



Article Multicomponent Reactions Promoted by Ecocatalyst from Metal Hyperaccumulating Plant Pluchea sagittalis

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Abstract: Phytoremediation has been considered a sustainable environmental technology for heavy metals decontamination. In this work, we evaluated the metal contents by inductively coupled plasma optical emission spectrometry (ICP-OES) of three plant species collected in a mine in the Brazilian Amazonia area. Based on this analysis, *Pluchea sagitallis* leaves were selected to prepare metallic ecocatalysts. The leaf ashes and the obtained ecocatalysts were characterized by ICP-OES, X-ray diffraction (XRD), scanning electron microscopy (SEM) and N₂-physisorption measurements. Moreover, they were evaluated in the Biginelli and Hantzsch multicomponent reactions, furnishing the corresponding 3,4-dihydropyrimidin-2-(1H)-ones and 1,4-dihydropyridines with good to excellent yields. The best ecocatalyst was easily recovered and recycled in up to six reactions without a significant decrease in its performance.

Keywords: heavy metal decontamination; *Pluchea sagitallis*; ecocatalysts; Biginelli and Hantzsch multicomponent reactions

1. Introduction

The development of more sustainable products and processes is one of the most important challenges of the present society [1] and, in this sense, in the last 30 years, green chemistry has played an increasingly significant role in various sectors, including academia, industry, regulatory agencies as well as other governmental organizations around the world.

Catalytic processes have unquestionably become a cornerstone within the green chemistry perspective, and their continuous advances have enabled the discontinuation of outdated stoichiometric methodologies to give place to more sustainable ones [2]. The immobilization of catalysts on solid supports is one of the best methods to improve the efficiency, stability, catalytic activity, and recovery of catalysts [3]. The most common catalysts are based on supported transition metals that are widely used in the manufacturing of fine and specialty chemicals [4–6]. However, despite the efficiency of these methods, the growth in metal use in the past few decades raises concern that supplies may be insufficient to meet demands in the future [7]. In this perspective, ecocatalysis is an emerging technology exploring the use of metal species originating from plants used in phytoremediation [8,9].



Citation: Alponti, L.H.R.; Picinini, M.; Urquieta-Gonzalez, E.A.; da Silva, C.S.; Silva, S.Y.S.; Silva, S.C.; de Oliveira, M.N.; Viera, J.; da Silva, M.F.d.G.F.; Corrêa, A.G. Multicomponent Reactions Promoted by Ecocatalyst from Metal Hyperaccumulating Plant *Pluchea sagittalis. Reactions* **2023**, *4*, 552–568. https://doi.org/10.3390/ reactions4040033

Academic Editors: Michela Signoretto and Federica Menegazzo

Received: 28 July 2023 Revised: 23 August 2023 Accepted: 27 September 2023 Published: 7 October 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). Soil contamination through toxic heavy metals may pose a great risk to human health as well as to the ecosystem. Natural contamination mainly results from volcanic eruption, and wind erosion, whereas anthropogenic sources emerge from the burning of fossil fuels, thermal power plants, smelters, industrial effluents, and mines. According to the United States Environmental Protection Agency (US-EPA), Cd, Pb, Hg, As, Cu, Ni, Co and Cr are the eight heavy metals most widespread in the environment [10]. Among several accessible technologies, plant-based phytoremediation is an eco-friendly, cost-effective, and ecologically viable technique. This bioremediation technique consists of the use of plants and their microbiota in the remediation of contaminated soils [11]. The hyperaccumulating plants absorb the contaminants, mainly the metals, through their roots, and later translocate them to their aerial parts [12]. Several plant species, including those developed by genetic engineering [13] or natural colonizer plants, have been described as metal-hyperaccumulating. For example, Olatunji et al. evaluated the potential of *Panicum maximum* (guinea grass) for selected heavy metal (Pb²⁺, Cr³⁺ and Cd²⁺) removal from contaminated soils [14].

Concerning the use of metal hyperaccumulator plants as an efficient renewable feedstock to the synthesis of Lewis acid catalysts, the group of Grison [15] developed new ecocatalysts by using numerous plant species, e.g., *Noccaea caerulescens, Anthyllis vulneraria*, and *Grevillea* spp. [16]. Liu et al. reported the synthesis of nanomaterials, including multi-walled carbon nanotubes (MWCNTs), nanoparticles and nanocomposites, using the shoots of *Sedum alfredii* Hance and *Brassica juncea* L., collected from a Cu–Zn mine area [17]. Furthermore, Harumain et al. demonstrated that *Arabidopsis* tissues contain palladium nanoparticles. The authors determined the Pd concentrations in the biomass that would be sufficient to obtain catalytically active material comparable to commercially available 3% Pd/C and carry out the Heck reaction of iodobenzene with methyl acrylate to yield trans-methyl cinnamate [18].

The multicomponent reactions (MCRs) comprise a set of chemical transformations that allow obtaining compounds containing three or more units of different reactants or reaction centers in a one-pot fashion, without isolation and purification of intermediates [19]. Aligned with green chemistry principles, these reactions have demonstrated a remarkable impact on the synthesis of complex products, with high atom economy and molecular diversity. In addition, the MCRs are straightforward for the synthesis of compounds with biological or pharmacological properties which is highly attractive for the pharmaceutical and agrochemical industries, among other applications [20]. Constanzo et al. reviewed the mechanisms of the Biginelli and Hantzsch MCRs which are useful tools for enhancing the chemical space in medicinal chemistry [21]. They focused on studies exploiting similarity and competition as an opportunity to switch from one reaction to another, thus opening the possibility of obtaining libraries of both 3,4-dihydropyrimidin-2-(1H)-ones (DHPMs) and 1,4-dihydropyridines (1,4-DHPs) scaffolds.

Few examples of MCRs promoted by ecocatalysts have been described in the literature [22–24], including the Biginelli reaction [25–27]. However, to the best of our knowledge, only one example of the Hantzsch reaction has been explored, in which a tandem 1,4-DHP synthesis-oxidation into pyridine was catalyzed by Mn²⁺ from hyperaccumulating plants of New Caledonia [28]. Thus, continuing our efforts in the development of sustainable synthetic methods, in this work new heterogeneous ecocatalysts were obtained from metalhyperaccumulating plants collected in a mining area of the Brazilian Amazonia and applied in the synthesis of DHPMs and 1,4-DHPs.

2. Materials and Methods

2.1. General Information

Commercially available reagents were purchased from Merck, Darmstadt, Germany and, when necessary, treated according to the procedures described in the literature. The purification of the products was performed using a flash chromatographic column, using silica gel 60 Å, 70–230 or 230–400 mesh. The thin layer chromatography (TLC) analyses

were carried out on silica gel 60 F254 plates supported on aluminum sheets and developed under ultraviolet light and/or stained in acid vanillin. The solvent excess was evaporated in a Buchi Rotavapor R-114 with a Buchi Watherbath B-490 bath Flawil, Switzerland. Nuclear Magnetic Resonance spectra (¹H and ¹³C NMR) were recorded on a Bruker ARX 400 MHz spectrometer, Germany. The chemical shifts (δ) are expressed in ppm and the coupling constants (J) in Hertz (Hz). To indicate the multiplicity of signs, the following abbreviations were used: s (singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet). Melting points (m.p.) were obtained on a Buchi M-560. Reactions using microwaves were performed using a CEM Discovery equipment, Matthews, NC, USA, coupled with a cooling system.

The plant species were collected in November 2017, in a mining area of the company Vale in the Sossego Mine, Canaã dos Carajás, Pará State, northern Brazil, and identified as *Cecropia pachystachya* (6°27′41.6″ S, 50°05′27.6″ W), *Pluchea sagittalis* (6°27′15.0″ S, 50°04′48.2″ W) and *Typha domingensis* (6°27′29.5″ S, 50°05′10.4″ W). The species were dried at room temperature in a circulation oven at 27 °C for 24 h, and then ground in a knife mill (NL-226/02).

The plants were digested in a microwave cavity oven Berghof Speedwave and the analytical measurements were carried out using an Inductively Coupled Plasma Optical Emission Spectrometer (ICP-OES) with axial and radial views iCAP 6000 Series Duo, Thermo Scientific, Waltham, MA, USA, equipped with a peristaltic pump, a concentric nebulizer, a cyclonic spray chamber and a quartz torch fitted with a quartz injector tube with 2.0 mm internal diameter. This instrument has a charge injection device (CID) detector and can operate in both radial and axial torch configurations.

Sample preparation for ICP-OES analyses in triplicate: the plant samples (500 mg) were accurately weighed directly in the Teflon-perfluoroalkoxy alkanes (PFA) digestion vessels and microwave-assisted digested using the Bergh of microwave cavity oven above described, using a HNO₃ solution (7 mol L⁻¹, 6.0 mL) and H₂O₂ (30% v/v, 2.0 mL) in each bottle. The following microwave heating program was applied: (1) 10 min to reach 170 °C, (2) 15 min hold at 200 °C. Subsequently, digests were diluted up to 30.0 mL with deionized water.

For catalyst analysis, a microwave-assisted digestion in a CEM MarsXpress, Matthews, NC, USA, at 180 °C, 600 psi for 25 min was employed. For **Cat B** it was used HNO₃ + H₂O₂ and the ICP-OES analysis was performed in an Agilent 5800 apparatus. For **Cat C** it was used HNO₃ + H₂O₂ + HF and ICP-OES analysis was performed in the Thermo Scientific iCAP 6000, Waltham, MA, USA above mentioned.

2.2. Preparation of the Catalysts

Cat A: *P. sagittalis* leaves (3 g) were ground and then dried in an oven at 105 °C for 72 h. The solid was placed in an Erlenmeyer flask containing an aqueous solution of H₂SO₄ (250 mL, 2.25 mol L⁻¹) and the mixture was stirred at 85 °C for 6 h. Then it was filtered under vacuum using a Büchner funnel with filter paper and washed with distilled water (3 × 10 mL). The combined filtrates were heated at 90 °C for 10 min. Under vigorous stirring, an aqueous solution of NH₄OH (2.25 mol L⁻¹) was added until pH 6. The obtained black solid was centrifuged, washed with distilled water (3 × 10 mL) and dried at 120 °C for 8 h. affording **Cat A** (1.1g).

