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A Cooperative Rh/Co-Catalyzed Hydroaminomethylation Reaction for the Synthesis of Terpene Amines

Alejandro Pérez Alonso,^[a] Doan Pham Minh,^[b] Daniel Pla,^{*[a]} and Montserrat Gómez^{*[a]}

An original bimetallic catalytic system based on Rh(I) and Co(0) in glycerol is described for the synthesis of biomass-derived amines through the tandem hydroaminomethylation reaction of terpenes, such as (*R*)-limonene, β -pinene and camphene. Under optimized conditions, this multicatalytic system is highly chemoselective (avoiding hydrogenations of substrates and aldehyde-based intermediates, and aldol condensations), exhib-

iting good-to-excellent regioselectivity towards linear amines. From a mechanistic viewpoint, cobalt mainly boosts the reductive amination, while rhodium shows a foremost role in the hydroformylation step. Regarding the nature of the organometallic species, catalytically inactive metal nanoparticles have been identified at the end of the reaction, proving the homogeneous nature of the bimetallic catalytic system.

Introduction

Amines are crucial intermediates in different industrial sectors, mainly due to their nucleophilic reactivity, and represent valuable feedstocks.^[1] Most of the industrially applicable amines (aliphatic or aromatic) are produced from fossil sources.^[2] For pharmaceutical and biological purposes, bio-sourced amines represent great interest, however a limited number of natural amines are thus far accessible other than alkaloids,^[3] amino acids and polymers such as chitosan from crustacean or insect chitin^[4] and poly(ϵ -L-lysine) produced by microorganisms.^[5] In the current trend for the sustainable synthesis of fine chemicals, biomass-derived compounds are of key significance towards the synthesis of amines amines by different catalytic approaches: hydroamination of alkenes, reductive amination of carbonyl compounds and hydroaminomethylation (HAM) of alkenes, among the most relevant strategies showing both high atom economy and low E factor.^[6] In contrast to the alkenes coming from fossil resources, few examples regarding HAM have been reported with bio-sourced substrates, in particular using terpenes as raw materials in combination with mainly primary and secondary amines,^[5,7] or ammonia under biphasic conditions.^[8] Generally, high syngas pressures (more than

60 bar) and high temperatures (80–130 °C) are required principally using homogeneous monometallic Rh-based catalysts (under tandem^[9] or two-step processes),^[10] and also combining Rh and Pd catalysts.^[11]

With the aim of enhancing the activity and selectivity of the HAM processes, homogeneous bimetallic Rh/Ir catalytic systems have been efficiently employed by Beller's group involving alkyl α -olefins^[12] and Hartwig's group using both alkyl and aryl α -olefins also including the natural compound methyl eugenol.^[13] Given the scarcity of both metals, the quest of more sustainable approaches led our group to boost the enamine hydrogenation step of monometallic Rh-catalyzed HAM reactions using glycerol as solvent taking advantage of the reducing behavior of the latter, as an eco-friendly alternative to iridium.^[14]

As stated above, the use of monoterpenes as substrates for the HAM processes requires quite harsh conditions. With the aim of working under milder conditions (temperature, pressure, metal loading), we sought to explore the effect of cobalt in the HAM of terpenes. Despite recent reports by Bouwman, Bickelhaupt and co-workers concluded from their quantum/chemical study that Co-based catalysts had a low chemoselectivity favoring the hydrogenation of alkenes and aldehydes (at 150 °C and 75 bar total pressure),^[15] one of the first experimental works on Co-catalyzed HAM reaction was described under even harsher conditions (up to 260 °C and 479–755 atm of syngas, using a high loading of metallic cobalt).^[16] On the other hand, Beller's group has lately reported a highly regioselective Co/Xantphos-derived catalytic system leading to linear amines, even using internal alkenes as substrate thanks to the Co-promoted isomerization of alkenes,^[17] albeit none of the reported works used terpenes. Based on these results, we decided to study the cooperativity of Rh- and Co-based catalysts in the challenging synthesis of terpene amines through multi-component HAM reaction, with the purpose of facilitating, in particular, the enamine hydrogenation step.

