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# Highly Selective Hydroaminomethylation of Internal Alkenes To Give Linear Amines

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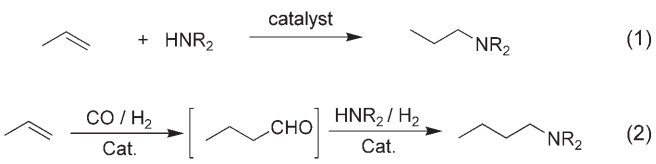
**Abstract:** The application of phenoxaphosphino-modified Xantphos-type ligands (**1**–**9**) in the rhodium-catalyzed hydroaminomethylation of internal olefins to give linear amines is reported. Excellent chemo- and regioselectivities have been obtained through the use of 0.1 mol% $[Rh(cod)_2]BF_4$/0.4 mol% xantphenoxaphos (**1**), providing a practical and environmentally attractive synthetic route for the preparation of amines from internal alkenes. For the first time, both functionalized internal olefins and mixtures of internal and terminal olefins have been converted highly selectively into linear amines. Investigations of the effects of the calculated natural bite angles of ligands on hydroaminomethylation shows that the regioselectivity for the linear product follows a similar trend to that seen in the hydroformylation of internal alkenes with the aid of these ligands. Hydroaminomethylation and each of its individual steps were monitored by high-pressure infrared spectroscopy. The results suggest that hydroaminomethylations take place by a sequential isomerization/hydroformylation/amination/hydrogenation pathway.

**Keywords:** amines · homogeneous catalysis · hydroaminomethylation · rhodium · Xantphos-type ligands

## Introduction

The catalytic formation of carbon–nitrogen bonds is of particular interest in organic chemistry, as a large number of nitrogen-containing molecules are of significant importance for both the bulk and the fine chemical industries—for the production of solvents, pharmaceutical intermediates, or emulsifiers, for example—and also in the fields of naturally occurring bioactive compounds such as alkaloids, amino acids, and nucleotides. Catalytic conversions might offer potential advantages over conventional methods of amine synthesis—such as nucleophilic substitutions of organic halides by amines, azides, or cyanides—in that they might avoid the production of (stoichiometric amounts of) salts, the use of more expensive starting materials, and/or the need for multistep synthetic routes. Potentially environmentally more benign methods for amine synthesis include catalytic substitutions of alcohols, reductive amination of carbonyl compounds, reduction of nitro or nitrile compounds, and hydrocyanation followed by hydrogenation. Unfortunately, though, the required starting compounds, such as nitro and nitrile derivatives, are often expensive or—in the cases of hydrocyanation and substitution of alcohols, for example—the necessarily drastic reaction conditions may be incompatible with the presence of other functional groups in the substrate. In such respects, both hydroamination[1] and hydroaminomethylation[2] (Scheme 1) should be perfectly suited to the synthesis of amines and to fulfilling today's need for "green chemistry".[3]

Obviously, both methods have high atom-economy[4] or atom efficiency[5] and start from readily available and inexpensive feedstocks: alkenes and amines. While hydroamination reactions, in spite of the considerable progress made in




Scheme 1. Hydroamination (1) and hydroaminomethylation (2) of olefins.

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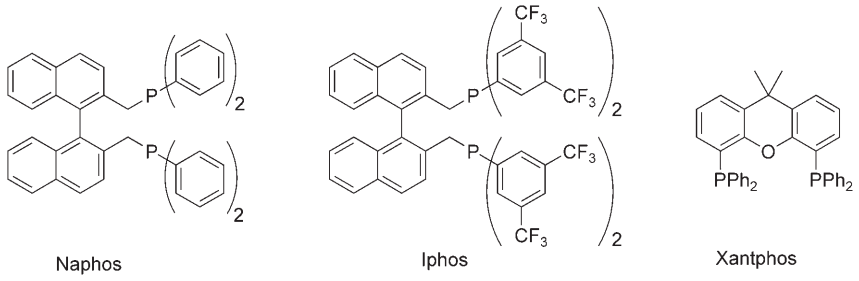
recent years, still need improvement with regard to generality, the one-pot hydroformylation/amination/hydrogenation domino sequence (the so-called hydroaminomethylation reaction) offers a versatile and selective route for the preparation of amines that is compatible with the use of many different alkenes and amines.

Hydroaminomethylation was discovered at BASF AG by Reppe, who used $[Fe(CO)_5]$ as catalyst in almost stoichiometric amounts.[6] Later on, cobalt and rhodium complexes evolved as catalysts for this reaction. Until the mid 1990s, research into this reaction—predominantly in industry—indicated that relatively harsh conditions ($>60$ bar; $>150\,^{\circ}C$) were required to give the corresponding amines from simple α-olefins in good yields.[7] In the last decade, however, work by Eilbracht et al. in particular has elegantly shown how to prepare a large number of functionalized amines by "ligand-free" (phosphine-free) hydroaminomethylation procedures.[8] The use of such catalysts often results in unsatisfactory regioselectivity in the initial hydroformylation stage, however, so it is in general difficult to obtain pure products because of similar physical properties of the produced isomers. As a solution to this, some of us have developed selective hydroaminomethylation procedures making use of modified Naphos- and Xantphos derivatives (Scheme 2) as the controlling ligands.[9]




Scheme 2. Structures of Naphos, Iphos, and Xantphos.

At this point it is important to note that, despite the apparent simplicity of the hydroaminomethylation reaction, it is still a challenge to control both the chemo- and regioselectivity of such processes with high selectivity. Whilst talking about regioselectivity, it is also noteworthy that all potential products (linear and branched ones) are of value in organic synthesis, albeit for different applications. The branched products, for example, are often worthwhile intermediates on smaller scales for elaborate organic synthesis and for natural product synthesis.

The linear products, on the other hand, are far more important for the chemical industry. With production on multi-hundred thousand tonne scales per year, linear aliphatic amines belong to the important bulk intermediates. Because of the comparably low prices of these products the corresponding feedstocks must be as cheap as possible, and in this regard internal olefins in refinery mixtures—raffinate-II, which consists of but-1-ene, (*E*/*Z*)-but-2-ene, and butane, for example—represent a more attractive feedstock than pure terminal olefins such as but-1-ene. The same is true for $C_6$, $C_8$, and $C_9$ olefins.

