Direct Synthesis of Bicyclic Guanidines through Unprecedented Palladium(II) Catalysed Diamination with Copper Chloride as Oxidant

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**General:** All organic reagents were purchased from Acros, if not noted otherwise. All palladium salts were purchased from Acros. \(N,N'-\text{di-Boc-}N'\)-trifluoromethane-sulfonylguanidine and \(N,N'-\text{di-Cbz-}N'\)-trifluoromethane-sulfonylguanidine were purchased from Fluka. \(N,N'-\text{di-Boc-}N'\)-trifluoromethane-sulfonylguanidine has been synthesised from \(N\)-\(N\)-\(di-(\text{tert-butoxycarbonyl})\)-guanidine\(^1\) according to literature procedure.\(^2\) Iodosobenzene diacetate was purchased from Aldrich. Dichloromethane was dried over calcium chloride and distilled from CaH\(_2\). Absolute DMF was purchased from Fischer Chemicals and stored over 4Å molecular sieves. Column chromatography was performed with silica gel (Merck, type 60, 0.063-0.2mm). NMR spectra were recorded on Bruker Avance 400 MHz, Bruker DPX 300 MHz and Bruker DRX 500 MHz spectrometers. All chemical shifts in NMR experiments are reported as ppm downfield from TMS. The following calibrations were used: CDCl\(_3\) \(\delta = 7.26\) and 77.00 ppm, C\(_6\)D\(_6\) \(\delta = 7.16\) and 128.0 ppm. MS (ESI-LCMS) experiments were performed using an Agilent 1100 HPLC with a Bruker micro-TOF instrument (ESI). Unless otherwise stated, a Supelco C8 (5cm x 4.6mm, 5µm particles) column was used with an linear elution gradient from 100% H\(_2\)O (0.5% HCO\(_2\)H) to 100% MeCN in 13min at a flow rate of 0.5mL/min. MS (EI) and HRMS experiments were performed on a Kratos MS 50 within the service centers at the Kekulé-Department, Bonn University. IR Spectra in the range of 4000-400 cm\(^{-1}\) were obtained on a Nicolet Magna 550 FT-IR Spectrometer with samples investigated as KBr pellets and the data is reported as cm\(^{-1}\).

**General Procedure for the Diamination of Guanidines**

**Copper bromide as oxidant:**

A solution of the guanidine (0.3 mmol, 1.0 eq.), CuBr\(_2\) (0.9 mmol, 3.0 eq.), K\(_2\)CO\(_3\) (0.3 mmol, 1.0 eq.) and Pd(OAc)\(_2\) (0.03 mmol, 0.1 eq.) in DMF (3 mL) was stirred at room temperature until TLC control showed complete conversion of the starting material. The reaction was stopped by addition of 2 mL saturated aqueous Na\(_2\)S\(_2\)O\(_3\) solution and stirred for additional 60 min. Water (5 mL) was
added and the mixture was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic phase was dried over MgSO$_4$ and the solvent removed under reduced pressure to yield analytically pure products.

**Copper chloride as oxidant:**
A solution of the guanidine (0.3 mmol, 1.0 eq.), CuCl$_2$ (0.63 mmol, 2.1 eq.), K$_2$CO$_3$ (0.3 mmol, 1.0 eq.) and Pd(OAc)$_2$ (0.03 mmol, 0.1 eq.) in DMF (3 mL) was stirred at room temperature until TLC control showed complete conversion of the starting material. The reaction was stopped by addition of 2 mL saturated aqueous Na$_2$S$_2$O$_3$ solution and stirred for additional 60 min. Water (5 mL) was added and the mixture was extracted with CH$_2$Cl$_2$ (3 x 20 ml). The organic phase was dried over MgSO$_4$ and the solvent removed under reduced pressure to yield analytically pure products.

**Synthesis of Starting Materials 1a-f and 3a-f**

Starting materials 1a-f and 3a-f were synthesised by treatment of the corresponding amine$^3$ with N,N’-di-Boc-N’-trifluoromethanesulfonylguanidine or N,N-di-Cbz-N’-trifluoromethanesulfonylguanidine following a literature procedure.$^2$

The amine (1.0 eq.) and NEt$_3$ (1.0 eq.) were dissolved in dry CH$_2$Cl$_2$ (4mL/mmol) and the trifluoromethanesulfonylguanidine was added in one portion. The reaction was stirred overnight at r.t. and stopped by addition of saturated NaHCO$_3$ solution (5 mL). 10 mL of CH$_2$Cl$_2$ were added and the organic phase was washed with brine. The organic phase was dried over MgSO$_4$ and the solvent was removed in vacuo. Column chromatography (silica, hexanes/CH$_2$Cl$_2$ 1:1 v/v) gave analytically pure products as white solids.
Analytical Data for New Compounds

**Bis-tert-butyl(2,2-diphenyl-pent-4-en-1-yl)amino-methylidyne-biscarbamate**

![Chemical Structure](image)

1a

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 92% yield.

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ = 1.34 (s, 9H), 1.42 (s, 9H), 2.85 (d, $J = 6.8$ Hz, 2H), 4.03 (d, $J = 4.8$ Hz, 2H), 4.88 (dd, $J = 1.2$, 10.4 Hz, 1H), 4.95 (dd, $J = 1.2$, 17.2 Hz, 1H), 5.36 (ddd, $J = 6.8$, 10.4, 17.2 Hz, 1H), 7.10-7.22 (m, 10H), 8.16 (br, 1NH). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ = 27.89, 28.22, 42.01, 47.87, 49.95, 79.10, 82.73, 118.52, 126.38, 128.04, 128.07, 133.54, 145.01, 152.73, 156.17.

MS (EI): m/z = 479.3 (70) [M$^+$], 423.2 (20), 406.2 (10), 367.1 (30), 350.1 (30), 326.1 (10), 264.1 (10), 220.1 (30), 216.0 (40), 207.1 (50), 178.1 (20), 160.0 (100), 129.1 (70), 116.1 (15), 91.1 (50). HRMS. calcd for C$_{28}$H$_{37}$N$_3$O$_4$: 479.2784, found: 479.2779. IR (KBr): $\nu$ = 3679, 3449, 3321, 3287, 3063, 3004, 2982, 2932, 1733, 1648, 1618, 1447, 1409, 1355, 1253, 1224, 1145, 1053, 908, 879, 810, 782, 757, 726, 699, 678.

**Bis-tert-butyl(2,2-dimethyl-pent-4-en-1-yl)amino-methylidyne-biscarbamate**

![Chemical Structure](image)

1b
Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 94 % yield.

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ = 0.88 (s, 6H), 1.43 (s, 9H), 1.44 (s, 9H), 1.95 (d, $J$ = 7.6 Hz, 2H), 3.18 (d, $J$ = 5.2 Hz, 2H), 5.00 (m, 2H), 5.74 (ddt, $J$ = 7.6, 10.4, 17.2 Hz, 1H), 8.44 (t, $J$ = 5.2 Hz, 1NH). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ = 25.03, 28.05, 28.30, 34.08, 44.37, 50.46, 79.05, 82.94, 117.80, 134.27, 153.39, 156.54, 163.68. MS (EI, eV): m/z (%): 355.2 [M]$^+$ (4), 314.2 (2), 299.1 (10), 282.1 (5), 258.1 (6), 243.1 (70), 226.1 (44), 202.0 (100), 198.1 (8), 161.0 (60), 143.0 (6), 117.0 (10), 96.0 (4), 72.0 (3), 57.0 (28). HRMS calcd for C$_{18}$H$_{33}$N$_3$O$_4$: 355.2471 found: 355.2473. IR (KBr): $\nu$ = 3680, 3434, 3328, 3079, 2980, 2968, 2932, 1731, 1652, 1623, 1575, 1473, 1457, 1414, 139, 1369, 1337, 1282, 1252, 1225, 1163, 1140, 1100, 1054, 809, 761, 640.

