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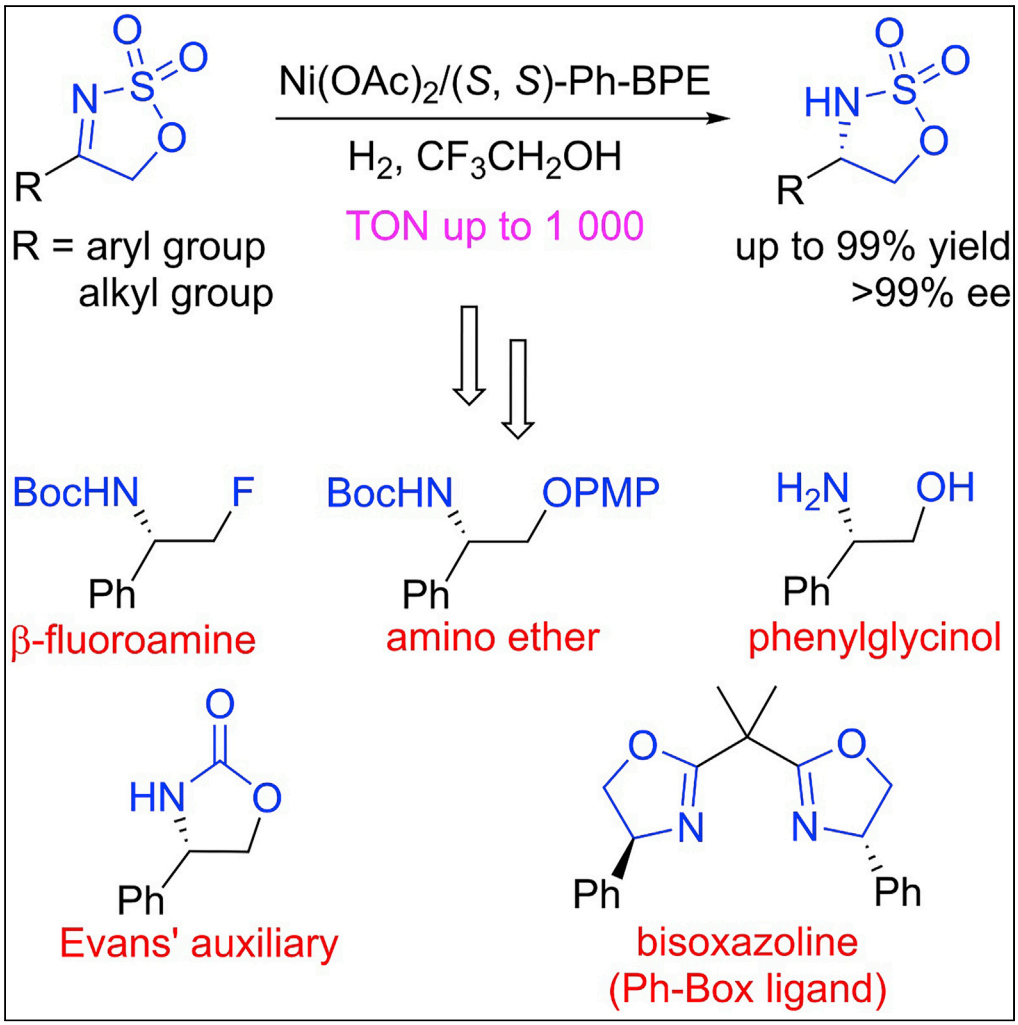

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HIGHLIGHTS

Ni-catalyzed asymmetric hydrogenation of cyclic sulfamidate imines

Efficient preparation of enantioenriched cyclic sulfamidates

Broad range of substrate scope

Gram-scale asymmetric hydrogenation with high TON

Liu et al., iScience 19, 63–73
September 27, 2019
https://doi.org/10.1016/j.isci.2019.07.004

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Nickel-Catalyzed Asymmetric Hydrogenation of Cyclic Sulfamidate Imines: Efficient Synthesis of Chiral Cyclic Sulfamidates

Yuanhua Liu,[1] Zhiyuan Yi,[1] Xuefeng Tan,[2] Xiu-Qin Dong,[1,*] and Xumu Zhang[1,2,3,*]

SUMMARY

Chiral cyclic sulfamidates are useful building blocks to construct compounds, such as chiral amines, with important applications. Often these compounds can only be generated through expensive precious metal catalysts. Here, Ni(OAc)$_2$/(*S, S*)-Ph-BPE-catalyzed highly efficient asymmetric hydrogenation of cyclic sulfamidate imines was successfully developed, affording various chiral cyclic sulfamidates with high yields and excellent enantioselectivities (up to 99% yield, >99% enantiomeric excess [ee]). This Ni-catalyzed asymmetric hydrogenation on a gram scale has been achieved with only 0.1 mol% catalyst loading in 99% yield with 93% ee. Other types of *N*-sulfonyl ketimines were also hydrogenated well to obtain the corresponding products with >99% conversion, 96%–97% yields, and 97%–>99% ee. In addition, this asymmetric methodology could produce other enantioenriched organic molecules, such as chiral β-fluoroamine, amino ether, and phenylglycinol. Moreover, a reasonable catalytic cycle was provided according to the deuterium-labeling studies, which could reveal a possible mechanism for this Ni-catalyzed asymmetric hydrogenation.

INTRODUCTION

Efficient synthesis of chiral cyclic sulfamidates has attracted great attention in the past decades, owing to their versatilities working as valuable intermediates for the construction of some important organic compounds and bioactive molecules (Aguilera and Fernandez-Mayoralas, 1996; Williams et al., 2003; Bower et al., 2004, 2007a, 2007b; 2007c, 2010; Jamieson et al., 2009; Lorion et al., 2010; Megia-Fernandez et al., 2011; Boulton et al., 1999; Wei and Lubell, 2000; Espino et al., 2001; Cohen and Halcomb, 2001, 2002; Atfani et al., 2001; Nicolaou et al., 2002; Meléndez and Lubell, 2003; Ni et al., 2007; Rönnholm et al., 2007; Baig et al., 2010, 2011; Venkateswarlu et al., 2014; Albu et al., 2016; Su et al., 2016; Chen et al., 2014; Kong et al., 2015; Liu et al., 2017; Wu et al., 2018). For example, ring-opening reactions of chiral cyclic sulfamidates can offer convenient and efficient access to chiral amines, amino alcohols, amino acids, and their derivatives (Boulton et al., 1999; Wei and Lubell, 2000; Espino et al., 2001; Cohen and Halcomb, 2001, 2002; Atfani et al., 2001; Nicolaou et al., 2002; Meléndez and Lubell, 2003; Ni et al., 2007; Rönnholm et al., 2007; Baig et al., 2010, 2011; Venkateswarlu et al., 2014; Albu et al., 2016; Su et al., 2016; Chen et al., 2014; Kong et al., 2015; Liu et al., 2017; Wu et al., 2018). So far the asymmetric catalytic synthetic methods of chiral cyclic sulfamidates were mainly focused on transition metal-catalyzed asymmetric intramolecular amidation of sulfamate esters (Liang et al., 2002; Liang et al., 2004; Fruit and Mueller, 2004; Zhang et al., 2005; Zalatan and Du Bois, 2008; Lin et al., 2008; Ichinose et al., 2011), additions of organoboron reagents to cyclic imines (Chen et al, 2014, 2018; Kong et al., 2015; Liu et al., 2017; Wu et al., 2018; Nishimura et al., 2012, 2013; Luo et al., 2012a, 2012b; Wang et al., 2013; Hepburn et al., 2013; Wang and Xu, 2013; Zhang et al., 2016a), and asymmetric reduction of cyclic ketimines (Wang et al., 2008; Yu et al., 2009; Kang et al., 2010; Lee et al.,2011, 2012; Han et al., 2011; Liu et al., 2019; Itsuno et al., 2014; Seo et al., 2015; Kim et al., 2018).

Asymmetric catalytic hydrogenation of prochiral unsaturated compounds has emerged as a powerful and effective approach for the construction of chiral compounds, which has made tremendous progress (Knowles, 1983; Noyori and Takaya, 1990; Noyori and Ohkuma, 2001; Tang and Zhang, 2003; Blaser et al., 2003; Cui and Burgess, 2005; Minnaard et al., 2007; Zhang et al., 2007, 2016b; Johnson et al., 2007; Zhou, 2007; Roseblade and Pfaltz, 2007; Fleury-Bregeot et al., 2010; Xie et al., 2011, 2012; Wang et al., 2012; Chen et al., 2013; Verendel et al., 2014, 2016b). Most of these powerful catalytic systems typically depended on scarce and precious transition metals, such as Ru, Rh, Ir, and Pd, which faced difficulties like limited resource, high cost, and environmental contamination. Therefore, it is important and necessary to devote much effort to developing cheap, earth-abundant, first-row transition metal catalytic systems.

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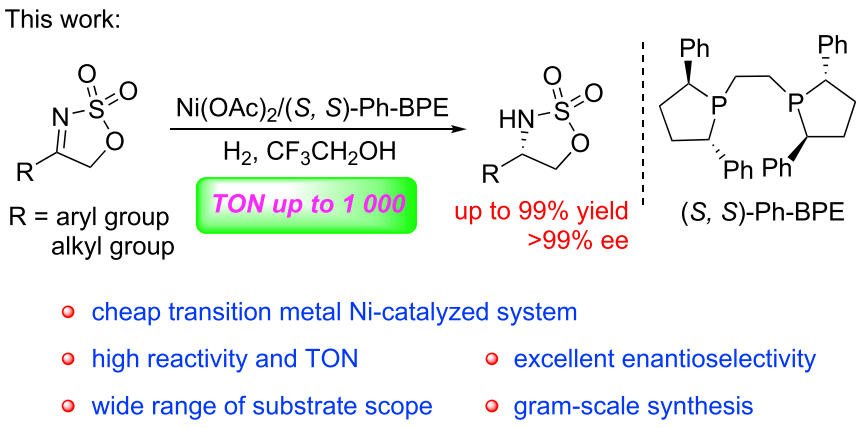
https://doi.org/10.1016/j.isci.2019.07.004



Scheme 1. Asymmetric Hydrogenation of Cyclic Sulfamidate Imines

Recently, the Fe-, Co-, and Ni-catalyzed asymmetric hydrogenation of prochiral unsaturated compounds has received great attention, which shows the great potential of first-row transition metals in catalytic asymmetric (transfer) hydrogenation (Morris, 2009, 2015; Chirik, 2015; Li et al., 2014, 2015, 2017; Bauer and Knölker, 2015; Sui-Seng et al., 2008; Zhou et al., 2011; Monfette et al., 2012; Friedfeld et al., 2013, 2016; Lagaditis et al., 2014; Sonnenberg et al., 2014; Lu et al., 2015; Chen et al., 2016; Hamada et al., 2008; Hibino et al., 2009; Dong et al., 2012; Yang et al., 2014, 2016; Guo et al., 2015; Xu et al., 2015; Shevlin et al., 2016; Gao et al., 2017; Zhao et al., 2019). Among these catalytic methodologies, Ni-catalyzed asymmetric hydrogenation is still in early stage, and there are a few related studies at present (Li et al., 2015, 2017; Hamada et al., 2008; Hibino et al., 2009; Dong et al., 2012; Yang et al., 2014, 2016; Guo et al., 2015; Xu et al., 2015; Shevlin et al., 2016; Gao et al., 2017; Zhao et al., 2019). In 2008 and 2009, Hamada and co-workers reported Ni-catalyzed asymmetric hydrogenation of α-amino-β-ketoester hydrochlorides and substituted aromatic α-aminoketone hydrochlorides through dynamic kinetic resolution (Hamada et al., 2008; Hibino et al., 2009). In 2016, Chirik and co-workers discovered Ni-catalyzed asymmetric hydrogenation of α,β-unsaturated esters (Shevlin et al., 2016). Recently, our group reported Ni-catalyzed asymmetric hydrogenation of functionalized enamides with excellent results (Gao et al., 2017; Li et al., 2017). Despite some progress having been made, it is still quite urgent to explore the wide range of substrate generality, high reactivity, excellent stereoselectivity, and high turnover numbers (TON) for the Ni-catalyzed asymmetric hydrogenation.

Asymmetric hydrogenation of cyclic sulfamidate imines is a direct and effective access to chiral sulfamidates. Zhou and co-workers established highly efficient Pd-catalyzed enantioselective hydrogenation of cyclic sulfamidate imines with excellent results (Wang et al., 2008). To the best of our knowledge, there is no example about cheap transition metal Ni-catalyzed asymmetric hydrogenation of cyclic sulfamidate imines. Herein, we successfully realized the highly efficient Ni-catalyzed asymmetric hydrogenation of cyclic sulfamidate imines to afford chiral cyclic sulfamidates with high yields and excellent enantioselectivities (Scheme 1, up to 99% yield, >99% enantiomeric excess [ee]), and the gram-scale hydrogenation can be easily achieved with only 0.1 mol% catalyst loading (TON = 1,000).

RESULTS

Optimization Reaction Conditions

We started initial investigation of the $Ni(OAc)_2$-catalyzed asymmetric hydrogenation of model substrate 4-phenyl-5H-1,2,3-oxathiazole 2,2-dioxide **1a** to evaluate a variety of important chiral diphosphine ligands (Figure 1) under 60 atm H_2 at 80°C in MeOH for 24 h. As shown in Table 1, full conversion and good to excellent enantioselectivities were obtained with (*S*)-Binapine and (*S, S*)-Ph-BPE as ligand (>99% conversion, 86%–92% ee, Table 1, entries 1 and 4). Although high catalytic activity was achieved, very poor enantioselective control was afforded in the presence of (*Rc, Sp*)-DuanPhos and (*S, S*)-Me-DuPhos (Table 1, entries 2 and 3). In addition, ligands (*R, S*)-WalPhos, (*S*)-SegPhos, and (*S*)-BINAP did not work in this reaction; no reaction was observed (Table 1, entries 5–7). Therefore, (*S, S*)-Ph-BPE was revealed to be superior with the best enantioselectivity (>99% conversion, 92% ee, Table 1, entry 4). To our delight, the same result can

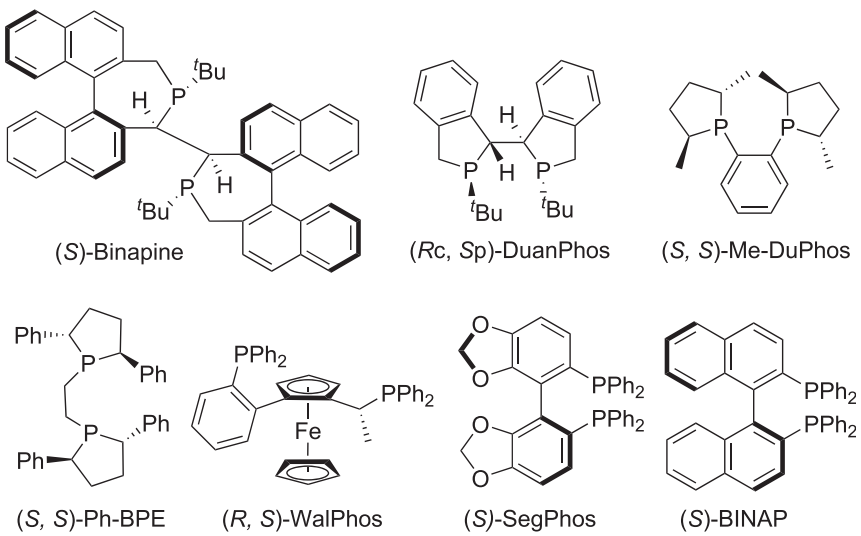
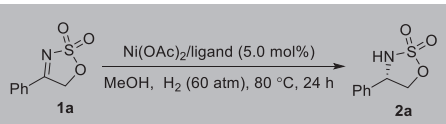


Figure 1. The Structure of Chiral Diphosphine Ligands

be achieved when the catalyst loading of $Ni(OAc)_2$/(*S, S*)-Ph-BPE was decreased from 5.0 mol% to 1.0 mol% (Table 1, entry 8).

Inspired by the promising results, the $Ni(OAc)_2$/(*S, S*)-Ph-BPE-catalyzed asymmetric hydrogenation of model substrate 4-phenyl-5H-1,2,3-oxathiazole 2,2-dioxide **1a** was carried out in different solvents. We found that moderate to high conversions and excellent enantioselectivities were obtained in several kinds of alcoholic solvents, such as MeOH, EtOH, ^{i}PrOH, CF_3CH_2OH, and $(CF_3)_2CHOH$ (62%–>99% conversions, 91%–94% ee, Table 2, entries 1–5). Poor conversions and moderate to good enantioselectivities were



Entry	Ligand	Conversion (%)[a]	ee (%)[b]
1	(*S*)-Binapine	>99	86
2	(*Rc, Sp*)-DuanPhos	>99	−2
3	(*S, S*)-Me-DuPhos	>99	−13
4	(*S, S*)-Ph-BPE	>99	92
5	(*R*)-WalPhos	NR	NA
6	(*S*)-SegPhos	NR	NA
7	(*S*)-BINAP	NR	NA
8[c]	(*S, S*)-Ph-BPE	>99	92

Table 1. Screening Ligands for Ni-Catalyzed Asymmetric Hydrogenation of 4-Phenyl-5H-1,2,3-oxathiazole 2,2-dioxide (1a)

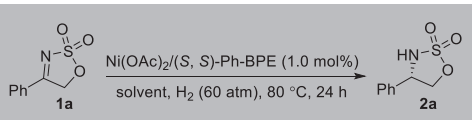
NR, no reaction; NA, not available.

Unless otherwise noted, all reactions were carried out with a $Ni(OAc)_2$/ligand/substrate **1a** (0.1 mmol) ratio of 1:1.1:20 in 1.0 mL MeOH under 60 atm H_2 at 80°C for 24 h. The configuration of **2a** was determined by comparing the optical rotation data with those reported in the literature (Wang et al., 2008; Kang et al., 2010; Lee et al., 2011).

[a]Conversion was determined by ^{1}H NMR analysis.

[b]ee was determined by chiral high-performance liquid chromatography analysis.

[c]1.0 mol% catalyst loading.



Entry	Solvent	Conversion (%)[a]	ee (%)[b]
1	MeOH	>99	92
2	EtOH	83	91
3	^{i}PrOH	62	92
4	CF_3CH_2OH	>99	94
5	$(CF_3)_2CHOH$	>99	93
6	CH_2Cl_2	NR	NA
7	THF	17	87
8	Toluene	22	82
9	Ethyl acetate	12	86
10	1,4-dioxane	7	58

Table 2. Screening Solvents for Ni-Catalyzed Asymmetric Hydrogenation of 4-Phenyl-5H-1,2,3-oxathiazole 2,2-dioxide (1a)

NR, no reaction; NA, not available.

Unless otherwise noted, all reactions were carried out with a $Ni(OAc)_2$/(*S*, *S*)-Ph-BPE/substrate **1a** (0.1 mmol) ratio of 1:1.1:100 in 1.0 mL solvent under 60 atm H_2 at 80°C for 24 h; the catalyst was pre-complexed in MeOH (0.1 mL for each reaction vial).

[a]Conversion was determined by ^{1}H NMR analysis.

[b]ee was determined by chiral high-performance liquid chromatography analysis.

provided in nonprotic solvents, such as tetrahydrofuran (THF), toluene, ethyl acetate, and 1,4-dioxane (7%–22% conversions, 58%–87% ee, Table 2, entries 7–10), and this reaction did not work in dichloromethane (Table 2, entry 6). Therefore, CF_3CH_2OH was selected as the best solvent to provide full conversion and the highest enantioselectivity (>99% conversion, 94% ee, Table 2, entry 4).

Substrate Scope Study

After establishing the optimized reaction conditions, we sought to examine the substrate scope generality of this Ni-catalyzed asymmetric hydrogenation of cyclic sulfamidate imines. As listed in Table 3, the Ni-catalyzed asymmetric hydrogenation of a variety of aryl-substituted cyclic sulfamidate imines could proceed smoothly, affording the desired hydrogenation products (**2a-2l**) with full conversions, high yields, and excellent enantioselectivities (>99% conversion, 94%–99% yields, 91%–>99% ee). Diverse aryl-substituted cyclic sulfamidate imines bearing electron-donating (**1b-1f**) or electron-withdrawing (**1g-1l**) substituents worked well in this asymmetric hydrogenation. It is worth noting that the hydrogenation product **2i** is an important intermediate for the synthesis of the enantiomer of piperazinone acid, which was one of the two main molecular motifs in clinical candidate MK-3207 (McLaughlin et al., 2013). In addition, the position of substituted group on the phenyl ring was also investigated; whether the substituted groups are on the *ortho*-, *meta*-, or *para*-position of the phenyl ring, these asymmetric reductions proceeded efficiently with excellent results. Interestingly, cyclic sulfamidate imines with substituents in *ortho*-position on the phenyl ring (**1b**, **1e**, **1g**) can provide chiral cyclic sulfamidates (**2b**, **2e**, **2g**) with higher enantioselectivities. When the phenyl ring was replaced with 2-naphthyl group, the substrate (**1m**) performed well with 97% yield and 92% ee. Moreover, the heteroaromatic substrate (**1n**) was hydrogenated with moderate reactivity and excellent enantioselectivity (65% conversion, 55% yield, 95% ee). It is noteworthy that the alkyl substrates (**1o-1p**) worked smoothly in this asymmetric hydrogenation, providing the desired products (**2o-2p**) with good to excellent results (>99% conversion, 96%–98% yields, and 83%–92% ee).

Encouraged by these promising reaction results, other types of ketimines were employed in this catalytic system. As shown in Scheme 2, the acetophenone and 2,3-dihydro-1H-inden-1-one-derived *N*-sulfonyl ketimines **1q** and **1r** worked efficiently under optimized reaction conditions; the corresponding

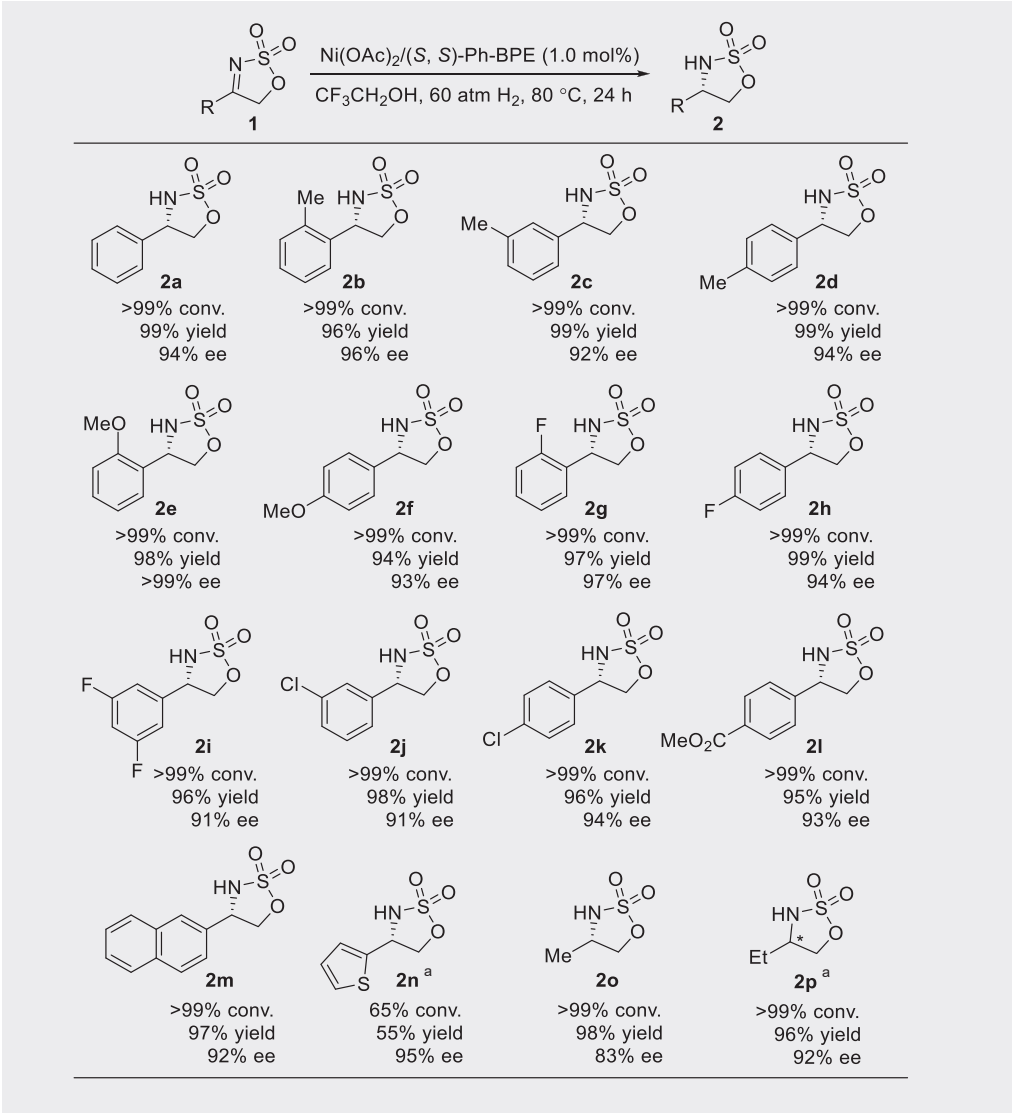


Table 3. Substrate Scope Study for Ni-Catalyzed Asymmetric Hydrogenation of Cyclic Sulfamidate Imines

Unless otherwise noted, all reactions were carried out with a $Ni(OAc)_2$/(*S, S*)-Ph-BPE/substrate **1** (0.1 mmol) ratio of 1:1.1:100 in 1.0 mL CF_3CH_2OH under 60 atm H_2 at 80°C for 24 h. Conversion was determined by ^1H NMR analysis. Yield is isolated yield. The ee value was determined by high-performance liquid chromatography on a chiral column.

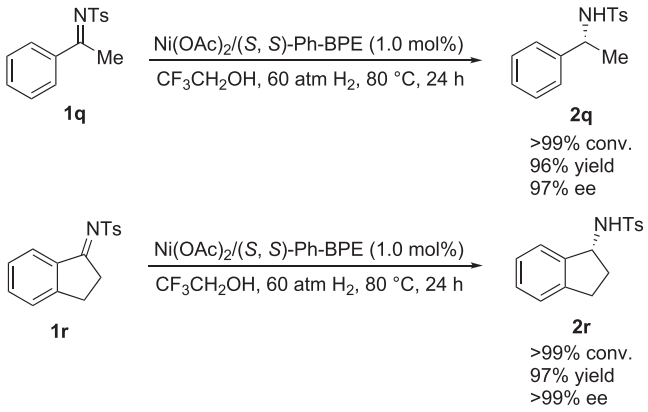
Superscript letter 'a' indicates S/C = 20, 36 h.

hydrogenation products **2q** and **2r** were obtained with full conversion, high yields, and excellent enantioselectivities (>99% conversion, 96%–97% yields, 97%–>99% ee).

Synthetic Application

The synthetic application potentiality of this Ni-catalyzed asymmetric hydrogenation was demonstrated by the gram-scale transformation. The asymmetric reduction of model substrate **1a** on the 6-mmol scale proceeded well in the presence of just 0.1 mol% catalyst loading (S/C = 1,000), affording product **2a** in 99% yield with 93% ee, which showed that our catalytic system had excellent catalytic activity (Scheme 3). In addition, >99% ee can be easily achieved in CH_2Cl_2/hexane through simple crystallization.

To reveal the great utility of this methodology, some derivatization reactions of hydrogenation product **2a** were conducted (Scheme 4). The *tert*-butoxycarbonyl (Boc) group was easily introduced on the nitrogen



Scheme 2. The Ni-Catalyzed Asymmetric Hydrogenation of Other N-Sulfonyl Ketimines

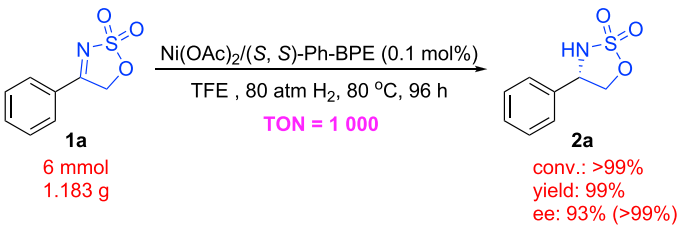
atom of hydrogenation product **2a** to prepare compound **3** without loss of enantiomeric purity (Kang et al., 2010). Also, it was treated with tetrabutylammonium fluoride to give enantioenriched β-fluoroamine **4** in 77% yield (Wu et al., 2018; Nishimura et al., 2013). In addition, compound **3** went through nucleophilic attack of 4-methoxyphenol, which led to chiral amino ether **5** in 76% yield (Wu et al., 2018; Nishimura et al., 2013). The hydrogenation product **2a** could also be efficiently reduced with $LiAlH_4$ to generate (*S*)-phenylglycinol **6** in 87% yield and without loss of ee value (>99% ee) (Chen et al., 2014; Liu et al., 2017), which is the key intermediate to construct chiral cyclic carbamate Evans' auxiliary (Jnoff et al., 2014) and bisoxazoline ligand (*S,S*)-Ph-Box (Corey et al., 1991; Cornejo et al., 2005; Ouhamou, 2010).

DISCUSSION

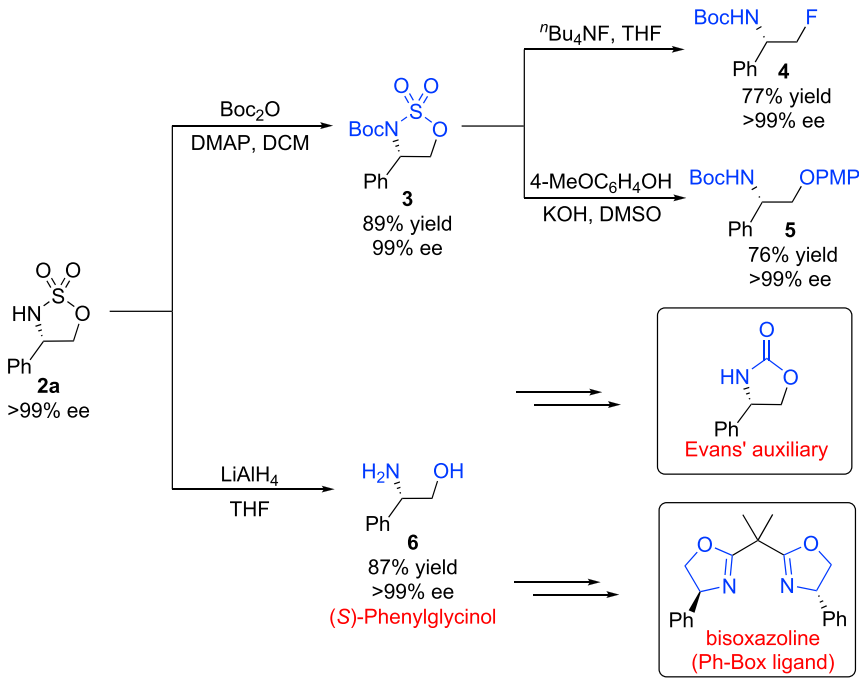
Mechanism Study

To explore the possible reaction mechanism for this Ni-catalyzed asymmetric hydrogenation, a series of isotopic labeling studies were conducted (Scheme 5). The cyclic sulfamidate imine **1a** was hydrogenated with 25 atm D_2 in CF_3CH_2OH; the deuterium atom was solely added at the benzylic position and partly at the nitrogen atom of the product. In addition, this reduction was repeated in the presence of H_2 and CF_3CH_2OD, and we found that the deuterium atom was just partly located at the nitrogen atom. Our hydrogenation product **2a** was dissolved and stirred in CF_3CH_2OD, and the deuterium atom was detected to be partly incorporated at the N-H position, which showed that proton exchange should occur in this process. These results suggested that the H atom at the benzylic position of the hydrogenation product was solely from H_2.

Based on these observations and previous studies (Shevlin et al., 2016; Gao et al., 2017), the possible catalytic mechanism of this transformation was presented in Scheme 6. The hydrogen was involved in heterolytic cleavage to form [Ni]-H intermediate (**II**) (Korstanje et al., 2015; Ashby and Halpern, 1991), and it then went through ligand exchange with cyclic sulfamidate imine **1a**, followed by enantioselective conjugated addition of [Ni]-H to C=N bond of imine to provide intermediate (**TSIII**). Subsequent protonation by AcOH released the product **2a**. The N-H group of product **2a** has the possibility of undergoing H-exchange with CF_3CH_2OH (or AcOH) to generate compound **2a′**. To our delight, the deuterium-labeling experimental observations above are consistent with this possible catalytic cycle pathway.



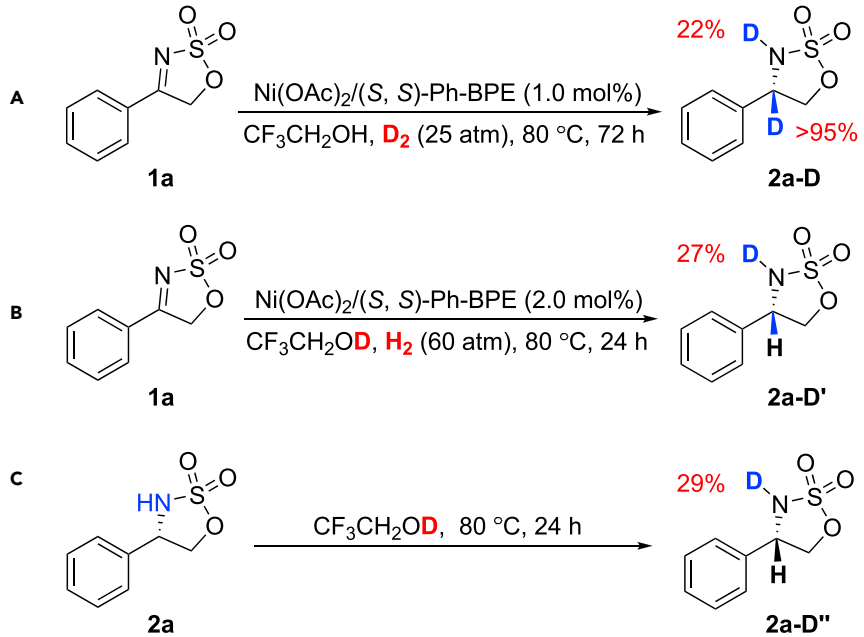
Scheme 3. Gram-Scale Asymmetric Hydrogenation of 1a with High TON



Scheme 4. Synthetic Transformations of Product 2a

Conclusion

In conclusion, the Ni-catalyzed asymmetric hydrogenation of cyclic sulfamidate imines was successfully realized, affording a variety of chiral cyclic sulfamidates with high yields and excellent enantioselectivities (up to 99% yield, >99% ee, and 1,000 TON). Other types of N-sulfonyl ketimines worked well to give the

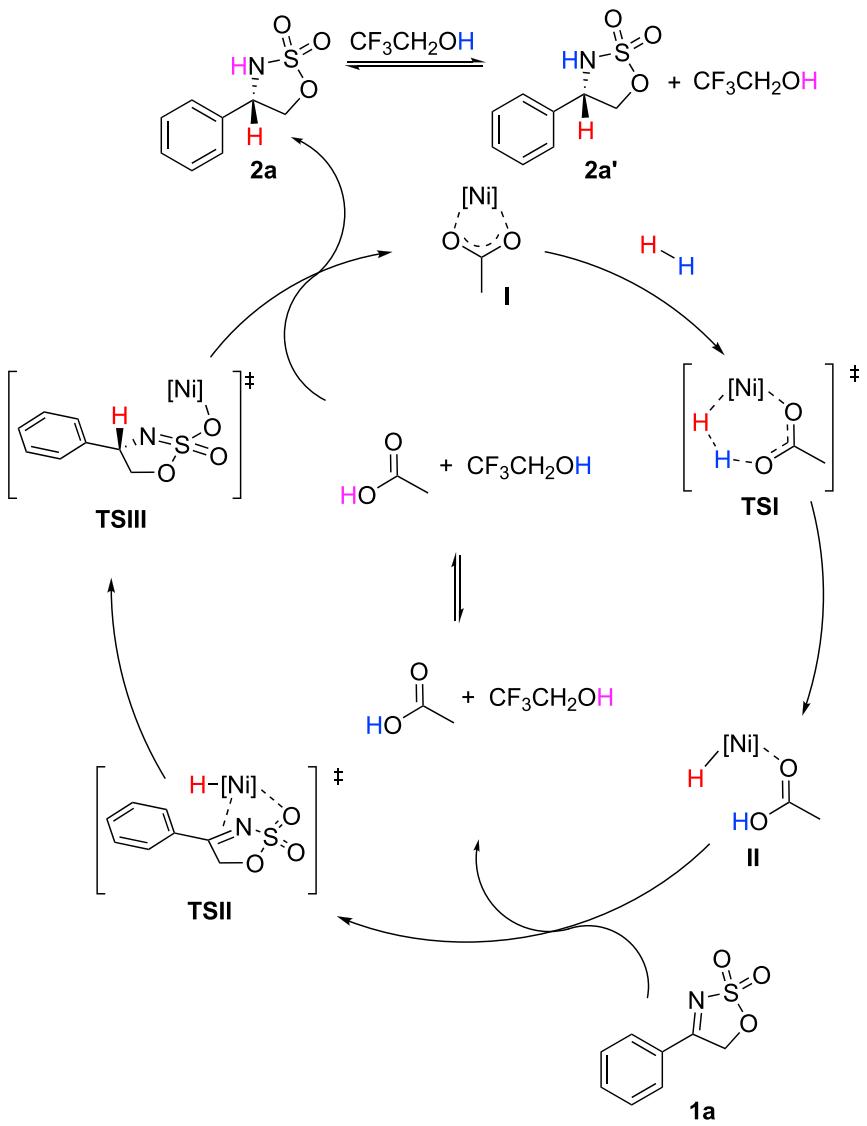


Scheme 5. Deuterium-Labeling Experiments

(A) The hydrogenation with D_2 in CF_3CH_2OH.

(B) The hydrogenation with H_2 in CF_3CH_2OD.

(C) The product **2a** stirring in CF_3CH_2OD.



Scheme 6. Proposed Catalytic Cycle for the Ni-Catalyzed Asymmetric Hydrogenation of 1a

corresponding hydrogenation products with full conversion, 96%–97% yields, and 97%–>99% ee. In addition, this asymmetric methodology owned great synthetic utility through various product derivations to construct some important enantioenriched organic molecules, such as chiral β-fluoroamine, amino ether, and phenylglycinol. Moreover, a reasonable catalytic cycle was provided to reveal a possible mechanism for this Ni-catalyzed asymmetric hydrogenation based on the deuterium-labeling studies. Further investigations on the detailed mechanisms of Ni-catalyzed asymmetric hydrogenation strategy are in progress in our laboratory.

Limitations of the Study

The six-membered cyclic sulfamidate imine was not suitable in this methodology.

METHODS

All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2019.07.004.

ACKNOWLEDGMENTS

We are grateful for financial support from the National Natural Science Foundation of China (Grant No. 21432007, 21502145), the Wuhan Morning Light Plan of Youth Science and Technology (Grant No. 2017050300307), the Fundamental Research Funds for Central Universities (Grant No. 2042018kf0202), and Shenzhen Nobel Prize Scientists Laboratory Project (Grant No. C17783101). The Program of Introducing Talents of Discipline to Universities of China (111 Project) is also appreciated.

AUTHOR CONTRIBUTIONS

Y.L. discovered the reported process, designed and carried out almost all the experiments, and composed the manuscript. Z.Y. participated in synthesizing partial substrates. X.T. helped in executing isotopic labeling studies. General guidance, project directing, and manuscript revisions were done by X.-Q.D. and X.Z.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: March 28, 2019
Revised: June 11, 2019
Accepted: June 28, 2019
Published: September 27, 2019

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Supplemental Information

Nickel-Catalyzed Asymmetric Hydrogenation of Cyclic Sulfamidate Imines: Efficient Synthesis of Chiral Cyclic Sulfamidates

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Supplemental Figures for ^{1}H and ^{13}C NMR spectra of substrate 1g, 1i, 1p, 1q, 1r

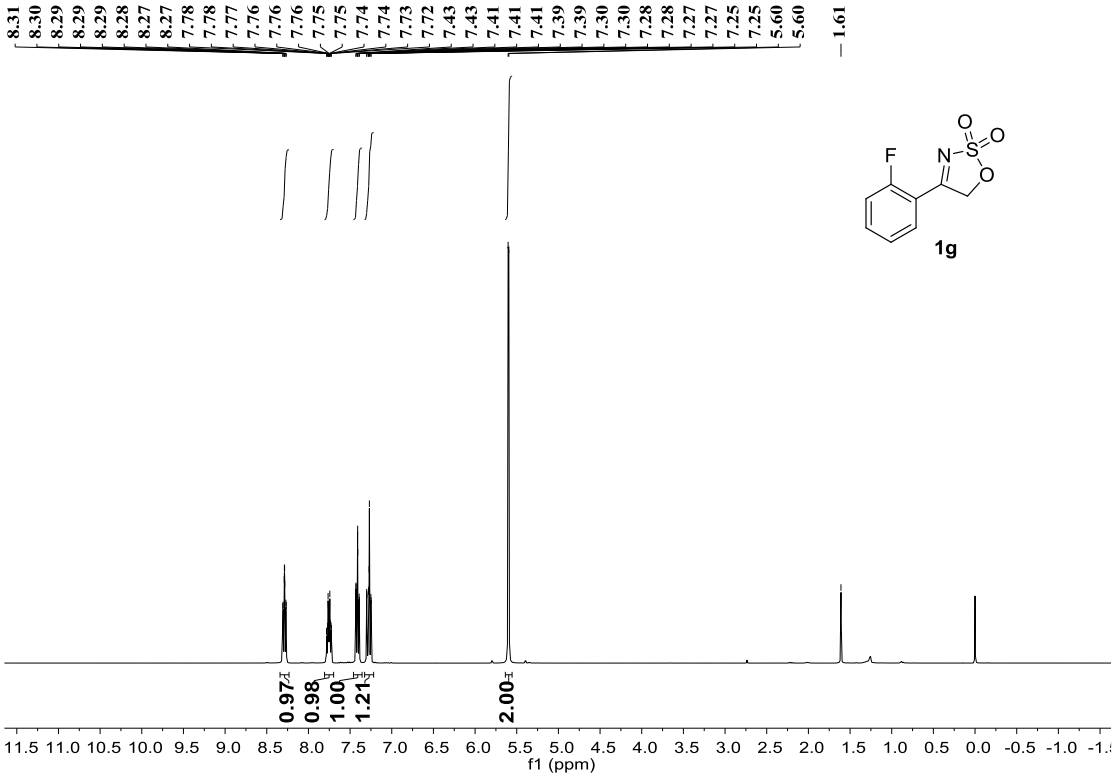


Figure S1. ^{1}H NMR spectrum of substrate **1g**, related to **Table 3**.

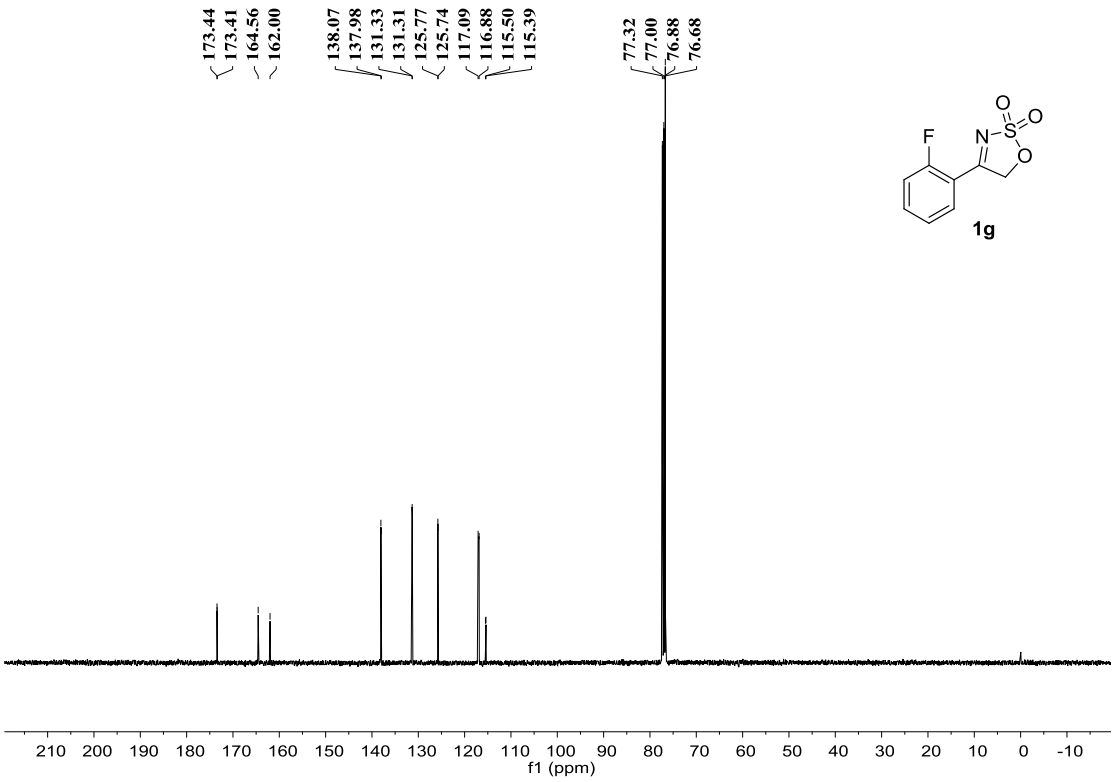


Figure S2. ^{13}C NMR spectrum of substrate **1g**, related to **Table 3**.

