Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.


**Supporting Information**

# Computational and Experimental Studies on Cu/Au-catalyzed Stereoselective Synthesis of 1,3-disubstituted allenes

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## General procedures

Reagents and solvents were purchased as reagent grade and used without further purification unless stated otherwise. Dichloromethane, acetonitrile and amines were freshly distilled from $CaH_2$. Cyclohexane and 1,4-dioxane were dried by distillation over sodium. $Au(PPh_3)Cl$ and $AgPF_6$ were provided for Strem Chemicals. $[(JohnPhos)Au(CH_3CN)][SbF_6]$ was commercial compound from Merck. Chloral hydrate was dried over sulfuric acid and distilled before use. All reactions were carried out under nitrogen atmosphere in oven- or flame-dried glassware with magnetic stirring. Chromatography refers to flash chromatography (FC) on $SiO_2$ 60 (0.02±0.063 mm) from Merck; ahead pressure of around 0.2 bar was applied. TLC was performed on aluminium-backed plates coated with silica gel 60 (230.240 mesh) with F254 indicator from Merck. The spots were visualized with UV light (254 nm) and/or staining with phosphomolybdic acid solution and subsequent heating. HPLC: Waters 616 pump controlled by a Waters 600s pump controller, with a Waters 717plus autosampler and a photoiodide array detector Waters 996. Solvents were HPLC grade and degassed with He. The optical rotation signals were measured on a Jasco P-2000 polarimeter using 0.13 and 1 decimeters cells at 254 nm (marked with the subscript D).UV/Vis and ECD spectra were recorded with a Jasco J-815 spectropolarimeter using one and ten centimeters thick quartz cuvettes at 25°C. $^{1}H$, $^{13}C$, $^{19}F$ and $^{31}P$ NMR spectra were recorded at 400, 100.6, 376 and 162 MHz, respectively with Bruker 600 MHz or 400 MHz spectrometers at room temperature. Chemical shifts are reported in ppm using residual solvent peaks as reference. Data are reported as follows: chemical shift, multiplicity (s: singlet, br s: broad singlet, d: doublet, t: triplet, m: multiplet, coupling constant (J in Hz) and integration. Mass spectrometry experiments were performed with a GCTOF mass spectrometer (Waters). Ions were generated by EI operating at 70 eV, and the samples were introduced in the source chamber as solids in a glass capillary.

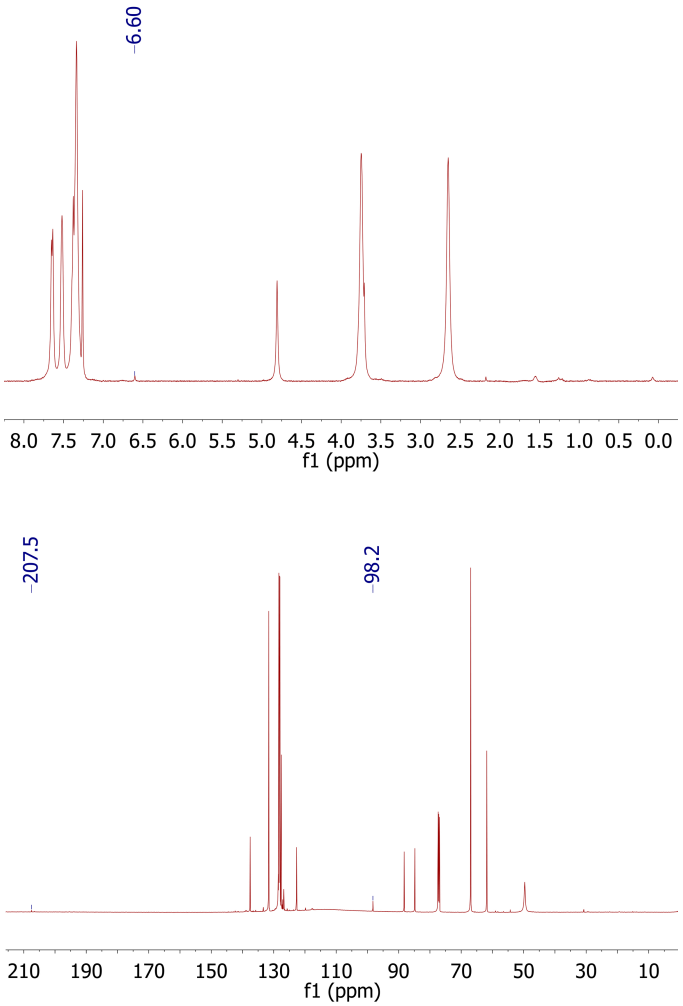



Figure S1- **$^{1}$H-NMR** (top) and **$^{13}$C-NMR** (bottom) spectra of the crude mixture of the CuBr-catalyzed reaction.

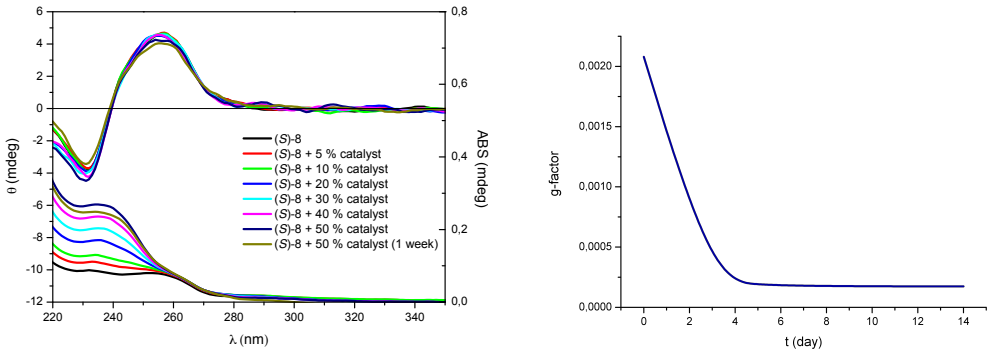
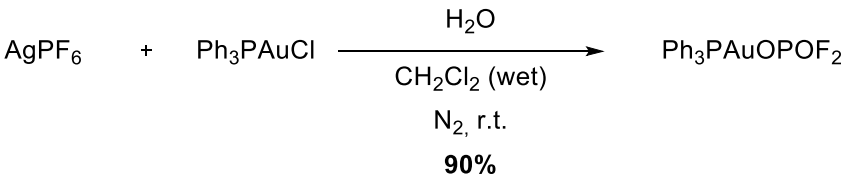



Figure S2- a) CD spectra of allene (*S*)-**5-Ph,Ph** with loads of catalyst in the reaction conditions; b) representation of g-factor vs time under ambient light of a solution of allene (*S*)-**5-Ph,Ph** in hexane**.**

## Synthesis and Characterization of the Compounds

*Synthesis of $Au(PPh_3)OPOF_2$*




To a solution of $Au(PPh_3)Cl$ (100 mol%, 0.06 mmol, 30 mg) in wet dichloromethane (3.2 mL), $AgPF_6$ was added (100 mol%, 0.06 mmol, 15 mg). The resulting mixture was stirred for 1 h at room temperature protected from ambient light. The solution was filtered through celite with the aid of dichloromethane and the solvent was eliminated under vacuum. A white solid was obtained in a 90% of yield (31 mg).
$^{1}$**H-NMR** (400 MHz, $CDCl_3$) $\delta$ 7.62 - 7.44 (m, 15 H); $^{13}$**C-NMR** (100 MHz, $CDCl_3$) $\delta$ 134.26, 134.13, 132.59, 132.57, 129.62, 129.50, 127.89, 127.23; $^{31}$**P-NMR** (162 MHz, $CDCl_3$) $\delta$ 27.25 (s), -12.91 (t, $J$ = 975.3 Hz); $^{19}$**F-NMR** (376 MHz, $CDCl_3$) $\delta$ -83.25 (d, $J$ = 972 Hz).