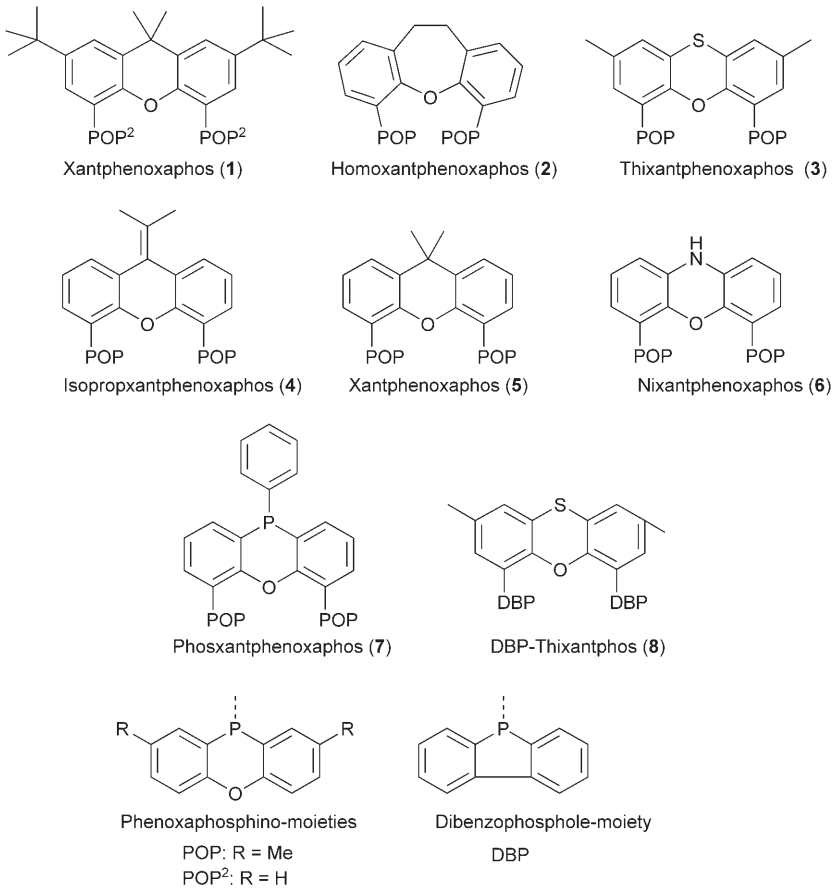
To transform internal olefins into linear amines, the following requirements have to be met by the catalyst: a) the hydroformylation of the terminal olefin has to be fast in relation to that of the internal isomer, since only branched products will be formed from internal olefins, b) the regioselectivity (*n*/*i* ratio) for the reaction between the catalyst and the terminal olefin has to be very high, and c) isomerization reactions have to be fast in relation to all the hydroformylation reactions, as the thermodynamic mixture of olefins contains less than 5% of the terminal alkene.

Not surprisingly, internal olefins are much less reactive, predominantly forming branched products with classic rhodium phosphine catalysts, so the selective linear functionalization of internal aliphatic olefins is an important goal in current catalysis research.[10] So far, this interesting reaction type has been studied mainly with regard to hydroformylations.[11] In the case of hydroaminomethylation the presence of amines poses additional difficulties, as the resulting basic reaction conditions prevent olefin isomerization reactions[12] and catalyze the formation of aldol condensation by-products. Thus, the aldehydes produced in situ should be rapidly converted into the amines in order to prevent side reactions. In addition, stoichiometric amounts of water are produced during hydroaminomethylation and could react with the catalyst, substrates, or products. Despite all these problems, the first methodology for the regioselective hydroaminomethylation of simple *internal* alkenes to give linear amines has recently been developed.[13] For this reaction a ligand (Iphos, Scheme 2) particularly suited for the hydroformylation of internal alkenes to provide linear aldehydes was employed. In most cases the selectivity during the initial hydroformylation step is preserved and is reflected in the good selectivity for the linear amine. Here we present a more general and practical rhodium catalyst, which allows efficient hydroaminomethylations with unprecedented selectivity (typically *n*:iso $>$ 95:5). The scope of the method has been investigated by hydroaminomethylation reactions with unfunctionalized and functionalized *internal* olefins with several amines. In addition, the selective hydroaminomethylation of olefin mixtures is presented for the first time.

## Results and Discussion

**Optimization of the model system**: To develop a more general hydroaminomethylation method for internal olefins we tested a series of wide-bite-angle ligands (**1**–**8**, Scheme 3)

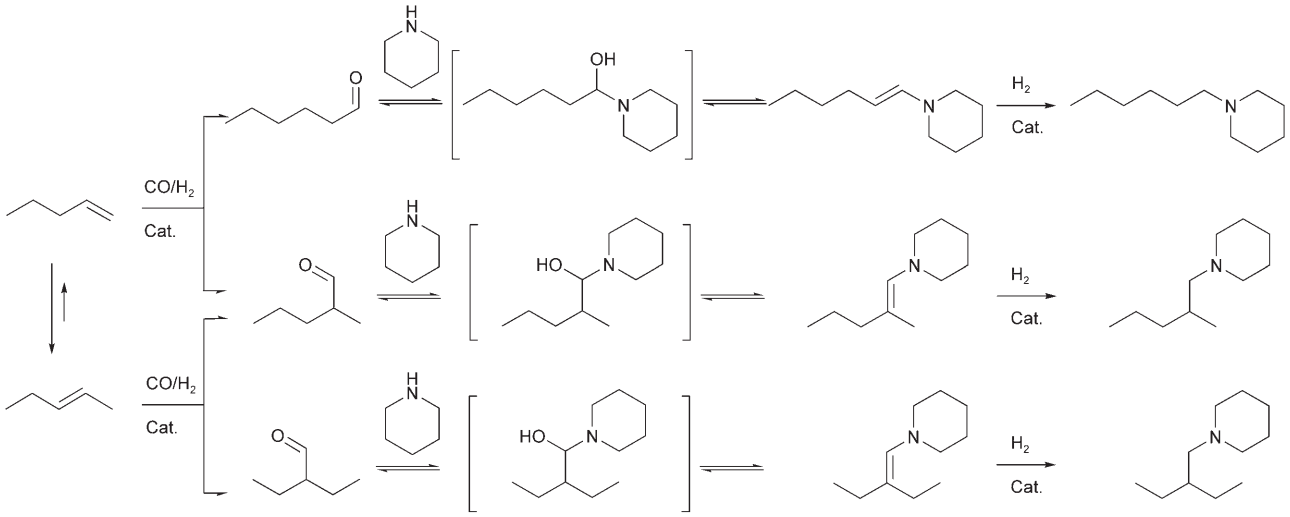



Scheme 3. Ligands tested for hydroaminomethylation of pent-2-ene.

specifically prepared to study the influence of the natural bite angle on hydroformylation,[14] which is the regioselectivity-determining step for the transformation of internal alkenes into linear amines.

Although the regioselectivity in the initial hydroformylation step might be retained, the influence of the different ligands on the consecutive amination and reduction reactions was unclear. Previous studies on hydroaminomethylation by our group[10,13] had shown that the reaction temperature, the solvent, and the partial pressures of hydrogen and carbon monoxide can have a major influence on the catalysis results with regard to side product formation, selectivity, and activity, and so we used the optimized conditions found for Xantphos as the ligand as a starting point for the screening of ligands **1**–**8** in hydroaminomethylation,[9a] as the structures of **1**–**8** are closely related to that of Xantphos. After some exploratory studies, the rhodium-catalyzed hydroaminomethylation of pent-2-ene and piperidine (Scheme 4) to produce *N*-hexylpiperidine with **1** as modifying ligand was used to investigate the influence of important reaction parameters (i.e., reaction time, $P_{CO}$, $P_{H_2}$, $T$, catalyst precursor, and solvent; see Table 1) more systematically. Results obtained with Iphos as ligand are also included as a reference.[13]

Under the optimized reaction conditions for Xantphos (solvent = methanol/toluene (1:1), $T$ = 125 °C, $P_{CO}$ = 7 bar (at room temperature), $P_{H_2}$ = 33 bar (at room temper-




Scheme 4. Hydroaminomethylation of pent-2-ene with piperidine.

