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Concise Synthesis of α-Trisubstituted Amines from Ketones Using *N*-Methoxyamines

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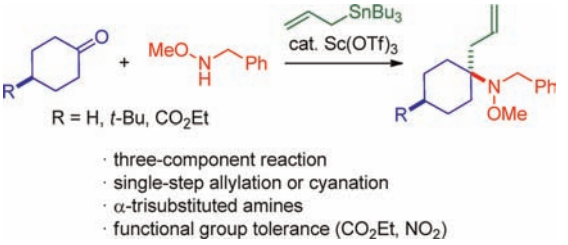
ABSTRACT



Three-component allylation and cyanation utilizing a ketone and an *N*-methoxyamine are reported. The high nucleophilicity of the *N*-methoxyamine and high electrophilicity of the corresponding iminium ion enable the concise synthesis of α-trisubstituted amines in a single step.

α-Trisubstituted amines are one of the most important structural motifs, embedded in a number of biologically active alkaloids such as halichlorine,[1] FR901483,[2] and histrionicotoxin[3] (Figure 1). The simplest approach to the structure is nucleophilic addition to a ketimine **3** derived from the condensation of a ketone **1** and a primary amine **2** (Scheme 1, **1** + **2** → **3** → **4**).[4] However, this approach suffers from several drawbacks: (1) poor electrophilicity of the ketimine **3** due to electronic and steric effects compared with aldimines, (2) the instability of ketimine **3**, and (3) α-deprotonation to form metal enamines. Functional group tolerance is also problematic because poorly electrophilic ketimines very often require reactive nucleophiles such as Grignard reagents. To circumvent these problems, general approaches have taken advantage of amines such as **5**, with a supporting functional group such as an *N*-sulfinyl amine,[4a,e] an *N*-benzoylhydrazine,[4b,f] or an *N*-diphenylphosphinoyl amide.[4c,d,f] These supporting functional groups render the imines more stable as well as more reactive to nucleophiles (**1** + **5** → **6** → **7**). Although these methodologies are very practical and offer high stereoselectivity, they require a three-step sequence that includes deprotection.

During our pursuit of new chemistry related to the nitrogen−oxygen bond, we discovered seemingly contradictory

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(1) (a) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867–3870. (b) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861–862. For a review, see: (c) Clive, D. L. J.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S. *Chem. Rev.* **2005**, *105*, 4483–4514.

(2) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37–44.

(3) (a) Daly, J. W.; Karle, I.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870–1875. For a review, see: (b) Sinclair, A.; Stockman, R. A. *Nat. Prod. Rep.* **2007**, *24*, 298–326.

(4) For selected reviews on synthesis of α-trisubstituted amines through nucleophilic addition to imines, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995. (b) Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5176–5186. (c) Shibasaki, M.; Kanai, M. *Org. Biomol. Chem.* **2007**, *5*, 2027–2039. (d) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853–2873. (e) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600–3740. (f) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704.

(5) We reported sequential nucleophilic addition to *N*-methoxyamide via an *N*-methoxyiminium ion; see: (a) Shirokane, K.; Kurosaki, Y.; Sato, T.; Chida, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 6369–6372. Kibayashi and Vincent/Kouklovsky reported similar reactions of *N*-alkoxylactams; see: (b) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534–5535. (c) Vincent, G.; Guillot, R.; Kouklovsky, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1350–1353.

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properties of *N*-methoxyamine **8** (Scheme 1). In general, the condensation of a highly nucleophilic amine derivative with a carbonyl group tends to give a poorly electrophilic iminium ion. However, the *N*-methoxyiminium ion **9**[5,6] exhibited unexpectedly high electrophilicty despite the high nucleophilicity of *N*-methoxyamine **8**.[7,8] Thus, the condensation of **8** with ketone **1** could generate *N*-methoxyiminium ion **9** with assistance of an acid, followed by nucleophilic addition to the resulting iminium ion **9** to give sterically hindered α-trisubstituted *N*-methoxyamine **10** in a single step. In addition, the *N*-methoxy group was easily removed with Zn in AcOH to give secondary amine **4**.

