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Controlled and Chemoselective Reduction of Secondary Amides

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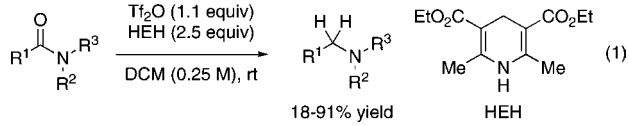
Abstract: This communication describes a metal-free methodology involving an efficient and controlled reduction of secondary amides to imines, aldehydes, and amines in good to excellent yields under ambient pressure and temperature. The process includes a chemoselective activation of a secondary amide with triflic anhydride in the presence of 2-fluoropyridine. The electrophilic activated amide can then be reduced to the corresponding iminium using triethylsilane, a cheap, rather inert, and commercially available reagent. Imines can be isolated after a basic workup or readily transformed to the aldehydes following an acidic workup. The amine moiety can be accessed via a sequential reductive amination by the addition of silane and Hantzsch ester hydride in a one-pot reaction. Moreover, this reduction tolerates various functional groups that are usually reactive under reductive conditions and is very selective to secondary amides.

The issue of chemoselectivity in carboxamide reduction has recently been a topic of marked interest due to its step-economical potential and cost effectiveness.[1] Finding mild, chemoselective, and general conditions for the reduction of amides is of great importance for pharmaceutical chemistry, as this could serve as a template for the direct formation of compounds possessing basic nitrogens or aldehydes.[2] In contrast, the high stability of carboxamides originates from their strong resonance and accounts for their low propensity to react with hydrides.[3] Thus, the most common approaches to their reduction employ nucleophilic metallic hydride donors, such as aluminum[4] and boron[5] reagents. Although they are reliable for the synthesis of amines, access to imines and aldehydes can be problematic due to the intrinsic high reactivity of the hydrides needed to effect the reduction. Moreover, low functional group tolerance, byproduct formation, costly purifications, and poor control over reduction to different oxidation states impair their applications.

To address these issues, direct reduction methods have been described to yield the corresponding aldehyde or imine. Among these, the use of Weinreb amides[6] or morpholine-derived amides[7] in combination with DIBAL are known to control the reduction outcome to aldehydes. Also, Buchwald reported a more general and chemoselective reduction of α-enolizable amides to aldehydes in the presence of $Ti(O\textit{i}\text{-}Pr)_4$ and Ph_2SiH_2.[8] Alternatively, the use of stoichiometric or excess amounts of Schwartz's reagent (Cp_2ZrHCl) can lead to the formation of a variety of aldehydes[9] or imines[10] with great functional group tolerance.

Recently, our group reported a metal-free chemoselective reduction of tertiary amides to amines mediated by activation with triflic anhydride (Tf_2O) and reduction with Hantzsch ester hydride (HEH) (eq 1).[11] In contrast, tertiary amines can be obtained by the catalytic hydrosilylation of amides in the presence of transition metals, such as Rh,[12a,b] Ru,[12c,d] Mo,[12e] Ti,[12f] Pt,[12g,h] Pd,[12h] and Fe.[12i,j] The most recent examples were published by Beller and exhibit a notable chemoselectivity level when the reduction of tertiary amides is catalyzed by $Zn(OAc)_2$ in presence of $(EtO)_3SiH$ at ambient temperature.[12k]



While the majority of these methods were shown to be effective for a large array of substituted tertiary amides, *only scarce examples of secondary amides underwent a controlled reduction to different oxidation states and with an appreciable level of functional group selectivity*. To address this issue, we report herein a versatile and highly functional group tolerant reduction methodology of secondary amides (**1**) giving access to imines (**2**), aldehydes (**3**), or amines (**4**) without the use of any metallic hydride (Scheme 1).