Table 1. The effect of various reaction parameters on hydroaminomethylation of pent-2-ene and piperidine.[a]

| Entry | Cat. | Ligand | $P_{CO}/P_{H_2}$ [bar] | Solvent | $t$ [h] | Conv. [%][b] | Total selec. [%][c] | Selectivity [%] | | | | l/b[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | lin. amine | iso amine | isoenamine | *N*-formylpiperidine | |
| 1 | A | Iphos | 7/33 | Tol/THF | 24 | 88 | 98 | 82 | 17 | – | 2 | 82:18 |
| 2 | A | **1** | 7/33 | Tol/MeOH | 12 | 70 | 91 | 66 | 25 | 8 | 1 | 73:27 |
| 3 | A | **1** | 7/33 | Tol/MeOH | 6 | 35 | 89 | 69 | 20 | 9 | 2 | 78:22 |
| 4 | A | **1** | 5/33 | Tol/MeOH | 12 | 80 | 96 | 86 | 10 | 2 | 2 | 90:10 |
| 5 | A | **1** | 5/33 | Tol/MeOH | 16 | 100 | 99 | 95 | 4 | – | – | 96:4 |
| 6 | A | **1** | 2.5/33 | Tol/MeOH | 16 | 75 | 97 | 94 | 3 | - | - | 96:4 |
| 7 | A | **1** | 10/33 | Tol/MeOH | 16 | 85 | 97 | 66 | 30 | 1 | 3 | 68:32 |
| 8 | A | **1** | 5/5 | Tol/MeOH | 16 | 53 | 93 | 87 | 6 | 2 | 1 | 94:6 |
| 9 | A | **1** | 5/15 | Tol/MeOH | 16 | 96 | 98 | 93 | 5 | 1 | 1 | 95:5 |
| 10 | A | **1** | 5/50 | Tol/MeOH | 16 | 93 | 99 | 91 | 8 | – | 1 | 92:8 |
| 11[f] | A | **1** | 5/33 | Tol/MeOH | 16 | 65 | 95 | 84 | 11 | 0.4 | 3 | 88:12 |
| 12 | B | **1** | 5/33 | Tol/MeOH | 16 | 95 | 94 | 90 | 4 | – | 1 | 96:4 |
| 13 | A | **1** | 5/33 | Tol | 16 | 90 | 82 | 70 | 12 | 7 | – | 85:5 |
| 14 | A | **1** | 5/33 | MeOH | 16 | 100 | 95 | 85 | 10 | – | 4 | 89:11 |
| 15 | A | **1** | 5/33 | anisole | 16 | 86 | 52 | 50 | 2 | 1[e] | – | 96:4 |

[a] Reaction conditions: Tol = toluene, pent-2-ene/piperidine 10/10 mmol, indicated pressures at room temperature, L/Rh = 1:4, Rh 0.1 mol%, ligand 0.4 mol%. A = $[Rh(cod)_2]BF_4$, B = $[Rh(CO)_2acac]$, temperature 125°C. [b] Conversion of piperidine at indicated reaction time. [c] Selectivity toward amines. [d] Linear to branched ratio. [e] 35% Linear enamine. [f] At 105°C.

ature), $t_{reaction}$ = 12 h, Table 1 entry 2), we observed only 70% conversion towards the formation of amines, with a low regioselectivity (73:27).

Additionally, the enamine generated in situ is not completely hydrogenated. Lower conversion, but a higher regioselectivity (78:22) for the linear amine, was obtained by reducing the reaction time to 6 h, due to the slower hydrogenation of the isoenamine (Table 1, entry 3). A longer reaction time of 16 h *and* a reduced CO pressure (to 5 bar) ensured complete conversion with very high regioselectivity (96:4; Table 1, entry 5). In fact, this constitutes the highest linear amine selectivity so far reported for any hydroaminomethylation of an internal olefin. Similar regioselectivity was obtained at lower pressures of 2.5 bar (Table 1, entry 6), but the conversions were not reproducible as the conversion levels ranged from 75% to >99%, which might be related to the reduced catalyst stability at these low CO pressures.[15] The positive effect of reducing the CO pressure on regioselectivity is consistent with results obtained in the hydroformylation of internal alkenes to linear aldehydes,[16] and can be explained in terms of an enhanced rate of isomerization, as this effectively reduces the amount of branched alkyl rhodium intermediate undergoing carbonylation. The efficiency of the enamine hydrogenation seems to increase at lower CO pressures, but this could be a side effect as a result of the increased regioselectivity, because linear enamines are in general easier to hydrogenate than branched enamines. Additionally, the formation of *N*-formylpiperidine is suppressed at lower CO pressures, which results in high chemoselectivities ranging from 97 to 99%.

A $H_2$ pressure of 33 bar is sufficient to ensure complete hydrogenation of all enamines, and a slightly higher regioselectivity (in relation to catalysis run under 50 bar of $H_2$) is obtained (Table 1; compare entries 5, 8–10). A lower reaction temperature of 105°C (Table 1, entry 11) is not sufficient to ensure full conversion and enamine hydrogenation. A good alternative catalyst precursor for $[Rh(cod)_2]BF_4$ is $[Rh(CO)_2(acac)]$ (Table 1, entry 12), although slightly lower conversions and chemoselectivities are obtained. Although it seems hard to understand with so much base present, the presence of $BF_4^-$ influences the amount of cationic rhodium species present during catalysis, this probably being the form that performs the enamine hydrogenation.[17] Entries 5 and 13–15 (Table 1) show that the solvent also has a dramatic effect on conversion and on chemo- and regioselectivity, which is not surprising as the solvent influences the aldehyde/enamine equilibrium as well as the rate of hydrogenation.[18] Of the solvent systems tested, a 1:1 mixture of methanol and toluene is in all respects the best reaction solvent. Excellent regioselectivities are observed in anisole, but unfortunately hydrogenation of the linear enamine is slow this solvent, resulting in a low chemoselectivity.

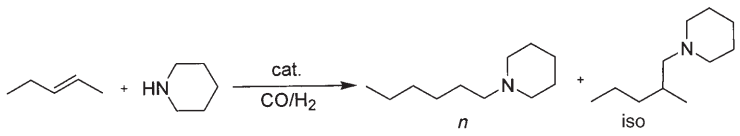
**The influence of the bite angle on hydroaminomethylation**: Although better results had been obtained at a CO pressure of 5 bar and with a reaction time of 16 h, we opted to study the effect of the different ligand structures at CO pressures of 7 bar with 12 h reaction times, as the differences between the various catalysts in terms of regioselectivity and conversion were expected to be larger and the effect of natural bite angle on the performance thus potentially more pronounced. Table 2 summarizes the results obtained with ligands **1**–**8**.

