Electronic Supporting Information (ESI)

Rearrangements and addition reactions of biarylazacyclooctynones and the implications to copper-free click chemistry

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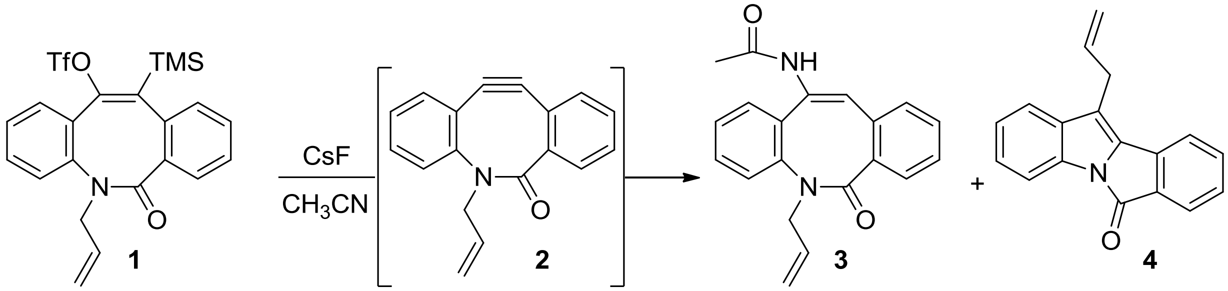
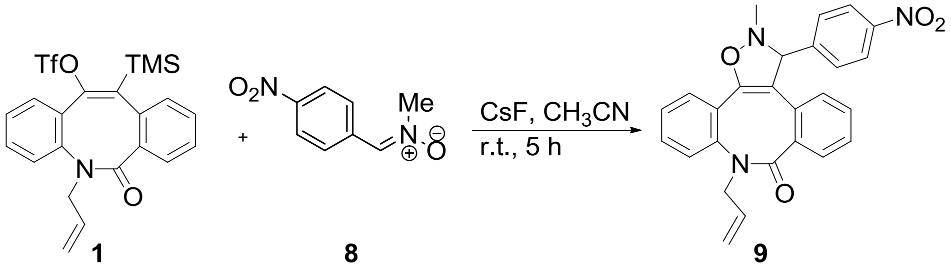
Synthetic Procedures and Characterization Data

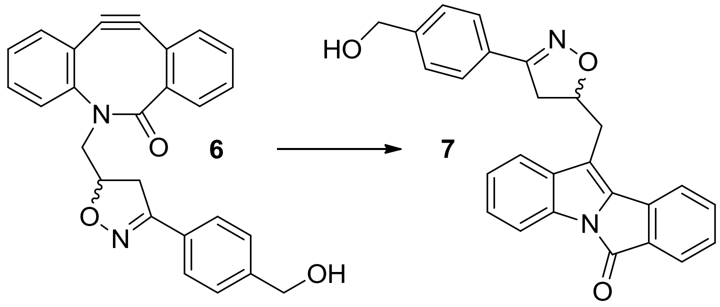
Initial Observation of the Rearrangement of BARAC



To a mixture of **1** (541.5 mg, 1.12 mmol, 1 equiv.) and CsF (1.02 g, 6.74 mmol, 6 equiv.) was added CH_3CN (96 mL) all at once. The solution was stirred vigorously for 45 min. The mixture was filtered to remove excess CsF. The filtrate was evaporated *in vacuo* and the crude oil was stored at -20 °C overnight. The crude was purified by silica gel column chromatography to yield **3** as white solid (324 mg, 1.01 mmol, 90 %, $\mathbf{R_f}$ = 0.16, Hx:EtOAc/1:1) and **4** as light yellow solid (7.6 mg, 0.03 mmol, 2.7 %, $\mathbf{R_f}$ = 0.6, Hx:EtOAc/8:2). **(*E*)-*N*-(5-allyl-6-oxo-5,6-dihydrodibenzo[*b*,*f*]azocin-12-yl)acetamide (3): ^{1}H-NMR (400 MHz, $CDCl_3$).** δ 7.54 (1 H, br s), 7.31 (1 H, dd, *J* = 7.2, 1.5 Hz), 7.1-7.25 (6 H, m), 7.02 (1 H, dd, *J* = 7.1, 1.1 Hz), 6.90 (1 H, br s), 5.95 (1 H, tdd, *J* = 17.0, 10.4, 6.4 Hz), 5.12 (2 H, m), 4.80 (1 H, dd, *J* = 14.7, 5.7 Hz), 4.14 (1 H, dd, *J* = 14.8, 7.0 Hz), 2.07 (3 H, s); **^{13}C-NMR (100 MHz, $CDCl_3$)**: δ 170.7, 168.4, 141.3, 137.0, 135.4, 133.9, 133.4, 129.6, 128.7, 128.4, 127.9, 127.9, 127.8, 127.1, 126.9, 117.9, 116.8, 100.0, 52.6, 24.5. **ESI-MS**: Calculated for $C_{20}H_{19}N_2O_2$ (M^+) = 319.14, Found 319.3.



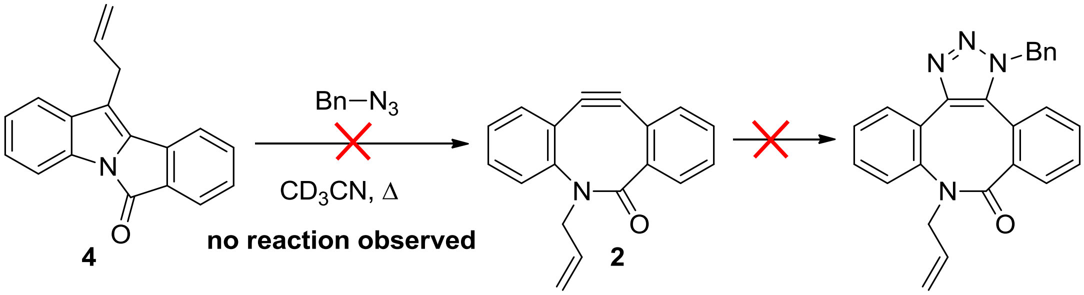
9-allyl-2-methyl-3-(4-nitrophenyl)-2,3-dihydrodibenzo[*b,f*]isoxazolo[5,4-*d*]azocin-8(9*H*)-one (9): To a mixture of **1** (50 mg, 0.10 mmol, 1 equiv.), **8** (26.7 mg, 0.10 mmol, 1 equiv.) and CsF (91 mg, 0.6 mmol, 6 equiv.) was added CH_3CN (0.7 mL) all at once. The solution was stirred vigorously for 5 h and the solvent was removed. The crude oil was purified by silica gel column chromatography (Hx:EtOAc/6:4, $\mathbf{R_f}$ = 0.3) to yield a light yellow oil (20.4 mg, 0.046 mmol, 46 %). **ESI-MS:** Calculated for $C_{26}H_{22}N_3O_4$ (M^+) = 440.15, Found 440.2.



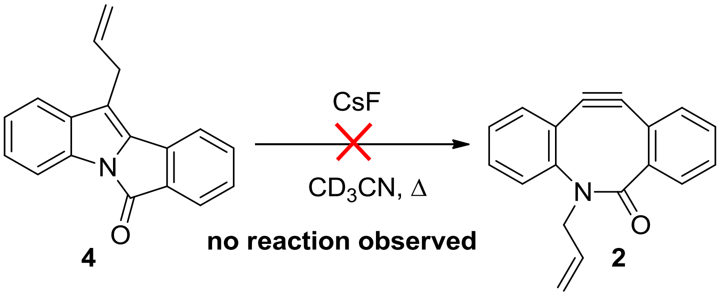
11-((3-(4-(hydroxymethyl)phenyl)-4,5-dihydroisoxazol-5-yl)methyl)-6H-isoindolo[2,1-a]indol-6-one (7): BARAC (**6**)[2] was dissolved in CD_3CN and stored at -20 ºC. Over time the solution turned from yellow to orange-red and a single red crystal was obtained. **^{1}H-NMR (400 MHz, $CDCl_3$)**: *δ* **^{13}C-NMR (100 MHz, $CDCl_3$)**: *δ* 7.77 (1 H, m), 7.64 (1 H, m), 7.59 (3 H, m), 7.51 (1 H, m), 7.43 (3 H, m), 7.37 (4 H, m), 7.31 (3 H, m), 7.22 (3 H, m), 7.18 (3 H, m), 7.14 (2 H, m), 5.28-5.40 (1 H, m), 5.22 (1 H, qd, *J* = 10.6, 6.3, 6.2, 6.2 Hz), 4.74 (4 H, m), 4.47 (2 H, ddd, *J* = 20.6, 15.0, 6.0 Hz), 4.09 (1H, t, *J* = 6.7, 6.7 Hz), 3.47 (1.5 H, dd, *J* = 16.8, 10.3 Hz), 3.24 (1.5 H, dd, *J* = 16.9, 6.3 Hz), 2.78 (1 H, s), 2.07 (2 H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 186.3, 159.6, 159.3, 158.9, 158.5, 158.1, 156.8, 156.6, 156.2, 143.0, 142.6, 141.0, 135.8, 134.5, 132.5, 131.0, 130.1, 129.7, 129.6, 128.9, 128.8, 128.2, 128.0, 127.8, 127.8, 127.4, 127.2, 127.1, 127.0, 126.9, 126.8, 126.3, 124.3, 123.8, 123.0, 122.3, 121.1, 121.0, 120.3, 119.1, 119.1, 118.9, 116.1, 115.5, 113.2, 110.8, 110.4, 109.7, 78.9, 78.7, 68.7, 64.9, 64.7, 60.9, 47.8, 47.8, 38.1, 37.9, 30.5, 29.5, 21.1, 21.1, 19.1, 17.3, 14.1, 13.9, 13.7. **ESI-MS:** Calculated for ($C_{26}H_{20}N_2O_3$) (M+) = 409.15, Found 409.2.

