NEW APPROACHES TO THE SYNTHESIS OF HETEROCYCLIC MOLECULES

By

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ABSTRACT OF THE DISSERTATION

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Whether found in nature or made in the lab, small fused-ring heterocyclic molecules have found many medicinal applications. Making these molecules by building up structural complexity in a cheap and efficient manner is a driving force in organic synthesis, particularly when trying to gain access to a single enantiomer of the product. A number of synthetic approaches make use of stoichiometric and costly reagents, and involve multiple changes in the oxidation state of the product. Many of the enantioselective approaches rely on inefficient chiral auxiliaries or recrystallization techniques.

This dissertation presents a new enantioselective approach to the synthesis of important lactam products, one that makes use of anion-binding by a thiourea organocatalyst to stabilize the ion pair intermediates. Enantioenriched γ- and δ-lactams have been prepared by this approach. A method by which to synthesize useful *N,S*-acetals directly by combining their thiol and amine precursors, and which requires just a catalytic amount of organic acid, is also disclosed. The reaction mechanisms of these novel transformations are also explored.

ACKNOWLEDGEMENTS

DEDICATION

To all the people who enjoy hunting down and reading other people's thesis acknowledgements.

Shine on, you crazy diamonds.

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Chapter 1. Introduction to Asymmetric Thiourea Organocatalysis

1.1 Organocatalysis

From the 1990s onwards, organocatalysis has grown as a field of interest and emerged as an attractive complement to traditional metal catalysis.[1] Many subsets of this field, defined by the use of a substoichiometric organic molecule to catalyse a reaction,[2] have been developed. Organocatalysts are typically more stable to air and moisture than transition metals, and are usually cheaper to build. One of the current drawbacks is that organocatalysts require higher catalyst loadings than transition metals, and often have issues with long-term turnover. Overcoming these hurdles is what drives the field toward the development of new organocatalysts that are more powerful and selective.

Organocatalysts can be roughly divided into two groups: those that form a temporary covalent bond with a substrate (e.g. iminium/enamine catalysis), and those that use non-covalent interactions to activate the substrates (e.g. hydrogen-bonding, ionic interactions) (Figure 1.1). This introduction will focus on the latter category, which includes hydrogen-bonding catalysis,[3] phase transfer catalysis, and Brønsted acid catalysis.[4] Although the interaction of organocatalysts with cationic substrates is well-developed, this introduction will focus in particular on the anionic examples from the literature.[5] When interacting with an ionic species, the catalyst can either remain neutral (anion-binding) or carry a counterion charge (anion-directing).

Figure 1.1 Non-covalent organocatalysis

Hydrogen bonding   Anion-binding   Anion-directing
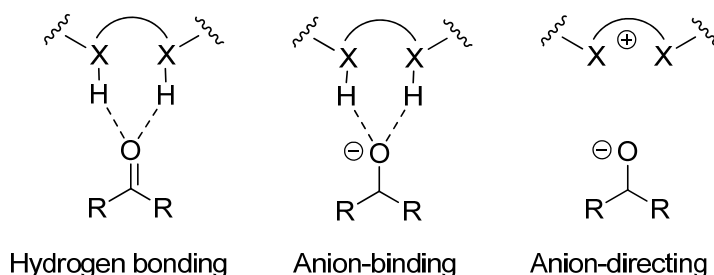
1.1.1. Thiourea Organocatalysis

Perhaps the most common functionality found in non-covalent organocatalysts is the thiourea functional group, which possesses two hydrogen-bond donors in the form of NH sites.[6,7] One of the first examples of this kind of organocatalytic hydrogen bond activation came from Hine, who used diphenol **1.1** to catalyze the aminolysis of an epoxide (Scheme 1.1).[8] Control experiments showed that the diphenol gave a rate acceleration factor of 12.5 relative to phenol, which indicates the importance of the dual hydrogen bonding structure.[9,10]

Scheme 1.1 Diphenol catalyzed aminolysis of epoxides.
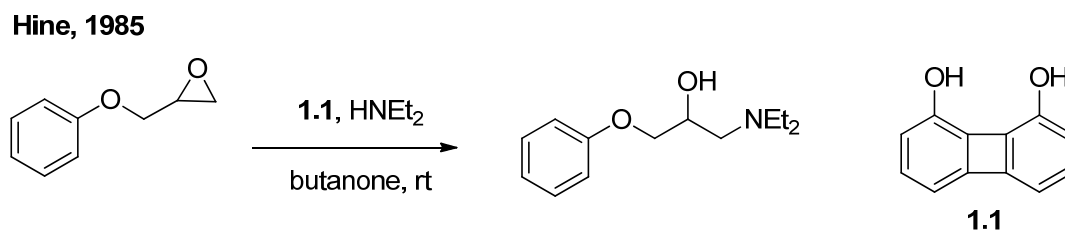
In 1994, Curran developed urea **1.2** to accelerate the cross-coupling of allyltributylstannane to an α-sulfinyl radical (Scheme 1.2).[11] Up to one equivalent of urea was required to give adequate diastereoselectivity. The catalyst is proposed to hydrogen bond to the sulfinyl group, activating it. The *meta*-trifluoromethyl group on the urea was used to increase the acidity of the NH protons, while the long alkyl chains improved urea solubility in organic solvents.

Scheme 1.2 Urea promoted allylation of α-sulfinyl radicals.
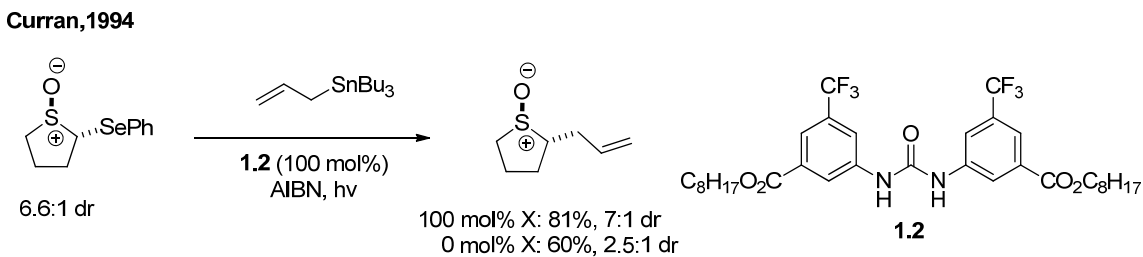
One year later, Curran reported that urea **1.2** also accelerated a Claisen rearrangement reaction at substoichiometric catalyst loadings (Scheme 1.3).[12] Crucially, urea **1.2** lost its activity when the amine groups were methylated, indicating that hydrogen bonding plays a key role in its mode of action.

Scheme 1.3 Urea catalyzed Claisen rearrangement.

Curran, 1995

$$0 \text{ mol\% catalyst } \mathbf{1.2}: k_{rel} = 1.0$$
$$40 \text{ mol\% catalyst } \mathbf{1.2}: k_{rel} = 5.0$$
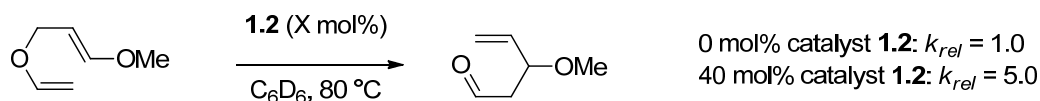
In 2002, Schreiner improved upon Curran's design by creating a more soluble thiourea version of the catalyst, **1.3** (Scheme 1.4).[13] The lipophilic chains can be replaced with additional trifluoromethyl groups, increasing the acidity of the NH protons. Thiourea **1.3** was able to catalyse the Diels-Alder reaction between a diene and an oxazolidinone through hydrogen bond donation to the substrate's carbonyl groups.

Scheme 1.4 Thiourea catalyzed Diels-Alder reactions.

Schreiner, 2002

78%, 4.3:1 dr
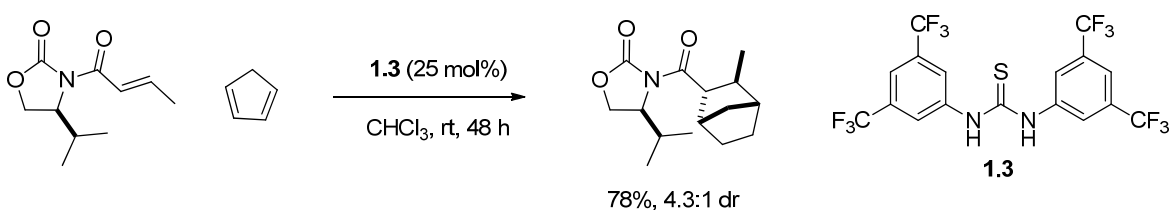
The first enantioselective thiourea catalyst **1.4** was developed in 1998 by Jacobsen – the catalytic activity was initially ascribed to the Schiff base functional group before the true mode of action was elucidated.[14] The catalyst **1.4** was first discovered to give high enantioselectivities in the Strecker reaction between an imine and a cyanide source (Scheme 1.5).

Scheme 1.5 Chiral thiourea catalyzed Strecker reaction.

Jacobsen, 1998

78%, 91% ee
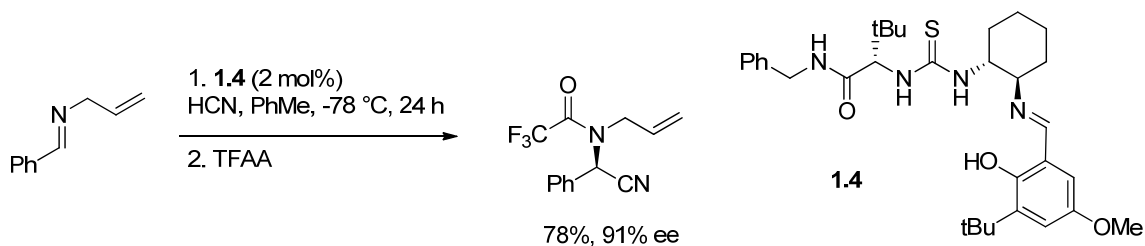
The field of asymmetric thiourea catalysis continued to expand. In 2003 Takemoto developed a new bifunctional thiourea catalyst **1.5** for an enantioselective Michael reaction (Scheme 1.6).[15] The catalyst contains a thiourea and a basic tertiary amino group to activate simultaneously a nucleophile and electrophile. Control experiments with separate thiourea and amine molecules show a significant loss in enantioselectivity and reactivity, establishing that bifunctional catalysts can give synergistic benefits in a reaction.

Scheme 1.6 Enantioselective Henry reaction with bifunctional thiourea.

Takemoto, 2003

86%, 93% ee
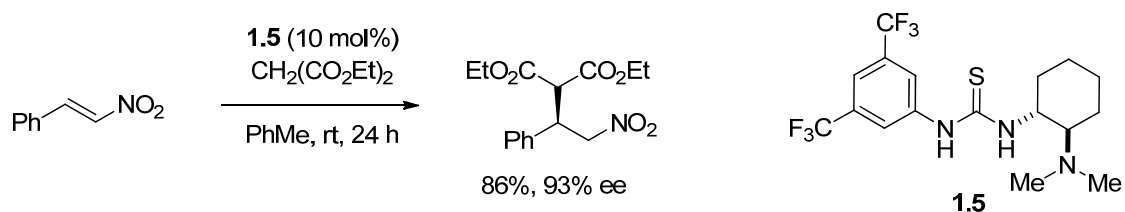
In 2004, Nagasawa reported a new chiral bisthiourea organocatalyst **1.6** that is capable of accelerating the Baylis-Hillman reaction between cyclohexanone and aldehydes (Scheme 1.7).[16] The catalyzed reaction is faster than promoted by a single urea or thiourea, and ^{1}H NMR studies show that the bisthiourea **1.6** interacts with both substrates simultaneously. Although the catalyst gives low enantioselectivities with aryl aldehydes, it works well for alkyl substrates.

Scheme 1.7 Enantioselective Baylis-Hillman Reaction with bisthiourea.

Nagasawa, 2004

72%, 90% ee
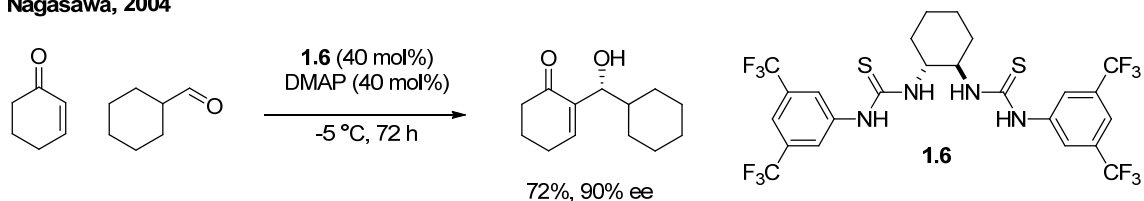
Since then, many other types of thiourea organocatalysts that combine novel chiral backbones with bifunctional reactivity sites have been developed .[6,17,18]

1.2 Chiral Ion Pair Organocatalysis

1.2.1   Phase Transfer Catalysis (PTC)

Although many of the initial thiourea organocatalysts were assumed to work exclusively through hydrogen-bonding interactions, ion pair organocatalysis had been well-developed prior to their introduction. A phase-transfer catalyst facilitates the transportation of a reactant from one solvent phase into another by forming an ion pair. The earliest examples of PTC rely on quarternary amine and phosphonium salts.[19] In 1984, a new chiral cinchona alkaloid-derived salt **1.7** was first used by Merck for an enantioselective alkylation reaction (Scheme 1.8).[20]

Scheme 1.8 Enantioselective alkylation by using PTC.

Grabowski. 1984

95%, 92% ee
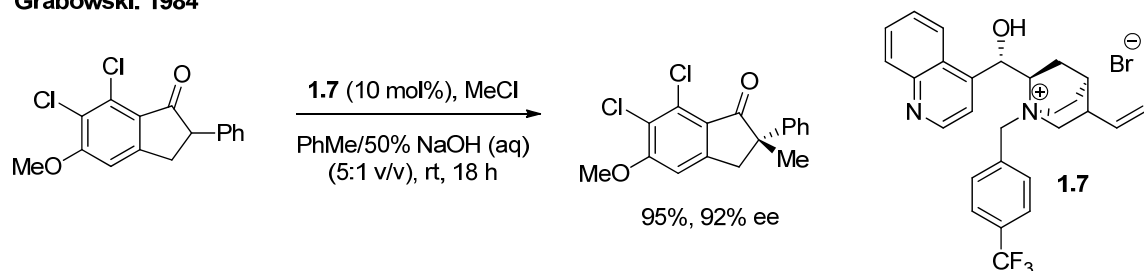
Cinchona alkaloids have found many uses in enantioselective PTC since then.[21] In 1999, Maruoka developed a novel ammonium salt **1.8** that gives improved enantioselectivities over

cinchonoium alkaloid catalysts in the Mukiyama-Aldol reaction, and creates a new class of PTC in the process (Scheme 1.9).[22]

Scheme 1.9 Enantioselective alkylation promoted by quaternary ammonium salts.

Maruoka, 1999
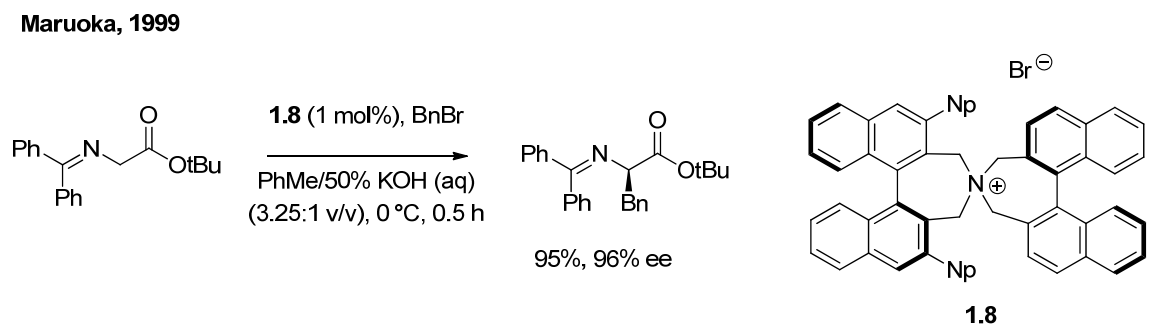
In 2002, Lacour developed an epoxidation reaction that uses a racemic phosphate and a chiral iminium counterion **1.9** to give enantioselectivities up to 76% ee (Scheme 1.10).[23] The tris(tetrachlorobenzenediolato)phosphate catalyst had previously been found to have high solubility in medium-polar organic solvents, and ,unlike other phosphate catalysts, does not partition into the aqueous layer.

Scheme 1.10 Enantioselective expoxidation reaction with chiral iminium salt.

LaCour, 2002
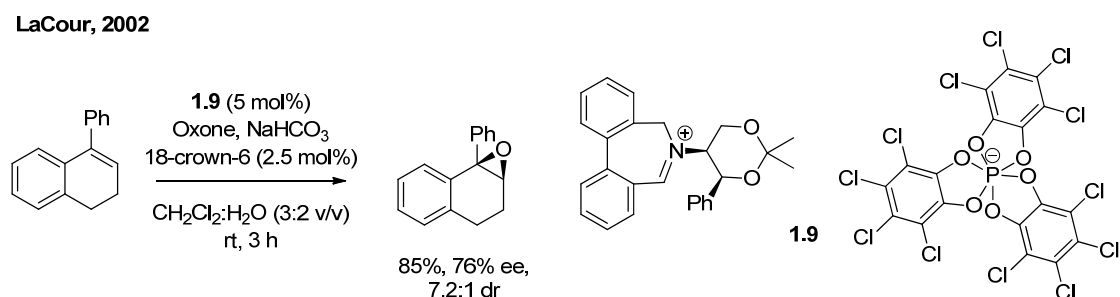
Although there are plenty of examples of chiral cation PTC in the literature, examples of asymmetric anionic PTC have only reported more recently. One of the earliest was reported by Toste in 2008, in an enantioselective etherification reaction that used chiral phosphoric acid **1.10** to extract Ag(I) from the solid phase into the liquid organic phase (Scheme 1.11).[24]

Scheme 1.11 Etherification promoted by anionic PTC.

Toste, 2008

87%, 96% ee

1.10
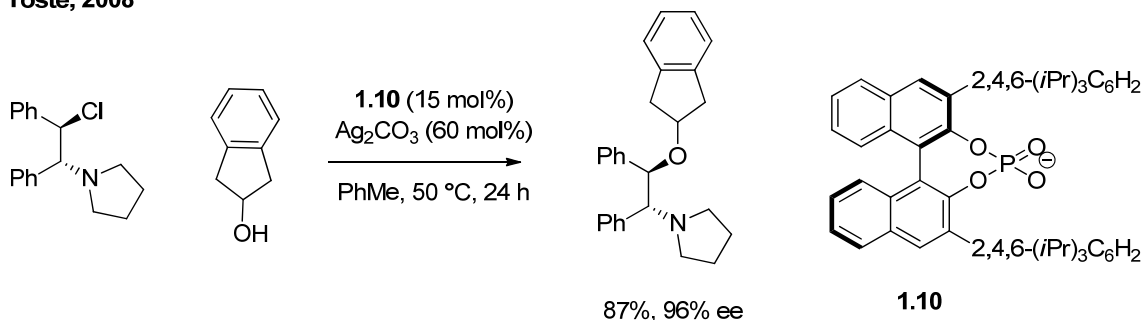
In 2015, Hamashima expanded the concept to an electrophilic fluorolactonization reaction that uses chiral acid **1.11** as an anionic PTC (Scheme 1.12).[25] The bifunctional chiral catalyst **1.11** is capable of hydrogen bonding to the substrate and also forming an ion pair to the electrophilic fluorinating reagent Selectfluor. PTC is particularly useful for electrophilic fluorination reactions, given the low solubility of Selectfluor in organic solvents when not part of an ion pair.

Scheme 1.12 Enantioselective fluorolactonization reaction using anionic PTC.

Hamashima, 2015

64%, 90% ee

1.11

Selectfluor

via intermediate
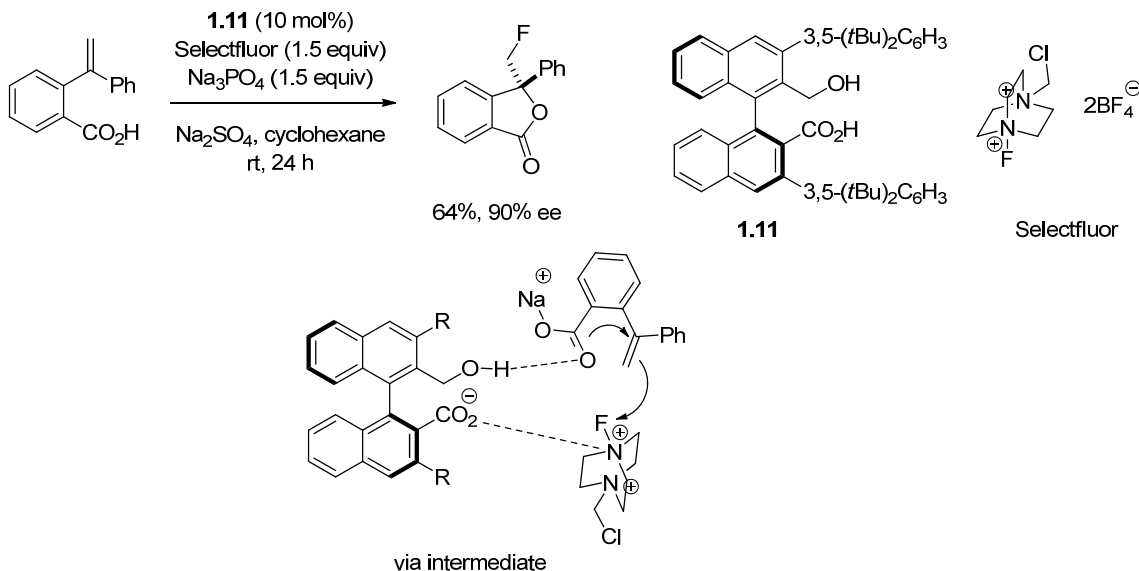
Following on from their initial disclosure of chiral anionic PTC, the Toste group has developed several enantioselective fluorination reactions that make use of their catalytic system. In

2016, Toste and Sigman developed another enantioselective fluorination reaction (Scheme 1.13).[26] Using an achiral boronic acid additive they are able to fine-tune the enantioselectivity. They propose a mechanism where the boronic acid complexes to the phosphoric acid catalyst **1.12**, bringing it into proximity with the chiral ion pair. Both enantiomers of the product could be obtained in high selectivity, depending on the boronic acid used.

Scheme 1.13 Enantioselective fluorination reactions using chiral PTC.
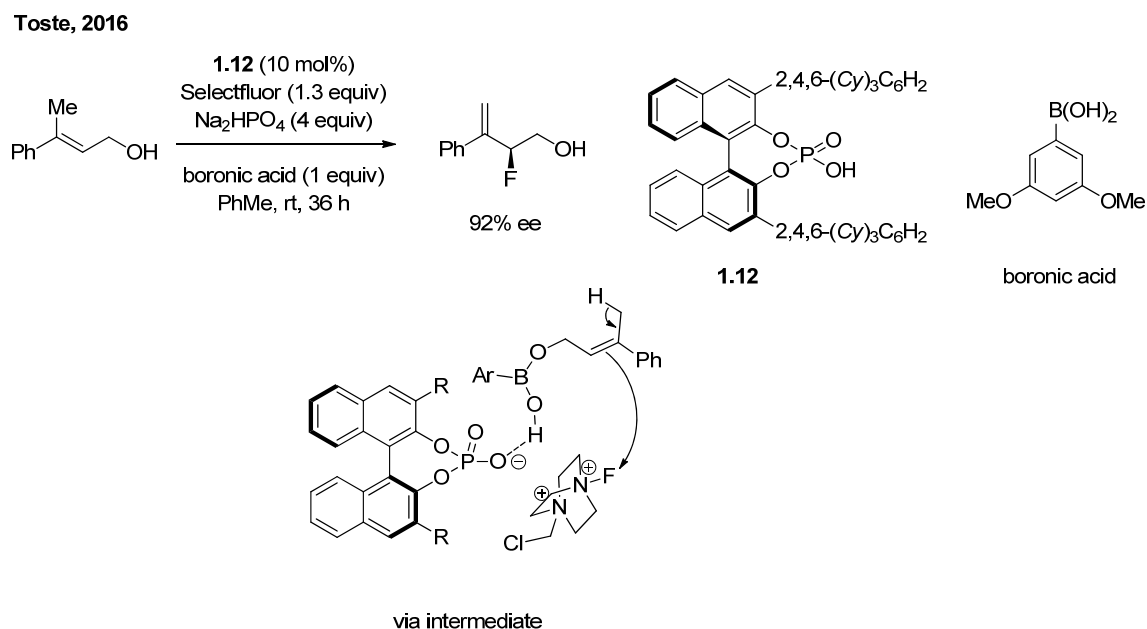
1.2.2   Anion-Directing Catalysis

In 2000, Arndtsen reported on the use of a copper salt of chiral borate **1.13** to catalyze an aziridination reaction (Scheme 1.14).[27] Only low enantioselectivities were reported (up to 10% ee) in this proof of concept study. Chiral borates have been used in other reactions, but only give low enantioselectivites.[28, 29]

Scheme 1.14 Aziridination reaction with chiral borate salt.

Arndtsen, 2000
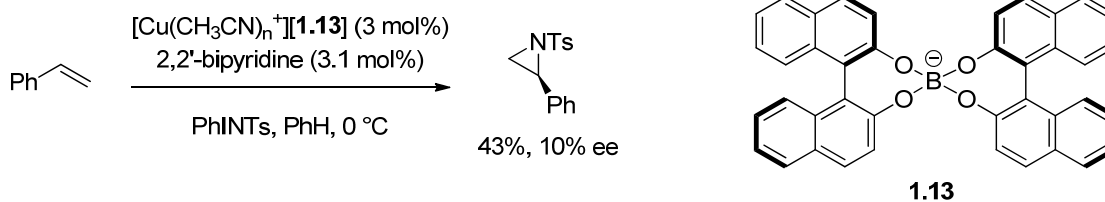
In 2006, List used a phosphoric acid amine salt **1.14** for an enantioselective hydrogen transfer reaction (Scheme 1.15).[30] MacMillan had previously disclosed a similar reaction that uses a chiral amine and achiral counterion to induce asymmetry.[31] The List group demonstrated that a chiral anion paired with an achiral amine could also induce asymmetry under almost identical reaction conditions. The cationic amine forms an iminium species with the aldehyde, which interacts with the chiral phosphate to form the alkylated product with high enantioselectivity.

Scheme 1.15 Enantioselective hydrogen transfer promoted by chiral anion catalysis.

List, 2006
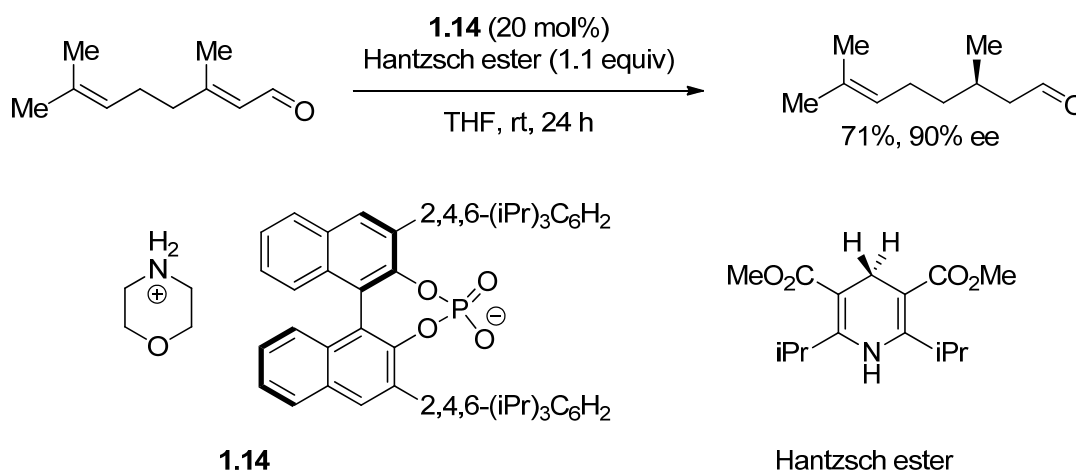
In 2009 Dixon reported an enantioselective Pictet-Spengler reaction that uses a chiral phosphoric acid **1.15** to generate an ion pair with the iminium intermediate (Scheme 1.16).[32]

Conventional Lewis acid catalysis is challenging with N-acyl iminium substrates, given their low basicity, but capture of the intermediate as an ion pair is relatively facile.

Scheme 1.16 Enantioselective Pictet-Spengler reaction promoted by chiral anion-directing catalysis.

Dixon, 2009
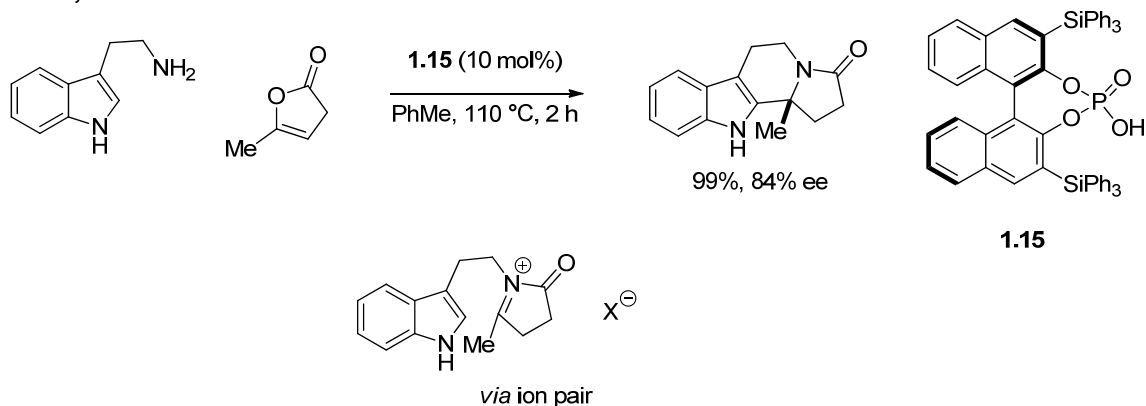
In 2011, Huang reported an enantioselective alkylation with a thiophosphoric acid catalyst **1.16** that also takes advantage of an iminium ion intermediate (Scheme 1.17).[33]

Scheme 1.17 Enantioselective alkylation reaction via chiral anion-directing catalysis.

