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Glycerol boosted Rh-catalyzed hydroaminomethylation reaction, a mechanistic insight

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Dedicated to the memory of Prof. Erika Martin (1963–2017)

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Supporting information for this article is given via a link at the end of the document and contains a general experimental section, optimization data, control tests, reaction monitoring and characterization data of selected organic compounds (¹H and ¹³C NMR, MS).

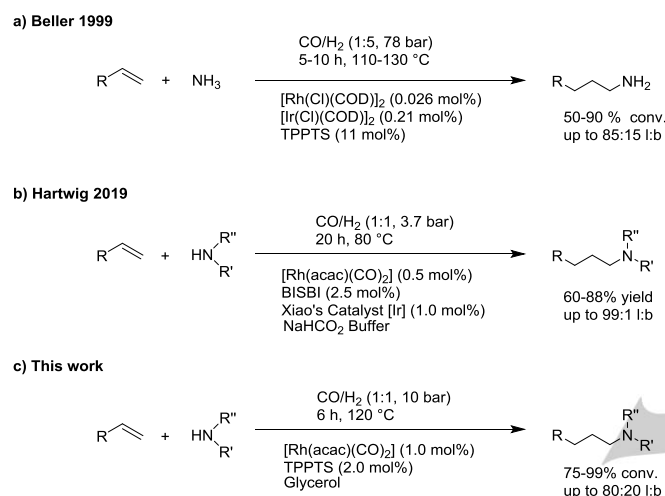
Abstract: In this contribution, we report a Rh-catalyzed hydroaminomethylation reaction of terminal alkenes in glycerol that proceeds efficiently under mild conditions to produce the corresponding amines in relatively high selectivity towards linear amines, moderate to excellent yields using a low catalyst loading (1 mol% [Rh], 2 mol% phosphine) and relative low pressure (H₂/CO, 1:1, total pressure 10 bar). This work sheds light on the importance of glycerol in enabling enamine reduction via hydrogen transfer. Moreover, the crucial role of Rh as chemoselective catalyst in the condensation step has been evidenced for the first time in the frame of the hydroaminomethylation reaction by precluding deleterious aldol condensation reactions. The hydroaminomethylation proceeds under a molecular regime; the outcome of catalytically active species into metal-based nanoparticles renders the catalytic system inactive.

Introduction

Among nitrogen compounds, amines play an important role as feedstock chemicals with a production on million-ton scale annually in the synthesis of agrochemicals, pharmaceuticals, solvents, dyes, monomers for polymerizations and functional materials, among the most important applications.^[1] Despite the production of amines often requires expensive and sometimes toxic substances through conventional methods, hydroaminomethylation (HAM) of alkenes offers an alternative synthesis from an environmental and economic point of view.^[2] HAM is a multi-component tandem transformation that consists of three consecutive steps: the metal-catalyzed hydroformylation of an alkene, followed by condensation of the resulting aldehyde with an amine leading to an enamine (or imine/iminium) intermediate that undergoes metal-catalyzed hydrogenation,

giving water as the only concomitant product.^[2a-g, 3] HAM is very attractive from an atom economy viewpoint, however it often requires harsh conditions, in particular using Rh-based systems,^[2a-g] despite its well-known ability to catalyze hydroformylation processes.^[4] In order to overcome this drawback, it is essential to design catalytic systems able to promote both hydroformylation and hydrogenation steps under relative mild conditions. In the literature, this approach has been considered and systems involving two catalysts have been described. Actually, Xiao^[5] and Han^[6] have employed a Rh-based catalyst together with an optically pure phosphoric acid as organocatalyst promoting imine hydrogenation towards the synthesis of chiral secondary amines, from styrene and aniline derivatives under mild conditions (total pressure: 2 – 11 bar; 25 – 50 °C; 16 – 72 h). For the synthesis of linear amines, Beller and coworkers reported a catalytic system constituted by Rh(I) and Ir(I) precursors (Ir/Rh ratio ca. 10/1) in the presence of an excess of TPPTS, taking advantage of the known performance of Ir-based systems in the hydrogenation of imines and enamines,^[7] leading to primary amines from terminal alkenes and ammonia (total pressure 78 bar; 110 – 130 °C; 5 – 10 h) with high regioselectivity (linear amines) and good chemoselectivity (primary amines) (Scheme 1a).^[8] More recently, Hartwig's group has also reported a Rh/Ir catalytic system constituted by [Rh(acac)(CO)₂]/BISBI (BISBI = 2,2'-bis(diphenylphosphinomethylene)-1,1'-biphenyl) and Xiao's catalyst, an Ir(III) organometallic complex stable in the presence of carbon monoxide;^[9] this catalytic system permits to work under milder conditions (total pressure 3.4 bar; 80 °C; 20 h), producing secondary linear amines from good to high yields, using a mixture of solvents (toluene/methanol) and an aqueous buffer solution of NaHCO₂ (Scheme 1b). Notably, the role of bidentate ligands, such as the diphosphine BISBI, has proven to be key for such high regioselectivities.^[10]

Based on these precedents and taking into account the properties of glycerol as solvent in a wide range of transformations,^[11] mainly involving metal-catalyzed homogeneous processes,^[12] but also metal nanoparticles^{[13],[14]} and catalyst-free reactions,^[15] we envisaged to explore the role of glycerol as hydrogen donor in the HAM reaction of terminal olefins catalyzed by [Rh(acac)(CO)₂]/TPPTS system through enhancing the reductive amination, which often is the rate limiting step of the HAM reaction (Scheme 1c).^[16] This contribution aims to provide a mechanistic insight, in particular related to the role of rhodium in the amine/aldehyde condensation step and the hydrogenation of the resulting enamine, in glycerol under mild reaction conditions.