Note: A kinetic experiment with **6** following the same procedure as kinetic studies of rearrangement of **2** under acidic conditions ([TFA] =0.03M, in $CDCl_3$) was performed. Several products were observed by LC-MS. The estimated yield of mixture of isomers of **7** is ~67%.

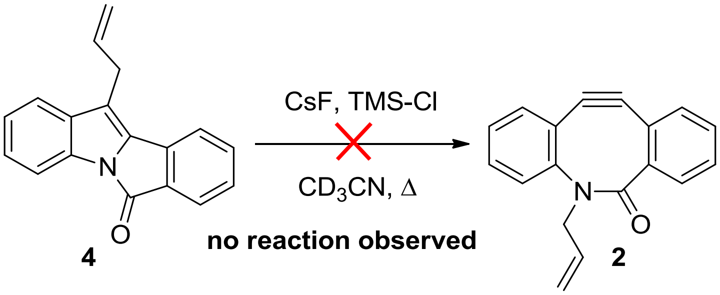
Investigations of Reversible Formation of 4



Experiment 1. To a mixture of **4** (3.5 mg, 0.0135 mmol, 1 equiv.) and benzyl azide (2 µL, 0.0162 mmol, 1.2 equiv.) was added CD_3CN (0.5 mL) all at once. The solution was stirred at r.t. for several days with no change observed by TLC or LC-MS. The mixture was transferred to an NMR tube and heated to 78 ºC for 1 h. No reaction was observed.



Experiment 2. CsF (2 mg, 0.0135 mmol, 1 equiv.) was added a solution of **4** (3.5 mg, 0.0135 mmol, 1 equiv.) in CD_3CN (0.5 mL). The solution was stirred at r.t. for several days with no change observed by TLC or LC-MS. The mixture was transferred to an NMR tube and heated to 78 ºC for 1 h. No reaction was observed.

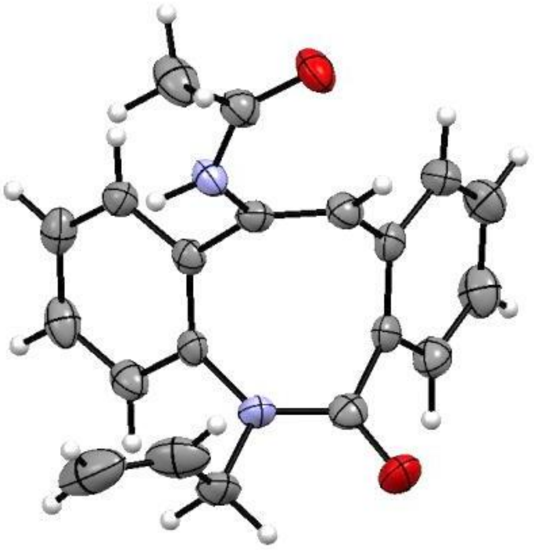


Experiment 3. Trimethylsilyl chloride (2 mL, 0.0135 mmol, 1 equiv.) was added to a solution of **4** (3.5 mg, 0.0135 mmol, 1 equiv.) and CsF (2 mg, 0.0135 mmol, 1 equiv.) in CD_3CN (0.5 mL). The solution was stirred at r.t. for several days with no change observed by TLC or LC-MS. The mixture was transferred to an NMR tube and heated to 78 ºC for 1 h. No reaction was observed.

X-ray Data Collection and Structure Solution for Compounds 3, 4, 5 and 7

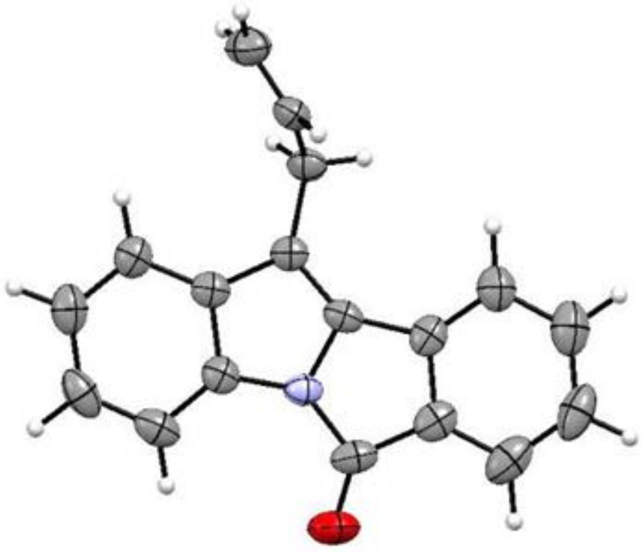
Single crystal X-ray diffraction data were measured on a Bruker Apex 2 Kuppa diffractometer at 100 K, using graphite monochromatized Mo K_α radiation (λ = 0.71073 Å). The unit cell was determined from randomly selected reflections obtained using the Bruker Apex2 automatic search, center, index, and least squares routines. Integration was carried out using the program SAINT, and an absorption correction was performed using SADABS.[1] The crystal structures were solved by direct methods and the structure was refined by full-matrix least-squares routines using the SHELXTL program suite.[2] All atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions and allowed to ride on the parent atoms. Structure was refined as a twin with twin matrix 1 0 0 0 -1 0 -1 0 -1 and BASF parameter 0.26104.

Crystal data and structural refinement of 3



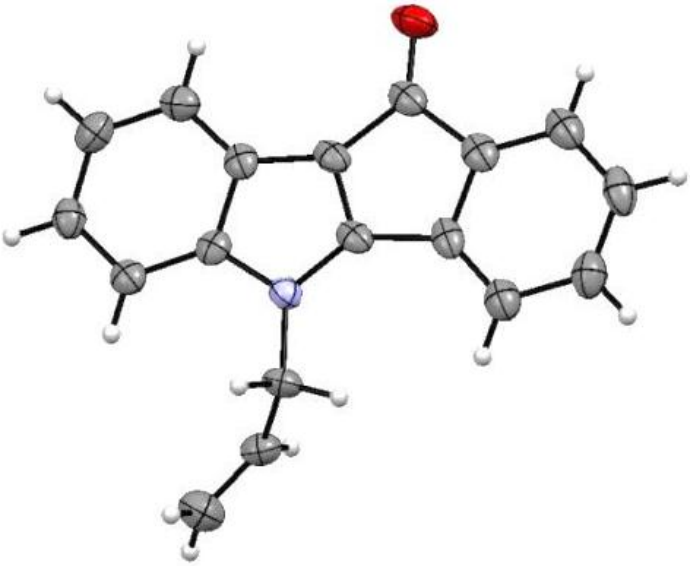
Empirical formula	C20 H18 N2 O2
Formula weight	318.36
Temperature	100.0(1) K
Wavelength	0.71070 A
Crystal system, space group	monoclinic, P21/n
Unit cell dimensions	a= 7.7470(5)A
	b= 26.1530(19)A
	c= 8.5985(6)A
	beta= 108.664(3)deg
Volume	1650.5(2)A^3
Z, Calculated density	4, 1.281 Mg/m^3
Absorption coefficient	0.084 mm^-1
F(000)	672
Crystal size	0.4×0.3×0.03 mm
Theta range for data collection	1.56 to 26.49 deg.
Limiting indices	-8<=h<=9, -30<=k<=32, -10<=l<=10
Reflections collected/unique	27855/ 3371
Completeness to theta 26.64	98.9%
Refinement method	Full---matrix least---squares on F^2
Data/restraints/parameters	3371/0/ 218
Goodness---of---fit on F^2	1.071
Final R indices [I>2sigma(I)]	R1= 0.0429, wR2= 0.0980
R indices (all data)	R1= 0.0644
Largest diff. peak and hole	-0.280 and 0.230 e.A^-3

