Electronic Supplementary Material (ESI) for Green Chemistry

Selective Carbon-Carbon Bond Formation : Terpenylations of Amines Involving Hydrogen Transfers

Zeyneb Sahli, Basker Sundararaju, Mathieu Achard and Christian Bruneau*

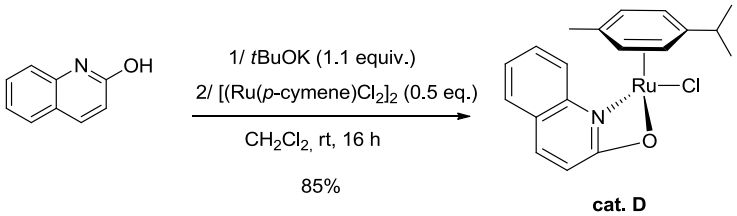
*UMR6226 CNRS – Université de Rennes, Sciences chimiques de Rennes,
Organometallics : Materials and Catalysis,
Campus de Beaulieu, 35042 Rennes Cedex (France)
Fax: (+33) 223236939;
E-mail: christian.bruneau@univ-rennes1.fr
Homepage : http://www.scienceschimiques.univ-rennes1.fr/en/home/teams/omc/

Supporting Information

General Experimental Details:

All reactions were carried out under an inert atmosphere with standard Schlenk techniques, unless otherwise mentioned. Toluene was distilled and purified by solvent purification system equipped with a series of activated filter columns. D (+) Camphor sulfonic acid and hydroxyquinoline were purchased from commercial sources and used as received. Proton magnetic resonance (1H NMR) spectra were recorded on Bruker GPX (300 MHz, 400 MHz and 500 MHz) spectrometers and carbon magnetic resonance (13C NMR) spectra were performed at 75, 100, 125 MHz. Chemical shifts (δ) are reported in parts per million relative to residual chloroform (7.26 ppm for ^{1}H; 77.0 ppm for ^{13}C). Coupling constants are reported in Hertz. ^{1}H NMR assignment abbreviations are the following: singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), broad singlet (bs), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). All reagents were weighed and handled in air, and refilled with an inert atmosphere of Argon at room temperature. HRMS were recorded on a Varian MAT 311 mass spectrometer with an EI source or on ZAB Spec TOF with an ESI source.

Preparation of cat. D



cat. D

2-Hydroxyquinoline (100 mg, 0.68 mmol) was dissolved in DCM (6 mL) in a Schlenk tube at room temperature under argon atmosphere. *t*BuOK (85 mg, 0.75 mmol) was then added and the mixture was stirred for one hour. $[RuCl_2(p\text{-cymene})]_2$ (210 mg, 0.34 mmol, 0.5 eq) was then added and the reaction mixture stirred for 16 h. The solvent was evaporated, and the crude mixture was dissolved in 8 mL of dry dichloromethane. Filtration by canulation to remove the inorganic salts followed by concentration *in vacuo* afforded **cat. D** as a yellow solid yield (250 mg, 85%); CCDC 918329 contains the supplementary crystallographic data for this complex. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, 1H, *J*= 8.90 Hz),7.50 (d, 2H, *J*= 7.6 Hz), 7.38 (d, 1H, *J*= 8.3 Hz), 7.18-7.16 (m, 1H), 6.22 (d, 1H, *J*= 9.0 Hz), 5.71-5.64 (m, 2H), 5.50 (d, 1H, *J*= 5.5 Hz), 5.39 (d, 1H, *J*=5.5 Hz), 2.92-2.89 (m, 1H), 2.31 (s, 3H), 1.22-1.19 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$), 175.7, 144.1, 138.4, 129.4, 127.9, 121.7, 121.2, 118.8, 113.4, 100.7, 96.1, 77.9, 78.9, 79.0, 75.9, 30.9, 21.3, 21.2, 18.1.

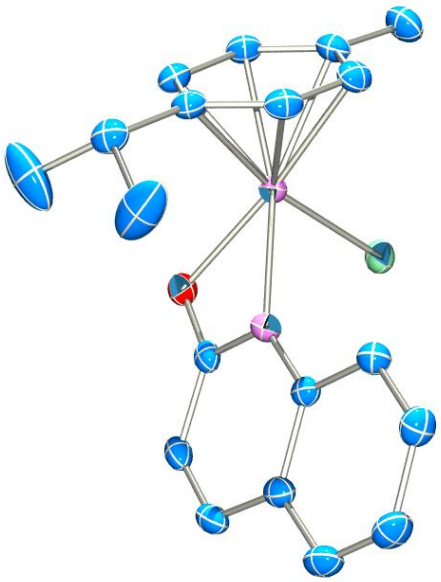


Figure 1. X-Ray structure of complex **cat. D**

General procedure for N-alkylation of cyclic amines with terpenes (I):

Procedure I with aldehydes:

Cyclic amine (1.05 equiv.) and aldehyde (6.65 mmol, 1 equiv.) were added into a Schlenk tube under an inert atmosphere. Subsequently formic acid (1.5 equiv.) was added dropwise. Then the reaction mixture was stirred at 100 °C in neat condition for 16 h and then allowed to cool down to room temperature. The crude mixture was analyzed by GC and purified by column chromatography on silica gel (Pentane/Diethyl ether/ triethylamine) to give the desired product **3** in 68-95 % isolated yields.