Huang, 2011
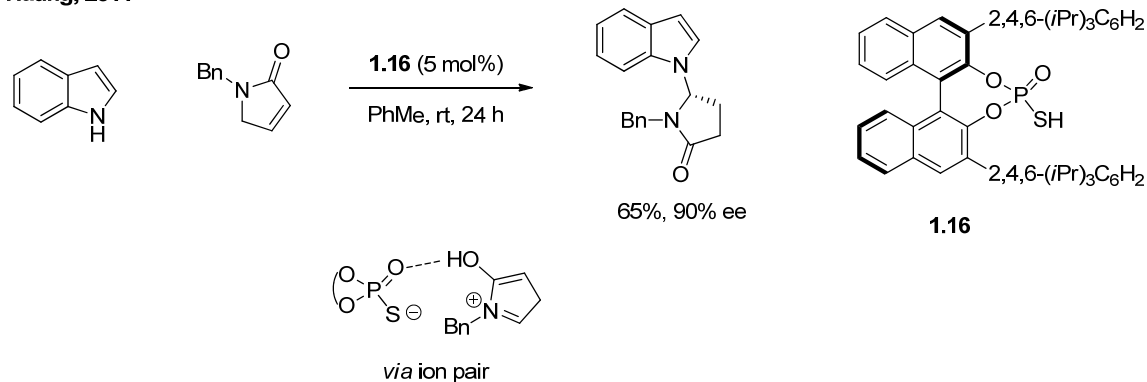
In addition to phosphoric and thiophosphoric acid catalysts, BINOL-derived catalysts developed recently feature stronger Brønsted acid groups such as triflylamides,[34] disulfonimides[35] and imidodiphosphates that are even more powerful as catalysts (Figure 1.2).[36]

Figure 1.2 Selected examples of BINOL-derived catalysts.
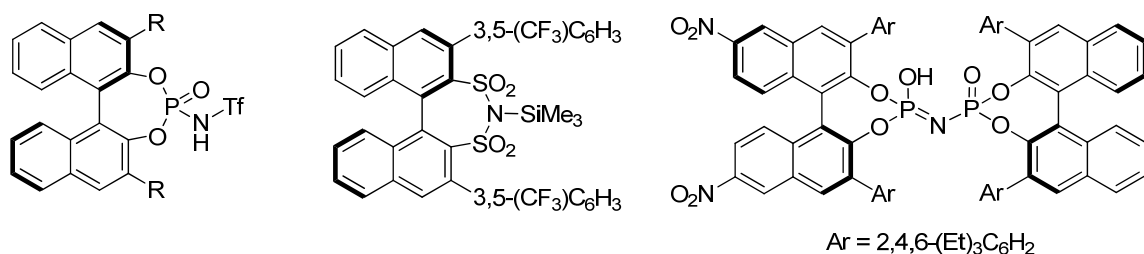
1.2.3 Anion-Binding Organocatalysis

In contrast to PTC or anion-directing catalysis wherein the catalyst is a charged species, anion-binding catalysis features a catalyst that remains neutral during the reaction. It binds to the charged anionic substrate, which then forms a chiral ion pair with a second substrate or reagent. Anion binding is well-established in nature, as it plays a role key role in ion channels and proteins. The sulfate binding protein (SBP) from *S. typhimurium* was determined in 1985 to function solely by hydrogen bonding interactions.[37] The chloride ion channel in *E. coli*. and *S. typhimurium* was characterised in 2002[38] and features charge stabilization from the amide and alcohol protons in the channel (Figure 1.3).

Figure 1.3 Selected examples of anion-binding in nature.

sulfate binding protein from Salmonella typhimurium   chloride ion channel
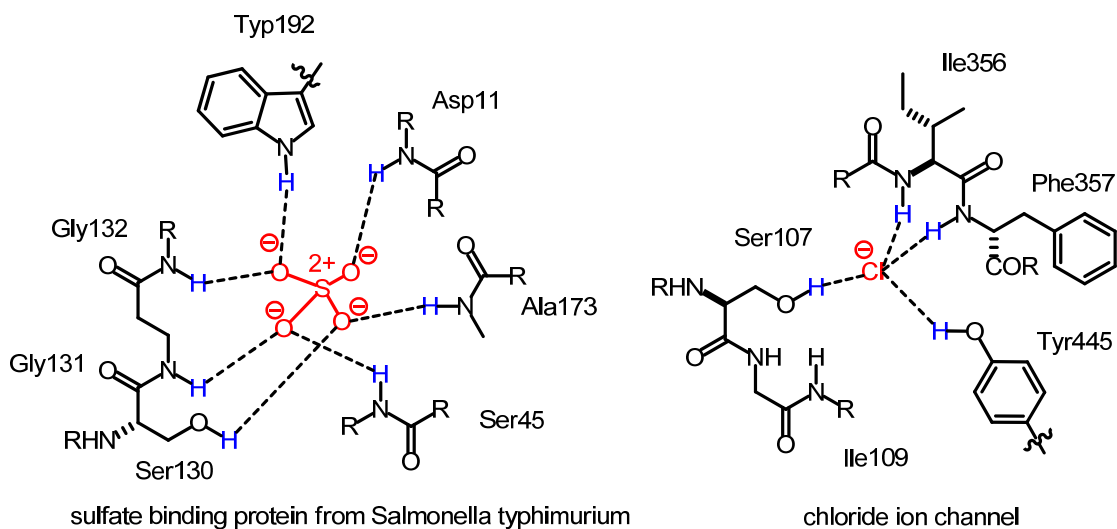
There are several examples of X-ray crystal structures published in the early 1990s that show that thioureas and ureas can strongly bind with anions (Figure 1.4).[39, 40] It was thus inevitable that anion-binding would be explored within the context of thiourea organocatalysis.

Figure 1.4 The binding of (thio)ureas to anions.
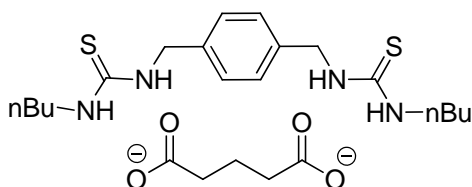
Hamilton, 1993　　　　　　　　　　　　　　　　　**Wllcox, 1992**
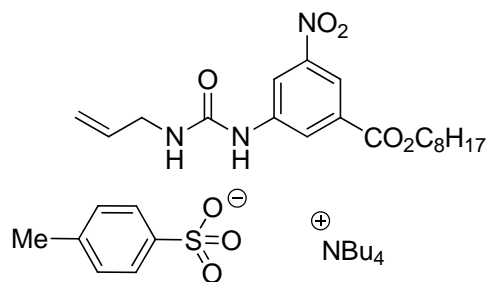
In 2006 Schreiner reported the acetalization reaction, catalyzed by thiourea **1.3,** between aryl aldehydes and ketones (Scheme 1.18).[41] A control study wherein a thiol and the orthoester were allowed to compete under analogous reaction conditions led to exclusive formation of the acetal. This suggests that a thiourea-assisted hydrolysis of the orthoester is part of the mechanism, because the corresponding thiol is unable to engage in anion-binding.

Scheme 1.18 Acetalization reaction via thiourea anion-binding.

Schreiner, 2006
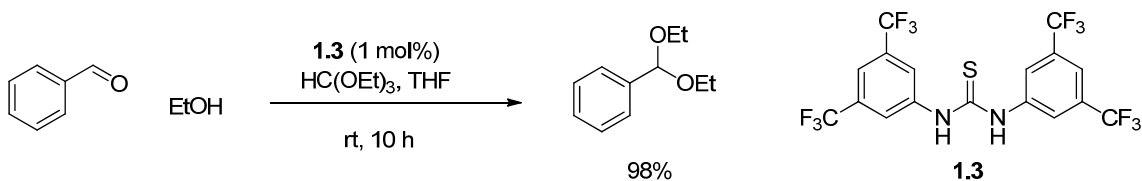
Although it was not known at the time of disclosure, the Jacobsen group's Strecker reaction (vide supra) was later determined to go through an anion-binding mechanism.[42] In 2007, Jacobsen proposed that an enantioselective Pictet-Spengler reaction worked through chloride ion abstraction by thiourea catalyst **1.17**, which confers enantioselectivity through a chiral ion pair (Scheme 1.19).[43] A

positive correlation between acidity of the halide leaving group and enantioselectivity helps support this hypothesis.

Scheme 1.19 Enantioselective Pictet-Spengler reactions via anion-abstraction.

Jacobsen, 2007

X = Cl   80%, 97% ee
X = Br   82%, 68% ee
X = I   75% <5% ee

1.17
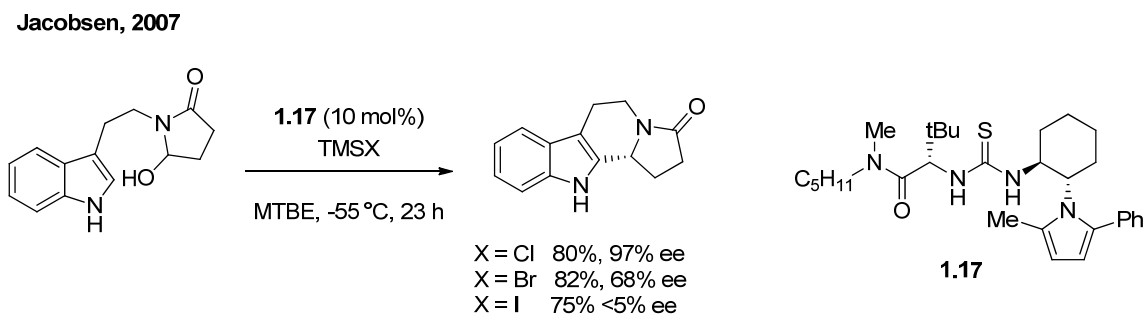
In 2009, the Seidel lab disclosed a new anion-binding concept for the kinetic resolution of amines.[44] An achiral nucleophilic catalyst is acylated in situ and the resulting cationic species is made chiral through interaction with the benzoate that is stabilized by hydrogen-bonding to thiourea catalyst **1.6**. Subsequent refinements in thiourea and nucleophilic catalyst design improve the selectivity of the reaction from s-factor = 10 to 27, while also permitting the catalyst to function at 20 mol% to 5 mol% levels (Scheme 1.20).[45] The concept was expanded to propargylic[46] and allylic amines,[47] and to the desymmetrization of diamines.[48,49]

Scheme 1.20 Kinetic Resolutions via anion-binding catalysis.

Nu-catalyst (x mol%)
HB-catalyst (x mol%)

PhMe, -78 °C, 1-2 h

0.5 equiv

Condition A: 45%, s-factor = 10
Condition B: 49%, s-factor = 27

Nu-catalyst
1.18

HB-catalyst
1.6

Nu-catalyst
1.19

HB-catalyst
1.20
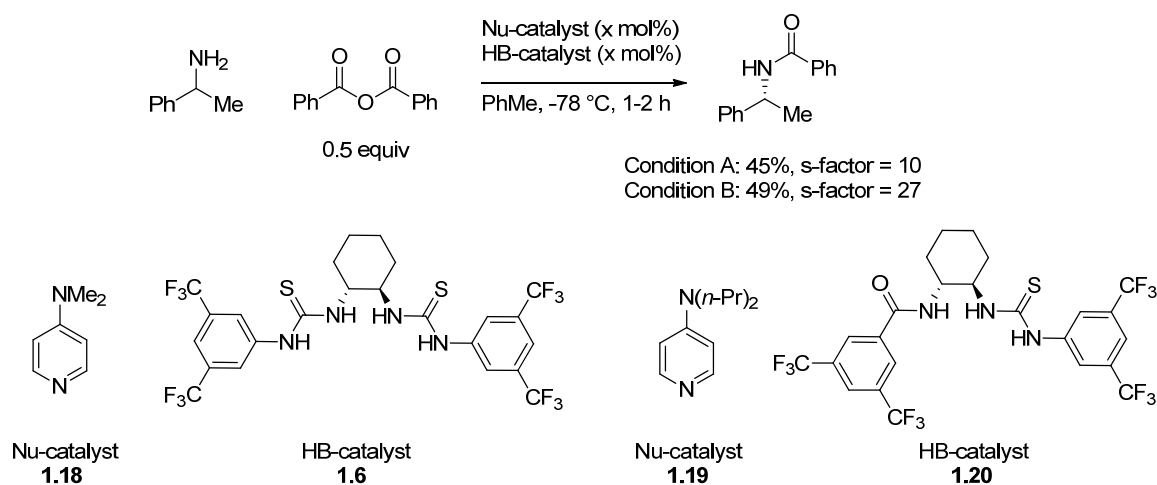
Seidel, 2009
Conditions A. **1.18** (20 mol%), **1.6** (20 mol%)

Seidel, 2012
Conditions B. **1.19** (5 mol%), **1.20** (5 mol%)

The Jacobsen group reported a similar catalytic concept in 2011 for an enantioselective acylation reaction (Scheme 1.21).[50] The effectiveness of the reaction depends upon using a benzoyl halide as an acylating reagent, which points to a halide abstraction as the initial reaction step. The silyl protecting group, combined subsequently with the fluoride ion in the rate determining step, leads to the key chiral ion pair when the enolate is bound to thiourea **1.21**.

Scheme 1.21 Enantioselective acylation via anion-binding catalysis.

Jacobsen, 2011

88%, 92% ee

via intermediate

1.21

1.22
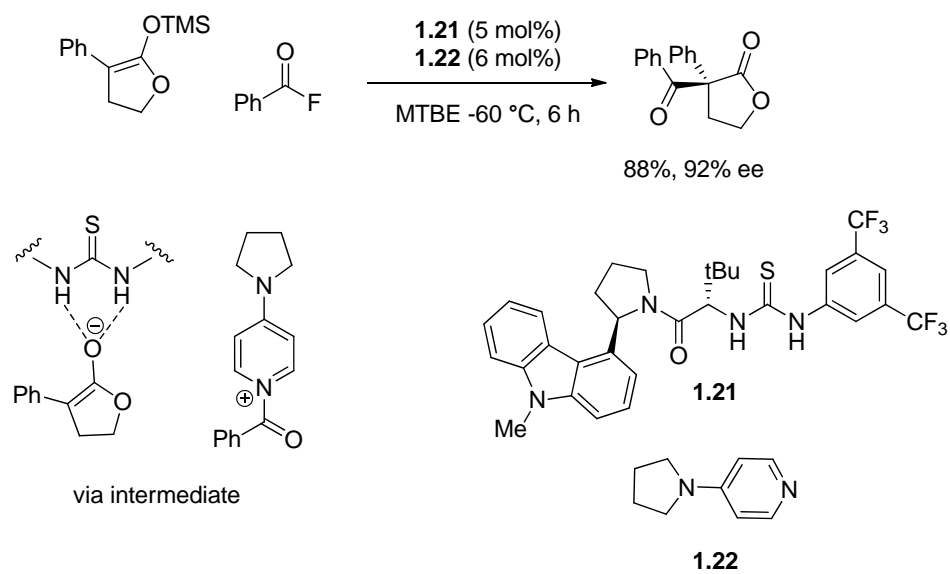
In 2013, the Seidel lab reported a new anion-binding concept involving a conjugate-base-stabilized Brønsted acid catalyst **1.23**. A carboxylic acid is covalently linked to the thiourea, and depronotonates to form an anion, subsequently forming a chiral ion pair with the reaction substrates (Scheme 1.22). This concept was initially applied to an intermolecular Povarov reaction,[51] Pictet-Spengler reaction[52] and enantioselective A3 reaction.[53]

Scheme 1.22 Enantioselective Povarov reactions via conjugate-base-stabilized Brønsted acid catalysis.

Seidel, 2013
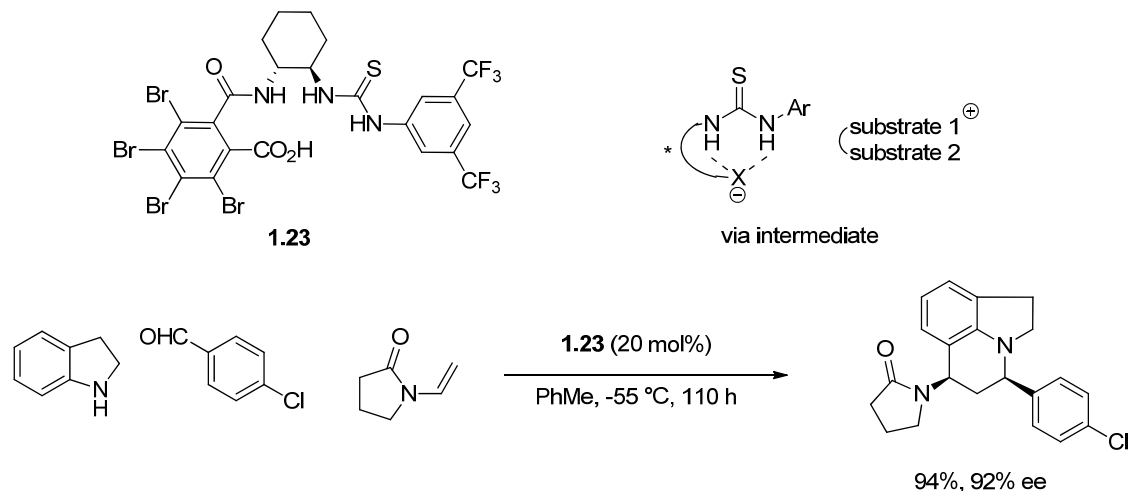
1.3 Summary and Objectives

The examples showcased above reveal the breadth of organocatalysis when it comes to addressing reactivity problems. Not only does the anion-binding approach allow for new ways to powerfully activate substrates that are otherwise slow to react under asymmetric catalysis, but it is also an underexploited approach compared to cation-binding catalysis.

In the context of the continuing interest in our group for tackling complex reactivity problems, this thesis explores novel applications of anion-binding catalysis to create new enantioselective reactions. Chapter 2 describes an enantioselective variant on a classic cycloaddition reaction between enolizable anhydrides and imines. Chapter 3 discusses efforts towards an enantioselective cycloaddition between alkoxyisocoumarins and imines. Chapter 4 discusses unrelated work on a new and redox-neutral approach to the synthesis of N,S-acetals.

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Chapter 2. Enantioselective Formal [4+2] Cycloadditions of Enolizable Anhydrides and Imines

2.1 Aims and Significance

Formal [4+2] cycloadditions of enolizable anhydrides and imines, first disclosed by Castagnoli, provide a powerful platform for the preparation of valuable lactams.[1,2] While early reports focused on succinic anhydride and acyclic imines, this chemistry was later expanded by Cushman and Haimova to include homophthalic anhydrides and dihydroisoquinolines (Scheme 2.1),[3,4] enabling the synthesis of a number of tetrahydroprotoberberine alkaloids such as (+)-canadine.[5,6]

Scheme 2.1 Racemic reactions between anhydrides and imines
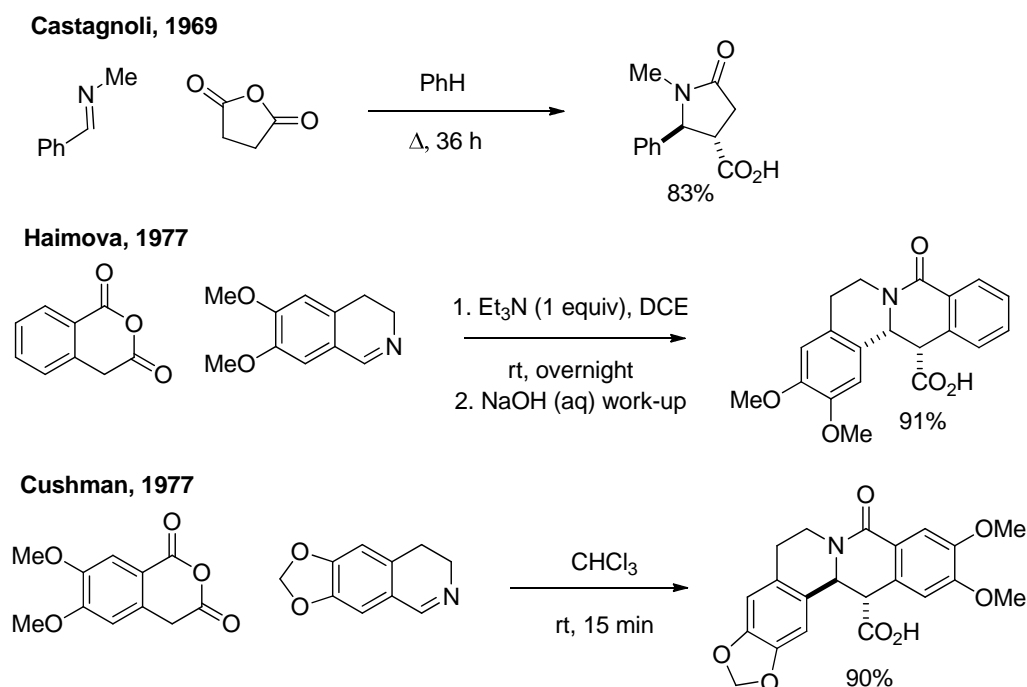
Small molecules with the same structural motif have been investigated as anti-malarials (e.g., (+)-SJ733)[7,8] and as anti-cancer agents, among others (Figure 2.1).[9-11] Due to the utility of the lactam products, numerous combinations and variations of the imine and anhydride structures have been explored.[12,13] Significant efforts have been devoted to rendering these reactions asymmetric including the use of chiral auxiliaries and recrystallizations.[14-18]

Figure 2.1 Biologically-relevant targets containing lactam scaffold

(+)-canadine

(+)-SJ733
Anti-malarial
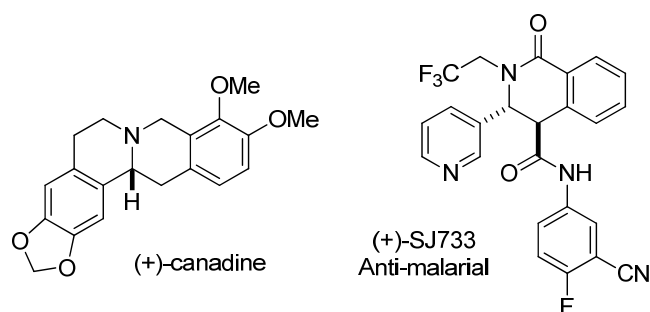
However, a catalytic enantioselective variant has remained elusive. The Connon group had already developed an enantioselective version of the mechanistically-distinct reaction between homophthalic anhydrides and aldehydes in high enantioselectivity (Scheme 2.2).[19] This chemistry was then expanded to ketones and other aldehydes.[20,21]

Scheme 2.2. Enantioselective reaction with homophthalic anhydride and aldehydes

Connon, 2012

2.1 (5 mol%)

MTBE (0.1 M), -15 °C, 22 h

98%
97% ee, >20:1 dr

2.1
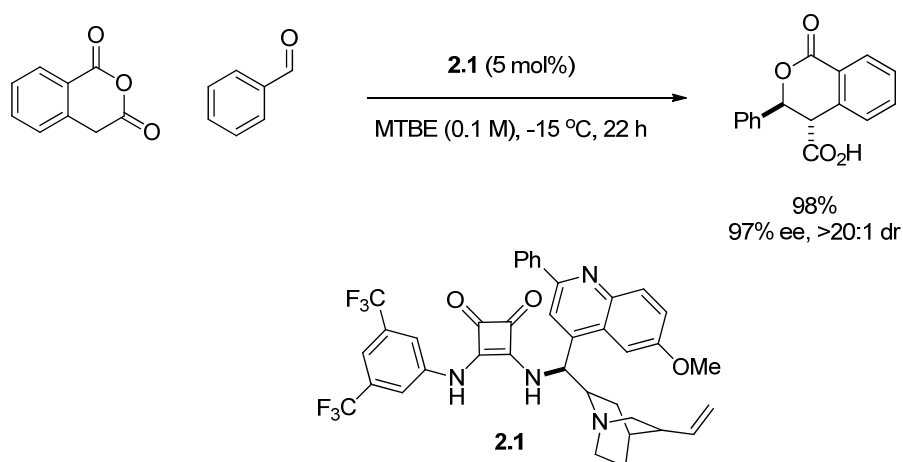
In 2016 Connon reported a moderately enantioselective version of the Cushman-Castagnoli reaction using electron-poor *N*-tosyl and *N*-mesyl imines and cinchona alkaloid catalyst **2.2** (Scheme 2.3). Control studies showed that *N*-alkyl and *N*-phenyl substrates possessed significant background reactions that made them unamenable to asymmetric catalysis. The diastereoselectivities for these substrates still proved poor.[22]

Scheme 2.3 Enantioselective reaction with *N*-sulfonyl imines.

Connon, 2016

95%
27/70% ee
36:64 dr (*cis:trans*)

Uncatalyzed reactions

R = nBu   24 h, 62%
R = Ph   4 h, 39%
R = Ts   24 h, 0%
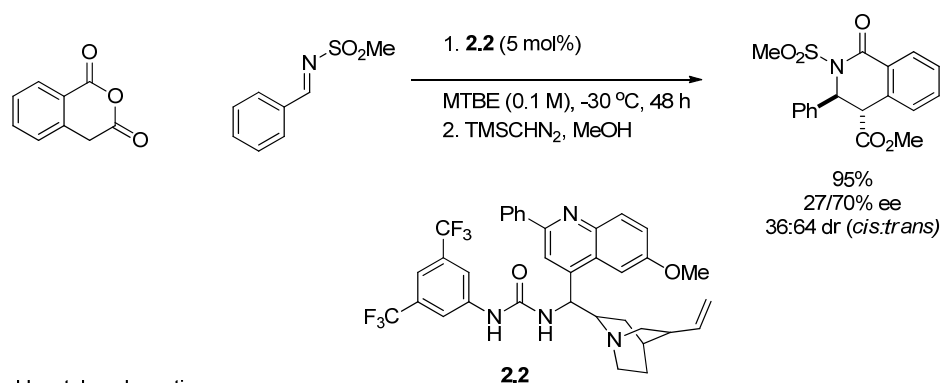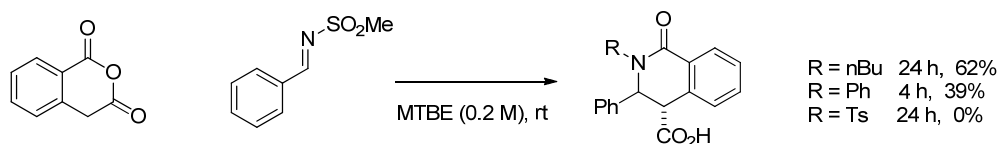
2.2 Enantioselective Formal [4+2] Cycloadditions with Homophthalic Anhydride and Imines

Different mechanisms have been proposed for the title reaction.[12,13] Cushman initially proposed an iminolysis pathway based on his experimental data,[23] while Kaneti proposed that a concerted [4+2] cycloaddition based upon computational studies was more plausible (Scheme 2.4).[24]

Scheme 2.4 Previously-proposed mechanisms for reaction of homophthalic anhydride and imines

Iminolysis Pathway

Concerted Cycloaddition Pathway
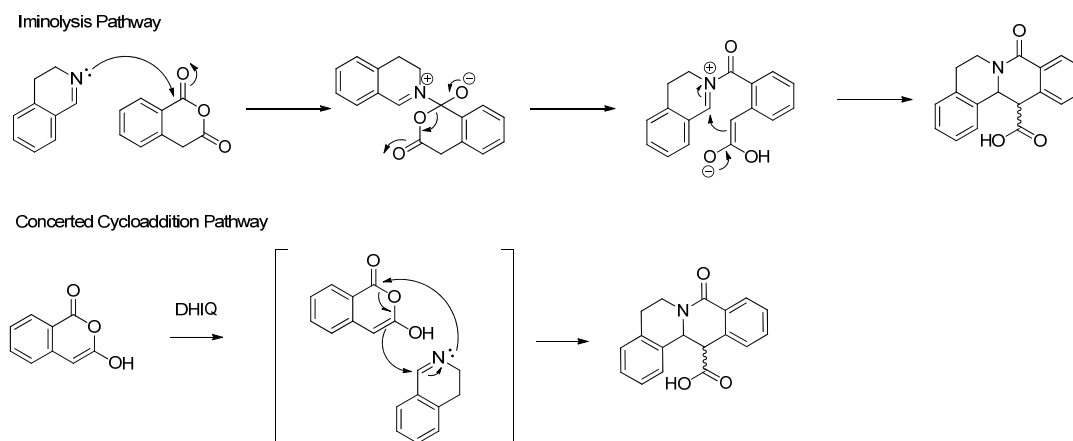
The perhaps most plausible mechanism for the reaction of homophthalic anhydride with simple imines is shown in Figure 2.2. Imine and homophthalic anhydride are thought to form hydrogen-bonded ion pair **2.3a** in equilibrium. Ion pair **2.3a**, which depending on the degree of proton transfer may also be considered as a complex of the imine with the enol form of the anhydride, undergoes a stereo-determining Mannich addition. Resulting intermediate **2.3b** then engages in intramolecular aminolysis of the anhydride to form the lactam product. This scenario is supported by recent computational studies by Cheong and Shaw on a closely-related reaction of imines with α-cyanosuccinic anhydride (Scheme 2.5),[25,26] and is consistent with the relatively high acidity of homophthalic anhydride ($pK_a = 8.15$).[27]

Figure 2.2 Proposed mechanism and ion pairing concept for enantioselective catalysis.
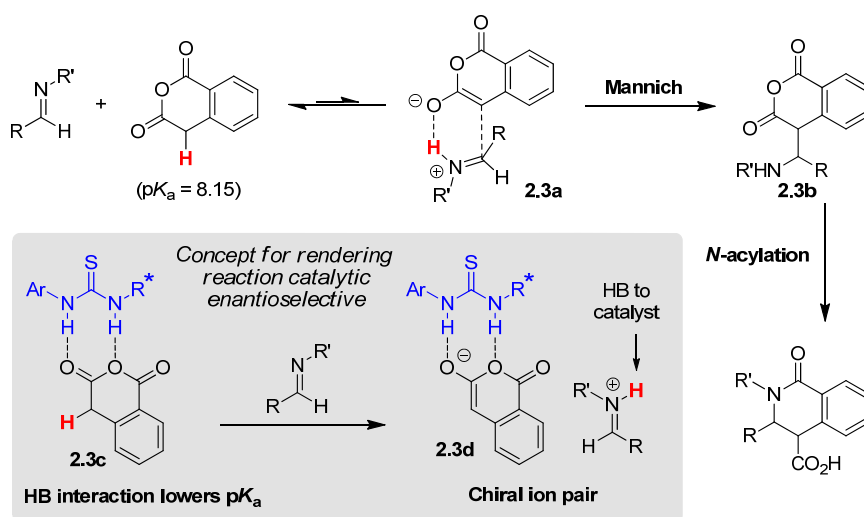
Scheme 2.5 Formal [4+2] cycloaddition between cyanosuccinic anhydrides and imines.
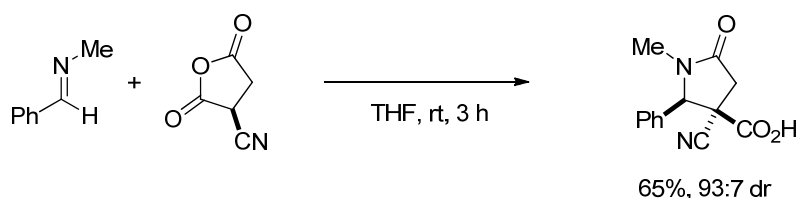
As classic modes of substrate activation appeared unsuitable, we conceived of a new anion binding/ion pairing approach in order to render this reaction catalytic enantioselective (Figure 2.2).[28-]

[51] Our concept is based on the notion that a hydrogen bonding (HB)[41-51] catalyst, which itself remains neutral throughout the reaction, can instill enantioselectivity by simultaneously interacting with an anionic nucleophile and a cationic electrophile. Specifically, we envisioned that the interaction of a chiral thiourea catalyst with homophthalic anhydride would result in increased substrate acidity via complex **2.3c**. This in turn would lower the barrier for ion pair formation, enabling the generation of chiral ion pair **2.3d**. Viewed from a different perspective, the presence of an anion receptor is expected to increase the equilibrium concentration of any ion pair intermediate. Interaction of the iminium ion in **2.3d** with a secondary hydrogen bonding acceptor site on the catalyst would contribute to the creation of a well-defined ion pair that is set up for an enantioselective Mannich addition step.

