Electronic Supplementary Information

Allyl Sulphides in Olefin Metathesis: Catalyst Considerations and Traceless Promotion of Ring-Closing Metathesis

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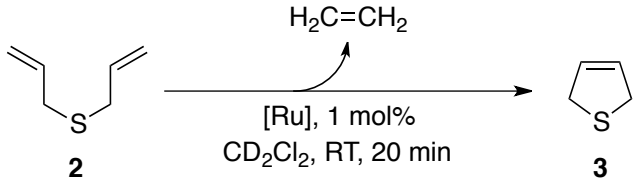
General experimental considerations

Proton nuclear magnetic resonance (^{1}H NMR) and proton-decoupled carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 400 MHz spectrometer. ^{1}H and ^{13}C NMR Spectra were assigned as fully as possible using COSY, HSQC, and DEPT-135 experiments. All chemical shifts are quoted on the δ scale in ppm using residual solvent as the internal standard (^{1}H NMR: $CDCl_3$ = 7.26; DMSO-d_6 = 2.50; CD_2Cl_2 = 5.32 and ^{13}C NMR: $CDCl_3$ = 77.0; DMSO-d_6 = 39.5; CD_2Cl_2 = 54.0). Coupling constants (*J*) are reported in hertz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, and a = apparent. Infrared (IR) spectra were recorded on a Fourier Transform spectrophotometer using thin films on NaCl plates for liquids and oils and KBr discs for solids and crystals. Absorption maxima (υ_{max}) are reported in wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were recorded on an electrospray ionization mass spectrometer with atmospheric pressure chemical ionization (APCI) capability and an orbitrap mass analyzer. Accurate mass (m/z) values are reported in Daltons. Thin layer chromatography (TLC) was carried out using aluminum backed 200 μm silica plates impregnated with a UV_{254} fluorophore. Visualization of the silica plates was achieved using a UV lamp (λ_{max} = 254 nm), and/or ammonium molybdate (5% in 2M H_2SO_4), and/or potassium permanganate (5% $KMnO_4$ in 1M NaOH with 5% potassium carbonate). Flash column chromatography was carried out using 60 Å, 40-63 mm silica gel. All solvents and reagents were used as received from commercial suppliers. Deionized water was used for chemical reactions unless otherwise indicated. 'Petrol' refers to the fraction of light petroleum ether boiling in the range 40-60 ºC. Brine refers to a saturated solution of sodium chloride. Anhydrous magnesium sulfate ($MgSO_4$) was used as a drying agent after reaction workup, as indicated. In instances where starting materials or reagents have been reported previously in the literature, references are provided that corroborate spectroscopic assignments and other analytical characterization.

Ring closing olefin metathesis of diallyl sulphide

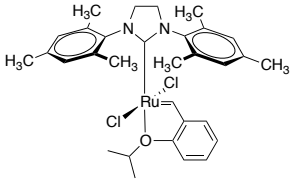
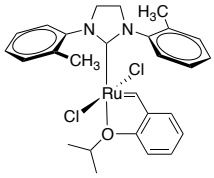
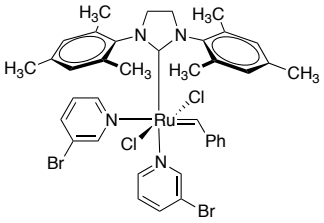
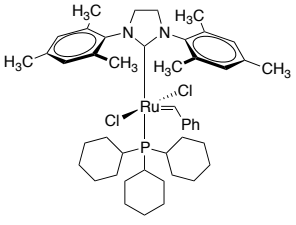


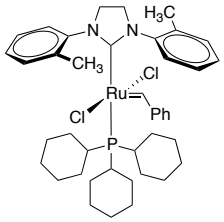
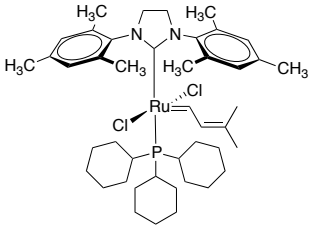
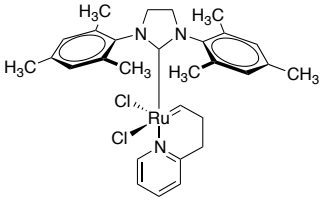
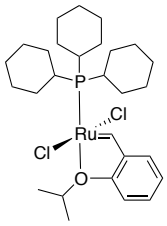
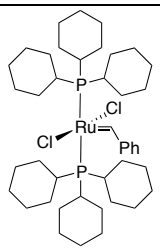
2 **3**

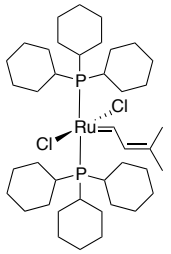
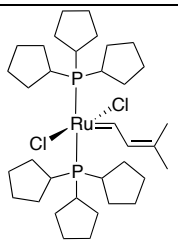
General Procedure: Diallyl sulphide **2** (23 mg, 0.20 mmol) was added to a 5 mL vial equipped with a magnetic stirring bar and placed under an atmosphere of nitrogen before dissolving in CD_2Cl_2 (0.40 mL). In a separate vial, the olefin metathesis catalyst (1 mol%) was added and placed under an atmosphere of

nitrogen before dissolving in CD_2Cl_2 (0.40 mL). The catalyst solution was then sparged with nitrogen and then transferred via syringe to the vial containing the diallyl sulphide. The reaction was stirred at room temperature for 20 minutes. After this time, the reaction was sparged with nitrogen for an additional 1-2 minutes to remove ethylene from solution. The reaction mixture was then transferred to an NMR tube and analyzed by ^{1}H NMR spectroscopy. Reaction conversions were determined by relative integration of the $C\underline{H}_2S$ proton signals of diallyl sulphide (δ = 3.09) and the 2,5-dihydrothiophene RCM product **3** (δ = 3.74). The results are summarized in the Table S1, along with ^{1}H NMR spectra.

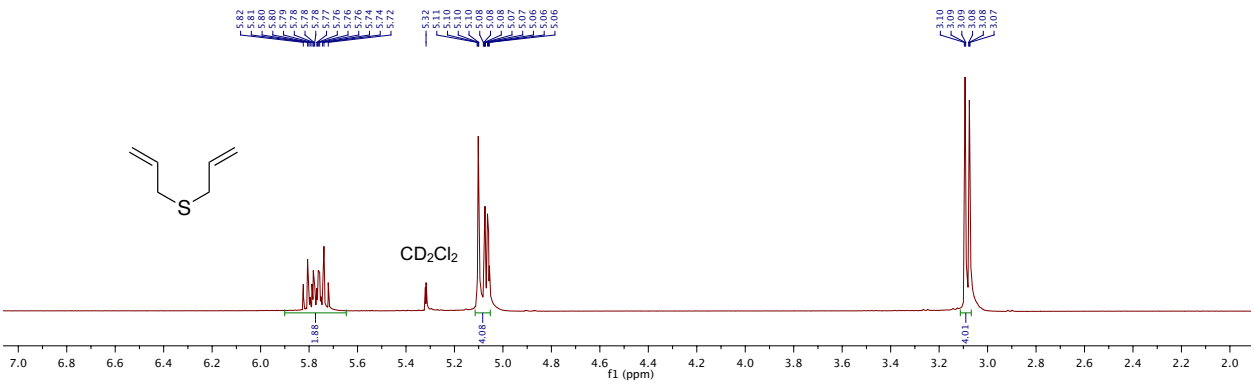
Table S1:

Entry	Catalyst (CAS No.)	Catalyst Number	Catalyst Reference	RCM conversion
1	 **(301224-40-8)**	**1**	Garber *et al*[1]	100%
2	 **(927429-61-6)**	**4**	Stewart *et al*[2]	88%
3	 **(900169-53-1)**	**5**	Love *et al*[3]	53%
4	 **(246047-72-3)**	**6**	Scholl *et al*[4]	11%

5	 **(927429-60-5)**	**7**	Stewart *et al*[2]	6%
6	 **(253688-91-4)**	**8**	Chatterjee *et al*[5]	3%
7	 **(802912-44-3)**	**9**	Ung *et al*[6]	0%
8	 **(203714-71-0)**	**10**	Kingsbury *et al*[7]	4%
9	 **(172222-30-9)**	**11**	Schwab *et al*[8]	6%

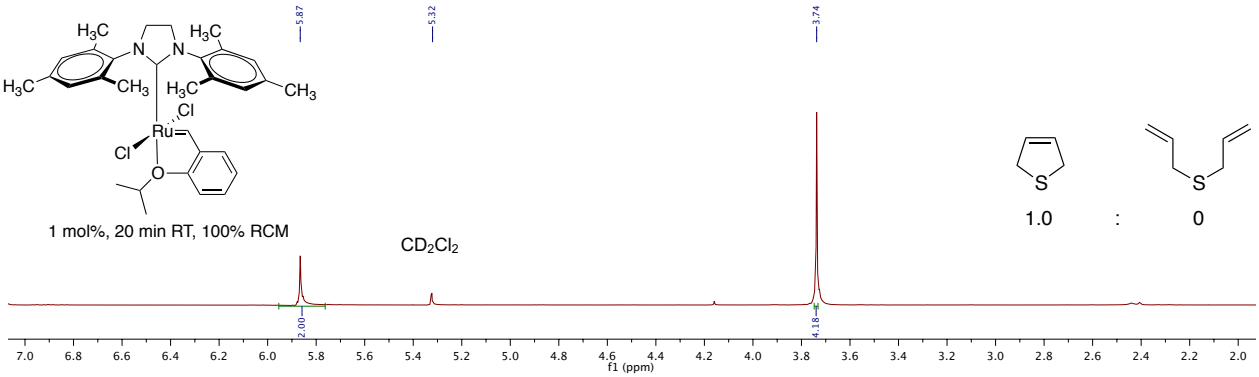
10	 **(194659-03-5)**	**12**	Wilhelm *et al*[9]	6%
11	 **(220883-08-9)**	**13**	Huang *et al*[10]	0%

^{1}H NMR (Starting material)



^{1}H NMR for RCM studies (Table S1)

Entry 1



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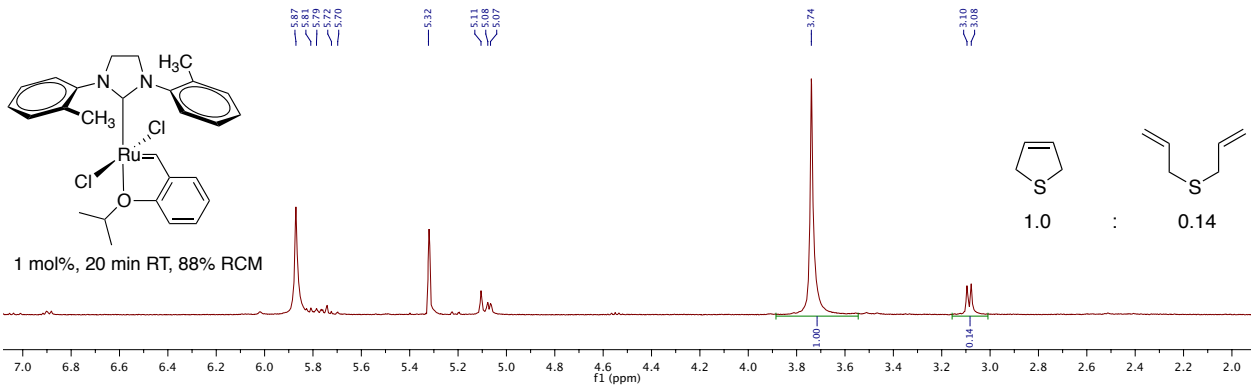

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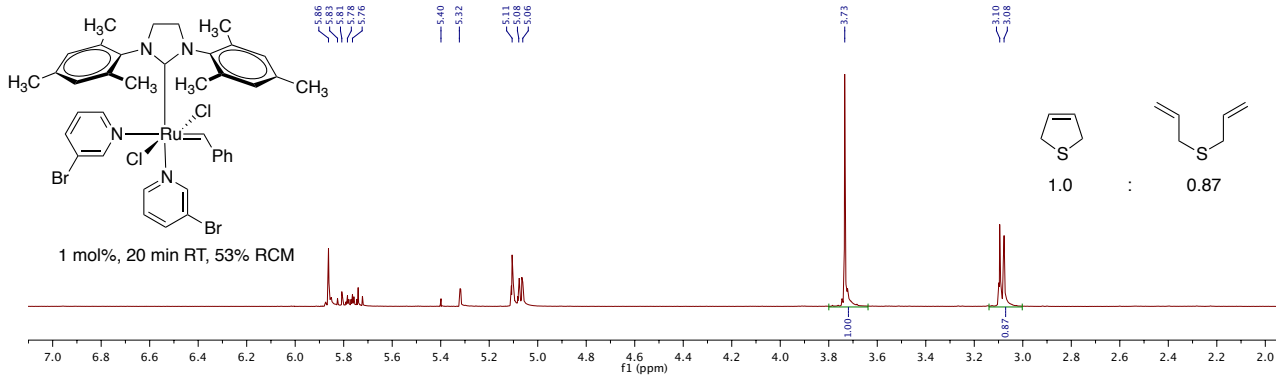

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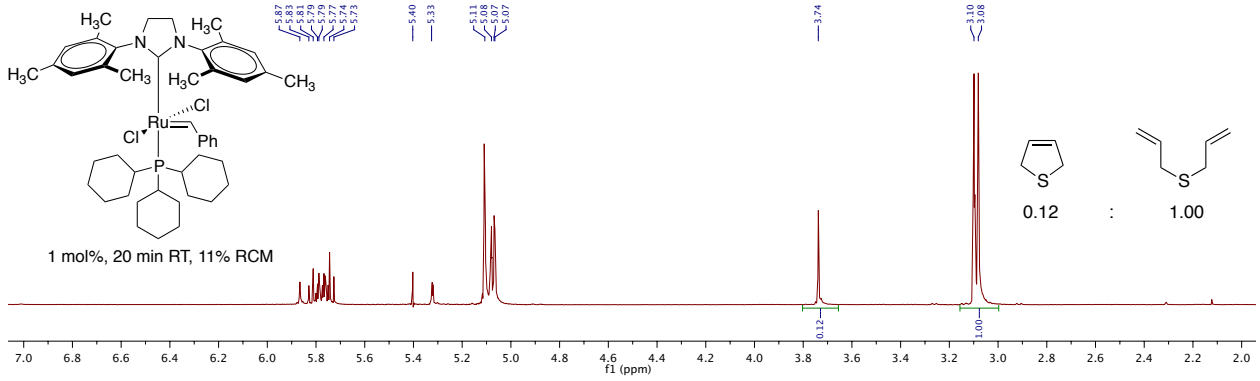

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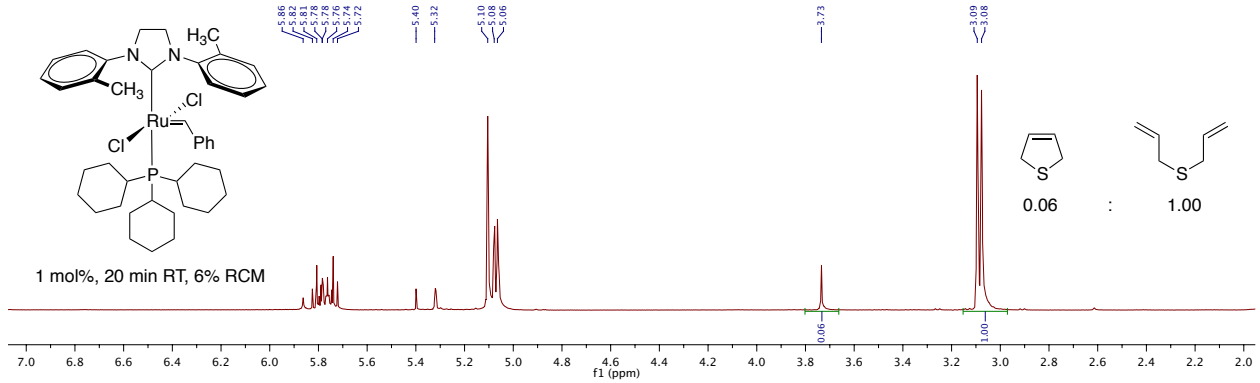

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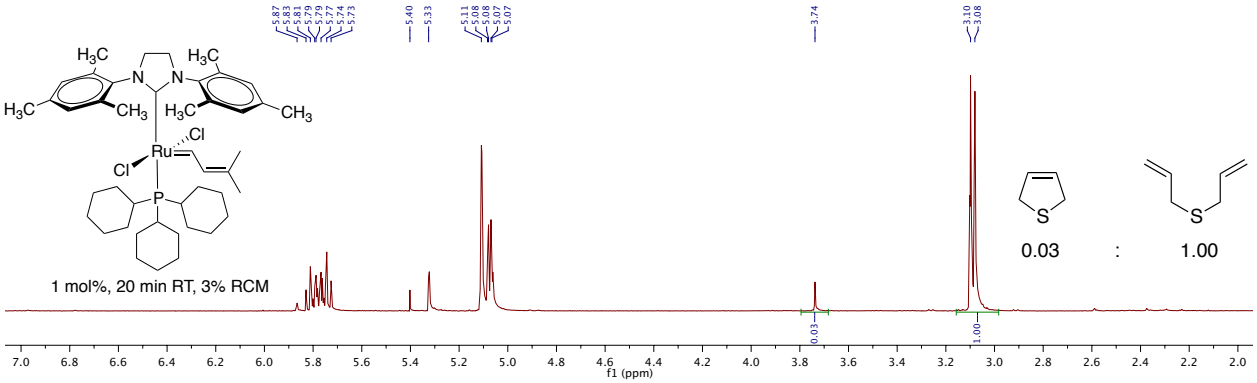

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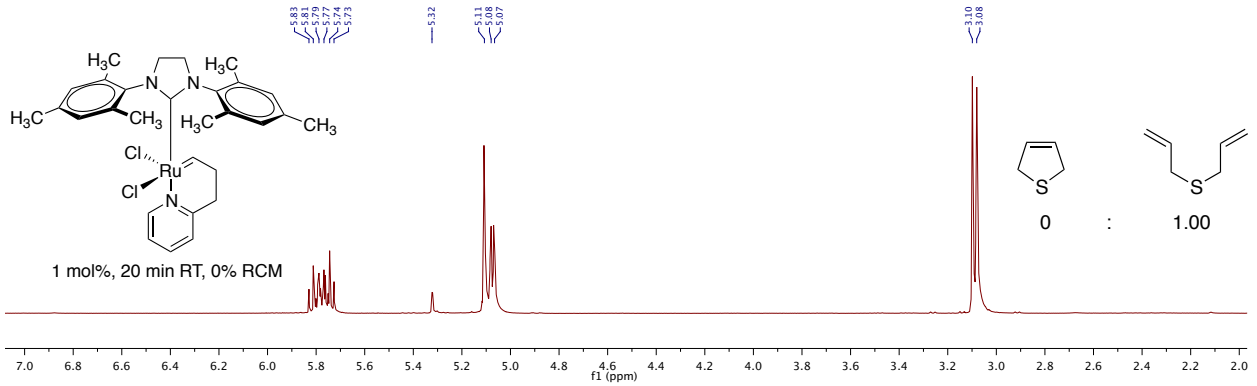