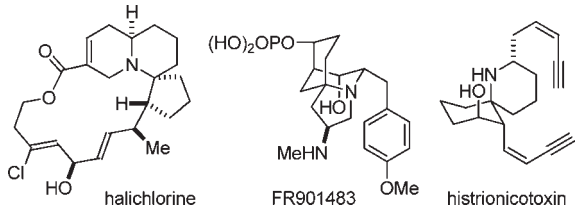
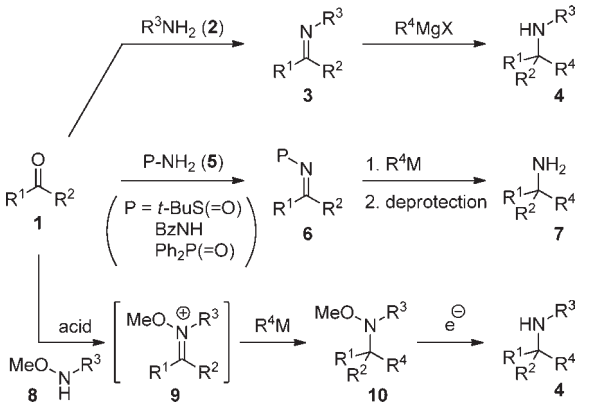


Figure 1. Representative natural products containing α-trisubstituted amines.

The present investigation commenced with a three-component allylation utilizing cyclohexanone **11**, a variety of *N*-substituted-*N*-benzylamines **12**, and allyltributylstannane

Scheme 1. Synthesis of α-Trisubstituted Amines **4** or **7** from Ketones **1**

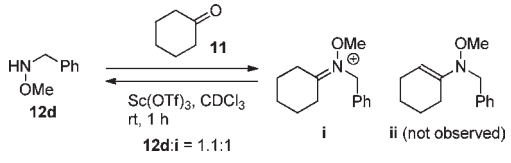


in the presence of a catalytic amount of $Sc(OTf)_3$ (Table 1).[9] The three-component reaction of *N*,*N*-disubstituted amine **12** is very challenging because of steric hindrance, which suppresses the condensation with cyclohexanone **11**. Indeed, use of Cbz-protected amine **12a** led to the generation of tertiary alcohol **14** in 41% yield through the direct allylation of ketone **11** (entry 1). *N*-Methyl-*N*-benzylamine **12b** gave neither α-trisubstituted amine **13b** nor tertiary alcohol **14** (entry 2). On the contrary, the condensation of primary *N*-benzylamine **12c** with cyclohexanone **11**, followed by allylation, gave secondary amine **13c** in low yield, probably because allyltributylstannane did not possess sufficient nucleophilicity for the imine (entry 3).[10] *N*-Methoxyamine **12d** was then exposed to the same allylation conditions (entry 4).[11] As we expected, *N*-methoxyamine **12d** exhibited high nucleophilicity and smoothly condensed with ketone **11** to generate a highly electrophilic *N*-methoxyiminium ion. The allylation with allyltributylstannane then took place, affording α-trisubstituted amine **13d** in 85% yield, along with a small amount of tertiary alcohol **14** in 7% yield. It is noteworthy that ketone **11** and *N*-methoxyamine **12d** were used in an equal molar ratio.

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

(7) Oxime ethers are known to be less electrophilic than the corresponding imines; see: (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438.

(8) When a solution of *N*-methoxybenzylamine **12d**, cyclohexanone **11**, and $CDCl_3$ was treated with $Sc(OTf)_3$, ^1H NMR analysis showed that **12d** and the *N*-methoxyiminium ion **i** existed as a ratio of 1.1:1 in equilibrium after 1 h. Enamine derivative **ii** was not detected during the analysis. This result might support the high electrophilicity of the *N*-methoxyiminium ions.

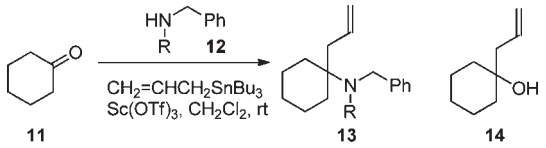


(9) For selected reviews on allylation to iminium intermediates, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293. (b) Puentes, C. O.; Kouznetsov, V. *J. Heterocycl. Chem.* **2002**, *39*, 595–614.

