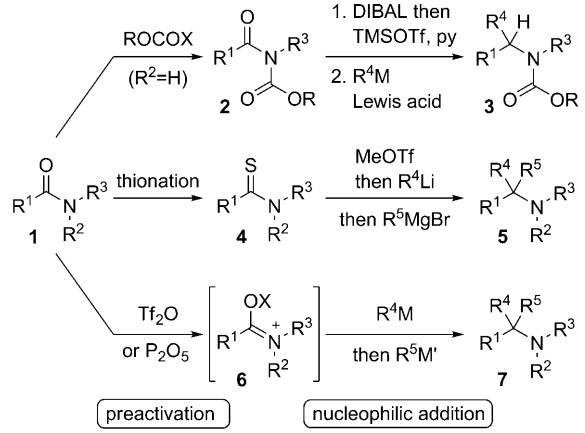
Synthetic Methods

DOI: 10.1002/anie.201001127

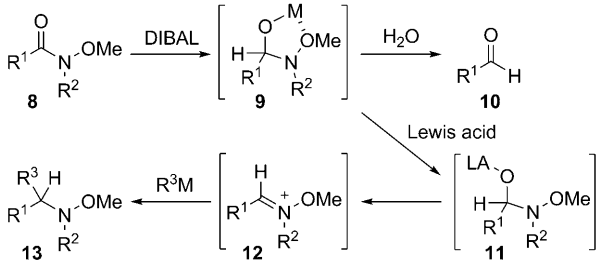
A Direct Entry to Substituted *N*-Methoxyamines from *N*-Methoxyamides via *N*-Oxyiminium Ions**

Kenji Shirokane, Yusuke Kurosaki, Takaaki Sato, and Noritaka Chida**

Amide functional groups play a significant role in a variety of areas such as medicinal drugs and chemical fibers. Therefore, the efficient synthesis of amide bonds has received much attention by organic chemists, making this one of the most reliable reactions in synthetic organic chemistry.[1] On the other hand, functionalization of the generated amide carbonyl groups is less explored than their construction. Amide carbonyl groups could potentially accept two organometallic reagents to furnish multisubstituted amines. However, direct nucleophilic addition requires harsh reaction conditions because of the high stability of amide carbonyl units.[2–6] The substrate scope is limited, and it is especially challenging to functionalize acyclic amides and macrolactams because of the instability of intermediates, which readily undergo hydrolysis. To overcome their inertness and poor substrate scope, preactivation of amides has been employed prior to nucleophilic addition (Scheme 1). The research groups of DeNinno[7] and Suh[8] independently reported efficient strategies that install acyl groups to give acyclic imides (**1**→**2**). In Suh's method, formation of an *N*,*O*-acetal TMS ether, and subsequent Lewis acid promoted nucleophilic addition gave **3** via acyclic *N*-acyliminium ions. Thionation of amide carbonyl groups is another practical approach (**1**→**4**).[9,10] Murai et al. demonstrated sequential reactions of acyclic thionium salts with organolithium and Grignard reagents (**1**→**4**→**5**).[10] A classical method, involving activation of acyclic amides with dehydrating reagents (Tf_2O, P_2O_5, etc.), has been widely used such as in the Bischler–Napieralski and Vilsmeier–Haack reactions (**1**→**6**→**7**).[11] Very recently, Huang and co-workers reported sequential addition to amides via iminium triflate intermediate **6**.[11d]



Scheme 1. Selected examples of the nucleophilic addition to amide carbonyl groups with the preactivation step. DIBAL = diisobutylaluminum hydride, py = pyridine, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.



Scheme 2. Synthesis of substituted *N*-methoxyamines by the sequential nucleophilic addition of *N*-methoxyamides without the preactivation step. LA = Lewis acid.

