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Organocatalytic Enantioselective Conjugate Addition of Isoxazol-5(4*H*)-Ones to Aurone-Derived Azadienes

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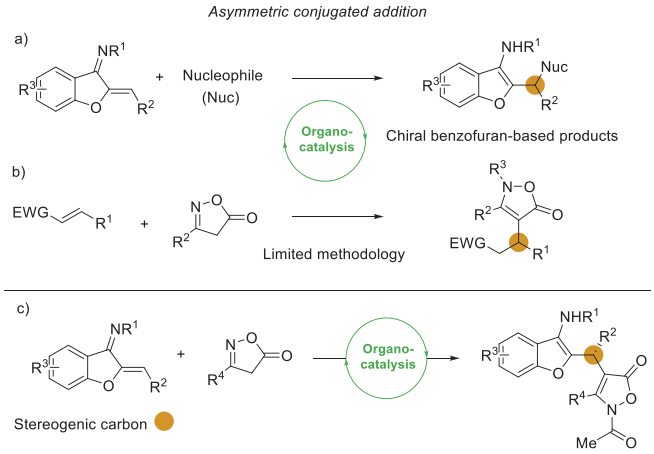
An efficient enantioselective organocatalytic conjugate addition of isoxazol-5(4*H*)-ones to aurone-derived azadienes under mild conditions has been developed. This methodology provides access to a wide range of chiral compounds featuring both benzofuran and isoxazole scaffolds in their structures achieving high yields and stereo control. Furthermore, the resulting adducts can be readily transformed into chiral β-benzofuran-branched carbonyl compounds in high yields and enantioselectivity in one-pot reaction through hydrolysis-decarboxylation of the isoxazole ring.

1. Introduction

Isoxazol-5(4*H*)-ones are important structural components in a wide variety of drugs and natural products.[1] These heterocycles are methylene active compounds due to the relatively acidic nature of the C4—H bond offering three potential nucleophilic sites within the ring: N2, C4, and the exocyclic carbonyl oxygen atom. Despite this, reactions typically occur at the N2 and C4 positions.[2] Moreover, they serve as synthetically versatile building blocks for the creation of ketones, alkynes, and other heterocycles.[3] However, despite their potential asymmetric methods for the alkylation of isoxazolin-5(4*H*)-ones are relatively limited especially in comparison to other five-membered heterocycles. There are a few successful examples of N2-regioselective organocatalytic chiral functionalization of isoxazol-5(4*H*)-ones using *para*-quinone methides (*p*-QMs) as electrophiles,[4a,b] and 1-acylamino-3-arylprop-2-yn-1-ols.[4d] On the other hand, organocatalytic strategies for the asymmetric C4-regioselective functionalization of isoxazol-5(4*H*)-ones have shown considerable promise with electrophiles such as nitroolefins,[5a] *N*-fluorobenzenesulfonimide,[5b] α'-alkylidene-2-cyclopentenones,[5c] β,γ-alkynyl-α-imino esters,[5d] and isatin-derived ketimines[5e] being effectively employed.

Benzofurans are also important heterocycles known for their widespread presence in nature and varied pharmacological properties.[6] In this context, aurone-derived azadienes characterized by their α,β-unsaturated imine structure are particularly valuable as electrophiles in asymmetric synthesis, enabling the formation of chiral compounds that incorporate the benzofuran group. This strategy facilitates the introduction of interesting nucleophiles leading to the formation of functionalized benzofurans derivatives.[7] Organocatalytic approaches using aurone-derived azadienes have been employed for the asymmetric formation of C—C bonds through conjugate addition with various nucleophiles such as γ-substituted β,γ-unsaturated γ-lactones,[8a] rhodanines,[8b] 3-homoacyl coumarins,[8c] 5*H*-thiazol-4-ones,[8d] 3-methylbenzofuran-2(3*H*)-ones,[8e] and α-aryl isocyanoacetates[8f] among others (Scheme 1a).



Scheme 1. Organocatalytic asymmetric conjugated reaction both isoxazol-5(4*H*)-ones and aurone-derived azadienes.

As previously mentioned, the use of isoxazol-5(4*H*)-ones as nucleophiles in asymmetric organocatalytic additions has been explored.[4,5] However, only a few successful methodologies have been reported for the alkylation of isoxazol-5(4*H*)-ones through organocatalytic asymmetric conjugate addition (Scheme 1b).[4a,b,5a] In this context our research group has described the first organocatalytic enantioselective C4-arylation of isoxazolinones using *o*-quinone diimides.[9] Notably, the newly developed procedure described here represents the first example of utilizing this privileged heterocycle as a nucleophile in asymmetric conjugate additions to α,β-unsaturated imines for alkylation purposes.

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Building on our expertise and continued interest in the use of isoxazol-5(4*H*)-ones[4a,5e,9] and aurone-derived azadienes[8f] in asymmetric additions as well as the synthetic potential and biological significance of both isoxazol-5(4*H*)-ones and benzofuran heterocycles, we have developed an organocatalytic asymmetric conjugate addition of isoxazol-5(4*H*)-ones to aurone-derived azadienes (Scheme 1c).This approach has been carefully designed to fully exploit the C4-regioselective nucleophilic properties of isoxazol-5(4*H*)-ones and the electrophilic reactivity of azadienes, enabling the efficient formation of new C—C bonds with high stereoselective control.

2. Results and Discussion

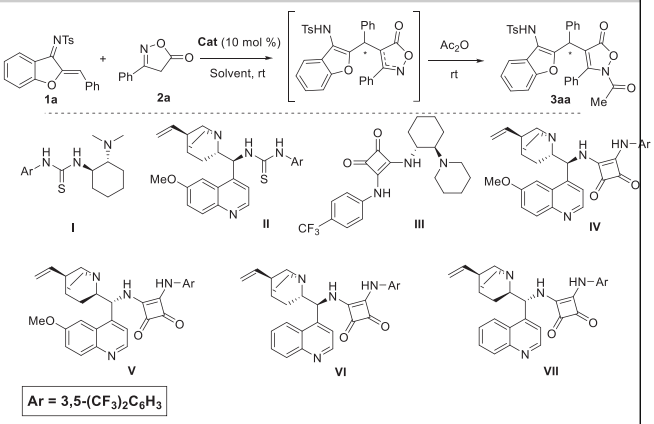
We initiated our study by examining the model reaction between aurone-derived azadiene **1a** and 3-phenylisoxazol-5(4*H*)-one (**2a**) in the presence of 10 mol% of Takemoto's catalyst **I** using dichloromethane as the solvent at room temperature (Table 1, entry 1). Interestingly, the desired conjugate addition product was obtained as a tautomer. To determine the enantiomeric ratio, the diastereomeric mixture was treated with acetic anhydride, yielding the *N*-acylated product **3aa** in 77% yield and with a fair enantiomeric ratio of 75:25. On the other hand, thiourea **II** derived of quinine gave product **3aa** in both low yield and low enantiomeric ratio (entry 2). The use of cyclohexane diamine-derived squaramide catalyst **III** led to a good yield and a higher enantiomeric ratio compared to the thiourea-based organocatalysts (entry 3 versus entries 1–2). Furthermore, an improvement in the enantiomeric ratio was observed when using squaramide **IV**, derived of quinine, as the catalyst (entry 4). At this stage, other squaramides derived from *Cinchona* alkaloids were tested (entries 5–7) with the best results being achieved with bifunctional squaramide **VI**, which provided a 69% yield and an enantiomeric ratio of 88:12 of **3aa** (entry 6).

The effect of different solvents on the reaction outcome was also explored. Interestingly, when the reaction was performed in 1,2-dichloroethane (DCE) resulted in an improved yield of **3aa** and a slightly increase in the enantiomeric ratio to 89:11 (entry 8). In contrast, employing chloroform led to a significantly lower yield of 53% and a reduced enantiomeric ratio of 78:22 (entry 9). When toluene was used, the reaction afforded product **3aa** in moderate yield (50%) and with a slightly lower enantiomeric ratio (84:16) compared to the halogenated solvents (entry 10 versus entries 7–8). Similarly, the use of tert-butyl methyl ether (MTBE) yielded compound **3aa** in similar yield and lower enantiomeric ratio compared to DCE (entry 11 versus entry 8).

Further optimization of the reaction conditions was conducted using DCE as the solvent. Performing the reaction under more dilute conditions (0.05 M for substrate **1a** instead of 0.1 M) resulted in an improved yield of **3aa** reaching 80% while maintaining the enantiomeric ratio at 89:11 (entry 12). Additionally, increasing the catalyst loading from 10 mol % to 15 mol % resulted in compound **3aa** being obtained in improved enantiomeric ratio of 92:08 (entry 13). The most significant improvement was achieved by adding 7.5 mol % benzoic acid as an additive[10] which increased the yield of **3aa** to 87% and further improved the enantiomeric ratio to 93:7 (entry 14).

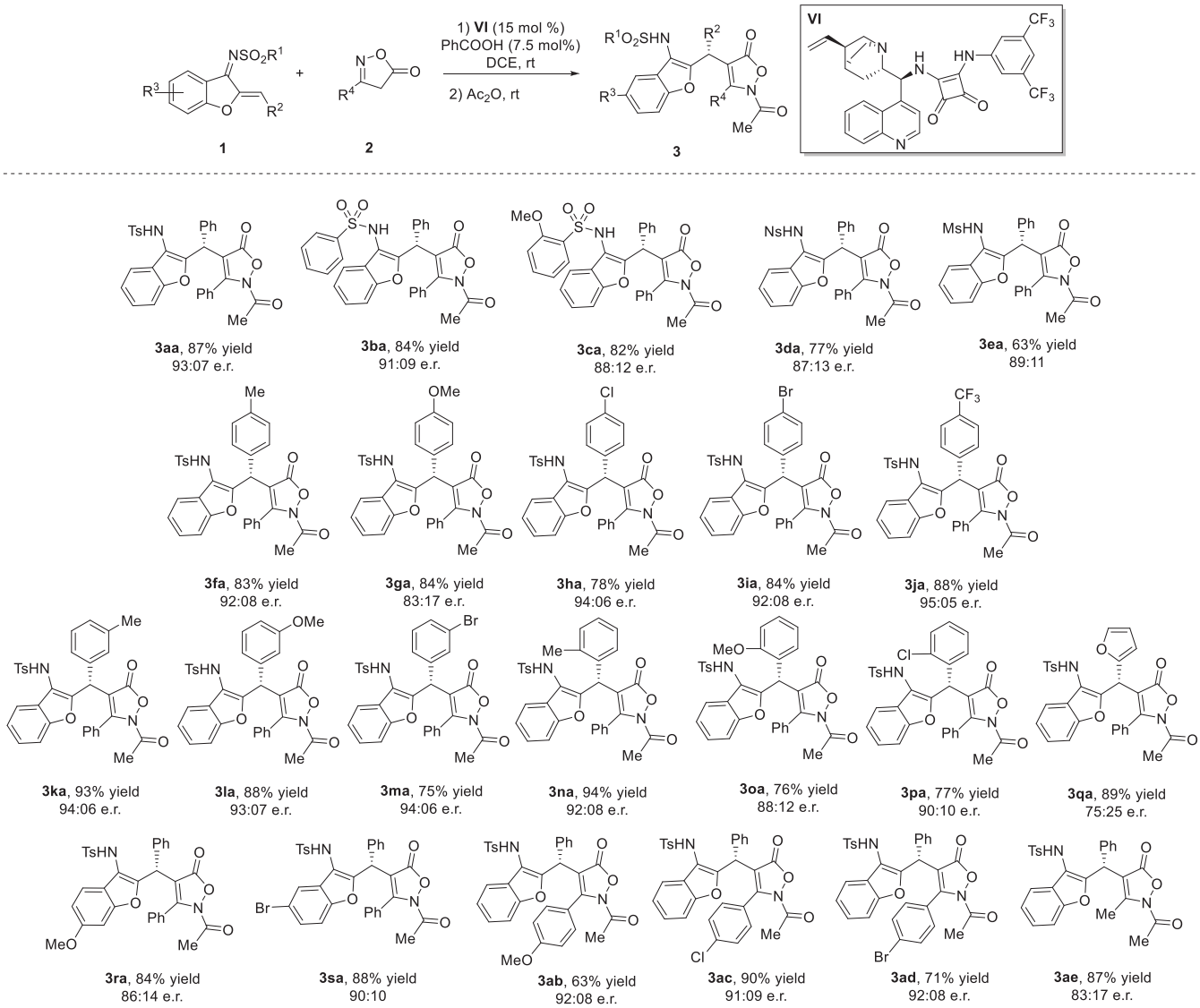
Based on the model proposed by Herrera and Diaz,[10] benzoic acid is likely to interact with the carbonyl groups of the squaramide through hydrogen bonding, thereby enhancing the acidity of the NH protons on the catalyst **VI**. However, at higher acid loadings, benzoic acid competes with 3-phenylisoxazol-5(4*H*)-one (**2a**) for deprotonation by the nitrogen of the quinuclidine, which explains the observed decrease in enantiomeric excess (entry 15).

Table 1. Optimization of the reaction conditions.



Entry[a]	Cat	Solvent	Yield [%][b]	er [%][c]
1	**I**	CH_2Cl_2	77	75:25
2	**II**	CH_2Cl_2	70	68:32
3	**III**	CH_2Cl_2	73	81:19
4	**IV**	CH_2Cl_2	48	84:16
5	**V**	CH_2Cl_2	68	85:15
6	**VI**	CH_2Cl_2	69	88:12
7	**VII**	CH_2Cl_2	77	85:15
8	**VI**	$Cl_2CH_2CH_2Cl_2$	74	89:11
9	**VI**	$CHCl_3$	53	78:22
10	**VI**	Toluene	50	84:16
11	**VI**	MTBE[d]	77	86:14
12[e]	**VI**	$Cl_2CH_2CH_2Cl_2$	80	89:11
13[e,f]	**VI**	$Cl_2CH_2CH_2Cl_2$	74	92:08
14[e,f,g]	**VI**	$Cl_2CH_2CH_2Cl_2$	87	93:07
15[e,f,h]	**VI**	$Cl_2CH_2CH_2Cl_2$	71	83:17

[a] **1a** (0.1 mmol), **2a** (0.1 mmol), **Cat** (0.01 mmol), solvent (1 mL), room temperature, 24 h.
[b] Yield of the isolated product.
[c] Determined by chiral HPLC.
[d] Tert-butyl methyl ether (MTBE).
[e] The reaction was carried out in 2 mL of DCE instead of 1 mL.
[f] The reaction was carried out with 15 mol% of catalyst loading.
[g] The reaction was carried out in presence of benzoic acid (0.0075 mmol).
[h] The reaction was carried out in presence of benzoic acid (0.015 mmol).

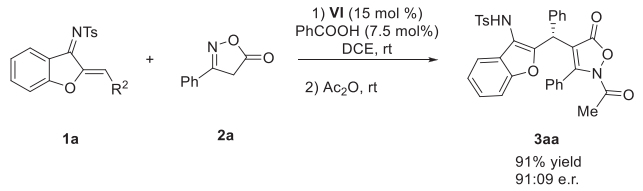


Scheme 2. Scope of the reaction. Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), benzoic acid (0.0075 mmol), **VI** (0.015 mmol), DCE (2 mL), room temperature, 24 h. Overall isolated yields. Enantiomeric ratio determined by chiral HPLC analysis.

With the best available conditions established (Table 1, entry 14), the scope and limitations of the reaction were studied, initially testing various imines derived from aurone-derived azadiene **1** with 3-phenylisoxazol-5(4*H*)-one (**2a**) (Scheme 2).

Initially, the effect of the substituent on the *N*-sulfonyl group was studied (**1b**–**1e**). Several arylsulfonyl imines with different R^1 groups, including phenyl- (**1b**), *o*-methoxyphenyl- (**1c**) or nosyl- (**1d**) sulfonylimines, as well as the methanesulfonyl imine **1e** were successfully tested affording the corresponding compounds with similar results, although none of these provided yields and enantioselectivities above those obtained with the tosylimine **1a**. Next, a wide range of *N*-tosyl aurone-derived azadienes (**1f**-**1q**) with differently substituted aromatic rings attached to the exocyclic double bond was reacted with 3-phenylisoxazol-5(4*H*)-one (**2a**), aiming to examine the impact of electronic and esteric effect of different substituents at the *para*, *meta*, and *ortho* positions on reaction yield and enantioselectivity.

As shown in Scheme 2, the electronic effects of various substituents in the *para* position of the aromatic ring (**1f**--**1j**) were investigated. Slightly electron-donating groups, such as the methyl group, produced product **3fa** in high yield and with good enantiomeric ratio (92:08). Azadiene **1f** substituted with a strongly electron-donating group, such as methoxy, influenced the enantiomeric ratio resulting in **3ga** in 84% yield and 83:17 er. In contrast, electron-withdrawing groups such as chloro and bromo, yielded the products **3ha** and **3ia** in both higher yields and higher enantiomeric ratios of 94:06 and 92:08, respectively. Interestingly, the trifluoromethyl substituent, an interesting substituent due to the unique properties of fluorinated groups[11] provided the corresponding product **3ja** in 88% yield and the highest 95:05 er. Our methodology proved to be robust for *meta*-substituted aurone-derived azadienes (**1k**–**1m**), bearing either electron-donating substituents, such as methyl and methoxy, or electron-withdrawing groups, such as bromo, yielded the corresponding adducts **3ka**-**3ma** with high yields and enantiomeric



Scheme 3. Reaction at 1 mmol scale.

ratios equal to or higher than 93:07. Notably, *ortho*-substituted phenyl rings attached to the exocyclic double bond bearing electron-withdrawing or electron-donating substituents were also tolerated (**1n**-**1p**) yielding the desired products **3na**-**3pa** in high yields and good to high enantioselectivities. Additionally, this study was extended to include an aurone-derived azadiene substituted with a heteroaromatic 2-furanyl group **1q** affording compound **3qa** in high yield (89%) and fair enantiomeric ratio (75:25). To further expand the substrate scope, azadienes derived from 4-methoxybenzofuran **1r** and 5-bromobenzofuran **1s** was tested. The corresponding desired products **3ra** and **3sa** were obtained with good results.

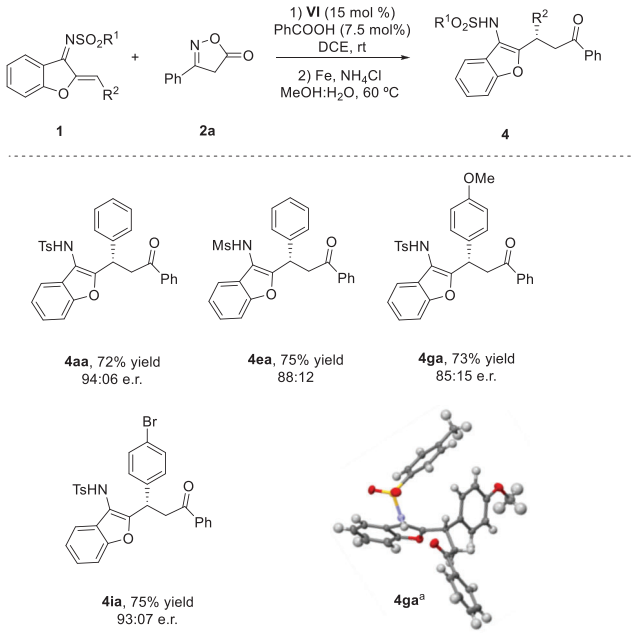
Finally, isoxazol-5(4*H*)-ones **2b**–**2d** bearing different substituents at position 3 were explored. Reactions with isoxazol-5(4*H*)-ones bearing *para*-substituted phenyl rings at C3 (**2b**–**2d**) afforded the desired products **3ab** and **3ad** with high enantiomeric ratios, similar to those obtained with isoxazol-5(4*H*)-one **2a**. Moreover, the reaction showed good tolerance for an aliphatic substituent, such as a methyl group at C3 in isoxazol-5(4*H*)-one **2e**, yielding the corresponding compound **3ae** in 87% yield and 83:17 e.r.

To assess the applicability and robustness of the protocol, a scalability study was performed (Scheme 3). In this study, 1 mmol of both the aurone-derived azadiene **1a** and 3-phenyl-isoxazol-5(4*H*)-one (**2a**) was reacted under the optimized conditions. The reaction afforded **3aa** in 91% yield with a 91:09 enantiomeric ratio consistent with the results obtained on smaller scale (0.1 mmol of reactants).

Finally to demonstrate the synthetic potential of the isoxazole ring and our protocol, we conducted a one-pot organocatalytic enantioselective addition of isoxazol-5(4*H*)-ones **2** to aurone-derived azadiene **1** followed by an iron-mediated hydrolysis-decarboxylation reaction (Scheme 4).[5e] This strategy produced chiral β-branched ketones **4** featuring a benzofuran ring at the beta position. While similar syntheses have been achieved through the organocatalytic 1,4-addition of activated ketones to azadienes,[12,13] the synthesis of ketones **4** via 1,4-addition of nonactivated ketones to azadienes forming an enol intermediate remains unreported. Our method offers a valuable route to those challenging substrates and otherwise difficult to access reactions.

The absolute configuration of the stereo genic center in compound **4ga** was determined to be *S* based on X-ray crystallographic analysis (Scheme 4). The configurations of the remaining compounds **4** and **3** were assigned as *S* and *R*, respectively, under the assumption of a uniform mechanistic pathway.[14]

Based on the obtained results and the observed absolute configuration we propose a plausible stereo-control model outlined in Figure 1. The bifunctional catalyst **VI** is responsible for activating both substrates and reorienting them. The isoxazol-5(4*H*)-one **2** is deprotonated by the tertiary amine of the quinuclidine ring while the aurone-derived azadiene **1** is activated through hydrogen bonding between the *N*-tosyl group and the squaramide. Additionally, benzoic acid modulates the acidity of the squaramide. Subsequently, approach of the isoxazol-5(4*H*)-one from the *Si* face of the azadiene's double bond leads to the corresponding addition product **3** with the observed stereochemistry.



Scheme 4. Synthesis of ketones **4**. Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), benzoic acid (0.0075 mmol), **VI** (0.015 mmol), DCE (2 mL), at 60 °C for 24 h. Overall isolated yields. Enantiomeric ratios determined by chiral HPLC analysis. X-ray structure of compound **4ga**. Flack parameter 0.037(18).

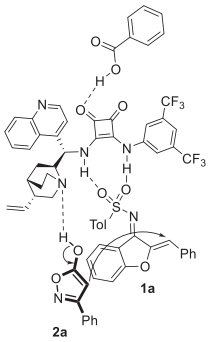


Figure 1. Proposed stereochemical model.

3. Conclusion

In conclusion, a novel enantioselective organocatalytic conjugate addition of isoxazol-5(4*H*)-ones to aurone-derived azadienes[15] was successfully developed under mild organocatalytic conditions. This procedure enables the efficient synthesis

of structurally complex chiral compounds with both benzofuran and isoxazole frameworks achieving good levels of enantioselectivity and high yields. Moreover, the versatility of the approach is demonstrated by the straightforward transformation of the adducts into chiral β-benzofuran-branched carbonyl compounds through hydrolysis-decarboxylation of the isoxazole ring in high yields and stereocontrols.

Supporting Information

The authors have cited additional references within the Supporting Information (Supporting Information).[16–19]

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Aurone-derived azadienes · Conjugate addition · Enantioselective · Isoxazol-5(4*H*)-ones · Organocatalysis

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[14] Deposition number CCDC 2411649 for **4ga**, contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[15] Following the indications of one of the reviewers, we tested our reaction conditions with the tosyl and mesyl imines derived from chalcone. Despite the reaction proceeding, a complex mixture containing Z and E isomers of enamine products as well as carbonyl compounds resulting from the hydrolysis of imine and enamine compounds was obtained. These drawbacks do not occur with substrates **1** due to their cyclic nature and to re-aromatization.

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Organocatalytic Enantioselective Conjugate Addition of Isoxazol-5(4*H*)-ones to Aurone-Derived Azadienes

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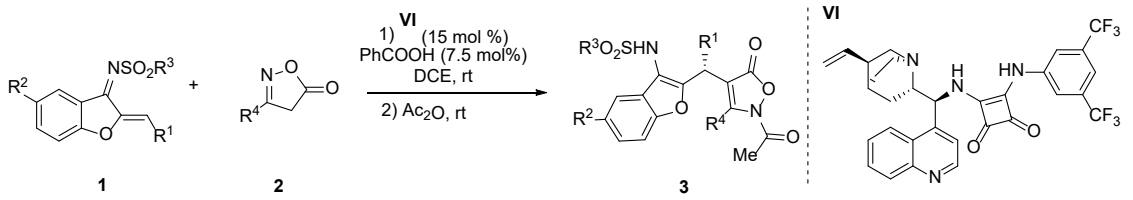
Experimental methods

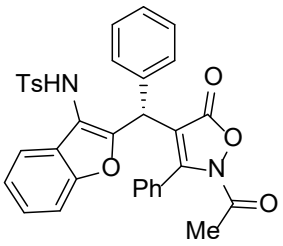
Unless it is stated otherwise, reactants were obtained from commercial sources and used directly without further purification. Reactions were monitored with Merck 60 F_{254} (reference 5554 Merk) silica gel plates. The eluted TLC plates were visualized under 254 nm UV light and revealed with stain solutions of cerium molybdate or potassium permanganate. Flash column chromatography was carried out using a Silica Gel Merck 60 stationary phase (reference 109385 Merck), with a 0.040-0.063 mm particle range size. The eluent was made to flow through the column with an air pump. NMR spectra were recorded using a Bruker Avance III 300 at 300 MHz for ^{1}H, or 75 MHz for ^{13}C. Signals of non-deuterated residual solvent were used as internal standard (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C in chloroform; and 2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C in DMSO-d_6.[16] Chemical shifts (δ) are expressed in ppm and coupling constants (*J*), in Hz. HRMS were recorded using a Waters Q-TOF spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV (ESI). Specific optical rotations were measured using a Bellingham+Stanley ADP430 polarimeter equipped with a LED light source, measuring at the sodium wavelength (D line, 589 nm) and a 1 dm path length cuvette. Concentrations are expressed in g/100 mL. Enantiomeric excesses were measured through HPLC analysis, using a Hitachi Elite Lachrom chromatograph with a Hitachi L-4500 or L-2455U UV diode array detectors. Daicel or Phenomenex columns with chiral stationary phases were employed, and the samples were eluted with mixtures of HPLC-grade hexane and isopropyl alcohol. Aurone-derived azadienes **1**,[17] isoxazol-5(4*H*)-ones **2**[18] and squaramide **VI**[19] were prepared according to literature procedures.

General procedure for the synthesis and characterization of the products 3



In a test tube, aurone-derived azadiene **1** (0.1 mmol), isoxazol-5(4*H*)-one **2** (0.1 mmol), catalyst **VI** (9 mg, 0.015 mmol), and benzoic acid (1 mg, 0.0075 mmol) are introduced and purged with nitrogen. The reaction mixture is dissolved in dry 1,2-dichloroethane (2 mL) and stirred at room temperature for 24 hours. After complete consumption of the starting substrates, acetic anhydride (20 μL, 0.2 mmol) is added, and the reaction is stirred at room temperature for 30 minutes. Subsequently, the mixture is purified by column chromatography using Hexane:EtOAc solvent mixtures.

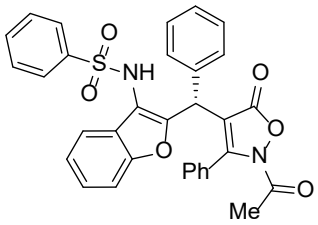
(*R*)-*N*-(2-((2-Acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3aa)



50.0 mg (87%) were obtained from **1a** (37.5 mg) and **2a** (16 mg). The enantiomeric excess (86%) was determined by HPLC (Chiralpak IC) hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 50.3 min, minor enantiomer: t_r = 40.0 min.

Yellow solid; m.p. = 96.2-97.8 ºC; $[\alpha]_D^{25}$ = -2.8 (*c* = 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.3 Hz, 2H), 7.44-7.34 (m, 3H), 7.34-7.27 (m, 3H), 7.25-7.20 (m, 2H), 7.16-7.08 (m, 4H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.96-6.90 (m, 2H), 6.50 (s, 1H), 5.05 (s, 1H), 2.38 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (C), 164.3 (C), 155.7 (C), 153.3 (C), 151.2 (C), 143.7 (C), 136.4 (C), 136.2 (C), 130.6 (CH), 129.5 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.3 (CH), 127.2 (CH), 126.8 (C), 125.9 (C), 124.8 (CH), 123.2 (CH), 119.8 (CH), 115.1 (C), 111.5 (CH), 107.6 (C), 37.4 (CH), 22.9 (CH_3), 21.4 (CH_3); HRMS (ESI) *m/z*: 579.1574 $[M+H]^+$, $C_{33}H_{27}N_2O_6S^+$ requires 579.1584.

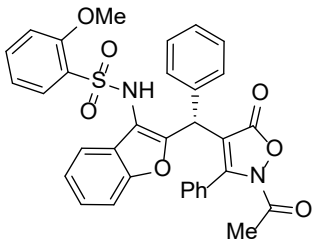
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)benzofuran-3-yl)benzenesulfonamide (3ba)



47 mg (84%) were obtained from **1b** (36 mg) and **2a** (16 mg). The enantiomeric excess (82%) was determined by HPLC (Phenomenex® Lux *i*-Amylose-1), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 34.7 min, minor enantiomer: t_r = 41.8 min.

Yellow oil; **[α]$_D^{25}$** = -1.6 (*c* = 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.60 (m, 2H), 7.45-7.31 (m, 7H), 7.24-7.17 (m, 5H), 7.08-7.05 (m, 2H), 7.02 (d, *J* =1.8 Hz, 1H), 7.01 (d, *J* = 4.0 Hz, 1H), 6.63 (s, 1H), 5.11 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 166.3 (C), 164.3 (C), 155.7 (C), 153.2 (C), 151.6 (C), 139.6 (C), 126.5 (C), 132.8 (CH), 130.6 (CH), 128.9 (CH), 128.53 (CH), 128.46 (CH), 128.3 (CH), 128.2 (CH), 127.4 (CH), 127.1 (CH), 126.9 (C), 125.8 (C), 124.7 (CH), 123.2 (CH), 119.4 (CH), 114.8 (C), 111.6 (CH), 107.6 (C), 37.6 (CH_3), 22.9 (CH_3); HRMS (ESI) *m/z*: 565.1415 $[M+H]^+$, $C_{32}H_{25}N_2O_6S^+$ requires 565.1428.

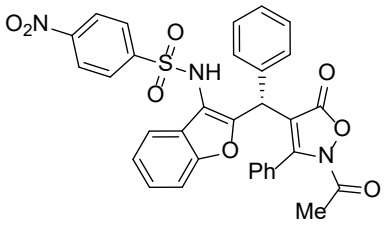
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)benzofuran-3-yl)-2-methoxybenzenesulfonamide (3ca)



46.4 mg (82%) were obtained from **1c** (39 mg) and **2a** (16 mg). The enantiomeric excess (76%) was determined by HPLC (Phenomenex® Lux *i*-Amylose-1), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 22.5 min, minor enantiomer: t_r = 27.0 min.

Yellow oil; $[\alpha]_D^{25}$ = +4.0 (*c* = 0.93, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.44-7.31 (m, 6H), 7.24-7.06 (m, 7H), 6.98 (s, 1H), 6.95 (d, *J* = 1.9 Hz, 1H), 6.93 (d, *J* = 3.9 Hz, 1H), 6.89-6.75 (m, 2H), 5.37 (s, 1H), 3.96 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C), 164.4 (C), 156.1 (C), 155.7 (C), 153.1 (C), 150.8 (C), 136.8 (C), 134.7 (CH), 130.5 (CH), 129.9 (CH), 128.6 (CH), 128.30 (CH), 128.26 (CH), 128.2 (CH), 127.9 (CH), 127.1 (CH), 127.0 (C), 126.0 (C), 124.6 (CH), 123.1 (CH), 120.5 (CH), 119.3 (CH), 115.3 (C), 112.0 (CH), 111.5 (CH), 107.7 (C), 56.3 (CH_3O), 37.3 (CH), 22.9 (CH_3), 22.9 (CH_3); HRMS (ESI) *m/z*: 595.1512 $[M+H]^+$, $C_{33}H_{27}N_2O_7S^+$ requires 595.1533.

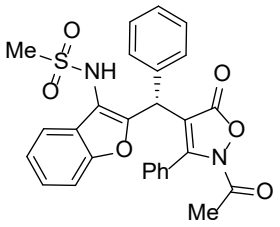
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)benzofuran-3-yl)-4-nitrobenzenesulfonamide (3da)



47 mg (77%) were obtained from **1d** (41 mg) and **2a** (16 mg). The enantiomeric excess (74%) was determined by HPLC (Chiralpak AD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 51.2 min, minor enantiomer: t_r = 54.7 min.

Yellow oil; $[\alpha]_D^{25}$ = +19.3 (c = 0.93, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H), 7.43-7.34 (m, 3H), 7.34-7.27 (m, 3H), 7.25-7.15 (m, 2H), 7.11-6.97 (m, 2H), 6.82 (d, J = 6.8 Hz, 2H), 4.99 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 166.9 (C), 164.2 (C), 155.9 (C), 153.5 (C), 151.1 (C), 149.8 (C), 144.8 (C), 135.6 (C), 130.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.5 (CH), 126.6 (C), 125.6 (C), 125.3 (CH), 124.0 (CH), 123.7 (CH), 119.8 (CH), 114.5 (C), 111.7 (CH), 107.3 (C), 37.0 (CH), 22.9 (CH_3); HRMS (ESI) *m/z*: 648.0816 $[M+K]^+$, $C_{32}H_{23}KN_3O_8S^+$ requires 648.0837.

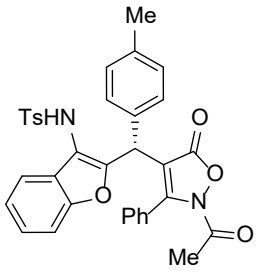
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)benzofuran-3-yl)methanesulfonamide (3ea)



31 mg (63%) were obtained from **1e** (30 mg) and **2a** (16 mg). The enantiomeric excess (78%) was determined by HPLC (Chiralpak IC), hexane:^{i}PrOH 80:20, 1.5 mL min^{-1}, major enantiomer: t_r = 41.2 min, minor enantiomer: t_r = 29.1 min.

Yellow oil; $[\alpha]_D^{25}$ = -59.3 (c = 0.63, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.64 (m, 1H), 7.50-7.34 (m, 6H), 7.32-7.26 (m, 5H), 7.25-7.22 (m, 2H), 6.77 (s, 1H), 5.42 (s, 1H), 2.64 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 164.3 (C), 156.3 (C), 153.0 (C), 151.1 (C), 137.1 (C), 130.8 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 126.7 (C), 126.0 (C), 125.0 (CH), 123.5 (CH), 119.7 (CH), 114.9 (C), 111.6 (CH), 107.1 (C), 40.2 (CH_3), 38.2 (CH), 22.9 (CH_3); HRMS (ESI) *m/z*: 503.1264 $[M+H]^+$, $C_{27}H_{23}N_2O_6S^+$ requires 503.1271.

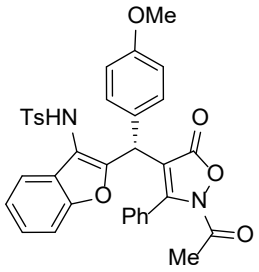
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(*p*-tolyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3fa)



49 mg (83%) were obtained from **1f** (39 mg) and **2a** (16 mg). The enantiomeric excess (84%) was determined by HPLC (Chiralpak AD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 63.7 min, minor enantiomer: t_r = 52.0 min.

Yellow oil; $[\alpha]_D^{25}$ = +1.7 (*c* = 0.98, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.3 Hz, 2H), 7.44-7.41 (m, 1H), 7.39-7.38 (m, 1H), 7.37-7.34 (m, 1H), 7.33-7.29 (m, 3H), 7.25-7.18 (m, 2H), 7.13-7.08 (m, 1H), 7.01 (d, *J* = 8.0 Hz, 2H), 8.97 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.1 Hz, 2H), 6.54 (s, 1H), 5.02 (s, 1H), 2.37 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3 (C), 164.3 (C), 155.5 (C), 153.2 (C), 151.4 (C), 143.7 (C), 136.5 (C), 133.4 (C), 130.5 (C), 129.4 (CH), 129.1 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.2 (CH), 126.9 (C), 125.9 (C), 124.7 (CH), 123.1 (CH), 119.7 (CH), 114.9 (C), 111.5 (CH), 107.8 (C), 37.2 (CH), 22.9 (CH_3), 21.4 (CH_3), 21.0 (CH_3); HRMS (ESI) *m/z*: 593.1736 $[M+H]^+$, $C_{34}H_{29}N_2O_4S^+$ requires 593.1741.

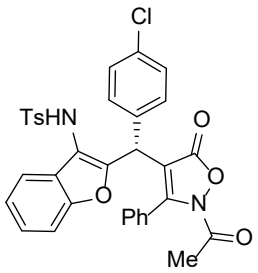
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(4-methoxyphenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3ga)



51 mg (84%) were obtained from **1g** (40.5 mg) and **2a** (16 mg). The enantiomeric excess (66%) was determined by HPLC (Chiralpak AD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 96.4 min, minor enantiomer: t_r = 76.7 min.

Yellow oil; $[\alpha]_D^{25}$ = +7.4 (*c* = 0.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 7.43 (d, *J* = 8.3 Hz, 2H), 7.40-7.29 (m, 4H), 7.26-7.20 (m, 2H), 7.19-7.13 (m, 2H), 7.07-7.02 (m, 1H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 6.49 (s, 1H), 4.94 (s, 1H), 3.69 (s, 3H), 2.31 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 164.4 (C), 158.8 (C), 155.6 (C), 153.3 (C), 151.6 (C), 143.8 (C), 136.6 (C), 130.7 (CH), 129.6 (CH), 129.4 (CH), 128.7 (CH), 128.6 (C), 128.4 (CH), 127.3 (CH), 127.1 (C), 126.1 (C), 124.8 (CH), 123.3 (CH), 119.9 (CH), 115.0 (C), 113.9 (CH), 111.6 (CH), 108.0 (C), 55.4 (CH_3), 36.9 (CH), 23.0 (CH_3), 21.6 (CH_3); HRMS (ESI) *m/z*: 609.1687 $[M+H]^+$, $C_{34}H_{29}N_2O_7S^+$ requires 609.1690.

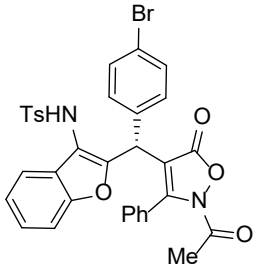
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(4-chlorophenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3ha)



49 mg (78%) were obtained from **1h** (41 mg) and **2a** (16 mg). The enantiomeric excess (88%) was determined by HPLC (Chiralpak IC), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 38.7 min, minor enantiomer: t_r = 31.5 min.

Yellow oil; $[\alpha]_D^{25}$ = +19.8 (c = 0.40, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.45 (m, 3H), 7.45-7.24 (m, 6H), 7.23-7.21 (m, 2H), 7.08 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.54 (s, 1H), 5.08 (s, 1H), 2.39 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C), 164.3 (C), 155.8 (C), 153.3 (C), 150.9 (C), 143.9 (C), 136.4 (C), 134.8 (C), 133.1 (C), 130.7 (CH), 129.5 (CH), 128.5 (CH), 128.4 (CH), 127.2 (C), 126.7 (C), 125.8 (C), 125.0 (CH), 123.4 (CH), 119.7 (CH), 115.2 (C), 111.6 (CH), 107.2 (C), 36.7 (CH), 22.9 (CH_3), 21.4 (CH_3); HRMS (ESI) *m/z*: 613.1189 $[M+H]^+$, $C_{33}H_{26}ClN_2O_6S^+$ requires 613.1195.

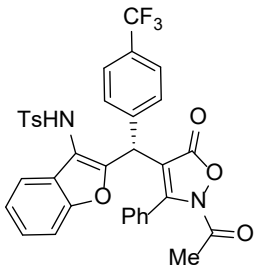
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(4-bromophenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3ia)



55 mg (84%) were obtained from **1i** (45 mg) and **2a** (16 mg). The enantiomeric excess (86%) was determined by HPLC (Chiralpak AD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 71.2 min, minor enantiomer: t_r = 66.6 min.

Yellow oil; $[\alpha]_D^{25}$ = -5.8 (c = 0.31, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.87 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.34-7.26 (m, 4H), 7.21 (d, J = 8.2 Hz, 2H), 7.17-7.11 (m, 2H), 7.08-7.01 (m, 2H), 6.97 (d, J = 8.5 Hz, 2H), 5.21 (s, 1H), 2.30 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.9 (C), 163.9 (C), 155.5 (C), 152.4 (C), 150.6 (C), 143.3 (C), 137.1 (C), 131.2 (CH), 130.3 (CH), 129.9 (CH), 129.5 (CH), 128.4 (CH), 127.9 (CH), 126.9 (C), 126.8 (CH), 125.2 (C), 124.4 (CH), 122.7 (CH),120.3 (C), 119.3 (CH), 114.8 (C), 111.3 (CH), 106.2 (C), 35.7 (CH), 22.9 (CH_3), 20.9 (CH_3); HRMS (ESI) *m/z*: 657.0683 $[M+H]^+$, $C_{33}H_{26}N_2O_6S^+$ requires 657.0689.

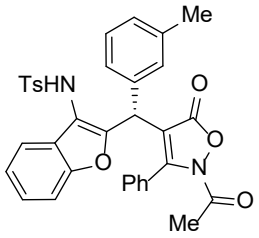
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(4-(trifluoromethyl)phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3ja)



56.5 mg (88%) were obtained from **1i** (44 mg) and **2a** (16 mg). The enantiomeric excess (90%) was determined by HPLC (Chiralpak IC), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 22.0 min, minor enantiomer: t_r = 19.1 min.

Yellow oil; $[\alpha]_D^{25}$ = +15.2 (c = 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.47 (m, 2H), 7.47-7.39 (m, 1H), 7.31-7.26 (m, 2H), 7.25-7.10 (m, 2H), 7.06 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 6.65 (s, 1H), 5.19 (s, 1H), 2.38 (s, 3H), 2.20 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.01 (CF_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (C), 164.4 (C), 156.1 (C), 153.6 (C), 150.7 (C), 144.0 (C), 140.4 (C), 136.5 (C), 130.9 (CH), 129.7 (CH), 129.6 (q, J = 32.6 Hz, C), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.3 (CH), 126.8 (C), 125.9 (C), 125.3 (CH), 125.2 (q, J = 5.3 Hz, CH), 123.7 (q, J = 219 Hz, CF_3), 123.6 (CH), 119.9 (CH), 115.7 (C), 111.7 (CH), 107.1 (C), 37.1 (CH), 23.0 (CH_3), 21.5 (CH_3); HRMS (ESI) *m/z*: 647.1451 $[M+H]^+$, $C_{34}H_{26}F_3N_2O_6S^+$ requires 647.1458.

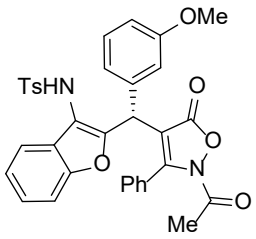
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(*m*-tolyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3ka)



55 mg (93%) were obtained from **1i** (39 mg) and **2a** (16 mg). The enantiomeric excess (88%) was determined using chiral HPLC (Chiralpak IC), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 46.3 min, minor enantiomer: t_r = 41.1 min.

Yellow oil; $[\alpha]_D^{25}$ = +2.2 (c = 0.32, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 8.3 Hz, 2H), 7.45-7.41 (m, 1H), 7.32-727 (m, 3H), 7.25-7.21 (m, 2H), 7.13 (td, J = 7.4, 1.0 Hz, 1H), 7.06-7.96 (m, 4H), 6.74-6.70 (m, 2H), 6.54 (s, 1H), 5.00 (s, 1H), 2.38 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C), 164.3 (C), 155.6 (C), 153.3 (C), 151.1 (C), 143.7 (C), 137.9 (C), 136.4 (C), 136.0 (C), 130.6 (CH), 129.4 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.2 (CH), 126.9 (C), 126.0 (C), 125.2 (CH), 124.7 (CH), 123.2 (CH), 119.8 (CH), 115.1 (C), 111.5 (CH), 107.7 (C), 37.3 (CH), 22.9 (CH_3), 21.39 (CH_3), 21.35 (CH_3); HRMS (ESI) *m/z*: 593.1732 $[M+H]^+$, $C_{34}H_{29}N_2O_6S^+$ requires 593.1741

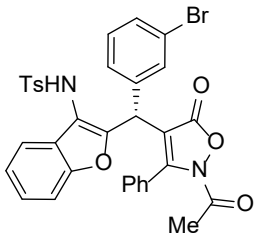
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(3-methoxyphenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3la)



53 mg (88%) were obtained from **1l** (40.5 mg) and **2a** (16 mg). The enantiomeric excess (86%) was determined by HPLC (Chiralpak AD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 53.9 min, minor enantiomer: t_r = 49.5 min.

Yellow oil; $[\alpha]_D^{25}$ = +7.8 (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 8.3 Hz, 2H), 7.45-7.42 (m, 1H), 7.42-7.27 (m, 5H), 7.26-7.20 (m, 2H), 7.06 (J = 7.9 Hz, 1H), 7.00 (J = 8.0 Hz, 2H), 6.71 (dd, J = 8.1 Hz, 2.1, 2H), 6.57-6.51 (m, 2H), 6.51-6.48 (m, 1H), 5.01 (s, 1H), 3.70 (s, 3H), 2.38 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C), 164.3 (C), 159.4 (C), 155.7 (C), 153.2 (C), 150.9 (C), 143.7 (C), 137.7 (C), 136.4 (C), 130.6 (CH), 129.3 (CH), 128.5 (CH), 128.2 (CH), 127.1 (CH), 126.8 (C), 125.9 (C), 124.8 (CH), 123.2 (CH), 120.5 (CH), 119.8 (CH), 115.1 (C), 114.3 (CH), 112.5 (CH), 111.5 (CH), 107.5 (C), 55.1 (CH_3O), 37.4 (CH), 22.9 (CH_3), 21.4 (CH_3). HRMS (ESI) *m/z*: 609.1674 $[M+H]^+$, $C_{34}H_{29}N_2O_7S^+$ requires 609.1690.

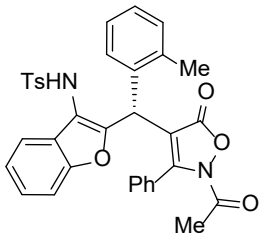
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(3-bromophenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3ma)



49.5 mg (75%) were obtained from **1m** (45 mg) and **2a** (16 mg). The enantiomeric excess (88%) was determined by HPLC (Chiralpak IC), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 41.8 min, minor enantiomer: t_r = 34.7 min.

Yellow oil; $[\alpha]_D^{25}$ = +16.6 (c = 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 8.3 Hz, 2H), 7.45-7.32 (m, 4H), 7.31-7.26 (m, 4H), 7.24 (d, J = 1.4 Hz, 1H), 7.16 (td, J = 7.4, 1.0 Hz, 1H), 7.01-6.93 (m, 4H), 6.90-6.86 (m, 1H), 5.02 (s, 1H), 2.38 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C), 164.3 (C), 155.8 (C), 153.4 (C), 150.3 (C), 143.8 (C), 138.1 (C), 136.2 (C), 131.2 (CH), 130.7 (CH), 130.3 (CH), 129.7 (CH), 129.5 (CH), 128.4 (CH), 128.3 (CH), 127.1 (CH), 126.7 (CH), 126.6 (C), 125.8 (C), 125.1 (CH), 123.4 (CH), 122.3 (C), 119.9 (CH), 115.5 (C), 111.6 (CH), 107.0 (C), 36.7 (CH), 22.9 (CH_3), 21.4 (CH_3); HRMS (ESI) *m/z*: 657.0665 $[M+H]^+$, $C_{33}H_{26}BrN_2O_6S^+$ requires 657.0689.

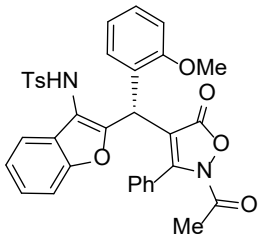
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(*o*-tolyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3na)



55.4 mg (94%) were obtained from **1n** (39 mg) and **2a** (16 mg). The enantiomeric excess (83%) was determined by HPLC (Chiralpak IC), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 50.4 min, minor enantiomer: t_r = 34.3 min.

Yellow oil; $[\alpha]_D^{25}$ = +56.2 (c = 0.42, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 8.3 Hz, 2H), 7.40.7.36 (m, 1H), 7.35-7.34 (m, 1H), 7.31-7.27 (m, 2H), 7.25-7.19 (m, 4H), 7.15-7.03 (m, 3H), 6.99-6.93 (m, 4H), 6.62 (s, 1H), 5.18 (s, 1H), 2.38 (s, 3H), 2.22 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 164.4 (C), 155.7 (C), 153.3 (C), 151.3 (C), 143.6 (C), 136.5 (C), 135.4 (C), 134.5 (C), 130.4 (CH), 130.3 (CH), 129.5 (CH), 128.7 (CH), 128.3 (CH), 128.0 (CH), 127.4 (CH), 127.0 (CH), 126.7 (C), 125.99 (C), 125.93 (CH), 124.7 (CH), 123.2 (CH), 119.8 (CH), 115.1 (C), 111.4 (CH), 106.9 (C), 34.7 (CH), 22.9 (CH_3), 21.4 (CH_3), 19.2 (CH_3); HRMS (ESI) *m/z*: 593.1732 $[M+H]^+$, $C_{34}H_{29}N_2O_6S^+$ requires 593.1741.

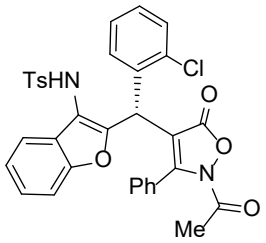
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(2-methoxyphenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3oa)



46.5 mg (76%) were obtained from **1o** (40.5 mg) and **2a** (16 mg). The enantiomeric excess (76%) was determined by HPLC (Chiralpak IC), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 63.5 min, minor enantiomer: t_r = 48.5 min.

Yellow oil; $[\alpha]_D^{25}$ = +71.3 (c = 0.93, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 8.3 Hz, 2H), 7.45-7.44 (m, 1H), 7.42-7.37 (m, 2H), 7.33-7.27 (m, 3H), 7.25-7.17 (m, 3H), 7.09 (td, J = 7.8, 1.7 Hz, 1H), 6.97 (dd, J = 7.5 Hz, 1.5 Hz, 1H), 6.90 (d, J = 8.0 Hz, 2H), 6.72-6.64 (m, 3H), 6.59 (dd, J = 8.3 , 1.1 Hz, 1H), 5.22 (s, 1H), 3.57 (s, 3H), 2.37 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9 (C), 164.4 (C), 155.9 (C), 155.4 (C), 153.5 (C), 150.9 (C), 143.3 (C), 136.3 (C), 130.3 (CH), 129.3 (CH), 129.2 (CH), 128.52 (CH), 128.45 (CH), 127.8 (CH), 126.97 (CH), 126.93 (C), 126.2 (C), 124.8 (CH), 123.8 (C), 123.3 (CH), 120.35 (CH), 120.18 (CH), 115.4 (C), 111.3 (CH), 109.7 (CH), 106.8 (C), 55.0 (CH_3O), 31.7 (CH), 23.0 (CH_3), 21.5 (CH_3); HRMS (ESI) *m/z*: 609.1680 $[M+H]^+$, $C_{34}H_{29}N_2O_7S^+$ requires 609.1690.

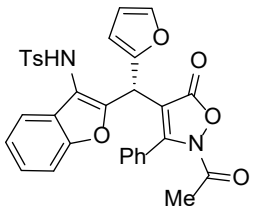
(*S*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(2-chlorophenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3pa)



47 mg (77%) were obtained from **1p** (41 mg) and **2a** (16 mg). The enantiomeric excess (80%) was determined by HPLC (Chiralcel OD-H), hexane:^{i}PrOH 90:10, 1.0 mL min^{-1}, major enantiomer: t_r = 38.9 min, minor enantiomer: t_r = 33.1 min.

Yellow oil; $[\alpha]_D^{25}$ = +129.6 (c = 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (ddd, J = 7.6, 1.6, 0.7 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.45-7.41 (m, 1H), 7.37-7.29 (m, 2H), 7.27 (m, 1H), 7.24-7.22 (m, 2H), 7.21-7.17 (m, 2H), 7.13-6.97 (m, 3H), 6.92 (dd, J = 7.4, 1.7 Hz, 1H), 6.85 (d, J = 8.0 Hz, 2H), 6.75 (s, 1H), 5.14 (s, 1H), 2.36 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 164.3 (C), 155.4 (C), 153.7 (C), 149.9 (C), 143.4 (C), 135.9 (C), 133.3 (C), 130.3 (CJ), 130.1 (CH), 129.5 (CH), 129.2 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 126.8 (CH), 126.6 (C), 126.4 (CH), 126.2 (C), 125.2 (CH), 123.6 (CH), 120.6 (CH), 116.0 (C), 111.4 (CH), 106.1 (C), 34.7 (CH), 22.9 (CH_3), 21.4 (CH_3); HRMS (ESI) *m/z*: 613.1181 $[M+H]^+$, $C_{33}H_{26}ClN_3O_4S^+$ requires 613.1195.

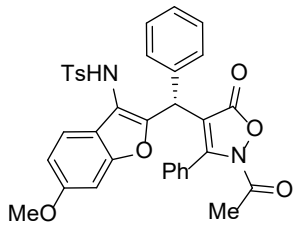
(*S*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(furan-2-yl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3qa)



51 mg (89%) were obtained from **1q** (36.5 mg) and **2a** (16 mg). The enantiomeric excess (50%) was determined by HPLC (Chiralpak AD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 63.9 min, minor enantiomer: t_r = 39.4 min.

Yellow oil; $[\alpha]_D^{25}$ = 3.5 (c = 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.47 (m, 3H), 7.45-7.38 (m, 2H), 7.38-7.26 (m, 5H), 7.22 (td, J = 7.5, 1.1 Hz, 1H), 7.06-7.03 (m, 1H), 7.00 (d, J = 7.8 Hz, 2H), 6.95 (s, 1H), 4.80 (s, 1H), 2.35 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 164.3 (C), 155.6 (C), 153.5 (C), 148.1 (C), 147.2 (C), 143.6 (C), 141.6 (CH), 136.0 (C), 130.5 (CH), 129.5 (CH), 128.4 (CH), 127.9 (CH), 127.0 (CH), 126.2 (C), 125.9 (C), 125.1 (CH), 123.5 (CH), 120.4 (CH), 115.7 (C), 111.3 (CH), 110.3 (CH), 109. 1 (CH), 105.9 (CH), 31.4 (CH), 22.9 (CH_3), 21.4 (CH_3); HRMS (ESI) *m/z*: 569.1369 $[M+H]^+$, $C_{31}H_{25}N_2O_7S^+$ requires 569.1377.

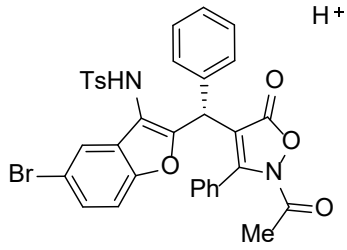
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)-6-methoxybenzofuran-3-yl)-4-methylbenzenesulfonamide (3ra)



51 mg (84%) were obtained from **1r** (40.5 mg) and **2a** (16 mg). The enantiomeric excess (72%) was determined by HPLC (Chiralpak AD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 54.8 min, minor enantiomer: t_r = 47.9 min.

Yellow oil; $[\alpha]_D^{25}$ = -16.5 (c = 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 8.3 Hz, 2H), 7.44-7.35 (m, 2H), 7.34-7.27 (m, 2H), 7.18-7.11 (m, 3H), 7.08 (d, J = 8.6 Hz, 2H), 7.02-6.96 (m, 2H), 6.97-6.90 (m, 2H), 6.87 (d, J = 2.1 Hz, 1H), 6.75 (d, J = 8.6, 2.2 Hz, 1H), 6.54 (s, 1H), 5.01 (s, 1H), 3.80 (s, 3H), 2.37 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C), 164.3 (C), 158.3 (C), 155.6 (C), 154.3 (C), 149.8 (C), 143.7 (C), 136.5 (C), 136.4 (C), 130.6 (CH), 129.5 (CH), 128.3 (CH), 128.3 (CH), 128.1 (CH), 127.2 (CH), 126.9 (C), 120.0 (CH), 119.1 (C), 115.0 (C), 112.4 (CH), 107.8 (C), 95.9 (CH), 55.7 (CH_3O), 37.3 (CH), 22.9 (CH_3), 21.4 (CH_3); HRMS (ESI) *m/z*: 609.1676 $[M+H]^+$, $C_{34}H_{29}N_2O_7S^+$ requires 609.1690.

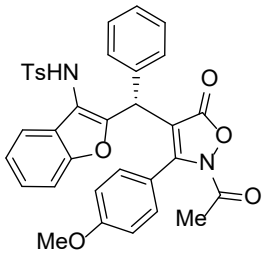
(*R*)-*N*-(2-((2-acetyl-5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)-5-bromobenzofuran-3-yl)-4-methylbenzenesulfonamide (3sa)



58 mg (88%) were obtained from **1s** (45 mg) and **2a** (16 mg). The enantiomeric excess (80%) was determined by HPLC (Chiralpak AD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 66.1 min, minor enantiomer: t_r = 44.2 min.

Yellow oil; **[**$\alpha]_D^{25}$ = -32.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.3 Hz, 2H), 7.46-7.29 (m, 6H), 7.25-6.99 (m, 9H), 6.85 (d, J = 1.9 Hz, 1H), 6.64 (s, 1H), 5.15 (s, 1H), 2.38 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3 (C), 164.3 (C), 155.8 (C), 153.5 (C), 151.8 (C), 144.3 (C), 143.5 (C), 139.1 (C), 136.5 (C), 136.4 (C), 130.7 (CH), 129.7 (CH), 129.6 (CH), 128.5 (CH), 128.3 (CH), 128.3 (CH), 127.6 (C), 127.53 (CH), 127.47 (CH), 127.3 (CH), 126.8 (C), 126.4 (CH), 122.1 (CH), 116.3 (C), 114.2 (C), 113.0 (CH), 107.3 (C), 37.7 (CH), 22.9 (CH_3), 21.5 (CH_3); **HRMS** (ESI) *m/z*: 657.0677 $[M+H]^+$, $C_{33}H_{26}BrN_2O_6S^+$ requires 657.0689.

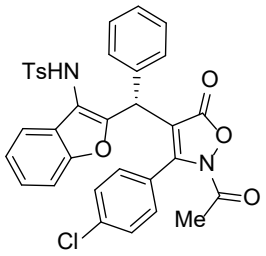
(*R*)-*N*-(2-((2-acetyl-3-(4-methoxyphenyl)-5-oxo-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3ab)



38 mg (63%) were obtained from **1a** (37.5 mg) and **2b** (19 mg). The enantiomeric excess (84%) was determined by HPLC (Chiralpak AD-H), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 60.6 min, minor enantiomer: t_r = 54.6 min.

Yellow oil; $[\alpha]_D^{25}$ = +8.2 (c = 0.77, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 8.3 Hz, 2H), 7.37-7.31 (m, 1H), 7.28-7.27 (m, 1H), 7.25-7.20 (m, 3H), 7.19-7.08 (m, 4H), 7.03-6.98 (m, 2H), 6.97-6.93 (m, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.64 (s, 1H), 5.09 (s, 1H), 3.82 (s, 3H), 2.38 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 164.6 (C), 161.4 (C), 155.9 (C), 153.3 (C), 151.2 (C), 143.7 (C), 136.5 (C), 136.3 (C), 130.4 (CH), 129.5 (CH), 128.3 (CH), 128.1 (CH), 127.2 (CH), 127.1 (CH), 125.9 (C), 124.7 (CH), 123.2 (CH), 119.9 (CH), 118.6 (C), 115.2 (C), 113.7 (CH), 111.5 (CH), 106.9 (C), 55.3 (CH_3O), 37.5 (CH), 23.1 (CH_3), 21.4 (CH_3); HRMS (ESI) *m/z*: 609.1684 $[M+H]^+$, $C_{34}H_{29}N_2O_7S^+$ requires 609.1690.

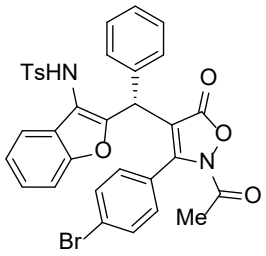
(*R*)-*N*-(2-((2-acetyl-3-(4-chlorophenyl)-5-oxo-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3ac)



55 mg (90%) were obtained from **1a** (37.5 mg) and **2c** (20 mg). The enantiomeric excess (82%) was determined by HPLC (Chirlpak IC), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 31.1 min, minor enantiomer: t_r = 23.0 min.

Yellow oil; $[\alpha]_D^{25}$ = +18.3 (c = 0.92, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 7.35-7.26 (m, 2H), 7.25-7.19 (m, 3H), 7.18-7.08 (m, 5H), 7.02 (d, J = 8.0 Hz, 2H), 6.98-6.94 (m, 2H), 6.77 (s, 1H), 5.12 (s, 1H), 2.38 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C), 164.6 (C), 154.5 (C), 153.2 (C), 151.0 (C), 143.8 (C), 136.8 (C), 136.5 (C), 136.3 (C), 129.9 (CH), 129.5 (CH), 128.4 (CH), 128.2 (CH), 127.3 (CH), 127.2 (CH), 125.8 (C), 125.2 (C), 124.8 (CH), 123.22 (CH), 119.6 (CH), 115.2 (C), 111.4 (CH), 108.1 (C), 37.5 (CH), 22.9 (CH_3), 21.4 (CH_3); HRMS (ESI) *m/z*: 613.1191 $[M+H]^+$, $C_{33}H_{26}ClN_2O_6S^+$ requires 613.1195.

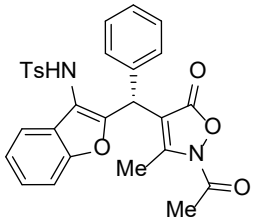
(*R*)-*N*-(2-((2-acetyl-3-(4-bromophenyl)-5-oxo-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3ad)



47 mg (71%) were obtained from **1a** (37.5 mg) and **2d** (24 mg). The enantiomeric excess (83%) was determined by HPLC (Chiralpak IC), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 48.4 min, minor enantiomer: t_r = 28.8 min.

Yellow oil; $[\alpha]_D^{25}$ = +15.6 (c = 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.35-7.30 (m, 1H), 7.30-7.15 (m, 6H), 7.11 (d, J = 8.0 Hz, 2H), 7.06-7.03 (m, 2H), 6.78 (s, 1H), 5.19 (s, 1H), 2.46 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 164.7 (C), 154.7 (C), 153.3 (C), 151.2 (C), 144.0 (C), 136.4 (C), 131.6 (CH), 130.3 (CH), 129.7 (CH), 128.6 (CH), 128.4 (CH), 127.5 (CH), 127.3 (CH), 125.9 (C), 125.3 (C), 125.0 (CH), 123.4 (CH), 119.7 (CH), 115.3 (C), 111.6 (CH), 108.8 (C), 37.6 (CH), 23.0 (CH_3), 21.6 (CH_3); HRMS (ESI) *m/z*: 657.0681 $[M+H]^+$, $C_{33}H_{26}BrN_2O_6S^+$ requires 657.0689.

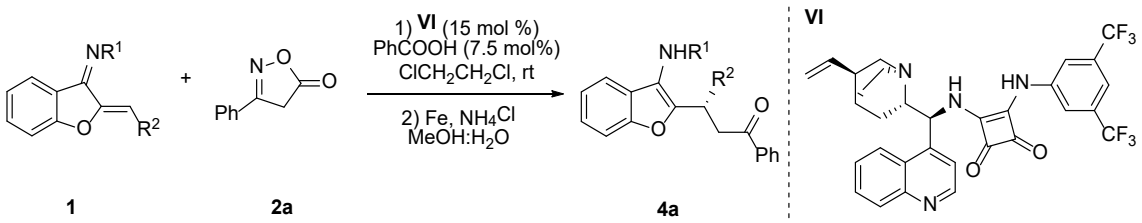
(*R*)-*N*-(2-((2-acetyl-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)(phenyl)methyl)benzofuran-3-yl)-4-methylbenzenesulfonamide (3ae)



45 mg (87%) were obtained from **1a** (37.5 mg) and **2e** (10 mg). The enantiomeric excess (66%) was determined by HPLC (Chiralpak IC), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 80.6 min, minor enantiomer: t_r = 44.7 min.

Yellow oil; $[\alpha]_D^{25}$ = -18.5 (c = 0.90, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (2H, d, J = 8.3 Hz, Ar), 7.47-7.44 (1H, m, Ar), 7.39-7.35 (1H, m, Ar), 7.30-7.27 (1H, m, Ar), 7.26-7.16 (4H, m, Ar), 7.02-6.97 (2H, m, Ar), 6.95 (2H, d, J =8.0 Hz, Ar), 6.89-6.88 (1H, m, Ar), 5.12 (1H, s, CH), 2.38 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.16 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0 (C), 165.1 (C), 155.3 (C), 153.5 (C), 151.3 (C), 143.7 (C), 136.3 (C), 136.0 (C), 129.5 (CH), 128.5 (CH), 127.7 (CH), 127.24 (CH), 127.16 (CH), 126.0 (C), 125.0 (CH), 123.5 (CH), 120.1 (CH), 115.6 (C), 111.4 (CH), 106.3 (C), 35.6 (CH), 22.8 (CH_3), 21.4 (CH_3), 14.2 (CH_3); HRMS (ESI) *m/z*: 517.1410 $[M+H]^+$, $C_{28}H_{25}N_2O_6S^+$ requires 517.1428.

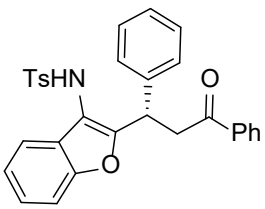
General procedure for the synthesis and characterization of the products 4



In a test tube, aurone-derived azadiene **1** (0.1 mmol), isoxazol-5(4*H*)-one **2a** (16 mg, 0.1 mmol), catalyst **VI** (9 mg, 0.015 mmol), and benzoic acid (1 mg, 0.0075 mmol) are introduced and purged with nitrogen. The mixture is then dissolved in dry 1,2-dichloroethane (2 mL) and stirred at room temperature for 24 hours. Once the starting substrates are consumed, the reaction mixture was concentrated under reduced pressure. Then, iron (56 mg, 1 mmol) and NH_4Cl (54 mg, 1 mmol) were added. The mixture was dissolved in 1 mL H_2O:MeOH (1:1) and allowed to react at 60 ºC for 24 hours.

After this time, the reaction mixture was filtered through celite, washed with MeOH and dichloromethane. The filtrate was concentrated under reduced pressure and purified by column chromatography using Hexane:EtOAc eluent mixtures.

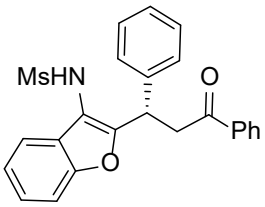
(*S*)-*N*-(2-(3-Oxo-1,3-diphenylpropyl)benzofuran-3-yl)benzenesulfonamide (4aa)



36 mg (72%) were obtained from **1a** (37.5 mg) and **2a** (16 mg). The enantiomeric excess (88%) was determined by HPLC (Chiralpak IC) hexane:^{i}PrOH 80:20, 1.5 mL min^{-1}, major enantiomer: t_r = 27.1 min, minor enantiomer: t_r = 16.8 min.

Yellow oil; $[\alpha]_D^{25}$ = -49.4 (c = 0.98, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.93 (m, 2H), 7.66-7.72 (m, 3H), 7.45-7.55 (m, 1H), 7.40-7.43 (m, 3H), 7.29-7.30 (m, 1H), 7.14-7.26 (m, 7H), 6.94-6.97 (m, 2H), 4.43 (dd, J = 3.8, 10.1 Hz, 1H), 3.86 (dd, J = 10.1, 18.4 Hz, 1H), 3.47 (dd, J = 3.8 , 18.4 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2 (C), 153.6 (C),153.1 (C), 143.8 (C), 139.4 (C), 136.6 (C), 136.1 (C), 133.9 (CH), 129.9 (CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 127.2 (CH), 126.3 (C), 124.5 (CH), 123.3 (CH), 120.8 (CH), 114.2 (C), 111.2 (CH), 43.5 (CH_2), 36.6 (CH), 21.6 (CH_3); HRMS (ESI) *m/z*: 482.1415 $[M+H]^+$, $C_{29}H_{24}NO_4S^+$ requires 482.1421.

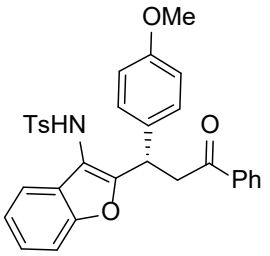
(*S*)-*N*-(2-(3-oxo-1,3-diphenylpropyl)benzofuran-3-yl)methanesulfonamide (4ea)



31 mg (75%) were obtained from **1e** (30 mg) and **2a** (16 mg). The enantiomeric excess (76%) was determined by HPLC (Chiralpak IC) hexane:iPrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 66.3 min, minor enantiomer: t_r = 38.8 min.

Yellow oil; $[\alpha]_D^{25}$ = +34.6 (*c* = 0.63, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.97-7.91 (m, 2H), 7.60-7.49 (m, 3H), 7.48-7.32 (m, 5H), 7.31-7.26 (m, 1H), 7.25-7.20 (m, 2H), 6.90 (s, 1H), 5.08 (dd, *J* = 10.0, 4.1 Hz, 1H), 4.13 (dd, *J* = 18.2, 10.0 Hz, 1H), 3.61 (dd, *J* = 18.1, 4.2 Hz, 1H), 3.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7 (C), 154.2 (C), 153.4 (C), 140.0 (C), 136.1 (C), 133.6 (CH), 128.9 (CH), 128.7 (CH), 128.13 (CH), 128.05 (CH), 127.4 (CH), 126.1 (C), 124.5 (CH), 123.4 (CH), 119.9 (CH), 113.6 (C), 111.4 (CH), 43.4 (CH_2), 40.0 (CH), 37.3 (CH); HRMS (ESI) *m/z*: 420.1254 $[M+H]^+$, $C_{24}H_{22}NO_4S^+$ requires 420.1264.

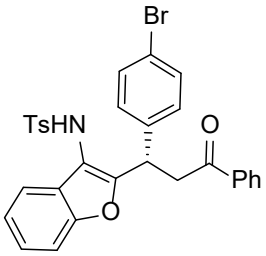
(*S*)-*N*-(2-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)benzofuran-3-yl)benzenesulfonamide (4ga)



37 mg (73%) were obtained from **1g** (40.5 mg) and **2a** (16 mg). The enantiomeric excess (70%) was determined by HPLC (Chiralpak IC), hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 44.0 min, minor enantiomer: t_r = 38.0 min.

Yellow oil; $[\alpha]_D^{25}$ = -72.5 (c = 0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.1 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.69-7.64 (m, 1H), 7.60-7.52 (m, 1H), 7.52-7.40 (m, 3H), 7.36-7.29 (m, 1H), 7.26-7.14 (m, 4H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 4.42 (dd, *J* = 9.9, 3.9 Hz, 1H), 3.81 (m, 4H), 3.46 (dd, *J* = 18.4, 4.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1 (C), 158.5 (C), 153.4 (C), 153.3 (C), 143.6 (C), 136.5 (C), 136.0 (C), 133.7 (CH), 131.4 (C), 129.7 (CH), 129.0 (CH), 128.6 (CH), 128.1 (CH), 127.5 (CH), 126.1 (C), 124.3 (CH), 123.1 (CH), 120.6 (CH), 113.70 (C), 113.65 (CH), 111.0 (CH), 55.2 (CH_3), 43.5 (CH_2), 35.7 (CH), 21.5 (CH_3); HRMS (ESI) *m/z*: 512.1513 $[M+H]^+$, $C_{30}H_{26}NO_5^+$ requires 512.1526.

(*S*)-*N*-(2-(1-(4-bromophenyl)-3-oxo-3-phenylpropyl)benzofuran-3-yl)benzenesulfonamide (4ia)



43 mg (75%) were obtained from **1i** (45 mg) and **2a** (16 mg). The enantiomeric excess (86%) was determined by HPLC (Chiralcel OD-H), hexane:^{i}PrOH 90:10, 1.0 mL min^{-1}, major enantiomer: t_r = 21.4 min, minor enantiomer: t_r = 26.4 min.

Yellow oil; $[\alpha]_D^{25}$ = -26.9 (c = 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.91 (m, 2H), 7.67-7.69 (m, 2H), 7.53-7.62 (m, 2H), 7.40-7.45 (m, 2H), 7.29-7.36 (m, 4H), 7.18-7.22 (m, 2H), 7.12-7.16 (m, 2H), 6.85-6.87 (m, 2H), 4.43 (dd, *J* = 4.0 Hz, 10.0 Hz, 1H), 3.82 (dd, *J* = 10.0, 18.3 Hz, 1H), 3.43 (dd, *J* = 4.0, 18.3 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9 (C), 153.6 (C), 152.6 (C), 143.9 (C), 138.5 (C), 136.6 (C), 136.0 (C), 134.0 (CH), 131.6 (CH), 129.9 (CH), 129.8 (CH), 128.9 (CH), 128.3 (CH), 127.7 (CH), 126.5 (C), 126.1 (C), 124.7 (CH), 123.4 (CH), 120.8 (CH), 114.4 (C), 111.2 (CH), 43.4 (CH2), 36.1 (CH), 21.7 (CH_3); HRMS (ESI) *m/z*: 560.0519 $[M+H]^+$, $C_{29}H_{23}BrNO_4S^+$ requires 560.0526.

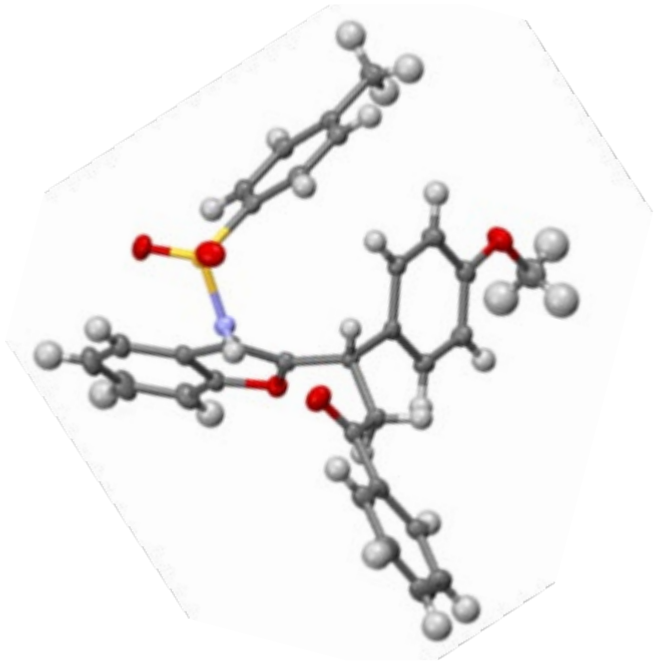


Figure S1. Ortep plot for the X-ray structure of compound **4ga**. Thermal ellipsoids drawn at the 50% probability level. Flack parameter 0.037(18).

Synthesis of 3aa at 1 mmol scale

In a round-bottom flask, aurone-derived azadiene **1a** (375 mg, 1 mmol), isoxazol-5(4*H*)-one **2** (160 mg, 1 mmol), catalyst **VI** (90 mg, 0.15 mmol), and benzoic acid (10 mg, 0.075 mmol) are introduced and purged with nitrogen. The reaction mixture is dissolved in dry 1,2-dichloroethane (20 mL) and stirred at room temperature for 24 hours. After complete consumption of the starting substrates, acetic anhydride (200 μL, 2 mmol) is added, and the reaction is stirred at room temperature for 30 minutes. Subsequently, the mixture is purified by column chromatography using Hexane:EtOAc solvent mixture to furnish 527 mg (91%) of **3aa** as a yellow solid. Enantiomeric excess (82%) was measured by HPLC (Chiralpak IC) hexane:^{i}PrOH 80:20, 1.0 mL min^{-1}, major enantiomer: t_r = 50.3 min, minor enantiomer: t_r = 40.0 min.

References

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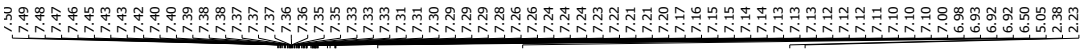
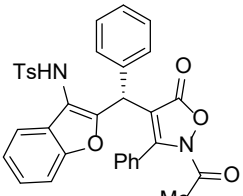
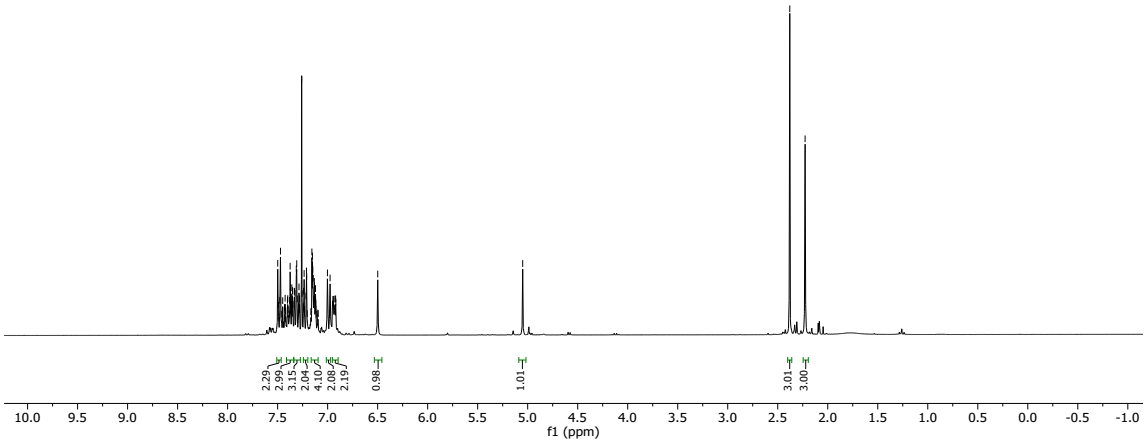
[19] W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450–5453.

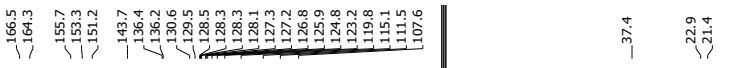
NMR Spectra

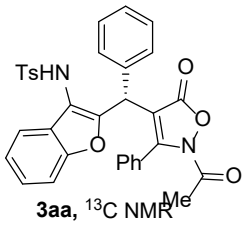




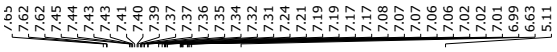
3aa, ^{1}H NMR
$CDCl_3$, 300 MHz

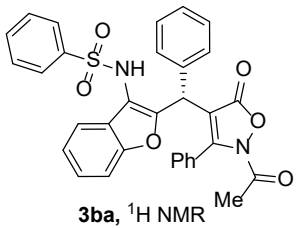




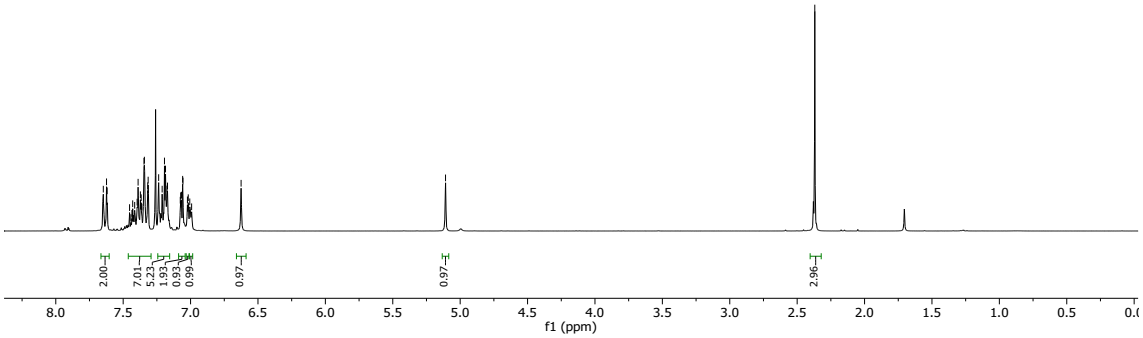


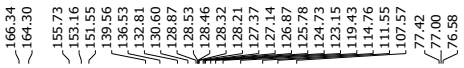
3aa, ^{13}C NMR
$CDCl_3$, 75 MHz

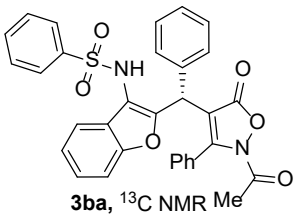




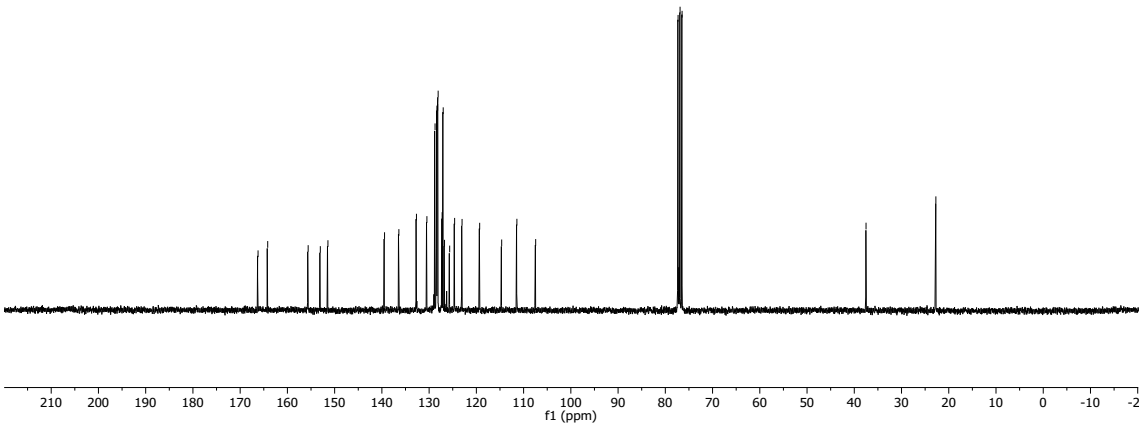
3ba, ^{1}H NMR
$CDCl_3$, 300 MHz

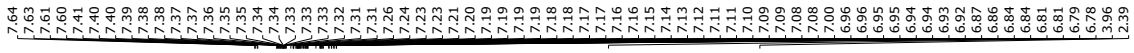


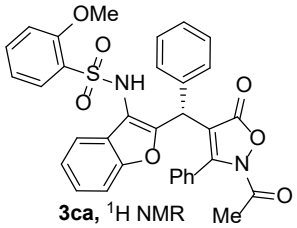




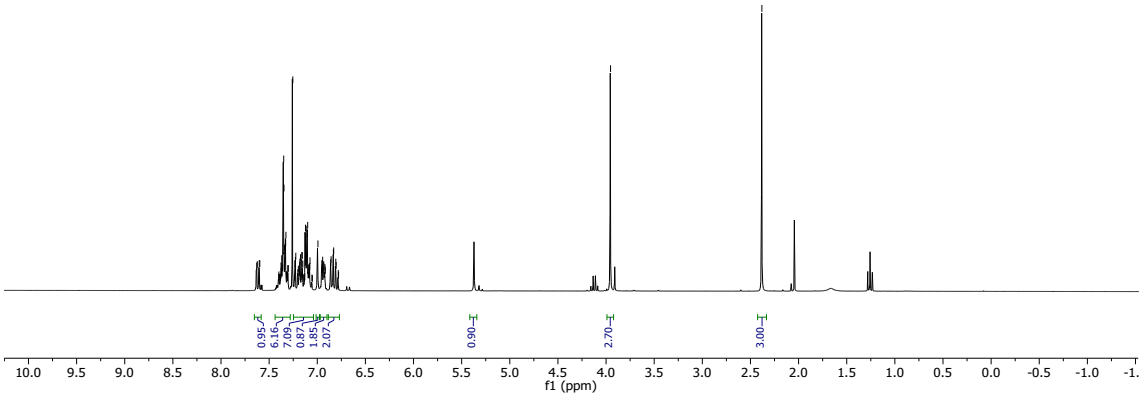
3ba, ^{13}C NMR
$CDCl_3$, 75 MHz

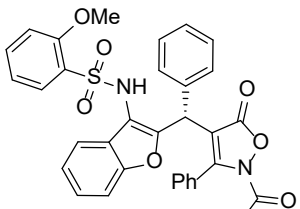




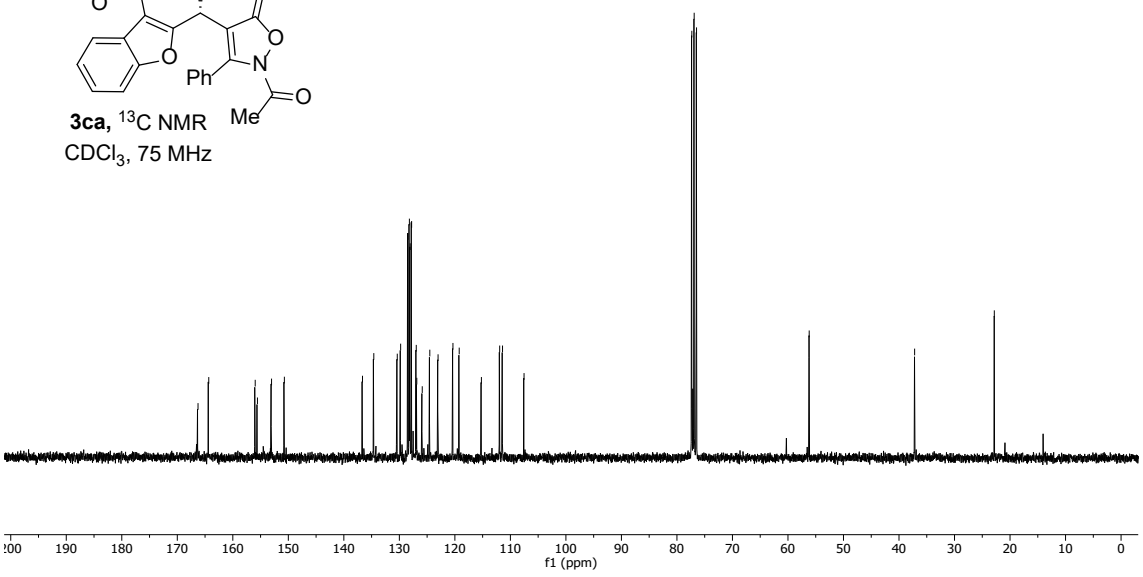


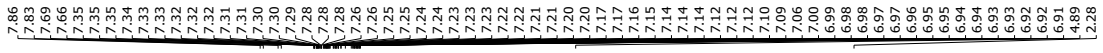
3ca, ^{1}H NMR
$CDCl_3$, 300 MHz

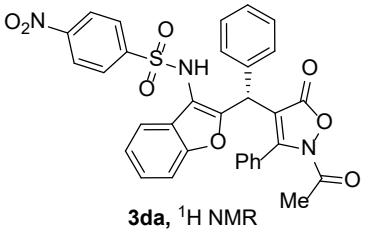




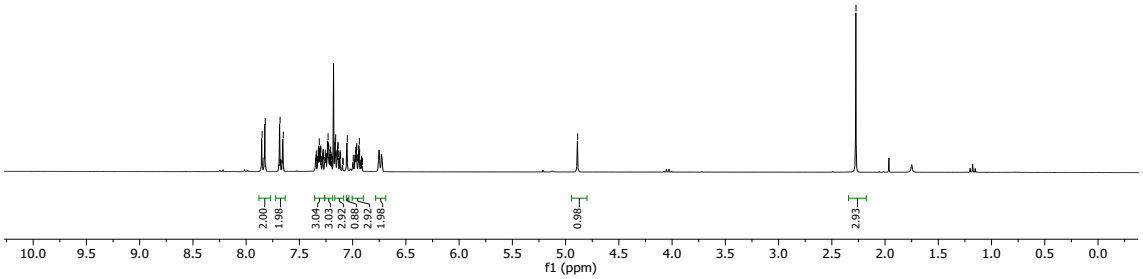
3ca, ^{13}C NMR
$CDCl_3$, 75 MHz

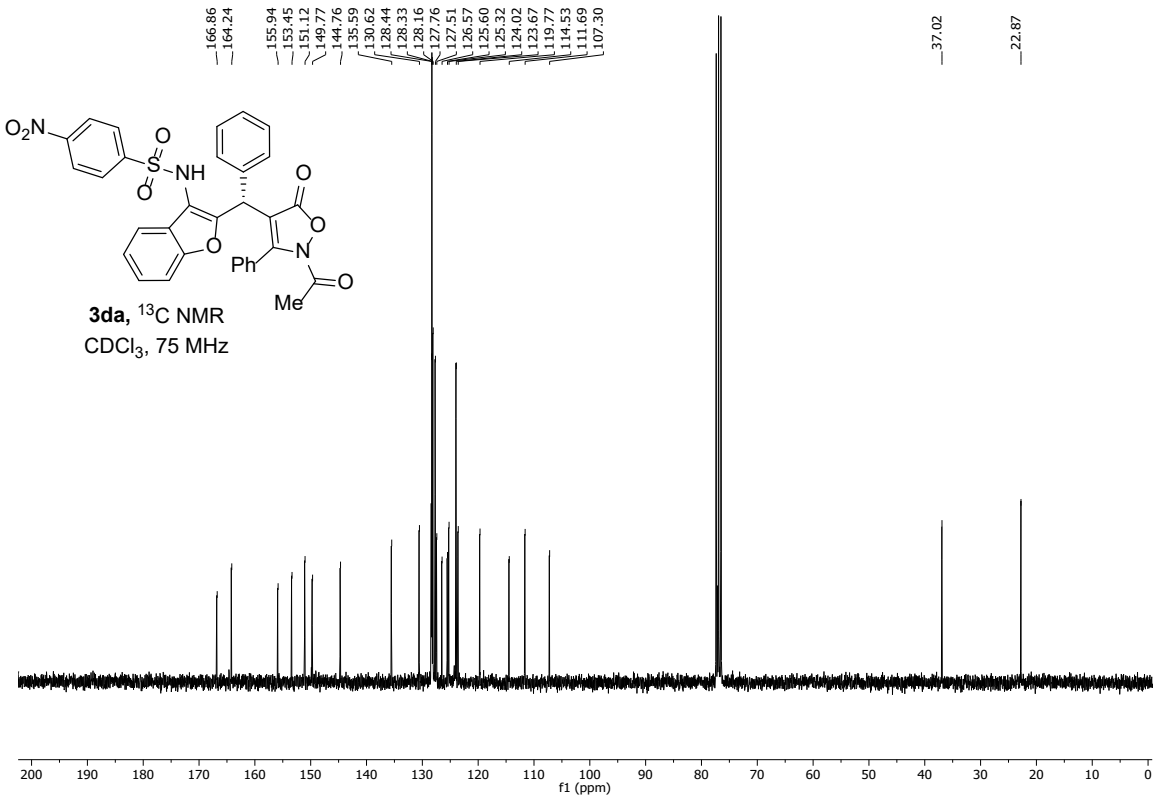




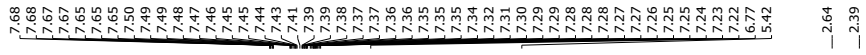


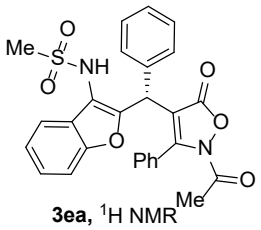
3da, ^{1}H NMR
$CDCl_3$, 300 MHz



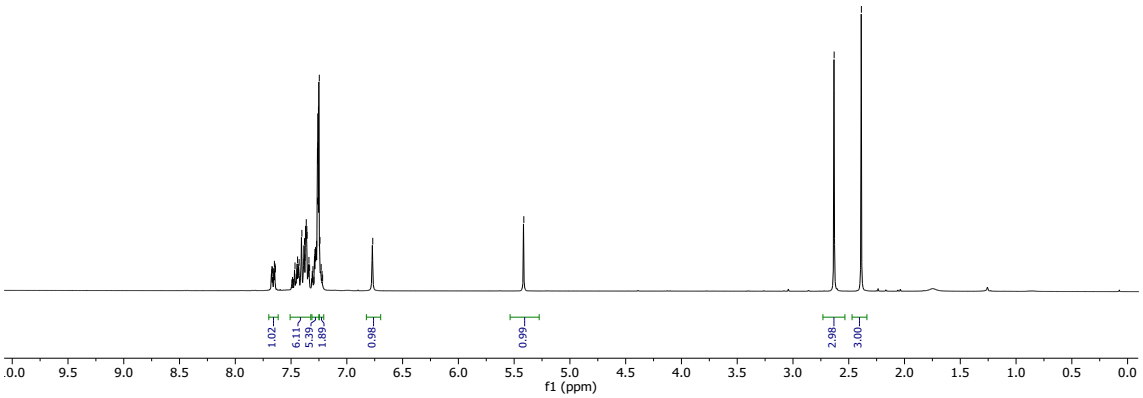


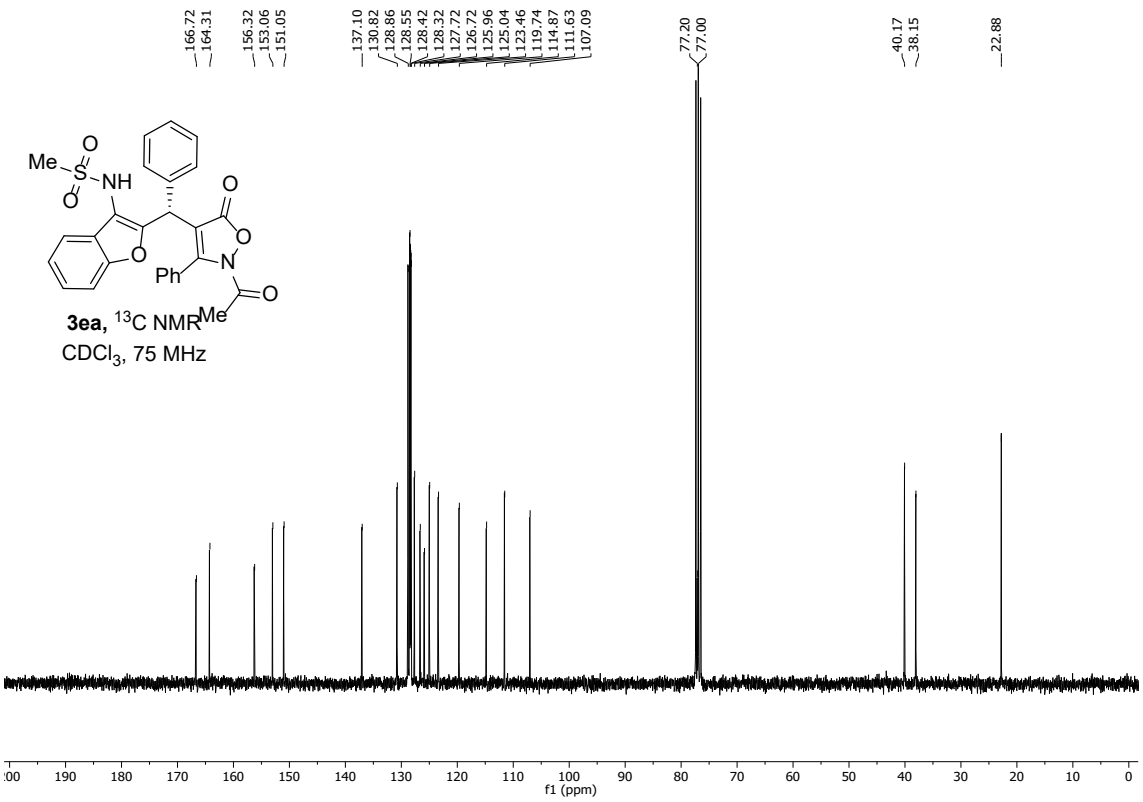
3da, ^{13}C NMR
$CDCl_3$, 75 MHz



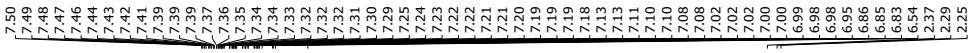


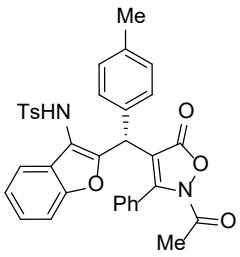
3ea, ^{1}H NMR
$CDCl_3$, 300 MHz



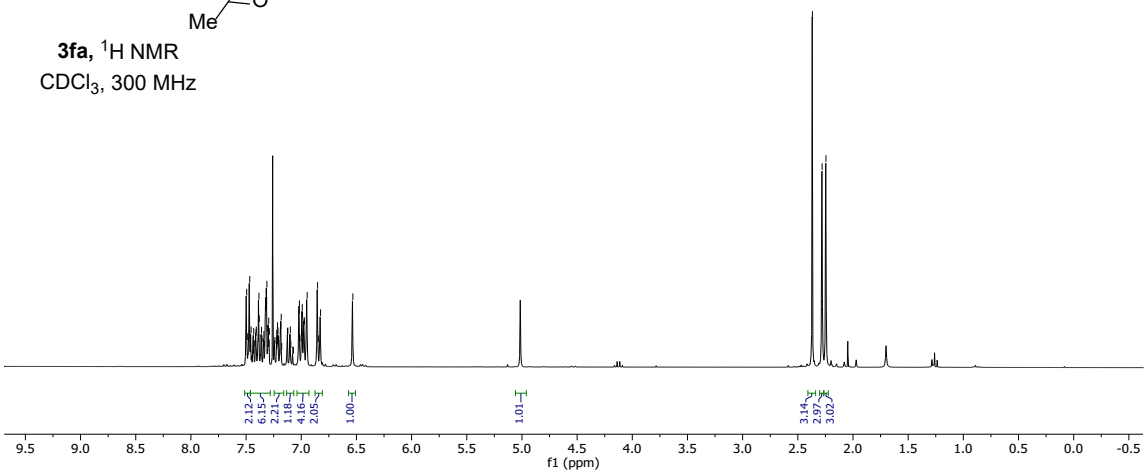


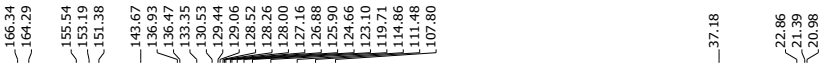
3ea, ^{13}C NMR
$CDCl_3$, 75 MHz

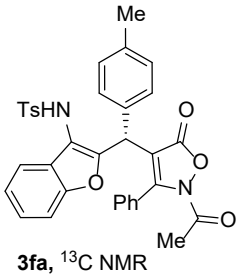




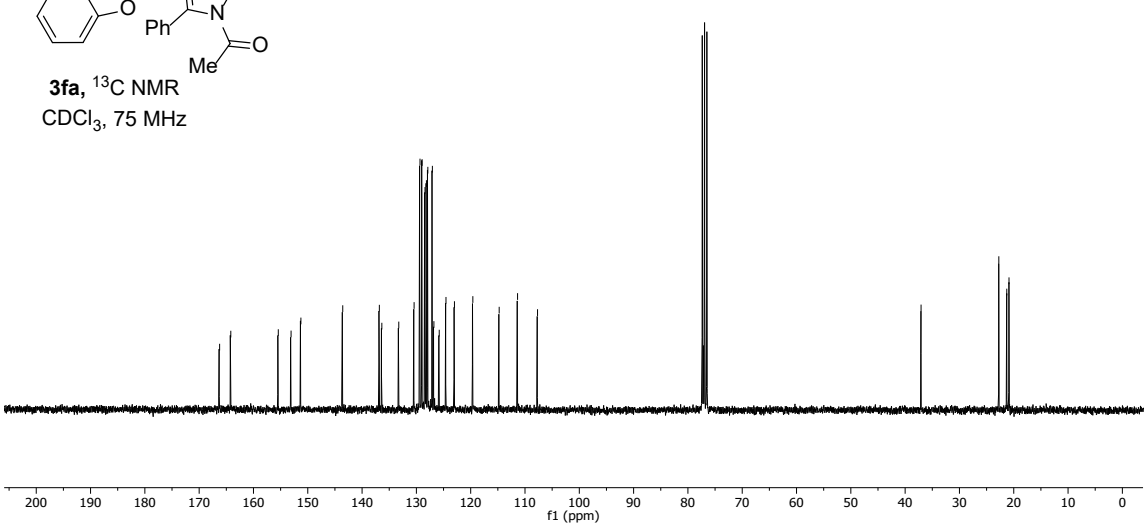
3fa, ^{1}H NMR
$CDCl_3$, 300 MHz

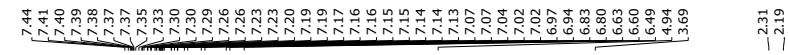


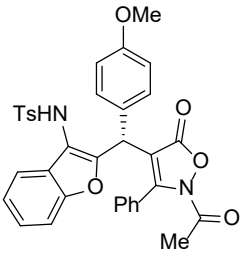




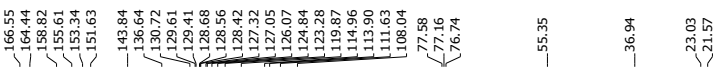
3fa, ^{13}C NMR
$CDCl_3$, 75 MHz

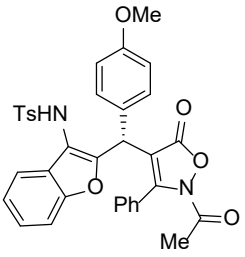




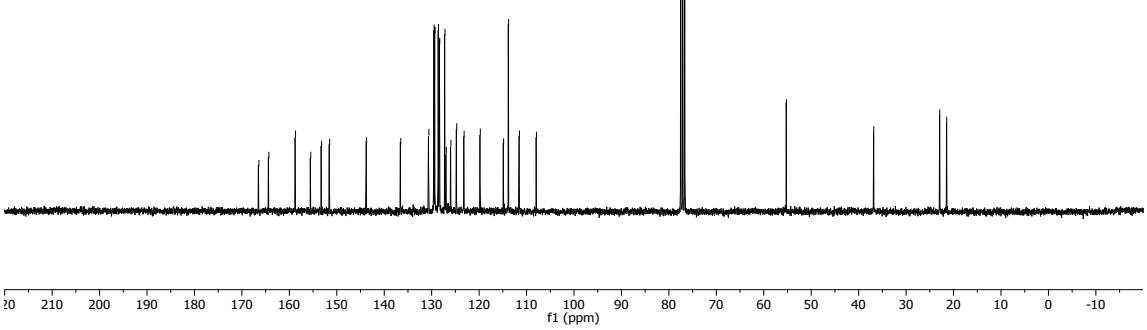


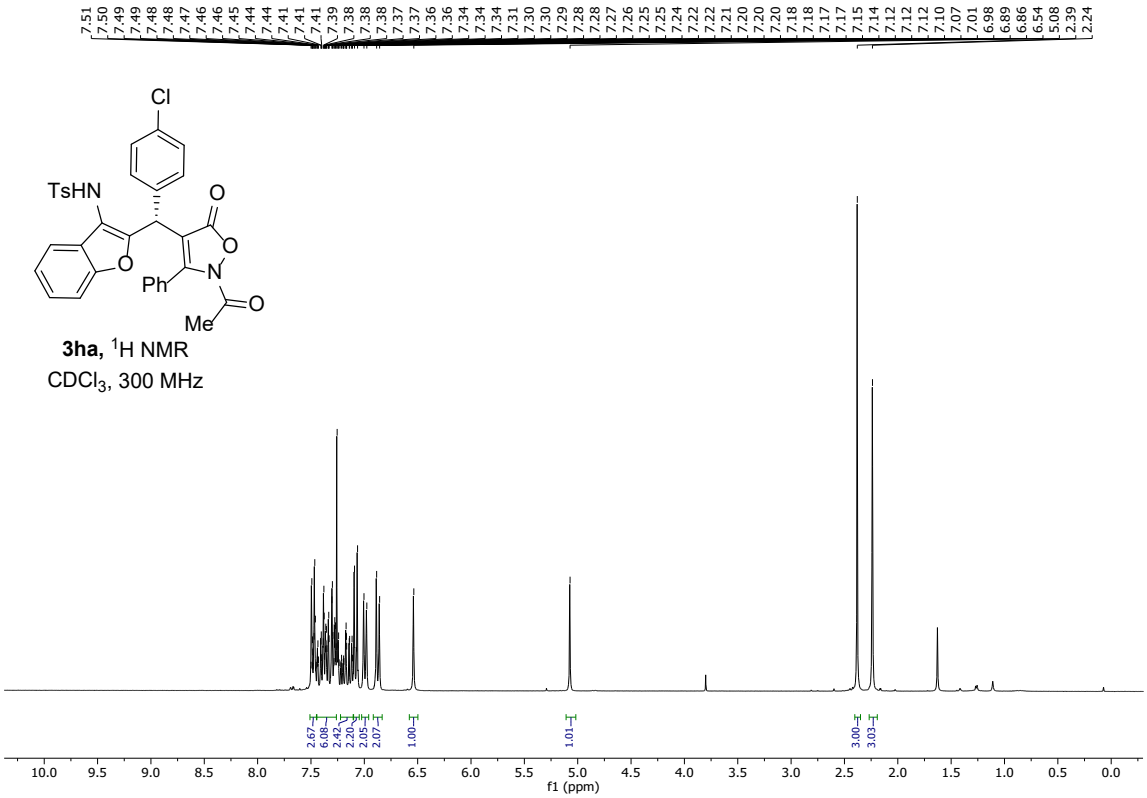
3ga, ^{1}H NMR
$CDCl_3$, 300 MHz



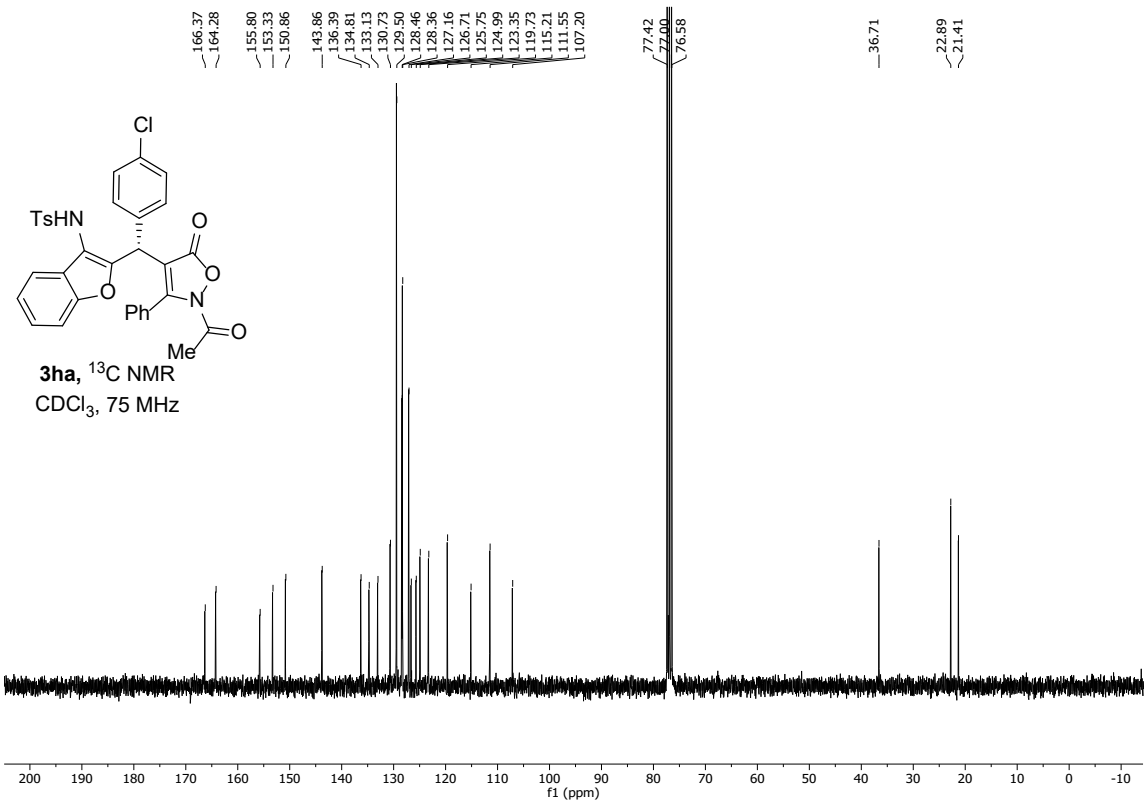


3ga, ^{13}C NMR
$CDCl_3$, 75 MHz

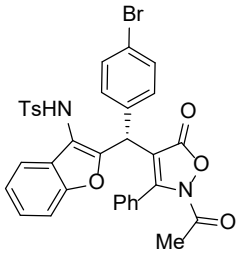




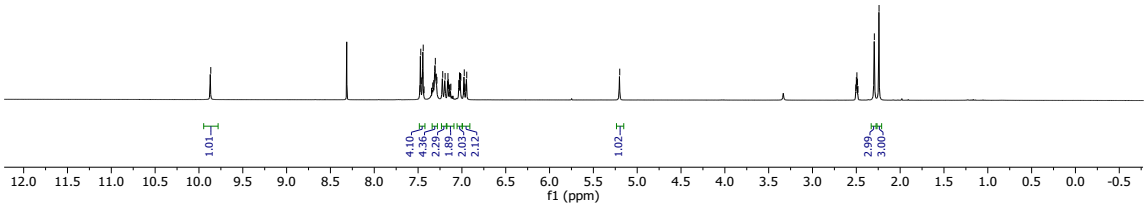
3ha, ^{1}H NMR
$CDCl_3$, 300 MHz

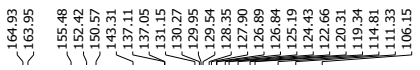


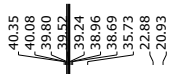
3ha, ^{13}C NMR
$CDCl_3$, 75 MHz

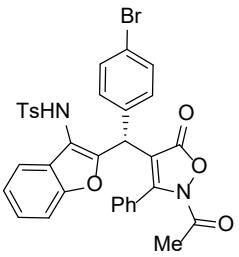


3ia, ^{1}H NMR
DMSO-d_6, 300 MHz

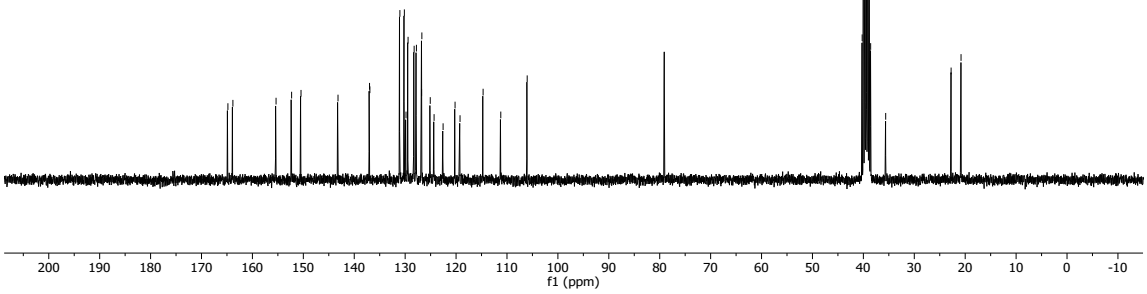


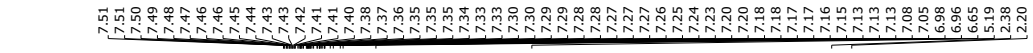


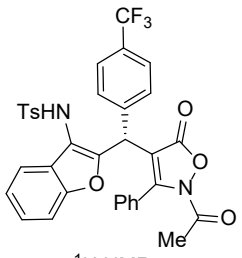




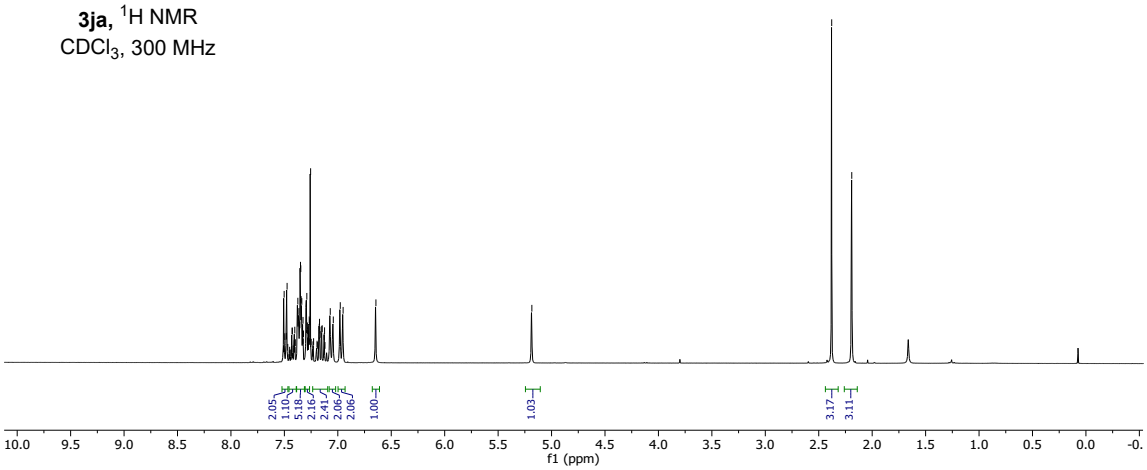
3ia, ^{13}C NMR
DMSO-d_6, 75 MHz

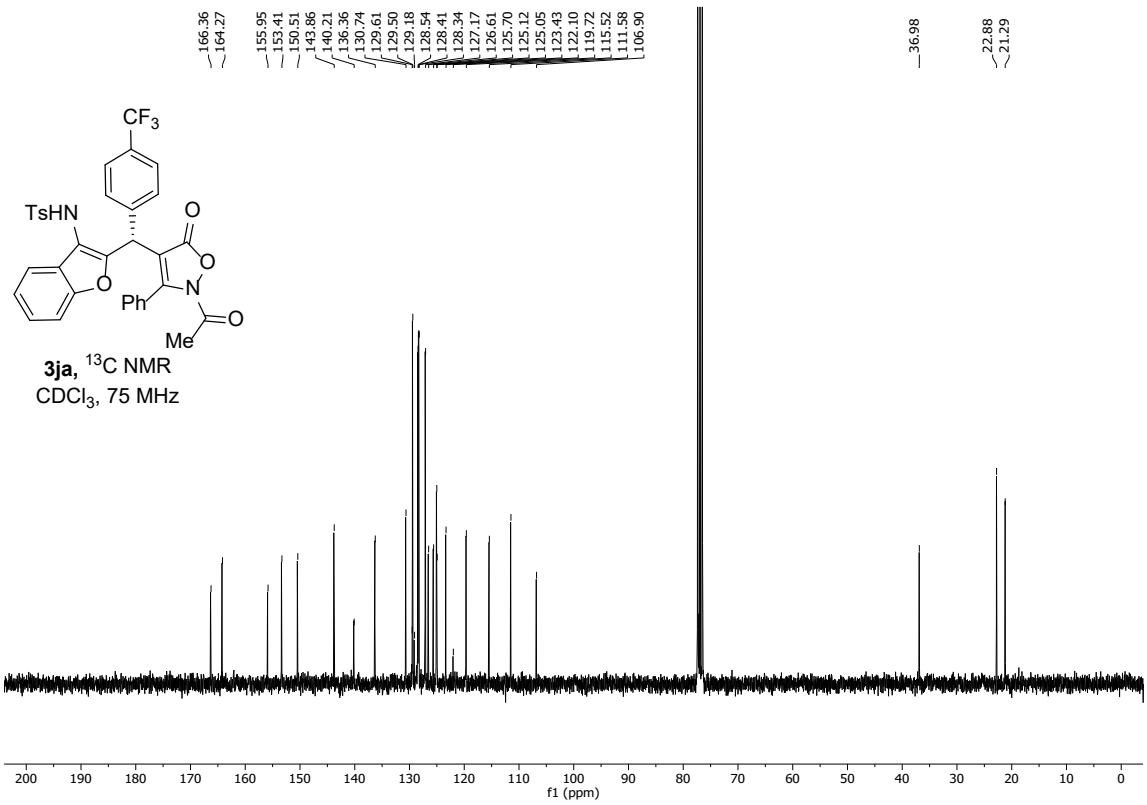




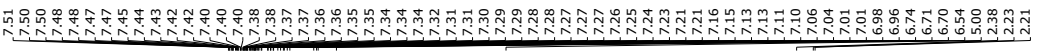


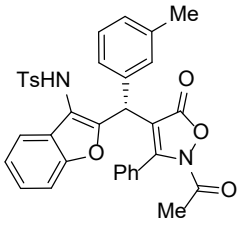
3ja, ^{1}H NMR
$CDCl_3$, 300 MHz



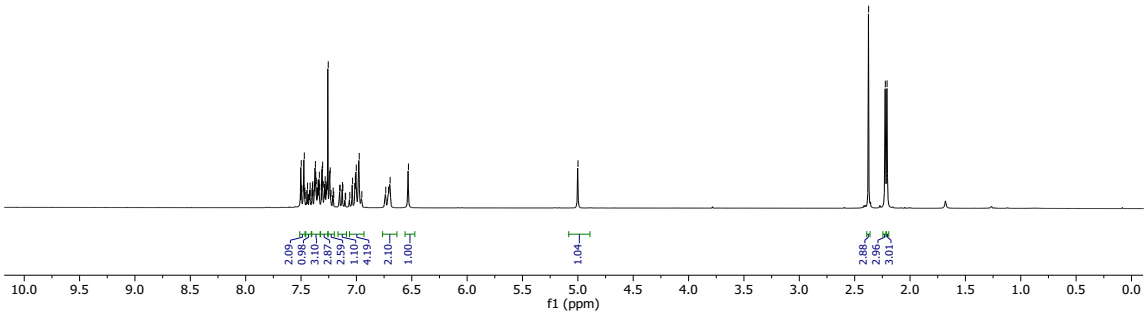


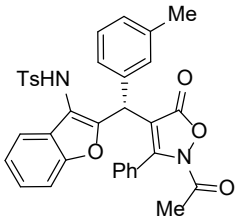
3ja, ^{13}C NMR
$CDCl_3$, 75 MHz



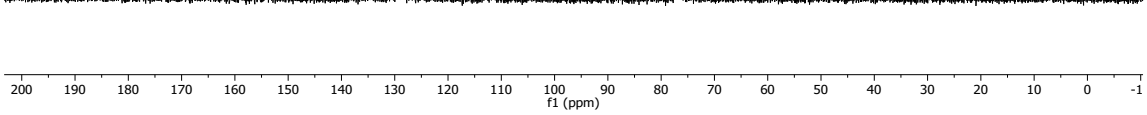


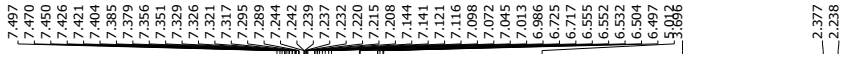
3ka, ^{1}H NMR
$CDCl_3$, 300 MHz

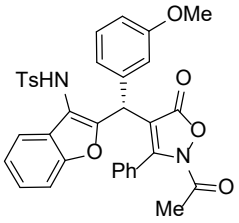




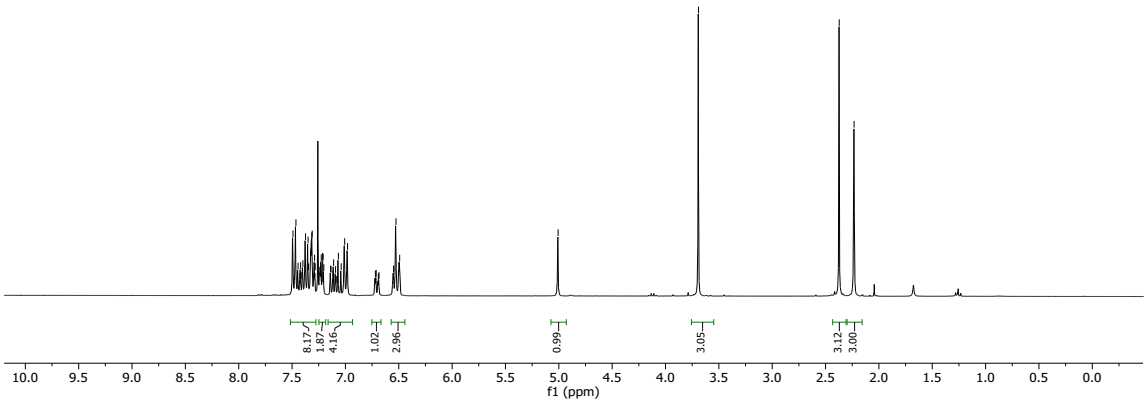
3ka, ^{13}C NMR
$CDCl_3$, 75 MHz

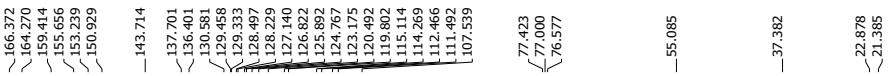


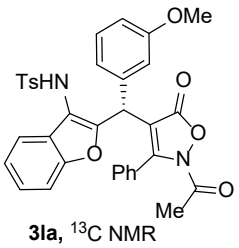




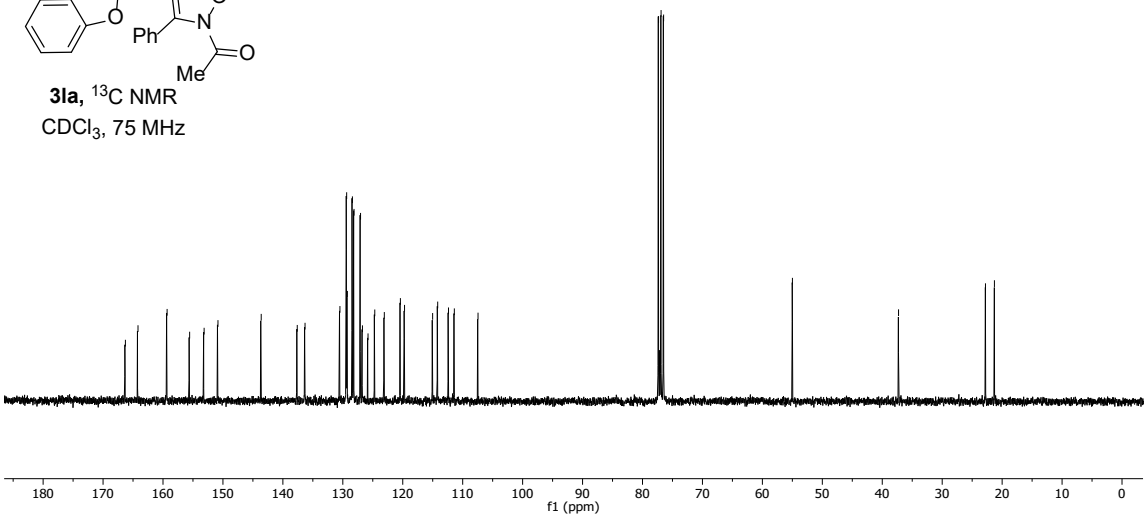
3la, ^{1}H NMR
$CDCl_3$, 300 MHz

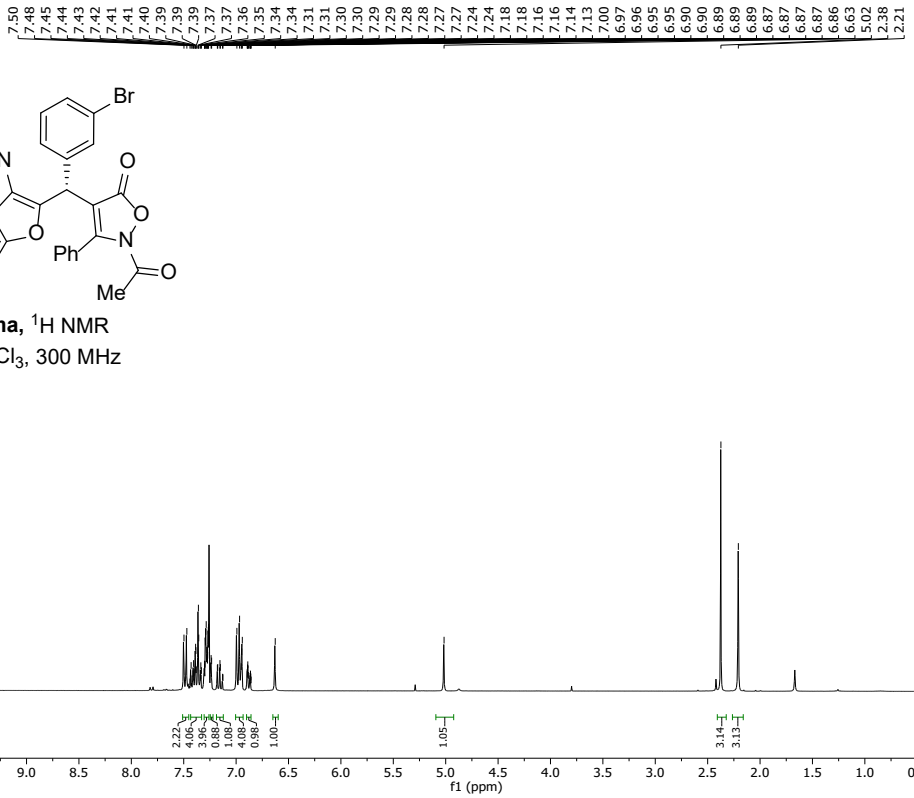




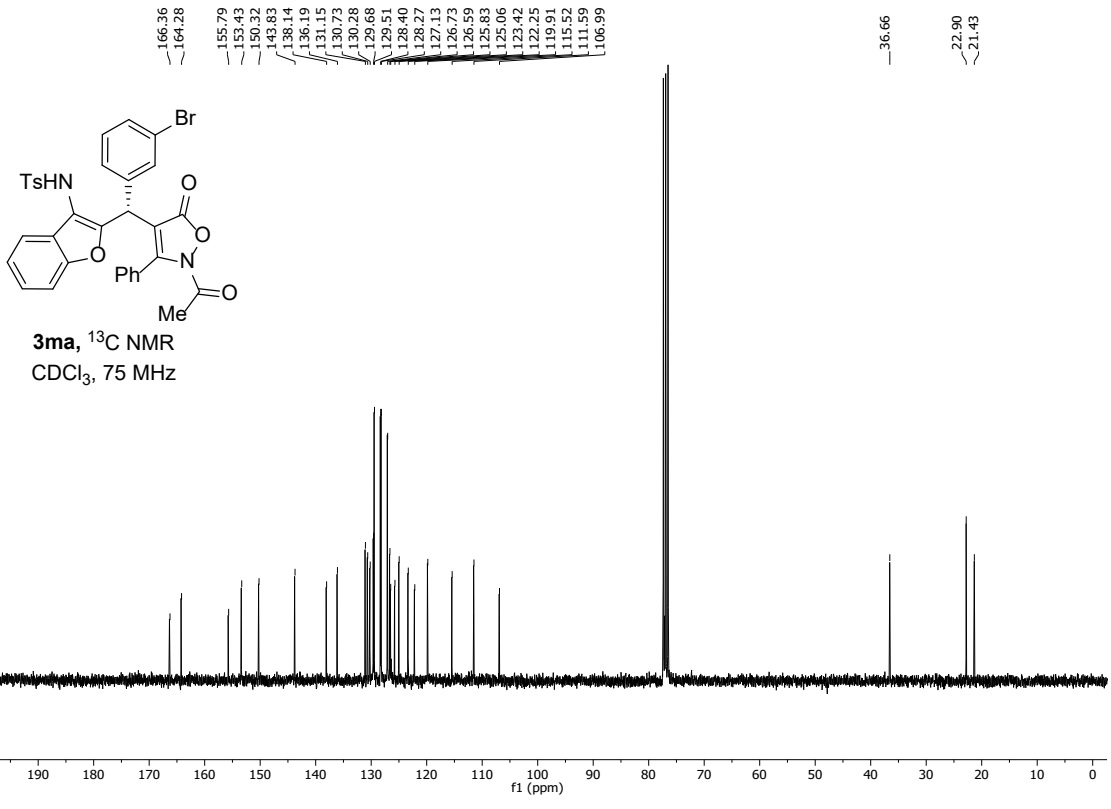


3la, ^{13}C NMR
$CDCl_3$, 75 MHz

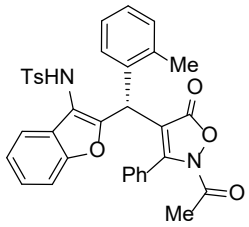




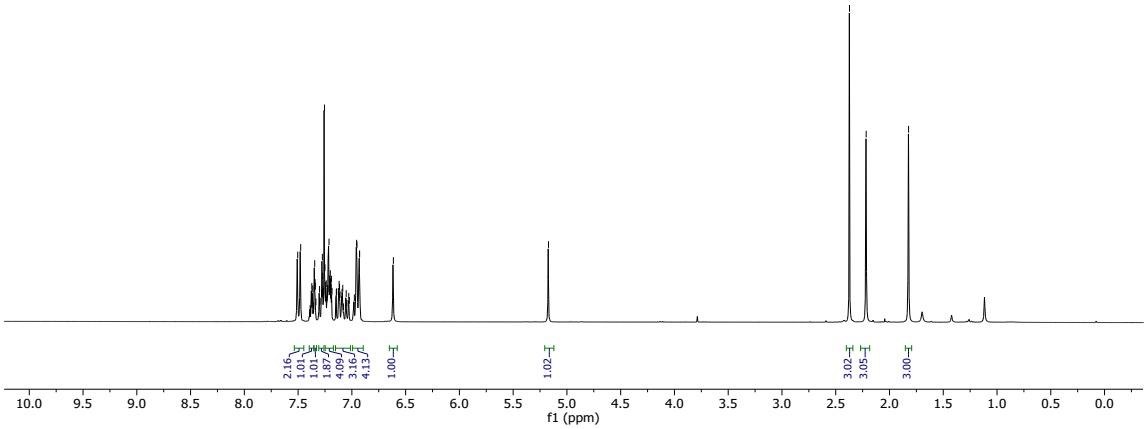
3ma, ^{1}H NMR
$CDCl_3$, 300 MHz

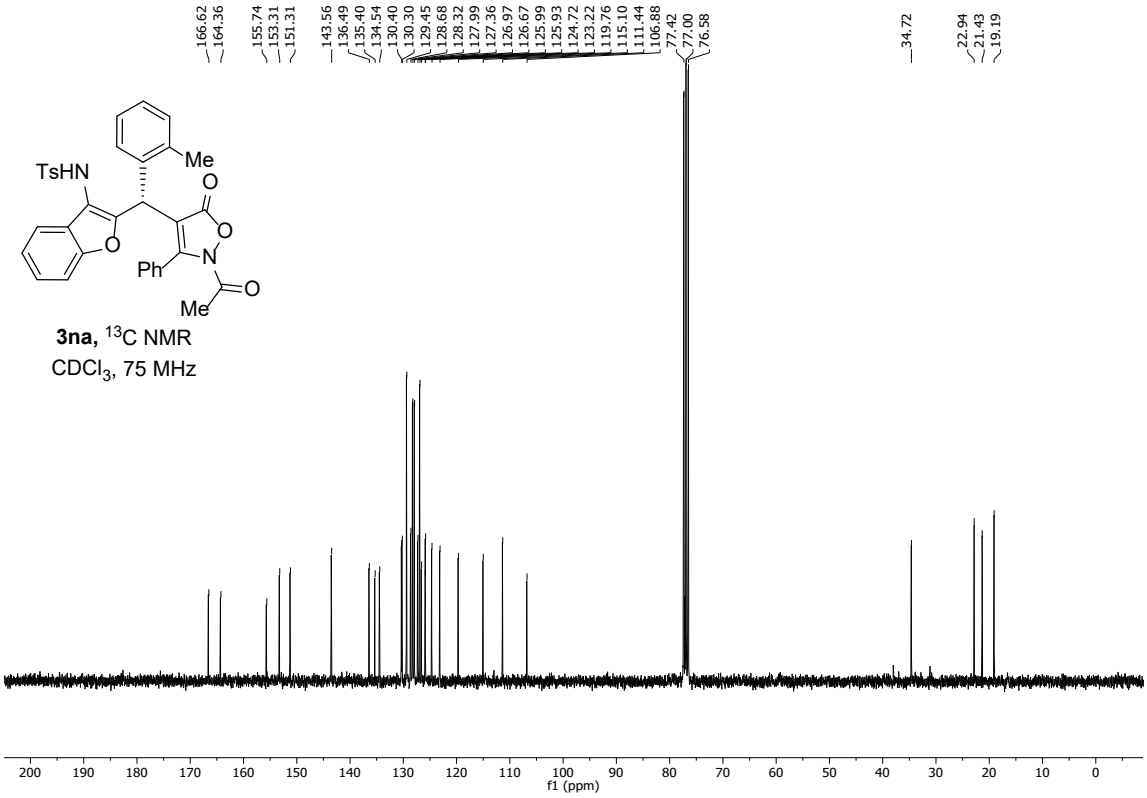


3ma, ^{13}C NMR
$CDCl_3$, 75 MHz

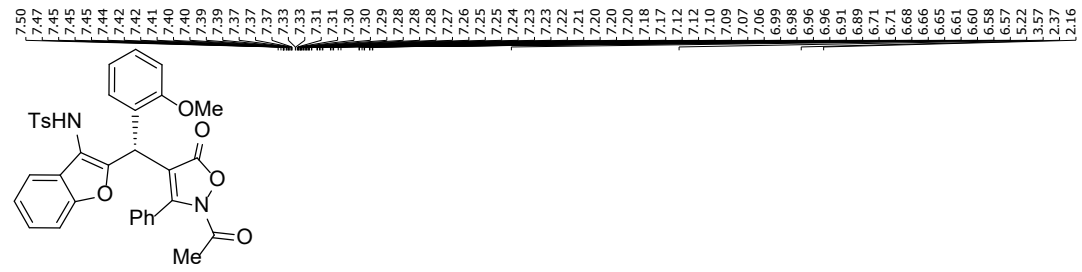


3na, ^{1}H NMR
$CDCl_3$, 300 MHz

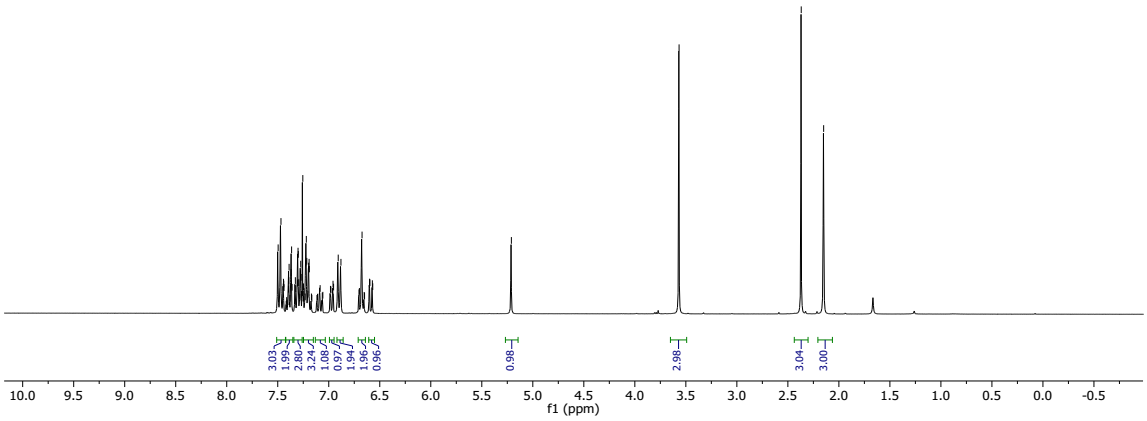


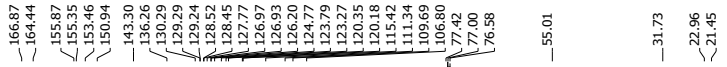


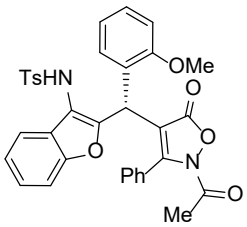
3na, ^{13}C NMR
$CDCl_3$, 75 MHz



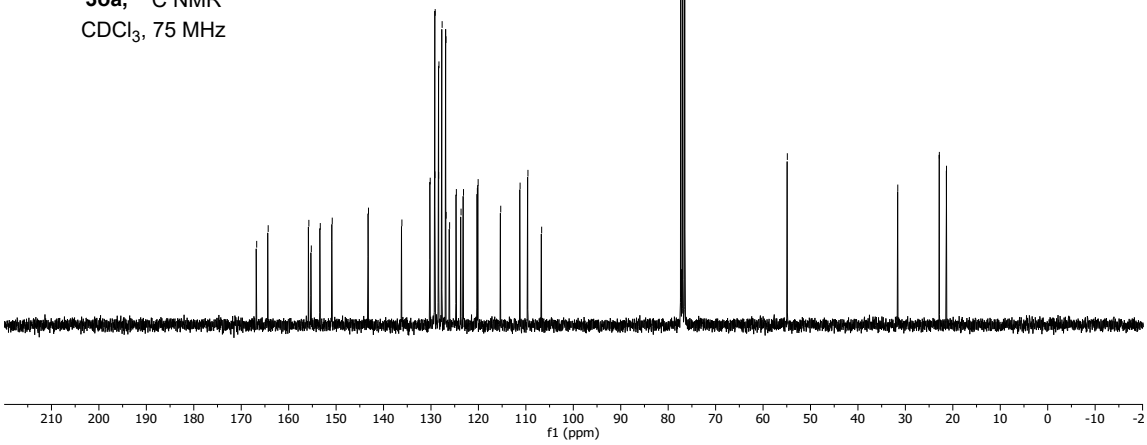
3oa, ^{1}H NMR
$CDCl_3$, 300 MHz

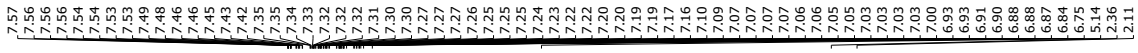


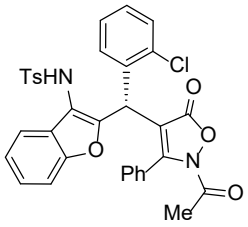




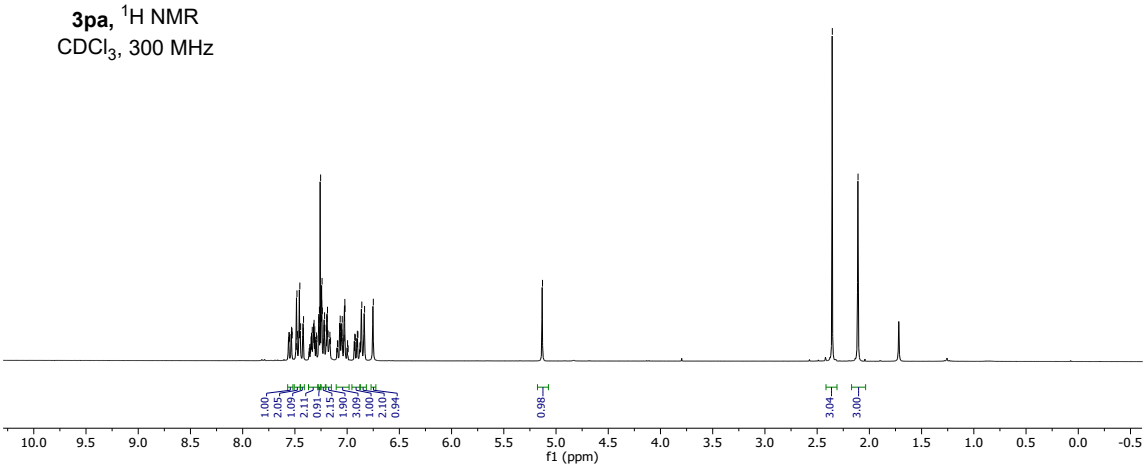
3oa, ^{13}C NMR
$CDCl_3$, 75 MHz

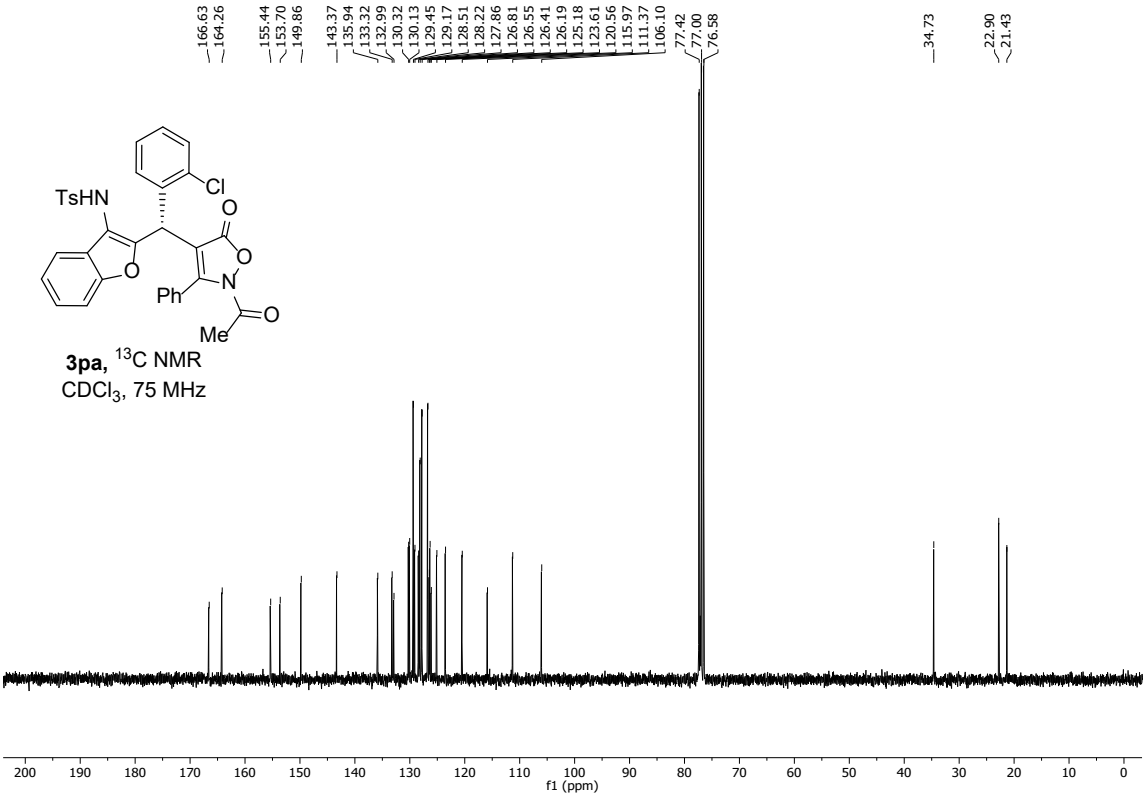




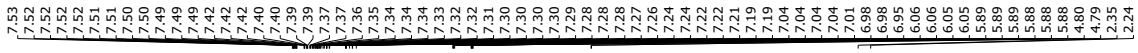


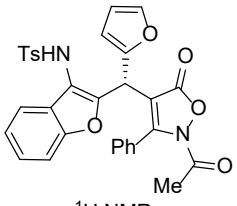
3pa, ^{1}H NMR
$CDCl_3$, 300 MHz



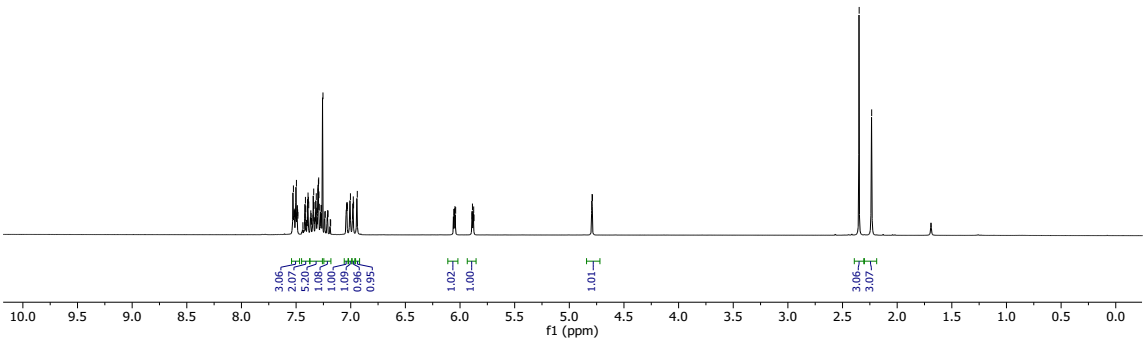


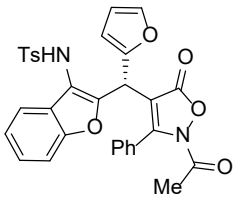
3pa, ^{13}C NMR
$CDCl_3$, 75 MHz



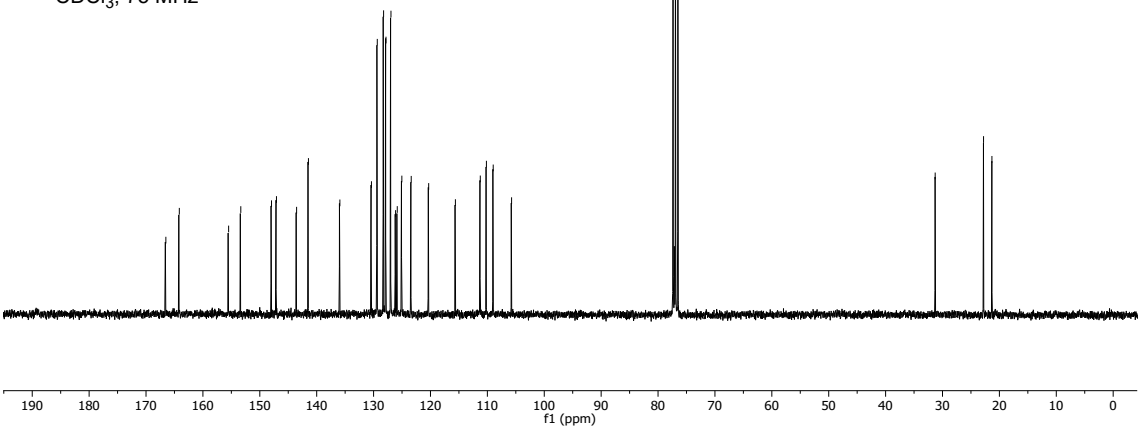


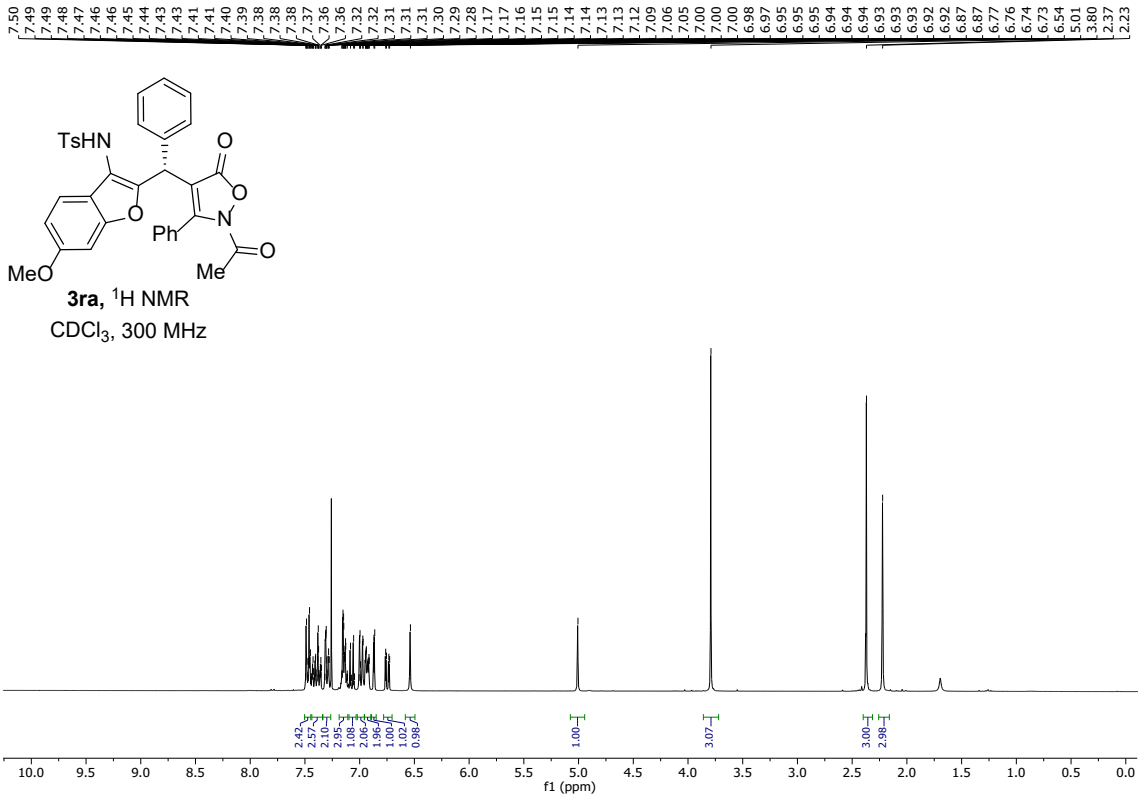
3qa, ^{1}H NMR
$CDCl_3$, 300 MHz





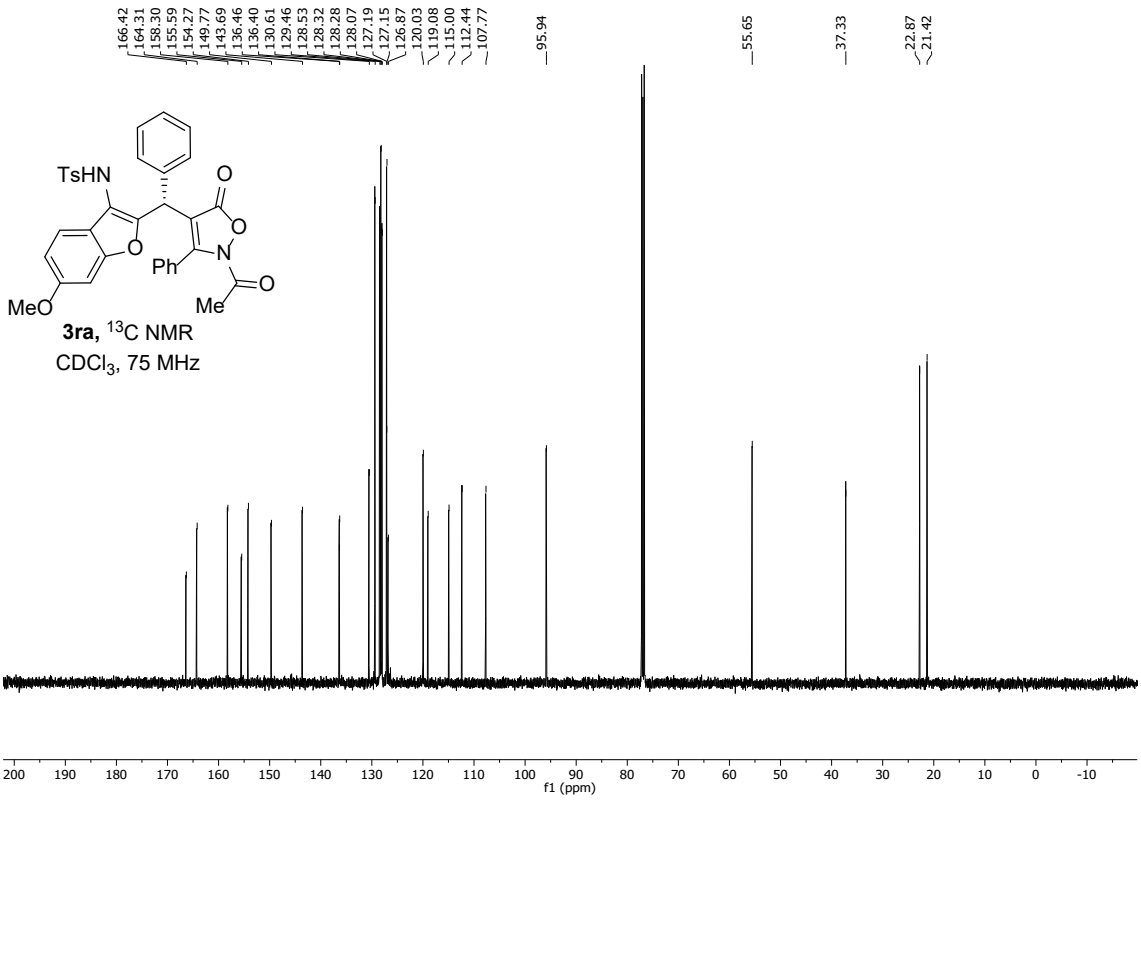
3qa, ^{13}C NMR
$CDCl_3$, 75 MHz





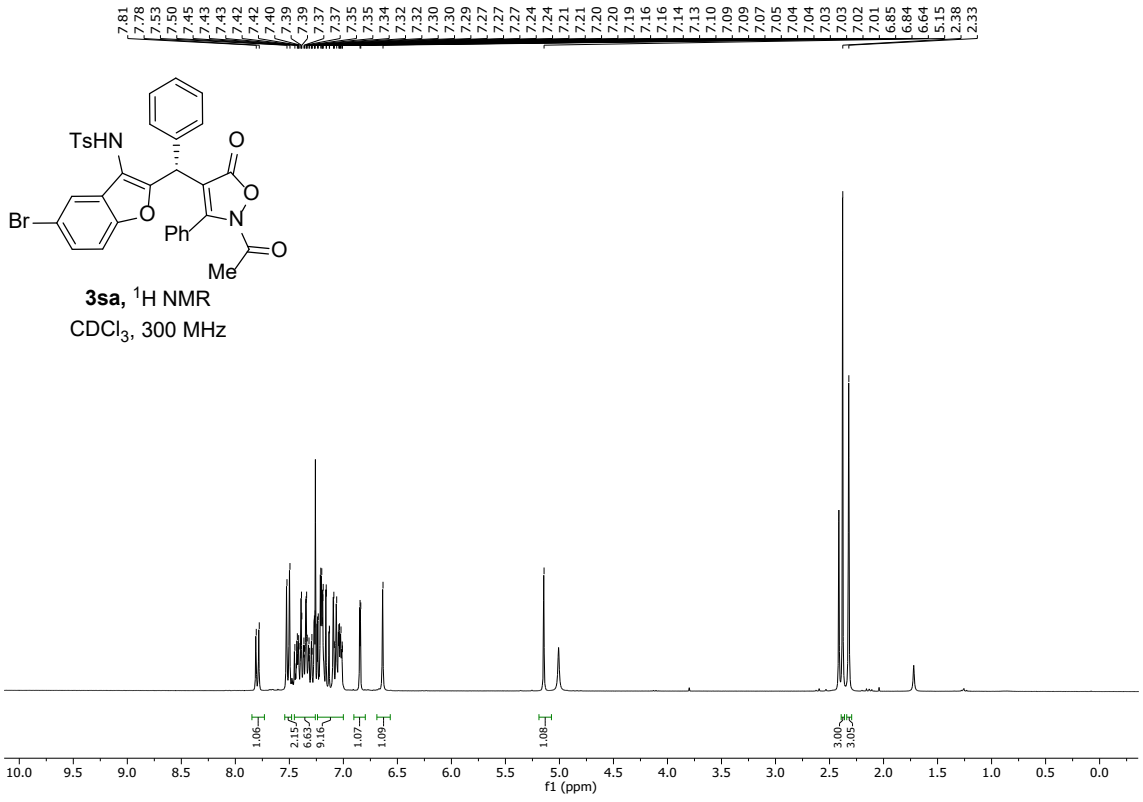
3ra, ^{1}H NMR

$CDCl_3$, 300 MHz

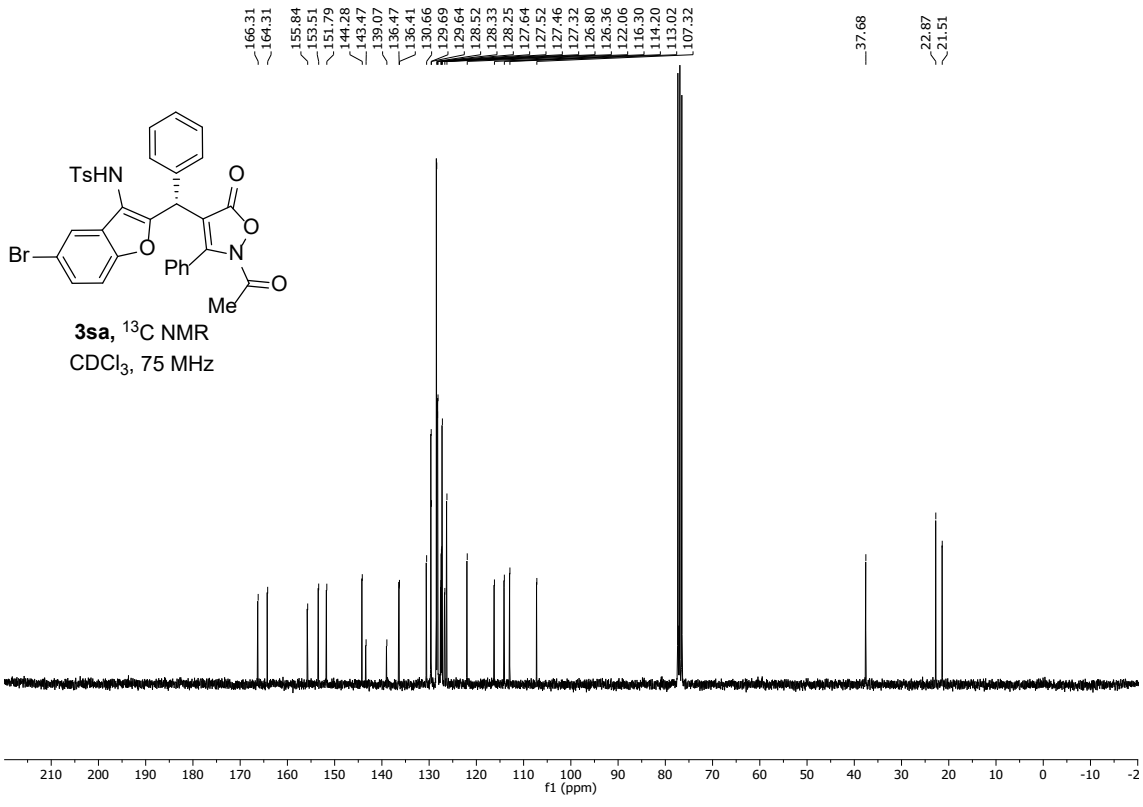


3ra, ^{13}C NMR

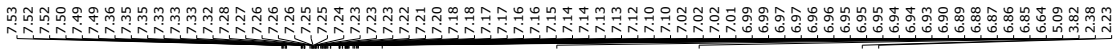
$CDCl_3$, 75 MHz

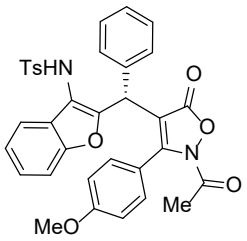


3sa, ^{1}H NMR
$CDCl_3$, 300 MHz

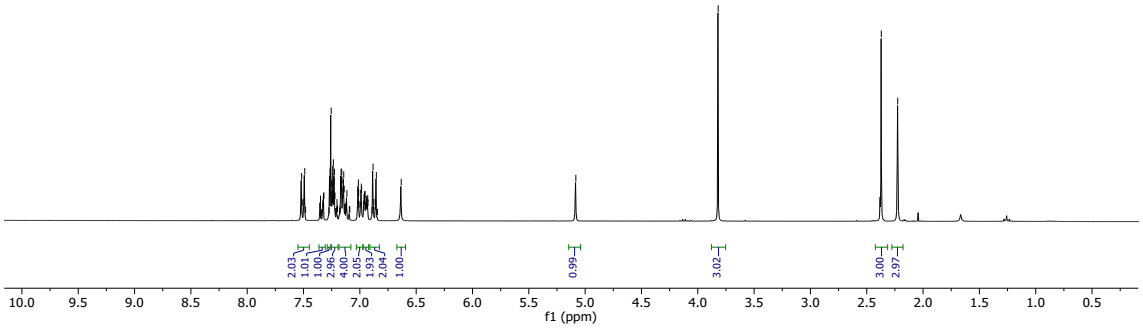


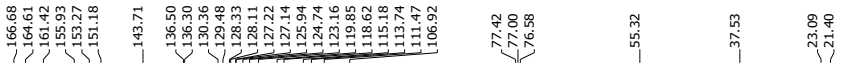
3sa, ^{13}C NMR
$CDCl_3$, 75 MHz

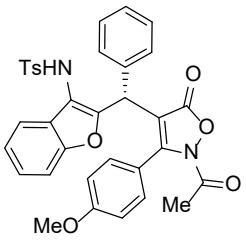




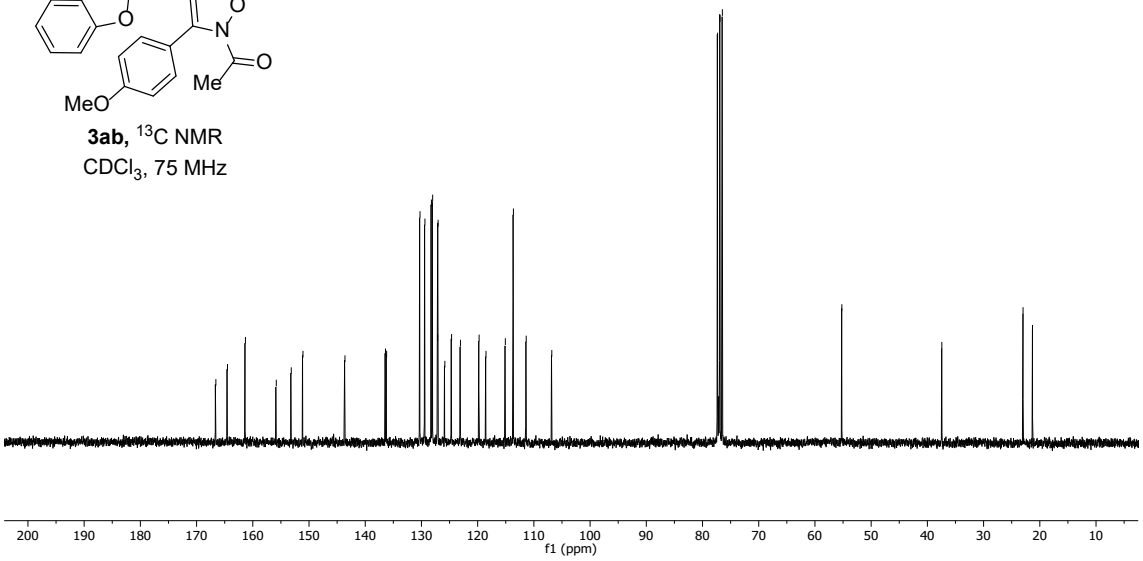
3ab, ^{1}H NMR
$CDCl_3$, 300 MHz

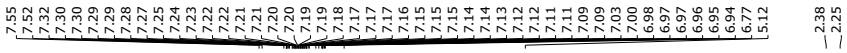


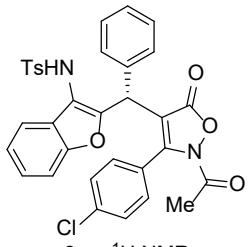




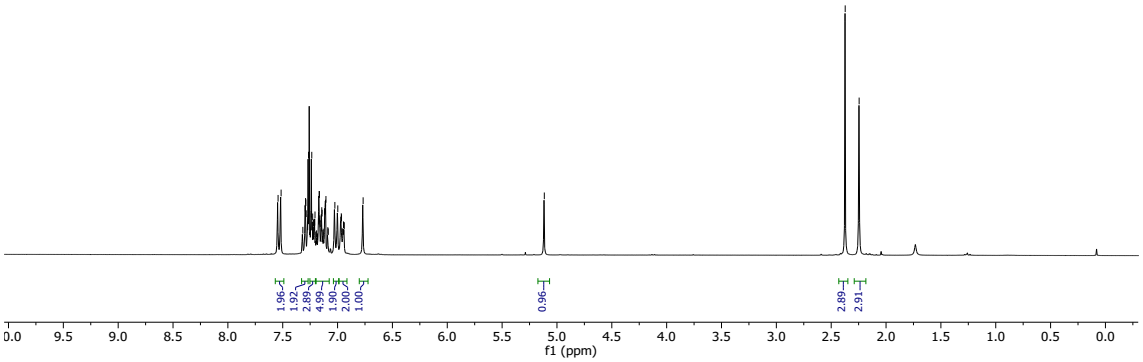
3ab, ^{13}C NMR
$CDCl_3$, 75 MHz

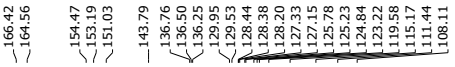


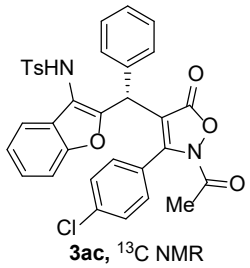




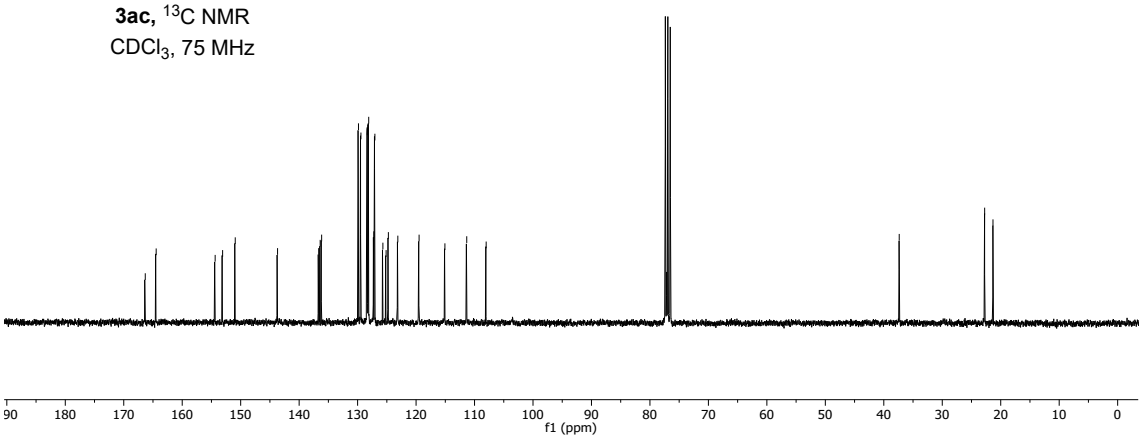
3ac, ^{1}H NMR
$CDCl_3$, 300 MHz

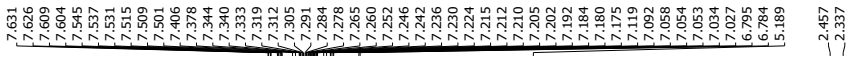


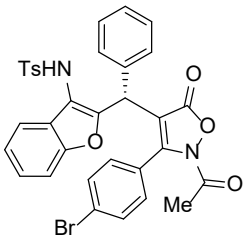




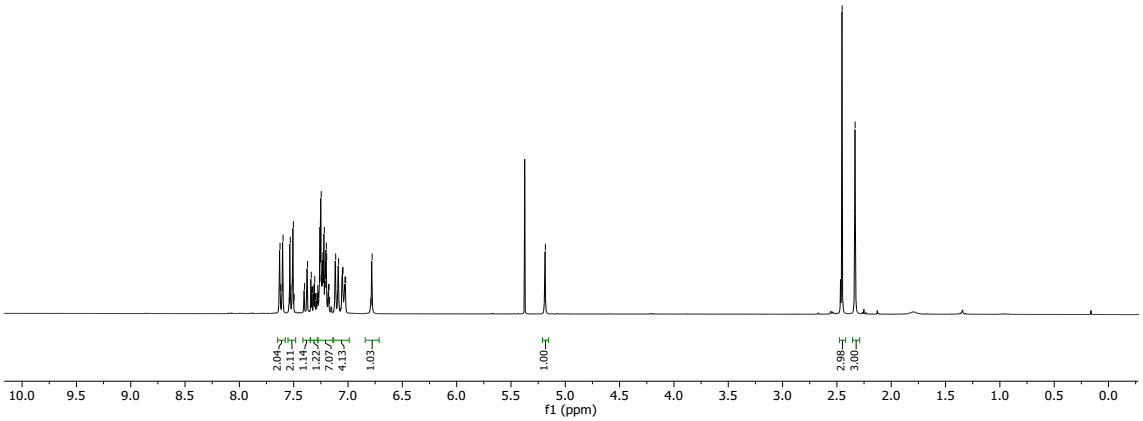
3ac, ^{13}C NMR
$CDCl_3$, 75 MHz

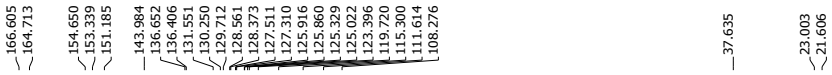


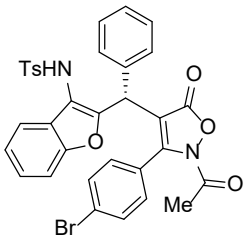




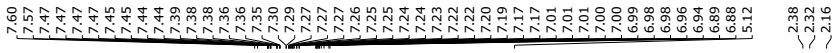
3ad, ^{1}H NMR
$CDCl_3$, 300 MHz

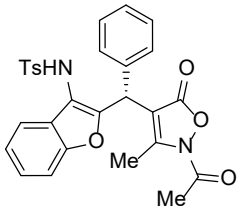






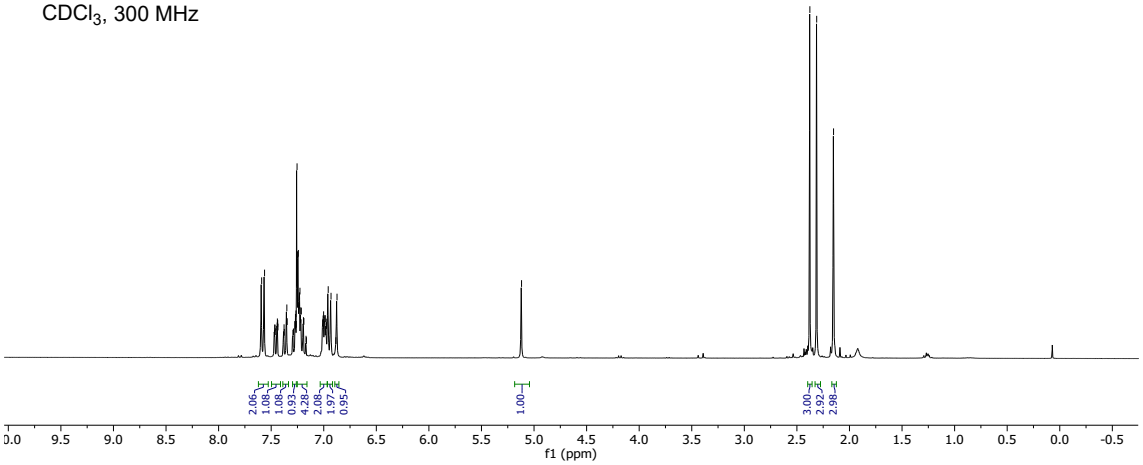
3ad, ^{13}C NMR
$CDCl_3$, 75 MHz

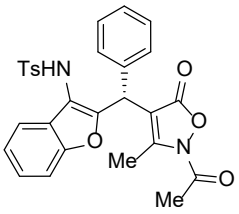




3ae, ^{1}H NMR

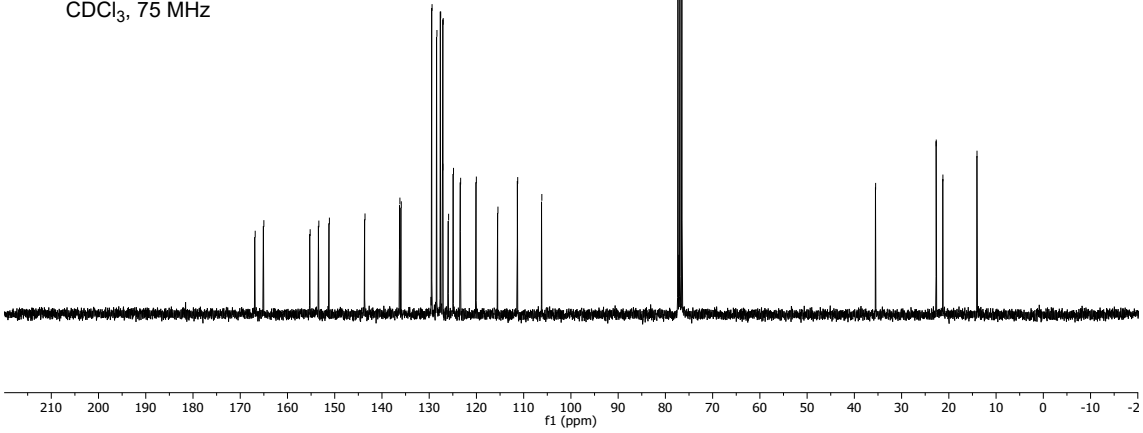
$CDCl_3$, 300 MHz

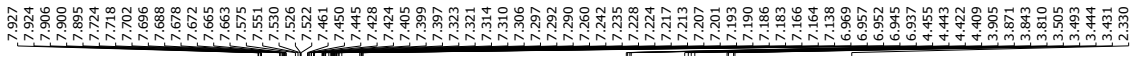


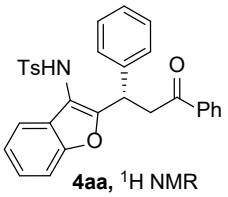


3ae, ^{13}C NMR

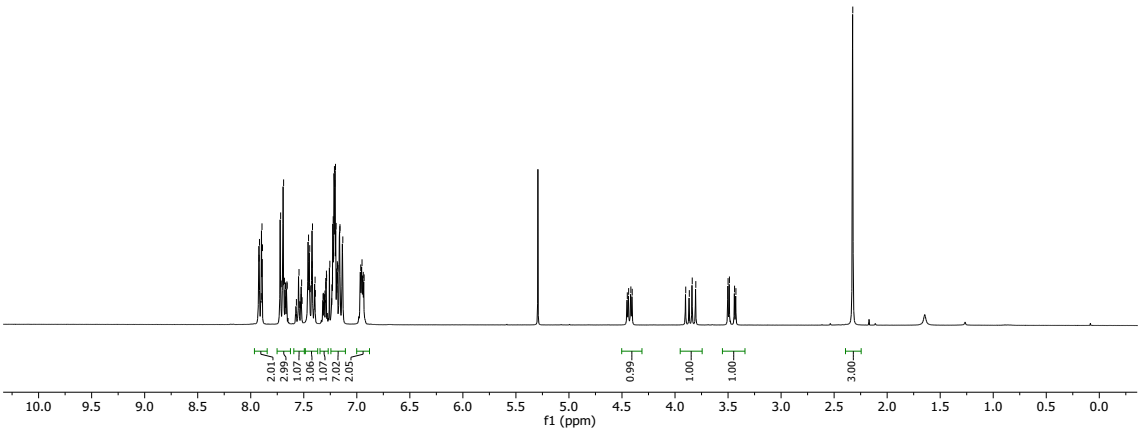
$CDCl_3$, 75 MHz

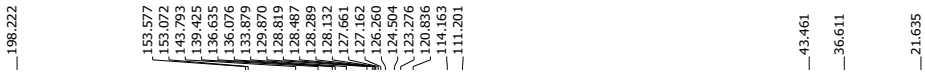


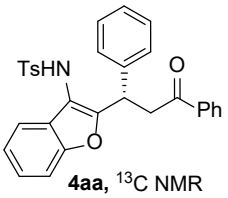




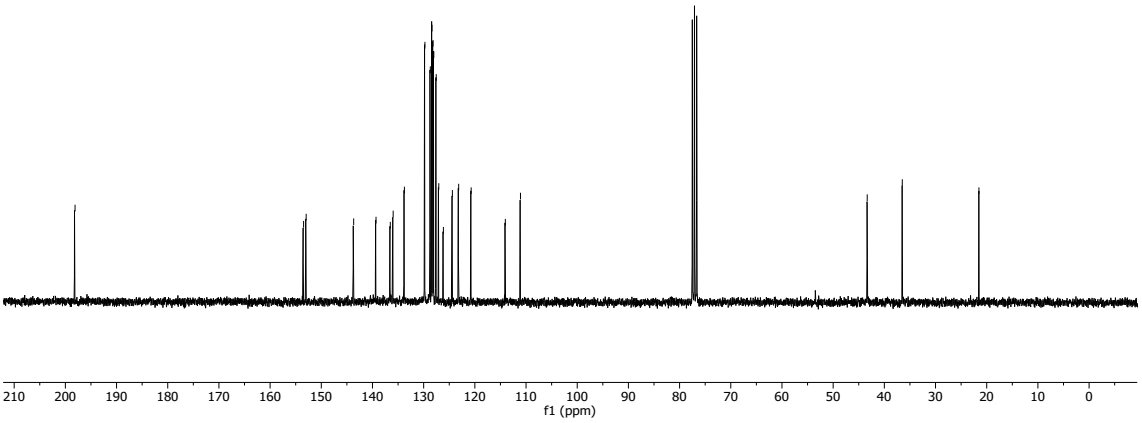
4aa, ^{1}H NMR
$CDCl_3$, 300 MHz

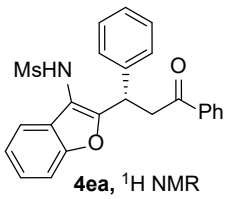




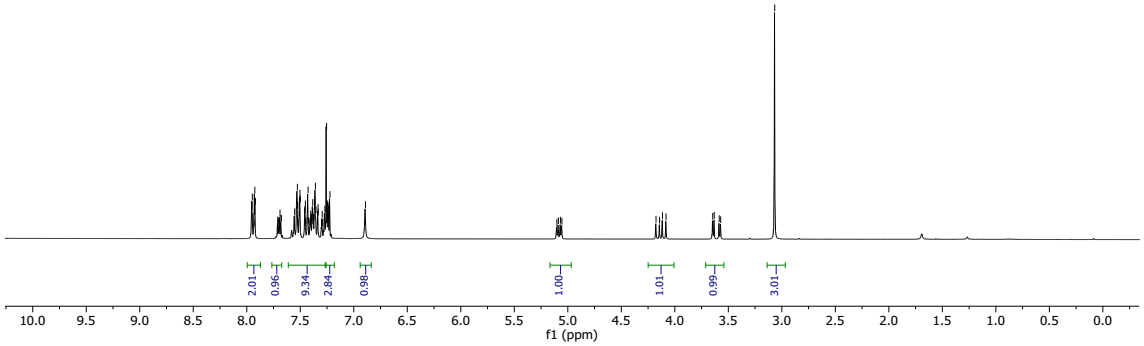


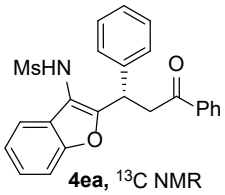
4aa, ^{13}C NMR
$CDCl_3$, 75 MHz



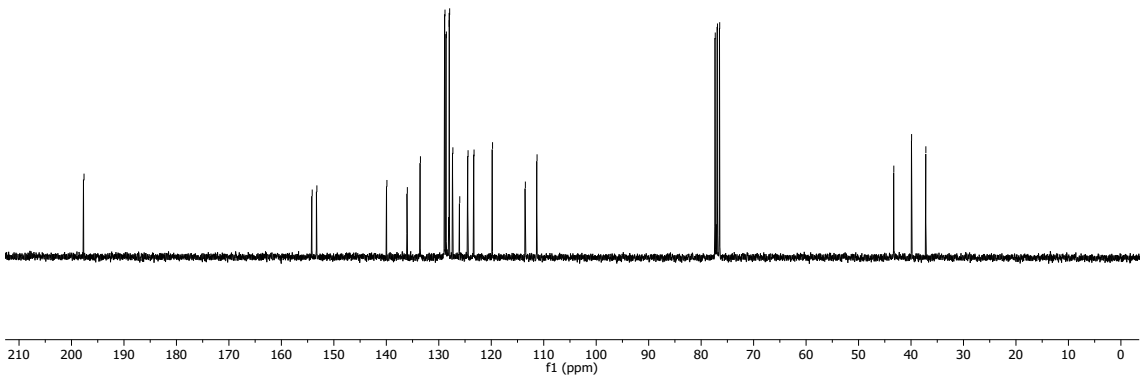


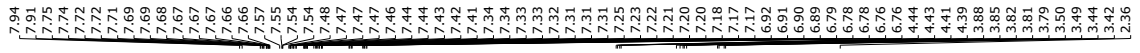
4ea, ^{1}H NMR
$CDCl_3$, 300 MHz

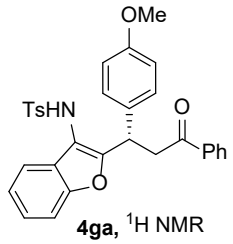




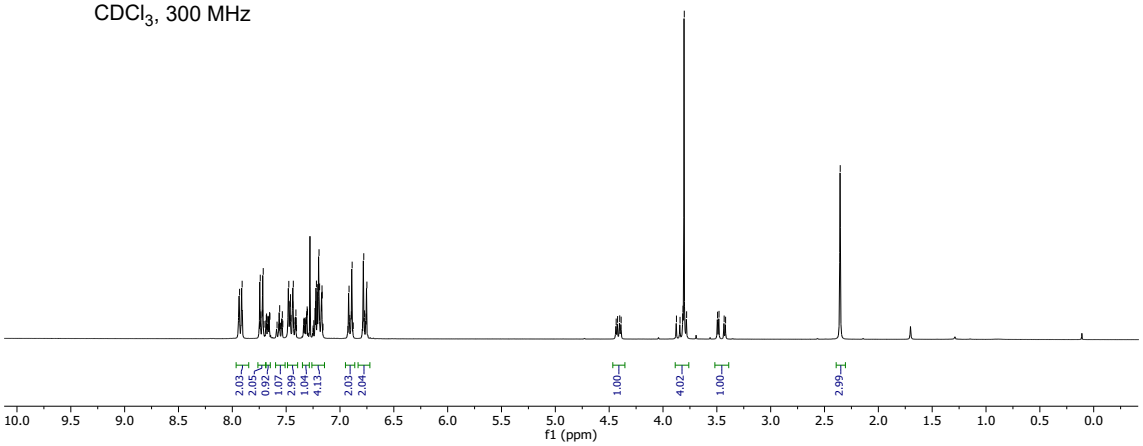
4ea, ^{13}C NMR
$CDCl_3$, 75 MHz

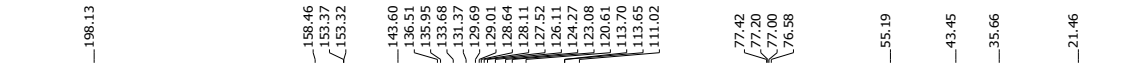


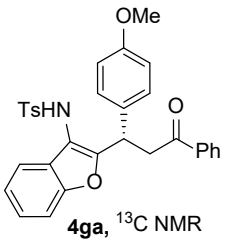




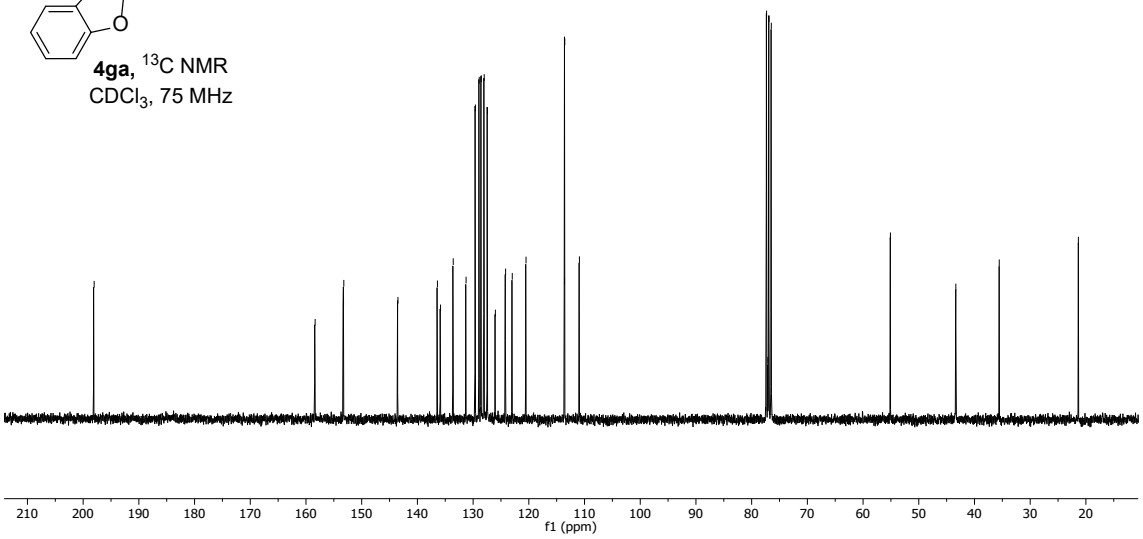
4ga, ^{1}H NMR
$CDCl_3$, 300 MHz

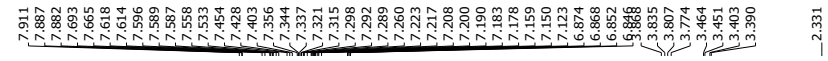


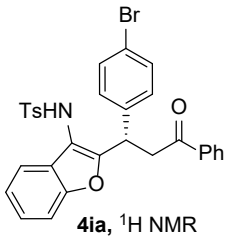




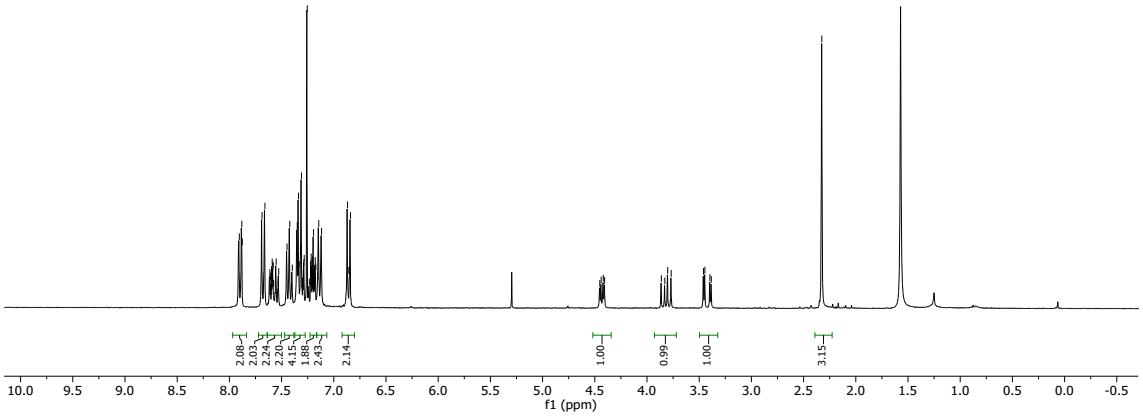
4ga, ^{13}C NMR
$CDCl_3$, 75 MHz

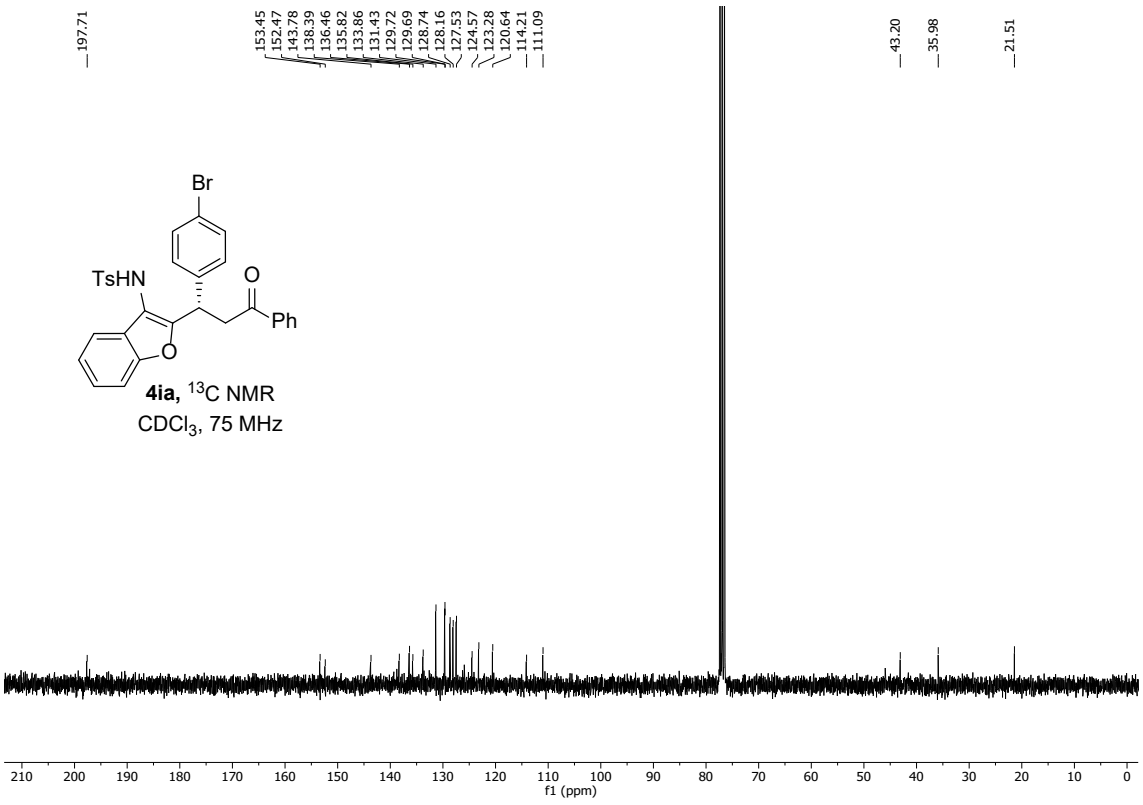






4ia, ^{1}H NMR
$CDCl_3$, 300 MHz

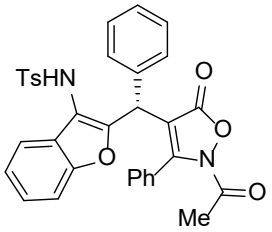




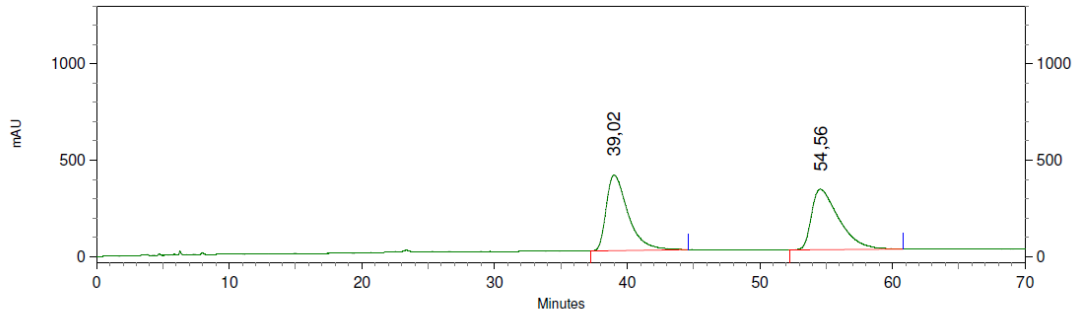
4ia, ^{13}C NMR
$CDCl_3$, 75 MHz

HPLC Spectra

Product 3aa



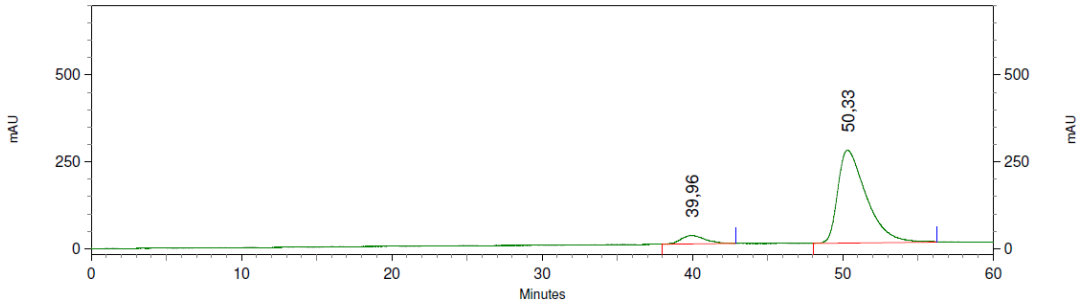
Non-enantioselective reaction



11: 231 nm, 4 nm
Results

Retention Time	Area	Area Percent
39,02	179902093	49,992
54,56	179962482	50,008

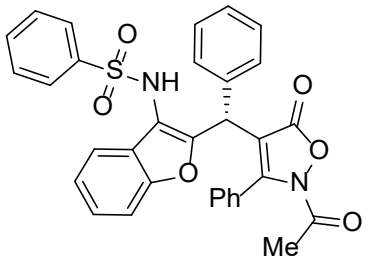
Enantioselective reaction



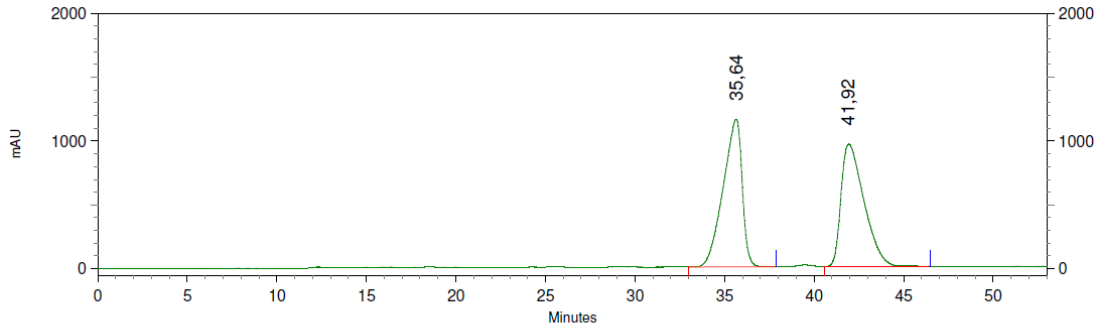
26: 293 nm, 4 nm
Results

Retention Time	Area	Area Percent
39,96	10816398	7,133
50,33	140830925	92,867

Product 3ba



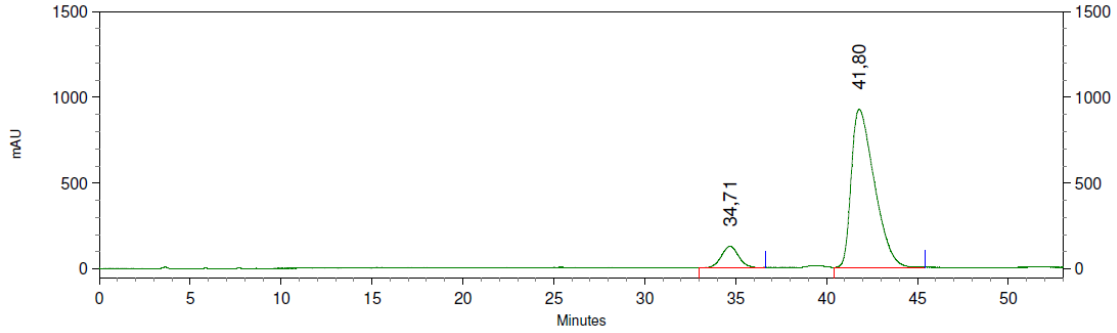
Non-enantioselective reaction



19: 291 nm, 4 nm
Results

Retention Time	Area	Area Percent
35,64	341488006	49,956
41,92	342089974	50,044

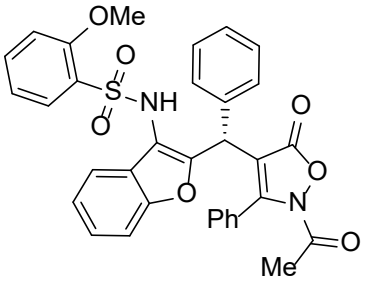
Enantioselective



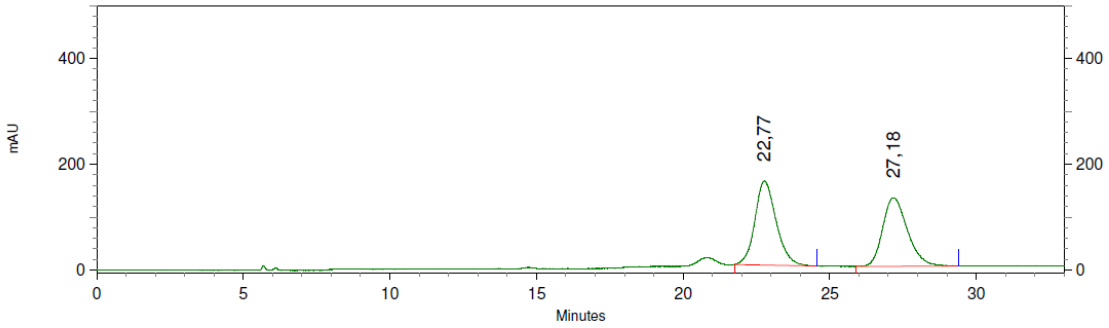
19: 291 nm, 4 nm
Results

Retention Time	Area	Area Percent
34,71	32297049	9,080
41,80	323382606	90,920

Product 3ca



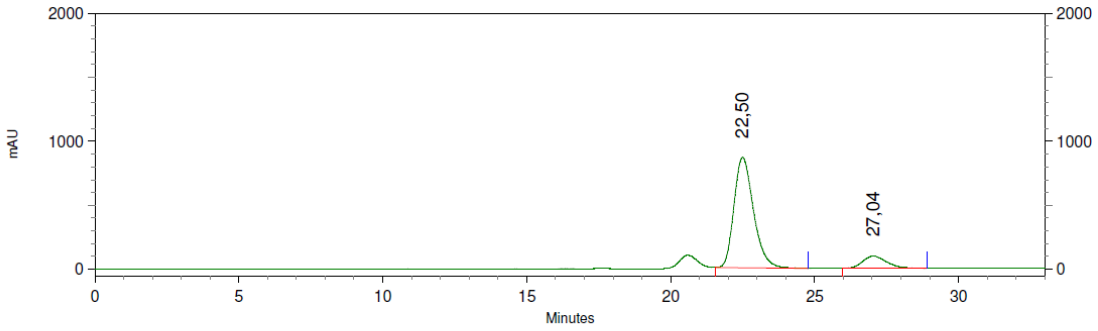
Non-enantioselective reaction



19: 291 nm, 4 nm
Results

Retention Time	Area	Area Percent
22,77	32185720	51,320
27,18	30530362	48,680

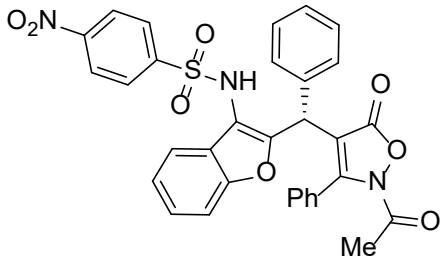
Enantioselective reaction



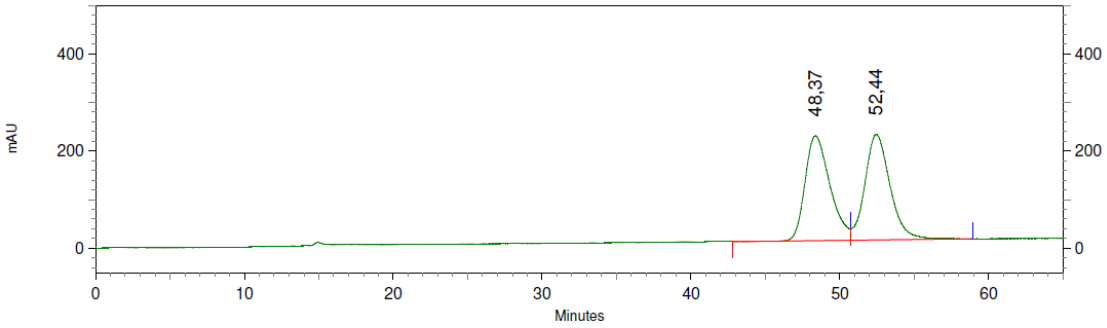
19: 291 nm, 4 nm
Results

Retention Time	Area	Area Percent
22,50	163154584	88,043
27,04	22157217	11,957

Product 3da



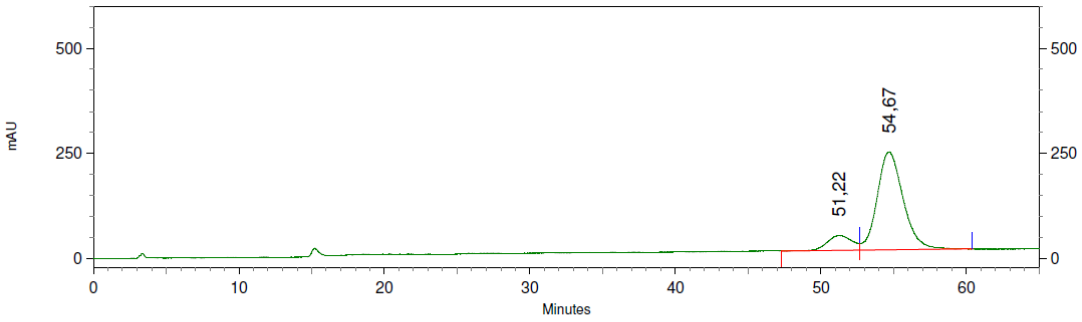
Non-enantioselective reaction



24: 295 nm, 4 nm
Results

Retention Time	Area	Area Percent
48,37	100523369	49,617
52,44	102074699	50,383

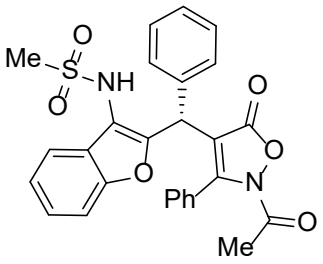
Enantioselective reaction



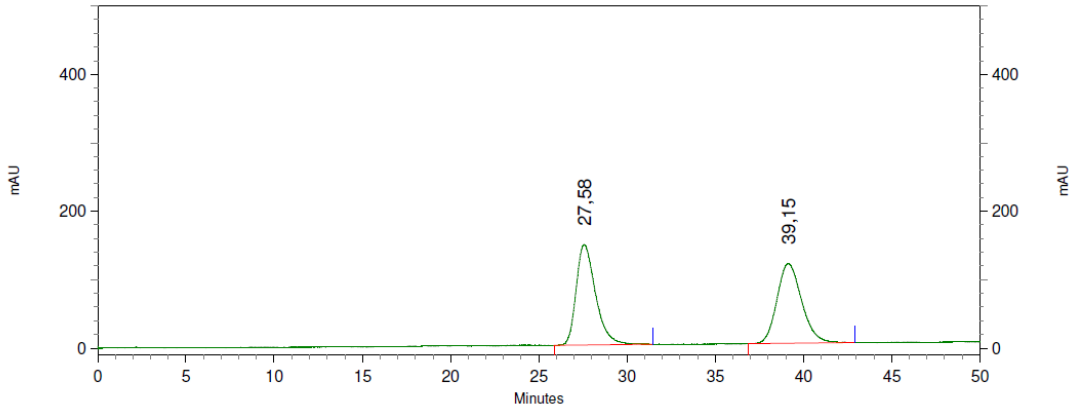
5: 255 nm, 4 nm Results

Retention Time	Area	Area Percent
51,22	16634931	12,588
54,67	115513945	87,412

Product 3ea



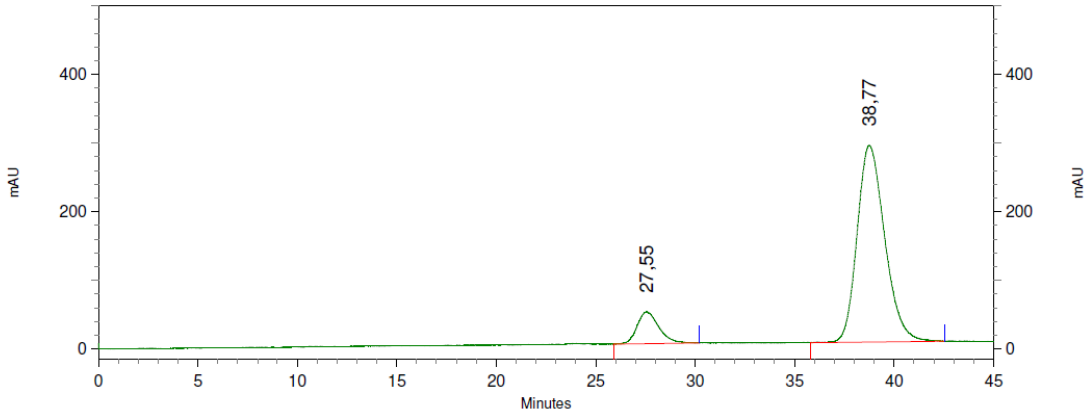
Non-enantioselective reaction



20: 290 nm, 4 nm
Results

Retention Time	Area	Area Percent
27,58	45051441	49,769
39,15	45470393	50,231

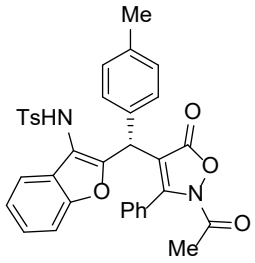
Enantioselective reaction



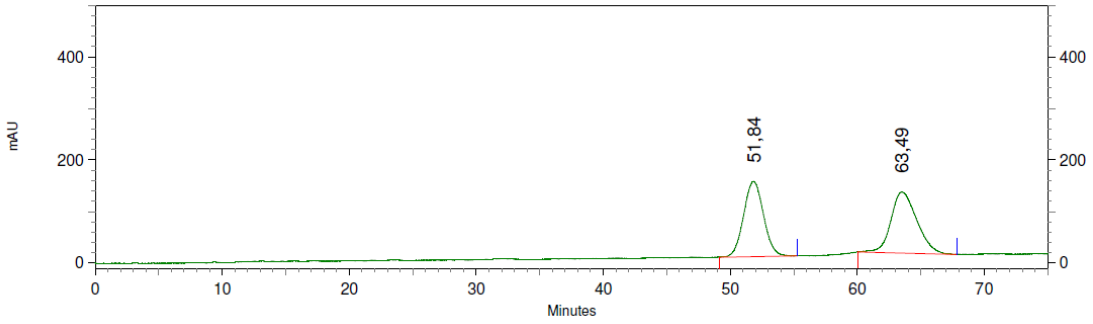
20: 290 nm, 4 nm
Results

Retention Time	Area	Area Percent
27,55	14136570	11,338
38,77	110550666	88,662

Product 3fa



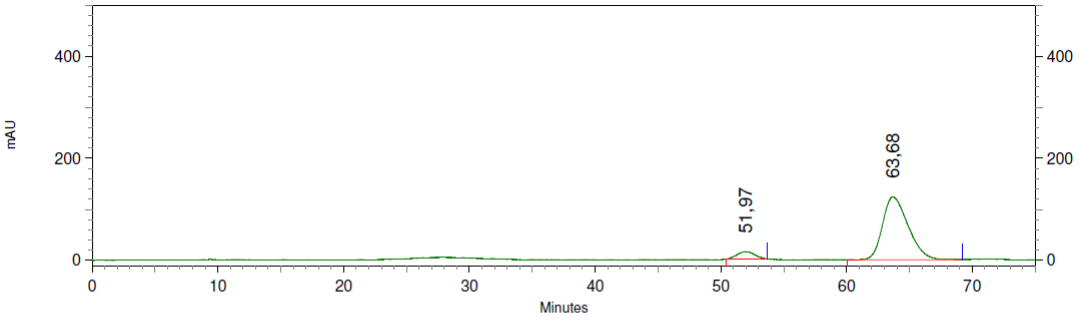
Non-enantioselective reaction



37: 299 nm, 4 nm
Results

Retention Time	Area	Area Percent
51,84	63718828	48,643
63,49	67274035	51,357

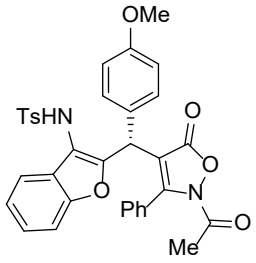
Enantioselective reaction



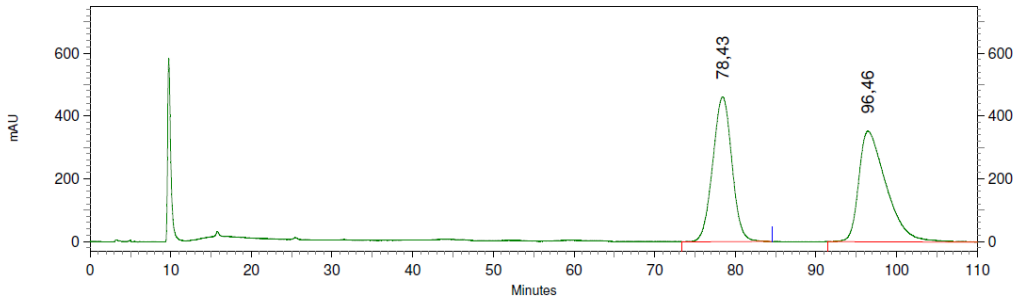
37: 299 nm, 4 nm
Results

Retention Time	Area	Area Percent
51,97	5739525	7,589
63,68	69888939	92,411

Product 3ga



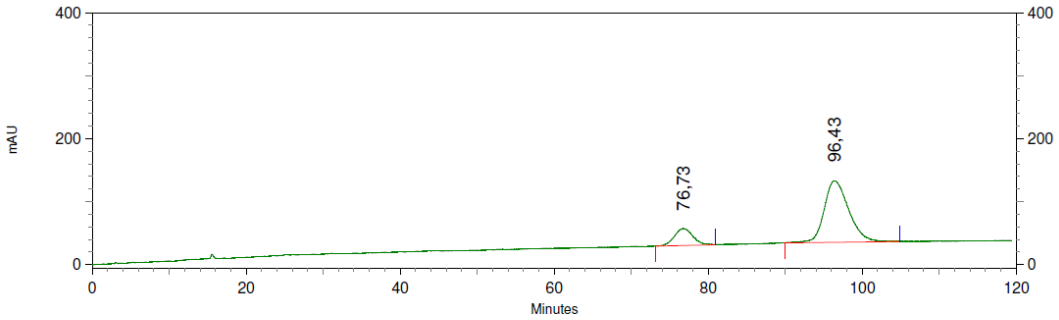
Non-enantioselective reaction



13: 230 nm, 4 nm
Results

Retention Time	Area	Area Percent
78,43	305306237	47,683
96,46	334974046	52,317

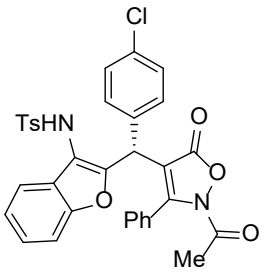
Enantioselective reaction



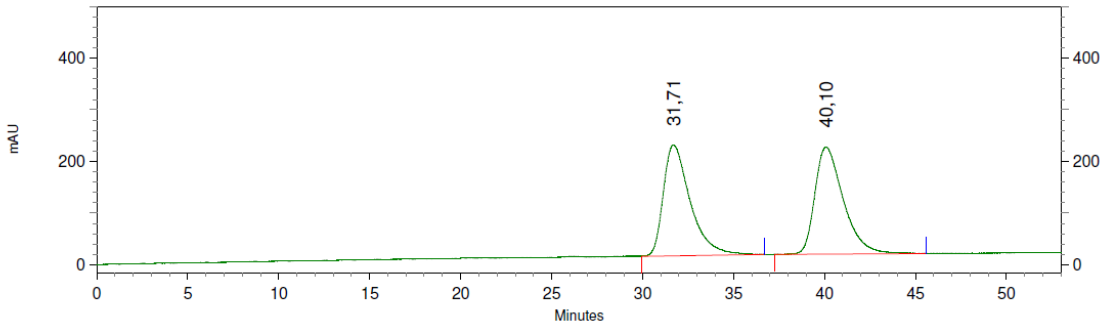
9: 252 nm, 4 nm Results

Retention Time	Area	Area Percent
76,73	18046390	17,256
96,43	86532281	82,744

Product 3ha



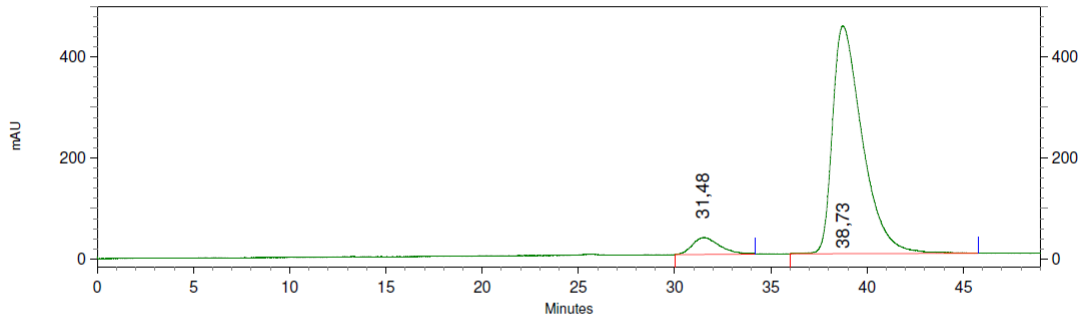
Non-enantioselective reaction



24: 295 nm, 4 nm
Results

Retention Time	Area	Area Percent
31,71	88494474	49,447
40,10	90473192	50,553

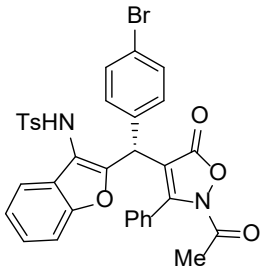
Enantioselective reaction



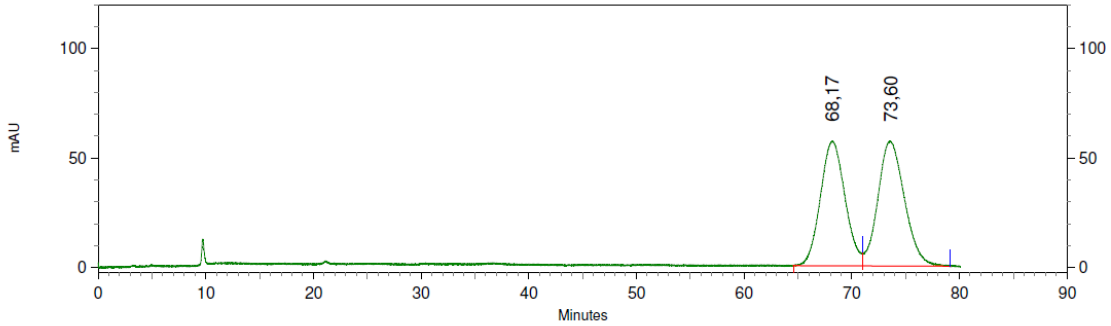
24: 295 nm, 4 nm
Results

Retention Time	Area	Area Percent
31,48	13211343	6,352
38,73	194786535	93,648

Product 3ia



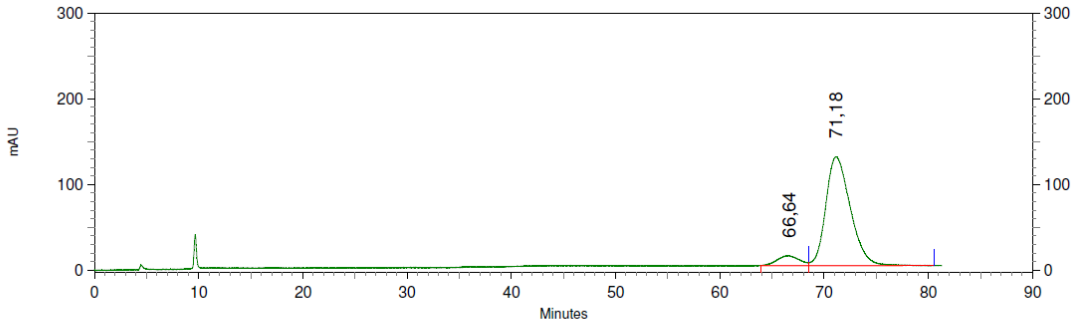
Non-enantioselective reaction



19: 291 nm, 4 nm
Results

Retention Time	Area	Area Percent
68,17	36242267	48,009
73,60	39248894	51,991

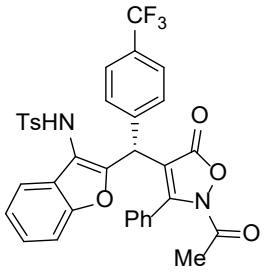
Enantioselective reaction



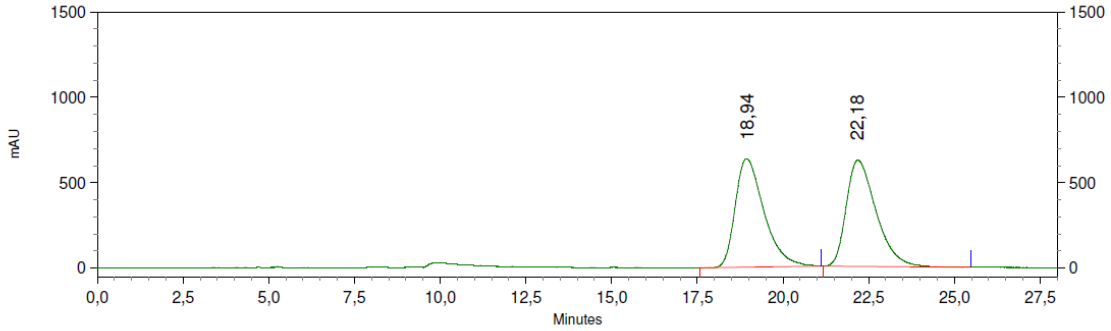
19: 291 nm, 4 nm
Results

Retention Time	Area	Area Percent
66,64	6978194	7,760
71,18	82946372	92,240

Product 3ja



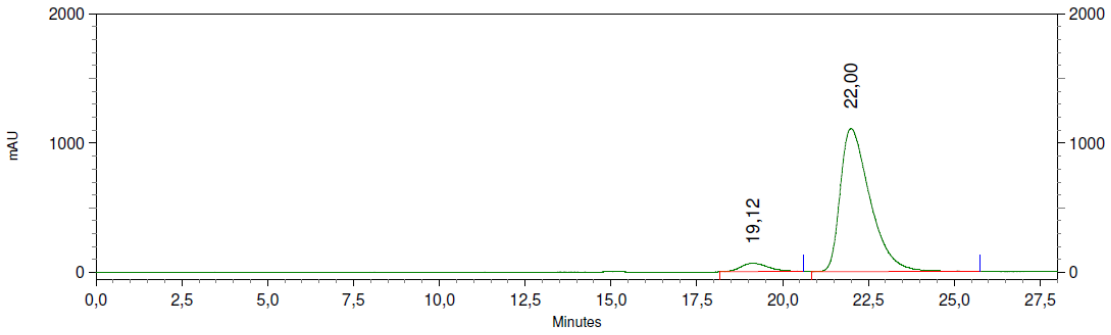
Non-enantioselective reaction



40: 290 nm, 4 nm
Results

Retention Time	Area	Area Percent
18,94	148187937	49,622
22,18	150443625	50,378

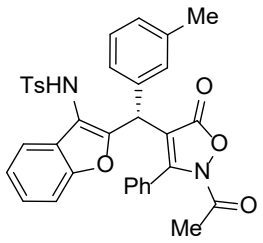
Enantioselective reaction



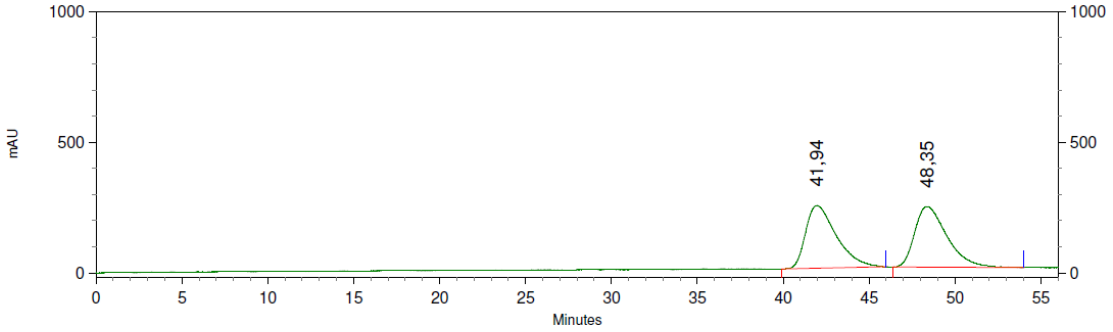
40: 290 nm, 4 nm
Results

Retention Time	Area	Area Percent
19,12	14569501	5,194
22,00	265948535	94,806

Product 3ka



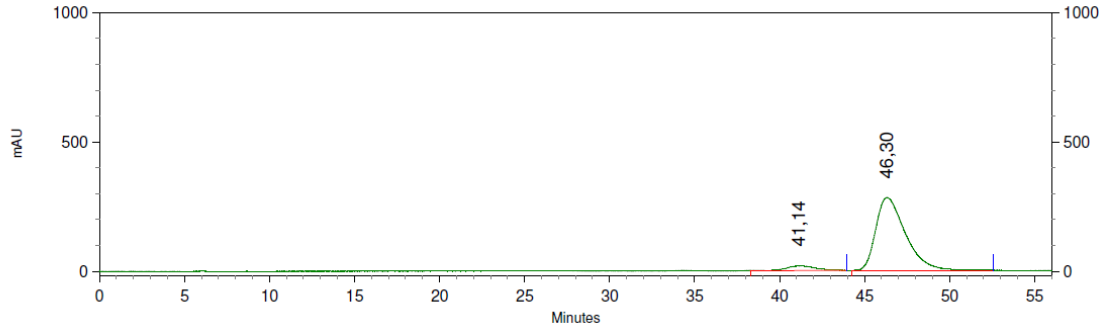
Non-enantioselective reaction



26: 293 nm, 4 nm
Results

Retention Time	Area	Area Percent
41,94	119168933	49,642
48,35	120889679	50,358

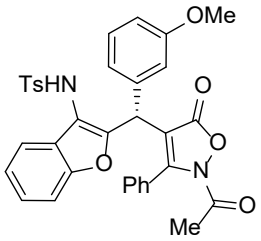
Enantioselective reaction



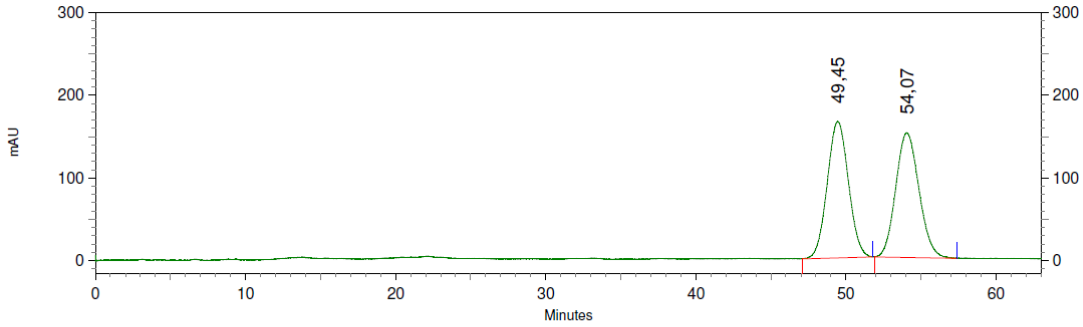
26: 293 nm, 4 nm
Results

Retention Time	Area	Area Percent
41,14	8646192	5,947
46,30	136750247	94,053

Product 3la



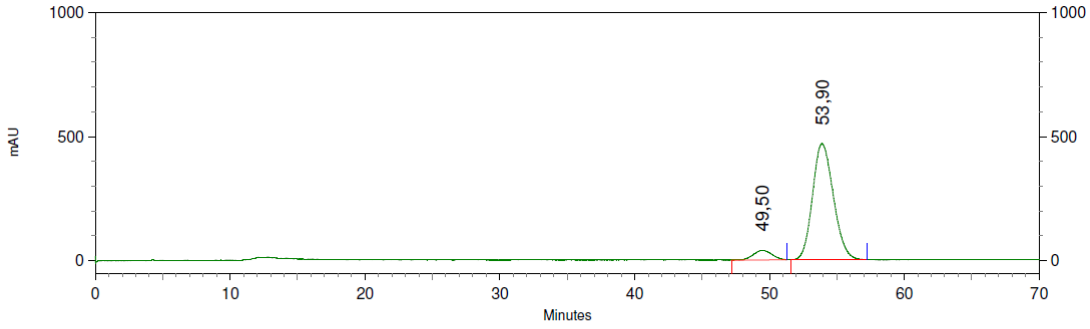
Non-enantioselective reaction



22: 285 nm, 4 nm
Results

Retention Time	Area	Area Percent
49,45	64713480	49,929
54,07	64896657	50,071

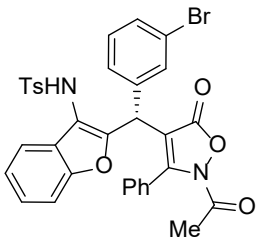
Enantioselective reaction



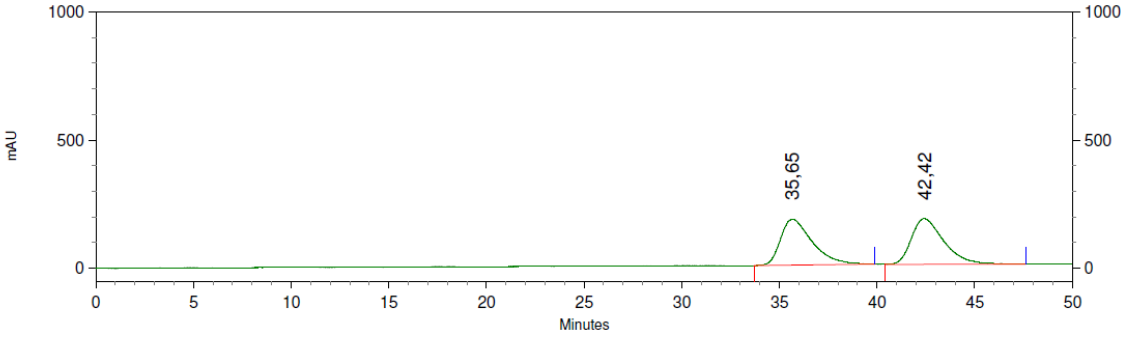
22: 285 nm, 4 nm
Results

Retention Time	Area	Area Percent
49,50	14886936	6,888
53,90	201236408	93,112

Product 3ma



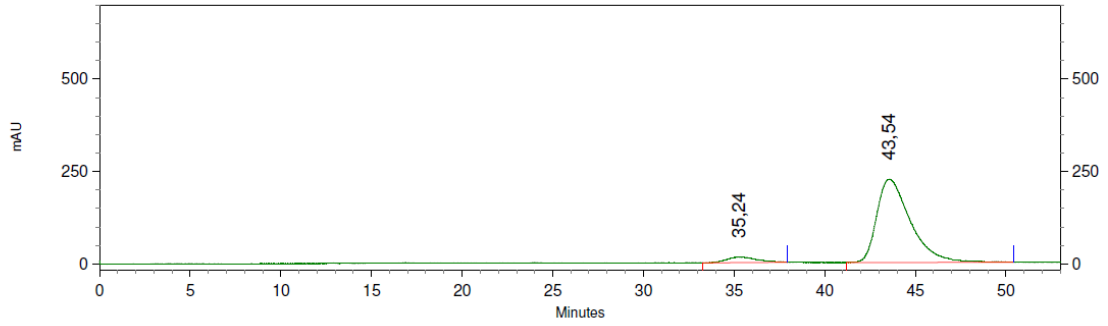
Non-enantioselective reaction



21: 279 nm, 4 nm
Results

Retention Time	Area	Area Percent
35,65	81088957	49,687
42,42	82109064	50,313

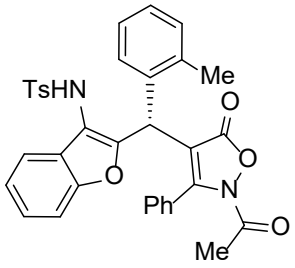
Enantioselective reaction



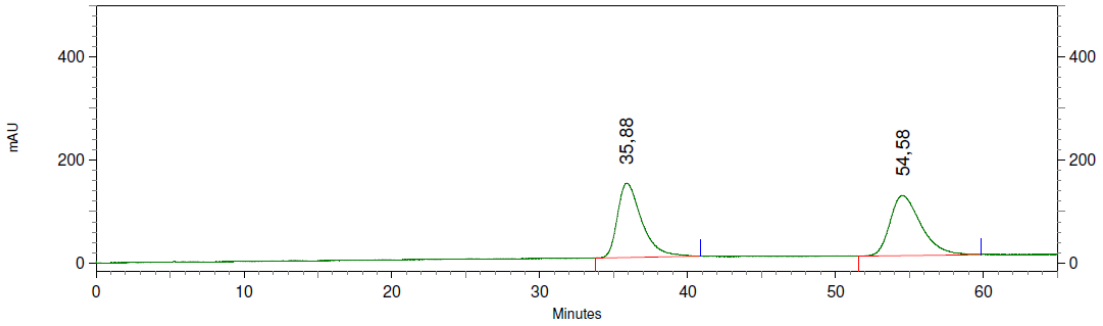
21: 279 nm, 4 nm
Results

Retention Time	Area	Area Percent
35,24	6990918	5,686
43,54	115963817	94,314

Product 3na



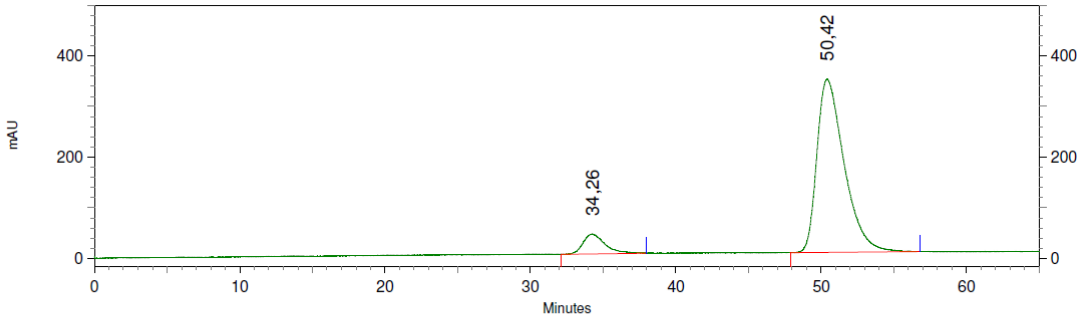
Non-enantioselective reaction



24: 295 nm, 4 nm
Results

Retention Time	Area	Area Percent
35,88	66055855	49,348
54,58	67800543	50,652

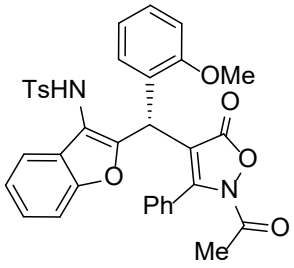
Enantioselective reaction



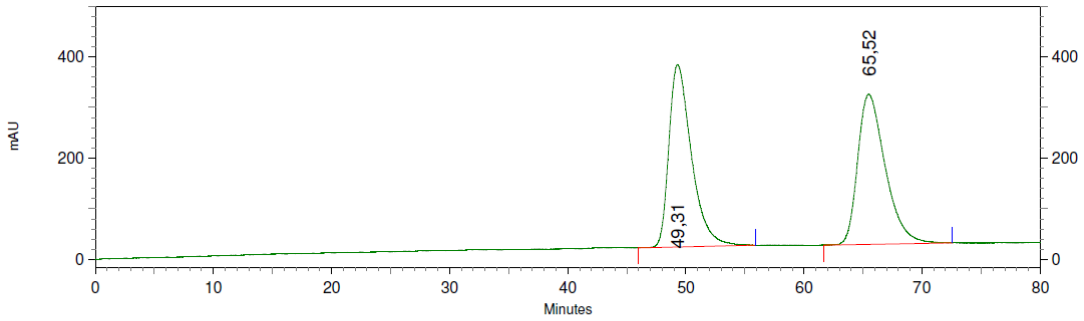
24: 295 nm, 4 nm
Results

Retention Time	Area	Area Percent
34,26	16638333	8,528
50,42	178465395	91,472

Product 3oa



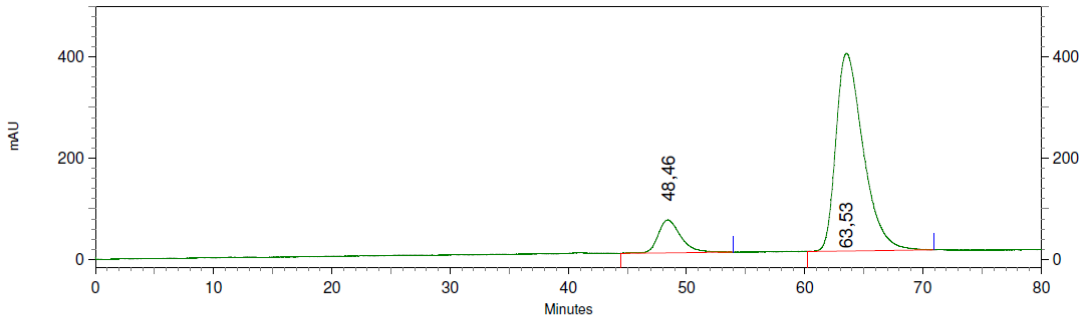
Non-enantioselective reaction



24: 295 nm, 4 nm
Results

Retention Time	Area	Area Percent
49,31	191072945	49,825
65,52	192418680	50,175

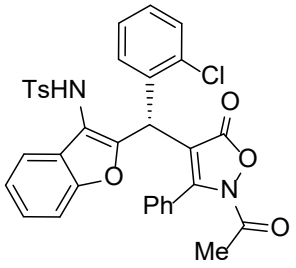
Enantioselective reaction



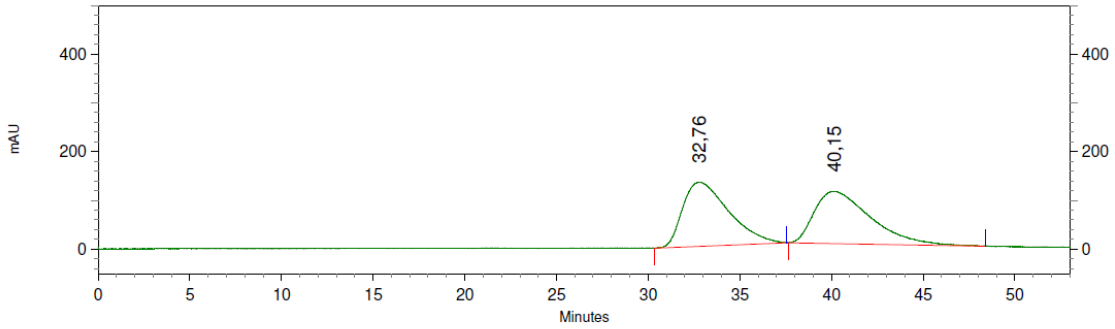
24: 295 nm, 4 nm
Results

Retention Time	Area	Area Percent
48,46	34448598	12,070
63,53	250967821	87,930

Product 3pa



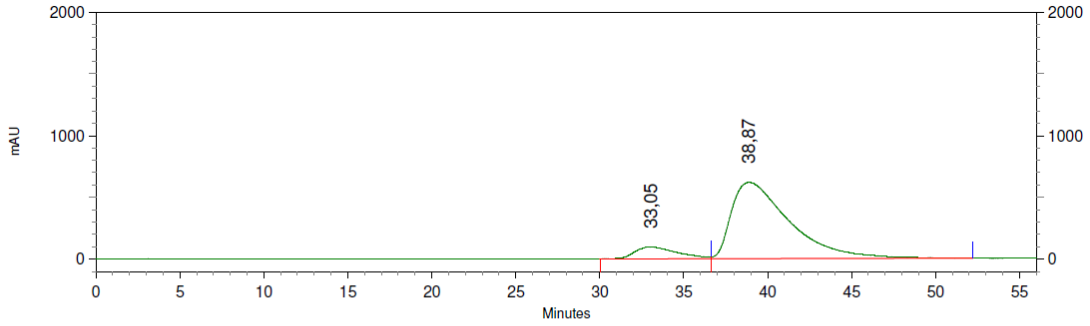
Non-enantioselective reaction



33: 291 nm, 4 nm
Results

Retention Time	Area	Area Percent
32,76	91911403	50,115
40,15	91488582	49,885

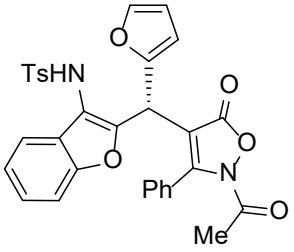
Enantioselective reaction



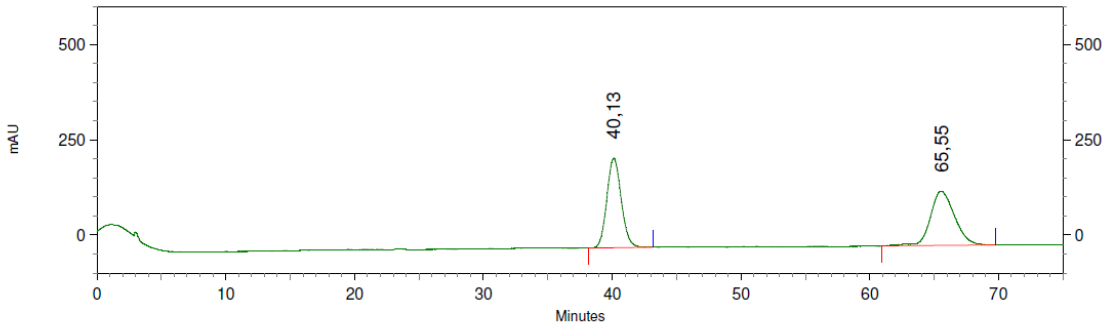
33: 291 nm, 4 nm
Results

Retention Time	Area	Area Percent
33,05	67517726	10,180
38,87	595708323	89,820

Product 3qa



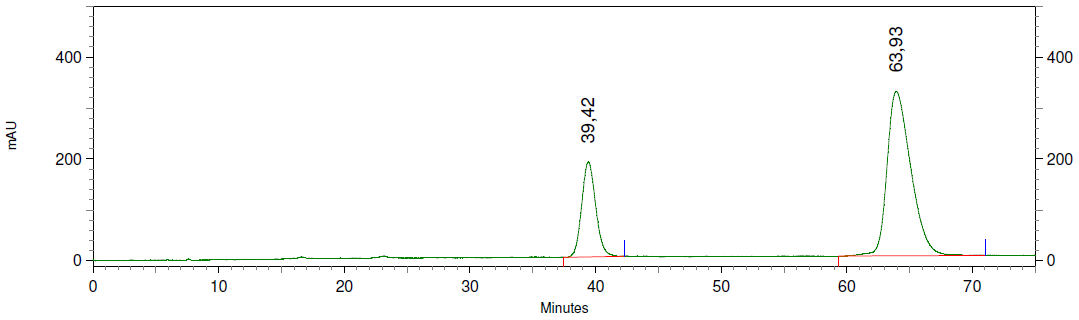
Non-enantioselective reaction



38: 297 nm, 4 nm
Results

Retention Time	Area	Area Percent
40,13	73276133	49,655
65,55	74294811	50,345

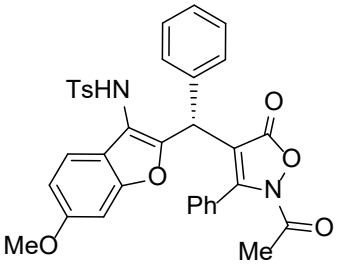
Enantioselective reaction



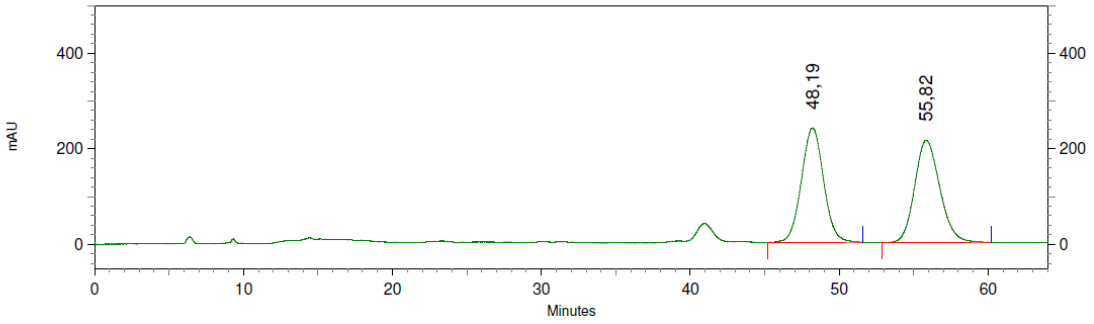
38: 297 nm, 4 nm
Results

Retention Time	Area	Area Percent
39,42	57780991	25,344
63,93	170201661	74,656

Product 3ra



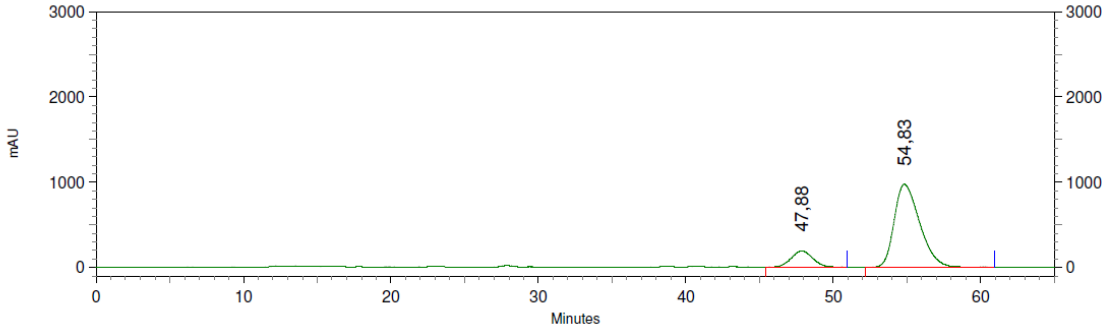
Non-enantioselective reaction



39: 294 nm, 4 nm
Results

Retention Time	Area	Area Percent
48,19	99489440	49,711
55,82	100644742	50,289

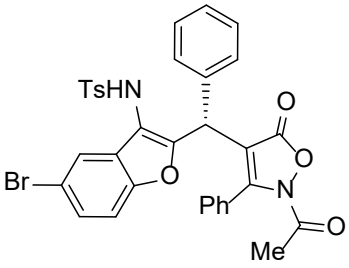
Enantioselective reaction



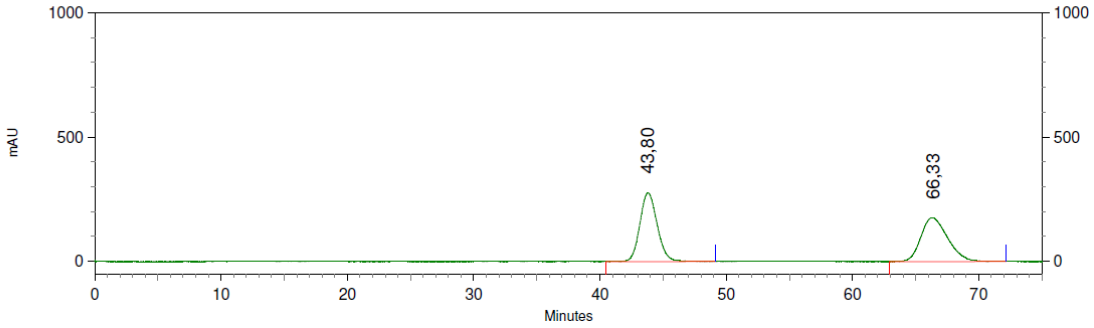
39: 294 nm, 4 nm
Results

Retention Time	Area	Area Percent
47,88	77769041	14,283
54,83	466725143	85,717

Product 3sa



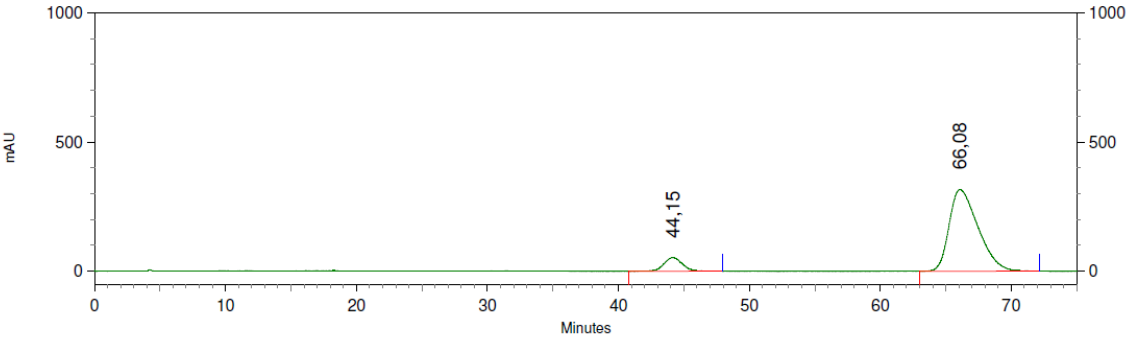
Non-enantioselective reaction



26: 293 nm, 4 nm
Results

Retention Time	Area	Area Percent
43,80	105877114	50,346
66,33	104423423	49,654

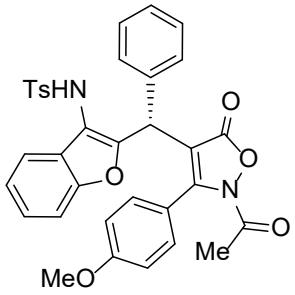
Enantioselective reaction



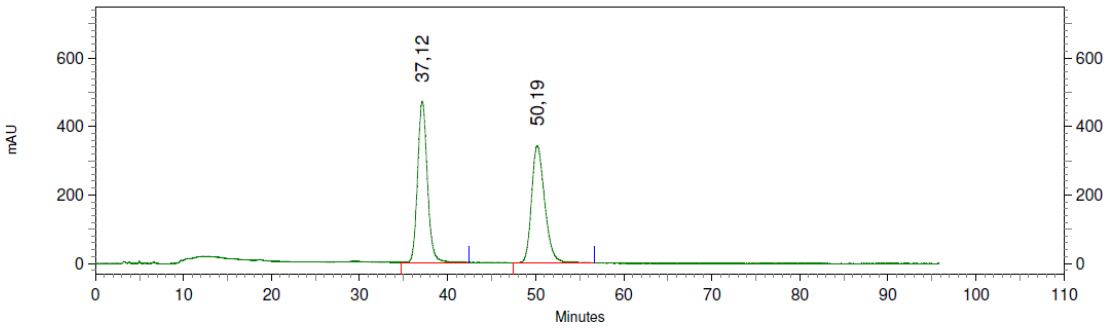
26: 293 nm, 4 nm
Results

Retention Time	Area	Area Percent
44,15	20837783	9,676
66,08	194508540	90,324

Product 3ab



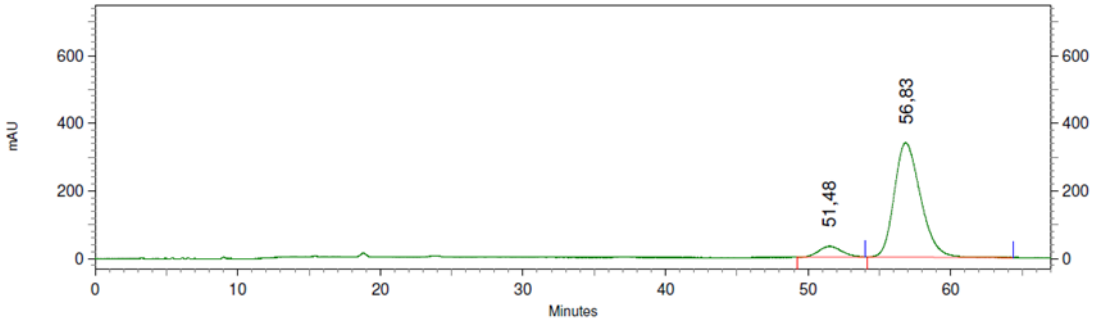
Non-enantioselective reaction



13: 230 nm, 4 nm
Results

Retention Time	Area	Area Percent
37,12	145670458	50,457
50,19	143034432	49,543

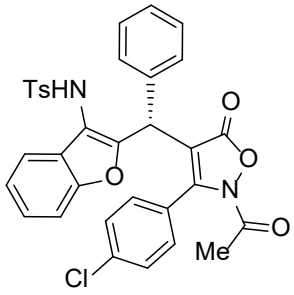
Enantioselective reaction



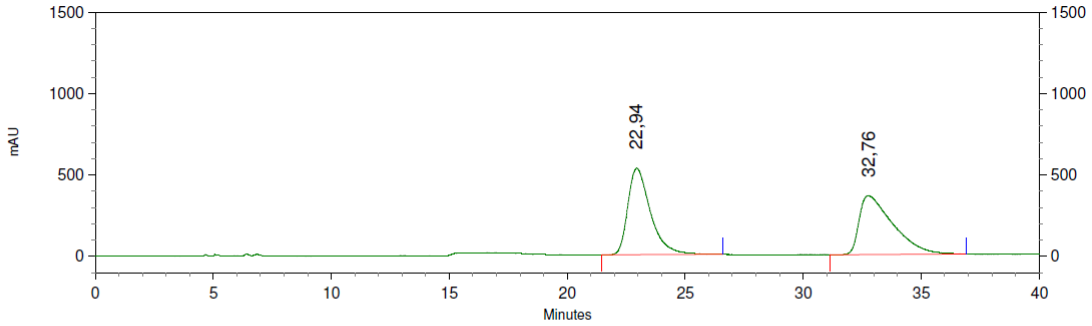
12: 248 nm, 4 nm
Results

Retention Time	Area	Area Percent
51,48	14756976	7,846
56,83	173316173	92,147

Product 3ac



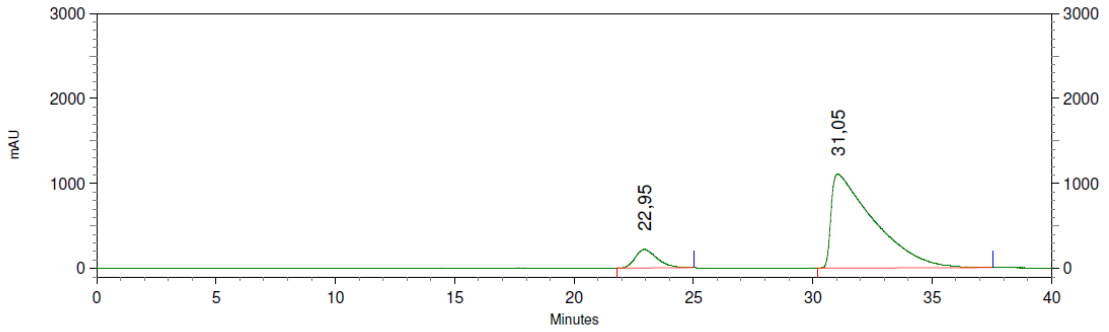
Non-enantioselective reaction



41: 304 nm, 4 nm
Results

Retention Time	Area	Area Percent
22,94	142195368	49,807
32,76	143296315	50,193

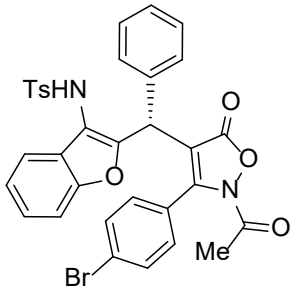
Enantioselective reaction



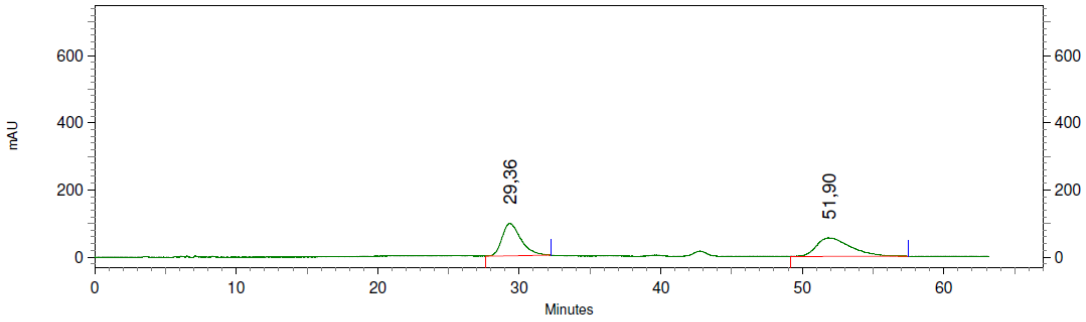
41: 304 nm, 4 nm
Results

Retention Time	Area	Area Percent
22,95	55854170	9,236
31,05	548889076	90,764

Product 3ad



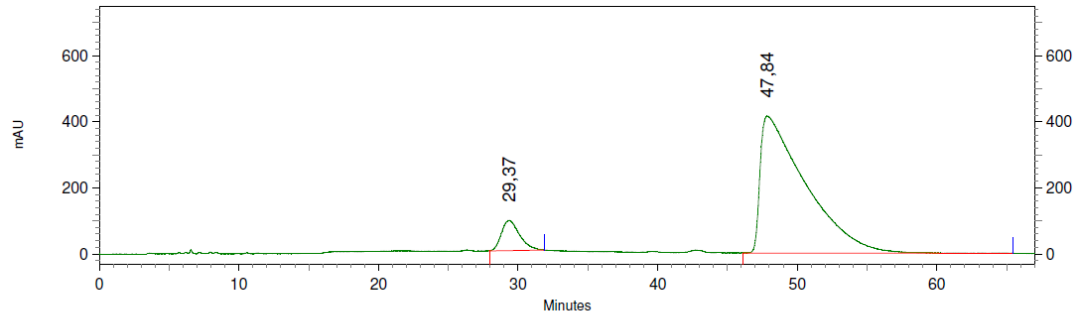
Non-enantioselective reaction



12: 248 nm, 4 nm
Results

Retention Time	Area	Area Percent
29,36	35657277	48,822
51,90	37377285	51,178

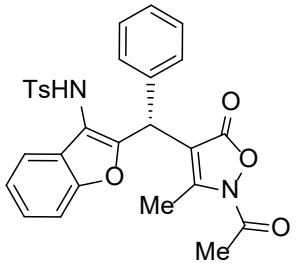
Enantioselective reaction



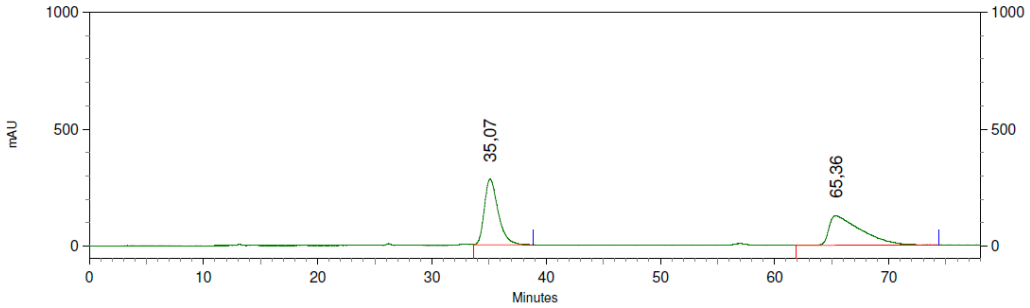
12: 248 nm, 4 nm
Results

Retention Time	Area	Area Percent
29,37	33326350	8,130
47,84	376616305	91,870

Product 3ae



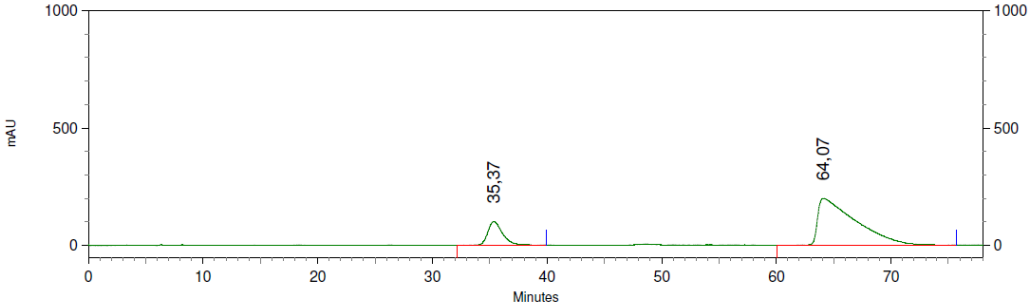
Non-enantioselective reaction



3: 286 nm, 4 nm Results

Retention Time	Area	Area Percent
35,07	93824769	49,048
65,36	97465813	50,952

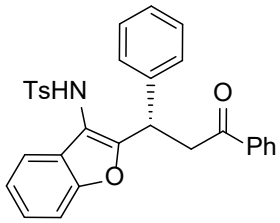
Enantioselective reaction



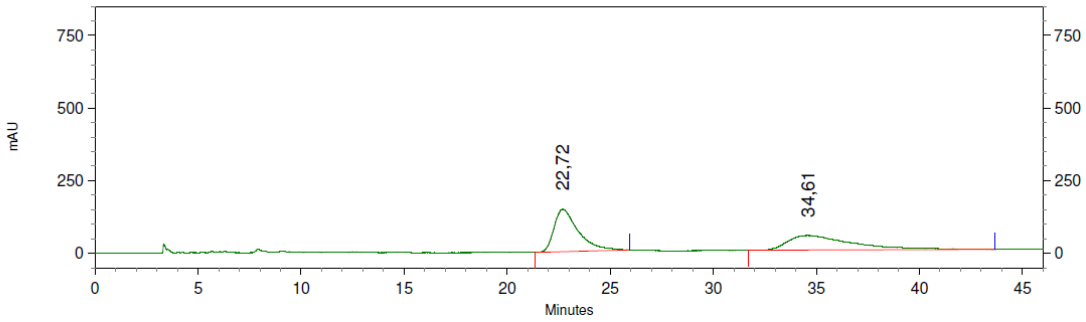
3: 286 nm, 4 nm Results

Retention Time	Area	Area Percent
35,37	36764297	16,549
64,07	185394759	83,451

Product 4aa



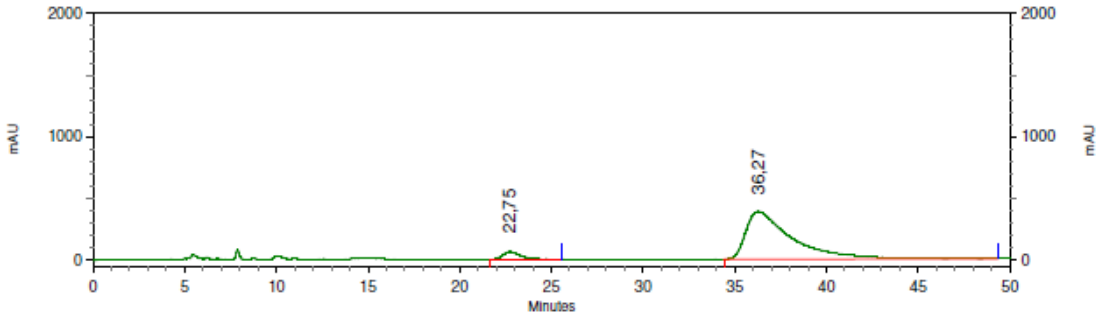
Non-enantioselective reaction



66: 249 nm, 4 nm
Results

Retention Time	Area	Area Percent
22,72	47925398	52,664
34,61	43076815	47,336

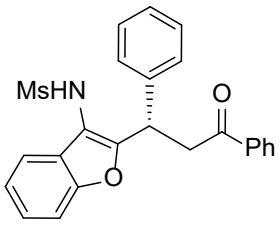
Enantioselective reaction



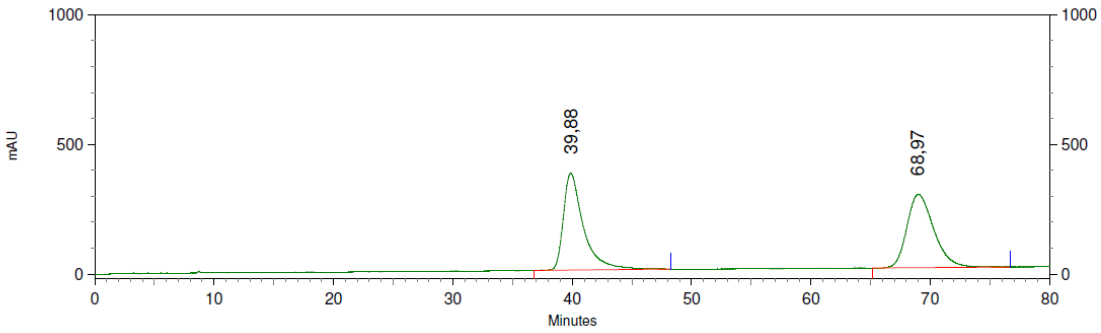
28: 258 nm, 4 nm
Results

Retention Time	Area	Area Percent
22,75	17797588	6,051
36,27	276352610	93,949

Product 4ea



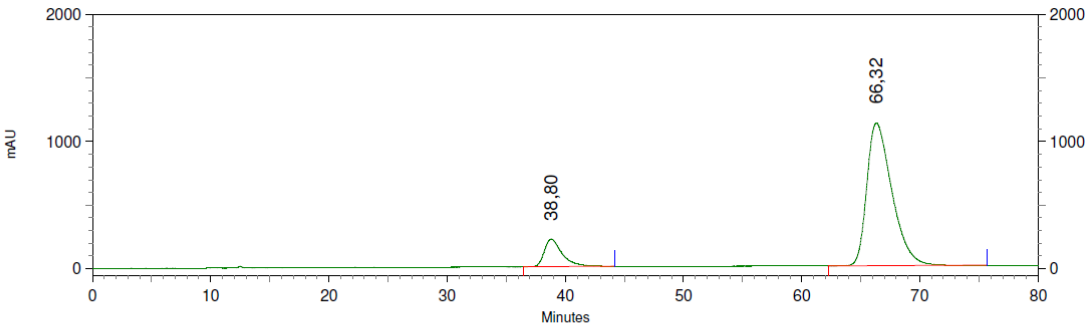
Non-enantioselective reaction



8: 246 nm, 4 nm Results

Retention Time	Area	Area Percent
39,88	174508122	49,666
68,97	176857662	50,334

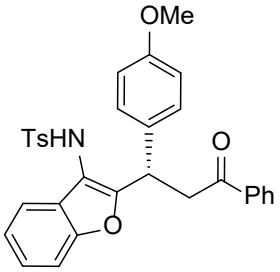
Enantioselective reaction



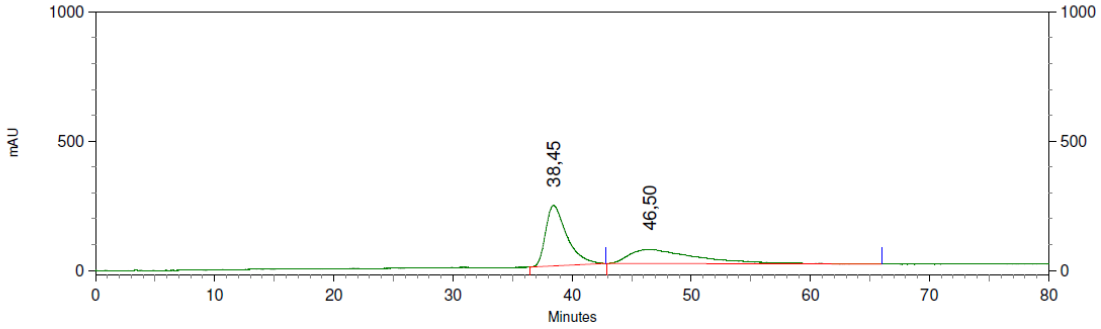
8: 246 nm, 4 nm Results

Retention Time	Area	Area Percent
38,80	91401640	12,130
66,32	662130401	87,870

Product 4ga



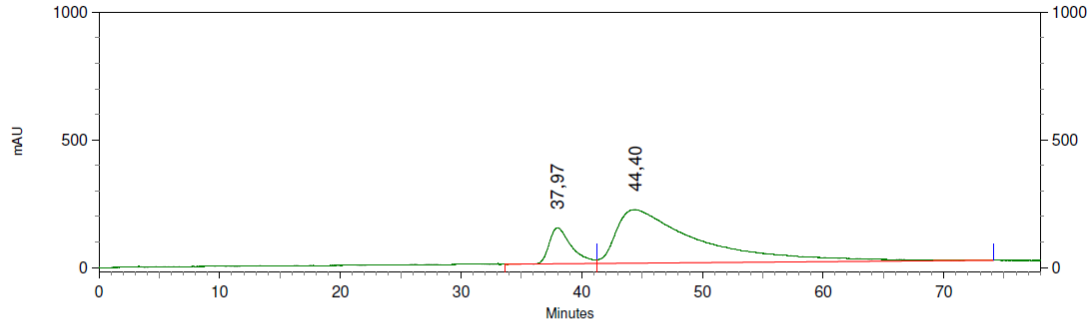
Non-enantioselective reaction



17: 238 nm, 4 nm
Results

Retention Time	Area	Area Percent
38,45	115930249	57,171
46,50	86847004	42,829

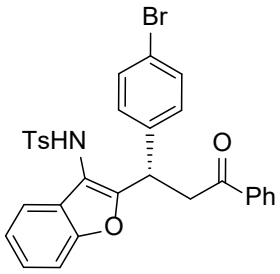
Enantioselective reaction



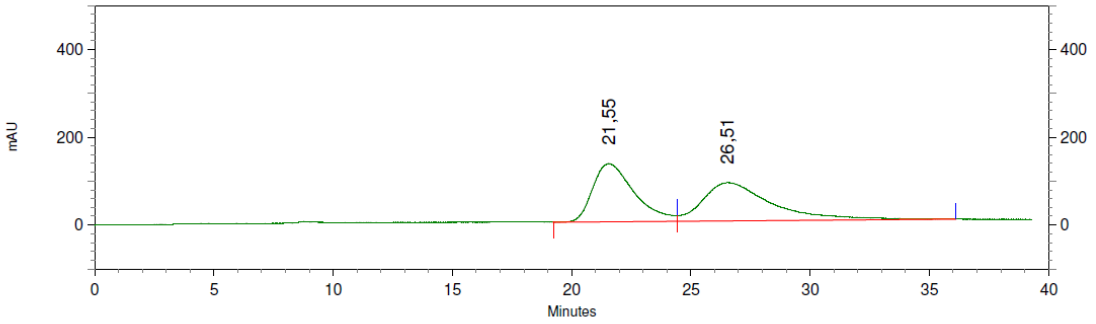
17: 238 nm, 4 nm
Results

Retention Time	Area	Area Percent
37,97	72377262	15,287
44,40	401092214	84,713

Product 4ia



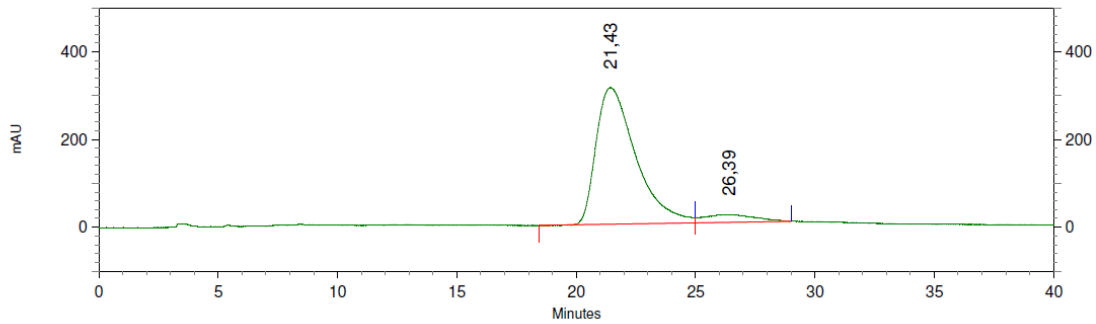
Non-enantioselective reaction



30: 248 nm, 4 nm
Results

Retention Time	Area	Area Percent
21,55	63921690	47,515
26,51	70607730	52,485

Enantioselective reaction



23: 220 nm, 4 nm
Results

Retention Time	Area	Area Percent
21,43	143735320	93,169
26,39	10537928	6,831