Protecting Groups

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Microwave-Assisted Deacylation of Unactivated Amides Using Ammonium-Salt-Accelerated Transamidation**

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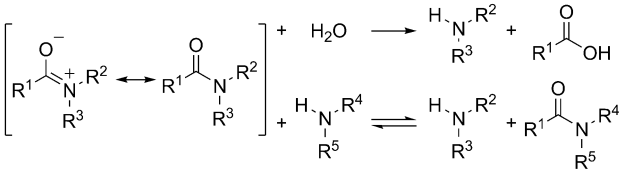
Amines are ubiquitous organic molecules in natural products and pharmaceuticals[1] and efficient synthesis of amines is an important topic in synthetic organic chemistry. Recent efforts to streamline organic synthesis favors the use of unprotected molecules in synthetic protocols,[2] but amine protection is still a reliable way to obtain satisfactory yields of the desired products and unprotected amines are often too reactive to avoid undesired reactions such as oxidation of amines.

Acyl groups are one of the most useful amine protecting groups because of their ability to reduce the nucleophilicity of amines and to prevent undesired side reactions.[3] Such acylated amines (amides) are well utilized in asymmetric hydrogenation of enamides[4] and kinetic resolutions,[5] and the acyl group is often essential for obtaining optically active amines with excellent enantioselectivity. Acylated amines were recently used in C–H activation reactions, in which acyl groups served as an efficient directing group.[6] Although the synthesis and application of acylated amines has attracted much attention, removal of the acyl groups from the amines, that is, amide bond cleavage, has generally not been explored in detail. Amide bonds are chemically robust because of the delocalization of the electrons across the amide, and thus classical hydrolysis of amides generally requires harsh reaction conditions, that is, strong acids or bases at high temperature (Scheme 1, top).[3] Such harsh reaction conditions limit the synthetic potential of acylated amines in terms of the compatibility of their functional groups. Methods to remove acyl groups from amides below room temperature have been developed to overcome this limitation, but stoichiometric amounts of moisture-sensitive reagents (oxalyl chloride and triphenyl phosphite chlorine complex) are required to activate the amides, and the reaction must be performed under anhydrous conditions.[7] Enzymatic methods, in which neutral reaction conditions can be used, are another option, but the high substrate specificity is limiting.[8]



Scheme 1. Deacylation of amides to amines.

Transamidation is the process of transferring an acyl group from one amine to another (Scheme 1, bottom).[9] This process can be considered amide deacylation to give deprotected amines. Because amines are more nucleophilic than water, transamidation could potentially be performed under less harsh reaction conditions than hydrolysis, and thus may be a good alternative for the deprotection of acylated amines. Despite its high potential to cleave amide bonds with the aid of amine nucleophiles, transamidation is thought to be difficult to apply for the deacylation of amides because: 1) traditional transamidation often requires a high temperature because robust amide bonds are cleaved in the processes, 2) transamidation is an equilibrium process which provides a mixture of the starting material and product thus requiring appropriate reaction conditions, and 3) separation of the liberated amines from the reaction mixture, including the starting amine, is difficult due to the similar chemical properties of the amines. Although recent efforts addressed some of these problems, the resulting transamidations were mostly limited to the reactions of either primary amides, to give secondary or tertiary amides with the concomitant liberation of ammonia, or an intramolecular variant, with the release of ring strains.[10] Among them, Gellman, Stahl, and co-workers reported aluminum or zirconium amide catalyzed intermolecular transamidations of secondary and tertiary amides, and some even proceeded at ambient temperature.[11] Most of the reactions using metal amide catalysts, however, provide equilibrium mixtures of starting materials and products. In addition, the metal amide complexes are highly basic and sensitive to acidic functionalities, which limits their substrate scope. Thus, practical application of transamidation for the deacylation of amides to amines requires further development. Herein, we report microwave-assisted transamidation for deacylation of unactivated amides to produce a variety of amines using readily available ammonium salts with ethylenediamine.

