

Stereolithography 3D Printed Catalytically-Active Devices in Organic Synthesis

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Supporting Information

1. General information	pag S2
2. Swelling test	pag S3
3. Synthesis of <i>N,N</i> -bis[3,5-bis(trifluoromethyl)phenyl]-Thiourea (4)	pag S4
4. Resin Formulation / Photopolymerization	pag S5
5. General procedure for the Friedel-Crafts alkylation	pag S6
6. Catalyst leaching test	pag S6
7. 3D Printing process	pag S7
8. NMR data	pag S8

1. General Information

Methods: Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F254 pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Flash chromatography was carried out on silica gel (230-400 mesh). Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Avance 300); proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard (CDCl_3 δ = 7.26 ppm). ^{19}F NMR spectra were recorded on 300 MHz spectrometers (Bruker Avance 300) operating at 282.1 MHz; fluorine chemical shifts are reported in ppm (δ) relative to CF_3Cl with the respective solvent resonance as the internal standard (CDCl_3 , δ = 77.0 ppm).

3D printed devices were realized using Formlabs Form 2 3D printer, microwave reaction were performed using a Discovery-SP CEM microwave and photopolymerization was pursued using a Shengtuo Kangtuo SK-818 UV lamp .

Materials: Dry solvents were purchased and stored under nitrogen over molecular sieves (bottles with crown caps). All chemicals were purchased from commercial suppliers and used without further purification unless otherwise specified. Clear V4 resin was purchased from <https://formlabs.com/> and used as received.

2. Swelling Test

Resistance to solvents was investigated by observing, measuring, and weighing cured resin cubes (originally measuring 1 cm × 1 cm × 1 cm) before and after soaking in a solvent for 24 hours and up to 3 months. Percentages were calculated according to the formula: $[(Vol_{Final} - Vol_{Start}) / Vol_{Start}] \times 100$ and are reported in tables S1 and S2. Pictures of results are reported in figure S1.

Solvent	Swelling (%)						
	24h	96h	120h	144h	1 week	8 days	3 months
CH ₂ Cl ₂	Red						
EtOH	Green	Green	Green	Green	Yellow	Red	
CHCl ₃	Green	Red					
Toluene	Green	Green	Green	Green	Green	Green	Green
THF	Green	Green	Yellow	Yellow	Red		
CH ₃ CN	Green	Green	Yellow	Yellow	Yellow	Red	
AcOEt	Green	Green	Green	Yellow	Yellow	Red	
DMF	Green	Yellow	Red				

■ Deformation less than 4 %;
 ■ Deformation less than 15%;
 ■ sample cracked

Table S1. Swelling test

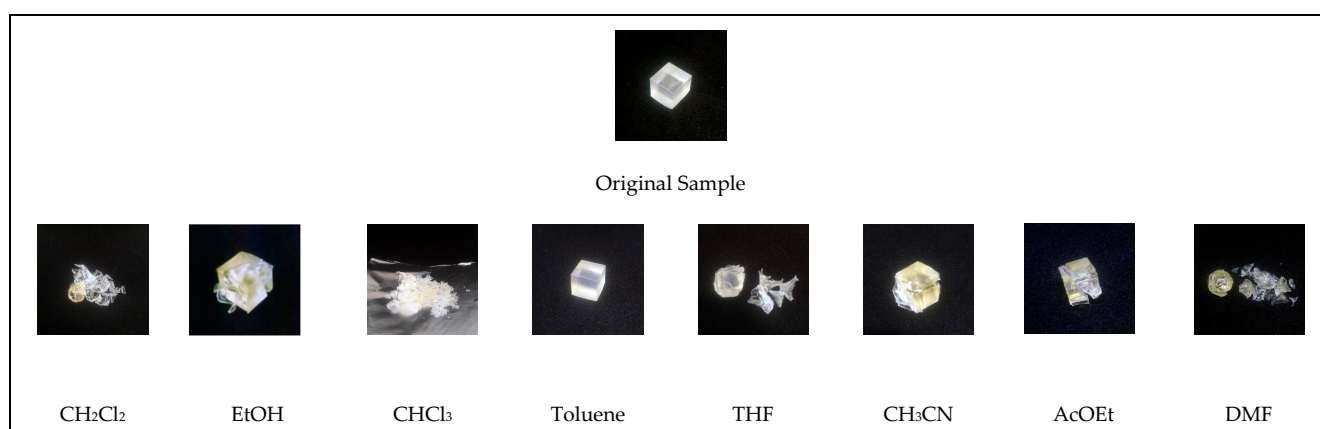


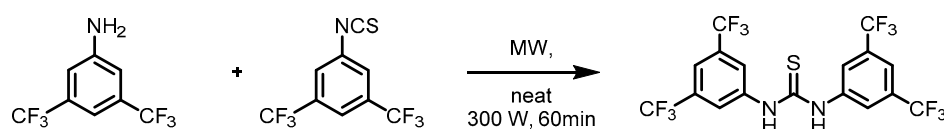
Figure S1. Devices deformation after the swelling test.

Reagent solution	(%)	
	24h	1 week
<i>N</i> -Me-Indole (0.15M)	■	■
Trans- β -nitrostyrene (0.1M)	■	■
1,3,5-trimethoxybenzene (0.03M)	■	■
Friedel Craft adduct 3 (0.1M)	■	■

■ Deformation less than 4%

Table S2. Swelling test performed with a solution of chemical compounds in toluene.

3. Synthesis of *N,N*-bis[3,5-bis(trifluoromethyl)phenyl]-Thiourea (4)



5-bis(trifluoromethyl)aniline (1.180 mL, 7.55 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.35 mL; 7.37 mmol) were loaded in a 35 ml CEM-microwave vial and irradiated at 300MW for 1 hour with a setup of 50 °C as a temperature limit. After this time, the reaction was cooled to room temperature, and the crude obtained was crystallized with chloroform. The final product was obtained as a white solid in 86% yield

^1H NMR (300MHz, DMSO- d_6): δ [ppm] = 10.65 (s, 2H), 8.21 (s, 4H), 7.88 (s, 2H).

^{19}F NMR (282.1 MHz, DMSO- d_6): δ [ppm] = -61.50 (s).

4. Resin Formulation / Photo-pholymerization

For 15wt% thiourea-embedded resin: In a dark container, Schreiner's thiourea 4 (25 g, 49.96 mmol) was suspended in 141.6 ml of "Clear V4" resin. The crude mixture was subjected to ultrasound irradiation for 3 hours and subjected to orbital shaker (400 rpm) for 3 hours, in order to obtain a clear solution. Final loading was calculated as a ration between the amount of thiourea suspended (mmol) and the total amount of the solution (g). Results are reported in table S3.

Sample	Thiourea (wt%)	Catalyst loading (mmol/g)
Resin #1	1	0.019
Resin #2	5	0.111
Resin #3	10	0.222
Resin #4	15	0.299
Resin #5	20	0.389

Table S3. catalyst loading of different resins

Photopolymerization was conducted by disposing 5g of resin at the desired loading in a Petri dish (7 cm diameter) which was subjected to irradiation using a UV Shark lamp (365 nm, 36W) for 2 hours. The thin layer disk obtained was then washed with iPrOH, sonicated for 20 min with iPrOH and dry over air for 24 hours (Figure S2). Small slivers of this material were then obtained by cutting the disk with scissors.

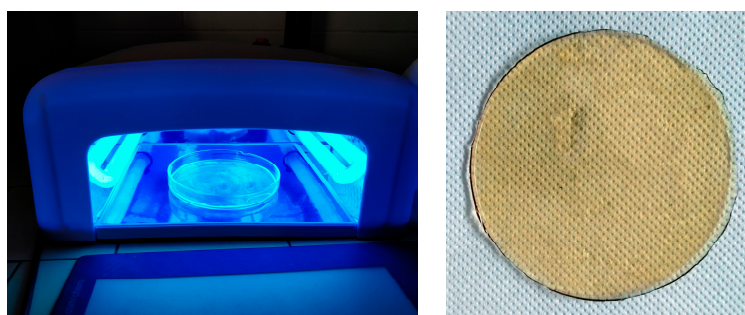
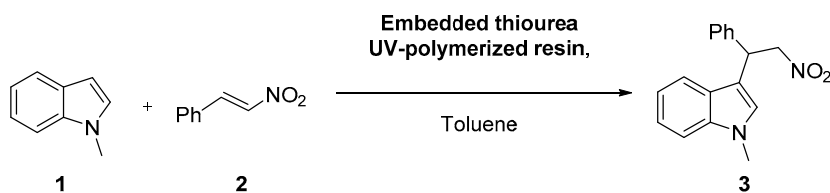


Figure S2. photo-pholymerization process (left) and final cured-resin disk.

5. General Procedure for the Friedel-Crafts Alkylation



This general procedure is referred to a reaction performed using 15wt% loading resin in a 1:1 embedded catalyst/substrate ratio (mol/mol).

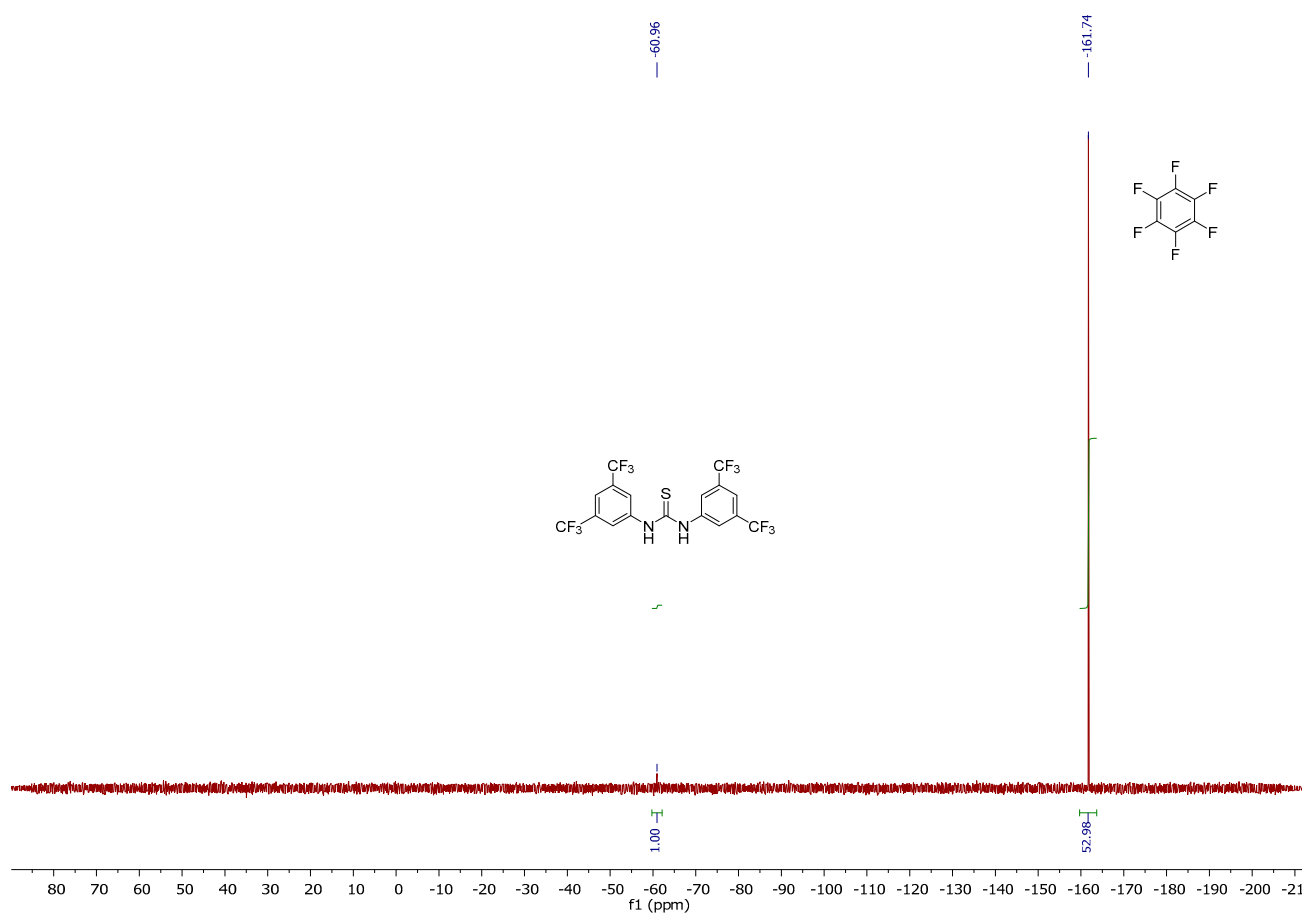
Catalyst-embedded devices (0.2 mmol, for a total amount of 669 mg) was loaded into an Agilent headspace vial of 20 ml, then trans-β-nitrostyrene (1 eq, 0.2 mmol, 800 µl of 0.25 M toluene solution), N-Me-indole (1.5 eq, 0.3 mmol, 800 µl of 0.375 M toluene solution) and 1,3,5-trimethoxybenzene (0.3 eq, 0.06 mmol, 400 µl of 0.15 M toluene solution) were added under nitrogen atmosphere. The reaction was subjected to orbital shaker (400 rpm/min) for the desired time.

After this time, 20 µl of the crude solution were dried under high vacuum and analyzed by ¹H NMR. Isolation of the desired product was performed by removing the catalytically active devices which were subsequently washed with 3 ml of toluene. The organic phases were then concentrated under reduced pressure, and the crude mixture was purified by column chromatography.

¹H NMR (300MHz, CDCl₃): δ [ppm] = 7.48 (d, J = 8.0 Hz, 1H), 7.40–7.20 (m, 8H), 7.15 – 7.05 (m, 1H), 6.89 (s, 2H), 5.21 (t, J = 8.0 Hz, 1H), 5.08 (dd, J = 12.4, 7.4 Hz, 1H), 4.96 (dd, J = 12.4, 8.5 Hz, 1H), 3.77 (s, 3H).

6. Catalyst Leaching Test

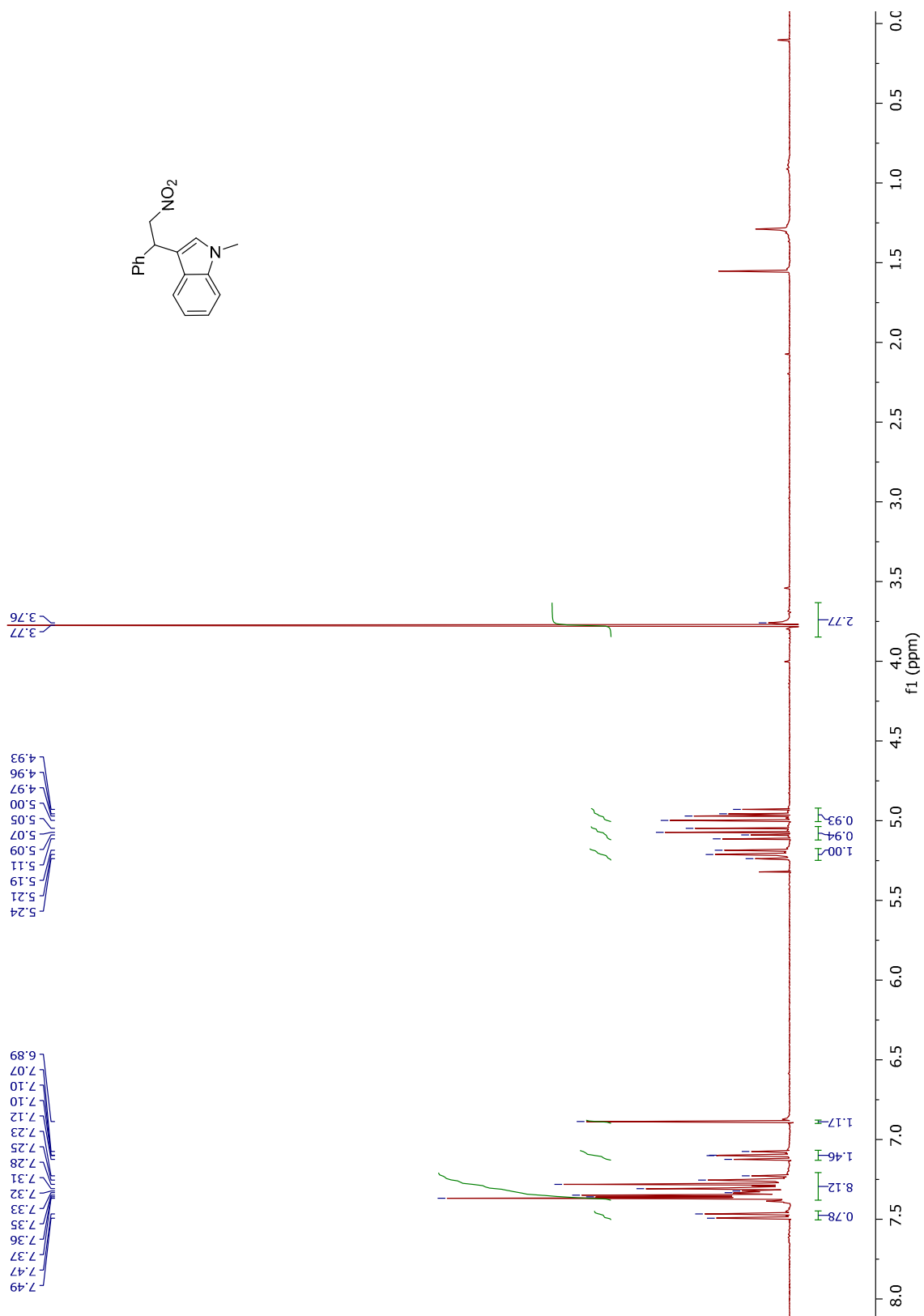
In an Agilent headspace vial, under nitrogen atmosphere, catalyst-embedded devices (as example: 303.3 mg of slivers derived from 10wt% thiourea-embedded resin – 0.222 mmol/g loading) were suspended in 1 ml of a 0.0173 M hexafluorobenzene toluene solution and subjected to orbital shaker (400 rpm/min) for 24 h. After this time, ¹⁹F NMR of the crude was acquired. The normalized ratio between signal at -61 ppm (thiourea 4) and signal at -161.7 ppm (reference) was used to calculate the catalyst leaching.



7. 3D Printing Process

The desired resin was loaded into an empty cartridge of Formlabs Form 2 SLA 3D printer. The file containing the printing information was then generated with Preform v 3.03 freeware software: (50 μm layer thickness, 34 ° C -- default parameters for Clear V4 resin). Software wizard was used to add supports and to generate multiple copies of devices on the same build plate. After the printing process, devices were removed from the building plate, sonicated in an iPrOH bath for 20 min, then sonicated twice in a toluene bath until the lost of weight was lower than 1%. After this washing process, devices were collected and dried over air prior to post-curing for 20 min under UV lamp.

8. NMR Data



Example of crude mixture for the determination of yield by NMR analysis:

