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Direct One-Pot Synthesis of α-Siloxy-Weinreb Amides from Aldehydes

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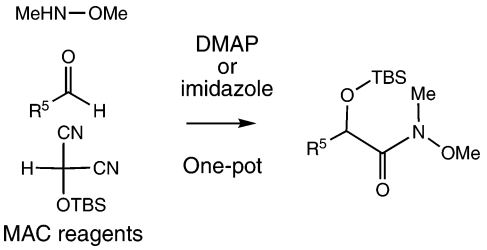
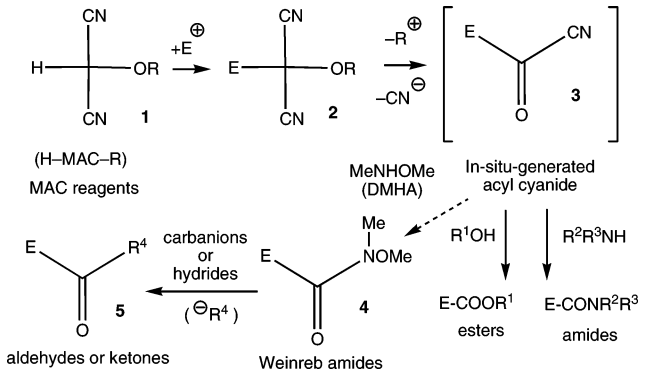


A one-pot method for synthesizing α-siloxy-Weinreb amides from aldehydes was developed with use of *N*,*O*-dimethylhydroxylamine and a masked acyl cyanide reagent bearing a *tert*-butyldimethylsilyl group avoiding the competitive reaction toward *N*-methoxy-*N*-methyl-2-amino-1-siloxymalononitrile.

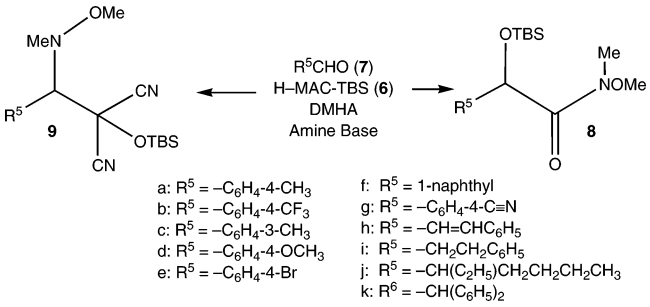
Weinreb amides[1] are versatile compounds that can be used to prepare aldehydes or ketones, since dual nucleophilic attack to its carbonyl group by hydrides or carbanions is efficiently prohibited. These preparations are typically carried out via a condensation reaction between *N*,*O*-dimethylhydroxylamine (DMHA) and an activated acyl compound, which is either prepared beforehand or generated in situ.

Masked acyl cyanide (MAC) reagent **1** (H-MAC-R)[2] generates such an activated acyl compound, an acyl cyanide **3**, during a three-component reaction (**1** + E^+ + either R^1OH or R^2R^3NH)[2−5] to afford esters or amides (Scheme 1). It is expected that Weinreb amide **4** may be prepared if DMHA is used instead (via dotted arrow). The $-C(CN)_2OR$ moiety can be used as a versatile functional group to prepare *not only* esters or amides

SCHEME 1



SCHEME 2



3 *but also* aldehydes or ketones **5** from **4** via addition reaction, using hydrides or carbanions, respectively.

As an example of **4**, compound **8** is a useful intermediate in the synthesis of α-hydroxyaldehydes or α-hydroxyketones (Scheme 2). However, several steps[6] are generally required for the preparation of **8** from an aldehyde, using an alternative masked $^-$COOH or $^-$COX reagent such as cyanide anion or ortho-thioesters.[7] In contrast, it was expected that MAC reagents bearing a migratory protecting group could be used to prepare **8** *in one-pot* from an aldehyde **7** via a reaction previously developed by us.[4] However, in contrast to our preliminary

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(1) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.

