Hydroformylation of 1,4-Diolefins in the Presence of Primary Amines Leading to Heterocyclic Compounds

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Abstract

The Rh(I)-catalysed hydroformylation of dienes in the presence of amines is applied to heterocyclic ring synthesis. Starting from 1,4-dienes pyrroles or eight-membered heterocycles are easily accessible. The selectivity of the reaction is controlled by the substitution pattern of the diolefin. © 1999 Elsevier Science Ltd. All rights reserved.

Medium sized heterocyclic ring systems as well as cyclopenta[b]pyrroles are of interest in organic and medicinal chemistry [1]. Considerable efforts have been made to accomplish their facile and convenient synthesis [2,3]. We recently investigated the hydroaminomethylation of various olefins and diolefins to generate secondary or tertiary acyclic amines under hydroformylation conditions in the presence of amines [4]. We now wish to report the application of the hydroaminomethylation in the synthesis of cyclic amines starting from substituted 1,4-pentadienes **1** in the presence of primary amines **2** (Scheme 1). In preliminary studies we used 3,3-disubstituted 1,4-pentadienes in order to suppress olefin isomerisation reactions. Depending on the substitution pattern in the diene either eight-membered heterocyclic systems of type **3** or cyclopentanellated pyrrole systems of type **4** are obtained.
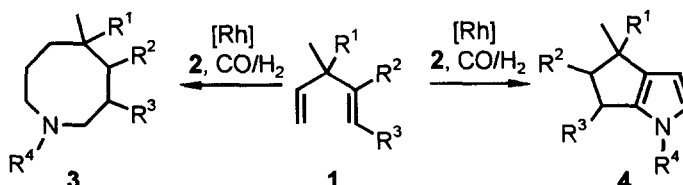
Scheme 1

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1,4-Pentadienes, if disubstituted only in the 3,3-position, undergo intramolecular pyrrole formation to give the bicyclic systems 7. As side products minor amounts of cyclopentanones 8 are obtained. Additional hydroxy functions in the C-3 substituents are also tolerated. The primary amine can be aliphatic as well as aromatic. The results are assembled in Table 1.
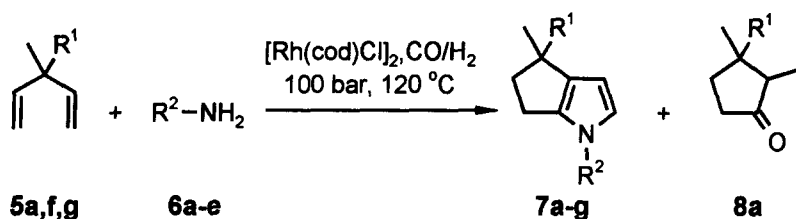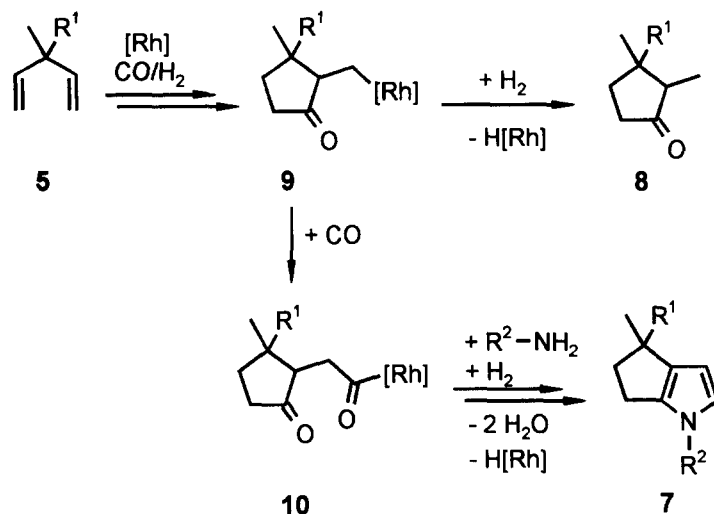

Scheme 2

Table 1: Reaction conditions for the synthesis of pyrroles 7

| entry	R^1	diene	R^2	amine	CO/H_2 [bar]	time [h]	product	yield[a] [%] 7	8
1	-CH₃	5a	butyl	6a	50 : 50	70	7a	54 (17)	<2
2	-CH₃	5a	isopropyl	6b	50 : 50	70	7b	38 (21)	8
5	-CH₃	5a	benzyl	6c	50 : 50	70	7c	54 (30)	7
6	-CH₃	5a	(R)-(+)-phenylethyl	6d	50 : 50	40	7d	47 (26)	-
7	-CH₃	5a	p-methoxyphenyl	6e	50 : 50	70	7e	31 (11)	17
8	-CH(OH)CH₃	5f	benzyl	6c	85 : 15	40	7f	(40)	-
9	-CH₂CH₂OH	5g	benzyl	6c	85 : 15	70	7g	(20)	-