Comparison of catalysis in the presence of ligands **1**–**7** shows the effect of natural bite angle on catalytic performance. The best results in terms of conversion and chemo- and regioselectivity were obtained when ligand **4**, with a natural bite angle of 114°, was employed. Surprisingly, the catalyst obtained in the presence of **6** gave high conversion into *N*-methylpiperidine.

The initial hydroformylation step is essential for good hydroaminomethylation of internal alkenes, so the results

Table 2. The effect of natural bite angle on hydroaminomethylation.[a]



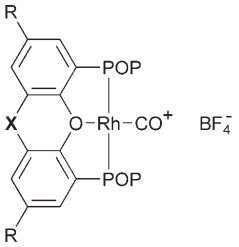

| Ligand | $\beta_n$ [°][b] | Conv. [%][c,d] | Total amine selec. [%][d,e] | Lin. amine [%][d] | Isoamine [%][d] | Isoenamine [%][d] | *N*-Formylpiperidine [%][d,f] | l/b[d] |
|---|---|---|---|---|---|---|---|---|
| **1** | 123.1 | 70 | 92 | 67 | 25 | 7 | 1 | 73:27 |
| **2** | 106.7 | 60 | 72 | 15 | 57 | 24[h] | 2 | 20:80 |
| **3** | 112.5 | 75 | 93 | 32 | 61 | 6 | 1 | 34:66 |
| **4** | 114.2 | 97 | 99 | 67 | 32 | – | 1 | 68:32 |
| **5** | 116.0 | 71 | 96 | 66 | 30 | 1 | 3 | 69:31 |
| **6** | 124.5 | 79 | 77 | 56 | 20 | – | 23[g] | 73:27 |
| **7** | 131.2 | 65 | 78 | 40 | 38 | 21 | 1 | 51:49 |
| **8** | 111.8 | 20 | 96 | 43 | 53 | – | 4 | 45:55 |

[a] Reaction conditions: CO (7 bar), $H_2$ (33 bar), substrate = 10 mmol (1:1), rhodium (0.1 mol%), ligand (0.4 mol%), ligand/Rh = 1:4, in toluene/methanol (1:1), time (12 h), temperature (125 °C). [b] As reported in reference [12h]. [c] Conversion of piperidine. [d] Linear to branched ratio, percent product, and conversion were determined after 12 h reaction time. [e] Selectivity toward amines. [f] *N*-Formylpiperidine. [g] *N*-Methylpiperidine. [h] 4% of linear enamine.

seem to contradict the results reported for the hydroformylation of *trans*-oct-2-ene with the same ligand series, as it was reported that an increase in natural bite angle resulted in a decrease in activity.[16] It is important to note, however, that differences in catalyst stability can mean that conversion and initial rate can be completely different. Additionally, the hydroaminomethylation reactions reported here were conducted under different reaction conditions, which might influence the performance of each catalytic system in a different manner.

In general, the regioselectivity in favor of the linear amine follows a trend similar to that observed for the hydroformylation of *trans*-oct-2-ene: an increase in bite angle results in an increase in regioselectivity for the linear product up to bite angles of 125°, whilst very wide bite angles produce decreases in regioselectivity, as was observed with **7**. The results strongly suggest that the regioselectivity during the initial hydroformylation step is retained during the subsequent steps of hydroaminomethylation.

Interestingly, the hydrogenation efficiency is strongly affected by the natural bite angle. Ligands with wide bite angles give faster hydrogenation, but this is at least in part also attributable to more facile hydrogenation of the linear enamine relative to the branched enamine. The rhodium complex(es) formed with **2** are inefficient even in hydrogenation of the *linear* enamine. Moreover, the concentrations




Scheme 5. Postulated intermediate cationic complexes of ligands **2**–**7**.

of the cationic rhodium species shown in Scheme 5 should be higher when ligands with wide bite angles are used, as such ligands facilitate the coordination of the oxygen in the ligand backbone to rhodium.[19] This cationic species is most probably involved in the hydrogenation step, as was found previously for the hydrogenation of aldehydes and alkenes in silica-based hydroformylation catalysts.

Hydroaminomethylation in the presence of the dibenzophosphole ligand **8** shows no enamine formation, indicating a very high hydrogenation activity and consequently a clean hydroaminomethylation procedure. The low level of conversion obtained for **8** relative to the rest of the ligands is attributed to slow catalyst pre-formation and demonstrates the importance of the nature of the phosphorus substituents as well as the ligand backbone.

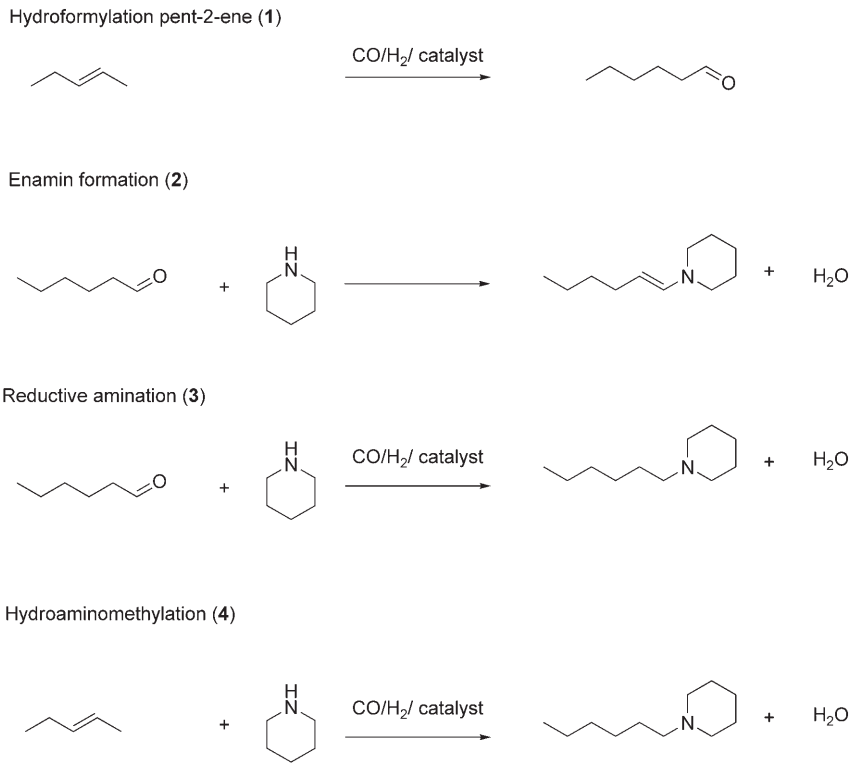
**High-pressure IR studies in situ**: To obtain more information on the influence of the catalyst on the individual reactions involved in this domino sequence we performed high-pressure infrared spectroscopy studies in situ. To the best of our knowledge no such investigations have previously been reported for hydroaminomethylation reactions.

In principle, the use of high-pressure infrared spectroscopy for hydroaminomethylation can be a powerful tool, especially since both intermediate products (the aldehyde ($\nu_{abs}$ = 1734 $cm^{-1}$) and the enamine ($\nu_{abs}$ = 1650 $cm^{-1}$)) and the aldol condensation side product ($\nu_{abs}$ = 1690 $cm^{-1}$) have strong and very specific absorption bands.