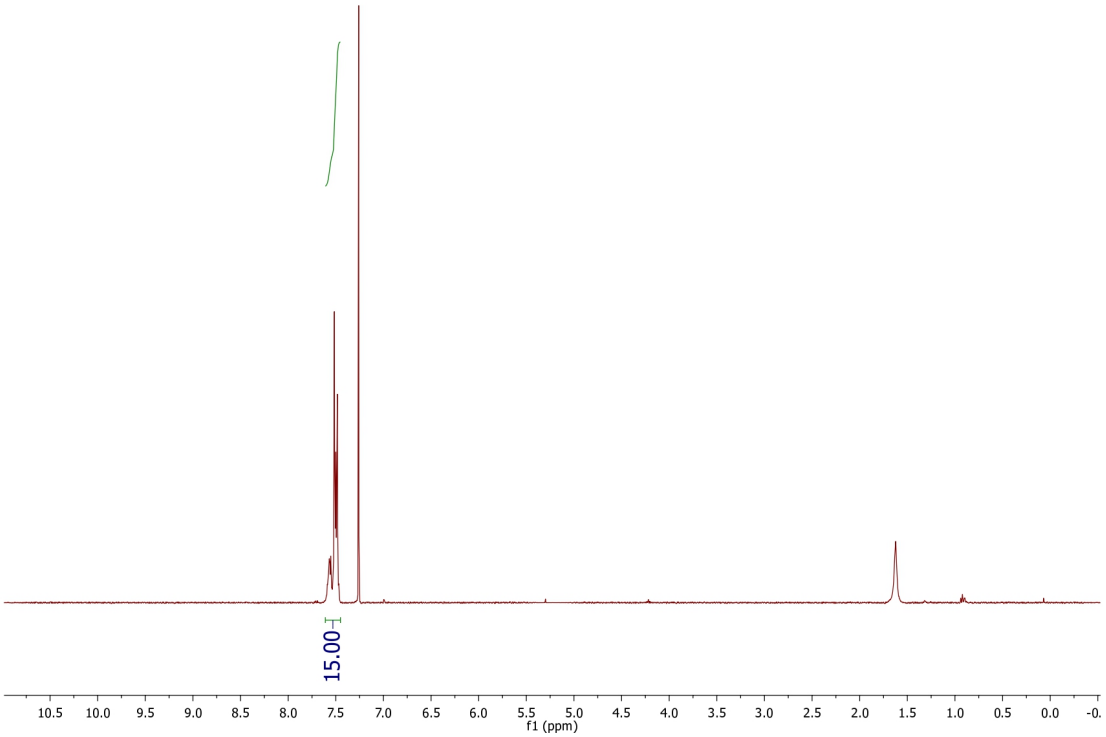



Figure S3- $^{1}$**H-NMR** (400 MHz, $CDCl_3$) spectra of $Au(PPh_3)OPOF_2$

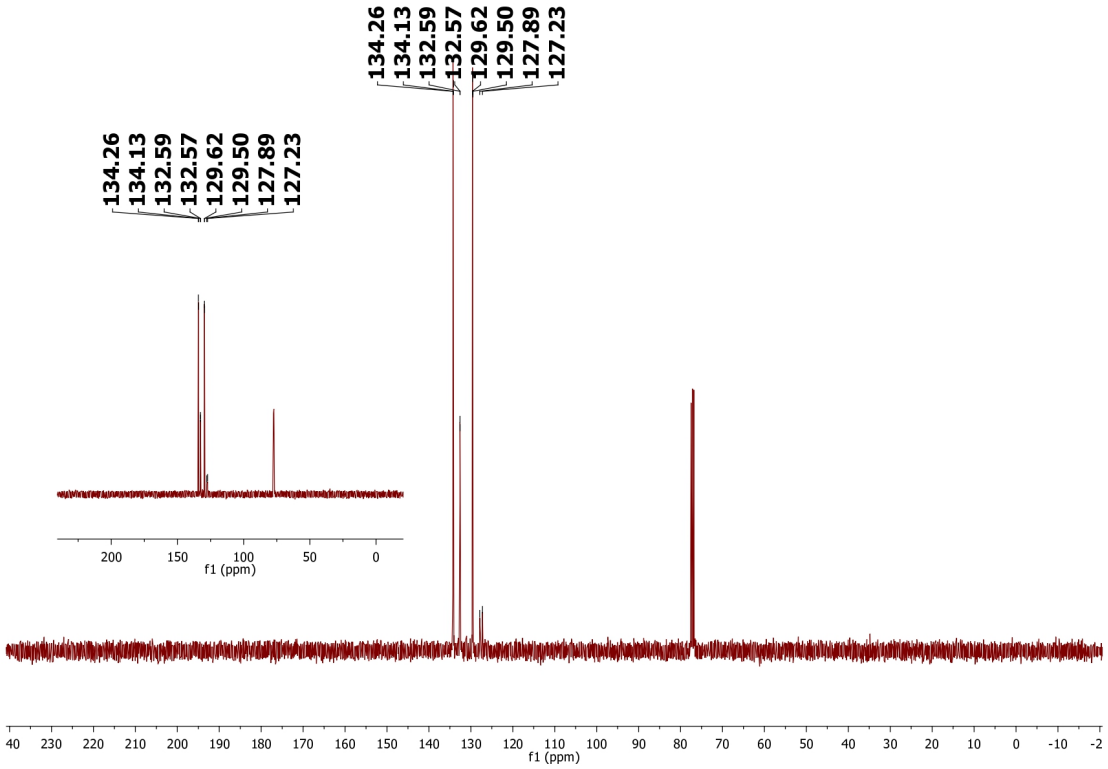



Figure S4- **$^{13}$C-NMR** (100 MHz, $CDCl_3$) spectra of $Au(PPh_3)OPOF_2$

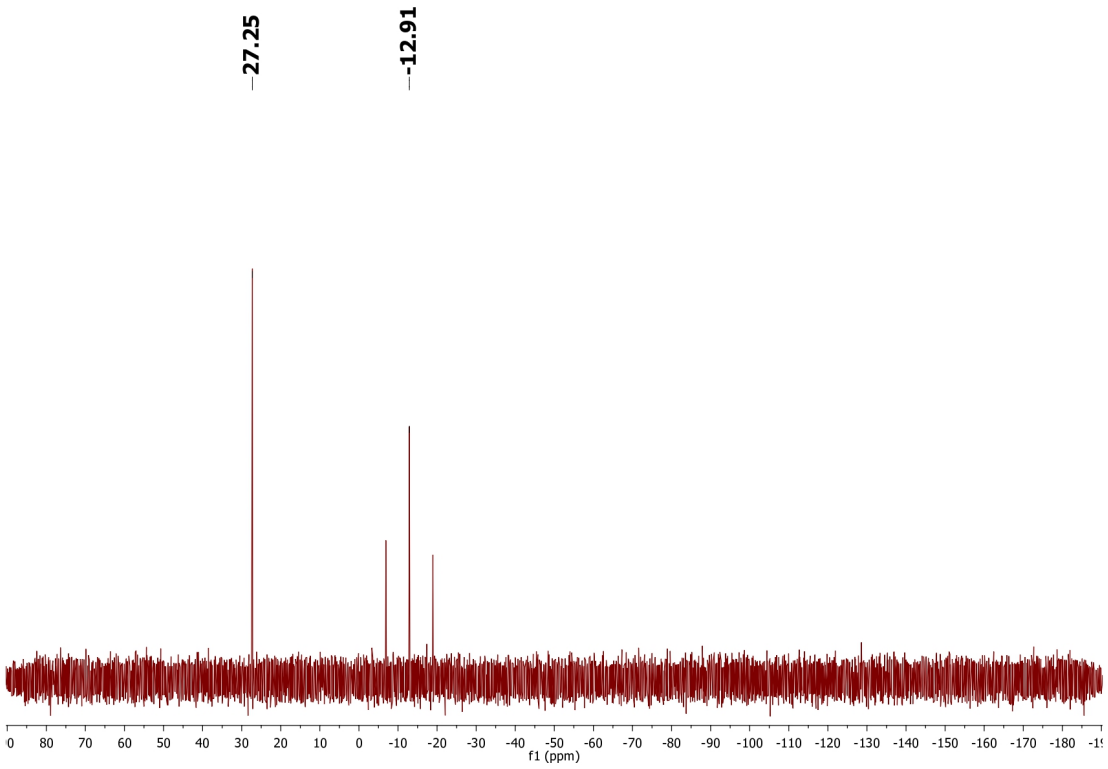



Figure S5- **$^{31}$P-NMR** (162 MHz, $CDCl_3$) spectra of $Au(PPh_3)OPOF_2$

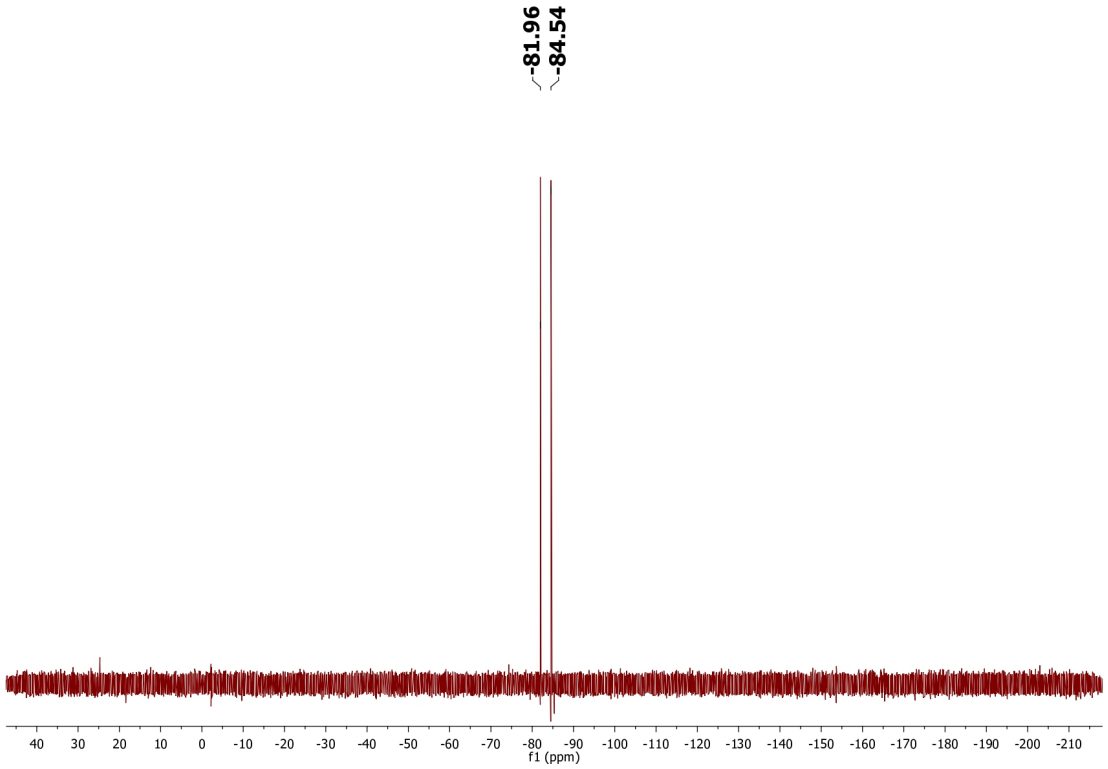
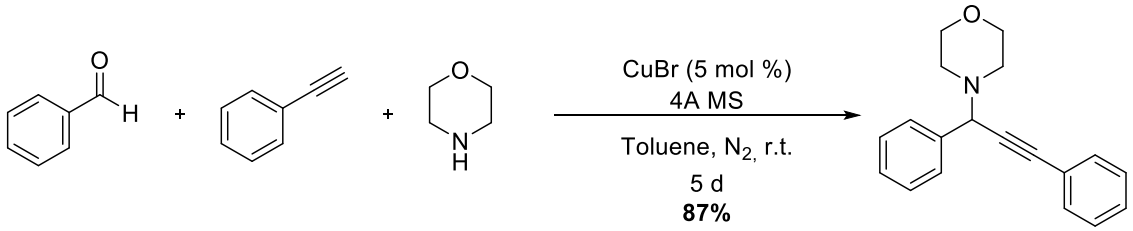


