Supplementary Material

A Novel, General Method for the Synthesis of Nitrile Oxides: Dehydration of *O*-Silylated Hydroxamic Acids

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Materials and Methods

All reagents and reaction solvents were obtained and purified before use when necessary. Non–aqueous reactions were performed in oven-dried glassware under a slight positive pressure of dry argon. Air- and moisture-sensitive liquids and solutions were transferred under inert atmosphere by cannula or syringe. Syringes employed were glass tight (Hamilton) or all polypropylene disposable (BBraun). Organic solutions were

concentrated by rotary evaporation at 40°C. Residual organic solvent was removed under high vacuum. Triethylamine, 2,6-lutidine, diisopropylamine, pyridine, and N-ethyl diisopropylamine were distilled from calcium hydride. THF, toluene, dichloromethane, and acetonitrile were dried and purified through activated alumina columns as described by Grubbs *et al.*[1] Methane sulfonyl chloride and triflic anhydride were distilled fractionally from phosphorous pentoxide.

Flash chromatography: silica gel 60 (230 – 400 mesh, 0.04 – 0.063 mm) from *Fluka* at rt and 0.3 – 0.4 mbar air pressure.

Thin layer chromatography (TLC): *Merck* 0.25 mm silica gel *60 F* plates. Visualization of the developed chromatogram was performed by either UV fluorescence at 254 nm or oxidative stain by ceric ammonium molybdate solution or $KMnO_4$ / $NaHCO_3$ water solution.

Melting points: *Büchi* 510 apparatus. All melting points were measured in open capillaries and are uncorrected.

IR spectra: *Perkin-Elmer Paragon 1000 Fourier Transform single beam spectraphotometer*. The samples were prepared as either KBr pellets or thin films on NaCl salt plates and are reported as absorption maxima in cm^{-1} with corresponding characteristic intensity (w = weak, m = medium, s = strong).

NMR spectra: ^1H, ^{13}C NMR spectra: *Varian Gemini-200, or –300* operating at 200 rsp. 300 MHz for ^1H-NMR, *Varian Mercury-300* operating at 300 MHz for ^1H-NMR and 75 MHz for ^{13}C-NMR or *Bruker AMX 400* operating at 400 MHz for ^1H-NMR and 100 MHz for ^{13}C-NMR. ^1H-NMR spectra were referenced internally to residual protion solvent signals. Data for ^1H are reported as follows: chemical shift (δ, ppm), multiplicity (*s*(singlet*), d(*doublet), *t*(triplet), *q*(quartet), and *m*(multiplet)), integration, coupling constant (*J*, Hz), and assignment. Data for ^{13}C are reported in terms of chemical shift (δ, ppm). When ^{13}C NMR spectras are assigned, DEPT were taken.

Mass spectra: EI mass spectra were performed by the MS service at ETH Zürich. EI-MS (*m/z* (%)): *VG-TRIBRID* spectrometer; spectra were measured at 70 eV.

Elemental analyses: Mikrolabor für Organische Chemie at ETH-Zürich.

O-Functionalized Hydroxamates

O-tert-Butyldiphenylsilylbenzhydroxamate

A solution of benzhydroxamic acid (0.50 g, 3.7 mmol, 1.0 equiv) in THF (2 ml) was added dropwise at 0 °C to a suspension of NaH (0.18 g, 7.5 mmol, 2.1 equiv) in THF (8 ml). The resulting mixture was stirred at this temperature for a further 5 min and treated with $^tBuPh_2SiCl$ (1.02 g, 3.7 mmol, 1.0 equiv). After being stirred for an additional 15

