl group.[9] If two different types of iridium-catalyzed reactions (dehydrosilylation and hydrosilylation) were achieved under the single catalytic system, *N*-hydroxyamide **1** could be directly converted to *N*,*O*-acetal **3**. Finally, addition of an acid or a fluoride reagent to **3** would afford nitrone **4** through the elimination of the hydroxy group, along with the cleavage of the silyl groups, in a one-pot process. While a number of oxidative approaches to nitrones from secondary amines have been reported,[10] catalytic reductive synthesis of nitrones from amides is unprecedented to the best of our knowlege.[11] Considering that formation of amides is well established, our method will become a promising synthetic tool to provide functionalized nitrones.

To test our hypothesis, we investigated the reaction of *N*-hydroxyamide **1a** (Table 1). Gratifyingly, treatment of a solution of **1a**

Scheme 1. Plan for Iridium-Catalyzed Reductive Formation of Nitrones from *N*-Hydroxyamides

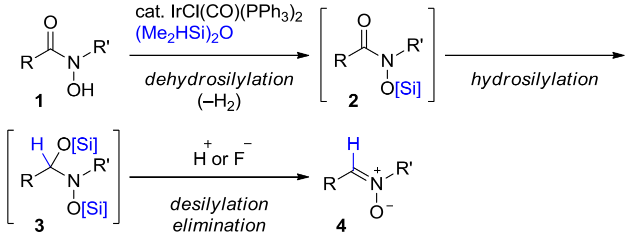
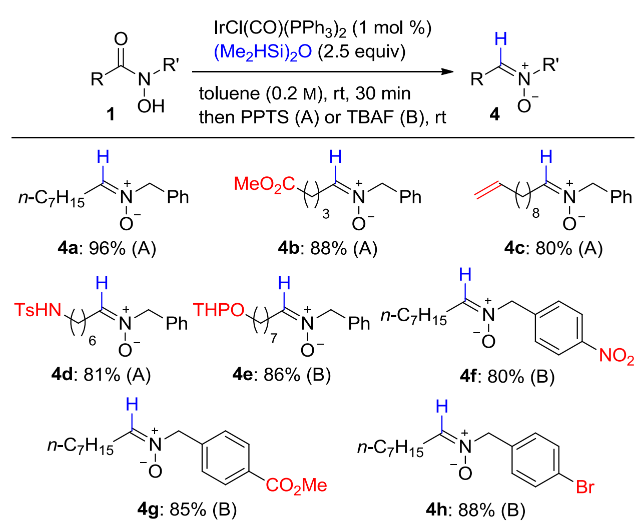


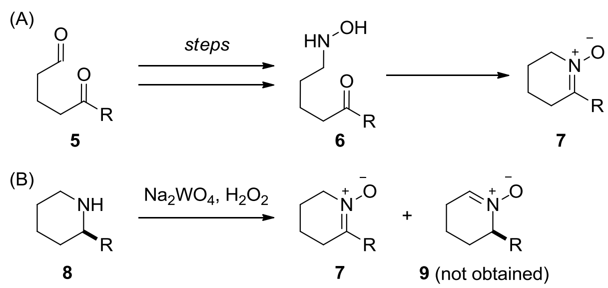
Table 1. Scope of Iridium-Catalyzed Reductive Formation of Nitrones from *N*-Hydroxyamides [a,b]



[a] **1** (1 equiv), [IrCl(CO)(PPh$_3$)$_2$] (1 mol %), (Me$_2$HSi)$_2$O (2.5 equiv), toluene (0.2 M), rt, 30 min; then <method A> PPTS (1 equiv), rt, 5 min; or <method B> TBAF (1 equiv), rt, 5 min. [b] Yield of isolated product after purification by column chromatography.

with (Me$_2$HSi)$_2$O (2.5 equiv) and the Vaska complex [IrCl(CO)(PPh$_3$)$_2$] (1 mol %) at room temperature, followed by addition of PPTS (method A), provided nitrone **4a** in 96% isolated yield. One of the salient features in this reaction is its high chemoselectivity. The reductive formation of the nitrone took place without reducing a methyl ester, which is generally more electrophilic than an amide carbonyl group (**4b**: 88%). Competing hydrosilylation of a terminal olefin was not observed (**4c**: 80%). A sulfonamide with an acidic proton did not disturb the reaction (**4d**: 81%). Addition of TBAF instead of PPTS was an alternative choice in the elimination step for *N*-hydroxyamide **1** with acid-sensitive functional groups such as a THP group (**4e**: 86%). Moreover, when *N*-hydroxyamides had electron withdrawing groups on aromatic groups, addition of TBAF resulted in better yields than use of PPTS, probably due to the slow elimination step (**4f**: 80%; **4g**: 85%; **4h**: 88%). The high chemoselectivity was also observed with nitro, aromatic ester and aryl bromide moieties under the developed reaction conditions.

