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Enantioselective Synthesis of Functionalized Diazaspirocycles from 4-Benzylideneisoxazol-5(4*H*)-one derivatives and Isocyanoacetate Esters

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Abstract. Enantioenriched spirocyclic compounds bearing three contiguous stereocenters and high functionalization were obtained through a formal [3+2] cycloaddition reaction catalyzed by a cooperative system. The spiro compounds were synthesized from 4-arylideneisoxazol-5-ones and isocyanoacetate esters using a bifunctional squaramide/Brønsted base organocatalyst derived from a Cinchona alkaloid and silver oxide as Lewis acid. This method afforded two out of the four possible diastereomers with good yields and high enantiomeric excess for both diastereomers.

Keywords: Asymmetric catalysis; Enantioselectivity; Heterocycles; Cycloaddition; Spiro compounds

Organic spirocycles are unique compounds that feature two rings connected through just one shared carbon (the spiroatom). This structural feature is often present in natural products isolated from different sources, from plants to marine organisms.[1] Examples of spirocompounds of natural origin include horsfiline, a natural product isolated from *Horsfielda superba*,[1d] β-vetivone, extracted from vetiver oil,[1e] or (–)-gleenol isolated from the brown alga *Taonia atomaria* (Figure 1).[1f] Spirocyclic compounds have also found some interesting applications as privileged ligands for asymmetric catalysis such as spinol,[2] or in the production of circularly polarized photoluminescence.[3] Furthermore, the spirocyclic motif is becoming a prevalent template in drug discovery,[4] since this structural feature conveys both increased three-dimensionality for potential improved activity, and novelty for patenting purposes. An example of spirocyclic drugs is the marketed fenspiride,[5] used for the treatment of some respiratory diseases (Figure 1).

For these reasons, the synthesis of spirocyclic compounds has received a growing interest in the last decade.[6] In this context, the catalytic enantioselective construction of a chiral spiro quaternary carbon results especially challenging. The synthesis of quaternary stereocenters, in general, is hampered by the huge steric hindrance and low steric dissimilarity of the two carbon substituents on the prochiral center. Furthermore, the generation of a spiro quaternary stereocenter often requires overcoming ring strain to install useful functionalities, and the diastereoselectivity needs to be controlled because the construction of spiro systems is often accompanied by the formation of additional stereocenters.

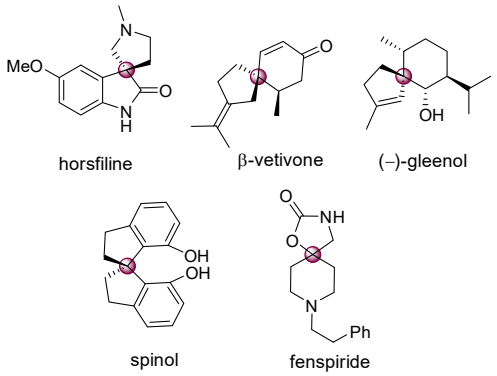


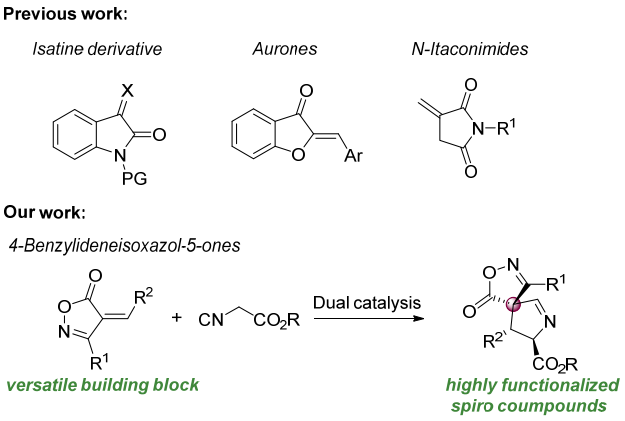
Figure 1. Selected examples of natural products and drugs with spirocyclic structure.

Among the different methodologies designed to achieve this goal, [7] cycloaddition reactions with cyclic compounds bearing an exocyclic double bond result especially appealing because of its simplicity and the vast variety of reaction partners that can participate in this kind of reactions. Five-membered nitrogen-containing heterocycles are privileged structures in medicinal chemistry. Among these, the spiropyrroline, [8] as well as the spiroisoxazol-5-one[9] scaffolds are featured in a great number of natural products, biologically active compounds and pharmaceuticals.

Isocyanoacetate esters are versatile scaffolds in organic synthesis and can participate as formal 1,3-

dipoles in cycloaddition reactions leading to five-membered nitrogen-containing heterocycles. [10] In the last years, this approach has been used in the enantioselective synthesis of several spirocyclic compounds (Scheme 1). Thus, the groups of Zhong, Wang, Yan, Shi and He have reported the addition of isocyanoacetate esters to different isatin derivatives for the preparation of spirooxindoles. [11] Also recently, the groups of Shao/He and Zhao have reported the synthesis of spirocycles by the reaction of isocyanoacetate esters with aurones or *N*-itaconimides, respectively. [12]

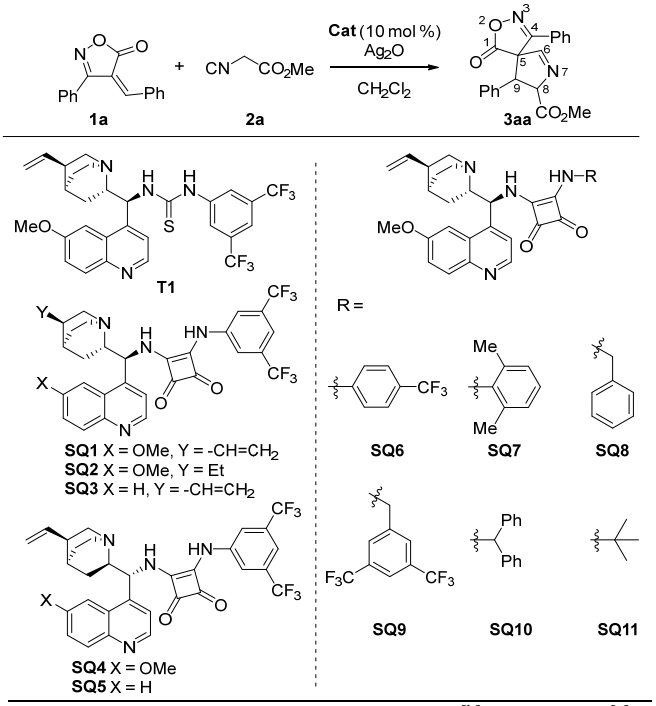
On the other hand, 4-arylideneisoxazol-5-ones, featuring an isoxazole-5-one ring with an exocyclic double bond, are structures present in natural products and other biologically active compounds, and have raised increased interest as electrophiles in Michael-type reactions, including organocatalyzed reactions. Moreover, the isoxazole-5-one ring is a versatile building block being used as synthetic equivalent of alkynes or ketones among others. [13] Following our research on enantioselective cycloaddition reactions with isocyanoacetate esters, [14] we report here the synthesis of chiral hybrid diazaspirocyclic compounds[15] combining a pyrroline and an isoxazol-5-one ring, via the formal [3+2] cycloaddition reaction of 4-benzylideneisoxazol-5-ones and isocyanoacetate esters (Scheme 1).



Scheme 1. Synthesis of spiro compounds employing isocyanoacetates as pronucleophiles.

In the onset of our research, the reaction between methyl isocyanoacetate (**2a**) and benzylidene-3-phenylisoxazol-5-one (**1a**) in dichloromethane was chosen to optimize the reaction conditions (Table 1). We started by checking bifunctional thiourea **T1** and squaramide **SQ1** catalysts in the presence of silver oxide following conditions previously established in our group, [14] which performed in a similar way providing the expected product **3aa** with good diastereoselectivity but low enantioselectivity (Table 1, entries 1 and 2). We also observed that silver oxide alone was able to catalyze the diastereoselective reaction in a non-enantioselective manner (Table 1, entry 3). To avoid this undesired background reaction, we performed the reaction with **T1** or **SQ1** in the absence of silver oxide (Table 1, entries 4 and 5). However, although in both cases the enantiomeric excess of the reaction product was improved under these conditions, the reaction required longer times and product **3aa** was obtained in low yield despite total consumption of the starting material. Also we observed that **SQ1** provided better enantioselectivity than **T1**.

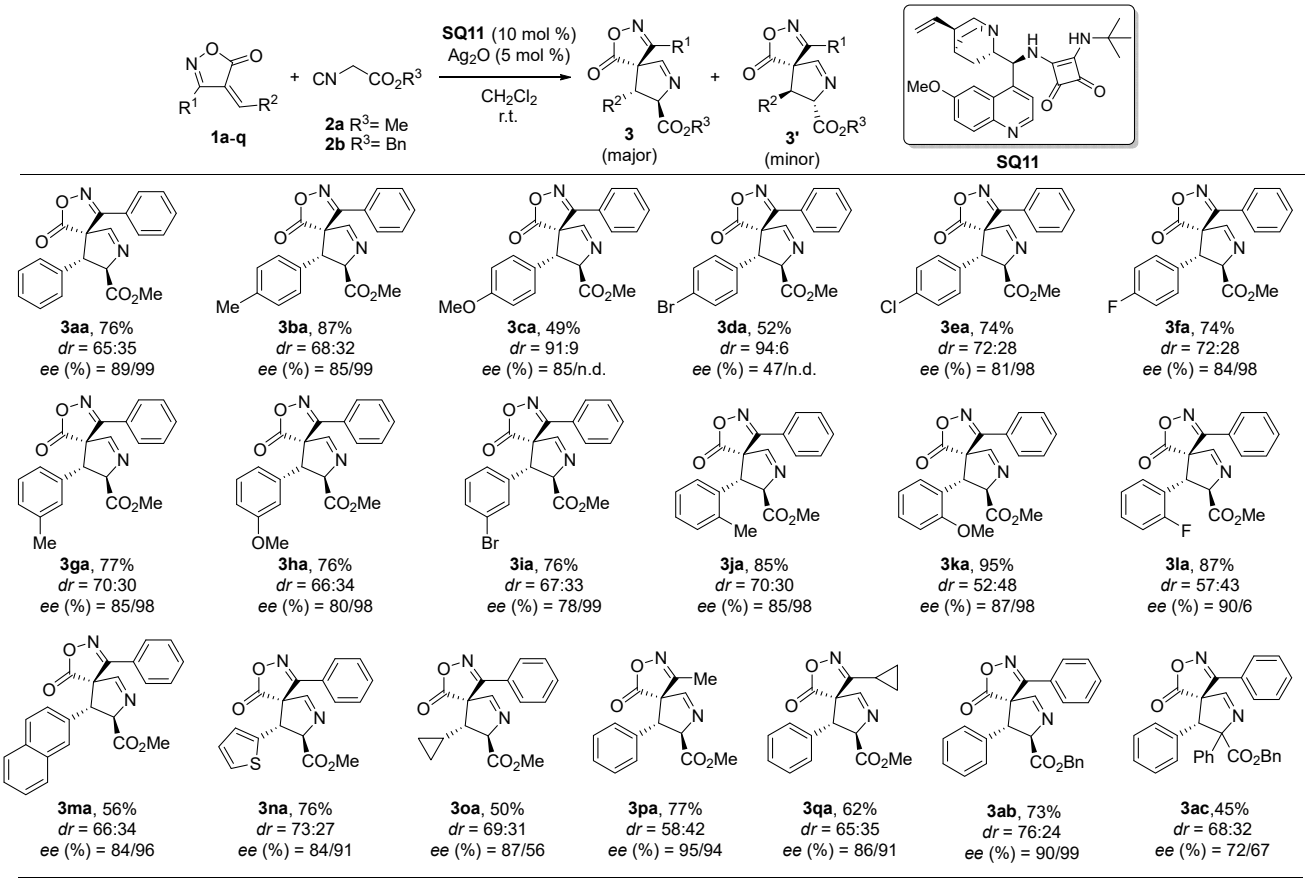
Table 1. Reaction of methyl isocyanoacetate (**2a**) and benzylidene-3-phenylisoxazol-5-one (**1a**). Conditions and catalyst screening.[a]



Entry	cat	Ag_2O	yield (%)	dr[b]	*ee* (%)[c]
1[d]	**T1**	5 mol %	54	91:9	38/60
2[d]	**SQ1**	5 mol %	44	89:11	39/44
3[d]	-	5 mol %	70	95:5	-
4[d]	**T1**	-	18	81:19	57/76
5[d]	**SQ1**	-	12	95:5	85/n.d.
6	**SQ1**	-	traces	n.d	89/n.d.
7	**SQ1**	5 mol %	55	75:25	80/98
8	**T1**	5 mol %	72	95:5	58/n.d.
9	**SQ2**	5 mol %	55	92:8	30/n.d.
10	**SQ3**	5 mol %	48	74:26	75/98
11	**SQ4**	5 mol %	47	79:21	-54/-93
12	**SQ5**	5 mol %	51	74:26	-71-94
13	**SQ6**	5 mol %	47	84:16	52/93
14	**SQ7**	5 mol %	67	84:16	30/95
15	**SQ8**	5 mol %	67	76:24	80/99
16	**SQ9**	5 mol %	71	79:21	80/96
17	**SQ10**	5 mol %	66	81:19	65/95
18[e]	**SQ9**	5 mol %	75	74:26	84/96
19	**SQ11**	5 mol %	76	65:35	89/99

[a] Conditions: **1a** (0.1 mmol), **2a** (0.13 mmol), **cat** (0.01 mmol), Ag_2O, CH_2Cl_2 (5 mL). [b] Determined by ^1H NMR. [c] Determined by HPLC over chiral stationary phases. [d] Reaction carried out in 1 mL of CH_2Cl_2. [e] Reaction carried out in 7.5 mL of CH_2Cl_2.

Table 2. Reaction of arylidene-3-phenylisoxazol-5-ones **1** and isocyanoacetate esters **2**. Reaction scope.[a]



[a] Conditions: **1** (0.25 mmol), **2** (0.33 mmol), **SQ11** (0.025 mmol), Ag_2O (0.0125 mmol), CH_2Cl_2 (19 mL); dr determined by ^1H NMR; *ee* determined by HPLC over chiral stationary phases.

Further investigation revealed that **1a** decomposed in great extent by standing in solution at the reaction concentration, bringing about the low yields observed. We also found out that decomposition rate of **1a** decreased in more diluted solution, unfortunately, the reaction of **1a** with the isocyano ester **2a** also slowed down and led to a small yield of **3aa**, although with high *ee* (Table 1, entry 6). At this point, addition of silver oxide to the diluted reaction accelerated the reaction and allowed to obtain the spirocyclic compound in 55%, with fair diastereoselectivity (75:25), and high enantiomeric excess for both diastereomers, 80% *ee* for the major diastereomer and 98% *ee* for the minor one (Table 1, entry 7). However, performing the reaction under these conditions with thiourea **T1** notably decreased the enantioselectivity (Table 1, entry 8).

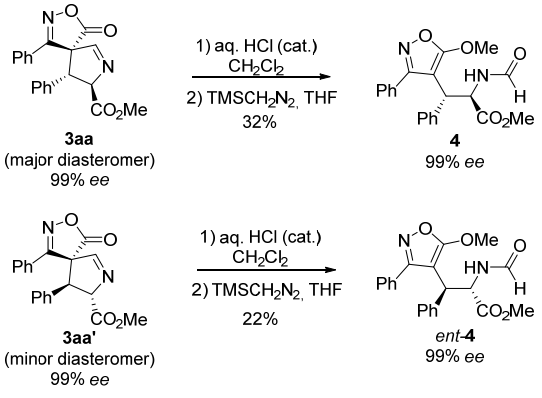
Other solvents and temperatures were tested, but none of these changes improved the results (see SI). Next, we carried out a screening of squaramide catalysts (Table 1, entries 9-17, see also SI). Catalyst **SQ2** derived from dihydroquinine improved the diastereoselectivity, but the enantiomeric excess suffered a dramatic decrease (Table 1, entry 9). Squaramide **SQ3**, derived from cinchonidine, performed with similar diastereoselectivity as **SQ1** but with silightly lower enantioselectivity (Table 1, entry 10). Squaramides **SQ3** and **SQ4**, derived from quinidine and cinchonine, respectively, delivered the opposite enantiomer but with lower enantioselectivity (Table 1, entries 11 and 12). Therefore, we decided to test other squaramides derived from quinine bearing an aniline or benzylamine derivative at the second amide moiety (Table 1, entries 13-17). Squaramides **SQ8**, **SQ9** lead to similar results as **SQ1**, with slightly better diastereoselectivity for **SQ9** (Table 1, entries 7, 15 and 16). At this point, further dilution of the reaction mixture allowed to improve the enantiomeric excess of **3aa** (Table 1, entry 18), despite some decrease of diastereoselectivity. Eventually, squaramide **SQ11** derived from *tert*-butylamine offered the best yield (76%), a slightly decreased diastereoselecivity (65:35), but the highest enantiomeric excess for both diastereomers (89% and 99%, respectively), under diluted conditions (Table 1, entry 19). Further attempts to improve the results by modifying the silver source, catalyst loading or **SQ**/Ag molar ratios were not successful (see SI).

Under the reaction conditions recorded in Table 1, entry 19, we studied the scope of the reaction (Table 2). Methyl isocyanoacetate (**2a**) was reacted with a number of 4-benzylidene-3-phenylisoxazol-5-one derivatives **1a-l** (R^1 = Ph, R^2 = aryl) bearing differently substituted aromatic rings attached to the exocyclic double bond. In general, the spirocyclic products were obtained in moderate to excellent yields, moderate

diastereoselectivities and high enantiomeric excesses in both diastereomers, somehow depending on the position and electronic nature of the substituent. Groups of either electron-donating or electron-withdrawing character at the para position of the phenyl group were tolerated. However, in the case of *p*-halophenyl groups the size and electronegativity of the halide was determinant, the enantioselectivity of the reaction increasing through the series Br<Cl<F (products **3da**, **3ea**, **3fa**).

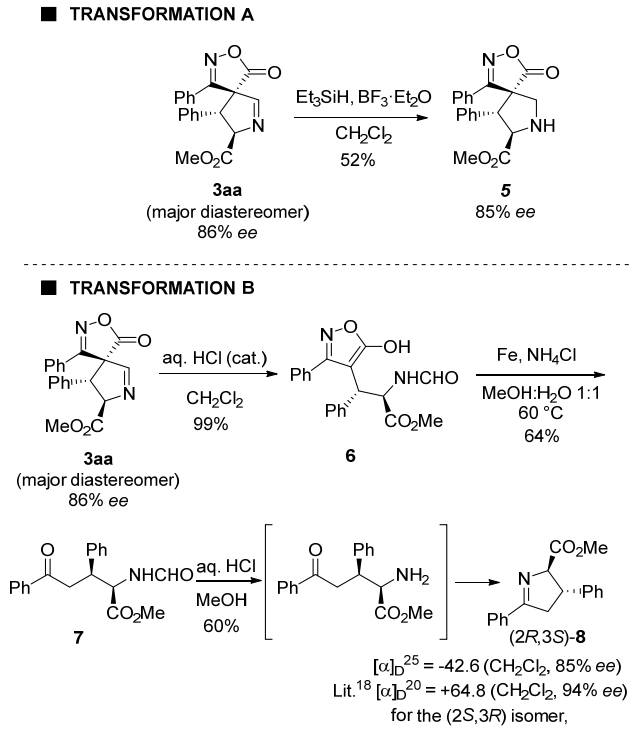
Electron-donating or electron-withdrawing groups at the *meta* (**1g-i**) or *ortho* (**1j-l**) positions were also compatible with the reaction. From these, compounds **1** having an *ortho*-substituted phenyl ring gave better yields although lower diastereomeric ratios, keeping the high enantiomeric excess in all the cases (products **3ja**, **3ka** and **3la**). Furthermore, the isoxazolone derivative can have a bulky naphthyl group (**1m**) providing spirocycle **3ma** with similar results to those obtained with phenyl derivatives.

Finally, compounds **1n** and **1o** bearing a heterocyclic 2-thienyl or a cyclopropyl group also reacted with methyl isocyanoacetate to give the expected products with good enantioselectivity. The substituent at the 3 position of the 4-benzilideneisoxazol-5-one can also be a methyl group, thus compound **1p** (R^1 = Ph, R^2 = Me) reacted with methyl isocyanoacetate providing **3pa** in good yield, fair diastereoselectivity and excellent enantioselectivity for both diastereomers. On the other hand, compound **1q** bearing a cyclopropyl group at this position yielded **3qa** with good results. Finally, benzyl isocyanoacetate (**2b**) could be used instead of methyl isocyanoacetate to give **3ab** upon reaction with **1a** with good results in terms of both diastereo- and enantioselectivity. The reaction can also be performed with α-substituted isocyanides such as methyl 2-isocyano-2-phenylacetate, although in this case the reaction product **3ac** was obtained with low yield (45%) and moderate diastereoselectivity and enantiomeric excess. Compound **3ac** was not stable and decomposed on standing in the NMR tube for a few days.



Scheme 2. Hydrolysis and *O*-methylation of product **3aa**.

It should be remarked that the cycloaddition reaction between the arylidene-3-phenylisoxazol-5-ones **1** and the isocyanoacetate esters **2** only gives two out of the four possible diastereomers. The relative stereochemistry of the two diastereomers produced in the reactions was determined by a combination of NMR experiments and synthetic transformations. Multiple ^1H–^1H nuclear Overhauser effect (NOE) spectroscopy experiments carried on **3ha** showed a *trans* disposition between the methyl ester group and the *m*-methoxyphenyl substituent, as well as a *trans* disposition between the phenyl group bonded to the isoxazol-5-one moiety and the *m*-methoxymethyl group, in the major diastereomer (see SI, Figure S1). A similar relative stereochemistry was assumed for the major diastereomer in all the cycloaddition reactions studied. Furthermore, when both diastereomers of compound **3aa** (**3aa'**) were separated[16] and subjected to hydrolysis and *O*-methylation, they afforded enantiomer products **4** and *ent*-**4**, respectively, without loss of enantiomeric excess (Scheme 2 and also SI). This fact, indicated that both diastereomers **3aa** and **3aa'** had identical configuration at the spiro carbon and opposite configurations at the two other stereogenic centers.



Scheme 3. Synthetic modifications and determination of the absolute stereochemical configuration of **3aa**.

Scheme 3 outlines some synthetic transformations of compound **3aa**. Transformation A shows the selective reduction of the imine group in the pyrrolinic moiety to give the pyrrolidine spirocycle **5** with moderate yield (52%) and preservation of the enantiomeric excess, using triethylsilane and trifluoroborane as a Lewis acid catalyst. Transformation B exploits the transformation potential of the isoxazol-5-one structure and was used to determine the absolute stereochemistry of compound

3aa by chemical correlation with a compound of known stereochemistry **8**. Acidic hydrolysis of the major diastereomer **3aa** gave quantitatively formamide **6**, which was transformed into the amidoketone **7** by reductive cleavage of the isoxazol-5-one ring with iron. [17] Further acidic hydrolysis of the formamide and concomitant cyclization of the intermediate aminoketone afforded pyrroline **8** without loss of enantiomeric excess and in 54% yield over the three steps. Compound **8** obtained in this way was assigned the (2*R*,3*S*) configuration as it showed identical spectroscopical features and opposite optical rotation sign compared with the known compound (2*S*,3*R*)-**8**.[18] Accordingly, the absolute stereochemistry for compound **3aa** (major diastereomer) should be (5*S*,8*R*,9*R*) and for compound **3aa'** (minor diastereomer) it should be (5*S*,8*S*,9*S*). For the remaining compounds **3**, the stereochemistry of both diastereomers was assigned upon the assumption of a uniform stereochemical pathway.[19]

In conclusion, we have developed an efficient, diastereo- and enantioselective synthesis of novel, highly functionalized spirocyclic compounds bearing a spiro quaternary and two tertiary stereocenters. The new spirocycles feature pyrroline and isoxazol-5-one rings, which are privileged structures in medicinal chemistry. The synthesis involved a formal [3+2] cycloaddition reaction between 4-arylideneisoxazol-5-ones and isocyanoacetate esters using a cooperative catalytic system that englobes a bifunctional squaramide/Brønsted base organocatalyst derived from a *Cinchona* alkaloid and silver oxide as Lewis acid. The transformation featured broad scope and simple operation, and delivered the resulting products in good yields, good diastereoselectivity (only two out of four possible diastereomers) and high enantiomeric excess. The potential applicability of the method has been shown by several transformations.

Experimental Section

Experimental procedure for the enantioselective reaction. Methyl isocyanoacetate (**2a**, 30 μL, 0.33 mmol) was added to a solution of 4-arylideneisoxazol-5-one (**1**, 0.25 mmol), organocatalyst **SQ11** (11.9 mg, 0.025 mmol) and silver oxide (2.9 mg, 0.0125 mmol) in dichloromethane (19 mL) protected from light. The reaction was stirred until complete consumption of compound **1** (TLC, *ca.* 12 h). The product **3** was obtained as a two diastereomer mixture after purification by flash chromatography eluting with hexane:EtOAc mixtures.

Acknowledgements

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[19] For a mechanistic proposal and stereochemical model see SI.

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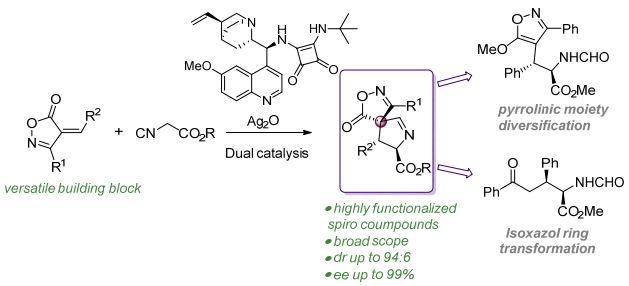

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Supporting Information

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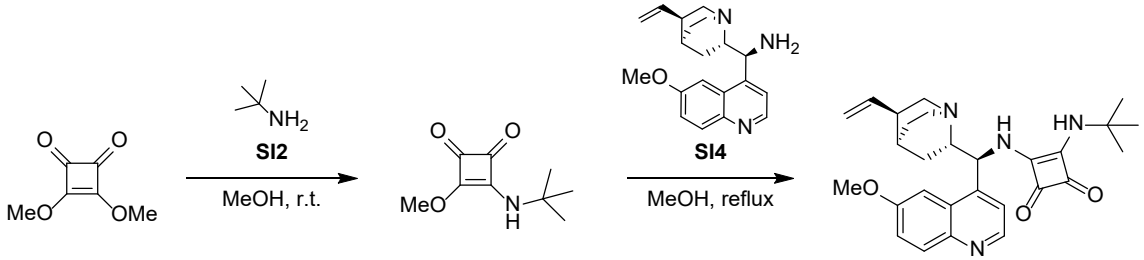
1. Experimental Procedures

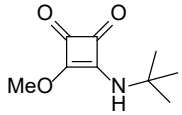
All enantioselective reactions were carried out in round-bottom flasks guarded from light by wrapping them in aluminum foil. Starting materials were obtained from commercial sources. Reactions were monitored by thin-layer chromatography using Silica Gel Merck 60 F_{254} plates (reference 5554 Merck). Eluted TLC plates are observed under 254 nm UV light and then developed with cerium molybdate or potassium permanganate stain solutions. Flash column chromatography was carried out with Silica Gel Merck 60 stationary phase (0,040-0,063 mm particle size, reference 109385 Merck). NMR spectra were recorded at 300 MHz or 400 MHz for ^{1}H, at 75 MHz or 101 MHz for ^{13}C, and at 282 MHz for ^{19}F. Residual non-deuterated solvent signals were used as internal standard (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C in $CDCl_3$, and 2.50 ppm for ^{1}H and 29.84 ppm for ^{13}C in acetone-d_6). Chemical shifts are given in ppm. Carbon multiplicities were assigned through DEPT experiments. High-resolution mass spectra were recorded in a Q-TOF spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV (ESI). Specific optical rotations were measured with a polarimeter equipped with a sodium lamp (D line, 589 nm), concentrations (*c*) are given in g/100 mL. Enantiomeric excess values were measured by HPLC analysis, employing a chromatograph equipped with an UV diode array detector and columns composed of a chiral stationary phase, either of Daicel or Phenomenex brands.

2. Synthesis and characterization data for squaramide SQ11

A two-step procedure is carried out starting from dimethyl squarate for the synthesis of squaramides.



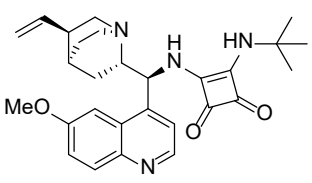
3-(*tert*-Butylamino)-4-methoxycyclobut-3-ene-1,2-dione (SI3)[1]



A modified literature procedure was employed.[1] Dimethyl squarate (**SI1**; 300 mg; 2.11 mmol) was dissolved in 3.2 mL MeOH. *tert*-Butylamine (**SI2**; 222 µL; 2.11 mmol) was then added and the reaction

was stirred for 24 h and followed by TLC analysis. The reaction mixture was purified by flash column chromatography (eluent gradient: Hexane:Et_2O 4:6 and 3:7) to yield 355 mg of **SI3** (92%). White solid; **^{1}H NMR** (400MHz, $CDCl_3$) δ 6.13 (bs, 1H, NH), 4.44 (s, 3H, MeO), 1.39 (s, 9H, ^{t}Bu).

3-(*tert*-Butylamino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (SQ11)[1]

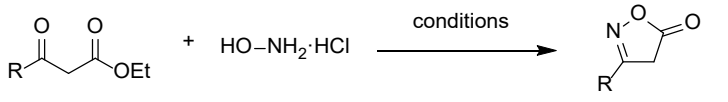


The title compound was synthesized following a modified literature protocol.[1] A solution of **SI3** (216 mg; 1.18 mmol) and 9-deoxy-9-*epi*-9-aminoquinine (**SI4**; 380 mg; 1.18 mmol) in MeOH (3.9 mL) was refluxed for 24 h. A precipitate was observed, and it was filtered and washed with cold MeOH, to obtain, combined with product isolated by flash column chromatography of the mother liquor (eluent gradient: Hexane:AcOEt 2:8, AcOEt:MeOH 9:1 and 8:2), 447 mg (80%) of catalyst **SQ11**. White solid; **^{1}H NMR** (300MHz, $CDCl_3$) δ 8.68 (d, J = 4.5 Hz, 1H, Ar), 8.02 (d, J = 9.2 Hz, 1H, Ar), 7.79 (s, 1H, Ar), 7.54 (d, J = 4.7 Hz, 1H, Ar), 7.40 (dd, J = 9.1, 2.4 Hz, 1H, Ar), 6.82 (bs, 1H, NH), 6.06 (bs, 1H, NH), 5.74 (ddd, J = 17.4, 10.3, 7.4Hz, 1H), 4.97 (d, J = 12.6 Hz, 1H), 4.93 (d, J = 5.9 Hz, 1H), 3.95 (s, 3H, MeO), 3.43 (bs, 2H), 3.13 (dd, J = 13.2, 11.1 Hz, 1H), 2.80–2.56 (m, 2H), 2.24 (bs, 1H), 1.72–1.35 (m, 4H), 1.20 (s, 9H, CH_3), 0.86–0.68 (m, 1H, $CH(CH_3)_3$).

3. Synthesis and characterization data for 4-alkylideneisoxazol-5-ones (1a-q)[2]

All 4-alkylideneisoxazol-5-ones were synthesized via a two-step procedure comprising a condensation reaction between a β-ketoester and hydroxylamine to obtain isoxazole-5-ones, which were subjected to a Knoevenagel condensation with the corresponding aldehyde.

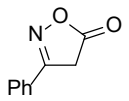
Isoxazol-5-ones



SI5a, R = Ph
SI5b, R = Me
SI5c, R = *c*-Pr

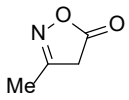
SI6a, R = Ph
SI6b, R = Me
SI6c, R = *c*-Pr

3-Phenylisoxazol-5(4*H*)-one (SI6a)[2]



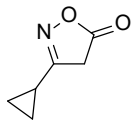
A procedure described in the literature was followed.[2] To a round-bottom flask containing hydroxylamine hydrochloride (4.0 g, 57.8 mmol, 1.0 equiv.) and K_2CO_3 (4.0 g, 28.9 mmol, 0.5 equiv.) was added a 1:1 EtOH:H_2O mixture (55 mL). The mixture was stirred for 5 min and ethyl benzoylacetate was added (**SI5a**, 10 mL, 57.8 mmol, 1.0 equiv.) After 20 h an abundant amount of precipitate was observed, which was filtered and washed with cold water to yield product **SI6a** (9.3 g, 99%), which was used without further purification. **^{1}H NMR** (300MHz, $CDCl_3$) δ 7.65–7.61 (m, 3H, Ar), 7.58–7.44 (m, 2H, Ar), 3.81 (s, 2H, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.7 (C, C=O), 163.0 (C, C=N), 132.2 (CH, Ar), 129.2 (CH, Ar), 127.6 (C, Ar), 126.6 (CH, Ar), 34.0 (CH_2).

3-Methylisoxazol-5(4*H*)-one (SI6b)[3]



A literature procedure was followed.[3] To a suspension of hydroxylamine hydrochloride (4.3 g, 62.4 mmol, 1.5 equiv.) in EtOH (80 mL) was added anhydrous sodium acetate (5.1 g, 62.4 mmol, 1.5 equiv.) and the mixture was stirred for 5 min. Ethyl acetoacetate (**SI5b**, 5.3 mL, 41.6 mmol, 1.0 equiv.) was added and the reaction was heated to reflux. After 1 h the complete consumption of the ethyl acetoacetate was observed (TLC), as well as the presence of the desired product and the oxime-type intermediate. 0.2 mL HCl 37% were added at room temperature and the reaction was brought again to reflux until complete consumption of the oxime intermediate (TLC, *ca*. 4 h). The reaction was filtered by gravity to remove the formed NaCl and the filtrate was concentrated under reduced pressure. The reaction crude was suspended in AcOEt, and a white precipitate appeared, which was filtered by gravity. The filtrate was concentrated under reduced pressure and purified through flash column chromatography (eluent gradient: Hexane:AcOEt 8:2, 7:3 and 5:5) to obtain 1.3 g of **SI6b** (32%). Oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.39 (q, J = 0.9 Hz, 2H, CH_2), 2.15 (d, J = 0.9 Hz, 3H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.2 (C, C=O), 163.4 (C, C=N), 37.0 (CH_3), 14.8 (CH_2).

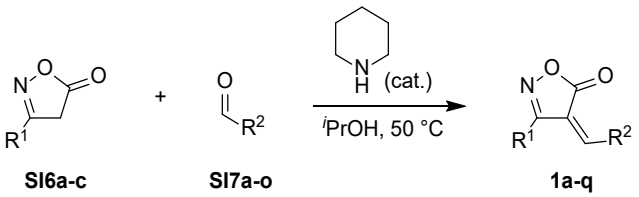
3-cyclopropylisoxazol-5(4H)-one (SI6c)[4]



A literature procedure was followed.[4] A mixture of hydroxylamine hydrochloride (1.1 g, 15.7 mmol) and methyl 3-cyclopropyl-3-oxopropanoate (**SI5c**, 1.7 mL, 14.1 mmol) was stirred for 5 min. Et_3N (2.2 mL, 15.7 mmol) was then added dropwise and the reaction was refluxed for 1.5 h. The

reaction was allowed to cool to room temperature and concentrated under reduced pressure. Purification by flash column chromatography afforded 1.46 g (83%) of **SI6c**. Oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.25 (t, J = 0.5 Hz, 2H, CH_2CO), 1.85–1.78 (m, 1H, ^{c}Pr), 1.09–1.06 (m, 2H, ^{c}Pr), 0.91-0.86 (m, 2H, ^{c}Pr); **^{13}C NMR** (75 MHz, CDCl3) δ 175.0 (C, C=O), 168.9 (C, C=N), 34.2 (CH_2, CH_2CO), 10.1 (CH, ^{c}Pr), 7.39 (CH2, ^{c}Pr).

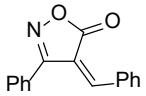
4-Alkylideneisoxazol-5-ones



SI6a-c **SI7a-o** **1a-q**

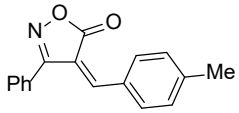
General procedure: According to a literature procedure,[3] to a 0.5 M solution of isoxazol-5-one **SI6** in ^{i}PrOH was added the aldehyde **SI7** (1.2 equiv.) Piperidine was then added (5 µL/mmol **SI6**) and the reaction was stirred at 50 °C. The reaction was monitored by TLC until complete consumption of the starting material. The mixture was allowed to stand at room temperature. In some cases, precipitation of the product was immediately observed, while in other cases it was necessary to keep the reaction overnight in the freezer until the product crashed out of the solution. The solid was filtered and washed with cold pentane.

(*Z*)-4-Benzylidene-3-phenylisoxazol-5(4*H*)-one (1a)[3]



From **SI6a** (2.16 g, 13.4 mmol) and benzaldehyde (1.64 mL, 16.1 mmol), 2.75 g (82%) of compound **1a** were obtained. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.32 (d, J = 8.8 Hz, 2H, Ar), 7.68–7.45 (m, 9H, Ar+CH=C); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.2 (C, C=O), 164.2 (C, C=N), 152.9 (CH), 134.3 (CH), 134.1 (CH), 132.5 (C), 131.2 (CH), 129.5 (CH), 129.1 (CH), 128.9 (CH), 127.5 (C), 119.0 (C).

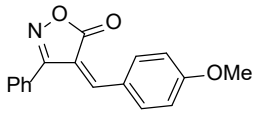
(*Z*)-4-(4-Methylbenzylidene)-3-phenylisoxazol-5(4*H*)-one (1b)[5]



From **SI6a** (0.31 g, 1.9 mmol) and *p*-tolualdehyde (0.27 mL, 2.3 mmol), 0.32 g of compound **1b** were obtained. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.25 (d, J = 8.3 Hz, 2H, Ar), 7.63–7.52 (m, 6H, Ar+CH=C), 7.32 (d, J = 8.4 Hz, 2H, Ar), 2.45 (s, 3H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.5 (C,

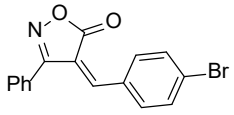
C=O), 164.3 (C, C=N), 152.9 (CH), 146.1 (C), 134.5 (CH), 131.1 (CH), 130.2 (CH), 130.0 (C), 129.4 (CH), 128.9 (CH), 127.66 (C), 117.63 (C), 22.2 (CH_3).

(*Z*)-4-(4-Methoxybenzylidene)-3-phenylisoxazol-5(4*H*)-one (1c)[6]



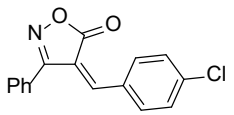
From **SI6a** (1.00 g, 6.2 mmol) and *p*-anisaldehyde (0.9 mL, 7.45 mmol), 0.59 g (34%) of compound **1c** were obtained. **^{1}H NMR** (300 MHz, Acetone-d_6) δ 8.55 (d, J = 8.8 Hz, 2H, Ar), 7.75 (1H, CH=C), 7.73–7.66 (m, 2H, Ar), 7.65–7.57 (m, 3H, Ar), 3.96 (s, 3H, MeO); **^{13}C NMR** (75 MHz, Acetone-d_6) δ 169.7 (C, C=O), 165.8 (C, C=N), 165.2 (C), 153.2 (CH), 138.1 (CH), 131.5 (CH), 130.0 (CH), 129.7 (CH), 128.9 (C), 127.0 (C), 115.9 (C), 115.3 (CH), 56.2 (CH_3).

(*Z*)-4-(4-Bromobenzylidene)-3-phenylisoxazol-5(4*H*)-one (1d)[7]



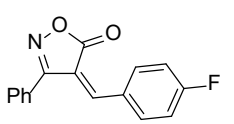
From **SI6a** (0.40 g, 2.5 mmol) and 4-bromobenzaldehyde (551 mg, 2.98 mmol), 0.55 g (67%) of compound **1d** were obtained. **^{1}H NMR** (300MHz, $CDCl_3$) δ 8.20 (d, J = 8.6 Hz, 2H, Ar), 7.65 (d, J = 8.7 Hz, 2H, Ar), 7.61–5.55 (m, 5H, Ar), 7.53 (1H, CH=C); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.1 (C, C=O), 164.0 (C, C=N), 151.2 (CH), 135.3 (CH), 132.6 (CH), 131.3 (CH), 131.3 (C), 129.7 (C), 129.5 (CH), 128.9 (CH), 127.3 (C), 119.5 (C).

(*Z*)-4-(4-Chlorobenzylidene)-3-phenylisoxazol-5(4*H*)-one (1e)[6]



From **SI6a** (0.68 g, 0.4 mmol) and 4-chlorobenzaldehyde (0.67 g, 0.48 mmol), 2.54 g (86%) of compound **1e** were obtained. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.29 (d, J = 8.8 Hz, 2H, Ar), 7.64–7.56 (m, 5H, Ar), 7.55 (1H, CH=C), 7.48 (d, J = 8.7 Hz, 2H, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.0 (C, C=O), 163.9 (C, C=N), 150.9 (CH), 140.7 (C), 135.2 (CH), 131.1 (CH), 130.7 (C), 129.4 (CH), 129.3 (CH), 128.7
(CH), 127.1 (C), 119.2 (C).

(*Z*)-4-(4-Fluorobenzylidene)-3-phenylisoxazol-5(4*H*)-one (1f)[8]



From **SI6a** (0.40 g, 2.48 mmol) and 4-fluorobenzaldehyde (0.31 mL, 2.98 mmol), 0.44 g (66%) of compound **1f** were obtained. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 8.7, 5.4 Hz, 2H, Ar), 7.65–7.54 (m, 6H, Ar+CH=C), 7.19 (dd, J = 8.8, 8.4Hz, 2H, Ar); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.3 (C, C=O), 166.2 (d, C, $^1J_{C\text{-}F}$ = 259.8 Hz), 164.1 (C, C=N), 151.3 (CH), 137.1 (d, CH, $^3J_{C\text{-}}$

$_F$ = 9.5 Hz), 131.2 (CH), 129.5 (CH), 129.1 (C), 128.9 (CH), 127.4 (C), 118.4 (d, C, $^4J_{C\text{-}F}$ = 2.4 Hz), 116.6 (d, CH, $^2J_{C\text{-}F}$ = 21.9 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −100.93 (tt, *J* = 8.2, 5.4 Hz).

(*Z*)-4-(3-Methylbenzylidene)-3-phenylisoxazol-5(4*H*)-one (1g)[9]

From **SI6a** (0.40 g, 2.48 mmol) and *m*-tolualdehyde (0.35 mL, 2.98 mmol), 0.27 g (41%) of **1g** were obtained. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.30 (td, *J* = 4.7, 1.9 Hz, 1H, Ar), 8.08 (s, 1H, CH=C), 7.65–7.51 (m, 6H, Ar), 7.41 (d, *J* = 4.5 Hz, 2H, Ar), 2.42 (s, 3H, CH_3); **^{13}C NMR** (75 MHz. $CDCl_3$) δ 168.2 (C, C=O), 164.2 (C, C=N), 153.2 (CH), 138.9 (C), 135.3 (CH), 134.8 (CH), 132.5 (C), 131.3 (CH), 131.1 (CH), 129.4 (CH), 128.9 (CH), 128.4 (CH), 127.6 (C), 118.6 (C), 21.4 (CH_3).

(*Z*)-4-(3-Methoxybenzylidene)-3-phenylisoxazol-5(4*H*)-one (1h)[10]

From **SI6a** (0.40 g, 2.48 mmol) and *m*-anisaldehyde (0.36 mL, 2.98 mmol), 0.39 g (57%) of **1h** were obtained. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.31 (t, *J* = 2.0 Hz, 1H, Ar), 7.67–7.50 (m, 7H, Ar+CH=C), 7.39 (t, *J* = 8.0 Hz, 1H, Ar), 7.16 (ddd, *J* = 8.4, 2.4, 0.6 Hz, 1H, Ar), 3.90 (s, 3H, MeO); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.3 (C, C=O), 164.2 (C, C=N), 159.9 (C), 153.0 (CH), 133.8 (C), 131.2 (CH), 129.9 (CH), 129.4 (CH), 128.9 (CH), 127.7 (CH), 127.5 (C), 121.9 (CH), 118.9 (C), 116.8 (CH), 55.7 (CH_3).

(*Z*)-4-(3-bromobenzylidene)-3-phenylisoxazol-5(4*H*)-one (1i)

From **SI6a** (1.0 g, 6.21 mmol) and 3-bromobenzaldehyde (0.88 mL, 7.45 mmol), 0.36 g (17%) of **1i** were obtained.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (t, *J* = 1.8 Hz, 1H, Ar), 8.34 (d, *J* = 7.9 Hz, 1H, Ar), 7.70 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H, Ar), 7.52 (s, 1H, CH=C), 7.39 (t, *J* = 7.9 Hz, 1H, Ar); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.8 (C, C=O), 163.9 (C, C=O), 150.7 (C, C=N), 136.8 (CH), 136.3 (CH), 134.1 (C), 132.1 (CH), 131.3 (CH), 130.6 (CH), 129.5 (CH), 128.8 (CH), 127.1 (C), 123.0 (C), 120.4 (C);); **HRMS** (ESI) *m/z*: 327.9971 $[M+H]^+$, $C_{16}H_{11}BrNO_2^+$ requires 327.9968.

(*Z*)-4-(2-Methylbenzylidene)-3-phenylisoxazol-5(4*H*)-one (1j)[10]

From **SI6a** (0.40 g, 2.48 mmol) and 2-methylbenzaldehyde (0.34 mL, 2.98 mmol), 0.34 g (52%) of **1j** were obtained. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.55 (d, J = 7.7 Hz, 1H, Ar), 8.00 (s, 1H, CH=C), 7.68–7.52 (m, 5H, Ar), 7.45 (td, J = 7.4, 1.4 Hz, 1H, Ar), 7.34 (t, J = 7.3 Hz, 1H, Ar), 7.27 (d, J = 6.9 Hz, 1H, Ar), 2.35 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.0 (C, C=O), 163.8 (C, C=N), 150.5 (CH),140.6 (C),133.9 (CH), 132.1 (CH), 131.2 (CH), 130.9 (CH), 130.7 (C), 129.4 (CH), 128.7 (CH), 127.5 (C), 126.4 (CH), 118.8 (C), 20.3 (CH_3).

(*Z*)-4-(2-Methoxybenzylidene)-3-phenylisoxazol-5(4*H*)-one (1k)[9]

From **SI6a** (0.40 g, 2.48 mmol) and *o*-anisaldehyde (405 mg, 2.98 mmol), 0.48 g (70%) of **1k** were obtained. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.86 (dd, J = 8.0, 1.7 Hz, 1H, Ar), 8.25 (s, 1H, CH=C), 7.66–7.60 (m, 2H, Ar), 7.59–7.52 (m, 4H, Ar), 7.08 (dddd, J = 7.9, 7.4, 1.1, 0.5 Hz, 1H, Ar), 6.93 (dd, J = 8.5, 1.0 Hz, 1H, Ar), 3.84 (s, 3H, MeO); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6 (C, C=O), 164.3 (C, C=N), 160.1 (C), 147.4 (CH), 136.6 (CH), 133.5 (CH), 131.0 (CH), 129.3 (CH), 128.8 (CH), 127.8 (C), 121.4 (C), 120.8 (CH), 117.3 (C), 110.8 (CH), 56.0 (CH_3).

(*Z*)-4-(2-fluorobenzylidene)-3-phenylisoxazol-5(4*H*)-one (1l)

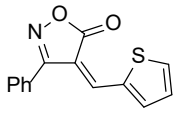
From **SI6a** (0.50 g, 3.10 mmol) and 2-fluorobenzaldehyde (0.4 mL, 3.72 mmol), 0.22 g (26%) if **1l** were obtained. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.95 (td, J = 7.9, 1.7 Hz, 1H, Ar), 7.66–7.53 (m, 6H, Ar), 7.33 (dt, J = 7.8, 0.9, 1H, Ar), 7.15 (ddd, J = 10.4, 8.4, 1.1 Hz, 1H, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.9 (C, C=O), 163.9 (C, C=N), 162.6 (d, C, $^1J_{C\text{-}F}$ = 257.3 Hz), 143.3 (d, CH, $^3J_{C\text{-}F}$ = 7.8 Hz), 136.5 (d, CH, $^3J_{C\text{-}F}$ = 9.4 Hz), 133.4 (CH), 131.3 (CH), 129.5 (CH), 128.8 (CH), 127.2 (C), 124.8 (d, CH, $^3J_{C\text{-}F}$ = 3.7 Hz), 120.7 (C), 120.3 (d, C, $^2J_{C\text{-}F}$ = 37.7 Hz), 115.8 (d, CH, $^2J_{C\text{-}F}$ = 22.0 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -110.59 (s); **HRMS** (ESI) *m/z*: 268.0761 $[M+H]^+$, $C_{16}H_{11}FNO_2^+$ requires 268.0768.

(*Z*)-4-(Naphthalen-2-ylmethylene)-3-phenylisoxazol-5(4*H*)-one (1m)

From **SI6a** (0.40 g, 2.48 mmol) and 2-naphthaldehyde (465 mg, 2.98 mmol), 0.52 g (70%) of **1m** were obtained. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.81 (s, 1H, Ar), 8.46 (dd, J = 8.7, 1.8 Hz, 1H, Ar), 7.96 (d, J = 8.2 Hz, 1H, Ar), 7.92 (d, J = 8.7 Hz, 1H, Ar), 7.88 (d, J = 8.0 Hz, 1H, Ar), 7.76 (s,

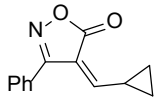
1H, CH=C), 7.68–7.51 (m, 7H, Ar); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.4 (C, C=O), 164.3 (C, C=N), 152.8 (CH), 137.2 (CH), 135.9 (C), 132.9 (C), 131.2 (CH), 130.3 (C), 130.1 (CH), 129.8 (CH), 129.5 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.0 (CH), 127.6 (C), 127.2 (CH), 118.7 (C); **HRMS** (ESI) *m/z*: 300.1023 $[M+H]^+$, $C_{20}H_{14}NO_2^+$ requires 300.1019.

(*Z*)-3-Phenyl-4-(thiophen-2-ylmethylene)isoxazol-5(4*H*)-one (1n)[11]



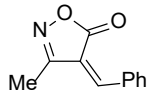
From **SI6a** (0.60 g, 3.72 mmol) and thiophene-2-carbaldehyde (0.41 mL, 4.47 mmol), 0.68 g (71%) of **1n** were obtained. Intense yellow solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, J = 3.8 Hz, 1H, Ar), 7.97 (dt, J = 5.0, 0.8 Hz, 1H, Ar), 7.78 (s, 1H, CH=C), 7.64–7.53 (m, 5H, Ar), 7.27 (dd, J = 5.2, 4.0 Hz, 1H, Ar); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.1 (C, C=O), 163.5 (C, C=N), 142.2 (CH), 141.6 (CH), 140.3 (CH), 136.8 (C), 131.1 (CH), 129.5 (CH), 129.0 (CH), 128.6 (CH), 127.7 (C), 113.59 (C).

(*Z*)-4-(Cyclopropylmethylene)-3-phenylisoxazol-5(4*H*)-one (1o)[12]



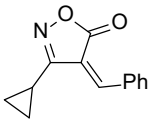
From **SI6a** (0.40 g, 2.48 mmol) and cyclopropane-carbaldehyde (0.22 mL, 2.98 mmol), 0.32 g (60%) of **1o** were obtained. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55-7.46 (m, 5H, Ar), 6.50 (d, J = 11.5 Hz, 1H, CH=C), 3.31 (dddd, J = 12.2, 11.5, 7.8, 4.4 Hz, 1H, ^{c}Pr), 1.49–1.42 (m, 2H, ^{c}Pr), 1.03–0.98 (m, 2H, ^{c}Pr); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.1 (C, C=O), 166.2 (CH), 161.2 (C, C=N), 131.0 (CH), 129.3 (CH), 128.3 (CH), 127.5 (C), 118.8 (C), 14.9 (CH), 13.7 (CH_2).

(*Z*)-4-Benzylidene-3-methylisoxazol-5(4*H*)-one (1p)[6]



Combined product of precipitation and flash column chromatography of the mother liquor (eluent gradient: Hexane:AcOEt 9.1, 8:2 and 6:4). From **SI6b** (1.31 g, 13.2 mmol) and benzaldehyde (1.61 mL, 15.8 mmol), 1.04 (42%) of **1p** were obtained. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.35 (d, J = 7.1 Hz, 2H, Ar), 7.63–7.47 (m, 3H, Ar), 7.43 (s, 1H, CH=C), 2.30 (s, 3H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.0 (C, C=O), 161.2 (C, C=N), 150.0 (CH), 134.1 (CH), 133.9 (CH), 132.4 (C), 129.2 (CH), 119.8 (C), 11.8 (CH_3).

(*Z*)-4-Benzylidene-3-cyclopropylisoxazol-5(4*H*)-one (1q)



From **SI6c** (0.44 g, 3.52 mmol) and benzaldehyde (0.43 mL, 4.2 mmol), 0.38 g (72%) of **1q** were obtained. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.37 (d, J = 6.9 Hz, 2H, Ar), 7.70 (s, 1H, CH=C), 7.63–7.46 (m, 3H, Ar), 1.84–1.74 (m, 1H, ^{c}Pr), 1.13–1.04 (m, 4H, ^{c}Pr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.4 (C, C=O), 165.3 (C, C=N), 149.9 (CH), 134.0 (CH), 133.9 (CH), 132.5 (C), 129.1 (CH), 120.0 (C), 6.6 (CH), 6.2 (CH_2); **HRMS** (ESI) *m/z*: 236.0691 $[M+Na]^+$, $C_{13}H_{11}NaNO_2^+$ requires 236.0682.

4. Synthesis and characterization data for products 3

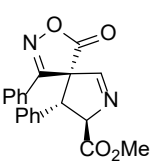
Enantioselective procedure

Methyl isocyanoacetate (**2a**, 30 μL, 0.33 mmol) was added to a solution of 4-arylideneisoxazol-5-one (**1**, 0.25 mmol), organocatalyst **SQ11** (11.9 mg, 0.025 mmol) and silver oxide (2.9 mg, 0.0125 mmol) in dichloromethane (19.2 mL), protected from light.[13] The reaction was stirred until complete consumption of compound **1** (TLC, *ca.* 12 h). The product **3** was obtained as a two diastereomer mixture after purification by flash chromatography, eluting with hexane:EtOAc mixtures.

Non-enantioselective procedure

A similar procedure was followed using 4-alkylideneisoxazol-5-one (**1**, 0.1 mmol), silver oxide (1.2 mg, 0.005 mmol) and methyl isocyanoacetate (**2a**, 12 μL, 0.13 mmol) in dichloromethane (1.0 mL) in the absence of **SQ11**. The reaction was stirred for 12 h and the product **3** was purified via flash chromatography, eluting with hexane:EtOAc mixtures.

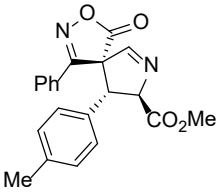
Methyl (5*S*,8*R*,9*R*)-1-oxo-4,9-diphenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (3aa)



39.9 mg (76%) of **3aa** were obtained from **1a** (62.3 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 89%, minor diastereomer: 98%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 18.6 min, minor enantiomer: t_r = 23.5 min, **minor diastereomer**: major enantiomer: t_r = 28.6 min, minor enantiomer: t_r = 32.4 min.

Orange oil; $[\alpha]_D^{25}$ –27.4 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, dr 65:35); **major 3aa**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81–7.72 (m, 3H, Ar+CH=N), 7.66–7.51 (m, 3H, Ar), 7.34–7.23 (m, 3H, Ar), 7.12–7.04 (m, 2H, Ar), 5.57 (dd, *J* = 10.3, 3.0 Hz, 1H, CHN), 4.43 (d, *J* = 10.3 Hz, 1H, CHPh), 3.37 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C, C=O), 170.5 (C, C=O), 163.5 (C, C=N), 160.3 (CH, CH=N), 132.7 (CH), 131.1 (C), 129.9 (CH), 129.2 (CH), 129.1 (CH), 128.2 (CH), 127.3 (CH), 126.3 (C), 76.2 (CH), 71.7 (C), 55.7 (CH), 53.1 (CH_3); **minor 3aa'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.76 (d, *J* = 2.9 Hz, 1H, CH=N), 7.48–7.38 (m, 2H, Ar), 7.21–7.13 (m, 2H, Ar), 7.04–6.97 (m, 3H, Ar), 6.77–6.68 (m, 3H, Ar), 5.20 (dd, *J* = 10.0, 3.1 Hz, 1H, CHN), 4.53 (d, *J* = 10.0 Hz, 1H, CHPh), 3.79 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.3 (C, C=O), 169.5 (C, C=O), 163.0 (C, C=N), 159.4 (CH, CH=N), 131.9 (CH), 131.5 (C), 129.2 (CH), 128.8 (CH), 128.5 (CH), 128.5 (CH), 127.4 (CH), 126.8 (C), 77.0 (CH), 71.5 (C), 56.4 (CH), 53.2 (CH_3); **HRMS** (ESI) *m/z*: 367.1291 $[M+H_3O]^+$, $C_{20}H_{19}N_2O_5^+$ requires 367.1288.

Methyl (5*S*,8*R*,9*R*)-1-oxo-4-phenyl-9-(*p*-tolyl)-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (3ba)

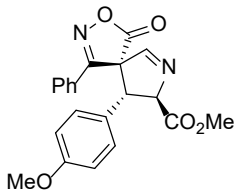


78.6 mg (87%) of **3ba** were obtained from **1b** (65.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 85%, minor diastereomer: 99%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 20.8 min, minor enantiomer: t_r = 22.4 min, **minor diastereomer**: major enantiomer: t_r = 30.4 min, minor enantiomer: t_r = 34.1 min.

Orange oil; $[\alpha]_D^{25}$ +2.4 (*c* 1.1, $CHCl_3$, for the diastereomeric mixture, dr 68:32); **major 3ba**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79–7.72 (m, 3H, Ar+C=N), 7.65–7.50 (m, 3H, Ar), 7.10 (d, *J* = 8.0 Hz, 2H, Ar), 6.98 (d, *J* = 8.1 Hz, 2H, Ar), 5.54 (dd, *J* = 10.3, 3.0 Hz, 1H. CHN), 4.40 (d, *J* = 10.3 Hz, 1H, CHAr), 3.77 (s, 3H, MeO), 2.29 (s, 3H, MeAr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.5 (C, C=O), 170.6 (C, C=O), 163.5 (C, C=N), 160.4 (CH, CH=N), 139.0 (C), 132.7 (CH), 129.9 (CH), 129.9 (CH), 128.1 (CH), 127.9 (C), 127.3 (CH), 126.4 (C), 76.3 (CH), 71.8 (C), 55.6 (CH), 53.1 (CH_3), 21.2 (CH_3); **minor 3ba'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.77 (d, *J* = 3.0 Hz, 1H, CH=N), 7.49–7.40 (m, 3H, Ar), 7.30 (d, *J* = 8.0 Hz, 2H, Ar), 6.88 (d, *J* = 7.9 Hz, 2H, Ar), 6.81 (d, *J* = 8.0 Hz, 2H, Ar), 5.16 (dd, *J* = 10.1, 3.1 Hz, 1H, CHN), 4.48 (d, *J* = 10.1 Hz, 1H, CHAr), 3.78 (s, 3H, MeO),

2.24 (s, 3H, MeAr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.3 (C, C=O), 169.5 (C, C=O), 163.0 (C, C=N), 159.5 (CH, CH=N), 138.4 (C), 131.8 (CH), 129.4 (CH), 129.1 (CH), 128.6 (C), 128.3 (C), 127.4 (CH), 126.9 (CH), 77.4 (CH), 71.5 (C), 56.5 (CH), 53.1 (CH_3), 21.1 (CH_3); **HRMS** (ESI) *m/z*: 381.1449 $[M+H_3O]^+$, $C_{21}H_{21}N_2O_5^+$ requires 381.1445.

