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Article

Fast and Highly Selective Continuous-Flow Catalytic Hydrogenation of a Cafestol–Kahweol Mixture Obtained from Green Coffee Beans

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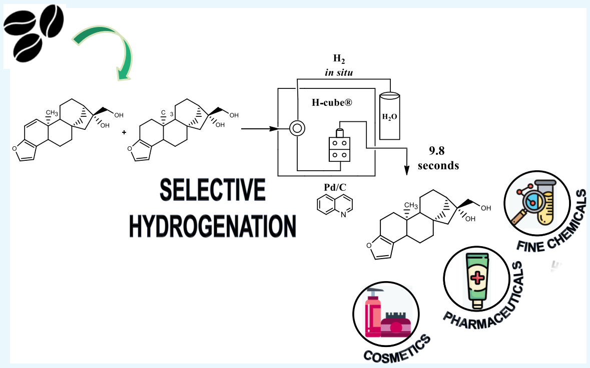
ABSTRACT: This work investigates batch and continuous-flow heterogeneous catalytic hydrogenation of a mixture of cafestol and kahweol (C&K) to obtain pure cafestol. These diterpenes were extracted from green coffee beans, and hydrogenation was performed using well-established palladium catalysts (Pd/C, Pd/$CaCO_3$, Pd/$BaSO_4$, and Pd/Al_2O_3) and a carbon black-supported Pd catalyst coated by a covalently tethered SiO_2 shell with mesoporous texture (Pd/CB@SiO_2), all partially deactivated with quinoline. Pd/C 10% poisoned with 1 wt % quinoline gave the best result for batch reaction, producing cafestol from kahweol with high selectivity (>99%) after 10 min. Excellent selectivity was also obtained with the catalyst Pd/CB@SiO_2 with only 1% Pd. In addition, Pd/C-quinoline adapted for continuous-flow experiments exhibited the best catalytic activity, also providing cafestol with excellent selectivity (>99%) after 9.8 s.



INTRODUCTION

The lipid fractions of green Robusta and Arabica coffees represent 7.7 to 18.0% of the total chemical composition of the beans. The pentacyclic diterpenes cafestol and kahweol (C&K) are the main representatives of the unsaponifiable fraction of the coffee oil.[1,2] In *Coffea arabica*, they may be present in free form (around 0.4% w/w of the lipid fraction) or esterified with different fatty acids (about 17%) such as linoleic (44%) and palmitic (30%).[3] Structurally, cafestol and kahweol are two *ent*-kaurene furane diterpenes that differ by one unsaturation between C1 and C2 (Figure 1).[4]

Cafestol has many biological activities reported such as antioxidant,[5,6] anti-inflammatory,[7,8] anticarcinogenic activities,[9] and photoprotection capacity,[10,11] which make this substance valuable to the pharmaceutical and cosmetic industries. The procedures described in the literature for the isolation of C&K from green coffee beans involve the direct saponification of all acylated cafestol and kahweol compounds.[12−14] Dias et al.[3] performed the isolation of free C&K from roasted coffee on an analytical scale using direct hot saponification (DHS) as a more efficient extraction method than Soxhlet and Bligh and Dyer.

Haworth et al. were the first to investigate the preparation of cafestol employing heterogeneous catalytic hydrogenation of a C&K mixture.[15] They observed that, after 30 min, kahweol transformed into cafestol in the presence of H_2 and 2% palladium on activated charcoal and ethanol as solvent. Nonetheless, the authors did not report the conversion of the reaction. Bertholet[16] hydrogenated a C&K mixture under batch conditions using palladium catalysts conditioned by lead acetate such as Pd/C, Pd/$BaSO_4$, Pd/Al_2O_3, and Lindlar catalyst. The reaction with 5 wt % Pd/C and Pd/$CaCO_3$, poisoned with Pb, transformed kahweol into cafestol (99%) after 2 h. Another experiment using Pd/Al_2O_3 poisoned with Pb converted only 45% of kahweol and produced furan-ring-opening products. A similar approach using Pd/$BaSO_4$ poisoned with Pb destroyed all the kahweol after 2 h. Despite the good results with the first two catalysts, the high toxicity associated with Pb is a massive problem for the preparation of highly pure pharmaceuticals and fine chemicals. Thus, alternative additives were studied to find suitable replacements for lead acetate, preserving the high conversion and selectivity. Quinoline is as a reversible modifier used in heterogeneous hydrogenation reactions with palladium catalysts to enhance reaction selectivity by modifying the catalyst surface properties.[17−19]

Hydrogenation reactions of the C&K mixture using batch strategies are usually effective. However, these processes have significant disadvantages, for instance, poor safety due to high

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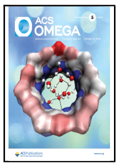

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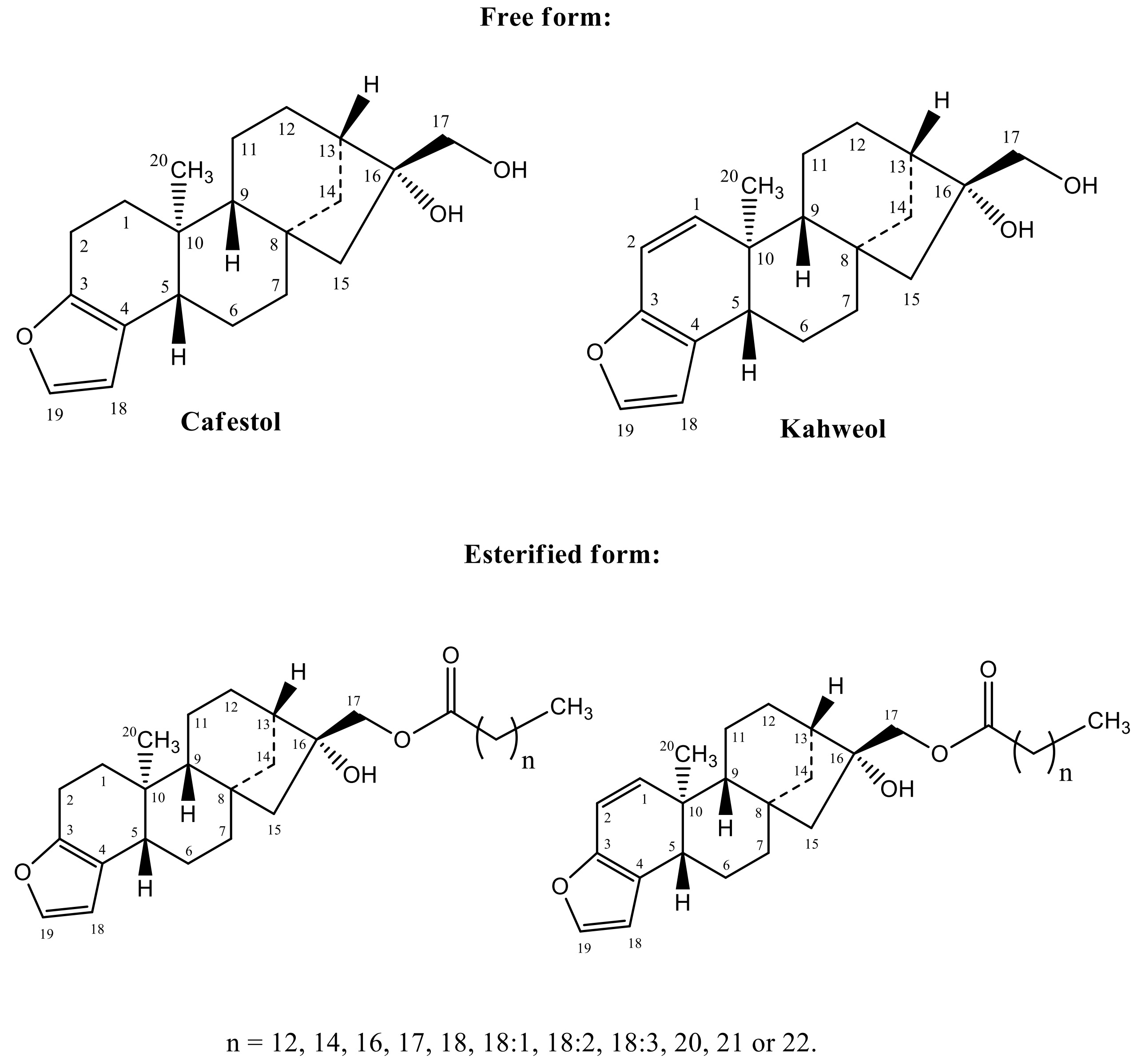

