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Rhodium-Catalyzed *Bis*-Hydroaminomethylation of Linear Aliphatic Alkenes with Piperazine

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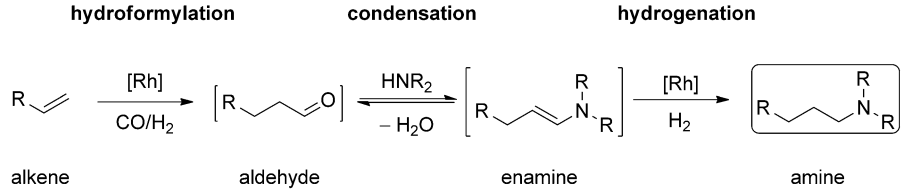
Abstract: An efficient protocol was developed to prepare a series of dialkylpiperazines *via* Rh-catalyzed *bis*-hydroaminomethylation of linear aliphatic alkenes with piperazine. The well-known Rh/Biphephos catalytic system was applied, yielding the desired dialkylpiperazines within six tandem catalytic steps, already at low catalyst loadings of 0.1 mol%. For the model alkene 1-octene, good yields and linearities of 80% and 77:23, respectively, were achieved under optimized conditions. Influences on the catalytic system regarding *n*/*iso* ratio, possible side reactions and the reaction path are discussed on the basis of yield *vs.* time plots and parameter optimization. With the developed general protocol, other linear, functionalized and branched substrates were effectively transformed to the corresponding linear *N,N*-disubstituted piperazines.

Keywords: carbonylation; high-pressure chemistry; homogeneous catalysis; hydroaminomethylation; hydroformylation; tandem catalysis

Introduction

Tandem reactions and related concepts involving transition metal catalysts that allow for the selective and atom-efficient synthesis of various functional groups and complex carbon scaffolds, within one reaction step, have attracted growing attention in recent years.[1–16] Their inherent advantage of reducing both waste and time is very attractive for academic researchers as well as industrial applications. Hence, more and more general concepts for the merger of two or more catalytic steps without the need for intermittent work-up of the intermediates have been developed. Of particular usefulness are tandem catalytic systems that allow for the selective synthesis of target molecules, which would not be accessible by a multistep approach, because the respective intermediate is not or only impracticably isolable. Besides the development of new methodologies for the combination of reaction steps, including necessary strategies to address catalyst incompatibilities and time resolved transformations,[17,18] the extension of existing tandem catalytic systems for example, for the conversion of renewable resources, has also great potential.[16]

Tandem catalytic systems triggered by hydroformylation for the transformation of olefins have emerged as a powerful platform for developing and expanding tandem catalytic strategies, not least due to the versatile chemistry of the aldehyde moiety.[19–22] One of the most prominent examples for tandem reactions under hydroformylation condition is hydroaminomethylation (HAM).[23,24] In this three-step tandem reaction amines are formed from olefins, typically catalyzed by ligand modified rhodium catalysts (Scheme 1). HAM consists of an initial hydroformylation of an olefin in the presence of syngas to form an aldehyde, which subsequently undergoes condensation with the amine substrate present. The thus formed enamine/imine is finally hydrogenated to the corresponding amine, catalyzed by the applied rhodium species. Hence, according to the taxonomy of dos Santos and Fogg, HAM is referred to as an auto-tandem catalytic reaction.[6] The development of HAM goes back to the pioneering work of W. Reppe on carbonylation of alkynes and alkenes in the 1940s at BASF/Ludwigshafen (Germany).[25,26] But only in the last two decades, it became a general tool for the production of various amines (fine chemicals, pharmaceuticals, etc.) from



Scheme 1. General hydroaminomethylation (HAM) of an alkene with a secondary amine.

olefins, particularly due to the work of Eilbracht,[27–33] Beller,[23,34–36] and Zhang.[37–42]

Generally, hydroaminomethylations are, however, limited to the aforementioned three auto-tandem catalytic steps and only scattered examples deal with the extension of this sequence. Among them are combinations of HAM with concurrent esterification of the applied amino acid,[43] formation of the required syngas atmosphere from CO_2 by preliminary reversed water-gas shift (RWGS) reaction[31] and the access to linear amines from internal alkenes by isomerizing hydroaminomethylation.[38,44–46]

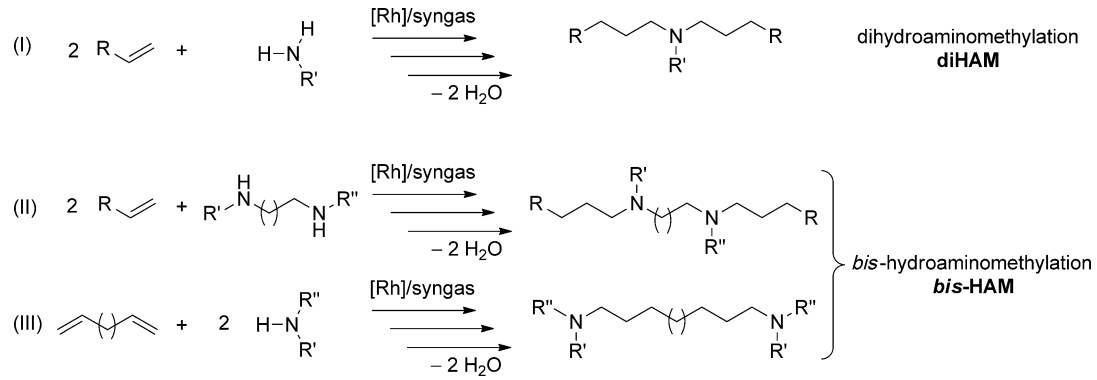
Another methodology for synthetic intensification of HAM is by principally "doubling" the reaction steps, which allows for the formation of two new C–N bonds under the same reaction conditions. Particularly for the formation of more complex structures, this appears a suitable approach. Two general principles exist in the two-fold HAM:

(i) The application of primary amines potentially leads to the formation of tertiary amines *via* the intermediate secondary amines, if a stoichiometric amount of olefin is present [reaction (I), Scheme 2]. For differentiation, we term this process "dihydroaminomethylation (diHAM)". If ammonia is applied as the amine substrate, a three-fold hydroaminomethylation is possible, and under some conditions also very likely, which analogously is referred to as "trihydroaminomethylation (triHAM)"

(ii) By employing a substrate bearing two reactive sites, a two-fold hydroaminomethylation is conceivable, in which two new independent C–N bonds are formed under the same reaction conditions [reactions (II) and (III), Scheme 2]. This can either be accomplished by applying a diolefin or a diamine in combination with the corresponding stoichiometric amount of amine or olefin, respectively. We refer to the term "*bis*-hydroaminomethylation (*bis*-HAM)" for these reactions, in accordance with Eilbracht et al.[27]

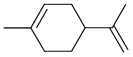
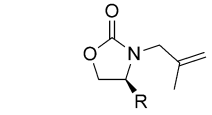
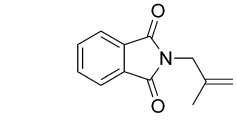
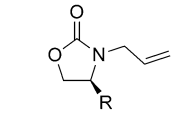
Only a few examples can be found in which either of the aforementioned concepts for the two-fold HAM have been achieved, and no general protocol has been developed so far.[19] In particular, *bis*-hydroaminomethylations applying a diamine and a monoolefin are especially rare. Table 1 summarizes *bis*-hydroaminomethylations in which piperazine (**3**), the most frequently used diamine component, was applied.