(10) The use of more reactive nucleophiles including a Grignard reagent gave secondary amines in good yields, although these approaches were not compatible with sensitive functional groups. For selected examples, see: (a) Bonjoch, J.; Diaba, F.; Puigbó, G.; Solé, D.; Segarra, V.; Santamaría, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, *7*, 2891–2897. (b) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847–1850. (c) Varlamov, A.; Kouznetsov, V.; Zubkov, F.; Chernyshev, A.; Shurupova, O.; Méndez, L. Y. V.; Rodríguez, A. P.; Castro, J. R.; Rosas-Romero, A. J. *Synthesis* **2002**, 771–783. (d) Dhudshia, B.; Tiburcio, J.; Thadani, A. N. *Chem. Commun.* **2005**, 5551–5553. (e) Kropf, J. E.; Meigh, I. C.; Bebbington, M. W. P.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 2046–2055. (f) Kaden, S.; Reissig, H.-U. *Org. Lett.* **2006**, *8*, 4763–4766. (g) Prusov., E.; Maier, M. E. *Tetrahedron* **2007**, *63*, 10486–10496.

(11) For selected examples on the three-component reaction with an aldehyde and an *N*-alkoxyamine via an *N*-methoxyiminium ion, see: Reference 6g 6k, and 6m. For selected examples on the three-component radical reactions with an aldehyde and an *N*-alkoxyamine, see: (a) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140–1157. (b) Cho, D. H.; Jang, D. O. *Chem. Commun.* **2006**, 5045–5047.

Table 1. Three-Component Allylation of Cyclohexanone **11** and *N*-Substituted Benzylamines **12**[a]



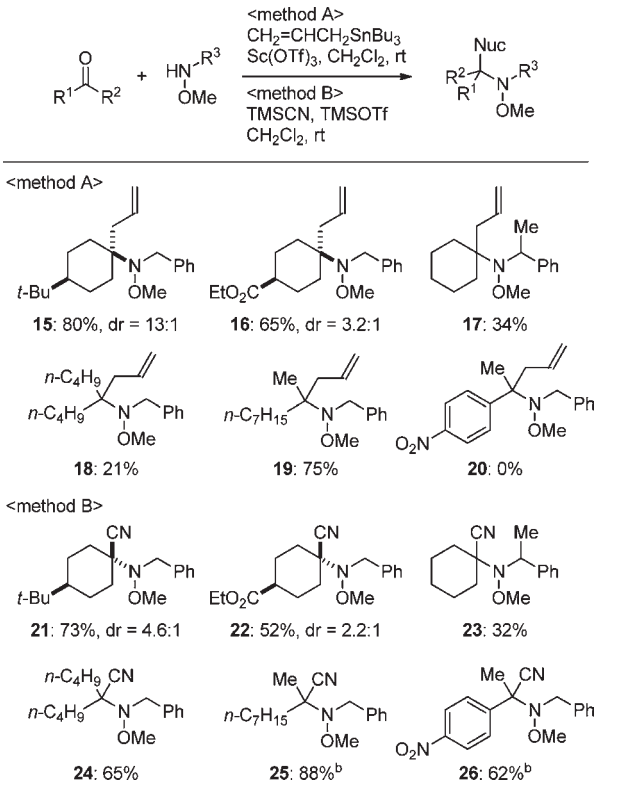
		yields (%)	
entry	**12**	**13**	**14**
1	**12a**: R = Cbz	0	41
2	**12b**: R = Me	0	0
3	**12c**: R = H	9	0
4	**12d**: R = OMe	85	7

[a] Conditions: **11** (1.0 equiv), **12** (1.0 equiv), CH_2=$CHCH_2SnBu_3$ (3.0 equiv), $Sc(OTf)_3$ (0.3 equiv), CH_2Cl_2 (2.0 M), rt.

Once we confirmed the unique properties of *N*-methoxyamine in the presence of $Sc(OTf)_3$, we then surveyed the scope of the three-component allylation with various ketones (Scheme 2, method A). The allylation of 4-*tert*-butylcyclohexanone took place from the equatorial side to give **15** in a highly diastereoselective manner.[12] One of the conspicuous features in our methodology is functional group tolerance. Because *N*-methoxyiminium ion **9** shown in Scheme 1 exhibited high electrophilicity, a strong nucleophile such as a Grignard reagent was not necessary. Thus, the allylation of ethyl 4-oxocyclohexanecarboxylate afforded **16** without affecting the ethyl ester (65%, dr = 3.2:1). Sterically hindered *N*-methoxyamine resulted in a decrease in yield (**17**: 34%). We then applied the reaction conditions to acyclic ketones. While the allylation of 5-nonanone gave **18** in low yield due to the large steric hindrance, 2-nonanone provided α-tertiary amine **19** in 75% yield. Unfortunately, the aromatic ketone failed to react even when an electron-withdrawing group was introduced on the aromatic ring.

The three-component reaction was applicable to the cyanation with TMSCN and TMSOTf (Scheme 2, method B).[13] In contrast to the allylation, when using 4-*tert*-butyl-cyclohexanone, the cyanide group attacked from the axial side probably due to its small size (**21**: 73%, dr = 4.6:1). The reaction proceeded in the presence of the ethyl ester (**22**: 52%, dr = 2.2:1). The branched *N*-methoxyamine led to a low yield as well as the allylation (**23**: 32%). The cyanation of sterically hindered ketones tended to give better yields than the allylation, inasmuch as 5-nonanone and 2-nonanone both afforded the products in good yield (**24**: 65%, **25**: 88%).

Scheme 2. Three-Component Allylation or Cyanation of Ketones and *N*-Methoxyamines[a]



[a] Conditions: <method A> ketone (1.0 equiv), *N*-methoxyamine (1.0 equiv), CH_2=$CHCH_2SnBu_3$ (3.0 equiv), $Sc(OTf)_3$ (0.3 equiv), CH_2Cl_2 (2.0 M), rt or <method B> ketone (1.0 equiv), *N*-methoxyamine (1.0 equiv), TMSCN (3.0 equiv), TMSOTf (1.0 equiv), CH_2Cl_2 (2.0 M), rt. [b] The reaction was performed at 80 °C.

The cyanation proceeded even with an aromatic ketone, which was not a suitable substrate in the allylation (**26**: 62%).

We then turned our attention to a two-component allylation using *N*-methoxyamine **27**,[14] which would result in a single-step synthesis of 2,2-disubstituted piperidines (Scheme 3).[15] The reaction of cyclohexanone with $Sc(OTf)_3$ in MeCN gave spiro-α-trisubstituted amine **28** in 84% yield. When using 4-*tert*-butylcyclohexanone, the allylsilane approached the *N*-methoxyiminium ion from the equatorial face, giving **29** in 73% yield as a single diastereomer.[16] We then attempted the reaction with acyclic ketones. The allylation of 2-nonanone proceeded in high yield, but poor diastereoselectivity (**30**: 87%, dr = 1.6:1). In the case of an aromatic ketone, the best result was obtained with 3.0 equiv of TFA instead of $Sc(OTf)_3$, leading to high

(12) The allylation of 4-*tert*-butyl-cyclohexanone with ammonia or a primary amine tended to proceed via an equatorial attack (dr = 2.0−6.7:1); see: Reference 10b and 10d.

