Electronic Supplementary Information

In Situ Preparation of a Multifunctional Chiral Hybrid Organic-Inorganic Catalyst for Asymmetric Multicomponent Reactions

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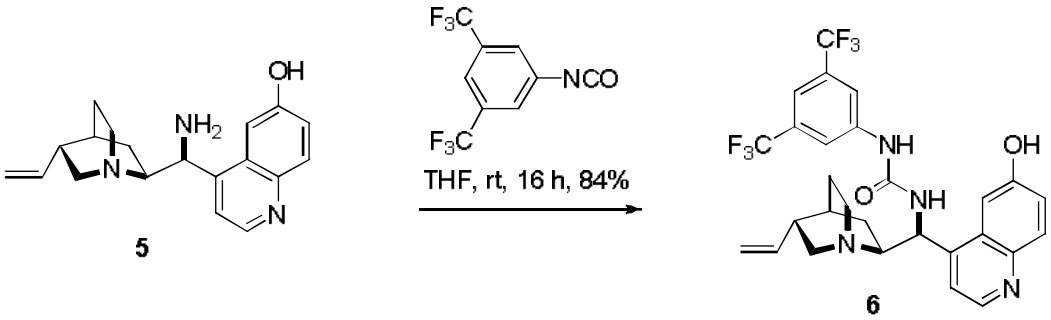
1. General Information. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Solvents employed in the reactions were purified using a solvent purification system (SPS) MBraun 800. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Reactions were monitored by thin layer chromatography on silica gel precoated aluminium plates using fluorescence quenching with UV light at 254 nm or $KMnO_4$. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.040-0.063 mm). Chemical yields refer to pure isolated substances unless stated otherwise. ^1H and ^{13}C NMR were recorded on a Bruker 300 spectrometer and the chemical shifts are reported in ppm relative to residual protio solvents signals. Data for ^1H NMR spectra are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublets), coupling constant and integration. Data for ^{13}C NMR spectra are reported in chemical shift (δ, ppm). High performance liquid chromatography (HPLC) was performed on Agilent Technologies 1220 Infinity Series instrument using a Daicel Chiralcel OJ (4.6 x 250 mm), Kromasil 5-AmyCoat (4.6 x 250 mm) and Kromasil 5-CelluCoat (4.6 x 250 mm). Optical rotations were measured on a Jasco P-1030 polarimeter using the yellow line at 589 nm and $[\alpha]_D^{20}$ values are reported in 10^{-1} dg cm^2 g^{-1}; concentration (c) is reported in g/100mL. C, N, and H contents were determined with a Carlo Erba 1106 elemental analyzer. Thermogravimetric and differential thermal analysis (TGA-DTA) were conducted in an air stream with a Metler Toledo TGA/SDTA 851E analyzer. Nitrogen adsorption isotherm was measured at 77 K with a Micromeritics ASAP 2010 volumetric adsorption analyzer. Before the measurement, the sample was outgassed for 12 hours at 80ºC. The BET specific surface area[1] was calculated from the nitrogen adsorption data in the relative pressure range from 0.04 to 0.2. The total pore volume[2] was obtained from the amount of N_2 adsorbed at a relative pressure of about 0.99. External surface area and micropore volume were estimated using the *t*-plot method in the *t* range from 3.5 to 5. The pore diameter and the pore size distribution were performed using the Barret-Joyner-Halenda (BJH) method[3] on the adsorption branch of the isotherms. Solid state MAS-NMR spectra were recorded at room temperature under magic angle spinning (MAS) in a Brucker AV-400 spectrometer: ^{19}F spectrum was measured at 376.28 MHz using a Bruker probe with 2.5 mm diameter zirconia rotors spinning at 25 kHz. It was collected using pulses of 4.5 μs corresponding to the flip angle of π/2 rad, and a recycle delay of 100 s to ensure the complete recovery of the magnetization. The single pulse ^{29}Si spectrum was acquired at 79.5 MHz with a 7 mm Bruker BL-7 probe using pulses of 3.5 μs corresponding to a flip angle of 3/4 π radians, and a recycle delay of 240 s. The ^{13}C cross-polarization (CP) spectrum was acquired by using a 7 mm Bruker BL-7 probe and at a sample spinning rate of 5kHz. ^{19}F, ^{13}C and ^{29}Si were referred to $CFCl_3$, adamantane and tetramethylsilane, respectively. For the detailed solid-state NMR investigations: All ^1H, ^{13}C, ^{15}N, ^{29}Si and ^{19}F NMR spectra of Figure S5 were acquired on a Bruker Avance III 500 MHz NMR spectrometer equipped with a 4 mm double resonance probe, with a sample spinning frequency of 12.5 kHz and a sample temperature of 283 K. Pulse programs are available on request. Processing of the spectra was done using the Topspin software package. For all the heteronuclear correlation spectra (Figures S6 and S7), SPINAL-64

heteronuclear decoupling was applied during t_2 ($\omega_1/2\pi$ ≈ 100 kHz). During t_1 eDUMBO-1_{22} homonuclear decoupling was applied with a rf amplitude of $\omega_1^H/(2\pi)$ = 100 kHz. Quadrature detection was achieved using the States-TPPI scheme by incrementing the phase of the ^{1}H spin-lock pulse of the CP step. A scaling factor of 0.56 was applied to correct the ^{1}H chemical shift scale.

FTIR spectra were recorded with a Nicolet 710 spectrometer (4 cm^{-1} resolution) using conventional greaseless cell. Self-supporting wafers of the hybrid material of *ca.* 10 mg cm^{-2} were outgassed at the indicated temperature (namely, room temperature, 70ºC, 100ºC, 200ºC or 400ºC). IR spectra of the organic precursors were recorded on KBr disks at room temperature.

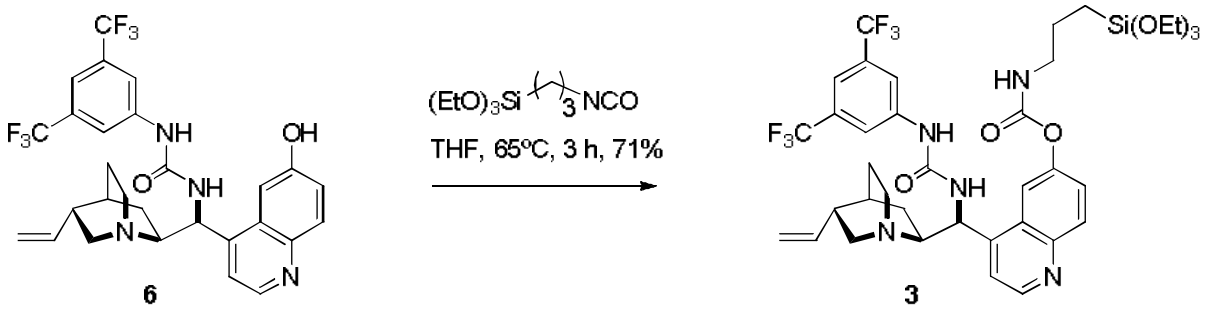
2. Catalyst synthesis and characterization

2.1 Synthesis of the organosilica precursor 3.



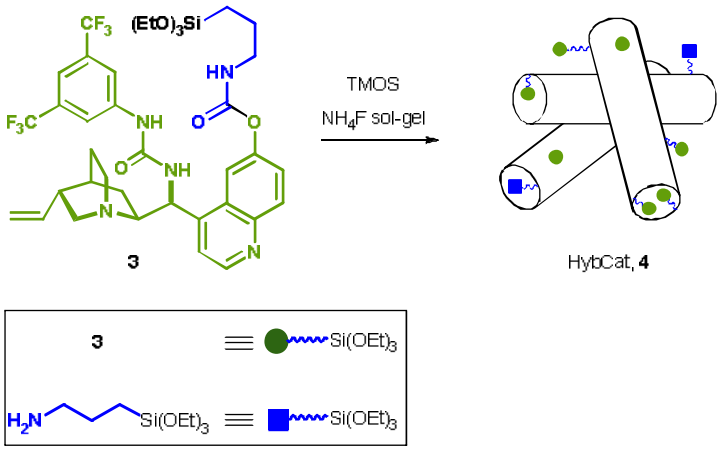
9-amino-(9-deoxy)*epi*-6-hydroxycinchonidine **5** was prepared from quinine according to a literature-known procedure.[4-5] The analytical data were identical in all respects to those previously reported.

9-urea-(9-deoxy)*epi*-6-hydroxycinchonidine 6. The product was prepared following adapted literature-known procedure for analogous Cinchona alkaloid derivatives.[4] To a solution of 9-amino-(9-deoxy)epi-6-hydroxycinchonidine **6** (700 mg, 2.26 mmol) in dry THF (6.6 mL) was slowly added a solution of 3,5-bis(trifluoromethyl)phenyl isocyanate (0.39 mL, 2.26 mmol) in 3.3 mL of dry THF at room temperature. The mixture was stirred overnight, and the solvent was then removed under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/MeOH/ aq NH_4OH = 300/5/1 as eluent) affording urea **6** (1.07 g, 1.90 mmol, 84% yield) as a yellow solid. $[\alpha]_D^{20}$ = -42.3 (c = 1, EtOH); **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.64 (d, *J* = 4.6 Hz, 1H), 7.95 (s, 1H), 7.92 (s, 2H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.53 (d, *J* = 4.7 Hz, 1H), 7.45 (s, 1H), 7.39 (dd, *J* = 9.1, 2.4 Hz, 1H), 5.92-5.81 (m, 1H), 5.52 (br m, 1H), 5.07-4.97 (m, 2H), 3.42-3.27 (m, 3H), 2.84-2.79 (m, 2H), 2.37 (br m, 1H), 1.76-1.65 (m, 3H), 1.48 (t, *J* = 11.4 Hz, 1H), 0.91 (dd, *J* = 12.8, 6.8 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 157.8, 156.7, 147.6, 144.4, 143.2, 142.6, 133.1 (q, *J* = 33.0 Hz), 131.5, 130.2, 124.8 (q, *J* = 270 Hz), 123.5, 120.7, 119.4, 119.1, 115.6 (sept, *J* = 3.7 Hz), 115.1, 105.9, 61.3, 56.9, 54.8, 42.1, 40.8, 28.9, 28.5, 27.0. **^{19}F-NMR (300 MHz, $CDCl_3$):** δ -64.6. **IR (KBr)**: υ 3315, 2946, 1678, 1572, 1474, 1388, 1278, 1177, 1130 cm^{-1}.



9-urea-(9-deoxy)*epi*-6-(3-triethoxysilyl)propylcarbamatecinchonidine 3. To a solution of **6** (330 mg, 0.58 mmol) in dry THF (4 mL) was slowly added at room temperature 3-isocyanatopropyl triethoxysilane (0.22 mL, 0.88 mmol). The mixture was stirred at 65ºC using a reflux condenser during 5 h. The solvent was then removed under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/MeOH/aq NH_4OH = 300/5/1 as eluent) affording product **3** (333 mg, 0.41 mmol, 71% yield) as a colorless solid. It should be noted that the reaction allows product formation in higher yield than reported, as determined by ^{1}H NMR of the crude mixture. Mislaid of product occurs due to reaction with the silica in the column chromatography (eluent: EtOAc:MeOH:NH_4OH 97:3:1) during purification. $[\alpha]_D^{20}$ = -37.7 (c = 1, EtOH), $[\alpha]_D^{20}$ = -72.6 (c = 1, $CHCl_3$). **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.83 (d, *J* = 4.6 Hz, 1H), 8.32 (d, *J* = 2.3 Hz, 1H), 8.09 (d, *J* = 9.1 Hz, 1H), 7.92 (s, 2H), 7.65 (d, *J* = 4.7 Hz, 1H), 7.61 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.44 (s, 1H), 5.84 (ddd, *J* = 17.5, 10.1, 7.7 Hz, 1H), 5.48 (br m, 1H), 4.99 (t, *J* = 14.9 Hz, 2H), 3.85 (q, *J* = 7.0 Hz, 6H), 3.34-3.20 (m, 5H), 2.85-2.73 (m, 2H), 2.35 (br m, 1H), 1.75-1.55 (m, 5H), 1.46-1.39 (m, 1H), 1.23 (t, *J* = 7.0 Hz, 9H), 0.93 (dd, *J* = 12.7, 6.8 Hz, 1H), 0.72-0.67 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 156.8, 156.6, 151.1, 150.5, 149.3, 146.9, 143.2, 142.7, 133.1 (q, *J* = 33.1 Hz), 131.4, 129.2, 126.6, 124.8 (q, *J* = 270 Hz), 119.6, 116.0, 115.6 (sept, *J* = 3.7 Hz), 115.0, 61.0, 59.6, 56.9, 44.8, 42.1, 40.9, 28.9, 28.6, 27.1, 24.3, 18.7, 8.5. **^{19}F-NMR (300 MHz, $CDCl_3$):** δ -64.6. **^{29}Si-NMR (60 MHz, $CDCl_3$):** δ -45.6. **IR (KBr)**: υ 3324, 2974, 2931, 2886, 1746, 1688, 1571, 1506, 1474, 1389, 1277, 1183, 1134, 949, 778 cm^{-1}.

2.2 Synthesis and characterization of the hybrid organic-inorganic catalyst 4



The hybrid organic-inorganic catalyst **4** was prepared using a NH_4F co-condensation route.[6] Tetramethylorthosilicate (TMOS) (0.93 mL, 6.24 mmol) and siloxane Cinchona alkaloid derivative **3** (760 mg, 0.94 mmol) were mixed in methanol (1 mL) at 298 K. After dissolution of precursors, a water solution of NH_4F (0.45 mL of a 0.043 M solution) was added under vigorous stirring. The reaction mixture has the following molar composition: $1SiO_2$:4MeOH:$4H_2O$:$0.00313NH_4F$ and the Si/NH_4F and TMOS/organosilane ratios were adjusted to 320 and 6.7 respectively. Hydrolysis and condensation of the silicon precursors was carried out under vigorous stirring at 298 K until gelation occurred. Then, the gel was aged for 24 h at 36ºC, and finally dried at 50ºC for another 14 h. The obtained yellow solid was ground to a fine powder and subsequently washed with water, ethanol and diethyl ether in consecutive steps to remove the organic molecules not incorporated into the material. The obtained hybrid solid was then dried under vacuum at 50ºC for 3 h. It was obtained 810 mg of the hybrid organic inorganic material (78% yield).

Sample	N%	C%	H%	S%	C/N
HybCat **4**	5.484	28.801	3.498	0.000	6.1

Table S1. Crude data from elemental analyses of the hybrid material **4**.

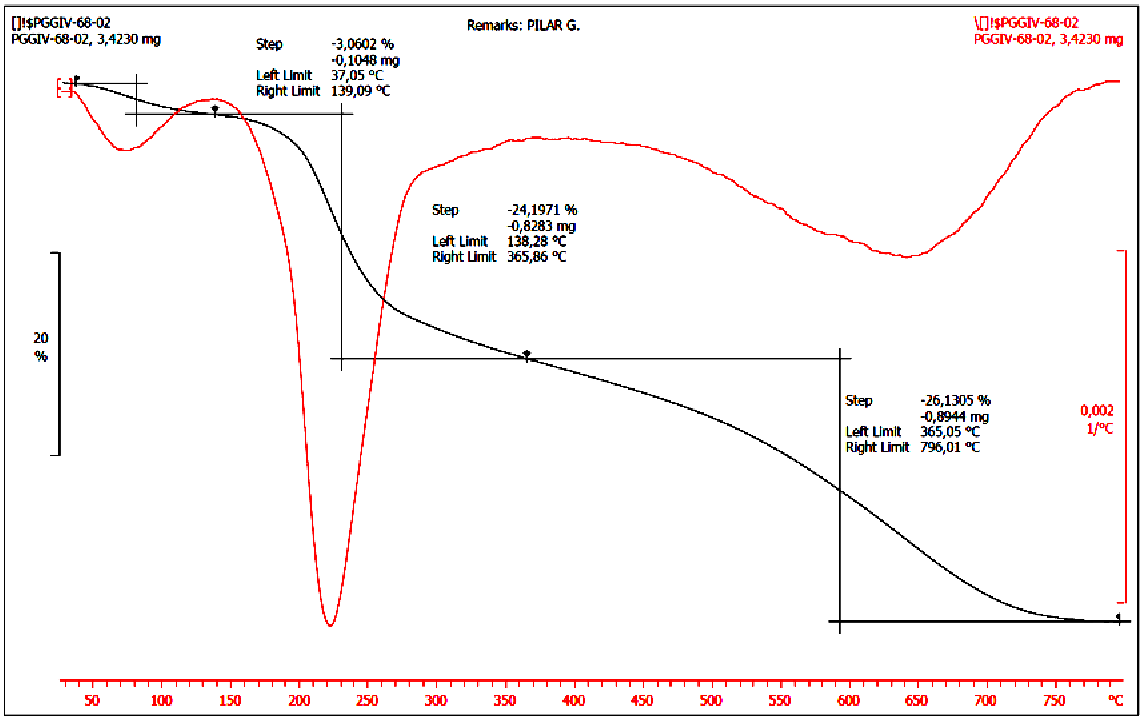


Figure S1. Thermogravimetric curve (TGA) and its corresponding derivative (DTA) of hybrid catalyst **4**.

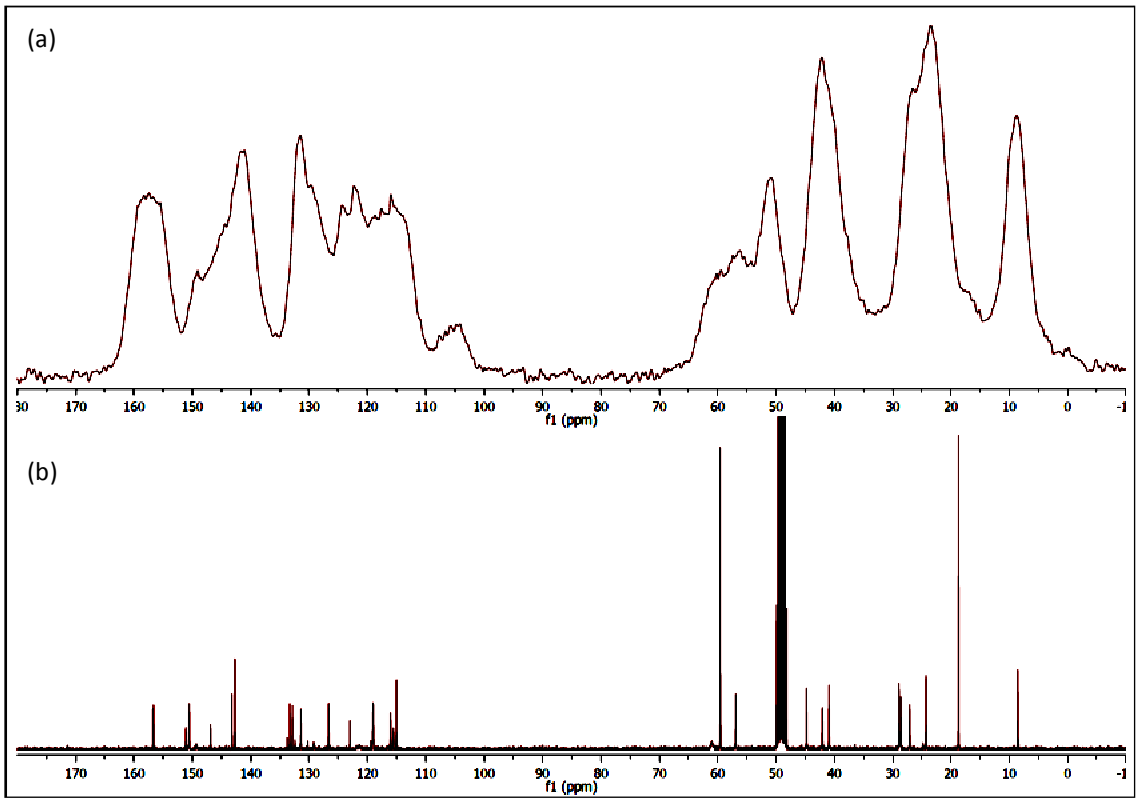


Figure S2. (a) ^{13}C-CP MAS NMR of hybrid organic-inorganic catalyst **4**. (b) ^{13}C NMR of derivative **3** in MeOH-d_4.

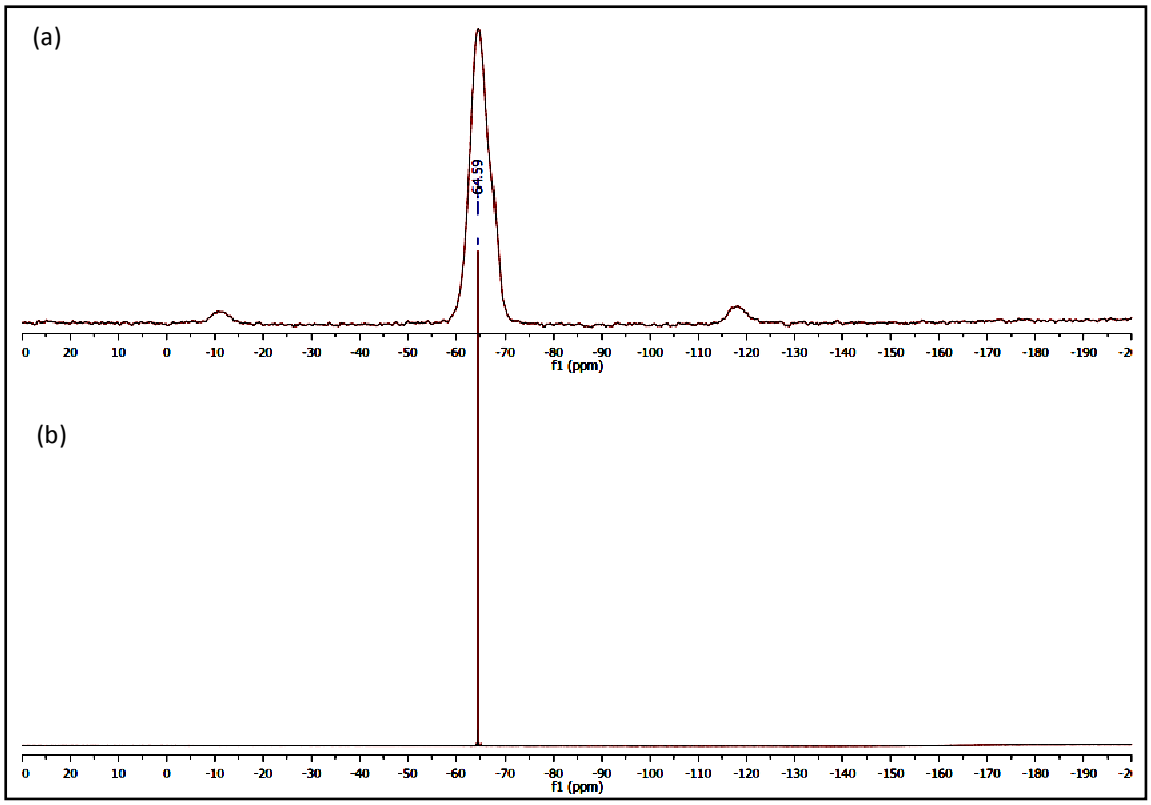


Figure S3. (a) ^{19}F MAS NMR of hybrid organic-inorganic catalyst **4**. (b) ^{19}F NMR of derivative **3** in MeOH-d_4.

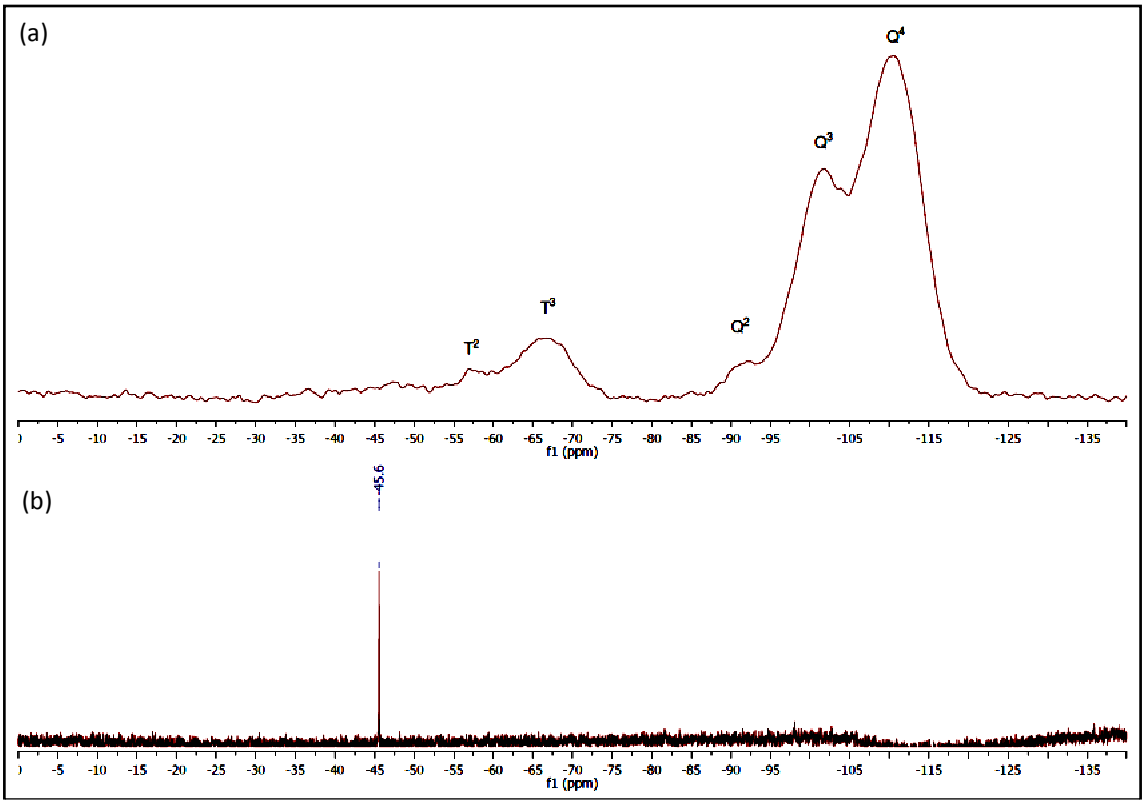


Figure S4. (a) ^{29}Si-BD MAS NMR of hybrid organic-inorganic catalyst **4** and assignment of T- and Q-type silicon atoms. (b) ^{29}Si NMR of derivative **3** in MeOH-d_4.

Detailed Solid-state NMR investigations

The hybrid organic-inorganic material was characterized by ^{1}H, ^{13}C, ^{15}N, ^{29}Si and ^{19}F solid-state NMR spectroscopy. Figure S5 shows the 1D ^{13}C, ^{15}N, ^{29}Si and ^{19}F recorded on the hybrid material **4**.

A two-dimensional ^{1}H-^{13}C heteronuclear correlation (HETCOR) spectrum recorded with a CP contact time of 0.25 ms is shown in Figure S6 (top spectrum). This spectrum displays mainly one-bond correlations. An assignment of the carbon-13 spectrum can be proposed from the analysis of this HETCOR spectrum and from the ^{1}H and ^{13}C chemical shifts of the precursor in solution. Although the HETCOR spectrum shows many overlapping correlations, several cross-peaks can be unambiguously identified and assigned to a single (^{1}H,^{13}C) pair, like for example the correlation at (ω_1,ω_2)=(0.9 ppm, 8.8 ppm) corresponding to the 3''' CH_2 group bonded to the silica surface, or the correlations at (ω_1,ω_2)=(4.8 ppm, 113 ppm) and (ω_1,ω_2)=(5.5 ppm, 140 ppm) corresponding to the CH_2=CH moiety. The ^{15}N CPMAS spectrum displays two resonances at 35 and 95 ppm that likely correspond to (i) the tertiary amine of the quinuclidine group and (ii) both the carbamate and urea moieties, respectively. As expected, the ^{29}Si CPMAS spectrum shows two resolved resonances corresponding to T and Q sites. Finally, the ^{19}F spectrum displays a peak at -60 ppm, as expected for CF_3 groups on a phenyl group. The long-range HETCOR spectra (Figure S6 middle and bottom spectra) show correlations between the aromatic protons and the carbon 3''' (in blue in the middle plot), as well strong correlations between aromatic protons and the carbonyls at 156 ppm (in red in the middle plot), thus confirming the integrity of the organic fragment inside the solid support.

Figure S7 shows a series of (^{1}H, ^{29}Si) HETCOR spectra recorded with CP contact times of 0.4, 1 and 4 ms. While the left spectrum shows the expected short-range correlations (i) between the protons of the 3''' CH_2 group and the silicon-29 T sites, and (ii) between the OH proton and the Q sites, several long-range correlations are observed on the HETCOR spectra recorded with longer contact times. Notably, clear correlations are observed between the aromatic and the quinuclidine protons and the Q sites, reflecting spatial proximities between the end of the organic fragment and the silica surface. Such proximities were further confirmed by recording a ^{19}F-^{29}Si CPMAS spectrum (Figure S7 b). The spectrum displays the silicon-29 resonances of both the T and Q sites, thus reflecting the presence of significant (through-space) dipolar interactions between the fluorine and silicon atoms. This spectrum further confirms the attachment of the cinchone-based derivative to the solid material.

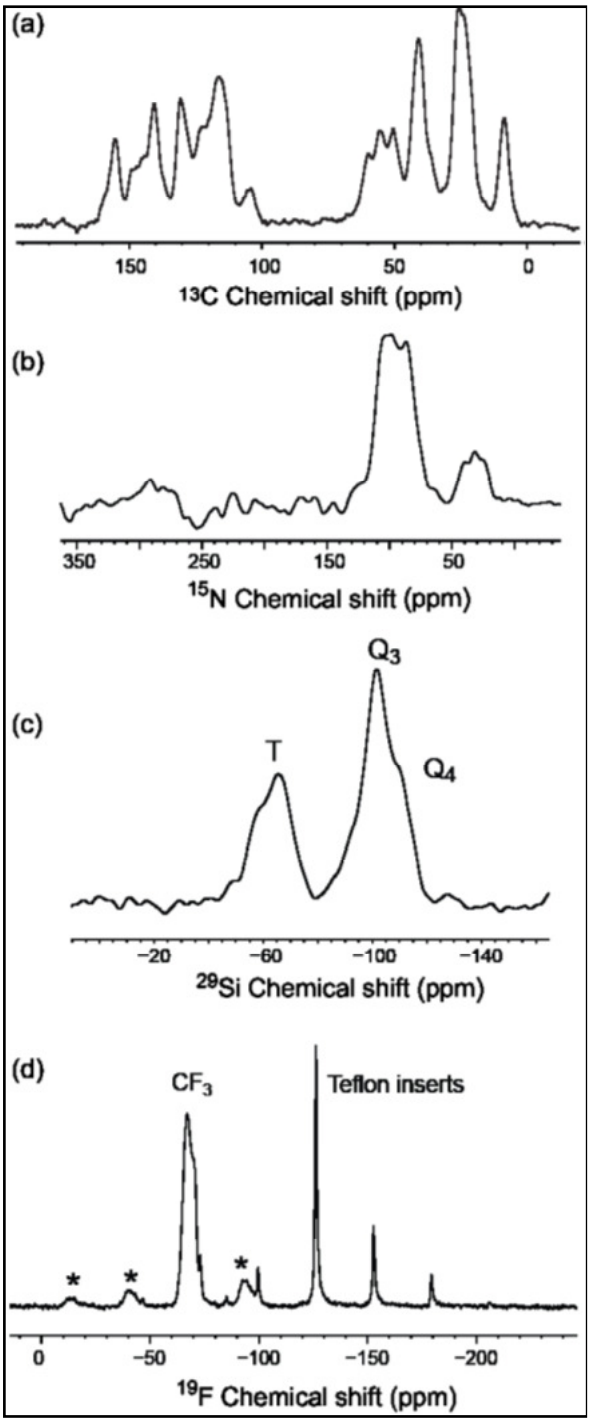


Figure S5. One-dimensional ^{13}C, ^{15}N, ^{29}Si and ^{19}F NMR spectra of the hybrid organic-inorganic catalyst **4**. (a) Carbon-13 CPMAS spectrum. A total of 1024 scans were accumulated with an interval between scans of 2 s. The CP contact time was 1 ms. (b) Nitrogen-15 CPMAS spectrum. A total of 32768 scans were accumulated with an interval between scans of 2.5 s. The CP contact time was 2 ms (c) Silicon-29 CPMAS spectrum. A total of 132 scans were accumulated with an interval between scans of 2 s. The CP contact time was 4 ms. (d) Fluorine-19 spectrum recorded with a spin echo experiment. A total of 512 scans were accumulated with an interval between scans of 2 s. The echo delay was 1.2 ms. The narrow resonances correspond to Teflon inserts used to restrict the sample volume.

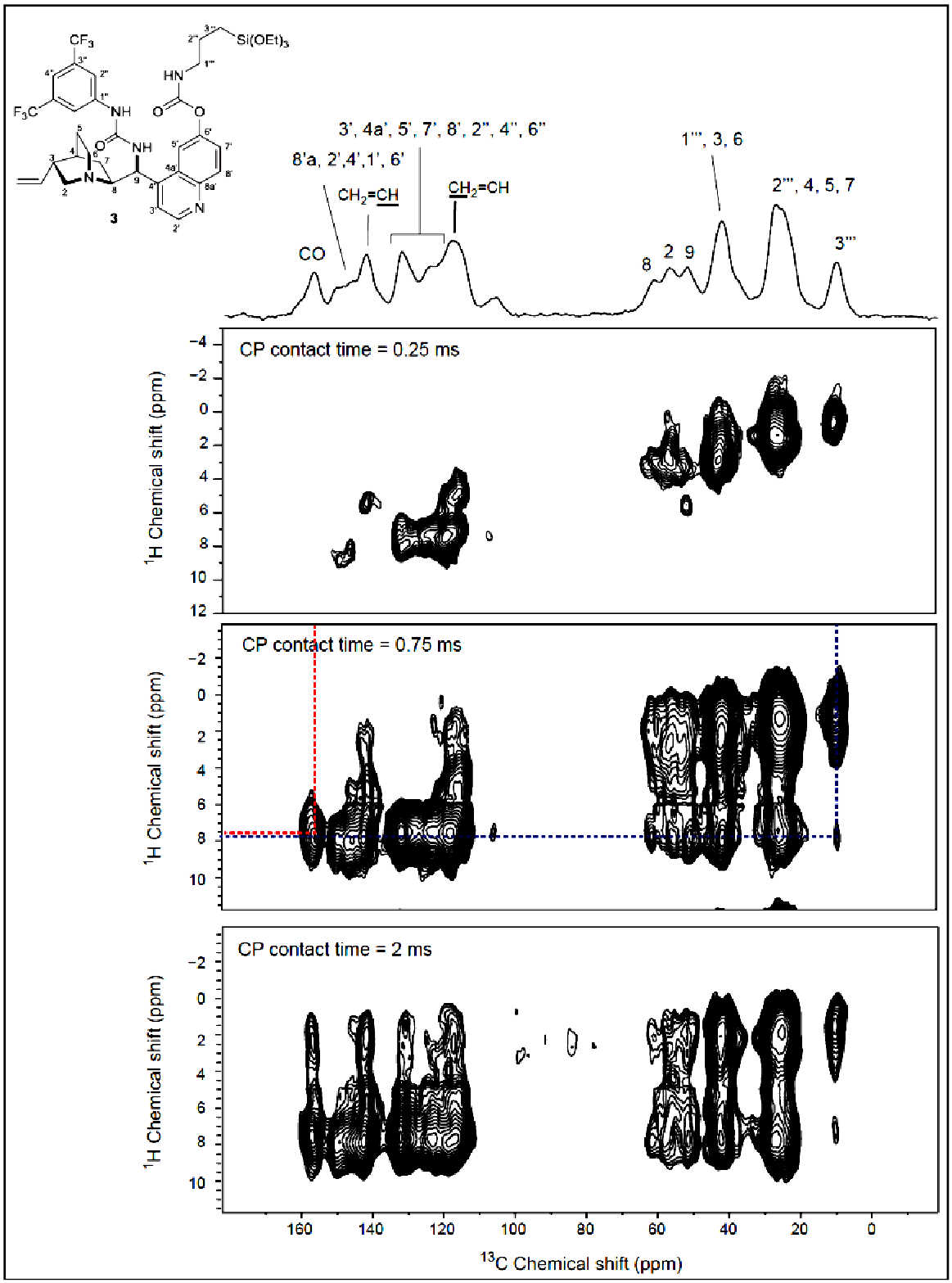


Figure S6. Contour plots of two-dimensional ^{1}H-^{13}C correlation spectra of the hybrid organic-inorganic catalyst. A total of 128 t_1 increments of 64 µs with 128 scans each were recorded. The overall acquisition times in t_1 and t_2 were 4 and 10 ms, respectively. The cross polarization contact time was 250 µs for the top spectrum, 750 µs for the middle spectrum and 2 ms for the bottom spectrum. The polarization interval was 2.5 s. The total experimental time was 11 hours for each experiment. The CPMAS spectrum of Figure S5 (a) is displayed on the top of the 2D spectra.

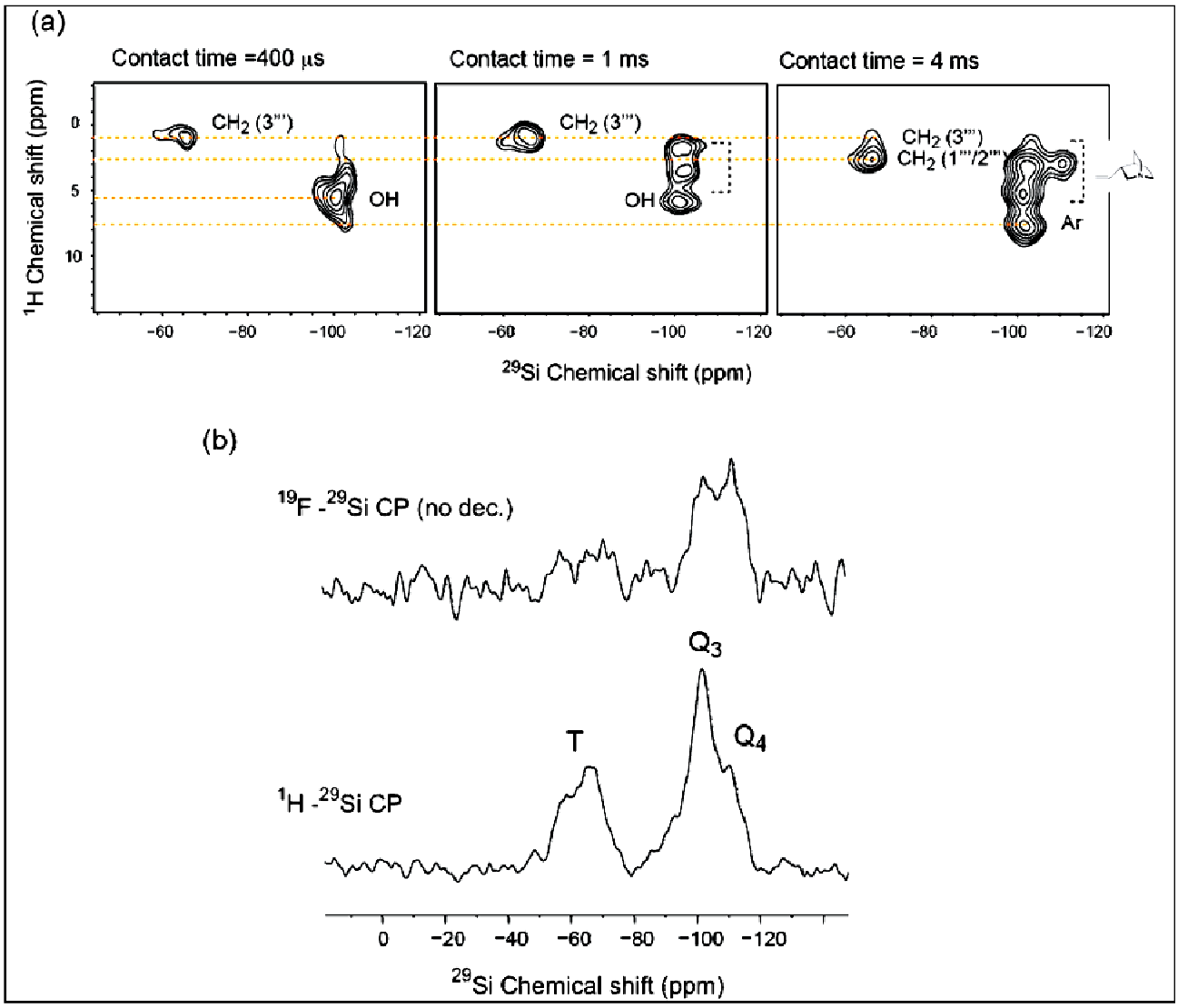


Figure S7. (a) Contour plots of two-dimensional ^{1}H-^{29}Si correlation spectra of the hybrid organic-inorganic catalyst. Left spectrum : a total of 64 t_1 increments of 64 µs with 256 scans each were recorded and the contact time for the CP step was 400 µs. Middle spectrum : a total of 64 t_1 increments of 64 µs with 256 scans each were recorded and the contact time for the CP step was 1 ms. Right spectrum: a total of 64 t_1 increments of 64 µs with 128 scans each were recorded and the contact time for the CP step was 4 ms. (b) Comparison between one-dimensional ^{1}H-^{29}Si and ^{19}F-^{29}Si CPMAS spectra. The ^{1}H-^{29}Si CPMAS spectrum was acquired with 132 scans. A contact time of 4 ms was used. The ^{19}F-^{29}Si CPMAS spectrum was acquired with 30720 scans with a contact time of 6 ms. No decoupling sequence was applied during the acquisition of this spectrum. A line broadening of 200 Hz was applied for both spectra.

Sample	BET Surface Area/m^2g^{-1}	External Surface/m^2g^{-1}	Micropore Volume/cm^3g^{-1}	Total Pore Volume/cm^3g^{-1}	Mean Pore Diameter/Å
HybCat **4**	111	111	0.00	0.15	29

Table S2. Textural Characteristic of the hybrid organic-inorganic material **4**.

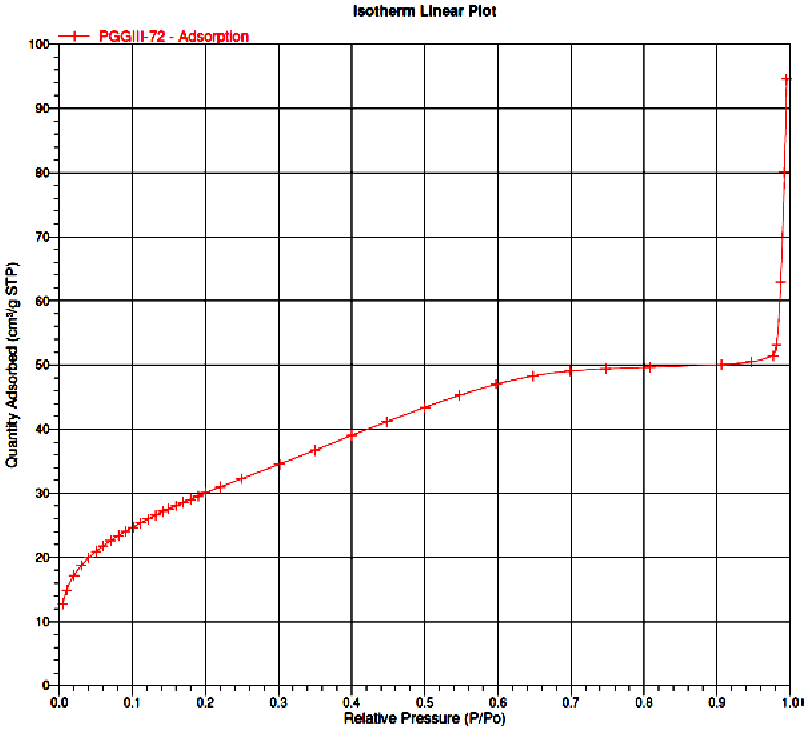


Figure S8. N_2 adsorption isotherm of the hybrid organic-inorganic catalyst **4**.