Notably, most of the olefins previously used (Table 1) readily formed linear aldehydes in the initial hydroformylation with high *n:iso* selectivities, as intended by the authors, due to their structure (cyclic or α-branched). Thus, no ligands were needed. In only a single example, a terminal alkene with no substituent at the α-position was applied but with major modification.[30] The initial hydroformylation of an *N*-allyloxazolidin-2-one derivative was conducted in the absence of piperazine, under the influence of Biphe-



Scheme 2. Distinction between dihydroaminomethylation [diHAM, (I)], and *bis*-hydroaminomethylation [*bis*-HAM, (II) and (III)].

Table 1. *Bis*-hydroaminomethylations of piperazine (**3**). NBD = norbornadiene; cod = cyclooctadiene.

Olefinic substrate	Category	Catalytic system	Tandem catalytic?	Yield [%]	Linearity	Reference
 cyclohexene	internal alkene	$[Rh(NBD)((CH_3)_2PPh)_3]^+PF_6^-$, no ligands	**yes**	70	–	[47]
 limonene	vinylidene compound	$HRh(CO)(PPh_3)_3$, no ligands	**no**, no *bis*-HAM products observed	89	not given	[48]
 *N*-(2-methylallyl)oxazolidin-2-ones	vinylidene compound	$[Rh(cod)Cl]_2$, no ligands	**yes**	81–91	not given	[30]
 2-(2-methylallyl)isoindoline-1,3-dione	vinylidene compound	$[Rh(cod)Cl]_2$ no ligands	yes	95	not given	[33]
 *N*-(allyl)oxazolidin-2-ones	allylic compound	$[Rh(cod)Cl]_2$ Biphephos as ligand	**no**, piperazine not present in 1st step	95	87:13	[30]
	linear aliphatic 1-alkene	presented in this work				

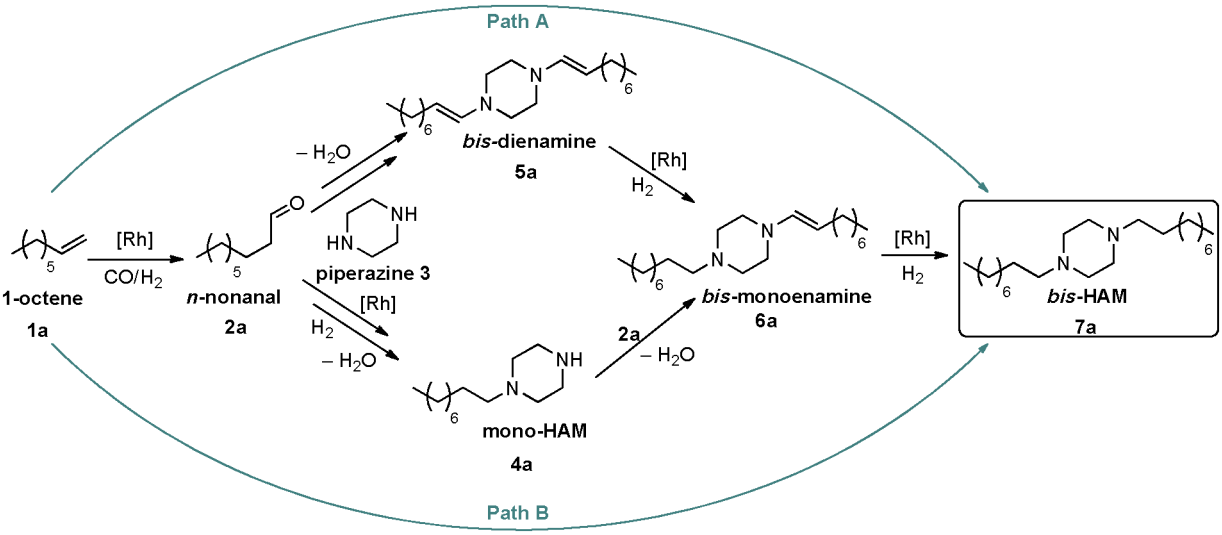
phos as ligand, to achieve reasonable selectivities for the linear aldehyde of 87% after 48 h with 1 mol% $[Rh(cod)Cl]_2$. In a second step, piperazine and additional [Rh] were added and the reductive amination of the linear aldehyde then furnished the desired *bis*-HAM product in a one-pot manner.

In our ongoing studies concerning hydroaminomethylations and the intensification of tandem catalytic protocols, we were interested to see whether *bis*-HAM of linear, unbiased alkenes with piperazine as the diamine component is possible, without the need for intermittent perturbation. We chose the [Rh]/Biphephos system for our investigations, as this was already shown to catalyze both the hydroformylation with high linear selectivities and the reductive amination.[30,49,50] Moreover, 1,4-*bis*-alkylated piperazines are accessible in *bis*-HAM yields, which have been otherwise synthesized by employing mono-alkylated piperazines under hydroaminomethylation conditions.[34,44,49–51] Additionally, symmetrical *bis*-alkylated piperazines exhibit biological activity and hence, their straightforward synthesis is of considerable interest.[52–54]

We herein wish to report our investigations towards the selective, *bis*-hydroaminomethylation of linear 1-alkenes with piperazine as the diamine component applying a ligand modified rhodium catalytic system. Additional to the development of a general protocol for the conversion of terminal olefins by optimizing the reactions conditions, the limitations and possible side reactions are discussed as well.

Results and Discussion

For optimizing the reaction conditions, we chose 1-octene (**1a**) and piperazine (**3**) as our model substrate system. Scheme 3 displays the anticipated reaction paths and thus the desired product **7a** and corresponding intermediates. Besides the linear aldehyde **2a**, branched aldehydes may be formed in the initial hydroformylation, which potentially result in the formation of regioisomers of each intermediate and products, which are not displayed in Scheme 3 for the sake of clarity. The final hydrogenation of enamines to amines in HAM reactions has already been revealed as the rate-limiting step in preliminary contributions. Hence, we envisioned the reaction to proceed *via bis*-dienamine intermediates **5a** and **6a** (Path A, Scheme 3). However, a reaction path *via* mono-HAM intermediate **4a** is also plausible (Path B, Scheme 3). The catalytic species was derived *in situ* from the ap-



Scheme 3. Intended reaction paths for the formation of linear *bis*-HAM product **7a**. Path A: *via bis*-dienamine **5a**; Path B: *via* mono-HAM intermediate **4a**. Possible branched derivatives and stoichiometric coefficients omitted for clarity.

plied precursor $Rh(acac)(CO)_2$ and Biphephos as ligand. Other ligands (Figure 1) did not show sufficient chemoselectivity in preliminary investigations. Toluene was chosen as solvent at a temperature of 120 °C and a syngas pressure of 40 bar, both represented typical HAM conditions (see the Supporting Information for experiments with other solvents).

