Synergistic Palladium-Phosphoric Acid Catalysis in (3 + 2) Cycloaddition Reactions Between Vinylcyclopropanes and Imines

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Supplementary Materials

Contents

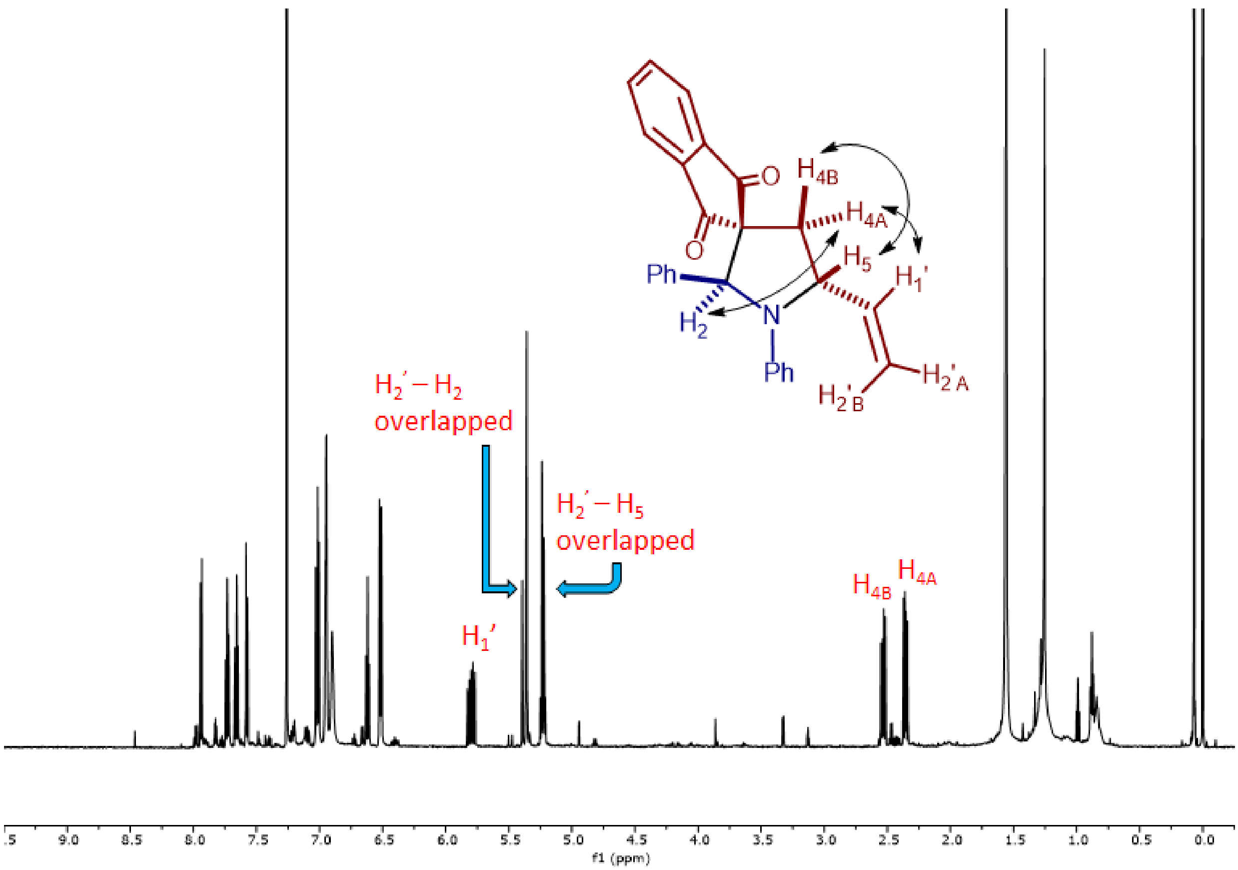
Assignment of the relative configuration of compound 4a by 1D NOESY NMR experiments.

Extensive chromatography on silica gel allowed to obtain the two diastereoisomers of **4a** in diastereoenriched form. This simplified the assignment of the relative configuration of the major and minor diastereoisomers obtained, which was carried out as follows:

-Major diastereoisomer (**4a**):

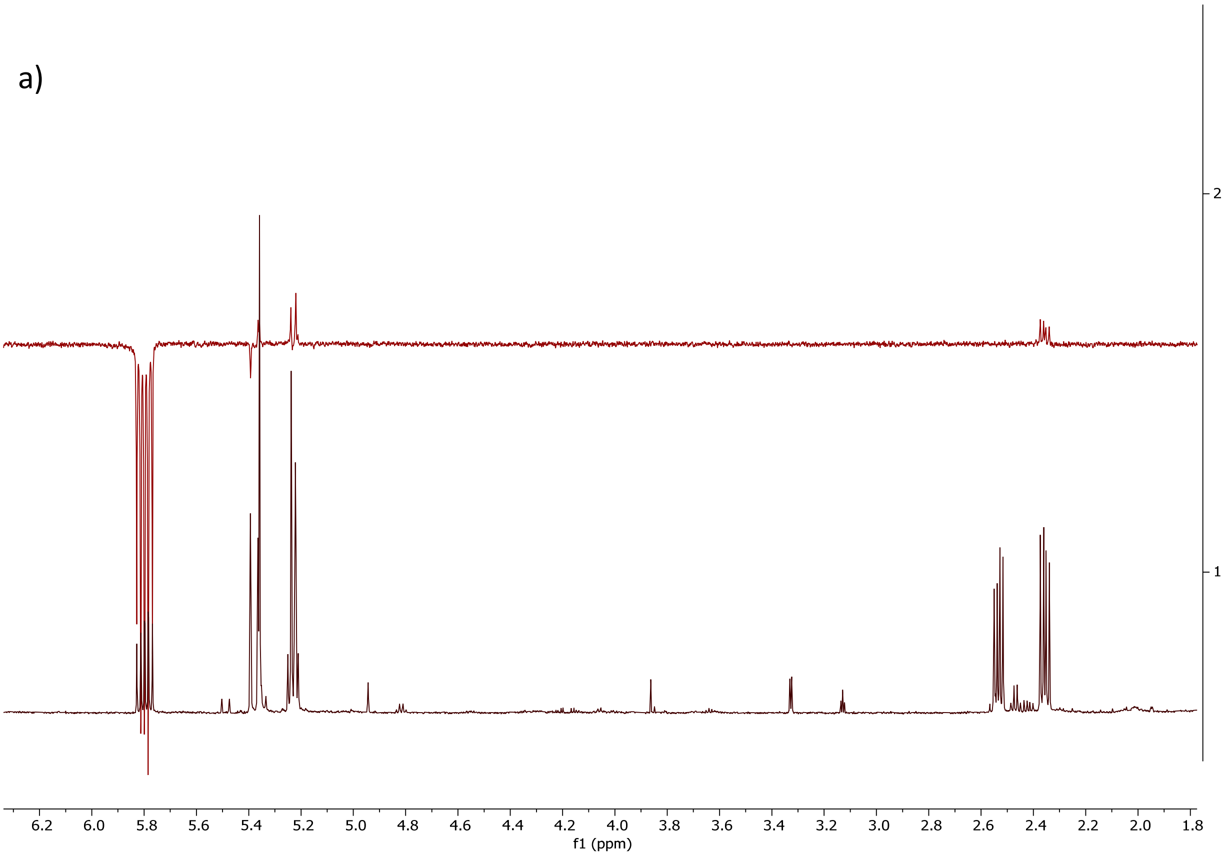
^{1}H NMR and 1D NOESY experiments:

Based on chemical shifts and multiplicities of the ^{1}H NMR spectrum:
-The signal at 5.80 ppm (ddd, J = 17.1, 9.8, 8.7 Hz, 1H) was assigned to H1′
-The signals at 2.54 (dd, J = 13.0, 7.1 Hz, 1H) and 2.36 (dd, J = 13.0, 7.8 Hz, 1H) were assigned to the two H4.
Then, 1D NOESY NMR experiments were performed:
a-Saturating the signal at 5.80 ppm (H1′), enhanced the signal at 2.36 ppm (dd). The latter signal corresponds to the proton *cis* to the vinyl group (H4A), and the signal at 2.54 ppm (dd) to the proton *trans* to the vinyl group (H4B).
b-Saturating the signal at 2.36 ppm (H4A), enhanced a singlet at 5.35 ppm. This singlet, superimposed in the ^{1}H NMR spectrum with the signals of H2′, was assigned to H2 based on multiplicity.
c-Saturating the signal at 2.54 ppm (H4B), did not enhance the same singlet at 5.35 ppm (H2). It enhanced instead a signal at 5.23 ppm, a quartet, which could be assigned to H5.
On these grounds, H2, H4A and H1′ should all be *cis* to each other. Therefore, the relative configuration of the major diastereoisomer of **4a** could be assigned as *trans*.



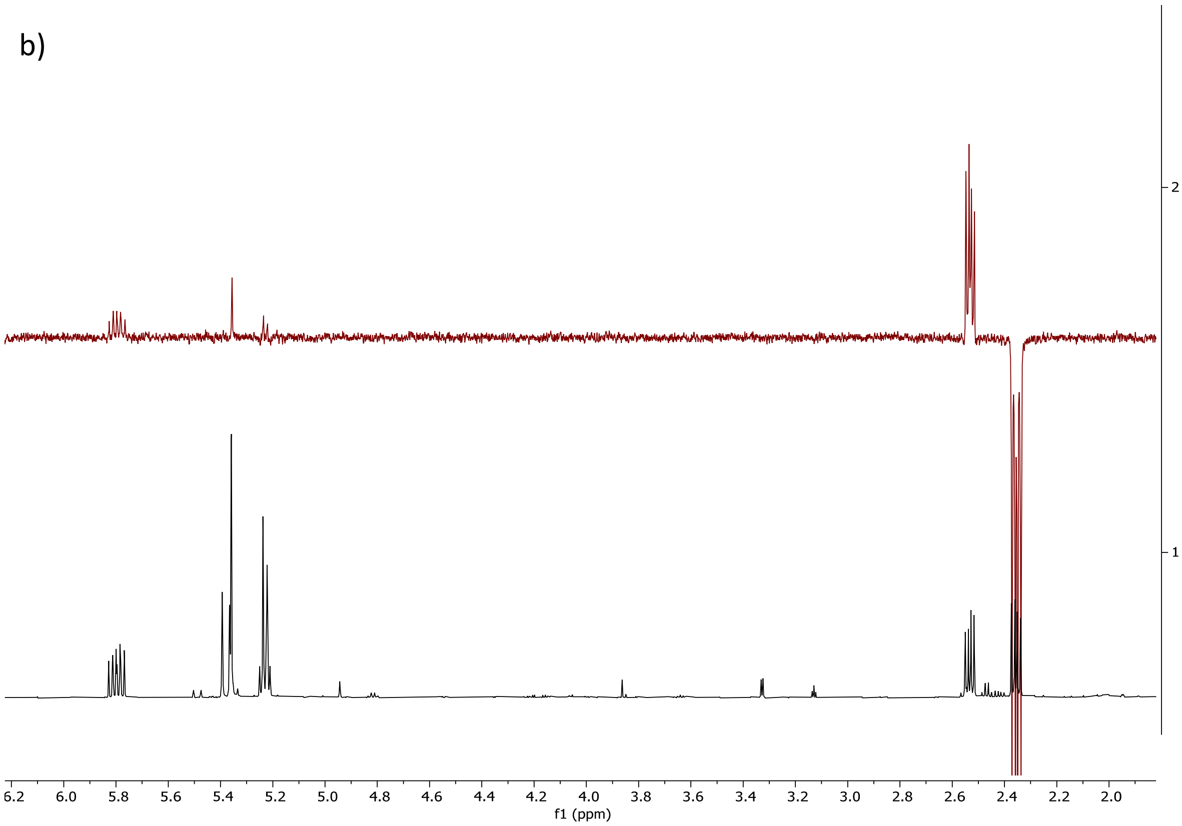
H2' – H2
overlapped
H2' – H5
overlapped
H1'
H4B
H4A
Ph
N
Ph
O
O
H2
H5
H1'
H2'A
H2'B
f1 (ppm)

a)



2
1
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
f1 (ppm)

b)