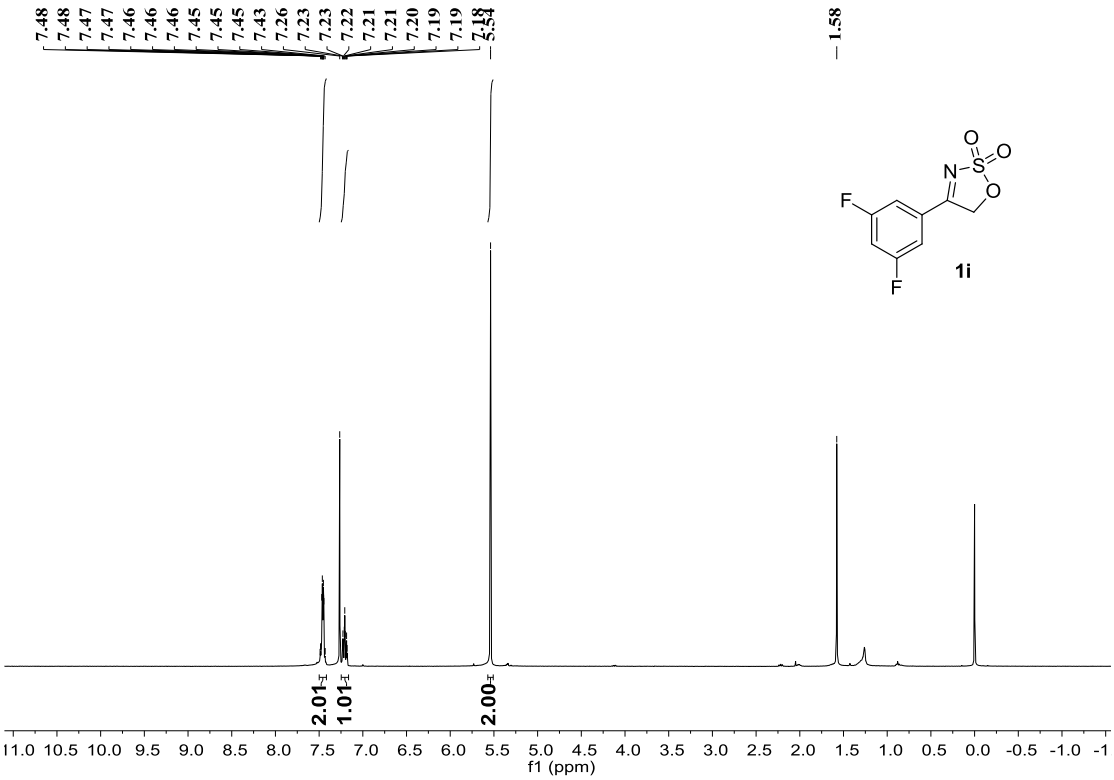


Figure S3. [1]H NMR spectrum of substrate **1i**, related to **Table 3**.

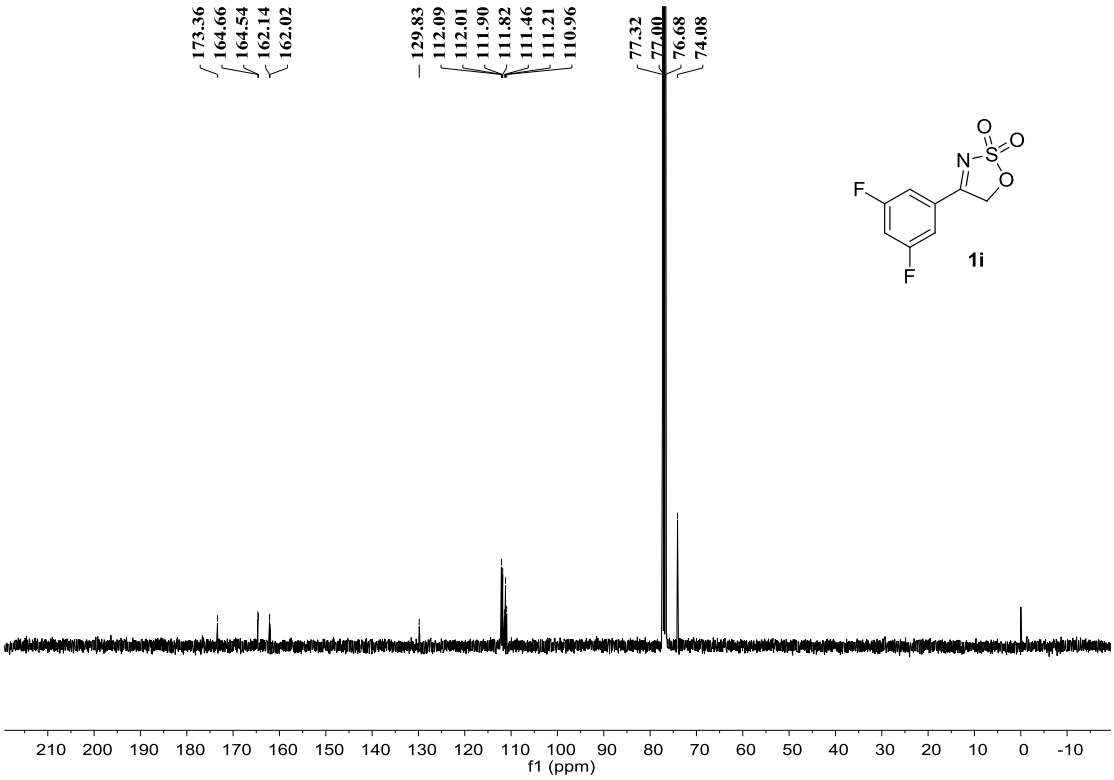


Figure S4. [13]C NMR spectrum of substrate **1i**, related to **Table 3**.

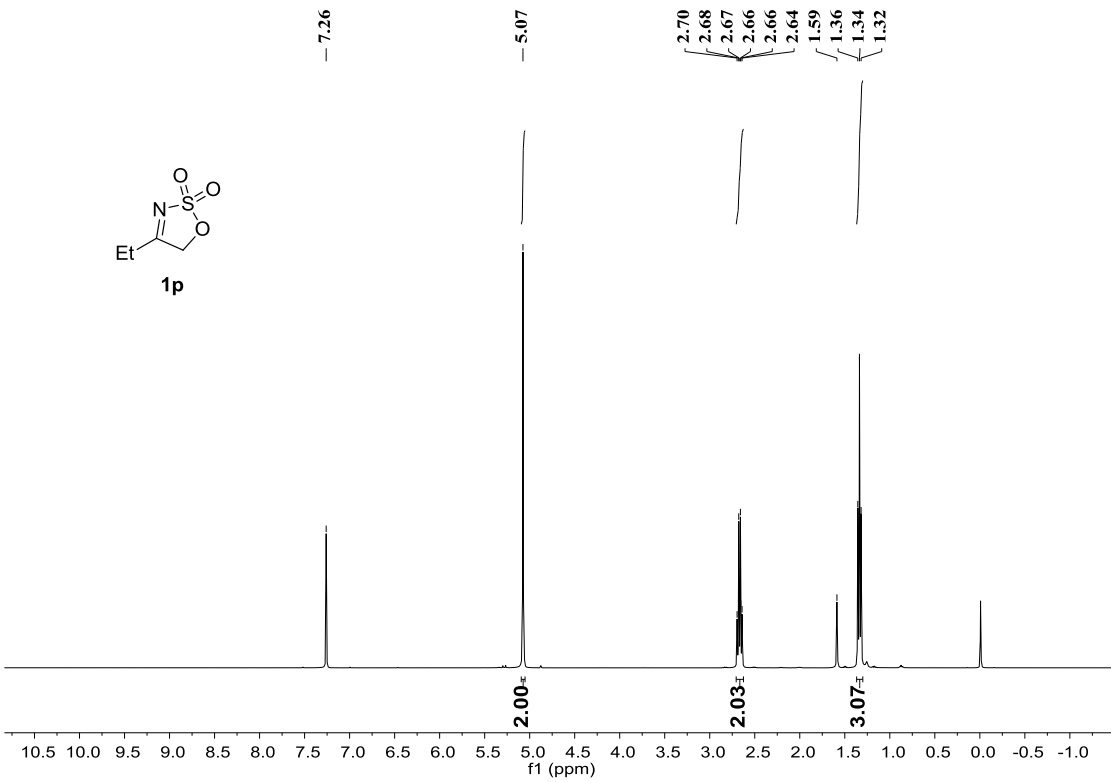


Figure S5. [1]H NMR spectrum of substrate **1p**, related to **Table 3**.

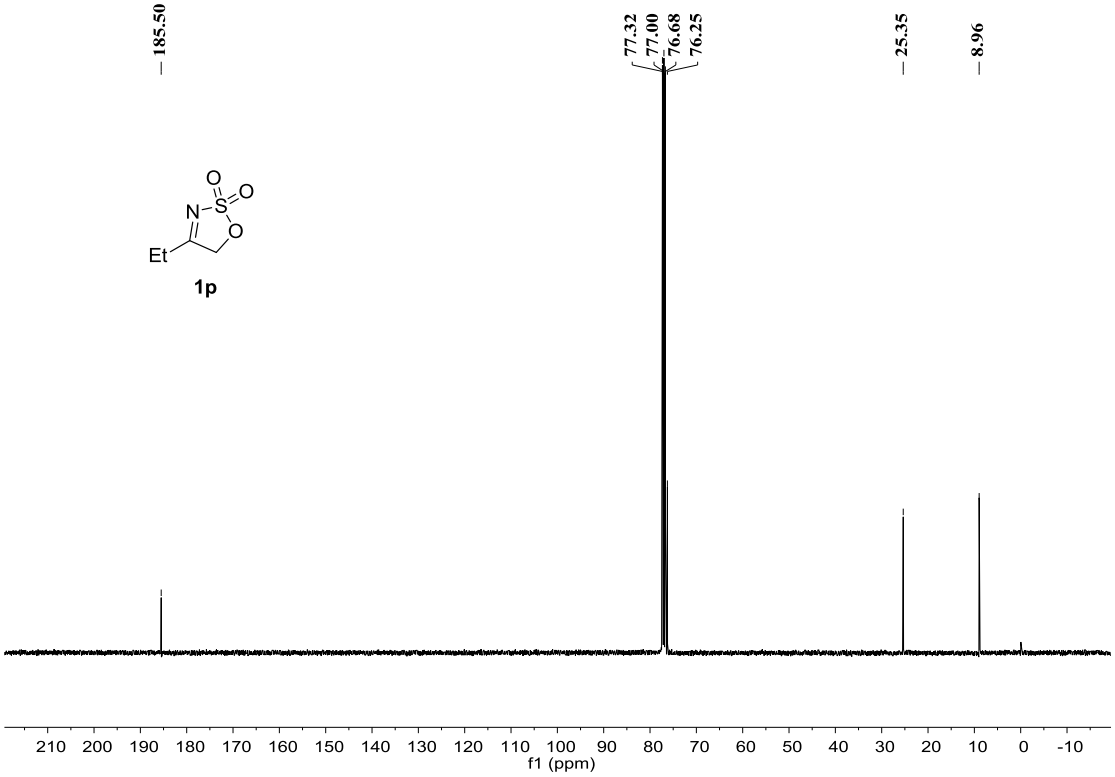


Figure S6. [13]C NMR spectrum of substrate **1p**, related to **Table 3**.

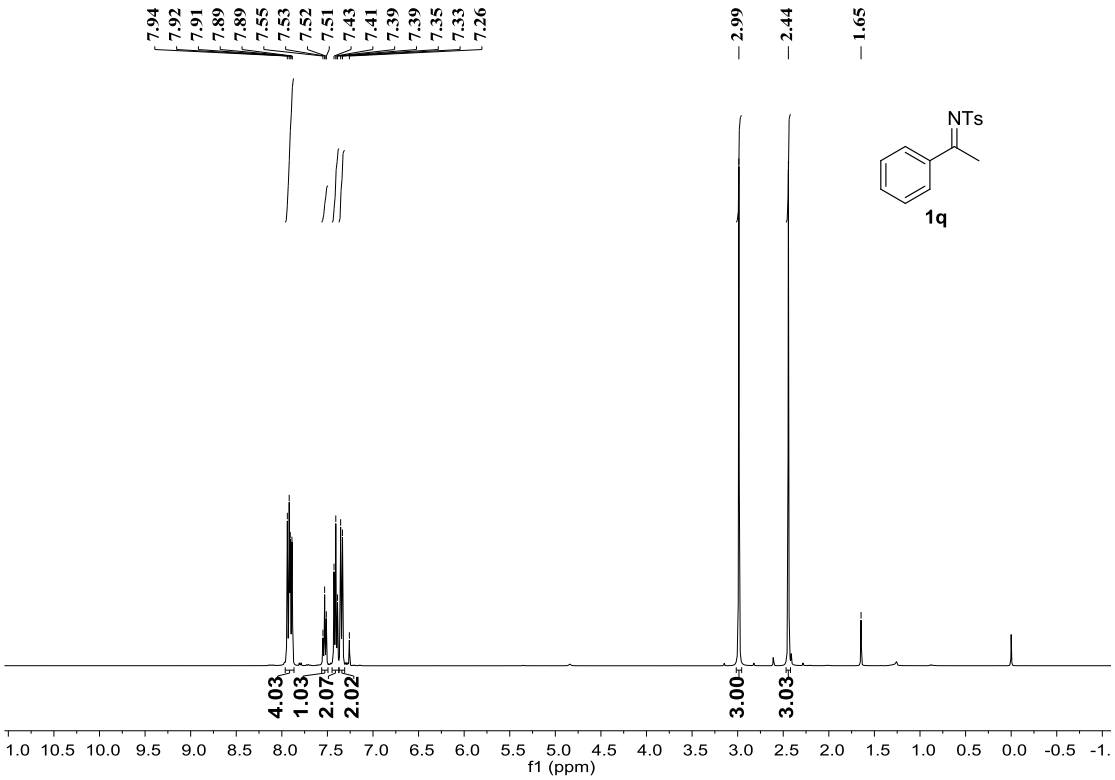


Figure S7. [1]H NMR spectrum of substrate **1q**, related to **Scheme 2**.

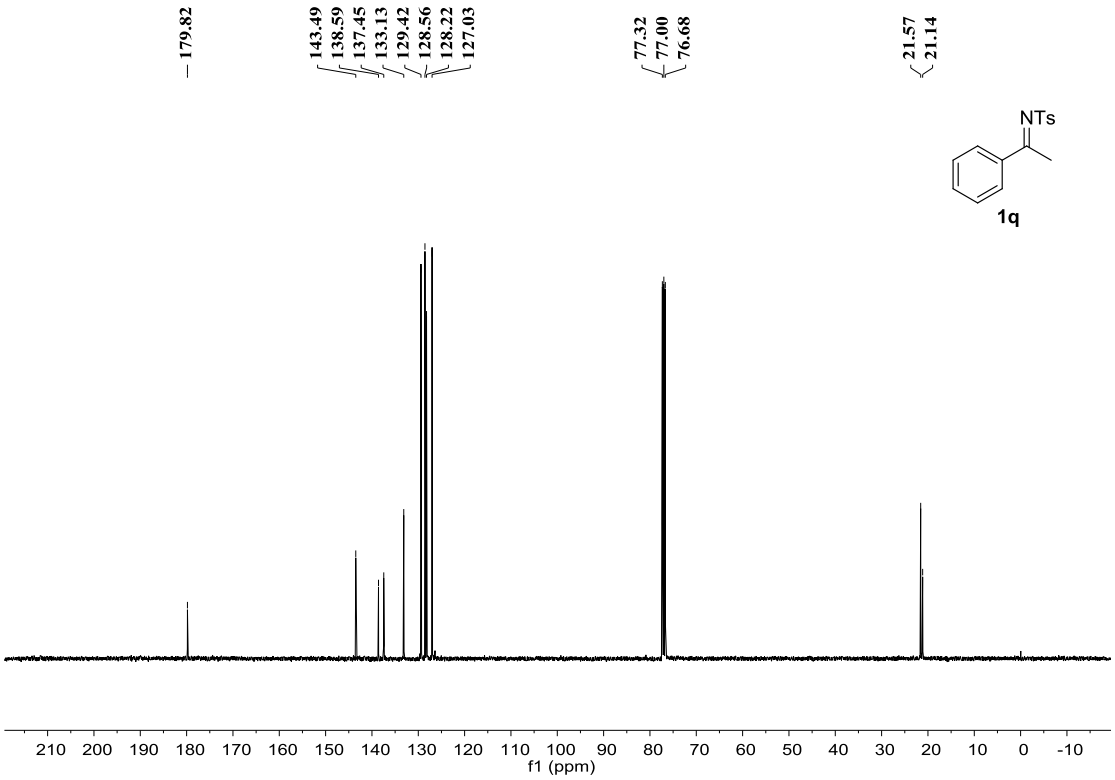


Figure S8. [13]C NMR spectrum of substrate **1q**, related to **Scheme 2**.

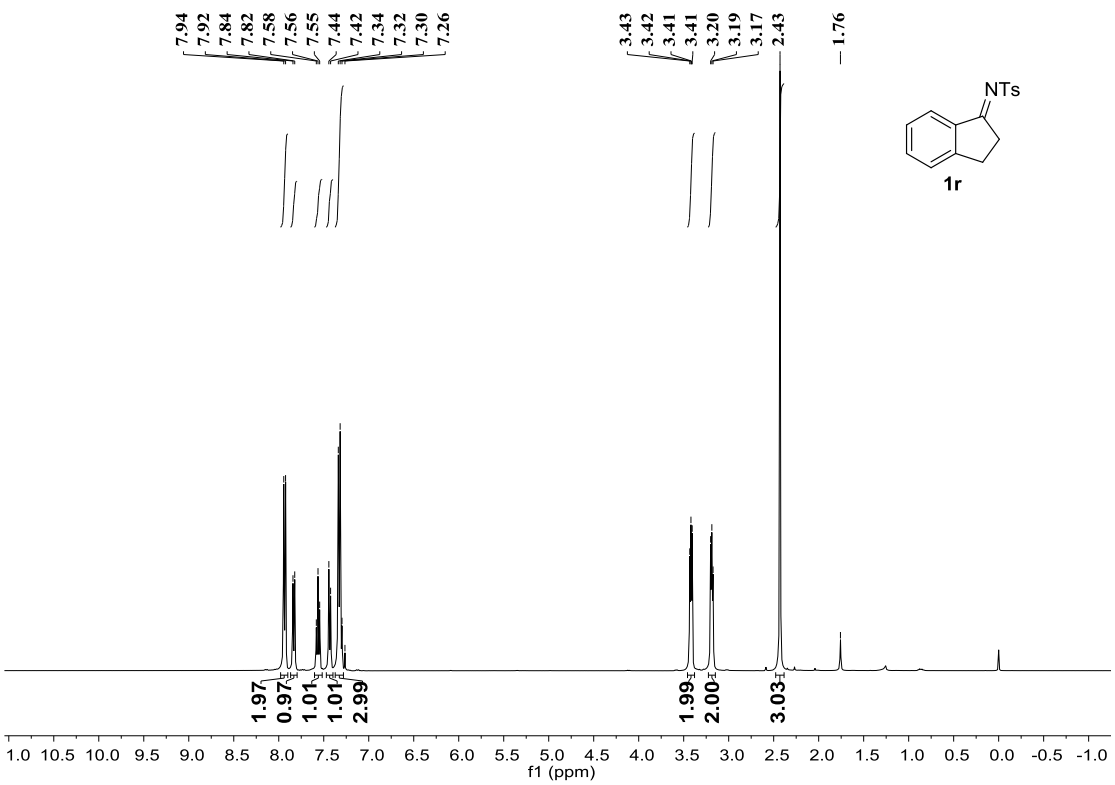


Figure S9. [1]H NMR spectrum of substrate **1r**, related to **Scheme 2**.

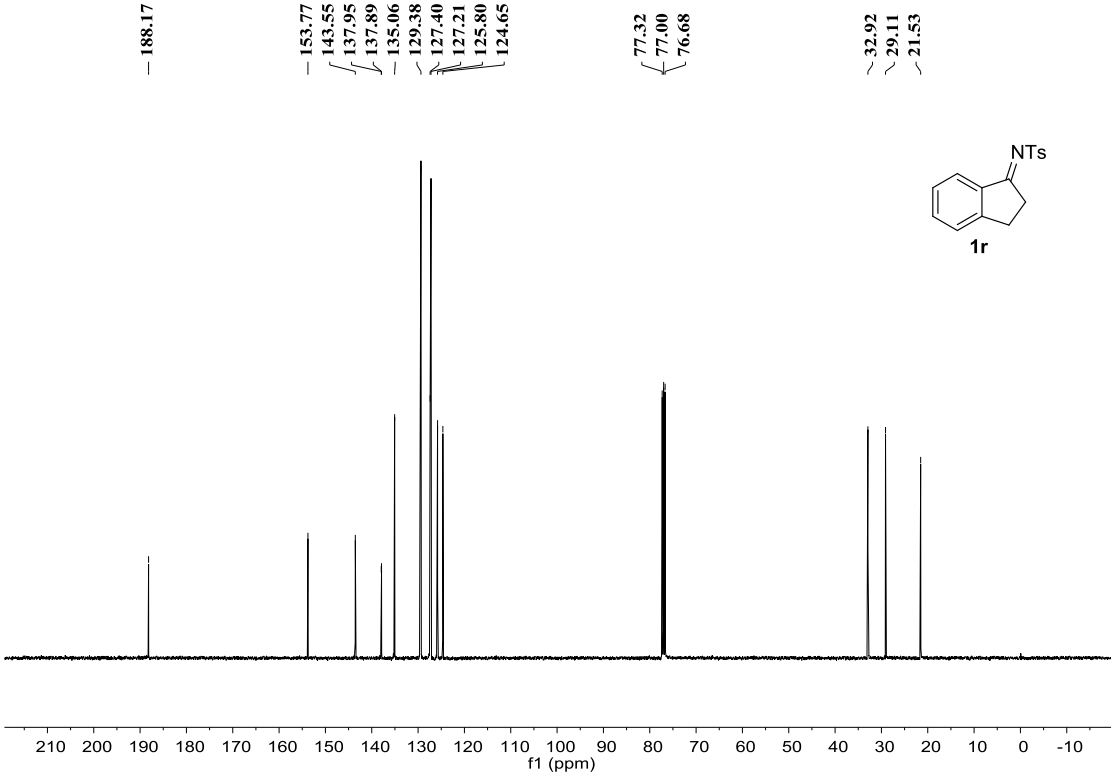


Figure S10. [13]C NMR spectrum of substrate **1r**, related to **Scheme 2**.

Supplemental Figures for ^{1}H and ^{13}C NMR spectra of products 2a-2r

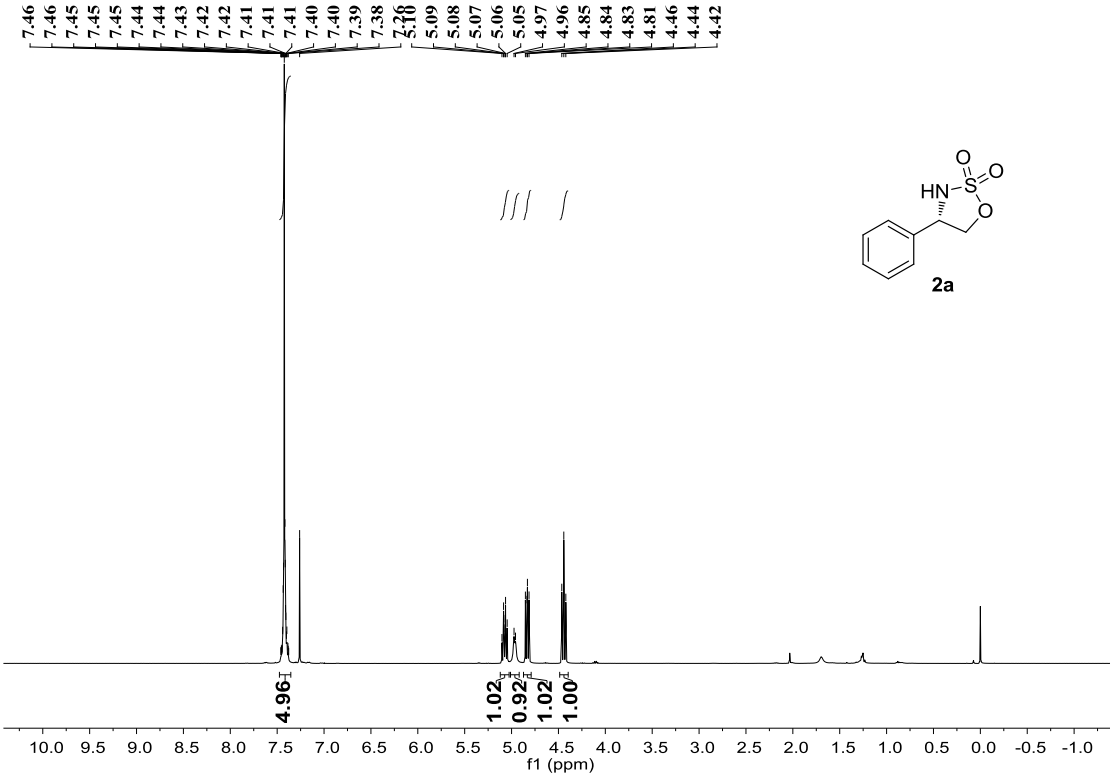


Figure S11. ^{1}H NMR spectrum of **2a**, related to **Table 3**.

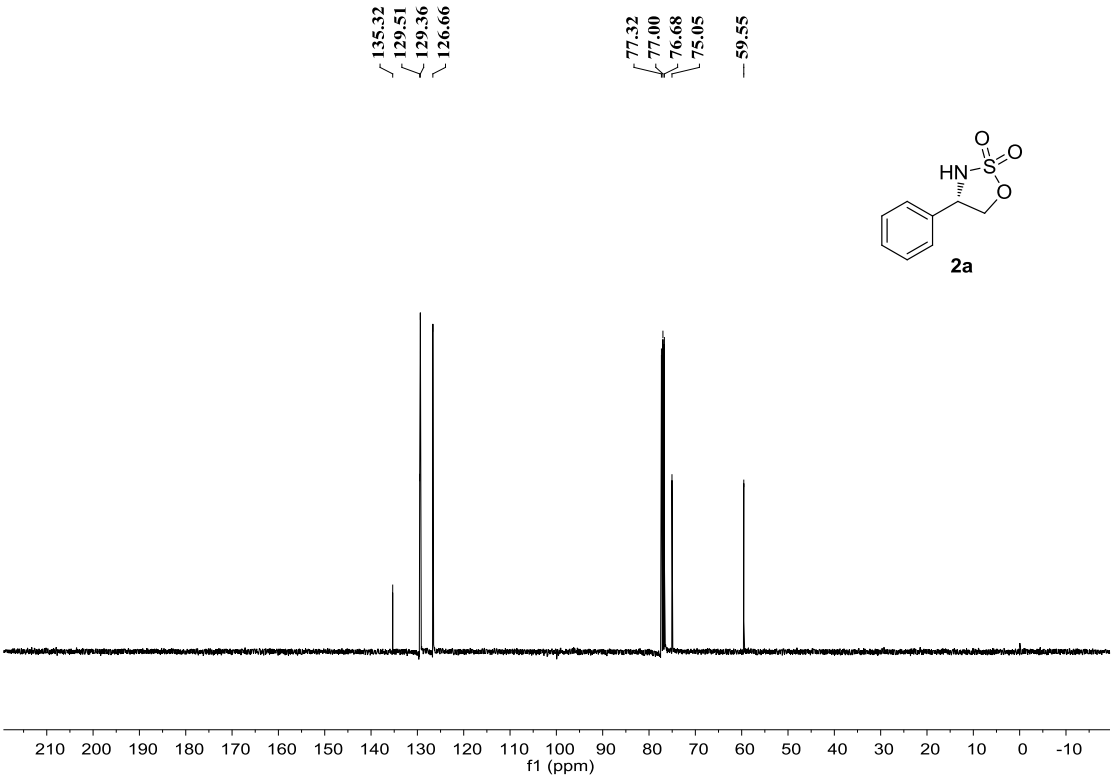


Figure S12. ^{13}C NMR spectrum of **2a**, related to **Table 3**.

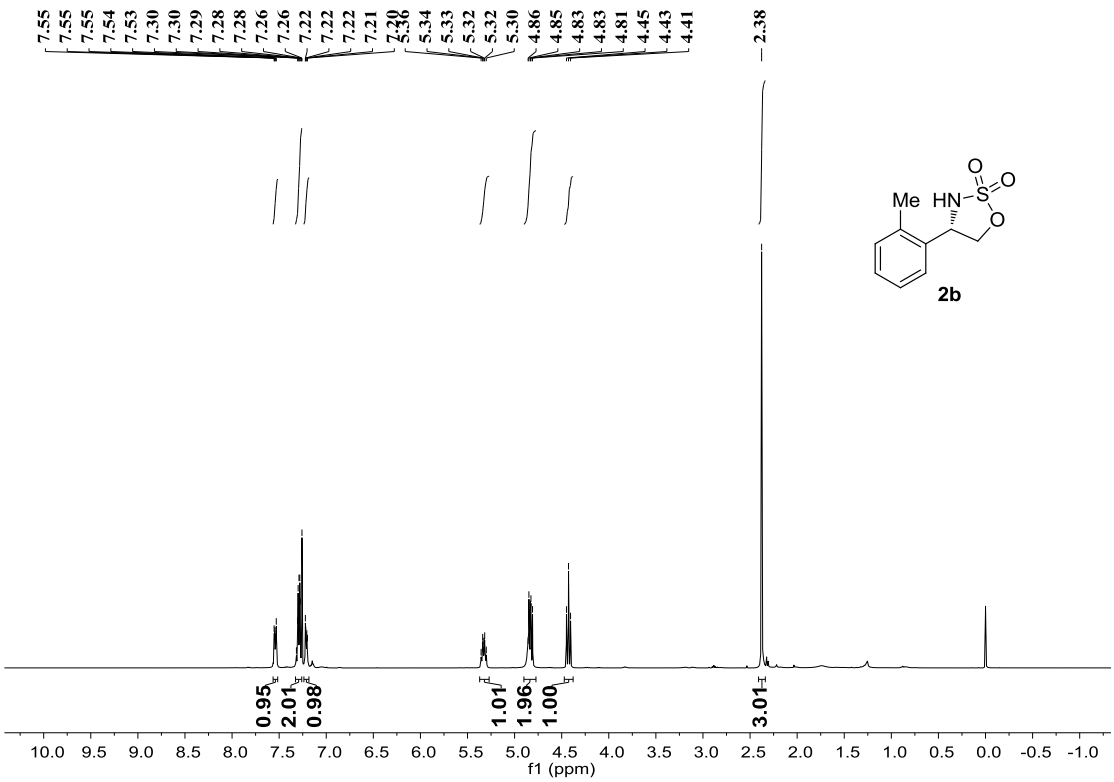


Figure S13. ^{1}H NMR spectrum of **2b**, related to **Table 3**.

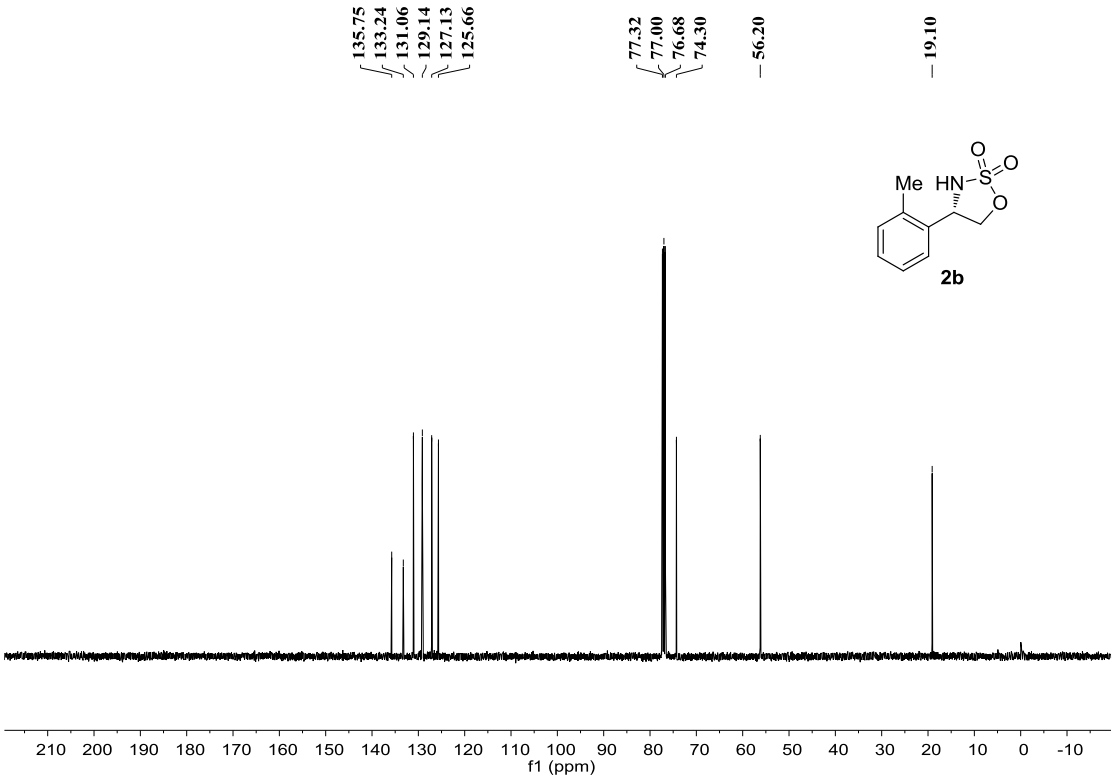


Figure S14. ^{13}C NMR spectrum of **2b**, related to **Table 3**.

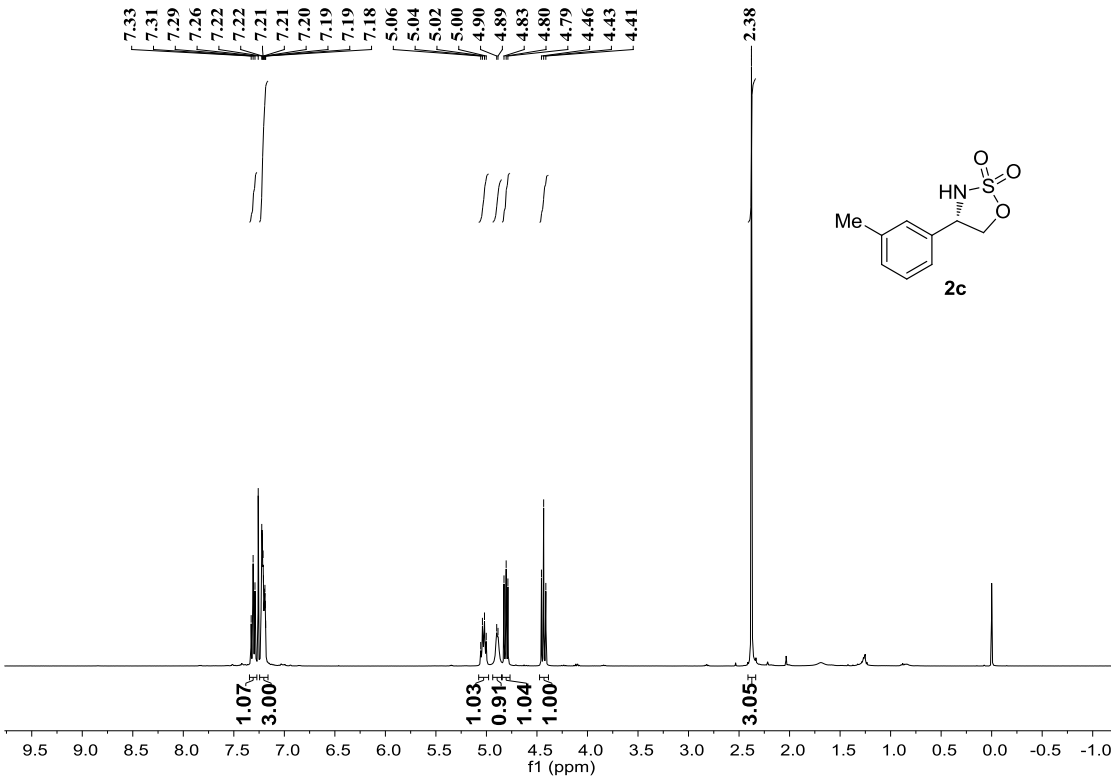


Figure S15. ^{1}H NMR spectrum of **2c**, related to **Table 3**.

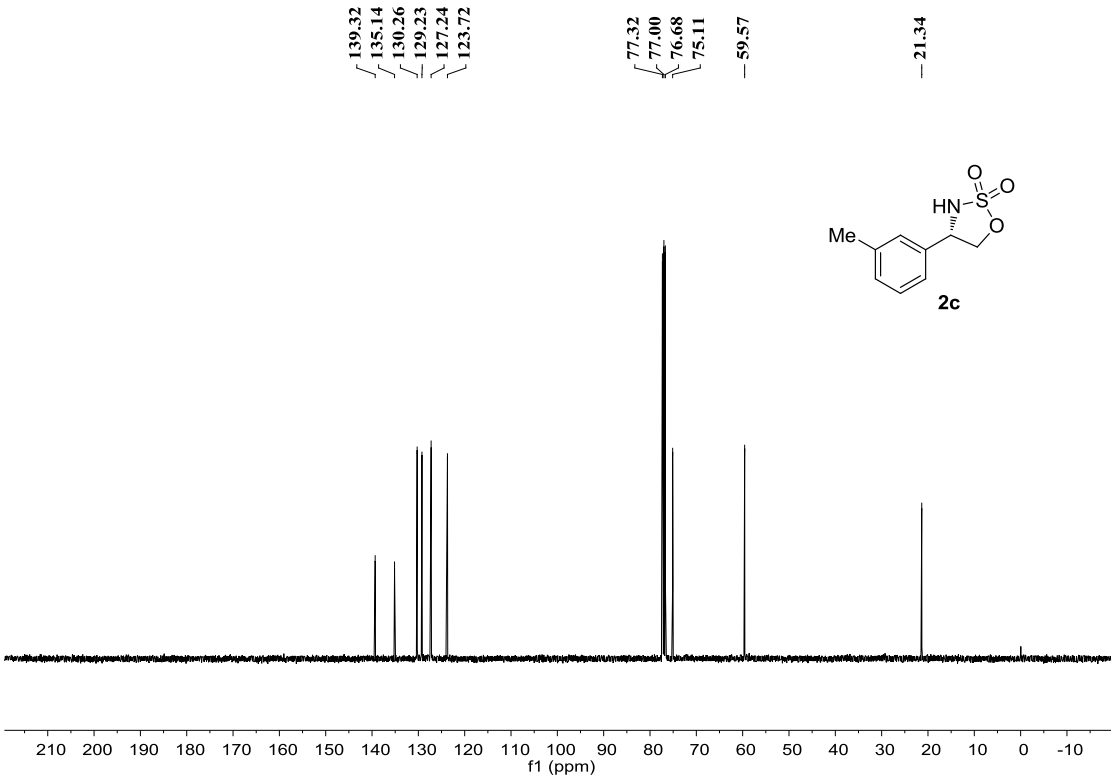


Figure S16. ^{13}C NMR spectrum of **2c**, related to **Table 3**.

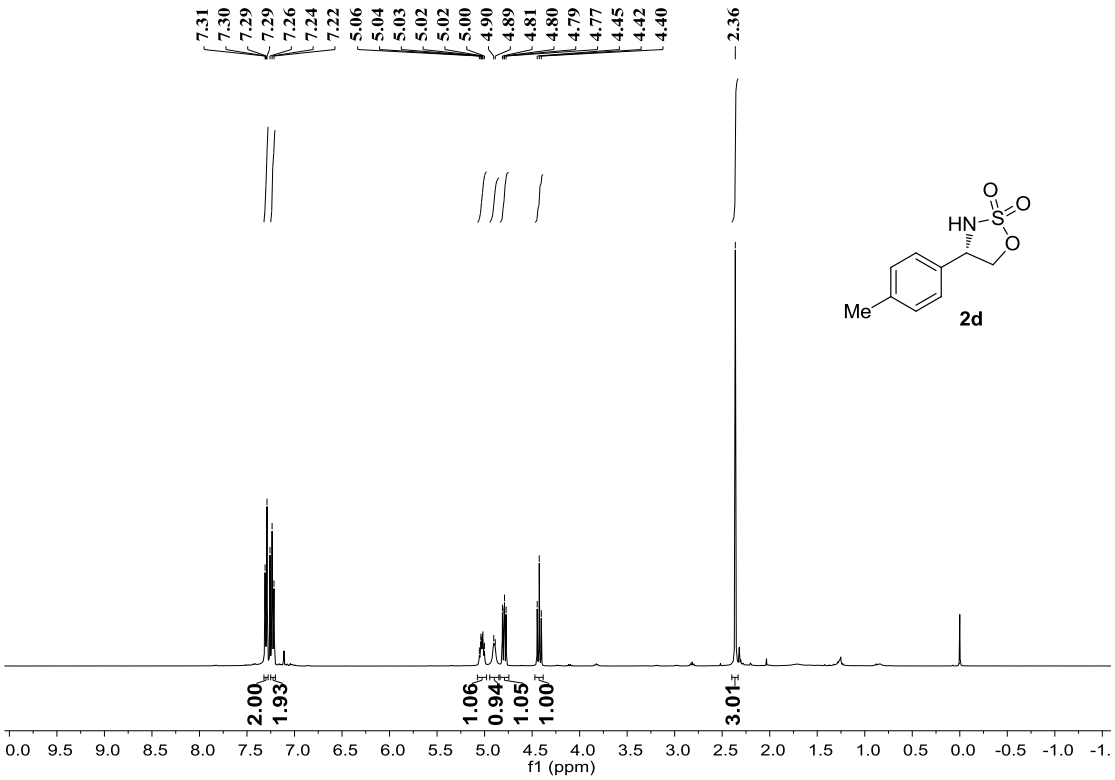


Figure S17. [1]H NMR spectrum of **2d**, related to **Table 3**.

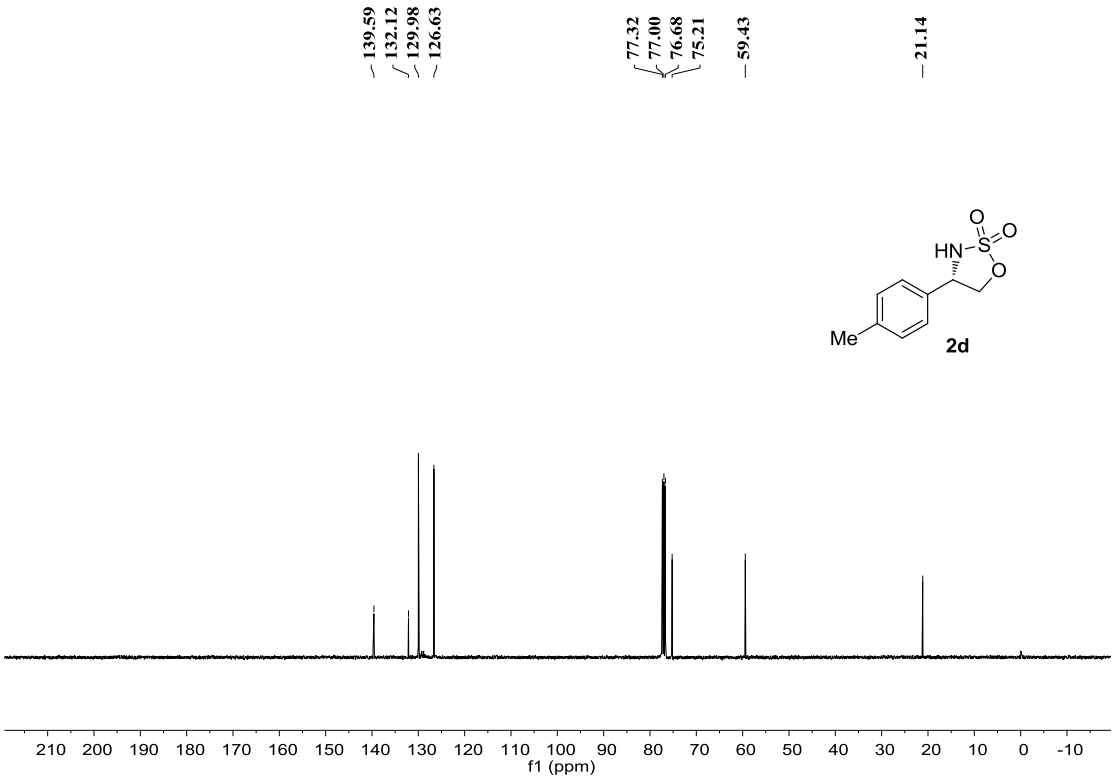


Figure S18. [13]C NMR spectrum of **2d**, related to **Table 3**.

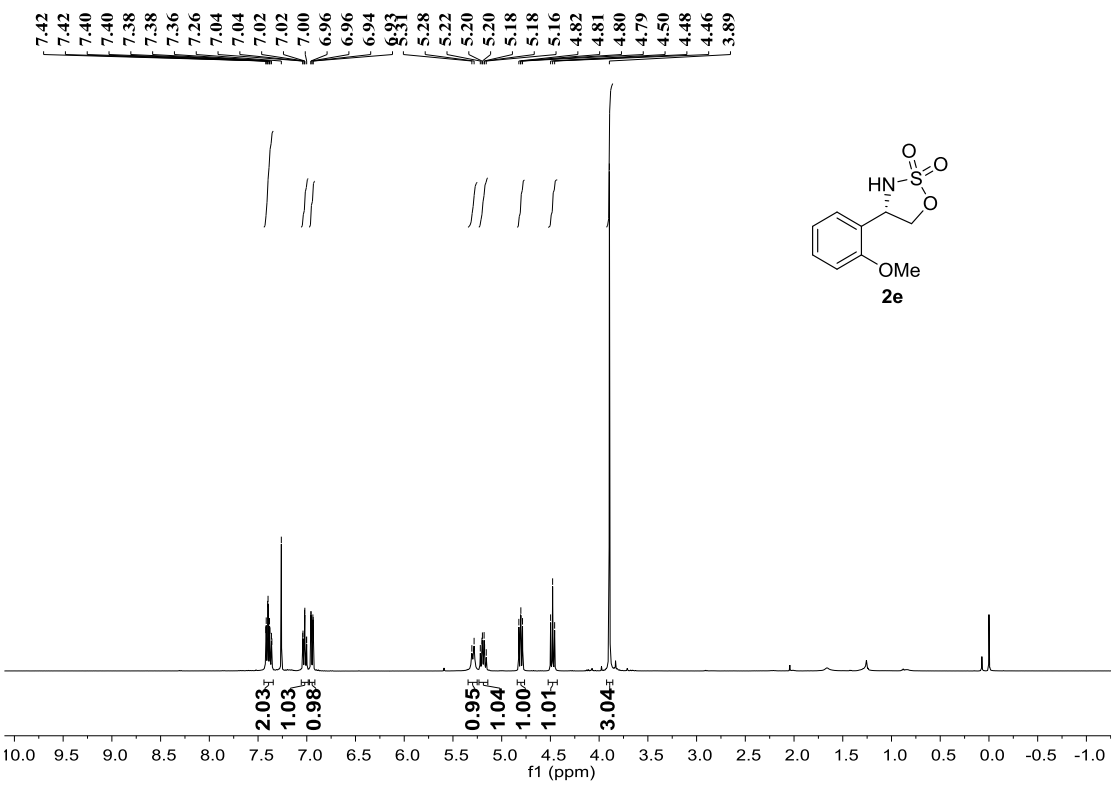


Figure S19. ^{1}H NMR spectrum of **2e**, related to **Table 3**.