Ashes: Dried and ground *P. sagittalis* leaves (19.0 g) were calcinated at 400 °C for 5 h (heating flow: $10 \degree C \min^{-1}$), furnishing the ashes as a dark grey solid (5.3 g).

Cat B: An aqueous solution of HCl (1 mol L⁻¹, 20 mL) was added to a flask containing the ashes (1.5 g) and the resulting mixture was stirred for 2 h at 60 °C, with a change in the color from dark to green. The mixture was filtered under vacuum using a sintered glass funnel containing celite. The resulting green solution was concentrated under vacuum. This solid (250 mg) was diluted in distilled water (10 mL) and montmorillonite K 10 (500 mg) was added. This mixture was stirred at 90 °C for 8 h and then was filtered under vacuum using a Büchner funnel with filter paper and washed with distilled water

 $(5 \times 10 \text{ mL})$. The resulting solid was dried in an oven at 120 °C for 3 h, furnishing **Cat B** as a beige solid (700 mg).

Cat C: The ashes (2.0 g) were stirred with formic acid 85% (40 mL) at 90 °C for 18 h. After reaching room temperature, the mixture was filtered under vacuum using a sintered glass funnel containing celite and washed with formic acid 85% (5 mL). The acid solution was discarded, and the solid residue (mixture of salts and celite) was transferred to a beaker and hot water was added (10 mL). Then, this mixture was filtered under vacuum using a Büchner funnel with filter paper and washed with distilled hot water (2 × 10 mL). This resulting filtrate solution was concentrated in vacuum furnishing **Cat C** as a white solid (900 mg).

The ashes and the cocatalysts were characterized by XRD, and to verify the textural (porosity and specific surface area) and morphological properties, the most active ecocatalysts were also characterized by N₂-physisorption measurements and Scanning Electron Microscopy (SEM) analyses. Powder X-ray diffraction (XRD) patterns were recorded between 5 and 80 (°2 θ) on a Rigaku MiniFlex 600 diffractometer using CuK α radiation ($\lambda = 1.542$ Å). The nitrogen adsorption/desorption isotherms were obtained at -196 °C using a Micromeritics ASAP-2420 apparatus, Norcross, GA, USA. Prior to the analysis, the sample was degassed for 4 h at 300 °C under a vacuum of 20 µm Hg [29]. The specific surface area and the pore size distribution were determined, respectively, from the Brunauer–Emmett–Teller (BET) equation [30] and Barrett–Joyner–Halenda (BJH) method applied to the adsorption branch [31,32]. The SEM analyses were carried out on a FEI INSPECT F50 scanning electron microscope, Hillsboro, OR, USA.

2.3. General Procedure for the Synthesis of Dihydropyrimidinones 3 (DHPMs)

In a sealed tube, a mixture of benzaldehyde (0.081 mL; 1 mmol), urea (0.072 g; 1.4 mmol), ethyl acetoacetate (0.127 mL; 1 mmol), and the catalyst (50 mg) was stirred at 80 °C in an oil bath for 12 h. The reaction progress was followed by TLC analyses. The mixture was diluted with ethanol (6 mL) and the catalyst was removed by filtration under vacuum using a Büchner funnel and washing with ethanol (3 \times 10 mL). The filtrate was collected, the solvent was evaporated under vacuum and the crude was purified by a chromatography column using hexane/ethyl acetate (7:3) as eluent. The DHPMs **3** were analyzed by melting point and NMR and the obtained data were identical to those from the literature.

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3a**) [33]: white solid (0.218 g, 84%); m.p. 204–206 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ: 9.21 (s, 1H), 7.75 (s, 1H), 7.35–7.30 (m, 2H), 7.24 (t, J = 6.1 Hz, 3H), 5.14 (brs, 1H), 3.98 (q, J = 7.0 Hz, 2H), 2.25 (s, 3H), 1.09 (t, J = 7.0 Hz, 3H). {¹H}¹³C NMR (DMSO-d₆, 100 MHz) δ: 165.8; 152.6; 148.8; 145.3; 128.9; 127.7; 126.7; 99.7; 59.7; 54.4; 18.2; 14.5.

Ethyl-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3b**) [34]: white solid (0.239 g, 81%); m.p. 214–216 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ : 9.32 (s, 1H), 7.84 (s, 1H), 7.45 (d, J = 7.1 Hz, 2H), 7.30 (d, J = 7.1 Hz, 2H), 5.20 (s, 1H), 4.08–4.00 (m, 2H), 2.31 (s, 6H), 1.15 (t, J = 6.0 Hz, 3H). {¹H}¹³C NMR (DMSO-d₆, 100 MHz) δ : 165.6; 152.4; 149.2; 144.2; 132.2; 128.9; 128.7; 99.3; 59.7; 53.9; 18.3; 14.5.

Ethyl 4-(4-cyanophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3c**) [33]: white solid (0.197 g, 69%); m.p. 170–172 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ: 9.34 (s, 1H), 7.87 (s, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.42 (d, J 8.1 Hz, 2H), 5.21 (brs, 1H), 3.98 (q, J = 7.0 Hz, 2H), 2.25 (s, 3H), 1.08 (t, J = 7.0 Hz, 3H).

Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3d**) [33]: yellow solid (0.218 g, 79%); m.p. 202–204 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ: 10.35 (s, 1H), 9.67 (s, 1H), 7.20–7.38 (m, 5H), 5.17 (brs, 1H), 2.29 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H). {¹H})¹³C NMR (DMSO-d₆, 100 MHz) δ: 174.7; 165.6; 145.5; 144.0; 129.0; 128.2; 126.8; 101.1; 60.0; 54.5; 17.6; 14.5.

5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**3e**) [33]: light yellow solid (0.193 g, 84%); m.p. 237–239 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 9.20 (s, 1H), 7.84 (d, J = 3.0 Hz, 1H), 7.34–7.22 (m, 5H), 5.25 (brs, 1H), 2.29 (s, 3H), 2.10 (s, 3H).

5-Acetyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**3f**) [**3**4]: yellow solid (0.230 g, 88%); m.p. 227–229 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ 9.25 (s, 1H), 7.88 (s, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 5.25 (brs, 1H), 2.28 (s, 3H), 2.12 (s, 3H).

2.4. General Procedure for the Synthesis of 1,4-Dihydropyridines 5 (DHPs)

In a sealed tube, a mixture of diketone or β -ketoester (1.0 mol), aldehyde (0.5 mol), ammonium acetate (1.25 mol), the catalyst (50 mg), and ethanol (0.5 mL) was stirred at 110 °C under microwave irradiation (300 W) for 20 min. The progress of the synthesis was verified by TLC analyses. Then the catalyst was removed by filtration under vacuum using a Büchner funnel and then washed with ethanol (3 × 10 mL). The filtrate was collected and after concentration under vacuum, the crude was purified by column chromatography using hexane/ethyl acetate 4:1 ratio as eluent. The 1,4-DHPs **5** were analyzed by melting point and NMR and the obtained data were identical to those from the literature.

3,3,6,6-Tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**5a**) [**35**]: light yellow solid (0.171 g, 98%); m.p. 276–278 °C. ¹H NMR (DMSO-d₆, 400 MHz) δ : 9.35 (s, 1H), 7.21 (d, J = 4.3 Hz, 4H), 7.12–7.06 (m, 1H), 4.87 (s, 1H), 2.53 (s, 1H), 2.49 (s, 1H), 2.40 (s, 1H), 2.36 (s, 1H), 2.25 (s, 1H), 2.21 (s, 1H), 2.06 (s, 1H), 2.02 (s, 1H), 1.07 (s, 6H), 0.92 (s, 6H). {¹H}¹³C NMR (DMSO-d₆, 100 MHz) δ : 194.8; 149.8; 147.6; 128.1; 128.0; 125.9; 111.9; 50.7; 33.3; 32.6; 29.6; 26.9.

(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**5b**) [35]: light yellow solid (0.180 g, 94%); m.p. 296–298 °C. ¹H NMR (CDCl₃, 400 MHz) δ : 7.70 (bs, 1H), 7.27 (d, J = 8.1 Hz, 3H), 7.15 (d, J = 8.1 Hz, 2H), 5.04 (s, 1H), 2.33 (d, J = 17.1 Hz, 2H), 2.28–2.21 (m, 4H), 2.15 (d, J = 16.3 Hz, 2H), 1.07 (s, 6H), 0.95 (s, 6H).

4-(3,3,6,6-Tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahy-droacridin-9-yl) benzonitrile (**5c**) [36]: light yellow solid (0.148 g, 79%); m.p. 298–300 °C. ¹H NMR (CDCl₃, 400 MHz) δ: 7.47 (dd, J = 18.6, 8.0 Hz, 4H), 6.00 (bs, 1H), 5.03 (s, 1H), 2.40–2.16 (m, 8H), 1.03 (s, 6H), 0.89 (s, 6H).

3,3,6,6-Tetramethyl-9-(thiophen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8 (2H,5H)-dione (5d) [37]: light orange solid (0.163 g, 92%); m.p. 292–294 °C. ¹H NMR (CDCl₃, 400 MHz) δ : 6.98 (d, J = 4.9 Hz, 1H), 6.92 (d, J = 3.1 Hz, 1H), 6.83–6.80 (m, 1H), 6.12 (bs, 1H), 5.40 (s, 1H), 2.37–2.25 (m, 8H), 1.10 (s, 6H), 1.04 (s, 6H).

Diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**5e**) [38]: light yellow solid (0.147g, 89%); m.p. 155–157 °C. ¹H NMR (CDCl₃, 400 MHz) δ : 7.20 (d, J = 7.4 Hz, 2H), 7.12 (t, J = 7.5 Hz, 2H), 7.04 (t, J = 7.2 Hz, 1H), 5.93 (s, 1H), 4.91 (s, 1H), 4.07–3.94 (m, 4H), 2.22 (s, 6H), 1.14 (t, J = 7,1 Hz, 6H). {¹H}¹³C NMR (CDCl₃, 100 MHz) δ : 167.8, 147.8, 144.2, 128.0, 127.8, 126.1, 104.0, 59.8, 39.6, 19.5, 14.3.

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5f**) [39]: light yellow solid (0.160 g, 88%); m.p. 129–131 °C. ¹H NMR (CDCl₃) δ: 7.19 (ABq, J = 8.3 Hz, 4H), 5.68 (s, 1H), 4.95 (s, 1H), 4.12–4.04 (m, 4H), 2.32 (s, 6H), 1.21 (t, J = 7.1 Hz, 6H).

