A Novel Transformation of Primary Amines to *N*-Monoalkylhydroxylamines

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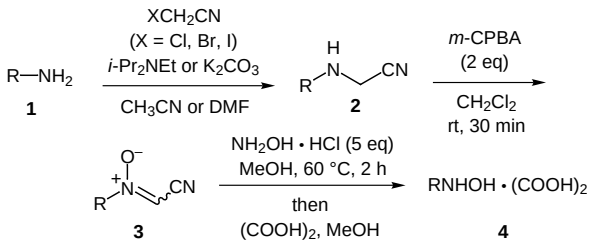
Abstract: A novel transformation of primary amines to the corresponding *N*-monoalkylhydroxylamines is described. The three-step protocol involves selective mono-cyanomethylation of primary amines, regioselective formation of nitrones by *m*-CPBA oxidation, and hydroxylaminolysis of the nitrones with hydroxylamine hydrochloride. The method is applicable for a wide range of primary amines, including alkyl, benzyl, and chiral.

Key words: amine, hydroxylamine, oxidation, cyanomethylation, nitrone

Since a variety of α-hydroxylamino acids and hydroxamic acids occur in nature, synthesis of their precursors, *N*-monoalkylhydroxylamines, has been a topic of considerable interest.[1,2] Direct oxidation of primary amines with hydrogen peroxide or *m*-CPBA is generally ineffective, often leading to further oxidation products such as nitroso and nitro compounds. While reduction of nitro compounds[3] or oximes[4] appears to be the most common and reliable method, it is not applicable to the synthesis of optically active *N*-monoalkylhydroxylamines. Selective oxidation of primary amines with dimethyldioxirane is applicable only to a limited range of substrates.[5] Hydroxylamines have also been synthesized from primary amines by way of oxidation of the corresponding Schiff bases.[6] The protocol is amenable to the synthesis of optically active hydroxylamines,[6b-d] although the intermediary of a relatively acid-labile Schiff base is one of its disadvantages. In the course of studies related to total synthesis of indole alkaloids, we investigated a protocol for the conversion of optically active primary amines to the corresponding hydroxylamines. We describe herein a novel method consisting of selective monocyanomethylation of primary amines, regioselective formation of nitrones, and hydroxylaminolysis of the nitrones (Scheme).



Scheme

First, we explored the optimum conditions for selective monocyanomethylation of primary amines. To this end, we developed three different procedures depending on the steric bulkiness of the alkyl substituent (Table). Primary amines bearing a primary alkyl substituent could be cyanomethylated with chloroacetonitrile and K_2CO_3 in acetonitrile at 60 °C (Conditions A). More hindered amines can be selectively converted to their cyanomethylated derivatives with bromoacetonitrile and Hünig's base (Conditions B). The highly sterically hindered amine such as 1-adamantamine was selectively cyanomethylated with iodoacetonitrile and K_2CO_3 (Conditions C).

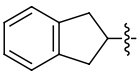
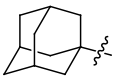
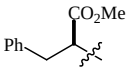
We have found that cyano group serves as a highly effective directing group for the regioselective formation of nitrones. For example, oxidation of cyanomethylamines with *m*-CPBA (2.0 equivalents) took place regioselectively to afford exclusively the desired nitrones **3a**–**i**. This remarkable regioselectivity, which may be due to the inductive effect of the cyano group, was also observed in the oxidation of substrates (**1h**, **1i**) derived from glycine and phenylalanine. The structures of the nitrones were unambiguously determined by extensive ^{1}H NMR studies.

The conversion of the nitrones to the desired *N*-monoalkylhydroxylamines was best achieved by a modification of the literature procedures.[6c,d] Namely, treatment of the nitrones with excess hydroxylamine hydrochloride (5 equivalents) in MeOH at 60 °C for 2 hours afforded the desired *N*-monoalkylhydroxylamines, which were isolated as the corresponding oxalates because of the instability of the free hydroxylamines. Yields, given in the Table, are based on the corresponding oxalic acid salts.