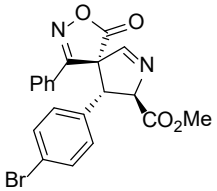
Methyl (5*S*,8*R*,9*R*)-9-(4-methoxyphenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]-nona-3,6-diene-8-carboxylate (3ca)



46.2 mg (49%) of **3ca** were obtained from **1c** (69.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 85%, minor diastereomer: n.d.) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 26.3 min, minor enantiomer: t_r = 28.4 min.

Orange oil; $[\alpha]_D^{25}$ –56.6 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, dr 91:9); **major 3ca**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80–7.72 (m, 3H, Ar+CH=N), 7.65–7.51 (m, 3H, Ar), 7.02 (d, *J* = 8.7 Hz, 2H, Ar), 6.82 (d, *J* = 8.8 Hz, 2H, Ar), 5.50 (dd, *J* = 10.4, 2.9 Hz, 1H, CHN), 4.39 (d, *J* = 10.3 Hz, 1H, CHAr), 3.78 (s, 3H, MeO), 3.77 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.5 (C, C=O), 170.6 (C, C=O), 163.5 (C, C=N), 160.4 (CH, CH=N), 160.1 (C), 132.7 (CH), 129.9 (CH), 129.5 (CH), 127.3 (CH), 126.4 (C), 122.6 (C), 114.6 (CH), 76.4 (CH), 71.8 (C), 55.6 (CH), 55.3 (CH_3), 53.1 (CH_3); **minor 3ca'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.50–7.41 (m, 2H, Ar), 7.34–7.28 (m, 3H, Ar), 7.08 (d, *J* = 7.2 Hz, 2H, Ar), 6.63 (d, *J* = 7.2 Hz, 2H, Ar), 5.13 (dd, *J* = 10.1, 3.1 Hz, 1H, CHN), 4.47 (d, *J* = 10.1 Hz, 1H, CHAr), 3.79 (s, 3H, MeO), 3.72 (s, 3H, MeO); **HRMS** (ESI) *m/z*: 397.1399 $[M+H_3O]^+$, $C_{21}H_{21}N_2O_6^+$ requires 397.1394.

Methyl (5*S*,8*R*,9*R*)-9-(4-bromophenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]-nona-3,6-diene-8-carboxylate (3da)

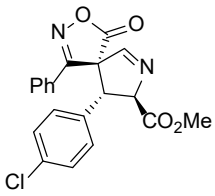


56.0 mg (52%) of **3da** were obtained from **1d** (82.0 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 47%, minor diastereomer: n.d) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 16.1 min, minor enantiomer: t_r = 19.2 min.

Orange oil; $[\alpha]_D^{25}$ –18.8 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, dr 94:6); **major 3da**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77–7.72 (m, 3H, Ar+CH=N), 7.65–7.53 (m, 3H,

Ar), 7.43 (d, J = 8.5 Hz, 2H), 6.97(d, J = 8.3 Hz, 2H), 5.50 (dd, J = 10.3, 3.0 Hz, 1H, CHN), 4.36 (d, J = 10.3 Hz, 1H, CHAr), 3.79 (s, 3H, MeO); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.3 (C, C=O), 170.3 (C, C=O), 163.3 (C, C=N), 160.2 (CH, CH=N), 132.9 (CH), 132.5 (CH), 130.1 (CH), 130.0 (C), 130.0 (CH), 127.3 (CH), 126.2 (C), 123.5 (C), 76.4 (CH), 71.6 (C), 55.2 (CH), 53.2 (CH_3); **minor 3da'**: **^{1}H NMR** (400 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 5.15 (dd, J = 10.0, 3.1 Hz, 1H, CHN), 4.44 (d, J = 10.0 Hz, 1H, CHAr), 3.80 (s, 3H, MeO); **HRMS** (ESI) *m/z*: 445.0384, 447.0367 $[M+H_3O]^+$, $C_{20}H_{18}BrN_2O_5^+$ requires 445.0394, 447.0373.

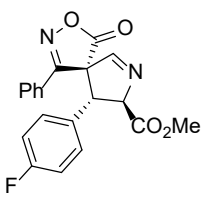
Methyl (5*S*,8*R*,9*R*)-9-(4-chlorophenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]-nona-3,6-diene-8-carboxylate (3ea)



70.6 mg (74%) of **3ea** were obtained from **1e** (70.9 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 81%, minor diastereomer: 98%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 14.8 min, minor enantiomer: t_r = 17.1 min, **minor diastereomer**: major enantiomer: t_r = 25.5 min, minor enantiomer: t_r = 27.7 min.

Orange oil; $[\alpha]_D^{25}$ +2.1 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, dr 72:28); **major 3ca**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78–7.71 (m, 3H, Ar+CH=N), 7.62–7.52 (m, 3H, Ar), 7.28 (d, J = 8.6 Hz, 2H, Ar), 7.03 (d, J = 8.5 Hz, 2H, Ar), 5.50 (dd, J = 10.2, 3.0 Hz, 1H, CHN), 4.38 (d, J = 10.3 Hz, 1H, CHAr), 3.79 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.3 (C, C=O), 170.3 (C, C=O), 163.3 (C, C=N), 160.2 (CH, CH=N), 135.3 (C), 132.9 (CH), 130.0 (CH), 129.7 (CH), 129.6 (C), 129.5 (CH), 127.3 (CH), 126.2 (C), 76.4 (CH), 71.6 (C), 55.1 (CH), 53.2 (CH_3); **minor 3ca'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.73 (d, J = 8.0 Hz, 2H, Ar), 6.66 (d, J = 8.3 Hz, 2H, Ar), 5.15 (dd, J = 10.3, 3.1 Hz, 1H, CHN), 4.46 (d, J = 10.0 Hz, 1H, CHAr), 3.80 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.1 (C, C=O), 169.3 (C, C=O), 162.7 (C, C=N), 159.4 (CH, CH=N), 134.6 (C), 132.1 (CH), 130.1 (C), 129.4 (CH), 129.0 (CH), 128.9 (CH), 128.4 (C), 126.8 (CH), 77.4 (CH), 71.3 (C), 55.9 (CH), 53.3 (CH_3); **HRMS** (ESI) *m/z*: 401.0890 $[M+H_3O]^+$, $C_{20}H_{18}ClN_2O_5^+$ requires 401.0899.

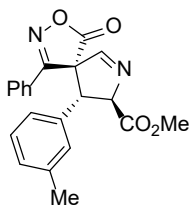
Methyl (5*S*,8*R*,9*R*)-9-(4-fluorophenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]-nona-3,6-diene-8-carboxylate (3fa)



68.1 mg (74%) of **3fa** were obtained from **1f** (66.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 84%, minor diastereomer: 98%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 16.2 min, minor enantiomer: t_r = 18.9 min, **minor diastereomer**: major enantiomer: t_r = 28.4 min, minor enantiomer: t_r = 31.2 min.

Orange oil; $[\alpha]_D^{25}$ –25.4 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, dr 72:28); **major 3fa**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 (d. *J* = 3.0 Hz, 1H, CH=N), 7.76–7.70 (m, 2H, Ar), 7.65–7.50 (m, 3H, Ar), 7.11–7.03 (m, 2H, Ar), 6.98 (t, *J* = 8.6 Hz, 2H, Ar), 5.50 (dd, *J* = 10.3, 3.0 Hz, 1H, CHN), 4.39 (d, *J* = 10.4 Hz, 1H, CHAr), 3.78 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C, C=O), 170.3 (C, C=O), 163.4 (C, C=N), 163.0 (d, $^1J_{C\text{-}F}$ = 247.5 Hz, C), 160.3 (CH, CH=N), 132.8 (CH), 130.1 (d, $^3J_{C\text{-}F}$ = 8.3 Hz, CH), 130.0 (CH), 128.5 (C), 127.3 (CH), 126.2 (C), 116.3 (d, $^2J_{C\text{-}F}$ = 21.7 Hz, CH), 76.5 (CH), 71.7 (C), 55.1 (CH), 53.2 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −112.19 (tt, *J* = 8.4, 5.2 Hz), **minor 3fa'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.50–7.42 (m, 2H, Ar), 7.35–7.27 (m, 3H, Ar), 6.78 (t, *J* = 8.6 Hz, 2H, Ar), 6.73–6.66 (m, 2H, Ar), 5.15 (dd, *J* = 10.0;3.1 Hz, 1H, CHN), 4.47 (d, *J* = 10.0 Hz, 1H, CHAr), 3.79 (s, 3H, MeO), **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.1 (C, C=O), 169.4 (C, C=O), 162.8 (C, C=N), 162.5 (d, $^1J_{C\text{-}F}$ = 246.8 Hz, C), 159.5 (CH, CH—N), 132.1 (CH), 129.3 (CH), 129.3 (d, $^3J_{C\text{-}F}$ = 8.3 Hz, CH), 127.3 (C), 126.8 (C), 126.8 (CH), 115.8 (d, $^2J_{C\text{-}F}$ = 21.7 Hz, CH), 77.4 (CH), 71.3 (C), 55.9 (CH), 53.2 (CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −112.78 (tt, *J* = 8.2, 5.2 Hz);); **HRMS** (ESI) *m/z*: 385.1188 $[M+H_3O]^+$, $C_{20}H_{18}FN_2O_5^+$ requires 385.1194.

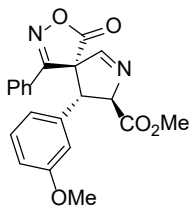
Methyl (5*S*,8*R*,9*R*)-1-oxo-4-phenyl-9-(*m*-tolyl)-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (3ga)



70.2 mg (77%) of **3ga** were obtained from **1g** (65.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 85%, minor diastereomer: 98%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 16.7 min, minor enantiomer: t_r = 20.5 min, **minor diastereomer**: major enantiomer: t_r = 29.0 min, minor enantiomer: t_r = 32.4 min.

Orange oil; $[\alpha]_D^{25}$ –21.9 (*c* 1.2, $CHCl_3$, for the diastereomeric mixture, dr 70:30); **major 3ga**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80–7.73 (m, 3H, Ar+CH=N), 7.66–7.52 (m, 3H, Ar), 7.22–7.07 (m, 2H, Ar), 6.92–6.85 (m, 2H, Ar), 5.55 (dd, *J* = 10.3, 3.0 Hz, 1H, CHN), 4.40 (d, *J* = 10.3 Hz, 1H, CHAr), 3.78 (s, 3H, MeO), 2.29 (s, 3H, MeAr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C, C=O), 170.5 (C, C=O), 163.5 (C, C=N), 160.3 (CH, CH=N), 138.9 (C), 132.7 (CH), 130.9 (C), 129.9 (CH), 129.1 (CH), 128.9 (CH), 128.2 (CH), 127.3 (CH), 126.4 (C), 125.3 (CH), 76.3 (CH), 71.8 (C), 55.7 (CH), 53.1 (CH_3), 21.5 (CH_3); **minor 3ga'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.50–7.40 (m, 2H, Ar), 7.34–7.27 (m, 3H, Ar), 7.06–7.01 (m, 2H, Ar), 7.00–6.96 (m, 2H, Ar), 5.18 (dd, *J* = 10.0, 3.1 Hz), 1H, CHN), 4.48 (d, *J* = 10.0 Hz, 1H, CHAr), 3.79 (s, 3H, MeO), 2.09 (s, 3H, MeAr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.3 (C, C=O), 169.5 (C, C=O), 163.0 (C, C=N), 159.4 (CH, CH=N), 138.5 (C), 131.8 (CH), 131.2 (C), 129.9 (CH), 129.3 (CH), 129.1 (CH), 128.7 (CH), 128.7 (C), 126.9 (CH), 124.8 (CH), 77.1 (CH), 71.5 (C), 56.6 (CH), 53.2 (CH_3), 21.3 (CH_3); **HRMS** (ESI) *m/z*: 381.1439 $[M+H_3O]^+$, $C_{21}H_{21}N_2O_5^+$ requires 381.1445.

Methyl (5*S*,8*R*,9*R*)-9-(3-methoxyphenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]-nona-3,6-diene-8-carboxylate (3ha)

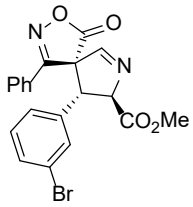


71.9 mg (76%) of **3ha** were obtained from **1h** (69.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 80%, minor diastereomer: 98%) was measured by HPLC (Lux® Amylose-1), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 18.2 min, minor enantiomer: t_r = 34.5 min, **minor diastereomer**: major enantiomer: t_r = 22.6 min, minor enantiomer: t_r = 26.4 min.

Orange oil; $[\alpha]_D^{25}$ –11.7 (*c* 1.1, $CHCl_3$, for the diastereomeric mixture, dr 67:33); **major 3ha**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80–7.73 (m, 2H, Ar), 7.76 (d, *J* = 3.0 Hz, 1H, CH=N), 7.66–7.52 (m, 3H, Ar), 7.21 (t, *J* = 8.0 Hz, 1H, Ar), 6.83 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H, Ar), 6.67 (dt, *J* = 7.8, 0.9 Hz, 1H, Ar), 6.61 (t, *J* = 2.2 Hz, 1H, Ar), 5.54 (dd, *J* = 10.3, 3.0 Hz, 1H, CHN), 4.40 (d, *J* = 10.3 Hz, 1H, CHAr), 3.78 (s, 3H, MeO), 3.74 (s, 3H, MeO); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4 (C, C=O), 170.5 (C, C=O), 163.6 (C, C=N), 160.3 (CH, CH=N), 159.9 (CH), 132.7 (CH), 132.6 (C), 129.9 (CH), 129.4 (C), 127.3 (CH), 126.4 (C), 120.3 (CH), 114.3 (CH), 114.1 (CH), 76.3 (CH), 71.7 (C), 55.6 (CH), 55.3 (CH_3), 53.1 (CH_3); **minor 3ha'**: **^{1}H NMR** (400 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.50–

7.33 (m, 3H, Ar), 7.33–7.26 (m, 2H, Ar), 7.07–7.03 (m, 1H, Ar), 7.00 (t, J = 8.0 Hz, 1H, Ar), 6.78 (dd, J = 7.4, 1.7 Hz, 1H, Ar), 6.70 (dd, J = 8.3, 2.5 Hz, 1H, Ar), 5.17 (dd, J = 9.9, 3.1 Hz, 1H, CHN), 4.50 (d, J = 10.0 Hz, 1H, CHAr), 3.79 (s, 3H, MeO), 3.58 (s, 3H, MeO); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3 (C, C=O), 169.5 (C, C=O), 162.9 (C, C=N), 159.7 (CH), 159.4 (CH, CH=N), 132.9 (C), 131.8 (CH), 130.3 (CH), 129.2 (CH), 128.6 (C), 128.0 (C), 126.8 (CH), 119.8 (CH), 112.9 (CH), 77.1 (CH), 71.5 (C), 56.4 (CH), 55.2 (CH_3), 53.2 (CH_3); **HRMS** (ESI) *m/z*: 397.1390 $[M+H_3O]^+$, $C_{21}H_{21}N_2O_6^+$ requires 397.1394.

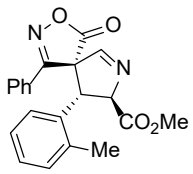
Methyl (5*S*,8*R*,9*R*)-9-(3-bromophenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]-nona-3,6-diene-8-carboxylate (3ia)



81.5 mg (76%) of **3ia** were obtained from **1i** (82.0 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 78%, minor diastereomer: 99%) was measured by HPLC (Lux® i-Amylose-1), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 15.1 min, minor enantiomer: t_r = 18.4 min, **minor diastereomer**: major enantiomer: t_r = 40.5 min, minor enantiomer: t_r = 48.2 min.

Orange oil; $[\alpha]_D^{25}$ –11.3 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, dr 67:33); **major 3ia**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79–7.71 (m, 3H, Ar+CH=N), 7.67–7.52 (m, 3H, Ar), 7.45 (ddd, J = 8.0, 1.8, 1.0 Hz, 1H, Ar), 7.21 (t, J = 1.6 Hz, 1H, Ar), 7.19 (t, J = 7.9 Hz, 1H, Ar), 7.05 (d, J = 7.8 Hz, 1H), 5.51 (dd, J = 10.2, 3.0, 1H, CHN), 4.37 (d, J =10.2 Hz, 1H, CHAr), 3.79 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.2 (C, C=O), 170.2 (C, C=O), 163.3 (CH, CH=N), 160.1 (CH, CH=N), 133.5 (C), 132.9 (CH), 132.4 (CH), 131.4 (CH), 130.7 (CH), 130.0 (CH), 127.3 (CH), 126.7 (CH), 126.1 (C), 123.2 (C), 76.4 (CH), 71.6 (C), 54.9 (CH), 53.3 (CH_3); **minor 3ia'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.76 (d, J = 3.1 Hz, 1H, CH=N), 7.52–7.46 (m, 2H, Ar), 7.38–7.28 (m, 3H, Ar), 7.00 (d, J = 7.8 Hz, 1H, Ar), 6.78–6.70 (m, 2H, Ar), 5.14 (dd, J = 9.9, 3.1 Hz, 1H, CHN), 4.45 (d, J = 9.9 Hz, 1H, CHAr), 3.80 (s, OMe); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.9 (C, C=O), 169.2 (C, C=O), 162.7 (CH, CH=N), 159.2 (CH, CH=N), 133.8 (C), 132.2 (CH), 131.8 (CH), 130.5 (CH), 130.4 (CH), 129.5 (CH), 128.4 (C), 126.9 (CH), 126.8 (CH), 122.9 (C), 77.2 (CH), 71.3 (C), 55.9 (CH), 53.3 (CH_3); **HRMS** (ESI) *m/z*: 445.0382, 447.0366 $[M+H_3O]^+$, $C_{20}H_{18}BrN_2O_5^+$ requires 445.0394, 447.0373.

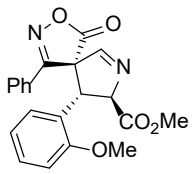
Methyl (5*S*,8*R*,9*R*)-1-oxo-4-phenyl-9-(*o*-tolyl)-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (3ja)



76.6 mg (85%) of **3ja** were obtained from **1j** (65.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 85%, minor diastereomer: 98%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 14.5 min, minor enantiomer: t_r = 21.2 min, **minor diastereomer**: major enantiomer: t_r = 31.0 min, minor enantiomer: t_r = 40.3 min.

Orange oil; $[\alpha]_D^{25}$ +7.1 (*c* 0.9, $CHCl_3$, for the diastereomeric mixture, dr 70:30); **major 3ja**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81–7.76 (m, 2H, Ar), 7.70 (d, 3.0 Hz, 1H, CH=N), 7.57–7.48 (m, 3H, Ar), 7.23–7.17 (m, 2H, Ar), 7.10–7.04 (m, 2H, Ar), 5.47 (dd, *J* = 9.7, 3.0 Hz, 1H, CHN), 4.86 (d, *J* = 9.8 Hz, 1H, CHAr), 3.76 (s, 3H, MeO), 1.81 (s, 3H, MeAr); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.6 (C, C=O), 170.5 (C, C=O), 163.3 (C, C=N), 160.2 (CH, CH=N), 137.9 (C), 132.7 (CH), 131.0 (CH), 129.8 (CH), 129.6 (C), 128.8 (CH), 128.4 (CH), 127.0 (CH), 126.8 (C), 126.7 (CH), 79.7 (CH), 71.3 (C), 53.1 (CH), 50.9 (CH_3), 19.7 (CH_3); **minor 3ja'**: **^{1}H NMR** (400 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.71 (d, *J* = 3.0 Hz, 1H, CH=N), 5.36 (dd, *J* = 8.6, 3.0 Hz, 1H, CHN), 4.79 (d, *J* = 8.7 Hz, 1H, CHAr), 3.79 (s, 3H, MeO), 2.27 (s, 3H, MeAr); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4 (C, C=O), 169.6 (C, C=O), 163.3 (C, C=N), 158.9 (CH, CH=N), 137.7 (C), 131.8 (CH), 131.2 (CH), 130.0 (C), 129.1 (CH), 129.1 (C), 128.2 (CH), 127.5 (CH), 126.8 (CH), 125.4 (CH), 80.0 (CH), 70.1 (C), 53.2 (CH), 52.7 (CH_3), 20.0 (CH_3); **HRMS** (ESI) *m/z*: 381.1440 $[M+H_3O]^+$, $C_{21}H_{21}N_2O_5^+$ requires 381.1445.

Methyl (5*S*,8*R*,9*R*)-9-(2-methoxyphenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]-nona-3,6-diene-8-carboxylate (3ka)

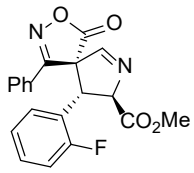


90.1 mg (95%) of **3ka** were obtained from **1k** (69.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 87%, minor diastereomer: 98%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 26.8 min, minor enantiomer: t_r = 35.6 min, **minor diastereomer**: major enantiomer: t_r = 50.1 min, minor enantiomer: t_r = 55.1 min.

Orange oil; $[\alpha]_D^{25}$ +20.2 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, dr 52:48); **major 3ka**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.0, 1.7 Hz, 2H, Ar), 7.68 (d, *J*

= 3.2 Hz, 1H, CH=N), 7.42 (d, *J* = 7.9 Hz, 1H, Ar), 7.25 (d, *J* = 8.4 Hz, 1H, Ar), 7.15 (t, *J* = 7.8 Hz, 1H, Ar), 6.96 (td, *J* = 7.6, 0.9 Hz, 1H, Ar), 6.90–6.83 (m, 2H, Ar), 5.36 (dd, *J* = 9.8, 3.1 Hz, 1H, CHN), 4.90 (d, *J* = 10.3 Hz, 1H, CHAr), 3.78 (s, 3H, MeO), 3.34 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.0 (C, C=O), 169.8 (C, C=O), 164.1 (C, C=N), 159.8 (CH, CH=N), 157.0 (C), 132.1 (CH), 129.4 (CH), 129.2 (CH), 128.2 (CH), 127.5 (C), 126.2 (CH), 121.2 (C), 120.8 (CH), 110.3 (CH), 76.6 (CH), 70.9 (C), 54.4 (CH), 53.1 (CH_3), 50.0 (CH_3); **minor 3ka'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.66 (d, *J* = 3.0 Hz, 1H, CH=N), 7.56–7.51 (m, 2H, Ar), 7.31 (t, *J* = 7.5 Hz, 2H, Ar), 7.08 (d, *J* = 7.8 Hz, 1H, Ar), 6.76 (d, *J* = 7.8 Hz, 1H, Ar), 6.74 (d, *J* = 8.4 Hz, 1H, Ar), 6.62 (d, *J* = 7.7 Hz, 1H, Ar), 6.48 (td, *J* = 7.5, 0.2 Hz, 1H, Ar), 5.64 (dd, *J* = 10.2, 3.0 Hz, 1H, CHN), 4.50 (d, *J* = 9.8 Hz, 1H, CHAr), 3.79 (s, 3H, MeO), 3.76 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.3 (C, C=O), 170.8 (C, C=O), 163.1 (C, C=N), 160.8 (CH, CH=N), 157.4 (C), 131.2 (CH), 130.0 (CH), 128.9 (CH), 128.6 (C), 126.8 (CH), 126.6 (CH), 120.2 (CH), 120.0 (C), 109.7 (CH), 76.1 (CH), 70.6 (C), 54.4 (CH), 53.0 (CH_3), 49.0 (CH_3); **HRMS** (ESI) *m/z*: 397.1389 $[M+H_3O]^+$, $C_{21}H_{21}N_2O_6^+$ requires 397.1394.

Methyl (5*S*,8*R*,9*R*)-9-(2-fluorophenyl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]-nona-3,6-diene-8-carboxylate (3la)

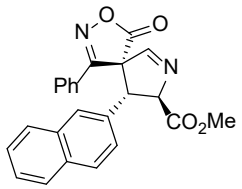


79.6 mg (87%) of **3la** were obtained from **1l** (66.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 90%, minor diastereomer: 96%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 16.2 min, minor enantiomer: t_r = 21.9 min, **minor diastereomer**: major enantiomer: t_r = 41.4 min, minor enantiomer: t_r = 49.4 min.

Orange oil; $[\alpha]_D^{25}$ +9.5 (*c* 1.1, $CHCl_3$, for the diastereomeric mixture, dr 57:43); **major 3la**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79–7.71 (m, 3H, Ar+CH=N), 7.63–7.50 (m, 3H, Ar), 7.45 (td, *J* = 7.6, 1.6 Hz, 1H, Ar), 7.35–7.27 (m, 1H, Ar), 7.23–7.13 (m, 1H, Ar), 7.03–6.93 (m, 1H, Ar), 5.61 (dd, *J* = 10.2, 3.0 Hz, 1H, CHN), 4.75 (d, *J* = 10.2 Hz, 1H, CHAr), 3.79 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.3 (C, C=O), 170.2 (C, C=O), 163.8 (C, C=N), 161.4 (d, $^1J_{C\text{-}F}$ = 247.6 Hz, C), 160.3 (CH, CH=N), 132.5 (CH), 130.8 (d, $^3J_{C\text{-}F}$ = 8.4 Hz, CH), 129.7 (CH), 129.1 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, CH), 127.2 (CH), 126.7 (C), 124.8 (d, $^3J_{C\text{-}F}$ = 3.8 Hz, CH), 118.7 (d, $^2J_{C\text{-}F}$ = 14.4 Hz, C), 115.8 (d, $^2J_{C\text{-}F}$ = 22.1 Hz, CH), 76.4 (CH), 71.1 (C), 53.2 (CH_3), 48.0 (CH); **minor 3la'**: **^{1}H NMR** (300

MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.72 (d, J = 3.2 Hz, 1H, CH=N), 7.37 (td, J = 7.5, 1.2 Hz, 1H, Ar), 7.25–7.09 (m, 3H, Ar), 7.03–6.93 (m, 3H, Ar), 6.68 (td, J = 7.6, 1.1, 1H, Ar), 6.62 (td, J = 7.1, 1.6, 1H, Ar), 5.37 (dd, J = 9.6, 3.1 Hz, 1H, CHN), 4.61 (d, J = 9.7 Hz, 1H, CHAr), 3.81 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.7 (C, C=O), 169.3 (C, C=O), 162.4 (C, C=N), 161.0 (d, $^1J_{C\text{-}F}$ = 245.7 Hz, C), 159.5 (CH, CH=N), 131.7 (CH), 130.1 (d, $^3J_{C\text{-}F}$ = 8.7 Hz, CH), 129.1 (CH), 128.4 (C), 127.7 (d, $^1J_{C\text{-}F}$ = 3.6 Hz, CH), 126.4 (CH), 124.0 (d, $^3J_{C\text{-}F}$ = 3.5 Hz, CH), 119.8 (d, $^2J_{C\text{-}F}$ = 15.5 Hz, C), 115.6 (d, $^2J_{C\text{-}F}$ = 21.8 Hz, CH), 76.9 (CH), 70.4 (C), 53.3 (CH_3), 49.1 (CH); **HRMS** (ESI) *m/z*: 385.1188 $[M+H_3O]^+$, $C_{20}H_{18}FN_2O_5^+$ requires 385.1194.

Methyl (5*S*,8*R*,9*R*)-9-(naphthalen-2-yl)-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]-nona-3,6-diene-8-carboxylate (3ma)

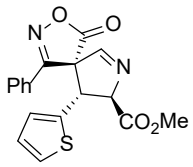


56.0 mg (56%) of **3ma** were obtained from **1m** (74.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 84%, minor diastereomer: 96%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 21.7 min, minor enantiomer: t_r = 27.2 min, **minor diastereomer**: major enantiomer: t_r = 39.7 min, minor enantiomer: t_r = 44.1 min.

Orange oil; $[\alpha]_D^{25}$ +22.9 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, dr 66:34); **major 3ma**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.85–7.74 (m, 6H, Ar+CH=N), 7.70–7.56 (m, 4H, Ar), 7.49 (dd, J = 6.2, 3.3 Hz, 2H, Ar), 7.15 (dd, J = 8.6, 1.8 Hz, 1H, Ar), 5.71 (dd, J = 10.3, 3.0 Hz, 1H, CHN), 4.61 (d, J = 10.3 Hz, 1H, CHAr), 3.78 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C, C=O), 170.5 (C, C=O), 163.5 (C, C=N), 160.4 (CH, CH=N), 133.4 (C), 133.3 (C), 132.8 (CH), 130.0 (CH), 129.1 (CH), 128.5 (C), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 126.9 (CH), 126.8 (CH), 126.4 (C), 125.5 (CH), 76.5 (CH), 71.8 (C), 56.0 (CH), 53.2 (CH_3); **minor 3ma'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.85– 7.74 (m, 6H, Ar+CH=N), 7.70–7.56 (m, 2H, Ar), 7.48–7.36 (m, 2H, Ar), 7.22–7.17 (m, 1H, Ar), 6.95 (d, J = 8.1 Hz, 1H, Ar), 5.34 (dd, J = 10.0;3.1 Hz, 1H, CHN), 4.68 (d, J = 10.0 Hz, 1H, CHAr), 3.79 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.3 (C, C=O), 169.5 (C, C=O), 162.9 (C, C=N), 159.4 (CH, CH=N), 133.0 (C), 132.8 (C), 131.8 (CH), 129.2 (CH), 128.9 (CH), 128.6 (C), 127.9 (CH), 127.6 (CH), 126.8 (CH),

126.7 (CH), 126.4 (C), 125.4 (CH), 77.4 (CH), 71.5 (C), 57.0 (CH), 53.2 (CH_3); **HRMS** (ESI) *m/z*: 417.1443 $[M+H_3O]^+$, $C_{24}H_{21}N_2O_5^+$ requires 417.1445.

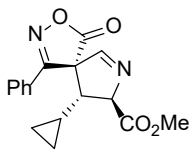
Methyl (5*S*,8*R*,9*R*)-1-oxo-4-phenyl-9-(thiophen-2-yl)-2-oxa-3,7-diazaspiro[4.4]-nona-3,6-diene-8-carboxylate (3na)



67.5 mg (76%) of **3na** were obtained from **1n** (63.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 84%, minor diastereomer: 91%) was measured by HPLC (Lux® i-Amylose-1), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 22.0 min, minor enantiomer: t_r = 17.2 min, **minor diastereomer**: major enantiomer: t_r = 30.4 min, minor enantiomer: t_r = 18.0 min.

Orange oil; $[\alpha]_D^{25}$ –82.7 (*c* 1.1, $CHCl_3$, for the diastereomeric mixture, dr 73:27); **major 3na**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 3.0 Hz, 1H, CH=N), 7.73 (dd, *J* = 8.2, 1.5 Hz, 2H, Ar), 7.65–7.51 (m, 3H, Ar), 7.23 (dd, *J* = 8.2, 1.5 Hz, 1H, Ar), 7.00–6.93 (m, 2H, Ar), 5.46 (dd, *J* = 10.2, 3.0 Hz, 1H, CHN), 4.64 (d, *J* = 10.2 Hz, 1H, CHAr), 3.81 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.0 (C, C=O), 170.1 (C, C=O), 163.4 (C, C=N), 160.6 (CH, CH=N), 133.0 (C), 132.8 (CH), 129.9 (CH), 127.3 (CH), 127.0 (CH), 126.7 (CH), 126.4 (CH), 126.2 (C), 77.9 (CH), 71.6 (C), 53.3 (CH), 51.1 (CH_3); **minor 3na'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.76 (d, *J* = 3.1 Hz, 1H, CH=N), 7.50–7.42 (m, 1H, Ar), 7.35–7.27 (m, 2H, Ar), 7.16–7.11 (m, 2H, Ar), 7.07 (dd, *J* = 5.1, 1.1 Hz, 1H, Ar), 6.73 (dd, *J* = 5.2, 3.6 Hz, 1H, Ar), 6.45 (d, *J* = 3.6 Hz, 1H, Ar), 5.11 (dd, *J* = 9.8, 3.1 Hz, 1H, CHN), 4.71 (dd, *J* = 9.8, 0.9 Hz, 1H, CHAr), 3.82 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.7 (C, C=O), 169.0 (C, C=O), 162.5 (C, C=N), 159.7 (CH, CH=N), 133.8 (C), 131.9 (CH), 129.2 (CH), 128.4 (C), 127.7 (CH), 127.2 (CH), 126.7 (CH), 125.8 (CH), 79.6 (CH), 71.5 (C), 53.3 (CH), 51.7 (CH_3); **HRMS** (ESI) *m/z* 373.0846 $[M+H_3O]^+$, $C_{18}H_{17}N_2O_5S^+$ requires 373.0853.

Methyl (5*S*,8*R*,9*R*)-9-cyclopropyl-1-oxo-4-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (3oa)

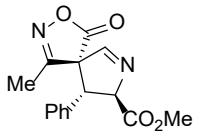


39.0 mg (50%) of **3oa** were obtained from **1o** (53.3 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 87%, minor diastereomer: 56%) was measured by HPLC (Lux® Amylose-1), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 12.6 min, minor enantiomer:

t_r = 15.4 min, **minor diastereomer**: major enantiomer: t_r = 19.5 min, minor enantiomer: t_r = 14.2 min.

Orange oil; $[\alpha]_D^{25}$ –42.7 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, dr 69:31); **major 3oa**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.67–7.61 (m, 3H, Ar+CH=N), 7.58–7.40 (m, 3H, Ar), 5.01 (dd, *J* = 9.3, 3.0 Hz, 1H, CHN), 2.41 (dd, *J* = 10.4, 9.2 Hz, 1H, CH^{c}Pr), 1.10 (dddd, *J* = 12.8, 9.2, 8.0, 4.8 Hz, 1H, ^{c}Pr), 0.53 (qq, *J* = 9.2, 4.6 Hz, 2H, ^{c}Pr), 0.17–0.05 (m, 2H, ^{c}Pr), −0.02–0.18 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.4 (C, C=O), 171.1 (C, C=O), 164.3 (C, C=N), 160.8 (CH, CH=N), 132.6 (CH), 129.7 (CH), 127.2 (CH), 126.3 (C), 78.9 (CH), 70.2 (C), 56.5 (CH), 53.1 (CH_3), 8.3 (CH), 4.0 (CH_2), 2.9 (CH_2); **minor 3oa'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 4.75 (dd, *J* = 8.8, 3.1 Hz, 1H, CHN), 2.53 (dd, *J* = 10.2, 8.7 Hz, 1H, CH^{c}Pr), 0.46–0.26 (m, 3H, ^{c}Pr), 0.20–0.00 (m, 2H, ^{c}Pr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.4 (C, C=O), 170.0 (C, C=O), 163.0 (C, C=N), 160.0 (CH, CH=N), 132.2 (CH), 129.3 (CH), 126.7 (CH), 80.6 (CH), 69.9 (C), 58.3 (CH), 53.1 (CH), 9.4 (CH_2), 5.5 (CH_3), 3.5 (CH_3); **HRMS** (ESI) *m/z*: 331.1285 $[M+H_3O]^+$, $C_{17}H_{19}N_2O_5^+$ requires 331.1288.

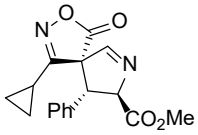
Methyl (5*S*,8*R*,9*R*)-4-methyl-1-oxo-9-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (3pa)



55.0 mg (77%) of **3pa** were obtained from **1p** (46.8 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 95%, minor diastereomer: 94%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 19.2 min, minor enantiomer: t_r = 34.1 min, **minor diastereomer**: major enantiomer: t_r = 25.4 min, minor enantiomer: t_r = 38.1 min.

Orange oil; $[\alpha]_D^{25}$ –151.9 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, dr 58:42); **major 3pa**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 3.0 Hz, 1H, CH=N), 7.34–7.29 (m, 3H, Ar), 7.22–7.16 (m, 2H, Ar), 5.49 (dd, *J* = 9.8, 3.0 Hz, 1H, CHN), 4.18 (d, *J* = 9.8 Hz, 1H, CHPh), 3.80 (s, 3H, MeO), 2.28 (s, 3H, CH_3); **minor 3pa'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.39 (d, *J* = 3.0 Hz, 1H, CH=N), 7.38–7.34 (m, 3H, Ar), 7.16–7.11 (m, 2H, Ar), 5.34 (dd, *J* = 9.8, 3.0 Hz, 1H, CHN), 4.53 (d, *J* = 9.8 Hz, 1H, CHPh), 3.85 (s, 3H, MeO), 1.61 (s, 3H, CH_3); **HRMS** (ESI) *m/z*: 305.1133 $[M+H_3O]^+$, $C_{15}H_{17}N_2O_5^+$ requires 305.1132.

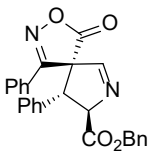
Methyl (5*S*,8*R*,9*R*)-4-cyclopropyl-1-oxo-9-phenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (3qa)



48.4 mg (62%) of **3qa** were obtained from **1q** (53.3 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 87%, minor diastereomer: 56%) was measured by HPLC (Lux® Amylose-1), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 24.0 min, minor enantiomer: t_r = 14.0 min, **minor diastereomer**: major enantiomer: t_r = 20.2 min, minor enantiomer: t_r = 14.7 min.

Orange oil; $[\alpha]_D^{25}$ –105.2 (*c* 1.0, $CHCl_3$, for the diastereomeric mixture, dr 65:35); **major 3qa**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 3.0 Hz, 1H, CH=N), 7.39–7.30 (m, 5H, Ar), 5.48 (dd, *J* = 9.9, 3.0 Hz, 1H, CHN), 4.36 (d, *J* = 9.9 Hz, 1H, CH^{c}Pr), 3.79 (s, 3H, MeO), 1.61 (tt, *J* = 7.9, 5.2 Hz, 1H, ^{c}Pr), 1.35–1.19 (m, 3H, ^{c}Pr), 0.91–0.79 (m, 1H, ^{c}Pr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.5 (C, C=O), 170.6 (C, C=O), 169.3 (C, C=N), 159.6 (CH, CH=N), 132.7 (C), 129.2 (CH), 128.5 (CH), 127.3 (CH), 77.2 (CH), 73.1 (C), 54.4 (CH), 53.2 (CH_3), 10.5 (CH_2), 9.0 (CH_2), 7.8 (CH); **minor 3qa'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.44 (d, *J* = 3.0 Hz, 1H, CH=N), 7.25–7.23 (m, 3H, Ar), 7.18–7.12 (m, 2H, Ar), 5.41 (dd, *J* = 9.0, 3.0 Hz, 1H, CHN), 4.53 (d, *J* = 9.9 Hz, 1H, CH^{c}Pr), 3.85 (s, 3H, MeO), 1.30–1.19 (m, 1H, ^{c}Pr), 1.00-0.91 (m, 2H, ^{c}Pr), 0.58 (dddd, *J* = 9.3, 8.1, 7.0, 4.6 Hz, 1H, ^{c}Pr), 0.27 (ddt, *J* = 9.7, 6.7, 4.8 Hz, 1H, ^{c}Pr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.1 (C, C=O), 169.7 (C, C=O), 167.7 (C, C=N), 159.4 (CH, CH=N), 131.4 (C), 129.4 (CH), 129.1 (CH), 128.6 (CH), 76.8 (CH), 72.6 (C), 55.2 (CH), 53.3 (CH_3), 10.0 (CH_2), 9.0 (CH_2), 8.6 (CH); **HRMS** (ESI) *m/z*: 331.1280 $[M+H_3O]^+$, $C_{17}H_{19}N_2O_5^+$ requires 331.1288.

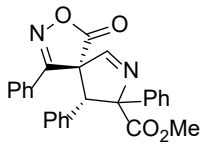
Benzyl (5*S*,8*R*,9*R*)-1-oxo-4,9-diphenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (3ab)



77.6 mg (73%) of **3ab** were obtained from **1r** (62.3 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 90%, minor diastereomer: 99%) was measured by HPLC (Lux® Amylose-1), hexane:^{i}PrOH 80:10, 1.0 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 31.5 min, minor enantiomer: t_r = 20.4 min, **minor diastereomer**: major enantiomer: t_r = 28.5 min, minor enantiomer: t_r = 18.7 min.

Orange oil; $[\alpha]_D^{25}$ –45.4 (*c* 0.9, $CHCl_3$, for the diastereomeric mixture, dr 76:24); **major 3ab**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79–7.72 (m, 3H, Ar+CH=N), 7.63–7.55 (m, 1H, Ar), 7.53–7.46 (m, 2H, Ar), 7.34–7.28 (m, 6H, Ar), 7.22–7.14 (m, 2H, Ar), 7.12–7.05 (m, 2H, Ar), 5.62 (dd, *J* = 10.4, 3.0 Hz, 1H, CHN), 5.20 (s, 2H, CH_2Ph), 4.41 (d, *J* = 10.3 Hz, 1H, CHPh); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C, C=O), 169.9 (C, C=O), 163.5 (C, C=N), 160.4 (CH, CH=N), 135.0 (C), 132.7 (CH), 131.0 (C), 129.9 (CH), 129.3 (CH), 129.1 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.3 (CH), 126.3 (C), 76.5 (CH), 71.7 (C), 67.7 (CH_2), 56.1 (CH); **minor 3ab'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 7.76 (d, *J* = 2.9 Hz, 1H), 6.70–6.67 (m, 2H, Ar), 5.24 (dd, *J* = 9.9, 3.0 Hz, 1H, CHN), 5.22 (s, 2H, CH_2Ph), 4.54 (d, *J* = 10.1 Hz, 1H, CHPh); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.2 (C, C=O), 169.0 (C, C=O), 162.9 (C, C=N), 159.5 (CH, CH=N), 134.5 (C), 131.8 (CH), 131.4 (C), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.5 (C), 128.2 (CH), 127.5 (CH), 126.8 (CH), 77.1 (CH), 71.4 (C), 67.7 (CH_2), 56.7 (CH); **HRMS** (ESI) *m/z*: 443.1594 $[M+H_3O]^+$, $C_{26}H_{23}N_2O_5^+$ requires 443.1601.

Methyl (5*S*,9*R*)-1-oxo-4,8,9-triphenyl-2-oxa-3,7-diazaspiro[4.4]nona-3,6-diene-8-carboxylate (3ac)



47.8 mg (45%) of **3ac** were obtained from **1a** (62.3 mg, 0.25 mmol). Enantiomeric excess (major diastereomer: 72%, minor diastereomer: 67%) was measured by HPLC (Lux® i-Amylose-1), hexane:^{i}PrOH 80:20, 1.5 mL min^{-1}, **major diastereomer**: major enantiomer: t_r = 32.1 min, minor enantiomer: t_r = 42.6 min, **minor diastereomer**: major enantiomer: t_r = 19.9 min, minor enantiomer: t_r = 14.2 min.

Colorless oil; $[\alpha]_D^{25}$ +62.8 (*c* 1.1, $CHCl_3$, for the diastereomeric mixture, dr 68:32); **major 3ac**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04 (s, 1H, CH=N), 7.54–7.46 (m, 2H, Ar), 7.46–7.40 (m, 2H, Ar), 7.40–7.27 (m, 6H, Ar), 7.25–7.19 (m, 3H, Ar), 7.07–7.01 (m, 2H, Ar), 4.15 (s, 1H, CHPh), 3.71 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C, C=O), 169.7 (C, C=O), 163.8 (C, C=N), 158.5 (CH, CH=N), 141.6 (C), 132.3 (CH), 131.2 (C), 130.7 (CH), 129.6 (CH), 129.3 (CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 126.9 (CH), 126.4 (C), 126.3 (CH), 87.0 (C), 72.2 (C), 64.3 (CH), 53.0 (CH_3); **minor 3ac'**: **^{1}H NMR** (300 MHz, $CDCl_3$), significative signals taken from the NMR spectrum of the diastereomeric mixture, δ 8.11 (s, 1H, CH=N), 7.80–6.80 (m, 15H, Ar), 4.92 (s, 1H, CHPh), 3.75 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.2 (C, C=O), 172.4 (C,

C=O), 164.1 (C, C=N), 160.1 (CH, CH=N), 139.3 (C), 132.5 (CH), 131.6 (CH), 131.0 (C), 129.8 (CH), 129.4 (CH), 128.7 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.2 (CH), 126.7 (C), 90.6 (C), 72.6 (C), 57.9 (CH), 53.8 (CH_3); **HRMS** (ESI) *m/z*: 443.1597 $[M+H_3O]^+$, $C_{26}H_{23}N_2O_5^+$ requires 443.1601.

5. Synthesis of compounds 3aa and 3aa' at 1 mmol scale

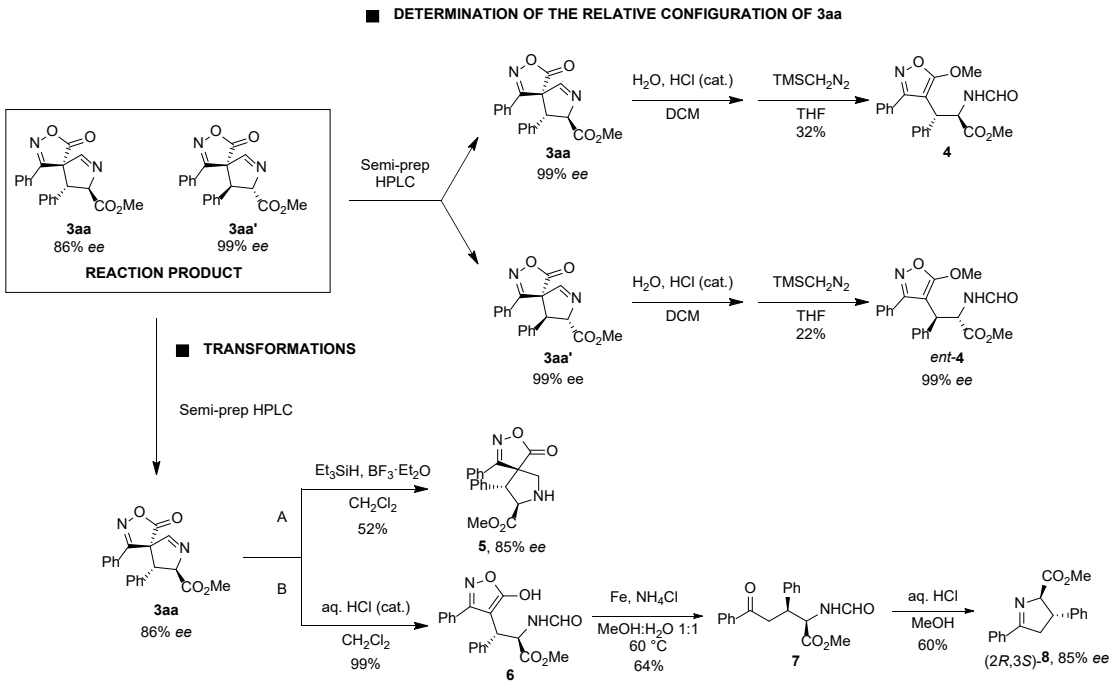
1a (249.3 mg, 1.0 mmol), the organocatalyst **SQ11** (47.5 mg, 0.10 mmol) and silver oxide (11.6 mg, 0.05 mmol) were dissolved in DCM (76.8 mL) and methyl isocyanoacetate (**2a**, 118 µL; 1.3 mmol; 1.3 equiv.) was added. The reaction was stirred for 20 h and the mixture was purified via flash column chromatography (Hexane:AcOEt 7:3) to furnish 240 mg (69%) of **3aa** as a diastereomeric mixture (dr 66:33). To carry out experiments for the determination of the stereochemistry of the reaction products and synthetic transformations, the diastereomers **3aa** and **3aa'** were separated by HPLC.

Major 3aa: Enantiomeric excess (86%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, major enantiomer: t_r = 18.4 min, minor enantiomer: t_r = 24.6 min. $[\alpha]_D^{25}$ –134.8 (*c* 1.0, $CHCl_3$, 86% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81–7.72 (m, 3H, Ar+CH=N), 7.66–7.51 (m, 3H, Ar), 7.34–7.23 (m, 3H, Ar), 7.12–7.04 (m, 2H, Ar), 5.57 (dd, *J* = 10.3, 3.0 Hz, 1H, CHN), 4.43 (d, *J* = 10.3 Hz, 1H, CHPh), 3.37 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (C, C=O), 170.5 (C, C=O), 163.5 (C, C=N), 160.3 (CH, CH=N), 132.7 (CH), 131.1 (C), 129.9 (CH), 129.2 (CH), 129.1 (CH), 128.2 (CH), 127.3 (CH), 126.3 (C), 76.2 (CH), 71.7 (C), 55.7 (CH), 53.1 (CH_3).

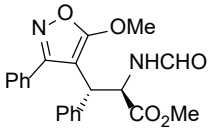
Minor 3aa' (contained aprox. 20% of **3aa**): Enantiomeric excess (99%) was measured by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 85:15, 1.0 mL min^{-1}, major enantiomer: t_r = 27.9 min, minor enantiomer: t_r = 32.3 min. $[\alpha]_D^{25}$ +195.1 (*c* 1.0, $CHCl_3$, 99% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 2.9 Hz, 1H, CH=N), 7.44 (tt, *J* = 7.5, 1.5 Hz, 1H, Ar), 7.35–7.21 (m, 2H, Ar), 7.17 (tt, *J* = 7.5, 1.5 Hz, 1H, Ar), 7.08 (t, *J* = 7.5 Hz, 2H, Ar), 7.00 (dd, *J* = 7.5, 1.5 Hz, 2H, Ar), 6.73 (d, *J* = 7.5 Hz, 2H, Ar), 5.20 (dd, *J* = 10.0, 3.1 Hz, 1H, CHN), 4.53 (d, *J* = 10.0 Hz, 1H, CHPh), 3.79 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.3 (C, C=O), 169.5 (C, C=O), 163.0 (C, C=N), 159.4 (CH, CH=N), 131.9 (CH), 131.5 (C), 129.2 (CH), 128.8 (CH), 128.5 (CH), 128.5 (CH), 127.4 (CH), 126.8 (C), 77.0 (CH), 71.5 (C), 56.4 (CH), 53.2 (CH_3).

6. Transformations of product 3aa (Scheme S1)

General scheme



Methyl (2*R*,3*R*)-2-formamido-3-(5-methoxy-3-phenylisoxazol-4-yl)-3-phenyl-propanoate (4)

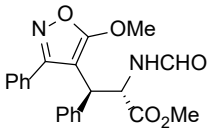


Compound **3aa** (8.4 mg, 0.024 mmol, 99% *ee*, obtained after chiral HPLC- CHIRALPAK® IC) was dissolved in dichloromethane (0.3 mL). Water (1 drop) and 2M HCl in Et_2O (1 drop) was added. After 4 hours, the volatiles were removed and the residue dried under vacuum in the presence of P_2O_5. The crude product (8.7 mg) was dissolved in dry THF (0.4 mL) under nitrogen atmosphere, 2.0 M (trimethylsilyl)diazomethane in Et_2O (38 µL, 0.076 mmol) was added and the reaction mixture was stirred overnight at room temperature. Purification by flash chromatography (Hexane:AcOEt 4:6) furnished 2.9 mg (32%) of compound **4**. Enantiomeric excess (99%) was determined by HPLC (CHIRALPAK® AD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 9.1 min, minor enantiomer: t_r = 15.7 min.

Colorless oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.03 (s, 1H, CHO), 7.48–7.37 (m, 4H, Ar), 7.37–7.23 (m, 6H, Ar), 6.35 (d, J = 9.3 Hz, 1H, CHPh), 5.42 (td, J = 9.0, 0.8 Hz, 1H, CHCO), 4.26 (s, 3H, MeO), 3.37 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.2 (C, CON), 169.8 (C, CO_2Me), 166.3 (C, C=N), 160.6 (CH, CHO), 138.4 (C, Ar), 130.1 (CH), 129.0 (C), 128.9 (CH), 128.9 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 90.1 (C), 58.9

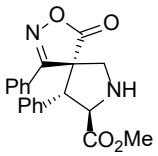
(CH_3), 54.0 (CH), 52.3 (CH_3), 42.4 (CH); **HRMS** (ESI) *m/z*: 403.1271 $[M+Na]^+$, $C_{21}H_{20}N_2NaO_5^+$ requires 403.1264.

Methyl (2*S*,3*S*)-2-formamido-3-(5-methoxy-3-phenylisoxazol-4-yl)-3-phenylpropanoate (*ent*-4)



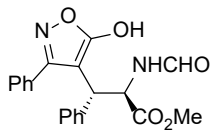
The previous procedure was performed with **3aa'** (8.0 mg, 0.022 mmol, 99% ee, obtained after chiral HPLC- CHIRALPAK® IC), which afforded 1.8 mg (22%) of *ent*-**4**. Enantiomeric excess (99%) was determined by HPLC (CHIRALPAK® AD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 15.7 min, minor enantiomer: t_r = 9.1 min. Spectroscopical data coincided with those observed for the previous compound **4**.

Methyl (5*S*,8*R*,9*R*)-1-oxo-4,9-diphenyl-2-oxa-3,7-diazaspiro[4.4]non-3-ene-8-carboxylate (5)



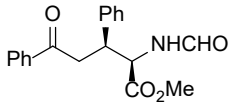
A modification of a literature procedure was employed.[12] To a solution of the major diastereomer **3aa** (10.0 mg, 0.029 mmol, *ee* 86% obtained by semi-preparative HPLC) and Et_3SiH (14 µL, 0.086 mmol) in dichloromethane (0.9 mL) was added $BF_3{\cdot}Et_2O$ (12 µL, 0.096 mmol). The reaction was stirred for 3 h and quenched with saturated $NaHCO_3$ (5 mL). Dichloromethane (10 mL) was added and the organic phase was washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (Hexane:AcOEt 7:3) afforded 5.3 mg (52%) of compound **5**. Enantiomeric excess (85%) was measured by HPLC (Lux® i-Amylose-1), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 17.9 min, minor enantiomer: t_r = 21.1 min. White foam; $[\alpha]_D^{25}$ –43.1 (*c* 0.4, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.00–7.93 (m, 2H, Ar), 7.63–7.53 (m, 3H, Ar), 7.29–7.23 (m, 3H, Ar), 7.11–7.04 (m, 2H, Ar), 4.71 (d, J = 9.9 Hz, 1H, $CHCO_2Me$), 4.26 (d, J = 9.8 Hz, 1H, CHPh), 3.97 (d, J = 12.1 Hz, 1H, CH^aNH), 3.69 (d, J = 12.0 Hz, 1H, CH^bNH), 3.68 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 179.0 (C, C=O), 172.7 (C, C=O), 165.3 (C, C=N), 132.4 (C), 132.2 (CH), 129.7 (CH), 129.0 (CH), 128.8 (CH), 128.3 (CH), 127.2 (C), 127.0 (C), 63.0 (CH), 62.2 (C), 57.8 (CH), 54.8 (CH_2), 52.8 (CH_3); **HRMS** (ESI) *m/z*: 373.1163 $[M+Na]^+$, $C_{20}H_{18}N_2NaO_4^+$ requires 373.1159.

Methyl (2*R*,3*R*)-2-formamido-3-(5-hydroxy-3-phenylisoxazol-4-yl)-3-phenylpropanoate (6)



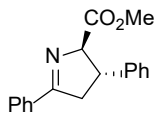
Diastereomer **3aa** (63.0 mg, 0.18 mmol, 86% *ee*, obtained by semi-preparative HPLC) was dissolved in dichloromethane (1 mL), H_2O (15 µL) and 2.0 M HCl solution in Et_2O (6 µL, 12 µmol) were added. The mixture was stirred for 4 h and concentrated under reduced pressure to yield 68.9 mg (99%) of **6**. White foam; $[\alpha]_D^{25}$ –72.7 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 11.0 (bs, 1H, OH), 8.41 (d, *J* = 9.4 Hz, 1H), 7.61–7.27 (m, 10H, Ar), 5.36 (dd, *J* = 9.3, 5.3 Hz, 1H, CHCO), 4.63 (d, *J* = 5.3 Hz, 1H, CHPh), 3.55 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.2 (CH, COH), 170.5 (C, CO_2Me), 163.9 (C, C=N), 162.0 (C, CHO), 138.3 (C), 131.7 (CH), 129.4 (CH), 128.9 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 126.0 (C), 96.0 (C), 55.2 (CH), 52.5 (CH_3), 40.8 (CH); **HRMS** (ESI) *m/z*: 389.1117 $[M+Na]^+$, $C_{20}H_{18}N_2NaO_5^+$ requires 389.1108.

Methyl (2*R*,3*S*)-2-formamido-5-oxo-3,5-diphenylpentanoate (7)



A literature procedure was employed.[3] Compound **6** (29.2 mg, 0.08 mmol, 86% *ee*), iron powder (44.5 mg, 0.80 mmol, 10.0 equiv.) and ammonium chloride (42.6 mg, 0.80 mmol) in MeOH:H_2O 1:1 (0.4 mL) was stirred at 60 °C. After 2 h, the reaction was filtered over celite and concentrated under reduced pressure. Purification by flash chromatography furnished 16.6 mg of product **7** (64%). Colorless oil; $[\alpha]_D^{25}$ –38.4 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 1.5, 0.8 Hz, 1H, CHO), 7.96–7.88 (m, 2H, Ar), 7.59–7.51 (m, 1H, Ar), 7.50–7.40 (m, 2H, Ar), 7.34–7.27 (m, 3H, Ar), 7.25–7.19 (m, 2H, Ar), 6.40 (d, *J* = 9.0 Hz, 1H, NH), 5.01 (ddd, *J* = 9.1, 8.3, 0.9 Hz, 1H, CHNH), 3.88 (dt, *J* = 8.3, 6.6, 1H, CHPh), 3.55 (dd, *J* = 6.6, 2.6 Hz, 2H, CH_2), 3.50 (s, 3H, MeO); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.2 (CH, CHO), 171.2 (C, C=O), 160.9 (C, C=O), 139.5 (C), 136.7 (C), 133.5 (CH), 128.9 (CH), 128.8 (CH), 128.2 (CH), 128.2 (CH), 127.8 (CH), 55.6 (CH), 52.3 (CH_3), 43.6 (CH), 41.7 (CH_2); **HRMS** (ESI) *m/z*: 326.1385 $[M+H]^+$, $C_{19}H_{20}N_2O_4^+$ requires 326.1387.

Methyl (2*R*,3*S*)-3,5-diphenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (8)



To a solution of compound **7** (16.6 mg, 0.051 mmol) in MeOH (0.6 mL) was added 0.1 M $HCl_{(aq)}$ (153 µL, 0.153 mmol). The reaction was stirred for 3 h and quenched with $NaHCO_3$(aq) 0.1 M (1.53 mL, 0.153 mmol). The methanol was removed under reduced pressure and the aqueous mixture was extracted

with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The mixture was chromatographed (Hexane:AcOEt 7:3) and 8.5 mg (60%) of **8** were obtained. The spectroscopical data is in accordance with the literature description.[14] Enantiomeric excess (85%) was determined by HPLC (CHIRALPAK® IC), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 12.8 min, minor enantiomer: t_r = 15.7 min.

Yellow oil; $[\alpha]_D^{25}$ –41.8 (*c* 0.7, $CHCl_3$), $[\alpha]_D^{25}$ –42.6 (*c* 0.7, CH_2Cl_2), reported in the literature[14] for the opposite enantiomer +64.8 (*c* 0.42, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96–7.88 (m, 2H, Ar), 7.53–7.40 (m, 3H, Ar), 7.37–7.29 (m, 2H, Ar), 7.28–7.20 (m, 3H, Ar), 4.97 (dt, *J* = 6.0, 1.9 Hz, 1H, CHN), 3.90 (dt, *J* = 9.7, 6.3 Hz, 1H, CHPh), 3.79 (s, 3H, MeO), 3.67 (ddd, *J* = 17.3, 9.7, 2.1 Hz, 1H, CH_2), 3.18 (ddd, *J* = 17.4, 6.5, 1.7 Hz, 1H, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.2 (C, C=O), 172.8 (C, C=N), 143.3 (C), 133.7 (C), 131.4 (CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 127.1 (CH), 127.1 (CH), 82.7 (CH), 52.6 (CH_3), 46.4 (CH), 44.9 (CH_2); **HRMS** (ESI) *m/z*: 302.1160 $[M+Na]^+$, $C_{18}H_{17}NNaO_2^+$ requires 302.1151.