2.5. Recycling of the Cat B

After the reagents were fully consumed, the reaction mixture was filtered under vacuum using a Büchner funnel. The residue was washed with ethanol (15×1 mL), dried at room temperature and then reused.

3. Results and Discussion

Rehabilitation of degraded areas by mining activities is required to safeguard the environment, hence being indispensable to achieving the sustainability of mining operations. Some plant species are able to tolerate high metal concentrations from metalliferous ecosystems; therefore, they might do better in phytoremediation processes than species from unsuitable ecosystems [40].

Santana et al. reported that *Setaria parviflora* and *Paspalum urvillei* tolerate and accumulate high iron concentrations in their tissues, thus favoring the possible use of these grasses in phytoextraction [41]. Batista et al. evaluated the Pb bioaccumulation potential of four plant species including embaúba (*Cecropia* sp.); however, none of the evaluated species met the hyperaccumulator criterion [42]. Rossato et al. evaluated the effects of lead on the growth, lead accumulation and physiological responses of *Pluchea sagittalis*, and concluded that this species is Pb-tolerant, being able to accumulate on average 6730 and 550 µg Pb g⁻¹ dry weight, respectively, in the roots and shoot, a physiological trait which may be exploited for the phytoremediation of contaminated soils and waters [43]. Moreover, *Typha domingensis* has been studied in the phytoremediation of barium-affected flooded soils [44].

In the search for hyperaccumulating plants, *Cecropia pachystachya*, *Pluchea sagittalis* and *Typha domingensis* were collected from a mining area in Canaã dos Carajás, northern Brazil, which is an iron oxide-copper-gold deposit. After drying and gridding, the aerial parts of these three plant species were digested and analyzed by inductively coupled plasma optical emission spectrometry (ICP-OES). Concentrations of Ba, Ca, Cd, Cr, Cu, Fe, K, Mg, Na, Ni, Pb and S were determined (see Supplementary Materials), and the most abundant transition metals were Fe, Cu and Ni (Table 1). Among the plant species, *P. sagittalis* (leaves and flowers) and *C. pachystachya* (branches) showed the highest concentration of these metals, thus *P. sagittalis* leaves were selected for the synthesis of ecocatalysts.

Table 1. Metal concentrations ¹ in plants collected in a mining area in northern Brazil.

Sample	Cu (mg kg $^{-1}$)	Ni (mg kg $^{-1}$)	Fe (mg kg ⁻¹)
Cecropia pachystachya leaves	83.0 ± 5.2	3.6 ± 0.7	350 ± 2
Cecropia pachystachya branches	374 ± 8	52.5 ± 3	3900 ± 0.05
Pluchea sagittalis leaves	567 ± 16	31.4 ± 1.4	$10,000 \pm 0.1$
Pluchea sagittalis flowers	174.1 ± 7.3	49.8 ± 3.2	3900 ± 0.02
Typha domingensis leaves	56.8 ± 4.1	23.7 ± 0.6	510 ± 1

¹ ICP-OES analyses carried out in triplicate.

In our first attempt, we followed the procedure described by Liu et al. [17] to obtain an ecocatalyst. Thus, H_2SO_4 was used to dissolve and remove the metals as well as to hydrolyze the cellulose from the *P. sagittalis* leaves. The formed precipitate was centrifuged, washed with deionized water, and dried at 120 °C for 8 h, and then subjected to acid digestion to be analyzed by ICP-OES. The analysis showed the presence of 17.7 mg kg⁻¹ of Cu, 998.5 mg kg⁻¹ of Fe and 0.7 mg kg⁻¹ of Ni in this material (**Cat A**). Figure 1 shows the diffractogram of **Cat A**, where the diffraction peaks, as a result of the preparation procedure, correspond to mascagnite (NH₄)₂SO₄. Diffraction peaks corresponding to crystalline phases containing Cu, Fe or Ni are not evident due to their low content in the ecocatalyst.

We then evaluated another procedure to prepare the ecocatalyst using ashes from the *P.* sagittalis leaves, which were obtained after calcination at 400 °C for 5 h (see Supplementary Materials). ICP-OES analysis showed the presence of Cu (1877 \pm 17.4 mg kg⁻¹), Ni (118 \pm 7.76 mg kg⁻¹) and Fe (34,491 \pm 1234 mg kg⁻¹). The X-ray diffractogram of the ashes (Figure 2) shows a solid composed of highly crystalline materials and corroborates the presence of the oxides corresponding to the more abundant metals determined by ICP-OES in the *P. sagittalis* leaves. In Figure 2 (by vertical lines), the 20 angles of the more intense peak related to Fe₂O₃ (33.15°) [45], CaO (37.35°) [46], CuO (39.79°) [47], K₂O (39.61°) [48], and MgO (42.96°) [49] are indicated, which, respectively, correspond to 104, 200, 111, 220 and 200 atomic plane of the considered metallic oxide. The other not-highlighted peaks in the diffractogram shown in Figure 2 are diffraction peaks corresponding to the different mentioned metallic phases. Furthermore, the diffractogram also shows the presence of

phosphorous oxide (P_2O_5) and silicon oxide (SiO₂) [50], whose more intense diffraction peak is located, respectively, at 2 θ angles of 26.25° [51] and 28.54° [52]. Further details are shown in the Supplementary Materials.



