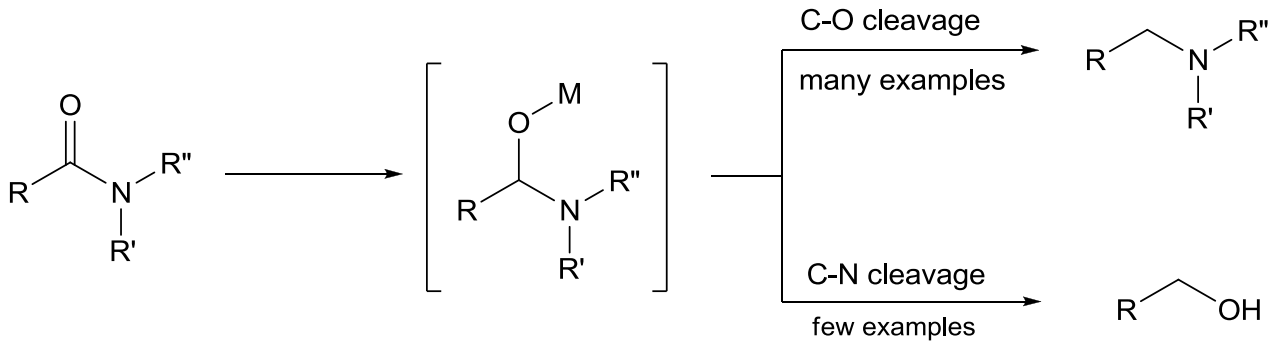
# Highly Chemoselective Reduction of Amides (Primary, Secondary, Tertiary) to Alcohols using $SmI_2$/Amine/$H_2O$ under mild conditions

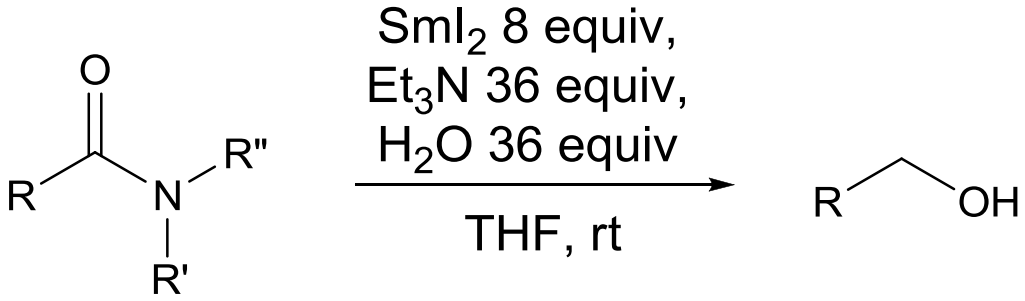
M. Szostak, M. Spain, A. J. Eberhart and D. Procter, *J. Am. Chem. Soc.*, **2014**, asap
Doi : 10.1021/ja412578t

# State of the art



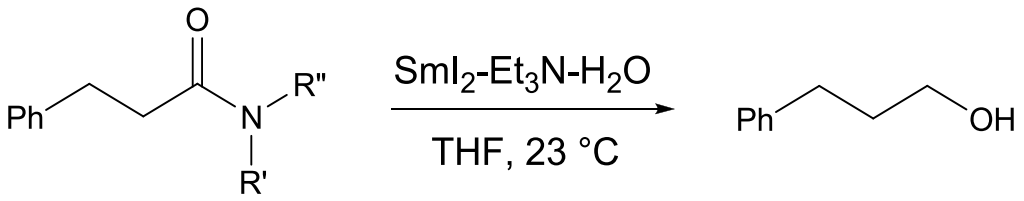

- Lots of examples involving C-O bond cleavage
- Few involving C-N bond cleavage
- C-N bond cleavage involves specifics substrates