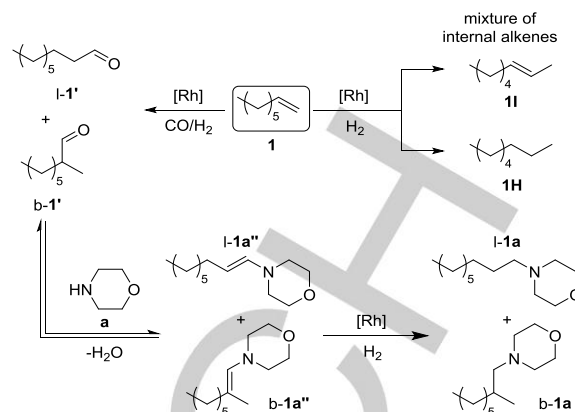


Scheme 1. Strategies to conduct the multi-step HAM reaction under tailored conditions for the synthesis of primary amines.

Results and Discussion

Based on the established HAM mechanism, terminal alkenes are initially transformed into the corresponding linear and branched aldehydes by hydroformylation, which then react with an amine to produce the corresponding enamine by a condensation reaction. Hydrogenation of these latter intermediates affords the expected amines, provided that side-reactions such as alkene isomerization or hydrogenation are precluded (Scheme 2, illustrating the case of oct-1-ene and morpholine).

We chose the HAM reaction of oct-1-ene (**1**) and morpholine (**a**) catalyzed by [Rh(acac)(CO)₂]/TPPTS in glycerol as benchmark reaction (Scheme 2). Under optimized conditions, high chemoselectivity was obtained towards the formation of amines **1a** at 120 °C and 10 bar (total pressure) of an equimolar CO:H₂ mixture, only observing minor alkene isomerization (less than 10%; see entry 1 in Table 1). Notably, the use of the diphosphine BISBI instead of TPPTS exhibited lower reactivity (50% conversion) and no selectivity enhancement (**1-1a** / **b-1a**, 70/30). The reaction optimization survey in terms of temperature, pressure, time, Rh/phosphine ratio and solvent (for further details, see Tables S1 and S2 in the Supporting Information) raised concerns on crucial solvent effects that merit a special discussion.



Scheme 2. Hydroaminomethylation benchmark reaction of Rh-catalyzed oct-1-ene (**1**) and morpholine (**a**). By-products from **1** are also indicated (**1H** and **1I**).

When toluene or dioxane were used, full conversion was observed (entries 2 and 3, Table 1), showing moderate chemoselectivity towards the HAM product due to competing olefin isomerization (mixture of internal alkenes) and substrate hydrogenation, albeit regioselectivity was similar for both solvents, leading to *ca.* 3:2 linear to branched ratio of **1a**. Despite the high conversion and high chemoselectivity towards the formation of amines obtained in cyclopentyl methyl ether (CPME), the reaction was not regioselective (entry 4, Table 1). Given the reported efficiency of alcohols in promoting HAM reactions,^[17] we sought to evaluate the effect of other protic solvents than glycerol. Whereas the use of water (entry 5, Table 1) led to an inactive catalytic system, both MeOH and butan-1-ol presented higher olefin isomerization (entries 6 and 7, Table 1) than glycerol (entry 1, Table 1). Thus, glycerol provided the best results in terms of chemo- and regioselectivity towards the formation of **1a**, outperforming both non-protic and other protic solvents in terms of deleterious olefin isomerization/hydrogenation side-reactions.

Table 1. Rh-catalyzed HAM of oct-1-ene and morpholine in different solvents.^[a]

Entry	Solvent	Conv. (%) ^[b]	Selectivity ^[b]				
			1I (%)	1H (%)	1a'' (%)	1a (%)	1-1a/b-1a
1	Glycerol	95	7	nd	nd	93	80/20
2	Toluene	98	21	23	nd	56	65/35
3	Dioxane	99	26	14	nd	60	66/34
4	CPME	>99	nd	nd	nd	95	50/50
5	H ₂ O	<5	nd	nd	nd	nd	nd
6	MeOH	99	19	nd	nd	81	70/30
7	Butan-1-ol	>99	26	nd	nd	73	70/30

[a] General conditions: 1 mmol of 1-octene, 1.5 mmol of morpholine, 1 mol% [Rh(acac)(CO)₂], 2 mol% TPPTS, 2 mL of solvent, 5 bar CO / 5 bar H₂ (pressure at room temperature), 120 °C, 6 h; nd = not determined; see Scheme 2 for the labelling of compounds. [b] Conversion, selectivity and

linear/branched ratio were determined by GC employing *n*-dodecane as internal standard. [c] Carried out at 80 °C. [d] 8% of aldehyde **1a'** detected by GC-MS.