In a model study we used high-pressure IR to follow the hydroformylation of pentene to hexanal (Scheme 6, Reaction 1), the condensation reaction between hexanal and piperidine (Scheme 6, Reaction 2), the reductive amination of hexanal (Scheme 6, Reaction 3), and the overall hydroaminomethylation reaction (Scheme 6, Reaction 4). In these experiments the catalyst was preformed in situ from [Rh(cod)$_2$]$BF_4$ and four equivalents of **1** in the high-pressure IR autoclave at 125 °C under a $CO/H_2$ (1:4) atmosphere. Subsequently, the substrates were introduced into the high-pressure IR autoclave by use of an overpressure of hydrogen gas and difference IR spectra were recorded every 5–15 min to monitor the changes in the absorption bands of the aldehyde, enamine, and aldol condensation products. The results are depicted in Figure 1.

Comparison of the rate of the hydroformylation of pent-2-ene to hexanal (Scheme 6, Reaction 1; Figure 1, ◆) and the rate of the condensation reaction between piperidine and hexanal to form the enamine (Scheme 6, Reaction 2;




Scheme 6. Different reaction steps (**1**–**3**) in the hydroaminomethylation (**4**) process.

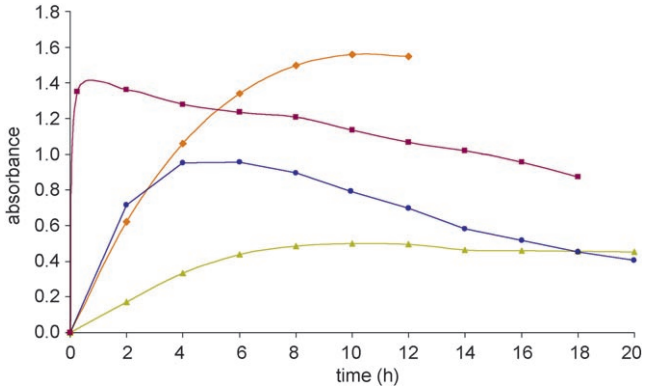



Figure 1. Various hydroaminomethylation reactions steps (sign, absorbance). Hydroformylation of pent-2-ene to hexanal in toluene/methanol (◆, hexanal), enamine formation and hydrogenation in toluene/methanol (■, enamine), and hydroaminomethylation in 2-MeTHF (●, enamine; ▲, hexanal). (See Experimental Section for reaction conditions and procedure.)

Figure 1, ■) at 125 °C shows that enamine formation is much faster than the hydroformylation step under hydroaminomethylation conditions. During hydroaminomethylation the formed aldehydes thus react directly with piperidine to form the enamine and water, and the enamine/water/aldehyde equilibrium is quickly established. If a catalyst system is not active in the subsequent hydrogenation reaction, aldehyde, water, and enamine remain, and the aldol condensation side product is formed.

When hexanal and piperidine are introduced into the autoclave with preformed [$RhH(CO)_2$(**1**)], the enamine formed is gradually hydrogenated to the desired amine. The hydrogenation reaction is in all instances much slower than the rate of hydroaminomethylation (Scheme 6, Reaction 3; Figure 1, ■), however, as not all enamine is hydrogenated, even after a prolonged reaction time of 18 h. It appears that the relative concentrations of aldehyde and enamine have a dramatic influence on the hydrogenation activity of the catalyst.

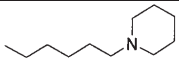
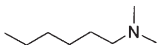
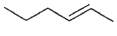
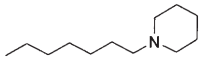
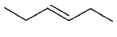
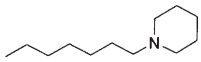
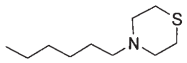
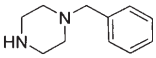
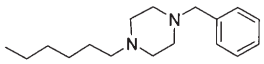
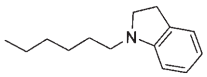
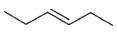
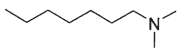
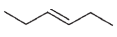
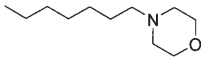
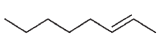
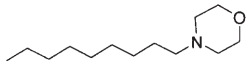
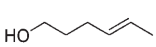
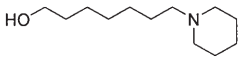
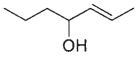
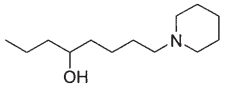
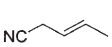
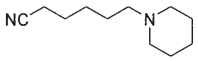
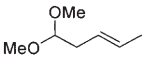
When the hydroaminomethylation (Scheme 6, Reaction 4) in methanol/toluene (1:1) was monitored by high-pressure IR, no absorptions corresponding to the aldehyde or enamine were observed. GC and GC/MS analysis of the reaction mixture corroborates the formation of *N*-hexylpiperidine. This observation strongly suggests that *the hydrogenation of the enamine is fast and not rate-determining* under these conditions.

The strong solvent effect on the hydroaminomethylation is shown by the reaction involving pent-2-ene and piperidine in 2-methyltetrahydrofuran (2-MeTHF). Here, hydrogenation of the enamine is less efficient, thus resulting in the formation of aldol side products (Figure 1, ●). It is common knowledge that the more polar environment that is obtained with MeOH increases the hydrogenation activity of Rh phosphine complexes. In 2-MeTHF, in addition to aldol condensation products, *N*-formylpiperidine, *N*-methylpiperidine, and *N*-hexanoylpiperidine are also formed, albeit in small amounts. The formation of these products can be explained in terms of a nucleophilic attack of the amine onto a rhodium acyl intermediate, which can take place under hydroaminomethylation conditions, either intra- or intermolecularly.[20]

**Selective hydroaminomethylation of functionalized internal olefins and mixtures**: Next, the generality of the catalytic procedure developed above was of interest to us. Obviously, the methodology would be of significant importance if it worked for the chemo- and regioselective hydroaminomethylation of a variety of internal olefins and olefinic mixtures, so the scope and limitations of the method were tested with the use of various unsaturated compounds and amines. Catalysis was performed under 5 bar of CO, with a reaction time of 16 h (Table 3). We were pleased to find that

Table 3. Hydroaminomethylation of various alkenes and amines.[a]

| Entry | Olefin | Amine | Major product | Conv.[%][b] | Amine selec. [%][c] | Yield [%][d] | *n*/iso[e] |
|---|---|---|---|---|---|---|---|
| 1 |  |  |  | 100 | 99 | 99 | 96:4 |
| 2 |  |  |  | 100 | 98 | 98 | 96:4 |
| 3 |  |  |  | 100 | 98 | 98 | 94:6 |
| 4 |  |  |  | 98 | 98 | 96 | 90:10 |
| 5 |  |  |  | 93 | 90 | 84 | 97:3 |
| 6 |  |  |  | 90 | 87 | 78 | 96:4 |
| 7[f] |  |  |  | 90 | 95 | 86 | 92:8 |
| 8 |  |  |  | 100 | 97 | 97 | 94:6 |
| 9 |  |  |  | 95 | 96 | 92 | 93:7 |
| 10 |  |  |  | 92 | 95 | 87 | 94:6 |
| 11 |  |  |  | 65 | 85[g] | 55 | 93:7 |
| 12[h] |  |  |  | 95 | 86[i] | 55 | 97:3 |
| 13 |  |  |  | 60 | 75[j] | 45 | 75:25 |
| 14 |  |  |  | 95 | 88 | 84 | 93:7 |
| 15 |  |  |  | 90 | 88 | 80 | 92:8 |
| 16 |  |  |  | 93 | 90 | 84 | 90:10 |
| 17 |  |  |  | 90 | 92 | 83 | 95:5 |
| 18 |  |  |  | 85 | 90 | 77 | 85:15 |