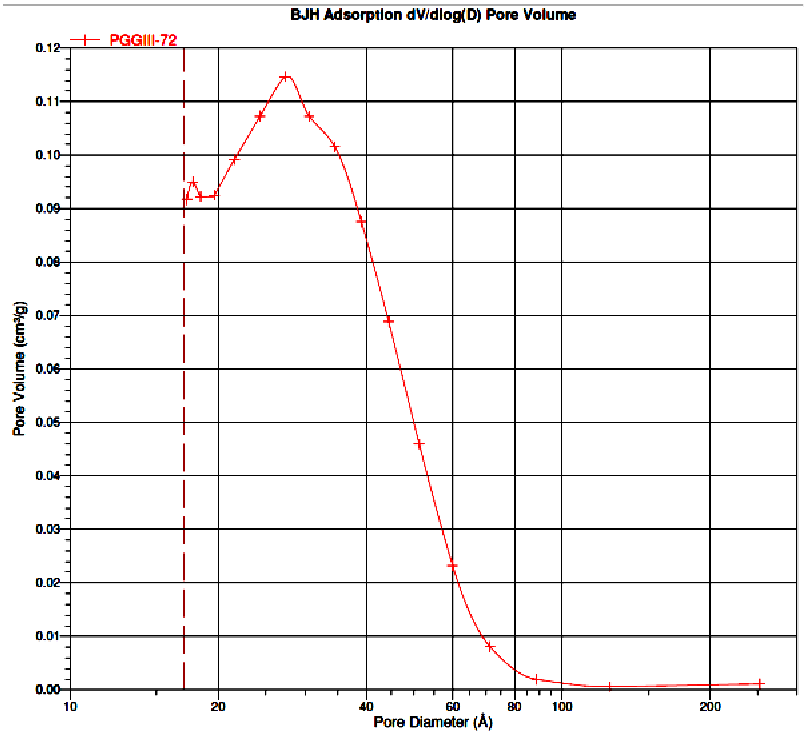


Figure S9. Pore size distribution, calculated by the BJH method, of the hybrid organic-inorganic catalyst **4**.

The hybrid material **4** was analyzed by FTIR spectrometry on self-supporting wafers. The wafer was outgassed at room temperature, 100ºC, 200ºC and 400ºC before the IR spectra were recorded. The IR spectra at different temperatures are illustrated above in Figure S7 and compared with that of derivative **3** (Figure S7, bottom). It should be highlighted that the carbonyl stretching band at around 1720 cm^{-1} observed for the hybrid solid at room temperature and 100ºC, was not detected at 200ºC, pointing out that organocatalyst degradation is occurring above 100ºC and therefore confirming the data obtained in the thermogravimetrical analysis.

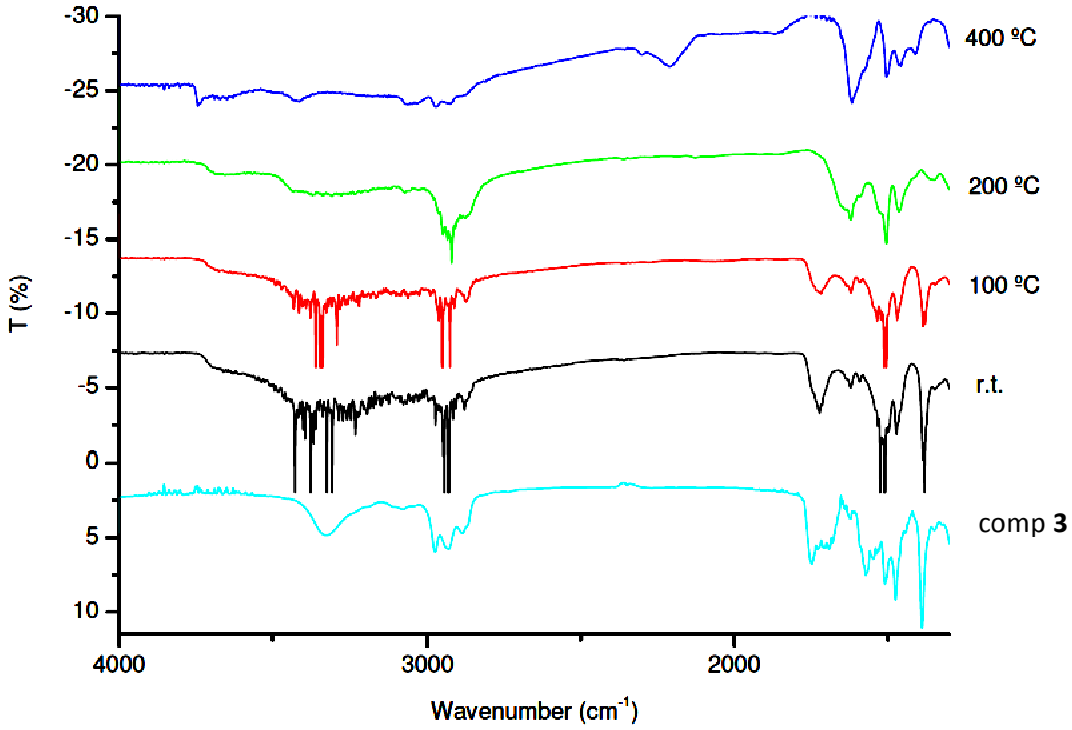


Figure S10. FTIR spectrum of derivative **3** recorded on a KBr disk at room temperature, and FTIR spectra of the hybrid material **4** recorded on self-supporting wafers outgassed at r.t., 100ºC, 200ºC and 400ºC.

In a different experiment it was analyzed the thermal stability over time and the wafer was outgassed and IR spectra recorded at room temperature and at 70ºC (that corresponds to the catalytic reaction temperature that will be presented later) at different times (1 h, 5 h and 24 h). The IR spectra (depicted below in Figure S8) are basically the same revealing that the organic moiety endures the temperature conditions used in the multicomponent transformation matter of this study.

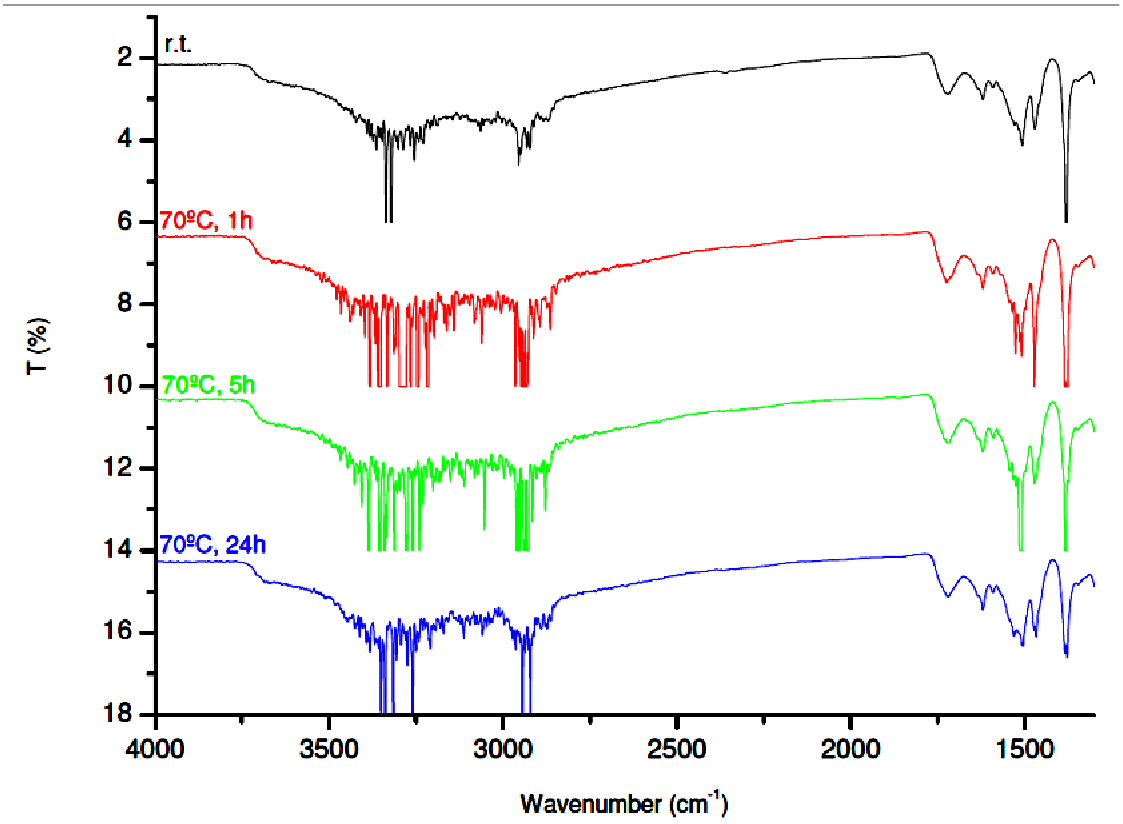
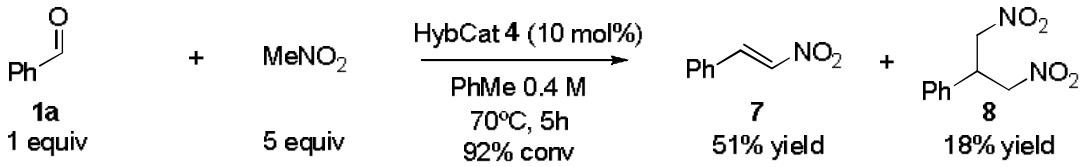


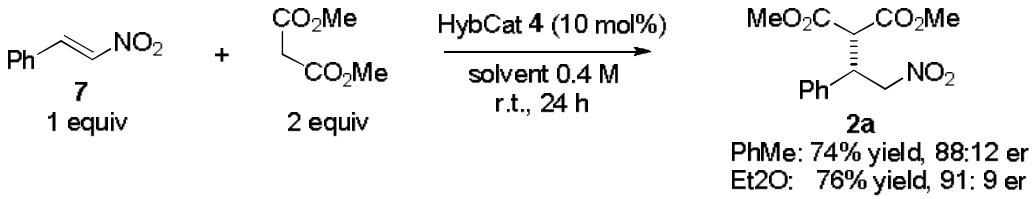
Figure S11. FTIR spectra of the hybrid material **4** recorded on self-supporting wafers outgassed at room temperature, 70ºC after 1h, 70ºC after 5h and 70ºC after 24 h.

3. Catalytic Studies

3.1 Multifunctional Hybrid Organic-Inorganic Material as Catalyst in two different reactions: Henry Condensation and Michael-Type Addition.



Hybrid material **4** (12.8 mg, 0.01 mmol organocatalyst, 10 mol%) was placed in a 2 mL glass vessel. Toluene (0.25 mL, 0.4 M) was then added, followed by benzaldehyde (10 µL, 0.1 mmol) and nitromethane (27 µL, 0.5 mmol). The reaction mixture was left to stir vigorously at 70ºC during 5 h. The products were analyzed by GC using dodecane as internal standard. Nitrostyrene **7** was formed in 51% yield along with by-product **8** in 18% yield, while 8% of benzaldehyde remain unreacted.

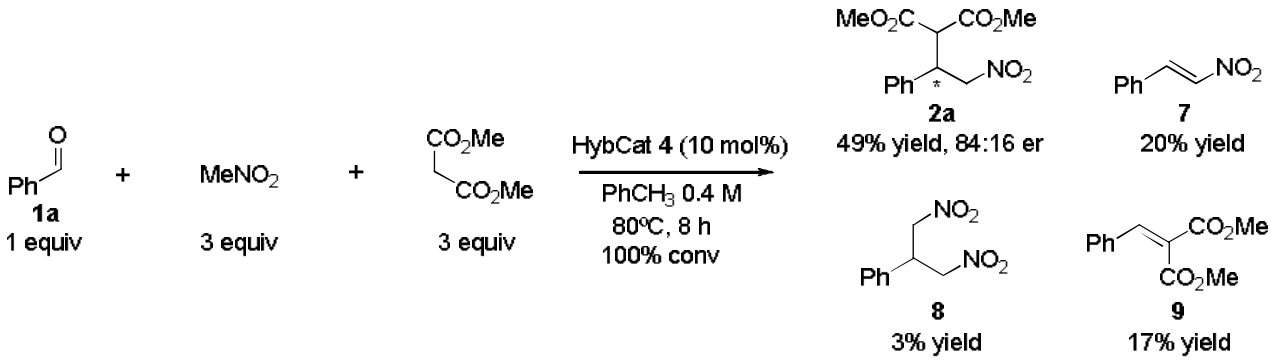


Hybrid material **4** (12.8 mg, 0.01 mmol organocatalyst, 10 mol%) was placed in a 2 mL glass vessel. Solvent (0.25 mL, 0.4 M) was then added, followed by *trans*-β-nitrostyrene **7** (15 mg, 0.1 mmol) and dimethylmalonate (23 µL, 0.2 mmol). The reaction mixture was left to stir vigorously at r.t. during 24 h. The products were analyzed by GC using dodecane as internal standard. Enantiomeric ratios were determined after preparative TLC purification using HPLC on a chiral stationary phase. The Michael adduct **2a** was formed in 74% yield with 88:12 er when using toluene as the reaction solvent. When the solvent of choice was diethyl ether, the product 2**a** was obtained in 76% yield and 91:9 er. Conversion in both experiments is around 85%.

3.2 Multifunctional Hybrid Organic-Inorganic Material as Catalyst in the Asymmetric Multicomponent Reaction (AMC): Henry Condensation + Asymmetric Michael-Type Addition. Optimization of the Reaction Conditions.

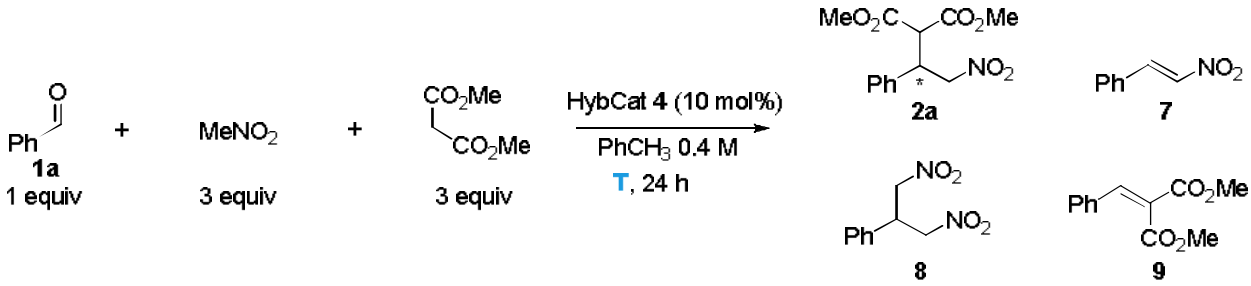
Hybrid material **4** was placed in a 2 mL glass vessel. Solvent was then added, followed by benzaldehyde (10 µL, 0.1 mmol), nitromethane and dimethylmalonate. The reaction mixture was left to stir vigorously at the required temperature for a given time. The products were analyzed by GC using dodecane as internal standard. Enantiomeric ratios were determined after preparative TLC purification using HPLC on a chiral stationary phase.

Initial Experiment



The initial experiment was performed as shown in the upper scheme, with 3 equivalents of nitromethane and 3 equivalents of dimethylmalonate in toluene (0.4 M) and at 80ºC using 10 mol% of organocatalyst loading. The reaction mixture was analyzed after 8 hours reaction time, when the desired product was formed in 49% yield and 84:16 er. Substantial amount of byproducts **8** and **9** are formed along with nitrostyrene **7** that could further be transformed into the desired product.

Temperature Screening

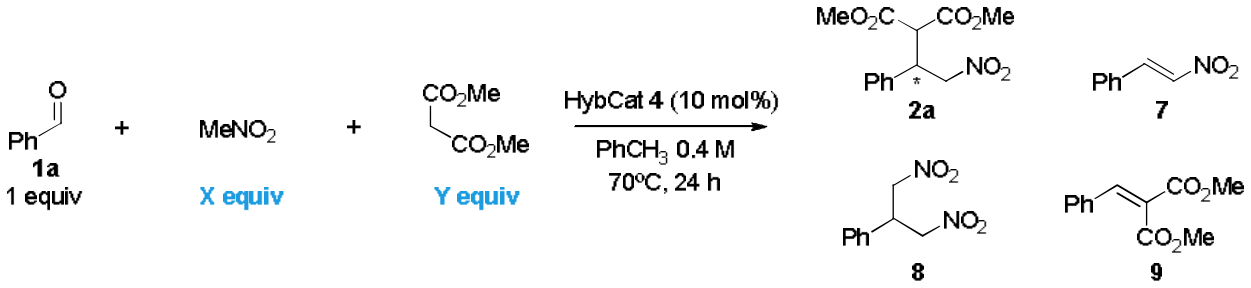


T (ºC)	by-products **8** + **9** combined yield (%)	**2a** yield (%)	**2a** er
50	7	9	87:13
60	20	58	87:13
70	20	63	85:15
80	22	63	82:18
90	19	61	82:18
100	21	59	81:19

Table S3. Temperature screening for the AMR of benzaldehyde, nitromethane and dimethylmalonate.

It was observed that the reaction proceeds very slowly at 50ºC and acceptable yields are achieved above 60ºC. As expected, enantioselectivity decreases at higher temperatures, although not a large effect is observed varying from 87:13 er at 50ºC to 81:19 er at 100ºC. The product yield passes through a maximum which occurs at the temperature of 70-80ºC. Optimum temperature with best compromise of yield, enantioselectivity and byproducts formation was demonstrated to be 70ºC.

Reagents Ratio Screening

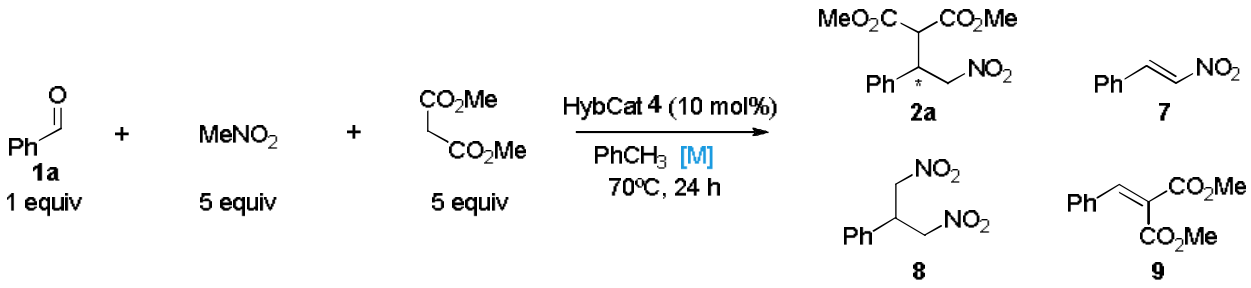


Entry	X equiv	Y equiv	by-products **8** + **9** combined yield (%)	**2a** yield (%)	**2a** er
1	3	3	20	63	85:15
2	3	1.5	18	50	85:15
3	3	5	23	61	86.5:13.5
4	5	5	14	75	86:14
5	7	5	15	73	86:14
6	10	5	18	75	84.5:15.5
7	3	3	20	63	85:15
8	5	5	14	75	86:14
9	7	7	16	74	85:15
10	10	10	16	76	86:14

Table S4. Reagents ratio screening for the AMR of benzaldehyde, nitromethane and dimethylmalonate.

While enantioselectivity appears not to be affected by changing reagents ratio and amounts, the latter fact does have an influence in yield and byproduct formation. At equal conditions, lowering amount of dimethylmalonate provoke a decrease in desired product formation (entries 1 and 2). Similar behavior was observed when diminishing nitromethane equivalents (entries 4 and 3), that was translated in lower yield. At the same amount of dimethylmalonate, the equivalents of nitromethane were altered (entries 3 to 6), finding out that while increased amounts of nitromethane does have a beneficial effect in product formation (entries 3 and 4) it does reach a limit when using 5 equivalents of the reagent. Combined yield of by-product varies from 14 to 23% and the nature of them depends as expected on the reagent on excess. Optimal conditions appear to make use of identical amount of the two reagents (entry 4). In view of these results, reagents ratio was fixed to 1 and several equivalents were used (entries 7 to 10). Product yield again reaches a limit at 75% with 5 equivalents of both reagents (entry 8).

Concentration Screening

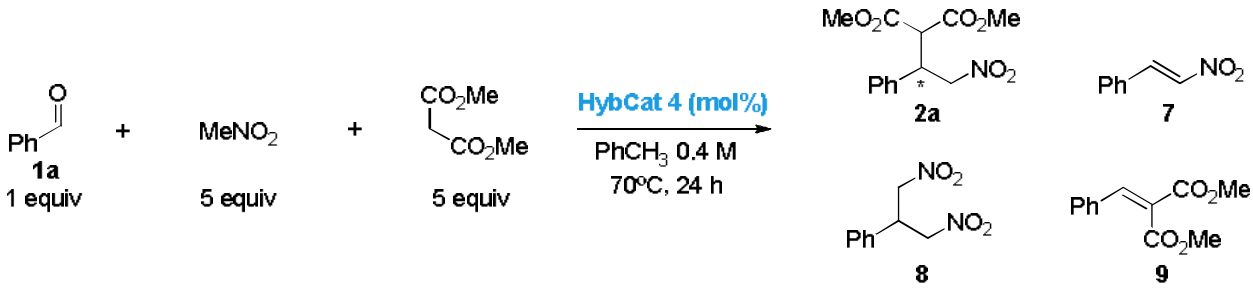


Entry	[M]	by-products **8** + **9** combined yield (%)	**2a** yield (%)	**2a** er
1	0.4	14	75	86:14
2	0.6	17	72	85.5:14.5

Table S5. Concentration screening for the AMR of benzaldehyde, nitromethane and dimethylmalonate.

Higher concentration than the usual 0.4 M was tested in the multicomponent reaction (i.e. 0.6 M, entry 2), resulting in no beneficial effect in terms of yield or enantioselectivity, being 0.4 M concentration the elected conditions in the matter transformation.

Catalyst Loading Screening

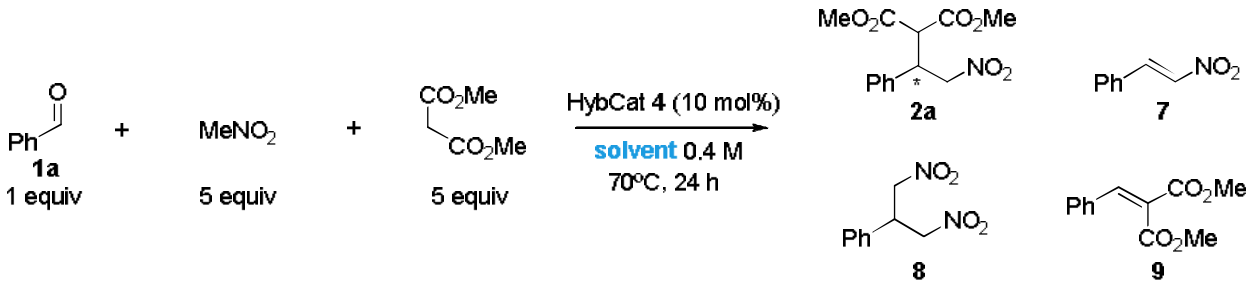


Entry	(mol%)	by-products **8** + **9** combined yield (%)	**2a** yield (%)	**2a** er
1	5	16	43	86:14
2	10	14	75	86:14
3	15	12	77	85.5:14.5
4	20	11	76	85.5:14.5

Table S6. Temperature screening for the AMR of benzaldehyde, nitromethane and dimethylmalonate.

The amount of the organocatalyst was varied from 5 to 20 mol% and it was observed that higher loading results in better performance in terms of yield and lower byproducts, although it was decided to stick to 10 mol% loading (entry 2) as the improvements are not that large with 15 and 20 mol% (entries 3 and 4 respectively).

Solvent Screening



solvent	by-products **8** + **9** combined yield (%)	**2a** yield (%)	**2a** er
PhMe	14	75	86:14
ethyl acetate	22	63	87:13
$CHCl_3$[a]	12	31	86.5:13.5
dioxane[b]	17	77	88:12

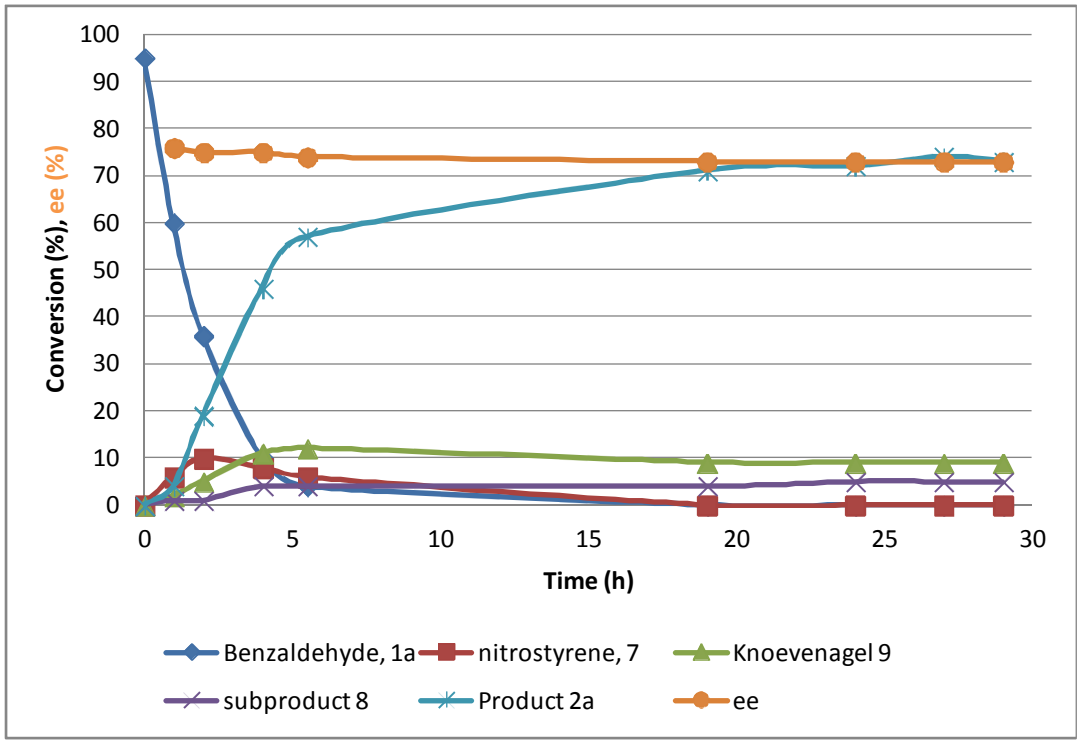
Table S7. Sovent screening for the AMR of benzaldehyde, nitromethane and dimethylmalonate. [a]The experiment was carried out at 60ºC. [b]36 h reaction time.

The solvent screening for the asymmetric multicomponent reaction was performed with only four different solvents: toluene, ethyl acetate, chloroform and dioxane. A full solvent screening was conducted for the asymmetric Michael-type addition of dimethylmalonate to *trans*-β-nitrostyrene at room temperature catalyzed by the hybrid material, turning out that the four mentioned solvents together with diethylether were the ones giving higher enantioselectivity and therefore the ones tested in the related multicomponent reaction. Although reaction performed in ethyl acetate allows product formation with slightly higher enantioselectivity, the yield of the desired product was lower compared to the procedure carried out in toluene, accompanied with higher amount of byproducts **8** and **9**. Results in chloroform may not be comparable as the reaction was performed at 60ºC. Dioxane turned out to be the optimum solvent in terms of enantioselectivity although longer reaction time was required to carry out the transformation in order to achieve good yield.

3.3 Multifunctional Hybrid Organic-Inorganic Material as Catalyst in the Asymmetric Multicomponent Reaction (AMC): Henry Condensation + Asymmetric Michael-Type Addition. Kinetic Studies.

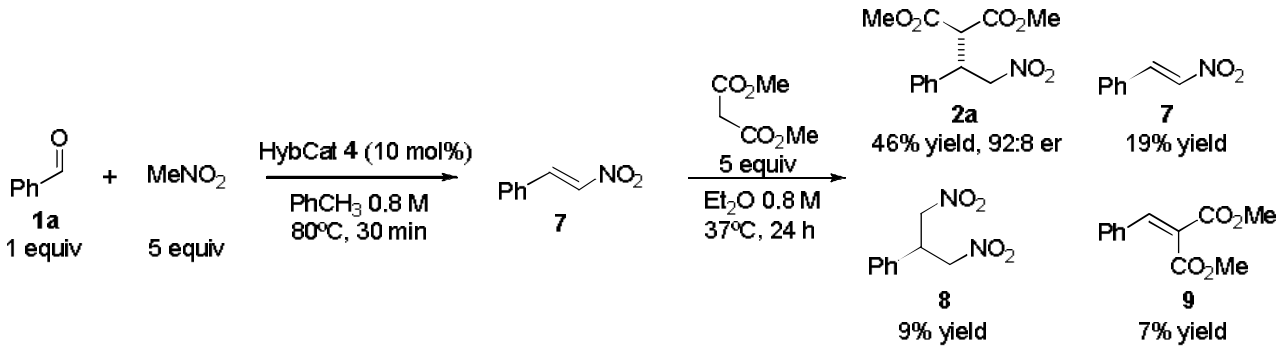
Hybrid material **4** (128 mg, 0.1 mmol organocatalyst, 10 mol%) was placed in a 10 mL round bottomed flask. Toluene (2.5 mL, 0.4 M) was then added, followed by benzaldehyde (102 µL, 1.0 mmol), nitromethane (0.27 mL, 5.0 mmol) and dimethylmalonate (0.57 mL, 5.0 mmol). The vessel was sealed and the reaction mixture was left to stir vigorously at 70ºC. Aliquots of the reaction mixture (75 µL) were taken at different times and the products were analyzed by GC using dodecane as internal standard. Enantiomeric ratios were determined after preparative TLC purification using HPLC on a chiral stationary phase.

The obtained results are depicted in the following graphic and commented below.



It was observed that in the presence of the hybrid material, 75% yield of the desired product can be obtained after 20 hours reaction time, being the selectivity 83%. The Knoevenagel byproduct **9** is formed in the first hours of the catalytic process when the presence of benzaldehyde is significant while formation of subproduct **8** needs an induction period of 2-3 hours confirming its stepwise formation. Intermediate nitrostyrene **7** is also detected and particularly in the early stage of the process. Figure 1 showcases as well that enantioselectivity of the formed product remains constant with the time.

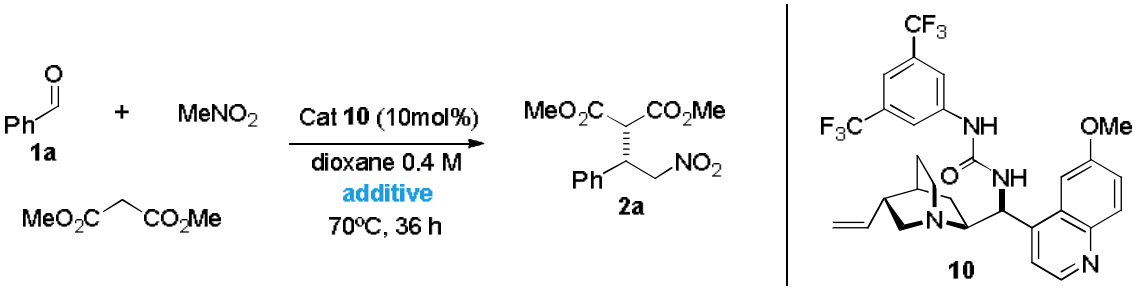
3.4 Multifunctional Hybrid Organic-Inorganic Material as Catalyst in the Sequential Procedure: Henry Condensation followed by Asymmetric Michael-Type Addition.



Hybrid material **4** (12.8 mg, 0.01 mmol organocatalyst, 10 mol%) was placed in a 2 mL glass vessel. Toluene (0.125 mL, 0.8 M) was then added, followed by benzaldehyde (10 µL, 0.1 mmol) and nitromethane (27 µL, 0.5 mmol). The mixture was left to stir vigorously at 80ºC during 30 min. It was then left to cool down to 37ºC and diethyl ether (0.125 mL, 0.8 M) was then added followed by dimethylmalonate (57 µL, 0.5 mmol) and afterwards left to stir vigorously at 37ºC during 24 h. The products were analyzed by GC using dodecane as internal standard. Enantiomeric ratios were determined after preparative TLC purification using HPLC on a chiral stationary phase. The Michael adduct **2a** was formed in 46% yield with 92:8 er.

3.5 Homogeneous Counterpart as Catalyst in the Asymmetric Multicomponent Reaction

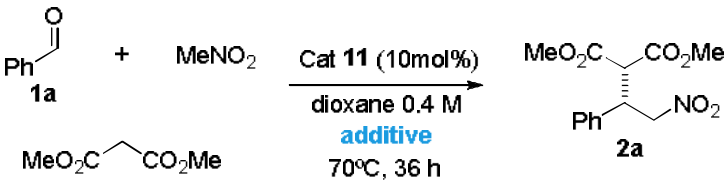
3.5.1 Experiments with Catalyst 10:

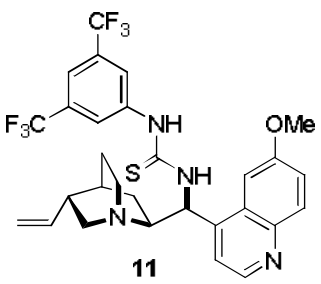


Catalyst **10** (5.8 mg, 0.01 mmol organocatalyst, 10 mol%) was placed in a 2 mL glass vessel. Dioxane (0.25 mL, 0.4 M) was then added, followed by benzaldehyde (10 µL, 0.1 mmol), nitromethane (27 µL, 0.5 mmol) and dimethylmalonate (57 µL, 0.5mmol). Afterwards, the corresponding additive (15 mg) was added. It was used the same amount of additive as hybrid solid catalyst was employed in the heterogeneous catalyzed reactions. The reaction mixture was left to stir vigorously at 70ºC during 36 h. The products were analyzed by ^{1}H NMR using Ph_3CH as internal standard. Enantiomeric ratios were determined after preparative TLC purification using HPLC on a chiral stationary phase. The attained results are shown in the following table.

additive	**2a** yield (%)	**2a** er
---	6	87:13
4 Å MS	10	84:16
Silica 100	6	89:11

3.5.2 Experiments with Catalyst 11:

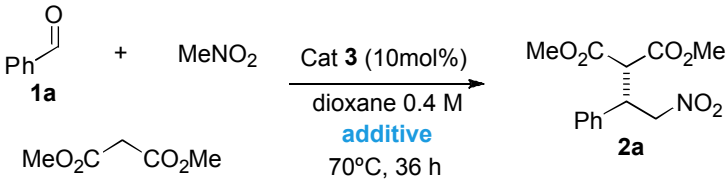


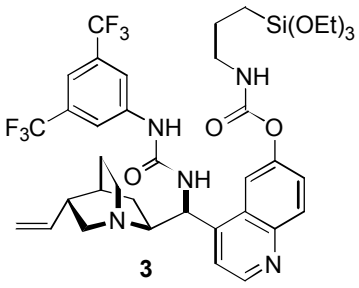


Catalyst **11** (5.9 mg, 0.01 mmol organocatalyst, 10 mol%) was placed in a 2 mL glass vessel. Dioxane (0.25 mL, 0.4 M) was then added, followed by benzaldehyde (10 µL, 0.1 mmol), nitromethane (27 µL, 0.5 mmol) and dimethylmalonate (57 µL, 0.5 mmol). Afterwards, the corresponding additive (15 mg) was added. It was used the same amount of additive as hybrid solid catalyst was employed in the heterogeneous catalyzed reactions. The reaction mixture was left to stir vigorously at 70ºC during 36 h. The products were analyzed by ^{1}H NMR using Ph_3CH as internal standard. Enantiomeric ratios were determined after preparative TLC purification using HPLC on a chiral stationary phase. The attained results are shown in the following table.

additive	**2a** yield (%)	**2a** er
---	6	87:13
4 Å MS	10	84:16
Silica 100	6	89:11

3.5.3 Experiments with Catalyst 3:

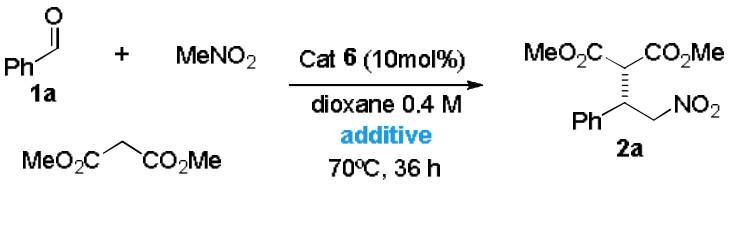


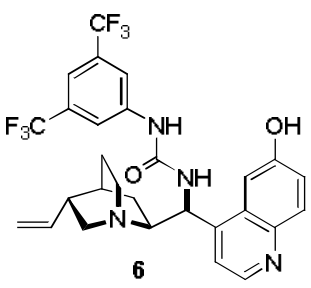


Catalyst **3** (8.1 mg, 0.01 mmol organocatalyst, 10 mol%) was placed in a 2 mL glass vessel. Dioxane (0.25 mL, 0.4 M) was then added, followed by benzaldehyde (10 µL, 0.1 mmol), nitromethane (27 µL, 0.5 mmol) and dimethylmalonate (57 µL, 0.5mmol). Afterwards, the corresponding additive (15 mg) was added. It was used the same amount of additive as hybrid solid catalyst was employed in the heterogeneous catalyzed reactions. The reaction mixture was left to stir vigorously at 70ºC during 36 h. The products were analyzed by ^{1}H NMR using Ph_3CH as internal standard. Enantiomeric ratios were determined after preparative TLC purification using HPLC on a chiral stationary phase. The attained results are shown in the following table.

additive	**2a** yield (%)	**2a** er
---	6	84:16
4 Å MS	7	80:20
Silica 100	19	88:12

3.5.4 Experiments with Catalyst 6:



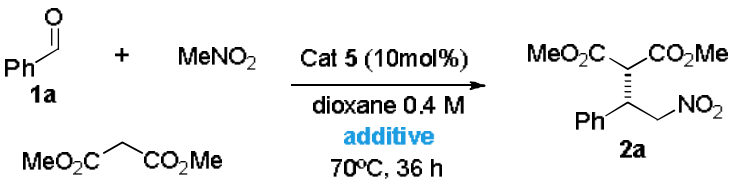


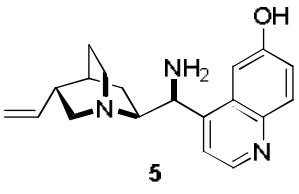
Catalyst **6** (5.6 mg, 0.01 mmol organocatalyst, 10 mol%) was placed in a 2 mL glass vessel. Dioxane (0.25 mL, 0.4 M) was then added, followed by benzaldehyde (10 µL, 0.1 mmol), nitromethane (27 µL, 0.5 mmol) and dimethylmalonate (57 µL, 0.5mmol). Afterwards, the corresponding additive (15 mg) was added. It was used the same amount of additive as hybrid solid catalyst was employed in the heterogeneous catalyzed reactions. The reaction mixture was left to stir vigorously at 70ºC during 36 h. The products were analyzed by ^{1}H NMR using Ph_3CH as internal standard. Enantiomeric ratios were determined after preparative TLC purification using HPLC on a chiral stationary phase. The attained results are shown in the following table.

additive	**2a** yield (%)	**2a** er
---	6	n.d.
4 Å MS	6	n.d.
Silica 100	7	n.d.

n.d. = not determined

3.5.5 Experiments with Catalyst 5:





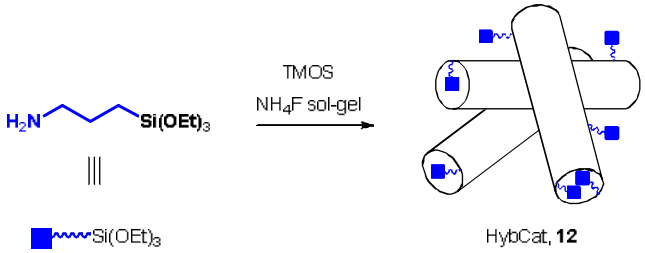
Catalyst **5** (3.1 mg, 0.01 mmol organocatalyst, 10 mol%) was placed in a 2 mL glass vessel. Dioxane (0.25 mL, 0.4 M) was then added, followed by benzaldehyde (10 µL, 0.1 mmol), nitromethane (27 µL, 0.5 mmol) and dimethylmalonate (57 µL, 0.5mmol). Afterwards, the corresponding additive (15 mg) was added. It was used the same amount of additive as hybrid solid catalyst was employed in the heterogeneous catalyzed reactions. The reaction mixture was left to stir vigorously at 70ºC during 36 h. The products were analyzed by ^{1}H NMR using Ph_3CH as internal standard. Enantiomeric ratios were determined after preparative TLC purification using HPLC on a chiral stationary phase. The attained results are shown in the following table.

additive	**2a** yield (%)	**2a** er
---	4	n.d.
4 Å MS	4	n.d.
Silica 100	4	n.d.

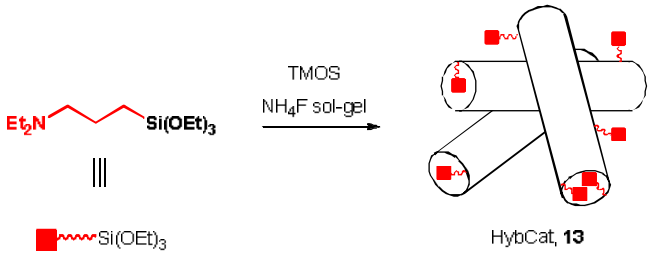
n.d. = not determined

3.6 Preparation and Test of amino functionalized silicas

3.6.1 Preparation of amino functionalized silicas 12 and 13.



The hybrid organic-inorganic catalyst **12** was prepared using a NH_4F co-condensation route.[6] Tetramethylorthosilicate (TMOS) (1.07 mL, 7.22 mmol) and aminopropyltriethoxysilane (0.12 mL, 0.5 mmol) were mixed in methanol (1.25 mL) at 298 K. After dissolution of precursors, a water solution of NH_4F (0.56 mL of a 0.043 M solution) was added under vigorous stirring. The reaction mixture has the following molar composition: $1SiO_2$:4MeOH:$4H_2O$:$0.00313NH_4F$ and the Si/NH_4F and TMOS/organosilane ratios were adjusted to 320 and 14.4 respectively. Hydrolysis and condensation of the silicon precursors was carried out under vigorous stirring at 298 K until gelation occurred. Then, the gel was aged for 24 h at 36ºC, and finally dried at 80ºC for another 14 h. The obtained white solid was ground to a fine powder and subsequently washed with water, ethanol, NH_4OH-ethanol solution and diethyl ether in consecutive steps to remove the organic molecules not incorporated into the material. The obtained hybrid solid was then dried under vacuum at 50ºC for 3 h. It was obtained 500 mg (quant) of the material.