min, the mixture was cautiously treated with glacial acetic (1 ml) and the reaction allowed to attain rt. It was subsequently diluted with water (10 ml) and extracted with Et_2O (3 x 15 ml). The organic extracts were washed with water (20 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave unpurified product as a white solid. Recrystallization from Et_2O / hexane, evaporation of the filtrate and second recrystallization gave 1.0 g (72 %) of pure white crystals.
mp: 138 – 139 °C.
^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.84-7.73 (*m*, 6H, Ar-H), 7.46-7.30 (*m*, 9H, Ar-H), 1.20 (*s*, 9H, $C(CH_3)_3$).
^{13}C-NMR (100 MHz, $CDCl_3$, *denotes minor rotamer peak): δ 166.9* (C), 158.8 (C), 135.7 (CH), 135.4* (CH), 133.2* (C), 132.2 (C), 131.7 (CH), 130.5* (CH), 130.4 (CH), 129.8* (CH), 128.9* (C), 128.5 (CH), 128.2* (CH), 128.0 (CH), 127.6* (CH), 126.9* (CH), 125.9 (CH), 27.2* (CH_3), 26.8 (CH_3), 19.6* (C), 19.2 (C).
IR (KBr): 3447*w*, 3205*m*, 3048*w*, 2957*m*, 2857*m*, 1653*s*, 1580*w*, 1515*m*, 1485*m*, 1427*m*, 1363*w*, 1312*w*, 1163*m*, 1116*s*, 1021*m*, 902*m*, 822*m*, 764*m*, 701*s*, 614*m*.
EI-MS: 377.1 (<1, $[M+H]^+$), 318.1 (8, $[M-C(CH_3)_3]^+$), 199.1 (100), 180.1 (50), 152.1 (3), 139.0 (5), 119.0 (9), 103.1 (5), 91.1 (3), 77.0 (9).
Anal. Calcd. for $C_{23}H_{25}NO_2Si$: C, 73.56; H, 6.71; N, 3.73. Found: C, 73.61; H, 6.62; N, 3.92.

***O-tert*-Butyldiphenylsilylhydrocinnamohydroxamate**

To a 0 °C solution of 3-phenylpropionic acid (2.0 g, 13 mmol, 1.0 equiv) and NEt_3 (2.8 ml, 20.0 mmol, 1.5 equiv) in THF (500 ml) was added $SOCl_2$ (1.2 ml, 16 mmol, 1.2 equiv) and the reaction was stirred at 0 °C for 75 min before *tert*-butyldiphenylsilylhydroxylamine (4.0 g, 15 mmol, 1.1 equiv) was added. The pale yellow mixture was stirred for 2 h before it was poured into ethyl acetate (300 ml) and washed with saturated, aqueous $NaHCO_3$ followed by water. After drying over anhydrous Na_2SO_4, the light brown solution was concentrated under reduced pressure which crystallized under high vacuum. Recrystallization from ether / hexane afforded 2.8 g of *O*-^{t}BuPh$_2$Si-hydrocinnamohydroxamate (52 %) as a light yellow solid.
mp: 112 – 114 °C.
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.73-7.70 (*m*, 4H, Ar-H), 7.50-7.39 (*m*, 6H, Ar-H), 2.83 (*t*, 2H, CH_2), 2.28 (s(br), 2H, CH_2), 1.15 (s, 9H, $C(CH_3)_3$).
^{13}C-NMR (100 MHz, $CDCl_3$, *denotes minor rotamer peak):169.9 (C), 161.8* (C), 140.4 (C), 135,7 (CH), 135.3* (CH), 131.2 (C), 130.3 (CH), 129.7* (CH), 128.4 (CH), 128.3* (CH), 128.2 (CH), 127.9 (CH), 127.6* (CH), 126.1 (CH), 35.2 (CH_2), 31.4 (CH_2), 27.1* (CH_3), 26.7 (CH_3), 19.4 (C), 19.0* (C).
IR (KBr): 3467*m*, 3211*s*, 3024*w*, 2941*m*, 2857*m*, 1667*s*, 1491*s*, 1427*m*, 1392*w*, 1365*w*, 1329*w*, 1268*w*, 1194*w*, 1119*m*, 1058*m*, 992*m*, 901*w*, 824*m*, 780*s*, 745*s*, 703*s*, 613*m*. DEI-EI-MS: 403.6 ([M^+], absent), 346.1 (30, $[M-C(CH_3)_3]^+$), 199.1 (100, $[SiO(C_6H_5)_2]^+$), 147.1 (2), 105,1(4), 91.1 (7), 77.0 (2).