2
1
6.2
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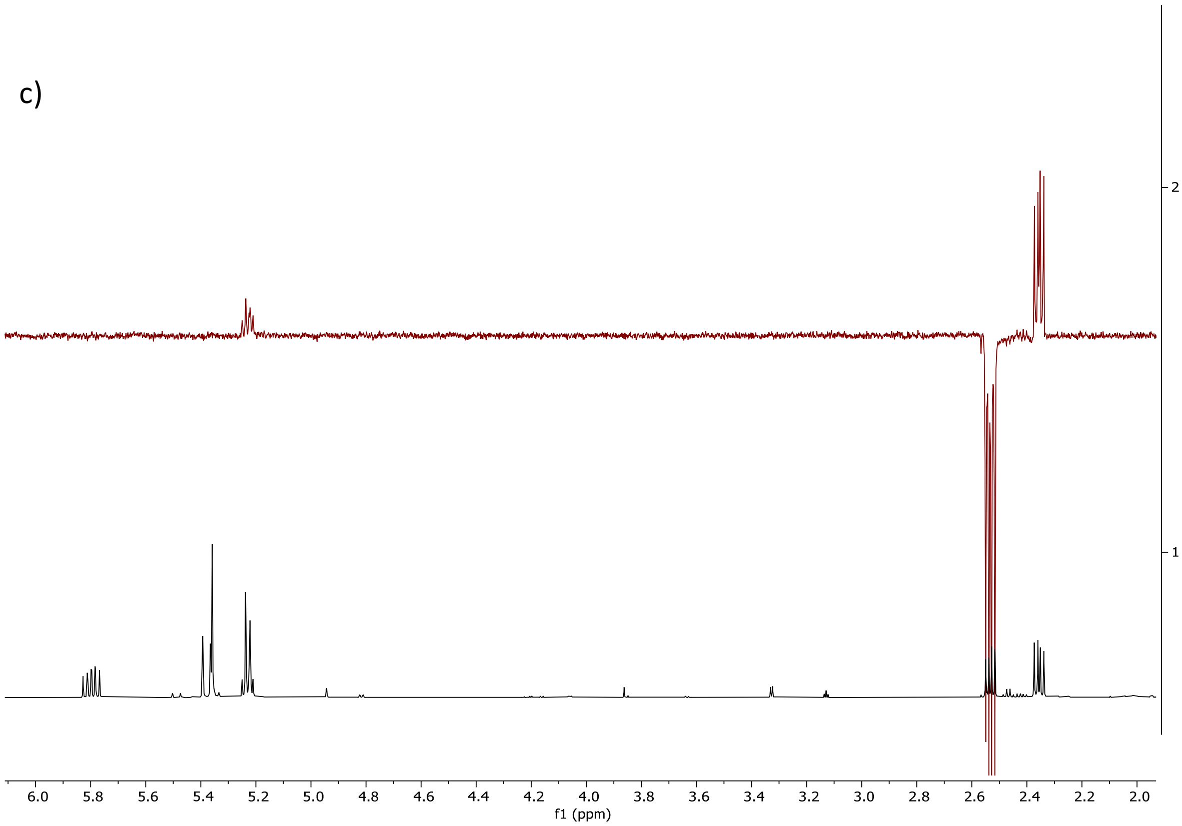
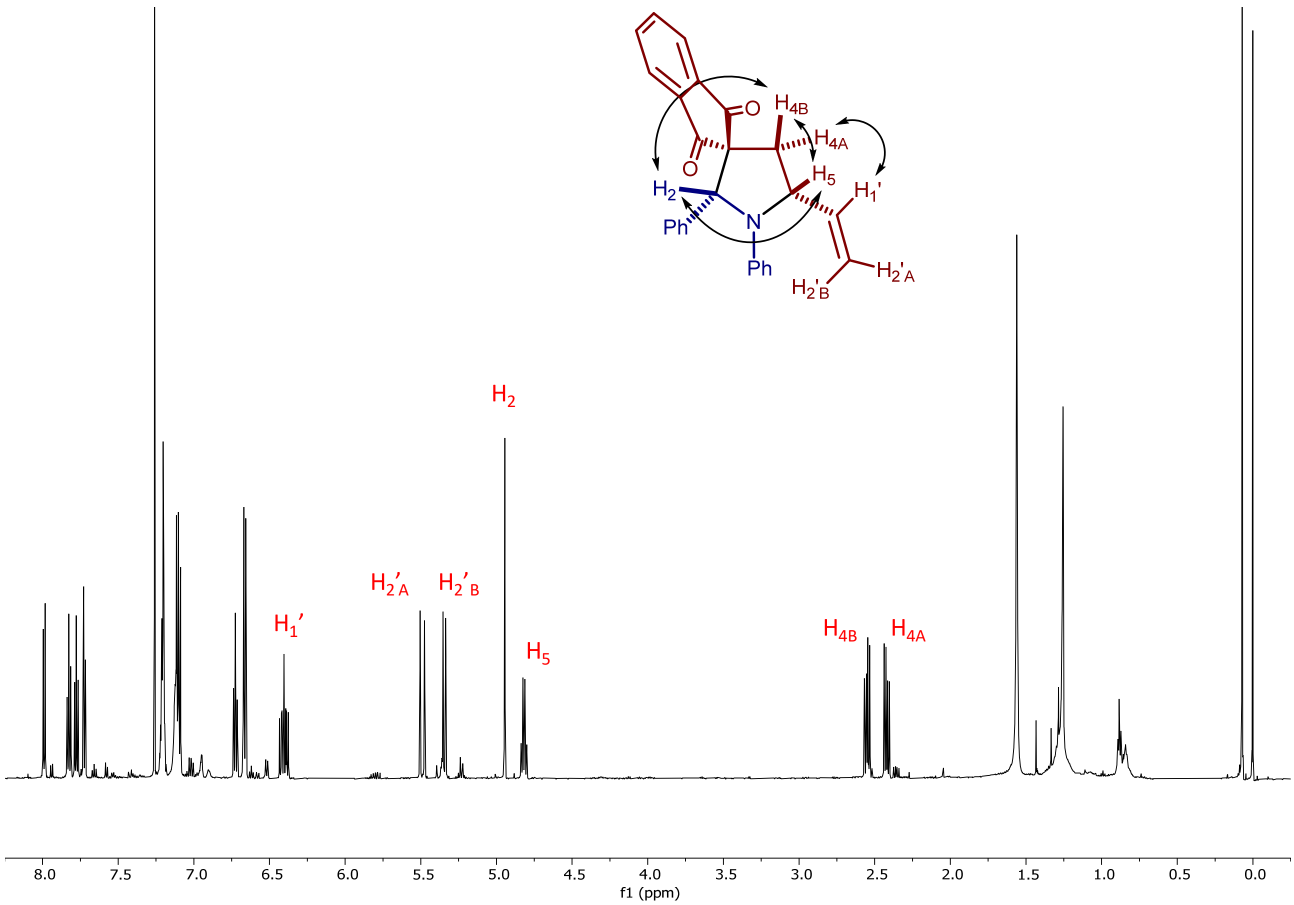
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
f1 (ppm)

c)

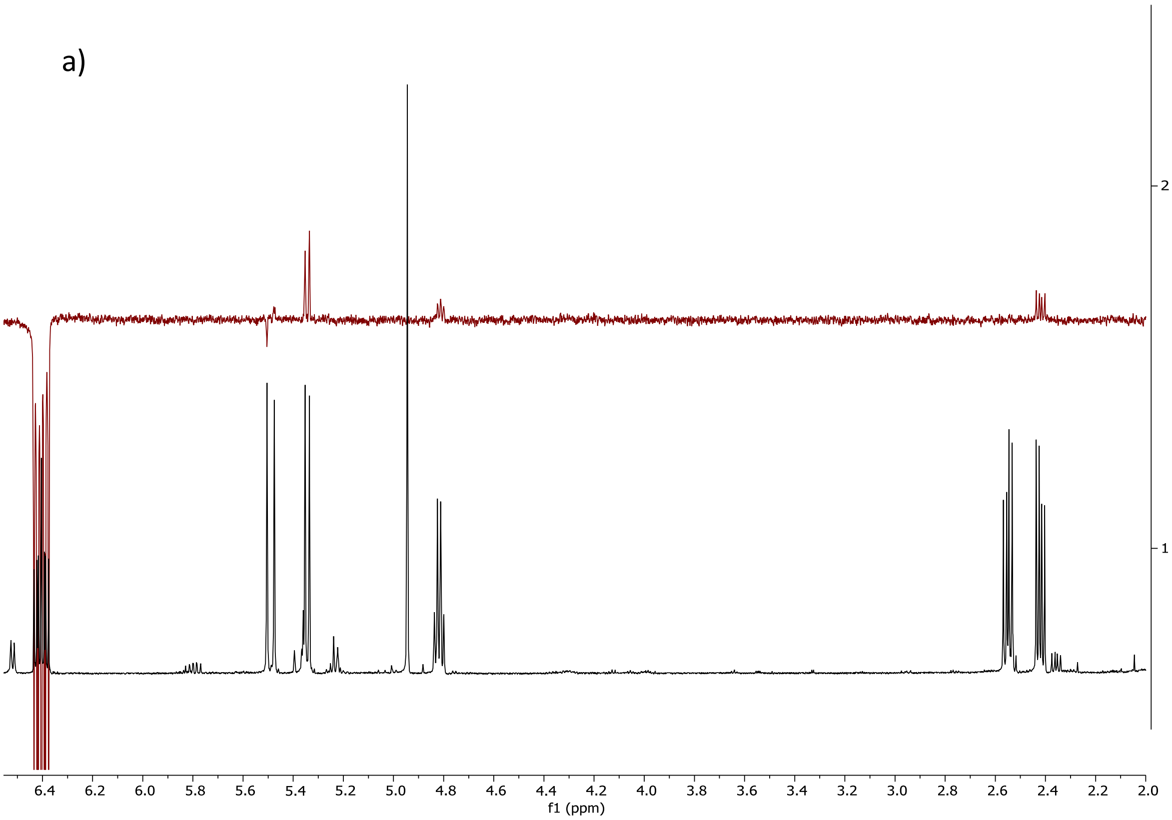


-Minor diastereoisomer (**4a**):

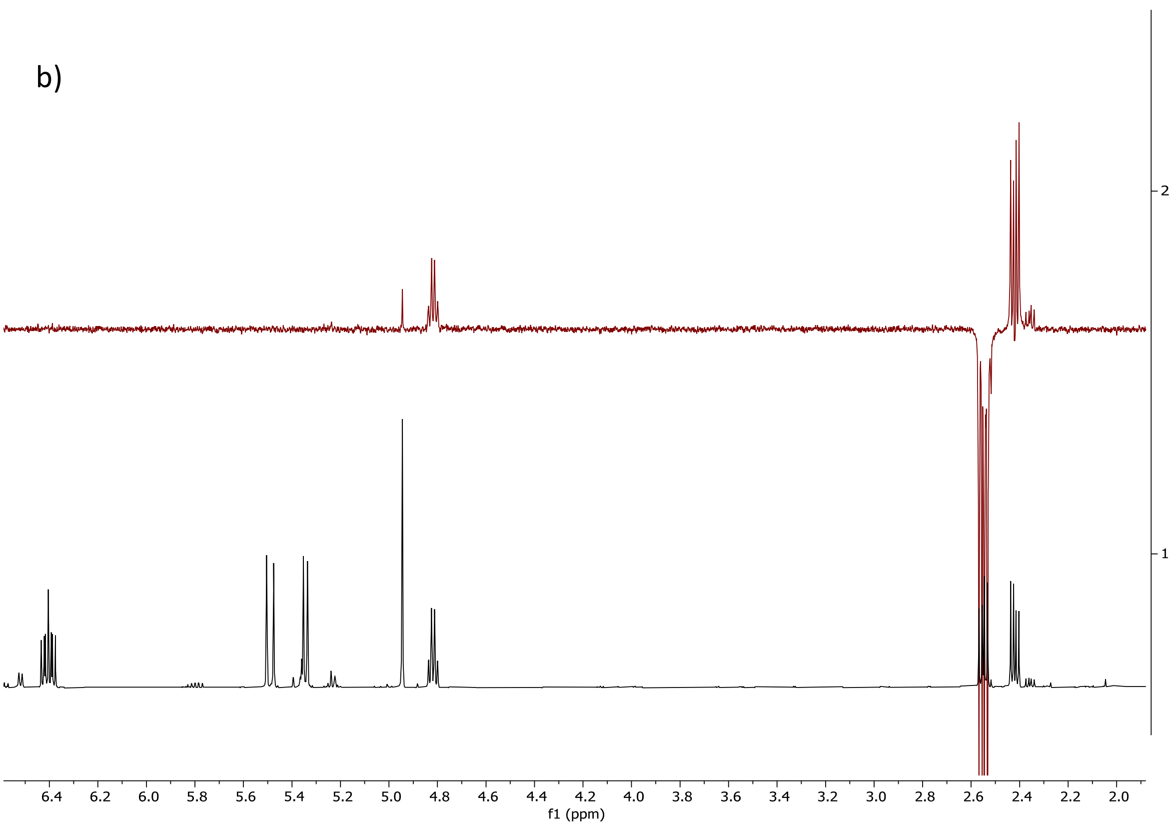
Based on chemical shifts and multiplicities of the ^{1}H NMR spectrum:
-The signal at 6.41 ppm (ddd, J = 17.5, 10.3, 7.4 Hz, 1H) was assigned to H1'.
-The signal at 5.48 ppm (d, J = 17.3 Hz, 1H) was assigned to H2'A.
-The signal at 5.34 ppm (d, J = 10.2 Hz, 1H) was assigned to H2'B.
-The signal at 4.95 ppm (s, 1H) was assigned to H2.
-The signal at 4.82 ppm (q, J = 7.5 Hz, 1H) was assigned to H5.
-The signals at 2.55 ppm (dd, J = 13.1-7.8 Hz, 1H) and 2.44 ppm (dd, J = 13.2, 7.3 Hz, 1H) were assigned to the two H4.
Then, 1D NOESY NMR experiments were performed:
a-Saturating the signal at 6.41 ppm (H1'), enhanced the signal at 2.44 ppm (dd). The latter signal corresponds to the proton *cis* to the vinyl group (H4A), and the signal at 2.55 ppm (dd) to the proton *trans* to the vinyl group (H4B).
b-Saturating the signal at 2.55 ppm (H4B), enhanced the signal at 4.95 ppm (s), corresponding to H2, and the signal at 4.82 ppm, corresponding to H5.
c-Saturating the signal at 4.82 ppm (H5), enhanced the signals at 4.95 ppm (H2), and at 2.55 ppm (H4B).
On these grounds, H2, H4B and H5 should all be *cis* to each other. Therefore, the relative configuration of the minor diastereoisomer of **4a** could be assigned as *cis*.



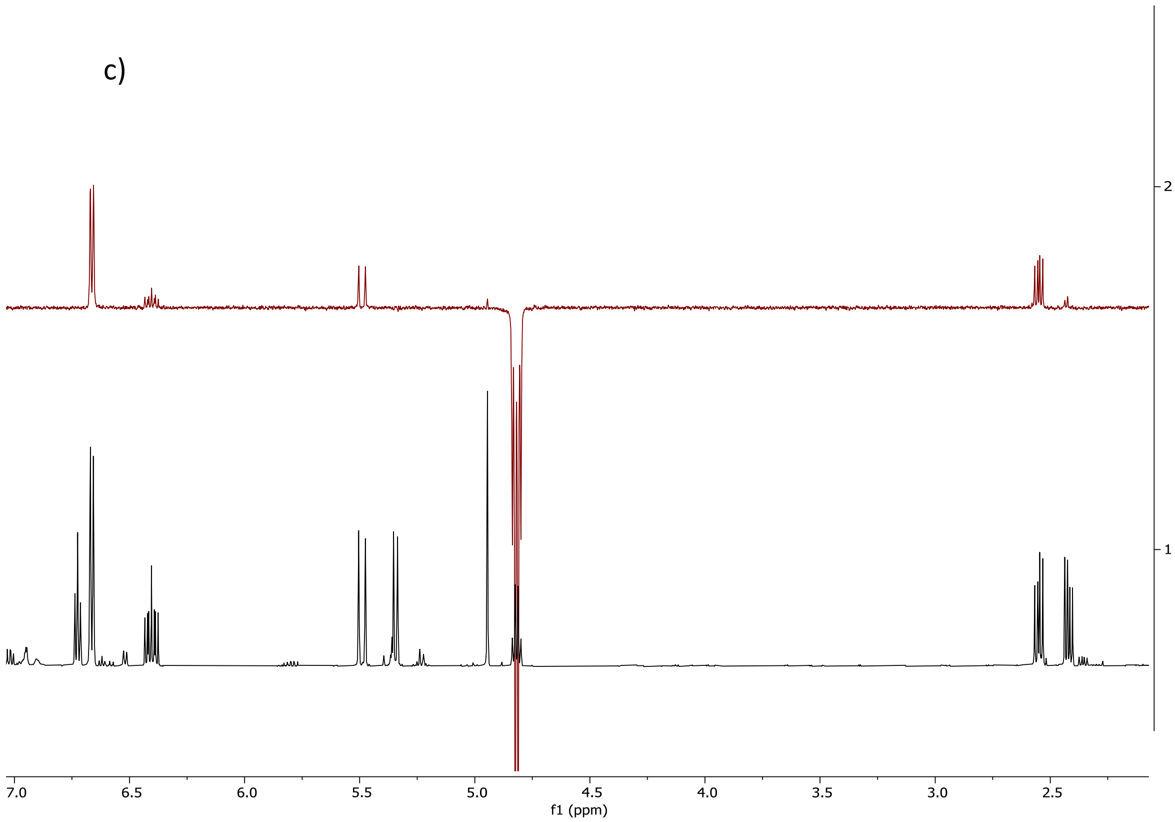
a)


2
1
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
f1 (ppm)

b)

