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Synthetic Methods |*Very Important Paper*|

VIP Two-step Synthesis of Multi-Substituted Amines by Using an *N*-Methoxy Group as a Reactivity Control Element

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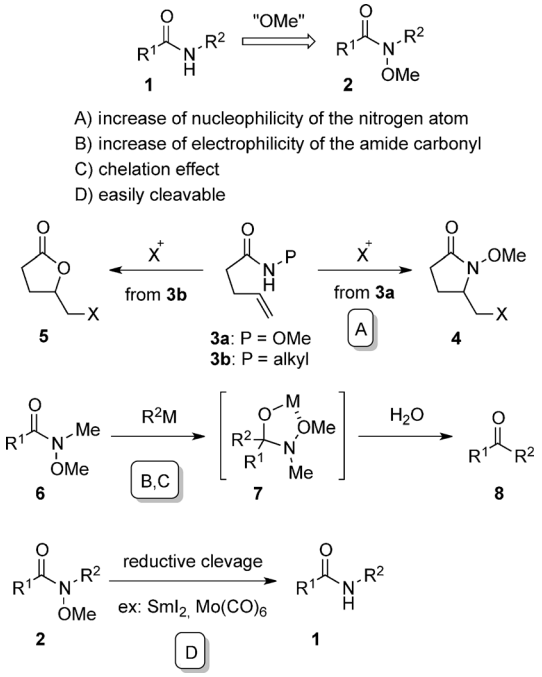
Abstract: The development of a two-step synthesis of multi-substituted *N*-methoxyamines from *N*-methoxyamides is reported. Utilization of the *N*-methoxy group as a reactivity control element was the key to success in this two-step synthesis. The first reaction involves a *N*-methoxyamide/aldehyde coupling reaction. Whereas ordinary amides cannot condense with aldehydes intermolecularly due to the poor nucleophilicity of the amide nitrogen, the *N*-methoxy group enhances the nucleophilicity of the nitrogen, enabling the direct coupling reaction. The second reaction in the two-step process was nucleophilic addition to the *N*-methoxyamides. Incorporation of the *N*-methoxy group into the amides increased the electrophilicity of the amide carbonyls and promoted the chelation effect. This nucleophilic addition enabled quick diversification of the products derived from the first step. The developed strategy was applicable to a variety of substrates, resulting in the elaboration of multi-substituted piperidines and acyclic amines, as well as a substructure of a complex natural alkaloid.

Introduction

Our research group has been exploring new synthetic strategies that take advantage of a heteroatom–heteroatom bond for the synthesis of biologically active complex natural products. In contrast to an isolated heteroatom, incorporation of a second heteroatom opens up new reactivities (Scheme 1). For example, although a carbonyl oxygen atom is the most nucleophilic site in an ordinary amide **1**, a nitrogen atom becomes the most reactive in *N*-methoxyamide **2** (effect A). This unique reactivity has been used in cationic lactamization (**3a**→**4**), which is not feasible with *N*-alkylamide **3b** because attack by the oxygen atom is preferred, giving lactone **5** exclusively.[1] Electrophilicity of the amide carbonyl can be enhanced by incorporation of the *N*-methoxy group (effect B). The well-known Weinreb ketone synthesis (**6**→**7**→**8**) uses this effect, together with the chelation effect of the *N*-methoxy group, to prevent addition of a second nucleophile (effect C).[2] The nitrogen–oxygen bond is a weak bond and easily cleavable with reducing reagents such as SmI_2 and $Mo(CO)_6$ (effect D, **2**→**1**). In this article, we describe the development of a two-step synthesis of multi-substituted *N*-methoxyamines from *N*-methoxyamides.[3] The unique properties imparted by the *N*-methoxy group enabled quick access to multi-substituted piperidines as well as acyclic amines.



Scheme 1. Unique properties of *N*-methoxyamides **2** and examples of their applications.

