A Three Component Tandem Reductive Aldol Reaction Catalyzed by N-Heterocyclic Carbene-Copper Complexes

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Supporting informations

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Materials and Reagents

THF and diethyl ether were distilled over sodium with benzophenone. Toluene was distilled over sodium, acetonitrile and CH_2Cl_2 were distilled over CaH_2.

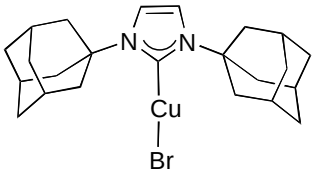
^1H and ^{13}C NMR spectra were recorded on a Bruker Avance II at 300 MHz for proton and 75 MHz for carbon. Chemical shifts (δ) are reported with respect to tetramethylsilane as internal standard in ppm. Abbreviations are: singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet (m) and broad (b).
Infrared spectra were recorded on Shimadzu FTIR-8400s. Intensities are indicated as following: weak (w), medium (m), strong (s), very strong (vs).
Mass spectra were recorded on spectrometers Thermo Finnigan MAT LQC and MAT TSQ 7000. Percentages are indicated relative to base peak.
GC analysis were made on Thermo Finnigan Trace GC with a CHIRALSIL-DEX CB column (25 m; 0,25 mm; 0.25 µm)

Imidazolium salts,[1] (IPr)CuCl[2] and (IMes)CuCl[3] were prepared following procedures reported in the literature.

Synthesis of NHC-Copper Complexes

1,3-Bis(adamantyl)imidazol-2-ylidene copper(I) bromide (IAd)CuBr:

In an oven-dried vial, copper(I) bromide (0.361 g, 2.52 mmol, 1 equiv), IAd·HCl (0.940 g, 2.52 mmol, 1 equiv) and sodium *tert*-butoxide (0.243 g, 2.52 mmol) were loaded inside a glovebox and stirred in dry THF (18 mL) overnight at room temperature outside of the glovebox. After filtration of the reaction mixture through a plug of Celite, the filtrate was mixed with hexane to form a precipitate. A second filtration afforded 0.996 g of the title complex.



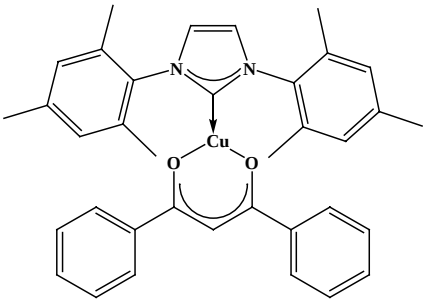
Yield: 79%
Off-white solid.
^1H NMR (300 MHz, $CDCl_3$): δ 1.78 (bs, 12 H), 2.28 (bs, 6 H), 2.40 (bs, 12 H), 7.04 (s, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 35.7, 44.8, 57.8, 115.2, 172.1.
Elemental analysis calcd for $C_{25}H_{40}BrCuN_2$ (510.05): C, 57.56; H, 6.72; N, 5.84. Found: C, 57.86; H, 6.49; N, 5.71.

Typical Procedure for the Synthesis of (NHC)Cu(DBM) Complexes:

NHC-copper halide complex (1 mmol, 1 equiv), dibenzoylmethane (224 mg, 1 mmol, 1 equiv), *t*-BuOK (112 mg, 1 mmol, 1 equiv) were introduced in a flame-dried Schlenk flask under an argon atmosphere. 5 mL of dry THF were added and the resulting bright orange suspension was stirred for 1 h at room temperature (all the following operations were carried out in open air except for **1c** and **2b**). The solution was filtered over Celite and the solvents

were removed under reduced pressure. Finally, the bright orange complex was crystallized from a CH_2Cl_2/cyclohexane mixture.

1,3-Bis(mesityl)imidazol-2-ylidene copper(I) dibenzoylmethanoate, (IMes)Cu(DBM) (1a):



Yield: 91%

^{1}H NMR (300 MHz, C_6D_6): δ 1.99 (s, 6 H), 2.23 (s, 12 H), 6.17 (s, 2 H), 6.56 (s, 1 H), 6.69 (s, 4 H), 7.11-7.14 (m, 6 H), 7.88-7.92 (m. 4 H).

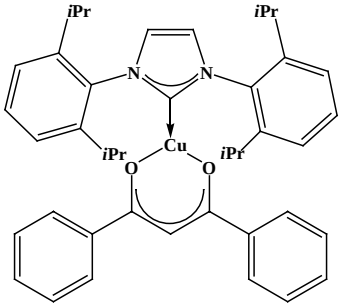
^{13}C NMR (75 MHz, C_6D_6): δ 17.9, 20.9, 93.7, 120.7, 127.5, 127.7, 129.4, 129.5, 135.2, 136.7, 138.6, 143.2, 184.0.

LRMS (ESI) *M/Z*: 671.5 (100%), 672.4 (40%), 673.4 (45%), 674.3 (20%). (isotopic distribution of $[(IMes)_2Cu]^+$

Elemental analysis calcd for $C_{36}H_{35}CuN_2O_2$ (591.23): C, 73.13; H, 5.96; N, 4.74. Found: C, 72.94; H, 5.93; N, 4.64.