As shown in the Table, a variety of *N*-monoalkylhydroxylamines could be synthesized by this protocol in high overall yields. In general, better yields were obtained when the sequence was carried out without isolation of the nitrone intermediates. Since the intermediate cyanomethylamines are stable, the present protocol is more reliable than the one employing Schiff bases for oxidation. It should be noted that this method is particularly useful for the preparation of chiral hydroxylamines. Thus, (*S*)-1-phenylethylamine (**1d**) was transformed to the corresponding hydroxylamine oxalate (**4d**) without loss of enantiomeric excess (entry 4).[6c] Furthermore, the method is amenable to the synthesis of α-hydroxylamino acid derivatives (entries 8, 9).[5,6b,d]

In summary, we have developed a novel methodology for conversion of primary amines to the corresponding

Table Synthesis of *N*-Monoalkylhydroxylamines

Entry	Amine	R	Conditions for Cyanomethylation[a]	Time (h)	Yield (%)	**2** to **3**[f] Yield (%)	**3** to **4**[g] Yield (%)	**2** to **4** Yield (%)
1	**1a**	$PhCH_2$-	A	24	95	78	76	82
2	**1b**	$PhCH_2CH_2$-	A	24	96	75	83	75
3	**1c**	$PhCH_2CH_2CH_2$-	A	24	93	65	79	74
4	**1d**		A	24	71	85	100	89[h]
			B	5	96			
5	**1e**		A	24	74	–	–	79
			B[b,c]	22	97			
6	**1f**	Ph_2CH-	B	15	98	73	80	55
7	**1g**		C	1	89	89	77	76
8	**1h**	BnO_2CCH_2-	B[d]	18	91	–	–	62
9	**1i**		B[c,e]	26	92	–	–	61[i]

[a] Conditions A: $ClCH_2CN$ (1.5 equiv), K_2CO_3 (2.0 equiv), CH_3CN, 60 °C; Conditions B: $BrCH_2CN$ (1.5 equiv), *i*-Pr_2NEt (2.0 equiv), CH_3CN, r.t.; Conditions C: ICH_2CN (2.0 equiv), K_2CO_3 (2.5 equiv), DMF, r.t.
[b] HCl salt of amine was used.
[c] $BrCH_2CN$ (1.3 equiv), *i*-Pr_2NEt (3.0 equiv).
[d] $BrCH_2CN$ (1.2 equiv), *i*-Pr_2NEt (2.0 equiv).
[e] $BrCH_2CN$ (2.0 equiv), *i*-Pr_2NEt (3.0 equiv).
[f] *m*-CPBA (2.0 equiv), CH_2Cl_2, r.t., 30 min.
[g] NH_2OH·HCl (5.0 equiv), MeOH, 60 °C, 2 h; work-up and treatment with $(COOH)_2$ MeOH.
[h] Optical purity of the product was determined by HPLC on a chiral column.
[i] Optical purity of the product was determined after reduction to the amino acid methyl ester; see experimental details.

N-monoalkylhydroxylamines by way of oxidation of the intermediate monocyanomethylamines. The present protocol seems to be applicable to a wide range of primary amines.

All non-aqueous reactions were carried out in oven-dried glass tubes under a slightly positive pressure of Ar. Commercial MeCN and MeOH were dried over 3 Å molecular sieves. All other reagents were commercially available and used without further purification, unless otherwise noted. Preparative flash chromatography was performed using Silica Gel 60 (spherical, 40−100 μm) purchased from Kanto Chemical Co., Inc. All products were characterized by ^{1}H NMR, ^{13}C NMR, and infrared (IR) spectroscopy. NMR spectra were obtained in $CDCl_3$, CD_3OD, or DMSO-d_6 on a JEOL LA-400 MHz spectrometer. All ^{1}H NMR spectra are reported in ppm relative to the methyl singlet of MeOH, DMSO, or a TMS internal standard. All ^{13}C NMR spectra are reported in ppm relative to the central line of the triplet for $CDCl_3$ at 77.0 ppm, the central line of the septet for CD_3OD at 49.0 ppm, or the central line of the septet for DMSO-d_6. IR spectra were recorded on a JASCO FT/IR-410; absorptions are reported in cm^{-1}. High-resolution mass spectra were obtained on a JEOL JMS-GCmate MS-DIP20 quadrupole at 70 eV using direct probe insertion at temperatures of 50 °C to 330 °C. Mps were determined using a Yanako MP-500V melting point apparatus and are uncorrected. Elemental analyses were carried out on a Yanako MT-6.