Procedure II with allylic alcohols:

To a stirred solution of allylic alcohol (1.2 equiv.) in 2 mL of toluene, Cyclic amine (1 equiv., 1.05 mmol), formic acid (1.1 equiv.) and **Cat. A** (5 mol %) were sequentially added. Then the reaction mixture was stirred at 150 °C for 16 h. The residue was directly purified by column chromatography (Et_2O/PE) to afford the alkylated amine **3** in 52-61% isolated yields.

Procedure III with alcohols:

Cyclic amine (11.7 mmol, 1 equiv.) and alcohol (1.05 equiv.) were added into the Schlenk tube under inert atmosphere. Then Catalyst **A** (1 mol %) was added and the reaction mixture was stirred at 140 °C in neat condition for 16 h and then allowed to cool down to room temperature. The crude mixture was analyzed by GC and purified by column chromatography on silica gel (pentane/ diethyl ether/ triethylamine) to give the desired product **3** in 54-63 % isolated yields.

Procedure IV dialkylation of piperazine with aldehydes:

Cyclic amine (11.7 mmol, 1 equiv.) and aldehyde (2 equiv.) were added into a Schlenk tube under an inert atmosphere. Subsequently formic acid (2 equiv.) was added dropwise. Then the reaction mixture was stirred at 100 °C in neat condition for 16 h and then allowed to cool down to room temperature. The crude mixture was analyzed by GC and purified by column chromatography on silica gel (Pentane/ Diethyl ether/ triethylamine) to give the desired products **3i** and **3j** in 49, 57 % isolated yields respectively.

General Procedure V for (β) C-H alkylation of amine (II)

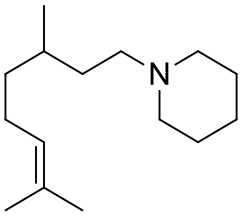
Procedure V for the preparation of amines 4:

See manuscript

Procedure VI for the preparation of amines 5:

To a stirred solution of amine **3 (**1 equiv., 0.44 mmol) in 1.5 mL of toluene was added aldehyde **2** (2 equiv.). Subsequently D-(+)-Camphor sulfonic acid (15 mol %) and catalyst **A** (3 mol %) were added and then the sealed Schlenk tube was stirred in at 150 °C (Oil bath temperature) for 18 h. After 18 h the reaction mixture was cooled down and then HCOOH (2 equiv.) was added and stirring was continued at 130 °C for 3 h. The crude mixture was directly taken for GC analysis and purified by column chromatography (Et_2O/PE) to afford the triterpenylated amine **5** as colorless oil.

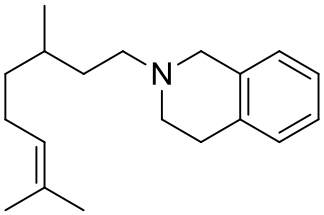
1-(3, 7-dimethyloct-6-en-1-yl) piperidine (3a)



Compound **3a** was prepared according to general procedure **I**, **II** and **III** after purification through column chromatography (Et_2O/PE/Et_3N: 2/8/0.025) in 81%, 57% and 58% yield, respectively and spectral data are in accordance with literature[1]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.23-5.20 (m, 1H), 2.29-2.26 (m, 6H), 2.09-1.98 (m, 2H), 1.67 (s, 3H), 1.57 (s, 3H), 1.56-1.51 (m, 6H), 1.45-1.38 (m, 1H),1.34-1.20(m, 4H), 0.92 (d, 3H, *J*= 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.0, 124.8, 57.6, 54.7, 37.2, 33.8, 31.3, 25.9, 25.6, 25.4, 24.5, 19.7, 17.6, HRMS calculated for $C_{15}H_{30}N^+$: $[M+H]^+$ 224.23783, found $[M+H]^+$ 224.2380.

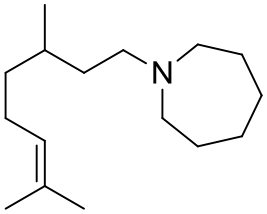
[1] (*a*) Sahli, Z.; Sundararaju, B.; Achard, M.; Bruneau, C. *Org. Lett.* **2011**, *13*, 3964. (*b*) Pagnoux-Ozherelyeva, A. ; Pannetier, N. ; Mbaye, M. D. ; Gaillard, S. ; Renaud, J. –L. *Angew. Chem. Int. Ed.* **2012**, *51*, 4976.