Anal. Calcd. for $C_{25}H_{29}NO_2Si$: C, 74.40; H, 7.24; N, 4.47. Found: C, 74.23; H, 7.02; N, 3.49.

***O-tert*-Butyldiphenylsilylcinnamohydroxamate**

To a solution of methyl cinnamate (3.2 g, 20 mmol, 1.0 equiv) and hydroxylamine hydrochloride (5.5 g, 80 mmol, 4.0 equiv) in MeOH (30 ml) was added dropwise a 5 M solution of KOH in MeOH (20 ml, 100 mmol, 5.0 equiv). After stirring for 36 h at rt, the methanol was evaporated to give a solid residue. This residue was dissolved in AcOH / water (50 : 50; 20 ml) and extracted with ethyl acetate (3 x 20 ml). After drying over anhydrous Na_2SO_4, concentration of the combined organic layers affords an oil, which, after azeotropic evaporation with toluene (2 x 10 ml) and EtOH (2 x 10 ml), afforded a solid. Washing with Et_2O gave cinnamohydroxamic acid (2.1 g, 65 %) as light red crystals (mp: 114 – 117 °C, lit.[2]: 119.5 °C).
The silylated hydroxamate was prepared by treating cinnamohydroxamic acid (2.0 g, 12 mmol, 1.0 equiv) with NaH (0.5 g, 14 mmol, 2.0 equiv) and ^{t}BuPh$_2$SiCl (3.1 ml, 12 mmol, 1.0 equiv) in THF (25 ml) as described above. Recrystallization from Et_2O / hexane gave of *O*-^{t}BuPh$_2$Si-cinnamohydroxamate (3.1 g, 62 %) as a light red solid.
mp: 174 – 176 °C.
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.77-7.74 (*m*, 4H, Ar-H), 7.47-7.32 (*m*, 13H, Ar-H, -CH=CH-), 6.5 (*s* (br), 1H, NH), 1.18 (*s*, 9H, $C(CH_3)_3$).
^{13}C NMR (100 MHz, $CDCl_3$, * denotes minor rotamer peak): 159.9 (C), 142.3* (C), 135.7 (CH), 135.3* (CH), 134.8 (CH), 134,6* (CH), 132.8 (C), 131.1 (C), 130.4* (CH), 129.9 (CH), 129.6* (CH), 128.9 (CH), 128.7 (CH), 128.0* (CH), 127.9* (CH), 127.7 (CH), 127.1* (CH), 116.2 (CH), 27.1* (CH_3), 26.8 (CH_3), 19.5* (C), 19.2 (C).
IR (KBr): 3467*w*(br), 3259*m*, 3079*w*, 2932*m*, 2858*m*, 1665*s*, 1636*s*, 1508*m*, 1471*w*, 1427*m*, 1348*w*, 1114*m*, 1050*s*, 1000*w*, 979*w*, 866*w*, 802*s*, 762*m*, 700*s*, 617*m*.
EI-MS: 401.6 ([M^+], absent), 344.1 (8, [M-$C(CH_3)_3$]$^+$), 206.1 (14), 199.1 (100, [$SiO(C_6H_5)_2$]$^+$), 181.1 (4), 145.1 (7), 129.1 (3), 84.0 (2).
Anal. Calcd. for $C_{25}H_{27}NO_2Si$: C, 74.77; H, 6.78; N, 3.49. Found: C, 74.61; H, 6.83; N, 3.53.