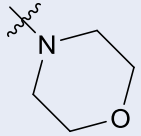
# Experiment design



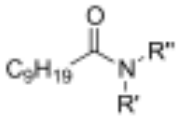
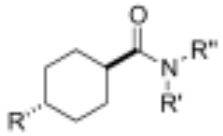
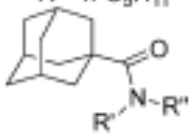
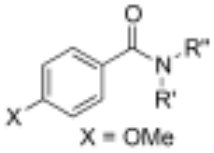
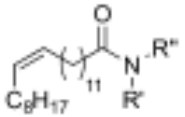
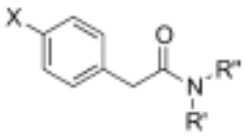
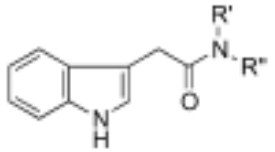
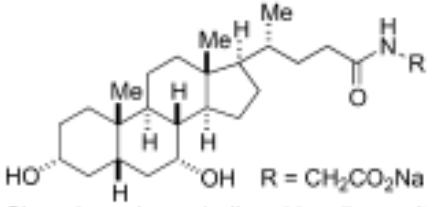
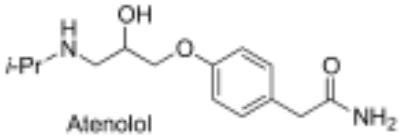

- Mild, operationnally conditions
- General method for primary, secondary, tertiary amides
- Excellent C-N bond cleavage selectivity

# Selected examples

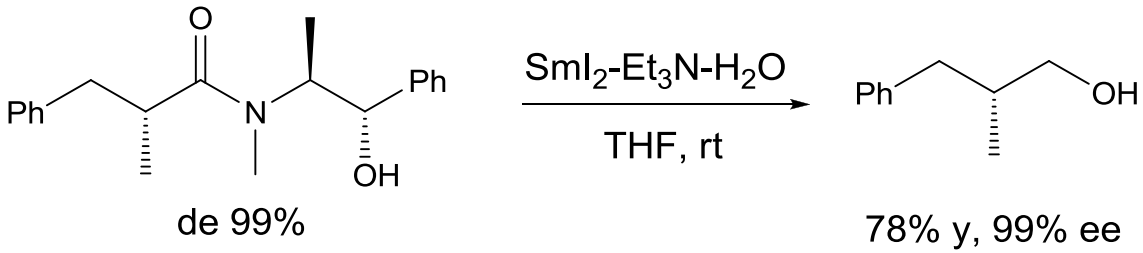



| Entry | NR'R" | Yield (%) | Selectivity |
|---|---|---|---|
| 1 | $NH_2$ | 82 | >95:5 |
| 2 | NH*n*-Bu | 89 | >95:5 |
| 3 | NHPh | 84 | >95:5 |
| 4 | $NEt_2$ | 82 | >95:5 |
| 5 | N(OMe)Me | 97 | >95:5 |
| 6 |  | 83 | >95:5 |
| 7 | N(*i*-Pr)$_2$ | <5 | >95:5 |

# Selected examples

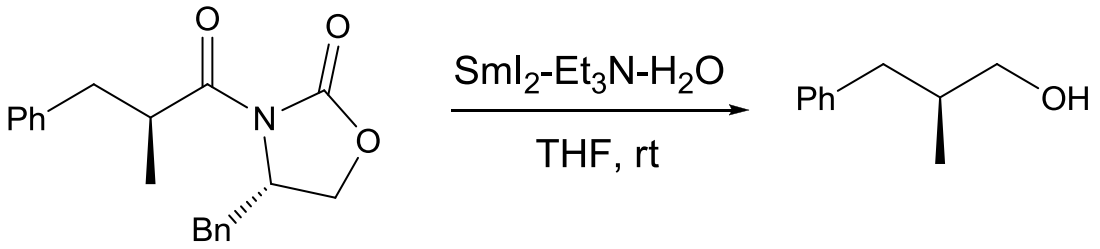
| entry | 3 | amide | NR'R" | yield (%) |
|---|---|---|---|---|
| 1 | 3a |  | $NH_2$ | 91 |
| 2 | 3b | | NH*n*-Bu | 76 |
| 3 | 3c |  R = *n*-$C_5H_{11}$ | $NH_2$ | 95 |
| 4 | 3d |  | $NH_2$ | 86 |
| 5 | 3e | | $NEt_2$ | 75 |
| 6 | 3f |  X = OMe | $NH_2$ | 93 |
| 7 | 3g | | NH*n*-Bu | 82 |
| 8 | 3h | | $NEt_2$ | 84 |
| 9 | 3i |  | $NH_2$ | 94 |
| 10 | 3j |  | X = H, NH*n*-Bu | 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, NH*n*-Bu | 91 |
| 16 | 3p |  | $NH_2$ | 82 |
| 17 | 3q |  Glycochenodeoxycholic acid sodium salt | R = $CH_2CO_2Na$ | 79 |
| 18 | 3r |  Atenolol | | 61 |

