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Synthetic Methods

Direct Transformation of Secondary Amides into Secondary Amines: Triflic Anhydride Activated Reductive Alkylation**

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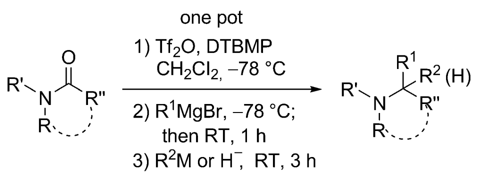
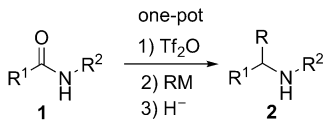
Amines are an important class of compounds that constitute the major body of bioactive natural products (alkaloids) and pharmaceuticals.[1] Amides are a class of easily available and highly stable compounds.[2] Consequently, the synthesis of amines by reductive alkylation of amides is of high relevance in organic synthesis,[3] and has been the focus of recent research.[4–6] The transformation of tertiary amides into amines has been achieved by indirect methods via thioamides.[4] Very recently, the direct transformation of tertiary amides into amines by reductive alkylation has been reported.[5,6] However, although the reductive mono- or diallylation of secondary lactams/amides[7,8] has been reported, a general method for the synthesis of secondary amines, with a variety of substituent patterns, has not yet been described. In addition, the secondary amide also serves as a powerful directing group in C–H activation.[9] Consequently, the development of a general and direct method for the transformation of secondary amides into secondary amines is highly desirable in synthetic organic chemistry.

As a continuation of our endeavour to develop step-economical syntheses,[10] we recently reported a direct method for the reductive alkylation of lactams/amides with Grignard and organolithium reagents (Scheme 1).[5] Herein, we report a one-pot synthesis of secondary amines by the reductive alkylation of secondary amides with organocerium reagents[11,12] using trifluoromethanesulfonic anhydride (Tf_2O)[13,14] as the activation reagent (Scheme 2).



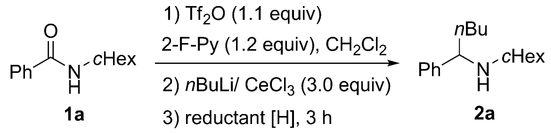
Scheme 1. One-pot transformation of tertiary amides into amines. Tf_2O = trifluoromethanesulfonic anhydride; DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.



Scheme 2. One-pot transformation of secondary amides into secondary amines.

The conversion of *N*-cyclohexylbenzamide **1a** into amine **2a** was chosen as a prototype reaction (Table 1). A CH_2Cl_2 solution of amide **1a** and 2-fluoropyridine[13j] (2-F-Py, 1.2 equiv) was successively treated with 1.1 molar equivalents of Tf_2O (−78 °C, then 0 °C), 3.0 molar equivalents of RM/$CeCl_3$ (−78 °C), and a reducing agent. It was found that triethylsilane was inactive in this reaction (Table 1, entry 1), while lithium aluminum hydride (Table 1, entry 2) and sodium borohydride (Table 1, entry 3) worked well to provide the desired amine in good yield. $NaBH_4$ was selected as the reducing agent as it is cheaper, less hazardous, and more easily handled than $LiAlH_4$. Moreover, the addition of methanol was found to accelerate the reaction (Table 1, entries 4 and 5). Thus, the optimized protocol for the direct conversion of secondary amides into amines was identified as successive treatment of a dichloromethane solution of amide and 2-fluoropyridine (1.2 equiv) with 1.1 molar equivalents of Tf_2O (−78 °C, then 0 °C), and 3.0 molar equivalents of RM/

Table 1: Influence of the reducing agent on the reductive alkylation of secondary amides.



Entry	Reductant [H]	Equiv	Yield[%][a]
1	Et_3SiH	3.0	no product
2	$LiAlH_4$	3.0	86
3	$NaBH_4$	3.0	75
4	$NaBH_4$, MeOH	3.0	87
5	$NaBH_4$, MeOH	2.0	88

[a] Yield of the isolated product. 2-F-Py = 2-fluoropyridine; *c*Hex = cyclohexyl.

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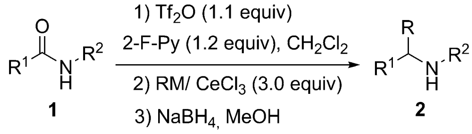
$CeCl_3$ (−78 °C), followed by reduction with 2.0 molar equivalents of $NaBH_4$ in methanol.

Under these optimized reaction conditions, the scope of this transformation was studied. As can be seen from Table 2, a variety of secondary amides, including aroyl (Table 2, entries 1–12), alkanoyl (Table 2, entries 13–19), and alkenoyl (Table 2, entry 20) amides, were transformed into the corresponding secondary amines in good to excellent yields. The substituents on the nitrogen atom of the secondary amides did not have much influence on the reaction efficiency, regardless

Table 2: Direct transformation of secondary amides **1** into amines **2**.