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Results and Discussion

(*R*)-Limonene (**1**) and morpholine (**a**) were chosen as benchmark reactants for the optimization of the HAM reaction parameters in neat glycerol (Table 1), under the conditions previously applied in our team for the HAM of simple terminal alkenes (such as oct-1-ene or styrene derivatives) catalyzed by rhodium/TPPTS [trisodium 3,3',3''-phosphanetriyltri(benzene-1-sulfonate)] catalytic system.^[14] In this case, unfortunately, under 10 bar total pressure (CO/H₂ = 1:1), the reaction did not proceed at 120 °C overnight using 1 mol% [Rh(acac)(CO)₂] and 2 mol% TPPTS as catalytic system (entry 1, Table 1). Increasing the pressure up to 40 bar, up to 60% conversion, and exclusive regioselectivity towards the corresponding linear amine **1a** was obtained due to the steric hampering of the isopropenyl moiety (entries 2–3, Table 1). Keeping a total pressure of 40 bar, but using 10 bar H₂, 10 bar CO and 20 bar N₂, the reaction proceeded smoothly, leading to only 10% yield of the expected amine (entry 4, Table 1). The reaction did not work in the absence of rhodium or in the absence of TPPTS (entries 5 and 6, Table 1). With the purpose of preserving relatively moderate conditions, a higher amount of Rh precursor was used, observing a beneficial effect (entries 7 and 8, Table 1). A temperature decrease resulted in a significant yield decrease (from 95% to 76%, entry 7 vs 9, Table 1).

From a mechanistic point of view, the slowest step in the HAM reaction mostly corresponds to the hydrogenation of the enamine.^[18] In the literature, some approaches to boost this step have been reported, such as the use of Rh/Ir bimetallic systems (Rh as hydroformylation promoter and Ir to facilitate enamine hydrogenation) described independently by Beller^[12] and Hartwig^[13] groups, as well as a monometallic Rh catalyst in glycerol where glycerol boosts the enamine reduction via

hydrogen transfer.^[14] This latter approach seems a better option from a sustainable perspective, despite the lack of efficiency obtained in our initial attempts using terpenes substrates (results shown in Table 1). In the literature, pressures higher than 60 bar or the addition of a supplementary catalyst are necessary to reduce the enamine intermediate in the synthesis of terpene amines by HAM (for selected contributions see:^[6a,7a,11,19]).

Taking into account the ability of Co-based catalysts in the hydrogenation of C–N multiple bonds,^[19b,20] we decided to apply a Rh/Co bimetallic homogeneous system. To the best of our knowledge, no examples are reported in the literature regarding this strategy.

Maintaining 1 mol% Rh, four different Co precursors were used in the HAM benchmark reaction (Table 2). Initially, 5 mol% of cobalt precursor and a large excess of TPPTS (12 mol%) were applied (entries 1–4, Table 2), obtaining the best catalytic behavior in terms of activity and selectivity, when [Co₂(CO)₈] and Co(OAc)₂ were used (entries 3–4, Table 2). With these two precursors, the amount of TPPTS was optimized (entries 5–8) down to 2 mol% with [Co₂(CO)₈], giving ca. 80% yield towards **1a** (entries 7–8, Table 2). Under these conditions, the reaction did not work in the absence of rhodium (entry 9, Table 2). Other polar solvents such as cyclopentylmethylether (CPME) and methanol (entries 10–11, Table 2) or apolar such as toluene (entry 12, Table 2), gave lower activity, proving the boosting role of glycerol in the enamine reduction. We used the benzyl

Table 1. Rh-catalyzed hydroaminomethylation of (*R*)-limonene and morpholine.^[a]

