DOI: 10.1002/adsc.201200835

A Practical Procedure for Reduction of Primary, Secondary and Tertiary Amides to Amines

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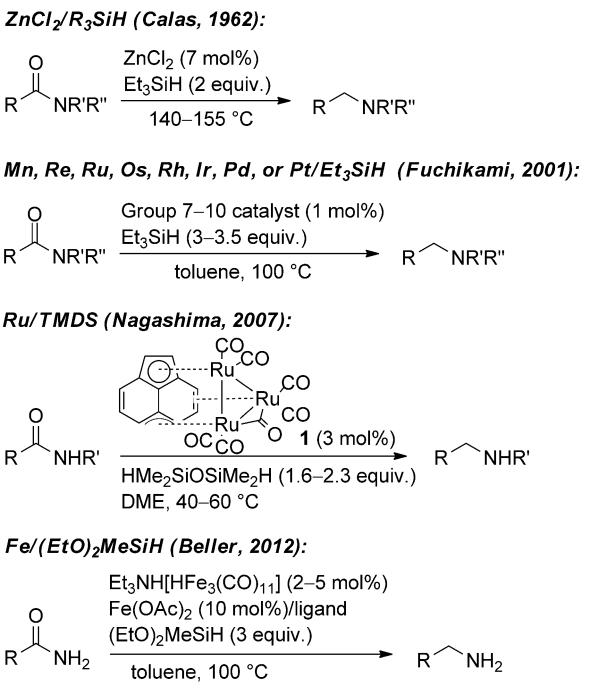
Received: September 16, 2012; Published online: January 7, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200835.

Abstract: A mild and general procedure for reduction of primary, secondary, and tertiary amides using catalytic triruthenium dodecacarbonyl and 1,1,3,3-tetramethyldisiloxane as reductant is described. The reaction is tolerant of numerous functional groups, and the amine products can often be isolated by direct crystallization as hydrochloride salts. The catalyst and silane are commercially available, air stable, and inexpensive, making the procedure accessible for both laboratory and large-scale applications.

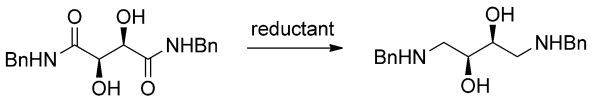
Keywords: amides; reduction; ruthenium; silanes

The reduction of carboxamides is a useful method for the synthesis of amines.[1] Historically, this transformation has been effected by powerful reducing reagents such as $LiAlH_4$ or BH_3.[2] While the reliability of these reagents has been amply demonstrated, their low functional group tolerance, often difficult associated work-up/isolation procedures, and safety concerns present challenges to large-scale applications. Recently, transition metal-catalyzed reductions of carboxamides with silanes have emerged as a safe and mild alternative to traditional alane- and borane-derived reagents. The pioneering report on this type of reduction in 1962 by Calas and co-workers described the $ZnCl_2$-catalyzed reduction of tertiary amides to tertiary amines with various trialkylsilanes at 140–155 °C (Scheme 1).[3] The following year Frainnet and Calas extended the reaction to the reduction of secondary amides.[3b] The use of group 7–10 metal catalysts for reductions of amides with silanes began in 1998 with the report of Ito and co-workers on the reduction of tertiary amides with Ph_2SiH_2 catalyzed by $RhH(CO)(PPh_3)_3$.[4] A key report from Fuchikami and Igarashi in 2001 described the reduction of tertiary amides with several metal catalysts, including Mn, Re, Ru, Os, Rh, Ir, Pt and Pd, in combination with trialkylsilanes (Scheme 1).[5] Osmium and ruthenium catalysts were found to be most effective, and several examples of tertiary amides were reduced using these catalysts with triethylsilane, as well as three examples of secondary amides and two examples of primary amides. Nagashima and co-workers have extensively studied the application of their novel catalyst ($\mu_3,\eta^2,\eta^3,\eta^5$-acenaphthylene)$Ru_3(CO)_7$ (**1**) to the hy-



Scheme 1. Selected metal-catalyzed reductions of carboxamides with silanes.

Table 1. Reagent screening for the reduction of **2**.