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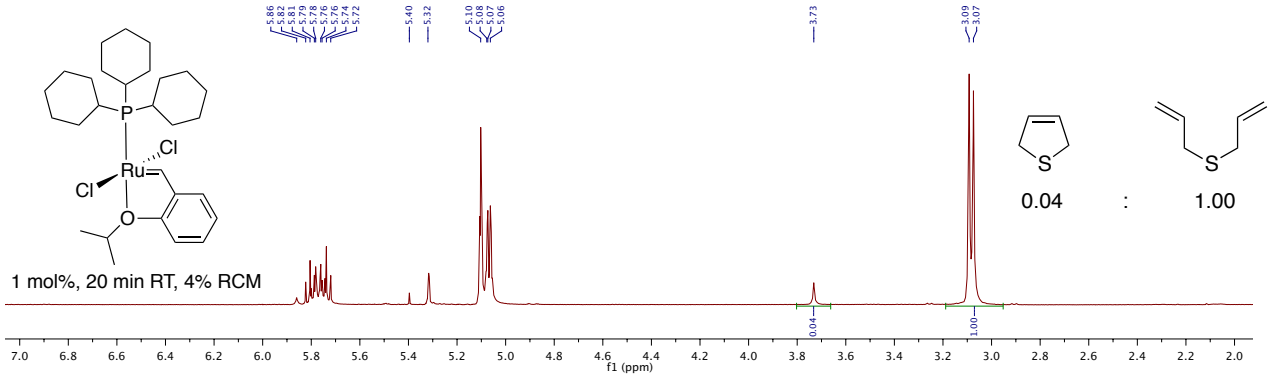

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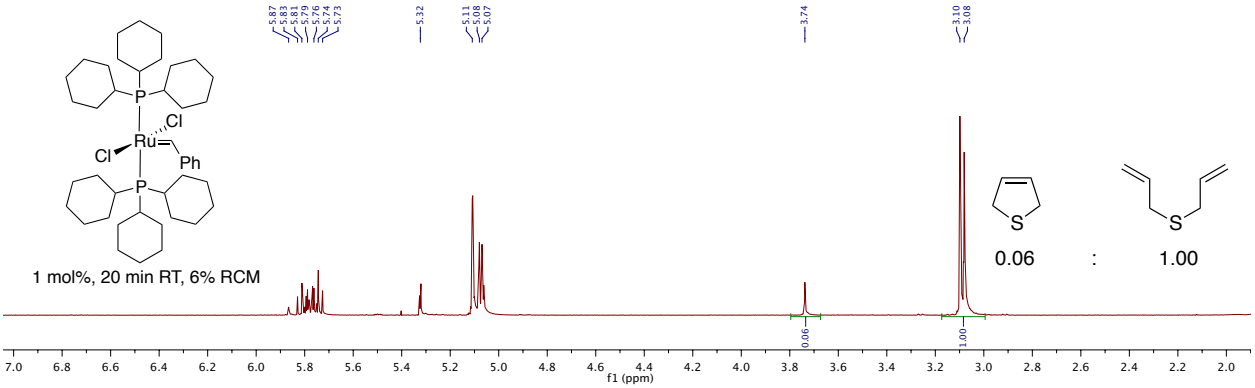

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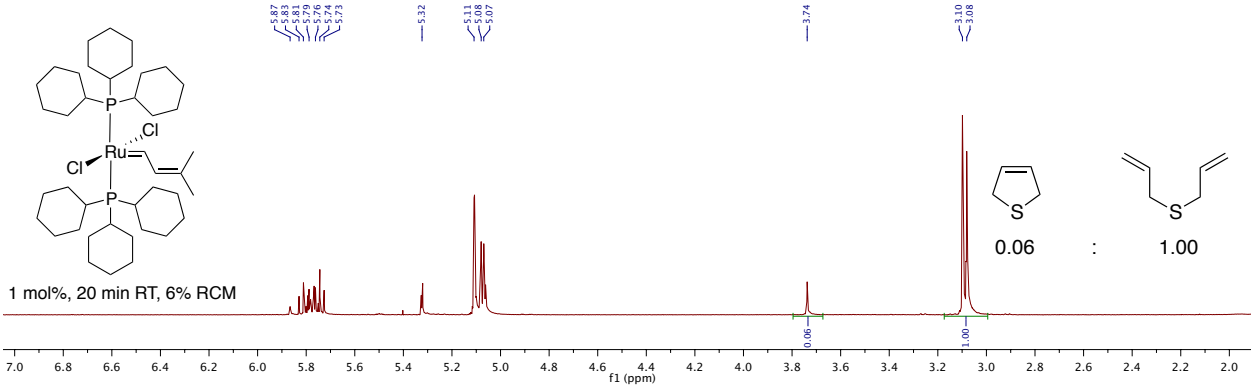

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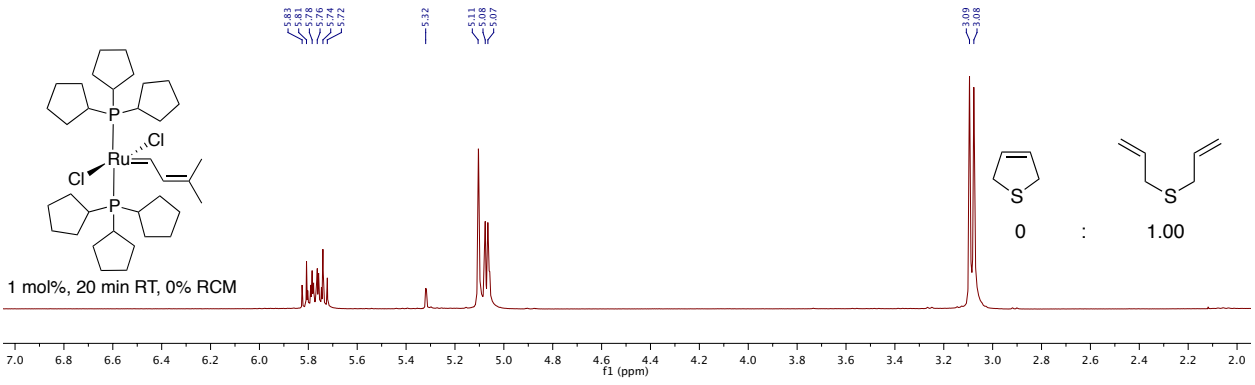
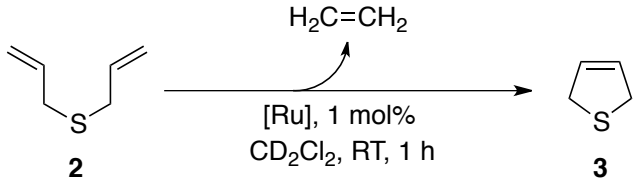


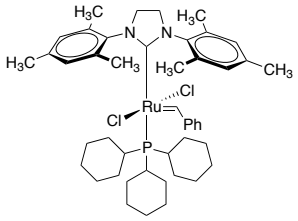
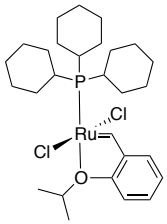
Ring closing olefin metathesis of diallyl sulphide (1 hour reaction with catalysts 6 and 10)



2 **3**

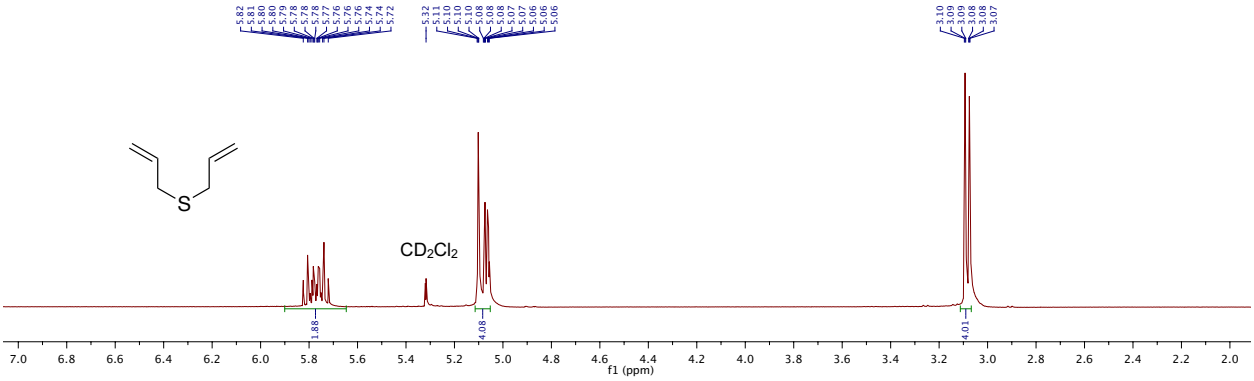
General Procedure: Diallyl sulphide **2** (23 mg, 0.20 mmol) was added to a 5 mL vial equipped with a magnetic stirring bar and placed under an atmosphere of nitrogen before dissolving in CD_2Cl_2 (0.40 mL). In a separate vial, the olefin metathesis catalyst (1 mol%) was added and placed under an atmosphere of nitrogen before dissolving in CD_2Cl_2 (0.40 mL). The catalyst solution was then sparged with nitrogen and then transferred via syringe to the vial containing the diallyl sulphide. The reaction was stirred at room temperature for 60 minutes. After this time, the reaction was sparged with nitrogen for an additional 1-2 minutes to remove ethylene from solution. The reaction mixture was then transferred to an NMR tube and analyzed by ^{1}H NMR spectroscopy. Reaction conversions were determined by relative integration of the C$\underline{H_2}$S proton signals of diallyl sulphide (δ = 3.09) and the 2,5-dihydrothiophene RCM product **3** (δ = 3.74). Note that the reaction mixture with catalyst **6** remains light pink throughout the reaction. The reaction mixture with catalyst **10** turns black within minutes.

Table S2:

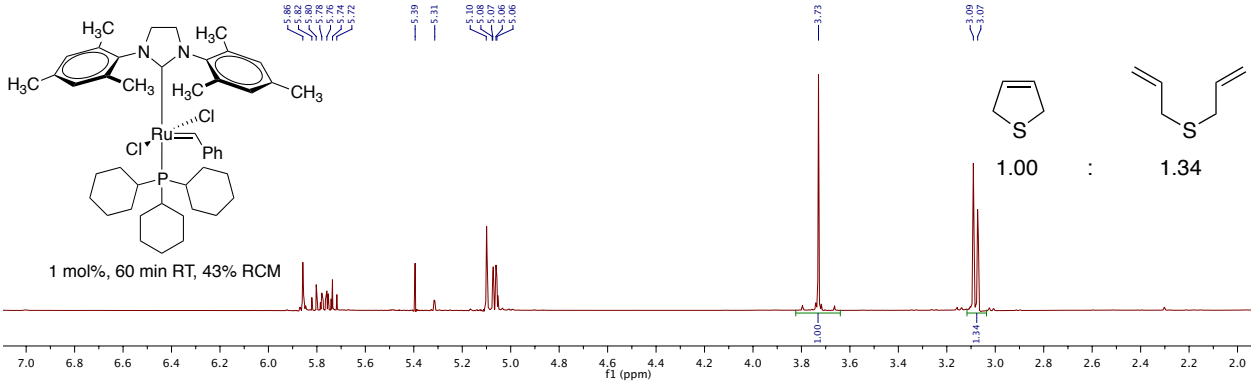
Entry	Catalyst (CAS No.)	Catalyst Number	RCM conversion
1	 **(246047-72-3)**	**6** **(1.7 mg)**	43%
2	 **(203714-71-0)**	**10** **(1.2 mg)**	6%

NMR Data from Table S2:

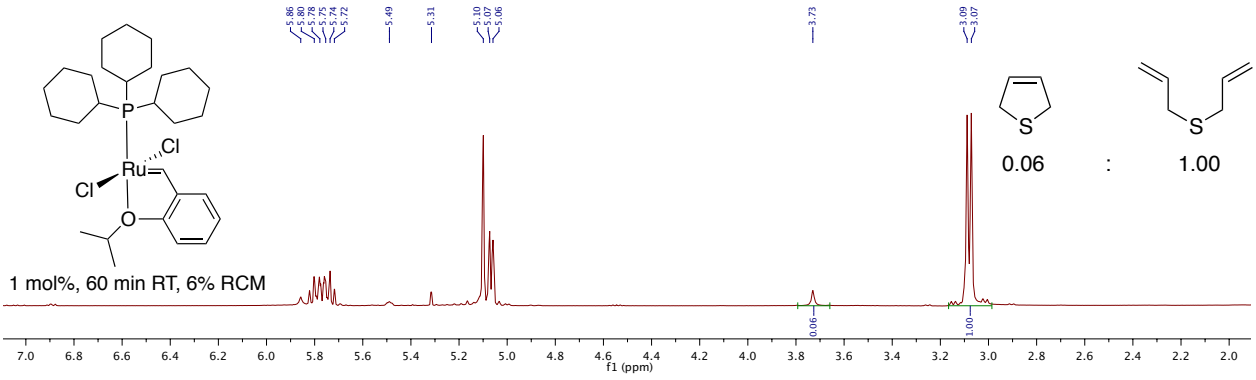
^{1}H NMR (Starting material)



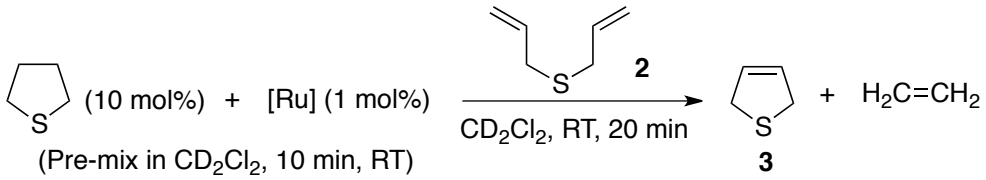
Entry 1



Entry 2

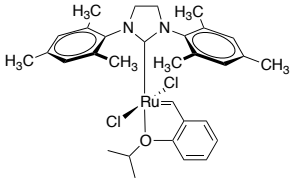
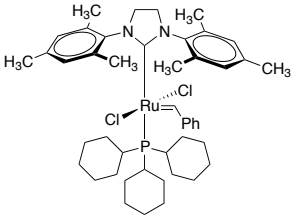


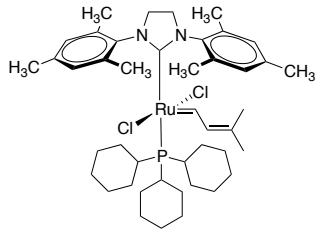
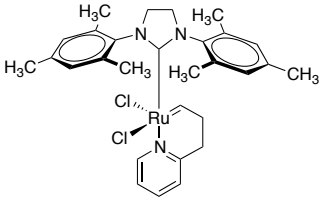
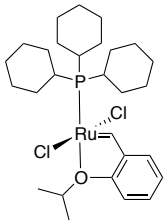
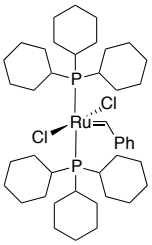
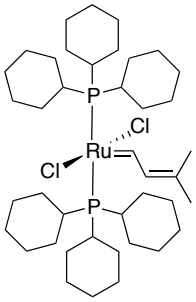
Examination of a cyclic thioether (tetrahydrothiophene) as potential inhibitor or activator of RCM



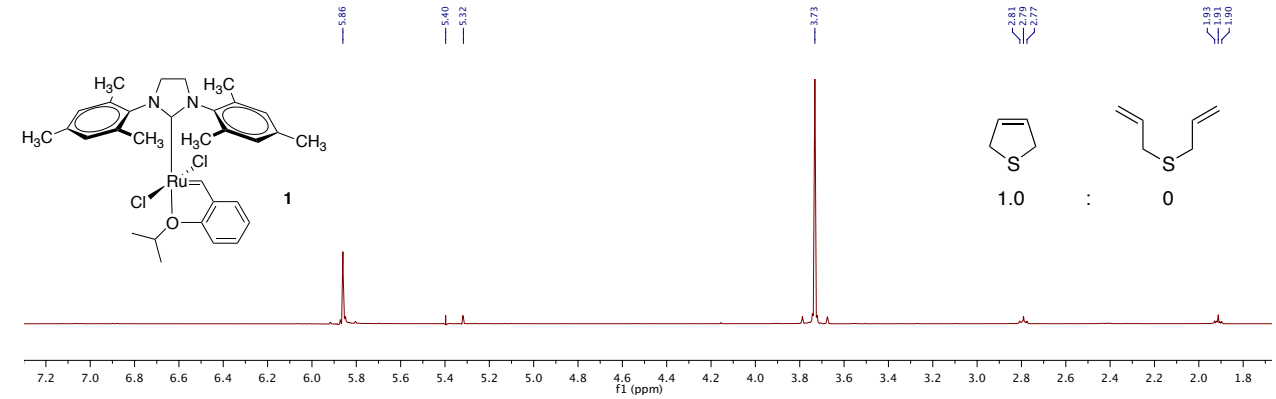
Diallyl sulphide **2** (23 mg, 0.20 mmol) was added to a 5 mL vial and placed under an atmosphere of nitrogen before dissolving in CD_2Cl_2 (0.40 mL). In a separate 5 mL vial equipped with a magnetic stirring bar, tetrahydrothiophene (1.7 μL, 0.020 mmol, 10 mol%) was added to CD_2Cl_2 (0.40 mL) by microsyringe and placed under an atmosphere of nitrogen. Next, the olefin metathesis catalyst (1 mol%) was added to the tetrahydrothiophene solution and stirred for 10 minutes at room temperature. After this time, the solution of catalyst was then added to the diallyl sulphide (**2**) solution by syringe. The reaction was stirred at room temperature for 20 minutes and then sparged with nitrogen for an additional 1-2 minutes to remove ethylene from solution. The reaction mixture was then transferred to an NMR tube and analyzed by ^{1}H NMR spectroscopy. Reaction conversions were determined by relative integration of the C$\underline{H}_2$S proton signals of diallyl sulphide (δ = 3.09) and the 2,5-dihydrothiophene RCM product **3** (δ = 3.74). The tetrahydrothiophene additive is seen at δ = 2.79 and 1.81. ^{1}H NMR spectra are shown after Table S3.

