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Semi-catalytic reduction of secondary amides to imines and aldehydes

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Semi-catalytic reduction of secondary amides to imines and aldehydes

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Secondary amides can be reduced by silane $HSiMe_2Ph$ into imines and aldehydes by a two-stage process involving prior conversion of amides into iminoyl chloride followed by catalytic reduction mediated by the ruthenium complex $[Cp(i\text{-}Pr_3P)Ru(NCCH_3)_2]PF_6$ (**1**). Alkyl and aryl amides bearing halogen, ketone, and ester groups were converted with moderate to good yields under mild reaction conditions to the corresponding imines and aldehydes. This procedure does not work for substrates bearing the nitro-group and fails for heteroaromatic amides. In the case of cyano substituted amides, the cyano group is reduced to imine.

Introduction

Amides are abundant in natural products, pharmaceuticals and agrochemical products,[1] but also are among the least reactive carbonyls. For example, their reduction presents a serious chemoselectivity problem if other, and usually more reactive functional groups, are present. Traditional reduction techniques are based on the application of alumo- and borohydrides, which are expensive, often pyrophoric, and generate a significant amount of waste upon the work-up.[2,3] Reductions of amides by these reagents to alcohols and amines are well established but show little compatibility with the presence of other functional groups.[4,5]

Silanes have recently received significant attention as reducing reagents due to their low toxicity, stability, ease of handing and accessibility from the by-products of the Direct Synthesis.[6] Catalytic hydrosilylation of tertiary amides to amines is known for Ti,[7] Mo,[8] Fe,[9] Ru,[10] Co,[11] Rh,[12] Ir,[13] Pt,[14] Zn,[15] and In[16] catalysts, and in some cases can even provide chemoselective reduction of amides in the presence of other functional groups.[9b,10b,13,15] Very recently Nolan et al. and Cui et al. reported a simple base-catalysed hydrosilylation of tertiary amides to amines,[17] and Beller et al. introduced hydrosilylation of amides to amines in the presence of boronic acids.[18,19]

In contrast, reduction of secondary amides to amines is much less developed.[9b,15b,20,21] In particular, Beller et al. reported a copper catalyst for chemoselective reduction of secondary amides by the inexpensive tetramethyldisiloxane (TMDS), and Reeves et al. developed a practical protocol by application of the Fichikami's catalyst $Ru_3(CO)_9$ and TMDS.[22]

Reduction of primary amides to primary amines has been accomplished only very recently,[12b,22,23] and can be compromised by the formation of nitriles, imines and secondary amines.[23a,b] In particular, Beller et al. reported a two-component iron catalytic system which converts amides into nitriles and reduces the *in situ* formed nitriles to amines in high yields.[23c]

Monoreduction of amides to aldehydes and imines is even more challenging but is of interest as an alternative method for the preparation of these important compounds and as a potential synthetic pathway in the transformation of amido groups. Relevant to this theme is the report by Ganem et al. on the conversion of secondary amides to imines by stoichiometric amount of the Schwartz' reagent, $(Cp_2ZrHCl)_n$.[24] The imine product was isolated by a simple filtration of the reaction mixture through Celite. Georg et al. reported that the related treatment of tertiary and secondary amides with Cp_2ZrHCl followed by filtering the reaction mixture through Celite affords aldehydes instead of imines. Good tolerance to such reactive functionalities as keto, ester, nitro, and cyano was observed.[25] Buchwald et al. developed monoreduction of amides to aldehydes catalysed by the inexpensive complex $Ti(O\textit{i}Pr)_4$, but this approach is applicable only to enolizable substrates.[26] Harrod et al. reported formation of aldehydes upon reduction of tertiary amides by $H_2SiMePh$ catalysed by Cp_2TiX_2 (X=F, Me).[27] Very recently Brookhart et al. have shown catalytic reduction of secondary amides to imines by using a commercially available iridium complex $[Ir(coe)_2Cl]_2$ and H_2SiEt_2.[1d,28] Full conversions were achieved with high efficiency at room temperature and a small catalyst load, and the imine products could be isolated by chromatography on basic alumina. Charette and co-workers reported a metal-free reduction of secondary amides by using pre-activation with triflic anhydride (Tf_2O) followed by reduction with $HSiEt_3$.[29] Good tolerance to several functional groups was observed. The corresponding imines were isolated by removing the triflate and silicon co-products in high vacuum to give analytically pure compounds. It was also found that the reaction can produce aldehydes when the reaction mixture is worked-up under acidic conditions.