[a] Reaction conditions: CO (5 bar), $H_2$ (33 bar), **1**/Rh = 1:4, substrate (10 mmol (1:1)), methanol/toluene (1:1), temperature (125 °C). [b] Conversion of piperidine after 16 h. [c] Selectivity toward amines. [d] Yield of amines. [e] Linear to branched ratio. [f] Temperature (125 °C), time (36 h). [g] 8% of hexylpiperidine. [h] Temperature (135 °C), time (30 h). [i] 27% of the *N*,*O*-acetal of 5-hydroxy-*N*-(oct-1-enyl)piperidine is obtained as the major side product. [j] Hydrogenation of the substrate is the major problem.

not only lower (but-2-ene, pent-2-ene, hex-3-ene), but also higher aliphatic olefins (e.g., oct-2-ene) react well with different secondary amines (piperidine, morpholine, thiomorpholine, *N*-benzylpiperazine, 2,3-dihydroindole, *N*,*N*-dimethylamine and morpholine) to give the corresponding linear products in good to excellent yields (78–99%) and with good to very good selectivities (l/b > 90:10) (Table 3, entries 1–10).

Notably, functionalized internal olefins such as the linear and branched unprotected olefinic alcohols were also efficiently converted into interesting amino alcohols with high *n*/iso ratios (Table 3, entries 11, 12). In the case of an unprotected allylic alcohol, however, together with the major 5-hydroxy-*N*-octylamine, the corresponding *N*,*O*-acetal—the cyclization product of the 5-hydroxy-*N*-(oct-1-enyl)piperidine—was obtained with a high *n*/iso ratio (99:1) (Table 3, entry 12). To the best of our knowledge no linear hydroaminomethylation of functionalized internal olefins to linear products has been reported so far.[21] We were also pleased to find that the unsaturated pent-3-ene dimethylacetal underwent selective hydroaminomethylation with different secondary amines to produce protected γ-aminoaldehydes (Table 3, entries 14–16), which are known to be synthetically useful intermediates.[22]

Pent-2-enenitrile is a bulk intermediate for the production of nylon monomers. Upon hydroaminomethylation, pent-2-enenitrile gave moderate yields of the linear amine (Table 3, entry 13), so it has also been shown for the first time that industrially important 6-aminohexanoic acid derivatives are accessible from bulk monomers by hydroaminomethylation. Among the different reactions studied, the hydroaminomethylations of pent-2-enenitrile and hept-2-en-4-ol and those with indoline as amine needed longer reaction times and higher reaction temperatures for complete hydrogenation of the corresponding enamine. However, the regioselectivity observed with use of a cationic rhodium precursor together with POP-Xantphos (**1**) was excellent, typically 96:4 in favor of the linear product.

In addition to secondary amines, aliphatic primary amines also reacted well with internal olefins to give good linear to branched ratios (Table 3, entries 17 and 18). The major product formed in this reaction, however, is the imine formed in situ, due to problems of hydrogenation under these conditions.

Finally, the high activity and selectivity of the POP-Xantphos ligand (**1**) in the hydroaminomethylation of oct-2-ene and hex-3-ene prompted us to apply the catalyst system in the hydroaminomethylation of an industrial mixture of octenes (Scheme 7). In this industrial mixture, less then 2% of the terminal olefin is present at the thermodynamic equilibrium.[23] In order to ensure high linear selectivity, only the oct-1-ene should be hydroaminomethylated (with high linear selectivity) and the remaining >98% of the olefins should be converted into oct-1-ene. To our delight, treatment of the octene mixture with piperidine or *N*,*N*-dimethylamine gave *N*-nonylpiperidine or *N*,*N*-dimethylnonylamine with high chemo- and regioselectivities (85% and 81%, respectively). It is evident that the catalyst should be even more active and selective for the industrially more important C-4 feedstocks.

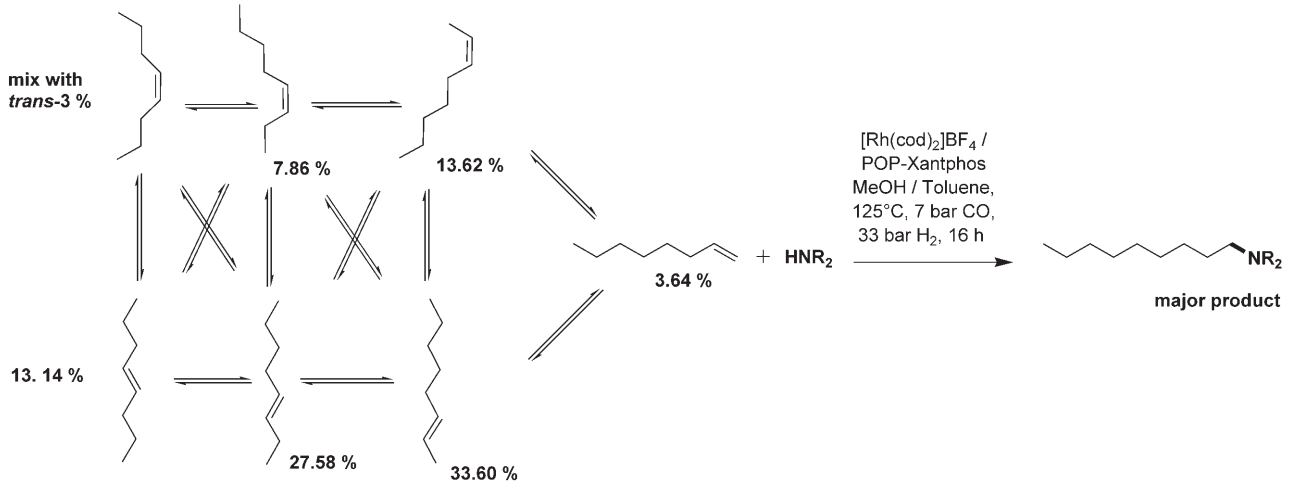
## Conclusion

A recently developed series of phenoxaphosphino- and dibenzophosphole-modified Xantphos-type ligands has been applied in rhodium-catalyzed hydroaminomethylation to produce synthetically important linear amines from economically and environmentally attractive *internal* olefins in very high yields and with very high regioselectivities (up to 96%). The natural bite angles of these ligands have a strong influence on the chemo- and regioselectivity of the reaction. Each separate step of the proposed hydroaminomethylation sequence has been monitored by high-pressure IR spectroscopy, which has shown that all reaction steps can take place under hydroaminomethylation conditions, although no aldehyde or enamine are observed under the catalytic conditions.