2-(3, 7-dimethyloct-6-en-1-yl)-1, 2, 3, 4-tetrahydroisoquinoline (3b)



Compound **3b** was prepared according to general procedure **I** after purification through column chromatography (Et_2O/PE/Et_3N: 2/8/0.025) in 65 % yield and spectral data are in accordance with literature[2]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04-7.00 (m, 3H), 6.94-6.92 (m, 1H), 5.03 (t, 1H, *J*= 7.0 Hz), 3.54 (s, 2H), 2.83 (t, 2H, *J*= 5.8 Hz), 2.66-2.63 (m, 2H), 2.46-2.41 (m, 2H), 1.96-1.88 (m, 2H),1.61 (s, 3H), 1.53 (s, 3H), 1.46-1.42 (m, 1H), 1.34-1.25 (m, 2H), 1.17-1.08 (m, 2H), 0.85 (d, 3H, *J*= 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.8, 134.3, 131.1, 128.6, 126.5, 126.0, 125.5, 124.8, 56.5, 56.3, 51.0, 37.2, 34.2, 31.1, 29.1, 25.7, 25.5, 19.7, 17.6, HRMS calculated for $C_{19}H_{30}N^+$: $[M+H]^+$ 272.23783, found $[M+H]^+$ 272.2376

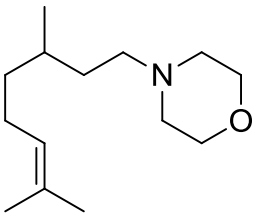
1-(3, 7-dimethyloct-6-en-1-yl)azepane (3c)



Compound **3c** was prepared according to general procedure **I**, **II** and **III** after purification through column chromatography (Et_2O/PE/Et_3N: 2/8/0.025) in 68%, 61%, 63% yield, respectively. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11 (t, 1H, *J*= 7.0Hz), 2.63 (t, 4H, *J*= 5.6Hz), 2.54-2.42 (m, 2H), 2.04-1.95 (m, 2H), 1.69 (s, 3H), 1.65-1.61 (m, 4H), 1.61-1.60 (m, 6H), 1.53-1.45(m, 2H), 1.37-1.29(m, 2H), 1.26, 1.13 (m, 2H), 0.90 (d, 3H, *J*= 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.1, 124.9, 56.4, 55.6, 37.2, 34.4, 31.1, 27.9, 27.0, 25.7, 25.5, 19.7, 17.6; GC-MS m/z (%): 237 (M^+, 3%), 152 (16%), 112 (81%); HRMS calculated for $C_{16}H_{32}N^+$: $[M+H]^+$ 238.25348, found $[M+H]^+$ 238.2537.

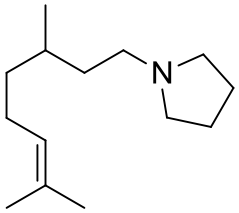
[2] Pagnoux-Ozherelyeva, A. ; Pannetier, N. ; Mbaye, M. D. ; Gaillard, S. ; Renaud, J. –L. *Angew. Chem. Int. Ed.* **2012**, *51*, 4976.

4-(3,7-dimethyloct-6-en-1-yl)morpholine (3d)



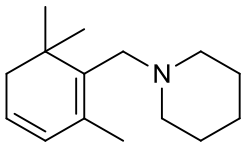
Compound **3d** was prepared according to general procedure **I** after purification through column chromatography (Et_2O/PE/Et_3N: 2/80.025) in 79% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 5.02 (t, 1H, *J*= 7.0Hz), 3.64 (t, 4H, *J*= 4.5 Hz), 2.40-2.36 (m, 4H), 2.29-2.22 (m, 2H), 1.94-1.86 (m, 2H), 1.61(s, 3H), 1.53 (s, 3H), 1.47-1.34 (m, 2H), 1.30-1.19 (m, 2H), 1.14-1.05 (m,1H), 0.82 (d, 3H, *J*= 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.1, 124.7, 67.0 57.2, 53.9, 37.2, 33.5, 31.0, 25.7, 25.4, 19.6, 17.6. HRMS calculated for $C_{14}H_{28}NO^+$: $[M+H]^+$226.21709 found $[M+H]^+$226.2169

1-(3,7-dimethyloct-6-en-1-yl) pyrrolidine (3e)



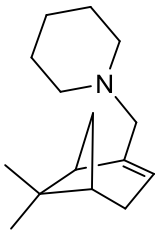
Compound **3e** was prepared according to general procedure **I**, **III** after purification through column chromatography (Et_2O/PE/Et_3N: 2/8/0.025) in 62, 54% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 5.02 (t, 1H, J=6.6Hz), 2.42-2.32 (m, 6H), 1.94-1.84 (m, 2H), 1.71-1.70 (m, 4H), 1.61 (s, 3H), 1.53 (s, 3H), 1.50-1.35 (m, 2H), 1.30-1.21(m, 2H), 1.14-1.05 (m, 1H), 0.82 (d, 3H, J= 6.4Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 131.0, 124.8, 37.2, 36.0, 31.1, 25.6, 25.4, 23.3, 19.7, 17.6, 54.6, 54.2, HRMS calculated for $C_{14}H_{28}N^+$: $[M+H]^+$ 210.22218, found $[M+H]^+$ 210.2220