Cyanomethylation of Primary Amines (Conditions A): Preparation of *N*-Cyanomethyl 2-phenylethylamine (2b); Typical Procedure

To a MeCN (30 mL) solution of 3-phenylethylamine (260 mg, 1.93 mmol) were added K_2CO_3 powder (532 mg, 3.85 mmol) and $ClCH_2CN$ (183.5 μL, 2.89 mmol). After stirring for 24 h at 60 °C, the resulting suspension was filtered through a pad of Celite, and the filtrate was concentrated on a rotary evaporator. Purification of the residue by flash column chromatography on silica gel (30% EtOAc in hexanes) gave the desired **2b** as a colorless oil (295 mg, 96%).

IR (film): ν = 3330, 3027, 2928, 2841, 2233, 1603, 1497, 1454, 1131, 1030, 872, 751, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.84 (t, *J* = 6.8 Hz, 2H), 3.02 (t, *J* = 6.8 Hz, 2H), 3.60 (s, 2H), 7.20−7.34 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.7, 37.3, 49.6, 117.6, 126.5, 128.6 (overlapping 4C), 138.9.

HRMS (EI): *m/z* calcd for $C_{10}H_{12}N_2$: 160.1000. Found: 160.1007.

***N*-Cyanomethylbenzylamine (2a)**
Colorless oil.

IR (film): ν = 3333, 3029, 2926, 2845, 2233, 1723, 1496, 1453, 1121, 872, 739, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.51 (s, 2H), 3.89 (s, 2H), 7.26−7.34 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.1, 52.1, 117.6, 127.5, 128.3, 128.5, 137.7.

Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.69; H, 6.90; N, 18.96.

***N*-Cyanomethyl-3-phenylpropylamine (2c)**
Colorless oil.

IR (film): ν = 3331, 3026, 2933, 2858, 2233, 1951, 1878, 1811, 1602, 1496, 1454, 1329, 1132, 1030, 873, 749, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.78−1.88 (m, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 2.77 (t, *J* = 6.8 Hz, 2H), 3.49 (s, 2H), 7.13−7.31 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9, 33.1, 37.1, 48.1, 117.8, 125.8, 128.2, 128.3, 141.5.

HRMS (EI): *m/z* calcd for $C_{11}H_{14}N_2$: 174.1157. Found: 174.1160.

Cyanomethylation of Primary Amines (Conditions B): Preparation of *(S)*-*N*-Cyanomethyl-1-phenylethylamine (2d); Typical Procedure
To an MeCN (20 mL) solution of (*S*)-1-phenylethylamine (1.01 g, 8.33 mmol) were added *i*-Pr_2NEt (2.90 mL, 16.7 mmol) and $BrCH_2CN$ (0.638 mL, 9.12 mmol). After stirring for 5 h at r.t., the reaction mixture was concentrated on a rotary evaporator. The residue was partitioned between sat. $NaHCO_3$, sat. NaCl, and $CHCl_3$. The aqueous layer was extracted twice with $CHCl_3$, and the combined organic extracts were washed with sat. NaCl, dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator to afford a crude product. Purification by flash column chromatography on silica gel (20% EtOAc in hexanes) gave (*S*)-*N*-cyanomethyl-1-phenylethylamine (**2d**) as a colorless oil (1.28 g, 96%).