Figure 1. Chemical structures of cafestol and kahweol in free and esterified form.

operating pressures of hydrogen, long reaction times (2 to 4 h), and the additional filtration step to remove the catalyst. A high-pressure continuous-flow system offers solutions to these problems. First, process safety is ensured by the *in situ* production of hydrogen through the electrolysis of water. Second, in this system, a gas−liquid mixture passes through a cartridge containing the catalyst that can be recovered by washing it with an appropriate solvent, without an impairment of the catalytic activity and selectivity. Last, it allows the chemical transformation to happen in a short time and solvent and energy economy in a much smaller space.[20]

This work presents a fast and highly selective procedure for the hydrogenation of C&K to produce pure cafestol applying a high-pressure continuous-flow technique with palladium catalysts partially deactivated with quinoline. The experiments were conducted in batch and continuous-flow conditions to compare the efficiency of the two systems.

■ RESULTS AND DISCUSSION

Batch Hydrogenation of the C&K Mixture. The experiments under batch conditions were performed using 5 mg of different palladium catalysts partially deactivated with 1 wt % quinoline. Table 1 summarizes the results of the selective hydrogenation of the C1−C2 double bond on the kahweol skeleton. The chromatograms are shown in the Supporting Information (Figures S2−S6).

The batch hydrogenation with 10% Pd/C resulted in the best outcome, producing cafestol (>99%) after 10 min with selectivity >99% (Table 1, entry 2). The increase of reaction time to 30 or 60 min did not affect the excellent conversion and selectivity (Table 1, entries 3 and 4). The reactions using the Pd/C 10% catalyst with 1 wt % quinoline did not produce dehydration products (DP), involving the loss of the C-16 tertiary hydroxyl group, and furan ring hydrogenation products (FRHP), proposed by Guerreiro et al.[21] and Lam et al.[22] (see Figures 2 and 3).

Table 1. Hydrogenation of C&K with Different Pd Catalysts Deactivated with 1 wt% Quinoline[a]

entry	catalyst	time (min)	conversion (%)	cafestol selectivity (%)[b]
1	Pd/C 10%	5	97.0	97.0
2	Pd/C 10%	10	100	>99.0
3	Pd/C 10%	30	100	>99.0
4	Pd/C 10%	60	100	>99.0
5	Pd/$CaCO_3$ 5%	5	92.0	90.0
6	Pd/$CaCO_3$ 5%	10	100	97.0
7	Pd/$CaCO_3$ 5%	30	100	96.0
8	Pd/$CaCO_3$ 5%	60	100	93.0
9	Pd/$BaSO_4$ 5%	5	79.0	79.0
10	Pd/$BaSO_4$ 5%	10	88.0	88.0
11	Pd/$BaSO_4$ 5%	30	100	91.0
12	Pd/$BaSO_4$ 5%	60	100	89.0
13	Pd/Al_2O_3 10%	5	69.0	62.0
14	Pd/Al_2O_3 10%	10	81.0	73.0
15	Pd/Al_2O_3 10%	30	94.0	82.0
16	Pd/Al_2O_3 10%	60	100	90.0
17	Pd/CB@SiO_2 1%	5	74.0	73.0
18	Pd/CB@SiO_2 1%	10	82.0	81.0
19	Pd/CB@SiO_2 1%	30	85.0	82.0
20	Pd/CB@SiO_2 1%	60	94.0	91.0

[a] Reaction conditions: 100 mg of C&K, 5 mg of Pd catalyst with 1 wt % quinoline, 100 mL of ethanol 95%, 30 psi H_2. [b] Selectivity values based on GC absolute area.

Other catalysts provided high conversions and selectivities like Pd/$CaCO_3$, Pd/$BaSO_4$, and Pd/Al_2O_3 (entries 6, 11, and 16, respectively). However, they also produced dehydration products (DP) and furan ring hydrogenation products (FRHP) in the range between 1 and 8%.[22,23]

Bertholet[16] reported that these catalysts, when conditioned by lead acetate, converted kahweol to cafestol only when the support used is calcium carbonate or active carbon. Barium sulfate destroys kahweol, and aluminum oxide only converts a minor proportion of this molecule. In this work, we saw that changing the modifier to quinoline better controls the catalyst activity, and it was possible to apply all catalysts available just by controlling the reaction time.

The Pd/CB@SiO_2 catalyst, with 1 wt % metal content determined by ICP analysis described by Haynes et al,[24] also achieved high selectivity (91%). However, it did not wholly consume kahweol after 60 min (Table 1, entry 20). The significant reduction of Pd content makes this process interesting despite the longer reaction time and the formation of by-products. The catalyst synthesized in this work is a carbon black-supported Pd catalyst coated by a covalently tethered SiO_2 shell with mesoporous texture.[25] The porous nature of the silica layer protected Pd from deleterious reactions, improved the accessibility of the underlying Pd nanoparticles in the hydrogenation reactions, and optimized the metal catalytic activity, thus avoiding the formation of collateral products.

Continuous-Flow Hydrogenation of the C&K Mixture. The experiments were performed in a H-Cube Mini Plus continuous-flow hydrogenation reactor (ThalesNano) using 5 or 10% Pd/C (30 × 4 mm, 113 mg) specific cartridges for the H-cube Mini Plus (see Figure S7 in the Supporting Information). A C&K solution (1 mg mL^{-1}) with 1 wt % quinoline was pumped into the system with different flow rates (Table 2). For comparison, all reactions in the continuous-flow system were conducted in the same parameters as the batch process (25 °C and 30 psi H_2 pressure). The flow rates were chosen based on expected residence times (10, 60, and 120 s), taking into account the gas−liquid mixture flow and reactor volume.

The Pd/C 5% catalyst with 1 wt % quinoline at 2.3 mL min^{-1} and residence time of 9.8 s (Table 2, entry 1) obtained the best selectivity (>99%), resulting in pure cafestol with no side product formation (Figure 4).

The time the substrates were in contact with the catalyst cartridge directly influenced the selectivity. By raising the residence time to 56.5 and 113.1 s, a considerable increase in the formation of multiple hydrogenation products happened, such as the loss of C-16 tertiary hydroxyl followed by hydrogenation of the double bonds of the furan ring (as suggested by ions *m/z* 300 and 302) and a product in which hydrogenation took place in one of the double bonds of the furan ring (*m/z* 318) (Figure 5), as proposed in Figures 2 and 3[21,22] (Table 2).

Unlike in the batch reaction, the catalyst Pd/C 10% did not show good selectivity results in continuous-flow reaction despite the excellent conversion (Table 2). Since the 5% Pd/C catalyst had an excellent conversion of kahweol with quick reactions, we decided to investigate the impact of quinoline addition and the increase of C&K concentration in the selectivity of the C&K mixture hydrogenation reaction.

Effect of Quinoline Addition on Reaction Selectivity of Continuous-Flow Hydrogenation of C&K. To better understand the influence of quinoline on the selectivity of the C&K hydrogenation reactions by continuous flow, they were carried out with and without quinoline (Table 3).

Quinoline was essential for reactivity control of the palladium catalyst in continuous-flow hydrogenation, with improvement on selectivity. In the reactions without quinoline, it was possible to observe a considerable amount of FRHP (17%) after 9.8 s. With 1 wt % quinoline, however, there was a total conversion of kahweol into cafestol (Table 3, entries 1 and 2; Figure 6).