1-((2,6,6-trimethylcyclohexa-1,3-dien-1-yl)methyl) piperidine (3f)



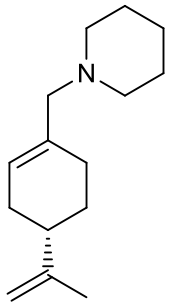
Compound **3f** was prepared according to general procedure **I** after purification through column chromatography (Et_2O/PE/Et_3N: 2/8/0.025) in 73 % yield. ^1H NMR (400 MHz, CD_2Cl_2): δ 5.69-5.67 (m, 1H), 5.64-5.59 (m, 1H), 2.86 (s, 2H), 2.30-2.23 (m, 4H), 1.89 (d, 2H, J=5.27Hz), 1.66 (s, 3H), 1.44-1.38 (m, 4H), 1.32-1.31 (m, 2H), 0.96 (s,6H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 135.9, 130.1, 128.0, 125.5, 57.0, 54.5, 40.9, 33.9, 26.7, 26.3, 25.1, 18.5, HRMS calculated for $C_{15}H_{26}N^+$: $[M+H]^+$ 220.20653, found $[M+H]^+$ 220.2066

1-(((1*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl) piperidine (3g)



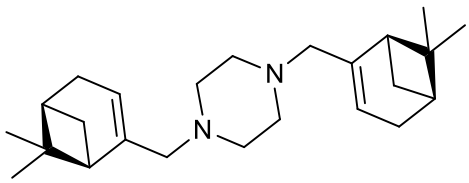
Compound **3g** was prepared according to general procedure **I** after purification through column chromatography (Et_2O/PE/Et_3N: 2/8/0.025) in 86% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 5.29-5.26 (m, 1H), 2.77 (d, 1H, *J*= 13.4 Hz), 2.65 (d, 1H, *J*= 13.3 Hz), 2.31-2.11 (m, 8H), 2.04-2.00 (m, 1H), 1.51-1.45 (m, 4H), 1.36-1.32(m, 2H), 1.20 (s, 3H), 1.05 (d, 1H, *J*= 8.5 Hz), 0.75 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 119.3, 65.2, 54.8, 44.5, 40.9, 37.9, 31.7, 31.3, 26.2, 25.9, 24.5, 21.0; HRMS calculated for $C_{15}H_{26}N^+$: $[M+H]^+$220.20653, found $[M+H]^+$220.2064. $[\alpha]_D^{20}$= - 4.5 (*c* 1, CH_2Cl_2)

(*S*)-1-((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)piperidine (3h)



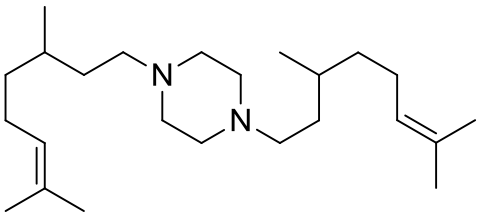
Compound **3h** was prepared according to general procedure **I** after purification through column chromatography (Et_2O/PE/Et_3N: 2/8/0.025) in 62% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 5.00-5.47 (m, 1H), 4.63 (s, 2H), 2.70-2.66 (m, 2H), 2.29-2.19 (m, 4H), 2.06-1.96 (m, 4H),1.90-1.85 (m, 1H), 1.76-1.71 (m, 1H), 1.66 (s, 3H), 1.51-1.45 (m, 5H), 1.38-1.32 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.1, 135.1, 123.5, 108.4, 66.3, 54.6, 41.3, 30.7, 27.8, 27.8, 26.0, 24.5, 20.7. HRMS calculated for $C_{15}H_{26}N^+$: $[M+H]^+$220.20653, found $[M+H]^+$220.2067. $[\alpha]_D^{20}$= - 6.0 (*c* 1, CH_2Cl_2)

1,4-bis(((1*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)piperazine (3i)



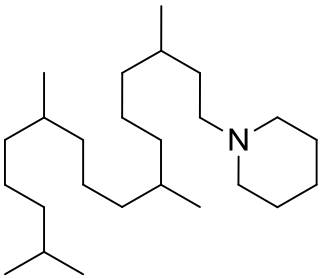
Compound **3i** was prepared according to general procedure **IV** after purification through column chromatography (Et_2O/PE: 2/8) in 49% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 5.28 (m, 2H), 2.82 (d, 2H, *J*= 12.7Hz), 2.68 (d, 2H, *J*= 13.3 Hz), 2.32-2.27 (m, 6H), 2.18-2.10 (m, 6H), 2.01-1.99 (m, 2H), 1.50 (s, 12H), 1.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 119.7, 77.2, 64.5, 53.4, 44.4, 40.9, 37.9, 31.7, 31.3, 26.2, 21.0; HRMS calculated for $C_{24}H_{39}N_2^+$: $[M+H]^+$355.31132, found $[M+H]^+$355.3111. $[\alpha]_D^{20}$= - 0.5 (*c* 1, CH_2Cl_2)

