CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201202639

Direct Nucleophilic Addition to *N*-Alkoxyamides

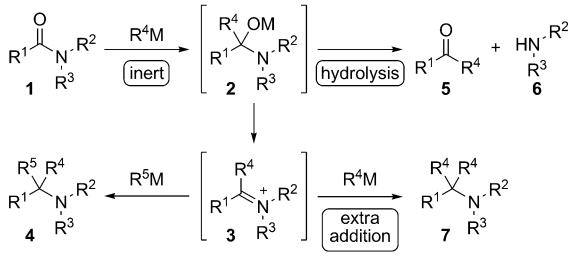
Yuta Yanagita, Hugh Nakamura, Kenji Shirokane, Yusuke Kurosaki, Takaaki Sato,* and Noritaka Chida*[a]

Abstract: While the synthesis of amide bonds is now one of the most reliable organic reactions, functionalization of amide carbonyl groups has been a long-standing issue due to their high stability. As an ongoing program aimed at practical transformation of amides, we developed a direct nucleophilic addition to *N*-alkoxyamides to access multisubstituted amines. The reaction enabled installation of two different functional groups to amide carbonyl groups in one pot. The *N*-alkoxy group played important roles in this reaction. First, it removed the requirement for an extra preactivation step prior to nucleophilic addition to activate inert amide carbonyl groups. Second, the *N*-alkoxy group formed a five-membered chelated complex after the first nucleophilic addition, resulting in suppression of an extra addition of the first nucleophile. While diisobutylaluminum hydride (DIBAL-H) and organolithium reagents were suitable as the first nucleophile, allylation, cyanation, and vinylation were possible in the second addition including inter- and intramolecular reactions. The yields were generally high, even in the synthesis of sterically hindered α-trisubstituted amines. The reaction exhibited wide substrate scope, including acyclic amides, five- and six-membered lactams, and macrolactams.

Keywords: allylation · amides · cyanation · nucleophilic addition · synthetic methods

Introduction

Amide functional groups are found in a wide variety of organic molecules including pharmaceuticals and functional materials. Therefore, the efficient synthesis of amide bonds has been extensively studied and is now one of the most promising reactions in modern organic synthesis.[1] On the other hand, transformation of the generated amide groups is less explored than their construction. Although amide carbonyl groups can potentially accept two organometallic reagents through nucleophilic addition to give multisubstituted amines, this transformation is far more challenging than with ketones and esters (Scheme 1, **1**→**2**→**3**→**4**).[2–5] The first nucleophilic addition to an amide carbonyl group (**1**→**2**) requires harsh reaction conditions because of the high stability of amide carbonyl moieties, caused by the resonance effect of the nitrogen atom. Even when the first addition is achieved, the generation of iminium ion **3** is not trivial due to the instability of *N*,*O*-acetal **2**, resulting in the formation of ketone **5** and amine **6**. In addition, the generated iminium ion **3** readily reacts with the remaining first nucleophile, again to afford **7** because iminium ion **3** is more electrophilic than the amide carbonyl itself.

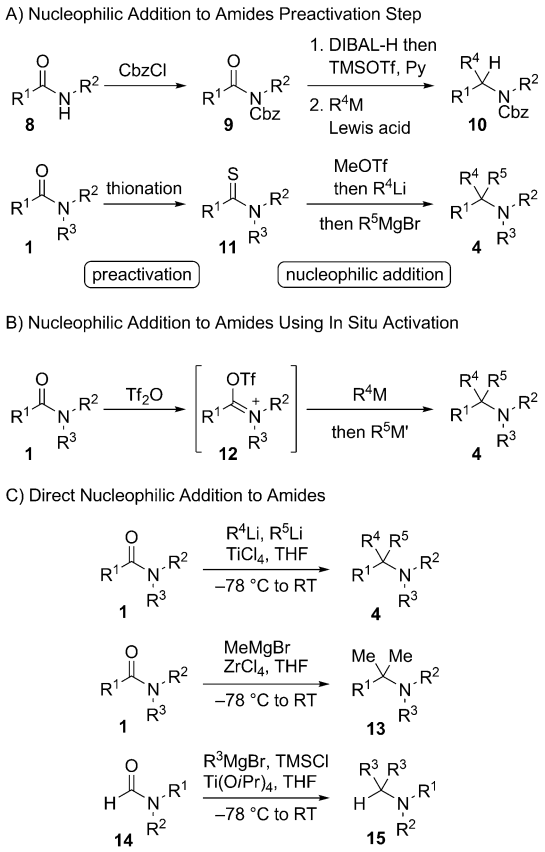


Scheme 1. Nucleophilic addition to amide carbonyl groups and its inherent problems.