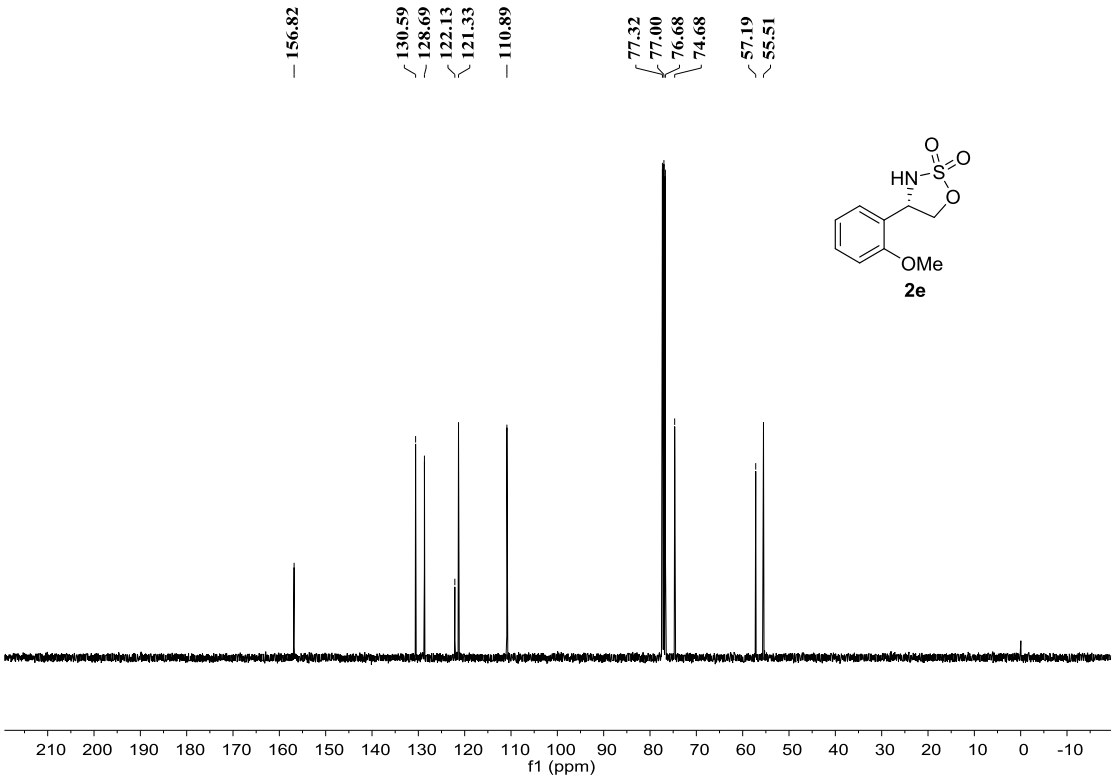


Figure S20. ^{13}C NMR spectrum of **2e**, related to **Table 3**.

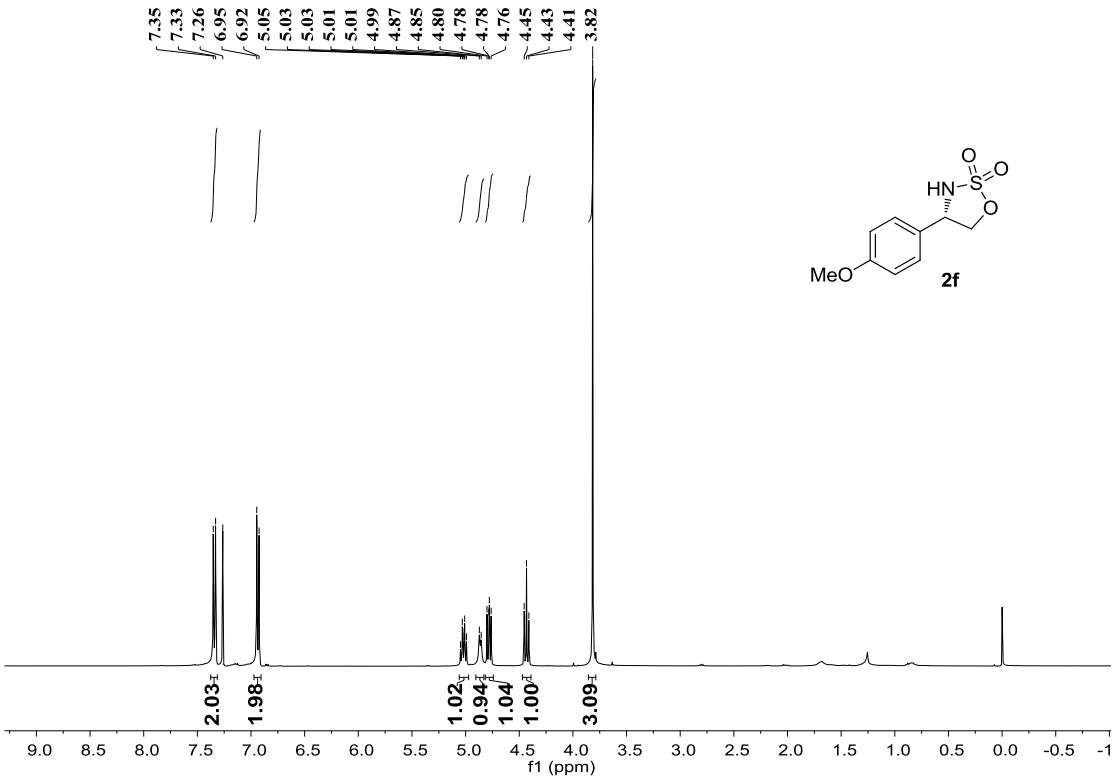


Figure S21. [1]H NMR spectrum of **2f**, related to **Table 3**.

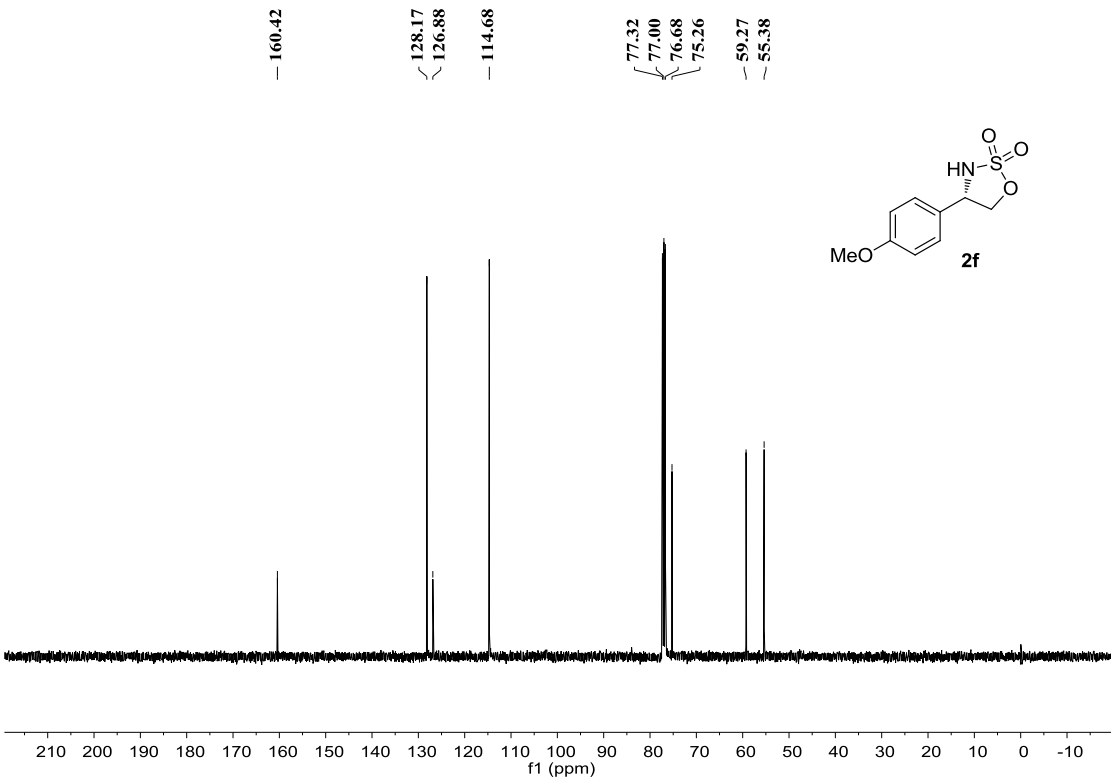


Figure S22. [13]C NMR spectrum of **2f**, related to **Table 3**.

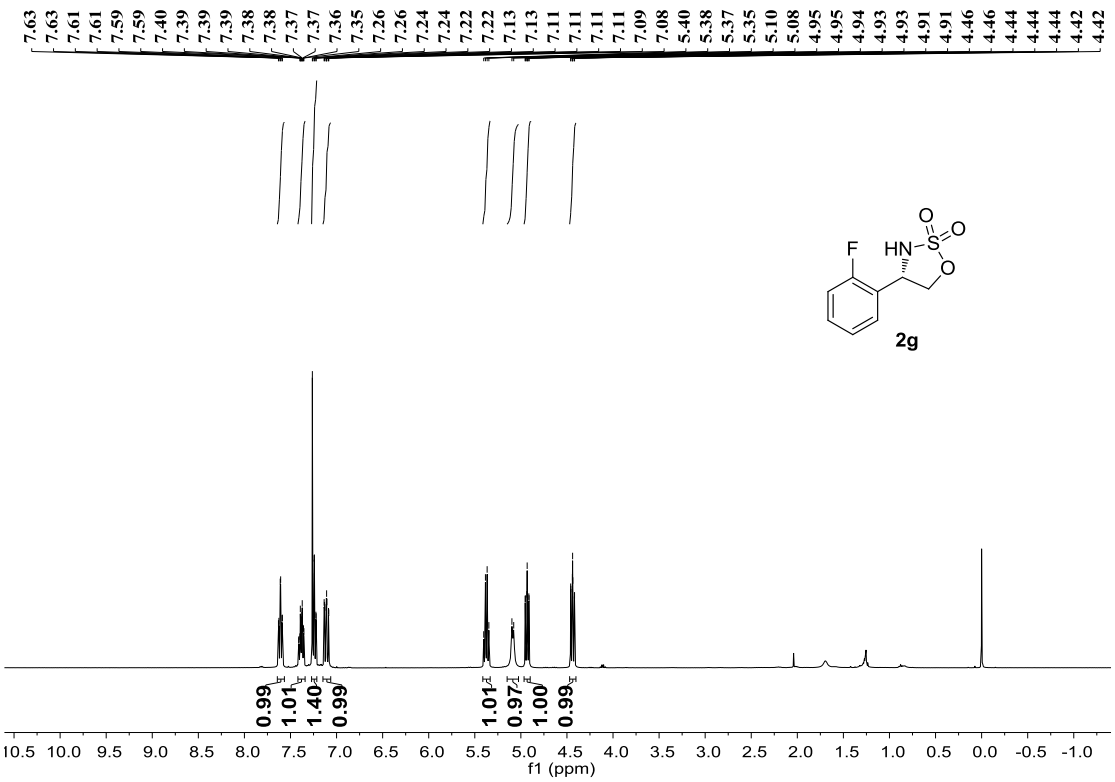


Figure S23. [1]H NMR spectrum of **2g**, related to **Table 3**.

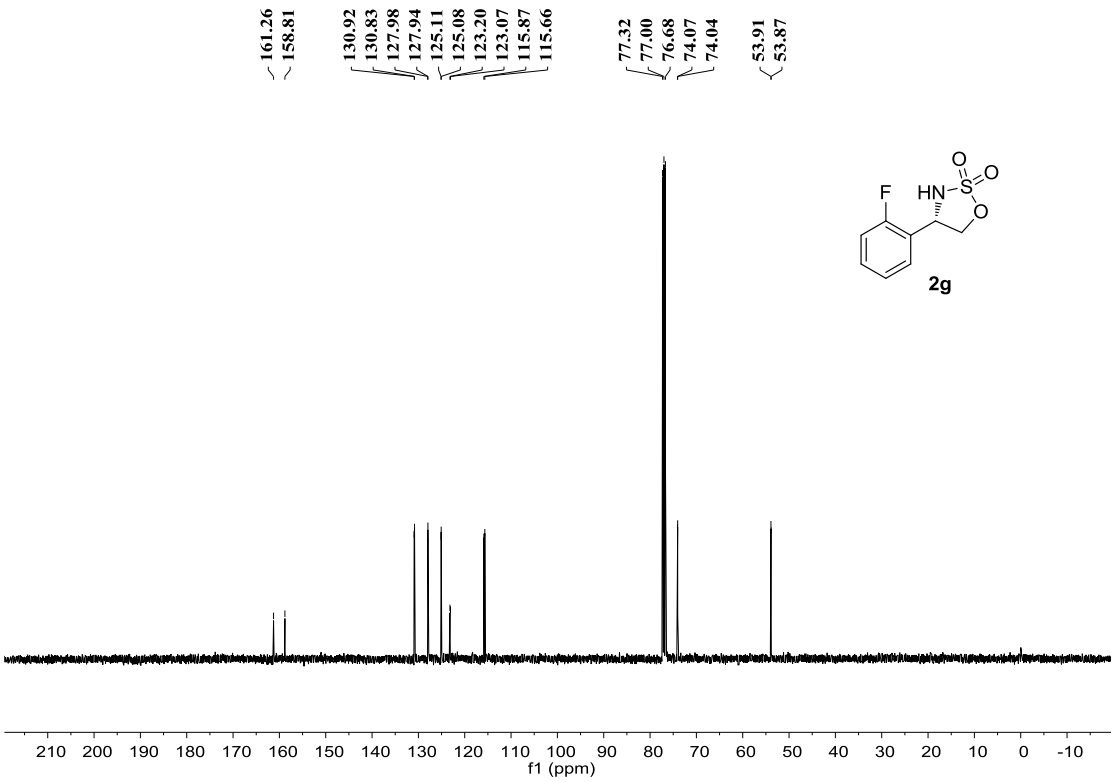


Figure S24. [13]C NMR spectrum of **2g**, related to **Table 3**.

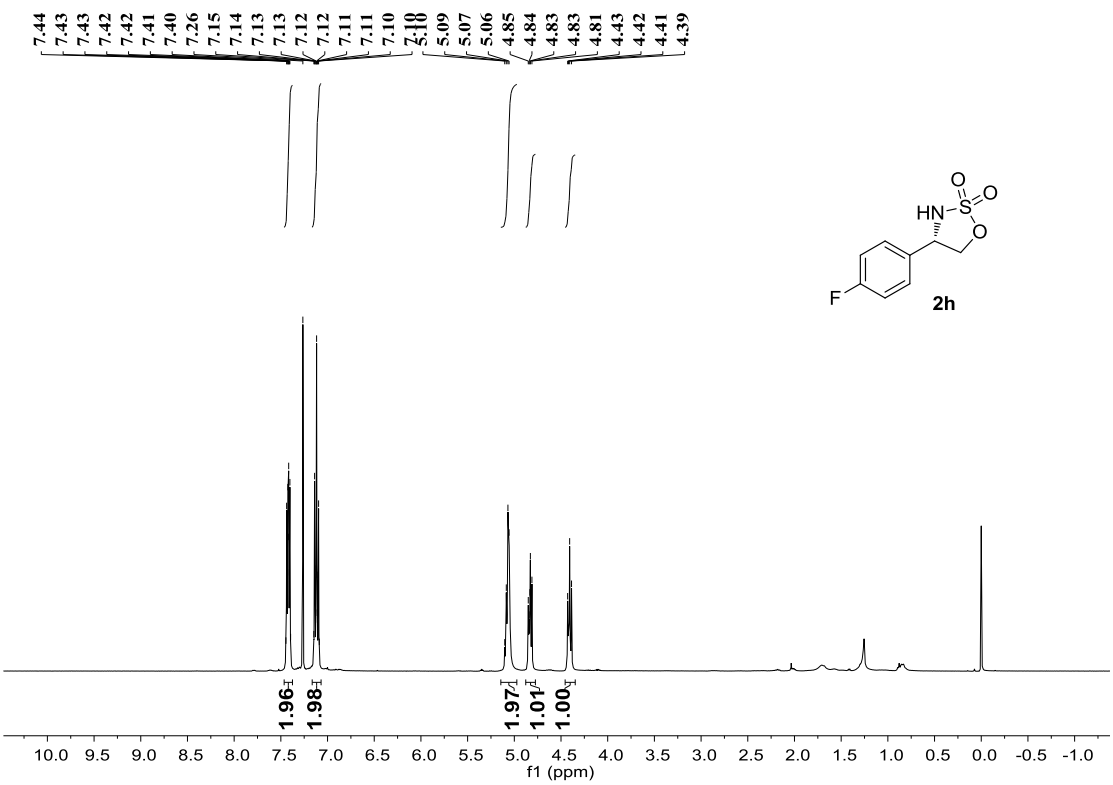


Figure S25. [1]H NMR spectrum of **2h**, related to **Table 3**.

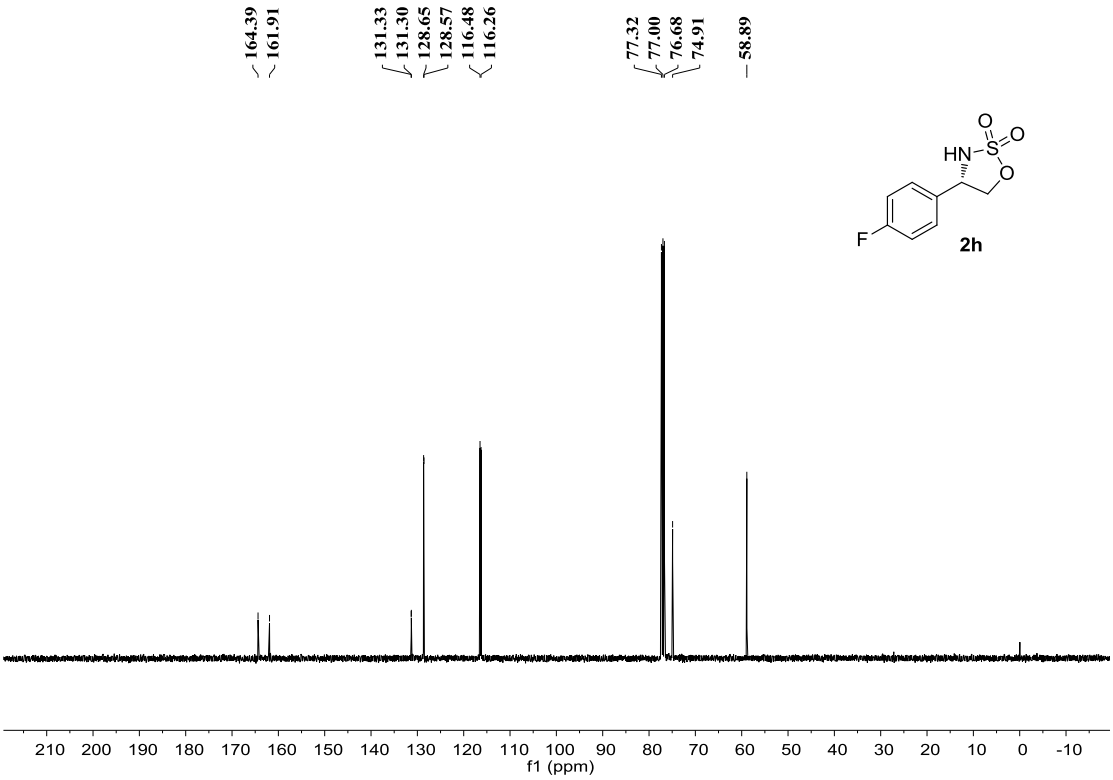


Figure S26. [13]C NMR spectrum of **2h**, related to **Table 3**.

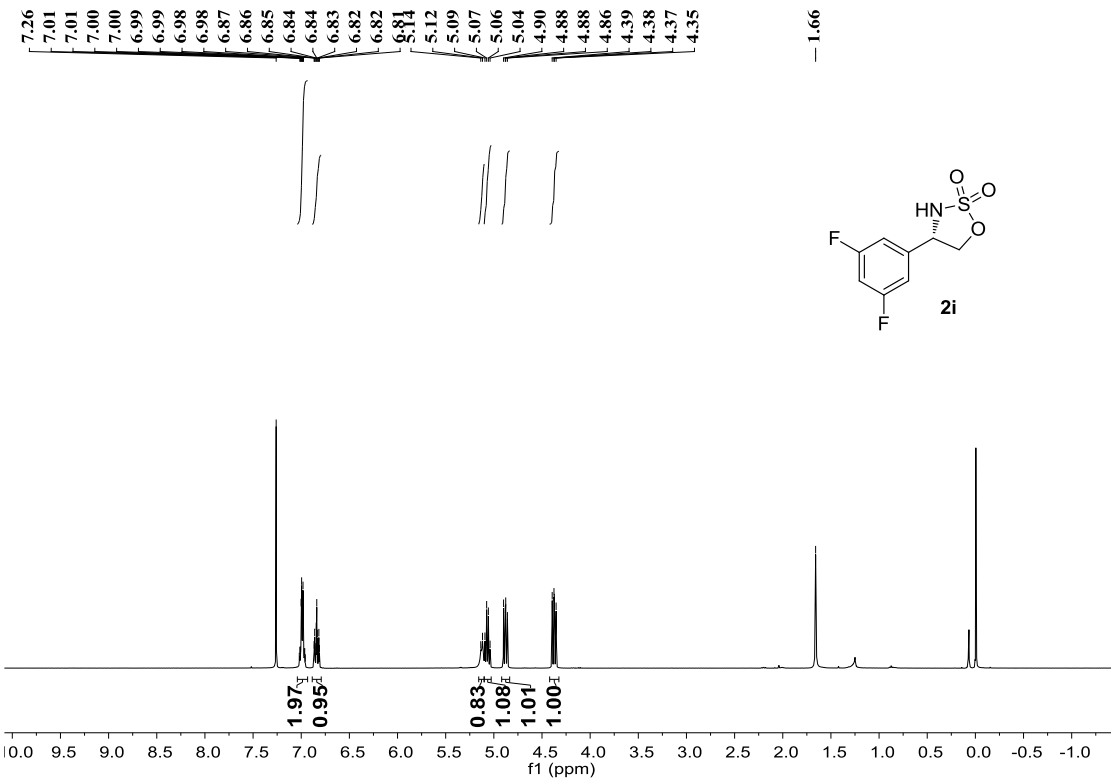


Figure S27. [1]H NMR spectrum of **2i**, related to **Table 3**.

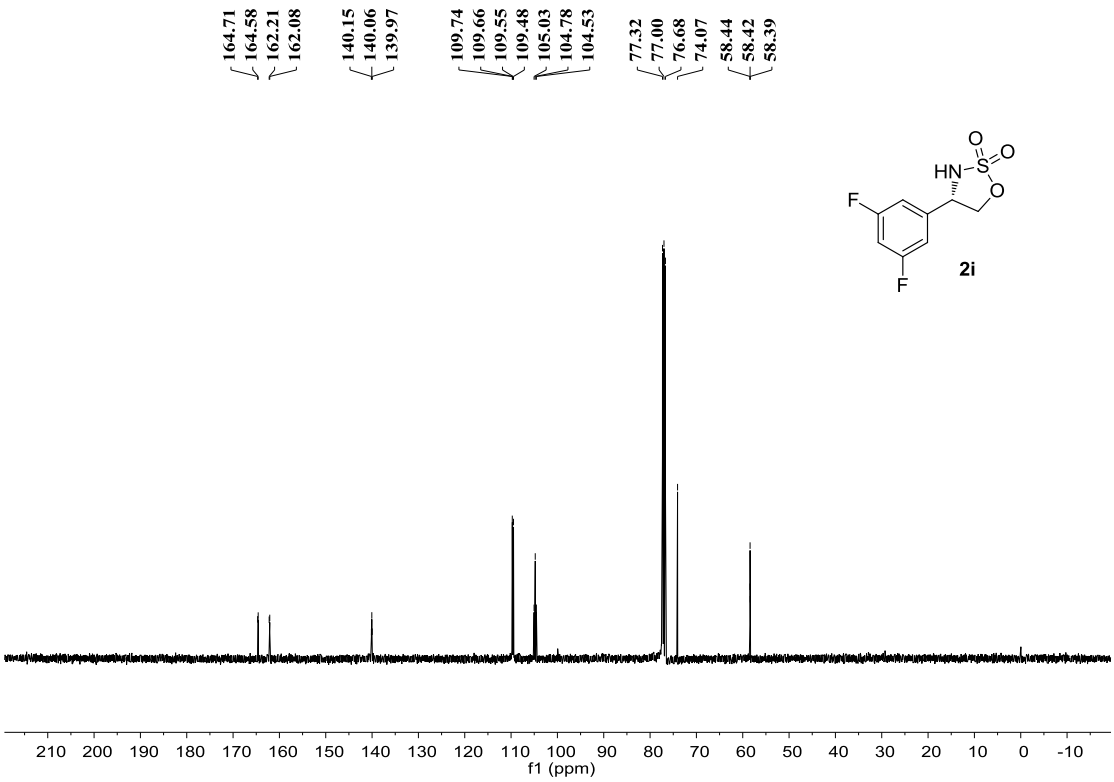


Figure S28. [13]C NMR spectrum of **2i**, related to **Table 3**.

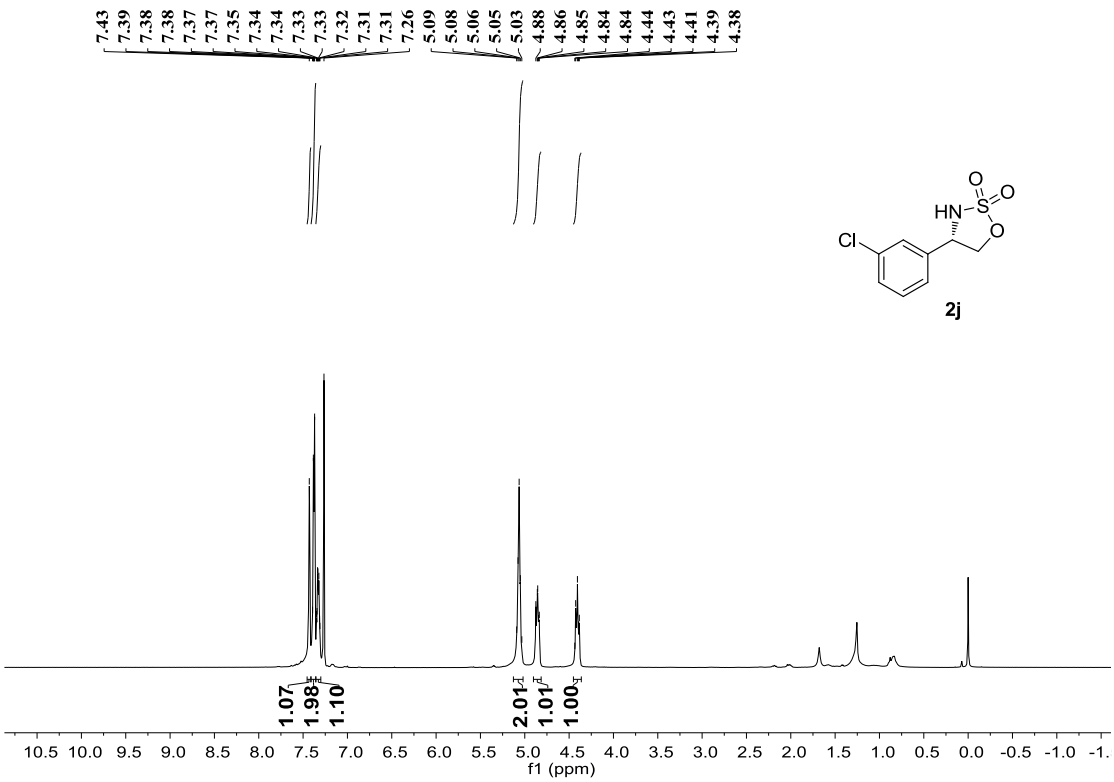


Figure S29. ^{1}H NMR spectrum of **2j**, related to **Table 3**.

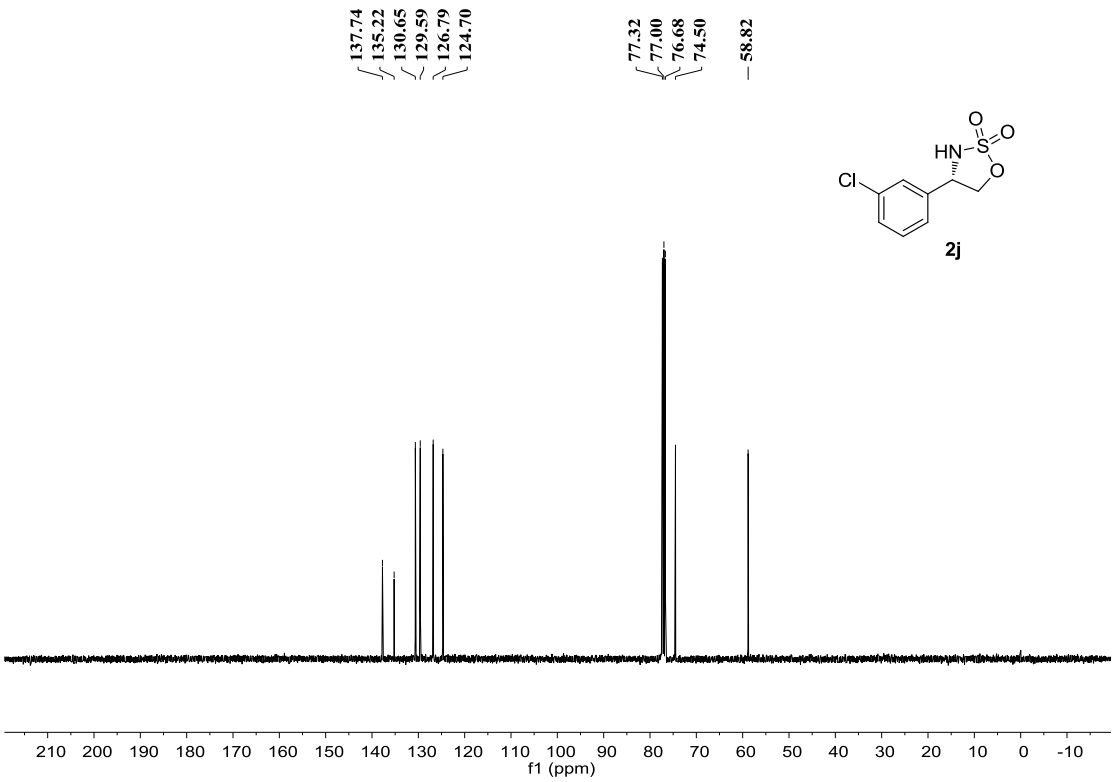


Figure S30. ^{13}C NMR spectrum of **2j**, related to **Table 3**.

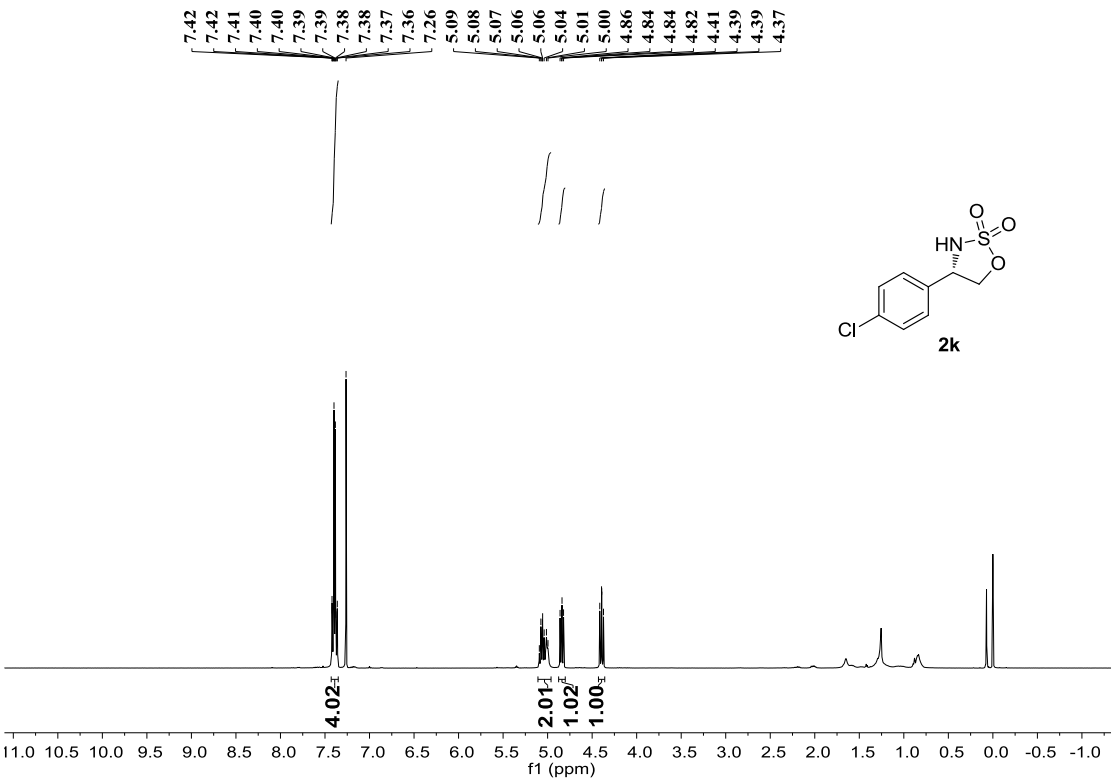


Figure S31. [1]H NMR spectrum of **2k**, related to **Table 3**.

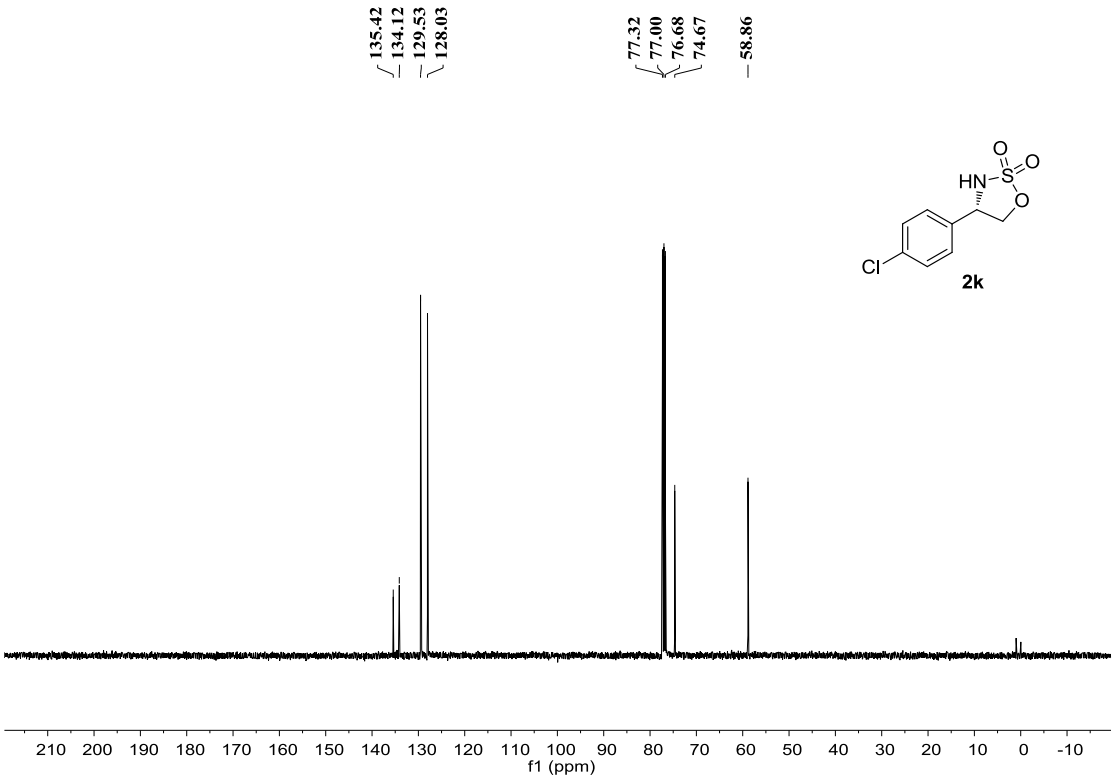


Figure S32. [13]C NMR spectrum of **2k**, related to **Table 3**.

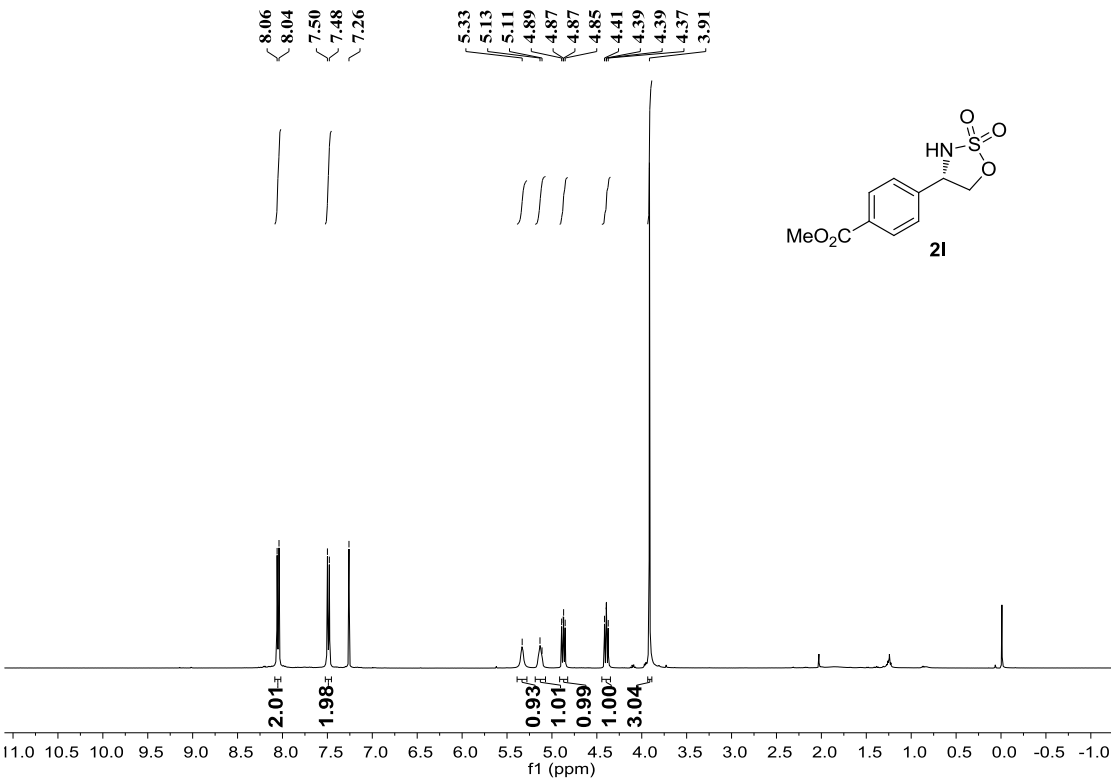


Figure S33. [1]H NMR spectrum of **2l**, related to **Table 3**.

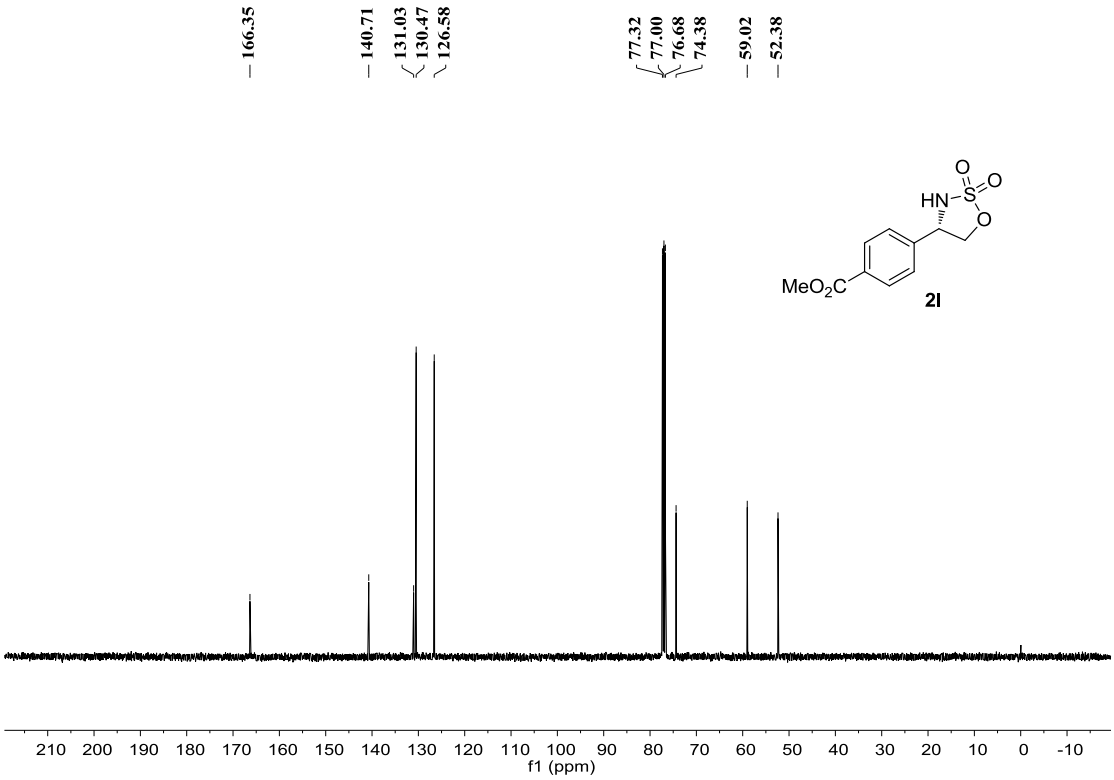


Figure S34. [13]C NMR spectrum of **2l**, related to **Table 3**.

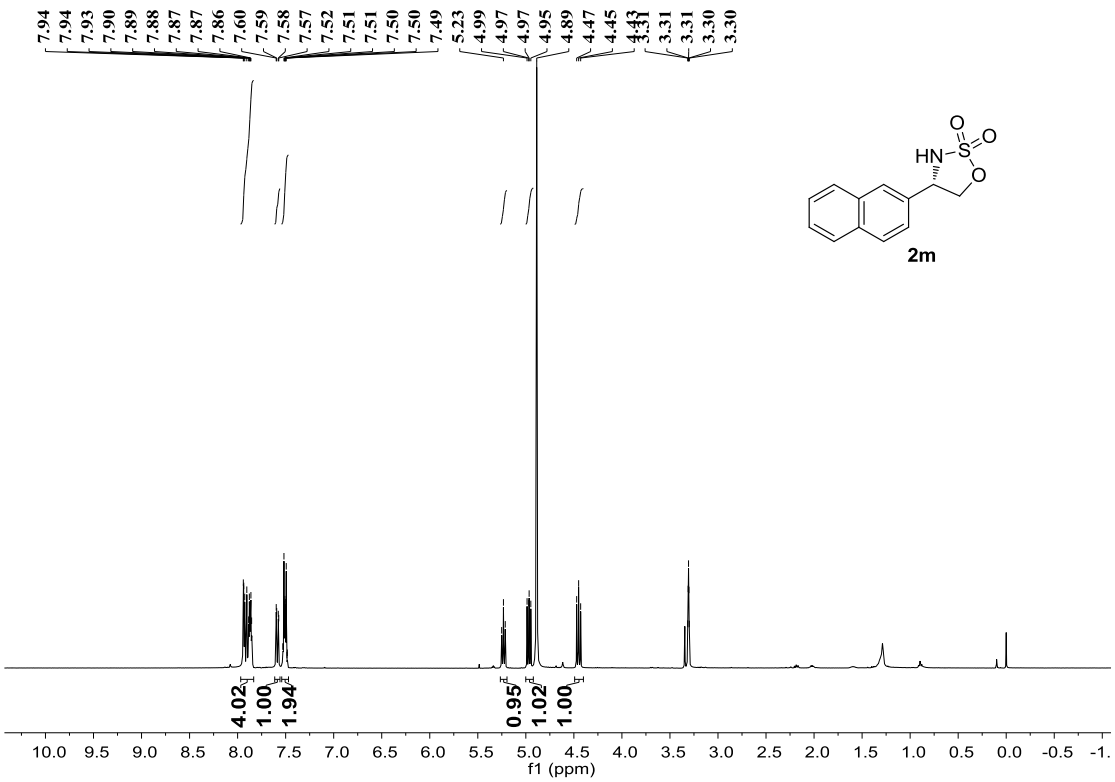


Figure S35. [1]H NMR spectrum of **2m**, related to **Table 3**.

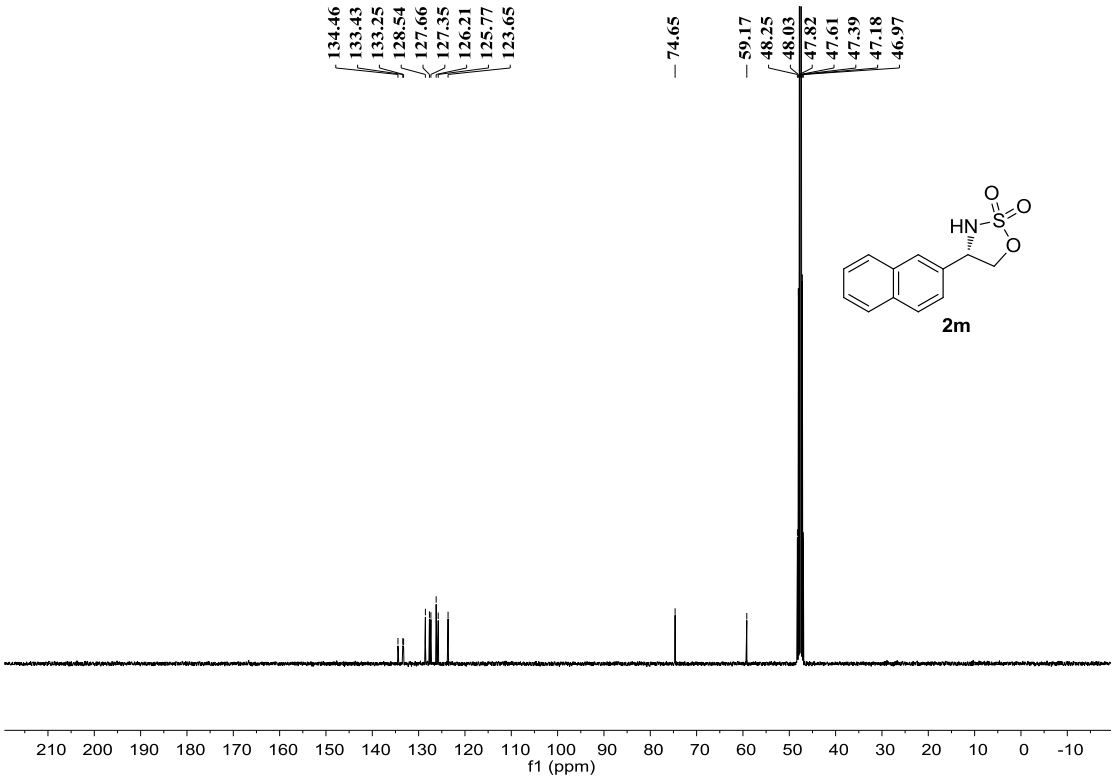


Figure S36. [13]C NMR spectrum of **2m**, related to **Table 3**.