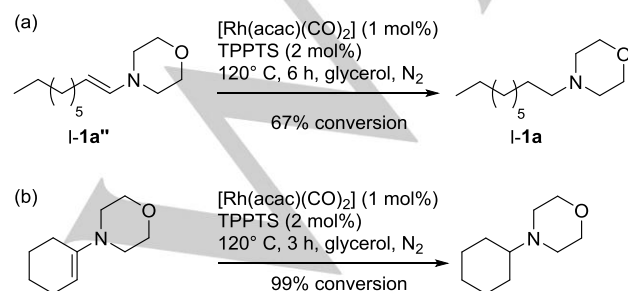
Taking into account the remarkable effect of glycerol and given the fact that hydrogenation of the imine-, iminium- or enamine-type intermediates is generally accepted as the rate determining step for Rh-catalyzed HAM,^[2a, 18] we considered that a hydrogen transfer (glycerol as reducing agent) could be operative in addition to the hydrogenation reaction,^[11e] enabling low pressure conditions while overriding the need for a metal-based co-catalyst.^[9] Thus, the nature of the hydrogen donor was further assessed with glycerol and butan-1-ol at 80 °C, revealing that enamine reduction was faster in the latter albeit with moderate **1a** selectivity (entries 1 and 2, Table 2). The effect of glycerol in boosting enamine reduction was observed when a solvent mixture of glycerol and butan-1-ol (0.25:0.75) was used, yielding a quantitative conversion and full chemoselectivity towards **1a**, showing a slight decrease in terms of regioselectivity (entries 1 and 2 vs 3, Table 2).

Table 2. Rh-catalyzed enamine reduction studies of oct-1-ene and morpholine benchmark reaction in glycerol, butan-1-ol and a mixture of both.^[a]

Entry	Solvent (glycerol:butan-1-ol)	Conv. (%) ^b	Selectivity ^{b)}		
			1a'' (%)	1a (%)	I-1a/b-1a
1	1:0	76	42	50 ^c	84/16
2	0:1	>99	41	51 ^d	84/16
3	0.25:0.75	>99	nd	>99	70/30

[a] General conditions: 1 mmol of 1-octene, 1.5 mmol of morpholine, 1 mol% of [Rh(acac)(CO)₂], 2 mol% of TPPTS, 2 mL of solvent, CO (5 bar)/H₂ (5 bar), 80 °C, 6 h; see Scheme 2 for the labelling of compounds. [b] Conversion, selectivity and linear/branched ratios were determined by GC employing *n*-dodecane as internal standard; nd, not determined. [c] 8% of aldehyde **1a'** detected by GC-MS. [d] 7% of aldehyde **1a'** detected by GC-MS.

With the aim of evidencing the plausible role of glycerol as reducing agent, the reaction of 4-[(*E*)-non-1-en-1-yl]morpholine intermediate (**I-1a''**)^[19] in glycerol under inert atmosphere, *i.e.* in the absence of molecular H₂, was carried out (Scheme 3a). Interestingly, up to 67% conversion of **I-1a''** to **I-1a** was obtained. This reactivity was confirmed by the hydrogen transfer of a tertiary enamine such as 4-(1-cyclohexen-1-yl)morpholine, yielding full conversion towards 4-cyclohexylmorpholine (Scheme 3b). Despite the ability of glycerol to reduce enamines,^[20] **I-1a''** was only slightly reduced in the absence of catalyst (less than 5%), proving that enamine hydrogen transfer is catalyzed by rhodium.



Scheme 3. Rh-catalyzed hydrogen transfer reaction of 4-[(*E*)-non-1-en-1-yl]morpholine (**a**) and 4-(1-cyclohexen-1-yl)morpholine (**b**) in glycerol (for ¹H NMR crude analysis, see Figure S1 in the Supporting Information).

We next investigated whether the in-situ generated aldehydes in the initial hydroformylation step of the HAM process could also undergo hydrogen transfer processes under the optimized reaction conditions. Thus, a control test with nonanal (**I-1'**) was carried out but no formation of nonan-1-ol was observed; alternatively, acetals from the reaction of the aldehyde and glycerol were obtained, because acetalization is probably faster than hydrogen transfer reaction.^[21]

We then focused on the reactivity of aldehydes towards enamine formation and subsequent reduction to give the desired amine products, while avoiding aldol condensation pathways (Table 3). Accordingly, the following control tests were carried out. First, the condensation between nonanal (**I-1'**) and morpholine (**a**) using a 1/1.5 molar ratio of reagents under inert atmosphere at 120 °C in the presence of catalyst, afforded full conversion but mainly yielding the aldol condensation product (62%) together with only 38% of the desired **I-1a** product (coming from the reduction of enamine **I-1a''** by glycerol as discussed above; entry 1, Table 3). Under H₂/CO pressure, the formation of **I-1a** was slightly improved (entry 2, Table 3). However, in the absence of catalyst, the aldol product was favored (up to 88%; entry 3, Table 3), indicating the benefic role of the Rh/TPPTS system in terms of chemoselectivity.