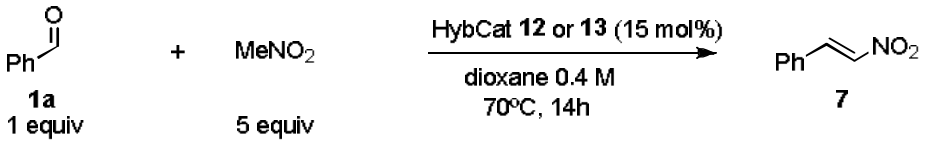


The hybrid organic-inorganic catalyst **13** was prepared using a NH_4F co-condensation route.[6] Tetramethylorthosilicate (TMOS) (1.07 mL, 7.22 mmol) and diethylaminopropyltriethoxysilane (0.12 mL, 0.5 mmol) were mixed in methanol (1.25 mL) at 298 K. After dissolution of precursors, a water solution of NH_4F (0.56 mL of a 0.043 M solution) was added under vigorous stirring. The reaction mixture has the following molar composition: $1SiO_2$:4MeOH:$4H_2O$:$0.00313NH_4F$ and the Si/NH_4F and TMOS/organosilane ratios were adjusted to 320 and 14.4 respectively. Hydrolysis and condensation of the silicon precursors was carried out under vigorous stirring at 298 K until gelation occurred. Then, the gel was aged for 24 h at 36ºC, and finally dried at 80ºC for another 14 h. The obtained white solid was ground to a fine powder and subsequently washed with water, ethanol, NH_4OH-ethanol solution and diethyl ether in consecutive steps to remove the organic molecules not incorporated into the material. The obtained hybrid solid was then dried under vacuum at 50ºC for 3 h. It was obtained 530 mg (quant.) of the hybrid material.

Sample	N%	C%	H%	S%	C/N
HybCat **12**	1.427	4.265	1.717	0.000	3.5

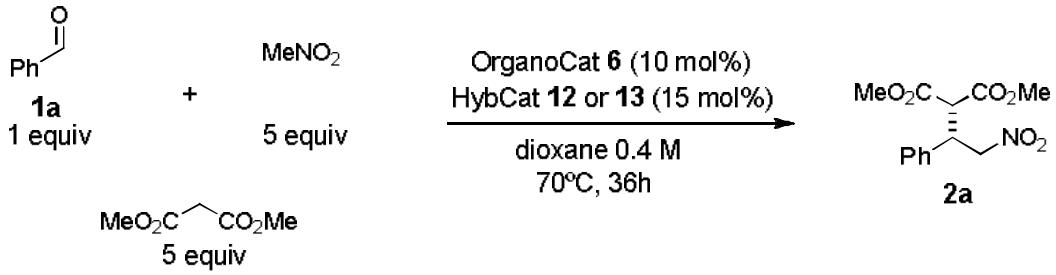
Table S8. Crude data from elemental analyses of hybrid materials **12** and **13**.

3.6.2 Catalytic tests of amino functionalized silicas 12 and 13: Henry Condensation and Multicomponent Reaction



Hybrid material (0.015 mmol organocatalyst, 15 mol%) was placed in a 2 mL glass vessel. Dioxane (0.25 mL, 0.4 M) was then added, followed by benzaldehyde (10 µL, 0.1 mmol) and nitromethane (27 µL, 0.5 mmol). The reaction mixture was left to stir vigorously at 70ºC during 14 h. The products were analyzed by GC using dodecane as internal standard. The attained results are shown in the following table.

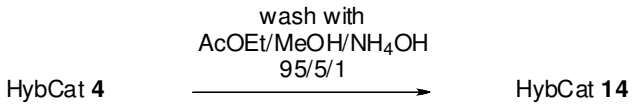
HybCat	**7** yield (%)
12	86
13	1



Hybrid material (0.015 mmol organocatalyst, 15 mol%) and organocatalyst **6** (5.7 mg, 0.01 mmol) were placed in a 2 mL glass vessel. Dioxane (0.25 mL, 0.4 M) was then added, followed by benzaldehyde (10 µL, 0.1 mmol), nitromethane (27 µL, 0.5 mmol) and dimethylmalonate (57 µL, 0.5 mmol). The reaction mixture was left to stir vigorously at 70ºC during 36 h. The products were analyzed by GC using dodecane as internal standard. Enantiomeric ratios were determined after preparative TLC purification using HPLC on a chiral stationary phase. The attained results are shown in the following table.

HybCat	**2a** yield (%)	**2a** er
12	83	88:12
13	12	86:14

3.7 Removal of adsorbed Organic Molecules 6 in HybCat 4 and Test Reaction.



HybCat **4** (200 mg) was poured in a funnel and extensively washed with a solution of AcOEt/MeOH/NH_4OH 95/5/1 until TLC analysis reveals that no more derivative **6** is coming out of the solid. The solid was then dried at 50ºC during 3 h. It was obtained 166 mg of the hybrid solid **14**. ^{13}C-CP MAS NMR of hybrid organic-inorganic catalyst **14** shows a substantial reduction in adsorbed molecules (by diminution of the signal at 105 ppm). Further washing off the solid didn't allow a complete removal of adsorbed molecules.

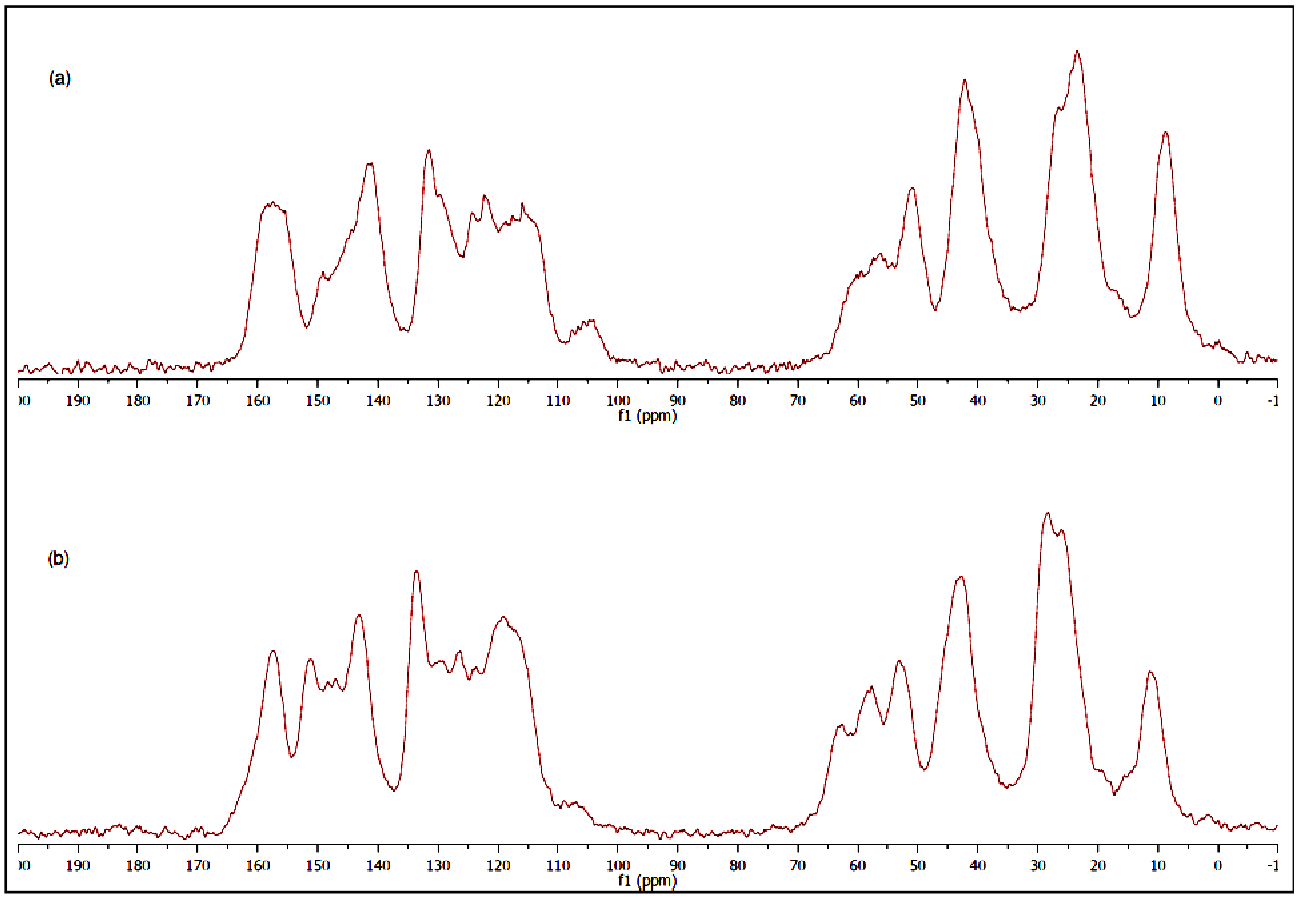
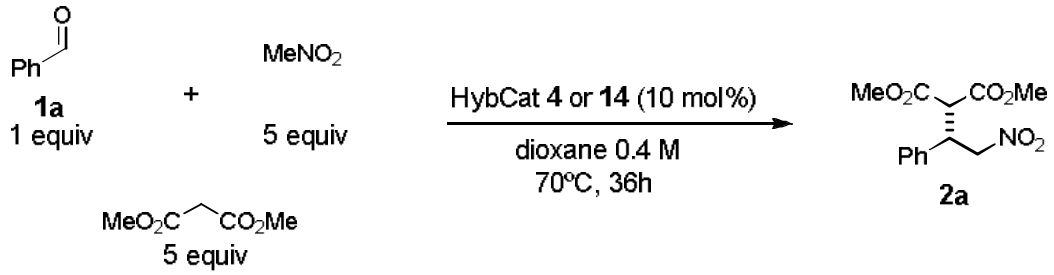


Figure S12. (a) ^{13}C-CP MAS NMR of HybCat **4**. (b) ^{13}C-CP MAS NMR of HybCat **14.**

Sample	N%	C%	H%	S%	C/N
HybCat **4**	5.484	28.801	3.498	0.000	6.1
HybCat **14**	4.834	23.636	3.262	0.000	5.7

Table S9. Crude data from elemental analyses of the hybrid material **4** and **14**.



Hybrid material **4** (12.8 mg, 0.01 mmol organocatalyst, 10 mol%) or Hybrid material **14** (14.5 mg, 0.010 mmol organocatalyst, 10 mol%) was placed in a 2 mL glass vessel. Dioxane (0.25 mL, 0.4 M) was then added, followed by benzaldehyde (10 µL, 0.1 mmol), nitromethane (27 µL, 0.5 mmol) and dimethylmalonate (57 µL, 0.5 mmol). The reaction mixture was left to stir vigorously at 70ºC during 36 h. The products were analyzed by GC using dodecane as internal standard. Enantiomeric ratios were determined after preparative TLC purification using HPLC on a chiral stationary phase. The attained results are shown in the following table.

HybCat	**2a** yield (%)	**2a** er
4 (12.8 mg, 10 mol%)	78	88:12
14 (14.8 mg, 10 mol%)	77	88:12
14 (12.8 mg, 9 mol%)	68	88:12

3.8 Preparation and Test of HybCat with varied TMOS/organosilane ration in the initial composition.

3.8.1 Preparation of HybCat with varied TMOS/organosilane ratio.

Apart from HybCat **4**, two other organosilica materials with different content of the cinchona derivative have been synthesized using the NH_4F co-condensation route. It was followed the same procedure as for HybCat **4** reported in page 5, and the following amounts were employed:

HybCat **4**: TMOS/organosilane ratio 6.7. (see page 5)

HybCat **15**: TMOS/organosilane ratio 19.

Tetramethylorthosilicate (TMOS) (0.6 mL, 4.0 mmol); Cinchona alkaloid derivative **3** (172 mg, 0.21 mmol); methanol (0.7 mL); water solution of NH_4F (0.30 mL of a 0.043 M solution). It was obtained 286 mg of the hybrid organic inorganic material (73% yield, organocatalyst content = 0.30 $mmolg^{-1}$, measured by EA)

HybCat **16**: TMOS/organosilane ratio 100.

Tetramethylorthosilicate (TMOS) (0.6 mL, 4.0 mmol); Cinchona alkaloid derivative **3** (32 mg, 0.04 mmol); methanol (0.65 mL); water solution of NH_4F (0.29 mL of a 0.043 M solution). It was obtained 256 mg of the hybrid organic inorganic material (95% yield, organocatalyst content = 0.07 $mmolg^{-1}$, measured by EA)

3.8.2 Characterization of HybCat with varied TMOS/organosilane ratio.

Sample	N%	C%	H%	S%	C/N
HybCat **4**	5.484	28.801	3.498	0.000	6.1
HybCat **15**	2.071	10.180	1.895	0.000	5.7
HybCat **16**	0.505	3.746	1.358	0.000	8.6

Table S10. Crude data from elemental analyses of the hybrid material **4**, **15** and **16**.

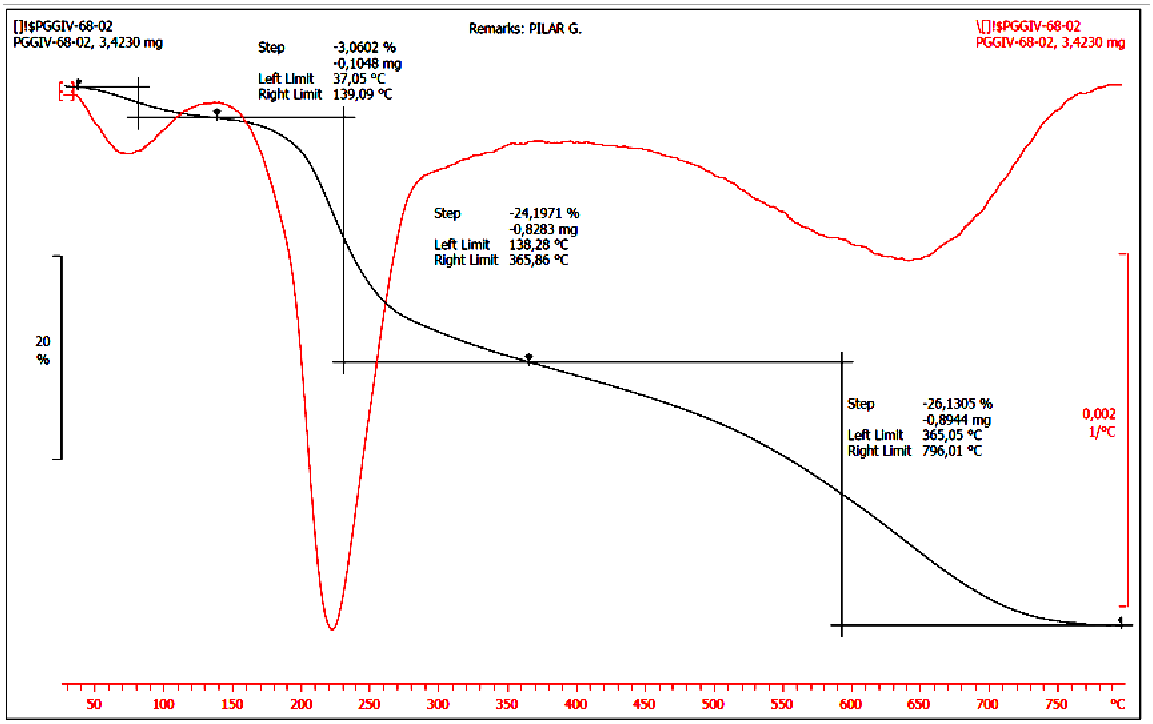


Figure S1. Thermogravimetric curve (TGA) and its corresponding derivative (DTA) of hybrid catalyst **4**.

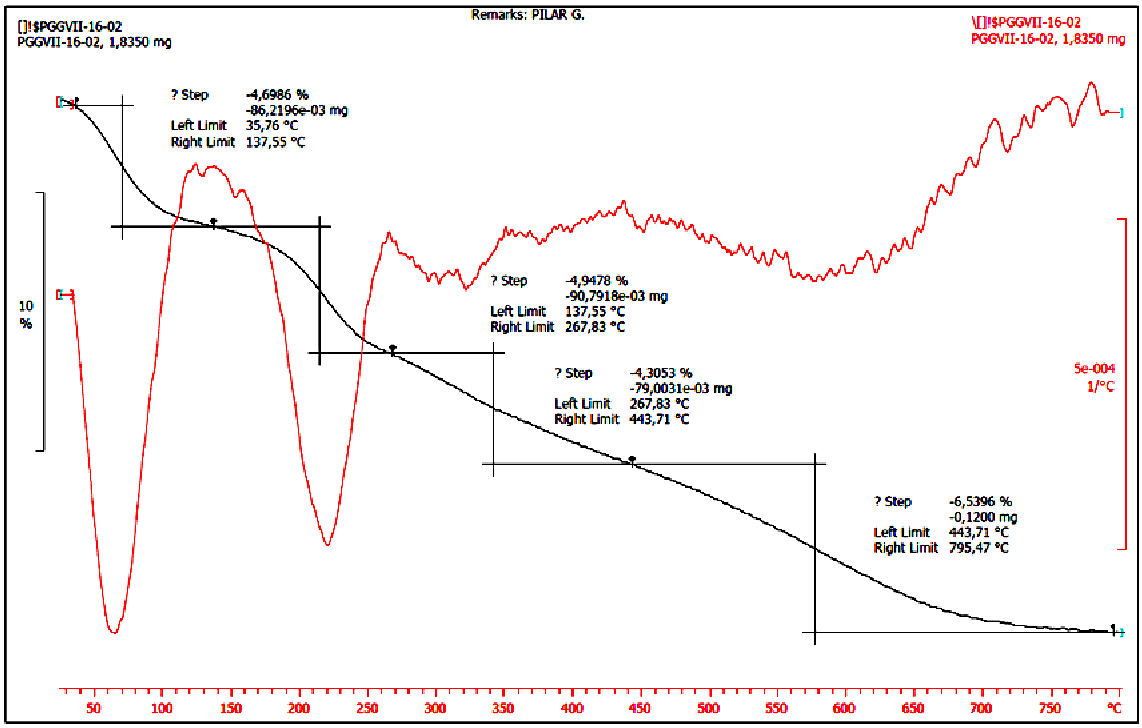


Figure S13. Thermogravimetric curve (TGA) and its corresponding derivative (DTA) of hybrid catalyst **15**.

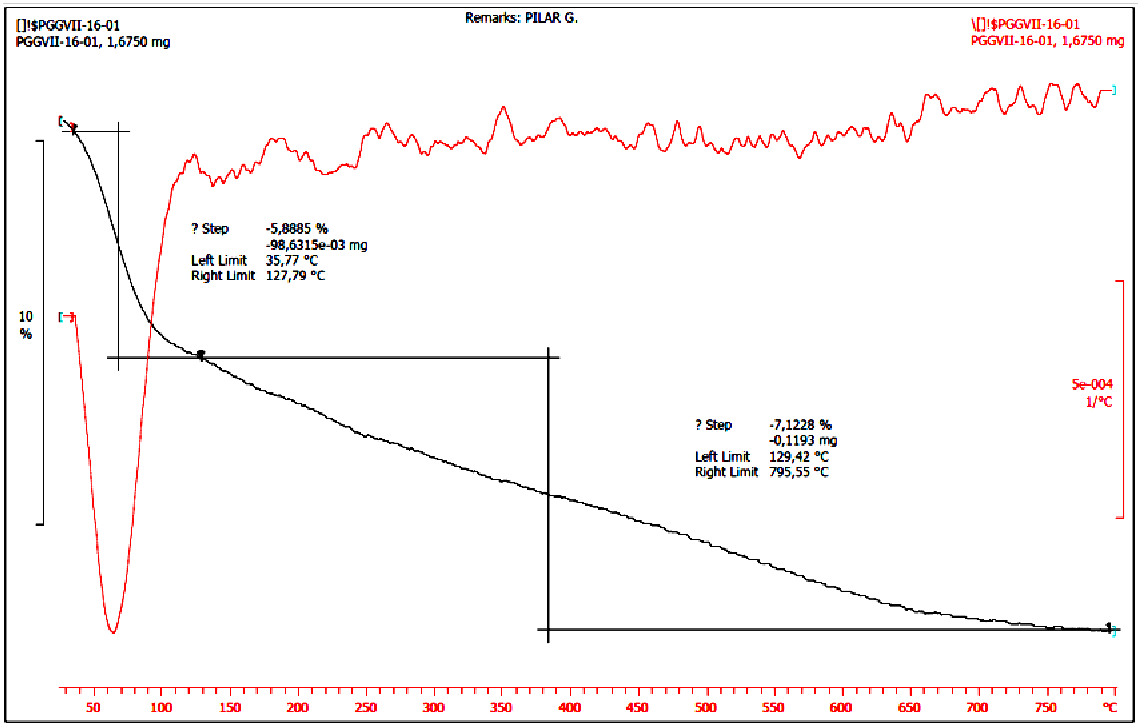


Figure S14. Thermogravimetric curve (TGA) and its corresponding derivative (DTA) of hybrid catalyst **16**.

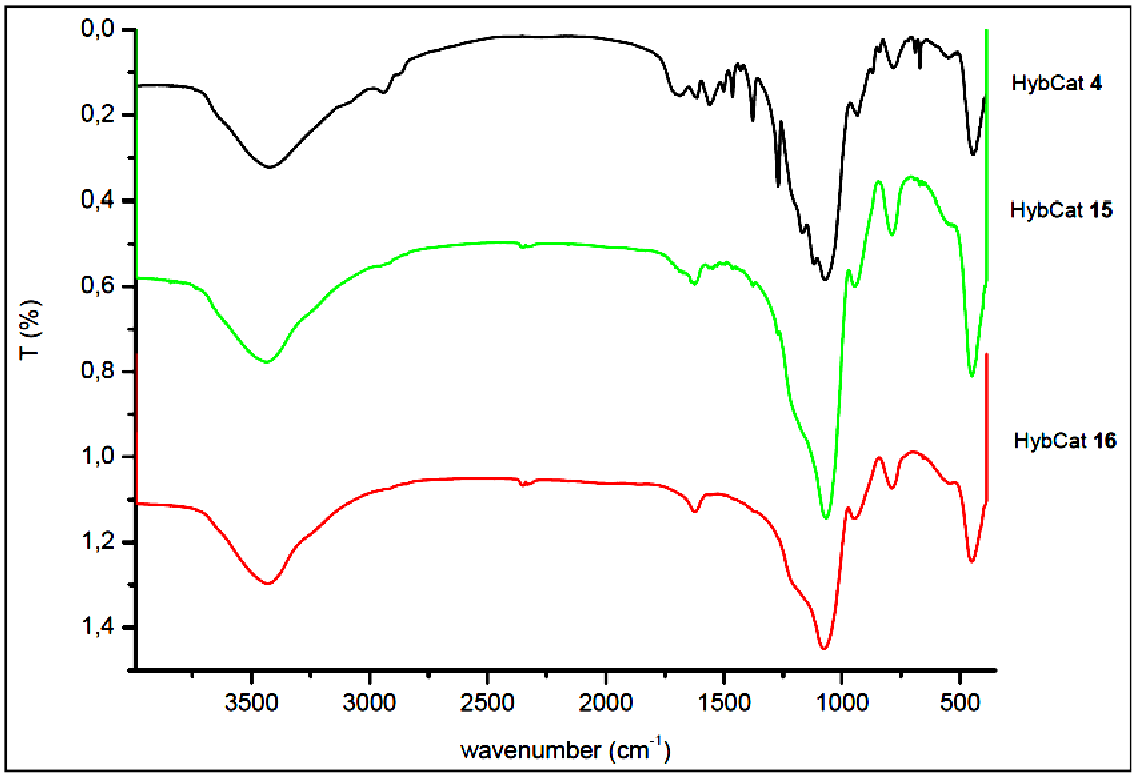


Figure S15. FTIR spectrum of HybCat **4**, **15** and **16** recorded on a KBr disk at room temperature

Textural Properties:

Sample	BET Surface Area/m^2g^{-1}	External Surface/m^2g^{-1}	Micropore Volume/cm^3g^{-1}	Total Pore Volume/cm^3g^{-1}	Mean Pore Diameter/Å
HybCat **4**	111	111	0.00	0.15	29
HybCat **15**	572	572	0.00	0.45	31
HybCat **16**	801	801	0.00	0.88	31

Table S11. Textural Characteristic of the hybrid organic-inorganic material **4, 15** and **16**.

The patterns of the N_2 isotherms are similar for the three solids (see below) with the change in the slope occurring at low partial pressure (P/Po around 0.3), which is typical of non-ordered siliceous mesoporous materials.

As expected, the hybrid materials with lower organic content show higher BET surface area.

Furthermore, it should be mentioned that the three organic-inorganic hybrid materials exhibit a notable mesoporous volume, as can be deduced from the N_2 adsorption isotherms. The materials present no microporosity as determined by the t-plot analysis.

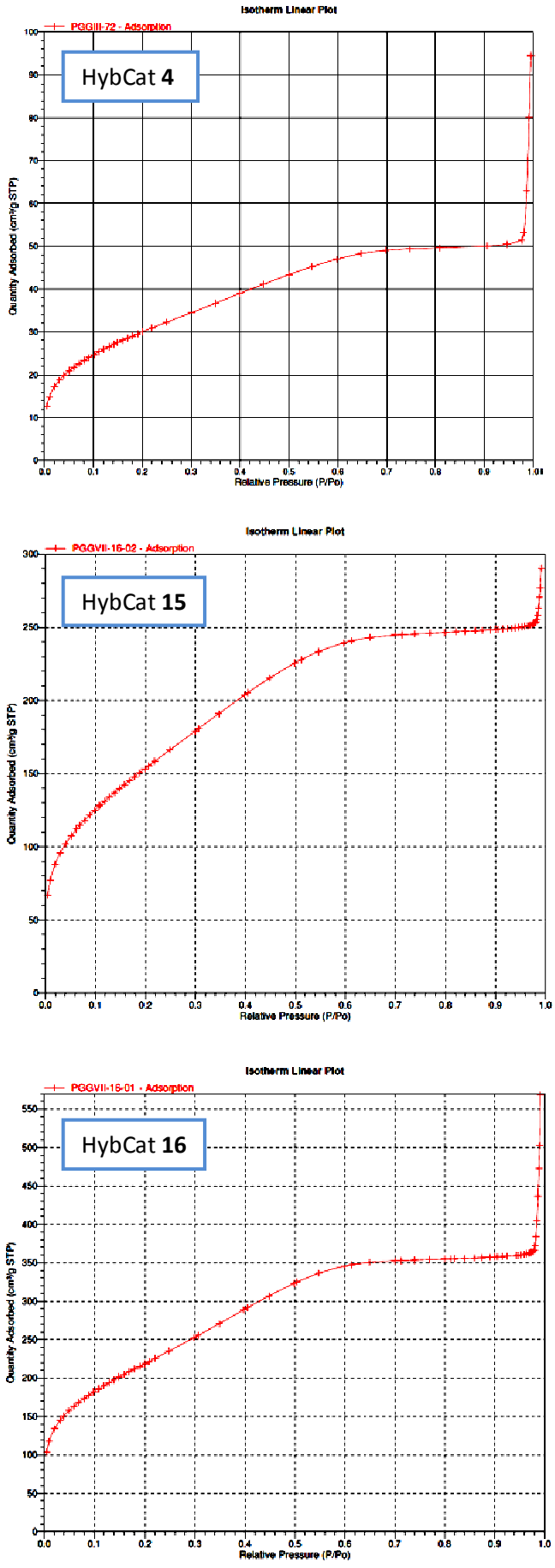


Figure S16. N_2 adsorption isotherm of the hybrid organic-inorganic catalyst **4, 15** and **16**.

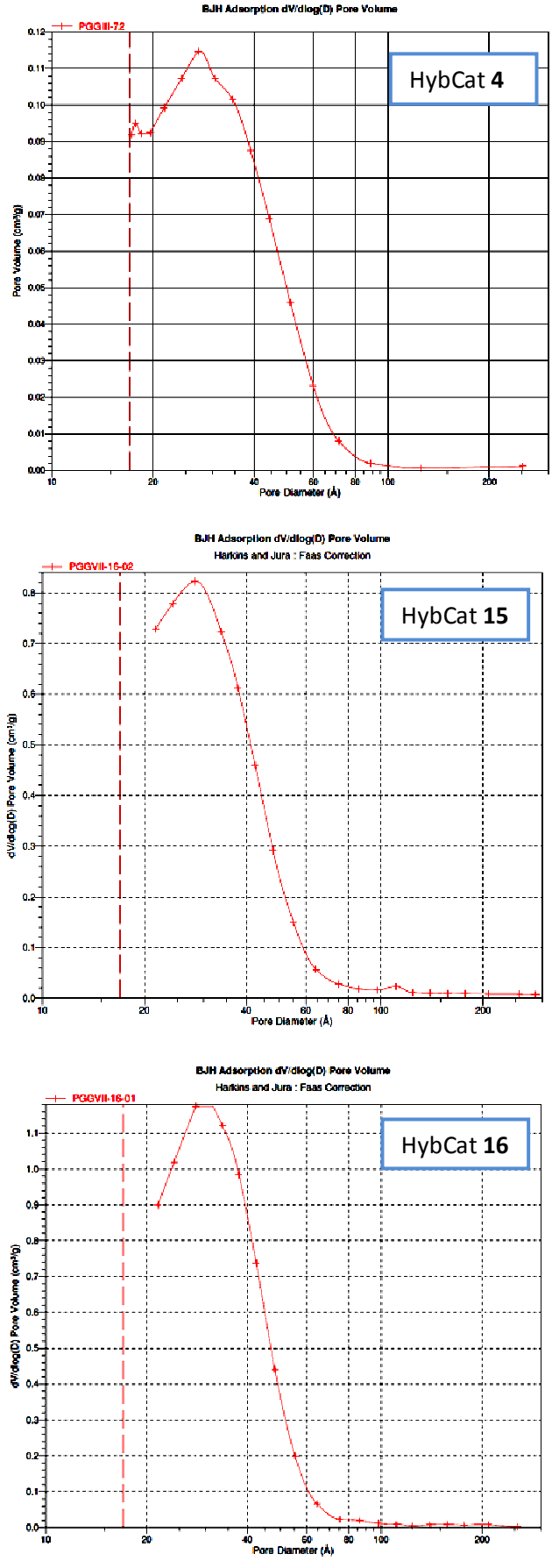
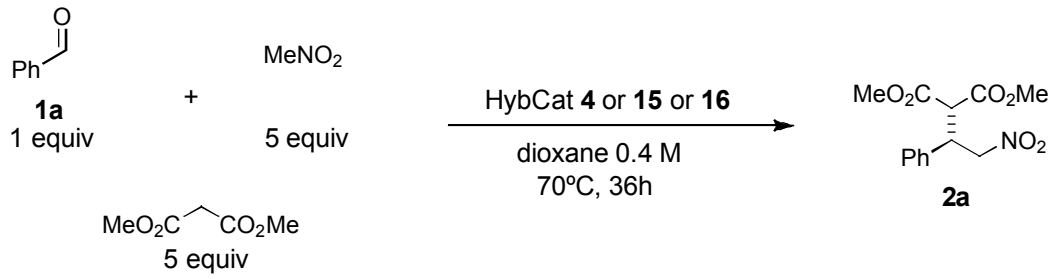


Figure S17. Pore size distribution, calculated by the BJH method, of the hybrid organic-inorganic catalyst **4, 15** and **16**.

3.8.3 Catalytic tests of HybCat 4, 15 and 16 with varied TMOS/organosilane ratio in the initial composition.



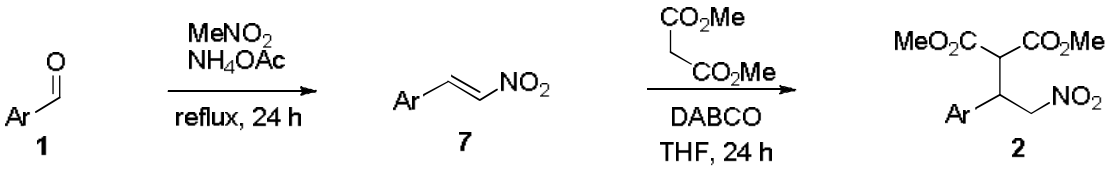
Hybrid material **4, 15** or **16** (the amount used is indicated in the table below) was placed in a 2 mL glass vessel. Dioxane (0.25 mL, 0.4 M) was then added, followed by benzaldehyde (10 µL, 0.1 mmol), nitromethane (27 µL, 0.5 mmol) and dimethylmalonate (57 µL, 0.5 mmol). The reaction mixture was left to stir vigorously at 70ºC during 36 h. The products were analyzed by GC using dodecane as internal standard. Enantiomeric ratios were determined after preparative TLC purification using HPLC on a chiral stationary phase. The attained results are shown in the following table.

HybCat	**2a** yield (%)	**2a** er
4 (12.8 mg, 10 mol%)	78	88:12
15 (12.8 mg, 4 mol%)	65	88:12
16 (12.8 mg, 1 mol%)	1	89:11
15 (34 mg, 10 mol%)	81	88:12
16 (90 mg, 6.5 mol%)	63	88:12

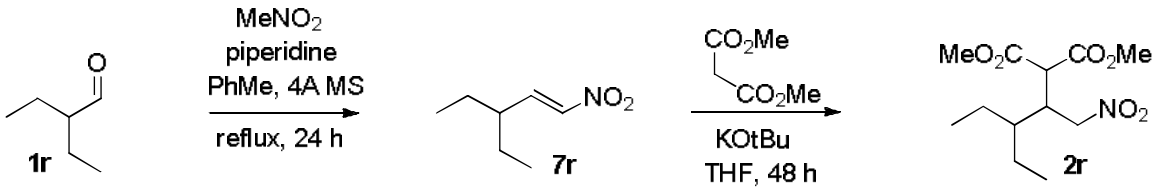
It was observed that when using identical amount of the solid materials (entries 1-3), yield of the desired product was lower for solid materials with lower organic content. In the case of using equal amount of active sites (and therefore varying the amount of catalyst), the two solids with higher organic content performed similarly. Slightly lower yield was achieved for HybCat **16** what should be attributed to employment of only 6.5 mol% catalyst loading. We could conclude from these data, that efficiency is slightly higher for hybrid materials with lower organocatalyst content. The enantioselectivity attained in all the cases is the same.

4. Preparation of the Racemates.

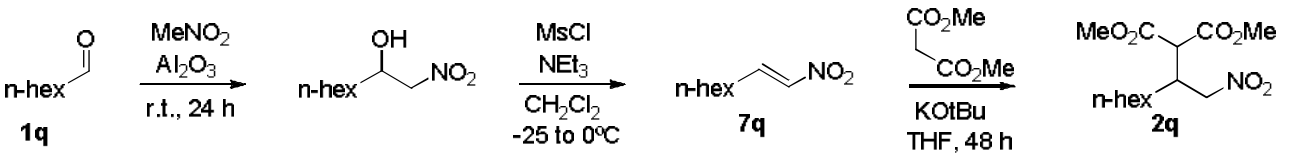
Racemates were prepared according to described procedures in two or three steps sequence.



Michael adducts **2** derived from aromatic aldehydes were prepare in two steps sequence[7-8] when the corresponding nitrostyrene was not commercially available. To a solution of the aryl aldehyde **1** (1 mmol) and nitromethane (7.7 mL) was added ammonium acetate (85 mg, 1.1 mmol). The solution was heated under reflux for 24 h. The reaction mixture was concentrated under reduced pressure and then dissolved in CH_2Cl_2/H_2O (1:1), the organics were extracted into CH_2Cl_2 (x 3), then washed with brine (x 1), dried with magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was submitted subsequently to the next step without further purification. The crude product **7** was dissolved in THF (1 mL) and then it was added dimethylmalonate (0.34 mL, 3 mmol) followed by DABCO (22.4 mg, 0.2 mmol). The mixture was left to stir at room temperature for 24 h. Solvent was then removed under reduced pressure and product purified afterwards by column chromatography using hexane/ethyl acetate as eluent.

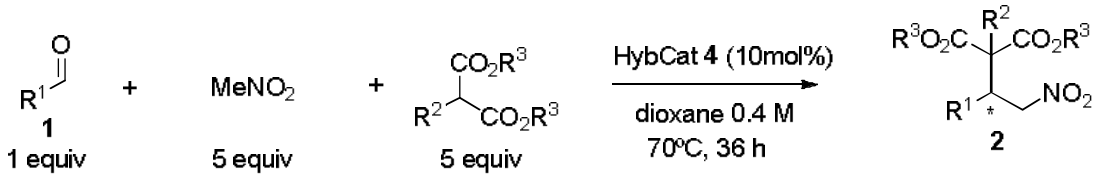


Racemate **2r** was prepared according to the upper scheme in two steps.[8-9] Anhydrous toluene (2.5 mL) was added under N_2 to a round bottom flask containing previously activated 4 Å molecular sieves (1 g). Aldehyde **1r** (135 µL, 1 mmol) was then added followed by nitromethane (54 µL, 1 mmol). A catalytic amount of piperidine was subsequently added (6 µL, 0.06 mmol) and the reaction was kept at reflux for 24 hours. The mixture was then filtered through a plug of celite using CH_2Cl_2 as eluent. After solvent removal, the product **7r** was purified by column chromatography using hexane/ethyl acetate as eluent (90:10) obtaining 85.4 mg (60% yield, 0.6 mmol). The product **7r** was then dissolved in THF (0.6 mL) and then it was added dimethylmalonate (0.20 mL, 1.8 mmol) followed by KO^tBu (3.3 mg, 0.03 mmol). The mixture was left to stir at room temperature for 48 h. The reaction mixture was then diluted with ethyl acetate, washed with HCl 1.0 M aq. (x1) and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product was purified afterwards by column chromatography using hexane/ethyl acetate as eluent (95:5).

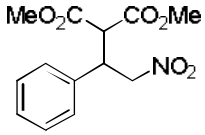


Racemate **2q** was prepared according to the upper scheme in three steps.[8,10] To a solution of the aldehyde **1q** (2.5 mmol) in nitromethane (1.5 mL) was added Al_2O_3 (0.5 g) at room temperature and stirred at the same temperature overnight. The reaction mixture was filtered through a sintered funnel to remove the Al_2O_3 and the filtrate was concentrated under reduced pressure to give the crude nitroalcohol. To a solution of the crude nitroalcohol in dichloromethane (3 mL) was added triethylamine (1.0 mL, 7.5 mmol) and mesyl chloride (0.39 mL, 5.0 mmol) at -25ºC while stirring. The reaction mixture was warmed to 0ºC over the duration of 1.5 h, after which the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with sat. aq. $CuSO_4$ (x 2) and brine (x 1). The organic layer was then dried (magnesium sulfate), filtered and concentrated under reduce pressure. The product **7q** was purified by column chromatography using hexane/ethyl acetate as eluent (90:10). Isolated product **7q** was then dissolved in THF (1.0 mL) and then it was added dimethylmalonate (0.30 mL, 2.66 mmol) followed by KO^tBu (5 mg, 0.04 mmol). The mixture was left to stir at room temperature for 48 h. The reaction mixture was then diluted with ethyl acetate, washed with HCl 1.0 M aq. (x1) and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **2q** was purified afterwards by column chromatography using hexane/ethyl acetate as eluent (95:5).

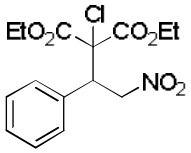
5. General Procedure for the Asymmetric Multicomponent Reaction: Henry Condensation + Asymmetric Michael-Type Addition



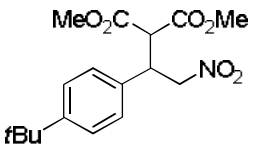
Hybrid material **4** (51.3 mg, 0.04 mmol organocatalyst, 10 mol%) was placed in a 3 mL glass vessel. Dioxane (1.0 mL, 0.4 M) was then added, followed by the corresponding aldehyde (0.4 mmol), nitromethane (108 µL, 2.0 mmol) and the corresponding malonate (0.23 mL, 2.0 mmol for dimethylmalonate and 0.32 mL, 2.0 mmol for diethyl 2-chloromalonate). The vessel was sealed and the reaction mixture was left to stir vigorously at 70ºC for 36 h. It was then left to cool down to room temperature and the catalyst was separated by filtration and washed with ethyl acetate. Volatile components were then removed under reduced pressure and the crude product was purified by column chromatography using hexane/ethyl acetate as eluent. Enantiomeric ratios were determined after column chromatography using HPLC on a chiral stationary phase.



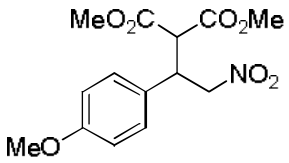
Methyl 2-carbomethoxy-4-nitro-3-phenyl-butyrate (2a): The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2a** as a colorless solid in 75% yield (84 mg, 0.3 mmol) and 88:12 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm, t (mayor) = 12.04 min and t (minor) = 13.31 min]. $[\alpha]_D^{20}$ = +3.86 (c = 1, $CHCl_3$) **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.30 – 7.12 (m, 5H), 4.90 – 4.76 (m, 2H), 4.18 (td, *J* = 8.7, 5.6 Hz, 1H), 3.80 (d, *J* = 9.0 Hz, 1H), 3.70 (s, 3H), 3.50 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 167.9, 167.2, 136.1, 129.0, 128.4, 127.9, 77.2, 54.8, 53.0, 52.8, 42.9. The absolute configuration of **(+)-2a** was determined to be (*S*) by comparing the optical rotation and the HPLC elution with literature data. Lit.[8] $[\alpha]_D^{25}$ = +5.9 (c = 1.02, $CHCl_3$), HPLC analysis: [Daicel chiralcel OD, hexane:isopropanol, 70:30, 0.9 mL/min, λ 220 nm, t (mayor) = 11.6 min, t (minor) = 13.7 min] for the (*S*)-isomer with 96% ee. (Kromasil 5-Cellucoat column is equivalent to Daicel chiralcel OD-H). Lit.[11] $[\alpha]_D^{25}$ = +4.40 (c = 1.02, $CHCl_3$) for the (*S*)-isomer with 93% ee.



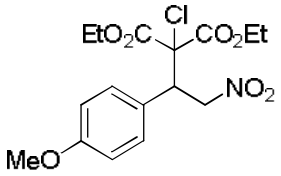
Ethyl 2-carboethoxy-2-chloro-4-nitro-3-phenyl-butyrate (2b): 50ºC and 1 M concentration were used. The crude was purified by column chromatography (hexane/ethylacetate 90/10) to yield **2b** as a colorless solid in 84% yield (116 mg, 0.34 mmol) and 92:8 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm, t (mayor) = 5.51 min and t (minor) = 7.02 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.32-7.23 (m, 5H), 5.16 (dd, *J* = 13.5, 3.4 Hz, 1H), 4.92 (dd, *J* = 13.5, 10.4 Hz, 1H), 4.56 (dd, *J* = 10.4, 3.4 Hz, 1H), 4.32-4.16 (m, 2H), 4.06-3.87 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 166.0, 164.3, 133.5, 129.3, 129.1, 128.7, 77.2, 71.9, 63.7, 63.6, 48.2, 13.7, 13.6.



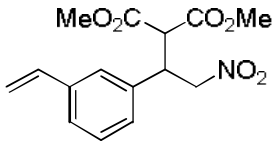
Methyl 2-carbomethoxy-4-nitro-3-(4-*tert*butylphenyl)butyrate (2c): The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2c** as a colorless solid in 71% yield (96 mg, 0.28 mmol) and 90:10 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 70:30, 1mL/min, 220 nm, t (mayor) = 7.32 min and t (minor) = 9.11 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.26-7.22 (m, 2H), 7.08-7.05 (m, 2H), 4.88-4.75 (m, 2H), 4.15 (td, *J* = 8.5, 5.8 Hz, 1H), 3.78 (d, *J* = 8.8 Hz, 1H), 3.67 (s, 3H), 3.48 (s, 3H), 1.20 (s, 9H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 168.0, 167.4, 151.2, 133.0, 127.5, 125.9, 77.4, 54.8, 52.9, 52.8, 42.5, 34.5, 31.2.



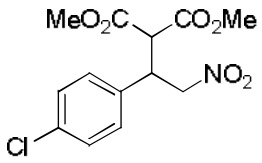
Methyl 2-carbomethoxy-4-nitro-3-(4-methoxyphenyl)butyrate (2d): The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2d** as a colorless solid in 84% yield (105 mg, 0.34 mmol) and 90:10 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm, t (mayor) = 16.02 min and t (minor) = 18.40 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.10-7.05 (m, 2H), 6.80-6.75 (m, 2H), 4.79 (qd, *J* = 13.0, 7.1 Hz, 2H), 4.12 (td, *J* = 9.0, 5.3 Hz, 1H), 3.76 (d, *J* = 9.2 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.51 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 168.0, 167.3, 159.5, 129.0, 127.9, 114.4, 77.2, 55.2, 54.9, 53.0, 52.8, 42.3.



