Highly Chemoselective Reduction of Amides (Primary, Secondary, Tertiary) to Alcohols using SmI₂/Amine/H₂O under Mild Conditions

Michal Szostak,* Malcolm Spain,† Andrew J. Eberhart,† and David J. Procter*

School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, United Kingdom

Supporting Information

ABSTRACT: Highly chemoselective direct reduction of primary, secondary, and tertiary amides to alcohols using SmI₂/amine/H₂O is reported. The reaction proceeds with C–N bond cleavage in the carbinolamine intermediate, shows excellent functional group tolerance, and delivers the alcohol products in very high yields. The expected C–O cleavage products are not formed under the reaction conditions. The observed reactivity is opposite to the electrophilicity of polar carbonyl groups resulting from the nₓ → π*ₓ C=O (X = O, N) conjugation. Mechanistic studies suggest that coordination of Sm to the carbonyl and then to Lewis basic nitrogen in the tetrahedral intermediate facilitate electron transfer and control the selectivity of the C–N/C–O cleavage. Notably, the method provides direct access to acyl-type radicals from unactivated amides under mild electron transfer conditions.

The reduction of carboxylic acid derivatives is among the most important and valuable processes in organic chemistry.¹ In particular, the reduction of amides has captured much attention as a practical method for the synthesis of amines from bench-stable amide precursors.² Over the past decades, many reagents and conditions for this transformation have been reported,³ including recent breakthroughs in highly chemoselective⁴ and metal-free reductions.⁵ However, in contrast to the reduction of amides to amines, which typically proceeds via C–O bond cleavage in the tetrahedral intermediate, the development of practical methods for the reduction of amides to alcohols via selective C–N bond scission remains a formidable challenge (Figure 1).

Very few examples of the chemoselective reduction of amides to alcohols have been reported. Early studies by Brown and co-workers based on typical metal hydride reagents (B–H, Al–H) revealed that the selective C–N cleavage is in principle feasible; however, only one reagent (LiEt₃BH) and for only one class of substrates (aromatic N,N-dimethylamides) afforded appreciable C–N cleavage selectivity.⁴ Subsequently, the groups of Hutchins,⁵a Singaram,⁵b,c and Myers⁵d,e studied metal amide–borane complexes for the reduction of sterically unhindered tertiary amides to alcohols. However, this chemistry highlighted a number of limitations, including the low reactivity and/or C–O bond cleavage selectivity for the reduction of primary and secondary amides, inadequate functional group tolerance, and the use of pyrophoric organometallic reagents that decrease the practicality of these methods. Recently, considerable advancements using catalytic hydrogenation have been reported.⁶–⁸

Milstein and co-workers developed a reduction of secondary and tertiary amides to alcohols that employs a Ru pincer catalyst at elevated temperatures and high H₂ pressures (THF, 110 °C, 10 atm) and proceeds in excellent yields and C–N cleavage selectivity.⁶ Ikariya and Bergens⁷ reported hydrogenation of activated secondary and tertiary amides/lactams using Ru catalysts at high temperatures and H₂ pressures (100 °C, 50 atm). Additionally, Enthaler and co-workers reported a bimetallic Mo complex for the catalytic hydrosilylation of N-aryl tertiary amides with good C–N scission chemoselectivity.⁸ However, these reactions suffer from limited substrate scope and typically require highly specialized pressure tube and glovebox equipment, which limits their laboratory application. Moreover, primary and secondary amides are difficult substrates because of the presence of free NH bonds. To date, a general method for the reduction of amides to alcohols with high C–N bond cleavage chemoselectivity under mild and practical reaction conditions has not been reported despite the significance of this transformation for the synthesis of fundamental building blocks, such as alcohols, from bench-stable amide precursors.

Herein we report the first general, highly chemoselective reduction of amides to alcohols.

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using the SmI₂/amine/H₂O reducing system via a single electron transfer mechanism. The reaction proceeds with excellent C–N bond cleavage selectivity at room temperature under mild, operationally simple reaction conditions. Notably, this process constitutes the first general method for the synthesis of ketyl-type radicals from unactivated amides.

