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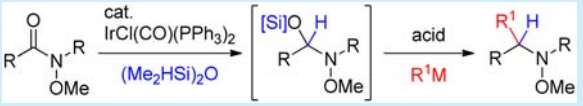
Iridium-Catalyzed Chemoselective Reductive Nucleophilic Addition to *N*-Methoxyamides

Minami Nakajima, Takaaki Sato,* and Noritaka Chida*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Supporting Information

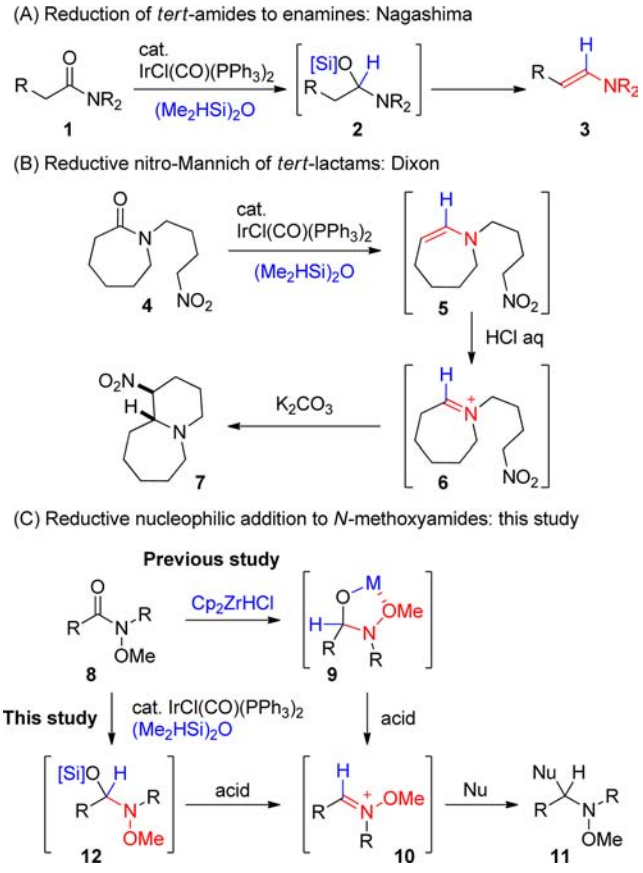
ABSTRACT: Iridium-catalyzed reductive nucleophilic addition to *N*-methoxyamides is reported. The reaction took place in high yields in the presence of a variety of sensitive functional groups such as esters and nitro groups. Mechanistic studies revealed that the reaction of *N*-methoxyamides proceeded without equilibrium to an enamine intermediate in contrast to that with *tert*-amides.



Functionalization of amide carbonyl groups has increasingly become an important tool to synthesize biologically active natural alkaloids and pharmaceuticals.[1−4] One of the most significant advances in this field is in chemoselectivity.[5] In general, transformation of amide carbonyl groups requires harsh conditions due to their high stability compared with ketones and esters. Recently, however, a number of useful methods have been reported in the presence of sensitive functional groups.[6−8] For example, Nagashima disclosed that the iridium-catalyzed hydrosilylation of *tert*-amide **1** formed the *N*,*O*-acetal intermediate **2**, which spontaneously underwent elimination to give enamine **3** (Scheme 1A).[8f] The reaction exhibited high chemoselectivity in the presence of a variety of sensitive functional groups including ketones, esters, and alkyl bromides. Very recently, Dixon developed the elegant reductive nitro-Mannich reaction of *tert*-lactam **4** by capitalizing on Nagashima's method (Scheme 1B).[6g] After exposure of **4** to Nagashima's conditions, the resulting enamine **5** was converted to iminium ion **6** with HCl. Addition of K_2CO_3 to the reaction mixture then induced the nitro-Mannich reaction to give bicyclic product **7** in a one-pot sequence. Although not explicitly discussed in their report, this method has the potential for high chemoselectivity. In this paper, we describe the iridium-catalyzed reductive nucleophilic addition to *N*-methoxyamides via a mechanism different from that of the *tert*-amides.