Substituted Isoxazolines

General procedure for the preparation of nitrile oxides and subsequent 1,3 dipolar cycloaddition with an olefin:

3-Phenyl-3a, 6,7,7a-tetrahydro-4,7-methano-benzo<d>2-isoxazoline (3a)[3]

To a – 40 °C solution of *O-tert*-butyldiphenylsilyl-benzhydroxamate (0.050 g, 0.13 mmol, 1.0 equiv) and NEt_3 (0.054 ml, 0.39 mmol, 3.0 equiv) in CH_2Cl_2 (2 ml) was added dropwise a 10 % - solution of triflate anhydride in CH_2Cl_2 (0.24 ml, 0.15 mmol, 1.1 equiv). After complete addition, the solution was allowed to warm to 0°C for 1 h and when norbornene (0.025 g, 0.27 mmol, 2.0 equiv) was added. The reaction mixture was warmed to rt and stirred for 5 h. After the reaction was complete, the solution was washed with water (3 x 3 ml). The aqueous mixture was extracted with ethyl acetate (3 x

5ml). The organic layers were washed with brine (5 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane / ethyl acetate 20:1) gave the product as a white solid (0.02 g, 86 %).
mp: 99 °C (lit.[4]: 99 – 100 °C)
^{1}H NMR (200MHz, $CDCl_3$): δ 7.75-7.72 (*m*, 2H, Ar-H), 7.42-7.40 (*m*, 3H, Ar-H), 4.67 (*d*, 1H, *J* = 8.3 Hz, -O-CH-), 3.52 (*d*, 1H, *J* = 8.3 Hz, =C-CH_2-), 2.60 (*d*, 1H, *J* = 19.9Hz), 1.63-1.18 (*m*, 6H).
Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.54. Found: C, 78.70; H, 7.02; N, 6.59.

3,5-Diphenyl-2-isoxazoline (3b)[5]

mp: 75 °C.
^{1}H NMR (200MHz, $CDCL_3$): δ 7.76-7.71 (*m*, 2H, Ar-H), 7.46-7.34 (*m*, 8H, Ar-H), 5.77 (*dd*, 1H, *J* = 10.8, 8.3 Hz, -O-CH-Ph), 3.81 (*dd*, 1H, *J* = 16.6, 10.8 Hz, =C-CH_2-), 3.37 (*dd*, 1H *J* = 16.6, 8.3 Hz, =C-CH_2-).
Anal. Calcd. for $C_{15}H_{15}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.54; H, 5.89; N, 6.27.

3,5-Diphenyl-2-isoxazoline-4-carboxylic acid methyl ester (3c)[6]

^{1}H NMR (200MHz, $CDCL_3$): δ 7.75-7.70 (*m*, 2H, Ar-H), 7.43-7.37 (*m*, 8H, Ar-H), 6.00 (*d*, 1H, *J* = 6.2 Hz, -O-CH-Ph), 4.48 (*d*, 1H, *J* = 6.2 Hz, =C-CH-CO_2-), 3.78 (*s*, 3H, -CO_2CH_3).
Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.45; H, 5.48; N, 4.98.

5-Phenyl-3-(2-phenylethenyl)-2-isoxazoline (3d)[7]

mp: 111 – 112 °C.
^{1}H NMR (200MHz, $CDCL_3$): δ 7.71-7.71 (*m*, 2H, Ar-H), 7.50-7.32 (*m*, 8H, Ar-H), 7.15 (*d*, 1H, *J* = 16.6 Hz, Ph-CH=C-), 6.74 (*d*, 1H, *J* = 16.6 Hz, =CH-C=N-), 5.70 (*dd*, 1H, *J* = 11.2, 8.3 Hz, -O-CH-Ph), 3.65 (*dd*, 1H, *J* = 17.0, 11.2 Hz, =C-CH_2-CPh), 3.21 (*dd*, 1H, *J* = 17.0, 8.3 Hz, =C-CH_2-CPh).
Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.77; H, 6.15; N, 5.63.

5-Phenyl-3-(2-phenylethyl)-2-isoxazoline (3e)

^{1}H NMR (200MHz, $CDCL_3$): δ 7.37-7.20 (*m*, 10H, Ar-H), 5.53 (*dd*, 1H, *J* = 10.8, 8.3 Hz, -O-CH-PH), 3.32 (*dd*, 1H, *J* = 17., 10.8 Hz, =C-CH_2-O), 2.86 (*dd*, 1H *J* = 17.0, 8.3 Hz, =C-CH_2-), 2.99-2.67 (*m*, 4H, Ph-CH_2-CH_2-C-).
^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1 141.5, 140.7, 128.9, 128.8, 128.6, 128.2, 126.6, 126.0, 81.5, 45.6, 32.7, 29.4.