Entry	Rh loading (mol%)	TPPTS loading (mol%)	T (°C)	p ^[b] (bar)	Conv. (yield) ^[c] (%)
1	1	2	120	10	0
2	1	2	120	20	18 (15)
3	1	2	120	40	60 (50)
4 ^[d]	1	2	120	40	12 (10)
5	–	2	120	40	0
6	1	–	120	40	0
7	2	4	120	40	97 (95)
8	5	10	120	40	99 (99)
9	2	4	60	40	77 (76)

[a] Results from duplicate experiments. Reaction conditions: 1 mmol of (*R*)-limonene and 1 mmol of morpholine, 0.01 mmol [Rh(acac)(CO)₂], 0.02 mmol of TPPTS, 2 mL of glycerol, 18 h. [b] Equimolar mixture of CO/H₂. [c] Determined by GC-FID using 1,3,5-tribromobenzene as internal standard. [d] Gas molar mixture: CO/H₂/N₂ = 10:10:20.

Table 2. Rh/Co-catalyzed hydroaminomethylation of (*R*)-limonene and morpholine.^[a]

Entry	Co precursor (Co mol%)	Phosphine, mol%	Solvent	Conv. (yield) ^[b] (%)
1	Co(BF ₄) ₂ (5)	TPPTS, 12	Glycerol	83 (70)
2	CoCl ₂ ·6H ₂ O (5)	TPPTS, 12	Glycerol	93 (90)
3	[Co ₂ (CO) ₈] (5) ^[c]	TPPTS, 12	Glycerol	99 (99)
4	Co(OAc) ₂ (5)	TPPTS, 12	Glycerol	95 (94)
5	[Co ₂ (CO) ₈] (5) ^[c]	TPPTS, 5	Glycerol	82 (78)
6	Co(OAc) ₂ (5)	TPPTS, 5	Glycerol	76 (75)
7	[Co ₂ (CO) ₈] (5) ^[c]	TPPTS, 2	Glycerol	81 (79)
8	Co(OAc) ₂ (5)	TPPTS, 2	Glycerol	67 (65)
9 ^[d]	[Co ₂ (CO) ₈] (5) ^[c]	TPPTS, 2	Glycerol	0 (0)
10	[Co ₂ (CO) ₈] (5) ^[c]	TPPTS, 2	CPME	69 (68)
11	[Co ₂ (CO) ₈] (5) ^[c]	TPPTS, 2	MeOH	75 (71)
12 ^[e]	[Co ₂ (CO) ₈] (5) ^[c]	PPh ₃ , 2	Toluene	30 (25)
13	[Co ₂ (CO) ₈] (5) ^[c]	BnPTA, 2	Glycerol	62 (52) ^[f]
14	[Co ₂ (CO) ₈] (5) ^[c]	BnPTA, 4	Glycerol	92 (80) ^[g]

[a] Results from duplicate experiments. Reaction conditions: 1 mmol of (*R*)-limonene and 1 mmol of morpholine, 0.01 mmol [Rh(acac)(CO)₂], 40 bar total pressure of CO/H₂ (1:1), 2 mL of glycerol, 120 °C, 18 h. [b] Determined by GC-FID using 1,3,5-tribromobenzene as internal standard. [c] Corresponding to 2.5 mol% [Co₂(CO)₈]. [d] In the absence of rhodium. [e] Triphenylphosphine was used instead of TPPTS due to its insolubility in toluene. [f] 10% of (*R*)-limonene hydrogenated product. [g] 12% of (*R*)-limonene hydrogenated product.

ammonium PTA derivative (BnPTA; PTA = 1,3,5-Triaza-7-phosphaadamantane) as glycerol-soluble phosphine,^[21] which led to a lower chemoselectivity than TPPTS, favoring the hydrogenation of (*R*)-limonene (entries 13–14 vs 7, Table 2).