[a] determined by gas chromatography (isolated yields)

As shown in Scheme 3 the pyrrole 7 is generated via a hydrocarbonylative cyclisation step leading to 9 as the key intermediate. This reaction is well known [5] and normally completed by a hydrogenolytic removal of the rhodium resulting in 8. In presence of primary amines 6, however, the rhodium alkyl intermediate 9 undergoes further insertion of carbon monoxide to form the rhodium acyl species 10, an analogue of 1,4-dicarbonyl compounds which are employed in the Paal-Knorr pyrrole synthesis [1b]. In this fashion 10 undergoes cyclisation with the primary amine to generate the pyrrole 7. Although not investigated in detail this reaction sequence satisfactorily explains the formation of the observed products 7 and 8. As known in heterocyclic ring

synthesis the different steps may occur in various order. The product selectivity can be controlled by the synthesis gas ratio. A higher hydrogen pressure ($CO:H_2$ = 20:80 bar) leads to enhanced hydrogenolysis of compound **9** and formation of cyclopentanone **8** (**7**:**8** = 61:39). At higher carbon monoxide pressure ($CO:H_2$ = 80:20 bar) the hydrogenolysis is completely suppressed (**7**:**8** = 100:0).
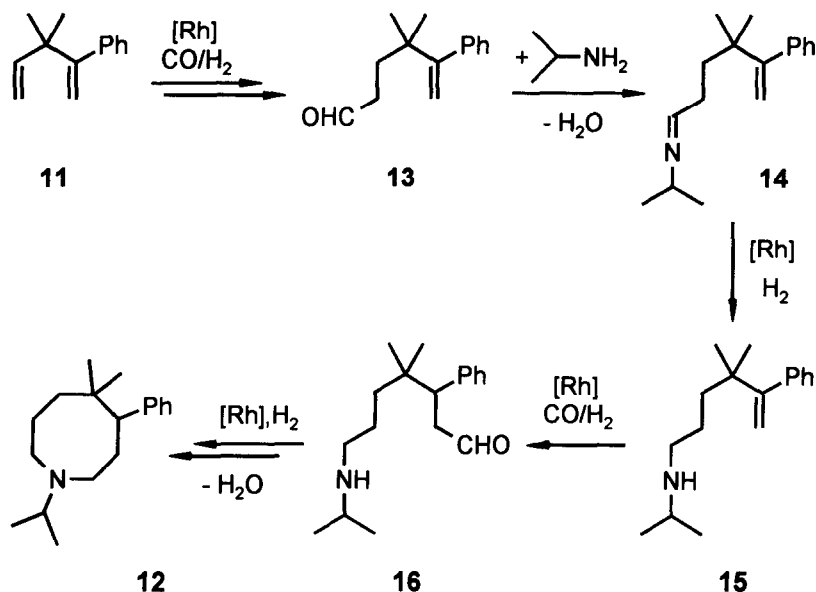

Scheme 3

In contrast to the unsubstituted dienes **5** 1,4-pentadienes with additional substituents at the double bond such as the monosubstituted diene **11** under similar conditions in the presence of primary amines do not lead to pyrroles. Instead, via an intramolecular hydroformylation-reductive-amination pathway diene **11** gives the eight-membered heterocycle **12** in 58 % yield.
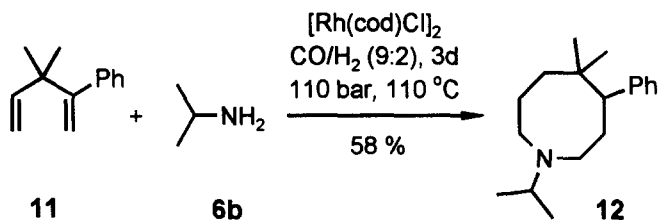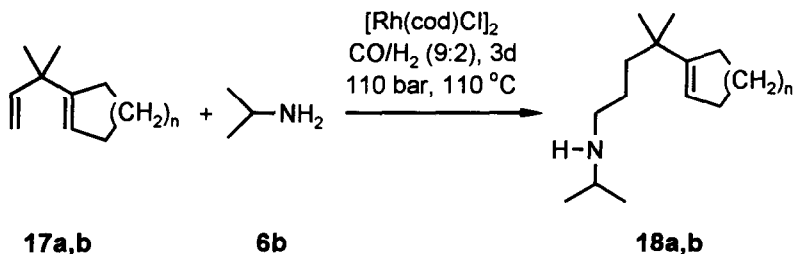

Scheme 4

The different chemoselectivities in the conversions of **5** and **12** is attributed to the lower reactivity of the substituted double bond of **11** [6]. As shown in Scheme 5 the less hindered double bond is preferentially hydroformylated with high regioselectivity towards the *n*-product **13** [4b]

and after a reductive amination with the primary amine the secondary amine **15** is generated. This undergoes intramolecular hydroaminomethylation of the less reactive double bond leading to the heterocycle **12**. An intermediate similar to **15** can be isolated (see **18** below).