2 **3**

Entry	Reagents and Conditions	Yield [%][a]
1	$LiAlH_4$, THF (ref.[16])	20
2	BH_3-THF, THF, 60 °C, 48 h	35
3	DIBALH, PhMe, 80 °C, 48 h	45
4	Tf_2O/Et_3SiH/Hantzsch ester	0
5	Et_3SiH (10 equiv.), $Ru_3(CO)_{12}$ (3 mol%), PhMe, 100 °C, 24 h	40
6	$(EtO)_3SiH$ (10 equiv.), $Ru_3(CO)_{12}$ (3 mol%), PhMe, 80 °C, 24 h	50
7	TMDS (12 equiv.), $Ru_3(CO)_{12}$ (3 mol%), PhMe, r.t., 24 h	78
8	TMDS (8 equiv.), $Ru_3(CO)_{12}$ (1 mol%), PhMe, 50 °C, 24 h	76 (65)[b]

[a] HPLC assay yield of **3**.
[b] Isolated yield of **3** as its bis-HCl salt.

drosilylation of carbonyl compounds (Scheme 1).[6] Their studies led to the identification of 1,1,3,3-tetramethyldisiloxane (TMDS) as a highly effective bifunctional silane for the reduction of tertiary and secondary amides in combination with catalyst **1**. In 2009 the groups of Beller and Nagashima both described iron-catalyzed reductions of tertiary amides using PMHS or TMDS as the reductant.[7] Beller's group reported in 2010 a $Zn(OAc)_2$-catalyzed reduction of tertiary amides using $(EtO)_3SiH$ or $(EtO)_2MeSiH$.[8] Subsequently, they extended the reaction to secondary amides by using $Zn(OTf)_2$ and TMDS in toluene at 100 °C.[9] Recently, Beller's group developed a $Cu(OTf)_2$/pybox-catalyzed reduction of secondary amides using TMDS in toluene at 65 °C.[10] Charette and co-workers reported the reduction of tertiary amides using a metal-free system of Tf_2O/Hantzsch ester,[11] and subsequently of secondary amides using Tf_2O/Et_3SiH/Hantzsch ester.[12] Huang and co-workers described a similar metal-free reduction of tertiary and secondary amides using $Tf_2O/NaBH_4$.[13] Lemaire and co-workers reported the reduction of primary amides using Ti(O-*i*-Pr)$_4$/PMHS.[14] Recently, Beller and co-workers reported a reduction of primary amides using a system composed of two iron catalysts and $(EtO)_2MeSiH$ (Scheme 1).[15] Brookhart has recently described a mild Ir-catalyzed reduction of tertiary amides with Et_2SiH_2.[16] Subsequently, Brookhart reported the room temperature reduction of secondary amides catalyzed by an Ir complex and Et_2SiH_2.[17]

While many of the above methods are useful for the reduction of tertiary amides, the available protocols for the more challenging reduction of secondary amides are far fewer. Furthermore, the methods known to reduce secondary amides often suffer from limited large-scale practicality due to expensive reagents (Tf_2O, Hantzsch ester, Ph_2SiH_2), non-commercially available reagents (**1**), and/or large amounts of arylsilane-derived waste or other organic by-products which complicate work-up and product isolation. We recently required an efficient and scalable method for the reduction of the tartrate-derived diamide **2**. Herein we present our survey of known protocols to the reduction of **2** and the arrival at the commercially available catalyst $Ru_3(CO)_{12}$ in combination with TMDS as a highly efficient and general system for reduction of not only secondary amides, but also of tertiary and even primary amides.

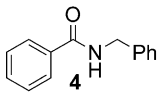
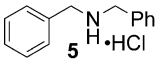
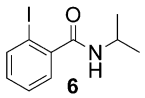
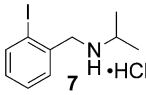
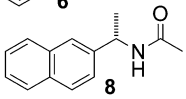
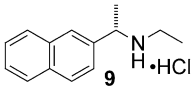
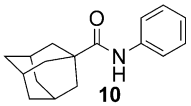
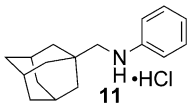
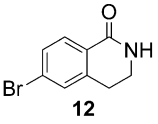
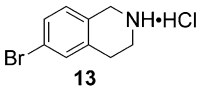
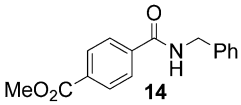
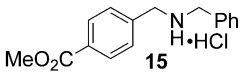
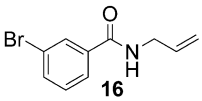
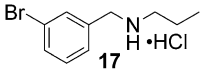
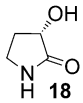
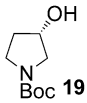
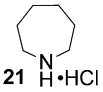
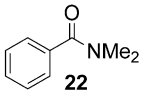
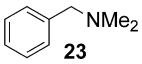
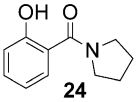
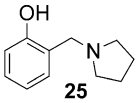
The reduction of **2** to **3** has been described by Rehse and co-workers using $LiAlH_4$ in THF.[18] Under these conditions a 20% yield of **3** was obtained (entry 1, Table 1). The use of BH_3 in THF at elevated temperature gave a somewhat improved yield (entry 2). Reduction with DIBALH in toluene at 80 °C gave a further increase in yield (entry 3). In addition to the low yields of the borane and DIBALH procedures, a further drawback was the exceptionally difficult and volume intensive work-up required for reactions with these reagents. We subsequently explored the reduction using silane reagents. The Tf_2O activation method of Charette (entry 4) gave a complex mixture of products, among which none of the desired diamine **3** could be detected. This was likely due in part to triflation of the hydroxy groups in **2** and subsequent side reactions. Conditions described by Fuchikami [Et_3SiH, $Ru_3(CO)_{12}$, toluene, 100 °C] gave **3** in low yield (entry 5), but relatively cleanly. Furthermore, the work-up was greatly simplified for this silane protocol relative to the borane and alane procedures. Intrigued by the possibilities of this reaction, we screened several alternative silanes and solvents in an attempt to find conditions which would effect the reduction at lower temperature. Triethoxysilane proved more effective (entry 6), as the reaction proceeded at 80 °C and gave a 50% assay yield of **3**.

Given the safety problems associated with $(EtO)_3SiH$, we sought alternative silanes.[8b] Nagashima and co-workers have shown that 1,1,3,3-tetramethyldisiloxane (TMDS) and other silanes possessing two proximal Si–H bonds are exceptionally effective for the reduction of secondary and tertiary amides using their novel (μ_3,η^2,η^3,η^5-acenaphthylene)$Ru_3(CO)_7$ catalyst **1**. Unfortunately, this catalyst is not commercially available. Nonetheless, when TMDS was used in the reduction of **2** with commercially available $Ru_3(CO)_{12}$ as catalyst, a dramatic increase in reactivity was observed (entries 7 and 8). The reaction proceeded at *room temperature* in 24 h, giving an assay yield of 78% of **3**. Reducing the catalyst loading from 3 to 1 mol% and the stoichiometry of TMDS from 12 to 8 equiv. and running at 50 °C resulted in similar yield (entry 8). The product could conveniently be isolated as its crystalline HCl salt by addition of HCl to the reaction mixture after completion of the reduction. We next explored the generality of the reaction conditions (Table 2). General conditions of 1 mol% $Ru_3(CO)_{12}$, 4 equiv. of TMDS, and 50 °C for 24 h were found to be effective for secondary (entries 1–9) and tertiary (entries 10–12) amides. The reaction was amenable to both *N*-aryl- and *N*-alkylamides, to cyclic and acyclic amides, and to benzamides as well as alkamides. Functional groups such as iodo (entry 2), bromo (entries 5 and 7), methyl ester (entry 6), hydroxy (entry 8), and phenol (entry 11) were tolerated. In the case of the ester substrate **14** (entry 6), the reaction was run at room temperature for 48 h using 2 equiv. of TMDS. Using these conditions, no reduction of the ester group was observed. The *N*-allyl secondary amide **16** was reduced to the corresponding *N*-propylamine **17**, presumably by alkene hydrosilylation and protodesilylation during the HCl work-up. Most secondary amine products could be isolated directly as their HCl salts by quenching the reaction with MeOH and adding anhydrous HCl in dioxane. This was not effective for the tertiary amine products, which were subjected to a standard aqueous work-up and chromatographic purification. In the case of entry 8, the product was protected *in situ* as a Boc carbamate by addition of MeOH, aqueous NaOH and Boc_2O to the reaction after completion of the reduction.

The reaction was further extended to primary amides (Table 3). For these more challenging substrates, an increase in temperature to 70 °C was necessary to achieve complete reaction in 24 h. Both aryl (entries 1–2) and alkyl (entries 3-6) primary amides were reduced to the corresponding primary amines in good yields. As with the reduction of secondary amides, the products could be directly crystallized as their HCl salts.

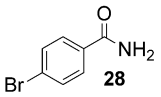
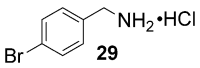
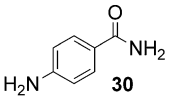
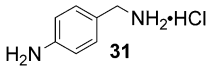
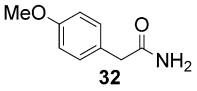
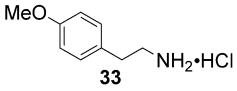
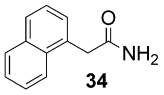
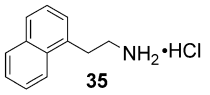
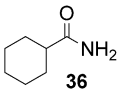
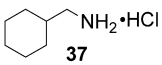
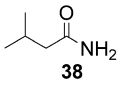
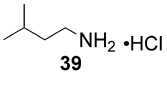
The mechanism of the reduction for primary amides warrants further comment. Calas noted in 1962 that primary amides were dehydrated to nitriles at high temperatures with Et_3SiH and catalytic $ZnCl_2$.[3a] Nagashima and co-workers have also shown

Table 2. Reduction of secondary and tertiary amides.[a]

Entry	Amide	Product	Yield [%][b]
1	 **4**	 **5**	93
2	 **6**	 **7**	89
3	 **8**	 **9**	90
4	 **10**	 **11**	84
5	 **12**	 **13**	93
6	 **14**	 **15**	78
7	 **16**	 **17**	74
8	 **18**	 **19**	71[c]
9	 **20**	 **21**	88
10	 **22**	 **23**	84[d]
11	 **24**	 **25**	79[d]
12	 **26**	 **27**	81[d]

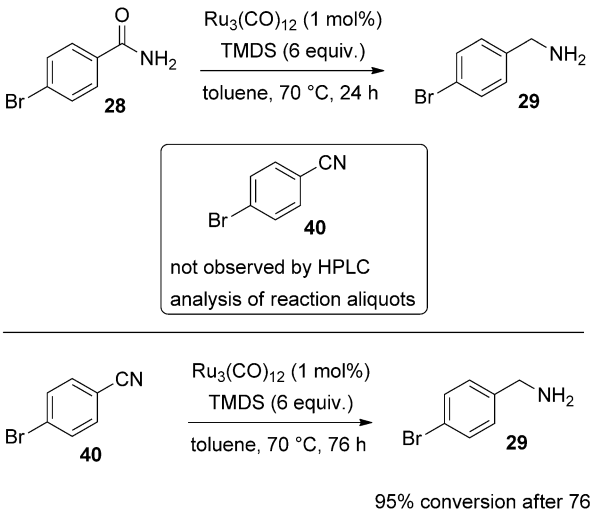
[a] *Reaction conditions:* amide (3.0 mmol), PhMe (1.5 mL), $Ru_3(CO)_{12}$ (1.0 mol%), TMDS (4 equiv), 50 °C, 24 h.
[b] Isolated yield of crystallized HCl salt.
[c] Reaction treated with MeOH, aqueous. NaOH and Boc_2O after reduction.
[d] Isolated yield of free base after chromatography on SiO_2.

Table 3. Reduction of primary amides.[a]

Entry	Amide	Product	Yield [%][b]
1	 **28**	 **29**	81
2	 **30**	 **31**	59
3	 **32**	 **33**	67
4	 **34**	 **35**	72
5	 **36**	 **37**	79
6	 **38**	 **39**	74

[a] *Reaction conditions:* amide (3.0 mmol), PhMe (1.5 mL), $Ru_3(CO)_{12}$ (1.0 mol%), TMDS (6 equiv.), 70 °C, 24 h.
[b] Isolated yield of crystallized HCl salt.

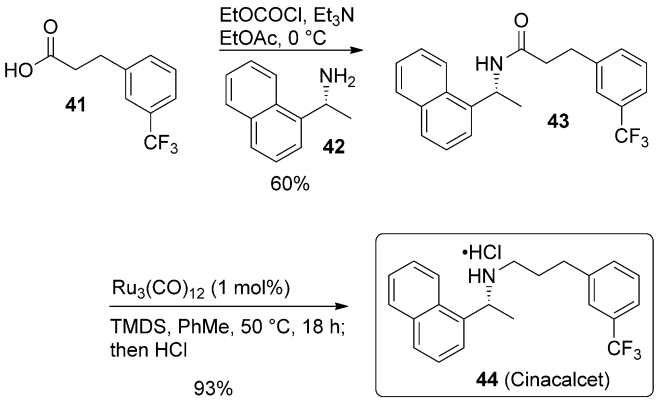
that primary amides are dehydrated to nitriles using their ruthenium catalyst **1** and various silanes, with the most efficient silane being 1,2-bis(dimethylsilyl)-ethane.[19] They found that the dehydration reaction also occurred using TMDS as silane with catalyst **1**, although with lesser efficiency. Furthermore, they found that $Ru_3(CO)_{12}$ gave a 10% yield of nitrile in combination with 1,2-bis(dimethylsilyl)ethane. They did not report the result of using $Ru_3(CO)_{12}$ with TMDS, however. Beller has reported the dehydration of primary amides to nitriles with iron catalysts or TBAF.[20] In addition, Beller's recently reported reduction of primary amides using two iron catalysts with $Me(EtO)_2SiH$ is described as proceeding through an initial dehydration by one Fe catalyst, followed by a reduction of the resultant nitrile by the second catalyst.[15] We therefore explored whether the present reduction proceeded through an initial dehydration to a nitrile intermediate (Scheme 2). The reduction of amide **28** to amine **29** was monitored by periodic HPLC analysis of aliquots to see if nitrile **40** could be observed. Throughout the course of the reaction, nitrile **40** was not observed by HPLC. While this result suggests the reduction does not proceed through a nitrile intermediate, if the reduction of the nitrile is very fast under the reaction conditions, it is possible that it is formed but not observed due to immediate reduction. To test this possibility, we subjected nitrile **40** to the reaction conditions. Interestingly, the reduction to **29** did occur smoothly but very slowly, requiring 76 h to reach 95% conversion by HPLC analysis. The facts that **40** was not observed in the reduction of amide **28** to **29**, and that **40** is reduced much more slowly than **28** to **29** under the reaction conditions suggest that the reaction does not proceed *via* an initial dehydration process.



Scheme 2. Tests for intermediacy of a nitrile in the primary amide reduction.

The utility of the reduction was demonstrated in a synthesis of the calcimimetic drug Cinacalcet (**44**) (Scheme 3).[21] The coupling of acid **41** with chiral amine **42** gave the amide **43** in 60% yield. Subsequent reduction of **43** under the standard conditions followed by HCl addition gave Cinacalcet hydrochloride **44** in 93% yield.

In conclusion, we have described a mild and general procedure for the reduction of primary, secondary, and tertiary amides to the corresponding amines. The catalyst and silane employed in the reduction are both commercially available. The reduction is tolerant of many functional groups. In the reduction of pri-



Scheme 3. Application of the reduction to a synthesis of **44**.

mary and secondary amides, the product amine usually may be directly precipitated after the reaction by adding HCl to the reaction mixture, thus allowing a simple isolation. This reagent system provides a convenient and general option for the reduction of a primary, secondary or tertiary amide, in contrast to many other reagent systems which are specific for a certain type of amide.

Experimental Section

General Procedure for 2° or 3° Amide Reduction

To a dry 1-neck, 25-mL, round-bottom flask equipped with a football shaped magnetic stir bar was charged amide (3.00 mmol, 1 equiv.) and $Ru_3(CO)_{12}$ (19.2 mg, 0.03 mmol, 1 mol%). The flask was sealed with a rubber septum and a nitrogen inlet needle was inserted in the septum. The flask was evacuated and filled with nitrogen. Toluene (1.5 mL) was charged followed by 1,1,3,3-tetramethyldisiloxane (TMDS, 2.12 mL, 12.00 mmol, 4 equiv.). The reaction mixture was stirred at room temperature for 10 min and then placed in a 50 °C oil bath and stirred for 24 h, or until complete conversion by HPLC analysis. The reaction mixture was cooled to room temperature.

HCl salt formation (works for most secondary amines): The reaction mixture was treated with 4 M HCl in dioxane (3.0 mL) and EtOAc (2–10 mL), stirred at room temperature for 30 min, and the resultant solid was filtered, washed with EtOAc and dried under vacuum. If necessary, the salt was recrystallized to upgrade the purity.

Free base isolation (used for tertiary amines or if the free base of a secondary amine is desired): The reaction mixture was treated with aqueous 1 N NaOH and CH_2Cl_2 and stirred at room temperature for 30 min. The layers were separated, and the organic phase was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash column chromatography on SiO_2.

General Procedure for Primary Amide Reduction

To a dry 1-neck, 25-mL, round-bottom flask equipped with a football shaped magnetic stir bar was charged amide (3.00 mmol, 1 equiv.) and $Ru_3(CO)_{12}$ (19.2 mg, 0.03 mmol, 1 mol%). The flask was sealed with a rubber septum and a nitrogen inlet needle was inserted in the septum. The flask was evacuated and filled with nitrogen. Toluene (1.5 mL) was charged followed by 1,1,3,3-tetramethyldisiloxane (TMDS, 3.18 mL, 18.00 mmol, 6 equiv.). The reaction mixture was stirred at room temperature for 10 min and then placed in a 70 °C oil bath and stirred for 24 h, or until complete conversion by HPLC analysis. The reaction mixture was cooled to room temperature. HCl salt formation was done as described above for reductions of secondary amides.

Procedures, spectral data, and copies of ^{1}H and ^{13}C NMR spectra are available in the Supporting Information.

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