(2) "H-MAC-R" is an abbreviation of H-$C(CN)_2O$-R. Nemoto, H.; Ibaragi, T.; Bando, M.; Kido. M.; Shibuya. M. *Tetrahedron Lett.* **1999**, *40*, 1319−1322.

(3) Stepwise reactions with MAC reagents: (a) Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 4515−4516. (b) Kubota, Y.; Nemoto, H.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 7195−7196. (c) Nemoto, H.; Kubota, Y.; Sasaki, N.; Yamamoto, Y. *Synlett* **1993**, 465−466. (d) Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1665−1666. (e) Yamamoto, Y.; Kubota, Y.; Honda, Y.; Fukui, H.; Asao, N.; Nemoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 3161−3162. (f) Nemoto, H.; Ma, R.; Ibaragi, T.; Suzuki, I.; Shibuya, M. *Tetrahedron* **2000**, *56*, 1463−1468. (g) Nemoto, H.; Ma, R.; Moriguchi, H.; Suzuki, I.; Shibuya, M. *J. Organomet. Chem.* **2000**, *611*, 445−448.

(4) One-pot reactions with MAC reagents: (a) Nemoto, H.; Ma, R.; Suzuki, I.; Shibuya, M. *Org. Lett.* **2000**, *2*, 4245−4247. (b) Nemoto, H.; Ma, R.; Li, X.; Suzuki, I.; Shibuya, M. *Tetrahedron Lett.* **2001**, *42*, 2145−2147. (c) Nemoto, H.; Kawamura, T.; Miyoshi, N. *J. Am. Chem. Soc.* **2005**, *127*, 14546−14547.

(5) A different type of reaction with DMHA and MAC reagents: Nemoto, H.; Ma, R.; Kawamura, T.; Kamiya, M.; Shibuya, M. *J. Org. Chem.* **2006**, *71*, 6038−6043.

(6) A typical example of the steps required: (1) nucleophilic attack to the aldehyde by a $^-$COOH equivalent; (2) protection of the resulting hydroxyl group; (3) unmasking of the moiety of the COOH equivalent; (4) preparation of activated carbonyl compound such as acid chloride; and (5) condensation with DMHA.

(7) Examples of alternative masked $^-$COOH or $^-$COX reagents: (a) Seebach, D.; Ehrig, V.; Leitz, H. F.; Henning, R. *Chem. Ber.* **1975**, *108*, 1946−1960. (b) Manas, A. R. B.; Smith, R. A. J. *J. Chem. Soc., Chem. Commun.* **1975**, 216−217. (c) Utimoto, K.; Wakabayashi, Y.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4279−4280. (d) Trost, B. M.; Quayle, P. *J. Am. Chem. Soc.* **1984**, *106*, 2469−2471. (e) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Tetrahedron* **1987**, *43*, 3533−3539. (f) Katritzky, A. R.; Yang, Z.; Lam, J. N. *Synthesis* **1990**, 666−669. (g) Satoh, T.; Onda, K.-I.; Yamakawa, K. *Tetrahedron Lett.* **1990**, *31*, 3567−3570. (h) Wasserman, H. H.; Ho, W.-B. *J. Org. Chem.* **1994**, *59*, 4364−4366. (i) Aggarwal, V. K.; Thomas, A.; Franklin, R. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1653−1654.

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TABLE 1. Reaction of Aldehydes with 6 (1.2 equiv), DMHA·HCl (1.2 equiv), and Amine Base (2.0 equiv) in Acetonitrile at Room Temperature[20]

entry	aldehyde	amine base	time	product (yield, %)	
1	**7a**	pyridine	2 h	**8a** (0)	**9a** (88)
2	**7a**	triethylamine	2 h	**8a** (23)	**9a** (57)
3	**7a**	imidazole	5 h	**8a** (73)	**9a** (0)
4	**7a**	DMAP	2 h	**8a** (91)	**9a** (0)
5	**7b**	pyridine	60 h	**8b** (44)	**9b** (8)