Table 2.1 Catalyst screen and reaction optimization. [a]
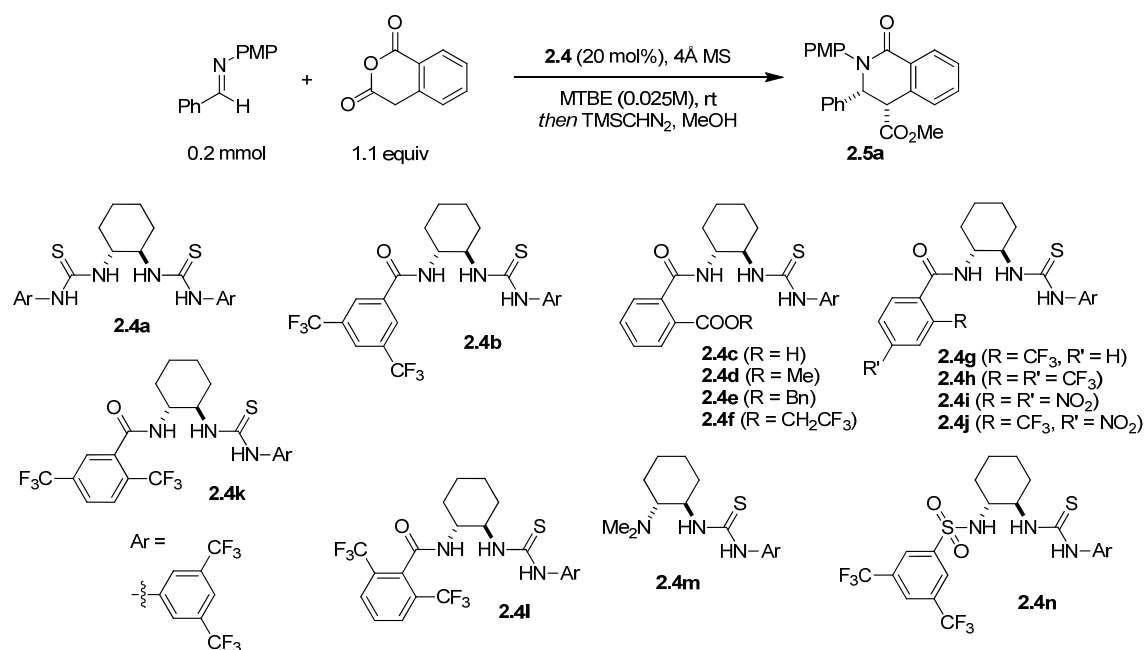
entry	catalyst	time (h)	yield (%)	ee (%)	dr
1	–	18	33	–	>19:1
2	**2.4a**	15	72	35	>19:1
3	**2.4b**	21	87	70	>19:1
4	**2.4c**	22	70	74	>19:1
5	**2.4d**	29	73	73	>19:1
6	**2.4e**	42	78	81	>19:1
7	**2.4f**	20	87	81	>19:1
8	**2.4g**	3	69	80	10:1
9	**2.4h**	1	94	88	>19:1
10	**2.4i**	16	81	70	>19:1
11	**2.4j**	20	84	71	10:1
12	**2.4k**	20	84	82	>19:1
13	**2.4l**	18	58	64	>19:1
14	**2.4m**	120	46	17	6:1
15	**2.4n**	19	48	59	>19:1
16[a]	**2.4h**	41	85	90	>19:1

a) At -40 °C.

2.2.1 Reaction Optimization

We initiated our survey with benzaldehyde-derived *N*-PMP imine and homophthalic anhydride (Table 2.1). In the absence of any catalyst, product **2.5a** was formed in 33% yield after 18 h (entry 1, reaction incomplete). The Nagasawa catalyst **2.4a**,[52,53] previously shown to be an efficient anion binding catalyst, provided product **6a** in good yield, excellent dr and moderate ee (entry 2). Amide-thiourea catalyst **2.4b** provided significant improvements with regard to ee (entry 3). Unexpectedly, application of Brønsted acid catalyst **2.4c** resulted in further improvements (entry 4). However, **2.4c**'s carboxylic acid functionality apparently plays no role in the catalytic process, considering that the corresponding esters performed equally well or better (entries 5–7). The most electron-deficient ester catalyst **2.4f** gave the most favorable result (entry 6). This prompted us to evaluate other electron-withdrawing groups *ortho* to the amide group, in absence or presence of other electron-withdrawing groups (entries 8–13). Amide-thiourea **2.4h** emerged as the superior catalyst

with regard to selectivity and speed, providing product **2.5a** in excellent yield, dr and 88% ee following a reaction time of just one hour (entry 9). Interestingly, all three regioisomeric catalysts **2.4b**, **2.4k** and **2.4l** were significantly less active and selective. As anticipated, bifunctional catalysts containing basic sites capable of deprotonating the anhydride, as exemplified by the Takemoto catalyst (**2.4m**),[54] provided poor results (entry 14). Replacement of the catalyst's amide moiety for sulfonamide proved unfruitful (cf. catalysts **2.4b** and **2.4n**, entries 3 and 15). Finally, product **2.5a** was obtained with 90% ee in a reaction conducted at –40 °C (entry 16). A range of other solvents and parameters were evaluated but did not result in any further improvements (Table 2.2).

Table 2.2 Additional reaction condition screen.
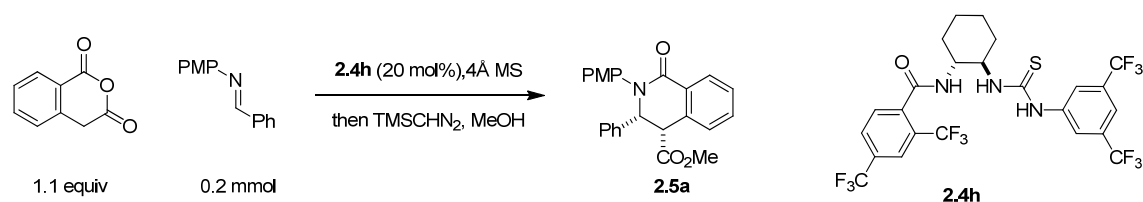
entry	solvent	conc. [M]	T [°C]	time (h)	yield (%)	ee (%)	dr
1[a]	MTBE	0.025	0	21	79	77	>19:1
2[a]	MTBE	0.025	rt	21	82	78	15:1
3[b]	MTBE	0.025	-55	118	85	85	>19:1
4	MTBE	0.025	-40	41	85	90	>19:1
5	MTBE	0.05	rt	8	66	79	1.5:1
6	MTBE	0.01	rt	20	85	82	>19:1
7	Cyclopentyl Methyl Ether	0.025	rt	2	88	74	19:1
8	Diethyl Ether	0.025	rt	2	87	79	10:1
9	Dibutyl Ether	0.025	rt	2	89	66	>19:1
10	DME	0.025	rt	2	30	53	11:1
11	Toluene	0.025	rt	19	76	69	3.5:1

a) With 10 mol% catalyst loading. b) With 15 mol% catalyst loading.

2.2.2 Substrate Scope

The scope of the reaction was found to be relatively broad (Scheme 2.6). Different *N*-aryl groups on the imine were well-tolerated (products **2.5b**–**2.5e**). However, an *N*-benzyl imine provided lower ee's and poor diastereoselectivity (**2.5f**). On the other hand, product **2.5g** with an *N*-*t*Bu group was formed with excellent ee. The remainder of the scope was evaluated with *N*-PMP imines. Imines derived from a range of aromatic aldehydes, bearing electronically diverse substituents in different ring positions, were readily accommodated. Imines derived from heterocyclic aldehydes also performed well, although a slight reduction in ee was noted for furan-containing product **2.5n**. An improved result could be obtained upon switching the PMP-group to *t*Bu (product **2.5o**). An aza diene imine species was also tested under these reaction conditions to provide product **2.5p** in excellent ee. Product **1.5p** was formed in competition with the corresponding 3,4-cycloaddition product[55] (not shown) which was obtained in racemic fashion. Imines derived from aliphatic aldehydes also participated in the title reaction. With the exception of *N*-benzyl product **2.5f**, all lactams were obtained predominantly as the kinetic *cis*-products. While diastereoselectivities were often found to be high, lower dr's may be due to epimerization of the initially formed products to their corresponding *trans*-isomers, a well-known process.[12]

Scheme 2.6 Substrate Scope
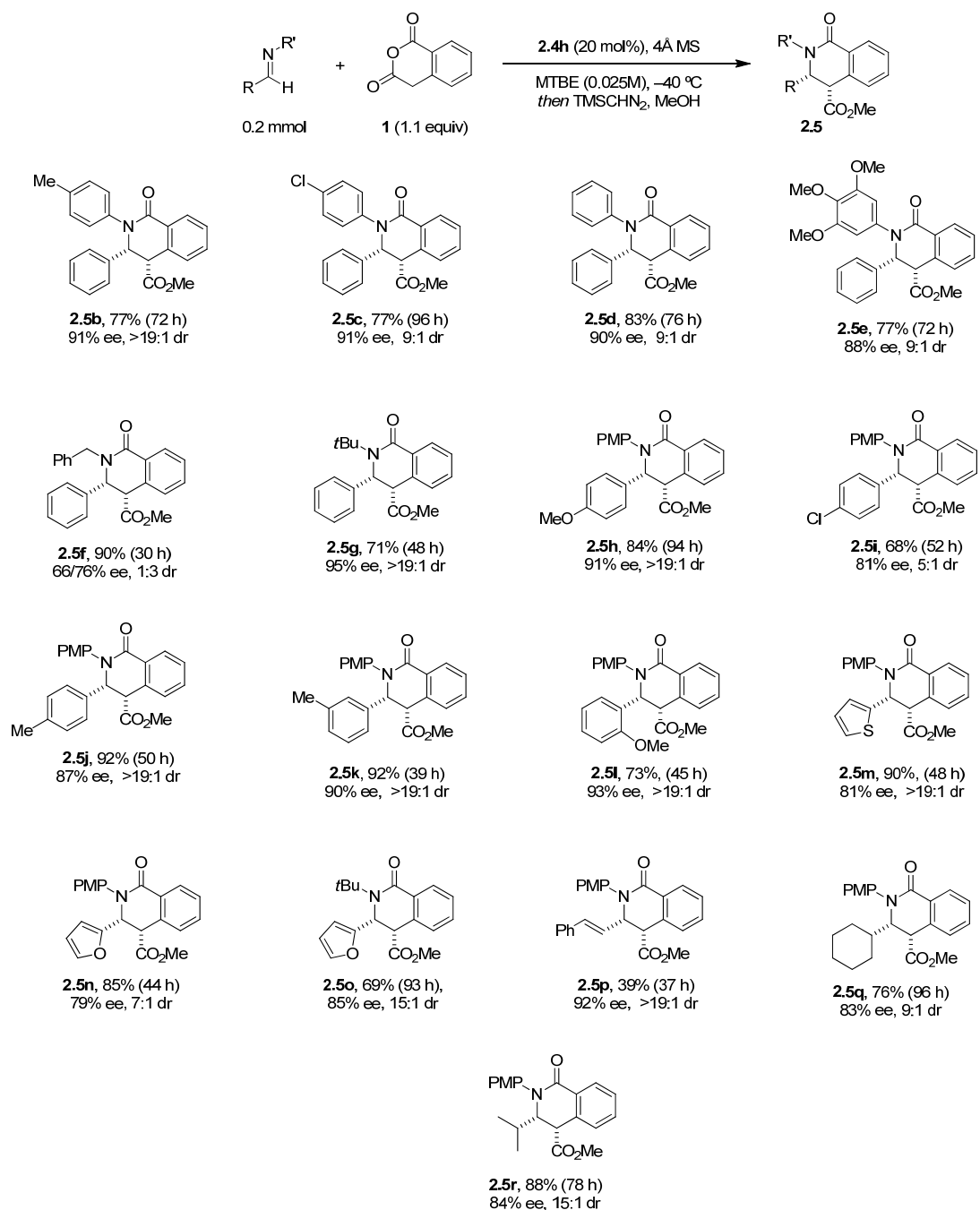
The reaction was also evaluated with 3,4-dihydroisoquinoline (DHIQ) substrates (Scheme 2.7). The substrates gave moderate enantioselectivities up to 66% ee, and required lowering the temperature to -55°C to slow down the fast background reaction.

Scheme 2.7 Substrate scope with 3,4-dihydroisoquinoline substrates

2.6a, 93% (38 h)
66% ee, 14:1 dr

2.6b, 85% (63 h)
64% ee, 19:1 dr

2.6c, 78% (39 h)
61% ee, 13:1 dr

2.6d, 89% (62 h)
32% ee, 19:1 dr
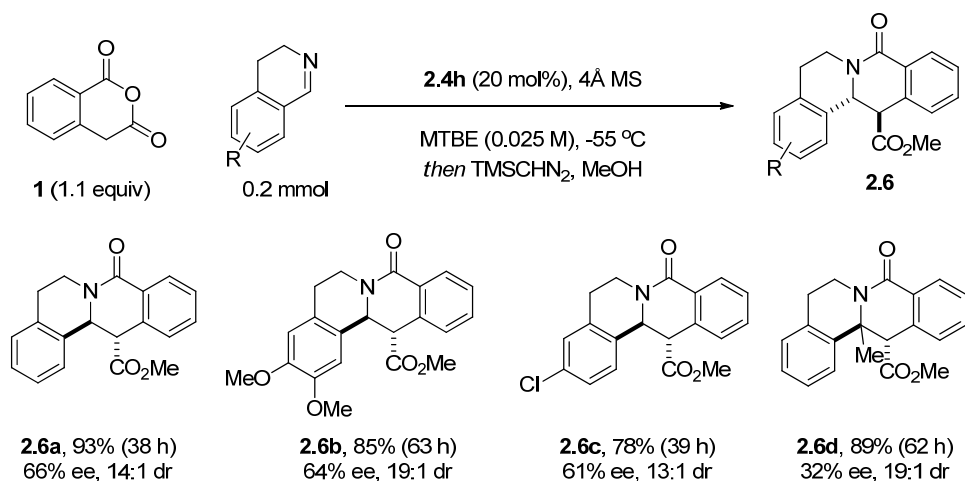
Lactam products could be readily modified (Scheme 2.8). Removal of the *N-t*Bu group in **2.5g** resulted in the formation of product **2.7** with excellent ee (eq 1).[56] Importantly, no epimerization was noted under these conditions. Epimerization of **2.7** to **2.8** was achieved in good yield upon exposure to DBU, albeit with some loss in ee (eq 2, unoptimized). Under similar conditions, epimerization of **2.5a** provided **2.9** (eq 3).

Scheme 2.8 Further transformations of lactams.

2.5g
>19:1 dr

2.7, 76%
95% ee, >19:1 dr

(1)

2.7, 95% ee
>19:1 dr

2.8, 82%
86% ee, 10:1 dr

(2)

2.5a
90% ee, >19:1 dr

2.9, 84%
80% ee, >19:1 dr

(3)
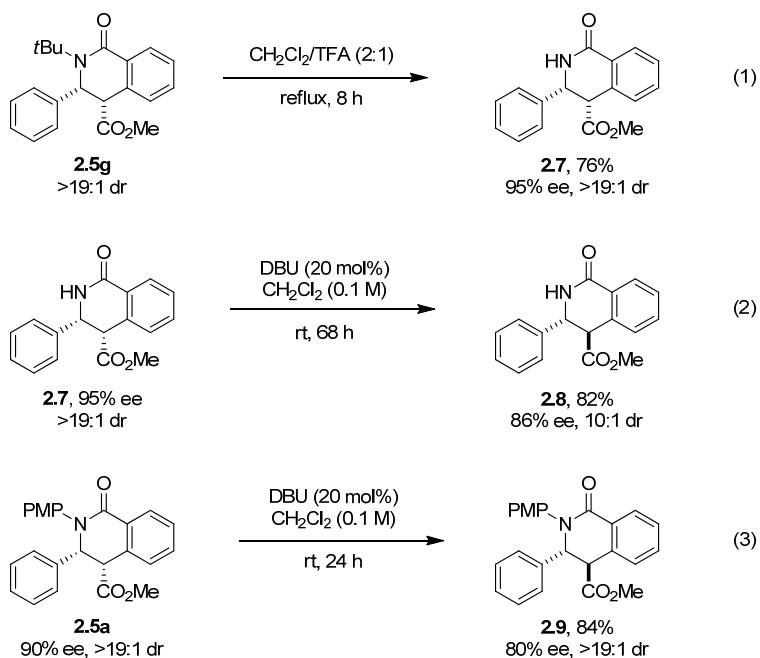
2.2.3 Mechanistic Consideration

To obtain insights into the mechanism of the reaction, we studied the dependence of product ee on catalyst ee (Figure 2.3). No nonlinear effects were noted, suggestive of a rate-limiting step that involves only one catalyst unit.
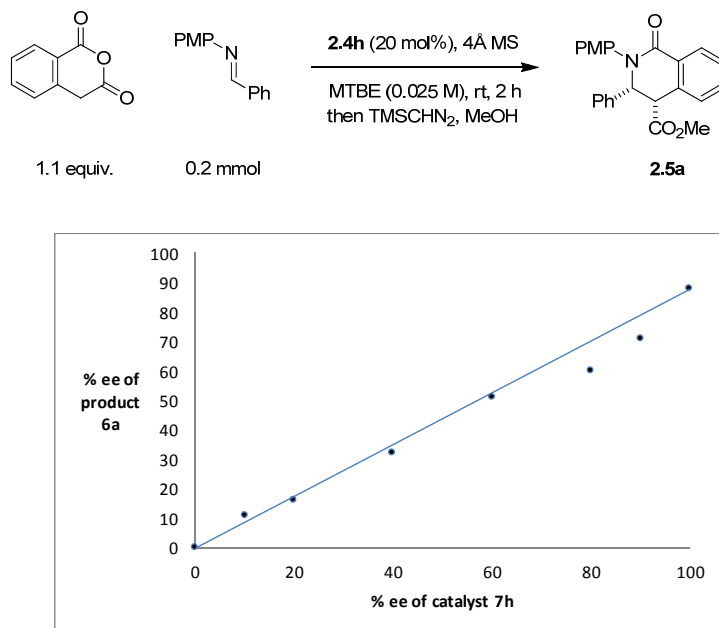
Figure 2.3 Non-linear effects study.

The organization of the proposed rate- and stereo-determining Mannich addition transition state (Figure 2.3), for the reaction of homophthalic anhydride and *N*-phenyl phenyl imine catalyzed by **2.4h**, was investigated by our collaborator Mathew Vetticatt (SUNY-Binghamton) using B3LYP-GD3[22]/6-311+G** PCM[59] (diethyl ether)//B3LYP/6-31G* calculations as implemented by Gaussian 09.[60] Consistent with our hypothesis, the reacting ion-pair benefits from bifunctional stabilization via H-bonding interactions with the catalyst structure. Analysis of the lowest energy transition structure leading to the major (*S,S*) enantiomer of product **2.5d** (*SS*-TS$_{Mannich}$, Figure 2.4) reveals the following key characteristics – (a) C–C bond formation is relatively early (2.30 Å); (b) enolate of homophthalic anhydride is bound to the catalyst via two strong H-bonding interactions with the thiourea NHs (1.88 Å and 2.20 Å); and (c) protonated imine is directed to the *re*-face of this catalyst-bound enolate via a

strong H-bonding interaction with the carbonyl oxygen of the amide moiety of the catalyst (1.91 Å). The corresponding transition structure leading to the minor (*R,R*) enantiomer of product (**RR-TS**$_{\textbf{Mannich}}$, Figure 2.4) benefits from very similar H-bonding interactions but is higher in energy ($\Delta\Delta G^{\ddagger}$ = 2.0 kcal/mol) than **SS-TS**$_{\textbf{Mannich}}$. This energy difference is consistent with the 90% experimental ee obtained for this reaction.

Figure 2.4 Lowest energy transition structures leading to the major and minor enantiomers of product **2.5d**. All distances are in Angstroms and some hydrogen atoms have been removed for clarity.
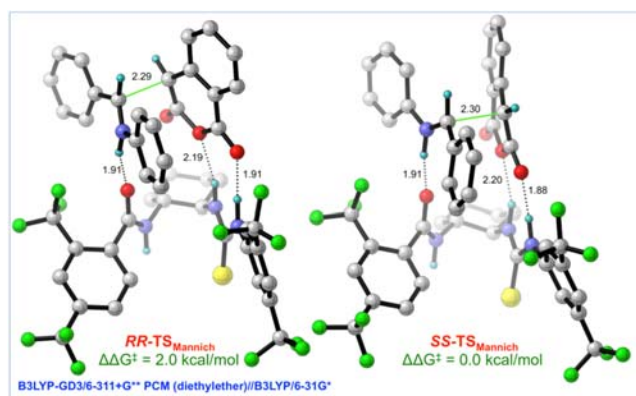
To identify the rate determining step in this reaction, we used ^{13}C natural abundance kinetic isotope effect (KIE) studies.[61] Unreacted homophthalic anhydride was recovered from the incomplete catalyzed reaction and the ratio of ^{12}C/^{13}C in the sample was analyzed by ^{13}C NMR and compared to unreacted starting material (Scheme 2.9). The difference between the isotope ratios at 75% conversion was used to determine the experimental KIEs. The homophthalic anhydride had to be derivatized to the diester to ensure adequate solubility in deuterated chloroform.

Scheme 2.9 Natural abundance ^{13}C KIE studies
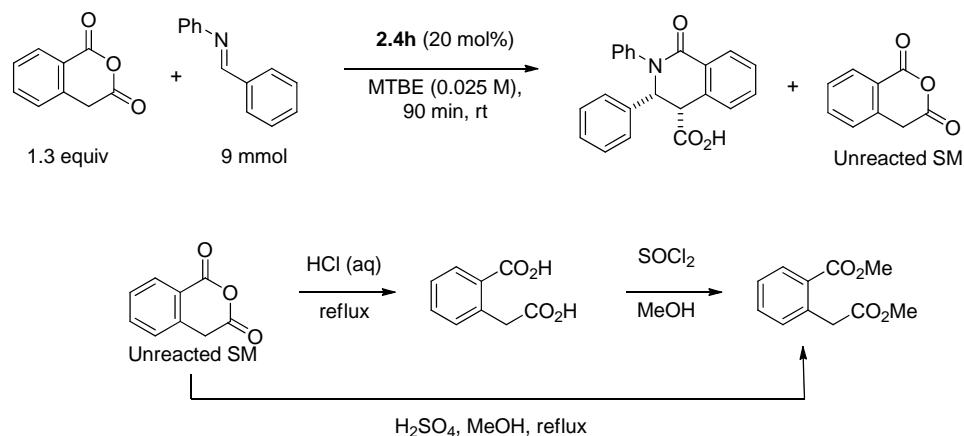
All of the potential transition structures were computed using the B3LYP-GD3 method[59,60] with the 6-31+G** basis set and the PCM solvent model for diethyl ether. The ^{13}C KIEs were computed from the scaled vibrational frequencies of the respective transition structures using the program ISOEFF98.[62] The experimental KIEs were found to average closest to deprotonation being the rate determining step, particularly at the Carbon 3 position (Table 2.3).

Table 2.3 Experimental and predicted KIEs for transition states
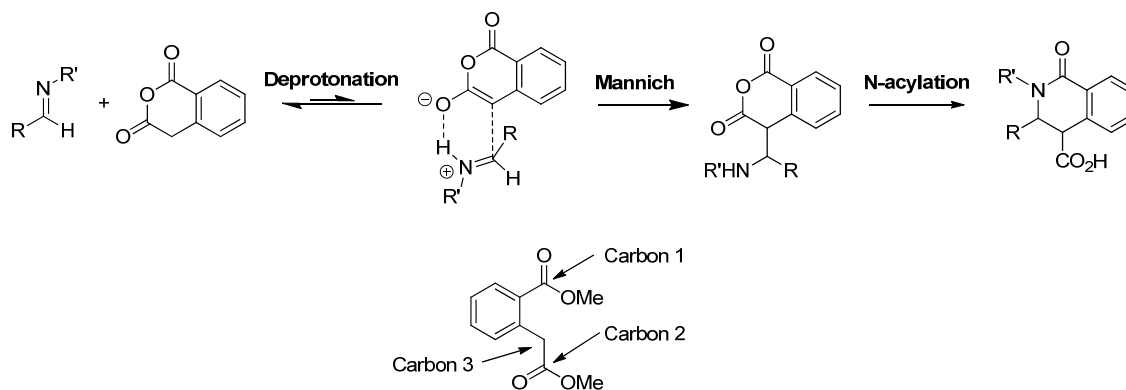
	Carbon 1	Carbon 2	Carbon 3
Experimental A	1.004 (5)	1.001 (4)	1.003 (4)
Experimental B	1.007 (3)	1.004 (4)	1.004 (5)
Experimental (A+B) Average	1.0055 (4)	1.0025 (4)	1.0035 (5)
Deprotonation-TS	1.002	1.008	1.007
Mannich-TS	1.003	1.008	1.026
Acylation-TS	1.0045	0.997	0.992

In summary, by making use of a new organocatalyst design we have developed the first catalytic enantioselective reactions of an enolizable anhydride with a range of simple imines. Combined computational and experimental studies helped to shed insight on the reaction mechanism and the role of the catalyst.

2.3 Enantioselective Formal [4+2] Cycloadditions with Phenylsuccinic Anhydrides and Imines

Next, we sought to expand the reaction scope to include other enolizable anhydrides. Castagnoli and Cushman had first used succinic anhydrides as substrates in the initial disclosure of the

stereoselective reaction in 1969.[1] Shaw had demonstrated in 2006 that phenylsuccinic anhydrides could react in a stereoselective fashion with open-chain imines after extended heating, without the need for additional reaction promoters (Scheme 2.10).[63] To date, these substrates hadn't been explored in any enantioselective reactions.

Scheme 2.10 Stereoselective reaction of phenylsuccinic anhydride and imines

Shaw, 2006

2.10 93%
9:1 dr
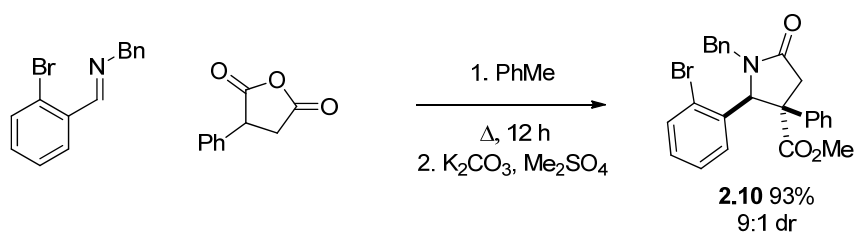
In developing an enantioselective version, we first examined the model reaction between phenylsuccinic anhydride and *N*-tert-butyl imine (Table 2.4). Moderate enantioselectivities were observed using catalyst **2.4h** according to our previously-developed conditions (entry 1). The absolute configuration for these products was not determined. It was found that non-polar aromatic solvents such as toluene and xylenes gave the much improved enantioselectivities and diastereoselectivity.