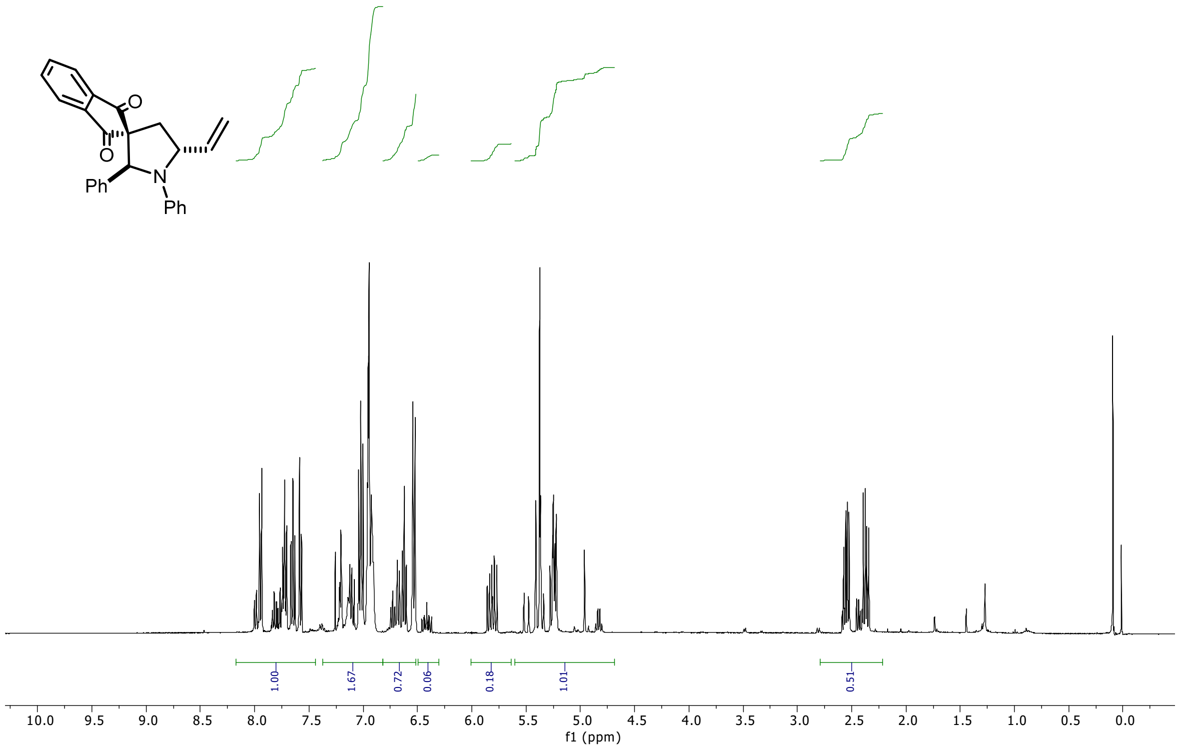

2
1
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
f1 (ppm)

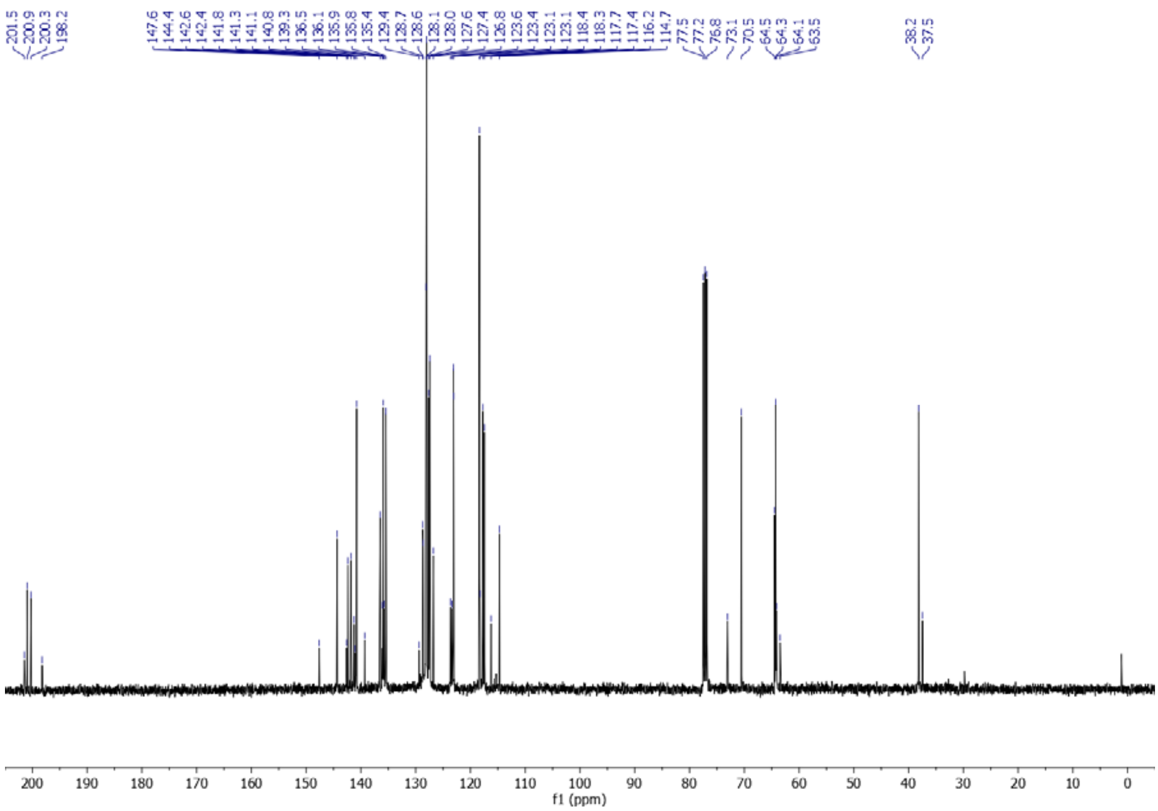
c)



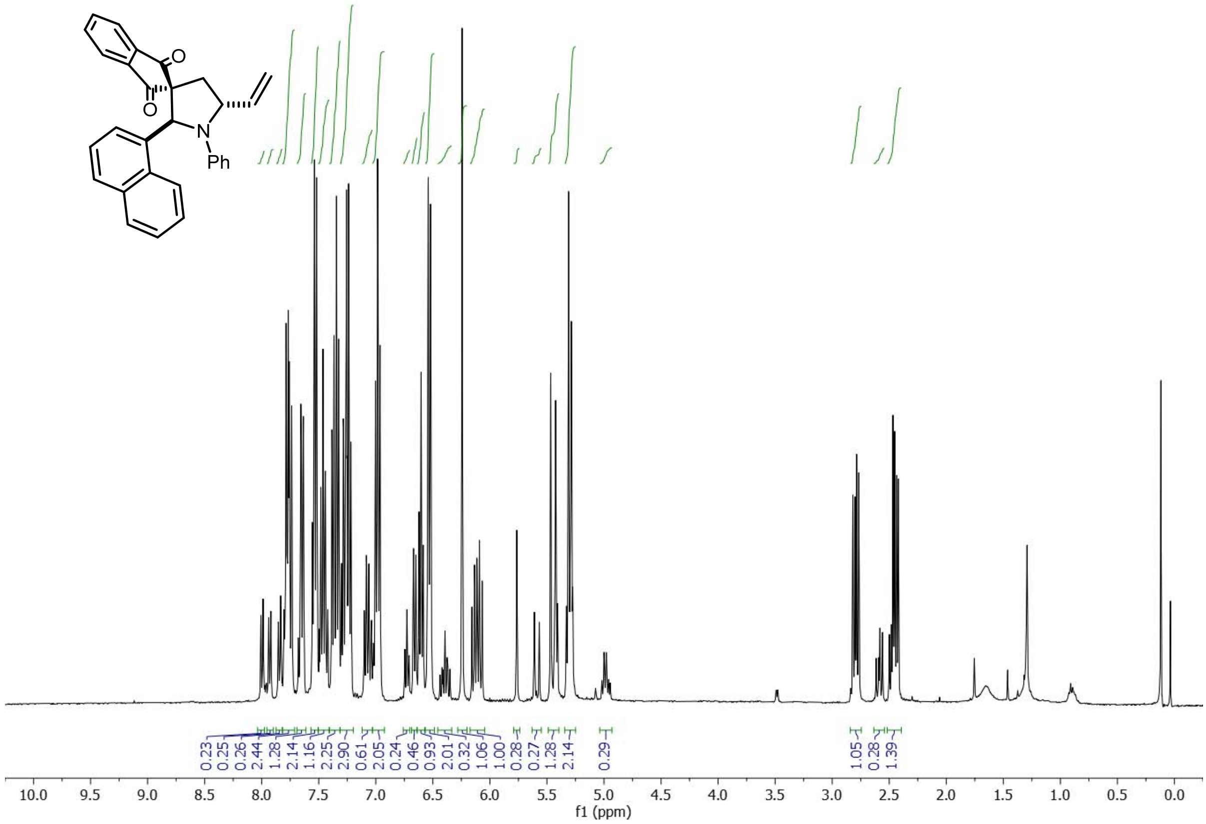
Copies of NMR spectra for compounds 4 and 5

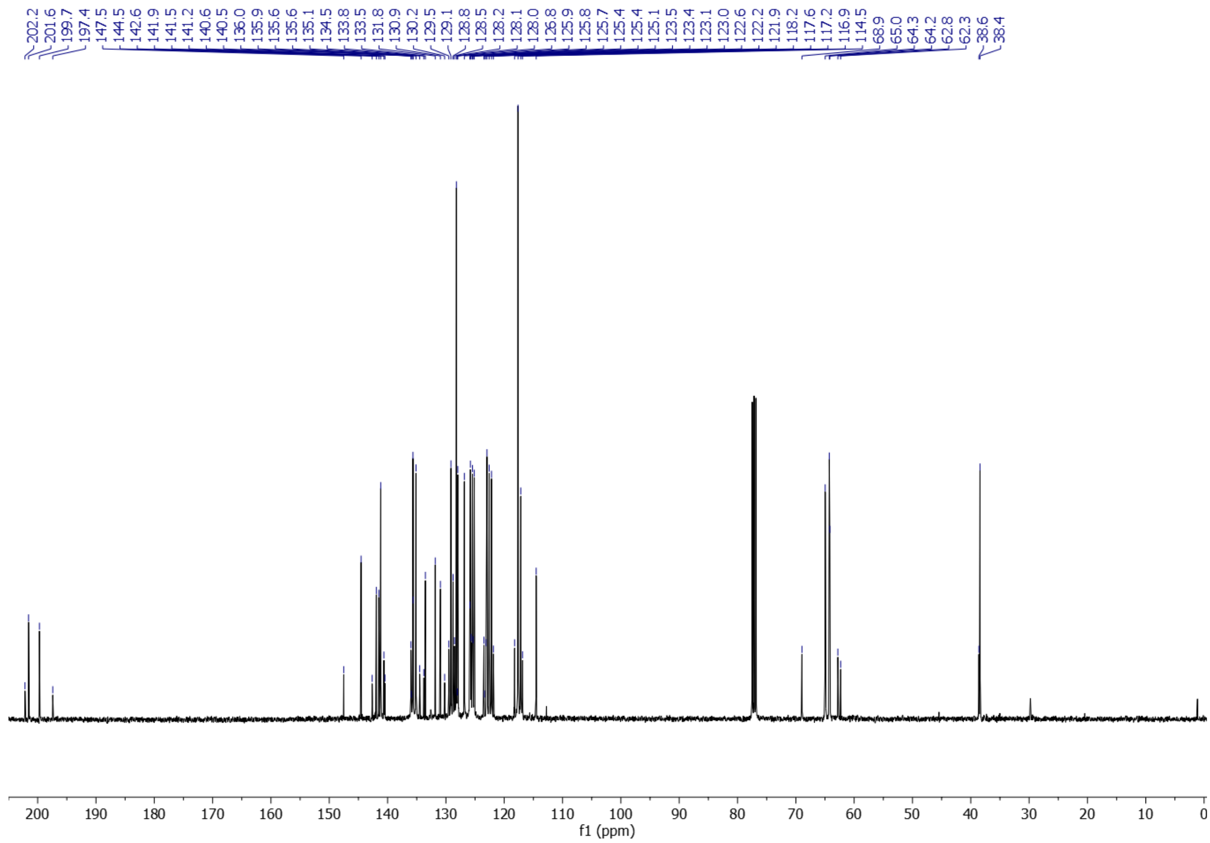
1',2'-diphenyl-5'-vinylspiro[indene-2,3'-pyrrolidine]-1,3-dione **4a** (*trans*/*cis* = 4.0 : 1)