We began our investigation of deacylation reactions on the basis of our recent findings in platinum-catalyzed direct amination of allylic alcohols.[12] Under reaction conditions for the direct allylation of amines, transamidation of *N*,*N*-dimethylformamide (DMF) with alkylamine proceeded to produce dimethylamine as a side product. Thus, we next evaluated the effective reaction conditions for transamidation. Using *N*-acetylbenzylamine (**1a**) and pentylamine (**2a**)

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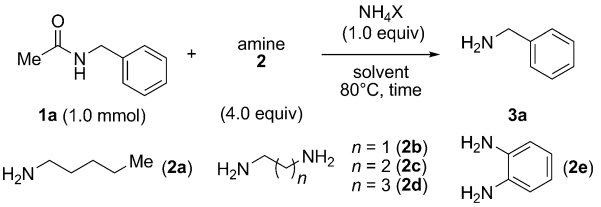
as model substrates, we screened various catalysts and reagents[13] and eventually found that an ammonium salt, a potential side product generated from $PtCl_2$ and amine during the generation of Pt^0, promoted transamidation to give the deprotected benzylamine (**3a**), albeit in low yield (Table 1, entry 1). Ammonium salt mediated or catalyzed transamidations of primary amides to secondary and tertiary

Table 1: Optimization of reaction conditions for deacylation.



Entry	Amine **2**	NH_4X	Solvent	*t* [h]	Yield [%][a]
1	**2a**	NH_4Cl	none	18	7
2	**2b**	NH_4Cl	none	18	29
3	**2c**	NH_4Cl	none	18	10
4	**2d**	NH_4Cl	none	18	8
5	**2e**	NH_4Cl	none	18	n.d.[b]
6	**2b**	NH_4Cl	EtOH	18	22
7	**2b**	NH_4Cl	toluene	18	12
8	**2b**	NH_4Br	none	18	36
9	**2b**	NH_4I	none	18	37
10	**2b**	nBu_4NBr	none	18	n.d.[b]
11[c]	**2b**	NH_4Br	none	5	90 (90)[d]
12	**2b**	NH_4Br	none	5	18
13[e]	**2b**	NH_4Br	none	24	87
14[c]	**2b**	none	none	5	n.d.[b]

[a] Yield was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Not detected. [c] Reaction was performed under microwave irradiation. [d] Yield of isolated product. [e] Reaction was performed at 100 °C.

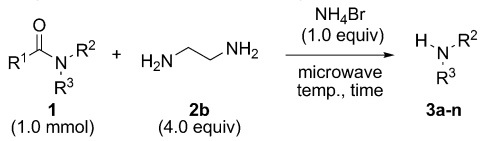
amides were previously reported,[9d,10b] but, in contrast to our results shown in entry 1 of Table 1, there was no transamidation of the secondary amides. We next optimized the reaction conditions.[13] First, several diamines having different chain lengths (**2b–d**) were examined for their ability to act as a nucleophile, and ethylenediamine (**2b**) was the most effective (entries 2–4),[14] whereas the less nucleophilic *o*-phenylenediamine (**2e**) was not effective (entry 5). The reaction also proceeded in either toluene or ethanol as the solvent, albeit in lower yields (entries 6 and 7). Examination of ammonium salts revealed that NH_4Br was more effective than NH_4Cl, and NH_4I was more effective than NH_4Br (entries 8 and 9). Although NH_4I gave the highest yield, we selected NH_4Br because it is nonhygroscopic and easy to handle. The acidic protons of the ammonium salt were essential because no reaction occurred with tetrabutylammonium bromide (entry 10). Finally, to accelerate the reaction, we examined the effect of microwave irradiation[15] and found that the reaction proceeded quite efficiently to give **3a** after a much shorter reaction time in 90% yield upon isolation (entry 11), compared to the conventional heating conditions (entry 12).[16] A comparable yield was obtained under conventional heating conditions at 100 °C for 24 hours (entry 13). No reaction occurred without the addition of the ammonium salt, even under microwave irradiation conditions (entry 14), thus clearly indicating that the ammonium salt was essential for achieving the high reactivity required for transamidation. Furthermore, isolation of the amine **3a** can be realized with an extractive workup because excess ethylenediamine (**2b**) and other side products are soluble in the aqueous layer.