1, 4-bis (3, 7-dimethyloct-6-en-1-yl) piperazine (3j)



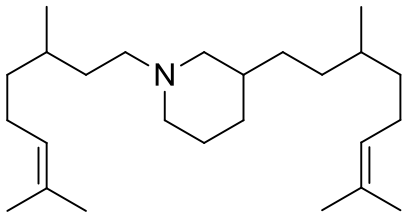
Compounds **3j** were prepared according to general procedure **IV** after purification through column chromatography (Et_2O/PE/Et_3N: 2/8/0.025) in 57% yield as a diastereoisomeric mixture. ^{1}H NMR (400 MHz, CDCl3): δ 5.01 (t, 2H, J= 7.0Hz), 2.52-2.20 (m, 12H), 1.93-1.83 (m, 4H), 1.61 (s, 6H), 1.52 (s, 6H), 1.48-1.41 (m, 2H), 1.39-1.32 (m, 2H), 1.29-1.20 (m, 4H), 1.13-1.04 (m, 2H), 0.82, 1.13(d, 6H, J=6.52Hz), ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.1, 124.8, 56.8, 53.4, 37.2, 33.8, 31.2, 25.7, 25.4, 19.7, 17.6, HRMS calculated for $C_{24}H_{47}N_2^+$: $[M+H]^+$ 363.37392, found $[M+H]^+$ 363.3741

1-(3, 7, 11, 15-tetramethylhexadecyl) piperidine (3k)



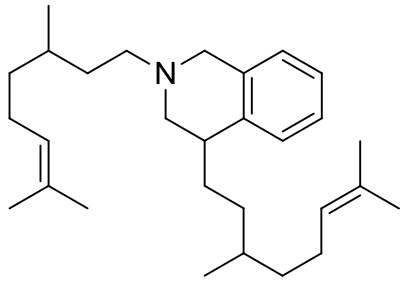
Compounds **3k** were prepared according to general procedure **II** after purification through column chromatography (Et_2O/PE:0.5/9.5) in 52% yield as mixture of stereoisomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.43-2.23 (m, 6H), 1.62-1.56 (m, 4H), 1.45-1.37 (m, 5H), 1.32-1.21 (m, 12H), 1.17-1.09 (m, 9H), 0.88 (d, 9H, J=6.6Hz), 0.86 (d, 6H, J= 7.2Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 57.9, 57.7, 54.7, 54.6, 54.5, 39.3, 37.5, 37.5, 37.4, 37.3, 37.3, 37.2, 34.1, 34.0, 32.7, 32.7, 31.7, 31.6, 27.9, 26.0, 24.7, 24.5, 24.4, 24.3, 22.7, 22.6, 19.9, 19.8, 19.7, 19.7, 19.6. HRMS calculated for $C_{25}H_{52}N^+$: $[M^+H]^+$ 366.40998, found $[M^+H]^+$ 366.40997.

1, 3-bis(3,7-dimethyloct-6-en-1-yl)piperidine (4a)



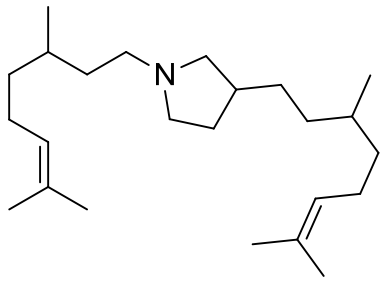
Compounds **4a** were prepared according to general procedure **V** after purification through column chromatography (Et_2O/PE/Et_3N: 1/9/0.025) in 80 % yield as a mixture of stereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.02 (t, 2H, *J*= 6.5 Hz), 2.85-2.80 (m, 2H), 2.26-2.20 (m, 2H), 1.98-1.82 (m, 4H), 1.69-1.66(m, 1H), 1.61 (s, 6H), 1.53 (s, 6H), 1.52-1.44 (m, 4H), 1.34-1.18 (m, 8H), 1.13-1.00 (m, 6H), 0.81 (d, 3H, *J*= 6.5 Hz), 0.78 (d, 3H, *J*= 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.0, 130.9, 125.0, 124.8, 61.0, 60.9, 60.7, 57.5, 54.6, 54.4, 37.2, 37.0, 37.0, 36.4, 36.4, 34.0, 33.9, 33.8, 32.6, 32.5, 32.1, 32.0, 31.3, 31.3, 31.1, 25.7, 25.5, 25.5, 19.7, 19.5, 19.5, 17.6; HRMS calculated for $C_{25}H_{48}N^+$: $[M+H]^+$ 362.37868 , found $[M+H]^+$ 362.3784 .