IR (neat, cm^{-1}): 3034 (m), 1737 (w), 1596 (m), 1550 (s), 1514 (s), 1456 (s), 1406 (vs).

l,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene copper(I) dibenzoylmethanate, (IPr)Cu(DBM) (1b):



Yield: 75%

^{1}H NMR (300 MHz, C_6D_6): δ 1.16 (d, *J* = 6.9 Hz, 12 H), 1.58 (d, *J* = 6.8 Hz, 12 H), 2.88-2.97 (m, 4 H), 6.42 (s, 2 H), 6.51 (s, 1 H), 7.03-7.20 (m, 12 H), 7.84-7-87 (m, 4 H).

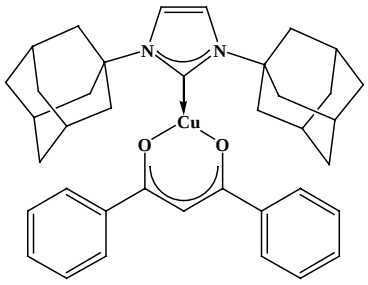
^{13}C NMR (75 MHz, C_6D_6): δ 24.1, 24.5, 29.0, 93.1, 121.7, 124.0, 127.4, 127.7, 129.5, 130.1, 136.2, 143.0, 146.2, 183.6.

LRMS (ESI) *M/Z*: 928.3 (100%), 929.3 (60 %), 930.3 (95%), 931.3 (50 %), 932.3 (25 %). (isotopic distribution of $[(IPr)_2Cu]^+$

Elemental analysis calcd for $C_{42}H_{47}CuN_2O_2$ (675.39): C, 74.69; H, 7.01; N, 4.14. Found: C, 74.35; H, 7.06; N, 4.06.

IR (neat, cm^{-1}): 2960 (m), 1596 (m), 1550 (s), 1515 (s), 1456 (s), 1400 (vs), 717 (s).

l,3-Bis(adamantyl)imidazol-2-ylidene copper(I) dibenzoylmethanate, (IAd)Cu(DBM) (1d):



Yield: 83%

^{1}H NMR (300 MHz, C_6D_6): δ 1.40-1.56 (m, 12 H), 1.94 (s, 6 H), 2.49 (s, 12 H), 6.66 (s, 2 H), 7.02 (s, 1 H), 7.22 (bs, 6 H), 8.24 (bs, 4 H).

^{13}C NMR (75 MHz, C_6D_6): δ 30.2, 36.1, 44.2, 57.8, 112.4, 114.2, 128.2, 129.9, 143.5, 184.9.

LRMS (ESI) *M/Z*: 735.6 (100 %), 736.6 (40 %), 737.6 (45 %), 738.5 (20 %). (isotopic distribution of $[(IAd)_2Cu]^+$

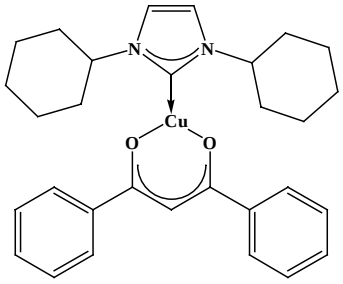
Elemental analysis calcd for $C_{38}H_{43}CuN_2O_2$ (623.31): C, 73.22; H, 6.95; N, 4.49. Found: C, 73.02; H, 7.06; N, 4.24.

IR (neat, cm^{-1}): 2906 (s), 1593 (s), 1546 (s), 1514 (s), 1454 (s), 1400 (vs), 721 (m).

Modified Procedure for the Synthesis of (NHC)Cu(DBM) Complexes:

Imidazolium salt (1 mmol, 1 equiv), CuCl (99 mg, 1 mmol, 1 equiv), dibenzoylmethane (224 mg, 1 mmol, 1 equiv), *t*-BuOK (224 mg, 2 mmol, 2 equiv) were introduced in a flame-dried Schlenk under argon atmosphere. 5 mL of dry THF were introduced and the resulting bright orange suspension was stirred for 1 h at room temperature (all the following operations were carried out in open air except for **1c** and **2b**). The solution was filtered over Celite and the solvents were removed under reduced pressure. Finally, the bright orange complex was crystallized from a CH_2Cl_2/cyclohexane mixture.

l,3-Bis(cyclohexyl)imidazol-2-ylidene copper(I) dibenzoylmethanate, (ICy)Cu(DBM) (1c):



Yield: 69%

Air-sensitive orange solid.

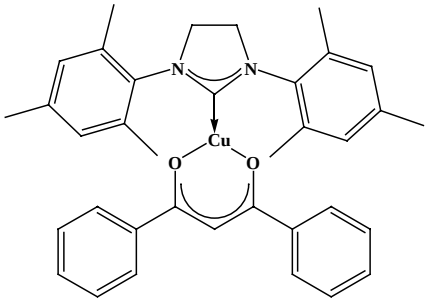
^{1}H NMR (300 MHz, C_6D_6): δ 0.9-1.90 (m, 20 H), 4.46 (bs, 2 H), 5.92 (s, 1 H), 6.46 (s, 2 H), 7.20 (bs, 6 H), 8.19 (bs, 4 H).