Scheme 2. Issues in Synthesis of Cyclic Nitrones

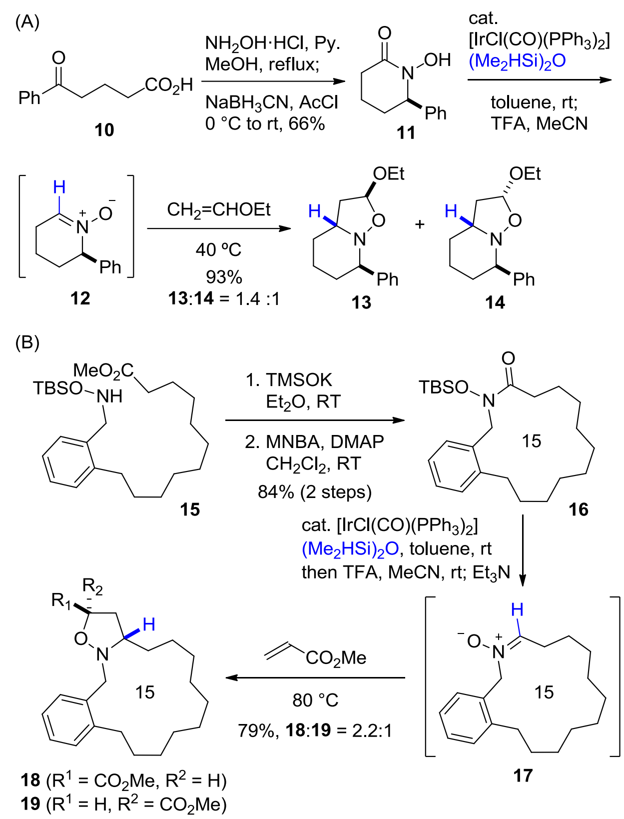


Although a number of studies related to nitrones have been documented, efficient synthesis of cyclic nitrones still remains a challenging task (Scheme 2).[1a,f] Condensation of a carbonyl group with a hydroxyamine has been utilized as the most promising method for the synthesis of acyclic nitrones. However, there are few examples of cyclic nitrones (**6**→**7**) due to the tedious preparation of the substrate **6** itself.[12] Synthesis of **6** requires extra steps in order to differentiate the two carbonyl groups in **5**, one of which is used for the installation of NH_2OH. The most promising methods for synthesis of cyclic nitrones is the oxidation of secondary amines (**8**→**7**).[10] The oxidative approach is known to afford more substituted nitrone **7** as the major product versus α-substituted nitrone **9**.[13,14]

We considered that our reductive method could be complementary to the oxidative approach, and a successful example is shown in Scheme 3A. Reductive amination of commercially available 5-ketoacid **10** and concomitant cyclization gave six-membered *N*-hydroxylactam **11** in 66% yield. The iridium-catalyzed reduction of **11**, followed by addition of TFA gave cyclic nitrone **12**. The resulting solution of **12** was then heated with ethyl vinyl ether at 40 °C in a one-pot sequence, promoting the [3+2] cycloaddition to give bicyclic isoxazolidines **13** and **14** in 93% combined yield (**13**:**14** = 1.4:1). This example demonstrated a number of synthetic advantages using our reductive method. First, *N*-hydroxylactam **11** was prepared in just one step from the commercially available compound **10**. Second, the reaction provided less accessible α-substituted nitrone **12**. Third, the one-pot [3+2] cycloaddition was possible without isolation of the cyclic nitrone, which is generally known to be an unstable compound.

A conspicuous example of our reductive method is its application to macrocyclic nitrones (Scheme 3B). Although macrocyclic nitrones have been desired over the years as key intermediates for the synthesis of biologically active natural products such as manzamine alkaloids,[15] development of methods to access macrocyclic nitrones remains one of the most challenging topics.[12b,16] However, we envisioned that this task could be achieved by combination of a reliable macrolactamization with our reductive approach. After hydrolysis of methyl ester **15** with TMSOK, macrolactamization of the resulting *N*-siloxyamino acid was then investigated. Interestingly, MNBA (2-methyl-6-nitrobenzoic anhydride), which is known as the Shiina reagent for macrolactonization,[17] proved to be the most effective, giving 15-membered *N*-siloxylactam **16** in 84% yield (2 steps).[18] As we expected, macrocyclic nitrone **17** was efficiently formed under the developed conditions, and then underwent [3+2] cycloaddition with methyl acrylate at 80 °C to give bicyclic isoxazolidines **18** and **19** in 79% combined yield (**18**:**19** = 2.2:1). It is noteworthy that oxidation of the corresponding macrocyclic secondary amine would form the nitrone at the benzylic position. However, our reductive method generated less accessible macrocyclic nitrone **17**.