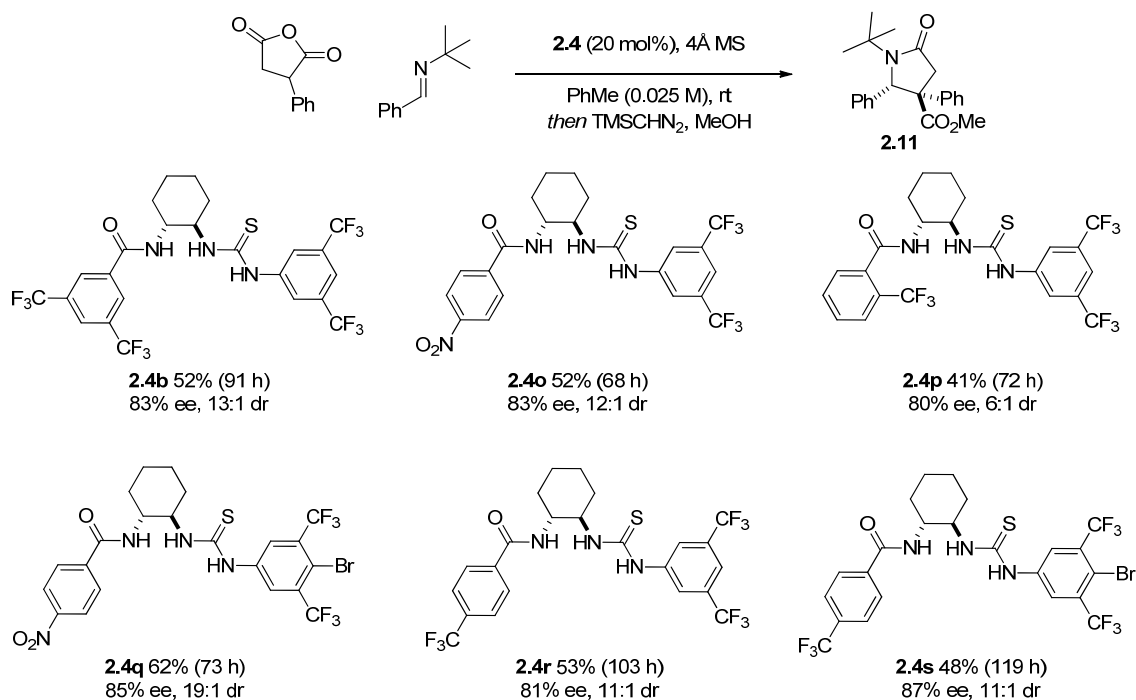**Table 2.4** Initial optimization of phenylsuccinic anhydride reaction
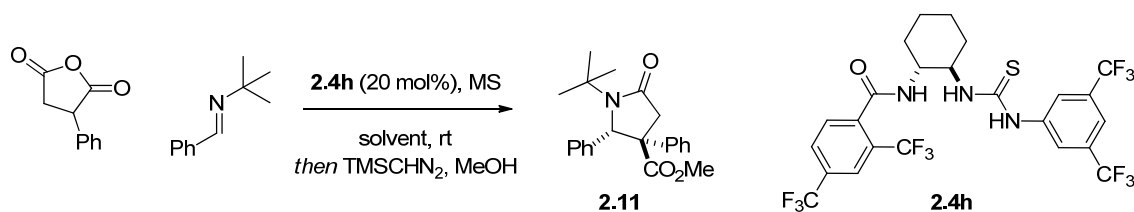
entry	solvent	conc (M)	MS	time (h)	T [°C]	yield (%)	ee (%)	dr
1	MTBE	0.025	-	70	rt	74	40	5:1
2	MTBE	0.05	-	26	rt	41	41	2:1
3	MTBE	0.05	4Å	116	rt	62	48	10:1
4	PhMe	0.05	4Å	118	rt	61	72	6:1
5	PhMe	0.025	4Å	76	rt	56	72	6:1
6	THF	0.05	4Å	74	rt	56	0	19:1
7	DCM	0.05	4Å	70	rt	44	11	9:1
8	Ether	0.05	4Å	68	rt	50	39	19:1
9	PhCF$_3$	0.05	4Å	48	rt	52	49	9:1
10	o-xylene	0.05	4Å	91	rt	64	74	13:1
11	mesitylene	0.05	4Å	118	rt	44	71	5:1
12	PhMe	0.1	4Å	29	rt	52	68	5:1
13	PhMe	0.05	3Å	71	rt	52	74	13:1
14	PhMe	0.05	5Å	69	rt	48	70	15:1
15	PhMe	0.05	4Å	121	0	35	77	6:1
16[a]	PhMe	0.05	4Å	74	rt	60	72	10:1
17[b]	PhMe	0.05	4Å	116	rt	79	70	6:1
18[b]	o-xylene	0.05	3Å	69	rt	77	82	6:1
19[b]	o-xylene	0.05	3Å	142	0	57	84	6:1
20[b]	o-xylene	0.025	4Å	73	rt	44	77	6:1
21[b]	o-xylene	0.025	3Å	72	rt	43	77	9:1

[a] With 1.3 equiv phenylsuccinic anhydride. [b] With 1.3 equiv imine.

After evaluating several thiourea catalysts (Scheme 2.11), it was found that 4-trifluoromethyl phenyl catalyst **2.4r** gave 87% ee, but poor yields. It is thought that product inhibition could be slowing the conversion. Adding an electron-withdrawing group such as bromine to the para position

3,5-trifluoromethylphenyl ring on **2.4s** led to increased enantioselectivities, although in some cases the yield also decreased.

Scheme 2.11 Catalyst screen with toluene as solvent.

2.4b 52% (91 h)
83% ee, 13:1 dr

2.4o 52% (68 h)
83% ee, 12:1 dr

2.4p 41% (72 h)
80% ee, 6:1 dr

2.4q 62% (73 h)
85% ee, 19:1 dr

2.4r 53% (103 h)
81% ee, 11:1 dr

2.4s 48% (119 h)
87% ee, 11:1 dr

Further reaction optimization with catalyst **2.4s** was conducted (Table 2.5). It was found that o-xylene at 0.025 M gave the highest enantioselectivity, although with cooling the yield dropped to 20% despite extended reaction times. Other non-polar solvents and xylenes also gave high enantioselectivities. In general, dilution form 0.05 M to 0.025 M led to higher enantioselectivities and improved dr. Adding an excess of the imine starting material improved the yields slightly, as did adding a basic additive such as pyridine.

Table 2.5 Further optimization of phenylsuccinic reaction conditions
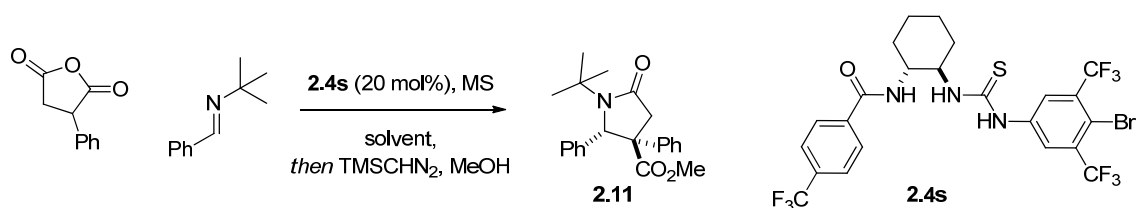
| entry	solvent	conc (M)	MS	time (h)	T [°C]	yield (%)	ee (%)	dr
1[a]	PhMe	0.05	4Å	52	rt	46	81	6:1
2[a]	PhMe	0.025	4Å	119	rt	48	87	11:1
3[a]	PhMe	0.025	3Å	70	rt	61	86	12:1
4[a]	o-xylene	0.025	3Å	98	rt	64	86	8:1
5[a]	o-xylene	0.025	4Å	72	rt	46	88	12:1
6[b]	o-xylene	0.025	4Å	164	0	20	89	9:1
7[a,c]	o-xylene	0,025	4Å	71	rt	50	87	11:1
8[a,d]	o-xylene	0.025	4Å	101	rt	54	87	12:1
9[b]	o-xylene	0.025	4Å	76	rt	58	87	13:1
10[f]	o-xylene	0.025	4Å	69	rt	47	86	13:1
11[a,e]	o-xylene	0.025	4Å	24	rt	26	86	10:1
12[b]	m-xylene	0.025	4Å	73	rt	0	-	-
13[b]	Xylenes	0.025	4Å	75	rt	16	60	5:1
14[b]	mesitylene	0.025	4Å	72	rt	69	84	3:1

a) With 1.3 equiv imine. b) With 1.5 equiv imine. c) Added anhydride then imine. d) With 200 mg MS. e) With 20 mol% pyridine. f) With 1.5 equiv anhydride.

A further catalyst screen led to 4-cyano catalyst **2.4t** which gave the product with 46% yield in 90% ee and almost exclusively the *syn* diastereomer at room temperature (Scheme 2.12). Adding basic additives led to a slight erosion of the ee and dr.

Scheme 2.12 Final conditions for phenylsuccinic anhydride reaction.
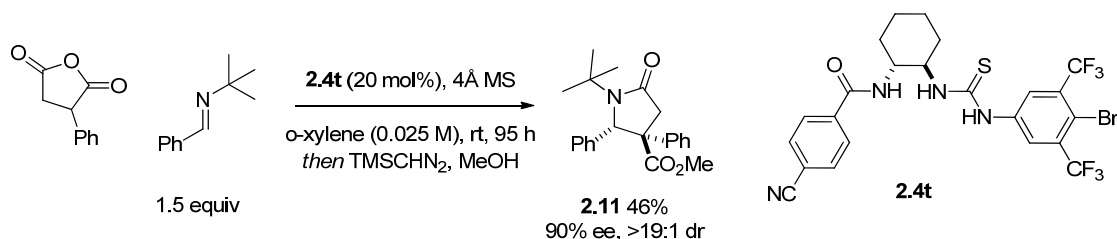
**2.4 Enantioselective Formal [4+2] Cycloadditions with Sulfonylsuccinic Anhydrides and Imines**

Next we turned our attention to sulfonicsuccinic anhydrides. The Shaw group had already demonstrated that these were a more reactive class of substrates in the diastereoselective reaction than phenylsuccinic anhydrides – able to react completely within 3 hours without heating (Scheme 2.13).[64] The carboxylic acid intermediate could easily be decarboxylated upon heating, although using trimethylsilyldiazomethane as the methylating reagent the Shaw group could isolate the methyl esters.

Scheme 2.13 Racemic reaction with sulfonylsuccinic anhydride sand imines

Shaw, 2014
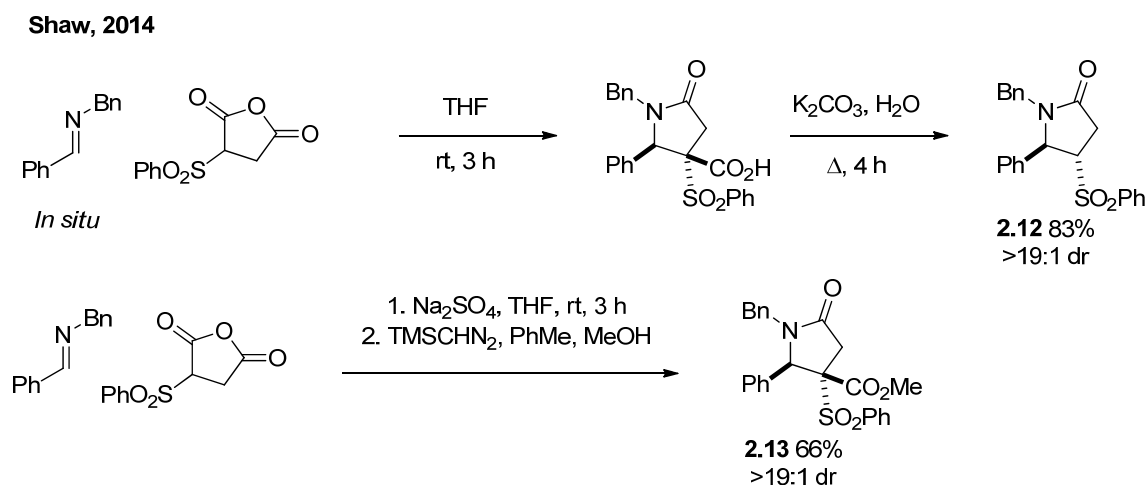
Starting with catalyst **2.4r**, the reaction between *N*-tertbutyl imine and sulfonylsuccinic anhydride was evaluated (Table 2.6). It was found that ethereal solvents such as MTBE were preferred for the enantioselective version of this reaction, and the presence of molecular sieves was crucial for ensuring high yields and improved enantioselectivities (entry 3-5). The presence of a strong electron-

withdrawing group para to the thiourea functionality was key to improving the ee (entry 1-3). The absolute configuration of these products was not established.

Table 2.6 Initial optimization of sulfonylsuccinic anhydride reaction conditions.
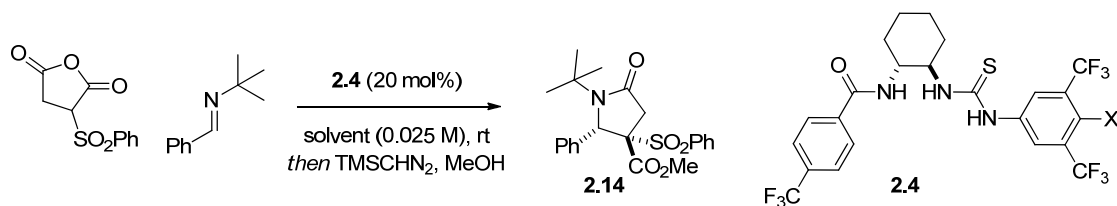
entry	solvent	X	MS	time (h)	yield (%)	ee (%)	dr
1	MTBE	H	-	2	46	47	19:1
2	MTBE	Br	-	7	48	56	19:1
3	MTBE	CN	-	7	31	67	19:1
4	MTBE	CN	4Å	25	61	70	19:1
5[a, b]	MTBE	CN	4Å	45	67	72	19:1
6	PhMe	Br	-	8	58	37	19:1
7	Ether	Br	-	26	63	46	19:1
8	THF	Br	-	71	0	-	-

[a] At 0 °C. [b] 1.5 equiv imine.

The best catalyst for the this reaction was established as 4-cyano **2.4t**, giving 75% ee at room temperature and 69% yield of a single diastereomer (Scheme 2.14). The moderate yields could be a result of some decarboxylation of the product, although that byproduct has not been isolated or viewed by ^{1}H NMR spectroscopy.

Scheme 2.14 Final conditions for sulfonylsuccinic anhydride reaction.
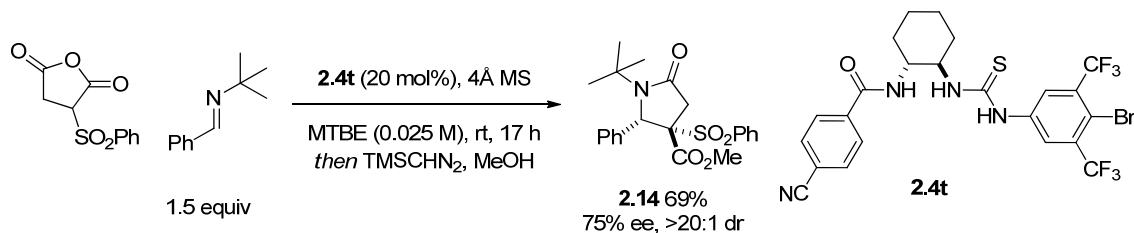
2.5 Towards the Enantioselective Synthesis of Quinazolinones

2.5.1 Background

We also sought to expand this chemistry to the enantioselective synthesis of quinazolinones.[65] These naturally-occurring compounds and their analogues have been investigated as weight loss aids,[66] analgesics[67] and anti-inflammatory agents (Figure 2.5).[68] The reaction to form quinazolines from isatoic anhydrides and imine proceeds through a decarboxylation step, which we hypothesized would drive the reaction forward and reduce product inhibition, a problem with the synthesis of isoquinoline derivatives.

**Figure 2.5** Natural products containing the quinazolinone scaffold

evodiamine   methaqualone   dievodiamine
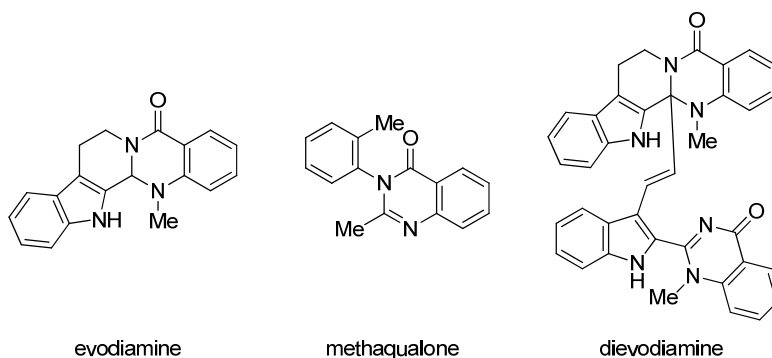
Several methods to make racemic quinazolinones have already been reported in the literature using unprotected[18] and *N*-alkylated isatoic anhydrides (Scheme 2.15).[69,70] These reactions usually proceed without a catalyst, but require high temperatures. We sought a milder approach to these compounds that would be more amenable to enantioselective catalysis.

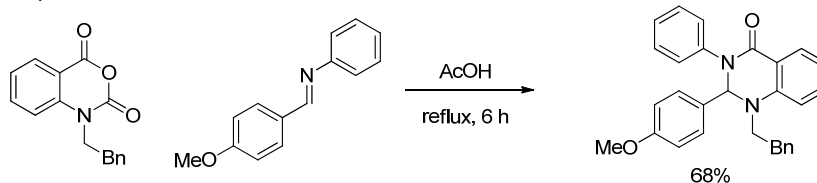**Scheme 2.15** Synthetic approaches to racemic quinazolinone substrates
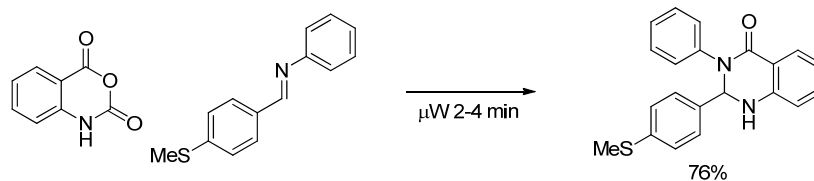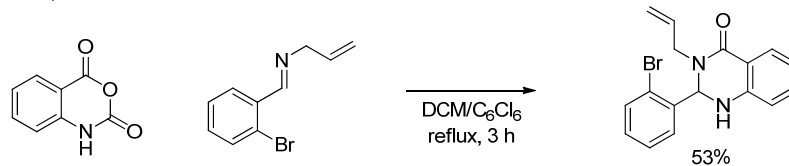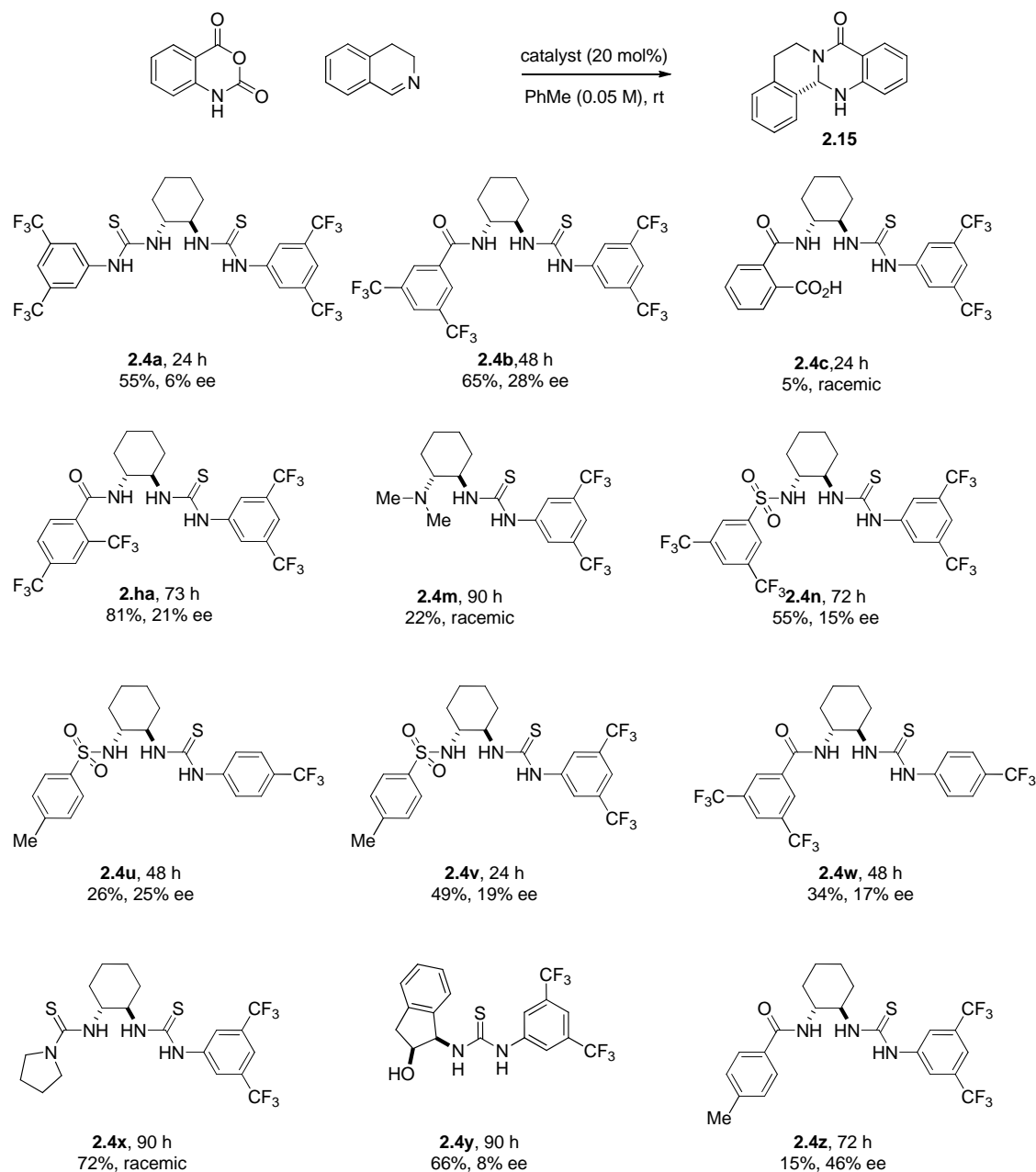

## 2.5.2 Reaction Optimization

We first conducted a catalyst screen of the reaction between isatoic anhydride and DHIQ, using toluene as the solvent (Scheme 2.16). It was found that amide thiourea catalysts were better than sulfonamides – with amide thiourea catalyst **2.4b** giving 28% ee (unknown absolute configuration). Organocatalysts developed by Ricci[71] and Takemoto[54] were also screened, but gave slower rates and almost no enantioselectivity. The *para*-methylphenyl amide thiourea **2.4z** gave increased enantioselectivities but poor conversion that couldn't be rectified with additional condition screening.

Scheme 2.16 Isatoic anhydride catalyst screen

2.15

2.4a, 24 h
55%, 6% ee

2.4b, 48 h
65%, 28% ee

2.4c, 24 h
5%, racemic

2.ha, 73 h
81%, 21% ee

2.4m, 90 h
22%, racemic

2.4n, 72 h
55%, 15% ee

2.4u, 48 h
26%, 25% ee

2.4v, 24 h
49%, 19% ee

2.4w, 48 h
34%, 17% ee

2.4x, 90 h
72%, racemic

2.4y, 90 h
66%, 8% ee

2.4z, 72 h
15%, 46% ee

Several solvents were screened in conjunction with sulfonamide **2.4v** (Table 2.7). It was found that pyridine as an additive improved the enantioselectivities slightly to 27% ee, in part through assisting in the solubility of the isatoic anhydride starting material. Increasing the concentration from 0.05 M to 0.1 M in toluene also improved the rate and enantioselectivity. However, the

enantioselectivities were so low that it was not seen worthwhile to pursue optimization of the reaction conditions further.

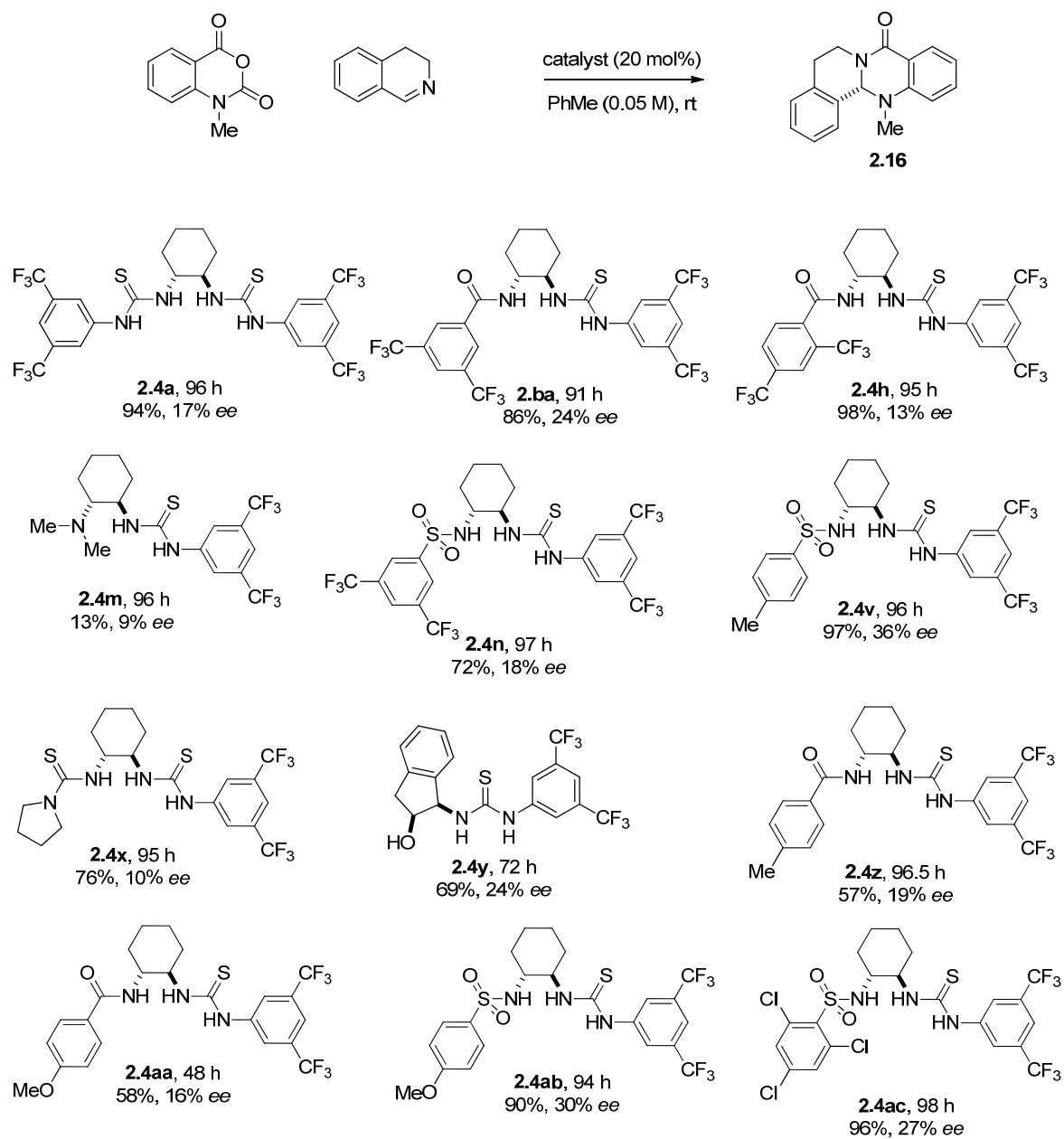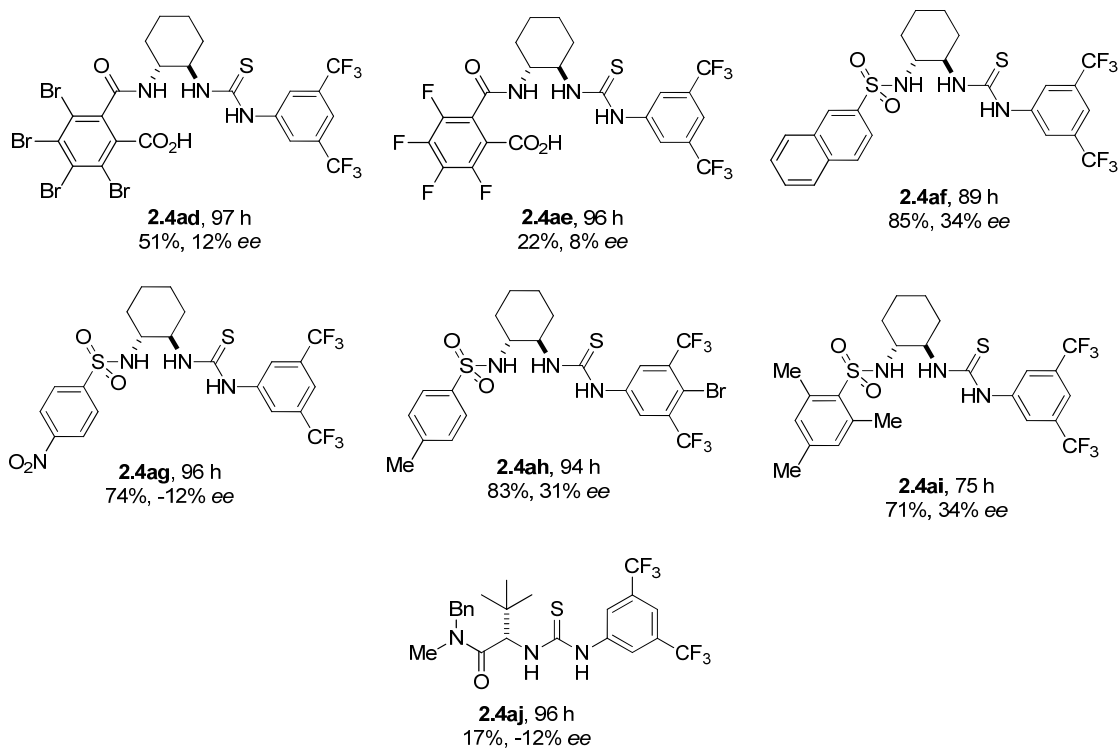**Table 2.7** Isatoic anhydride reaction condition screen
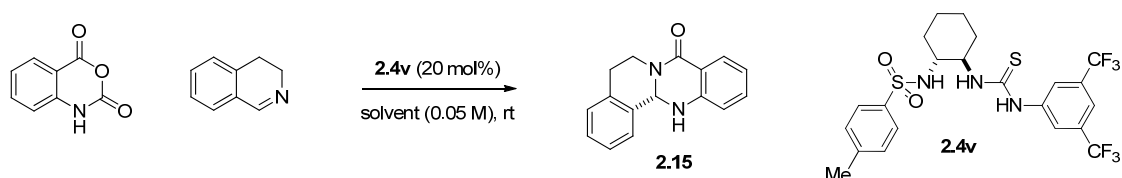
entry	solvent	time (h)	yield (%)	ee (%)
1	PhMe	24	49	19
2[a]	PhMe	44	49	27
3[b]	PhMe	44	77	26
4	PhCF$_3$	48	83	24
5	THF	48	62	10

a) With 20 mol% pyridine. b) At 0.1 M concentration.

Next we turned out attention to *N*-Methylisatoic anhydride as a substrate. A number of sulfonamide and thiourea catalysts were screened, using toluene as the solvent (Scheme 2.17). *N*-Methylisatoic anhydride reacting with DHIQ was found to give higher enantioselectivities than the isatoic anhydrides (unknown absolute configuration), although the rate of conversion was slower. In this reaction, sulfonamide **2.4v** was found be the best catalyst, affording the desired product with 36% ee.