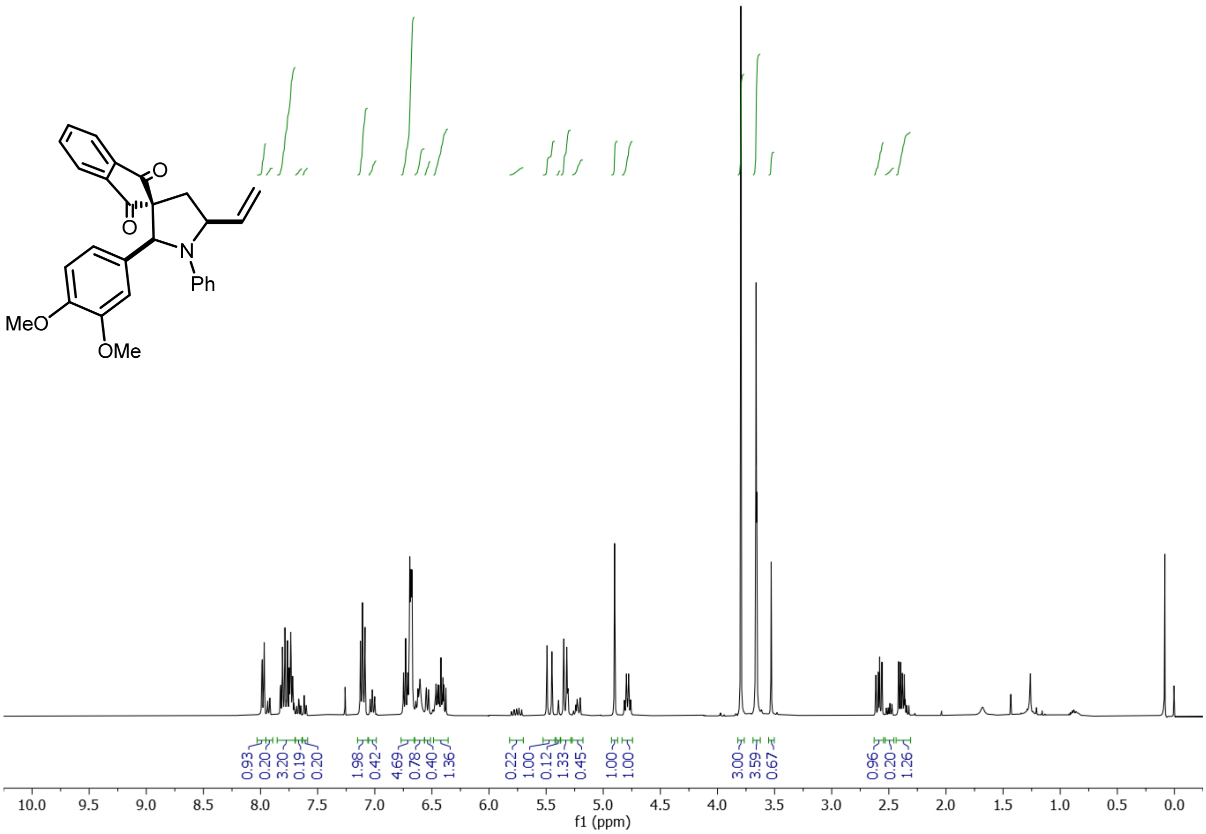


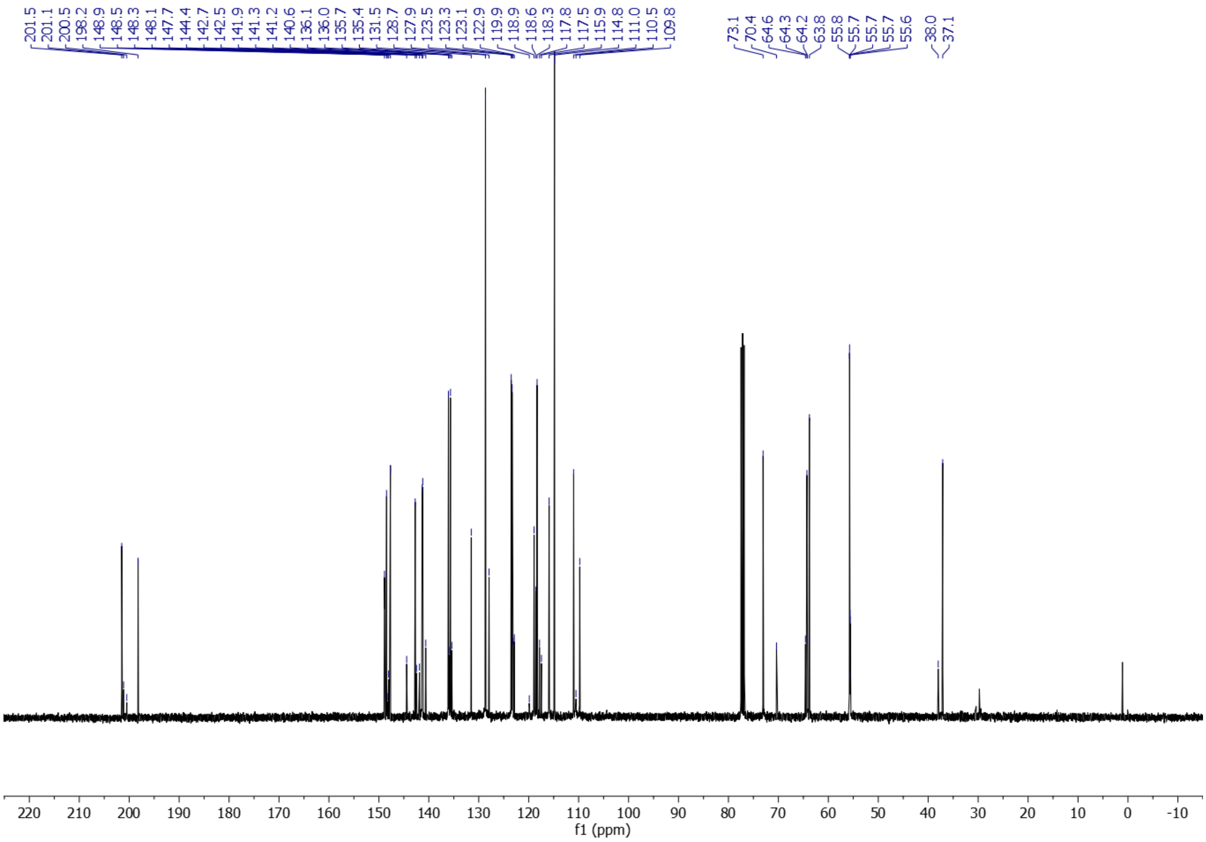
2'-(naphthalen-1-yl)-1'-phenyl-5'-vinylspiro[indene-2,3'-pyrrolidine]-1,3-dione **4b** (*trans*/*cis* = 3.0 : 1)



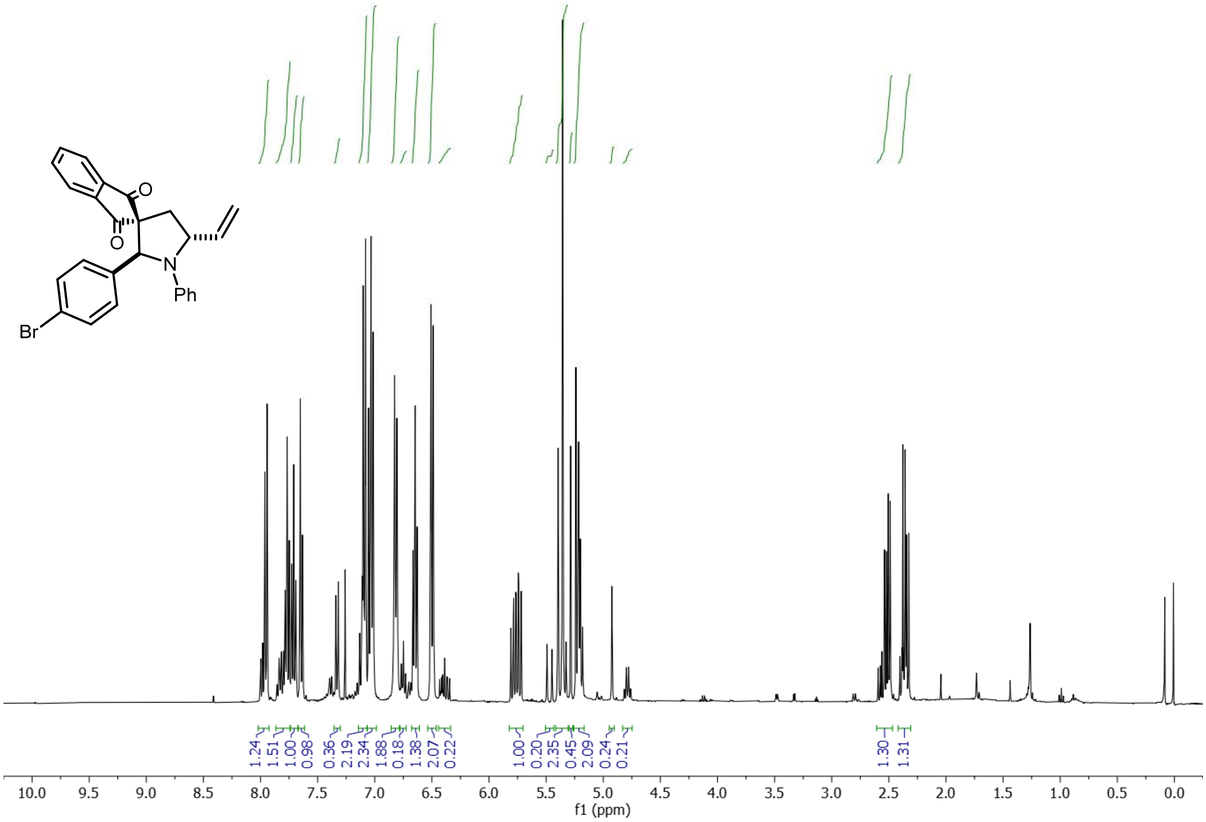


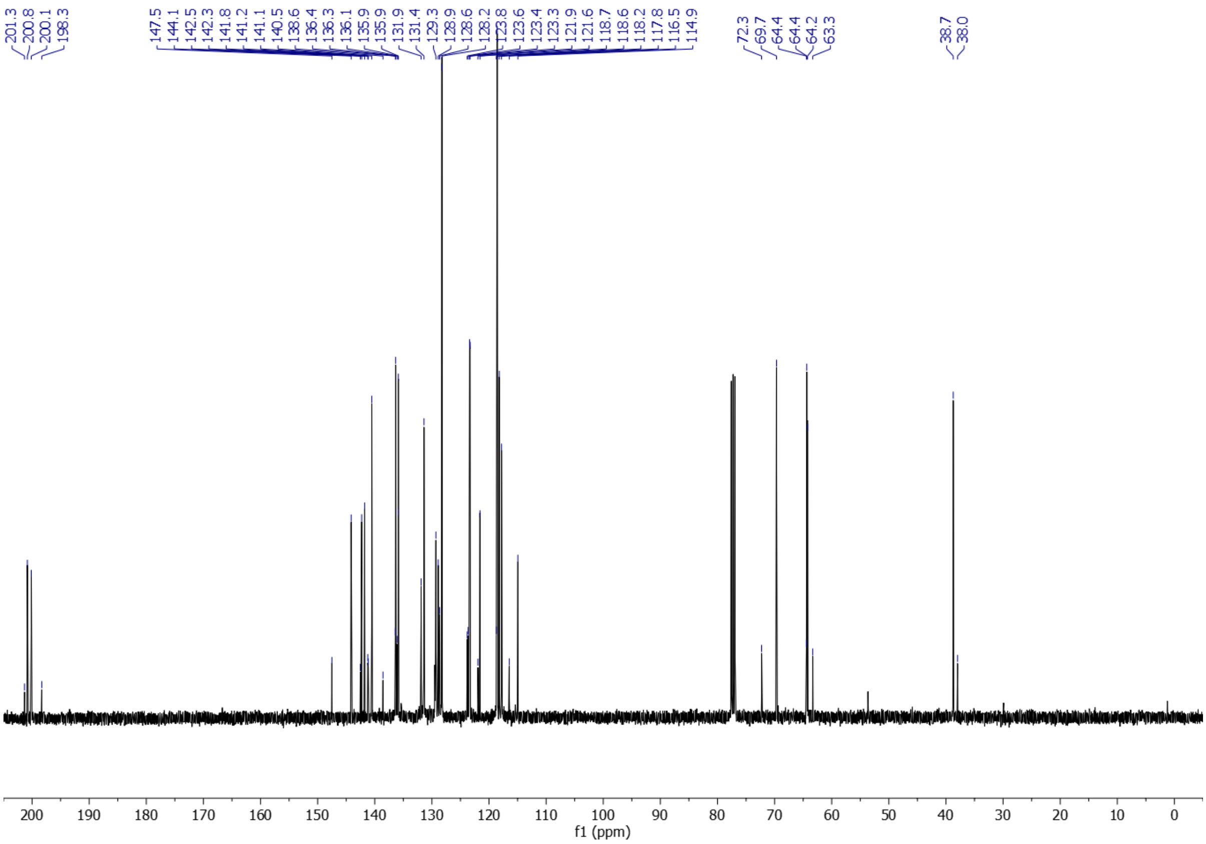
2'-(3,4-Dimethoxyphenyl)-1'-phenyl-5'-vinylspiro[indene-2,3'-pyrrolidine]-1,3-dione **4c** (*trans*/*cis* = 1 : 4.2)



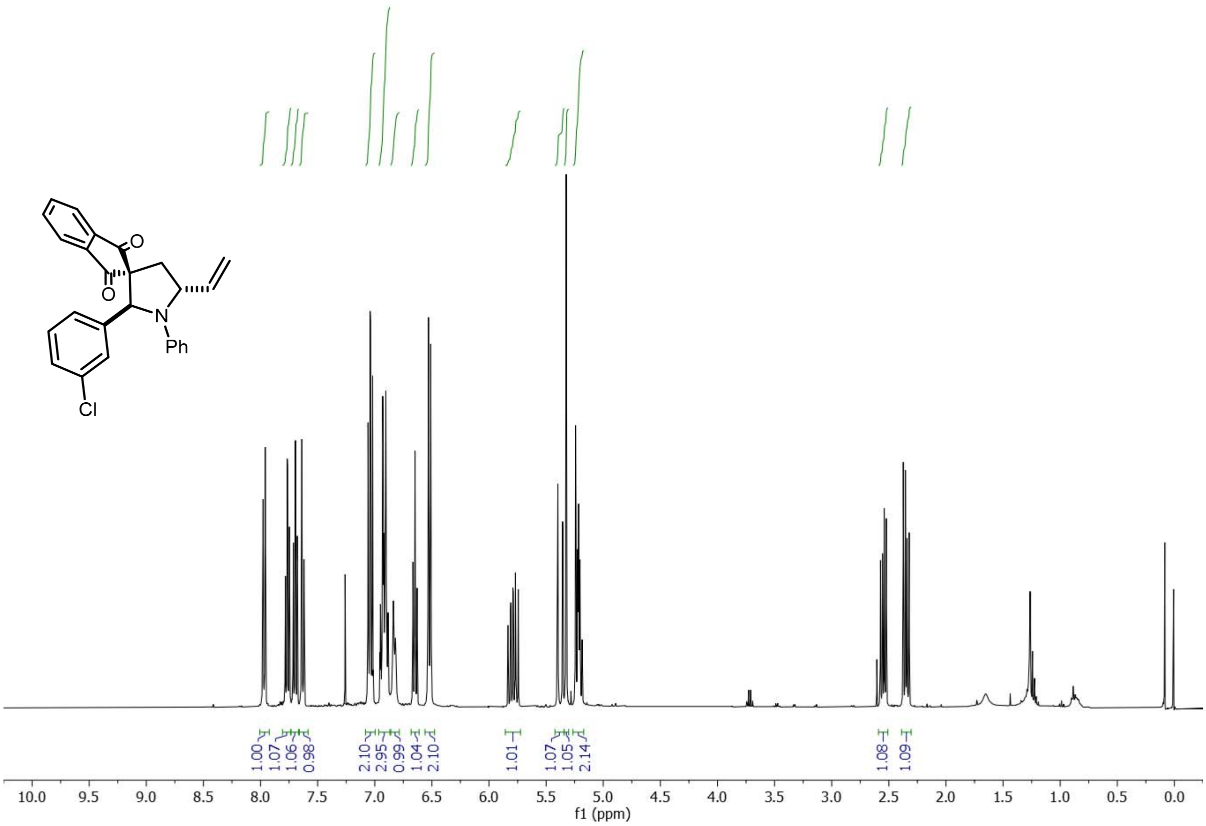


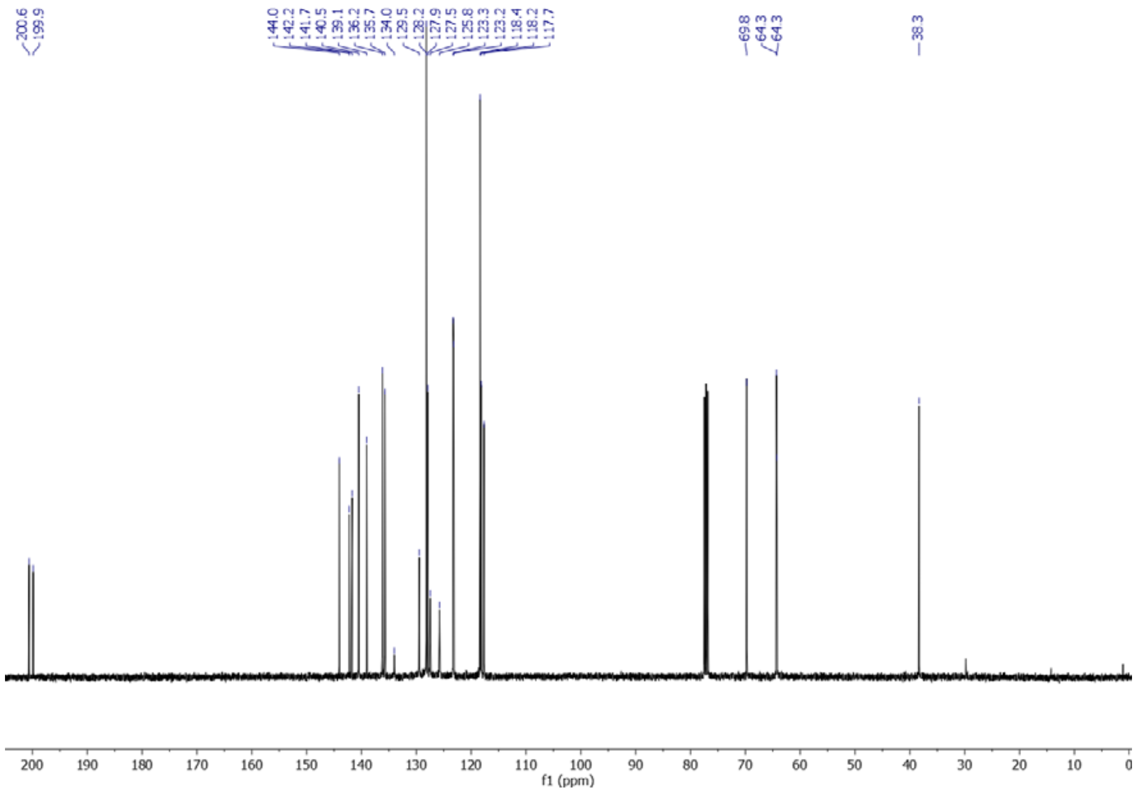
2'-(4-Bromophenyl)-1'-phenyl-5'-vinylspiro[indene-2,3'-pyrrolidine]-1,3-dione **4d** (*trans*/*cis* = 3.5 : 1)



