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Microwave-Assisted Reductive Amination under Heterogeneous Catalysis for the Synthesis of β-Adrenergic Agonist and Related Structures

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Abstract: Reductive amination is a powerful tool in sustainable organic synthesis that allows chemists to access a wide range of valuable amine products using renewable feedstocks and mild reaction conditions, with minimal waste generation. Practical applications can be found in various fields, including pharmaceuticals, contributing to greener and more sustainable chemical processes. In this work, we present a heterogeneous (Rh and Pt) catalyzed protocol for the fast and efficient synthesis of ractopamine hydrochloride (β-adrenergic drug) under microwave-assisted reductive amination protocol starting from raspberry ketone and octopamine. Microwave (MW) successfully accelerated the hydrogenation reaction and reduced the reaction time from 13 h to only 3 h under mild conditions (50 °C at 10 bar). The best catalysts were Pt/C and Rh/C, which led to high conversion and selectivity towards ractopamine:HCl. Different solvents and ketone substrates were also experimented. Acetophenone, cyclohexanone, and 2-butanone reacted at lower H_2 pressure (5 bar), and highest selectivity was observed with cyclohexanone (99%). These preliminary experiments may be useful for further process improvements in the synthesis of β-adrenergic agonists and related structures and underline the positive synergy between MW and heterogeneous catalysis.

Keywords: reductive amination; process intensification; microwave-assisted reactions; transition-metal catalysts; ractopamine:HCl; raspberry ketone

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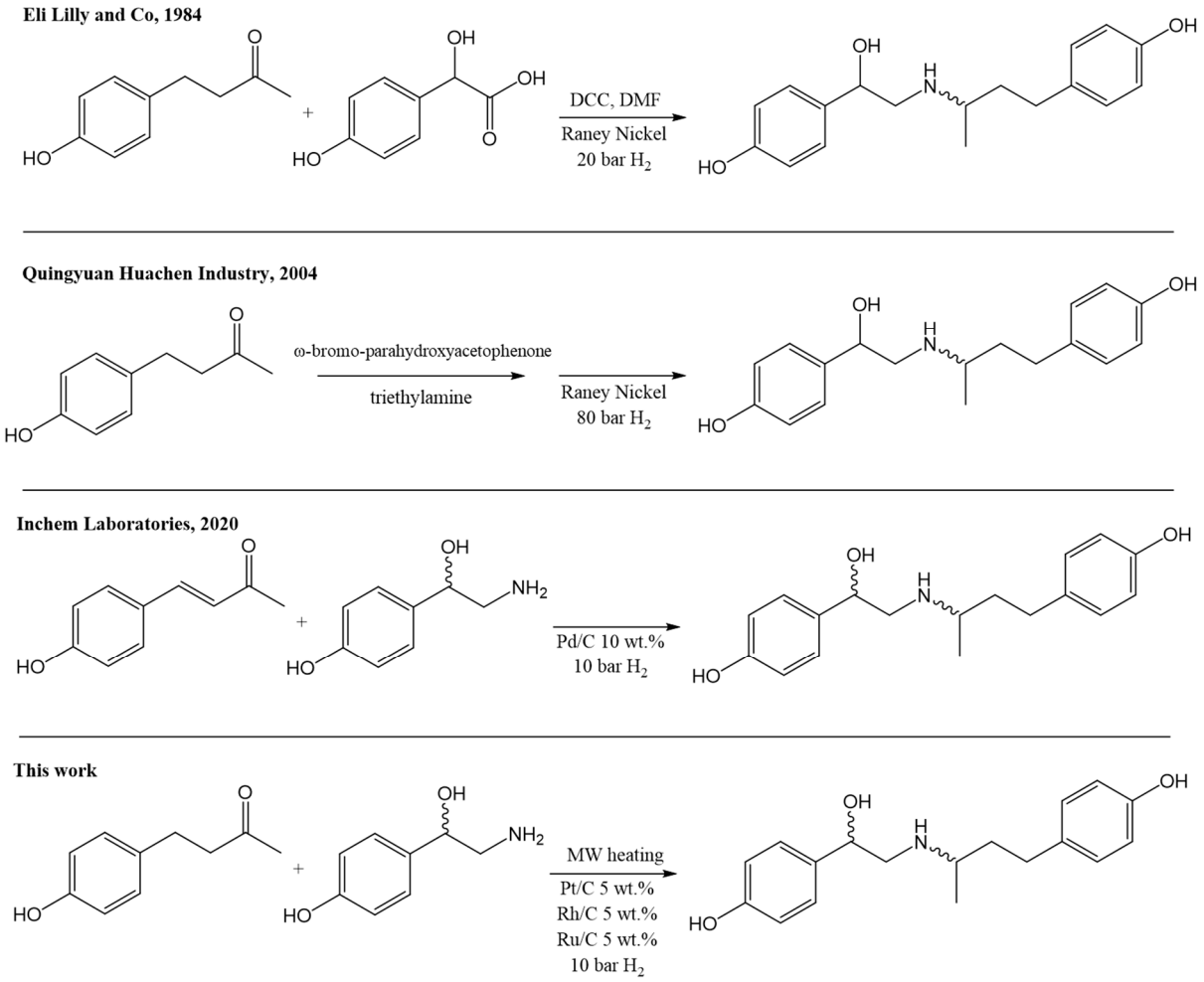
1. Introduction