Scheme 5

Increasing the sterical crowding at one of the double bonds of **5** e. g. by integrating the double bond into a ring system suppresses the heterocyclic ring closure completely. Only the non-substituted double bond is hydroaminomethylated whereas the trisubstituted ring double bond due to sterical reasons remains unaffected [4b] (Scheme 6). Even after increased reaction times to up to five days no cyclisation products are detected. Therefore dienes **17a** and **17b** under identical conditions give the monohydroaminomethylation products **18a,b** in excellent yields.
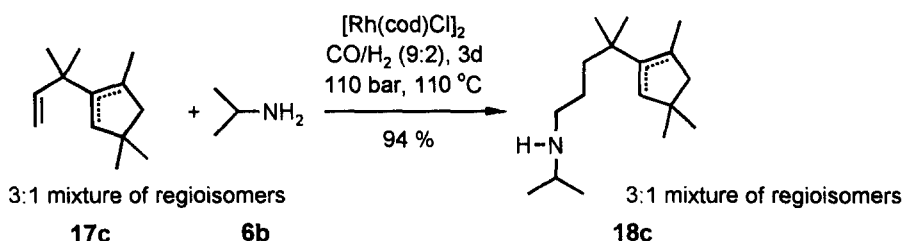

Scheme 6

Table 2: Hydroaminomethylation of double bond substituted 3,3-dimethylpentadienes 17

entry	diene	n	product	yield [%][a]
10	17a	2	18a	84
11	17b	4	18b	93
12	17c[b]	1	18c[b]	94

a) isolated yields; b) mixture of regioisomers (ca. 3 : 1)

The analogous five- and seven-membered ring containing dienes under similar conditions do not show selective conversions. Probably rearrangements and ring opening reactions occur and lead to a complex reaction mixture. However, if the five-membered ring is substituted with methyl groups (17c) selective monohydroaminomethylation takes place. The methyl groups due to their conformational effects obviously inhibit the side reactions mentioned above.

3:1 mixture of regioisomers
17c   **6b**

3:1 mixture of regioisomers
18c

Scheme 7

In conclusion we have shown that pyrroles and medium sized heterocycles are easily accessible from diolefinic compounds via ring closing hydroaminomethylation. This convenient and efficient multistep methodology allows variations of the diene and the amine leading to cyclisation products with different substitution patterns. Further investigations concerning the synthesis of larger heterocyclic systems starting from heterofunctionalised diallylic systems are in current progress.

Experimental Section

All basic chemicals were purchased from commercial sources. Column chromatography was carried out on alumina N (act. I) from ICN Biomedicals, Eschwege, or with silica gel 60 from Merck, Darmstadt. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 or DRX 400 spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard (multiplicities marked with an asterisk * are not in line with first order spectra). Infra red spectra were performed on a Nicolet Impact 400 D, mass spectra on a Finnigan CA 5 and elemental analysis on a Leco, CHNS-932. Analytical gas chromatography was performed on a Fisons 8130 gas chromatograph

with 30 m CP sil-5 capillaries. GC-MS spectra were obtained by using a comparable capillary and a Finnigan MAT 8320 (MS). Pressure reactions have been carried out in autoclaves (type A, 250 ml, PTFE-insert) from Berghof, Eningen.

General procedure A: Hydroaminomethylation of **5** with primary amines **6**

The diolefin **5** (5.2 mmol), amine **6** (5.3 mmol), [Rh(cod)Cl]$_2$ (0.5 mol-% based on the amount of the diolefin) and dry dioxane (20 ml) were placed in an autoclave. After flushing with argon the reactor was pressurised with 50 bar hydrogen and 50 bar carbon monoxide and heated to 120 °C for 70 h. After removing the solvent by rotary evaporation the catalyst was done away by column filtration. The products were separated and purified by column chromatography on neutral alumina (act. I).

General procedure B: Hydroaminomethylation of **11**, **17a-c** with isopropylamine (**6b**)

The diolefins **11**, **17a-c** (4.8 mmol), **6b** (5.9 mmol), [Rh(cod)Cl]$_2$ (0.5 mol-% based on the amount of the diolefin) and dry dioxane (10 ml) were placed in an autoclave. After flushing with argon the reactor was pressurised with 20 bar hydrogen and 90 bar carbon monoxide and heated to 110 °C for 70 h. After removing the solvent by rotary evaporation the catalyst was removed by column filtration. The products were separated and purified by column chromatography on silica.