With the optimized reaction conditions in hand, we first examined the scope of structurally different acylated aliphatic amines (Table 2). Various acylated primary amines (**1a–h**) were deprotected to afford the corresponding amines **3a–h** in good yield upon isolation (entries 1–10). The efficiency of this reaction was not affected by air and moisture (entry 1). It is noteworthy that a catalytic amount of NH_4Br was also effective to give amine **3a** in 84% yield (entry 2). In the case of the amide **1b**, a typical product in asymmetric hydrogenation of enamides and kinetic resolutions,[4,5] the reaction could be used on a 10 mmol scale without difficulty (entry 4). Unprotected indole (entry 6) and phenol (entry 7) moieties were tolerated under the reaction conditions, and tryptamine (**3d**) and tyramine (**3e**) were obtained in 81 and 98% yield, respectively. In addition to the acetyl group, the propionyl, chloroacetyl, and benzoyl groups in **1f–h** were reacted to afford amines in high yields (entries 8–10). Amides derived from secondary amines (**1i–n**) also reacted to give amines **3i–n** in good yield (entries 11–16). It is noted that a 2-pyridinecarbonyl group, a directing group in C–H functionalization reactions,[6] was efficiently removed at 60 °C after 5 hours (entry 14). Formyl and trifluoroacetyl amides of sterically congested dibenzylamine smoothly reacted to afford the product **3m** in 97 and 86% yield (entries 15 and 16).

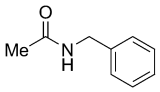
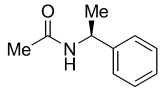
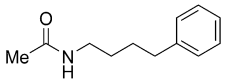
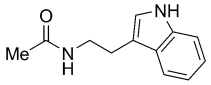
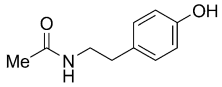
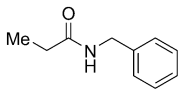
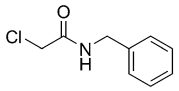
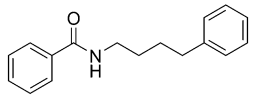
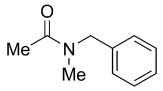
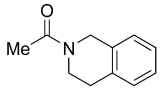
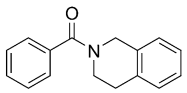
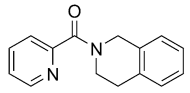
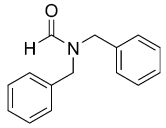
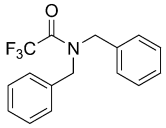
The reaction conditions were next applied to the deprotection of a variety of functionalized anilides (**4**; Table 3). Anilides with both electron-donating groups (entries 1 and 2) and electron-withdrawing groups (entries 3–5) were good substrates under the reaction conditions. Functional group compatibility was next examined in detail. Protic functionalities, such as phenol (entry 6), alcohol (entry 7), and even an unprotected carboxylic acid (entry 8), were compatible under the reaction conditions to provide the desired anilines **5f–h** in high yield. Moreover, acid-labile MOM (entry 9), MEM (entry 10), and THP (entry 11) protecting groups, and base-labile TIPS and TBS groups (entries 12 and 13) were tolerated under the reaction conditions. Notably, reactions of **4l** and **4m** under conventional acidic or basic hydrolysis conditions afforded mainly undesired products with concomitant removal of the silyl groups, thus suggesting the superiority of our system.[13] Nitrogen-containing functionalities such as *p*-toluenesulfonamide (entry 14) and imidazole (entry 15) were also tolerated.

To demonstrate the utility of the current deacylation method, we examined reactions of several key acylated amine intermediates obtained from recent valuable catalytic reactions (Scheme 2). Our results indicated that deprotection of *N*-acetyl-1-(1-naphthyl)ethylamine (**1o**), which was obtained from rhodium-catalyzed asymmetric hydrogenation of enamides,[17] proceeded smoothly to give amine **3o**, a key component of Cinacalcet[18] which is used for the treatment of

Table 2: Scope of amides derived from aliphatic amines.