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[13] Although all enantioselective reactions reported in this SI were carried out protected from light, later control experiments have shown that this is not indeed required.
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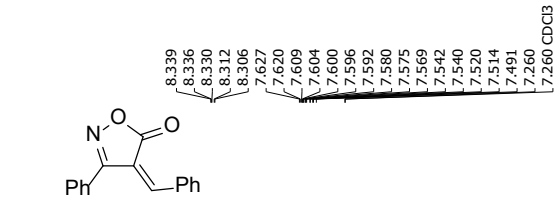
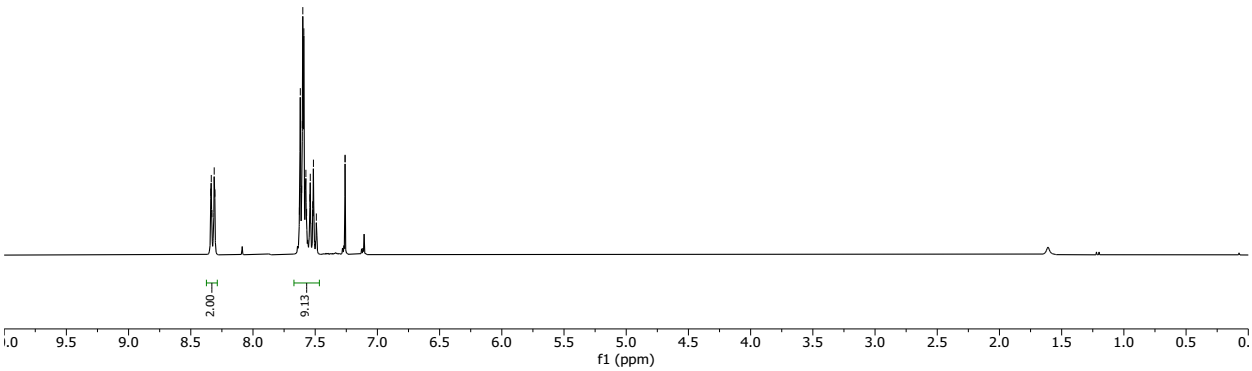
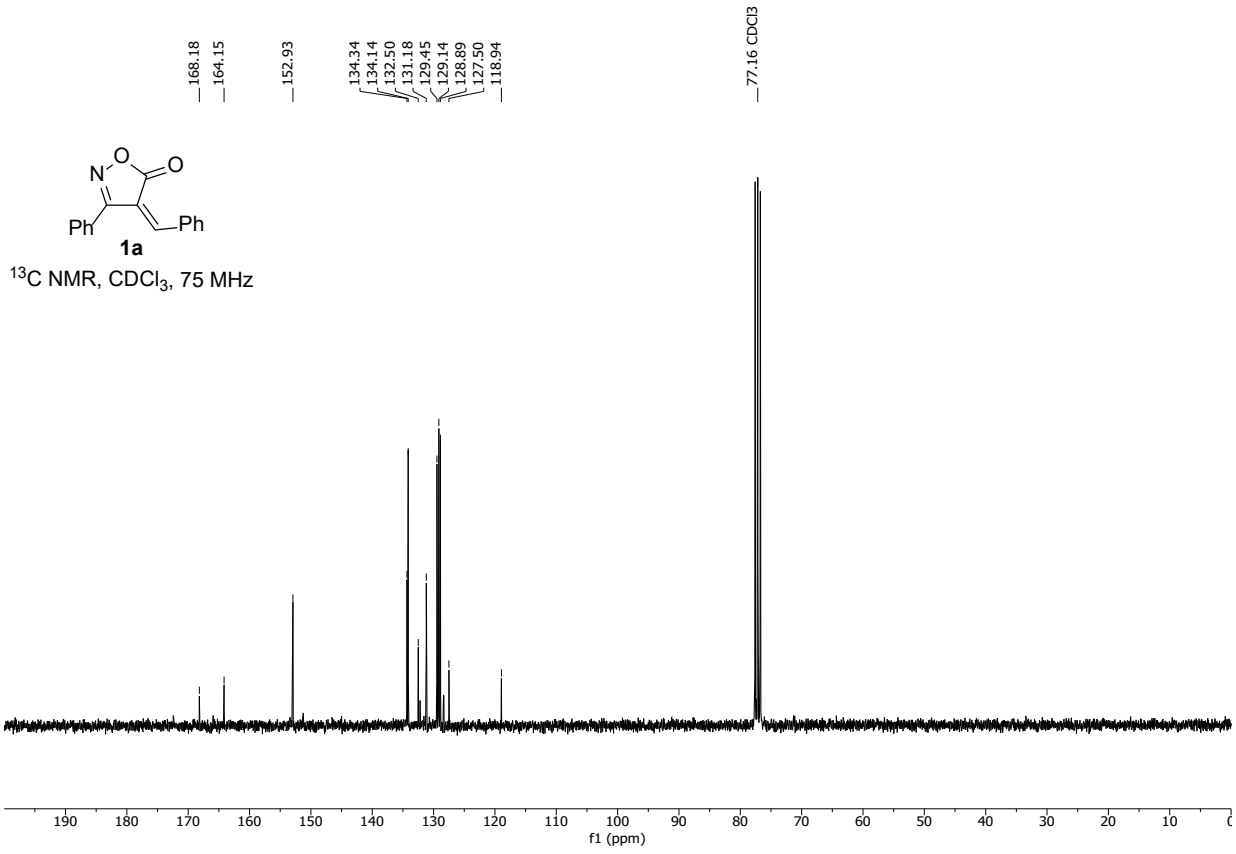
8. NMR spectra