Crystal data and structural refinement of 4



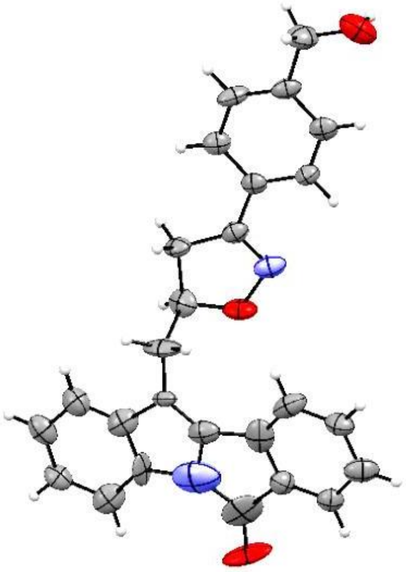
Empirical formula	C18 H13 N O
Formula weight	259.29
Temperature	100.0(1) K
Wavelength	0.71070 A
Crystal system, space group	monoclinic, P21/c
Unit cell dimensions	a= 17.1588(13)A
	b= 7.6525(7)A
	c= 20.1851(16)A
	beta= 107.382(3)deg
Volume	2529.4(4)A^3
Z, Calculated density	8, 1.362 Mg/m^3
Absorption coefficient	0.085 mm^-1
F(000)	1088
Crystal size	0.5×0.2×0.03 mm
Theta range for data collection	2.11 to 24.71 deg.
Limiting indices	-19<=h<=20, -9<=k<=8, -23<=l<=22
Reflections collected/unique	59114/ 4276
Completeness to theta 26.64	98.7%
Refinement method	Full---matrix least---squares on F^2
Data/restraints/parameters	4276/0/ 465
Goodness---of---fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1= 0.0354, wR2= 0.0965
R indices (all data)	R1= 0.0487
Largest diff. peak and hole	-0.239 and 0.181 e.A^-3

Crystal data and structural refinement of 5



Empirical formula	C18 H13 N O
Formula weight	259.29
Temperature	100.0(1) K
Wavelength	0.71070 A
Crystal system, space group	monoclinic, P21/c
Unit cell dimensions	a=17.189(2)
	b=7.7634(6)
	c=19.771 (2)
	beta=107.401(4)deg
Volume	2517.6(4) A^3
Z, Calculated density	8, 1.368 Mg/m^3
Absorption coefficient	0.091 mm^-1
F(000)	1088
Crystal size	0.6×0.1×0.1 mm
Theta range for data collection	1.24 to 31.45 deg.
Limiting indices	-23<=h<=25, -9<=k<=10, -28<=l<=26
Reflections collected/unique	64552/6824
Completeness to theta 26.64	98.7%
Refinement method	Full---matrix least---squares on F^2
Data/restraints/parameters	6824/0/361
Goodness---of---fit on F^2	1.030
Final R indices [I>2sigma(I)]	R1=0.054, wR2=0.148
R indices (all data)	R1=0.090
Largest diff. peak and hole	-0.202 and 0.552 e.A^-3

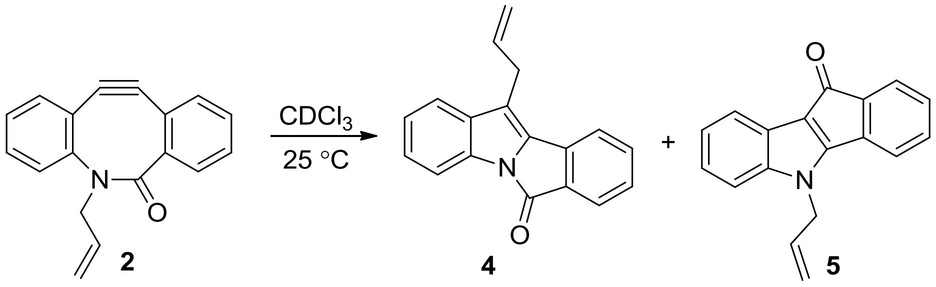
Crystal data and structural refinement of 7



Empirical formula	C26 H20 N2 O3
Formula weight	408.44
Temperature	100.0(1) K
Wavelength	0.71070 A
Crystal system, space group	monoclinic, P21/c
Unit cell dimensions	a=5.4793(18)A
	b=20.849(7)A
	c=17.361(6)A
	beta=98.866(18) deg
Volume	1959.6(11) A^3
Z, Calculated density	4, 1.384 Mg/m^3
Absorption coefficient	0.091 mm^-1
F(000)	856
Crystal size	0.4×0.2×0.01 mm
Theta range for data collection	1.54 to 26.64 deg.
Limiting indices	-5<=h<=6, -25<=k<=25, -21<=l<=21
Reflections collected/unique	39606/15281
Completeness to theta 26.64	98.5%
Refinement method	Full---matrix least---squares on F^2
Data/restraints/parameters	39904/0/283
Goodness---of---fit on F^2	1.048
Final R indices [I>2sigma(I)]	R1=0.127, wR2=0.272
R indices (all data)	R1=0.273
Largest diff. peak and hole	-0.419 and 0.711 e.A^-3

Kinetic data for the rearrangement reactions of 2

Neutral conditions



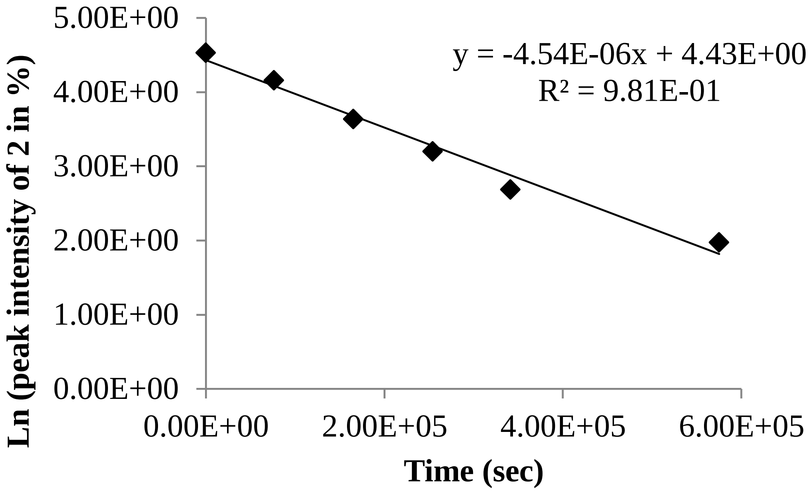


Figure S1. Plot of Ln ([**2**]) vs. time for the rearrangement reaction under neutral conditions as monitored by ^{1}H-NMR in $CDCl_3$ at 25 ± 0.1 ºC.

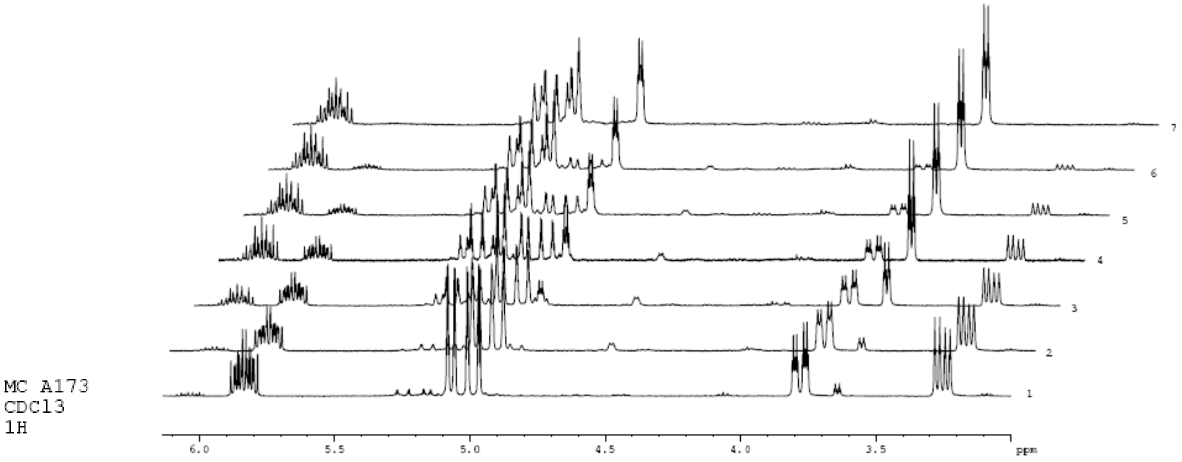
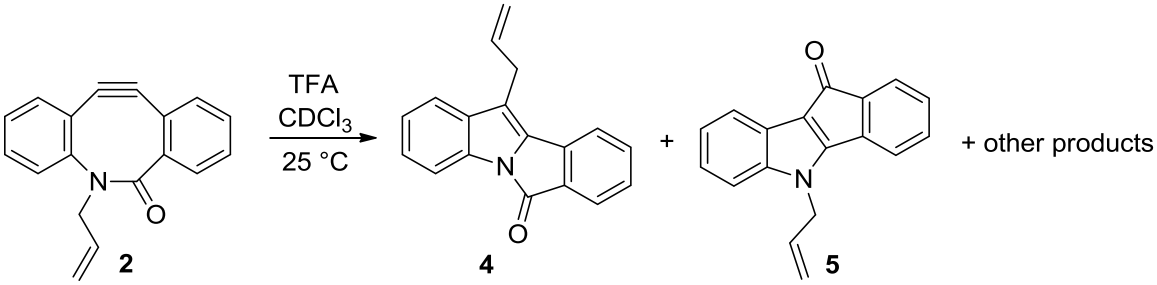


Figure S1a. Overlay of ^{1}H-NMR spectra showing the progression of the rearrangement reaction over time. Reaction was done under in $CDCl_3$ at 25 ± 0.1 ºC.