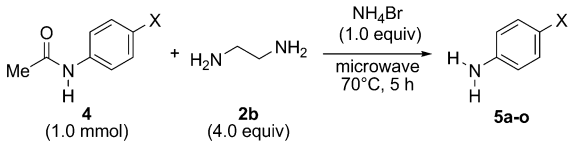


1 (1.0 mmol) + **2b** (4.0 equiv) → **3a-n**

Entry	Amide **1**		*T* [°C]	*t* [h]	Yield [%][a]
1[b]		**1a**	80	5	87
2[c]		**1a**	90	10	84
3		**1b**	80	10	93
4[d]		**1b**	80	10	94
5		**1c**	80	5	89
6		**1d**	80	5	81
7		**1e**	80	5	98
8		**1f**	80	5	88
9		**1g**	50	5	87
10		**1h**	90	10	81
11		**1i**	80	10	95
12		**1j**	70	5	>99
13		**1k**	90	5	94
14		**1l**	60	5	91
15		**1m**	80	10	97
16		**1n**	50	3	86

[a] Yield of isolated products. [b] Reaction was performed under air in the presence of 1.0 equivalent of H_2O. [c] 10 mol% of NH_4Br were used. [d] Reaction was performed on a 10 mmol scale.

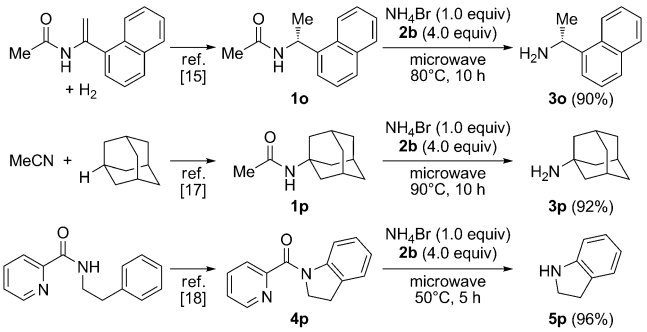
Table 3: Scope of functionalized acetanilide derivatives.



4 (1.0 mmol) + **2b** (4.0 equiv) → **5a-o**

Entry	Acetanilide **4**	Yield [%][a]
1	**4a**: X = OMe	>99
2	**4b**: X = NH_2	>99
3	**4c**: X = F	97
4	**4d**: X = Cl	>99
5	**4e**: X = Br	96
6	**4f**: X = OH	>99
7	**4g**: X = CH_2OH	84
8	**4h**: X = COOH	81
9	**4i**: X = OMOM	99
10	**4j**: X = CH_2OMEM	89
11	**4k**: X = CH_2OTHP	93
12	**4l**: X = CH_2OTIPS	83
13	**4m**: X = CH(Me)OTBS	78
14	**4n**: X = CH_2NHTs	92
15	**4o**: X = CH_2(1-imidazolyl)	94

[a] Yield of isolated product. MOM = methoxymethyl, MEM = (2-methoxyethoxy)methyl; THP = 2-tetrahydropyranyl, TIPS = triisopropylsilyl, TBS = *tert*-butyldimethylsilyl, Ts = *p*-toluenesulfonyl.



Scheme 2. Application to deacylation of important amides.

secondary hyperparathyroidism, in 90% yield. The current method was also applicable to deacylation of sterically congested *N*-acetylamantadine (**1p**)[19] and *N*-(2-*p*yridinecarbonyl)indoline (**4p**),[20] products from catalytic C–H bond functionalization reactions, to give amantadine (**3p**) and indoline (**5p**) in 93 and 96% yield, respectively.

In summary, we developed microwave-assisted transamidation for the deacylation of unactivated amides to generate amines. The reactions proceed at 50–90°C with readily available ammonium salts and ethylenediamine as reagents without special care regarding air and moisture. This method is applicable to a variety of acylated amines and compatible with a wide range of functional groups, including unprotected carboxylic acids, phenols, alcohols, and indoles, as well as acid-labile MOM, MEM, and THP groups, and base-labile TIPS and TBS groups. Understanding the detailed reaction mechanism, its application to the synthesis of important

molecules, and further improvement of the reaction efficiency are currently underway in our laboratory.