^{13}C NMR (75 MHz, C_6D_6): δ 25.4, 25.6, 34.6, 60.8, 93.8, 116.8, 127.6, 128.2, 130.1, 130.6, 178.2, 184.7.

LRMS (ESI) *M/Z*: 527.5 (100%), 528.5 (30%), 529.4 (45%). (isotopic distribution of $[(ICy)_2Cu]^+$

IR (neat, cm^{-1}): 2930 (s), 2852 (m), 1666 (m), 1595 (m), 1548 (m), 1514 (m), 1452 (m), 1402 (vs), 717 (m).

1,3-Bis(mesityl)-4,5-dihydroimidazol-2-ylidene copper(I) dibenzoylmethanate, (SIMes)Cu(DBM) (2a):



Yield: 78%

^{1}H NMR (300 MHz, C_6D_6): δ 1.96 (s, 6 H), 2.42 (s, 12 H), 3.19 (s, 4 H), 6.48 (s, 1 H), 6.70 (s, 4 H), 7.10-7.15 (m, *J* = 4.2 Hz, 6 H), 7.87 (d, *J* = 4.2 Hz, 4 H).

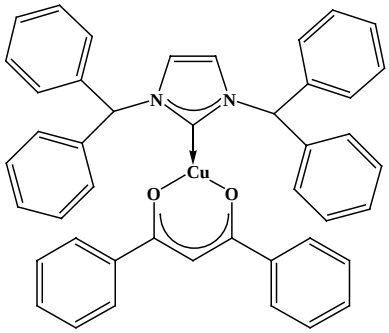
^{13}C NMR (75 MHz, C_6D_6): δ 18.1, 20.9, 50.4, 93.8, 127.5, 127.7, 129.5, 129.7, 136.2, 137.7, 143.1, 184.0.

LRMS (ESI) *M/Z*: 675.4 (100%), 676.4 (45%), 677.4 (55%), 678.4 (20%). (isotopic distribution of $[(SIMes)_2Cu]^+$

Elemental analysis calcd for $C_{36}H_{37}CuN_2O_2$ (593.24): C, 72.88; H, 6.28; N, 4.72. Found: C, 72.18; H, 6.37; N, 4.45.

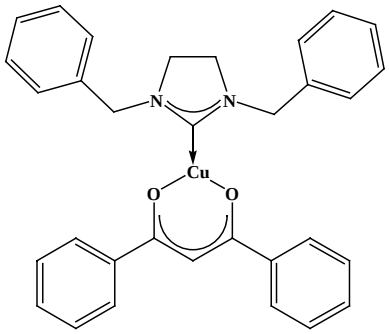
IR (neat, cm^{-1}): 2918 (m), 1596 (s), 1556 (s), 1514 (s), 1473 (s), 1456 (s), 1406 (vs), 1263 (s), 734 (s).

l,3-Bis(benzhydryl)imidazol-2-ylidene copper(I) dibenzoylmethanate (IBh)Cu(DBM) (1e):



Yield: 58%
^{1}H NMR (300 MHz, C_6D_6): δ 5.90 (s, 1 H), 6.45 (s, 4 H), 7.01 (bs, 18 H), 7.72 (s, 4 H), 8.10 (s, 6 H).
^{13}C NMR (75 MHz, C_6D_6): δ 68.7, 93.9, 119.2, 127.1, 128.7, 128.8, 128.9, 140.1, 184.9, 191.6.
LRMS (ESI) *M/Z*: 863.4 (100%), 864.4 (75%), 865.3 (60%), 866.2 (30%). (isotopic distribution of $[(IBh)_2Cu]^+$
Elemental analysis calcd for $C_{44}H_{35}CuN_2O_2$ (687.32): C, 76.89; H, 5.13; N, 4.07. Found: C, 76.42; H, 5.49; N, 4.64.
IR (neat, cm^{-1}): 3047 (m), 3028 (m), 2987 (m), 1710 (s), 1593 (s), 1548 (s), 1514 (s), 1475 (s), 1454 (vs), 1218 (s).

l,3-Bis(benzyl)-4,5-dihydroimidazol-2-ylidene copper(I) dibenzoylmethanate (SIBn)Cu(DBM) (2b):



N.B.: Due to sensitivity of the complex, no purification was carried out.
^{1}H NMR (300 MHz, C_6D_6): δ 2.49 (s, 4 H), 4.55 (s, 4 H), 7.05-7.35 (m, 17 H), 8.23 (d, *J* = 4.2 Hz, 4 H).
^{13}C NMR (75 MHz, C_6D_6): δ 45.6, 54.8, 94.0, 127.1, 127.6, 128.3, 128.5, 129.5, 130.1, 136.9, 143.0, 184.8.
LRMS (ESI) *M/Z*: 563 (100%), 564 (50%), 565 (45%). (isotopic distribution of $[(SIBn)_2Cu]^+$
IR (neat, cm^{-1}): 2904 (m), 1693 (s), 1672 (s), 1546 (m), 1519 (m), 1494 (m), 1452 (vs), 1396 (s), 1245 (s), 700 (s).