The selectivity towards the desired amine substantially enhanced when a large excess of morpholine was used (**I-1'/a** ratio of 0.1/3), leading up to 71% of **I-1a** (entry 4, Table 3). These latter conditions, but under H₂/CO pressure, gave 98% of **I-1a** (entry 5, Table 3); in the absence of catalyst, aldol condensation products were obtained up to 49% yield (entry 6, Table 3), in agreement with the trend observed using a lower excess of morpholine (entry 3, Table 3). These results proved that both a low concentration of aldehyde (probably shifting the equilibrium towards the formation of enamine **I-1a''** by the amine excess) and the presence of the rhodium catalyst are necessary in order to prevent the formation of aldol condensation products, as well as the reducing effect of glycerol facilitating the enamine reduction. Consequently, under catalytic conditions, the condensation step must be fast enough to avoid the accumulation of aldehydes throughout reaction; in this step, rhodium plays a crucial role in the chemoselectivity, hampering the formation of aldol condensation products. This reactivity behavior was corroborated by the GC-MS monitoring of the benchmark reaction under catalytic conditions (see below).

Table 3. Reductive amination controls in glycerol.^[a]

Entry	I-1'/a (mmol)	Catalyst	CO/H ₂ (bar)	Selectivity ^{b)}	
				I-1a (%)	aldol by-product (%)
1	1/1.5	[Rh(acac)(CO) ₂], TPPTS	CO/H ₂	38	62
2	1/1.5	[Rh(acac)(CO) ₂], TPPTS	H ₂ /CO	42	58
3	1/1.5	None	None	38	62
4	1/3	[Rh(acac)(CO) ₂], TPPTS	CO/H ₂	71	29
5	1/3	[Rh(acac)(CO) ₂], TPPTS	H ₂ /CO	98	2
6	1/3	None	None	49	51

1	1.0/1.5	Yes	0/0	38	62
2	1.0/1.5	Yes	5/5	49	51
3	1.0/1.5	Non	5/5	7 ^[c]	88
4	0.1/3.0	Yes	0/0	71 ^[d]	n.d.
5	0.1/3.0	Yes	5/5	98	2
6	0.1/3.0	Non	5/5	51	49 ^[d]

[a] General conditions: nonanal (**1-1'**), morpholine (**a**), 1 mol% of [Rh(acac)(CO)₂] and 2 mol% of TPPTS unless otherwise noted, 2 mL of glycerol, CO (5 bar) : H₂ (5 bar) unless otherwise noted, 120 °C, 6 h; see Table S3 in the Supporting Information for full details. [b] Conversion (full conversion observed for the experiments indicated in the table), chemo- and regio-selectivity were determined by ¹H NMR and GC using *n*-dodecane as internal standard; n.d., not determined. [c] 5% of the enamine **1-1a''** was observed. [d] 71% conversion. [d] The aldol condensation product (35%) further condenses with morpholine to yield a by-product in 14% (*m/z* 335).

Despite high pressures are usually required for hydroaminomethylation,^[4b, 4c] the methodology described herein permitted to work under relative low pressure. Notably, in the absence of morpholine, the hydroformylation of oct-1-ene towards **1-1'** and **b-1'** in glycerol only worked under high pressure (25 bar H₂ / 25 bar CO), favoring the formation of the branched regioisomer (**1-1'**/**b-1'** ratio of 36/64, see Table S4 in the Supporting Information). Thus, this behavior suggests that the amine is involved in the hydroformylation step,^[4b, 22] probably by coordination to the rhodium center, modifying the energy of intermediates and transition states^[23] and in consequence influencing the rate and selectivity of the hydroformylation reaction.^[24]

In order to assess the organic compounds present throughout the HAM reaction, reaction monitoring studies were performed by GC-MS and FTIR (Figure 1 and Figure S3 in the Supporting Information, respectively). The GC-MS study evidenced that the aldehyde intermediates (**1-1'** and **b-1'**) arising from olefin hydroformylation, were present at rather low concentrations throughout the reaction in agreement with the behavior observed for the condensation step (see above). Thus, after 30 min of reaction, the molar fraction of enamine intermediates **1a''** is consistently higher than the corresponding aldehyde precursors **1'**, indicating that the reduction of the former represents the rate-determining step for the overall HAM reaction. Despite the operando FTIR method did not permit the detection of organometallic intermediates or aldehydes under catalytic conditions due to their low concentration (see Figure S3 in the Supporting Information), the reaction profiles of oct-1-ene (**1**) conversion (disappearance of the C=C stretching band at 1641 cm⁻¹), together with the presence of a transient enamine intermediate **1a''** (967 cm⁻¹ band formation and decay) and the formation of the amine **1a** (C-N stretching band at 1031 cm⁻¹ increase) are consistent with GC monitoring data (Figure 1) and ¹H NMR analysis of the reaction mixture after the 24 h operando FTIR monitoring (see Figure S4 in the Supporting Information; for a control FTIR monitoring, see Figure S5).