In 2014, we reported the chemoselective nucleophilic addition to *N*-methoxyamide **8** (Scheme 1C).[7] Reduction of **8** with the Schwartz reagent [Cp_2ZrHCl][9] gave five-membered chelated intermediate **9**.[8d,e,10] Treatment of **9** with an acid then induced nucleophilic addition with a nucleophile via *N*-oxyiminium ion **10**, giving substituted *N*-methoxyamine **11**. *N*-Methoxyamine **11** is known to undergo further unique transformations such as reductive cleavage of the *N*-methoxy group and direct oxidation to nitrones. We achieved high chemoselectivity in this reaction and applied it to the concise total synthesis of gephyrotoxin.[7b,e] Unfortunately, our success depended on the unique reactivity of the equimolar Schwartz reagent, which is a relatively expensive chemical. To overcome this issue, we applied Nagashima's catalytic method. Treatment of *N*-methoxyamide **8** with $(Me_2HSi)_2O$ in the presence of a

Scheme 1. Chemoselective Reductive Nucleophilic Addition to *tert*-Amides and *N*-Methoxyamides



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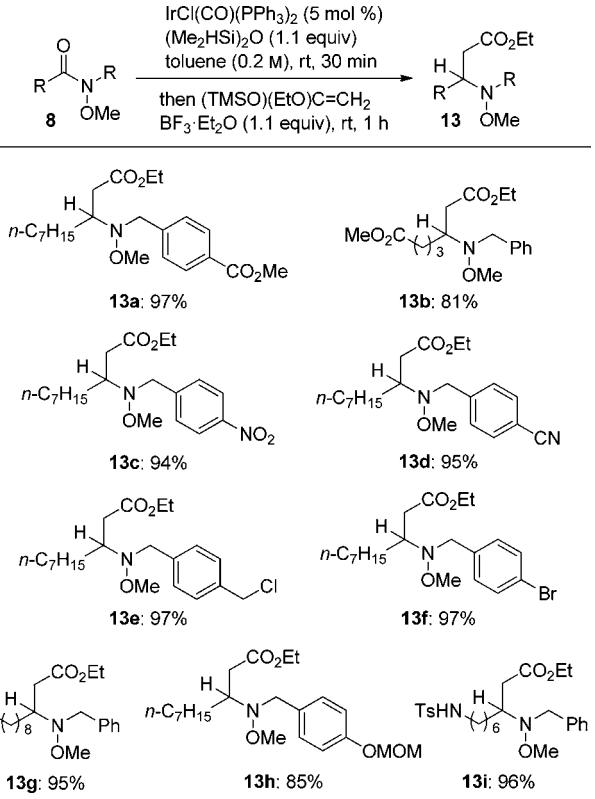
catalytic amount of the Vaska complex $[IrCl(CO)(PPh_3)_2]$ would induce hydrosilylation to give *N,O*-acetal **12**. While the labile *N,O*-acetal intermediate derived from *tert*-amide **1** spontaneously converted to enamine **3**, we expected that *N,O*-acetal **12** from *N*-methoxyamide **8** would remain in the *N,O*-acetal form due to the lower electron-donating ability of the *N*-methoxyamine than the *tert*-amine, preventing the elimination process to form the enamine.[11] The subsequent addition of an acid to *N,O*-acetal **12** would enable nucleophilic addition via *N*-oxyiminium ion **10** as in the previous method with the Schwartz reagent.

The iridium-catalyzed reductive nucleophilic addition to *N*-methoxyamide **8** was first realized with the silyl ketene acetal in the presence of $BF_3{\cdot}Et_2O$ (Scheme 2). A solution of *N*-

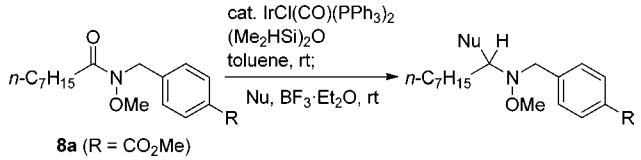
Scheme 2. Chemoselective Reductive Mannich Reaction to *N*-Methoxyamides

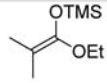
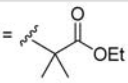
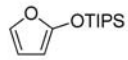
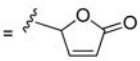
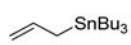
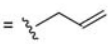
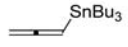
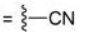
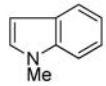
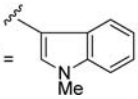


methoxyamide **8a** and $(Me_2HSi)_2O$ (1.1 equiv) in toluene was treated with a catalytic amount of the Vaska complex $[IrCl(CO)(PPh_3)_2]$ (5 mol %) for 30 min. The silyl ketene acetal (1.2 equiv) and $BF_3{\cdot}Et_2O$ (1.1 equiv) were then added in a one-pot sequence. As expected, the reductive Mannich reaction took place in excellent yield without affecting the more electrophilic methyl ester (**13a**: 97%). The reaction of the *N*-methoxyamides occurred in high yields (81−97%) with high chemoselectivities in the presence of a variety of sensitive functional groups. A more electrophilic aliphatic methyl ester remained intact (**13b**: 81%). Other electrophilic functional groups were well tolerated such as nitro, nitrile, and benzyl chloride (**13c**: 94%; **13d**: 95%; **13e**: 97%). Undesired reductions of the aryl bromide and the olefin were not observed under the developed conditions (**13f**: 97%; **13g**: 95%). Although the reaction required the assistance of $BF_3{\cdot}Et_2O$, the acetal group was not affected under these acidic conditions (**13h**: 85%). The presence of a sulfonamide did not interfere with the reductive nucleophilic addition (**13i**: 96%).