The Pd/C 5% catalyst, without quinoline and increased residence time (56.5 s), favored the formation of FRHP

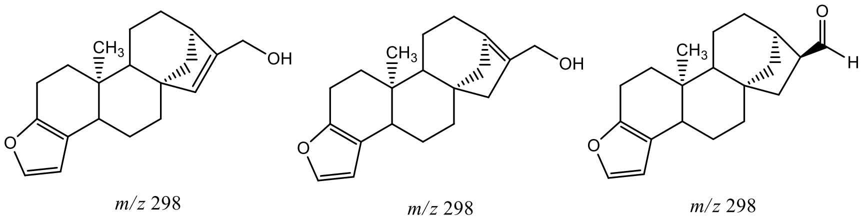

Figure 2. Dehydration products from cafestol.

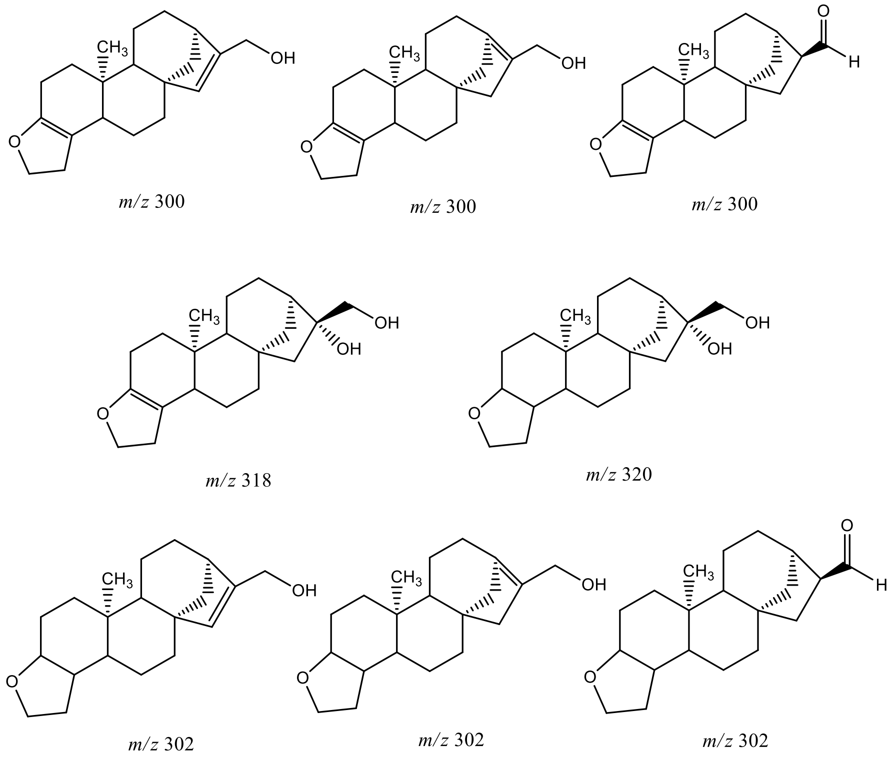

Figure 3. Furan ring hydrogenation products (FRHP).

Table 2. Continuous-Flow Hydrogenation of C&K with Pd/C and Quinoline[a]

entry	catalyst	flow rate (mL min^{-1})	residence time (s)	conversion (%)	cafestol selectivity (%)[b]
1	Pd/C 5%	2.3	9.8	100	>99
2	Pd/C 5%	0.4	56.5	100	61
3	Pd/C 5%	0.2	113.1	100	<1
4	Pd/C 10%	2.3	9.8	100	33
5	Pd/C 10%	0.4	56.5	100	<1
6	Pd/C 10%	0.2	113.1	100	<1

[a] Reaction conditions: solution of C&K in ethanol (1 mg mL^{-1}) with 1.04 μL of quinoline (1 wt % catalyst), 113 mg of Pd/C catalyst, 25 °C, flow rates of 2.3, 0.4, and 0.2 mL min^{-1}. [b] Selectivity values based on GC absolute area.

products, primarily isomers of m/z 302. With quinoline, the same reaction had a selectivity of 61%, and 39% of FRHP was observed (Table 3, entry 4). All kahweol was converted to FRHP when the residence time was 113 s, with quinoline or not (Table 3, entries 5 and 6).

Yu[26] reported that quinoline improves hydrogenation selectivity and suppresses adverse reactions by blocking the active sites of the catalyst, affecting its electronic properties and diluting its adsorption sites. In this study, we found that the use of quinoline was indispensable to achieve excellent conversion and selectivity results without the use of lead-poisoned catalysts, such as the traditional Lindlar catalyst.

To determine the time that 1 wt % quinoline was able to maintain selectivity, the system was kept in the optimized conditions (flow rate 2.3 mL min^{-1}, room temperature, system pressure of 30 psi, and 1 wt % quinoline) for 45 min (Figure 7). A C&K solution of 1 mg mL^{-1} was used for this experiment. Reaction selectivity and quinoline consumption were monitored by GC.

The reaction had excellent results in the first 20 min (Figure 7). The catalyst performance was not stable after that period due to a significant reduction in selectivity, 80% after 25 min and 60% after 35 min. The drop in selectivity can be ascribed to quinoline leaching by the solvent flow. The catalyst can be flushed away during continuous-flow reaction regenerating the reactive catalyst.

In order to investigate how long the catalyst remains at the same selectivity producing pure cafestol, 1 wt % quinoline was added to the C&K mixture every 20 min. The selectivity was monitored by GC−MS (Figure 8). The reposition of quinoline stabilized the catalyst performance for 4800 s with excellent conversion (>99%) and selectivity (>99%). During the entire 80 min-long experiment, there was no significant reduction in catalyst activity. The test produced 258 mg of cafestol, starting with C&K at 1 mg mL^{-1}.

Effect of C&K Concentration in Continuous-Flow Hydrogenation. The concentration of C&K solutions was gradually increased (1, 10, 20, and 50 mg mL^{-1}) and introduced into the H-cube continuous-flow system by a mini HPLC pump. The results were collected under steady-state conditions (30 psi H_2, 2.3 mL min^{-1}, and room temperature) and analyzed by GC−MS. The selectivity was kept constant up to 20 mg mL^{-1} C&K (Figure 9A), with the formation of cafestol only. The increase in concentration to 50 mg mL^{-1} possibly saturates the catalytic sites and decreases conversion to 91% besides the formation of by-products (3%) (Figure 9B).

Batch versus Continuous-Flow Productivity. The productivities for batch and continuous-flow reactions were calculated with eq 1, considering that the best condition for cafestol production was achieved in both processes (Table 4). The most successful batch reaction was the one using the Pd/