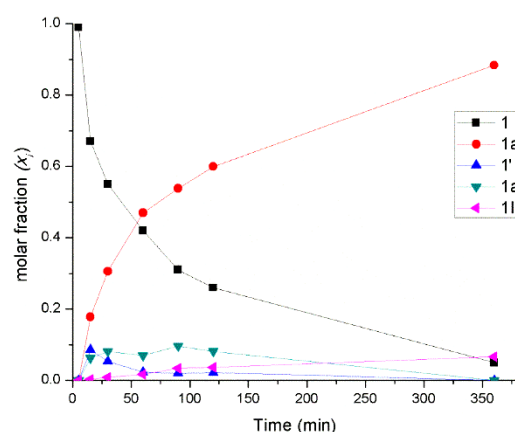
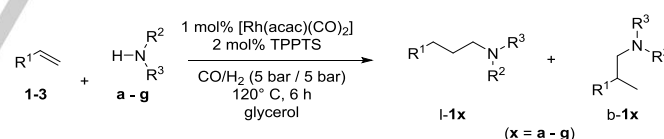






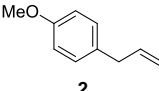

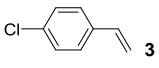

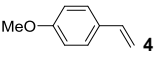

Figure 1. Monitoring by GC-MS of the hydroaminomethylation of oct-1-ene (**1**) and morpholine (**a**) catalyzed by Rh(I)/TPPTS catalyst in glycerol. Reaction conditions: 1 mmol of **1**, 1.5 mmol of **a**, 1 mol% of [Rh(acac)(CO)₂], 2 mol% of TPPTS, 2 mL of glycerol, CO (5 bar)/H₂ (5 bar), 120 °C. Molar fraction of products (*x_i*) was determined by GC using *n*-dodecane as internal standard. For detailed data, see Table S5 in the Supporting Information.

Alternative mechanistic HAM approaches consisting on the direct C–C coupling of oct-1-ene with 4,4'-methylene dimorpholine aminal, *N*-formylmorpholine or *N*-(methylene)morpholinium chloride did not work under the optimized reaction conditions. Despite Rh nanoparticles were detected after the reaction by TEM (see Figure S6 in the Supporting Information), preformed Rh nanoparticles were totally inactive in the HAM benchmark reaction (see Figure S7 in the Supporting Information), indicating that hydroaminomethylation operates under a molecular regime.

Table 4. Reaction scope of Rh-catalyzed HAM in glycerol.^[a]



Entry	Alkene	Amine	Conv. (%) ^[b]	Selectivity ^[b]	
				1x (%) ^[c]	1-1x/b-1x
1			94	86 (14)	70/30
2			78	>99 (n.d.)	80/20 ^[f]
3			78	84 (16)	75/25
4			77	92 (8)	70/30

5			75	78 (8) ^[d]	60/40 ^[g]
6			80	71 (10) ^[e]	85/15 ^[g]
7			81	92 (n.d.)	85/15
8			91	96 (n.d.) ^[h]	80/20
9			>99	97 (n.d.) ^[i]	80/20

[a] General conditions: 1 mmol of alkene (**1** – **4**), 1.5 mmol of amine (**a** – **g**), 1 mol% of [Rh(acac)(CO)₂], 2 mol% of TPPTS, 2 mL of glycerol, 5 bar CO / 5 bar H₂ (pressure at room temperature), 120 °C, 6 h. [b] Conversion, chemo- and regio-selectivity were determined by GC using *n*-dodecane as internal standard. [c] In brackets, percentage of internal alkenes from oct-1-ene. [d] 14% of tertiary amine was formed. [e] 19% of tertiary amine was formed. [f] Linear/branched ratio determined by ¹H and ¹³C NMR. [g] Linear/branched for the tertiary amine was not determined. [h] 4% 4-chloroethylbenzene. [i] 3% 4-ethylanisole. [j] Reaction conditions: 1 mmol of 4-vinylanisole, 1.5 mmol of morpholine, 1 mol% [Rh(acac)(CO)₂], 1 mol% of TPPTS in 2 mL of glycerol, 5 bar CO / 15 bar H₂ (pressure at room temperature), 120 °C, 10 h.

With the optimized experimental conditions for the benchmark reaction, the HAM reaction scope was evaluated using primary and secondary amines, including aniline derivatives (**a** – **g**), as well as different terminal alkenes (**1** – **4**) giving high conversions towards the expected products (75 – 94% conversion, Table 4). Concerning chemoselectivity, for secondary amines, the expected amine product was mainly obtained (entries 1–4, Table 4). However, with cyclohexylamine and aniline (entries 5–6, Table 4), ca. 15 – 20% of tertiary amine was formed together with the expected secondary amine products, due to the highest reactivity of secondary amines, thus competing with the primary amine substrates. Modifying the ratio oct-1-ene/aniline (1/0.5, 1/1.5, 1/2), the selectivity was not improved; as expected, a higher amount of aniline favored the formation of bis-(octyl)phenyl amine (up to 33%, see Table S6 in the Supporting Information).