The developed conditions allowed us to use a variety of organometallic reagents in the nucleophilic step without disturbing the high chemoselectivity (Table 1). For example,

Table 1. Scope of Nucleophiles[a]



entry	nucleophile	product	yield[b]
1		**14**: R^3 = 	84%
2[c]		**15**: R^1 = 	81% dr = 1.7:1
3[c]		**16**: R^1 = 	85%
4[c]		**17**: R^3 = 	88%
5[c,d]	NC-TMS	**18**: R^1 = 	80%
6[c]		**19**: R^1 = 	72%

[a]Conditions: **8a** (1 equiv), $[IrCl(CO)(PPh_3)_2]$ (5 mol %), $(Me_2HSi)_2O$ (1.1 equiv), toluene (0.2 M), rt, 30 min; nucleophile (1.2 equiv), $BF_3{\cdot}Et_2O$ (1.1 equiv), rt, 1 h. [b]Yield of isolated product after purification by column chromatography. [c]$Sc(OTf)_3$ (10 mol %) was used instead of $BF_3{\cdot}Et_2O$. [d]2 equiv of NC-TMS were used. [e]The reaction was performed at −40 °C for 12 h.

the dimethyl silyl ketene acetal provided **14** in spite of the large steric hindrance (**14**: 84%). The γ-butenolide was directly installed to the amide carbonyl group through the vinylogous Mannich reaction (15:81%, dr = 1.7:1). Allylation, propargylation, and the Strecker-type reaction were possible with $Sc(OTf)_3$ (10 mol %) instead of $BF_3{\cdot}Et_2O$ (**16**: 85%; **17**: 88%; **18**: 80%). *N*-Methylindole was successfully installed at −40 °C (**19**: 72%).

^1H NMR experiments were performed to elucidate the intermediate produced by the iridium-catalyzed reduction of *N*-methoxyamide **8a** (Figure 1). Addition of $(Me_2HSi)_2O$ to a solution of **8a** in d_8-toluene did not affect the ^1H NMR spectrum of **8a** (spectra A and B). Upon treatment of the solution of **8a** and $(Me_2HSi)_2O$ with the Vaska complex $[IrCl(CO)(PPh_3)_2]$ (5 mol %), a newly generated intermediate was observed in the ^1H NMR spectrum (spectrum C), which contained a doublet−doublet peak at δ 4.85 (J = 7.2, 5.8 Hz) and two doublet peaks at δ 3.82 (J = 14.3 Hz) and δ 3.89 (J = 14.3 Hz). These peaks corresponded to the C8 methine and C9 benzyl methylene of *N,O*-acetal **12a**, respectively. Thus, the ^1H NMR studies revealed that the iridium-catalyzed reduction of the *N*-methoxyamide resulted not in the formation of the enamine, but the *N,O*-acetal.

To confirm whether the reaction proceeded via the enamine or not, a control experiment was conducted with *N*-