The development of practical nucleophilic addition reactions to amides must address two key issues. The first is enhancement of the poor electrophilicity of the amide carbonyl group. The second is sequential installation of two different nucleophiles by preventing multiple addition of the first nucleophile. To overcome these issues, most practical nucleophilic additions so far have utilized a preactivation step. This extra step renders the amide carbonyl group more reactive and suppresses extra addition of the first nucleophile (Scheme 2 A). One of the more useful examples is preactivation of the acyclic amide to an imide (DeNinno,[6] Suh,[7] **8**→**9**→**10**). In Suh's methodology,[7] reduction of **9** with diisobutylaluminum hydride (DIBAL-H), followed by trapping with TMSOTf and pyridine in situ gave an *N*,*O*-acetal TMS

[a] Y. Yanagita, H. Nakamura, K. Shirokane, Y. Kurosaki, Dr. T. Sato, Prof. 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
Fax: (+81) 45-566-1551
E-mail: takaakis@applc.keio.ac.jp
chida@applc.keio.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201202639.



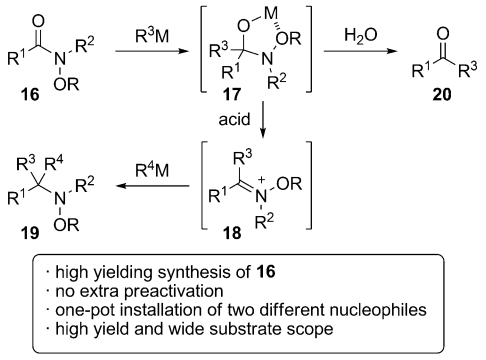
Scheme 2. Selected examples of nucleophilic addition to amide carbonyl groups: A) Use of a preactivation step, B) in situ activation, and C) direct nucleophilic addition. DIBAL-H = diisobutylaluminum hydride, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

ether, which underwent Lewis acid promoted nucleophilic addition to provide **10**. Although only a hydride (DIBAL-H) could be used as the first nucleophile and a three-step procedure was required, significant improvement of the substrate scope including acyclic amides[7a] and macrolactams[7b] was realized. Thionation of the amide carbonyl groups is another practical preactivation strategy (**1**→**11**→**4**).[8] Murai reported sequential nucleophilic additions of acyclic thionium salts with two different carbon nucleophiles involving organolithium and Grignard reagents.[8f,g] To circumvent the extra preactivation step, "in situ activation" was developed by using Tf_2O/2,6-di-*tert*-butyl-4-methylpyridine (Scheme 2B).[9] This approach dramatically expanded the nucleophilic addition to amides. Bélanger[9c,f] and Huang[9d,e] independently reported sequential nucleophilic additions via iminium triflate (**1**→**12**→**4**). Two different carbon nucleophiles were installed in one pot, resulting in the formation of sterically hindered α-trisubstituted amines.[10] On the other hand, some direct nucleophilic additions to amide carbonyl groups without a preactivation step have been reported (Scheme 2C).[11] The key to success was utilization of oxophilic Lewis acids such as $TiCl_4$ (Schiess: **1**→**4**[11b]), $ZrCl_4$ (Denton: **1**→**13**[11d]) and Ti(O*i*Pr)$_4$/TMSCl (de Meijere: **14**→**15**[11e]). Unfortunately, direct nucleophilic additions tended to exhibit low yields and could only install two identical functional groups except in the approach developed by Schiess.[11b]

In this paper, we disclose full details of our investigations on the direct nucleophilic addition to *N*-alkoxyamides without an extra preactivation step.[12] The reaction allowed two different organometallic reagents to be used in one pot. In many cases, these nucleophilic addition reactions proceeded in high yields and showed a wide substrate scope including acyclic amides, five- or six-membered lactams, and macrolactams.

Results and Discussion

Our laboratory has been exploring practical transformations of amide groups and, in this context, initiated a program to develop a direct nucleophilic addition to amide carbonyl groups. As noted earlier, the reaction requires a new approach to enhance the electrophilicity of amide carbonyl groups without a preactivation step and to install two different nucleophiles in one pot. Our fundamental idea to solve these issues is the utilization of *N*-alkoxyamides **16**, which are readily prepared by condensation between a carboxylic acid and an *N*-methoxyamine (Scheme 3). Treatment of **16**



Scheme 3. Direct nucleophilic addition to *N*-alkoxyamides.