# Enantioselective pathway




de 99%

78% y, 99% ee

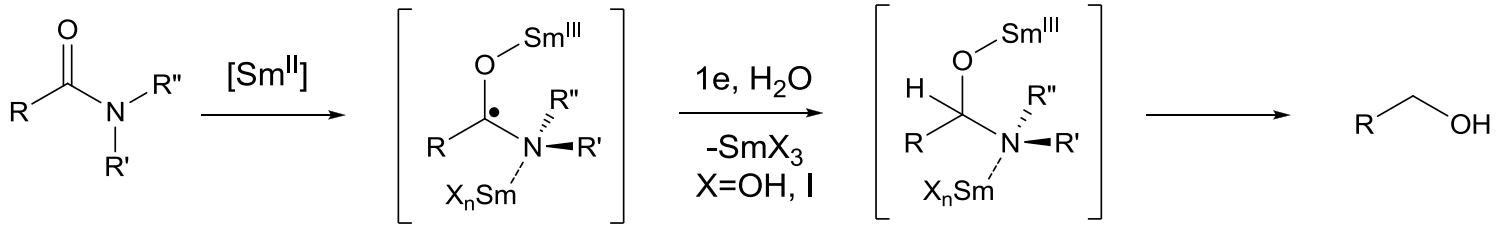



de 99%

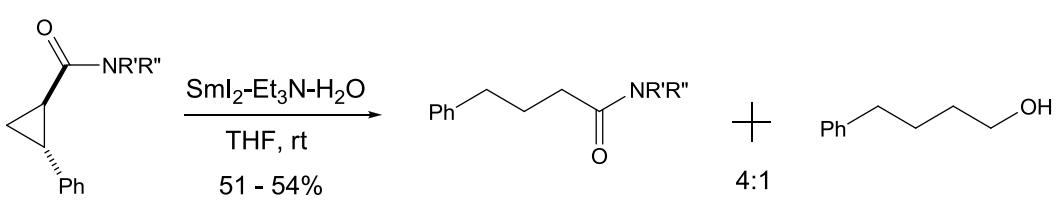
81% y, 99,5% ee

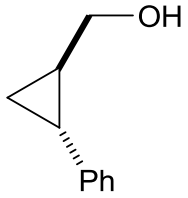
# Mechanistic studies

- Proposed mechanism




- Radical clock fragmentation

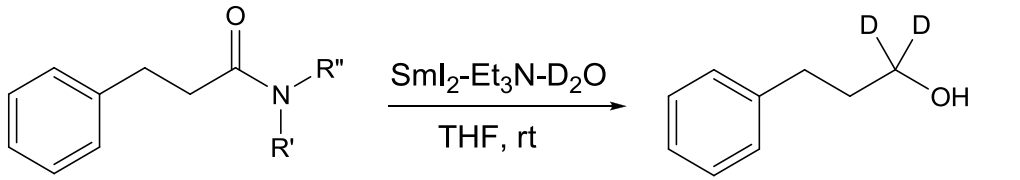



not detected

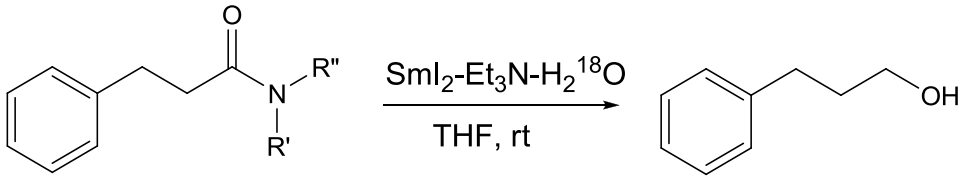
# Mechanistic studies

- $D_2O$ incorporation study




89%, 83 to 97 D incorp.

- $H_2{}^{18}O$ incorporation study




89%, 2 to 14% $^{18}O$ incorp.

# Conclusion

- General method to obtain alcohol from amide
- High yield and selectivity
- Large scope
- Mechanism to clarify

# Thank you for your attention