Synthesis of starting materials

3,3-Dimethyl glutaric acid is reduced to the diol which is converted to the dibromide which can be eliminated to result in diene **5a** [5]. The precursor of **5g** is obtained from a rearrangement and an esterification of 3-methylpent-2,4-dien-1-ol [7]. The following reduction with LiAlH$_4$ leads to **5g** [7]. The precursor of **5f** is synthesised from methyl vinyl ketone via a pinacol reduction with zinc followed by a pinacol rearrangement [8]. The thus generated diene can be reduced with LiAlH$_4$ to give **5f** [8]. The dienes **11** and **17** were obtained via elimination [9] of homoallylic alcohols. These alcohols arise from a Grignard reaction of prenyl bromide with the corresponding alkanone derivative in presence of AlCl$_3$ and zinc [10]. The catalyst precursor [RhCl(cod)]$_2$ was prepared from cyclooctadiene and RhCl$_3$*3H$_2$O as described [11].

Synthesis of pyrroles 7

1-Butyl-4,4-dimethyl-1,4,5,6-tetrahydro-cyclopenta[b]pyrrole (7a). Following general procedure A **5a** (500 mg) and **6a** (388 mg) were converted to give 672 mg of a mixture of **7a** (54 % GLC yield) and **8a** (<2 % GLC yield). Purification by column chromatography (hexane as eluent) leads to 168 mg (17 %) **7a**. ^{1}H NMR (400 MHz, CDCl$_3$, 20 °C): δ [ppm] = 0.92 (t, J = 7.4 Hz,

3H), 1.21 (s, 6H), 1.32 (sext., J = 7.4 Hz, 2H), 1.70 (qui, J = 7.4 Hz, 2H), 2.19 (t*, J = 6.8 Hz, 2H), 2.64 (t*, J = 6.8 Hz, 2H), 3.71 (t*, J = 7.4 Hz, 2H), 5.84 (d, J = 2.6 Hz, 1H), 6.47 (d, J = 2.6 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C): δ [ppm] = 13.7 (CH$_3$), 20.0 (CH$_2$), 23.6 (CH$_2$), 29.6 (2xCH$_3$), 33.3 (CH$_2$), 39.2 (C$_q$), 45.8 (CH$_2$), 47.6 (CH$_2$), 100.3 (CH), 122.3 (CH), 135.2 (C$_q$), 135.3 (C$_q$). IR (neat): ṽ [cm^{-1}] = 3112 w, 3092 w, 2956 vs, 2860 vs, 2715 w, 1627 w, 1565 m, 1517 m, 1495 s, 1459 s, 1378 m, 1359 s, 1307 m, 1247 m, 1209 m, 1129 m, 1104 m, 1030 m, 814 m, 703 s, 679 s. GC-MS (EI, 70 eV): m/z [%] = 191 (M$^+$; 52), 176 (100), 147 (5), 134 (15), 120 (18), 118 (8), 103 (7), 93 (4), 77 (2), 65 (2), 57 (2).

1-Isopropyl-4,4-dimethyl-1,4,5,6-tetrahydro-cyclopenta[*b*]pyrrole (7b). Following general procedure A **5a** (500 mg) and **6b** (296 mg) were converted to give 669 mg of a mixture of **7b** (38 % GLC yield) and **8a** (8 % GLC yield). Purification by column chromatography (petrol ether (PE)$_{30/60}$: methyl-*tert.*butyl ether (MTBE) = 20 : 1 as eluent) leads to 195 mg (21 %) **7b**.

^{1}H NMR (400 MHz, CDCl$_3$, 20 °C): δ [ppm] = 1.21 (s, 6H), 1.40 (d, J = 6.8 Hz, 6H), 2.18 (t*, J = 6.9 Hz, 2H), 2.69 (t*, J = 6.9 Hz, 2H), 4.12 (sept, J = 6.8 Hz, 1H), 5.85 (d, J = 2.8 Hz, 1H), 6.55 (d, J = 2.8 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C): δ [ppm] = 23.4 (CH$_3$), 24.4 (CH$_2$), 29.7 (2xCH$_3$), 38.7 (C$_q$), 45.8 (CH$_2$), 49.5 (CH), 100.0 (CH), 119.5 (CH), 134.2 (C$_q$), 135.6 (C$_q$). IR (neat): ṽ [cm^{-1}] = 3092 vw, 2955 vs, 2859 m, 1683 w, 1667 w, 1482 w, 1463 m, 1383 w, 1366 m, 1360 m, 1293 w, 1261 vs, 1243 m, 1221 w, 1124 m, 1098 vs, 1088 vs, 1019 vs, 805 vs. GC-MS (EI, 70 eV): m/z [%] = 177 (M$^+$; 51), 162 (100), 120 (62), 93 (5), 80 (11), 51 (8).