Reductive amination is an important and versatile organic reaction that finds extensive applications in sustainable synthetic processes and has been intensively investigated in both academia and industry [1,2]. Mechanistically, the reaction begins with a condensation step in which the carbonyl compound reacts with ammonia or an amine to form the corresponding imine, followed by reduction of the imine to the alkylamine product [3]. Many of these reduction steps require the presence of a catalyst to activate the reducing agent [4], and transition-metals (such as Ru, Rh, Pd, Ag, Ir, Pt, and Au) have also been used extensively [5] in the preparation of active pharmaceutical ingredients (APIs) [6,7]. Despite its cost, Rh shows remarkable activity for such a reaction, as shown in the recent literature [8–11], and has the potential to be employed in robust hydrogenation catalysts with low metal loading. A Rh/Al_2O_3-catalyzed reductive amination of furfural and other aldehydes, especially those associated with biomass, was recently reported by Chatterjee, Kawanami, and coworkers using an aqueous solution of NH_3 [12]. A very high selectivity to furfurylamine (~92%) was documented by the authors in only 120 min at 80 °C with the chance to reuse the catalyst several times.

Moreover, reductive amination has attracted considerable attention in recent years in sustainable organic synthesis due to its environmental advantages and broad synthetic utility [13,14]. Apart from its versatility, as primary, secondary, and tertiary alkylamines are readily available, reductive amination usually exhibits good atom economy, which means that most of the atoms present in the starting materials end up in the desired product. This minimizes waste generation and maximizes resource utilization. In addition, reductive amination can often be carried out under mild conditions with remarkable energy saving [15]. In this framework, microwave heating (MW) is a mature technology that could be exploited to boost the sustainability of reductive amination protocols. Indeed, MW promotes the remarkable reduction of reaction time and yields enhancement and cleaner reactions compared to conventional thermal heating. MW irradiation is, therefore, a suitable tool to overcome the limitations encountered in challenging organic reactions, such as direct reductive amination in the presence of heterogeneous catalysts and gaseous reagents. In particular, the use of metallic nanoparticles as catalysts also allows a positive synergy with microwave (MW) heating [16,17], an alternative technology that allows a faster heating rate and less side-reaction on the surface of the reactor [18], which with convective heating are usually hotter than the bulk, at least in the laboratory scale. In this work, we present a Rh-catalyzed optimized protocol for the fast and sustainable synthesis of ractopamine (a β-adrenergic compound) under MW-assisted protocol.