With the optimized conditions in hand (see entry 7, Table 2), we studied the reaction scope of the process, with two other monoterpenes, β -pinene (**2**) and camphene (**3**), and two other amines, diphenylamine (**b**) and *N*-methylaniline (**c**) (Figure 1), obtaining moderate to good yields (30–79%). Diphenylamine led to lower yields (30–63%) than morpholine (71–79%) and *N*-methylamine (55–78%), probably due to its lower nucleophilicity compared to the other two amines. Regarding the terpene substrates, limonene gave the highest yields (63–79%) in comparison with β -pinene and camphene (30–72%) most likely due to steric reasons. Concerning the regioselectivity, morpholine and diphenylamine led to the formation of the corresponding linear amines, however *N*-methylaniline gave linear/branched amine ratios in the range 9:1. The bigger cone angle of diphenylamine (136°) compared to *N*-methylaniline (126°) can presumably impact in the regioselectivity, favoring the linear isomer by steric reasons.^[22]

After proving the efficiency of the Rh/Co catalytic system in the synthesis of terpene amines by a tandem methodology, we performed some control experiments to better understand the

reaction pathway. In a first time, we studied independently each step of the HAM reaction (hydroformylation, condensation, and enamine hydrogenation). Regarding the hydroformylation (Table 3), Rh- and Rh/Co-based catalysts led to the linear aldehyde **4**, being more active the bimetallic catalyst (entry 1 vs 3, Table 3), but in both cases leading to a low chemoselectivity (entries 1 and 3, Table 3), with an important amount of the (*R*)-limonene hydrogenation product (up to 42%) and the presence of the aldol condensation by-product (up to 6%). The monometallic Co catalyst only gave the substrate hydrogenation (entry 2, Table 3), evidencing its lower efficiency towards hydroformylation compared to rhodium. It is important to highlight that independently of the catalyst and in the absence of morpholine, the substrate hydrogenation is favored. This behavior can be explained because, under HAM conditions (presence of amine), the concentration of the aldehyde intermediate is low due to the fast condensation with the amine, in agreement with our previous studies (monitoring of HAM reaction by GC),^[14] in consequence, the hydroformylation reaction is shifted towards the aldehyde production and the formation of by-products such as aldols can be minimized operating under HAM conditions, in accordance with the kinetic study recently reported by Hamel and coworkers.^[18a] To sum up, the higher efficiency exhibited by the bimetallic system in comparison to the Rh monometallic catalyst towards the formation of the aldehyde **4**, can be associated to the cooperative effect of both metals more than that caused by the amount of phosphine available for rhodium, based on the effect of TPPTS in the HAM reaction (entries 3, 5 and 7, Table 2).

For the study of the condensation step between the aldehyde and the amine, citronellal was chosen as terpenoid substrate, working under 40 bar pressure of N₂ in order to apply the same total pressure than in the optimized HAM conditions (Table 4). Rh/TPPTS catalytic system favored the condensation giving a mixture of the enamine **5a** (36%) and its corresponding amine **5aH** (17%). This result in the absence of H₂ demonstrates the role of glycerol as reducing agent (entry 1, Table 4).^[14] Co/

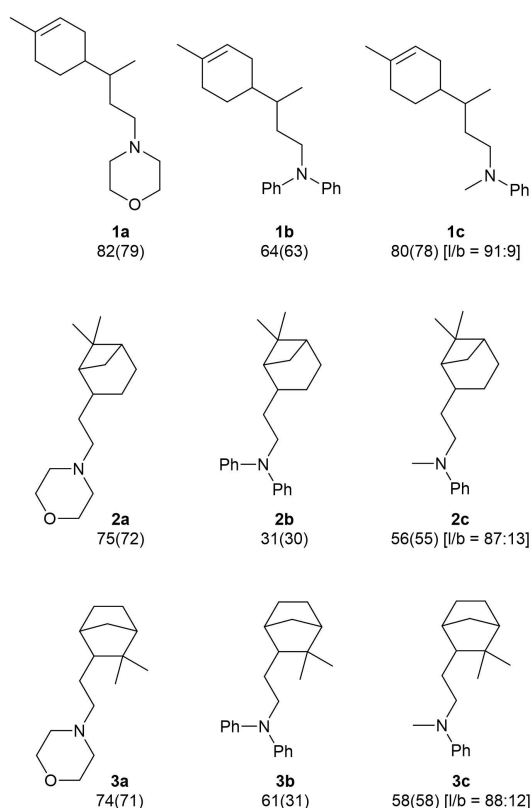
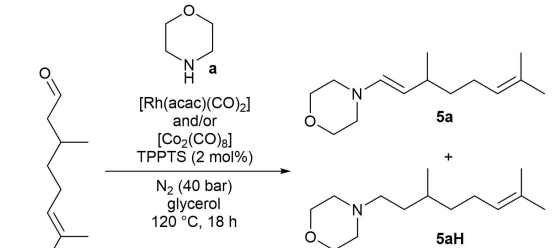