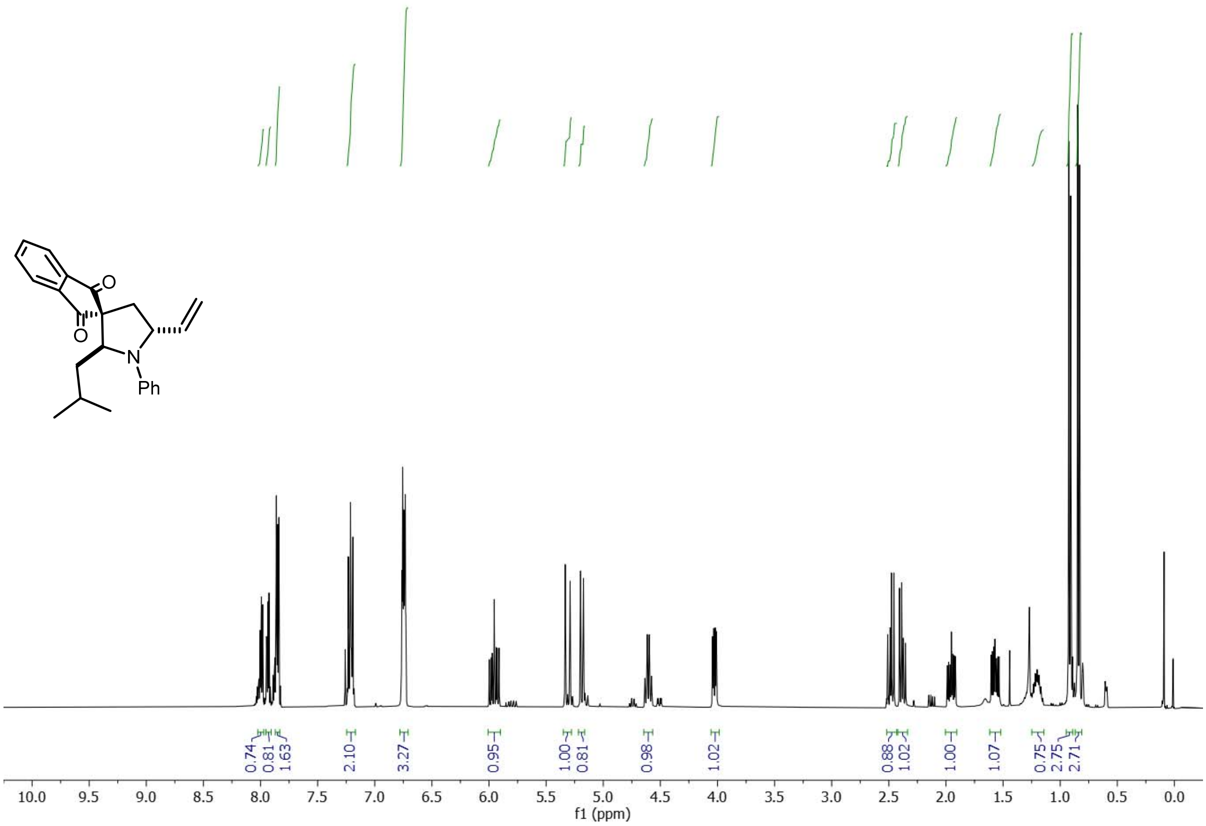


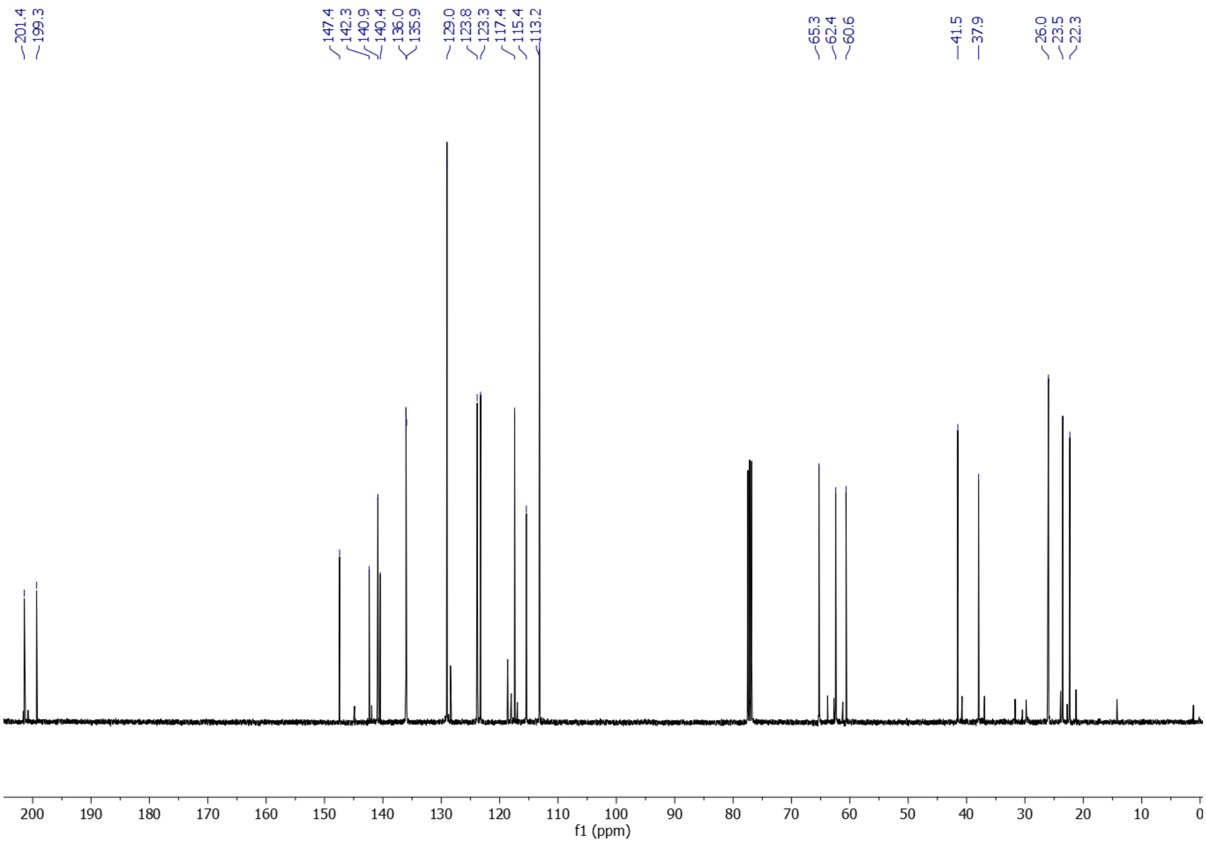
2'-(3-Chlorophenyl)-1'-phenyl-5'-vinylspiro[indene-2,3'-pyrrolidine]-1,3-dione **4e** (*trans*/*cis* = 10.0 : 1)



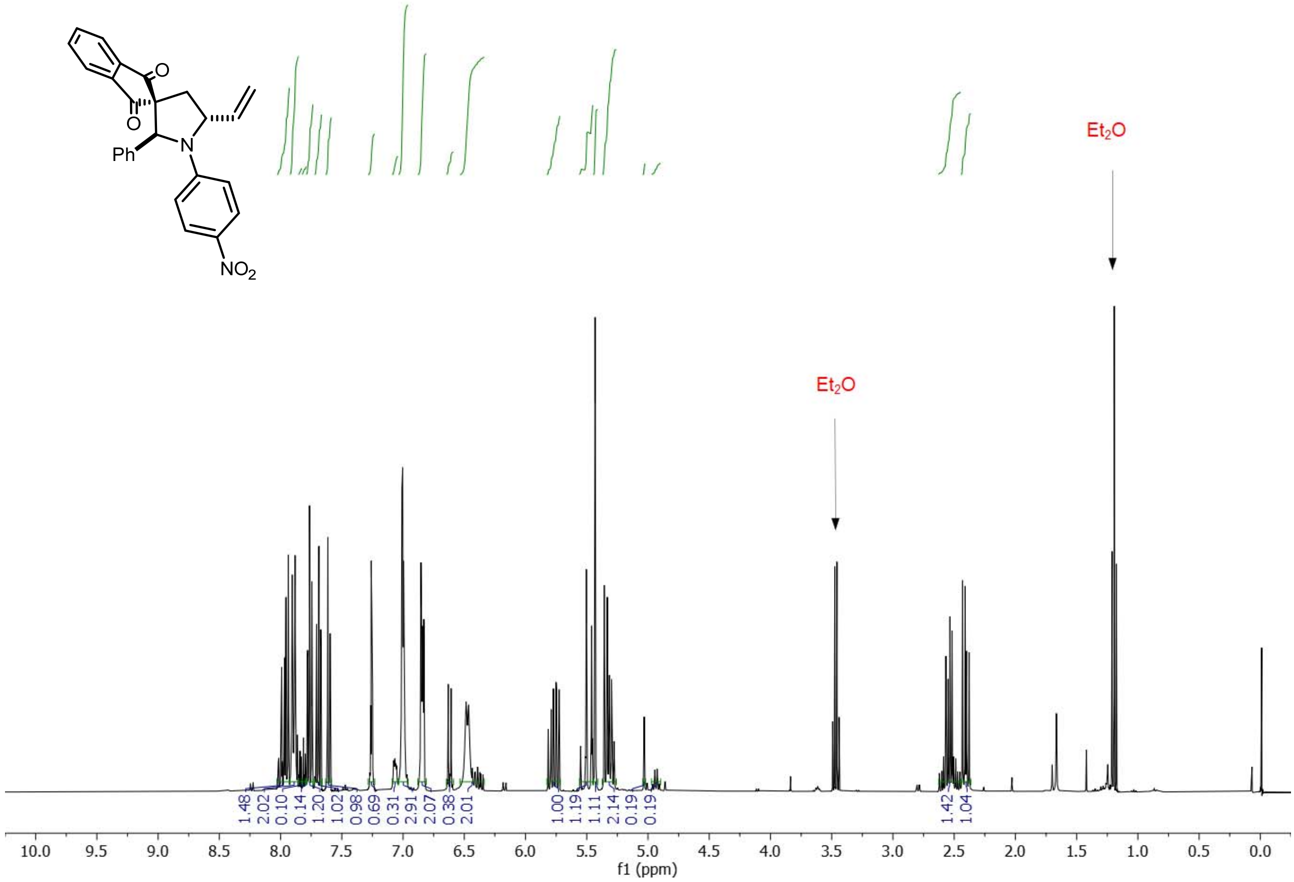


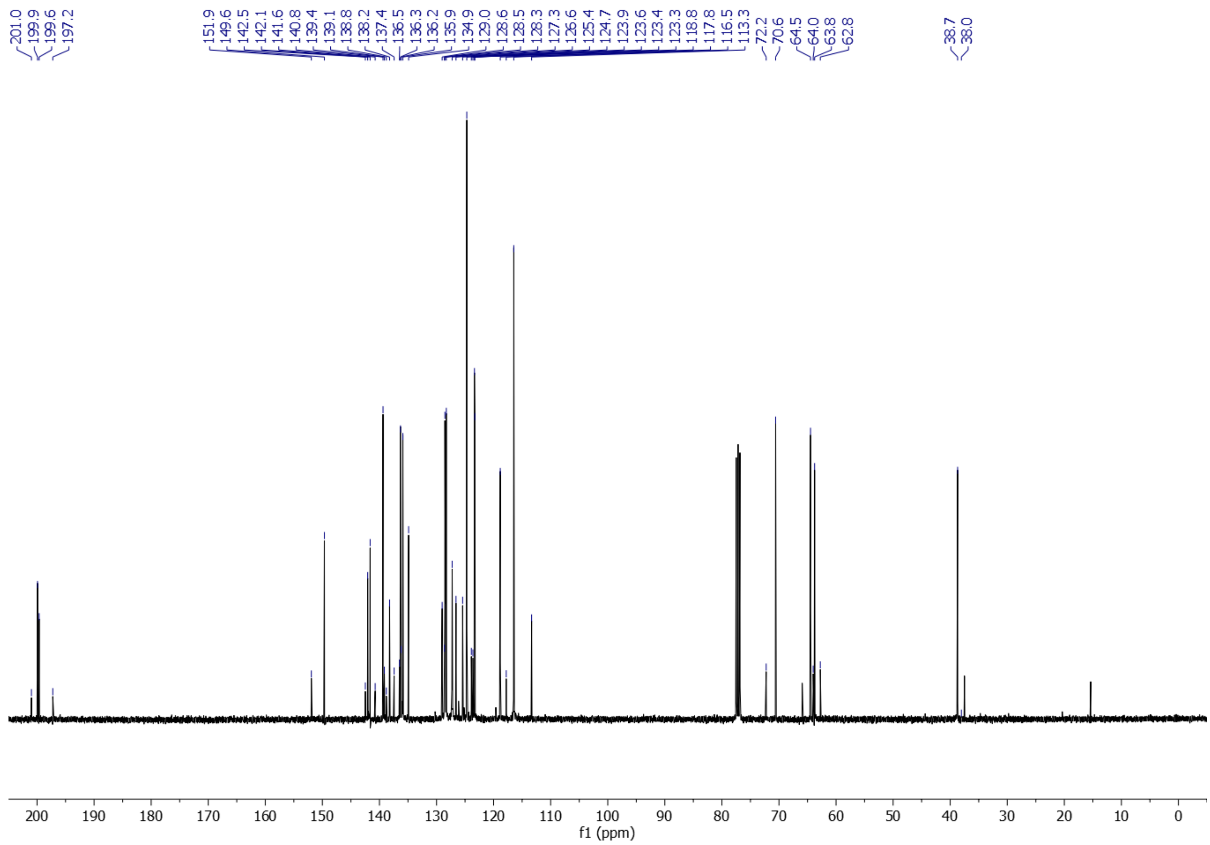
2'-Isobutyl-1'-phenyl-5'-vinylspiro[indene-2,3'-pyrrolidine]-1,3-dione **4f** (*trans*/*cis* = 9.5 : 1)