Results and Discussion

Piperidines are among the most common and important structural motifs seen in a number of natural products including ge-

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phyrotoxin (**9**),[4] cylindricine A (**10**)[5] and kouamine (**11**)[6] (Figure 1). However, synthesis of highly substituted piperidines is not trivial even in modern organic chemistry, and typically requires multi-step synthesis. To overcome this issue, we envisioned a two-step synthesis of 2,3,6-trisubstituted piperidine **14** from *N*-methoxyamide **12**[7] (Scheme 2, **12**→**13**→**14**). The

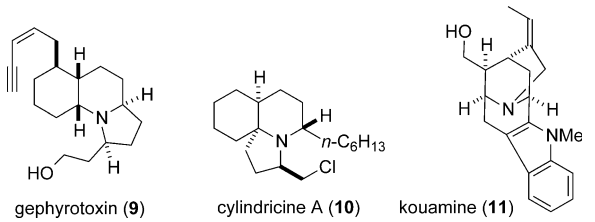
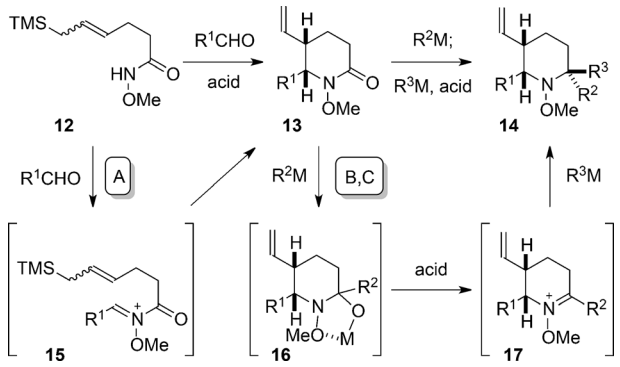


Figure 1. Representative natural products possessing multi-substituted piperidines.

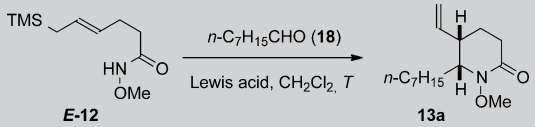


Scheme 2. Plan for two-step synthesis of multi-substituted piperidines using inherent reactivities of *N*-methoxyamides.

success of this process is highly dependent upon the assistance of the *N*-methoxy group as a reactivity control element. The first step is an acid-mediated direct coupling of *N*-methoxyamide **12** with an aldehyde, followed by spontaneous intramolecular allylation of the generated *N*-acyliminium ion **15** to give 2,6-disubstituted *N*-methoxypiperidone **13**.[8] Intermolecular condensation of an ordinary amide with an aldehyde is very challenging due to the poor nucleophilicity of the amide nitrogen atom. However, incorporation of a methoxy group on the nitrogen atom results in an increase of the nucleophilicity (Scheme 1, effect A), and enables direct coupling with the aldehyde. The second step in the two-step sequence is a nucleophilic addition to *N*-methoxylactam **13**, affording 2,3,6-trisubstituted *N*-methoxypiperidine **14**.[9–11] This nucleophilic addition takes advantage of both the increased electrophilicity of the *N*-methoxyamide and the chelation effect in the same way as the Weinreb ketone synthesis (Scheme 1, effects B and C). In other words, the addition of the first nucleophile R^2–M to the *N*-methoxylactam would smoothly provide the five-membered chelated intermediate **16**. Although Weinreb's method gives a ketone after hydrolysis, our nucleophilic addition would afford *N*-oxyiminium ion **17**[12] upon treatment of **16** with acid. The generated **17** would then react with mild nucleophiles to provide *N*-methoxypiperidine **14** in a one-pot process. Moreover, the *N*-methoxy group of **14** could be easily cleaved under reductive conditions if necessary (Scheme 1, effect D).

Our studies began by examining the intermolecular condensation of *N*-methoxyamide ***E*-12** with octanal **18** (Table 1). The nature of the Lewis acid was crucial in this coupling reaction.

Table 1. Optimization of intermolecular coupling of *N*-methoxyamide ***E*-12** with octanal **18**.[a]



Entry	Lewis acid	Temp [°C]	Yield [%][b]
1	$Sc(OTf)_3$	RT	0
2	$TiCl_4$	−78	0
3	$SnCl_4$	−78	0
4	TMSOTf	−78 to −20	trace
5[c]	cat. $Bi(OTf)_3/LiClO_4$	0 to RT	53
6	$BF_3{\cdot}Et_2O$	−20	85
7[d]	$BF_3{\cdot}Et_2O$	−20	90

[a] Reaction conditions: ***E*-12** (140 μmol), octanal **18**(1.5 equiv), Lewis acid (2 equiv), CH_2Cl_2 (0.2 M), 3 h. [b] Yield of isolated product after purification by column chromatography. [c] $Bi(OTf)_3$ (5 mol%) and $LiClO_4$ (3 equiv) were added. [d] $BF_3{\cdot}Et_2O$ (6 equiv) was added.

No desired product **13a** was formed with $Sc(OTf)_3$, $TiCl_4$, $SnCl_4$, or TMSOTf (Table 1, entries 1–4). However, addition of 5 mol% $Bi(OTf)_3$ and $LiClO_4$ (3 equiv)[13] to a solution of ***E*-12**, octanal **18** (1.5 equiv) in CH_2Cl_2 initiated the coupling to give **13a** in 53% yield (Table 1, entry 5). The reaction took place in completely *cis*-stereoselective fashion with **13a** isolated as the sole diastereomer. The yield of **13a** was improved to 85% with two equivalents of $BF_3{\cdot}Et_2O$ at −20 °C, along with recovery of ***E*-12** in 12% yield (Table 1, entry 6). In order to consume the starting material ***E*-12**, six equivalents of $BF_3{\cdot}Et_2O$ were employed, giving **13a** in 90% yield without detrimental effect on the stereoselectivity (Table 1, entry 7; TMS = trimethylsilyl, Tf = triflate).

With optimized conditions in hand, the substrate scope of the coupling reaction with a variety of aldehydes was surveyed (Table 2). Despite using an excess amount of $BF_3{\cdot}Et_2O$, aldehydes with a variety of functional groups were tolerated under these conditions. The coupling reaction between ***E*-12** and aldehyde **19** with the hydroxy group protected as a TBDPS ether proceeded in 92% yield (Table 2, entry 2, **13b**: 92%). Alkyl bromide and methyl ester moieties did not interfere with this transformation (Table 2, entries 3 and 4, **13c**: 80%, **13d**: 92%). Carbamates including an acid-sensitive Boc group were compatible with these reaction conditions (Table 2, entries 5 and 6, **13e**: 92%, **13f**: 75%; Boc = *tert*-butyloxycarbonyl). Although 2-aryl acetaldehydes **24** and **25** tend to be easily enolizable, the coupling reactions took place smoothly, with **13g** and **h** isolated in 78 and 92% yields, respectively (Table 2, entries 7 and 8). The sterically hindered *iso*-butyraldehyde **26** required a longer reaction time (3 h vs. 2 d), but still gave the *cis*-cyclized product **13i** in 67% yield (Table 2, entry 9).

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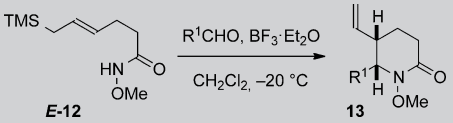
Table 2. The substrate scope in the intermolecular coupling of *N*-methoxyamide ***E*-12**.[a]



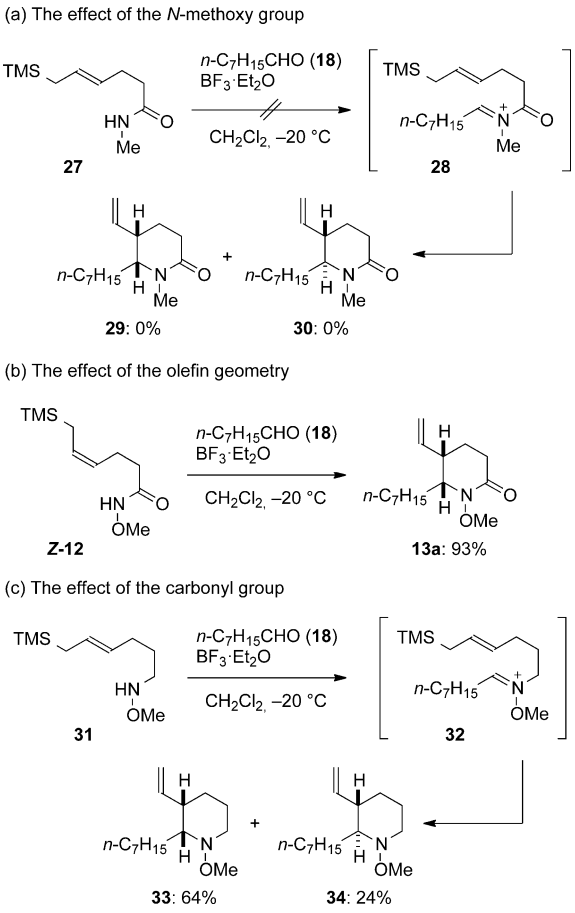
Entry	R^1CHO	Yield of **13** [%][b]
1	n-$C_7H_{15}CHO$ (**18**)	**13a**: 90
2	$TBDPSO(CH_2)_3CHO$ (**19**)	**13b**: 92
3	$Br(CH_2)_3CHO$ (**20**)	**13c**: 80
4	$MeO_2C(CH_2)_2CHO$ (**21**)	**13d**: 92
5	$CbzN(Bn)(CH_2)_5CHO$ (**22**)	**13e**: 92
6	$BocN(Bn)(CH_2)_5CHO$ (**23**)	**13f**: 75
7	$PhCH_2CHO$ (**24**)	**13g**: 78[c]
8	$2,5\text{-}(MeO)_2\text{-}C_6H_3CH_2CHO$ (**25**)	**13h**: 92[c]
9[d]	*i*PrCHO (**26**)	**13i**: 67

[a] Reaction conditions: ***E*-12** (140 μmol), R^1CHO (1.5 equiv), $BF_3{\cdot}Et_2O$ (4–6 equiv), CH_2Cl_2 (0.2 M), −20 °C, 3–12 h. [b] Yield of isolated product after purification by column chromatography. [c] The diastereomeric ratios of **13g** and **13h** were 11:1 in favour of the *cis*-product. [d] The reaction time was 2 days.

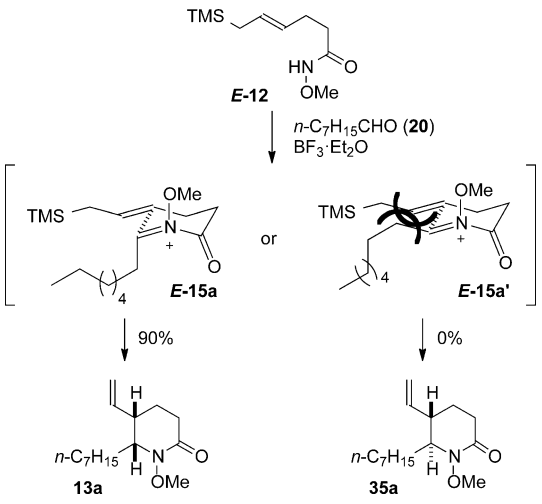
The *N*-methoxy group as a reactivity control element played a significant role in the amide/aldehyde coupling reaction (Scheme 3a). To confirm this beneficial effect, the *N*-methoxy group in ***E*-12** was replaced by the *N*-methyl group. The reaction of *N*-methylamide **27** instead of *N*-methoxyamide ***E*-12** under optimized conditions provided no desired product **29** or **30**. This failure was likely due to the poor nucleophilicity of the nitrogen atom. However, the assistance of the *N*-methoxy group of ***E*-12** increased the nucleophilicity of the nitrogen atom over the oxygen atom, and made the direct intermolecular coupling with octanal **18** possible.

One of the conspicuous features in this coupling reaction was complete *cis*-stereoselectivity in the intramolecular allylation process.[14–16] The origin of the high stereoselection was studied experimentally by changing two factors in *N*-methoxyamide ***E*-12**: 1) the geometry of the allylsilane, and 2) the effect of the carbonyl group (Scheme 3b and c). Treatment of a solution of ***Z*-12** and octanal **18** under optimized conditions gave **13a** in 93% yield as a single diastereomer. This result clearly suggested that the geometry of the olefin had no significant effect on either the yield or the diastereoselectivity. On the other hand, replacement of the amide carbonyl with a methylene group showed a significant effect on the diastereoselectivity. The reaction of *N*-methoxyamine **31** under identical conditions to *N*-methoxyamide ***E*-12** took place through *N*-oxyiminium ion **32**, providing 2,3-*cis*-piperidine **33** in 64% yield, along with 24% of the 2,3-*trans*-isomer **34**.

The stereochemical outcome of the amide–aldehyde coupling was rationalized on the basis of the above control experiments (Scheme 4). Condensation of ***E*-12** and octanal **18** formed transient *N*-acyl-*N*-oxyiminium ions, which might exist in equilibrium between ***E*-15a** and **15a**′. We believed that the highest level of *cis*-preference could be accounted for by the balance between the 1,3-diaxial interaction and the gauche-type interaction of the alkyl side chain in each transition state. In transition state ***E*-15a**′, the large gauche-type interaction between the alkyl side chain and the allyl silane was dominant, preventing the cyclization to *trans*-product **35a**. On the other hand, the 1,3-diaxial interaction of the alkyl side chain in ***E*-15a** was not critical, because one of the two substituents was the amide carbonyl which points outside the ring. This mechanism was also supported by a control experiment using *N*-methoxy-



Scheme 3. Control experiments of the *N*-methoxyamide/aldehyde coupling reaction.