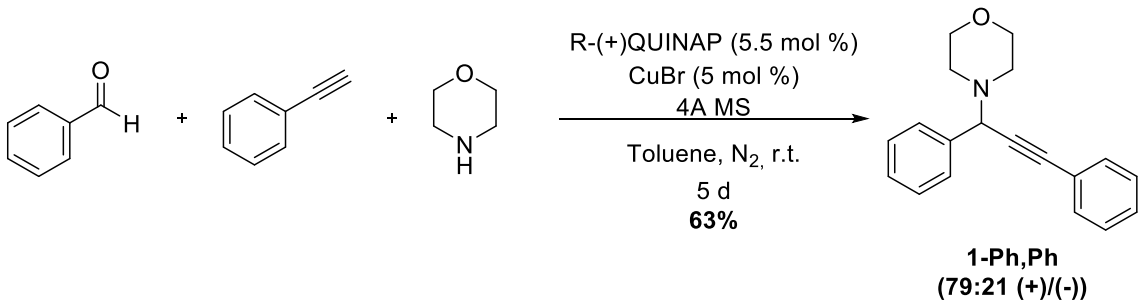

Figure S6- **$^{19}$F-NMR** (376 MHz, $CDCl_3$) spectra of $Au(PPh_3)OPOF_2$

## Synthesis of 4-(1,3-diphenyl-2-propyn-1-yl)-morpholine *(1-Ph,Ph)*[1]




**1-Ph,Ph**

A 10 mL round-bottomed flask equipped with a magnetic stirrer was charged with copper (I) bromide (5 mol%, 0.05 mmol, 13 mg). Anhydrous toluene (5 mL) was added and the mixture was stirred at room temperature for 30 min. Then, molecular sieves (4 Å, 0.9 g) were added, followed by phenylacetylene (100 mol%, 1 mmol, 210 µL), benzaldehyde (100 mol%, 1 mmol, 192 µL) and morpholine (100 mol%, 1 mmol, 165 µL). The reaction mixture was stirred for 48 hours at 60 °C. The molecular sieves were removed by filtration and washed with diethyl ether. The solvent was eliminated in vacuo and the residue was purified by silica gel chromatography (Hexane:EtAcO, 95:5) yielding **1-Ph,Ph** (454 mg, 87%).




A dried and nitrogen-flushed flask was charged with freshly copper(I) bromide (5 mol%, 0.05 mmol, 4 mg) and R-(+)-QUINAP (5.5 mol%, 0.55 mol , 11.4 mg) in dry toluene (2.4 mL). After stirring this mixture for 30 minutes, molecular sieves (4 Å, 236 mg), phenylacetylene (100 mol%, 0.47 mmol, 52 µL), benzaldehyde (100 mol%, 0.47 mmol, 48 µL) and morpholine (100 mol%, 0.47 mmol, 41 µL) were added. The resulting mixture was stirred at room temperature for 5 days. The molecular sieves were removed by filtration and washed with diethyl ether. The solvent was eliminated in vacuo and the residue purified by silica gel chromatography (Hexane:EtAcO, 95:5) yielding **1-Ph,Ph** (82 mg, 63%, 52% ee).
**HPLC** (Chiralpak IA, Hexane:AcOEt (98:2), 1.6 mL/min): $t_R$ (min)= 22.1 **(-)-1-Ph,Ph**, 26.7 **(+)-1-Ph,Ph**;[3,4] **$^1$H-NMR (**400 MHz, $CDCl_3$) $\delta$ 7.70 - 7.59 (m, 2H), 7.58 - 7.47 (m, 2H), 7.41 - 7.29, (m, 6H), 4.80 (s, 1H), 3.86-3.66 (m, 4H), 2.67-2.62 (m, 4H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$) $\delta$ 137.6, 131.6, 128.4, 128.2, 128.1 (x2), 127.6, 88.4, 84.9, 66.9, 61.8, 49.7; $[\alpha]_D^{23}$ = -3.7 (c = 0.018 g/mL, chloroform).

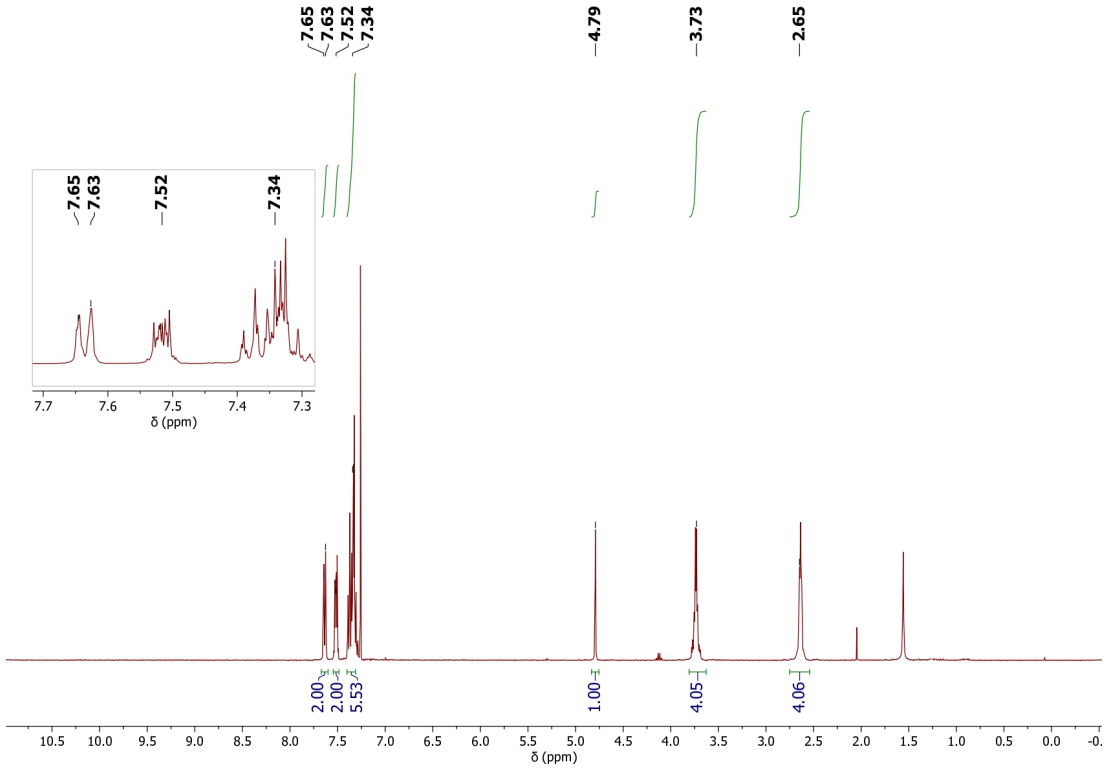



Figure S7- **$^1$H-NMR (**400 MHz, $CDCl_3$) spectra of **1-Ph,Ph**

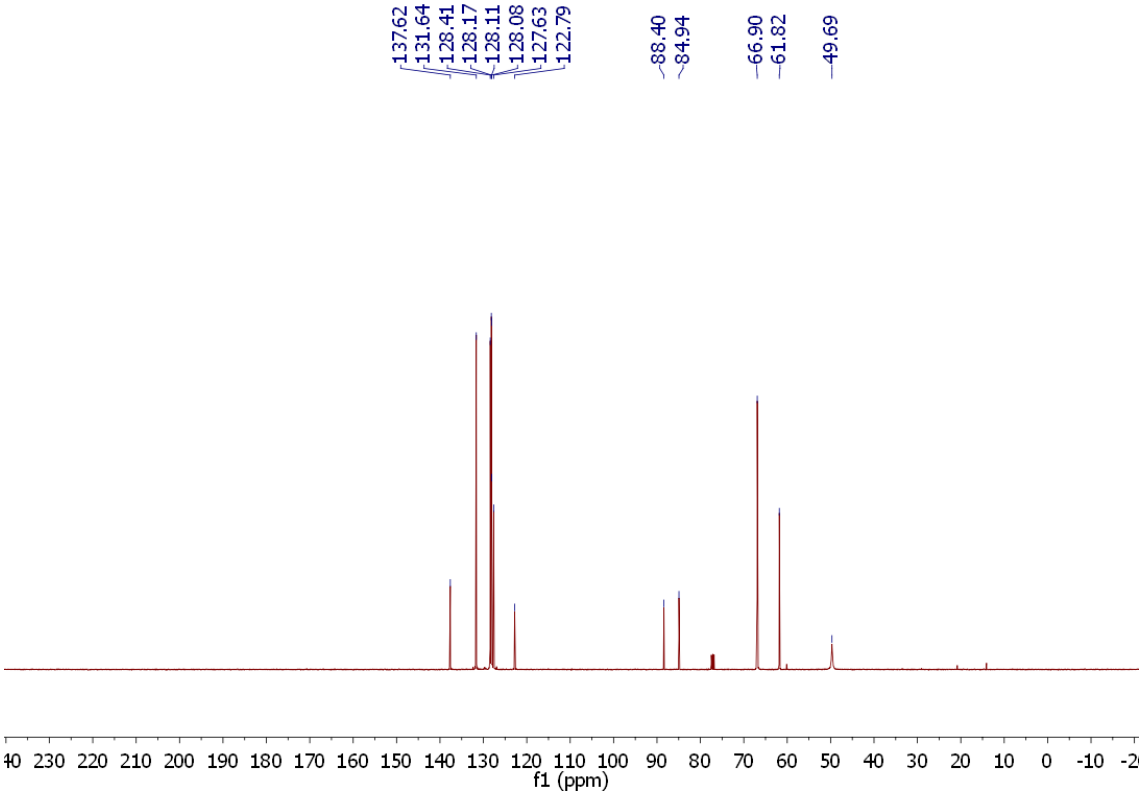
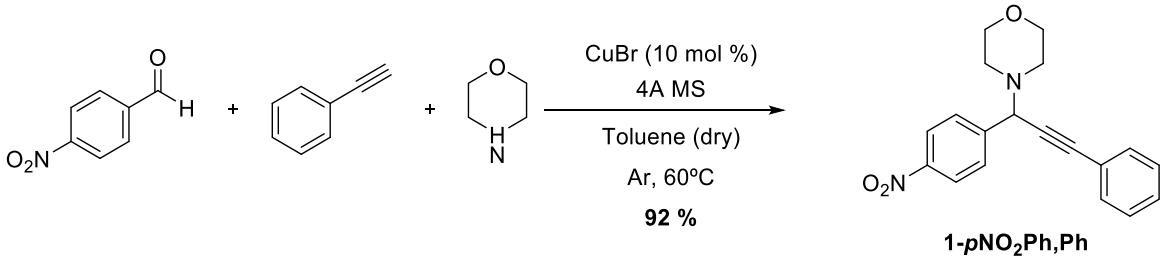