TABLE 2. Reaction of Various Aromatic Aldehydes with 6 (1.2 equiv), DMHA·HCl (1.2 equiv), and DMAP (2.0 equiv) in Acetonitrile at Room Temperature for 2 h[20]

entry	aldehyde	product	yield, %
1	**7b**	**8b**	84
2	**7c**	**8c**	90
3	**7d**	**8d**	93
4	**7e**	**8e**	89
5	**7f**	**8f**	87
6	**7g**	**8g**	87

prediction, we unexpectedly observed the formation of **9** as a sole product using H-MAC-TBS **6**.[5,8]

In this paper, we report a method for the synthesis of α-siloxy-Weinreb amides **8** from aldehydes in one pot using DMHA and a MAC reagent bearing a silyl group as R. We initially examined the reaction using **7a**. A tertiary amine was used as a base to neutralize the hydrochloride salt of DMHA and activate **6** to generate the corresponding carbanion. As anticipated, **9a** was obtained as the major product (88% yield) from **7a** when pyridine was used (Table 1, entry 1). When triethylamine was used, the desired product **8a** was obtained in 23% yield, although **9a** was still a major product. In contrast, when either imidazole or 4-(*N*,*N*-dimethylamino)pyridine (DMAP) was used, the desired Weinreb amide **8a** was the only product obtained (entries 3 and 4). It is notable that when **7b** was used in the reaction, **8b** was produced as a major product even with pyridine, although the reaction was slowed down considerably (entry 5).[9]

Thus, it was found that the ratio of the products obtained via two competitive reactions differed dramatically depending upon the base used, and it was confirmed that imidazole or DMAP was an effective base for the synthesis of Weinreb amides.

Next, we examined the synthesis of α-siloxy-Weinreb amides **8** from various aldehydes **7** in one pot. The optimum conditions discovered in the previous experiment—described in entry 4 of Table 1—were applied to various aromatic aldehydes (Table 2). Aldehydes bearing an electron-rich aromatic ring (entries 2−5) smoothly converted to **8** even when midrange steric repulsion was present (entries 2 and 5). It is noteworthy that even electron-deficient aromatic aldehydes were converted to **8** within 2 h (entries 1 and 6), which contrasts with the result shown in Table 1, entry 5. Thus, it was shown that not only is DMAP essential in terms of chemoselectivity to produce **8**, *but* it also accelerates the desired one-pot reaction.

Next, we attempted to apply the optimized conditions for saturated aliphatic aldehydes and conjugated enals. Unfortunately, under the conditions described in Table 2, the desired Weinreb amides **8h**−**k** were not obtained from **7h**−**k**. After several attempts,[10] the reaction conditions were optimized for nonaromatic aldehydes, as shown in Table 3. The use of non-salt DMHA gave better results than the hydrochloride salt. Imidazole was found to be superior to DMAP in this reaction, and ether was a better solvent than acetonitrile.

TABLE 3. Reaction of Several Nonaromatic Aldehydes with 6 (1.2 equiv), DMHA (1.2 equiv, non-salt amine), and Amine Base in Ether at Room Temperature for 2 h

entry	aldehyde	amine base (equiv)	product	yield, %
1	**7h**	DMAP (2.0 equiv)	**8h**	64
2	**7h**	imidazole (2.0 equiv)	**8h**	92
3	**7i**	DMAP (2.0 equiv)	**8i**	64
4[a]	**7i**	imidazole (3.0 equiv)	**8i**	71
5[a]	**7j**	imidazole (3.0 equiv)	**8j**	67
6[a]	**7k**	imidazole (3.0 equiv)	**8k**	55

[a] 3.0 equiv of **6** was used.

In conclusion, a one-pot method was developed for the synthesis of α-siloxy-Weinreb amides from aldehydes. The competitive reaction toward 2-amino-1-siloxymalononitrile[9] can be effectively suppressed by using a silylated MAC reagent *either* with DMAP in acetonitrile for aromatics *or* with imidazole in ether for nonaromatic aldehydes.