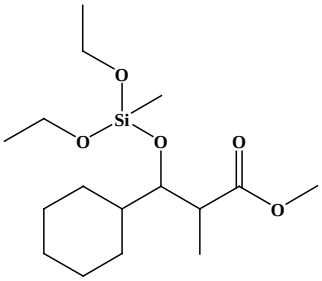
Typical Procedure for Tandem Hydrosilylation-Aldolization Reactions:

A flame-dried flask under argon was loaded with the (NHC)copper complex (0.01 mmol, 0.01 equiv). 5 mL of freshly distilled toluene were introduced, followed by sequential addition of the olefin (1.1 mmol, 1.1 equiv), the electrophile (1 mmol, 1 equiv) and the silane (1.2 mmol, 1.2 equiv). After 1 hour of reaction under argon, the solution was stirred another one in open air. The volatile compounds were removed under reduced pressure and the residue was purified by chromatography on triethylamine pacified silica gel. The product was isolated as mixture of diastereoisomers.

Attribution of relative stereochemistry was done by deprotection of the alcohol with ammonium fluoride (MeOH, rt, 1h) and comparison of NMR spectra with literature.[4]

N.B.: In some cases, some epimerization of compounds bearing an aromatic substituent was observed during the purification.

Methyl 3-cyclohexy-3-(diethoxy(methyl)silyloxy)-2-methylpropanoate 9a:



Yield: 70%

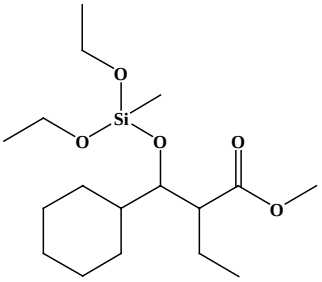
^{1}H NMR (300 MHz, $CDCl_3$): δ *anti*: 0.10 (s, 3 H), 1.08 (d, *J* = 7.1 Hz, 3 H), 1.16-1.92 (m, 17 H), 2.67-2.75 (m, 1 H), 3.66 (s, 3 H), 3.77-80 (m, 4 H), 3.89 (dd, *J* = 7.8; 3.5 Hz, 1 H). *Syn*: 0.10 (s, 3 H), 1.15 (d, *J* = 7.1 Hz, 3 H), 1.16-1.92 (m, 17 H), 2.63-2.67 (m, 1 H), 3.66 (s, 3 H), 3.77-80 (m, 4 H), 3.96 (dd, *J* = 6.2; 5.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDC1_3$): δ *anti*: -6.8, 13.7, 18.3, 26.2, 26.3, 26.7, 30.2, 40.1, 44.2, 51.6, 58.4, 78.7, 176.0. *Syn*: -6.7, 11.2, 18.3, 26.3, 26.5, 26.6, 29.7, 41.9, 42.8, 51.7, 58.4, 78.2, 175.8.

LRMS (CI) *M/Z*: 245 (20%), 287 (100%), 288 (20%).

IR (neat, cm^{-1}): 2974 (m), 2921 (s), 2854 (m), 1737 (vs), 1261 (s), 1026 (s), 958 (s), 823 (s), 792 (m), 773 (m).

Methyl 2-{cyclohexyl[diethoxy(methyl)silyloxy]methyl} butanoate 9b:



Yield: 75%

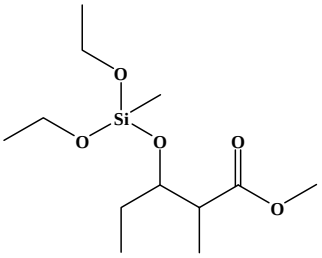
^{1}H NMR (300 MHz, $CDCl_3$): δ *anti*: 0.09 (s, 3 H), 0.86 (t, *J* = 7.4 Hz, 3 H), 1.10-1.80 (m, 20 H), 2.53-2.61 (m, 1 H), 3.67 (s, 3 H), 3.73-3.80 (m, 5 H), 3.87 (dd, *J* = 8.0; 3.2 Hz, 1 H). *Syn*: 0.11 (s, 3 H), 0.87 (t, *J* = 7.4 Hz, 3 H), 1.10-1.80 (m, 20 H), 2.46-2.52 (m, 1 H), 3.67 (s, 3 H), 3.73-3.80 (m, 5 H).

^{13}C NMR (75 MHz, $CDC1_3$): δ *anti*: -6.8, 12.1, 18.3, 22.1, 26.0, 26.4, 26.7, 30.4, 40.5, 51.3, 58.3, 78.3, 175.3. *Syn*: -6.5, 12.2, 18.3, 21.8, 26.4, 26.6, 26.9, 30.3, 42.6, 51.4, 58.3, 78.1, 175.2.

LRMS (CI) *M/Z*: 245 (20%), 301 (100%), 302 (20%).

IR (neat, cm^{-1}): 2927 (m), 1737 (vs), 1263 (m), 1166 (s), 1070 (s), 959 (s), 823 (m).