$[\alpha]_D^{27}$ −217 (*c* 1.23, $CHCl_3$).

IR (film): ν = 3335, 2968, 2235, 1957, 1887, 1818, 1494, 1452, 1207, 1132, 870, 763 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.8 Hz, 3H), 3.23 (d, *J* = 16.8 Hz, 1H), 3.53 (d, *J* = 17.6 Hz, 1H), 4.01 (q, *J* = 6.5 Hz, 1H), 7.26−7.34 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7, 34.8, 56.5, 117.7, 126.7, 127.4, 128.5, 142.7.

Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.94; H, 7.57; N, 17.35.

***N*-Cyanomethyl-2-indanamine (2e)**
Colorless oil.

IR (film): ν = 3329, 3022, 2938, 2900, 2839, 2234, 1475, 1459, 1426, 1363, 1219, 1134, 1024, 871, 744 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.78 (dd, *J* = 4.8, 15.6 Hz, 2H), 3.22 (dd, *J* = 6.8, 15.6 Hz, 2H), 3.66 (s, 2H), 3.81−3.88 (m, 1H), 7.15−7.23 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.7, 39.5, 58.3, 118.0, 124.7, 126.7, 140.9.

HRMS (EI): *m/z* calcd for $C_{11}H_{12}N_2$: 172.1000. Found: 172.1006.

***N*-Cyanomethyldiphenylmethylamine (2f)**
Mp: 73.9−74.7 (Et_2O/hexanes).

IR (KBr): ν = 3434, 3336, 3029, 2924, 2845, 2240, 1631, 1598, 1491, 1453, 1411, 1132, 1085, 1029, 877, 745, 703 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.54 (s, 2H), 5.07 (s, 1H), 7.20−7.45 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.1, 65.6, 117.5, 127.1, 127.6, 128.7, 141.7.

Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.80; H, 6.45; N, 12.53.

***N*-Cyanomethyl glycine benzyl ester (2h)**
Colorless oil.

IR (film): ν = 3346, 3034, 2954, 2236, 1741, 1498, 1456, 1392, 1193, 1150, 974, 875, 753, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.57 (d, *J* = 4.2 Hz, 2H), 3.66 (d, *J* = 5.1 Hz, 2H), 5.19 (s, 2H), 7.35−7.38 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.8, 49.2, 67.0, 117.2, 128.5, 128.6, 128.7, 131.2, 170.9.

HRMS (EI): *m/z* calcd for $C_{11}H_{12}N_2O_2$: 204.0899. Found: 204.0901.

***N*-Cyanomethyl phenylalanine methyl ester (2i)**
Colorless oil.

$[\alpha]_D^{28}$ +7.4 (c 0.822, $CHCl_3$).

IR (film): ν = 3339, 3029, 2952, 2238, 1735, 1495, 1436, 1268, 1210, 1175, 991, 873, 748, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.92 (dd, *J* = 13.6, 8.0 Hz, 1H), 3.11 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.53−3.55 (m, 2H), 3.68−3.74 (m, 1H), 3.75 (s, 3H), 7.18−7.34(m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.9, 39.1, 52.2, 61.0, 117.1, 127.1, 128.7, 129.1, 136.1, 173.2.

HRMS (EI): *m/z* calcd for $C_{12}H_{14}N_2O_2$: 218.1055. Found: 218.1053.

Cyanomethylation of Primary Amines (Conditions C): Preparation of *N*-Cyanomethyl-1-adamantanamine (2g); Typical Procedure
To a DMF (9 mL) solution of 1-adamantanamine (419 mg, 2.77 mmol) were added K_2CO_3 (956 mg, 6.92 mmol) and ICH_2CN (300 μL, 4.15 mmol). After stirring for 1 h at r.t., the reaction mixture was partitioned between Et_2O and 3N NaOH. The aqueous layer was thoroughly extracted with Et_2O four times, and the combined organic extracts were washed with sat. NaCl, dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator. The crude material (712 mg) was purified by flash column chromatography on silica gel (50% Et_2O in hexanes) to give **2g** (467 mg, 89%) as slightly yellow crystals; mp: 50.5−51.4 °C (hexanes).