Bis-tert-butyl(1-allylcyclohexyl-methyl)amino-methylydene- biscarbamate

$\text{N} \begin{array}{c} \text{NBoc} \\ \text{HN} \\ \text{NH} \end{array}$

$1$c

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 89 % yield.

$^1$H NMR (CDCl$_3$, 400MHz): $\delta$ = 1.25-1.57 (m, 10H), 1.49 (s, 18H), 2.09 (d, $J$ = 7.6 Hz, 2H), 3.30 (d, 5.0 Hz, 2H), 5.02-5.11 (m, 2H), 5.79 (ddt, $J$ = 7.6, 9.9, 17.0 Hz, 1H), 8.45 (s, 1NH). $^{13}$C NMR (CDCl$_3$, 100MHz): $\delta$ = 21.31, 26.11, 28.05, 28.30, 33.58, 36.42, 40.21, 47.29, 79.03, 82.89, 117.70, 133.97, 153.37, 156.46, 163.73. MS (EI) m/z = 395.3 [M]$^+$ (10), 354.2 (15), 339.2 (10), 298.2 (15), 283.1 (50), 266.1 (30), 242.1 (100), 217.1 (5), 186.0 (10), 161.0 (50), 148.0 (10), 143.0 (10), 99.0 (10), 95.1 (15), 81.1 (15), 57.1 (25). HRMS. calc.: 395.2784, found: 395.2780. IR (FT-IR, Ge): $\nu$ = 3335, 2978, 2928, 1718, 1639, 1415, 1366, 1330, 1134, 1056, 798.
Dibenzyl(2,2-diphenyl-pent-4-en-1-yl)amino-methylidene-biscarbamate

\[\text{Ph} \quad \text{N} \quad \text{NCbz} \quad \text{N} \quad \text{NCbz} \quad \text{Ph} \]

1d

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 97 % yield.

\(^1\)H NMR (CDCl\(_3\), 400 MHz) = 2.94 (d, \(J = 7.0\) Hz, 2H), 4.15 (d, \(J = 5.0\) Hz, 2H), 4.98 (dd, \(J = 2.1, 10.2\) Hz, 1H), 5.04 (dd, \(J = 2.1, 17.2\) Hz, 1H), 5.10 (s, 2H), 5.13 (s, 2H), 5.43 (ddt, \(J = 7.0, 10.2, 17.2\) Hz, 1H), 7.20-7.44 (m, 20H), 8.21 (t, \(J = 5.0\) Hz, 1NH). \(^13\)C NMR (CDCl\(_3\), 100 MHz) = 42.05, 47.93, 49.80, 67.05, 67.95, 118.69, 126.57, 127.83, 127.95 (2C), 128.23, 128.36, 128.43, 128.57, 128.67, 133.42, 134.51, 136.82, 144.79, 153.46, 156.05, 163.61. MS (EI): m/z = 547.2 (40) [M\(^+\)], 504.1 (30), 460.1 (10), 439.2 (10), 355.1 (15), 261.1 (10), 207.1 (70), 165.1 (10), 129.1 (60), 108.1 (25), 91.1 (100), 79.1 (20). HRMS. calcd for C\(_{34}\)H\(_{33}\)N\(_3\)O\(_4\): 547.2471, found: 547.2465. IR (KBr): \(\nu = 3670, 3439, 3279, 3087, 3064, 3030, 2930, 2900, 1722, 1647, 1585, 1496, 1427, 1392, 1324, 1201, 1149, 1087, 1055, 916, 803, 756, 746, 698, 585, 497.

Dibenzyl(2,2-dimethyl-pent-4-en-1-yl)amino-methylidene-biscarbamate

\[\text{Ph} \quad \text{N} \quad \text{NCbz} \quad \text{N} \quad \text{NCbz} \]

1e

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 87 % yield.

\(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta = 0.84\) (s, 6H), 1.94 (d, \(J = 7.6\) Hz, 2H), 3.19 (d, \(J = 5.6\) Hz, 2H), 4.96 (m, 1H), 5.00 (m, 1H), 5.03 (s, 2H), 5.08 (s, 2H), 5.71 (ddt, \(J = 7.6, 9.4, 17.5\) Hz, 1H), 7.14-7.32 (m, 10H), 8.41 (s, 1NH). \(^13\)C NMR (CDCl\(_3\),
100MHz): δ = 24.80, 34.08, 44.11, 50.30, 66.90, 67.91, 117.80, 127.67, 127.88, 128.19, 128.27, 128.49, 128.57, 133.96, 134.41, 136.70, 153.83, 156.20, 163.62. MS(El) m/z = 423.2 [M]+ (10), 382.2 (5), 341.1 (5), 288.2 (7), 208.1 (15), 181.1 (10), 166.1 (5), 124.0 (5), 108.0 (25), 91.0 (100), 79.0 (25), 55.1 (10). HRMS. calc.: 423,2158, found: 423.2140. IR (FT-IR, Ge): ν = 3326, 3078, 3033, 2959, 2903, 1729, 1648, 1628, 1428, 1388, 1349, 1329, 1253, 1209, 1146, 1054, 989, 912, 749.

Dibenzyl(1-allylcyclohexyl-methyl)amino-methylidene-biscarbamate

![1f](attachment:image)

1f

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 85 % yield.

$^1$H NMR (CDCl$_3$, 400MHz): δ =1.20-1.52 (m, 10H), 2.07 (d, J = 7.6 Hz, 2H), 3.31 (d, J = 5.3 Hz, 2H), 5.00-5.08 (m, 2H), 5.09 (s, 2H), 5.14 (s, 2H), 5.76 (ddt, J = 7.6 , 10.2, 17.2 Hz, 1H), 7.15-7.40 (m, 10H), 8.42 (s, 1NH). $^{13}$C NMR (CDCl$_3$, 100MHz): δ = 21.16, 21.22, 25.96, 33.45, 36.47, 40.18, 66.94, 67.97, 117.83, 127.72, 127.88, 128.26, 128.33, 128.56, 128.64, 133.66, 134.46, 136.80, 153.89, 156.19, 163.69. MS (El, eV): m/z (%): 463.3 [M]+ (10), 422.2 (15), 420.1 (8), 348.2 (6), 328.2 (14), 314.1 (5), 271.1 (3), 248.1 (15), 228.1 (20), 206.1 (5), 189.1 (5), 152.1 (5), 123.1 (7), 108.0 (43), 91.0 (100), 79.0 (22), 77.0 (15), 65.1 (5), 51.0 (3). HRMS: calcd for C$_{27}$H$_{33}$N$_3$O$_4$: 463,2471 found: 463.2446. IR (FT-IR, Ge): ν = 2926, 2854, 1753, 1620, 1452, 1395, 1341, 1298, 1258, 1163, 1127, 1086, 1010, 740.

Bis-tert-butyl(2,2-diphenyl-hex-5-en-1-yl)amino-methylidene-biscarbamate
Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 96 % yield.

^1^H NMR (CDCl₃, 400MHz): δ = 1.40 (s, 9H), 1.50 (s, 9H), 1.79-1.87 (m, 2H), 2.13-2.20 (m, 2H), 4.14 (d, J = 5.0 Hz, 2H), 4.88 (d, J = 10.2 Hz, 1H), 4.95 (d, J = 17.2 Hz, 1H), 5.73 (ddt, J = 6.7, 10.2, 17.2 Hz, 1H), 7.14-7.32 (m, 10H), 8.09 (s, 1NH). ^13^C NMR (CDCl₃, 100MHz): δ = 27.88, 28.23, 28.77, 36.56, 47.73, 50.15, 78.99, 82.66, 114.37, 126.34, 128.00, 128.12, 138.64, 145.44, 152.62, 156.38, 163.53. MS (El): m/z = 493.3 (50) [M^+], 437.2 (10), 420.2 (10), 381.1 (15), 364.2 (30), 340.1 (15), 234.1 (30), 221.1 (80), 216.1 (50), 180.1 (30), 167.1 (50), 160.0 (100), 143.1 (20), 117.1 (20), 98.0 (15), 91.0 (30). HRMS. calcd for C_{29}H_{39}N_{3}O_{4}: 493.2941, found: 493.2935. IR (KBr): ν = 3678, 3433, 3322, 3290, 3098, 1725, 1647, 1578, 1449, 1410, 1359, 1340, 1272, 1253, 1225, 1145, 1016, 908, 808, 769, 756, 700, 668.