In initial investigations, we noticed a strong influence of the syngas ratio upon the outcome of the experiment. Therefore, the syngas ratio was first optimized systematically in a range of H_2/CO from 1 to 4 (Table 2). Besides the anticipated intermediates and products displayed in Scheme 3, side products resulting from unintended side reactions were identified in the reaction mixture after *bis*-hydroaminomethylation (Scheme 4). Hydrogenation of the starting alkene **1a** [reaction (I)] to alkane **8a** and aldol condensation of the intermediate aldehyde **2a** [reaction (II)] to aldol condensate **9a** are typical side and consecutive reactions under hydroformylation conditions. However, a third yet literature unknown reaction proceeded under our chosen reaction conditions, which led to products with higher molecular mass (by GC-MS) and longer retention time (GC-FID) as the desired *bis*-HAM product **7a**. We assumed the formation of higher condensates **10a** (more than two equivalents aldehyde per piperazine molecule) by consecutive reactions of the intermediate mono-HAM product **4a** and the aldol condensation product **9a** [reaction (III)]. This transformation and the resultant structure of the higher condensates **10a** will be explored in detail later on.

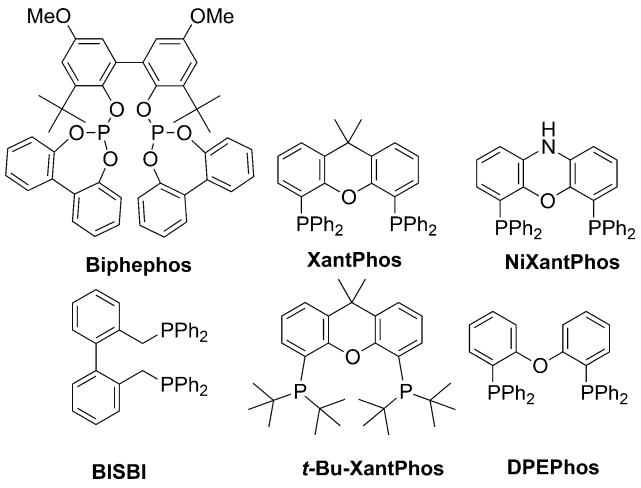
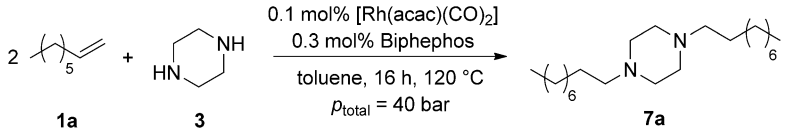


Figure 1. Ligands applied in the *bis*-hydroaminomethylation of 1-octene with piperazine.

In all experiments from the initial syngas ratio variation, both 1-octene (**1a**) and piperazine (**3**) were fully converted and *bis*-HAM product **7a** represented the major product in the reaction mixture. As expected, hydrogenation of the starting alkene was more prominent the higher the syngas ratio (H_2/CO) was, with 18% yield for *n*-octane (**8a**) at a ratio of 4 (entry 1.7). A comparable trend was found for the mono-HAM product **4a**, which was yielded in 14% at a syngas ratio of 4 (entry 1.7). Both hydrogenation and mono-HAM product formation were only low until a syngas ratio of 2. Highest yields for the desired *bis*-HAM products **7a** were achieved with a syngas ratio between 1 and 2 (entries 1.1–1.5) ranging from 70% to 86%. Nevertheless, especially the *n:branched* ratios within the products seemed to be highly sensitive to the syngas ratio: with increasing hydrogen content from 1 to 1.35, linearity increased while higher ratios of >1.5 resulted in decreasing linearity. Highest linear selectivity of 77:23 was observed at a syngas ratio of 1.35 H_2/CO representing the best compromise

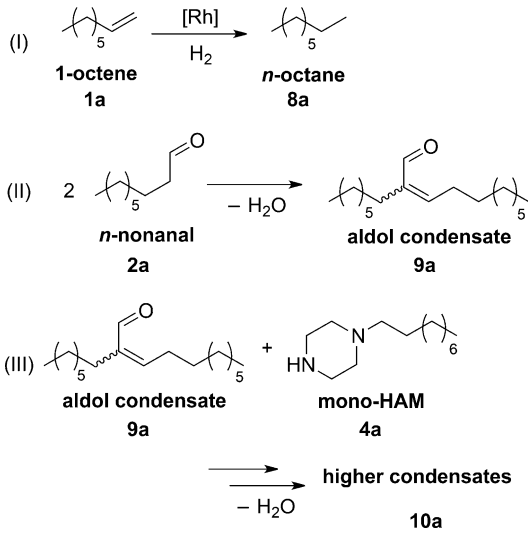
Table 2. *Bis*-hydroaminomethylation of 1-octene with piperazine: Initial screening of syngas ratio.[a]



		Substrates		Intermediates		Product		Side Products		
Entry	H_2/CO ratio	X_{1a}	X_3	Y_{4a}	Y_{5a+6a}	Y_{7a}	linear:branched	Y_{8a}	Y_{9a}	Y_{10a}
1.1	1	>99	>99	3	0	82	61:39	4	<1	8
1.2	1.2	>99	>99	7	1	70	66:34	4	<1	10
1.3	1.35	>99	>99	5	<1	80	77:23	3	<1	10
1.4	1.5	>99	>99	2	0	86	58:42	4	<1	4
1.5	2	>99	>99	6	0	77	63:37	6	<1	5
1.6	3	>99	>99	13	6	50	59:41	12	<1	3
1,7	4	>99	>99	14	5	37	35:65	18	<1	1
1.8[b]	1.35	>99	>99	16	10	35	82:18	11	2	4
1.9[c]	1.35	>99	>99	2	<1	82	65:35	5	<1	10

[a] *Reaction conditions:* n_{1a} = 5 mmol, **3**/**1a** = 0.5, 0.1 mol% $Rh(acac)(CO)_2$, 0.3 mol% Biphephos, 5 mL toluene, p_{total} = 40 bar, T = 120 °C, t = 16 h, 750 rpm. Conversions (X) and yields (Y) in [%], determined *via* GC-FID with dibutyl ether as internal standard.
[b] p_{total} = 20 bar.
[c] p_{total} = 50 bar,

between overall yield and linearity (entry 1.3). Both product linearity and yield showed to be influenced not only by the ratio but also by the total pressure of the syngas. Whereas a low pressure of 20 bar favored product linearity (82%) at low yield for *bis*-HAM product **7a** (35%), a higher pressure of 50 bar yielded 82% *bis*-HAM product **7a** at only moderate linearity (65%) (entries 1.8 and 1.9). At 20 bar syngas (H_2/CO 1.35), the activity of the whole reaction sequence was lower, resulting in an incomplete hydroaminomethylation (entry 1.8).