1a

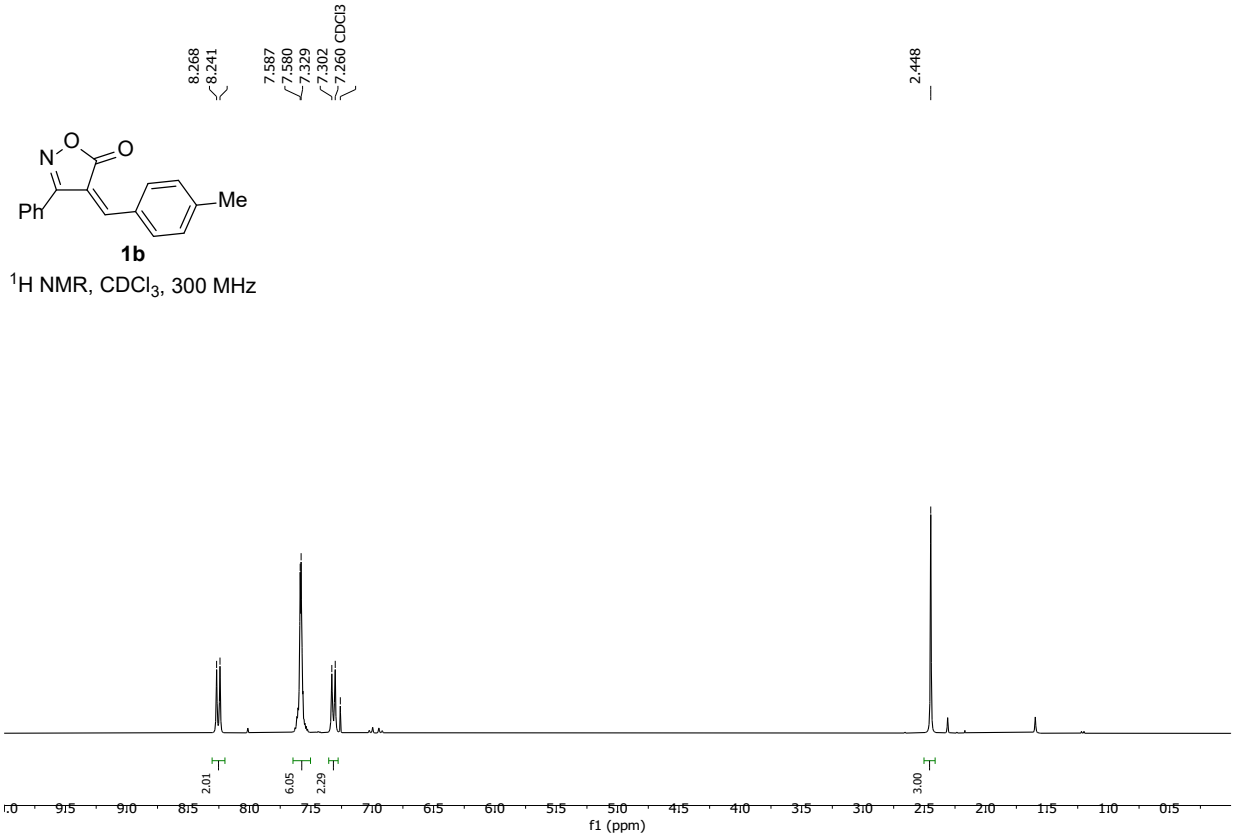
^{1}H NMR, $CDCl_3$, 300 MHz





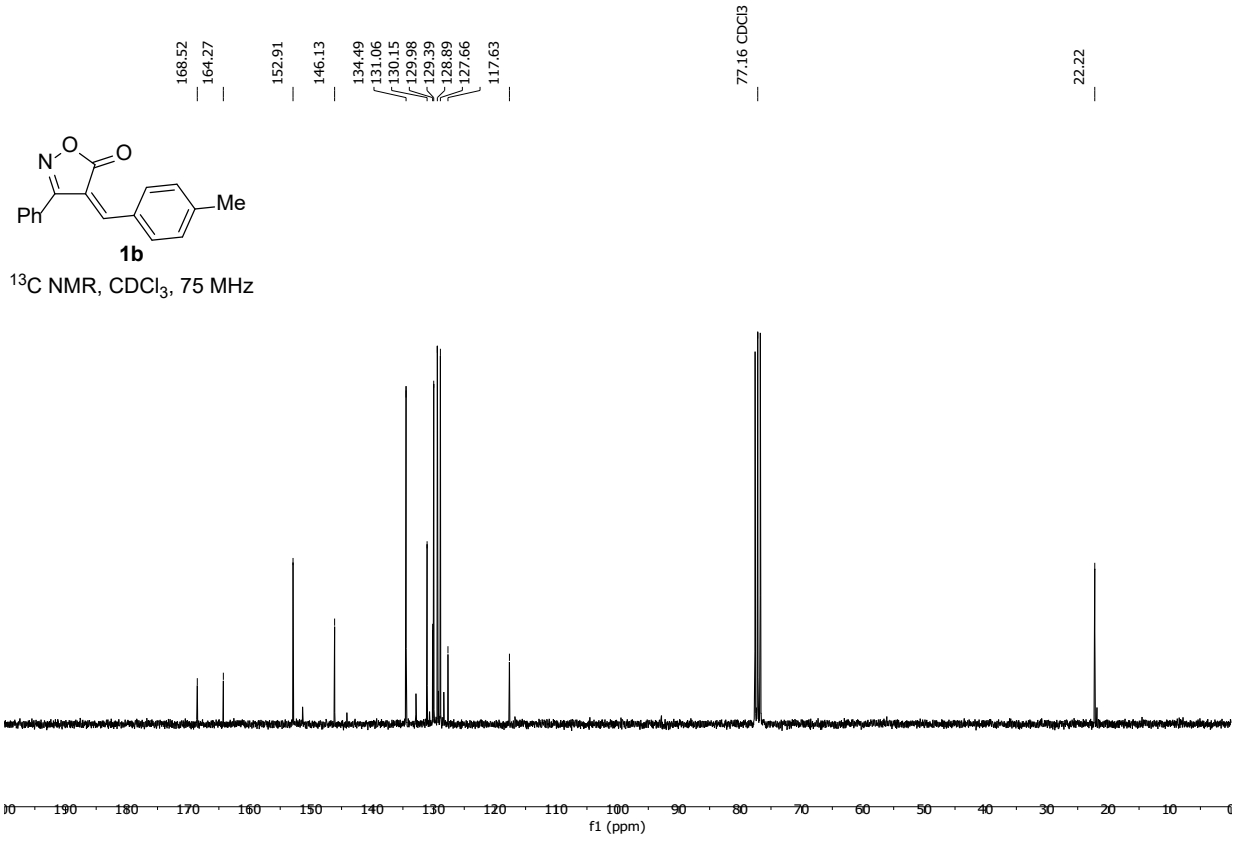
1a

^{13}C NMR, $CDCl_3$, 75 MHz



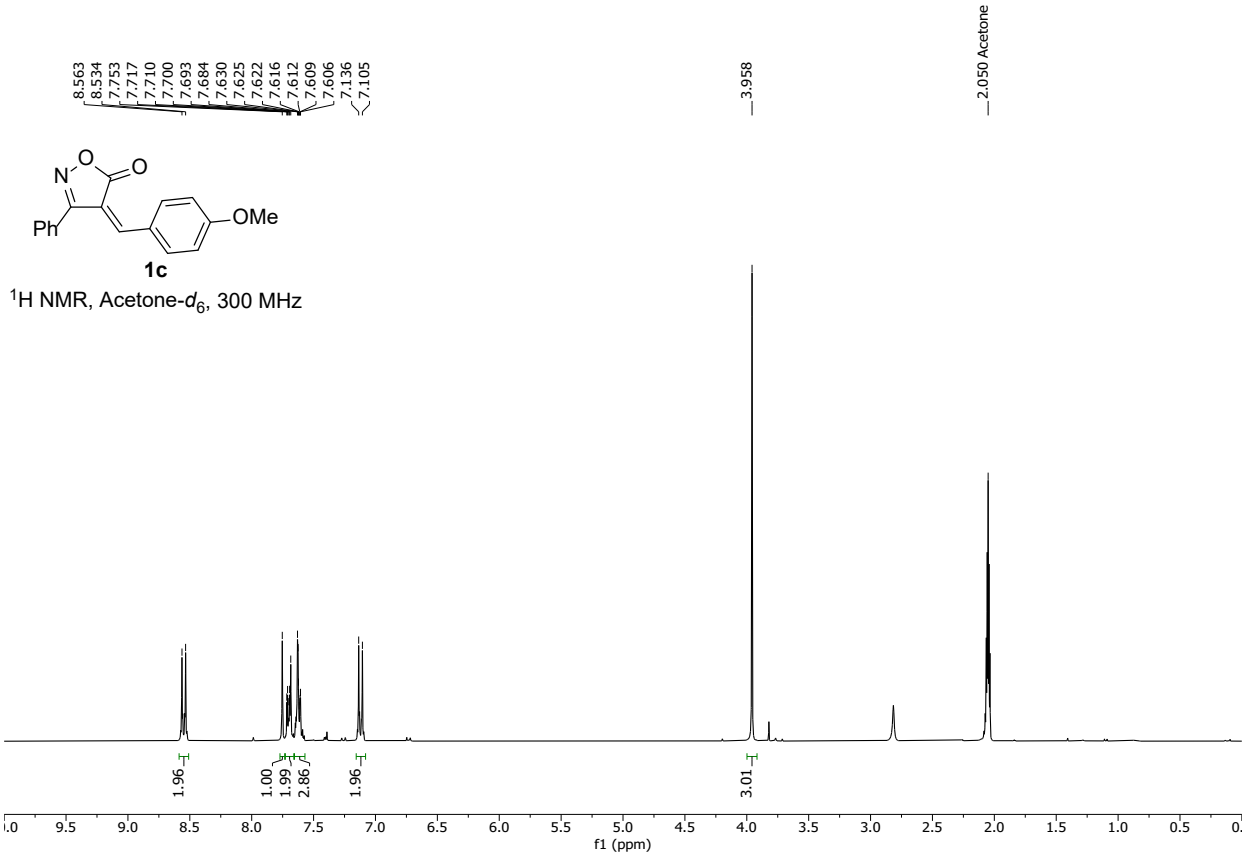
1b

^{1}H NMR, $CDCl_3$, 300 MHz



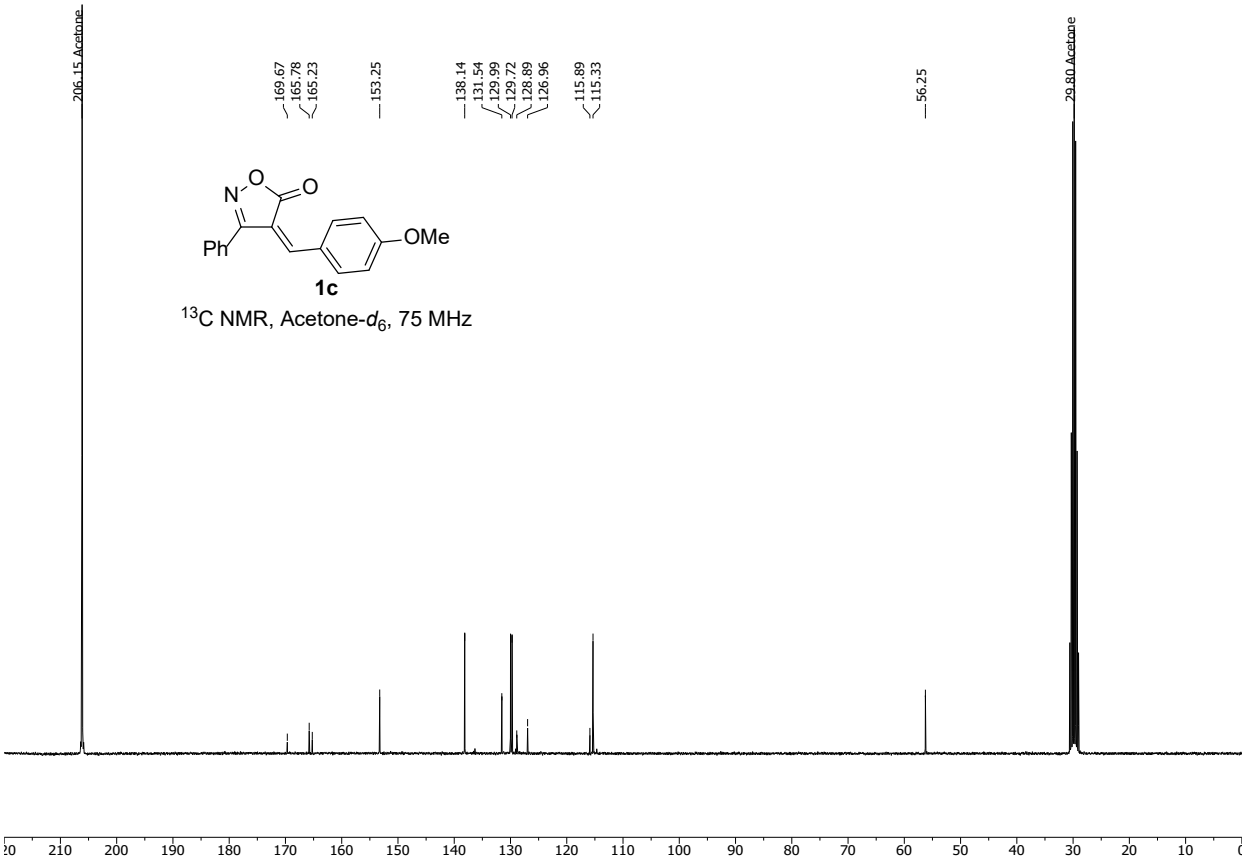
1b

^{13}C NMR, $CDCl_3$, 75 MHz



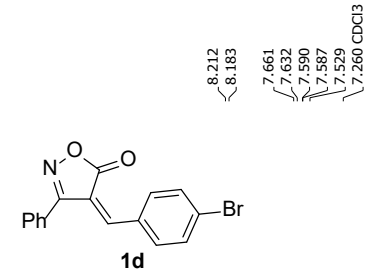
1c

^{1}H NMR, Acetone-d_6, 300 MHz



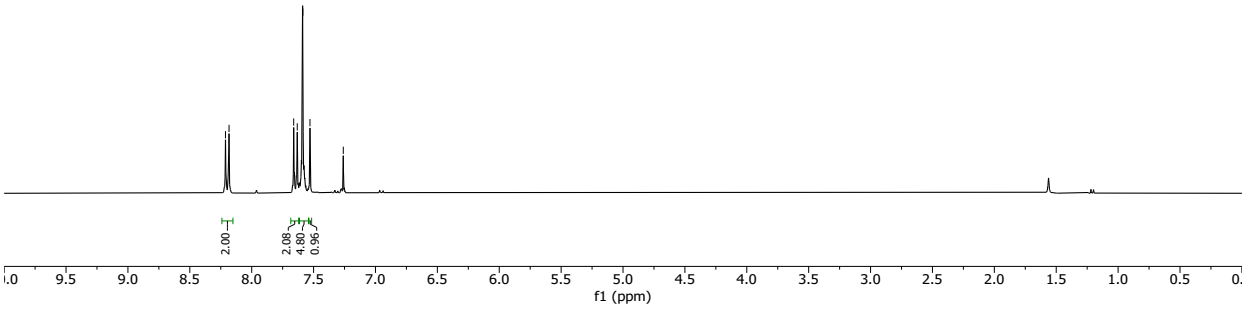
1c

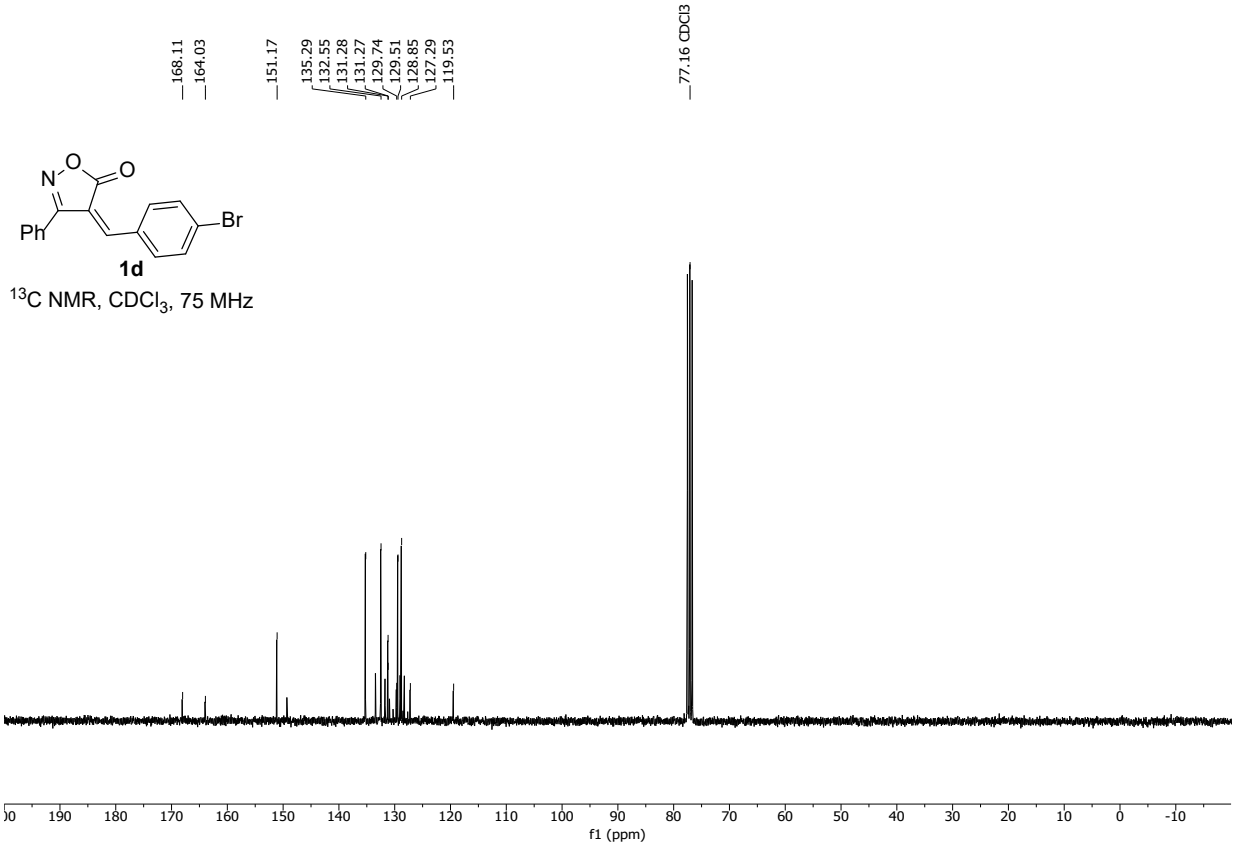
^{13}C NMR, Acetone-d_6, 75 MHz



1d

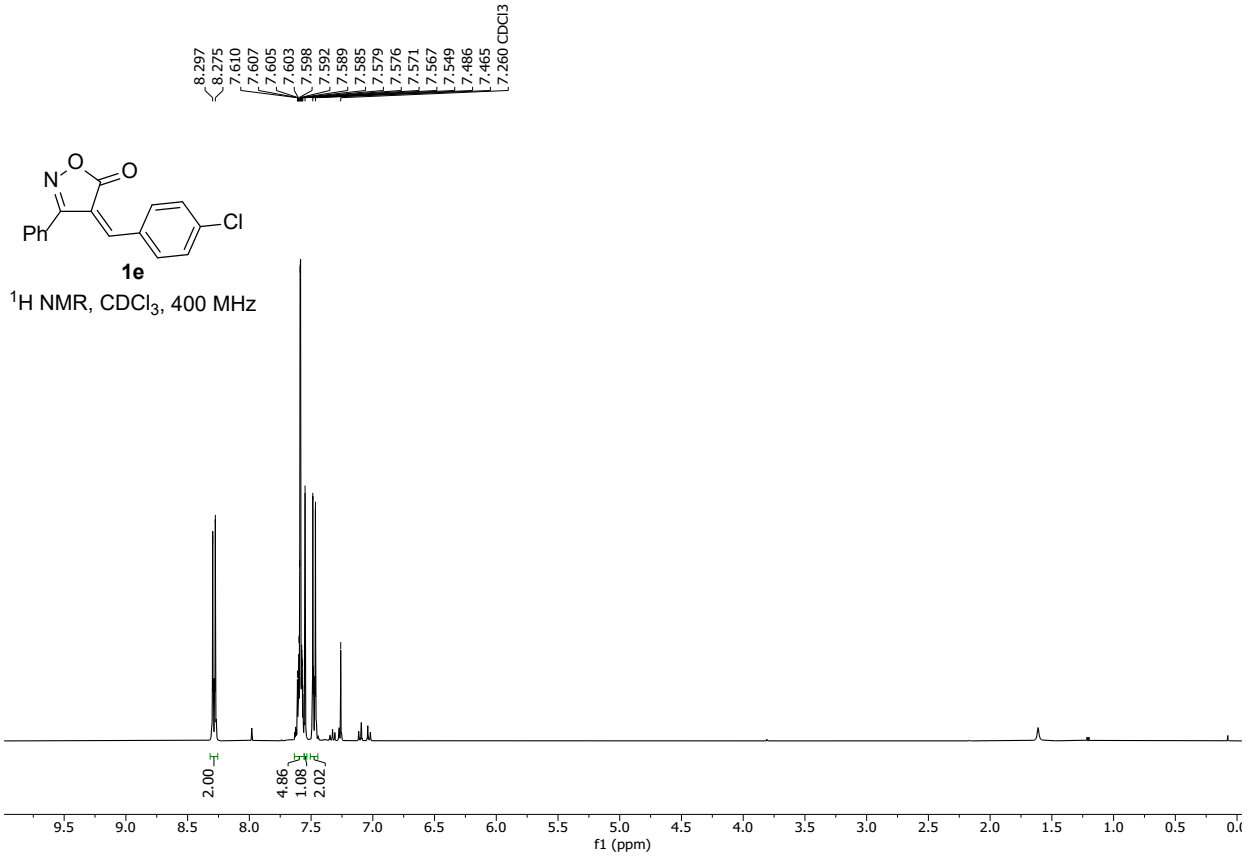
^{1}H NMR, $CDCl_3$, 300 MHz





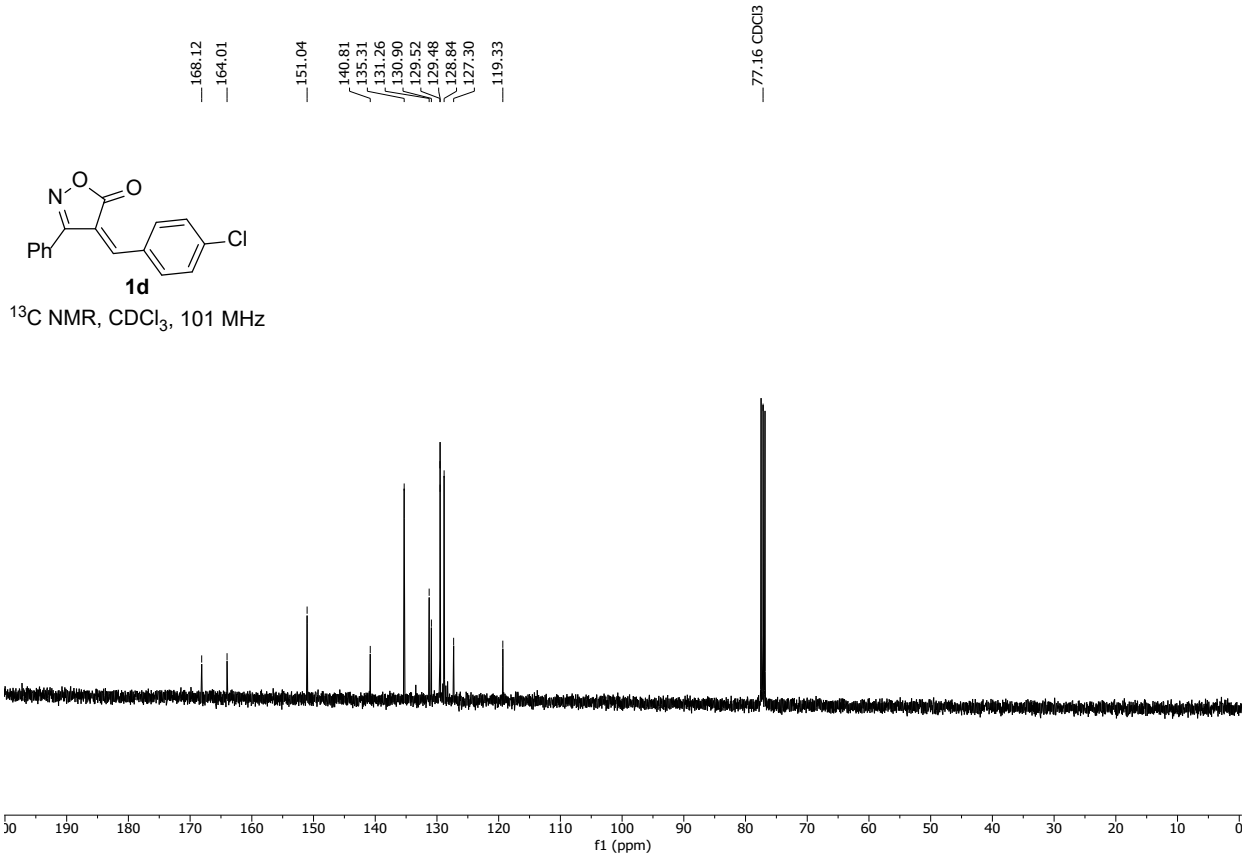
1d

^{13}C NMR, $CDCl_3$, 75 MHz



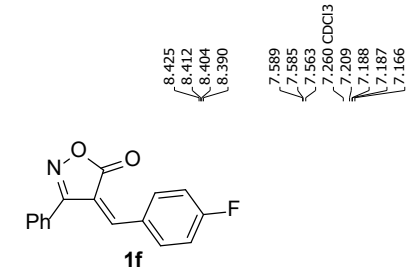
1e

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



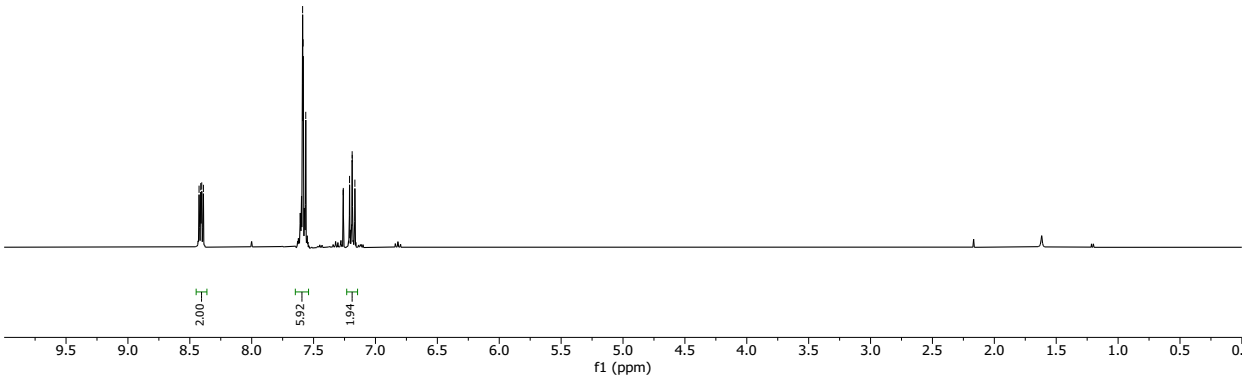
1d

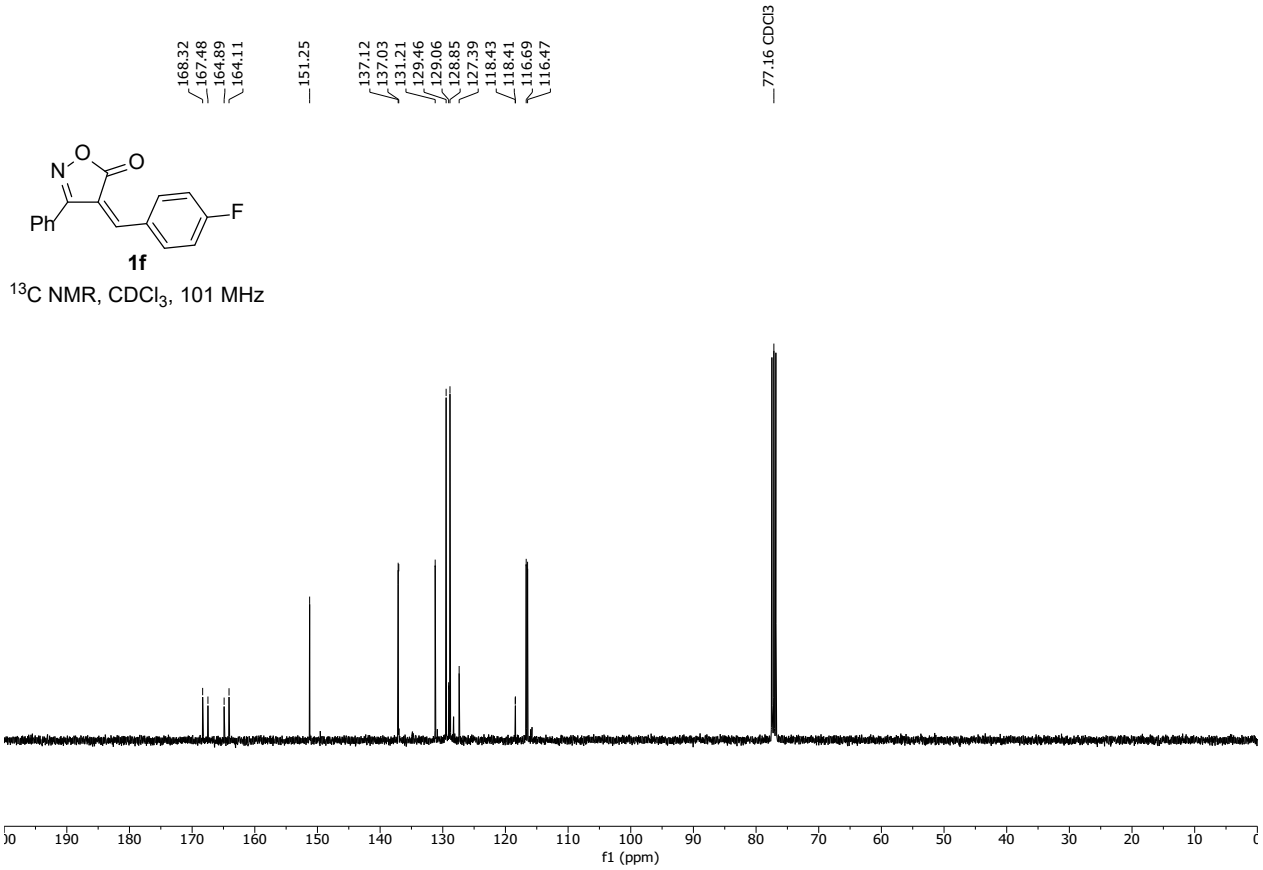
^{13}C NMR, $CDCl_3$, 101 MHz



1f

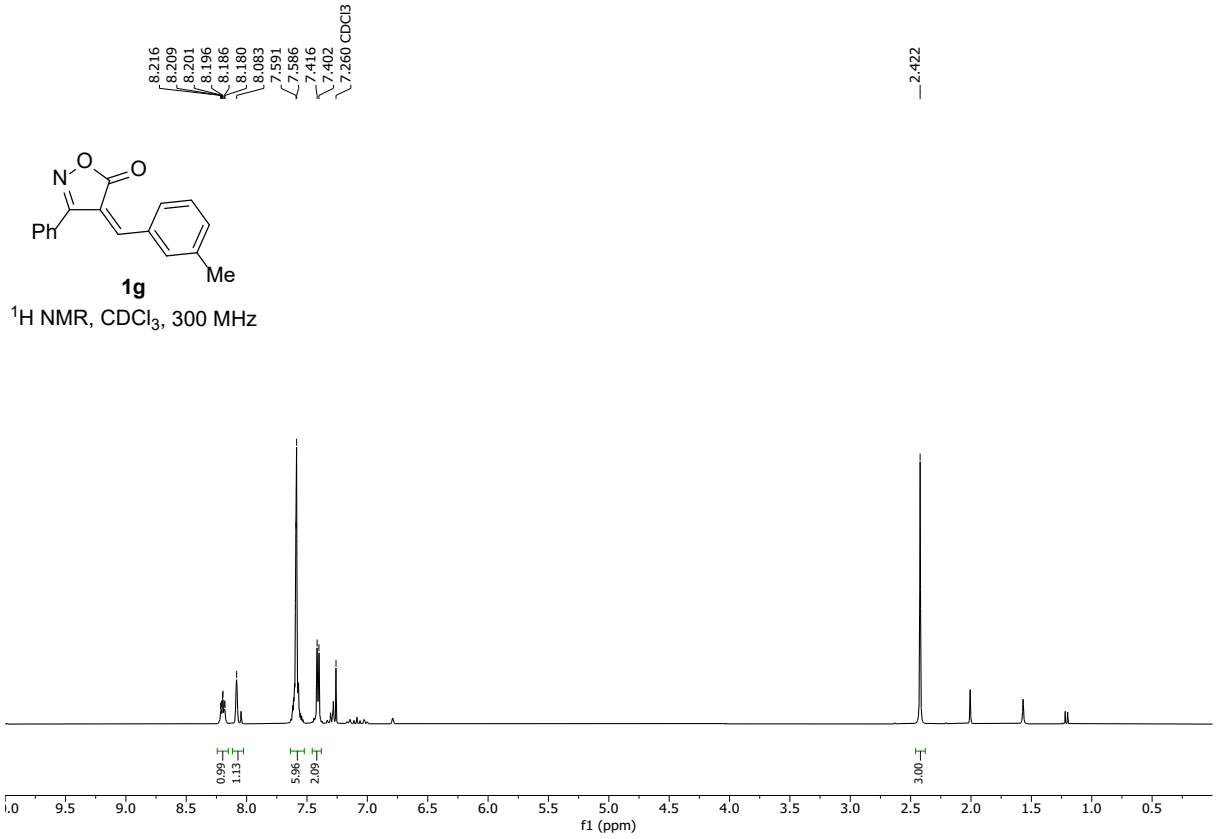
^{1}H NMR, $CDCl_3$, 400 MHz





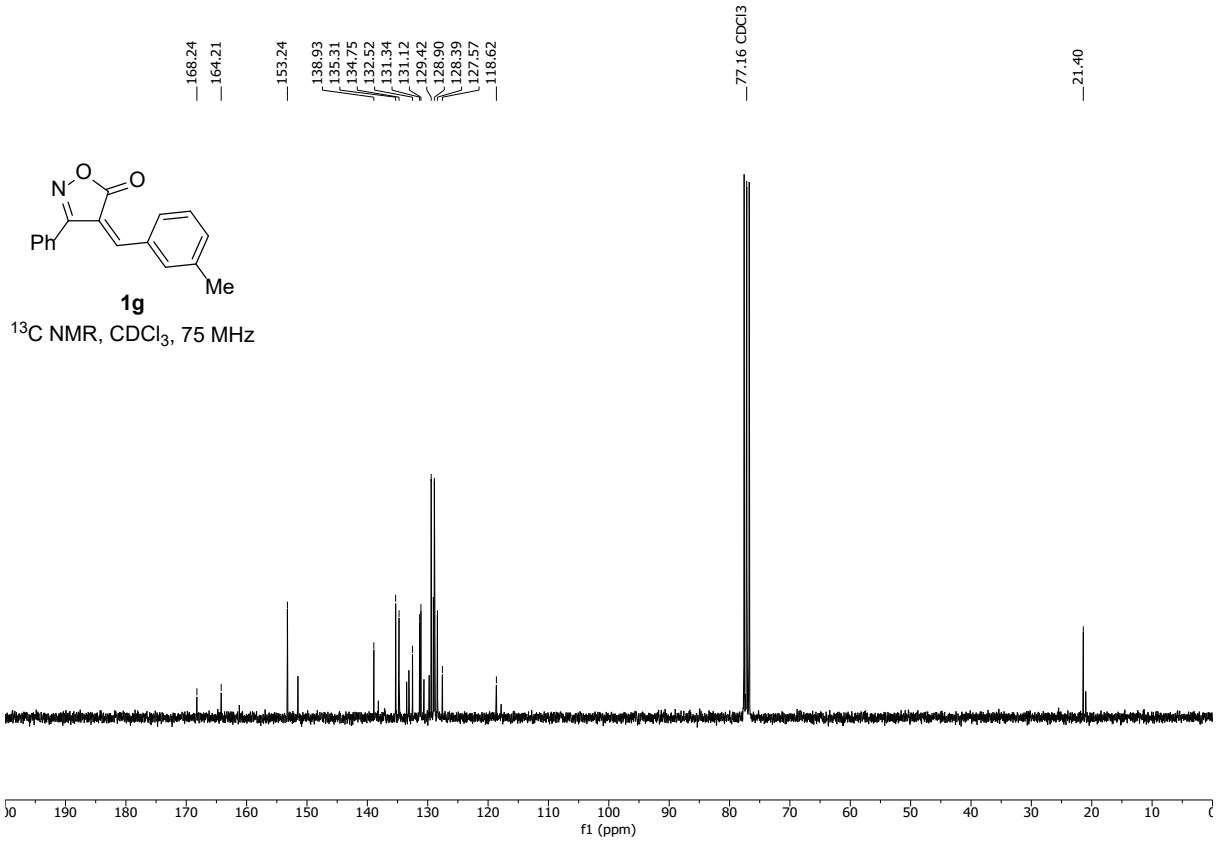
1f

^{13}C NMR, $CDCl_3$, 101 MHz



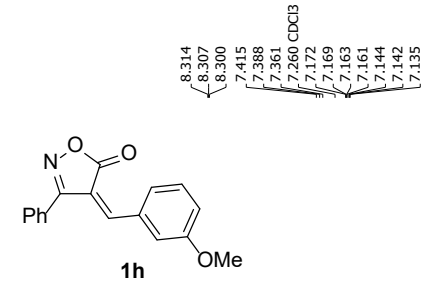
1g

^{1}H NMR, $CDCl_3$, 300 MHz



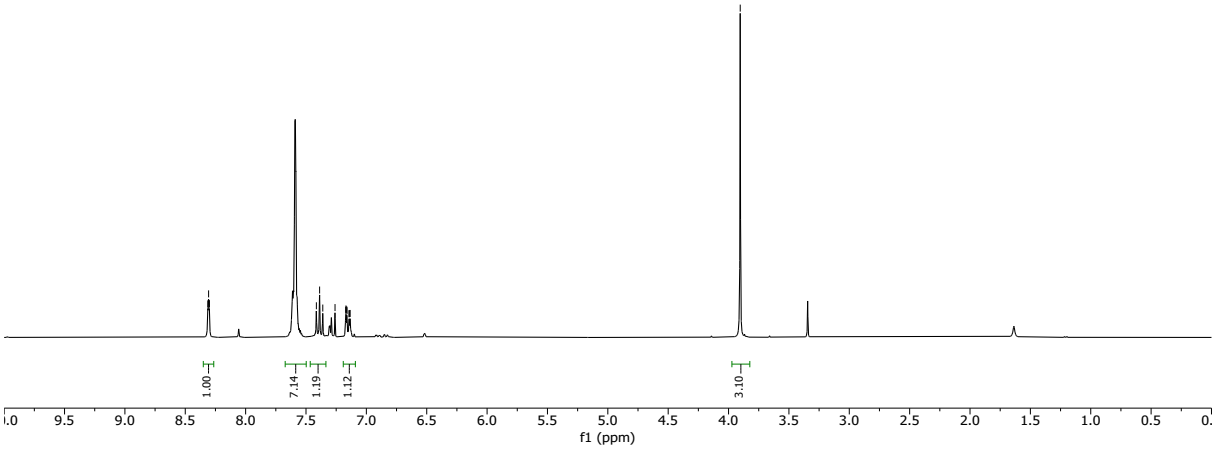
1g

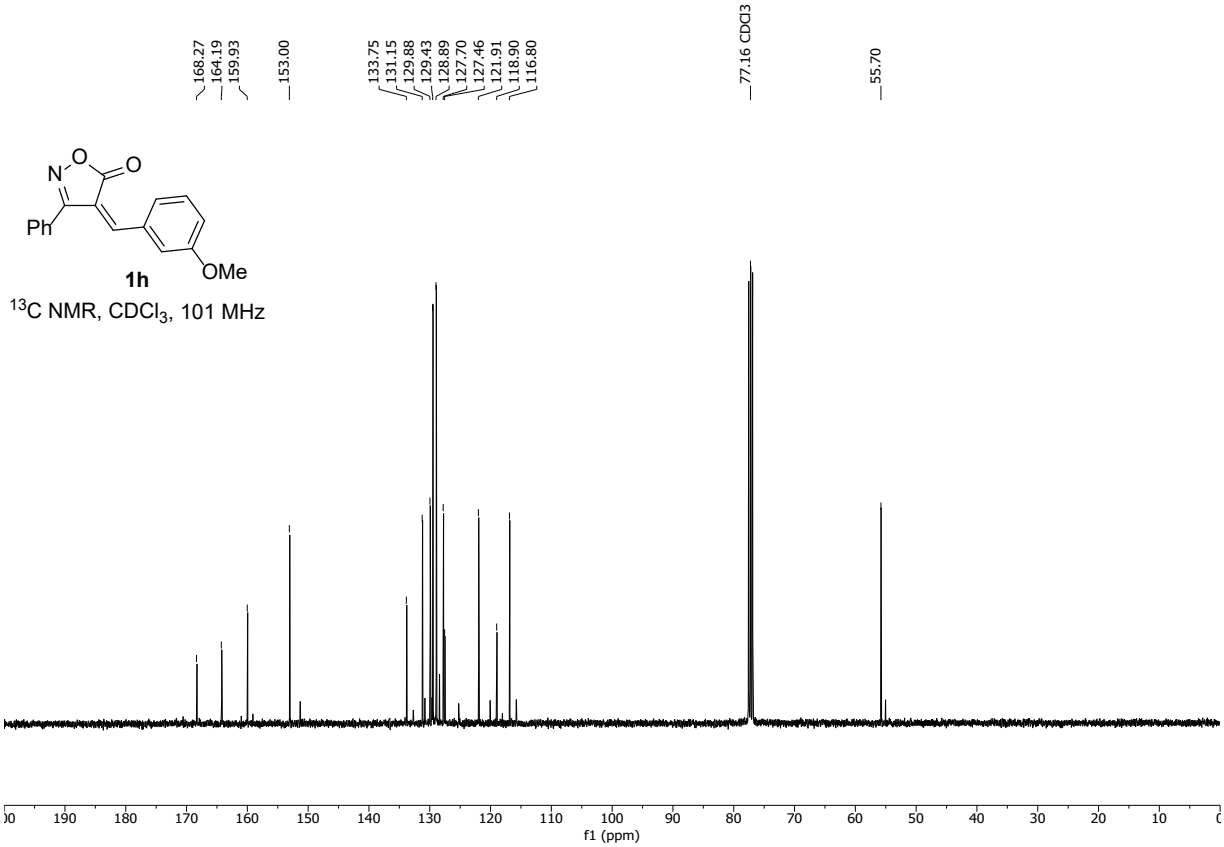
^{13}C NMR, $CDCl_3$, 75 MHz



1h

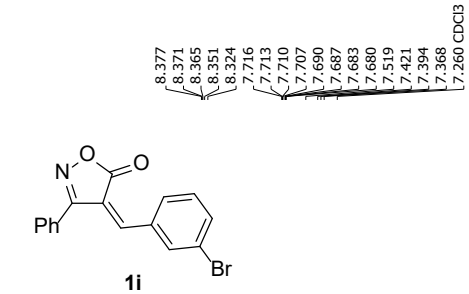
^{1}H NMR, $CDCl_3$, 300 MHz





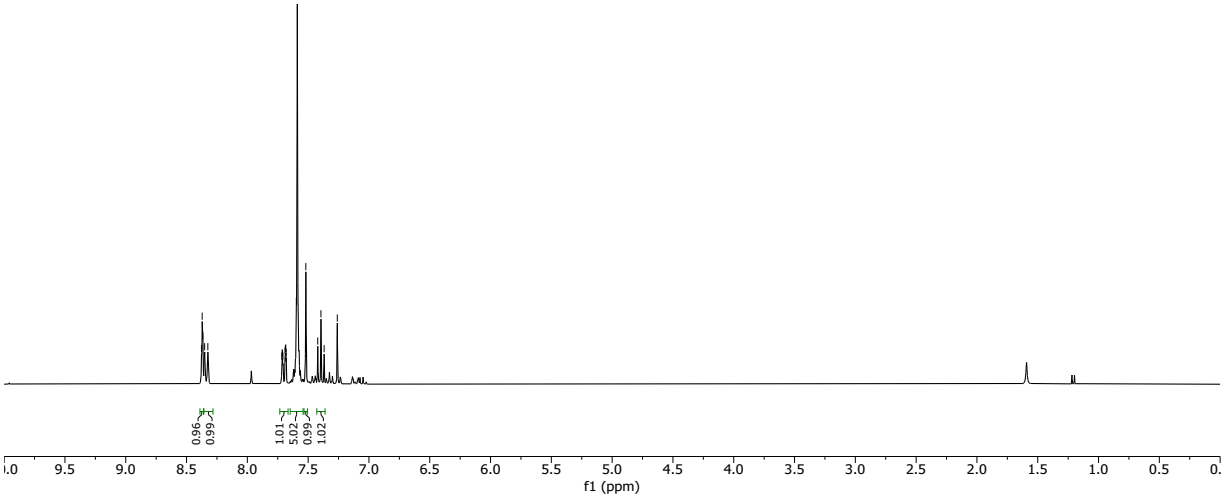
1h

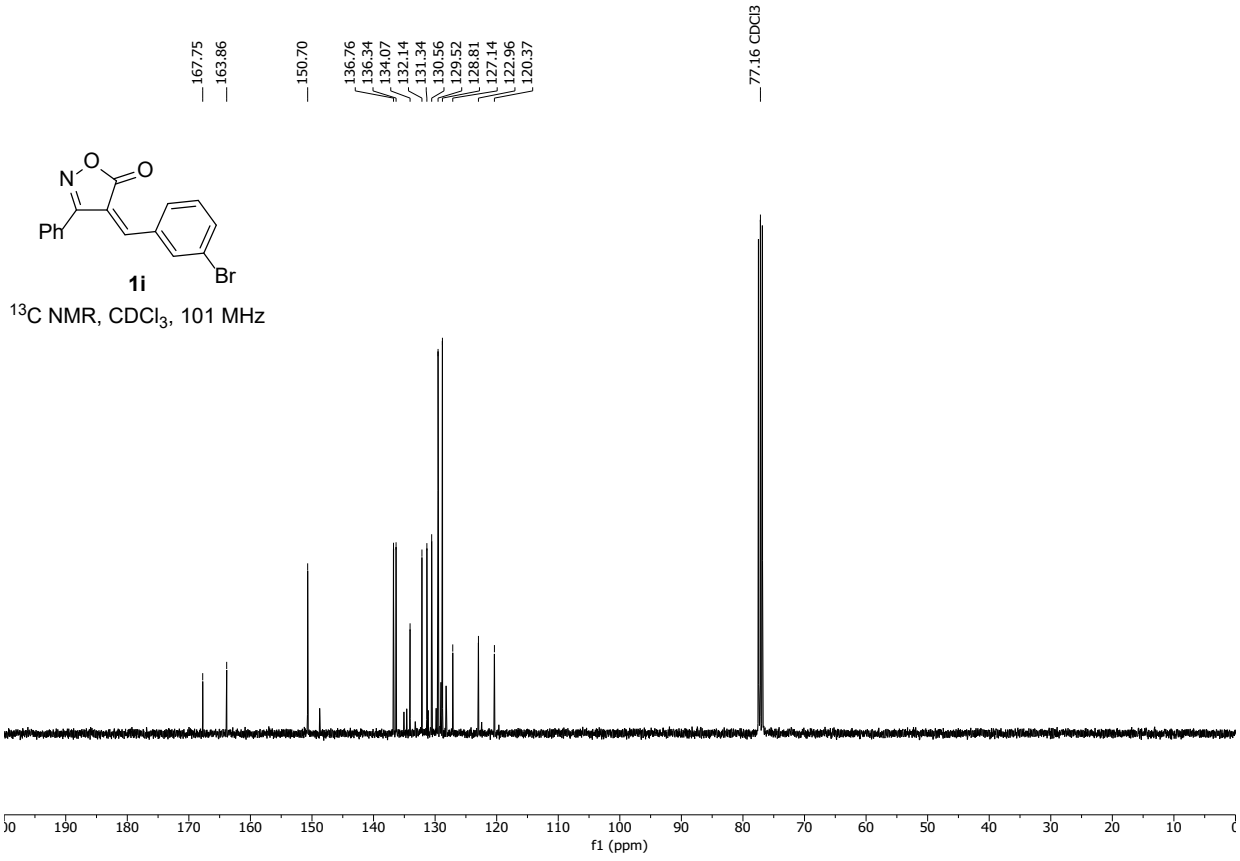
^{13}C NMR, $CDCl_3$, 101 MHz



1i

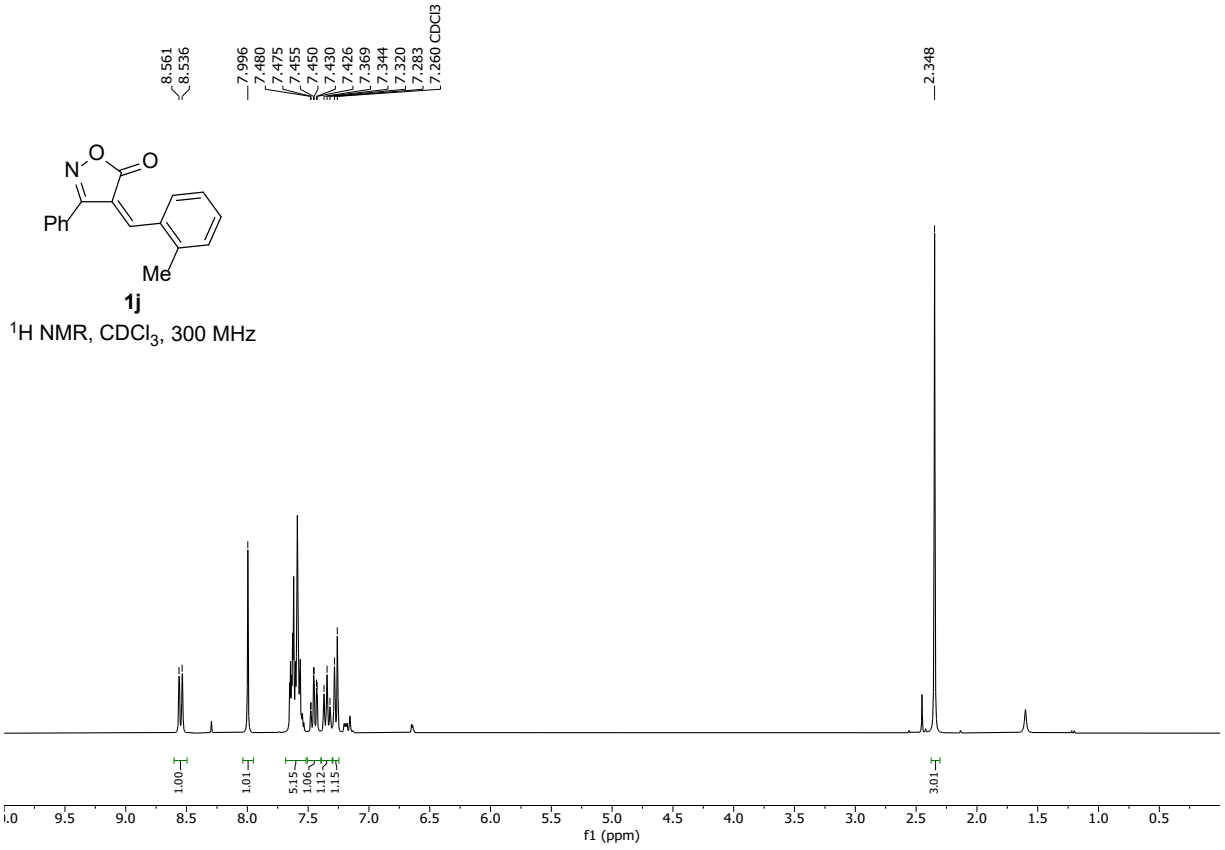
^{1}H NMR, $CDCl_3$, 300 MHz





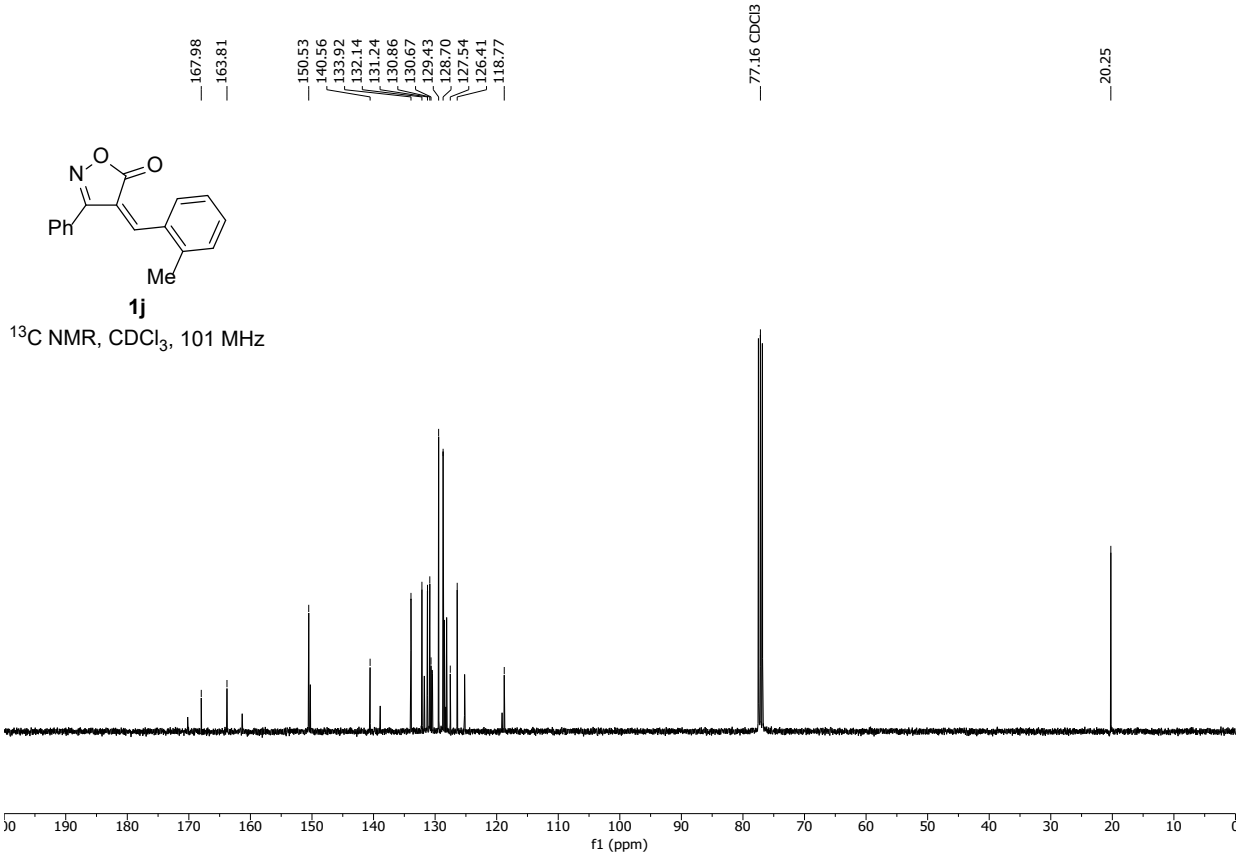
1i

^{13}C NMR, $CDCl_3$, 101 MHz



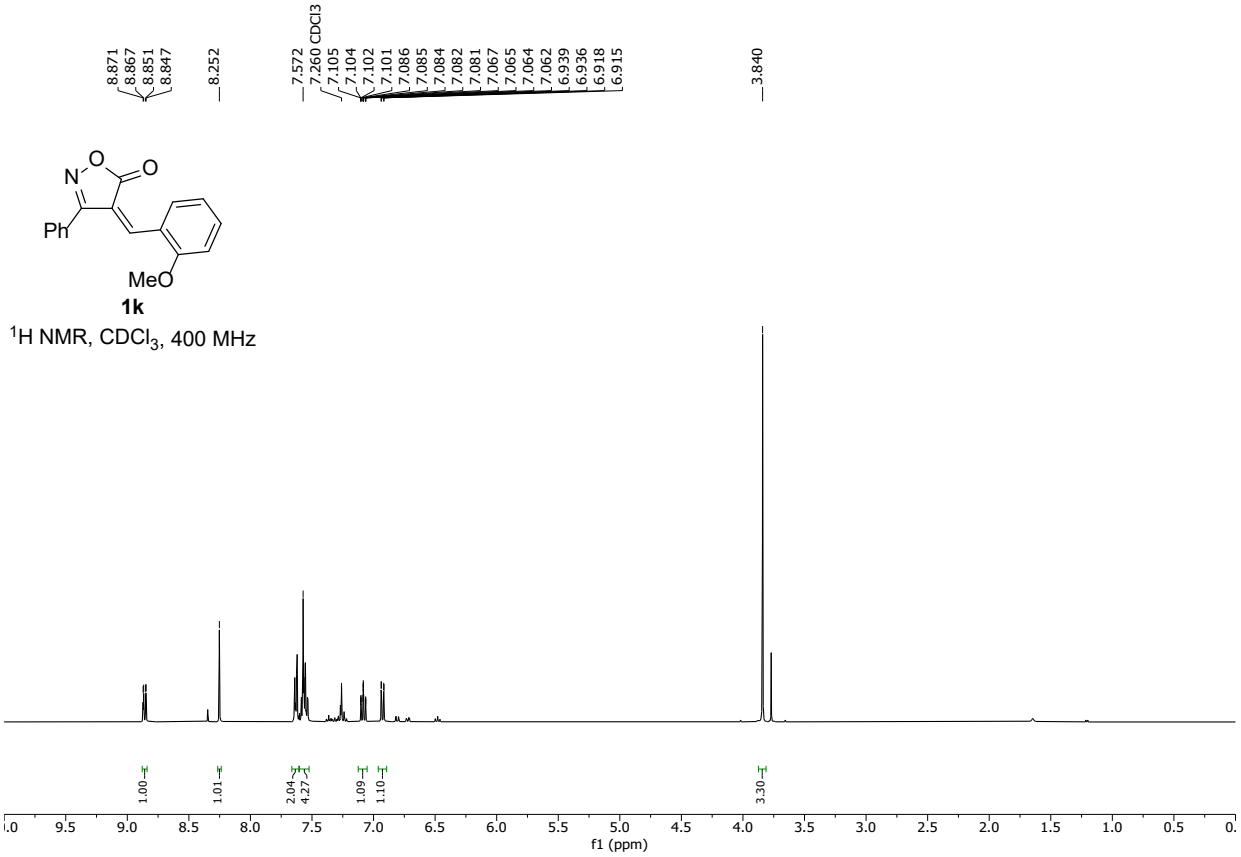
1j

^{1}H NMR, $CDCl_3$, 300 MHz



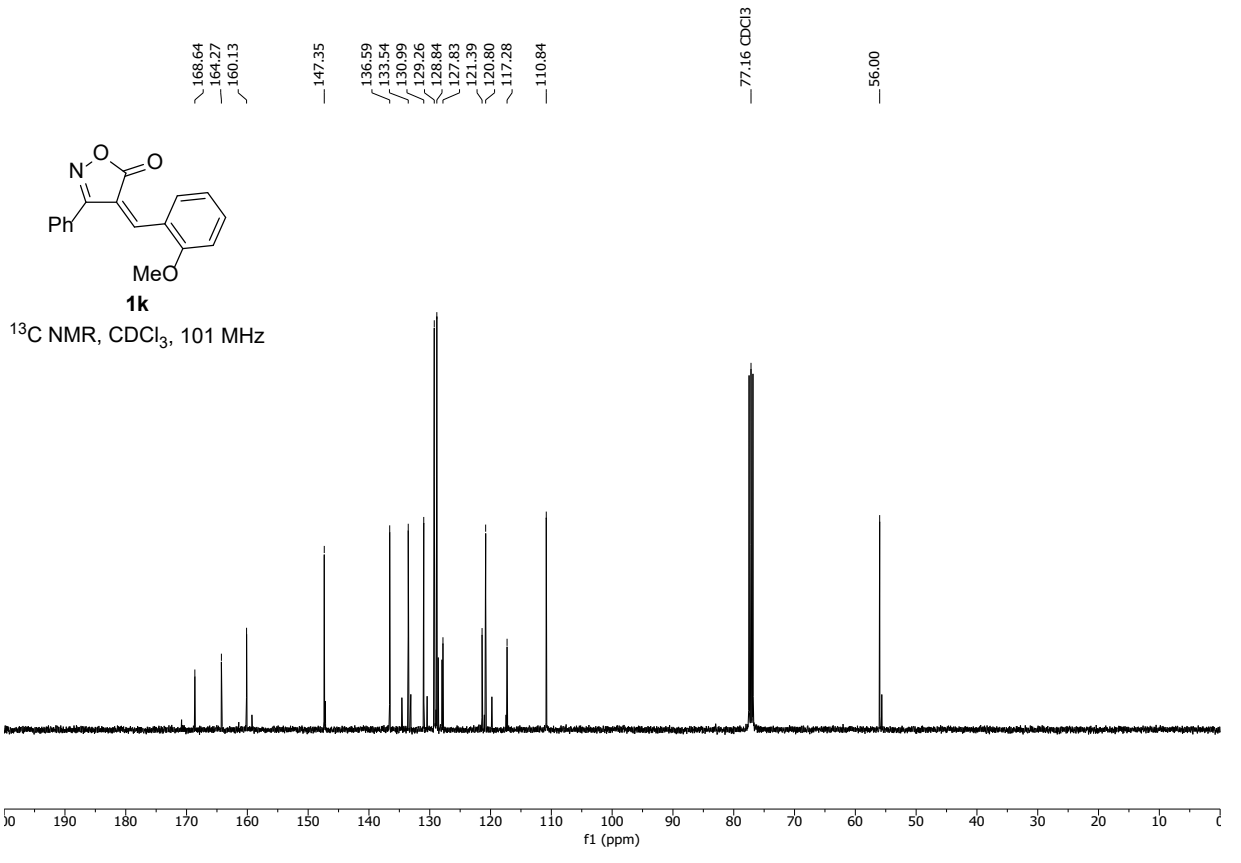
1j

^{13}C NMR, $CDCl_3$, 101 MHz



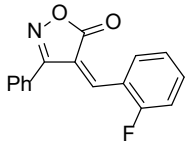
1k

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



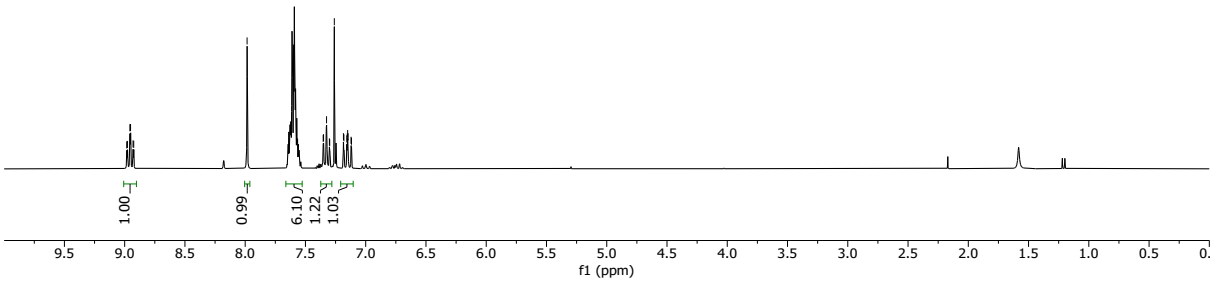
1k

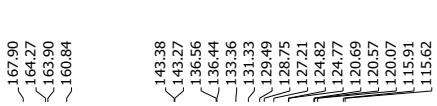
^{13}C NMR, $CDCl_3$, 101 MHz

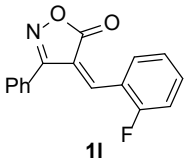


1l

^{1}H NMR, $CDCl_3$, 300 MHz

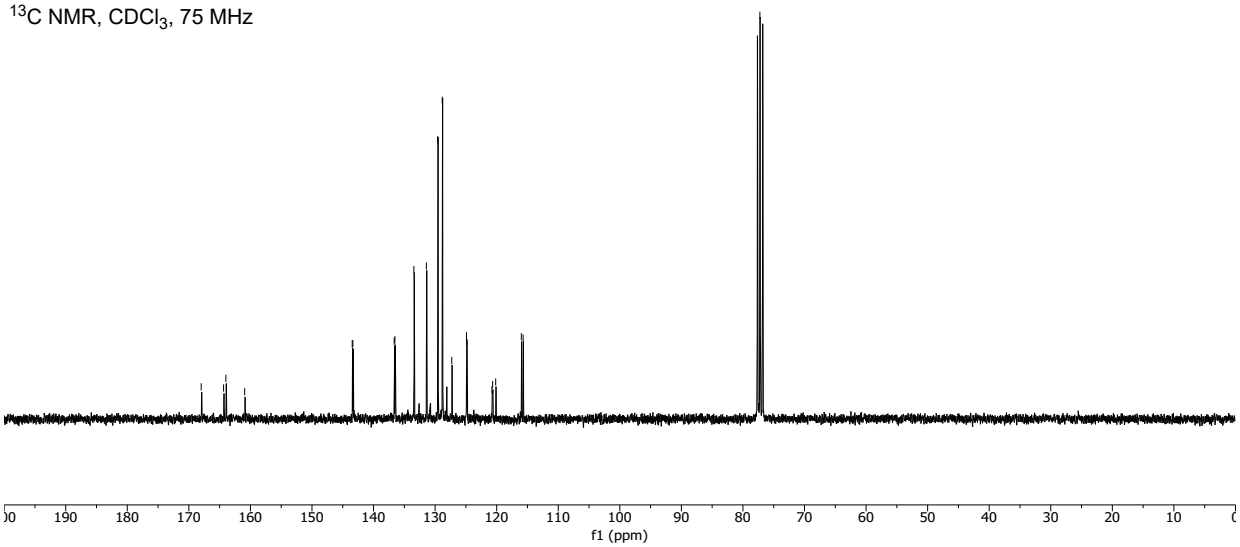


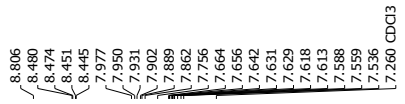


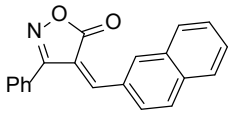


1l

^{13}C NMR, $CDCl_3$, 75 MHz

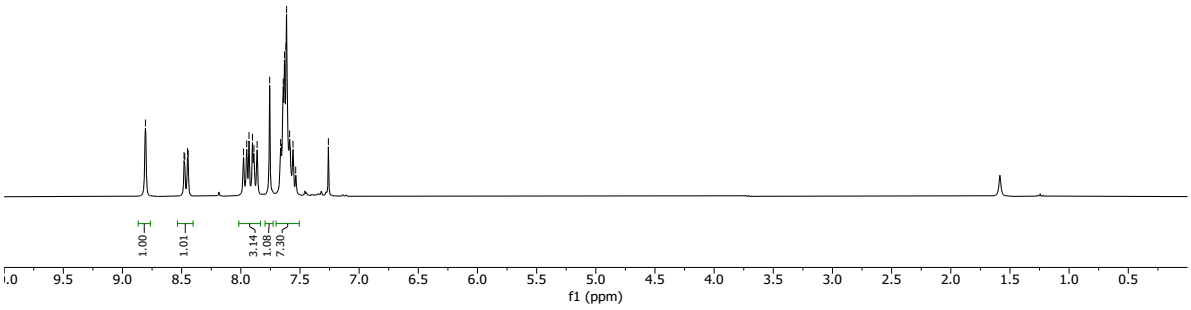


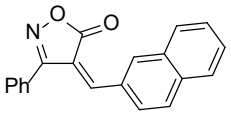




1m

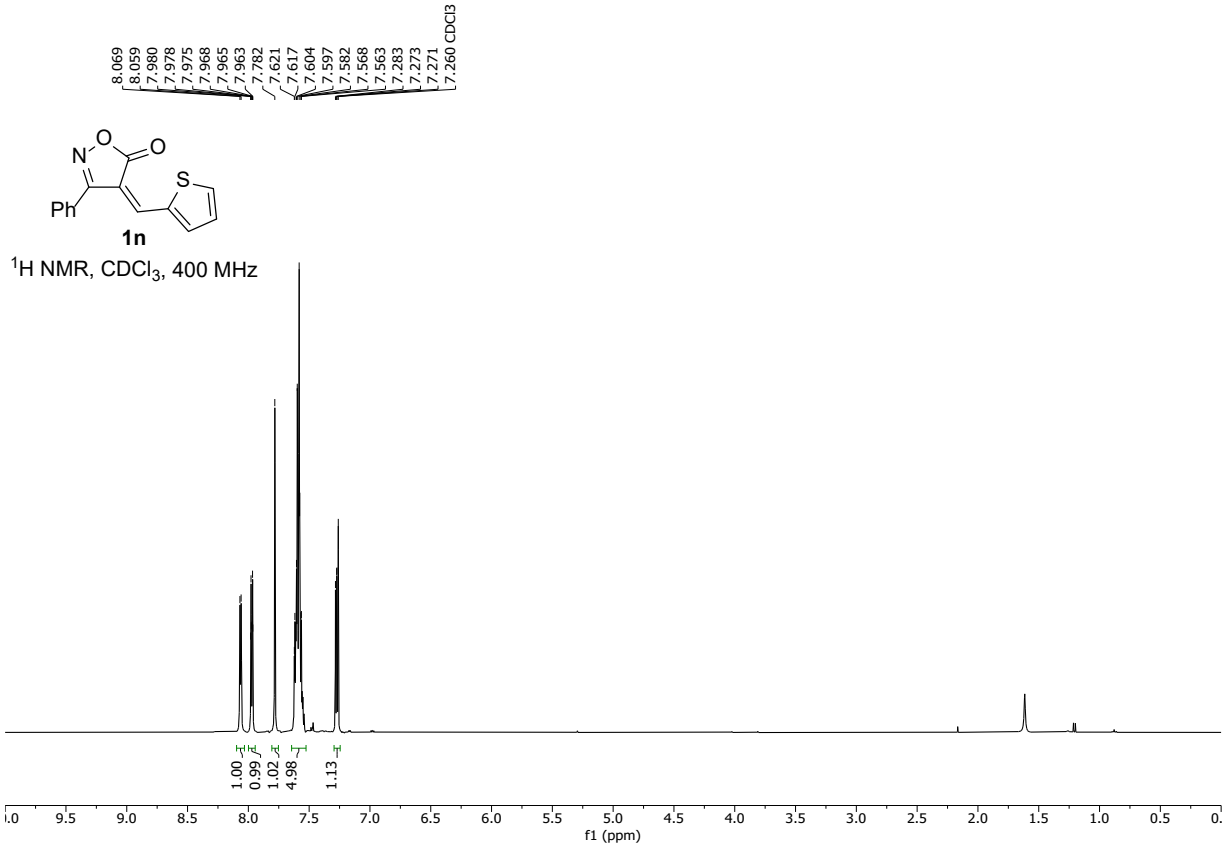
^{1}H NMR, $CDCl_3$, 300 MHz





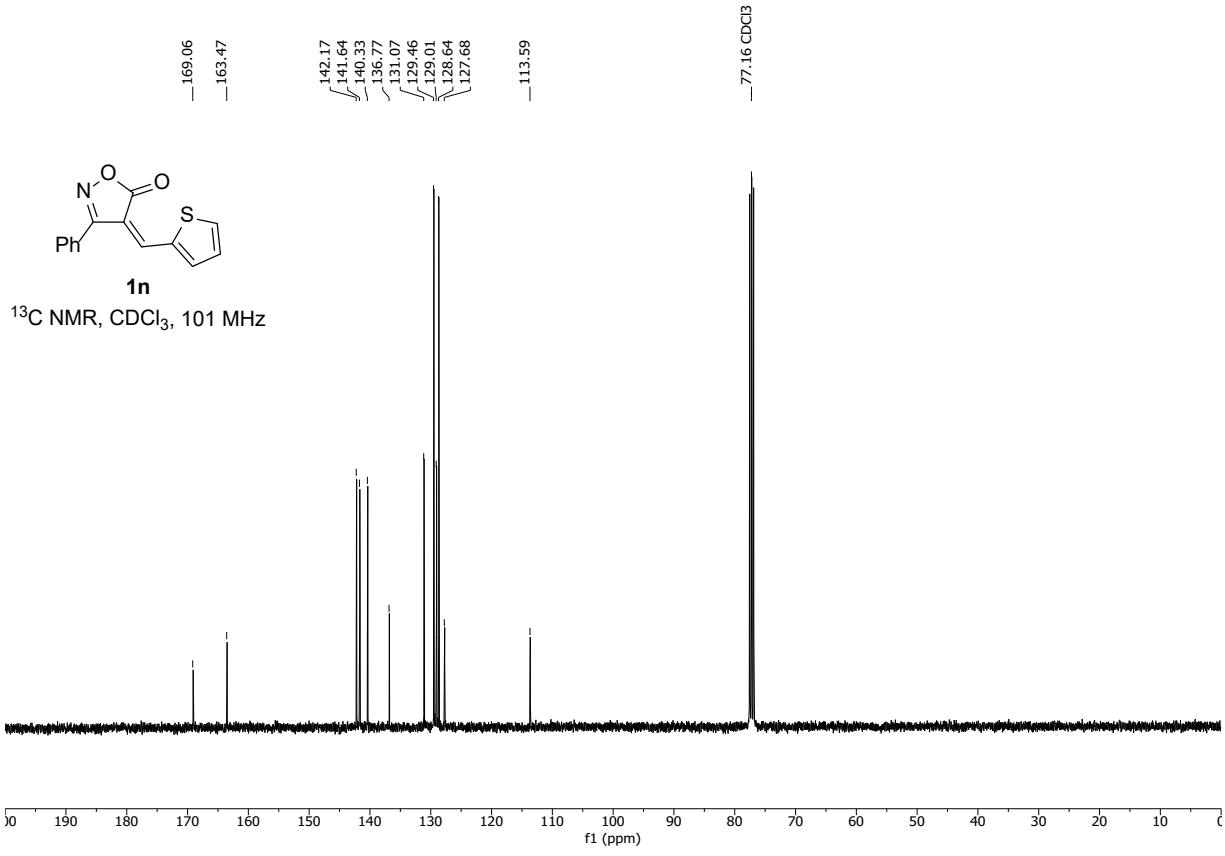
1m

^{13}C NMR, $CDCl_3$, 75 MHz



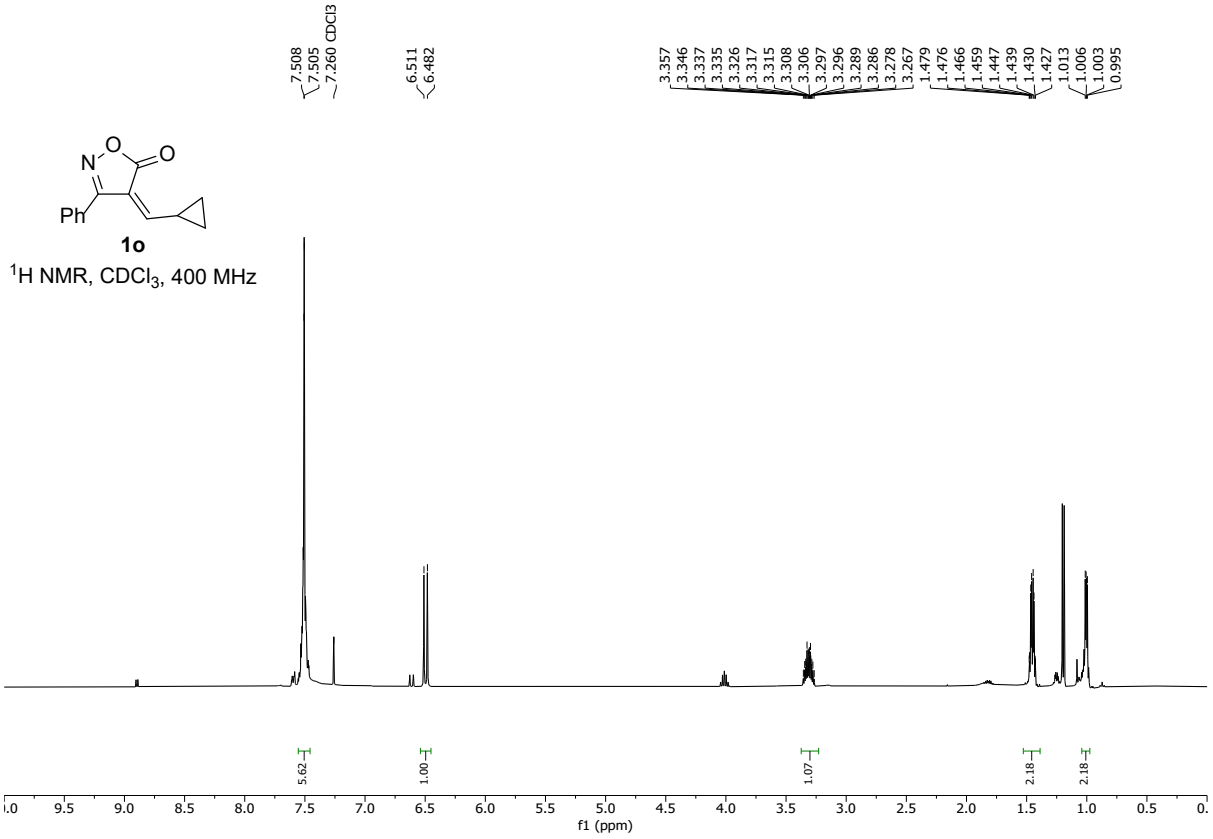
1n

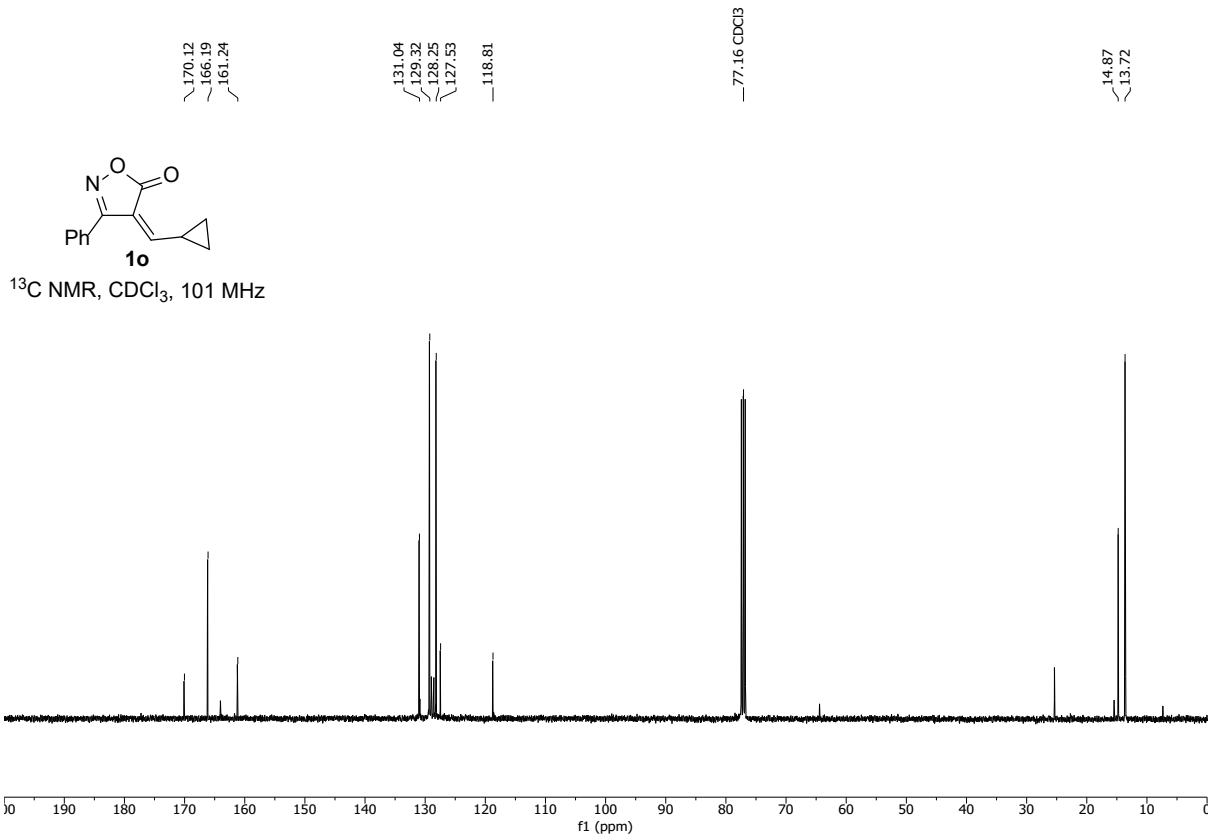
^{1}H NMR, $CDCl_3$, 400 MHz

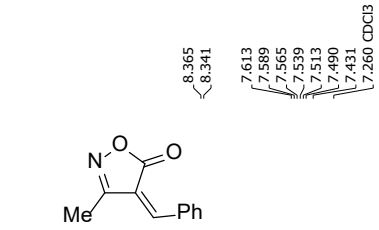


1n

^{13}C NMR, $CDCl_3$, 101 MHz

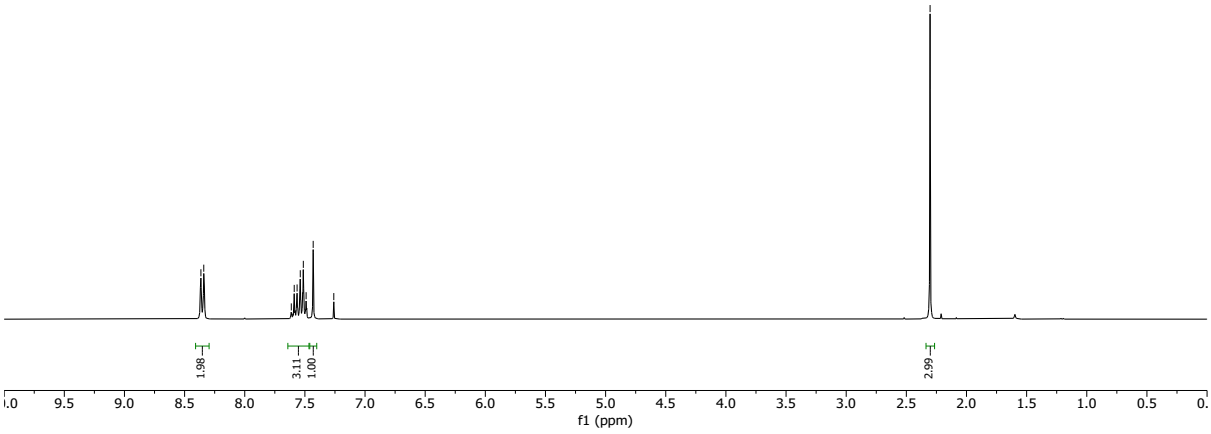

7.508
7.505
7.260 CDCl3
6.511
6.482
3.357
3.346
3.337
3.335
3.326
3.317
3.315
3.308
3.306
3.297
3.296
3.289
3.286
3.278
3.267
1.479
1.476
1.466
1.459
1.447
1.439
1.430
1.427
1.013
1.006
1.003
0.995
O
N
O
Ph
1o
1H NMR, CDCl3, 400 MHz
5.62
1.00
1.07
2.18
2.18
f1 (ppm)

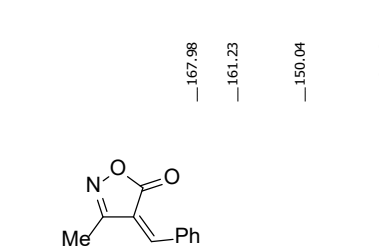

170.12
166.19
161.24
131.04
129.32
128.25
127.53
118.81
77.16 CDCl3
14.87
13.72
O
N
O
Ph
1o
13C NMR, CDCl3, 101 MHz
f1 (ppm)



1p

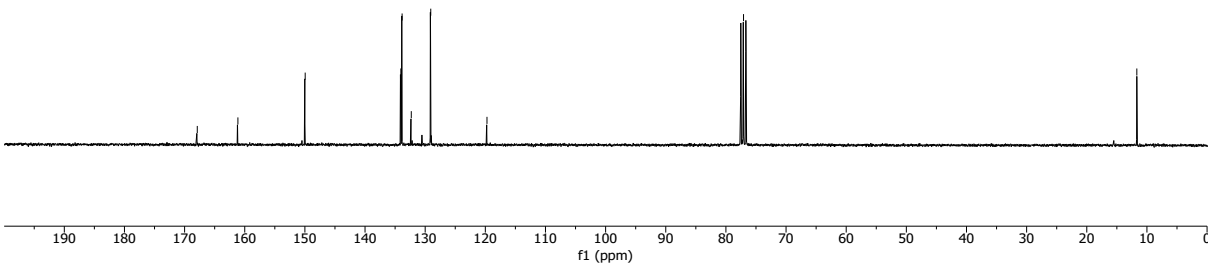
^{1}H NMR, $CDCl_3$, 300 MHz

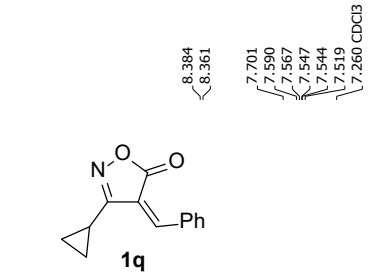




1p

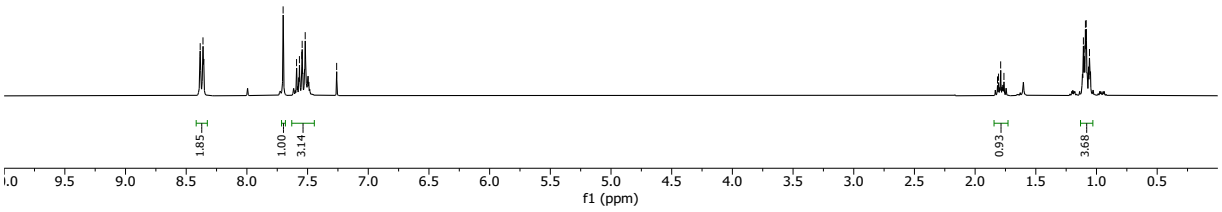
^{13}C NMR, $CDCl_3$, 75 MHz

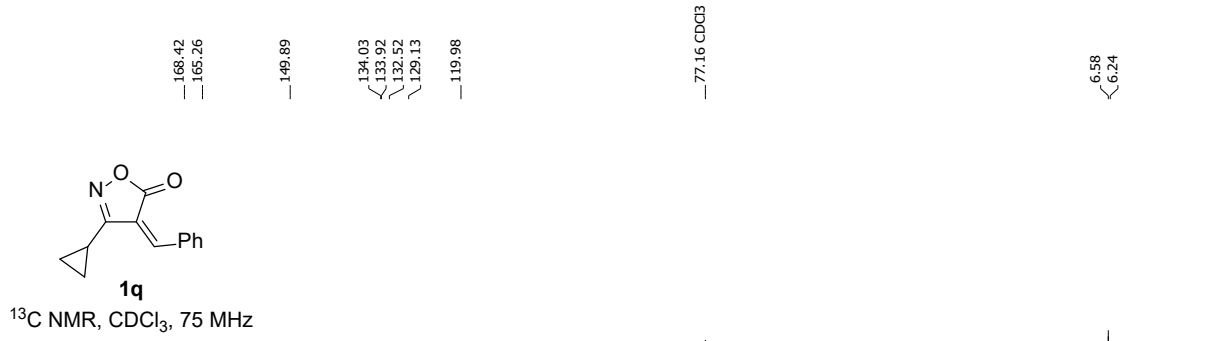




1q

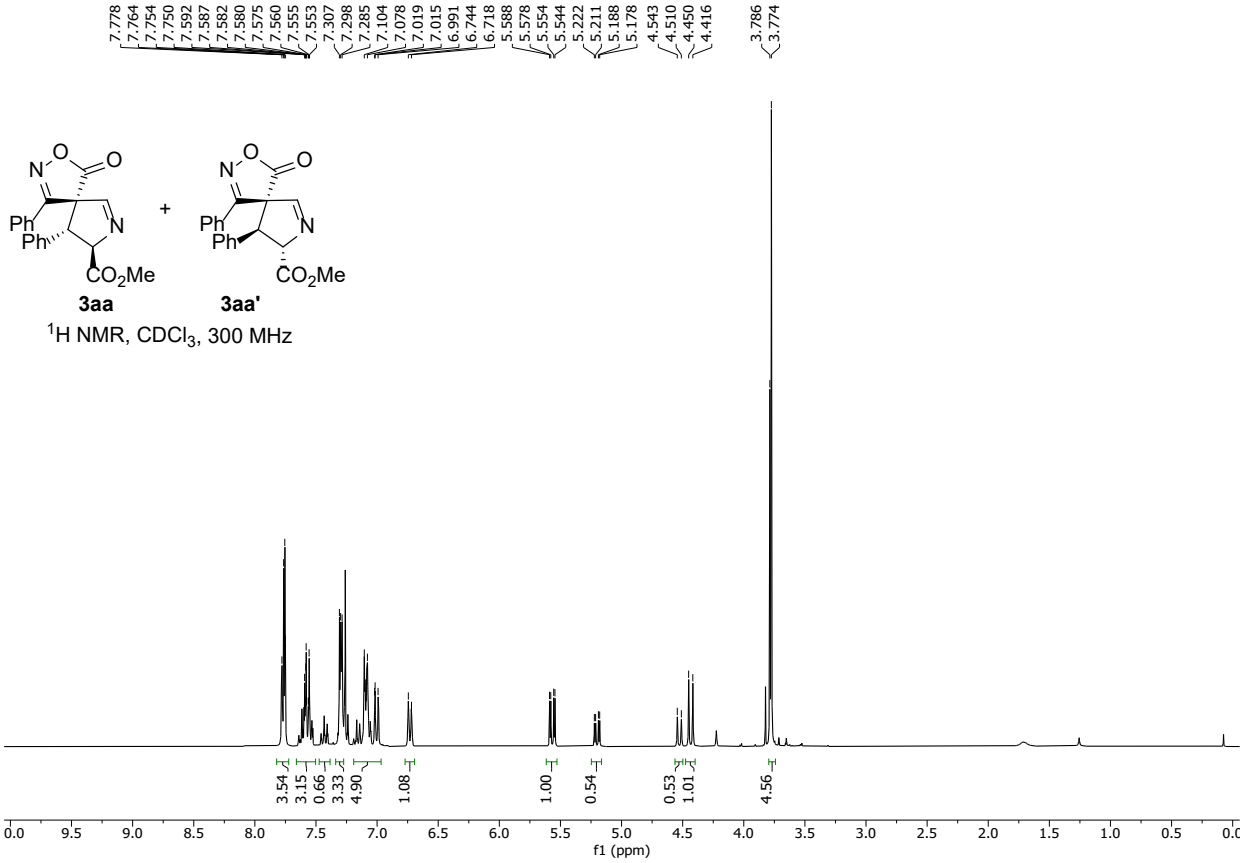
^{1}H NMR, $CDCl_3$, 300 MHz

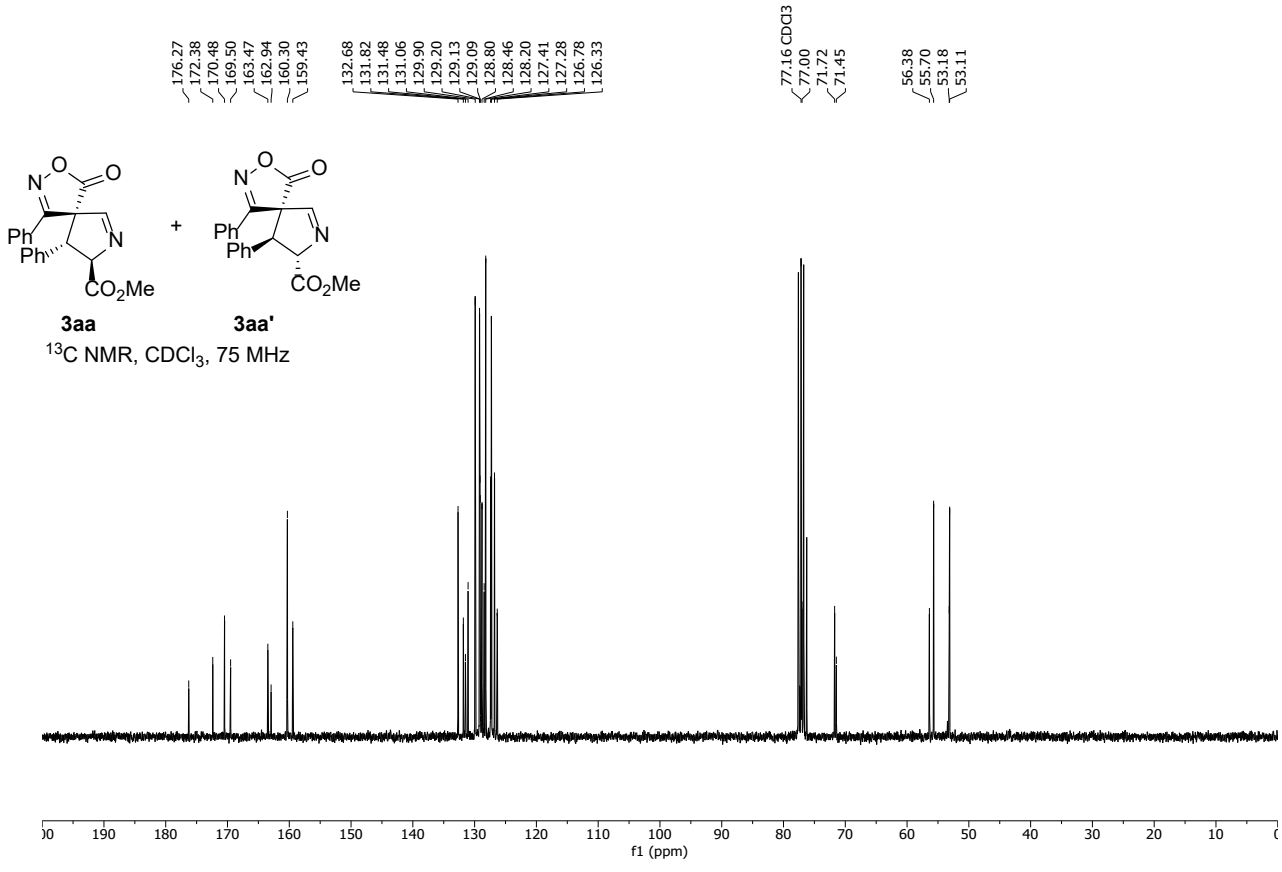


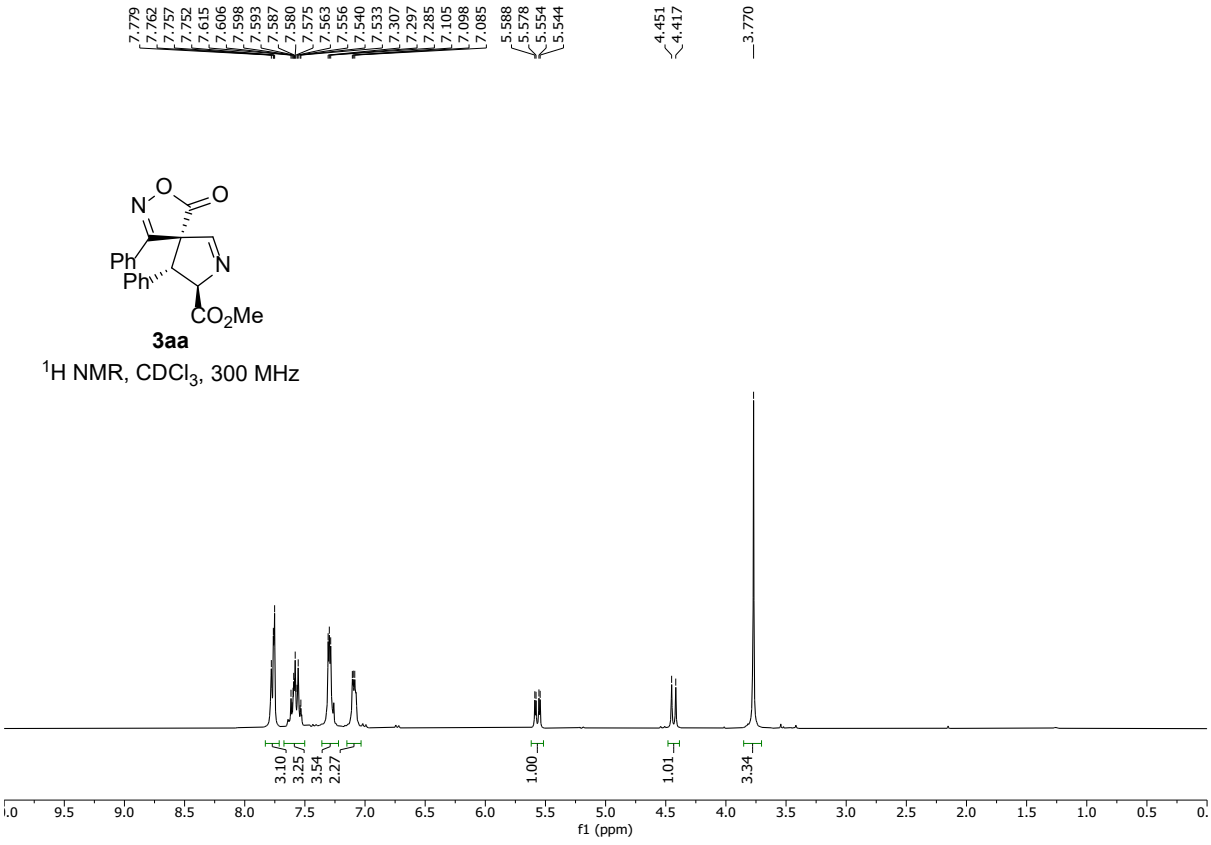


1q

^{13}C NMR, $CDCl_3$, 75 MHz

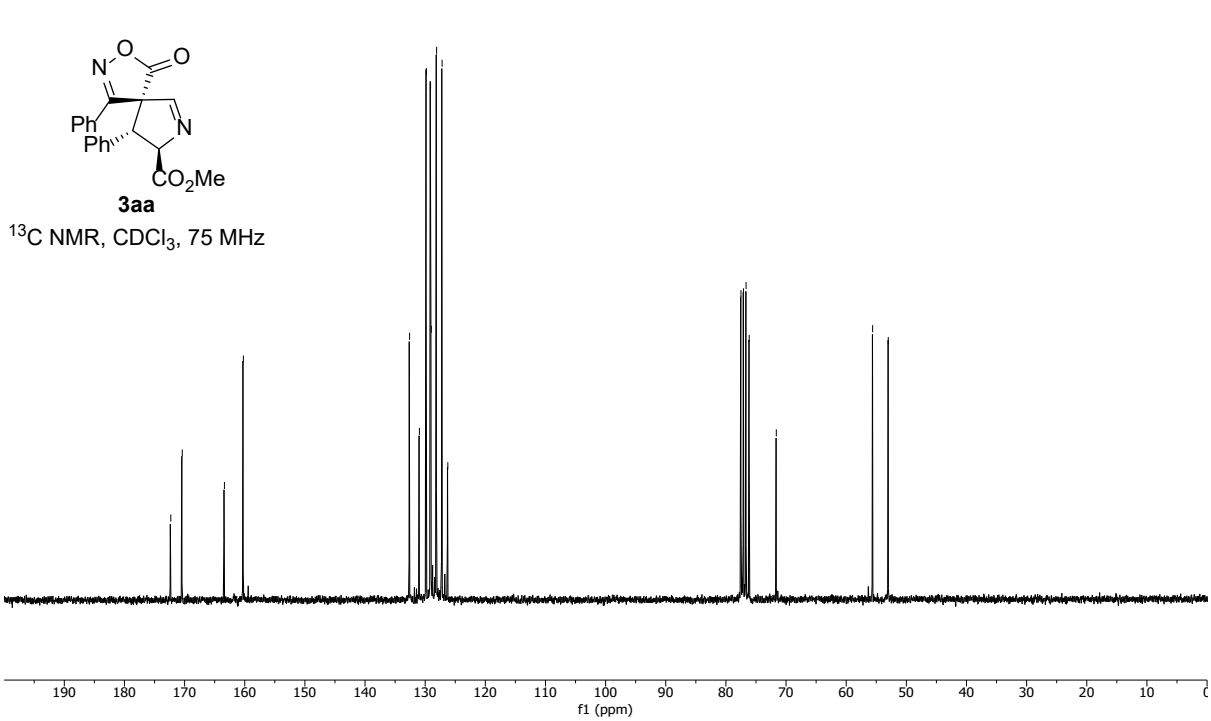

7.778
7.764
7.754
7.750
7.592
7.587
7.582
7.580
7.575
7.560
7.555
7.553
7.307
7.298
7.285
7.104
7.078
7.019
7.015
6.991
6.744
6.718
5.588
5.578
5.554
5.544
5.222
5.211
5.188
5.178
4.543
4.510
4.450
4.416
3.786
3.774
Ph
Ph
N
O
O
CO2Me
+
3aa
3aa'
1H NMR, CDCl3, 300 MHz
3.54
3.15
0.66
3.33
4.90
1.08
1.00
0.54
0.53
1.01
4.56
f1 (ppm)


176.27
172.38
170.48
169.50
163.47
162.94
160.30
159.43
132.68
131.82
131.48
131.06
129.90
129.20
129.13
129.09
128.80
128.46
128.20
127.41
127.28
126.78
126.33
77.16 CDCl3
77.00
71.72
71.45
56.38
55.70
53.18
53.11
Ph
Ph
N
O
O
CO2Me
+
3aa
3aa'
13C NMR, CDCl3, 75 MHz
f1 (ppm)



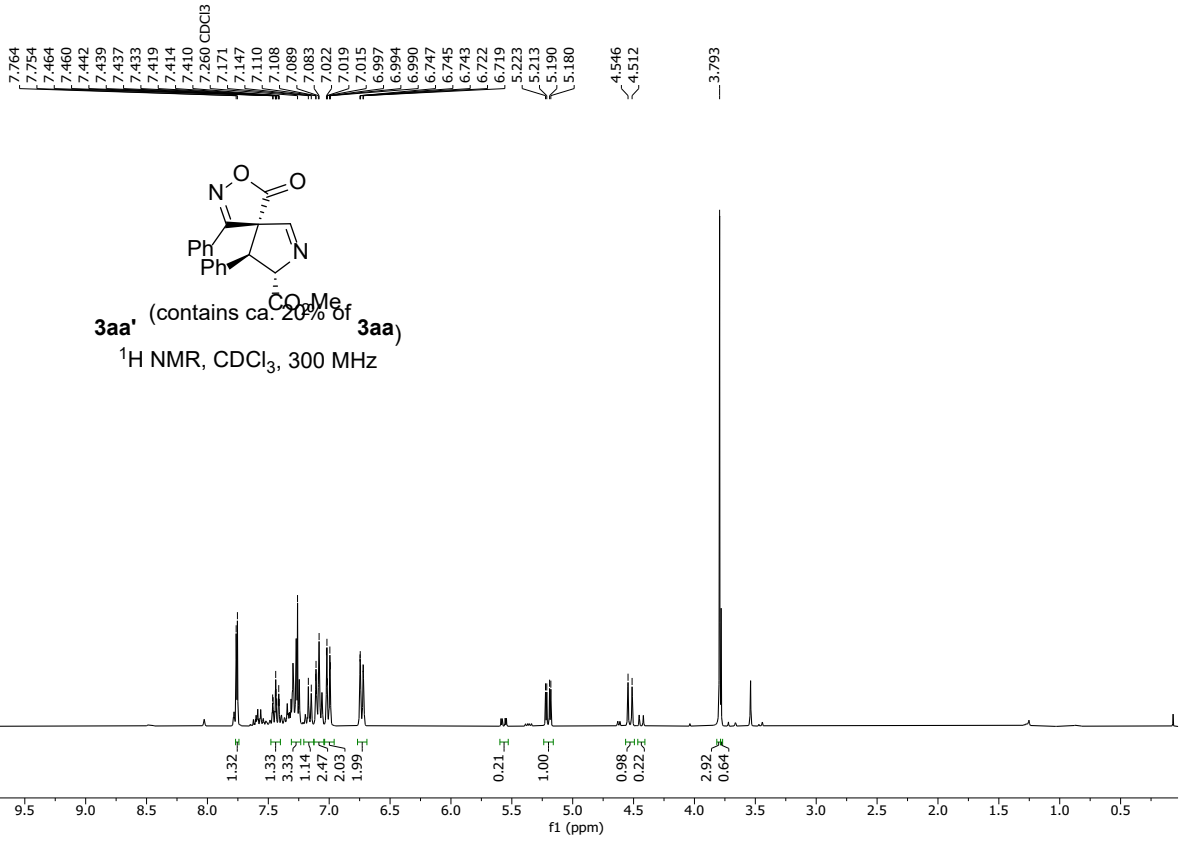
3aa

^{1}H NMR, $CDCl_3$, 300 MHz



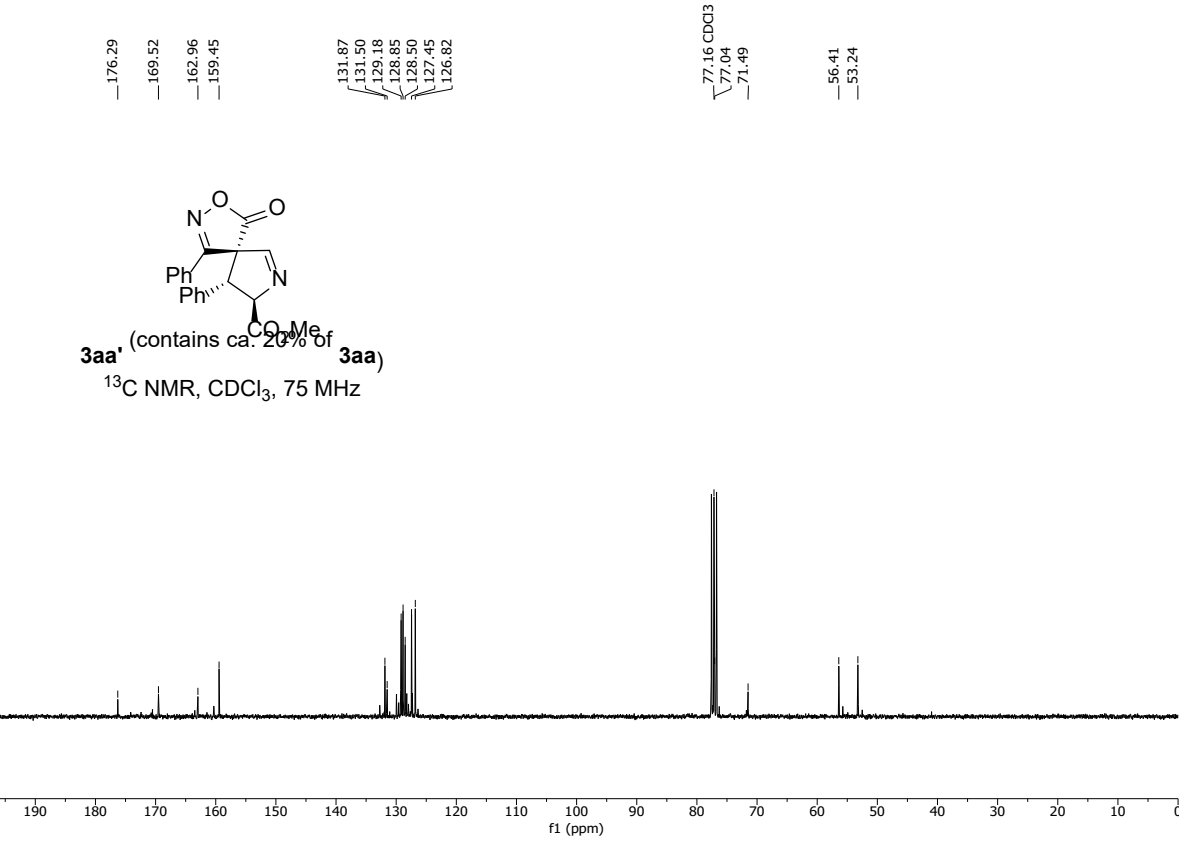
3aa

^{13}C NMR, $CDCl_3$, 75 MHz



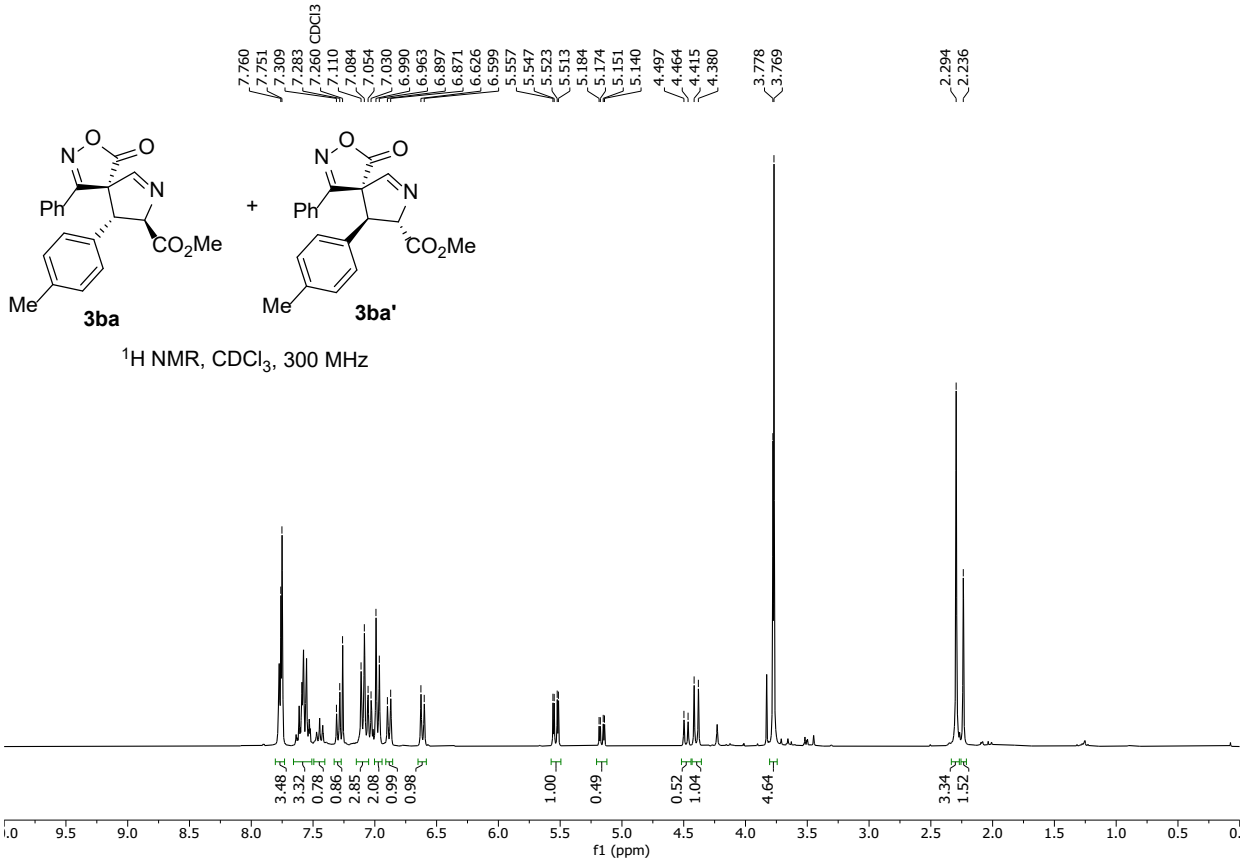
3aa' (contains ca. 20% of **3aa**)