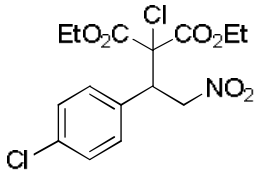
Ethyl 2-carboethoxy-2-chloro-4-nitro-3-(4-methoxyphenyl)butyrate (2e): The reaction was carried out at 50ºC at 1 M concentration (0.4 mL of dioxane). The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2e** as a colorless solid in 93% yield (139 mg, 0.37 mmol) and 90:10 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm, t (mayor) = 7.21 min and t (minor) = 9.07 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.24-7.20 (m, 2H), 6.78-6.73 (m, 2H), 5.14 (dd, *J* = 13.3, 3.4 Hz, 1H), 4.87 (dd, *J* = 13.3, 10.5 Hz, 1H), 4.51 (dd, *J* = 10.5, 3.4 Hz, 1H), 4.31-4.15 (m, 2H), 4.08-3.89 (m, 2H), 3.70 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 166.1, 164.4, 160.0, 130.5, 125.2, 114.1, 77.3, 72.1, 63.6, 63.5, 55.2, 47.6, 13.8, 13.7.



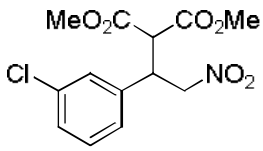
Methyl 2-carbomethoxy-4-nitro-3-(3-vinylphenyl)butyrate (2f): The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2f** as a colorless liquid in 80% yield (99 mg, 0.32 mmol) and 87:13 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm, t (minor) = 12.63 min and t (mayor) = 13.90 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.28-7.14 (m, 3H), 7.06-7.03 (m, 1H), 6.60 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.67 (dd, *J* = 17.6, 0.7 Hz, 1H), 5.20 (dd, *J* = 10.9, 0.5 Hz, 1H), 4.90-4.78 (m, 2H), 4.18 (td, *J* = 8.5, 5.9 Hz, 1H), 3.80 (d, *J* = 8.9 Hz, 1H), 3.69 (s, 3H), 3.50 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 167.8, 167.2, 138.4, 136.5, 136.2, 129.2, 127.0, 126.2, 126.0, 114.8, 77.2, 54.7, 53.0, 52.9, 42.8.



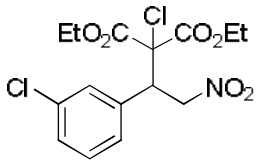
Methyl 2-carbomethoxy-4-nitro-3-(4-chlorophenyl)butyrate (2g): The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2g** as a colorless solid in 75% yield (94.5 mg, 0.30 mmol) and 88:12 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 70:30, 1mL/min, 220 nm, t (mayor) = 10.03 min and t (minor) = 13.34 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.26-7.21 (m, 2H), 7.13-7.08 (m, 2H), 4.84 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.77 (dd, *J* = 13.3, 9.0 Hz, 1H), 4.15 (td, *J* = 9.0, 5.2 Hz, 1H), 3.76 (d, *J* = 9.0 Hz, 1H), 3.69 (s, 3H), 3.51 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 167.6, 167.0, 134.7, 134.4, 129.3, 129.2, 77.2, 54.5, 53.1, 52.9, 42.3.



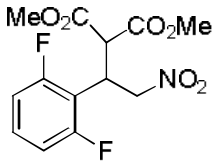
Ethyl 2-carboethoxy-2-chloro-4-nitro-3-(4-chlorophenyl)butyrate (2h): The reaction was carried out at 50ºC at 1 M concentration (0.4 mL of dioxane). The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2h** as a colorless solid in 72% yield (109 mg, 0.29 mmol) and 93:7 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm, t (mayor) = 5.65 min and t (minor) = 8.15 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.28-7.21 (m, 4H), 5.15 (dd, *J* = 13.6, 3.4 Hz, 1H), 4.86 (dd, *J* = 13.5, 10.5 Hz, 1H), 4.54 (dd, *J* = 10.5, 3.4 Hz, 1H), 4.32-4.16 (m, 2H), 4.09-3.91 (m, 2H), 1.22 (t, *J* = 7.0 Hz, 1H), 1.07 (t, *J* = 7.1 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 165.8, 164.2, 135.2, 132.0, 130.7, 129.0, 76.9, 71.6, 63.8, 63.7, 47.6, 13.7.



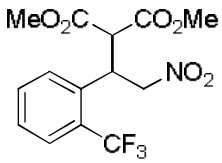
Methyl 2-carbomethoxy-4-nitro-3-(3-chlorophenyl)butyrate (2i): The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2i** as a colorless liquid in 71% yield (89.5 mg, 0.28 mmol) and 88:12 e.r. as determined by HPLC analysis [Kromasil 5-AmyCoat, *n*-hexane/isopropanol = 90:10, 1 mL/min, 220 nm, t (minor) = 17.29 min and t (mayor) = 19.87 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.21-7.16 (m, 3H), 7.08-7.04 (m, 1H), 4.86 (dd, *J* = 13.4, 5.3 Hz, 1H), 4.79 (dd, *J* = 13.4, 8.8 Hz, 1H), 4.16 (td, *J* = 8.8, 5.3 Hz, 1H), 3.76 (d, *J* = 8.8 Hz, 1H), 3.70 (s, 3H), 3.53 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 167.6, 167.0, 138.3, 134.9, 130.3, 128.7, 128.2, 126.1, 76.9, 54.5, 53.1, 53.0, 42.5.



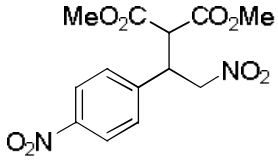
Ethyl 2-carboethoxy-2-chloro-4-nitro-3-(3-chlorophenyl)butyrate (2j): The reaction was carried out at 50ºC at 1 M concentration (0.4 mL of dioxane). The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2j** as a colorless oil in 67% yield (101 mg, 0.27 mmol) and 92:8 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm, t (mayor) = 5.88 min and t (minor) = 7.19 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.29-7.16 (m, 4H), 5.16 (dd, *J* = 13.7, 3.3 Hz, 1H), 4.88 (dd, *J* = 13.7, 10.4 Hz, 1H), 4.54 (dd, *J* = 10.4, 3.3 Hz, 1H), 4.32-4.17 (m, 2H), 4.10-3.94 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 165.8, 164.1, 135.5, 134.5, 130.0, 129.7, 129.3, 127.4, 76.8, 71.5, 63.8, 47.9, 13.7.



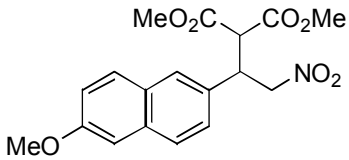
Methyl 2-carbomethoxy-4-nitro-3-(2,6-difluorophenyl)butyrate (2k): The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2k** as a colorless liquid in 73% yield (93 mg, 0.29 mmol) and 89:11 e.r. as determined by HPLC analysis [Kromasil 5-AmyCoat, *n*-hexane/isopropanol = 90:10, 1 mL/min, 220 nm, t (mayor) = 12.04 min and t (minor) = 17.25 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.25-7.15 (m, 1H), 6.82 (t, *J* = 8.5 Hz, 2H), 4.91-4.75 (m, 2H), 4.73-4.65 (m, 1H), 3.90 (d, *J* = 10.2 Hz, 1H), 3.73 (s, 3H), 3.46 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 167.4, 166.8, 163.0 (d, *J* = 8 Hz), 159.2 (d, *J* = 7.6 Hz), 130.6 (t, *J* = 8 Hz), 112.3 (t, *J* = 17 Hz), 112.1-111.8 (m), 75.5 (t, *J* = 3 Hz), 53.2, 52.8, 52.4 (t, *J* = 2 Hz), 33.0.



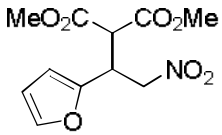
Methyl 2-carbomethoxy-4-nitro-3-(2-trifluoromethylphenyl)butyrate (2l): The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2l** as a colorless liquid in 70% yield (98 mg, 0.28 mmol) and 89:11 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 70:30, 1mL/min, 220 nm, t (mayor) = 6.13 min and t (minor) = 11.18 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.65 (d, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 5.09 (dd, *J* = 13.3, 7.6 Hz, 1H), 4.87 (dd, *J* = 13.3, 4.5 Hz, 1H), 4.58 (td, *J* = 7.5, 4.5 Hz, 1H), 4.04 (d, *J* = 7.4 Hz, 1H), 3.68 (s, 3H), 3.58 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 167.9, 167.1, 135.0, 132.3, 129.1, 128.5, 127.9, 127.2 (q, *J* = 6 Hz), 124.1 (q, *J* = 272 Hz), 76.5, 53.9, 53.0, 38.0.



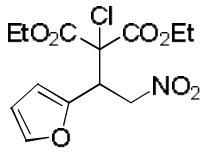
Methyl 2-carbomethoxy-4-nitro-3-(4-nitrophenyl)butyrate (2m): The crude mixture was purified by column chromatography using hexane/ethylacetate (80/20) to yield **2m** as a yellow solid in 76% yield (99 mg, 0.30 mmol) and 85:15 e.r. as determined by HPLC analysis [Chiralcel OJ, *n*-hexane/isopropanol = 60:40, 1.5mL/min, 220 nm, t (mayor) = 23.49 min and t (minor) = 27.80 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 8.15-8.12 (m, 2H), 7.40-7.37 (m, 2H), 4.94-4.81 (m, 2H), 4.30 (td, *J* = 8.6, 5.7 Hz, 1H), 3.81 (d, *J* = 8.8 Hz, 1H), 3.71 (s, 3H), 3.54 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 167.3, 166.8, 147.9, 143.5, 129.1, 124.2, 76.7, 54.1, 53.3, 53.2, 42.5.



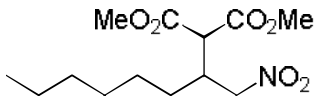
Methyl 2-carbomethoxy-4-nitro-3-(6-methoxy-2-naphthyl)butyrate (2n): The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2n** as a colorless solid in 82% yield (119 mg, 0.33 mmol) and 87:13 e.r. as determined by HPLC analysis [Chiralcel OJ, *n*-hexane/isopropanol = 40:60, 1.5mL/min, 220 nm, t (minor) = 22.97 min and t (mayor) = 28.63 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.60 (dd, *J* = 8.7, 4.2 Hz, 2H), 7.53 (d, *J* = 1.6 Hz, 1H), 7.21 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.05 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.00 (d, *J* = 2.5 Hz, 1H), 4.92-4.87 (m, 2H), 4.30 (dt, *J* = 7.7, 7.1 Hz, 1H), 3.87 (d, *J* = 9.1 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.43 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 167.9, 167.3, 158.1, 134.3, 131.1, 129.4, 128.8, 127.7, 127.1, 125.7, 119.4, 105.6, 77.5, 55.3, 54.9, 53.0, 52.8, 43.0.



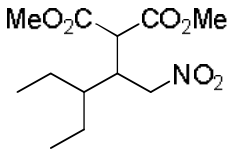
Methyl 2-carbomethoxy-4-nitro-3-(2-furyl)butyrate (2o): The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2o** as a yellow liquid in 71% yield (77 mg, 0.28 mmol) and 91:9 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 70:30, 1mL/min, 220 nm, t (mayor) = 6.98 min and t (minor) = 15.17 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.28 (dd, *J* = 1.9, 0.7 Hz, 1H), 6.22 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.15 (d, *J* = 3.3 Hz, 1H), 4.89-4.79 (m, 2H), 4.32 (td, *J* = 7.8, 5.4 Hz, 1H), 3.87 (d, *J* = 7.8 Hz, 1H), 3.69 (s, 3H), 3.62 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 167.5, 167.2, 149.4, 142.9, 110.6, 108.4, 75.3, 53.1, 53.0, 52.7, 36.8.



Ethyl 2-carboethoxy-2-chloro-4-nitro-3-(2-furyl)butyrate (2p): The reaction was carried out at 50ºC at 1 M concentration (0.4 mL of dioxane). The crude mixture was purified by column chromatography using hexane/ethylacetate (90/10) to yield **2p** as a colorless oil in 93% yield (124 mg, 0.37 mmol) and 92:8 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm, t (mayor) = 5.49 min and t (minor) = 7.84 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 7.29 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.30-6.28 (m, 1H), 6.25 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.04 (dd, *J* = 13.6, 3.4 Hz, 1H), 4.91 (dd, *J* = 13.6, 9.9 Hz, 1H), 4.74 (dd, *J* = 9.9, 3.3 Hz, 1H), 4.32-4.08 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 5.7 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 165.5, 164.5, 147.1, 143.3, 140.7, 75.0, 70.5, 63.8, 43.3, 13.8, 13.7.

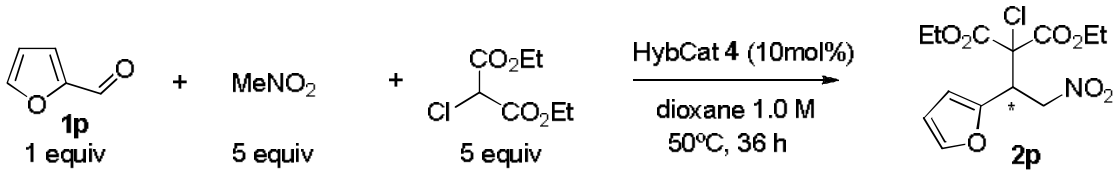


Methyl 2-carbomethoxy-4-nitro-3-hexylbutyrate (2q): The reaction was carried out in toluene as solvent during 48 h. The crude mixture was purified by column chromatography using hexane/ethylacetate (95/5) to yield **2q** as a colorless liquid in 41% yield (47 mg, 0.16 mmol) and 72:28 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 90:10, 1mL/min, 220 nm, t (mayor) = 5.67 min and t (minor) = 9.79 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 4.64 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.46 (dd, *J* = 13.4, 6.7 Hz, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.69 (d, *J* = 5.8 Hz, 1H), 2.88-2.77 (m, 1H), 1.40-1.20 (m, 10H), 0.81 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 168.4, 168.2, 76.5, 52.8, 52.7, 52.3, 37.0, 31.5, 30.0, 28.9, 26.5, 22.5, 14.0.



Methyl 2-carbomethoxy-4-nitro-3-(1-ethylpropyl)butyrate (2r): The reaction was carried out in toluene as solvent during 48 h. The crude mixture was purified by column chromatography using hexane/ethylacetate (95/5) to yield **2r** as a colorless liquid in 47% yield (52.1 mg, 0.19 mmol) and 76:24 e.r. as determined by HPLC analysis [Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 90:10, 1mL/min, 220 nm, t (mayor) = 5.60 min and t (minor) = 10.20 min]. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 4.63 (dd, *J* = 14.2, 5.2 Hz, 1H), 4.49 (dd, *J* = 14.2, 6.2 Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 3.60 (d, *J* = 6.0 Hz, 1H), 3.15-3.09 (m, 1H), 1.29-1.18 (m, 5H), 0.85 (dt, *J* = 11.1, 7.1 Hz, 6H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 168.7, 168.6, 75.1, 52.9, 52.7, 51.2, 42.7, 38.4, 22.7, 22.4, 11.9, 11.4.

6. Catalyst reuse in the Asymmetric Multicomponent Reaction: Henry Condensation + Asymmetric Michael-Type Addition



Hybrid material **4** (25.6 mg, 0.02 mmol organocatalyst, 10 mol%) was placed in a 2 mL glass vessel. Dioxane (0.2 mL, 1.0 M) was then added, followed by furfural (17 µL, 0.2 mmol), nitromethane (54 µL, 1.0 mmol) and diethyl 2-chloromalonate (162 µL, 1.0 mmo). The vessel was sealed and the reaction mixture was left to stir vigorously at 50ºC for 36 h. It was then left to cool down to room temperature and the catalyst was separated by centrifugation and washed with ethyl acetate. Volatile components were then removed under reduced pressure and the crude product was analyzed by ^{1}H NMR using Ph_3CH as internal standard. Enantiomeric ratio was determined after preparative TLC purification using HPLC on a chiral stationary phase.

The hybrid solid was further successively washed with EtOH, H_2O and Et_2O, and dried at 50ºC for 2 hours before submitting it to the next run. The resulting recovered catalyst was weighed and the next reaction was run using amounts of solvent and reactant proportional to the recovered catalyst amount to maintain the same substrate/catalyst ratio and substrate concentration.

The attained results are shown in the following table.

run	yield (%)	er
run 1	90	93:7
run 2	93	91:9
run 3	85	93:7
run 4	54	92:8
run 5	18	91:9

The solid catalyst was analyzed by elemental analysis after each run, and the data is shown in Table S12. These data showcased degradation and/or leaching of the organocatalyst which ultimately affects catalyst performance.

Sample	N%	C%	H%	S%	C/N
HybCat **4** pristine	5.484	28.801	3.498	0.000	6.1
HybCat **4** after run1	4.112	20.017	2.927	0.000	5.7
HybCat **4** after run2	3.761	18.440	2.683	0.000	5.7
HybCat **4** after run3	3.341	18.452	2.550	0.000	6.4
HybCat **4** after run5	2.859	14.806	2.330	0.000	5.7

Table S12. Crude data from elemental analyses of the hybrid material **4**.

7. ^{1}H, ^{13}C, ^{19}F and ^{29}Si NMR Spectra:

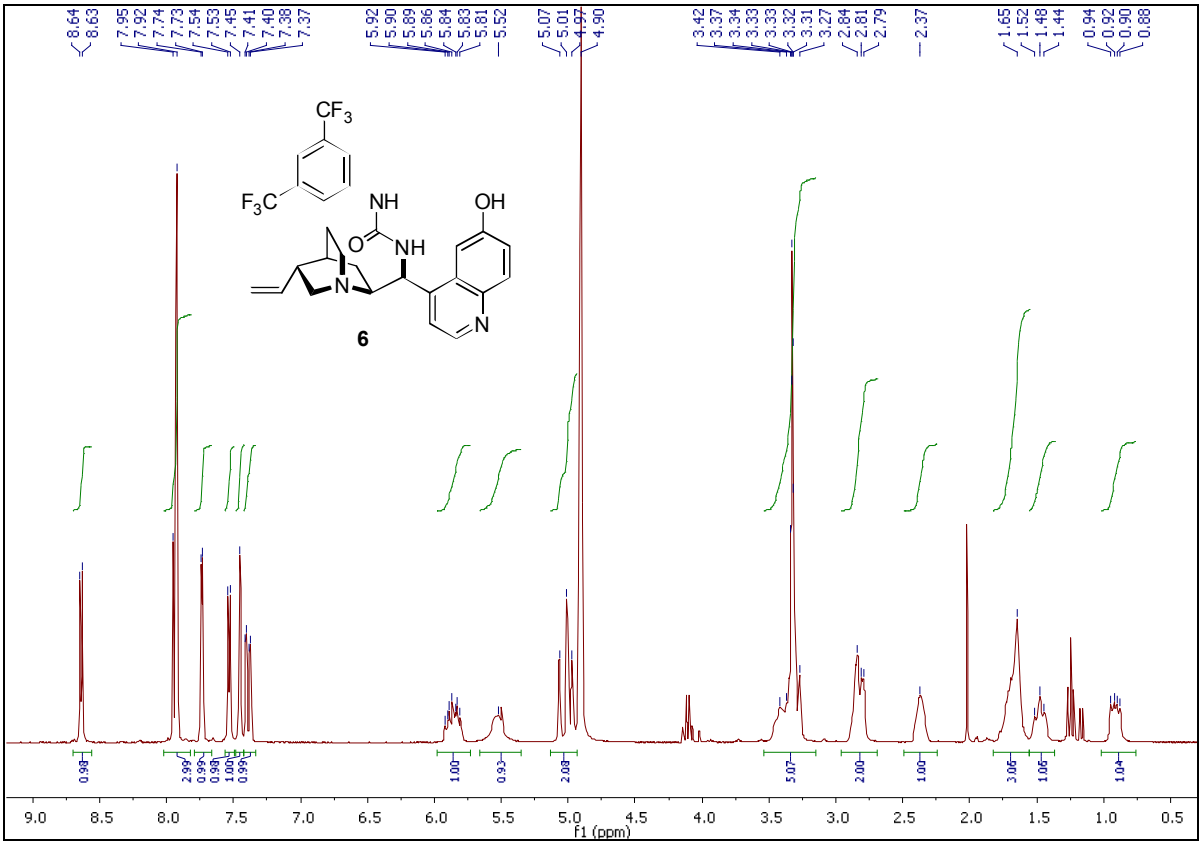


Figure S18. ^{1}H NMR (300 MHz, MeOH-d_4)

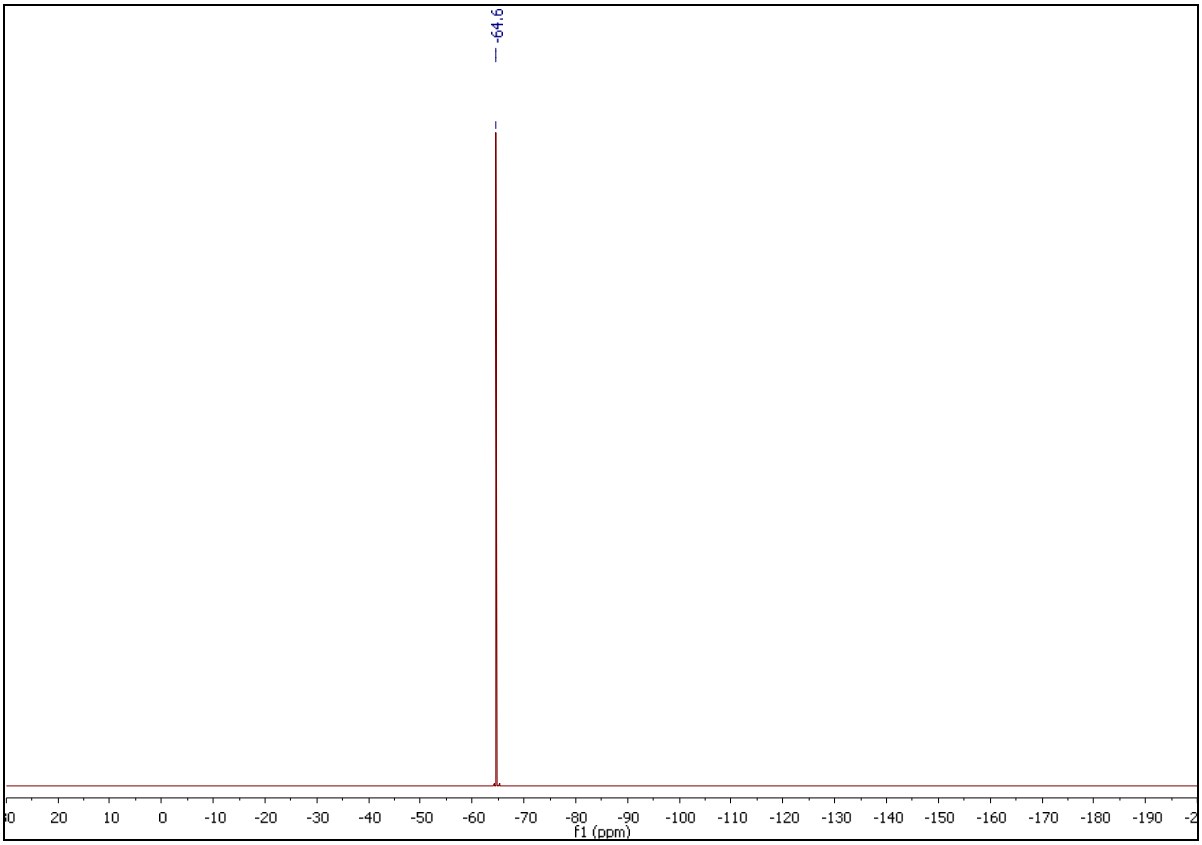


Figure S19. ^{19}F NMR (300 MHz, MeOH-d_4)

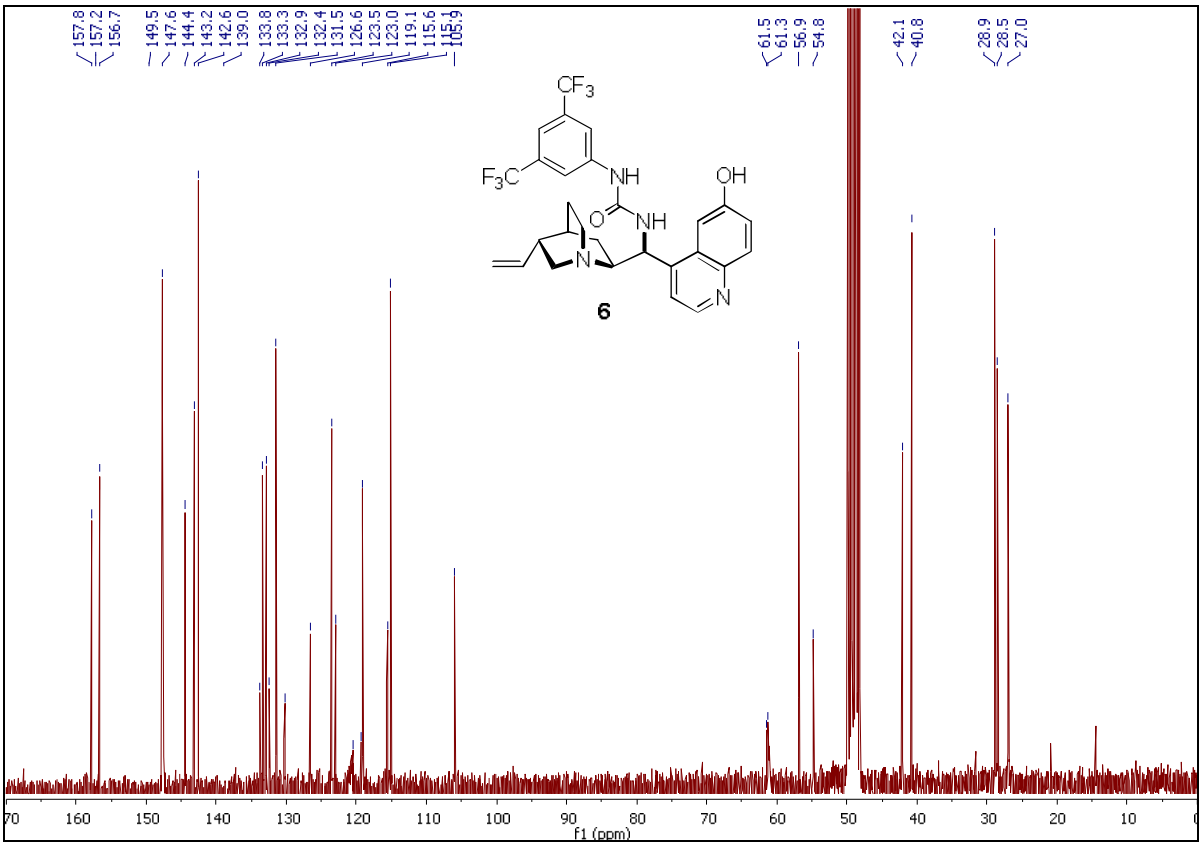


Figure S20. ^{13}C NMR (75 MHz, MeOH-d_4)

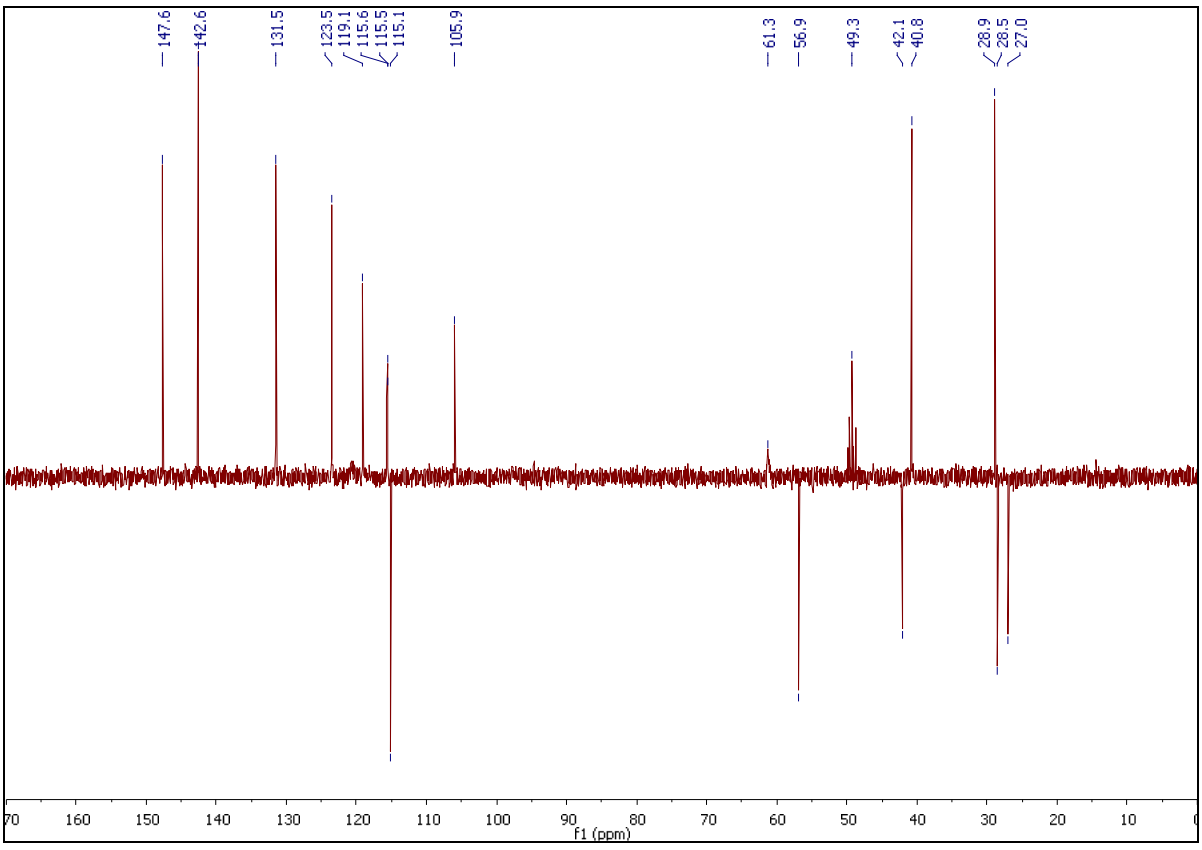


Figure S21. ^{13}C DEPT NMR (75 MHz, MeOH-d_4)

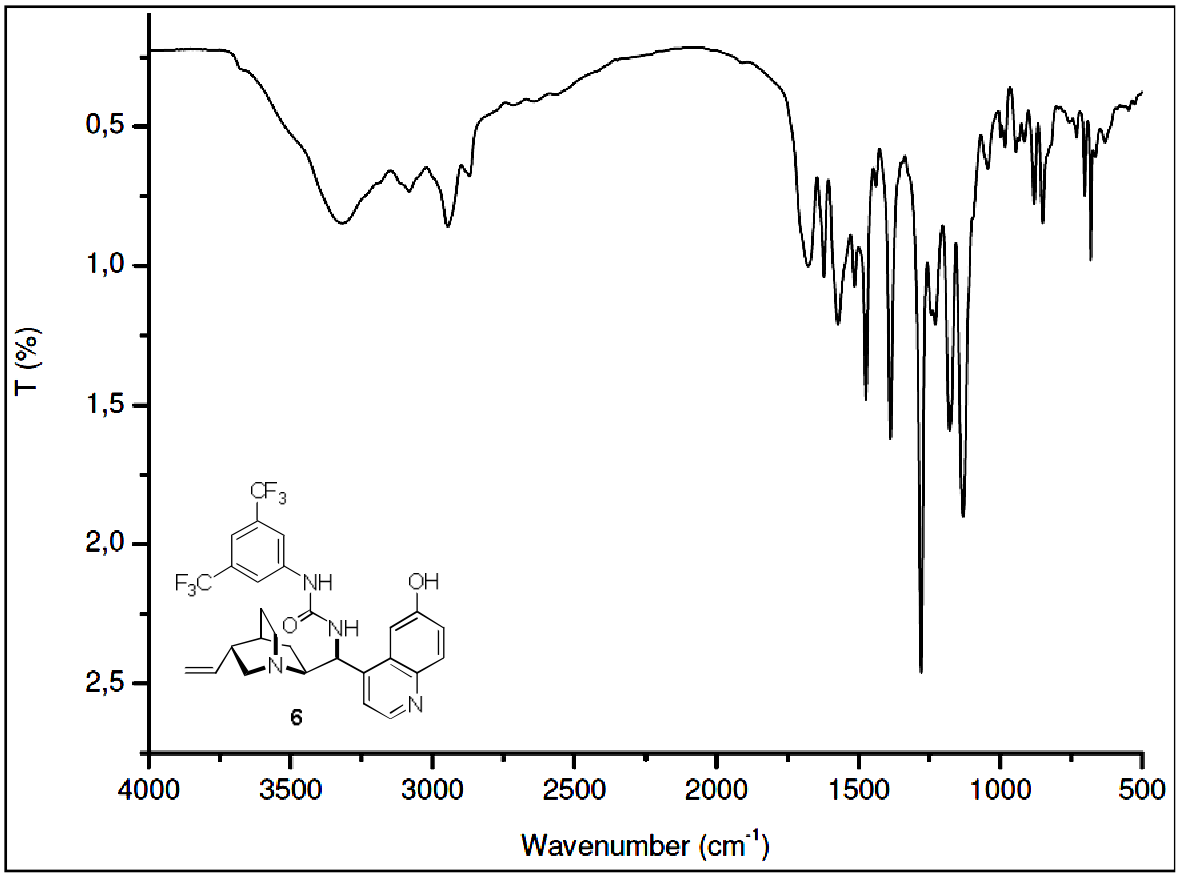


Figure S22. FTIR spectrum.

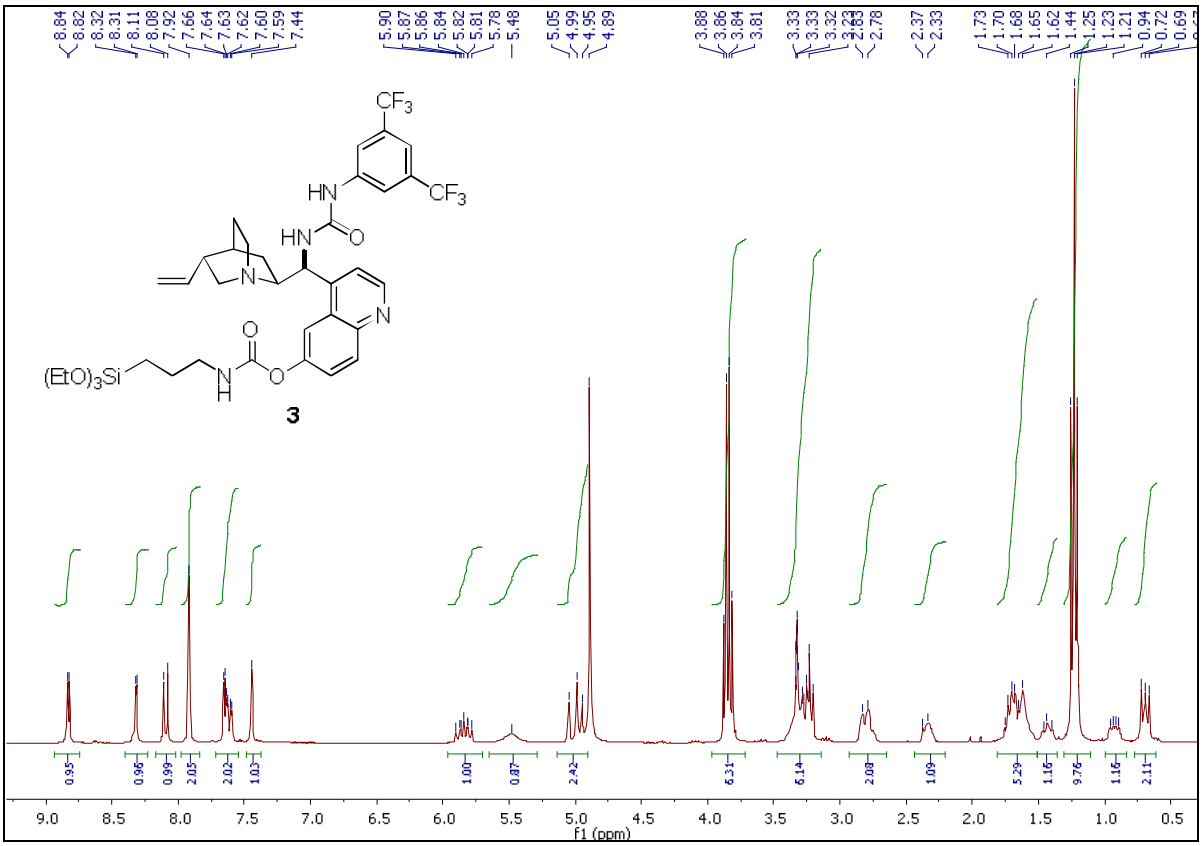


Figure S23. ^{1}H NMR (300 MHz, MeOH-d_4)

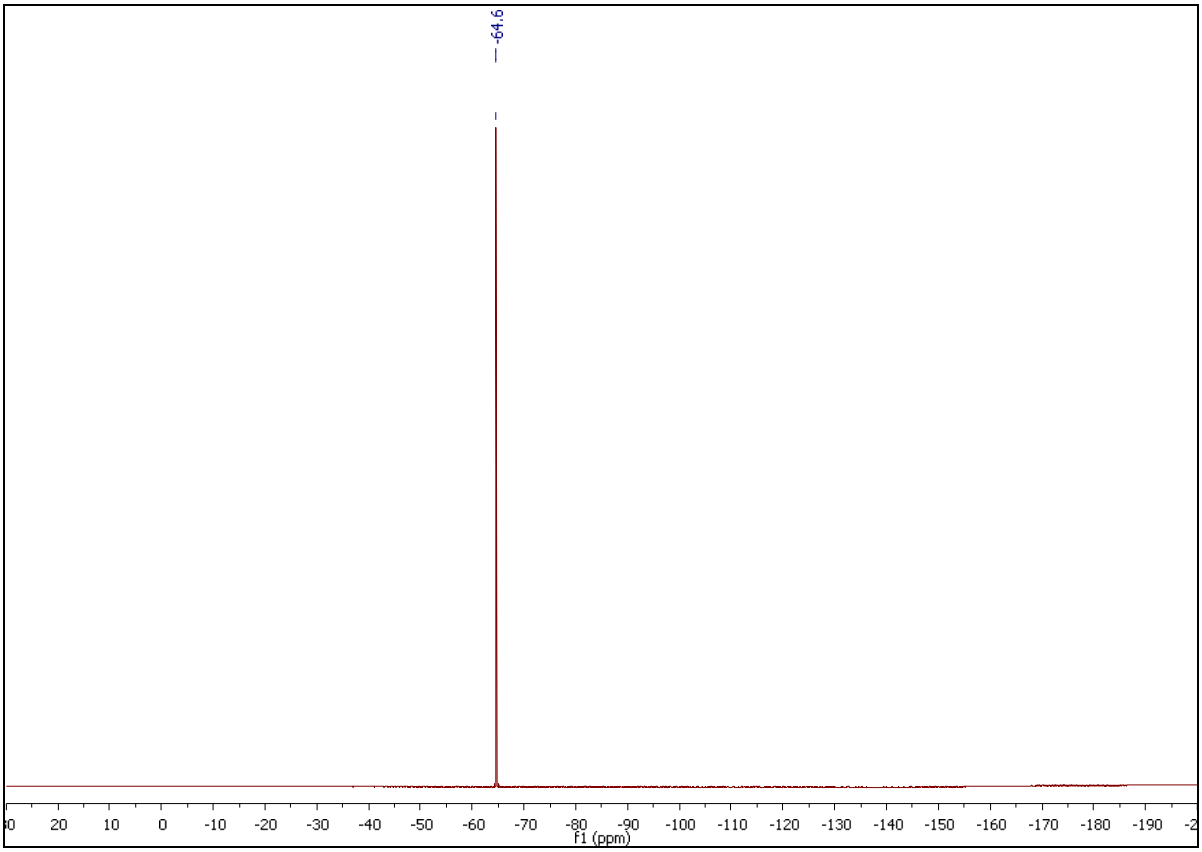


Figure S24. ^{19}F NMR (300 MHz, MeOH-d_4)

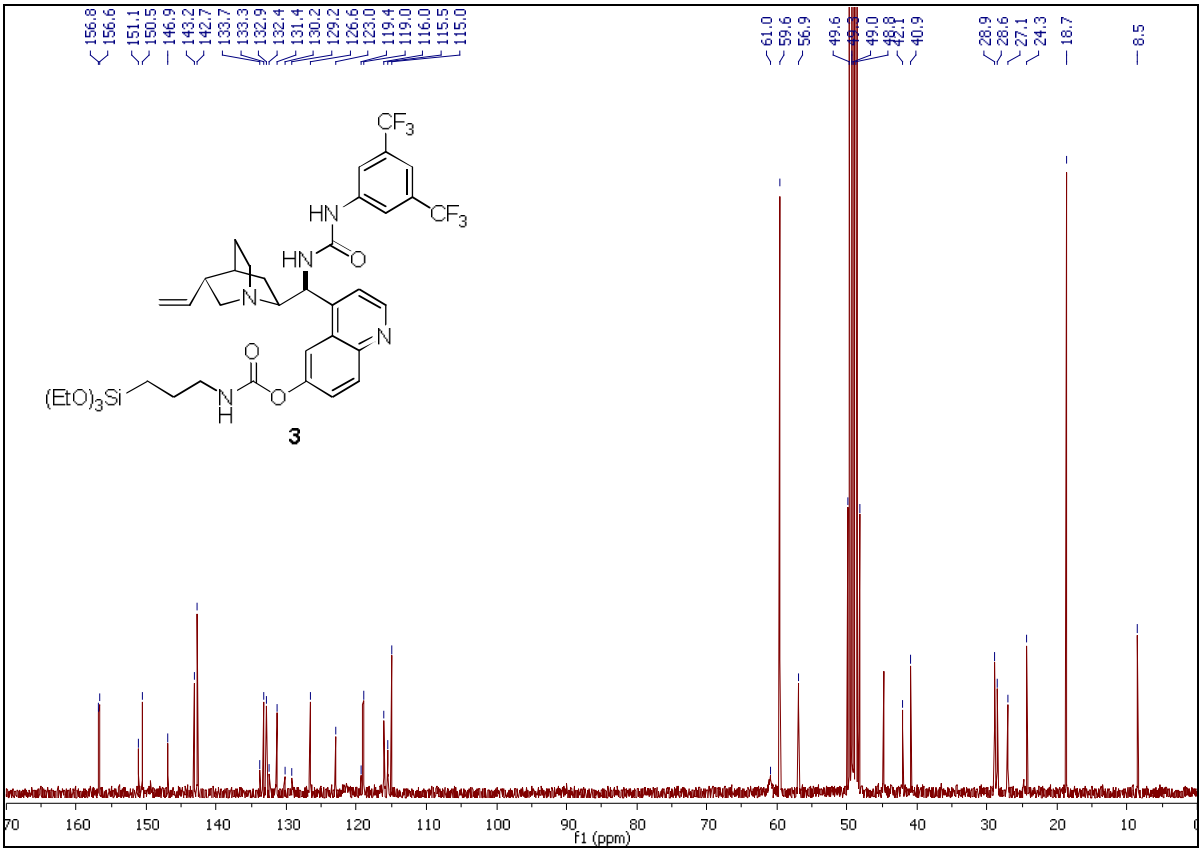


Figure S25. ^{13}C NMR (75 MHz, MeOH-d_4)