Figure S8- **$^{13}$C-NMR** (100 MHz, $CDCl_3$) spectra of **1-Ph,Ph**

## *S*ynthesis of 4-(3-(4-nitrophenyl)-1-phenylprop-2-yn-1-yl)morpholine (1-*p*$NO_2$Ph,Ph)




**1-*p*$NO_2$Ph,Ph**

A round-bottom flask equipped with a magnetic stirrer, flame-dried under vacuum, filled with Ar and coupled to a condenser, was charged with *p*-nitrobenzaldehyde (100 mol%, 1.32 mmol, 200 mg), freshly prepared copper (I) bromide (10 mol%, 0.15 mmol, 25 mg) and dry toluene (3.5 mL). Then, phenylacetylene (100 mol%, 1.32 mmol, 150 µL), morpholine (100 mol%, 1.32 mmol, 115 µL) and molecular sieves (4Å, 1000 mg) were added. The reaction mixture was stirred at 60 °C for 72 h. Molecular sieves were removed by vacuum filtration and washed with dichloromethane. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (Hexane:EtAcO, 85:15) yielding **1-*p*$NO_2$Ph,Ph** (385 mg, 92%).

Compound **(±)-1-*p*$NO_2$Ph,Ph** was resolved by chiral semipreparative HPLC (Chiralpak IA column (particle size of 5µm; 10 mm ø x 250 mm)). Elution was done with a mixture of Hexane:EtAcO (93:7) at a flow rate of 2.5 mL/min. Under these conditions a sample of **(±)-1-p$NO_2$Ph,Ph** (0.18 M, injection 15 µL) was resolved into its enantiomers with a retention time ($t_R$) of 23 and 29 minutes for **(-)-1-*p*$NO_2$Ph,Ph** and **(+)-1-*p*$NO_2$Ph,Ph**, respectively. $[\alpha]_D^{23}$ = –4.6 ° (c = 0.005 g/mL, hexane); $[\alpha]_D^{23}$ = + 4.6 ° (c = 0.005 g/mL, hexane)

**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$ 8.23 (d, *J* = 8.8 Hz, 2H), 7.86 (d, *J*= 8.3 Hz, 2H), 7.57-7.47 (m, 2H), 7.37 (d, *J* = 2.2 Hz, 3H), 4.88 (s, 1H), 3.75 (d, *J* = 4.2 Hz, 4H), 2.63 (m, 4H); **$^{1}$H-NMR** (400 MHz, MeCN) $\delta$ 8.22 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.44 – 7.37 (m, 3H), 4.98 (s, 1H), 3.70 - 3.60 (m, 4H), 2.70 –2.46 (m, 4H) ; **$^{13}$C-NMR** (100 MHz, MeCN) $\delta$ 148.7, 146.7, 132.7, 130.4, 129.8, 129.6, 124.4, 123.4, 90.0, 84.8, 67.6, 61.9, 50.7. **HR-EI-MS** *m/z (%)*: $[M]^{+}$calcd for $^{12}C_{19}{}^{1}H_{18}{}^{14}N_2{}^{16}O_3$ 322.1317, found 322.1317 (100); $[M+H]^{+\cdot}$ calcd for $^{12}C_{18}{}^{13}C^{1}H_{11}{}^{14}N_2{}^{16}O_3$ 323.1351, found 323.1351.

| | *$t_R$ (min)* | *area (µV.s)* |
|---|---|---|
| ***(±)-1-p$NO_2$Ph,Ph*** | 23 | 35931272 |
| | 29 | 35825904 |
| ***(-)-1-p$NO_2$Ph,Ph*** | 23 | 11309470 |
| ***(+)-1-p$NO_2$Ph,Ph*** | 29 | 16675243 |

Table S1- Chromatographic data of **(±)-1-*p*$NO_2$Ph,Ph** and its enantiomers **(-)-1-*p*$NO_2$Ph,Ph** and **(+)-1-*p*$NO_2$Ph,Ph**

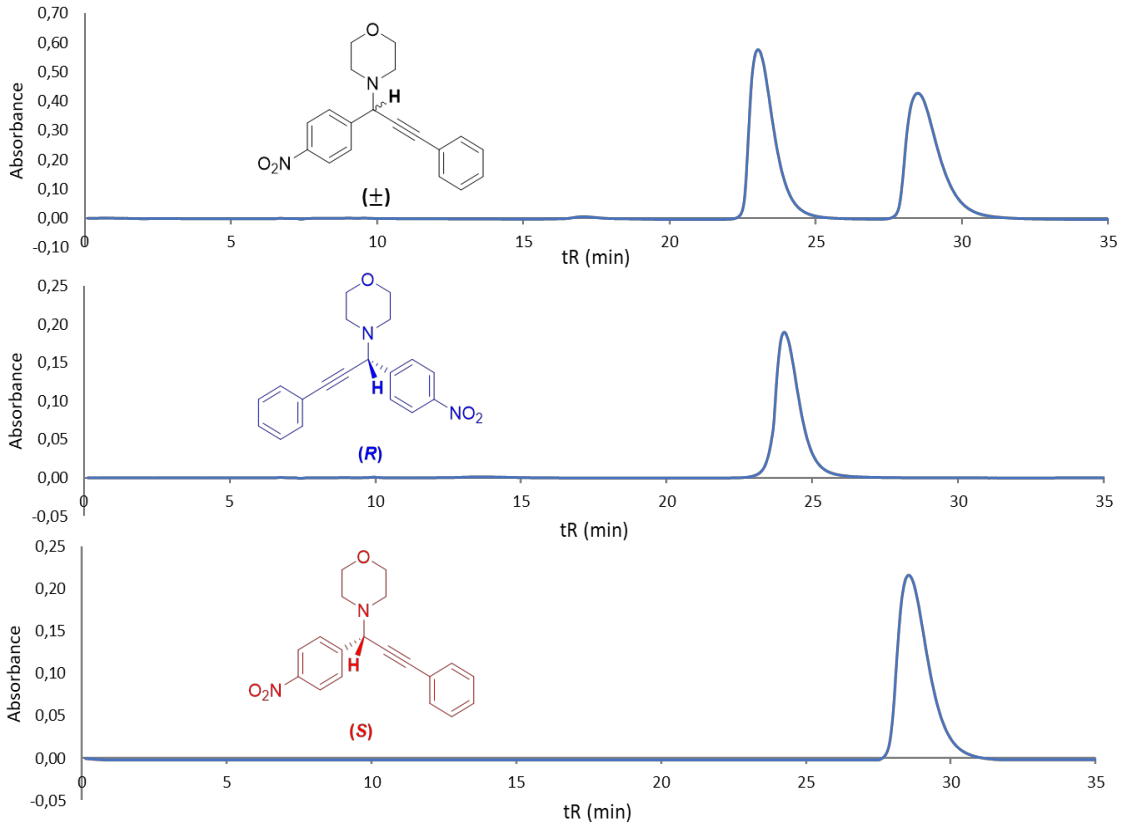



Figure S9- Chromatograms of **(±)-1-*p*$NO_2$Ph,Ph** (top) and its enantiomers **(-)-1-*p*$NO_2$Ph,Ph** (middle) and **(+)-1-*p*$NO_2$Ph,Ph** (bottom)