IR (KBr): ν = 3436, 2905, 2849, 2238, 1631, 1450, 1360, 1142, 1098, 873 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.58−1.71 (m, 12H), 2.10 (br s, 3H), 3.57 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.1, 29.3, 36.2, 42.2, 51.2, 120.0.

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.79; H, 9.28; N, 14.68.

Nitrone (3d); Typical Procedure
(*S*)-*N*-Cyanomethyl-1-phenylethylamine (**2d**, 1.50 g, 9.39 mmol) was dissolved in CH_2Cl_2 (50 mL). To this solution was added *m*-CPBA (approx. 70%, 5.09 g, 20.7 mmol) in several portions at 0 °C. After stirring for 20 min at r.t., aqueous $Na_2S_2O_3$ and sat. $NaHCO_3$ were added and the resulting mixture was stirred for an additional 20 min. The mixture was then extracted thrice with CH_2Cl_2, the combined extracts were washed with sat. NaCl, dried ($MgSO_4$),

filtered, and concentrated on a rotary evaporator to afford the crude product as a yellow solid. Purification by flash column chromatography (30% to 80% EtOAc in hexanes gradient) gave **3d** (1.29 g, 79%) as white crystals; mp 91.3−91.9 (EtOAc/hexanes); $[\alpha]_D^{28}$ +83 (*c* 0.494, $CHCl_3$).

IR (KBr): ν = 3098, 2222, 1541, 1452, 1442, 1377, 1295, 1181, 1074, 1007, 748, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.83 (d, *J* = 6.8 Hz, 3H), 5.18 (quint, *J* = 7.2 Hz, 1H), 6.67 (s, 1H), 7.43 (br s, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0, 79.5, 105.8, 112.2, 127.4, 129.2, 129.8, 136.2.

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.70; H, 5.86; N, 15.92.

Nitrone 3a
Colorless oil.

IR (film): ν = 3110, 2222, 1719, 1545, 1497, 1456, 1319, 1215, 1027, 960, 769, 709 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.02 (s, 2H), 6.58 (s, 1H), 7.32−7.48 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.1, 107.5, 112.5, 130.0, 130.3, 130.7, 131.0.

HRMS (EI): *m/z* calcd for $C_9H_8N_2O$: 160.0637. Found: 160.0642

Nitrone 3b
Mp: 77.0−78.2 °C (EtOAc/hexanes).

IR (KBr): ν = 3108, 2223, 1545, 1492, 1456, 1415, 1270, 1195, 1085, 961, 756, 710 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.21 (t, *J* = 7.0 Hz, 2H), 4.12 (t, *J* = 7.0 Hz, 2H), 6.37 (s, 1H), 7.17−7.37 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.7, 68.6, 107.4, 111.8, 127.5, 128.6, 129.0, 135.9.

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.85; H, 5.86; N, 16.03.

Nitrone 3c
Colorless oil.

IR (film): ν = 3110, 2932, 2220, 1603, 1543, 1496, 1454, 1418, 1342, 1277, 1190, 965, 746, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.22−2.30 (m, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 3.91 (t, *J* = 7.4Hz, 2H), 6.66 (s, 1H), 7.16−7.33 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.6, 32.0, 66.1, 107.2, 112.0, 126.6, 128.3, 128.7, 139.4.

HRMS (EI): *m/z* calcd for $C_{11}H_{12}N_2O$: 188.0949. Found: 188.0948.

Nitrone 3e
Mp: 140−141.2 °C dec. (EtOAc/hexanes).