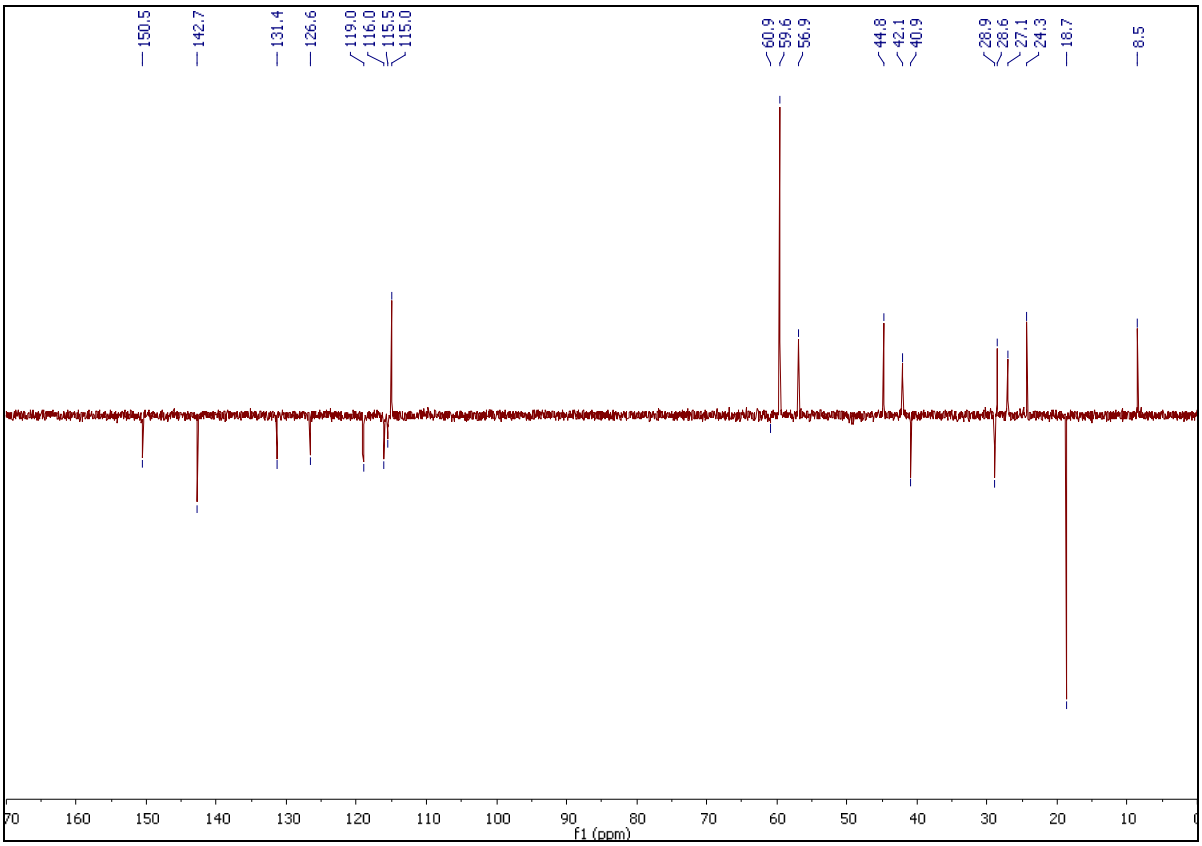


Figure S26. ^{13}C DEPT NMR (75 MHz, MeOH-d_4)

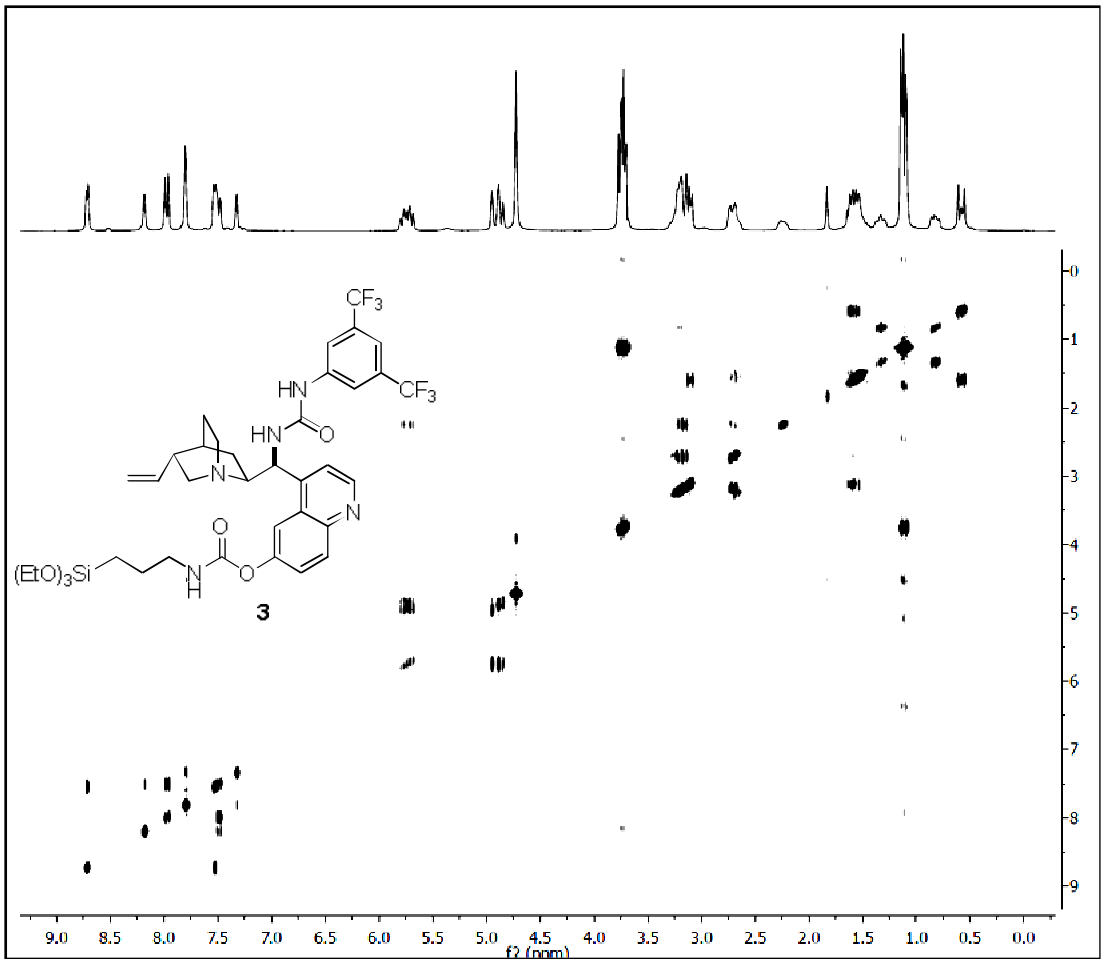


Figure S27. COSY NMR (MeOH-d_4)

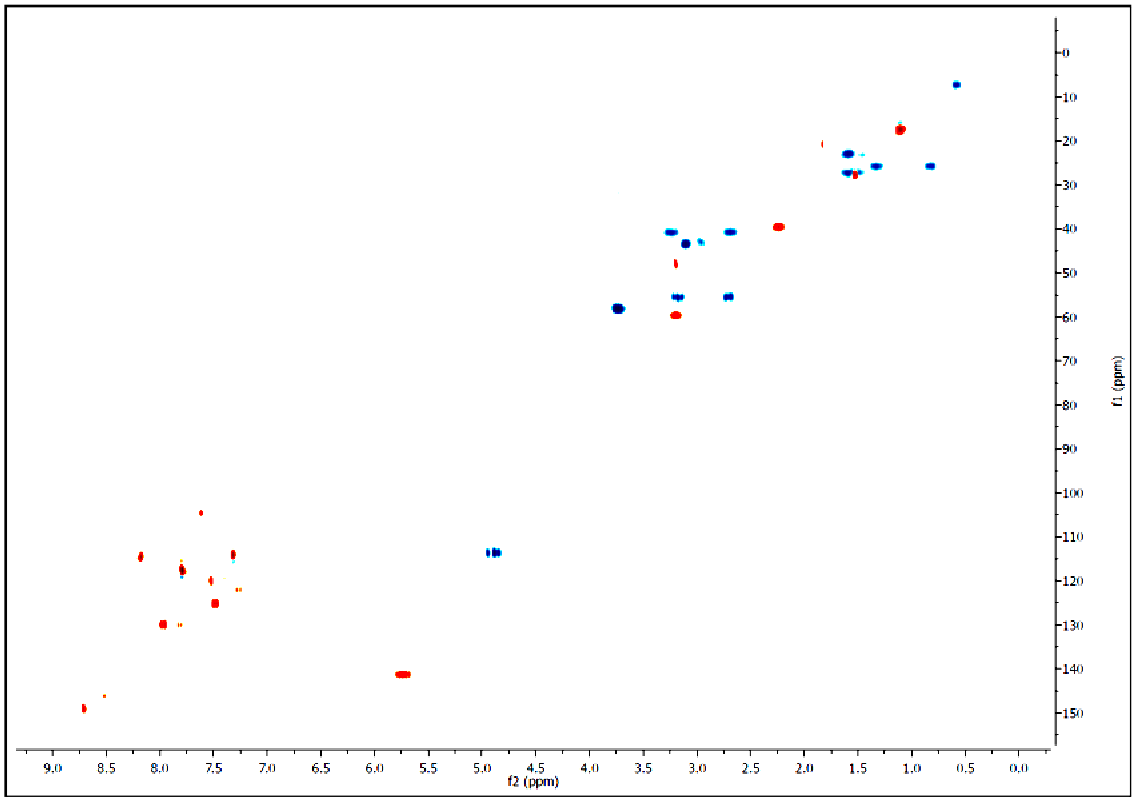


Figure S28. HSQC NMR (MeOH-d_4)

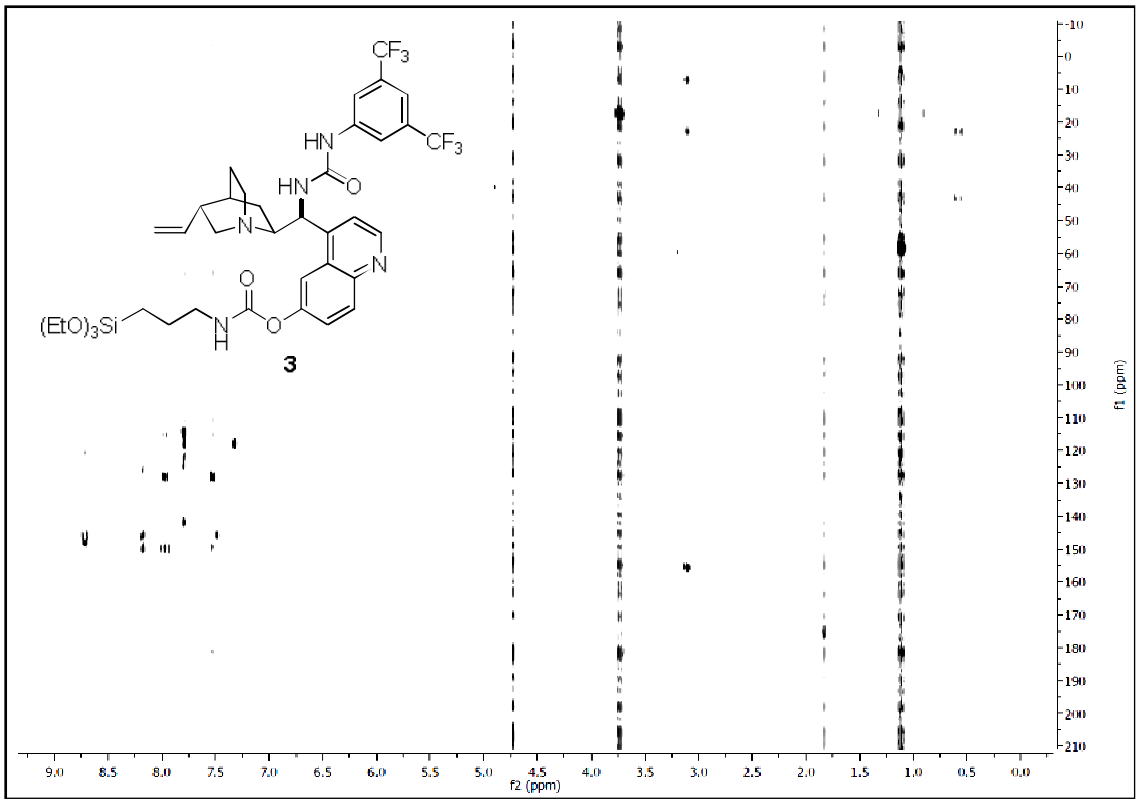


Figure S29. HMBC NMR (MeOH-d_4)

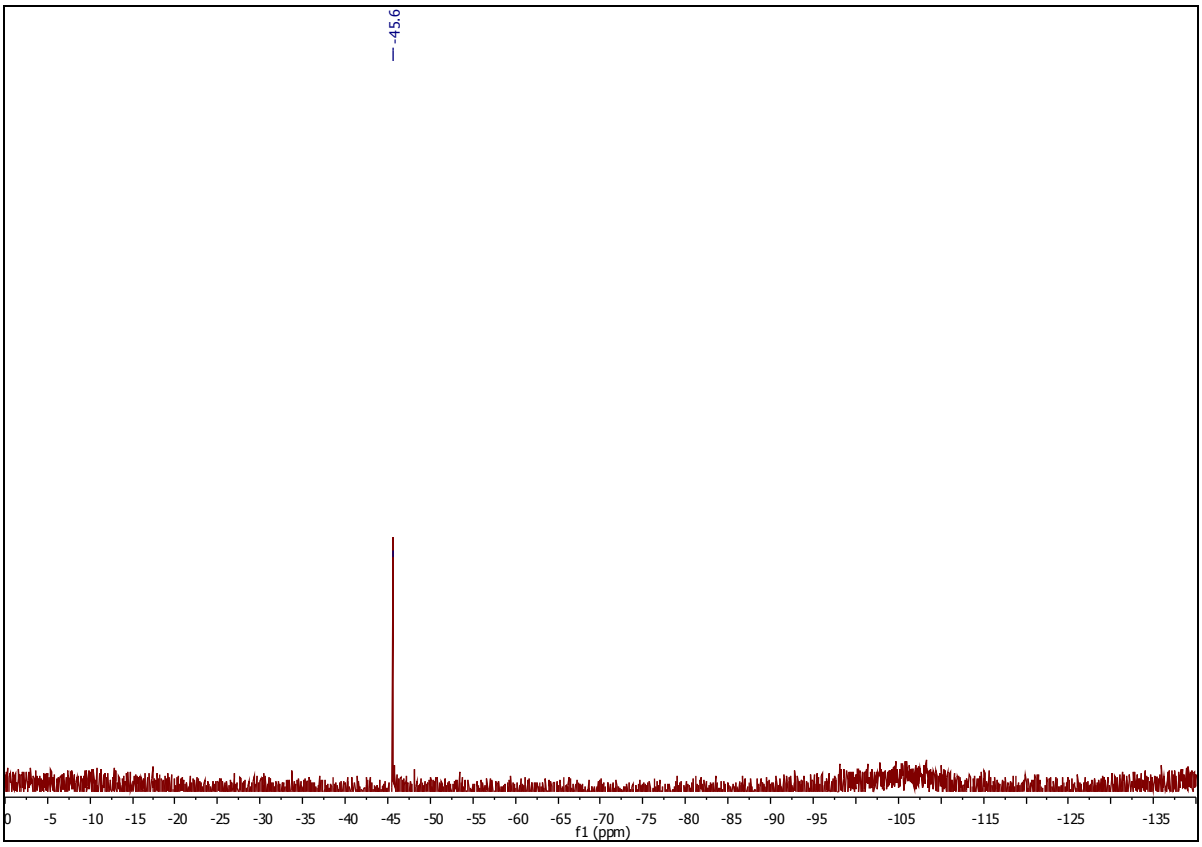


Figure S30. ^{29}Si NMR (60 MHz, MeOH-d_4)

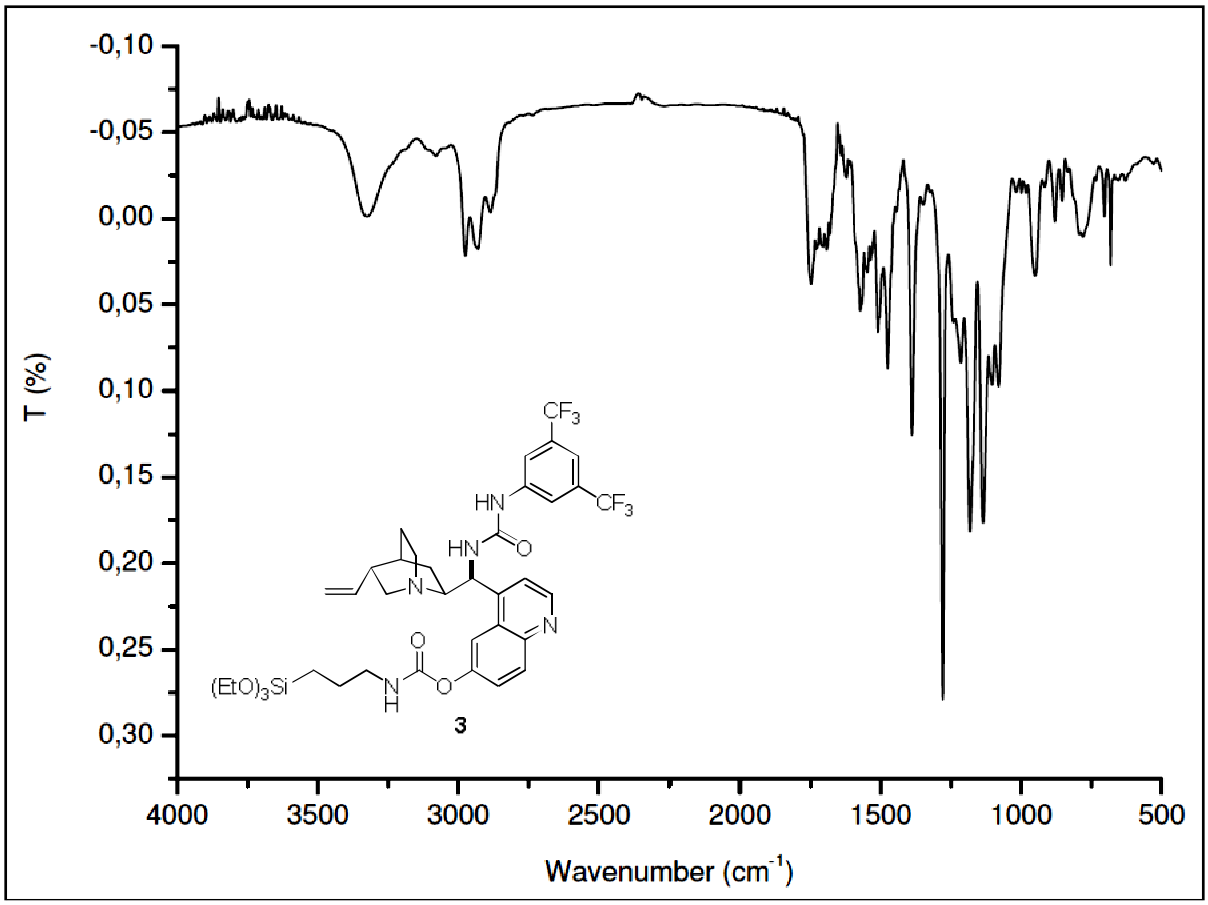


Figure S31. FTIR spectrum.

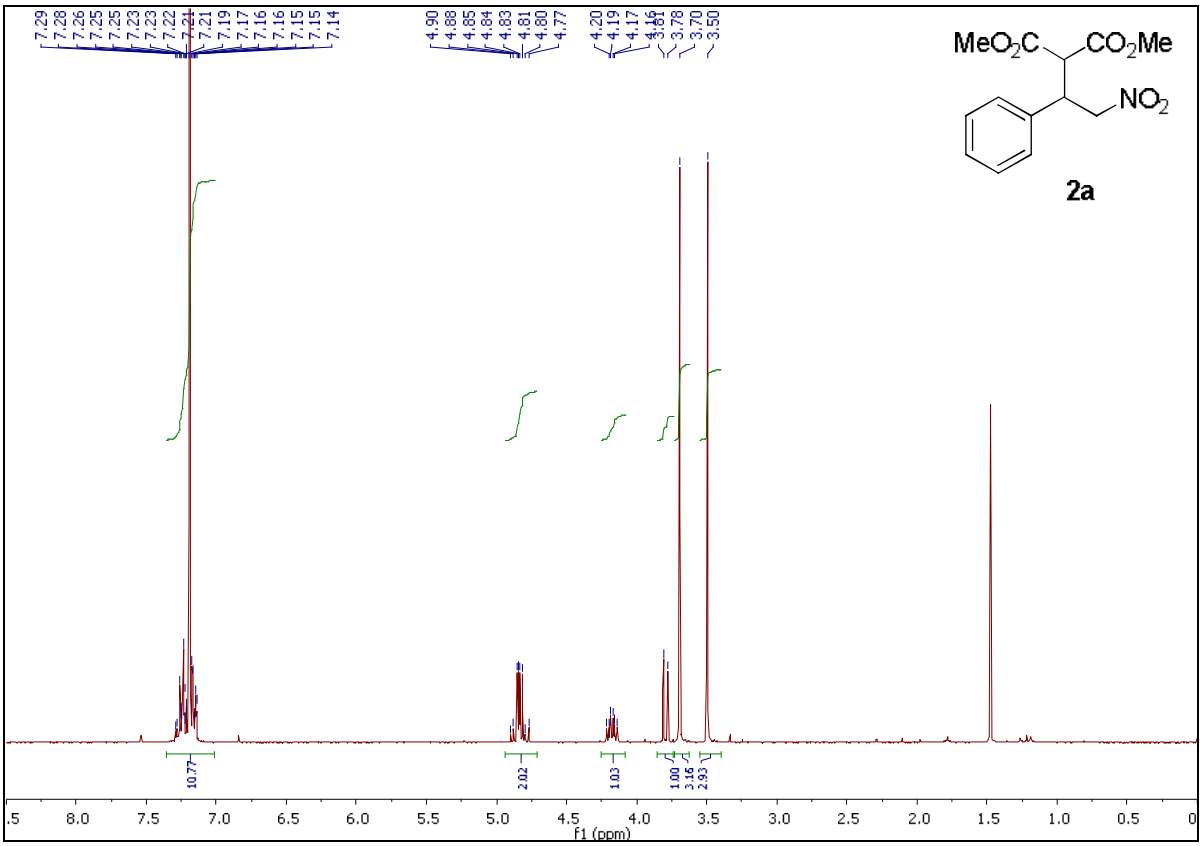


Figure S32. ^{1}H NMR (300 MHz, $CDCl_3$)

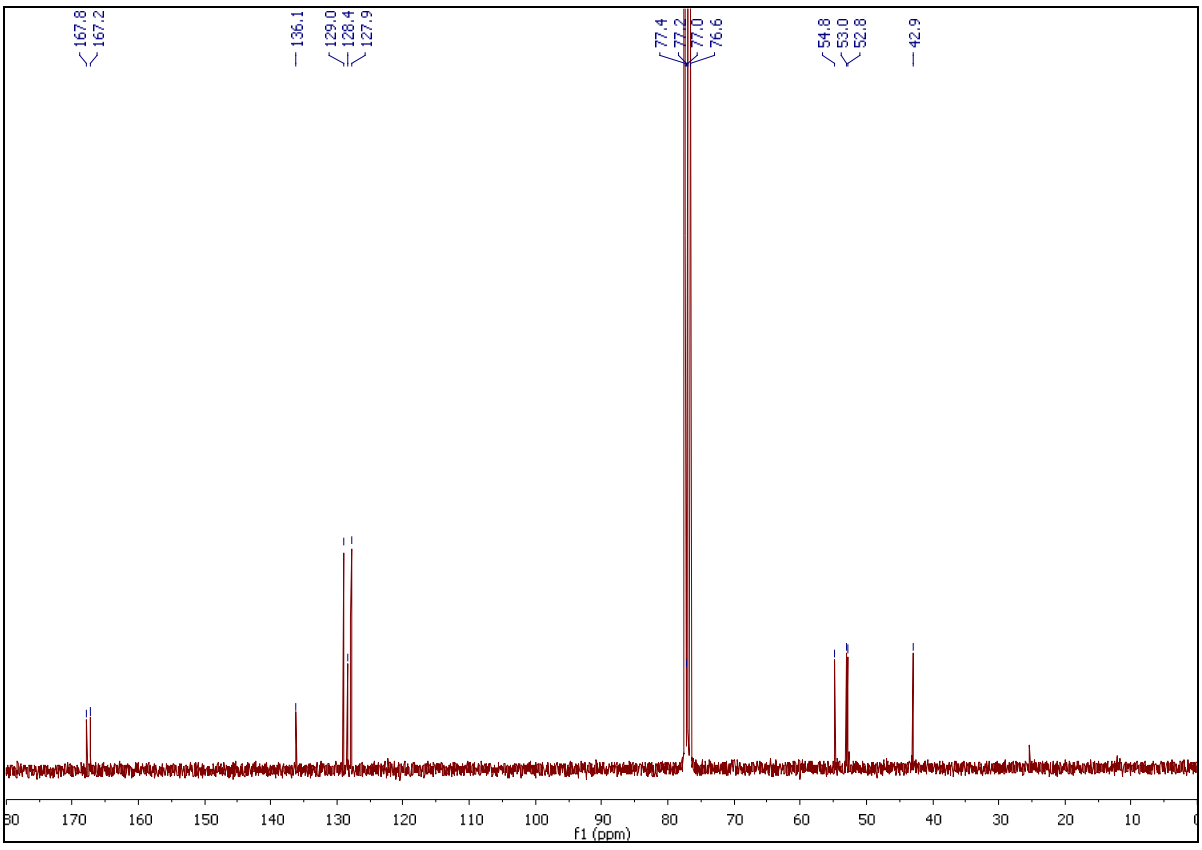


Figure S33. ^{13}C NMR (75 MHz, $CDCl_3$)

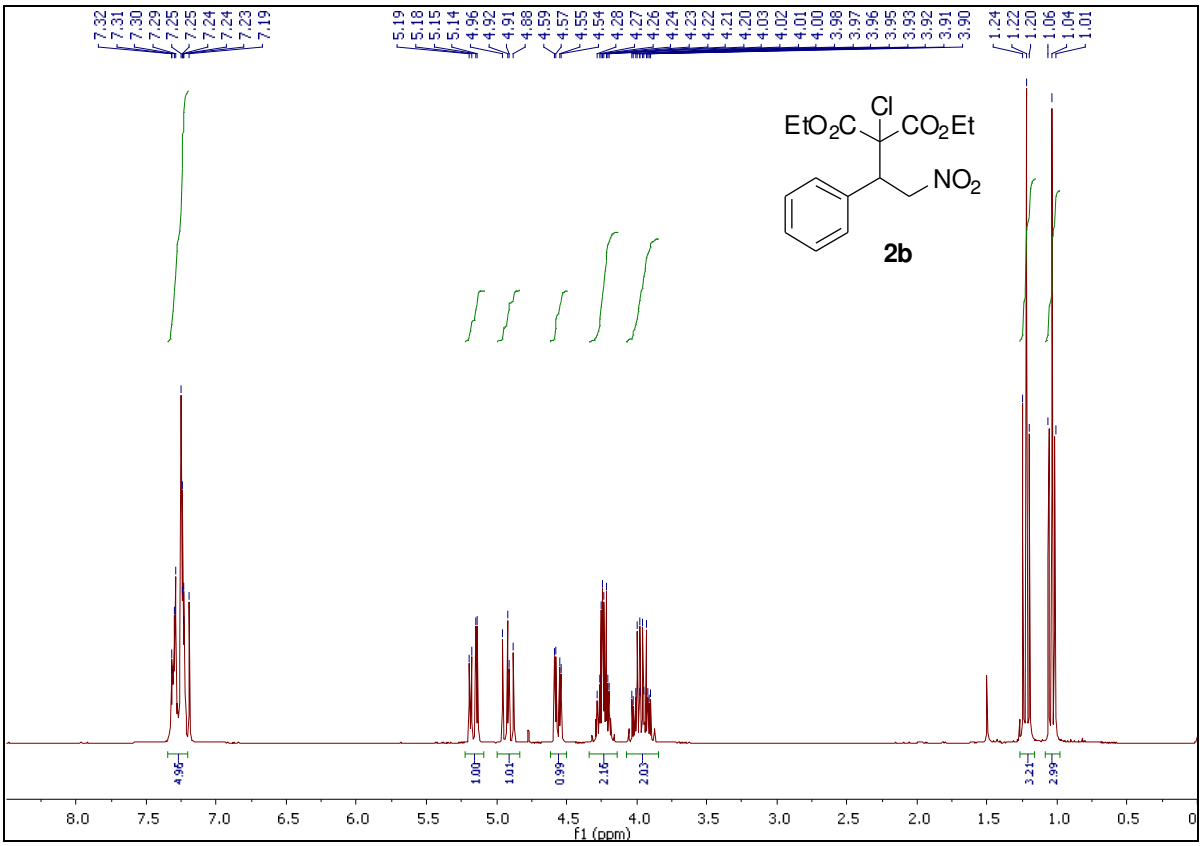


Figure S34. ^{1}H NMR (300 MHz, $CDCl_3$)

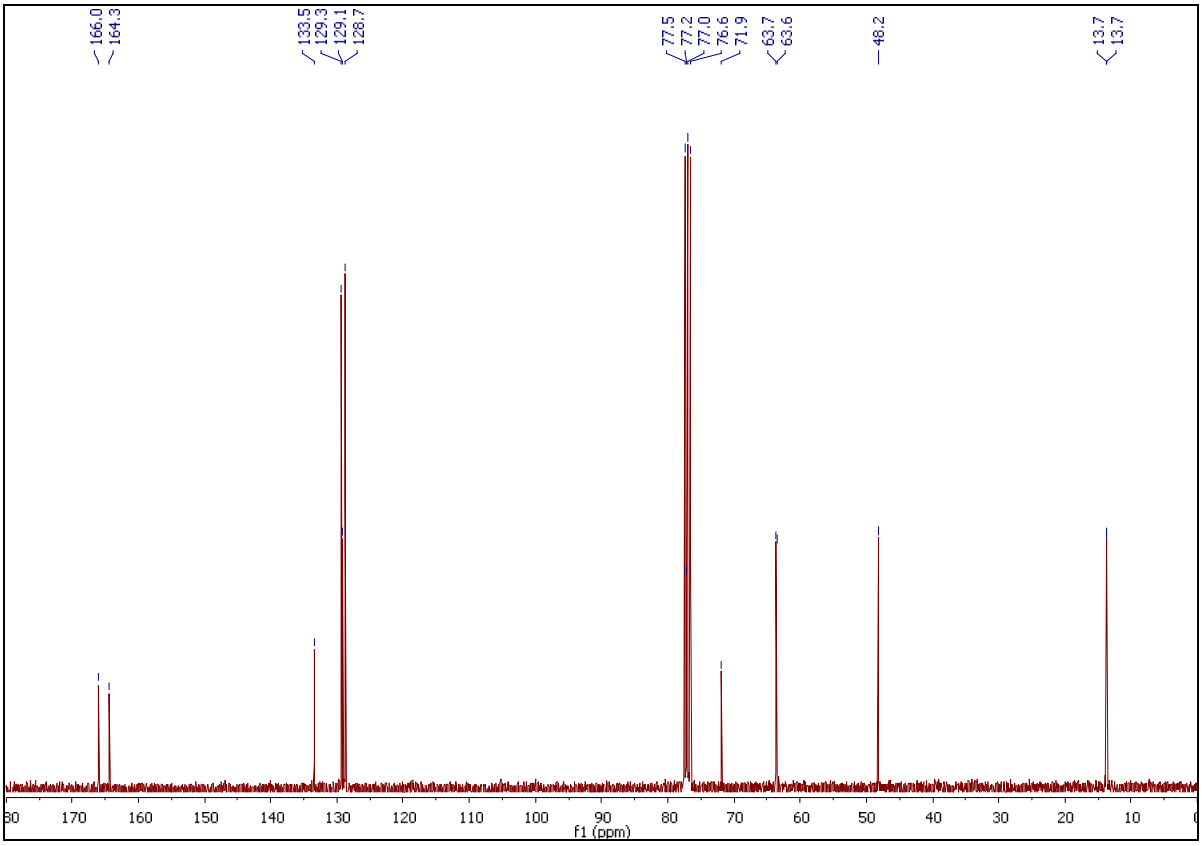


Figure S35. ^{13}C NMR (75 MHz, $CDCl_3$)

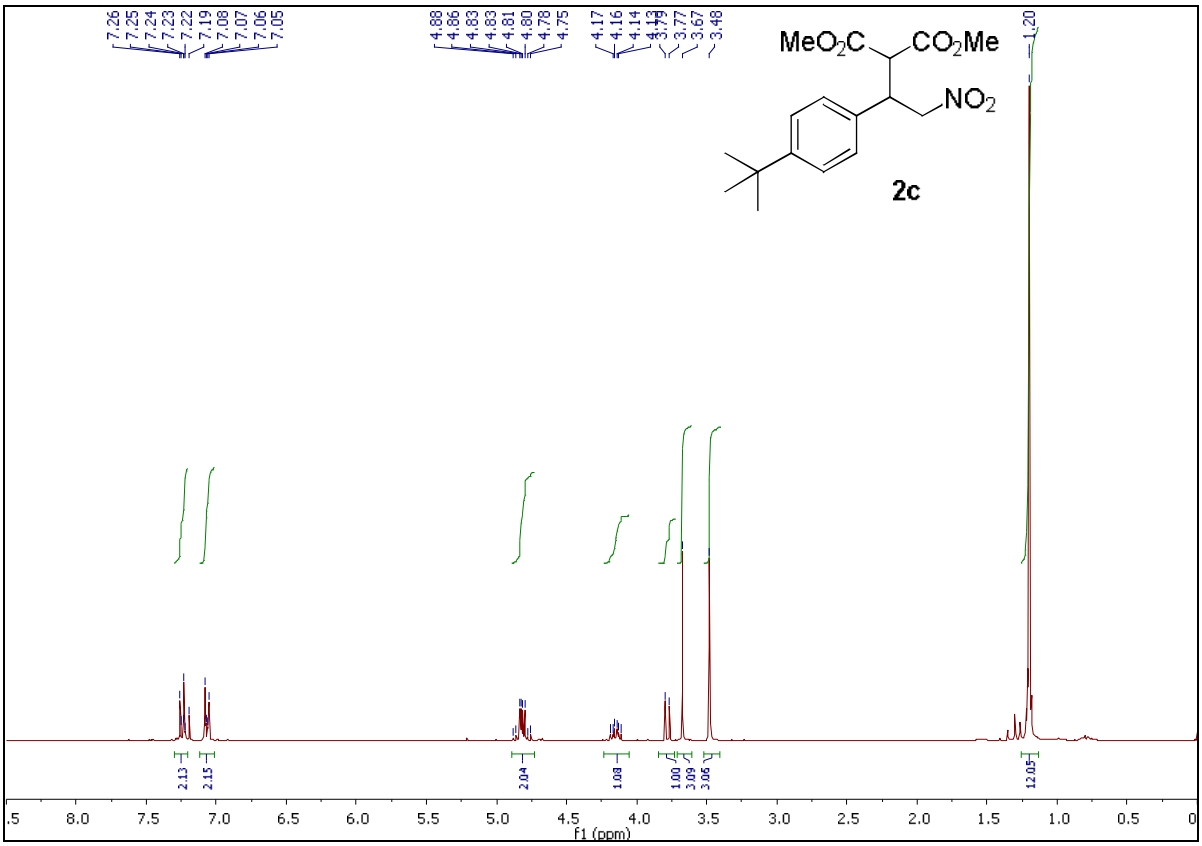


Figure S36. ^{1}H NMR (300 MHz, $CDCl_3$)

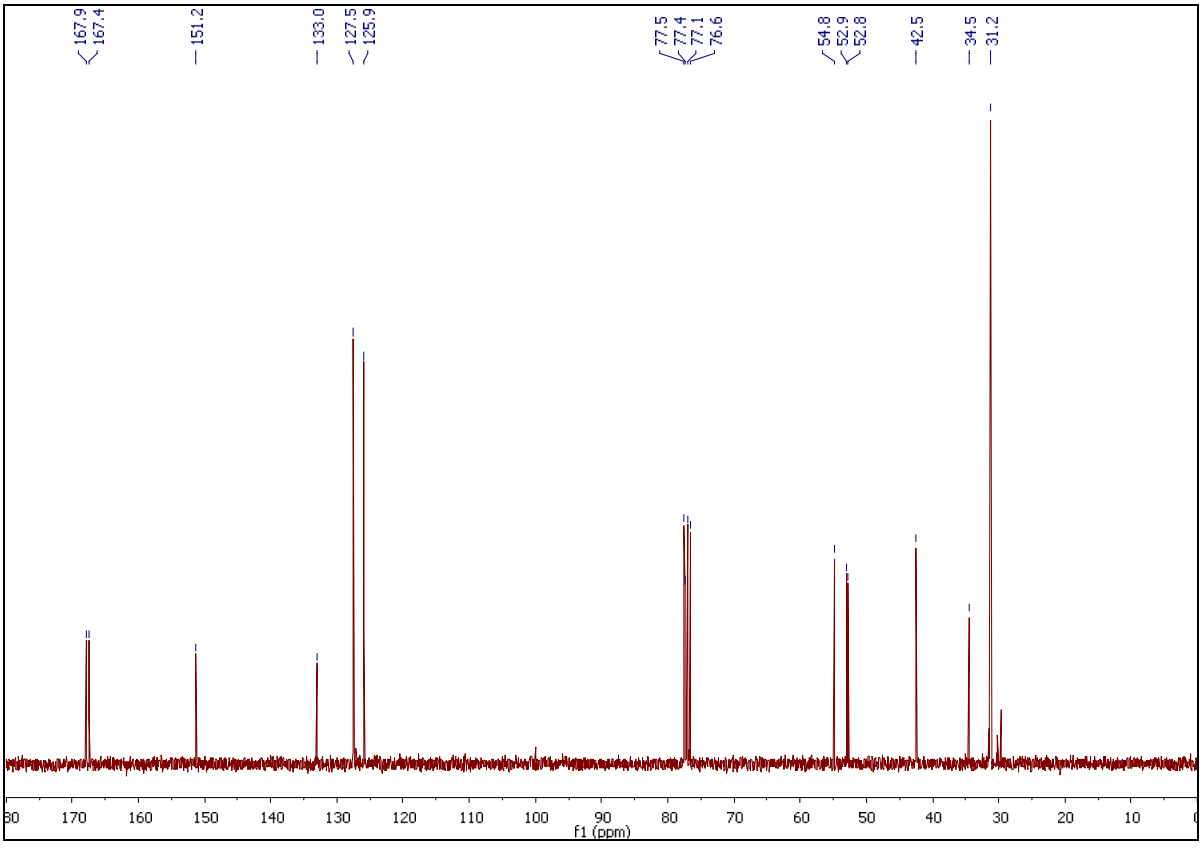


Figure S37. ^{13}C NMR (75 MHz, $CDCl_3$)

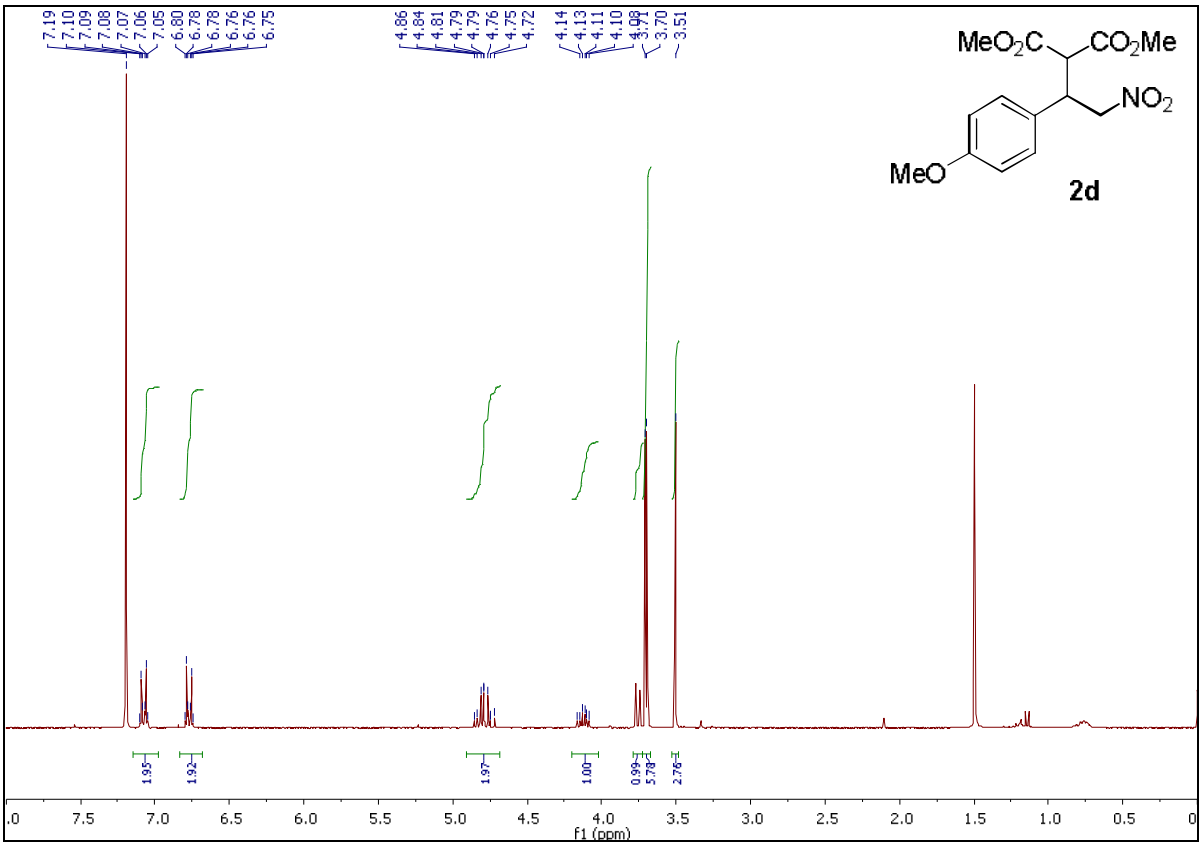


Figure S38. ^{1}H NMR (300 MHz, $CDCl_3$)