Acidic conditions



The rate measurements of rearrangement of **2** at five different concentrations of TFA were performed using NMR spectroscopy at 25 ± 0.1 ºC. All stock solutions including dissolution of **2** were done in fresh pre-neutralized deuterated chloroform.

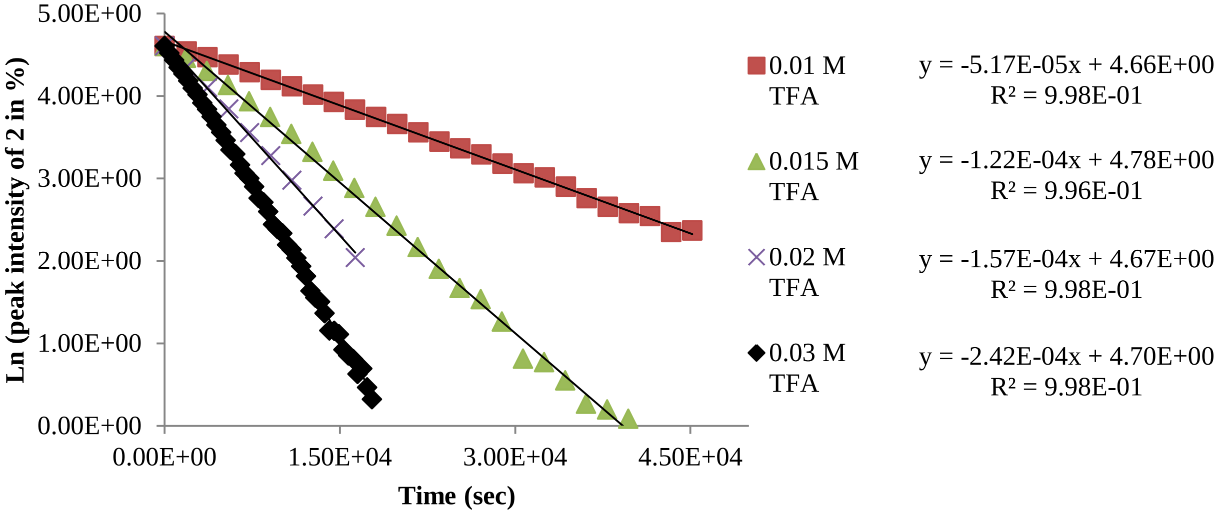


Figure S2. Plot of Ln ([**2**]) vs. time for the rearrangement reactions under acidic conditions as monitored by ^{1}H-NMR in $CDCl_3$ at 25 ± 0.1 ºC.

Acid catalysis ([TFA] = 0.01 M)

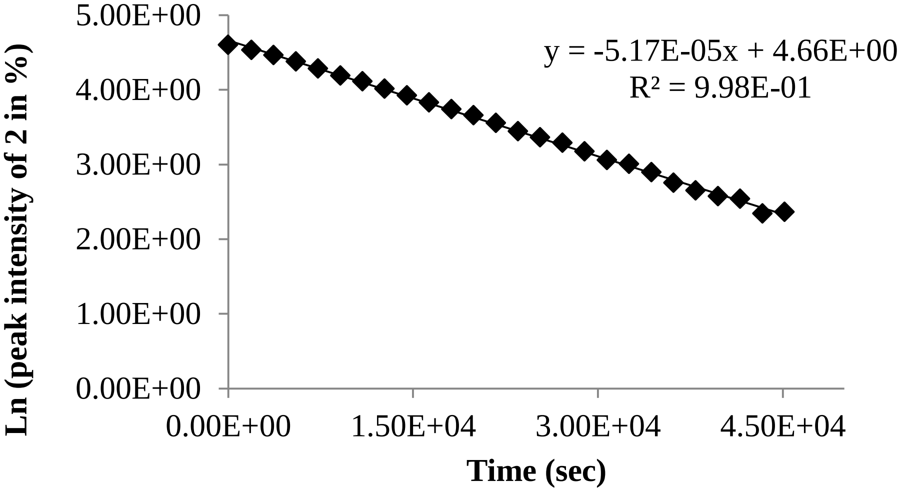


Figure S3. Plot of Ln ([**2**]) vs. time for the rearrangement reaction under acidic ([TFA] = 0.01 M) conditions as monitored by ^{1}H-NMR in $CDCl_3$ at 25 ± 0.1 ºC.

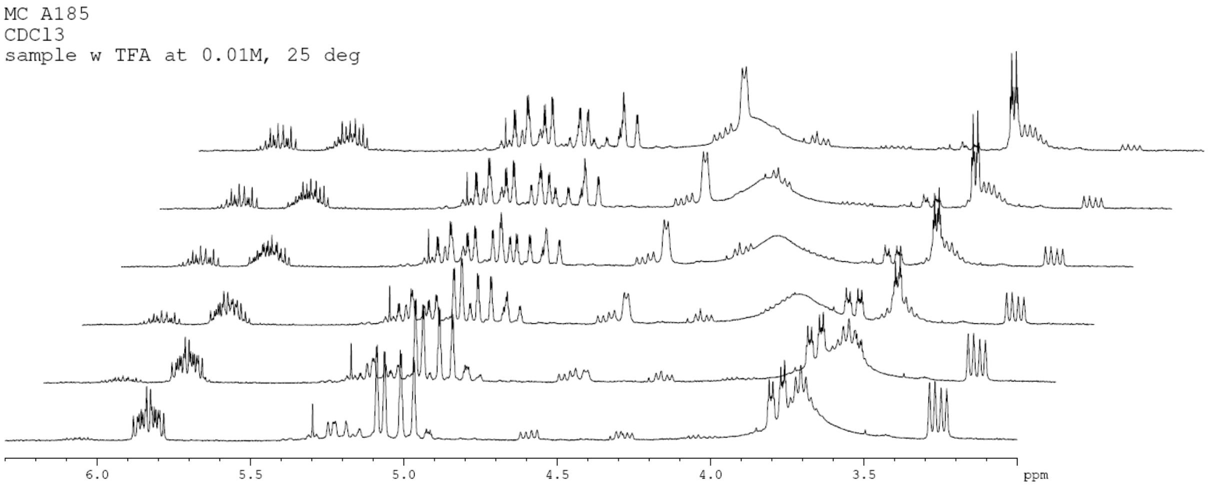


Figure S3a. Overlay of ^{1}H-NMR spectra showing the progression of the rearrangement reaction over time. Reaction was done under acidic ([TFA] = 0.01 M) conditions in $CDCl_3$ at 25 ± 0.1 ºC.

Acid catalysis ([TFA] = 0.015 M)

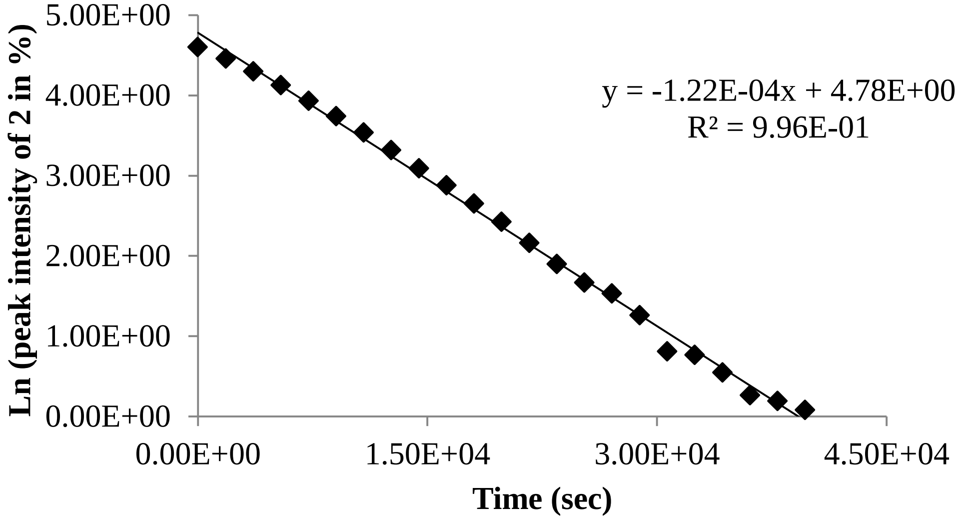


Figure S4. Plot of Ln ([**2**]) vs. time for the rearrangement reaction under acidic ([TFA] = 0.015 M) conditions as monitored by ^{1}H-NMR in $CDCl_3$ at 25 ± 0.1 ºC.