Ractopamine hydrochloride is the common name for 4-[3-[[2-hydroxy-2-(4-hydroxyphenyl) ethyl] amino] butyl] phenol hydrochloride. It occurs in four stereoisomers (RR, RS, RS, SS), and it is a bioactive molecule defined as a phenyl ethanolamine β-adrenoceptor agonist (β-agonists) [19]. The β-agonists redirects nutrients away from fat deposition to muscle deposition, involving the modulation of metabolic pathways and signals in muscle and lipid cells to enhance protein accretion. Other mechanisms also include regulation of hormone release and modification of blood flow [20]. Ractopamine:HCl is currently used as a feed additive to improve the feed efficiency and the carcass leanness in swine and cattle, as allowed in the USA, Canada, Japan, and Mexico [21].

The synthetic method of producing the ractopamine hydrochloride has been introduced following several routes in the existing literature. In particular, two methods are introduced in the Eli Lilly and Co patent [22]. The first method involves the synthesis of ractopamine:HCl using raspberry ketone and right-hydroxymandelic acid as raw materials. The latter involves the use of *p*-hydroxyphenylethanol amine instead of hydroxymandelic acid. These synthetic pathways do not lead to complete conversions and high selectivity, leading to the formation of numerous by-products. Additionally, the reaction conditions, separation, and purification processes are all quite challenging. Another synthetic approach was proposed by the Chengdu Organic Chemistry Institute, Chinese Academy of Sciences, in their patent [23] and developed by Jie Shaoing. Starting from raspberry ketone, this method included a ketoxime reaction followed by a condensation reaction with ω-bromo-*p*-hydroxyacetophenone and triethylamine under low-temperature conditions. Subsequently, a catalytic hydrogenation step was required to yield the ractopamine:HCl. However, ractopamine is currently synthetized via reductive amination between raspberry ketone and octopamine (Scheme 1) [24], in which the hydrogenation step can be easily catalyzed by a heterogeneous metal-based catalyst [25,26] such as Pt [27–29] or Pd [30,31], which can be easily recovered and reused. More recently, a patent from Inchem Laboratories Pvt Ltd. reports the synthesis of ractopamine hydrochloride starting from 4-*p*-tolybut-3-en-2-one and octopamine by reductive amination over a Pd/C 10 wt.% catalyst at 50 °C and H_2 (10 bar, for 20 h) [32].



Scheme 1. Comparison of the synthetic methods to produce ractopamine from the existing literature [22,23,32].

In this work, we present a study on the MW-assisted synthesis of ractopamine in which Pt/C, Ru/C, and Rh/C (all 5 wt.%) were tested as heterogenous catalysts. Their activity has been screened at different temperatures and hydrogen pressures in the presence of MW heating. Further, the reaction was performed in different solvents, and different ketone substrates were considered for the reaction with octopamine in the optimized conditions, with the objective to highlight the positive influence of MW and heterogeneous catalysis as well as the key parameters for the optimal yield.

2. Materials and Methods

The heterogeneous Pt/C, Ru/C, and Rh/C 5 wt.% catalysts and the ketones were purchased from Sigma-Aldrich (Merck KGaA, Darmstadt, Germany). Octopamine HCl, raspberry ketone, and ractopamine HCl were supplied by Huvepharma Italy Srl.

As a general procedure, the reagents were weighed and dissolved in a previously prepared stock solution of KOH in MeOH and stirred briefly. The pH was then checked with litmus paper and adjusted with glacial acetic acid added dropwise. The appropriate amount of catalyst was then added and suspended under stirring, then transferred to the selected reactor.

The batch reaction with conventional heating was performed in a 300 mL PolyBlock reactor equipped with a PTFE impeller for stirring. The reactor has a minimum working volume of 41 mL and operates up to 100 bar and 250 °C. A sampling valve on the bottom

allows the removal of the crude reaction mixture for analysis. The reactor was flushed three times with 2 bar of N_2 before the appropriate pressure of H_2 was introduced.