**Bis-tert-butyl(2,2-dimethyl-hex-5-en-1-yl)amino-methylidyne-biscarbamate**

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 90 % yield.

^1^H NMR (CDCl₃, 400 MHz) δ = 0.92 (s, 6H), 1.31 (m, 2H), 1.47 (s, 18H), 2.01 (dtt, J = 1.2, 6.4, 10.4 Hz, 2H), 3.22 (d, J = 5.2 Hz, 2H), 4.89 (dtt, J = 0.8, 1.2, 10.0 Hz, 1H), 4.98 (dtt, J = 1.2, 1.2, 17.2 Hz, 1H), 5.76 (dtt, J = 6.4, 10.0, 17.2 Hz, 1H), 8.46 (br, 1NH). ^13^C NMR (CDCl₃, 100 MHz) δ = 25.26, 28.15, 28.38, 28.45, 33.72, 38.99, 50.64, 79.17, 83.06, 114.28, 139.14, 153.48, 156.62, 163.76. MS (El, eV): m/z (%): 369.3 [M]^+ (8), 313.2 (10), 296.2 (6), 273.2 (4), 257.1 (100),...
240.1 (58), 212.1 (14), 203.1 (45), 196.1 (8), 161.0 (96), 148.0 (42), 143.0 (10), 117.0 (12), 98.0 (19), 86.0 (4), 69.1 (8), 57.1 (54). HRMS calcd for $\text{C}_{19}\text{H}_{35}\text{N}_3\text{O}_4$: 369.2628 found: 369.2633. IR (FT-IR, Ge): $\nu = 3381, 3328, 2963, 2932, 1721, 1646, 1618, 1412, 1364, 1339, 1254, 1138, 1058, 809$.

**Bis-tert-butyl(1-but-3-en-1-yl-cyclohexyl-methyl)amino-methylidyene-biscarbamate**

![Chemical Structure 3c]

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 92 % yield.

$^1\text{H}$ NMR (CDCl$_3$, 400MHz): $\delta = 1.20-1.45$ (m, 12H), 1.47 (s, 18H), 1.92-2.01 (m, 2H), 3.28 (d, $J = 5.0$ Hz, 2H), 4.87 (dd, $J = 1.8$, 10.2 Hz, 1H), 4.97 (dd, $J = 1.8$, 17.0 Hz, 1H), 5.75 (ddt, $J = 6.4$, 10.2, 17.0 Hz, 1H), 8.39 (t, $J = 5.0$ Hz, 1NH). $^{13}\text{C}$ NMR (CDCl$_3$, 100MHz): $\delta = 21.23, 26.09, 27.34, 27.94, 28.19, 33.75, 34.58, 35.70, 47.02, 78.88, 82.77, 114.03, 139.11, 153.28, 156.39, 163.60$. MS (ESI-LCMS): m/z (%): 410.5 [M+H]$^+$ (100). HRMS: calcd for $\text{C}_{22}\text{H}_{39}\text{N}_3\text{O}$: 409.2941, found: 409.2954 IR (FT-IR, Ge): $\nu = 3336, 2977, 2924, 2851, 1720, 1643, 1615, 1447, 1411, 1365, 1339, 1250, 1135, 1056, 810, 765$.

**Dibenzy(2,2-diphenyl-hex-5-en-1-yl)amino-methylidyene-biscarbamate**

![Chemical Structure 3d]

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 88 % yield.
$^1$H NMR (CDCl$_3$, 400MHz): $\delta = 1.82$-$1.92$ (m, 2H), 2.19-$2.26$ (m, 2H), 4.22 (d, $J = 5.3$ Hz, 2H), 4.91 (dd, $J = 1.7$, 10.2 Hz, 1H), 4.96 (dd, $J = 1.7$, 17.2 Hz, 1H), 5.09 (s, 2H), 5.17 (s, 2H), 5.75 (ddt, $J = 6.4$, 10.2, 17.2 Hz, 1H), 7.21-$7.46$ (m, 20H), 8.12 (t, $J = 5.3$ Hz, 1NH). $^{13}$C NMR (CDCl$_3$, 100MHz): $\delta = 28.60$, 36.59, 48.03, 49.91, 66.97, 67.86, 114.48, 126.47, 127.78, 127.88, 127.92, 128.23, 128.30, 128.36, 128.49, 128.59, 134.45, 136.74, 138.29, 145.02, 153.29, 156.10, 163.62. MS (ESI-LCMS): m/z (%): 562.6 [M+H]$^+$ (100). HRMS: calcd for C$_{35}$H$_{35}$N$_3$O$_4$: 561.2628, found: 561.2614. IR (FT-IR, Ge): $\nu = 2961$, 2928, 2858, 1729, 1649, 1615, 1425, 1388, 1345, 1261, 1245, 1208, 1151, 1085, 1052, 909, 804.

Dibenzy(2,2-dimethyl-hex-5-en-1-yl)amino-methylidyne-biscarbamate

![3e](image)

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 95 % yield.

$^1$H NMR (CDCl$_3$, 400MHz): $\delta = 0.85$ (s, 6H), 1.22-1.29 (m, 2H), 1.91-1.99 (m, 2H), 3.20 (d, $J = 5.3$ Hz, 2H), 4.84 (ddd, $J = 1.5$, 1.9, 10.2 Hz, 1H), 4.92 (ddd $J = 1.5$, 1.9, 17.2 Hz, 1H), 5.04 (s, 2H), 5.08 (s, 2H), 5.70 (ddt, $J = 6.4$, 10.2, 17.2 Hz, 1H), 7.14-7.35 (m, 10 H), 8.40 (t, $J = 5.3$ Hz, 1NH). $^{13}$C NMR (CDCl$_3$, 100MHz): $\delta = 24.89$, 28.14, 33.58, 38.77, 50.51, 66.87, 67.89, 114.17, 127.66, 127.88, 128.17, 128.25, 128.56, 134.39, 138.67, 153.83, 156.17, 163.60. MS (EI, eV): m/z (%): 437.3 [M]$^+$ (8), 383.2 (5), 341.2 (8), 302.2 (10), 286.2 (5), 222.1 (10), 189.1 (11), 108.0 (22), 91.0 (100), 79.0 (12), 55.1 (8). HRMS: calcd for C$_{25}$H$_{31}$N$_3$O$_4$: 437.2315. found: 437.2321. IR (FT-IR, Ge): $\nu = 3327$, 3089, 3034, 2962, 3894, 1731, 1649, 1626, 1581, 1429, 1389, 1350, 1322, 1254, 1207, 1141, 1053, 911, 746.
Dibenzyl(1-but-3-en-1-yl-cyclohexyl-methyl)amino-methylidene-biscarbamate

3f

Synthesised according to the general synthesis of starting materials. Isolated as a white solid in 94 % yield.

$^1$H NMR (CDCl$_3$, 400MHz): $\delta$ = 1.16-1.43 (m, 12H), 1.86-1.95 (m, 2H), 3.27 (d, $J$ = 5.3 Hz, 2H), 4.83 (dd, $J$ = 1.5, 10.2 Hz, 1H), 4.91 (dd, $J$ = 1.5, 17.0 Hz, 1H), 5.04 (s, 2H), 5.08 (s, 2H), 5.70 (ddt, $J$ = 6.7, 10.2, 17.0 Hz, 1H), 7.14-7.32 (m, 10H), 8.35 (t, $J$ = 5.3 Hz, 1NH). $^{13}$C NMR (CDCl$_3$, 100MHz): $\delta$ = 21.18, 25.98, 27.25, 33.63, 34.60, 35.68, 47.05, 66.88, 67.93, 114.19, 127.69, 127.89, 128.21, 128.30, 128.51, 128.60, 134.42, 136.75, 138.84, 153.89, 156.14, 163.64. MS (EI): m/z = 477.2 (10)[M$^+$], 369.2 (10), 342.2 (10), 326.2 (10), 262.1 (10), 235.1 (10), 189.1 (10), 108.0 (50), 107.0 (40), 95.1 (25), 91.0 (100), 79.1 (40), 77.0 (20). HRMS calcd for C$_{28}$H$_{35}$N$_3$O$_4$: 477.2628, found: 477.2625. IR (KBr): $\nu$ = 3674, 3440, 3329, 3069, 3034, 2930, 2855, 1725, 1655, 1629, 1589, 1498, 1455, 1425, 1391, 1338, 1274, 1262, 1237, 1197, 1146, 1051, 907, 804, 742, 695, 670, 584.