In the hopes of discovering practical transformations of amides, we initiated a program aimed at developing a novel one-pot transformation of acyclic *N*-methoxyamides to give substituted *N*-methoxyamines without the preactivation step. The realization of this process is outlined in Scheme 2. Treatment of *N*-methoxyamide **8** with DIBAL is known to produce the chelated five-membered intermediate **9**. In the well-known Weinreb ketone synthesis, hydrolysis of chelated intermediate **9** gives aldehyde **10** without extra nucleophilic addition to the aldehyde carbonyl group.[12] On the other hand, our reaction would require the capture of intermediate **9** with a Lewis acid, thus generating *N*-oxyiminium ion **12** via hemiaminal **11**. The resulting *N*-oxyiminium ion **12** would undergo a nucleophilic addition to give *N*-methoxyamine **13**.[13–15] *N*-Methoxyamine **13** could undergo further unique transformations such as direct oxidation to nitrons.[16] Salient features of this process are: 1) high yielding synthesis of *N*-methoxyamides by condensation between a carboxylic acid and a *N*-methoxyamine;[17] 2) exclusion of the preactivation step as a result of the higher electrophilicity of *N*-methoxyamides compared to ordinary amides; 3) one-pot installation

[*] K. Shirokane, Y. Kurosaki, Dr. T. Sato, Prof. Dr. N. Chida
Department of Applied Chemistry
Faculty of Science and Technology, Keio University
3-14-1, Hiyoshi, Kohoku-ku, Yokohama 223-8522 (Japan)
Fax: (+81) 45-566-1551
E-mail: takaakis@applc.keio.ac.jp
chida@applc.keio.ac.jp
Homepage: http://www.applc.keio.ac.jp/~chida/index.html

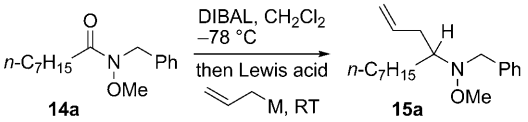
[**] This research was supported by a Grant-in-Aid for Young Scientists (B) from MEXT (21750049) and the Otsuka Pharmaceutical Co. Award in Synthetic Organic Chemistry (Japan).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201001127.

of a carbon nucleophile to amides; and 4) wide substrate scope including acyclic and macrocyclic systems.

Our investigations began by examining the reaction of *N*-benzyl-*N*-methoxyoctanamide **14a** with DIBAL and allyltrimethylsilane (Table 1).[18] Treatment of **14a** with DIBAL at −78 °C, and subsequent addition of allyltrimethylsilane without Lewis acid provided octanal and *N*-benzyl-*N*-methoxyamine, because the corresponding *N*-oxyiminium ion was not formed and the chelated five-membered intermediate was simply hydrolyzed (Table 1, entry 1). Next, we attempted to trap the chelated intermediate with acetic anhydride under Rychnovsky's conditions,[6] which gave octanal in addition to *N*-benzyl-*N*-methoxyamine (Table 1, entry 2).[19] However, when 1.1 equivalents of $BF_3{\cdot}Et_2O$ was used instead of acetic anhydride and DMAP, the desired amine **15a** was isolated in 32% yield (Table 1, entry 3). Of the Lewis acids screened, TMSOTf[8,20] and $Sc(OTf)_3$ proved to be the most effective, and provided **15a** in 70% and 71% yield, respectively (Table 1, entries 5 and 6). A catalytic amount of $Sc(OTf)_3$ (0.3 equiv) led to a significant decrease in yield (Table 1, entry 7). The best result was obtained when allyltributylstannane was employed as a stronger nucleophile, and gave **15a** in 92% yield (Table 1, entry 8).[21]

Table 1: Optimization of the reaction conditions in the intermolecular allylation of **14a**.[a]



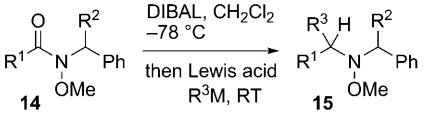
14a **15a**

Entry	Lewis acid	M	Yield [%][b]
1	none	TMS	0
2	Ac_2O, DMAP[c]	TMS	0
3	$BF_3{\cdot}OEt_2$	TMS	32
4	$SnCl_4$	TMS	60
5	TMSOTf	TMS	70
6	$Sc(OTf)_3$	TMS	71
7	$Sc(OTf)_3$[d]	TMS	11
8	$Sc(OTf)_3$	$SnBu_3$	92