Methyl 3-[diethoxy(methyl)silyloxy]-2-methylpentanoate 9c:



Yield: 75%

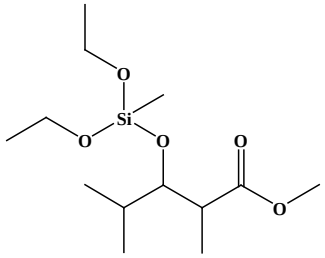
^{1}H NMR (300 MHz, $CDCl_3$): δ *anti*: 0.11 (s, 3 H), 0.92 (t, *J* = 7.3 Hz, 3 H), 1.15 (d, *J* = 7.0 Hz, 3 H), 1.17-1.23 (m, 6 H), 1.50-1.60 (m, 2 H), 2.64-2.71 (m, 1 H), 3.67 (s, 3 H), 3.75-3.85 (m, 4 H), 4.01-4.20 (m, 1 H). Syn: 0.13 (s, 3 H), 0.91 (t, *J* = 7.3 Hz, 3 H), 1.09 (d, *J* = 7.1 Hz, 3 H), 1.17-1.23 (m, 6 H), 1.50-1.60 (m, 2 H), 2.52-2.58 (m, 1 H), 3.67 (s, 3 H), 3.75-3.85 (m, 4 H), 4.01-4.20 (m, 1 H).

^{13}C NMR (75 MHz, $CDC1_3$): δ *anti*: -6.6, 9.1, 12.6, 18.3, 28.0, 45.3, 51.6, 58.4, 75.1, 175.5. *Syn*: -6.6, 9.9, 11.3, 18.3, 26.2, 44.6, 51.6, 58.4, 74.9, 175.1.

LRMS (CI) *M/Z*: 233 (100%), 247 (30%).

IR (neat, cm^{-1}): 2972 (m), 1737 (vs), 1263 (m), 1197 (m), 1170 (m), 1078 (s), 786 (w).

Methyl 3-[diethoxy(methyl)silyloxy]-2,4-dimethylpentanoate 9d:



Yield: 78%

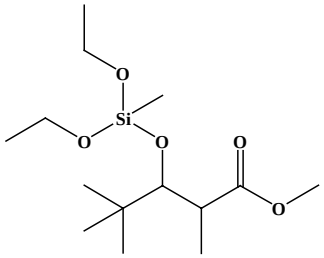
^{1}H NMR (300 MHz, $CDCl_3$): δ *anti*: 0.09 (s, 3 H), 0.84 (d, *J* = 6.7 Hz, 3 H), 0.93 (d, *J* = 7 Hz, 3 H), 1.07 (d, *J* = 7.1 Hz, 3 H), 1.08-1.22 (m, 6 H), 1.78-1.82 (m, 1 H), 2.59-2.71 (m, 1 H), 3.65 (s, 3 H), 3.73-3.80 (m, 4 H), 3.87-3.93 (m, 1 H). *Syn*: 0.10 (s, 3 H), 0.88 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 1.15 (d, *J* = 7 Hz, 3 H), 1.08-1.22 (m, 6 H), 1.62-1.70 (m, 1 H), 2.59-2.71 (m, 1 H), 3.65 (s, 3 H), 3.73-3.80 (m, 4 H), 3.87-3.93 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ *anti*: -6.9, 13.8, 18.3, 20.1, 30.0, 44.8, 51.6, 58.3, 79.1, 175.9. *Syn*: -6.7, 11.8, 17.8, 19.7, 32.2, 43.4, 51.6, 58.3, 78.9, 175.7.

LRMS (CI) *M/Z*: 205 (20%), 247 (100%), 249 (20%).

IR (neat, cm^{-1}): 2972 (m), 1741 (vs), 1263 (m), 1168 (m), 1078 (s), 823 (w), 788 (w).

Methyl 3-[diethoxy(methyl)silyloxy]-2,4,4-trimethylpentanoate 9e:



Yield: 80%

^{1}H NMR (300 MHz, $CDCl_3$): δ *anti*: 0.12 (s, 3 H), 0.89 (s, 9 H), 1.15-1.25 (m, 9 H), 2.62-2.67 (m, 1 H), 3.65 (s, 3 H), 3.75-3.85 (m, 4 H), 4.01 (d, *J* = 4.5 Hz, 1 H). *Syn*: 0.13 (s, 3 H), 0.91 (s, 9 H), 1.15-1.25 (m, 9 H), 2.72-2.78 (m, 1 H), 3.51 (d, *J* = 5.0 Hz, 1 H), 3.63 (s, 3 H), 3.75-3.85 (m, 4 H).

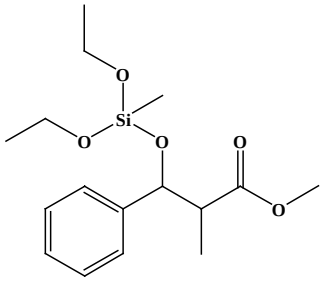
^{13}C NMR (75 MHz, $CDC1_3$): δ *anti*: -6.7, 13.3, 18.3, 26.6, 36.5, 41.6, 51.7, 58.4, 79.8, 176.8.

Syn: -6.6, 16.4, 18.3, 26.6, 36.5,43.0, 51.3, 58.2, 82.9, 176.7.

LRMS (CI) *M/Z*: 261 (100%).

IR (neat, cm^{-1}): 2972 (m), 1741 (vs), 1263 (m), 1166 (m), 1072 (s), 956 (m), 823 (m), 788 (w).