N-2,2-Diphenyl-pent-4-en-1-ylguanidine

8

A 0.16 mmol sample of 1a was stirred in 1mL TFA for 1h. Then 5 mL Et$_2$O and 5 mL H$_2$O were added and the reaction was quenched by addition of Na$_2$CO$_3$ until pH≥8 was reached. The mixture was separated and the aqueous phase extracted with Et$_2$O (3x10 mL). The organic extracts were combined, dried over
MgSO$_4$ and concentrated to give the free guanidine as analytically pure compound.

$^1$H NMR (CDCl$_3$/MeOD, 400MHz): $\delta = 2.90$ (d, $J = 6.8$ Hz, 2H), 3.80 (s, 2H), 4.98 (dd, $J = 1.2$, 10.4 Hz, 1H), 5.06 (dd, $J = 1.2$, 17.2 Hz, 1H), 5.29 (ddd, $J = 6.8$, 10.4, 17.2 Hz, 1H), 6.83 (br, 1NH), 7.14 (d, $J = 8.0$ Hz, 2H), 7.20 (t, $J = 7.6$ Hz, 1H), 7.28 (dd, $J = 7.6$, 8.0 Hz, 2H).

$^{13}$C NMR (CDCl$_3$/MeOD, 100 MHz): $\delta =$ 40.94, 47.75, 49.42, 118.73, 126.67, 127.45, 128.28, 130.04, 144.21, 157.45. MS (ESI-LCMS): m/z (%): 280.6 [M+H]$^+$ (3), 179.2 (100), 165.2 (98), 91.3 (74).

HRMS (MALDI-TOFTOF) calcd for C$_{18}$H$_{22}$N$_3$: 280.1808, found: 280.1790. IR (FT-IR, Ge): $\nu =$ 3378, 3196, 3096, 3032, 2983, 2961, 2937, 1683, 1658, 1625, 1201, 1181, 1137, 837, 801, 757, 722, 700.

**tert-Butyl 3-(tert-butoxycarbonylimino)-6,6-diphenyltetrahydro-1H-pyrrolo[1,2-c]imidazole-2(3H)-carboxylate**

![Structure of 2a]

2a

Synthesised according to the general diamination procedures using CuBr$_2$ and CuCl$_2$. Isolated as a white solid, respective yields see Schemes 1 and 2.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 1.50 (s, 9H), 1.51 (s, 9H), 2.37 (t, $J = 9.2$ Hz, 1H), 2.54 (dd, $J = 4.8$, 11.2 Hz, 1H), 3.52 (d, $J = 11.2$ Hz, 1H), 3.72 (dd, $J = 7.0$, 9.7 Hz, 1H), 3.97 (m, 1H), 4.05 (dd, $J = 9.7$, 9.9 Hz, 1H), 4.46 (d, $J = 11.2$ Hz, 1H), 7.15-7.32 (m, 10H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 27.93, 28.01, 43.97, 50.00, 55.86, 57.02, 57.14, 79.18, 82.53, 126.27, 126.49, 126.58, 126.70, 126.78, 128.35, 128.39, 128.47, 145.02, 149.44, 153.76. MS (EI, eV): m/z (%): 477.3 [M]$^+$ (4), 421.3 (4), 366.2 (20), 348.2 (40), 322.2 (70), 304.2 (20), 278.2 (16), 222.2 (8), 179.1 (20), 142.1 (12), 128.1 (20), 123.1 (26), 110.1 (18), 98.1 (30), 91.1 (15), 84.1 (10), 57.1 (100). HRMS calcd for C$_{28}$H$_{35}$N$_3$O$_4$: 477.2628,
found: 477.2632. IR (FT-IR, Ge): $\nu$ [cm$^{-1}$] = 3323, 3286, 3026, 3003, 2981, 2931, 1732, 1646, 1616, 1447, 1408, 1354, 1327, 1252, 1142, 1053, 810, 758, 700.

(E)-tert-Butyl 3-(tert-butoxycarbonylimino)-6,6-dimethyltetrahydro-1H-pyrrolo[1,2-c]imidazole-2(3H)-carboxylate

Synthesised according to the general diamination procedures using CuBr$_2$ and CuCl$_2$. Isolated as a white solid, respective yields see Schemes 1 and 2.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.10 (s, 6H), 1.44 (s, 18H), 1.82 (dd, $J$ = 6.0, 12.0 Hz, 1H), 2.98 (d, $J$ = 10.8 Hz, 1H), 3.09 (d, $J$ = 10.8 Hz, 1H), 3.53 (dd, $J$ = 7.2, 10.4 Hz, 1H), 4.02 (dd, $J$ = 8.8, 10.4 Hz, 1H), 4.14 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 27.54, 28.63, 28.12, 28.24, 41.56, 46.46, 50.78, 56.92, 59.89, 78.89, 82.43, 149.69, 154.36, 159.64. MS (EI, eV): m/z (%): 354.4 [M$^+$] (10), 298.1 (5), 280.1 (5), 254.1 (10), 242.0 (50), 224.0 (100), 198.1 (95), 180.0 (70), 154.0 (56), 123.0 (16), 110.0 (10), 98.0 (32), 83.0 (6), 57.0 (52). HRMS: calcd for C$_{18}$H$_{31}$N$_3$O$_4$: 353.2315 found: 353.2310. IR (FT-IR, Ge): $\nu$ [cm$^{-1}$] = 3000, 2969, 2958, 2930, 2871, 1737, 1681, 1616, 1382, 1367, 1315, 1260, 1147, 1097.

tert-Butyl 3'-(tert-butoxycarbonylimino)tetrahydrospiro[cyclohexane-1,6'-pyrrolo[1,2-c]imidazole]-2'(3'H)-carboxylate

Synthesised according to the general diamination procedures using CuBr$_2$ and CuCl$_2$. Isolated as a white solid, respective yields see Schemes 1 and 2.
H NMR (400 MHz, CDCl₃): δ = 1.39 (s, 9H), 1.40 (s, 9H), 1.2-1.5 (m, 10H), 1.90 (dd, J = 5.8, 12.3 Hz, 1H), 2.98 (d, J = 11.4 Hz, 1H), 3.13 (d, J = 11.7 Hz, 1H), 3.46 (dd, J = 6.7, 10.2 Hz, 1H), 3.95 (t, J = 11.8 Hz, 1H), 4.03 (m, 1H).

C NMR (100 MHz, CDCl₃): δ = 22.7, 23.6, 25.5, 27.8, 27.9, 35.5, 37.3, 44.2, 45.2, 50.5, 55.7, 57.2, 78.5, 82.0, 149.4, 153.9, 159.4. MS (EI, eV): m/z (%): 393.3 [M]+ (10), 338.2 (5), 293.2 (5), 282.2 (50), 264.2 (90), 238.2 (100), 220.2 (60), 194.2 (40), 142.1 (20), 138.1 (40), 98.0 (15), 57.1 (30). HRMS calcd for C₂₁H₃₅N₃O₄: 393.2628, found: 393.2623. IR (FT-IR, Ge): ν [cm⁻¹] = 2928, 2857, 1737, 1680, 1619, 1594, 1589, 1496, 1491, 1389, 1314, 1267, 1142, 1075, 1004.