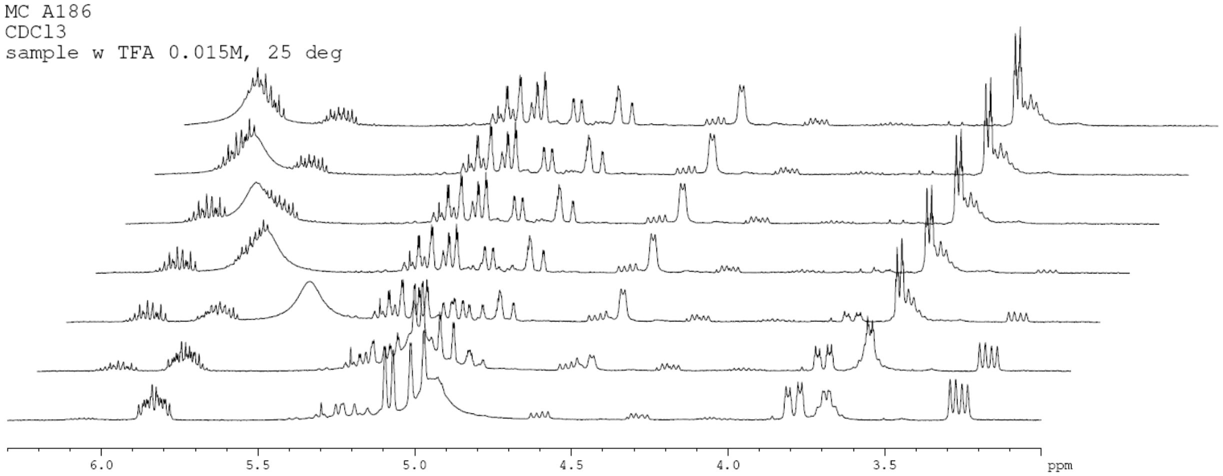


Figure S4a. Overlay of ^{1}H-NMR spectra showing the progression of the rearrangement reaction over time. Reaction was done under acidic ([TFA] = 0.015 M) conditions in $CDCl_3$ at 25 ± 0.1 ºC.

Acid catalysis ([TFA] = 0.02 M)

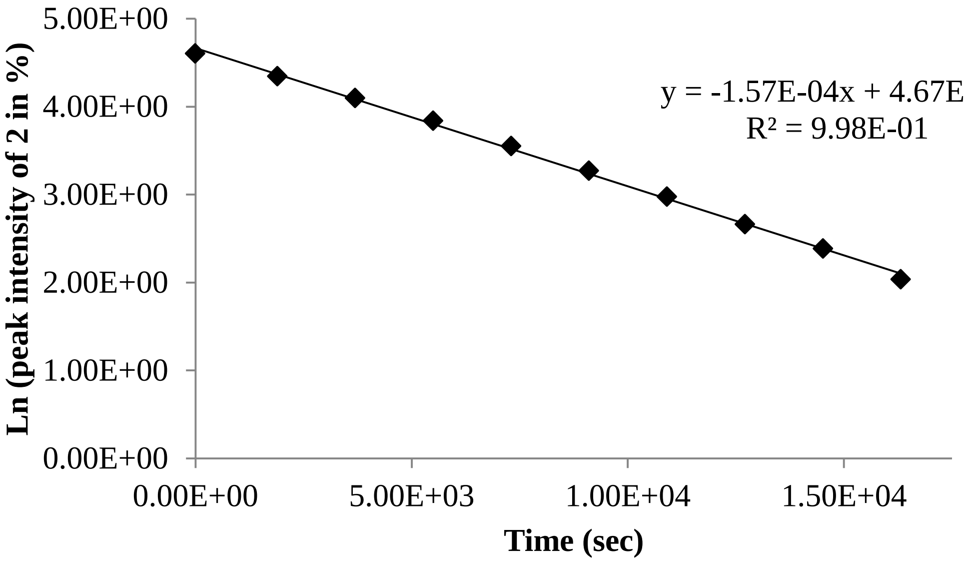


Figure S5. Plot of Ln ([**2**]) vs. time for the rearrangement reaction under acidic ([TFA] = 0.02 M) conditions as monitored by ^{1}H-NMR in $CDCl_3$ at 25 ± 0.1 ºC.

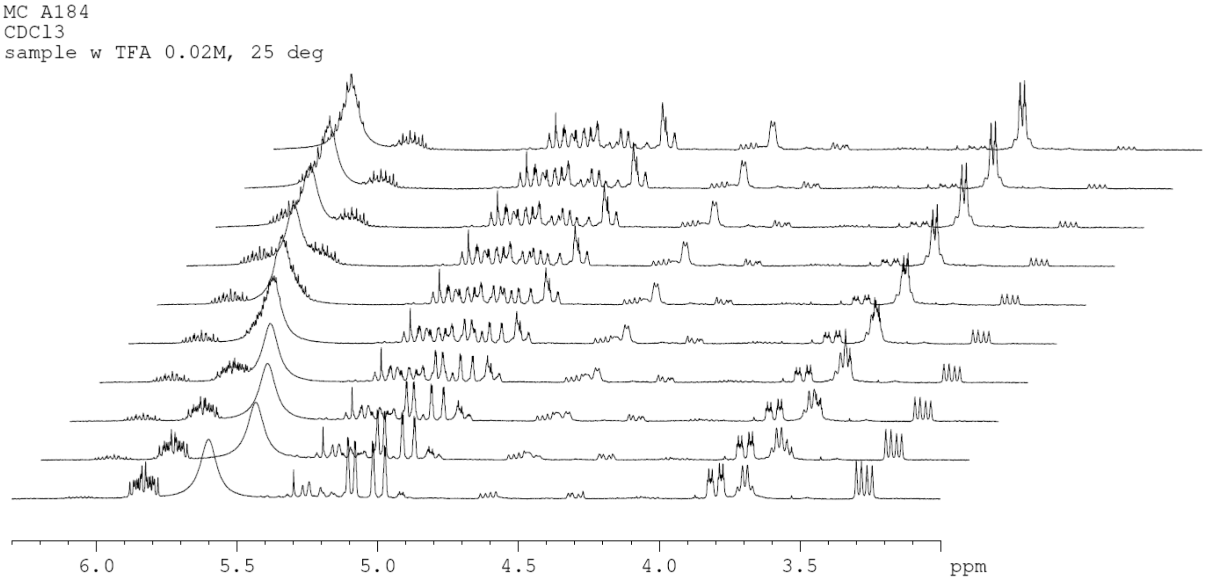


Figure S5a. Overlay of ^{1}H-NMR spectra showing the progression of the rearrangement reaction over time. Reaction was done under acidic ([TFA] = 0.02 M) conditions in $CDCl_3$ at 25 ± 0.1 ºC.

Acid catalysis ([TFA] = 0.03 M)

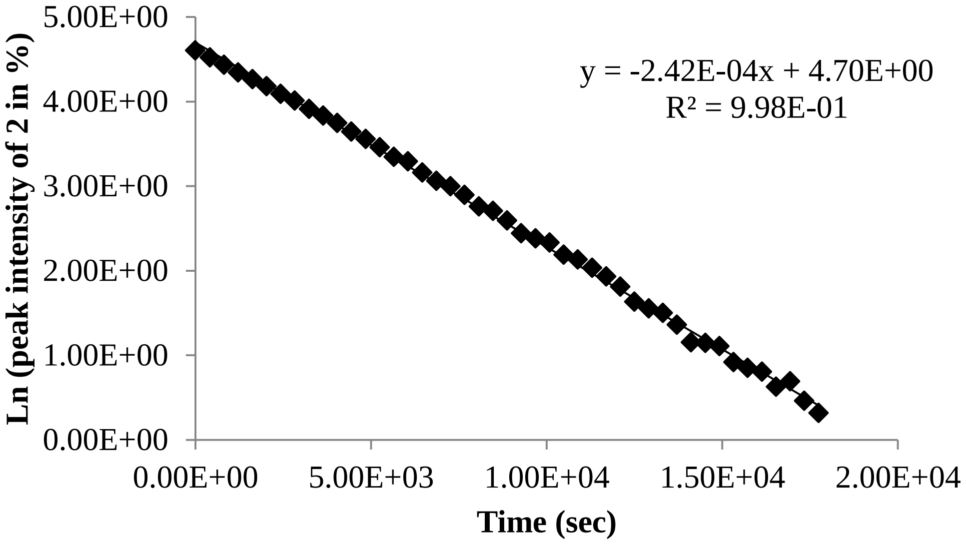


Figure S6. Plot of Ln ([**2**]) vs. time for the rearrangement reaction under acidic ([TFA] = 0.03 M) conditions as monitored by ^{1}H-NMR in CDCl$_3$ at 25 ± 0.1 ºC.