[a] Reaction conditions: **14a** (0.11 mmol), DIBAL in toluene (1.01 M,1.1 equiv), CH_2Cl_2, −78 °C, 0.5 h, then Lewis acid (1.1 equiv), $CH_2{=}CHCH_2M$ (3 equiv), RT, 1.5 h. [b] Yield of isolated product after purification by column chromatography on silica gel. [c] Ac_2O (1.3 equiv) and DMAP (1.3 equiv) were used instead of a Lewis acid. [d] $Sc(OTf)_3$ (0.3 equiv) was used. DMAP = *N*,*N*-4-dimethylaminopyridine.

With the optimized reaction conditions in hand, the scope of the sequential nucleophilic addition of various acyclic *N*-methoxyamides was surveyed (Table 2). The intermolecular allylation of the linear substrates **14a** and **14b** with allyltributylstannane gave the products in high yields (Table 2, entries 1 and 2). The reaction with branched substrates **14c** and **14d** proceeded in slightly lower yields than the linear ones probably owing to steric hindrance, and exhibited low diastereoselectivity (Table 2, entries 3 and 4). The method was also applicable to cyanation of *N*-methoxyamides with TMSCN, and proceeded without Lewis acid (Table 2, entries 5–8).[22] However, higher yields were observed when three equivalents of $SnCl_4$ was used (Table 2, entries 9–12). Use of $SnCl_4$ had some effects on the diastereoselectivity with branched *N*-methoxyamides. While cyanation of **14c** and **14d** without Lewis acid showed poor diastereoselectivity (Table 2, entries 7 and 8), the reaction with $SnCl_4$ led to an increase in diastereoselectivity (Table 2, entries 11 and 12).

Table 2: Substrate scope in intermolecular allylation and cyanation.[a]



14 **15**

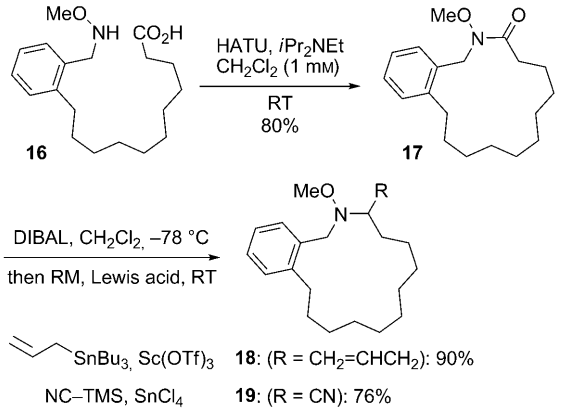
14a: R^1 = *n*-C_7H_{15}, R^2 = H **14c**: R^1 = *n*-C_7H_{15}, R^2 = Me
14b: R^1 = Ph, R^2 = H **14d**: R^1 = Ph, R^2 = Me

Entry	14	R^3M	Lewis acid	Yield [%][b]	d.r.[c]
1	**14a**	$CH_2{=}CHCH_2SnBu_3$	$Sc(OTf)_3$	92	–
2	**14b**	$CH_2{=}CHCH_2SnBu_3$	$Sc(OTf)_3$	91	–
3	**14c**	$CH_2{=}CHCH_2SnBu_3$	$Sc(OTf)_3$	72	1.6:1
4	**14d**	$CH_2{=}CHCH_2SnBu_3$	$Sc(OTf)_3$	72	1.4:1
5	**14a**	NC−TMS	none	48	–
6	**14b**	NC−TMS	none	55	–
7	**14c**	NC−TMS	none	69	1:1
8	**14d**	NC−TMS	none	53	1.4:1
9	**14a**	NC−TMS	$SnCl_4$	83	–
10	**14b**	NC−TMS	$SnCl_4$	70	–
11	**14c**	NC−TMS	$SnCl_4$	79	4.2:1
12	**14d**	NC−TMS	$SnCl_4$	65	4.1:1