Methyl 3-[diethoxy(methyl)silyloxy]-2-methyl-3-phenylpropanoate 9f:



Yield: 72%

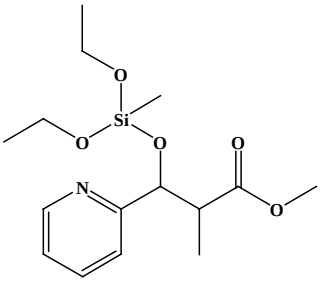
^{1}H NMR (300 MHz, $CDCl_3$): δ *anti*: -0.07 (s, 3 H), 0.87 (d, *J* = 7.1 Hz, 3 H), 1.05-1.15 (m, 6 H), 2.81-2.87 (m, 1 H), 3.57-3.70 (m, 4 H), 3.71 (s, 3 H), 4.93 (d, *J* = 9.3 Hz, 1 H), 7.20-7.35 (m, 5 H). *Syn*: 0.00 (s, 3 H), 1.05-1.15 (m, 6 H), 1.19 (d, *J* = 7.0 Hz, 3 H), 2.70-2.77 (m, 1 H), 3.55 (s, 3 H), 3.57-3.70 (m, 4 H), 5.18 (d, *J* = 6.1 Hz, 1 H), 7.20-7.35 (m, 5 H).

^{13}C NMR (75 MHz, $CDC1_3$): δ *anti*: -6.6, 13.9, 18.2, 48.7, 51.6, 58.4, 77.3, 127.2, 127.6, 128.3, 141.4, 175.6. *Syn*: -6.6, 12.0, 18.2, 48.7, 51.6, 58.4, 75.7, 126.4, 127.6, 128.1, 142.4, 174.6.

LRMS (CI) *M/Z*: 119 (60%), 121 (30%), 281 (100%).

IR (neat, cm^{-1}): 2972 (m), 1737 (vs), 1454 (m), 1265 (s), 1166 (111), 1026 (s), 958 (m), 825 (m), 792 (m), 702 (w).

Methyl 3-[diethoxy(methyl)silyloxy]-2-methyl-3-(pyridine-2-yl)propanoate 9g:



Yield: 72%

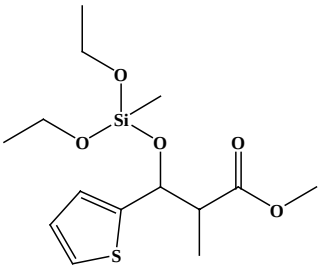
^{1}H NMR (300 MHz, $CDCl_3$): δ *anti*: 0.03 (s, 3 H), 0.97 (d, *J* = 7.1 Hz, 3 H), 1.08-1.22 (m, 6 H), 2.95-3.10 (m, 1 H), 3.67 (s, 3 H), 3.70-3.85 (m, 4 H), 5.16 (d, *J*= 7.7 Hz, 1 H), 7.13-7.17 (m, 1 H), 7.42-7.49 (m, 1 H), 7.51-7.70 (m, 1 H), 8.50-8.55 (m, 1H). *Syn*: 0.08 (s, 3 H), 1.04 (d, *J* = 7 Hz, 3 H), 1.08-1.22 (m, 6 H), 2.95-3.10 (m, 1 H), 3.66 (s, 3 H), 3.70-3.85 (m, 4 H), 5.47 (d, *J* = 4.1 Hz, 1 H), 7.13-7.17 (m, 1 H), 7.42-7.49 (m, 1 H), 7.51-7.70 (m, 1 H), 8.50-8.55 (m, 1H).

^{13}C NMR (75 MHz, $CDC1_3$): δ *anti*: 5.5, 13.2, 18.3, 47.4, 51.7, 58.4, 77.4, 121.6, 122.7, 136.4, 148.9, 161.7, 174.6. *Syn*: -6.7, 10.0, 18.3, 46.1, 51.7, 58.2, 76.0, 121.0, 122.2, 136.4, 148.9, 161.7, 174.6.

LRMS (CI) *M/Z*: 118 (35%), 146 (60%), 282 (100%).

IR (neat, cm^{-1}): 2974 (m), 1739 (vs), 1267 (m), 1064 (s), 777 (m).

Methyl 3-[diethoxy(methyl)silyloxy]-2-methyl-3-(thiophen-2-yl)propanoate 9h:



Yield: 72%

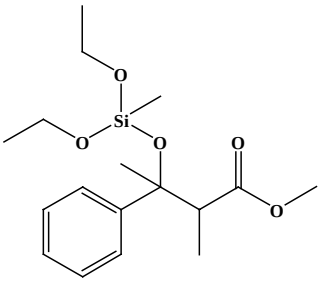
^{1}H NMR (300 MHz, $CDCl_3$): δ *anti*: -0.03 (s, 3 H), 0.95 (d, *J* = 7.1 Hz, 3 H), 1.10-1.17 (m, 6 H), 2.75-2.90 (m, 1 H), 3.60-3.80 (m, 4 H), 3.71 (s, 3 H), 5.26 (d, *J* = 9.0 Hz, 1 H), 6.85-6.95 (m, 2 H), 7.15-7.30 (m, 1 H). *Syn*: 0.03 (s, 3 H), 1.10-1.17 (m, 6 H), 1.26 (d, *J* = 6.9 Hz, 3 H), 2.75-2.90 (m, 1 H), 3.57 (s, 3 H), 3.60-3.80 (m, 4 H), 5.42 (d, *J* = 6.7 Hz, 1 H), 6.85-6.95 (m, 2 H), 7.15-7.30 (m, 1 H).