Scheme 1. Strategy for the Controlled Reduction of Secondary Amides

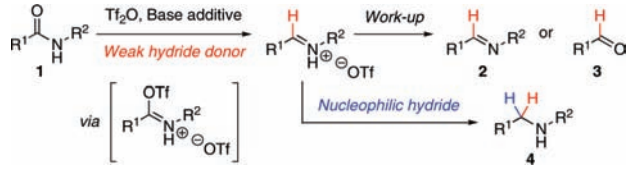
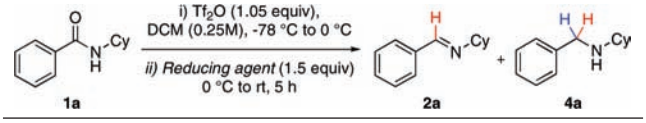


Table 1. Effect of the Reductant



entry	reducing agent	ratio **2a**:**4a**[a]	yield (%)[a] **2a**	**4a**
1	$NaBH_3CN$	0:100	0	38
2	Bu_3SnH	3:97	1	37
3	HEH	47:53	17	19
4	Et_3SiH	100:0	77	0
5	Et_3SiH[b]	100:0	98	0
6	Et_3SiH/HEH[b,c]	0:100	0	96

[a] Obtained by analysis of the crude mixture by ^1H NMR using Ph_3CH as an internal standard. [b] Reduction was performed with 1.1 equiv of Et_3SiH and 1.1 equiv of 2-fluoropyridine as base additive. [c] Reduction was performed with 1.1 equiv of Et_3SiH for 5 h followed by 1.4 equiv of HEH for 12 h.

During the exploration of different reduction conditions,[13] we found that treating *N*-cyclohexylbenzamide **1a** under our previously reported HEH reduction conditions (eq 1) led to a sluggish reaction that gave a mixture of products and was nonreproducible for different secondary amides. By lowering the amount of HEH in the reaction mixture to 1.5 equiv and performing the activation process from −78 to 0 °C, we observed a 47:53 mixture of imine

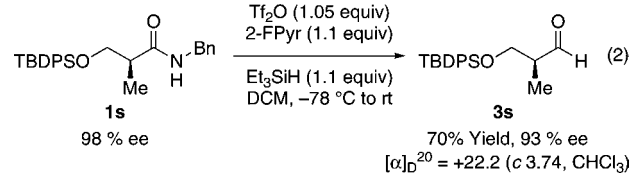
2a versus amine **4a** (Table 1, entry 3). We then hypothesized that, if the reaction were performed with a less nucleophilic hydride source than HEH, the reaction could be controlled in favor of the formation of imine **2a**. In 2009, Mayr demonstrated that organosilanes were weaker hydride donors than 1,4-dihydropyridine derivatives in DCM.[14] We then verified this by performing the reaction in the presence of Et_3SiH. To our delight, the crude mixture exclusively showed the presence of imine **2a** in 77% yield (Table 1, entry 4).

Afterward, we recognized the need to buffer the resulting acidic mixture of this reaction. As demonstrated in many Tf_2O-mediated electrophilic activation conditions suited for secondary amides,[15] the incorporation of 2-halopyridine derivatives as non-nucleophilic and slightly basic additives in the reaction media was found to be crucial to achieve an appreciable level of efficiency.[16,17] We thus explored base additives, finding that 2-fluoropyridine (2-FPyr) was the optimal choice for ease of purification.[13]

By further optimizing the amount of base, solvent, concentration, and the silane's nature, we were pleased to find that treating amide **1a** in the presence of 1.1 equiv of 2-fluoropyridine, 1.05 equiv of Tf_2O, and 1.1 equiv of Et_3SiH gave an optimal 98% yield for imine **2a** without the observation of amine **4a** by ^{1}H NMR analysis of the crude mixture (Table 1, entry 5).[13]