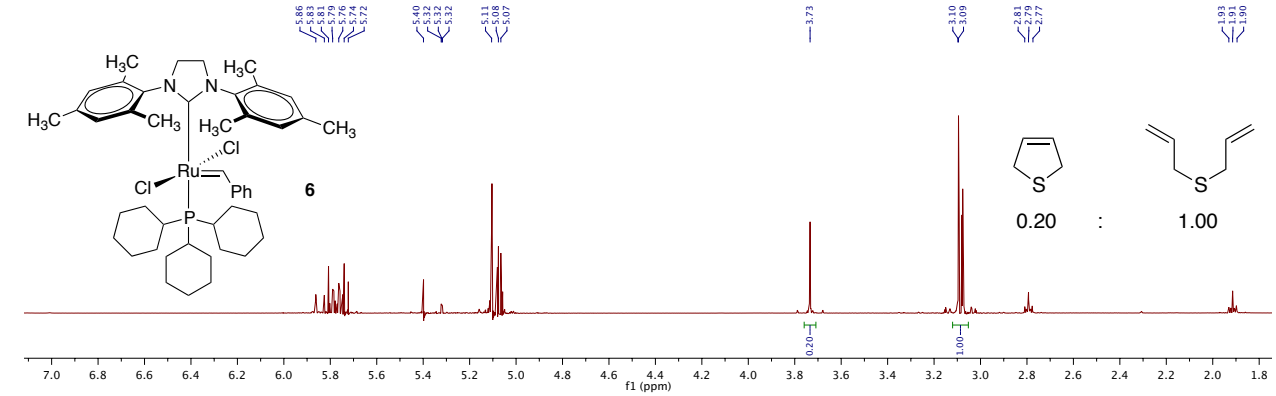
Table S3:

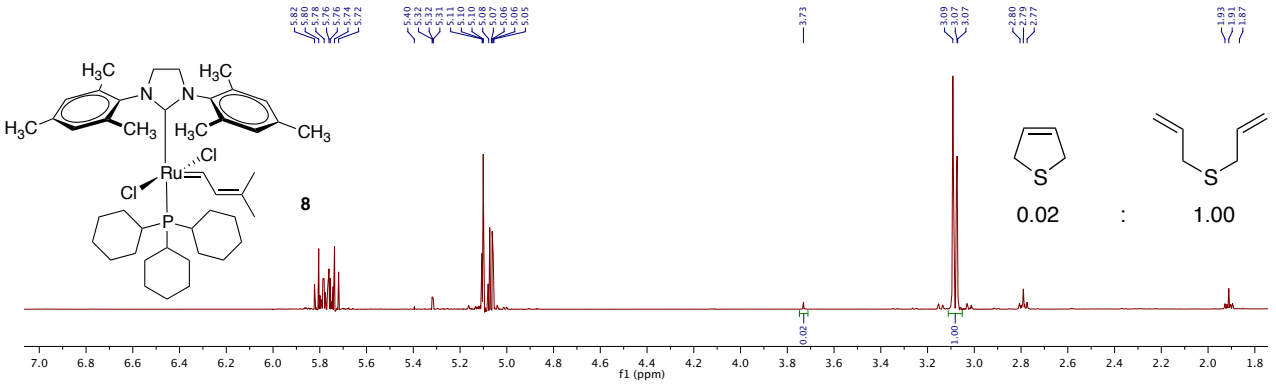
Entry	Catalyst (CAS No.)	Catalyst Number	RCM conversion
1		**1**	100%
2		**6**	17%

3		**8**	2%
4		**9**	0%
5		**10**	2%
6		**11**	4%
7		**12**	3%

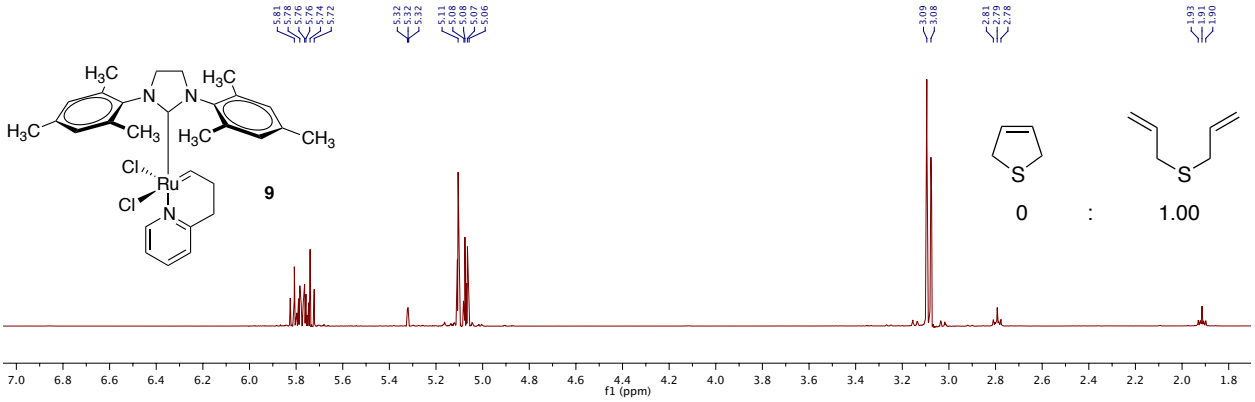
^{1}H NMR Data for tetrahydrothiophene additive experiments (Table S3)

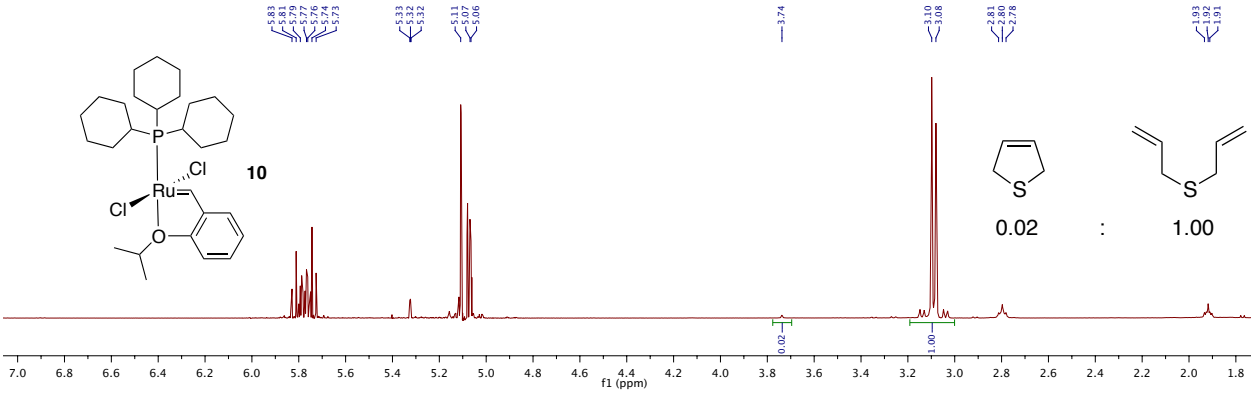


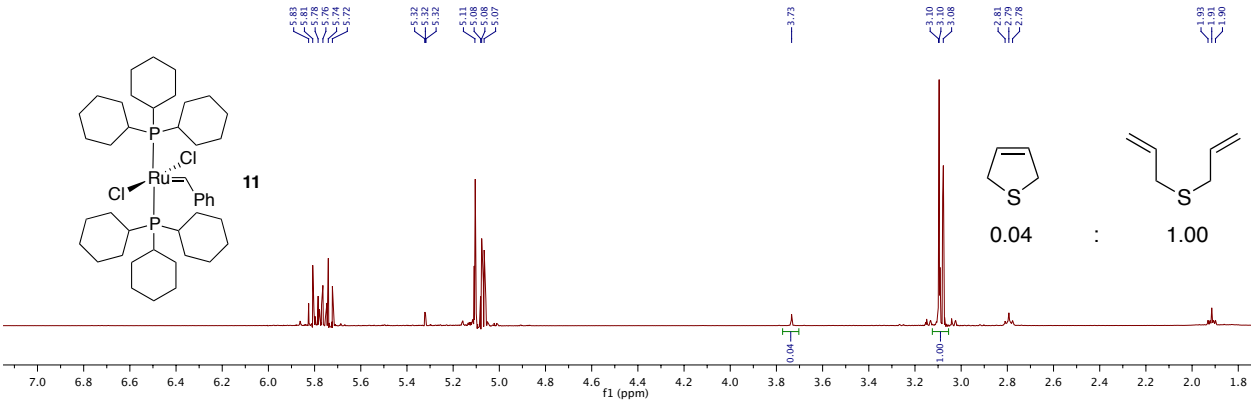




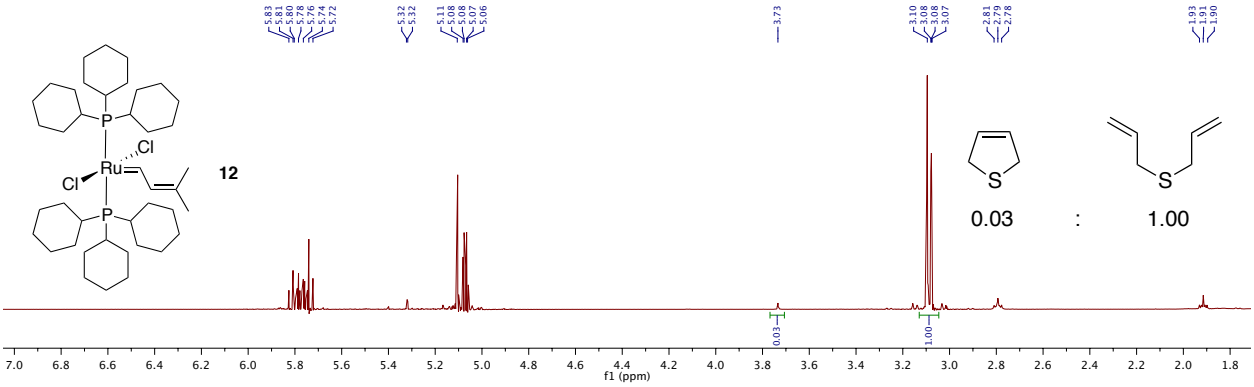
^{1}H NMR Data for tetrahydrothiophene additive experiments (Table S3) (continued)



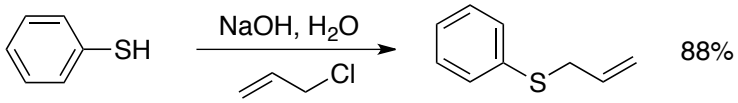




^{1}H NMR Data for tetrahydrothiophene additive experiments (Table S3) (continued)



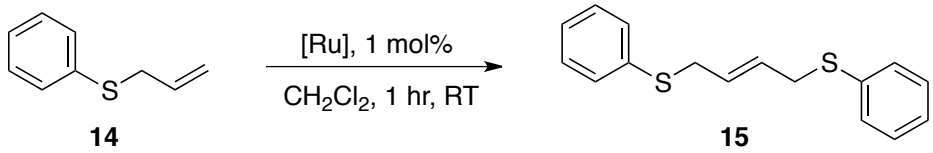
Allyl phenyl sulphide (14)[11]



14

Sodium hydroxide (1.57 g, 39.2 mmol) was added to a 100 mL round bottom flask and dissolved in 50 mL of deionized water. The stirred solution was cooled to 0 ºC and then thiophenol (4.0 mL, 39.1 mmol) was added. The resulting mixture was stirred for 10 minutes before allyl chloride (3.3 mL, 45.9 mmol) was added. The reaction mixture was placed under a nitrogen atmosphere and stirred at room temperature for 8 hours. After this time, the mixture was transferred to a separatory funnel and diluted with diethyl ether (250 mL). The organic layer was separated and then washed successively with 1 M NaOH (3 × 100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product, allyl phenyl sulphide **14**, was isolated as a colorless liquid and was used without further purification (5.16 g, 88% yield). IR (ν_{max}, film): 3078, 2916, 1944, 1852, 1636, 1584, 1480, 1438, 1229, 1089, 919, 737, 690. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.58 (2H, dt, *J* = 6.9, 1.2, C$\underline{H}_2$S), 5.10 (1H, m, CH=C$\underline{H}$H), 5.17 (1H, m, CH=CH$\underline{H}$), 5.87-5.97 (1H, m, C$\underline{H}$=CH$_2$), 7.21 (1H, tt, *J* = 7.3, 1.3, CH_{Ar}), 7.31 (2H, m, CH_{Ar}), 7.39 (2H, m, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.2 (C$\underline{H}_2$S), 117.7 (CH=C$\underline{H}_2$), 126.3, 128.9, 129.9 (3 × CH_{Ar}) , 133.6 (C$\underline{H}$=CH$_2$), 136.0 ($4°_{Ar}$).

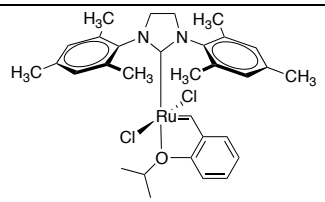
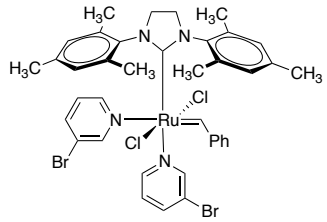
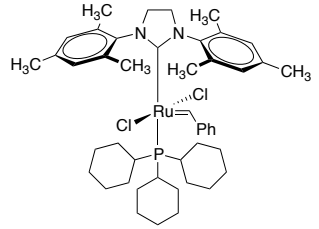
Olefin cross-metathesis on allyl phenyl sulphide (14)

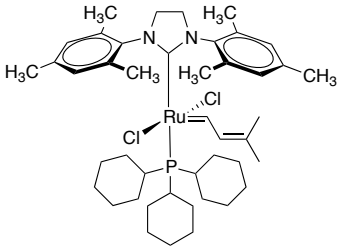
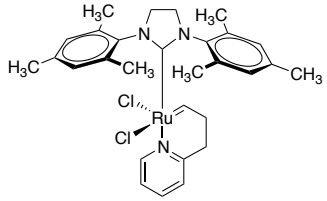
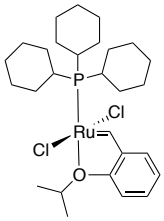
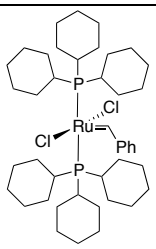
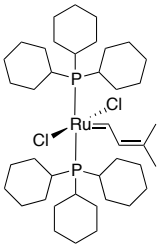


14 **15**

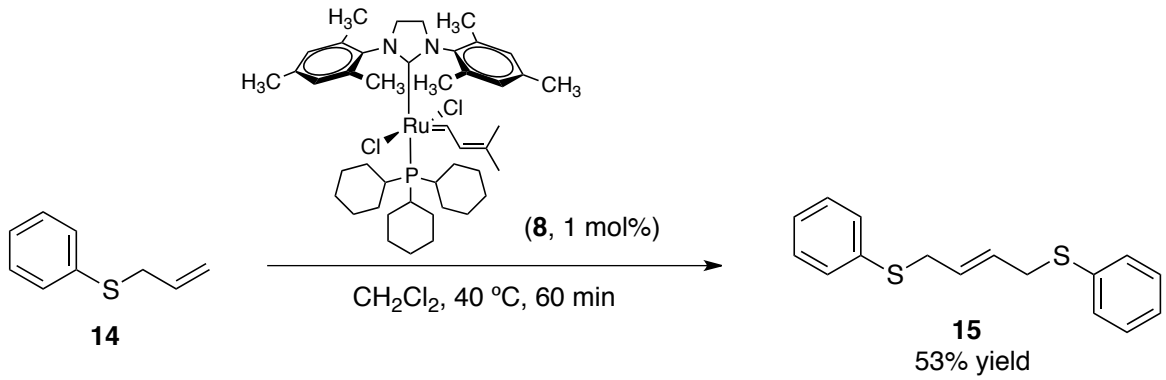
General procedure: Allyl phenyl sulphide (**14**) (205 mg, 1.37 mmol) was added to a 25 mL round bottom flask and placed under an atmosphere of nitrogen before dissolving in CH_2Cl_2 (12 mL). The olefin metathesis catalyst (1 mol%) was then added as a solid and the reaction was stirred for 1 hour at room temperature. After this time, the reaction was concentrated under reduced pressure and purified directly by column chromatography (5% EtOAc in petrol). The cross-metathesis product **15** was isolated as a white solid. Isolated yields for each catalyst are listed below. The *E* to *Z* ratio of the product was determined by the relative integration of the $C\underline{H}_2S$ signals in the ^{1}H NMR spectrum (δ = 3.46 for the *E* isomer; δ = 3.39 for the *Z* isomer). Characterization data for major *E* isomer[11]: m.p. = 65-67 ºC. IR (ν_{max}, KBr): 2360, 2341, 1749, 1437, 1223, 1093, 963, 893. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.46 (4H, d, *J* = 5.7, $C\underline{H}_2S$), 5.59-5.62 (2H, m, HC=CH), 7.15-7.28 (10H, m, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.9 ($\underline{C}H_2S$), 126.3 (CH_{Ar}), 128.7, 128.8 (CH_{Ar} and $H\underline{C}=\underline{C}H$), 129.9 ($CH_{Ar}$), 135.8 ($4^{o}_{Ar}$). Isolated yields for each catalyst system are reported in Table S4.