Benzyl 3-(benzyloxycarbonylimino)-6,6-diphenyltetrahydro-1H-pyrrolo-[1,2-c]imidazole-2(3H)-carboxylate

Synthesised according to the general diamination procedures using CuBr₂ and CuCl₂. Isolated as a white solid, respective yields see Schemes 1 and 2.

H NMR (400 MHz, CDCl₃): δ = 2.34 (t, J = 11.4 Hz, 1H), 2.57 (dd, J = 4.7, 11.4 Hz, 1H), 3.41 (d, J = 11.4 Hz, 1H), 3.73 (dd, J = 7.9, 10.2 Hz, 1H), 3.99 (m, 1H), 4.13 (dd J = 8.8, 10.2 Hz, 1H), 4.33 (d, J = 11.4 Hz, 1H), 5.12 (d, J = 12.3 Hz, 1H), 5.15 (d, J = 12.3 Hz, 1H), 5.16 (d, J = 12.3 Hz, 1H), 5.25 (d, J = 12.3 Hz, 1H), 7.08 (d, J = 7.0 Hz, 2H), 7.17-7.21 (m, 4H), 7.24-7.33 (m, 10H), 7.38-7.42 (m, 4H). C NMR (100 MHz, CDCl₃): δ = 43.88, 50.18, 56.03, 56.58, 57.25, 67.25, 68.17, 126.36, 126.73, 126.90, 127.66, 128.09, 128.15, 128.20, 128.26, 128.45, 128.49, 128.57, 135.18, 136.79, 144.69, 144.95, 150.96, 153.95, 159.93. MS (ESI-LCMS): m/z: 568.2 (M+Na), 546.3 (M+H), 520.3, 478.2, 435.2, 412.2, 368.2. HRMS (ESI-MicroTOF) calcd for C₃₄H₃₂N₃O₄⁺: 546.2393, found: 546.3284. IR (FT-IR, Ge): ν [cm⁻¹] = 2960, 2927, 1781, 1718, 1651, 1496, 1450, 1389, 1335, 1297, 1259, 1217, 1162, 1126, 1083, 913, 803, 757.
Benzyl 3-(benzyloxycarbonylimino)-6,6-dimethyltetrahydro-1H-pyrrolo[1,2-c]imidazole-2(3H)-carboxylate

2e

Synthesised according to the general diamination procedures using CuBr$_2$ and CuCl$_2$. Isolated as a white solid, respective yields see Schemes 1 and 2.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.11 (s, 3H), 1.12 (s, 3H), 1.43 (dd, $J$ = 9.2, 12.1 Hz, 1H), 1.88 (dd, $J$ = 5.6, 12.1 Hz, 1H), 2.93 (d, $J$ = 11.2 Hz, 1H), 3.06 (d, $J$ = 11.2 Hz, 1H), 3.06 (d, $J$ = 7.0, 9.3 Hz, 1H), 4.17 (ps, $J$ = 9.0 Hz, 1H), 4.23 (m, 1H), 5.16 (d, $J$ = 12.4 Hz, 1H), 5.26 (d, $J$ = 12.4 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 27.3, 27.4, 41.6, 46.0, 50.7, 56.9, 59.4, 67.1, 68.0, 127.6, 128.0, 128.1, 128.2, 128.4, 135.2, 136.8, 151.0, 154.0, 159.8. MS (El, eV): m/z (%): 421.2 [M]$^+$ (44), 314.2 (10), 287.2 (52), 270.2 (18), 231.1 (4), 224.1 (30), 180.1 (28), 153.1 (20), 123.0 (4), 91.0 (100), 65.1 (4), 55.1 (6). HRMS calcd for C$_{24}$H$_{27}$N$_3$O$_4$: 421.2002, found: 421.2006. IR (FT-IR, Ge): $\nu$ [cm$^{-1}$] = 3365, 3065, 3034, 2959, 2894, 1786, 1751, 1720, 1642, 1599, 1458, 1390, 1339, 1299, 1262, 1170, 1107, 1012, 802, 737.

Benzyl 3'-(benzyloxycarbonylimino)tetrahydrospiro[cyclohexane-1,6'-pyrrolo[1,2-c]imidazole]-2'(3'H)-carboxylate

2f

Synthesised according to the general diamination procedures using CuBr$_2$ and CuCl$_2$. Isolated as a white solid, respective yields see Schemes 1 and 2.
**tert-Butyl 6,6-dimethyl-3-oxohexahydroimidazo[1,5-a]pyridine-2(1H)-carboxylate**

![Chemical Structure](image)

Synthesised according to general diamination conditions using CuBr₂. Isolated in 85% as a white solid.

**1H NMR (400 MHz, CDCl₃):** \( \delta = 0.93 \) (s, 6H), 0.96 (m, 1H), 1.34 (dd, \( J = 3.6 \), 14.4 Hz, 1H), 1.43 (m, 1H), 1.50 (s, 9H), 1.68 (m, 1H), 2.43 (d, \( J =13.2 \) Hz, 1H), 3.33 (m, 2H), 3.54 (dd, \( J = 2.0 \), 13.2 Hz, 1H), 3.89 (td, \( J = 11.6 \) Hz, 4.4 Hz, 1H), 7.93 (br, 1NH). **13C NMR (100 MHz, CDCl₃):** \( \delta = 23.29, 27.74, 28.10, 28.24, 28.68, 30.13, 36.61, 47.38, 50.57, 51.41, 56.11, 82.00, 151.00, 153.09.** MS (EI, eV): m/z: 268.2 \([\text{M}^+]\) (20), 253.2 (2), 212.1 (3), 195.1 (18), 168.1 (100), 153.1 (6), 139.1 (2), 125.1 (2), 112.0 (8), 99.0 (48), 85.0 (4), 69.1 (2), 57.1 (34). HRMS calcd for \( \text{C}_{14}\text{H}_{28}\text{N}_{2}\text{O}_{3} \): 268.1787 found: 268.1783. IR (FT-IR, Ge): \( \nu \) [cm\(^{-1}\)] = 2961, 1754, 1436, 1360, 1338, 1268, 1170, 1116, 1084, 1008, 772.
tert-Butyl 3-(tert-butoxycarbonylimino)-6,6-diphenylhexahydroimidazo-[1,5-a]pyridine-2(1H)-carboxylate

5a

Synthesised according to the general diamination procedure using CuCl$_2$. Isolated as a white solid, respective yields see Scheme 2.

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ = 1.47 (s, 9H), 1.50 (m, 1), 1.57 (s, 9H), 1.91 (dq, $J$ = 3.2, 13.2 Hz, 1H), 2.32 (dt, $J$ = 2.6, 13.2 Hz, 1H), 2.66 (dq, $J$ = 2.9, 13.8 Hz, 1H), 2.82 (d, $J$ = 14 Hz, 1H), 3.23 (t, $J$ = 10.2 Hz, 1H), 3.59-3.69 (m, 1H), 4.05 (dd, $J$ = 8.2, 10.2 Hz, 1H), 4.92 (dd, $J$ = 2.1, 14.0 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ = 26.71, 28.03, 28.27, 33.68, 45.71, 49.64, 50.78, 53.10, 78.78, 82.32, 126.07, 126.51, 126.60, 127.64, 128.29, 128.57, 143.74, 146.45, 149.87, 150.45, 159.12. MS (EI, eV): m/z (%): 491.2 (40), 435.2 (25), 391.2 (40), 362.1 (100), 335.1 (70), 318.1 (40), 291.1 (50), 180.1 (40), 165.0 (25), 142.0 (15), 124.0 (60), 98.0 (20), 91.0 (15), 57.1 (30). HRMS calcd for C$_{29}$H$_{37}$N$_3$O$_4$: 491.2784, found: 491.2791. IR (FT-IR, Ge): $\nu$ [cm$^{-1}$] = 3061, 2975, 2929, 2865, 1750, 1679, 1617, 1450, 1368, 1274, 1142, 800.