1-Benzyl-4,4-dimethyl-1,4,5,6-tetrahydro-cyclopenta[*b*]pyrrole (7c). Following general procedure A **5a** (500 mg) and **6c** (568 mg) were converted to give 1.122 g of a mixture of **7c** (54 % GLC yield) and **8a** (7 % GLC yield). Purification by column chromatography (PE$_{30/60}$: MTBE = 50 : 1 as eluent) leads to 348 mg (30 %) **7c**.

^{1}H NMR (400 MHz, CDCl$_3$, 20 °C): δ [ppm] = 1.22 (s, 6H), 2.18 (t*, J = 6.8 Hz, 2H), 2.53 (t*, J = 6.8 Hz, 2H), 4.92 (s, 2H), 5.89 (d, J = 2.5 Hz, 1H), 6.51 (d, J = 2.5 Hz, 1H), 7.08 (m, 2H), 7.28 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C): δ [ppm] = 23.5 (CH$_2$), 29.7 (2xCH$_3$), 39.3 (C$_q$), 45.9 (CH$_2$), 51.5 (CH$_2$), 101.0 (CH), 123.0 (CH), 127.0 (CH), 127.4 (CH), 128.6 (CH), 135.6 (C$_q$), 136.0 (C$_q$), 138.3 (C$_q$). IR (neat): ṽ [cm^{-1}] = 3087 w, 3063 w, 3029 w, 2950 vs, 2859 s, 2792 w, 1495 s, 1454 s, 1378 w, 1358 m, 1306 w, 1251 m, 1123 m, 1106 w, 1029 w, 733 s, 699 vs, 679 s. MS (EI, 70 eV): m/z [%] = 225 (M$^+$; 37), 210 (100), 160 (2), 140 (2), 91 (47), 65 (5). HRMS calc. for C$_{16}$H$_{19}$N: 225.15175; found: 225.1510.

1-(4-Methoxy-phenyl)-4,4-dimethyl-1,4,5,6-tetrahydro-cyclopenta[*b*]pyrrole (7d). Following general procedure A **5a** (500 mg) and **6d** (640 mg) were converted to give 1.334 g of a mixture of **7d** (31 % GLC yield) and **8a** (17 % GLC yield). Purification by column chromatography ($PE_{30/60}$: MTBE = 10 : 1 as eluent) leads to 139 mg (11 %) **7d**.

^{1}H NMR (400 MHz, CDCl$_3$, 20 °C): δ [ppm] = 1.27 (s, 6H), 2.24 (t*, J = 6.8 Hz, 2H), 2.82 (t*, J = 6.8 Hz, 2H), 3.81 (s, 3H), 6.03 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 2.8 Hz, 1H), 6.92 (d, J = 8.9 Hz, 2H), 7.29 (d, J = 8.9 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C): δ [ppm] = 25.3 (CH$_2$), 29.7 (2xCH$_3$), 39.0 (C$_q$), 45.7 (CH$_2$), 55.5 (CH$_3$), 102.5 (CH), 114.4 (CH), 122.0 (CH), 122.3 (CH), 134.2 (C$_q$), 134.5 (C$_q$), 137.7 (C$_q$), 157.1 (C$_q$). IR (neat): ṽ [cm^{-1}] = 3093 vw, 3003 vw, 2950 vs, 2858 m, 1655 vw, 1639 vw, 1559 w, 1522 vs, 1473 m, 1463 s, 1451 m, 1378 m, 1289 m, 1270 s, 1247 vs, 1176 m, 1158 s, 1127 m, 1026 s, 831 s, 827 vs, 712 m. MS (EI, 70 eV): m/z [%] = 241 (M$^+$; 35), 233 (16), 226 (100), 197 (9), 113 (14), 77 (4). Anal. Calcd. for C$_{16}$H$_{19}$NO (241.3): C, 79.6; H, 7.9; N, 5.8. Found: C, 79.4; H, 7.9; N, 5.7.

4,4-Dimethyl-1-(1-(*R*)-ethyl-phenyl)-1,4,5,6-tetrahydro-cyclopenta[*b*]pyrrole (7e). Following general procedure A **5a** (500 mg) and **6e** (630 mg) were converted to give 566 mg **7e** (47 % GLC yield). Purification by column chromatography ($PE_{30/60}$ as eluent) leads to 323 mg (26 %) **7e**.