The MW-assisted reductive amination reactions were performed in a MW autoclave (SynthWAVE by Milestone srl, Sorisole, Italy) in 15 mL glass vials provided with magnetic stirring (500 rpm) all inside a 1 L PTFE reaction chamber filled with 200 mL of brine solution used to absorb the excess radiation. The reaction chamber was flushed three times with 2 bar of N_2 before the appropriate H_2 pressure was introduced. A heating ramp of 2 min was used, with a maximum MW power of 800 W.

After the reaction, the crude was recovered and filtered over paper to recover the catalyst. The filtrate was dried under vacuum, redissolved in pyridine, and derivatized with N,O-*Bis*(trimethylsilyl)trifluoroacetamide (BSTFA) prior to the GC–MS analysis. The obtained chromatograms and fragmentation patterns are reported in the supplementary information file.

The GC–MS equipment used was an Agilent Technologies 6850 Network GC System fitted with a 5973 Network Mass Selective Detector, a 7683B Automatic Sampler and a capillary column Mega 5MS (length 30 m; i.d. 0.25 mm; film thickness 0.25 µm, Mega s.r.l., Legnano, Italy). The HPLC–DAD equipment used for the diastereomeric ratio determination was an Agilent 1100 using a Hypersil ODC C18 column (5 µm particles diameter and 4.6 mm × 250 mm). The mobile phases were an ammonium hydroxide orthophosphate buffer (A) and acetonitrile (B). The peaks were recorded at 226 nm.

3. Results

The optimization of ractopamine synthesis was primarily investigated using a commercial Pt/C (5 wt.%) catalyst as a reference material for the hydrogenation step. The reductive amination between octopamine and raspberry ketone was firstly performed in batches at the laboratory scale under conventional heating (Scheme 1). A KOH solution in MeOH was prepared and slowly added with the reagents, and the pH adjusted with glacial acetic acid at 6.5. The hydrogenation step was performed at 50 °C under H_2 pressure (5 bar). In these conditions, 13 h were necessary to achieve a complete coupling and hydrogenation of the reagents for a final 98.9% yield of ractopamine:HCl. With these batch conditions as reference, we moved on to the MW experiments (Table 1). At first, the influence of temperature and H_2 pressure on the ractopamine yield was studied. It was observed that increasing the temperature from 50 to 80 °C did increase the yield but at the expense of selectivity. Increasing the H_2 pressure from 5 to 10 bar instead provided an increase of both conversion and selectivity at 50 °C.

Table 1. Influence of temperature and hydrogen pressure.

Entry	T (°C)	H_2 (bar)	Conversion (%)	Selectivity (%)	Yield (%)
1	50	5	10.0	63.2	6.3
2	80	5	87.2	47.0	41.0
3	50	10	91.6	94.5	86.6

Reaction conditions: 1 eq. raspberry ketone, 1 eq. octopamine, 1 eq. KOH, 5 mL MeOH/H_2O 1:1, 10 mg Pt/C 5 wt.%, 3 h.

The main byproduct observed is imine, resulting from the coupling between raspberry ketone and octopamine but without hydrogenation. Further, upon HPLC analysis (Appendix A, Figure A1, Table A1) to assess the diastereomeric ratio (RS-SR/SS-RR), which resulted in 47/53 that falls in the reference ratio for the commercial product (RS-SR 45–49%). Having established 50 °C and 10 bar pressure of H_2 as the optimal reaction conditions, we compared the activity of Pt/C 5 wt.% with other heterogeneous catalysts based on Rh and Ru with the same support and metal loading (Table 2). Results show that Pt and Rh have similar activities, while Ru despite having a comparable conversion does not promote the hydrogenation step, thus only leading to the intermediate imine (supplementary information, Figures S7 and S8). Rh/C was also tested with 5 bar of H_2. In this case, its activity out-

performed Pt/C, but both conversion and selectivity dropped compared to the reaction performed at 10 bar. The reaction crude from the Rh/C reaction was also found within the acceptable diastereomeric ratio and with the same 47/53 value as for the Pt/C test (Appendix A, Figure A2, Table A2).