Scheme 4. Plausible mechanistic rational for *cis*-selective intramolecular allylation of ***E*-12**.

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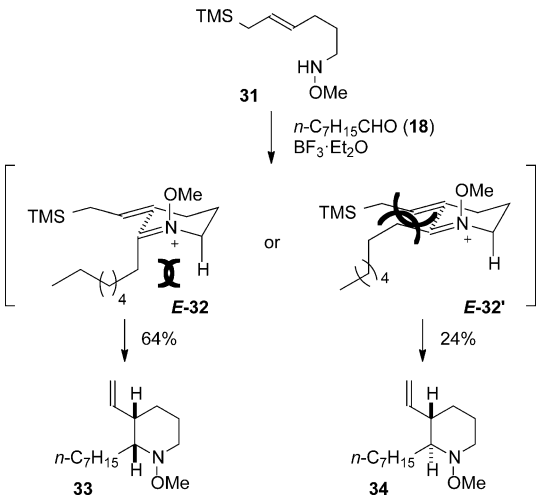
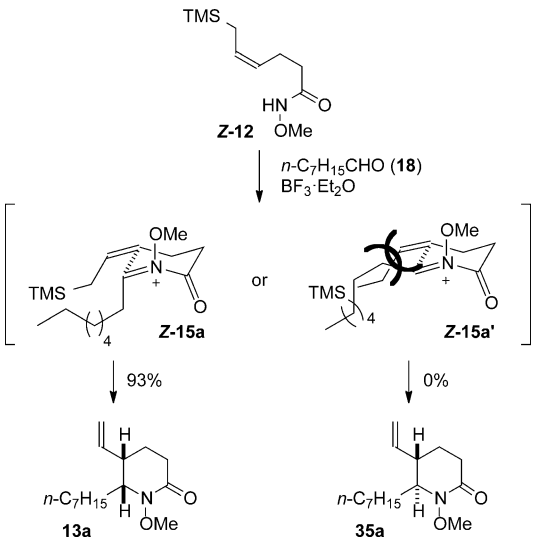
amine **31** (Scheme 5). Condensation of **31** with octanal **18** would lead to the formation of *N*-oxyiminium ions ***E*-32** and ***E*-32′**. While transition state ***E*-32'** had a similar gauche interaction as seen in ***E*-15a′**, transition state ***E*-32** possessed a larger 1,3-diaxial interaction than ***E*-15a**, because the amide carbonyl group was replaced with the methylene in ***E*-32**. As a result, the formation of *trans*-product **34** was competitive, resulting in the low diastereoselectivity in the coupling reaction of *N*-methoxyamine **31**.



Scheme 5. Plausible mechanistic rational for intramolecular allylation of *N*-methoxyamine **31**.

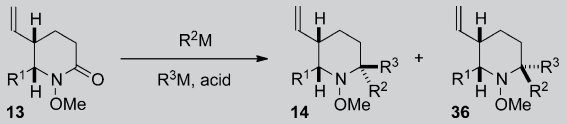
The control experiment using ***Z*-12** in Scheme 3 showed that the stereoselectivity was not affected by the olefin geometry. The reaction of ***Z*-12** probably took place in accordance with similar transition states derived from ***E*-12** as shown in Scheme 4 (Scheme 6). The condensation of ***Z*-12** might give rise to an equilibrium between ***Z*-15a** and **15a**′. The cyclization from transition state ***Z*-15a'** was unfavorable due to the dominant gauche-type interaction. Therefore, the reaction of ***Z*-12** also gave *cis*-product **13a** via transition state **Z-15a** as a single diastereomer.

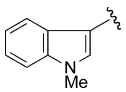


Scheme 6. Plausible mechanistic rational for *cis*-selective intramolecular allylation of ***Z*-12**.

Having the first step in the two-step synthesis established, we turned our attention to the next nucleophilic addition to *N*-methoxylactams **13** (Table 3). Our research group has been intensively studying nucleophilic addition to *N*-alkoxyamides.[3,10] This reaction enabled quick diversification of the *N*-methoxylactams **13** and gave a number of multi-substituted

Table 3. Nucleophilic addition to *N*-methoxylactams **13**.