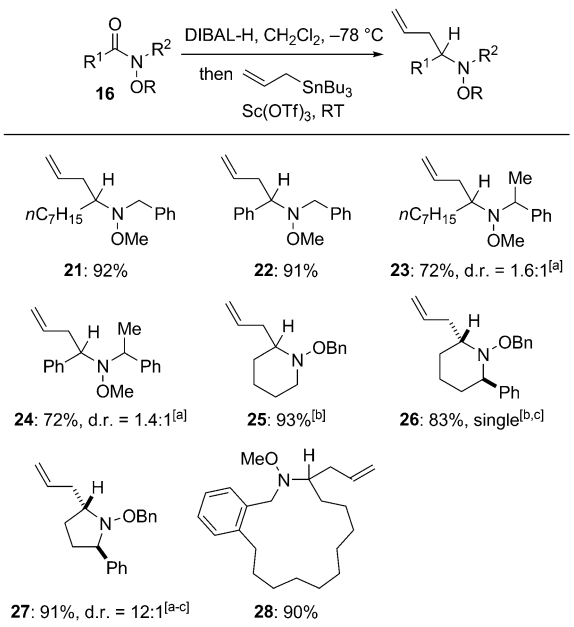
with an organometallic reagent is known to produce the five-membered chelated intermediate **17**. Whereas the well-known Weinreb ketone synthesis[13] provides ketone **20** after hydrolysis of **17** without extra addition of the nucleophile, our approach requires the capture of intermediate **17** with acid. The resulting *N*-oxyiminium ion **18**[14,15] would then undergo a second nucleophilic addition to give multisubstituted *N*-alkoxyamines **19**. The *N*-alkoxy group would play important roles in this reaction. First, it enhances the electrophilicity of the amide carbonyl (inherent activation), resulting in elimination of the extra preactivation step. Second, the *N*-alkoxy group possesses chelation ability and is able to form the relatively stable intermediate **17**, which would suppress the extra addition of the first nucleophile. Moreover, the *N*-alkoxy group in the resulting multisubstituted amine **19** could enable further unique transformations such as re-

ductive cleavage of the *N*-alkoxy group to give secondary amines, and direct oxidation to nitrones.[16]

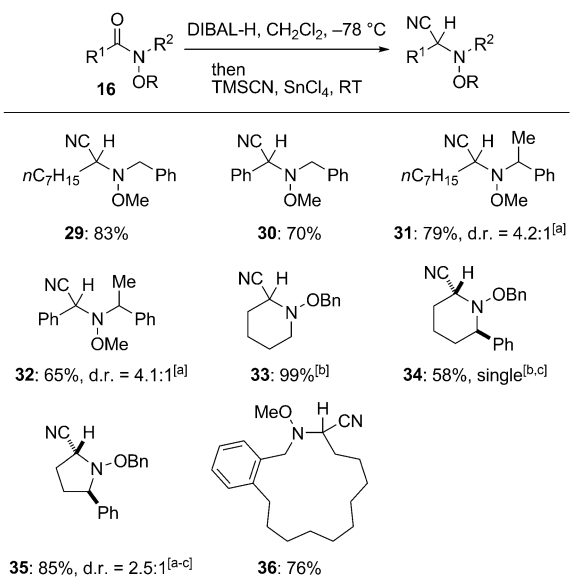
Direct nucleophilic addition to *N*-alkoxyamides was first realized by using *N*-benzyl-*N*-methoxyoctanamide with DIBAL-H and allyltributylstannane (Scheme 4).[17] Treatment of a solution of *N*-methoxyamide in CH_2Cl_2 with DIBAL-H at −78 °C and subsequent addition of allyltributylstannane in the presence of $Sc(OTf)_3$ afforded *N*-methoxyamine **21** in 92% yield in one pot. Performing the reaction without $Sc(OTf)_3$ resulted in simple hydrolysis of the chelated intermediate, leading to the recovery of octanal and *N*-benzyl-*N*-methoxyamine. This result indicated that assistance of $Sc(OTf)_3$ was essential to form the corresponding *N*-oxyiminium ion from the five-membered chelated intermediate. The direct reductive allylation was found to be highly general with respect to the structure of the *N*-alkoxyamides. Reaction of the linear substrate derived from benzoic acid gave product **22** in 91% yield. Sterically hindered branched amides showed slightly lower yields than the linear amides (**23**: 72%, **24**: 72%). Unfortunately, poor diastereoselectivities were observed in both cases. This methodology enabled the one-pot synthesis of substituted piperidines and pyrrolidines from the corresponding *N*-benzyloxylactams[18] (**25**–**27**: 83–93%). In the case of α-phenyl-substituted lactams, acetonitrile as an additional solvent was necessary in the allylation step to provide **26** and **27** in 83 and 91% yields, respectively.[19] The second allylating reagent approached from the opposite side of the phenyl group, leading to the highest level of diastereoselectivities. The most conspicuous example of our methodology was application to a macrocyclic lactam.[20] It is known that nucleophilic addition to macrolactams is highly challenging because the iminium intermediate is unstable, and readily undergoes hydrolysis to give the corresponding amino aldehyde. However, the developed conditions allowed the reductive allylation to furnish 15-membered macrocyclic amine **28** in 90% yield.