We have recently reported a Ru catalysed reduction of acid chlorides by $HSiMe_2Ph$, which is applicable to aromatic and aliphatic substrates and tolerates the presence of functional groups.[30] Given the fact that isoelectronic iminoyl chlorides are readily accessible from secondary amides, we became interested in the extension of this methodology to chemoselective reduction of amides. Here we report the application of this two-step approach to the preparation of imines and aldehydes from secondary amides.

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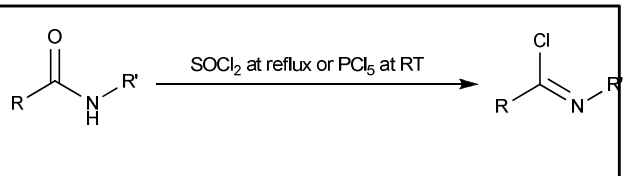
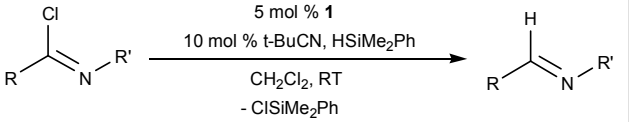
Results and discussion

Reduction of amides to imines. Secondary amides are easily converted to iminoyl chlorides upon reactions with PCl_5 at room temperature or upon refluxing (70°C) with $SOCl_2$ (Scheme 1).[31] The corresponding iminoyl chlorides were obtained with good to high yields (60-98%).



Scheme 1. Conversion of secondary amides to iminoyl chlorides

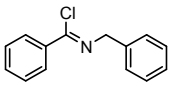
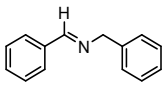
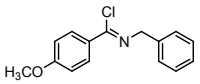
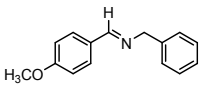
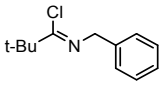
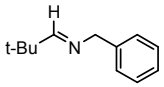
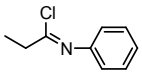
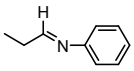
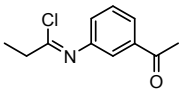
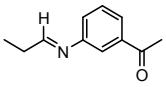
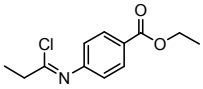
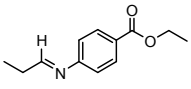
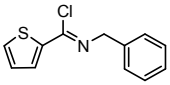
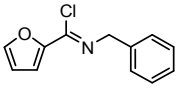
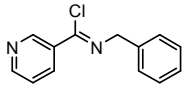
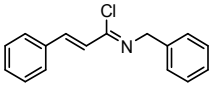
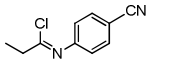
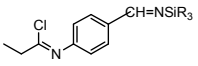
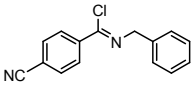
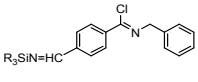
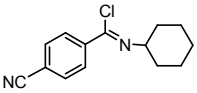
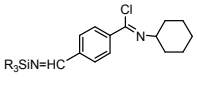
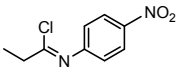
In the initial NMR screening, we found that complex [Cp(*i*-Pr_3P)Ru($NCCH_3$)$_2$]PF_6 (**1**) catalyses the reduction of iminoyl chlorides by $HSiMe_2Ph$ at room temperature, affording high NMR yields of the corresponding imines (Scheme 2). To avoid a possible catalyst deactivation, excess *t*-BuCN was added to the reaction mixture, as this was found to be beneficial for the reduction of corresponding acid chlorides.[30]



Scheme 2. Reduction of iminoyl chlorides catalysed by **1**.

Full conversion of PhCCl=NCH_2Ph into the imine PhCH=NCH_2Ph was observed in only 15 min (Table 1, entry 1). The reactions of iminoyl chlorides bearing electron donating substituents, such as methoxy and *t*-butyl groups, were achieved with high conversions, although they required much longer reaction times (Table 1, entry 2 and 3). Alkyl substituted substrates also showed good conversion after 30 min (Table 1, entry 4). To our delight, we also found that reductions under these catalytic conditions tolerate the presence of keto- and ester groups (Table 1, entries 5, 6 and 15). But in contrast to the related reduction of acid chlorides, heterocyclic substrates do not react cleanly, affording a mixture of unidentified compounds (Table 1, entries 7, 8 and 9). Alkene bearing substrate also produced a mixture of compounds (Table 1, entry 10). Another difference with acid chlorides is that reduction of iminoyl chloride did not tolerate the presence of the cyano group. In the latter case, the products of nitrile hydrosilylation were obtained (Table 1, entries 11, 12 and 13). Finally, a mixture of unidentified compounds was produced upon attempted reduction of an iminoyl chloride with a nitro substituent (Table 1, entry 14).