Figure 1. Synthesis of terpene amines by Rh/Co-catalyzed using (*R*)-limonene (**1**), β -pinene (**2**) and camphene (**3**) as alkenes and morpholine (**a**), diphenylamine (**b**) and *N*-methylaniline (**c**) as secondary amines. Conversions and yields (in brackets) determined by GC-FID using 1,3,5-tribromobenzene as internal standard. The linear/branched ratio (in square brackets) was determined by ¹H NMR. For reaction conditions, see entry 7 of Table 2.

Entry	Rh (mol %)	Co (mol %)	Conv. (yield) (%) ^[b]
1	1	–	27 (17) ^[d]
2	–	5 ^[d]	23 (0) ^[e]
3	1	5 ^[d]	94 (45) ^[f]

[a] Results from duplicate experiments. Reaction conditions: 1 mmol of (*R*)-limonene, 0.01 mmol [Rh(acac)(CO)₂] and/or 0.025 mmol of [Co₂(CO)₈] (0.05 mmol of total Co), 0.02 mmol TPPTS, 40 bar total pressure of CO/H₂ (1:1), 2 mL of glycerol, 120 °C, 18 h. [b] Determined by GC-FID using 1,3,5-tribromobenzene as internal standard. [c] 10% of (*R*)-limonene hydrogenated products. [d] Corresponding to 2.5 mol% [Co₂(CO)₈]. [e] (*R*)-limonene hydrogenated products. [f] 42% of (*R*)-limonene hydrogenated products and 6% of the aldol condensation product.

Table 4. Metal-catalyzed condensation of citronellal and morpholine.^[a]



Entry	Rh (mol%)	Co (mol%)	Conv. (yield) (%) ^[b]
1	1	–	86 (36, 5a ; 17, 5aH) ^[d]
2	–	5 ^[c]	45 (8, 5a ; 7, 5aH) ^[e]
3	1	5 ^[c]	97 (40, 5a ; 38, 5aH) ^[f]
4	–	–	5 (4, 5a)

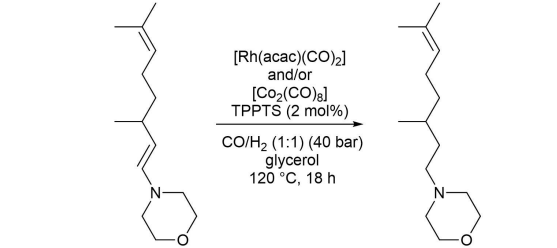
[a] Results from duplicate experiments. Reaction conditions: 1 mmol of citronellal, 1 mmol of morpholine, 0.01 mmol [Rh(acac)(CO)₂] and/or 0.025 mmol of [Co₂(CO)₈] (0.05 mmol of total Co), 0.02 mmol TPPTS, 40 bar N₂, 2 mL of glycerol, 120 °C, 18 h. [b] Determined by GC-FID using 1,3,5-tribromobenzene as internal standard. [c] Corresponding to 2.5 mol% [Co₂(CO)₈]. [d] 21% and 4% of aldol condensation by-products. [e] 8% of an isomerization by-product of **5a**, as well as 16% and 3% of aldol condensation by-products. [f] 12% of an aldol condensation by-product.