Concerning regioselectivity, the linear isomer was the major product in all cases, with a maximum l/b ratio of 85/15 (entries 5 and 7, Table 4). Ammonia-based reagents (NH₃(aq), NH₄OAc) and sulfonamide derivatives (methylsulfonamide, *p*-tolylsulfonamide) did not react under these reaction conditions. Unfortunately, di- and trisubstituted alkenes (cyclooctene, ethyloleate, α -pinene, α -methylstyrene, 4-octene, limonene) did not undergo HAM (conversions lower than 20%, see Table S7 in the Supporting Information).

Furthermore, aryl-substituted alkenes, such as 4-allylanisole (**2**), 4-chlorostyrene (**3**) and 4-methoxystyrene (**4**) showed good to excellent conversions towards HAM, together with high linear-to-branched outcomes (entries 7–9, Table 4). These results are particularly interesting for styrene derivatives, because the formation of the branched regioisomer in the Rh-catalyzed hydroformylation step is generally favored;^[2a] however, the nature of ligand and solvent triggers a non-innocent effect on the regioselectivity, reversing this trend as proven by Zhang's group;

they obtained the best linear/branched ratio using a tetraphosphorus-based ligand and *tert*-amyl alcohol as solvent.^[25]

Conclusion

This contribution sheds light on the mechanism of multi-step Rh-catalyzed hydroaminomethylation in glycerol. For the benchmark reaction (oct-1-ene and morpholine as reagents), we evidenced paramount solvent effects in the reactivity of Rh-based catalytic systems, revealing the role of glycerol as reducing agent. Actually, we demonstrated that both Rh-catalyzed hydrogenation and hydrogen transfer processes cooperate to favor enamine reduction under relative low pressure (5 bar H₂ / 5 bar CO). Moreover, we have shown that the enamine formation proceeds via a chemoselective condensation promoted by rhodium; under these conditions aldol reactions are precluded in contrast to the non-catalyzed organic condensation. The results described herein highlight both the fast rhodium-promoted condensation of the aldehyde with the amine to selectively form the enamine intermediate, as well as the role of glycerol as a hydrogen transfer agent, boosting the Rh-catalyzed reduction of this transient enamines and thus permitting to work at relative low pressure.

The reaction scope of terminal alkenes and amines showed the versatility of the process exhibiting excellent chemoselectivity towards the formation of secondary and tertiary amines, with high linear-to-branched regioselectivity, including styrene derivatives (up to 85:15).

Overall, the results reported herein stress the fact that glycerol enables a Rh-based catalytic system working under molecular regime, to perform one-pot HAM cascade reaction to reach a reactivity behavior that was thus far limited to multi-catalytic systems,^[5-6, 8-9] in particular those based on Rh/Ir bimetallic catalysts for the synthesis of linear amines.^[9]

Experimental Section

General procedure for catalytic hydroaminomethylation. In a stainless steel reactor vessel (100 mL) were placed the desired amount of [Rh(acac)(CO)₂] and tris(3-sulfophenyl)phosphine trisodium salt (TPPTS) together with glycerol (2 mL), the selected olefin (1 mmol), the selected secondary or primary amine (1.5 mmol) and *n*-dodecane as internal standard (1 mmol). The reactor was pressurized with the selected proportion of CO/H₂ at the desired pressure, temperature and time. After the reaction was completed, the reactor vessel was cooled to room temperature and consecutively depressurized. Products were extracted with cyclohexane (5 x 3 mL), filtered through a Celite column and analyzed by gas chromatography to determine conversion and selectivity. Products were isolated and characterized by ¹H and ¹³C NMR, and MS. The Rh content of extracted organic products was in the range of 0.01–0.08 ppm as determined by ICP-AES analyses.

Synthesis of Rh nanoparticles. In a Fisher-Porter bottle, [Rh(acac)(CO)₂] (13.0 mg, 0.05 mmol) and TPPTS (28.5 mg, 0.05 mmol) were dissolved in 10 mL of glycerol at room temperature under Ar. The system was then pressurized with 3 bar of H₂ and stirred at 80 °C during 18 h. The Fisher-Porter bottle was cooled down to room temperature and depressurized. The resulting black homogeneous solution of dispersed nanoparticles was dried under vacuum (0.05 mmHg) at 80 °C for 18 h to

remove volatile organic compounds. The as-prepared Rh nanoparticles were characterized by TEM (see Figure S7 in the Supporting Information).