Entry	13	Conditions	R^2	R^3	Combined yield [%][a]	Diastereomeric ratio[b]
1	**13a**: $R^1 = n\text{-}C_7H_{15}$	DIBAL-H, CH_2Cl_2, −78 °C; TMSCN, $SnCl_4$, RT	H	CN	87	**14a**:**36*a*** = 2.2:1
2		DIBAL-H, CH_2Cl_2, −78 °C; $CH_2{=}CHCH_2SnBu_3$, $Sc(OTf)_3$, RT	H	$CH_2CH{=}CH_2$	86	**14b**:**36*b*** = 4.1:1
3		DIBAL-H, CH_2Cl_2, −78 °C; *N*-methylindole, $Sc(OTf)_3$, −40 °C	H		88	**14c**:**36c** = 14:1
4		Cp_2ZrHCl, $(CH_2Cl)_2$, RT; $CH_2{=}C(OTIPS)Ph$, 20 mol% $Sc(OTf)_3$, RT	H	CH_2COPh	65	**14d**: single diastereomer
5		MeLi, THF, −78 °C; TMSCN, $SnCl_4$, MeCN, RT	Me	CN	83	**14e**:**36e** = 1:4.0
6	**13d**: $R^1 = MeO_2C(CH_2)_2$	Cp_2ZrHCl, $(CH_2Cl)_2$, RT; TMSCN, 10 mol% $Sc(OTf)_3$, RT	H	CN	86	**14f**:**36f** = 1:4.3
7		Cp_2ZrHCl, $(CH_2Cl)_2$, RT; $CH_2{=}CHCH_2SnBu_3$, 30 mol% $Sc(OTf)_3$, −30 °C	H	$CH_2CH{=}CH_2$	74	**14g**:**36g** = 4.2:1

[a] Yield of isolated product after purification by column chromatography. [b] The diastereomeric ratio was determined by ^1H NMR spectroscopy.

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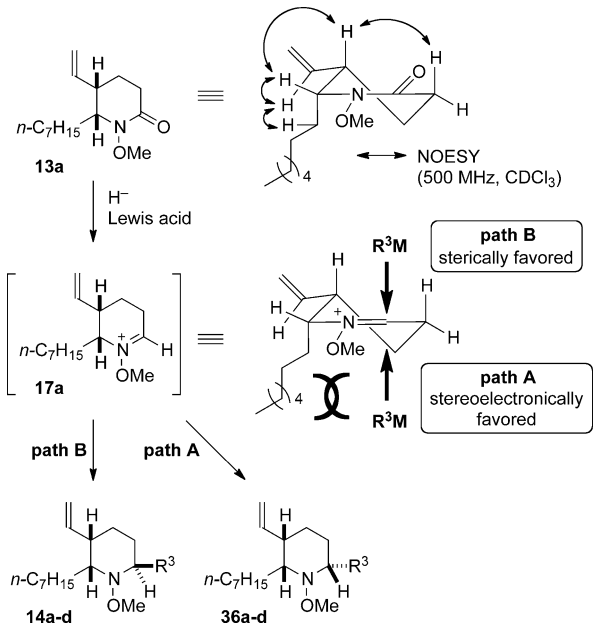
piperidines **14**. *N*-Methoxylactam **13a** was exposed to a variety of nucleophiles (Table 3). Reduction of **13a** with DIBAL-H at −78 °C and subsequent addition of TMSCN and $SnCl_4$ afforded a 2.2:1 diastereomeric mixture of **14a** and **36a** in 87% yield (Table 3, entry 1; DIBAL-H = diisobutylaluminium hydride). Reductive allylation of **13a** took place with allyltributylstannane and $Sc(OTf)_3$, giving **14b** and **36b** in 86% yield with 4.1:1 diastereoselectivity (Table 3, entry 2). Reductive Pictet–Spengler reaction with *N*-methylindole smoothly proceeded at −40 °C in a highly diastereoselective manner (Table 3, entry 3, 88%, **14c**:**36c** = 14:1). A reductive Mannich reaction was possible by use of the Schwartz reagent [Cp_2ZrHCl] as a reductant, providing **14d** in 65% yield as a single diastereomer (Table 3, entry 4). When an organolithium reagent was employed as the first nucleophile, α-trisubstituted amines were synthesized in a one-pot sequence in spite of the steric congestion. Thus, treatment of a solution of **13a** with methyl lithium at −78 °C followed by addition of TMSCN and $SnCl_4$ gave α-trisubstituted amines **14e** and **36e** in 83% yield (Table 3, entry 5). Interestingly, **36e** was isolated as a major diastereomer with 4.0:1 diastereoselectivity. Nucleophilic addition to *N*-methoxylactam **13d** was more challenging because the methyl ester moiety was incompatible with both DIBAL-H and organolithium reagents. However, our chemoselective variant[3] of the nucleophilic addition using the Schwartz reagent was highly effective with substrates bearing sensitive functional groups.[17,18] The reduction of *N*-methoxylactam **13d** with the Schwartz reagent[19–21] at room temperature followed by the addition of TMSCN and 20 mol% $Sc(OTf)_3$ furnished a 1:4.3 diastereomeric mixture of **14f** and **36f** in 86% yield (Table 3, entry 6). The reaction was completely chemoselective, and proceeded without affecting the reactive methyl ester or terminal olefin. The corresponding allylation of **13d** gave **14g** as a major diastereomer (Table 3, entry 7, 74%, **14g**:**36g** = 4.2:1). Thus, the two-step procedure including *N*-methoxyamide/aldehyde coupling and subsequent nucleophilic addition to the resulting *N*-methoxylactam proved to be highly practical to afford a variety of multi-substituted piperidines.

