



# A novel efficient and chemoselective method for the reduction of nitriles using the system silane/oxo-rhenium complexes

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## ABSTRACT

This work reports the reduction of nitriles to the corresponding primary amines with silanes catalyzed by oxo-rhenium complexes. The catalytic system  $\text{PhSiH}_3/\text{ReO}_2(\text{PPh}_3)_2$  (10 mol %) reduced efficiently a series of nitriles in the presence of a wide range of functional groups such as  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{CF}_3$ ,  $-\text{OCH}_3$ ,  $-\text{SCH}_3$ ,  $-\text{SO}_2\text{CH}_3$  and  $-\text{NHTs}$ .

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## 1. Introduction

Amines constitute an important class of compounds in the manufacture of agrochemicals, dyes, pharmaceutical and other industrial products. Consequently, the synthesis of amines is an active field in medicinal chemistry and modern organic synthesis.

The reduction of nitriles is a powerful tool to synthesize primary amines and it is also a fundamental process in organic chemistry. Conventional methods for accomplishing this transformation use catalytic hydrogenation<sup>1–7</sup> or strong hydride donors, such as aluminium hydrides<sup>8</sup> or boranes.<sup>9–11</sup> However, these methods suffer from harsh reaction conditions, such as high temperatures, pressures, use of pyrophoric reducing agents and low functional group tolerance.

In contrast, silanes or siloxanes are stable to air and moisture and they are also mild and environmentally benign reducing agents. However, these reagents are known to be poor reducing agents, due to their low capacity to donate hydrogen atoms or hydrides. To overcome this limitation, several combinations of a silane or a siloxane with transition-metal catalyst have been studied. For example, Lemaire and co-workers<sup>12</sup> have developed a method for the reduction of nitriles using the system tetramethyldisiloxane/titanium(IV) isopropoxide. Nevertheless, this procedure requires 100 mol % of titanium complex.

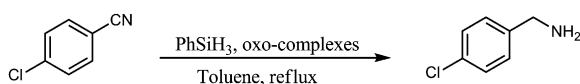
Toste and co-workers<sup>13,14</sup> have also studied the activation of Si–H bond with the high valent oxo-complex  $\text{ReO}_2(\text{PPh}_3)_2$ . The novel catalytic system silane/ $\text{ReO}_2(\text{PPh}_3)_2$  proved to be very efficient for the hydrosilylation of aldehydes and ketones. We have extended this result to the activation of Si–H,<sup>15,16</sup> B–H<sup>17</sup> and P–H<sup>18</sup> bonds by oxo-rhenium and oxo-molybdenum complexes. We and other groups also described the efficient hydrosilylation of aldehydes and ketones,<sup>15,16,19–22</sup> the C–C,<sup>23</sup> C–S,<sup>23</sup> C–N<sup>24</sup> and C–P<sup>18,25</sup> bond formation and also the reduction of several functional groups, such as aromatic nitro compounds,<sup>26</sup> imines,<sup>21,27,28</sup> amides,<sup>29</sup> esters,<sup>30</sup> sulfoxides,<sup>17,31–35</sup> pyridine *N*-oxides<sup>31</sup> and alkenes<sup>36</sup> with the catalytic systems silane/oxo-complexes or borane/oxo-complexes.

The high biological and chemical importance of primary amines, still justifies the search for novel catalyst systems, leading to efficient and highly chemoselective methods for their synthesis. In continuation of our interest in developing organic reductions catalyzed by high valent oxo-complexes, herein, we report a novel method for the reduction of nitriles catalyzed by oxo-rhenium complexes.

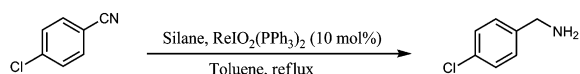
## 2. Results and discussion

Initially we studied the reduction of the test substrate 4-chlorobenzonitrile catalyzed by several oxo-rhenium, oxo-molybdenum, oxo-tungsten and oxo-vanadium complexes with different silanes, and using several solvents, in order to assess the best reaction conditions (Tables 1–3). The progress of the reactions was monitored by thin layer chromatography or by <sup>1</sup>H NMR.