With the new catalyst system, functionalized internal olefins have been hydroaminomethylated for the first time in high yields and with unprecedentedly high regioselectivities (up to 96%). Remarkably, an industrial octene mixture is also selectively hydroaminomethylated to provide the linear amine.

## Experimental Section

**General procedures**: All air- or water-sensitive operations were performed by use of standard Schlenk techniques under purified argon. Toluene was distilled from sodium, 2-methyltetrahydrofuran from sodium/benzophenone. Cyclohexane, methanol, and piperidine were distilled from $CaH_2$. Pent-2-ene was either distilled or purified by percolation over neutral activated alumina. Chemicals were purchased from Acros Chimica, and Aldrich Chemical Co. 2,7-Di-*tert*-butyl-9,9-dimethyl-4,5-bis(10-phenoxaphosphino)xanthene (**1**),[11d] 4,5-bis(2,8-dimethyl-10-phenoxaphosphino)-10,11-dihydrodibenzo[*b*,*f*]oxepine (**2**),[11h] 4,5-bis(2,8-dimethyl-10-phenoxaphosphino)-2,7-dimethylphenoxathiin (**3**),[11h] 4,5-bis(2,8-dimethyl-10-phenoxaphosphino)-9-isopropylidenexanthene (**4**),[11h] 4,5-bis(2,8-dimethyl-10-phenoxaphosphino)-9,9-dimethylxanthene (**5**),[11h] 4,5-bis(2,8-dimethyl-10-phenoxaphosphino)phenoxazine (**6**),[11h] 4,5-bis(2,8-dimethyl-10-phenoxaphosphino)-10-phenylphenoxaphosphine (**7**),[11h] and 4,5-bis(9-dibenzo[*b*,*d*]phospholyl)-2,7-dimethylphenoxathiin (**8**)[11h] were prepared by literature procedures. Silica gel 60 (70–230 and




Scheme 7. First selective hydroaminomethylation of an olefinic mixture (R = alkyl).

230–400 mesh) from Merck was used for column chromatography. Infrared spectra were recorded on a Nicolet 510 FT-IR spectrophotometer. High-pressure IR spectra were measured in a 50 mL home-made stainless steel autoclave fitted with a mechanical stirrer and ZnS windows.[24] Synthesis gas ($CO/H_2$, 1:1, 99.9%) was purchased from Air Liquide. Gas chromatographic analyses were run on a Hewlett–Packard HP 5890 chromatograph with FID detector and a HP5 column (cross-linked 5% PhMe siloxane). GC/MS analyses were conducted on an Agilent-6890N instrument with a HP5 column.

**Hydroaminomethylation**: The hydroaminomethylation reactions were carried out in a 200-mL home-made stainless steel autoclave or in a Parr stainless steel autoclave (100 mL). In a typical experiment, the autoclave was loaded with a solution of $[Rh(cod)_2]BF_4$ (0.1 mol%), ligand (0.4 mol%), pent-2-ene (10.0 mmol), and piperidine (10.0 mmol) in a methanol/toluene mixture (1:1, 30 mL). Subsequently, the autoclave was pressurized with CO (7 bar) and hydrogen (33 bar) and heated to 125°C. After 12 h the autoclave was allowed to cool to room temperature and the gases were vented. The reaction mixture was dried over $MgSO_4$ and analyzed by GC with bis(methoxyethyl)ether as an external standard, and by GC/MS.

**High-pressure FT-IR experiments**: In a typical experiment the high-pressure IR autoclave was charged with a solution of $[Rh(cod)_2]BF_4$ (0.1 mol%) and four equivalents of ligand in a methanol/toluene mixture (1:1, 15 mL). The autoclave was purged three times with $CO/H_2$ (1:1, 10 bar), pressurized with CO (7 bar) and $H_2$ (28 bar), and heated to 125°C. Catalyst formation was monitored over time. Next, a mixture of pent-2-ene and piperidine was introduced with an overpressure of hydrogen to a total pressure of 50 bar, the pressure that would be reached at $T = 125$°C when the autoclave was pressurized with 7 bar CO and 33 bar $H_2$ at room temperature (as in the standard hydroaminomethylation method). IR spectra were recorded every 15 min. After 12 h, the autoclave was cooled to room temperature and the gases were vented. The reaction mixture was dried over $MgSO_4$ and analyzed by GC with use of bis(methoxyethyl)ether as an external standard and by GC/MS.

**Physical data for amines**

***N*-Hexylpiperidine**:[20] Yield: 98% (GC). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.26–2.33 (br m, 4H), 2.21 (t, $J$ = 7.9 Hz, 2H), 1.51 (quint, $J$ = 5.6 Hz, 4H), 1.41–1.45 (m, 2H), 1.38–1.43 (m, 2H), 1.21–1.28 (m, 6H), 0.81 ppm (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 60.05, 55.01, 32.41, 27.85, 27.24, 26.31, 24.87, 22.99, 14.41 ppm; GC-MS (EI, 70 eV): $m/z$: 169 $[M]^+$, 154, 140, 124, 98, 84, 70, 55, 41, 29; HRMS calcd for $C_{11}H_{23}N$ $[M]^+$: 169.18388; found: 169.18304.

***N*-Heptylpiperidine**:[25] Yield: 98% (GC). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.30–2.42 (br m, 4H), 2.25 (t, $J$ = 7.8 Hz, 2H), 1.63 (quint, $J$ = 5.6 Hz, 4H), 1.52–1.57 (m, 2H), 1.44–1.49 (m, 2H), 1.23–1.36 (m, 8H), 0.89 ppm (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 60.02, 55.05, 32.46, 30.01, 28.53, 27.96, 26.35, 25.06, 23.17, 14.45 ppm; GC-MS (EI, 70 eV): $m/z$: 183 $[M]^+$, 168, 154, 140, 124, 98, 84, 70, 55, 41, 29; HRMS calcd for $C_{12}H_{25}N$ $[M]^+$: 183.19869; found: 183.19810.

***N*-Nonylpiperidine**:[26] Yield: 99% (GC). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.47–2.53 (br m, 4H), 2.40 (t, $J$ = 7.6 Hz, 2H), 1.72 (quint, $J$ = 5.6 Hz, 4H), 1.62–1.66 (m, 2H), 1.55–1.60 (m, 2H), 1.34–1.46 (m, 12H), 1.01 ppm (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 60.08, 55.02, 32.27, 30.01, 29.95, 29.67, 28.17, 27.30, 26.32, 24.88, 23.05, 14.46 ppm; GC-MS (EI, 70 eV): $m/z$: 211 $[M]^+$, 196, 182, 168, 154, 140, 124, 110, 98, 84, 70, 55, 41, 29; HRMS calcd for $C_{14}H_{29}N$ $[M]^+$: 211.22819; found: 211.23000.