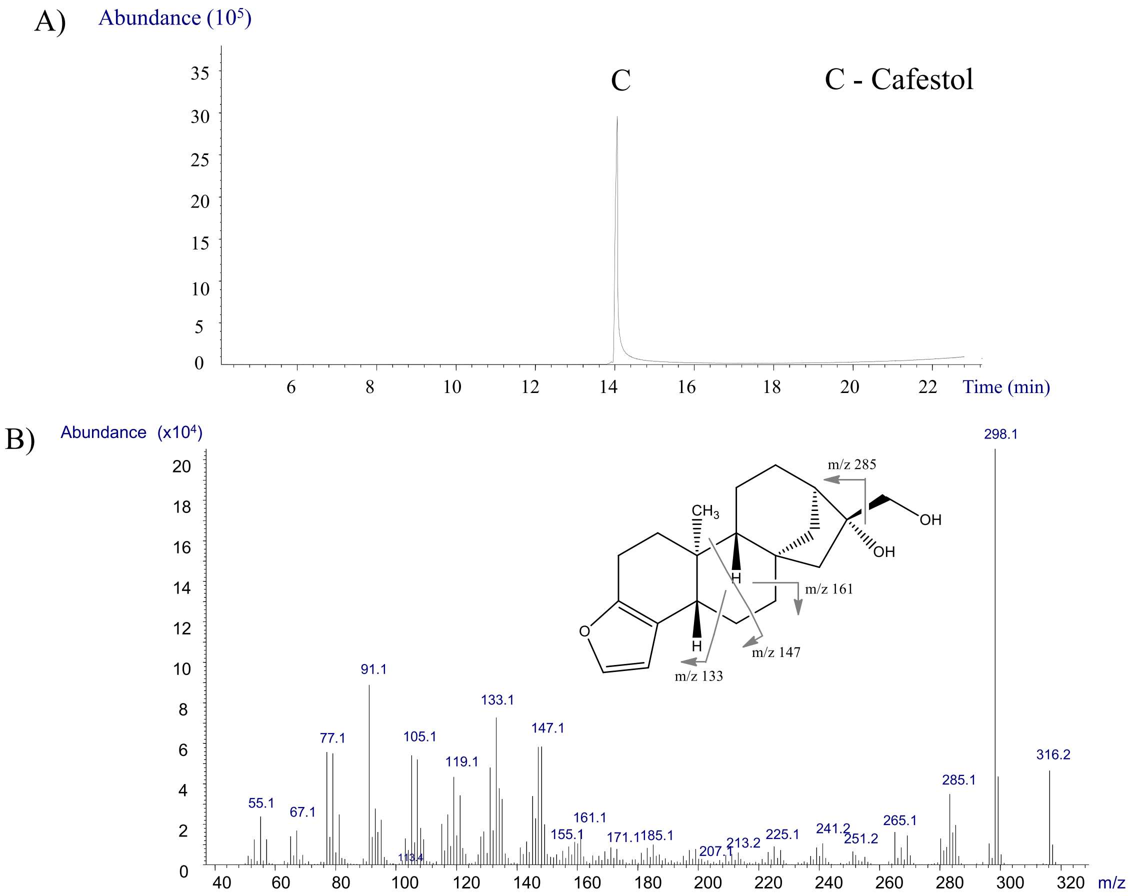

Figure 4. (A) GC−MS chromatograms of 9.8 s hydrogenation reaction under continuous-flow conditions using Pd/C 5% with 1 wt % quinoline. (B) Mass spectrum of cafestol (14 min).

C 10% catalyst with 1 wt % quinoline and 10 min of reaction time (see Table 1, entry 2). For the continuous-flow hydrogenation, the best results were achieved using the Pd/C 5% catalyst cartridge with 1 wt % quinoline and 9.8 s of reaction time (see Table 2, entry 1). The productivities were calculated considering the cafestol mass-produced in both processes (calculated by HPLC. Chromatograms shown in the Supporting Information), the mass of the Pd/C catalyst used in both methods, and the reaction times.

$$\text{productivity} = \frac{\text{mmol cafestol}}{\text{reaction time (h)} \times \text{catalyst load (mg)}} \tag{1}$$

Although the H-Cube Mini Plus uses cartridges with large catalyst mass (133 mg), it does not influence the reaction conversion due to the short contact time promoted by the continuous-flow system. Even when the batch reaction had a catalyst mass 20 times higher, the continuous-flow process managed to be more productive, providing pure cafestol 60 times faster than the batch process.

■ CONCLUSIONS

Two processes to obtain pure cafestol from kahweol through heterogeneous catalytic hydrogenation were carried out by batch and continuous-flow hydrogenation using Pd/C catalysts with 1 wt % quinoline. Thus far, only batch hydrogenation of kahweol from the C&K mixture has been done in ambient conditions using Lindlar catalysts poisoned with lead acetate, a unfriendly compound.

In batch experiments, the conversion is dependent on the type of palladium support. From several palladium catalysts tested, Pd/C obtained the best selectivity results, including the carbon black-supported Pd catalyst coated by a covalently tethered SiO_2 shell with mesoporous texture (Pd/CB@SiO_2), synthesized in this work.

Quinoline was fundamental for the reactivity control of palladium catalysts with considerable improvement in selectivity.

■ EXPERIMENTAL SECTION

Materials and Reagents. Green Arabica coffee beans were purchased from a farm in São José do Vale do Rio Preto, Rio de Janeiro State, Brazil, located at latitude 22°11′40″S, 42°58′22″W and altitude 650−850 m, in 2016. Potassium hydroxide (KOH, Isofar, PA), methanol (MeOH, Scilab, 99.9%), and *tert*-butyl methyl ether (TBME, Tedia, 99.8%) were used in C&K extraction. Flash silica gel 60 (Vetec), hexane (Tedia, ACS), and ethyl acetate (Tedia, ACS) were used in C&K purification by column chromatography (CC). Ethanol (EtOH, Sigma, 95.0%), quinoline (Sigma, 98.0%), palladium catalysts (Sigma), and Pd/C 5% and 10% CatCart (ThalesNano) were used for hydrogenation reactions. The aluminum TLC plates, silica gel coated with the fluorescent indicator F_{254} (20 × 20 cm) were purchased from Merck.

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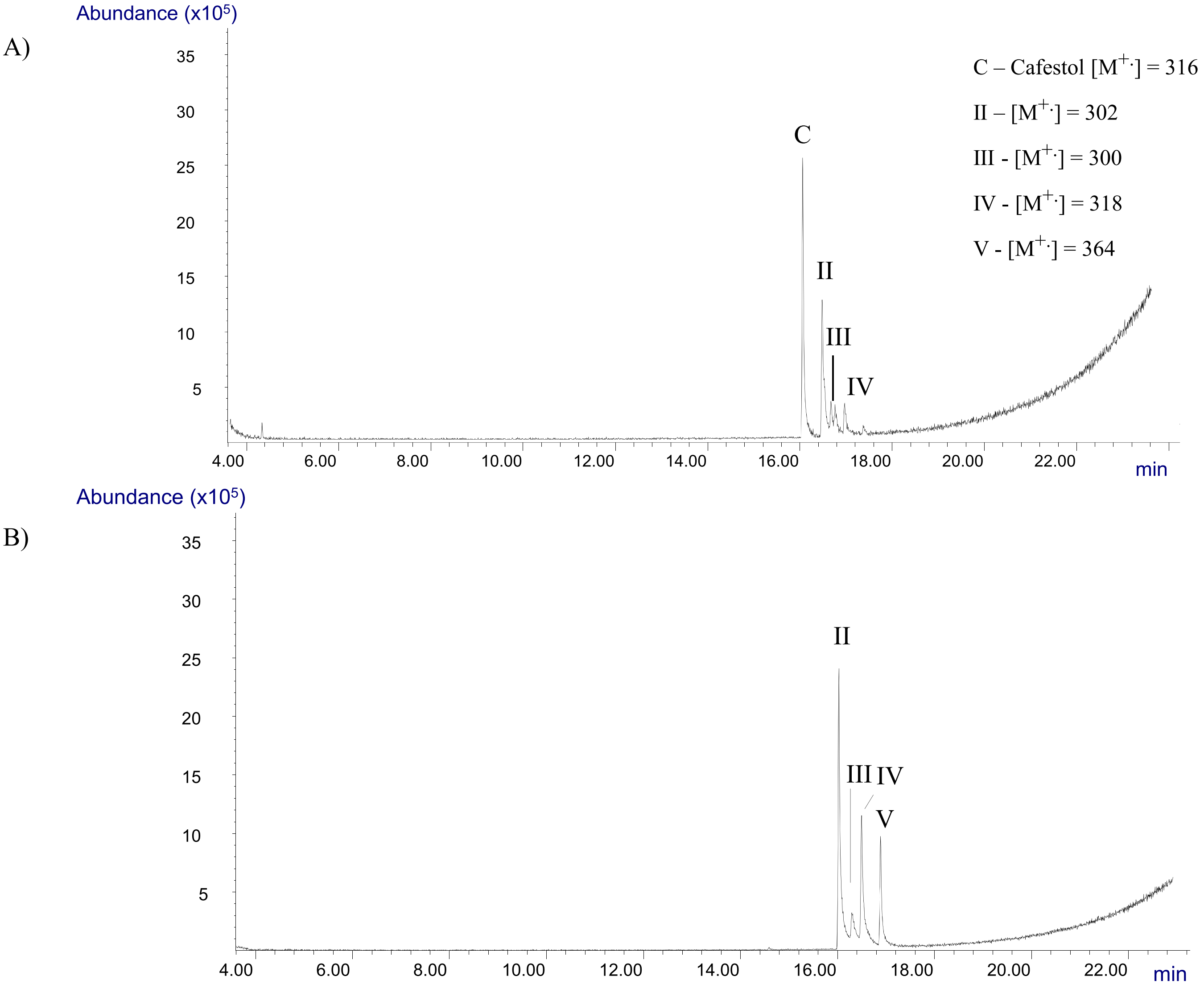

Figure 5. GC−MS chromatograms of hydrogenation reactions under continuous-flow conditions using Pd/C 5% with 1 wt % quinoline. (A) 56.5 s reaction time and (B) 113.1 s. Peaks II, III, IV, and V are FRHP (see Figure 3).