^{13}C NMR (75 MHz, $CDC1_3$): δ *anti*: -5.6, 13.8, 18.2, 49.2, 51.7, 58.5, 124.5, 125.3, 126.4, 145.2, 175.1. *Syn*: -5.6, 12.7, 18.2, 49.5, 51.7, 58.5, 72.0, 124.2, 126.0, 126.4, 146.6, 174.3.

LRMS (CI) *M/Z*: 183 (100%), 245 (30%), 287 (75%).

I.R. (neat, cm^{-1}): 2974 (m), 1739 (vs), 1434 (w), 1265 (m), 1166 (m), 1053 (s), 960 (m), 825 (m), 790 (m).

Methyl 3-[diethoxy(methyl)silyloxy]-2-methyl-3-phenylbutanoate 10:



Yield: 78%

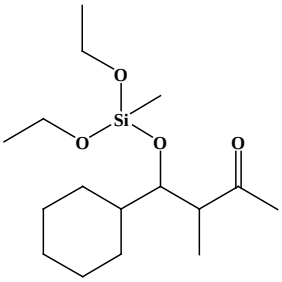
^{1}H NMR (300 MHz, $CDCl_3$): δ *erythro*: -0.08 (s, 3 H), 1.11 (d, *J* = 7.2 Hz, 3 H), 1.10-1.20 (m, 6 H), 1.83 (s, 3 H), 2.94 (q, *J* = 7 Hz, 1 H), 3.47 (s, 3 H), 3.63-3.85 (m, 4 H), 7.29-7.43 (m, 5 H). *Threo*: 0.02 (s, 3 H), 0.93 (d, *J* = 7.1 Hz, 3 H), 1.10-1.20 (m, 6 H), 1.82 (s, 3 H), 2.83 (q, *J* = 7.1 Hz, 1 H), 3.62 (s, 3 H), 3.63-3.85 (m, 4 H), 7.29-7.43 (m, 5 H).

^{13}C NMR (75 MHz, $CDC1_3$): δ *erythro*: -4.5, 13.0, 18.2, 27.1, 51.4, 52.8, 58.2, 78.7, 125.3, 127.2, 127.9, 146.2, 174.4. *Threo*: -4.6, 12.6, 18.2, 25.1, 51.3, 53.0, 58.2, 78.2, 125.6, 127.0, 127.9, 146.6, 174.8.

LRMS (CI) *M/Z*: 191 (100%), 233 (35%), 253 (50%), 295 (80%).

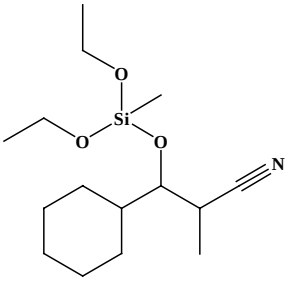
IR (neat, cm^{-1}): 2974 (m), 1737 (vs), 1446 (w) 1265 (m), 1168 (m), 1076 (s), 962 (w), 825 (w), 755 (w).

4-Cyclohexyl-4-[diethoxy(methyl)silyloxy]-3-methylbutan-2-one 11:



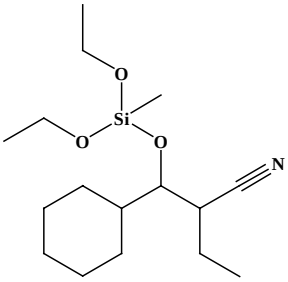
Yield: 70%
^{1}H NMR (300 MHz, $CDCl_3$): δ *anti*: 0.09 (s, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H), 1.10-1.95 (m, 17 H), 2.17 (s, 3 H), 2.75-2.85 (m, 1 H), 3.75-3.85 (m, 4 H), 3.89 (dd, *J* = 7.7; 3.5 Hz, 1 H). *Syn*: 0.10 (s, 3 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 1.10-1.95 (m, 17 H), 2.15 (s, 3 H), 2.65-2.70 (m, 1 H), 3.75-3.85 (m, 4 H), 3.98 (dd, *J* = 6; 5 Hz, 1 H).
^{13}C NMR (75 MHz, $CDC1_3$): δ *anti*: -6.8, 13.5, 18.3, 26.4, 26.7, 30.2, 30.3, 40.7, 50.7, 58.4, 78.8, 212.3. *Syn*: -6.4, 11.1, 18.3, 26.0, 26.5, 28.6, 29.1, 30.0, 42.0, 50.3, 58.4, 77.7, 211.5.
LRMS (CI) *M/Z*: 245 (20%), 271 (100%).
IR (neat, cm^{-1}): 2927 (m), 1712 (vs), 1450 (m), 1263 (m), 1166 (m), 1060 (s), 956 (m), 823 (m), 786 (m), 771 (m)

3-Cyclohexyl-3-[diethoxy(methyl)silyloxy]-2-methylpropanenitrile 12a:



Yield: 74%
^{1}H NMR (300 MHz, $CDCl_3$): δ *anti*: 0.16 (s, 3 H), 1.17-1.23 (m, 6 H), 1.33 (d, *J* = 7.2 Hz, 3 H), 0.95-1.95 (m, 11 H), 2.80-2.88 (m, 1 H), 3.55 (dd, *J* = 6.7; 3.5 Hz, 1 H), 3.78-3.85 (m, 4 H).
^{13}C NMR (75 MHz, $CDC1_3$): δ *anti*: -6.5, 15.7, 18.3, 25.9, 26.7, 29.4, 30.3, 42.3, 58.6, 77.9, 121.3.
LRMS (CI) *M/Z*: 105 (40%), 24 (100%).
IR (neat, cm^{-1}): 2927 (111), 2241 (w), 1448 (m), 1388 (m), 1265 (s), 1060 (s), 958 (m), 823 (m), 790 (m), 773 (m).