tert-Butyl 3-(tert-butoxycarbonylimino)-6,6-dimethylhexahydroimidazo-[1,5-a]pyridine-2(1H)-carboxylate

5b

Synthesised according to the general diamination procedure using CuCl$_2$. Isolated as a white solid, respective yields see Scheme 2.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.90 (s, 3H), 0.91 (s, 3H), 1.28 (m, 1H), 1.44 (s, 9H), 1.46 (s, 9H), 1.45 (m, 2H), 1.71 (dd, $J$ = 3.6 Hz, 12.8 Hz, 1H), 2.41 (d, $J$ = 12.8 Hz, 1H), 3.37 (m, 2H), 3.68 (dd, $J$ = 1.6 Hz, 12.8 Hz, 1H), 4.01 (m, 1H).
\(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 23.20, 27.13, 27.91, 28.14, 28.55, 29.98, 36.29, 50.68, 52.36, 53.27, 78.51, 82.12, 149.97, 151.21, 159.28\). MS (El, eV): m/z (%) = 368.5 \([\text{M}]^+\) (1), 312.4 (4), 255.9 (1), 212.2 (100), 168.2 (35). HRMS calcd for C\(_{19}\)H\(_{33}\)N\(_3\)O\(_4\): 367.2471, found: 367.2479. IR (FT-IR, Ge): \(\nu \text{ [cm}^{-1}\text{]} = 2961, 2930, 1752, 1700, 1434, 1392, 1361, 1269, 1250, 1160, 1117, 1082, 1050, 1025, 1008, 854, 773.

**tert-Butyl 3'-\(\text{tert-butoxycarbonylimino}\)tetrahydro-1'\(\text{H}\)-spiro[cyclohexane-1,6'-imidazo[1,5-a]pyridine]-2'(3'H)-carboxylate**

![5c]

Synthesised according to the general diamination procedure using CuCl\(_2\). Isolated as a white solid, respective yields see Scheme 2.

\(^1\text{H}\) NMR (CDCl\(_3\), 400 MHz) \(\delta = 1.12-1.54\) (m, 12H), 1.45 (s, 9H), 1.47 (s, 9H), 1.65-1.72 (m, 2H), 2.31 (d, \(J = 13.2\) Hz, 1H), 3.35-3.46 (m, 2H), 3.97-4.05 (m, 2H). \(^{13}\text{C}\) NMR (CDCl\(_3\), 100 MHz) \(\delta = 21.24, 21.35, 26.35, 26.49, 28.00, 30.65, 32.57, 34.20, 37.88, 50.12, 50.72, 53.51, 78.42, 82.14, 149.99, 151.38, 159.21\). MS (El, eV): m/z (%): 408.3 \([\text{M}]^+\) (10), 407.2 (25), 351.2 (25), 295.1 (55), 278.1 (100), 251.1 (75), 208.1 (25), 206.1 (20), 143.0 (20), 57.1 (20). HRMS calcd for C\(_{22}\)H\(_{38}\)N\(_3\)O\(_4\)^+: 408.2857, found: 408.2865. IR (FT-IR, Ge): \(\nu \text{ [cm}^{-1}\text{]} = 2973, 2927, 2847, 1774, 1741, 1706, 1678, 1619, 1450, 1363, 1259, 1160, 1104, 1012, 855, 769.

**Benzyl 3-(benzyloxy carbonylimino)-6,6-diphenylhexahydroimidazo[1,5-a]-pyridine-2(1\(\text{H}\))-carboxylate**

![5d]
Synthesised according to the general diamination procedure using CuCl₂. Isolated as a white solid, respective yields see Scheme 2.

1H NMR (400 MHz, CDCl₃): δ = 1.20 (ddd, J = 2.4 Hz, 12.4, 13.6 Hz, 1H), 1.90 (qd, J = 3.2 Hz, 13.6 Hz, 1H), 2.32 (dt, J = 3.2 Hz, 13.6 Hz, 1H), 2.69 (qd, J = 2.8 Hz, 12.4 Hz, 1H), 2.88 (d, J = 14.0 Hz, 1H), 3.32 (t, J = 10.4 Hz, 1H), 3.66 (m, 1H), 4.16 (dd, J = 8.4 Hz, 10.4 Hz, 1H), 4.95 (dd, 2.4 Hz, 14.0 Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 5.10 (d, J = 12.0 Hz, 1H), 5.16 (d, J = 12.0 Hz, 1H), 5.19 (d, J = 12.0 Hz, 1H), 7.13-7.45 (m, 20H).

13C NMR (100 MHz, CDCl₃): δ = 26.72, 33.52, 45.73, 49.67, 50.48, 52.98, 67.23, 68.20, 126.16, 126.38, 126.56, 127.40, 127.55, 128.16, 128.21, 128.36, 128.42, 128.47, 128.63, 135.03, 137.06, 143.35, 146.16, 149.95, 151.13, 159.44. MS (EI, eV): m/z (%): 560.5 [M]+ (100), 516.5 (28), 473.4 (12), 452.3 (10), 408.3 (4), 380.3 (4), 91.3 (11). HRMS calcd for C₃₅H₃₃N₅O₄: 559.2471, found: 559.2470. IR (FT-IR, Ge): ν [cm⁻¹] = 3064, 2948, 2886, 1761, 1669, 1613, 1487, 1403, 1269, 1190, 1165, 1147, 1116, 1099, 1041, 736.

Benzyl 3-(benzyloxycarbonylimino)-6,6-dimethylhexahydroimidazo-[1,5-a]pyridine-2(1H)-carboxylate

5e

Synthesised according to the general diamination procedure using CuCl₂. Isolated as a white solid, respective yields see Scheme 2.

1H NMR (CDCl₃, 400 MHz) δ = 0.86 (s, 3H), 0.87 (s, 3H), 1.25 (dd, J = 10.8, 14.4 Hz, 1H), 1.44 (ddd, J = 3.6, 10.8, 14.0 Hz, 2H), 1.68 (m, 1H), 2.39 (d, J = 13.2 Hz, 1H), 3.37 (m, 1H), 3.42 (dd, J = 8.4, 10.0 Hz, 1H), 3.63 (dd, J = 1.6, 12.8 Hz, 1H), 4.06 (dd, J = 8.0, 9.6 Hz, 1H), 4.97 (s, 2H), 5.02 (d, J = 12.0 Hz, 1H), 5.09 (d, J = 12.0 Hz, 1H), 7.15-7.31 (m, 10H).

13C NMR (CDCl₃, 100 MHz) δ = 23.16, 27.20, 28.53, 30.09, 36.13, 50.39, 52.50, 53.10, 67.12, 68.14, 127.44, 128.05, 128.19, 128.29, 128.34, 128.43, 135.09, 137.04, 150.80, 151.29, 159.64. MS (EI,
eV): m/z (%) = 435.2 [M]+ (4), 302.2 (60), 257.2 (5), 195.1 (7), 168.1 (100), 151.1 (12), 108.0 (24), 91.0 (77), 79.0 (11), 65.0 (6). HRMS calcd for C_{25}H_{29}N_{3}O_{4}: 435.2158, found: 435.2163. IR (FT-IR, Ge): ν [cm⁻¹] = 3035, 2950, 1759, 1674, 1622, 1454, 1400, 1337, 1268, 1219, 1177, 1154, 1115, 1042, 753, 733, 711.

**Benzyl 3’-(benzyloxycarbonylimino)tetrahydro-1’H-spiro[cyclohexane-1,6’-imidazo[1,5-a]pyridine]-2'(3’H)-carboxylate**

![5f](image)

Synthesised according to the general diamination procedure using CuCl₂. Isolated as a white solid, respective yields see Scheme 2. 