TPPTS catalyst was less active obtaining an equimolar amount of **5a** and **5aH** (45% conversion; 15% of **5a** and **5aH**; entry 2, Table 4). In both cases, chemoselectivity was low, also obtaining alcohols and aldol condensation by-products (see Figure S1 in the Supporting Information). When the bimetallic-based catalytic system was used, higher conversion (97%) and chemoselectivity (40% of **5a** and 38% of **5aH**) were observed (entry 3, Table 4). In the absence of any catalyst, the reaction led to a lower conversion but exclusively giving the enamine (entry 4, Table 4). These controls proved that: i) both Rh- and Co-based species act as Lewis acid promoting the condensation step, the Rh catalytic system being more efficient and selective; ii) Co/TPPTS catalyst promotes the hydrogen transfer involving glycerol as reducing agent; and iii) the presence of both catalysts strongly decreases the formation of by-products.

With the purpose of studying the slowest step of the HAM tandem process (enamine hydrogenation),^[18a] we used the enamine **5a** as substrate (Table 5). We decided to use the syngas mixture since carbon monoxide can have a plausible effect in the nature of organometallic intermediates. For both monometallic and bimetallic catalysts, the conversion was high (more than 93%) with high chemoselectivity (yields of the amine **5aH** higher than 75%). For both monometallic systems, the formation of citronellal (from the enamine hydrolysis) was higher (up to 15% in the case of the Rh catalyst) than in the case of the bimetallic system (not detected), probably due to the cobalt boosting effect for the enamine reduction (by both hydrogenation and hydrogen transfer pathways).

From the results shown in Tables 3–5, we can conclude that cobalt mainly acts in the reductive amination, while rhodium has a preponderant role in the hydroformylation step. Thus, the bimetallic Rh/Co catalytic system enhances specially the reductive amination (condensation and enamine reduction,

Table 5. Metal-catalyzed enamine reduction.^[a]



Entry	Rh (mol%)	Co (mol%)	Conv. (yield) (%) ^[b]
1	1	–	93 (75) ^[c]
2	–	5 ^[d]	94 (86) ^[e]
3	1	5 ^[d]	98 (92)

[a] Results from duplicate experiments. Reaction conditions: 1 mmol of **5a**, 0.01 mmol [Rh(acac)(CO)₂] and/or 0.025 mmol of [Co₂(CO)₈], 0.02 mmol TPPTS, 40 bar total pressure of CO/H₂ (1:1), 2 mL of glycerol, 120 °C, 18 h. [b] Determined by GC-FID using 1,3,5-tribromobenzene as internal standard. [c] 15% of citronellal. [d] Corresponding to 2.5 mol% [Co₂(CO)₈]. [e] 8% of citronellal.

Tables 4 and 5) while aldehyde is quickly consumed in the presence of the amine towards the formation of the enamine.

With the purpose of studying the stability of the homogeneous catalytic system under the working conditions, we explored the possibility to recycle the catalytic system taking into account the beneficial effect of glycerol on the stabilization of organometallic complexes and intermediates, as proven in Rh-catalyzed Pauson-Khand reactions.^[23] For that we carried out the study of the benchmark reaction under the optimized conditions (see entry 7 of Table 2). Unfortunately, after the first run both conversion and yield dropped to ca. 60% (see Figure S2 in the Supporting Information). TEM analyses after each run were carried out, evidencing the formation of metal nanoparticles, as observed previously in our group for Rh-catalyzed HAM reactions of alkyl and aromatic alkenes (see Figure S3 in the Supporting Information).^[14] The size of the metal nanoparticles increased after each run, up to attaining a mean diameter of 3.4 nm after the 4th run, behavior in agreement with a progressive adsorption of molecular species on initially formed clusters. Furthermore, we analyzed by ICP-AES the organic crudes (before column chromatography purification) extracted from the glycerol catalytic mixture with dichloromethane (see Table S1 in the Supporting Information). The cobalt content was low and constant along the four runs (0.2–0.6 ppm); in contrast, the rhodium content was relatively high for the first run (2.1 ppm) while after the successive runs it remained low and constant (0.3–0.7 ppm). This trend seems to point that both Co and Rh nanoparticles can be formed under the reductive HAM reaction conditions, favored by the high affinity of glycerol to immobilize metal nanoparticles.^[24] Accordingly, we could prove that the Rh/Co catalytic system leads to the formation of metal nanoparticles under reductive conditions upon HAM completion, triggering its deactivation and in consequence evidencing the catalytic homogenous behavior of the Rh/Co system.