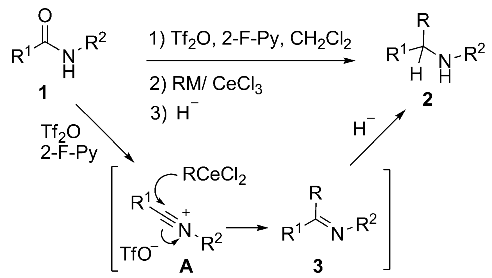
Entry	Substrate	RM	Product (Yield [%])[a]	Entry	Substrate	RM	Product (Yield [%])[a]
1	**1a**	*n*BuLi	**2a** (88)	11	**1g**	*n*BuMgBr	**2j** (84)
2	**1a**	*i*PrMgBr	**2b** (84)	12	**1h**	*n*BuMgBr	**2k** (79)
3	**1a**	PhMgBr	**2c** (82)	13	**1i**	*n*BuMgBr	**2l** (89)
4	**1a**	Ph—≡—Li	**2d** (79)	14	**1j**	*n*BuMgBr	**2m** (90)
5	**1b**	*n*BuLi	**2e** (86)	15	**1k**	*n*BuMgBr	**2n** (64)
6	**1b**	*n*BuMgBr	**2e** (91)	16	**1l**	*n*BuLi	**2o** (82)
7	**1c**	*n*BuMgBr	**2f** (85)	17	**1l**	BnMgBr	**2p** (84)
8	**1d**	*n*BuLi	**2g** (75)	18	**1m**	*n*BuMgBr	**2q** (76)
9	**1e**	*n*BuLi	**2h** (68)	19	**1n**	BnMgBr	**2r** (81)
10	**1f**	*n*BuMgBr	**2i** (81)	20	**1o**	*n*BuMgBr	**2s** (75)

[a] Reaction conditions: 1) amide (1.0 mmol), 2-fluoropyridine (1.2 mmol), Tf2O (1.1 mmol), CH2Cl2 (4 mL), −78 °C, then 0 °C, 10 min; 2) RM/CeCl3 (3.0 mmol), −78 °C, 1 h; 3) NaBH4 (2.0 mmol), MeOH (5 mL), RT, 3 h. [b] Yield of the isolated product. Bn = benzyl.

of their identity: *n*-alkyl (Table 2, entries 5–7, 11–13, 15, 18–20), *sec*-alkyl (Table 2, Table 2, entries 1–4, 8–10, 16–17), or aryl (Table 2, entry 14). The reaction also went smoothly with hindered amides, such as **1m** (Table 2, entry 18). Functional groups such as an ether (Table 2, entry 9), an aromatic bromide (Table 2, entry 10), thiophene (Table 2, entry 12), a terminal C=C double bond (Table 2, entry 19), and a conjugated C=C double bond (Table 2, entry 20) were well tolerated. It should be noted that the reaction of α,β-unsaturated amides led to a highly selective 1,2-addition (Table 2, entry 20).

With regard to the organocerium reagents, alkyl (Table 2, entries 1, 2, 5–16, 18, 20), benzyl (Table 2, entries 17 and 19), aryl (Table 2, entry 3), and alkynyl (Table 2, entry 4) cerium reagents, generated from either organolithiums or Grignard reagents, worked well for the direct conversion of secondary amides into secondary amines.

A plausible mechanism for the direct transformation of secondary amides **1** into secondary amines **2** is shown in Scheme 3. The reaction may involve the formation of the highly electrophilic nitrilium ion intermediate **A**[11] upon the action of Tf_2O/2-fluoropyridine (2-F-Py). Trapping of the nitrilium ion **A** with an organocerium reagent ($RM/CeCl_3$) forms ketimine **3**,[15] which upon further reduction gives the corresponding secondary amine.



Scheme 3. Proposed reaction mechanism.

In summary, the first general method for the direct transformation of secondary amides into secondary amines with different substituent patterns has been developed. The significance and advantages of the method are: 1) the method is general, allowing the introduction of a variety of substituents; 2) organocerium reagents with high nucleophilicity yet attenuated basicity are used as the alkylating reagents, and are generated in situ from either Grignard reagents and organolithium reagents; 3) both $LiAlH_4$ and $NaBH_4$ can be used as the reducing reagent; 4) the ketimines **3** can also be isolated.[15] Considering the broad spectrum of bioactivities exhibited by amines, along with the high stability, easy availability, and versatile uses of the secondary amide reactants, this versatile and mild method should find application in the synthesis of *N*-containing bioactive molecules and medicinal agents.

Experimental Section

General procedure for the direct transformation of secondary amides **1** into secondary amines **2**. Tf_2O (185 μL, 1.1 mmol, 1.1 equiv) was added dropwise to a cooled (−78 °C) solution of amide **1** (1.0 mmol, 1.0 equiv) and 2-fluoropyridine (103 μL, 1.2 mmol, 1.2 equiv) in dichloromethane (4 mL). The reaction was warmed to 0 °C in an ice bath and stirred for 10 min. The mixture was then cannulated into freshly prepared organocerium reagent (3.0 mmol, 3.0 equiv) in THF (15 mL) at −78 °C and stirred for 1 h. Methanol (5 mL) and sodium borohydride (76 mg, 2.0 mmol) were added. The reaction mixture was warmed to RT and stirred for 3 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with 5–10 % ethyl acetate in *n*-hexane) to afford the desired amine **2**.

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[15] Ketimines **3a–3d** were isolated and characterized (see the Supporting information for details).