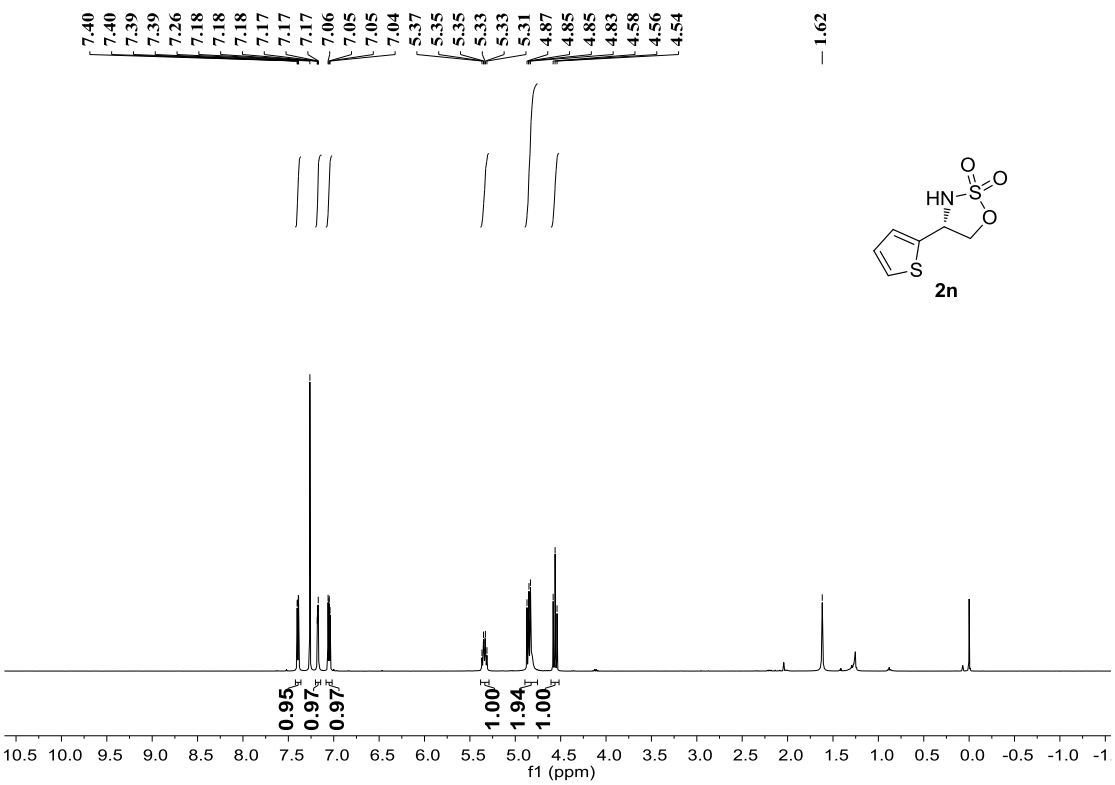


Figure S37. [1]H NMR spectrum of **2n**, related to **Table 3**.

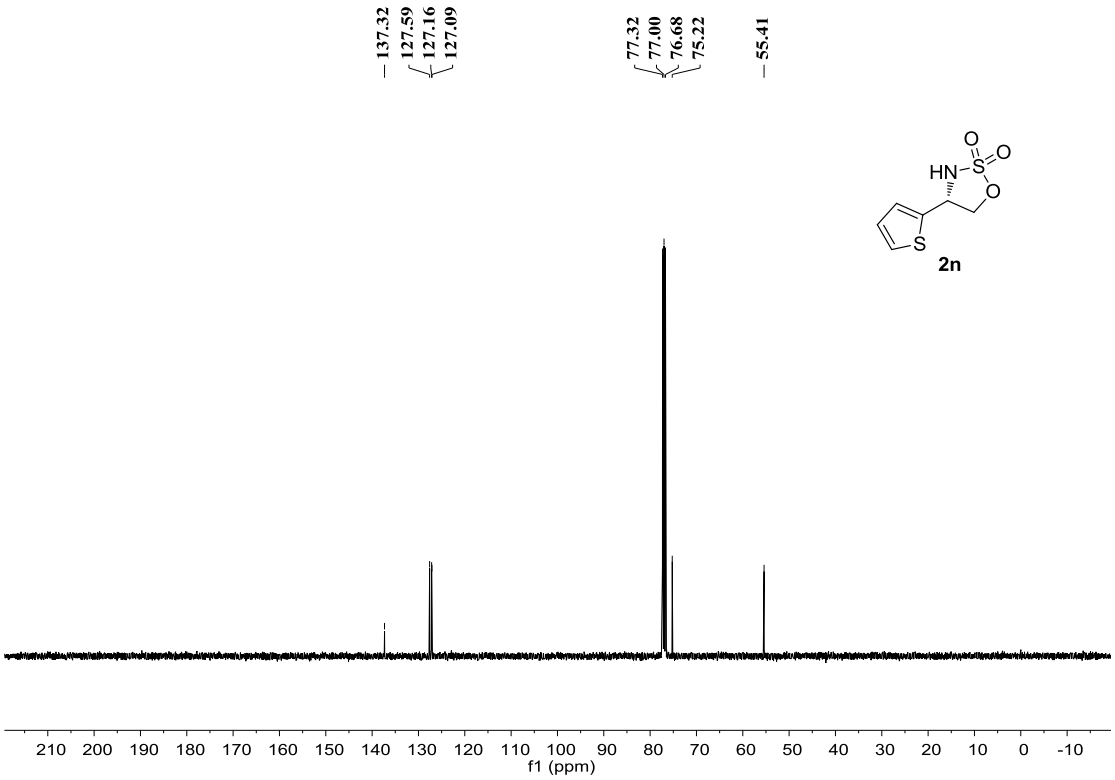


Figure S38. [13]C NMR spectrum of **2n**, related to **Table 3**.

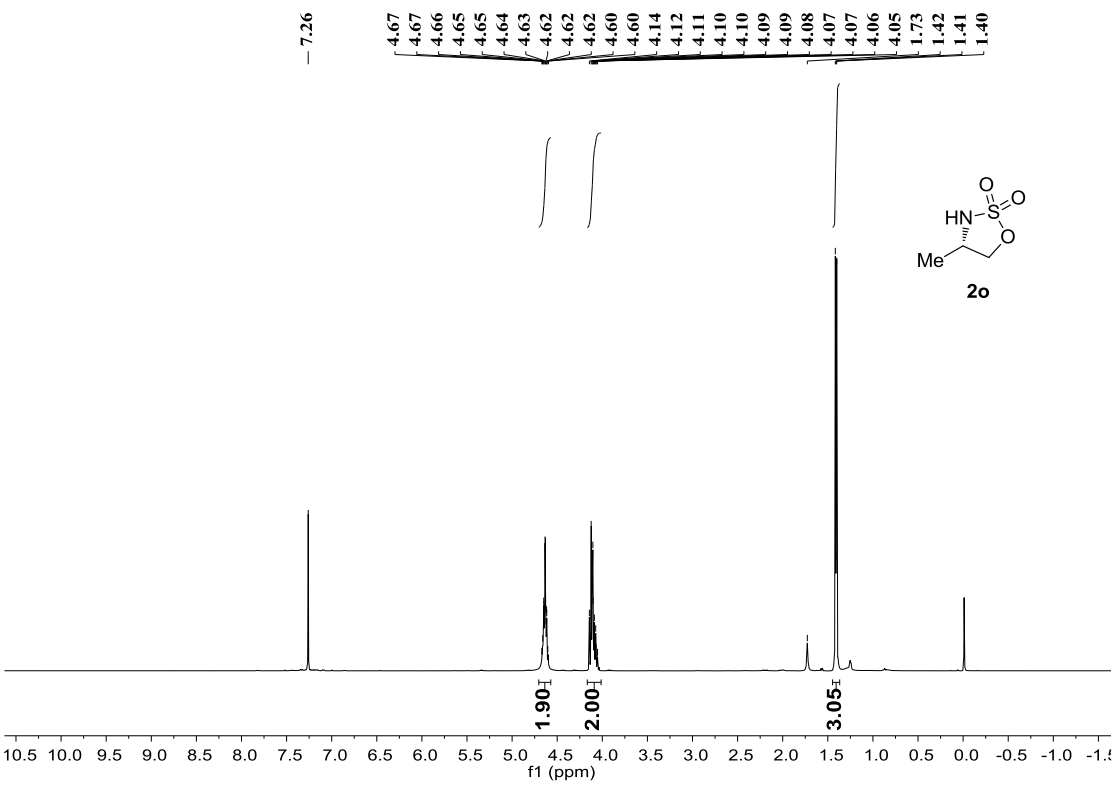


Figure S39. ^{1}H NMR spectrum of **2o**, related to **Table 3**.

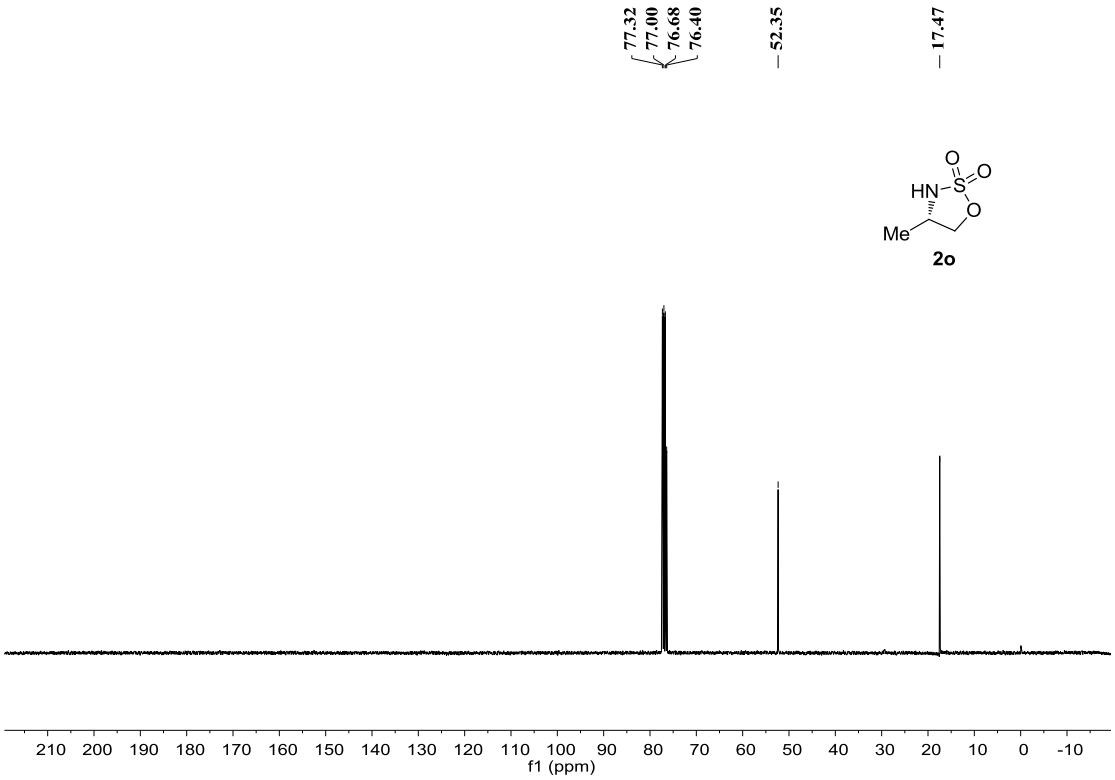


Figure S40. ^{13}C NMR spectrum of **2o**, related to **Table 3**.

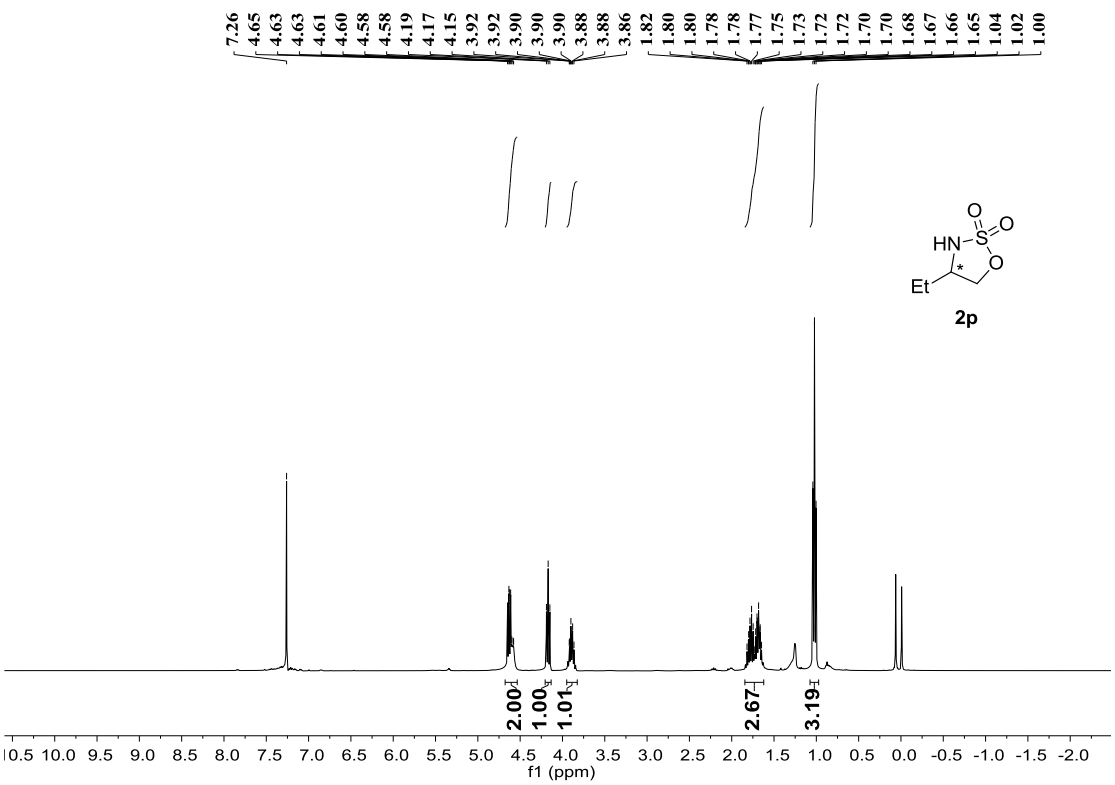


Figure S41. [1]H NMR spectrum of **2p**, related to **Table 3**.

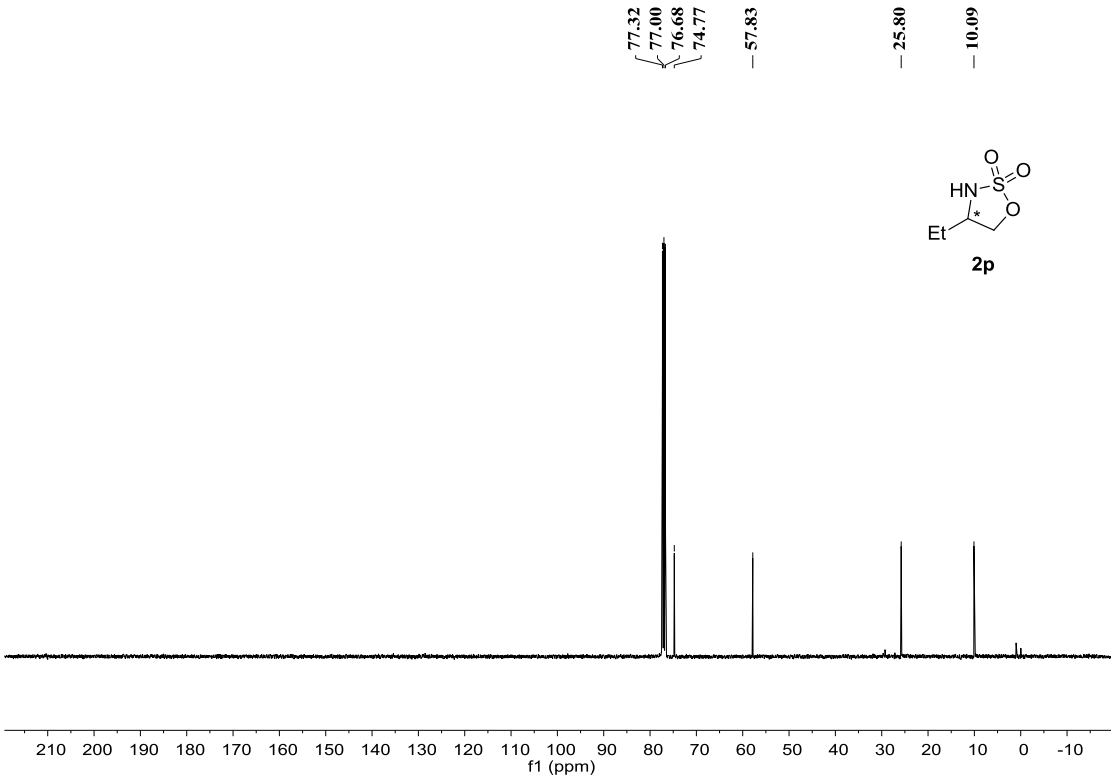


Figure S42. [13]C NMR spectrum of **2p**, related to **Table 3**.

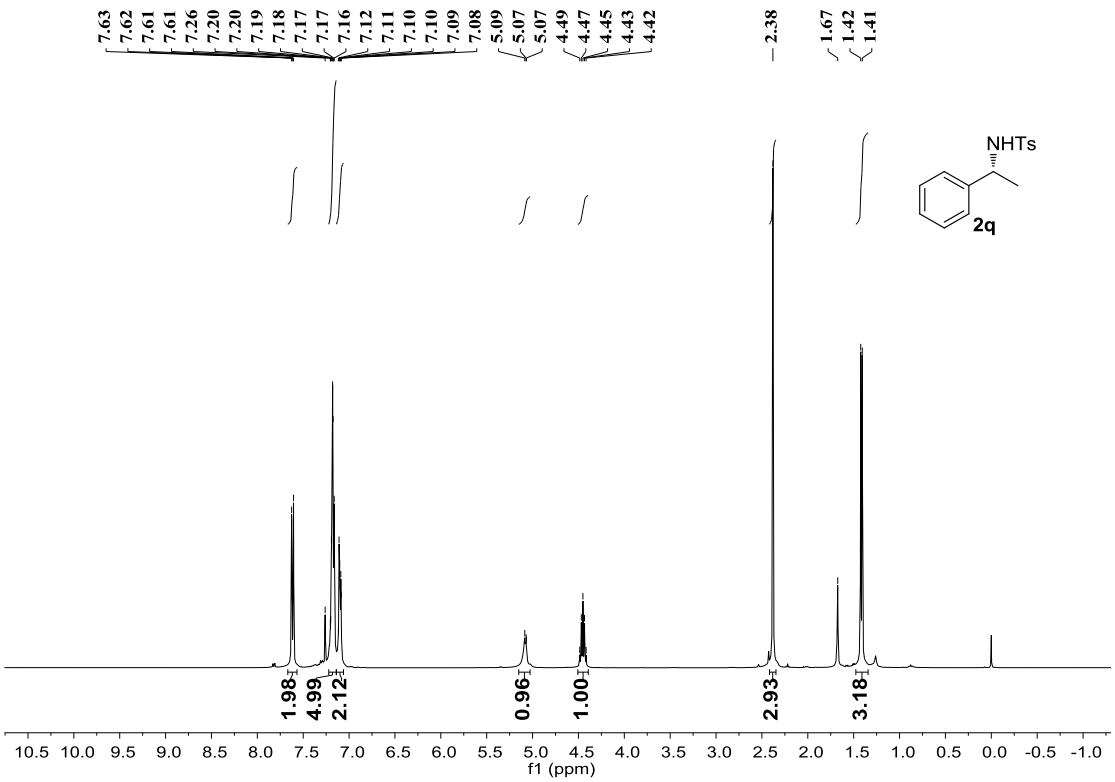


Figure S43. [1]H NMR spectrum of **2q**, related to **Scheme 2**.

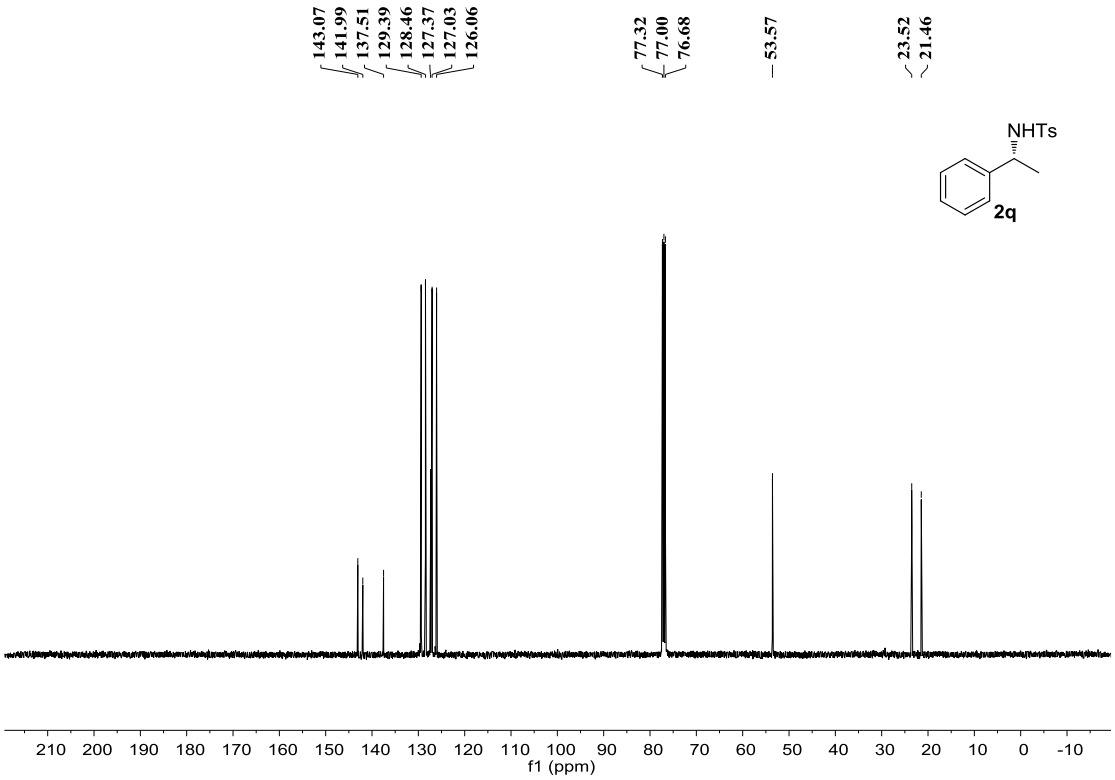


Figure S44. [13]C NMR spectrum of **2q**, related to **Scheme 2**.

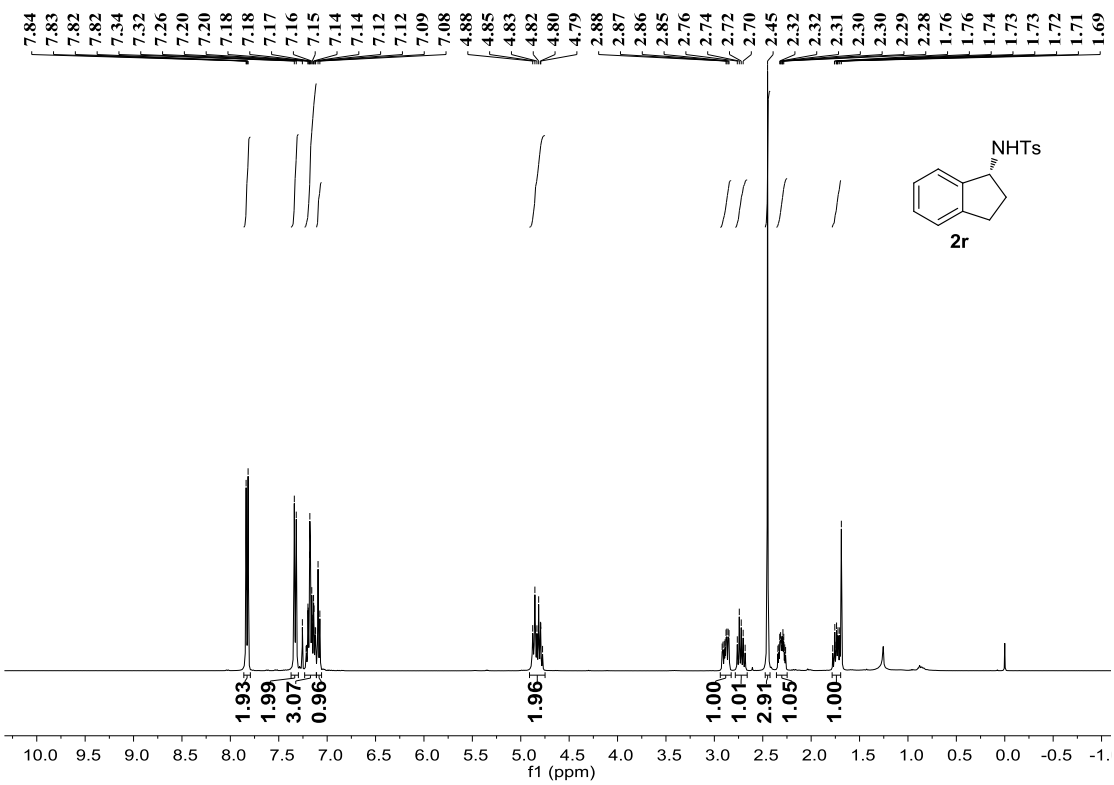


Figure S45. [1]H NMR spectrum of **2r**, related to **Scheme 2**.

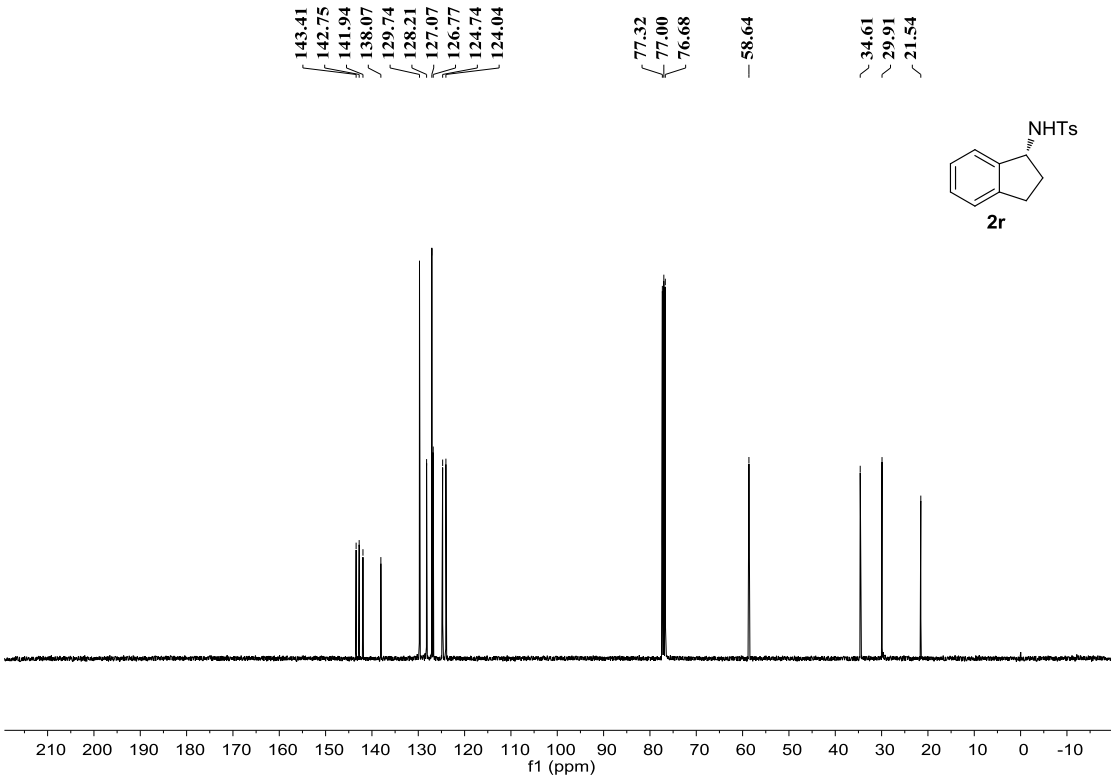


Figure S46. [13]C NMR spectrum of **2r**, related to **Scheme 2**.

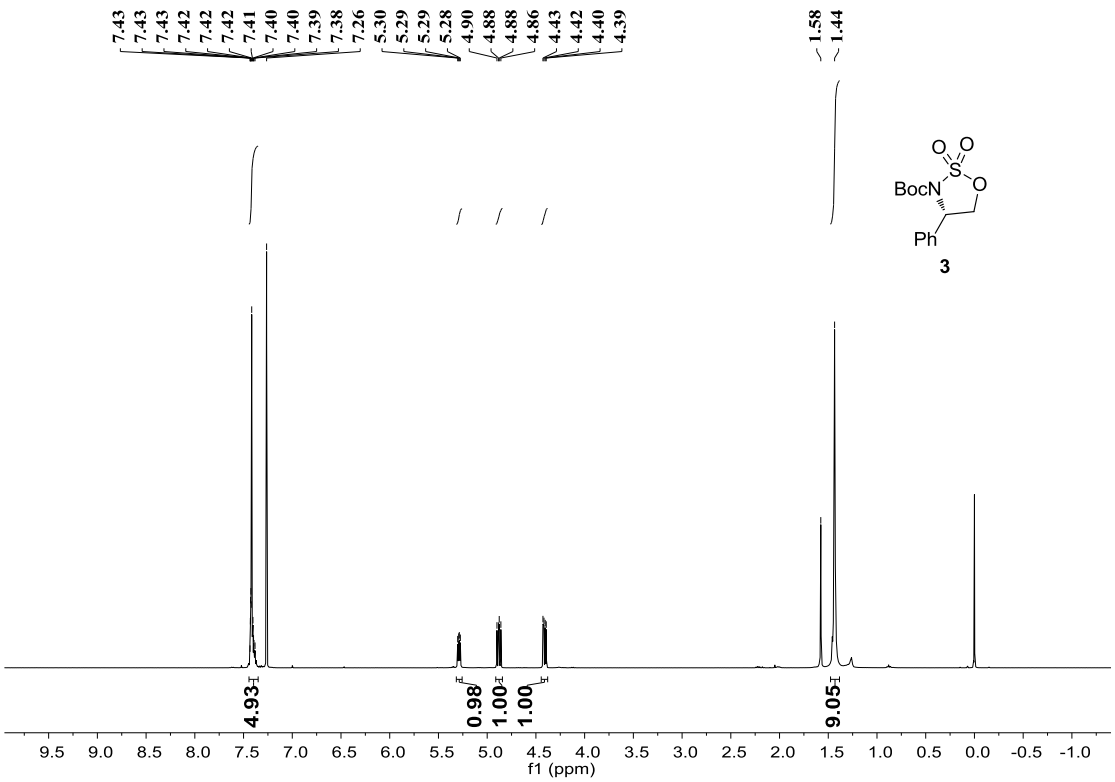


Figure S47. [1]H NMR spectrum of **3**, related to **Scheme 4**.

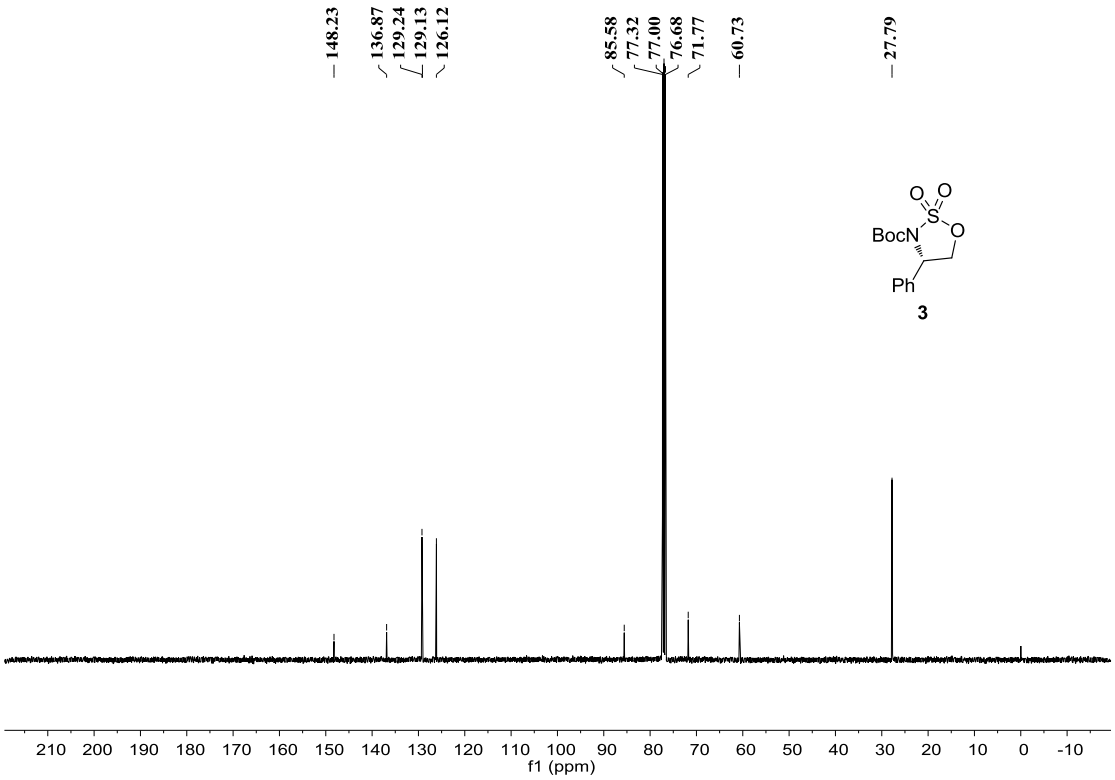


Figure S48. [13]C NMR spectrum of **3**, related to **Scheme 4**.

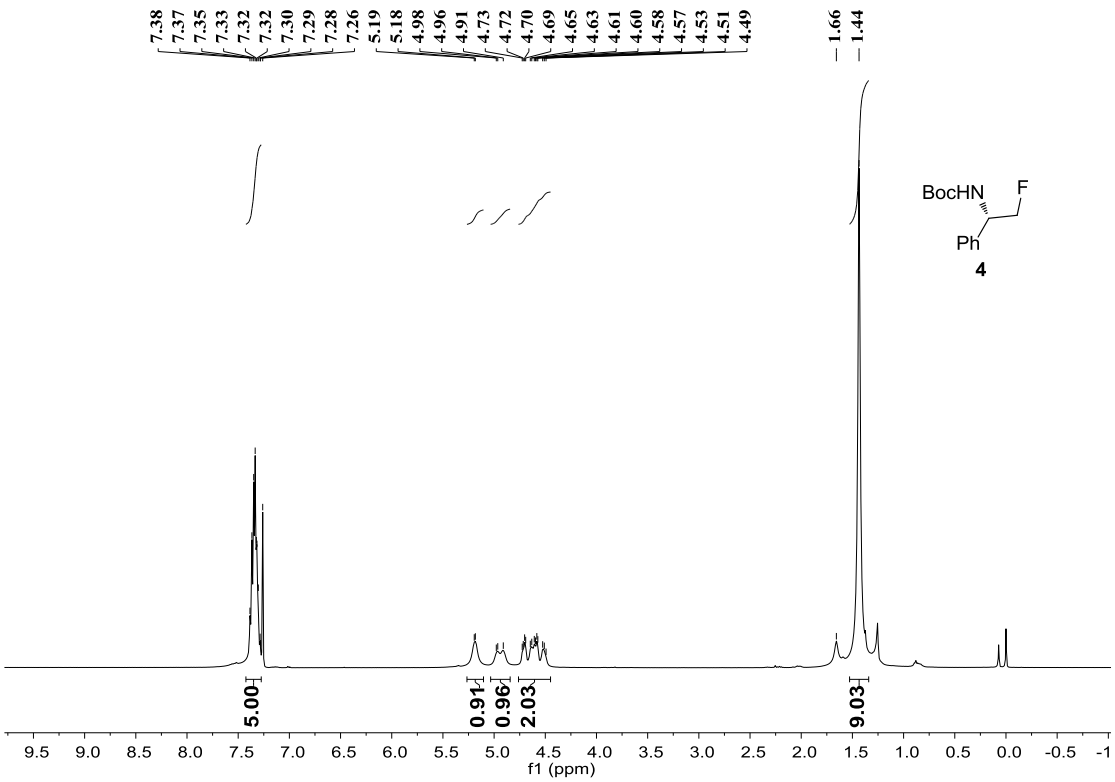


Figure S49. ^{1}H NMR spectrum of **4**, related to **Scheme 4**.

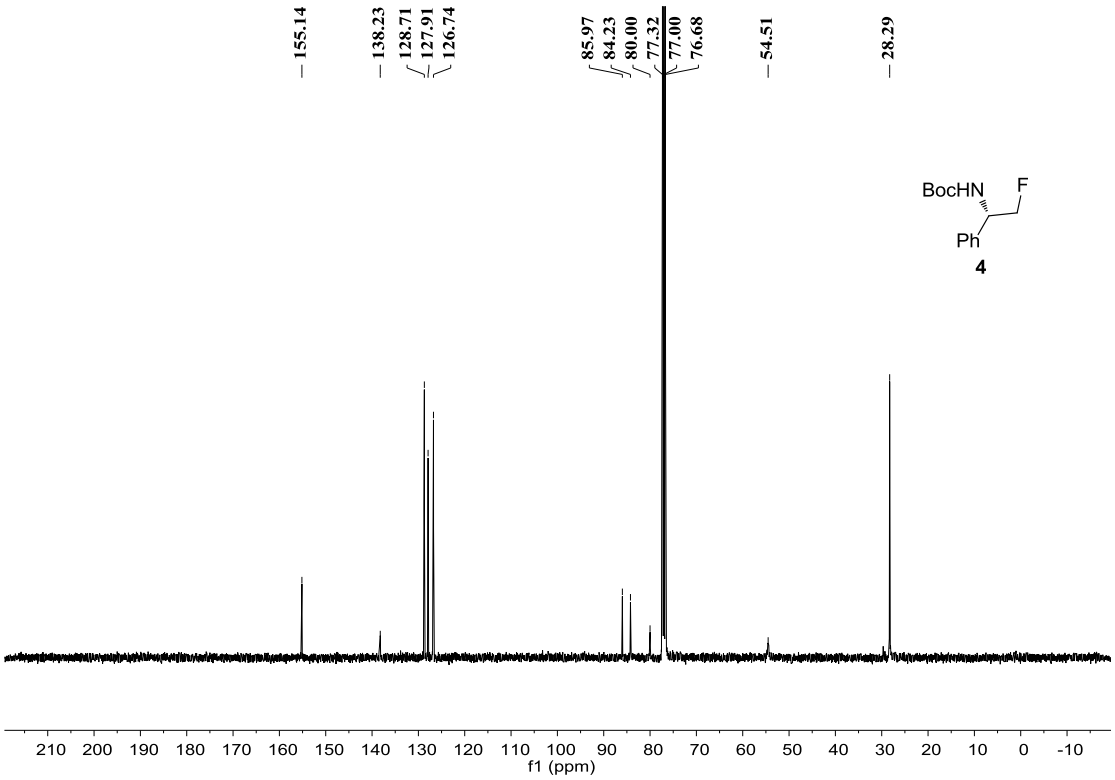


Figure S50. ^{13}C NMR spectrum of **4**, related to **Scheme 4**.

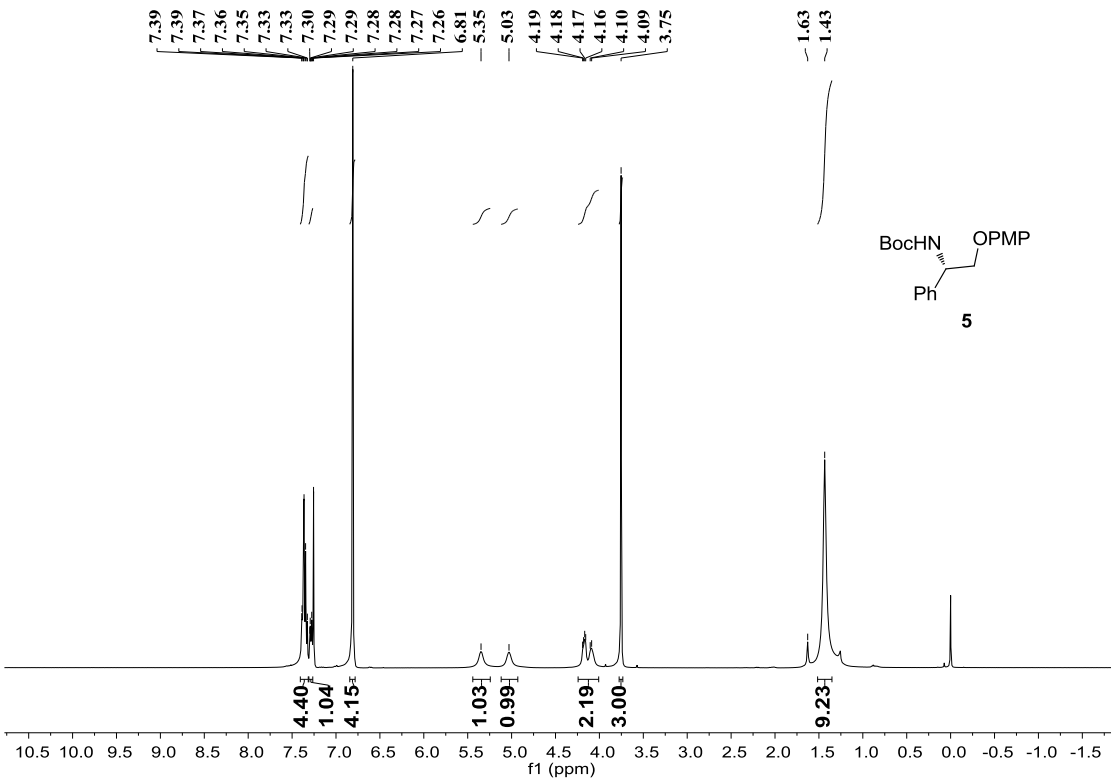


Figure S51. ^{1}H NMR spectrum of **5**, related to **Scheme 4**.

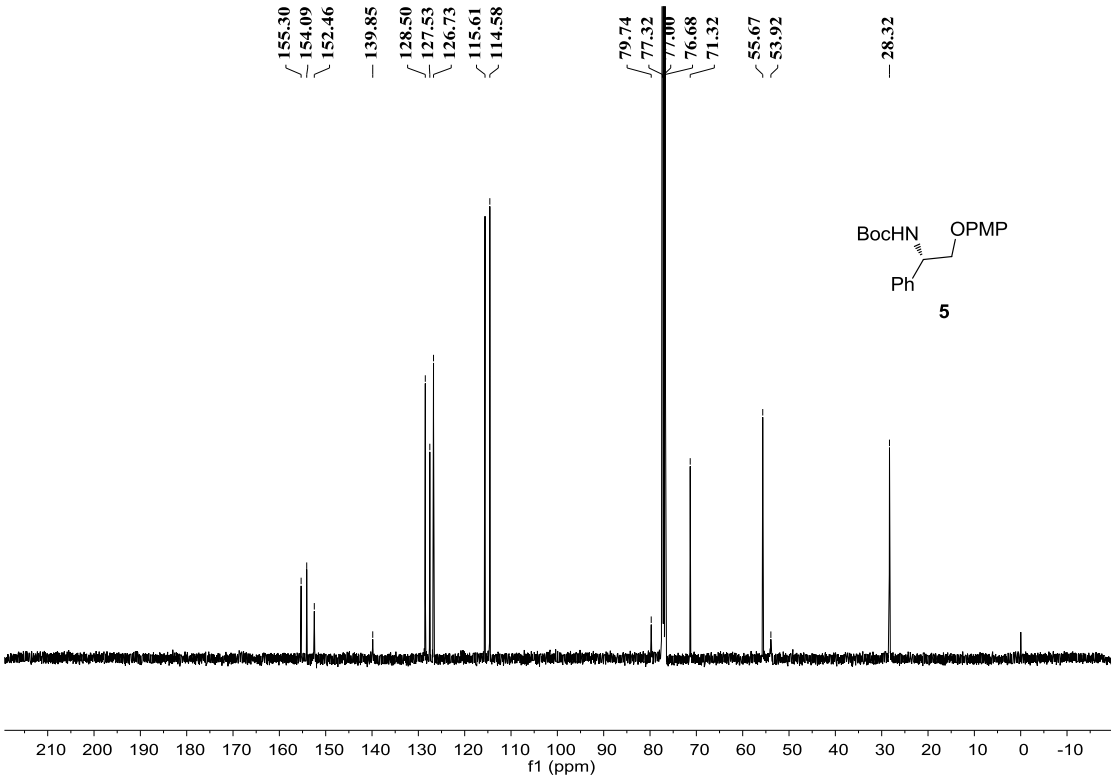


Figure S52. ^{13}C NMR spectrum of **5**, related to **Scheme 4**.