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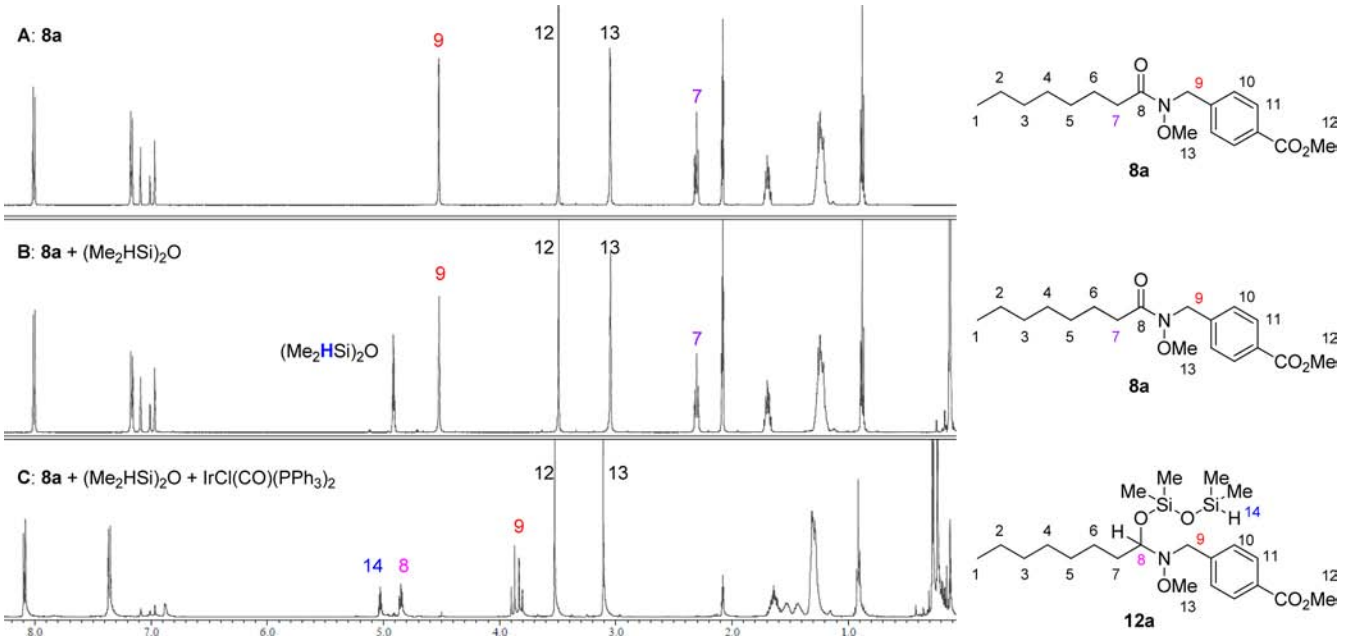
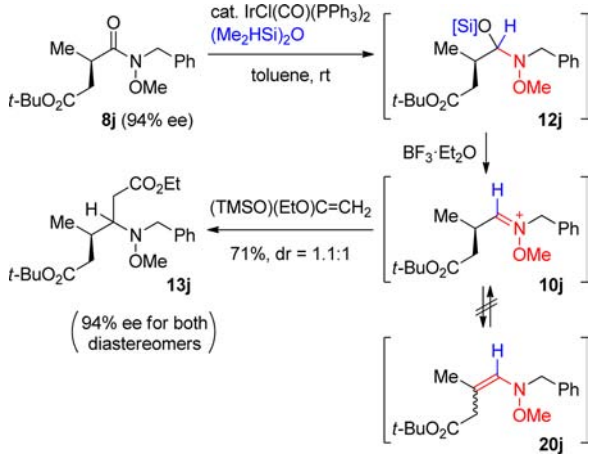


Figure 1. ^{1}H NMR spectra (500 MHz) in the iridium-catalyzed reduction of *N*-methoxyamide **8a**. (A) *N*-Methoxyamide **8a** in d_8-toluene; (B) *N*-methoxyamide **8a** and $(Me_2HSi)_2O$ in d_8-toluene; (C) *N*-methoxyamide **8a**, $(Me_2HSi)_2O$, and $[IrCl(CO)(PPh_3)_2]$ (5 mol %) in d_8-toluene, 30 min.

methoxyamide **8j** bearing the asymmetric carbon center at the α-position of the amide carbonyl group (Scheme 3). The

Scheme 3. Control Experiment to Elucidate the Reaction Intermediate



iridium-catalyzed reduction of **8j** (94% ee) formed *N*,*O*-acetal **12j**, which was subsequently treated with the silyl ketene acetal and $BF_3{\cdot}Et_2O$ in a one-pot process. The nucleophilic addition afforded a 1.1:1 mixture of two diastereomers **13j** in 71% yield. Interestingly, the enantiomeric excesses of both diastereomers were retained at 94% ee. This experiment revealed that *N*-oxyiminium ion **10j** was not in equilibrium with enamine **20j**, which would cause racemization of the products **13j**. Although the reaction of **8j** resulted in poor diastereoselectivity, the control experiment also suggested that the reductive nucleophilic addition to the *N*-methoxyamides might become a useful method with high 1,2-asymmetric induction, whereas that of the *tert*-amides would be unlikely due to the racemization via the enamine intermediate as shown in Scheme 1.

In conclusion, we have developed an iridium-catalyzed reductive nucleophilic addition to *N*-methoxyamides. The reaction took place in high yield with high chemoselectivity in the presence of a variety of sensitive functional groups. Mechanistically, the reduction step does not form an enamine, but an *N*,*O*-acetal, in contrast to the case with *tert*-amides. Treatment of the resulting *N*,*O*-acetal intermediate with an organometallic reagent and an acid provided a substituted *N*-methoxyamine without racemization at the α-position. These mechanistic insights promise future development of the nucleophilic addition to *N*-methoxyamides with 1,2-asymmetric induction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; 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.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: takaakis@applc.keio.ac.jp.
*E-mail: chida@applc.keio.ac.jp.

Notes

The authors declare no competing financial interest.

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