Experimental Section

General Procedure for the Synthesis of 8 (aromatic aldehydes). To a solution of aldehyde (1.0 mmol), DMHA·HCl (117 mg, 1.2 mmol), and **6** (236 mg, 1.2 mmol) in acetonitrile (3 mL) was added DMAP (244 mg, 2.0 mmol) at room temperature, and the resulting mixture was stirred for 2 h, and then concentrated in vacuo. The residue was purified by silica gel column chromatography to afford **8**.

General Procedure for the Synthesis of 8 (nonaromatic aldehydes). To a solution of aldehyde (1.0 mmol), DHMA (0.54 mL, 2.2 M in ether, 1.2 mmol), and **6** (236 mg, 1.2 mmol) in ether (5 mL) was added imidazole (136 mg, 2.0 mmol) at room temperature. The resulting mixture was stirred for 2 h, and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford **8**.

***N*-Methoxy-*N*-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-methylphenyl)acetamide (8a):** colorless oil; FT-IR ($CHCl_3$) 2931, 1670, 1255, 1086, 999, 867, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (d, $J = 8.0$ Hz, aromatic, 2H), 7.13 (d, $J = 8.0$ Hz, aromatic, 2H), 5.55 (s, CH−C═O, 1H), 3.51 (s, NO−Me, 3H), 3.13 (s, N−Me, 3H), 2.33 (s, C−OMe, 3H), 0.91 (s, Si−CMe_3, 9H), 0.12 (s, Si−Me, 3H), 0.00 (s, Si−Me, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C) δ 172.7 (C═O), 137.5 (aromatic C), 136.7 (aromatic C), 129.0 (aromatic CH × 2), 126.8 (aromatic CH × 2), 73.6 (asymmetric CH), 60.7 (O−CH_3), 33.3 (N−CH_3), 25.9 (Si−CMe_3), 21.1 (C−CH_3), 18.4 (Si−C), −4.8 (Si−CH_3), −5.0 (Si−CH_3). Anal. Calcd for $C_{17}H_{29}NO_3Si$: C, 63.12; H, 9.04; N, 4.33. Found: C, 62.75; H, 8.92; N, 4.28.

***N*-Methoxy-*N*-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-trifluromethylphenyl)acetamide (8b):** colorless oil; FT-IR (neat) 2933, 1686, 1326, 1166, 1128, 1068, 870, 839, 782 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60 (d, $J = 8.7$ Hz, aromatic, 2H), 7.58 (d, $J = 8.7$ Hz, aromatic, 2H), 5.64 (s, CH−C═O, 1H), 3.58 (s, NO−Me, 3H), 3.15 (s, N−Me, 3H), 0.93 (s, Si−CMe_3, 9H), 0.14 (s, Si−Me, 3H), 0.06 (s, Si−Me, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C) δ 171.6 (C═O), 143.7 (aromatic, C), 130.3 (aromatic, C), 127.1 (aromatic CH × 2), 125.6 (aromatic CH × 2), 124.3 (q, J_{C-F}

(8) Even trace amounts of **8** were not observed but **9** was obtained in the study described in ref 5 because we fortuitously used only pyridine as a base at that time.

(9) When chemoselective synthesis of **9** is desirable starting from an aldehyde bearing an electron-deficient R^5 group, a MAC reagent bearing a nonmigratory group can be used.[5]

(10) The temperature, solvent, and so on were chosen according to the best conditions described in ref 4 for one-pot synthesis of α-siloxyamides.

= 272.1 Hz, CF_3), 73.3 (asymmetric CH), 61.0 (NO−CH_3), 33.2 (N−CH_3), 25.9 (SiC−$(CH_3)_3$), 18.4 (Si−C), −4.7 (Si−CH_3), −5.0 (Si−CH_3); Anal. Calcd for $C_{17}H_{26}F_3NO_3Si$: C, 54.09; H, 6.94; N, 3.71. Found: C, 54.06; H, 6.99; N, 3.69.