Table S4:

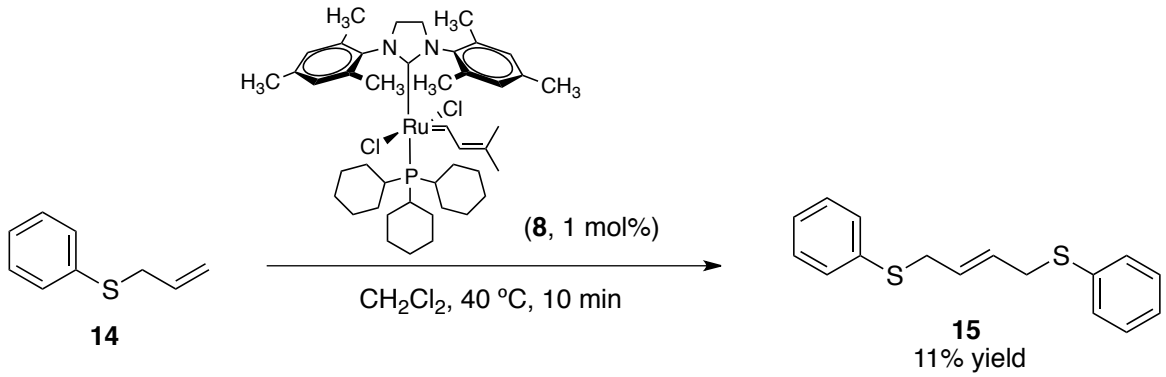
Entry	Catalyst	Catalyst Number	Yield cross-metathesis	E:Z
1		**1**	66%	1.00 : 0.05
2		**5**	59%	1.00 : 0.13
3		**6**	84%	1.00 : 0.05

4		**8**	3%	1.00 : 0.16
5		**9**	0%	-
6		**10**	64%	1.00 : 0.17
7		**11**	19%	1.00 : 0.15
8		**12**	0%	-

Cross-metathesis initiation studies using catalyst 8

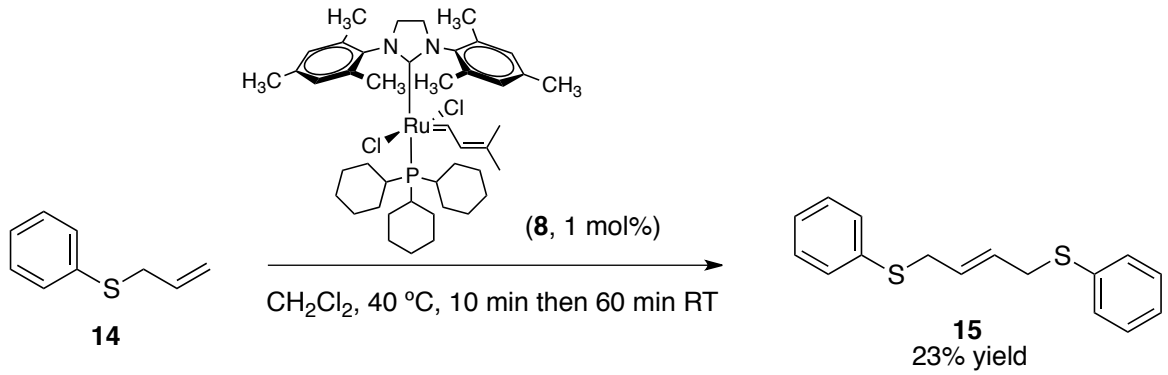


Allyl phenyl sulphide (**14**) (205 mg, 1.37 mmol) was added to a 25 mL round bottom flask and placed under an atmosphere of nitrogen before dissolving in CH_2Cl_2 (12 mL). Olefin metathesis catalyst **8** (11 mg, 1 mol%) was then added as a solid and the reaction was heated to reflux and stirred 1 hour. After this time, the reaction was concentrated under reduced pressure and purified directly by column chromatography (5% EtOAc in petrol). The cross-metathesis product **15** was isolated as a white solid (98 mg, 53% yield, *E* : *Z* = 1.00 : 0.18). The *E* to *Z* ratio of the product was determined by the relative integration of the C$\underline{H_2}$S signals in the ^{1}H NMR spectrum (δ = 3.46 for the *E* isomer; δ = 3.39 for the *Z* isomer). This experiment reveals that **8** is active in the cross-metathesis of **14** at 40 ºC.



Allyl phenyl sulphide (**14**) (205 mg, 1.37 mmol) was added to a 25 mL round bottom flask and placed under an atmosphere of nitrogen before dissolving in CH_2Cl_2 (12 mL). Olefin metathesis catalyst **8** (11 mg, 1 mol%) was then added as a solid and the reaction was heated to reflux and stirred 10 min. After this time, the reaction was cooled to room temperature under a stream of nitrogen, concentrated under reduced pressure, and purified directly by column chromatography (5% EtOAc in petrol). The cross-metathesis product **15** was isolated as a white solid (21 mg, 11% yield, *E* : *Z* = 1.00 : 0.24). The *E* to *Z* ratio of the

product was determined by the relative integration of the C$\underline{H}_2$S signals in the ^{1}H NMR spectrum (δ = 3.46 for the *E* isomer; δ = 3.39 for the *Z* isomer).

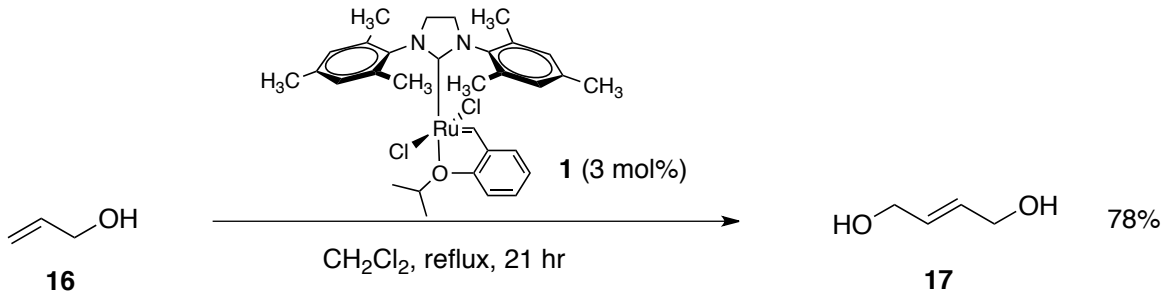


14

15
23% yield

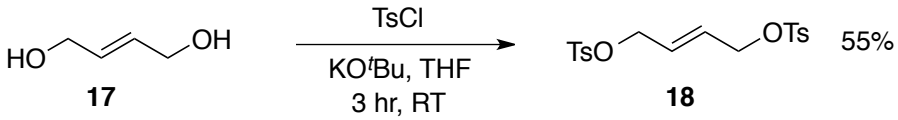
Allyl phenyl sulphide (**14**) (205 mg, 1.37 mmol) was added to a 25 mL round bottom flask and placed under an atmosphere of nitrogen before dissolving in CH_2Cl_2 (12 mL). Olefin metathesis catalyst **8** (11 mg, 1 mol%) was then added as a solid and the reaction was heated to reflux and stirred 10 min. After this time, the flask was removed from the oil bath and cooled to room temperature with a stream of nitrogen. The reaction was stirred further for 60 minutes at room temperature before concentrating under reduced pressure. The mixture was then purified directly by column chromatography (5% EtOAc in petrol) to provide cross-metathesis product **15** as a white solid (43 mg, 23% yield, *E* : *Z* = 1.00 : 0.23). The *E* to *Z* ratio of the product was determined by the relative integration of the C$\underline{H}_2$S signals in the ^{1}H NMR spectrum (δ = 3.46 for the *E* isomer; δ = 3.39 for the *Z* isomer). This experiment, along with the previous experiment, illustrates that the catalyst can be initiated by a brief period of heating (10 min, 40 ºC) and turnover can still proceed at room temperature. Therefore, the low reactivity of catalyst **8** in the cross-metathesis of **14** at room temperature is due to slow initiation.

Cross-metathesis of allyl alcohol (synthesis of 17)[11]



Grubbs-Hoveyda second generation catalyst (**1**) (11 mg, 0.018 mmol) was added to a 25 mL round bottom flask and placed under an atmosphere of nitrogen. Degassed CH_2Cl_2 (5 mL) was added to the reaction flask, followed by allyl alcohol (1.20 mL, 17.6 mmol). The flask was then equipped with a condenser and heated at reflux. After 1 hour of reaction time, a second portion of catalyst was added (11 mg, 0.018 mmol). After 5 additional hours of reaction time, a third and final portion of catalyst was added (11 mg, 0.018 mmol). The reaction was continued at reflux for a total reaction time of 21 hours. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting mixture was then purified by column chromatography (10% MeOH in CH_2Cl_2) to provide the product of cross-metathesis as a clear liquid (565 mg, 78% yield). IR (ν_{max}, film): 3330, 1420, 1086, 994. ^{1}H NMR (400 MHz, MeOD): δ = 4.05 (4H, d, *J* = 3.6, C<u>H</u>$_2$OH), 4.62 (2H, br s, OH), 5.79-5.80 (2H, m, C<u>H</u>=C<u>H</u>). ^{13}C NMR (100 MHz, MeOD): δ = 63.0 (<u>C</u>H$_2$OH), 131.3 (<u>C</u>H=<u>C</u>H).

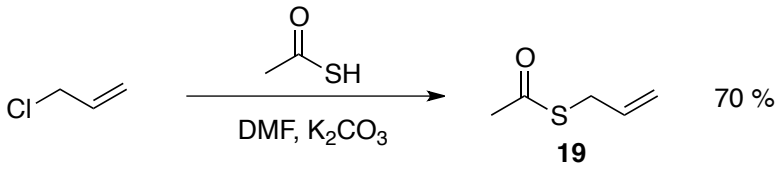
Di-Tosylate 18[12]



Diol **17** (1.677 g, 19.0 mmol) was added to a 100 mL round bottom flask and placed under a nitrogen atmosphere before dissolving in anhydrous THF (50 mL). In a separate 250 mL round bottom flask, *p*-toluenesulfonyl chloride (14.88 g, 78.0 mmol) was placed under a nitrogen atmosphere and dissolved in anhydrous THF (50 mL). The solution containing diol **17** was cooled to 0 ºC before KO^{t}Bu (4.70 g, 41.9 mmol) was added in several portions over 10 minutes. The resulting solution was then added slowly via syringe to the *p*-toluenesulfonyl chloride solution over the course of 30 minutes at room temperature. After the addition was complete, the reaction was stirred for 3 hours at room temperature. The reaction was then quenched by the addition of NH_4Cl (50 mL of a saturated aqueous solution). The mixture was then transferred to a separatory funnel and diluted with EtOAc (200 mL) and then washed successively with H_2O (3 × 100 mL) and brine (100 mL). The organic layer was isolated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The mixture was further purified by column chromatography (10%

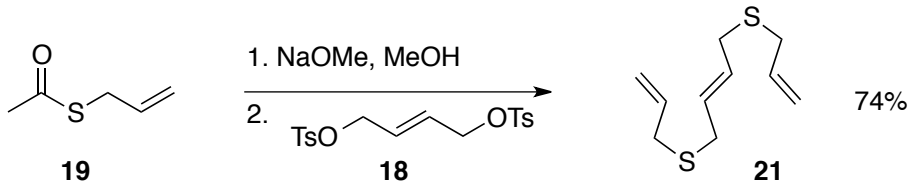
EtOAc in petrol) to provide the product **18** as a white solid (4.18 g, 55% yield). m.p. = 83-84 ºC. IR (ν_{max}, KBr): 3046, 2952, 1353, 1190, 1169, 1092, 934, 806, 652. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (6H, s, 2 × CH_3), 4.42 (4H, d, *J* = 4.3, 2 × $C\underline{H}_2OTs$), 5.68-5.70 (2H, m, $\underline{H}C{=}C\underline{H}$), 7.30 (4H, d, *J* = 8.5, CH_{Ar}), 7.71 (4H, d, *J* = 8.5, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (CH_3), 68.9 ($\underline{C}H_2OTs$), 127.6 ($H\underline{C}{=}\underline{C}H$), 127.9 ($CH_{Ar}$), 130.0 ($CH_{Ar}$), 132.8, 145.1 ($4^{o}_{Ar}$). HRMS (m/z, ESI$^+$): found 419.0595 $[M+Na]^+$; $C_{18}H_{20}O_6S_2Na$ requires 419.0594.

Allyl thioacetate (19)[11]



DMF (50 mL) was added to a 500 mL round bottom flask followed by K_2CO_3 (21.4 g, 155 mmol) and allyl chloride (14.9 mL, 183 mmol). The reaction was placed under an atmosphere of nitrogen, cooled to 0 ºC, and thioacetic acid (10.0 mL, 141 mmol) was added slowly. Gas evolution was accommodated through use of an exit needle in the septum. The reaction was allowed to warm to room temperature and was stirred for 90 minutes. After this time, the reaction was transferred to a separatory funnel and diluted with Et_2O (500 mL) and H_2O (250 mL). The organic layer was separated and washed further with $NaHCO_3$ (250 mL of a saturated aqueous solution), H_2O (250 mL), and brine (250 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a volume of about 100 mL. The resulting solution was then distilled directly (~50 mbar). After the diethyl ether fraction was removed at room temperature, the oil bath was heated to 80 ºC. Thioester **19** distilled at 56 ºC (50 mbar) and was collected as a yellow liquid (11.38 g, 70% yield). IR (ν_{max}, film): 3087, 2983, 2924, 2255, 1699, 1638, 1422, 1354, 1235, 1138, 1112. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (3H, s, CH_3), 3.52 (2H, d, *J* = 7.0, CH_2S), 5.09 (1H, m, CH=C$\underline{H}$H), 5.22 (1H, m, CH=CH$\underline{H}$), 5.74-5.85 (1H, m, C$\underline{H}{=}CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.2 (CH_3), 31.8 ($\underline{C}H_2S$), 117.6 (CH=$\underline{C}H_2$), 132.9 ($\underline{C}H{=}CH_2$), 194.6 (C=O).

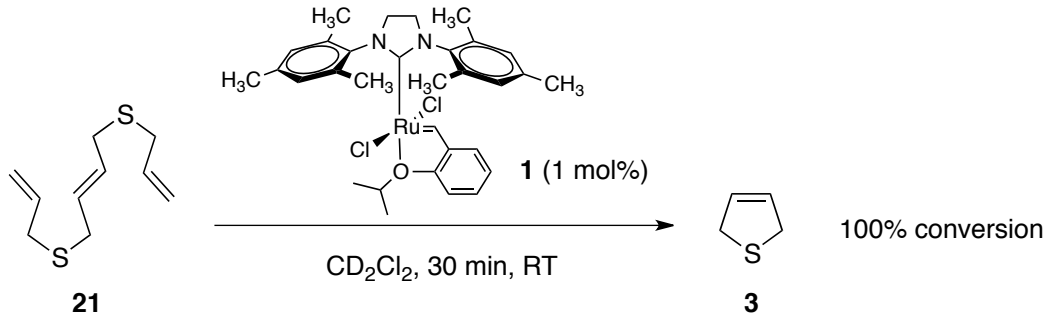
Relay metathesis substrate triene 21



Allyl thioacetate (**19**) (59 mg, 0.51 mmol) was added to a 25 mL round bottom flask and placed under an atmosphere of nitrogen. Anhydrous methanol (5 mL) was added and the stirred solution was then cooled

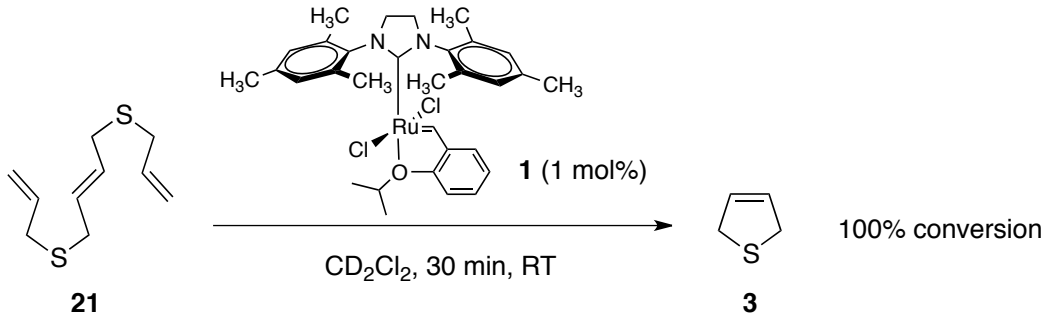
to 0 ºC. Sodium methoxide (28 mg, 0.52 mmol) was added in one portion. The reaction was stirred for 10 minutes and then warmed to room temperature. Di-tosylate **18** (100 mg, 0.25 mmol) was added in one portion and the resulting mixture was stirred vigorously for 15 hours at room temperature. After this time, the reaction was cooled to 0 ºC and quenched with 1M HCl (20 mL) and transferred to a separatory funnel and diluted with 100 mL EtOAc. The organic layer was collected and then washed successively with 1M HCl (2 × 100 mL) and brine (100 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (10% EtOAc in petrol). The product, triene **21**, was isolated as a clear oil (37 mg, 74% yield). IR (ν_{max}, film): 3080, 3020, 3003, 2973, 2905, 1639, 1430, 1220, 998, 960, 913, 742. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.04-3.07 (8H, m, 4 × C<u>H</u>$_2$S), 5.03-5.09 (4H, m, CH=C<u>H</u>$_2$) 5.44-5.47 (2H, m, C<u>H</u>=C<u>H</u>), 5.68-5.78 (2H, m, C<u>H</u>=CH$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.0 (S<u>C</u>H$_2$CH=CH<u>C</u>H$_2$S), 33.5 (<u>C</u>H$_2$CH=CH$_2$), 117.2 (CH=<u>C</u>H$_2$), 129.0 (SCH$_2$<u>C</u>H=<u>C</u>HCH$_2$S), 134.2 (<u>C</u>H=CH$_2$). $C_{10}H_{16}S_2$ requires C, 59.94%; H, 8.05%; S, 32.01%. Found C, 59.98%; H, 8.16%; S, 31.89%

Relay metathesis on triene 21

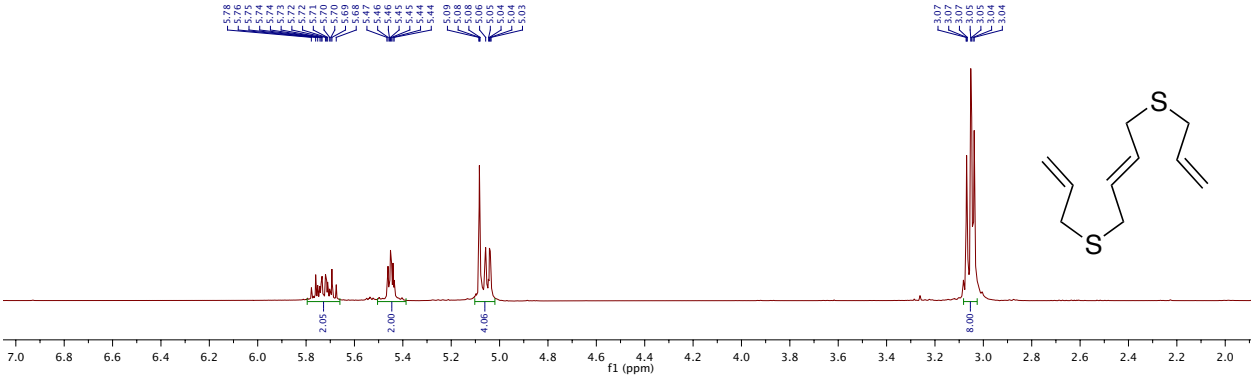


21 **3**

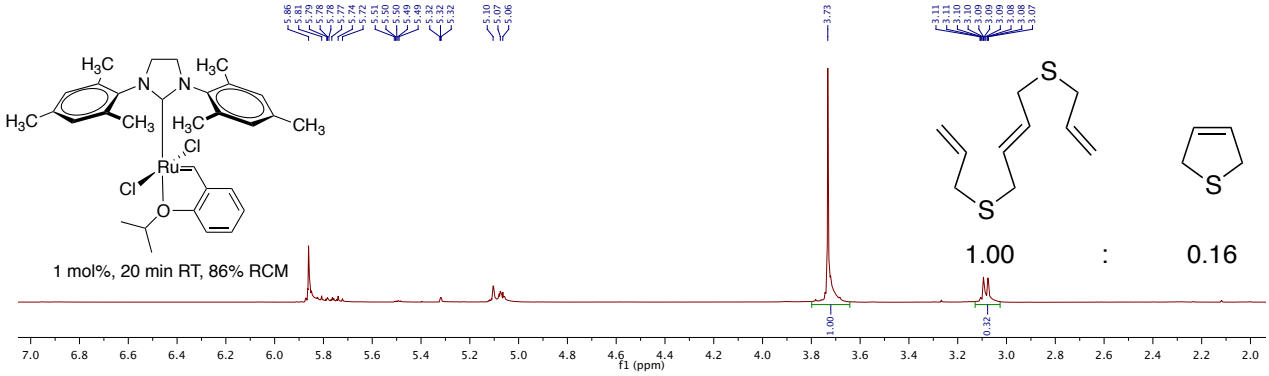
Triene **21** (31 mg, 0.15 mmol) was added to a 5 mL vial equipped with a magnetic stirring bar and placed under an atmosphere of nitrogen before dissolving in CD_2Cl_2 (0.4 mL). In a separate vial, Grubbs-Hoveyda II catalyst (1.0 mg, 0.0015 mmol) was prepared in a solution of degassed CD_2Cl_2 (0.4 mL) under an atmosphere of nitrogen. The catalyst solution was then added to the triene and the reaction was stirred under nitrogen for 30 minutes. After this time, nitrogen was bubbled through the reaction mixture for 2 minutes to remove ethylene gas. The reaction mixture was then transferred to an NMR tube and analyzed directly by ^{1}H NMR spectroscopy. Full conversion to 2,5-dihydrothiophene (**3**) was observed. Under the same conditions, 86% conversion was observed after 20 minutes of reaction time. NMR spectra of the reaction progression are shown on the following page.