Figure 1. XRD diffractogram corresponding to Cat A. The vertical violet lines indicate the pattern diffraction peaks corresponding to $(NH_4)_2SO_4$.



Figure 2. X-ray diffractogram of the ashes, highlighting (vertical lines) the more intense diffraction peak of the oxides corresponding to the most abundant elements determined by ICP-OES analysis in the *P. sagittalis* leaves.

Continuing our efforts, we evaluated a different procedure to obtain the ecocatalyst using ashes from the *P. sagittalis* leaves. Thus, after calcination at 400 °C for 5 h, the resulting ashes were treated with aqueous HCl for 2 h at 60 °C. The mixture was filtered over celite, and the solution was concentrated under vacuum. The resulting solid was diluted in water and mixed with montmorillonite K 10 (MK10) at 90 °C for 8 h [53]. This mixture was then filtrated, the solid was washed with water, and oven dried at 120 °C for 3 h, furnishing **Cat B**. ICP-OES analysis showed the presence of Cu (35.21 \pm 2.75 mg kg⁻¹), however, the amount of Ni was below the limit of quantification.

Consistent with this quantitative chemical analysis, the X-ray diffractogram of **Cat B** (Figure 3) shows diffraction peaks only corresponding to the MK10 clay [54,55] and does not show any diffraction peak corresponding to the crystalline phases of CuO, NiO or Fe₂O₃, although iron was present in a significative high content in the ashes of *P. sagittalis* leaves. Except for SiO₂, a component of the MK10 [55], no diffraction peaks are observed related to CaO, K₂O, MgO and P₂O₅, the oxides corresponding to the other more abundant elements in the ashes. Here, it is important to point out that the non-evidence of CuO diffraction peaks in **Cat B** means that copper is highly dispersed over the MK10 clay.



Figure 3. XRD diffractogram of **Cat B** showing solely peaks corresponding to the MK10 clay (vertical red lines indicating the MK10 pattern diffraction peaks).

With the aim of improving the ecocatalyst, the *P. sagitallis* leaves ashes were heated with formic acid at 90 °C for 18 h, then were filtered over celite and the solid was washed with formic acid and hot water [56]. The resulting solution was concentrated under vacuum furnishing a white solid (**Cat C**). Interestingly, ICP-OES analysis showed the presence of both Cu (961 \pm 8.72 mg kg⁻¹) and Ni (32.2 \pm 0.347 mg kg⁻¹). The XRD diffractogram of **Cat C** (not shown), showed the same main diffraction peaks of the ashes (Figure 2), evidencing that after the above-described procedure, the resultant solid practically maintained the ashes composition.

To explore the efficiency of these novel ecocatalysts, we tested them in the Biginelli reaction [57,58]. This MCR is considered one of the most well-designed methodologies for

the synthesis of dihydropyrimidinones **3** (DHPMs), a very important family of compounds, mostly known for their diverse pharmacological properties, acting as antibacterial, antiviral, calcium channel modulators, anti-cancer, or anti-hypertensive agents [59–61].

Thus, the Biginelli reaction was carried out using benzaldehyde (1), ethyl acetoacetate (2) and urea (Table 2). In order to compare our catalysts with previous reports in the literature, initially, we tested $CuCl_2.2H_2O$ at r.t., with a 4 M solution of HCl in dioxane and 2-MeTHF as solvent (entries 1–3), as described by Pawłowski et al. [62]. By using 1 mol% of the catalyst for 24 h, only 20% yield of compound **3a** was obtained, whereas, with 5 mol% (for 12 or 24 h), a large increase in yield (62 or 96%) was observed. When the reaction was carried out in the absence of Cu(II), only a 21% yield was obtained (entry 4). We then tested Cat A in the same conditions (entry 5) and compound **3a** was obtained in 60% yield. Looking for a more sustainable condition, we tested **Cat B**, **Cat C**, the ashes and MK10 (entries 5–9) in a solvent-free reaction at 80 °C and the desired product **3a** was obtained with moderate to good yields (61 to 84%). The reaction was also evaluated under microwave irradiation using **Cat B** or ashes; however, only traces of the product and decomposition of the starting materials were observed probably due to the high energy (entries 10 and 11).

Table 2. Synthesis of DHPM 3a using different catalysts.



^a unless otherwise noted, all reactions were carried out using benzaldehyde (1) (1 mmol), ethyl acetoacetate (2) (1 mmol), urea (1.4 mmol) and catalyst (50 mg). ^b isolated yield after column chromatography. ^c HCl 4M in dioxane (2.0 mL) and 2-MeTHF (0.5 mL) at r.t. ^d solvent-free at 80 °C under conventional heating for 12 h. ^e solvent-free under microwave irradiation at 300 W for 20 min. ^f MSMA: mean specific metallic activity.