Table 3. Continuous-Flow Hydrogenation of C&K with Pd/C at Different Times, with or without Quinoline[a]

entry	catalyst	flow rate (mL min^{-1})	residence time (s)	quinoline (% w/w)	conversion (%)	cafestol selectivity (%)[b]	DP (%)	FRHP (%)
1	Pd/C 5%	2.3	9.8	0	89	72	0	17
2	Pd/C 5%	2.3	9.8	1	100	>99	0	<1
3	Pd/C 5%	0.4	56.5	0	100	<1	0	>99
4	Pd/C 5%	0.4	56.5	1	100	61	0	39
5	Pd/C 5%	0.2	113.1	0	100	<1	0	>99
6	Pd/C 5%	0.2	113.1	1	100	<1	0	>99

[a] Reaction conditions: solution of C&K in ethanol (1 mg mL^{-1}), 1.04 μL of quinoline (1 wt % catalyst), 113 mg of Pd/C catalyst, 25 °C, flow rates of 2.3, 0.4, and 0.2 mL min^{-1}. DP: dehydration products; FRHP: furan ring hydrogenation products. [b] Selectivity values based on GC absolute area.

Isolation of the C&K Mixture and Cafestol Acquirement. The procedure used for isolation of the C&K mixture from green coffee beans was performed according to Novaes et al.[27] The mixture of C&K used in this work was obtained as a white solid (>99% by GC) with a mass ratio of 3:1 between cafestol and kahweol, respectively. The method was able to isolate 5.1 g kg^{-1} of C&K from green coffee beans.

The cafestol standard used for the calibration curve was obtained by a continuous-flow hydrogenation protocol reported in this work (see Table 2, entry 1) followed by purification by column chromatography (CC) to remove quinoline. The purification was performed using a glass column (60 × 2.5 cm) fully packed with 30 g of flash silica gel suspended in hexane. Five hundred milligrams of unpurified cafestol was mixed with 2 g of flash silica gel and suspended in

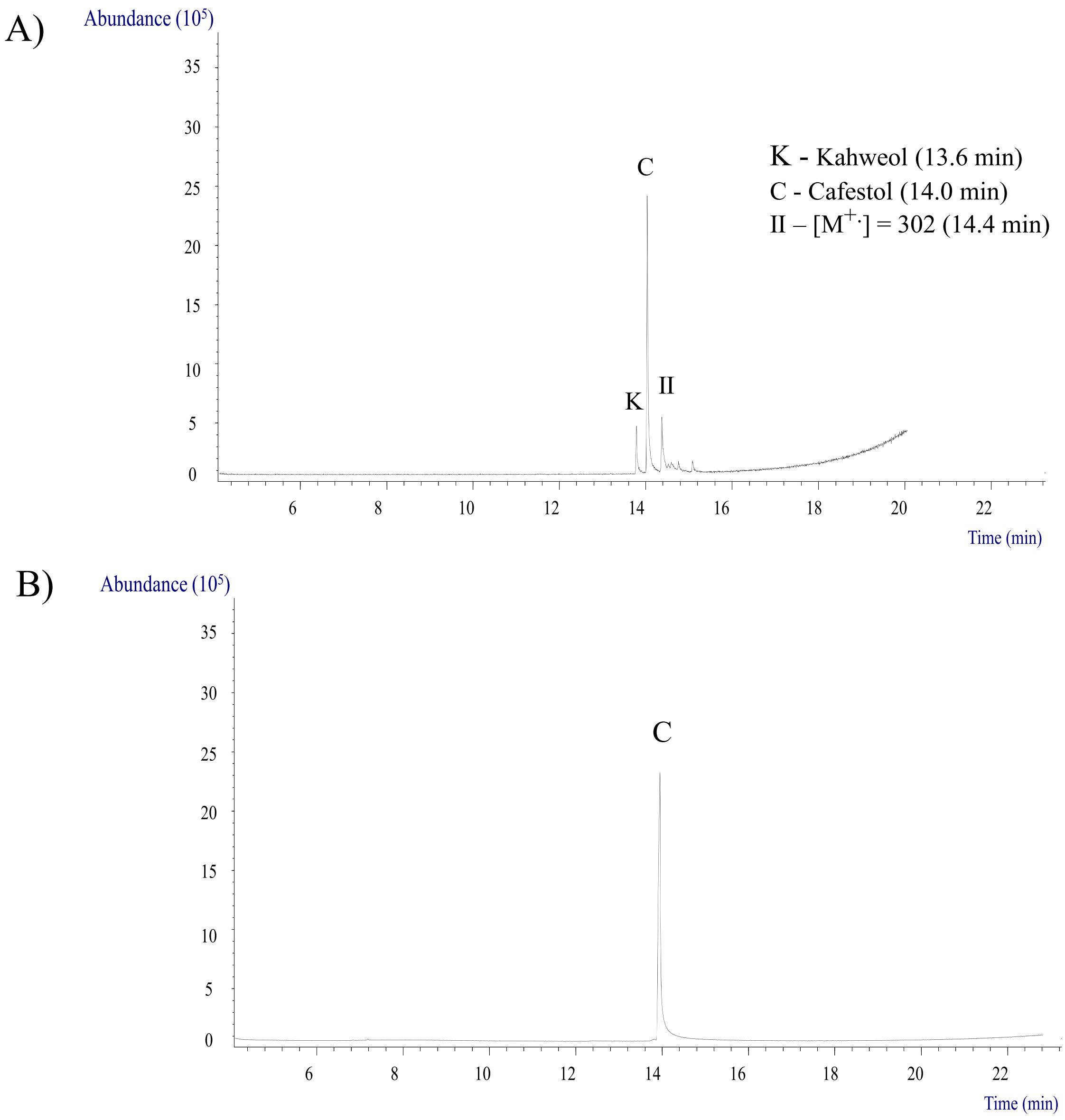

Figure 6. GC−MS chromatograms of 9.8 s hydrogenation reaction under continuous-flow conditions (A) without quinoline and (B) with 1 wt % quinoline. Peak II - FRHP (see Figure 3).

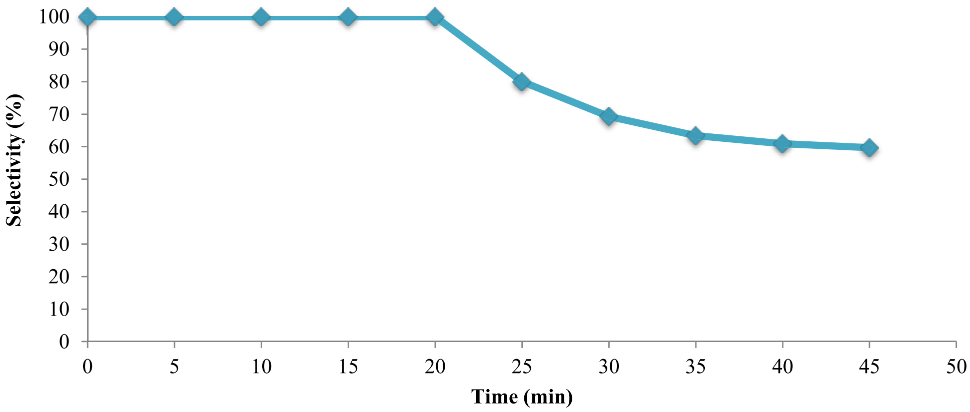

Figure 7. Dependence of quinoline percentage on reaction selectivity of C&K hydrogenation continuous-flow reaction in the optimized conditions (flow rate 2.3 mL min^{-1}, room temperature, system pressure of 30 psi, and 1 wt % quinoline).