[a] Reaction conditions: **14** (0.11 mmol), DIBAL in toluene (1.01 M,1.3 equiv), CH_2Cl_2, −78 °C, 0.5 h, then $Sc(OTf)_3$ (1.3 equiv) or $SnCl_4$ (3 equiv), R^3M (3 equiv), RT, 1.5 h. [b] Yield of isolated product after purification by column chromatography on silica gel. [c] The diastereomeric ratios were determined by ^1H NMR analysis.

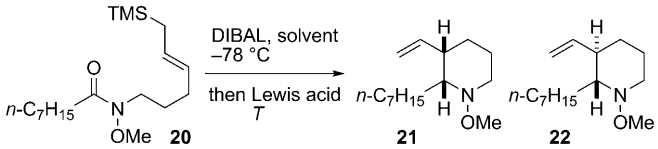
One of the conspicuous advantages of utilizing amidation is a reliable preparation of macrocyclic compounds. By combining macrolactamization[1] with our process, we could access macrocyclic amines like the ones embedded in natural products such as manzamine A[23] and madangamine A.[24,25] As a demonstration of this concept, we synthesized macrocyclic amines **18** and **19** (Scheme 3). A solution of *N*-methoxyamino acid **16** in CH_2Cl_2 was added over 15 hours (using a syringe pump) to a solution of HATU and iPr_2NEt, and gave 15-membered macrolactam **17** in 80% yield, along with 8% yield of the dimer. Reduction with DIBAL, and subsequent Lewis acid promoted allylation and cyanation gave **18** and **19** in 90% and 76% yield, respectively.

We then turned our attention to intramolecular reactions to generate substituted azacycles from acyclic *N*-methoxyamides (Table 3).[26] Reduction of **20** (bearing an (*E*)-allylsilane group) with DIBAL at −78 °C and subsequent addition of $SnCl_4$ at room temperature induced the diastereoselective intramolecular allylation, thus favoring the unusual *cis* arrangement (**21**/**22** = 2.9:1).[27–29] The nature of the Lewis acid had some effect on reaction efficiency (Table 3, entries 1–3). The best results in terms of both yield and diastereoselectivity were obtained with $Sc(OTf)_3$ (Table 3, entry 3). The reaction proceeded even at −40 °C, albeit with a prolonged reaction time (12 h; Table 3, entry 4). The replacement of CH_2Cl_2 with THF had a detrimental effect on diastereoselectivity (Table 3, entry 5). Although the factors controlling the *cis* preference



Scheme 3. Approach to macrocyclic azacycles through macrolactamization and sequential nucleophilic addition. HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.

Table 3: Diastereoselective intramolecular allylation of acyclic *N*-methoxyamide **20**.[a]



Entry	Lewis acid	Solvent	*T* [°C]	Yield of **21** + **22** [%][b]	**21**/**22**
1	$SnCl_4$	CH_2Cl_2	RT	69	2.9:1
2	TMSOTf	CH_2Cl_2	RT	77	3.5:1
3	$Sc(OTf)_3$	CH_2Cl_2	RT	88	5.0:1
4	$Sc(OTf)_3$	CH_2Cl_2	-40	72	5.3:1
5	$Sc(OTf)_3$	THF	RT	91	1.8:1

[a] **20** (60 μmol), DIBAL in toluene (1.01 M, 1.3 equiv), CH_2Cl_2, −78 °C, 0.5 h, then Lewis acid (1.3 equiv), 1.5 h. [b] Combined yield of isolated products after purification by column chromatography on silica gel. THF = tetrahydrofuran.

are yet to be clarified, we have developed this novel cyclization to give *cis*-2,3-disubstituted piperidines from acyclic *N*-methoxyamides.