Scheme 4. Observed side-products and their formation in the *bis*-hydroaminomethylation of **1a** and **3**.

Considering typical *n:iso* ratios for the hydroformylation of linear α-olefins with the [Rh]/Biphephos system of about 95%,[55,56] these rather low linearities were unexpected. Hence, we performed test reactions to explore whether hydroformylation under our chosen conditions is generally unselective or if the low regioselectivity is based on other phenomena (Table 3).

Indeed, in the absence of an amine component, a regioselectivity in the hydroformylation of 1-octene (**1a**) of 95:5 with full conversion after 2 h was achieved under similar reaction conditions compared to entry 1.3. Only minor hydrogenation to octane (**8a**, 5%) and negligible yield for aldol condensation product **9a** were observed (entry 2.1). Comparable yields have been observed when equimolar amounts of water were added (entry 2.2). Hence, a drastic change in the regioselectivity, for example, by substantial hydrolysis of the diphosphite ligand by water liberated during condensation under HAM conditions, is not observed. The presence of equimolar amounts of a tertiary diamine component (tetramethylethylenediamine), which intrinsically is unsuitable for HAM, lowered the hydroformylation activity (entry 2.3). Under these conditions, conversion of **1a** was not completed, but regioselectivity was almost untouched (97%, entry 2.2). We therefore deduce that diamines do not coordinate to the rhodium metal center to such an extent that regioselectivity changes significantly. With *N*-methylpiperazine, the corresponding HAM product was formed in 67% yield with a linearity of 93:7 (entry 2.3). We consequently assumed the regioselectivity in the hydroformylation under our chosen *bis*-

Table 3. Test reactions for investigating *n*:*branched* ratios under different conditions.[a]

		Substrates		Products		Side Products		
Entry	Additional reagent	X_{1a}	$X_{diamine}$	$Y_{main\ product}$	linear:branched	Y_{8a}	Y_{9a}	Y_{10a}
2.1[b]	none	>99	–	94	95:5	5	<1	–
2.2[b]	H_2O	>99	–	93	94:6	6	1	–
2.3[c]	tetramethylethylenediamine	94	–	86	97:3	7	1	–
2.4[d]	*N*-methylpiperazine	>99	88	67	93:7	4	5	18

[a] *Reaction conditions:* n_{1a} = 5 mmol, $n_{additional\ reagent}$ = 5 mmol, 0.1 mol% $Rh(acac)(CO)_2$, 0.3 mol% Biphephos, 5 mL toluene, p_{total} = 40 bar (H_2/CO = 1.35), T = 120 °C, t = 2 h, 750 rpm. Conversions (X) and yields (Y) in [%], determined *via* GC-FID with dibutyl ether as internal standard.
[b] Main product: C_9 aldehydes.
[c] Main product: C_9 aldehydes, diamine/olefin 0.5.
[d] Main product: 1-methyl-4-nonylpiperazine, diamine/olefin = 1.

HAM conditions to be 93:7. Noteworthy, by applying the piperazine derivative (entry 2.3), aldol condensation products **9a** and higher condensates **10a** occurred, this led to the assumption that these side reactions were organocatalyzed rather than Brønsted base-catalyzed.

In the contemplation of *bis*-HAM product linearity, only those products are designated "linear" that result from the two-fold condensation of *n*-nonanal (**2a**) with piperazine. Hence, statistically a maximum linearity for *bis*-HAM products of 0.93 × 0.93 = 0.86 (≙86:14) can be achieved if the regioselectivity of 93:7 from entry 2.3 is considered. In fact we observed a maximum selectivity to the linear product of 77% (entry 1.3). Consequently, *n*-nonanal (**2a**) preferably reacted in the observed side reactions [reactions (II) and (III), Scheme 4], in comparison to branched aldehydes. Indeed, GC-FID and GC-MS analyses revealed that aldol condensation products **9a** were exclusively and higher condensates **10a** were almost fully formed from linear aldehyde **2a**. As a result, the *n*:*branched* ratio was *in situ* lowered (Δ in Figure 2) by subsequent reactions of the linear aldehyde **2a** to either aldol condensation product **9a** or higher condensates **10a**, leading to an overall lower linearity within the desired *bis*-HAM products **7a**.

With these assumptions, a general optimization of the reaction conditions was performed, in order to maintain high linearity within hydroformylation and to promote the path towards the desired *bis*-HAM products. In Table 4, a summary of the performed variations from the general conditions (Table 1, entry 1.3) is shown, for detailed results please see the Supporting Information.

Highest yields of 91% for the desired products **7a** were achieved at low ligand loadings of 0.1 mol% due to a high hydroformylation activity of the ligand-free Rh-centers, but at the expense of linearity (entry 3.2). Ligand excess almost completely inhibited the formation of *bis*-HAM products in favor of higher condensates **10a** (entry 3.3). Substoichiometric amounts of piperazine of 0.2 equivalents as expected furnished only low yield (33%) for *bis*-HAM product **7a**, although high linearities were observed (87%, entry 3.4). 0.4

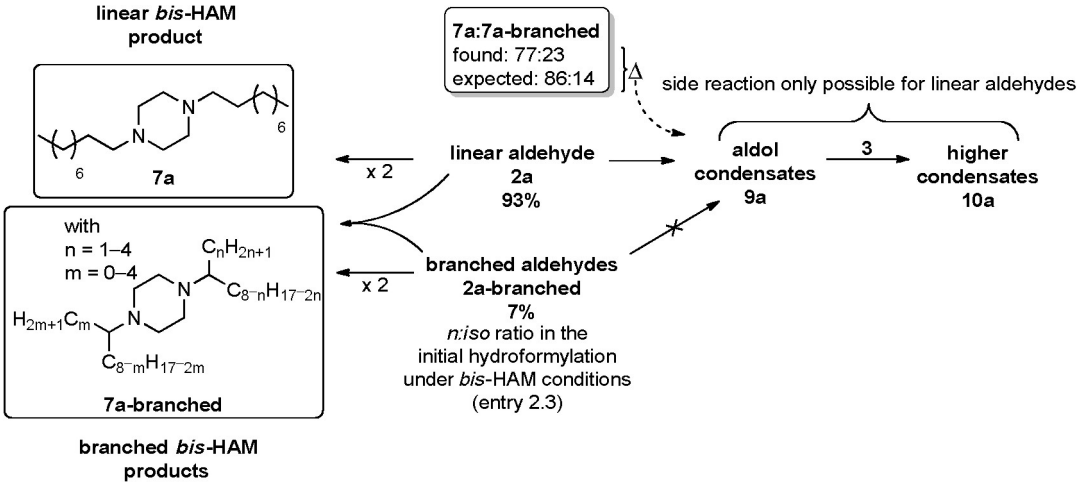
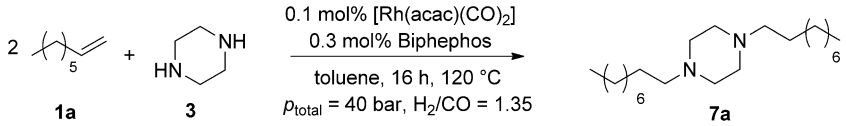


Figure 2. Formation of linear *vs.* branched *bis*-HAM products.