The method was applicable to the Strecker type reaction with TMSCN (Scheme 5).[21] In contrast to reductive allylation, the cyanation proceeded without Lewis acid (**29**: 48%). However, addition of three equivalents of $SnCl_4$ significantly improved the yield to afford **29** in 83% yield. The substrate scope of the reductive cyanation was then surveyed under the optimized conditions. Acyclic amides underwent the cyanation in good yields (**30**–**32**: 65–79%). In contrast to allylation, the reaction of branched amides proceeded with moderate diastereoselectivities (**31**: d.r. = 4.2:1, **32**: d.r. = 4.1:1). *N*-Benzyloxylactams were also viable substrates for the cyanation (**33**–**35**: 58–99%). Interestingly, while the five-membered lactam led to poor diastereoselectivity (**35**: d.r. = 2.5:1), the six-membered lactam proceeded in a completely diastereoselective manner (**34**: single diastereoisomer). The reaction of the challenging 15-membered macrolactam gave **36** in reasonable yield.

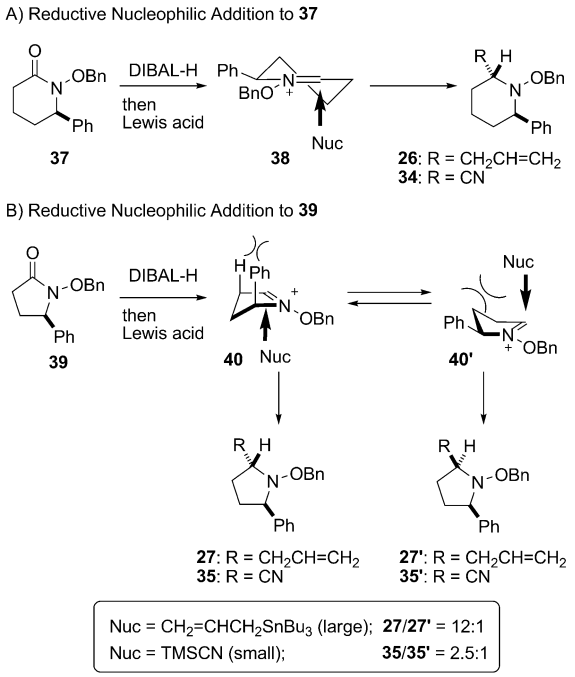
The stereochemical outcomes of the reductive allylation and cyanation of α-phenyl-substituted lactams **37** and **39** were rationalized on the basis of transient *N*-oxyiminium ions (Scheme 6). DIBAL-H mediated reduction of six-mem-



Scheme 4. Substrate scope for the direct reductive allylation. Reagents and conditions: **16** (0.11 mmol), DIBAL-H (1.01 M in toluene, 1.3 equiv), CH_2Cl_2 (0.1 M), −78 °C, 0.5 h, then $CH_2{=}CHCH_2SnBu_3$ (3 equiv), $Sc(OTf)_3$ (1.3 equiv), RT, 1.5 h. [a] The diastereomeric ratios were determined by ^1H NMR spectroscopic analysis. [b] The reaction was performed in THF (0.1 M) instead of CH_2Cl_2. [c] CH_3CN (0.3 M) was added prior to addition of $CH_2{=}CHCH_2SnBu_3$.



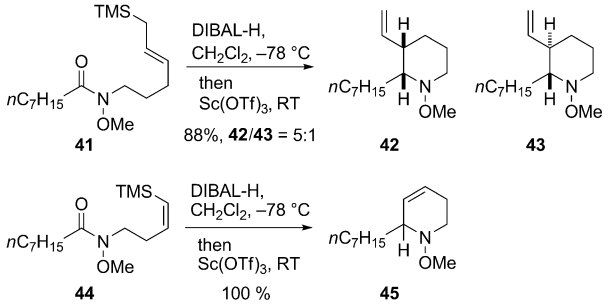
Scheme 5. Substrate scope for the direct reductive cyanation. Reagents and conditions: **16** (0.11 mmol), DIBAL-H (1.01 M in toluene, 1.3 equiv), CH_2Cl_2 (0.1 M), −78 °C, 0.5 h, then TMSCN (3 equiv), $SnCl_4$ (3 equiv), RT, 1.5 h. [a] The diastereomeric ratios were determined by ^1H NMR spectroscopic analysis. [b] The reaction was performed in THF (0.1 M) instead of CH_2Cl_2. [c] CH_3CN (0.3 M) was added prior to addition of TMSCN.



Scheme 6. Possible rationale for the stereochemical outcomes in the reductive nucleophilic additions of α-phenyl-substituted lactams **37** and **39**.

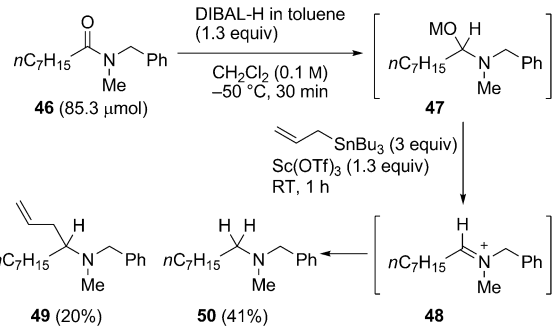
bered lactam **37** and subsequent addition of Lewis acid formed *N*-oxyiminium ion **38**, in which the large phenyl group adopted the pseudoequatorial position (Scheme 6A). The second nucleophile then approached from the opposite side of the phenyl group through a stereoelectronically preferred axial attack.[22] In the case of five-membered lactam **39**, the inside-attack model reported by Woerpel would account for the stereoselectivity (Scheme 6B).[23] When a large nucleophile such as allyltributylstannane was employed, the steric interaction between the nucleophile and the phenyl group in transition state **40′** would dominate, leading to the formation of **27** in high diastereoselectivity via transition state **40** (**27**/**27′** = 12:1). On the other hand, the steric interaction in **40′** would be suppressed when smaller TMSCN was employed. The generation of **35′** via transition state **40′** could then compete due to the relatively increased 1,3-diaxial-like steric interaction in transition state **40**, resulting in the poor diastereoselectivity (**35**/**35′** = 2.5:1).

We then turned our attention to an intramolecular version to generate substituted azacycles from acyclic *N*-alkoxyamides (Scheme 7).[24–26] Treatment of *N*-methoxyamide **41** bearing an (*E*)-allylsilane group[27] with DIBAL-H, followed by subsequent addition of $Sc(OTf)_3$, promoted the cyclization to give 2,3-disubstituted piperidines **42** and **43** in 88% combined yield. Interestingly, the reaction proceeded in a diastereoselective fashion, favoring the unusual *cis* arrangement (**42**/**43** = 5:1). We then found that the methodology allowed the use of not only allylsilane but also (*Z*)-vinylsilane.[28] Treatment of **44** with DIBAL-H, followed by subsequent addition of $Sc(OTf)_3$, initiated the intramolecular reductive vinylation to provide **45** in quantitative yield.[29]



Scheme 7. Intramolecular cyclization of *N*-methoxyamides.

To confirm the beneficial effects of the *N*-alkoxy group, a control experiment with *N*-benzyl-*N*-methyloctanamide (**46**) was attempted under the optimized conditions (Scheme 8).



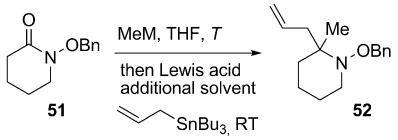
Scheme 8. Control experiment without the *N*-methoxy group.

First, it was observed that the DIBAL-H-mediated reduction was not complete at −78 °C without the *N*-alkoxy group, and the reaction needed to be performed at −50 °C. The resulting solution was then treated with allyltributylstannane and $Sc(OTf)_3$ at room temperature, providing the desired amine **49** in 20% yield, along with the over-reduced byproduct **50** in 41% yield. In other words, *N*,*O*-acetal **47** did not form a tightly chelated complex and was quickly converted into iminium ion **48**, which underwent further DIBAL-H-mediated reduction to give **50**. These two observations clearly indicated that the *N*-alkoxy group enhanced the electrophilicity of the amide carbonyl and suppressed the extra addition of DIBAL-H through the tight chelation, resulting in successful installation of two different functional groups in one pot.

α-Trisubstituted amines are among the most important structural motifs embedded in a number of biologically active natural products. Despite their ubiquity, their efficient synthesis is not trivial because of the steric congestion imposed by the three attached carbon atoms and the one nitrogen atom. Our nucleophilic addition to *N*-alkoxyamides has the potential to solve this challenging task by employing a carbon nucleophile in the first addition. If successful, α-trisubstituted amines could be constructed from easily accessible *N*-alkoxyamides in one pot. To test the feasibility of the reaction, six-membered *N*-benzyloxylactam **51**[30] was ex-

posed to a variety of methylmetallic reagents (Table 1). The resulting chelated intermediate was then treated with $Sc(OTf)_3$ and allyltributylstannane at room temperature. After extensive investigation, an organolithium reagent proved to be the best nucleophile in the first addition, providing **52** in 47% yield (Table 1, entries 1–3). Addition of acetonitrile prior to the second allylation dramatically improved the yield of **52** (Table 1, entries 3 and 4).

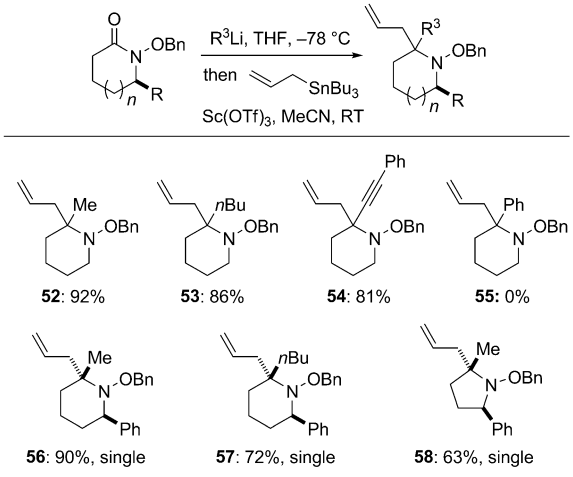
Table 1. Optimization of the synthesis of α-trisubstituted amine **52** from *N*-benzyloxylactam **51** in one pot.[a]



Entry	MeM	Temp. [°C]	Additional solvent	Yield [%][b]
1	Me_3Al	−20	none	5
2	MeMgBr	−78	none	12
3	MeLi	−78	none	47
4	MeLi	−78	CH_3CN (0.3 M)	92

[a] Reaction conditions: **51** (0.15 mmol), MeM (1.3 equiv), THF (0.1 M), 10 min, then additive, $CH_2{=}CHCH_2SnBu_3$ (3 equiv), $Sc(OTf)_3$ (1.3 equiv), RT, overnight. [b] Yield of isolated product after purification by column chromatography.

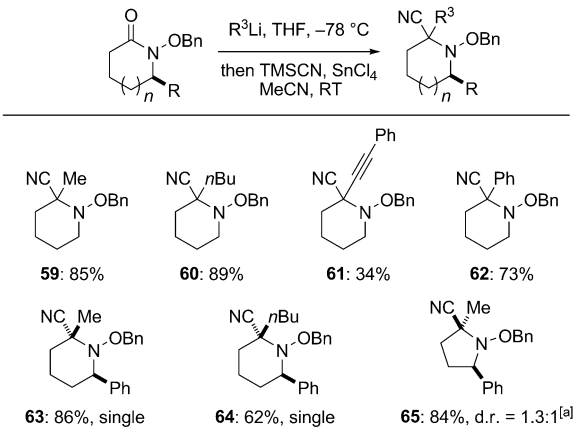
With optimized conditions in hand, the scope of the reaction was investigated (Scheme 9). Variation in the organolithium reagent was possible, and suitable reagents included methyl lithium, *n*-butyl lithium, and lithium acetylide (**52**: 92%, **53**: 86%, **54**: 81%), but not phenyl lithium (**55**: 0%). *N*-Benzyloxylactams with an α-phenyl-substituent also proved to be viable substrates. The reactions with methyl lithium and *n*-butyl lithium smoothly took place in spite of



Scheme 9. Substrate scope for the synthesis of α-trisubstituted amines from *N*-benzyloxylactams through allylation in one pot. Reagents and conditions: lactam (0.15 mmol), R^3Li (1.3 equiv), THF (0.1 M), 10 min, then CH_3CN (0.3 M), $CH_2{=}CHCH_2SnBu_3$ (3 equiv), $Sc(OTf)_3$ (1.3 equiv), RT, overnight.

fairly congested steric environments, affording **56** and **57** in 90 and 72% yields, respectively. It is noteworthy that the reactions proceeded with complete diastereoselectivity through a transition state similar to that depicted in Scheme 6 to give multisubstituted piperidines as a single diastereoisomer. The reaction with the five-membered lactam occurred without loss of diastereoselectivity (**58**: 63%).

We then turned our attention to the Strecker type reaction with TMSCN (Scheme 10). Use of methyl lithium and *n*-butyl lithium gave the products in high yields (**59**: 85%, **60**: 89%). Lithium acetylide led to a low yield because exposure of the chelated intermediate to $SnCl_4$ formed a



Scheme 10. Substrate scope for the synthesis of α-trisubstituted amines from *N*-benzyloxylactams through cyanation in one pot. Reagents and conditions: lactam (0.15 mmol), R^3Li (1.3 equiv), THF (0.1 M), −78 °C, 10 min, then CH_3CN (0.3 M), TMSCN (3 equiv), $SnCl_4$ (1.3 equiv), RT, overnight. [a] The diastereomeric ratios were determined by ^1H NMR spectroscopic analysis.

stable conjugated enamine that prevented the second cyanation (**61**: 34%). In contrast to the allylation, phenyl lithium was a viable organolithium reagent, giving **62** in 73% yield. The reaction was also tolerant towards *N*-benzyloxylactams bearing an α-phenyl substituent. While a five-membered lactam exhibited poor diastereoselectivity, slightly favoring the β-cyanide (**65**: 84%, d.r. = 1.3:1), six-membered lactams provided α-cyanides as single diastereoisomers (**63**: 86%, **64**: 62%). Thus, our methodology enabled the installation of two different carbon nucleophiles to an amide carbonyl group in one pot. The yield of the nucleophilic addition was generally high in spite of significant steric hindrance.

Conclusion

We have developed a practical, direct nucleophilic addition to *N*-alkoxyamides. Salient features of our methodology are: 1) high yielding synthesis of *N*-alkoxyamides, 2) exclusion of the extra preactivation step prior to nucleophilic addition, 3) installation of two different organometallic reagents in one pot, and 4) generally high yields and a wide substrate

scope that includes acyclic amides, lactams, and macrocyclic lactams. In addition, α-trisubstituted amines were easily accessible by utilization of organolithium reagents in the first addition. We believe that the developed methodology will be applicable to the synthesis of multifunctionalized amines found in pharmaceuticals and biologically active alkaloids.

Acknowledgements

This research was supported by a Grant-in-Aid for Young Scientists (B) from MEXT (24750045), the Otsuka Pharmaceutical Co. Award in Synthetic Organic Chemistry, Japan, and JSPS fellow to K.S. (24·1843). We thank Professor Takeshi Noda and Ms. Yuka Shibaoka, Kanagawa Institute of Technology, for their assistance with mass spectrometric analysis.

[1] For selected recent 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 a review on the functionalization of carbonyl groups in ketones, esters, and amides, see: D. Seebach, *Angew. Chem.* **2011**, *123*, 99–105; *Angew. Chem. Int. Ed.* **2011**, *50*, 96–101.

[3] Related nucleophilic additions of esters with higher electrophilicity than amides were reported. For examples of one-pot conversions of acyclic esters into 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.

[4] For examples of 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; e) Y. Nishimoto, Y. Inamoto, T. Saito, M. Yasuda, A. Baba, *Eur. J. Org. Chem.* **2010**, 3382–3386; f) Y. Inamoto, Y. Nishimoto, M. Yasuda, A. Baba, *Org. Lett.* **2012**, *14*, 1168–1171.

[5] For examples of 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.

[6] 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.

[7] 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.

[8] For a review on nucleophilic additions to thioamides, see: a) T. Murai, Y. Mutoh, *Chem. Lett.* **2012**, *41*, 2–8. For selected examples of nucleophilic additions to acyclic thioamides, see: b) Y. Tamaru, T. Harada, S. Nishi, Z. Yoshida, *Tetrahedron Lett.* **1982**, *23*, 2383–2386; c) A. Ishida, T. Nakamura, K. Irie, T. Oh-ishi, *Chem. Pharm. Bull.* **1985**, *33*, 3237–3249; d) Y. Tominaga, S. Kohra, A. Hosomi, *Tetrahedron Lett.* **1987**, *28*, 1529–1532; e) Y. Tominaga, Y. Matsuoka, H. Hayashida, S. Kohra, A. Hosomi, *Tetrahedron Lett.* **1988**, *29*, 5771–5774; f) T. Murai, Y. Mutoh, Y. Ohta, M. Murakami, *J. Am. Chem. Soc.* **2004**, *126*, 5968–5969; g) T. Murai, F. Asai, *J. Am. Chem. Soc.* **2007**, *129*, 780–781.

[9] For selected examples of sequential nucleophilic additions by 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; e) K.-J. Xiao, Y. Wang, K.-Y. Ye, P.-Q. Huang, *Chem. Eur. J.* **2010**, *16*, 12792–12796; f) G. Bélanger, G. O'Brien, R. Larouche-Gauthier, *Org. Lett.* **2011**, *13*, 4268–4271; g) J. W. Medley, M. Movassaghi, *Angew. Chem.* **2012**, *124*, 4650–4654; *Angew. Chem. Int. Ed.* **2012**, *51*, 4572–4576; h) K.-J. Xiao, A.-E. Wang, P.-Q. Huang, *Angew. Chem.* **2012**, *124*, 8439–8442; *Angew. Chem. Int. Ed.* **2012**, *51*, 8314–8317. For chemoselective reduction of secondary amides to ketones and ketimines using triflic anhydride, see: i) W. S. Bechara, G. Pelletier, A. B. Charette, *Nat. Chem.* **2012**, *4*, 228–234; j) K.-J. Xiao, A.-E. Wang, Y.-H. Huang, P.-Q. Huang, *Asian J. Org. Chem.* **2012**, *1*, 130–132.

[10] Lu reported the synthesis of α-tertiary α-silylamines from aryl sulfonylimidates by using a related sequential nucleophilic addition, see: X.-J. Han, M. Yao, C.-D. Lu, *Org. Lett.* **2012**, *14*, 2906–2909.