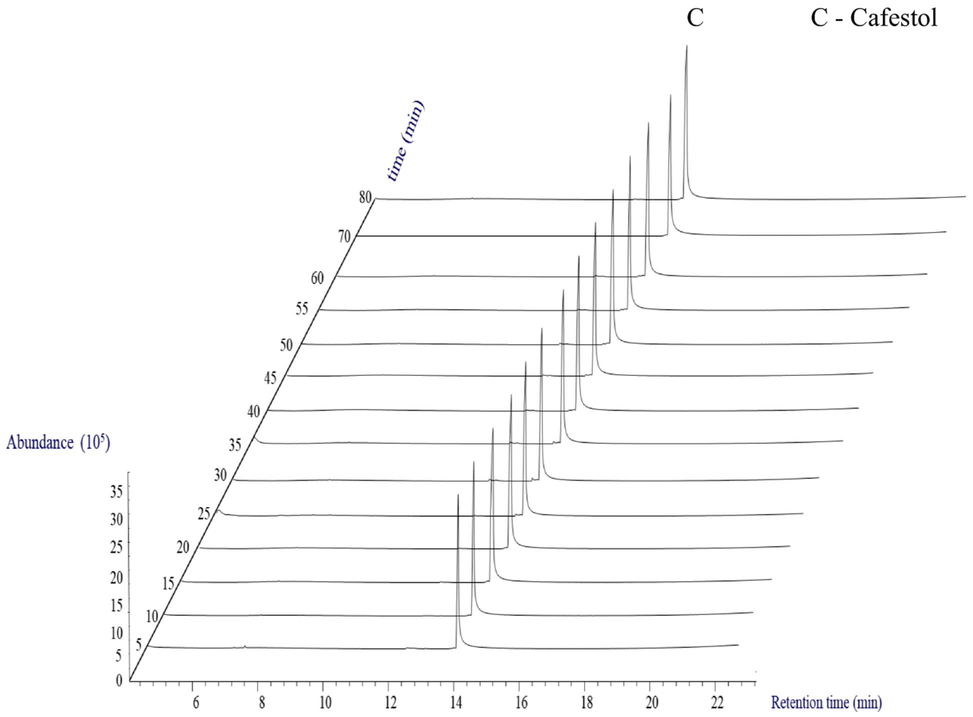

Figure 8. GC−MS chromatograms of continuous-flow hydrogenation of cafestol and kahweol mixture during the 80 min-long experiment.

50 mL of methanol. After, the solvent was removed under vacuum, and the material was applied at the top of the column. Hexane/ethyl acetate (10:0 (200 mL), 9:1 (200 mL), 8:2 (200 mL), and 1:1 v/v (600 mL)) were used as mobile phases in gradient mode at atmospheric pressure (flow rate ν = 2.5 cm min^{-1}). Pure cafestol was collected from the hexane/ethyl acetate phase 1:1 v/v giving 420 mg of white solid (>99% by GC). NMR spectral data and melting point value are in accordance with Novaes et al.[27]

Cafestol ($C_{20}H_{28}O_3$): white solid; m.p. 153.5−154.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.25 (1H, d, J = 1.8 Hz, H19), 6.22 (1H, d, J = 1.8 Hz, H18), 5.31 (1H, s, C16−OH), 3.82 (1H, d, J = 11.1 Hz, H17a), 3.70 (1H, d, J = 11.1 Hz, H17b), 2.62 (2H, dd, J = 5.8, 2.7 Hz, H2), 2.27 (1H, dq, J = 12.6, 2.7 Hz, H5), 2.07−2.03 (3H, m, H13, H1, H14), 1.82 (1H, ddd, J = 12.9, 6.2, 3.1 Hz, 455 H6), 1.74−1.51 (10H, m, H6, H7, H11, H12, H14, H15), 1.27−1.23 (1H, m, H1), 1.19 (1H, d, J = 7.7 Hz, H9), 0.84 (3H, s, H20). ^{13}C NMR (500 MHz, $CDCl_3$, δ ppm): 148.8 (C, C3), 457140.7 (CH, C19), 120.2 (C, C4), 108.4 (CH, C18), 82.1 (C, C16), 66.4 (CH_2, C17), 53.4458 (CH_2, C15), 52.2 (CH, C9), 45.5 (CH, C13), 44.8 (C, C8), 44.3 (CH, C5), 41.0 (CH_2, C7), 38.7 (C, C10), 38.3 (CH_2, C14), 35.8 (CH_2, C1), 26.2 (CH_2, $C1_2$), 23.2 (CH_2, C6), 20.8 (CH_2, C2), 19.1 (CH_2, C11), 13.5 (CH_3, C20).

Preparation of the Pd/CB@SiO_2 Catalyst. The carbon black-supported Pd catalyst, coated by a covalently tethered SiO_2 shell with mesoporous texture (Pd/CB@SiO_2), was prepared according to a previously described protocol:[24,25] one gram of carbon black (CB) support dispersed in 100 mL of Na_2CO_3 2.5 wt % aqueous solution was stirred for 15 min at room temperature. Fifty six milligrams of Na_2PdCl_4 (corresponding to a theoretical 2.0 wt % loading) dissolved in 20 mL of distilled water was added dropwise to the suspension within 1 h. Five grams of $NaBH_4$ diluted in 20 mL of distilled water was then added. The suspension was stirred for 2 h. Finally, the catalyst (Pd/CB) was filtered out, washed with distilled water (1 L), and dried. Two grams of CB was introduced into a 250 mL round-bottom flask containing 100 mL of toluene. Six milliliters of $SOCl_2$ was added, and the mixture was heated for 5 h (120 °C). Then, it was filtered out and extensively washed with toluene (500 mL). One gram of the resulting material (CB-Cl) was introduced into a 250 mL round-bottom flask containing 100 mL of dichloromethane. One milliliter of APTES was added, and the mixture was stirred for 24 h at room temperature. Finally, the material (CB-APTES) was filtered out, washed with dichloromethane (250 mL) and methanol (250 mL), and dried overnight under vacuum at 100 °C. A nominal 2.5 wt % Pd (71 mg Na_2PdCl_4) amount was engaged to counterbalance the dilution effects of the covering layer and so to keep the same wt % Pd loading. Two hundred and fifty milligrams of Pd/CB-APTES was introduced into a 100 mL round bottom flask containing 25 mL of distilled water. Then, 10 mL of NaOH (0.1 M) was added, and the mixture was sonicated for 10 min. To this suspension, 0.571 g of CTAB was added and the solution was heated at 60 °C. Seventy milliliters of TEOS was added dropwise within 30 min. This suspension was further stirred for 3 h and 30 min and then charged into a propylene bottle, which was closed tightly and heated at 100 °C for 3 days. The product was filtered out, washed with ethanol (250 mL), and dried at 100 °C overnight. In the end, the CTAB template was removed by refluxing in ethanol the solid material (Pd/CB@SiO_2) for 24 h.

The solid catalyst was characterized by X-ray photoelectron spectroscopy (XPS), transmission electron microscopy (TEM), thermogravimetric analysis (TGA), elemental analyses (ICP), and N_2 physisorption according to the protocol described by Haynes et al.[24]

Procedure for Batch Hydrogenation Experiments. Hydrogenation experiments in the batch mode were carried out using a shaker hydrogenation apparatus (Parr) (see Figure S1 in the Supporting Information). In a 500 mL reaction