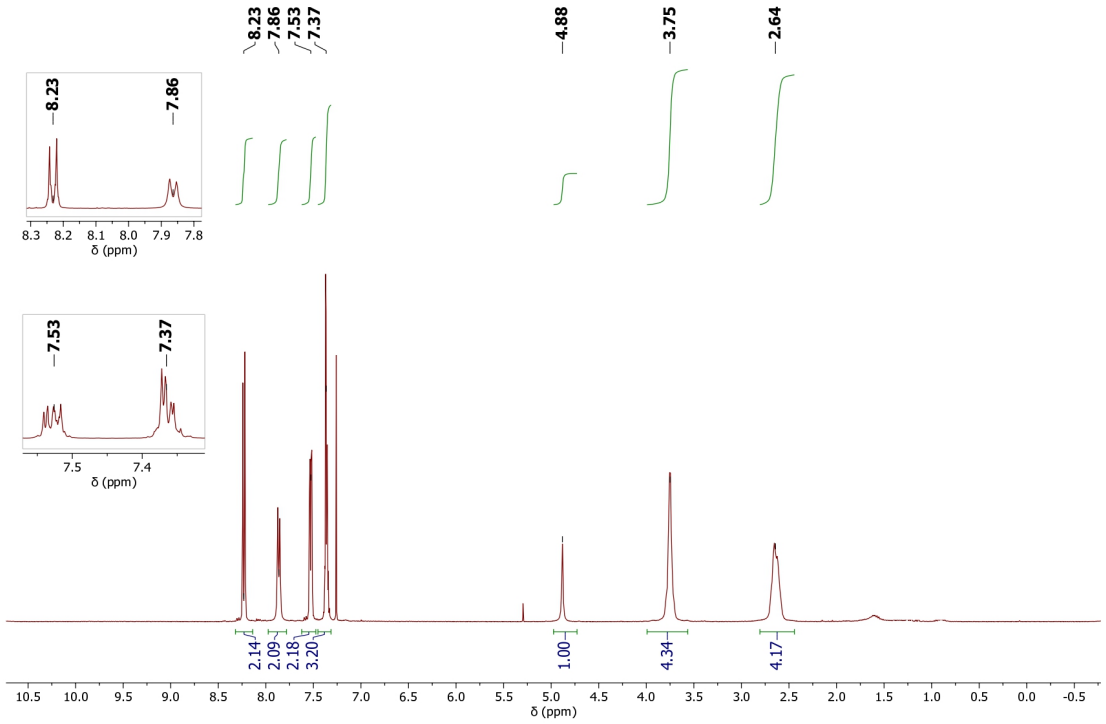



Figure S10- **$^{1}$H-NMR** (400 MHz, $CDCl_3$) spectra of **1-*p*$NO_2$Ph,Ph**

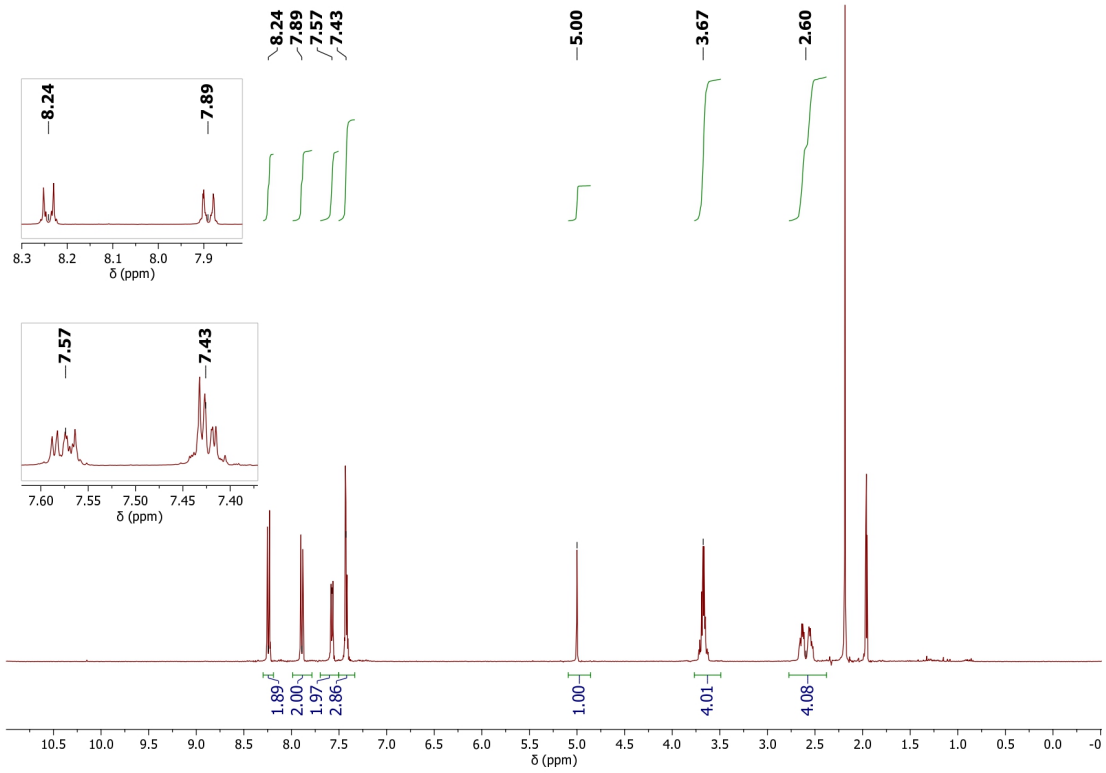



Figure S11-**$^{1}$H-NMR** (400 MHz, MeCN) spectra of **1-*p*$NO_2$Ph,Ph**

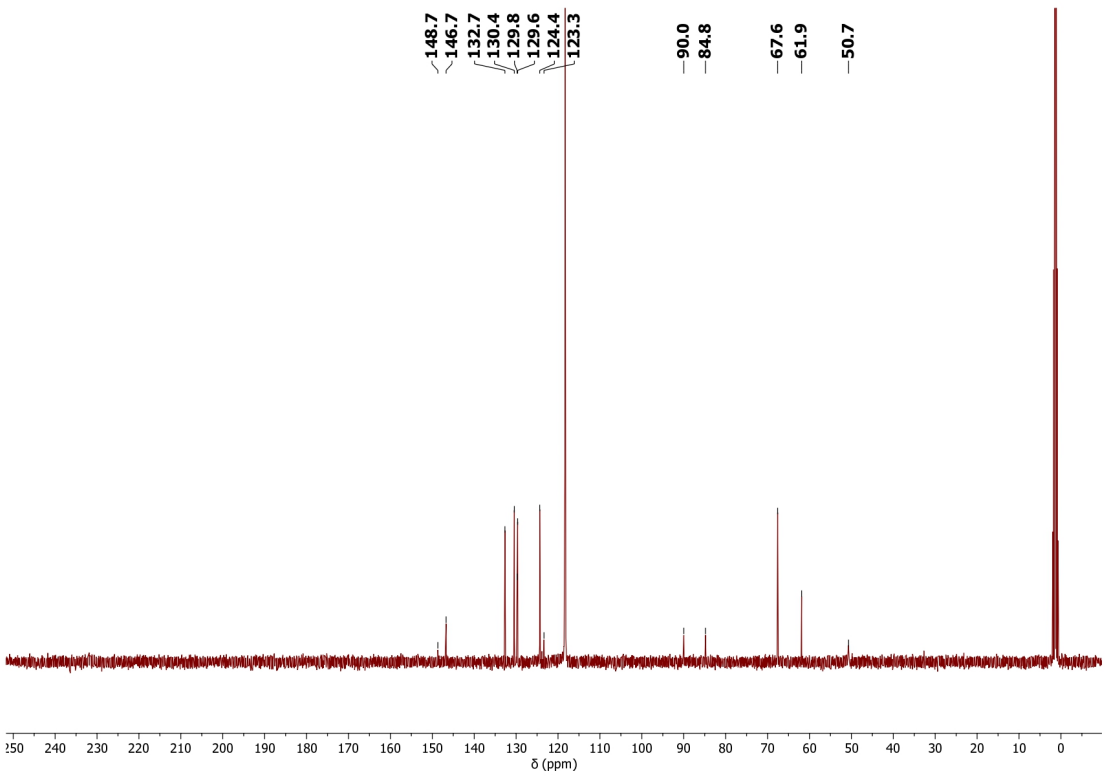
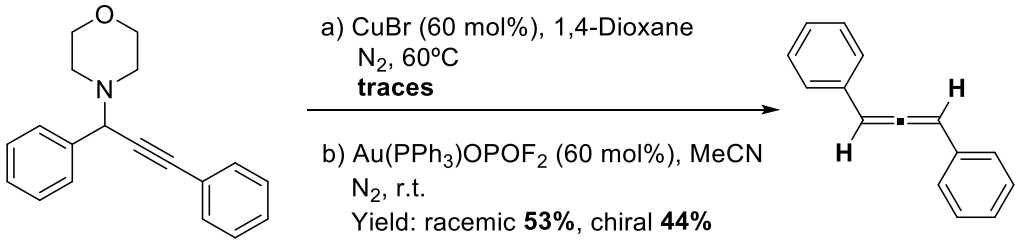



Figure S12- **$^{13}$C-NMR** (100 MHz, MeCN) spectra of **1-*p*NO$_2$Ph,Ph**

*Synthesis of 1,3-diphenylpropa-1,2-diene (5-Ph,Ph)*




**1-Ph,Ph** **5-Ph,Ph**

*a) Cu-catalyzed reaction* [2]

In a schlenk tube freshly prepared CuBr (60 mol%, 0.6 mmol, 25 mg) was added to a solution of propargylamine **1-Ph,Ph** (100 mol%, 1 mmol, 82 mg) in dry 1,4-dioxane (0.6 mL) under nitrogen atmosphere. After stirring the resulting mixture for 6 days at 80 °C the solvent was removed under reduced pressure. Traces of the corresponding allene **5-Ph,Ph** were obtained after 6 days of reaction time as indicated by the appearance of the allene $^{1}$H-NMR signal at 6.60 ppm and $^{13}$C-NMR signals at 98.2 and 207.5 ppm.

*b) Au-catalyzed reaction*

*Racemic reaction:* In a NMR-tube was introduced a solution of **1-Ph,Ph** (100 mol%, 0.035 mmol, 40 mg) in deuterate acetonitrile (0.6 mL) followed by Au(PPh$_3$)OPOF$_2$ (30 mol %, 0.011 mmol, 6 mg) and dry cyclohexane (3.5 µL) as internal standard. After 30 minutes another 30 mol % of the catalyst was charged. The resulting mixture was kept under nitrogen atmosphere at r.t. protected from light for 6 days to afford the allene in a 53% (calculated by NMR).

*Chiral reaction:* When a solution of **(-)- 1-Ph,Ph** (100 mol%, 0.13 mmol, 36 mg) in dry acetonitrile (2.6 mL) followed by $Au(PPh_3)OPOF_2$ (30 mol%, 0.039 mmol, 22 mg). After 30 minutes another 30 mol % of the catalyst was charged. The resulting mixture was stirred under nitrogen atmosphere at r.t. protected from the light for 6 days, affording allene **5-Ph,Ph** in 44 % (calculated by NMR). The crude mixture was filtered through a silica path.

**HPLC** (Phenomenex Lux 5µ/L Amylose-2, hexane/2-propanol (0.5 %), 0.5 mL/min): $t_R$ (min)= 8.55 (*R*), 9.27 (*S*); **$^1$H-NMR** (400 MHz, $CDCl_3$) *δ* 7.34 (m, 8H), 7.23 (m, 2H), 6.60 (s, 2H); **$^{13}$C-NMR** (100 MHz, $CDCl_3$) *δ* 207.9, 133.7, 128.9, 127.5, 127.1, 98.6.