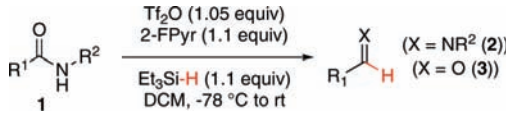
We next investigated the chemoselectivity of the reaction by substituting the aryl of the benzamide by various functional groups susceptible to reduction with strong nucleophilic hydride donors (Table 2). The reaction was found to be very effective for the formation of imines when the medium is quenched in basic conditions and aldehydes when the crude mixture is hydrolyzed in the presence of an aqueous buffer of citric acid and THF. As shown in Table 2, the reaction is high-yielding for amides containing an electron-withdrawing substituent on the aryl group, such as a cyano (entry 2), a nitro (entry 3), an ester (entry 5), and an α,β-unsaturated ester (entry 9). The optimized conditions were also applied to amides bearing the even more electrophilic azido (entry 4), aryl acetate (entry 10), and aldehyde (entry 6) substituents, achieving high yields and an unprecedented chemoselectivity for these groups. Another remarkable result is the complete selectivity obtained for the secondary amide versus a tertiary amide when the electrophilic activation step was performed at −20 °C instead of 0 °C (entry 8).[13] The electron-rich *N*-cyclohexylthiophene-2-carboxamide **1k** (entry 11) afforded good yields for the reduction to imine **2k** and aldehyde **3k**. Alternatively, deuterated aldehydes could be obtained when Et_3SiD was used instead of Et_3SiH (entry 13).[9b] The methodology can also be extended to conjugated vinylic and aliphatic secondary amides (entries 14−18). In certain cases, the imines were found to be unstable, and their corresponding iminium compounds were analyzed by crude ^{1}H NMR.[13] All these reductions were found to be very selective for the secondary amide moiety by ^{1}H NMR analysis of the crude mixture, as no over-reduction byproduct derived from the other functionalities present was observed.

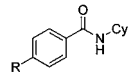
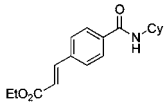
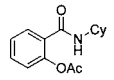
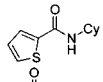
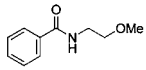
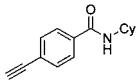
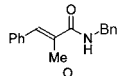
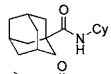
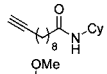
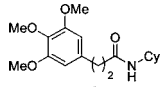
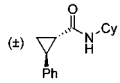
The optimized reduction conditions can also be applied to an enantioenriched secondary amide (**1s**) derived from the commercially available (*S*)-Roche's ester (eq 2). Indeed, aldehyde **3s** was isolated with a 70% yield and 93% ee, showing that a racemization pathway via the formation of an enamine intermediate is not predominant. This observation is consistent with preliminary results obtained by Movassaghi et al. during their studies on the formation of pyridine and pyrimidine substrates with amides possessing an α-enolizable chiral center.[16,17a]



We were also interested in accessing a variety of secondary amines with high chemoselectivities comparable to those observed in the imine or aldehyde syntheses (Table 3). After investigating different reduction conditions and hydride sources,[13] we observed that a subsequent addition of 1.4 equiv of HEH *in situ* gave an excellent 96% yield for amine **4a** by ^{1}H NMR (Table 1, entry 6).[18] Interestingly, HEH is known as a stoichiometric and nonmetallic alternative in hydrogen-transfer reactions.[19,11] In our case, the tandem Et_3SiH/HEH reduction was successfully applied to a variety of substrates, as shown in Table 3. Indeed, the reaction tolerates

Table 2. Reduction of Secondary Amides to Imines and Aldehydes

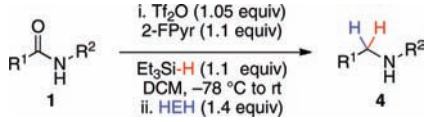


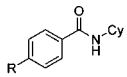
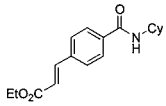
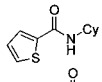
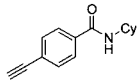
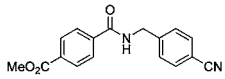
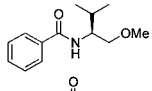
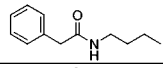
entry	amide		yield imine (%)[a,b,c]		yield aldehyde (%)[a,d]	
1		**1a** R=H	**2a**	81	**3a**	89
2		**1b** R=CN	**2b**	88	**3b**	89
3		**1c** R=NO_2	**2c**	84	**3c**	81
4		**1d** R=N_3	**2d**	88	**3d**	89
5		**1e** R=CO_2Me	**2e**	95	**3e**	90
6		**1f** R=CHO	**2f**	(81)[e]	**3f**	84[e]
7		**1g** R=$PO(OEt)_2$	**2g**	(65)	**3g**	64
8		**1h** R=$CONEt_2$	**2h**	99[f]	**3h**	95[f]
9		**1i**	**2i**	96	**3i**	96
10		**1j**	**2j**	80[e]	**3j**	84[e]
11		**1k**	**2k**	85	**3k**	80
12		**1l**	**2l**	79	**3a**	85
13		**1m**	**2m**	95	**3m** / **3m'**	94 / 90[g]
14		**1n**	**2n**	(75)	**3n**	92
15		**1o**	**2o**	78[h]	**3o**	70[h]
16		**1p**	**2p**	(80)	**3p**	72
17		**1q**	**2q**	(75)	**3q**	70
18		**1r**	**2r**	(83)	**3r**	84

[a] Isolated yields. [b] Yield in parentheses obtained by ^{1}H NMR using Ph_3CH as internal standard. [c] Workup performed with aqueous $NaHCO_3$. [d] Workup performed with aqueous citric acid/THF. [e] Reduction with Et_3SiH was performed at 0 °C for 5 h. [f] Activation of the amide was done at −78 °C for 1 h, followed by −20 °C for 1 h, and 0 °C for 10 min. [g] Reduction was performed with Et_3SiD instead of Et_3SiH. [h] 1.3 equiv of Et_3SiH was used instead of 1.1 equiv of Et_3SiH.

the presence of sensitive groups, such as a nitrile, nitro, azido, ester, tertiary amide, α,β-unsaturated ester, and an alkyne (entries 2−6, 8, and 10). The nitrogen branch can also be varied without affecting the efficiency of the reaction: a substituted *N*-benzyl amide and a hindered valine-derived amide reacted smoothly, leading to the corresponding amines in 77% and 89% yield, respectively (entries 11 and 12). Also, amides possessing alkyl substituents α to the carbonyl reacted well under these conditions (entries 13 and 14). It is noteworthy that all of the amines were isolated by employing a simple acid−base extraction, thereby simplifying the purification step.

Table 3. Reduction of Secondary Amides to Amines



entry	amide		yield amine (%)[a]	
1		**1t** R=Br	**4b**	86
2		**1b** R=CN	**4c**	87
3		**1c** R=NO_2	**4d**	90
4		**1d** R=N_3	**4e**	89
5		**1e** R=CO_2Me	**4f**	90
6		**1h** R=$CONEt_2$	**4g**	90[b]
7		**1u** R=OMe	**4h**	81[c]
8		**1i**	**4i**	71
9		**1k**	**4j**	86
10		**1m**	**4k**	90
11		**1v**	**4l**	77
12		**1w**	**4m**	89
13		**1x**	**4n**	85
14		**1y**	**4o**	75

[a] Isolated yields. [b] Activation of the amide was done at −78 °C for 1 h, followed by −20 °C for 1 h, and 0 °C for 10 min. [c] 2.0 equiv of HEH was used instead of 1.4 equiv.

In summary, this work represents an integral and broad complement to the available and efficient tertiary amide reduction methods (*vide supra*). In that sense, general and chemoselective conditions were developed to control the reduction outcome of secondary amides to imine, aldehyde, and amine oxidation states. We expect this method to be useful in the total synthesis of more complex molecules by optimizing the step-economy in synthesis planning. Further efforts are ongoing to apply this reduction methodology to other carbonyl moieties, and the results will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for each reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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