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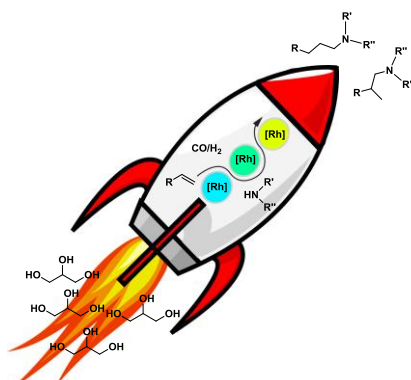
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- [1] a) M. B. Smith, *March's advanced organic chemistry: reactions, mechanisms, and structure*, John Wiley & Sons, **2020**; b) K. Eller, E. Henkes, R. Rossbacher, H. Höke, *Ullmann's Encyclopedia of Industrial Chemistry* **2000**; c) D. Crozet, M. Urrutigoity, P. Kalck, *ChemCatChem* **2011**, *3*, 1102.
- [2] For selected contributions, see: a) P. Kalck, M. Urrutigoity, *Chem. Rev.* **2018**, *118*, 3833; b) T. Rische, P. Eilbracht, *Synthesis* **1997**, *1997*, 1331; c) C. Chen, X.-Q. Dong, X. Zhang, *Org. Chem. Front.* **2016**, *3*, 1359; d) M.-N. Birkholz, Z. Freixa, P. W. van Leeuwen, *Chem. Soc. Rev.* **2009**, *38*, 1099; e) X.-F. Wu, X. Fang, L. Wu, R. Jackstell, H. Neumann, M. Beller, *Acc. Chem. Res.* **2014**, *47*, 1041; f) J. F. Hartwig, *Science* **2002**, *297*, 1653; g) A. Behr, M. Fiene, C. Buß, P. Eilbracht, *Eur. J. Lipid Sci. Technol.* **2000**, *102*, 467.
- [3] a) T. Sperger, I. A. Sanhueza, I. Kalvet, F. Schoenebeck, *Chem. Rev.* **2015**, *115*, 9532; b) O. Diebolt, P. W. N. M. van Leeuwen, P. C. J. Kamer, *ACS Catal.* **2012**, *2*, 2357; c) M. Ahmed, A. M. Seayad, R. Jackstell, M. Beller, *J. Am. Chem. Soc.* **2003**, *125*, 10311.
- [4] a) P. C. J. Kamer, A. van Rooy, G. C. Schoemaker, P. W. N. M. van Leeuwen, *Coord. Chem. Rev.* **2004**, *248*, 2409; b) P. W. N. M. van Leeuwen, C. Claver, *Rhodium Catalyzed Hydroformylation*, Springer Netherlands, **2006**; c) A. Börner, R. Franke, *Hydroformylation: Fundamentals, Processes, and Applications in Organic Synthesis*, Wiley, **2016**; d) R. Franke, D. Selent, A. Börner, *Chem. Rev.* **2012**, *112*, 5675.
- [5] B. Villa-Marcos, J. Xiao, *Chin. J. Catal.* **2015**, *36*, 106.
- [6] J. Meng, X.-H. Li, Z.-Y. Han, *Org. Lett.* **2017**, *19*, 1076.
- [7] a) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713; b) A. Bartoszewicz, N. Ahlsten, B. Martin-Matute, *Chem. Eur. J.* **2013**, *19*, 7274; c) A. Baeza, A. Pfaltz, *Chem. Eur. J.* **2009**, *15*, 2266; d) G.-H. Hou, J.-H. Xie, P.-C. Yan, Q.-L. Zhou, *J. Am. Chem. Soc.* **2009**, *131*, 1366.
- [8] B. Zimmermann, J. Herwig, M. Beller, *Angew. Chem. Int. Ed.* **1999**, *38*, 2372.
- [9] S. Hanna, J. C. Holder, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2019**, *58*, 3368.
- [10] Y. Wang, J. Chen, M. Luo, H. Chen, X. Li, *Catal. Commun.* **2006**, *7*, 979.
- [11] a) J. I. García, H. García-Marín, E. Pires, *Green Chem.* **2014**, *16*, 1007; b) A. E. Díaz-Álvarez, J. Francos, B. Lastra-Barreira, P. Crochet, V. Cadierno, *Chem. Commun.* **2011**, *47*, 6208; c) A. E. Díaz-Álvarez, J. Francos, P. Croche, V. Cadierno, *Curr. Green Chem.* **2014**, *1*, 51; d) A. Wolfson, C. Dlugy, Y. Shotland, *Environ. Chem. Lett.* **2007**, *5*, 67; e) A. Wolfson, C. Dlugy, Y. Shotland, D. Tavor, *Tetrahedron Lett.* **2009**, *50*, 5951.
- [12] a) M. Rodríguez-Rodríguez, P. Llanes, C. Pradel, M. A. Pericàs, M. Gómez, *Chem. Eur. J.* **2016**, *22*, 18247; b) C. Vidal, J. García-Álvarez, *Green Chem.* **2014**, *16*, 3515; c) F. Chahdoura, L. Dubrulle, K. Fourmy, J. Durand, D. Madec, M. Gómez, *Eur. J. Inorg. Chem.* **2013**, *2013*, 5138; d) A. Azua, J. A. Mata, E. Peris, F. Lamaty, J. Martínez, E. Colacino, *Organometallics* **2012**, *31*, 3911; e) A. E. Díaz-Álvarez, P. Crochet, V. Cadierno, *Catal. Commun.* **2011**, *13*, 91.
- [13] For selected reviews, see: a) I. Favier, D. Pla, M. Gómez, *Chem. Rev.* **2020**, *120*, 1146; b) F. Fiévet, S. Ammar-Merah, R. Brayner, F. Chau, M. Giraud, F. Mammeri, J. Peron, J. Y. Piquemal, L. Sicard, G. Viau, *Chem. Soc. Rev.* **2018**, *47*, 5187; c) I. Favier, D. Pla, M. Gómez, *Catal. Today* **2018**, *310*, 98; d) T. Dang-Bao, D. Pla, I. Favier, M. Gómez, *Catalysts* **2017**, *7*, 207.