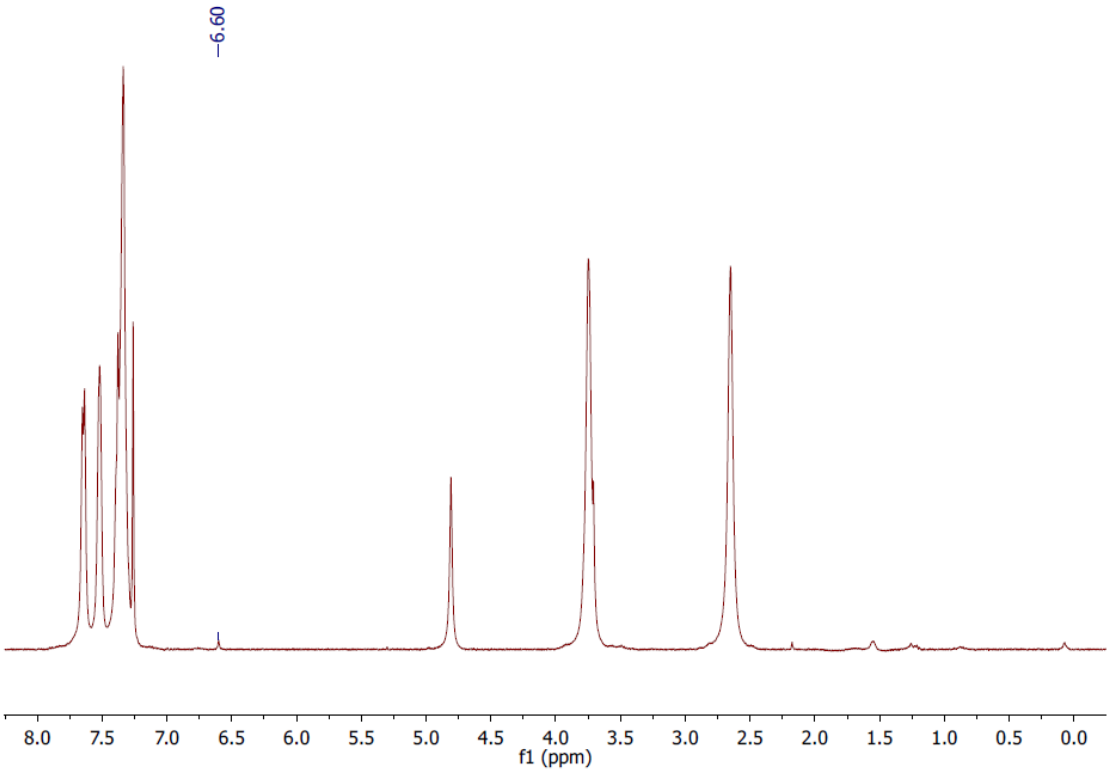



Figure S13- **$^1$H-NMR** (400 MHz, $CDCl_3$) spectra of the crude mixture of the CuBr-catalyzed reaction

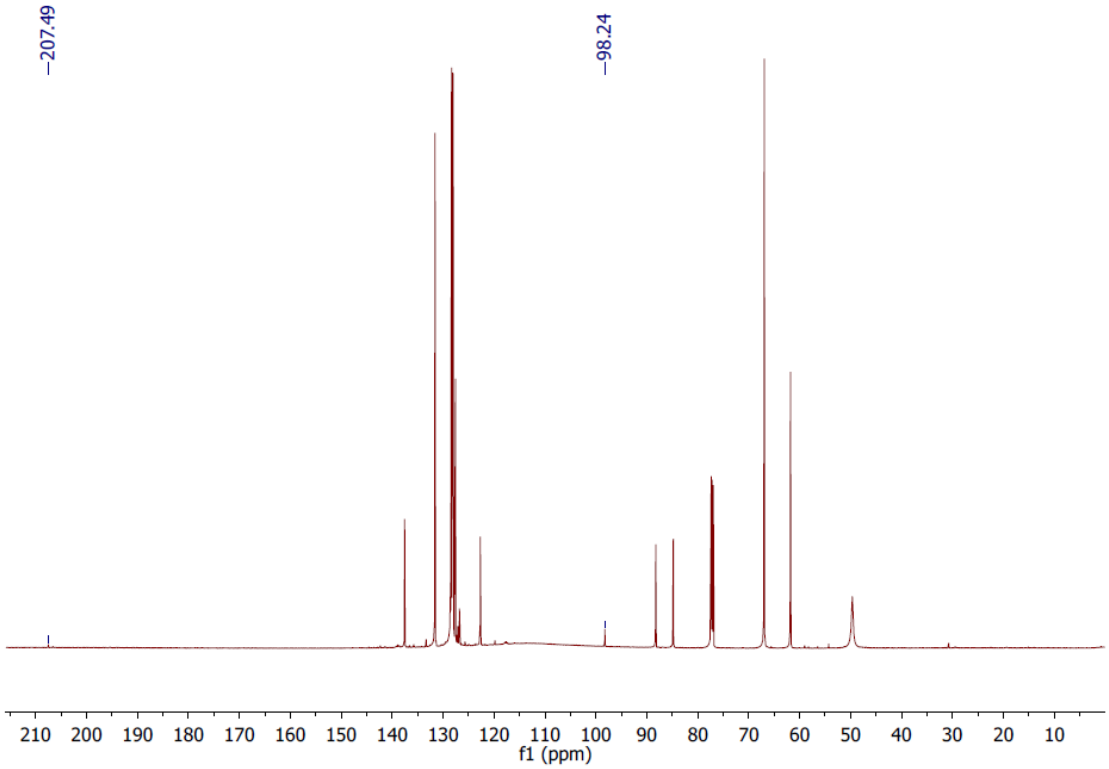



Figure S14- **$^{13}$C-NMR** (100 MHz, $CDCl_3$) spectra of the crude mixture of the CuBr-catalyzed reaction

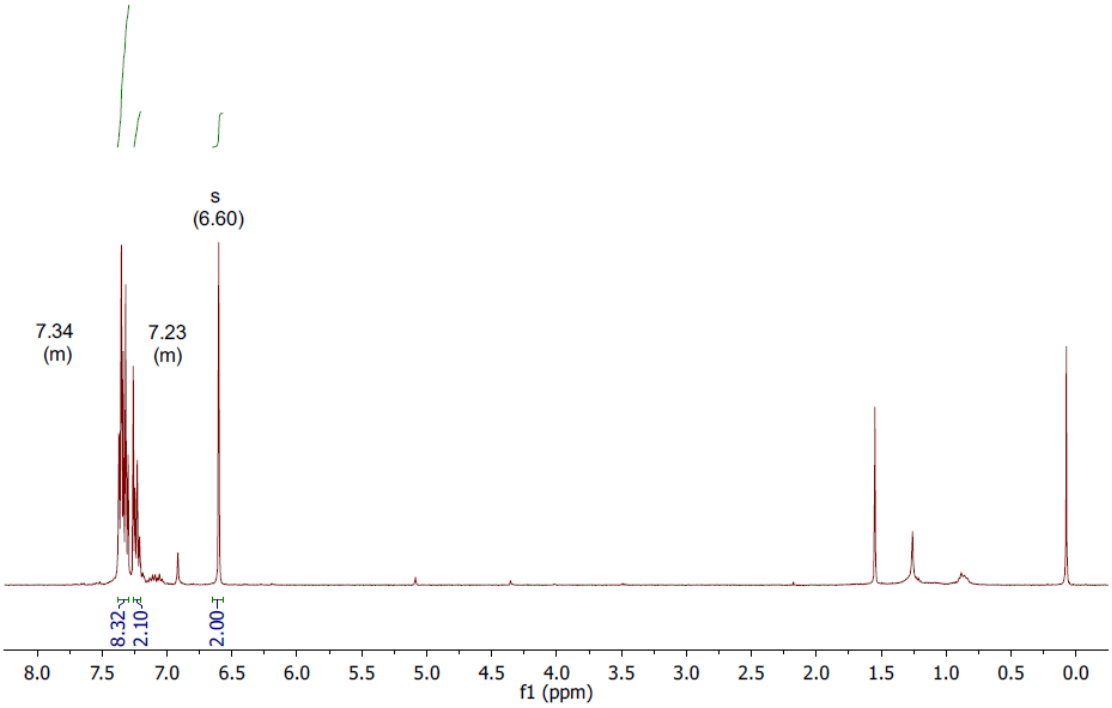



Figure S15- **$^{1}$H-NMR** (400 MHz, $CDCl_3$) spectra of the crude mixture of the Au($PPh_3$)$OPOF_2$-catalyzed reaction

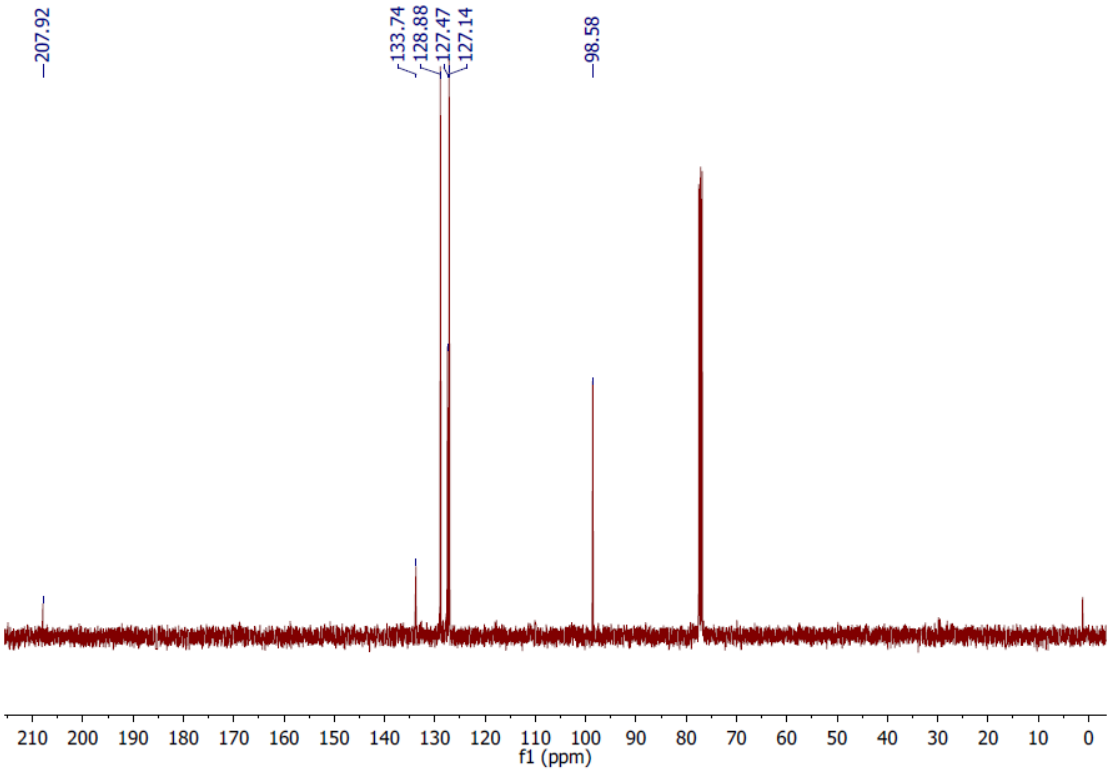
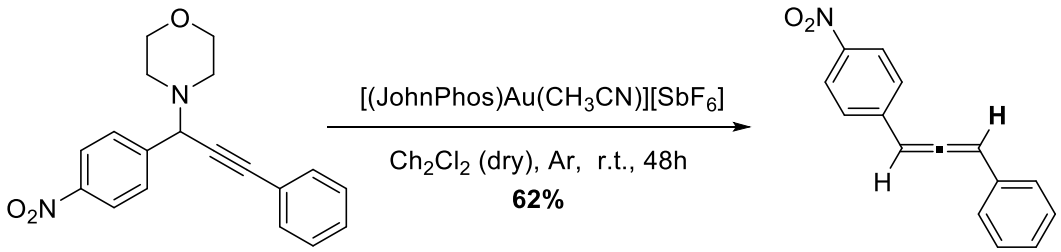



Figure S16- **$^{13}$C-NMR** (100 MHz, $CDCl_3$) spectra of the crude mixture of the Au($PPh_3$)$OPOF_2$-catalyzed reaction

*Synthesis of 1-phenyl-4-(p-nitrophenyl)-propa-1,2-diene (5-p$NO_2$Ph,Ph)*




**1-*p*$NO_2$Ph,Ph** **5-*p*$NO_2$Ph,Ph**

*Racemic synthesis:* A dried and argon-flushed flask equipped with a magnetic stirrer was charged with [(JohnPhos)Au($CH_3CN$)][$SbF_6$] (30 mol%, 0.019 mol, 14 mg). A solution of **(±)-1-*p*$NO_2$Ph,Ph** (100 mol%, 0.093 mmol, 30 mg) in dry dichloromethane (0.5 mL) was introduced. After stirring the resulting mixture for 3 days at r.t., the solvent was removed under reduced pressure. The crude mixture was filtered through a silica path, previously neutralized with $Et_3N$, with the aid of hexane:EtAcO (90:10) to separate the allene product and the solvent was removed under reduced pressure yielding 1-phenyl-4-(p-nitrophenyl)-propa-1,2-diene (**5-*p*$NO_2$Ph,Ph**) (14 mg, 62%) that resulted to be unstable.

*Chiral synthesis:* The same procedure was used with **(+)-1-*p*$NO_2$Ph,Ph** (100 mol%, 0.047 mmol, 15 mg) or **(-)-1-*p*$NO_2$Ph,Ph**) with [(JohnPhos)Au($CH_3CN$)][$SbF_6$]] (30 mol%, 0.019 mol, 14 mg).

Analytical HPLC with a chiral stationary phase, Phenomenex Lux 5u Amylose-2 column (4.6 mm x 250 mm) was used to check if the configuration was maintained in the formation of the allene in each case. A mixture of hexane:i-PrOH (99.5:0.5) was used as mobile phase and the elution was done at a flow rate

of 1 mL/min. A sample of allene **(±)-5-*p*NO$_2$Ph,Ph** (2 mg dissolved in 2 mL of the eluent; injection 5 µL) was separated into two peaks with a retention time ($t_R$) of 20 and 25 minutes for **(-)-5-*p*NO$_2$Ph,Ph** and **(+)-5-*p*NO$_2$Ph,Ph**, respectively. HPLC was also employed to measure the enantiomeric excess (ee) of the products resulting in 90 % for **(-)-5-*p*NO$_2$Ph,Ph** and 90 % for **(+)-5-*p*NO$_2$Ph,Ph**.

**$^1$H-NMR** (400 MHz, $CDCl_3$) $\delta$ 8.17 (d, $J$ = 8.8 Hz, 2H), 7.48 (d, $J$ = 8.8 Hz, 3H), 7.34 (d, $J$ = 4.4 Hz, 4H), 6.71 (d, $J$ = 6.5 Hz, 1H), 6.66 (d, $J$ = 6.5 Hz, 1H); **$^1$H-NMR** (400 MHz, MeCN) $\delta$ 8.20 (d, $J$ = 8.8 Hz, 2H), 7.59 (d, $J$ = 8.8 Hz, 2H), 7.45 – 7.37 (m, 4H), 6.84 (s, 2H); **$^{13}$C-NMR** (100 MHz, MeCN) $\delta$ 210.4, 142.1, 130.0, 129.9, 128.9, 128.5, 128.1, 125.1, 99.7, 98.1; **HR-EI-MS** *m/z* (%): [M]+ calcd for $^{12}C_{15}{}^{1}H_{11}{}^{14}N^{16}O_2$ 237.0790, found 237.0793; $[M+H]^+$ calcd for $^{12}C_{14}{}^{13}C^{1}H_{11}{}^{14}N^{16}O_2$ 238.0823, found 238.0827.

| | $t_R$ *(min)* | *area (µV.s)* |
|---|---|---|
| *(±)-5-pNO$_2$Ph,Ph* | 19 | 24372439 |
| | 25 | 24088316 |
| *(-)-5-pNO$_2$Ph,Ph* | 20 | 198643580 |
| | 25 | 9932179 |
| *(+)-5-pNO$_2$Ph,Ph* | 20 | 2286701 |
| | 24 | 21413163 |

Table S2- Chromatographic data of **(±)-5-*p*NO$_2$Ph,Ph** and its enantiomers **(-)-5-*p*NO$_2$Ph,Ph** and **(+)-5-*p*NO$_2$Ph,Ph**.

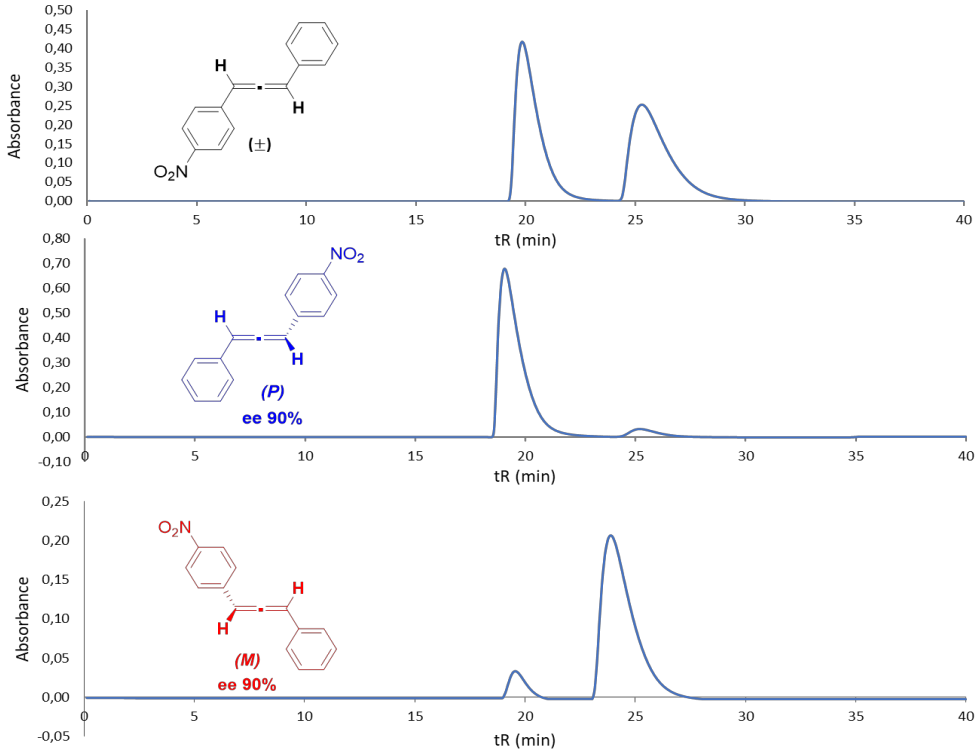



Figure S17- Chromatograms of **(±)-5-*p*NO$_2$Ph,Ph** (top) and its enantiomers **(-)-5-*p*NO$_2$Ph,Ph** (middle) and **(+)-5-*p*NO$_2$Ph,Ph** (bottom).

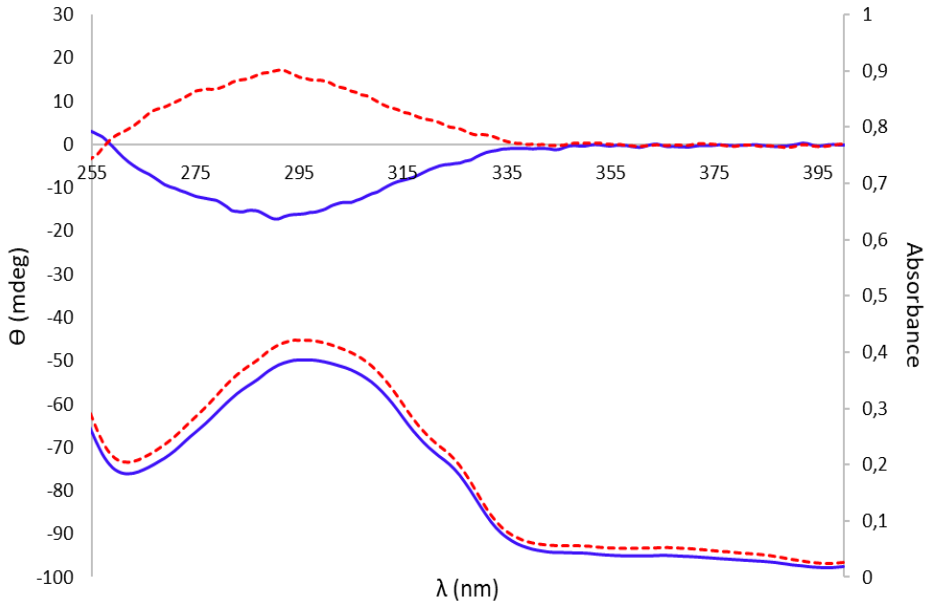



Figure S18- CD and UV/Vis spectra of **(-)-5-*p*NO$_2$Ph,Ph** (blue solid line) and **(+)-5-*p*NO$_2$Ph,Ph** (red dashed line) recorded in hexane [3.10$^{-4}$ M]

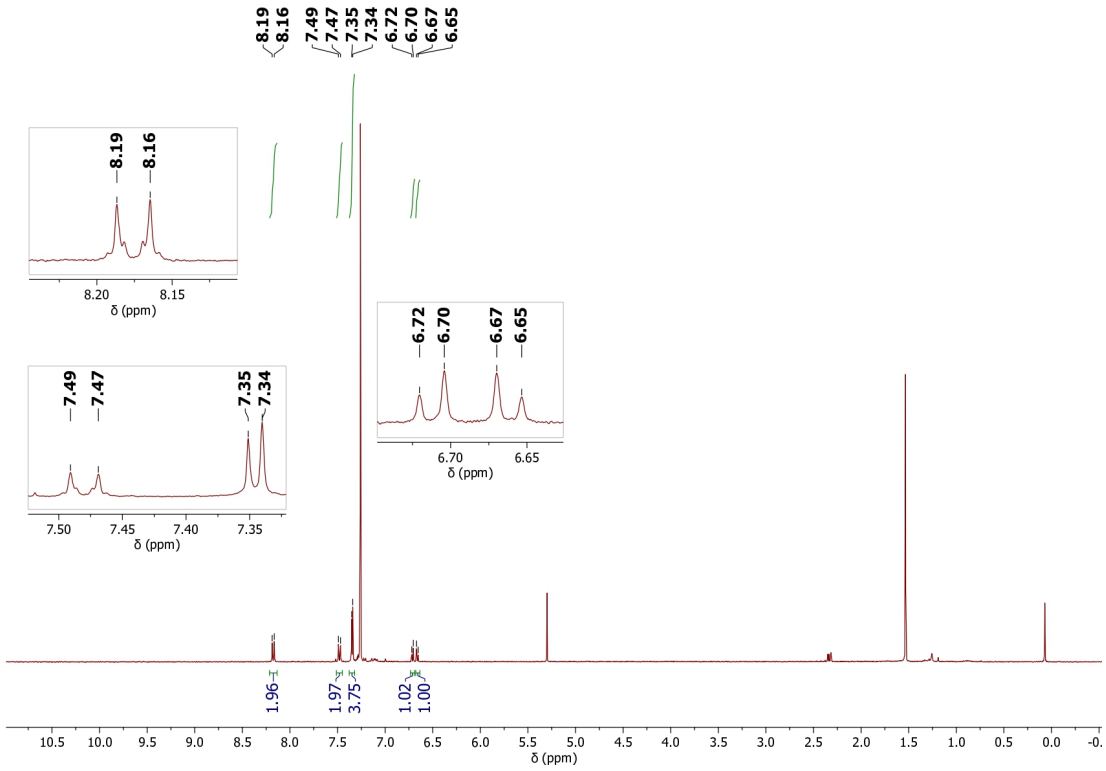



Figure S19- **$^1$H-NMR** (400 MHz, $CDCl_3$) spectra of **5-*p*NO$_2$Ph,Ph**

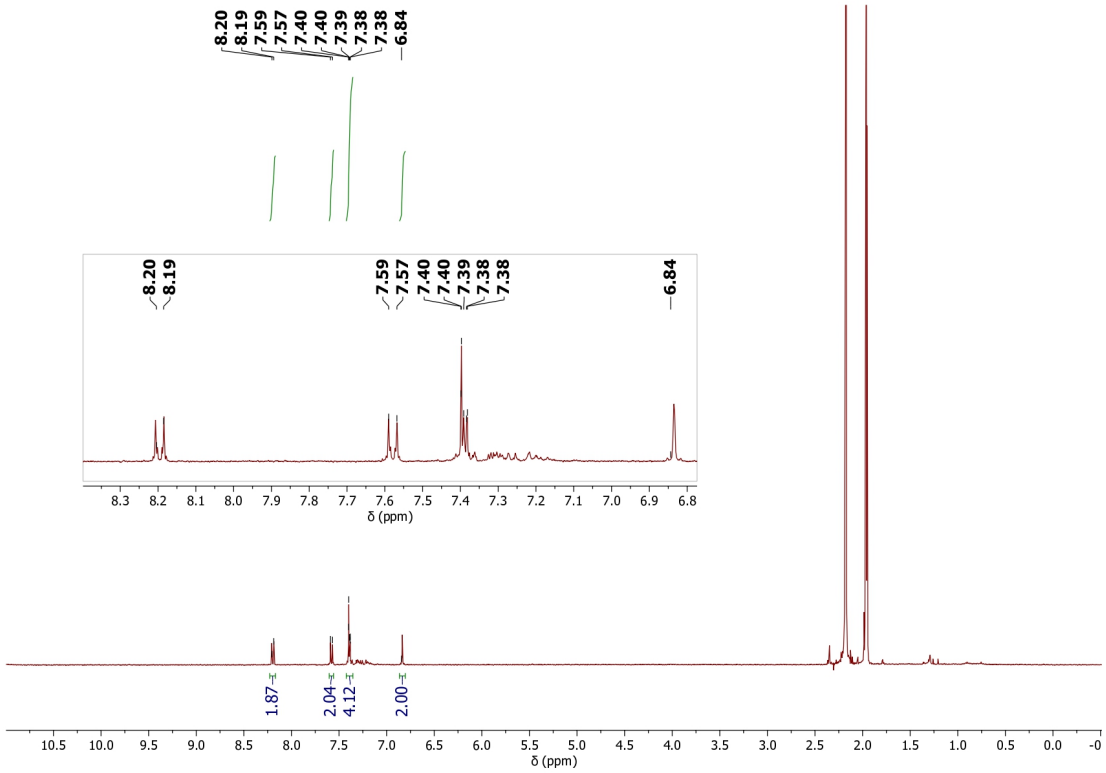



Figure S20- **$^{1}$H-NMR** (400 MHz, MeCN) spectra of **5-*p*$NO_2$Ph,Ph**

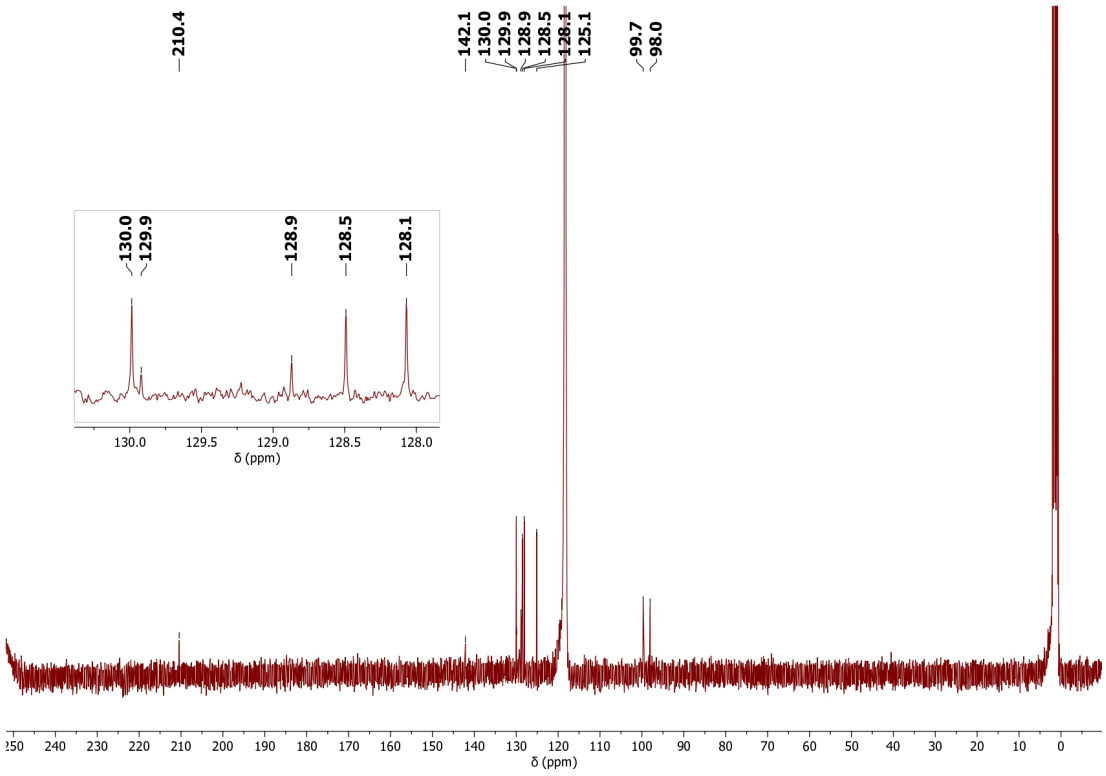



Figure S21- **$^{13}$C-NMR** (100 MHz, MeCN) spectra of **5-*p*$NO_2$Ph,Ph**

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