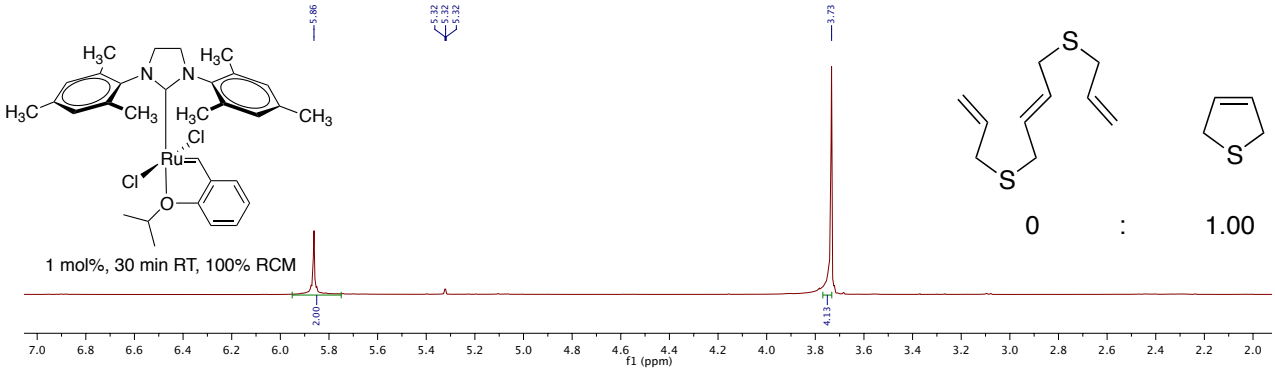
t = 0 min



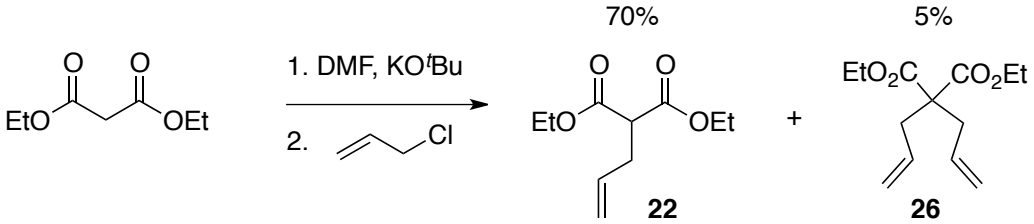
t = 20 min



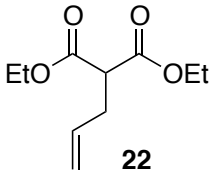
t = 30 min



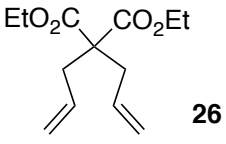
Diethyl 2-allylmalonate (22)[13] and diethyl 2,2-diallylmalonate[14] (26)



Diethyl malonate (1.623 g, 10.13 mmol) was added to a 100 mL round bottom flask and dissolved in DMF (50 mL). The stirred solution was cooled to 0 ºC before potassium *tert*-butoxide (1.14 g, 10.1 mmol) was added over a period of 5 minutes. Allyl chloride (778 mg, 10.17 mmol) was then added and the reaction was allowed to warm to room temperature. After a total of 12 hours of reaction time, the reaction was then cooled again to 0 ºC and quenched with 2M HCl (2 mL). The mixture was then transferred to a separatory funnel and diluted with EtOAc (100 mL) before washing sequentially with H_2O (3 × 50 mL) and then brine (50 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was then purified by column chromatography (5% EtOAc in petrol). The diallylated minor product **26** eluted first (130 mg, 5% yield), followed by the monoallylated product **22** (1.41 g, 70% yield). Characterization data for both products is listed below.



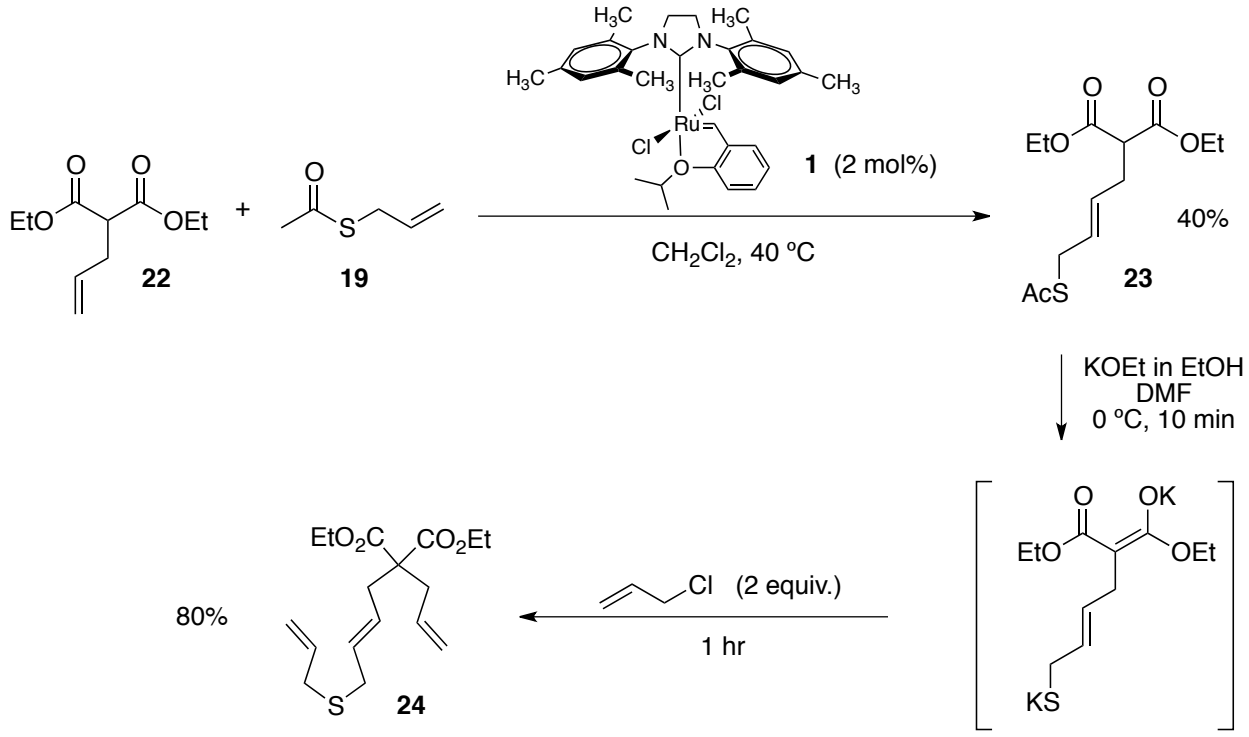
IR (ν_{max}, film): 3076, 2977, 2930, 1746, 1460, 1438, 1370, 1332, 1370, 1332, 1263, 1233, 1148, 1019, 913, 849. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (6H, t, *J* = 7.14, 2 × $CH_2\underline{CH_3}$), 2.60 (2H, t, *J* = 7.6, $\underline{CH_2}CH{=}CH_2$), 3.38 (1H, t, *J* = 7.6, Hα), 4.16 (4H, q, *J* = 7.14, 2 × $\underline{CH_2}CH_3$), 5.01 (1H, dd, *J* = 10.2, 1.5, CH=C$\underline{H}$H), 5.08 (1H, dd, *J* = 17.0, 1.5, CH=CH$\underline{H}$), 5.69-5.79 (1H, m, C$\underline{H}$=CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 ($CH_2\underline{C}H_3$), 32.8 ($\underline{C}H_2CH{=}CH_2$), 51.6 (Cα), 61.3 ($\underline{C}H_2CH_3$), 117.4 (CH=$\underline{C}H_2$), 134.0 ($\underline{C}H{=}CH_2$), 168.8 (C=O). HRMS (m/z, ESI$^+$): found 223.0943 $[M+Na]^+$; $C_{10}H_{16}NaO_4$ requires 223.0941.



IR (ν_{max}, film): 3080, 2977, 2926, 1729, 1635, 1438, 1366, 1280, 1208, 1139, 1028, 917, 853. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (6H, t, *J* = 8.0, 2 × $CH_2\underline{CH_3}$), 2.62 (4H, d, *J* = 8.4, 2 × $\underline{CH_2}CH{=}CH_2$), 4.16 (4H, q, *J* = 8.0, 2 × $\underline{CH_2}CH_3$), 5.07-5.11 (4H, m, 2 × CH=C$\underline{H_2}$), 5.58-5.69 (2H, m, 2 × C$\underline{H}$=CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 ($CH_2\underline{C}H_3$), 36.7 ($\underline{C}H_2CH{=}CH_2$), 57.2 (Cα), 61.2 ($\underline{C}H_2CH_3$), 119.1

(CH=$\underline{C}H_2$), 132.3 ($\underline{C}H=CH_2$), 170.7 (C=O). HRMS (m/z, ESI^+): found 263.1256 $[M+Na]^+$; $C_{13}H_{20}O_4Na$ requires 262.1254.

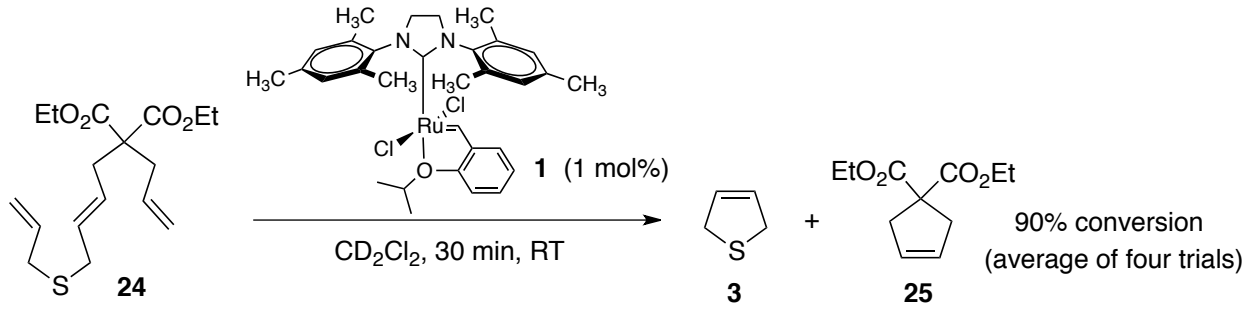
Synthesis of relay metathesis substrate triene 24



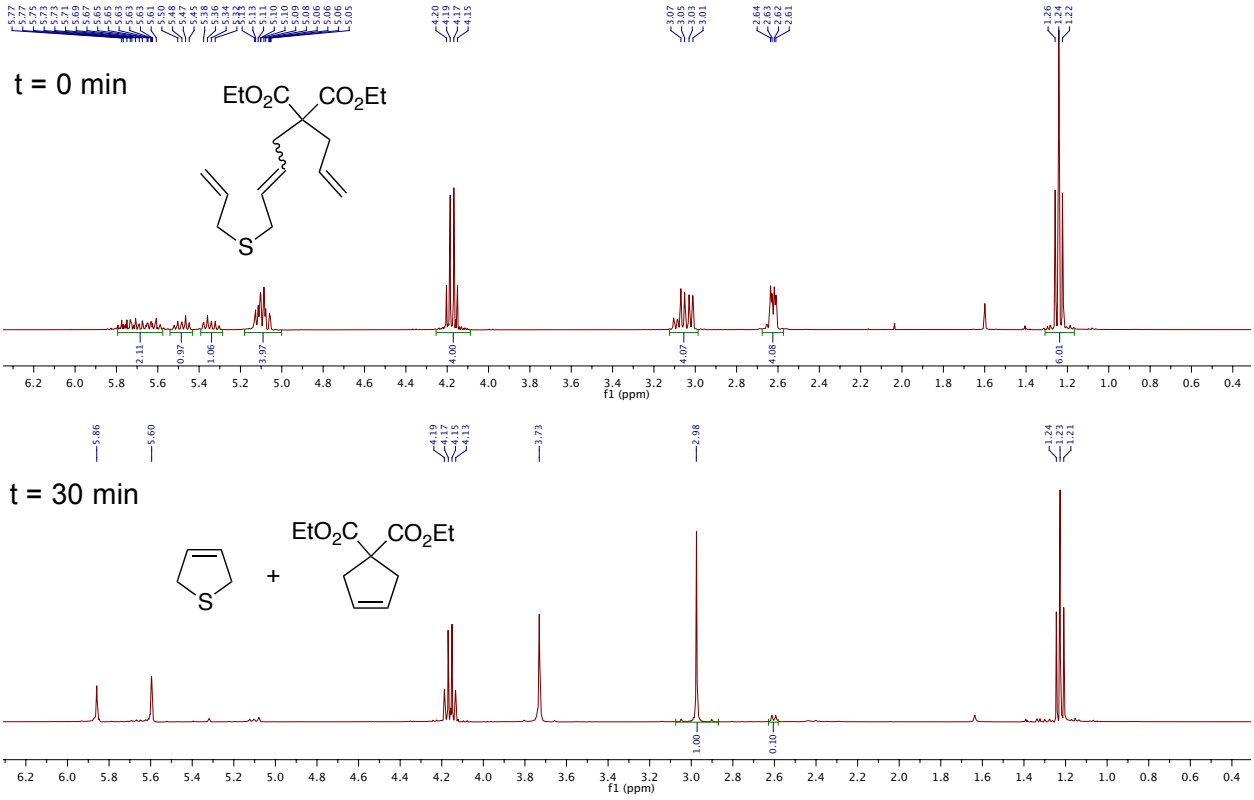
Diethyl 2-allylmalonate (**22**) (401 mg, 2.00 mmol) and allyl thioacetate (**19**) (346 mg, 3.0 mmol) were added to a 25 mL round bottom flask and dissolved in degassed CH_2Cl_2 (10 mL). Grubbs-Hoveyda second generation catalyst **1** (27 mg, 0.043 mmol, 2 mol%) was added in one portion to the stirred solution and then the flask was equipped with a condenser and heated at reflux for four hours. After this time, the reaction was cooled to room temperature and then concentrated under reduced pressure. The resulting residue was then purified by column chromatography (5% EtOAc in petrol to 10% EtOAc in petrol) to separate cross-metathesis product **23** from self-metathesis products. The desired product **23** (R_f = 0.24, 10% EtOAc in petrol) was isolated as an oil (233 mg, 40% yield) that was carried to the next step without further manipulation (see next). NMR data for major alkene isomer isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (6H, t, *J* = 7.1, 2 × $CH_2C\underline{H}_3$), 2.31 (3H, s, CH_3), 2.58 (2H, t, *J* = 7.50, $C\underline{H}_2CH=CHCH_2S$), 3.36 (1H, t, *J* = 7.5, Hα), 3.46 (2H, d, *J* = 7.4, $CH=CHC\underline{H}_2S$), 4.15-4.21 (4H, q, *J* = 7.1, 2 × $C\underline{H}_2CH_3$), 5.48-5.63 (2H, m, $C\underline{H}=C\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 30.4, 31.0, 31.4, 51.7, 61.4, 127.9, 129.4, 168.7, 195.1.