We recently reported the reduction of esters using SmI₂/amine/H₂O. This reagent system efficiently mediates the reduction of esters, lactones, and carboxylic acids under mild conditions via open-shell reaction pathways, which are orthogonal to the traditional closed-shell mechanisms. We sought to apply this chemistry to the reduction of unactivated amides. We started our investigation by screening the reactions sought to apply this chemistry to the reduction of unactivated amides a selectivity and yield (Table 1). Primary, secondary, and tertiary amides (entries 1-3) were reduced by SmI₂/amine/H₂O.12 This reagent system is orthogonal to the traditional closed-shell mechanisms.13 We found that radicals from unactivated amides generate and protonated by H₂O in a series of electron transfer steps.

Next, the substrate scope of the reaction was investigated with regard to substitution at the α carbon of the amide with the knowledge that there is an unmet need for the reduction of primary and secondary amides (cf. tertiary amides) to alcohols using existing hydride-mediated and hydrogenation methodologies (Table 2). Amides with increasing steric demand at the α carbon were suitable substrates for the reduction (entries 1–5), including a very hindered N,N-dimethyl adamantyl amide (entry 5). Aromatic amides could be reduced to the corresponding alcohols with excellent C–N cleavage selectivity (entries 6–8). The method is compatible with a broad range of functional groups, including terminal and internal amines (see the SI; isomerization of an internal cis olefin was not observed); aryl fluorides, chlorides, bromides; trifluoromethylenophenyl groups; aryl ethers; aromatic rings; and electron-rich heterocycles such as indoles (entries 9–16). In all cases, excellent selectivity for the C–N cleavage was observed. Furthermore, complex biologically active steroid scaffolds and drug molecules bearing unprotected alcohols and amines were subjected directly to the reaction conditions to afford the corresponding alcohols in high yields (entries 17 and 18). In contrast, acidic protons are not tolerated by the recently disclosed highly chemoselective methodologies (Table 2). Amides featuring substituents known to afford mixtures of C–N/C–O cleavage products with other reagents were amenable to the Sm(II) reduction protocol and that useful levels of chemoselectivity were obtained with these substrates (entries 13 and 14). We note, however, that N,N-disopropylamide was unreactive under our reaction conditions (entry 15).17

Alicyclic amides (Table 1, entries 6–8), including strained azetidine (entry 6) and aziridine (see the SI) substrates resulted in high selectivity for C–N cleavage. Several amides bearing a directing functionality were subjected to the reaction conditions to determine whether Sm(II) chelation could influence the C–N cleavage selectivity (entries 9–12). In all cases, only alcohol products were formed, suggesting that chelation does not override the inherent reaction pathway. We also found that amides featuring substituents known to afford mixtures of C–N/C–O cleavage products with other reagents were amenable to the Sm(II) reduction protocol and that useful levels of chemoselectivity were obtained with these substrates (entries 13 and 14). We note, however, that N,N-disopropylamide was unreactive under our reaction conditions (entry 15).

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Table 1. Reduction of Amides to Alcohols Using SmI₂

| entry | NR′R″ | yield (%) | selectivity |
|-------|-------|-----------|-------------|
| 1     | 1a    | NH₂       | 82          | >95:5       |
| 2     | 1b    | NH₅-Bu    | 89          | >95:5       |
| 3     | 1c    | NH₅-C₄H₇ | 88          | >95:5       |
| 4     | 1d    | NHP₅       | 84          | >95:5       |
| 5     | 1e    | NEt₃      | 82          | >95:5       |
| 6     | 1f    | N          | 98          | >95:5       |
| 7     | 1g    | n = 0     | 90          | >95:5       |
| 8     | 1h    | n = 2     | 81          | >95:5       |
| 9     | 1i    | N(O(OMe))Me | 97         | >95:5       |
| 10    | 1j    | 83        | >95:5       |
| 11    | 1k    | 79        | >95:5       |
| 12    | 1l    | 81        | >95:5       |
| 13    | 1m    | NHBO₂     | 92          | >95:5       |
| 14    | 1n    | 99        | >95:5       |
| 15    | 1o    | N(i-Pr)₂ | <5          | >95:5       |

Conditions: R = Ph(CH₂)₂, SmI₂ (8 equiv), THF, Et₃N, H₂O, 23 °C. See the SI for full experimental details.