Table 2. Heterogeneous catalyst screening.

Entry	Catalyst	H_2 (bar)	Conversion (%)	Selectivity (%)	Yield (%)
1	Pt/C	10	91.6	94.5	86.6
2	Rh/C	10	81.0	91.9	74.4
3	Ru/C	10	73.0	n.d.	-
4	Rh/C	5	47.0	80.4	37.8

Reaction conditions: 1 eq. raspberry ketone, 1 eq. octopamine, 1 eq. KOH, 5 mL MeOH/H_2O 1:1, 10 mg Pt/C or Rh/C 5 wt.%, 50 °C, 10 bar H_2, 3 h.

Different solvents were also tested for the reaction in order to scout for greener and safer alternatives to methanol (Figures 1 and 2). Isopropanol (*i*PrOH), 2-methyltetrahydrofuran (MTHF), and cyclopenthylmethylether (CPME) were thus selected. However, the methanolic solution proved to be the optimal solvent for both catalysts. The second-best result was achieved with CPME both over Pt/C (39.1% yield) and Rh/C (51.3% yield).

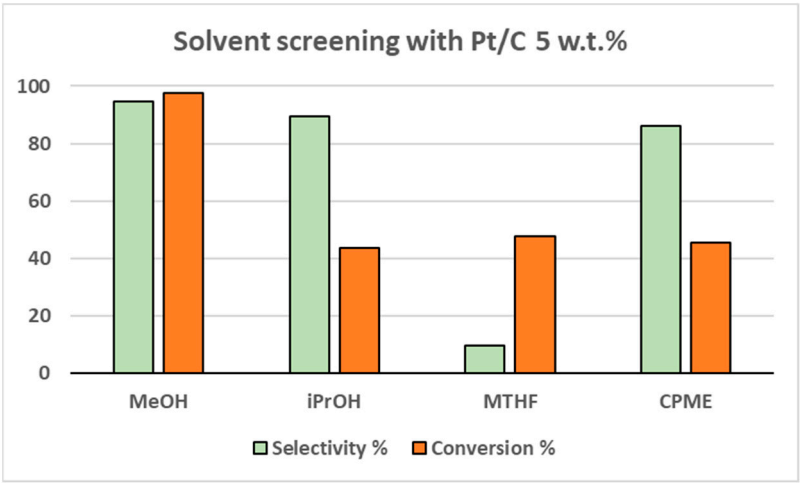


Figure 1. Solvent screening over Pt/C 5 wt.%.

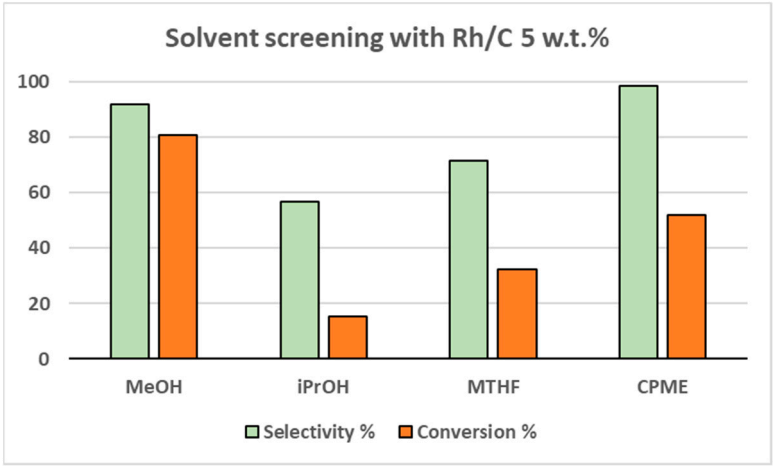


Figure 2. Solvent screening over Rh/C 5 wt.%.