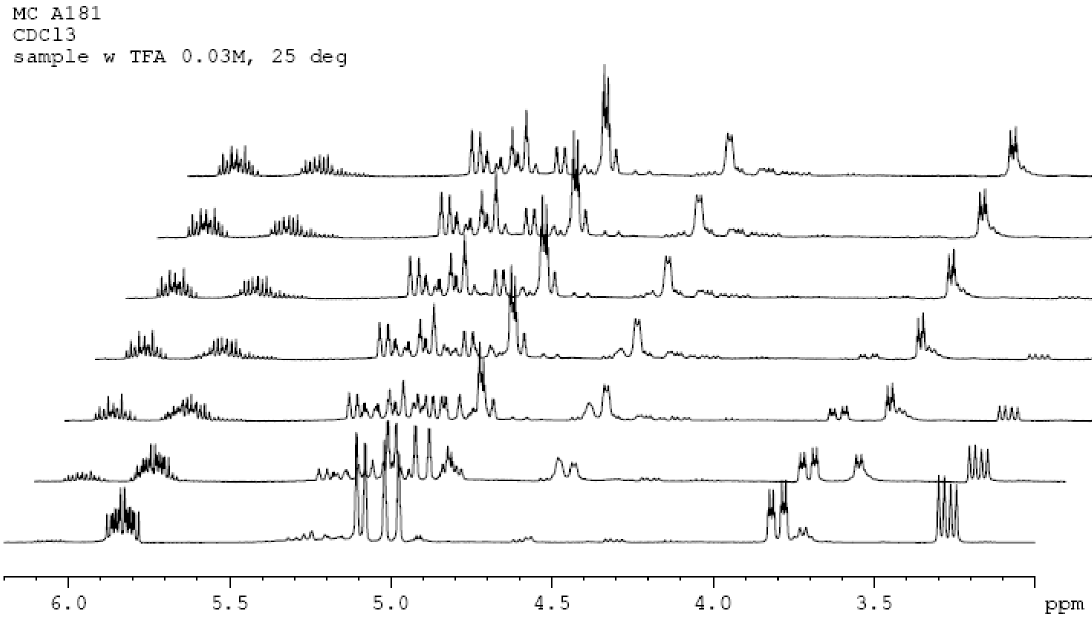
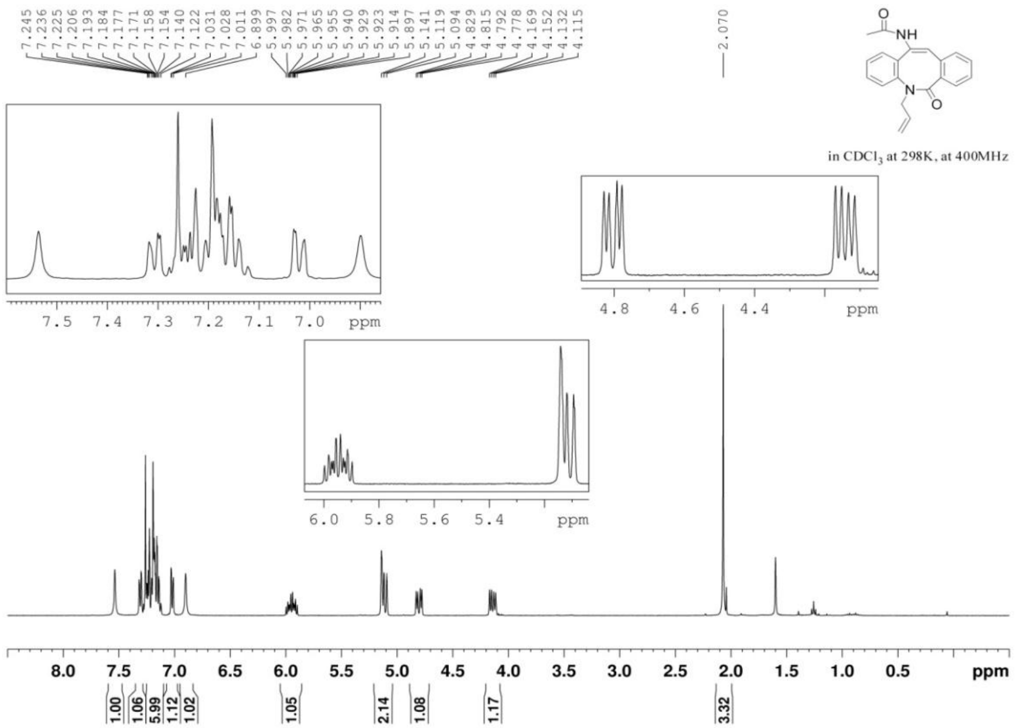


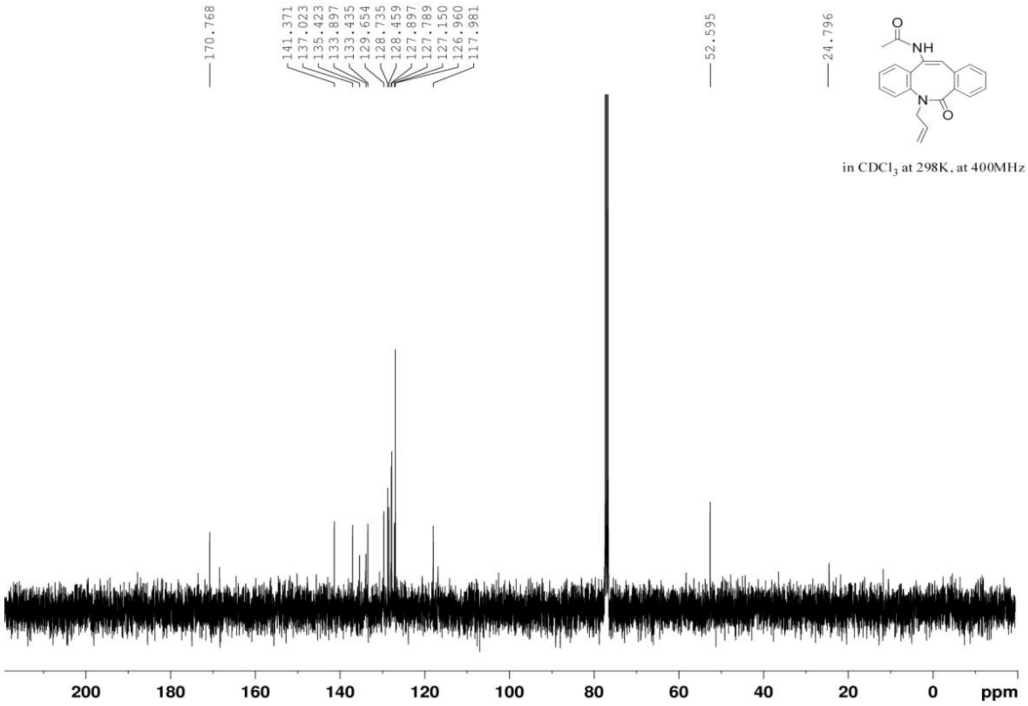
Figure S6a. Overlay of ^{1}H-NMR spectra showing the progression of the rearrangement reaction over time. Reaction was done under acidic ([TFA] = 0.03 M) conditions in CDCl$_3$ at 25 ± 0.1 ºC.

References.

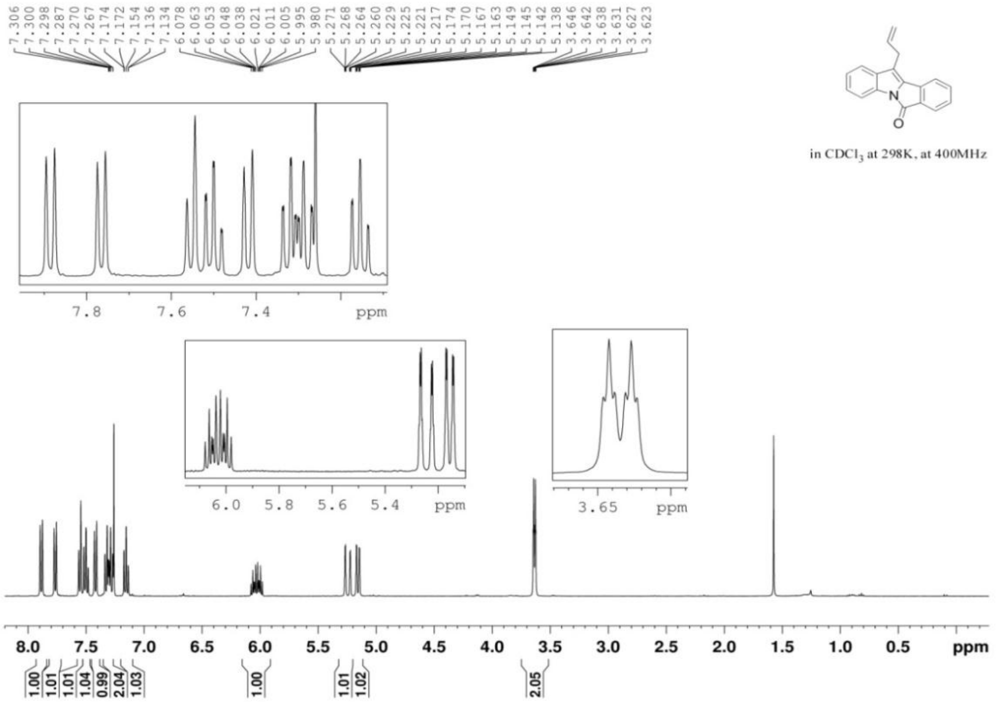
1. G. M. Sheldrick, SADABS Version 2.03, University of Gottingen, Germany, 2002.
2. G. M. Sheldrick, SHELXTL, Version 6.10; Bruker AXS Inc., Madison, Wisconsin, USA, 2000.