^{1}H NMR, $CDCl_3$, 300 MHz

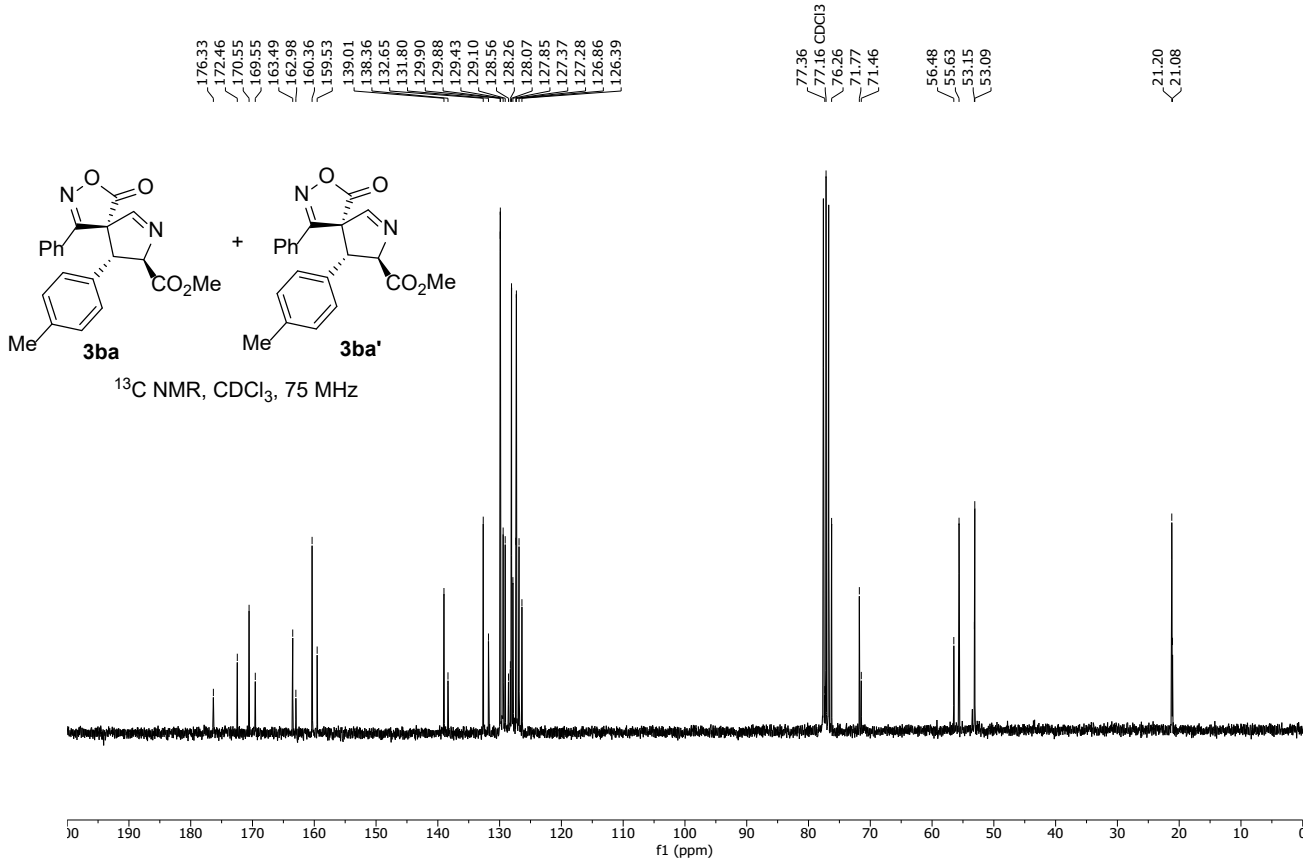


3aa' (contains ca. 20% of **3aa**)

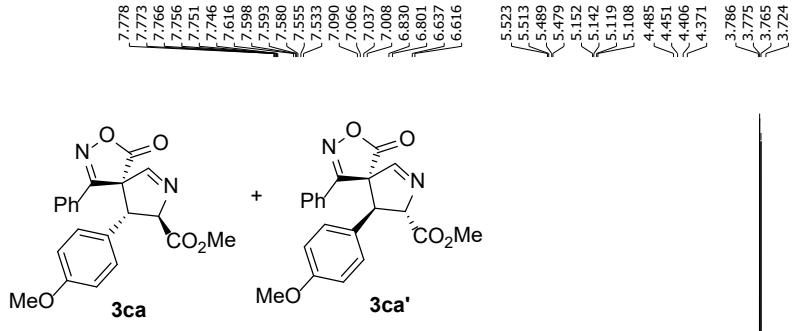
^{13}C NMR, $CDCl_3$, 75 MHz



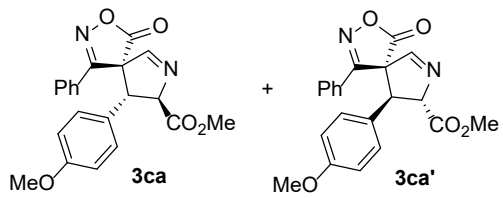
^{1}H NMR, $CDCl_3$, 300 MHz



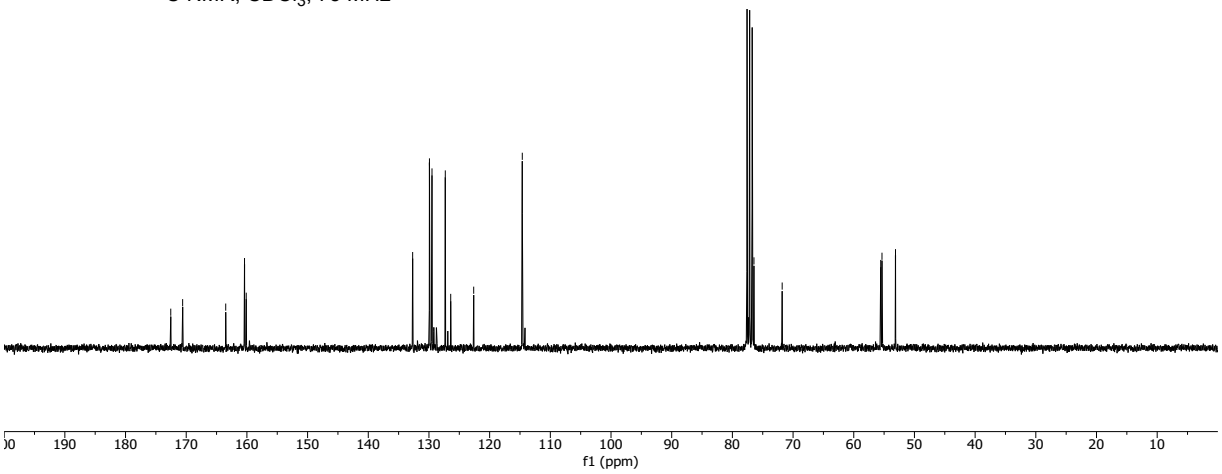
^{13}C NMR, $CDCl_3$, 75 MHz

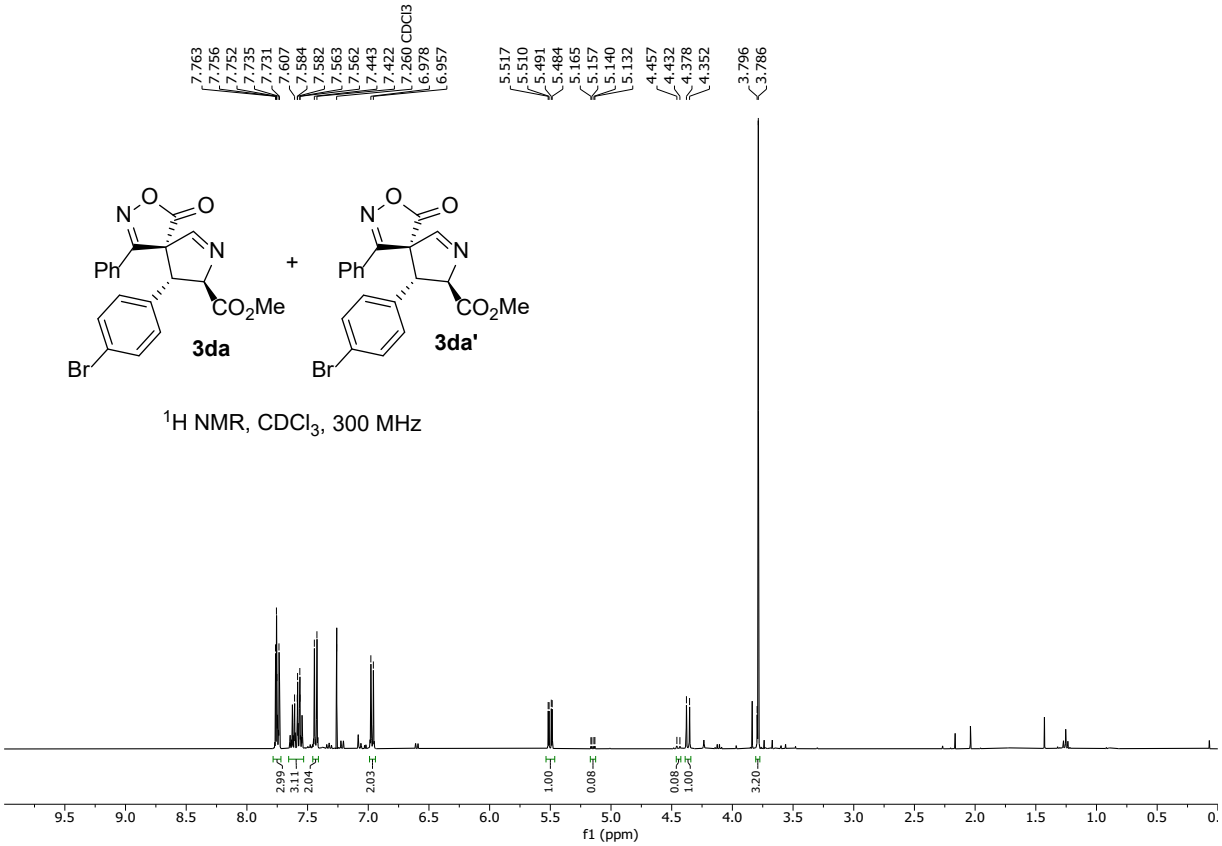


^{1}H NMR, $CDCl_3$, 300 MHz

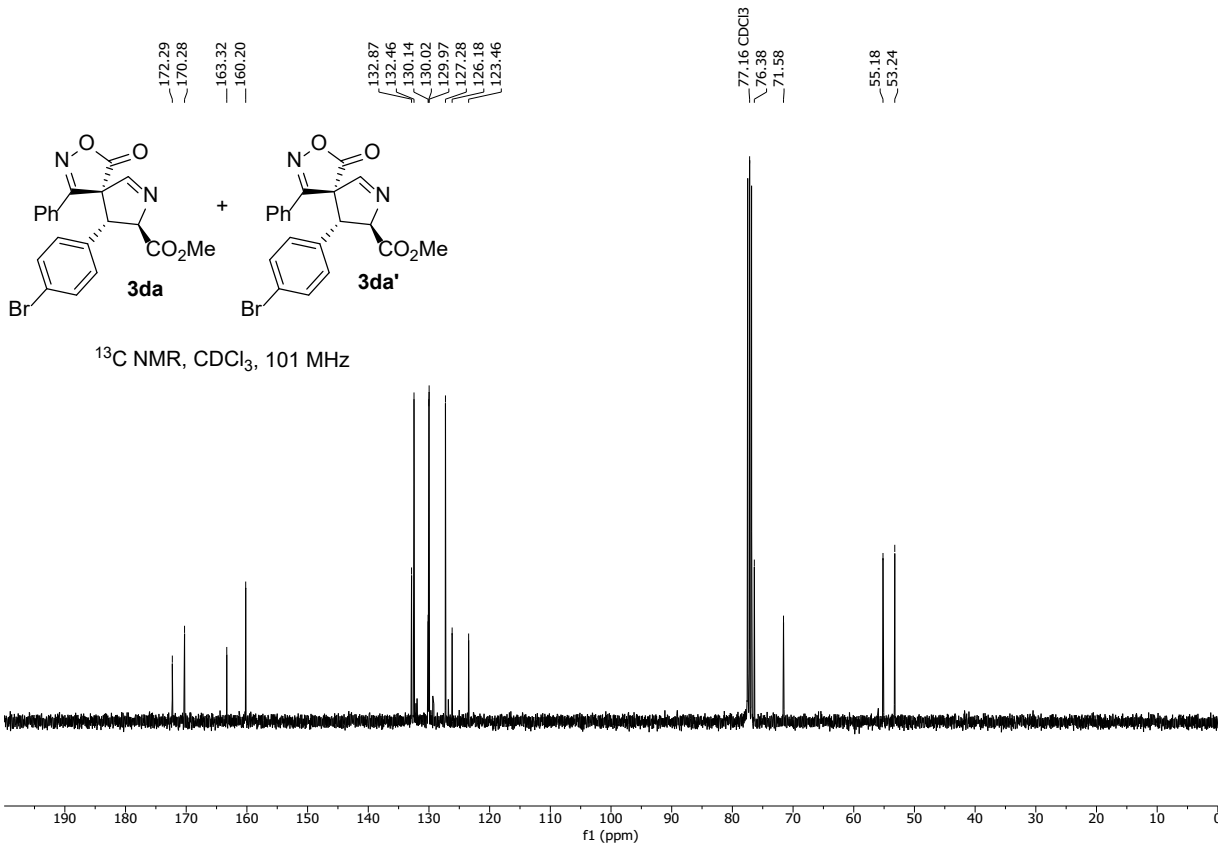


^{13}C NMR, $CDCl_3$, 75 MHz

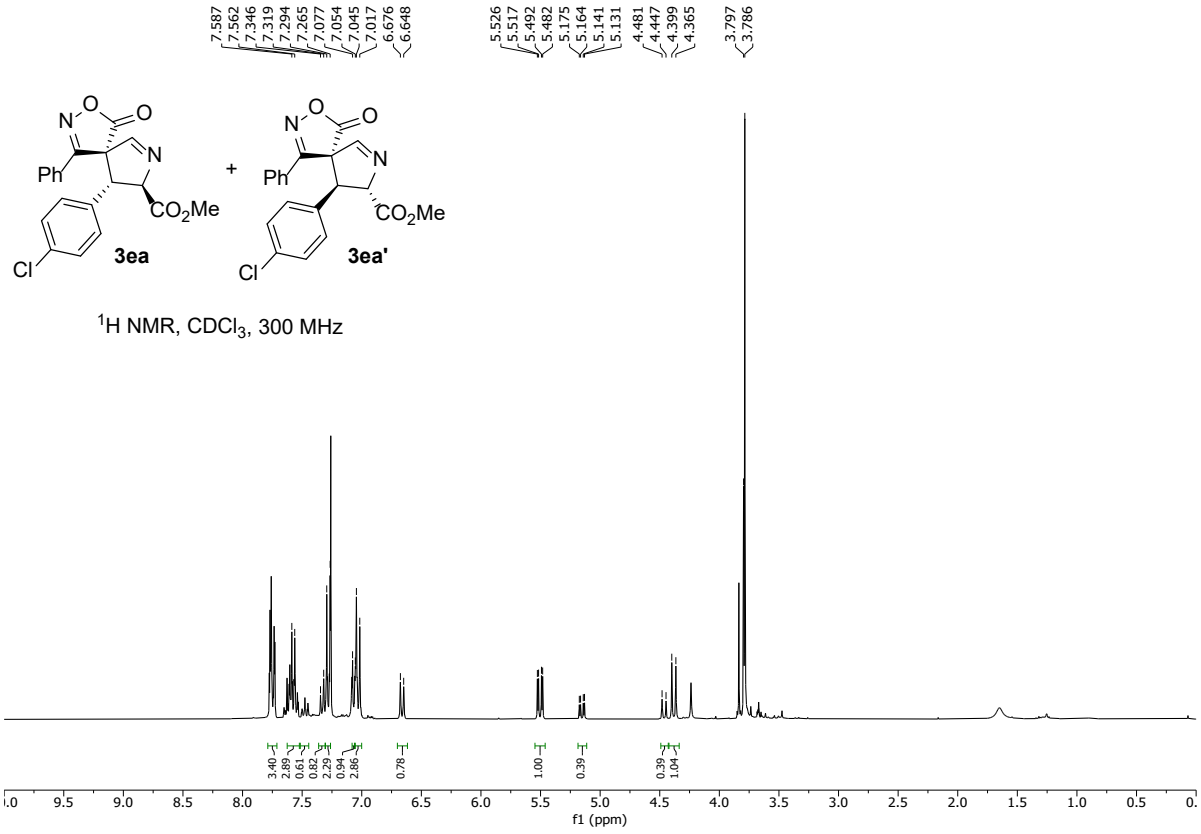




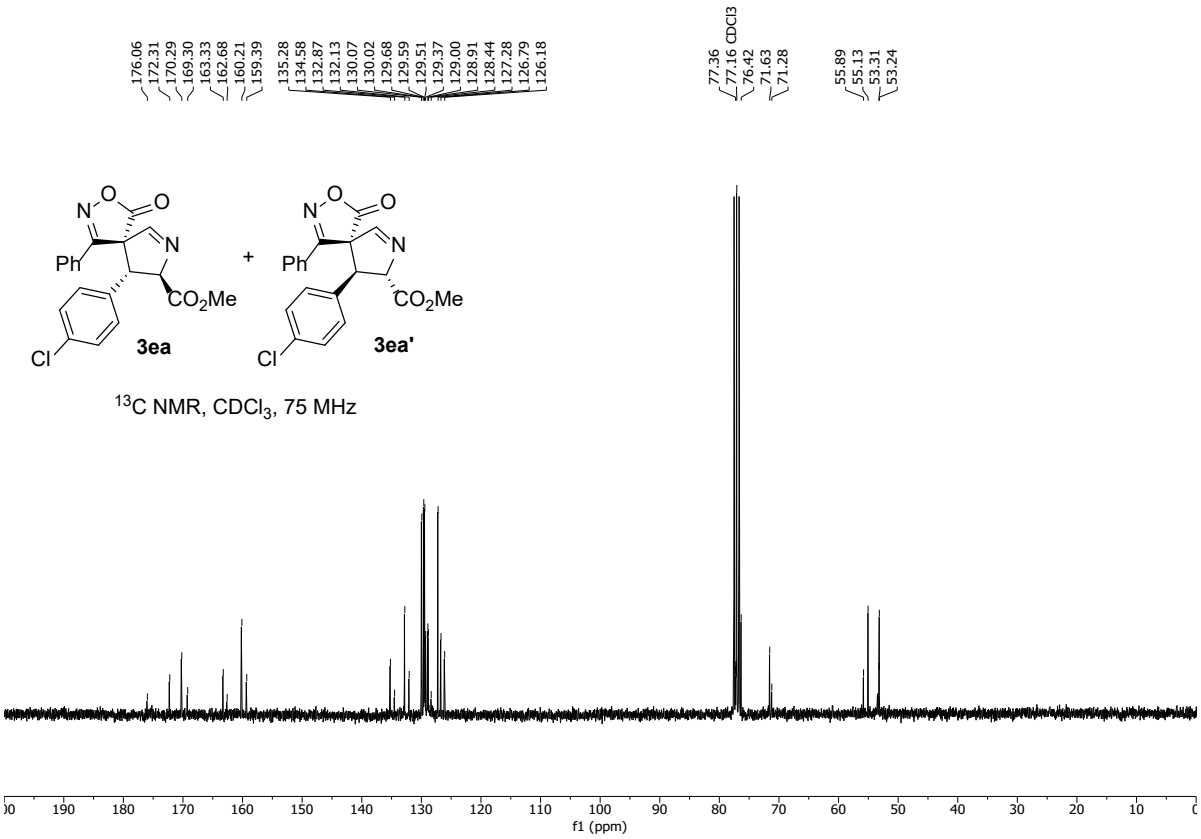
^{1}H NMR, $CDCl_3$, 300 MHz



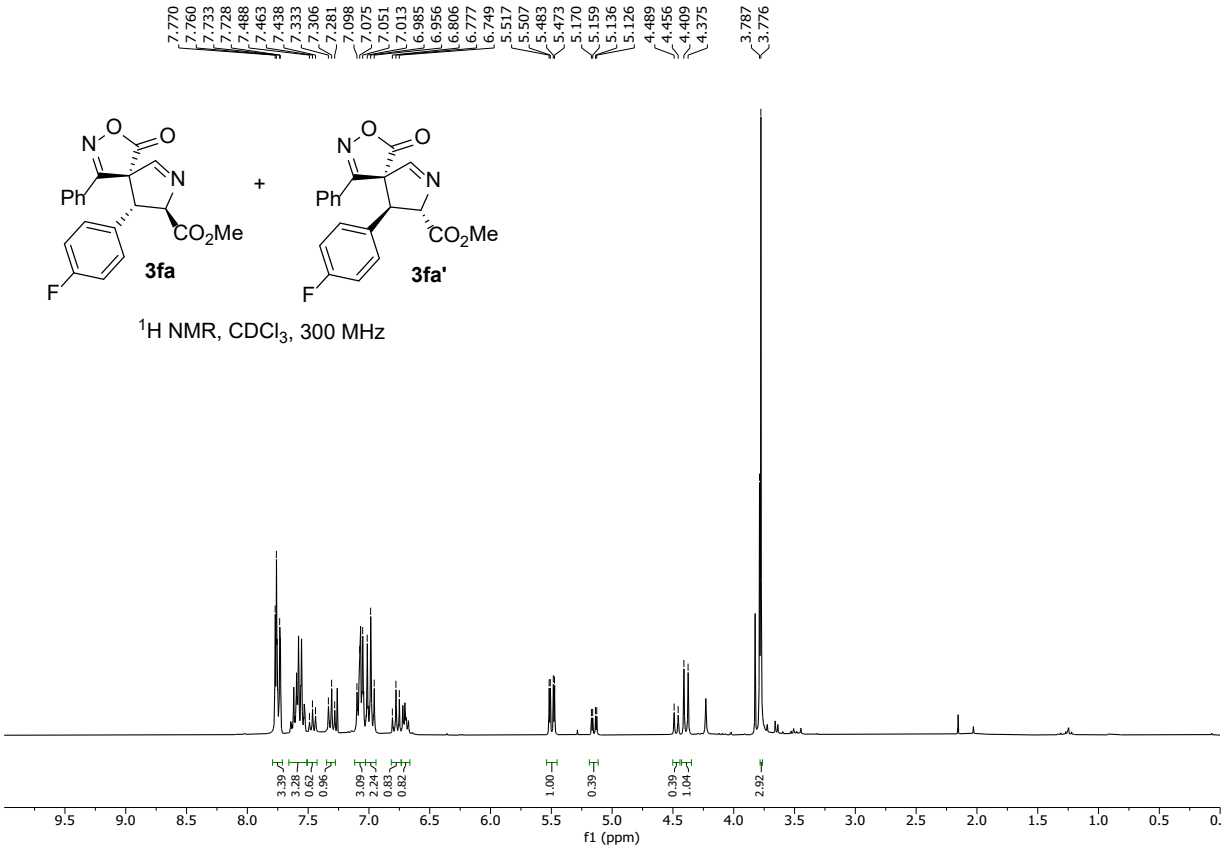
^{13}C NMR, $CDCl_3$, 101 MHz

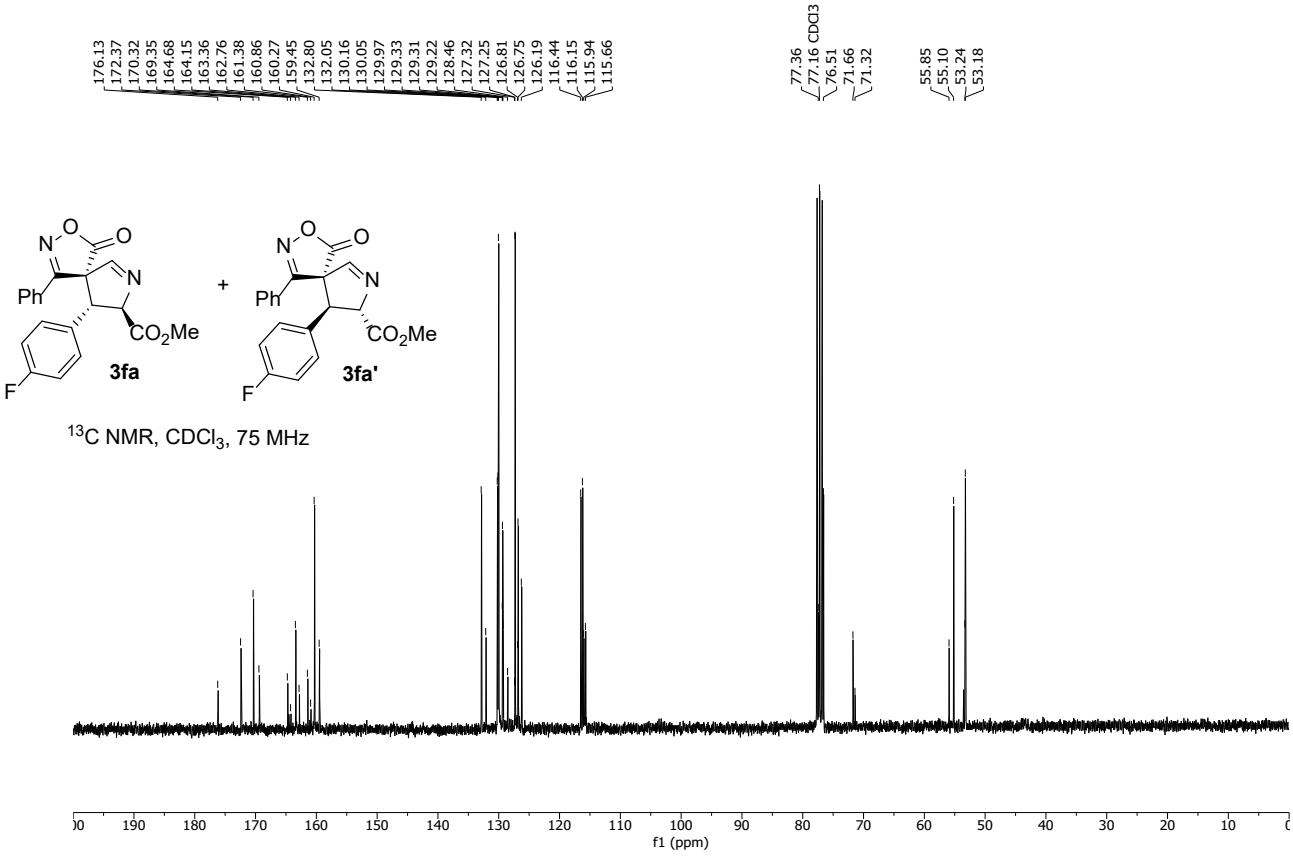


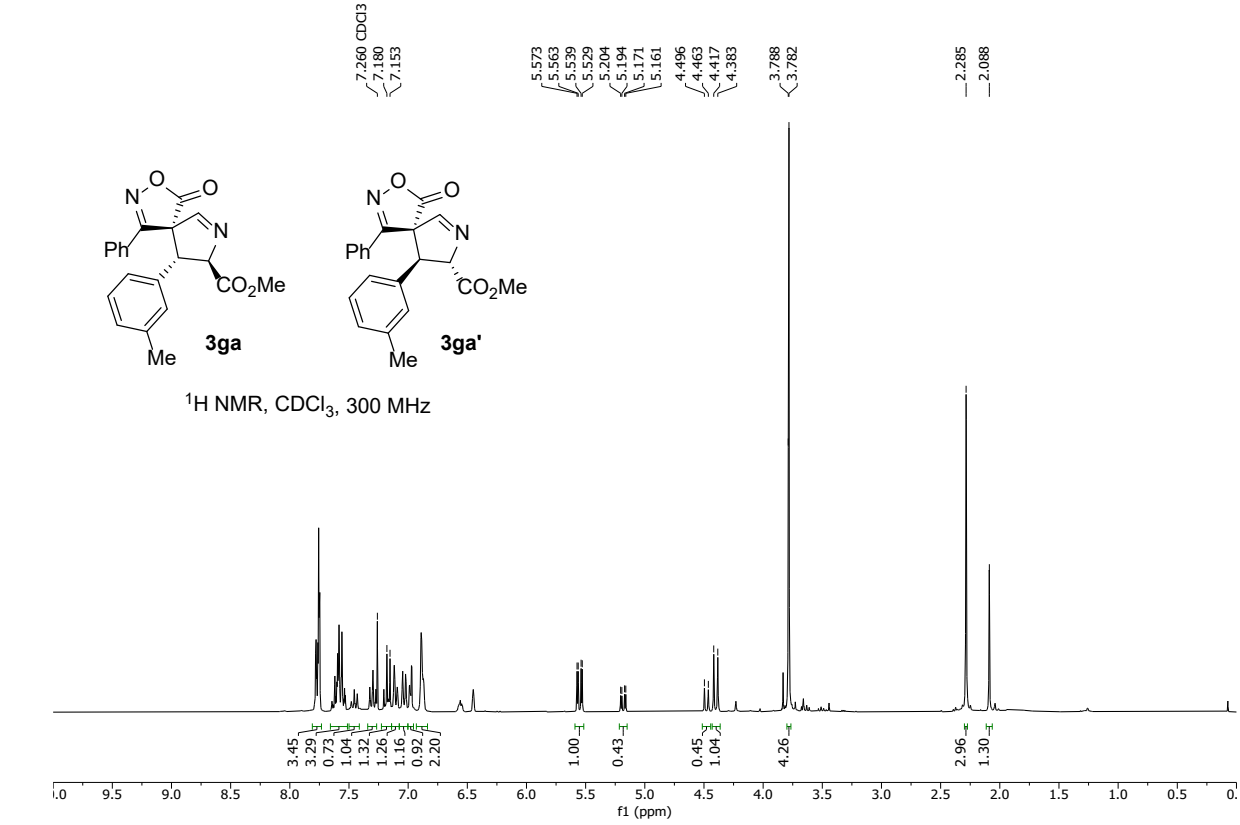
^{1}H NMR, $CDCl_3$, 300 MHz

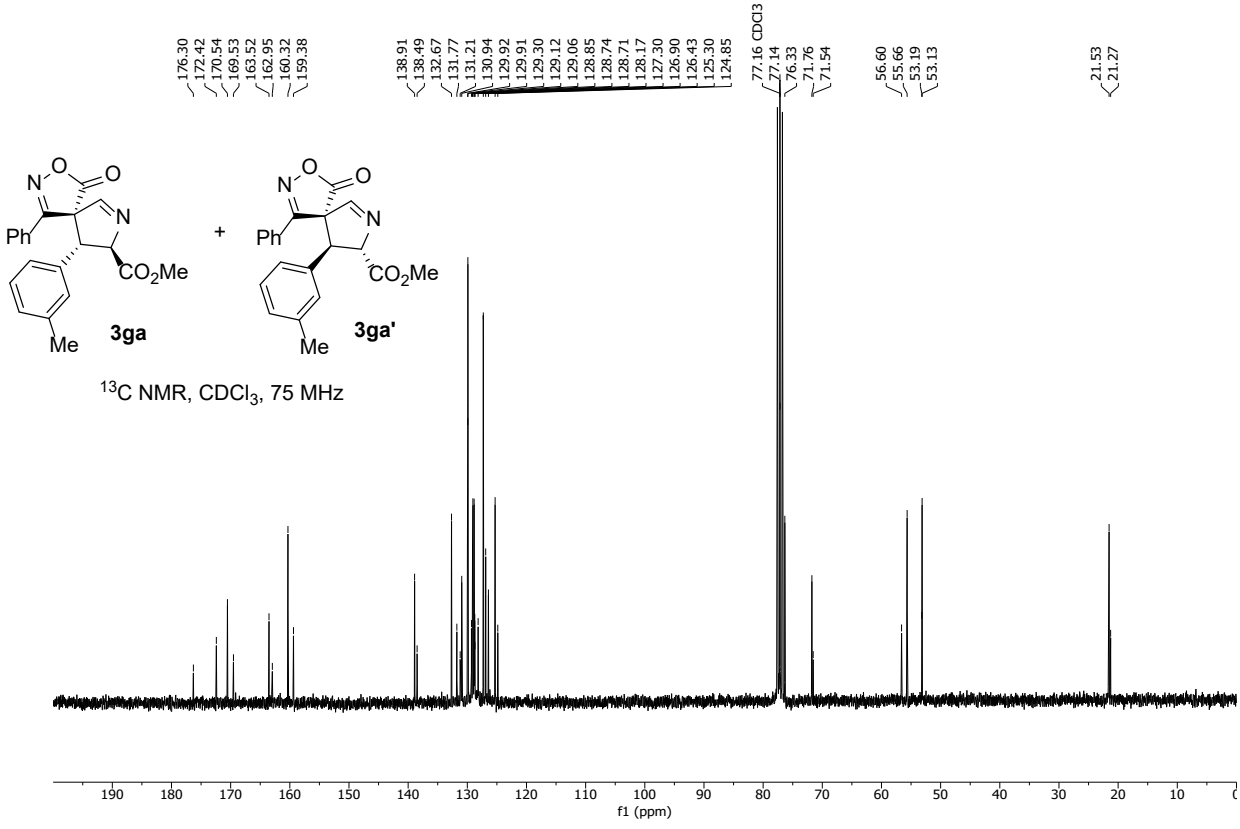


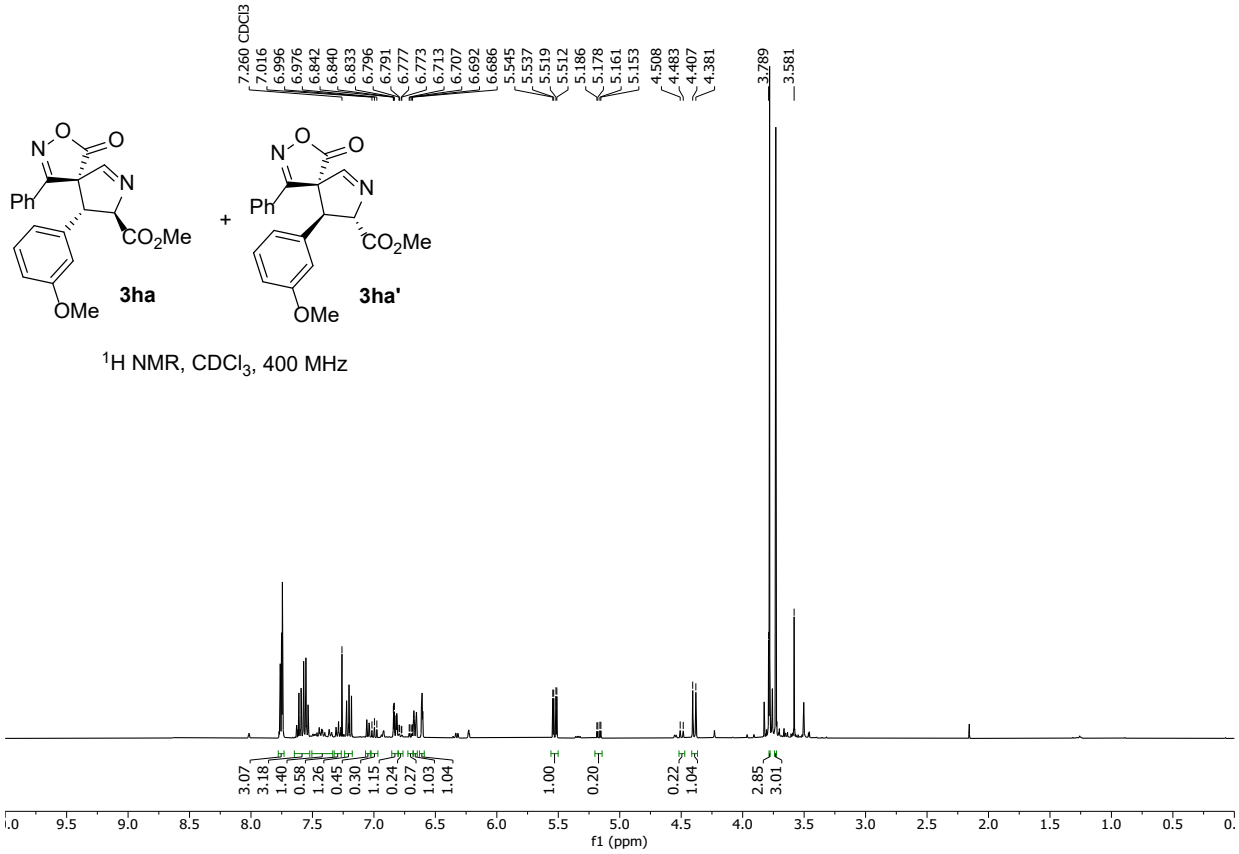
^{13}C NMR, $CDCl_3$, 75 MHz


7.770
7.760
7.733
7.728
7.488
7.463
7.438
7.333
7.306
7.281
7.098
7.075
7.051
7.013
6.985
6.956
6.806
6.777
6.749
5.517
5.507
5.483
5.473
5.170
5.159
5.136
5.126
4.489
4.456
4.409
4.375
3.787
3.776
Ph
CO2Me
F
3fa
3fa'
1H NMR, CDCl3, 300 MHz
3.39
3.28
0.62
0.96
3.09
2.24
0.83
0.82
1.00
0.39
0.39
1.04
2.92
f1 (ppm)

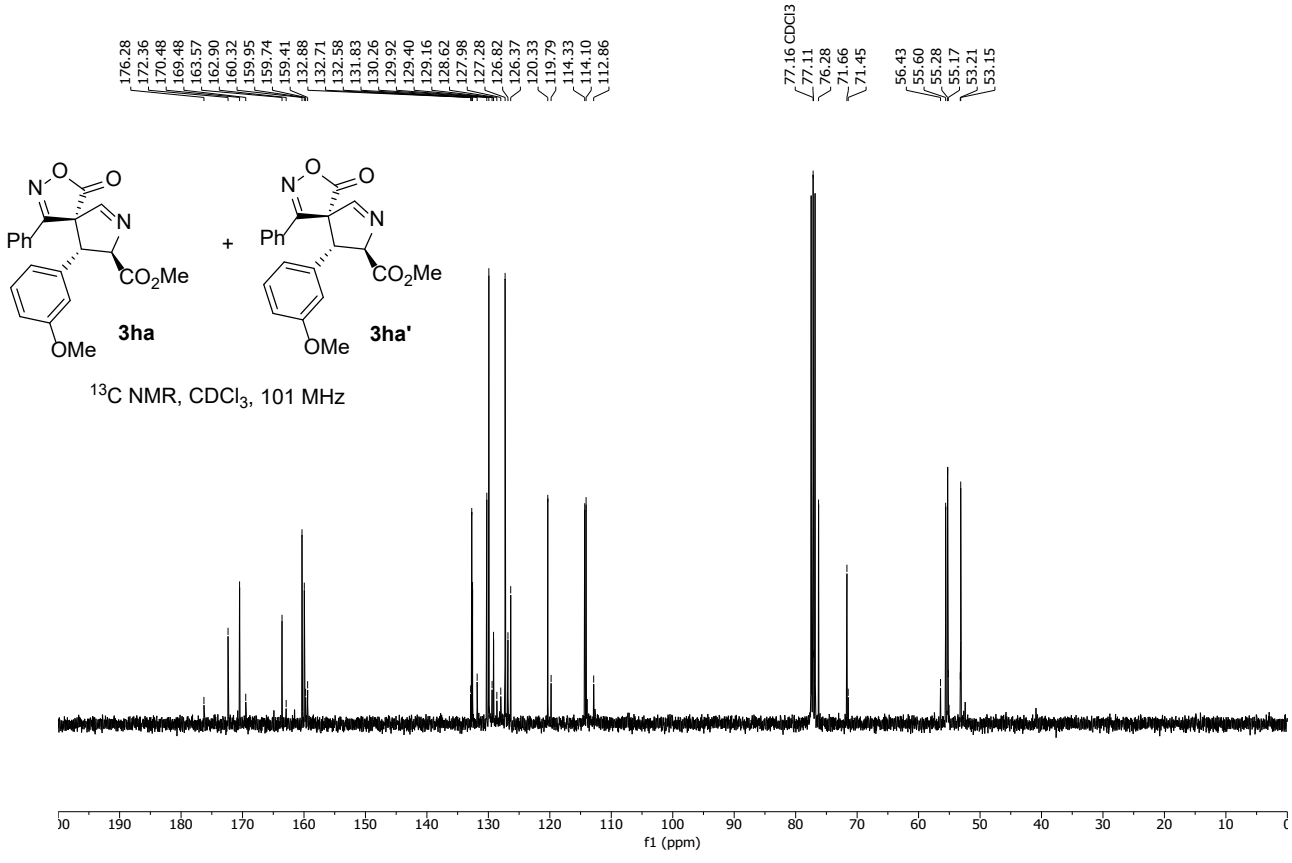

176.13
172.37
170.32
169.35
164.68
164.15
163.36
162.76
161.38
160.86
160.27
159.45
132.80
132.05
130.16
130.05
129.97
129.33
129.31
129.22
128.46
127.32
127.25
126.81
126.75
126.19
116.44
116.15
115.94
115.66
77.36
77.16 CDCl3
76.51
71.66
71.32
55.85
55.10
53.24
53.18
Ph
CO2Me
F
3fa
3fa'
13C NMR, CDCl3, 75 MHz
f1 (ppm)


7.260 CDCl3
7.180
7.153
5.573
5.563
5.539
5.529
5.204
5.194
5.171
5.161
4.496
4.463
4.417
4.383
3.788
3.782
2.285
2.088
Ph
CO2Me
Me
3ga
3ga'
1H NMR, CDCl3, 300 MHz
3.45
3.29
0.73
1.04
1.32
1.26
1.16
0.92
2.20
1.00
0.43
0.45
1.04
4.26
2.96
1.30
f1 (ppm)

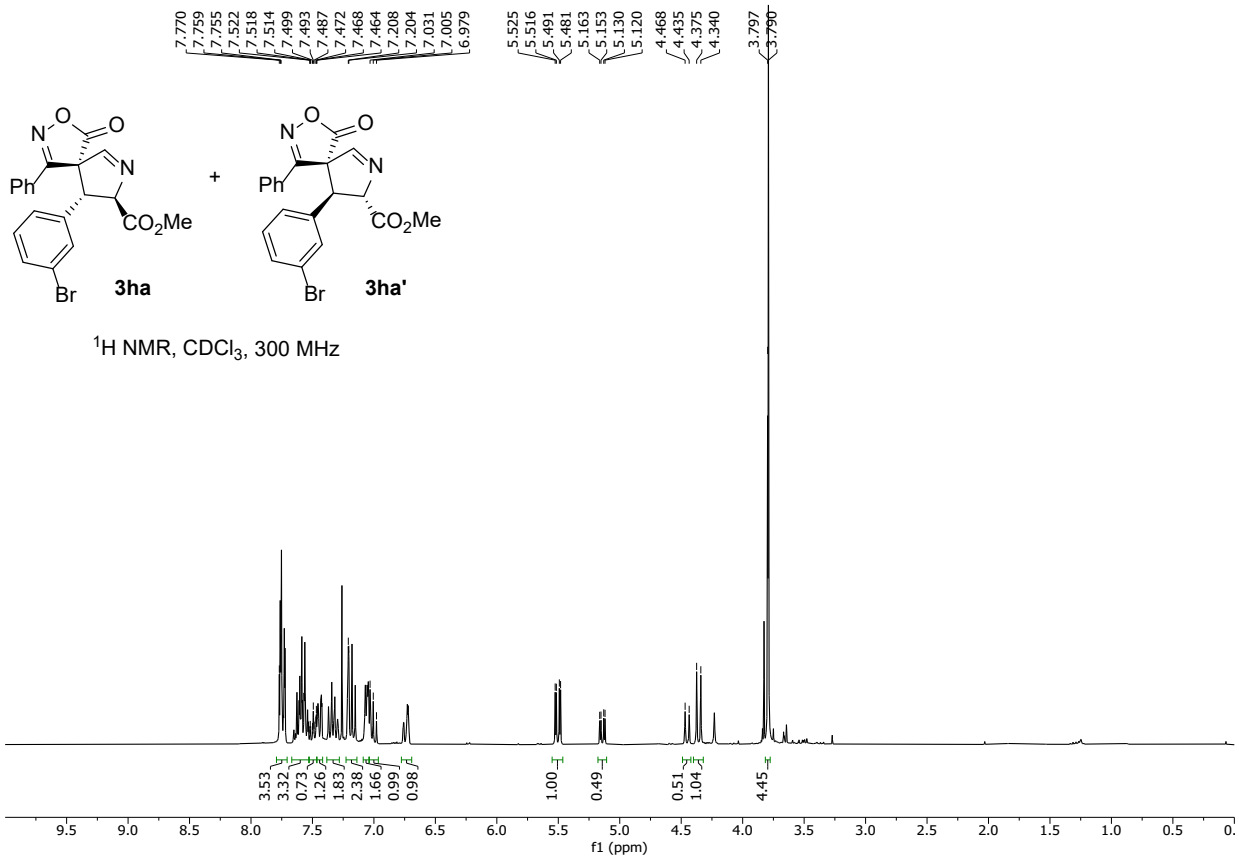

176.30
172.42
170.54
169.53
163.52
162.95
160.32
159.38
138.91
138.49
132.67
131.77
131.21
130.94
129.92
129.91
129.30
129.12
129.06
128.85
128.74
128.71
128.17
127.30
126.90
126.43
125.30
124.85
77.16 CDCl3
77.14
76.33
71.76
71.54
56.60
55.66
53.19
53.13
21.53
21.27
Ph
CO2Me
Me
3ga
3ga'
13C NMR, CDCl3, 75 MHz
f1 (ppm)

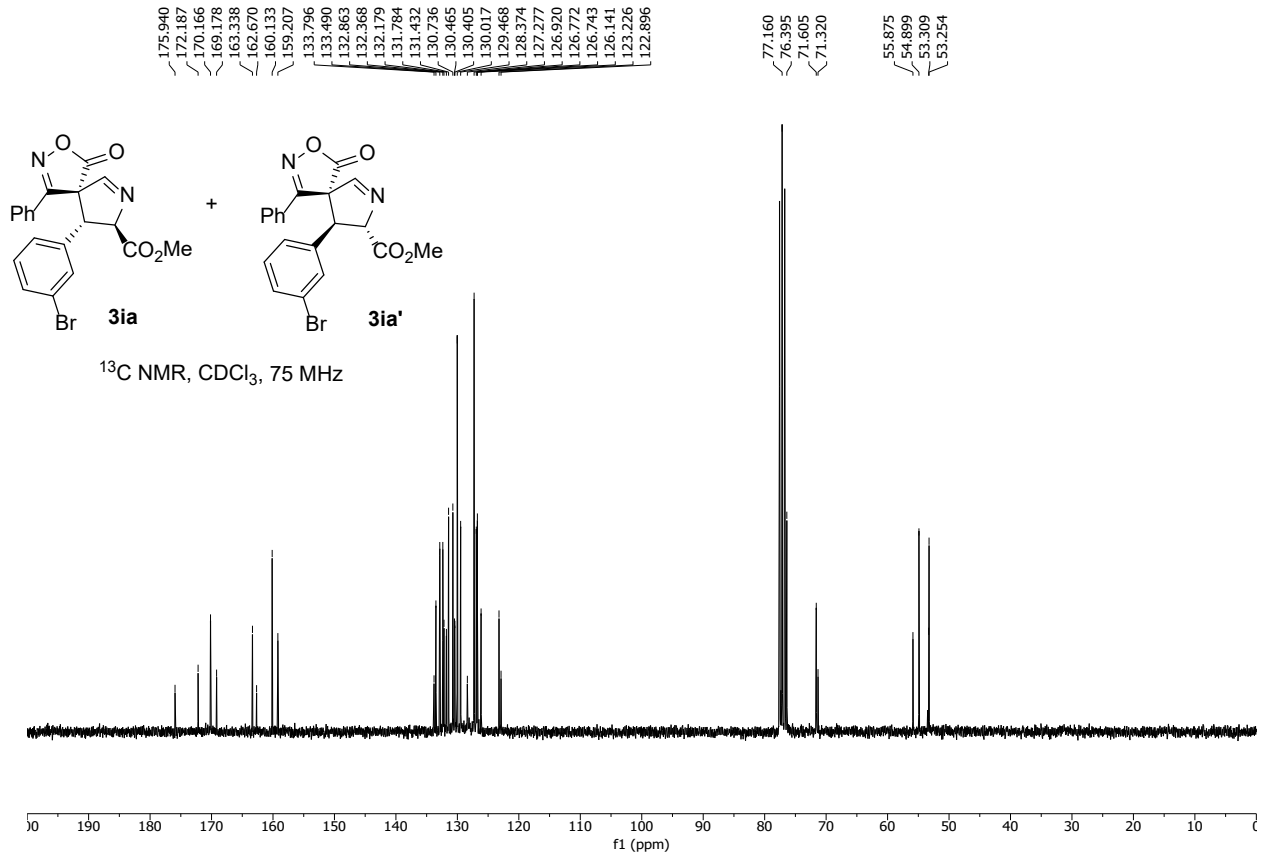


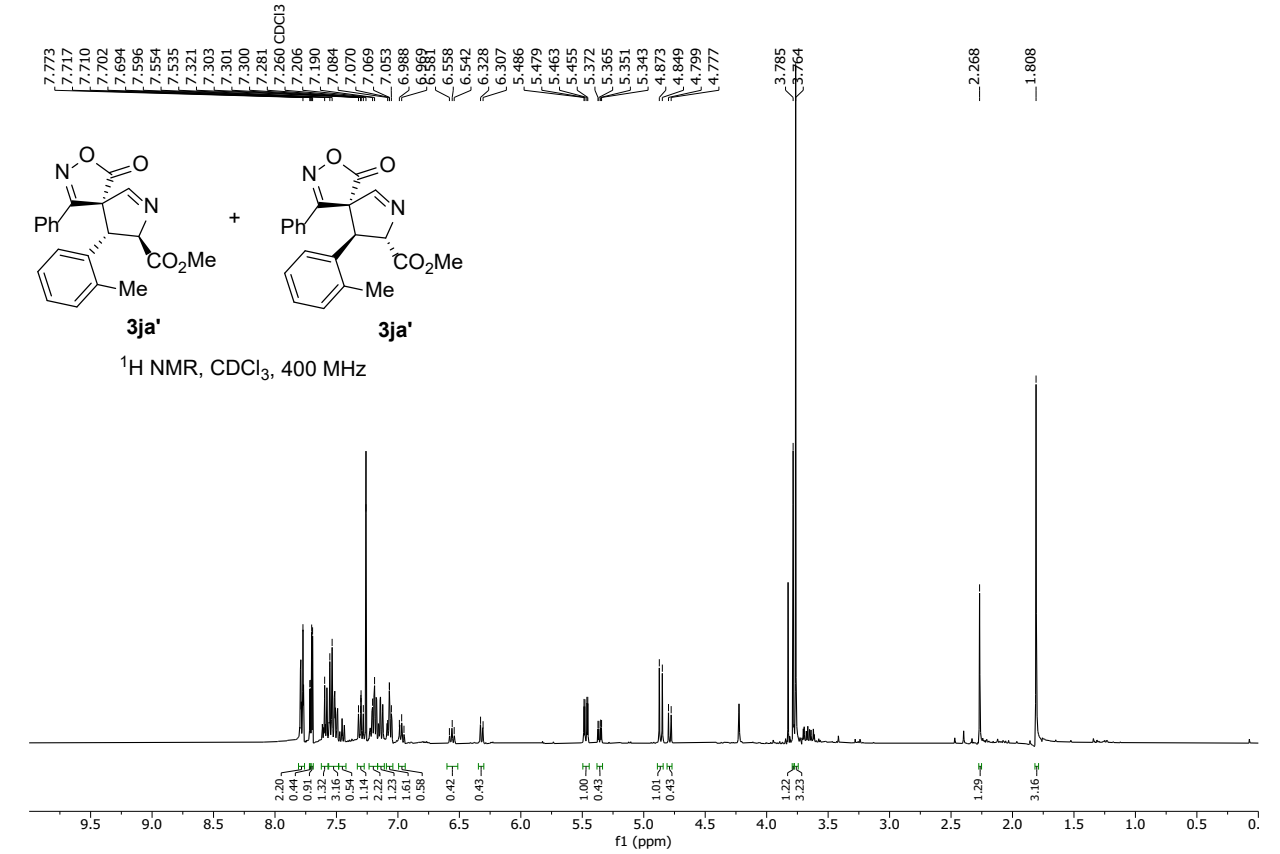
^{1}H NMR, $CDCl_3$, 400 MHz

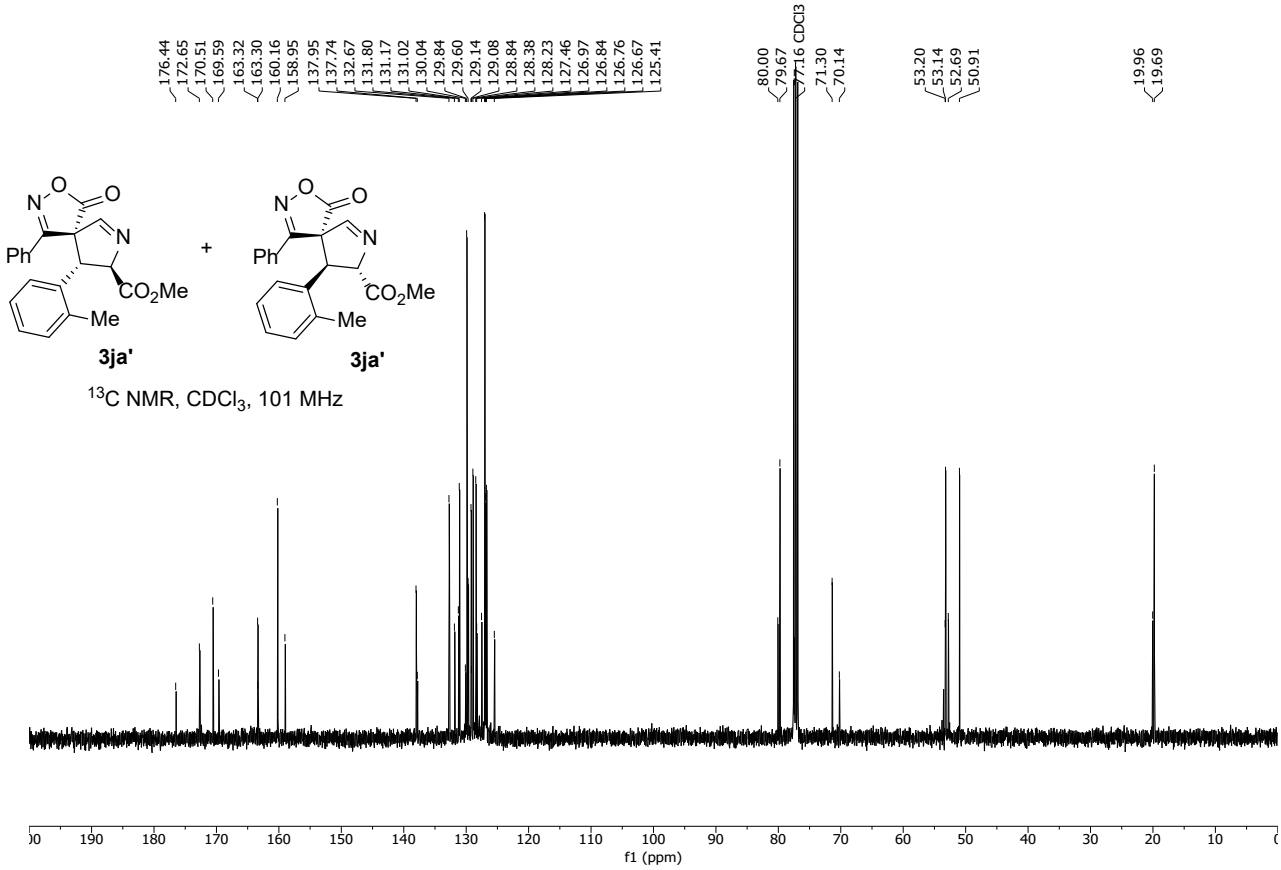


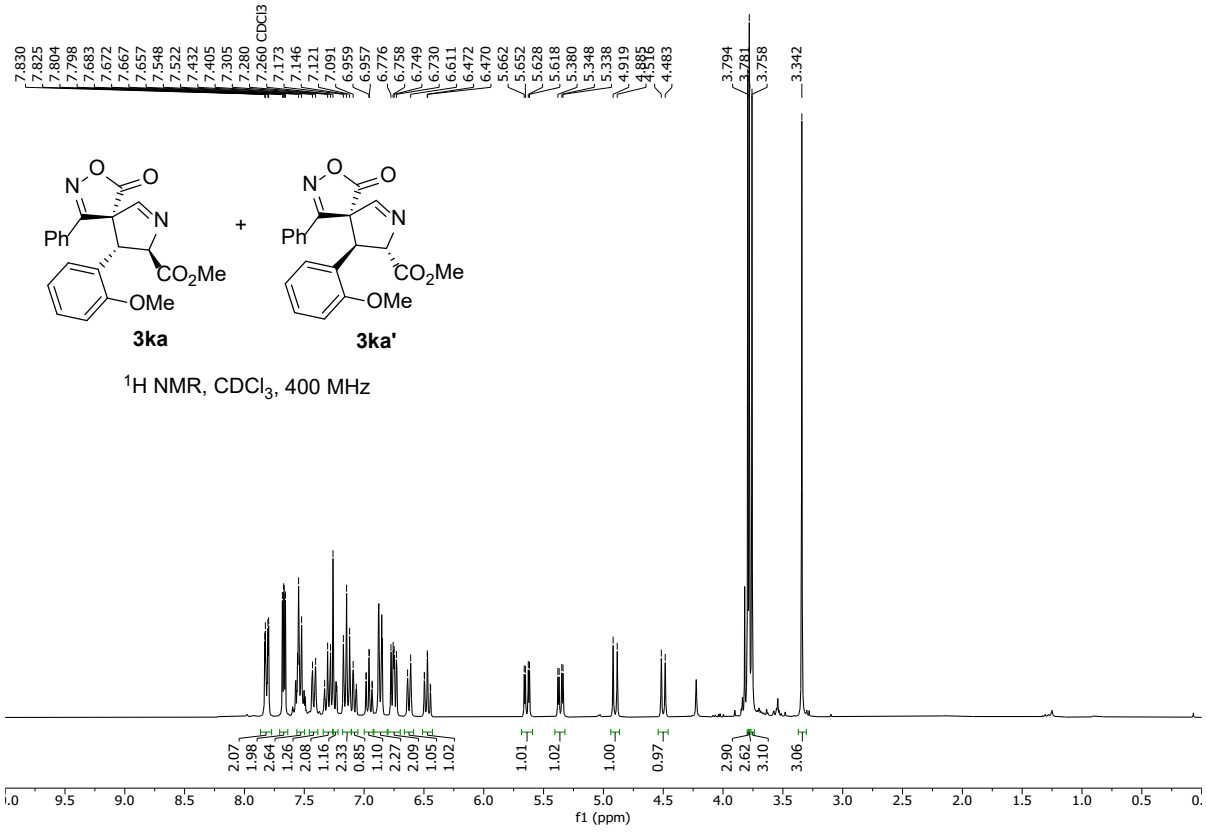
^{13}C NMR, $CDCl_3$, 101 MHz


7.770
7.759
7.755
7.522
7.518
7.514
7.499
7.493
7.487
7.472
7.468
7.464
7.208
7.204
7.031
7.005
6.979
5.525
5.516
5.491
5.481
5.163
5.153
5.130
5.120
4.468
4.435
4.375
4.340
3.797
3.790
Ph
CO2Me
Br
3ha
3ha'
1H NMR, CDCl3, 300 MHz
3.53
3.32
0.73
1.26
1.83
2.38
1.66
0.99
0.98
1.00
0.49
0.51
1.04
4.45
f1 (ppm)


175.940
172.187
170.166
169.178
163.338
162.670
160.133
159.207
133.796
133.490
132.863
132.368
132.179
131.784
131.432
130.736
130.465
130.405
130.017
129.468
128.374
127.277
126.920
126.772
126.743
126.141
123.226
122.896
77.160
76.395
71.605
71.320
55.875
54.899
53.309
53.254
Ph
CO2Me
Br
3ia
3ia'
13C NMR, CDCl3, 75 MHz
f1 (ppm)


7.773
7.717
7.710
7.702
7.694
7.596
7.554
7.535
7.321
7.303
7.301
7.300
7.281
7.260 CDCl3
7.206
7.190
7.084
7.070
7.069
7.053
6.988
6.558
6.542
6.328
6.307
5.486
5.479
5.463
5.455
5.372
5.365
5.351
5.343
4.873
4.849
4.799
4.777
3.785
3.764
2.268
1.808
Ph
CO2Me
Me
3ja'
3ja'
1H NMR, CDCl3, 400 MHz
f1 (ppm)