Scheme 2.17 N-Methylisatoic anhydride catalyst screen

catalyst (20 mol%)

PhMe (0.05 M), rt

2.16

2.4a, 96 h
94%, 17% *ee*

2.ba, 91 h
86%, 24% *ee*

2.4h, 95 h
98%, 13% *ee*

2.4m, 96 h
13%, 9% *ee*

2.4n, 97 h
72%, 18% *ee*

2.4v, 96 h
97%, 36% *ee*

2.4x, 95 h
76%, 10% *ee*

2.4y, 72 h
69%, 24% *ee*

2.4z, 96.5 h
57%, 19% *ee*

2.4aa, 48 h
58%, 16% *ee*

2.4ab, 94 h
90%, 30% *ee*

2.4ac, 98 h
96%, 27% *ee*

2.4ad, 97 h
51%, 12% *ee*

2.4ae, 96 h
22%, 8% *ee*

2.4af, 89 h
85%, 34% *ee*

2.4ag, 96 h
74%, -12% *ee*

2.4ah, 94 h
83%, 31% *ee*

2.4ai, 75 h
71%, 34% *ee*

2.4aj, 96 h
17%, -12% *ee*

A range of solvents were screened in conjunction with the sulfonamide catalyst **2.4v** (Table 2.8). Toluene as solvent gave the best conversion, with non-polar solvents generally giving higher enantioselectivities and yields than more polar solvents. Ethyl acetate as a solvent gave slightly higher enantioselectivity than toluene, but the rate of reaction was considerably slower.

Table 2.8 *N*-Methylisatoic anhydride solvent screen
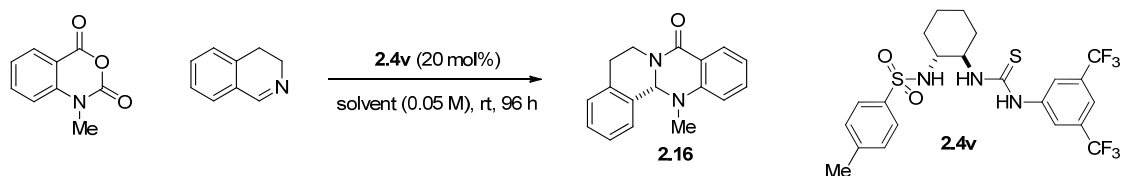
entry	solvent	yield (%)	ee (%)
1	PhMe	97	36
2	PhCF$_3$	83	31
3	Dioxane	9	20
4	Diethyl ether	67	33
5	MTBE	60	30
6	Ethyl acetate	56	37
7	Chloroform	32	18
8	Acetonitrile	78	18

The yields and enantioselectivities for the reaction between *N*-Methylisatoic anhydride and DHIQ were still poor, with the reaction requiring 4 days at room temperature to reach complete conversion. Basic additives were therefore screened to see if they could promote the reaction (Scheme 2.18) Using sulfonamide **2.4v** as the catalyst in toluene it was found that 25 mol% pyridine as an additive had little effect on the rate or product ee, with larger quantities leading to an erosion of enantioselectivity. It was suspected that the product ee was eroding over time under normal reaction conditions, reducing the viability of the reaction.

Scheme 2.18 Basic additives in *N*-Methylisatoic anhydride reaction

20 mol% pyridine: 93 h, 84%, 35% ee

50 mol% pyridine: 97 h, 35%, 17% ee
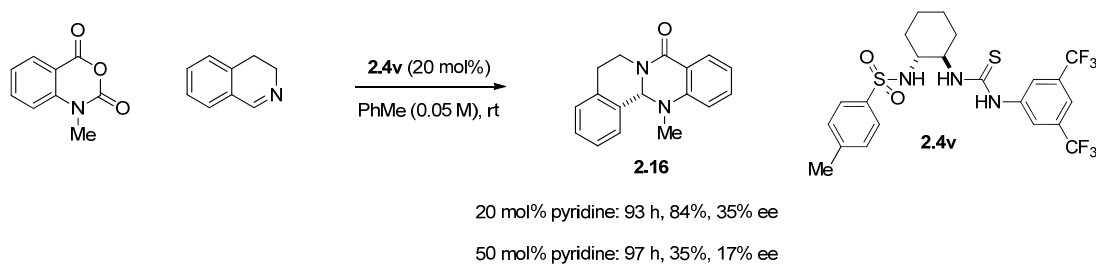
2.6 Summary

In summary we have developed a new catalyst system for the synthesis of enantioenriched lactams from enolizable anhydrides and imines, and applied the chemistry with homophthalic anhydride, phenylsuccinic and sulfonylsuccinic anhydrides to give γ and δ-lactam products in moderate to high ee. This formal [4+2] cycloaddition reaction represents a rare case of asymmetric ion-pairing catalysis in which a neutral catalyst simultaneously interacts with an anionic nucleophile and a cationic electrophile that subsequently combine without generation of byproducts. An approach to synthesize enantioenriched quinazolinone alkaloids was also developed, but suffered from low enantioselectivities and poor reaction rates.

Experimental Section

General Information: Reagents and solvents were purchased from commercial sources and were purified by distillation or recrystallization prior to use. Reactions were run under a nitrogen atmosphere unless stated otherwise. Purification of reaction products was carried out by flash column chromatography using EM Reagent silica gel 60 (230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, and potassium permanganate, Dragendorff-Munier or anisaldehyde stains, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 7.26 ppm, (CD$_3$)$_2$SO at 2.50 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet, comp = complex; integration; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 77.16 ppm, (CD$_3$)$_2$SO at 39.52 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer or on a Finnigan 2001 Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. HPLC analysis was carried out on an Agilent 1100 series instrument with auto sampler and multiple wavelength detectors. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P–2000 polarimeter at 589 nm and at 20 °C. Racemic products were prepared using racemic **2.4h**. Homophthalic anhydride,[72] 3-(phenylsulfonyl)dihydrofuran-2,5-dione,[64] 3,4-dihydroisoquinoline,[73] 6,7-dimethoxy-3,4-dihydroisoquinoline,[74] 6-chloro-3,4-dihydroisoquinoline,[75] 1-methyl-3,4-dihydroisoquinoline[76] and imine precursors[77] were prepared according to previously published procedures. Catalysts **2.4a**,[78] **2.4b**,[79] **2.4c**,[80] **2.7m**[54] were prepared according to previously published procedures.

Synthesis of Catalysts

Scheme S1
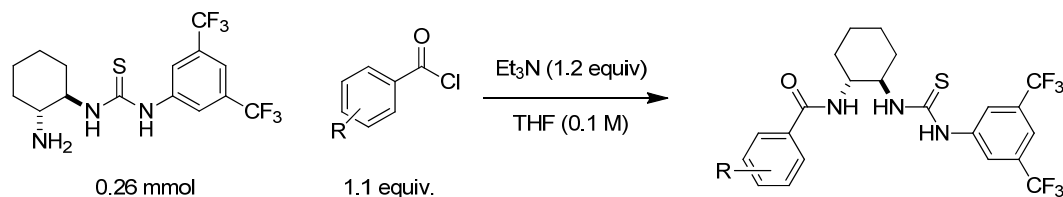
General Procedure A for Catalyst Synthesis (Scheme S1):

To a solution of aminothiourea (100 mg, 0.26 mmol) in THF (1.6 mL) was added triethylamine (38

μL, 0.31 mmol, 1.2 equiv) followed by the corresponding acyl chloride (0.29 mmol, 1.1 equiv) in THF

(1 mL, 0.1 M) and stirred at room temperature until starting material was consumed, as indicated by

TLC analysis. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography

on silica gel. The resulting solid was dried under high vacuum.

Methyl **2-(((1*R*,2*R*)-2-(3-(3,5-**

bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carbamoyl)benzoate (2.4d): To a solution of
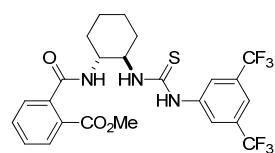
thiourea **2.4c** (107 mg, 0.2 mmol) in THF (3 mL, 0.07 M) was added MeOH

(1 mL) followed by trimethylsilyldiazomethane (2.0 M in diethyl ether, 0.15

mL, 1.5 equiv). The reaction mixture was stirred at room temperature until

the starting material was consumed, as indicated by TLC analysis. The reaction mixture was then

quenched with 5 drops of glacial acetic acid, concentrated *in vacuo* and purified by flash

chromatography on silica gel. The resulting solid was dried under high vacuum. Compound **2.4d** was

obtained as a white solid in 69% yield (76 mg); R_f = 0.43 (EtOAc/hexanes 1:1 v/v); mp: 199–202

ºC; $[\alpha]_D^{20}$ +96.48 (c 0.5, CHCl$_3$); IR (KBr) 3330, 2939, 2856, 1716, 1631, 1537, 1275, 1129, 1128,

1091, 859, 646, 521 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.12 (s, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.77

(s, 2H), 7.65 (d, *J* = 6.1 Hz, 1H), 7.59–7.50 (m, 1H), 7.49–7.34 (comp, 4H), 4.60–4.66 (m , 1H), 4.09–

3.98 (m, 1H), 3.50 (s, 3H), 2.36–2.25 (comp, 2H), 2.01–1.90 (comp, 2H), 1.66–1.41 (comp, 4H); ^{13}C

NMR (125 MHz, (CD$_3$)$_2$SO) δ 180.85, 170.31, 165.78, 155.65, 153.12, 142.00, 138.13, 130.1 (q, J_{C-F} = 32.7 Hz), 129.53, 123.26 (q, J_{C-F} = 275.5 Hz), 121.92, 121.40, 116.23, 59.75, 54.79, 29.32, 23.90, 23.20, 20.76, 14.08; *m/z* (ESI–MS) 546.1 [M – H]$^-$.

Benzyl 2-(((1R,2R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carbamoyl)benzoate (2.4e): Following general procedure A, compound **2.4e** was obtained as a white solid in 64% yield

(103 mg); R$_f$ = 0.36 (EtOAc/hexanes 3:7 v/v); mp: 84–87 ºC; [α]$_D^{20}$ +93.14 (c 0.5, CHCl$_3$); IR (KBr) 3335, 3303, 2970, 2935, 2853, 1713, 1636, 1542, 1365, 1279, 1217, 1120, 528 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.98 (s, 1H), 7.93 (d, *J* = 6.8 Hz, 1H), 7.79 (s, 2H), 7.71 (d, *J* = 7.3 Hz, 1H), 7.55 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.42–7.32 (comp, 3H), 7.31–7.27 (comp, 4H), 7.18–7.11 (comp, 2H), 5.04 (d, *J* = 12.2 Hz, 1H), 4.90 (d, *J* = 12.1 Hz, 1H), 4.72–4.62 (m, 1H), 4.05–3.96 (m, 1H), 2.38–2.27 (m, 1H), 2.16–2.06 (m, 1H), 1.97–1.87 (comp, 2H), 1.62 –1.38 (comp, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 181.59, 170.23, 167.75, 140.94, 136.33, 134.80, 132.03, 131.36 (q, J_{C-F} = 33.4 Hz), 130.82, 130.67, 129.92, 129.84, 128.58, 128.39, 127.20, 123.16 (q, J_{C-F} = 272.8 Hz) 122.43 (m), 117.32 (m), 110.15, 67.77, 56.85, 55.94, 32.61, 32.43, 25.29, 25.00; *m/z* (ESI–MS) 622.3 [M – H]$^-$.

**2,2,2-trifluoroethyl 2-(((1R,2R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carba-moyl) benzoate (2.4f):** Following general procedure A, compound **2.4f** was obtained as a white solid in 49% yield (78 mg); R$_f$ = 0.28 (EtOAc/hexanes 3:7 v/v); mp:
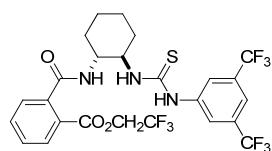
158–160 ºC; [α]$_D^{20}$ +39.20 (c 0.5, CHCl$_3$); IR (KBr) 3300, 3257, 3016, 2946, 2127, 1739, 1720, 1637, 1550, 1279, 1206, 895, 528 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.86 (s, 1H), 7.86–7.73 (comp, 3H), 7.64–7.57 (m, 1H), 7.52–7.44 (comp, 2H), 7.25–7.17 (m, 1H), 4.77–4.65 (m, 1H), 4.45–4.32 (m, 1H), 4.28–4.17 (m, 1H), 4.11–3.96 (m, 1H), 2.38–2.21 (comp, 2H), 2.02–1.88 (comp, 2H), 1.55–1.38 (comp, 4H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 181.50, 170.00, 165.88,

140.74, 136.97, 133.00, 131.61 (q, J_{C-F} = 33.4 Hz), 131.05, 130.41, 127.75, 127.42, 123.11 (q, J_{C-F} =

272.8 Hz), 122.71 (q, J_{C-F} = 276.9 Hz), 117.56, 61.36 (q, J_{C-F} =36.9), 56.87, 56.09, 32.51, 32.38,

25.22, 24.95; *m/z* (ESI–MS) 614.2 [M – H]⁻ .

N-((1R,2R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)-2-
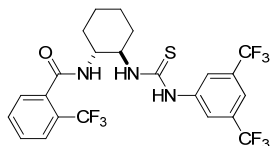
(trifluoromethyl)benzamide (2.4g): Following general procedure A, compound **2.4g** was obtained as a white solid in 51% yield (74 mg); R_f = 0.39 (EtOAc/hexanes 3:7 v/v); mp: 100–104 ºC; $[\alpha]_D^{20}$ +53.16 (c 0.5, CHCl₃); IR (KBr) 3320, 3006, 2942, 1736, 1717, 1513, 1474, 1365, 1279,

1134, 681, 529 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.22 (s, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.64–7.56

(comp, 3H), 7.53–7.46 (m, 1H), 7.47–7.40 (comp, 3H), 7.34 (d, *J* = 8.3 Hz, 1H), 4.88–4.68 (m, 1H),

4.07–3.85 (m, 1H), 2.44–2.22 (comp, 2H), 2.11–1.88 (comp, 2H), 1.66–1.35 (comp, 4H); ¹³C NMR

(125 MHz, CDCl₃) δ 181.75, 169.88, 140.57, 134.40, 132.33, 131.43 (q, J_{C-F} = 33.4 Hz), 130.92,

127.79, 126.99 (q, J_{C-F} = 6.8, 5.7 Hz), 123.59 (q, J_{C-F} = 273.6 Hz), 123.09 (q, J_{C-F} = 272.8 Hz),

122.86, 117.72 (m), 57.12, 55.70, 33.04, 32.32, 25.25, 24.93; *m/z* (ESI–MS) 556.7 [M – H]⁻.

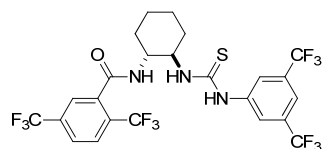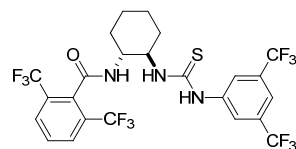**N-((1R,2R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)-2,4-**
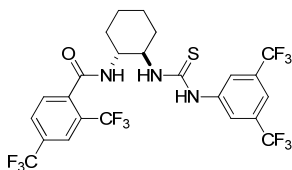
bis(trifluoromethyl)benzamide (2.4h): Following general procedure A, compound **2.4h** was obtained as a white solid in 76% yield (741 mg); R_f = 0.37 (EtOAc/Hexanes 3:7 v/v); mp: 212–213 ºC; $[\alpha]_D^{20}$ +47.68 (c 0.5, CHCl₃); IR (KBr) 3353, 3017, 3068, 2947, 2931, 2870, 1738, 1654, 1560,

1459, 1347, 1282, 1071, 969, 721 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.93 (s, 1H), 7.88 (s, 1H),

7.77 (d, *J* = 8.1 Hz, 1H), 7.69–7.61 (comp, 3H), 7.51 (s, 2H), 7.30 (d, *J* = 5.9 Hz, 1H), 4.81–4.70 (m,

1H), 4.02–3.92 (m, 1H), 2.43–2.19 (comp, 2H), 2.03–1.90 (comp, 2H), 1.60–1.37 (comp, 4H); ¹³C

NMR (125 MHz, CDCl₃) δ 181.62, 168.20, 140.25, 137.81, 133.31 (q, J_{C-F} = 34.1 Hz), 131.86 (q, J_{C-F}

= 33.5 Hz), 129.48, 128.92, 128.18 (q, J_{C-F} = 33.0 Hz), 124.29, 123.00 (q, J_{C-F} = 272.7 Hz), 122,88 (q,

J_{C-F} = 247.3 Hz), 122.79, 122.69 (q, J_{C-F} = 273.0 Hz), 118.14, 56.90, 56.23, 32.83, 32.27, 25.09,

24.83; *m/z* (ESI–MS) 624.5 [M – H]⁻.

N-((1R,2R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)-2,4-dinitrobenzamide
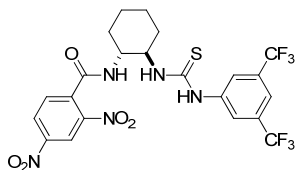
(2.4i): Following general procedure A, compound **2.4i** was obtained as an orange solid in 73% yield (109 mg); R_f = 0.21 (EtOAc/Hexanes 3:7 v/v); mp: 123–126 ºC; $[\alpha]_D^{20}$ +57.10 (c 0.5, CHCl₃); IR (KBr) 3288, 3069, 2941, 1741, 1545, 1386, 1349, 1279, 1179, 1135, 886, 700 cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 8.73 (s, 1H), 8.59 (s, 1H), 8.51 (d, *J* = 8.2 Hz, 1H), 8.30 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.58 (s, 1H), 7.53 (s, 1H), 7.36 (d, *J* = 7.2 Hz, 1H), 4.79–4.58 (m, 1H), 4.04–3.85 (m, 1H), 2.47–2.36 (m, 1H), 2.33–2.25 (m, 1H), 2.12–1.90 (comp, 2H), 1.75–1.36 (comp, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 181.64, 166.28, 148.78, 146.01, 139.66, 136.87, 132.13 (q, J_{C-F} = 33.7 Hz), 130.34, 128.83, 122.92 (q, J_{C-F} = 271.3 Hz), 122.88, 120.29, 118.62, 58.60, 55.87, 32.64, 32.26, 24.86, 24.85; *m/z* (ESI–MS) 578.5 [M – H]⁻.

**N-((1R,2R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)-4-nitro-2-**
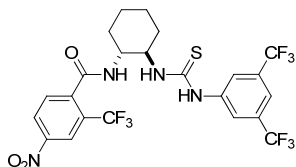
(trifluoromethyl)benzamide (2.4j): Following general procedure A, compound **2.4j** was obtained as a yellow solid in 75% yield (118 mg); R_f = 0.31 (EtOAc/hexanes 3:7 v/v); mp: 113–115 ºC; $[\alpha]_D^{20}$ +59.60 (c 0.5, CHCl₃); IR (KBr) 3328, 3095, 2943, 2863, 1541, 1313, 1178, 1135, 886, 708 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.79 (s, 1H), 8.48 (s, 1H), 8.39 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.63 (s, 2H), 7.51 (s, 1H), 7.47–7.37 (comp, 2H), 4.81–4.59 (m, 1H), 4.06–3.90 (m, 1H), 2.38–2.22 (comp, 2H), 2.03–1.92 (m, 2H), 1.61–1.36 (comp, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 181.49, 167.37, 148.63, 139.95, 139.86, 131.97 (q, J_{C-F} = 33.6 Hz), 129.73, 128.98 (q, J_{C-F} = 33.8 Hz), 127.36, 122.92 (q, J_{C-F} = 272.8 Hz), 122.44 (q, J_{C-F} = 274.7 Hz)122.63, 122.59, 118.32, 57.16, 56.33, 32.79, 32.21, 25.01, 24.80; *m/z* (ESI–MS) 601.2 [M – H]⁻.

***N*-((1*R*,2*R*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)-2,5-**

bis(trifluoromethyl)benzamide (2.4k): Following general procedure A, compound **2.4k** was obtained as a white solid in 73% yield (149 mg); R_f = 0.54 (EtOAc/hexanes 3:7 v/v); mp: 205–208 ºC; $[\alpha]_D^{20}$ +40.10 (c 0.5, CHCl₃); IR (KBr) 3328, 3005, 2939, 2863, 1701, 1549, 1392, 1294, 1088, 681, 530 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.89 (s, 1H), 7.77 (comp, 2H), 7.72 (s, 1H), 7.64 (s, 2H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.47 (s, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 4.85–4.68 (m, 1H), 4.06–3.88 (m, 1H), 2.42–2.22 (comp, 2H), 2.03–1.95 (comp, 2H), 1.75–1.32 (comp, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 181.57, 168.14, 140.14, 135.38, 134.83 (q, $J_{C\text{-}F}$ = 34.5, 33.7 Hz), 131.69 (q, $J_{C\text{-}F}$ = 33.6 Hz), 127.94 (q, $J_{C\text{-}F}$ = 4.9 Hz), 127.78 (q, $J_{C\text{-}F}$ = 3.8, 3.2 Hz),123.01 (q, $J_{C\text{-}F}$ = 272.7 Hz), 122,74 (q, $J_{C\text{-}F}$ = 233.1 Hz), 122,56 (q, $J_{C\text{-}F}$ = 273.5 Hz), 122.38,117.88, 57.17, 55.95, 32.90, 32.29, 25.13, 24.88; *m/z* (ESI–MS) 624.1 [M – H]⁻.

***N*-((1*R*,2*R*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)-2,6-**

bis(trifluoromethyl)benzamide (2.4): Following general procedure A, compound **2.4l** was obtained as an off-white solid in 18% yield (31 mg); R_f = 0.41 (EtOAc/hexanes 3:7 v/v); mp: >250 ºC; $[\alpha]_D^{20}$ +24.38 (c 0.5, CHCl₃); IR (KBr) 3466, 3316, 3005, 2970, 1739, 1717, 1541, 1436, 1370, 1218, 529 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.90 (s, 1H), 7.92–7.82 (comp, 2H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.64–7.50 (comp, 4H), 7.48 (s, 1H), 4.79–4.53 (m, 1H), 4.04–3.90 (m, 1H), 2.33 (comp, 2H), 2.01–1.70 (comp, 2H), 1.58–1.35 (comp, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 182.10, 165.86, 140.19, 132.95, 131.49 (q, $J_{C\text{-}F}$ = 33.5 Hz), 130.59, 130.39, 130.17, 128.86 (q, $J_{C\text{-}F}$ = 32.2 Hz) , 123.65, 123.07 (q, $J_{C\text{-}F}$ = 272.9 Hz), 118.25, 57.57, 55.84, 32.57, 31.43, 24.80, 24.75; *m/z* (ESI–MS) 624.0 [M – H]⁻.

N-((1*R*,2*R*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)-3,5-
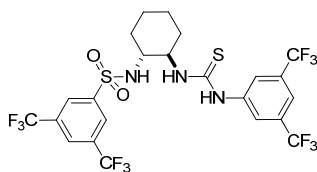
bis(trifluoromethyl)benzenesulfonamide (2.4n): Following general procedure A, compound **2.4n** was obtained as a white solid in 47% yield (80 mg); R_f = 0.16 (EtOAc/hexanes 2:8 v/v); mp: 82–85 °C; $[\alpha]_D^{20}$ +29.08 (c 0.5, CHCl₃); IR (KBr) 3006, 2970, 2946, 1754, 1706, 1436, 1356, 1211, 1137, 528 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.30 (comp, 3H), 8.05 (s, 1H), 7.83 (s, 2H), 7.68 (s, 1H), 6.77 (s, 1H), 6.47 (d, *J* = 8.3 Hz, 1H), 4.58–4.38 (m, 1H), 3.37–3.19 (m, 1H), 2.26–2.12 (m, 1H), 1.81–1.68 (comp, 3H), 1.43–1.18 (comp, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 181.62, 144.51, 138.46, 133.12 (q, J_{C-F} = 34.6 Hz), 132.93 (q, J_{C-F} = 34.0 Hz), 127.02, 126.33, 124.63, 122.86 (q, J_{C-F} = 272.9 Hz), 122.51 (q, J_{C-F} = 273.4 Hz), 120.01, 59.51, 57.95, 33.68, 32.15, 24.59, 24.40; *m/z* (ESI–MS) 660.0 [M – H]⁻.

Synthesis and Characterization Data of Products

General Procedure B for Asymmetric Cycloaddition to Form Methyl Ester:

An oven-dried vial was charged with homophthalic anhydride (36 mg, 0.22 mmol, 1.1 equiv), catalyst **2.4h** (25 mg, 0.04 mmol, 0.2 equiv), powdered 4 Å molecular sieves (200 mg) and MTBE (8 mL, 0.025 M). The reaction mixture was cooled to –40 °C and then charged with the imine (0.2 mmol, 1 equiv). The reaction mixture was stirred at –40 °C until the imine could no longer be detected by TLC analysis, then MeOH (1 mL) and trimethylsilyldiazomethane (0.2 mL, 2.0 M in diethyl ether, 0.4 mmol, 2 equiv) was added and the reaction allowed to warm to room temperature. After one hour the reaction was quenched with 5 drops of glacial acetic acid. The reaction mixture was filtered through celite, concentrated and purified by flash column chromatography on silica gel. The resulting product was dried under high vacuum.

**General Procedure C for Asymmetric Cycloaddition to Form Carboxylic Acid:**

An oven-dried vial was charged with homophthalic anhydride (36 mg, 0.22 mmol, 1.1 equiv), catalyst **2.4h** (25 mg, 0.04 mmol, 0.2 equiv), powdered 4 Å molecular sieves (200 mg) and MTBE (8 mL,

0.025 M). The reaction mixture was cooled to –40 °C and then charged with the imine (0.2 mmol, 1 equiv). The reaction mixture was stirred at –40 °C until the imine could no longer be detected by TLC analysis. The reaction mixture was then warmed to room temperature, quickly filtered through celite, concentrated and purified by flash column chromatography on silica gel. The resulting carboxylic acid product was dried under high vacuum.

General Procedure D for Removal of *tert*-Butyl Amide Protecting Group:

An oven-dried vial was charged with amide (0.1 mmol) and TFA/CH$_2$Cl$_2$ (1.5 mL, 1:2 v/v). The reaction mixture was stirred at reflux for 8 h. The reaction mixture was diluted with CH$_2$Cl$_2$ (1 mL) and washed with sat. Na$_2$CO$_3$ (aq, 3 x 1 mL). The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated. The crude mixture was purified by flask column chromatography on silica gel. The resulting product was dried under high vacuum.
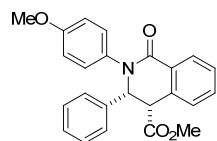
(3*R*,4*S*)-methyl 2-(4-methoxyphenyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5a): Following general procedure B, compound **2.5a** was obtained as an off-white solid in 85% yield (66 mg, >19:1 dr); R$_f$ = 0.21 (EtOAc/hexanes 3:7 v/v); mp: 130–134 °C; [α]$_D^{20}$ –12.2 (c 0.5, CHCl$_3$, 90% ee); IR (KBr) 3495, 3309, 3055, 2911, 1720, 1686, 1667, 1662, 1654, 1512 1347, 1287, 1248 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.30 (d, *J*=8.4 Hz, 1H), 7.55–7.45 (comp, 3H), 7.27–7.19 (m, 1H), 7.16 (app t, *J* = 7.4 Hz, 2H), 7.04 (d, *J* = 9.1 Hz, 2H), 6.98 (d, *J* = 7.1 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 1H), 5.30 (d, *J* = 6.1 Hz, 1H), 4.91 (d, *J* = 6.2 Hz, 1H), 3.76 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.68, 163.89, 158.48, 136.97, 134.67, 132.78, 132.63, 129.40, 128.86, 128.70, 128.58, 128.37, 128. 17, 128.04, 127.85, 114.41, 66.02, 55.50, 52.14, 50.01; *m/z* (ESI–MS) 385.5 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t$_R$ = 13.3 min (minor) and t$_R$ = 50.8 min (major).

The absolute configuration was assigned by analogy.

(3R,4S)-methyl 1-oxo-3-phenyl-2-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5b):
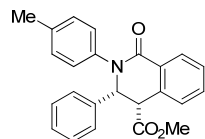
Following general procedure B, compound **2.5b** was obtained as a white solid in 77% yield (58 mg, >19:1 dr); R_f = 0.30 (EtOAc/hexanes 3:7 v/v); mp: 165–167 ºC; $[\alpha]_D^{20}$ +31.6 (c 0.5, CHCl$_3$, 91% ee); IR (KBr) 3032, 2951, 1736, 1694, 1495, 1462, 1310, 1235, 1178, 908, 761, 700 518, 404 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 8.28 (d, J = 8.4 Hz, 1H), 7.61–7.40 (comp, 3H), 7.24–7.20 (m, 1H), 7.19–7.13 (comp, 2H), 7.07 (d, J = 8.1 Hz, 2H), 7.03–6.96 (comp, 4H), 5.32 (d, J = 6.1 Hz, 1H), 4.93 (d, J = 6.1 Hz, 1H), 3.64 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.30, 163.59, 139.87, 139.31, 137.00, 132.47, 132.35, 129.84, 129. 73, 129.54, 128.87, 128.71, 128.56, 128.03, 126.60, 110.15, 65.15, 53.09, 51.92, 21.22; *m/z* (ESI–MS) 371.9 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.1 min (major) and t_R = 40.1 min (minor).

The absolute configuration was assigned by analogy.

(3R,4S)-methyl 2-(4-chlorophenyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate
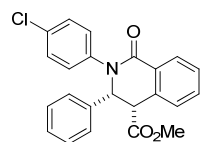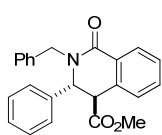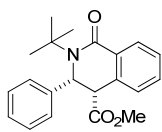

(2.5c): Following general procedure B, compound **2.5c** was obtained as a white solid in 77% yield (60 mg, 9:1 dr); R_f = 0.43 (EtOAc/hexanes 3:7 v/v); mp: 102–103 ºC; $[\alpha]_D^{20}$ +17.0 (c 0.5, CHCl$_3$, 91% ee); IR (KBr) 3423, 2701. 2387, 2385, 2351, 1515, 1485, 1422, 1223, 1092, 530 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.29 (d, J = 7.7 Hz, 1H), 7.58–7.44 (comp, 4H), 7.25–7.20 (comp, 2H), 7.18 (app t, J = 7.4 Hz, 2H), 7.09 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 7.2 Hz, 2H), 5.33 (d, J = 6.0 Hz, 1H), 4.86 (d, J = 6.0 Hz, 1H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.55, 163.84, 140.25, 136.64, 132.94, 132.89, 132.85, 129.27, 128.98, 128.90, 128.77, 128.58, 128.36, 127.92, 126.80, 126.45, 65.69, 52.24, 50.14; *m/z* (ESI–MS) 392.2 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 16.8 min (minor) and t_R = 108.1 min (major).

The absolute configuration was assigned by analogy.

(3R,4S)-2-(4-chlorophenyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic   acid
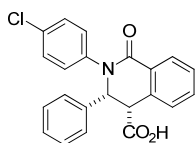
(2.5ca): Following general procedure C, compound **2.5ca** was obtained as a white foam in 83% yield (59 mg, 9:1 dr); R_f = 0.37 (MeOH/CH$_2$Cl$_2$ 1:9 v/v); mp: 193–194 °C; $[\alpha]_D^{20}$ +21.2 (c 0.5, CHCl$_3$, 91% ee); IR (KBr) 3047, 3038, 1728, 1634, 1578, 1492, 1389, 1228, 1174, 1162, 1092, 1015 cm^{-1}; ^{1}H NMR (500 MHz, (CD$_3$)$_2$SO) δ 12.96 (br. s, 1H), 8.06 (d, J = 7.6 Hz, 1H), 7.65–7.55 (comp, 2H), 7.53–7.45 (m, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.17 (comp, 3H), 7.07–7.02 (comp, 2H), 5.53 (d, J = 5.7 Hz, 1H), 4.85 (d, J = 5.2 Hz, 1H); ^{13}C NMR (125 MHz, (CD$_3$)$_2$SO) δ 170.37, 162.99, 140.36, 137.02, 134.54, 132.35, 130.73, 129.17, 128.88, 128.43, 128.09, 127.94, 127.90, 127.80, 127.68, 127.58, 64.11, 49.18; m/z (ESI–MS) 378.3 [M+H]$^+$.

The absolute configuration was assigned by X-Ray crystallography.
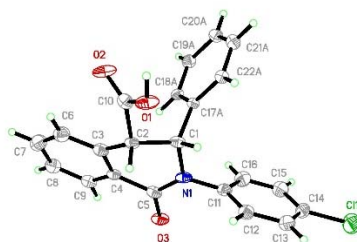
Enantioenriched compound **2.5ca** was crystallized from hexanes/EtOAc through slow diffusion at room temperature.

The requisite CIF has been deposited with the CCDC (deposition # 1502939).

**(*3R,4S*)-methyl 1-oxo-2,3-diphenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5d):**
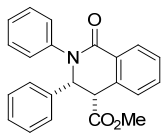
Following general procedure B, compound **2.5d** was obtained as a white solid in 83% yield (59 mg, 9:1 dr); R_f = 0.30 (EtOAc/hexanes 3:7 v/v); mp: 148–152 ºC; $[\alpha]_D^{20}$ +18.2 (c 0.5, CHCl$_3$, 90% ee); IR (KBr) 3065, 2953, 1735, 1656, 1604, 1491, 1450, 1409, 1313, 1234, 1165, 988 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.29 (d, *J* = 8.6 Hz, 1H), 7.55–7.47 (comp, 3H), 7.29 (dd, *J* = 15.7, 8.4 Hz, 2H), 7.21 (d, *J* = 7.0 Hz, 2H), 7.19–7.12 (comp, 4H), 6.99 (d, *J* = 8.6 Hz, 2H), 5.36 (d, *J* = 6.0 Hz, 1H), 4.92 (d, *J* = 6.0 Hz, 1H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.28, 163.51, 142.51, 139.30, 132.54, 132.35, 129.71, 129.54, 129.19, 128.91, 128.75, 128.60, 128.07, 127.17, 126.79, 126.57, 65.08, 53.11, 51.95; *m/z* (ESI–MS) 358.2 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.1 min (major) and t_R = 35.9 min (minor).

The absolute configuration was assigned by analogy.

**(*3R,4S*)-methyl 1-oxo-3-phenyl-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5e):** Following general procedure B, compound **2.5e** was obtained as a white solid in 77% yield (69 mg, 9:1 dr); R_f = 0.11 (EtOAc/hexanes 3:7 v/v); mp: 68–71 ºC; $[\alpha]_D^{20}$ –8.20 (c 0.5, CHCl$_3$, 88% ee); IR (KBr) 3506, 3421, 3296, 3183, 3005, 2922, 2361, 1742, 1717, 1507, 1457, 1382, 1222, 1128, 701 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.31 (d, *J* = 8.3 Hz, 1H), 7.59–7.45 (comp, 3H), 7.25–7.15 (comp, 3H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.28 (s, 2H), 5.26 (d, *J* = 6.3 Hz, 1H), 4.93 (d, *J* = 6.2 Hz, 1H), 3.80 (s, 3H), 3.65 (s, 6H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.60, 163.75, 153.37, 137.55, 137.32, 132.83, 132.78, 129.54, 128.87, 128.83, 128.66, 128.24, 127.98, 127.95, 127.67, 104.60, 66.04, 60.91, 56.05, 52.20, 49.81; *m/z* (ESI–MS) 448.0 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t_R = 11.7 min (minor) and t_R = 27.8 min (major).
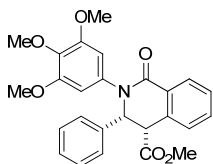
The absolute configuration was assigned by analogy.

rel-(3R,4R)-methyl 2-benzyl-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5f):

Following general procedure B, compound **2.5f** was obtained as an off-white solid in 90% yield (67 mg, 3:1 dr); R_f = 0.39 (EtOAc/hexanes 3:7 v/v); mp: 123–127 °C; $[\alpha]_D^{20}$ +19.8 (c 0.5, CHCl$_3$, 76/66% ee); IR (KBr) 3914, 3843, 3513, 3509, 3495, 3321, 2884, 3460, 2339, 1697, 1643, 1441, 1354, 1198, 1025, 738, 700 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) (major diastereomer) δ 8.27 (d, J = 7.5 Hz, 1H), 7.48–7.37 (comp, 2H), 7.36–7.27 (comp, 5H), 7.27–7.21 (comp, 3H), 7.09–7.05 (comp, 2H), 7.03 (d, J = 7.3 Hz, 1H), 5.73 (d, J = 14.6 Hz, 1H), 5.13 (s, 1H), 3.88 (s, 1H), 3.63 (d, J = 14.6 Hz, 2H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.98, 164.09, 138.60, 137.17, 132.28, 129.05, 129.00, 128.91, 128.71, 128.66, 128.59, 128.35, 128.16, 127.87, 127.71, 126.44, 60.56, 52.68, 51.66, 48.97; m/z (ESI–MS) 372.7 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, n-hexane/i-PrOH = 95/05, Flow rate = 1 mL/min, UV = 230 nm, t_R = 18.9 min (major) and t_R = 21.2 min (minor).

(3R,4S)-methyl 2-(tert-butyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate

(2.5g): Following general procedure B, compound **2.5g** was obtained as a clear oil in 71% yield (48 mg, >19:1 dr); R_f = 0.56 (EtOAc/hexanes 3:7 v/v); $[\alpha]_D^{20}$ −51.9 (c 1.0, CHCl$_3$, 95% ee); IR (KBr) 3491, 3297, 3202, 2921, 2729, 1750, 1720, 1684, 1496, 1383, 1257, 1199, 1081, 1014, 726, 701 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.31–8.16 (m, 1H), 7.49–7.29 (comp, 3H), 7.23–7.08 (comp, 3H), 6.93 (d, J = 7.2 Hz, 2H), 5.40 (d, J = 5.5 Hz, 1H), 4.69 (d, J = 5.4 Hz, 1H), 3.70 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.11, 164.54, 138.08, 131.89, 131.49, 131.40, 128.42, 128.32, 128.10, 127.86, 127.74, 127.38, 59.53, 52.07, 51.10, 29.00; m/z (ESI–MS) 338.0 [M+H]$^+$; HPLC: Daicel Chiralpak AD-H, n-hexane/i-PrOH = 97/03, Flow rate = 0.5 mL/min, UV = 254 nm, t_R = 20.1 min (minor) and t_R = 21.1 min (major).

The absolute configuration was assigned by analogy.

(3R,4S)-2-(*tert*-butyl)-3-(4-chlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid
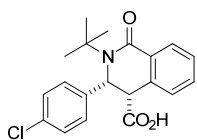
(2.5ga): Following general procedure C, compound **2.5ga** was obtained as a white solid in 78% yield (56 mg, >19:1 dr); R_f = 0.41 (MeOH/ CH_2Cl_2 1:9 v/v); mp: 201–203 ºC; The ee was determined after methylation and deprotection (below); $[\alpha]_D^{20}$ –197.2 (c 0.5, $CHCl_3$, 88% ee); IR (KBr) 34596, 3237, 3224, 3018, 2964, 2711, 2343, 1825, 1647, 1513, 1486, 1343, 1112, 927, 529 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27–8.14 (m, 1H), 7.46–7.41 (comp, 3H), 7.11 (d, J = 7.9 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 5.45 (d, J = 5.1 Hz, 1H), 4.73 (d, J = 4.3 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.43, 164.92, 136.36, 134.31, 132.26, 131.24, 131.13, 129.39, 128.67, 128.28, 128.14, 127.34, 59.85, 58.71, 50.63, 29.04; *m/z* (ESI–MS) 359.1 [M+H]$^+$.

The absolute configuration was assigned by X-Ray crystallography.
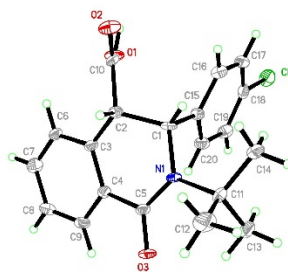
Enantioenriched compound **2.5ga** was crystallized from hexanes/CHCl$_3$ through slow diffusion at room temperature.

The requisite CIF has been deposited with the CCDC (deposition # 1502938).
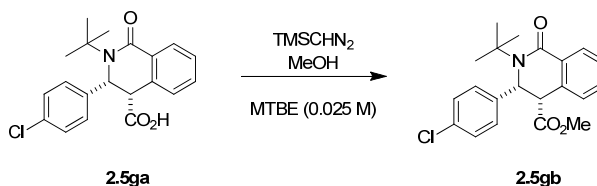
Compound **2.5ga** was transformed into **2.5gb** using the standard methylation procedure to give a white solid in 92% yield (68 mg, >19:1 dr); R_f = 0.49 (EtOAc/hexanes 3:7 v/v); mp: 71–73 °C; The ee was determined after deprotection (below); $[\alpha]_D^{20}$ –204.2 (c 0.5, CHCl₃, 88% ee); IR (KBr) 3459, 3005, 2970, 1733, 1716, 1651, 1435, 1366, 1218, 1093, 903, 529 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.23–8.19 (m, 1H), 7.42 (d, J = 9.0 Hz, 2H), 7.36–7.32 (m, 1H), 7.12 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.37 (d, J = 5.7 Hz, 1H), 4.68 (d, J = 5.6 Hz, 1H), 3.73 (s, 3H), 1.49 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 170.01, 164.44, 136.80, 134.31, 132.10, 131.29, 131.23, 129.16, 128.73, 128.23, 128.08, 127.35, 59.56, 58.92, 52.23, 51.00, 29.05; m/z (ESI–MS) 372.8 [M+H]⁺.

2.5gb   2.5gc
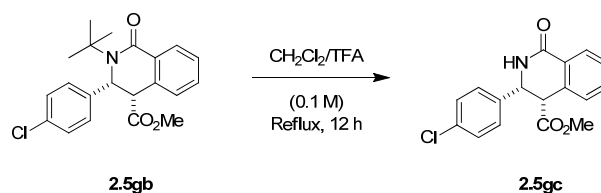
Compound **2.5gb** was transformed in **2.5gc** using general procedure D to give an off-white solid in 73% yield (25 mg, >19:1 dr); R_f = 0.24 (MeOH/ CH₂Cl₂ 5:95 v/v); mp: 101–103 °C; $[\alpha]_D^{20}$ +94.8 (c 0.5, CHCl₃, 88% ee); IR (KBr) 3214, 3206, 3077, 2862, 1730, 1667, 1602, 1579, 1465, 1447, 1382, 1240, 1212, 1089, 1057, 851, 770, 617 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.21 (d, J = 7.1 Hz, 1H), 7.55–7.46 (comp, 3H), 7.40 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.1 Hz, 1H), 5.96 (s, 1H), 5.18 (d, J = 4.8 Hz, 1H), 4.04 (d, J = 4.8 Hz, 1H), 3.45 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 169.36, 136.66, 136.27, 135.00, 132.93, 129.83, 129.45, 128.96, 128.98, 127.97, 127.62, 110.16, 57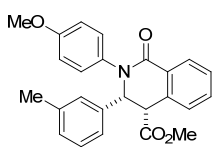.20, 52.28, 51.64; m/z (ESI–MS) 316.4 [M+H]⁺; HPLC: Daicel Chiralpak AD-H, n-hexane/i-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t_R = 13.3 min (major) and t_R = 24.3 min (minor).

The absolute configuration was assigned by analogy.

(*3R,4S*)-methyl   2,3-bis(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate
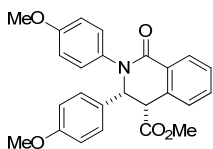
(2.5h): Following general procedure B, compound **2.5h** was obtained as a white

solid in 84% yield (73 mg, >19:1 dr); R_f = 0.13 (EtOAc/hexanes 3:7 v/v); mp:

128–130 ºC; $[\alpha]_D^{20}$ +23.4 (c 1.0, CHCl$_3$, 91% ee); IR (KBr) 3504, 3453, 3169,

3021, 2922, 2244, 1751, 1662, 1508, 1249, 1178, 1031, 832, 732, 655 cm^{-1}; ^{1}H NMR (500 MHz,

CDCl$_3$) δ 8.29 (d, *J* = 8.3 Hz, 1H), 7.55–7.44 (comp, 3H), 7.04 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 8.8

Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 5.24 (d, *J* = 6.1 Hz, 1H), 4.88 (d, *J* = 6.1

Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.77, 163.82,

159.67, 158.48, 134.72, 132.88, 132.60, 129.43, 129.04, 128.92, 128.84, 128.41, 128.12, 127.91,

114.40, 113.94, 65.49, 55.52, 55.20, 52.15, 50.00; *m/z* (ESI–MS) 418.3 [M+H]$^+$; HPLC: Daicel

Chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t$_R$ = 17.6 min

(minor) and t$_R$ = 55.1 min (major).

The absolute configuration was assigned by analogy.

(*3R,4S*)-methyl 3-(4-chlorophenyl)-2-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-
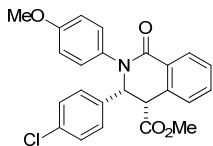
carboxylate (2.5i):   Following general procedure B, compound **2.5i** was

obtained as a white solid in 68% yield (66 mg, 5:1 dr); R_f = 021 (EtOAc/hexanes

3:7 v/v); mp: 75–78 ºC; $[\alpha]_D^{20}$ +67.8 (c 0.5, CHCl$_3$, 96% ee); IR (KBr) 3474,

3453, 3054, 2884, 2751, 2730, 2441, 1717, 1684, 1567, 1436, 1364, 1218, 529

cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.29 (d, *J* = 6.4 Hz, 1H), 7.56–7.52 (m, 1H), 7.51–7.45 (comp,

2H), 7.15 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 9.0 Hz,

2H), 5.29 (d, *J* = 6.1 Hz, 1H), 4.91 (d, *J* = 6.1 Hz, 1H), 3.78 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (125

MHz, CDCl$_3$) δ 169.56, 163.75, 158.62, 135.62, 134.66, 134.41, 132.81, 132.52, 129.25, 128.98,
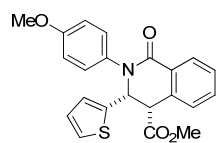
128.86, 128.39, 128,36, 128.02, 127.82, 114.54, 65.36, 55.55, 52.28, 49.84; *m/z* (ESI–MS) 422.9

[M+H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV =

230 nm, t$_R$ = 30.1 min (major) and t$_R$ = 84.9 min (minor).

The absolute configuration was assigned by analogy.

(*3R,4S*)-methyl 2-(4-methoxyphenyl)-1-oxo-3-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5j): Following general procedure B, compound **2.5j** was obtained as a clear oil in 92% yield (74 mg, >19:1 dr); R_f = 0.27 (EtOAc/hexanes 3:7 v/v); $[\alpha]_D^{20}$ –19.0 (c 0.5, CHCl$_3$, 87% ee); IR (KBr) 3495, 3336, 3230, 3013, 2873, 2720, 2340, 1718, 1513, 1506, 1435, 1364, 1223, 1092, 903, 529 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.28 (d, *J* = 8.2 Hz, 1H), 7.54–7.45 (comp, 3H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 5.26 (d, *J* = 6.1 Hz, 1H), 4.89 (d, *J* = 6.1 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.74, 163.93, 158.45, 138.42, 134.77, 133.84, 132.83, 132.61, 129.45, 129.32, 128.81, 128.33, 128.11, 127.86, 127.68, 114.40, 65.79, 55.51, 52.14, 50.03, 21.23; *m/z* (ESI–MS) 402.0 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t$_R$ = 11.3 min (major) and t$_R$ = 32.3 min (minor).
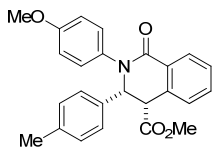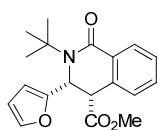
The absolute configuration was assigned by analogy.

(*3R,4S*)-methyl 2-(4-methoxyphenyl)-1-oxo-3-(m-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5k): Following general procedure B, compound **2.5k** was obtained as a white solid in 92% yield (74 mg, >19:1 dr); R_f = 0.23 (EtOAc/hexanes 3:7 v/v); mp: 64–65 ºC; $[\alpha]_D^{20}$ +8.05 (c 0.5, CHCl$_3$, 90% ee); IR (KBr) 3474, 3439, 3424, 3022, 2730, 2455, 1722, 1661, 1462, 1365, 1218, 529 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.29 (d, *J* = 8.5 Hz, 1H), 7.55–7.45 (comp, 3H), 7.08–7.00 (comp, 4H), 6.82–6.75 (comp, 4H), 5.26 (d, *J* = 6.1 Hz, 1H), 4.90 (d, *J* = 6.1 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.69, 164.17, 158.49, 138.12, 136.70, 134.61, 132.91, 132.71, 129.49, 129.34, 128.75, 128.54, 128.47, 128.30, 128.16, 127.91, 124.86, 114.39, 65.99, 55.46, 52.09, 50.03, 21.54; *m/z* (ESI–MS) 402.6 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH =

80/20, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.9 min (minor) and t_R = 40.4 min (major).

The absolute configuration was assigned by analogy.

**(3R,4S)-methyl 3-(2-methoxyphenyl)-2-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5l):** Following general procedure B, compound **2.5l** was obtained as an off-white solid in 73% yield (68 mg, >19:1 dr); R_f = 0.16 (EtOAc/hexanes 3:7 v/v); mp: 73–77 ºC; $[\alpha]_D^{20}$ +42.4 (c 0.5, CHCl$_3$, 93% ee); IR (KBr) 3505, 3423, 3012, 2882, 2729, 2539, 2530, 1755, 1743, 1435, 1365, 1217, 528 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.27 (d, J = 8.7 Hz, 1H), 7.50–7.42 (comp, 2H), 7.23 (app d, J = 7.0 Hz, 1H), 7.16 (app t, J = 7.4 Hz, 1H), 7.09 (d, J = 8.9 Hz, 2H), 7.02 (d, J = 7.7 Hz, 1H), 6.80 (d, J = 8.9 Hz, 2H), 6.78–6.70 (comp, 2H), 5.91 (d, J = 5.8 Hz, 1H), 4.85 (d, J = 5.7 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.08, 164.48, 158.24, 156.78, 134.87, 133.55, 132.55, 129.56, 129.45, 128.80, 128.70, 128.06, 128.00, 127.19, 124.78, 120.64, 114.26, 110.23, 57.91, 55.49, 51.97, 49.94; m/z (ESI–MS) 418.1 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, n-hexane/i-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t_R = 14.9 min (minor) and t_R = 30.4 min (major).
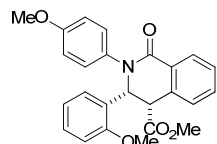
The absolute configuration was assigned by analogy.

(3R,4S)-methyl 2-(4-methoxyphenyl)-1-oxo-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5m): Following general procedure B, compound **2.5m** was obtained as a yellow solid in 90% yield (71 mg, >19:1 dr); R_f = 0.21 (EtOAc/hexanes 3:7 v/v); mp: 67–70 ºC; $[\alpha]_D^{20}$ –30.2 (c 0.5, CHCl$_3$, 81% ee); IR (KBr) 3435, 3304, 3203, 3137, 3022, 2729, 2360, 2330, 1718, 1654, 1512, 1436, 1363, 1222, 708, 530 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.26 (d, J = 9.1 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.57 (app td, J = 7.6, 1.5 Hz, 1H), 7.53–7.48 (m, 1H), 7.11–7.07 (comp, 3H), 6.86 (d, J = 9.0 Hz, 2H), 6.81–6.77

(m, 1H), 6.67 (dd, *J* = 3.7, 1.0 Hz, 1H), 5.54 (d, *J* = 5.4 Hz, 1H), 4.91 (d, *J* = 5.4 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.27, 163.59, 158.75, 139.51, 134.37, 132.84, 132.77, 129.42, 129.09, 128.44, 128.36, 128.01, 127.73, 126.35, 126.18, 114.53, 62.16, 55.56, 52.36, 49.74; *m/z* (ESI–MS) 395.2 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, Flow rate = 0.5 mL/min, UV = 230 nm, t$_R$ = 33.5 min (major) and t$_R$ = 164.3 min (minor).

The absolute configuration was assigned by analogy.

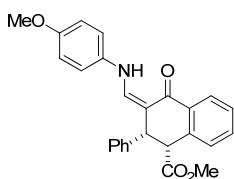**(3R,4S)-methyl 3-(furan-3-yl)-2-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5n):** Following general procedure B, compound **2.5n** was obtained as a brown oil in 85% yield (68 mg, 7:1 dr); R$_f$ = 0.16 (EtOAc/hexanes 3:7 v/v); [α]$_D$^{20} −5.10 (c 0.5, CHCl$_3$, 79% ee); IR (KBr) 3494, 3116, 2913, 1717, 1666, 1613, 1434, 1364, 1223, 1015, 753, 530 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.24 (d, *J* = 7.4 Hz, 1H), 7.57–7.50 (comp, 2H), 7.48–7.43 (m, 1H), 7.21 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.12 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.17 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.96 (d, *J* = 3.3 Hz, 1H), 5.37 (d, *J* = 5.4 Hz, 1H), 4.77 (d, *J* = 5.3 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.64, 164.08, 158.65, 150.31, 142.69, 134.38, 133.28, 132.51, 129.39, 129.01, 128.25, 128.17, 127.36, 114.49, 110.53, 109.56, 59.66, 55.58, 52.49, 48.76; *m/z* (ESI–MS) 378.9 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t$_R$ = 14.7 min (major) and t$_R$ = 49.6 min (minor).
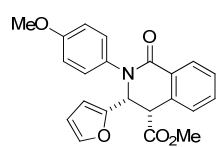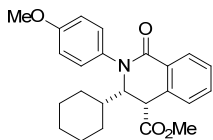
The absolute configuration was assigned by analogy.

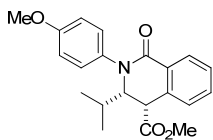**(3R,4S)-methyl 2-(tert-butyl)-3-(furan-2-yl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5o):** Following general procedure B, compound **2.5o** was obtained as a clear oil in 69% yield (45 mg, 15:1 dr); $R_f = 0.44$ (EtOAc/hexanes 3:7 v/v); The ee was determined after deprotection (see below): $[\alpha]_D^{20}$ –24.9 (c 1.0, CHCl$_3$, 85% ee); IR (KBr) 2996, 2970, 1744, 1716, 1676, 1364, 1217, 1202, 819, 752 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.18 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.45 (app td, J = 7.5, 1.5 Hz, 1H), 7.40 (app t, J = 7.5 Hz, 1H), 7.14 (app t, J = 1.6 Hz, 1H), 7.04 (s, 1H), 5.81 (s, 1H), 5.38 (d, J = 5.0 Hz, 1H), 4.55 (d, J = 4.9 Hz, 1H), 3.78 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.01, 164.51, 143.05, 140.52, 132.30, 131.89, 131.46, 128.27, 127.94, 127.25, 123.59, 109.95, 59.00, 52.23, 51.55, 50.34, 29.04; m/z (ESI–MS) 328.0 [M+H]$^+$.

2.5o   2.5oa
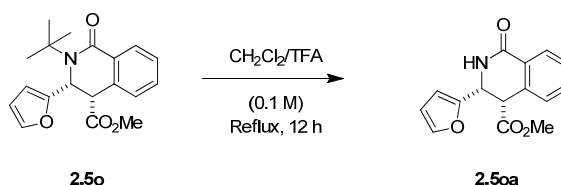
To determine the enantiopurity, compound **2.5o** was transformed to **2.5oa** using general procedure D to give a white solid in 81% yield (22 mg, 15:1 dr); $R_f = 0.23$ (MeOH/CH$_2$Cl$_2$ 5:95 v/v); mp: 124–126 ºC; $[\alpha]_D^{20}$ +66.6 (c 0.5, CHCl$_3$, 85% ee); IR (KBr) 3016, 3004, 2970, 2126, 1739, 1526, 1365, 1228, 1217, 896, 528 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.17 (d, J = 7.7 Hz, 1H), 7.56–7.43 (comp, 3H), 7.34 (d, J = 7.2 Hz, 1H), 7.25 (s, 1H), 6.40 (s, 1H), 6.01 (s, 1H), 5.29–5.06 (m, 1H), 4.20–3.92 (m, 1H), 3.56 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.82, 165.66, 144.16, 140.31, 137.39, 135.21, 132.80, 128.91, 128.89, 127.66, 123.03, 108.87, 52.31, 50.75, 49.90; m/z (ESI–MS) 270.0 [M+H]$^+$; HPLC: Daicel Chiralpak AD-H, n-hexane/i-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.5 min (major) and t_R = 14.3 min (minor).

The absolute configuration was assigned by analogy.

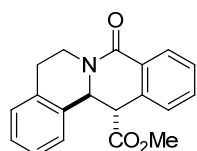**(3S,4S)-methyl 2-(4-methoxyphenyl)-1-oxo-3-((E)-styryl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5p):** Following general procedure B, compound **2.5p** was obtained as a yellow solid in 39% yield (32 mg, >19:1 dr); R_f = 0.16 (EtOAc/hexanes 3:7 v/v); mp: 72–73 ºC; $[\alpha]_D^{20}$ +25.4 (c 0.5, CHCl$_3$, 92% ee); IR (KBr) 3425, 3305, 3117, 3012, 2731, 2483, 1684, 1513, 1364, 1223, 1092, 530 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.21 (d, J = 8.7 Hz, 1H), 7.54 (app td, J = 7.5, 1.4 Hz, 1H), 7.52–7.43 (comp, 2H), 7.26 (s, 1H), 7.26–7.24 (comp, 2H), 7.24–7.21 (comp, 2H), 7.21–7.17 (comp, 2H), 6.91 (d, J = 8.9 Hz, 2H), 6.39 (d, J = 15.8 Hz, 1H), 6.17 (dd, J = 15.8, 8.7 Hz, 1H), 4.85 (dd, J = 8.5, 5.0 Hz, 1H), 4.55 (d, J = 4.8 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.00, 163.85, 158.60, 136.05, 134.49, 134.06, 133.82, 132.49, 129.35, 129.20, 128.93, 128.68, 128.30, 127.57, 126.82, 124.68, 114.53, 64.17, 55.59, 52.42, 49.83; m/z (ESI–MS) 414.3 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, n-hexane/i-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t_R = 14.8 min (major) and t_R = 48.6 min (minor).
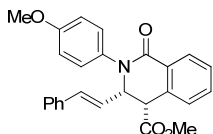
The absolute configuration was assigned by analogy.

In addition, racemic compound **2.5pa** was also isolated as a yellow solid in 32% yield (26 mg, 2:1 dr); R_f = 0.25 (EtOAc/hexanes 3:7 v/v); mp: 147–150 ºC; IR (KBr) 3459, 3005, 2970, 2947, 1739, 1661, 1511, 1435, 1365, 1228, 1217, 528 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) (major diastereomer) δ 12.37 (d, J = 12.0 Hz, 1H), 8.15 (d, J = 9.2 Hz, 1H), 7.50–7.40 (comp, 2H), 7.36–7.27 (comp, 3H), 7.23–7.15 (comp, 2H), 7.11 (d, J = 13.1 Hz, 1H), 6.96 (d, J = 9.0 Hz, 2H), 6.90–6.75 (comp, 2H), 4.47 (d, J = 4.8 Hz, 1H), 4.11 (d, J = 5.3 Hz, 1H), 3.76 (s, 3H), 3.55 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 186.36, 171.81, 155.99, 144.63, 140.46, 136.81, 134.90, 134.07, 131.92, 128.77, 128.29, 127.82, 127.67, 127.05, 117.60, 114.90, 105.06, 55.53, 52.03, 51.75, 47.61; m/z (ESI–MS) 414.2 [M+H]$^+$.

(*3S,4S*)-methyl 3-cyclohexyl-2-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5q): Following general procedure B, compound **2.5q** was obtained as an off-white solid in 76% yield (60 mg, 9:1 dr); R_f = 0.29 (EtOAc/hexanes 3:7 v/v); mp: 68–70 ºC; $[\alpha]_D^{20}$ -41.6 (c 0.5, CHCl$_3$, 83% ee); IR (KBr) 3483, 3311, 3026, 2922, 2732, 1718, 1659, 1363, 1221, 1136, 530 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.10 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.57–7.49 (m, 1H), 7.41 (app t, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 4.64 (d, *J* = 4.5 Hz, 1H), 4.27 (app t, *J* = 4.7 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 1.67 (s, 1H), 1.54 (s, 2H), 1.33 (dd, *J* = 21.8, 7.3 Hz, 3H), 1.02–0.91 (comp, 5H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.84, 164.34, 158.11, 140.73, 134.78, 132.42, 129.95, 129.17, 128.72, 127.92, 126.69, 124.03, 114.20, 66.40, 55.53, 52.27, 47.51, 41.47, 31.50, 30.30, 26.73, 26.49, 25.99; *m/z* (ESI–MS) 394.1 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.1 min (major) and t_R = 34.4 min (minor).
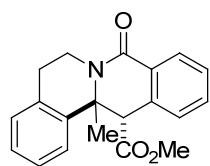
The absolute configuration was assigned by analogy.

(3S,4S)-methyl 3-isopropyl-2-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.5r): Following general procedure B, compound **2.5r** was obtained as an orange oil in 88% yield (63 mg, 15:1 dr); R_f = 0.36 (EtOAc/hexanes 3:7 v/v); $[\alpha]_D^{20}$ +4.76 (c 0.6, CHCl$_3$, 84% ee); IR (KBr) 3300, 3003, 2970, 2860, 1715, 1644, 1544, 1440, 1384, 1299, 1032, 758, 671, 665, 529 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.11 (d, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.51 (app td, *J* = 7.6, 1.4 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.35 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 4.59 (d, *J* = 4.7 Hz, 1H), 4.32 (dd, *J* = 4.7 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 2.10 – 1.99 (m, 1H), 0.74 (d, *J* = 4.6 Hz, 3H), 0.73 (d, *J* = 4.7 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.84, 164.33, 158.16, 134.58, 132.32, 129.96, 128.91, 128.78, 127.93, 126.65, 114.18, 66.39, 55.54, 52.27, 47.35, 31.17, 20.92, 19.97; *m/z* (ESI–

MS) 354.3 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.6 min (major) and t_R = 34.1 min (minor).

The absolute configuration was assigned by analogy

**(*13S,13aS*)-methyl   8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (2.6a):** Following the general procedure B at -55 ºC, compound 2.**6a** was obtained as a white solid in 93% yield (57 mg, >19:1 dr); R_f = 0.24 (EtOAc/hexanes 3:7 v/v); mp: 159–160 ºC; [α]$_D^{20}$ –142.2 (c 0.5, CHCl$_3$, 65% *ee*); IR (KBr) 3493, 3302, 3248, 2914, 2364, 1734, 1648, 1463, 1366, 1518, 1004, 913, 783, 744, 530 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.15 (app dd, *J* = 7.7, 1.4 Hz, 1H), 7.49 (app dd, *J* = 7.5, 1.4 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.25–7.19 (comp, 2H), 7.19–7.14 (comp, 3H), 5.34 (d, *J* = 9.0 Hz, 1H), 4.89 (dd, *J* = 12.2, 4.7 Hz, 1H), 4.18 (d, *J* = 9.0 Hz, 1H), 3.76 (s, 3H), 3.15–3.03 (comp, 2H), 2.92–2.84 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.33, 163.81, 136.87, 135.04, 134.17, 132.35, 129.44, 128.89, 128.62, 128.39, 127.84, 126.78, 126.52, 125.61, 58.07, 52.52, 51.93, 40.99, 29.88; *m/z* (ESI–MS) 309.0 [M+2H]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 18.1 min (major) and t_R = 20.2 min (minor).

(*13R,13aS*)-methyl   2,3-dimethoxy-8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (2.6b): Following the general procedure B at -55 ºC, compound 2.**6b** was obtained as a white solid in 85% yield (65 mg, >19:1 dr); R_f = 0.11 (EtOAc/hexanes 3:7 v/v); mp: 167–169 ºC; [α]$_D^{20}$ –210.2 (c 0.5, CHCl$_3$, 64% *ee*); IR (KBr) 3490, 3476, 3117, 3012, 2732, 2345, 2321, 1726, 1520, 1418, 1250, 1111, 744 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.16 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.48 (td, *J* = 7.5, 1.5 Hz, 1H), 7.43 (t, *J* = 7.0 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.72 (s, 1H), 6.70 (s, 1H), 5.26 (d, *J* = 10.1 Hz, 1H), 4.97–4.89 (m, 1H), 4.08 (d, *J* = 10.1 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.06–2.93 (comp, 2H), 2.81–2.74 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.65, 163.97, 148.47, 147.56, 135.51, 132.40, 129.34, 128.96, 128.62, 128.38, 126.13, 125.53,
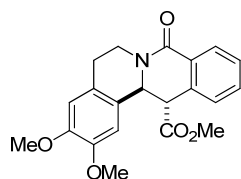
112.02, 109.68, 57.88, 56.16, 55.99, 53.43, 52.43, 40.73, 29.77; *m/z* (ESI–MS) 368.1 [M+H]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 35.8 min (minor) and t_R = 42.1 min (major).

(*13S,13aS*)-methyl 3-chloro-8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (2.6c): Following the general procedure B at -55 ºC, compound 2.**6c** was obtained as a white solid in 78% yield (53 mg, >19:1 dr); R_f = 0.26 (EtOAc/hexanes 3:7 v/v); mp: 80–81 ºC; $[\alpha]_D^{20}$ –64.1 (c 1.0, CHCl$_3$, 61% *ee*); IR (KBr) 3078, 3013, 2925, 2321, 1716, 1659, 1519, 1494, 1455, 1360, 1276, 1183, 914, 873, 826, 767, 659, 627, 616, 530 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.14 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.17–7.13 (comp, 2H), 7.09 (d, *J* = 8.4 Hz, 1H), 5.31 (d, *J* = 8.9 Hz, 1H), 4.91 (d, *J* = 4.5 Hz, 1H), 4.15 (d, *J* = 8.9 Hz, 1H), 3.77 (s, 3H), 3.14–3.00 (comp, 2H), 2.89–2.80 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.16, 163.77, 138.86, 134.77, 133.76, 132.75, 132.50, 129.41, 128.95, 128.52, 128.43, 127.03, 126.90, 126.68, 57.74, 52.64, 51.76, 40.73, 29.70; *m/z* (ESI–MS) 343.5 [M+2H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 95/05, Flow rate = 1 mL/min, UV = 230 nm, t_R = 48.5 min (major).and t_R = 53.9 min (minor).
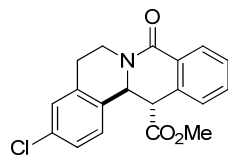
(*13S,13aS*)-methyl 13a-methyl-8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (2.6d): Following the general procedure B at -55 ºC, compound 2.**6d** was obtained as a white solid in 89% yield (57 mg, >19:1 dr); R_f = 0.37 (EtOAc/hexanes 3:7 v/v); mp: 113–116 ºC; $[\alpha]_D^{20}$ –205.8 (c 0.5, CHCl$_3$, 32% *ee*); IR (KBr) 3510, 3488, 3348, 3296, 2927, 2712, 1718, 1653, 1436, 1363, 1091, 895, 773, 721, 530 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.17 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.52–7.47 (m, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.33–7.16 (comp, 4H), 7.04 (d, *J* = 7.5 Hz, 1H), 5.14 (ddd, *J* = 12.6, 4.4, 1.8 Hz, 1H), 4.19 (s, 1H), 3.74 (s, 3H), 3.08–2.99 (m, 1H), 2.88–2.81 (comp, 2H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.42, 163.09, 139.16, 136.05, 134.67, 132.43, 129.84, 128.77, 128.55, 128.16, 127.43,

126.41, 126.34, 126.00, 62.01, 57.88, 52.03, 36.77, 31.28, 21.09;   *m/z* (ESI–MS) 322.3 [M+H]$^+$;

HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R =

8.6 min (minor) and t_R = 9.9 min (major).

(3R,4S)-methyl 1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.7):   Following
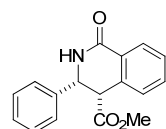
general produce D, compound **2.7** was obtained as a white solid in 72% yield (60 mg,

19:1 dr); R_f = 0.09 (EtOAc/hexanes 3:7 v/v); mp: 151–153 ºC; [α]$_D^{20}$ –263.4 (c 0.5,

CHCl$_3$, 95% ee); IR (KBr) 3558, 3447, 3339, 2692, 2368, 2355, 1608, 1435, 1363,

1222, 1166, 1082, 900, 530 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.22 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.55–

7.46 (comp, 2H), 7.45–7.37 (comp, 5H), 7.32–7.28 (m, 1H), 5.98 (s, 1H), 5.21 (d, *J* = 4.9 Hz, 1H),

4.06 (d, *J* = 4.7 Hz, 1H), 3.43 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.53, 165.94, 137.72, 135.23,

132.72, 129.17, 129.05, 128.87, 128.83, 127.54, 126.48, 57.70, 52.10, 51.85;   *m/z* (ESI–MS) 282.5

[M+H]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 80/20, Flow rate = 1 mL/min, UV =

230 nm, t_R = 11.2 min (major) and t_R = 25.9 min (minor).

The absolute configuration was assigned by X-Ray crystallography.
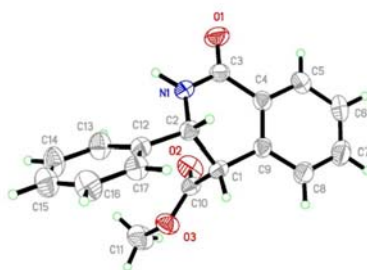
Enantioenriched compound **2.7** was crystallized from hexanes/EtOAc through slow diffusion at room

temperature.

The requisite CIF has been deposited with the CCDC (deposition # 1502937).

(*3R,4R*)-methyl 1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (2.8): To a solution
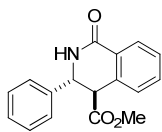
of **2.7** (28 mg, 0.1 mmol) in CH_2Cl_2 (1 mL, 0.1 M) at room temperature was added

DBU (3.0 L, 0.2 equiv). The resulting solution was stirred at room temperature for

68 h before being purified directly by flash column chromatography. Compound **2.8**

was obtained as a white solid in 82% yield (23 mg, 10:1 dr); R_f = 0.09 (EtOAc/hexanes 3:7 v/v); mp:

97–99 ºC; $[\alpha]_D^{20}$ –51.0 (c 0.5, CHCl₃, 86% ee); IR (KBr) 3567, 3467, 3316, 3231, 3032, 2970, 1726,

1663, 1509, 1227, 924, 730, 701, 528 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.17 (d, *J* = 1.5 Hz, 1H),

7.52–7.41 (comp, 2H), 7.36–7.27 (comp, 5H), 7.13 (d, *J* = 7.9 Hz, 1H), 6.11 (s, 1H), 5.24 (dd, *J* = 6.7,

2.7 Hz, 1H), 4.14 (d, *J* = 6.7 Hz, 1H), 3.68 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.25, 165.15,

139.41, 134.28, 132.96, 129.09, 128.69, 128.53, 128.35, 127.73, 126.74, 126.47, 57.42, 52.74, 52.54;

m/z (ESI–MS) 282.4 [M+H]⁺; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 80/20, Flow

rate = 1 mL/min, UV = 230 nm, t_R = 10.8 min (major) and t_R = 18.0 min (minor).

The absolute configuration was assigned by analogy.

(*3R,4R*)-methyl   2-(4-methoxyphenyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-
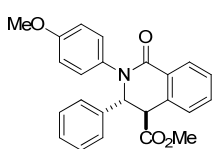
carboxylate (2.9): To a solution of **2.5a** (50 mg, 0.126 mmol) in CH_2Cl_2 (1.3

mL, 0.1 M) at room temperature was added DBU (3.9 L, 0.2 equiv). The

resulting solution was stirred at room temperature for 24 h before being purified

directly by flash column chromatography. Compound **2.9** was obtained as a white solid in 84% yield

(42 mg, >19:1 dr); R_f = 0.20 (EtOAc/hexanes 3:7 v/v); mp: 192–194 ºC; $[\alpha]_D^{20}$ +18.8 (c 0.5, CHCl₃,

80% ee); IR (KBr) 3467, 3005, 2970, 2949, 1736, 1654, 1426, 1365, 1217, 1092, 898, 528 cm⁻¹; ¹H

NMR (500 MHz, CDCl₃) δ 8.27–8.20 (m, 1H), 7.48–7.39 (comp, 2H), 7.29–7.15 (comp, 6H), 7.14 (s,

2H), 6.85 (dd, *J* = 8.5, 5.5 Hz, 2H), 5.58 (d, *J* = 4.2 Hz, 1H), 3.99 (d, *J* = 4.3 Hz, 1H), 3.76 (s, 3H),

3.74 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.31, 163.63, 158.44, 139.30, 135.33, 132.42, 132.33,

129.69, 129.56, 128.86, 128.69, 128.54, 128.06, 126.60, 114.44, 65.27, 55.52, 53.06, 51.84; *m/z*

(ESI–MS) 387.4 [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, Flow rate = 1 mL/min, UV = 230 nm, t_R = 11.2 min (minor) and t_R = 13.2 min (major).

The absolute configuration was assigned by analogy.

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Chapter 3. Towards the Enantioselective Synthesis of Tetrahydroprotoberberines

3.1 Background

3.1.1 Tetrahydroberberine Alkaloids

Naturally-occurring alkaloids from the tetrahydroprotoberberine family (Figure 3.1) have been investigated as antioxidants,[1] acetylcholinesterase inhibitors[2] and for the treatment of cancer.[3] These alkaloids are found in nature as chiral compounds. However, there exist few methods to make these compounds in a catalytic, enantioselective fashion. Several previous approaches have relied on chiral auxiliaries[4] or recrystallization.[5,6]

Figure 3.1 Natural products containing the tetrahydroprotoberberine scaffold

(+)-canadine   (+)-corydaline   (+)-thalictrifoline
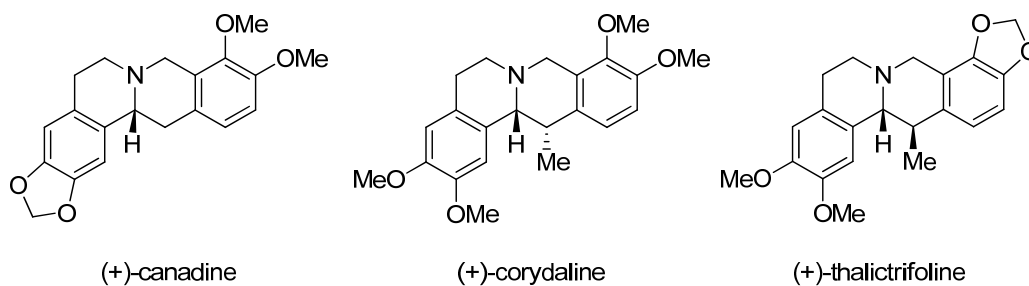
3.1.2 Enantioselective Mukaiyama-Mannich reactions

The first reaction between an aldehyde and a silyl enol ether was disclosed by Mukaiyama in 1973 (Scheme 3.1, eq 1).[7] It was promoted by stoichiometric amounts of titanium chloride. In 1977 using almost identical conditions, the Ojima group used an imine instead of an aldehyde substrate to access β-amino esters (Scheme 3.1, eq 2).[8]

Scheme 3.1 Initial Mukaiyama-Mannich disclosures

Mukaiyama, 1973

(1)

73%

Ojima, 1977

(2)

85%
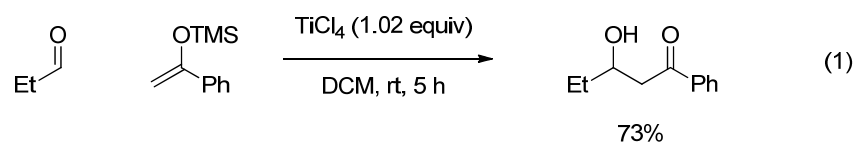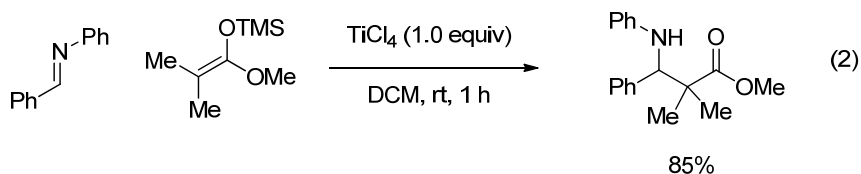
The first example of an enantioselective Mukaiyama Mannich type reaction between a silyl enol other and an imine was reported by Yamamoto in 1994 (Scheme 3.2, eq 3).[9] The group used stoichiometric amounts of chiral borate **3.1** to obtain β-amino ester products with high enantioselectivity. The Kobayashi group was the first to disclose a catalytic enantioselective version of the reaction, using substoichiometric amounts of zirconium catalyst **3.2** and *N*-methylimidazole as an additive (Scheme 3.2, eq 4).[10] In 2004 the Akiyama group developed an organocatalytic approach using chiral phosphoric acid catalyst **3.3** (Scheme 3.2, eq 5).[11]

Scheme 3.2 Enantioselective Mukaiyama-Mannich reactions with silyl enol ethers

Yamamoto, 1994

58%, 96% ee

3.1

(3)

Kobayashi, 1997

69%, 95% ee

3.2

(4)

Akaiyama, 2004

99%, 96% ee
87:13 dr

3.3

(5)
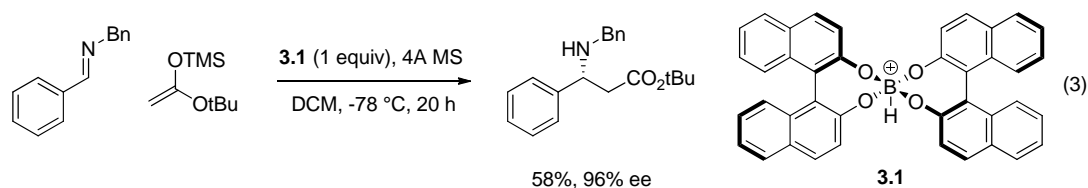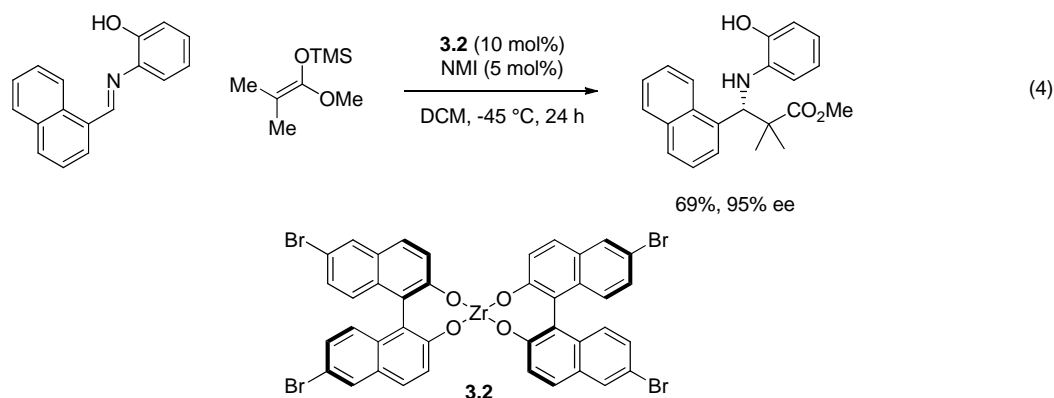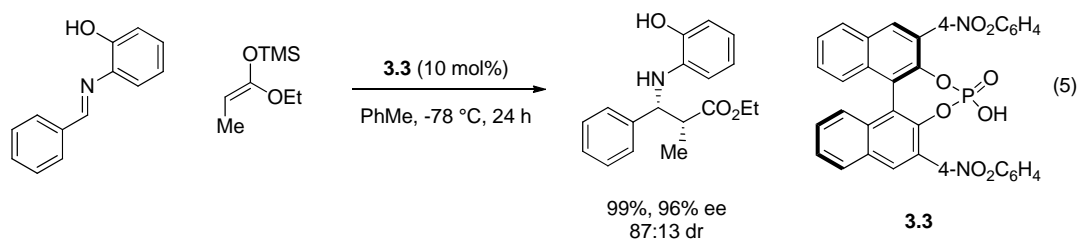
Most of the Mukaiyama-Mannich reactions reported have been used in the synthesis of β-amino esters. In 1978 Boyd reported an addition of amino-benzopyranones to imines to make the δ-lactam product (Scheme 3.3, eq 6).[12] The morpholino lactam analogue was isolated as the *cis* isomer. In 2007 Pohmaktor reported a diastereoselective approach to γ-lactams from 2,5-bis(trimethysilyloxy)furans that was catalyzed by scandium triflate (Scheme 3.3, eq 7).[13]

Scheme 3.3 Mukaiyama-Mannich reactions to form lactams

Boyd, 1978

(6)

77%

Pohmaktor, 2007

1. Sc(OTf)$_3$ (5 mol%)
THF, -78 °C to rt

2. NH$_4$Cl, rt, 1 h

(7)

86%, 99:1 dr
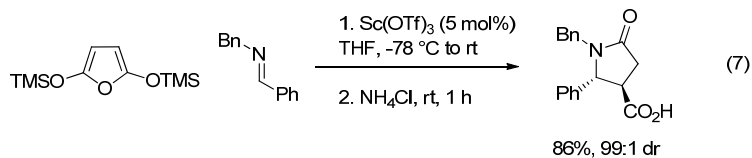
3.1.3 Synthesis of δ-Lactams through a Formal [4+2] Cycloaddition

As we developed a new catalytic enantioselective approach to the synthesis of lactams[14] we sought to access tetrahydroprotoberberine analogues from the formal [4+2] cycloaddition reaction between homophthalic anhydride and 3,4-dihydroisoquinoline (DHIQ), where the intermediates are captured in a chiral ion pair by the hydrogen-bonding (HB) catalyst. After deprotonation of the anhydride by the imine to form an enol, the reaction proceeds through a concerted Mannich/*N*-acylation pathway (Scheme 3.4, Mechanism A). However, the competing uncatalyzed reaction between homophthalic anhydride and DHIQ was very fast, and the addition of catalyst only led to moderate enantioselectivities at -50 °C. We therefore considered an alternative approach where the DHIQ would react with a "pre-formed" enol species, stabilized as an enol ether and reacting through a Mukaiyama-Mannich pathway (Scheme 3.4, Mechanism B). We hypothesized this reaction would be significantly slower, and thus more susceptible to catalysis. The other advantage of using alkoxyisocoumarins for the synthesis of lactams is that the products are easily isolated as alkyl esters without the need for an additional step to methylate the carboxylic acid.

Scheme 3.4 Formal [4+2] cycloadditions to form lactams
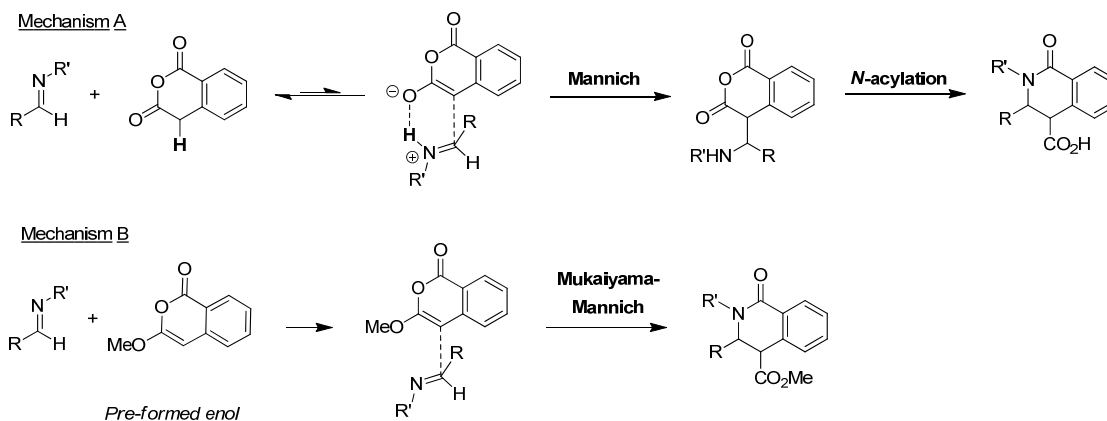
3.2 Lewis Acid promoted Racemic Reaction of MIC and DHIQ

3.2.1 Background

In addition to the catalytic, enantioselective formal [4+2] cycloaddition, we developed a racemic version of the reaction using boron trifluoride diethyl etherate as a Lewis acid promoter. There are several examples in the literature of Lewis acids promoting the reaction between homophthalic anhydride and imines,[15-18] but none make use of alkoxyisocoumarins as a substrate.

3.2.2 Reaction Development and Scope

The reaction conditions for this reaction were developed by our collaborators (Neyra Jamal and Spencer Knapp, Rutgers University). Catalytic amounts of $BF_3.OEt_2$, as well as several other Lewis acids including $HAuCl_3.3H_2O$, $Zn(OTf)_2$ and $Ni(acac)_2$, were screened but gave no product formation. Stoichiometric quantities of $BF_3.OEt_2$, AgOAc and $Ti(O^iPr)_3Cl$ were then screened - only $BF_3.OEt_2$ led to appreciable product formation. Out of dichloromethane, toluene and acetonitrile, the latter gave the highest yields. Sodium methoxide was added after the reaction was quenched to

epimerize the ~1:1 diastereomeric mixture of products to the thermodynamic *trans* isomer. A mixture

of electron poor and rich imines were tolerated under these conditions (Scheme 3.5). DHIQ and *N*-

benzylimine substrates required gentle heating to generate the corresponding products **3.4m** and **3.4n**.

Scheme 3.5 Scope of racemic Lewis acid promoted reaction

1. 3Å MS, BF$_3$.OEt$_2$ (1.1 equiv), MeCN (0.4 M), rt
2. NaOMe (2.0 M) MeOH, rt, 0.5 h

3.4

3.4a, 4 h, 63%
>19:1 dr

3.4b, 26 h, 61%
>19:1 dr

3.4c, 19 h, 81%
>19:1 dr

3.4d, 20 h, 72%
>19:1 dr

3.4e, 26 h, 73%
>19:1 dr

3.4f, 5 h, 68%
>19:1 dr

3.4g, 48 h, 45%
>19:1 dr

3.4h, 2 h, 95%
>19:1 dr

3.4i, 21 h, 71%
>19:1 dr

3.4j, 25 h, 77%
>19:1 dr

3.4k, 47 h, 66%
>19:1 dr

3.4l, 5 h, 69%
>19:1 dr

3.4m, 48 h, 45 °C, 73%
>19:1 dr

3.4n, 72 h, 45 °C, 33%
>19:1 dr
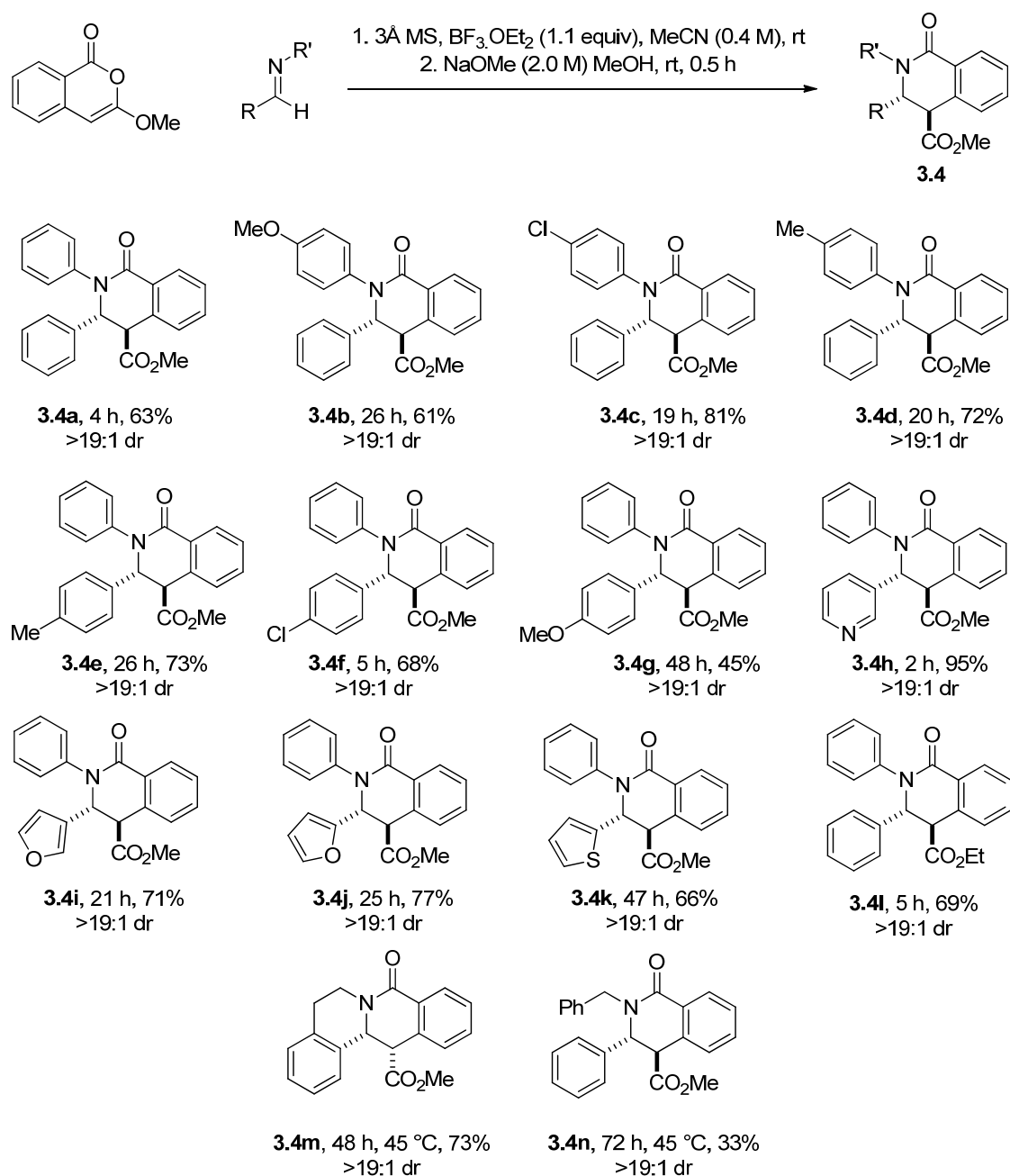
3.3 Enantioselective Formal [4+2] Cycloaddition of Alkoxyisocoumarins and Imines

3.3.1 Catalyst Screen

Starting with a model reaction between methoxiosocoumarin (MIC) and DHIQ in toluene, a diverse set of organocatalysts was screened (Scheme 3.6). Although the background reaction was negligible, many common organocatalysts were found to be ineffective. Schreiner's thiourea **3.15**[19] and Nagasawa's bisthiourea **3.16**[20] both gave good conversion to lactam **3.5a** after a few days at room temperature. Sulfonamide catalyst **3.17** gave promising enantioselectivities and yield after three days.