Appendix 1 -^{1}H and ^{13}C NMR of 3

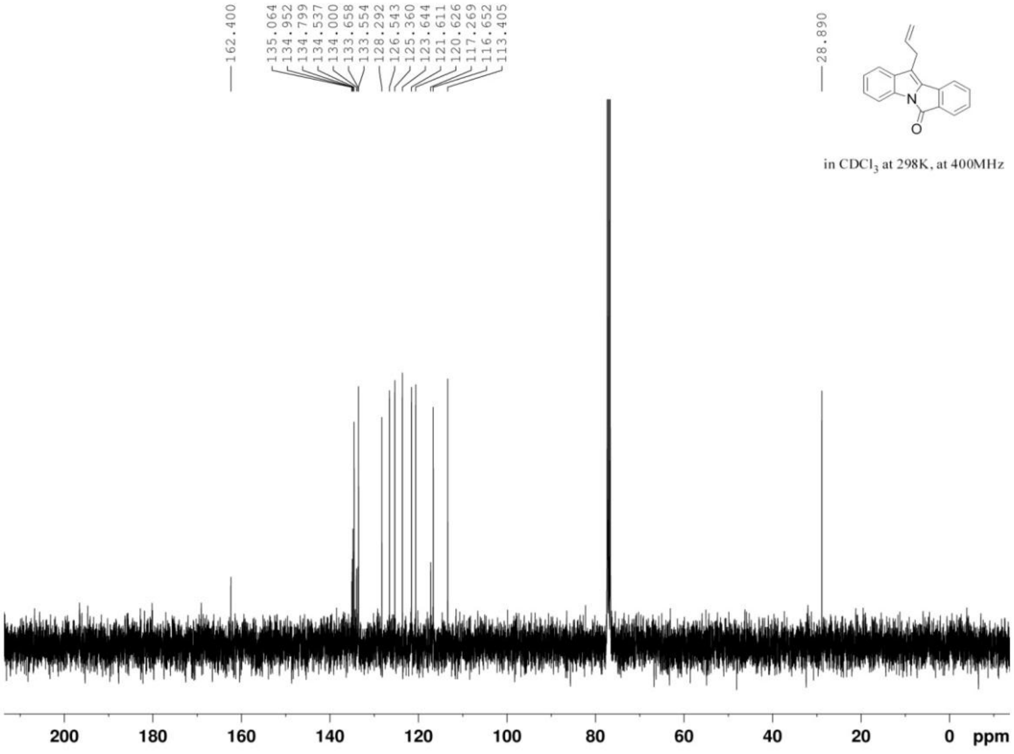




Appendix 2 -^{1}H and ^{13}C NMR of 4

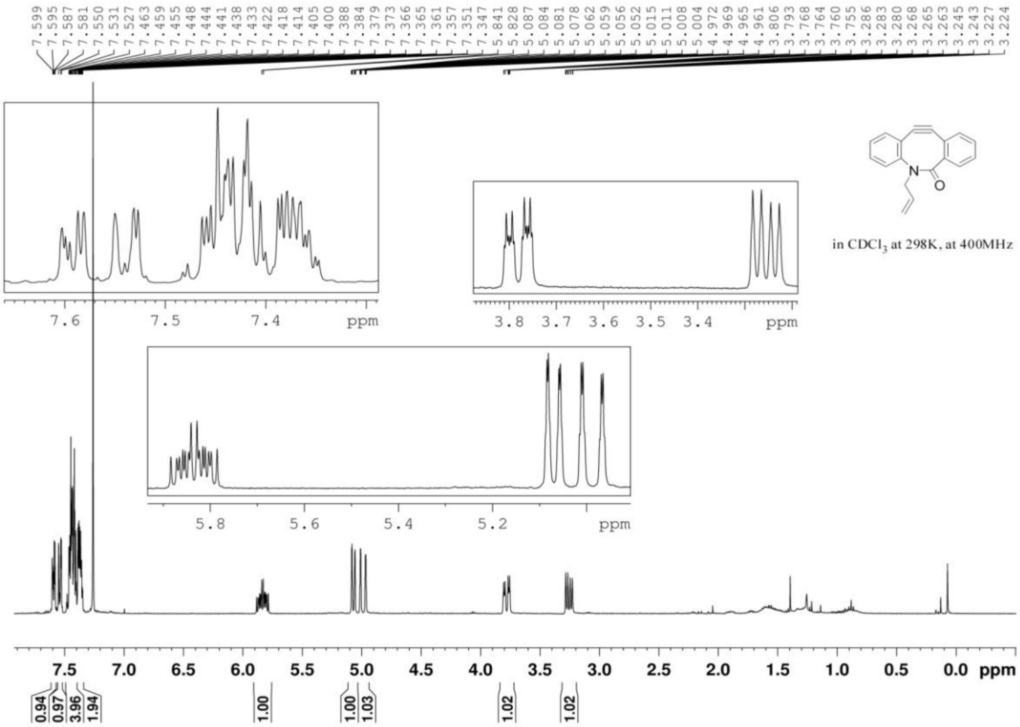


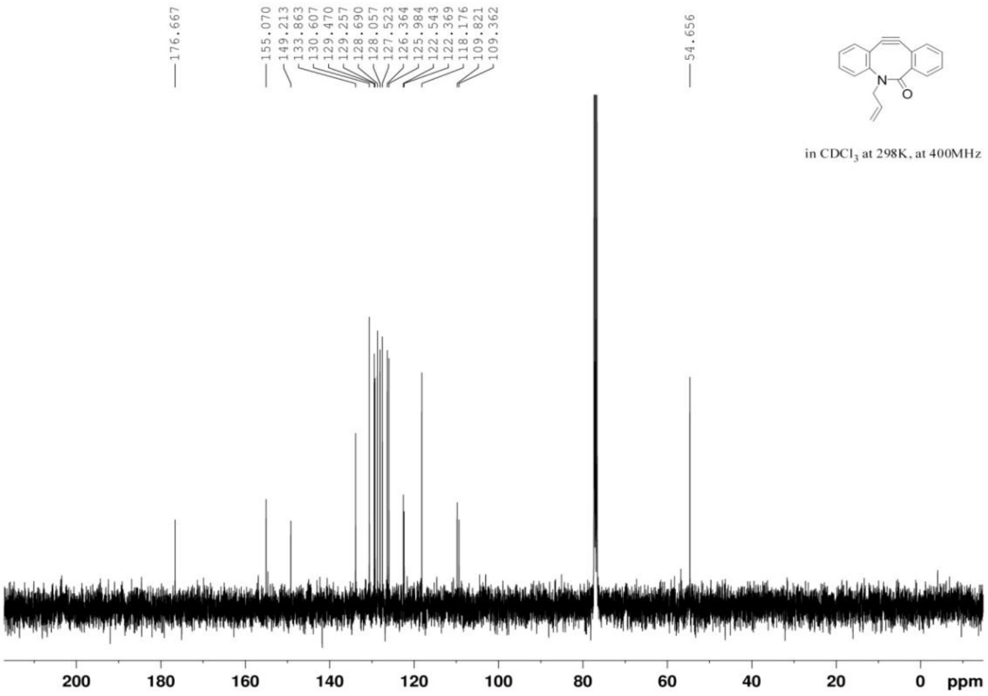
in CDCl$_3$ at 298K, at 400MHz



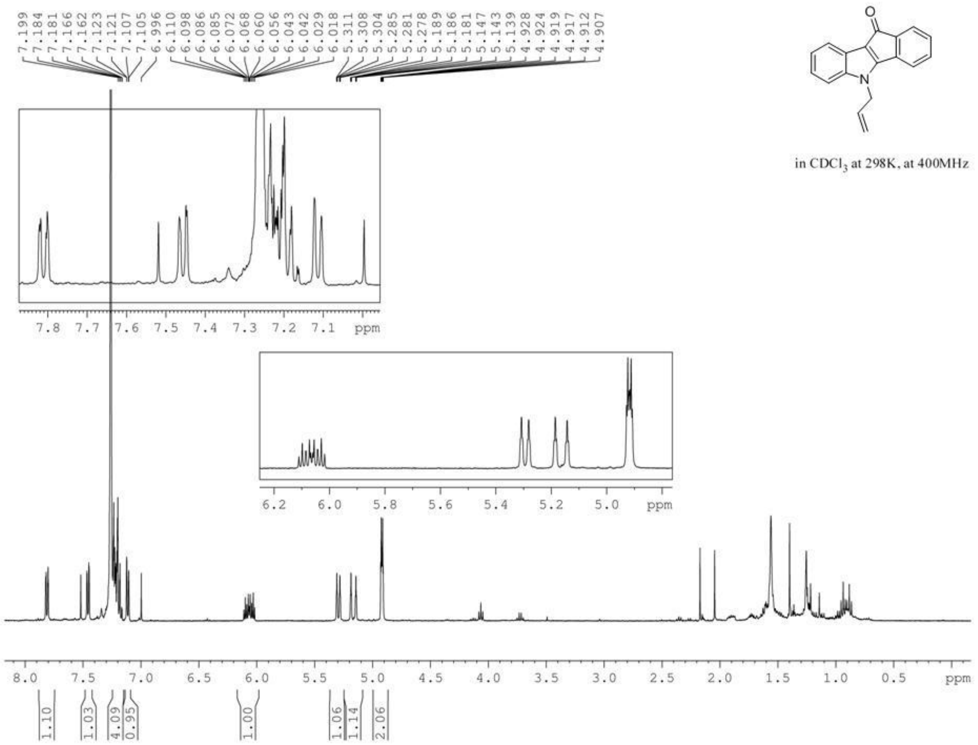
in CDCl$_3$ at 298K, at 400MHz