176.44
172.65
170.51
169.59
163.32
163.30
160.16
158.95
137.95
137.74
132.67
131.80
131.17
131.02
130.04
129.84
129.60
129.14
129.08
128.84
128.38
128.23
127.46
126.97
126.84
126.76
126.67
125.41
80.00
79.67
77.16 CDCl3
71.30
70.14
53.20
53.14
52.69
50.91
19.96
19.69
Ph
CO2Me
Me
3ja'
3ja'
13C NMR, CDCl3, 101 MHz
f1 (ppm)


7.830
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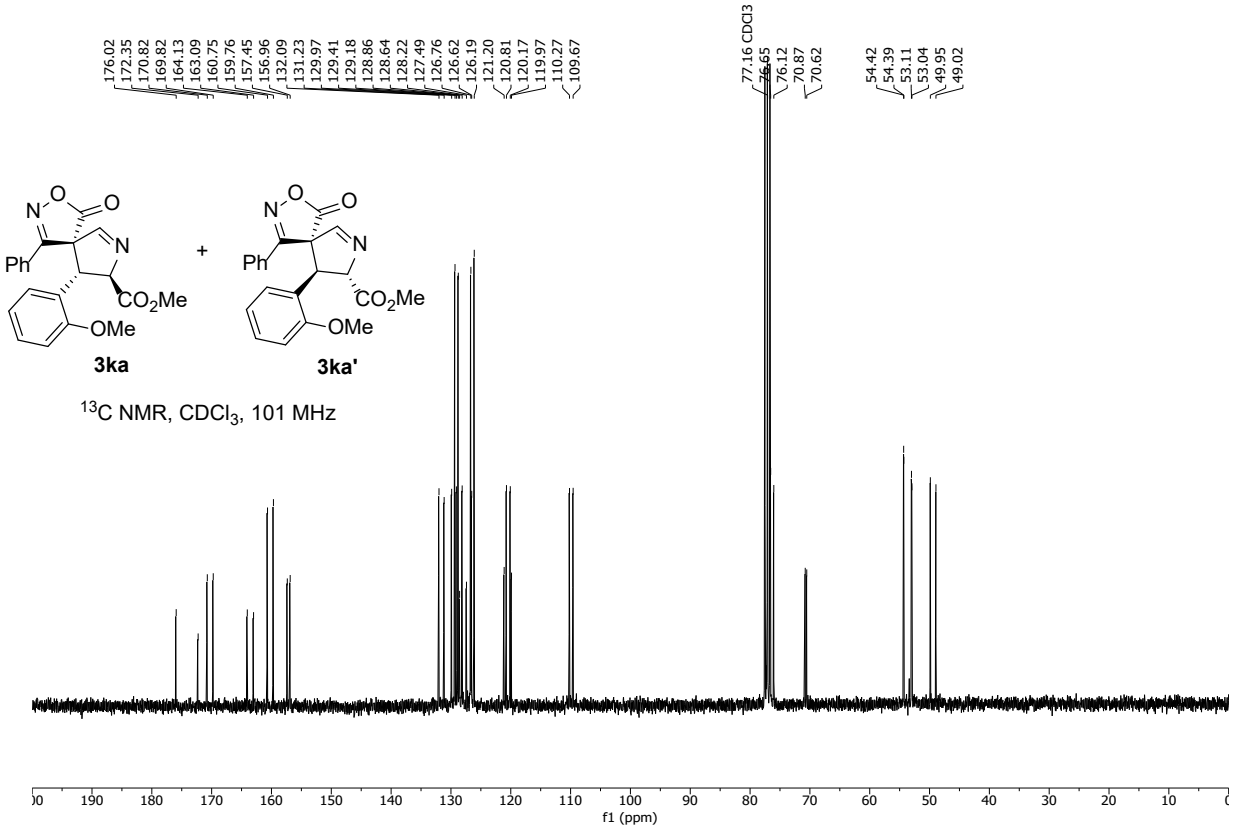
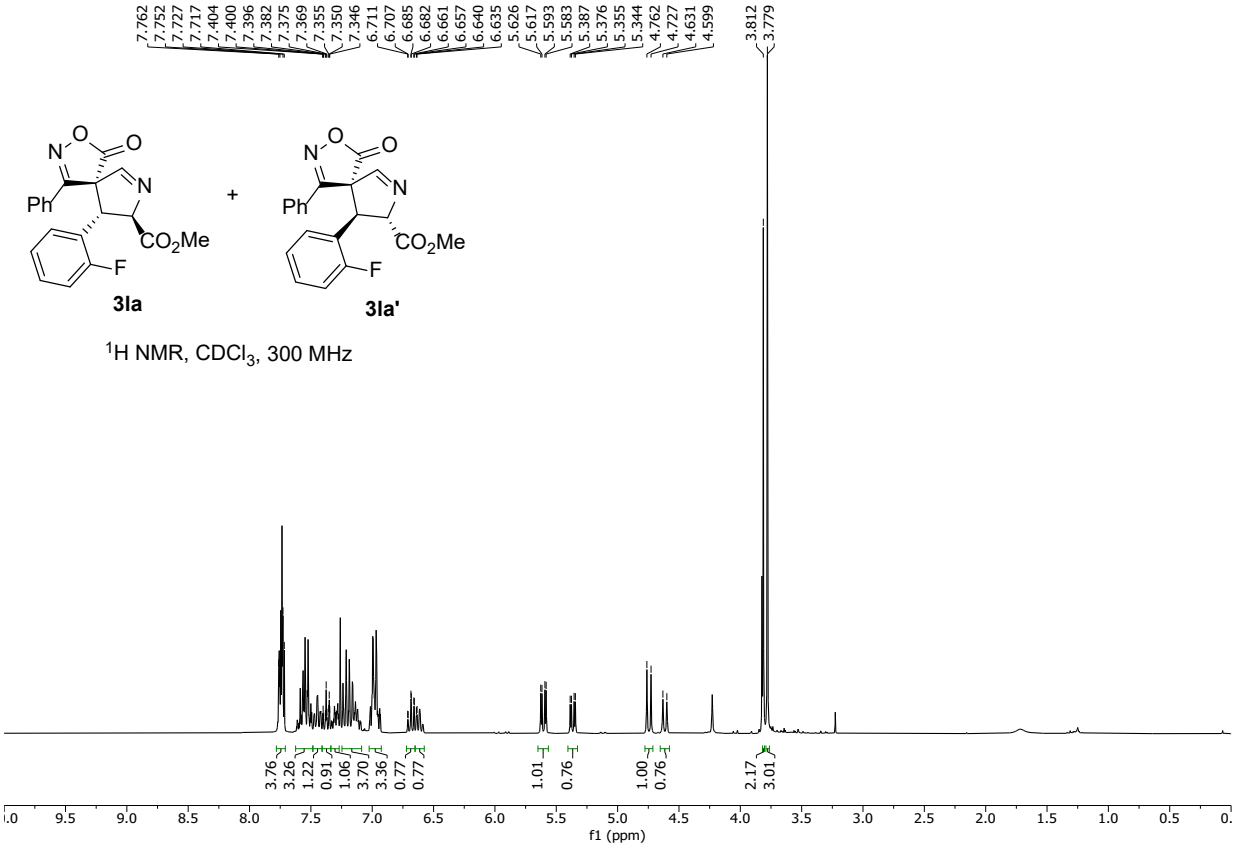
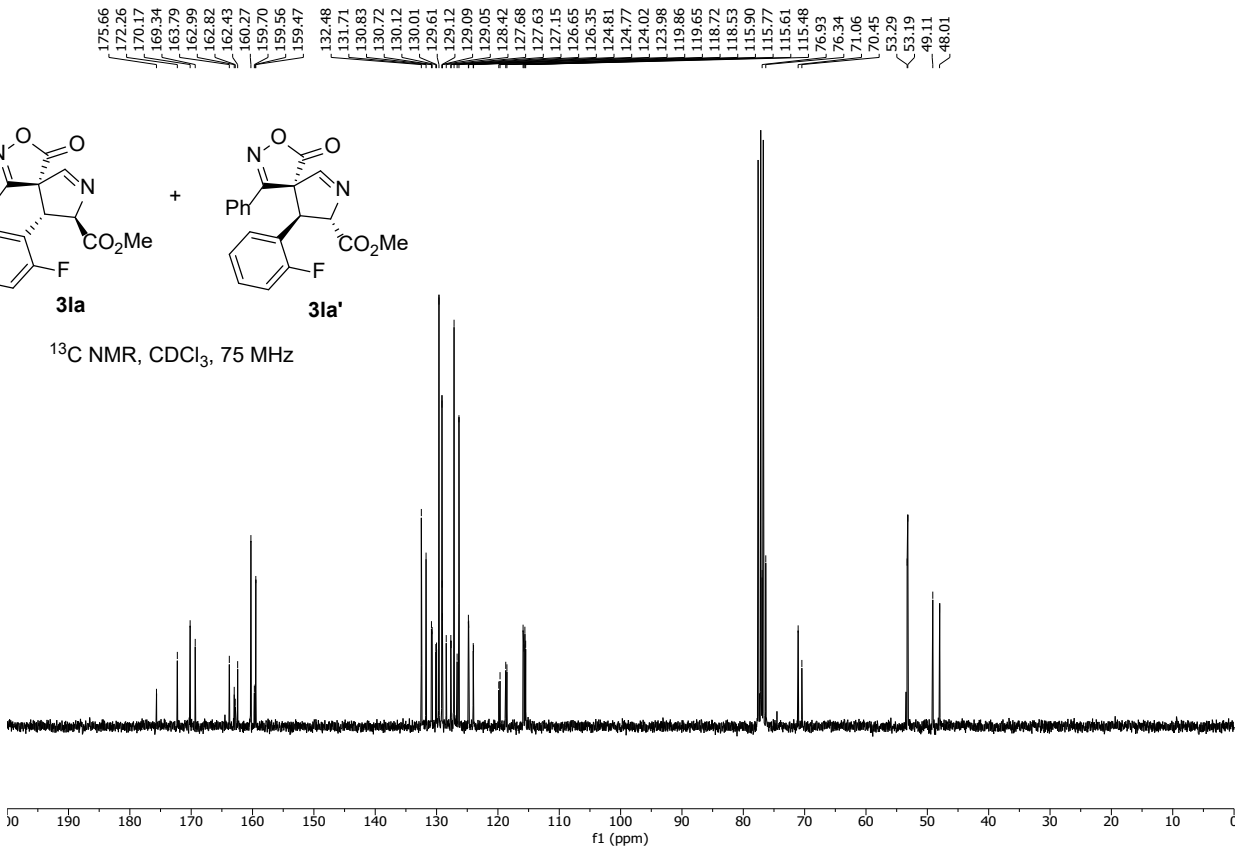
7.804
7.798
7.683
7.672
7.667
7.657
7.548
7.522
7.432
7.405
7.305
7.280
7.260 CDCl3
7.173
7.146
7.121
7.091
6.959
6.957
6.776
6.758
6.749
6.730
6.611
6.472
6.470
5.662
5.652
5.628
5.618
5.380
5.348
5.338
4.919
4.885
4.516
4.483
3.794
3.781
3.758
3.342
Ph
CO2Me
OMe
3ka
3ka'
1H NMR, CDCl3, 400 MHz
2.07
1.98
2.64
1.26
2.08
1.16
2.33
0.85
1.10
2.27
2.09
1.05
1.02
1.01
1.02
1.00
0.97
2.90
2.62
3.10
3.06
f1 (ppm)


176.02
172.35
170.82
169.82
164.13
163.09
160.75
159.76
157.45
156.96
132.09
131.23
129.97
129.41
129.18
128.86
128.64
128.22
127.49
126.76
126.62
126.19
121.20
120.81
120.17
119.97
110.27
109.67
77.16 CDCl3
76.65
76.12
70.87
70.62
54.42
54.39
53.11
53.04
49.95
49.02
Ph
CO2Me
OMe
3ka
3ka'
13C NMR, CDCl3, 101 MHz
f1 (ppm)



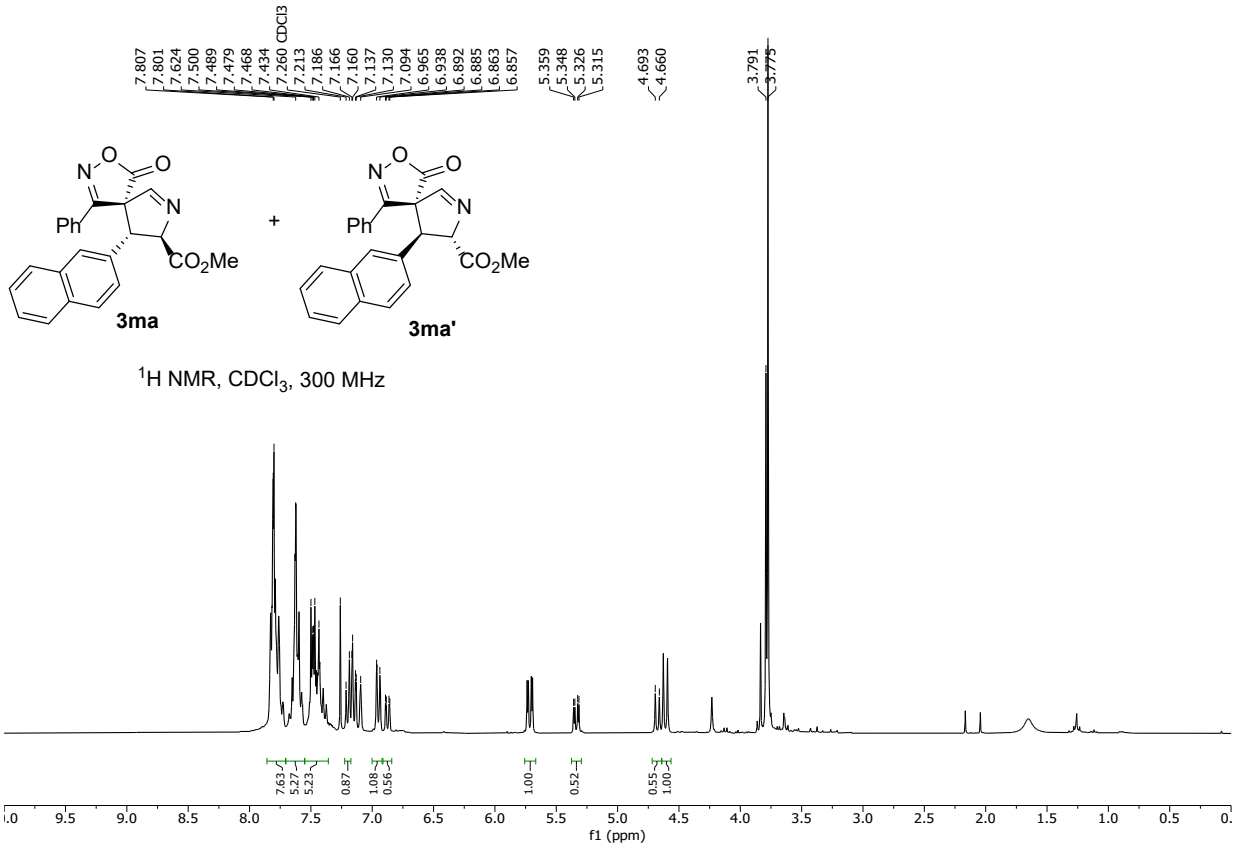
3Ia + **3Ia'**

^{1}H NMR, $CDCl_3$, 300 MHz

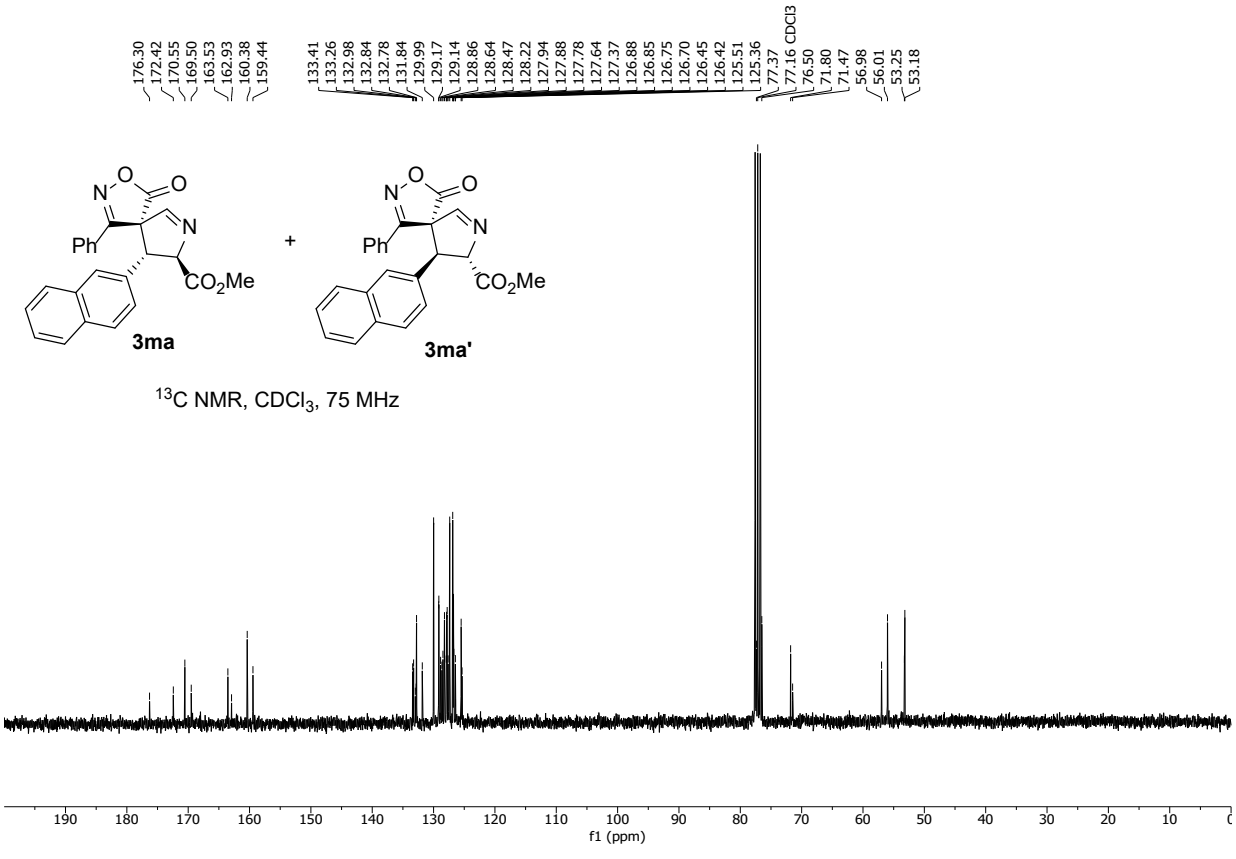


3Ia + **3Ia'**

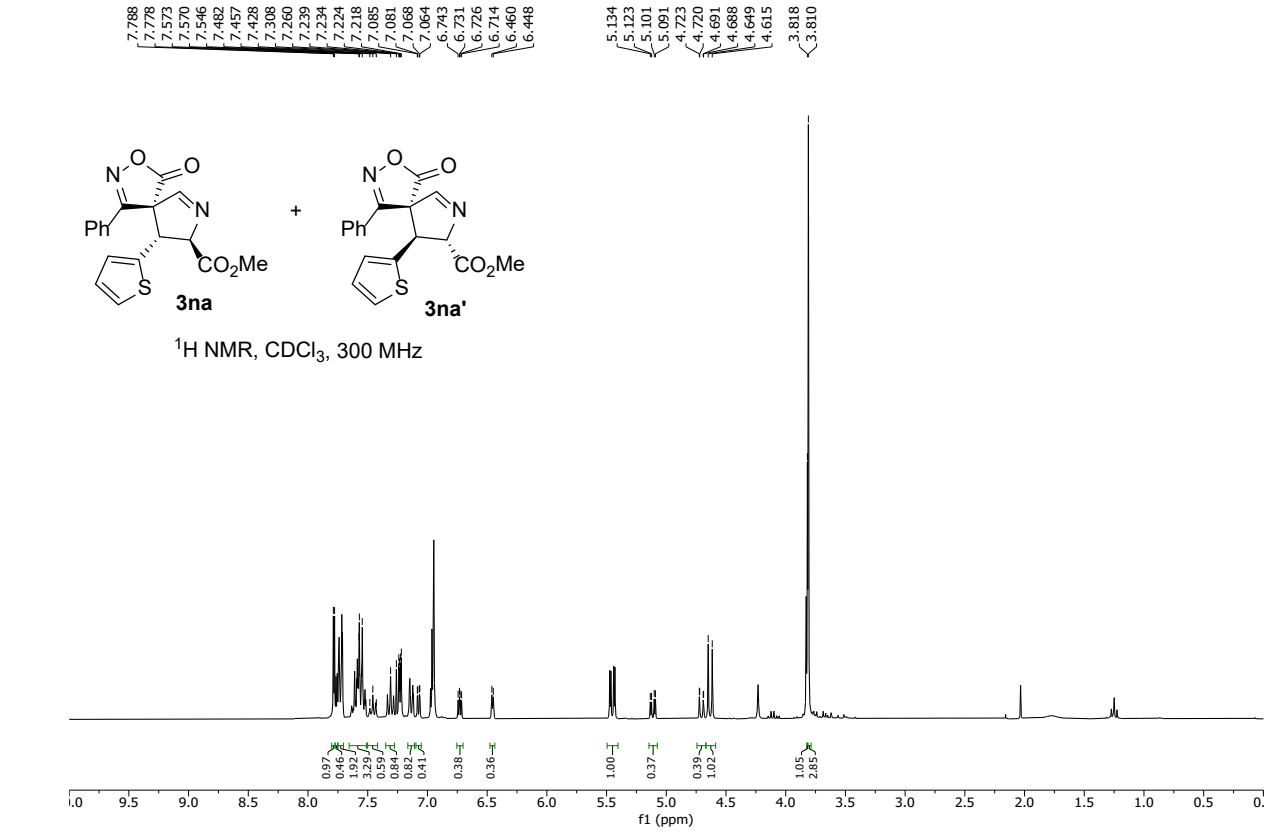
^{13}C NMR, $CDCl_3$, 75 MHz

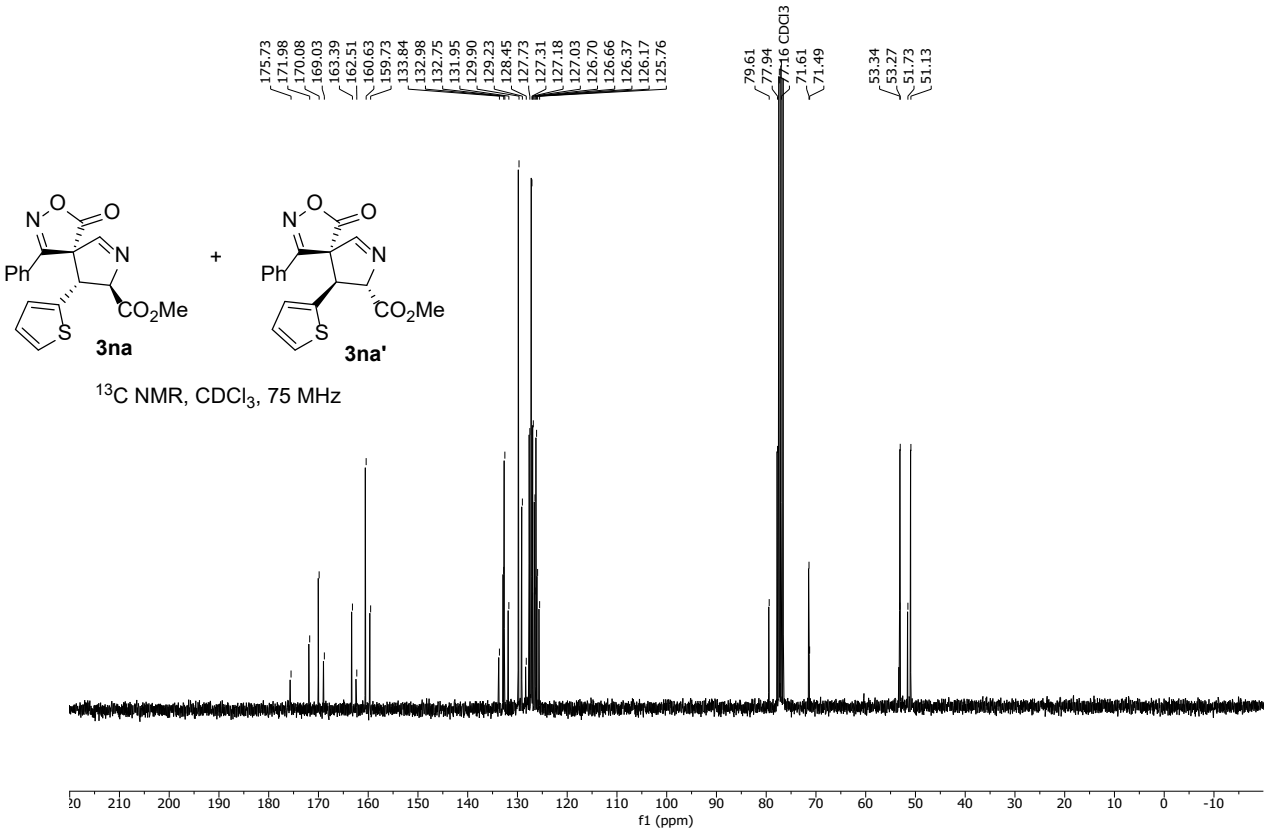


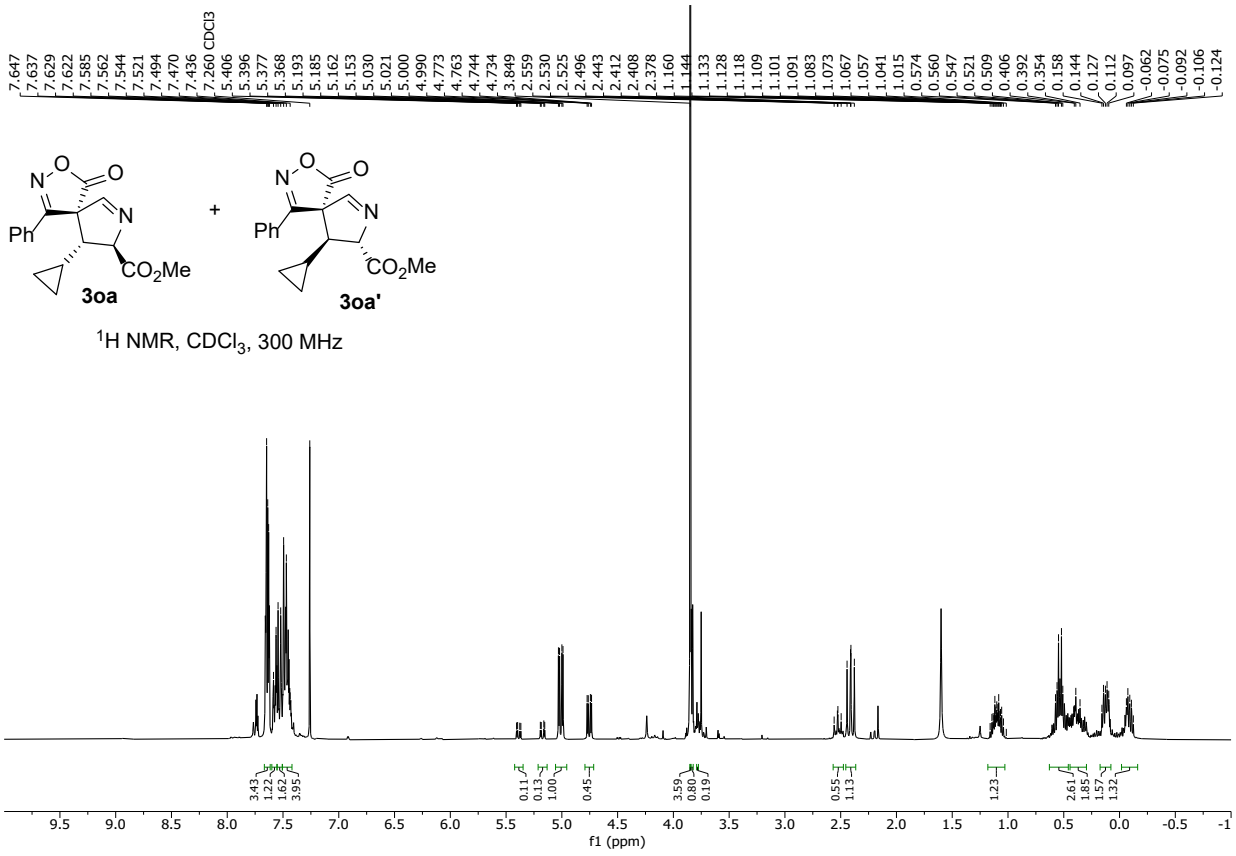
^{1}H NMR, $CDCl_3$, 300 MHz



^{13}C NMR, $CDCl_3$, 75 MHz


7.788
7.778
7.573
7.570
7.546
7.482
7.457
7.428
7.308
7.260
7.239
7.234
7.224
7.218
7.085
7.081
7.068
7.064
6.743
6.731
6.726
6.714
6.460
6.448
5.134
5.123
5.101
5.091
4.723
4.720
4.691
4.688
4.649
4.615
3.818
3.810
Ph
CO2Me
3na
3na'
1H NMR, CDCl3, 300 MHz
f1 (ppm)


175.73
171.98
170.08
169.03
163.39
162.51
160.63
159.73
133.84
132.98
132.75
131.95
129.90
129.23
128.45
127.73
127.31
127.18
127.03
126.70
126.66
126.37
126.17
125.76
79.61
77.94
77.16 CDCl3
71.61
71.49
53.34
53.27
51.73
51.13
Ph
CO2Me
3na
3na'
13C NMR, CDCl3, 75 MHz
f1 (ppm)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7.637
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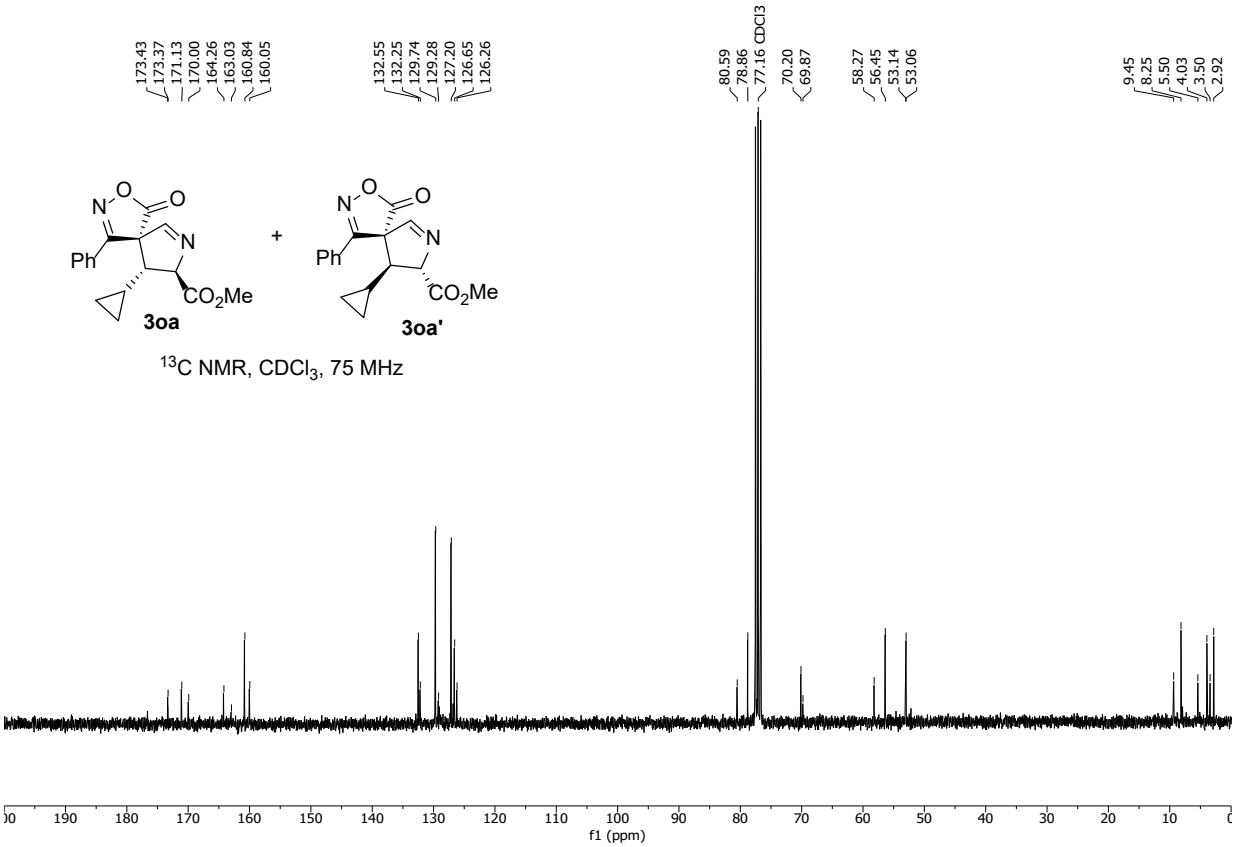
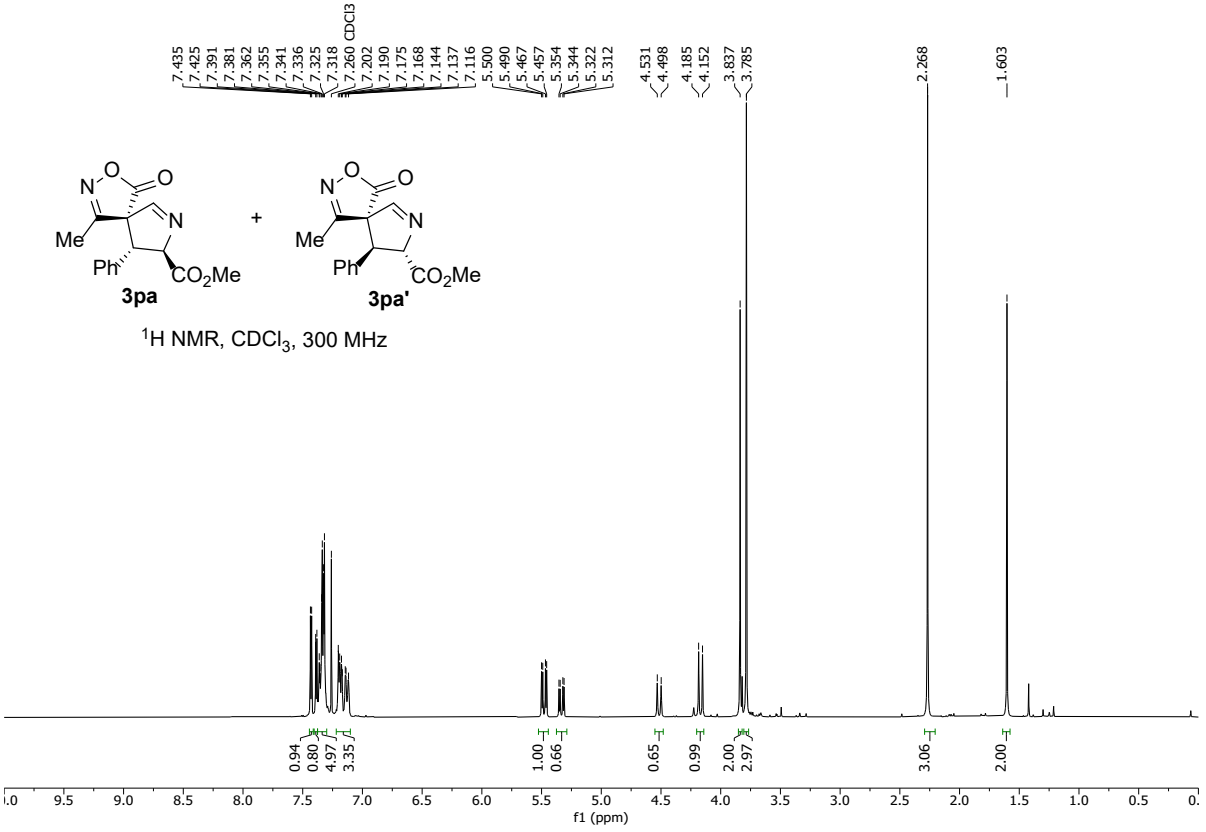
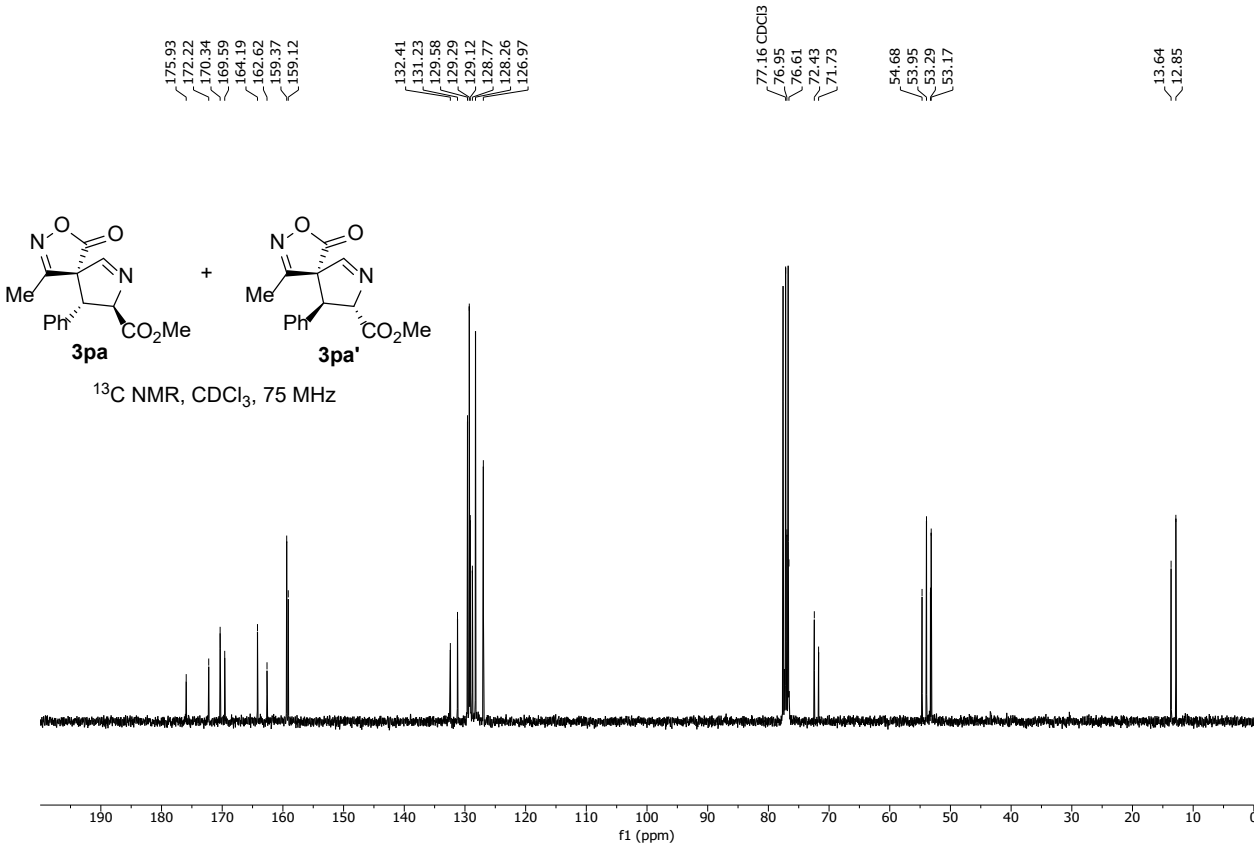
7.622
7.585
7.562
7.544
7.521
7.494
7.470
7.436
7.260 CDCl3
5.406
5.396
5.377
5.368
5.193
5.185
5.162
5.153
5.030
5.021
5.000
4.990
4.773
4.763
4.744
4.734
3.849
2.559
2.530
2.525
2.496
2.443
2.412
2.408
2.378
1.160
1.144
1.133
1.128
1.118
1.109
1.101
1.091
1.083
1.073
1.067
1.057
1.041
1.015
0.574
0.560
0.547
0.521
0.509
0.406
0.392
0.354
0.158
0.144
0.127
0.112
0.097
-0.062
-0.075
-0.092
-0.106
-0.124
Ph
CO2Me
3oa
3oa'
1H NMR, CDCl3, 300 MHz
3.43
1.22
1.62
3.95
0.11
0.13
1.00
0.45
3.59
0.80
0.19
0.55
1.13
1.23
2.61
1.85
1.57
1.32
f1 (ppm)

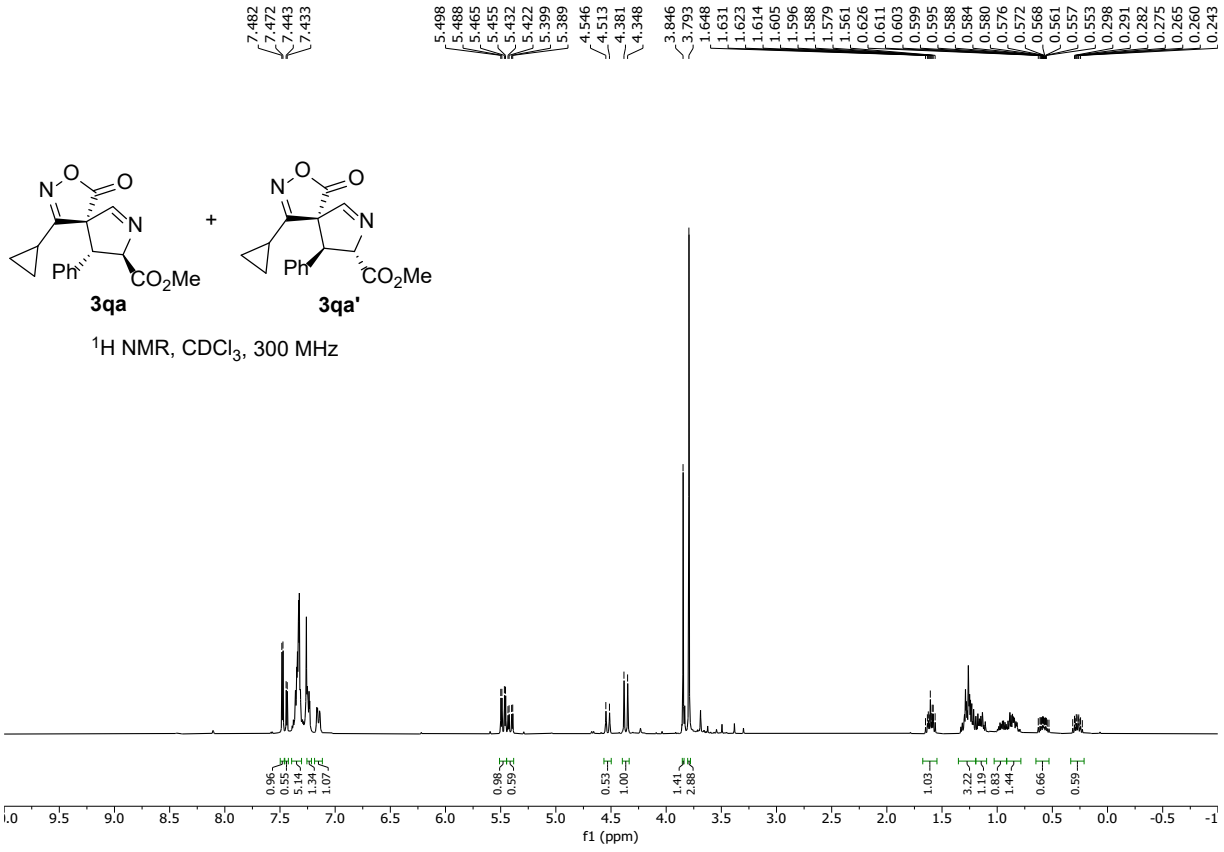

173.43
173.37
171.13
170.00
164.26
163.03
160.84
160.05
132.55
132.25
129.74
129.28
127.20
126.65
126.26
80.59
78.86
77.16 CDCl3
70.20
69.87
58.27
56.45
53.14
53.06
9.45
8.25
5.50
4.03
3.50
2.92
Ph
CO2Me
3oa
3oa'
13C NMR, CDCl3, 75 MHz
f1 (ppm)

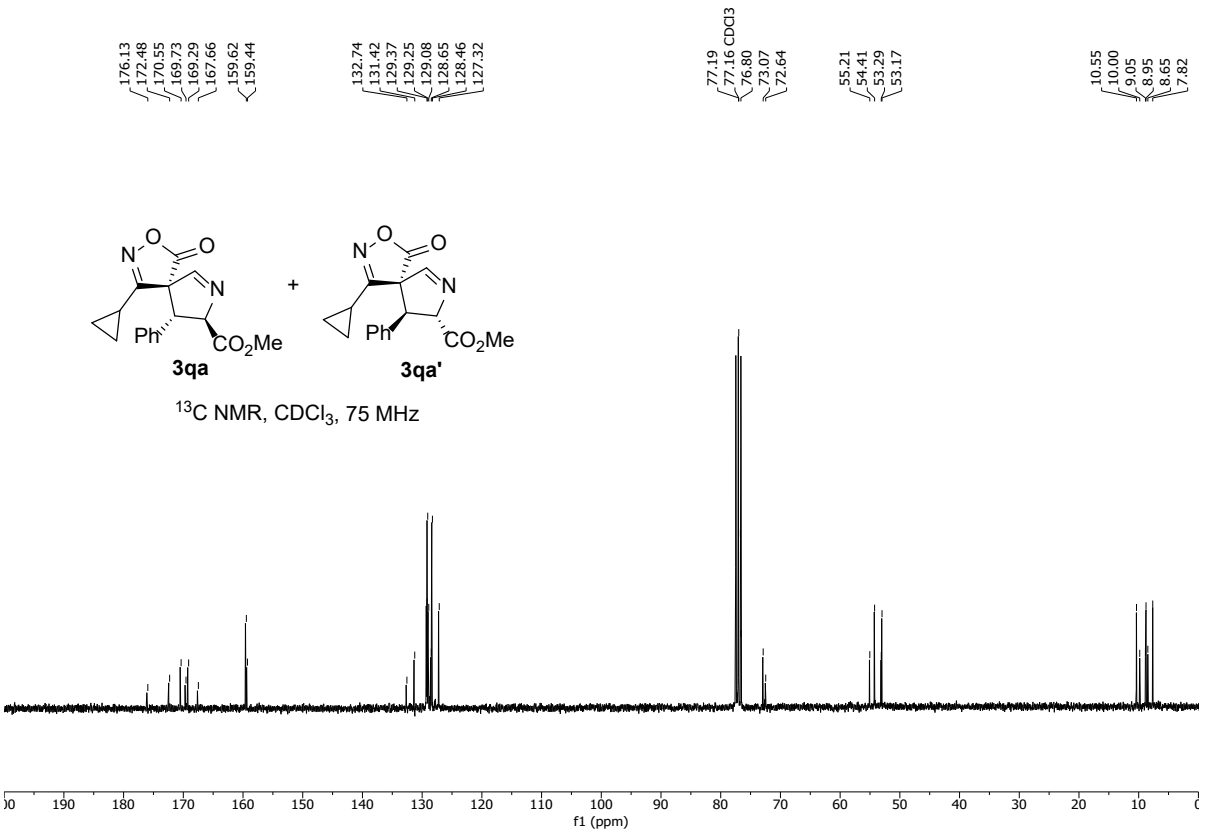


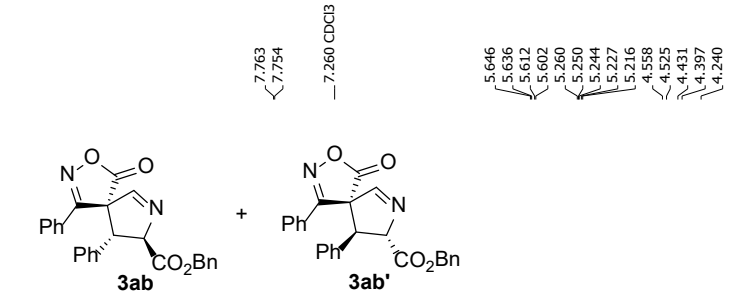
^{1}H NMR, $CDCl_3$, 300 MHz



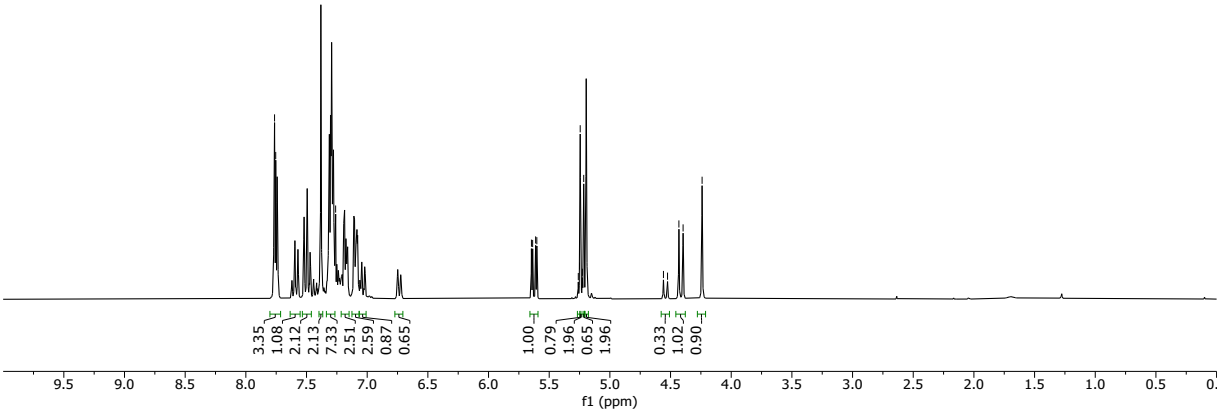
^{13}C NMR, $CDCl_3$, 75 MHz

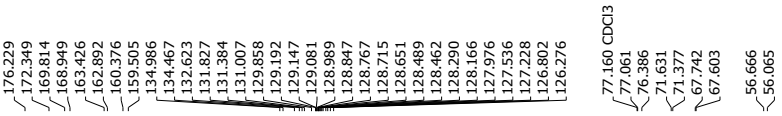

7.482
7.472
7.443
7.433
5.498
5.488
5.465
5.455
5.432
5.422
5.399
5.389
4.546
4.513
4.381
4.348
3.846
3.793
1.648
1.631
1.623
1.614
1.605
1.596
1.588
1.579
1.561
1.626
0.611
0.603
0.599
0.595
0.588
0.584
0.580
0.576
0.572
0.568
0.561
0.557
0.553
0.298
0.291
0.282
0.275
0.265
0.260
0.243
3qa
3qa'
1H NMR, CDCl3, 300 MHz
f1 (ppm)

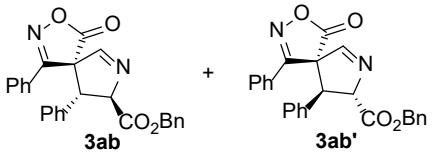

176.13
172.48
170.55
169.73
169.29
167.66
159.62
159.44
132.74
131.42
129.37
129.25
129.08
128.65
128.46
127.32
77.19
77.16 CDCl3
76.80
73.07
72.64
55.21
54.41
53.29
53.17
10.55
10.00
9.05
8.95
8.65
7.82
3qa
3qa'
13C NMR, CDCl3, 75 MHz
f1 (ppm)