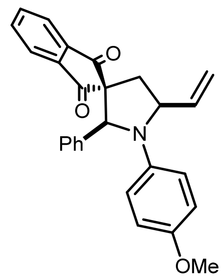


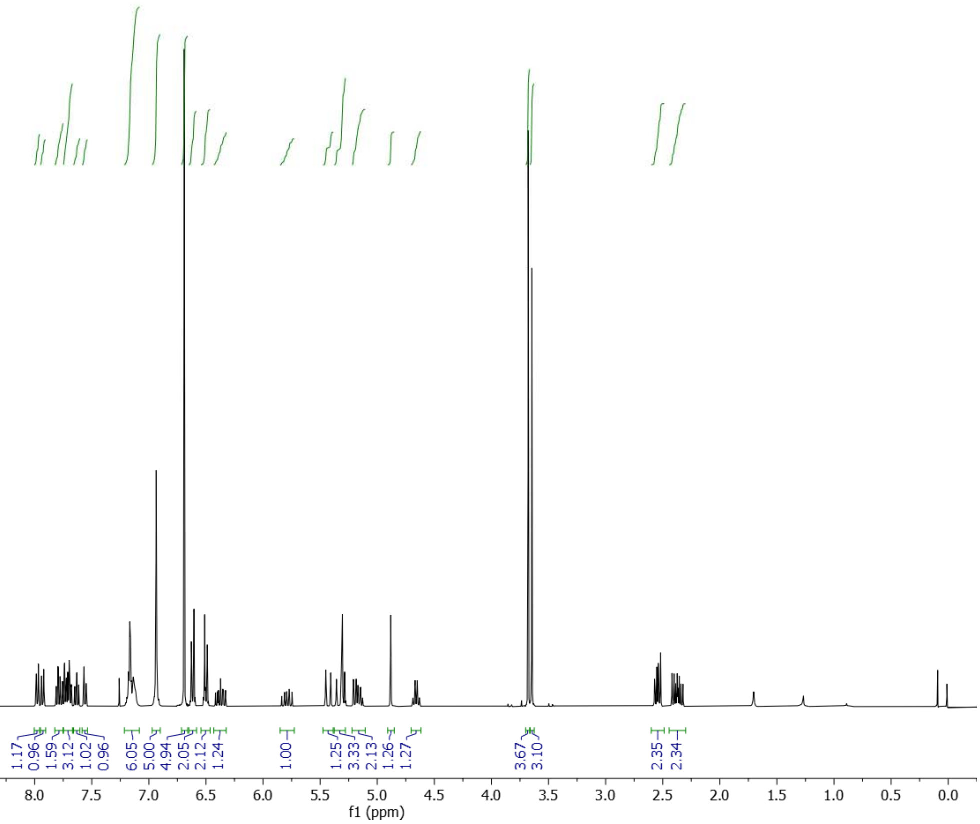
1'-(4-Nitrophenyl)-2'-phenyl-5'-vinylspiro[indene-2,3'-pyrrolidine]-1,3-dione **4g** (*trans*/*cis* = 4.8 : 1)

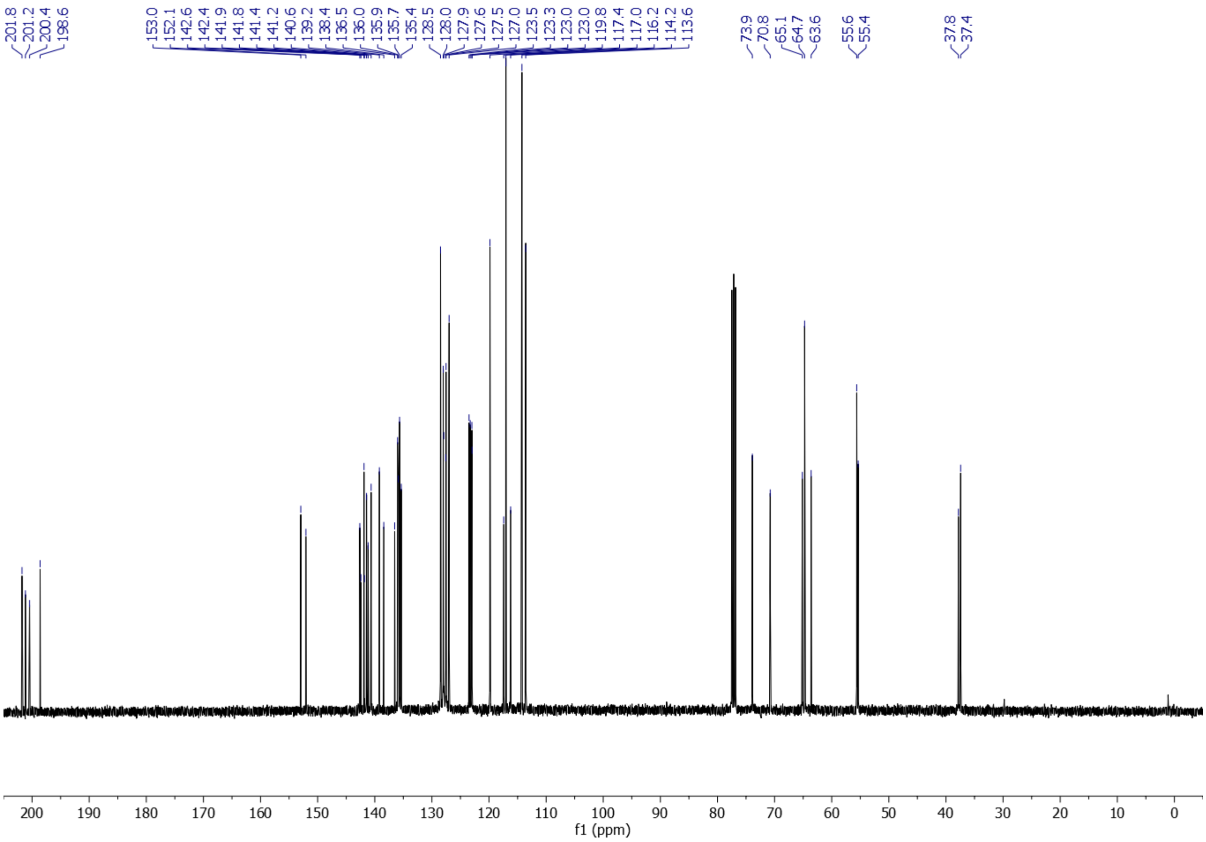




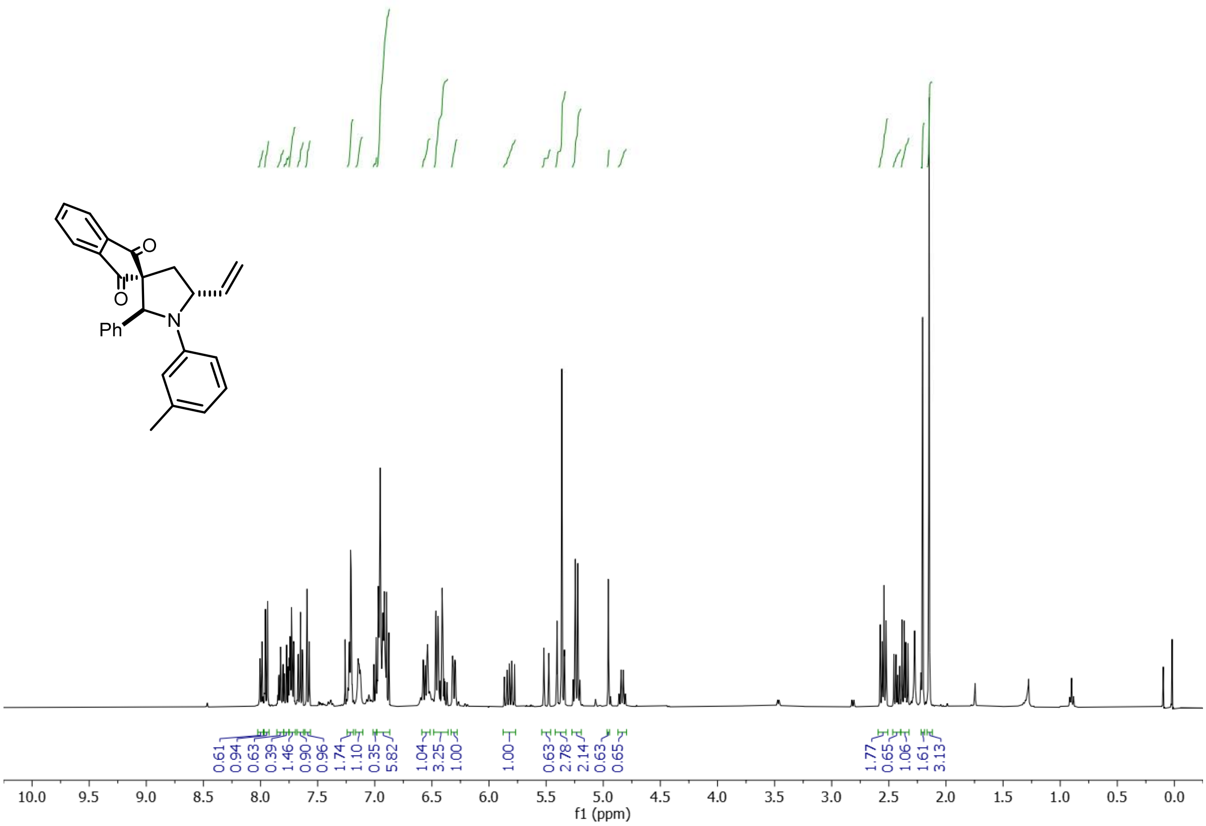
1'-(4-Methoxyphenyl)-2'-phenyl-5'-vinylspiro[indene-2,3'-pyrrolidine]-1,3-dione **4h** (*trans*/*cis* = 1 : 1.2)