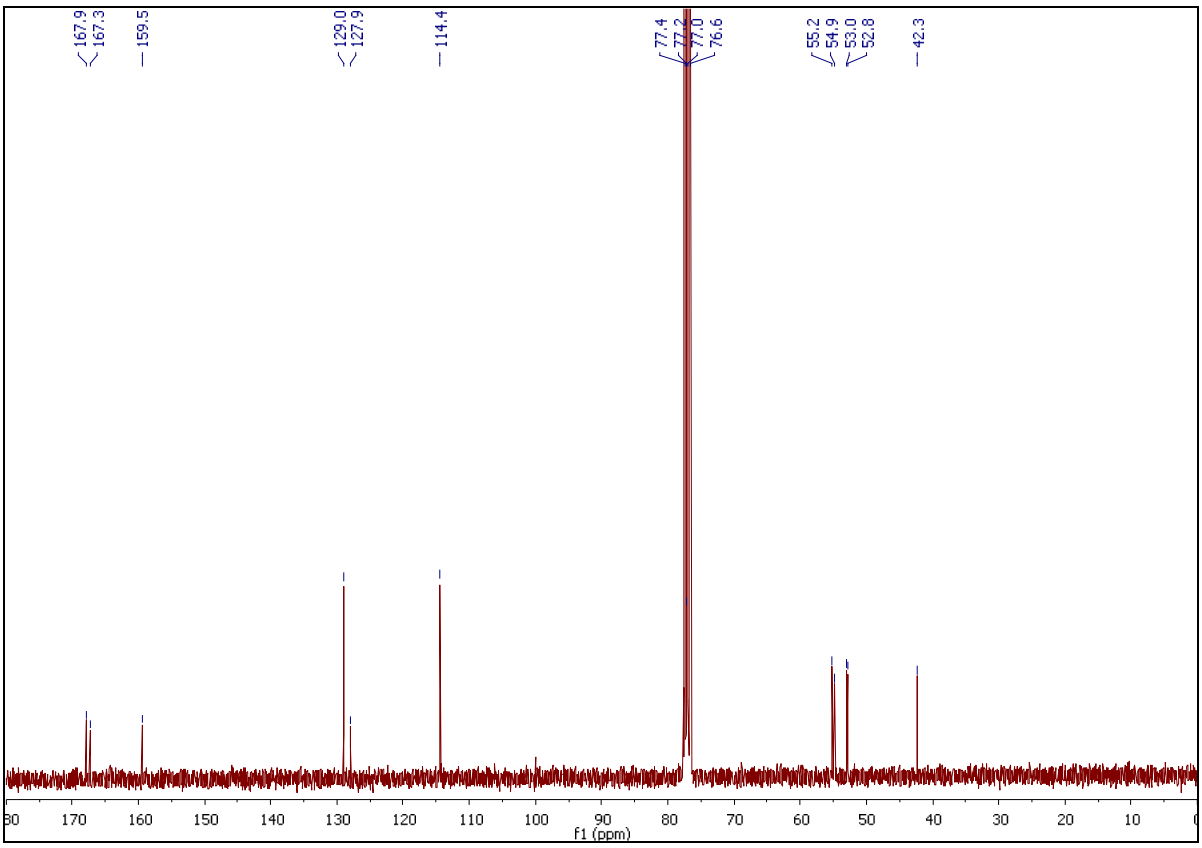


Figure S39. ^{13}C NMR (75 MHz, $CDCl_3$)

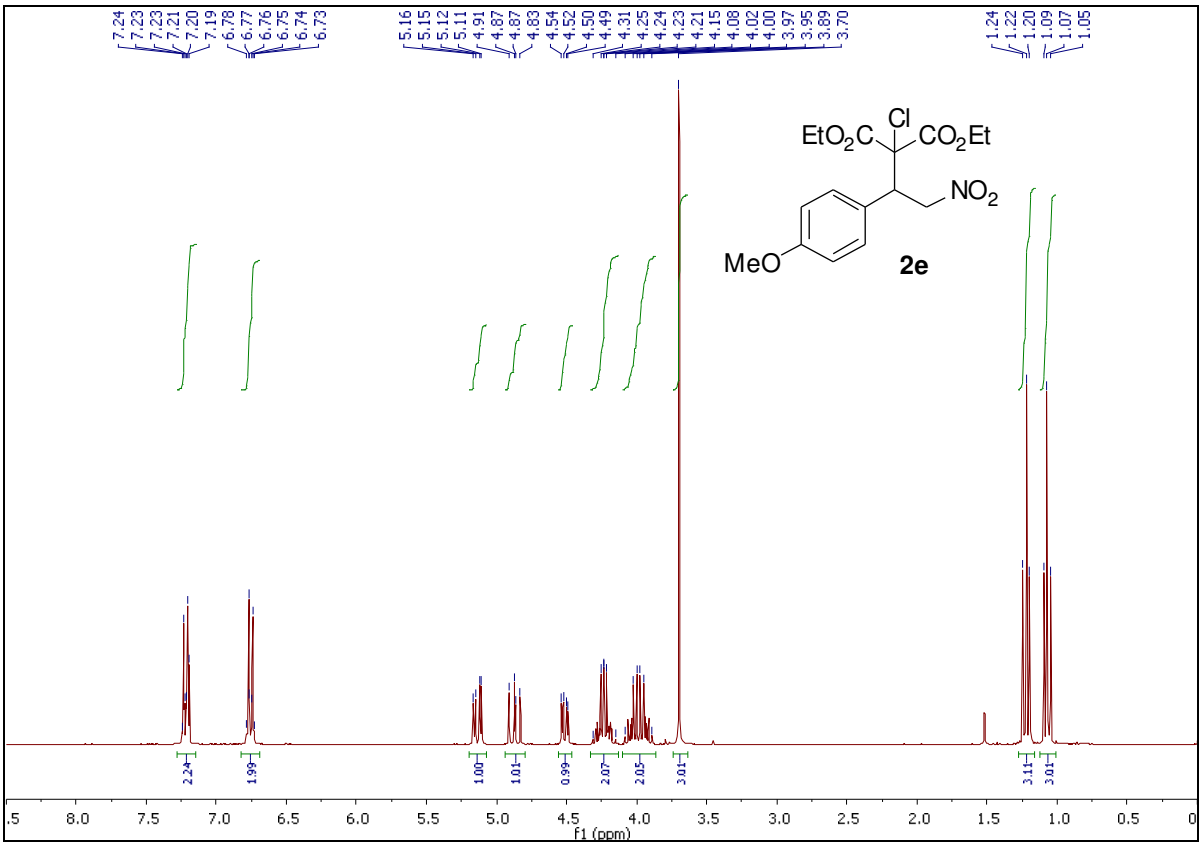


Figure S40. ^{1}H NMR (300 MHz, $CDCl_3$)

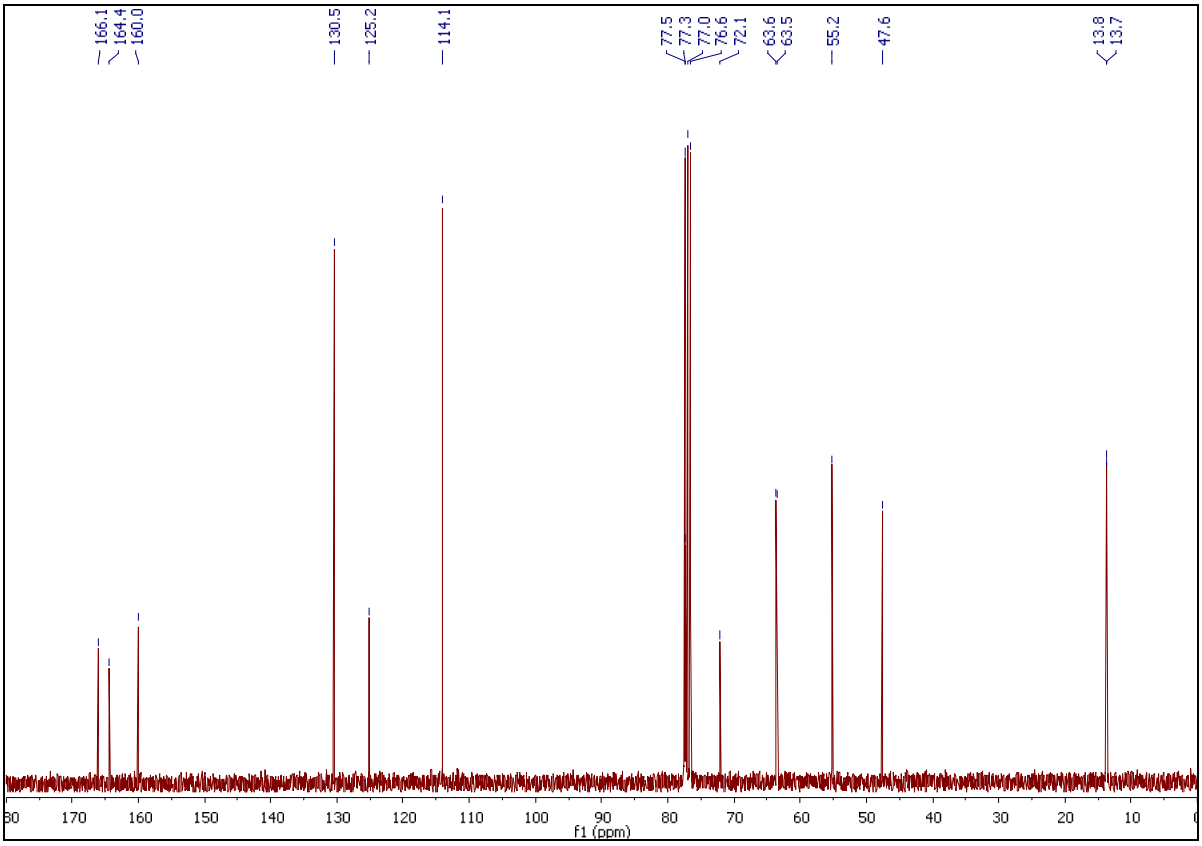


Figure S41. ^{13}C NMR (75 MHz, $CDCl_3$)

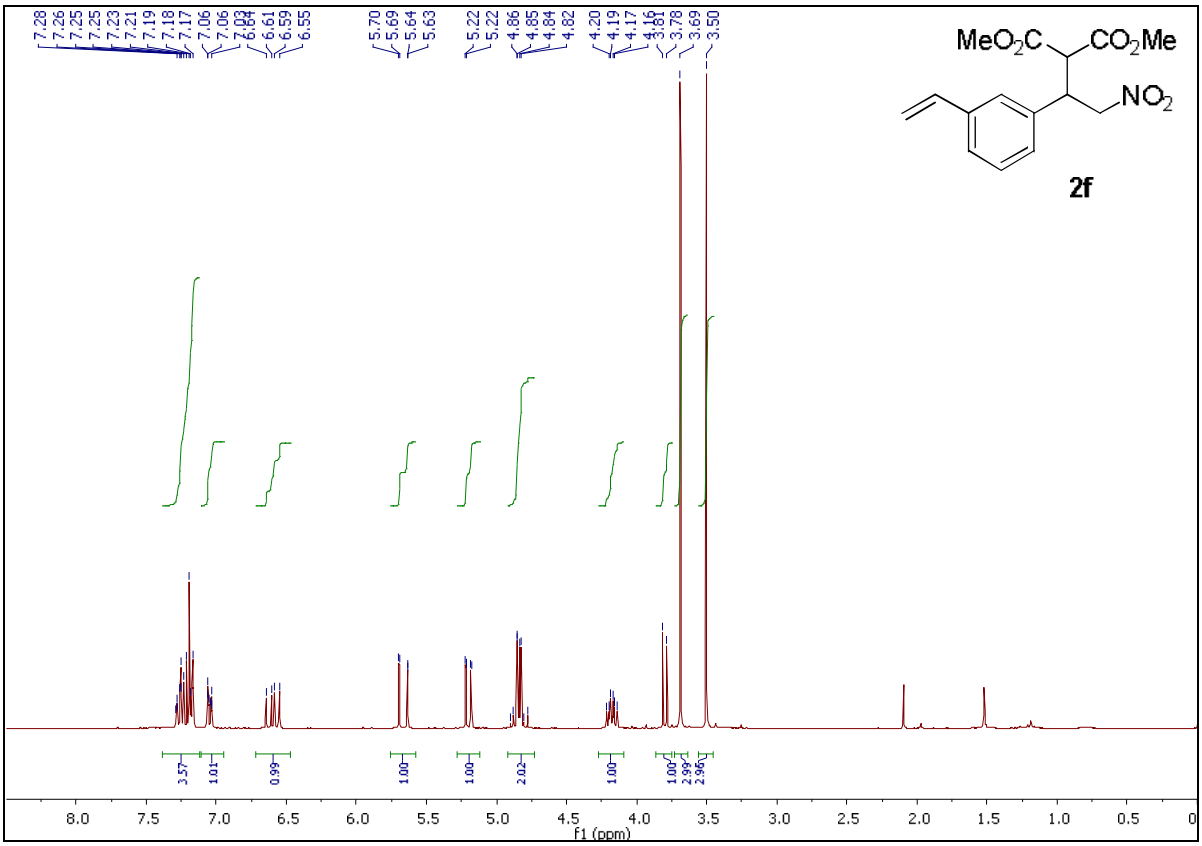


Figure S42. ^{1}H NMR (300 MHz, $CDCl_3$)

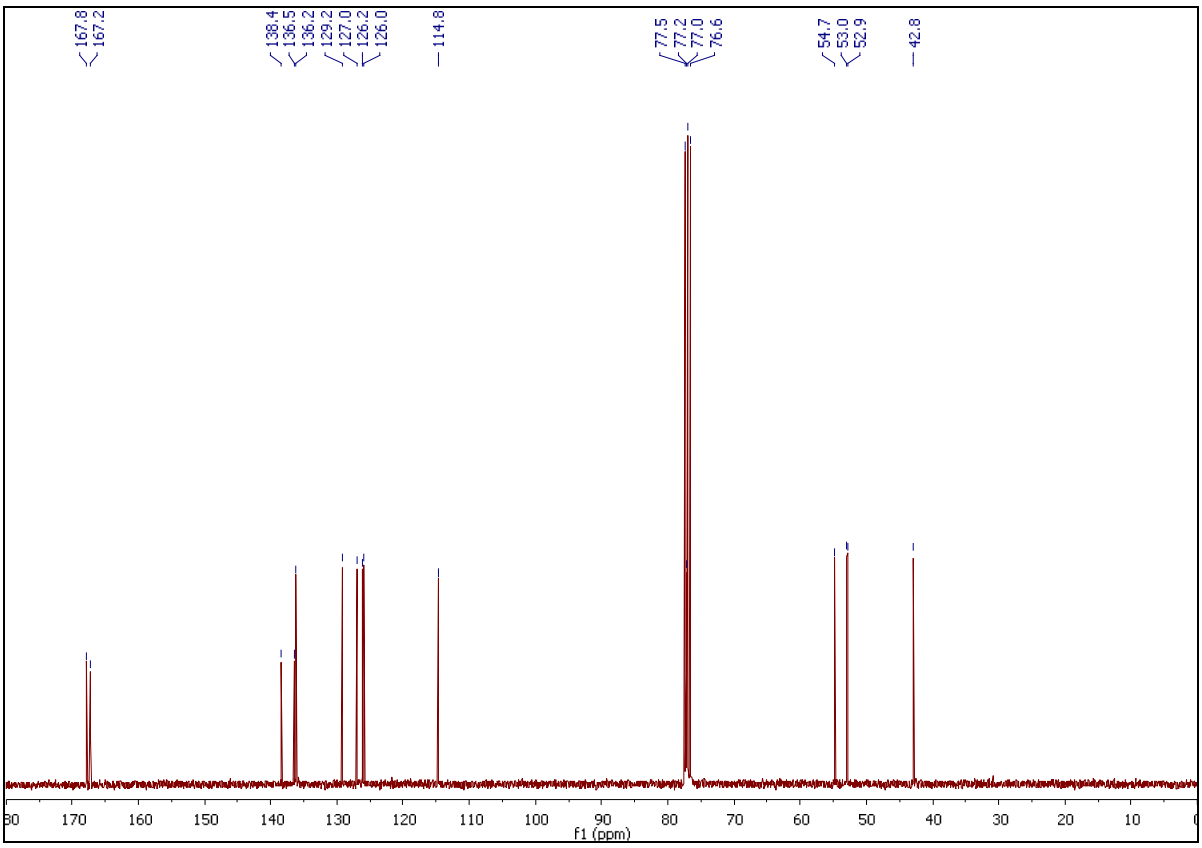


Figure S43. ^{13}C NMR (75 MHz, $CDCl_3$)

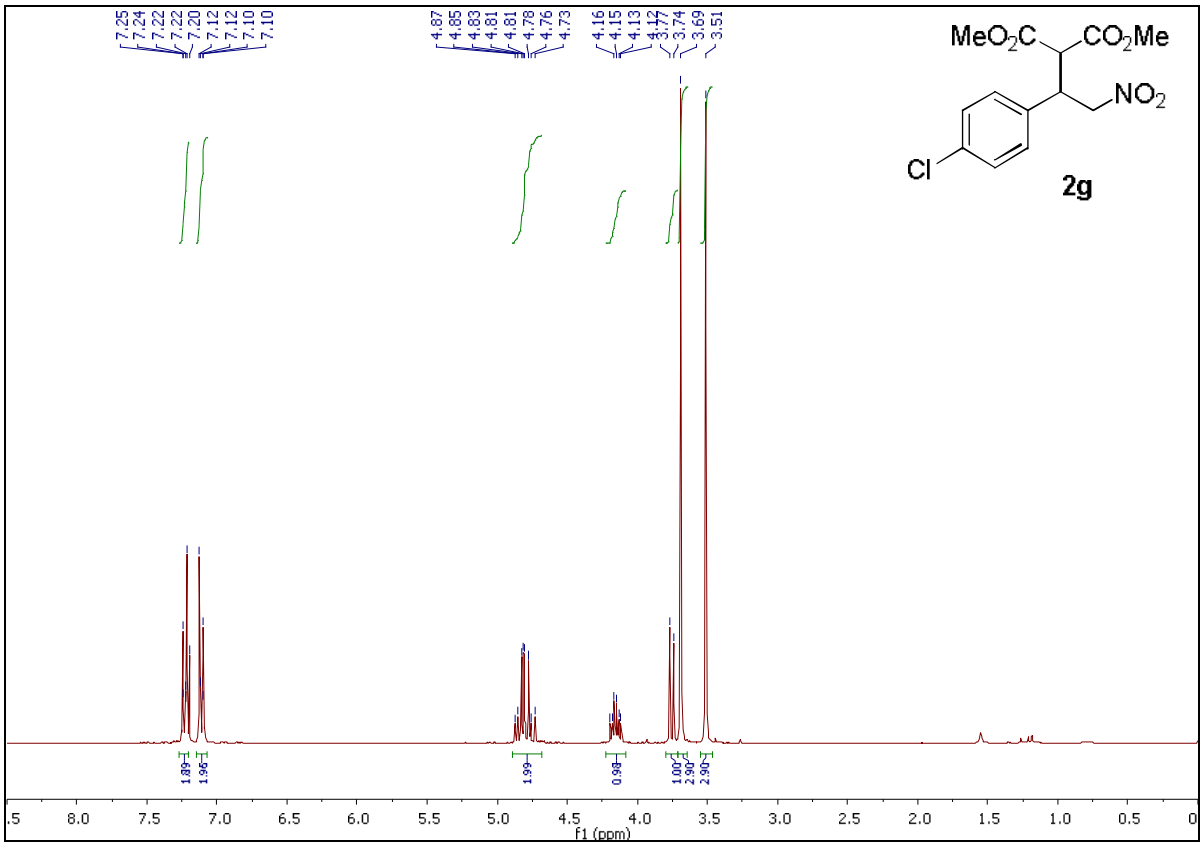


Figure S44. ^{1}H NMR (300 MHz, $CDCl_3$)

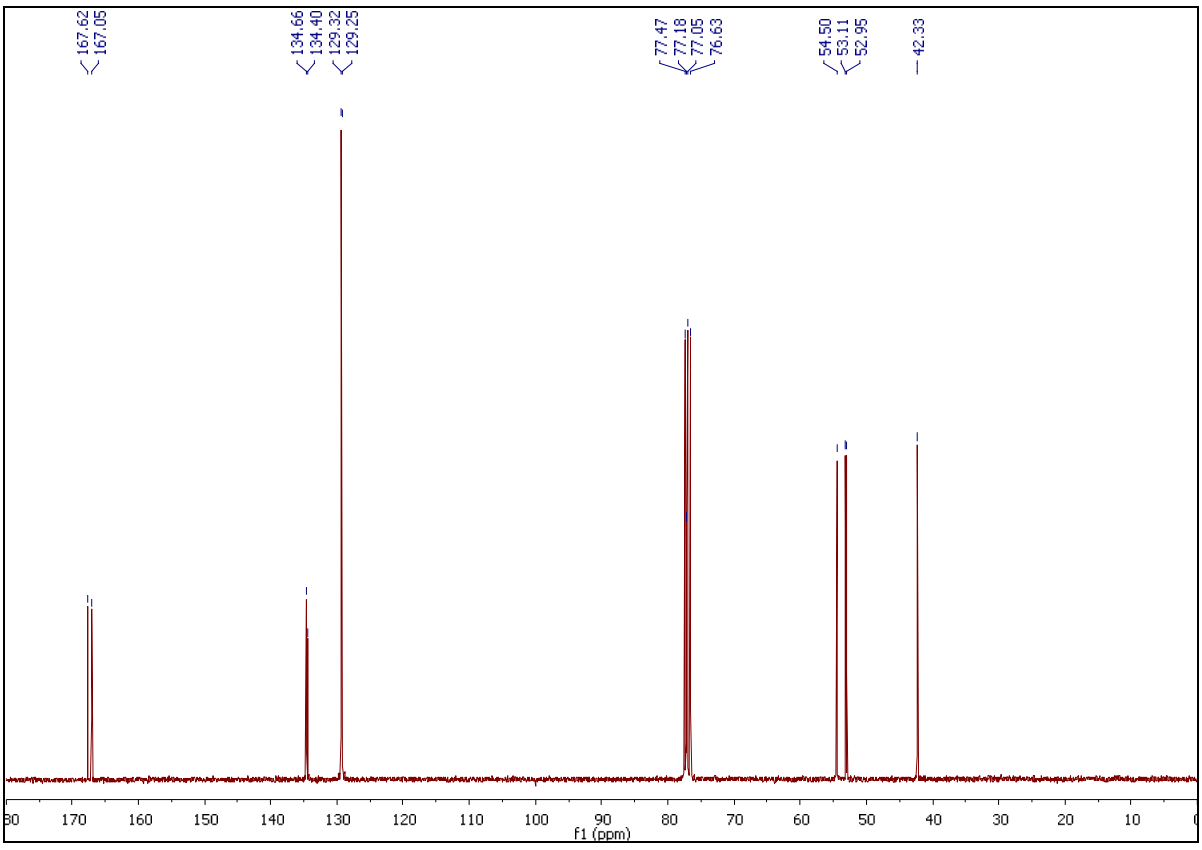


Figure S45. ^{13}C NMR (75 MHz, $CDCl_3$)

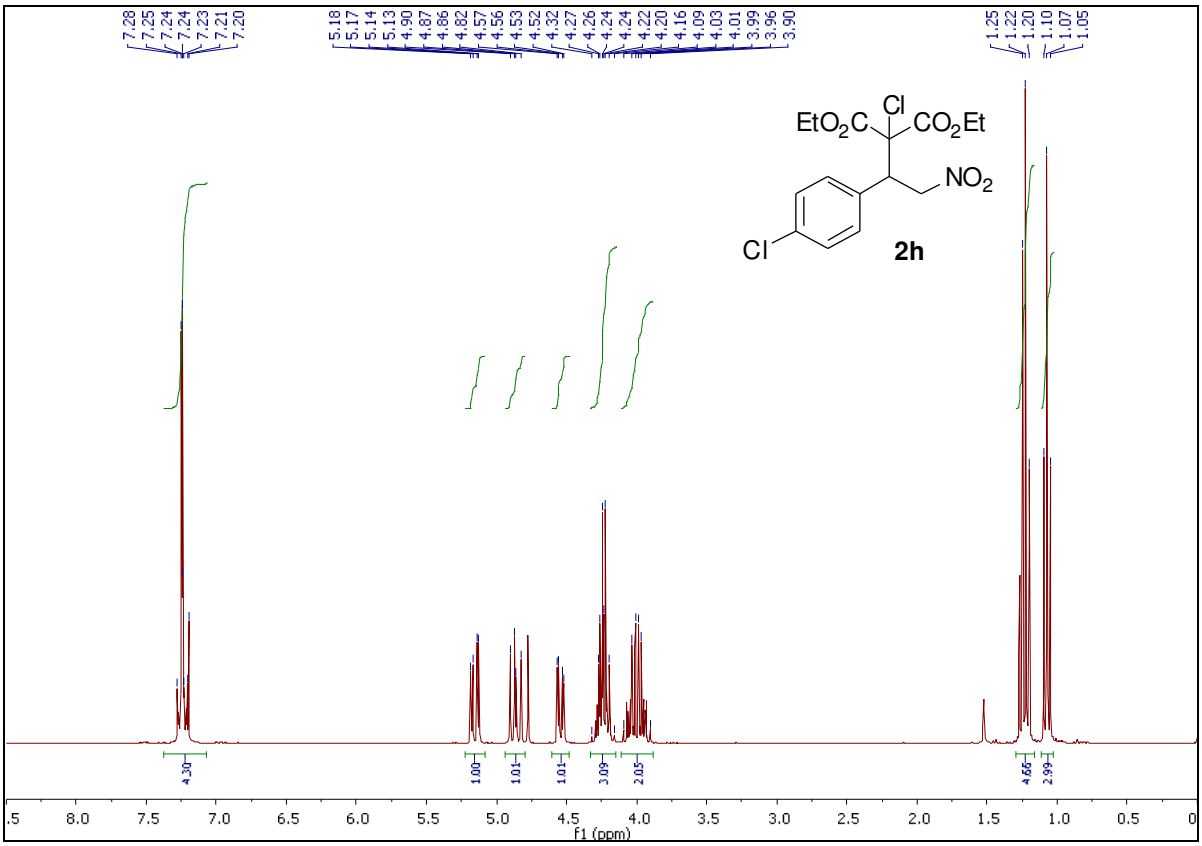


Figure S46. ^{1}H NMR (300 MHz, $CDCl_3$)

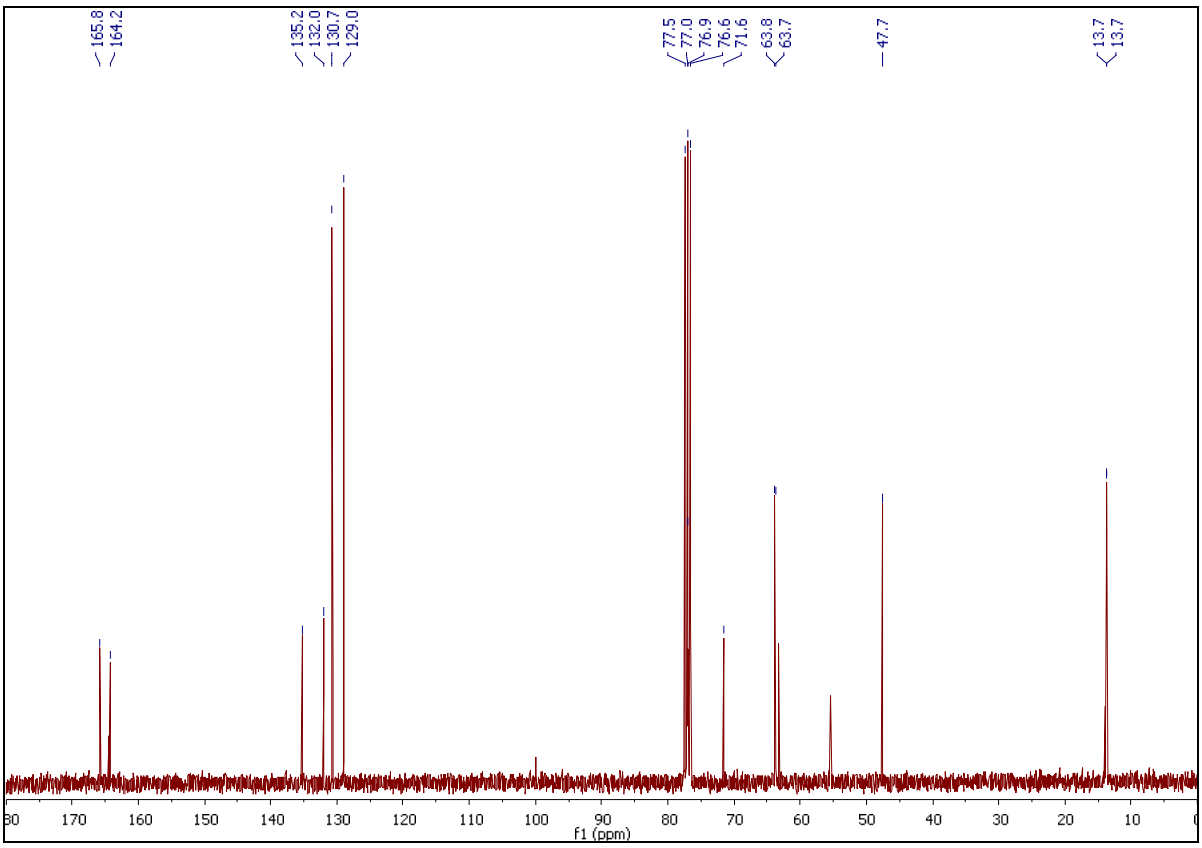


Figure S47. ^{13}C NMR (75 MHz, $CDCl_3$)

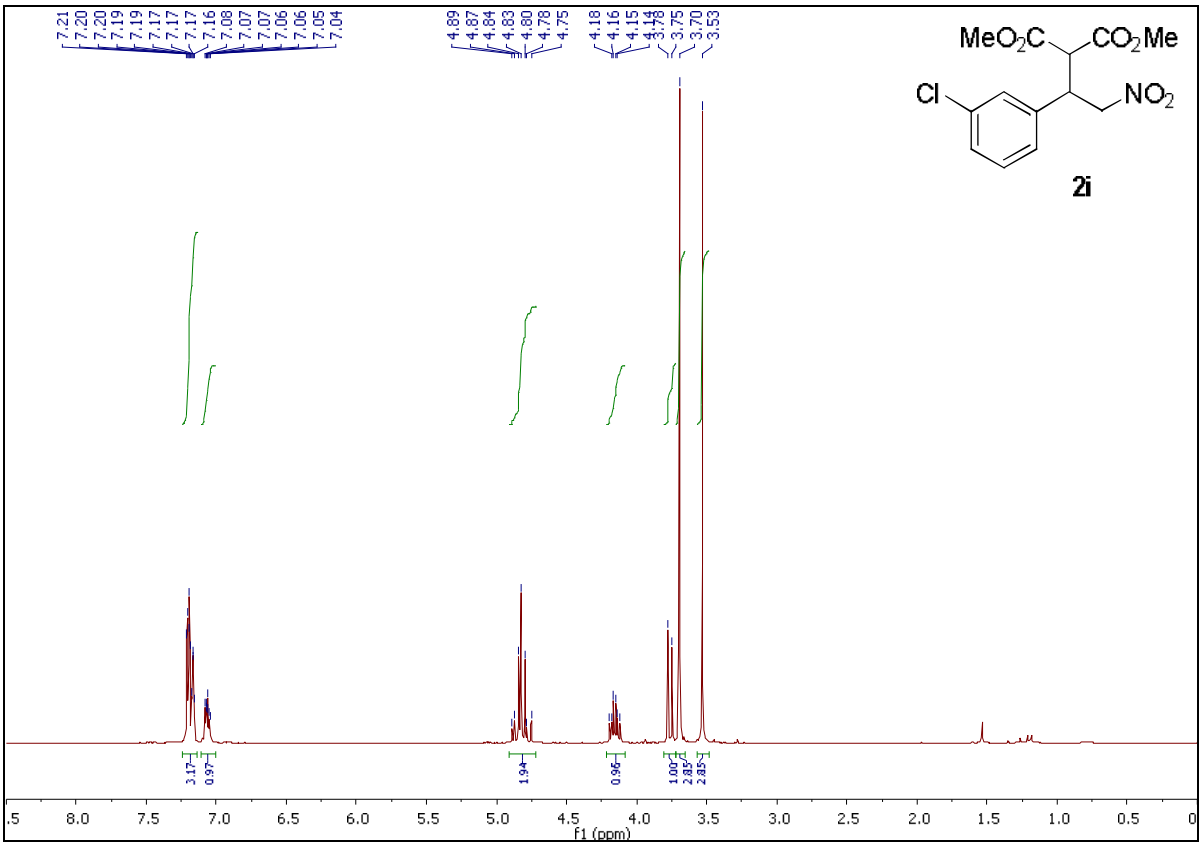


Figure S48. ^{1}H NMR (300 MHz, $CDCl_3$)

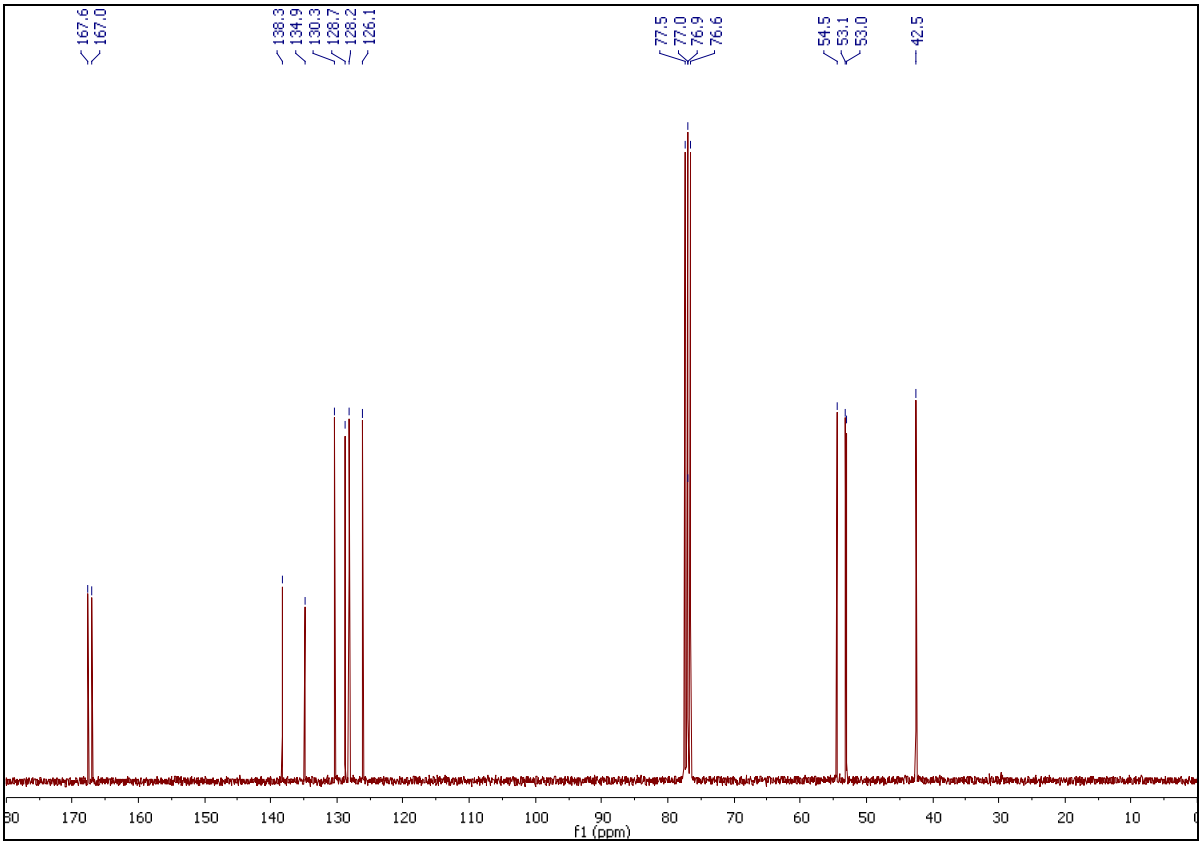


Figure S49. ^{13}C NMR (75 MHz, $CDCl_3$)

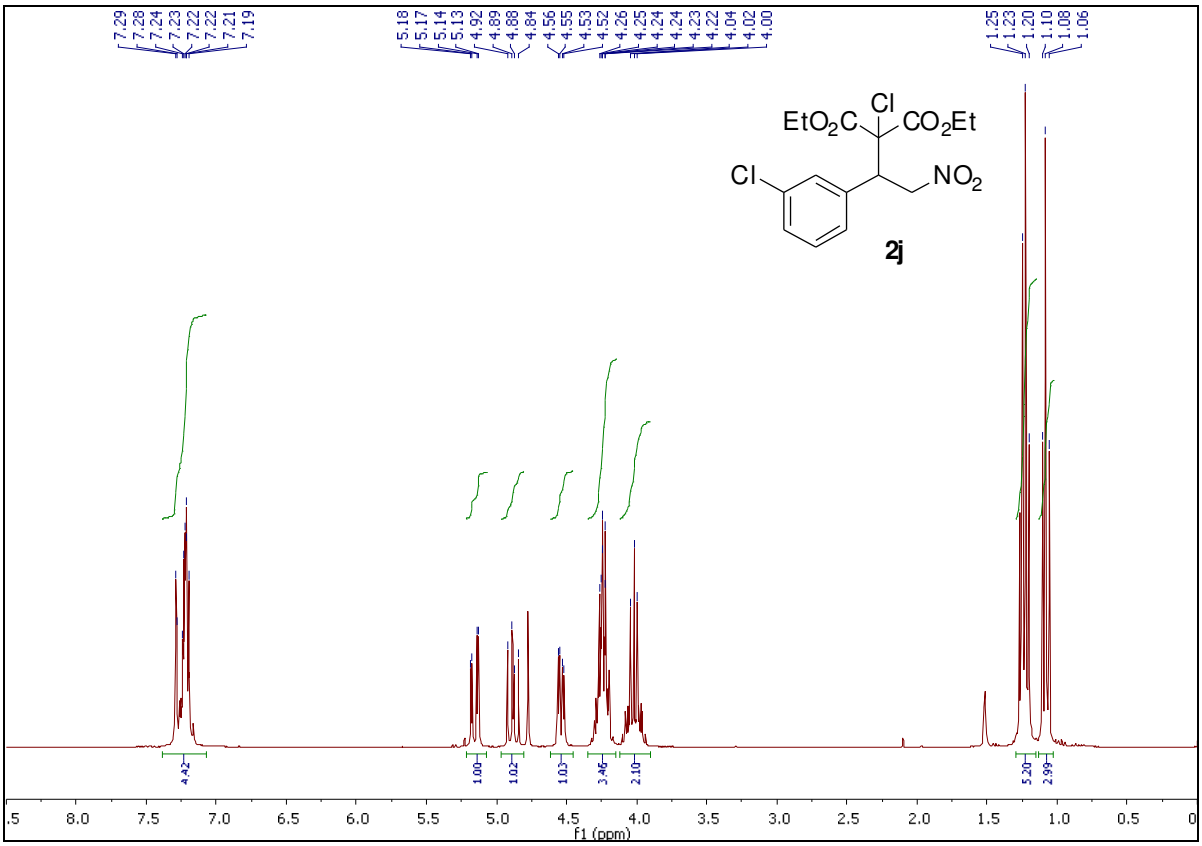


Figure S50. ^{1}H NMR (300 MHz, $CDCl_3$)

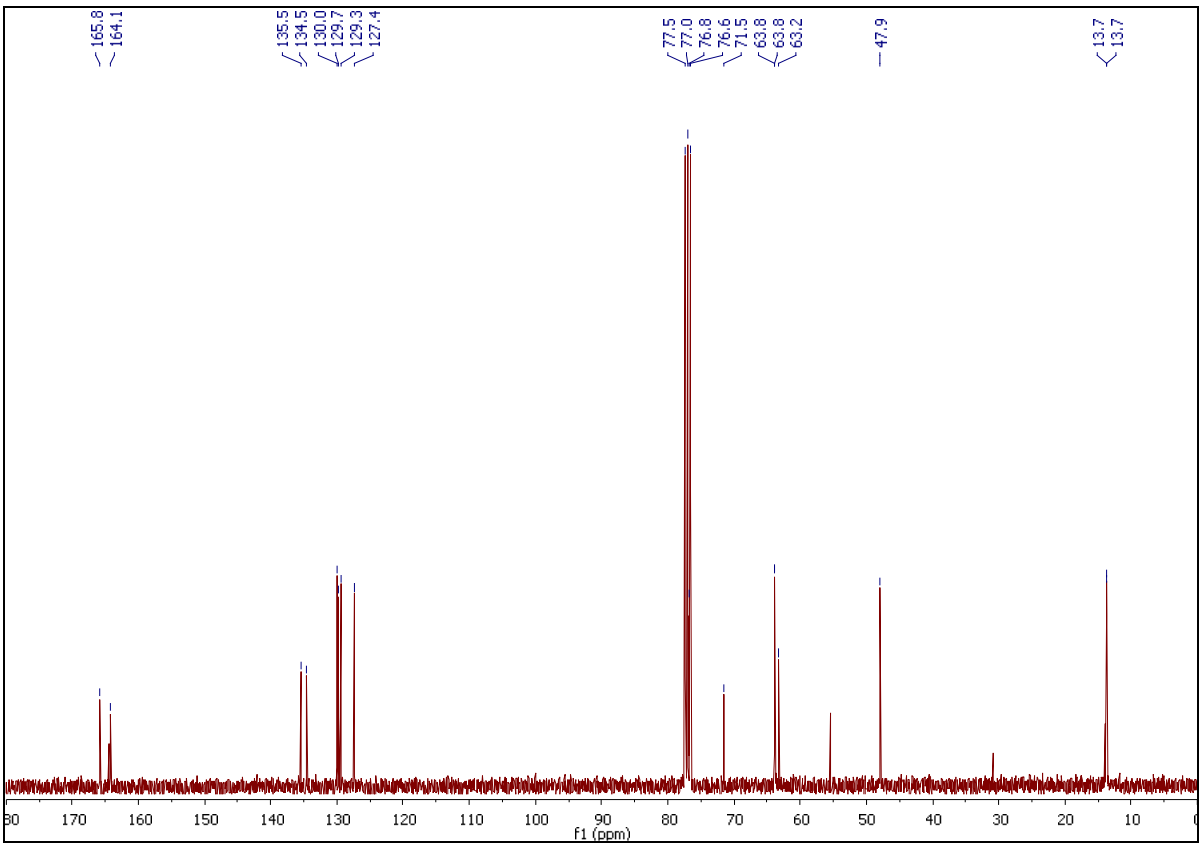


Figure S51. ^{13}C NMR (75 MHz, $CDCl_3$)

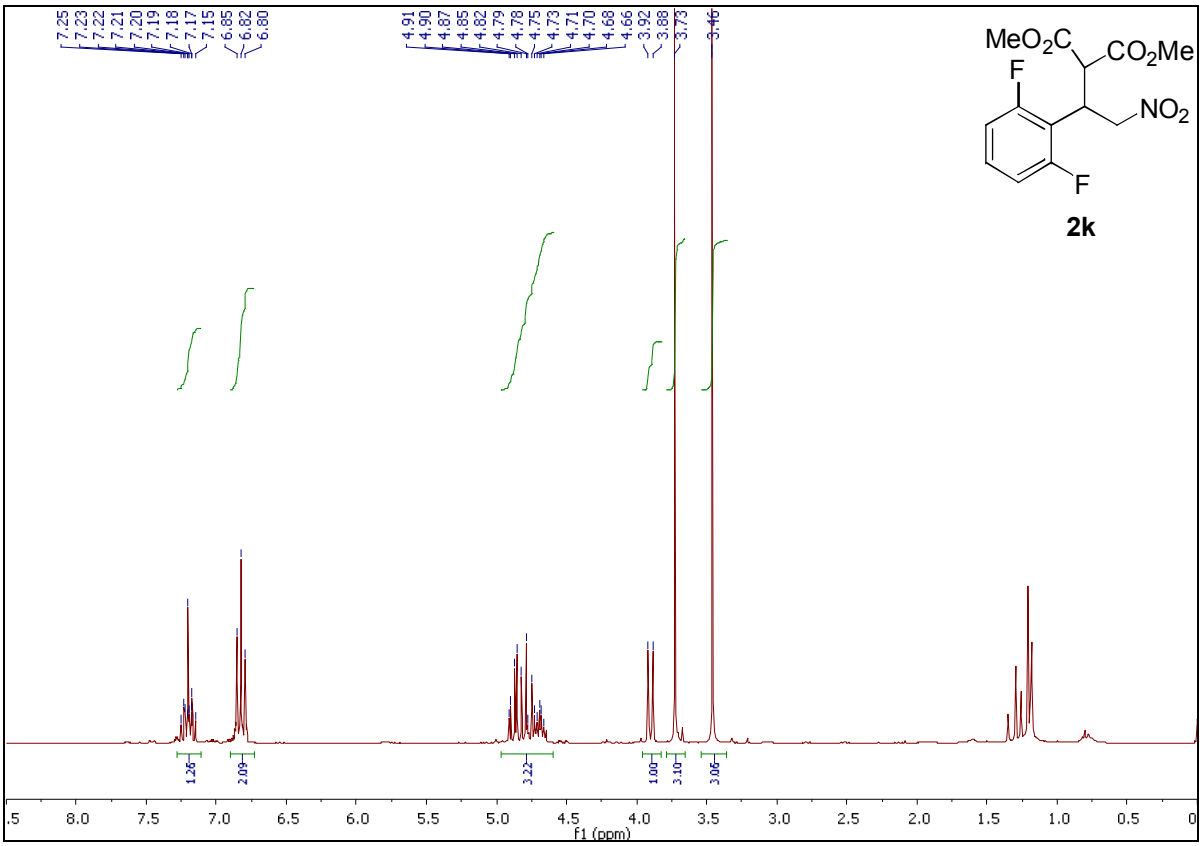


Figure S52. ^{1}H NMR (300 MHz, $CDCl_3$)