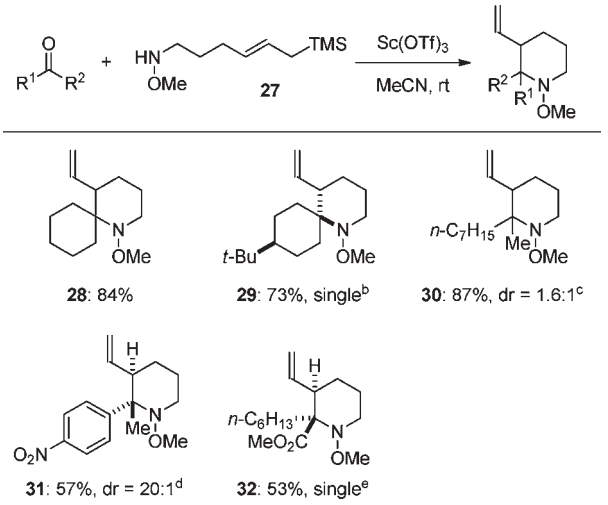
(13) For selected recent reviews on Strecker reaction, see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094. (b) Ohfune, Y.; Shinada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1115–1129. (c) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795–2827. (d) Vilaivan, T.; Bhanthumnavin, W.;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

(14) In general, the poorly nucleophilic allylsilane gave a lower yield than the allylstannane in the three-component reaction. The allylsilane was employed in the two-component reaction due to the high stability.

(15) For selected examples on the two-component reaction with *N*-monosubstituted amines, see: (a) Monfray, J.; Gelas-Mialhe, Y.; Gramain, J.-C.; Remuson, R. *Tetrahedron: Asymmetry* **2005**, *16*, 1025–1034. (b) Amorde, S. M.; Jewett, I. T.; Martin, S. F. *Tetrahedron* **2009**, *65*, 3222–3231.

(16) The structure of **29** was determined by single-crystal X-ray analysis (CCDC 864124). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 3. Two-Component Allylation for the Construction of 2,2-Disubstituted Piperidines[a]



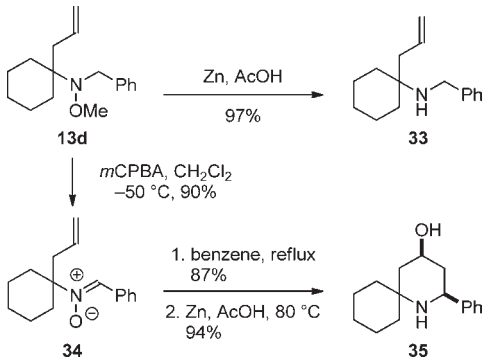
[a] Conditions: ketone (1.0 equiv), *N*-methoxyamine **27** (1.0 equiv), $Sc(OTf)_3$ (1.0 equiv), MeCN (0.1 M), rt. [b] The reaction was performed at 80 °C. [c] The reaction was performed at 50 °C. [d] The reaction was performed at 60 °C with TFA (3.0 equiv) instead of $Sc(OTf)_3$. [e] TFA (1.0 equiv) was used instead of $Sc(OTf)_3$.

diastereoselectivity (**31**: 57%, dr = 20:1). A ketoester could be used for this two-component reaction with 1.0 equiv of TFA and provided α,α-disubstituted amino acid derivative **32** in 53% yield as a single diastereomer.

As shown in Scheme 4, *N*-methoxyamines are readily converted into potentially useful amines. As a demonstration, we first cleaved the *N*-methoxy group of **13d** with Zn in AcOH, affording secondary amine **33** in 97% yield. One of the unique transformations related to *N*-methoxyamines is direct oxidation to nitrones.[17] Thus, the treatment of **13d** with *m*CPBA at −50 °C led to the formation of nitrone **34** in 90% yield without affecting the terminal olefin. According

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

Scheme 4. Transformations of *N*-Methoxyamines



to the procedure reported by Varlamov, Kouznetsov, and Zubkov, nitrone **34** was then transformed to spiroamine **35** as a single diastereomer through 1,3-dipolar cycloaddition, followed by cleavage of the N−O bond.[10c]

In conclusion, we have developed novel multicomponent reactions to access α-trisubstituted amines in a single step by taking advantage of the high nucleophilicity of *N*-methoxyamines as well as the high electrophilicity of the *N*-methoxyiminium ions. The resulting *N*-methoxyamines could undergo a variety of further transformations, leading to useful secondary amines. Studies on the enantioselective variant of this reaction are in progress.

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Supporting Information Available. Experimental procedures; copies of ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.