Table 4. Screening of various reaction parameters.[a]



Entry	Exception from general conditions	Substrates X_{1a}	X_3	Intermediates Y_{4a}	Y_{5a+6a}	Products Y_{7a}	linear:branched	Side Products Y_{8a}	Y_{9a}	Y_{10a}
3.1	none	>99	>99	5	<1	80	77:23	3	<1	10
3.2	0.10 mol% Biphephos	>99	>99	2	<1	91	62:38	4	<1	2
3.3	0.62 mol% Biphephos	>99	72	3	13	4	(46:54)	10	1	26
3.4[b]	0.2 equiv. piperazine	>99	>99	<1	1	33	87:13	8	12	7
3.5[c]	0.4 equiv. piperazine	>99	>99	<1	<1	75	68:32	4	6	5
3.6	$T=80$ °C	>99	>99	9	12	39	56:44	5	5	4
3.7	$T=100$ °C	>99	>99	12	0	67	55:45	4	<1	9
3.8	T=140 °C	>99	>99	16	0	47	62:38	5	<1	3

[a] *General conditions:* $n_{1a}=5$ mmol, **3**/**1a**=0.5, 0.1 mol% Rh(acac)$(CO)_2$, 0.3 mol% Biphephos, 5 mL toluene, $p_{total}=40$ bar (H_2/CO=1.35), $T=120$ °C, $t=16$ h, 750 rpm. Conversions (X) and yields (Y) in [%], determined *via* GC-FID with dibutyl ether as internal standard.
[b] 33% aldehydes were observed.
[c] 5% aldehydes

equivalents piperazine gave 75% yield for the desired *bis*-HAM products, despite lower selectivity to the linear product (68%, entry 3.5). Under these conditions, aldehyde intermediates **2a** and aldol products **9a** were observed for the first time to a significant extent *in lieu* of a reaction partner towards HAM products. A lower reaction temperature of 80 °C was not sufficient for complete enamine hydrogenation (entry 3.6) while at 100 °C linearity was low (entry 3.7, 55%). A higher reaction temperature of 140 °C also led to lower *bis*-HAM yield of only 47% at moderate linearity (62%, entry 3.8).

At the optimized reaction conditions, 80% of the desired *bis*-HAM products **7a** were obtained with a linearity of 77% within six auto-tandem catalytic steps. During the course of optimization, some rele-

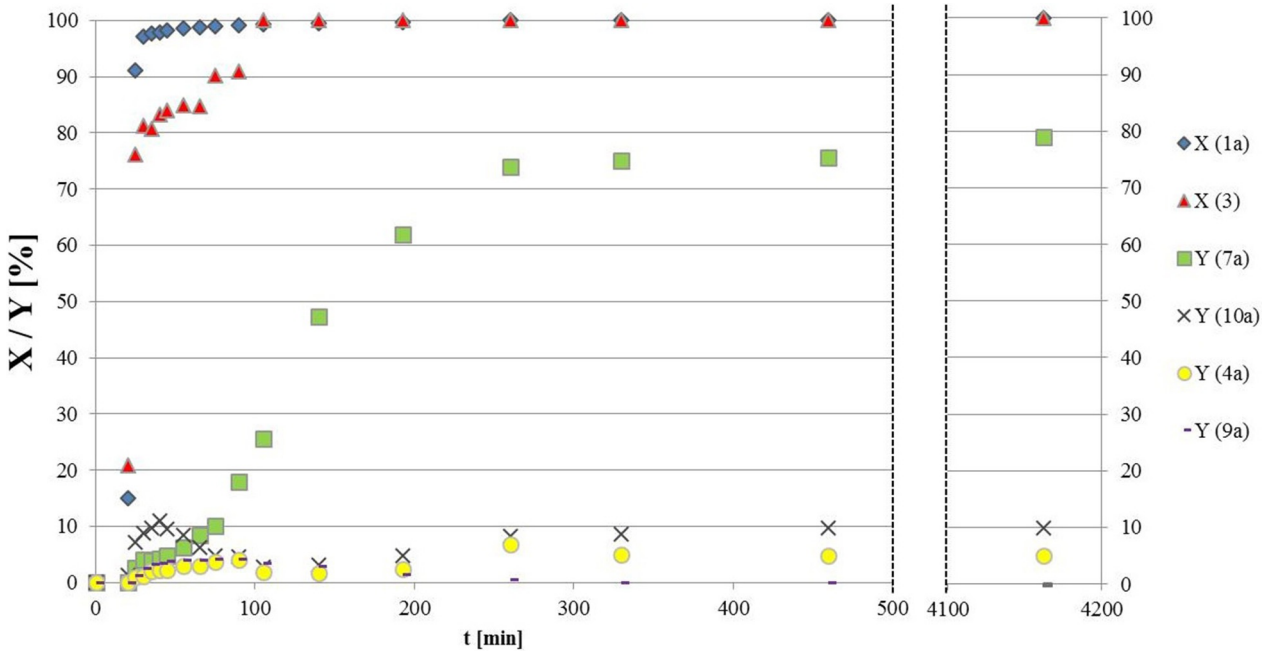


Figure 3. Yield (Y) and conversion (X) *vs.* time plot in the *bis*-HAM of 1-octene (**1a**) with piperazine (**3**). *Reaction conditions:* $n_{1a}=68.18$ mmol, **3**/**1a**=0.5, 0.1 mol% Rh(acac)$(CO)_2$, 0.3 mol% Biphephos, 68 mL toluene, $p_{total}=40$ bar (H_2/CO=1.35), $T=120$ °C, 750 rpm. Conversions (X) and yields (Y) in [%], determined *via* GC-FID with *n*-dodecane as internal standard.