^{1}H NMR (400 MHz, CDCl$_3$, 20 °C): δ [ppm] = 1.19 (s, 3H), 1.22 (s, 3H), 1.79 (d, J = 7.0 Hz, 3H), 2.11 (t*, J = 5.8 Hz, 1H), 2.15 (t*, J = 5.8 Hz, 1H), 2.42 (m, 1H), 2.51 (m, 1H), 5.17 (qua, J = 7.0 Hz, 1H), 5.90 (d, J = 2.6 Hz, 1H), 6.64 (d, J = 2.6 Hz, 1H), 7.04 (d, J = 7.3 Hz, 2H), 7.28 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C): δ [ppm] = 21.8 (CH$_3$), 24.4 (CH$_2$), 29.7 (2xCH$_3$), 38.8 (C$_q$), 45.7 (CH$_2$), 56.9 (CH), 100.5 (CH), 120.7 (CH), 125.8 (CH), 127.1 (CH), 128.5 (CH), 135.3 (C$_q$), 136.1 (C$_q$), 143.7 (C$_q$). IR (neat): ṽ [cm^{-1}] = 3088 w, 3063 w, 3028 w, 2978 s, 2957 vs, 1603 w, 1494 m, 1482 m, 1449 s, 1377 m, 1359 s, 1246 s, 1222 w, 1126 w, 1027 w, 737 w, 699 vs, 680 s. MS (EI, 70 eV): m/z [%] = 239 (M$^+$; 90), 224 (100), 208 (4), 182 (5), 167 (4), 135 (12), 120 (96), 105 (85), 103 (33), 93 (12), 91 (18), 79 (44), 77 (48), 65 (8), 58 (13), 51 (10), 44 (9), 39 (9). Anal. Calcd. for C$_{17}$H$_{21}$N (239.4): C, 85.3; H, 8.8; N, 5.9. Found: C, 85.1; H, 8.8; N, 6.1.

1-(1-Benzyl-4-methyl-1,4,5,6-tetrahydro-cyclopenta[*b*]pyrrol-4-yl)-ethanol (7f). Following general procedure A **5f** (656 mg) and **6c** (568 mg) were converted to give 536 mg **7f** (40 % isolated yield) after purification by column chromatography (hexane : MTBE = 2 : 1 as eluent) as a 1 : 1.4 mixture of diastereoisomers.

^{1}H NMR (400 MHz, CDCl$_3$, 20 °C): δ [ppm] = 1.18 (2xd, J = 6.3 Hz, 3H), 1.20 (2xs, 3H), 1.65 (s, 1H), 2.02 (m, 1H), 2.51 (m, 3H), 3.62 (qua, J = 6.3 Hz, 0.5H), 3.83 (qua, J = 6.3 Hz, 0.5H), 4.92 (s, 2H), 5.91 (2xd, J = 2.5 Hz, 1H), 6.56 (d, J = 2.5 Hz, 1H), 7.04 (m, 2H), 7.24 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C): δ [ppm] = 17.3, 18.8 (CH$_3$), 23.6, 24.0 (CH$_2$), 23.9, 24.0 (CH$_3$), 38.0, 41.6 (CH$_2$), 48.5, 48.6 (C$_q$), 51.5 (CH$_2$), 73.6, 74.7 (CH), 101.7, 102.9 (CH), 123.6, 123.8 (CH), 126.8, 126.8 (CH), 127.4 (CH), 128.6 (CH), 129.5, 130.7 (C$_q$), 137.6, 137.9 (C$_q$), 138.0 (C$_q$). IR (neat): ṽ [cm^{-1}] = 3466 m, 3088 w, 3063 w, 3030 m, 2959 vs, 2924 vs, 2855 s, 1496 vs, 1455 vs, 1439 m, 1372 m, 1356 s, 1328 m, 1303 m, 1264 m, 1243 m, 1119 m, 1078 s, 1028 m, 734 s, 700 vs, 685 s. MS (EI, 70 eV): m/z [%] = 255 (M$^+$; 6), 210 (100), 134 (3), 91 (36), 65 (4). Anal. Calcd. for C$_{17}$H$_{21}$NO (255.4): C, 80.0; H, 8.3; N, 5.5. Found: C, 79.9; H, 8.6; N, 5.6.

2-(1-Benzyl-4-methyl-1,4,5,6-tetrahydro-cyclopenta[b]pyrrol-4-yl)-ethanol (7g). Following general procedure A **5g** (328 mg, 2.6 mmol) and **6c** (284 mg, 2.7 mmol) were converted to give 130 mg **7g** (20 % isolated yield) after purification by column chromatography (PE$_{30/60}$: MTBE = 1 : 1 as eluent).