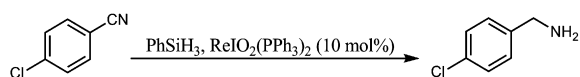
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**Table 1**  
Reduction of 4-chlorobenzonitrile with PhSiH<sub>3</sub> catalyzed by oxo-complexes<sup>a</sup>

Entry	Catalyst	Catalyst (mol %)	Time	Conversion <sup>b</sup> (%)
1	ReIO <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	10	5	100
2	ReIO <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	5	24	40
3	ReOCl <sub>3</sub> (PPh <sub>3</sub> ) <sub>2</sub>	10	24	100
4	ReOCl <sub>3</sub> (dppm)	10	24	No reaction
5	Re <sub>2</sub> O <sub>7</sub>	10	24	No reaction
6	MTO	10	24	No reaction
7	HReO <sub>4</sub>	10	24	No reaction
8	MoO <sub>2</sub> Cl <sub>2</sub>	10	24	No reaction
9	MoO <sub>2</sub> (acac) <sub>2</sub>	10	24	No reaction
10	WO <sub>2</sub> Cl <sub>2</sub>	10	24	No reaction
11	VO(acac) <sub>2</sub>	10	24	No reaction
12	Without catalyst	—	24	No reaction

<sup>a</sup> All reactions were carried out with 1.0 mmol of nitrile and 300 mol % of PhSiH<sub>3</sub>.<sup>b</sup> Conversion was determined by <sup>1</sup>H NMR.**Table 2**  
Reduction of 4-chlorobenzonitrile with different silanes catalyzed by ReIO<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub><sup>a</sup>

Entry	Silane	Silane (mol %)	Time (h)	Conversion <sup>b</sup> (%)
1	PhSiH <sub>3</sub>	300	5	100
2	PhSiH <sub>3</sub>	200	24	100
3	PhMe <sub>2</sub> SiH	300	24	No reaction
4	Et <sub>3</sub> SiH	350	24	No reaction
5	PMHS	400	24	No reaction
6	Without silane	—	24	No reaction

<sup>a</sup> All reactions were carried out with 1.0 mmol of nitrile and 10 mol % of ReIO<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>.<sup>b</sup> Conversion was determined by <sup>1</sup>H NMR.**Table 3**  
Reduction of 4-chlorobenzonitrile in different solvents<sup>a</sup>

Entry	Solvent	Temperature	Time (h)	Conversion <sup>b</sup> (%)
1	Toluene	Reflux	5	100
2	Toluene	rt	24	60
3	Benzene	Reflux	24	100
4	THF	Reflux	48	40
5	CH <sub>2</sub> Cl <sub>2</sub>	Reflux	24	47
6	CHCl <sub>3</sub>	Reflux	23	30
7	Methanol	Reflux	24	20

<sup>a</sup> All reactions were carried out with 1.0 mmol of nitrile and 300 mol % of silane.<sup>b</sup> Conversion was determined by <sup>1</sup>H NMR.

In this work, we tested the catalytic activity of the oxo-rhenium complexes ReIO<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, ReOCl<sub>3</sub>(PPh<sub>3</sub>)<sub>2</sub>, ReOCl<sub>3</sub>(dppm), Re<sub>2</sub>O<sub>7</sub>, CH<sub>3</sub>ReO<sub>3</sub> (MTO) and HReO<sub>4</sub>. The best results were obtained with ReIO<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (10 mol %) and PhSiH<sub>3</sub> (300 mol %) in refluxing toluene under air atmosphere, affording the complete reduction of 4-chlorobenzonitrile after 5 h (Table 1, entry 1). Using only 5 mol % of this catalyst, the corresponding amine was obtained in only 40% after 24 h (Table 1, entry 2). The complex ReOCl<sub>3</sub>(PPh<sub>3</sub>)<sub>2</sub> (10 mol %) was also very efficient, allowing the complete reduction of 4-chlorobenzonitrile, but this reaction required long reaction time (24 h) (Table 1, entry 3). In contrast, no reaction was observed in the presence of 10 mol % of the complexes ReOCl<sub>3</sub>(dppm), Re<sub>2</sub>O<sub>7</sub>, MTO and HReO<sub>4</sub> (Table 1, entries 4–7).