Thioester **23** (169 mg, 0.59 mmol) was added to a 25 mL round bottom flask, dissolved in DMF (8.0 mL), and placed under an atmosphere of nitrogen. In a separate reaction vessel, potassium *tert*-butoxide (141 mg, 1.26 mmol) was dissolved in ethanol (1.0 mL) to provide a solution of potassium ethoxide in ethanol. The resulting solution was then added dropwise to the reaction flask at 0 ºC. The reaction was stirred for 10 minutes at 0 ºC before allyl chloride (0.10 mL, 1.2 mmol) was added via syringe. The reaction was then allowed to warm to room temperature and then stirred for an hour. After this time, the reaction was quenched with H_2O (15 mL) and transferred to a separatory funnel along with EtOAc (50 mL). The organic layer was separated and washed further with H_2O (5 × 20 mL) and then brine (20 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (10% EtOAc in petrol) to provide triene **24** (R_f = 0.51, 10% EtOAc in petrol) as an oil (154 mg, 80% yield). Data for the major alkene isomer is listed below. IR (ν_{max}, film): 3076, 2986, 2930, 2905, 1734, 1272, 1212, 1152, 1084, 1019, 913, 853. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (6H, t, *J* = 7.1, 2 × $CH_2C\underline{H}_3$), 2.61-2.64 (4H, m, 2 × $C\underline{H}_2C\alpha$), 3.02 (2H, d, *J* = 7.6), 3.06 (2H, d, *J* = 7.1) (2 × $C\underline{H}_2S$), 4.18 (4H, q, *J* = 7.1, 2 × $C\underline{H}_2CH_3$), 5.05-5.13 (4H, m, 2 × $C\underline{H}_2$=CH), 5.30-5.38 (1H, m), 5.45-5.52 (1H, m) ($C\underline{H}$=$C\underline{H}$), 5.59-5.79 (2H, m) (2 × CH_2=$C\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 ($CH_2\underline{C}H_3$), 32.2, 33.3 (2 × $\underline{C}H_2S$), 35.2, 36.8 (2 × $\underline{C}H_2C\alpha$), 57.4 (Cα), 61.2 ($\underline{C}H_2CH_3$), 117.2, 119.2 (2 × $\underline{C}H_2$=CH), 126.8, 130.7 ($\underline{C}H$=$\underline{C}H$), 132.2, 134.2 (2 × CH_2=$\underline{C}H$), 170.7 (C=O). HRMS (m/z, ESI^+): found 327.1623 $[M+H]^+$; $C_{17}H_{27}O_4S$ requires 327.1625.

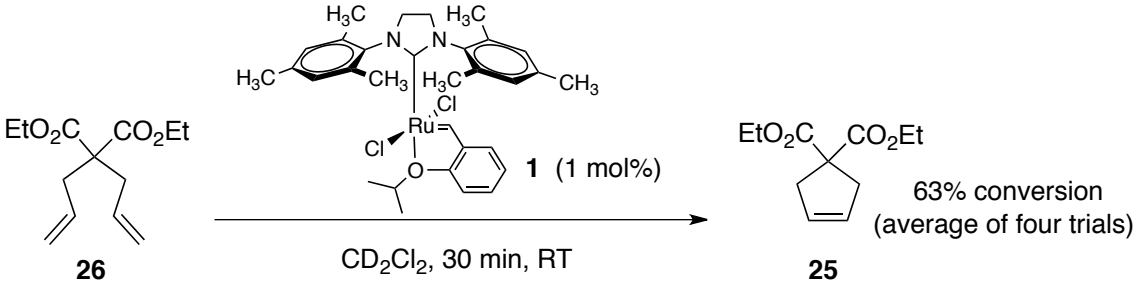
Relay metathesis on triene 24



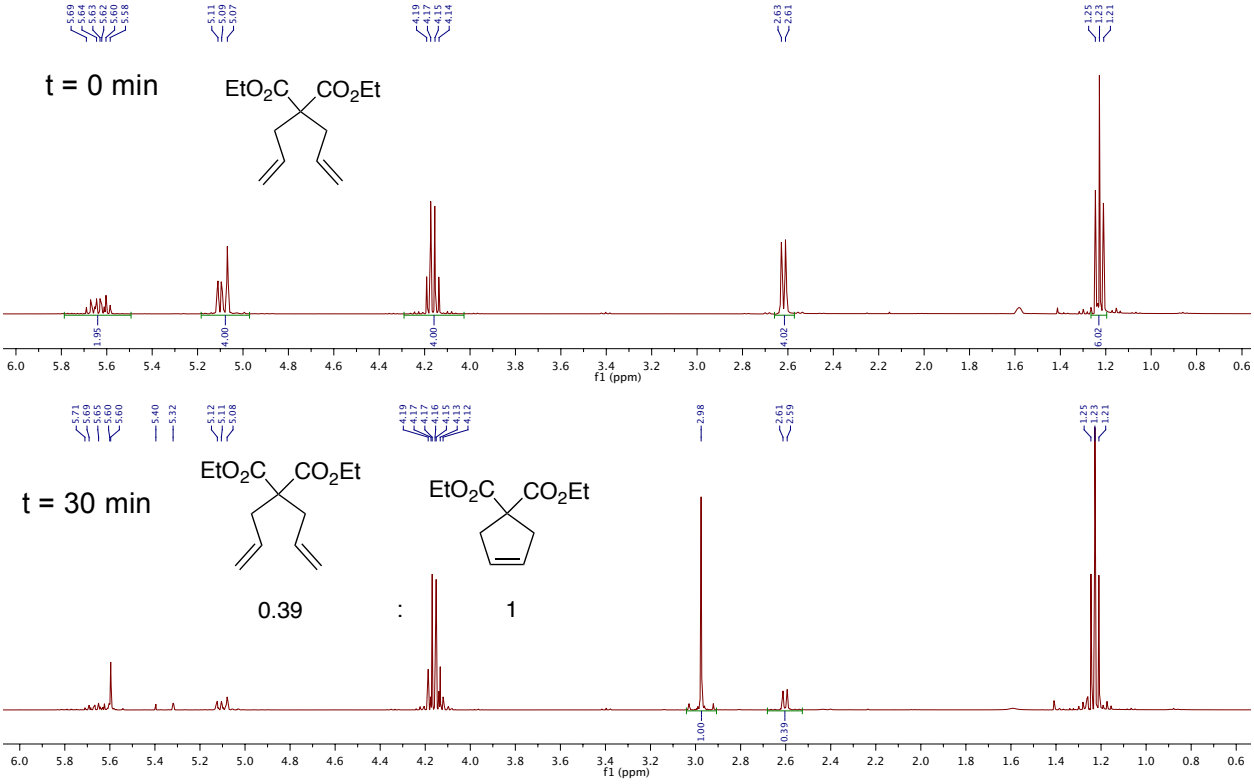
A fresh solution of Grubbs-Hoveyda second generation catalyst **1** was prepared in CD_2Cl_2 at a concentration of 1.3 mg per mL and kept under nitrogen. A 750 μL aliquot of this catalyst solution (1.0 mg, 1.5 μmol, 1 mol% catalyst) was then transferred by syringe to a second vial containing triene **24** (50 mg, 0.15 mmol). The reaction was stirred at room temperature for 30 minutes under an atmosphere of nitrogen. After this time, the solution was diluted with 750 μL of CD_2Cl_2 and then sparged with nitrogen for 2 minutes to remove ethylene. The resulting solution was then analyzed directly by ^{1}H NMR which revealed 90% conversion to the cyclized products. This experiment was repeated three additional times with conversions of 92%, 90%, and 89%. NMR data is shown below for both the starting material and an allyl sulphide promoted ring-closing metathesis that resulted in 90% conversion (the median conversion of four trials).



Ring-closing metathesis on diethyl 2,2-diallylmalonate (26)



A fresh solution of Grubbs-Hoveyda second generation catalyst (**1**) was prepared in CD_2Cl_2 at a concentration of 1.3 mg per mL and kept under nitrogen. A 750 μL aliquot of this catalyst solution (1.0 mg, 1.5 μmol, 1 mol% catalyst) was then transferred by syringe to a second vial containing diene **26** (36 mg, 0.15 mmol). The reaction was stirred at room temperature for 30 minutes under an atmosphere of nitrogen. After this time, the solution was diluted with 750 μL of CD_2Cl_2 and then sparged with nitrogen for 2 minutes to remove ethylene. The resulting solution was then analyzed directly by ^{1}H NMR where reaction conversions were determined by the relative integration of the allylic protons in the starting material **26** (δ = 2.60) and product **25** (δ = 2.98). The reaction was run four times to reveal conversions of 72%, 60%, 60%, and 58%. NMR data is shown below for both the starting material and the product of ring closing metathesis that resulted in 60% conversion (the median conversion of four trials).



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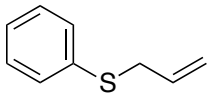
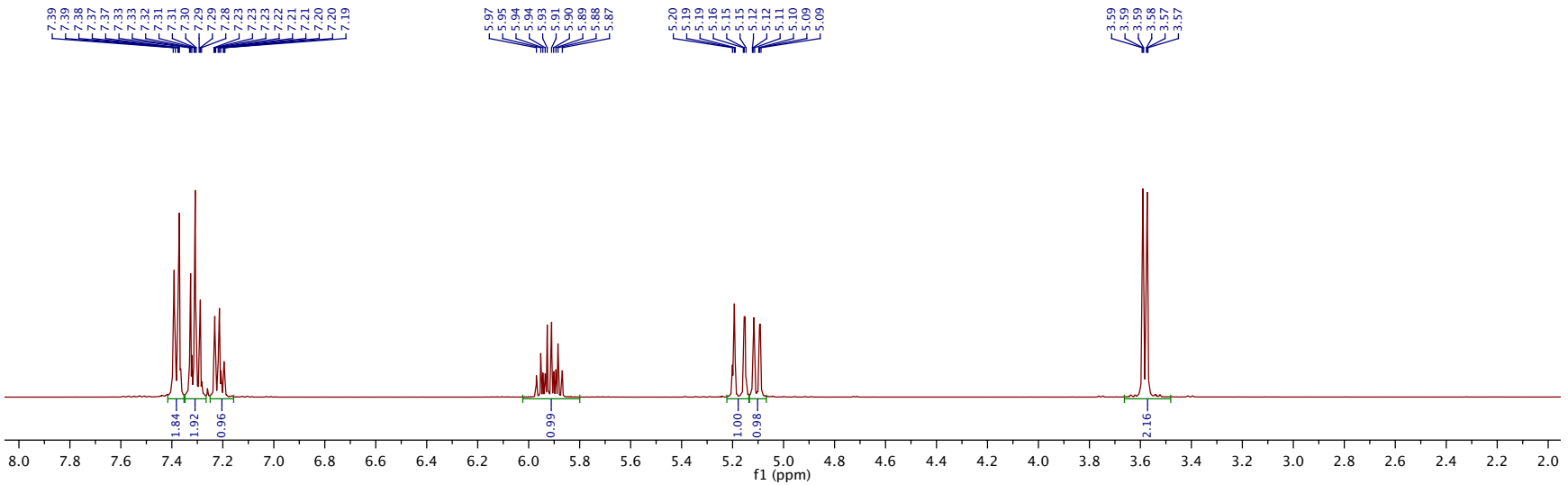
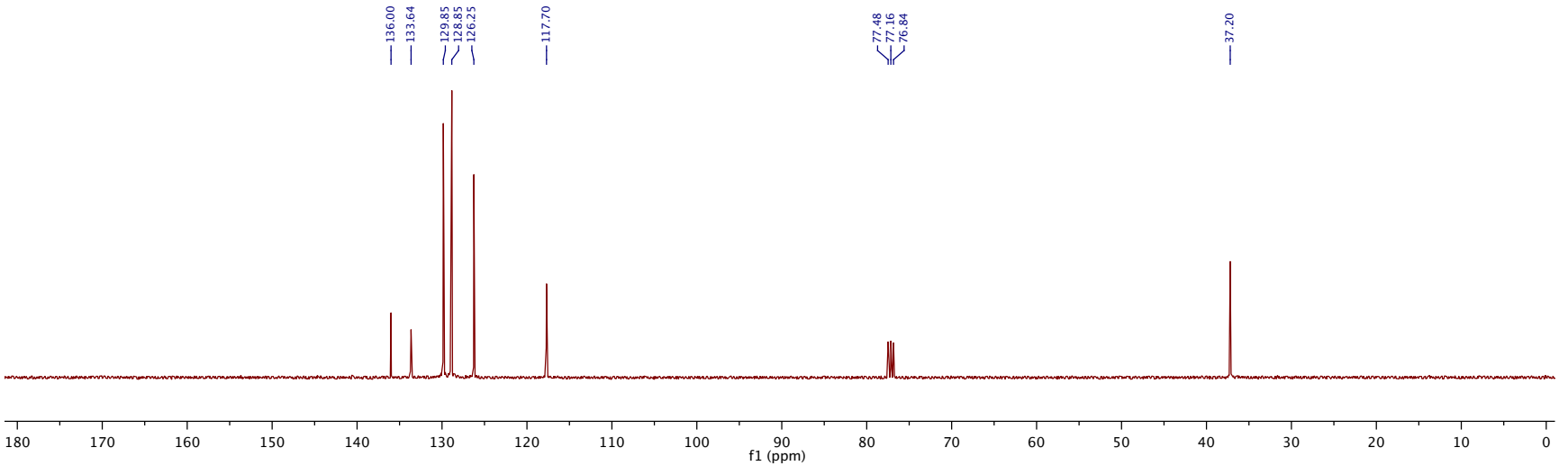


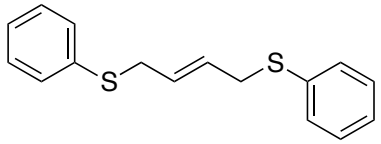
14

^{1}H NMR (400 MHz, $CDCl_3$)



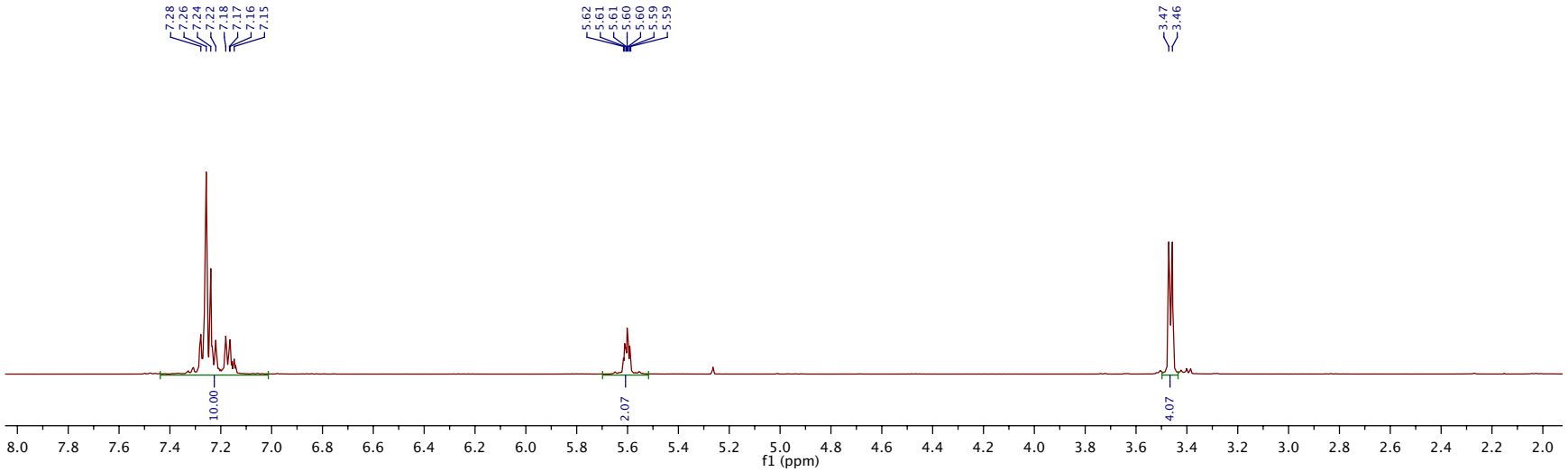
^{13}C NMR (100 MHz, $CDCl_3$)



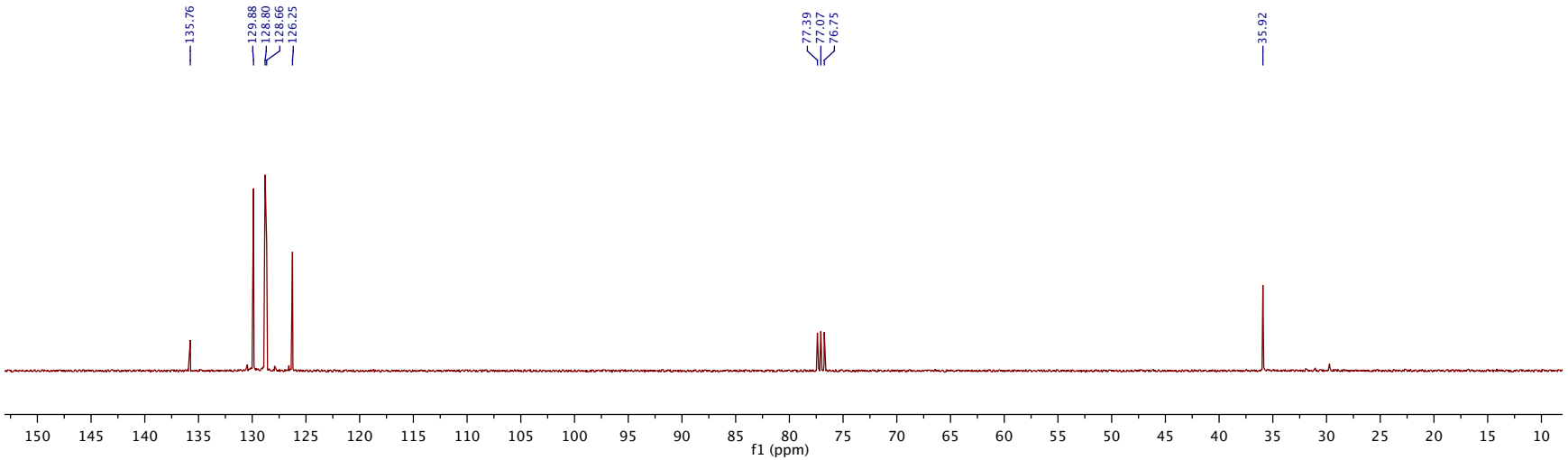


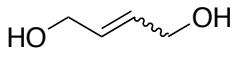
15

^{1}H NMR (400 MHz, $CDCl_3$)