2,4-bis (3,7-dimethyloct-6-en-1-yl)-1,2,3,4-tetrahydroisoquinoline (4b)



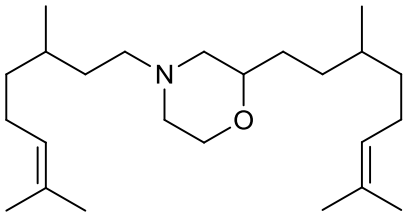
Compounds **4b** were prepared according to general procedure **V** after purification through column chromatography (Et_2O/PE: 1/9) in 68 % yield as a mixture of stereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12-6.90 (m, 4H), 5.02-5.00 (m, 2H), 3.60-3.39 (m, 2H), 2.74-2.69 (m, 1H), 2.57-2.36 (m, 4H), 1.94-1.89 (m,4H), 1.61(s, 6H), 1.53 (s, 6H),1.46-1.26 (m, 8H), 1.18-1.06 (m, 5H), 0.85-0.81(m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.8, 134.3, 132.3, 131.1, 128.6, 126.6, 126.1, 125.5, 124.8, 56.5, 56.3, 51.0, 37.2, 34.2, 31.1, 29.1, 25.7, 25.5, 19.7, 17.6. HRMS calculated for $C_{29}H_{49}N$+: $[M+H]^+$ 410.37868, found $[M+H]^+$ 410.3784

1,3-bis(3,7-dimethyloct-6-en-1-yl) pyrrolidine (4c)



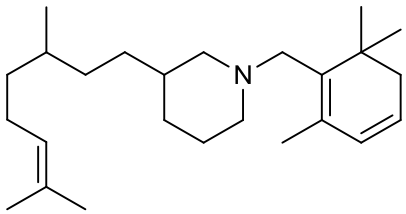
Compounds **4a** were prepared according to general procedure **V** after purification through column chromatography (Et_2O/PE/Et_3N: 1/9/0.025) in 62 % yield as a mixture of stereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.08-5.02 (m, 2H), 2.74-2.55 (m, 2H), 2.41-2.24 (m, 4H), 1.96-1.86 (m, 6H), 1.60 (s, 6H), 1.52 (s, 6H), 1.39-1.36 (m, 1H), 1.29-1.18 (m, 8H), 1.11-0.98(m, 4H), 0.81-0.79(m,6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.0, 129.9, 123.9, 123.9,59.9, 53.8, 53.6, 53.2, 53.9, 53.2, 53.1, 39.0, 36.7, 36.7, 36.2, 36.0, 35.0, 34.8, 34.6, 31.5, 31.5, 30.1, 32.1, 32.1, 32.1, 29.9, 29.8, 24.6, 24.5, 24.5, 24.4, 22.3, 18.7, 18.6, 18.5, 16.6
.

2, 4-bis (3,7-dimethyloct-6-en-1-yl)morpholine (4d)



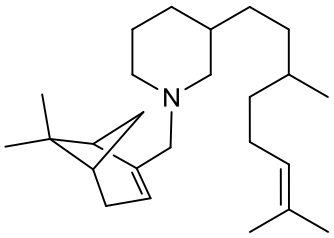
Compounds **4d** were prepared according to general procedure **V** after purification through column chromatography (Et_2O/PE/Et_3N: 1/9/0.025) in 69% yield as a mixture of stereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03-5.00 (m, 2H), 3.78 (d, 1H, *J*= 11.0 Hz), 3.58 (t, 1H, *J*= 11.2 Hz), 3.40-3.34 (m, 1H), 2.71-2.62 (m, 2H), 2.26-2.23(m, 2H), 1.99-1.82 (m, 6H), 1.61 (s, 6H), 1.53 (s, 6H), 1.30-1.24 (m,7H), 1.11-1.02 (m, 5H), 0.88-0.80 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.1, 130.0, 123.9, 123.7, 75.2, 75.1, 65.8, 56.1, 52.5, 52.3, 36.2, 36.0, 32.5, 31.4, 30.3, 30.1, 28.7, 24.7, 24.5, 18.7, 18.4, 16.6. HRMS calculated for $C_{24}H_{46}NO^+$: $[M^+H]^+$ 364.35794, found $[M^+H]^+$ 364.3585.