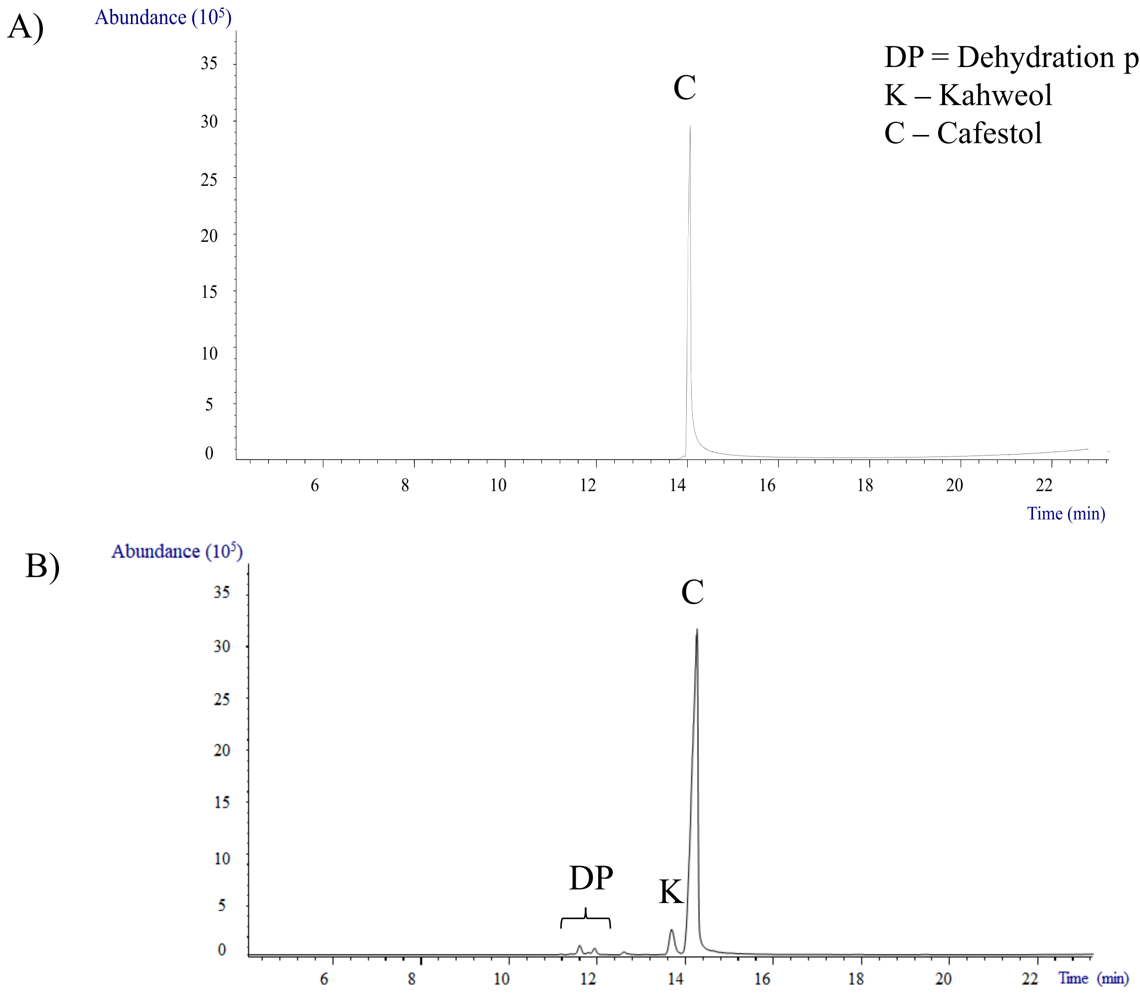

Figure 9. GC−MS chromatograms of 9.8 s hydrogenation reaction under continuous-flow conditions (A) with 20 mg mL^{-1} C&K solution and 1 wt % quinoline and (B) with 50 mg mL^{-1} C&K solution and 1 wt % quinoline (DP - dehydration products. See Figure 2).

Table 4. Batch and Continuous-Flow Productivities

	cafestol (mmol)	reaction time (h)	catalyst load (mg)	productivity (mmol h^{-1} mg^{-1})	productivity continuous flow/batch ratio
batch	0.00450	0.1667	5	0.0054	3
continuous flow	0.00507	0.0027	113	0.0166	

bottle, 100 mg of C&K was added with 5 mg of Pd catalyst with 1, 3, and 5 wt % quinoline and 100 mL of ethanol 95%. After purging three times, 30 psi H_2 was added and shaking was started. The reaction mixture was kept at room temperature for 5, 10, 30, and 60 min. Then, the shaking was stopped, and H_2 pressure was released. The resultant mixture was filtered to remove the catalyst.

Procedure for Continuous-Flow Experiments. Continuous-flow experiments were performed in a high-pressure continuous-flow hydrogenator reactor H-Cube Mini Plus (ThalesNano; see Figure S7 in the Supporting Information), which supplied a H_2 flow produced from electrolysis of water to the central reactor module in which a 30 mm catalyst cartridge was installed, packed with 113 mg of Pd/C catalyst. The dead volume of the system was 0.131 mL. The corresponding total flow-through volume (including feed lines, reactor, and product lines) was 3.13 mL. The operational temperature was 25 °C. First, pure ethanol was pumped through the system before reaching the set temperature (25 °C) and pressure (30 psi). The system was operated with ethanol 95% at different flow rates (0.2, 0.4, and 2.3 mL min^{-1}) and hydrogen flow around 70 mL min^{-1}. Once the reaction conditions were stable, ethanol was exchanged by a solution of C&K in ethanol (1, 10, 20, and 50 mg mL^{-1}) with 1.04 μL of quinoline. Then, each reaction was operated for 9.8, 56.5, and 113.1 s as a function of corresponding flow rates of 2.3, 0.4, and 0.2 mL min^{-1}. Afterward, the samples were collected and analyzed by GC−MS.

GC−MS-FID and HPLC-UV Analyses. The reactions were analyzed, after filtration, using an Agilent 6890 gas chromatograph equipped with an FID detector and a mass spectrometer (MS) Agilent 5973 N. Helium (99.9992% purity) was used as carrier gas at 2 mL min^{-1} in constant flow mode in a DB-17HT capillary column (50% phenyl and 50% methylsiloxane, 10 m × 0.25 mm × 0.15 μm, Agilent Technologies). The injection was made in pulsed split mode (1:10) at 330 °C, 1.0 μL of each reaction solution. The oven temperature was set at 90 (0.25 min) to 300 °C in 10 °C min^{-1} for both the FID (at 300

°C) and MSD (transfer line at 330 °C). Mass spectra were obtained in scan mode (45−800 Da). The identification of cafestol was performed by comparison of the retention times with pure standard and mass spectral acquisition.

Cafestol quantification for batch and continuous-flow productivity calculation was performed using an HPLC system (Agilent, 1200 series) with a Quat pump (Agilent, G1311A), an autosampler (Agilent, G1329A), and a diode array detector (DAD, Agilent, G1315D). A C-18 column (Zorbax, 150 mm × 4.6 mm, 5 μm particle size, and 100 Å pore size) was used at room temperature. The mobile phase was water (A) and acetonitrile (B) 55:45 in isocratic mode. The flow was set at 0.7 mL min^{-1}. Peaks were monitored at 230 nm. The calibration curve was determined in the range of 10−90 mg mL^{-1} performed in triplicate, using a cafestol standard at 25 mg L^{-1} in methanol. The correlation coefficient of the linear regression was >0.99.

Quantitative Determination of Palladium Using Energy-Dispersive X-ray Fluorescence (EDXRF). The quantity of Pd present in the solid and liquid samples was determined using an energy-dispersive X-ray fluorescence (EDXRF) spectrometer from Bruker Nano GmbH (M4 Tornado, Germany). On this typical commercial spectrometer, the X-ray tube is an Rh micro-focus side window powered by a low-power HV-generator and cooled by air. The spot size of 25 μm is obtained using a poly-capillary lens in a Mo Kα mode. The X-ray generator was operated at 50 kV and 600 μA, and different filters were used to reduce the background (100 μm Al/50 μmTi/25 μm Cu). The energy resolution of a detector (thermoelectrically cooled silicon-drift-detector) was 142 eV for 5.9 keV (Mn Kα). Measurements were carried out under 20 mbar vacuum conditions. An in-built camera allows visualizing the operating area and permits the analysis in a fully automated mode. According to the required resolution, the counting time and the scanning spatial resolution could be freely selected. The sample was placed directly on a sample holder (360 mm × 260 mm), which was attached to a stage translatable along the *XY*. The scanning step size used was 25 μm, and the time per analyzed point was 0.5 ms × 3 cycles. Each selected area was analyzed over a period to accumulate sufficient data points for high-resolution mapping. Data output was obtained through the X-ray intensities of specific X-ray peaks corresponding to the element signals measured in each point defined by its *X* and *Y* coordinates (μm). The data were converted using the software's function into a data matrix, from which *XY* contour maps (two-dimensional maps) of the data were generated for each element.