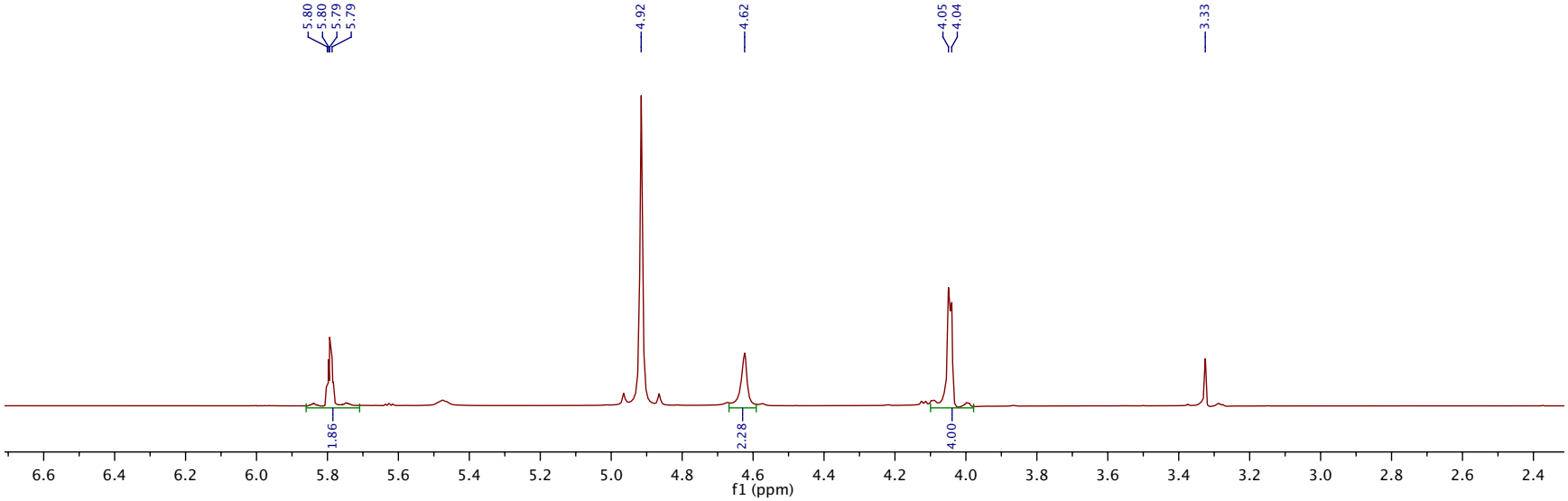
^{13}C NMR (100 MHz, $CDCl_3$)



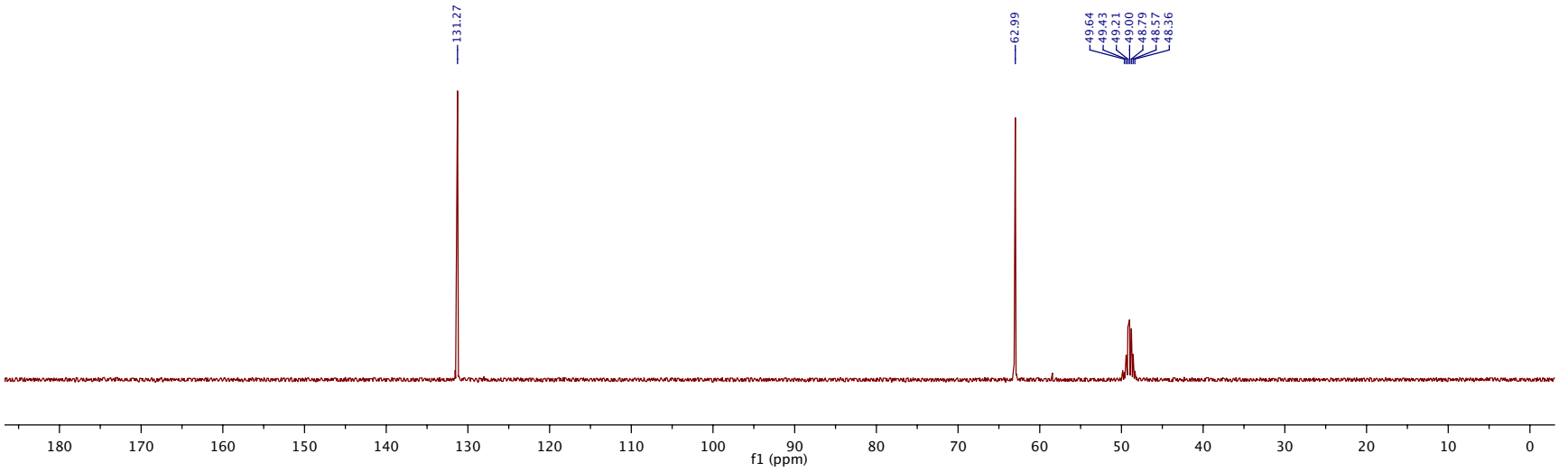


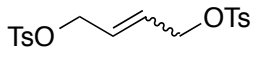
17

^{1}H NMR (400 MHz, MeOD)



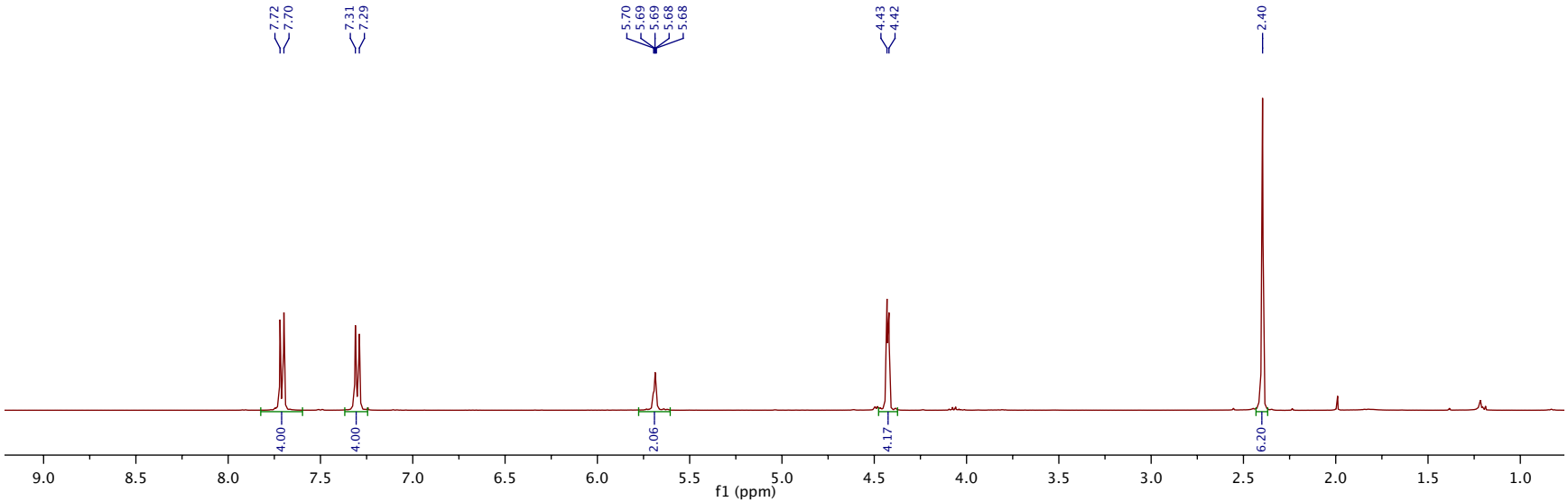
^{13}C NMR (100 MHz, MeOD)



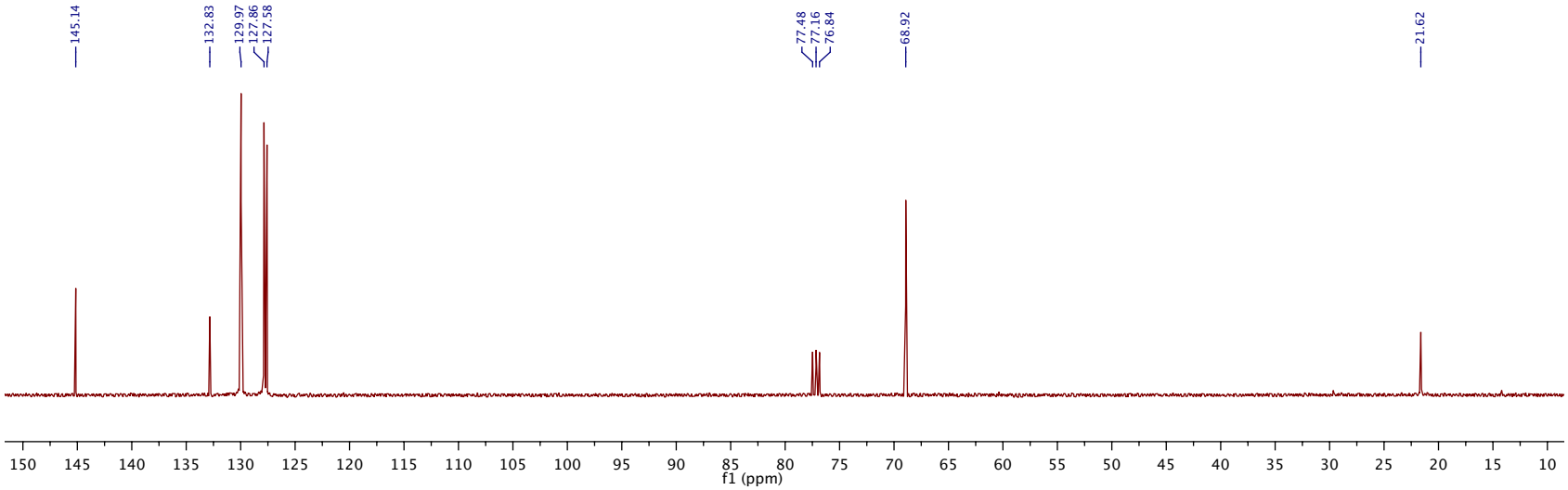


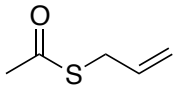
18

^{1}H NMR (400 MHz, $CDCl_3$)



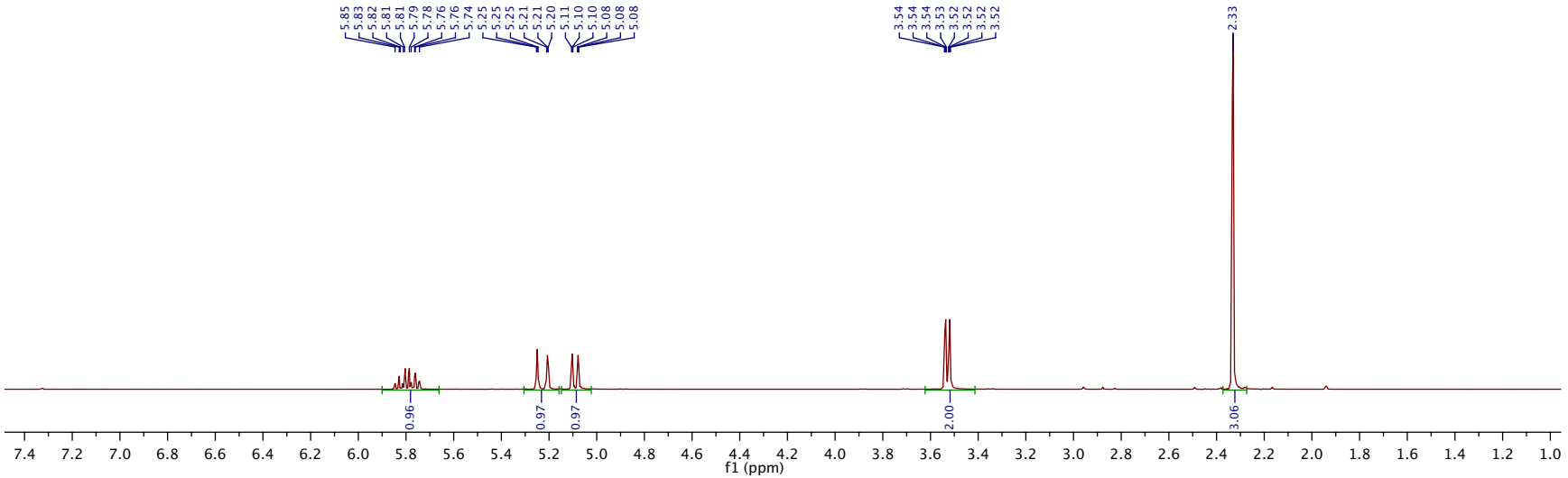
^{13}C NMR (100 MHz, $CDCl_3$)



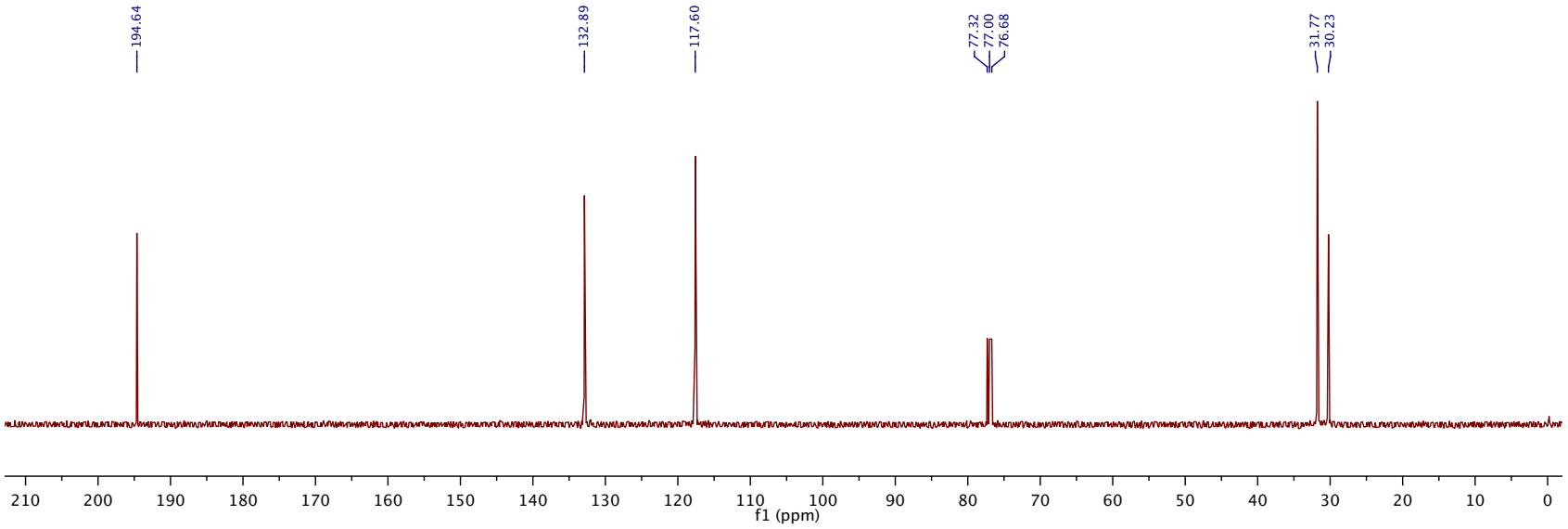


19

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



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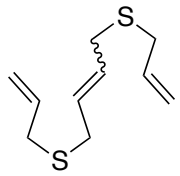
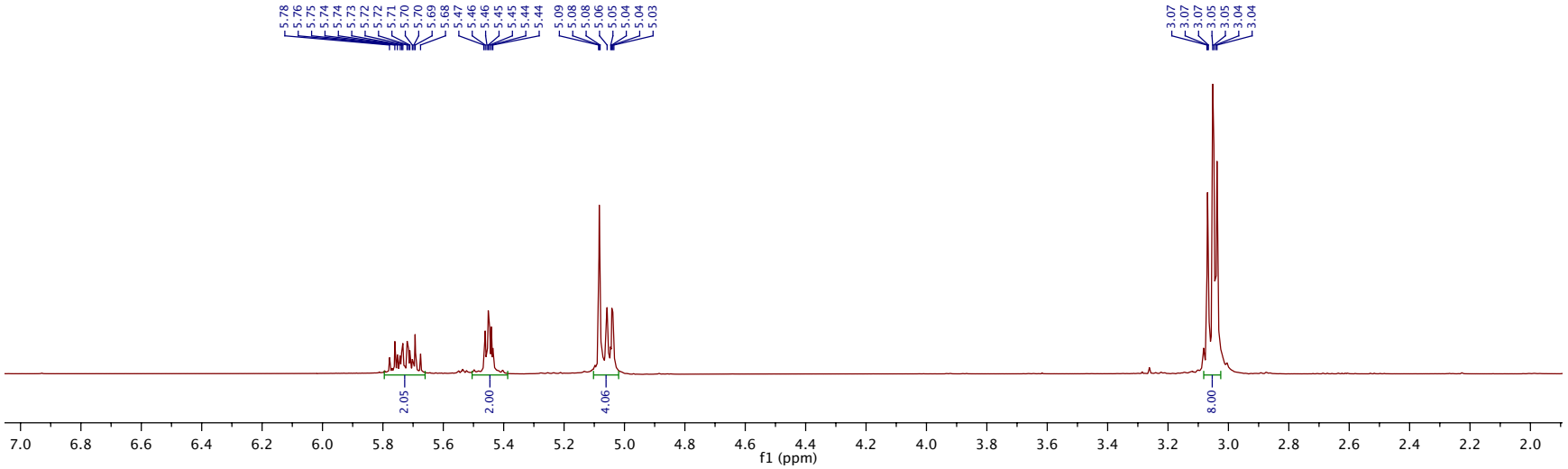
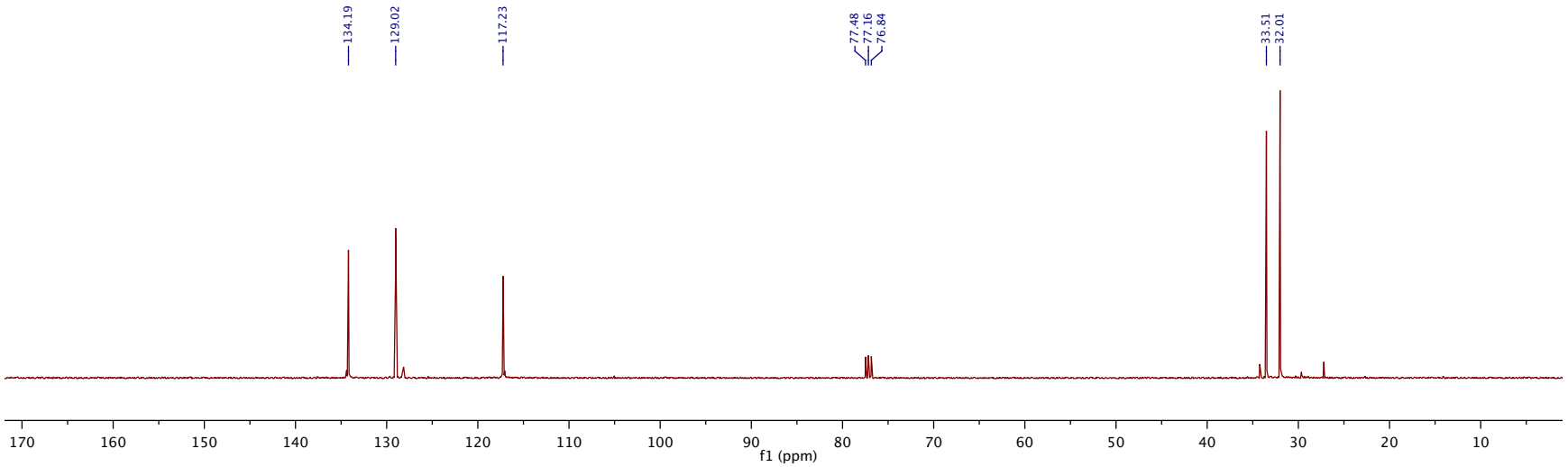