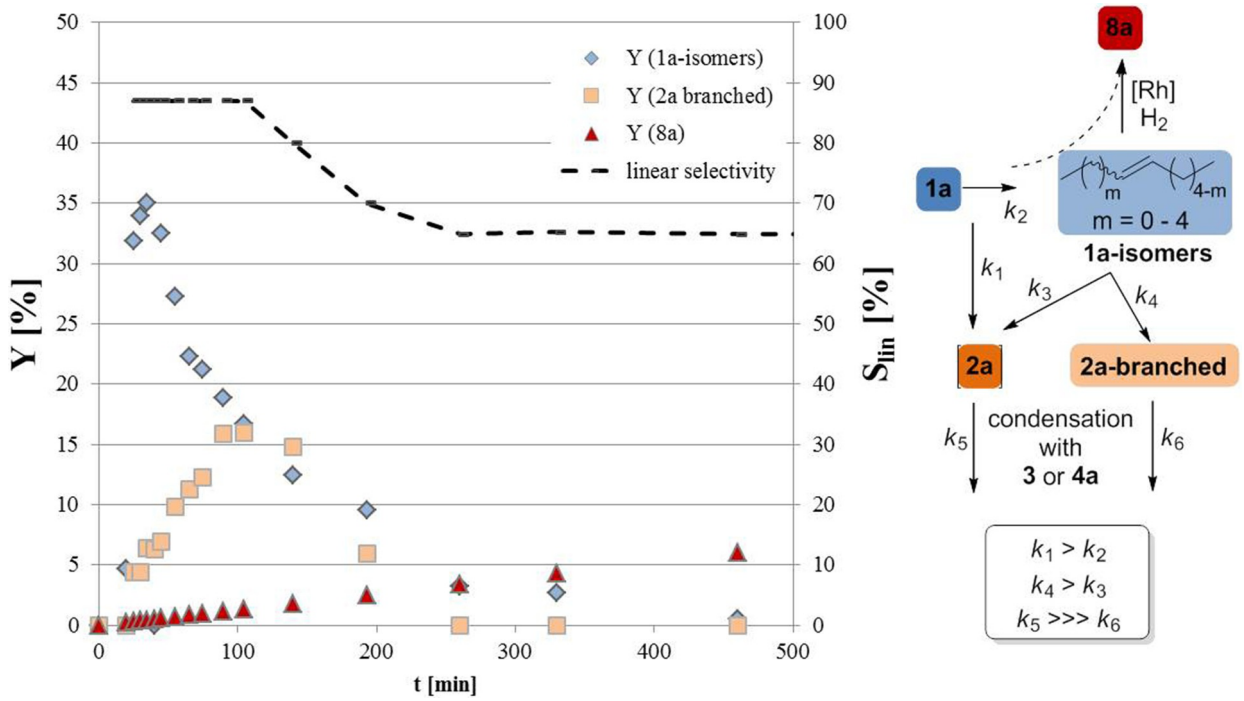


Figure 4. Yield (Y) *vs.* time plot of the C_8/C_9 fraction in the *bis*-HAM of 1-octene (**1a**) with piperazine (**3**). *Conditions:* see Figure 3.

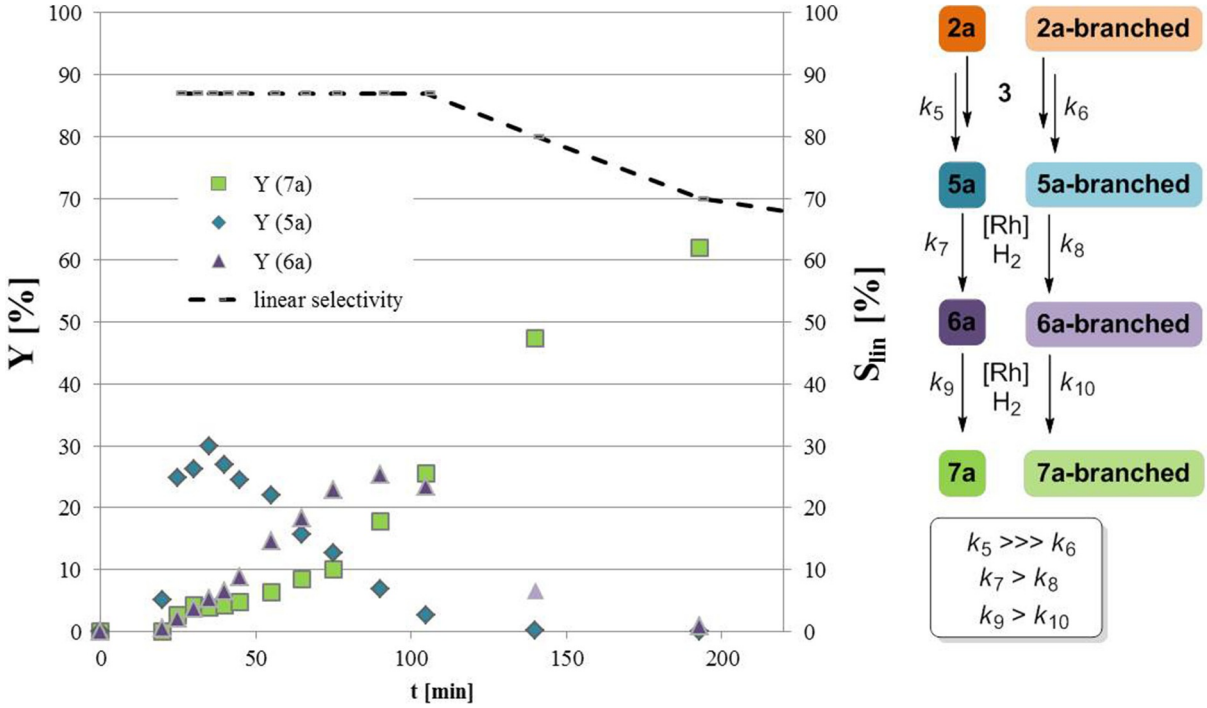


Figure 5. Yield (Y) *vs.* time plot of the *bis*-product fraction in the *bis*-HAM of 1-octene with piperazine. *Conditions:* see Figure 3.

vant aspects of the reaction were revealed and insight into the promotion of different paths by relevant reaction parameters was gained. In order to understand this complex reaction network in even more detail, conversion and yield *vs.* time plots were recorded on a larger reaction scale in a 300-mL autoclave (Figure 3, Figure 4, and Figure 5).

Conversion (X) of both starting materials was fast with 1-octene (**1a**) being almost fully consumed already after about 40 min. Piperazine (**3**) was fully converted after only 100 min. *Bis*-HAM product formation already started after about 30 min but only became significant after 100 min, and reached already 74% yield after 260 min. Prolongation of the reaction time to 70 h (4162 min) only led to an increase in yield of about 5%. Aldol condensation product **9a** behaved like a typical intermediate, proving that indeed a subsequent reaction consumed it. Parallel to the conversion of aldol intermediate **9a**, the yield for the higher condensates **10a** increased, giving evidence that indeed higher condensates contain aldol intermediates as proposed in Scheme 4.

The fact that 1-octene (**1a**) and piperazine (**3**) were not converted in parallel motivated us to take a more detailed look in the progress of the C_8 and C_9 fraction of the product mixture (Figure 4).