Finally, to broaden the scope of our study, other ketones were used as substrates for the reaction (Table 3). Acetophenone, cyclohexanone, and 2-butanone were selected to provide an array of cyclic, linear, aromatic, and aliphatic substrates. While acetophenone gave low selectivity in the tested conditions, both cyclohexanone and 2-butanone gave excellent results over both Pt/C and Rh/C. Further, using 10 bar pressure of H_2 was a disadvantage since selectivity was lower than that with 5 bar only. This lack of selectivity derives from two competing reactions: the hydrogenation of the aromatic ring (in acetophenone) and the reduction to the corresponding alcohol. Both reactions are favored by a higher H_2 pressure.

Table 3. Conversion of ketone substrates over Pd/C and Rh/C 5 wt.%.

Entry	Catalyst	Substrate	H_2 (Bar)	Conversion (%)	Selectivity (%)	Yield (%)
1	Pt/C	Acetophenone	5	n.d.	n.d.	-
2			10	89.6	29.2	26.2
3		Cyclohexanone	5	>99	>99	>99
4			10	>99	>99	>99
5		2-Butanone	5	>99	80.2	80.2
6			10	>99	96.3	96.3
7	Rh/C	Acetophenone	5	>99	8.2	8.2
8			10	>99	8.0	8.0
9		Cyclohexanone	5	>99	82.7	82.7
10			10	>99	22.1	22.1
11		2-Butanone	5	>99	92.4	92.4
12			10	>99	50.2	50.6

Reaction conditions: 1 eq. ketone, 1 eq. octopamine, 1 eq. KOH, 5 mL MeOH/H_2O 1:1, 10 mg Pt/C or Rh/C 5 wt.%, 50 °C, 3 h.

4. Conclusions

The effect of temperature and hydrogen pressure was studied for the synthesis of ractopamine by reductive amination. Increasing the temperature from 50 to 80 °C had a positive effect on the conversion, but at the expense of selectivity, while increasing the H_2 pressure from 5 to 10 bar improved the yield from 6.3 to 86.6%. Different heterogeneous catalysts were tested for the reaction, and both Pt/C and Rh/C (5 wt.%) were found to be suitable for the reaction, which was completed in 3 h instead of 13 h as in the batch tests using conventional heating. Finally, various ketone substrates were coupled with octopamine, demonstrating the flexibility of the setup that allows yields of up to 99% even at 5 bar of H_2.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pr11092602/s1.

Author Contributions: Conceptualization, G.C. and E.C.G.; formal analysis, F.B. and E.C.; investigation, F.B., M.C. and G.G.; data curation, G.G. and E.C.; writing—original draft preparation, F.B. and M.C.; writing—review and editing, E.C.G. and G.C.; supervision, E.C.G. and G.C. All authors have read and agreed to the published version of the manuscript.

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Appendix A

The best reaction conditions disclosed for the MW-assisted synthesis of ractopamine (50 °C with MW for 180 min and H_2 (10 bar), using Pt/C (5% *w*/*w*) (Table 2, entry 1) were

deeply investigated in terms of product characterization via HPLC–DAD. The analysis was performed using the HPLC validate method described in detail in paragraph 2, and the results are reported in the Figure A1 and Table A1, showing that the newly synthesized ractopamine HCl is on specification [33].