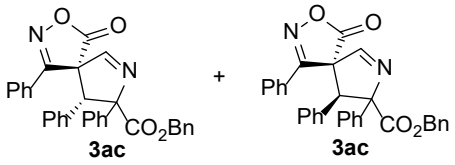
^{1}H NMR, $CDCl_3$, 300 MHz





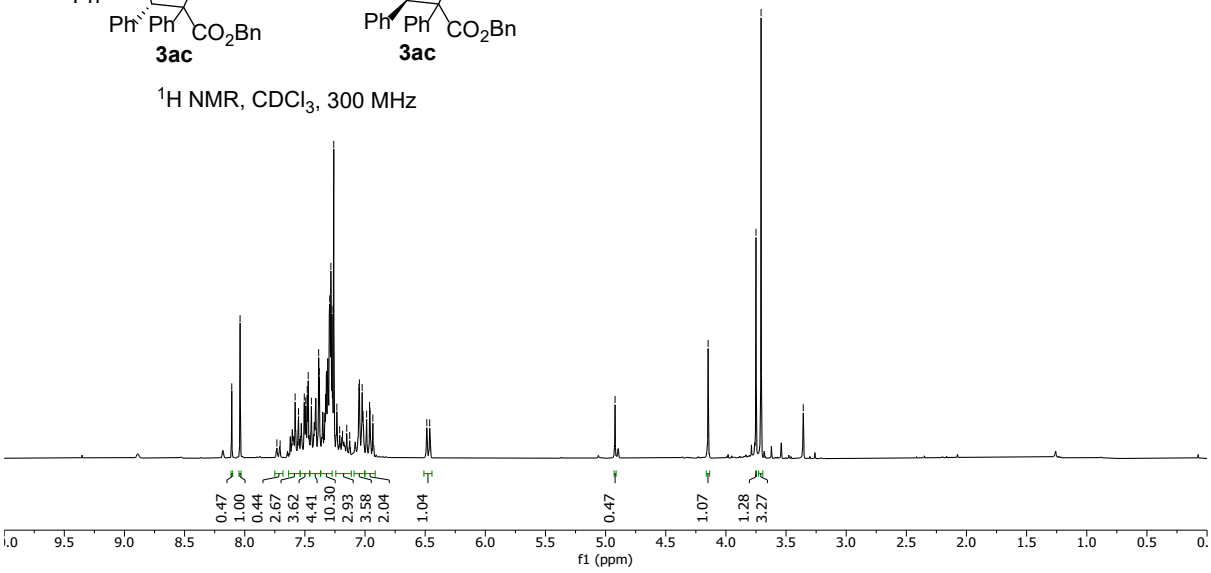


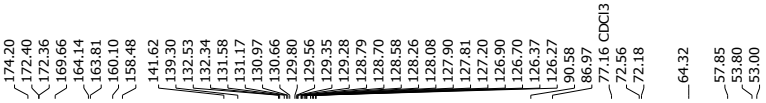
^{13}C NMR, $CDCl_3$, 75 MHz

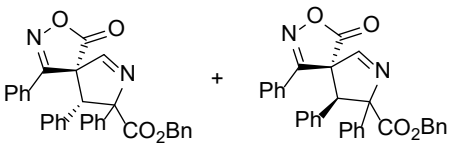


3ac **3ac**

^{1}H NMR, $CDCl_3$, 300 MHz

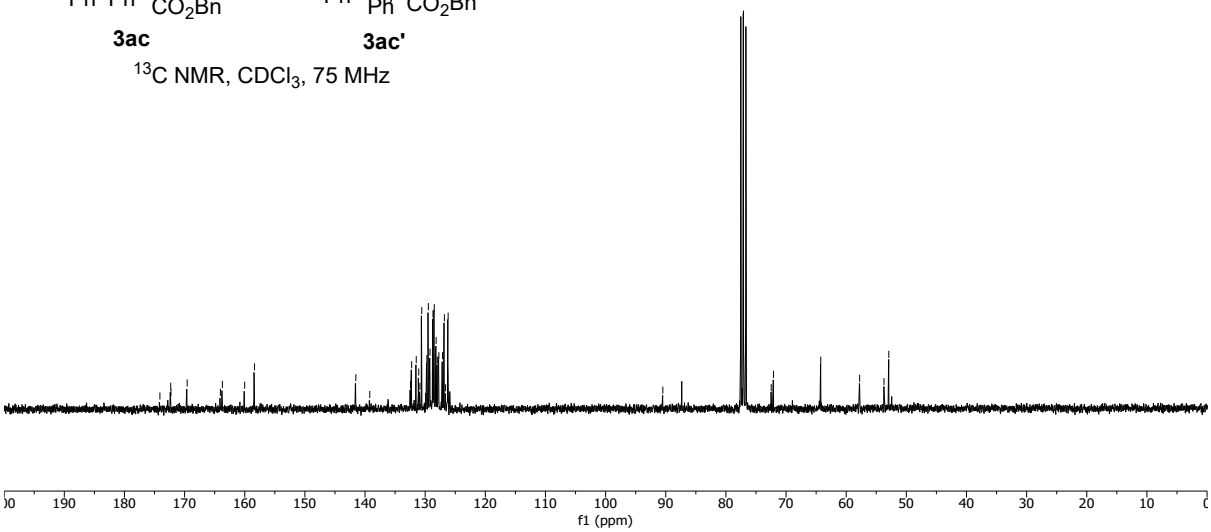


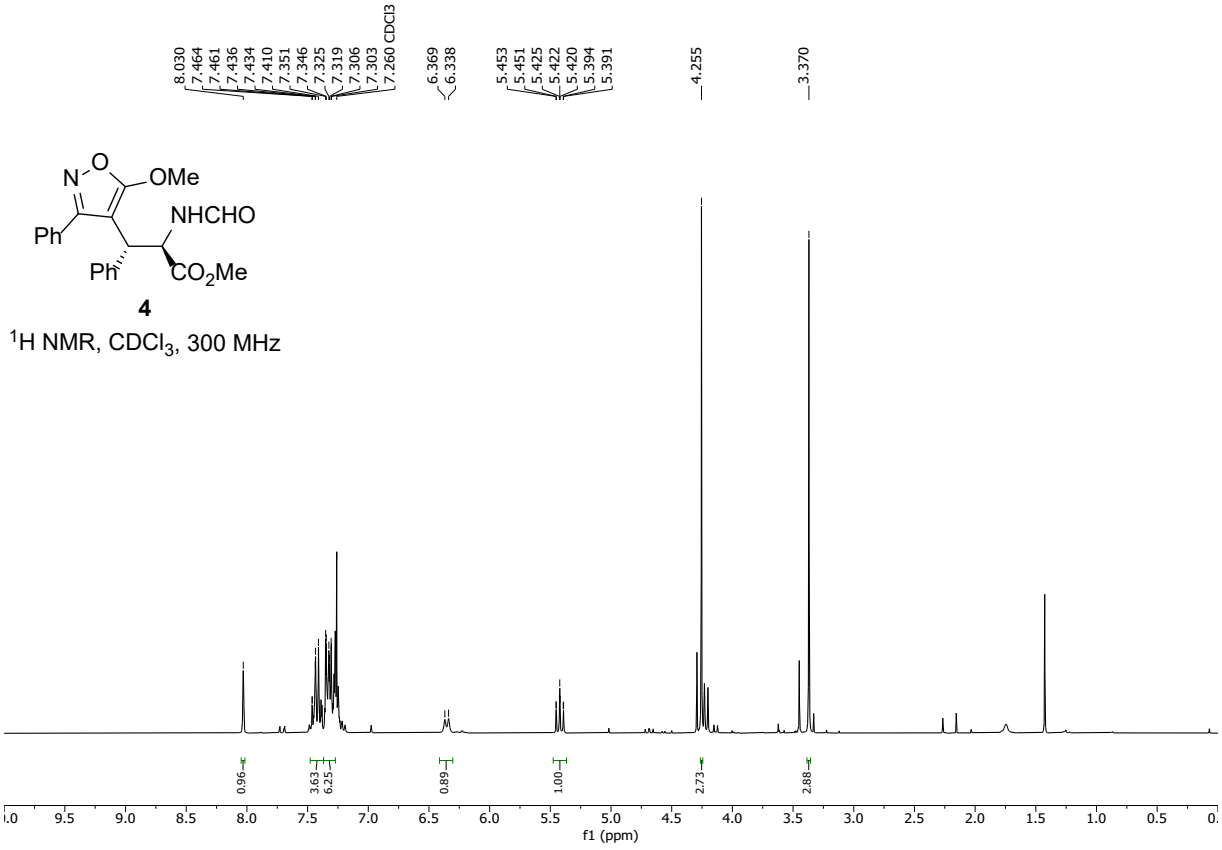




3ac **3ac'**

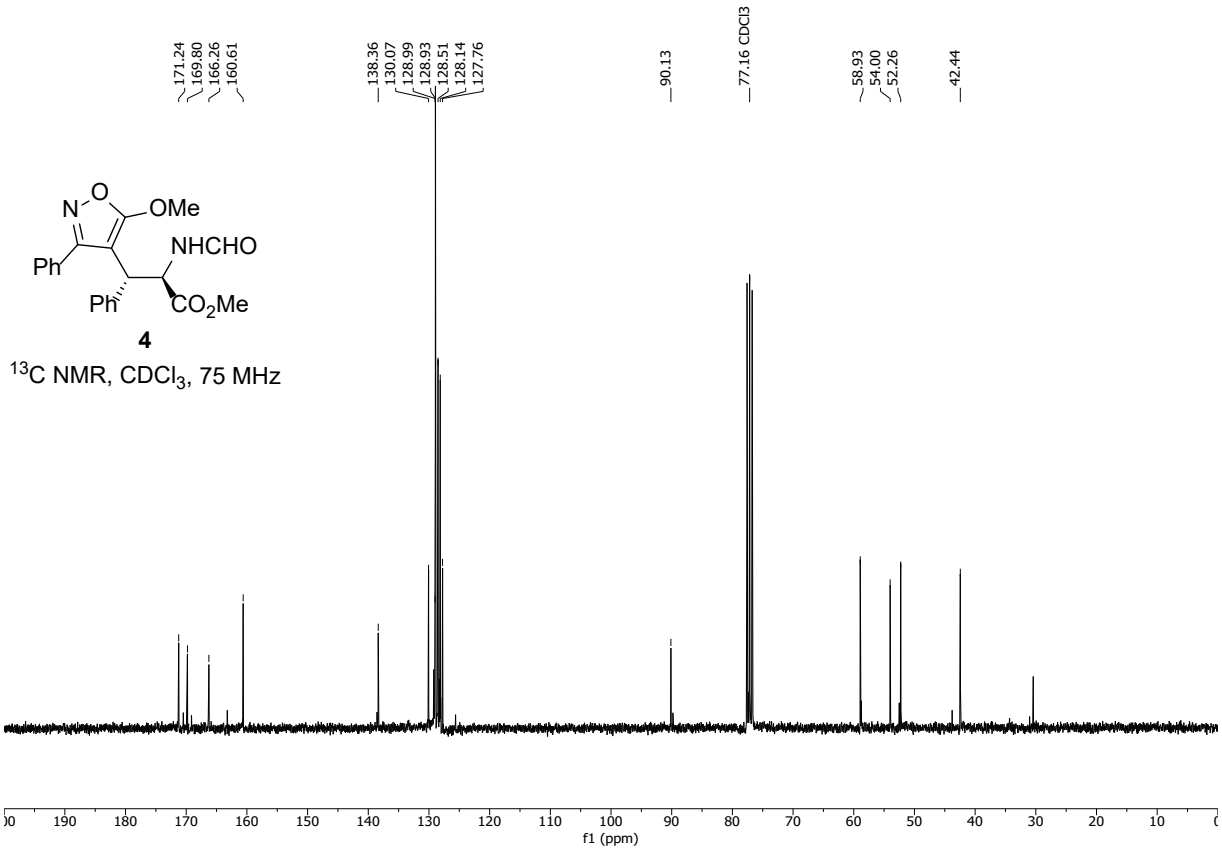
^{13}C NMR, $CDCl_3$, 75 MHz





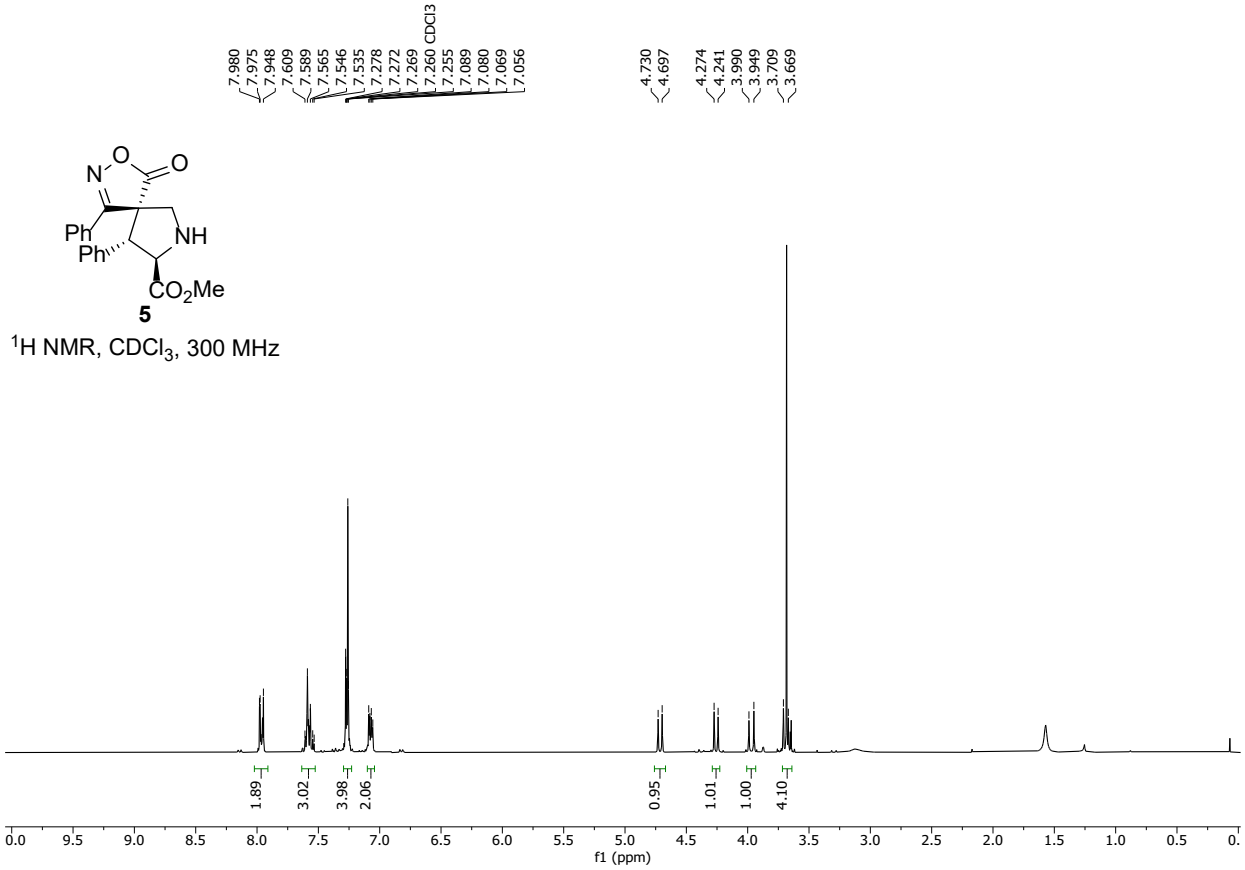
4

^{1}H NMR, $CDCl_3$, 300 MHz



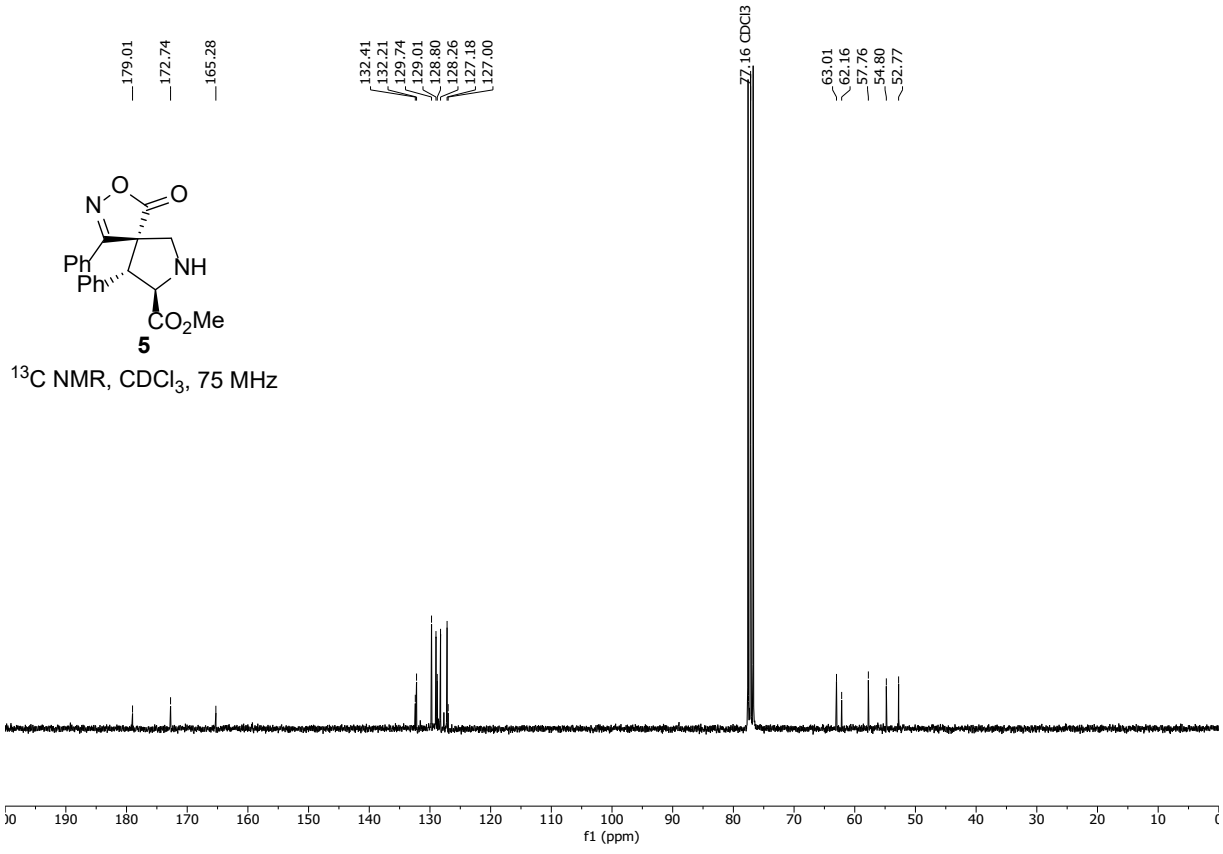
4

^{13}C NMR, $CDCl_3$, 75 MHz



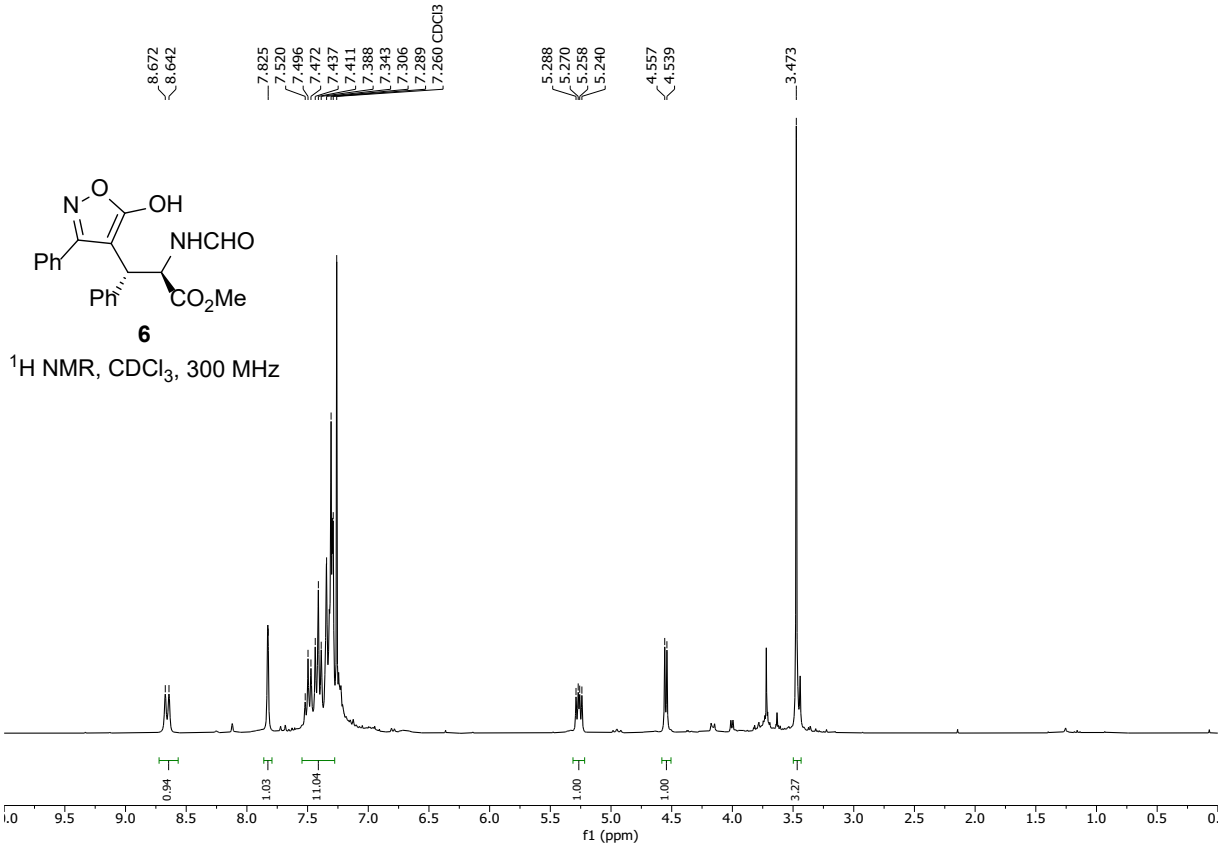
5

^{1}H NMR, $CDCl_3$, 300 MHz



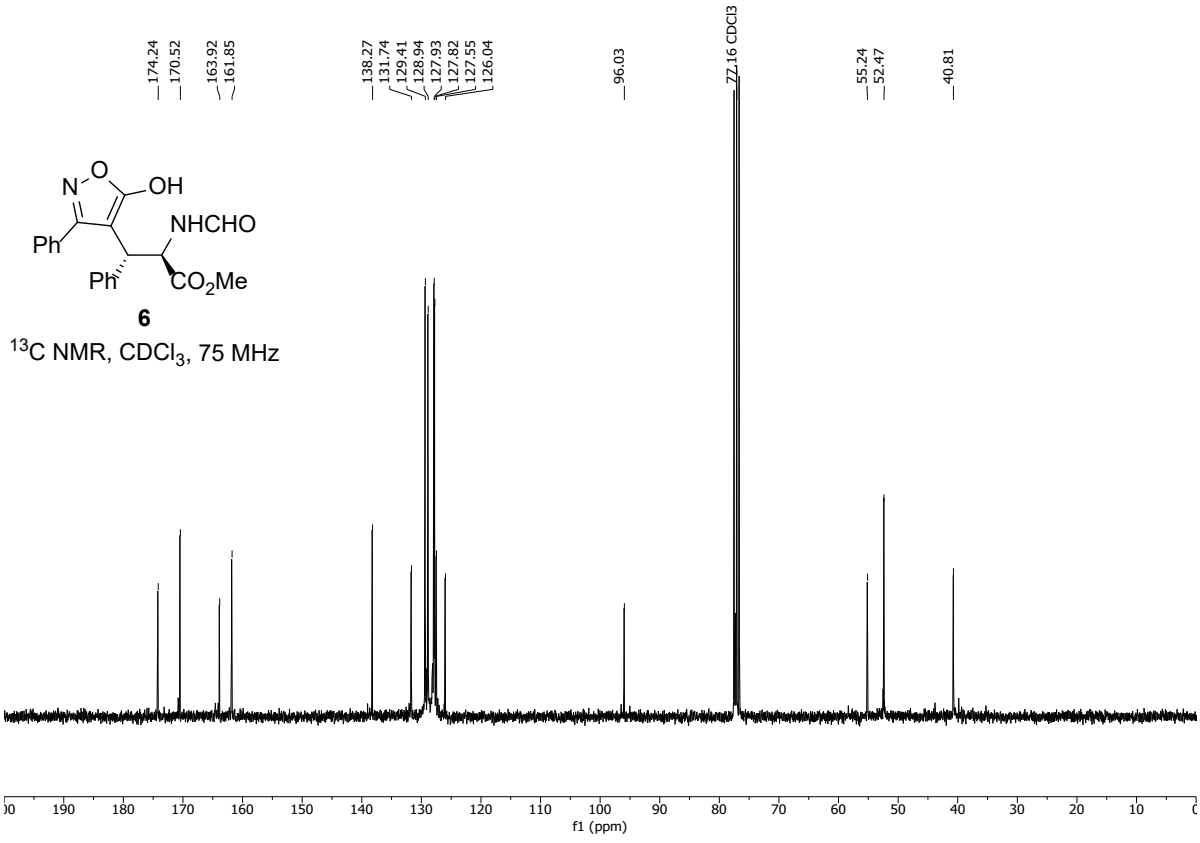
5

^{13}C NMR, $CDCl_3$, 75 MHz



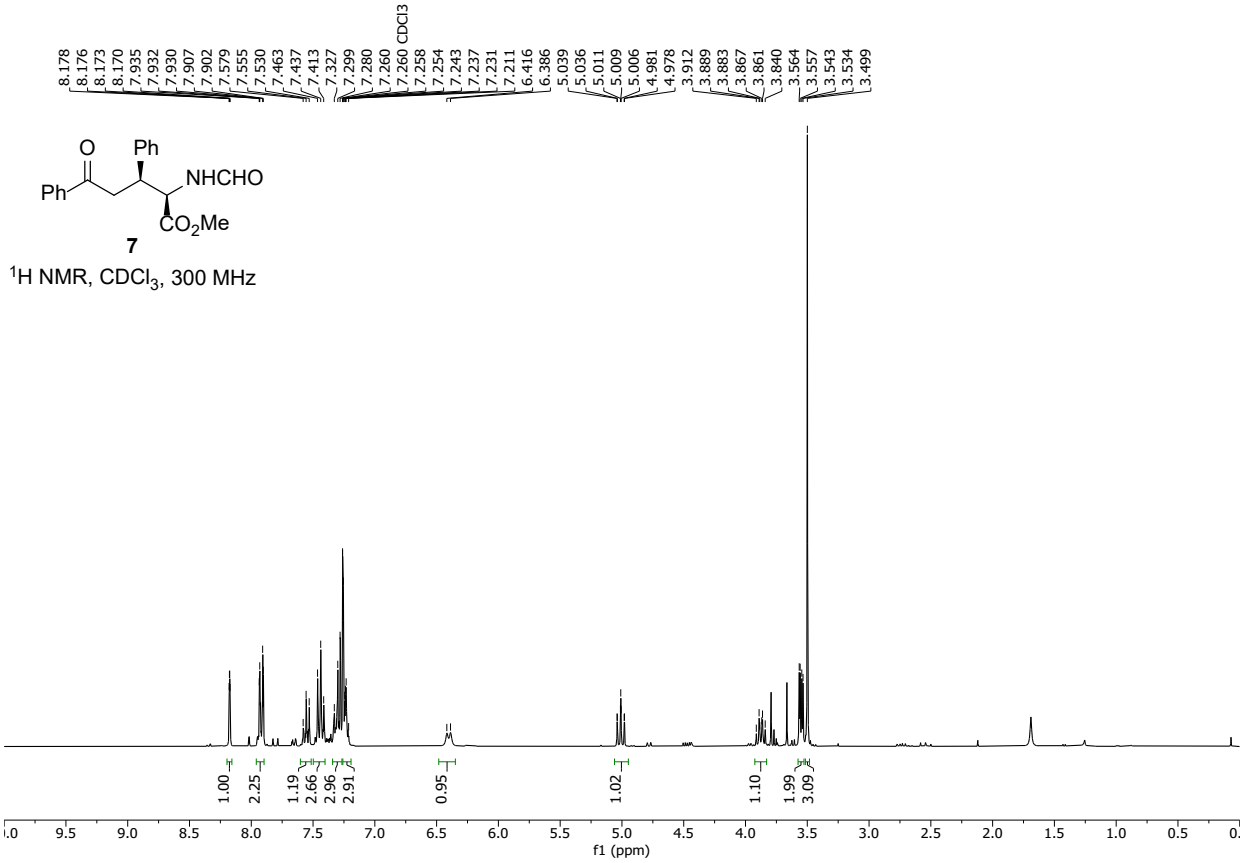
6

^{1}H NMR, $CDCl_3$, 300 MHz

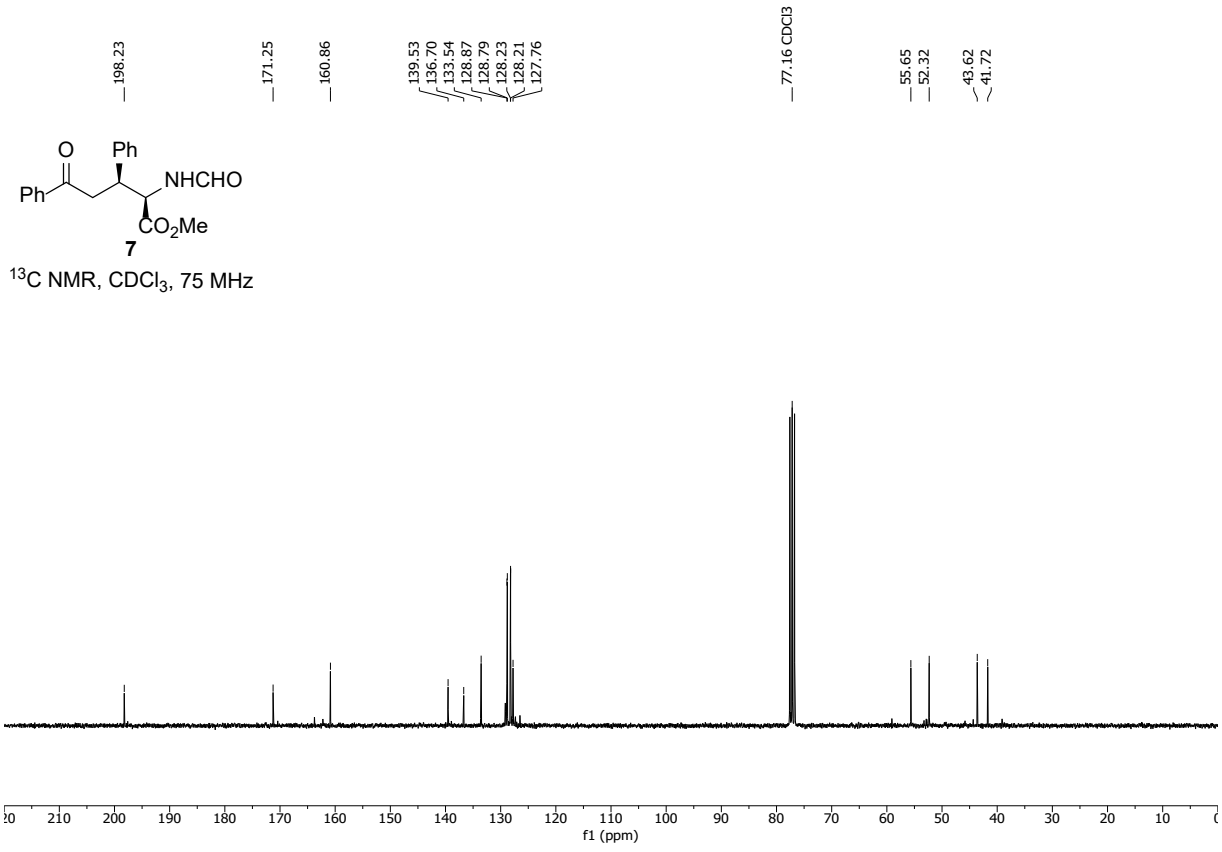


6

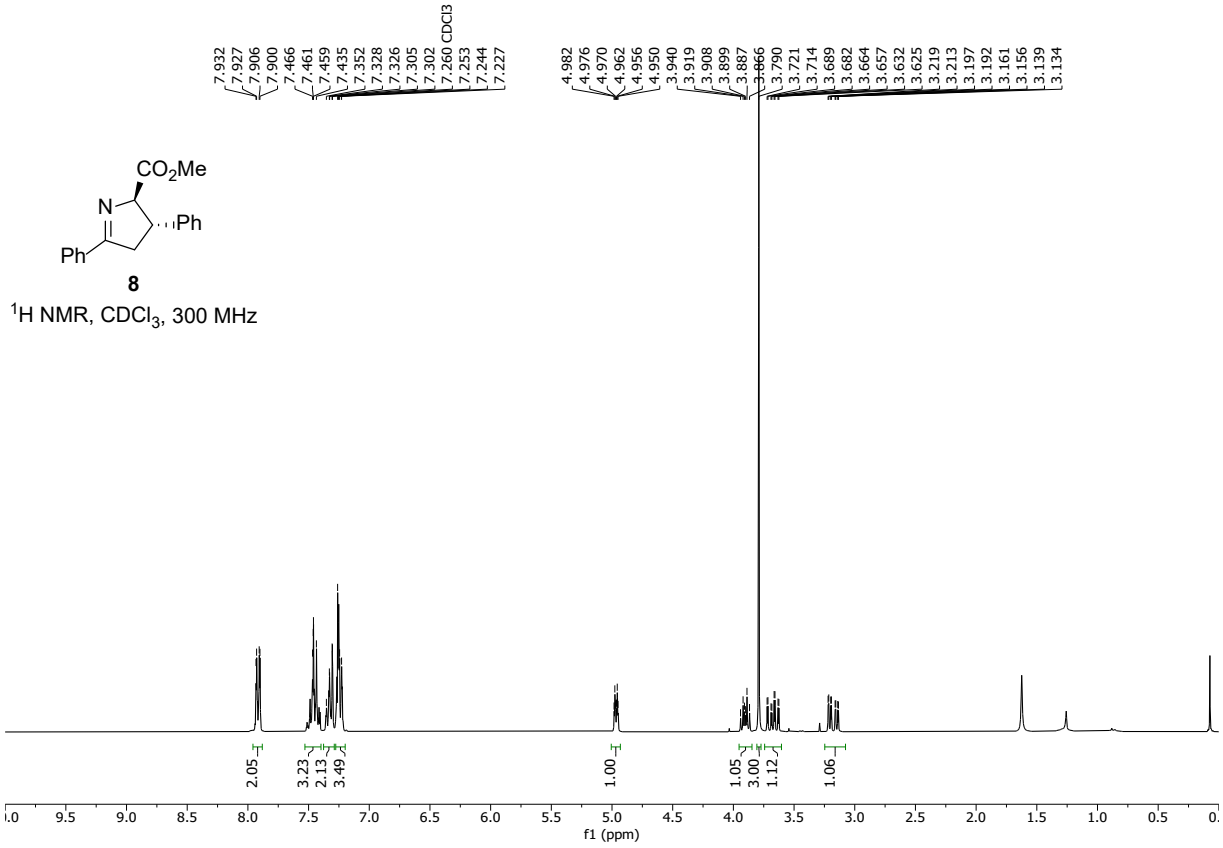
^{13}C NMR, $CDCl_3$, 75 MHz



^{1}H NMR, $CDCl_3$, 300 MHz

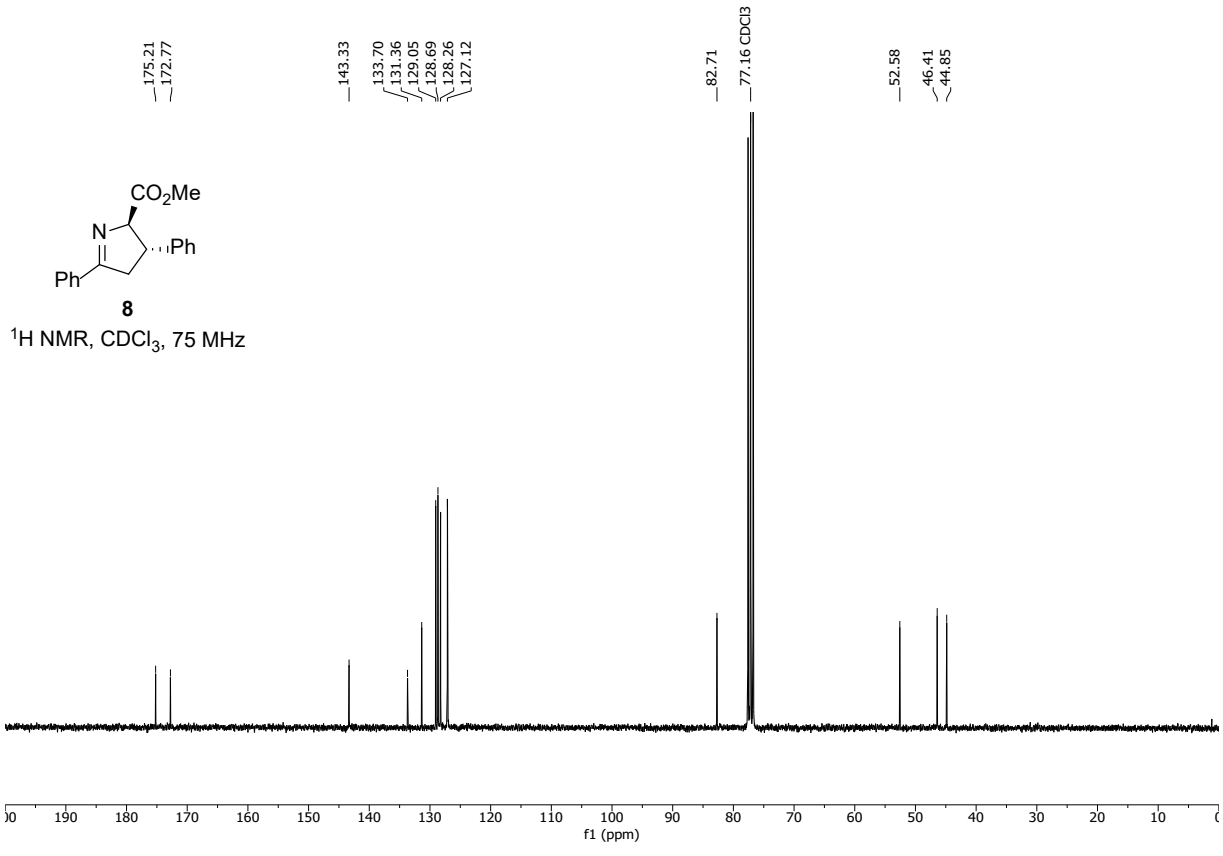


^{13}C NMR, $CDCl_3$, 75 MHz



8

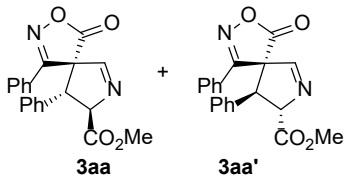
^{1}H NMR, $CDCl_3$, 300 MHz



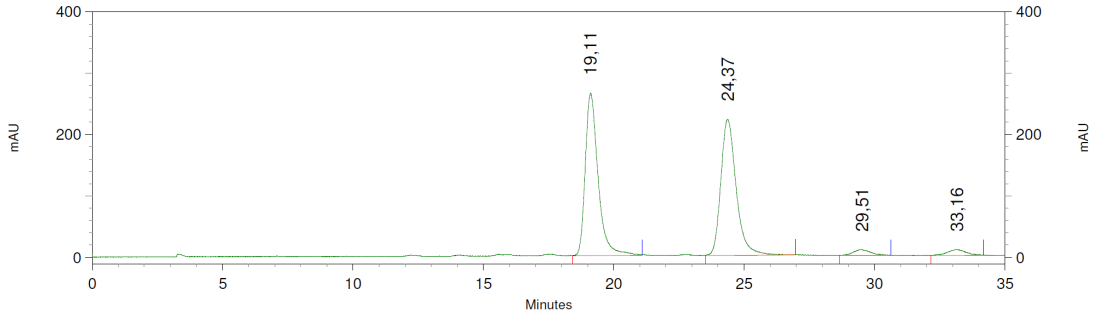
8

^{1}H NMR, $CDCl_3$, 75 MHz

9. HPLC chromatograms



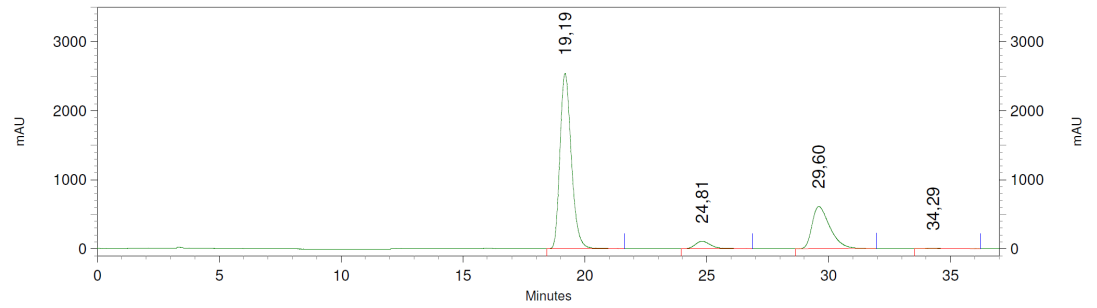
Racemic product (diastereomeric mixture)



4: 259 nm, 4 nm Results

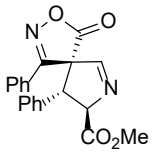
Retention Time	Area	Area Percent
19,11	36260642	47,595
24,37	36295696	47,641
29,51	1770029	2,323
33,16	1858853	2,440

Enantioenriched product (diastereomeric mixture)



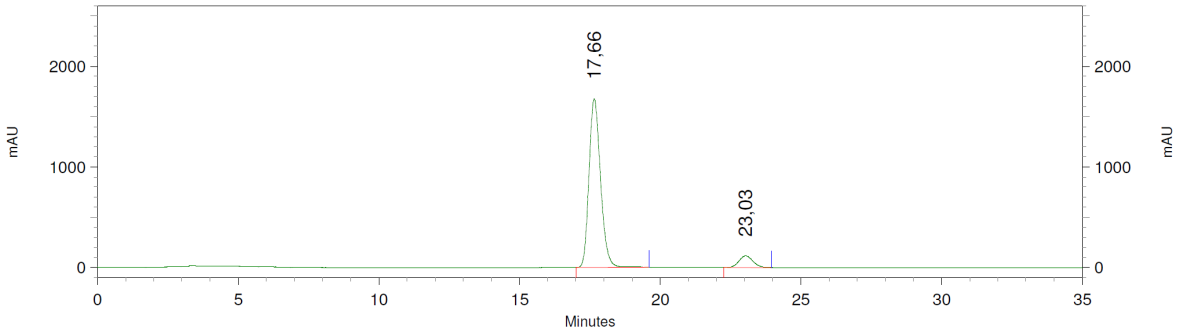
4: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
19,19	329899544	69,374
24,81	19956318	4,197
29,60	124280715	26,135
34,29	1401816	0,295



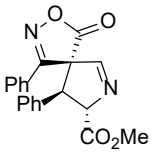
3aa

Separated 3aa



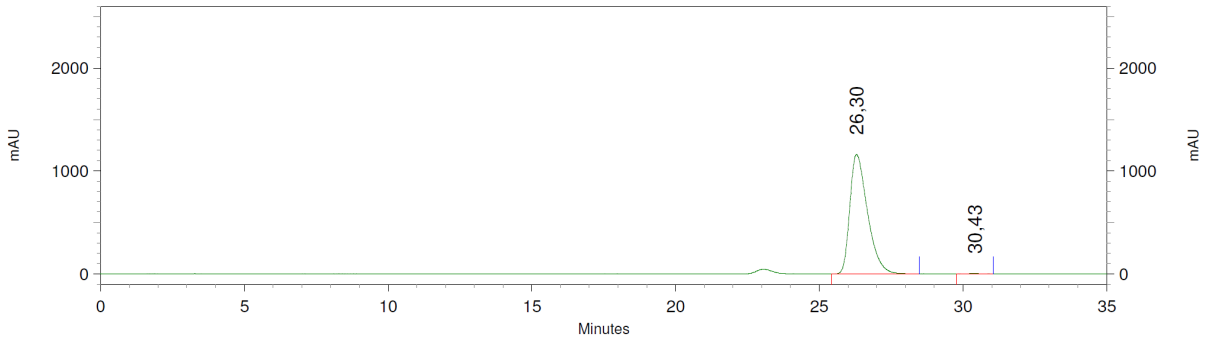
4: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
17,66	190404529	92,285
23,03	15917168	7,715



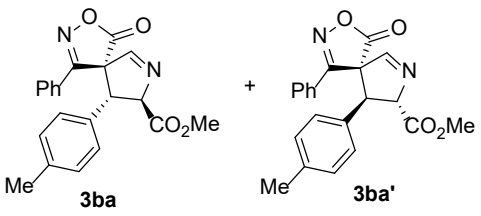
3aa'

Separated 3aa'

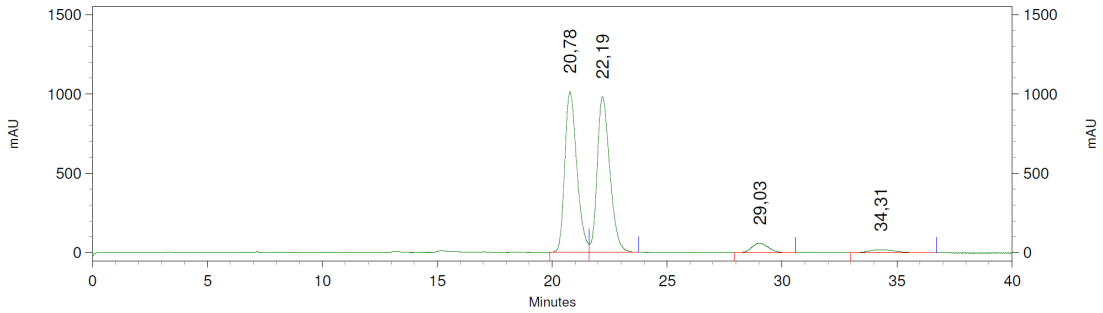


4: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
26,30	199295557	99,671
30,43	657187	0,329



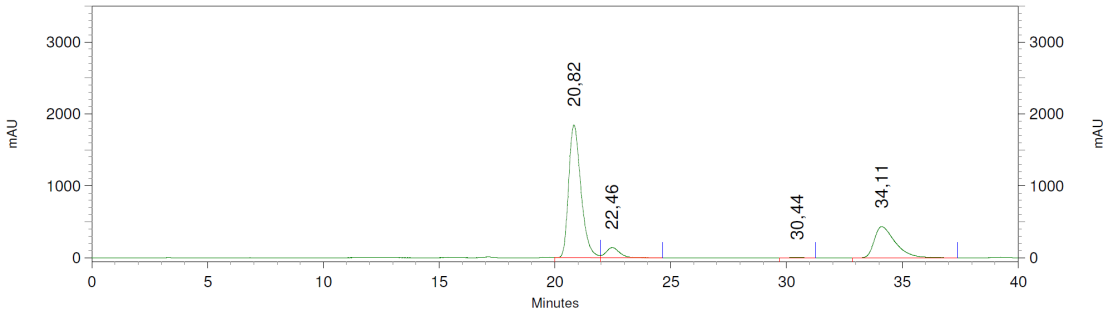
Racemic product (diastereomeric mixture)



4: 259 nm, 4 nm Results

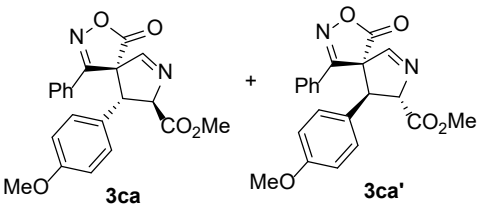
Retention Time	Area	Area Percent
20,78	148063595	46,824
22,19	149504015	47,279
29,03	12312972	3,894
34,31	6334028	2,003

Enantioenriched product (diastereomeric mixture)

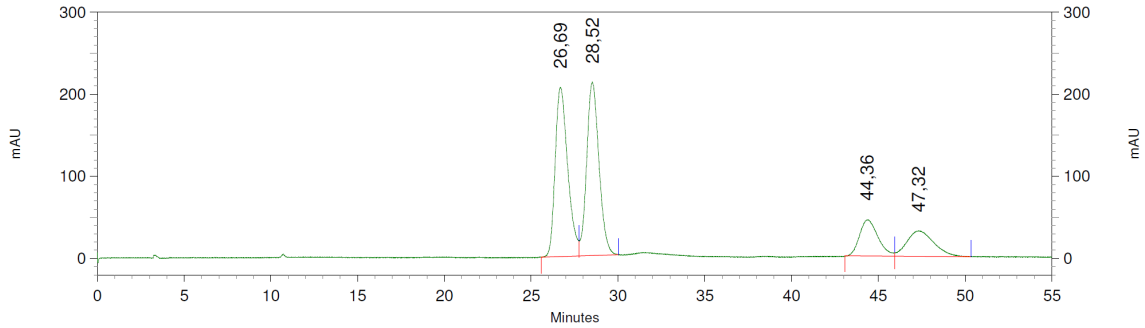


4: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
20,82	272225007	67,312
22,46	22511778	5,566
30,44	733317	0,181
34,11	108952681	26,940



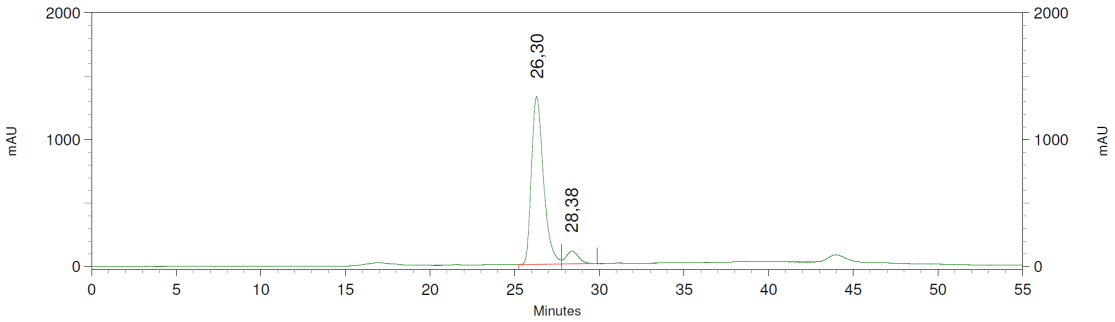
Racemic product (diastereomeric mixture)



4: 259 nm, 4 nm Results

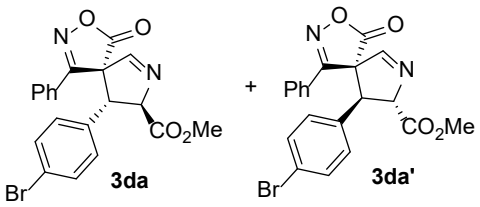
Retention Time	Area	Area Percent
26,69	41339434	37,775
28,52	41664693	38,072
44,36	13017925	11,895
47,32	13414377	12,258

Enantioenriched product (diastereomeric mixture)

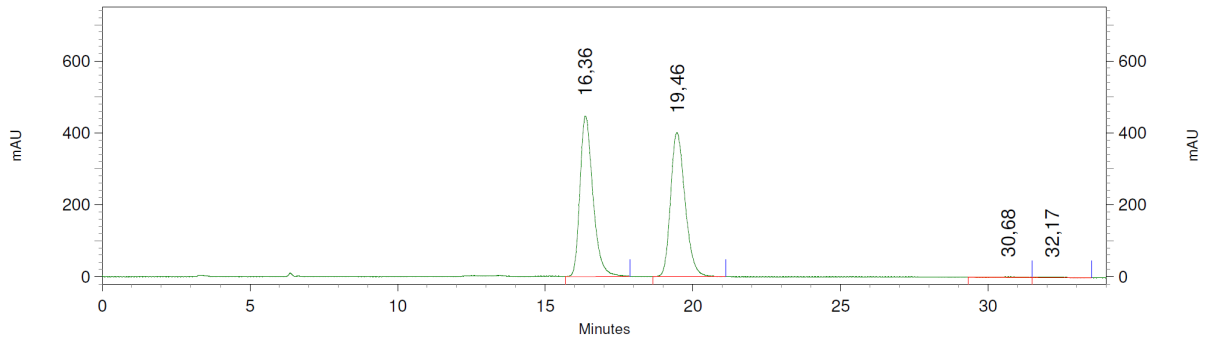


4: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
26,30	261507660	92,714
28,38	20551537	7,286



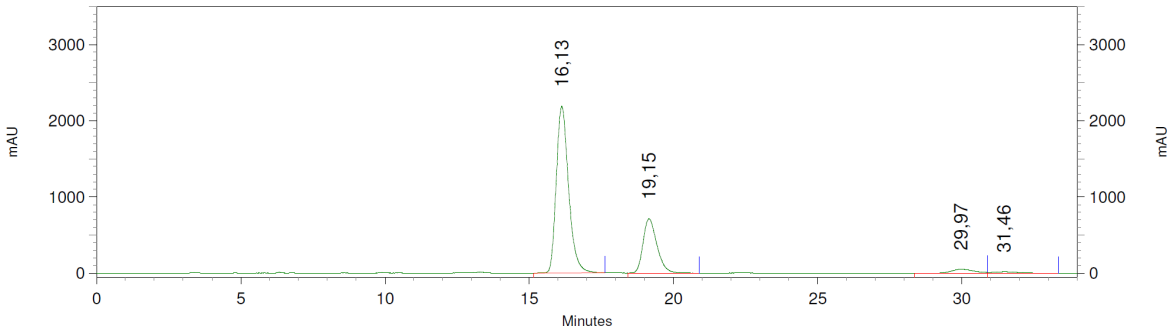
Racemic product (diastereomeric mixture)



4: 256 nm, 4 nm Results

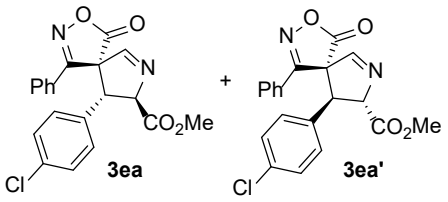
Retention Time	Area	Area Percent
16,36	54530180	49,522
19,46	54717371	49,692
30,68	454556	0,413
32,17	410989	0,373

Enantioenriched product (diastereomeric mixture)

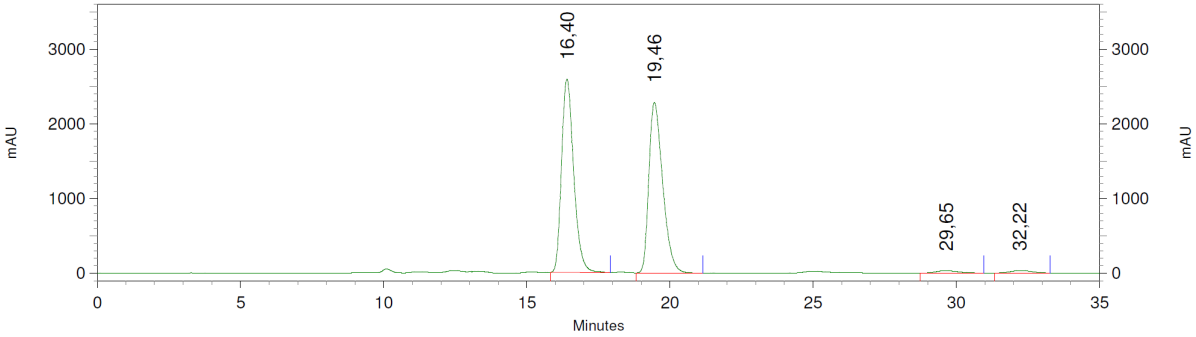


4: 256 nm, 4 nm Results

Retention Time	Area	Area Percent
16,13	260549912	70,391
19,15	95120813	25,698
29,97	10621628	2,870
31,46	3855424	1,042



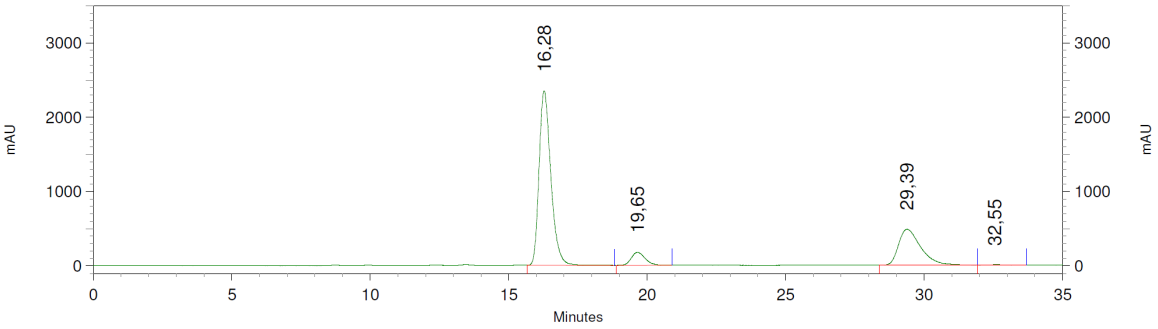
Racemic product (diastereomeric mixture)



4: 259 nm, 4 nm Results

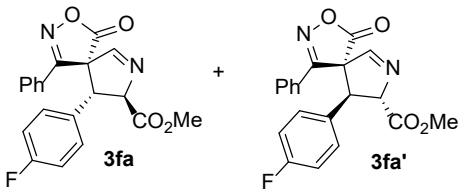
Retention Time	Area	Area Percent
16,40	306858695	48,975
19,46	306356269	48,894
29,65	6713449	1,071
32,22	6639348	1,060

Enantioenriched product (diastereomeric mixture)

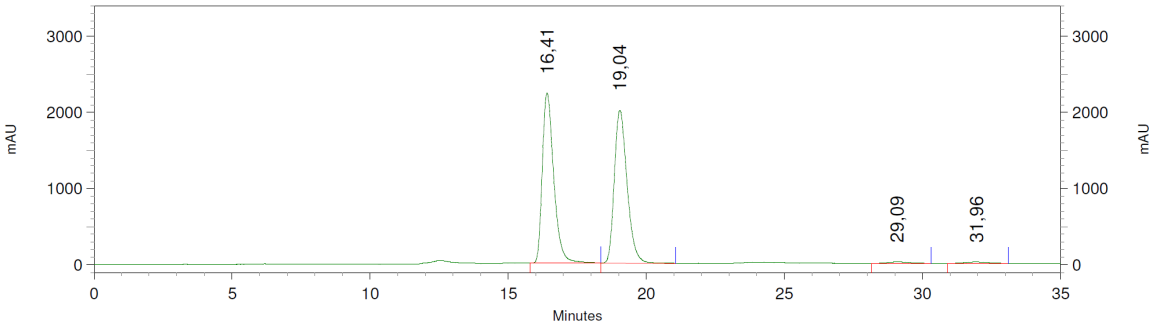


4: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
16,28	276628431	67,406
19,65	24906984	6,069
29,39	107855034	26,281
32,55	1001219	0,244



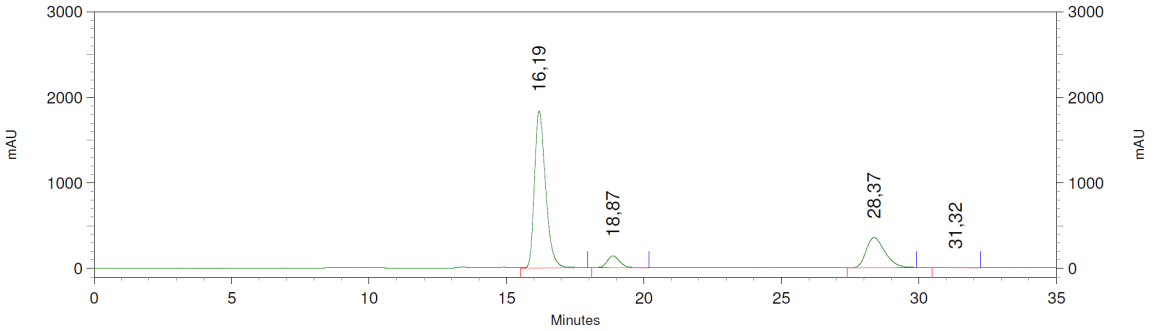
Racemic product (diastereomeric mixture)



4: 259 nm, 4 nm Results

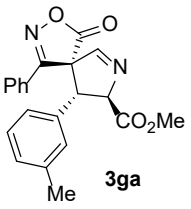
Retention Time	Area	Area Percent
16,41	259127111	49,209
19,04	258274391	49,047
29,09	4559499	0,866
31,96	4624232	0,878

Enantioenriched product (diastereomeric mixture)

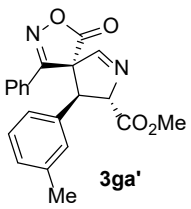


4: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
16,19	206196743	70,637
18,87	17781750	6,092
28,37	67338010	23,068
31,32	592524	0,203

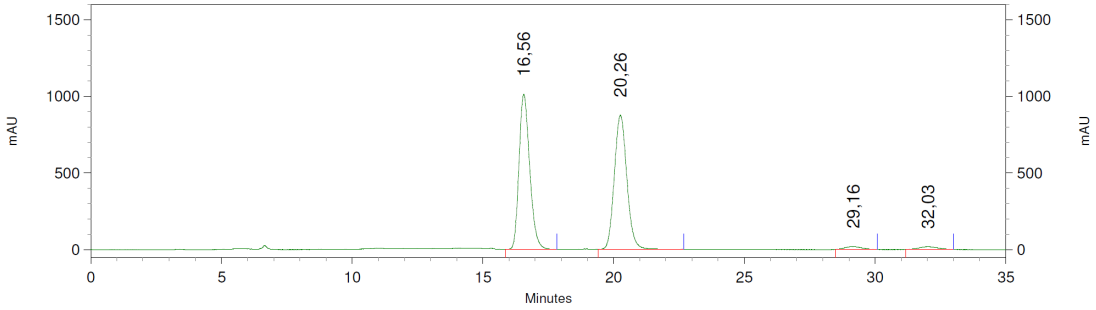


3ga



3ga'

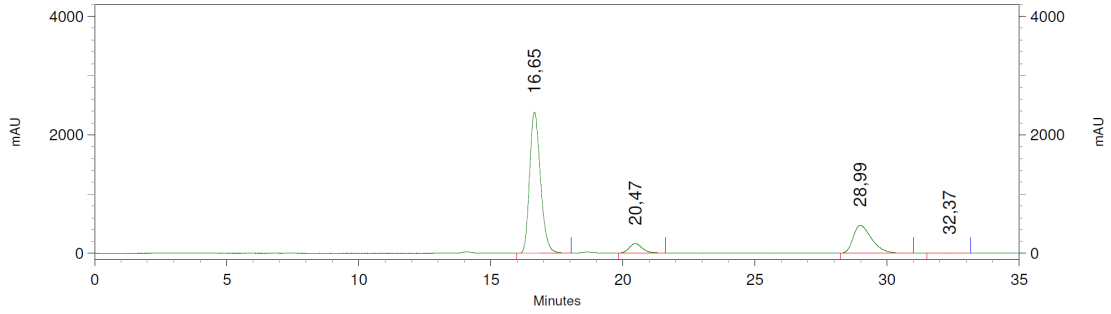
Racemic product (diastereomeric mixture)



14: 259 nm, 4 nm
Results

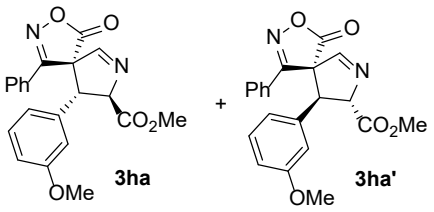
Retention Time	Area	Area Percent
16,56	115180345	48,238
20,26	116833950	48,930
29,16	3267496	1,368
32,03	3495778	1,464

Enantioenriched product (diastereomeric mixture)

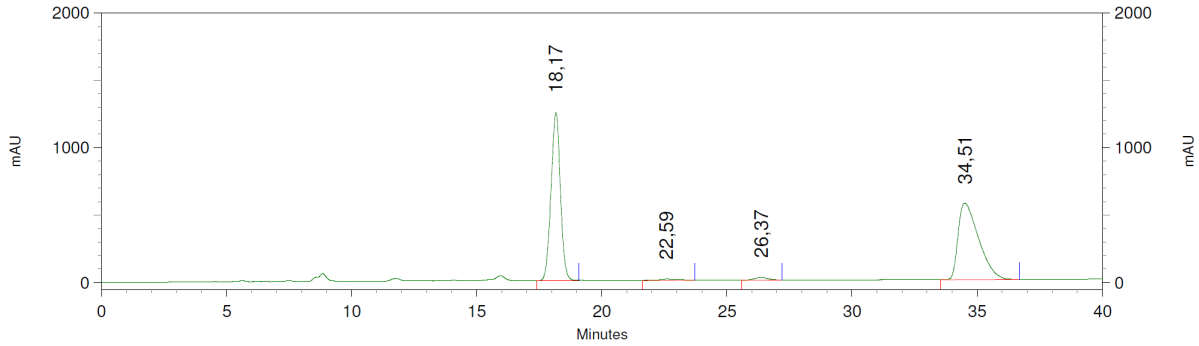


4: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
16,65	273413532	70,579
20,47	21537142	5,560
28,99	91673364	23,664
32,37	765148	0,198



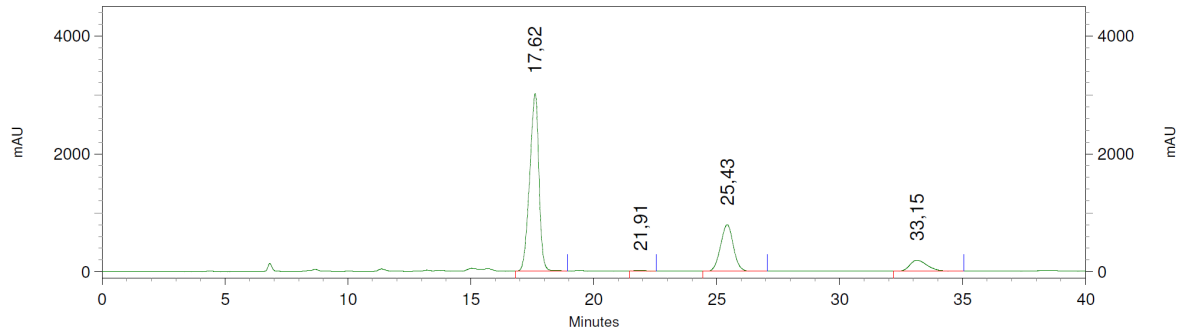
Racemic product (diastereomeric mixture)



8: 259 nm, 4 nm Results

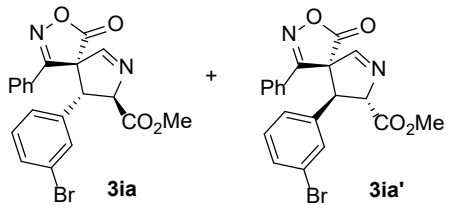
Retention Time	Area	Area Percent
18,17	129764460	49,109
22,59	1663525	0,630
26,37	3099430	1,173
34,51	129707993	49,088

Enantioenriched product (diastereomeric mixture)

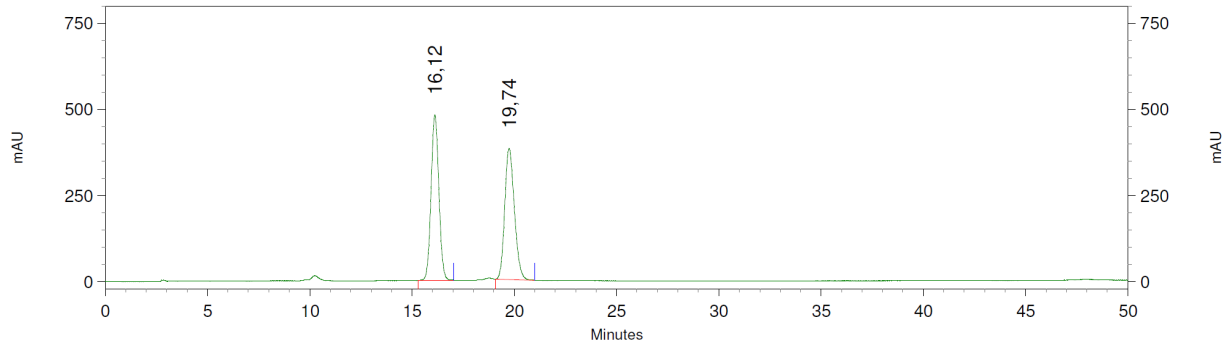


8: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
17,62	315620725	67,295
21,91	1357502	0,289
25,43	115079353	24,537
33,15	36955218	7,879



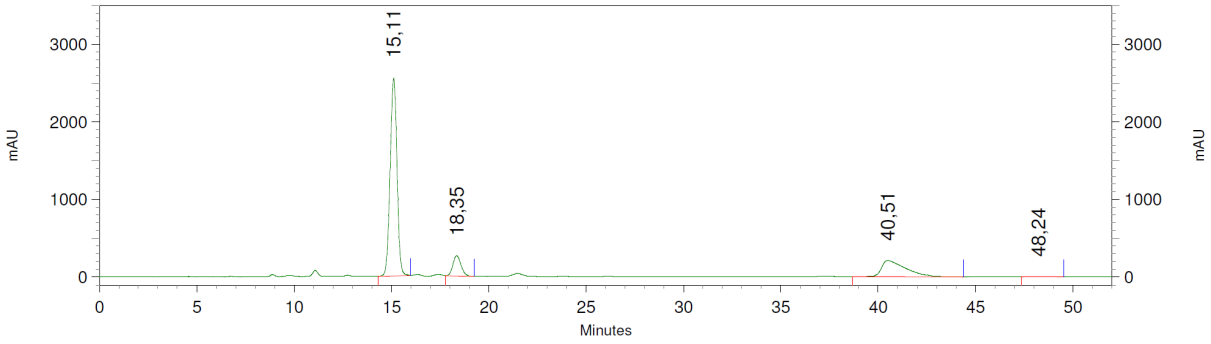
Racemic product (diastereomeric mixture)



4: 259 nm, 4 nm Results

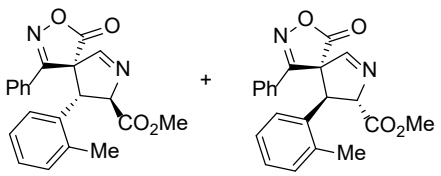
Retention Time	Area	Area Percent
16,12	50859548	50,473
19,74	49906379	49,527

Enantioenriched product (diastereomeric mixture)



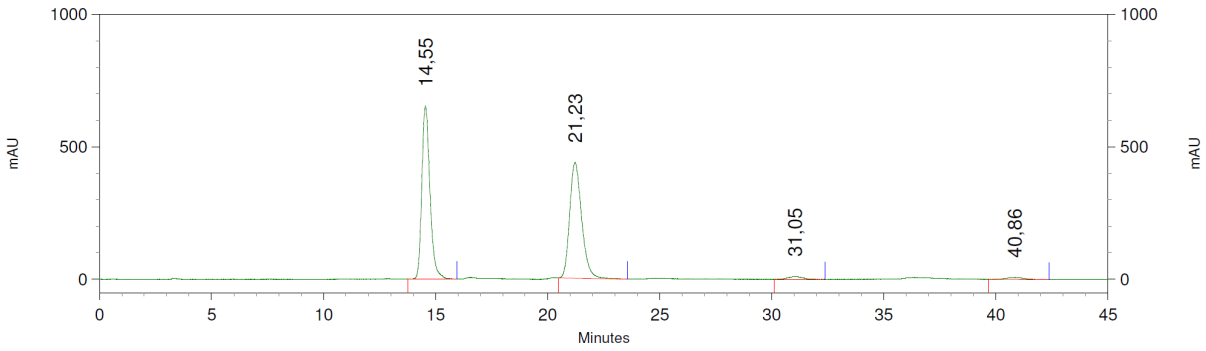
4: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
15,11	248964949	70,756
18,35	30633343	8,706
40,51	71891107	20,432
48,24	374509	0,106



3ja' 3ja'

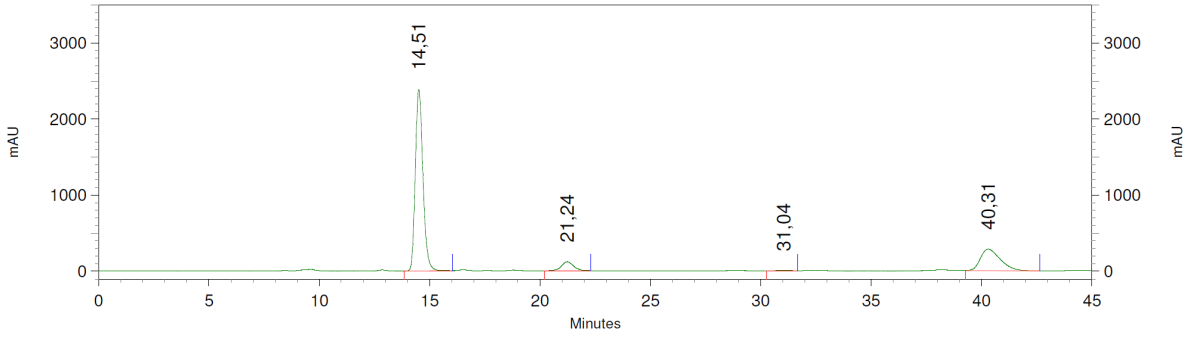
Racemic product (diastereomeric mixture)



4: 259 nm, 4 nm Results

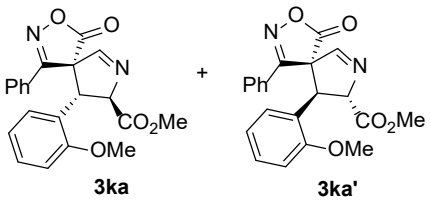
Retention Time	Area	Area Percent
14,55	65720599	48,737
21,23	65172176	48,330
31,05	2064512	1,531
40,86	1890537	1,402

Enantioenriched product (diastereomeric mixture)

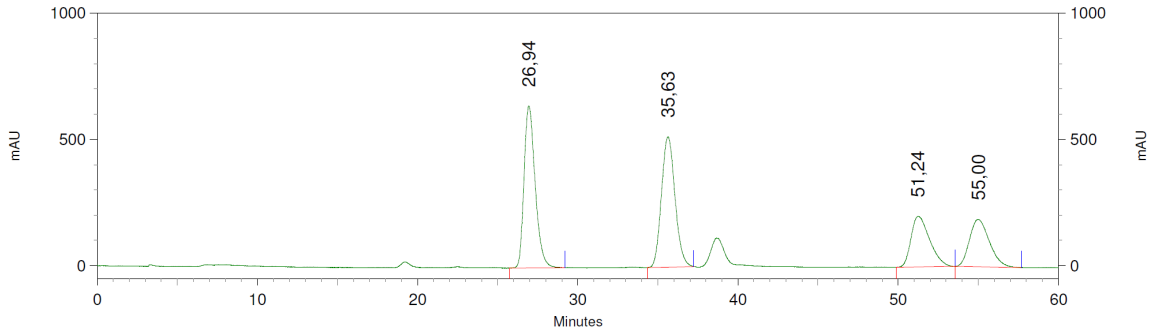


4: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
14,51	229997704	71,893
21,24	18391857	5,749
31,04	847731	0,265
40,31	70678975	22,093



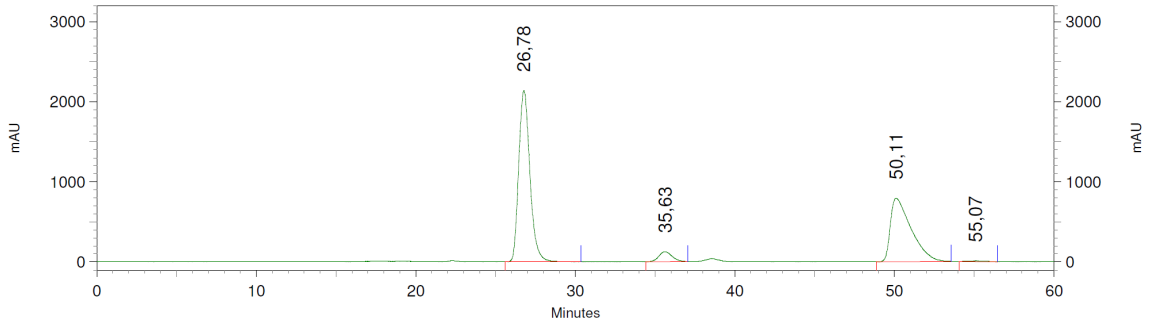
Racemic product (diastereomeric mixture)



4: 259 nm, 4 nm Results

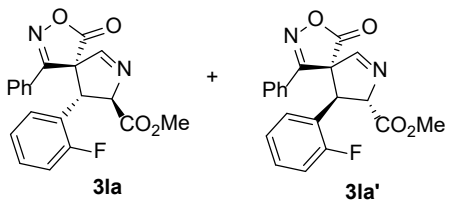
Retention Time	Area	Area Percent
26,94	123637503	33,023
35,63	121326087	32,405
51,24	64772670	17,300
55,00	64667244	17,272

Enantioenriched product (diastereomeric mixture)

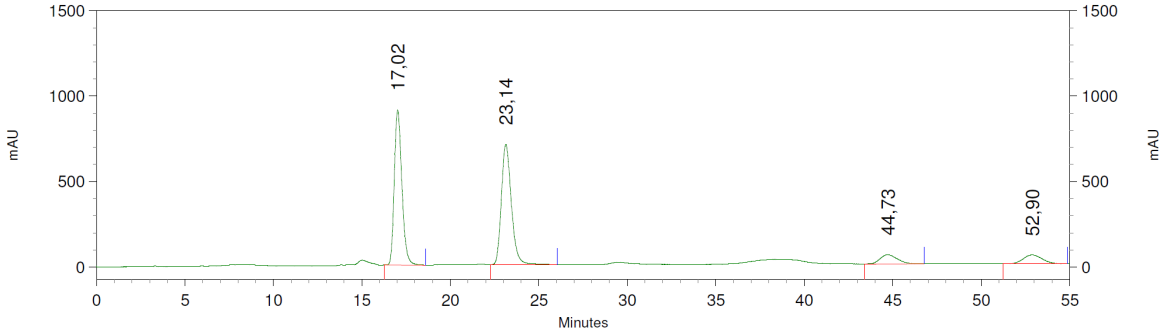


4: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
26,78	417309112	56,743
35,63	28626119	3,892
50,11	286778238	38,994
55,07	2722380	0,370



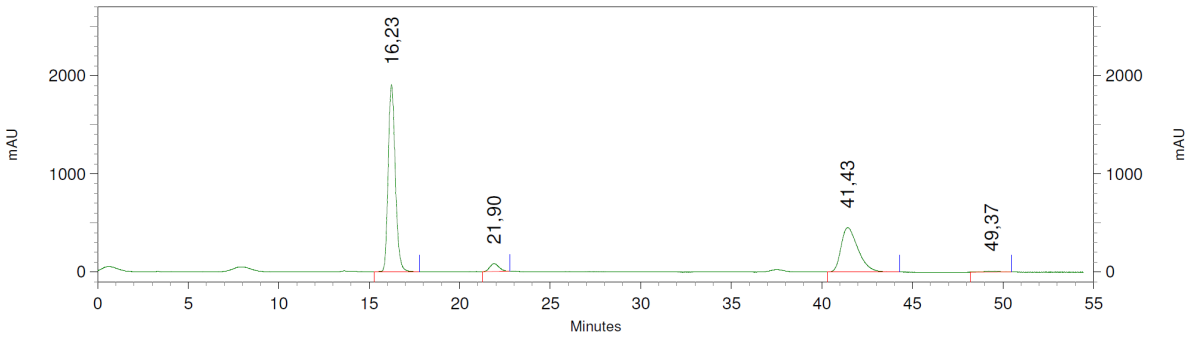
Racemic product (diastereomeric mixture)



14: 259 nm, 4 nm
Results

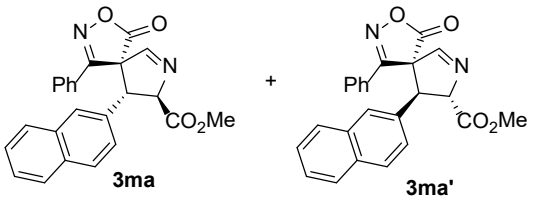
Retention Time	Area	Area Percent
17,02	107982563	43,295
23,14	110836380	44,439
44,73	14765743	5,920
52,90	15827414	6,346

Enantioenriched product (diastereomeric mixture)

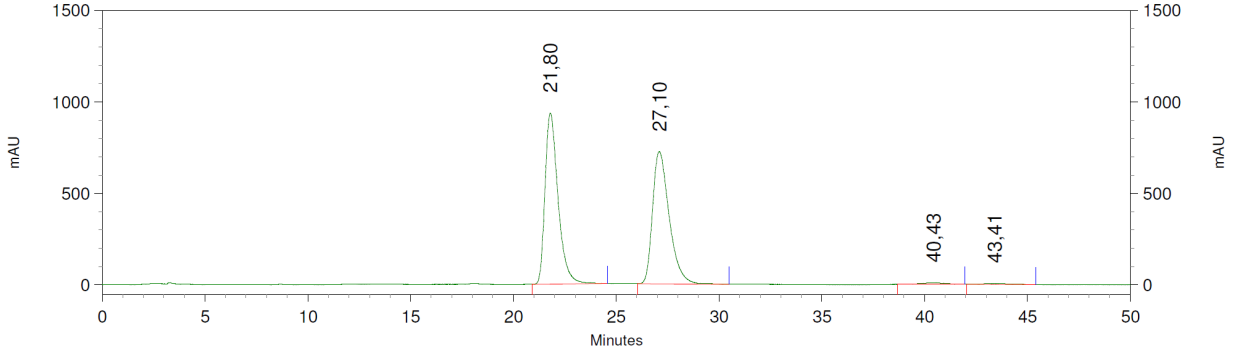


14: 259 nm, 4 nm
Results

Retention Time	Area	Area Percent
16,23	208179677	61,395
21,90	11275321	3,325
41,43	117263502	34,583
49,37	2363596	0,697



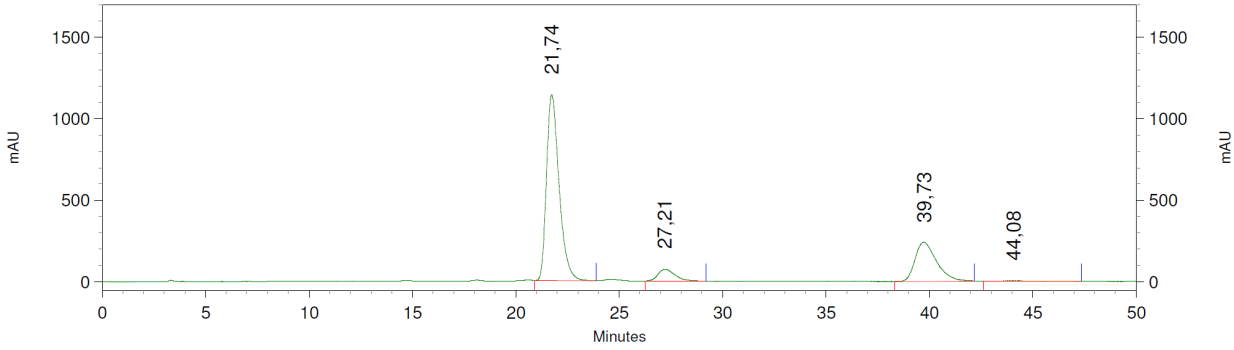
Racemic product (diastereomeric mixture)



4: 259 nm, 4 nm Results

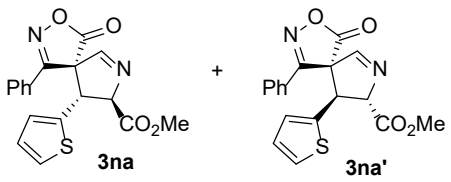
Retention Time	Area	Area Percent
21,80	165078269	49,527
27,10	162698933	48,813
40,43	3366080	1,010
43,41	2165969	0,650

Enantioenriched product (diastereomeric mixture)

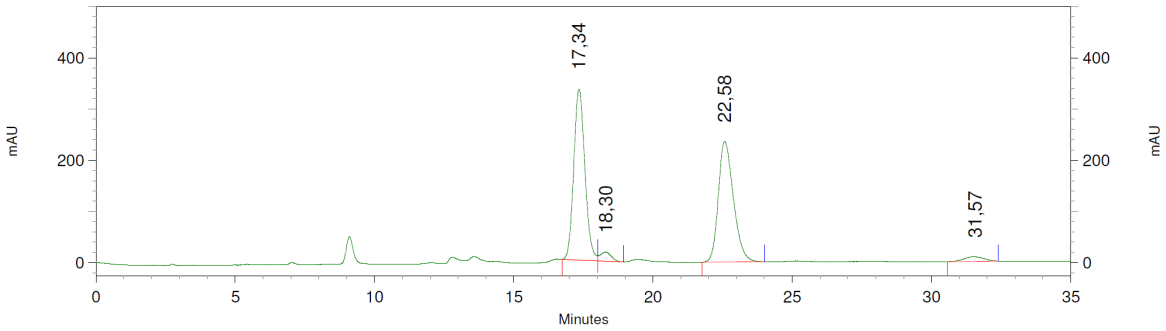


4: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
21,74	193648126	68,878
27,21	16653830	5,924
39,73	69495112	24,719
44,08	1348460	0,480



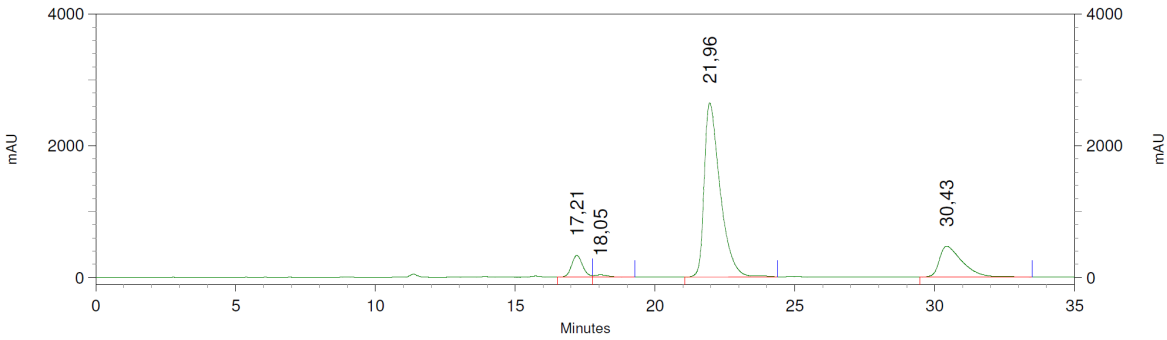
Racemic product (diastereomeric mixture)



4: 259 nm, 4 nm Results

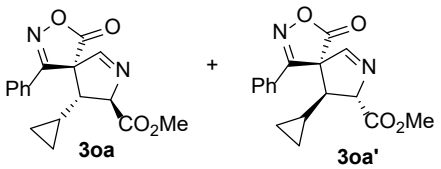
Retention Time	Area	Area Percent
17,34	37007661	48,501
18,30	1937792	2,540
22,58	35536801	46,573
31,57	1820875	2,386

Enantioenriched product (diastereomeric mixture)

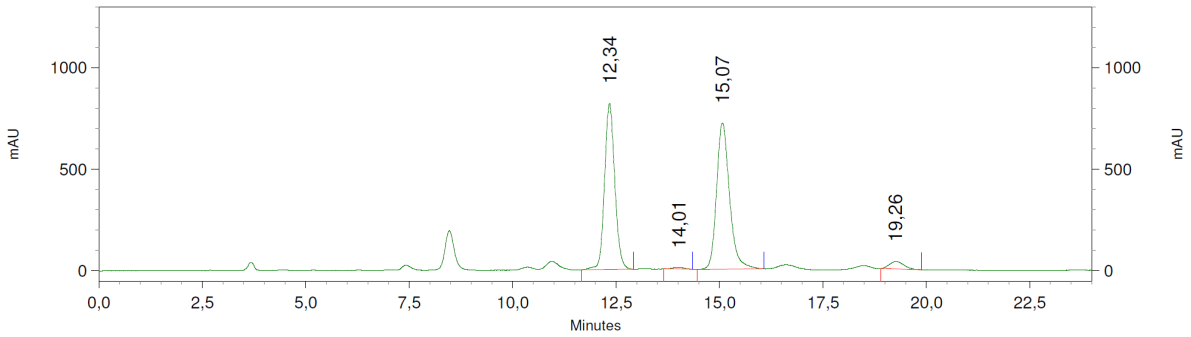


4: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
17,21	36545334	6,455
18,05	4879460	0,862
21,96	418615756	73,937
30,43	106137963	18,746



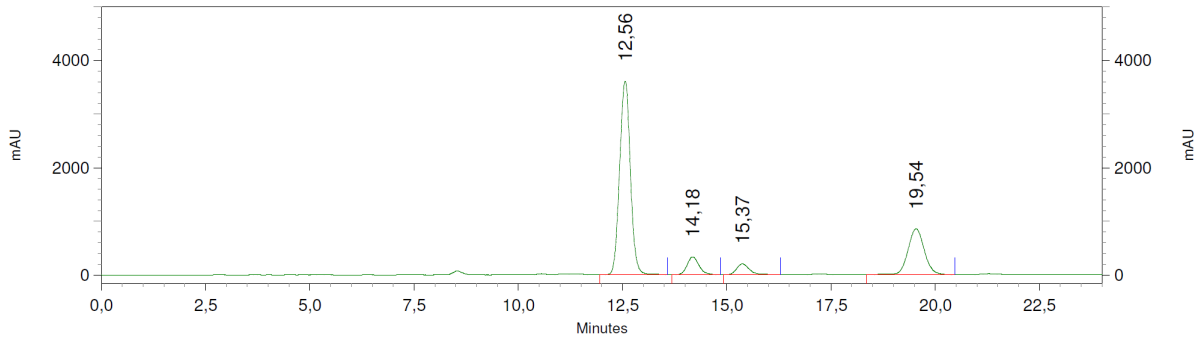
Racemic product (diastereomeric mixture)



4: 271 nm, 4 nm Results

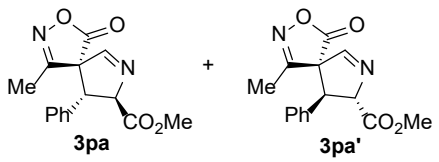
Retention Time	Area	Area Percent
12,34	56438940	45,577
14,01	719096	0,581
15,07	63061041	50,925
19,26	3613186	2,918

Enantioenriched product (diastereomeric mixture)

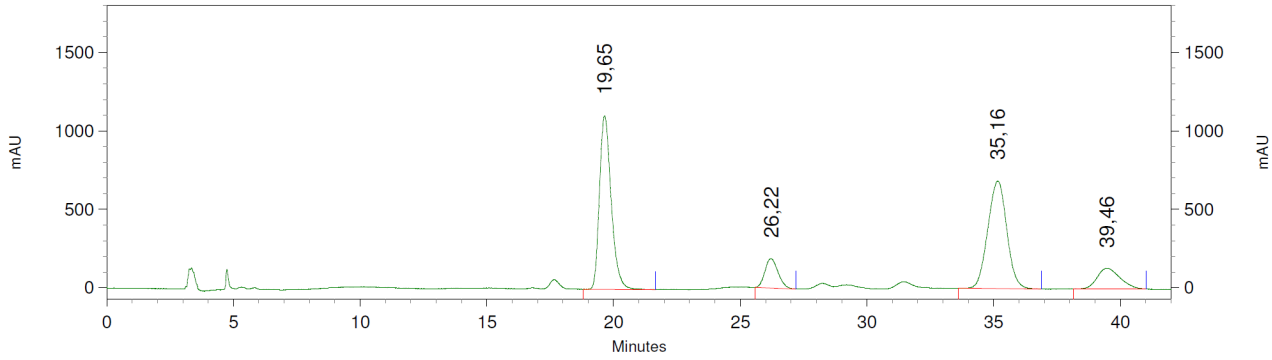


4: 271 nm, 4 nm Results

Retention Time	Area	Area Percent
12,56	258708566	65,061
14,18	26638159	6,699
15,37	17977077	4,521
19,54	94316974	23,719



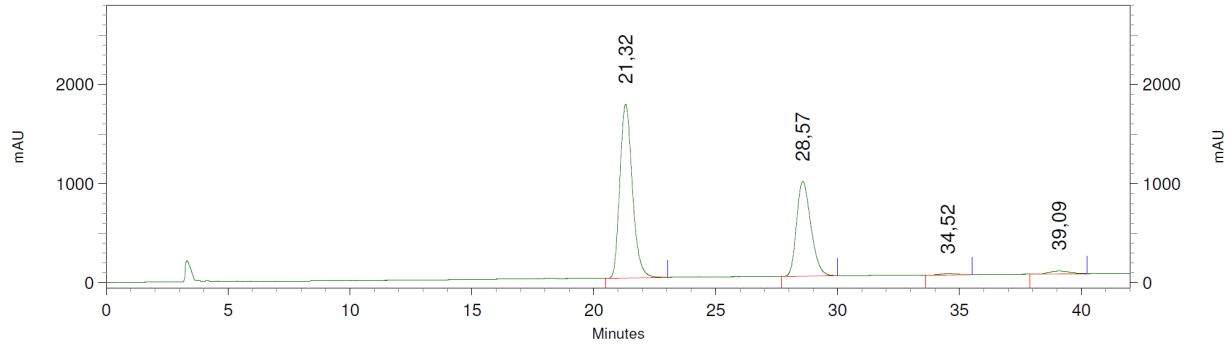
Racemic product (diastereomeric mixture)



18: 206 nm, 4 nm
Results

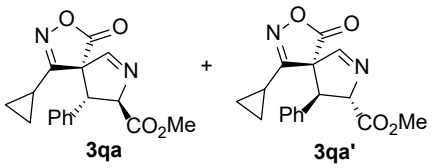
Retention Time	Area	Area Percent
19,65	142738248	41,279
26,22	27009203	7,811
35,16	142738169	41,279
39,46	33303081	9,631

Enantioenriched product (diastereomeric mixture)

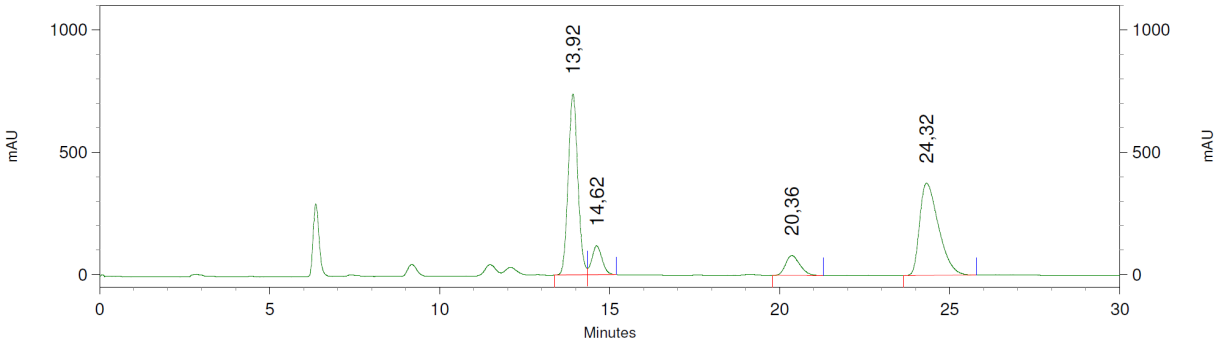


18: 206 nm, 4 nm
Results

Retention Time	Area	Area Percent
21,32	250712968	60,227
28,57	156127256	37,505
34,52	2560095	0,615
39,09	6882911	1,653



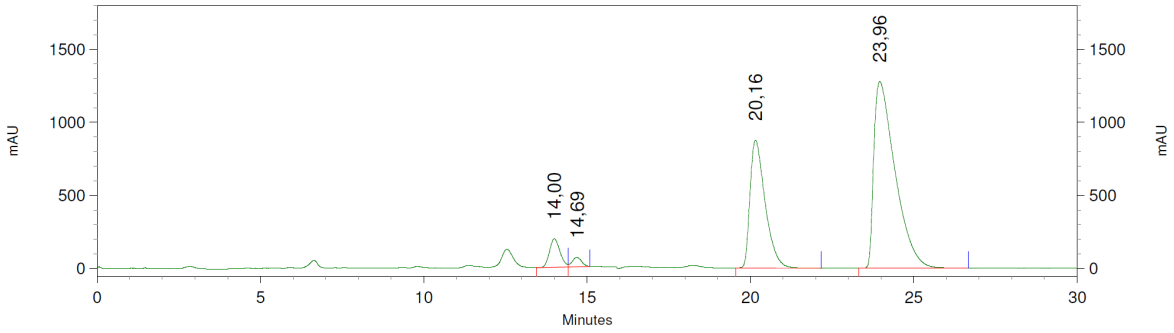
Racemic product (diastereomeric mixture)



9: 220 nm, 4 nm Results

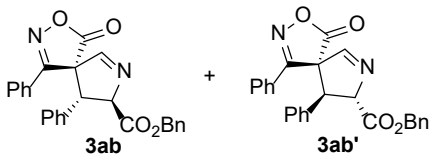
Retention Time	Area	Area Percent
13,92	58130546	42,793
14,62	9847241	7,249
20,36	9596289	7,064
24,32	58268102	42,894

Enantioenriched product (diastereomeric mixture)

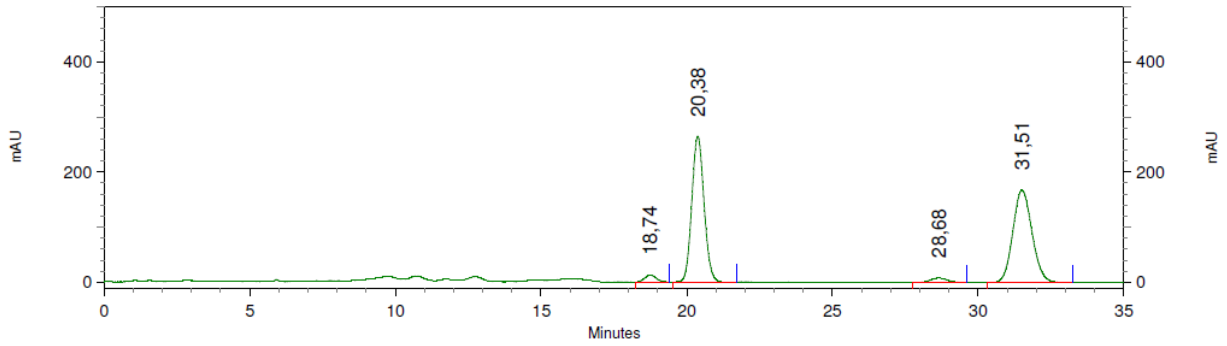


9: 220 nm, 4 nm Results

Retention Time	Area	Area Percent
14,00	17597891	4,804
14,69	5266988	1,438
20,16	112416730	30,688
23,96	231039705	63,070



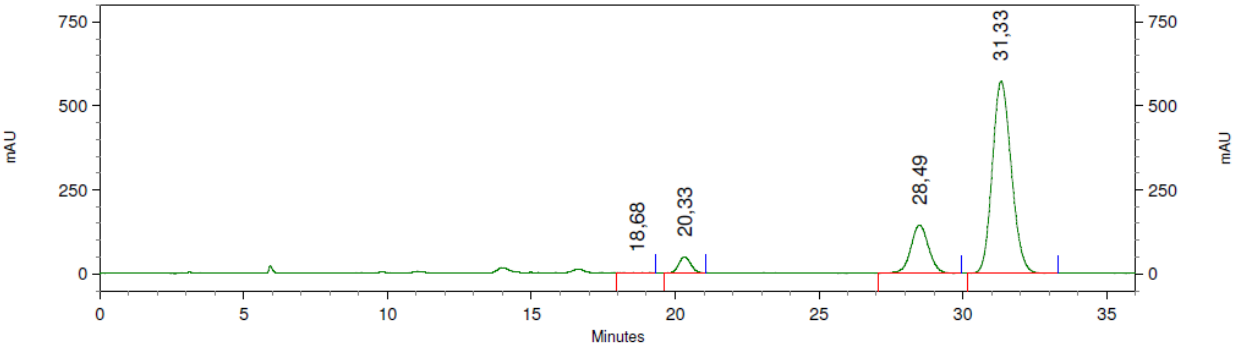
Racemic product (diastereomeric mixture)



2: 259 nm, 4 nm Results

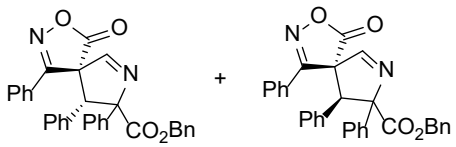
Retention Time	Area	Area Percent
18,74	1364636	2,125
20,38	30795316	47,954
28,68	1324693	2,063
31,51	30734242	47,859

Enantioenriched product (diastereomeric mixture)



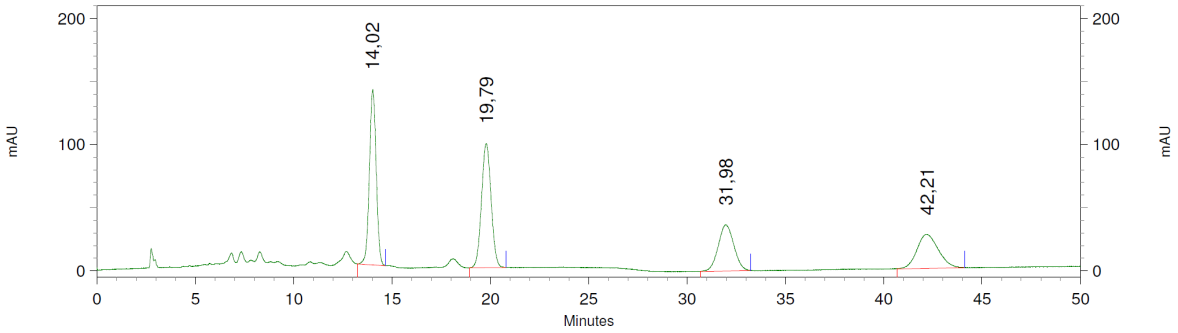
2: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
18,68	161861	0,119
20,33	5521170	4,075
28,49	24667245	18,206
31,33	105137022	77,599



3ac **3ac'**

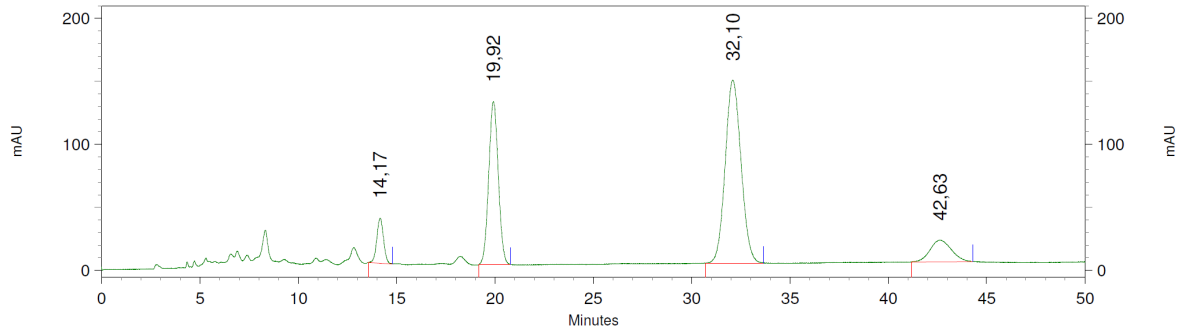
Racemic product (diastereomeric mixture)



22: 275 nm, 4 nm
Results

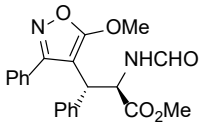
Retention Time	Area	Area Percent
14,02	13291874	31,060
19,79	13320975	31,128
31,98	8077948	18,876
42,21	8103740	18,936

Enantioenriched product (diastereomeric mixture)



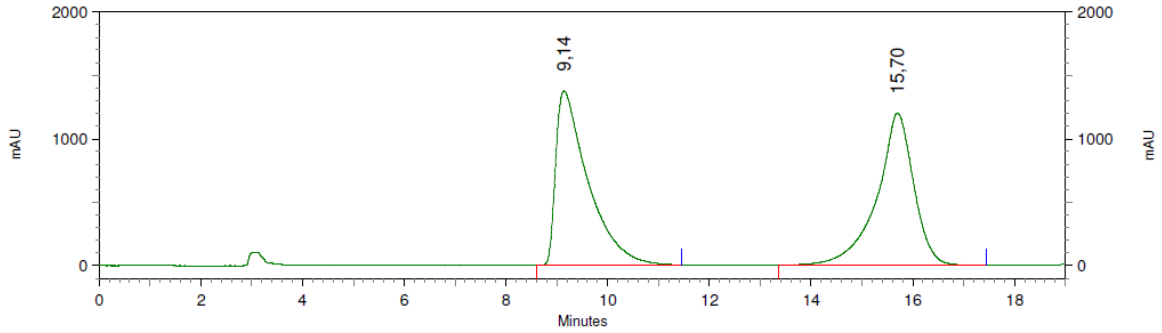
22: 275 nm, 4 nm
Results

Retention Time	Area	Area Percent
14,17	3400993	5,810
19,92	17449296	29,809
32,10	32497310	55,515
42,63	5190156	8,866



4

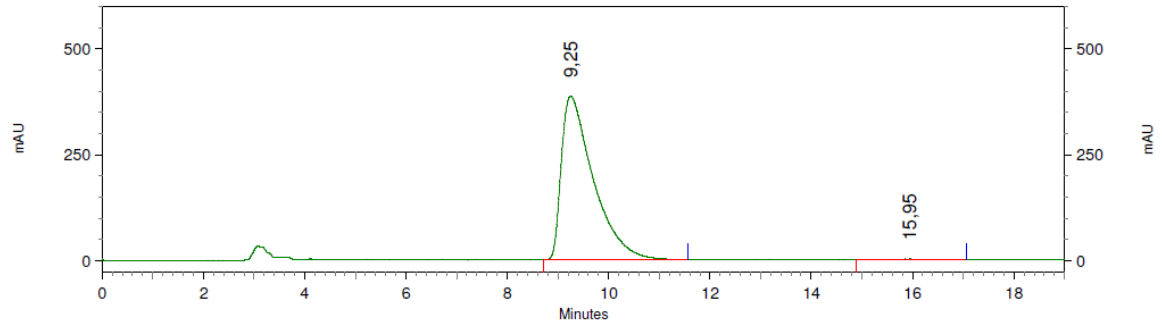
Racemic product



18: 220 nm, 4 nm
Results

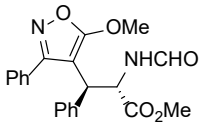
Retention Time	Area	Area Percent
9,14	241238429	50,001
15,70	241227713	49,999

Prepared from major diastereomer 3aa (*ee* 99%)



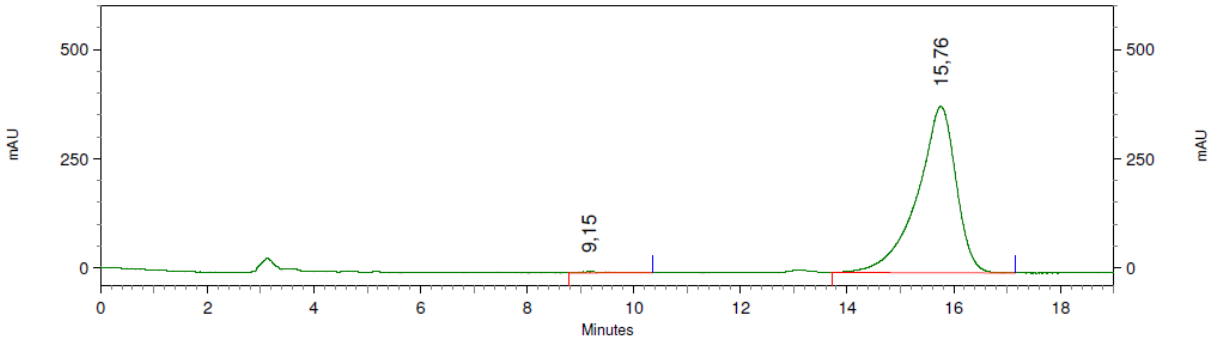
18: 220 nm, 4 nm
Results

Retention Time	Area	Area Percent
9,25	67669807	99,415
15,95	398370	0,585



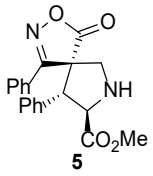
ent-**4**

Prepared from minor diastereomer 3aa' (*ee* 99%)



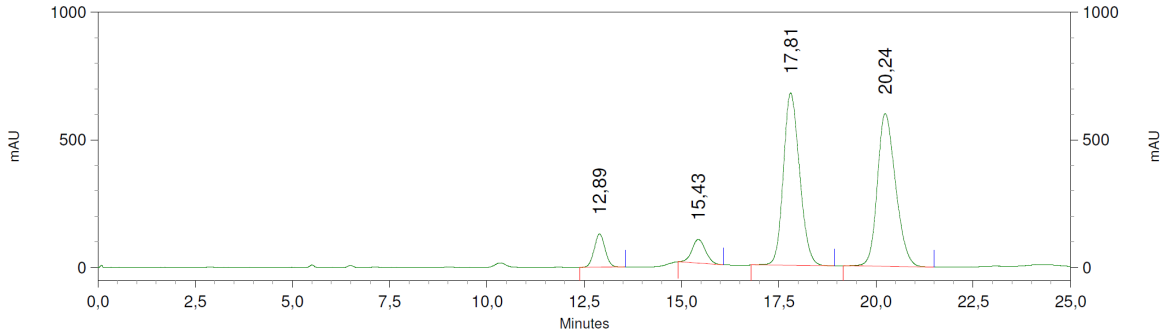
18: 220 nm, 4 nm
Results

Retention Time	Area	Area Percent
9,15	415378	0,537
15,76	76926251	99,463



5

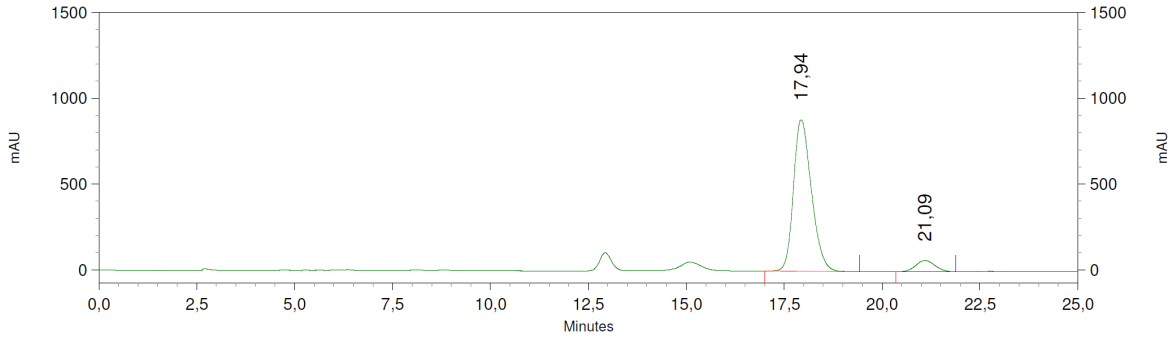
Racemic product



2: 259 nm, 4 nm Results

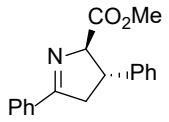
Retention Time	Area	Area Percent
12,89	10108791	5,770
15,43	9007293	5,141
17,81	78157757	44,613
20,24	77918515	44,476

Enantioenriched product



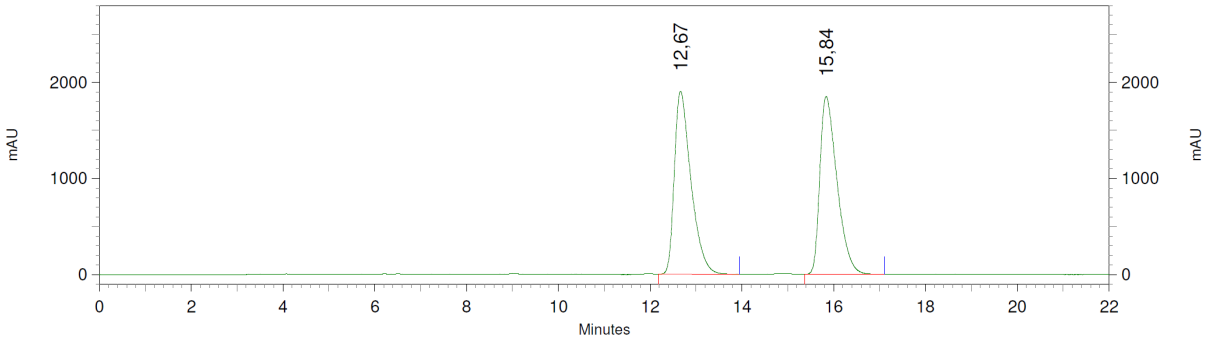
14: 259 nm, 4 nm Results

Retention Time	Area	Area Percent
17,94	112119966	92,622
21,09	8931114	7,378



8

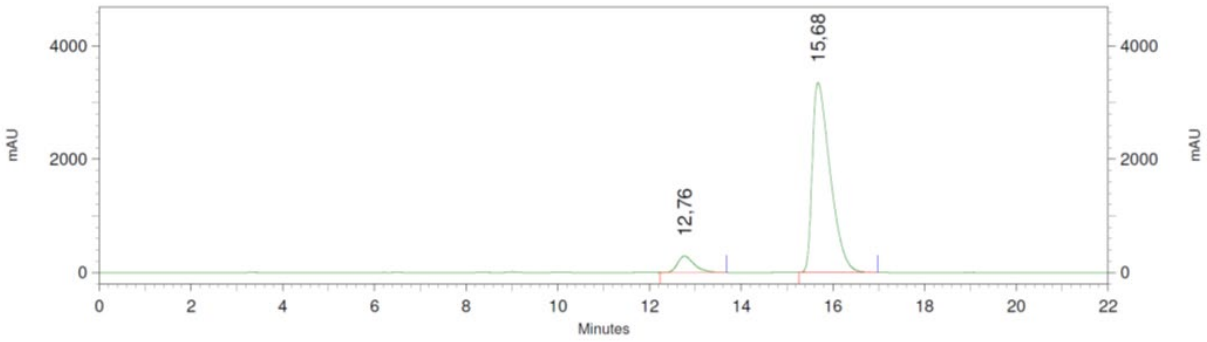
Racemic product



21: 254 nm, 4 nm
Results

Retention Time	Area	Area Percent
12,67	191409155	50,018
15,84	191271137	49,982

Enantioenriched product

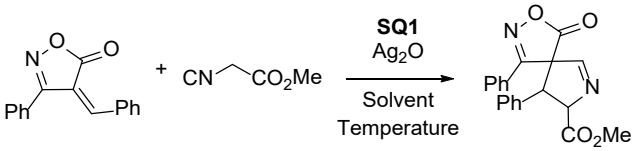


21: 254 nm, 4 nm
Results

Retention Time	Area	Area Percent
12,76	29213733	7,467
15,68	362025779	92,533

10. Optimization of the reaction conditions. Additional experiments

Table S1. Solvent and temperature optimization.

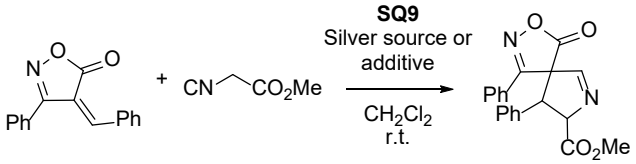


1a **2a** **3aa**

Entry[a]	Solvent	T (°C)	Yield (%)[b]	dr[c]	*ee* (%)[d]
1	CH_2Cl_2	r.t.	55	75:25	80/98
2	CH_2Cl_2	0	36	86:14	38/88
3	$CHCl_3$	r.t.	47	83:17	56/93
4	DCE	r.t.	43	95:5	71/91
5	Dioxane	r.t.	31	75:25	80/96
6	THF	r.t.	61	95:5	60/n.d.
7	MTBE	r.t.	15	79:21	64/86
8	Toluene	r.t.	12	91:9	11/54

[a] Conditions: **1a** (0.1 mmol), **2a** (0.13 mmol), **SQ1** (0.01 mmol), Ag_2O (0.005 mmol), CH_2Cl_2 (5 mL). [b] Isolated yield after column chromatography. [c] Determined by ^1H NMR. [d] Determined by HPLC over chiral stationary phases.

Table S2. Silver source screening.

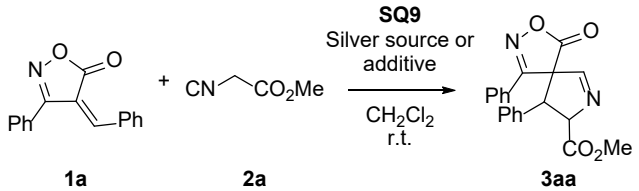


1a **2a** **3aa**

Entry[a]	Silver source or additive	Yield (%)[b]	dr[c]	*ee* (%)[d]
1	Ag_2O	75	74:26	84/96
2	$AgNO_3$	77	78:22	64/94
3	AgOAc	75	75:25	80/96
4	Ag_2CO_3	66	74:26	80/95
5	$AgSbF_6$	17	73:27	75/95
6	AgCl	26	80:20	64/93
7	CuO	Traces	-	-
8	Et_3N	Traces	-	-

[a] Conditions: **1a** (0.1 mmol), **2a** (0.13 mmol), **SQ7** (0.01 mmol), additive (0.005 mmol), CH_2Cl_2 (7.5 mL). [b] Isolated yield after column chromatography. [c] Determined by ^1H NMR. [d] Determined by HPLC over chiral stationary phases.

Table S3. Catalyst loading and molar ratios of the cooperative catalytic system optimization.

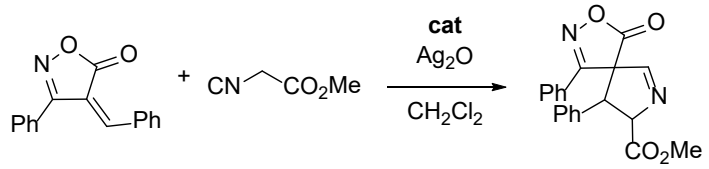


1a **2a** **3aa**

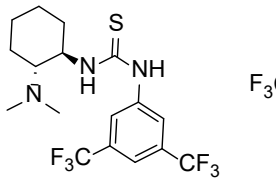
Entry[a]	**SQ7** (mol %)	Ag_2O (mol %)	Yield (%)[b]	dr[c]	*ee* (%)[d]
1	10	5	75	74:26	84/96
2	10	2,5	52	78:22	82/99
3	10	10	65	82:12	80/92
4	5	5	73	79:21	72/95
5	5	2,5	67	73:27	70/92

[a] Conditions: **1a** (0.1 mmol), **2a** (0.13 mmol), CH_2Cl_2 (7.5 mL). [b] Isolated yield after column chromatography. [c] Determined by ^1H NMR. [d] Determined by HPLC over chiral stationary phases.

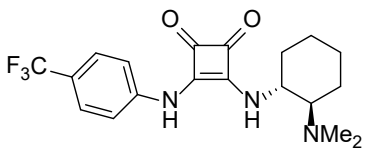
Table S4. Other organocatalysts tested under the initial conditions.



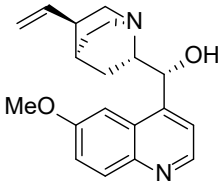
1a **2a** **3aa**



1



2



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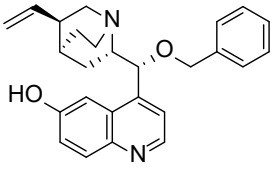

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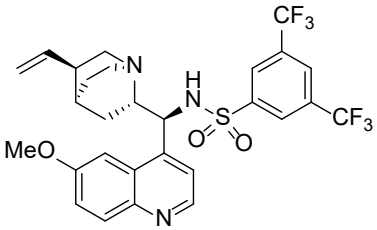
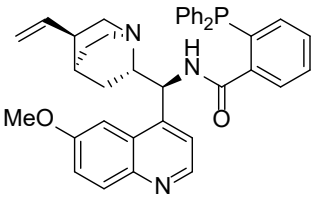


5



6

Entry[a]	**cat**	Yield (%)[b]	dr[c]	*ee* (%)[d]
1	1	69	95:5	17/n.d.
2	2	42	95:5	7/nd
3	3	62	95:5	4/nd
4	4	55	95:5	3/nd
5	5	56	95:5	16/nd
6	6	52	95:5	14/nd

[a] Conditions: **1a** (0.1 mmol), **2a** (0.13 mmol), **cat** (0.01 mmol), Ag_2O (0.05 mmol), CH_2Cl_2 (5 mL). [b] Isolated yield after column chromatography. [c] Determined by ^1H NMR. [d] Determined by HPLC over chiral stationary phases.

11. NOE experiments on 3ha

The relative stereochemistry of the major diastereomer was determined by multiple ^{1}H-^{1}H nuclear Overhauser effect (NOE) spectroscopy experiments on compound **3ha** (Figure 2). When irradiation was performed on the pyrrolinic proton D, positive NOE was observed over aromatic protons F and E, indicating the *cis* disposition between hydrogen D and the *m*-methoxyphenyl group. Further confirmation was obtained when positive NOE resulted on proton D after irradiating the aromatic protons F and E. Repeating this process on pyrrolinic proton C afforded positive NOE over the *ortho* protons of the phenyl group bonded to the isoxazol-5-one moiety, which allowed us to ascertain the relative configuration of both aromatic substituents as *trans*. Finally, performing the experiment over proton G of the *m*-methoxyphenyl group didn't yield observable NOE on the phenyl substituent of the isoxazole-5-one moiety.

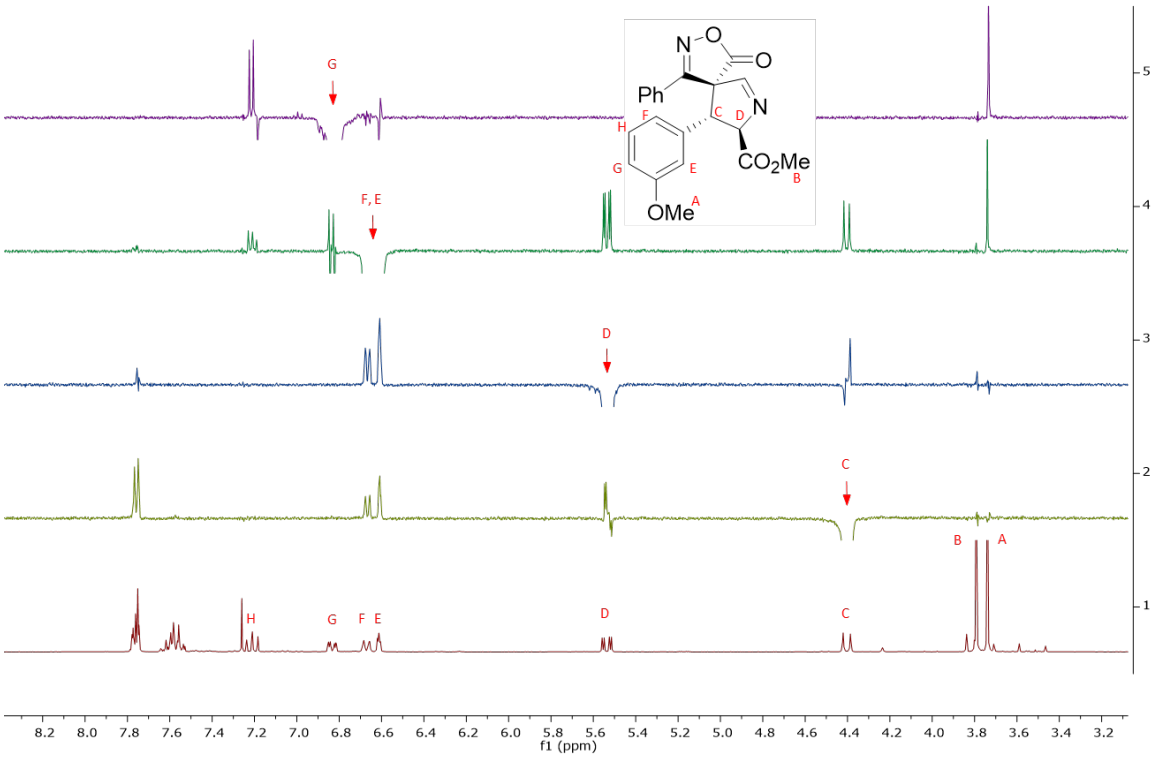
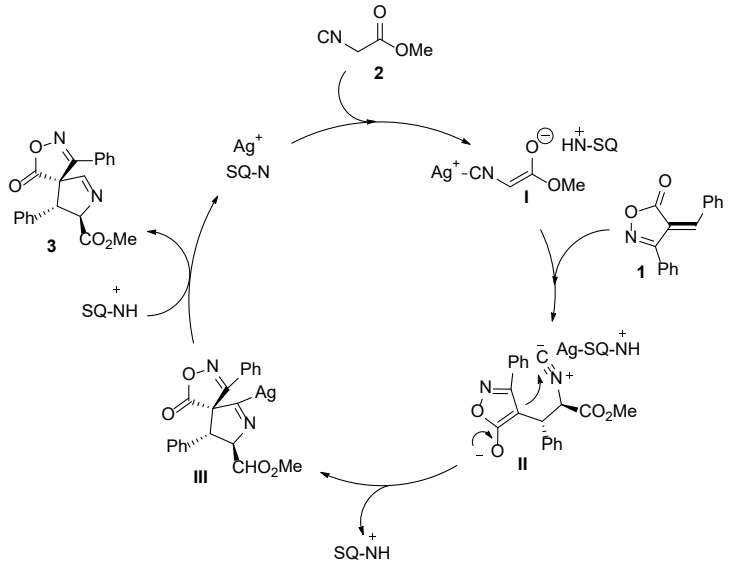


Figure S1. ^{1}H-NMR NOE experiments for **3ha**.

12. Mechanistic proposal and stereochemical model

Scheme S2 shows a plausible mechanism for the formal [3+2] cycloaddition. The reaction takes place in a stepwise manner. Initial deprotonation of the isocyanoacetate **2** by the basic bifunctional squaramide assisted by silver would give the corresponding enolate **I** that would undergo nucleophilic conjugate addition to the exocyclic double bond of **1** to give the aromatic anion **II**, followed by intramolecular addition of the anion to the isocyanide giving cyclized intermediate **III**, which after Ag^{+}/H^{+} exchange with the catalyst conjugate acid would provide the cycloaddition product **3** and releases the catalyst.



Scheme S2. Proposed mechanistic cycle for the formal [3+2] reaction

The observed stereochemistry indicates the preferential attack of the *Re* face of the isocyanoacetate enolate to the *Re* face of the exocyclic double bond. Figure S2 shows the proposed stereochemical model. Thus, the arylideneisoxazolone **1** would be electrophilically activated by forming a hydrogen bond with the squaramide moiety leaving the *Re* face of the double bond exposed to attack of the isocyanoacetate, which would be directed by hydrogen bonding (or ion-ion interaction) with the protonated tertiary nitrogen of the quinuclidine ring in the bifunctional organocatalyst.

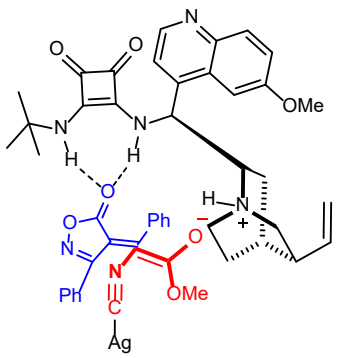


Figure S2. Stereochemical model