Experimental Section

General procedure for deacylation of unactivated amides to amines: Ammonium bromide (1.0 mmol), acylated amine **1** (1.0 mmol), and ethylenediamine **2b** (4.0 mmol) were added to 10 mL glass test tube equipped with a magnetic stir bar, and the tube was sealed with a cap. The test tube was heated with stirring at the indicated temperature and time under microwave-irradiation conditions. The crude reaction mixture was diluted with dichloromethane and the deprotected amine was extracted with 1M aqueous HCl solution. The aqueous layer was basified with 1M aqueous NaOH solution and back-extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and evaporated to give the amine **3**.

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Keywords: amides · amine · microwave chemistry · protecting groups · synthetic methods

[1] a) P. M. Dewick in *Medicinal Natural Products*: *A Biosynthetic Approach*, *3rd ed.*, Wiley, West Sussex, **2009**, pp. 311–484; b) D. J. Mack, M. Brichacek, A. Plichta, J. T. Njardarson, *Top 200 Pharmaceutical Products by Worldwide Sales in 2009.* http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster. **2012**, Retrieved Mar. 24, **2012**.

[2] a) W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976; b) I. S. Young, P. S. Baran, *Nat. Chem.* **2009**, *1*, 193.

[3] a) P. G. M. Wuts, T. W. Greene, *Protective Groups in Organic Synthesis*, *4th ed.*, Wiley-Interscience, Hoboken, **2006**, pp. 773–789; for the stability of amide bonds, see: b) W. Mabey, T. Mill, *J. Phys. Chem. Ref. Data* **1978**, *7*, 383.

[4] a) K. Gopalaiah, H. B. Kagan, *Chem. Rev.* **2011**, *111*, 4599; b) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713; c) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753.

[5] a) E. Busto, V. Gotor-Fernández, V. Gotor, *Chem. Rev.* **2011**, *111*, 3998; b) C. E. Müller, P. R. Schreiner, *Angew. Chem.* **2011**, *123*, 6136; *Angew. Chem. Int. Ed.* **2011**, *50*, 6012; c) H. Pellissier, *Adv. Synth. Catal.* **2011**, *353*, 1613.

[6] a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; b) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; c) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; d) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074.

[7] a) S. G. Koenig, C. P. Vandenbossche, H. Zhao, P. Mousaw, S. P. Singh, R. P. Bakale, *Org. Lett.* **2009**, *11*, 433; b) A. Spaggiari, L. C. Blaszczak, F. Prati, *Org. Lett.* **2004**, *6*, 3885.

[8] For example, see: a) E. Busto, V. Gotor-Fernández, V. Gotor, *Chem. Soc. Rev.* **2010**, *39*, 4504; b) H. K. Chenault, J. Dahmer, G. M. Whitesides, *J. Am. Chem. Soc.* **1989**, *111*, 6354.

[9] For reviews, see: a) M. E. González-Rosende, E. Castillo, J. Lasri, J. Sepúlveda-Arques, *Prog. React. Kinet. Mech.* **2004**, *29*, 311; b) M. B. Smith, J. March, in *March's Advanced Organic Chemistry*, *5th ed.*, Wiley-Interscience, New York, **2001**, p. 503. For selected earlier examples of transamidation, see: c) E. Bon, D. C. H. Bigg, G. Bertrand, *J. Org. Chem.* **1994**, *59*, 4035; d) A. Galat, G. Elison, *J. Am. Chem. Soc.* **1943**, *65*, 1566.