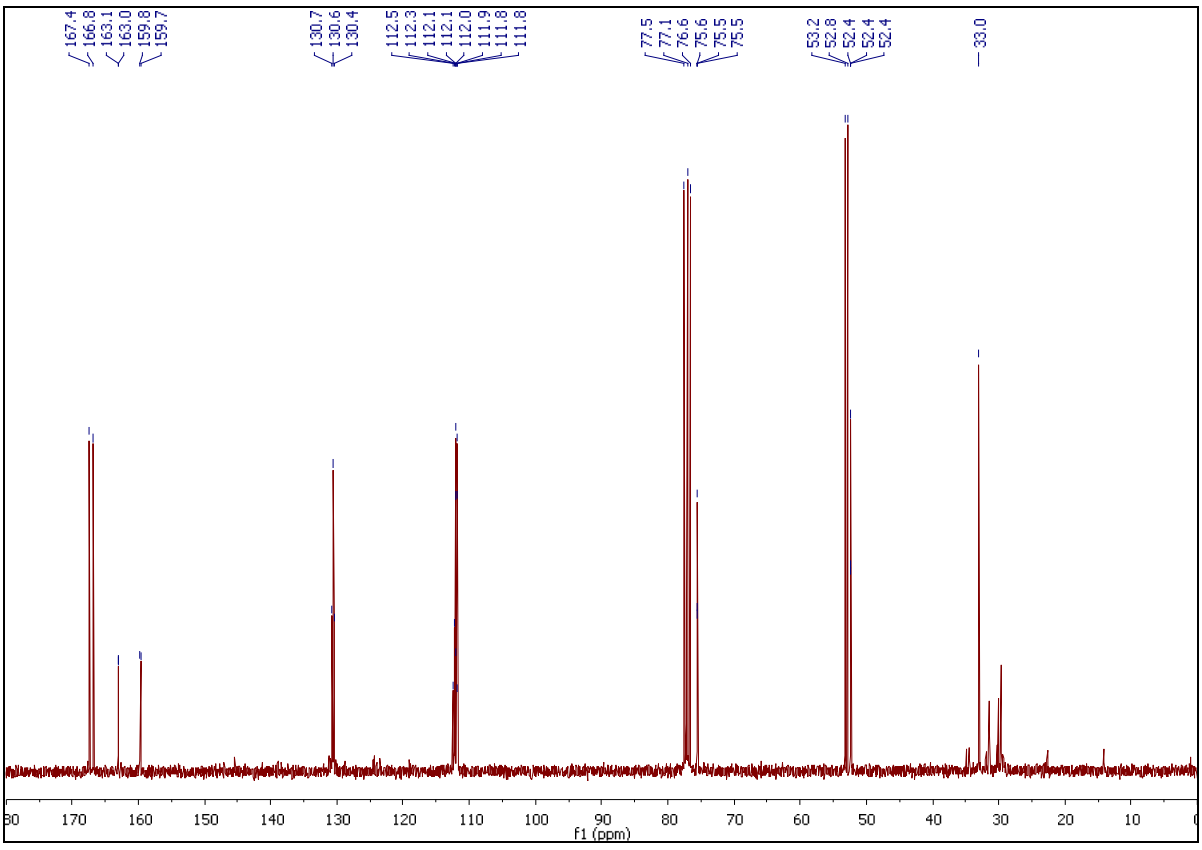


Figure S53. ^{13}C NMR (75 MHz, $CDCl_3$)

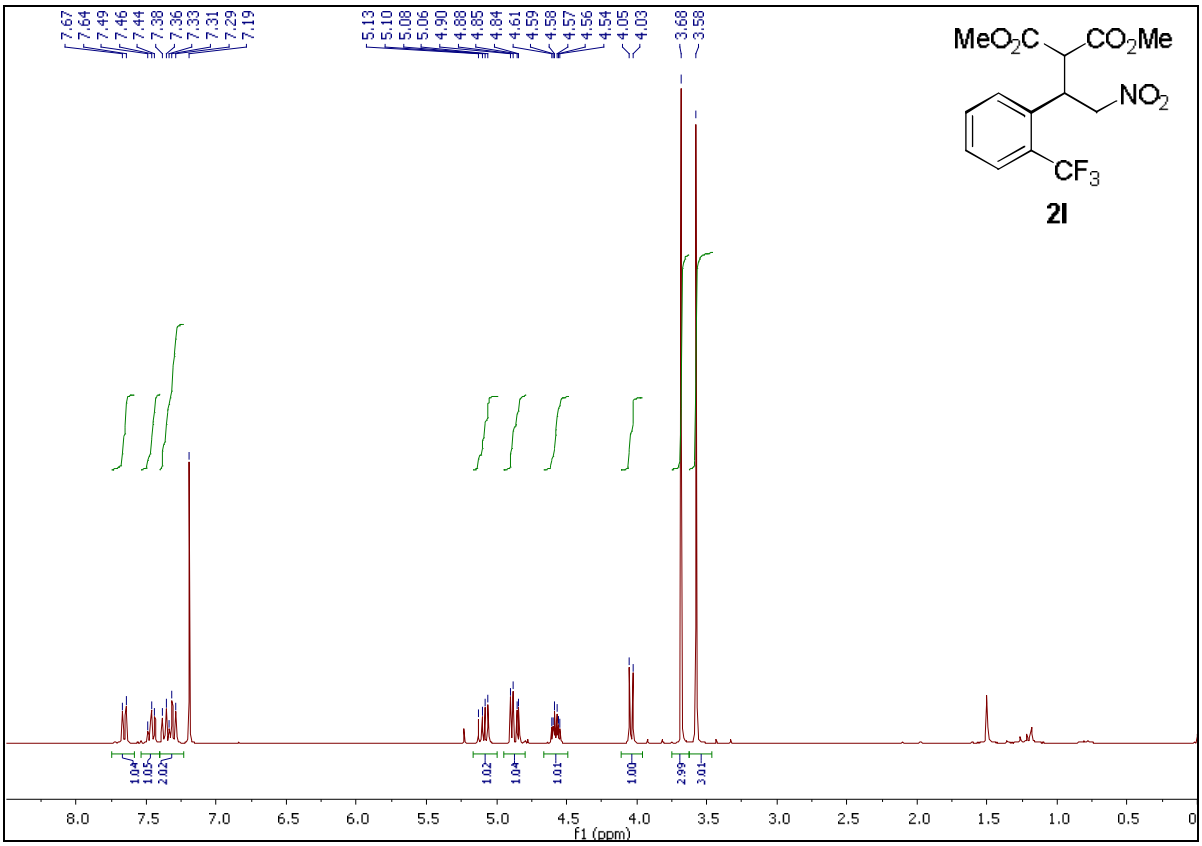


Figure S54. ^{1}H NMR (300 MHz, $CDCl_3$)

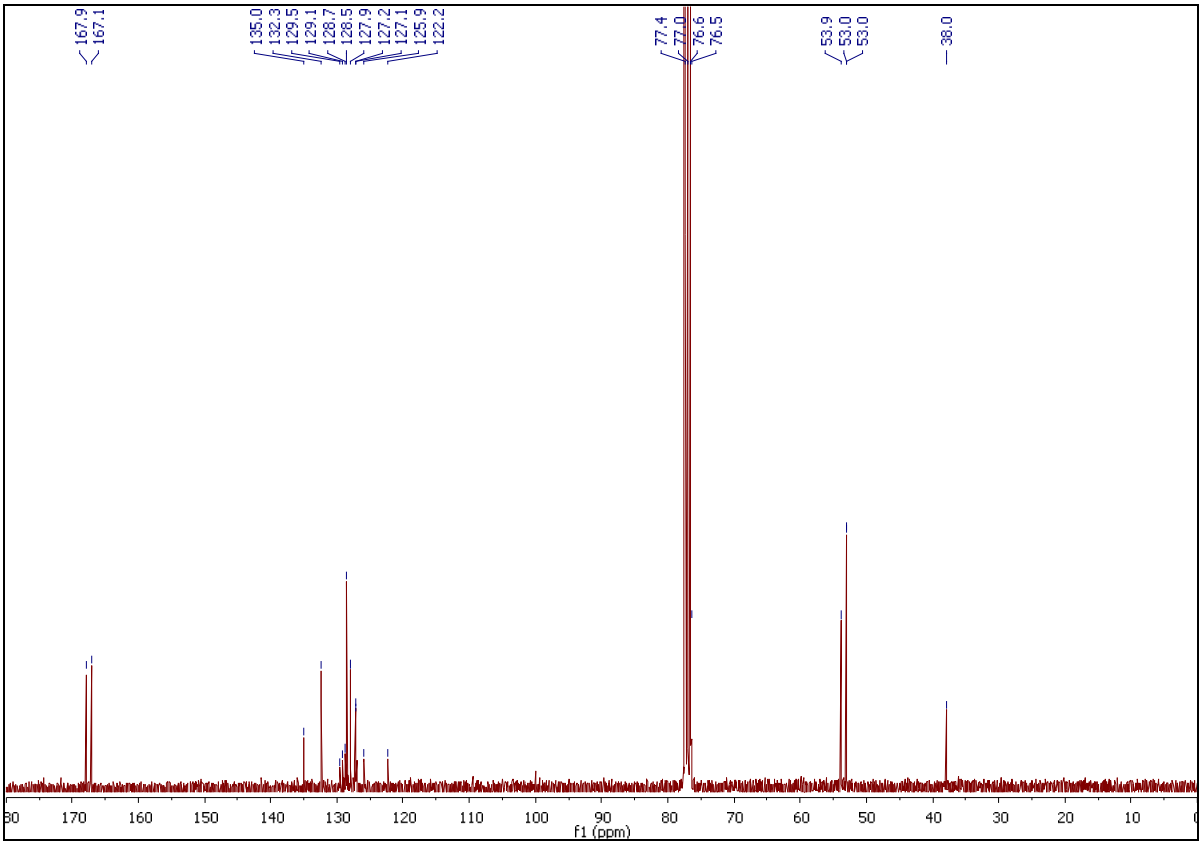


Figure S55. ^{13}C NMR (75 MHz, $CDCl_3$)

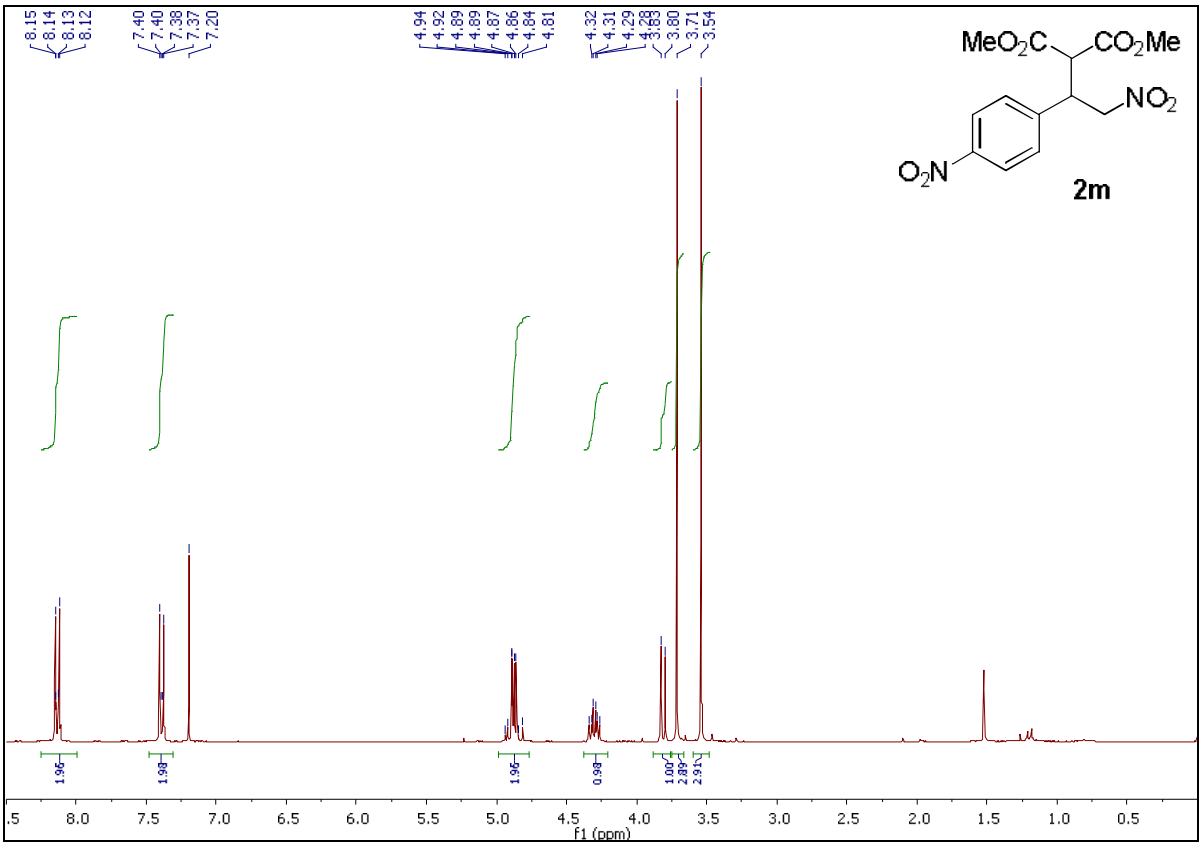


Figure S56. ^{1}H NMR (300 MHz, $CDCl_3$)

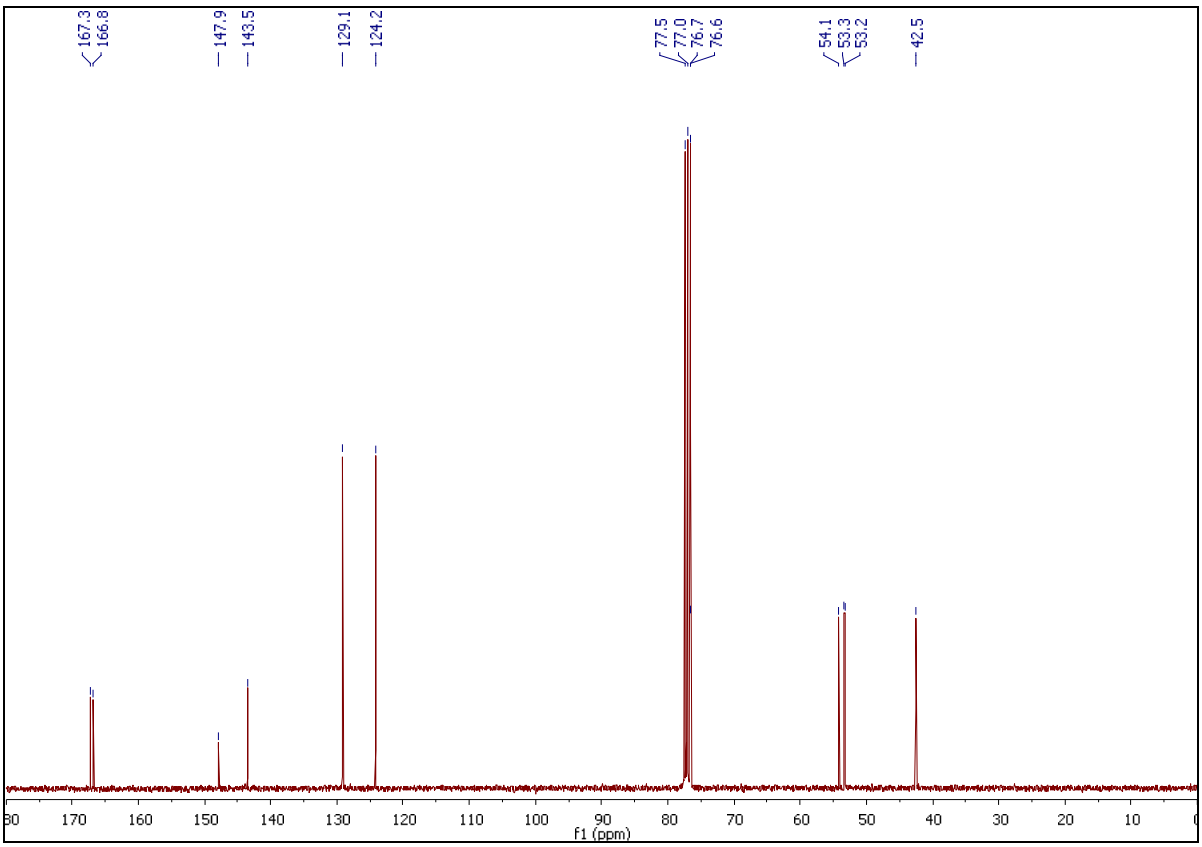


Figure S57. ^{13}C NMR (75 MHz, $CDCl_3$)

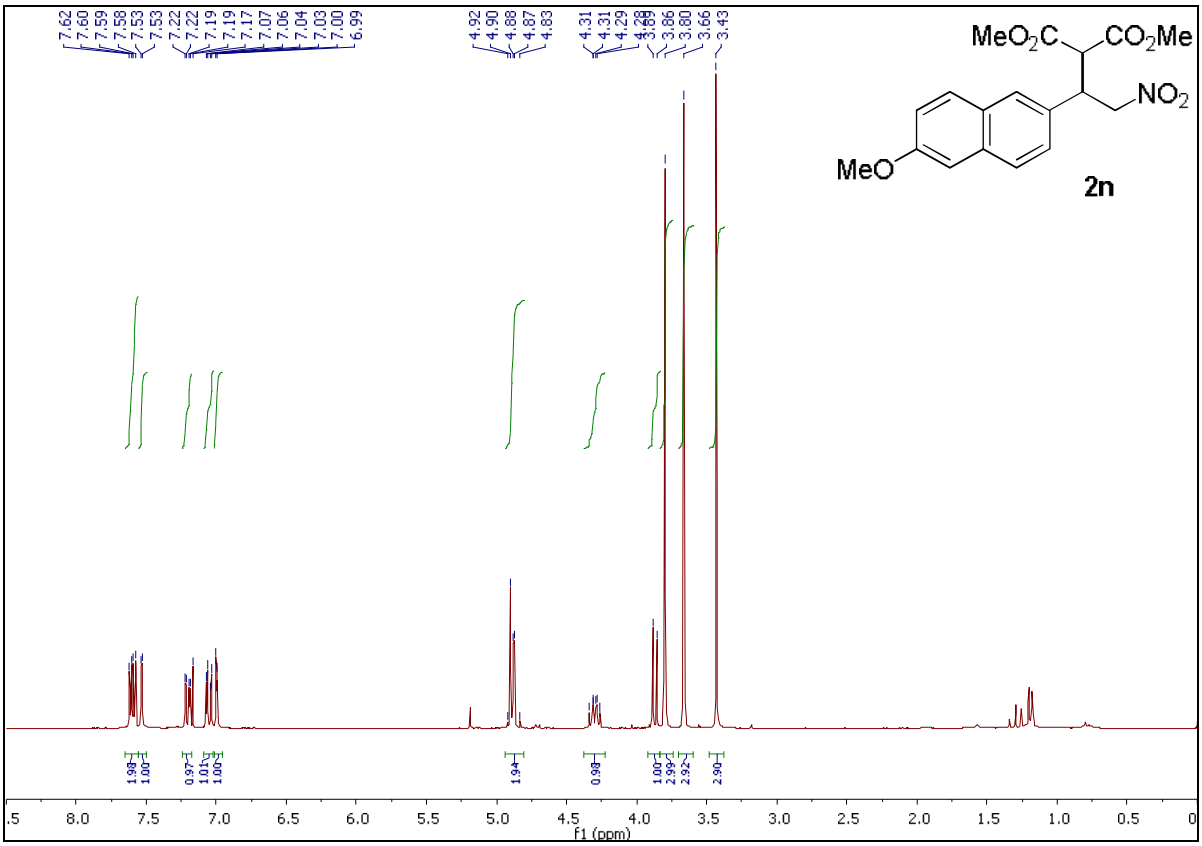


Figure S58. ^{1}H NMR (300 MHz, $CDCl_3$)

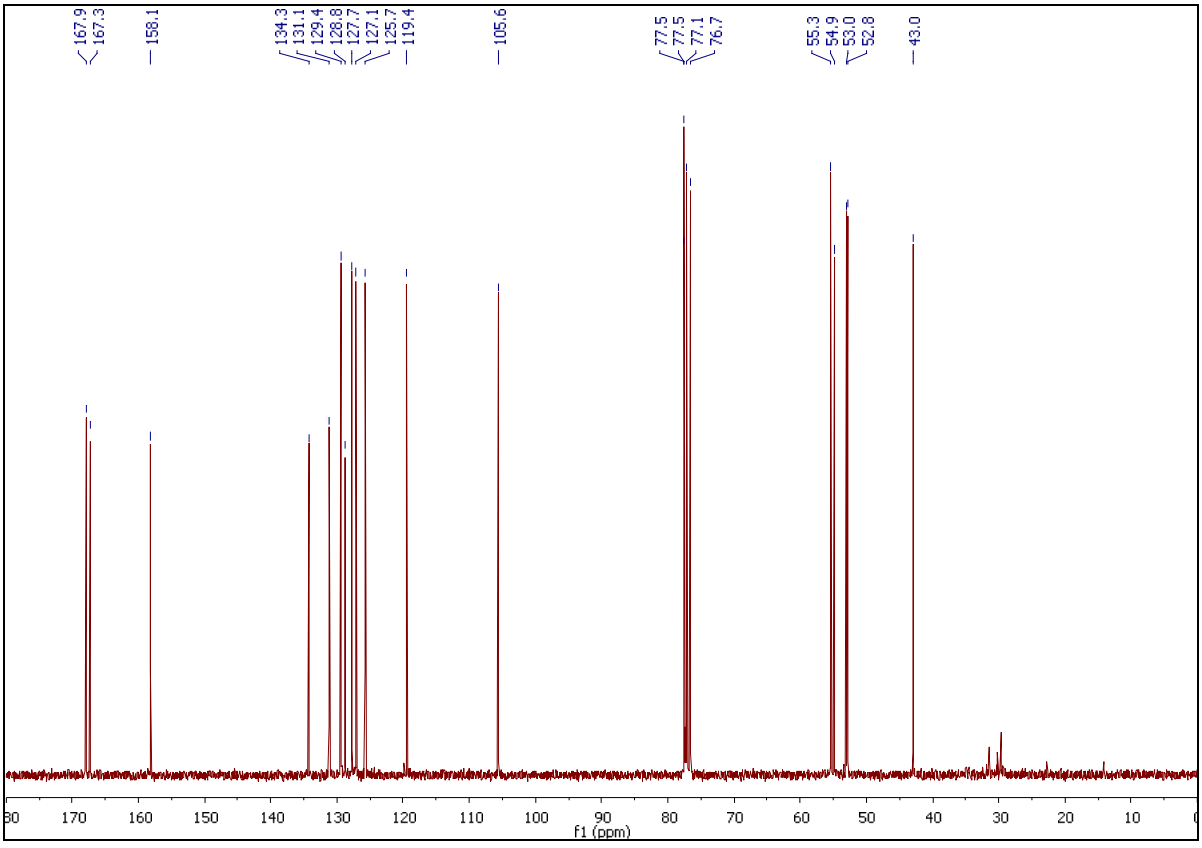


Figure S59. ^{13}C NMR (75 MHz, $CDCl_3$)

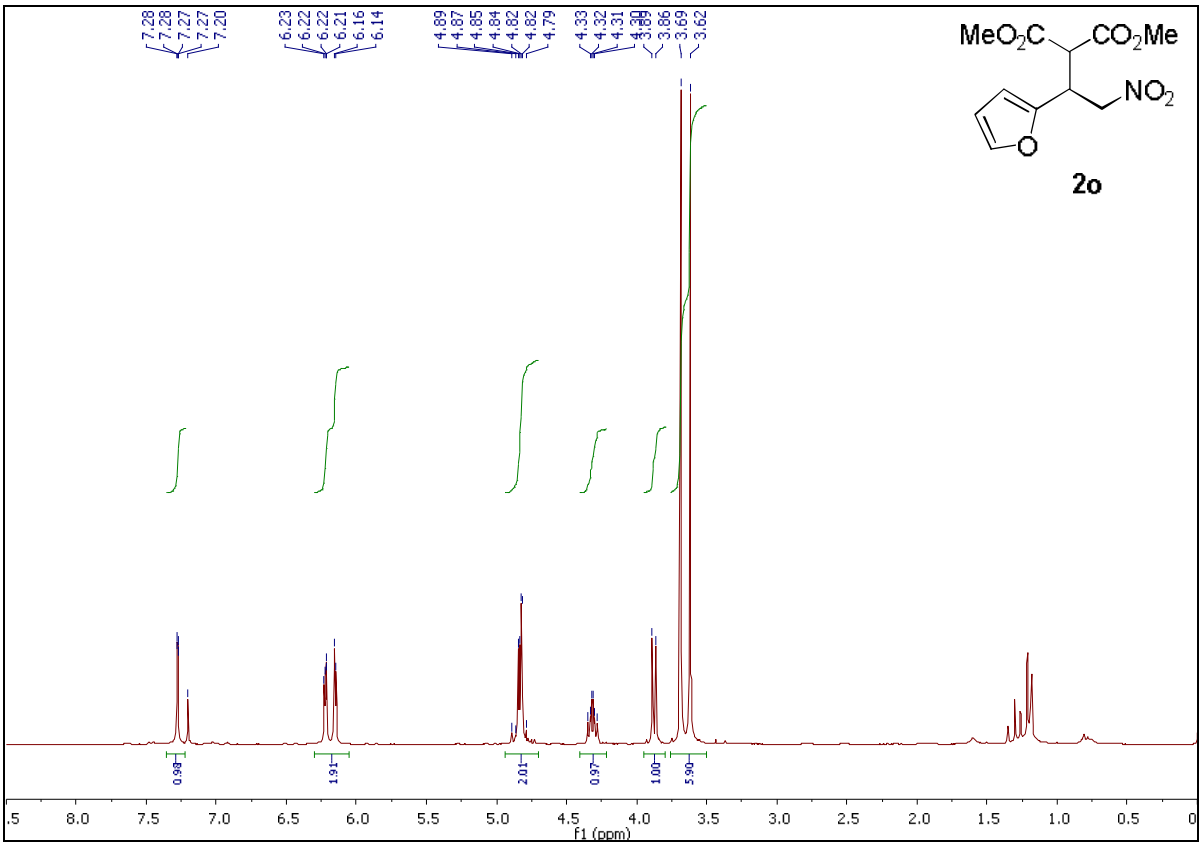


Figure S60. ^{1}H NMR (300 MHz, $CDCl_3$)

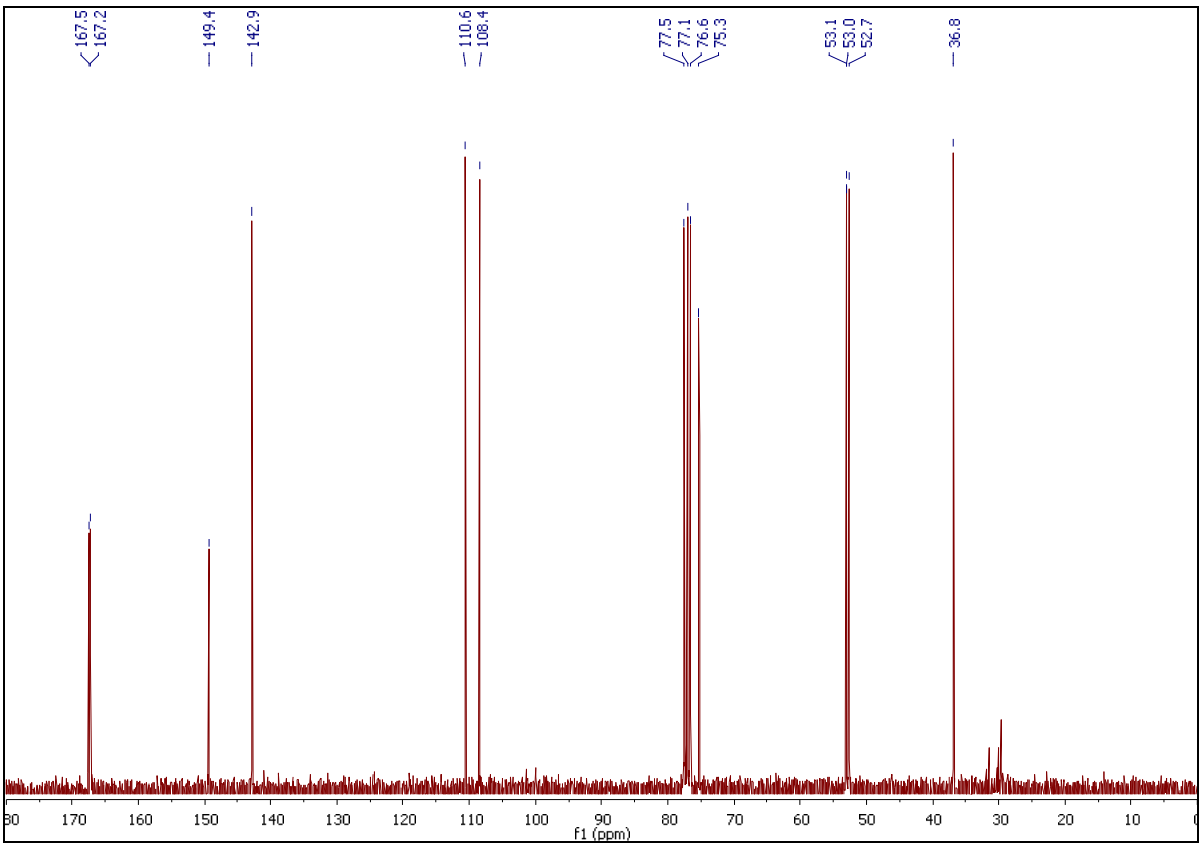


Figure S61. ^{13}C NMR (75 MHz, $CDCl_3$)

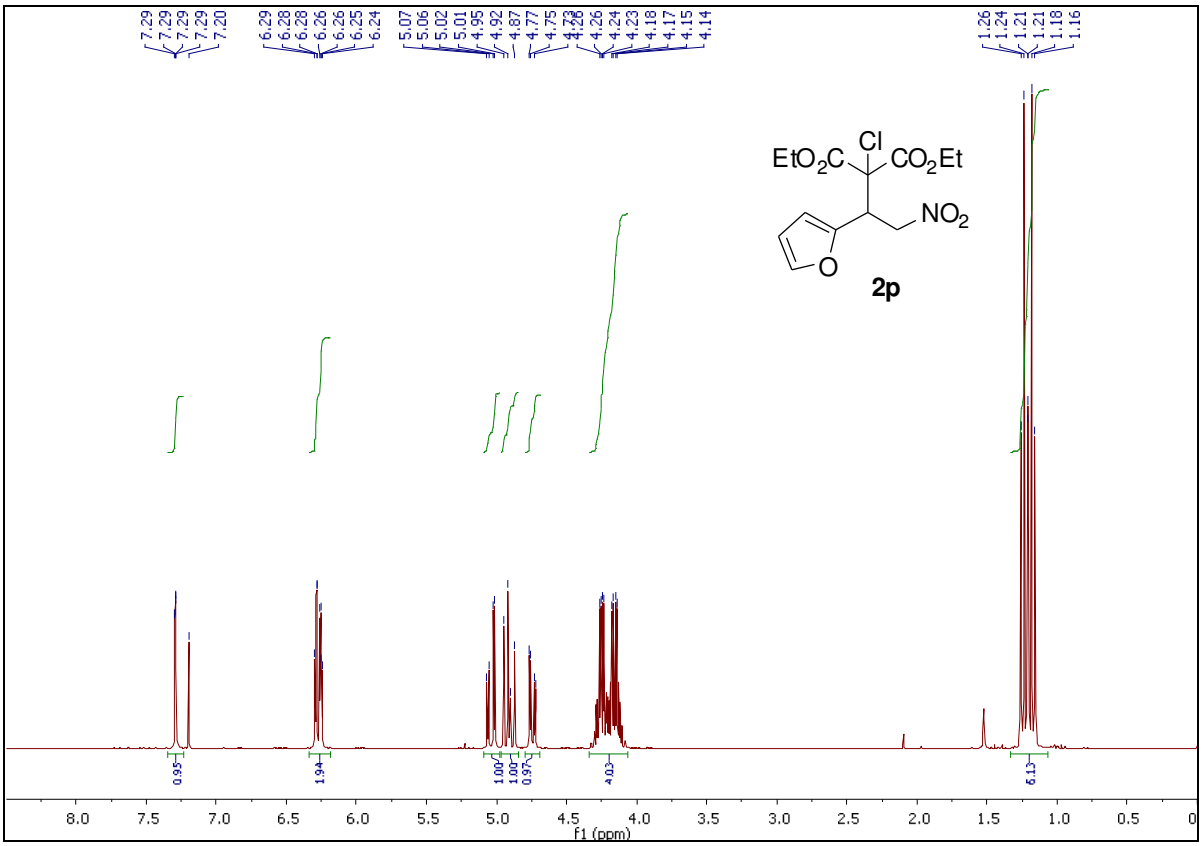


Figure S62. ^{1}H NMR (300 MHz, $CDCl_3$)

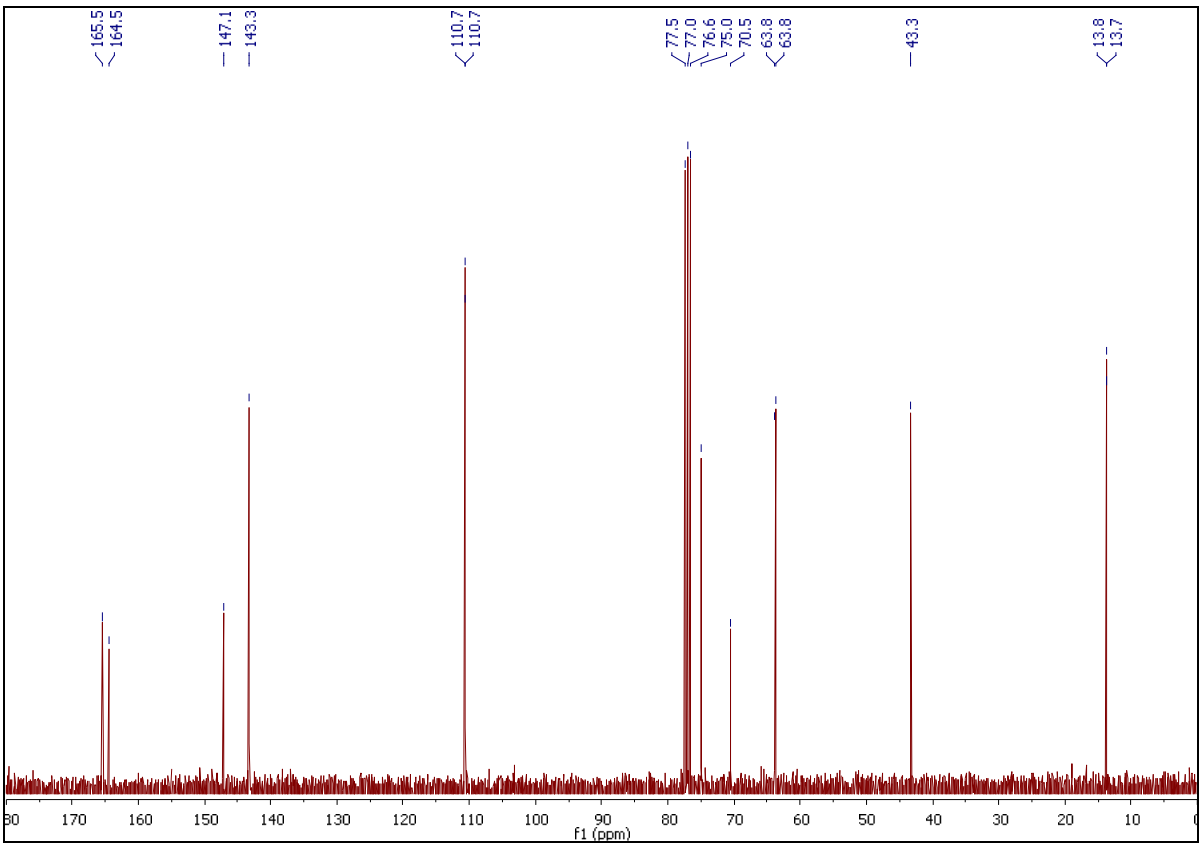


Figure S63. ^{13}C NMR (75 MHz, $CDCl_3$)

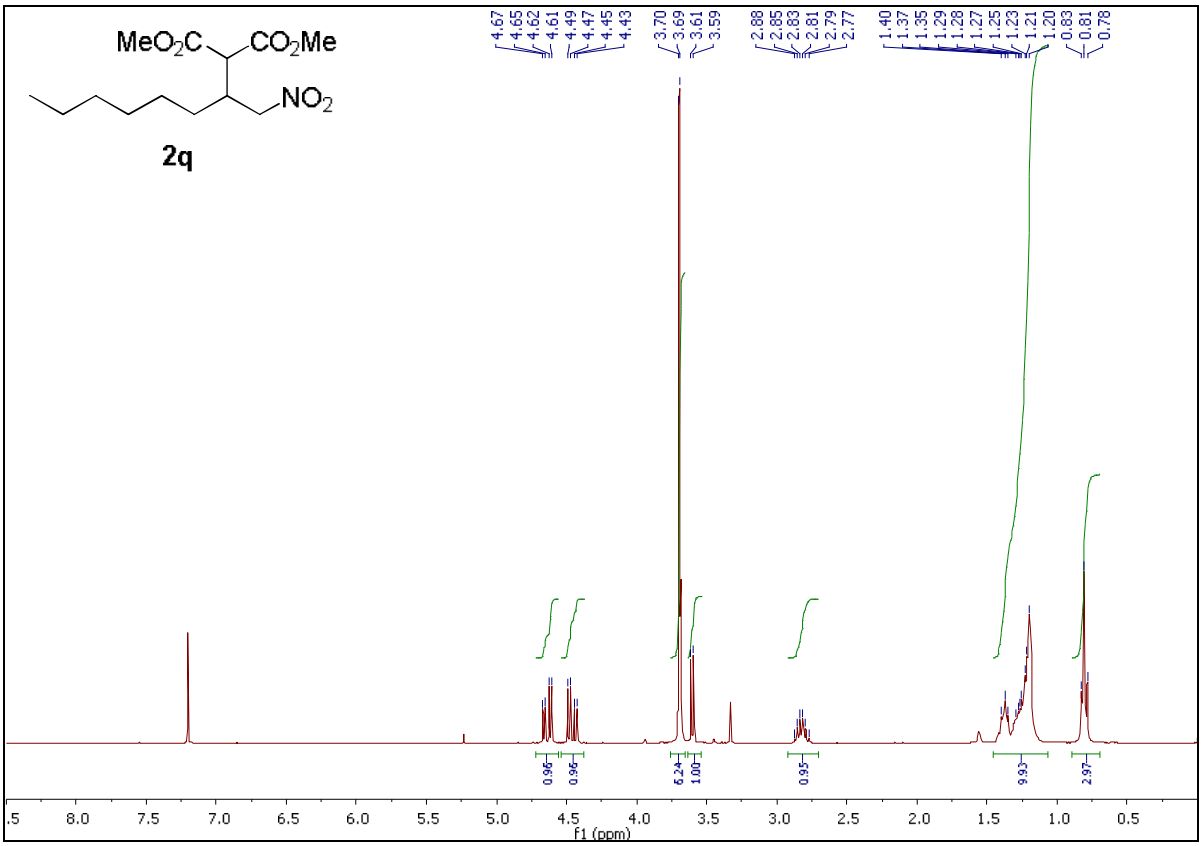


Figure S64. ^{1}H NMR (300 MHz, $CDCl_3$)

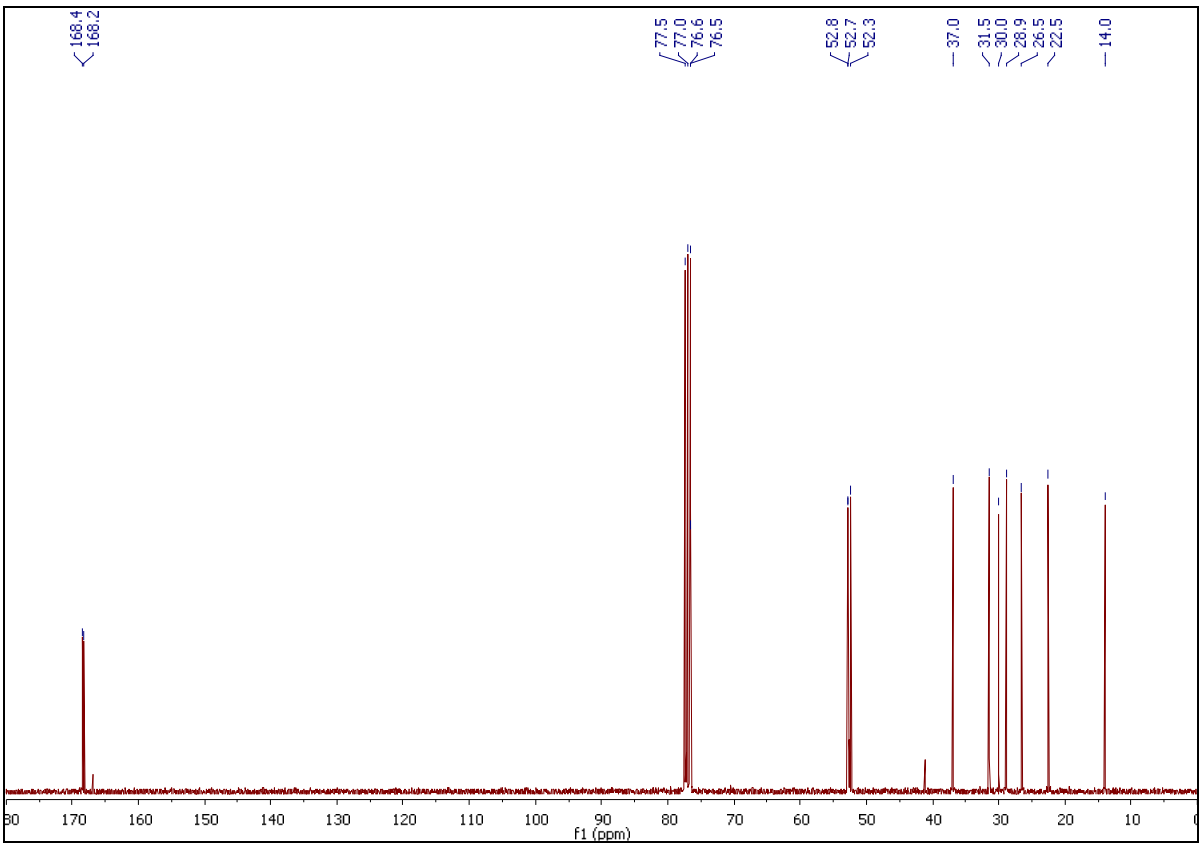


Figure S65. ^{13}C NMR (75 MHz, $CDCl_3$)