Table 1. NMR scale screening of the reduction of iminoyl chlorides to imines.[a]

Entry	Substrate	Product	Time	Yield[b]
1			15m	99%
2			14h	90%
3			14h	95%
4			30m	80%
5			90m	93%
6			3h	86%
7		Mixture of products	13h	90%[c]
8				NR
9		Mixture of products	24h	99%[c]
10		Mixture of products	12h	99%[c]
11			2.5h	30%[c]
12			40m	90%[c,d]
13			3h	99%[c,d]
14				NR

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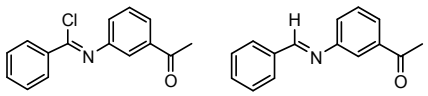
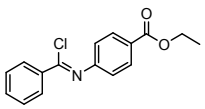
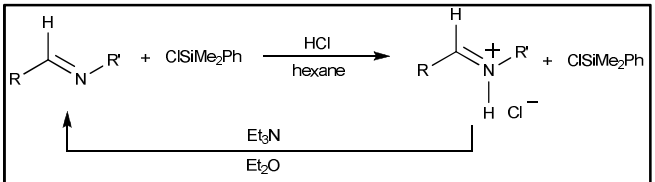
15		20h	65%
16			NR

[a] 5 mol % **1**, 25 mol % *t*-BuCN, substrate (0.05-0.1 mmol), $HSiMe_2Ph$ (1.1 eq), CH_2Cl_2 (0.5 mL), room temperature. [b] NMR yields. [c] Conversion of iminoyl chloride. [d] 1.5eq $HSiMe_2Ph$

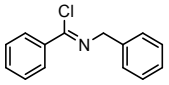
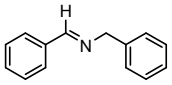
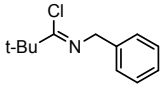
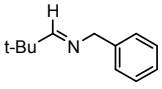
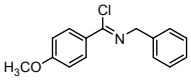
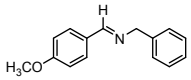
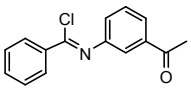
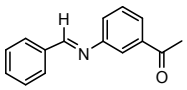
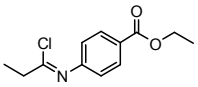
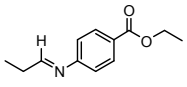
With these results of NMR scale reactions in hands, preparative scale reductions were attempted. The reaction of $PhCCl{=}NCH_2Ph$ required a slightly longer reaction time compared with the NMR scale reaction (Table 2, entry 1). The catalyst can be easily removed from the reaction mixture by adding a non-polar solvent. Several literature approaches to imine isolation were studied. Attempted removal of $ClSiMe_2Ph$ (*M*r= 170.71) from the crude reaction mixture in high vacuum in a similar fashion to the removal of Et_3SiOTf (*M*r= 264.34) in the procedure reported by Charette,[29] was unsuccessful in that a significant amount of silane was left even upon drying the mixture for 5 hours at 60 mbar. On the other hand, TLC on basic alumina (Alumina G 1000 um, from Analtech) lead to imine decomposition even when the experiment was performed with dry solvents (hexane and ethyl acetate mixtures) in the glove-box. To circumvent these problems, the imine product was separated from the $ClSiMe_2Ph$ by-product by precipitating the iminium salt upon addition of 1 equiv. HCl in ether, extraction with Et_2O, and finally regeneration of the imine by adding Et_3N (Scheme 3). The target imine, $PhCH{=}NCH_2Ph$, was isolated in a moderate yield (43%).



Scheme 3. Isolation of imines from the reaction mixture.

Reductions of *t*-$BuCCl{=}NCH_2Ph$ was achieved quite smoothly (Table 2, entry 2), and the imine, *t*-$BuCH{=}NCH_2Ph$ was obtained in 57% isolated yield following the same isolation protocol. The reaction of an iminoyl chloride bearing a ketone group was also achieved and the product was obtained in a moderate yield (Table 2, entry 4). Unfortunately, although the reductions initially produced the corresponding imines, attempted isolation of $4\text{-}CH_3OC_6H_4CH{=}NCH_2Ph$ and $CH_3CH_2CH{=}NC_6H_4CO_2CH_2CH_3$ failed because of decomposition of the products upon isolation (Table 2, entry 3 and 5).

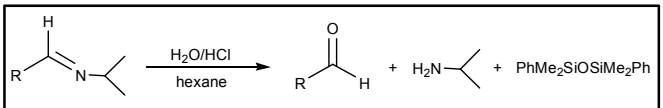
Table 2. Preparative scale reduction of iminoyl chlorides to imines.[a]

Entry	Substrate	Product	Time	Conv.
1			50m	100% (43%)[b]
2			25m	100% (57%)[b]
3			5h	100%
4			7d	98% (40%)[b]
5			3h	90%

[a] 5 mol % **1**, 20 mol % *t*-BuCN, substrate (1.2-6.0 mmol), $HSiMe_2Ph$ (1 eq), CH_2Cl_2 (12 mL), room temperature. [b] isolated yield.

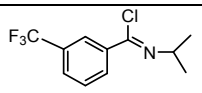
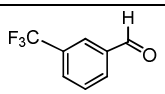
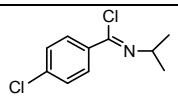
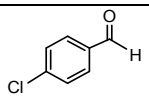
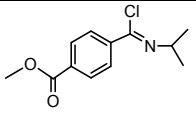
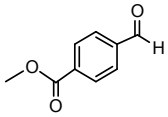
Reduction of imidoyl chlorides to aldehydes. Due to the difficulty of isolating imines, we studied reduction of iminoyl chlorides to aldehydes. Aldehydes are useful building blocks for organic synthesis and are widely used in industrial processes. To achieve efficient isolation of aldehydes, isopropyl-substituted iminoyl chlorides were employed, because after reduction and hydrolysis these substrates give the highly volatile amine *i*-$PrNH_2$ as a co-product (Scheme 4).

Reduction of iminoyl chlorides bearing both electron-withdrawing and electron-donating substituents was achieved under the conditions of Scheme 3. In the case of $3\text{-}CF_3C_6H_4CCl{=}NCH(CH_3)_2$, the corresponding imine was obtained as a sole product and the aldehyde, $3\text{-}CF_3PhCHO$, was isolated in a moderate yield after acid hydrolysis and chromatography on silica (Table 3, entry 1). Mixtures of imine and aldehyde were obtained in the reaction of $4\text{-}ClC_6H_4CCl{=}NCH(CH_3)_2$ and $4\text{-}CH_3O_2CC_6H_4CCl{=}NCH(CH_3)_2$, although the formation of aldehydes was almost negligible (Table 3, entries 2 and 3). The corresponding aldehydes were separated from the reaction mixtures by following the same isolation procedure.



Scheme 4. Isolation of aldehydes from the reaction mixture.

Table 3. Reduction of iminoyl chlorides to aldehyde.[a]

Entry	Substrate	Product	Time	Isolated yield[b]
1			70m	64%
2			50m	51%
3			30m	46%

[a] 5 mol % **1**, 20 mol % *t*-BuCN, substrate (1.0-1.6 mmol), $HSiMe_2Ph$ (1 eq), CH_2Cl_2 (12 mL), room temperature. [b] isolated yield of aldehyde after hydrolysis and chromatography.

Experimental

General methods and instrumentation

Solvents were pre-dried by using Grubbs-type purification columns and stored in ampoules equipped with Teflon valve. Deuterated solvents were dried over sodium, potassium or CaH_2 as appropriate, distilled under reduced pressure and stored in Teflon valve ampoules. NMR samples were prepared in New Era tubes equipped with J. Young type Teflon valves. NMR spectra were obtained at room temperature with a Bruker DPX-300 and Bruker DPX-600 instruments (^{1}H: 300 and 600 MHz; ^{13}C: 75.5 and 151 MHz). ^{1}H and ^{13}C spectra were referenced internally to residual protio-solvent (^{1}H) or solvent (^{13}C) resonances and are reported relative to tetramethylsilane (δ = 0 ppm). Chemical shifts are quoted in δ (ppm) and coupling constants in Hertz. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer as Nujol mulls between NaCl windows. All data are quoted in wavenumbers (cm^{-1}). The catalyst $[Cp(i\text{-}Pr_3P)Ru(NCCH_3)_2]PF_6$ (**1**) was prepared according to the literature procedure.[32] Details of the syntheses of secondary amides and iminoyl chlorides are given in the Supplementary Information.