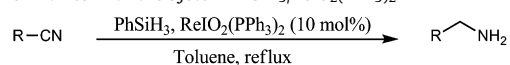
The oxo-complexes MoO<sub>2</sub>Cl<sub>2</sub>, MoO<sub>2</sub>(acac)<sub>2</sub>, WO<sub>2</sub>Cl<sub>2</sub> and VO(acac)<sub>2</sub> were also tested in the reduction of 4-chlorobenzonitrile, but they

proved to be inefficient (Table 1, entries 8–11). Finally, in the absence of catalyst, the reduction did not occur (Table 1, entry 12).

The reduction of 4-chlorobenzonitrile was also studied with the silanes phenylsilane, dimethylphenylsilane, triethylsilane and polymethylhydrosiloxane (PMHS). The results obtained show that PhSiH<sub>3</sub> was the most efficient reducing agent tested. Using 300 mol % of PhSiH<sub>3</sub>, the reduction was complete after 5 h at refluxing toluene (Table 2, entry 1). Similar reduction with only 200 mol % of PhSiH<sub>3</sub> also afforded the amine in 100% conversion, but the reaction required 24 h (Table 2, entry 2). In contrast, no reaction was observed using PhMe<sub>2</sub>SiH, Et<sub>3</sub>SiH, PMHS or in the absence of silane (Table 2, entries 3–6).

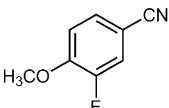
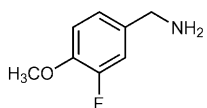
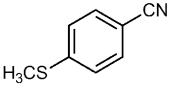
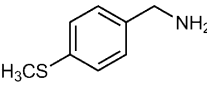
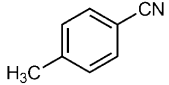
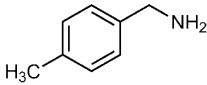
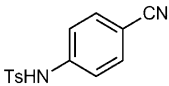
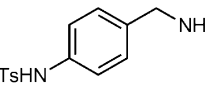
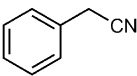
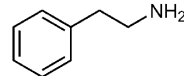
In Table 3 are summarized the results of the search for the appropriate solvent. We found that toluene was the best solvent for this reduction at reflux temperature, leading to the complete reduction of 4-chlorobenzonitrile in 5 h (Table 3, entry 1). Similar reduction at room temperature only afforded the amine in 60% conversion after 24 h (Table 3, entry 2). In benzene, the amine was also obtained in 100% conversion, but this reduction required 24 h (Table 3, entry 3). In contrast, tetrahydrofuran, dichloromethane, chloroform and methanol produced the corresponding amine in moderate to low yields (Table 3, entries 4–7).

To evaluate the general applicability of the catalytic system PhSiH<sub>3</sub>/ReIO<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (10 mol %), we investigated the reduction of a series of nitriles at refluxing toluene under air atmosphere (Table 4). Generally, good to excellent yields of amines were obtained, as hydrochloride salts, including amines bearing electron-withdrawing- or electron-donating groups.

**Table 4**  
Reduction of nitriles with the system PhSiH<sub>3</sub>/ReIO<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub><sup>a</sup>

Entry	Substrate	Product	Time (h)	Yield <sup>b</sup>
1			5	92
2			1	88
3			5	83
4			3	82
5			4	84
6			5	84
7			24	91
8			24	90

**Table 4** (continued)

Entry	Substrate	Product	Time (h)	Yield <sup>b</sup>
9			16	89
10			15	91
11			24	88
12			3	51
13			24	92

<sup>a</sup> All reactions were carried out with 1.0 mmol of nitrile and 300 mol % of PhSiH<sub>3</sub>.

<sup>b</sup> The products were isolated as hydrochloride salt.

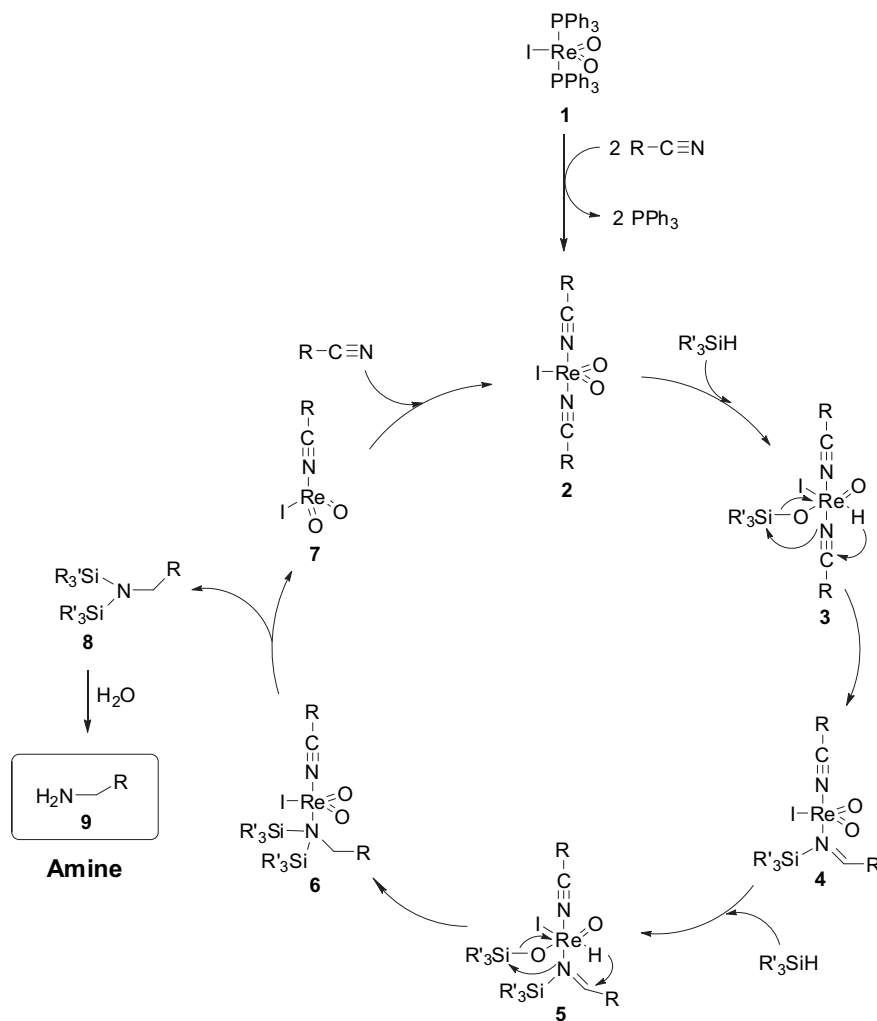
The reduction of nitriles containing the functional groups –Cl, –F, –Br, –I, –CF<sub>3</sub> and –SO<sub>2</sub>CH<sub>3</sub> were completed within 1–5 h and the corresponding amines hydrochloride salts were isolated in high yields (Table 4, entries 1–6).

Benzonitrile and 1-naphthonitrile were also successfully reduced under the optimized reaction conditions in excellent yields after 24 h (Table 4, entries 7 and 8). The reduction of aromatic nitriles containing the electro-donating groups OCH<sub>3</sub>, SCH<sub>3</sub> and CH<sub>3</sub>, were also performed in good yields (Table 4, entries 9–11). However, these reactions required more time than the reduction of nitriles bearing electron-withdrawing groups (Table 4, entries 1–6). The reduction of the substrate containing the NHTs group afforded the corresponding amine in moderate yield (Table 4, entry 12).

Finally, the substrate versatility of this novel method was further demonstrated by the reduction of phenylacetone nitrile in good isolated yield after 24 h (Table 4, entry 13).

The results obtained demonstrate that this novel methodology for the reduction of nitriles is highly chemoselective, tolerating several functional groups, such as –Cl, –F, –Br, –I, –CF<sub>3</sub>, –OCH<sub>3</sub>, –SCH<sub>3</sub>, –SO<sub>2</sub>CH<sub>3</sub> and –NHTs (Table 4, entries 1–6, 9–10 and 12).

Mechanistically, we suggest that the reduction of nitriles with the system silane/oxo-rhenium complexes involves the followed steps: coordination of two nitriles to the rhenium with liberation of two phosphines, affording the complex ReO<sub>2</sub>(nitrile)<sub>2</sub> **2**; formation of the hydride species (nitrile)<sub>2</sub>(O)Ir(H)OSiR<sub>3</sub>' **3** as result of the addition of



**Scheme 1.** Proposed catalytic cycle for the reduction of nitriles with the system silane/ReO<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>.

the Si–H bond of the silane to one of the oxo-rhenium bond; dihydrosilylation of the nitrile to the corresponding *N*-disilylamine **8**; formation of amine **9** by hydrolysis of *N*-disilylamine, probably, due to the presence of a trace of water in the reaction mixture (Scheme 1).

In comparison with the method using the system tetramethyldisiloxane/titanium(IV) isopropoxide,<sup>12</sup> our procedure required less quantity of catalyst (10 mol %), in contrast to the 100 mol % of titanium(IV) isopropoxide.

Furthermore, this novel methodology avoid the formation of secondary amines, by unwanted side-reaction, which is a general problem observed in the reduction of nitriles by catalytic hydrogenation.

Another important benefit of this method is that the reduction can be carried out in simple, readily available laboratory equipment, in contrast to catalytic hydrogenation, which demands handling of hydrogen gas and often requires rather expensive high-pressure equipment.

Other advantages of this methodology include high isolated yields, good chemoselectivity, easy work-up and preparation of the catalyst<sup>13</sup> and also the stability of the catalyst towards air and moisture, allowing the reaction to be carried out under air atmosphere.

### 3. Conclusion

In conclusion, we have demonstrated that the catalytic system PhSiH<sub>3</sub>/ReIO<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> is very efficient for the reduction of a variety of nitriles. This novel methodology is highly chemoselective, tolerating a large range of functional groups, such as –Cl, –F, –Br, –I, –CF<sub>3</sub>, –OCH<sub>3</sub>, –SCH<sub>3</sub>, –SO<sub>2</sub>CH<sub>3</sub> and –NHTs. We believe that this procedure will be an alternative to the existing methods for the reduction of nitriles.

## 4. Experimental section

### 4.1. General information

All the reactions were carried out in air atmosphere and without any dry solvents. Nitriles and catalysts were obtained from commercial suppliers and were used without further purification. ReIO<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> was prepared using the method reported by Toste.<sup>13</sup> Flash chromatography was performed on MN Kieselgel 60 M 230–400 mesh. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were measured on a Bruker Avance II 400 MHz and 300 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from an internal standard. <sup>1</sup>H NMR and <sup>13</sup>C NMR data of the products are consistent with those of the commercial products.

### 4.2. General procedure for the reduction of nitriles with the system PhSiH<sub>3</sub>/ReIO<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>

To a solution of ReIO<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (10 mol %) in toluene (3 mL) were added the nitrile (1 mmol) and PhSiH<sub>3</sub> (300 mol %). The reaction mixture was stirred at reflux temperature under air atmosphere and the progress of the reaction was monitored by TLC or <sup>1</sup>H NMR. Upon completion, the reaction mixture was cooled to ambient temperature, stirred with charcoal during 3 min and then filtered through a plug of alumina/Celite. To the filtrate was added an ethereal solution of HCl (1.5 mol) to induce the precipitation of

amine hydrochloride salts. The solids were isolated upon filtration and then washed with *n*-hexane to afford the pure amine hydrochloride salts, which are all known compounds.

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