[10] For selected recent examples, see: a) M. Zhang, S. Imm, S. Bähn, L. Neubert, H. Neumann, M. Beller, *Angew. Chem.* **2012**, *124*, 3971; *Angew. Chem. Int. Ed.* **2012**, *51*, 3905; b) C. L. Allen, B. N. Atkinson, J. M. Williams, *Angew. Chem.* **2012**, *124*, 1412; *Angew. Chem. Int. Ed.* **2012**, *51*, 1383; c) P. Starkov, T. D. Sheppard, *Org. Biomol. Chem.* **2011**, *9*, 1320; d) T. A. Dineen, M. A. Zajac, A. G. Myers, *J. Am. Chem. Soc.* **2006**, *128*, 16406; e) S. Çalimsiz, M. A. Lipton, *J. Org. Chem.* **2005**, *70*, 6218; f) A. Klapars, S. Parris, K. W. Anderson, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 3529; g) A. Vasudevan, C. I. Villamil, S. W. Djuric, *Org. Lett.* **2004**, *6*, 3361; h) J. Lasri, M. E. Gonzalez-Rosende, J. Sepulveda-Arques, *Org. Lett.* **2003**, *5*, 3851.

[11] a) N. A. Stephenson, J. Zhu, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc.* **2009**, *131*, 10003; b) J. M. Hoerter, K. M. Otte, S. H. Gellman, Q. Cui, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 647; c) D. A. Kissounko, J. M. Hoerter, L. A. Guzei, Q. Cui, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc.* **2007**, *129*, 1776; d) J. M. Hoerter, K. M. Otte, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 5177; e) D. A. Kissounko, L. A. Guzei, S. H. Gellman, S. S. Stahl, *Organometallics* **2005**, *24*, 5208; f) S. E. Eldred, D. A. Stone, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc.* **2003**, *125*, 3422.

[12] a) T. Ohshima, Y. Miyamoto, J. Ipposhi, Y. Nakahara, M. Utsunomiya, K. Mashima, *J. Am. Chem. Soc.* **2009**, *131*, 14317. See also: b) K. Das, R. Shibuya, Y. Nakahara, N. Germain, T. Ohshima, K. Mashima, *Angew. Chem.* **2012**, *124*, 154; *Angew. Chem. Int. Ed.* **2012**, *51*, 150; c) M. Utsunomiya, Y. Miyamoto, J. Ipposhi, T. Ohshima, K. Mashima, *Org. Lett.* **2007**, *9*, 3371.

[13] See the Supporting Information for full details.

[14] Preformed HCl salts of **2b** gave comparable results (31–33% yield), thus suggesting that ammonium salts of **2b** are the active species.[13]

[15] a) M. A. Herrero, J. M. Kremsner, C. O. Kappe, *J. Org. Chem.* **2008**, *73*, 36; b) B. A. Roberts, C. R. Strauss, *Acc. Chem. Res.* **2005**, *38*, 653; c) B. L. Hayes, *Aldrichimica Acta* **2004**, *37*, 66.

[16] Although it is possible that the internal temperature of the closed reaction vessel, as measured externally, we performed a reaction in an open vessel with a microfiber thermometer inserted in the reaction mixture and obtained a comparable result (85% yield) under otherwise identical reaction conditions.[13]

[17] T. Imamoto, K. Tamura, Z. Zhang, Y. Horiuchi, M. Sugiya, K. Yoshida, A. Yanagisawa, I. D. Gridnev, *J. Am. Chem. Soc.* **2012**, *134*, 1754.

[18] O. Thiel, C. Bernard, R. Larsen, M. J. Martinelli, M. T. Raza, WO2009/002427 A2, **2008**.

[19] Q. Michaudel, D. Thevenet, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 2547.

[20] a) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3; b) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7.

Communications

Protecting Groups

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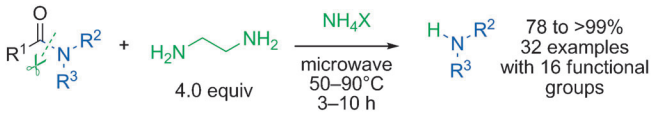
Microwave-Assisted Deacylation of Unactivated Amides Using Ammonium-Salt-Accelerated Transamidation



The combination of an ammonium salt and ethylenediamine promotes deacylation of a variety of unactivated amides to give the corresponding amines in high yields without the use of strong acids or bases. The reactions proceed without special care regarding air and moisture, and tolerate a wide range of functional groups.