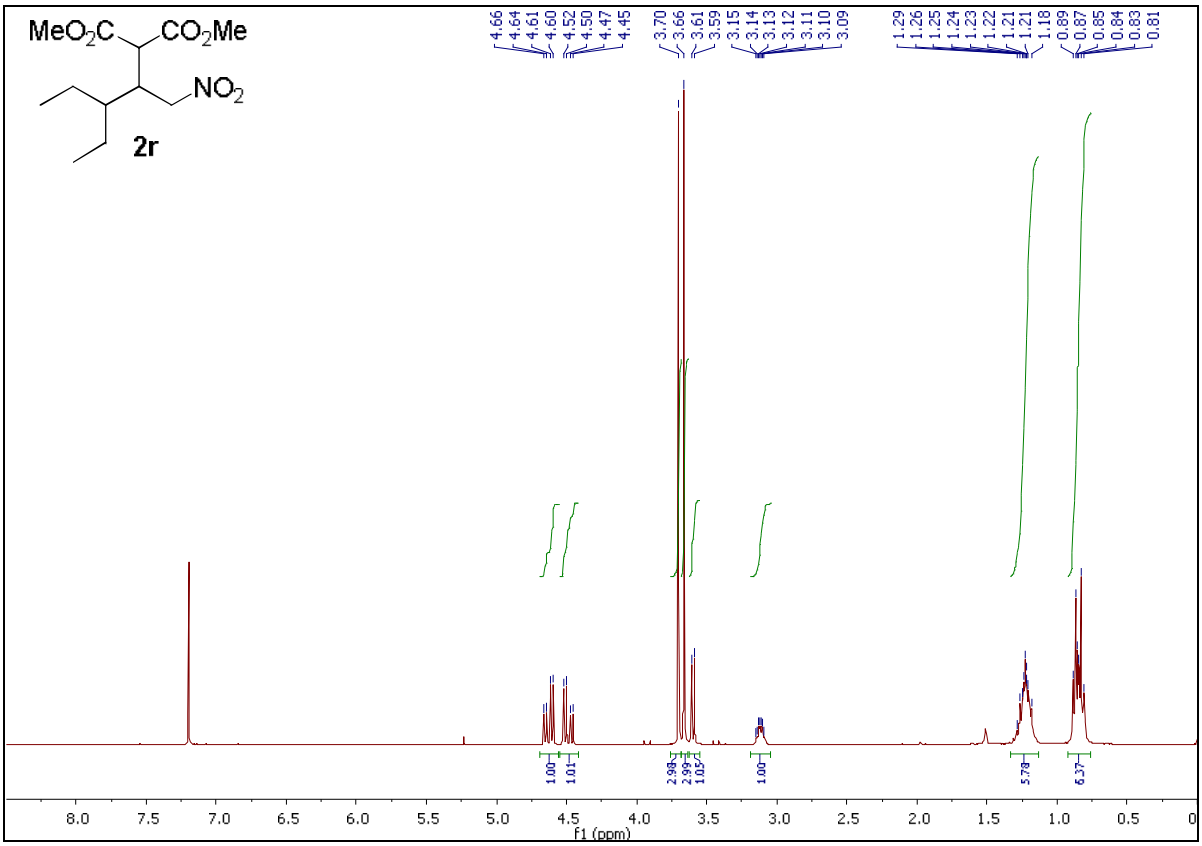


Figure S66. ^{1}H NMR (300 MHz, $CDCl_3$)

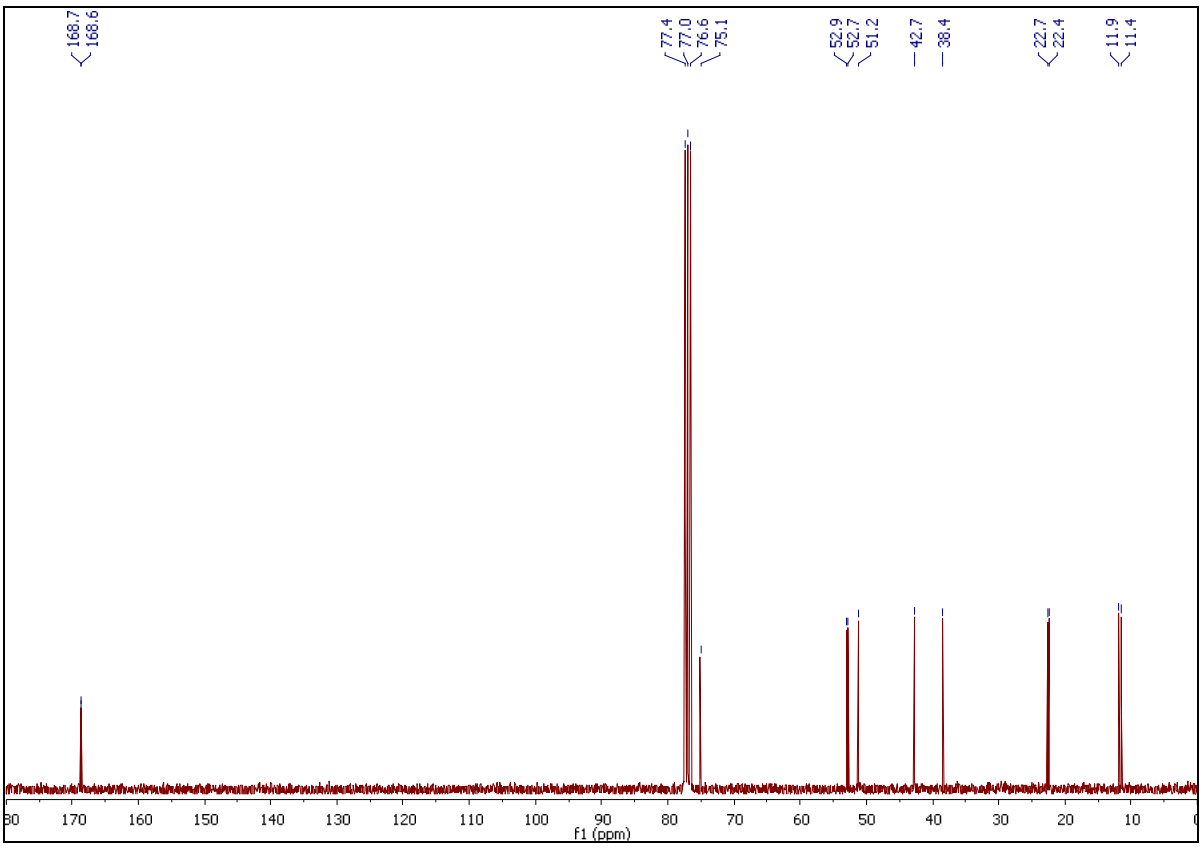


Figure S67. ^{13}C NMR (75 MHz, $CDCl_3$)

8. Chiral HPLC traces:

Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm

Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\5-Cellucoat\r.
26-04-2012 23-49-04.dat
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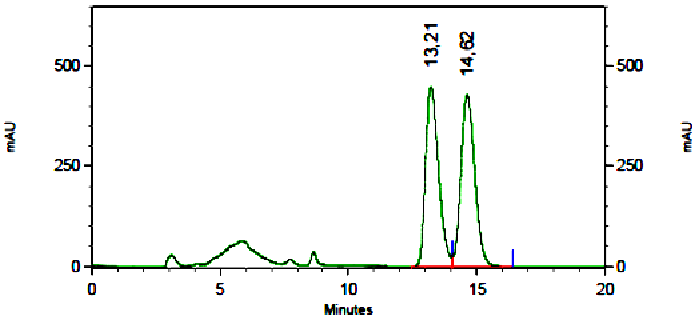
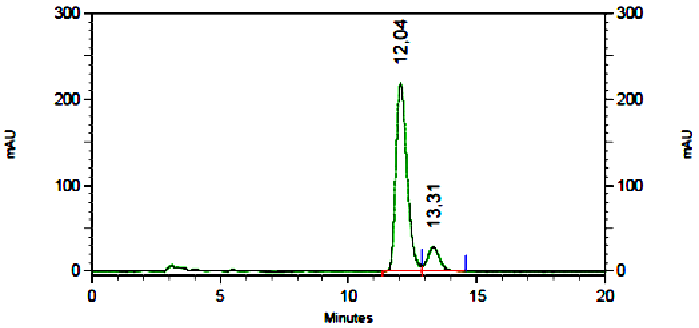
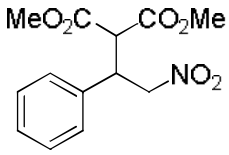
Acquired: 26/04/2012 23:50:25







2a

VWD: Signal A, 220 nm Results

Retention Time	Area	Area %
12.037	110885071	87.87
13.307	15311717	12.13
Totals	126196788	100.00

Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm

Area % Report

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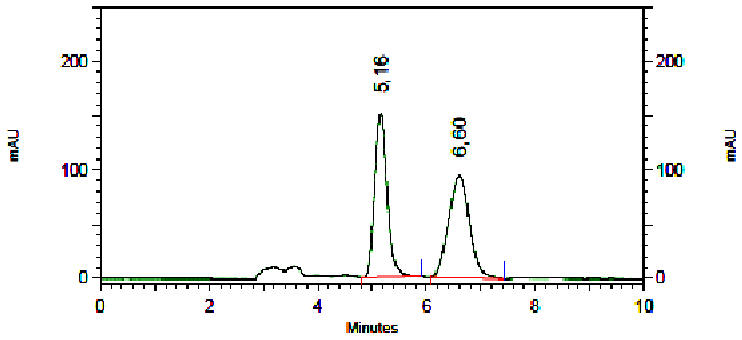
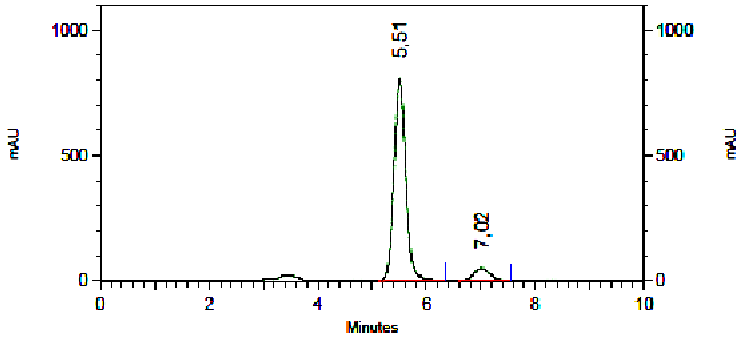
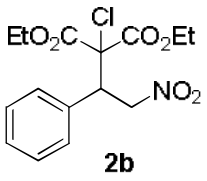
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 20/04/2012 15:38:06







2b

VWD: Signal A, 220 nm Results

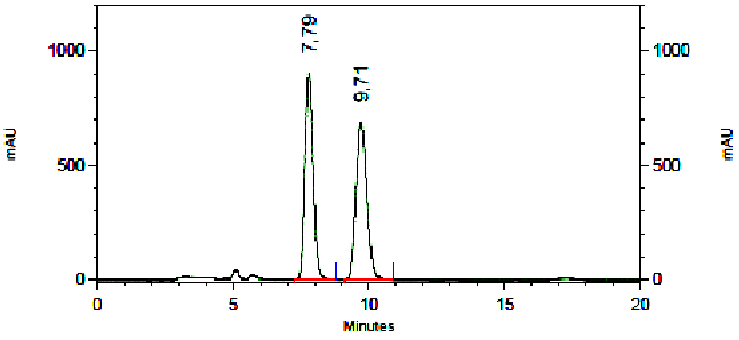
Retention Time	Area	Area %
5,510	201666141	92,42
7,017	16535249	7,58

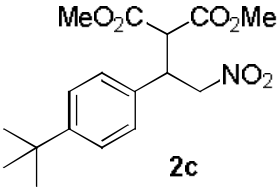
Totals	218201390	100,00

Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 70:30, 1mL/min, 220 nm

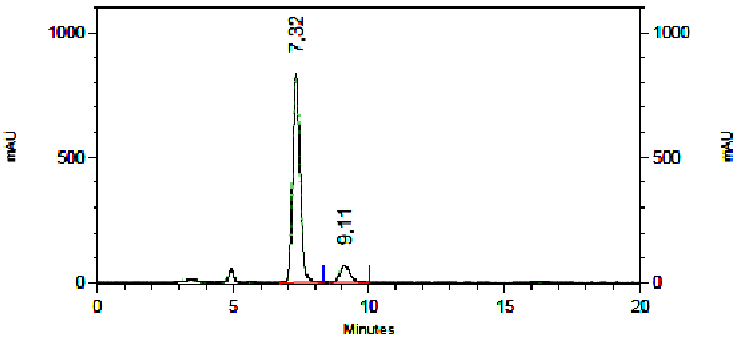
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\5-Cellucoat\r
27-04-2012 2-25-15.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 27/04/2012 2:26:38





2c



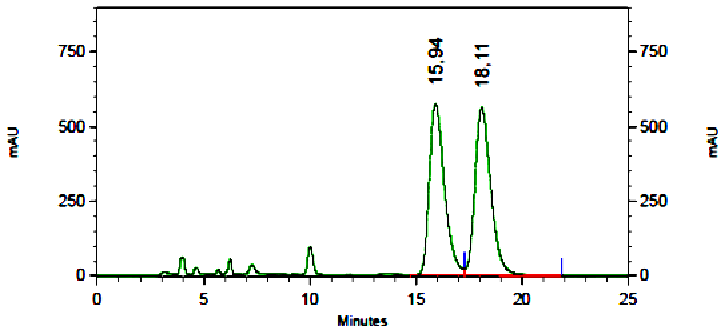
VWD: Signal A, 220 nm Results

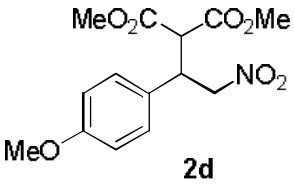
Retention Time	Area	Area %
7,320	265893341	90,27
9,107	28647099	9,73
Totals	294540440	100,00

Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm

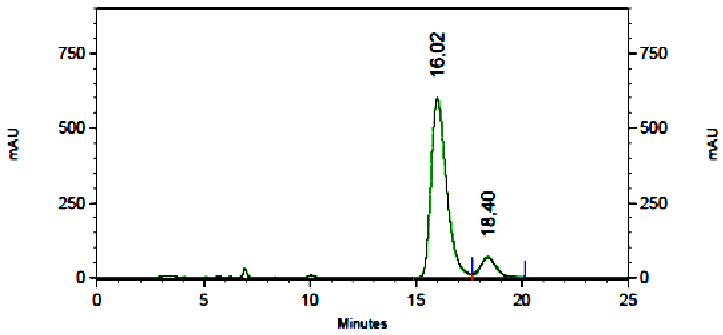
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\HTE PGGiv-21-16-30.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 21/05/2012 21:17:57





2d



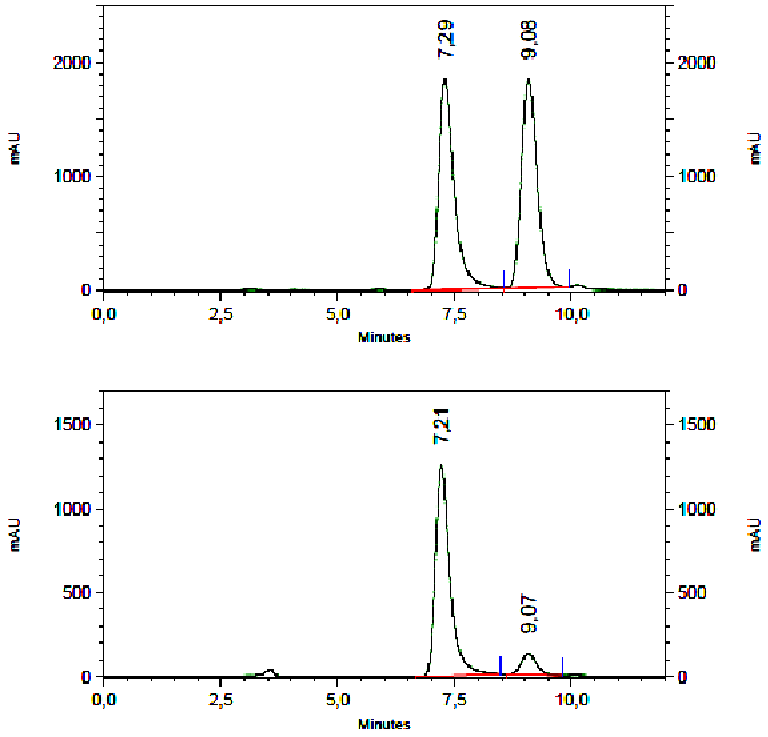
VWD: Signal A, 220 nm Results

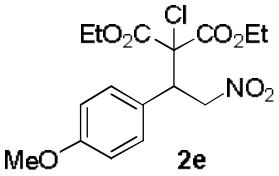
Retention Time	Area	Area %
16.020	509806019	89.63
18.400	58978806	10.37
Totals		
	568784825	100.00

Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm

Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\5-Cellucoat\
13-05-2012 15-10-31.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 13/05/2012 15:11:52





2e

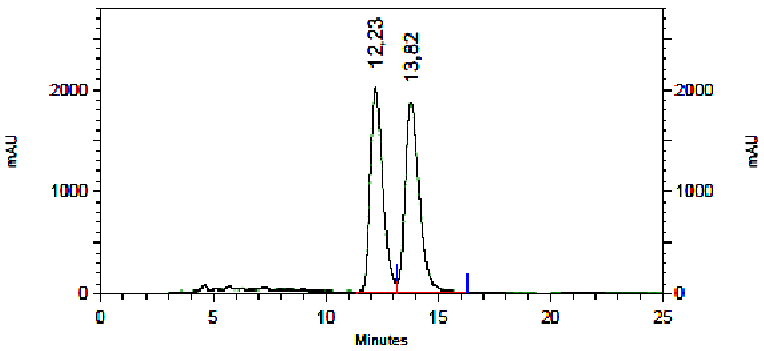
VWD: Signal A, 220 nm Results

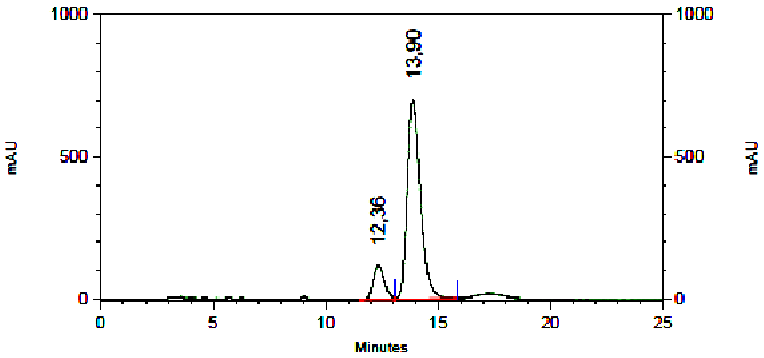
Retention Time	Area	Area %
7,213	454234401	90,32
9,073	48693334	9,68
Totals		
	502927735	100,00

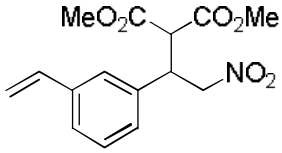
Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm

Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\HTE\PGGv-22-09-05.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1ml
Acquired: 21/05/2012 22:10:30







2f

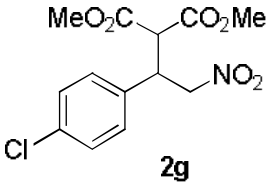
VWD: Signal A, 220 nm Results

Retention Time	Area	Area %
12,357	69260061	12,63
13,900	479240947	87,37
Totals	548501008	100,00

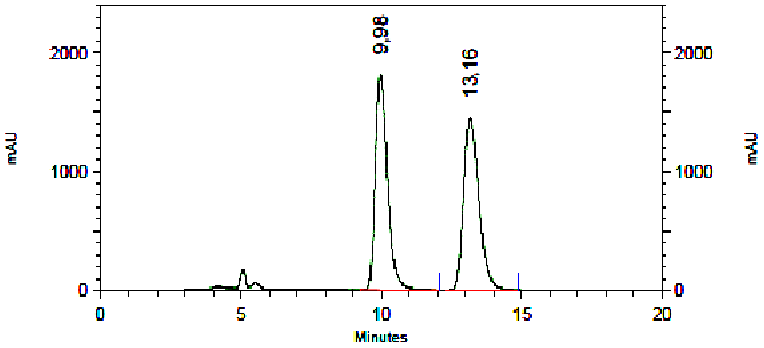
Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 70:30, 1mL/min, 220 nm

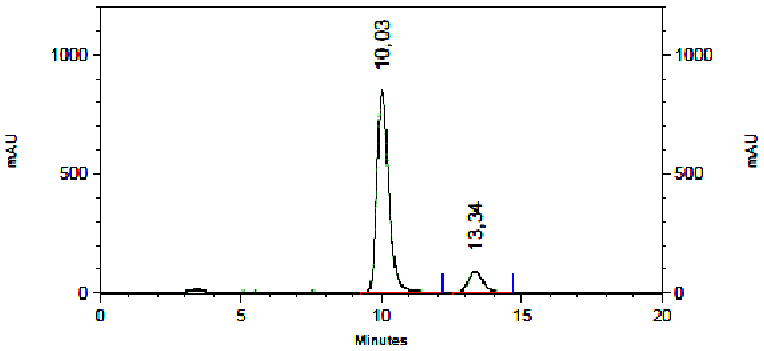
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\HTE\PGGv-0-20-38.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 22/05/2012 0:22:03



2g





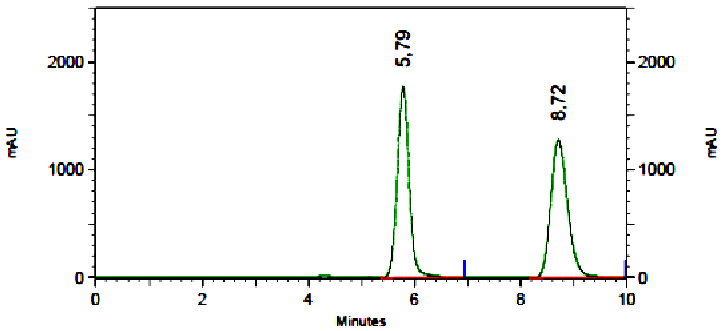
VWD: Signal A, 220 nm Results

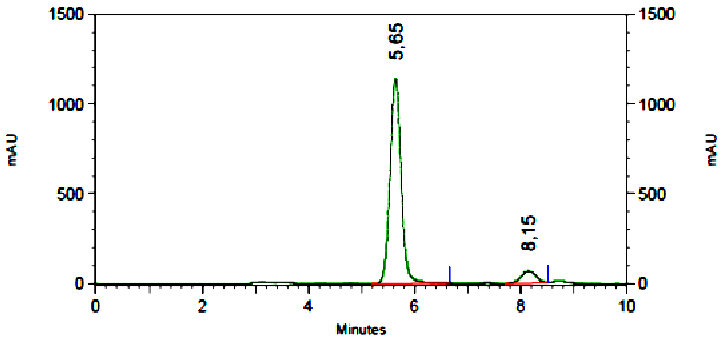
Retention Time	Area	Area %
10,033	419381361	88,48
13,340	54579812	11,52
Totals	473961173	100,00

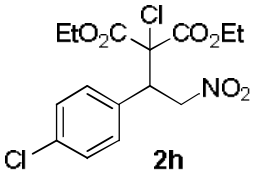
Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm

Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\5-Cellucoat\a dil 24-04-2012 17-54-56.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 24/04/2012 17:56:19







2h

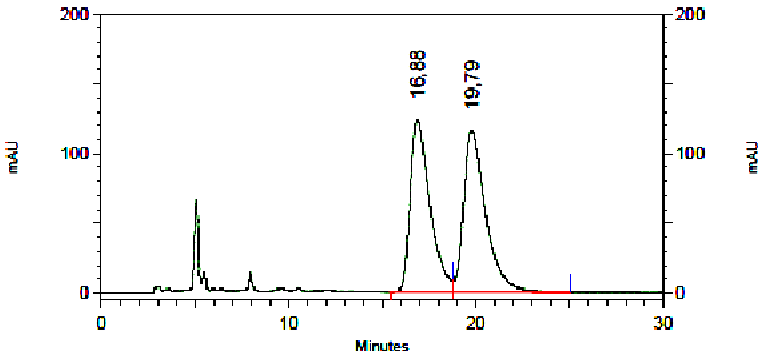
VWD: Signal A, 220 nm Results

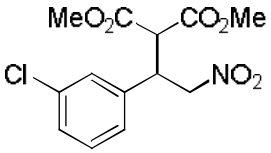
Retention Time	Area	Area %
5.647	277349951	92.84
8.153	21375861	7.16
Totals		
	298725812	100.00

Conditions: Kromasil 5-AmyCoat, *n*-hexane/isopropanol = 90:10, 1mL/min, 220 nm

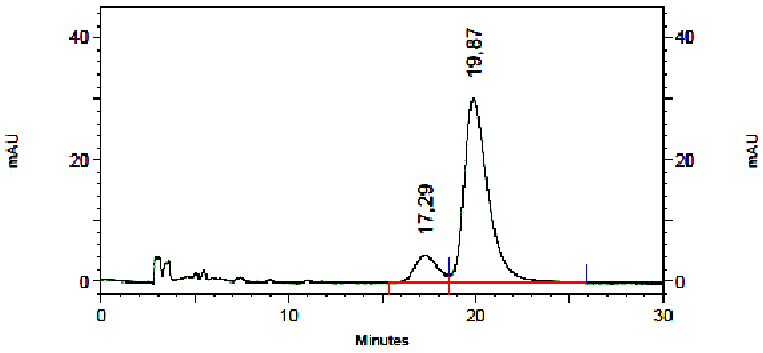
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\HTE\PGGV-10-22-27.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 22/05/2012 10:23:48





2i



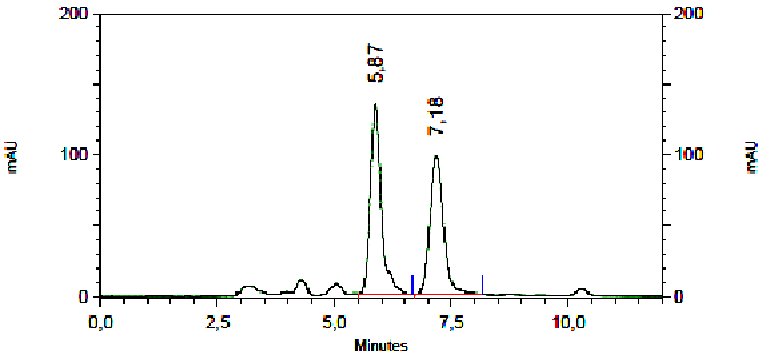
VWD: Signal A, 230 nm Results

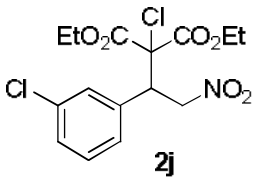
Retention Time	Area	Area %
17,290	6476096	12,47
19,873	45474473	87,53
Totals	51950569	100,00

Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm

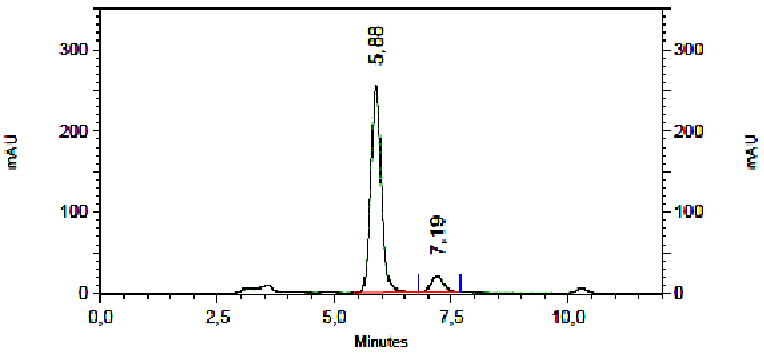
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\HTE\PGGv-6-31-27.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 22/05/2012 6:32:51





2j



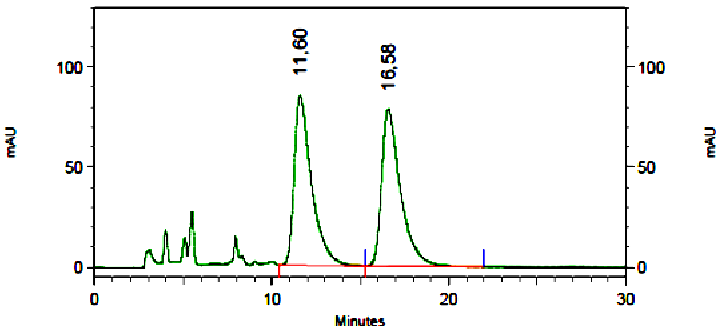
VWD: Signal A, 220 nm Results

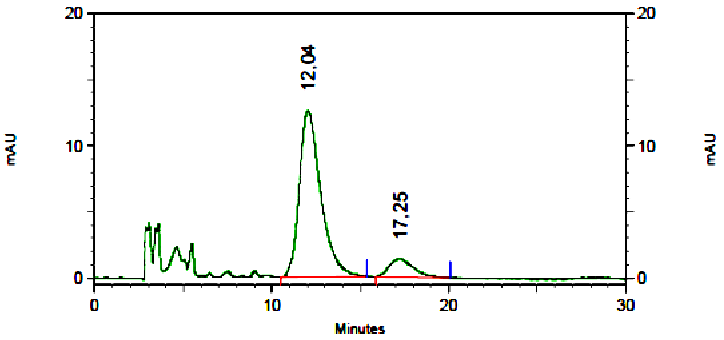
Retention Time	Area	Area %
5,883	66949887	91,72
7,190	6043654	8,28
Totals	72993541	100,00

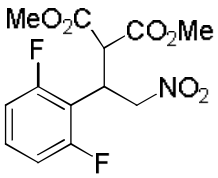
Conditions: Kromasil 5-AmyCoat, *n*-hexane/isopropanol = 90:10, 1mL/min, 220 nm

Area % Report

Data File: C:\EZChrom Elite Enterprise\Projects\Default\Data\PilarG\HTE PGGV 11-24-57.dat
Method: C:\EZChrom Elite Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 22/05/2012 11:26:25







2k

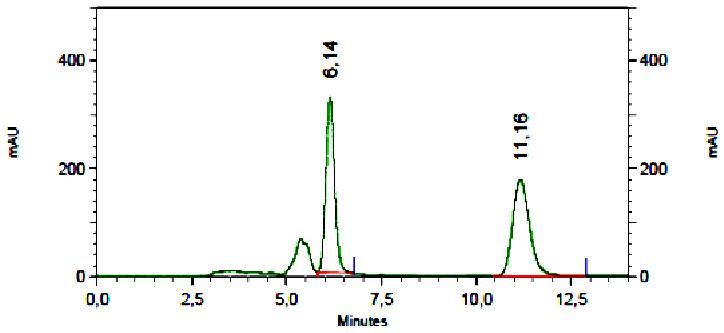
VWD: Signal A, 230 nm Results

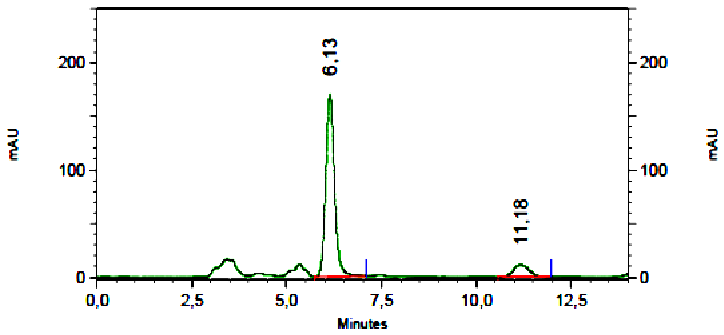
Retention Time	Area	Area %
12.043	17878994	88.66
17.250	2286405	11.34
Totals		
	20165399	100.00

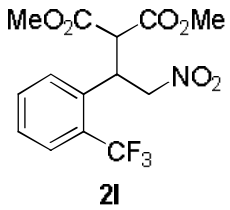
Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 70:30, 1mL/min, 220 nm

Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\HTE PGG\–1-13-18.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 22/05/2012 1:14:42







2l

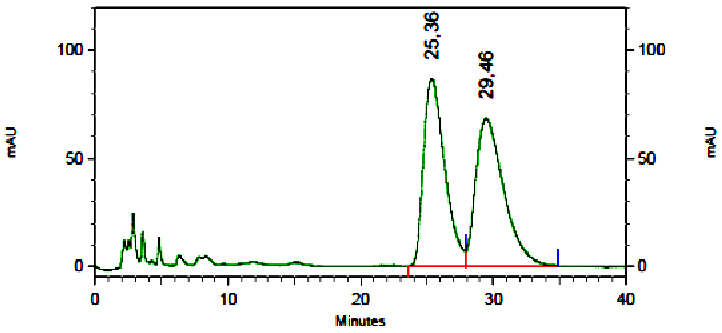
VWD: Signal A, 220 nm Results

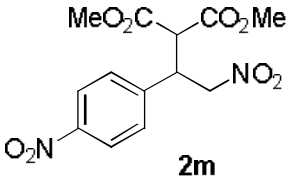
Retention Time	Area	Area %
6.133	45650579	88.88
11.177	5711871	11.12
Totals		
	51362450	100.00

Conditions: Chiralcel OJ, *n*-hexane/isopropanol = 60:40, 1.5mL/min, 220 nm

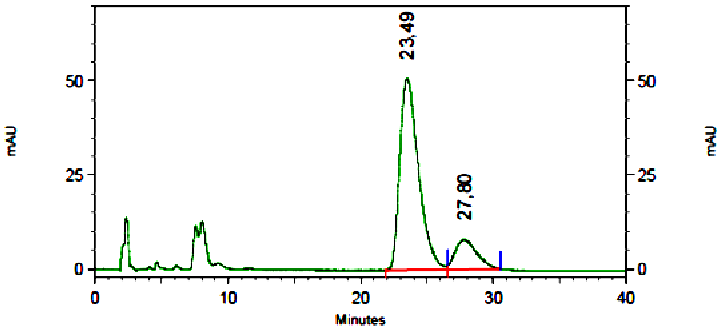
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\OJ\PGGV-5C
10-39-27.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL.
Acquired: 27/04/2012 10:40:52





2m



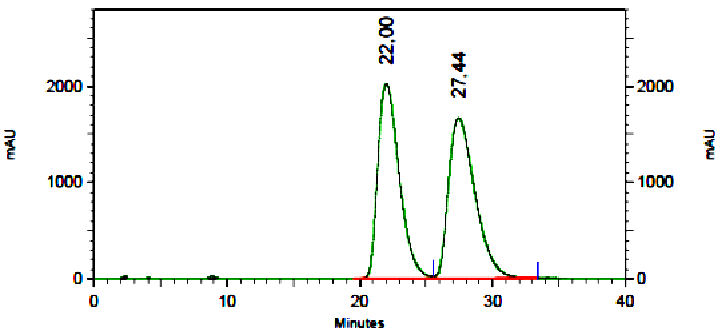
VWD: Signal A, 220 nm Results

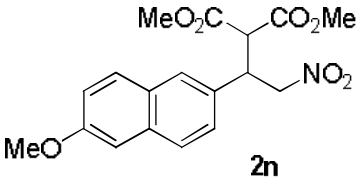
Retention Time	Area	Area %
23.490	84307044	84.76
27.797	15154037	15.24
Totals	99461081	100.00

Conditions: Chiralcel OJ, *n*-hexane/isopropanol = 40:60, 1.5mL/min, 220 nm

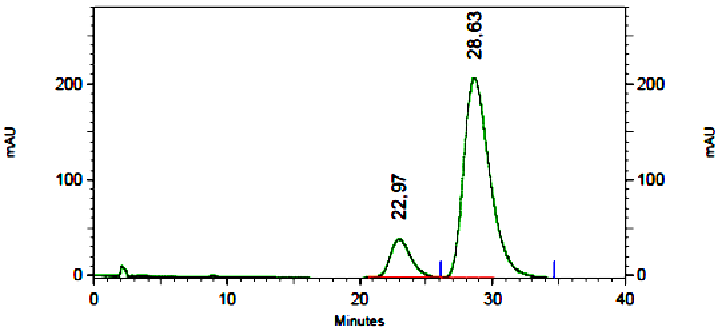
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\OJ\PGGV-5(
16-55-16.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 14/05/2012 16:56:34





2n



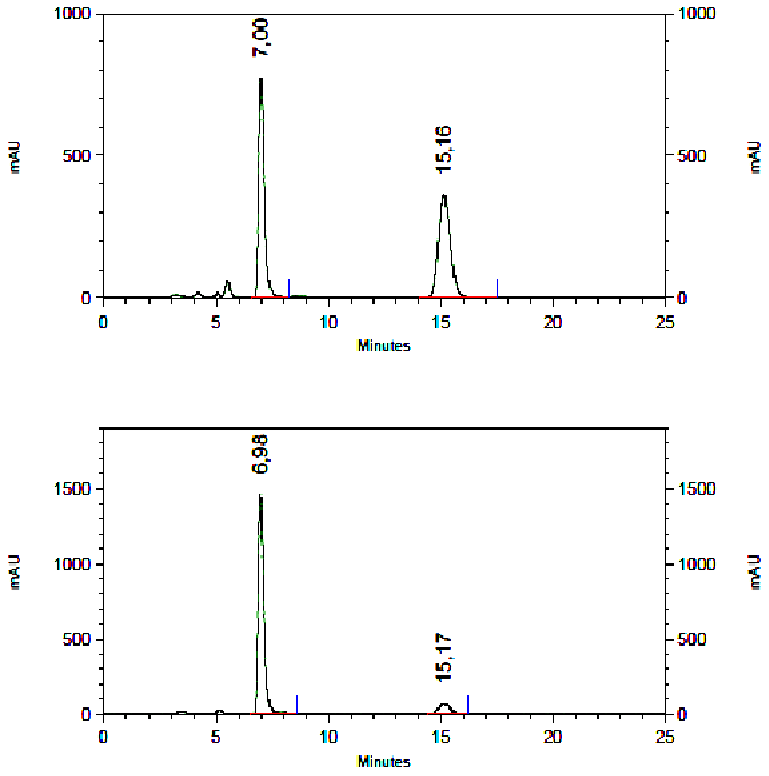
VWD: Signal A, 220 nm Results

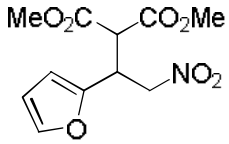
Retention Time	Area	Area %
22.967	71227692	13.00
28.633	476758672	87.00
Totals		
	547986364	100.00

Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 70:30, 1mL/min, 220 nm

Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\HTE\PGGv-2-05-50.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 22/05/2012 2:07:13





2o

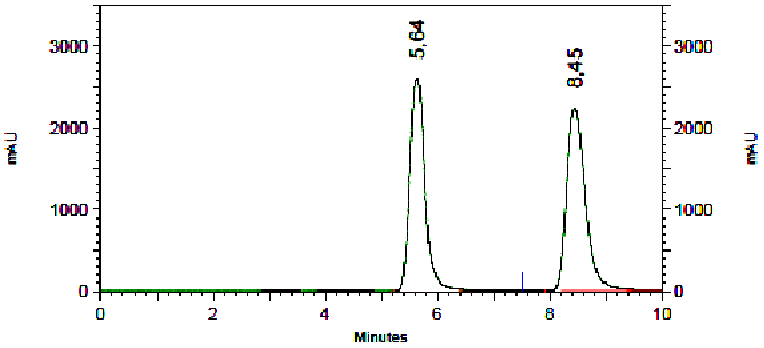
VWD: Signal A, 220 nm Results

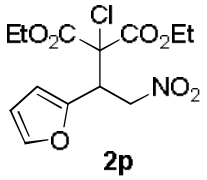
Retention Time	Area	Area %
6,980	425850290	90,75
15,167	43418238	9,25
Totals	469268528	100,00

Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 80:20, 1mL/min, 220 nm

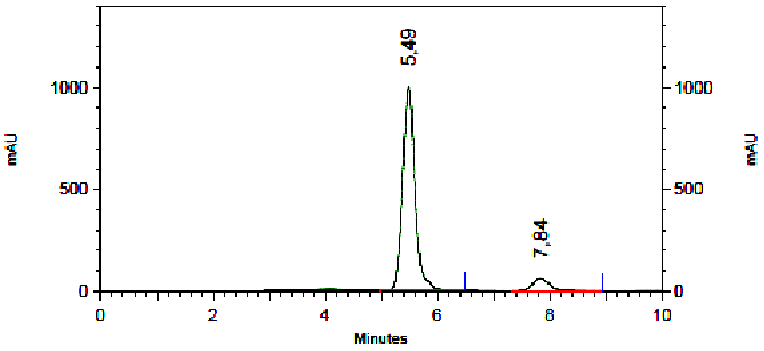
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\5-Cellucoat\dil 24-04-2012 18-28-49.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 24/04/2012 18:30:16





2p



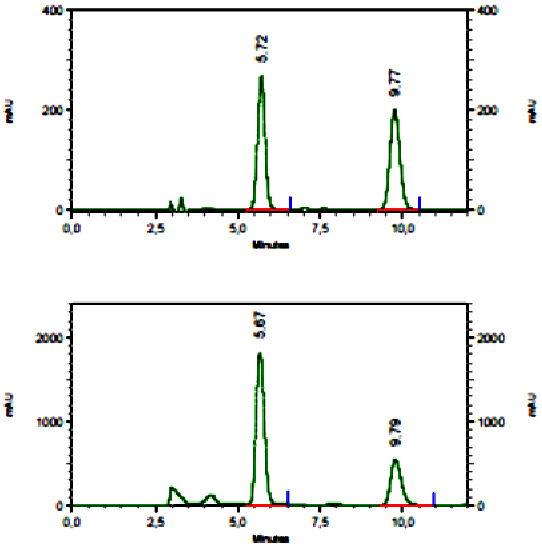
VWD: Signal A, 220 nm Results

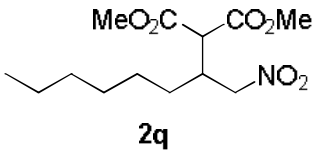
Retention Time	Area	Area %
5,493	256195223	91,73
7,837	23098758	8,27
Totals	279293981	100,00

Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 90:10, 1mL/min, 220 nm

Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\5-Cellucoat\P0
59b.dat Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL 2
Acquired: 23/01/2012 13:05:23





2q

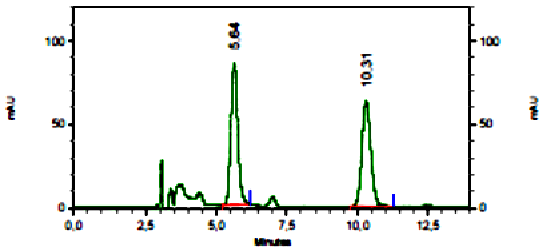
VWD: Signal A, 220 nm Results

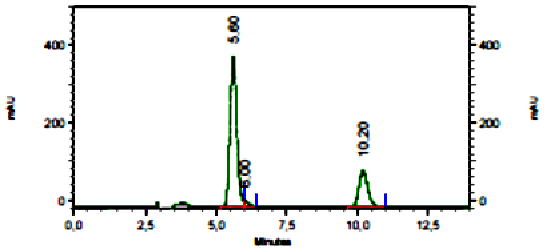
Retention Time	Area	Area %
5.670	531188426	72.13
9.787	205238186	27.87
Totals	736426612	100.00

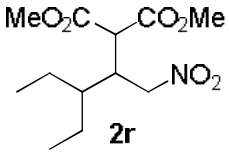
Conditions: Kromasil 5-Cellucoat, *n*-hexane/isopropanol = 90:10, 1mL/min, 220 nm

Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\PilarG\5-Cellucoat\a
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\Pilar5 8020 1mL
Acquired: 23/01/2012 18:42:02







2r

Subtract 1 Results

Retention Time	Area	Area %
5.603	109815088	74.94
6.000	2514673	1.72
10.200	34211537	23.35
Totals	146541298	100.00

9. References

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