***N*-Hexylmorpholine**:[27] Yield: 92% (GC). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 3.63 (t, $J$ = 4.8 Hz, 4H), 3.32–3.69 (m, 4H), 2.24 (t, $J$ = 7.9 Hz, 2H), 1.40–1.43 (m, 2H), 1.19–1.26 (m, 6H), 0.81 ppm (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz): $\delta$ = 65.97, 58.25, 52.81, 30.79, 26.20, 25.53, 21.60, 13.04 ppm; GC-MS: $m/z$: 171 $[M]^+$, 156, 142, 126, 100, 84, 70, 56, 42, 29; HRMS calcd for $C_{10}H_{21}NO$ $[M]^+$: 171.16258; found: 171.16231.

***N*-Hexylthiomorpholine**: Yield: 92% (GC). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 3.68–3.75 (m, 4H), 3.50 (t, $J$ = 5.6 Hz, 4H), 2.80 (t, $J$ = 5.6 Hz, 2H), 2.47–2.54 (m, 2H), 1.42–1.53 (m, 6H), 1.03 ppm (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 58.50, 54.10, 30.80, 27.00, 26.20, 25.60, 21.60, 13.10 ppm; GC-MS (EI, 70 eV): $m/z$: 187 $[M]^+$, 126, 116, 88, 70, 57, 42, 29; elemental analysis calcd (%) for $C_{10}H_{21}NS$: C 64.22, H, 11.22, N 7.48, S 17.10; found: C 64.32, H 11.54, N 6.99, S 17.43.

***N*-Hexyl-*N*′-benzylpiperazine**:[28] Yield: 94% (GC). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.24–7.34 (m, 5H), 3.55 (s, 2H), 3.37–3.41 (m, 8H), 2.83 (t, $J$ = 5.2 Hz, 2H), 2.35–2.55 (m, 2H), 1.47–1.55 (m, 6H), 0.88–0.95 ppm (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 138.6, 129.5, 128.6, 127.4, 63.53, 59.36, 53.71, 53.54, 32.22, 27.88, 27.36, 23.01, 14.56 ppm; GC-MS (EI, 70 eV): $m/z$: 260 $[M]^+$, 189, 161, 146, 128, 114, 98, 91, 84, 70, 58, 42, 29; HRMS calcd for $C_{17}H_{28}N_2$ $[M]^+$: 260.22714; found: 260.22525.

***N*-(7-Hydroxyheptyl)piperidine**:[29] Yield: 97% (GC). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 3.66 (t, $J$ = 5.6 Hz, 2H), 3.45 (t, $J$ = 5.5 Hz, 2H), 3.02–3.07 (m, 4H), 2.40–2.66 (m, 2H), 1.80–1.95 (m, 2H), 1.42–1.76 (m, 6H), 0.79–0.93 ppm (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 62.73, 59.95, 54.93, 33.14, 29.76, 28.10, 27.00, 26.14, 26.09, 24.75 ppm; GC-MS (EI, 70 eV): $m/z$: 199 $[M]^+$, 182, 169, 154, 140, 124, 110, 98, 84, 70, 55, 41, 31; HRMS calcd for $C_{12}H_{25}NO$ $[M]^+$: 199.19333; found: 199.19362.

***N*-Hexyl-2,3-dihydro-1*H*-indole**: Yield: 86% (GC). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.66–7.52 (m, 4H), 3.58 (t, $J$ = 8.3 Hz, 2H), 3.39 (t, $J$ = 7.3 Hz, 2H), 3.20 (t, $J$ = 8.3 Hz, 2H), 1.75–1.81 (m, 2H), 1.57–1.67 (m, 6H), 1.16 ppm (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 153.2, 130.5, 127.7, 124.8, 119.8, 107.3, 53.53, 49.87, 32.21, 29.04, 27.88, 23.16, 21.91, 14.66 ppm; GC-MS (EI, 70 eV): $m/z$: 203 $[M]^+$, 188, 174, 158, 144, 132, 117, 91, 77, 65, 51, 41, 29; elemental analysis calcd (%) for $C_{14}H_{21}N$: C 82.70, H 10.41, N 6.89; found: C 82.58, H 10.21, N 6.60.

***N*-(5-Cyanopentyl)piperidine**: Yield: 45% (GC). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 3.41 (t, $J$ = 5.7 Hz, 2H), 3.24 (t, $J$ = 5.7 Hz, 2H), 2.39–2.43 (m, 4H), 2.20–2.30 (m, 6H), 1.70–1.78 ppm (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 119.6, 55.53, 49.99, 27.12, 27.01, 26.38, 25.76, 25.19, 20.55 ppm; GC-MS (EI, 70 eV): $m/z$: 180 $[M]^+$, 165, 151, 140, 124, 110, 98, 84, 70, 55, 41, 28; HRMS calcd for $C_{11}H_{20}N_2$ $[M]^+$: 180.16271; found: 180.17890.

***N*-(6,6-Dimethoxyhexyl)thiomorpholine**: Yield: 80% (GC). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.28 (t, $J$ = 5.5 Hz, 1H), 3.23–3.33 (m, 4H), 2.26–2.30 (m, 4H), 2.61 (s, 6H), 2.32–2.39 (m, 2H), 1.51–1.54 (m, 2H), 1.26–1.42 ppm (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 104.7, 59.68, 55.42, 52.79, 32.80, 28.34, 27.77, 26.79, 24.87 ppm; GC-MS (EI, 70 eV): $m/z$: 247 $[M]^+$, 232, 216, 200, 186, 172, 154, 142, 116, 98, 88, 81, 75, 55, 42, 29; HRMS calcd for $C_{12}H_{25}NO_2S$ $[M]^+$: 247.16060; found: 247.16057.

***N*-(6,6-Dimethoxyhexyl)dimethylamine**: Yield: 84% (GC). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.52 (t, $J$ = 5.7 Hz, 1H), 3.47 (m, 6H), 2.33–2.38 (m, 2H), 2.40 (s, 6H), 2.34–2.38 (m, 2H), 1.59–1.64 ppm (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 104.7, 60.03, 52.84, 45.72, 32.72, 27.93, 27.62, 24.85 ppm; GC-MS (EI, 70 eV): $m/z$: 189 $[M]^+$, 174, 158, 142, 114, 98, 81, 75, 58, 42, 29; HRMS calcd for $C_{10}H_{23}NO_2$ $[M]^+$: 189.17288; found: 189.17282.

***N*-(5-Hydroxyoctyl)piperidine**: Yield: 66% (GC). $^1$H NMR (400 MHz, [D$_6$]benzene): $\delta$ = 3.53 (m, 1H), 2.26 (m, 4H), 2.23 (t, $J$ = 6.8 Hz, 2H), 2.15–2.21 (m, 6H), 1.33–1.49 (m, 6H), 1.14–1.23 (m, 4H), 0.93 ppm (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 70.82, 59.35, 54.90, 40.46, 37.74, 27.09, 26.26, 24.94, 23.78, 19.40, 14.49 ppm; GC-MS (EI, 70 eV): $m/z$: 213 $[M]^+$, 196, 170, 184, 156, 140, 124, 110, 98, 84, 70, 55, 41, 29; HRMS calcd for $C_{13}H_{27}NO$ $[M]^+$: 213.20962; found: 213.20982.

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