3-(3,7-dimethyloct-6-en-1-yl)-1-((2, 6, 6-trimethylcyclohexa-2,4-dien-1-yl) methyl) piperidine (4e)



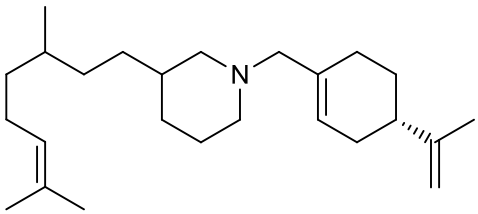
See manuscript

1-(((1R, 5S)-6, 6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-3-(3, 7-dimethyloct-6-en-1-yl)piperidine (4f)



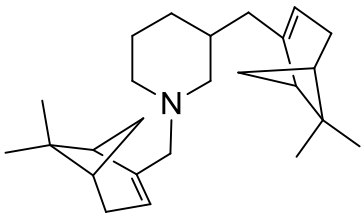
Compounds **4f** were prepared according to general procedure **V** after purification through column chromatography (Et_2O/PE/Et_3N: 1/9/0.025) in 56% yield as a stereoisomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.30-5.25 (m, 1H), 5.02 (t, 1H, *J*= 7.0 Hz), 2.80-2.62 (m, 4H), 2.31-2.02 (m, 6H), 1.94-1.64 (m, 9H), 1.61 (s, 3H), 1.53 (s, 3H), 1.20 (s, 6H), 1.07-1.05 (m, 4H), 0.76 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ. 144.8, 129.9, 124.0, 118.3, 64.0, 64.0, 59.6, 53.9, 53.4, 43.4, 43.4, 39.9, 36.9, 36.0, 35.4, 33.0, 31.6, 31.5, 30.7, 30.3, 25.2, 24.7, 24.5, 20.0, 18.5, 18.5, 16.6. HRMS calculated for $C_{25}H_{44}N^+$: $[M+H]^+$ 358.34738, found $[M+H]^+$ 385.3471

3-(3, 7-dimethyloct-6-en-1-yl)-1-(((S)-4-(prop-1-en-2-yl) cyclohex-1-en-1 yl)methyl)piperidine (4g)



Compounds **4g** were prepared according to general procedure **V** after purification through column chromatography (Et_2O/PE/Et_3N: 1/9/0.025) in 60%, yield as a mixture of stereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.52-5.49 (m, 1H), 5.02 (t, 1H, J=6.7Hz), 4.63(s, 2H), 2.77-2.63 (m, 4H), 2.09-1.99 (m, 4H), 1.91-1.84(m, 4H), 1.76-1.72(m, 2H), 1.66 (s, 3H), 1.61 (s, 3H), 1.52 (s, 3H), 1.48-1.45 (m, 1H), 1.42-1.36(m, 4H), 1.28-1.18 (m, 4H), 1.11-1.03 (m, 4H), 0.78 (d, 3H, *J*= 6.2Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 150.1, 150.0, 135.1, 130.9, 125.0, 123.6, 123.5, 108.4, 66.3, 66.2, 66.0, 54.6, 54.4, 54.3, 41.3, 41.3, 41.2, 37.2, 37.0, 37.0, 36.3, 34.0, 33.8, 32.6, 32.5, 31.5, 31.3, 31.1, 30.7, 27.8, 27.7, 25.9, 25.7, 25.5, 25.5, 25.4, 20.9, 20.8, 20.7, 19.6, 19.5, 17.6. HRMS calculated for $C_{25}H_{44}N^+$: $[M+H]^+$ 358.34738 , found $[M+H]^+$ 358.3471.

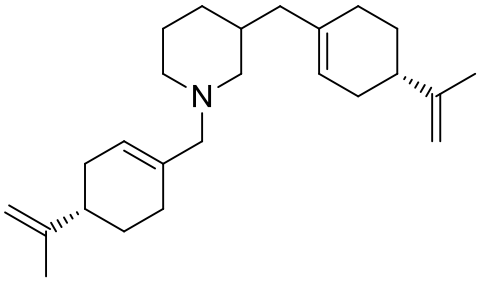
3-(((1R, 5S)-6, 6-dimethylbicyclo[3.1.1]hept-2-en-2-yl) methyl)-1-(((1S, 5R)-6, 6-dimethylbicyclo[3.1.1] hept-2-en-3-yl) methyl) piperidine (4h)



Compounds **4h** were prepared according to general procedure **V** after purification through column chromatography (Et_2O/PE/Et_3N: 2/8/0.025) in 57% yield with a 62% diastereoisomeric excess. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.28-5.26 (m, 1H), 5.10-5.05 (m, 1H), 2.81-2.61(m, 4H), 2.29-2.25 (m, 3H), 2.20-2.19 (m, 6H), 2.08-2.00 (m, 3H), 1.76-1.70(m, 3H), 1.20-1.18 (m, 6H), 1.12-1.10(m, 2H), 1.07-1.05 (m, 2H), 0.80-0.72 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 146.5, 145.4, 119.5, 117.2, 117.2, 65.0, 61.0, 60.6, 54.8, 54.2, 46.0,

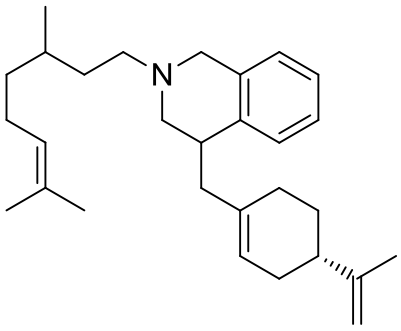
45.9, 44.6, 44.5, 42.6, 42.5, 40.9, 40.8, 37.9, 37.9, 33.8, 33.544, 31.8, 31.3, 26.3, 26.2, 25.2, 21.1, 21.0; GC-MS m/z (%): 353 (M^+, 3.7%), 284 (7.5%), 230 (20%), 217 (30.%), 85 (38%).

