

Modified Pickering Catalysis: Green Transfer Hydrogenation of the Tri-substituted Olefin of Tetrahydrocannabinol

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ABSTRACT: Green transfer hydrogenation of the trisubstituted olefin within the tetrahydrocannabinol scaffold, has been performed using minimal amount of organic solvent in water, on the basis of a modified Pickering catalysis, with greater selectivity over standard industrial conditions with decreased reaction times under ambient conditions. Examples of various solvents, surfactants, and observation of europium in the selectivity of the hydrogenated products are given.

Pickering catalysis is a novel technique employing microemulsions of solid supported catalysts with a biphasic system to hydrogenate or conduct synthesis in a greener manner [1]; Recent demonstrations [2,3] of palladium doped silica or palladium doped hercynite allows the biphasic hydrogenation of nitro-arenes to substituted anilines, using water as one of the main biphasic sources of solvent, employing green techniques within the hydrogenation. The downside of pickering catalysis is the synthesis of the solid supported catalysts. The solid supported catalysts require a silica core ligand to a precious metal catalyst, which require additional synthetic steps and purification. A demonstration of straying from classical solid support catalyst within pickering catalysis, led to a demonstration of surfactant induced nanoparticles of palladium, for the hydrogenation of olefins [4]. The potential for these methods is great but limited reactions have been reported, regarding the hydrogenation of olefins and functional groups.

Tri-substituted and tetra-substituted olefins are renowned for being the most difficult types of functional groups to hydrogenate. Tetrasubstituted olefins are found in many privileged scaffolds with important multiple stereocenters found in many natural products in the realm of biochemistry. Trisubstituted olefins also provide important impacts in the realm and are found in common and uncommon-place compounds. In particular the trisubstituted olefin found in the natural product, Tetrahydrocannabinol (THC). THC plays an important role in an ever-growing field of chemistry and biology with the potential to treat diseases and ailments that are currently being researched [5].

In previous studies [6-8], the standard hydrogenation technique for the transformation of THC which includes the tri-substituted olefin to produce the biologically relevant Hexahydrocannabinol (HHC) creating diastereomers of R or S HHC, includes the use of Pd/C with hydrogen gas bubbled in an ethanolic solution at standard pressure, creating various mixtures of (R/S) diastereomers. Various changes in the catalyst type/loading, solvent, and additives, can achieve diastereoselective results as shown by Garg et al, through hydrogen atom transfers (HAT), although without regard to green principles or scalability. Hydrogen transfer (HT) process which include reagents like formic acid, sodium formate, ammonium formate, silanes, and quaternary ammonium halides to name a few [8,9] can follow within the guidelines of a green hydrogenative additive and or reagent depending on concentration and choice of solvent. The

importance of performing hydrogenation under green principles is pertinent for reduction of waste and environmental impacts [10].

A general screening of a few catalysts under standard conditions was done, as shown below in table 1 to give a benchmark of the HHC output to observe changes in selectivity, and reaction times.

Catalyst	Solvent	Time	loading	% THC	% (R)-HHC	% (S)-HHC
Pd(OH) ₂ /C	MeOH	16Hr	10 mol %	3.411	64.557	31.934
Pd(OAc) ₂	MeOH	16Hr	10 mol %	2.508	62.01	35.481
Pd/C	MeOH	16Hr	10 mol %	56.722	18.93	24.348
Pt/C	MeOH	16Hr	10 mol %	8.215	44.57	47.215

Table 1: Initial catalyst screening, to benchmark initial selectivity and reaction times. Under ambient conditions, STP, 20°C in MeOH.

The use of pickering conditions, we found that due to the low solubility of hydrogen in water (1.6mg/L), a limitation of the process would be using hydrogen gas. Using a Proton transfer reagent in aqueous solution such as ammonium formate can help facilitate the hydrogen concentration within the water. The addition of minimal amounts of methanol would also create a hyper-saturated biphasic system to occur where released hydrogen can get absorbed in the methanol. As mentioned previously solid supported catalyst require additional synthetic and purification steps, wherein the formation of surfactant induced formation of nanoparticles in-situ is possibly cleaner and faster, especially in a system with extreme lipophilic compound creating micelles within a biphasic solvent system [11,12]. Through the aforementioned thoughts, a modified pickering catalysis fits and was adopted to allow a greener hydrogenation technique to provided.

In this communication, we herein report the first-time green hydrogenation of the tri-substituted olefin found in the privileged natural product THC scaffold. Following a modified Pickering condition observing diastereomer selectivity using various chiral additives, solvents, surfactants, and catalysts within a mainly water system. We also report the use of europium acetate as an additive, we observed increased reaction rate facilitating the hydrogenation of THC. The use of microemulsion and a proton transfer reagent to induce the nanoparticle formation is modified from the standard pickering conditions.