In summary, we have developed a useful sequential nucleophilic addition to *N*-alkoxyamides with DIBAL and a variety of organometallic reagents in one-pot. The method eliminates the preactivation step, which is usually a requisite for the functionalization of amide carbonyl groups. The reaction can be applied to challenging acyclic amides and macrolactams. Studies on installing a carbon unit, instead of the hydride group with DIBAL, in the first nucleophilic addition are in progress.

Received: February 24, 2010
Revised: June 9, 2010
Published online: July 29, 2010

Keywords: allylation · amides · cyanation · cyclization · macrocycles

[1] For selected reviews on amide bond formation, see: a) J. M. Humphrey, A. R. Chamberlin, *Chem. Rev.* **1997**, *97*, 2243 – 2266; b) F. Albericio, R. Chinchilla, D. J. Dodsworth, C. Nájera, *Org. Prep. Proced. Int.* **2001**, *33*, 203 – 313; c) S.-Y. Han, Y.-A. Kim, *Tetrahedron* **2004**, *60*, 2447 – 2467; d) C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827 – 10852; e) E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606 – 631.

[2] For selected examples on direct conversion of acyclic amides into α,α-dimethylamines, see: a) F. Kuffner, E. Polke, *Monatsh. Chem.* **1951**, *82*, 330 – 335; b) D. J. Calderwood, R. V. Davies, P. Rafferty, H. L. Twigger, H. M. Whelan, *Tetrahedron Lett.* **1997**, *38*, 1241 – 1244; c) S. M. Denton, A. Wood, *Synlett* **1999**, 55 – 56.

[3] For selected examples on direct conversion of acyclic amides into imines or iminium ions with Schwartz's reagent, see; a) D. J. A. Schedler, A. G. Godfrey, B. Ganem, *Tetrahedron Lett.* **1993**, *34*, 5035 – 5038; b) D. J. A. Schedler, J. Li, B. Ganem, *J. Org. Chem.* **1996**, *61*, 4115 – 4119; c) J. T. Spletstoser, J. M. White, A. R. Tunoori, G. I. Georg, *J. Am. Chem. Soc.* **2007**, *129*, 3408 – 3419.

[4] Related nucleophilic additions of esters with higher electrophilicity than amides have been reported. For examples on one-pot conversion of acyclic esters to alcohols via aluminum acetals, see: a) S. Kiyooka, M. Shirouchi, *J. Org. Chem.* **1992**, *57*, 1 – 2; b) R. Polt, M. A. Peterson, L. DeYoung, *J. Org. Chem.* **1992**, *57*, 5469 – 5480.

[5] For examples on the transformation of acyclic esters into ethers or alcohols via monosilyl acetals, see: a) S. Kiyooka, M. Shirouchi, Y. Kaneko, *Tetrahedron Lett.* **1993**, *34*, 1491 – 1494; b) D. Sames, Y. Liu, L. DeYoung, R. Polt, *J. Org. Chem.* **1995**, *60*, 2153 – 2159; c) H. Shinokubo, K. Oshima, K. Utimoto, *Chem. Lett.* **1995**, 461 – 462; d) H. Shinokubo, J. Kondo, A. Inoue, K. Oshima, *Chirality* **2003**, *15*, 31 – 37.

[6] For examples on the transformation of acyclic esters into ethers via α-acetoxy ethers, see: a) V. H. Dahanukar, S. D. Rychnovsky, *J. Org. Chem.* **1996**, *61*, 8317 – 8320; b) D. J. Kopecky, S. D. Rychnovsky, *J. Org. Chem.* **2000**, *65*, 191 – 198; c) I. Kadota, A. Ohno, K. Matsuda, Y. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 6702 – 6703.

[7] a) M. P. DeNinno, C. Eller, *Tetrahedron Lett.* **1997**, *38*, 6545 – 6548; b) M. P. DeNinno, C. Eller, J. B. Etienne, *J. Org. Chem.* **2001**, *66*, 6988 – 6993.

[8] a) Y.-G. Suh, D.-Y. Shin, J.-K. Jung, S.-H. Kim, *Chem. Commun.* **2002**, 1064 – 1065; b) Y.-G. Suh, S.-H. Kim, J.-K. Jung, D.-Y. Shin, *Tetrahedron Lett.* **2002**, *43*, 3165 – 3167; c) J.-W. Jung, D.-Y. Shin, S.-Y. Seo, S.-H. Kim, S.-M. Paek, J.-K. Jung, Y.-G. Suh, *Tetrahedron Lett.* **2005**, *46*, 573 – 575.

[9] For selected examples on nucleophilic additions to acyclic thioamides, see: a) Y. Tamaru, T. Harada, S. Nishi, Z. Yoshida, *Tetrahedron Lett.* **1982**, *23*, 2383 – 2386; b) A. Ishida, T. Nakamura, K. Irie, T. Oh-ishi, *Chem. Pharm. Bull.* **1985**, *33*, 3237 – 3249; c) Y. Tominaga, S. Kohra, A. Hosomi, *Tetrahedron Lett.* **1987**, *28*, 1529 – 1532; d) Y. Tominaga, Y. Matsuoka, H. Hayashida, S. Kohra, A. Hosomi, *Tetrahedron Lett.* **1988**, *29*, 5771 – 5774.

[10] a) T. Murai, Y. Mutoh, Y. Ohta, M. Murakami, *J. Am. Chem. Soc.* **2004**, *126*, 5968 – 5969; b) T. Murai, F. Asai, *J. Am. Chem. Soc.* **2007**, *129*, 780 – 781.

[11] For selected examples on sequential nucleophilic addition using dehydrating reagents, see: a) P. Magnus, A. H. Payne, L. Hobson, *Tetrahedron Lett.* **2000**, *41*, 2077 – 2081; b) P. Magnus, L. Gazzard, L. Hobson, A. H. Payne, T. J. Rainey, N. Westlund, V. Lynch, *Tetrahedron* **2002**, *58*, 3423 – 3443; c) R. Larouche-Gauthier, G. Bélanger, *Org. Lett.* **2008**, *10*, 4501 – 4504; d) K.-J. Xiao, J.-M. Luo, K.-Y. Ye, Y. Wang, P.-Q. Huang, *Angew. Chem.* **2010**, *122*, 3101 – 3104; *Angew. Chem. Int. Ed.* **2010**, *49*, 3037 – 3040.

[12] a) S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815–3818; for selected recent reviews on Weinreb amide, see: b) V. K. Khlestkin, D. G. Mazhukin, *Curr. Org. Chem.* **2003**, *7*, 967–993; c) S. Balasubramaniam, I. S. Aidhen, *Synthesis* **2008**, 3707–3738.

[13] For Kibayashi's pioneer work involving Grignard addition and subsequent hydride reduction to six-membered *N*-alkoxylactams, see: H. Iida, Y. Watanabe, C. Kibayashi, *J. Am. Chem. Soc.* **1985**, *107*, 5534–5535.

[14] For selected examples on reactions via *N*-oxyiminium ions as the key intermediates, see: a) B. Hardegger, S. Shatzmiller, *Helv. Chim. Acta* **1976**, *59*, 2765–2767; b) R. Plate, R. H. M. van Hout, H. Behm, H. C. J. Ottenheijm, *J. Org. Chem.* **1987**, *52*, 555–560; c) A. Padwa, D. C. Dean, *J. Org. Chem.* **1990**, *55*, 405–406; d) P. H. H. Hermkens, J. H. van Maarseveen, P. L. H. M. Cobben, H. C. J. Ottenheijm, C. G. Kruse, H. W. Scheeren, *Tetrahedron* **1990**, *46*, 833–846; e) M. Tiecco, L. Testaferri, M. Tingoli, L. Bagnoli, *J. Chem. Soc. Chem. Commun.* **1995**, 235–236; f) M. C. McMills, D. L. Wright, J. D. Zubkowski, E. J. Valente, *Tetrahedron Lett.* **1996**, *37*, 7205–7208; g) R. Grigg, Z. Rankovic, M. Thoroughgood, *Tetrahedron* **2000**, *56*, 8025–8032; h) T. Yamashita, N. Kawai, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2005**, *127*, 15038–15039; i) H. A. Dondas, R. Grigg, J. Markandu, T. Perrior, T. Suzuki, S. Thibault, W. A. Thomas, M. Thornton-Pett, *Tetrahedron* **2002**, *58*, 161–173; j) Z. Peng, J. Song, W. Liao, R. Ma, S.-H. Chen, G. Li, R. Ando, *Lett. Org. Chem.* **2006**, *3*, 455–458; k) H. Nemoto, R. Ma, T. Kawamura, M. Kamiya, M. Shibuya, *J. Org. Chem.* **2006**, *71*, 6038–6043; l) X. Zheng, X. Wang, J. Chang, K. Zhao, *Synlett* **2006**, 3277–3283; m) H. Nemoto, R. Ma, H. Moriguchi, T. Kawamura, M. Kamiya, M. Shibuya, *J. Org. Chem.* **2007**, *72*, 9850–9853; n) S. K. Jackson, A. Karadeolian, A. B. Driega, M. A. Kerr, *J. Am. Chem. Soc.* **2008**, *130*, 4196–4201.

[15] For selected examples on reactions via *N*-acyl-*N*-oxyiminium ions as the key intermediates, see: a) C. M. Marson, S. Pucci, *Tetrahedron Lett.* **2004**, *45*, 9007–9010; b) X. Zheng, X. Wang, J. Chang, K. Zhao, *Synlett* **2006**, 3277–3283; c) F. Frebault, N. S. Simpkins, A. Fenwick, *J. Am. Chem. Soc.* **2009**, *131*, 4214–4215.

[16] For selected examples on the direct oxidation of *N*-alkoxyamines into nitrons, see a) J. J. Tufariello, G. B. Mullen, J. J. Tegeler, E. J. Trybulski, S. C. Wong, S. A. Ali, *J. Am. Chem. Soc.* **1979**, *101*, 2435–2442; b) S. A. Ali, M. I. M. Wazeer, *Tetrahedron Lett.* **1993**, *34*, 137–140; c) K. Nagasawa, A. Georgieva, H. Koshino, T. Nakata, T. Kita, Y. Hashimoto, *Org. Lett.* **2002**, *4*, 177–180.

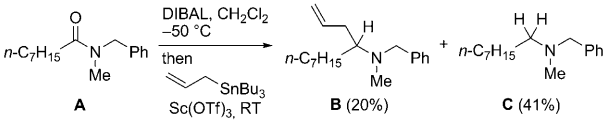
[17] For synthesis of *N*-methoxyamides, see the Supporting Information.

[18] For selected reviews on allylation via iminium intermediates, see; a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207–2293; b) C. O. Puentes, V. Kouznetsov, *J. Heterocycl. Chem.* **2002**, *39*, 595–614.

[19] Suh disclosed that *N*-acyl *N,O*-acetals were not formed under Rychnovsky conditions (Ac_2O, Py), see Ref. [8a,b].

[20] For selected examples on trapping of hemiaminals with a TMS group, see: a) A. P. Johnson, R. W. A. Luke, A. N. Boa, *J. Chem. Soc. Perkin Trans. 1* **1996**, 895–905; b) G. Blond, T. Billard, B. R. Langlois, *J. Org. Chem.* **2001**, *66*, 4826–4830; c) D. Ferraris, B. Young, C. Cox, T. Dudding, W. J. Drury III, L. Ryzhkov, A. E. Taggi, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 67–77; d) I. H. Jeong, S. L. Jeon, Y. K. Min, B. T. Kim, *Tetrahedron Lett.* **2002**, *43*, 7171–7174.