Conclusion

An efficient bimetallic Rh/Co-based catalyst has enabled the preparation of bio-sourced homologated terpenic amines by tandem hydroaminomethylation reactions, leading to the synthesis of **1a–c**, **2a–c** and **3a–c** in moderate to good yields (30–79%) and exhibiting excellent chemoselectivity towards the formation of tertiary amines, with high linear-to-branched regioselectivity. Mechanistic studies revealed the role of Rh facilitating the initial hydroformylation reaction, as well as its contribution in combination with Co in promoting a fast condensation of the aldehyde and the amine that precludes aldol side-reactions by keeping the former in low concentration throughout the reaction, driving the formation of the enamine intermediate in high selectivity. In addition, the role of Co and glycerol in boosting the reduction of the transient enamine via hydrogenation and hydrogen transfer processes, respectively, have been evidenced. Thus, the cooperative effect of both metals and glycerol towards empowering the HAM reaction of reluctant biomass-derived terpene substrates has been demonstrated. These results suggest that only molecular metal-based species are catalytically active and their decomposition leads to agglomeration pathways yielding nanoparticle systems that are no longer active towards HAM.

Experimental Section

General information, the procedure for the catalytic recycling and characterization data of the organic products could be found in the Supporting Information.

General procedure for hydroaminomethylation reactions: The terpene (1.0 mmol) and the amine (1.5 mmol) were dissolved in 2 mL of dried glycerol in the presence of the corresponding catalyst (from 1 to 5 mol% of Rh and/or Co). Once the autoclave was sealed, it was pressurized at the working pressure and the reactor was heated up to 120 °C. After depressurization and cooling down to room temperature, the glycerol was extracted with CH₂Cl₂ (3 × 4 mL) and the combined organic extracts were filtered through Celite. The combined organic fractions were analyzed by gas chromatography coupled to mass spectrometer and FID detectors, using 1,3,5-tribromobenzene as internal standard, unless otherwise stated.

Supporting Information

The following supporting information is available: General experimental information and general procedure for catalytic recycling, Figures S1–S3, Table S1, characterization data of organic compounds (**1a**, **2a**, **3a**, **1b**, **2b**, **3b**, **1c**, **2c**, and **3c**), ¹H and ¹³C NMR spectra of selected terpene amine products. The following additional references have been cited within the Supporting Information.^[25–29]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Cobalt · Cooperative effects · Glycerol · Hydroaminomethylation · Rhodium

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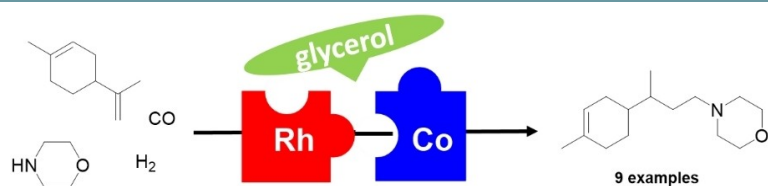
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with glycerol, acting as a boosting solvent, leads to an efficient and selective process for the four-component hydroaminomethylation reaction.

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1 – 7

A Cooperative Rh/Co-Catalyzed Hydroaminomethylation Reaction for the Synthesis of Terpene Amines