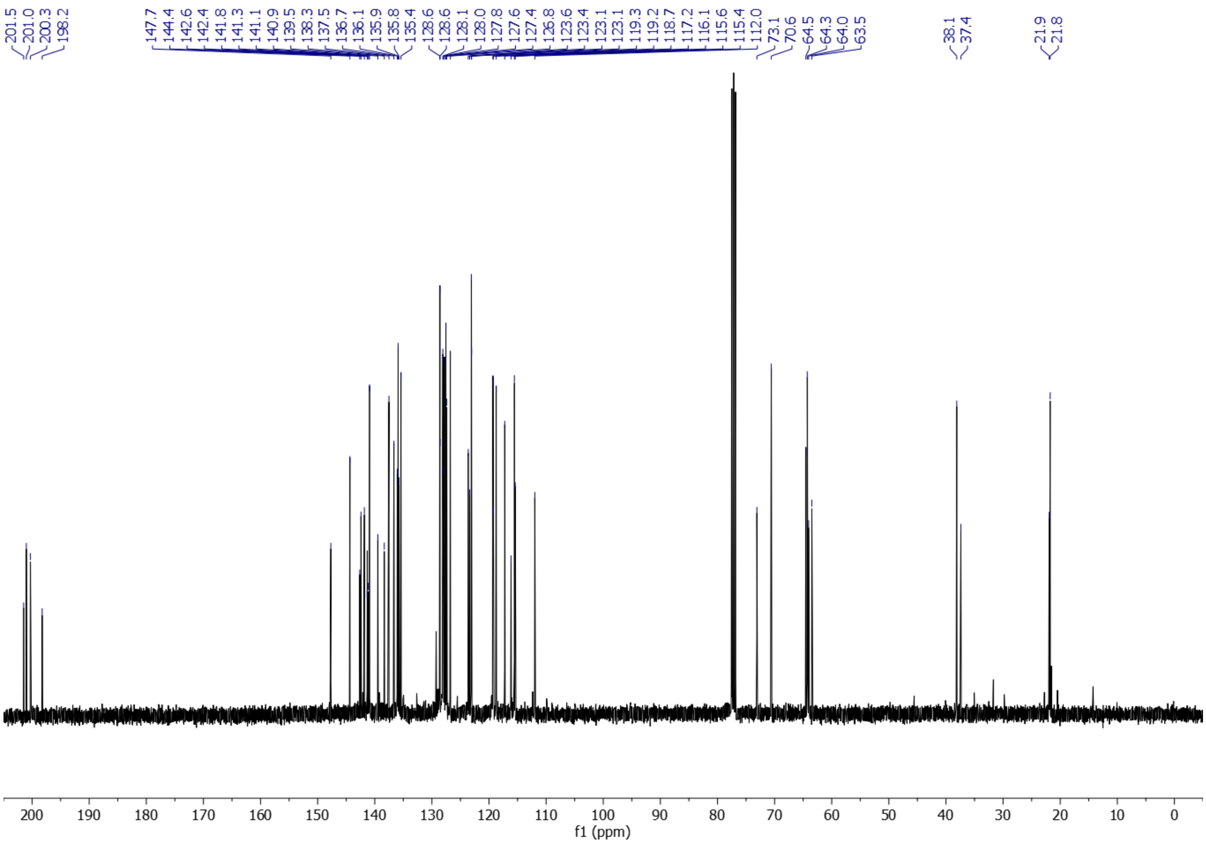




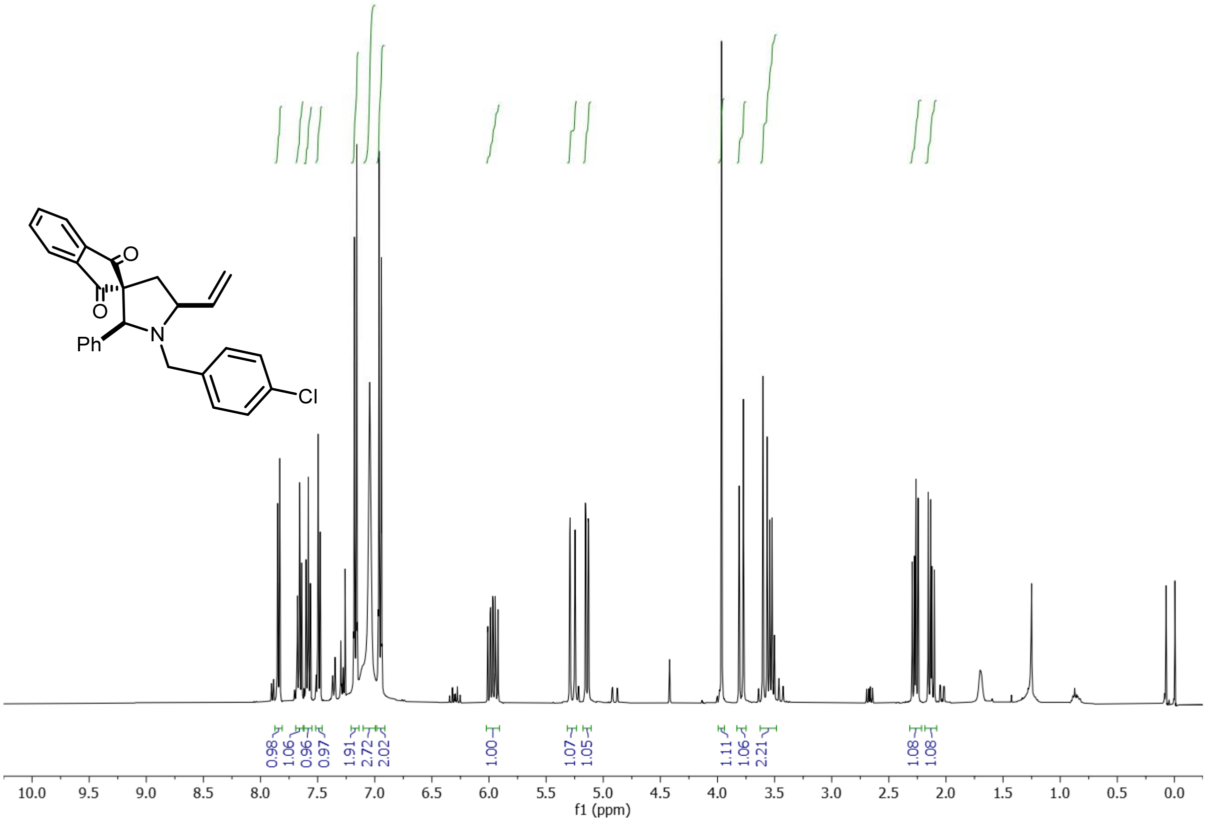


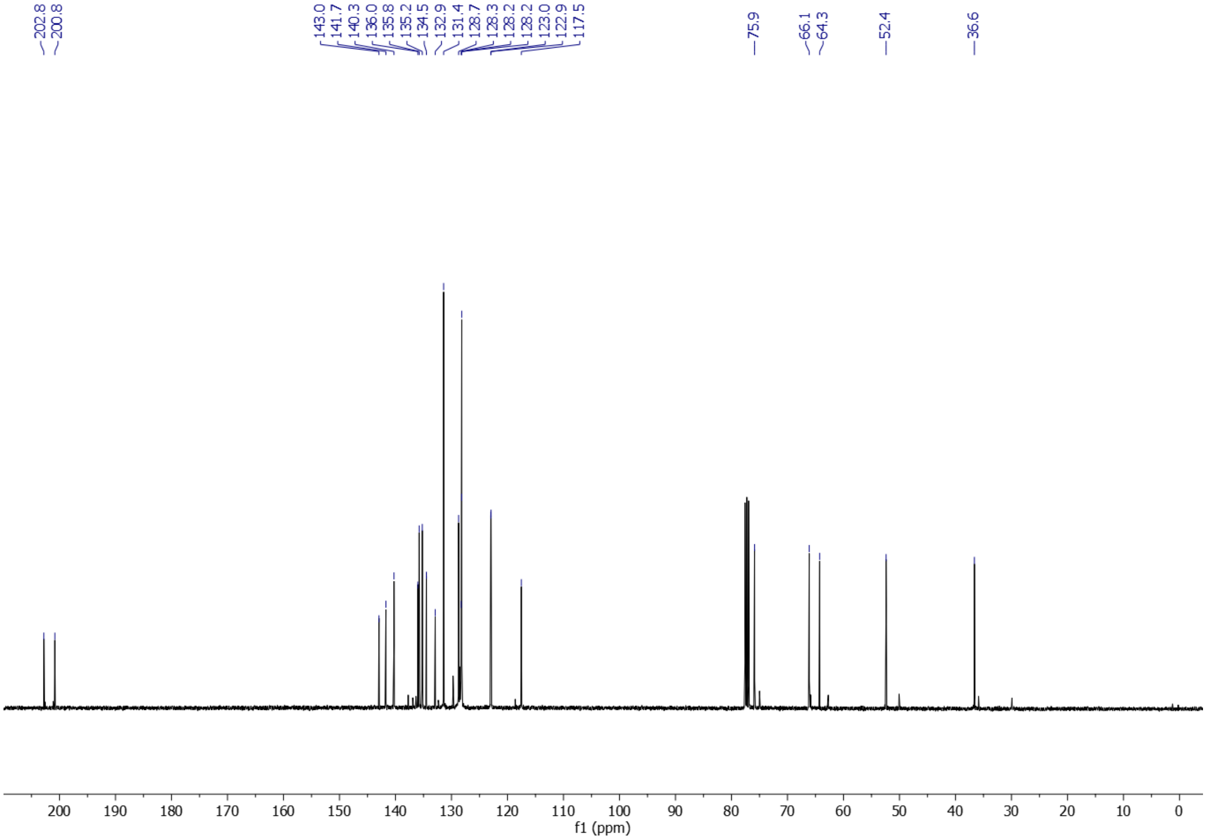
2'-Phenyl-1'-(m-tolyl)-5'-vinylspiro[indene-2,3'-pyrrolidine]-1,3-dione **4i** (*trans*/*cis* = 1.6 : 1)



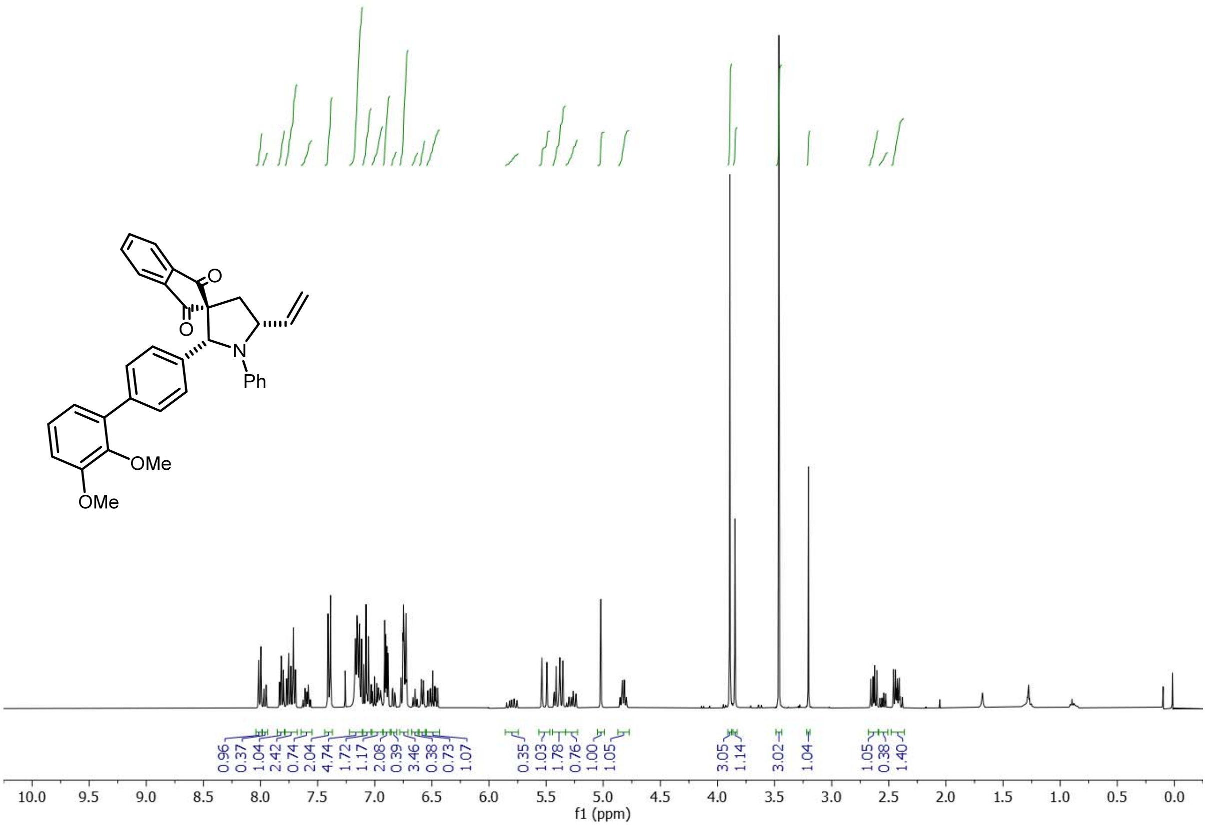


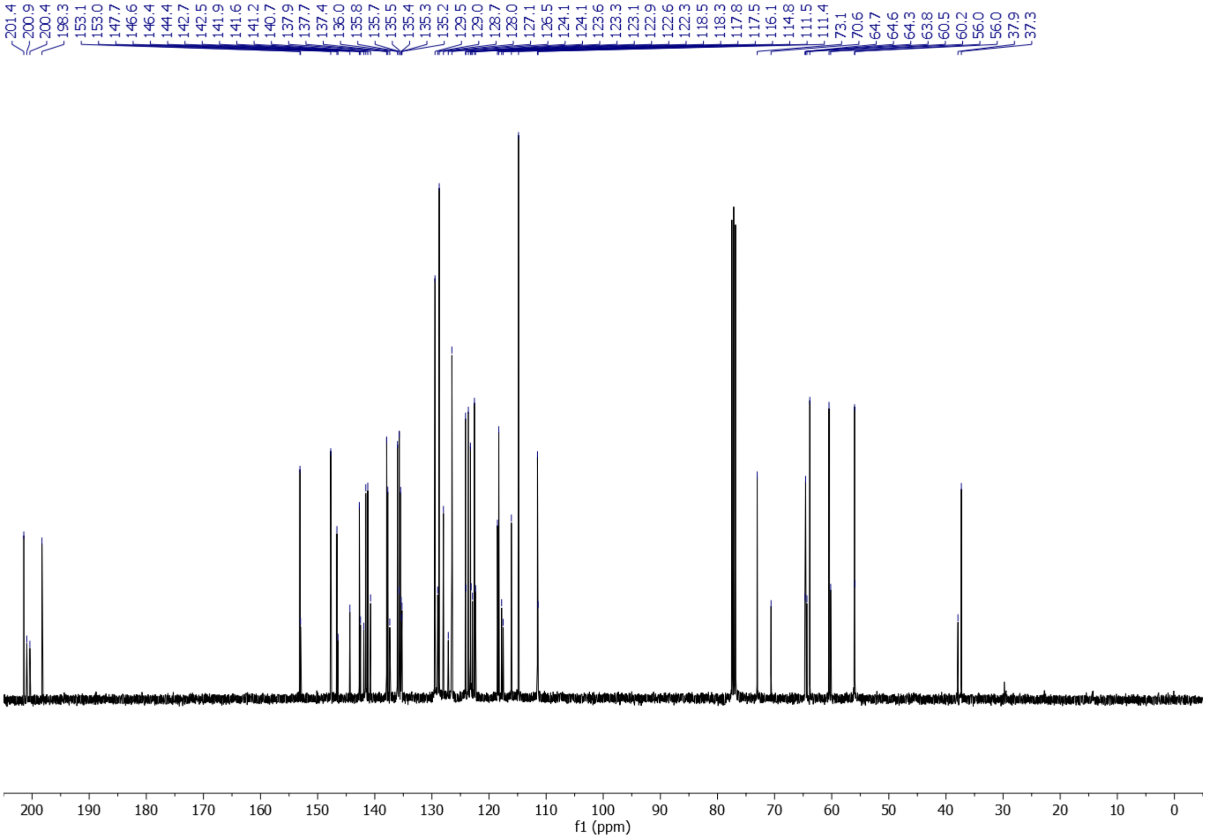
1'-(4-Chlorobenzyl)-2'-phenyl-5'-vinylspiro[indene-2,3'-pyrrolidine]-1,3-dione **4j** (*trans*/*cis* = 1 : 9.2)





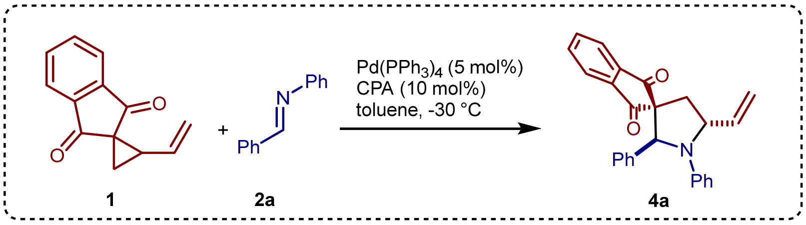
2'-(2',3'-Dimethoxy-[1,1'-biphenyl]-4-yl)-1'-phenyl-5'-vinylspiro[indene-2,3'-pyrrolidine]-1,3-dione **5** (*trans*/*cis* = 1 : 2.8)

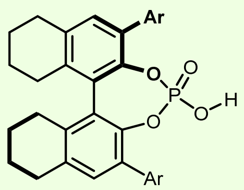




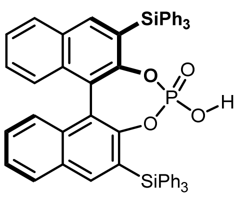
Screening of chiral catalysts and reaction conditions in the enantioselective reaction between 1 and 2a

-Screening of chiral phosphoric acid catalysts: selected results

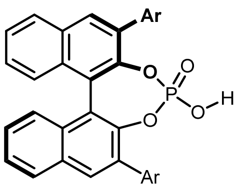




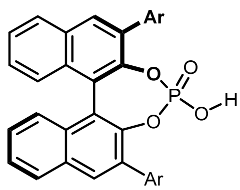
3d: Ar = 9-anthryl
81% yield
trans/*cis* = 3.2 : 1
42% ee (*trans*)
11% ee (*cis*)



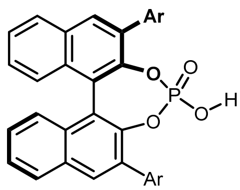
87% yield
trans/*cis* = 1.8 : 1
10% ee (*trans*)
rac (*cis*)



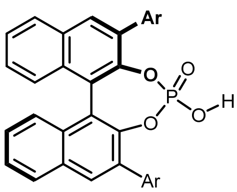
Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$
95% yield (RT, n.r. at -30 °C)
trans/*cis* = 1 : 1.8
rac (*trans*)
11% ee (*cis*)



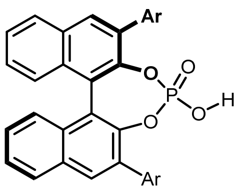
Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
81% yield
trans/*cis* = 1 : 2.5
10% ee (*trans*)
rac (*cis*)



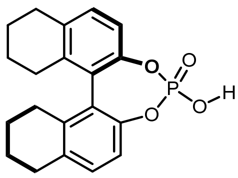
Ar = 1-naphthyl
82% yield
trans/*cis* = 2.0 : 1
13% ee (*trans*)
rac (*cis*)



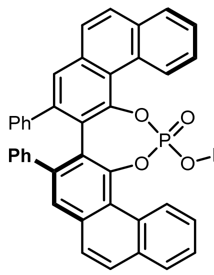
Ar = 4-PhC$_6$H$_4$
88% yield
trans/*cis* = 1.5 : 1
6% ee (*trans*)
10% ee (*cis*)



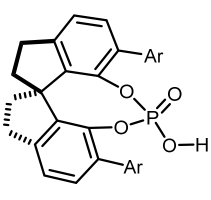
Ar = 4-NO$_2$C$_6$H$_4$
86% yield
trans/*cis* = 1 : 2.0
14% ee (*trans*)
5% ee (*cis*)



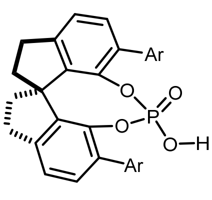
92% yield
trans/*cis* = 1.2 : 1
9% ee (*trans*)
14% ee (*cis*)



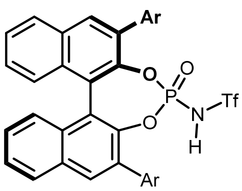
86% yield
trans/*cis* = 1 : 2.0
7% ee (*trans*)
rac (*cis*)



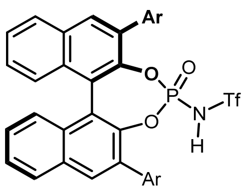
Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
>95% conversion*
trans/*cis* = 2.5 : 1
3% ee (*trans*)
5% ee (*cis*)



Ar = 9-anthryl
>95% conversion*
trans/*cis* = 1.6 : 1
33% ee (*trans*)
8% ee (*cis*)



Ar = 9-anthryl
87% yield
trans/*cis* = 1 : 1.7
rac (*trans*)
rac (*cis*)

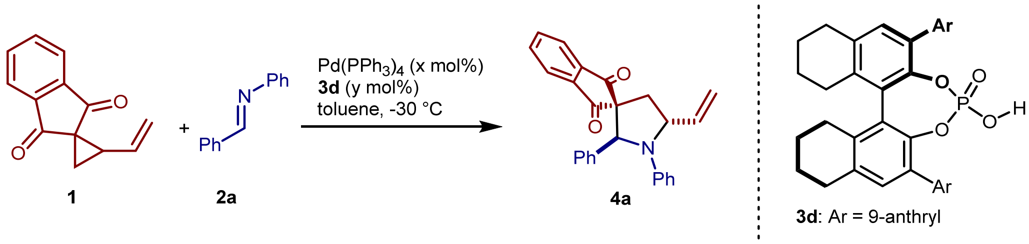


Ar = 9-phenanthryl
93% yield
trans/*cis* = 1 : 1.6
rac (*trans*)
rac (*cis*)

Conditions: VCP **1** (0.05 mmol), imine **2a** (0.06 mmol), Pd(PPh$_3$)$_4$ (5 mol%), chiral phosphoric acid (CPA) (10 mol%), toluene (0.2 mL), -30 °C.

* Conditions: VCP **1** (0.05 mmol), imine **2a** (0.06 mmol), Pd(PPh$_3$)$_4$ (10 mol%), chiral phosphoric acid (CPA) (5 mol%), toluene (0.6 mL), -30 °C.