***N*-Methoxy-*N*-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(2-methylphenyl)acetamide (8c):** colorless crystal, mp 36−38 °C (from hexane/ethyl acetate); FT-IR (KBr) 2934, 1686, 1463, 1254, 1127, 1082, 1000, 875, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.36 (m, aromatic, 1H), 7.23−7.06 (m, aromatic, 3H), 5.65 (s, CH−C═O, 1H), 3.20 (s, NO−Me, 3H), 3.14 (s, N−Me, 3H), 2.40 (s, C−Me, 3H), 0.88 (s, Si−CMe_3, 9H), 0.11 (s, Si−Me, 3H), 0.00 (s, Si−Me, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1 (C═O), 138.1 (aromatic C), 136.0 (aromatic C), 130.5 (aromatic CH), 128.6 (aromatic CH), 127.8 (aromatic CH), 125.9 (aromatic CH), 72.2 (asymmetric CH), 60.4 (NO−CH_3), 33.0 (N−CH_3), 25.9 (SiC−Me_3), 19.1 (benzylic CH_3), 18.4 (Si−C), −4.5 (Si−CH_3), −4.8 (Si−CH_3). Anal. Calcd for $C_{17}H_{29}NO_3Si$: C, 63.12; H, 9.04; N, 4.33. Found: C, 63.05; H, 9.07; N, 4.33.

***N*-Methoxy-*N*-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-methoxyphenyl)acetamide (8d):** colorless oil; FT-IR (neat) 2932, 2857, 1682, 1513, 1250, 1082, 1035, 869, 838, 778 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, J = 8.4 Hz, aromatic, 2H), 6.85 (d, J = 8.4 Hz, aromatic, 2H), 5.55 (s, CH−C═O, 1H), 3.78 (s, C−OMe, 3H), 3.50 (s, NO−Me, 3H), 3.12 (s, N−Me, 3H), 0.91 (s, SiC−Me_3, 9H), 0.11 (s, Si−Me, 3H), 0.03 (s, Si−Me, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C) δ 172.4 (C═O), 159.5 (aromatic C), 131.8 (aromatic C), 128.2 (aromatic CH × 2), 113.9 (aromatic CH × 2), 73.2 (asymmetric CH), 60.8 (NO−CH_3), 55.3 (C−OCH_3), 33.2 (N−CH_3), 25.9 (SiC−Me_3), 18.4 (Si−C), −4.7 (Si−CH_3), −4.9 (Si−CH_3). Anal. Calcd for $C_{17}H_{29}NO_4Si$: C, 60.14; H, 8.61; N, 4.13. Found: C, 60.06; H, 8.54; N, 3.97.

***N*-Methoxy-*N*-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-bromophenyl)acetamide (8e):** colorless crystal, mp 40−41 °C (from hexane/ethyl acetate); FT-IR (KBr) 2930, 1682, 1256, 1127, 1083, 866, 837, 779 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45 (d, J = 8.3 Hz, aromatic, 2H), 7.32 (d, J = 8.3 Hz, aromatic, 2H), 5.54 (s, CH−C═O, 1H), 3.54 (s, NO−Me, 3H), 3.12 (s, N−Me, 3H), 0.91 (s, SiC−Me_3, 9H), 0.11 (s, Si−Me, 3H), 0.04 (s, Si−Me, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C) δ 171.9 (C═O), 138.8 (aromatic C), 131.5 (aromatic CH × 2), 128.6 (aromatic CH × 2), 121.9 (Br−C), 73.1 (asymmetric CH), 60.9 (NO−CH_3), 33.2 (N−CH_3), 25.9 (SiC−Me_3), 18.4 (Si−C), −4.7 (Si−CH_3), −4.9 (Si−CH_3). Anal. Calcd for $C_{16}H_{26}BrNO_3Si$: C, 49.48; H, 6.75; N, 3.61. Found: C, 49.38; H, 6.69; N, 3.64.