\(^1\text{H}\) NMR (CDCl₃, 400 MHz) δ = 1.09-1.51 (m, 12H), 1.64 (dt, J = 2.8, 14.3 Hz, 2H), 2.28 (d, J = 13.5 Hz, 1H), 3.38-3.46 (m, 2H), 3.97-4.09 (m, 2H), 4.97 (s, 2H), 5.00 (d, J = 12.3 Hz, 1H), 5.09 (d, J = 12.3 Hz, 1H), 7.14-7.32 (m, 10H). \(^{13}\text{C}\) NMR (CDCl₃, 100 MHz) δ = 21.28, 21.42, 26.31, 26.57, 30.67, 32.68, 34.33, 37.89, 50.05, 50.50, 53.49, 67.15, 68.20, 127.47, 128.11, 128.20, 128.37, 128.39, 128.50, 135.19, 137.20, 150.94, 151.38, 159.72. MS (ESI-LCMS): m/z (%): 476 [M+H]+ (100). HRMS (MALDI-TOFTOF) calcd for C_{28}H_{34}N_{3}O_{4}: 476.2544, found: 476.2501. IR (FT-IR, Ge): ν [cm⁻¹] = 2926, 2850, 1761, 1671, 1617, 1452, 1400, 1267, 1175, 1156, 1109, 1042, 753.
Deprotection procedures

**Tetrahydro-1'H-spiro[cyclohexane-1,6'-pyrrolo[1,2-c]imidazole]-2'(3'H)-imine hydrotrifluoroacetate**

The \(N,N'\)-bis-Boc protected guanidine 2c (0.15 mmol) is treated with trifluoroacetic acid (1 mL) in dichloromethane (1 mL) and stirred for 60 min at room temperature. The solution is then concentrated under reduced pressure to yield the analytically pure deprotected guanidine in 99% yield.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.36-1.61\) (m, 11H), 2.05 (dd, \(J = 6.1, 12.6\) Hz, 1H), 3.15 (d, \(J = 11.1\) Hz, 1H), 3.22 (d, \(J = 11.1\) Hz, 1H), 3.53 (dd, \(J = 4.1, 9.1\) Hz, 1H), 3.87 (persistence, \(J = 9.3\) Hz, 1H), 4.28 (m, 1H), 6.5-7.7 (broad, 2NH), 8.46 (s, 1NH). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 22.86, 23.62, 25.44, 35.60, 37.63, 43.09, 45.90, 47.39, 57.36, 60.98, 161.59\) (TFA anion not detected).

**Tetrahydro-1'H-spiro[cyclohexane-1,6'-imidazo[1,5-a]pyridin]-3'(2'H)-imine hydrotrifluoroacetate**

The \(N,N'\)-bis-Boc protected guanidine 5c (0.5 mmol) is treated with neat trifluoroacetic acid (1 mL) and stirred for 30 min at room temperature. Diethyl ether (10 mL) is added and the reaction is quenched by careful addition of solid
Na₂CO₃. When the CO₂ evolution ceases, 10 mL of H₂O are added and the addition of Na₂CO₃ is continued until pH = 11. The organic layer is separated and the aqueous phase is extracted with diethyl ether (3 x 15 mL), dried and concentrated under reduced pressure to yield the analytically pure deprotected guanidine in 99% yield.

\[ \text{Na}_2\text{CO}_3 \]

When the CO₂ evolution ceases, 10 mL of H₂O are added and the addition of Na₂CO₃ is continued until pH = 11. The organic layer is separated and the aqueous phase is extracted with diethyl ether (3 x 15 mL), dried and concentrated under reduced pressure to yield the analytically pure deprotected guanidine in 99% yield.

\[ ^1\text{H NMR (400 MHz, CDCl}_3\text{)): } \delta = 1.20-1.50 \text{ (m, 11H), 1.91 \text{ (m, 2H), 1.86 (d, } J = 14.0 \text{ Hz, 1H), 2.62 (d, } J = 13.6 \text{ Hz, 1H), 3.23 (dd, } J = 6.4, 8.8 \text{ Hz, 1H), 3.69 (m, 1H), 3.72 (d, } J = 14.0 \text{ Hz, 1H), 3.77 (d, } J = 8.8 \text{ Hz, 1H), 7.76 (br, 2NH), 8.53 (br, 1NH).} \]

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3\text{)): } \delta = 21.05, 21.31, 25.84, 26.22, 30.55, 33.04, 33.25, 37.34, 47.33, 50.99, 58.37, 158.00 \text{ (TFA anion not detected).} \]

\[ \text{MS (ESI-LCMS): } m/z (\%): 208.3 (100), 84.1 (8). \]

HRMS (MALDI-TOFTOF) calcd for C₁₂H₂₂N₅⁺: 208.1808, found: 208.1824. IR (FT-IR, Ge): \[ \nu [\text{cm}^{-1}] = 3355, 2931, 2853, 1668, 1579, 1452, 1202, 1133, 836, 801, 720. \]

**Aminochlorination and Aminoacetoxylation Procedures**

2-(Chloromethyl)-4,4-diphenylpyrrolidine-1-carboximidamide

\[ \text{Synthesised under the conditions of the general diamination procedure for} \]

\[ \text{guanidines using CuCl}_2 \text{ as oxidant.} \]

\[ ^1\text{H NMR (MeOH-d}_4\text{, 400 MHz): } \delta = 2.78 \text{ (dd, } J = 8.8, 12.8 \text{ Hz, 1H), 2.95 (ddd, } J = 1.6, 6.8, 12.8 \text{ Hz, 1H), 3.59 (dd, } J = 2.0, 11.6 \text{ Hz, 1H), 3.83 (m, 2H), 4.14 (ddd, } J = 2.0, 6.8, 12.4 \text{ Hz, 1H), 4.40 (dd, } J = 1.6, 10.8 \text{ Hz, 1H), 7.10-7.26 (m, 10H).} \]

\[ ^{13}\text{C NMR (MeOH-d}_4\text{, 100 MHz): } \delta = 40.47, 43.55, 52.58, 56.81, 57.84, 125.65, 126.16, 126.71, 128.16, 128.51, 128.65, 143.33, 143.63, 155.02. \]

\[ \text{MS (ESI-LCMS): } m/z (\%): 314.3 [M+H]^+ (63), 196.2 (27), 91.5 (27), 78.39 (100). \]

HRMS (MALDI-TOFTOF) calcd for C₁₈H₂₁ClN₃⁺: 314.1419, found: 314.1435. IR (FT-IR, Ge): \[ \nu [\text{cm}^{-1}] = 3355, 2931, 2853, 1668, 1579, 1452, 1202, 1133, 836, 801, 720. \]
(1-(N,N'-bis(tert-Butoxycarbonyl)carbamimidoyl)-4,4-diphenylpyrrolidin-2-yl)methyl ethanoate

A solution of the precursor 1a (0.45 mmol, 1.0 eq.), oxidant (0.90 mmol, 2.0 eq.), sodium acetate (0.45 mmol, 1.0 eq.) and Pd(OAc)$_2$ (0.045 mmol, 10% mol) in CH$_2$Cl$_2$ (4.5 mL) was stirred overnight at room temperature. The reaction was quenched by addition of sat. aqueous Na$_2$S$_2$O$_3$ solution, the organic phase was separated and the aqueous phase extracted with dichloromethane several times. The combined organic layers were dried over MgSO$_4$ and the solvent was removed under reduced pressure. The product was purified by flash-chromatography on silica gel (dichloromethane) to give compound 10 in 90% yield.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.41$ (s, 18H), 1.99 (s, 3H), 2.56 (dd, $J = 10.4, 12.0$ Hz, 1H), 2.71 (ddd, $J = 1.6, 6.8, 12.4$ Hz, 1H), 3.92 (d, $J = 12.0$ Hz, 4.18 (t, $J = 10.4$ Hz), 4.33 (br, 1H), 4.53 (br, 1H), 7.05-7.23 (10H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 20.90, 28.11, 52.61, 56.32, 59.66, 63.04, 79.20, 81.96, 126.26, 126.59, 126.65, 126.65, 128.54, 128.69, 143.97, 145.01, 150.31, 154.01, 170.96.