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steps and that proton transfer is not involved in the rate-determining step of the reaction. (3) Control experiments using H$_2^{18}$O (2.59% $^{18}$O incorporation, primary amide; 4.19%, secondary amide; 14.20%, tertiary amide) showed that amide hydrolysis, or hydrolysis of an iminium intermediate, is not a predominant pathway. (4) Selectivity studies demonstrated the following order of amide reactivity: 1° > 2° > 3°. Moreover, >95:5 selectivity was obtained in the reduction of primary amides over esters and activated over aliphatic secondary amides. (5) A Hammett study performed using a series of 4-substituted 2-phenylacetamides showed a large positive $\rho$ value of 0.52 ($R^2 = 0.98$), which can be compared with the $\rho$ value of 0.49 for ionization of phenylacetic acids in H$_2$O at 25 °C. (6) The Taft correlation study, obtained by plotting $\log(k_{obs})$ versus $E$ for a series of N-alkyl-3-phenylpropanamides showed a large positive slope of 0.92 ($R^2 = 0.99$). The results from the Hammett and Taft studies are consistent with a mechanism involving Sm coordination to the substrate and buildup of partial negative charge on the carbon of the amide carbonyl.

Overall, these results are in agreement with a mechanism involving coordination of the azaphilic Lewis acid Sm to nitrogen either before or after the initial electron transfer. We postulate that the high chemoselectivity for C–N versus C–O cleavage results from the fact that a protonated hemiaminal is not formed in the reaction. Furthermore, collapse of the carbinolamine intermediate with selective C–N cleavage is likely promoted by the coordination of SmX$_3$ (X = I, OH) to the Lewis basic nitrogen (see Figure 1B).

In summary, the first general reduction of primary, secondary, and tertiary amides to alcohols using Sm$_2$/amine/H$_2$O has been developed. The reaction proceeds with high selectivity for C–N bond cleavage under mild and operationally simple reaction conditions. The mechanism involves reversible first electron transfer and electrophilic activation of the amide bond. This protocol demonstrates a broad substrate scope and provides the corresponding alcohols in excellent yields with chemoselectivity orthogonal to that of existing closed-shell processes. We fully expect that this method will be of great interest for the synthesis of functionalized alcohol-containing building blocks. Studies of the application of Sm(II) to chemoselective reductions and reductive cyclizations of functional groups are underway and will be reported shortly.

### Table 2. Substrate Scope in the Reduction of Amides to Alcohols Using SmI$_2$

| entry | 3 | amide | NR'R'' | yield (%) |
|-------|---|-------|--------|-----------|
| 1     | 3a | NHR' | NH$_2$ | 91        |
| 2     | 3b | NHR'' | NH$_2$ | 76        |
| 3     | 3c | NHR'' | NH$_2$ | 95        |
| 4     | 3d | NHR' | NH$_2$ | 86        |
| 5     | 3e | NHR'' | NEt$_3$ | 75       |
| 6     | 3f | NHR' | NH$_2$ | 93        |
| 7     | 3g | NHR'' | NEt$_3$ | 82      |
| 8     | 3h | X = MeO | NH$_2$ | 91     |
| 9     | 3i | X = H | NH$_2$ | 94        |
| 10    | 3j | X = H, NHR'' | NH$_2$ | 96     |
| 11    | 3k | X = F | NH$_2$ | 94        |
| 12    | 3l | X = Cl | NH$_2$ | 85        |
| 13    | 3m | X = Br, NH$_2$ | 63     |
| 14    | 3n | X = CF$_3$, NH$_2$ | 73     |
| 15    | 3o | X = MeO, NHR'' | NEt$_3$ | 84    |
| 16    | 3p | NHR' | NH$_2$ | 82        |
| 17    | 3q | Glycochomodesoxyacid sodium salt | R = CH$_3$CO$_2$Na | 79 |
| 18    | 3r | Anesoki | | 61 |

“Conditions: SmI$_2$ (4–8 equiv), THF, Et$_3$N, H$_2$O, 23 °C. See the SI for full experimental details.

### Scheme 1. Reduction of Enantioenriched Amides to Alcohols Using SmI$_2$

### Scheme 2. Studies Designed To Probe the Mechanism of the Reduction of Amides to Alcohols using SmI$_2$ (R', R'' = H; for R' = H, R'' = n-Bu and R', R'' = Et, See the SI)

#### A) Radical clock fragmentation

#### B) D$_2$O incorporation study

#### C) H$_2^{18}$O incorporation study
† david.j.procter@manchester.ac.uk
Corresponding Authors

ASSOCIATED CONTENT

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

AUTHOR INFORMATION

Corresponding Authors
michal.szostak@manchester.ac.uk
david.j.procter@manchester.ac.uk

Author Contributions
M. Spain and A. J. Eberhart contributed equally.

Notes
The authors declare no competing financial interest.

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