3-(((R)-4-(prop-1-en-2-yl) cyclohex-1-en-1-yl) methyl)-1-(((S)-4-(prop-1-en-2-yl) cyclohex-1-en-1-yl)methyl)piperidine (4 i)



Compounds **4i** were prepared according to general procedure **V** after purification through column chromatography (Et_2O/PE/Et_3N: 1/9/0.025) in 71%, yield with a 5% diastereoisomeric excess. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.52-5.46 (m, 1H), 5.34-5.30 (m, 1H), 4.63 (s, 4H), 2.76-2.62 (m, 4H), 2.10-2.00 (m, 6H), 1.94-1.86 (m, 4H), 1.78-1.72 (m,4H), 1.66 (s, 6H), 1.42-1.36 (m, 4H), 1.21-1.15 (m, 2H), 0.86-0.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 149.1, 149.1, 134.5, 120.8, 107.3, 107.4, 65.0, 134.0, 122.6, 59.5, 53.3, 41.9, 40.3, 40.2, 32.8, 29.8, 29.7, 27.7, 26.9, 26.8, 24.3, 19.7. HRMS calculated for $C_{25}H_{40}N^+$: $[M+H]^+$ 354.31608, found $[M+H]^+$ 354.3164

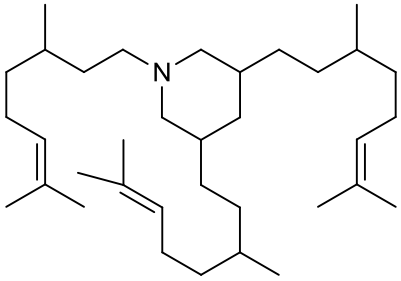
2-(3, 7-dimethyloct-6-en-1-yl)-4-((4-(prop-1-en-2-yl) cyclohex-1-en-1-yl) methyl)-1, 2, 3, 4-tetrahydroisoquinoline (4j)



Compounds **4j** were prepared according to general procedure **V** after purification through column chromatography (Et_2O/PE: 1/9) in 67% yield as a mixture of stereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10-7.04 (m, 3H), 6.94-6.92(m, 1H), 5.42-5.40 (m, 1H), 5.05-5.02 (m, 1H), 4.66 (s, 2H), 3.62-3.60 (m, 1H), 3.38-3.34 (m, 1H), 2.87-2.84 (m, 1H), 2.60-2.54 (m,

1H), 2.43-2.26 (m, 5H), 2.20-2.05(m, 3H), 1.94-1.87 (m, 4H), 1.68 (s, 3H), 1.60(s, 3H),1.53 (s, 3H), 1.35-1.10(m, 7H), 0.85-0.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.0, 148.9, 138.1, 134.7, 134.5, 134.1, 130.1, 127.1, 125.3, 125.0, 124.4, 123.8, 122.0, 107.5, 56.1, 55.5, 53.6, 53.1, 43.8, 43.0, 40.3, 40.0, 36.2, 35.3, 35.0, 33.2, 29.9, 29.8, 27.8, 27.2, 26.8, 24.7, 24.5, 19.9, 19.8, 18.7, 16.6; HRMS calculated for $C_{29}H_{44}N^+$: $[M+H]^+$ 406.34738 , found $[M+H]^+$406.3476

1, 3, 5-tris (3,7-dimethyloct-6-en-1-yl)piperidine (5a)



Compounds **5a** were prepared according to general procedure **VI** after purification through column chromatography (Et_2O/PE: 1/9) in 53% yield as a mixture of stereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.02 (t, 3H, J=6.77Hz), 2.84-2.82 (m, 2H), 2.26-1.20 (m, 2H), 1.90-1.80 (m, 6H), 1.61 (s, 9H), 1.53 (s, 9H), 1.46-1.42(m, 4H), 1.30-1.21 (m,12H),1.10-1.03 (m, 9H), 0.80-0.77 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ. 130.0, 129.9, 124.0, 123.8, 123.9, 60.0, 60.1, 59.8, 59.7, 56.3, 37.5, 36.2, 36.0, 36.0, 35.3, 33.0, 33.0, 32.9, 31.6, 31.6, 31.2, 31.1, 30.4, 24.7, 24.5, 24.4, 18.7, 18.5, 18.5, 16.6. ; GC-MS m/z (%): 499 (M^+, 8%), 430 (10%), 414 (37%), 374 (37%).