^{1}H NMR (400 MHz, CDCl$_3$, 20 °C): δ [ppm] = 1.24 (s, 3H), 1.55 (m, 1H), 1.78 (m, 1H), 1.87 (m, 1H), 2.15 (m, 1H), 2.28 (m, 1H), 2.52 (t, J = 6.9 Hz, 2H), 3.68 (m, 2H), 4.93 (s, 2H), 5.90 (d, J = 2.8 Hz, 1H), 6.55 (d, J = 2.8 Hz, 1H), 7.05 (m, 2H), 7.28 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C): δ [ppm] = 23.7 (CH$_2$), 28.7 (CH$_3$), 41.5 (C$_q$), 44.2 (CH$_2$), 45.2 (CH$_2$), 51.5 (CH$_2$), 60.9 (CH$_2$), 101.5 (CH), 123.8 (CH), 126.8 (CH), 127.4 (CH), 128.6 (CH), 133.4 (C$_q$), 136.4 (C$_q$), 138.1 (C$_q$). IR (neat): ṽ [cm^{-1}] = 3346 m, 3088 w, 3063 w, 3029 m, 2927 vs, 2859 vs, 1495 s, 1453 vs, 1415 m, 1392 w, 1354 m, 1308 w, 1254 m, 1180 m, 1141 m, 1099 s, 1076 s, 1053 s, 1027 s, 733 s. GC-MS (EI, 70 eV): m/z [%] = 256 (M$^+$; 6), 240 (18), 222 (8), 210 (100), 170 (22), 117 (8), 91 (95), 73 (21).

Hydroaminomethylation of substituted dienes

1-Isopropyl-5,5-dimethyl-4-phenylazocane (12). Following general procedure B (2,2-dimethyl-1-methylenebut-3-enyl)-benzene (**11**) (830 mg) and **6b** (350 mg) were converted to give 773 mg **12** (58 % GLC yield). Purification by column chromatography (PE$_{30/60}$ and 1 % EtOH as eluent) leads to 340 mg (27 %) **12**.

^{1}H NMR (400 MHz, CDCl$_3$, 20 °C): δ [ppm] = 0.71 (s, 3H), 0.80 (s, 3H), 0.95 (d, J = 6.6 Hz, 6H), 1.42-1.49 (m, 2H), 1.59-1.71 (m, 3H), 1.75-1.84 (m, 1H), 2.40-2.72 (m, 4H), 2.87 (sept, J = 6.6 Hz, 1H), 3.12 (dd, J = 7.6 Hz, 2.4 Hz, 1H), 7.21 (m, 5H). ^{13}C NMR (100 MHz, CDCl$_3$,

20 °C): δ [ppm] = 17.7 (CH_3), 19.4 (CH_3), 24.1 (CH_3), 25.7 (CH_2), 29.0 (CH_3), 32.9 (CH_2), 35.9 (C_q), 40.5 (CH_2), 48.1 (CH), 50.9 (CH_2), 52.2 (CH_2), 56.1 (CH), 125.3 (CH), 127.2 (2xCH), 130.1 (2xCH), 146.8 (C_q). IR (neat): $\tilde{v}$ [cm^{-1}]= 3090 vw, 3059 w, 3026 m, 2963 vs, 2928 vs, 2870 s, 2805 m, 2771 w, 1659 w, 1600 w, 1492 m, 1452 s, 1384 s, 1362 s, 1261 w, 1240 w, 1212 w, 1195 w, 1173 m, 1110 m, 1088 w, 1031 w, 761 w, 752 w, 704 vs. MS (EI, 70 eV): m/z (%) = 260 ($M^{+}+1$, 100), 244 (9), 174 (12), 100 (29), 91 (6), 72 (15), 56 (15). Anal. Calcd. for $C_{18}H_{29}N$ (259.4): C, 83.3; H, 11.3; N, 5.4. Found: C, 82.9; H, 11.1; N, 5.5.

4-(1-Cyclohexenyl)-4-methylpentyl-isopropylamine (18a). Following general procedure B 1,1-dimethyl-allyl-1-cyclohexene (**17a**) (720 mg) and **6b** (350 mg) were converted to give 900 mg (84 %) **18a** isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ [ppm] = 0.98 (s, 6H), 1.04 (d, J = 6.2 Hz, 6H), 1.29 (d, J = 3.2 Hz, 4H), 1.51-1.60 (m, 4H), 1.89-2.03 (m, 5H), 2.52 (t, 2H), 2.76 (sept, J = 6.2 Hz, 1H), 5.40 (t, J = 3.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ [ppm] = 22.5 (CH_2), 22.9 (2xCH_3), 23.3 (CH_2), 24.2 (CH_2), 25.5 (CH_2), 25.7 (CH_2), 27.1 (2xCH_3), 38.0 (C_q), 38.4 (CH_2), 48.4 (CH_2), 48.6 (CH), 119.3 (CH), 143.0 (C_q). IR (neat): $\tilde{v}$ [cm^{-1}] = 3049 vw, 2963 vs, 2929 vs, 2872 s, 2857 s, 2837 s, 1655 vw, 1473 m, 1448 m, 1379 m, 1362 m. MS (EI, 70 eV): m/z (%) = 223 (M^{+}, 32), 208 (69), 194 (4), 180 (5), 163 (3), 152 (34), 100 (88), 99 (72), 98 (100), 95 (50), 85 (44), 84 (61), 83 (52), 81 (77), 79 (49), 72 (97), 70 (58), 69 (60). Anal. Calcd. for $C_{15}H_{29}N$ (223.4): C, 80.7; H, 13.1; N, 6.3. Found: C, 80.7; H, 13.1; N, 6.5.