IR (KBr): ν = 3446, 3088, 2221, 1538, 1486, 1418, 1321, 1173, 997, 752 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.38 (dd, *J* = 8.4, 16.4 Hz, 2H), 3.53 (dd, *J* = 5.8, 16.6 Hz, 2H), 4.97 (tt, *J* = 5.8, 8.4 Hz, 1H), 6.83 (s, 1H), 7.23 (br s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.2, 76.3, 105.8, 112.1, 124.5, 127.6, 138.7.

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.68; H, 5.55; N, 15.08.

Nitrone 3f
Mp: 113.0−114.6 °C (EtOAc/hexanes).

IR (KBr): ν = 3435, 3104, 2222, 1534, 1497, 1456, 1281, 1159, 748, 726, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.34 (s, 1H), 6.76 (s, 1H), 7.27−7.43 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.6, 108.0, 112.2, 128.4, 129.1, 129.5, 134.8.

HRMS (EI): *m/z* calcd for $C_{15}H_{12}N_2O$: 236.0949. Found: 236.0946.

Nitrone 3g
Mp: 187.0−190.0 °C (EtOAc/hexanes).

IR (KBr): ν = 3130, 2926, 2857, 2214, 1524, 1458, 1406, 1168, 1058, 1017, 917, 726 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.67−1.78 (m, 6H), 2.09 (br s, 6H), 2.27 (br s, 3H), 6.81 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.6, 35.5, 40.8, 74.7, 103.0, 113.0.

Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.57; H, 7.80; N, 13.62.

(*S*)-1-Phenylethylhydroxylamine Oxalate (4d); Typical Procedure
Nitrone (**3d**, 117 mg, 0.674 mmol) was dissolved in MeOH (3.5 mL) and NH_2OH•HCl (234 mg, 3.37 mmol) was added. After stirring for 2 h at 60 °C, the resulting mixture was cooled to r.t., diluted with $CHCl_3$ (30 mL), and filtered through a pad of Celite. The filtrate was concentrated, and the residue was partitioned between $CHCl_3$ and sat. $NaHCO_3$. The aqueous layer was extracted twice with $CHCl_3$, and the combined extracts were washed with sat. NaCl, dried ($MgSO_4$), and filtered. To the filtrate was added a MeOH solution of $(COOH)_2$ (91.1 mg, 1.01 mmol), and the resulting suspension was concentrated to dryness. The white solid obtained was triturated with Et_2O, and collected by suction. After drying in vacuo, analytically pure **4d** (153 mg, quant.) was obtained as white crystals; mp: 163.0−167.0 °C, dec. (MeOH/Et_2O); $[\alpha]_D^{28}$ −3.1 (*c* 1.06, MeOH). After conversion to the corresponding *N*-benzoylhydroxylamine, enantiomeric excess of the product was determined to be 95% by chiral HPLC analysis (DAICEL CHIRALPAK AS, 4.6 mm I. D. × 250 mm, *i*-PrOH/*n*-hexane (40/60), 1.0 mL/min, 30 °C) using the racemic compound as the reference.

IR (KBr): ν = 3220, 2987, 2578, 1761, 1610, 1483, 1458, 1210, 986, 961, 775, 714, 702 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 1.68 (d, *J* = 6.8 Hz, 3H), 4.52 (q, *J* = 6.9 Hz, 1H), 7.39−7.50 (m, 5H).

^{13}C NMR (100 MHz, CD_3OD): δ = 16.1, 62.9, 129.9, 130.1, 130.6, 136.0, 166.4.

Anal. Calcd for $C_8H_{11}NO$•$(COOH)_2$: C, 52.86; H, 5.77; N, 6.16. Found: C, 52.65; H, 5.70; N, 6.09.

Benzylhydroxylamine Oxalate (4a)
Mp: 148.9−150.5 °C (MeOH/Et_2O).

IR (KBr): ν = 3425, 2945, 1703, 1634, 1457, 1404, 1264, 752, 721, 698 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 4.36 (s, 2H), 7.38−7.45 (m, 5H).

^{13}C NMR (100 MHz, CD_3OD): δ = 56.3, 130.0, 130.5, 130.8, 131.8, 165.0.