The stereochemical rationale for the reductive nucleophilic addition of *N*-methoxylactam **13a** was shown in Scheme 7. NOESY experiment (500 MHz, $CDCl_3$) indicated that *N*-methoxylactam **13a** existed as a half-chair conformation, in which the alkyl side chain adopted the pseudoaxial position. We believed that transient *N*-oxyiminium ion **17a** might exist as a half-chair conformation similar to **13a**. The nucleophile R^3M then approached from either the α-side (path A) or the β-side (path B), giving multi-substituted piperidines **36a–d** or **14a–d**, respectively. Although the stereoelectronic effect preferred the path A through the axial attack,[22] the steric effect favored the path B due to the steric repulsion with the alkyl side chain. The proposed mechanism agreed well with the observation that the bulkier nucleophile R^3-M such as *N*-methylindole exhibited higher diastereoselectivity, favoring piperidines **14** via the path B (Table 3, entries 1–4). The similar stereochemical outcome was also observed with *N*-methoxylactam **13d**. While the reaction with a small nucleophile such as TMSCN preferred

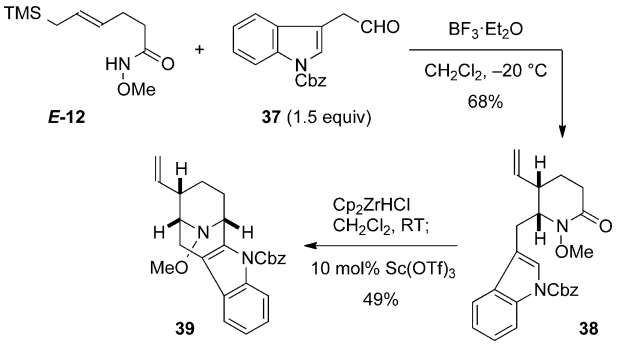


Scheme 7. Plausible mechanistic rational for reductive nucleophilic addition of **13a**.

36f (Table 3, entry 6), larger allyltributylstannane provided **14g** as a major diastereomer (Table 3, entry 7).

As a demonstration to show that the developed method was applicable to complex molecules relating to natural alkaloids, we took an interest in the quick synthesis of a tetracyclic structure embedded in kouamine (**11**) depicted in Figure 1 (Scheme 8). Although indolyl aldehyde **37** tends to be acid-sensitive and easily enolizable, the coupling reaction with *N*-methoxyamide ***E*-12** smoothly took place in 68% yield in *cis*-selective fashion. Treatment of the resulting *N*-methoxylactam **38** with the Schwartz reagent, followed by addition of a catalytic amount of $Sc(OTf)_3$, induced the reductive intramolecular Pictet–Spengler cyclization to give the tetracyclic compound **39** in reasonable yield. It is noteworthy that this reductive cyclization was also highly chemoselective without touching the indole carbamate despite its similar electrophilicity to the *N*-methoxylactam.

All successful examples in the first coupling reaction thus far are two-component reactions employing *N*-methoxyamide **12**,



Scheme 8. Two-step synthesis of multi-substituted *N*-methoxypiperidines via Pictet/Spengler reaction.