4-(1-Cyclooctenyl)-4-methylpentyl-isopropylamine (18b). Following general procedure B 1-(1,1-dimethylallyl)-cyclooctene (**17b**) (860 mg) and **6b** (370 mg) were converted to give 1.120 g (93 %) **18b** isolated yield.

^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ [ppm] = 1.01 (s, 6H), 1.04 (d, J = 6.2 Hz, 6H), 1.31-1.33 (m, 3H), 1.49 (m, 9H), 2.05 (br s, 3H), 2.17 (t, J = 6.0 Hz, 2H), 2.51 (t, J = 6.7 Hz, 2H), 2.76 (sept, J = 6.2 Hz, 1H), 5.36 (t*, J = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ [ppm] = 22.9 (2xCH_3), 25.7 (CH_2), 25.8 (CH_2), 26.2 (CH_2), 26.4 (2xCH_3), 27.6 (2xCH_2), 29.1 (CH_2), 30.8 (CH_2), 38.8 (CH_2), 39.3 (C_q), 48.3 (CH_2), 48.6 (CH), 122.6 (CH), 145.9 (C_q). IR (neat): $\tilde{v}$ [cm^{-1}] = 3335 vw, 3046 vw, 2963 vs, 2926 vs, 2853 vs, 1473 s, 1448 s, 1380 m, 1362 m, 1336 vw, 1320 vw, 1260 m, 1171 m, 1123 m, 1086 m, 1047 w, 1035 w, 1017 w, 876 m, 841 vw. MS (EI, 70 eV): m/z (%) = 252 ($M^{+}+1$, 24), 180 (5), 140 (17), 99 (55), 84 (40), 72 (100), 55 (19). Anal. Calcd. for $C_{17}H_{33}N$ (251.5): C, 81.2; H, 13.2; N, 5.6. Found: C, 80.8; H, 13.4; N, 5.9.

Isopropyl[4-methyl-4-(3,3,5-trimethyl-1-cyclopentenyl)-pentyl]-amine (18c) / Isopropyl[4-methyl-4-(2,4,4-trimethyl-1-cyclopentenyl)-pentyl]amine (18c'). Following general procedure B a 3:1 mixture of 1-(1,1-dimethylallyl)-3,3,5-trimethyl-1-cyclopentene (**17c**) and 1-(1,1-dimethylallyl)-2,4,4-trimethyl-1-cyclopentene (**17c'**) (800 mg) and **6b** (370 mg) were converted to give 1.060 g (94 %) **18c/18c'** isolated yield in a 3:1 mixture.

^{1}H NMR (400 MHz, CDCl$_3$, 20 °C): δ [ppm] = 0.97-1.09 (m, 42H), 1.17-1.23 (m, 4H), 1.36-1.39 (m, 6H), 1.69 (br s, 3H), 1.88-1.94 (m, 2H), 2.10 (br s, 2H), 2.53-2.54 (m, 4H), 2.75-2.80 (m, 2H), 5.14 (s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$, 20 °C): δ [ppm] = 22.8 (2xCH$_3$), 22.9 (4xCH$_3$), 25.7 (CH$_2$), 25.9 (CH$_2$), 28.2 (2xCH$_3$), 28.4 (CH$_3$), 28.6 (CH$_3$), 29.3 (CH$_3$), 29.6 (CH$_3$), 30.2 (2xCH$_3$), 35.0 (C$_q$), 35.9 (C$_q$), 36.5 (C$_q$), 39.4 (CH$_2$), 40.0 (CH), 40.2 (CH$_2$), 42.3 (C$_q$), 48.4 (2xCH$_2$), 48.6 (2xCH), 49.4 (CH$_2$), 50.7 (CH$_2$), 56.1 (CH$_2$), 128.7 (C$_q$), 135.5 (CH), 138.3 (C$_q$), 151.2 (C$_q$). IR (neat): $\tilde{v}$ [cm^{-1}] = 3337 vw, 3038 vw, 2957 vs, 2864 vs, 2832 s, 1698 vw, 1678 vw, 1626 vw, 1466 s, 1379 s, 1362 s, 1336 m, 1320 m, 1260 w, 1218 vw, 1172 m, 1123 m, 1086 m, 1042 vw, 876 vw, 853 w, 803 vw. MS (EI, 70 eV): m/z (%) = 252 (M$^+$+1, 100), 140 (24), 99 (12), 84 (12), 72 (56), 58 (9). Anal. Calcd. for C$_{17}$H$_{33}$N (251.5): C, 81.2; H, 13.2; N, 5.6. Found: C, 81.3; H, 13.2; N, 5.2.

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