Scheme 3. Formation and Application of Cyclic and Macrocyclic Nitrones



To elucidate the actual intermediates in the iridium-catalyzed reduction, ^{1}H NMR experiments with *N*-hydroxyamide **1a** were performed (Figure 1). Treatment of a solution of **1a**, which existed as a 4:1 mixture of rotamers in d$_8$-toluene, with $(Me_2HSi)_2O$ (2.5 equiv) in the absence of the Vaska complex did not promote the reaction (Spectra A and B). However, treatment of **1a** with $(Me_2HSi)_2O$ (1.2 equiv) in the presence of the Vaska complex (1 mol %) resulted in the disappearance of the broad singlet peak at δ 9.08 ppm from the *N*-hydroxy group to suggest the formation of *N*-siloxyamide **2a** (Spectrum C). In contrast, use of $(Me_2HSi)_2O$ (2.5 equiv) and the Vaska complex (1 mol %) dramatically changed the ^{1}H NMR spectrum, which indicated the formation of *N*,*O*-acetal **3a** (Spectrum D). Spectrum D shows the disappearance of the broad singlet peak at δ 9.08 ppm from the *N*-hydroxy group, and contains a doublet of doublets at δ 4.96 ppm (J = 7.8, 5.0 Hz) for the C8 methine. Two doublet peaks at δ 3.96 ppm (J = 13.5 Hz) and δ 3.91 ppm (J = 13.5 Hz) rather than a singlet indicates the presence of two diastereotopic protons corresponding to the C9 benzylic methylene group. Generation of two resonances at δ 5.05 ppm (sep, J = 2.8 Hz, 1H, Si-H) and 4.88 ppm (sep, J = 2.8 Hz, 1H, Si-H), and eight methyl signals clearly suggests that intermediate **3a** possesses

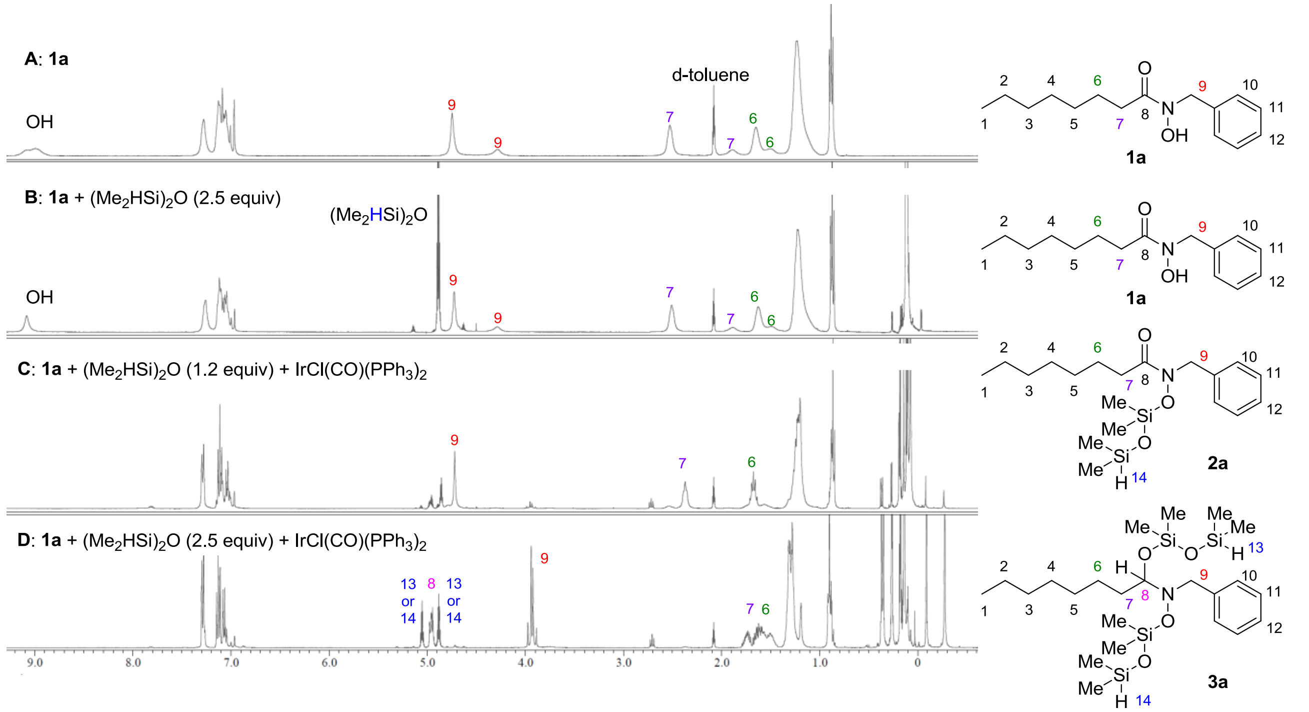


Figure 1. [1]H NMR spectra (400 MHz) in the iridium-catalyzed reductive formation of *N*-hydroxyamide **1a**. (A) *N*-hydroxyamide **1a** in d$_8$-toluene; (B) *N*-hydroxyamide **1a** and $(Me_2HSi)_2O$ (2.5 equiv) in d$_8$-toluene; (C) *N*-hydroxyamide **1a**, $(Me_2HSi)_2O$ (1.2 equiv) and $[IrCl(CO)(PPh_3)_2]$ (1 mol %) in d$_8$-toluene, 30 min; (D) *N*-hydroxyamide **1a**, $(Me_2HSi)_2O$ (2.5 equiv) and $[IrCl(CO)(PPh_3)_2]$ (1 mol %) in d$_8$-toluene, 30 min. d$_8$-toluene, 30 min

two silyl groups. *N*,*O*-Acetal **3a** was found to be a relatively stable compound. When the reaction was quenched without addition of PPTS, the [1]H NMR spectrum of the crude sample was identical to that of *N*,*O*-acetal **3a**, although purification by silica gel column chromatography resulted in degradation to nitrone **4a**. Formation of *N*,*O*-acetal **3a** was also confirmed by the ESI-MS spectrum (M + H$^+$: 516.2820). Thus, as hypothesized in Scheme 1B, we concluded that the reaction of *N*-hydroxyamide **1a** took place through the initial dehydrogenative silylation of **1a**, followed by hydrosilylation of amide carbonyl **2a**, giving the corresponding *N*,*O*-acetal **3a**.

In summary, we have developed an unprecedented reductive approach to nitrones from *N*-hydroxyamides. The reaction proceeded via two different types of iridium-catalyzed reactions involving dehydrosilylation of the *N*-hydroxy group, and hydrosilylation of the amide carbonyl under the single catalytic system using the Vaska complex $[IrCl(CO)(PPh_3)_2]$ and $(Me_2HSi)_2O$. [1]H NMR studies clearly suggested that the *N*-siloxyamide and the *N*,*O*-acetal were the actual intermediates in this catalytic reaction. The method showed high chemoselectivity in the presence of a variety of functional groups such as a methyl ester. The clear utility of our methodology was demonstrated in the synthesis and application of functionalized cyclic and macrocyclic nitrones.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and copies of [1]H NMR and [13]C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.
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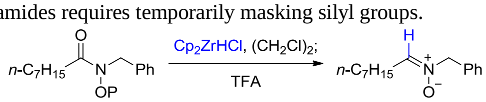
(5) A preliminary experiment using *N*-hydroxyamide **1a** and the Schwartz reagent did not provide any desired product **4a**. However, we discovered that exposure of the corresponding *N*-siloxyamide **i** to the Schwartz reagent, followed by addition of TFA (trifluoroacetic acid) led to the formation of nitrone **4a** in 94% yield. These results indicated that the reduction of *N*-hydroxyamides requires temporarily masking silyl groups.



1a (P = H): 0%, **i** (P = TBS): 94% **4a**

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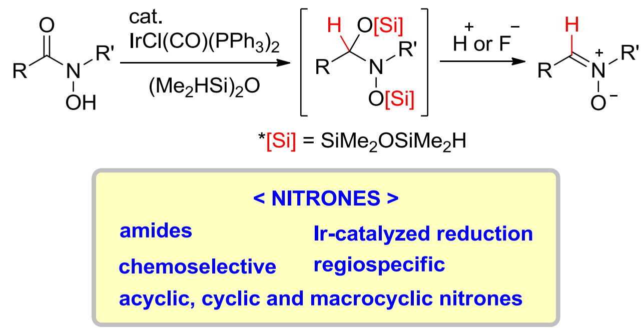
(18) The macrolactamization required the protection of the *N*-hydroxy group as a TBS ether.

TOC Graphic


cat.
IrCl(CO)(PPh$_3$)$_2$
(Me$_2$HSi)$_2$O
$\overset{+}{H}$ or $\overset{-}{F}$
*[Si] = SiMe$_2$OSiMe$_2$H
< NITRONES >
amides
Ir-catalyzed reduction
chemoselective
regiospecific
acyclic, cyclic and macrocyclic nitrones