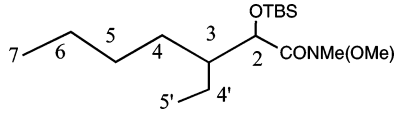
***N*-Methoxy-*N*-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(1-naphthyl)acetamide (8f):** colorless crystal, mp 79−80 °C (from hexane/ethyl acetate); FT-IR (neat) 2931, 1679, 1254, 1121, 878, 838, 787 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.40 (d, J = 8.3 Hz, aromatic, 2H), 7.89−7.75 (m, aromatic, 2H), 7.62 (d, J = 7.2 Hz, aromatic, 1H), 7.55−7.39 (m, aromatic, 2H), 6.11 (s, CH−C═O, 1H), 3.11 (s, NO−Me and N−Me, 6H), 0.88 (s, SiC−Me_3, 9H), 0.13 (s, Si−Me, 3H), −0.04 (s, Si−Me, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 55 °C) δ 172.8 (C═O), 135.5 (aromatic C), 133.8 (aromatic C), 131.0 (aromatic C), 128.6 (aromatic CH), 128.5 (aromatic CH), 126.4 (aromatic CH), 126.2 (aromatic CH), 125.6 (aromatic CH), 125.1 (aromatic CH), 124.6 (aromatic CH), 73.0 (asymmetric CH), 60.5 (NO−CH_3), 32.9 (N−CH_3), 25.8 (SiC−Me_3), 18.4 (Si−C), −4.7 (Si−CH_3), −4.9 (Si−CH_3). Anal. Calcd for $C_{20}H_{29}NO_3Si$: C, 66.81; H, 8.13; N, 3.90. Found: C, 66.95; H, 8.06; N, 4.01.

***N*-Methoxy-*N*-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-2-(4-cyanophenyl)acetamide (8g):** colorless oil; FT-IR (KBr) 2932, 2230, 1681, 1255, 1131, 868, 839, 781 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.64 (d, J = 8.2 Hz, aromatic, 2H), 7.57 (d, J = 8.2 Hz, aromatic, 2H), 5.61 (s, CH−C═O, 1H), 3.60 (s, NO−Me, 3H), 3.14 (s, N−Me, 3H), 0.92 (s, SiC−Me_3, 9H), 0.14 (s, Si−Me, 3H), 0.06 (s, Si−Me, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C) δ 171.3 (C═O), 145.0 (aromatic C), 132.2 (aromatic CH × 2), 127.4 (aromatic CH × 2), 118.6 (aromatic C), 112.0 (C≡N), 73.1 (asymmetric CH), 61.1 (NO−CH_3), 33.2 (N−CH_3), 25.8 (SiC−Me_3), 18.4 (Si−C), −4.7 (Si−CH_3), −5.0 (Si−CH_3). Anal. Calcd for $C_{17}H_{26}N_2O_3Si$: C, 61.04; H, 7.83; N, 8.37. Found: C, 60.88; H, 7.82; N, 8.2.

(3*E*)-*N*-Methoxy-*N*-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-4-phenylbut-3-enamide (8h): colorless oil; FT-IR ($CHCl_3$) 2939, 1671, 1464, 1254, 1119, 993, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49−7.35 (m, aromatic, 2H), 7.35−7.22 (m, aromatic, 3H), 6.73 (d, J = 15.8 Hz, olefinic, 1H), 6.33 (dd, J = 15.8, 5.9 Hz, olefinic, 1H), 5.23 (d, J = 5.9 Hz, CH−C═O, 1H), 3.73 (s, NO−Me, 3H), 3.23 (s, N−Me, 3H), 0.95 (s, SiC−Me_3, 9H), 0.16 (s, Si−Me, 3H), 0.13 (s, Si−Me, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C) δ 171.9 (C═O), 136.4 (aromatic C), 131.6 (aromatic CH), 128.4 (aromatic CH × 2), 127.7 (aromatic CH × 2), 126.6 (olefinic CH), 126.5 (olefinic CH), 72.0 (asymmetric CH), 61.1 (NO−CH_3), 32.8 (N−CH_3), 25.7 (SiC−Me_3), 18.3 (Si−C), −4.8 (Si−CH_3), −4.9 (Si−CH_3); EI-HRMS calcd for $C_{18}H_{29}NO_3Si$ [M^+] 335.1917, found 335.1953.