Anal. Calcd for C_7H_9NO•$1.23(COOH)_2$: C, 48.54; H, 4.93; N, 5.98. Found: C, 48.05; H, 5.03; N, 6.09.

2-Phenylethylhydroxylamine Oxalate (4b)
Mp: 158.0−161.2 °C, dec. (MeOH/Et_2O).

IR (KBr): ν = 3431, 2598, 1721, 1629, 1498, 1458, 1403, 1280, 1189, 741, 701, 609 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 3.03 (t, *J* = 8.2 Hz, 2H), 3.44 (t, *J* = 8.2 Hz, 2H), 7.23−7.35 (m, 5H).

^{13}C NMR (100 MHz, CD_3OD): δ = 30.7, 53.3, 128.2, 129.8, 130.0, 137.6, 163.4.

Anal. Calcd for $C_8H_{11}NO•(COOH)_2$: C, 52.63; H, 5.74; N, 6.11. Found: C, 52.66; H, 5.72; N, 5.97.

3-Phenylpropylhydroxylamine Oxalate (4c)
Mp: 162.4−163.9 °C, dec. (MeOH/Et_2O).

IR (KBr): ν = 3415, 2957, 1720, 1628, 1518, 1453, 1404, 1279, 1220, 749, 721, 704 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 1.93 (quint, *J* = 7.8 Hz, 2H), 2.65 (t, *J* = 7.8 Hz, 2H), 3.10 (t, *J* = 7.8 Hz, 2H), 7.08−7.22 (m, 5H).

^{13}C NMR (100 MHz, CD_3OD): δ = 26.4, 33.4, 51.7, 127.4, 129.4, 129.6, 141.7, 165.5

Anal. Calcd for $C_9H_{13}NO•(COOH)_2$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.48; H, 6.19; N, 5.83.

2-Indanylhydroxylamine Oxalate (4e)
Mp: 206.4−210.8 °C, dec. (DMF).

IR (film): ν = 3416, 3216, 3025, 2523, 1741, 1632, 1485, 1233, 754, 744, 719 cm^{-1}.

Due to this compound's insolubility in various solvents, NMR spectra were taken for the free hydroxylamine.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.89 (dd, *J* = 16.4, 3.9 Hz, 2H), 3.11 (dd, *J* = 16.4, 6.8 Hz, 2H), 3.92−3.99 (m, 1H), 7.12−7.25 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.7, 62.22, 124.8, 126.5. 141.1.

Anal. Calcd for $C_9H_{11}NO•1.13(COOH)_2$: C, 53.87; H, 5.32; N, 5.58. Found: C, 53.81; H, 5.37; N, 5.84.

Diphenylmethylhydroxylamine Oxalate (4f)
Mp: 160.3−160.9 °C, dec. (MeOH/Et_2O).

IR (KBr): ν = 3431, 3282, 2869, 1739, 1625, 1497, 1456, 1398, 1224, 1017, 698 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 5.24 (s, 1H), 7.20−7.44 (m, 10H), 8.60 (br s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 69.4, 127.2, 127.7, 128.3, 140.7, 163.1.

Anal. Calcd for $C_{13}H_{13}NO•1.5(COOH)_2$: C, 57.52; H, 4.83; N, 4.20. Found: C, 57.23; H, 5.21; N, 4.58.

1-Adamantylhydroxylamine Oxalate (4g)
Mp: 205.0−209.0 °C, dec. (MeOH/Et_2O).

IR (KBr): ν = 3420, 3088, 2917, 2855, 1703, 1635, 1573, 1404, 1233, 1010, 723 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.55−1.68 (m, 6H), 1.77 (br s, 6H), 2.10 (br s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.0, 35.4, 36.0, 58.1, 164.7.

Anal. Calcd for $C_{10}H_{17}NO•1.24(COOH)_2$: C, 53.75; H, 7.04; N, 5.02. Found: C, 53.72; H, 7.09; N, 5.14.