IR (thin film, $CHCl_3$): 3027*m*, 2923*w*, 2358*w*, 1603*m*, 1494*m*, 1453*m*, 1362*w*, 1314*w*, 1077*w*, 1029*w*, 872*m*, 757*m*, 698*s*, 562*w*, 530*w*.
EI-MS: 251.1 (100, $[M]^+$), 234.1 (18, $[M\text{-}OH]^+$), 174.1 (9, $[M\text{-}C_6H_5]^+$), 160.1 (12, $[M\text{-}C_7H_7]^+$), 145.1 (38, $[M\text{-}C_7H_7O]^+$), 130.1 (14), 117.1 (15), 104.1 (78, $[C_8H_8]^+$), 91.1 (74, $[C_7H_7]^+$), 77.1(19, $[C_6H_5]^+$).
EI-HRMS: 251.1307 (M^+, $C_{17}H_{17}NO$, calc. 251.1310).
Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.05; H, 6.94; N, 5.56.

3-(2-Phenylethyl)-3a, 6,7,7a-tetrahydro-4,7-methano-benzo<d>-2-isoxazoline (3f)

^{1}H NMR (200MHz, $CDCL_3$): δ 7.37-7.20 (*m*, 5H, Ar-H), 4.43 (*d*, 1H, *J* = 8.3 Hz, -O-CH-C-), 2.96 (*t*, 3H, *J* = 8.3), 2.76-2.46 (*m*, 3H), 2.33 (*s* (br), 1H), 1.62-1.39 (*m*, 3H), 1.24-1.10 (*m*, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2, 140.9, 128.5, 126.2, 86.1, 59.5, 42.8, 38.2, 32.5, 32.1, 28.5, 27.2, 22.7.
IR (thin film): 3025*w*, 2958*s*, 2872*m*, *2360*w, 1718*w*, 1603*w*, 1496*m*, 1453*s*, 1313*m*, 1258*m*, 1076*m*, 1029*m*, 951*m*, 917*m*, 873*m*, 821*w*, 752*m*, 699*s*, 667*w*, 570*w*, 501*w*.
EI-MS: 241.1 (100, $[M]^+$), 212.1 (43, $[M\text{-}C_2H_3]^+$), 184.1 (21, $[M\text{-}C_4H_9]^+$), 105.0 (58, $[C_8H_8]^+$), 91.1 (82, $[C_7H_7]^+$), 77.1(19, $[C_6H_5]^+$).
EI-HRMS: 241.1473 (M^+, $C_{16}H_{19}NO$, calc. 241.1467).
Anal. Calcd. for $C_{16}H_{20}NO$: C, 79.30; H, 8.32; N, 5.78. Found: C, 79.35; H, 8.27; N, 5.76.

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[1] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518.
[2] Jones, Mason, *J. Am. Chem. Soc.* **1927**, *47*, 2534.
[3] For analytical data, see: A. Nagarajan, P. M. Krishna, *J. Indian Chem. Soc*. **1993**, *70*, 134; *Indian J. Chem. Sect. B.* **1993**, *32*, 471.
[4] A. Corsaro, G. Perrini, V. Pistaro, P. Quadrelli, A. G. Invernizzi, P. Caramella, *Tetrahedron*, **1996**, *52*, 6421.
[5]For analytical data, see:T. Shono, Y. Matsumura, K. Tsubata, T. Kamada, K. Kishi, *J. Org. Chem.* **1989**, *54*, 2249.
[6]For analytical data, see: M. A. Weidner-Wells, S. A. Fraga-Spano, I. J. Turchi, *J. Org. Chem.* **1998**, *63*, 6319.
[7] For analytical data, see: E. Díaz, H. Barrios, R. A. Toscano, F. Yuste, *J. Heterocyclic Chem.*, **1992**, *29*, 1325.