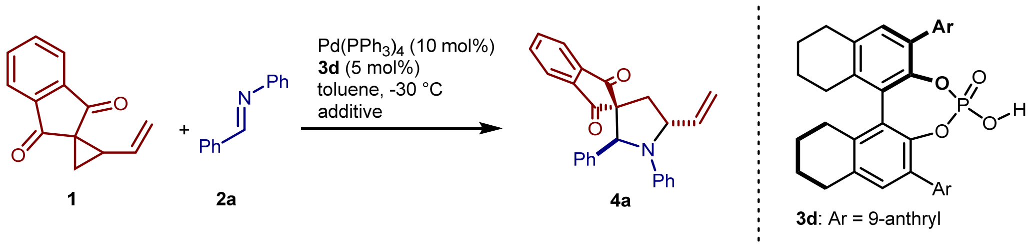
-Screening of the two catalysts loadings: selected results



Entry[1]	Pd(PPh$_3$)$_4$ [x mol%]	3d [y mol%]	Yield [%]	*trans/cis*	ee (*trans*) [%]	ee (*cis*) [%]
1	5	10	81	3.2 : 1	42	11
2	5	15	64	2.0 : 1	52	11
3	5	20	57	1 : 1.8	52	23
4	5	5	88	5.3 : 1	58	15
5	***10***	***5***	***66***	***7.0 : 1***	***60***	***35***
6	10	2.5	low	n.d.	56	31
7	5	2.5	low	n.d.	60	32

[1] Conditions: VCP **1** (0.05 mmol), imine **2a** (0.06 mmol), Pd(PPh$_3$)$_4$ (x mol%), chiral phosphoric acid **3d** (y mol%), toluene (0.2 mL), -30 °C.

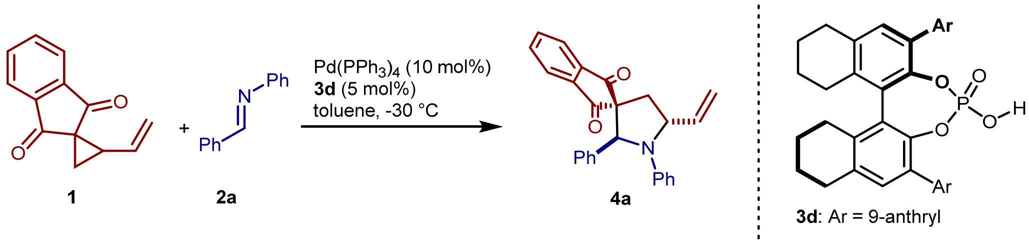
-Screening of additives/drying agents: selected results



Entry[1]	Additive	Yield [%]	*trans/cis*	ee (*trans*) [%]	ee (*cis*) [%]
1	***none***	***66***	***7.0 : 1***	***60***	***35***
2	5 Å MS	56	3.2 : 1	12	48
3	4 Å MS	89	2.2 : 1	10	53
4	3 Å MS	91	2.4 : 1	10	53
5	MgSO$_4$	86	1.1 : 1	49	rac
6	AcOH	>95%[2]	12.5 : 1	24	n.d.
7	TBACl	<10	-	-	-

[1] Conditions: VCP **1** (0.05 mmol), imine **2a** (0.06 mmol), Pd(PPh$_3$)$_4$ (10 mol%), chiral phosphoric acid **3d** (5 mol%), toluene (0.2 mL), additive, -30 °C. [2] Conversion.

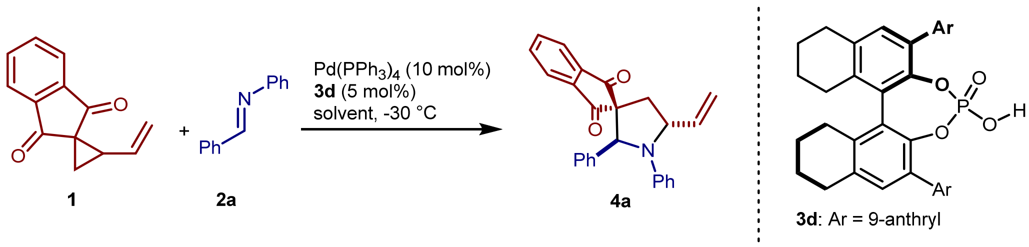
-Effect of the dilution: selected results



Entry[1]	Toluene [M]	Yield [%]	*trans/cis*	ee (*trans*) [%]	ee (*cis*) [%]
1	0.25	66	7.0 : 1	60	35
2	0.5	>99	1.9 : 1	61	rac
3	***0.125***	***80***	***14 : 1***	***62***	***n.d.***
4	***0.083***	***>95[2]***	***12.3 : 1***	***60***	***n.d.***
5	0.0625	66	26 : 1	60	n.d.

[1] Conditions: VCP **1** (0.05 mmol), imine **2a** (0.06 mmol), $Pd(PPh_3)_4$ (10 mol%), chiral phosphoric acid **3d** (5 mol%), toluene (x mL), -30 °C. [2] Conversion.

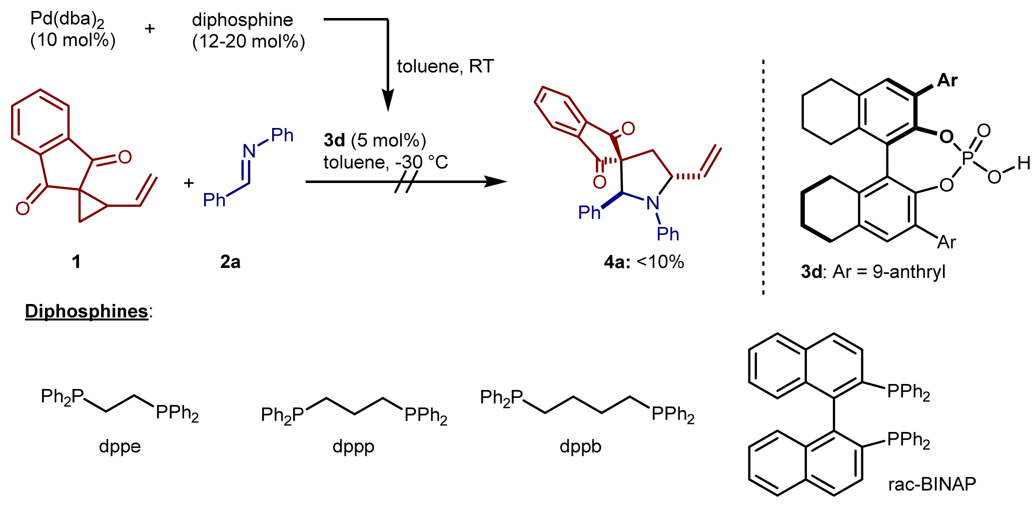
-Solvent screening: selected results



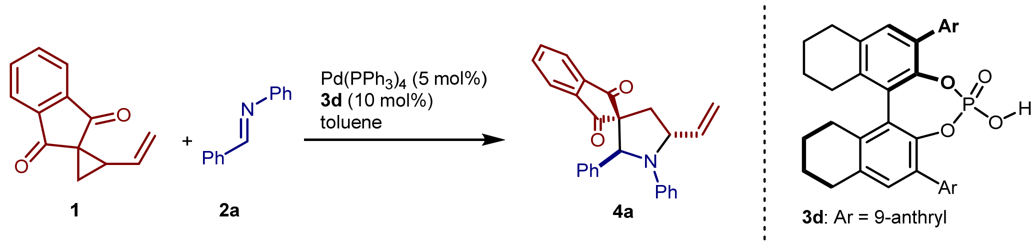
Entry[1]	Solvent	Conversion [%]	*trans/cis*	ee (*trans*) [%]	ee (*cis*) [%]
1	***toluene***	***>95***	***12.3 : 1***	***60***	***n.d.***
2	EtOAc	>95	18 : 1	32	n.d.
3	THF	>95	11 : 1	16	n.d.
4	CH_2Cl_2	>95	5.2 : 1	14	6
5	$C_6H_5CF_3$	>95	4.6 : 1	50	rac

[1] Conditions: VCP **1** (0.05 mmol), imine **2a** (0.06 mmol), $Pd(PPh_3)_4$ (10 mol%), chiral phosphoric acid **3d** (5 mol%), solvent (0.6 mL), -30 °C.

-Phosphine ligands screening: selected results



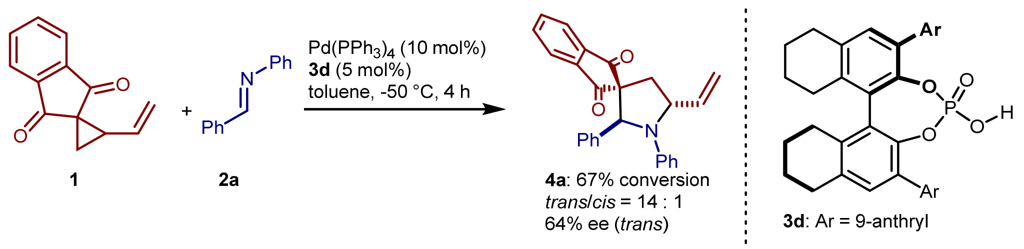
-Temperature screening: selected results



Entry[1]	T [°C]	t [h]	Conversion [%]	*trans/cis*	ee (*trans*) [%]
1	-30	4	>95	12.3 : 1	60
2	***-50***	***6***	***67***	***14 : 1***	***64***
3	-70	18	>95	3.5 : 1	62

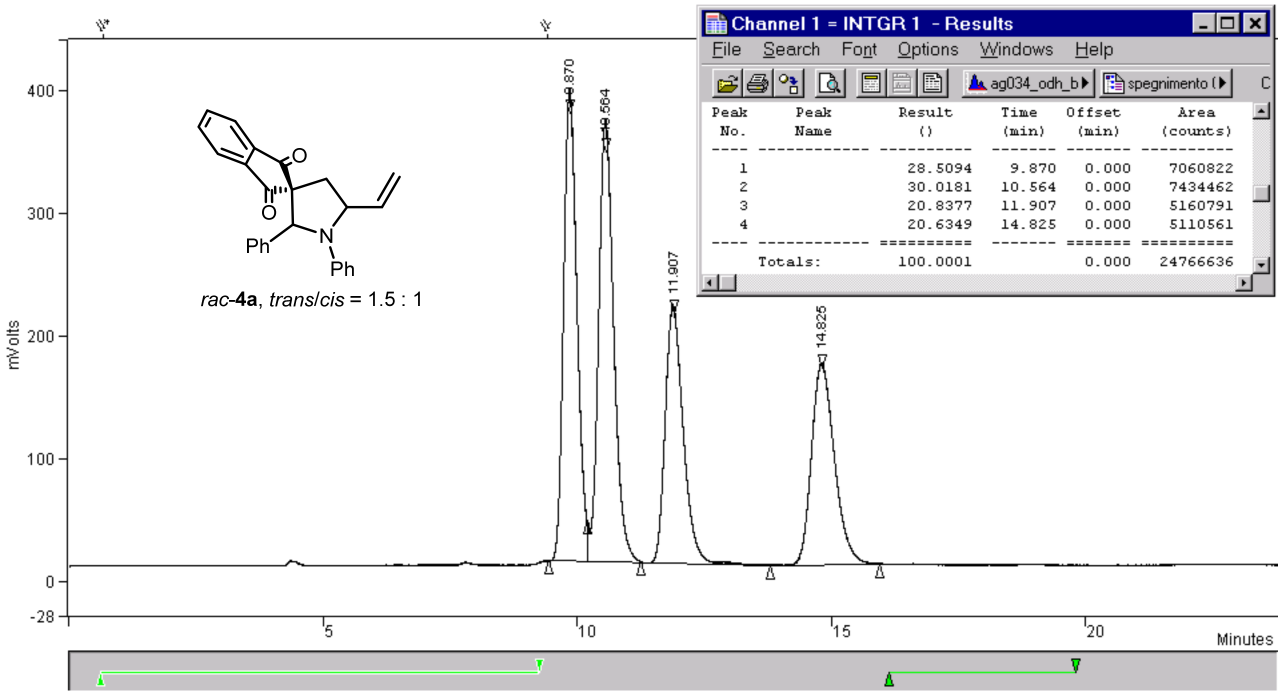
[1] Conditions: VCP **1** (0.05 mmol), imine **2a** (0.06 mmol), Pd(PPh$_3$)$_4$ (10 mol%), chiral phosphoric acid **3d** (5 mol%), solvent (0.6 mL), -30 °C.

-Preliminarily optimised conditions:

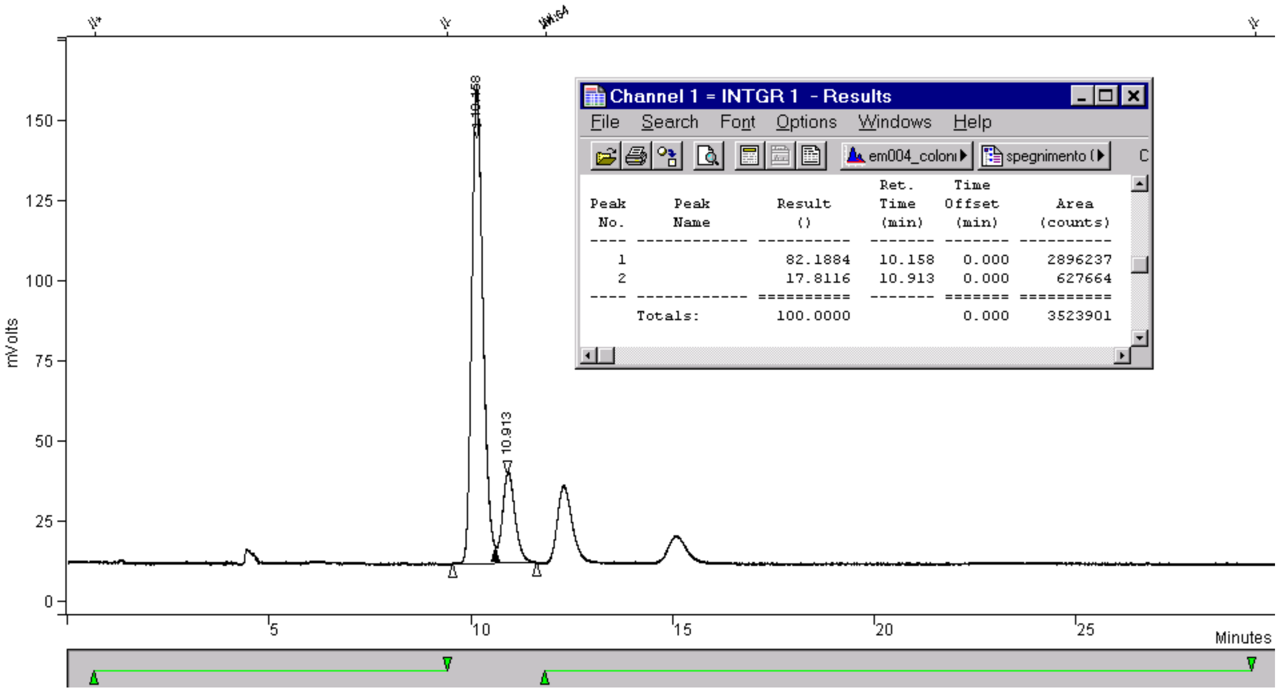


Copies of the HPLC traces for racemic and enantioenriched 4a

Racemic **4a**:



Enantioenriched **4a**: integration values for the major *trans*-diastereoisomer:



Enantioenriched **4a**: integration values for the minor *cis*-diastereoisomer: