

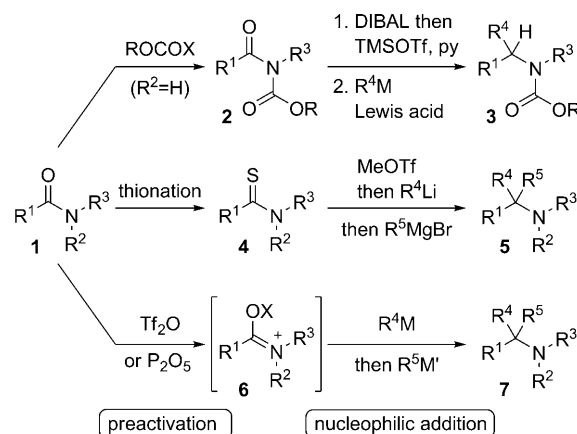
Synthetic Methods

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

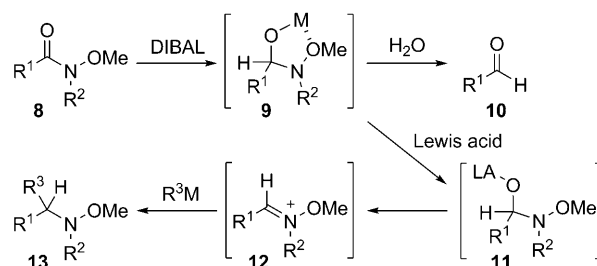
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Amide functional groups play a significant role in a variety of areas such as medicinal drugs and chemical fibers. Therefore, the efficient synthesis of amide bonds has received much attention by organic chemists, making this one of the most reliable 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 (Tf₂O, P₂O₅, 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]

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



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.

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

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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

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

Entry	Lewis acid	M	Yield [%] ^[b]
1	none	TMS	0
2	Ac ₂ O, DMAP ^[c]	TMS	0
3	BF ₃ ·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), CH₂Cl₂, −78 °C, 0.5 h, then Lewis acid (1.1 equiv), CH₂=CHCH₂M (3 equiv), RT, 1.5 h. [b] Yield of isolated product after purification by column chromatography on silica gel. [c] Ac₂O (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.

−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 BF₃·Et₂O 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]

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

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

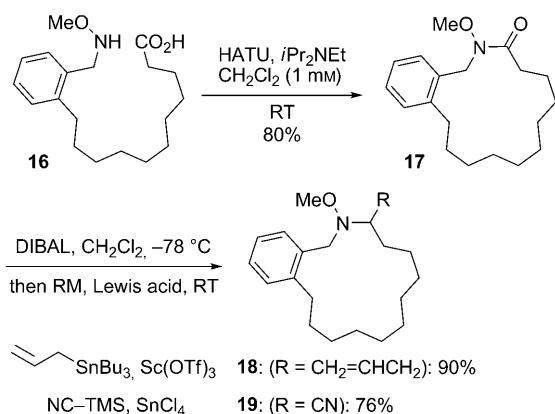
14a: R ¹ = <i>n</i> -C ₇ H ₁₅ , R ² = H		14c: R ¹ = <i>n</i> -C ₇ H ₁₅ , R ² = Me			
14b: R ¹ = Ph, R ² = H		14d: R ¹ = Ph, R ² = Me			
Entry	14	R ³ M	Lewis acid	Yield [%] ^[b]	d.r. ^[c]
1	14a	CH ₂ =CHCH ₂ SnBu ₃	Sc(OTf) ₃	92	–
2	14b	CH ₂ =CHCH ₂ SnBu ₃	Sc(OTf) ₃	91	–
3	14c	CH ₂ =CHCH ₂ SnBu ₃	Sc(OTf) ₃	72	1.6:1
4	14d	CH ₂ =CHCH ₂ SnBu 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), CH₂Cl₂, −78 °C, 0.5 h, then Sc(OTf)₃ (1.3 equiv) or SnCl₄ (3 equiv), R³M (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.

three equivalents of SnCl₄ was used (Table 2, entries 9–12). Use of SnCl₄ 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 SnCl₄ led to an increase in diastereoselectivity (Table 2, entries 11 and 12).

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 CH₂Cl₂ was added over 15 hours (using a syringe pump) to a solution of HATU and *i*Pr₂NEt, 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 SnCl₄ 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 CH₂Cl₂ 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 ₂ Cl ₂	RT	69	2.9:1
2	TMSOTf	CH ₂ Cl ₂	RT	77	3.5:1
3	Sc(OTf) ₃	CH ₂ Cl ₂	RT	88	5.0:1
4	Sc(OTf) ₃	CH ₂ Cl 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), CH₂Cl₂ –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.

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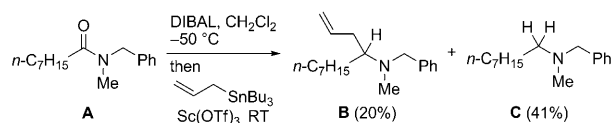
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