We were quite surprised to see a good share of the converted alkene **1a** being isomerized to internal olefins **1a-**isomers. After only 35 min, 35% internal isomers were formed, which subsequently reacted further until no alkenes were detected in the product mixture after 460 min. However, considering the early consumption of **1a** as seen in Figure 3, formation of **2a** is faster than isomerization ($k_1 > k_2$, Figure 4). In contrast, no linear aldehyde **2a** was detected throughout the reaction sequence, despite intermediate yields for the branched aldehydes **2a**-branched of up to 16%. Hence, condensation of *n*-nonanal (**2a**) with **3** is much faster than condensation of branched aldehydes ($k_5 >>> k_6$, Figure 4). A very interesting insight into the progress of the reaction was given by the selectivity of linear *bis*-HAM products **7a**: until a reaction time of about 100 min, selectivity towards linear products was on a high level with 87%. Noteworthy, this is the level that would result if a *n:branched* ratio of 93% in the initial hydroformylation is considered (Figure 2). After 100 min, branched aldehydes started to react and selectivity decreased until no branched aldehydes were left and the final *n:branched* ratio for the *bis*-HAM products **7a** was maintained throughout the reaction sequence.

Remarkably, although 35% internal olefins **1a**-isomers were present, not all of these were transformed to branched aldehydes, as can be seen from the final linearity. Hence, not only the isomerization of terminal into internal olefins was feasible under the chosen conditions, but also the back reaction of **1a**-isomers to **1a**, which was subsequently converted into linear aldehyde **2a**. However, once internal alkenes have been formed, the formation of branched aldehydes over the linear aldehyde **2a** dominated ($k_4 > k_3$, Figure 4). This behavior of isomerizing hydroformylation of terminal olefins into linear aldehydes with a [Rh]/Biphephos system was previously described by Carpentier et al.[55] The formation of the hydrogenation product **8a** followed a linear trend, presumably due to its formation from internal olefins, which have almost equal tendency to hydrogenation.

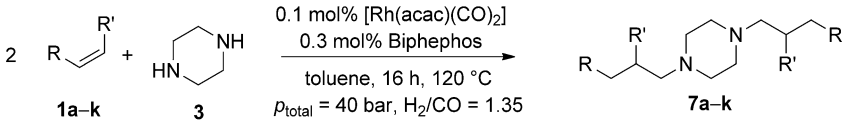
One could conclude that for highest linearity of *bis*-HAM products **7a**, a termination of the reaction after 100 min would be sufficient. However, the detailed analysis of the reaction progress within the fraction of *bis*-condensation products (**5a**, **6a**, **7a**) revealed that hydrogenation of the enamine intermediates remained the rate-limiting step and, hence, hydrogenation was only completed after 200 min (Figure 5). Additionally, a minor amount of *bis*-monoenamine species **6a** remained in the product mixture. We assumed that hydrogenation of branched enamines, which resulted from the condensation of **3** with branched aldehydes **2a**-branched, is slower ($k_7 > k_8$; $k_9 > k_{10}$, Figure 5). As a result, conversion of *bis*-monoenamine species **6a** after 200 min furnished branched *bis*-HAM products **7a**-branched, rather than linear products, which matched the further decrease in linearity after most of the branched aldehyde and the *bis*-dienamine was converted. On the other hand, one can conclude that *bis*-HAM products **7a** indeed arose from two different reactions paths:

(i) At first, hydroformylation of **1a** led to *n*-nonanal (**2a**) which directly condensed with **3** to form *bis*-dienamine intermediate **5a** as intended in Scheme 3, Path A and shown in Figure 5. This intermediate is subsequently hydrogenated to the desired *bis*-HAM product. *Via* this Path A, most of the desired linear *bis*-HAM product **7a** was formed.

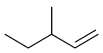
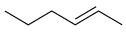
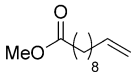
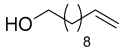
(ii) *Via* the other, subsequent reaction path, octene isomers (**1a**-isomers) were converted into branched aldehyde intermediates (**2a**-branched), which reacted more slowly with piperazine (**3**) or an intermediate mono-HAM product **4a**, respectively ($k_5 >>> k_6$, Figure 4). Hydrogenation of the resulting branched enamine intermediates led to branched *bis*-HAM-products **7a**-branched at the expense of linear HAM product selectivity.

In summary, *bis*-HAM of linear aliphatic 1-alkenes is a very complex reaction network, in which different reaction paths and intermediates occur, and are influenced by different reaction parameters to different extents, which makes a linear correlation of the conditions very difficult. In consideration of the variety of possible side products, intermediates and *bis*-HAM products, the formation of the linear *bis*-HAM product **7a** from 1-octene (**1a**) and piperazine **3** within six tandem catalytic steps at a yield of 80% with 77% linearity, encouraged us to explore other substrates under our optimized reaction conditions (Table 5).

Table 5. Substrate scope under the optimized reaction conditions.[a]



1a–k 3 7a–k

Entry	Olefin	Substrates X_{1a-k}	Substrates X_3	Intermediates Y_{4a-k}	Intermediates $Y_{(5+6)a-k}$	Products Y_{7a-k}	Products linear:branched	Side Products Y_{8a-k}	Side Products Y_{9a-k}	Side Products Y_{10a-k}
4.1	 **1a**	>99	>99	5	<1	80	77:23	3	<1	10
4.2	 **1b**	>99	>99	7	<1	73	66:34	<1	<1	17
4.3	 **1c**	>99	>99	<1	<1	95	47:53	<1	<1	<1
4.4	 **1d**	>99	>99	1	<1	66	75:25	<1	<1	28
4.5	 **1e**	>99	>99	9	<1	87	>99:1	<1	<1	<1
4.6	 **1f**	>99	>99	12	<1	65	5:95	<1	<1	<1
4.7	 **1g**	90[a]	50	11	30	11	–	<1	–	–
4.8	 **1h**	74	70	13[b]	56	<1	–	<1	–	–
4.9	 **1i**	>99	>99	10	<1	88	60:40	<1	<1	<1
4.10	 **1j**	>99	>99	<1	<1	70	72:28	5	8	17
4.11	 **1k**	>99	>99	<1	<1	72	70:30	4	6	17

[a] *Reaction conditions:* n_{1a-k} = 5 mmol, **3**/**1a–k** = 0.5, 0.1 mol% $Rh(acac)(CO)_2$, 0.3 mol% Biphephos, 5 mL toluene, p_{total} = 40 bar (H_2/CO = 1.35), T = 120 °C, t = 16 h, 750 rpm. Conversions (X) and yields (Y) in [%], determined *via* GC-FID with dibutyl ether as internal standard.
[b] 35% aldehyde **2g** was observed.
[c] Non-hydrogenated **4h**.

