COMMUNICATION

Organocatalytic enantioselective 1,6-*aza*-Michael addition of isoxazolin-5-ones to *p*-quinone methides

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Abstract: A thiourea-Brønsted base bifunctional catalyst allowed the enantioselective 1,6-*aza*-Michael addition of isoxazolin-5-ones to *p*-quinone methides to give isoxazolin-5-ones having a chiral diarylmethyl moiety attached to the N atom with fair to good yields and enantiomeric excesses. To the best of our knowledge this reaction represents the first example of enantioselective *N*-alkylation of isoxazolin-5-ones as well as the first example of enantioselective 1,6-*aza*-Michael reaction involving *p*-quinone methides.

Asymmetric conjugate addition reactions constitute one of the most powerful and efficient methods for the enantioselective construction of C-C and C-X bonds. Excellent levels of regio- (1,4-*vs* 1,2- addition) and stereoselectivity have been achieved for 1,4-conjugate additions of a range of nucleophiles and Michael acceptors.[1] Compared with the 1,4-addition reaction, the enantioselective 1,6-conjugate addition is more challenging because of the longer distance between the carbonyl and the reaction site (reduced reactivity and stereogenic control) as well as for the presence of an additional electrophilic atom (regioselectivity).[2] Nevertheless excellent results in terms of regio- and enantioselectivity have been obtained by using metal-catalysis[3] or organocatalysis.[4] In this context, *p*-quinone methides (*p*-QMs), characterized by a six-membered cyclic bis-vinylogous enone framework prone to aromatize, have emerged as reactive electrophiles in enantioselective 1,6-conjugate additions to give compounds possessing a chiral diarylmethyl unit.[5] Most examples involve carbon nucleophiles,[5,6] although the addition of $B_2(pin)_2$ and thioacetic acid have been also reported.[7] However, there are no examples on enantioselective 1,6-conjugate addition of nitrogen nucleophiles to *p*-QMs, to the best of our knowledge,[8] although the enantioselective *N*-akylation of 2,3-disubstituted indoles with the related *aza*-*p*-QMs has been reported.[9]

On the other hand, the isoxazolin-5-one heterocyclic moiety is found in a variety of natural products isolated from different plant families[10] and insects.[11] Many of these compounds show biological activity and, therefore, the isoxazol-5-one group has become a platform for the development of new drug candidates. Examples include compounds with antibacterial[12] and cytostatic[13] activities as well as enzyme inhibitors for hormone-sensitive lipase,[14] human neutrophil elastase,[15] p38 MAP*a* kinase[16] and NAD^+-dependent protein deacetylases (Figure 1).[17] Isoxazol-5-ones are also being studied for the development of new materials for photonic applications.[18] Furthermore, isoxazol-5-ones are highly functionalized and show a rich panorama of chemical reactivity, being used in organic synthesis as versatile building blocks.[19]

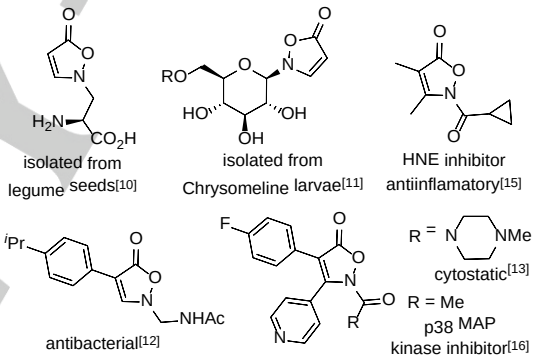

Figure 1. Examples of natural and bioactive *N*-substituted isoxazolin-5-ones

Accordingly, the development of new procedures for the synthesis of this particular heterocyclic and its decoration constitutes an important goal for organic chemists. Despite this, the use of isoxazolin-5-ones as nucleophiles in enantioselective reactions is still underdeveloped. Ma reported the first example consisting of a sequential conjugate addition/dearomative fluorination with nitroolefins catalyzed by a bifunctional chiral tertiary amino-thiourea catalyst.[20] Later, Wang described the organocatalytic asymmetric fluorination of 4-substituted isoxazolinones.[21] Peters reported the regioselective *C*-alkylation of 4-substituted isoxazolinones forming quaternary stereocenters by a palladium-catalyzed 1,4-addition to vinyl ketones.[22] The same group reported later a regioselective asymmetric *C*-allylation of isoxazolinones via a iridium-catalyzed *N*-allylation followed by a spontaneous *aza*-Cope rearrangement. In this study, *N*-allylated products were obtained when allyl carbonates substituted with alkyl chains were used.[23] Finally, an organocatalytic asymmetric four-component [5+1+1+1] cycloaddition via a cascade process that involves a double alkylation at C4 in isoxazolinones has been developed by Du and Chen, recently.[24]

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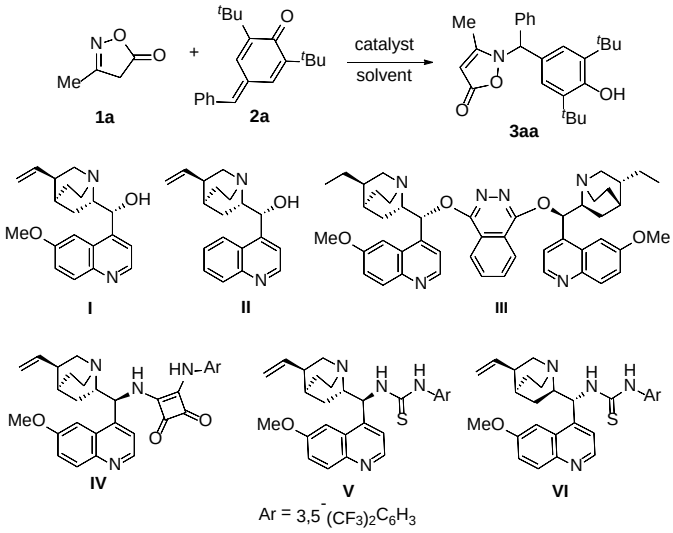
In this communication, we report our results on the asymmetric *N*-alkylation of isoxazolinones via a 1,6-*aza*-Michael addition to *p*-QMs to give isoxazolinones bearing a chiral diarylmethyl motif attached to the N atom (Scheme 1). To the best of our knowledge, this is the first example of asymmetric 1,6-nucleophilic addition of *N*-nucleophiles to *p*-QMs.



Scheme 1. Reaction between 3-methyl-4(*H*)-isoxazol-5-one (**1a**) and *p*-QM **2a**, and organocatalysts used in this study.

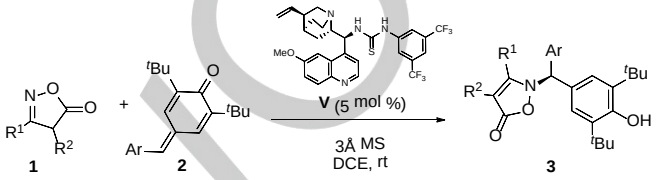
Table 1. *Enantioselective addition of* 3-methyl-4(*H*)-isoxazol-5-one (**1a**) *to* p-QM **2a**. Optimization of the reaction conditions. [a]

entry	catalyst	solvent	yield [%][b]	*ee* [%][c]
1	**I**	toluene	30	56
2	**II**	toluene	36	52
3	**III**	toluene	30	25
4	**IV**	toluene	31	9
5	**V**	toluene	48	66
6	**VI**	toluene	23	37
7	**V**	DCE	42	85
8[d]	**V**	DCE	48	86
9[d,e]	**V**	DCE	65	87

[a] **1a** (0.1 mmol), **2a** (0.1 mmol), catalyst (0.005 mmol), solvent (1 mL), room temperature, 6 days. [b] Yield after column chromatography. [c] Determined by HPLC using chiral stationary phases. [d] Reaction carried out with **1a** (0.1 mmol) and **2a** (0.15 mmol). [e] Reaction carried out in the presence of 3 Å MS (32 mg).

The reaction between 3-methy-4(*H*)-isoxazol-5-one (**1a**) and *p*-QM **2a** in toluene at room temperature was used for the optimization of the reaction conditions (see also SI). Several organocatalyst (5 mol %) including *Cinchona* alkaloid bases as well as bifunctional squaramides and thioureas were screened. In all the cases the main reaction product obtained was the *N*-alkylated isoxazolinone **3aa** (Scheme 1). The best result in terms of enantioselectivity (66% *ee*) was obtained with quinine-derived thiourea **V** (Table 1, entry 5). Changing the solvent to dichloroethane (DCE) allowed to increase the enantiomeric excess of the reaction product to 85% (Table 1, entry 7). The yield of the reaction could be improved by adding an excess of *p*-QM (Table 1, entry 8). Finally, using 3 Å MS as an additive permitted further increase of the enantioselectivity, compound **3aa** being obtained in 65% yield and 87% *ee* (Table 1, entry 9).

Table 2. Enantioselective 1,6-*aza*-Michael addition of 4(*H*)-isoxazol-5-ones **1** to *p*-quinone methides **2** catalyzed by thiourea **V**. Reaction scope.[a]



entry	**1**	R^1	R^2	**2**	Ar	t [d]	**3**	yield [%][b]	*ee* [%][c]
1	**1a**	Me	H	**2a**	Ph	6	**3aa**	65	87
2	**1b**	Et	H	**2a**	Ph	6	**3ba**	51	81
3	**1c**	Pr	H	**2a**	Ph	6	**3ca**	50	81
4	**1d**	Ph	H	**2a**	Ph	6	**3da**	77	54
5	**1e**	^{c}Pr	H	**2a**	Ph	1	**3ea**	78	89
6	**1f**	Me	Me	**2a**	Ph	1	**3fa**	62	47
7	**1a**	Me	H	**2b**	*p*-MeC_6H_4	6	**3ab**	23	72
8	**1a**	Me	H	**2c**	*p*-$MeOC_6H_4$	6	**3ac**	66	62
9	**1a**	Me	H	**2d**	*p*-ClC_6H_4	6	**3ad**	62	88
10	**1a**	Me	H	**2e**	*p*-$O_2NC_6H_4$	6	**3ae**	74	84
11	**1a**	Me	H	**2f**	*o*-$MeOC_6H_4$	6	**3af**	43	48
12	**1a**	Me	H	**2g**	*o*-ClC_6H_4	6	**3ag**	47	89
13	**1a**	Me	H	**2h**	*o*-BrC_6H_4	6	**3ah**	43	90
14	**1a**	Me	H	**2i**	*m*-$MeOC_6H_4$	6	**3ai**	20	25
15	**1a**	Me	H	**2j**	*m*-ClC_6H_4	6	**3aj**	36	81
16	**1a**	Me	H	**2k**	*m*-$O_2NC_6H_4$	6	**3ak**	56	77
17	**1e**	^{c}Pr	H	**2c**	*p*-$MeOC_6H_4$	1	**3ec**	75	79
18	**1e**	^{c}Pr	H	**2d**	*p*-ClC_6H_4	1	**3ed**	78	88
19	**1e**	^{c}Pr	H	**2e**	*p*-$O_2NC_6H_4$	1	**3ee**	80	86
20	**1e**	^{c}Pr	H	**2g**	*o*-ClC_6H_3	1	**3eg**	76	92
21	**1e**	^{c}Pr	H	**2i**	*m*-$MeOC_6H_4$	2	**3ei**	82	82
22	**1e**	^{c}Pr	H	**2j**	*m*-ClC_6H_4	1	**3ej**	80	88
23[d]	**1e**	^{c}Pr	H	**2a**	Ph	1	**3ea**	71	86

[a] **1a** (0.1 mmol), **2a** (0.15 mmol), **V** (0.005 mmol), DCE (1 mL), 3 Å MS (32 mg), room temperature. [b] Yield after column chromatography. [c] Determined by HPLC using chiral stationary phases. [d] Reaction carried out with 1 mmol of **1e**.

Under these conditions, we examined next the scope of the reaction (Table 2).The effect of the substitution on the isoxazolinone ring was first tested with *p*-QM **2** (Table 2, entries 1-6). Increasing the bulk of the substituent at C3 in the oxazolinone from methyl to propyl caused a decrease of yield and enantioselectivity (Table 2, entires 1-3). Isoxazolinone **1d** bearing a phenyl ring at this position also reacted with good yield but moderate enantioselectivity (Table 2, entry 4). On the other hand, the presence of a cyclopropyl group attached at C3 increased the reactivity of the oxazolinone and allowed to obtain the corresponding product **3ea** with good yield (78%) and 89% *ee* (Table 2, entry 5). The disubstituted 3,4-dimethy-4(*H*)-isoxazol-5-onone (**1f**) also reacted quick but the expected product **3fa** was obtained with only 47% *ee* (Table 2, entry 6).

Next we examined the scope regarding the *p*-quinone methide partner. In general, *p*-QMs having aryl groups substituted with electron-donating substituents at either position reacted with isoxazolinone **1a** with lower yields and enantioselectivities than their analogues having aryl groups substituted with electron-withdrawing groups (Table 2, entries 7, 8 and 11 *vs* entries 9, 10, 12, 15 and 16). Furthermore, it was found that, for a same substituent, *ortho*- or *para*- substituted rings performed better than *meta*-substituted ones (Table 2, entries 7-10 vs entries 14-16).

We also examined the reaction of cyclopropyl-substituted isoxazolinone **1e** with a number of *p*-QMs (Table 2, entries 17-22). Again, we found better results in terms of yield and enantioselectivity compared with the reactions with methyl-substituted isoxazolinone **1a**. In this case, good results were obtained even for *p*-QMs having *ortho*-, *meta*- or *para*-substituted phenyl rings. Finally, it should be noted that the reaction between isoxazolinone **1e** and *p*-QM **2a** was scaled up to 1 mmol scale with just a minor erosion on the yield and enantioselectivity (Table 2, entry 23).

The configuration of the stereogenic center in compound **3ad** was determined to be (*S*) on the basis of X-ray crystallographic analysis (Figure 2);[25] the stereochemistry of the remaining compounds **3** was assigned on the assumption of a uniform stereochemical pathway.

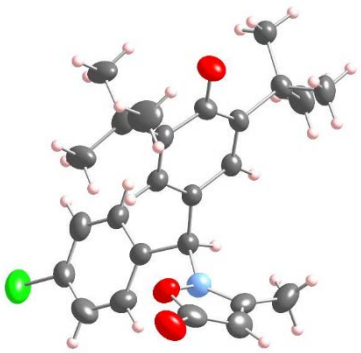


Figure 2. Ortep plot for the X-ray structure of compound **3ad**. The thermal ellipsoids are drawn at the 50% probability level. Flack parameter -0.07(9).

In summary, a bifunctional thiourea-Brønsted base catalyst allowed the first asymmetric 1,6-*aza*-Michael addition to *p*-quinone methides. Isoxazolinones were used as *N*-nucleophiles to give isoxazolinones having a chiral diarylmethyl moiety attached to the N atom. The reaction is broad in scope and provided the expected products with fair to good yields and high enantiomeric excesses. Further research to extend this enantioselective reaction to other nitrogen-containing compounds is underway in our laboratory.

Experimental Section

General procedure for the 1,6-*aza*-Michael addition. A round bottom flask was charged with the *para*-quinone methide **2** (0.15 mmol), isoxazolin-5-one **1** (0.1 mmol), 3Å MS (32 mg) and thiourea **V** (3.7 mg, 0.005 mmol). 1,2-Dichloroethane (1 mL) was added and the mixture was stirred at room temperature until completion (TLC). The MS was removed by filtration and the resulting solution was chromatographed on silica gel eluting with hexane:EtOAc mixtures to give compound **3**.

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Keywords: Asymmetric catalysis • enantioselectivity • conjugate addition • heterocycles • alkylation

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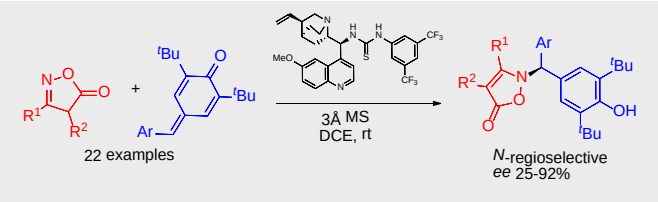
[25] CCDC 1961393 contain the supplementary crystallographic data for compound **3ad**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Asymmetric organocatalysis

COMMUNICATION



A bifunctional organocatalyst allowed the enantioselective 1,6-*aza*-Michael addition of isoxazolin-5-ones to *p*-quinone methides to give isoxazolin-5-ones having a chiral diarylmethyl moiety attached to the N atom with fair to good yields and enantiomeric excesses.

Ricardo Torán, Carlos Vila, Amparo Sanz-Marco, M.Carmen Muñoz, José R. Pedro, and Gonzalo Blay**

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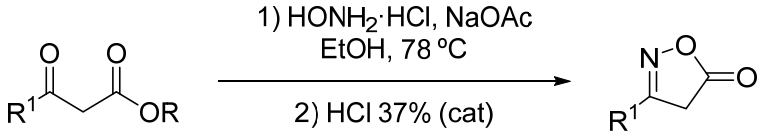
Organocatalytic enantioselective 1,6-*aza*-Michael addition of isoxazolin-5-ones to *p*-quinone methides

Index:

Materials and methods.

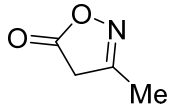
All reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. NMR spectra were run at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR using residual nondeuterated solvent ($CHCl_3$) as internal standard (δ 7.26 and 77.0 ppm, respectively). Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a Q-TOF spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV (ESI). Specific optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary phase columns from Daicel or Phenomenex.

General procedure for the synthesis of isoxazole-5-ones (1a-1d).[1,2]



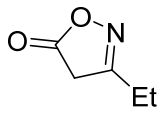
To a round bottom flask charged with $HONH_2 \cdot HCl$ (1.5 eq) in EtOH (0.5 M respect to the *β*-ketoester), is added NaOAc (1.5 eq). The mixture is allowed to stir at room temperature for 5 min. Then, the *β*-ketoester (1 eq) is added. The reaction is heated to reflux until no more starting material is detected on TLC (one typically observes the presence of both the final product and the oxime intermediate). At this point, the solution is allowed to cool to room temperature, $HCl_{37\%}$ (5 μL/ mmol *β*-ketoester) is added, and the solution is heated back to reflux until no more oxime can be observed on TLC (4-6h). Next, the solution is filtered and concentrated under reduced pressure. If necessary, the crude material can be purified by recrystallization or flash column chromatography.

3-Methylisoxazol-5(4*H*)-one (1a)[1]



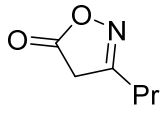
From ethyl acetoacetate (2.0 g, 15.4 mmol), 1.45 g (95%) of compound **1a** were obtained after column chromatograph.; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.39 (2H, q, *J* = 0.9 Hz, CH_2), 2.16 (3H, t, *J* = 0.9 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.3 (C, C=O), 163.6 (C=N), 36.9 (CH_2), 14.7 (CH_3).

3-Ethylisoxazol-5(4*H*)-one (2b)[1]



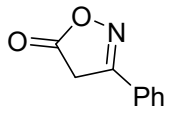
From ethyl 3-oxopentanoate (1.0 g, 6.93 mmol), 768.9 mg (98%) of compound **1b** were obtained after column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.38 (2H, s, CH_2-C=O), 2.50 (2H, q, *J* = 7.5 Hz, CH_2-CH_3), 1.23 (3H, t, *J* = 7.5 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.2 (C, C=O), 167.7 (C, C=N), 35.6 (CH_2, CH_2-C=O), 22.8 (CH_2, Et), 10.1 (CH_3, Et).

3-Propylisoxazol-5(4*H*)-one (1c)[2]



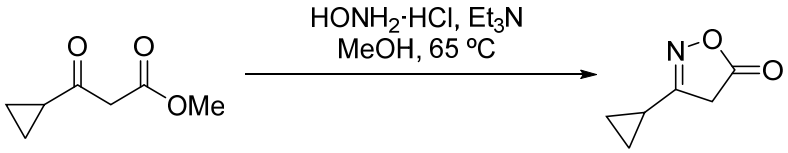
From ethyl 3-oxohexanoate (1.0 g, 6.33 mmol), 739.8 mg (92%) of compound **1c** were obtained after column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.37 (2H, s, C*H*$_2$-CO), 2.44 (2H, t, *J* = 7.5 Hz, C*H*$_2$-CH_2-CH_3), 1.64 (2H, sextuplet, *J* = 7.5 Hz, CH_2-*CH*$_2$-CH_3), 1.00 (3H, t, *J* = 7.5 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.3 (C, C=O), 166.8 (C, C=N), 35.7 (CH_2, CH_2-C=O), 30.9 (CH_2, *C*H_2-CH_2-CH_3), 19.3 (CH_2, CH_2-*C*H_2-CH_3), 13.6 (CH_3, CH_2-CH_2-CH_3).

3-Phenylisoxazol-5(4*H*)-one (1d)[1]



From ethyl 3-oxo-3-phenylpropanoate (1.0 g, 5.20 mmol), 721.1 mg (86%) of compound **1d** were obtained after column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$), δ 7.68 (2H, dt, J_1 = 5.7 Hz, J_2 = 1.5 Hz, Ar), 7.67-7.47 (3H, m, Ar), 3.81 (2H, t, *J* =2.7 Hz, CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$), δ 174.7 (C, C=O), 163.1 (C, C=N), 132.1 (CH, Ar), 129.2 (CH, Ar), 127.5 (C, Ar), 126.6 (CH, Ar), 33.9 (CH_2, CH_2-CO).

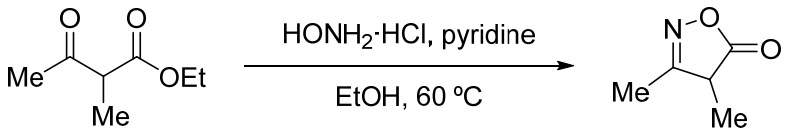
Synthesis of 3-cyclopropylisoxazol-5(4*H*)-one (1e).[3]



Et_3N (2.19 mL, 15.8 mmol) is added to a solution of HONH2·HCl (1.09 g, 15.8 mmol) in MeOH (37 mL). The mixture is stirred at room temperature for 5 min and methyl 3-cyclopropyl-3-oxopropanoate (2.00 g, 14.1 mmol) is added. The reaction is heated to reflux for 3 hours, then allowed to cool to room temperature, filtered and washed woth EtOAc (30 mL). The filtrate was concentrated under reduced pressure and chromatographed eluting with EtOC to give 1.47 g (83%) of compound **1e**. **^{1}H NMR**

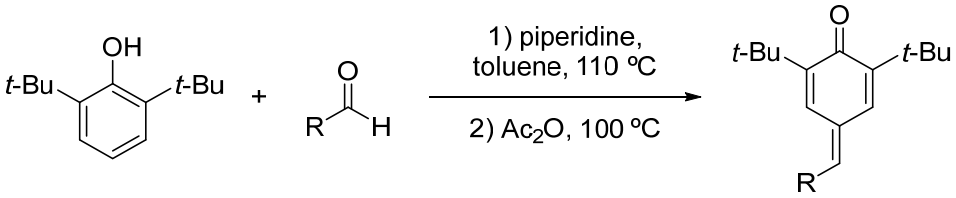
(300 MHz, $CDCl_3$) δ 3.25 (2H, t, *J* = 0.5 Hz, CH_2), 1.85-1.78 (1H, m, *c*-Pr), 1.09-1.06 (2H, m, *c*-Pr), 0.91-0.86 (2H, m, *c*-Pr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.0 (C, C=O), 168.9 (C, C=N), 34.2 (CH_2, CH_2-CO), 10.1 (CH, *c*-Pr), 7.39 (CH_2, *c*-Pr).

Procedure for the synthesis of 3,4-dimethylisoxazol-5(4*H*)-one (1f).[4]



Pyridine (3.35 mL, 41.6 mmol) is added to a solution of $HONH_2$·HCl (1.92 g, 27.7 mmol) in EtOH (14 mL). The mixture is stirred at room temperature for 5 min and ethyl 2-methyl-3-oxobutanoate (2.00 g, 13.9 mmol) is added. The reaction mixture is heated to 60 ºC for x hours until no starting material is detected (TLC) and allowed to cool to rt. H_2O (40 mL) is added and the mixture is extracted with EtOAc (3 × 40 mL), the organic layer is washed with 1M HCl (20 mL) and brine (2 × 20 mL). The combined organic layer is dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Column chromatography gave 0.988 mg (63%) of compound **1f. ^{1}H NMR** (300 MHz, $CDCl_3$), δ 3.30 (1H, q, *J* = 7.8 Hz, CH_{imine}), 2.14 (1.50H, s, $CH_{3,\ enamine}$), 2.10 (3H, s, $CH_{3,\ imine}$), 1.77 (1.50H, s, $CH_{3,\ enamine}$), 1.45 (3H, s, $CH_{3,\ imine}$).

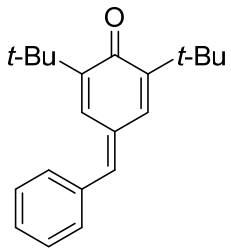
General procedure for the synthesis of *p*-quinone methides (2a-2n).[5-6]



A mixture of aldehyde (4.85 mmol) and 2,6-di-*tert*-butylphenol (1.0 g, 4.85 mmol) in toluene (20 mL) was placed in a round bottom flask provided with a Dean-Stark system. The mixture was brought to reflux and piperidine (0.96 mL, 4.85 mmol) was dropwise added within an hour and the resultant mixture was stirred at reflux temperature for further 12 hours. The reaction mixture was cooled to 100 ºC and acetic anhydride (0.92 mL, 9.7 mmol) was added and the resulting solution was stirred for 30 minutes at the same temperature. The reaction mixture was then cooled to room temperature and poured into ice cold water (50 mL) and extracted with dichloromethane (2 × 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and

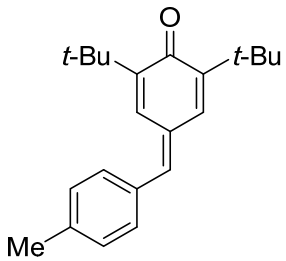
concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain a pure *p*-quinone methide.

4-Benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (2a)[5]



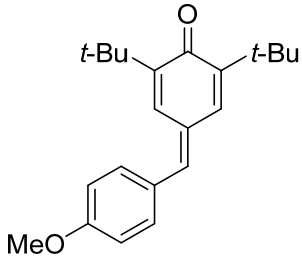
From 2,6-di-*tert*-butylphenol (2.0 g, 9.69 mmol) and benzaldehyde (0.98 mL, 9.69 mmol), 1.49 g (52%) of compound **2a** were obtained after column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 (1H, d, *J* = 2.4 Hz), 7.27-7.17 (5H, m), 6.98 (1H, s), 6.84 (1H, d, *J* = 2.4 Hz), 1.17 (9H, s), 1.13 (9H, s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.6 (C), 147.8 (C), 145.9 (C), 142.5 (CH), 135.1 (CH), 131.9 (C), 130.3 (CH), 129.0 (C), 128.7 (CH), 127.8 (CH), 35.4 (C), 34.9 (C), 29.5 (CH_3), 29.4 (CH_3).

2,6-Di-*tert*-butyl-4-(4-methylbenzylidene)cyclohexa-2,5-dien-1-one (2b)[5]



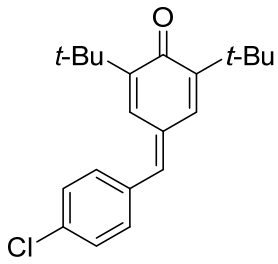
From 2,6-di-*tert*-butylphenol (1.0 g, 4.85 mmol), and 4-methylbenzaldehyde (0.57 mL, 4.85 mmol), 598.4 mg (40%) of compound **2b** were obtained after column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 2.3 Hz), 7.38 (1H, s), 7.36 (1H, s), 7.27 (1H, s), 7.25 (1H, s), 7.16 (1H, s), 7.01 (1H, d, *J* = 2.3 Hz), 2.41 (3H, s), 1.34 (9H, s), 1.31 (9H, s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.5 (C), 149.7 (C), 148.1 (C), 140.6 (CH), 135.1 (C) 134.9 (CH), 134.4 (C), 132.4 (C), 131.5 (CH), 129.1 (CH), 127.3 (CH), 35.5 (C), 35.0 (C), 29.5 (CH_3), 29.4 (CH_3).

2,6-Di-*tert*-butyl-4-(4-methoxybenzylidene)cyclohexa-2,5-dien-1-one (2c)[5]



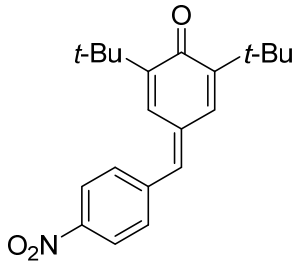
From 2,6-di-*tert*-butylphenol (1.0 g, 4.85 mmol) and 4-methoxybenzaldehyde (0.59 mL, 4.85 mmol), 849.8 mg (54%) of compound **2c** were obtained after column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56-7.60 (1H, m), 7.45-7.43 (2H, m), 7.13 (1H, s), 7.00-7.09 (2H, m), 6.97 (1H, m), 3.87 (3H, s), 1.33 (9H, s), 1.32 (9H, s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.5 (C), 160.6 (C), 148.9 (C), 147.2 (C), 142.7 (CH), 135.4 (CH), 132.2 (CH), 130.5 (C), 128.6 (C), 127.8 (CH), 114.4 (CH), 55.8 (CH_3O), 35.4 (C), 34.9 (C), 29.6 (CH_3), 29.5 (CH_3).

2,6-Di-*tert*-butyl-4-(4-chlorobenzylidene)cyclohexa-2,5-dien-1-one (2d)[5]



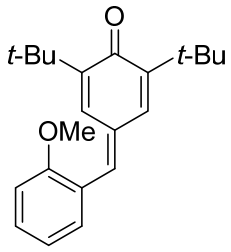
From 2,6-di-*tert*-butylphenol (1.0 g, 4.85 mmol), and 4-chlorobenzaldehyde (0.68 g, 4.85 mmol), 733.7 mg (46%) of compound **2d** were obtained after column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44-7.36 (5H, m), 7.11 (1H, s), 6.98 (1H, d, J = 2.4 Hz), 1.33 (9H, s), 1.29 (9H, s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.6 (C), 149.1 (C), 147.5 (C), 142.8 (CH), 139.5 (C), 135.3 (CH), 133.2 (C), 131.4 (C), 130.5 (CH), 129.6 (CH), 127.9 (CH), 35.4 (C), 34.9 (C), 29.5 (CH_3), 29.4 (CH_3).

2,6-Di-*tert*-butyl-4-(4-nitrobenzylidene)cyclohexa-2,5-dien-1-one (2e)[5]



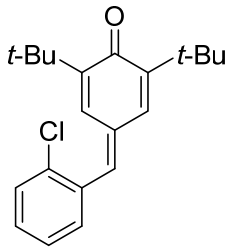
From 2,6-di-*tert*-butylphenol (1.0 g, 4.85 mmol), and 4-nitrobenzaldehyde (0.73 g, 4.85 mmol), 856.1 mg (52%) of compound **2e** were obtained after column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60-7.63 (2H, m), 7.55-7.57 (2H, m), 7.37 (1H, d, J = 2.4 Hz), 7.15 (1H, s), 7.01 (1H, d, J = 2.4 Hz), 1.33 (9H, s), 1.29 (9H, s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.4 (C), 150.7 (C), 149.1 (C), 147.4 (C), 142.3 (C), 138.3 (CH), 134.4 (C), 134.3 (CH), 130.7 (CH), 126.6 (CH), 123.9 (CH), 35.5 (C), 35.1 (C), 29.5 (CH_3), 29.4 (CH_3).

2,6-Di-*tert*-butyl-4-(2-methoxybenzylidene)cyclohexa-2,5-dien-1-one (2f)[5]



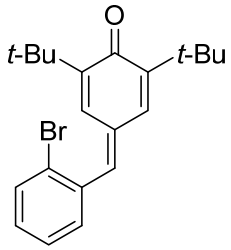
From 2,6-di-*tert*-butylphenol (1.0 g, 4.85 mmol), and 2-methoxybenzaldehyde (0.59 mL, 4.85 mmol), 676.7 mg (43%) of compound **2f** were obtained after column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 (1H, d, J = 2.3 Hz), 7.42 (2H, m), 7.36 (1H, s), 7.07 (1H, d, J = 2.3 Hz), 6.94-7.04 (2H, m), 3.89 (3H, s), 1.34 (9H, s), 1.29 (9H, s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.7 (C), 158.3 (C), 148.9 (C), 147.4 (C), 138.7 (CH), 135.3 (CH), 131.8 (CH), 131.6 (C), 130.8 (CH), 128.3 (CH), 124.9 (C), 120.5 (CH), 110.8 (CH), 55.5 (CH_3), 35.4 (C), 34.9 (C), 29.5 (CH_3), 29.4 (CH_3).

2,6-Di-*tert*-butyl-4-(2-chlorobenzylidene)cyclohexa-2,5-dien-1-one (2g)[5]



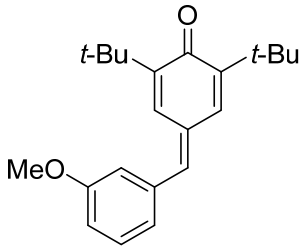
From 2,6-di-*tert*-butylphenol (1.0 g, 4.85 mmol), and 2-chlorobenzaldehyde (0.54 mL, 4.85 mmol), 845.4 mg (53%) of compound **2g** were obtained after column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.50-7.30 (6H, m), 7.07 (1H, d, J = 2.3 Hz), 1.34 (9H, s), 1.27 (9H, s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.6 (C), 149.7 (C), 148.3 (C), 138.6 (CH), 134.8 (C), 134.6 (CH), 134.1 (C), 132.8 (C), 132.1 (CH), 130.1 (CH), 130.0 (CH), 127.6 (CH), 126.6 (CH), 35.4 (C), 35.1 (C), 29.5 (CH_3), 29.4 (CH_3).

4-(2-Bromobenzylidene)-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (2h)[6]



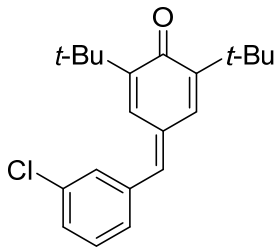
From 2,6-di-*tert*-butylphenol (1.0 g, 4.85 mmol), and 2-bromobenzaldehyde (0.57 mL, 4.85 mmol), 1.01 g (56%) of compound **2h** were obtained after column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.68 (1H, d, J = 2.3 Hz), 7.40 (1H, s), 7.38 (1H, s), 7.28-7.25 (1H, m), 7.23 (1H, s), 7.07 (1H, d, J = 2.3 Hz), 1.34 (9H, s), 1.27 (9H, s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.6 (C), 149.7 (C), 148.3 (C), 140.8 (CH), 135.8 (C), 134.6 (CH), 133.2 (CH), 132.6 (C), 132.2 (CH), 127.6 (CH), 127.2 (CH), 125.1 (C), 35.4 (C), 35.1 (C), 29.5 (CH_3), 29.4 (CH_3).

2,6-Di-*tert*-butyl-4-(3-methoxybenzylidene)cyclohexa-2,5-dien-1-one (2i)[5]



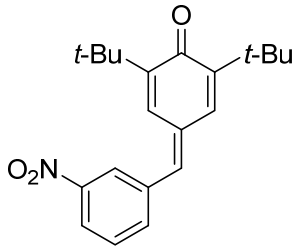
From 2,6-di-*tert*-butylphenol (1.0 g, 4.85 mmol), and 3-methoxybenzaldehyde (0.59 mL, 4.85 mmol), 660.9 mg (42%) of compound **2i** were obtained after column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56 (1H, d, J = 2.3 Hz), 7.36 (1H, t, J = 7.9 Hz), 7.16 (1H, s), 7.00 (4H, m), 3.85 (3H, s), 1.36 (9H, s), 1.30 (9H, s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.5 (C), 159.7 (C), 149.3 (C), 147.8 (C), 142.4 (CH), 137.2 (C), 135.1 (CH), 129.8 (CH), 127.8 (CH), 127.9 (CH), 122.9 (C), 115.2 (CH), 55.3 (CH_3), 35.4 (C), 34.9 (C), 29.5 (CH_3), 29.4 (CH_3).

2,6-Di-*tert*-butyl-4-(3-chlorobenzylidene)cyclohexa-2,5-dien-1-one (2j)[5]



From 2,6-di-*tert*-butylphenol (1.0 g, 4.85 mmol), and 3-chlorobenzaldehyde (0.55 mL, 4.85 mmol), 909.2 mg (57%) of compound **2j** were obtained after column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44-7.30 (5H, m), 7.10 (1H, s), 6.99 (1H, d, J = 2.3 Hz), 1.32 (9H, s), 1.29 (9H, s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.5 (C), 149.8 (C), 148.3 (C), 140.0 (CH), 137.6 (C), 134.7 (C), 134.6 (CH), 132.8 (C), 130.0 (CH), 129.9 (CH), 128.8 (CH), 128.2 (CH), 127.2 (CH), 35.5 (C), 35.0 (C), 29.5 (CH_3), 29.4 (CH_3).

2,6-Di-*tert*-butyl-4-(3-nitrobenzylidene)cyclohexa-2,5-dien-1-one (2k)[6]

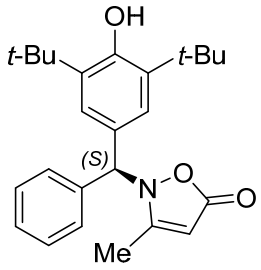


From 2,6-di-*tert*-butylphenol (1.0 g, 4.85 mmol) and 3-nitrobenzaldehyde (0.73 g, 4.85 mmol), 806.7 mg (49%) of compound **2k** were obtained after column chromatography **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.33 (1H, m), 8.25 (1H, m), 7.75 (1H, d, J = 7.9 Hz), 7.64 (1H, t, J = 7.9 Hz), 7.40 (1H, d, J = 2.3 Hz), 7.15 (1H, s), 7.02 (1H, d, J = 2.3 Hz), 1.33 (9H, s), 1.29 (9H, s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.4 (C), 150.6 (C), 148.9 (C), 147.4 (C), 138.1 (CH), 135.6 (C), 133.8 (C), 129.8 (CH), 126.5 (CH), 124.8 (CH), 123.3 (CH), 35.5 (C), 35.1 (C), 29.5 (CH_3), 29.4 (CH_3).

General procedure for the enantioselective synthesis of *N*-alkylated isoxazolin-5-ones (3).

A round bottom flask was charged with the *para*-quinone methide **2** (0.15 mmol), isoxazolin-5-one **1** (0.1 mmol), 3Å MS (32 mg) and thiourea **V** (3.7 mg, 0.005 mmol). 1,2-Dichloroethane (1 mL) was added and the mixture was stirred at room temperature until completion (TLC). The MS was removed by filtration and the resulting solution was chromatographed on silica gel eluting with hexane:EtOAc mixtures to give compound **3**.

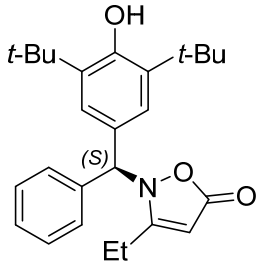
(*S*)-2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-3-methylisoxazol-5(2*H*)-one (3aa).



From 9.9 mg of **1a** and 44.2 mg of **2a**, were obtained 25.6 mg (65%) of **3aa**. Enantiomeric excess (87%) was determined using chiral HPLC (Chiralcel OD-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 12.2 min, major enantiomer t_r = 13.7 min.

Yellow solid; **m.p.** = 167.9-169.8 ºC; **[α]$_D^{25}$** = + 12.9 (*c* = 0.85, $CHCl_3$, 87% ee); **^{1}H NMR** (300 MHz, $CDCl_3$), δ 7.36-7.26 (5H, m, Ar), 7.03 (2H, s, Ar), 6.04 (1H, s, C*H*-N), 5.27 (1H, s, OH), 5.02 (1H, q, *J* = 0.9 Hz, C*H*-COO), 2.20 (3H, d, *J* = 0.9 Hz, CH_3), 1.38 (18H, s, *t*-Bu); **^{13}C NMR** (75 MHz, $CDCl_3$), δ 170.9 (C, C=O), 163.6 (C, C=*C*-N), 153.7 (C, Ar), 137.0 (C, Ar), 135.9 (C, Ar), 128.5 (CH, Ar), 128.2 (CH, Ar), 128.2 (C, Ar), 126.8 (C, Ar), 125.1 (CH, Ar), 91.0 (CH, C=*C*-C=O), 68.3 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 13.9 (CH_3); **IR** 3400, 2951, 1702 (C=O), 1565, 758, 703 cm^{-1}; **HRMS** (ESI) m/z: 416.2191 $[M+Na]^+$, $C_{25}H_{31}NNaO_3^+$ requires 416.2196.

(*S*)-2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-3-ethylisoxazol-5(2*H*)-one (3ba).

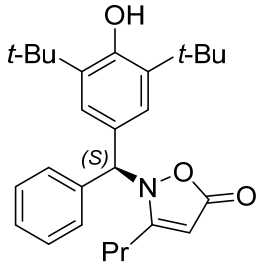


From 11.3 mg of **1b** and 44.2 mg of **2a**, were obtained 20.8 mg (51%) of **3ba**. Enantiomeric excess (81%) was determined using chiral HPLC (Chiralcel OD-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 8.2 min, major enantiomer t_r = 11.9 min

Yellow solid; **m.p.** = 154.8-157.1 ºC; **[α]$_D^{25}$** = + 10.3 (*c* = 0.72, $CHCl_3$, 81% ee); **^{1}H NMR** (300 MHz, $CDCl_3$), δ 7.36-7.28 (5H, m, Ar), 7.01 (2H, s, Ar), 6.04 (1H, s, C*H*-N), 5.26 (1H, s, OH), 5.04 (1H, s, C*H*-COO), 2.53 (2H, q, *J* = 7.5 Hz, CH_2), 1.38 (18H, s, *t*-Bu), 1.25 (3H, t, *J* = 7.5 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$), δ 171.0 (C, C=O), 169.3 (C, C=*C*-N), 153.7 (C, Ar), 137.1 (C, Ar), 135.9 (C, Ar), 128.5

(CH, Ar), 128.2 (CH, Ar), 128.1 (CH, Ar), 126.9 (C, Ar), 125.1 (CH, Ar), 89.2 (CH, C=*C*-C=O), 68.1 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 20.4 (CH_2), 11.5 (CH_3); **IR** ν 3392, 2948, 1699 (C=O), 1426, 913, 880, 763, 699 cm^{-1}; **HRMS** (ESI) m/z: 430.2352 $[M+Na]^+$, $C_{26}H_{33}NNaO_3^+$ requires 430.2353.

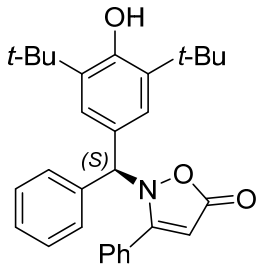
(*S*)-2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-3-propylisoxazol-5(2*H*)-one (3ca).



From 12.7 mg of **1c** and 44.2 mg of **2a**, were obtained 24.9 mg (59%) of **3ca**. Enantiomeric excess (81%) was determined using chiral HPLC (Chiralcel OD-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 7.9 min, major enantiomer t_r = 9.8 min

Yellow solid; **m.p.** = 117.5-121.8 ºC; $[\alpha]_D^{25}$ = + 19.4 (*c* = 0.91, $CHCl_3$, 81% ee); **^{1}H NMR** (300 MHz, $CDCl_3$), δ 7.36-7.27 (5H, m, Ar), 7.01 (2H, s, Ar), 6.06 (1H, s, C*H*-N), 5.27 (1H, s, OH), 5.03 (1H, s, C*H*-COO), 2.50 (2H, t, *J* = 7.5 Hz, CH_2) 1.69 (2H, sextuplet, *J* = 7.5 Hz, CH_2), 1.38 (18H, s, *t*-Bu), 1.00 (3H, t, *J* = 7.5 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$), δ 171.1 (C, C=O), 167.9 (C, C=*C*-N), 153.7 (C, Ar), 137.1 (C, Ar), 135.9 (C, Ar), 128.5 (CH, Ar), 128.2 (CH, Ar), 128.1 (CH, Ar), 127.0 (C, Ar), 125.0 (CH, Ar), 89.6 (CH, C=*C*-C=O), 68.1 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 28.8 (CH_2), 20.7 (CH_2), 13.7 (CH_3); **IR** ν 3367, 2950, 1699 (C=O), 1435, 1118, 885, 763, 705 cm^{-1}; **HRMS** (ESI) m/z: 444.2497 $[M+Na]^+$, $C_{27}H_{35}NNaO_3^+$ requires 444.2509.

(*S*)-2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-3-phenylisoxazol-5(2*H*)-one (3da).

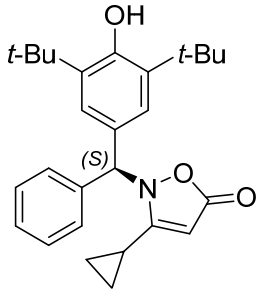


From 16.2 mg of **1d** 44.2 mg of **2a**, were obtained 34.6 mg (77%) of **3da**. Enantiomeric excess (65%) was determined using chiral HPLC (Chiralpak IC), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 26.8 min, major enantiomer t_r = 21.1 min

Yellow solid; **m.p.** = 160.9-165.5 ºC; $[\alpha]_D^{25}$ = + 19.8 (*c* = 1.10, $CHCl_3$, 77% ee) **^{1}H NMR** (300 MHz, $CDCl_3$), δ 7.59-7.46 (5H, m, Ar), 7.33-7.32 (5H, m, Ar), 6.85 (2H, s, Ar), 6.00 (1H, s, C*H*-N), 5.38 (1H, s, OH), 5.25 (1H, s, C*H*-COO), 1.35 (18H, s, *t*-Bu); **^{13}C NMR** (75 MHz, $CDCl_3$), δ 171.1 (C, C=O), 169.5 (C, C=*C*-N), 153.7 (C, Ar), 136.9 (C, Ar), 135.5 (CH, Ar), 131.5 (C, Ar), 129.4 (C, Ar), 128.4 (CH,

Ar), 128.3 (C, Ar), 128.2 (CH, Ar), 127.9 (CH, Ar), 127.8 (CH, Ar), 126.1 (CH, Ar), 125.6 (CH, Ar) 93.9 (CH, C=*C*-C=O), 70.9 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu); **IR** ν 2959, 1718 (C=O), 1435, 1099, 763, 735, 691 cm^{-1}; **HRMS** (ESI) m/z: 456.2527 $[M+H]^+$, $C_{30}H_{34}NO_3^+$ requires 456.2533.

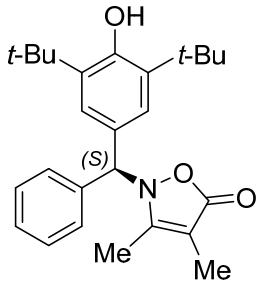
(*S*)-3-Cyclopropyl-2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)isoxazol-5(2*H*)-one (3ea).



From 12.5 mg of **1e** and 44.2 mg of **2a**, were obtained 32.7 mg (78%) of **3ea**. Enantiomeric excess (89%) was determined using chiral HPLC (Chiralpak AD-H), hexane/*i*-PrOH 85:15, 1 mL/min. Minor enantiomer t_r = 6.7 min, major enantiomer t_r = 8.4 min.

Yellow solid; **m.p.** = 146.1-147.5 ºC; **$[\alpha]_D^{25}$** = + 9.2 (*c* = 1.09, $CHCl_3$, 89% ee); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.37-7.31 (5H, m, Ar), 7.07 (2H, Ar), 6.28 (1H, s, C*H*-N), 5.26 (1H, s, OH), 4.68 (1H, d, *J* = 0.6 Hz, C*H*COO), 1.74-1.65 (1H, m, *c*-Pr), 1.38 (18H, s, *t*-Bu), 1.14-1.09 (2H, m, *c*-Pr), 0.79-0.71 (2H, m, *c*-Pr); **^{13}C NMR** (75 MHz, $CDCl_3$), δ 171.3 (C, C=O), 171.1 (C, C=*C*-N), 153.7 (C, Ar), 137.2 (C, Ar), 135.7 (C, Ar), 128.4 (CH, Ar), 128.3 (CH, Ar), 128.0 (CH, Ar), 126.9 (C, Ar), 125.4 (CH, Ar), 85.7 (CH, C=*C*-C=O), 68.7 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 9.5 (CH_2, *c*-Pr), 9.2 (CH_2, *c*-Pr), 7.9 (CH, *c*-Pr); **IR** ν 3419, 2952, 1697 (C=O), 1552, 1433, 1138, 1118, 916, 760 cm^{-1}; **HRMS** (ESI) m/z: 442.2359 $[M+Na]^+$, $C_{27}H_{33}NNaO_3^+$ requires 442.2353.

(*S*)-2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-3,4-dimethylisoxazol-5(2*H*)-one (3fa).

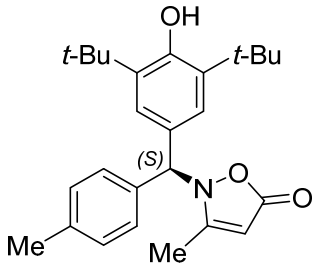


From 11.3 mg of **1f** and 44.2 mg of **2a**, were obtained 25.3 mg (62%) of **3fa**. Enantiomeric excess (47%) was determined using chiral HPLC (Chiralpak AY-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 9.9 min, major enantiomer t_r = 12.9 min.

Yellow solid; **m.p.** = 142.6-143.9 ºC; **$[\alpha]_D^{25}$** = + 4.2 (*c* = 1.27, $CHCl_3$, 47% ee); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.32-7.30 (5H, m, Ar), 7.04 (2H, s, Ar), 5.95 (1H, s, C*H*-N), 5.25 (1H, s, OH), 2.14 (3H, s, CH_3), 1.71 (3H, s, CH_3), 1.38 (18H, s, *t*-Bu); **^{13}C NMR** (75 MHz, $CDCl_3$), δ 171.9 (C, C=O), 160.3 (C, C=*C*-N), 153.7 (C, Ar), 137.0 (C, Ar), 135.8 (C, Ar), 128.4 (CH, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 127.0 (C,

Ar), 125.1 (CH, Ar), 113.6 (CH, Ar), 100.7 (CH, C=*C*-C=O), 68.8 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 11.7 (CH_3), 6.74 (CH_3); **IR** ν 3559, 2955, 1701 (C=O), 1623, 1433, 1114, 1030, 747, 702 cm^{-1}; **HRMS** (ESI) m/z: 430.2357 $[M+Na]^+$, $C_{26}H_{33}NNaO3^+$ requires 430.2353.

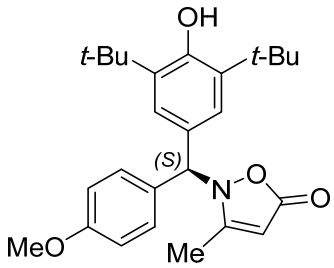
(*S*)-2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(*p*-tolyl)methyl)-3-methylisoxazol-5(2*H*)-one (3ab).



From 9.9 mg of **1a** and 46.2 mg of **2b**, were obtained 9.3 mg (23%) of **3ab**. Enantiomeric excess (72%) was determined using chiral HPLC (Chiralcel OD-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 10.2 min, major enantiomer t_r = 15.2 min.

Yellow solid; **m.p.** = 52.3-53.5 ºC; **$[\alpha]_D^{25}$** = + 1.2 (*c* = 0.72, $CHCl_3$, 72% ee); **^{1}H NMR** (300 MHz, $CDCl_3$), δ 7.15 (4H, m, Ar), 7.03 (2H, s, Ar), 6.00 (1H, s, C*H*-N), 5.26 (1H, s, OH), 5.01 (1H, q, *J* = 0.9 Hz, C*H*COO), 2.35 (3H, s, CH_3), 2.19 (3H, d, *J* = 0.9 Hz, CH_3), 1.38 (18H, s, *t*-Bu); **^{13}C NMR** (75 MHz, $CDCl_3$), δ 170.9 (C, C=O), 163.6 (C, C=*C*-N), 153.7 (C, Ar), 137.9 (C, Ar), 135.9 (C, Ar), 133.9 (C, Ar), 129.2 (CH, Ar), 128.2 (CH, Ar), 127.1 (C, Ar), 124.9 (CH, Ar), 90.9 (CH, C=*C*-C=O), 68.1 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 21.1 (CH_3), 12.9 (CH_3); **IR** ν 3322, 2953, 1695 (C=O), 1574, 1433, 1120, 926, 780 cm^{-1}; **HRMS** (ESI) m/z: 430.2354 $[M+Na]^+$, $C_{26}H_{33}NNaO_3^+$ requires 430.2538.

(*S*)-2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl)-3-methylisoxazol-5(2*H*)-one (3ac).

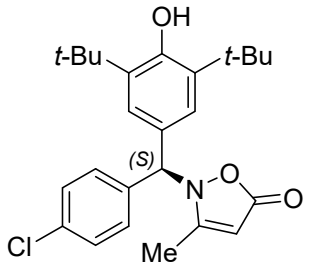


From 9.9 mg of **1a** and 48.7 mg of **2c**, were obtained 28.0 mg (66%) of **3ac**. Enantiomeric excess (62%) was determined using chiral HPLC (Chiralpak AY-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 19.9 min, major enantiomer t_r = 25.3 min.

Yellow solid; **m.p.** = 138.9-146.1 ºC; **$[\alpha]_D^{25}$** = + 1.1 (*c* = 0.93, $CHCl_3$, 62% ee); **^{1}H NMR** (300 MHz, $CDCl_3$), δ 7.22-7.18 (2H, m, Ar), 7.03 (2H, s, Ar), 6.88-6.85 (2H, m, Ar), 6.00 (1H, s, C*H*-N), 5.25 (1H, s, OH), 5.01 (1H, q, *J* = 0.9 Hz, C*H*-COO), 3.81 (3H, s, MeO), 2.20 (3H, d, *J* = 0.9 Hz, CH_3), 1.39 (18H, s, *t*-Bu); **^{13}C NMR** (75 MHz, $CDCl_3$), δ 170.9 (C, C=O), 163.6 (C, C=*C*-N), 159.4 (C, Ar), 153.6 (C, Ar), 135.9 (C, Ar), 129.6 (CH,

Ar), 128.9 (C, Ar), 127.3 (C, Ar), 124.8 (CH, Ar), 113.9 (CH, Ar), 91.1 (CH, C=*C*-C=O), 67.9 (CH, C-N), 55.3 (CH_3, OMe), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 12.9 (CH_3); **IR** ν 3625, 2956, 1716 (C=O), 1511, 1434, 1237, 1176, 752 cm^{-1}; **HRMS** (ESI) m/z: 446.2297 $[M+Na]^+$, $C_{26}H_{33}NNaO_4^+$ requires 446.2302.

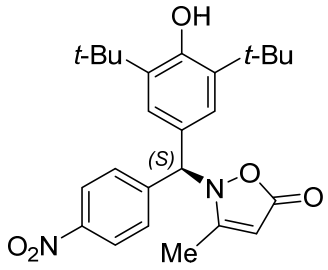
(*S*)-2-((4-Chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)-3-methylisoxazol-5(2*H*)-one (3ad).



From 9.9 mg of **1a** and 49.5 mg of **2d**, were obtained 26.5 mg (62%) of **3ad**. Enantiomeric excess (88%) was determined using chiral HPLC (Chiralpak AY-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 12.5 min, major enantiomer t_r = 13.5 min

Yellow solid; **m.p.** = 154.8-157.1 ºC; **$[\alpha]_D^{25}$** = + 11.2 (*c* = 0.88, $CHCl_3$, 88% ee); **^{1}H NMR** (300 MHz, $CDCl_3$), δ 7.35-7.31 (2H, m, Ar), 7.26-7.21 (2H, m, Ar), 7.00 (2H, s, Ar), 5.99 (1H, s, C*H*-N), 5.30 (1H, s, OH), 5.04 (1H, q, *J* = 0.9 Hz, C*H*-COO), 2.21 (3H, d, *J* = 0.9 Hz, CH_3), 1.39 (18H, s, *t*-Bu); **^{13}C NMR** (75 MHz, $CDCl_3$), δ 170.7 (C, C=O), 163.9 (C, C=*C*-N), 153.9 (C, Ar), 136.1 (C, Ar), 135.6 (C, Ar), 134.1 (C, Ar), 129.6 (CH, Ar), 128.7 (CH, Ar), 126.4 (C, Ar), 124.9 (CH, Ar), 91.7 (CH, C=*C*-C=O), 67.7 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 12.9 (CH_3); **IR** ν 3411, 2967, 1721 (C=O), 1489, 1435, 1235, 1136, 859, 762 cm^{-1}; **HRMS** (ESI) m/z: 450.1795 $[M+Na]^+$, $C_{25}H_{30}ClNNaO_3^+$ requires 450.1806.

(*S*)-2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(4-nitrophenyl)methyl)-3-methylisoxazol-5(2*H*)-one (3ae).

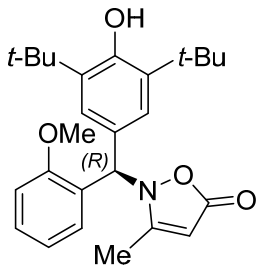


From 9.9 mg of **1a** and 51.0 mg of **2e**, were obtained 32.5 mg (74%) of **3ae**. Enantiomeric excess (84%) was determined using chiral HPLC (Chiralcel OD-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 25.1 min, major enantiomer t_r = 38.2 min

Orange solid; **m.p.** = 158.6-159.8 ºC; **$[\alpha]_D^{25}$** = + 7.7 (*c* = 1.08, $CHCl_3$, 84% ee); **^{1}H NMR** (300 MHz, $CDCl_3$), δ 8.23-8.18 (2H, m, Ar), 7.51-7.48 (2H, m, Ar), 7.00 (2H, s, Ar), 6.05 (1H, s, C*H*-N), 5.35 (1H, s, OH), 5.09 (1H, q, *J* = 0.6 Hz, C*H*-COO), 2.24 (3H, d, *J* = 0.6 Hz, CH_3), 1.39 (18H, s, *t*-Bu); **^{13}C NMR** (75 MHz, $CDCl_3$), δ 170.4 (C, C=O), 164.5 (C,

C=*C*-N), 154.3 (C, Ar), 147.6 (C, Ar), 144.7 (C, Ar), 136.4 (C, Ar), 129.1 (CH, Ar), 125.4 (C, Ar), 125.2 (CH, Ar), 123.6 (CH, Ar), 92.9 (CH, C=*C*-C=O), 67.8 (CH, C-N), 34.4 (C, *t*-Bu), 30.1 (CH_3, *t*-Bu), 13.0 (CH_3); **IR** ν 3317, 2953, 1704 (C=O), 1518, 1342, 1199, 919, 764, 704 cm^{-1}; **HRMS** (ESI) m/z: 461.2037 $[M+Na]^+$, $C_{25}H_{30}N_2NaO_5^+$ requires 461.2047.

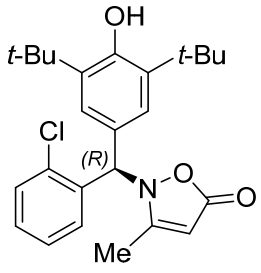
(*R*)-2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(2-methoxyphenyl)methyl)-3-methylisoxazol-5(2*H*)-one (3af).



From 9.9 mg of **1a** and 48.7 mg of **2f**, were obtained 18.2 mg (43%) of **3af**. Enantiomeric excess (48%) was determined using chiral HPLC (Chiralpak AY-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 16.5 min, major enantiomer t_r = 19.7 min.

Yellow oil; **$[\alpha]_D^{25}$** = + 12.1 (*c* = 1.12, $CHCl_3$, 48% ee); **^{1}H NMR** (300 MHz, $CDCl_3$), δ 7.28-7.20 (4H, m, Ar), 6.99 (2H, d, Ar), 6.58 (1H, s, C*H*-N), 5.22 (1H, s, OH), 4.90 (1H, q, *J* = 0.9 Hz, C*H*COO), 3.80 (3H, s, OMe), 2.20 (3H, d, *J* = 0.9 Hz, CH_3), 1.35 (18H, s, *t*-Bu); **^{13}C NMR** (75 MHz, $CDCl_3$), δ 170.9 (C, C=O), 167.8 (C, C=*C*-N), 156.4 (C, Ar), 135.8 (C, Ar), 130.5 (C, Ar), 129.6 (CH, Ar), 127.6 (CH, Ar), 124.5 (CH, Ar), 120.9 (CH, Ar), 110.4 (CH, Ar), 88.4 (CH, C=*C*-C=O), 60.2 (CH, C-N), 55.5 (CH_3, MeO), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 12.5 (CH_3); **IR** ν 3630, 2955, 1718 (C=O), 1599, 1433, 1239, 1105, 753 cm^{-1}; **HRMS** (ESI) m/z: 446.2297 $[M+Na]^+$, $C_{26}H_{33}NNaO_4^+$ requires 446.2302.

(*R*)-2-((2-Chlorophenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)-3-methylisoxazol-5(2*H*)-one (3ag).

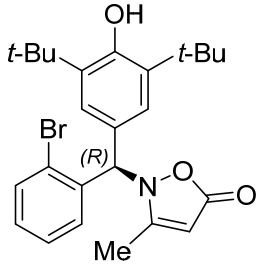


From 9.9 mg of **1a** and 49.5 mg of **2g**, were obtained 20.2 mg (47%) of **3ag**. Enantiomeric excess (89%) was determined using chiral HPLC (Chiralpak IC), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 53.7 min, major enantiomer t_r = 60.5 min.

Yellow solid; **m.p.** = 123.5-129.2 ºC; **$[\alpha]_D^{25}$** = + 25.2 (*c* = 1.01, $CHCl_3$, 89%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46-7.40 (2H, m, Ar), 7.33-7.35 (2H, m, Ar), 6.94 (2H, s, Ar), 6.56 (1H, s, C*H*-N), 5.26 (1H, s, OH), 5.01 (1H, q, *J* = 0.9 Hz, C*H*COO), 2.24 (3H, d, *J* = 0.9 Hz, CH_3), 1.38 (18H, s, *t*-Bu); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.7 (C, C=O), 167.8 (C, C=*C*-N), 153.7 (C, Ar), 136.1 (C, Ar), 134.8 (C, Ar), 133.3

(C, Ar), 130.8 (CH, Ar), 129.7 (CH, Ar), 127.3 (CH, Ar), 126.3 (C, Ar), 124.4 (CH, Ar), 89.3 (CH, C=*C*-C=O), 63.6 (CH, C-N), 34.3 (C, *t*-Bu), 30.1 (CH_3, *t*-Bu), 12.6 (CH_3); **IR** ν 2955, 1725 (C=O), 1559, 1433, 1115, 885, 754 cm^{-1}; **HRMS** (ESI) m/z: 450.1802 $[M+Na]^+$, $C_{25}H_{30}NNaO_3^+$ requires 450.1806.

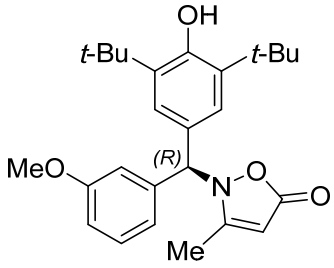
(*R*)-2-((2-Bromophenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)-3-methylisoxazol-5(2*H*)-one (3ah).



From 9.9 mg of **1a** and 55.9 mg of **2h**, were obtained 20.2 mg (43%) of **3ah**. Enantiomeric excess (90%) was determined using chiral HPLC (Chiralpak AY-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 19.2 min, major enantiomer t_r = 20.9 min.

Yellow solid; **m.p.** = 132.1-133.4 ºC; $[\alpha]_D^{25}$ = +7.5 (*c* = 1.01, $CHCl_3$, 90% ee); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (1H, dd, J_1 = 7.9, J_2 = 1.3 Hz, Ar), 7.44 (1H, dd, J_1 = 7.8, J_2 = 1.8 Hz, Ar), 7.32 (1H, td, J_1 = 7.6, J_2 = 1.4 Hz, Ar), 7.23-7.18 (2H, m, Ar), 6.92 (2H, s, Ar), 6.53 (1H, s, C*H*-N), 5.26 (1H, s, OH), 5.02 (1H, q, *J* = 0.8 Hz, C*H*COO), 2.25 (3H, d, *J* = 0.8 Hz, CH_3), 1.38 (18H, s, *t*-Bu); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.7 (C, C=O), 162.7 (C, C=*C*-N), 153.7 (C, Ar), 136.5 (C, Ar), 136.1 (C, Ar), 132.9 (CH, Ar), 130.9 (CH, Ar), 129.9 (CH, Ar), 127.9 (CH, Ar), 126.4 (C, Ar), 124.4 (CH, Ar), 123.9 (C, Ar), 89.2 (CH, C=*C*-C=O), 66.2 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 12.7 (CH_3); **IR** ν 3423, 2957, 1705 (C=O), 1571, 1161, 1120, 911, 751 cm^{-1}, **HRMS** (ESI) m/z: 494.1303 $[M+Na]^+$, $C_{26}H_{30}BrNNaO_3^+$ requires 494.1301.

(*R*)-2-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(3-methoxyphenyl)methyl)-3-methylisoxazol-5(2*H*)-one (3ai).

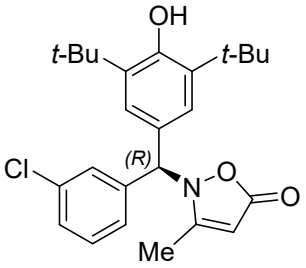


From 9.9 mg of **1a** and 48.7 mg of **2i**, were obtained 8.8 mg (20%) of **3ai**. Enantiomeric excess (25%) was determined using chiral HPLC (Chiralcel OD-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 14.9 min, major enantiomer t_r = 21.0 min.

Yellow oil; $[\alpha]_D^{25}$ = + 1.7 (*c* = 0.63, $CHCl_3$, 25% ee); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.29-7.24 (1H, m, Ar), 7.04 (2H, s, Ar), 6.88-6.82 (3H, m, Ar), 5.99 (1H, s, C*H*-N), 5.27 (1H, s, OH), 5.02 (1H, q, *J* = 0.9 Hz, C*H*COO), 3.78 (3H, s, MeO), 2.20 (3H, d, *J* = 0.9 Hz, CH_3), 1.38 (18H, s, *t*-Bu), **^{13}C NMR** (75 MHz, CDCl3), δ 170.9 (C, C=O), 163.7 (C,

C=*C*-N), 159.7 (C, Ar), 153.7 (C, Ar), 138.6 (C, Ar), 135.9 (C, Ar), 129.6 (CH, Ar), 126.6 (C, Ar), 125.1 (CH, Ar), 120.5 (CH, Ar), 113.9 (CH, Ar), 113.6 (CH, Ar), 91.2 (CH, C=*C*-C=O), 68.2 (CH, C-N), 34.3 (C, *t*-Bu), 30.1 (CH_3, *t*-Bu), 12.9 (CH_3); **IR** ν 3375, 2950, 1690 (C=O), 1431, 1263, 1159, 911, 760 cm^{-1}; **HRMS** (ESI) m/z: 446.2297 $[M+Na]^+$, $C_{26}H_{33}NNaO_4^+$ requires 446.2302.

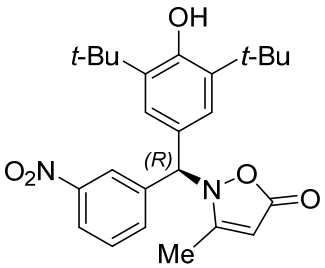
(*R*)-2-((3-Chlorophenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)-3-methylisoxazol-5(2*H*)-one (3aj).



From 9.9 mg of **1a** and 49.5 mg of **2j**, were obtained 15.5 mg (36%) of **3aj**. Enantiomeric excess (81%) was determined using chiral HPLC (Chiralpak AY-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 11.8 min, major enantiomer t_r = 13.1 min.

Brown solid; **m.p.** = 145.7-148.8 ºC; **$[\alpha]_D^{25}$** = + 10.2 (*c* = 1.10, $CHCl_3$, 81% ee); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33-7.29 (3H, m, Ar), 7.19-7.17 (1H, m, Ar), 6.94 (2H, s, Ar), 5.97 (1H, s, C*H*-N), 5.30 (1H, s, OH), 5.05 (1H, q, *J* = 0.9 Hz, C*H*COO), 2.21 (3H, d, *J* = 0.6 Hz, CH_3), 1.39 (18H, s, *t*-Bu); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.6 (C, C=O), 163.9 (C, C=*C*-N), 154.0 (C, Ar), 139.3 (C, Ar), 136.2 (C, Ar), 134.5 (C, Ar), 129.8 (CH, Ar), 128.4 (CH, Ar), 128.3 (CH, Ar), 126.4 (CH, Ar), 126.0 (C, Ar), 125.1 (CH, Ar), 91.8 (CH, C=*C*-C=O), 67.7 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 12.9 (CH_3); **IR** ν 2955, 1703 (C=O), 1571, 1433, 1121, 882, 769 cm^{-1}; **HRMS** (ESI) m/z: 450.1801 $[M+Na]^+$, $C_{25}H_{30}ClNNaO_3^+$ requires 450.1806.

(*R*)-2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(3-nitrophenyl)methyl)-3-methylisoxazol-5(2*H*)-one (3ak).

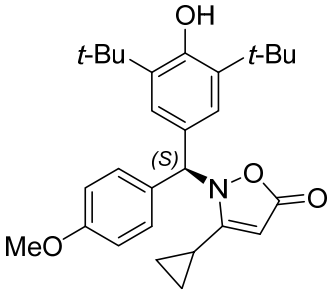


From 9.9 mg of **1a** and 50.8 mg of **2k**, were obtained 24.4 mg (56%) of **3ak**. Enantiomeric excess (77%) was determined using chiral HPLC (Chiralcel OD-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 27.7 min, major enantiomer t_r = 18.7 min.

Brown solid; **m.p.** = 131.3-133.4 ºC; **$[\alpha]_D^{25}$** = +8.1 (*c* = 1.22, $CHCl_3$, 77% ee); **^{1}H NMR** (300 MHz, CDC_{l3}) δ 8.21-8.18 (2H, m, Ar), 7.68 (1H, d, *J* =7.8 Hz, Ar), 7.55 (1H, m, Ar), 7.02 (2H, s, Ar), 6.05 (1H, s, C*H*-N), 5.35 (1H, s, OH), 5.10 (1H, q, *J* = 0.9 Hz,

C*H*COO), 2.25 (3H, d, *J* = 0.9 Hz, CH_3), 1.39 (18H, s, *t*-Bu); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.4 (C, C=O), 164.6 (C, C=*C*-N), 154.3 (C, Ar), 148.3 (C, Ar), 139.6 (C, Ar), 136.4 (C, Ar), 134.3 (CH, Ar), 129.5 (CH, Ar), 125.2 (C, Ar), 125.1 (CH, Ar), 123.2 (CH, Ar), 123.1 (CH, Ar), 93.0 (CH, C=*C*-C=O), 67.7 (CH, C-N), 34.4 (C, *t*-Bu), 30.1 (CH_3, *t*-Bu), 13.6 (CH_3); **IR** ν 3580, 2957, 1729 (C=O), 1522, 1435, 1341, 909, 738 cm^{-1}; **HRMS** (ESI) m/z: 461.2044 $[M+Na]^+$, $C_{26}H_{33}NNaO_4$ + requires 461.2047.

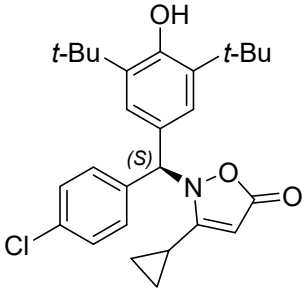
(*S*)-3-Cyclopropyl-2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl)isoxazol-5(2*H*)-one (3ec).



From 12.5 mg of **1e** and 48.7 mg of **2c**, were obtained 33.6 mg (75%) of **3ec**. Enantiomeric excess (79%) was determined using chiral HPLC (Chiralpak AD-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 13.4 min, major enantiomer t_r = 21.5 min.

Yellow solid; **m.p.** = 141.9-144.2 ºC; **$[\alpha]_D^{25}$** = + 0.6 (*c* = 1.12, $CHCl_3$, 79% ee); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.28-7.23 (2H, m, Ar), 7.02 (2H, s, Ar), 6.88 (2H, m, Ar) 6.24 (1H, s, C*H*-N), 5.25 (1H, s, OH), 4.67 (1H, d, *J* = 0.6 Hz, C*H*COO), 1.74-1.65 (1H, m, *c*-Pr), 1.39 (18H, s, *t*-Bu), 3.81 (3H, s, OMe), 1.14-1.08 (2H, m, *c*-Pr), 0.78-0.72 (2H, m, *c*-Pr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.3 (C, C=O), 171.1 (C, C=*C*-N), 159.3 (C,Ar), 153.5 (C, Ar), 135.7 (C, Ar), 129.8 (CH, Ar), 129.2 (C, Ar), 127.3 (CH, Ar), 125.1 (CH, Ar), 113.7 (C, Ar), 85.6 (CH, C=*C*-C=O), 68.4 (CH, C-N), 55.2 (CH_3, MeO), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 9.4 (CH_2, *c*-Pr), 9.3 (CH_2, *c*-Pr), 7.9 (CH, *c*-Pr); **IR** ν 3421, 2954, 1695 (C=O), 1511, 1435, 1235, 1112, 764 cm^{-1}; **HRMS** (ESI) m/z: 472.2459 $[M+Na]^+$, $C_{28}H_{35}NNaO_4^+$ requires 472.2458.

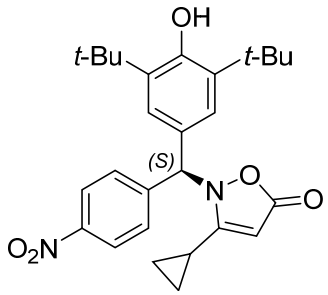
(*S*)-2-((4-Chlorophenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)-3-cyclopropylisoxazol-5(2*H*)-one (3ed).



From 12.5 mg of **1e** and 49.3 mg of **2d**, were obtained 35.3 mg (78%) of **3ed**. Enantiomeric excess (88%) was determined using chiral HPLC (Chiralpak AY-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 15.5 min, major enantiomer t_r = 17.5 min.

Yellow solid; **m.p.** = 164.1-165.4 ºC; **$[\alpha]_D^{25}$** = + 20.8 (*c* = 1.18, $CHCl_3$, 88% ee); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.34-7.27 (4H, m, Ar), 7.04 (2H, Ar), 6.23 (1H, s, C*H*-N), 5.29 (1H, s, OH), 4.68 (1H, d, *J* = 0.6 Hz, C*H*COO), 1.73-1.64 (1H, m, *c*-Pr), 1.39 (18H, s, *t*-Bu), 1.16-1.11 (2H, m, *c*-Pr), 0.84-0.66 (2H, m, *c*-Pr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.5 (C, C=O), 171.1 (C, C=*C*-N), 153.8 (C, Ar), 135.9 (C, Ar), 135.8 (C, Ar), 133.9 (C, Ar), 129.8 (CH, Ar), 128.6 (CH, Ar), 126.4 (C, Ar), 125.4 (CH, Ar), 86.4 (CH, C=*C*-C=O), 68.2 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 9.7 (CH_2, *c*-Pr), 9.3 (CH_2, *c*-Pr), 7.9 (CH, *c*-Pr); **IR** ν 3384, 2957, 1697 (C=O), 1552, 1435, 1105, 877 cm^{-1}; **HRMS** (ESI) m/z: 476.1965 $[M+Na]^+$, $C_{27}H_{32}ClNNaO_3^+$ requires 476.1963.

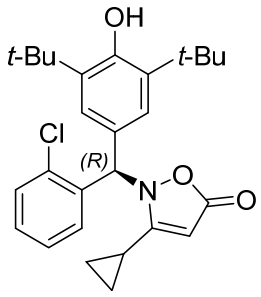
(*S*)-3-Cyclopropyl-2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-nitrophenyl)methyl)isoxazol-5(2*H*)-one (3ee).



From 12.5 mg of **1e** and 50.9 mg of **2e**, were obtained 37.2 mg (80%) of **3ee**. Enantiomeric excess (86%) was determined using chiral HPLC (Chiralcel OD-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 25.9 min, major enantiomer t_r = 22.1 min.

Yellow solid; **m.p.** = 87.5-89.9 ºC; **$[\alpha]_D^{25}$** = + 10.5 (*c* = 1.24, $CHCl_3$, 86% ee); **^{1}H NMR** (300 MHz, $CDCl_3$) 8.23-8.20 (2H, m, Ar), 7.57-7.55 (2H, m, Ar), 7.04 (2H, s, Ar), 6.29 (1H, s, C*H*-N), 5.33 (1H, s, OH), 4.73 (1H, d, *J* = 0.6 Hz, C*H*COO), 1.75-1.66 (1H, m, *c*-Pr), 1.39 (18H, s, *t*-Bu), 1.21-1.15 (2H, m, *c*-Pr), 0.87-0.80 (1H, m, *c*-Pr), 0.75-0.68 (1H, m, *c*-Pr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.1 (C, C=O), 170.8 (C, C=*C*-N), 154.2 (C, Ar), 147.5 (C, Ar), 147.5 (C, Ar), 144.9 (C, Ar), 136.2 (C, Ar), 129.2 (CH, Ar), 125.6 (CH, Ar), 125.4 (C, Ar), 123.5 (CH, Ar), 87.4 (CH, C=*C*-C=O), 68.5 (CH, C-N), 34.4 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 10.2 (CH_2, *c*-Pr), 9.3 (CH_2, *c*-Pr), 8.0 (CH, *c*-Pr); **IR** ν 3449, 2961, 1701 (C=O), 1517, 1343, 1234, 1108, 702 cm^{-1}; **HRMS** (ESI) m/z: 487.2201 $[M+Na]^+$, $C_{27}H_{32}N_2NaO_5^+$ requires 487.2203.

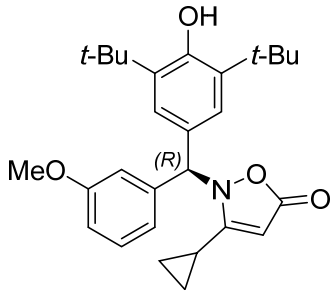
(*R*)-2-((2-Chlorophenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)-3-cyclopropylisoxazol-5(2*H*)-one (3eg).



From 12.5 mg of **1e** and 49.3 mg of **2g**, were obtained 34.8 mg (76%) of **3eg**. Enantiomeric excess (92%) was determined using chiral HPLC (Chiralpak AY-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 12.6 min, major enantiomer t_r = 14.1 min.

Yellow solid; **m.p.** = 124.4-125.2 ºC; **$[\alpha]_D^{25}$** = -5.6 (*c* = 1.16, $CHCl_3$, 92% ee); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.55-7.49 (1H, m, Ar), 7.42-7.36 (1H, m, Ar), 7.28-7.23 (2H, m, Ar), 7.03 (2H, s, Ar), 6.77 (1H, s, C*H*-N), 5.22 (1H, s, OH), 4.67 (1H, d, *J* = 0.6 Hz, C*H*COO), 1.74-1.66 (1H, m, *c*-Pr), 1.34 (18H, s, *t*-Bu), 1.11-1.02 (2H, m, *c*-Pr), 0.75-0.62 (2H, m, *c*-Pr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.1 (C, C=O), 170.1 (C, C=*C*-N), 153.7 (C, Ar), 135.9 (C, Ar), 135.1 (C, Ar), 133.3 (C, Ar), 130.5 (CH, Ar), 129.6 (CH, Ar), 129.5 (CH, Ar), 127.2 (CH, Ar), 126.2 (C, Ar), 124.7 (C, Ar), 84.5 (CH, C=*C*-C=O), 64.2 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 9.1 (CH_2, *c*-Pr), 8.8 (CH_2, *c*-Pr), 7.6 (CH, *c*-Pr); **IR** ν 3632, 2955, 1733 (C=O), 1582, 1431, 1235, 1161, 911, 752 cm^{-1}; **HRMS** (ESI) m/z: 476.1965 $[M+Na]^+$, $C_{27}H_{32}ClNNaO_3^+$ requires 476.1963.

(*R*)-3-cyclopropyl-2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(3-methoxyphenyl)methyl)isoxazol-5(2*H*)-one (3ei).

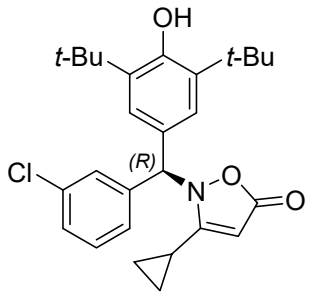


From 12.5 mg of **1e** and 48.7 mg of **2i**, were obtained 36.7 mg (82%) of **3ei**. Enantiomeric excess (82%) was determined using chiral HPLC (Chiralpak AY-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 19.8 min, major enantiomer t_r = 28.5 min.

White solid; **m.p.** = 56.1-57.1 ºC; **$[\alpha]_D^{25}$** = + 5.8 (*c* = 1.22, $CHCl_3$, 82% ee); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.30-7.23 (1H, m, Ar), 7.08 (2H, s, Ar), 6.93-6.84 (3H, m, Ar), 6.24 (1H, s, C*H*-N), 5.27 (1H, s, OH), 4.68 (1H, d, *J* = 0.6 Hz, C*H*COO), 3.78 (3H, s, MeO), 1.73-1.64 (1H, m, *c*-Pr), 1.39 (18H, s, *t*-Bu), 1.14-1.08 (2H, m, *c*-Pr), 0.84-0.70 (2H, m, *c*-Pr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.2 (C, C=O), 171.1 (C, C=*C*-N), 159.6 (C, Ar), 153.7 (C, Ar), 138.8 (C, Ar), 135.8 (C, Ar), 129.4 (CH, Ar), 126.7 (C, Ar), 125.4 (CH, Ar), 120.7 (CH, Ar), 114.1 (CH, Ar), 113.4 (CH, Ar), 85.8 (CH, C=*C*-C=O), 68.7 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 9.5 (CH_2, *c*-Pr), 9.2 (CH_2, *c*-Pr), 7.9 (CH, *c*-Pr);

IR ν 3630, 2955, 1716 (C=O), 1578, 1433, 1049, 784, 771 cm^{-1}; **HRMS** (ESI) m/z: 472.2459 $[M+Na]^+$, $C_{28}H_{35}NNaO_4^+$ requires 472.2458.

(*R*)-2-((3-Chlorophenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)-3-cyclopropylisoxazol-5(2*H*)-one (3ej).



From 12.5 mg of **1e** and 49.3 mg of **2j**, were obtained 35.3 mg (78%) of **3ej**. Enantiomeric excess (88%) was determined using chiral HPLC (Chiralpak AD-H), hexane/*i*-PrOH 90:10, 1 mL/min. Minor enantiomer t_r = 11.3 min, major enantiomer t_r = 13.3 min.

White solid; **m.p.** = 57.1-58.8 ºC; $[\alpha]_D^{25}$ = + 22.4 (*c* = 1.18, $CHCl_3$, 88% ee); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.26-7.36 (1H, m, Ar), 7.30-7.24 (3H, m, Ar), 7.05 (2H, s, Ar), 6.22 (1H, s, C*H*-N), 5.30 (1H, s, OH), 4.69 (1H, d, *J* = 0.6 Hz, C*H*COO), 1.74-1.64 (1H, m, *c*-Pr), 1.39 (18H, s, *t*-Bu), 1.19-1.10 (2H, m, *c*-Pr), 0.84-0.77 (1H, m, *c*-Pr), 0.74-0.68 (1H, m, *c*-Pr); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.5 (C, C=O), 171.1 (C, C=*C*-N), 153.9 (C, Ar), 139.5 (C, Ar), 135.9 (C, Ar), 134.3 (C, Ar), 129.6 (CH, Ar), 128.4 (CH, Ar), 128.2 (CH, Ar), 126.5 (CH, Ar), 126.0 (C, Ar), 125.5 (CH, Ar), 86.5 (CH, C=*C*-C=O), 68.3 (CH, C-N), 34.3 (C, *t*-Bu), 30.2 (CH_3, *t*-Bu), 9.9 (CH_2, *c*-Pr), 9.2 (CH_2, *c*-Pr), 7.9 (CH, *c*-Pr); **IR** ν 3449, 2950, 1720 (C=O), 1597, 1414, 1116, 930, 777 cm^{-1}; **HRMS** (ESI) m/z: 476.1965 $[M+Na]^+$, $C_{27}H_{32}ClNNaO_3^+$ requires 476.1963.

Synthesis of compound 3ea at 1 mmol scale.

In a round bottom flask charged with the *para*-quinone methide **2a** (441.7 mg, 1.5 mmol) and the isoxazolin-5-one **1e** (125.1 mg, 1 mmol) is added 3Å MS (320 mg) and the thiourea **V** (37 mg, 10 mol %). Then 1,2-dichloroethane (10 mL) is added and the mixture is allowed to stir at rt for 24 hours. Then, the reaction is purified by flash column chromatography obtaining 297.9 mg (71%) of **3ea** (86% ee).

References

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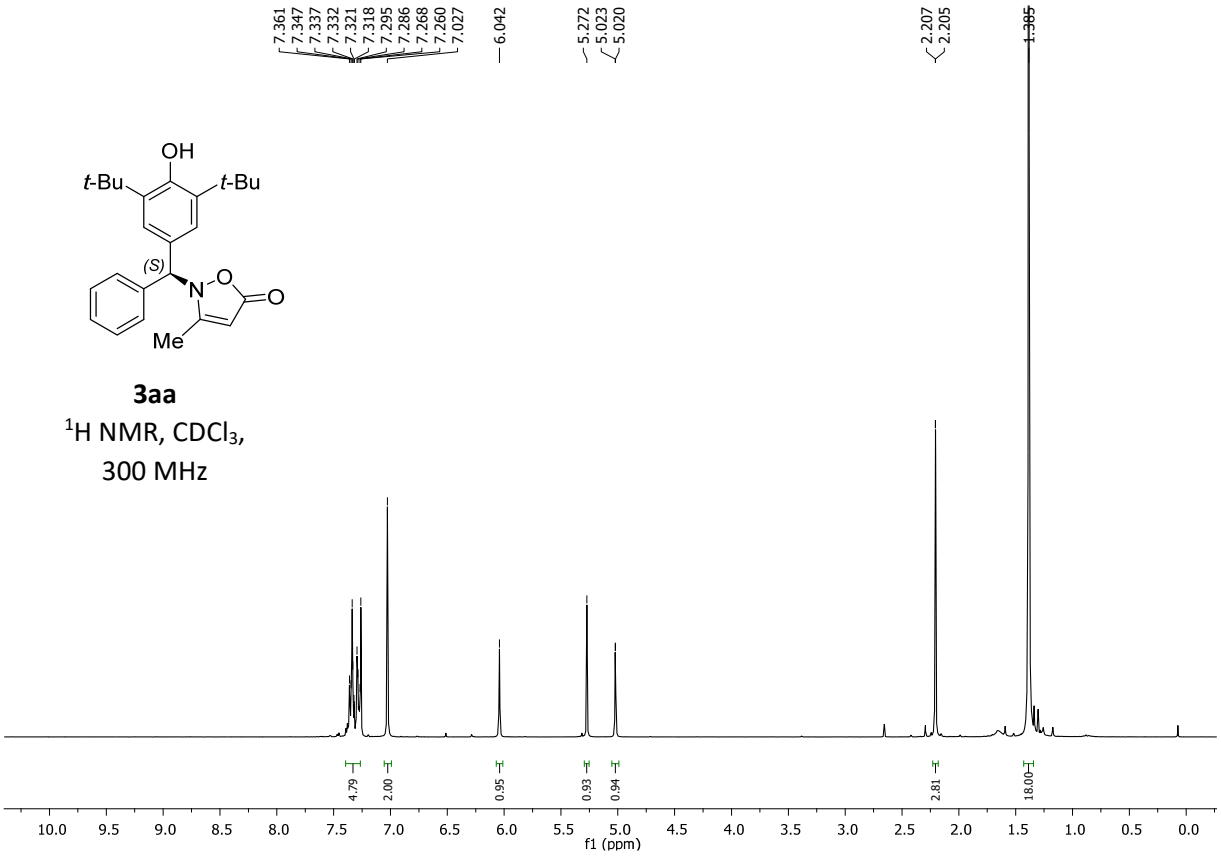
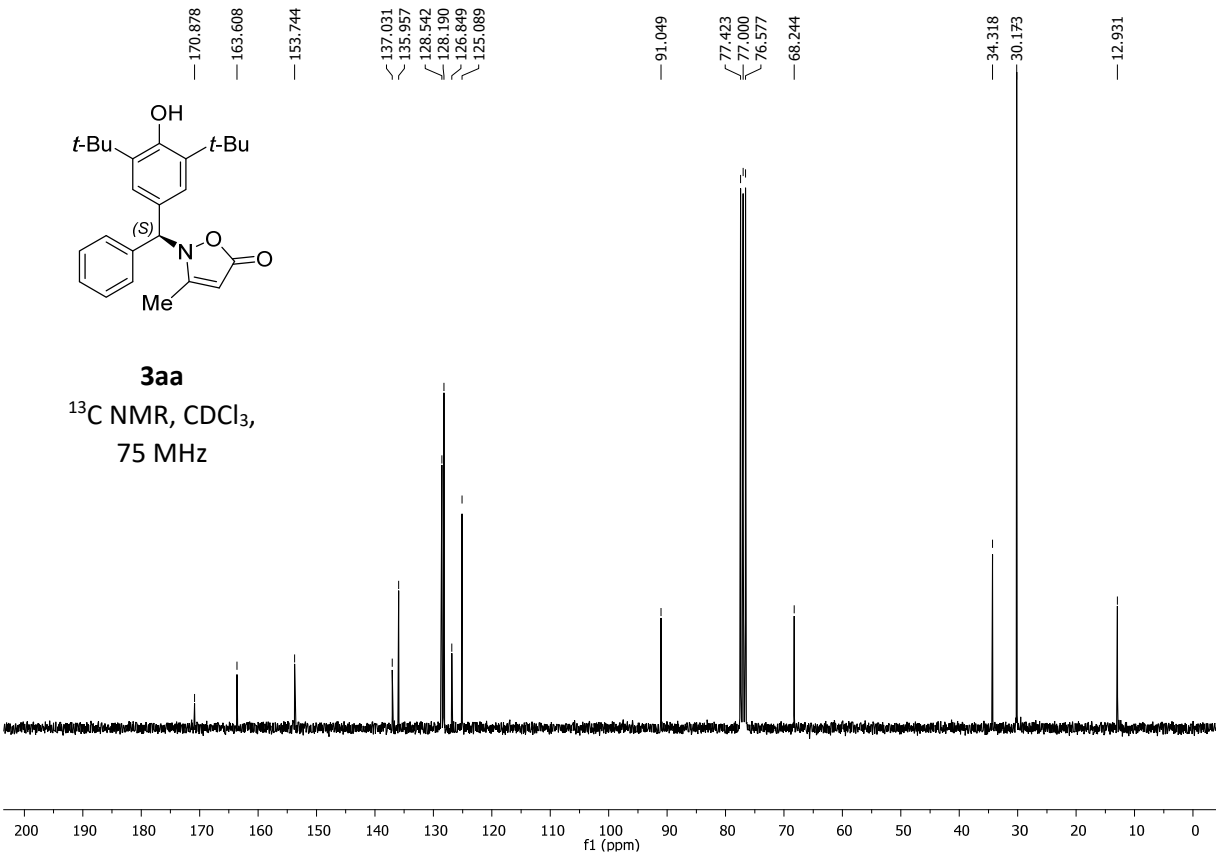
[6] B. Xiong, G. Wang, C. Zhou, Y. Liu, W. Xu, W. Xu, C. Yang, K. Tang *Eur. J. Org. Chem.* **2019**, *2019*, 3273-3282.



3aa

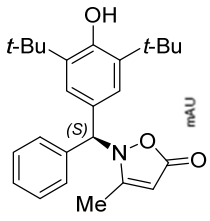
^{1}H NMR, $CDCl_3$,
300 MHz

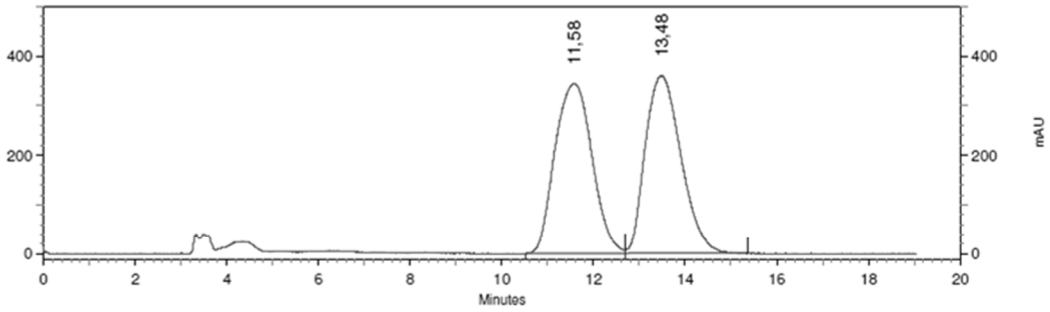


3aa

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

Compound **3aa**





3: 270 nm, 4 nm Results

Retention Time	Area	Area Percent
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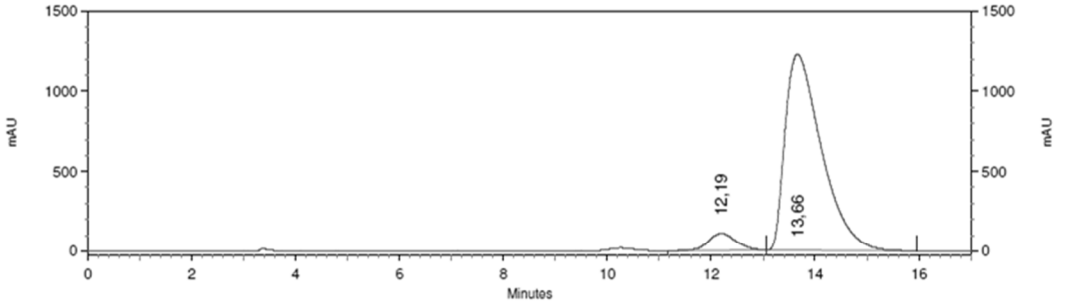
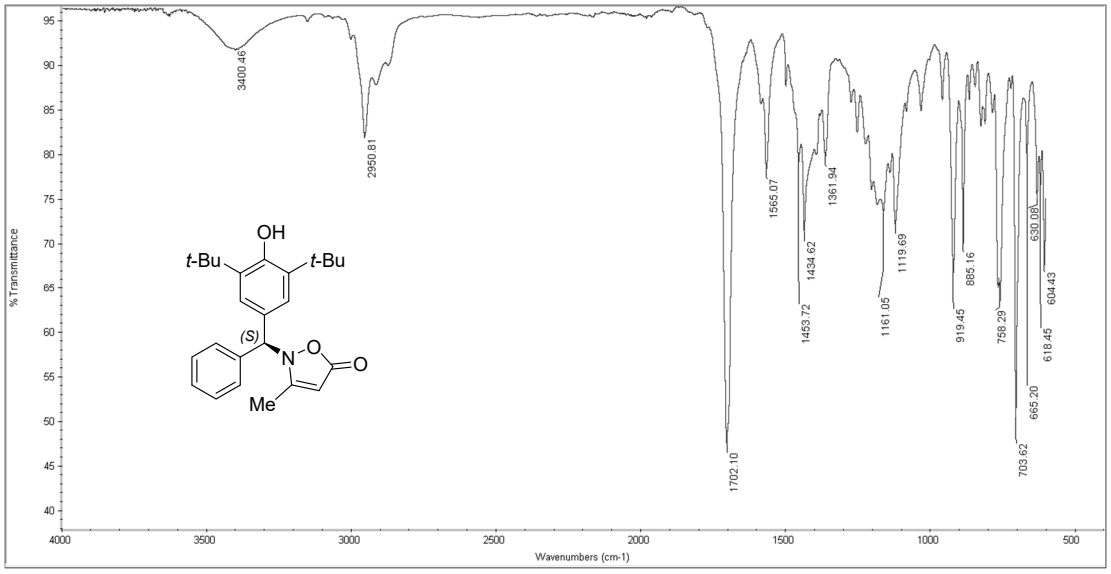
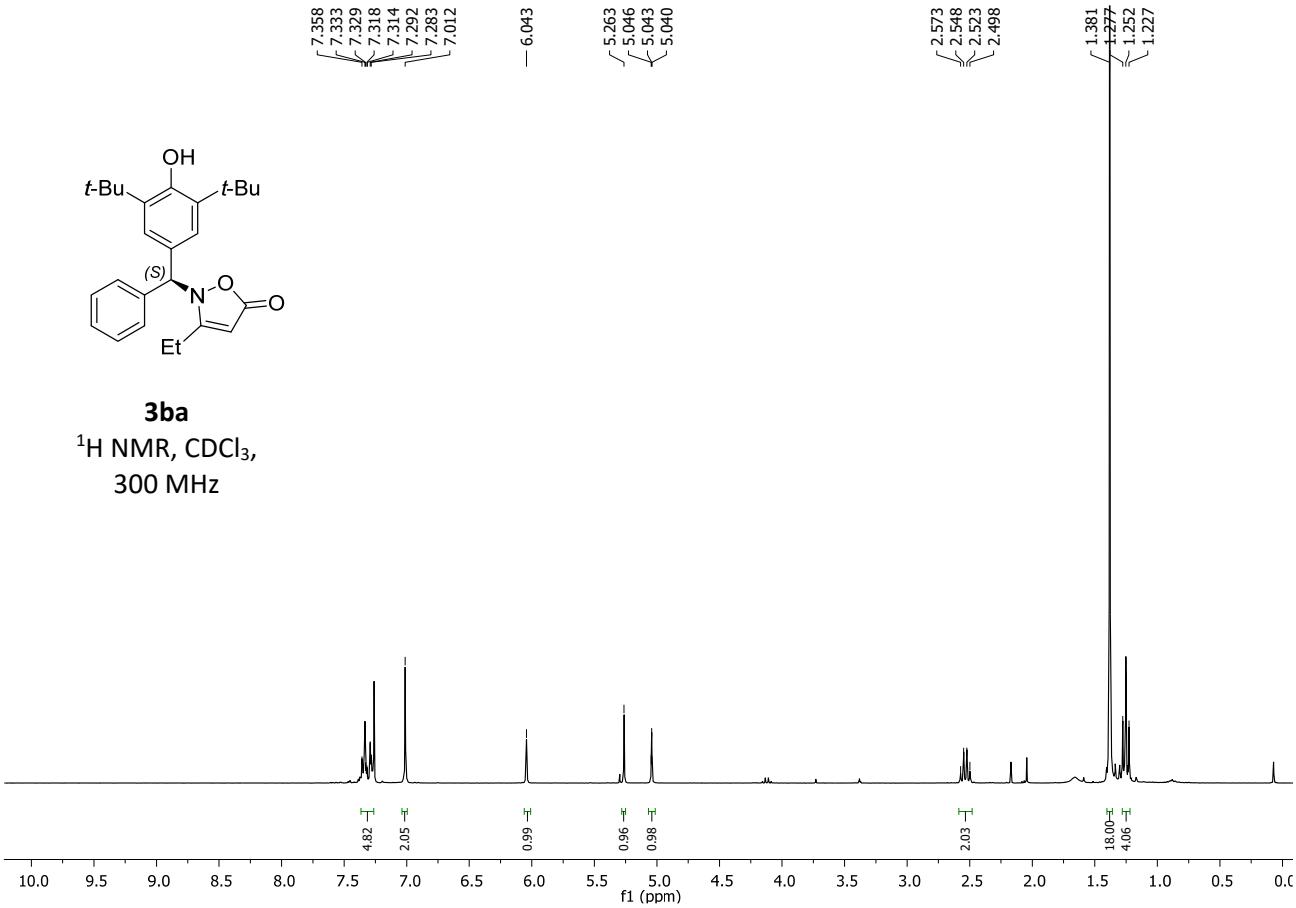
13,48	77907582	50,159



14: 270 nm, 4 nm Results

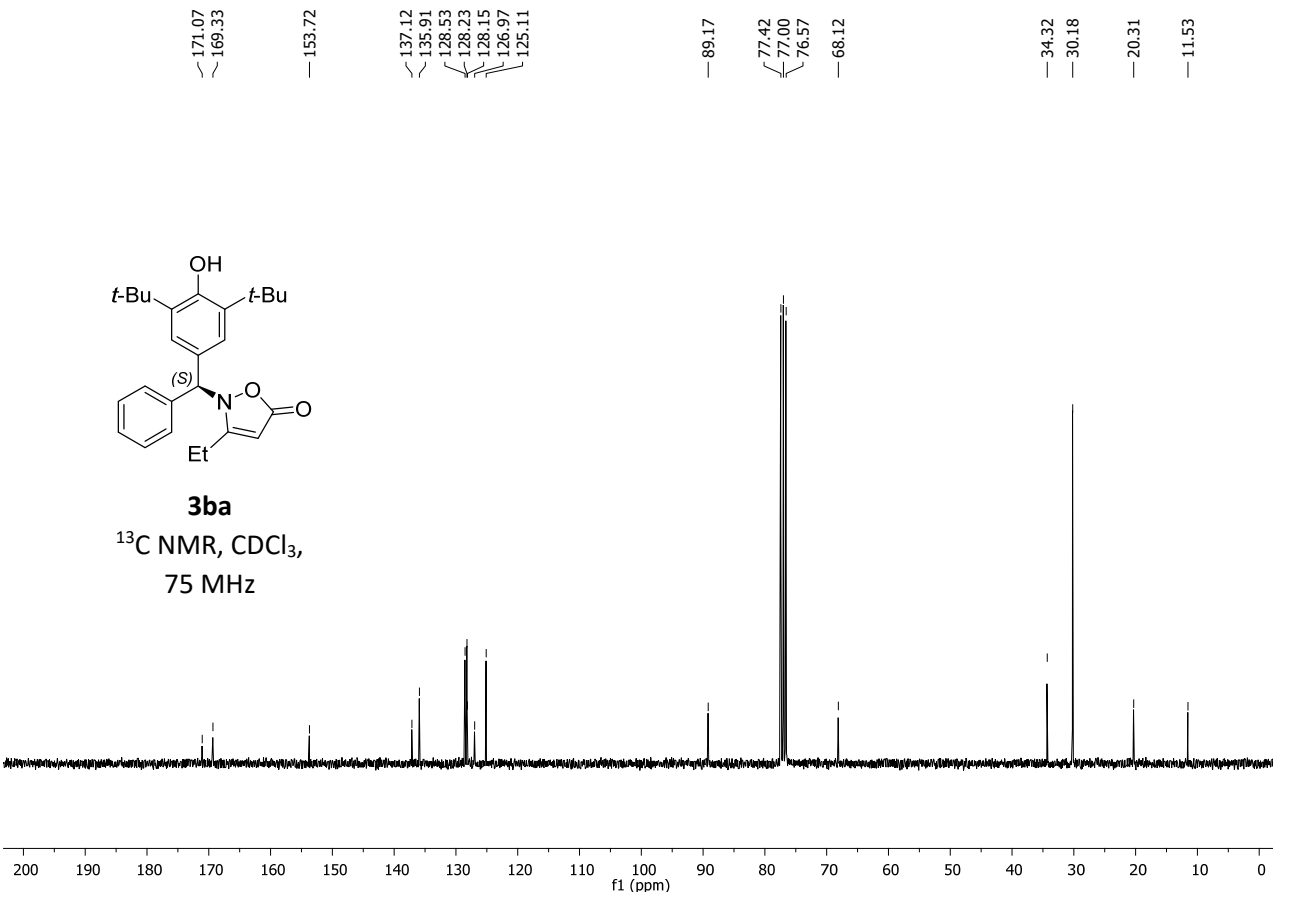
Retention Time	Area	Area Percent
12,19	16368611	6,395
13,66	239602039	93,605





3ba

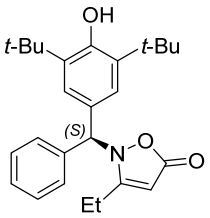
^{1}H NMR, $CDCl_3$,
300 MHz

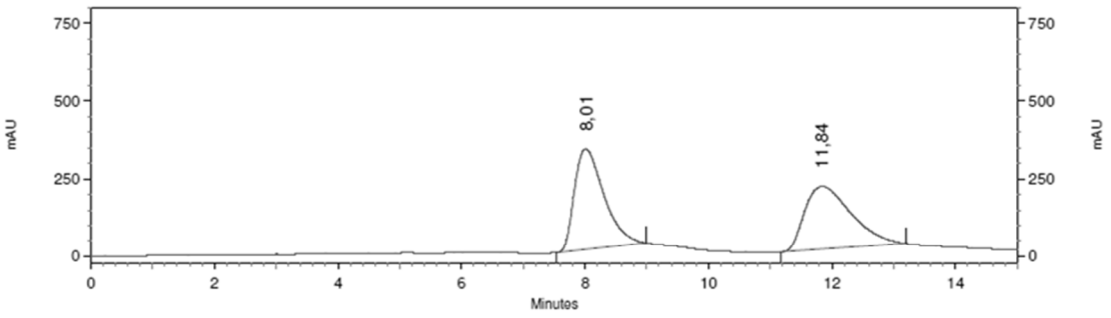


3ba

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

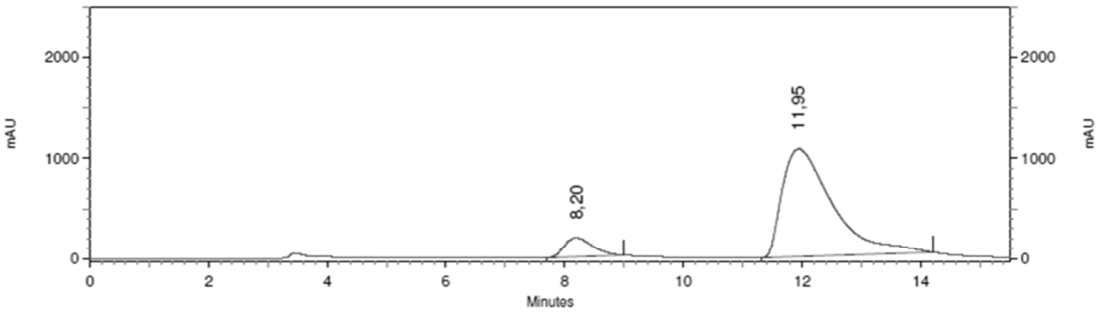
Compound **3ba**





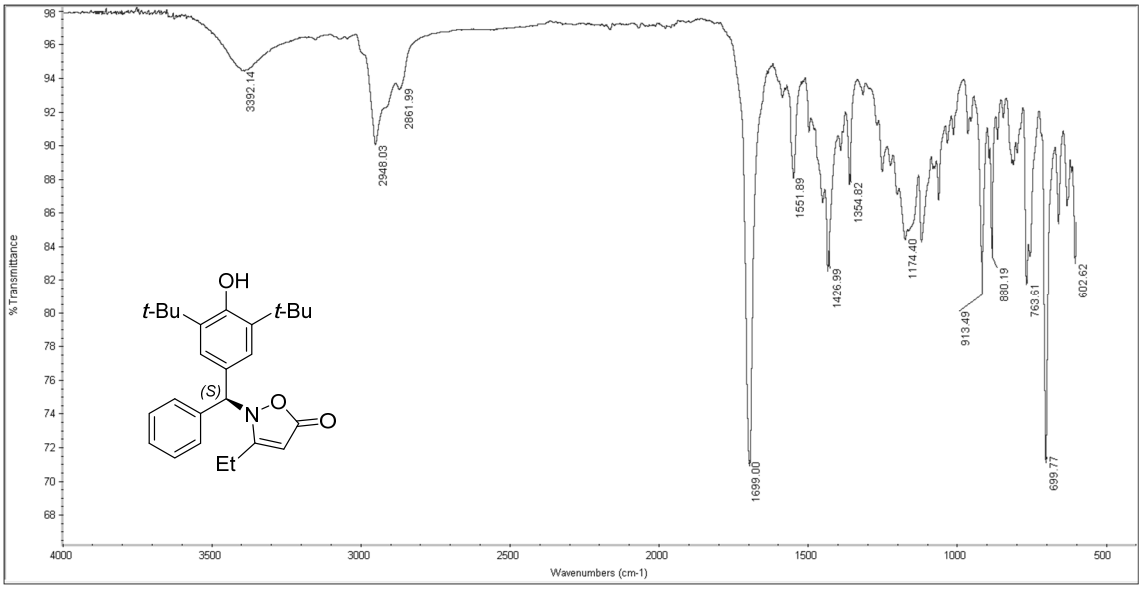
16: 270 nm, 4 nm
Results

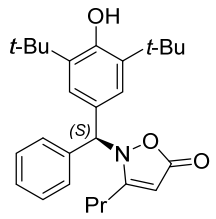
Retention Time	Area	Area Percent
8,01	43247732	50,334
11,84	42674261	49,666



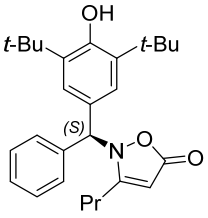
16: 270 nm, 4 nm
Results

Retention Time	Area	Area Percent
8,20	25262223	9,092
11,95	252588836	90,908



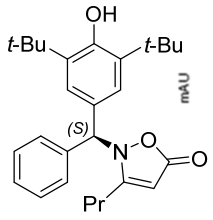


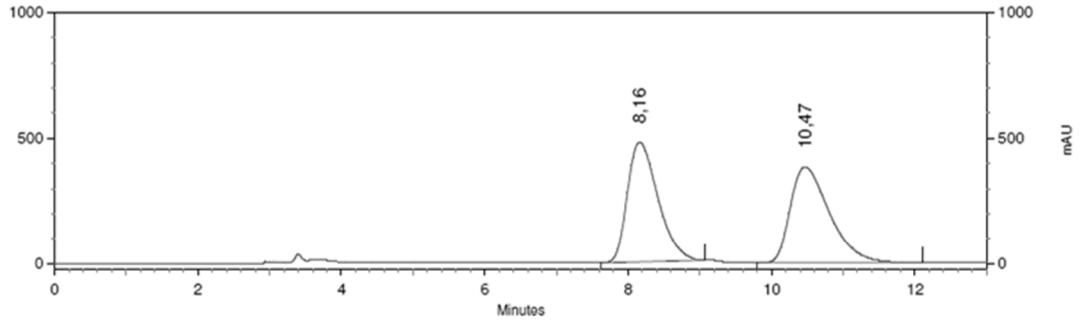
3ca
^{1}H NMR, $CDCl_3$,
300 MHz



3ca
^{13}C NMR, $CDCl_3$,
75 MHz

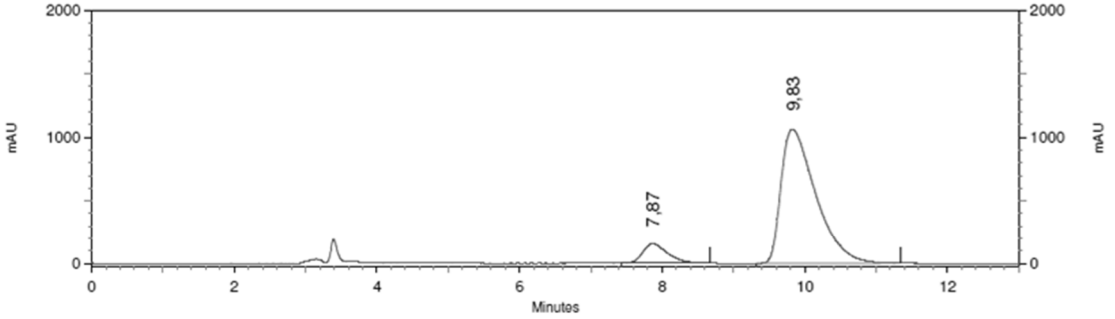
Compound **3ca**





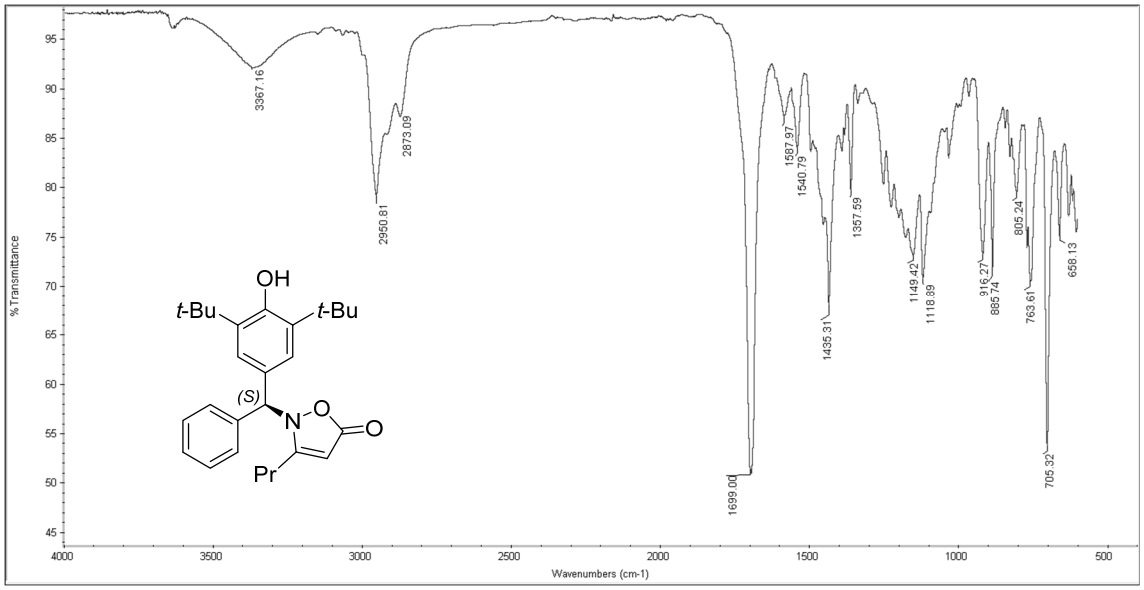
16: 283 nm, 4 nm
Results

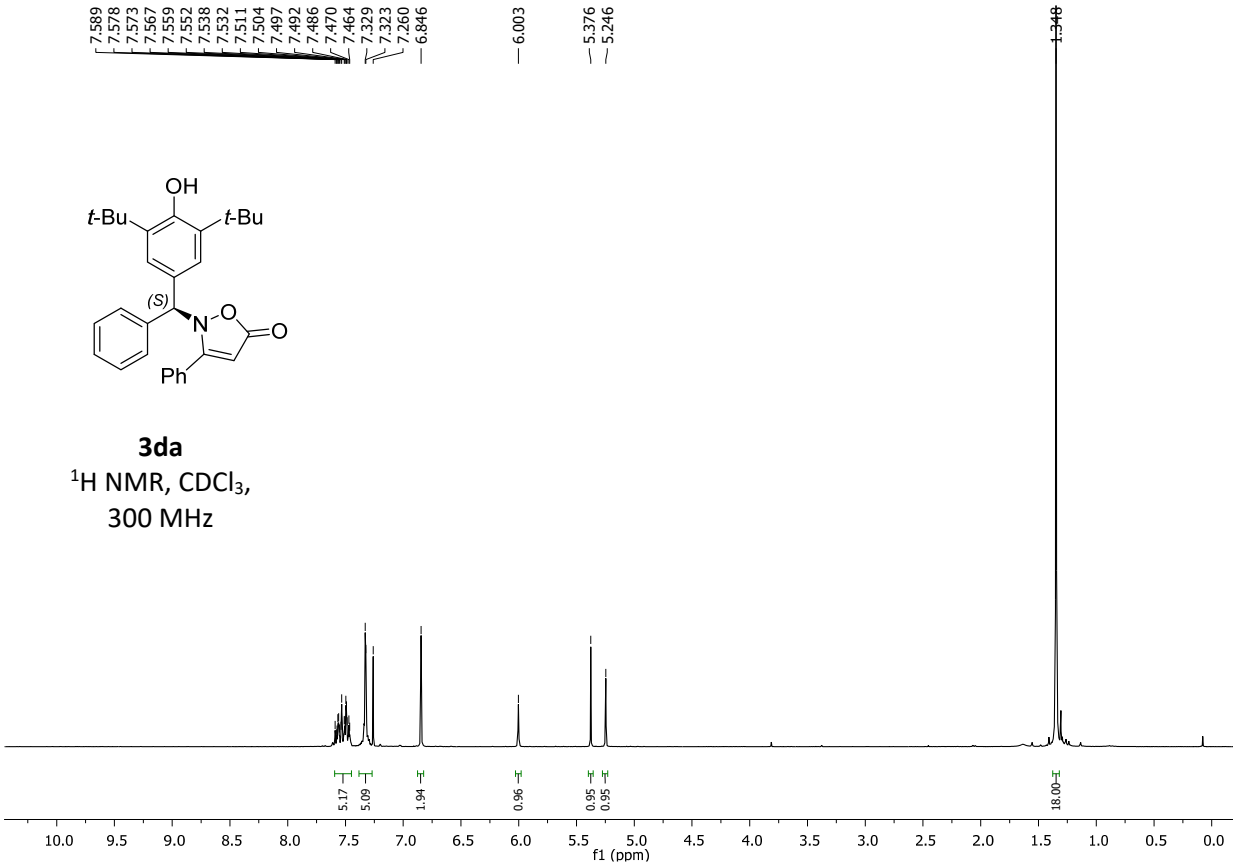
Retention Time	Area	Area Percent
8,16	56847636	49,281
10,47	58505396	50,719



16: 283 nm, 4 nm
Results

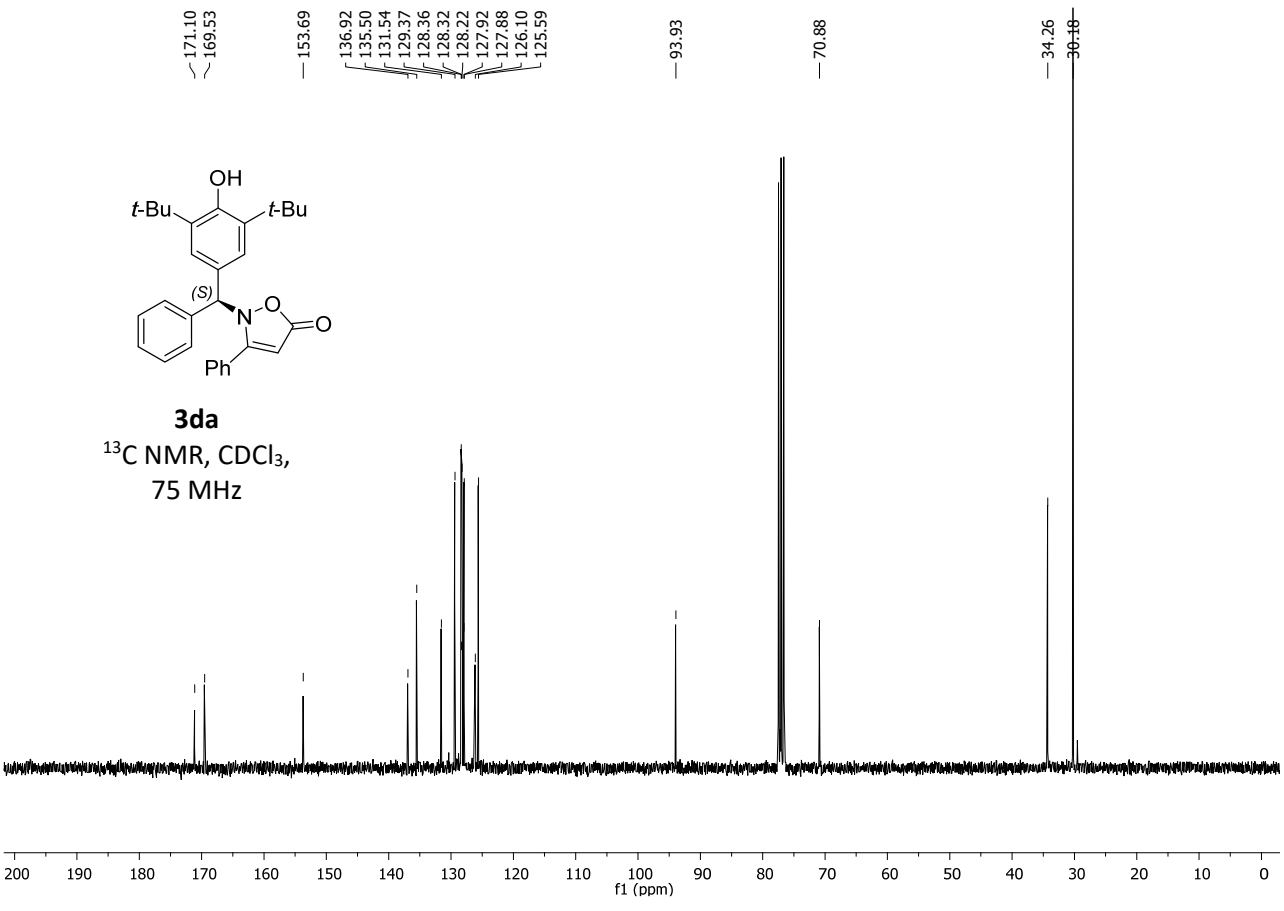
Retention Time	Area	Area Percent
7,87	14895881	9,357
9,83	144305084	90,643





3da

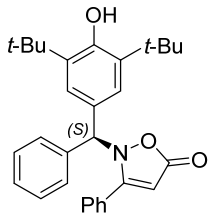
^{1}H NMR, $CDCl_3$,
300 MHz

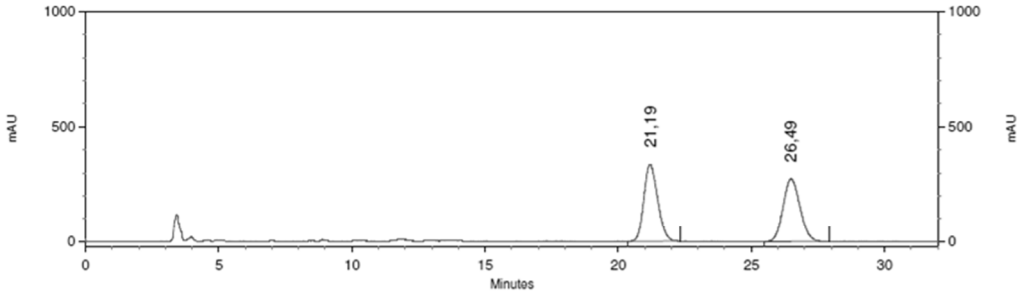


3da

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

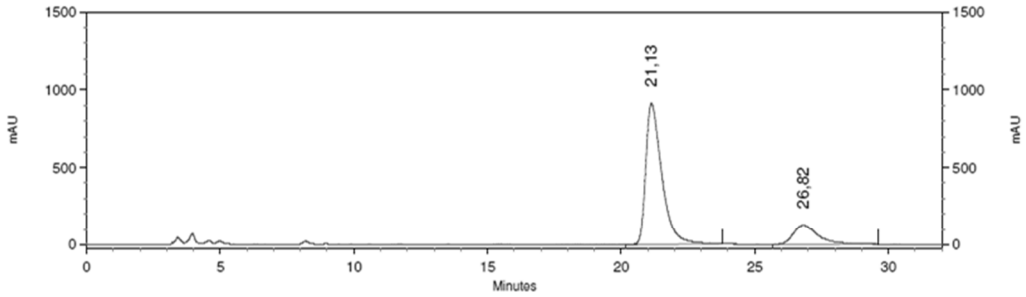
Compound **3da**





17: 270 nm, 4 nm
Results

Retention Time	Area	Area Percent
21,19	48706139	49,953
26,49	48797798	50,047



17: 270 nm, 4 nm
Results

Retention Time	Area	Area Percent
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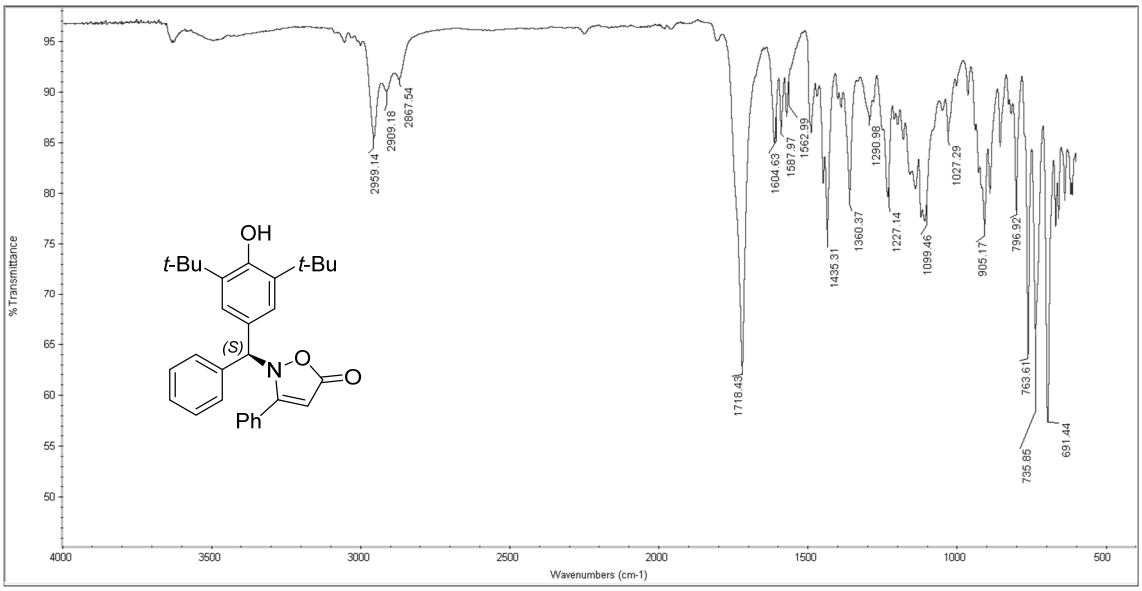
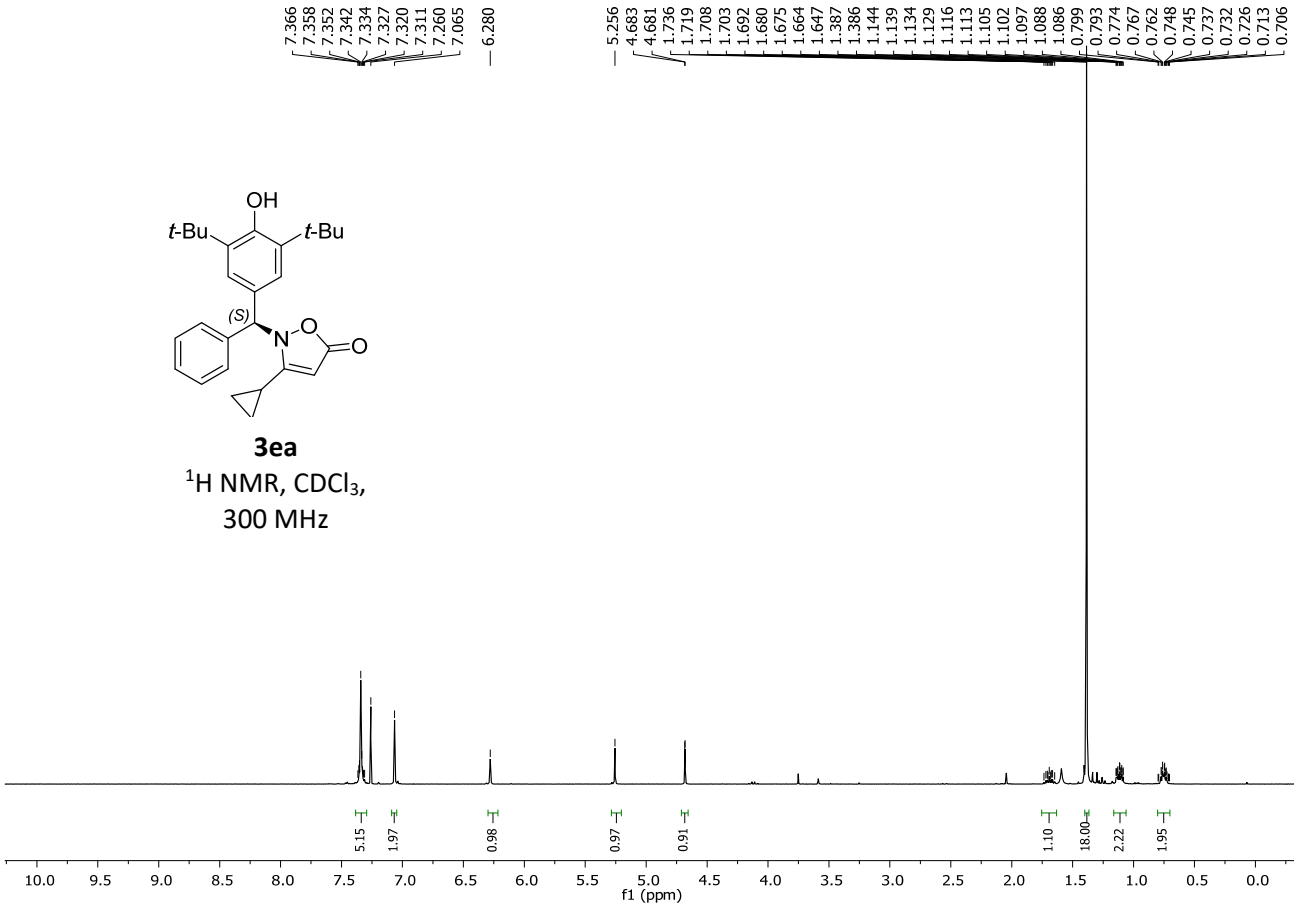
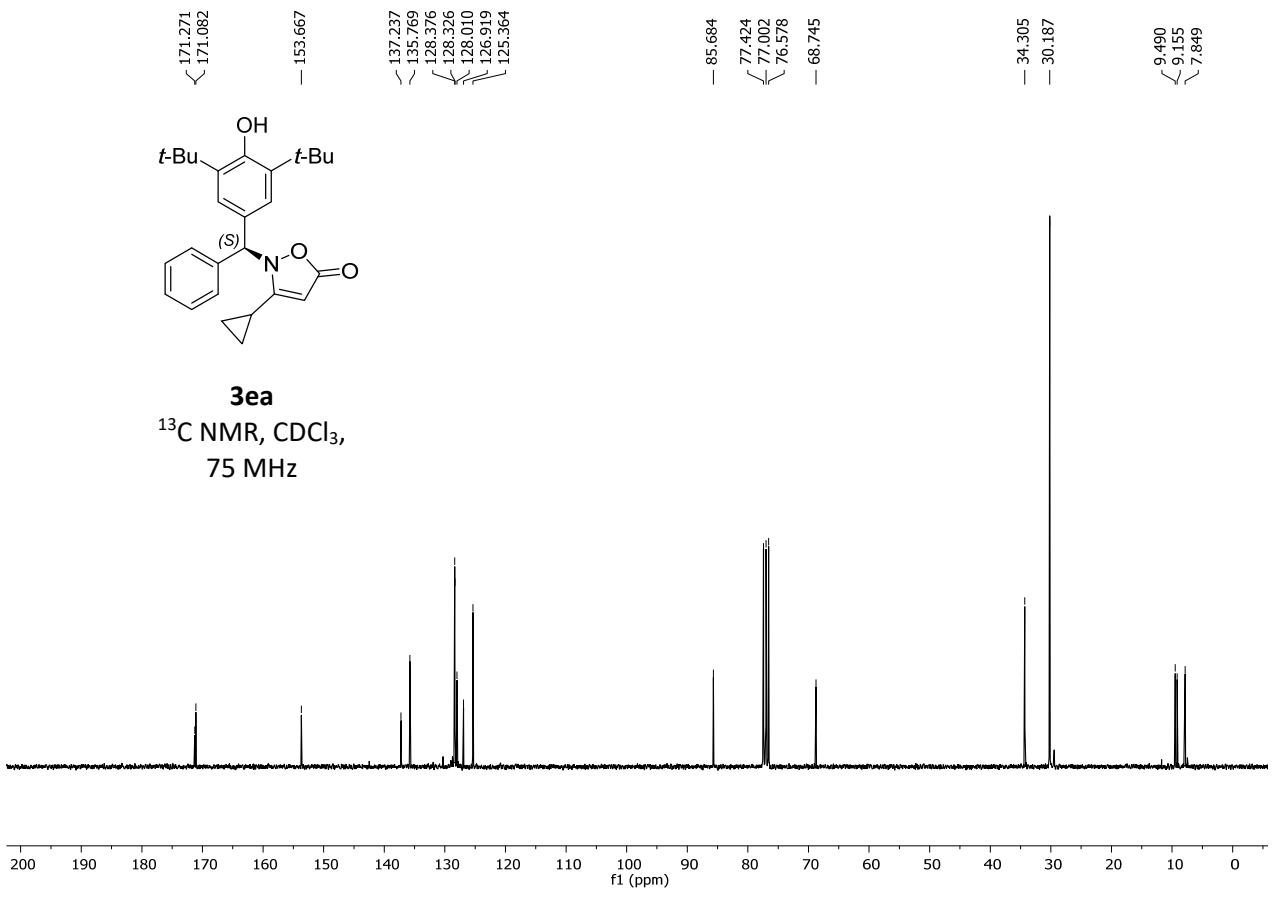
26,82	32690420	17,635





3ea

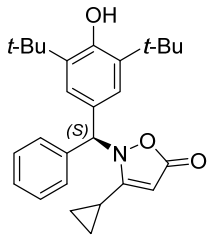
^{1}H NMR, $CDCl_3$,
300 MHz

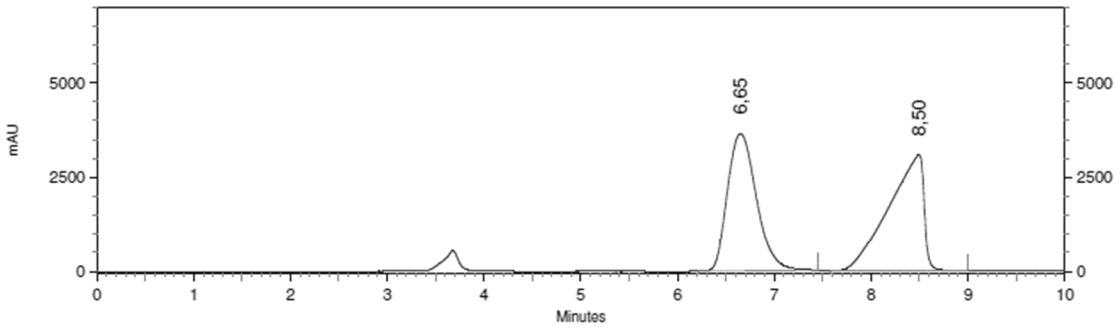


3ea

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

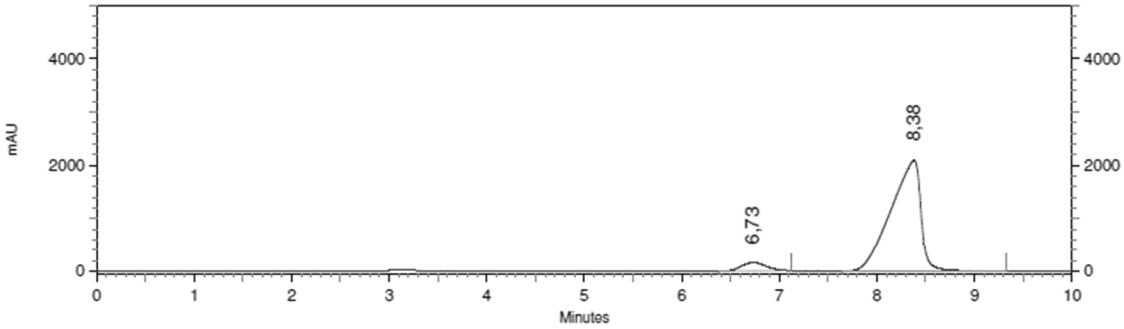
Compound **3ea**





1: 275 nm, 4 nm Results

Retention Time	Area	Area Percent
6,65	304608804	49,278
8,50	313539565	50,722



1: 275 nm, 4 nm Results

Retention Time	Area	Area Percent
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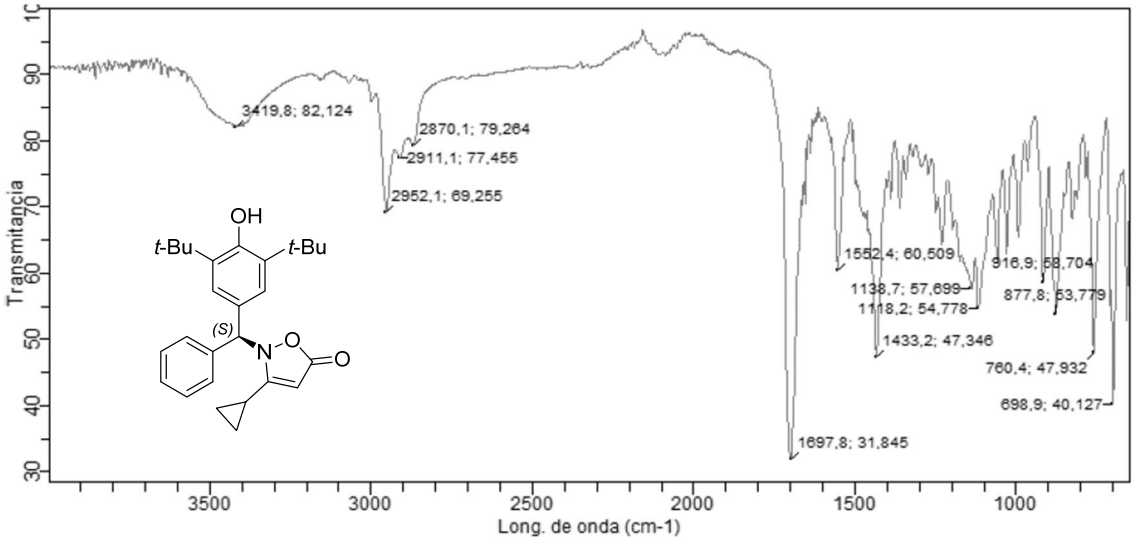
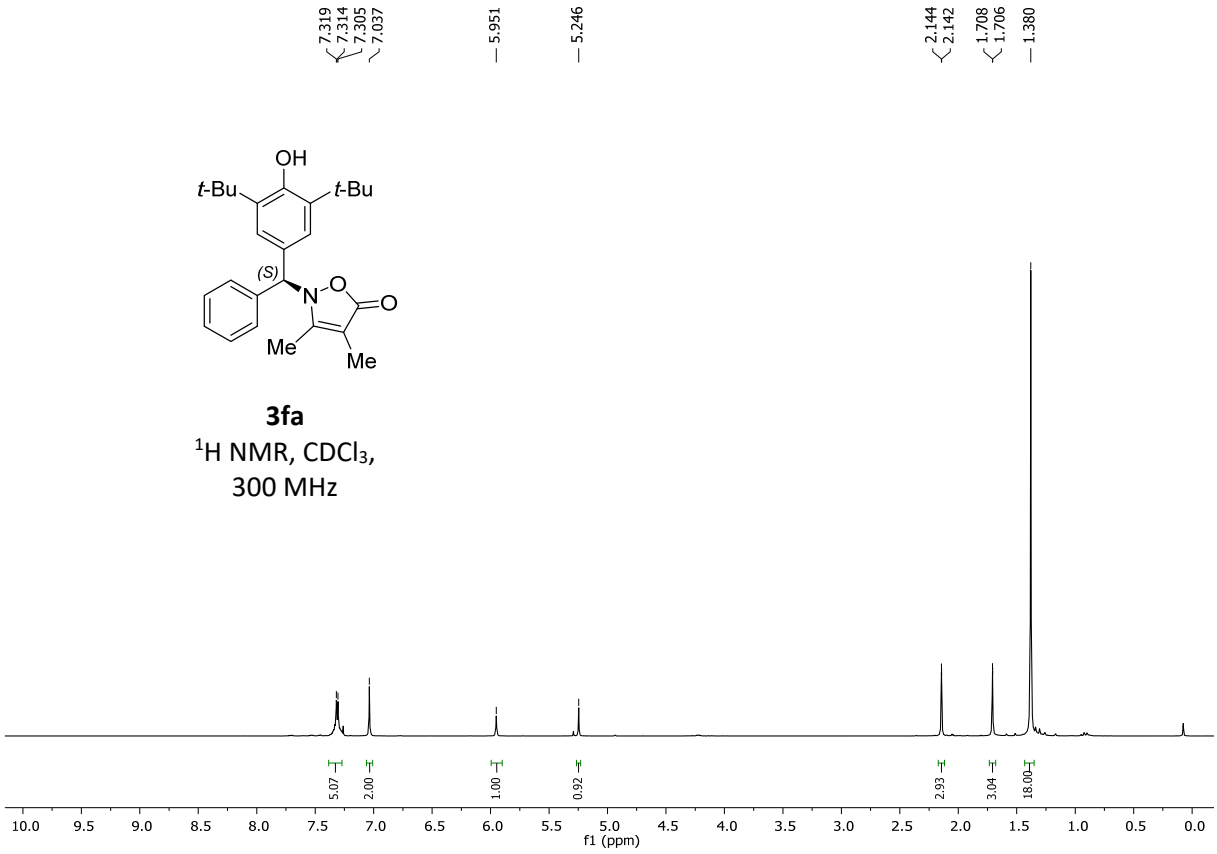
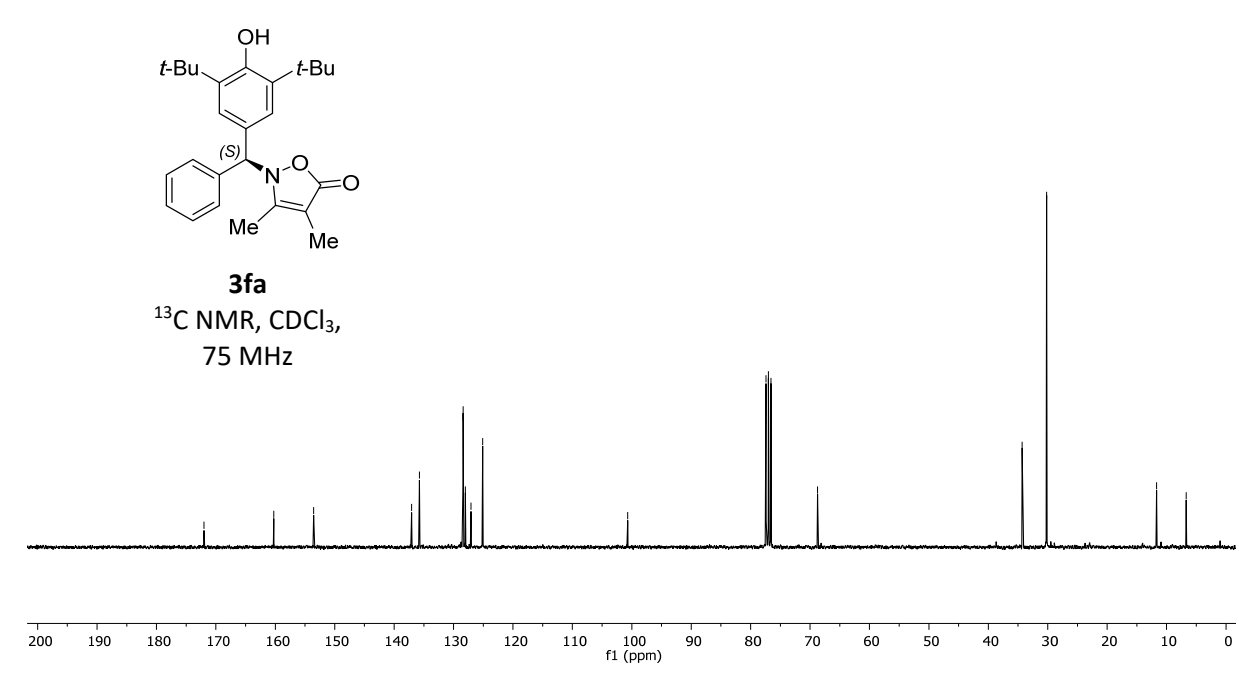
8,38	179611657	94,338





3fa

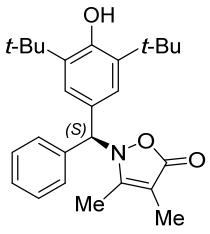
^{1}H NMR, $CDCl_3$,
300 MHz

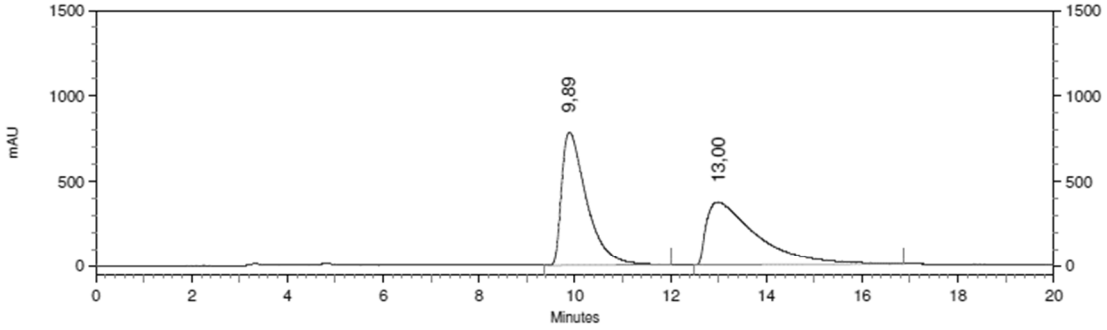


3fa

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

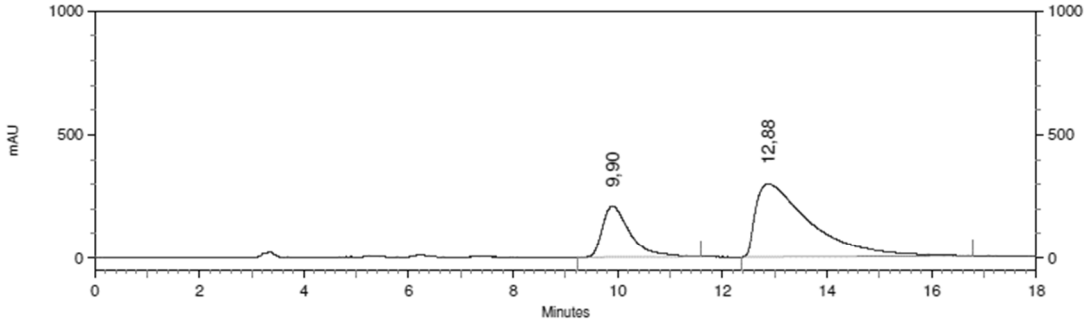
Compound **3fa**





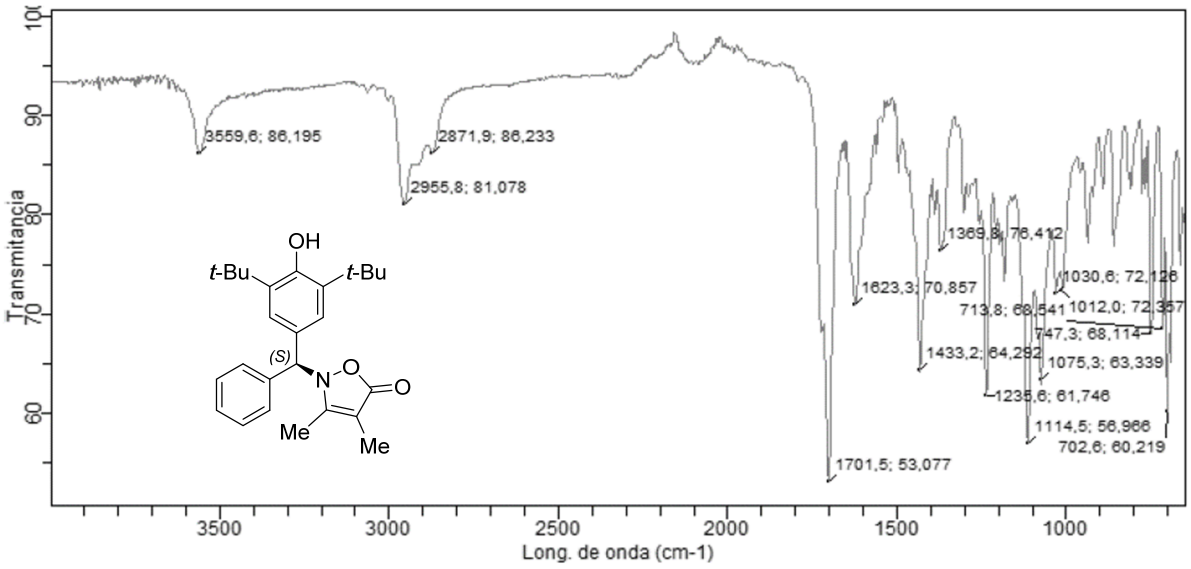
18: 270 nm, 4 nm
Results

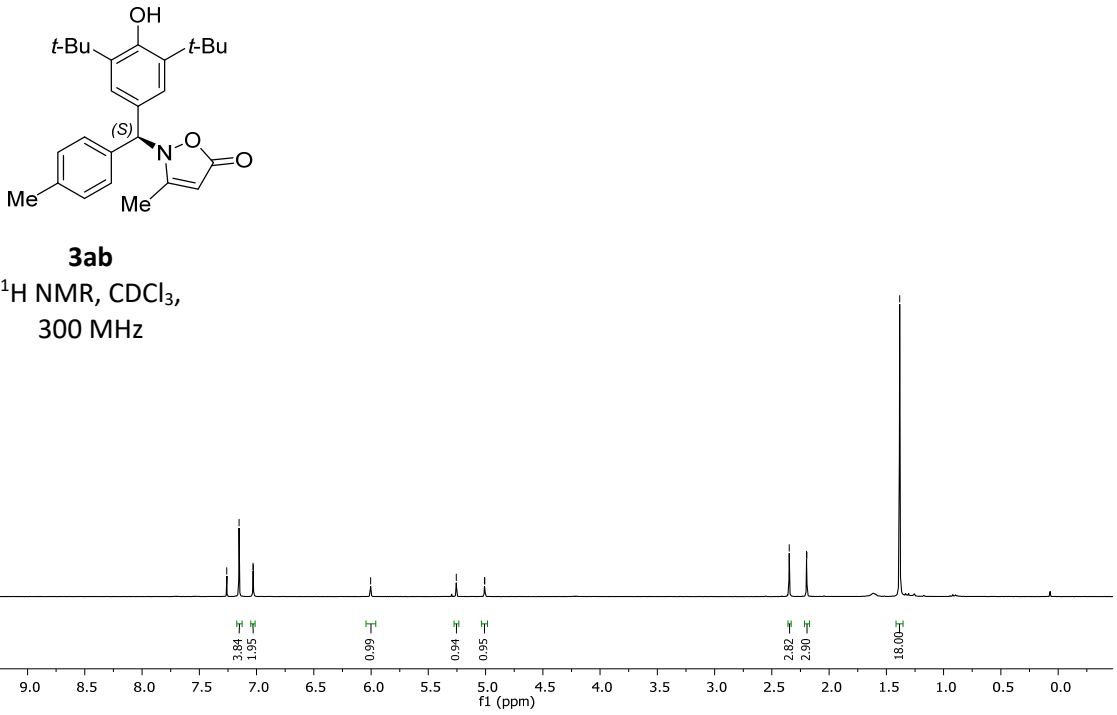
Retention Time	Area	Area Percent
9,89	114302447	51,103
13,00	109368629	48,897



18: 270 nm, 4 nm
Results

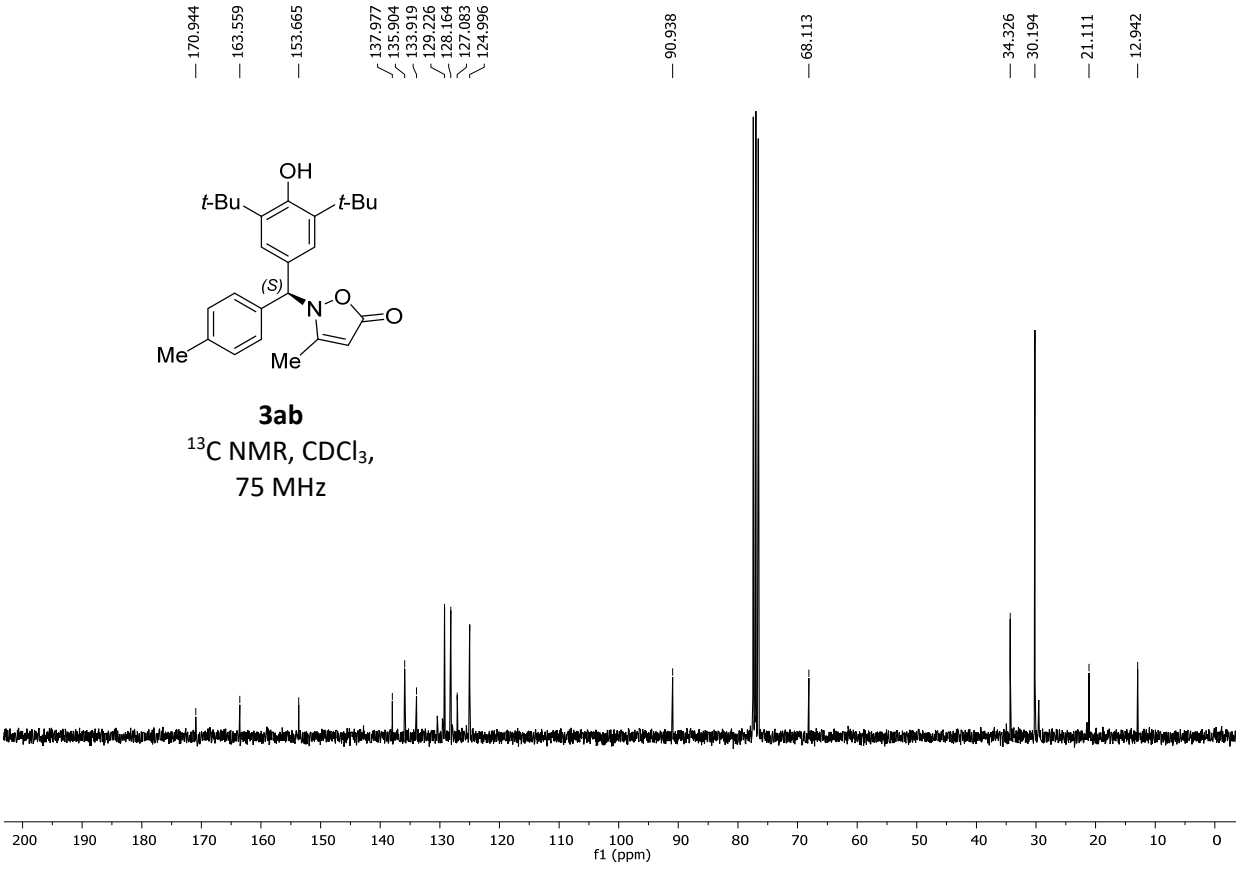
Retention Time	Area	Area Percent
9,90	30926669	26,268
12,88	86808559	73,732





3ab

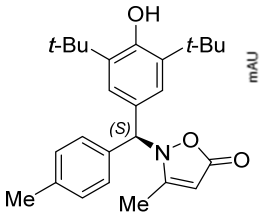
^{1}H NMR, $CDCl_3$,
300 MHz

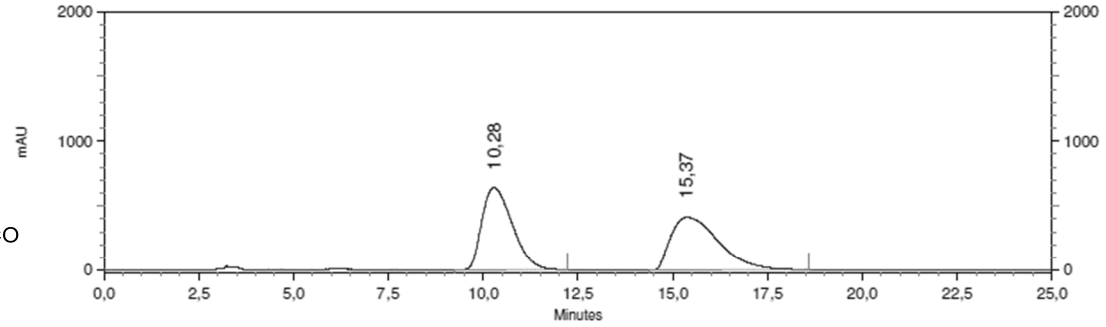


3ab

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

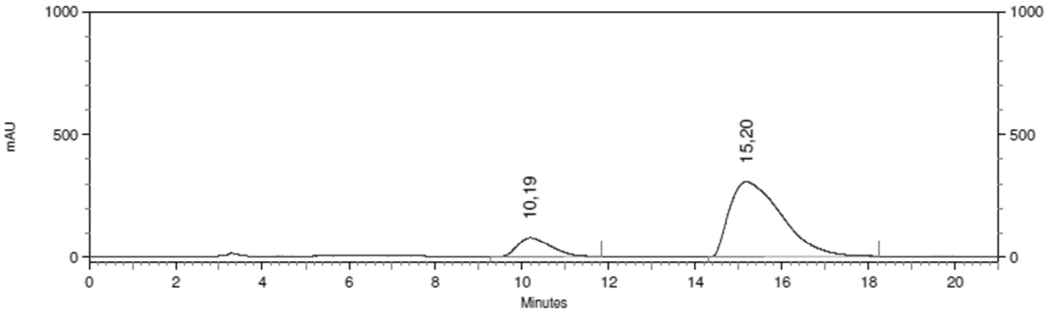
Compund **3ab**





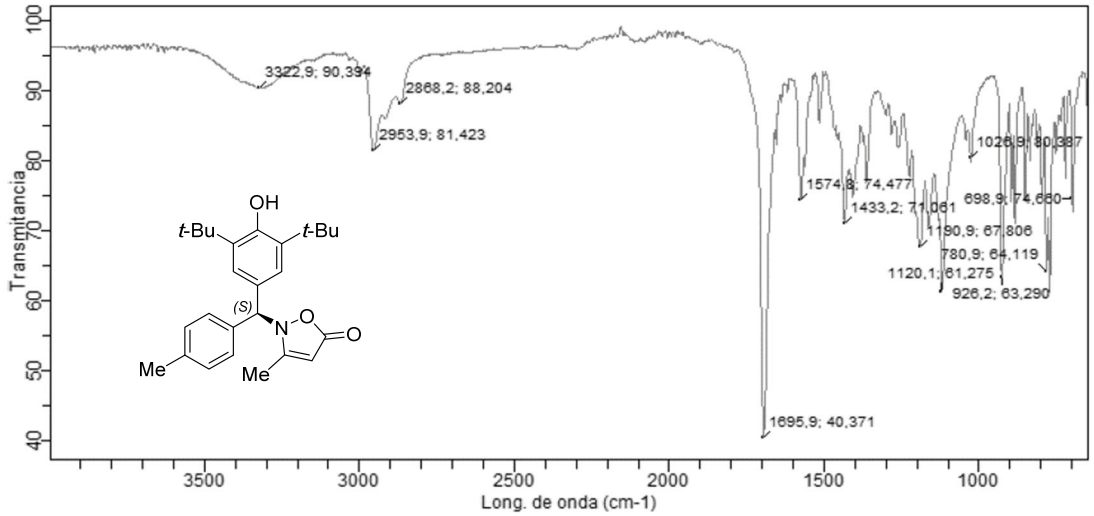
18: 270 nm, 4 nm
Results

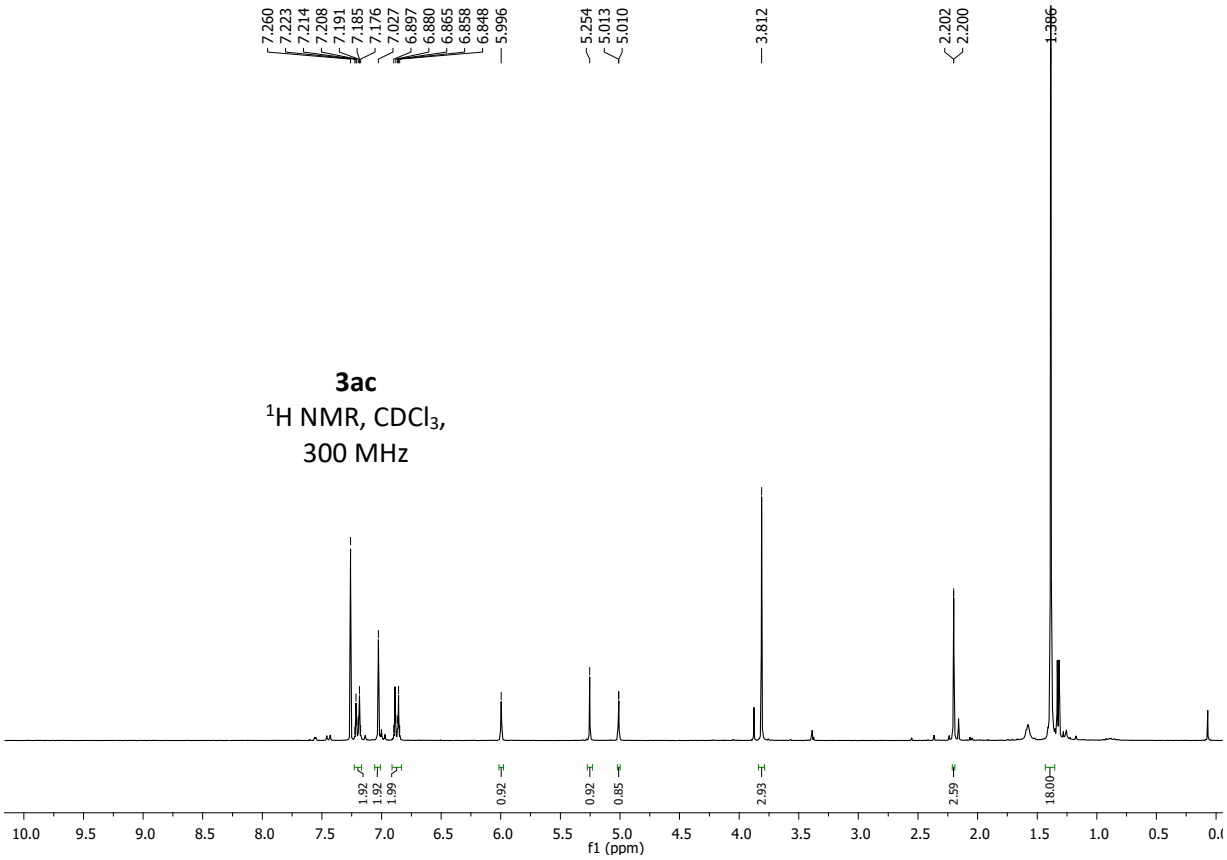
Retention Time	Area	Area Percent
10,28	143460399	49,892
15,37	144083176	50,108



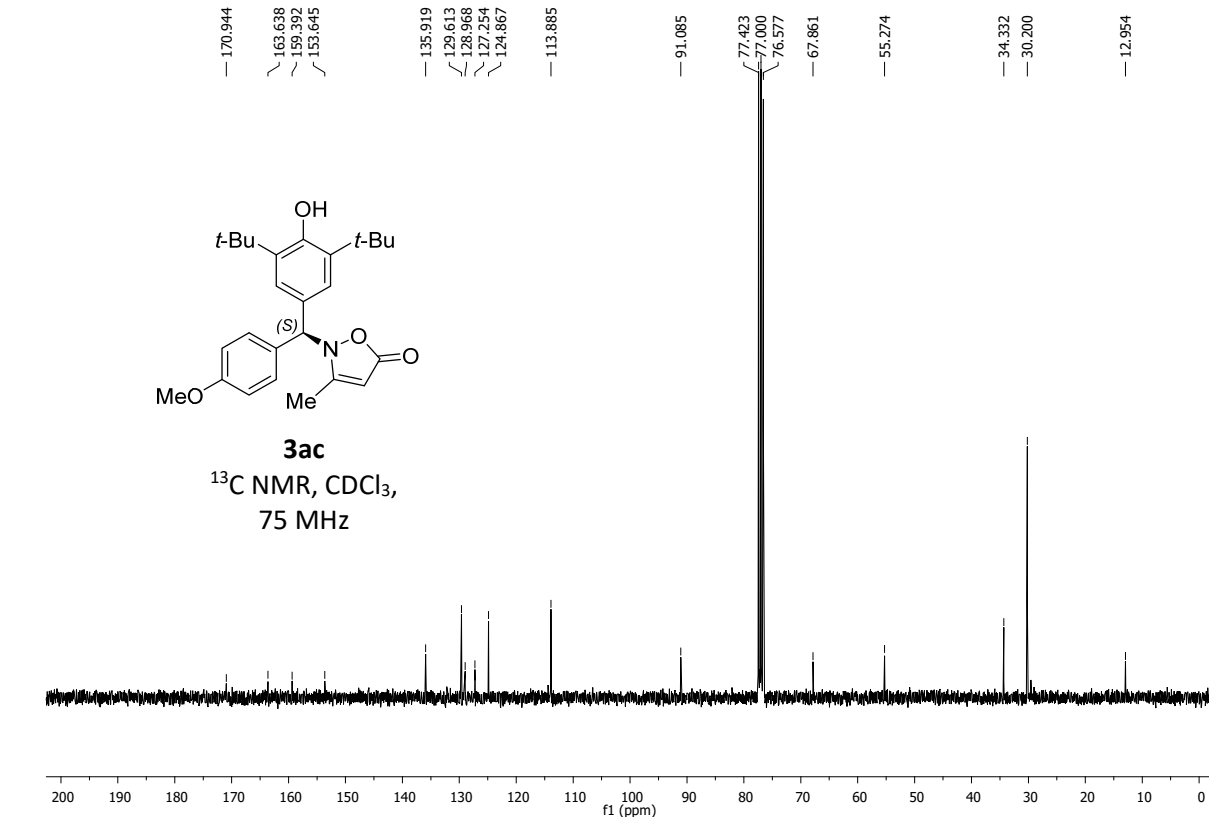
18: 270 nm, 4 nm
Results

Retention Time	Area	Area Percent
10,19	16823885	14,027
15,20	103112216	85,973



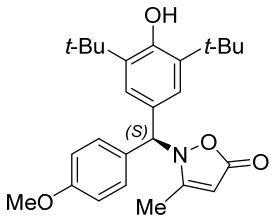


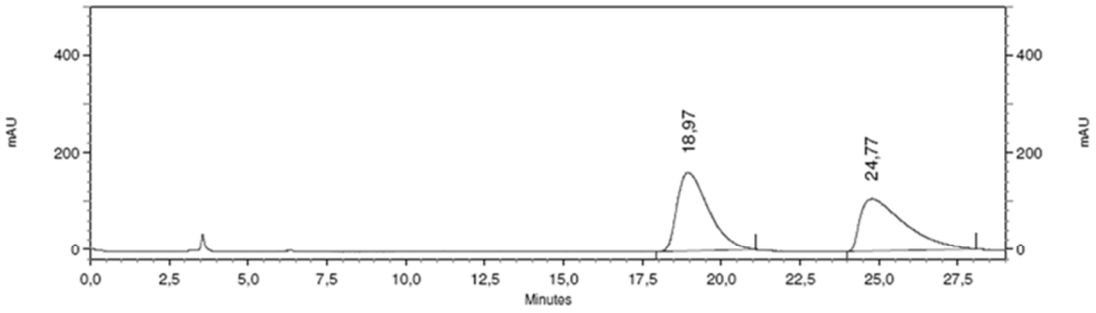
3ac
^{1}H NMR, $CDCl_3$,
300 MHz



3ac
^{13}C NMR, $CDCl_3$,
75 MHz

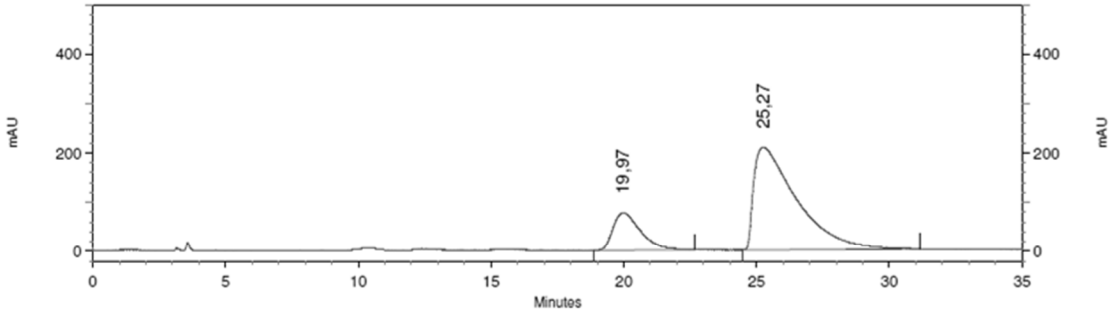
Compound **3ac**





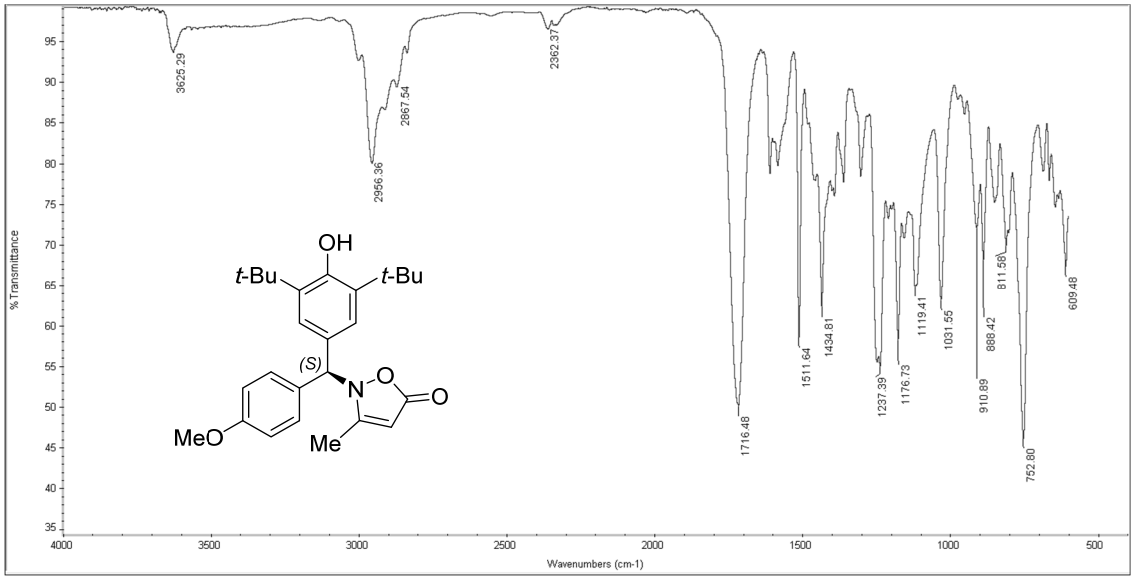
15: 270 nm, 4 nm
Results

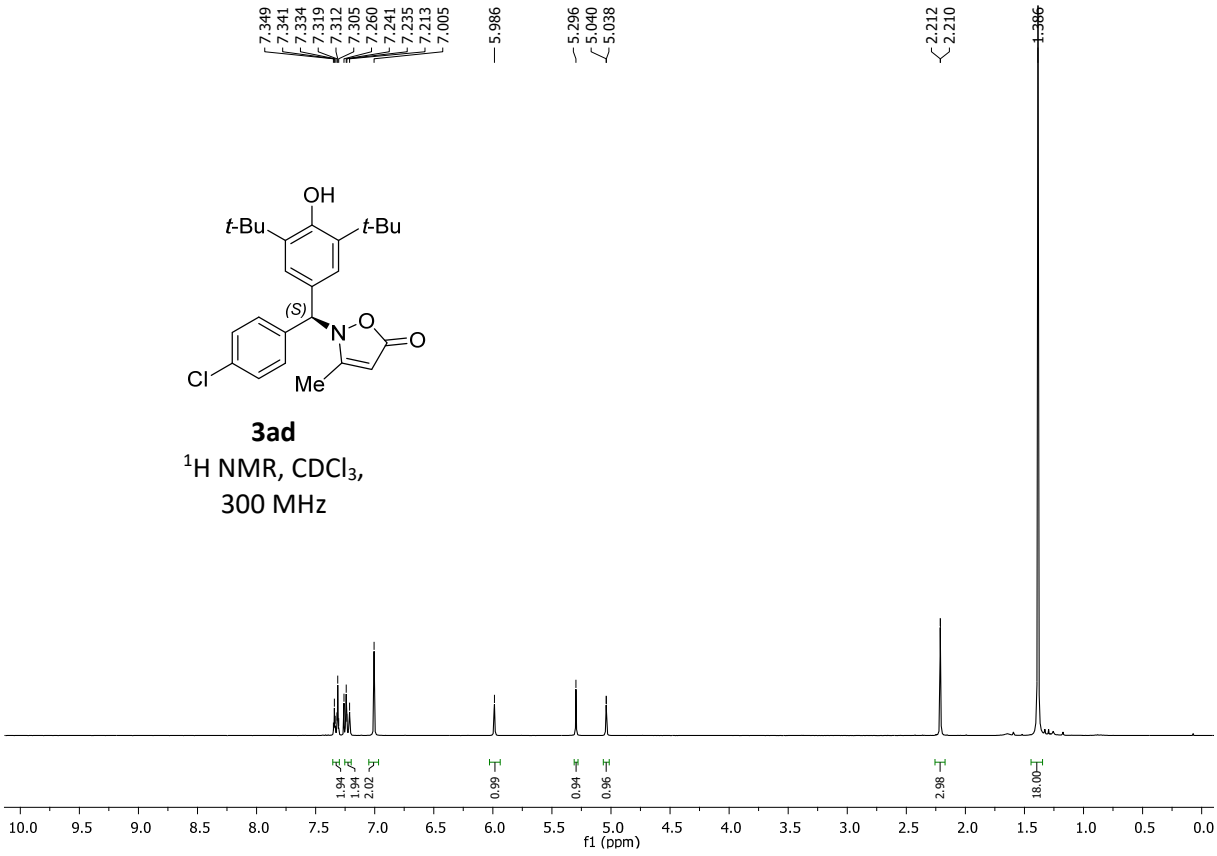
Retention Time	Area	Area Percent
18,97	45269687	51,239
24,77	43079988	48,761



16: 270 nm, 4 nm
Results

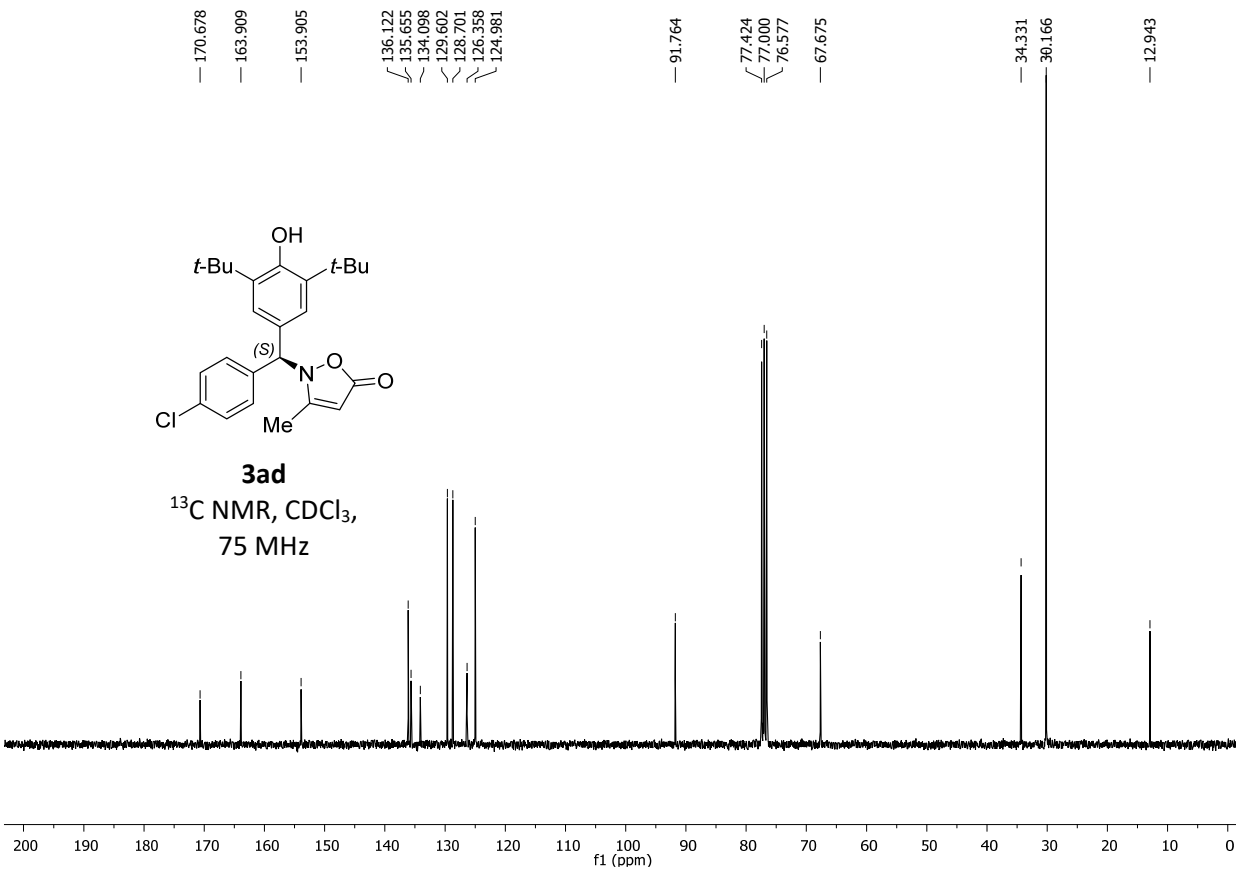
Retention Time	Area	Area Percent
19,97	22493896	19,125
25,27	95122539	80,875





3ad

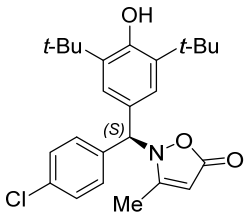
^{1}H NMR, $CDCl_3$,
300 MHz

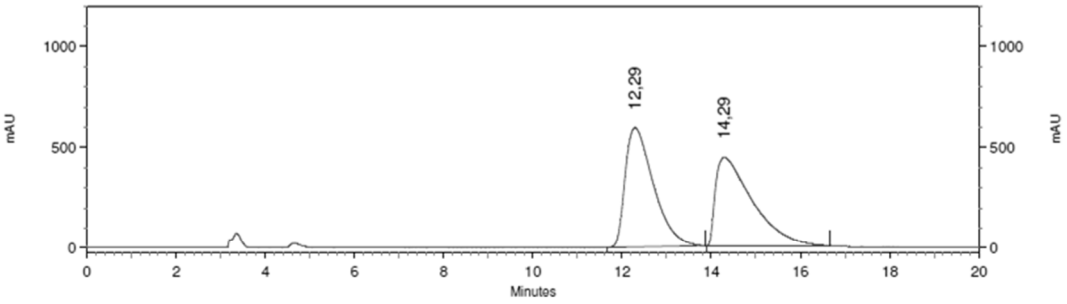


3ad

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

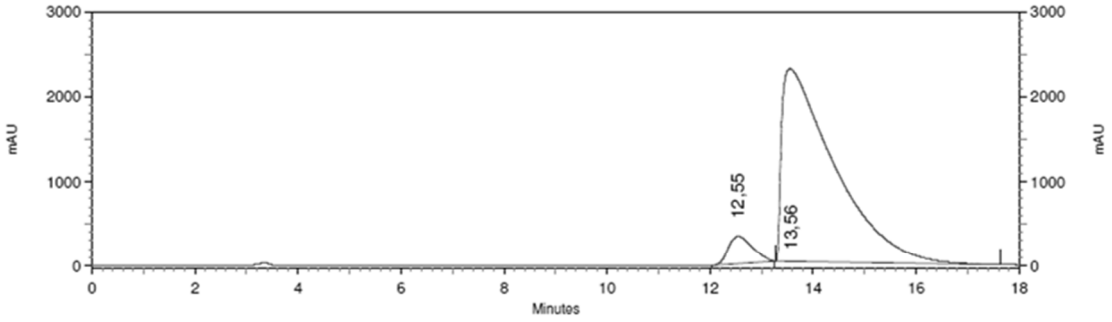
Compound **3ad**





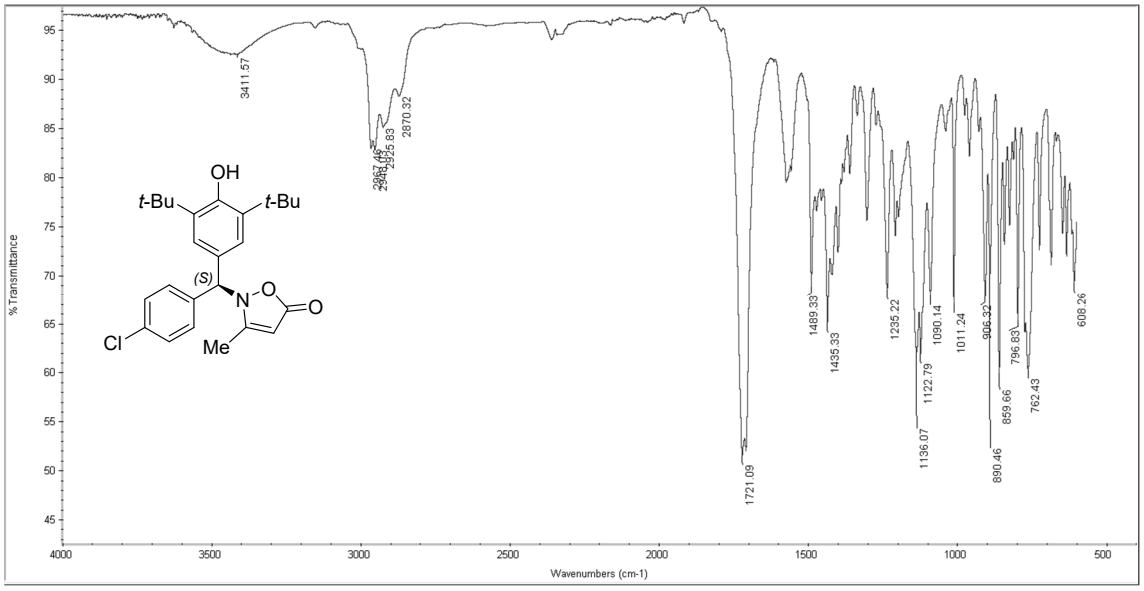
15: 270 nm, 4 nm
Results

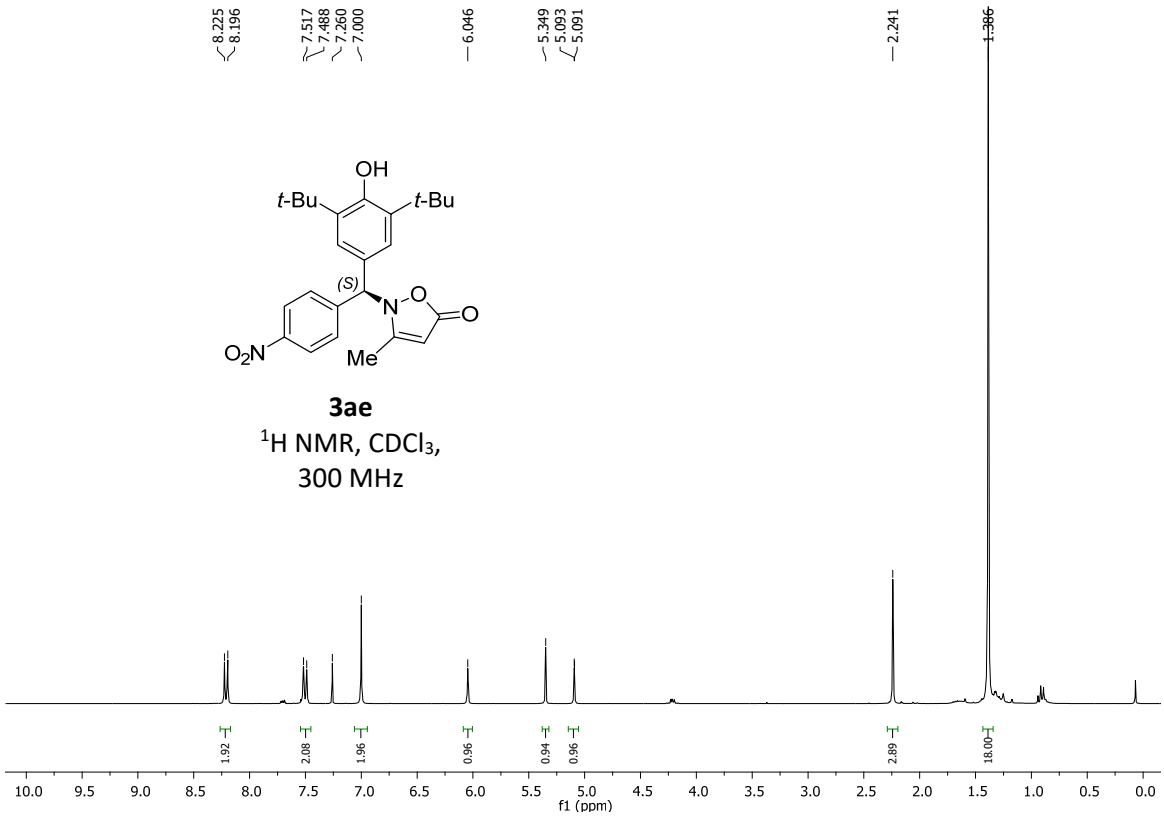
Retention Time	Area	Area Percent
12,29	105405905	50,755
14,29	102269970	49,245



16: 270 nm, 4 nm
Results

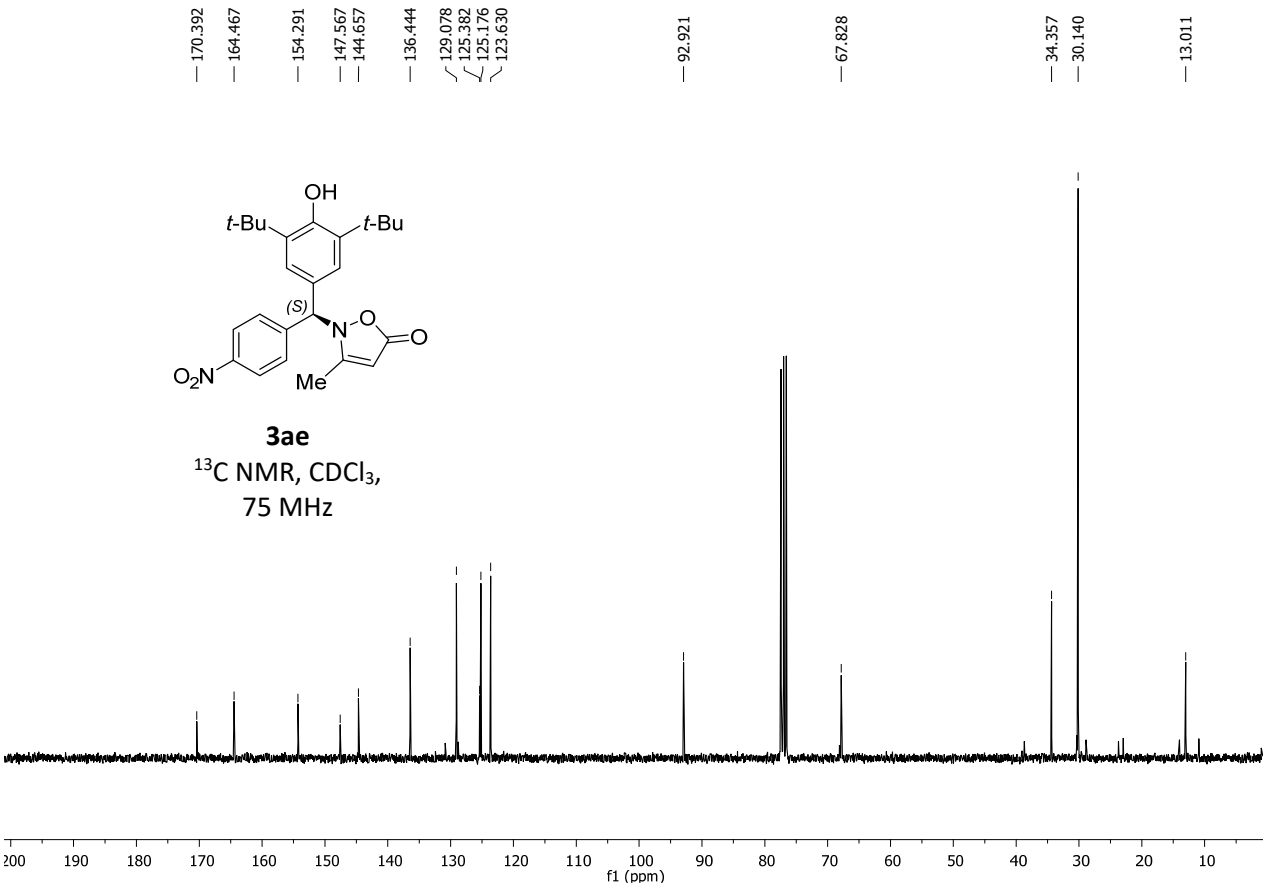
Retention Time	Area	Area Percent
12,55	42893898	6,201
13,56	648871761	93,799





3ae

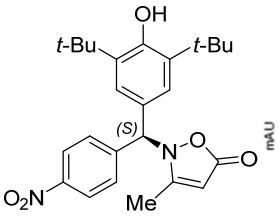
^{1}H NMR, $CDCl_3$,
300 MHz

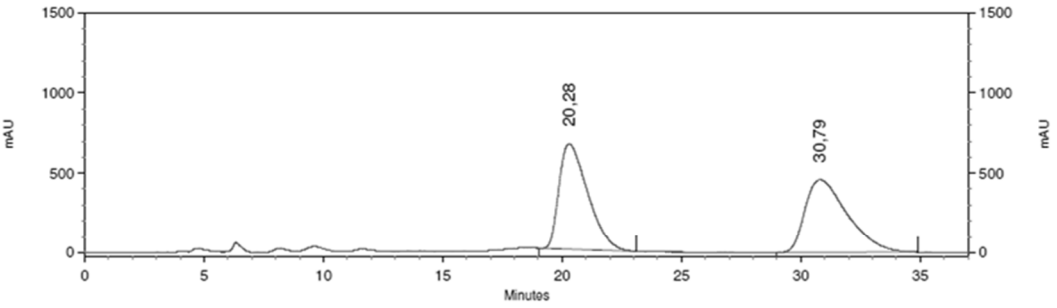


3ae

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

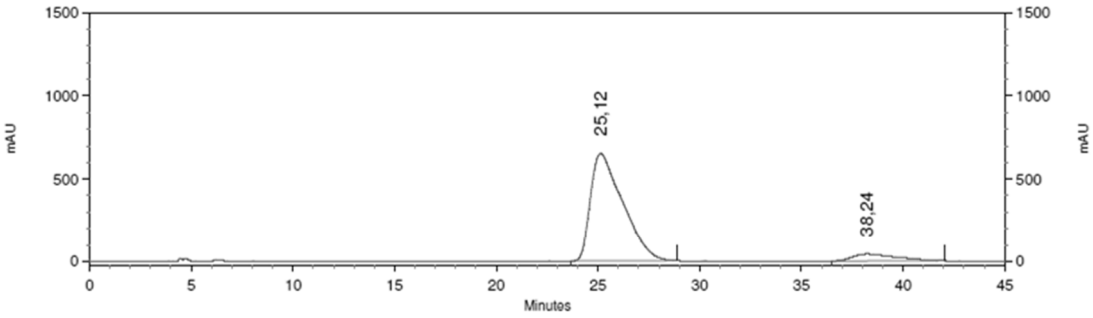
Compound **3ae**





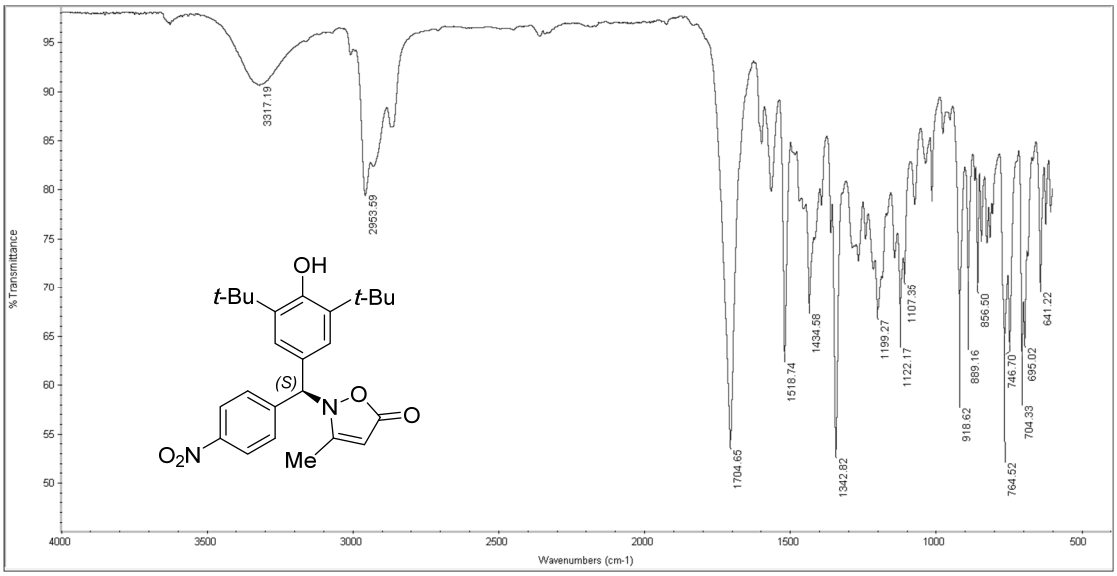
15: 270 nm, 4 nm
Results

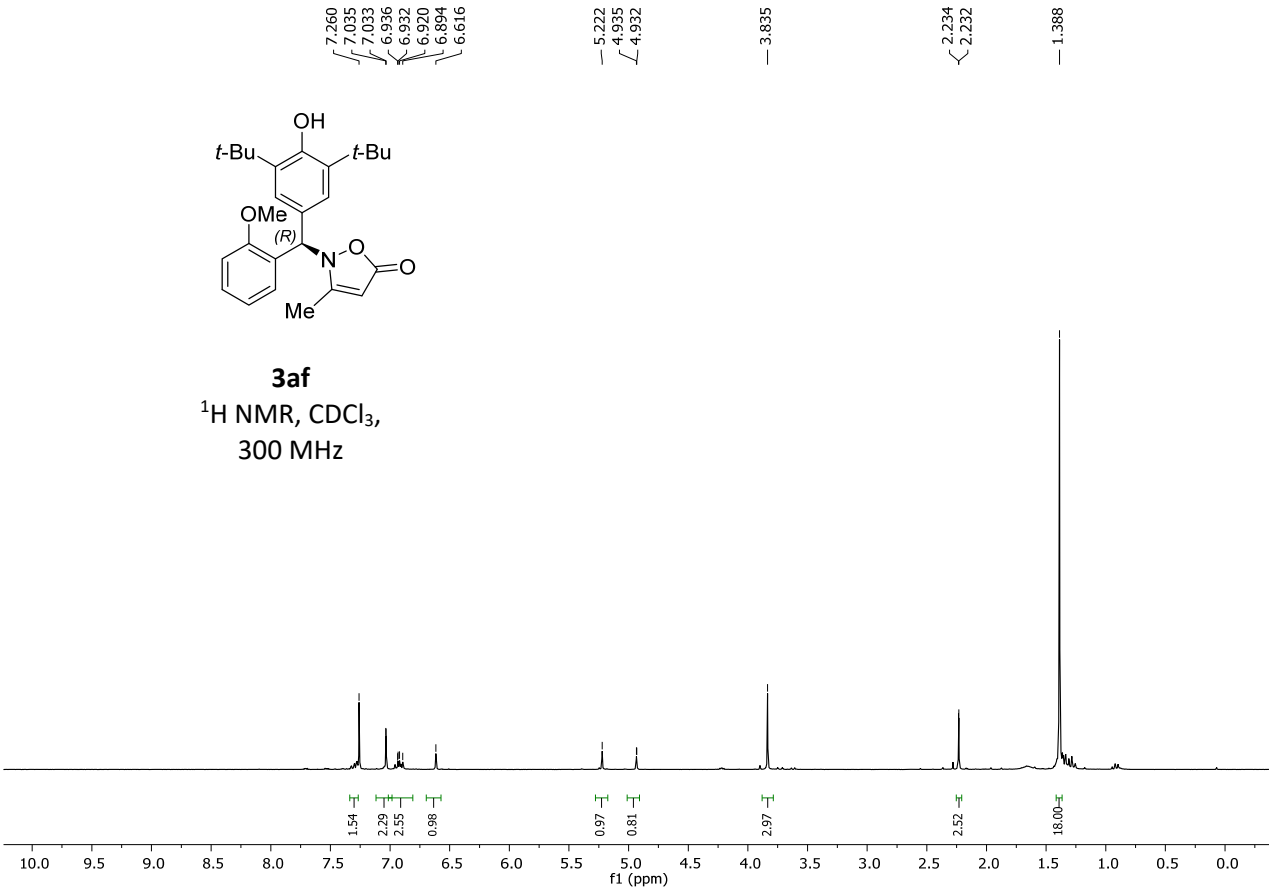
Retention Time	Area	Area Percent
20,28	222527841	49,668
30,79	225498288	50,332



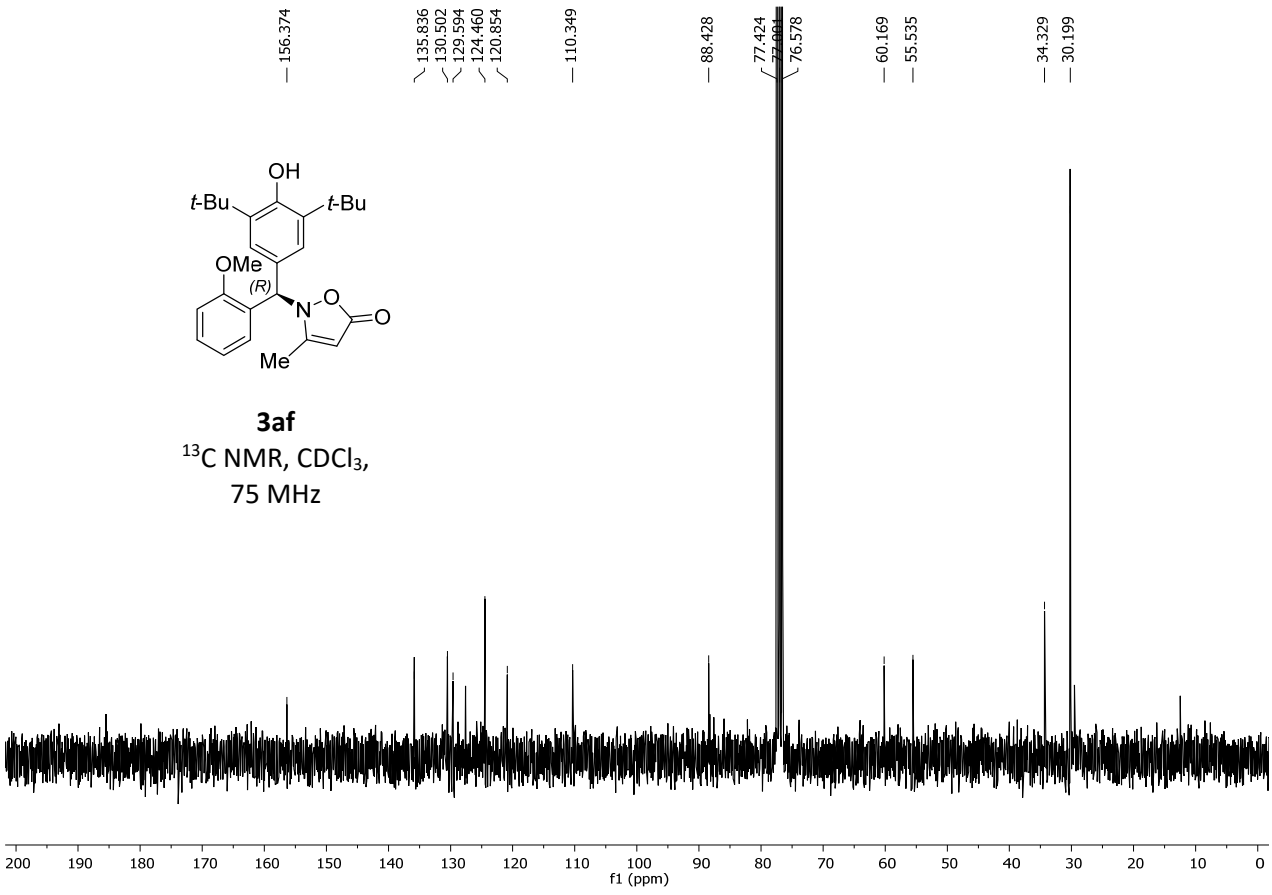
16: 270 nm, 4 nm
Results

Retention Time	Area	Area Percent
25,12	288370126	92,034
38,24	24960812	7,966



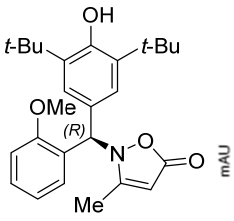


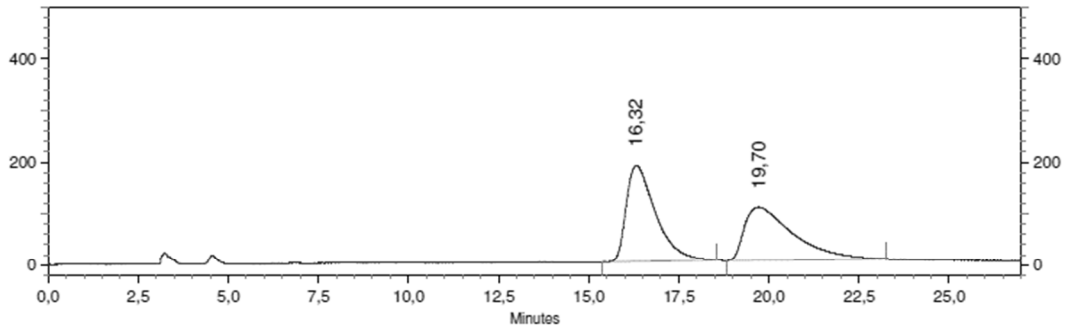
3af
^{1}H NMR, $CDCl_3$,
300 MHz



3af
^{13}C NMR, $CDCl_3$,
75 MHz

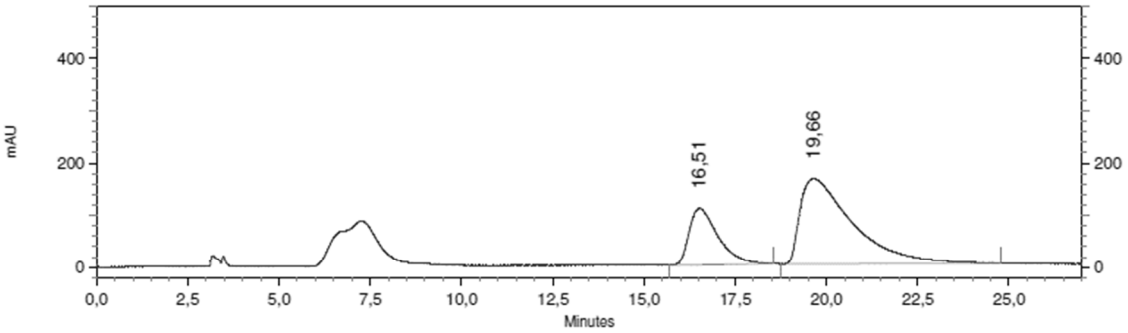
Compound **3af**





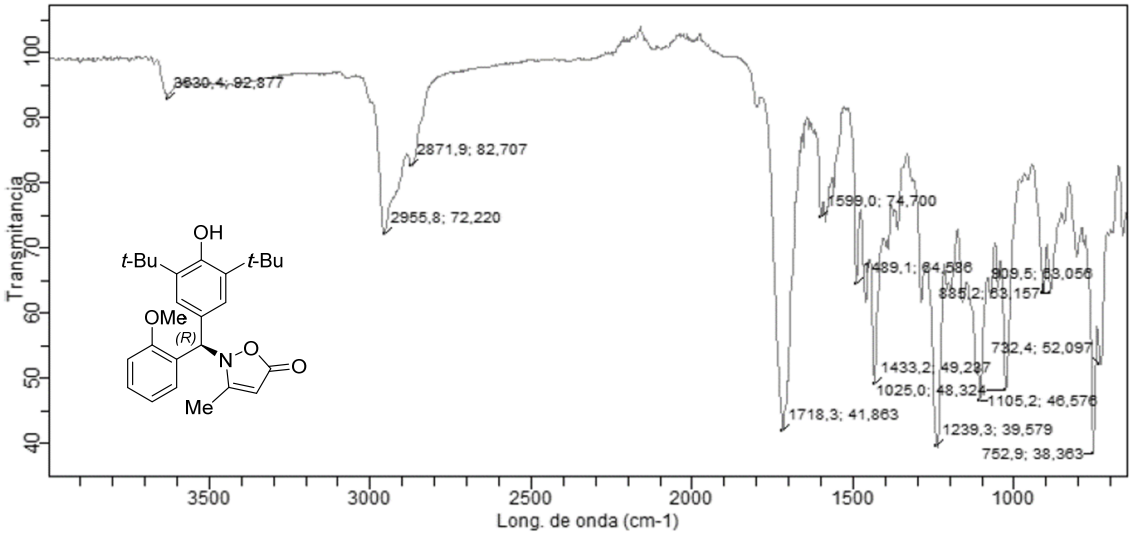
18: 270 nm, 4 nm
Results

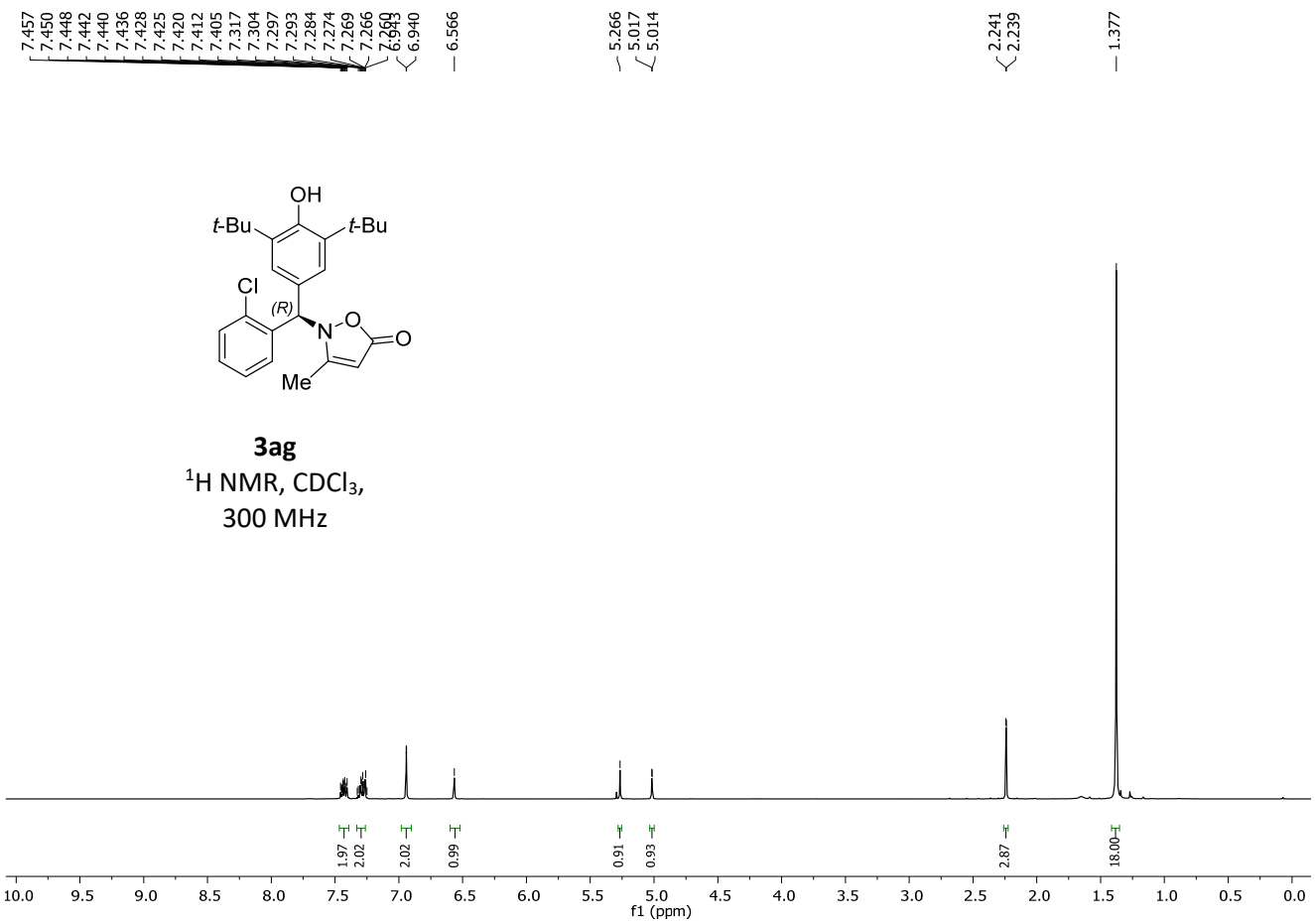
Retention Time	Area	Area Percent
16,32	42339058	52,169
19,70	38819171	47,831



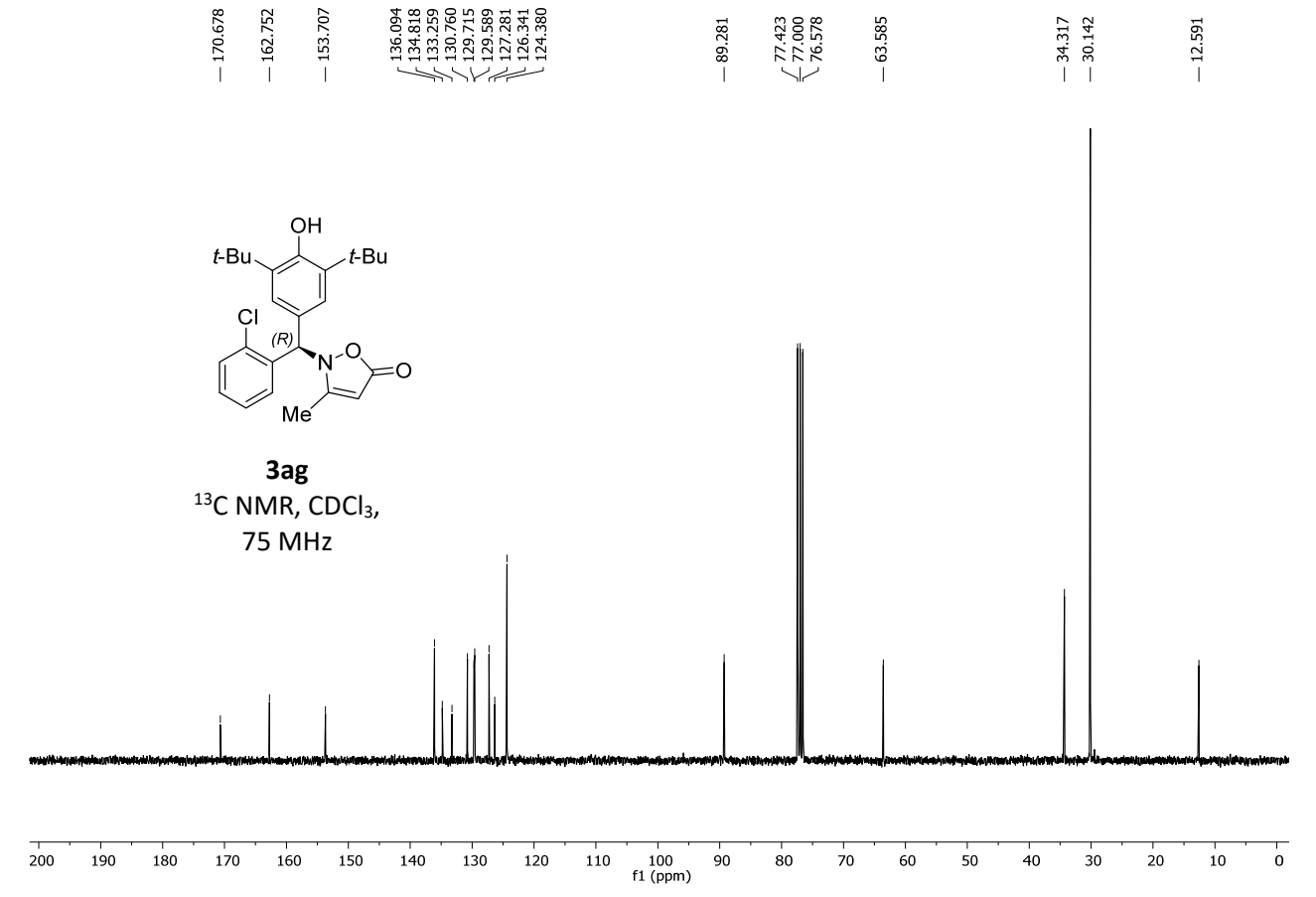
18: 270 nm, 4 nm
Results

Retention Time	Area	Area Percent
16,51	24199330	26,862
19,66	65889351	73,138



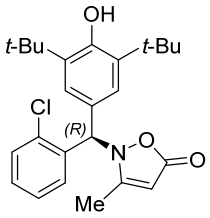


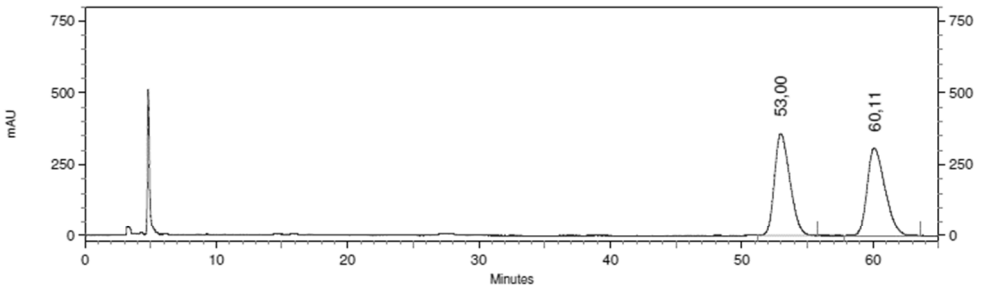
3ag
^{1}H NMR, $CDCl_3$,
300 MHz



3ag
^{13}C NMR, $CDCl_3$,
75 MHz

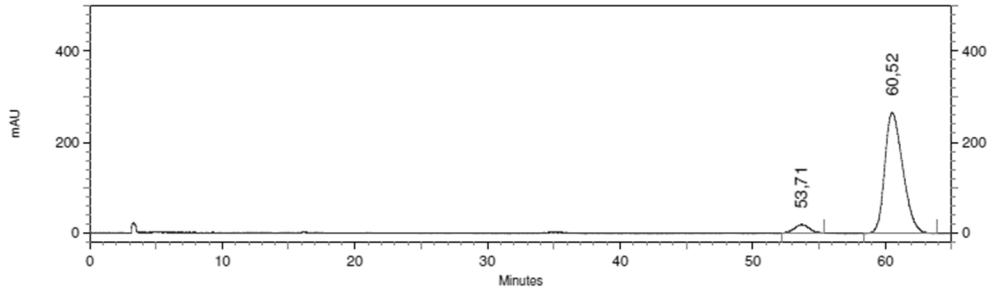
Compound **3ag**





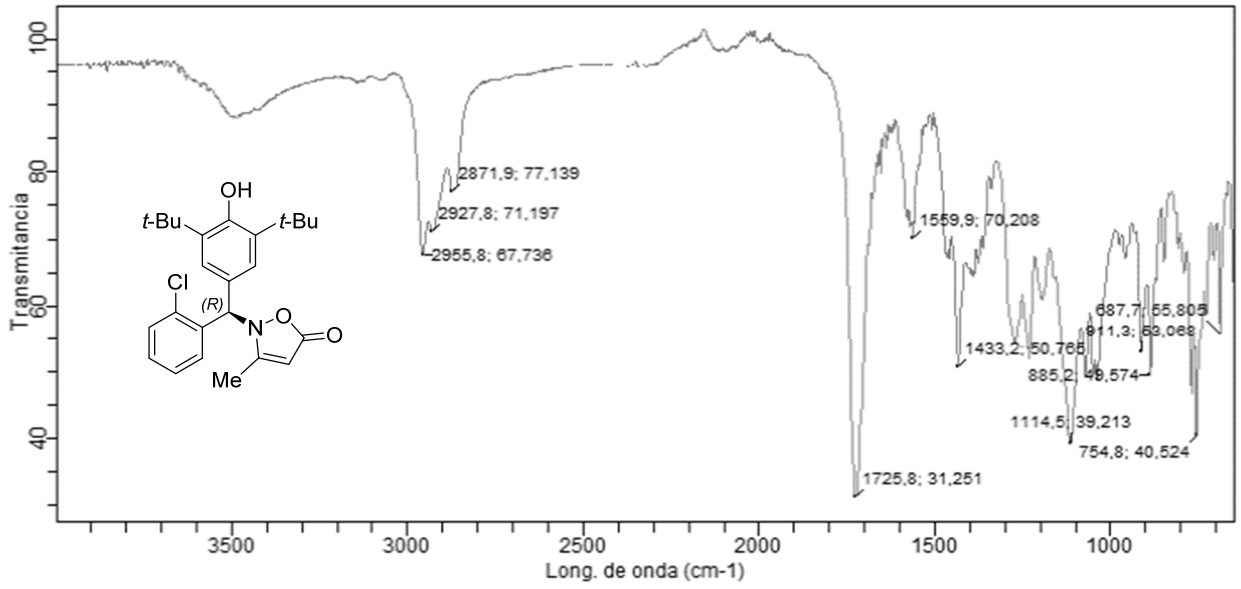
18: 270 nm, 4 nm
Results

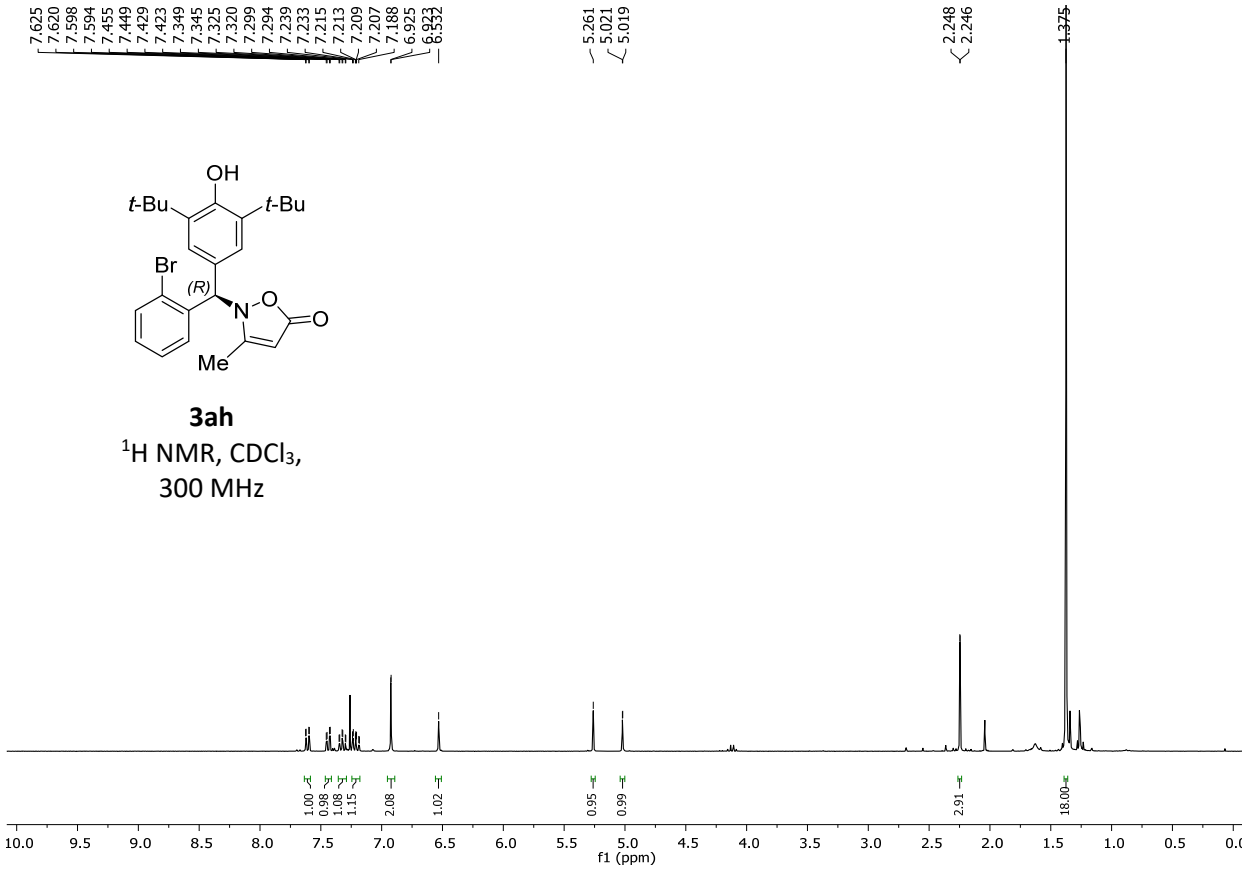
Retention Time	Area	Area Percent
53,00	117374495	49,974
60,11	117497600	50,026



18: 270 nm, 4 nm
Results

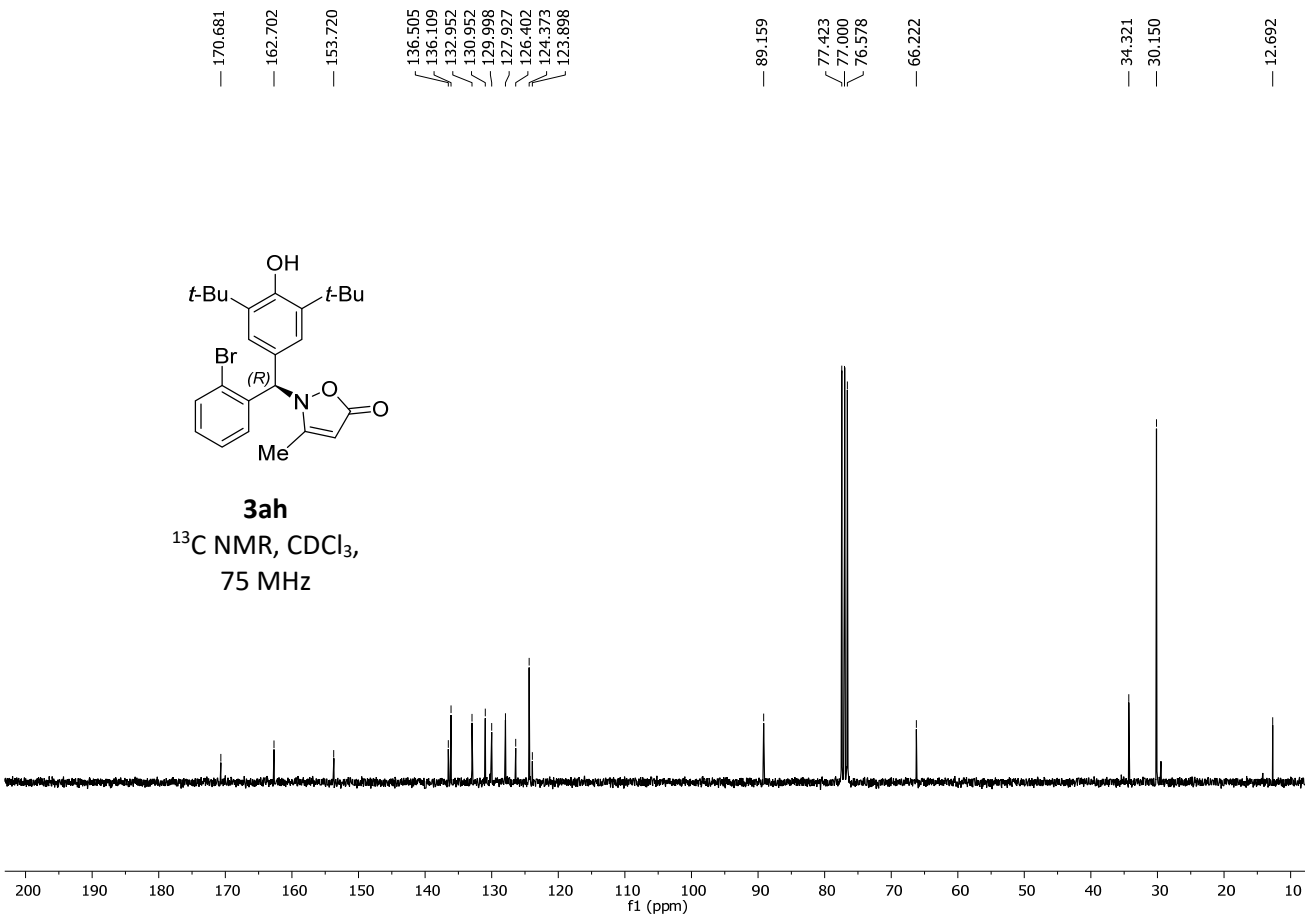
Retention Time	Area	Area Percent
53,71	5872684	5,482
60,52	101254910	94,518





3ah

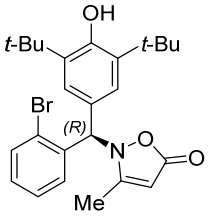
^{1}H NMR, $CDCl_3$,
300 MHz

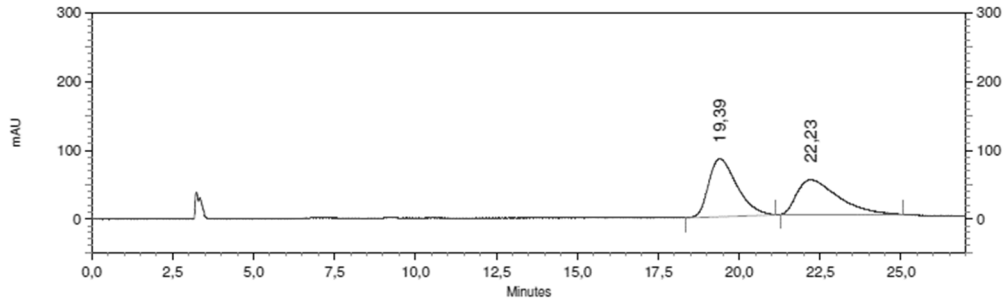


3ah

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

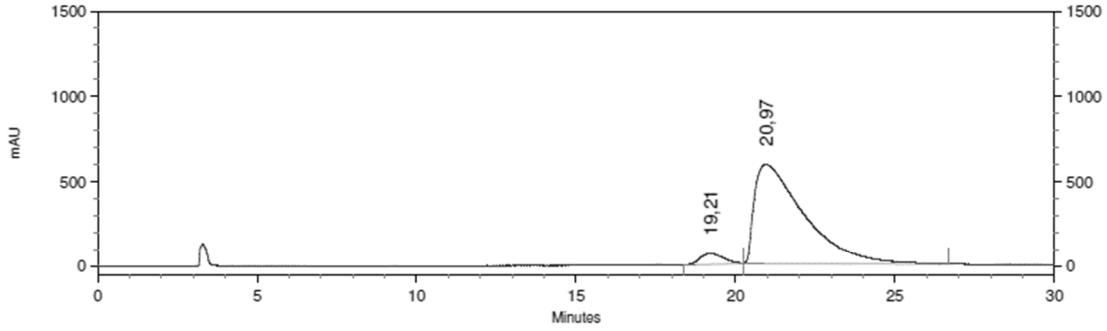
Compound **3ah**





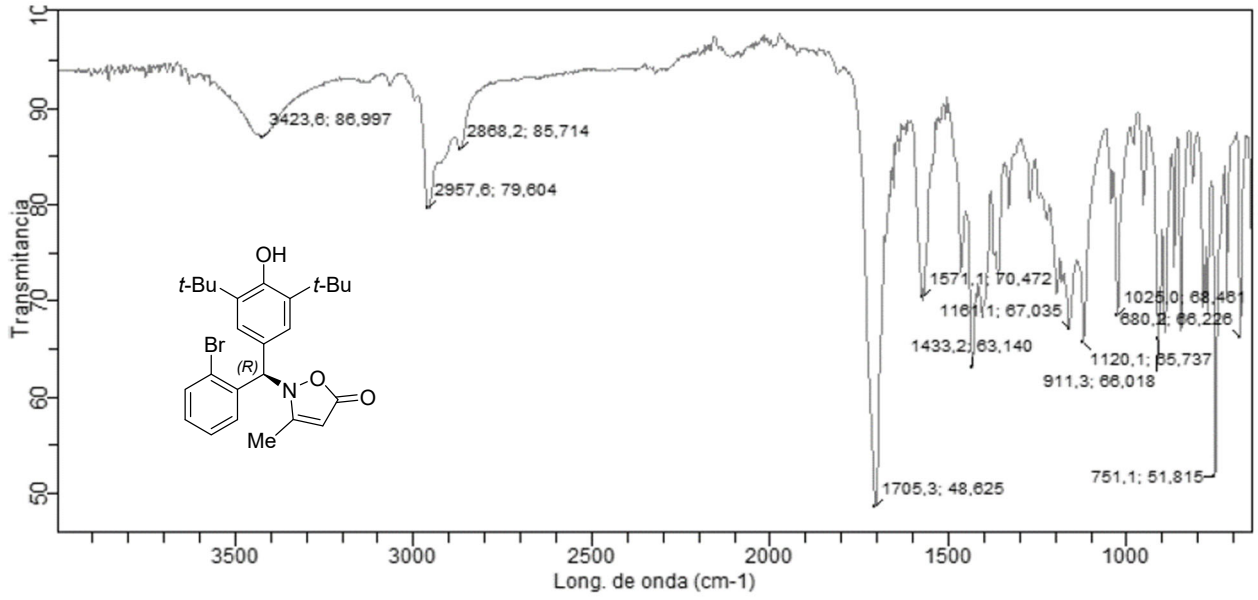
13: 270 nm, 4 nm
Results

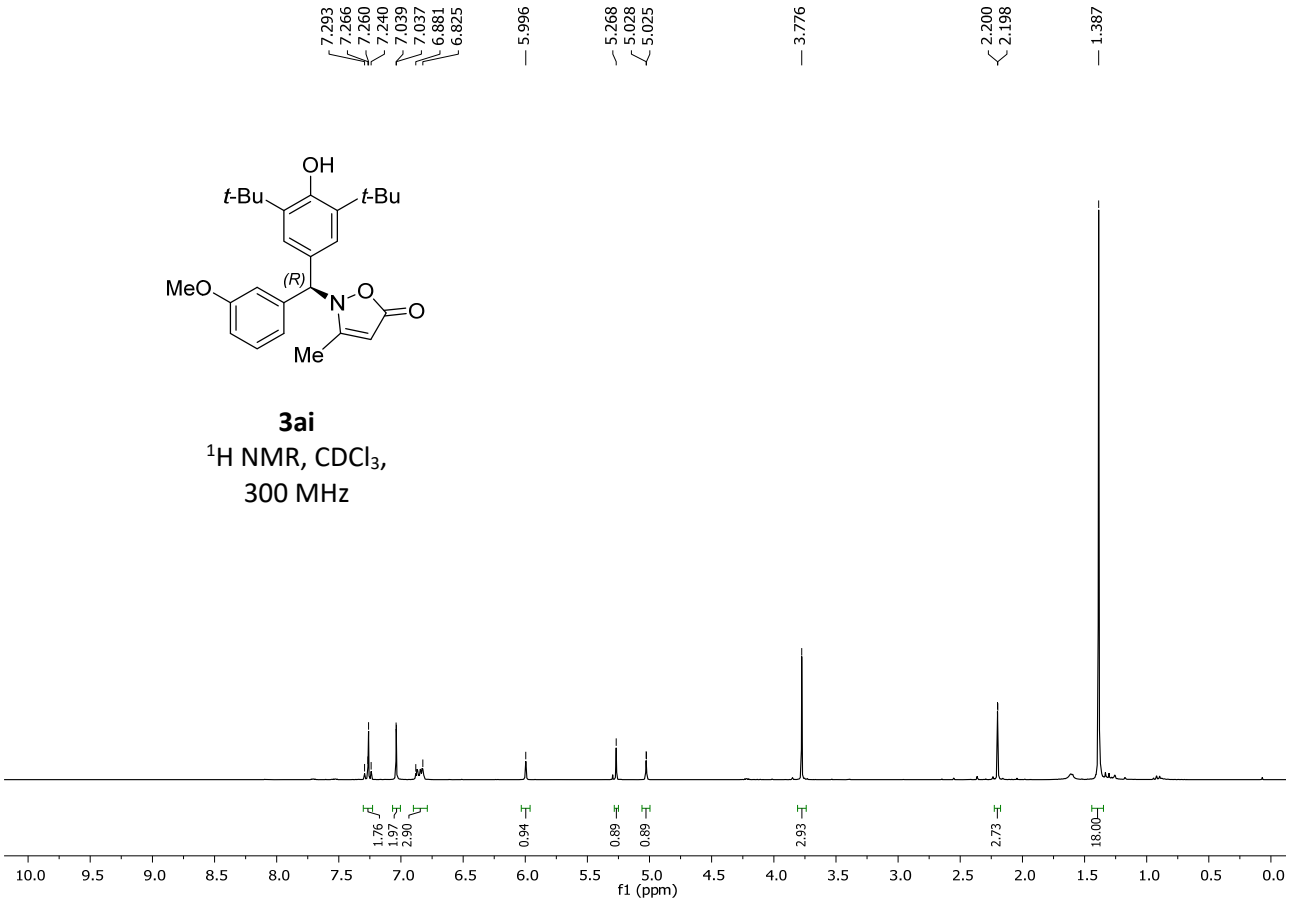
Retention Time	Area	Area Percent
19,39	20477853	53,133
22,23	18062795	46,867



13: 270 nm, 4 nm
Results

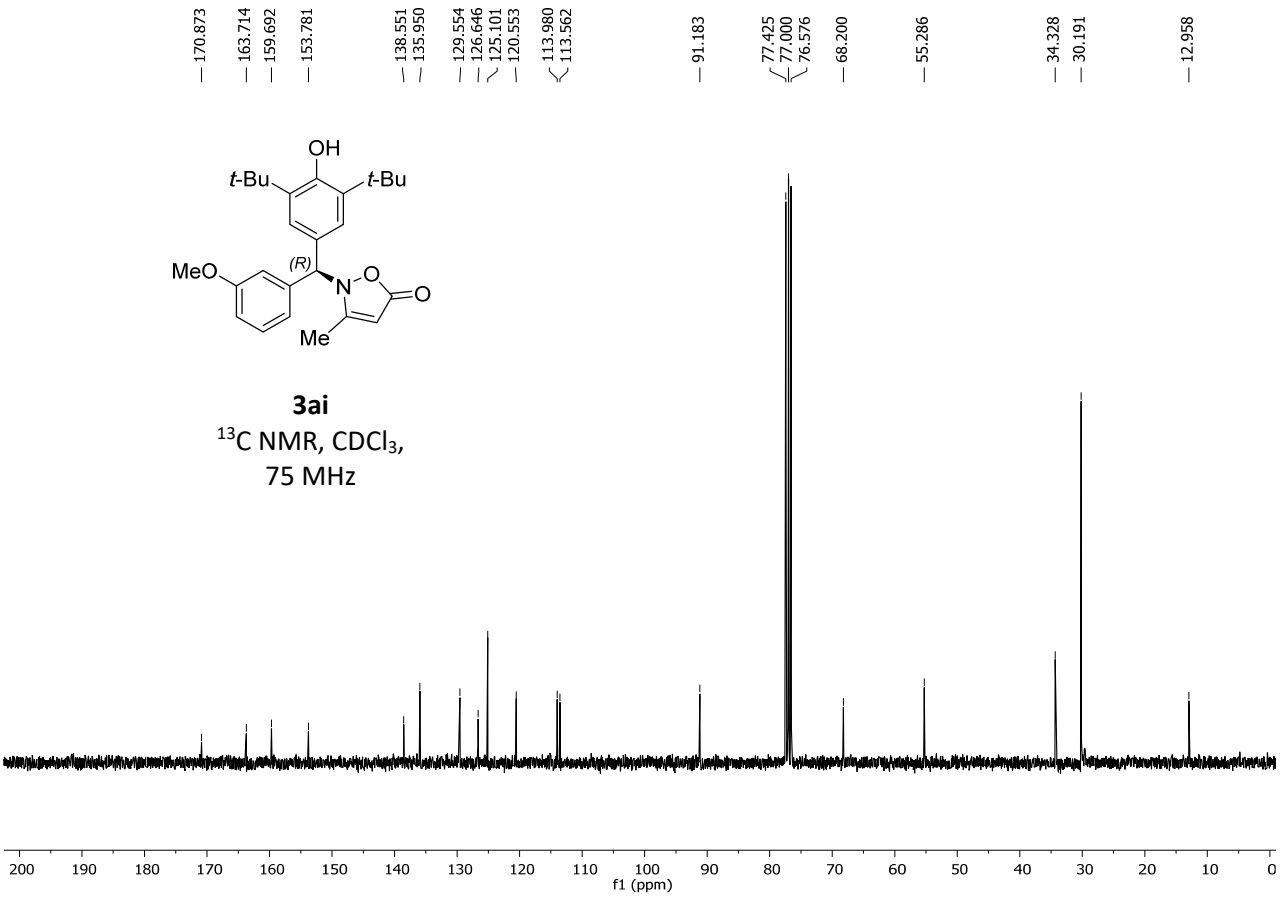
Retention Time	Area	Area Percent
19,21	13208379	4,892
20,97	256776805	95,108





3ai

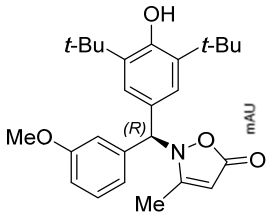
^{1}H NMR, $CDCl_3$,
300 MHz

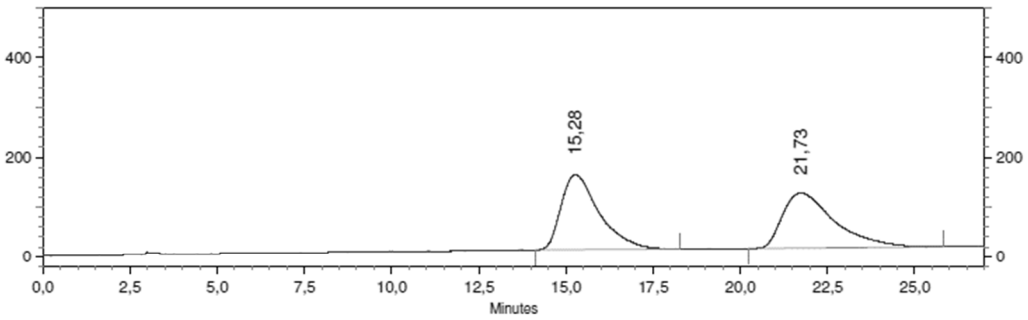


3ai

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

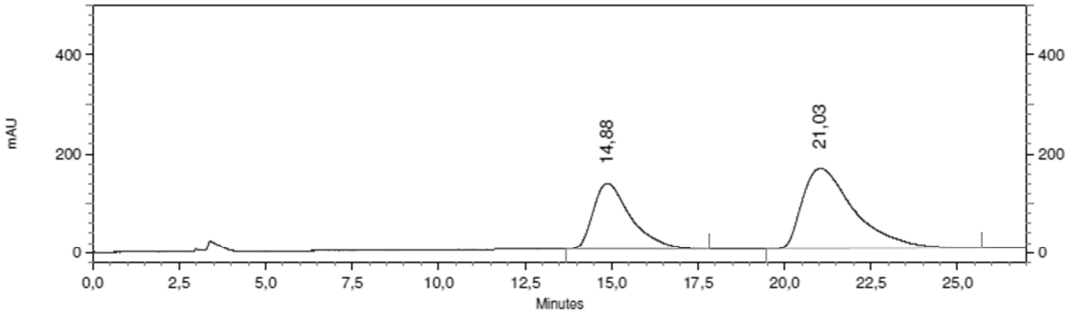
Compound **3ai**





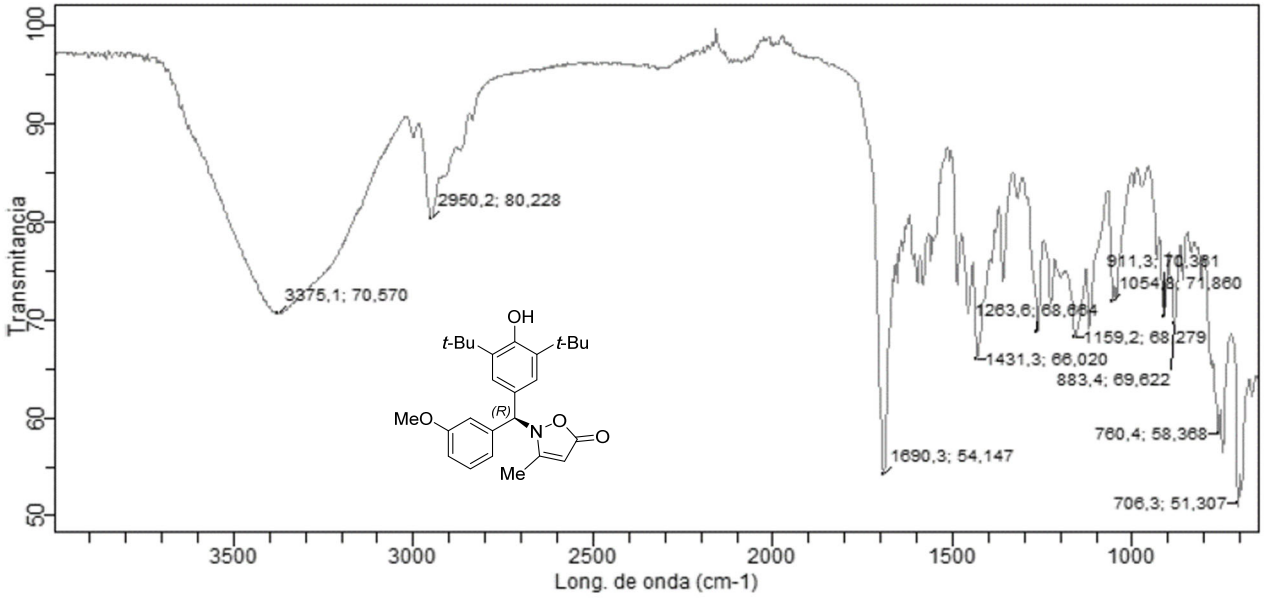
19: 270 nm, 4 nm
Results

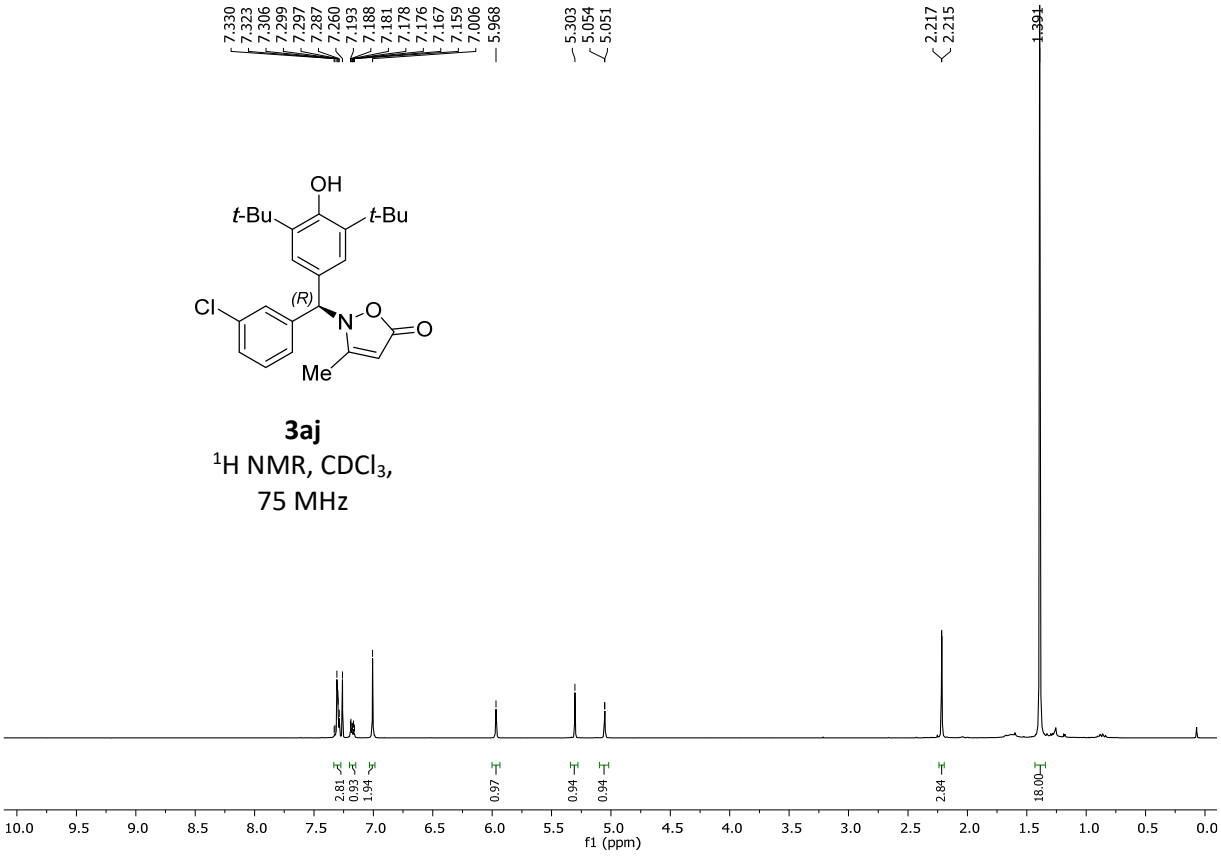
Retention Time	Area	Area Percent
15,28	45651596	49,862
21,73	45904351	50,138



19: 270 nm, 4 nm
Results

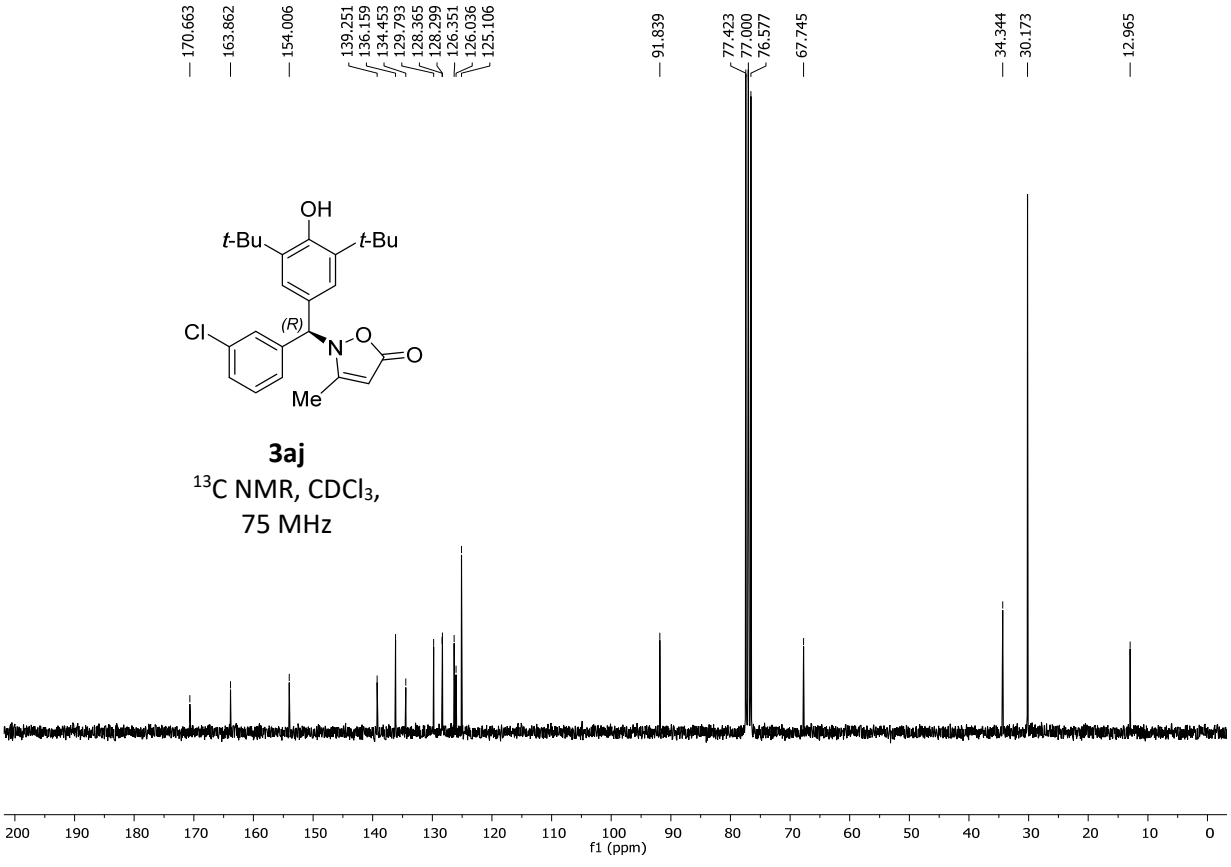
Retention Time	Area	Area Percent
14,88	40306787	37,225
21,03	67972729	62,775





3aj

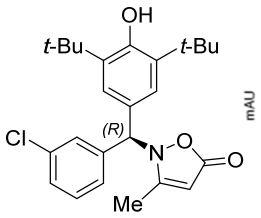
^{1}H NMR, $CDCl_3$,
75 MHz

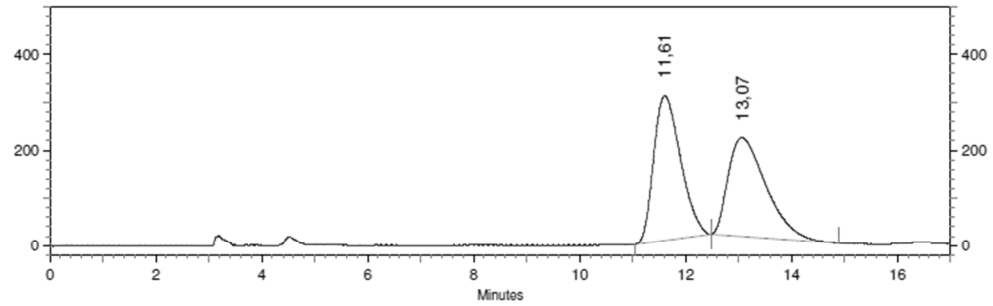


3aj

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

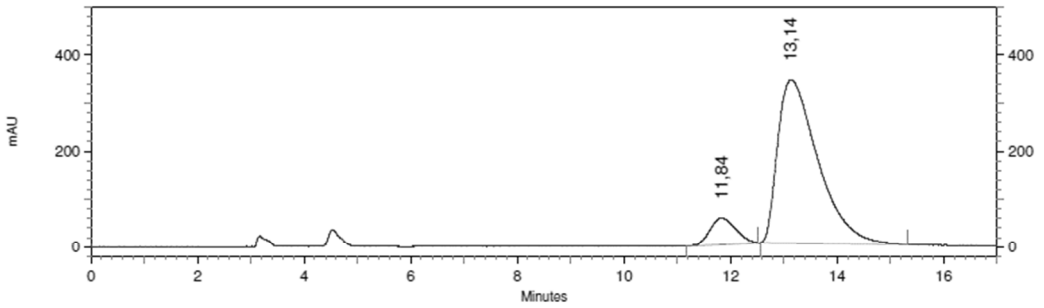
Compound **3aj**





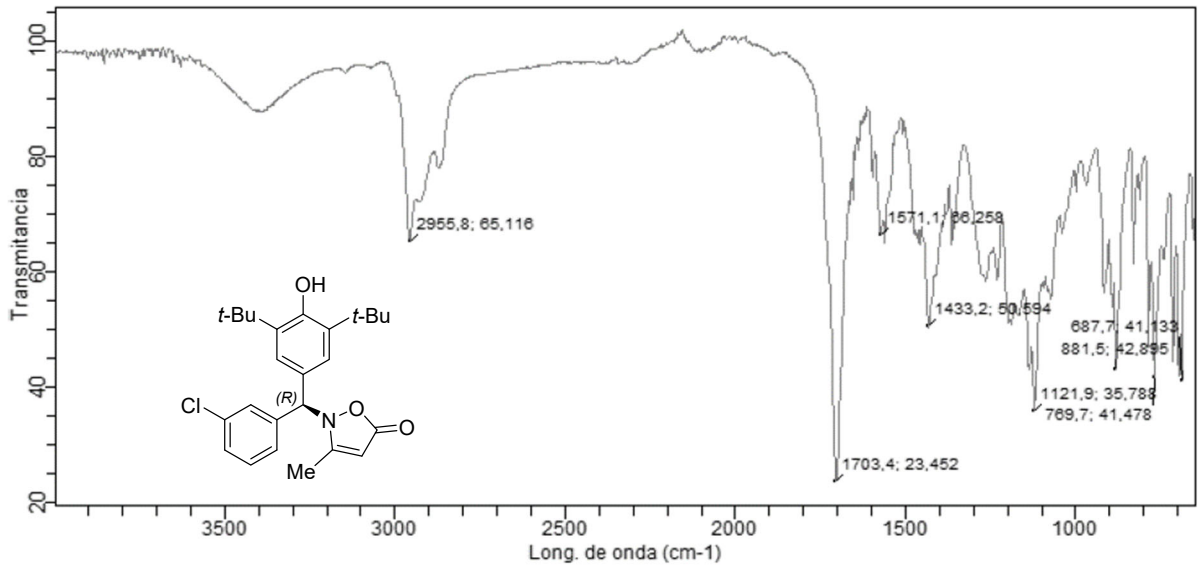
18: 270 nm, 4 nm
Results

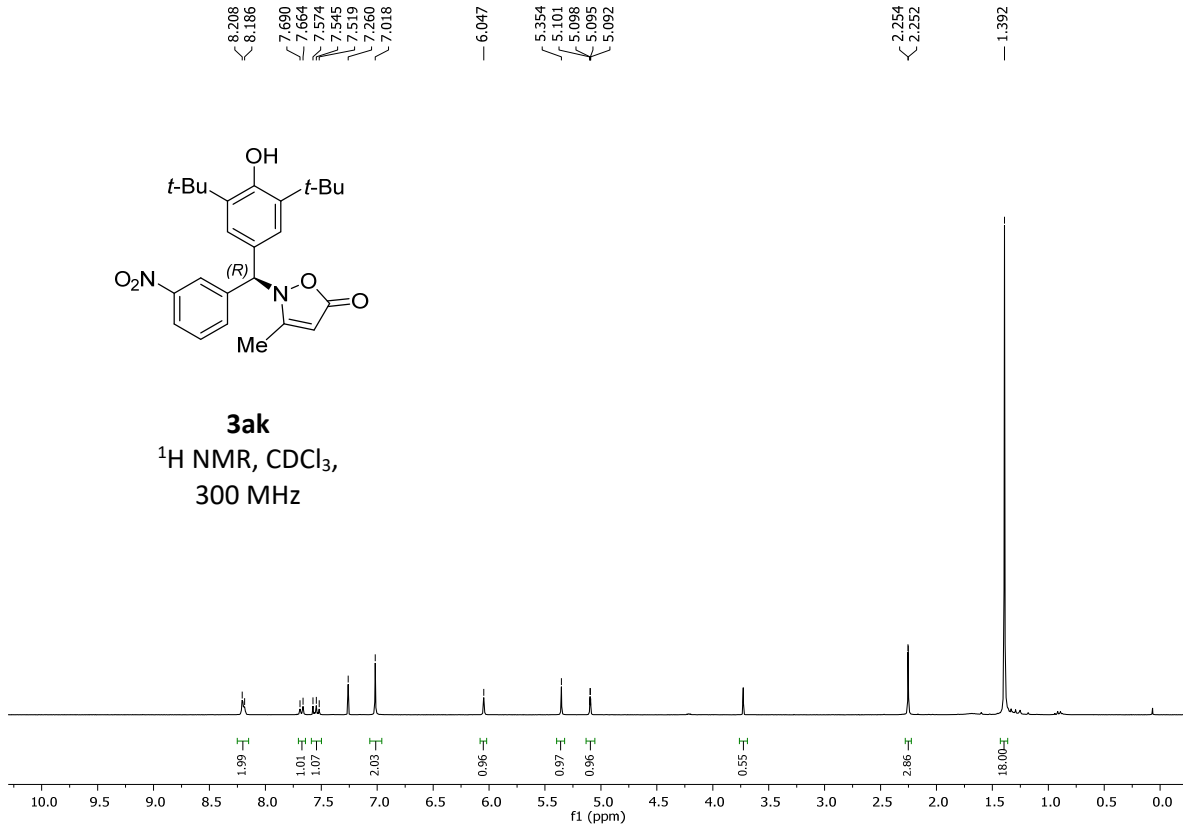
Retention Time	Area	Area Percent
11,61	42825670	50,968
13,07	41198172	49,032



18: 270 nm, 4 nm
Results

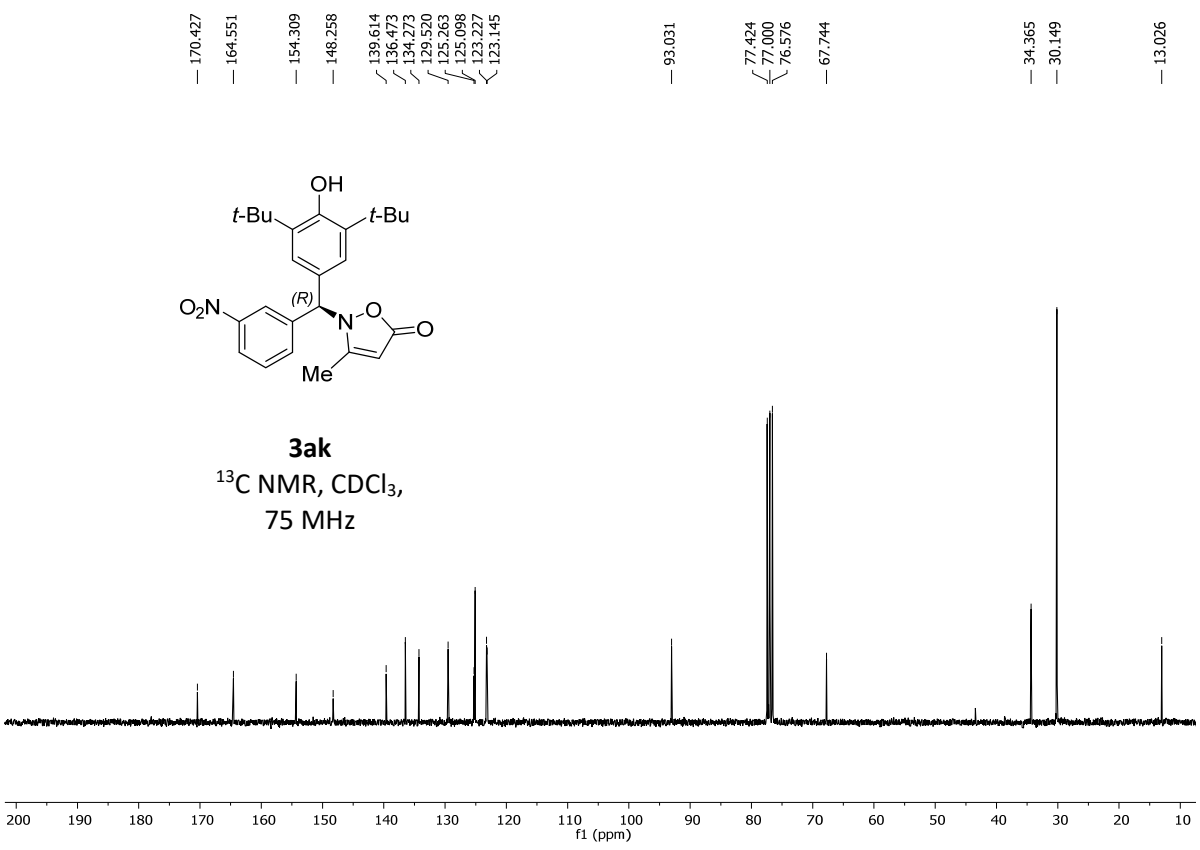
Retention Time	Area	Area Percent
11,84	7511466	9,507
13,14	71502273	90,493





3ak

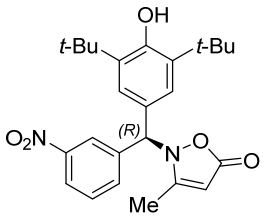
^{1}H NMR, $CDCl_3$,
300 MHz

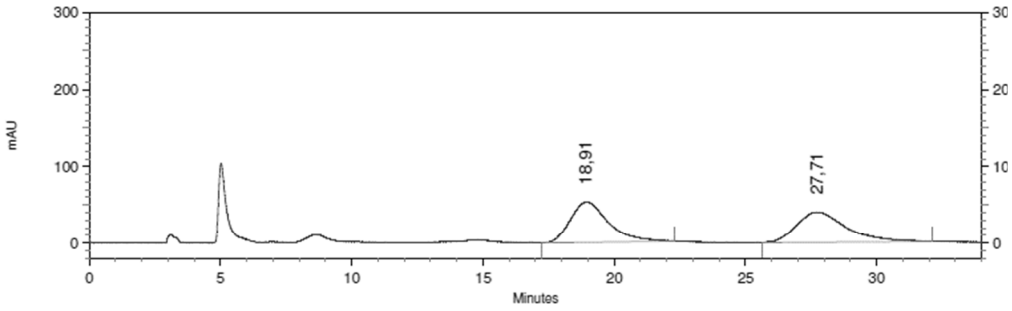


3ak

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

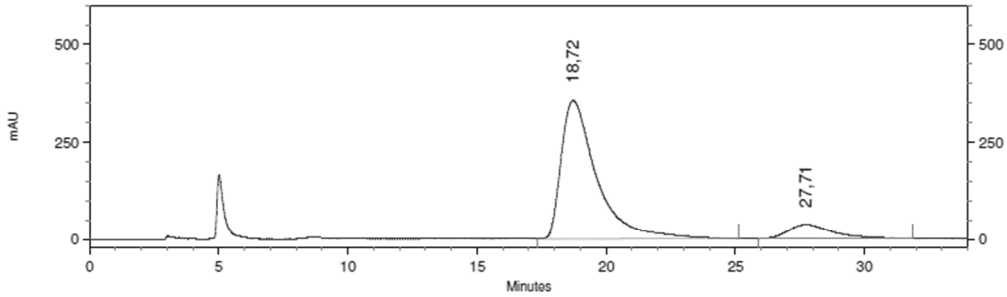
Compound **3ak**





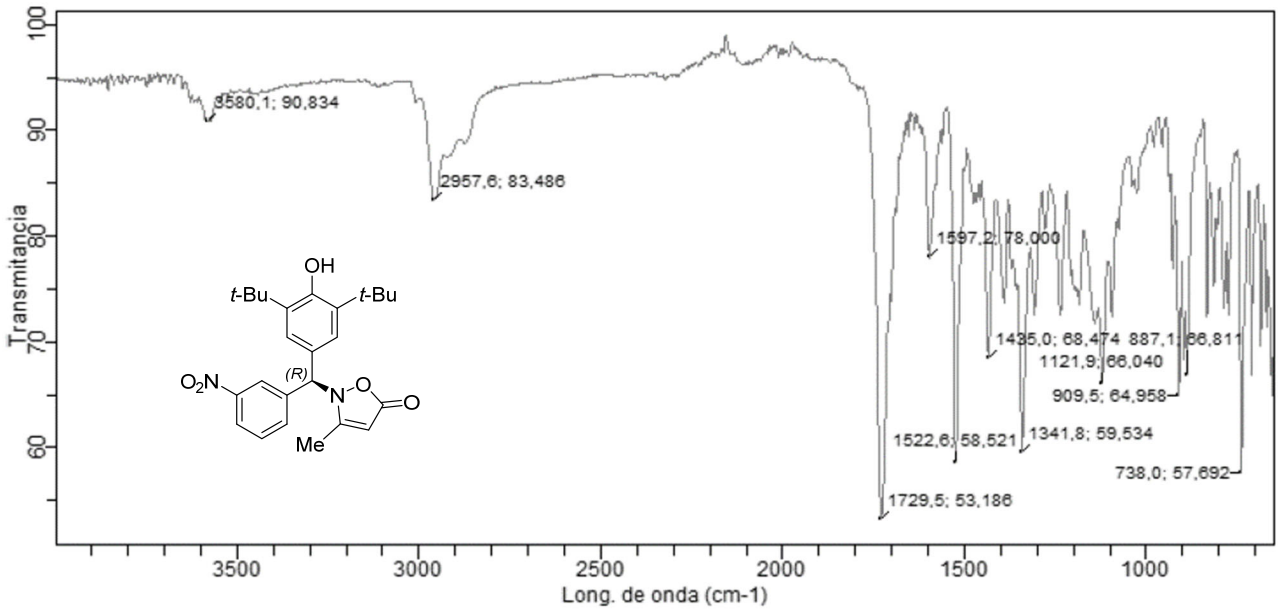
18: 270 nm, 4 nm
Results

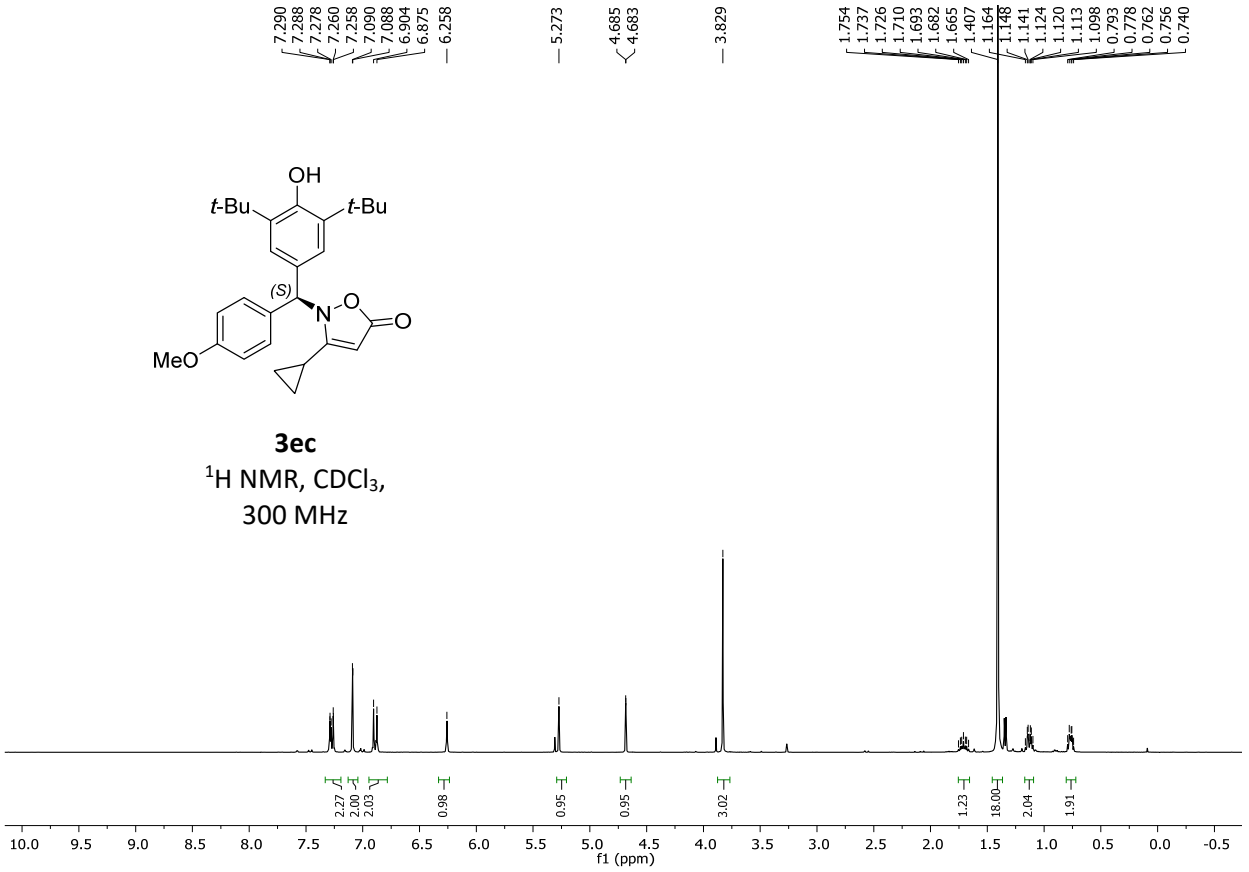
Retention Time	Area	Area Percent
18,91	21542909	50,374
27,71	21223399	49,626



13: 270 nm, 4 nm
Results

Retention Time	Area	Area Percent
18,72	136947646	88,435
27,71	17909094	11,565

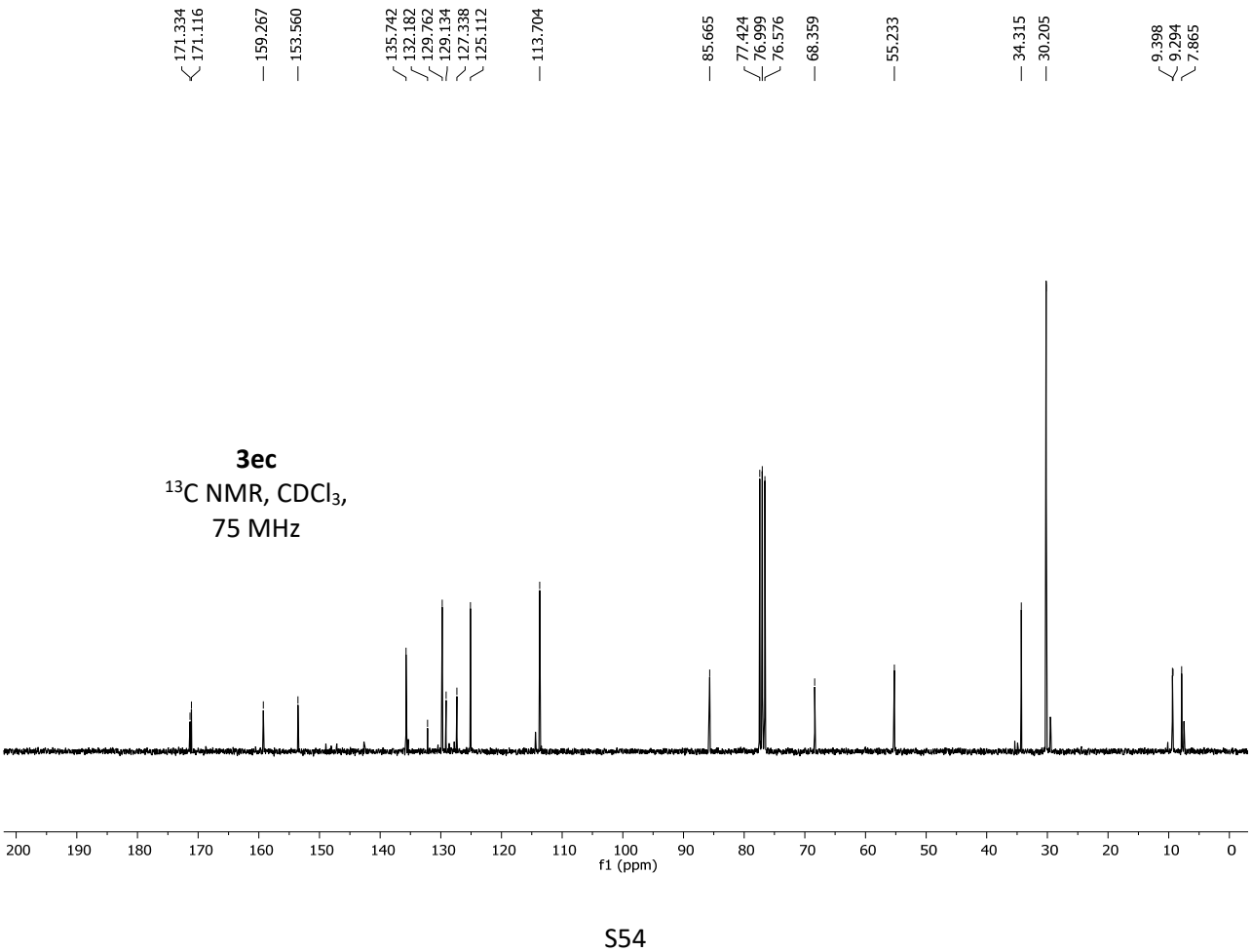




3ec

^{1}H NMR, $CDCl_3$,

300 MHz

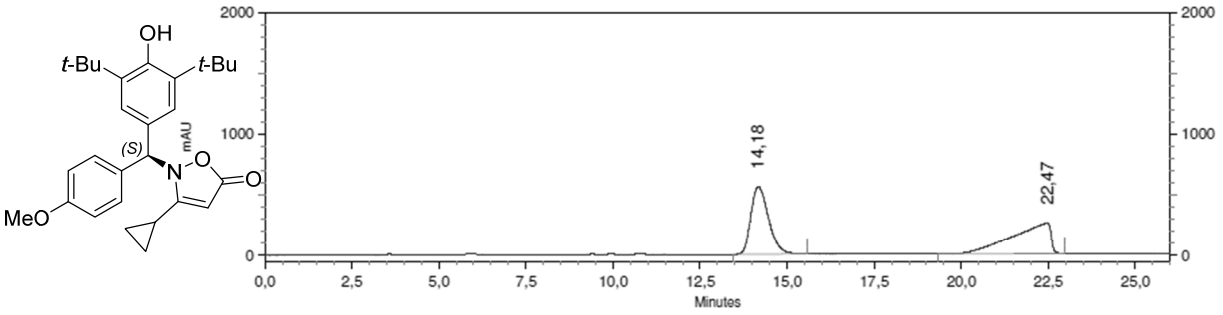


3ec

^{13}C NMR, $CDCl_3$,

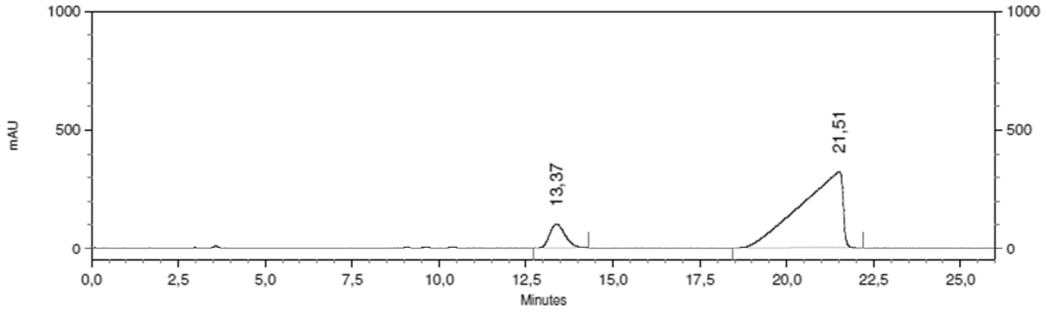
75 MHz

Compound **3ec**



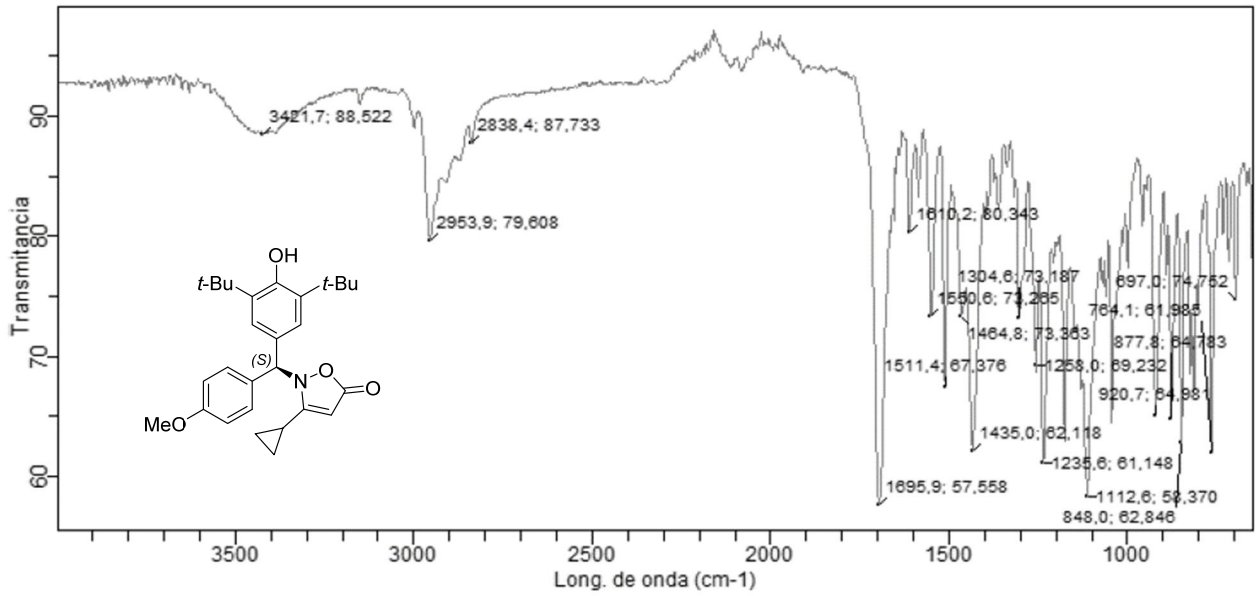
18: 270 nm, 4 nm
Results

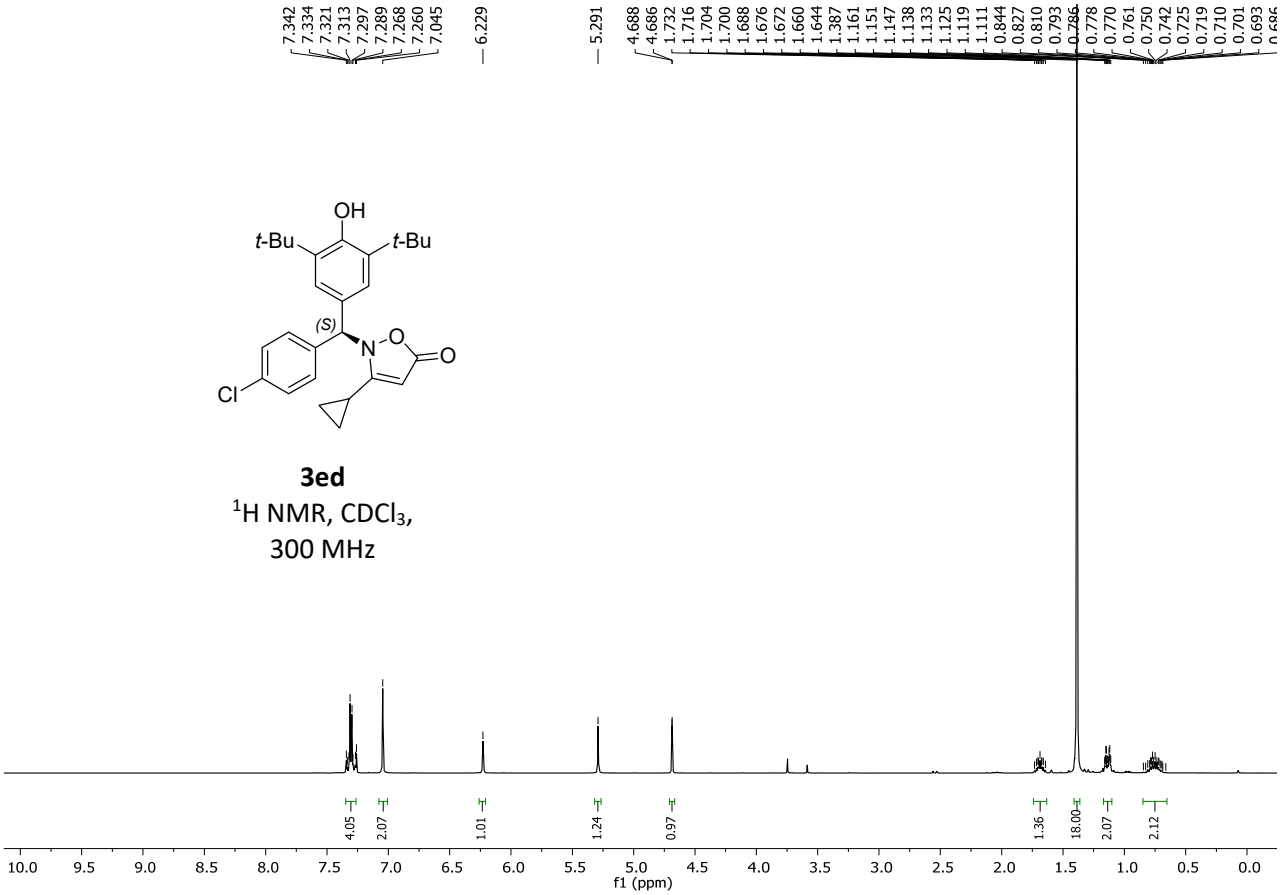
Retention Time	Area	Area Percent
14,18	79377637	50,000
22,47	79378225	50,000



18: 270 nm, 4 nm
Results

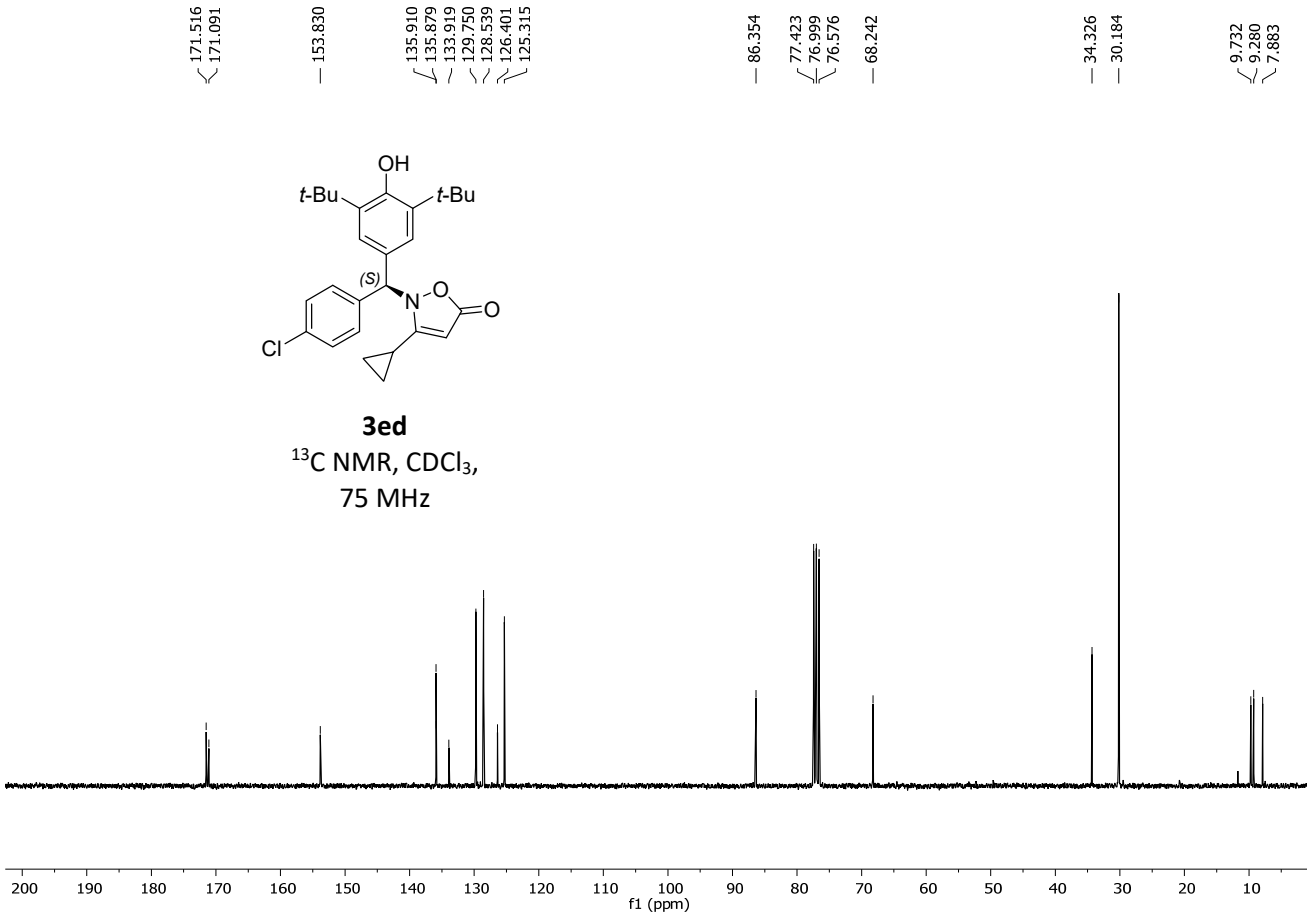
Retention Time	Area	Area Percent
13,37	12858997	10,485
21,51	109778660	89,515





3ed

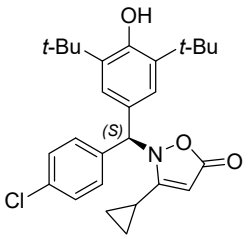
^{1}H NMR, $CDCl_3$,
300 MHz

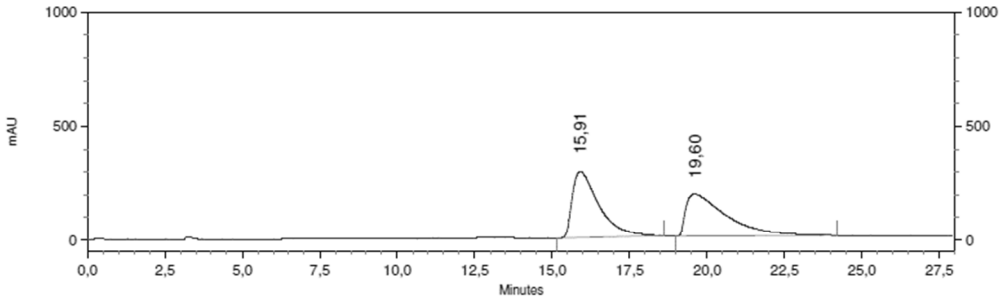


3ed

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

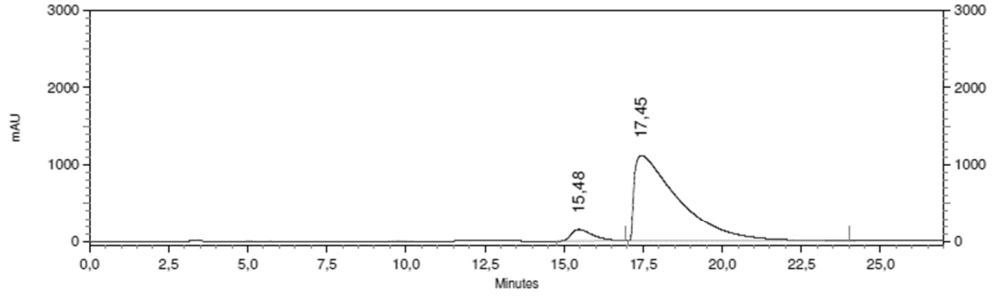
Compound **3ed**





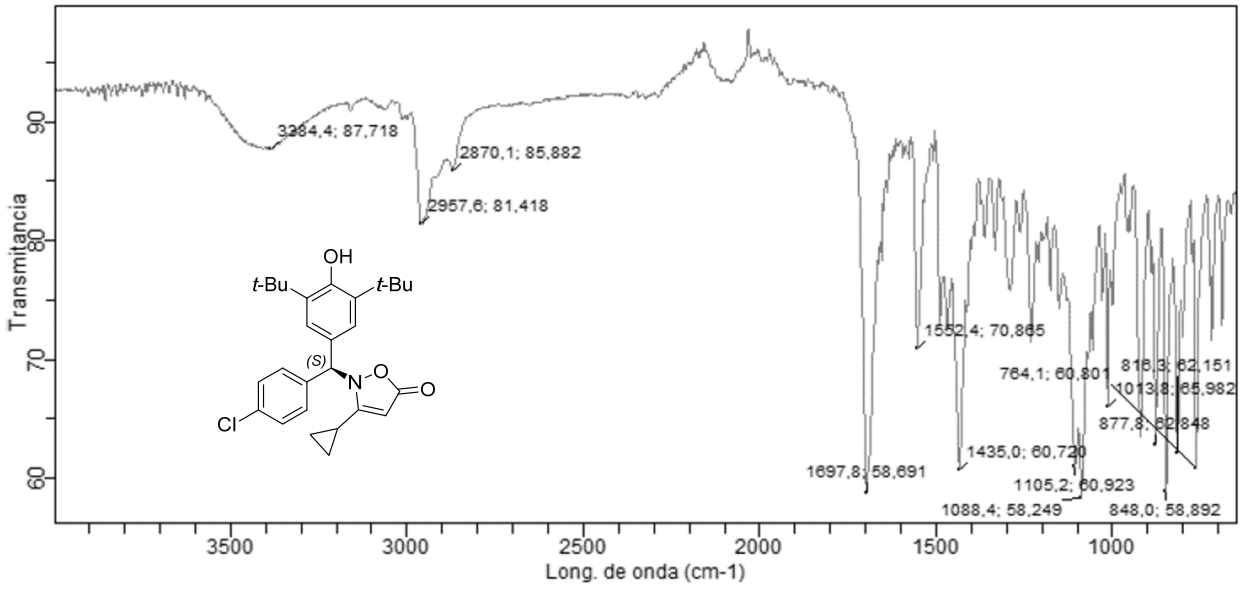
18: 270 nm, 4 nm
Results

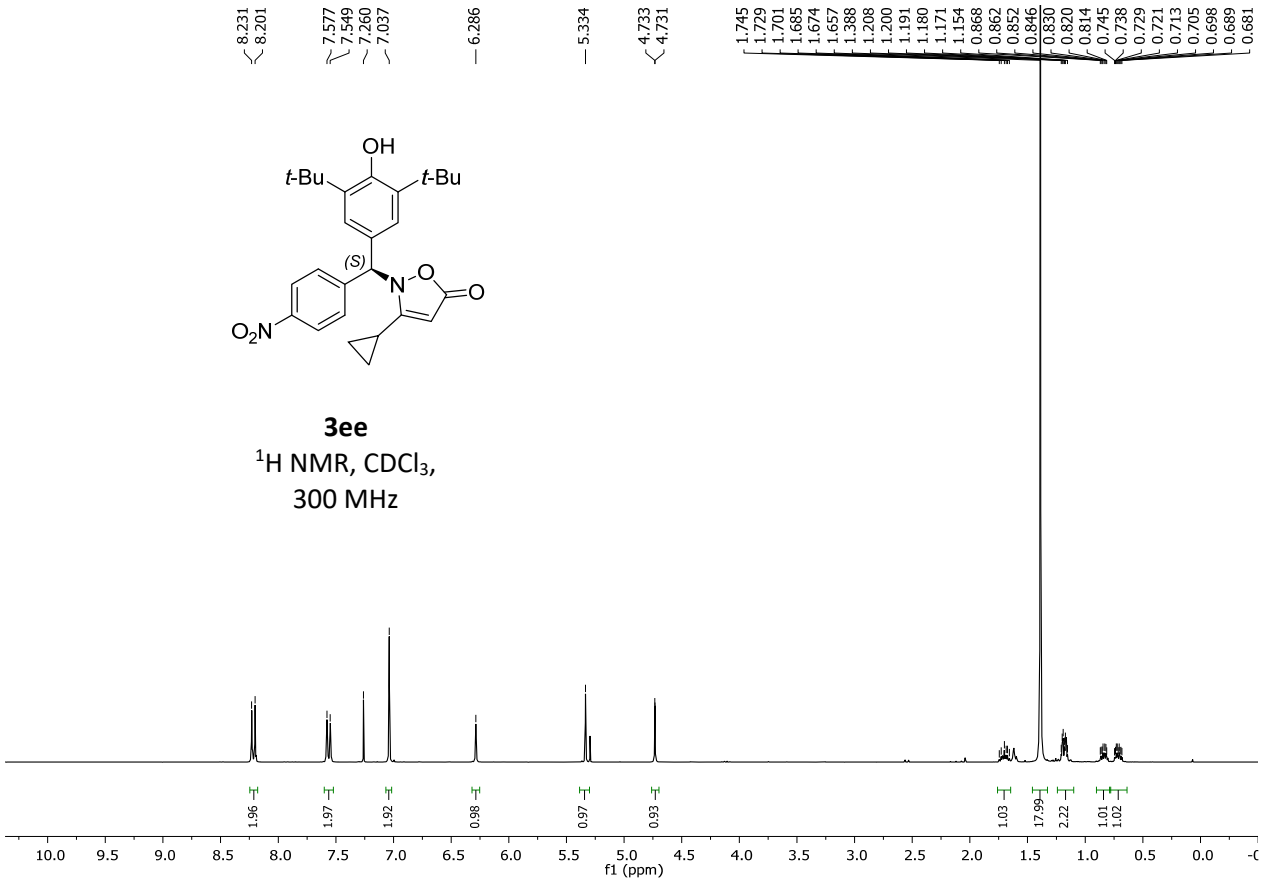
Retention Time	Area	Area Percent
15,91	70545607	50,810
19,60	68296814	49,190



18: 270 nm, 4 nm
Results

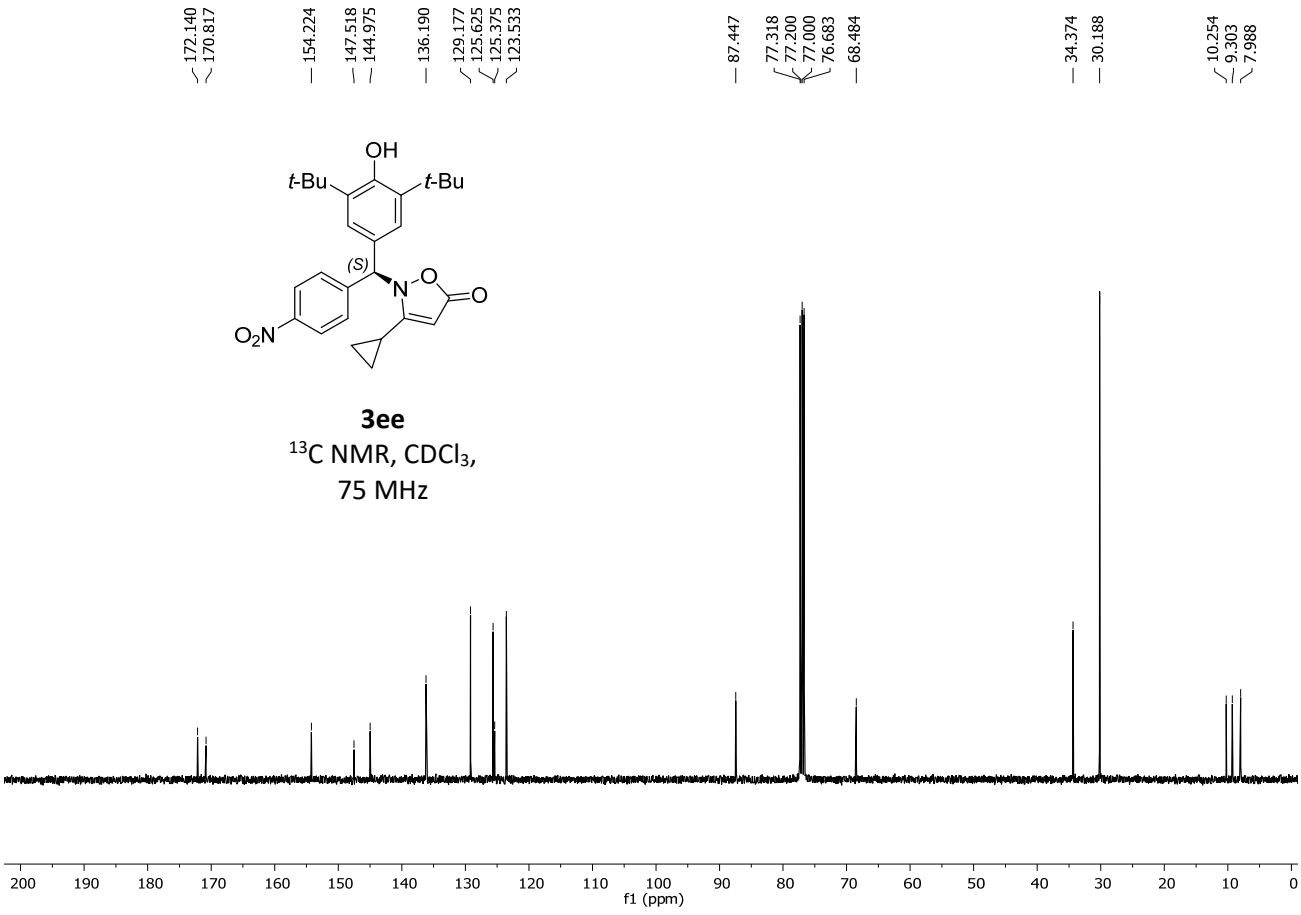
Retention Time	Area	Area Percent
15,48	28096306	6,037
17,45	437309476	93,963





3ee

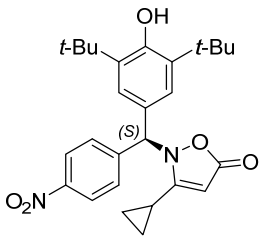
^{1}H NMR, $CDCl_3$,
300 MHz

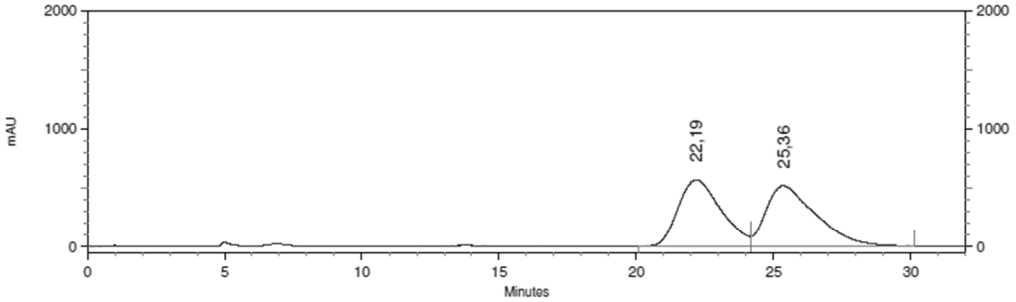


3ee

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

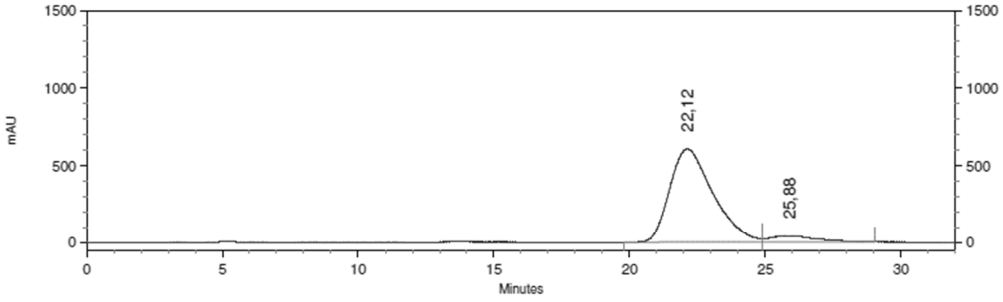
Compound **3ee**





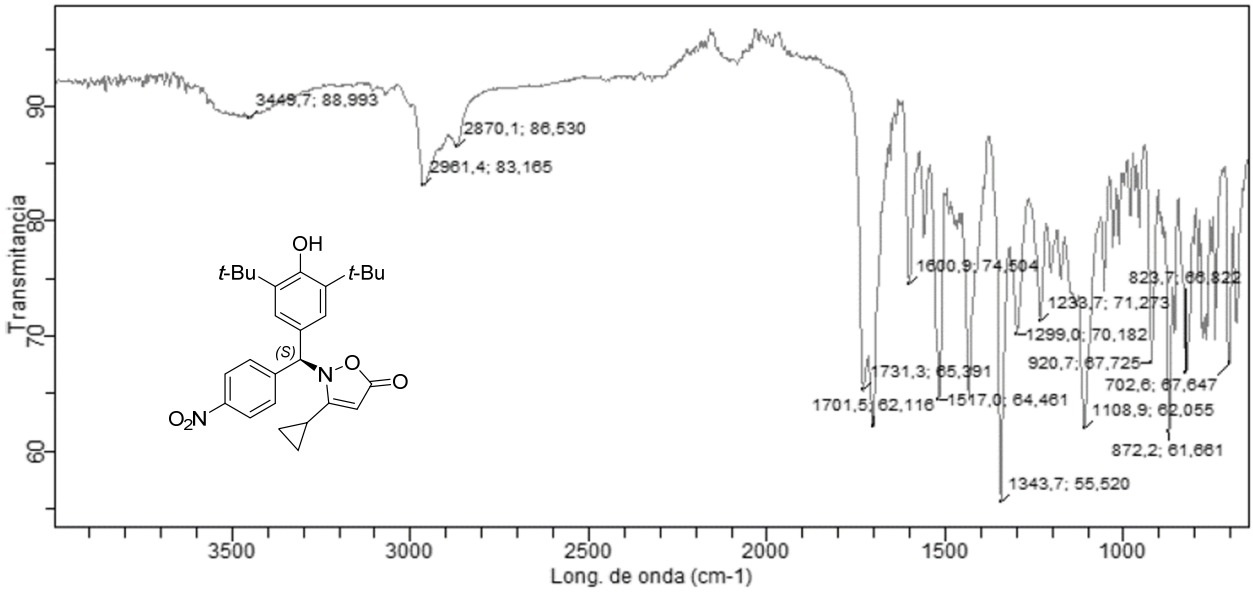
19: 270 nm, 4 nm
Results

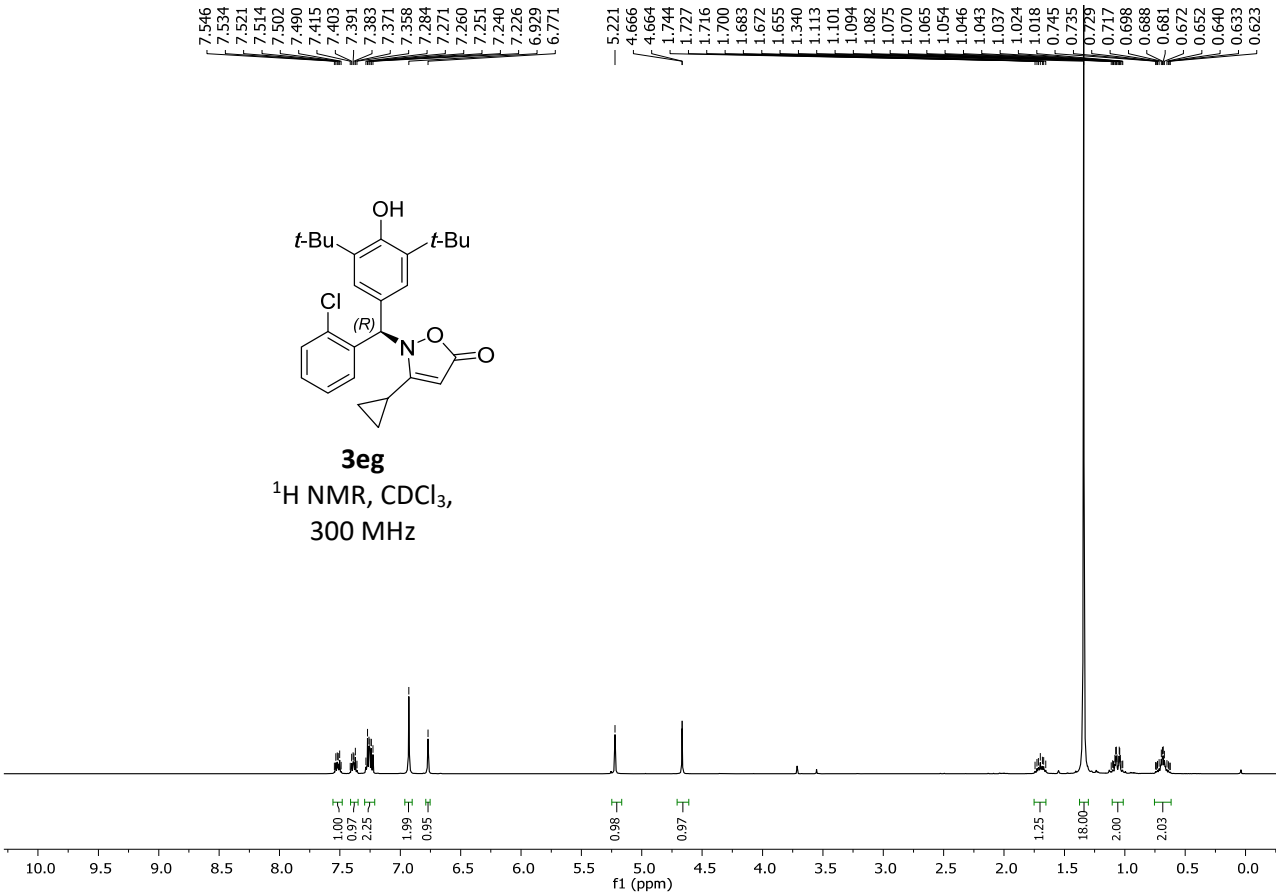
Retention Time	Area	Area Percent
22,19	246183501	48,666
25,36	259675010	51,334



19: 270 nm, 4 nm
Results

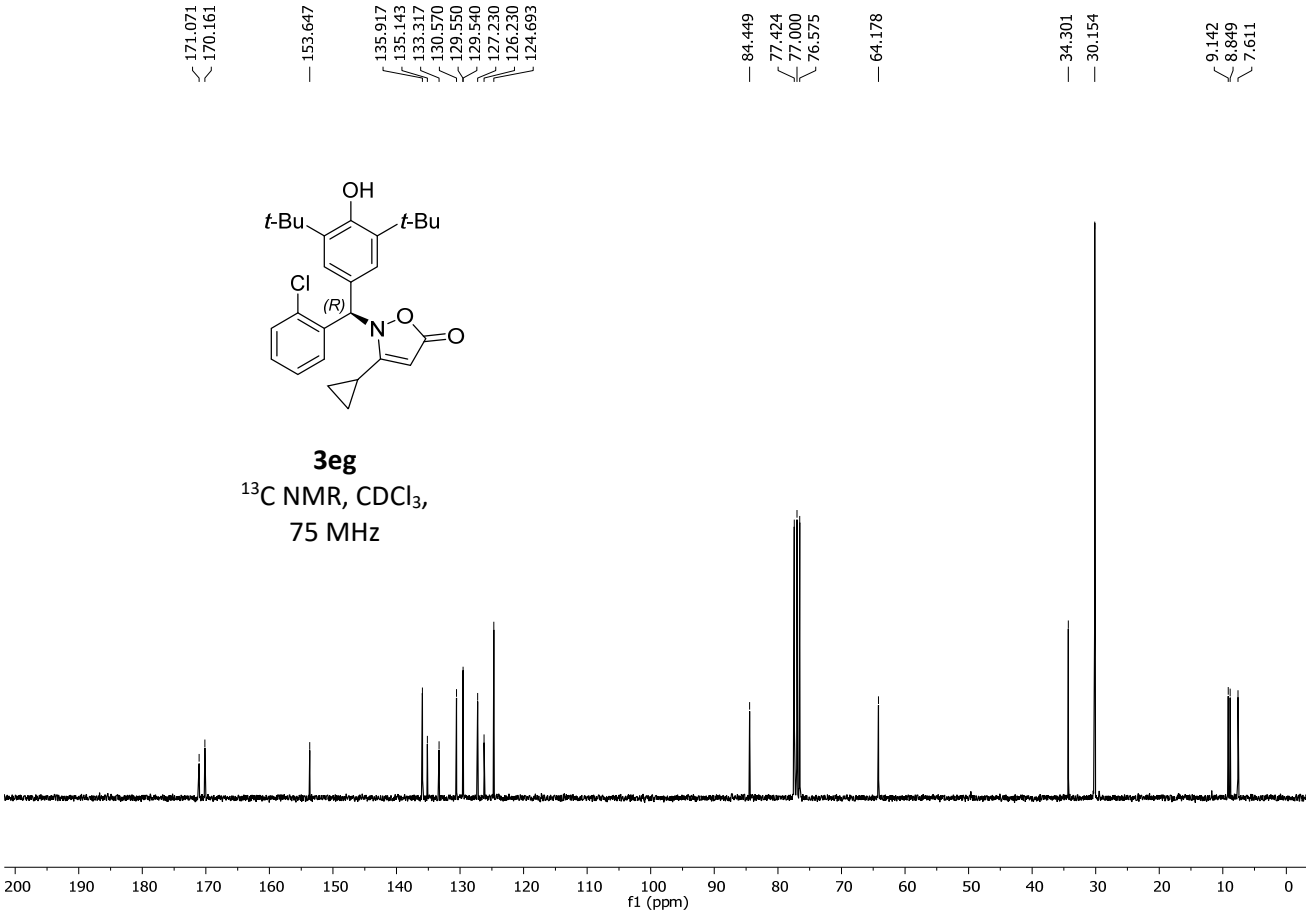
Retention Time	Area	Area Percent
22,12	270603193	93,185
25,88	19790623	6,815





3eg

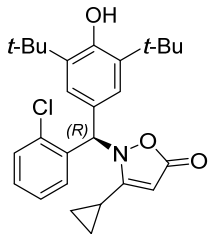
^{1}H NMR, $CDCl_3$,
300 MHz

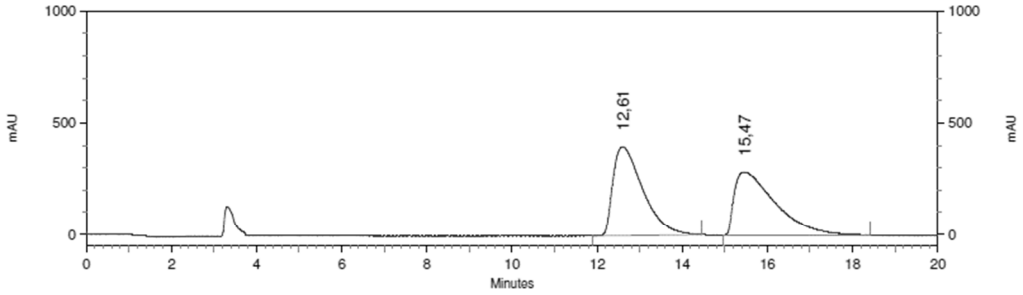


3eg

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

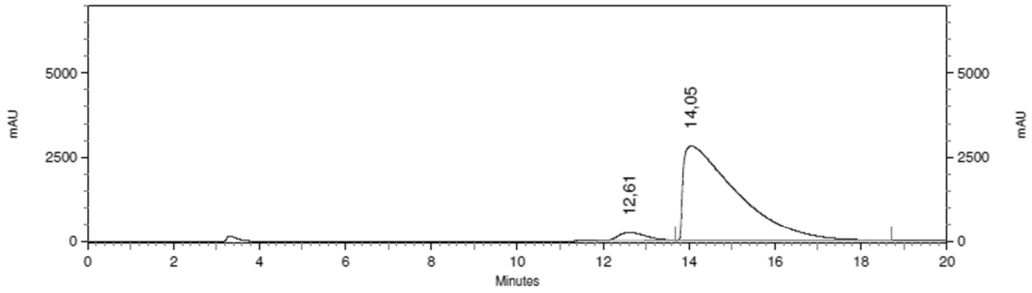
Compound **3eg**





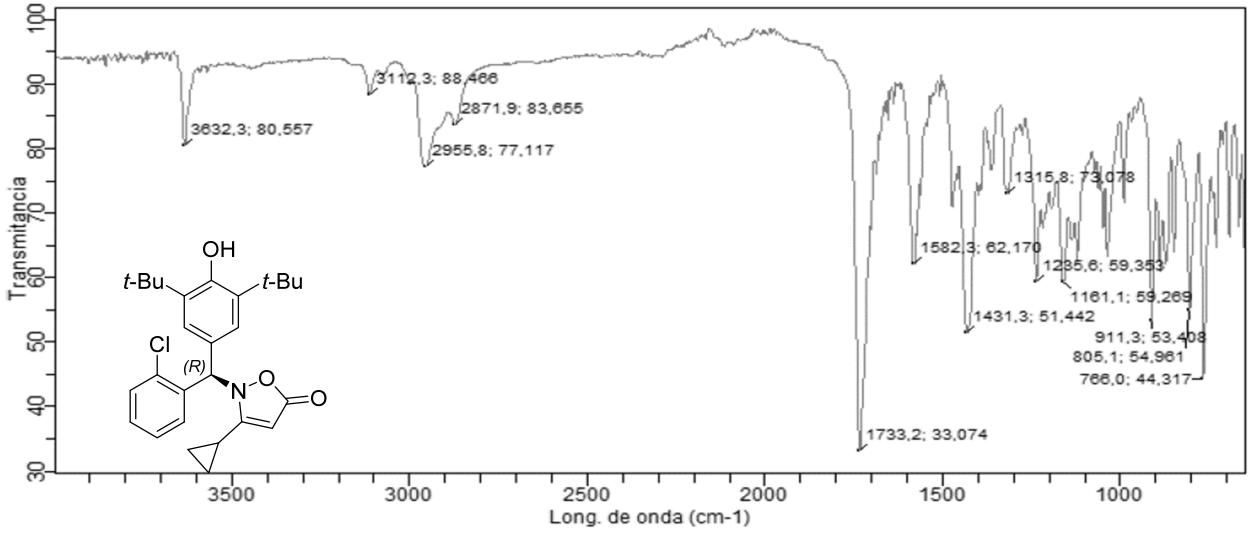
14: 244 nm, 4 nm
Results

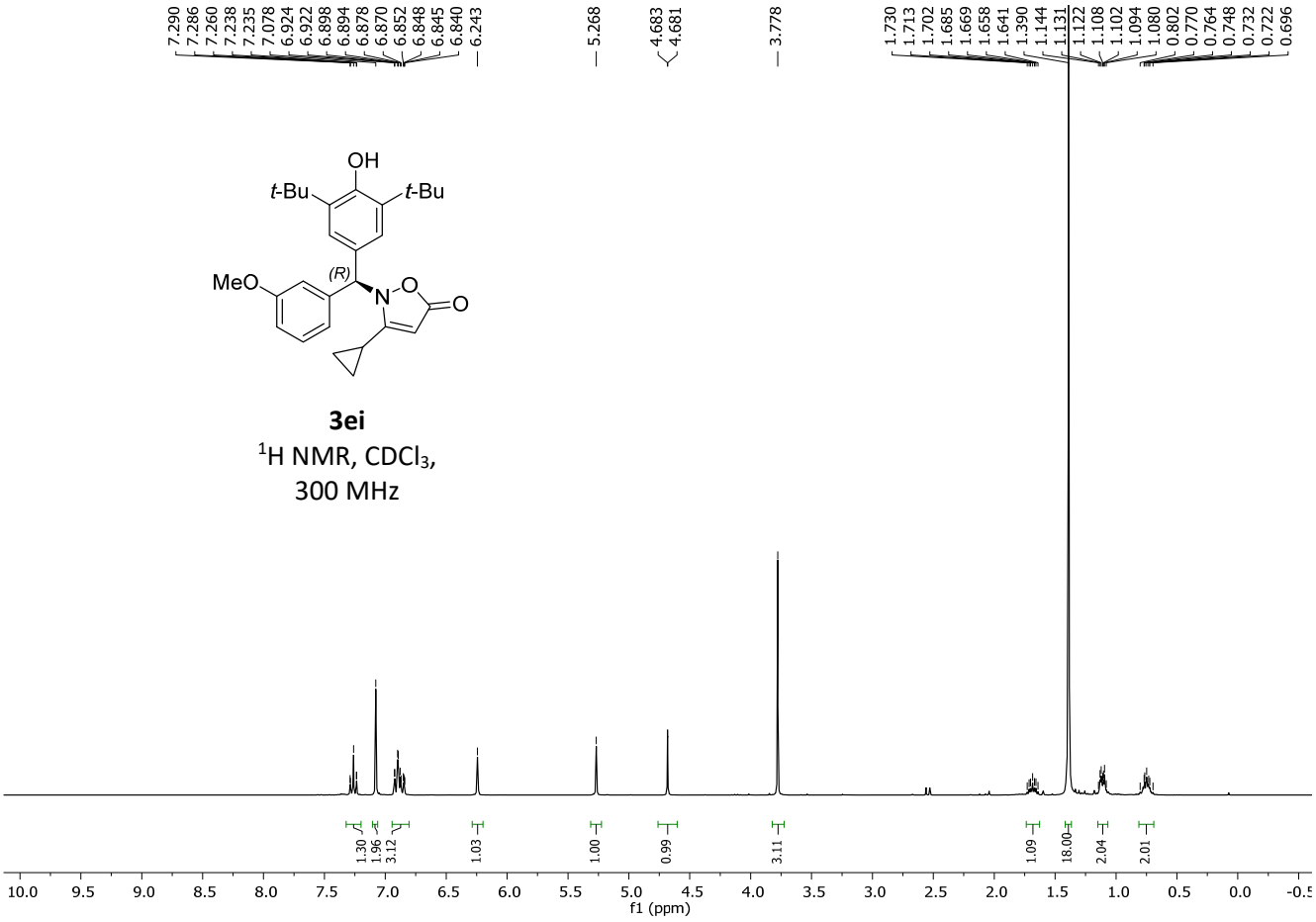
Retention Time	Area	Area Percent
12,61	78571546	50,299
15,47	77637291	49,701



18: 270 nm, 4 nm
Results

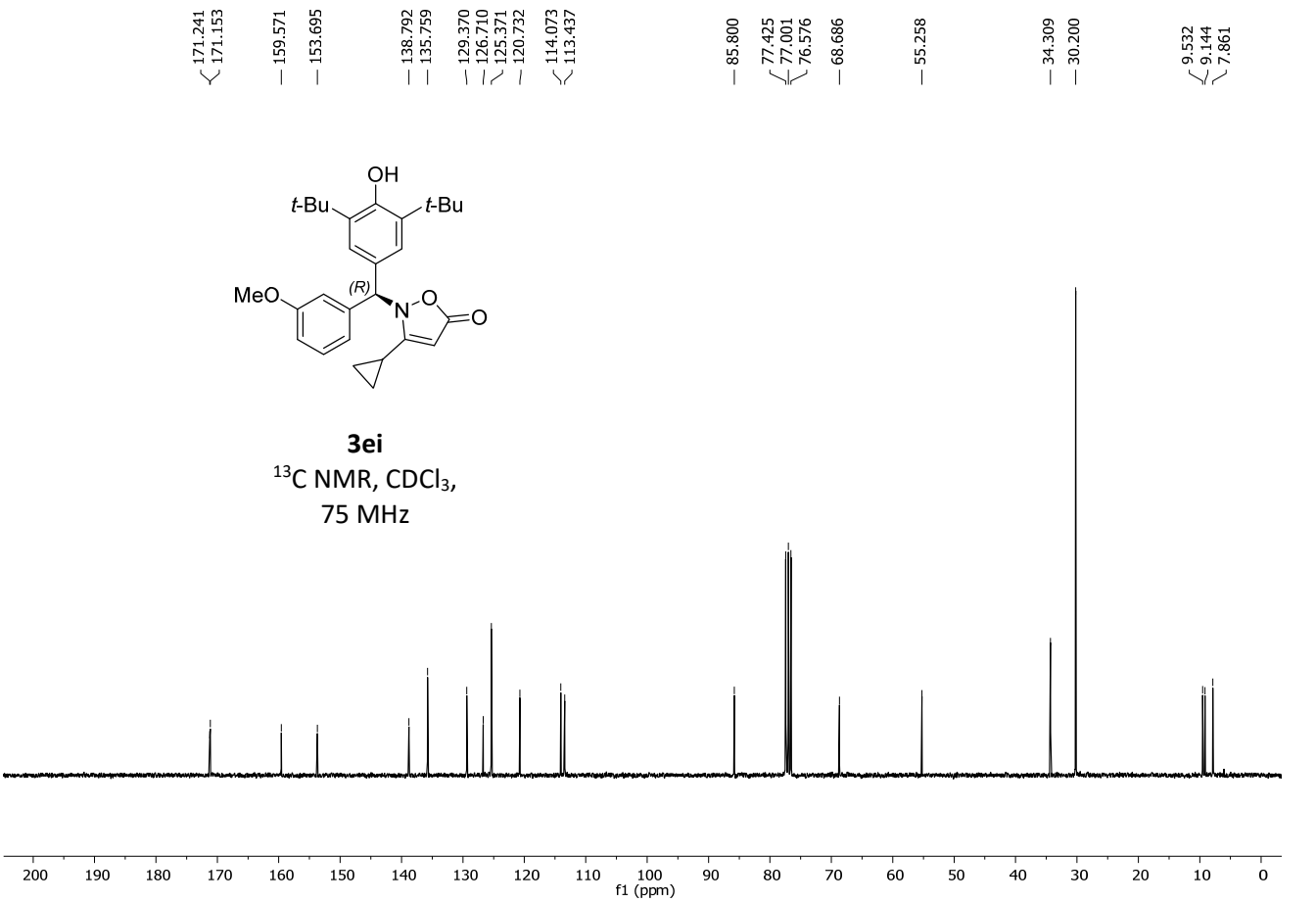
Retention Time	Area	Area Percent
12,61	42598081	4,138
14,05	986867069	95,862





3ei

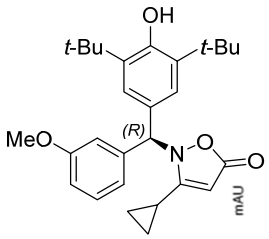
^{1}H NMR, $CDCl_3$,
300 MHz

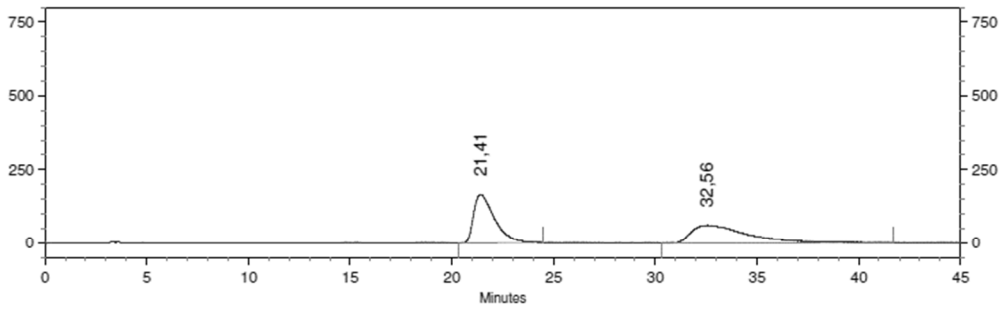


3ei

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

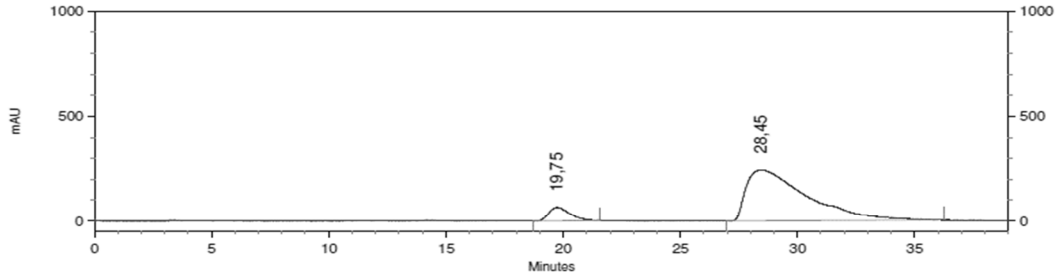
Compound **3ei**





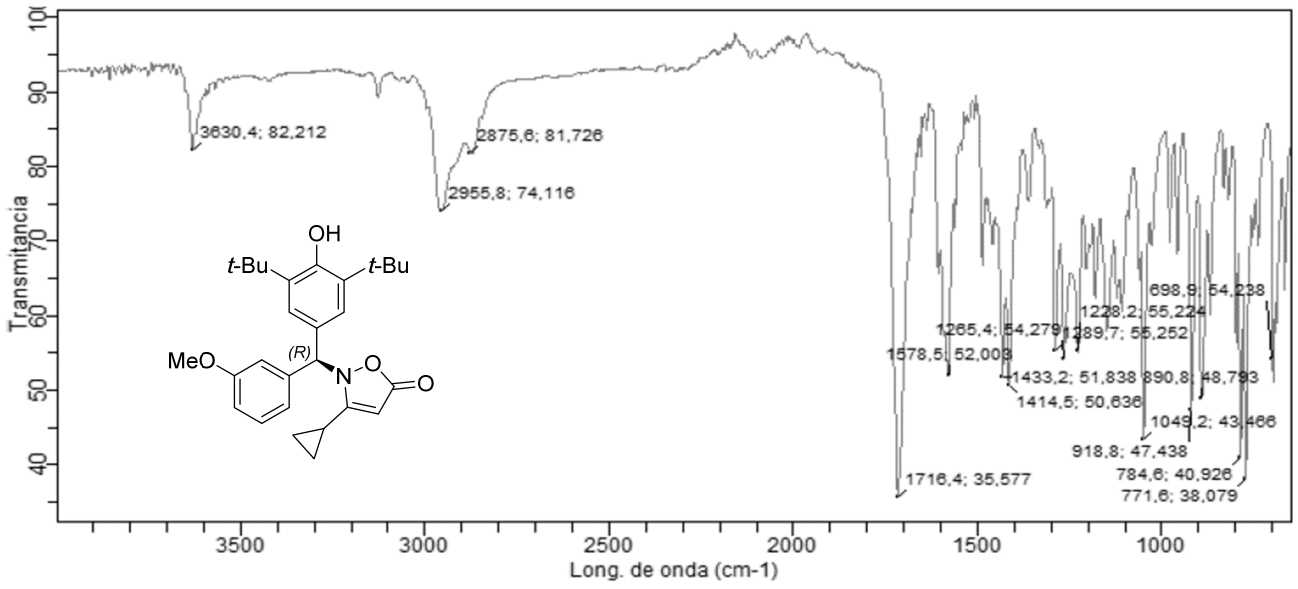
19: 270 nm, 4 nm
Results

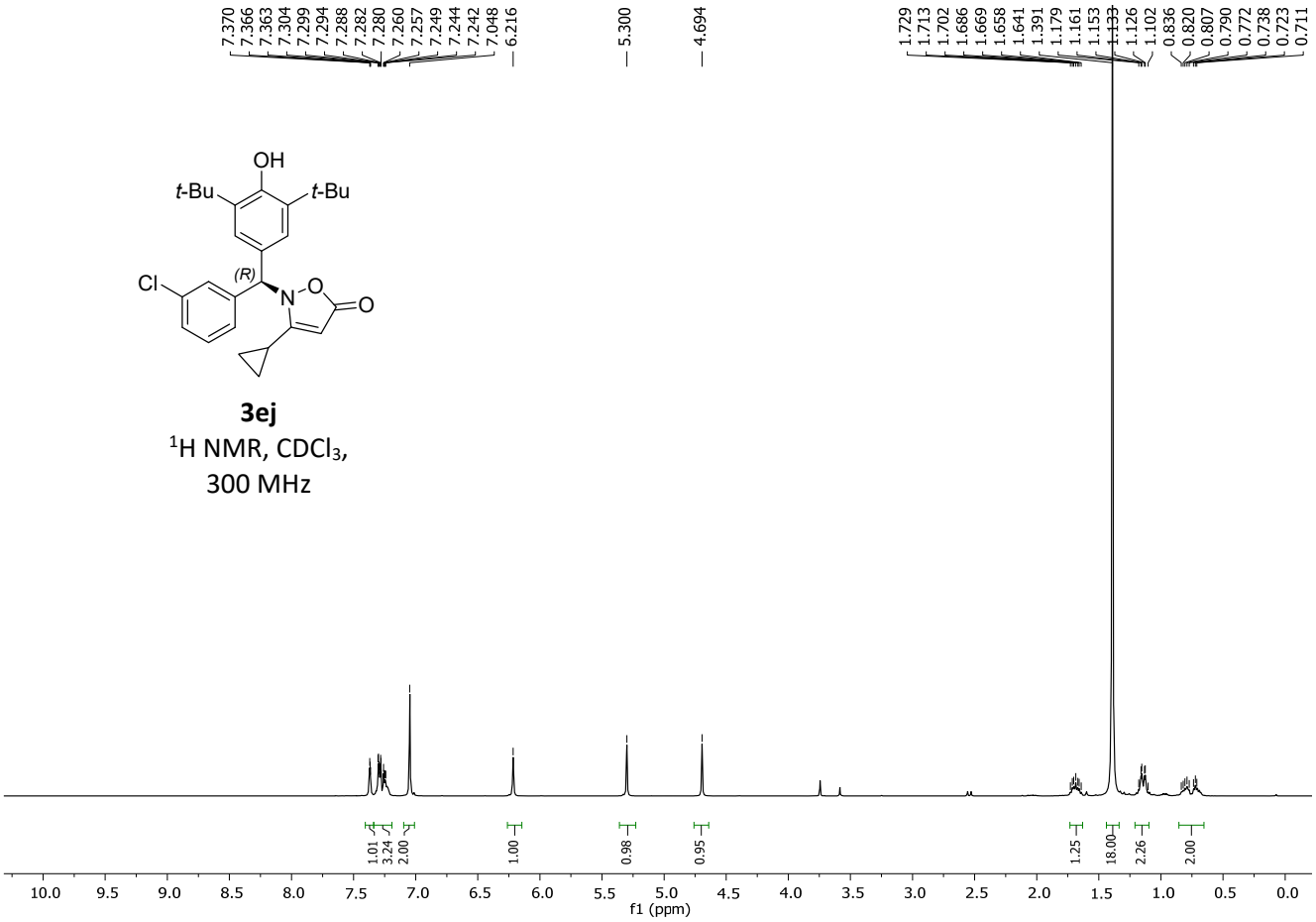
Retention Time	Area	Area Percent
21,41	47899978	49,491
32,56	48886206	50,509



19: 270 nm, 4 nm
Results

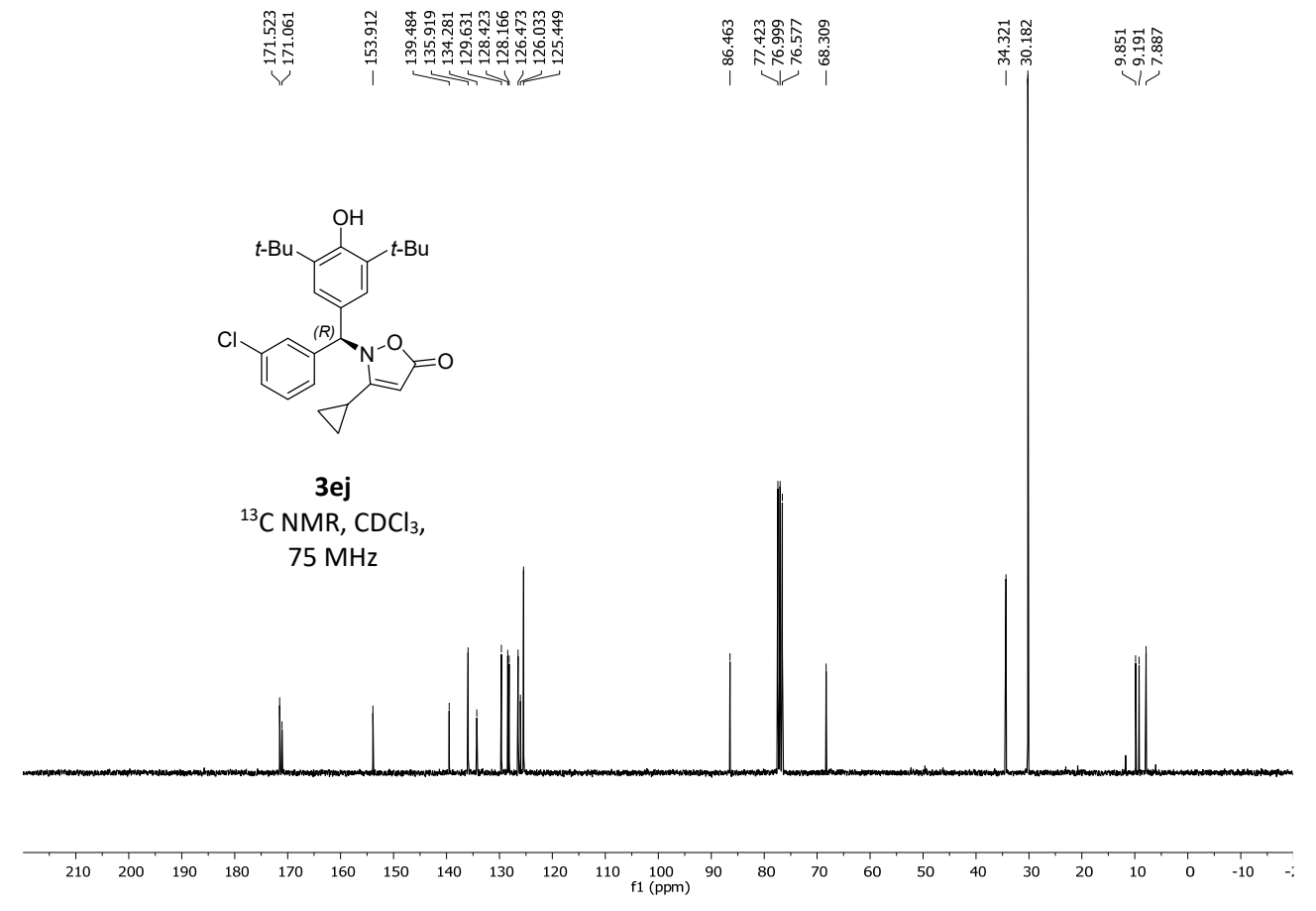
Retention Time	Area	Area Percent
19,75	16971436	8,735
28,45	177324020	91,265





3ej

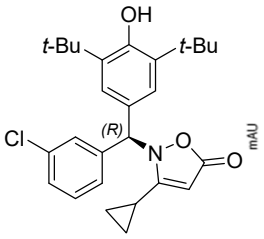
^{1}H NMR, $CDCl_3$,
300 MHz

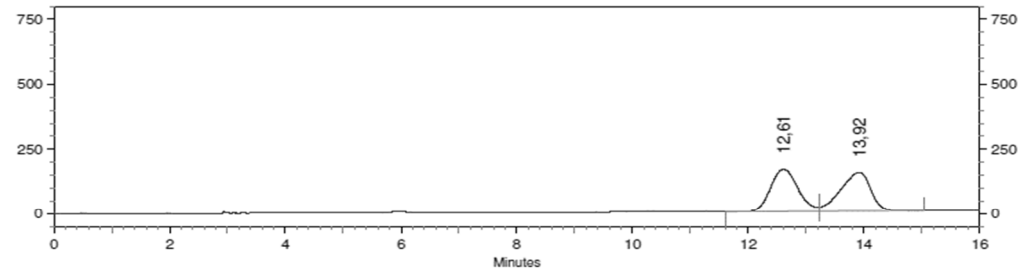


3ej

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

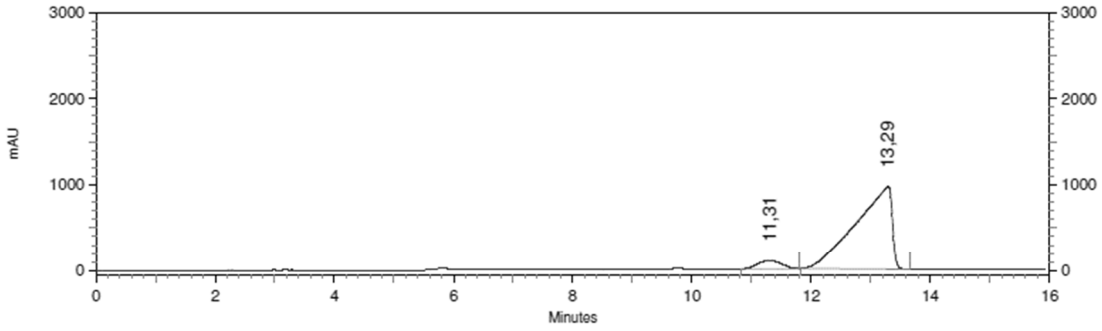
Compound **3ej**





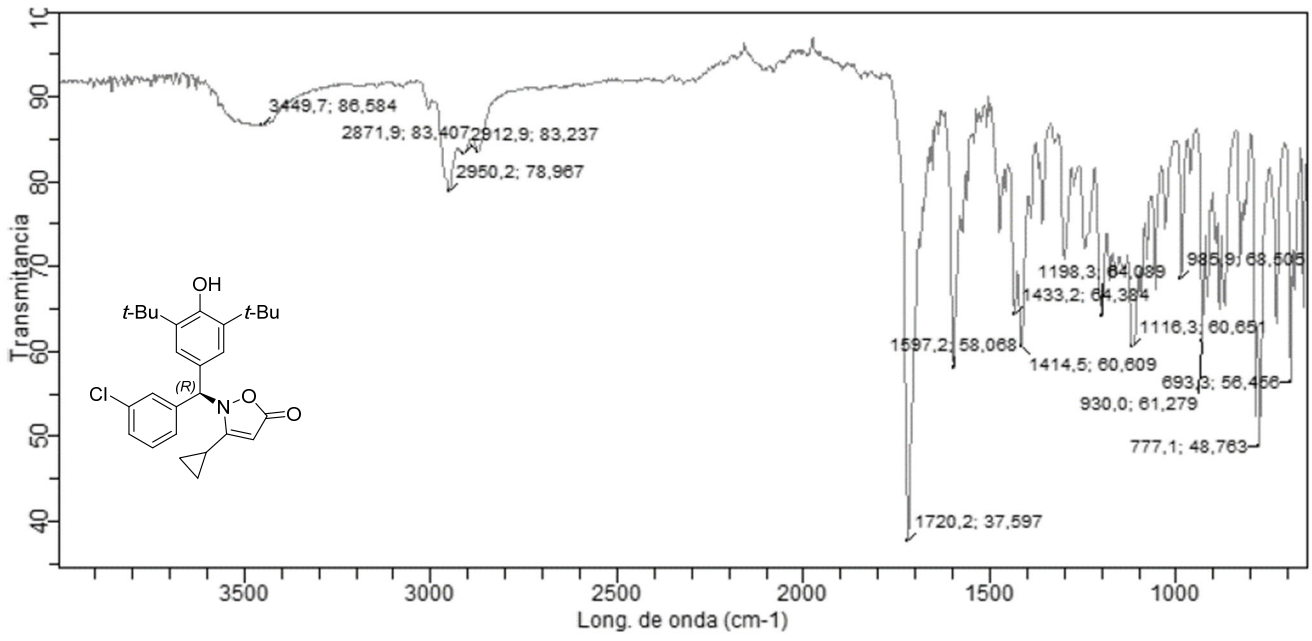
19: 270 nm, 4 nm
Results

Retention Time	Area	Area Percent
12,61	21755299	49,873
13,92	21866388	50,127



19: 270 nm, 4 nm
Results

Retention Time	Area	Area Percent
11,31	10839055	6,169
13,29	164853877	93,831



Additional optimization experiments

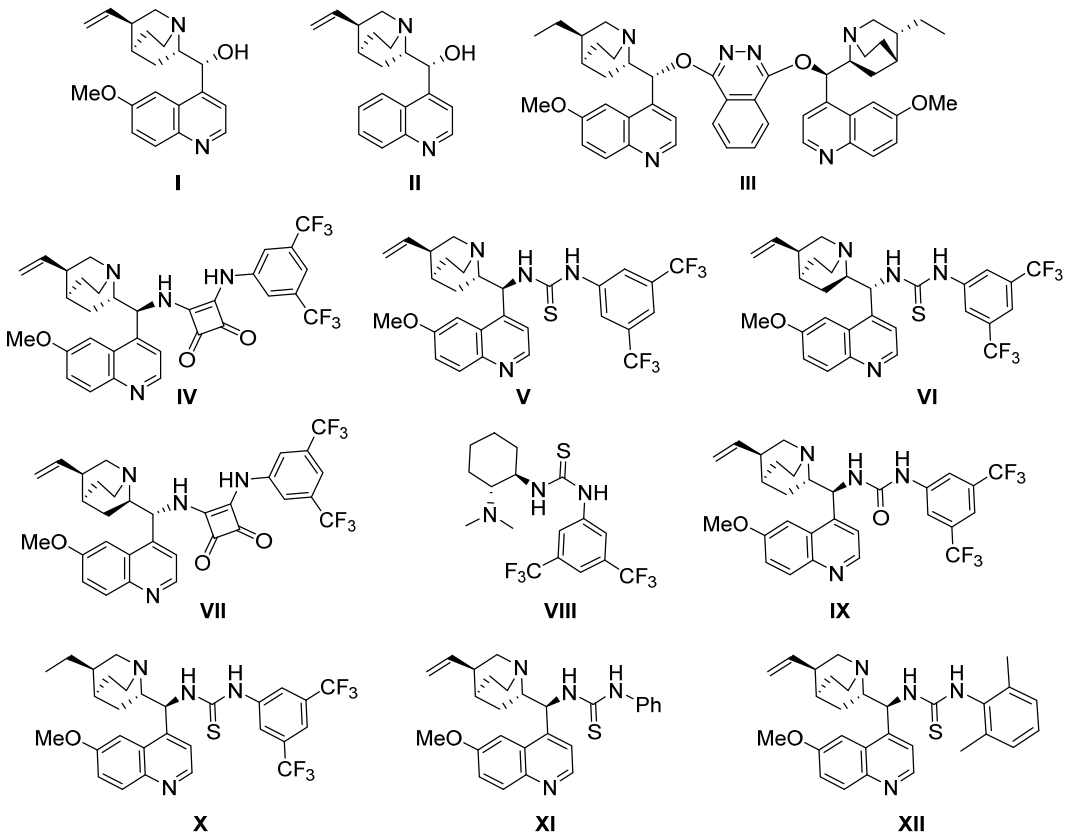
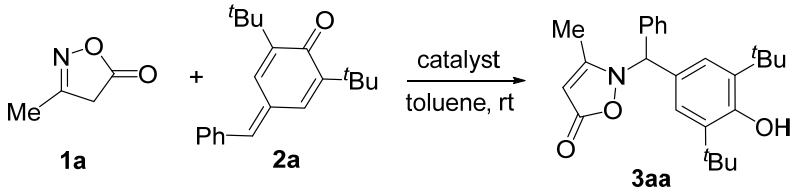


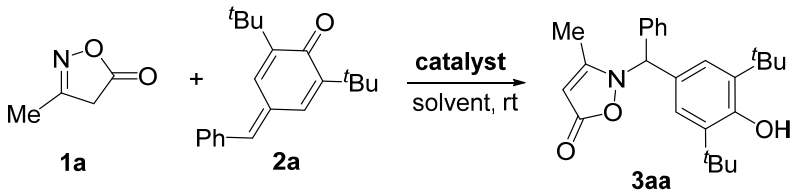
Table S1. Enantioselective addition of 3-methyl-4(*H*)-isoxazol-5-one (**1a**) to *p*-QM **2a**. Screening of ligands.[a]



entry	catalyst	yield [%][b]	*ee* [%][c]
1	**I**	30	56
2	**II**	36	52
3	**III**	30	25
4	**IV**	31	9
5	**V**	48	66
6	**VI**	23	37
7	**VII**	24	24
8	**VIII**	41	20
9	**IX**	49	58

[a] **1a** (0.1 mmol), **2a** (0.1 mmol), catalyst (0.005 mmol), toluene (1 mL), room temperature, 6 days. [b] Yield after column chromatography. [c] Determined by HPLC using chiral stationary phases.

Table S2. Enantioselective addition of 3-methyl-4(*H*)-isoxazol-5-one (**1a**) to *p*-QM **2a**. Screening of solvents.[a]

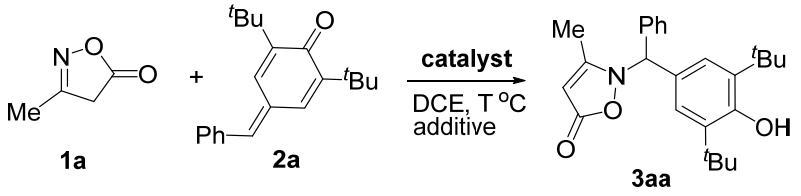


1a **2a** **3aa**

entry	catalyst	solvent	yield [%][b]	*ee* [%][c]
1	**V**	toluene	48	66
2	**V**	MTBE	34	61
3	**V**	Et_2O	33	58
4	**V**	EtOAc	38	57
5	**V**	Acetonitrile	26	23
6	**V**	DCM	61	76
7	**V**	$CHCl_3$	27	74
8	**V**	DCE	42	85
9	**X**	DCE	37	85

[a]**1a** (0.1 mmol), **2a** (0.1 mmol), catalyst **VIII** (0.005 mmol), solvent (1 mL), room temperature, 6 dayst. [b] Yield after column chromatography. [c] Determined by HPLC using chiral stationary phases.

Table S3. Enantioselective addition of 3-methyl-4(*H*)-isoxazol-5-one (**1a**) to *p*-QM **2a**. Effect of temperature, molar ratio and additives.[a]



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

entry	catalyst	catalyst [mol %]	1a/2a [molar ratio]	additive	*T* [°C]	yield [%][b]	*ee* [%][c]
1	**V**	5	1:1	-	r.t.	42	85
2	**V**	5	1:1	-	0	26	81
3	**V**	5	1.5:1	-	r.t.	43	79
4	**V**	5	1:1.5	-	r.t.	48	86
5	**V**	2.5	1:1.5	-	r.t.	37	61
6	**V**	10	1:1.5	-	r.t.	85	81
7	**XI**	5	1:1.5	-	r.t.	44	65
8	**XII**	5	1:1.5	-	r.t.	nd	11
9	**V**	5	1:1.5	3 Å MS	r.t.	65	87
10	**V**	5	1:1.5	4 Å MS	r.t.	57	87
11	**V**	5	1:1.5	5 Å MS	r.t.	59	85

[a] **1a** (0.1 mmol), **2a**, catalyst (0.005 mmol), DCE (1 mL), additive (32 mg), room temperature, 6 days. [b] Yield after column chromatography. [c] Determined by HPLC using chiral stationary phases.