The general reaction condition under ambient conditions of the water microemulsion was prepared by mixing 100mg of THC in 0.5mL MeOH (0.06M), adding the solubilized material into a 40mL scintillation vial, containing 3.5mg of Pd(OH)₂ (~10mol%), adding 6mL of DI H₂O. Adding small amount of MeOH (1mL) to loosen catalyst and cannabinoid off the wall of the vial, making an effective concentration of (~0.04M) cannabinoid to total solvent. Surfactants contained tocopheryl polyethylene glycol succinate (TPGS) (100 mg), and 5 equivalents of Ammonium formate (100mg), and Europium Acetate (40mg, ~10 mol %), other conditions and exclusions were performed as described in table 2. A small PTFE coated stir bar (10mm) was placed in the scintillation vials, the scintillation vials were fitted with a snug fitted septum, with the septum being taped to ensure no leakage were to occur. A double ballooned syringe was filled with hydrogen gas equipped with a 5-inch spinal needle, submerged into the solution to allow bubbling of hydrogen to occur, and the stir bar spinning at 300 RPM to allow facile absorption of hydrogen. No heating or pressure was applied, all reactions were carried out in ambient conditions.

The reaction mixture is a milky white color, while stirring, with reaction progression is correlated to the color change, where it becomes dark gray similar to a light graphite color. Small aliquots (0.1mL) were taken throughout the 24hr time period and transferred to sample scintillation vials. Samples were extracted with small amounts of toluene, to ensure maximum amount of cannabinoid from water emulsion can be observed on an HPLC spectrum. The color change is not a definitive parameter to determine reaction completion but plays a major role within this case as progression is monitored, color changes reach from milky white to graphite color. Palladium microemulsion was monitored at T=0hr and T=8hrs using UV-VIS as shown below in figure 1.

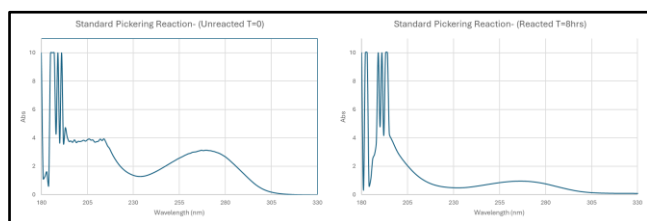


Figure 1: UV-Vis spectrum of the microemulsion of Pd(OH)₂ (0.002M Pd²⁺) and H₂O/MeOH. Spectrum on left is the emulsion with no hydrogen standalone mixture of reagents. Spectrum on the right is the reacted mixture of reagents with hydrogen over an 8hr time period.

UV-Vis can be used to observe the Pd²⁺ ions in solution and their absorbance can change according to absorption of hydrogen and their redox state [4]. UV-Vis was conducted on the unreacted microemulsion where we see absorbance at 270nm which has a slightly broad absorbance. In comparison to the reacted reaction mixture, the absorbance changes and shifts by about 4nm to the left as the peak is at 266nm. The reacted peak has a much broader almost undefined peak, which we can assume the palladium is being activated. Since the cannabinoid forms an emulsion and the use of

Pd(OH)₂/C as the catalyst is a fine powder, the formation of pseudo-micelles can be observed with the biphasic system Pd²⁺ ions would be in the biphasic system as the transfer hydrogenation is conducted. The unreacted sample was an opaque milky concoction compared to the reacted reaction which became a gray/cloudy mixture which reaction did occur as shown above.

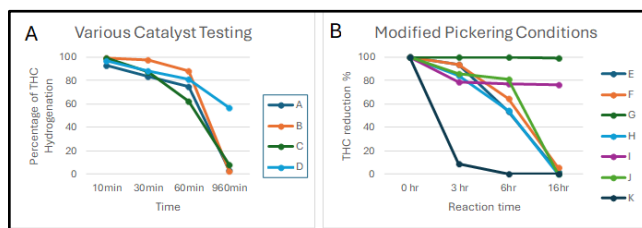


Figure 2A-C: All reactions were done at room temperature with a set compound concentration of 0.05M, at 1 atm. **Figure 2A** depicts the general reaction times of catalyst screening. All catalysts did not have a ratio higher than 2.5 R:S. (A) Pd(OH)₂/C, (B) Pd(OAc)₂, (C) Pt/C, (D) Pd/C. **Figure 2B:** Selected Pickering conditions depicting general reaction conditions. (E) Pd(OH)₂, Eu(OAc)₃, MeOH, H₂O, (R/S ratio 1:1) (F) Pd(OH)₂, Eu(OAc)₃, TPGS, H₂O/MeOH (10:1), NH₄COO, (R/S ratio 3.4:1) (G) Pd(OAc)₂, Eu(OAc)₃, H₂O/MeOH (10:1), NH₄COO, No H₂, (H) Pd(OAc)₂, Eu(OAc)₃, TPGS, H₂O/MeOH (10:1), NH₄COO, (R/S ratio 3:1) (I) HS157, NH₄COO, H₂O/MeOH (10:1), (R/S ratio 1.5:1) (J) HS157, NH₄COO, H₂O/MeOH (10:1), Eu(OAc)₃, (R/S ratio 1:1) (K) Pd(OH)₂, NH₄COO, H₂O/MeOH, No H₂ (R/S ratio 1.5:1).

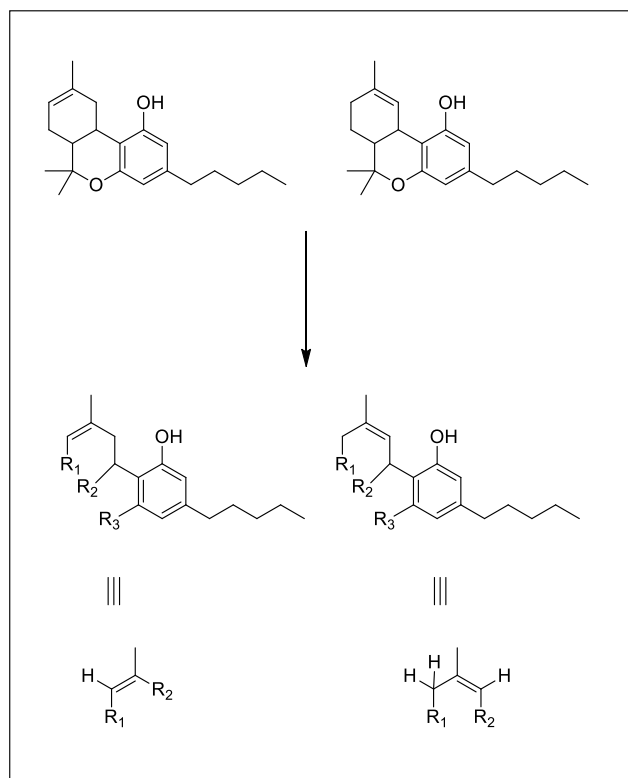


Figure 3: depicts the desired olefin for hydrogenation.

Hydrogenation of THC to HHC catalyzed by a microemulsion of Pd(OH)₂/C formed micelle were initially performed in a 10:1 H₂O/MeOH mixture at room temperature (20°C).

Depicted above in figure 2A, several catalysts were screened, the catalyst that performed the best were selected to be pushed forward for the water conditions. Pd(OH)₂ and Pd(OAc)₂ were the chosen catalysts. Reaction F and G were the standard reaction which consisted of Pd(OH)₂ or Pd(OAc)₂, a surfactant in this case TPGS, Europium acetate, ammonium formate and a ratio initially 10:1 of H₂O and MeOH.

These initial conditions help facilitate a transfer hydrogenation with reactions being complete after 8hrs. Reactions without hydrogen (K) and (G) relied on ammonium formate proton transfer to produce hydrogen leading it to being adsorbed on the catalyst might facilitate the hydrogenation with success of reaction K of full completion but limited selectivity while reaction G resulted in no reaction. The only difference between both reactions was the use of Pd(OAc)₂ and Eu(OAc)₃ in G and Pd(OH)₂ in K. Bis(1,5-cyclooctadiene)diiridium(I) dichloride (HS157) was tried for a selective reactivity. As shown in the above figure, reaction (I) stagnated around the 3hr time period whereas reaction (J) completed within 8hrs and both reactions exhibited no selectivity, but Eu(OAc)₃ did seem to assist in the reaction completion as that is the only difference between both reactions. Europium acetate was used in all reactions and increased reaction rates, and selectivity were observed except in reactions using palladium acetate and HS157.

The logic to increase selectivity by using chiral additives and/or chiral europium additives was not successful. Various water-soluble chiral additives as shown in SI table 1, such as (+)-tartaric acid, and proline were used but did not result in selective hydrogenation. Chiral europium additives were used such as EuFOD and Eu(FACAM)₃ which consists of either electronegative fluoro-camphor ligands or fluoro-ethyl camphor ligands with increasing bulk, which slowed the reaction completely with no selectivity except for reaction 18 (SI Table 1) which needs further investigation. Which led to blocking the alcohol of the cannabinoid to allow for an either face or back attack of the olefin but saw slowed reaction rate, with

The Results of the experiments were well received due to green transfer hydrogenation of the tri-substituted olefin of THC. Mild selectivity was produced, and no isolation of final product was conducted due to incomplete selectivity, which we are currently pursuing and optimizing to increase the greenness and selectivity of the hydrogenation. Also, our group is exploring the use of europium acetate as a co-catalyst within the biphasic system to understand its role and further applications in transfer hydrogenation under water conditions to increase its niche use. As well ongoing experiments of various surfactants and conditions are currently being explored.

ASSOCIATED CONTENT

Supporting information contains tables of various conditions ran for Pickering catalysis as well as the UV-Vis raw data. This material is available free of charge via the Internet at <https://pubs.acs.org>.

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally. (match statement to author names with a symbol)

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ABBREVIATIONS

HHC, Hexahydrocannabinol; Pd/C, Palladium on Carbon; STP, standard temperature and pressure, THC, Tetrahydrocannabinol; TPGS, tocopheryl polyethylene glycol succinate

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Pickering Conditions