1-(Benzyloxycarbonyl)-methylhydroxylamine Oxalate (4h)
Mp:135.2−136.1 °C (MeOH/Et_2O).

IR (KBr): ν = 3440, 1758, 1613, 1416, 1221, 758, 721 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.63 (s, 2H), 5.15 (s, 2H), 7.30−7.39 (m, 5H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.7, 65.6, 128.0, 128.0, 128.4, 136.0, 161.7, 170.3.

Anal. Calcd for $C_9H_{11}NO_3•1.07(COOH)_2$: C, 48.24; H, 4.78; N, 5.05. Found: C, 48.15; H, 5.09; N, 5.27.

(*S*)-1-Methoxycarbonyl-2-phenylethylhydroxylamine Oxalate (4i)
Mp: 143.2−144.9 °C, dec. (MeOH/Et_2O).

$[\alpha]_D^{28}$ +19.5 (*c* 1.134, MeOH).

IR (KBr): ν = 3444, 3146, 2717, 1895, 1752, 1585, 1395, 1300, 1226, 1070, 756, 719, 699 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.77−2.80 (m, 2H), 3.55 (s, 3H), 3.65−3.70 (m, 1H), 7.16−7.28 (m, 5H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 34.8, 51.4, 66.7, 126.4, 128.2, 129.1, 137.5, 161.2, 173.3.

Anal. Calcd for $C_{10}H_{13}NO_3.(COOH)_2$: C, 50.53; H, 5.30; N, 4.91. Found: C, 50.36; H, 5.18; N, 4.88.

The optical purity of the product **4i** was established after reduction with Zn/HOAc. The optical rotation of the corresponding amino acid methyl ester hydrochloride was in good agreement with that of the commercial starting compound and that reported in the literature.[7] (Reduction product of **4i**, $[\alpha]_D^{27}$ +36.3° (*c* 2.0, EtOH); starting compound **1i**•HCl, $[\alpha]_D^{27}$ +36.5° (*c* 2.0, EtOH); Lit.,[7] $[\alpha]_D$ +37° (*c* 2, EtOH)).

Conversion of Cyanomethylated Amines to *N*-Monoalkylhydroxylamines without Purification of the Intermediate Nitrones, (*S*)-*N*-1-Phenylethylhydroxylamine
(*S*)-*N*-Cyanomethyl-1-phenylethylamine (**2d**, 1.28 g, 8.01 mmol) was dissolved in CH_2Cl_2 (20 mL). To the solution at 0 °C was added *m*-CPBA (approx. 60%, 4.6 g, 16 mmol) in several portions. After the mixture was stirred for 30 min at r.t., aqueous $Na_2S_2O_3$ and sat. $NaHCO_3$ were added, and the resulting mixture was stirred for an additional 20 min. The mixture was extracted thrice with $CHCl_3$, and the combined extracts were washed with sat. NaCl, dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator to afford the crude product (1.45 g) as a yellow solid. The solid was dissolved in MeOH (15 mL), and NH_2OH•HCl (2.58 g, 40.1 mmol) was added. After stirring for 2 h at 60 °C, the resulting white suspension was cooled to r.t., diluted with CH_2Cl_2 (30 mL), and filtered through a pad of Celite. The filtrate was concentrated, and the residue was partitioned between $CHCl_3$ and sat. $NaHCO_3$. The aqueous layer was extracted twice with $CHCl_3$, and the combined extracts were washed with sat. NaCl, dried ($MgSO_4$), and filtered. To the filtrate was added a MeOH solution of $(COOH)_2$ (1.44 g, 16.0 mmol), and the resulting suspension was concentrated to dryness. The white solid obtained was triturated with Et_2O/hexanes (1:1), and collected by suction. After drying in vacuo, analytically pure (*S*)-*N*-1-phenylethylhydroxylamine (**4d**) (1.49 g, 82%) was obtained as a white solid.

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