1-Hexene (**1b**) gave under the optimized reaction conditions slightly lower yields for the *bis*-HAM product **7b** with 73% besides also lower linearity (66%, entry 4.1) compared to **1a**. Branched 1-hexene derivatives such as 3-methyl-1-pentene (**1d**) and 3,3-dimethyl-1-butene (**1e**) led to higher linearity within the *bis*-HAM products with 75% for **7d** and >99% for **7e**, respectively. The double bond in **1e** is not able to isomerize and is in proximity to a bulky substituent. Hence, the linear aldehyde **2e** was formed almost exclusively, yielding the corresponding *bis*-HAM product **7e** in a very good yield of 87% with almost perfect linearity. For 1-dodecene (**1c**), an excellent *bis*-HAM product **7c** yield was observed with 95%. However, linearity for this long-chain linear alkene was rather low with only 47% (entry 4.3), presumably due to the increased possible internal isomers *via* isomerization. If an internal linear alkene (2-hexene **1f**) was directly applied as the substrate, slightly lower yields for the *bis*-HAM products were observed in comparison to **1b** (65%, entry 4.6). Nevertheless, isomerizing hydroformylation yields 5% linear *bis*-HAM product **7a** after all, which corresponds to an *n:branched* ratio within the initial hydroformylation of 22%. Cyclic substrates such as cyclohexene (**1g**) and cyclooctene (**1h**) did not lead to promising *bis*-HAM yields (entries 4.7 and 4.8). Hydroformylation of these substrates under the chosen conditions seemed to be less active resulting in incomplete conversion of the substrates. For cyclohexene (**1g**), 35% of the intermediate aldehyde **2g** was found in the product mixture, proving that branched aldehydes are less active in condensation with piperazine. Although 11% *bis*-HAM product **7g** can be found for cyclohexene, in contrast to cyclooctene (**1h**),which did not gave any *bis*-HAM products **7h** at all. In both cases,

enamine intermediates (**5+6g** and **5+6h**) were the main products from the reaction path, once again showing that branched enamines are less active in hydrogenation. Styrene (**1i**) gave very good yields of 88% *bis*-HAM product **7i**, at a remarkable linearity of 60% (entry 4.9). The developed protocol was also applicable to the remotely functionalized terminal olefins methyl 10-undecenoate (**1j**) and 10-undecenol (**1k**). The corresponding α,ω-diester **7j** and α,ω-diol **7k** were obtained in high yields with 70% and 72%, respectively (entries 4.10 and 4.11).

Conclusions

The *bis*-hydroaminomethylation of linear aliphatic 1-alkenes was successfully performed for the first time with high yields and selectivities towards linear products. In the model system of 1-octene and piperazine as the diamine component, the corresponding *bis*-alkylated piperazine was furnished in 80% yield with a linear selectivity of 77% within six auto-tandem catalytic steps. Key to success was on the one hand, the incorporation of the very efficient [Rh]/Biphephos catalyst system at low loadings of only 0.1 mol% to ensure high chemo- and regioselectivity. On the other hand, careful adjustment of the reaction parameters proved to be crucial to achieve high yields and selectivities and to suppress unwanted side reactions. By thorough parameter optimizations and recording yield *vs.* time plots, a detailed understanding of the reaction system, the reaction path leading to the desired products and the relation between side products, intermediates and hydroaminomethylation products was gained. Under optimized reaction conditions, other olefins such as branched 1-alkenes, internal alkenes, styrene, cycloalkenes and olefins with alcohol and ester groups were successfully transformed into the corresponding *bis*-hydroaminomethylation products with moderate to excellent yields and linearities. Especially the possibility to elegantly link two ester or alcohol functionalities *via* a piperazine ring under the formation of linear α,ω-bifunctional components opens up a new tandem-catalytic methodology for the atom-economic formation of potential polyester monomers.

Experimental Section

General Procedure for *Bis*-Hydroaminomethylation of 1-Octene with Piperazine

In a typical experiment, 1.3 mg $Rh(acac)(CO)_2$ (5 μmol, 0.1 mol%), 11.8 mg Biphephos (15 μmol, 0.3 mol%) and 213.5 mg piperazine (2.5 mmol, 50 mol%) were weighed into a custom-made stainless steel autoclave equipped with a magnetic stirring bar under air. After closing the reactor with its upper part and replacing the air by argon, 0.79 mL 1-octene (561.1 mg, 5 mmol, 100 mol%) and 5 mL toluene (4.35 g) were subsequently introduced by syringe in an argon counter stream. The sealed reactor was placed over a stirring plate and left for 30 min. The pressure was adjusted to 34 bar syngas (CO/H_2 1:1) and then to 40 bar with H_2 (H_2:CO 23:17 bar = 1.35:1). The reactor was placed in a preheated aluminum plate on a commercial magnetic stirrer at 120 °C for 16 h at a stirring rate of 750 rpm. After that, the reactor was cooled to room temperature using a water/ice bath and the pressure was carefully released in a fumehood. The reactor was opened and for quantitative GC analysis, an aliquot was withdrawn. In the case of preparative isolation of the product, the reaction mixture was transferred to a 100-mL round-bottom flask, the autoclave was rinsed with toluene and the solvent of the combined solutions was removed using a rotary evaporator. The crude reaction product was subjected to column chromatography using cyclohexane/EtOAc 10/1→2/1. The isolated linear *bis*-HAM product 1,4-dinonylpiperazine was obtained as a colorless liquid; yield: 54%. ^{1}H NMR ($CDCl_3$, 25 °C, 500.13 MHz): δ = 0.87 (t, $^3J_{H,H}$ = 7.0 Hz, 6H), 1.27 (m, 24H), 1.48 (m, 4H), 2.31 (t, $^3J_{H,H}$ = 8.0 Hz, 4H), 2.47 (br. s, 8H); ^{13}C NMR ($CDCl_3$, 25 °C, 125.77 MHz): δ = 14.46 (2C), 23.04 (2C), 27.34 (2C), 28.05 (2C), 29.66–29.98 (6C), 32.26 (2C), 53.71 (4C), 59.31 (2C); EI-MS (70 eV): *m/z* = 338 (M^+, 12.52%), 225 (100), 226 (26.17), 70 (18.43), 197 (13.59), 338 (12.52), 168 (9.6), 170 (8.92), 99 (7.71), 156 (7.32), 98 (6.1), 184 (5.64), 182 (4.9); ESI-HR-MS: *m/z* = 339.37313, calculated for $C_{22}H_{47}N_2^+$ $[M-H]^+$: 339.37338.

General Procedure for Yield *vs.* Time-Plot Investigations in the *Bis*-Hydroaminomethylation of 1-Octene with Piperazine

According to the above mentioned procedure, the reaction was performed in a 300-mL Parr reactor and the scale of the reaction was increased by the factor 13.636, which equals the increase in reactor size. For quantitative GC-FID analysis, 4680.3 mg *n*-dodecane were introduced to the reaction mixture from the beginning. Aliquots were regularly withdrawn from the autoclave *via* a valve by a capillary dipping into the solution with the aid of the internal pressure. The capillary was flushed twice with reaction mixture before 0.5 mL solution were filled into a liquid nitrogen precooled GC vial and immediately frozen and stored in liquid nitrogen. For GC-FID analysis, the melted sample was diluted with 2-propanol and analyzed.

For more detailed experimental information please see the Supporting Information.

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