***N*-Methoxy-*N*-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-4-phenylbutanamide (8i):** colorless oil; FT-IR ($CHCl_3$) 3010, 2938, 1670, 1463, 1254, 1121, 997, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.14 (m, aromatic, 5H), 4.53 (t, J = 5.8 Hz, CH−C═O, 1H), 3.58 (s, NO−Me, 3H), 3.18 (s, N−Me, 3H), 2.93−2.75 (m, one proton of $-CH_2-$, 1H), 2.74−2.58 (m, one proton of $-CH_2-$, 1H), 2.08−1.91 (m, Ph−CH_2-, 2H), 0.94 (s, SiC−Me_3, 9H), 0.09 (s, Si−Me, 3H), 0.07 (s, Si−Me, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C) δ 174.2 (C═O), 141.8 (aromatic C), 128.5 (aromatic CH × 2), 128.4 (aromatic CH × 2), 125.9 (aromatic CH), 70.0 (asymmetric CH), 61.1 (NO−CH_3), 36.2 (CH_2), 33.0 (N−CH_3), 31.7 (Ph−CH_2), 26.0 (SiC−Me_3), 18.4 (Si−C), −4.5 (Si−CH_3), −5.0 (Si−CH_3); EI-HRMS calcd for $C_{18}H_{32}NO_3Si$ [MH]$^+$ 338.2151, found 338.2155.

***N*-Methoxy-*N*-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-3-ethylheptanamide (8j) (a mixture of diastereomers by the presence of two asymmetric centers at C_2 and C_3):** colorless oil; FT-IR ($CHCl_3$) 2954, 1670, 1464, 1253, 1157, 1090, 999, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.51 (br s, CH−C═O, 1H), 3.69 (s, NO−Me, 3H), 3.20 (s, N−Me, 3H), 1.72−1.43 (m, aliphatic, 2H), 1.43−1.08 (m, aliphatic, 7H), 0.97−0.79 (m, aliphatic, 6H), 0.91 (s, SiC−Me_3, 9H), 0.06 (s, Si−Me, 3H), 0.04 (s, Si−Me, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C) δ 174.7 and 174.7 (C═O), 72.2 and 72.1 (CH at C_2), 61.0 and 61.0 (NO−CH_3), 43.5 and 43.2 (CH at C_3), 33.1 and 33.1 (N−CH_3), 29.5 and 29.5 (CH_2 at C_5), 29.4 and 28.0 (CH_2 at C_4), 25.9 and 25.9 (SiC−Me_3), 23.1 and 22.9 (CH_2 at C_6), 21.3 and 21.3 (CH_2 at C_4), 18.4 and 18.4 (Si−C), 14.0 and 14.0 (CH_3 at C_7), 11.7 and 11.3 (CH_3 at $C_{5'}$), −4.5 and −4.5 (Si−CH_3), −5.2 and −5.2 (Si−CH_3); EI-HRMS calcd for $C_{17}H_{38}NO_3Si$ [MH]$^+$ 331.2623, found 331.2603.



***N*-Methoxy-*N*-methyl-2-[(*tert*-butyldimethylsilyl)oxy]-3,3-diphenylpropanamide (8k):** colorless crystals, mp 77−78 °C (from hexane/ethyl acetate); FT-IR ($CHCl_3$) 3007, 2938, 1663, 1462, 1253, 1105, 996, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47−7.39 (m, 2H, aromatic), 7.35−7.09 (m, 8H, aromatic), 5.21 (d, J = 8.8 Hz, CH−C═O, 1H), 4.51 (d, J = 8.8 Hz, Ph_2CH-, 1H), 3.45 (s, NO−Me, 3H), 3.01 (s, N−Me, 3H), 0.68 (s, SiC−Me_3, 9H), −0.04 (s, Si−Me, 3H), −0.20 (s, Si−Me, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C) δ 172.4 (C═O), 141.1 (aromatic C), 140.8 (aromatic C), 129.6 (aromatic CH × 2), 129.2 (aromatic CH × 2), 128.3 (aromatic CH × 2), 128.2 (aromatic CH × 2), 126.7 (aromatic CH), 126.5 (aromatic CH), 73.4 (CH−OSi), 61.0 (NO−Me), 55.7 (Ph_2-CH), 32.9 (N−Me), 25.6 (SiC−Me_3), 18.1 (Si−C), −4.7 (Si−Me), −5.4 (Si−Me). Anal. Calcd for $C_{23}H_{33}NO_3Si$: C, 69.13; H, 8.32; N, 3.51. Found: C, 68.91; H, 8.33; N, 3.49.