[21] As a control experiment, tertiary amide **A** was reduced with DIBAL (1.3 equiv) at −50 °C, and subsequent treatment with $Sc(OTf)_3$ (1.3 equiv) and allyltributylstannane (3 equiv) at room temperature, gave amine **B** and the reduced product **C** in 20% and 41% yield, respectively. These results confirmed the beneficial effect of *N*-methoxy groups.



[22] For selected recent reviews on the Strecker reaction, see: a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094; b) Y. Ohfune, T. Shinada, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1115–1129; c) H. Gröger, *Chem. Rev.* **2003**, *103*, 2795–2827; d) T. Vilaivan, W. Bhanthumnavin, Y. Sritana-Anant, *Curr. Org. Chem.* **2005**, *9*, 1315–1392; e) G. K. Friestad, A. K. Mathies, *Tetrahedron* **2007**, *63*, 2541–2569.

[23] a) R. Sakai, T. Higa, C. W. Jefford, G. Bernardinelli, *J. Am. Chem. Soc.* **1986**, *108*, 6404–6405; b) H. Nakamura, S. Deng, J. Kobayashi, Y. Ohizumi, Y. Tomotake, T. Matsuzaki, Y. Hirata, *Tetrahedron Lett.* **1987**, *28*, 621–624.

[24] F. Kong, R. J. Andersen, T. M. Allen, *J. Am. Chem. Soc.* **1994**, *116*, 6007–6008.

[25] Suh reported a three-step synthesis of macrocyclic amines from macrolactams using α-alkoxy carbamates, see Ref. [8b]. Ganem reported one example on transformation of a macrolactam into the corresponding imine, see Ref. [3a].

[26] For selected reviews on intramolecular cyclizations of iminium ions, see: a) W. N. Speckamp, H. Hiemstra, *Tetrahedron* **1985**, *41*, 4367–4416; b) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817–3856; c) J. Royer, M. Bonin, L. Micouin, *Chem. Rev.* **2004**, *104*, 2311–2352; d) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *Chem. Rev.* **2004**, *104*, 1431–1628.

[27] For selected examples of allylsilane cyclization in the *cis*-selective manner, see: a) H. Hiemstra, H. P. Fortgens, W. N. Speckamp, *Tetrahedron Lett.* **1985**, *26*, 3155–3158; b) C. Y. Hong, N. Kado, L. E. Overman, *J. Am. Chem. Soc.* **1993**, *115*, 11028–11029; c) D. A. Heerding, C. Y. Hong, N. Kado, G. C. Look, L. E. Overman, *J. Org. Chem.* **1993**, *58*, 6947–6948.

[28] For selected examples of allylsilane cyclization in the *trans*-selective manner, see: a) H. Hiemstra, M. H. A. M. Sno, R. J. Vijn, W. N. Speckamp, *J. Org. Chem.* **1985**, *50*, 4014–4020; b) C. Agami, D. Bihan, R. Morgentin, C. Puchot-Kadouri, *Synlett* **1997**, 799–800; c) M. Suginome, T. Iwanami, Y. Ito, *J. Org. Chem.* **1998**, *63*, 6096–6097; d) C. Agami, D. Bihan, L. Hamon, C. Puchot-Kadouri, *Tetrahedron* **1998**, *54*, 10309–10316; e) H. Huang, T. F. Spande, J. S. Panek, *J. Am. Chem. Soc.* **2003**, *125*, 626–627; f) S. S. Kinderman, R. de Gelder, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra, F. P. J. T. Rutjes, *J. Am. Chem. Soc.* **2004**, *126*, 4100–4101; g) S. M. Amorde, A. S. Judd, S. F. Martin, *Org. Lett.* **2005**, *7*, 2031–2033; h) S. M. Amorde, I. T. Jewett, S. F. Martin, *Tetrahedron* **2009**, *65*, 3222–3231.

[29] The configuration of **21** and **22** was determined by NOESY experiments after removal of the methoxy group with SmI_2 in THF at room temperature, see the Supporting Information.