To better understand the catalytic metallic effect on the reaction described in Table 2 and considering the chemical metallic composition determined by ICP shown above, we calculated a mean specific metallic activity (MSMA), defined as the ratio of the produced mol number of the **3a** compound to the sum of the µmols number of Cu, Fe and Ni present in the **Cat A**, **Cat B**, **Cat C** and ashes. As can be seen in Table 2, the MSMA of **Cat B** is much higher than **Cat A**, **Cat C** and ashes, behavior that clearly shows the best catalytic performance of **Cat B**, which indicates an important synergetic effect between the supported metallic species and the MK10 support.

The condition described in Table 2, entry 6, i.e., solvent-free reaction using **Cat B** at 80 °C, has been chosen to evaluate the scope and limitation of this protocol (Figure 4). In

this regard, the shown six DHPM compounds, containing electron donor or withdrawing groups at the aldehyde, ethyl acetoacetate or pentane-2,4-dione, urea or thiourea were obtained in good yields (69–88%). However, to successfully achieve compounds **3b**, **3c** and **3f**, a minimum amount of ethanol (0.5 mL) was necessary to solubilize the starting materials.



Figure 4. Yield (%) of DHPMs 3a-f synthesized via Biginelli reaction using Cat B at 80 °C for 12 h.

The ecocatalysts were then evaluated in the Hantzsch reaction [63] for the synthesis of 1,4-dihydropyridine **5a** (1,4-DHP) using benzaldehyde (1), dimedone (4), ammonium acetate and ethanol as solvent under microwave irradiation [3] (Table 3). This class of compounds has been extensively studied due to their potent biological activities, including commercially available drugs [52–64].



Table 3. Ecocatalysts obtained from *P. sagitallis* leaves in the synthesis of 1,4-DHP 5a.

^a unless otherwise noted, reactions were performed using benzaldehyde (1) (0.5 mmol), dimedone (4) (1.0 mmol), ammonium acetate (1.25 mmol), catalyst (50 mg) and ethanol (0.5 mL) under microwave irradiation at 110 °C and 300 W for 20 min. ^b isolated yield after column chromatography.

Initially, we tested the ashes in different loadings (Table 3, entries 1–3) and observed that lower yields were obtained with high amounts of the catalyst, which could be acting as an adsorbent instead [65,66]. Thus, we defined 50 mg as the best catalyst amount and then tested **Cat B** and **Cat C** (entries 4–5) and observed that all of them were efficient in promoting the MCR, **Cat B** being outstanding, furnishing the 1,4-DHP 5a in 98% yield. As this catalyst is supported over the MK10 clay, we also tested only the clay (entry 6) and observed a significant yield decrease, evidencing that the copper incorporation was essential for the ecocatalyst performance. We then evaluated the recyclability of **Cat B** by filtering the solid during the workup, washing with ethanol and drying under vacuum at room temperature. To our delight, the catalyst could be reused in up to six reaction cycles without a significant loss in yield (Figure 5).



Figure 5. Yields (%) of compound 5a for each reaction cycle using recycled Cat B.

Based on these results, **Cat B** was selected to continue our study; the scope and limitations of the microwave-assisted Hantzsch reaction using ethanol as solvent were explored. Once again, electron donor or withdrawing groups at the aldehyde **1**, including a heteroaromatic (**5d**), and ethyl acetoacetate or dimedone (**4**), were evaluated and the desired products **5** obtained in good to excellent yields (79–98%) (Figure 6).



Figure 6. Yield (%) of 1,4-DHPs **5a–f** synthesized via microwave-assisted Hantzsch reaction using **Cat B** and ethanol at 110 °C for 20 min.

In Table 4 it is possible to compare our results in the synthesis of compounds **3a** and **5a** using **Cat B** with other heterogenous catalysts reported in the literature [67–75]. Most of the catalysts were employed in the Biginelli reaction using ethanol (entries 3 and 4) or in a solvent-free condition (entries 1, 2, 5 and 6) under conventional heating, furnishing DHPM **3a** with good to high yields (72–97%). Concerning the Hantzsch reaction (entries 1, 2, 8 and 9), the 1,4-DHP **5a** was obtained in good to excellent yields (79–97%). **Cat B** proved to be more efficient, since **5a** could be prepared in 98% yield under microwave irradiation (entry 10).

Entry	Catalyst and Reaction Conditions	Cat. Recycling (cycles)	3a, Yield (%)	5a, Yield (%)	Ref.
1	BNPs@SiO ₂ (CH ₂) ₃ NHSO ₃ H, solvent-free, 80 °C, 30 min or EtOH, 70 °C, 35 min	5	97	97	[67]
2	NiFe ₂ O ₄ @SiO ₂ @KIT-6-SO ₃ H, solvent-free, 100 °C, 10 min or EtOH, reflux, 80 °C, 55 min	5	95	93	[68]
3	Fe-C-O-Mo alloy, EtOH, reflux, 2.5 h	8	92	-	[69]
4	bentonite/ $H_4[W_{12}SiO_{40}]$, EtOH, 80 °C, 5 h	-	86	-	[70]
5	NH ₄ H ₂ PO ₄ /MCM-41, solvent-free, 100 °C, 6 h	6	72	-	[71]
6	H ₃ PW ₁₂ O ₄₀ @MIL-101, solvent-free, 100 °C, 60 min	4	90	-	[72]
7	SiO ₂ -CuCl ₂ , MeCN, MW, 80 °C, 15 min	5	90	-	[73]
8	[ImSi][PF ₆]@xanthan, EtOH, 80 °C, 37 min	5	-	93	[74]
9	H ₂ SO ₄ -activated montmorillonite, solvent-free, MW, 110 °C, 14 min	4	-	79	[75]
10	Cat B , solvent-free, 80 °C, 12 h or EtOH, MW, 110 °C, 20 min	6	84	98	this work

Table 4. Comparison of Cat B performance with earlier reported protocols.