[11] We reported the direct chemoselective allylation of tertiary and secondary amides with Schwartz reagent, see: Y. Oda, T. Sato, N. Chida, *Org. Lett.* **2012**, *14*, 950–953; for selected examples of direct nucleophilic additions, see: a) F. Kuffner, E. Polke, *Monatsh. Chem.* **1951**, *82*, 330–335; b) M. Schiess, Diss. ETH Nr. 7935, ETH Zürich (CH), **1986**; c) D. J. Calderwood, R. V. Davies, P. Rafferty, H. L. Twigger, H. M. Whelan, *Tetrahedron Lett.* **1997**, *38*, 1241–1244; d) S. M. Denton, A. Wood, *Synlett* **1999**, 55–56; e) O. Tomashenko, V. Sokolov, A. Tomashevskiy, H. A. Buchholz, U. Welz-Biermann, V. Chaplinski, A. de Meijere, *Eur. J. Org. Chem.* **2008**, 5107–5111.

[12] Part of this work was published as a preliminary account, see: a) K. Shirokane, Y. Kurosaki, T. Sato, N. Chida, *Angew. Chem.* **2010**, *122*, 6513–6516; *Angew. Chem. Int. Ed.* **2010**, *49*, 6369–6372; for an example of direct conversion of *N*-alkoxyamides, see: b) G. Vincent, R. Guillot, C. Kouklovsky, *Angew. Chem.* **2011**, *123*, 1386–1389; *Angew. Chem. Int. Ed.* **2011**, *50*, 1350–1353; Kibayashi reported pioneering work involving Grignard addition and subsequent hydride reduction to six-membered *N*-alkoxylactams, see: c) H. Iida, Y. Watanabe, C. Kibayashi, *J. Am. Chem. Soc.* **1985**, *107*, 5534–5535.

[13] a) S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815–3818; for selected recent reviews on Weinreb amides, 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.

[14] For selected examples of reactions involving *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. Ali 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; o) Y. Kurosaki, K. Shirokane, T. Oishi, T. Sato, N. Chida, *Org. Lett.* **2012**, *14*, 2098–2101.

[15] For selected examples of reactions involving *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 of the direct oxidation of *N*-alkoxyamines to nitrons, see a) Ref. [14m]; b) 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; c) S. A. Ali, M. I. M. Wazeer, *Tetrahedron Lett.* **1993**, *34*, 137–140; d) K. Nagasawa, A. Georgieva, H. Koshino, T. Nakata, T. Kita, Y. Hashimoto, *Org. Lett.* **2002**, *4*, 177–180.

[17] For selected reviews on the allylation to 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.

[18] The *N*-benzyloxy group instead of the *N*-methoxy group was used because the product derived from the *N*-methoxylactam was highly volatile.

[19] Although the role of CH_3CN is not clear, the yields were improved, irrespective of the nucleophile used, when the sterically hindered lactams were employed as the reaction substrates.

[20] Suh et al. reported a three-step synthesis of macrocyclic amines from macrolactams by using α-alkoxy carbamates, see Ref. [17b].

[21] 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.

[22] a) R. V. Stevens, *Acc. Chem. Res.* **1984**, *17*, 289–296; b) P. Deslongchamps, *Stereolectronic Effects in Organic Chemistry*, Pergamon, New York, **1983**, Chapter 6.

[23] a) C. H. Larsen, B. H. Ridgway, J. T. Shaw, K. A. Woerpel, *J. Am. Chem. Soc.* **1999**, *121*, 12208–12209; b) D. M. Smith, K. A. Woerpel, *Org. Lett.* **2004**, *6*, 2063–2066.

[24] 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.

[25] For selected examples of allylsilane cyclizations in a *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.

[26] For selected examples of allylsilane cyclizations in a *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.

[27] The allylsilane instead of the allylstannane was employed in the intramolecular cyclization because of the straightforward synthesis. While the intermolecular reaction with allyltrimethylsilane led to a low yield, the intramolecular version with allylsilane showed the sufficient nucleophilicity.

[28] For a selected review on vinylsilane cyclization, see: T. A. Blumenkopf, L. E. Overman, *Chem. Rev.* **1986**, *86*, 857–873.

[29] The reaction might proceed through a [3,3]-sigmatropic rearrangement and subsequent intramolecular allylation, see: G. W. Daub, D. A. Heerding, L. E. Overman, *Tetrahedron* **1988**, *44*, 3919–3930.

[30] Unfortunately, acyclic *N*-alkoxyamides were not suitable substrates for the synthesis of α-trisubstituted amines. Although the first addition with organolithium reagents proceeded smoothly, the second allylation or cyanation was not observed.

Received: July 25, 2012
Revised: October 2, 2012
Published online: November 14, 2012