2-{Cyclohexyl[diethoxy(methyl)silyloxy]methyl}butanenitrile 12b:



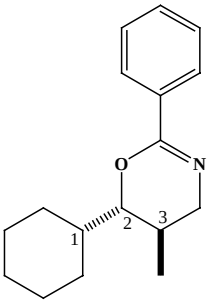
Yield: 54%
^{1}H NMR (300 MHz, $CDCl_3$): δ *anti*: 0.10 (s, 3 H), 0.85-1.95 (m, 22 H), 2.55-2.60 (m, 1 H), 3.57 (dd, *J* = 6.9; 3.1 Hz, 1 H), 3.70-3.78 (m, 4 H).
^{13}C NMR (75 MHz, $CDC1_3$): δ *anti*: -6.4, 12.2, 18.3, 21.6, 26.0, 26.4, 26.8, 38.5, 42.5, 58.6, 76.5, 120.5.
LRMS (CI) *M/Z*: 105 (50%), 133 (40%), 268 (100%).
IR (neat, cm^{-1}): 2925 (m), 2239 (w), 1450 (m), 1265 (m), 1078 (vs), 960 (m), 821 (m), 788 (m).

Determination of Relative Stereochemistry of Nitrile Compounds:

3-Cyclohexyl-3-hydroxy-2-methylpropanenitrile was synthesized from acrylonitrile, cyclohexanecarboxaldehyde and phenylsilane using the general procedure of hydrosilylation-aldolization. The resulting β-hydroxynitrile (1 mmol, 1 equiv) was added to a suspension of $LiAlH_4$ (4 mmol, 4 equiv) in 5 mL of dry Et_2O at 0°C. The solution was stirred overnight and neutralized with 2.5 mL of $NaOH_{aq}$ 6 M. The product was extracted with 4 x 5 mL of Et_2O, dried on $MgSO_4$ and concentrated under reduced pressure. The corresponding aminoalcohol (1 mmol, 1 equiv) was added to a solution of triethylorthobenzoate (1.1 mmol, 1.1 equiv) in

10 mL of 1,2-dichloroethane. 1 drop of CF_3CO_2H was added and the solution was heated at 80°C for 3 h. After cooling, the volatile compounds were removed under reduced pressure and the crude product was purified by chromatography on silica gel (cyclohexane/AcOEt : 85/15).

6-Cyclohexyl-5-methyl-2-phenyl-5,6-dihydro-4H-1,3-oxazine



Yield over three steps: 65%.
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (d, *J* = 6.7 Hz, 3 H), 1.20-1.90 (m, 12 H), 1.90-2.03 (m, 1H), 3.15 (dd, *J* = 16.5; 4.5 Hz, 1 H), 3.59 (dd, *J* = 16.5; 9.6 Hz, 1 H), 3.73 (dd, *J* = 9.0; 2.7 Hz, 1 H), 7.30-7.45 (m, 3 H), 7.90-7.93 (m, 2H).
^{13}C NMR (75 MHz, $CDC1_3$): δ 15.0, 25.6, 26.3, 26.6, 26.8, 27.3, 30.0, 39.0, 50.8, 84.4, 127.1, 128.1, 130.3, 134.3, 156.6.
LRMS (CI) *M/Z*: 258 (100%).
IR (neat, cm^{-1}): 2925 (s), 2852 (m), 1654 (vs), 1448 (m), 1334 (m), 1263 (s), 1126 (s), 696 (s).

^{13}C NMR showed splitting of two of the carbons of the cycle, indicating an atropoisomerism. ^{1}H NMR showed coupling constants of 9 Hz (J_{H2-H3}) and 2 Hz (J_{H2-H1}) for the hydrogen 1.

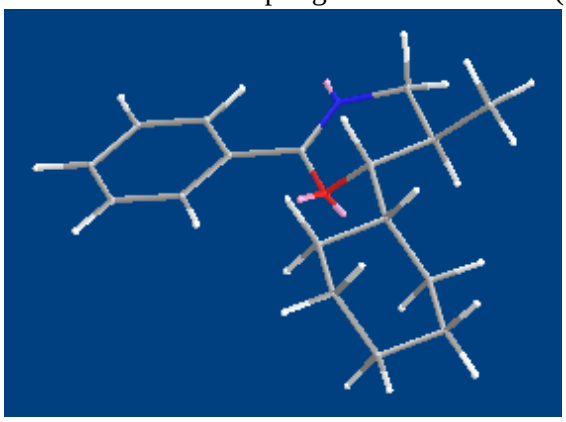


Figure 1 : proposed structure of the oxazoline

References

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