2-[(*tert*-Butyldimethylsilyl)oxy]-2-cyano-3-(*N*-methoxy-*N*-methyl)-amino-3-(4-methylphenyl)propionitrile (9a): colorless needle, mp 50−51 °C (hexane/ethyl acetate); IR ($CHCl_3$) 2960, 2933, 2887, 1472, 1266, 1135, 1039, 846, 829 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (d, J = 7.7 Hz, 2H, aromatic CH × 2), 7.15 (d, J = 7.7 Hz, 2H, aromatic CH × 2), 3.99 (s, 1H, benzylic), 3.72 (s, 3H, CH_3O-), 2.48 (s, 3H, CH_2N-), 2.35 (s, 3H, CH_3-aromatic), 0.67 (s, 9H, *t*-Bu), 0.28 (s, 3H, Si−CH_3), 0.06 (s, 3H, Si−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.4 (C, aromatic), 130.0 (C, aromatic), 129.8 (CH × 2, aromatic), 129.1 (CH × 2, aromatic), 116.3 (C, −CN), 114.9 (C, −CN), 79.5 (CH, −CH−aromatic), 66.1 (C, $-C(CN)_2$), 59.8 (CH_3, O−CH_3), 42.7 (CH_3, N−CH_3), 25.0 (CH_3 × 3, *t*-Bu), 21.2 (CH_3, CH_3-Ar), 17.9 (C, *t*-Bu), −4.6 (CH_3, Si−CH_3), −5.0 (CH_3, Si−CH_3). Anal. Calcd for $C_{19}H_{29}N_3O_2Si$: C, 63.47; H, 8.13; N, 11.69. Found: C, 63.41; H, 8.19; N, 11.54.

2-[(*tert*-Butyldimethylsilyl)oxy]-2-cyano-3-(*N*-methoxy-*N*-methyl)-amino-3-(4-trifluromethylphenyl)propionitrile (9b): colorless oil; IR ($CHCl_3$) 2935, 2861, 2244, 1326, 1171, 1135, 841 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.41 (d, J = 9.2 Hz, 2H, aromatic CH × 2), 7.61 (d, J = 9.2 Hz, 2H, aromatic CH × 2), 4.13 (s, 1H, benzylic), 3.74 (s, 3H, CH_3O-), 2.50 (s, 3H, CH_2N-), 0.64 (s, 9H, *t*-Bu), 0.30 (s, 3H, Si−CH_3), 0.07 (s, 3H, Si−CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.8 (C, aromatic), 131.8 (q, J_{C-F} = 23.0 Hz), 130.6 (C, aromatic), 125.4 (q, J_{C-F} = 3.7 Hz), 123.2 (q, J_{C-F} = 272.1 Hz), 115.8 (C, −CN), 114.4 (C, −CN), 79.1 (CH, −CH−Ar), 65.8 (C, $-C(CN)_2$), 59.9 (CH_3, O−CH_3), 42.7 (CH_3, N−CH_3), 24.8 (CH_3 × 3, *t*-Bu), 17.8 (C, *t*-Bu), −4.6 (CH_3, Si−CH_3), −5.0 (CH_3, Si−CH_3). Anal. Calcd for $C_{19}H_{26}F_3N_3O_2Si$: C, 55.19; H, 6.34; N, 13.78. Found: C, 55.14; H, 6.33; N, 13.88.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **8h**−**k** and **9a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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