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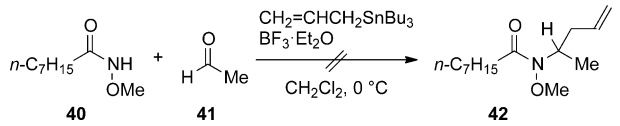
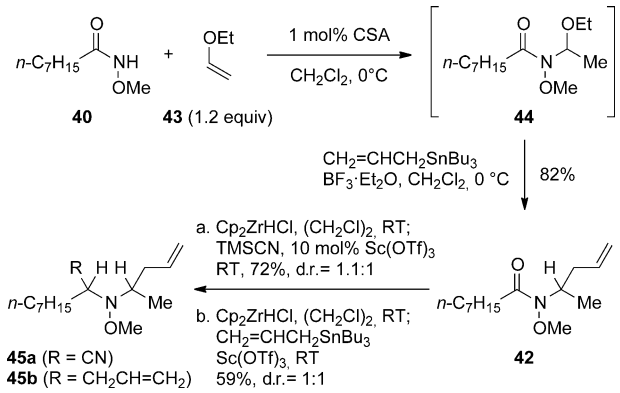
which possesses the allylic silane in the same molecule as the nucleophilic moiety. In order to render the developed method more general, we attempted a three-component coupling reaction using *N*-methoxyamide **40**, acetaldehyde **41**, and allyltributylstannane in the presence of $BF_3{\cdot}Et_2O$ (Scheme 9). Unfortunately, initial attempts were unsuccessful due to the direct allylation of acetaldehyde **41** by allyltributylstannane.



Scheme 9. Attempted three-component coupling of *N*-methoxyamide **40**.

The issue in the three-component coupling reaction is the unfavorable reactivity of each component; the addition of allyltributylstannane to acetaldehyde **41** was much faster than the addition of *N*-methoxyamide **40**, and prevented the formation of the *N*-acyliminium ion. To overcome this reactivity, we took advantage of an enol ether as the aldehyde equivalent (Scheme 10). First, *N*-methoxyamide **40** and ethyl vinyl ether



Scheme 10. The two-step synthesis of multi-substituted *N*-methoxyamines through three-component coupling reaction of *N*-methoxyamides **40**.

43 were pre-coupled in the presence of a catalytic amount of CSA (1 mol%). The resulting *N*,*O*-acetal **44** was then subjected to $BF_3{\cdot}Et_2O$-mediated allylation via the *N*-acyliminium ion, giving **42** in 82% yield in a one-pot process. The nucleophilic additions of *N*-methoxyamide **42** including the reductive cyanation and allylation provided **45a** and **b** in 72 and 59% yields, respectively.

Conclusion

We have documented a two-step synthesis of multi-substituted *N*-methoxyamines involving an *N*-methoxyamide–aldehyde coupling reaction and subsequent nucleophilic addition to amide carbonyls. The key to success was utilization of the *N*-methoxy group as a reactivity control element. The first coupling reaction between the amide and aldehyde took place with enhancement of the nucleophilicity of the nitrogen atom by assistance of the *N*-methoxy group. The next nucleophilic addition was achieved by taking advantage of both the high electrophilicity of amide carbonyls and the chelation effect of *N*-methoxyamides. The developed synthesis enabled quick supply of a set of various 2,3,6-trisubstituted *N*-methoxypiperidines including a substructure of a complex alkaloid. The method was then applied to a three-component coupling reaction, giving acyclic compounds through *N*,*O*-acetals. Thus, we successfully demonstrated that a reactivity control element is a powerful tool to explore practical chemical reactions for synthesis of complex molecules.

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Keywords: amides · nitrogen · nucleophilic addition · piperidine · reactivity control

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FULL PAPER

Synthetic Methods

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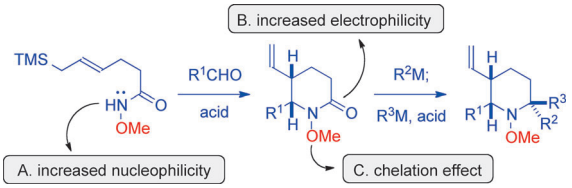
■■ – ■■

VIP Two-step Synthesis of Multi-Substituted Amines by Using an *N*-Methoxy Group as a Reactivity Control Element



Remote control: A two-step synthesis of multi-substituted *N*-methoxyamines including amide/aldehyde coupling and nucleophilic addition to amide carbonyls is reported (see scheme). Incorporation of the *N*-methoxy group to the amides dramatically changes their reactivities, and enables quick access to diverse multi-substituted piperidines and acyclic substituted amines. TMS = trimethylsilyl.

Amine Synthesis

In "old man flower", a Japanese story, the kind old man sprinkled ashes and made dead trees blossom all over. Incorporation of a methoxy group to an amide group opens the door to new reactivities and allows beautiful chemical transformations to blossom in organic synthesis. For more details, see the Full paper by T. Sato, N. Chida et al. on page ■■ ff. We thank Miwako Yoritate and Takamasa Wada for their assistance with artwork.

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