MS (EI, eV): m/z (%): 537.4 [M]$^+$ (18), 477.4 (20), 425.3 (3), 408.3 (5), 390.3 (2), 381.3 (10), 363.3 (12), 347.2 (2), 338.2 (5), 320.2 (10), 290.2 (30), 276.2 (4), 260.2 (40), 222.2 (30), 205.2 (45), 192.1 (13), 180.1 (25), 165.1 (20), 144.1 (12), 141.1 (20), 123.1 (20), 97.1 (8), 91.1 (22), 69.1 (5), 59.1 (100), 56.1 (58). HRMS calcd for C$_{30}$H$_{39}$N$_3$O$_6$: 537.2839, found: 537.2847. IR (FT-IR, Ge): $\nu$ [cm$^{-1}$] =

$^\nu$ [cm$^{-1}$] = 3351, 3168, 2957, 2936, 1660, 612, 1497, 1437, 1388, 1202, 1180, 1132, 802, 730.
3055, 3028, 3009, 2978, 2931, 2899, 1745, 1636, 1611, 1419, 1367, 1295, 1233, 1141, 1116, 1061.
Stereochemical Analysis

Synthesis of labelled compound (E)-1a-d1: Selectively deuterated guanidine (E)-1a-d1 was prepared according to the general procedure for starting material synthesis using selectively labelled allylic bromide. The latter was obtained following a literature procedure using Schwartz reagent. The labelled allylic bromide was used as described before to obtain the guanidines.

\[
\text{NH} \quad \text{NBoc} \quad \text{NH} \\
\text{Ph} \quad \text{NBoc} \quad \text{Ph}
\]

(E)-1a-d1

90% Deuteration grade.

\(^1\)H NMR (400 MHz, CDCl₃): \(\delta = 1.42 \ (s, 9H), 1.49 \ (s, 9H), 2.92 \ (dd, J = 1.2, 7.2 \ Hz, 2H), 4.10 \ (d, J = 4.8 \ Hz, 2H), 5.00 \ (dd, J = 1.6, 17.2 \ Hz, 1H), 5.42 \ (td, J = 7.2, 17.2 \ Hz, 1H), 7.18-7.33 \ (m, 10H), 8.23 \ (t, J = 4.8 \ Hz, 1NH). \ \ ^{13}\)C NMR (100 MHz, CDCL₃): \(\delta = 27.83, 28.17, 41.92, 47.75, 49.87, 78.94, 82.64, 118.20 \ (t, J = 25.0 \ Hz), 126.33, 128.00, 128.02, 133.37, 144.99, 152.70, 156.17. \ \ \ \ \ \ \ \ \ \ \ \ \ \ IR \ (FT-IR, Ge): \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ ν = 3305, 2980, 2935, 1786, 1726, 1634, 1560, 1415, 1367, 1324, 1136, 1057, 814, 756, 701.

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Deuterated compound (E)-1a-d₁ underwent clean diamination to a single diastereomeric product. From the coupling constant of the resulting isomer of 2a-d₁ the relative syn-configuration could be unambiguously determined.

![Chemical structure of 2a-d₁](image)

**2a-d₁**

¹H NMR (400 MHz, CDCl₃): δ = 1.41 (s, 9H), 1.42 (s, 9H), 2.24 (dd, J = 10.4, 11.2 Hz, 1H), 2.44 (dd, J = 4.8, 11.2 Hz, 1H), 3.41 (d, J = 11.2 Hz, 1H), 3.87 (ddd, J = 4.8 Hz, 9.2 Hz, 10.4 Hz, 1H), 3.94 (d, Jsyn = 9.2 Hz, 1H), 4.35 (d, J = 11.2 Hz, 1H), 7.06-7.24 (m, 10H).

¹³C NMR (100 MHz, CDCl₃): δ = 27.97, 28.05, 44.03, 49.66 (t, J = 21.5 Hz), 55.63, 56.98, 57.14, 78.99, 82.40, 126.27, 126.60, 126.74, 126.80, 128.41, 128.51, 145.15, 145.35, 149.45, 153.82, 159.66.

MS (ESI-LCMS): m/z (%): 479.3 [M+H]⁺ (1), 423.4 (5), 367.3 (22), 323.4 (100), 297.3 (5), 279.3 (67), 237.2 (5). IR (FT-IR, Ge): ν [cm⁻¹] = 2966, 2930, 1748, 1635, 1559, 1451, 1368, 1255, 1128, 847, 771.
Data on X-Ray Structure Determination

**Compound 5d:**

![Compound 5d](image)

**Table S-1.** Crystal data and structure refinement for 5d.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>streuff1</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C33 H33 N3 O4</td>
</tr>
<tr>
<td>Formula weight</td>
<td>559.64</td>
</tr>
<tr>
<td>Temperature</td>
<td>173(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Triclinic, P-1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 9.9630(5) Å  alpha = 89.717(3) deg.</td>
</tr>
<tr>
<td></td>
<td>b = 10.0620(5) Å  beta = 76.596(3)deg.</td>
</tr>
<tr>
<td></td>
<td>c = 15.7850(5) Å  gamma = 67.802(2)deg</td>
</tr>
<tr>
<td>Volume</td>
<td>1419.21(11) Å³</td>
</tr>
<tr>
<td>Z, Calculated density</td>
<td>2, 1.310 Mg/m³</td>
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<tr>
<td>F(000)</td>
<td>592</td>
</tr>
</tbody>
</table>
Crystal size 0.40 x 0.35 x 0.30 mm
Diffractometer Nonius KappaCCD
Theta range for data collection 1.33 to 27.50 deg.
Reflections collected / unique 9485 / 6465 [R(int) = 0.0218]
Absorption correction None
Refinement method Full-matrix least-squares on F^2
Data / restraints / parameters 6465 / 0 / 388
Goodness-of-fit on F^2 1.050
Final R indices [I>2sigma(I)] R1 = 0.0480, wR2 = 0.1300
R indices (all data) R1 = 0.0755, wR2 = 0.1162
Compound 7:

![Compound 7 Image](image-url)

**Table S-1.** Crystal data and structure refinement for 7.

<table>
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<th>Property</th>
<th>Value</th>
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<tbody>
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<tr>
<td>Empirical formula</td>
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<tr>
<td>Temperature</td>
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<tr>
<td>Wavelength</td>
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</tr>
<tr>
<td>Crystal system, space group</td>
<td>Monoclinic, $P\ 2_1/c$</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>$a = 13.8901(9)$ Å</td>
</tr>
<tr>
<td></td>
<td>$b = 5.9564(2)$ Å</td>
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<tr>
<td></td>
<td>$c = 22.1517(11)$ Å</td>
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<tr>
<td></td>
<td>beta = 120.178(3) deg.</td>
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<tr>
<td>Volume</td>
<td>1584.33(14) Å^3</td>
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<tr>
<td>Property</td>
<td>Value</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Z, Calculated density</td>
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<td>Absorption coefficient</td>
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</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.086 mm^-1</td>
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<td>F(000)</td>
<td>680</td>
</tr>
<tr>
<td>Crystal size</td>
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<tr>
<td>Diffractometer</td>
<td>Nonius KappaCCD</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.70 to 27.54 deg.</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>9509 / 3631 [R(int) = 0.0515]</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>None</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F^2</td>
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<tr>
<td>Data / restraints / parameters</td>
<td>3631 / 0 / 208</td>
</tr>
<tr>
<td>Goodness-of-fit on F^2</td>
<td>1.038</td>
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<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
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<tr>
<td>R indices (all data)</td>
<td>R1 = 0.1240, wR2 = 0.1798</td>
</tr>
</tbody>
</table>
Spectral Reproduction of Starting Materials and Products
\[ \text{Chemical Structure} \]

\[ 3c \]
43
\[ \text{Diagram of molecule 2a with N-Boc and Ph groups} \]
$2b$
N-Boc

N-Boc

2c
$$\text{Ph}$$

$$\text{N-Cbz}$$

$$\text{N-Cbz}$$

$$\text{2d}$$
2e
1 J. A. Castillo-Meléndez, B. T. Golding *Synthesis* 2004, **10**, 1655