Supporting Information

One-pot green synthesis of β-artemether/ arteether

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All the reagents were purchased from Sigma-Aldrich Chemical Co., Lancaster and were used directly without further any purification. NMR spectra were obtained using the Brucker DRX 200 and 300 MHz spectrometers. Chemical shifts (ŭ) are given in parts per million relative to TMS, coupling constants (*J*) in hertz. Elemental analysis was performed using a Perkin Elmer Autosystem XL Analyzer. Melting points were measured using a COMPLAB melting-point apparatus. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light.

Preparation of cellulose sulfuric acid.

To a magnetically stirred mixture of 5.00 g of cellulose (DEAE for column chromatography, Merck) in 20 ml of n-hexane, 1.0 g of chlorosulfonic acid (9 mmol) was added dropwise at 0 ^{0}C over 2 h. HCl gas was removed from the reaction vessel immediately. After the addition was complete, the mixture was stirred

for 2 h. Then, the mixture was ýltered, washed with 30 ml of acetonitrile, and dried at room temperature to obtain 5.47 g cellulose sulfuric acid as a white powder. [K]

General procedure for the arteether from artemisinin in one-pot.

To a solution of artemisinin (200 mg, 0.71 mmol) in ethanol (15 mL) and trimethyl orthoacetate (0.5 mL) was added $NaBH_4$ (67 mg, 1.77 mmol, 2.5 equ.) and cellulose sulfuric acid (0.015 g). Reaction mixture was was carried out at -5 to 0°C for 60 min, and then stirred at room temperature for 1.5 h. Then we added a solution of sodium bicarbonate to quenched the reaction. The slurry was stirred in an below 20 ^{0}C for 1 h and allowed to settle for 30 min. Solid crude arteether was collected by ýltration, and the cake was washed with of ethanol. The reaction mass was heated to 40± 5 ^{0}C in water. The reaction mass was seeded with pure ϭï arteether. Then it was filtered, washed with chilled 50% solution of ethanol in water and dried.

General procedure for the artemether from artemisinin in one-pot.

Artemisinin (200 mg, 0.71 mmol) in methanol (15 ml) and trimethylorthoformate (0.5 ml), cellulose sulfuric acid (0.015 g), was carried out at -5 to 0°C for 60 min, and then stirred at room temperature for 1.5 h. The reaction was monitored by TLC and HPLC to check completion of the reaction. The cellulose sulfuric acid was removed by filtration, the filtrate was concentrated. Then we added a solution of sodium bicarbonate to terminate the reaction. Then, follow above recrystallization method.

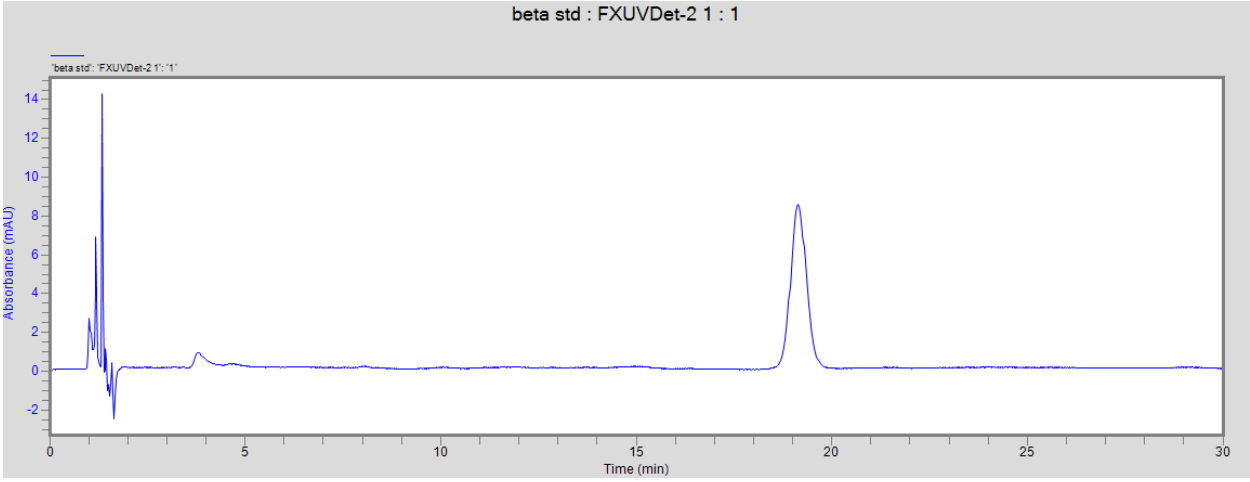
HPLC Analytical

HPLC was carried out on a C18 column (250 mm, 4 mm, and 5 µm) (Merck). The injection volume was 20 µl and the column efþuent was monitored at 215 nm. The mobile phase consisted of acetonitrile and

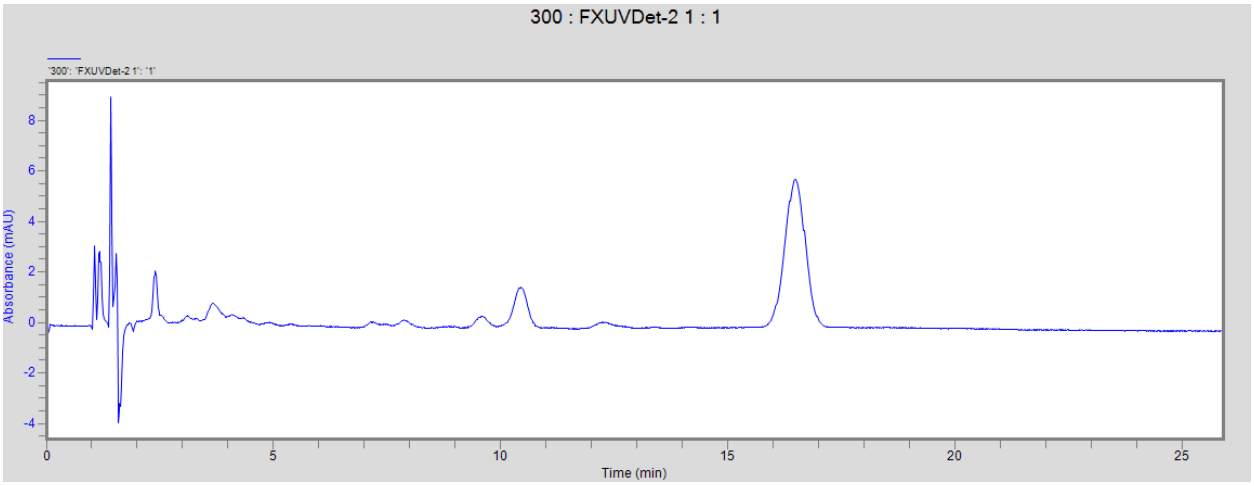
water, at a flow rate of 1ml/min. The optimized mobile phase was composed of 70% acetonitrile and 30% water. The detection was performed at 216 nm and the injection volume was 20 µL.

Catalyst optimization plot and Reusability

Reusability of solid acid catalyst is address the green methodology of the reaction. After completion of reaction, cellulose sulfuric acid was recovered from the reaction mixture by simple filtration, washed properly with acetone, and dried in oven for 3 h at 70 °C prior to its use in the absence of fresh catalyst. It was noticed that catalyst exhibited quite good reusability at least four additional times in subsequent reactions under the same reaction conditions without any remarkable loss in productivity. The catalyst loading was optimized by synthesis of arteether as an model reaction. Reaction took place in 2.5 h with 0.015 g of catalyst loading and almost 82% yield was obtained. Lowering the catalyst loading to 0.005-0.01 g results in 75-78% yield of arteether with a longer reaction time of more than 2.5 h, whereas increasing the concentration of catalyst has no significant effect on the yield of the reaction . Thus our present study enabled us to find the efficient amount of catalyst which is summarized in figure.

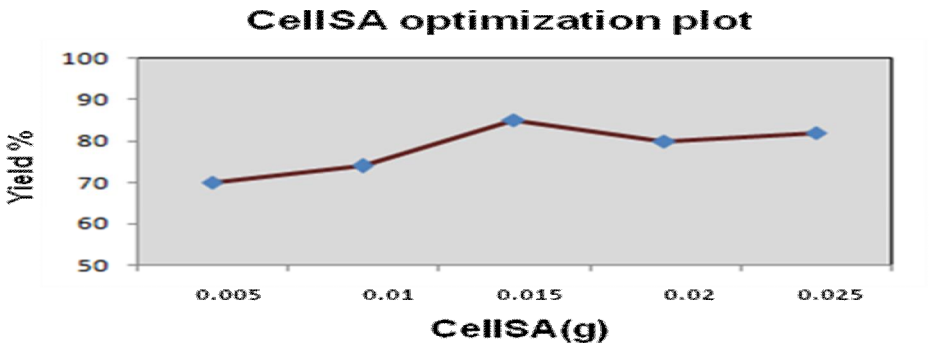


HPLC Chromatograms of crystallized β- artether



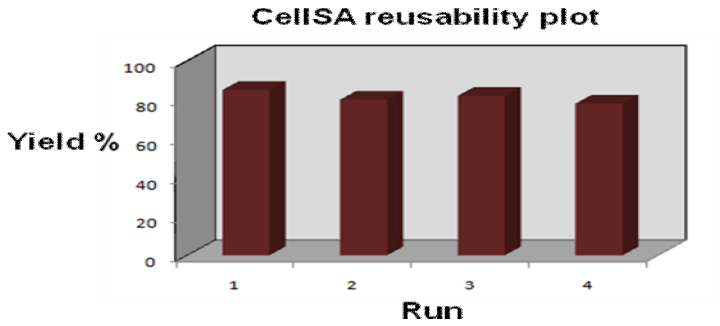
HPLC Chromatograms of reaction after 2.5 hr (a) α-Artether and (b) β- Artether

Optimization of solid acid catalyst: Cellulose sulfuric acid

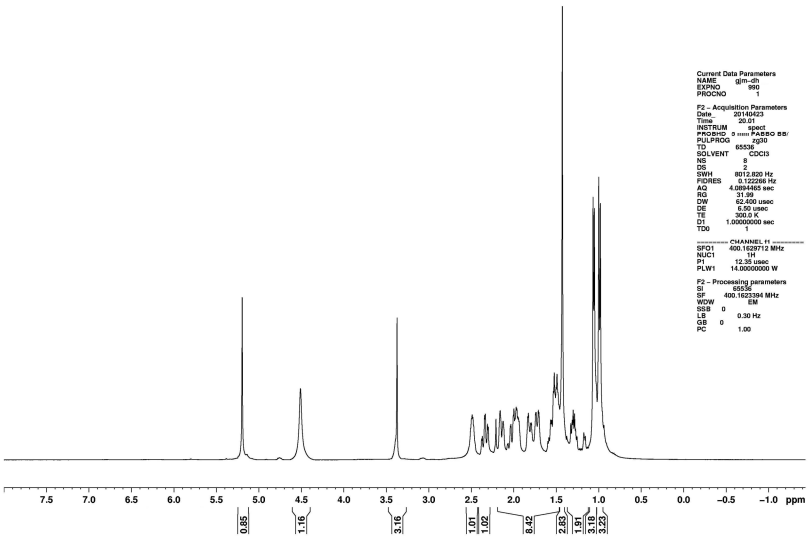


Catalyst optimization plot

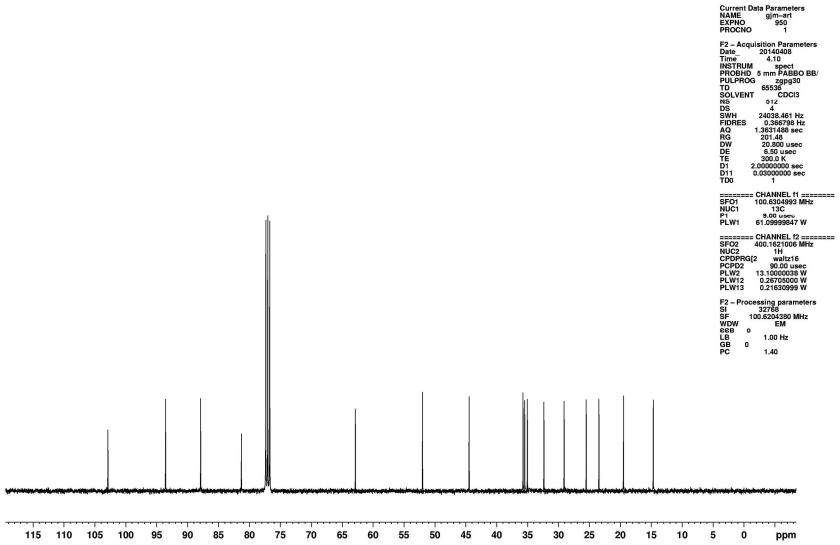
Recycling of the Immobilized Catalyst:



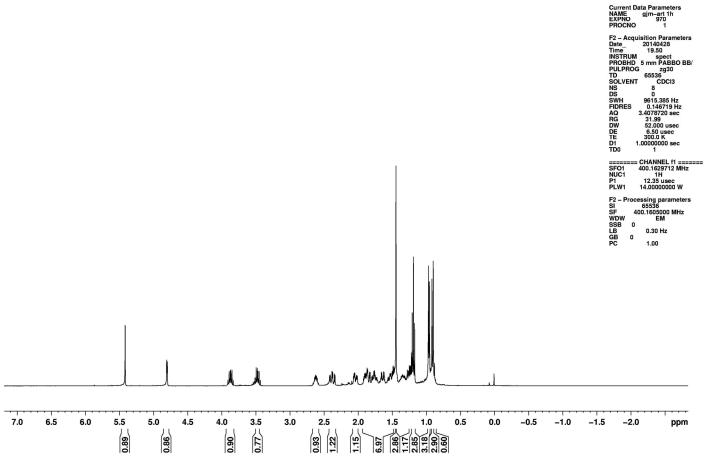
Reusability of catalyst



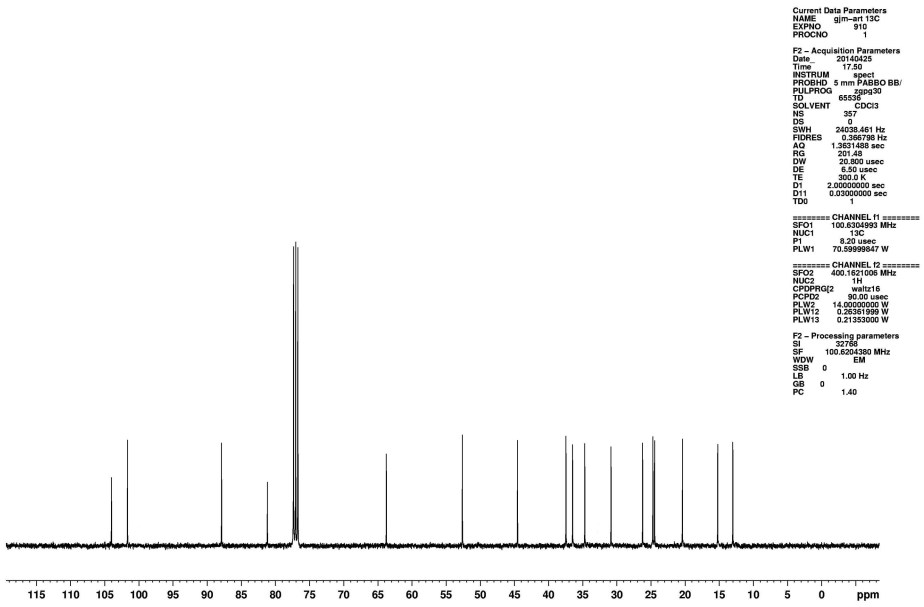
^{1}H NMR spectra of β- Artemether



^{13}C NMR spectra of β- Artemether



^{1}H NMR spectra of β- Arteether



^{13}C NMR spectra of β- Arteether