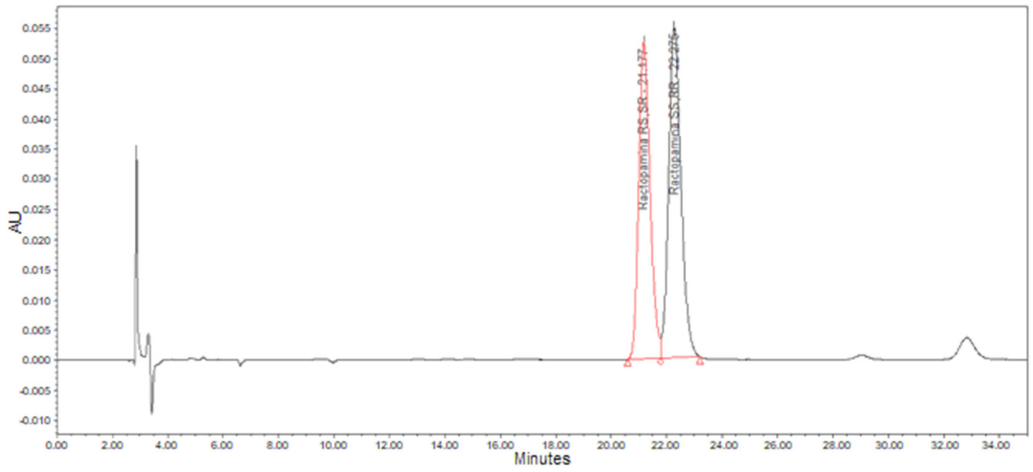

Figure A1. HLPC Chromatogram—diastereomeric ratio determination at the best reaction conditions: 50 °C with MW for 180 min and H_2 (10 bar), using Pt/C 5% as catalyst.

Table A1. Diastereomeric ratio of the sample obtained at the best reaction conditions: 50 °C with MW for 180 min and H_2 pressure (10 bar), using Pt/C 5% *w*/*w* as catalyst.

Name	Retention Time	Area	% Area	Specification
Ractopamine *RS*,*SR*	21.177	1,497,290	47.00	*RS*,*SR* 45–49%
Ractopamine *SS*,*RR*	22.275	1,688,481	53.00	

The *RS*,*SR* diastereomeric ratio was also evaluated for the ractopamine HCl sample synthetized with MW for 180 min at 50 °C and H_2 (10 bar) with Rh/C as catalyst (Table 2, entry 2). The analysis was performed using the HPLC validate method described in detail in paragraph 2 and the results demonstrate that the sample is on specification (Figure A2, Table A2) [31].

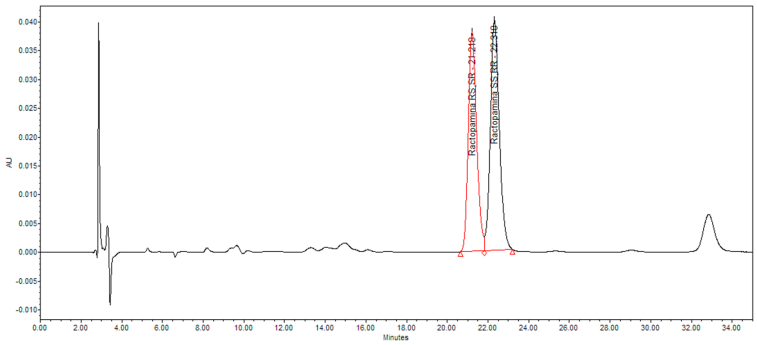

Figure A2. HPLC Chromatogram—diastereomeric ratio determination at the best reaction conditions: 50 °C with MW for 180 min and H_2 (10 bar), using Rh/C 5% *w*/*w* as catalyst.

Table A2. Diastereomeric ratio of the sample obtained at the best reaction conditions: 50 °C with MW for 180 min and H_2 (10 bar), using Rh/C 5% *w*/*w* as catalyst.

Name	Retention Time	Area	% Area	Specification
Ractopamine *RS*,*SR*	21.218	1,085,144	47.06	*RS*,*SR* 45–49%
Ractopamine *SS*,*RR*	22.318	1,220,961	52.94	

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