Analyses performed by XRF for batch and continuous-flow samples collected at the packed-bed reactor outlet after the hydrogenation reaction, both *in natura* and concentrated under an inert solid, showed no detectable palladium concentration (see Figure S15 in the Supporting Information for further details). Aiming to determine the metal composition of the palladium supported on active carbon catalyst at the end of reactions, an X-ray diffraction (XRD) analysis of palladium was also carried out, as evidenced by the presence of both Pd^0 and PdO, as a consequence of the hydrogenation reaction. These results demonstrate the robustness of the catalyst since no palladium leakage was evidenced in the reaction medium.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c01835.

> Schematic illustrations of the batch and continuous-flow experiments, GC−MS chromatograms of hydrogenation experiments, mass spectra of the products, HPLC chromatograms of cafestol quantification analyses, and quantitative determination of the palladium on active carbon catalyst using energy-dispersive X-ray fluorescence analysis (PDF)

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) Durán, C. A. A.; Tsukui, A.; Santos, F. K. F.; Martinez, S. T.; Bizzo, H. R.; Rezende, C. M. Café: Aspectos Gerais e seu Aproveitamento para além da Bebida. *Rev. Virtual Quim.* **2017**, *9*, 107−134.

(2) Speer, K.; Kölling-Speer, I. The lipid fraction of the coffee bean. *Braz. J. Plant Physiol.* **2006**, *18*, 201−216.

(3) Dias, R. C. E.; De Faria, A. F.; Mercadante, A. Z.; Bragagnolo, N.; Benassi, M. d. T. Comparison of Extraction Methods for Kahweol and Cafestol Analysis in Roasted Coffee. *J. Braz. Chem. Soc.* **2013**, *24*, 492−499.

(4) Tsukui, A.; Oigman, S. S.; Rezende, C. M. Óleo de Grãos de Café Cru: Diterpenos Cafestol e Caveol. *Rev. Virtual Quim.* **2014**, *6*, 16−33.

(5) Lee, K. J.; Choi, J. H.; Jeong, H. G. Hepatoprotective and antioxidant effects of the coffee diterpenes kahweol and cafestol on carbon tetrachloride-induced liver damage in mice. *Food Chem. Toxicol.* **2007**, *45*, 2118−2125.

(6) Sridevi, V.; Giridhar, P. Antioxidant potential of free diterpenes cafestol and kahweol rich extractives of coffee beans. *Can. J. Basic Appl. Sci.* **2015**, *3*, 78−84.

(7) Kim, J. Y.; Jung, K. S.; Lee, K. J.; Na, H. K.; Chun, H.-K.; Kho, Y.-H.; Jeong, H. G. The coffee diterpene kahweol suppress the inducible nitric oxide synthase expression in macrophages. *Cancer Lett.* **2004**, *213*, 147−154.

(8) Shen, C.-P.; Luo, J.-G.; Yang, M.-H.; Kong, L.-Y. Cafestol-Type Diterpenoids from the Twigs of *Tricalysia fruticosa* with Potential Anti-inflammatory Activity. *J. Nat. Prod.* **2015**, *78*, 1322−1329.

(9) Cavin, C.; Holzhaeuser, D.; Scharf, G.; Constable, A.; Huber, W. W.; Schilter, B. Cafestol and kahweol, two coffee specific diterpenes with anticarcinogenic activity. *Food Chem. Toxicol.* **2002**, *40*, 1155−1163.

(10) Savian, A. L.; Varella, F. T.; Athayde, M. L.; Da Silva, C. d. B. Desenvolvimento e avaliação preliminar da estabilidade de emulsão não-iônica O/A contendoóleo de café verde como potencializador de fator de proteção solar. *Rev. Bras. Farm.* **2011**, *91*, 82−88.

(11) Lee, K. J.; Jeong, H. G. Protective effects of kahweol and cafestol against hydrogen peroxide-induced oxidative stress and DNA damage. *Toxicol. Lett.* **2007**, *173*, 80−87.

(12) De Roos, B.; Van der Weg, G.; Urgert, R.; Van de Bovenkamp, P.; Charrier, A.; Katan, M. B. Levels of Cafestol, Kahweol, and Related Diterpenoids in Wild Species of the Coffee Plant Coffea. *J. Agric. Food Chem.* **1997**, *45*, 3065−3069.

(13) Dias, R. C. E.; Campanha, F. G.; Vieira, L. G. E.; Ferreira, L. P.; Marraccini, P.; Benassi, M. D. T. Evaluation of Kahweol and Cafestol in Coffee Tissues and Roasted Coffee by a New High-Performance Liquid Chromatography Methodology. *J. Agric. Food Chem.* **2010**, *58*, 88−93.

(14) Zhang, C.; Linforth, R.; Fisk, I. D. Cafestol extraction yield from different coffee brew mechanisms. *Food Res. Int.* **2012**, *49*, 27−31.

(15) Haworth, R. D.; Jubb, A. H.; Mckenna, J. Cafestol. Part I. *J. Chem. Soc.* **1955**, 1983−1989.

(16) Bertholet, R. Preparation of cafestol. *United States Utility Patent* US4,692,534A, 1987, 4, 692, 534.

(17) Nijhuis, T. A.; van Koten, G.; Moulijn, J. A. Optimized palladium catalyst systems for the selective liquid-phase hydrogenation of functionalyzed alkynes. *Appl. Catal., A.* **2003**, *238*, 259−271.

(18) Chen, Y.; Wang, Z.; Mao, S.; Wang, Y. Rational design of hydrogenation catalysts using nitrogen-doped porous carbon. *Chin. J. Catal.* **2019**, *40*, 971−979.

(19) Cao, Y.; Mao, S.; Li, M.; Chen, Y.; Wang, Y. Metal/Porous Carbon Composites for Heterogeneous Catalysis: Old Catalysts with Improved Performance Promoted by N-Doping. *ACS Catal.* **2017**, *7*, 8090−8112.

(20) De Souza, J. M.; Galaverna, R.; De Souza, A. A. N.; Brocksom, T. J.; Pastre, J. C.; De Souza, R. O. M. A.; De Oliveira, K. T. Impact of continuous flow chemistry in the synthesis of natural products and active pharmaceutical ingredients. *An. Acad. Bras. Cienc.* **2018**, *90*, 1131−1174.

(21) Guerreiro, G.; Suárez, M.; Moreno, G. Chemosystematic study of diterpenoids in green coffee beans. *20th International Colloquium on the Chemistry of Coffee.* Paris: ASIC: 2005, 292−296.

(22) Lam, L. K. T.; Sparnins, V. L.; Wattenberg, L. W. Effects of Derivatives of Kahweol and Cafestol on the Activity of Glutathione S-Transferase in Mice. *J. Med. Chem.* **1987**, *30*, 1399−1403.

(23) Bruckner, R. *Advanced Organic Chemistry: Reaction Mechanisms*; 1st ed.; Elsevier: Academic Press: New York, 2001; pp. 104−106.

(24) Haynes, T.; Ersen, O.; Dubois, V.; Desmecht, D.; Nakagawa, K.; Hermans, S. Protecting a Pd/CB catalyst by a mesoporous silica layer. *App.Catal., B.* **2019**, *241*, 196−204.

(25) Haynes, T.; Dubois, V.; Hermans, S. Particle size effect in glucose oxidation with Pd/ CB catalysts. *Appl. Catal., A* **2017**, *542*, 47−54.

(26) Yu, J. Discovery that quinoline and triphenylphosphine alter the electronic properties of hydrogenation catalysts. *Chem. Commun.* **1998**, 1103−1104.

(27) Novaes, F. J. M.; Lima, F. A.; Calado, V.; Marriott, P. J.; de Aquino Neto, F. R.; Rezende, C. M. Isolating Valuable Coffee Diterpenes by Using an Inexpensive Procedure. *Ind. Crops Prod.* **2020**, *152*, 112494.

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