- [14] a) T. Dang-Bao, C. Pradel, I. Favier, M. Gómez, *ACS Appl. Nano Mater.* **2019**, *2*, 1033; b) A. Reina, A. Serrano-Maldonado, E. Teuma, E. Martín, M. Gómez, *Catal. Commun.* **2018**, *104*, 22; c) A. Reina, I. Favier, C. Pradel, M. Gómez, *Adv. Synth. Catal.* **2018**, *360*, 3544; d) T. Dang-Bao, C. Pradel, I. Favier, M. Gómez, *Adv. Synth. Catal.* **2017**, *359*, 2832; e) A. Reina, C. Pradel, E. Martín, E. Teuma, M. Gómez, *RSC Adv.* **2016**, *6*, 93205; f) F. Chahdoura, C. Pradel, M. Gómez, *Adv. Synth. Catal.* **2013**, *355*, 3648; g) F. Chahdoura, C. Pradel, M. Gómez, *ChemCatChem* **2014**, *6*, 2929; h) F. Chahdoura, I. Favier, C. Pradel, S. Mallet-Ladeira, M. Gómez, *Catal. Commun.* **2015**, *63*, 47; i) F. Chahdoura, S. Mallet-Ladeira, M. Gómez, *Org. Chem. Front.* **2015**, *2*, 312.
- [15] M. Rodríguez-Rodríguez, E. Gras, M. A. Pericàs, M. Gómez, *Chem. Eur. J.* **2015**, *21*, 18706.
- [16] J. A. Fuentes, P. Wawrzyniak, G. J. Roff, M. Bühl, M. L. Clarke, *Catal. Sci. Technol.* **2011**, *1*, 431.
- [17] a) A. de Oliveira Dias, M. G. P. Gutiérrez, J. A. A. Villarreal, R. L. L. Carmo, K. C. B. Oliveira, A. G. Santos, E. N. dos Santos, E. V. Gusevskaya, *Appl. Catal., A* **2019**, *574*, 97; b) B. Hamers, E. Kosciusko - Morizet, C. Müller, D. Vogt, *ChemCatChem* **2009**, *1*, 103.
- [18] S. Tin, T. Fanjul, M. L. Clarke, *Beilstein J. Org. Chem.* **2015**, *11*, 622.
- [19] a) *Prepared as described in the following reference*; b) W. Sucrow, H. Minas, H. Stegemeyer, P. Geschwinder, H. R. Murawski, C. Krüger, *Chem. Ber.* **1985**, *118*, 3332.
- [20] See the following reference for the non-catalyzed reduction of enamines by alcohols: A. Gilbert Cook, *Tetrahedron Lett.* **2010**, *51*, 3762.
- [21] This assumption was confirmed by the reduction of 4-phenyl-3-buten-2-one by glycerol, which gave a mixture of 4-phenylbutan-2-one (reduction of C=C) and 4-phenylbutan-2-ol (reduction of both C=C and C=O), thus predominating hydrogen transfer reactions over acetalization (see Figure S2 in the Supporting Information).
- [22] a) X. Luo, D. Tang, M. Li, *Int. J. Quantum Chem.* **2006**, *106*, 1844; b) G. Alagona, R. Lazzaroni, C. Ghio, *J. Mol. Model.* **2011**, *17*, 2275; c) K. Nozaki, T. Matsuo, F. Shibahara, T. Hiyama, *Organometallics* **2003**, *22*, 594; d) C. Kubis, M. Sawall, A. Block, K. Neymeyr, R. Ludwig, A. Börner, D. Selent, *Chem. Eur. J.* **2014**, *20*, 11921; e) M. Sparta, K. J. Børve, V. R. Jensen, *J. Am. Chem. Soc.* **2007**, *129*, 8487.
- [23] For Rh(I) and Rh(III) complexes containing morpholine, see: a) M. G. L. Petrucci, A.-M. Lebus, A. K. Kakkar, *Organometallics* **1998**, *17*, 4966; b) M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, T. E. Müller, *Eur. J. Inorg. Chem.* **1999**, *1999*, 1121; c) M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, J. Herwig, T. E. Müller, O. R. Thiel, *Chem. Eur. J.* **1999**, *5*, 1306; d) M. Schmidlehner, P.-S. Kuhn, C. M. Hackl, A. Roller, W. Kandöller, B. K. Keppler, *J. Organomet. Chem.* **2014**, *772-773*, 93.
- [24] U. Gellrich, T. Koslowski, B. Breit, *Catal. Sci. Technol.* **2015**, *5*, 129.
- [25] a) S. Yu, Y.-m. Chie, Z.-h. Guan, Y. Zou, W. Li, X. Zhang, *Org. Lett.* **2009**, *11*, 241; b) S. Li, K. Huang, J. Zhang, W. Wu, X. Zhang, *Org. Lett.* **2013**, *15*, 3078.

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A multitasking monometallic Rh-based catalytic system in glycerol enables tandem hydroaminomethylation reaction under a molecular regime, via low pressure hydroformylation, Lewis acid-assisted condensation and enamine reduction boosted by hydrogen transfer.

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