To find elements to understand the better catalytic performance of the prepared **Cat B**, despite it accentuating the minor metallic content than that present in the ashes and **Cat C**, we used textural and morphological additional data, respectively, determined from N₂ physisorption measurements and SEM images. As can be seen from the physisorption isotherms in Figure 7, **Cat B** presents a clear behavior of a mesoporous solid (Figure 7a, Table 5), with a narrower mesopore size distribution (Figure 7b) than **Cat C** (Figure 7a, Table 5) and the clearly non-porous ashes (Figure 7a, Table 5).



Figure 7. (a) N₂ adsorption isotherms of *P. sagitallis* leaves ashes, **Cat B** and **Cat C**; (b) and (c) mesopore size distribution of **Cat B** and **Cat C**, respectively.

Catalyst	BET Area (m ² g ⁻¹)	Total Pore Volume (cm ³ g ^{-1})
Cat B	232	0.286
Cat C	33	0.061
Ashes	4	0.009

The porosity presented by **Cat C** mainly results from its interparticle porosity (Figure 7c). Then, **Cat B** presents a substantially higher specific surface area (Table 5)

that is a consequence of the presence of the MK10 clay, a well-known and catalytically applied layered aluminosilicate [76,77], which was added during the synthesis of **Cat B** and possesses a superficial area close to $250 \text{ m}^2 \text{ g}^{-1}$ [78]. Consequently, over the specific surface area of the MK10 clay, the lower amount of the supported catalytically active metallic species is highly dispersed, a behavior that was confirmed by its XRD diffractogram (Figure 3), which does not show metallic oxide diffraction peaks. Consistent with their structural and textural properties, the SEM images of Figure 8 show that **Cat B** (Figure 8a,c) is formed by agglomerates of considerably smaller particles than **Cat C** (Figure 8b,d).





Figure 8. SEM images: (a,c) Cat B; (b,d) Cat C.

The superior textural properties of **Cat B** than **Cat C** can support its better catalytic performance as a consequence of the higher dispersion of their metallic active species, despite the enormous difference between their contents, which were determined by ICP-OES chemical analyses. For example, the Cu content in **Cat B** was 35.21 mg kg⁻¹, which was lower when compared with the Cu content in **Cat C** (961 mg kg⁻¹). Because of its lower specific surface area (Table 5) and presence of CuO agglomerates of less dispersed particles, as was evidenced by N₂ physisorption and XRD data, respectively, the ashes presented lower catalytic activity than **Cat B** and **Cat C** (Tables 2 and 3).

4. Conclusions

In summary, we evaluated the metal contents of three plant species collected on a mine in the Brazilian Amazonia by ICP-OES and selected the *P. sagitallis* leaves to prepare ecocatalysts. The *P. sagitallis* leaves ashes, **Cat B** and **Cat C** were analyzed by ICP-OES and characterized by XRD, N₂-physisorption measurements and SEM analyses. These catalysts were then successfully employed in the Biginelli and Hantzsch MCRs, furnishing the corresponding 3,4-dihydropyrimidin-2-(1H)-ones and 1,4-dihydropyridines with good to excellent yields. The best catalyst (**Cat B**) could be easily recovered and reused in the Hantzsch reaction in up to six runs without a significant decrease in its performance, demonstrating the feasibility of the use of hyperaccumulating plants as a source of heterogeneous catalysts.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/reactions4040033/s1, Figure S1: *Pluchea sagittalis* leaves (a) dried and ground. (b) ashes after calcination.; Figure S2: Enlarged ashes diffractogram between 25 and 45° 20. Figures S3–S19: ¹H and ¹³C NMR spectra of compounds **3a–f** and **5a–f**. Table S1: Metal concentrations (ICP-OES) in plants collected at a mining area on northern Brazil.

Author Contributions: L.H.R.A.: organic synthesis work. S.Y.S.S., S.C.S. and M.N.d.O.: plants identification, collection, drying and gridding. C.S.d.S. and J.V.: ICP-EOS analyses. M.F.d.G.F.d.S.: contributions to manuscript writing. M.P.: ashes and catalysts characterization. E.A.U.-G.: analysis, manuscript writing and revision. A.G.C.: coordination of organic synthesis work, manuscript writing and revision. All authors have read and agreed to the published version of the manuscript.

Funding: The authors gratefully acknowledge FAPESP (grants 2013/07600-3, 2014/50249-8, 2014/ 50918-7, 2018/12367-0 and 2021/12394-0), FAP's (ICAAF n. 037/2011), GlaxoSmithKline, CAPES (Finance Code 001), and CNPq (grant 429748/2018-3 and 302140/2019-0) for funding and fellowships.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary Materials.

Conflicts of Interest: The authors declare no conflict of interest.

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