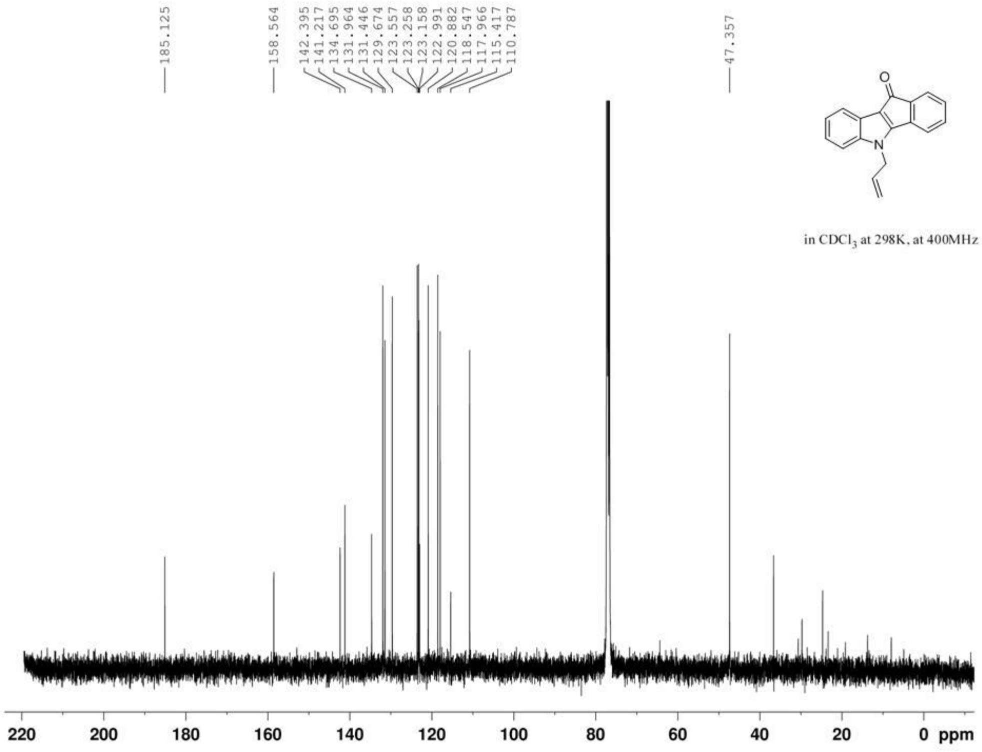
Appendix 3 -^{1}H and ^{13}C NMR of 2



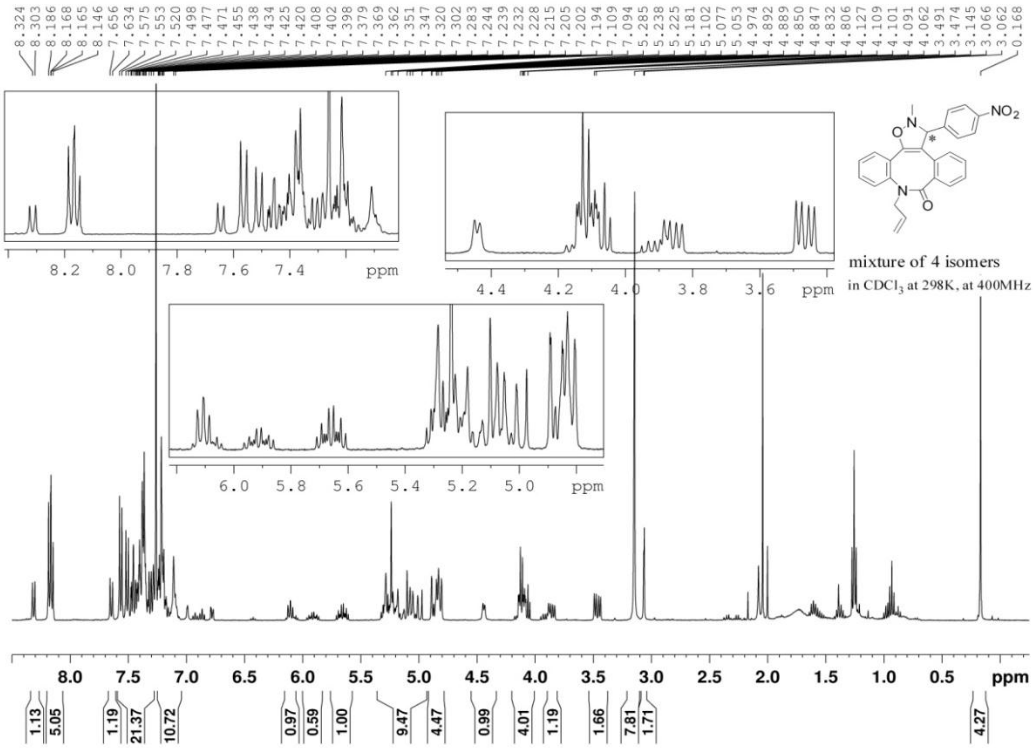


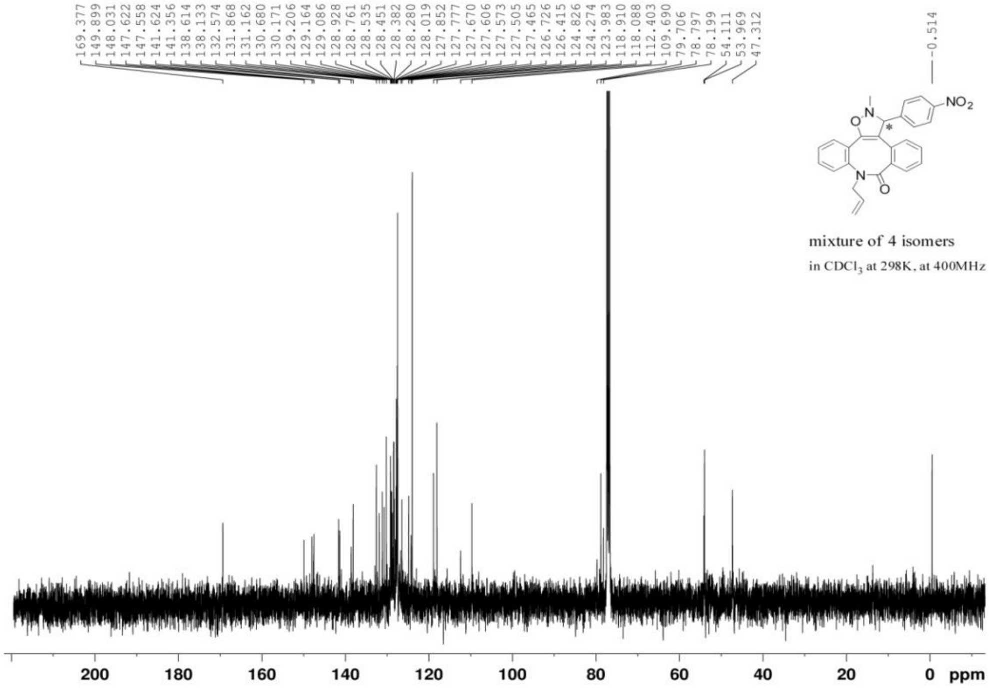
Appendix 4 -^{1}H and ^{13}C NMR of 5





Appendix 5 -^{1}H and ^{13}C NMR of 9





Appendix 6 -^{1}H and ^{13}C NMR of 7