General procedure for the reduction of iminoyl chlorides to imines. In a representative procedure, a solution of $HSiMe_2Ph$ (145.0 µL, 1.04 mmol) and $PhCCl{=}NCH_2Ph$ (150.0 mg, 0.69 mmol) in 0.3 mL of CD_2Cl_2 was added to a solution of $[CpRu(PPr^i_3)(CH_3CN)_2]PF_6$ (20 mg, 0.034 mmol) and *t*-BuCN (15 µL, 0.17 mmol) in 0.3 mL of CD_2Cl_2. The formation of $PhCH{=}NCH_2Ph$ was periodically monitored by NMR spectroscopy. Volatiles we removed under vacuum and the residue was dissolved in hexane and filtered. To this mixture, comprised primarily of $PhCH{=}NCH_2Ph$ and $ClSiMe_2Ph$, was added 1 eq. of 2 M HCl in Et_2O to give a precipitate. The precipitate was filtered and treated with 1.2 eq. of Et_3N in Et_2O. The solution was filtered and the filtrate was dried under vacuum. The product $PhCH{=}NCH_2Ph$ was obtained as a yellow oil in 43 % yield.

^{1}H NMR ($CDCl_3$): δ 8.44 (s, 1, Ph*C*H=NCH_2Ph), 7.39-7.86 (m, 10, *Ph*CH=NCH_2*Ph*), 4.88 (s, 2, PhCH=N*C*H_2Ph). ^{1}H-^{13}C HSQC (CD_2Cl_2): δ 65.4 (s, PhCH=N*C*H_2Ph), 162.1 (s, Ph*C*H=NCH_2Ph), 127.05-130.82 (s, *Ph*CH=NCH_2*Ph*).

General procedure for the reduction of iminoyl chlorides to aldehydes. The reduction was performed as discussed above with the following modification. After the reaction was complete, the catalyst was removed by extracting the products with hexanes. Then the mixture of imine and $ClSiMe_2Ph$ was hydrolysed by adding 1 M HCl solution. The organic products (aldehyde and $PhMe_2SiOSiMe_2Ph$) were then extracted with CH_2Cl_2 and the solution was dried over $MgSO_4$. In a representative example of the reduction of $F_3CC_6H_4CH{=}NPr^i$, 3-$F_3CC_6H_4CHO$ was isolated by chromatography over silica using 15:1 hexane:ethyl acetate as eluent to give the product as a colourless oil (89 mg, 64% yield).

^{1}H NMR (CH_2Cl_2): δ 10.02 (s, 1, C*H*O), 8.10 (s, 1, C_6H_4), 8.03 (d, J (H-H) = 8.15 Hz, 1, C_6H_4), 7.84 (d, J (H-H) = 8.15 Hz, 1, C_6H_4), 7.64 (t, J(H-H) = 7.72 Hz, 1, C_6H_4). ^{19}F NMR ($CDCl_3$): δ -62.94 (s, 1, 3-CF_3PhCHO). ^{1}H-^{13}C HSQC ($CDCl_3$): δ 186.3 (*C*HO) 132.4 (C_6H_4), 131.0 (C_6H_4), 129.7 (C_6H_4), 126.5 (C_6H_4).

Conclusions

We have developed a two-stage catalytic reduction of secondary amides by silane $HSiMe_2Ph$ mediated by the Ru complex **1**. Alkyl and aryl amides bearing halogen, ketone, and ester groups were converted with moderate to good yields to the corresponding imines and aldehydes under mild reaction conditions. This procedure does not work for substrates bearing the nitro-group and fails for heteroaromatic amides. In the case of cyano substituted amides, the cyano group is reduced to imine.

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Notes and references

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Electronic Supplementary Information (ESI) available: syntheses of secondary amides and iminoyl chlorides and their reduction to imines and aldehydes. See DOI: 10.1039/b000000x/

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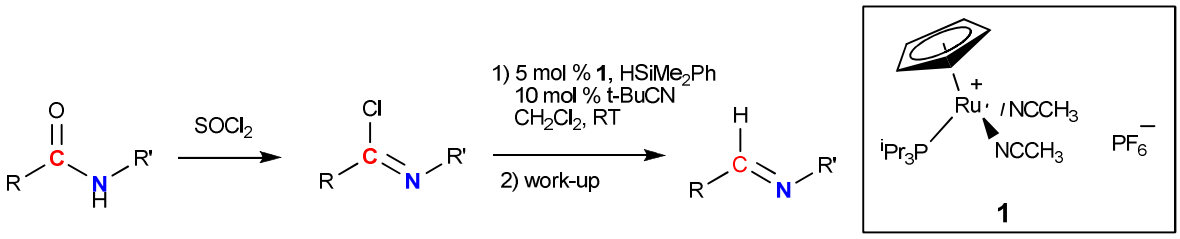

Ruthenium catalyzed reduction of iminoyl chlorides by $HSiMe_2Ph$ allows for a two-step conversion of secondary amides into imines and aldehydes.