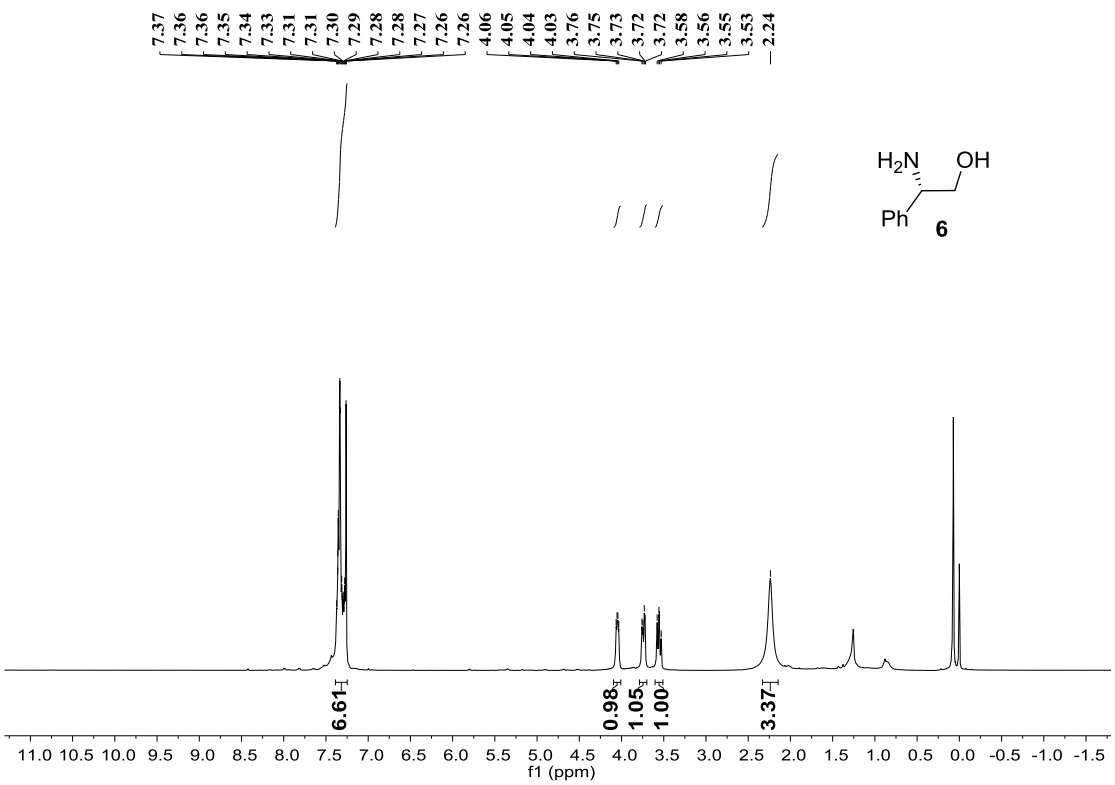


Figure S53. ^{1}H NMR spectrum of **6**, related to **Scheme 4**.

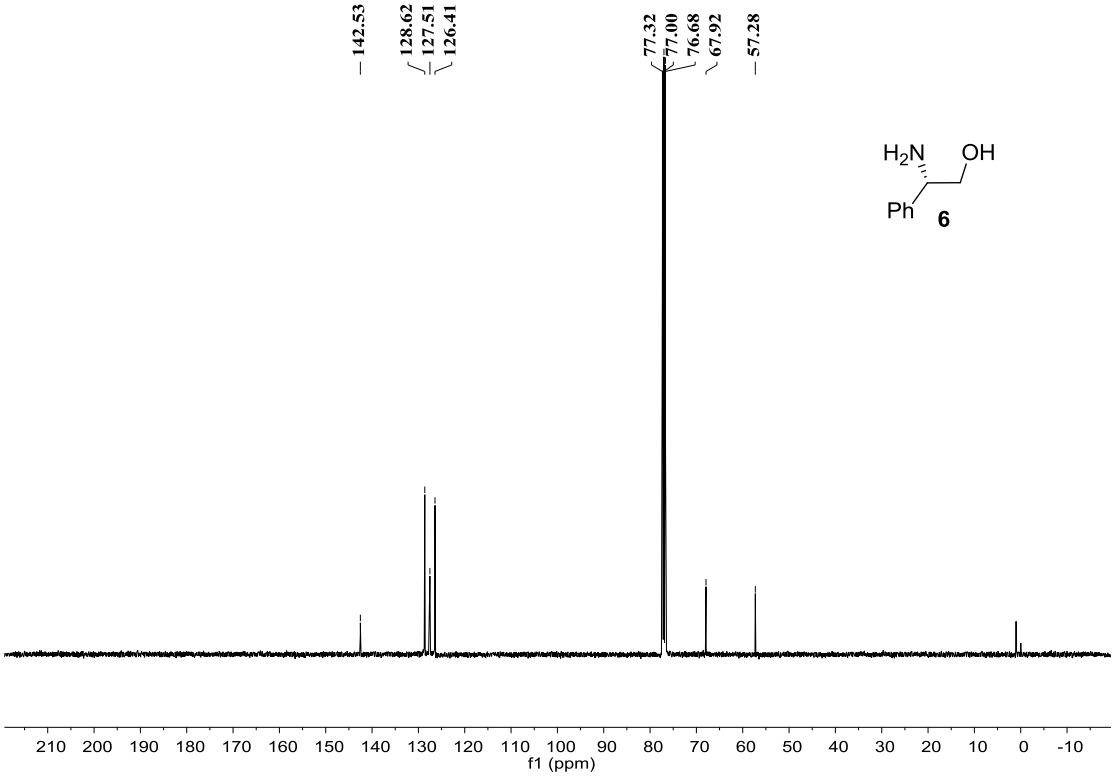


Figure S54. ^{13}C NMR spectrum of **6**, related to **Scheme 4**.

Supplemental Figures for ^{1}H spectra of deuterium labeling studies

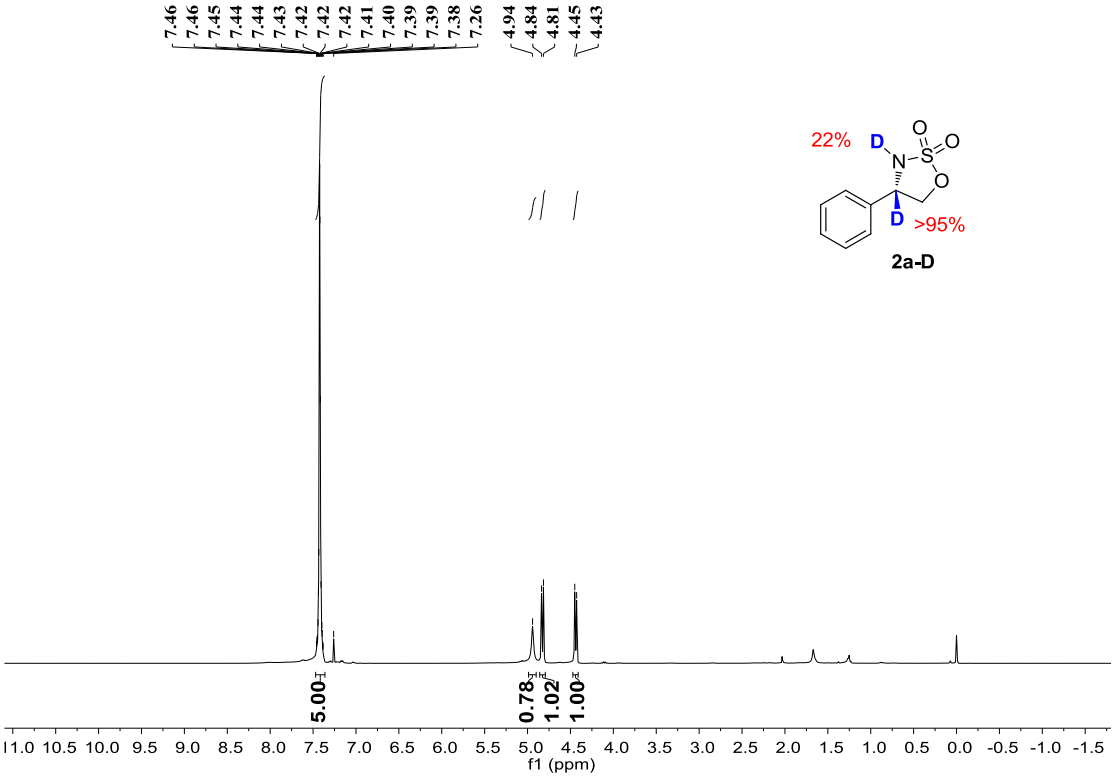


Figure S55. ^{1}H NMR spectrum of **2a-D**, related to **Scheme 5**.

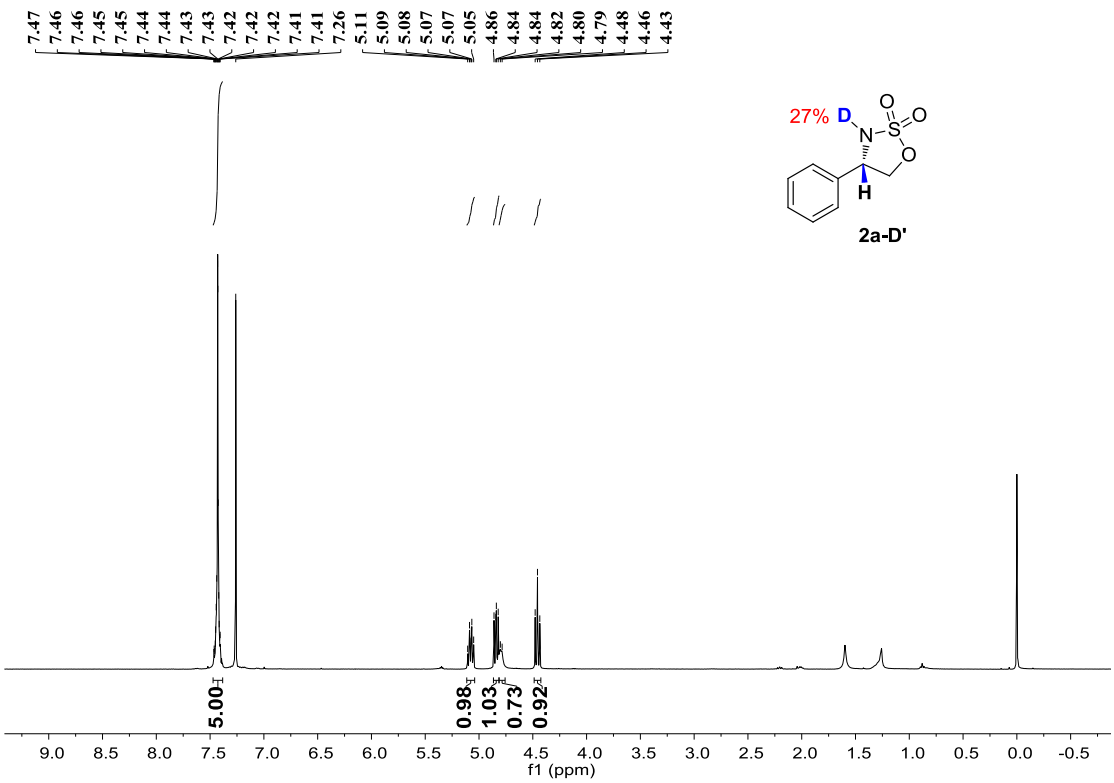


Figure S56. ^{1}H NMR spectrum of **2a-D'**, related to **Scheme 5**.

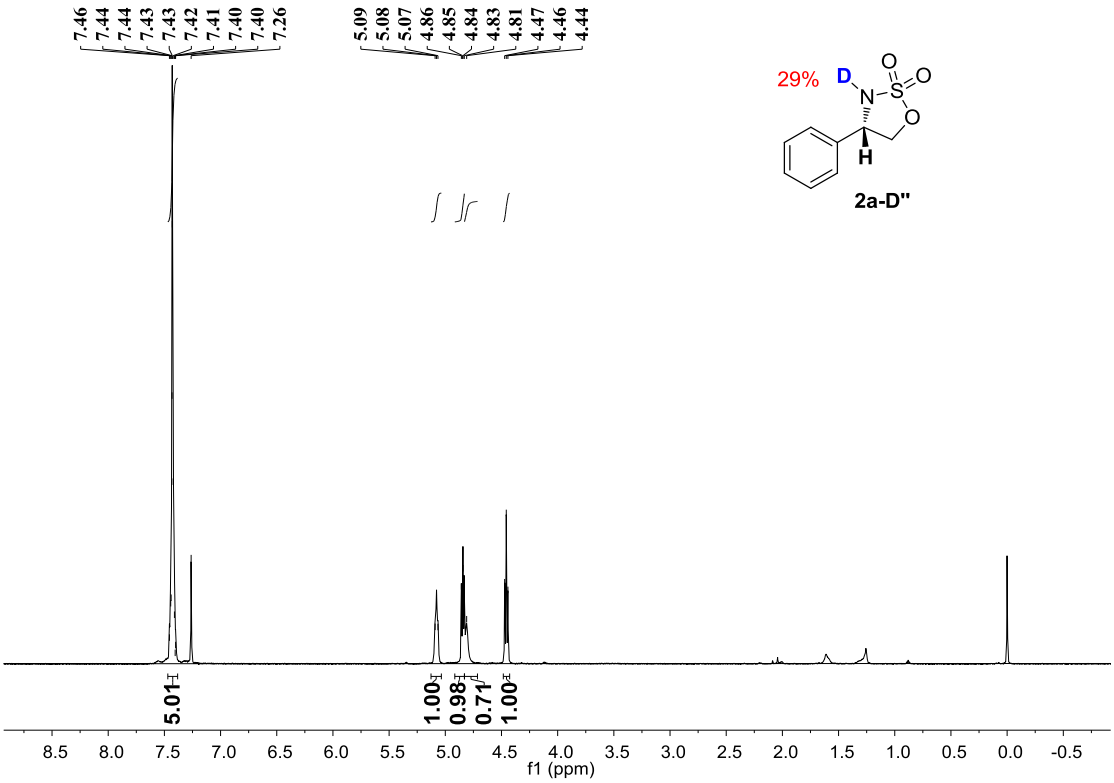
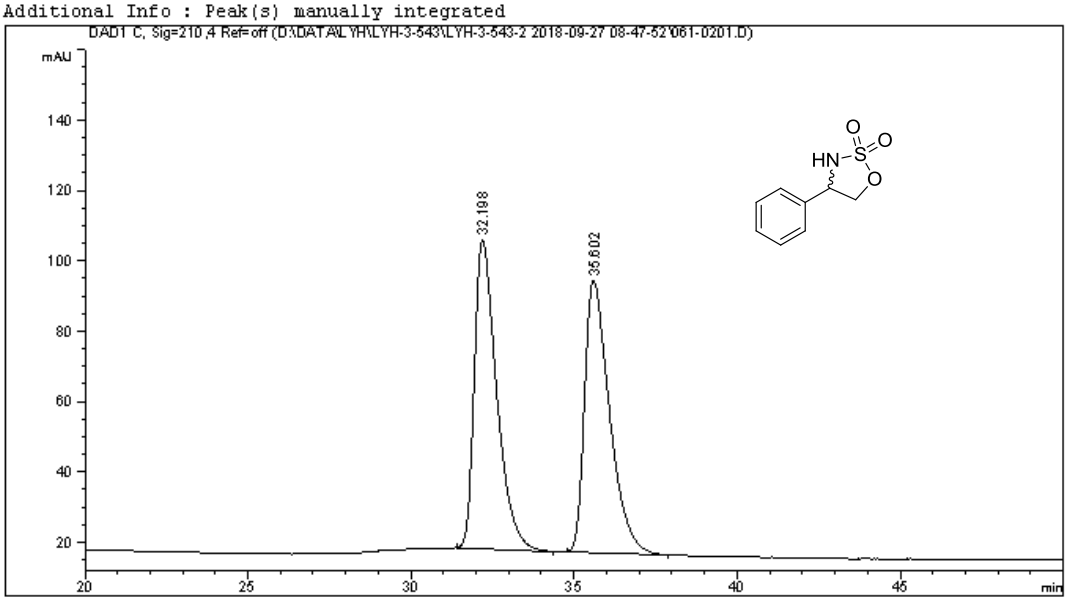


Figure S57. ^{1}H NMR spectrum of **2a-D''**, related to **Scheme 5**.

Supplemental Figures for HPLC and GC spectra

Data File D:\DATA\LYH\LYH-3-543\LYH-3-543-2 2018-09-27 08-47-52\061-0201.D
Sample Name: LYH-3-543-RAC

Acq. Operator	:	Seq. Line	: 2
Acq. Instrument	: Instrument 2	Location	: Vial 61
Injection Date	: 9/27/2018 9:01:28 AM	Inj	: 1
		Inj Volume	: 10.000 µl
Acq. Method	: D:\DATA\LYH\LYH-3-543\LYH-3-543-2 2018-09-27 08-47-52\DAD-0J(1-6)-80-20-1ML-10UL-ALL-60MIN.M		
Last changed	: 9/26/2018 10:04:39 PM		
Analysis Method	: D:\METHOD\GUAN YUQING\LONGJIAO\DAD-0D(1-2)-90-10-1ML-5UL-ALL-20MIN.M		
Last changed	: 12/25/2018 10:30:22 PM (modified after loading)		
Additional Info	: Peak(s) manually integrated		



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

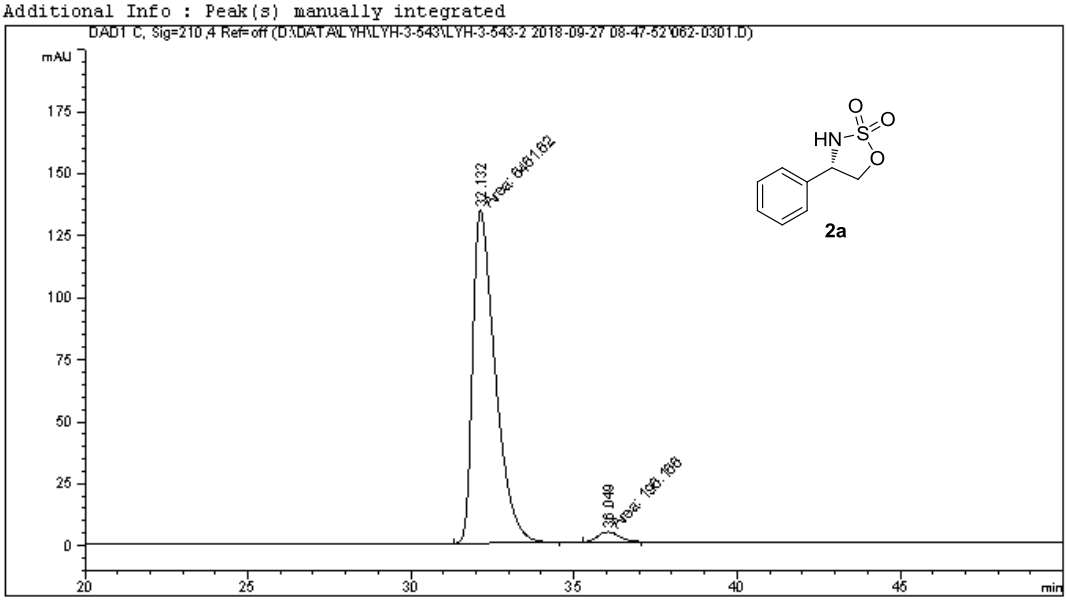
Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.198	BB	0.7109	4172.94092	87.74211	50.3033
2	35.602	BB	0.7859	4122.62061	77.33921	49.6967
Totals :				8295.56152	165.08132	

Figure S58. HPLC spectrum of racemic-**2a**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-543\LYH-3-543-2 2018-09-27 08-47-52\062-0301.D
Sample Name: LYH-3-543

```
======================================================================
Acq. Operator   :                               Seq. Line :   3
Acq. Instrument : Instrument 2                   Location : Vial 62
Injection Date  : 9/27/2018 10:02:33 AM               Inj :   1
                                                Inj Volume : 1.000 µl
Acq. Method     : D:\DATA\LYH\LYH-3-543\LYH-3-543-2 2018-09-27 08-47-52\DAD-0J(1-6)-80-20-1ML
                  -1UL-ALL-70MIN.M
Last changed    : 5/26/2018 10:41:19 AM
Analysis Method : D:\METHOD\GUAN YUQING\LONGJIAO\DAD-0D(1-2)-90-10-1ML-5UL-ALL-20MIN.M
Last changed    : 12/25/2018 10:32:32 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

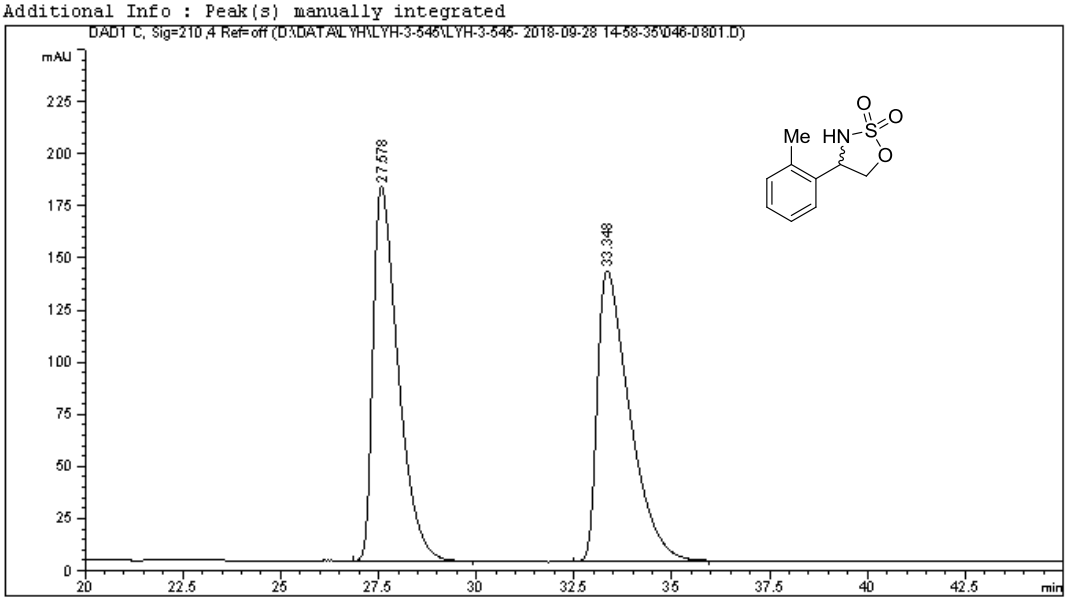



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  32.132 MM    0.8022 6461.62354  134.24660  97.0536
   2  36.049 MM    0.7759  196.16588    4.21382   2.9464

Totals :                  6657.78941  138.46042
```


Figure S59. HPLC spectrum of **2a**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\046-0801.D
Sample Name: LYH-3-545--3-RAC

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :   8
    Acq. Instrument : Instrument 2                    Location : Vial 46
    Injection Date  : 9/28/2018 7:11:16 PM                 Inj :   1
                                                     Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\DAD-0J(1-6)-80-20-1ML-
                      1UL-ALL-45MIN.M
    Last changed    : 5/26/2018 10:39:50 AM
    Analysis Method : D:\METHOD\GUAN YUQING\LONGJIAO\DAD-0D(1-2)-90-10-1ML-5UL-ALL-20MIN.M
    Last changed    : 12/25/2018 10:50:54 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

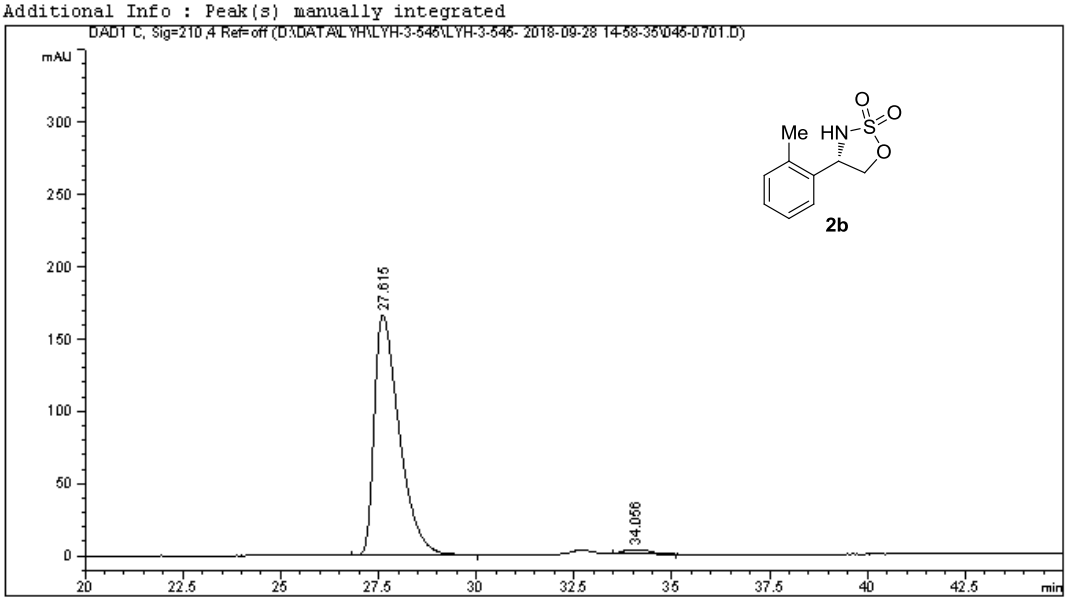



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  27.578 BB    0.6569 7998.21191  179.82443  49.9757
       2  33.348 BB    0.8326 8005.98926  139.69931  50.0243

    Totals :                  1.60042e4   319.52374
```


Figure S60. HPLC spectrum of racemic-**2b**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\045-0701.D
Sample Name: LYH-3-545-3-0-ME

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :   7
    Acq. Instrument : Instrument 2                    Location : Vial 45
    Injection Date  : 9/28/2018 6:25:19 PM                 Inj :   1
                                                     Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\DAD-0J(1-6)-80-20-1ML-
                      1UL-ALL-45MIN.M
    Last changed    : 5/26/2018 10:39:50 AM
    Analysis Method : D:\METHOD\GUAN YUQING\LONGJIAO\DAD-0D(1-2)-90-10-1ML-5UL-ALL-20MIN.M
    Last changed    : 12/25/2018 10:54:34 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

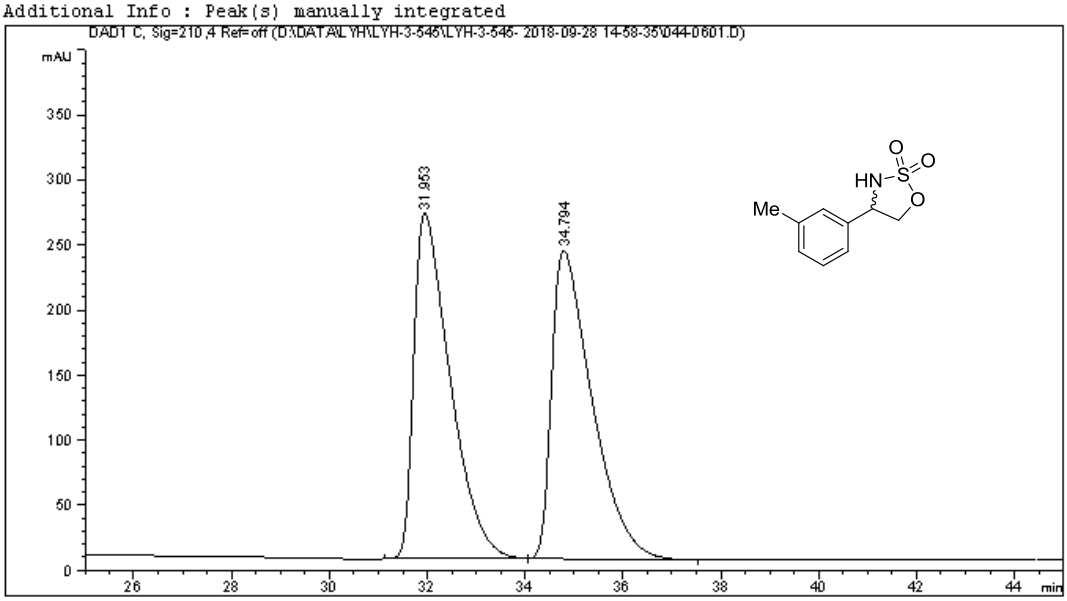



```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]        %
    ----|-------|----|-------|----------|----------|--------|
       1  27.615 BB    0.6558 7379.36572  166.28188  98.1909
       2  34.056 BB    0.5418  135.95619    2.99401   1.8091

    Totals :                  7515.32191  169.27588
```


Figure S61. HPLC spectrum of **2b**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\044-0601.D
Sample Name: LYH-3-545-2-RAC

```
======================================================================
Acq. Operator   :                                Seq. Line :   6
Acq. Instrument : Instrument 2                    Location : Vial 44
Injection Date  : 9/28/2018 5:39:20 PM                 Inj :   1
                                                 Inj Volume : 1.000 µl
Acq. Method     : D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\DAD-0J(1-6)-80-20-1ML-
                  1UL-ALL-45MIN.M
Last changed    : 5/26/2018 10:39:50 AM
Analysis Method : D:\METHOD\GUAN YUQING\LONGJIAO\DAD-0D(1-2)-90-10-1ML-5UL-ALL-20MIN.M
Last changed    : 12/25/2018 10:45:43 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

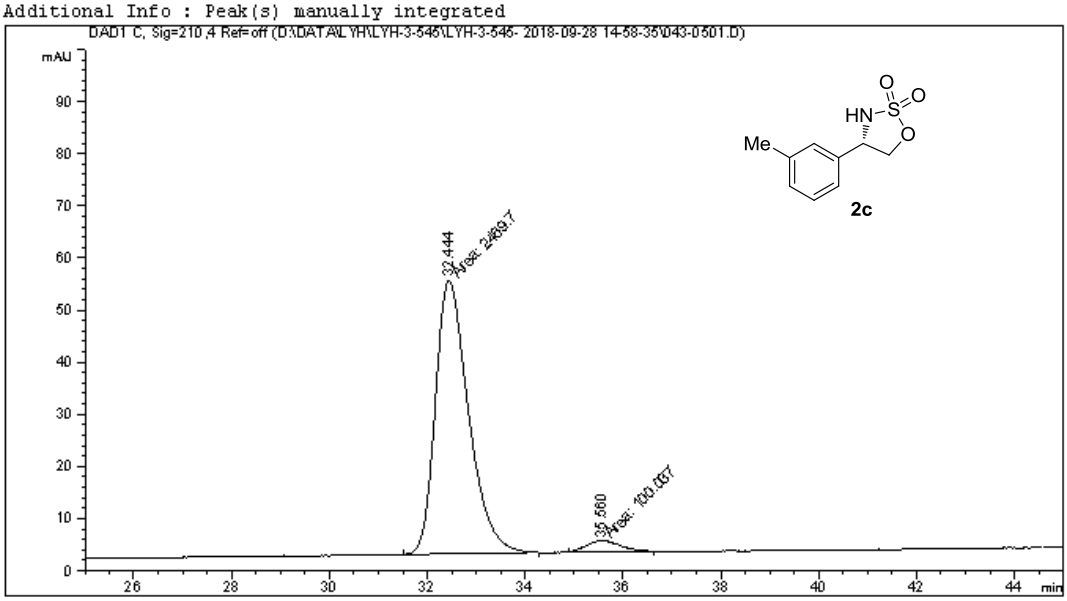



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  31.953 BB    0.7594 1.36279e4   265.23636  50.1177
   2  34.794 BB    0.8267 1.35639e4   236.64755  49.8823

Totals :                  2.71917e4   501.88391
```


Figure S62. HPLC spectrum of racemic-**2c**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\043-0501.D
Sample Name: LYH-3-545-2-M-ME

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :   5
    Acq. Instrument : Instrument 2                    Location : Vial 43
    Injection Date  : 9/28/2018 4:53:25 PM                 Inj :   1
                                                     Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\DAD-0J(1-6)-80-20-1ML-
                      1UL-ALL-45MIN.M
    Last changed    : 5/26/2018 10:39:50 AM
    Analysis Method : D:\METHOD\GUAN YUQING\LONGJIAO\DAD-0D(1-2)-90-10-1ML-5UL-ALL-20MIN.M
    Last changed    : 12/25/2018 10:47:03 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

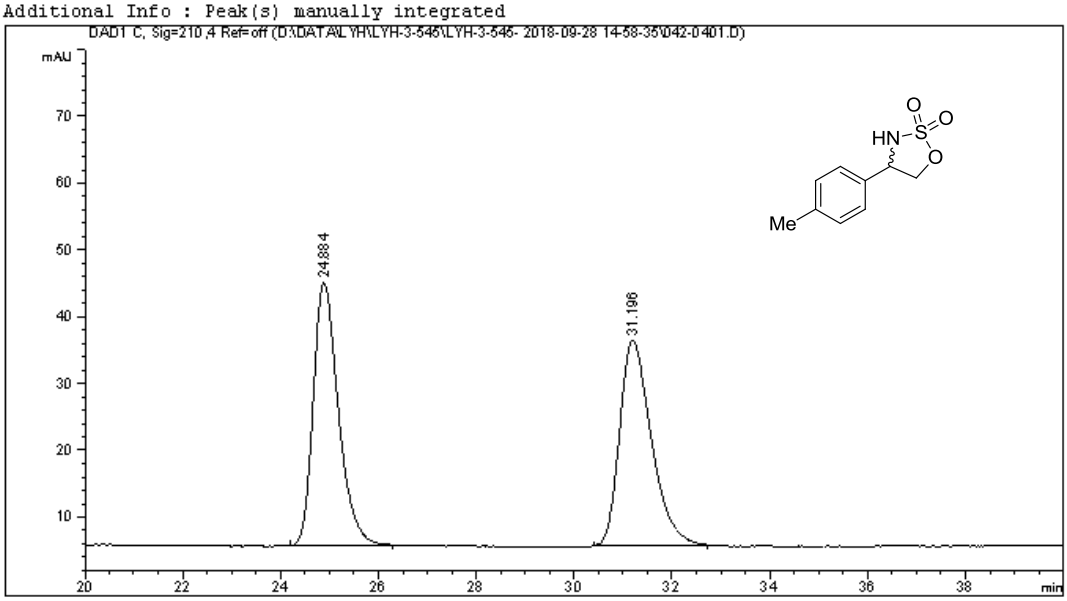



```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  32.444 MM    0.7848 2469.69800   52.45188  96.1071
       2  35.560 MM    0.8008  100.03698    2.08198   3.8929

    Totals :                  2569.73498   54.53386
```


Figure S63. HPLC spectrum of **2c**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\042-0401.D
Sample Name: LYH-3-545-1-RAC

```
======================================================================
Acq. Operator   :                                Seq. Line :   4
Acq. Instrument : Instrument 2                    Location : Vial 42
Injection Date  : 9/28/2018 4:07:29 PM                 Inj :   1
                                                 Inj Volume : 1.000 µl
Acq. Method     : D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\DAD-0J(1-6)-80-20-1ML-
                  1UL-ALL-45MIN.M
Last changed    : 5/26/2018 10:39:50 AM
Analysis Method : D:\METHOD\GUAN YUQING\LONGJIAO\DAD-0D(1-2)-90-10-1ML-5UL-ALL-20MIN.M
Last changed    : 12/25/2018 10:39:31 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

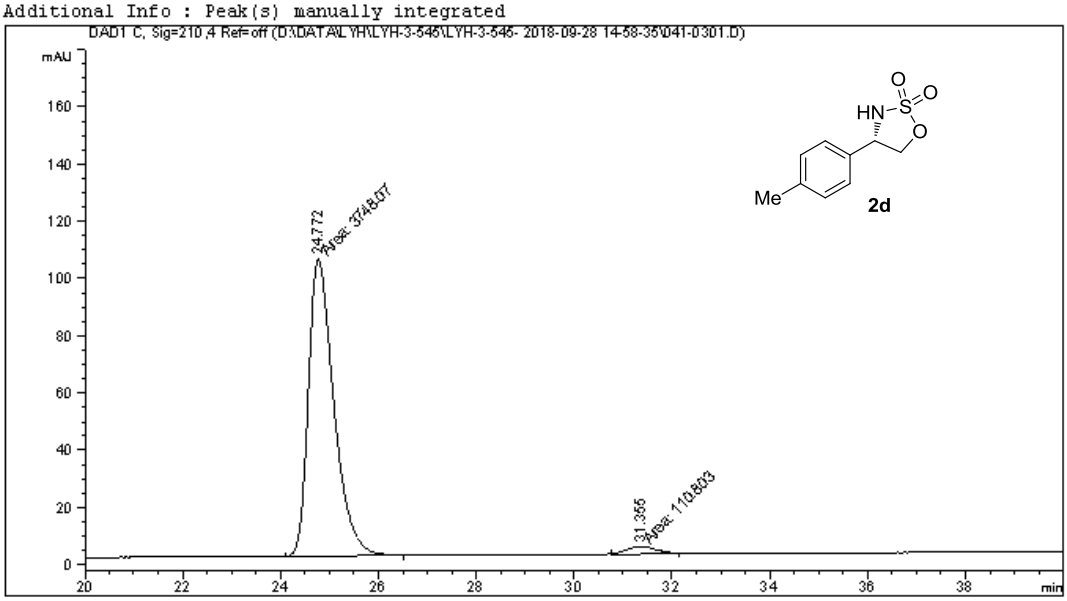



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  24.884 BB    0.5364 1397.81140   39.35040  50.1821
   2  31.196 BB    0.6650 1387.66504   30.83534  49.8179

Totals :                  2785.47644   70.18573
```


Figure S64. HPLC spectrum of racemic-**2d**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\041-0301.D
Sample Name: LYH-3-545-1-P-ME

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :   3
    Acq. Instrument : Instrument 2                    Location : Vial 41
    Injection Date  : 9/28/2018 3:21:34 PM                Inj :   1
                                                     Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\DAD-0J(1-6)-80-20-1ML-
                      1UL-ALL-45MIN.M
    Last changed    : 5/26/2018 10:39:50 AM
    Analysis Method : D:\METHOD\GUAN YUQING\LONGJIAO\DAD-0D(1-2)-90-10-1ML-5UL-ALL-20MIN.M
    Last changed    : 12/25/2018 10:42:02 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

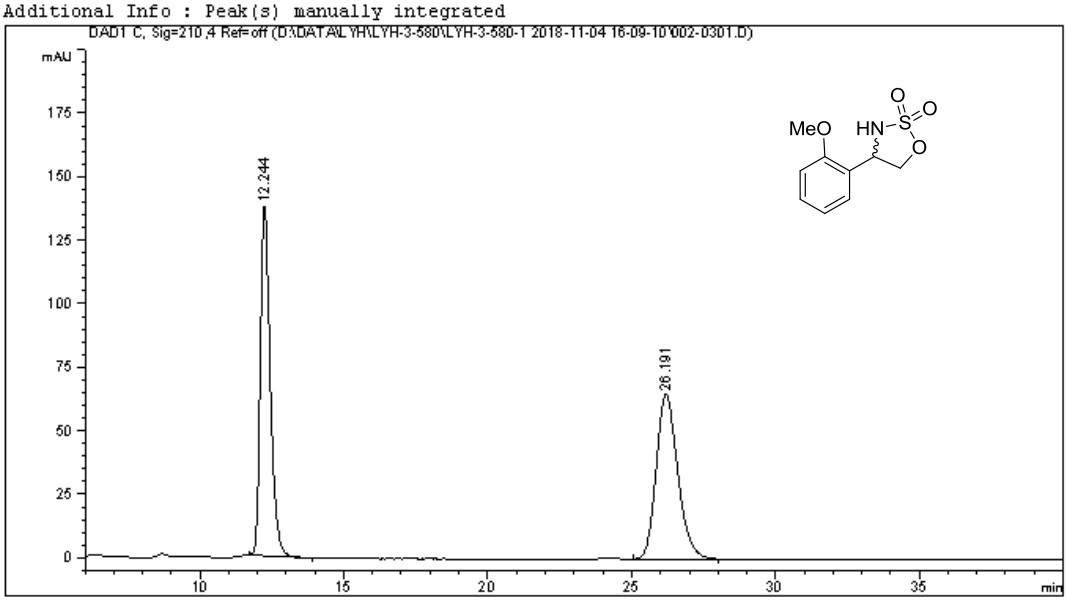



```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]        %
    ----|-------|----|-------|----------|----------|--------|
       1  24.772 MM    0.6011 3748.07056  103.92886  97.1286
       2  31.355 MM    0.7079  110.80266    2.60875   2.8714

    Totals :                  3858.87321  106.53761
```


Figure S65. HPLC spectrum of **2d**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-580\LYH-3-580-1 2018-11-04 16-09-10\002-0301.D
Sample Name: LYH-3-580-1-RAC

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :   3
    Acq. Instrument : Instrument 2                    Location : Vial 2
    Injection Date  : 11/4/2018 5:27:22 PM                 Inj :   1
                                                     Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-580\LYH-3-580-1 2018-11-04 16-09-10\DAD-0D(1-2)-80-20-1ML
                      -1UL-ALL-60MIN.M
    Last changed    : 10/30/2018 4:40:22 PM
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 2:33:33 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

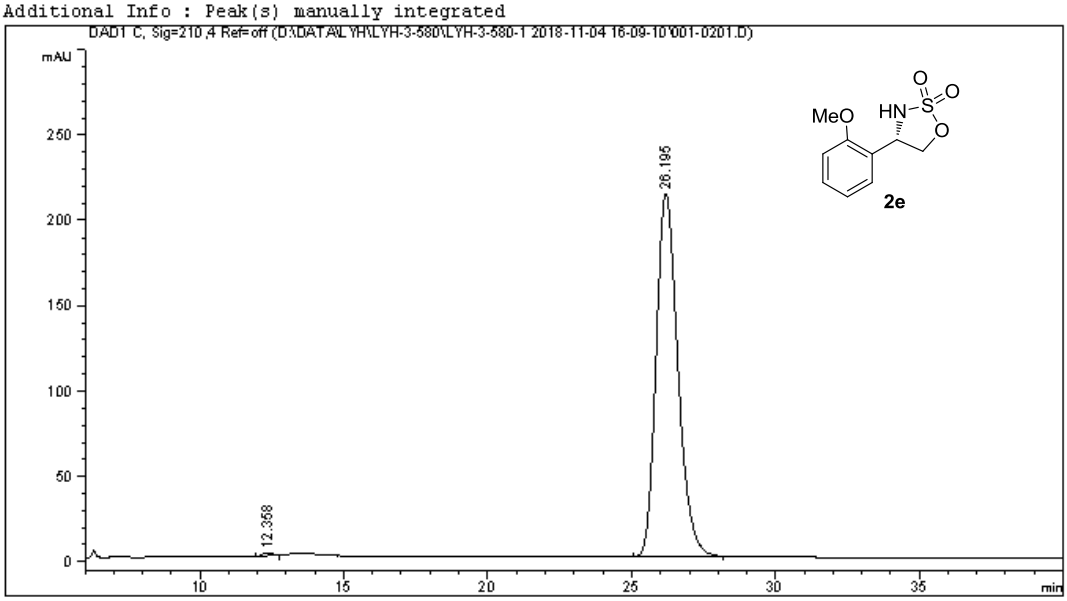



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  12.244 BB    0.3694 3315.74609  137.44514  49.4795
       2  26.191 BB    0.7652 3385.50952   64.83857  50.5205

    Totals :                  6701.25562  202.28371
```


Figure S66. HPLC spectrum of racemic-**2e**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-580\LYH-3-580-1 2018-11-04 16-09-10\001-0201.D
Sample Name: LYH-3-580-1

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :   2
    Acq. Instrument : Instrument 2                    Location : Vial 1
    Injection Date  : 11/4/2018 4:26:30 PM                 Inj :   1
                                                   Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-580\LYH-3-580-1 2018-11-04 16-09-10\DAD-0D(1-2)-80-20-1ML
                      -1UL-ALL-60MIN.M
    Last changed    : 10/30/2018 4:40:22 PM
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 2:36:20 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

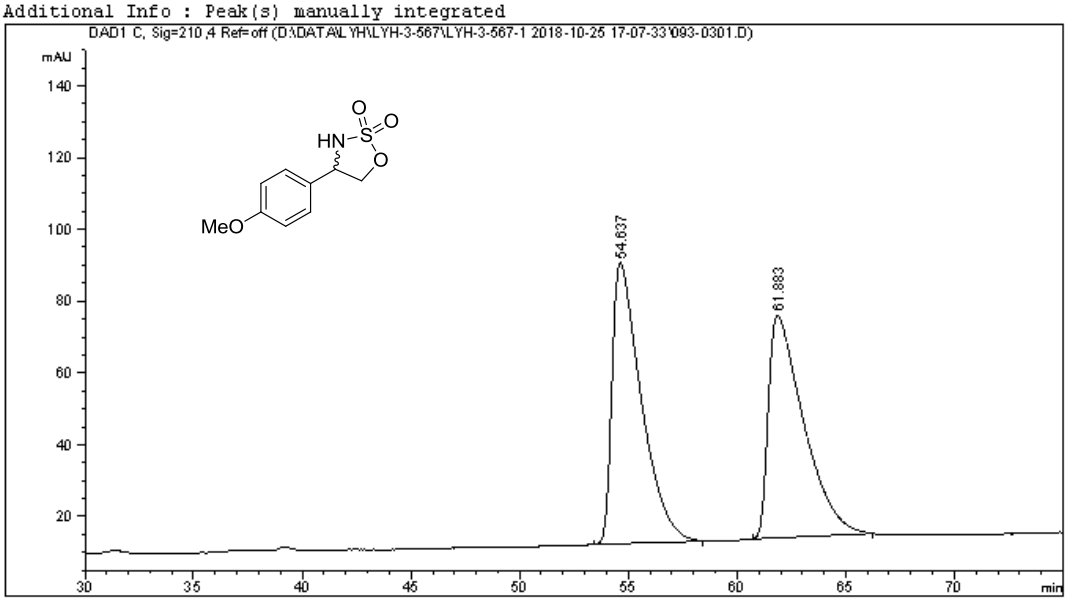



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  12.358 BB    0.2612   37.25900    1.73079   0.3330
       2  26.195 BB    0.8060 1.11507e4   212.57550  99.6670

    Totals :                  1.11880e4   214.30629
```


Figure S67. HPLC spectrum of **2e**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-567\LYH-3-567-1 2018-10-25 17-07-33\093-0301.D
Sample Name: LYH-3-567-1-P-MeO-RAC

```
    ======================================================================
    Acq. Operator   :                               Seq. Line :   3
    Acq. Instrument : Instrument 2                   Location : Vial 93
    Injection Date  : 10/25/2018 6:40:42 PM               Inj :   1
                                                  Inj Volume : 10.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-567\LYH-3-567-1 2018-10-25 17-07-33\DAD-0J(1-6)-80-20-1ML
                      -10UL-ALL-95MIN.M
    Last changed    : 10/25/2018 6:41:21 PM
                      (modified after loading)
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 2:28:43 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

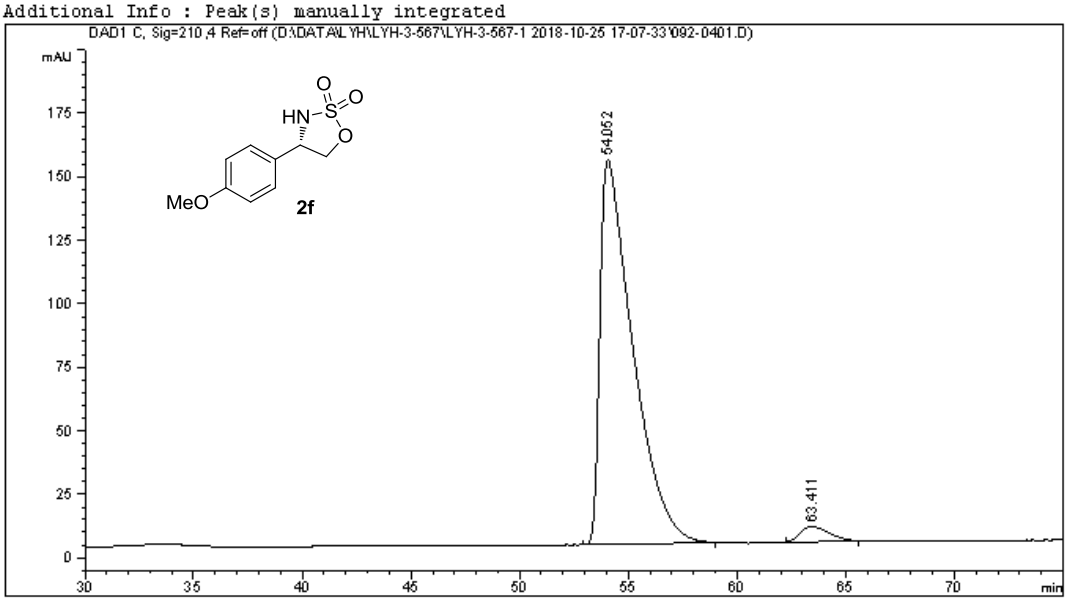



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  54.637 BB    1.2281 7293.77783   78.20206  51.0906
       2  61.883 BB    1.3213 6982.38818   61.93572  48.9094

    Totals :                  1.42762e4   140.13778
```


Figure S68. HPLC spectrum of racemic-**2f**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-567\LYH-3-567-1 2018-10-25 17-07-33\092-0401.D
Sample Name: LYH-3-567-1-P-MeO

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :   4
    Acq. Instrument : Instrument 2                    Location : Vial 92
    Injection Date  : 10/25/2018 8:01:47 PM               Inj :   1
                                                    Inj Volume : 10.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-567\LYH-3-567-1 2018-10-25 17-07-33\DAD-0J(1-6)-80-20-1ML
                      -10UL-ALL-95MIN.M
    Last changed    : 10/25/2018 6:41:21 PM
                      (modified after loading)
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 2:31:00 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

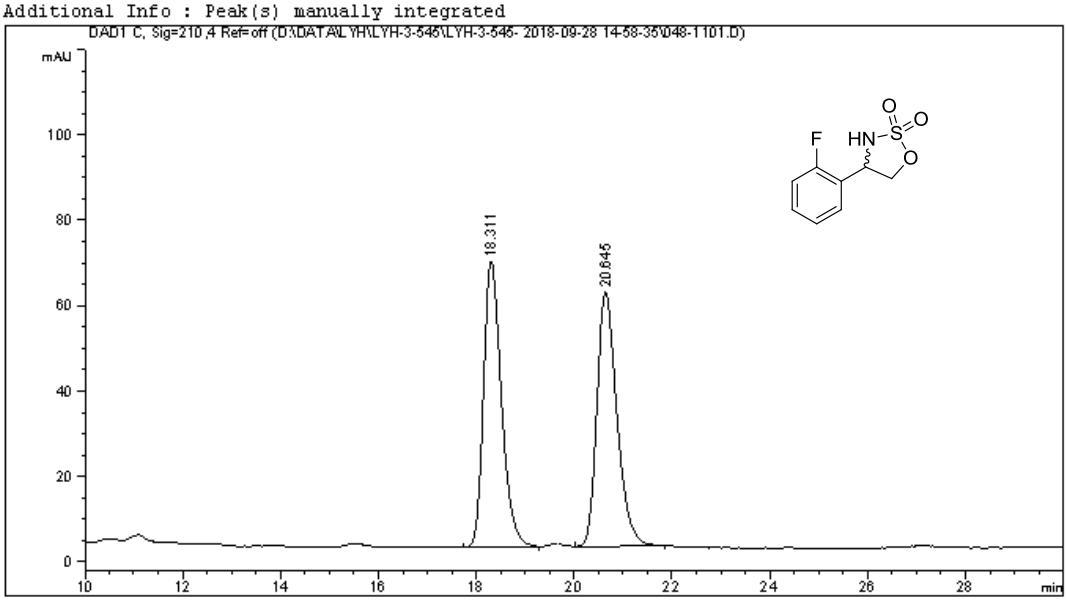



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  54.052 BB    1.3663 1.59079e4   151.33786  96.6091
       2  63.411 BB    1.0690  558.35150    6.15138   3.3909

    Totals :                  1.64662e4   157.48924
```


Figure S69. HPLC spectrum of **2f**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\048-1101.D
Sample Name: LYH-3-545-4-RAC

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :  11
    Acq. Instrument : Instrument 2                    Location : Vial 48
    Injection Date  : 9/28/2018 9:19:09 PM                 Inj :  1
                                                     Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\DAD-0J(1-6)-80-20-1ML-
                      1UL-ALL-35MIN.M
    Last changed    : 5/26/2018 10:38:45 AM
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/27/2018 10:30:13 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

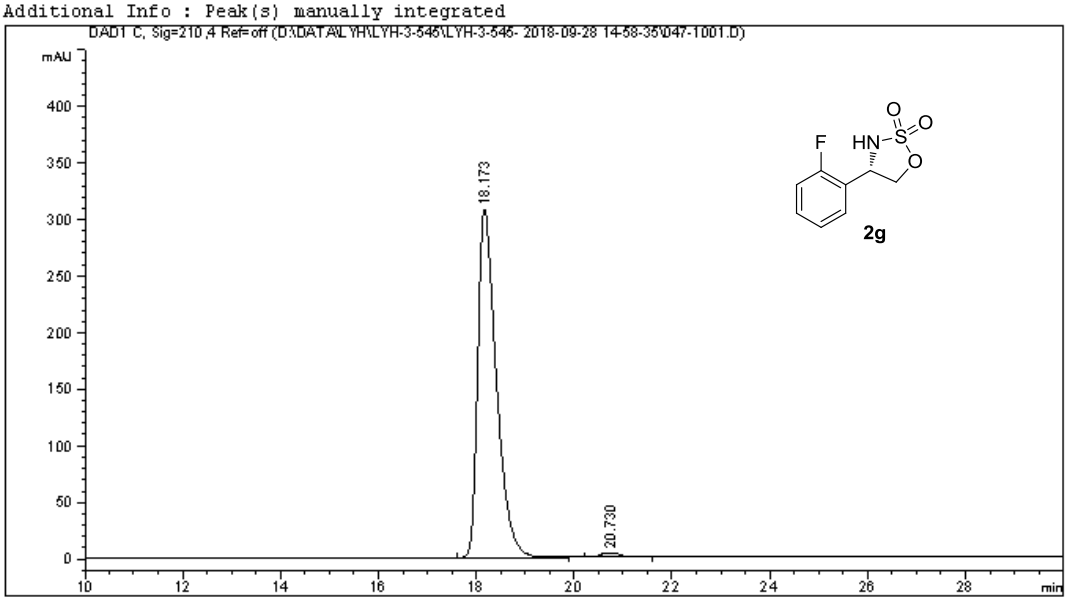



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  18.311 BB    0.3854 1696.46033   67.00771  50.0658
       2  20.645 BB    0.4312 1692.00281   59.59421  49.9342

    Totals :                  3388.46313  126.60192
```


Figure S70. HPLC spectrum of racemic-**2g**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\047-1001.D
Sample Name: LYH-3-545-4-0-F

```
======================================================================
Acq. Operator   :                                Seq. Line :  10
Acq. Instrument : Instrument 2                    Location : Vial 47
Injection Date  : 9/28/2018 8:43:12 PM                 Inj :   1
                                                 Inj Volume : 1.000 µl
Acq. Method     : D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\DAD-0J(1-6)-80-20-1ML-
                  1UL-ALL-35MIN.M
Last changed    : 5/26/2018 10:38:45 AM
Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
Last changed    : 12/27/2018 10:32:26 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

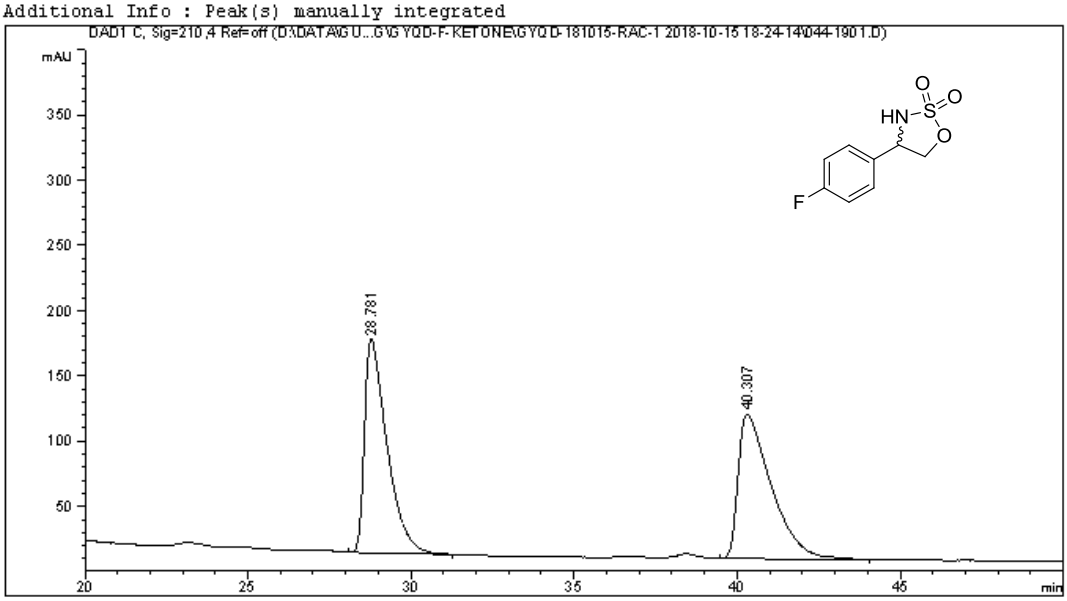



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  18.173 BB    0.4023 8127.69287  307.53677  98.6577
   2  20.730 BB    0.3455  110.57897    3.86787   1.3423

Totals :                  8238.27184  311.40464
```


Figure S71. HPLC spectrum of **2g**, related to **Table 3**.

Data File D:\DATA\GU...QING\GYQD-F-KETONE\GYQD-181015-RAC-1 2018-10-15 18-24-14\044-1901.D
Sample Name: LYH-3-557-2-P-F-RAC

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :  19
    Acq. Instrument : Instrument 2                    Location : Vial 44
    Injection Date  : 10/16/2018 11:11:51 AM              Inj :   1
                                                    Inj Volume : 10.000 µl
    Acq. Method     : D:\DATA\GUAN YUQING\GYQD-F-KETONE\GYQD-181015-RAC-1 2018-10-15 18-24-14\DAD
                      -OJ(1-6)-80-20-1ML-10UL-ALL-60MIN.M
    Last changed    : 9/26/2018 10:04:39 PM
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-OJ(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 1:55:12 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

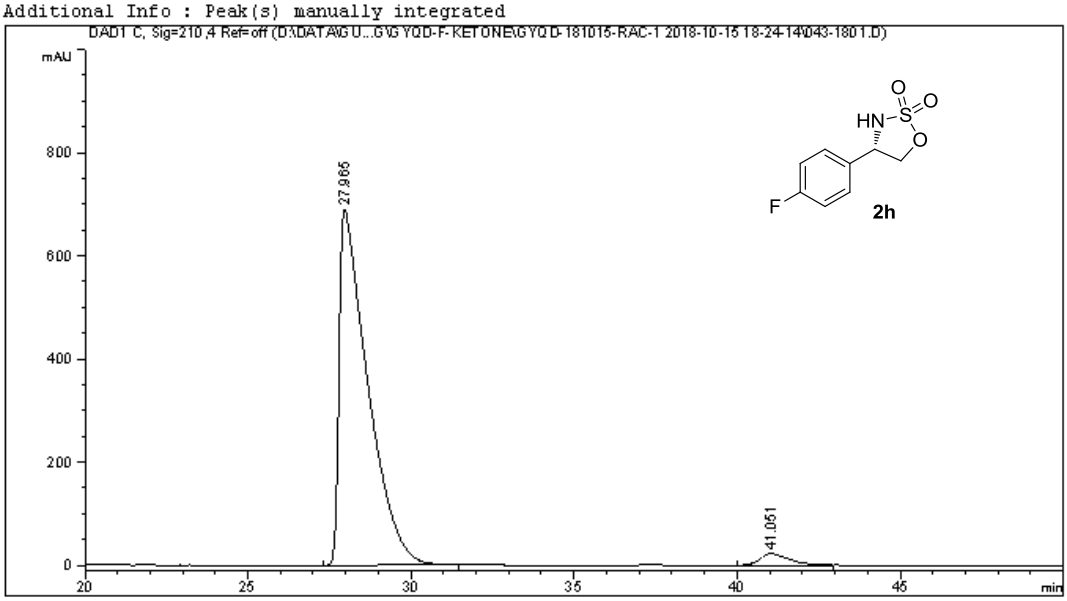



```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  28.781 BB    0.6811 7836.08398  163.50844  50.0849
       2  40.307 BB    0.9446 7809.50879  111.02328  49.9151

    Totals :                  1.56456e4   274.53172
```


Figure S72. HPLC spectrum of racemic-**2h**, related to **Table 3**.

Data File D:\DATA\GU...QING\GYQD-F-KETONE\GYQD-181015-RAC-1 2018-10-15 18-24-14\043-1801.D
Sample Name: LYH-3-557-2-P-F

```
======================================================================
Acq. Operator   :                               Seq. Line :  18
Acq. Instrument : Instrument 2                   Location : Vial 43
Injection Date  : 10/16/2018 10:10:44 AM              Inj :   1
                                                Inj Volume : 10.000 µl
Acq. Method     : D:\DATA\GUAN YUQING\GYQD-F-KETONE\GYQD-181015-RAC-1 2018-10-15 18-24-14\DAD
                  -0J(1-6)-80-20-1ML-10UL-ALL-60MIN.M
Last changed    : 9/26/2018 10:04:39 PM
Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
Last changed    : 12/28/2018 1:57:33 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

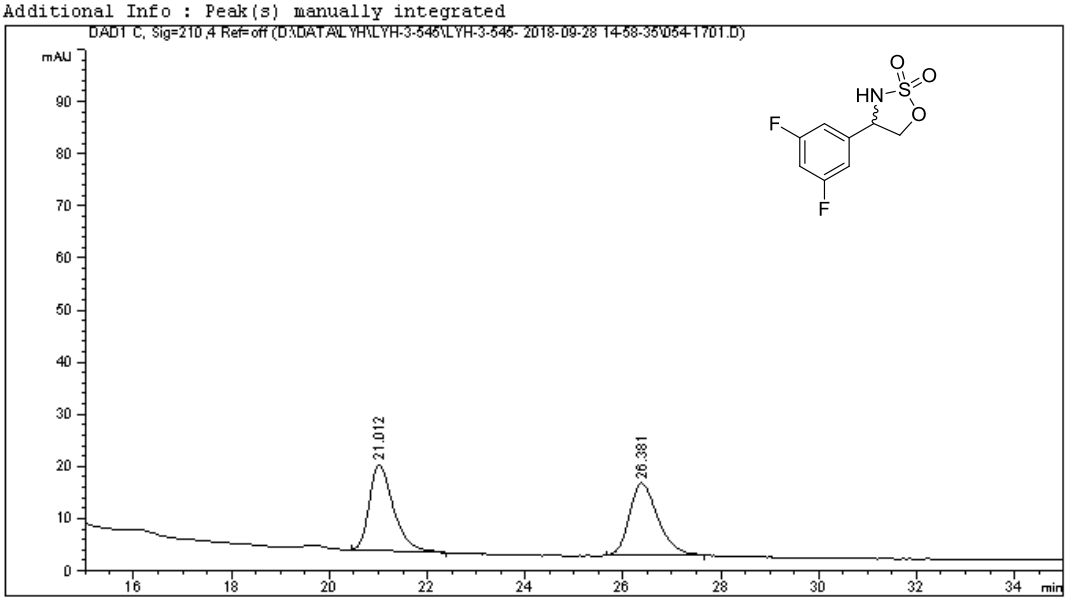



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  27.965 BB    0.8159 4.19006e4   688.59662  96.8857
   2  41.051 BB    0.7947 1346.85828   21.68349   3.1143

Totals :                  4.32475e4   710.28011
```


Figure S73. HPLC spectrum of **2h**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\054-1701.D
Sample Name: LYH-3-545-7-RAC

```
======================================================================
Acq. Operator   :                                Seq. Line :  17
Acq. Instrument : Instrument 2                    Location : Vial 54
Injection Date  : 9/29/2018 3:25:01 AM                 Inj :  1
                                                 Inj Volume : 1.000 µl
Acq. Method     : D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\DAD-0J(1-6)-80-20-1ML-
                  1UL-ALL-35MIN.M
Last changed    : 5/26/2018 10:38:45 AM
Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
Last changed    : 12/27/2018 10:50:49 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

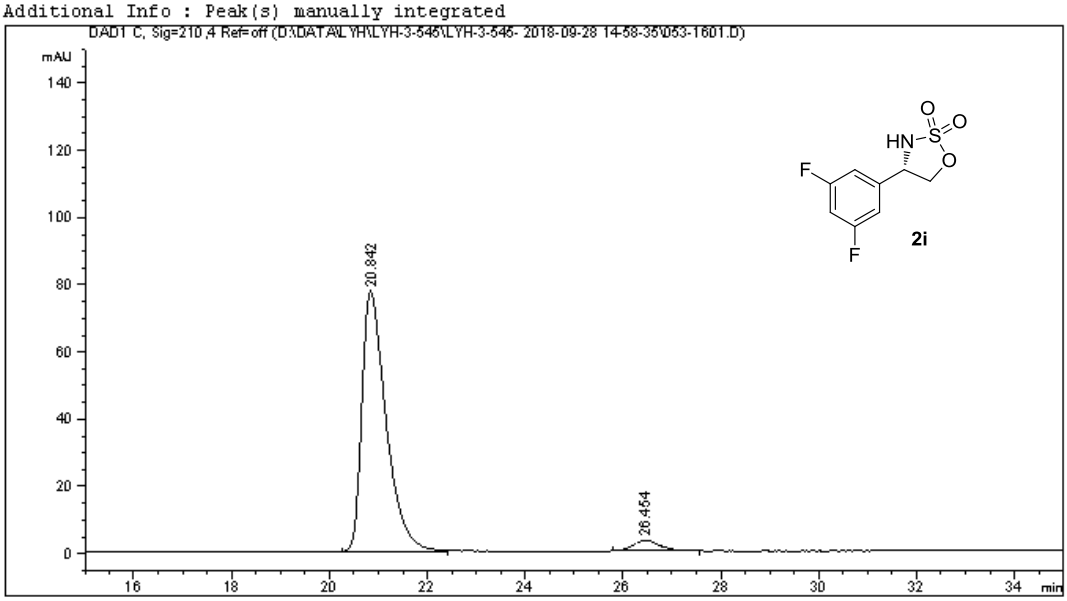



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  21.012 BB    0.4774  562.93109   16.52714  50.0767
   2  26.381 BB    0.5200  561.20599   13.81212  49.9233

Totals :                  1124.13708   30.33926
```


Figure S74. HPLC spectrum of racemic-**2i**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\053-1601.D
Sample Name: LYH-3-545-7-3,5-F

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :  16
    Acq. Instrument : Instrument 2                    Location : Vial 53
    Injection Date  : 9/29/2018 2:49:03 AM                 Inj :  1
                                                     Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-545\LYH-3-545- 2018-09-28 14-58-35\DAD-0J(1-6)-80-20-1ML-
                      1UL-ALL-35MIN.M
    Last changed    : 5/26/2018 10:38:45 AM
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/27/2018 10:52:12 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

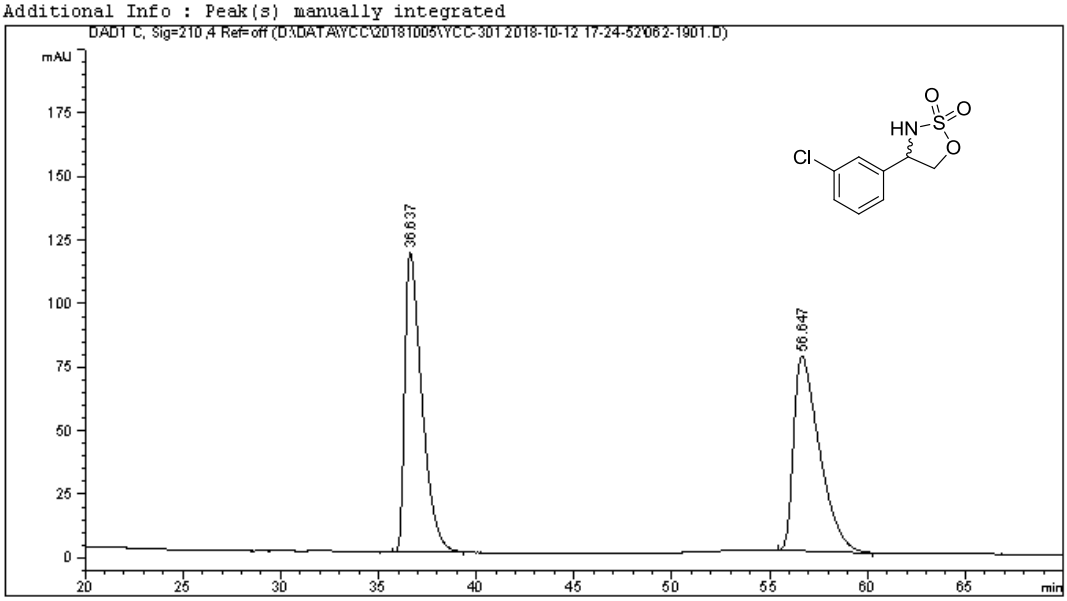



```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  20.842 BB    0.5106 2646.26685   77.45506  95.5243
       2  26.454 BB    0.4840  123.98939    3.10415   4.4757

    Totals :                  2770.25623   80.55920
```


Figure S75. HPLC spectrum of **2i**, related to **Table 3**.

Data File D:\DATA\YCC\20181005\YCC-301 2018-10-12 17-24-52\062-1901.D
Sample Name: LYH-3-554-2-M-Cl-RAC

```
======================================================================
Acq. Operator   :                                Seq. Line :  19
Acq. Instrument : Instrument 2                    Location : Vial 62
Injection Date  : 10/13/2018 6:18:13 AM               Inj :   1
                                                 Inj Volume : 1.000 µl
Acq. Method     : D:\DATA\YCC\20181005\YCC-301 2018-10-12 17-24-52\DAD-0J(1-6)-80-20-1ML-1UL-
                  ALL-70MIN.M
Last changed    : 5/26/2018 10:41:19 AM
Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
Last changed    : 12/28/2018 2:20:40 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

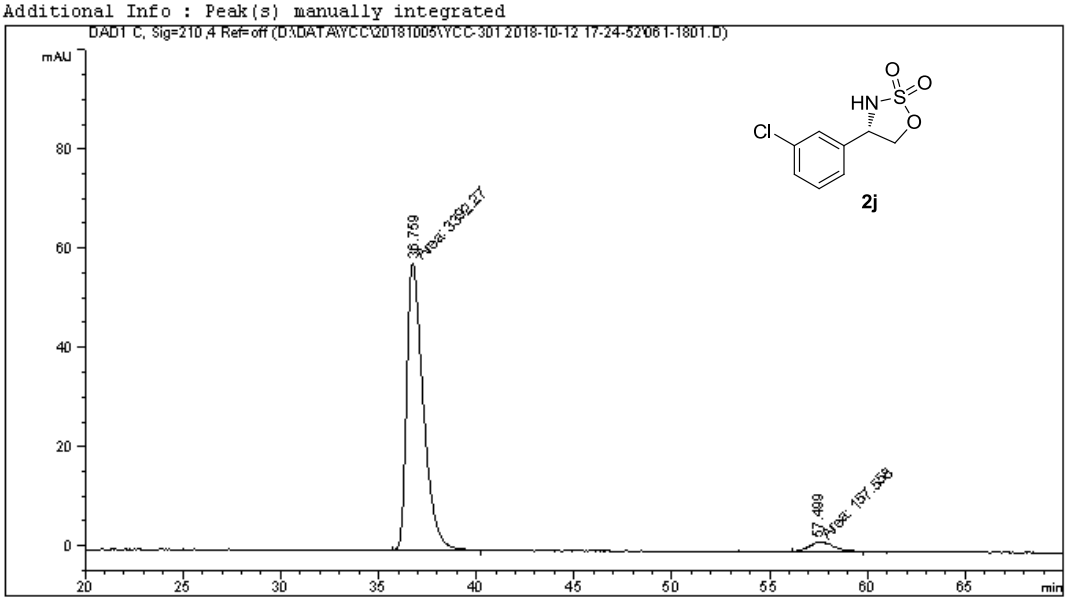



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  36.637 BB    0.8445 7124.72217  117.98212  50.2363
   2  56.647 BB    1.0870 7057.70947   76.74080  49.7637

Totals :                 1.41824e4   194.72292
```


Figure S76. HPLC spectrum of racemic-**2j**, related to **Table 3**.

Data File D:\DATA\YCC\20181005\YCC-301 2018-10-12 17-24-52\061-1801.D
Sample Name: LYH-3-554-2-M-Cl

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :  18
    Acq. Instrument : Instrument 2                    Location : Vial 61
    Injection Date  : 10/13/2018 5:07:19 AM               Inj :   1
                                                    Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\YCC\20181005\YCC-301 2018-10-12 17-24-52\DAD-0J(1-6)-80-20-1ML-1UL-
                      ALL-70MIN.M
    Last changed    : 5/26/2018 10:41:19 AM
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 2:21:55 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

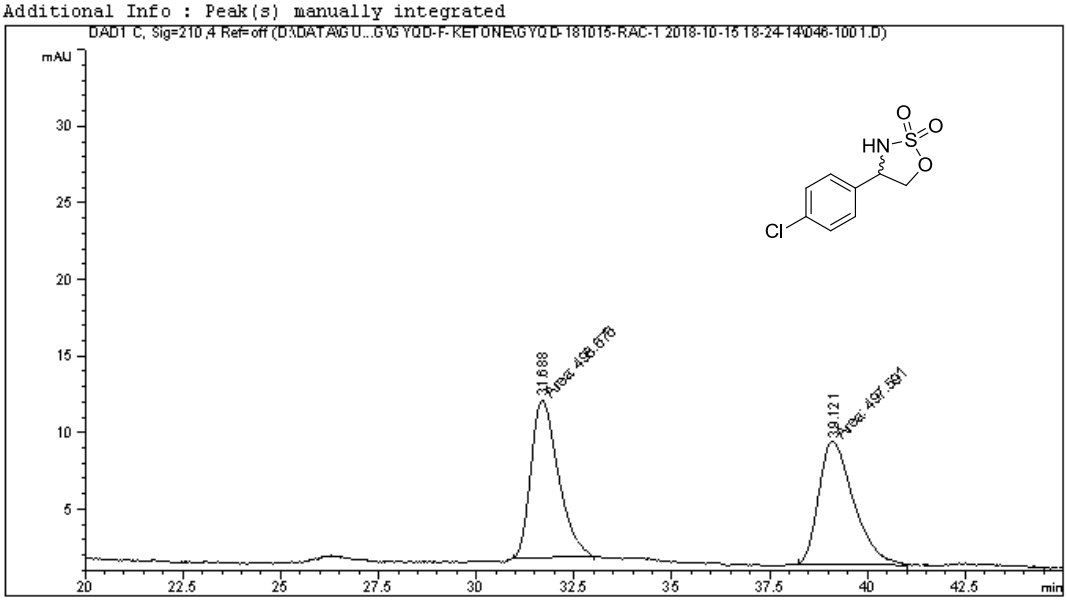



```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  36.759 MM    0.9759 3392.26538   57.93180  95.5615
       2  57.499 MM    1.3698  157.55803    1.91701   4.4385

    Totals :                  3549.82341   59.84881
```


Figure S77. HPLC spectrum of **2j**, related to **Table 3**.

Data File D:\DATA\GU...QING\GYQD-F-KETONE\GYQD-181015-RAC-1 2018-10-15 18-24-14\046-1001.D
Sample Name: LYH-3-557-3-P-CL-RAC

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :  10
    Acq. Instrument : Instrument 2                    Location : Vial 46
    Injection Date  : 10/16/2018 1:07:52 AM               Inj :   1
                                                    Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\GUAN YUQING\GYQD-F-KETONE\GYQD-181015-RAC-1 2018-10-15 18-24-14\DAD
                      -OJ(1-6)-80-20-1ML-1UL-ALL-45MIN.M
    Last changed    : 5/26/2018 10:39:50 AM
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-OJ(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 1:44:15 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

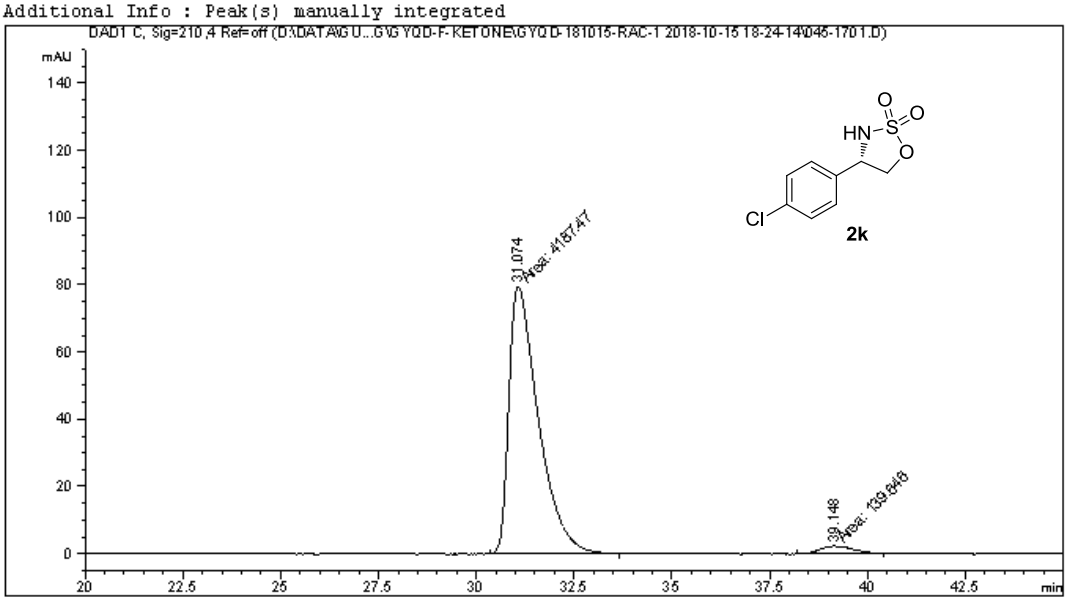



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  31.688 MM    0.8097  498.67606   10.26517  50.0545
       2  39.121 MM    1.0374  497.59082    7.99429  49.9455

    Totals :                   996.26688   18.25946
```


Figure S78. HPLC spectrum of racemic-**2k**, related to **Table 3**.

Data File D:\DATA\GU...QING\GYQD-F-KETONE\GYQD-181015-RAC-1 2018-10-15 18-24-14\045-1701.D
Sample Name: LYH-3-557-3-P-CL

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :  17
    Acq. Instrument : Instrument 2                    Location : Vial 45
    Injection Date  : 10/16/2018 9:24:38 AM               Inj :   1
                                                    Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\GUAN YUQING\GYQD-F-KETONE\GYQD-181015-RAC-1 2018-10-15 18-24-14\DAD
                      -0J(1-6)-80-20-1ML-1UL-ALL-45MIN.M
    Last changed    : 5/26/2018 10:39:50 AM
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 1:50:27 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

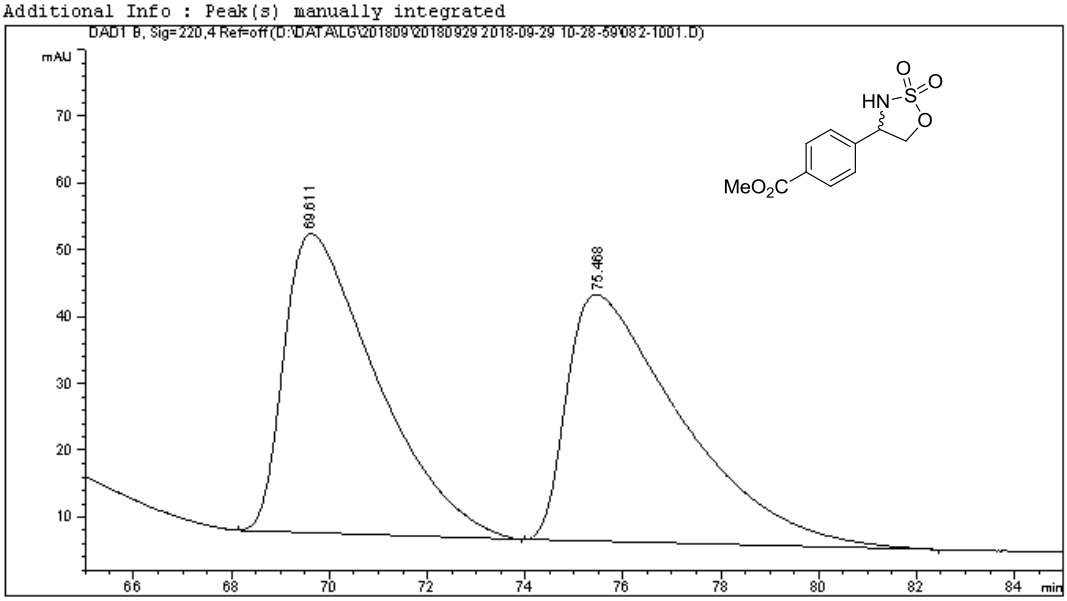



```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  31.074 MM    0.8756 4187.46729   79.70943  96.7728
       2  39.148 MM    0.9882  139.64626    2.35521   3.2272

    Totals :                  4327.11354   82.06464
```


Figure S79. HPLC spectrum of **2k**, related to **Table 3**.

Data File D:\DATA\LG\201809\20180929 2018-09-29 10-28-59\082-1001.D
Sample Name: LYH-3-545-5-RAC

```
======================================================================
Acq. Operator   :                                Seq. Line :  10
Acq. Instrument : Instrument 2                    Location : Vial 82
Injection Date  : 9/29/2018 1:31:03 PM                 Inj :   1
                                                 Inj Volume : 10.000 µl
Acq. Method     : D:\DATA\LG\201809\20180929 2018-09-29 10-28-59\DAD-0J(1-6)-80-20-1ML-10UL-
                  ALL-95MIN.M
Last changed    : 9/29/2018 10:46:14 AM
Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
Last changed    : 12/27/2018 10:43:43 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

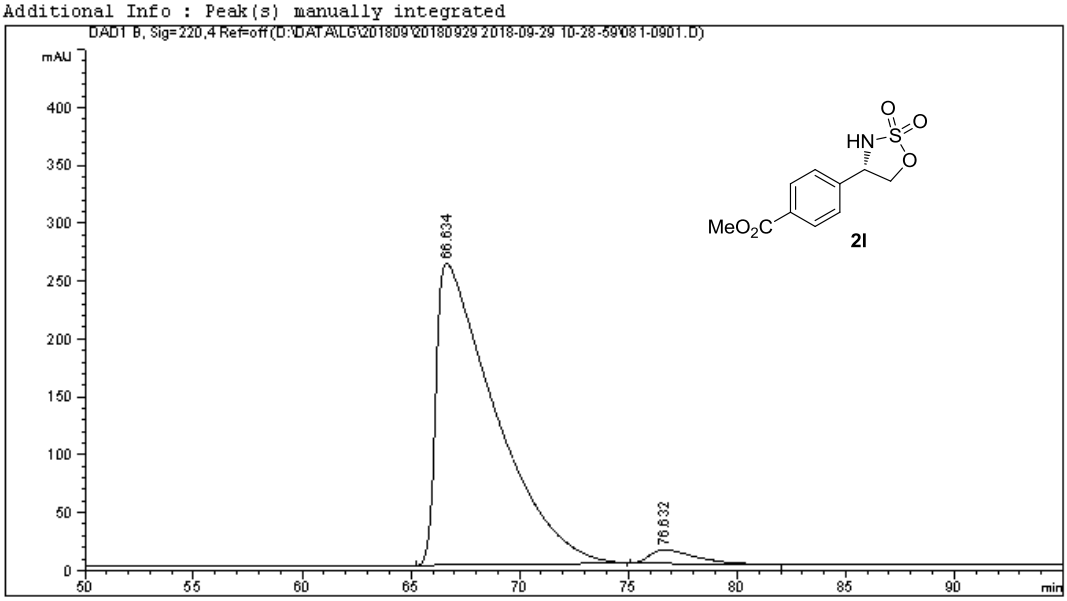



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  69.611 BB    1.7085 5889.37354   44.77717  49.5159
   2  75.468 BB    1.9027 6004.52637   36.93422  50.4841

Totals :                 1.18939e4    81.71139
```


Figure S80. HPLC spectrum of racemic-**2l**, related to **Table 3**.

Data File D:\DATA\LG\201809\20180929 2018-09-29 10-28-59\081-0901.D
Sample Name: LYH-3-545-5-P-COOME

```
==========================================================================
Acq. Operator   :                                Seq. Line :   9
Acq. Instrument : Instrument 2                    Location : Vial 81
Injection Date  : 9/29/2018 11:54:57 AM               Inj :   1
                                                 Inj Volume : 10.000 µl
Acq. Method     : D:\DATA\LG\201809\20180929 2018-09-29 10-28-59\DAD-0J(1-6)-80-20-1ML-10UL-
                  ALL-95MIN.M
Last changed    : 9/29/2018 10:46:14 AM
Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
Last changed    : 12/27/2018 10:47:20 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

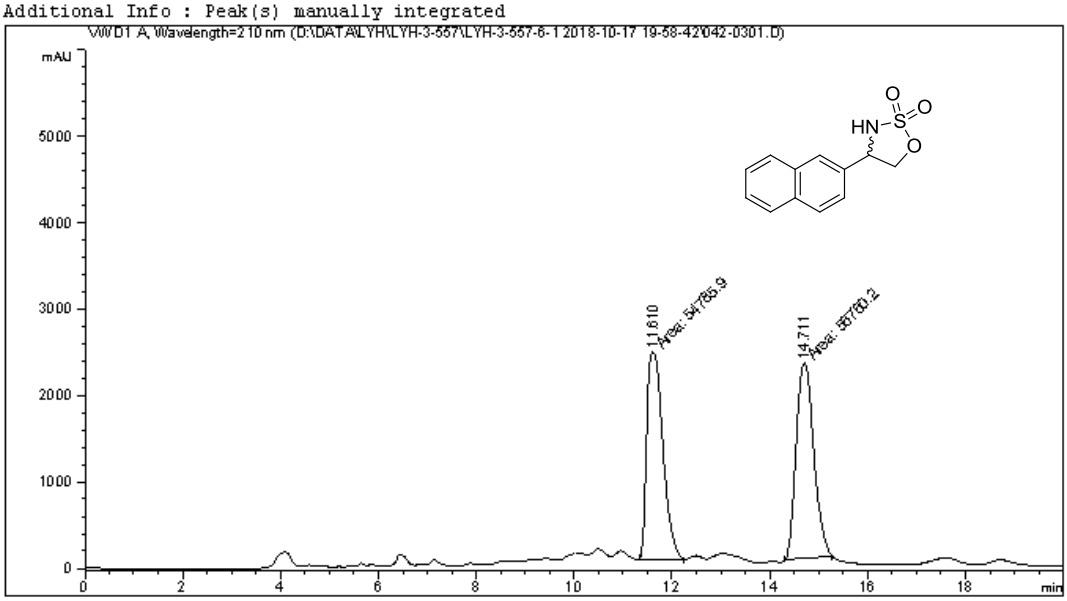



```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  66.634 BB    2.3960 4.91264e4   260.99466  96.6570
   2  76.632 BB    1.7273 1699.08276   11.56984   3.3430

Totals :                  5.08254e4   272.56450
```


Figure S81. HPLC spectrum of **2l**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-557\LYH-3-557-6-1 2018-10-17 19-58-42\042-0301.D
Sample Name: lyh-3-557-6-RAC

```
    ======================================================================
    Acq. Operator   :                               Seq. Line :   3
    Acq. Instrument : Instrument 1                   Location : Vial 42
    Injection Date  : 10/17/2018 8:31:16 PM              Inj :   1
                                                   Inj Volume : 5.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-557\LYH-3-557-6-1 2018-10-17 19-58-42\VWD-AD(1-2)-80-20-0
                      .8ML-5UL-210NM-20MIN.M
    Last changed    : 6/19/2018 3:41:44 PM
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 2:05:11 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

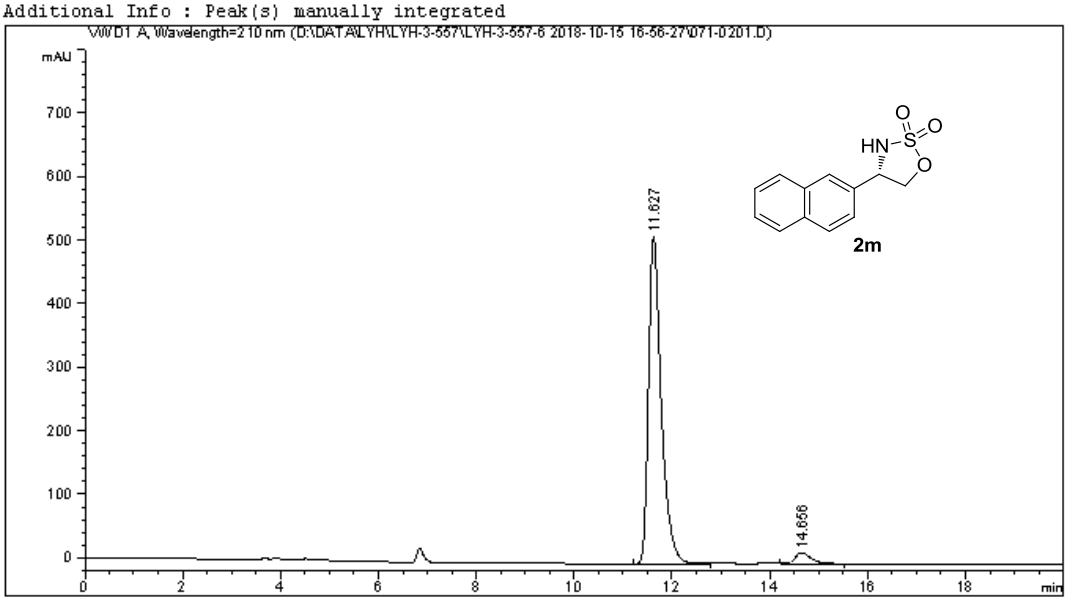



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: VWD1 A, Wavelength=210 nm

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  11.610 MM    0.3807 5.47859e4  2398.24341  49.1151
       2  14.711 MM    0.4191 5.67602e4  2257.27930  50.8849

    Totals :                  1.11546e5  4655.52271
```


Figure S82. HPLC spectrum of racemic-**2m**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-557\LYH-3-557-6 2018-10-15 16-56-27\071-0201.D
Sample Name: LYH-3-557-6

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :   2
    Acq. Instrument : Instrument 1                    Location : Vial 71
    Injection Date  : 10/15/2018 5:08:09 PM               Inj :   1
                                                    Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-557\LYH-3-557-6 2018-10-15 16-56-27\VWD-AD(1-2)-80-20-0.
                      8ML-1UL-210NM-20MIN.M
    Last changed    : 6/15/2018 3:09:14 PM
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 2:07:31 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

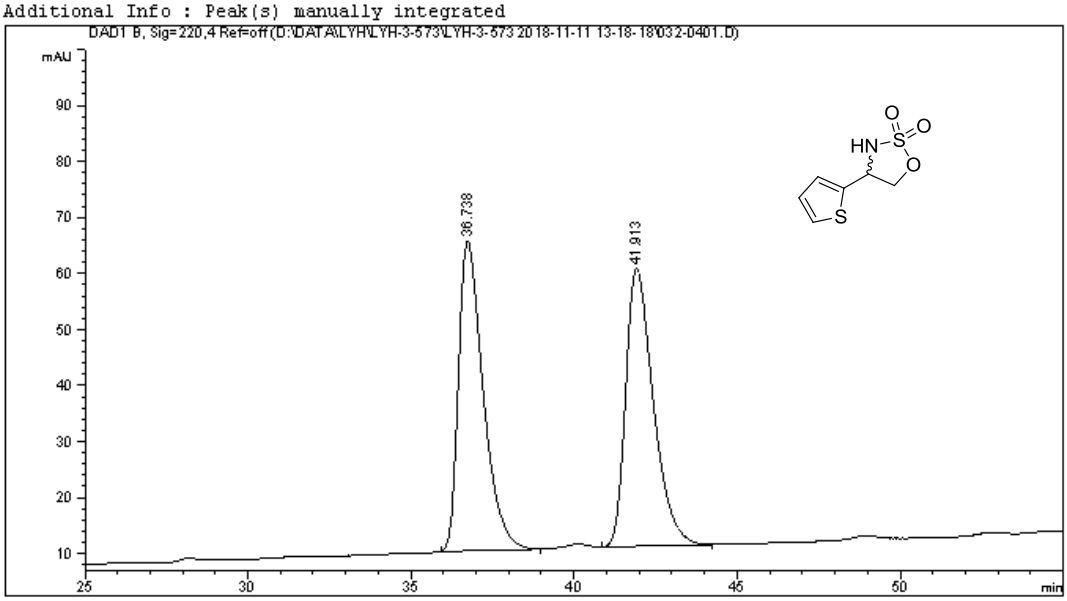



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: VWD1 A, Wavelength=210 nm

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  11.627 BB    0.2695 9311.71582  516.10852  96.0172
       2  14.656 BB    0.3329  386.25497   17.40781   3.9828

    Totals :                  9697.97079  533.51633
```


Figure S83. HPLC spectrum of **2m**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-573\LYH-3-573 2018-11-11 13-18-18\032-0401.D
Sample Name: LYH-3-573-RAC

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :   4
    Acq. Instrument : Instrument 2                    Location : Vial 32
    Injection Date  : 11/11/2018 2:42:43 PM               Inj :   1
                                                    Inj Volume : 10.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-573\LYH-3-573 2018-11-11 13-18-18\DAD-0J(1-6)-80-20-1ML-
                      10UL-ALL-60MIN.M
    Last changed    : 9/26/2018 10:04:39 PM
    Analysis Method : D:\METHOD\LWD\DAD-AD(1-2)-93-7-1ML-3UL-ALL-40MIN.M
    Last changed    : 1/9/2019 10:25:45 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

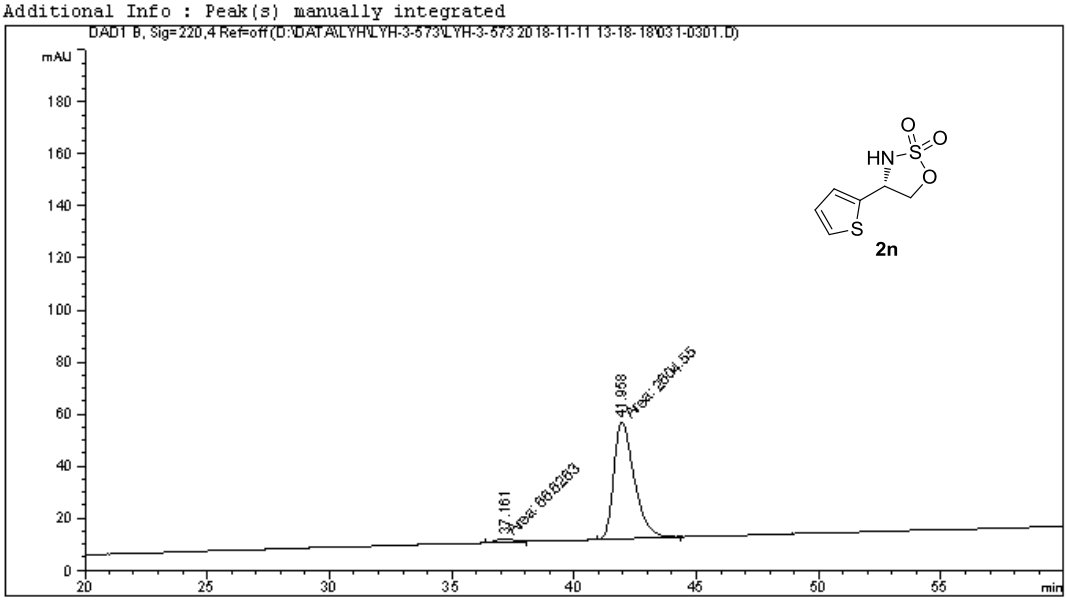



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 B, Sig=220,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  36.738 BB    0.7621 2911.97192   55.32295  49.9281
       2  41.913 BB    0.8291 2920.35938   49.58599  50.0719

    Totals :                  5832.33130  104.90894
```


Figure S84. HPLC spectrum of racemic-**2n**, related to **Table 3**.

Data File D:\DATA\LYH\LYH-3-573\LYH-3-573 2018-11-11 13-18-18\031-0301.D
Sample Name: LYH-3-573

```
=====================================================================
Acq. Operator   :                                Seq. Line :   3
Acq. Instrument : Instrument 2                    Location : Vial 31
Injection Date  : 11/11/2018 1:41:37 PM               Inj :   1
                                                 Inj Volume : 10.000 µl
Acq. Method     : D:\DATA\LYH\LYH-3-573\LYH-3-573 2018-11-11 13-18-18\DAD-0J(1-6)-80-20-1ML-
                  10UL-ALL-60MIN.M
Last changed    : 9/26/2018 10:04:39 PM
Analysis Method : D:\METHOD\LWD\DAD-AD(1-2)-93-7-1ML-3UL-ALL-40MIN.M
Last changed    : 1/9/2019 10:34:35 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  37.161 MM    0.7781   66.62634    1.42711   2.4943
   2  41.958 MM    0.9670 2604.55225   44.89145  97.5057

Totals :                  2671.17859   46.31856
```

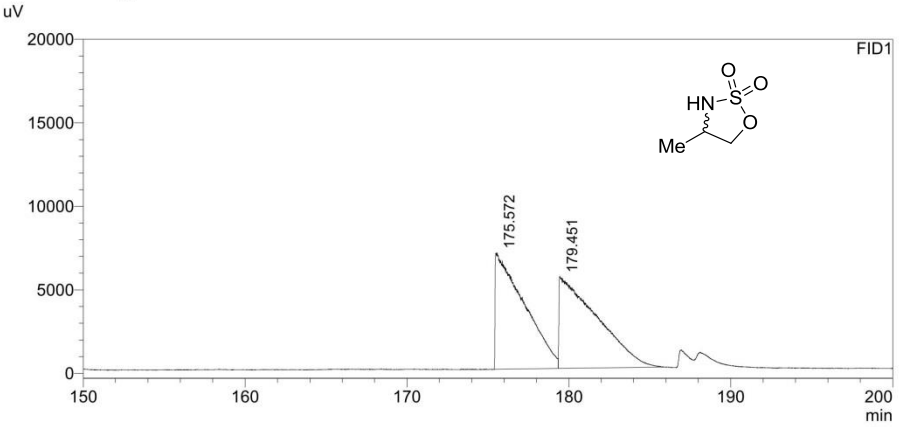

Figure S85. HPLC spectrum of **2n**, related to **Table 3**.

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: lyh-3-600-rac-me005		
Sample ID	:		
Data Filename	: lyh-3-600-rac-me005.gcd		
Method Filename	: beta dex-325-1ul-20-1-250-70(0)-0.3-160(30)-260-330min.gcm		
Batch Filename	: lyh-3-600-20190115-2.gcb		
Vial #	: 33	Sample Type	: Unknown
Injection Volume	: 1 uL		
Date Acquired	: 2019-1-15 21:14:07	Acquired by	: System Administrator
Date Processed	: 2019-1-16 9:11:13	Processed by	: System Administrator

<Chromatogram>



<Peak Table>

FID1

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	175.572	859571	6966	49.258		M	
2	179.451	885459	5490	50.742		V M	
Total		1745030	12457				

D:\DATA FILE\lyh\data\lyh-3-600-rac-me005.gcd

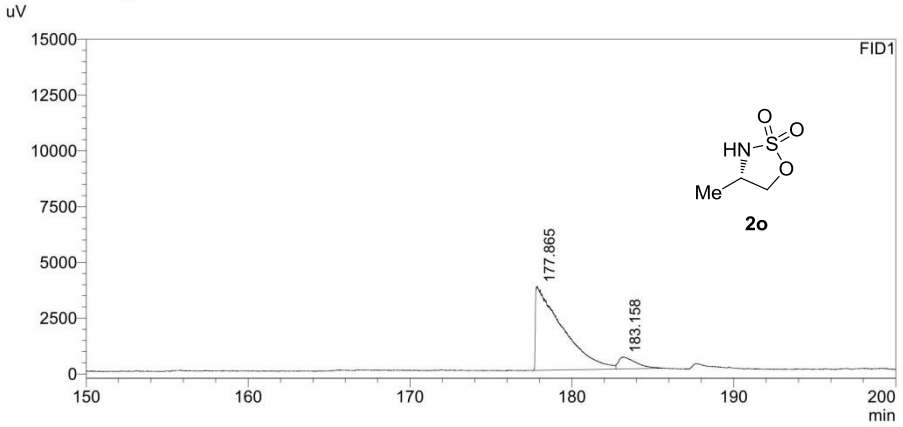
Figure S86. GC spectrum of racemic-**2o**, related to **Table 3**.

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: lyh-3-600-ee-me005		
Sample ID	:		
Data Filename	: lyh-3-600-ee-me005.gcd		
Method Filename	: beta dex-325-1ul-20-1-250-70(0)-0.3-160(30)-260-330min.gcm		
Batch Filename	: lyh-3-600-20190115-2.gcb		
Vial #	: 34	Sample Type	: Unknown
Injection Volume	: 1 uL		
Date Acquired	: 2019-1-16 2:49:31	Acquired by	: System Administrator
Date Processed	: 2019-1-16 9:10:47	Processed by	: System Administrator

<Chromatogram>



<Peak Table>

FID1

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	177.865	432793	3759	91.627		M	
2	183.158	39550	534	8.373		V M	
Total		472343	4292				

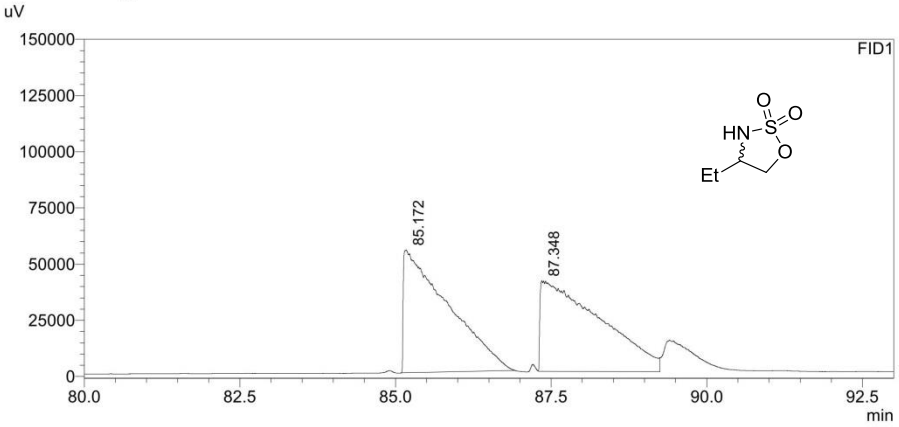
Figure S87. GC spectrum of **2o**, related to **Table 3**.

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: lyh-4-637-Et-rac		
Sample ID	:		
Data Filename	: lyh-4-637-Et-rac-1.gcd		
Method Filename	: beta dex-325-1ul-10-1-250-70(0)-1-160(30)-260-120min.gcm		
Batch Filename	: lyh-4-637-Et-1.gcb		
Vial #	: 27	Sample Type	: Unknown
Injection Volume	: 1 uL		
Date Acquired	: 2019-1-6 14:47:22	Acquired by	: System Administrator
Date Processed	: 2019-1-16 11:58:24	Processed by	: System Administrator

<Chromatogram>



<Peak Table>

FID1

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	85.172	2718249	54637	50.139		M	
2	87.348	2703172	40236	49.861		M	
Total		5421421	94872				

D:\DATA FILE\lyh\data\lyh-4-637-Et-rac-1.gcd

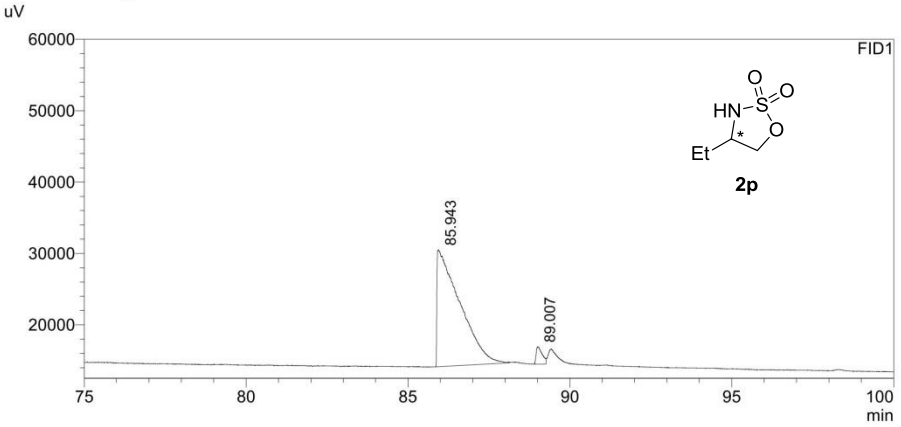
Figure S88. GC spectrum of racemic-**2p**, related to **Table 3**.

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: lyh-4-641-ee		
Sample ID	:		
Data Filename	: lyh-4-641-ee.gcd		
Method Filename	: beta dex-325-1ul-20-1-250-70(0)-1-160(30)-260-120min.gcm		
Batch Filename	: lyh-4-641-ee.gcb		
Vial #	: 30	Sample Type	: Unknown
Injection Volume	: 1 uL		
Date Acquired	: 2019-1-12 14:24:58	Acquired by	: System Administrator
Date Processed	: 2019-1-16 11:47:47	Processed by	: System Administrator

<Chromatogram>



<Peak Table>

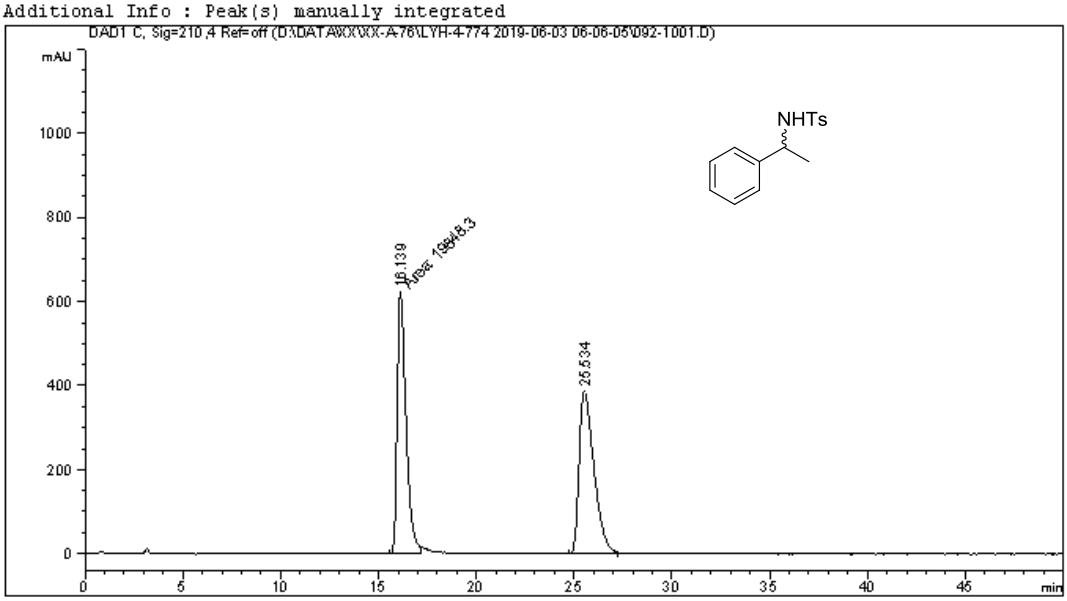
FID1

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	85.943	803340	16382	96.195		M	
2	89.007	31778	2447	3.805		M	
Total		835118	18829				

Figure S89. GC spectrum of **2p**, related to **Table 3**.

Data File D:\DATA\XX\XX-A-76\LYH-4-774 2019-06-03 06-06-05\092-1001.D
Sample Name: LYH-4-774-1-RAC

```
======================================================================
Acq. Operator   :                                Seq. Line :  10
Acq. Instrument : Instrument 2                    Location : Vial 92
Injection Date  : 6/3/2019 9:47:55 AM                 Inj :   1
                                                 Inj Volume : 3.000 µl
Acq. Method     : D:\DATA\XX\XX-A-76\LYH-4-774 2019-06-03 06-06-05\DAD-0J(1-6)-80-20-1ML-3UL-
                  ALL-60MIN.M
Last changed    : 11/10/2018 5:20:50 PM
Analysis Method : D:\METHOD\TL\DAD-0J(1-6)-95-5-0.5ML-3UL-ALL-20MIN.M
Last changed    : 6/6/2019 10:18:48 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

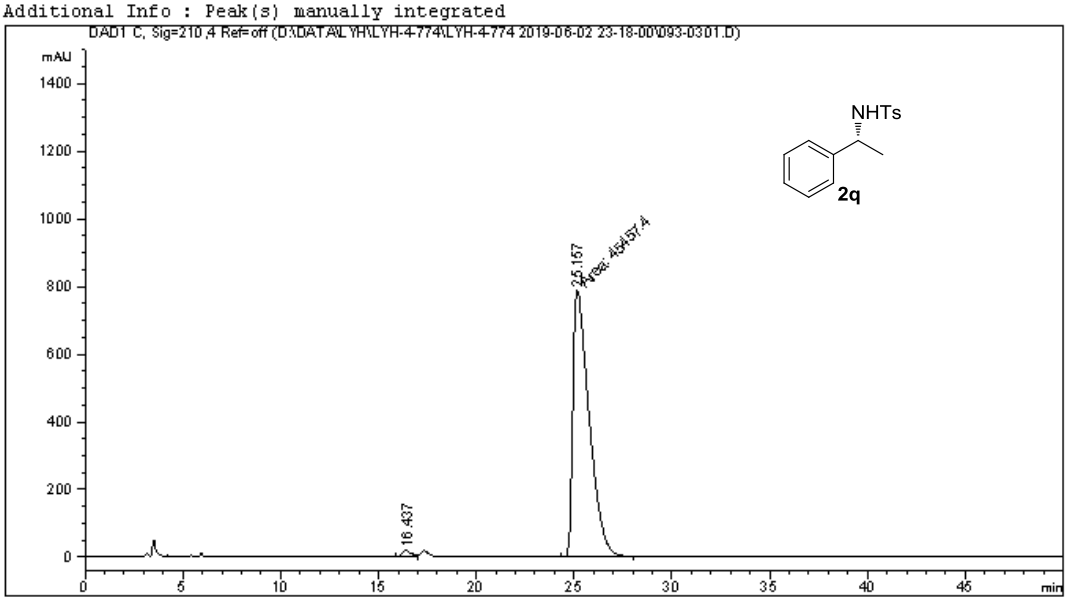



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  16.139 MF    0.5301 1.98483e4   624.09387  49.2557
   2  25.534 VV    0.6287 2.04481e4   388.10342  50.7443

Totals :                  4.02965e4  1012.19730
```


Figure S90. HPLC spectrum of racemic-**2q**, related to **Scheme 2.**

Data File D:\DATA\LYH\LYH-4-774\LYH-4-774 2019-06-02 23-18-00\093-0301.D
Sample Name: LYH-4-774-1-EE

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :   3
    Acq. Instrument : Instrument 2                    Location : Vial 93
    Injection Date  : 6/3/2019 12:30:59 AM                 Inj :   1
                                                   Inj Volume : 3.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-4-774\LYH-4-774 2019-06-02 23-18-00\DAD-0J(1-6)-80-20-1ML-
                      3UL-ALL-60MIN.M
    Last changed    : 11/10/2018 5:20:50 PM
    Analysis Method : D:\METHOD\TL\DAD-0J(1-6)-95-5-0.5ML-3UL-ALL-20MIN.M
    Last changed    : 6/6/2019 10:21:51 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

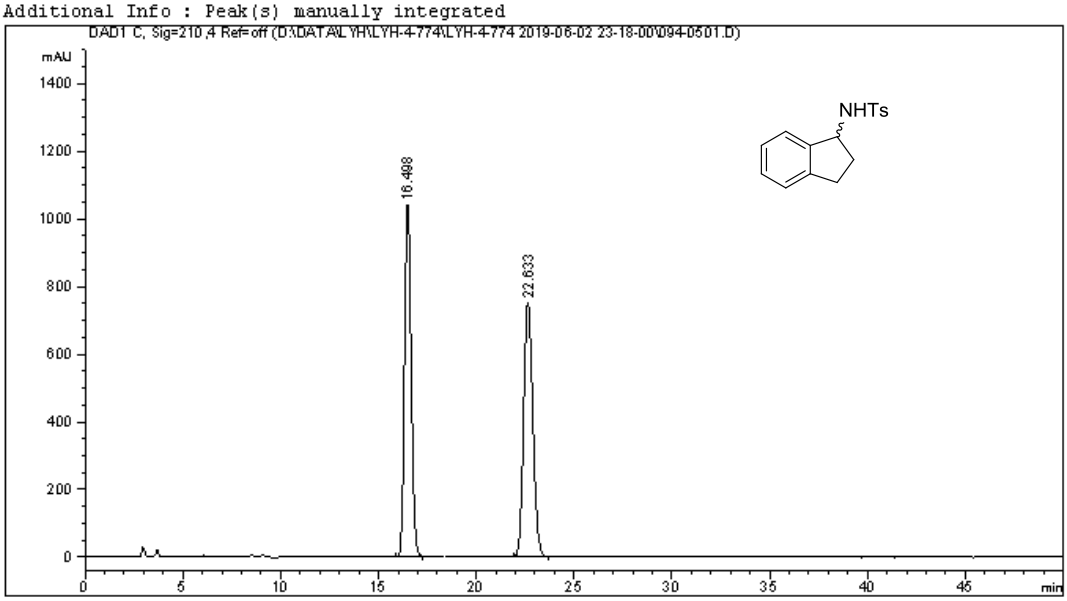



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  16.437 BV    0.4059  617.98169   18.30194   1.3412
       2  25.157 MM    0.9620 4.54574e4   787.54706  98.6588

    Totals :                  4.60753e4   805.84900
```


Figure S91. HPLC spectrum of **2q**, related to **Scheme 2.**

Data File D:\DATA\LYH\LYH-4-774\LYH-4-774 2019-06-02 23-18-00\094-0501.D
Sample Name: LYH-4-774-2-RAC-AD

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :   5
    Acq. Instrument : Instrument 2                    Location : Vial 94
    Injection Date  : 6/3/2019 1:43:00 AM                 Inj :   1
                                                    Inj Volume : 5.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-4-774\LYH-4-774 2019-06-02 23-18-00\DAD-0D(1-2)-90-10-1ML-
                      5UL-ALL-80MIN.M
    Last changed    : 11/26/2018 9:09:07 AM
    Analysis Method : D:\METHOD\TL\DAD-0J(1-6)-95-5-0.5ML-3UL-ALL-20MIN.M
    Last changed    : 6/6/2019 10:11:55 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

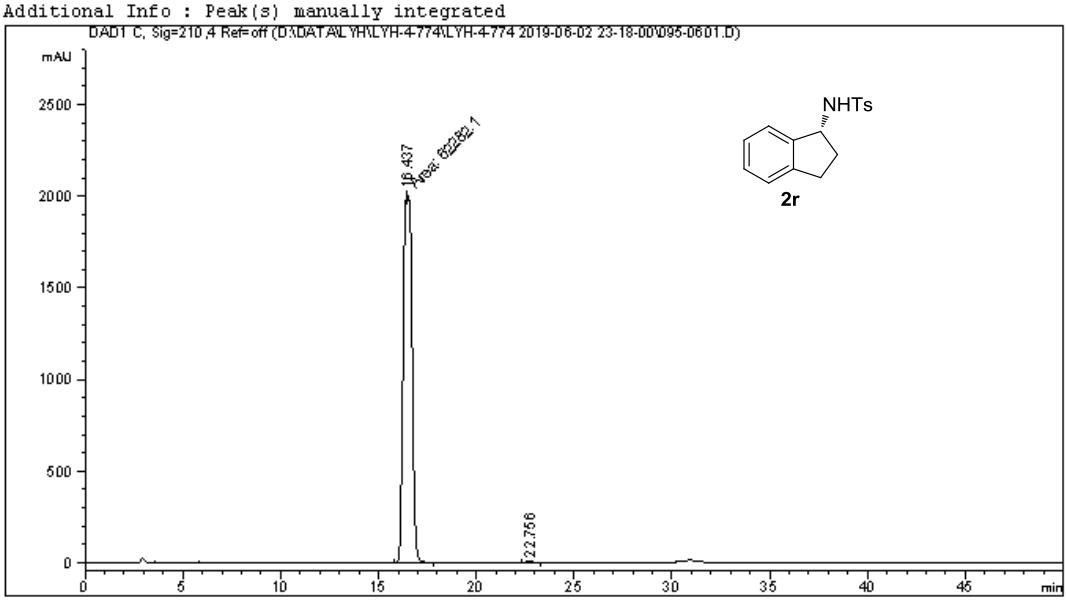



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  16.498 BV    0.3325 2.43383e4  1042.15796  49.7626
       2  22.633 BV    0.4756 2.45705e4   751.10913  50.2374

    Totals :                  4.89088e4  1793.26709
```


Figure S92. HPLC spectrum of racemic-**2r**, related to **Scheme 2.**

Data File D:\DATA\LYH\LYH-4-774\LYH-4-774 2019-06-02 23-18-00\095-0601.D
Sample Name: LYH-4-774-2-EE-AD

```
==========================================================================
Acq. Operator   :                                Seq. Line :   6
Acq. Instrument : Instrument 2                    Location : Vial 95
Injection Date  : 6/3/2019 3:04:01 AM                 Inj :   1
                                                 Inj Volume : 5.000 µl
Acq. Method     : D:\DATA\LYH\LYH-4-774\LYH-4-774 2019-06-02 23-18-00\DAD-0D(1-2)-90-10-1ML-
                  5UL-ALL-80MIN.M
Last changed    : 11/26/2018 9:09:07 AM
Analysis Method : D:\METHOD\TL\DAD-0J(1-6)-95-5-0.5ML-3UL-ALL-20MIN.M
Last changed    : 6/6/2019 10:13:50 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

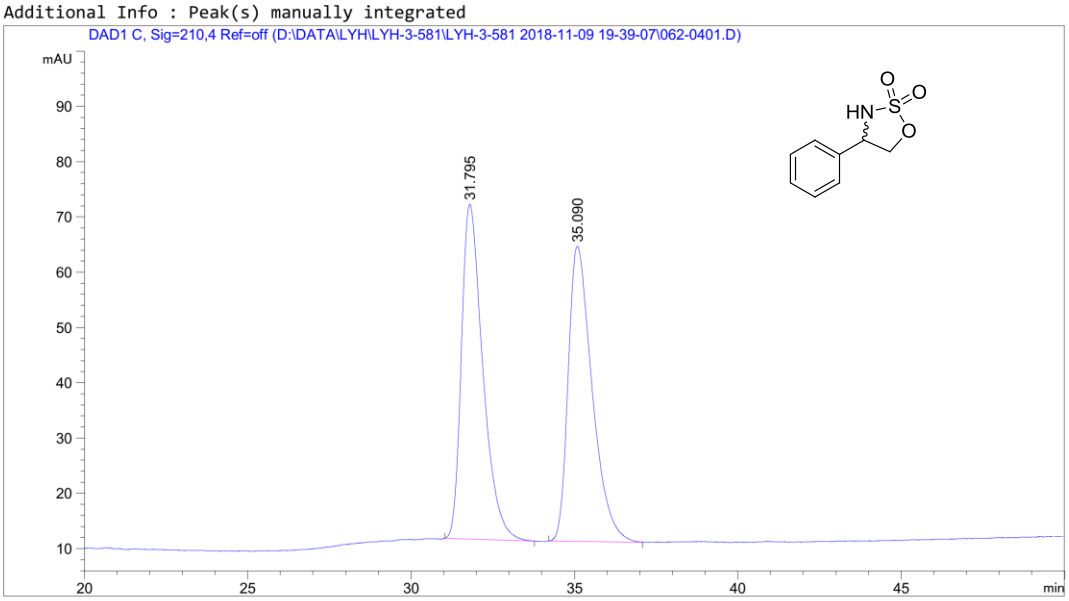



```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  16.437 MM    0.5121 6.22821e4  2026.84070  99.5511
   2  22.756 VV    0.3557  280.82431    9.31576   0.4489

Totals :                  6.25629e4  2036.15646
```


Figure S93. HPLC spectrum of **2r**, related to **Scheme 2**.

Data File D:\DATA\LYH\LYH-3-581\LYH-3-581 2018-11-09 19-39-07\062-0401.D
Sample Name: LYH-3-581-RAC

```
======================================================================
Acq. Operator   :                               Seq. Line :   4
Acq. Instrument : Instrument 2                   Location : Vial 62
Injection Date  : 11/9/2018 9:03:09 PM                Inj :   1
                                               Inj Volume : 10.000 µl
Acq. Method     : D:\DATA\LYH\LYH-3-581\LYH-3-581 2018-11-09 19-39-07\DAD-OJ(1-6)-80-20-1ML-
                  10UL-ALL-60MIN.M
Last changed    : 11/9/2018 9:55:13 PM
                  (modified after loading)
Analysis Method : D:\METHOD\LWD\DAD-OD(1-2)-95-5--1ML-3UL-ALL-60MIN.M
Last changed    : 1/3/2019 10:41:47 AM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

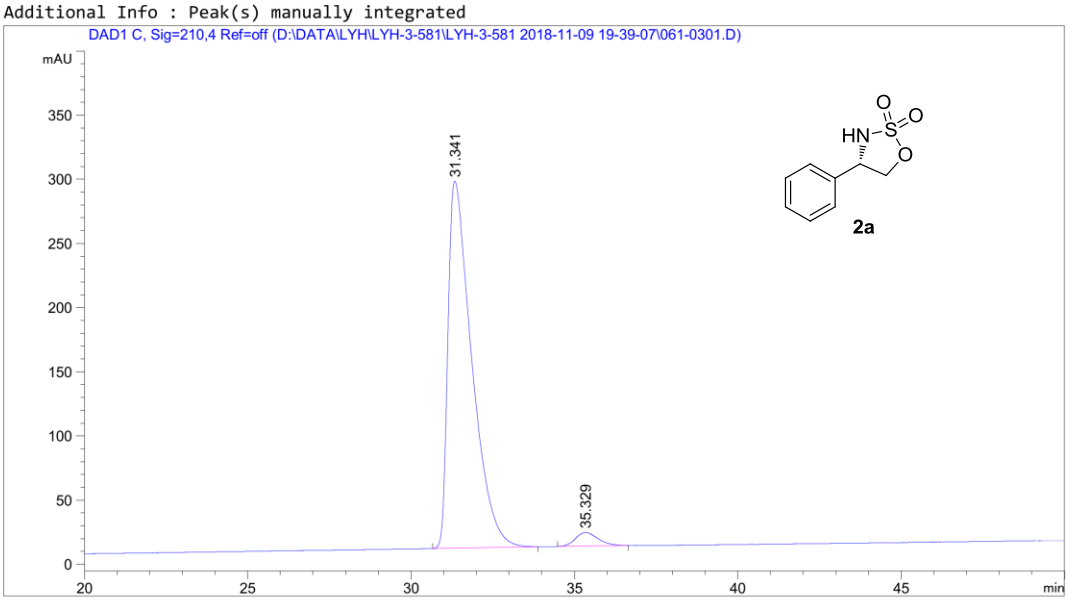



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  31.795 BB    0.6649 2758.07764   60.60914  50.2964
   2  35.090 BB    0.7598 2725.56958   53.37018  49.7036

Totals :                  5483.64722  113.97932
```


Figure S94. HPLC spectrum of racemic-**2a**, related to **Scheme 3**.

Data File D:\DATA\LYH\LYH-3-581\LYH-3-581 2018-11-09 19-39-07\061-0301.D
Sample Name: LYH-3-581

```
======================================================================
Acq. Operator   :                              Seq. Line :   3
Acq. Instrument : Instrument 2                  Location : Vial 61
Injection Date  : 11/9/2018 8:02:03 PM               Inj :   1
                                               Inj Volume : 1.000 µl
Acq. Method     : D:\DATA\LYH\LYH-3-581\LYH-3-581 2018-11-09 19-39-07\DAD-OJ(1-6)-80-20-1ML-
                  1UL-ALL-60MIN.M
Last changed    : 5/26/2018 10:40:39 AM
Analysis Method : D:\METHOD\LWD\DAD-OD(1-2)-95-5--1ML-3UL-ALL-60MIN.M
Last changed    : 1/3/2019 10:46:46 AM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

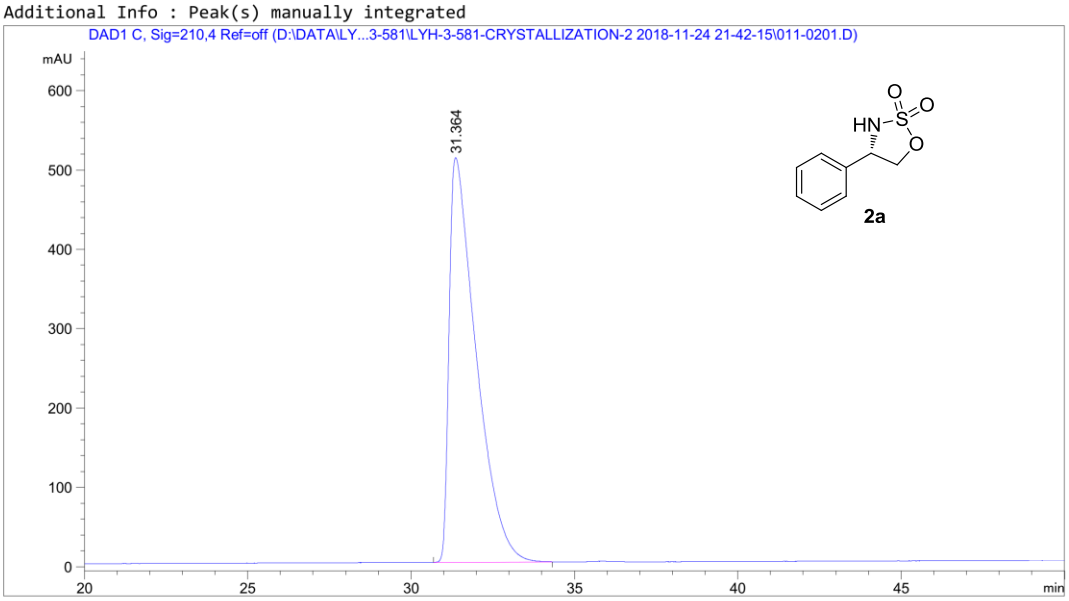



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  31.341 BB    0.7314 1.44461e4   285.94577  96.5711
   2  35.329 BB    0.6199  512.92615   10.57457   3.4289

Totals :                  1.49590e4   296.52034
```


Figure S95. HPLC spectrum of **2a**, related to **Scheme 3**.

Data File D:\DATA\LYH\LYH-3-581\LYH-3-581-CRYSTALLIZATION-2 2018-11-24 21-42-15\011-0201.D
Sample Name: LYH-3-581-crystallization-2

```
======================================================================
Acq. Operator   :                              Seq. Line :   2
Acq. Instrument : Instrument 2                  Location : Vial 11
Injection Date  : 11/24/2018 9:54:26 PM              Inj :   1
                                              Inj Volume : 10.000 µl
Acq. Method     : D:\DATA\LYH\LYH-3-581\LYH-3-581-CRYSTALLIZATION-2 2018-11-24 21-42-15\DAD-
                  OJ(1-6)-80-20-1ML-10UL-ALL-60MIN.M
Last changed    : 9/26/2018 10:04:39 PM
Analysis Method : D:\METHOD\LWD\DAD-OD(1-2)-95-5--1ML-3UL-ALL-60MIN.M
Last changed    : 1/3/2019 10:49:04 AM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

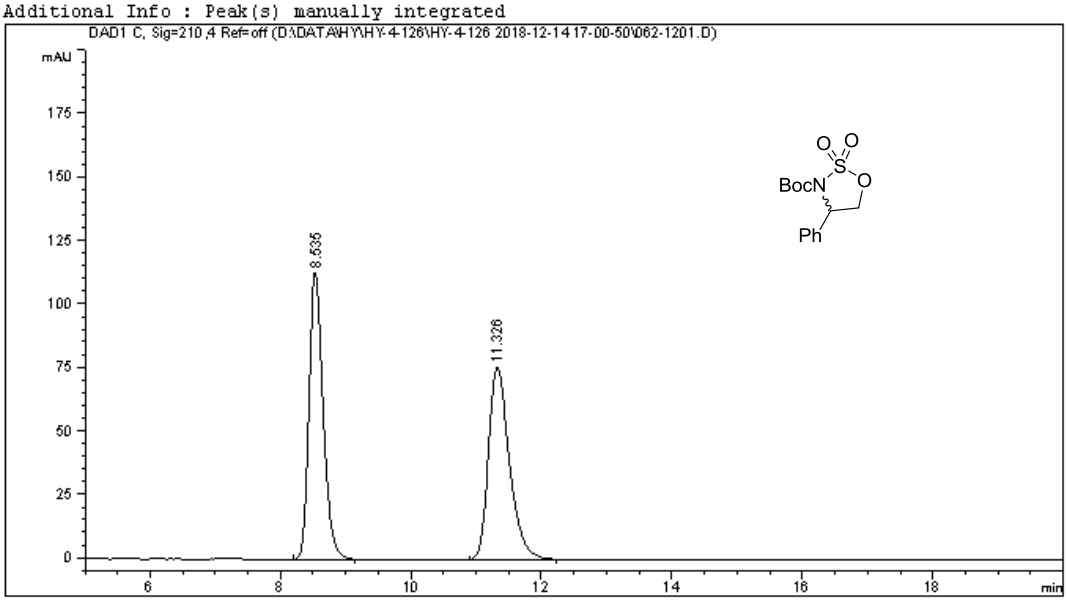



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=210,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  31.364 BB    0.7964 2.92119e4   509.88867 100.0000

Totals :                  2.92119e4   509.88867


======================================================================
```


Figure S96. HPLC spectrum of **2a** (Crystallization), related to **Scheme 3**.

Data File D:\DATA\HY\HY-4-126\HY-4-126 2018-12-14 17-00-50\062-1201.D
Sample Name: LYH-3-613-RAC-BOC-SUBSTRATE

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :  12
    Acq. Instrument : Instrument 2                    Location : Vial 62
    Injection Date  : 12/14/2018 9:14:36 PM               Inj :   1
                                                     Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\HY\HY-4-126\HY-4-126 2018-12-14 17-00-50\DAD-0D(1-2)-80-20-1ML-1UL-
                      ALL-60MIN.M
    Last changed    : 12/14/2018 9:46:59 PM
                      (modified after loading)
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 2:41:06 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

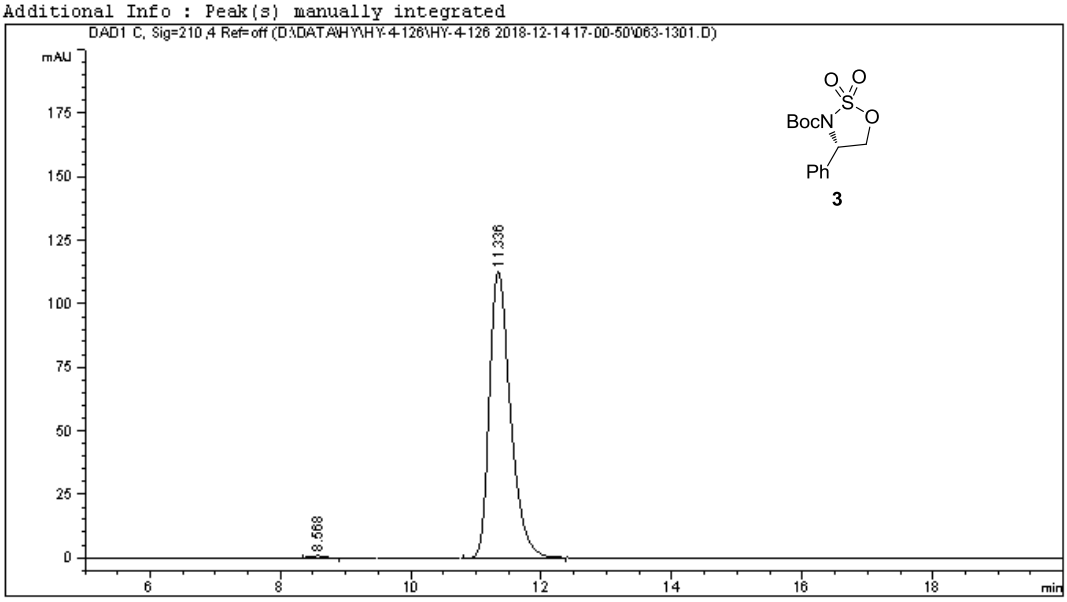



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   8.535 BB    0.2299 1704.14636  113.03381  50.2537
       2  11.326 BB    0.3302 1686.93750   75.62927  49.7463

    Totals :                  3391.08386  188.66309
```


Figure S97. HPLC spectrum of racemic-**3**, related to **Scheme 4**.

Data File D:\DATA\HY\HY-4-126\HY-4-126 2018-12-14 17-00-50\063-1301.D
Sample Name: LYH-3-616-EE-BOC-SUBSTRATE

```
    ====================================================================
    Acq. Operator   :                                Seq. Line :  13
    Acq. Instrument : Instrument 2                    Location : Vial 63
    Injection Date  : 12/14/2018 9:48:30 PM               Inj :   1
                                                     Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\HY\HY-4-126\HY-4-126 2018-12-14 17-00-50\DAD-0D(1-2)-80-20-1ML-1UL-
                      ALL-60MIN.M
    Last changed    : 12/14/2018 9:49:04 PM
                      (modified after loading)
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 2:41:06 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

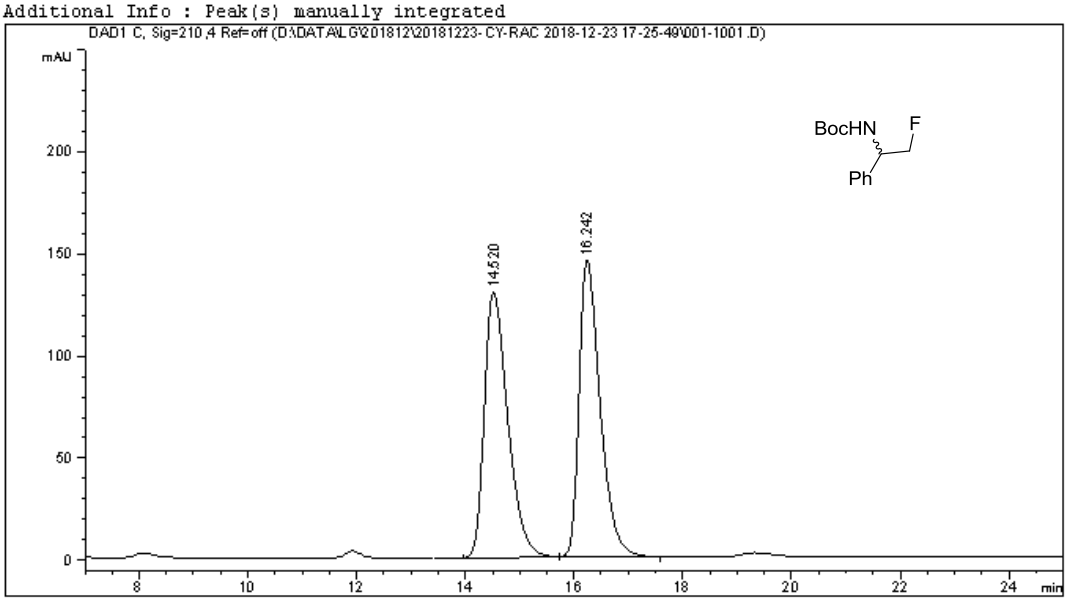



```
    ====================================================================
                           Area Percent Report
    ====================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   8.568 BB    0.1940   16.37181    1.04960   0.6433
       2  11.336 BB    0.3378 2528.56885  112.67541  99.3567

    Totals :                  2544.94065  113.72500
```


Figure S98. HPLC spectrum of **3**, related to **Scheme 4**.

Data File D:\DATA\LG\201812\20181223-CY-RAC 2018-12-23 17-25-49\001-1001.D
Sample Name: LYH-3-622-NH-F-RAC

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :  10
    Acq. Instrument : Instrument 2                    Location : Vial 1
    Injection Date  : 12/23/2018 8:48:40 PM               Inj :   1
                                                    Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\LG\201812\20181223-CY-RAC 2018-12-23 17-25-49\DAD-0J(1-6)-95-5-1ML-
                      1UL-ALL-60MIN.M
    Last changed    : 12/23/2018 9:13:53 PM
                      (modified after loading)
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 2:52:54 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

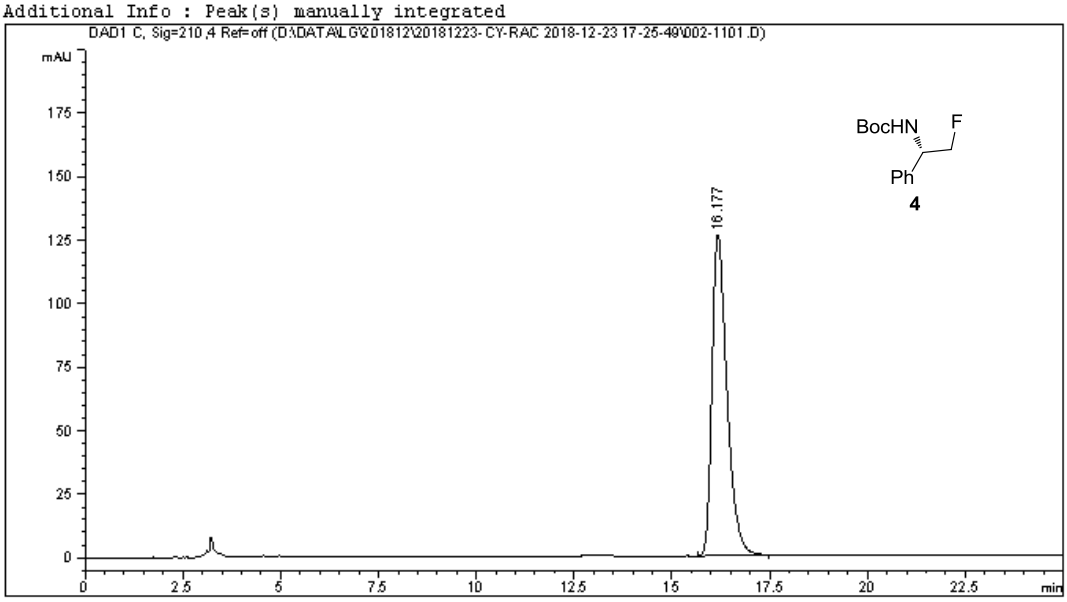



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  14.520 BB    0.4499 3898.82642  130.00089  50.0098
       2  16.242 BB    0.4030 3897.29517  145.24863  49.9902

    Totals :                  7796.12158  275.24951
```


Figure S99. HPLC spectrum of racemic-**4**, related to **Scheme 4**.

Data File D:\DATA\LG\201812\20181223-CY-RAC 2018-12-23 17-25-49\002-1101.D
Sample Name: LYH-3-622-NH-F-EE

```
    ======================================================================
    Acq. Operator   :                                Seq. Line :  11
    Acq. Instrument : Instrument 2                    Location : Vial 2
    Injection Date  : 12/23/2018 9:19:33 PM               Inj :  1
                                                    Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\LG\201812\20181223-CY-RAC 2018-12-23 17-25-49\DAD-0J(1-6)-95-5-1ML-
                      1UL-ALL-60MIN.M
    Last changed    : 12/23/2018 9:13:53 PM
                      (modified after loading)
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 2:55:48 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```

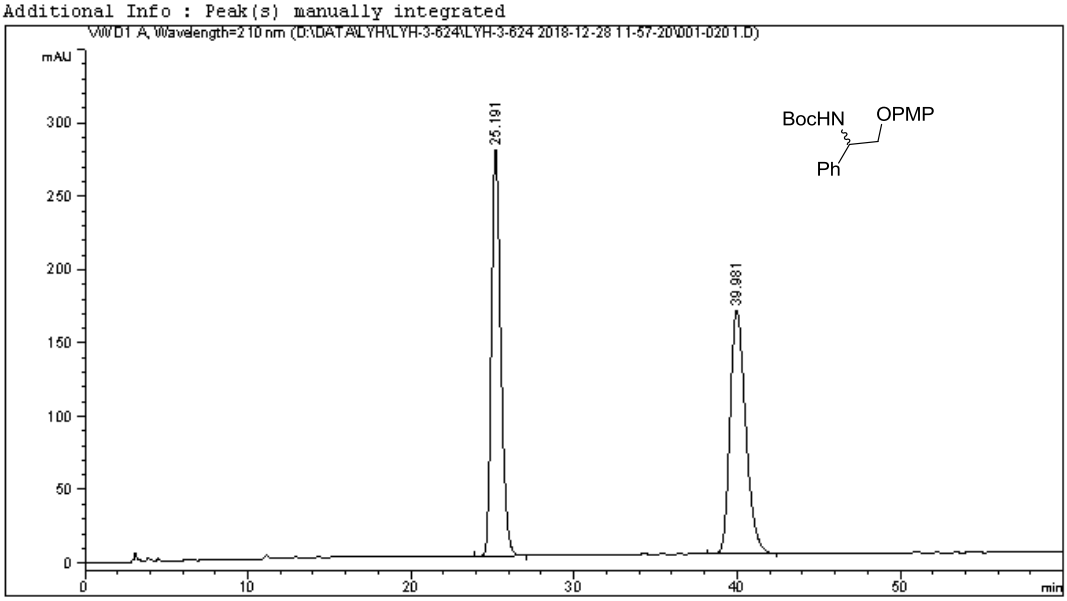



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,4 Ref=off

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  16.177 BB    0.3972 3374.46802  126.51146 100.0000

    Totals :                  3374.46802  126.51146
```


Figure S100. HPLC spectrum of **4**, related to **Scheme 4**.

Data File D:\DATA\LYH\LYH-3-624\LYH-3-624 2018-12-28 11-57-20\001-0201.D
Sample Name: LYH-3-624-RAC

```
======================================================================
Acq. Operator   :                               Seq. Line :   2
Acq. Instrument : Instrument 1                   Location : Vial 1
Injection Date  : 12/28/2018 12:09:00 PM             Inj :   1
                                                Inj Volume : 1.000 µl
Acq. Method     : D:\DATA\LYH\LYH-3-624\LYH-3-624 2018-12-28 11-57-20\VWD-AD(1-2)-95-5-1ML-
                  1UL-210NM-60MIN.M
Last changed    : 5/25/2018 9:31:30 AM
Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
Last changed    : 12/28/2018 2:57:56 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

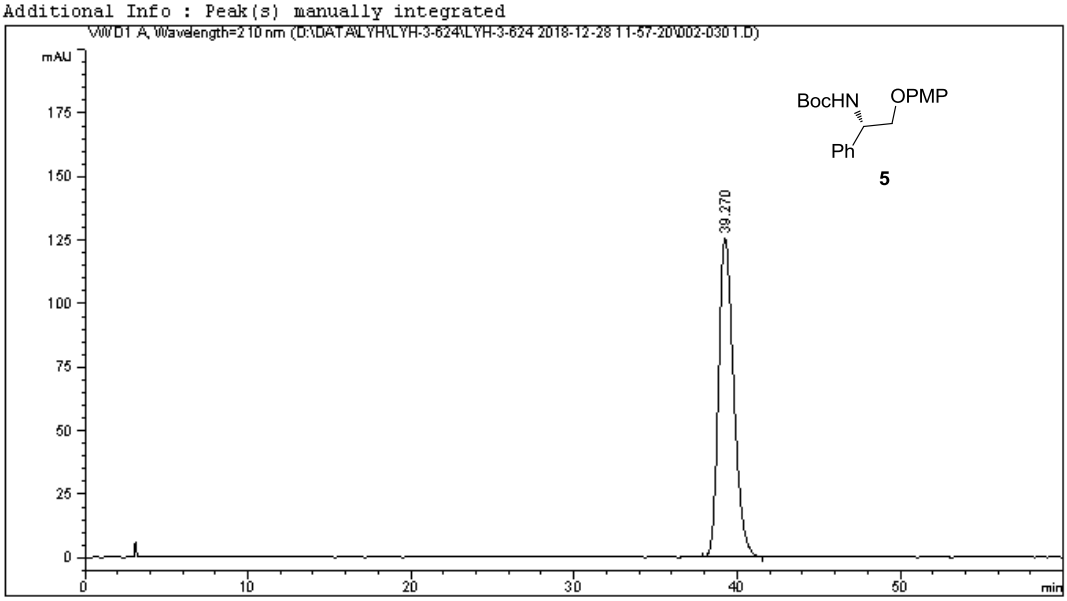



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  25.191 BB    0.6082 1.1006le4   277.19391  49.9842
   2  39.981 BB    1.0242 1.1013le4   165.95868  50.0158

Totals :                 2.20192e4   443.15259
```


Figure S101. HPLC spectrum of racemic-**5**, related to **Scheme 4**.

Data File D:\DATA\LYH\LYH-3-624\LYH-3-624 2018-12-28 11-57-20\002-0301.D
Sample Name: LYH-3-624

```
    ======================================================================
    Acq. Operator   :                               Seq. Line :   3
    Acq. Instrument : Instrument 1                   Location : Vial 2
    Injection Date  : 12/28/2018 1:09:45 PM              Inj :   1
                                                   Inj Volume : 1.000 µl
    Acq. Method     : D:\DATA\LYH\LYH-3-624\LYH-3-624 2018-12-28 11-57-20\VWD-AD(1-2)-95-5-1ML-
                      1UL-210NM-60MIN.M
    Last changed    : 5/25/2018 9:31:30 AM
    Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-95-5-1ML-5UL-ALL-120MIN.M
    Last changed    : 12/28/2018 2:59:17 PM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```



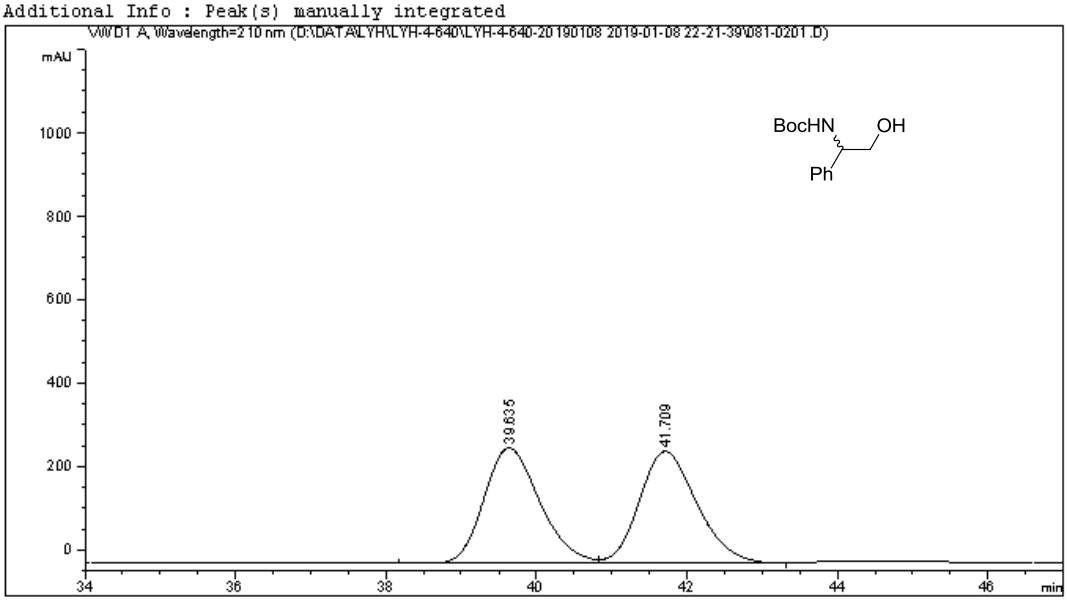

```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: VWD1 A, Wavelength=210 nm

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  39.270 BB    0.9983 8127.20410  125.54246 100.0000

    Totals :                  8127.20410  125.54246


    ======================================================================
```

Instrument 2 12/28/2018 2:59:22 PM

Figure S102. HPLC spectrum of **5**, related to **Scheme 4**.

Data File D:\DATA\LYH\LYH-4-640\LYH-4-640-20190108 2019-01-08 22-21-39\081-0201.D
Sample Name: LYH-4-640-RAC

```
======================================================================
Acq. Operator   :                              Seq. Line :   2
Acq. Instrument : Instrument 1                  Location : Vial 81
Injection Date  : 1/8/2019 10:34:15 PM               Inj :   1
                                               Inj Volume : 1.000 µl
Acq. Method     : D:\DATA\LYH\LYH-4-640\LYH-4-640-20190108 2019-01-08 22-21-39\VWD-AD(1-2)-92
                  -8-0.3ML-1UL-210NM-70MIN.M
Last changed    : 1/8/2019 10:17:36 PM
Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-96-4-0.8ML-5UL-ALL-110MIN.M
Last changed    : 1/12/2019 10:05:28 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```

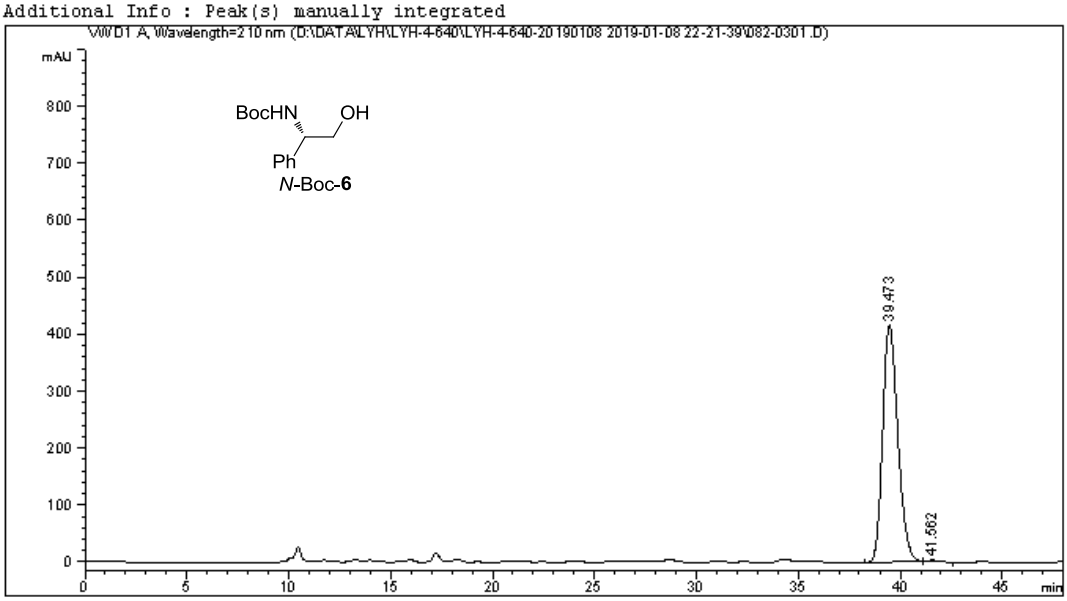



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  39.635 BV    0.7949 1.43188e4   277.06824  49.9931
   2  41.709 VB    0.8210 1.43228e4   268.66327  50.0069

Totals :                  2.86416e4   545.73151
```


Figure S103. HPLC spectrum of racemic-*N*-Boc-**6**, related to **Scheme 4**.

Data File D:\DATA\LYH\LYH-4-640\LYH-4-640-20190108 2019-01-08 22-21-39\082-0301.D
Sample Name: LYH-4-640-EE

```
======================================================================
Acq. Operator   :                                Seq. Line :   3
Acq. Instrument : Instrument 1                    Location : Vial 82
Injection Date  : 1/8/2019 11:45:01 PM                Inj :   1
                                                 Inj Volume : 1.000 µl
Acq. Method     : D:\DATA\LYH\LYH-4-640\LYH-4-640-20190108 2019-01-08 22-21-39\VWD-AD(1-2)-92
                  -8-0.3ML-1UL-210NM-70MIN.M
Last changed    : 1/8/2019 10:17:36 PM
Analysis Method : D:\METHOD\GUAN YUQING\DAD-0J(1-6)-96-4-0.8ML-5UL-ALL-110MIN.M
Last changed    : 1/12/2019 10:01:11 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  39.473 BB    0.7961 2.15158e4   416.24026  99.6387
   2  41.562 BB    0.5986   78.01003    1.90973   0.3613

Totals :                  2.15938e4   418.15000
```


Figure S104. HPLC spectrum of *N*-Boc-**6**, related to **Scheme 4**.

Transparent Methods

General remarks

All reactions and manipulations that were sensitive to air or moisture were performed in an argon-filled glovebox or using standard Schlenk techniques. Unless otherwise noted, all reagents and solvents were purchased from commercial suppliers and used without further purification. Anhydrous solvents were purchased from J&K Chemicals company, degassed with N_2 and transferred by syringe. Column Chromatography was performed with silica gel (300-400 mesh). Thin layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker ADVANCE III (400 MHz) spectrometer with $CDCl_3$, CD_3OD or DMSO-d_6 as the solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in parts per million (ppm, δ scale) downfield from TMS at 0.00 ppm and referenced to the $CDCl_3$ at 7.26 ppm (for ^{1}H NMR) or 77.0 ppm (for ^{13}C NMR). Data are reported as: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz) and signal area integration in natural numbers. ^{13}C NMR analyses were run with decoupling. Enantiomeric excess values were determined by Daicel chiral column on an Agilent 1260 Series HPLC instrument. Optical rotations $[\alpha]_D^{25}$ were measured on a PERKIN ELMER polarimeter 343 instrument.

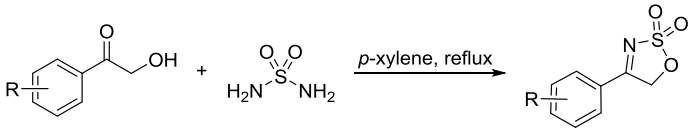
All the starting aromatic α-hydroxy ketones are the known compounds and were prepared according to the reported literature. [1-4] Aliphatic α-hydroxy ketones were purchased from J&K Chemicals company.

General procedure for the synthesis of substrates

1) **Synthesis of cyclic sulfamidate imines:**

Method A:

Scheme S1:

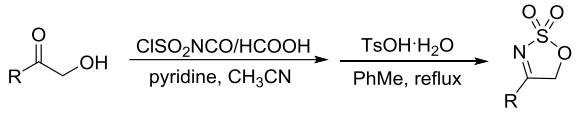


Substrates **1a-1d** and **1f-1n** were synthesized according to the procedure: [5] the corresponding α-hydroxy ketone (8.0 mmol, 1.0 equiv.) and sulfamide (12.0 mmol, 1.5 equiv.)

were added in 50 mL of *p*-xylene and the solution was refluxed at 150 °C until full consumption of the α-hydroxy ketone by TLC monitoring. The solution was concentrated to remove *p*-xylene under reduced pressure. And the crude was diluted with EtOAc and washed with water and then brine. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1 to 3:1) and recrystallized with hexane and CH_2Cl_2 to give the corresponding cyclic sulfamidate imines.

Method B:

Scheme S2:



Substrates **1e**, **1o** and **1p** were synthesized according to the procedure: [6,7] Formic acid (30 mmol, 1.5 equiv.) was added dropwise to neat chlorosulfonyl isocyanate (30 mmol, 1.5 equiv.) at 0 °C with stirring. Vigorous gas evolution was observed during the addition process. The resulting viscous suspension was stirred at 0 °C until the mixture solidified. 20 mL acetonitrile was added and the solution was stirred for 30 min at room temperature to afford a solution of $ClSO_2NH_2$.

The reaction mixture was cooled to 0 °C and a solution of corresponding α-hydroxy ketone (20 mmol, 1.0 equiv.) and pyridine (30 mmol, 1.5 equiv.) in 10 mL acetonitrile was added dropwise. The reaction was warmed to room temperature and stirred for overnight. The solution was filtered through a short silica column and washed with EtOAc. The solvent was removed in vacuo and then added toluene and *p*-toluenesulfonic acid (0.1 equiv.), and the reaction mixture was heated to reflux for 1-2 h. The solvent was evaporated, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate to give the desired cyclic sulfamidate imines.

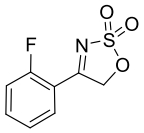
2) Synthesis of N-sulfonyl imines:

The N-sulfonyl imine substrates **1q** and **1r** was prepared according to previously reported method with slight modifications [8]: In a 100 mL round-bottomed flask fitted with a condenser was charged with the ketone (30 mmol, 1.0 equiv.), *p*-toluenesulfonamide (33 mmol, 1.1 equiv.)

and $Ti(OEt)_4$ (39 mmol, 1.3 equiv.) in dry toluene (60 mL), and the solution was refluxed at 150 °C until full consumption of the ketone by TLC monitoring. The solution was cooled to room temperature, diluted with EtOAc, quenched with saturated $NaHCO_3$ until no more precipitate was produced, and filtered through a pad of celite. The crude product was purified by flash chromatography on silica gel using mixtures of petroleum ether and EtOAc as the eluent.

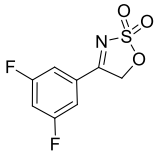
The characterization data of compounds **1a**, **1b**, **1d**, **1h**, **1o** are in accordance with the reported data in the literature. [6] The characterization data of compounds **1f**, **1j-1k**, **1m-1n** are in accordance with the reported data in the literature. [5] The characterization data of compounds **1c**, **1e**, **1l** are in accordance with the reported data in the literature. [7]

4-(2-fluorophenyl)-5*H*-[1, 2, 3]-oxathiazole 2, 2-dioxide **1g**



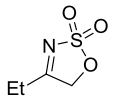
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31-8.27 (m, 1H), 7.78-7.72 (m, 1H), 7.43-7.39 (m, 1H), 7.30-7.25 (m, 1H), 5.60 (d, *J* = 3.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.43 (d, *J* = 3.0 Hz), 163.28 (d, *J* = 256.0 Hz), 138.03 (d, *J* = 9.0 Hz), 131.32 (d, *J* = 2.0 Hz), 125.76 (d, *J* = 3.0 Hz), 116.99 (d, *J* = 21.0 Hz), 115.45 (d, *J* = 11.0 Hz), 76.88.

4-(3,5-difluorophenyl)-5*H*-[1, 2, 3]-oxathiazole 2, 2-dioxide **1i**



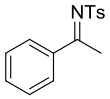
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.43 (m, 2H), 7.26-7.18 (m, 1H), 5.54 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.36, 164.60 (d, *J* = 12.0 Hz), 162.08 (d, *J* = 12.0 Hz), 129.83, 112.09-110.96 (m), 74.08.

4-ethyl-5*H*-[1, 2, 3]-oxathiazole 2,2-dioxide **1p**



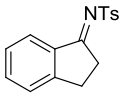
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (s, 2H), 2.70-2.64 (m, 2H), 1.34 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.50, 76.25, 25.35, 8.96.

4-methyl-N-(1-phenylethylidene) benzenesulfonamide **1q**



White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 -7.89 (m, 4H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.99 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.82, 143.49, 138.59, 137.45, 133.13, 129.42, 128.56, 128.22, 127.03, 21.57, 21.14.

N-(2, 3-dihydro-1H-inden-1-ylidene)-4-methylbenzenesulfonamide **1r**



Light green solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 3H), 3.43-3.41 (m, 2H), 3.20-3.17 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.17, 153.77, 143.55, 137.95, 137.89, 135.06, 129.38, 127.40, 127.21, 125.80, 124.65, 32.92, 29.11, 21.53.

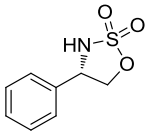
General procedure for the asymmetric hydrogenation

A stock solution was made by mixing $Ni(OAc)_2$ with (*S*, *S*)-Ph-BPE in a 1:1.1 molar ratio in CF_3CH_2OH and stirred at room temperature for 4-5 h until forming homogeneous yellow solution in a argon-filled glovebox. An aliquot of the catalyst solution (0.2 mL, 0.001 mmol) was transferred by syringe into the vials with different substrates **1** (0.1 mmol for each) in CF_3CH_2OH (0.8 mL). The vials were subsequently transferred into an autoclave before closed it, and moved it out from golvebox. The autoclave quickly purged with hydrogen gas for three times, then pressurized to 60 atm H_2. The reaction was then stirred at 80 °C for 24 h. After completed, the hydrogen gas was released slowly and carefully. The solution was diluted with EtOAc and passed through a short column of silica gel (eluant: EtOAc) to remove the metal complex, and

concentrated in vacuo. The ee values of all compounds **2** were determined by HPLC analysis or GC analysis on a chiral stationary phase.

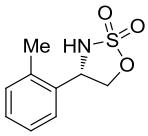
The absolute configurations of products **2a-2f**, **2h**, **2j-2o** were determined by comparison of analytical data (optical rotation) with the literature. [5-7] The absolute configurations of products **2q-2r** were determined by comparison of analytical data (optical rotation) with the literature. [9-10] The absolute configurations of others were assigned by analogy.

(*S*)-4-phenyl-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2a**



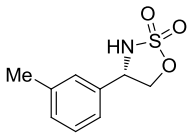
White solid; >99% conv., 19.7 mg, 99% yield, 94% ee; $[\alpha]_D^{25}$ = +29.7 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 32.1 min (major), 36.0 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.38 (m, 5H), 5.10-5.05 (m, 1H), 4.97 (d, *J* = 6.3 Hz, 1H), 4.83 (dd, *J* = 8.7, 6.8 Hz, 1H), 4.44 (t, *J* = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.32, 129.51, 129.36, 126.66, 75.05, 59.55.

(*S*)-4-(*o*-tolyl)-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2b**



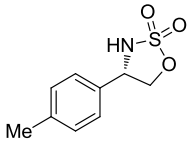
Pale yellow solid; >99% conv., 20.5 mg, 96% yield, 96% ee; $[\alpha]_D^{25}$ = +17.3 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 27.6 min (major), 34.1 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.53 (m, 1H), 7.30-7.26 (m, 2H), 7.22-7.20 (m, 1H), 5.36-5.30 (m, 1H), 4.86-4.81 (m, 2H), 4.43 (t, *J* = 8.6 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.75, 133.24, 131.06, 129.14, 127.13, 125.66, 74.30, 56.20, 19.10.

(*S*)-4-(*m*-tolyl)-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2c**



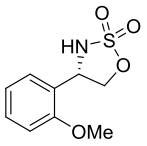
Pale yellow solid; >99% conv., 21.0 mg, 99% yield, 92% ee; $[\alpha]_D^{25}$ = +28.4 (c =1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 32.4 min (major), 35.6 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.5 Hz, 1H), 7.22-7.18 (m, 3H), 5.06-5.00 (m, 1H), 4.89 (d, *J* = 5.1 Hz, 1H), 4.83-4.79 (m, 1H), 4.43 (t, *J* = 8.6 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.32, 135.14, 130.26, 129.23, 127.24, 123.72, 75.11, 59.57, 21.34.

(*S*)-4-(*p*-tolyl)-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2d**



Pale yellow solid; >99% conv., 21.1 mg, 99% yield, 94% ee; $[\alpha]_D^{25}$ = +22.3 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 24.8 min (major), 31.4 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.29 (m, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 5.06-5.00 (m, 1H), 4.90 (d, *J* = 6.5 Hz, 1H), 4.81-4.77 (m, 1H), 4.42 (t, *J* = 8.7 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.59, 132.12, 129.98, 126.63, 75.21, 59.43, 21.14.

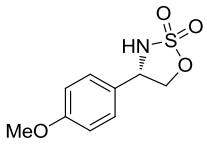
(*S*)-4-(2-methoxyphenyl)-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2e**



White solid; >99% conv., 22.5 mg, 98% yield, >99% ee; $[\alpha]_D^{25}$ = +42.2 (c = 0.7, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OD-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 12.4 min (minor), 26.2 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.36 (m, 2H), 7.04-7.00 (m, 1H), 6.95 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.29 (d, *J* = 9.2 Hz, 1H), 5.22-5.16 (m, 1H), 4.82-4.79 (m, 1H), 4.48 (t, *J* = 8.3

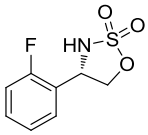
Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.82, 130.59, 128.69, 122.13, 121.33, 110.89, 74.68, 57.19, 55.51.

(*S*)-4-(4-methoxyphenyl)-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2f**



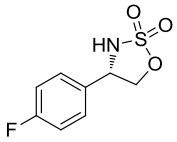
Pale yellow solid; >99% conv., 21.5 mg, 94% yield, 93% ee; $[\alpha]_D^{25}$ = +17.3 (c = 0.7, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 54.1 min (major), 63.4 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 5.05-4.99 (m, 1H), 4.86 (d, *J* = 6.9 Hz, 1H), 4.80-4.76 (m, 1H), 4.43 (t, *J* = 8.7 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.42, 128.17, 126.88, 114.68, 75.26, 59.27, 55.38.

(*S*)-4-(2-fluorophenyl)-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2g**



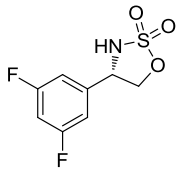
Pale yellow solid; >99% conv., 20.7 mg, 97% yield, 97% ee; $[\alpha]_D^{25}$ = +15.6 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 18.2 min (major), 20.7 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.59 (m, 1H), 7.40-7.35 (m, 1H), 7.26-7.22 (m, 1H), 7.13-7.08 (m, 1H), 5.40-5.35 (m, 1H), 5.09 (d, *J* = 7.8 Hz, 1H), 4.95-4.91 (m, 1H), 4.46-4.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.04 (d, *J* = 245.0 Hz), 130.88 (d, *J* = 9.0 Hz), 127.96 (d, *J* = 4.0 Hz), 125.10 (d, *J* = 3.0 Hz), 123.14 (d, *J* = 13.0 Hz), 115.77 (d, *J* = 21.0 Hz), 74.06 (d, *J* = 3.0 Hz), 53.89 (d, *J* = 4.0 Hz).

(*S*)-4-(4-fluorophenyl)-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2h**



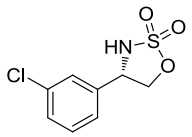
Pale yellow solid; >99% conv., 21.0 mg, 99% yield, 94% ee; $[\alpha]_D^{25}$ = +23.9 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 28.0 min (major), 41.1 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.15-7.10 (m, 2H), 5.10-5.06 (m, 2H), 4.85-4.81 (m, 1H), 4.43-4.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.15 (d, *J* = 248.0 Hz), 131.32 (d, *J* = 3.0 Hz), 128.61 (d, *J* = 8.0 Hz), 116.37 (d, *J* = 22.0 Hz), 74.91, 58.89.

(*S*)-4-(3,5-difluorophenyl)-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2i**



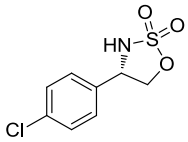
White solid; >99% conv., 22.6 mg, 96% yield, 91% ee; $[\alpha]_D^{25}$ = +14.9 (c = 0.7, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 20.8 min (major), 26.5 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01-6.98 (m, 2H), 6.87-6.81 (m, 1H), 5.13 (d, *J* = 7.2 Hz, 1H), 5.09-5.04 (m, 1H), 4.90-4.86 (m, 1H), 4.39-4.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.40 (dd, *J* = 250.0, 13.0 Hz), 140.06 (t, *J* = 9.0 Hz), 109.61 (q, *J* = 18.0, 7.0 Hz), 104.78 (t, *J* = 25.0 Hz), 74.07, 58.42 (t, *J* = 2.0 Hz).

(*S*)-4-(3-chlorophenyl)-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2j**



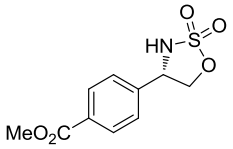
Pale yellow solid; >99% conv., 22.9 mg, 98% yield, 91% ee; $[\alpha]_D^{25}$ = +17.3 (c = 0.7, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 36.8 min (major), 57.5 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.39-7.37 (m, 2H), 7.35-7.31 (m, 1H), 5.09-5.03 (m, 2H), 4.88-4.84 (m, 1H), 4.44-4.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.74, 135.22, 130.65, 129.59, 126.79, 124.70, 74.50, 58.82.

(*S*)-4-(4-chlorophenyl)-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2k**



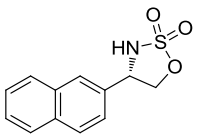
Pale yellow solid; >99% conv., 22.5 mg, 96% yield, 94% ee; $[\alpha]_D^{25}$ = +13.6 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 31.1 min (major), 39.1 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.36 (m, 4H), 5.09-5.00 (m, 2H), 4.86-4.82 (m, 1H), 4.41-4.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.42, 134.12, 129.53, 128.03, 74.67, 58.86.

(*S*)-4-[2, 2-dioxido-(1, 2, 3)-oxathiazolidin-4-yl] phenyl acetate **2l**



Yellow solid; >99% conv., 24.4 mg, 95% yield, 93% ee; $[\alpha]_D^{25}$ = +17.3 (c = 0.8, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 220 nm; t_R = 66.6 min (major), 76.6 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 5.33 (s, 1H), 5.12 (d, *J* = 9.1 Hz, 1H), 4.89-4.85 (m, 1H), 4.41-4.37 (m, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.35, 140.71, 131.03, 130.47, 126.58, 74.38, 59.02, 52.38.

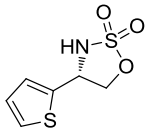
(*S*)-4-(naphthalen-2-yl)-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2m**



Yellow solid; >99% conv., 24.2 mg, 97% yield, 92% ee; $[\alpha]_D^{25}$ = +20.3 (c = 0.6, MeOH); The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 80:20; flow rate = 0.8 mL/min; UV detection at 210 nm; t_R = 11.6 min (major), 14.7 min (minor). ^{1}H NMR (400 MHz, CD_3OD) δ 7.94–7.86 (m, 4H), 7.59 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.52-7.49 (m, 2H), 5.23 (t, *J* = 7.5 Hz, 1H), 4.99-4.95 (m, 1H), 4.45 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR

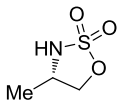
(100 MHz, CD_3OD) δ 134.46, 133.43, 133.25, 128.54, 127.66, 127.35, 126.21, 126.20, 125.77, 123.65, 74.65, 59.17.

(*R*)-4-(thiophen-2-yl)-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2n**



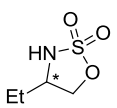
White solid; 65% conv., 11.3 mg, 55% yield, 95% ee; $[\alpha]_D^{25}$ = +4.3 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 220 nm; t_R = 37.2 min (minor), 42.0 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.18-7.17 (m, 1H), 7.05 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.37-5.31 (m, 1H), 4.87-4.83 (m, 2H), 4.56 (t, *J* = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.32, 127.59, 127.16, 127.09, 75.22, 55.41.

(*S*)-4-methyl-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2o**



Colorless oil; >99% conv., 13.4 mg, 98% yield, 83% ee; $[\alpha]_D^{25}$ = +28.3 (c = 0.7, $CHCl_3$); The enantiomeric excess was determined by GC (Supelco β-DEX^{TM}325, df = 0.25 μm, 0.25 mm i.d.×30 m, fused silica capillary column); carrier gas, N_2 (flow 1.2 mL/min); injection temp, 250 °C; initial column temperature, 70 °C; progress rate, 0.3 °C/min; final column temperature, 160 °C; this temperature is held for 30min; detector temp, 260 °C; t_R = 177.9 min (major), 183.2 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67-4.60 (m, 2H), 4.14-4.05 (m, 2H), 1.41 (t, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.40, 52.35, 17.47.

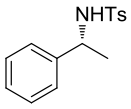
(-)-4-ethyl-[1, 2, 3]-oxathiazolidine 2, 2-dioxide **2p**



Orange oil; >99% conv., 14.5 mg, 96% yield, 92% ee; $[\alpha]_D^{25}$ = −11.3 (c = 0.6, MeOH); The enantiomeric excess was determined by GC (Supelco β-DEX^{TM}325, df = 0.25 μm, 0.25 mm

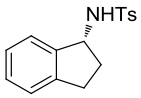
i.d.×30 m, fused silica capillary column); carrier gas, N_2 (flow 1.2 mL/min); injection temp, 250 °C; initial column temperature, 70 °C; progress rate, 1.0 °C/min; final column temperature, 160 °C; this temperature is held for 30 min; detector temp, 260 °C; t_R = 85.9 min (major), 89.0 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65-4.58 (m, 2H), 4.17 (t, *J* = 8.1 Hz, 1H), 3.92-3.86 (m, 1H), 1.82-1.65 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.77, 57.83, 25.80, 10.09.

(*R*)-4-methyl-N-(1-phenylethyl) benzenesulfonamide **2q**



White solid; >99% conv., 26.4 mg, 96% yield, 97% ee; $[\alpha]_D^{25}$ = +55.6 (c = 1.1, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 16.4 min (minor), 25.2 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.61 (m, 2H), 7.20 -7.16 (m, 5H), 7.12-7.08 (m, 2H), 5.08 (d, *J* = 7.2 Hz, 1H), 4.49-4.42 (m, 1H), 2.38 (s, 3H), 1.41 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.07, 141.99, 137.51, 129.39, 128.46, 127.37, 127.03, 126.06, 53.57, 23.52, 21.46.

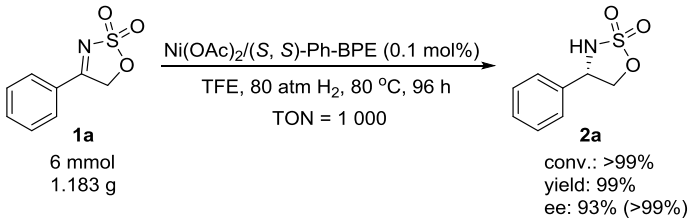
(*R*)-N-(2, 3-dihydro-1H-inden-1-yl)-4-methylbenzenesulfonamide **2r**



Pale yellow solid; >99% conv., 27.8 mg, 97% yield, >99% ee; $[\alpha]_D^{25}$ = +29.7 (c = 0.58, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OD-H column, hexane: isopropanol = 90:10; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 16.4 min (major), 22.8 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.82 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.20-7.12 (m, 3H), 7.08 (d, *J* = 7.4 Hz, 1H), 4.88-4.79 (m, 2H), 2.88-2.85 (m, 1H), 2.76-2.70 (m, 1H), 2.45 (s, 3H), 2.32-2.28 (m, 1H), 1.76-1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.41, 142.75, 141.94, 138.07, 129.74, 128.21, 127.07, 126.77, 124.74, 124.04, 58.64, 34.61, 29.91, 21.54.

Procedure for asymmetric hydrogenation with gram-scale

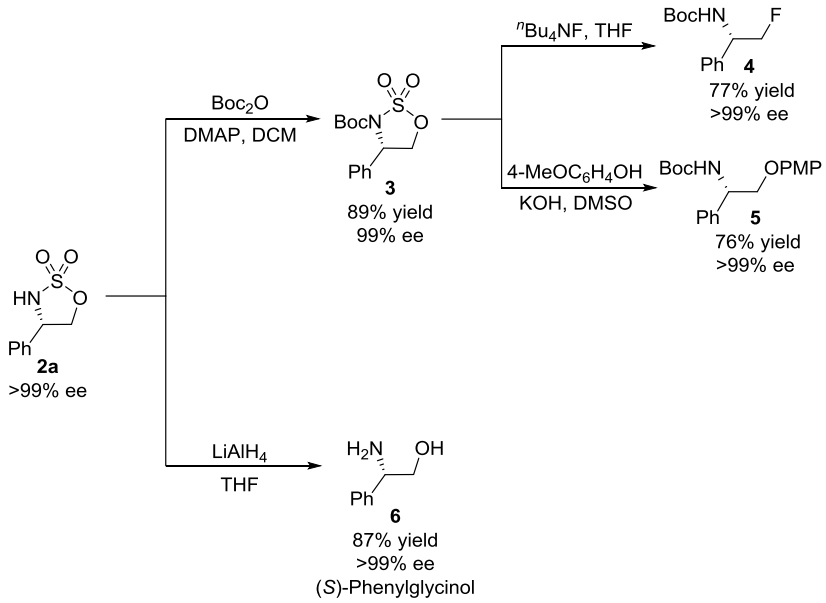
Scheme S3:



A stock solution was made by mixing $Ni(OAc)_2$ with (*S*, *S*)-Ph-BPE in a 1:1.1 molar ratio in CF_3CH_2OH and stirred at room temperature for 4-5 h until forming homogeneous yellow solution in a argon-filled glovebox. An aliquot of the catalyst solution (1.2 mL, 0.006 mmol) was transferred by syringe into the vials charged with substrate **1a** (6.0 mmol) in 0.8 mL CF_3CH_2OH. The vial was transferred into an autoclave, which was subsequently charged with hydrogen gas. The reaction was then stirred under 80 atm H_2 at 80 °C for 4 days. After completed, the hydrogen gas was released slowly and carefully. The solution was passed through a short column of silica gel (eluant: EtOAc) to afford the **2a** (1.19 g, >99% conversion, 99% yield, 93% ee). And >99% ee can be obtained through simple crystallization in CH_2Cl_2/hexane.

Synthetic transformation

Scheme S4:



Synthesis of (*S*)-tert-butyl 4-phenyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide 3:

To a solution of (*S*)-**2a** (199.2 mg, 1.0 mmol, >99% ee) and 4-dimethylaminopyridine (DMAP, 24.4 mg, 0.2 mmol) in 3 mL dry dichloromethane was added di-tert-butyldicarbonate (327.4 mg, 1.5 mmol) and the mixture was stirred at room temperature for overnight. After solvent

evaporation, the residue was purified by silica gel column chromatography to afford the product **3** as white solid (265.0 mg, 89% yield, 99% ee). The absolute configuration of product **3** was determined by comparison of analytical data (optical rotation) with the literature. [7] $[\alpha]_D^{25}$ = +44.0 (c = 0.8, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OD-H column, hexane: isopropanol = 80:20; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 8.6 min (minor), 11.3 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.38 (m, 5H), 5.29 (dd, *J* = 6.7, 4.2 Hz, 1H), 4.88 (dd, *J* = 9.3, 6.7 Hz, 1H), 4.41 (dd, *J* = 9.3, 4.2 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.23, 136.87, 129.24, 129.13, 126.12, 85.58, 71.77, 60.73, 27.79.

Synthesis of (*S*)-tert-butyl (2-fluoro-1-phenylethyl) carbamate 4:

To a solution of **3** (29.9 mg, 0.1 mmol) in 1 mL dry THF was added ^{n}Bu$_4$NF (0.2 mL, 0.2 mmol, 2 equiv., 1 M in THF) and the reaction was stirred at 60 °C overnight. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give the desired product **4** as white solid (18.4 mg, 77% yield, >99% ee). [11-12] The absolute configuration of product **4** was determined by comparison of analytical data (optical rotation) with the literature.[13] $[\alpha]_D^{25}$ = +29.7 (c = 0.9, $CHCl_3$); The enantiomeric excess was determined by HPLC on Chiralcel OJ-H column, hexane: isopropanol = 95:5; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 14.5 min (minor), 16.2 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.19-5.18 (m, 1H), 4.98-4.91 (m, 1H), 4.73-4.49 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.14, 138.23, 128.71, 127.91, 126.74, 85.10 (d, *J* = 174.0 Hz), 80.00, 54.51, 28.29.

Synthesis of (*S*)-tert-butyl (2-(4-methoxyphenoxy)-1-phenylethyl) carbamate 5:

The compound **3** (59.9 mg, 0.2 mmol) and 4-methoxyphenol (49.7 mg, 0.4 mmol, 2 equiv.) were dissolved in 1 mL DMSO, KOH (50 μL, 8 M) was added and the reaction was stirred at room temperature overnight. The reaction was diluted with water and extracted with DCM, washed with brine and dried on anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography to afford the product **5** as colorless oil solid (51.9 mg, 76% yield, >99% ee). [11-12] The absolute configuration of product **5** was assigned by analogy with the literature. [11-12] $[\alpha]_D^{25}$ = +7.9 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined

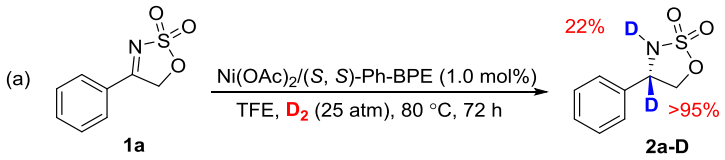
by HPLC on Chiralpak AD-H column, hexane: isopropanol = 95:5; flow rate = 1.0 mL/min; UV detection at 210 nm; t_R = 25.2 min (minor), 39.3 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.33 (m, 4H), 7.30-7.27 (m, 1H), 6.81 (s, 4H), 5.35 (s, 1H), 5.03 (s, 1H), 4.19-4.09 (m, 2H), 3.75 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.30, 154.09, 152.46, 139.85, 128.50, 127.53, 126.73, 115.61, 114.58, 79.74, 71.32, 55.67, 53.92, 28.32.

Synthesis of (*S*)-Phenylglycinol 6:

To a suspension of lithium aluminum hydride (46 mg, 1.2 mmol) in anhydrous THF (5 mL), a solution of (*S*)-**2a** (79.7 mg, 0.4 mmol) in anhydrous THF (5 mL) was added dropwise under N_2 protected. After refluxed overnight, the mixture was cooled to room temperature and quenched with water (10 mL). The THF was removed under vacuum and the aqueous layer was extracted with DCM three times (20 mL×3), and the combined organic layers were dried over Na_2SO_4 and concentrated to provide the desired product as pale yellow solid (48.0 mg, 87% yield, >99% ee). The ee values of (*S*)-Phenylglycinol **6** was determined with *N*-Boc-**6** by converting to tert-butyl (2-hydroxy-1-phenylethyl) carbamate according to the reported literature. [14] The enantiomeric excess was determined by HPLC on Chiralpak AD-H column, hexane: isopropanol = 92:8; flow rate = 0.3 mL/min; UV detection at 210 nm; t_R = 39.5 min (major), 41.6 min (minor). $[\alpha]_D^{25}$ = +37.4 (c = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H), 4.06-4.03 (m, 1H), 3.76-3.72 (m, 1H), 3.56 (dd, *J* = 10.8, 8.4 Hz, 1H), 2.24 (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.53, 128.62, 127.51, 126.41, 67.92, 57.28.

Deuterium labeling studies

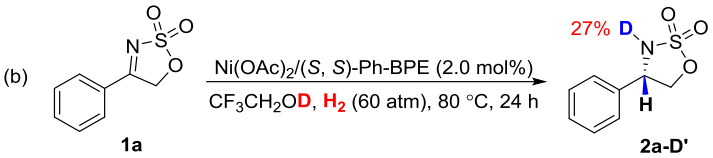
Scheme S5:



A stock solution was made by mixing $Ni(OAc)_2$ with (*S*, *S*)-Ph-BPE in a 1:1.1 molar ratio in CF_3CH_2OH and stirred at room temperature for 4-5 h until forming homogeneous yellow solution in a argon-filled glovebox. An aliquot of the catalyst solution (0.2 mL, 0.001 mmol) was transferred by syringe into the vial charged with substrate **1a** (0.1 mmol) in CF_3CH_2OH (0.8 mL).

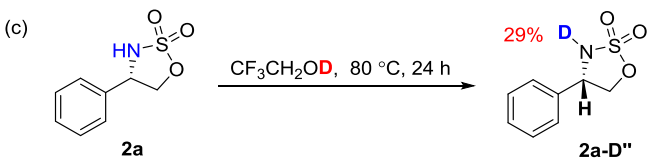
The vial was subsequently transferred into an autoclave before closed it, and moved it out from golvebox. The autoclave quickly purged with deuterium gas for three times, then pressurized to 25 atm D_2. The reaction was then stirred at 80 °C for 72 h. After completed, the D_2 gas was released slowly and carefully. The solution was diluted with EtOAc and passed through a short column of silica gel (eluant: EtOAc) to remove the metal complex. The solvent was evaporated under reduced pressure to afford the desired compound and was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.38 (m, 5H), 4.94 (s, 0.78 H), 4.83 (d, *J* = 8.8 Hz, 1H), 4.44 (d, *J* = 8.7 Hz, 1H).

Scheme S6:



A stock solution was made by mixing $Ni(OAc)_2$ with (*S*, *S*)-Ph-BPE in a 1:1.1 molar ratio in CF_3CH_2OD and stirred at room temperature for 4-5 h until forming homogeneous yellow solution in a argon-filled glovebox. An aliquot of the catalyst solution (0.2 mL, 0.002 mmol) was transferred by syringe into the vial charged with substrate **1a** (0.1 mmol) in CF_3CH_2OD (0.8 mL). The vial was subsequently transferred into an autoclave before closed it, and moved it out from golvebox. The autoclave quickly purged with hydrogen gas for three times, then pressurized to 60 atm H_2. The reaction was then stirred at 80 °C for 24 h. After completed, the H_2 gas was released slowly and carefully. The solution was diluted with EtOAc and passed through a short column of silica gel (eluant: EtOAc) to remove the metal complex. The solvent was evaporated under reduced pressure to afford the desired compound and was determined by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.38 (m, 5H), 5.11-5.05 (m, 1H), 4.84 (dd, *J* = 8.7, 6.8 Hz, 1H), 4.79 (d, *J* = 6.5 Hz, 0.73 H), 4.46 (t, *J* = 8.6 Hz, 1H).

Scheme S7:



Compound **2a** (10 mg) was dissolved in 0.5 mL CF_3CH_2OD and stirred at 80 ℃ for 24 h. After completed, the solvent was evaporated under reduced pressure to afford the desired compound and was determined by ^1H NMR analysis. ^1H NMR (600 MHz, $CDCl_3$) δ 7.46-7.40 (m, 5H), 5.08 (t, *J* = 7.6 Hz, 1H), 4.84 (dd, *J* = 8.8, 6.8 Hz, 1H), 4.81 (brs, 0.71 H), 4.46 (t, *J* = 8.7 Hz, 1H).

Supplemental Reference

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