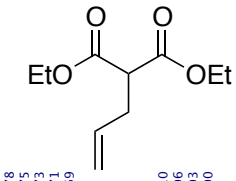
21



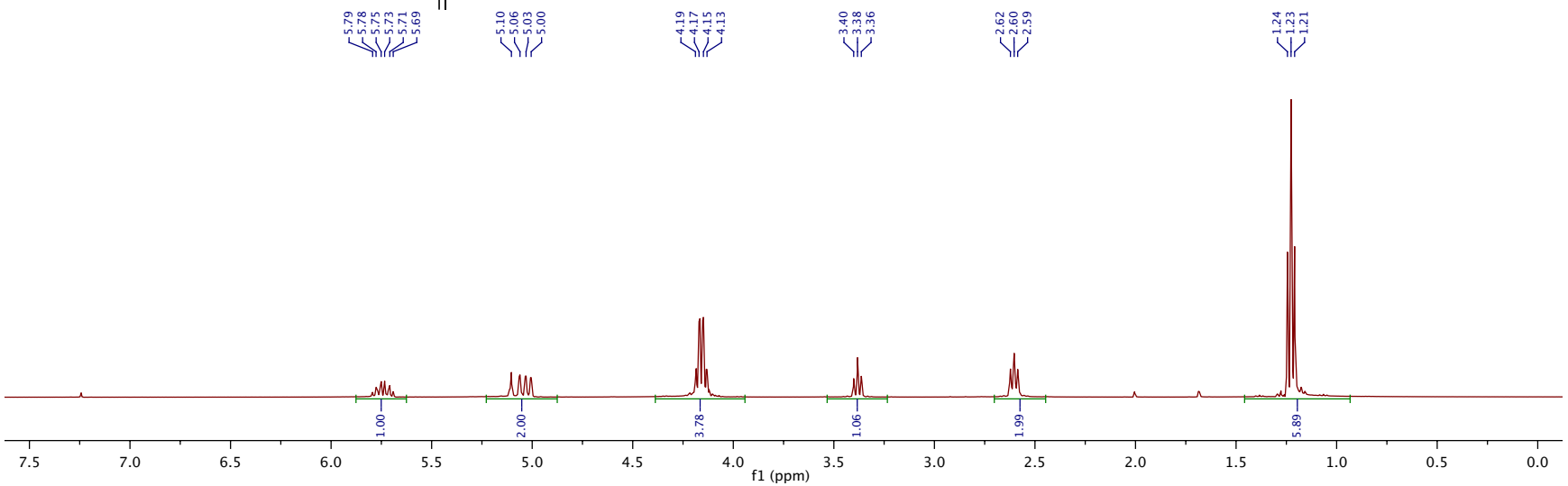
^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



22



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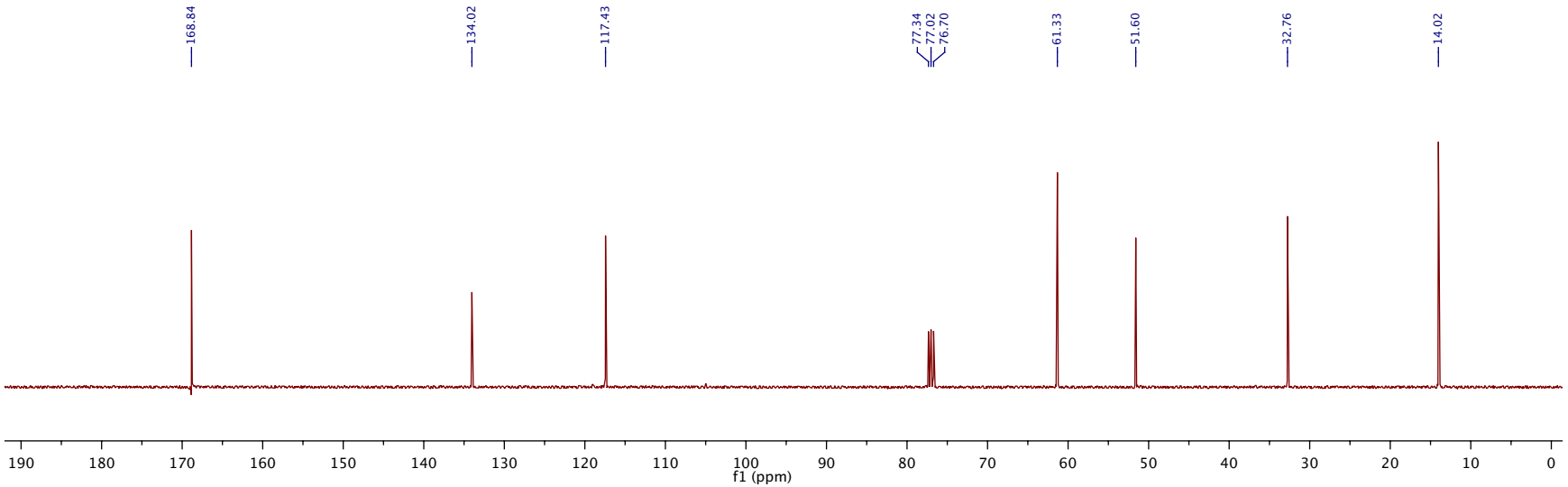

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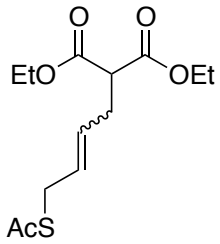

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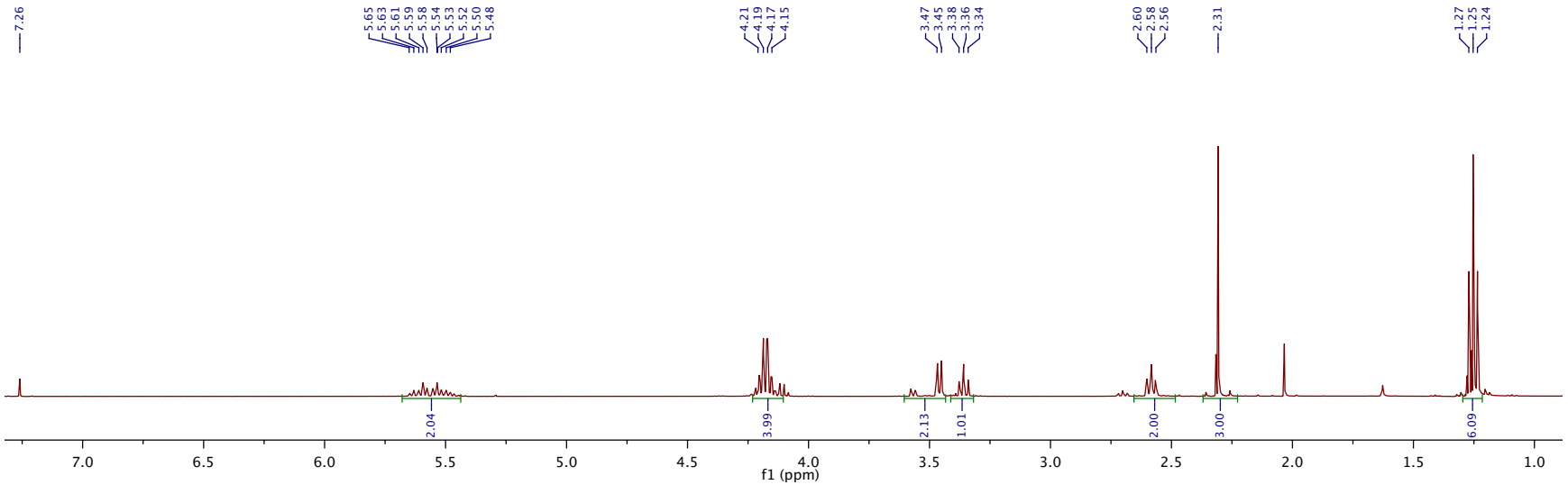
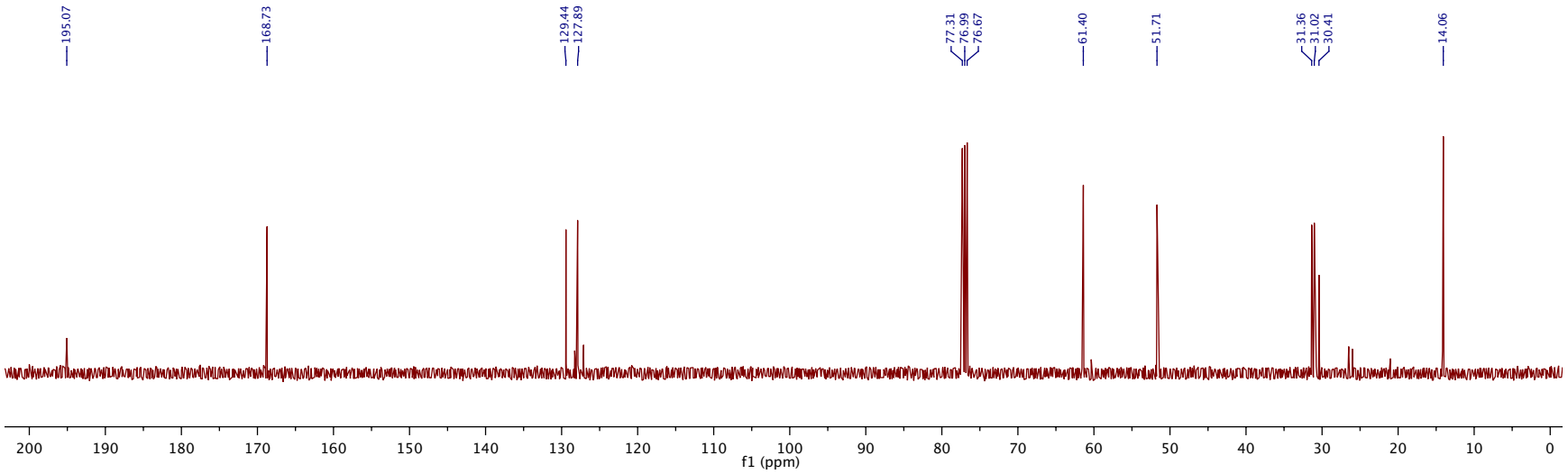


^{13}C NMR (100 MHz, $CDCl_3$)



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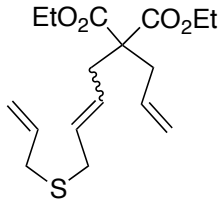

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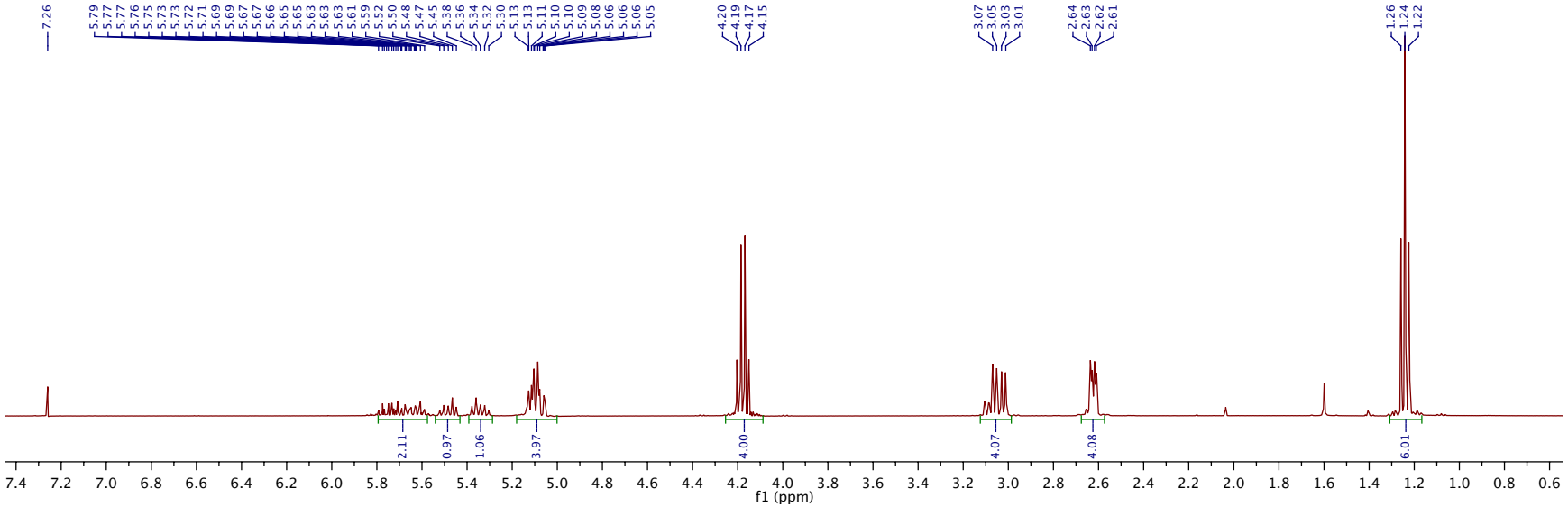
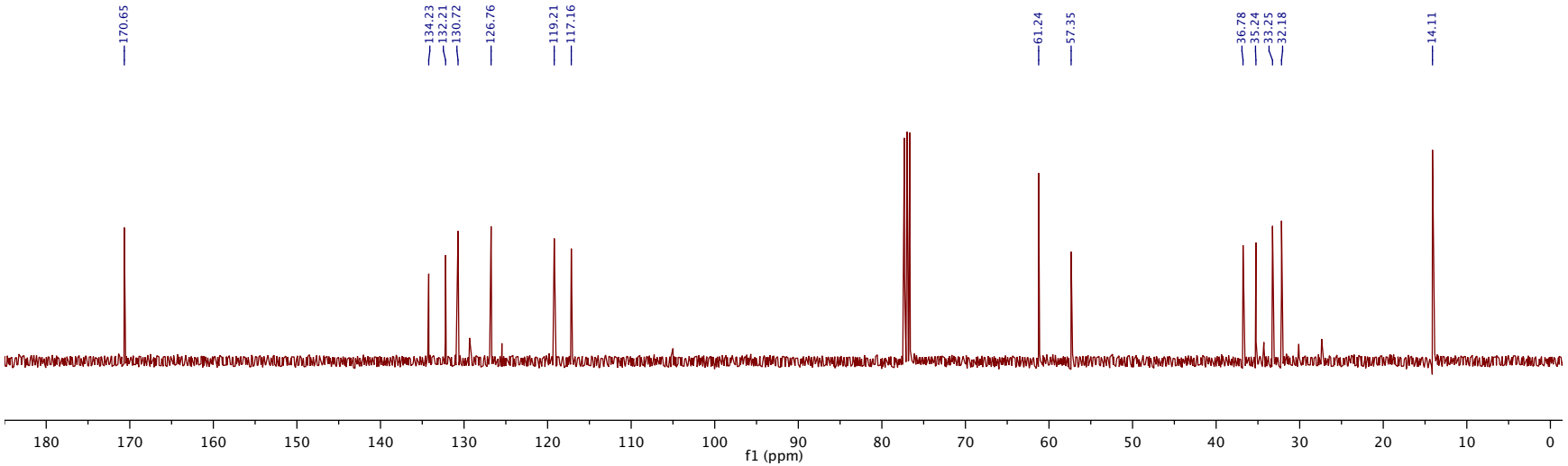
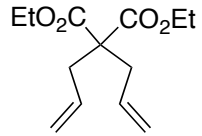


^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



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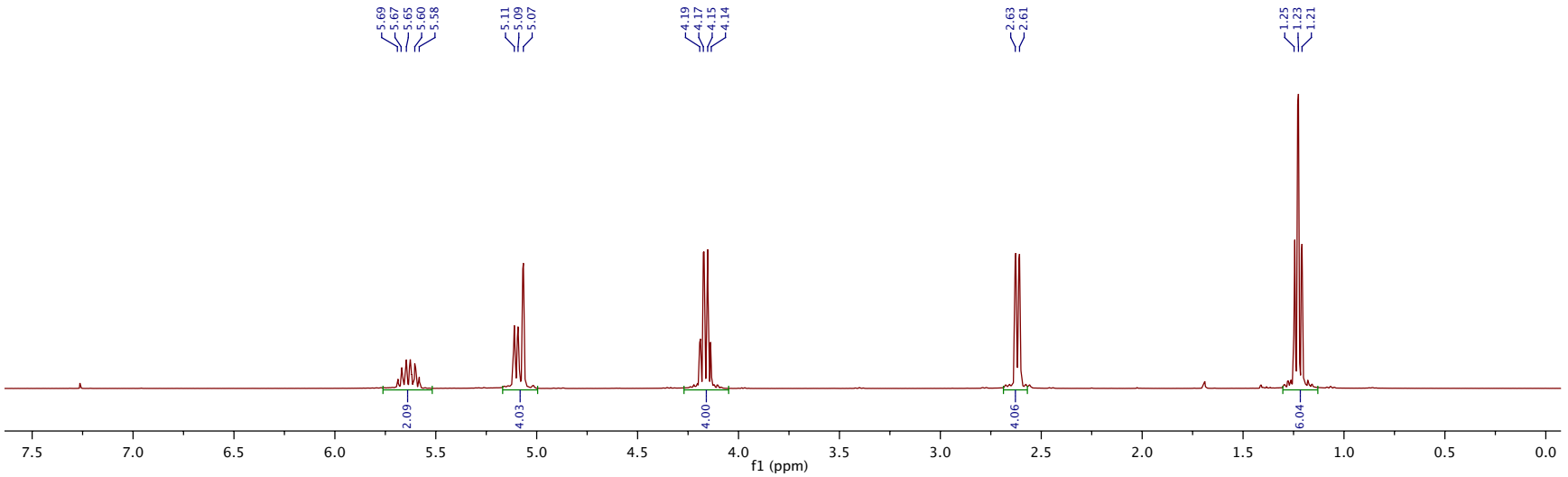

^{13}C NMR (100 MHz, $CDCl_3$)