Scheme 3.6 Catalyst screen
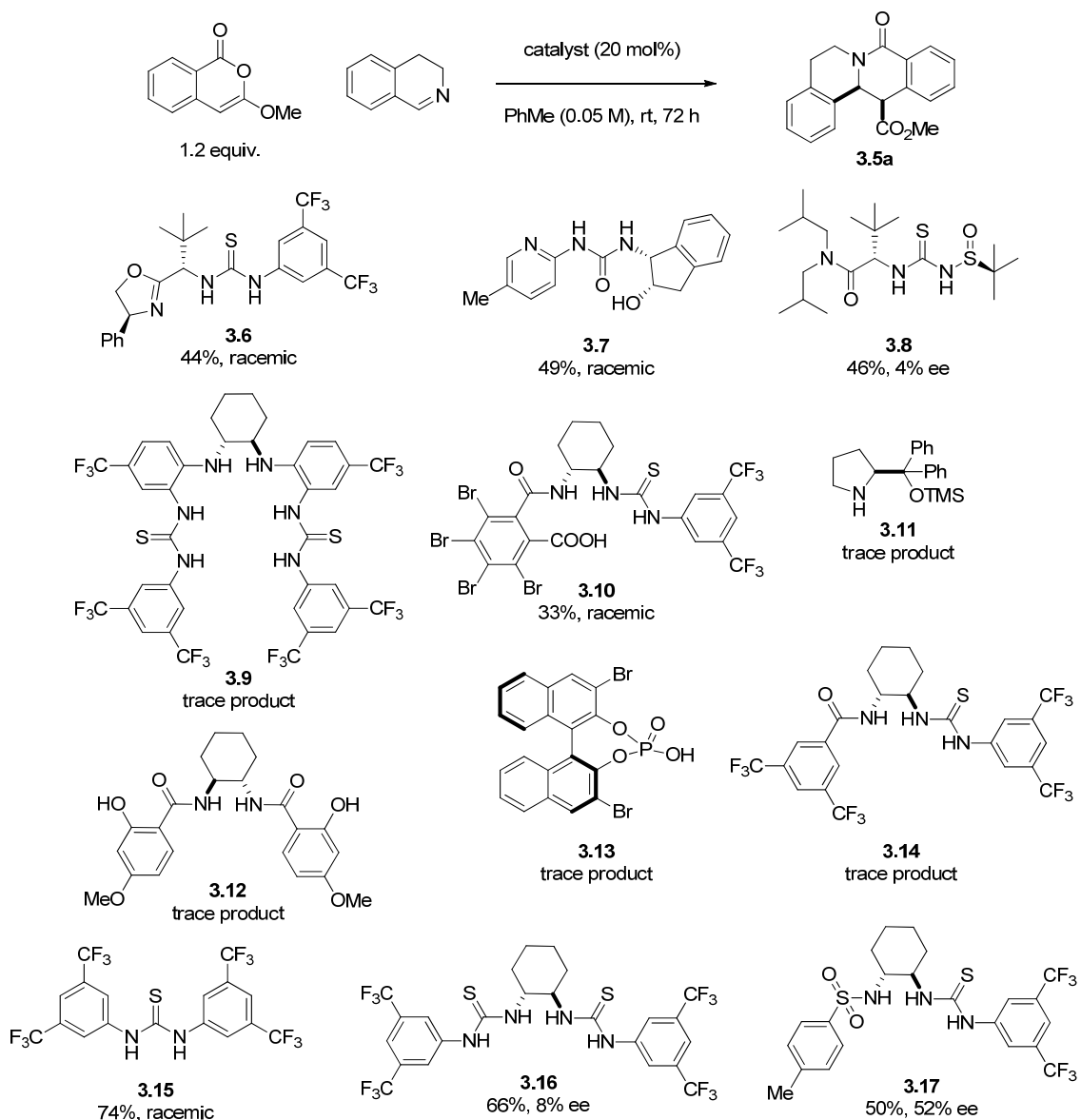
A broad range of modifications was carried out on the sulfonamide catalyst **3.17** structure (Scheme 3.7). Different electron-withdrawing and –donating groups were examined on the sulfonamide aryl ring, but none improved upon the initial hit. Electron-withdrawing groups such as 3,5-bis(trifluoromethyl)phenyl had an accelerating effect on the reaction, but gave poorer enantioselectivities.

Scheme 3.7 Screen of aryl sulfonamide catalysts

78%	74%	56%	48%	59%
8 % *ee*, 5.7:1 dr	18% *ee*, 9:1 dr	17% *ee*, 9:1 dr	20% *ee*, >20:1 dr	32% *ee*, >20:1 dr
50%	53%	25%	19%	17%
52% *ee*, 9:1 dr	21% *ee*, >20:1 dr	28% *ee*, >20:1 dr	30% *ee*, 9:1 dr	8% *ee*, >20:1 dr
54%	42%	29.5 h, 27%	26 h, 36%	44%
40% *ee*, >20:1 dr	racemic, >20:1 dr	28% *ee*, >20:1 dr	58% *ee*, >20:1 dr	racemic >20:1 dr
		PhCF$_3$ as solvent	PhCF$_3$ as solvent	
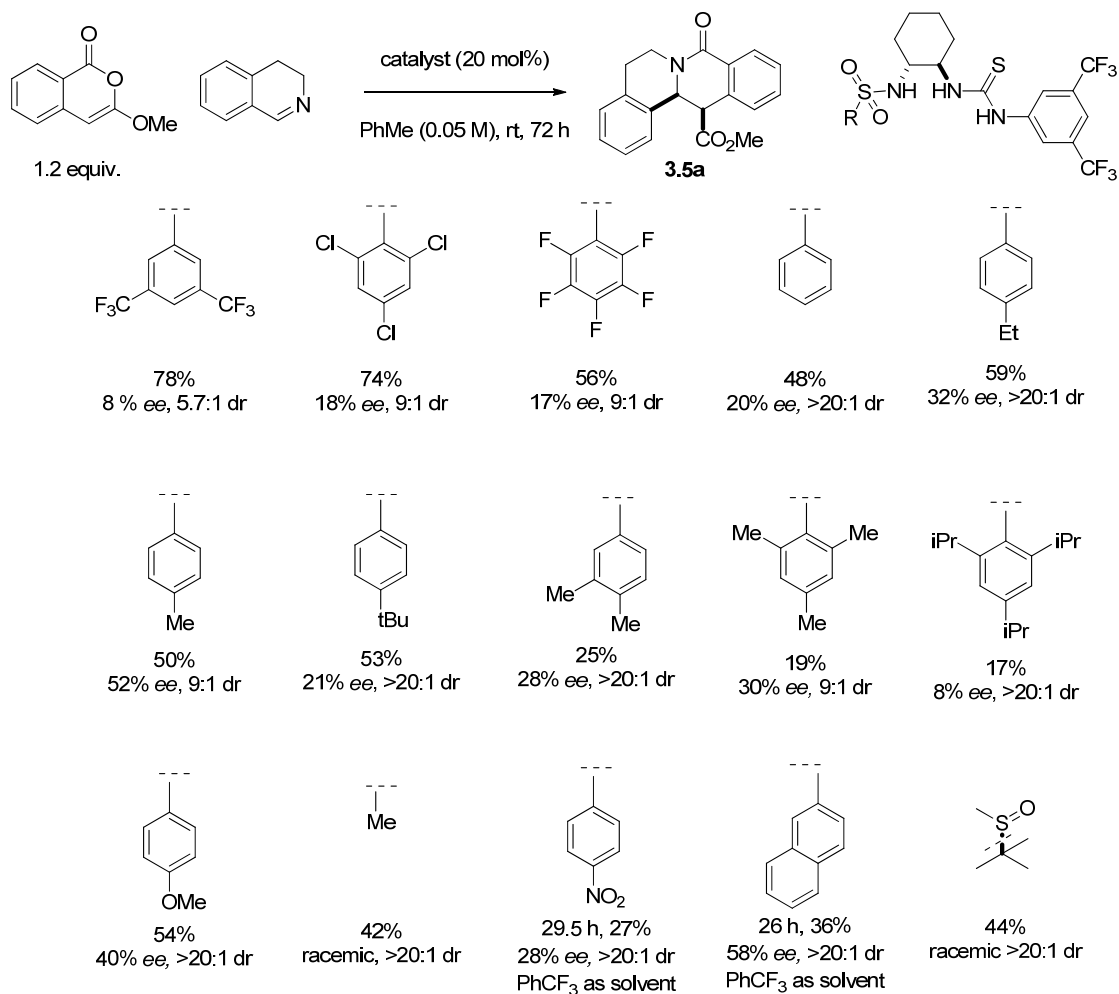
Further modifications were carried out on the thiourea side of the catalyst, the sulfonamide group was also replaced with a diphenyl phosphine (Scheme 3.8). Most modifications had a strongly-detrimental effect on the reactivity and enantioselectivity, with none improving on catalyst **3.17**.

Scheme 3.8 Screen of *para*-methylphenyl sulfonamide catalysts
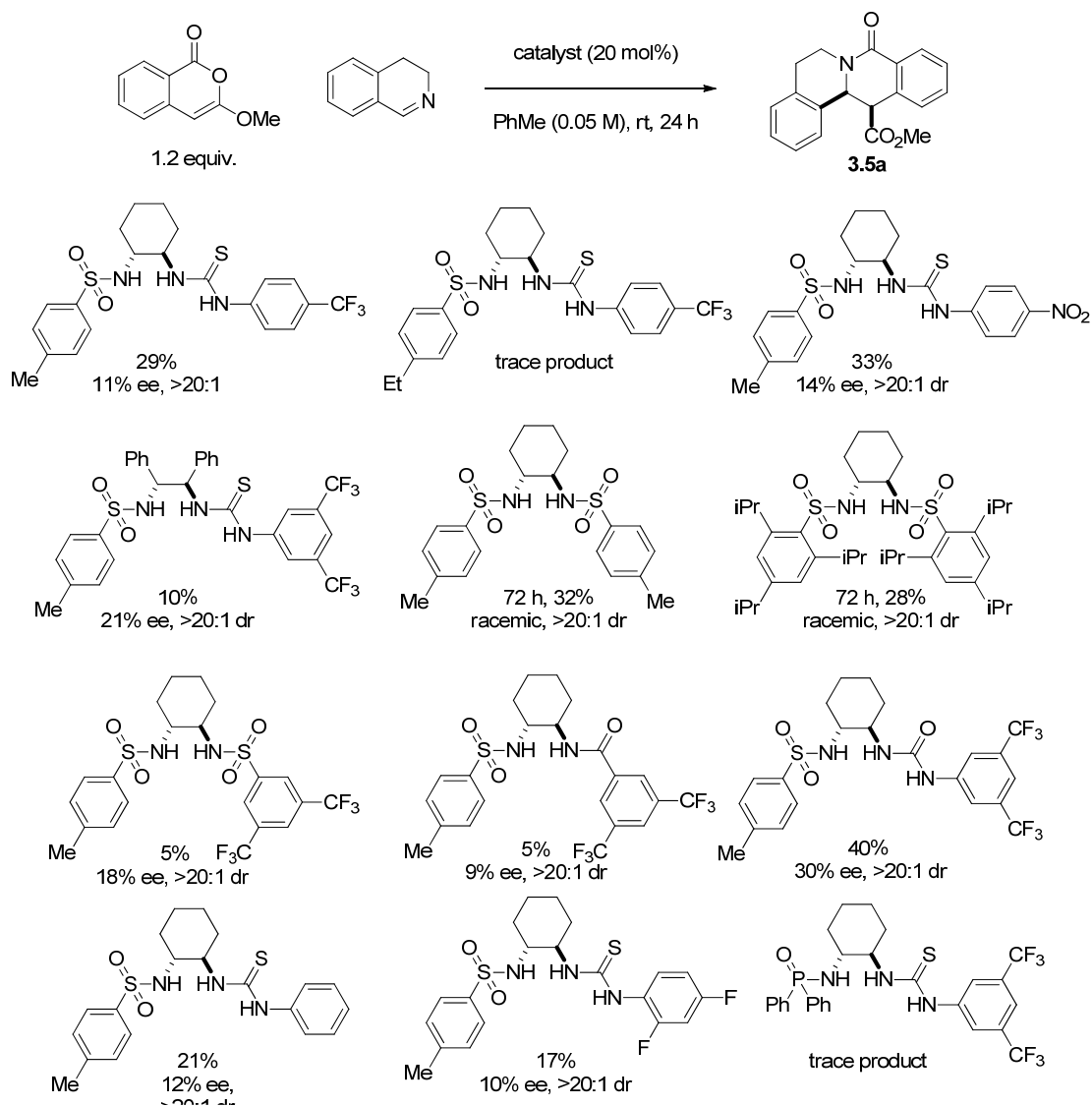
3.3.2 Reaction Optimization

With catalyst **3.17** settled upon as the optimal design, solvents were screened (Table 3.1). Solvents such as chloroform and dichloromethane accelerated the reaction rate, but eroded the enantioselectivities. Non-polar solvents such as toluene and trifluorotoluene (PhCF$_3$) gave lower

yields but the best enantioselectivities. It was found that PhCF$_3$ was the best solvent, giving 56% ee at room temperature.

Next, both acidic and basic additives were evaluated as a way to improve the reaction rate. Weak organic acids were found to slow the reaction rates. However, weak bases such as pyridine had an accelerating rate on the reaction, without a significant erosion of enantioselectivity.

Table 3.1 Additive and solvent screen for MIC reaction

entry	additive (mol %)	solvent	yield (%)	ee (%)	dr
1	0	PhMe	50	52	>20:1
2[a]	0	PhCF$_3$	47	56	>20:1
3	0	DCM	70	49	>20:1
4	0	CHCl$_3$	61	46	>20:1
5	0	PhMe:DCM (3:1)	68	52	>20:1
6	0	PhMe:DCM (9:1)	51	31	>20:1
7	Acetic Acid (20)	PhMe:DCM (3:1)	50	30	>20:1
8	Acetic Acid (50)	PhMe:DCM (3:1)	15	52	>20:1
9	Benzoic Acid (20)	PhMe:DCM (3:1)	15	35	>20:1
10	Benzoic Acid (50)	PhMe:DCM (3:1)	28	32	>20:1
11	Pyridine (20)	PhMe:DCM (3:1)	80	32	>20:1
12[a]	Pyridine (10)	PhMe	39	50	>20:1

13	Pyridine (20)	PhMe	65	50	>20:1
14	Pyridine (25)	PhMe	76	50	>20:1
15[a]	Pyridine (50)	PhMe	34	50	>20:1
16	Imidazole (20)	PhMe	65	44	>20:1
17	DABCO (20)	PhMe	49	30	>20:1
18	2,6-Lutidine (20)	PhMe	71	50	>20:1
19[a]	*N,N*-dimethylaniline (20)	PhMe	64	49	>20:1
20[a]	CuCl (20)	PhMe	13	7	>20:1
21[a]	H_2O (100)	PhMe	0	-	-

[a] Reaction run for 24 h.

A study of yield against time (Figure 3.2) showed that without basic additives, in the presence of catalyst **3.17** the reaction had fast conversion in the first few hours at room temperature (40% yield after 5 hours), which slowed over time (50% yield after 24 hours). This implied product inhibition was playing a role. The substoichiometric use of basic additives accelerated the initial rates of conversion and led to higher overall product yields. With 25 mol% pyridine the yield of product was 76% after 24 hours, with the conversion was mostly finished within that time frame.

Figure 3.2 Role of basic additives on conversion
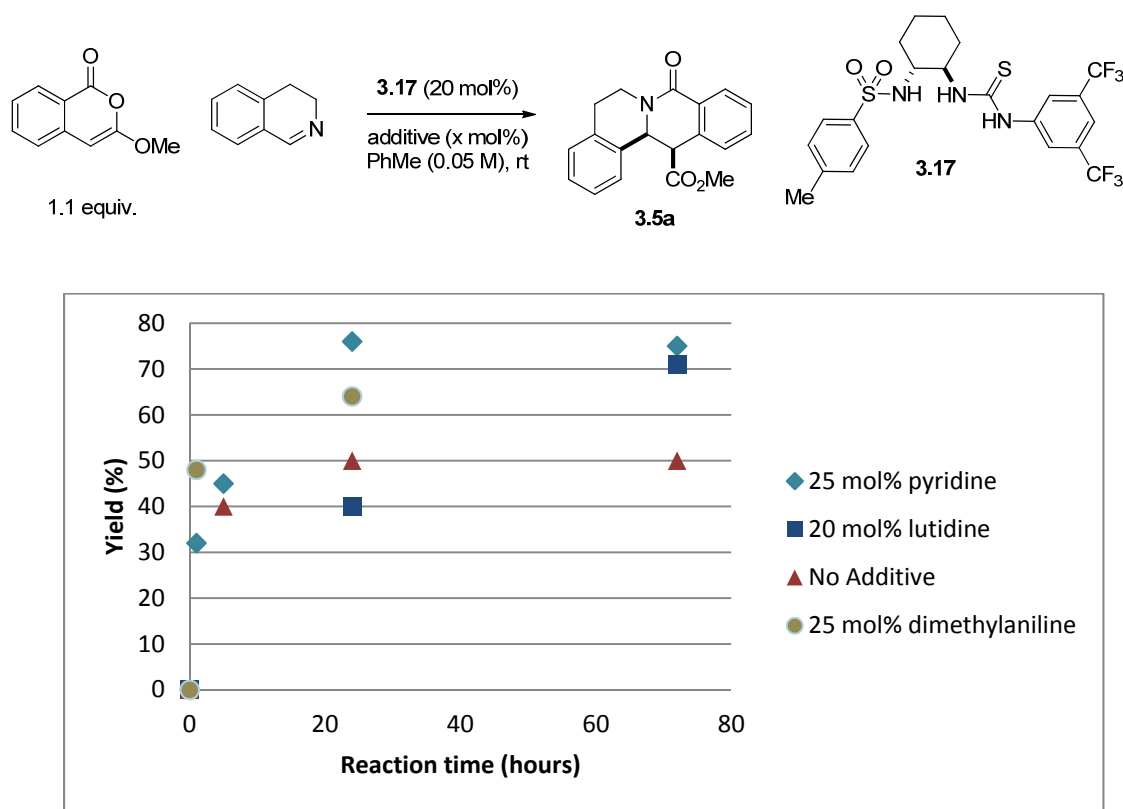
We next screened different alkoxyisocoumarins in the reaction with DHIQ (Table 3.2). It was found that ethyl isocoumarin (EIC) conferred better enantioselectivities than MIC (Entry 1-2, 65% ee compared to 52% ee), reacting at a similar rate. Increasing the electron-withdrawing strength of the alkyl group led to faster reactions (Entry 7-10), but did not improve the enantioselectivity.

Table 3.2 Evaluation of alkoxyisocoumarins
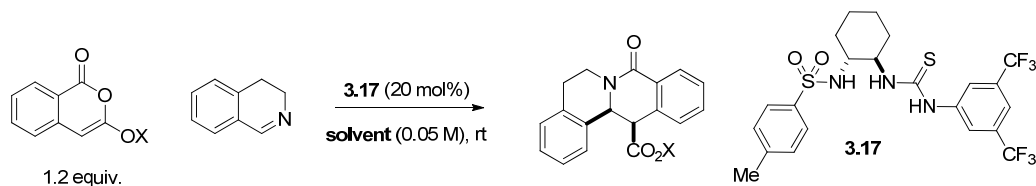
entry	X	solvent	time (h)	yield (%)	ee (%)	dr
1	Me	PhMe	24	50	52	>20:1
2	Et	PhMe	24	47	65	>20:1
3	*n*-Pr	PhMe	24	24	53	>20:1
4	*i*-Pr	PhMe	24	7	51	>20:1
5	*n*-Bu	PhMe	24	39	57	>20:1
6	Bn	PhMe	24	0	--	--
7	CH_2CH_2Cl	PhMe	24	67	52	>20:1
8	CH_2CH_2Cl	$PhCF_3$	24	65	68	>20:1
9[a]	CH_2CH_2Cl	$PhCF_3$	64	42	74	>20:1
10	CH_2CF_3	PhMe	24	94	18	>20:1
11	$CH_2CH_2OCH_3$	PhMe	24	0	--	--

[a] Reaction run at 0 °C.

We next examined the effect of concentration and temperature on the reaction with MIC (Table 3.3). It was found that increasing the concentration had a positive effect on rate and enantioselectivity (Entry 1-4 and 5-7). The product was isolated with 73% yield and 63% ee using 0.5 M $PhCF_3$ at room temperature. However, cooling the reaction to 0 °C and below led to less than 20% product yields and modest enantioselectivity gains up to 74% ee, even at 0.5 M concentration (Entry 9-11).

Table 3.3 Reaction concentration and temperature screen for MIC
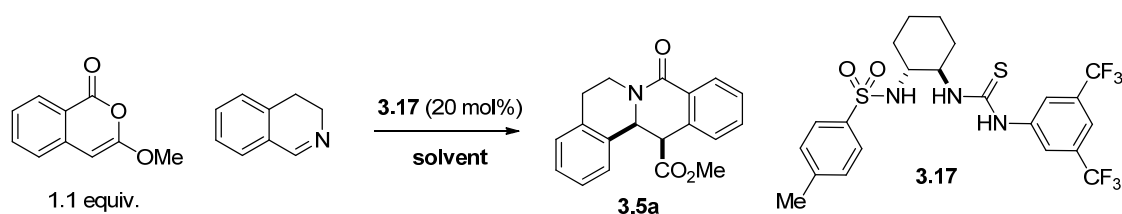
entry	solvent	conc. (M)	T [°C]	time (h)	yield (%)	ee (%)	dr
1	PhMe	0.05	rt	24	50	52	>20:1
2	PhMe	0.1	rt	24	50	55	>20:1
3	PhMe	0.2	rt	24	51	45	>20:1
4	PhMe	0.5	rt	48	87	58	>20:1
5	PhCF$_3$	0.05	rt	24	47	56	>20:1
6	PhCF$_3$	0.1	rt	24	38	59	>20:1
7	PhCF$_3$	0.5	rt	48	73	63	>20:1
8	PhCF$_3$	2	rt	26	86	45	>20:1
9	PhMe	0.05	0	62.5	17	50	>20:1
10	PhCF$_3$	0.5	-10	48	19	74	>20:1
11	PhCF$_3$	0.5	-25	88.5	20	74	>20:1

A similar study on the reaction conditions with EIC (Table 3.4) showed that increasing the concentration from 0.05 M up to 0.5 M did not improve the enantioselectivity in either toluene of PhCF$_3$. Adding a *para*-bromo group to the thiourea side of catalyst **3.17** led to a slight improvement in % ee at room temperature (up to 75% ee), but increased the amount of product inhibition, without much further improvement on cooling to 0 °C. The best results were obtained at 0 °C with pyridine as a basic additive, which gave 61% yield and 81% ee.

Table 3.4 Reaction condition screen for EIC

3.5b
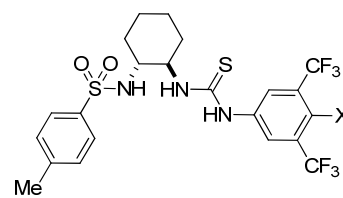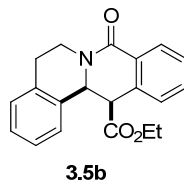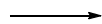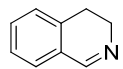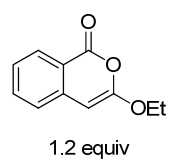
entry	X	solvent	conc. (M)	T [°C]	time (h)	yield (%)	ee (%)	dr
1	H	PhMe	0.025	rt	24	24	51	>20:1
2	H	PhMe	0.05	rt	24	47	65	>20:1
3	H	PhCF$_3$	0.05	rt	24	55	68	>20:1
4	H	PhCF$_3$	0.05	0	64	35	84	>20:1
5[a]	H	PhCF$_3$	0.05	0	121	61	81	>20:1
6[b]	H	PhCF$_3$	0.05	0	92	33	81	>20:1
7[a,c]	H	PhCF$_3$	0.05	0	94	48	81	>20:1
8	H	PhMe	0.05	0	49	4	72	>20:1
9[a]	H	PhMe	0.05	0	47	12	72	>20:1
10	H	PhMe	0.1	0	45	17	78	>20:1
11[d]	H	PhMe	0.05	rt	24	28	60	>20:1
12[e]	H	PhMe	0.05	rt	24	18	64	>20:1
13[f]	H	PhMe	0.05	rt	24	30	63	>20:1
14[g]	H	PhMe	0.05	rt	24	26	20	>20:1
15[h]	H	PhMe	0.05	rt	24	0	--	--
16	Br	PhCF$_3$	0.05	rt	24	14	75	>20:1
17	Br	PhCF$_3$	0.05	0	74	11	71	>20:1
18[a]	Br	PhCF$_3$	0.05	0	95	40	77	>20:1

19	Br	PhMe	0.05	rt	24	30	65	>20:1
20	Br	PhCF$_3$	0.2	rt	26	56	67	>20:1
21	H	PhCF$_3$	0.1	rt	24	48	67	>20:1
22	H	PhCF$_3$	0.2	rt	24	66	67	>20:1
23	H	PhCF$_3$	0.5	rt	24	79	65	>20:1
24	H	PhMe	0.2	rt	48	84	63	>20:1
25	H	PhCF$_3$	0.5	-15	24	14	77	>20:1
26	H	PhCF$_3$	0.5	-10	72	0	--	--
27	H	PhCF$_3$	0.05	-10	72	Trace	--	--

[a] With pyridine (20 mol%). [b] With pyridine (50 mol%). [c] With 4Å MS. [d] EIC (1.0 equiv), DHIQ (1.2 equiv). [e] EIC (1.0 equiv), DHIQ (1.5 equiv). [f] EIC (1.0 equiv). [g] With Schreiner's catalyst **3.15** (20 mol%). [h] With DMSO (20 mol%).

With the optimized conditions established, several DHIQ analogues were reacted with MIC or EIC (Scheme 3.9). These gave moderate to good enantioselectivities.

Scheme 3.9 Substrate scope

3.5a, 120 h, 72%
74% ee, >19:1 dr

3.5b, 121 h, 61%
81% ee, >19:1 dr

3.5c, 138 h, 80%
82% ee, >19:1 dr

3.5d, 118 h, 64%
79% ee, >19:1 dr
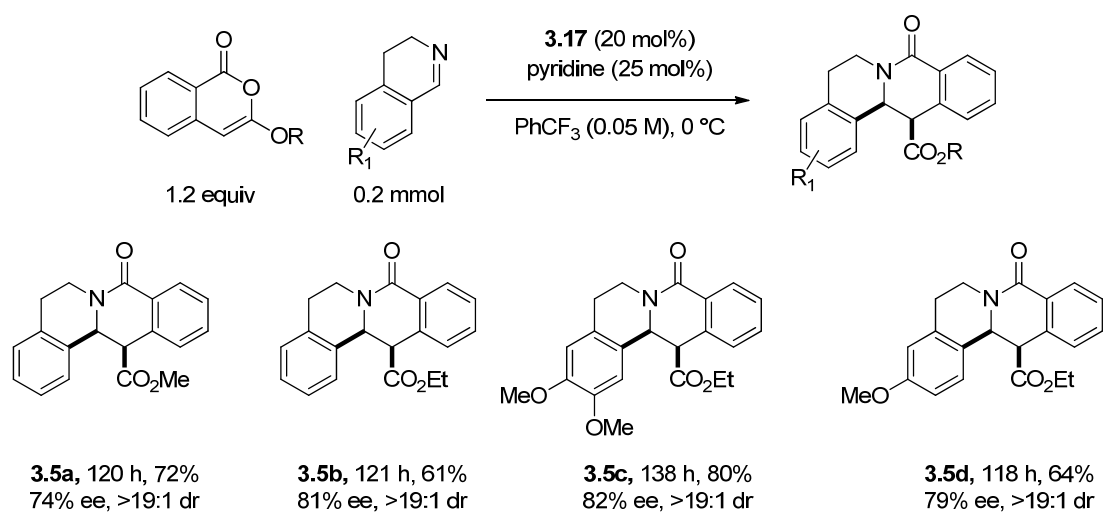
3.3.3 Mechanistic Considerations

Our thorough catalyst screen had shown that sulfonamide **3.17** was the best catalyst for this reaction, although its exact role in inducing enantioselectivity was unclear. We sought to better understand the observed reactivity patterns by trying to quantify the hydrogen bond donor capacity of the organocatalysts tested. Using a phosphine oxide probe approach developed by Schreiner,[21] we titrated several sulfonamide catalysts against the probe and monitored the probe chemical shift by ^{31}P NMR spectroscopy. A greater change in the chemical shift of the phosphine oxide probe upon titration correlated to stronger binding strength of the catalyst, and therefore to its stronger hydrogen bond donor ability (Figure 3.3).

One of the strongest organocatalysts studied is the Schreiner's catalyst **3.15**, which was previously determined to give a Δδ of 7.95 ppm in the binding study. The bisthiourea catalyst **3.16** had been previously studied using this technique was also found to have a strong hydrogen bond donor ability. Both of these catalysts had given good conversions in our initial catalyst screens, albeit with no stereoselectivity. Sulfonamide **3.17** was also found to be a strong hydrogen bond donor with a Δδ of 5.79 ppm, although the penta-fluoro catalyst **3.18** was stronger with a Δδ of 5.92 ppm, even though it gave poorer enantioselectivities. Although catalyst reactivity appears to correlate with hydrogen bond donor strength in these reactions, catalyst selectivity is not exclusively correlated.

Figure 3.3 Hydrogen bond donor strength of organocatalysts

3.14
^{31}P NMR Δδ = 5.17 ppm

3.15
^{31}P NMR Δδ = 7.95 ppm

3.16
^{31}P NMR Δδ = 7.05 ppm (lit)
= 7.07 ppm (experimental)

3.17
^{31}P NMR Δδ = 5.79 ppm

3.18
^{31}P NMR Δδ = 5.92 ppm

3.19
^{31}P NMR Δδ = 4.81 ppm

3.20
^{31}P NMR Δδ = 4.77 ppm

3.21
^{31}P NMR Δδ = 4.22 ppm

3.22
^{31}P NMR Δδ = 3.83 ppm

3.23
^{31}P NMR Δδ = 0.77 ppm
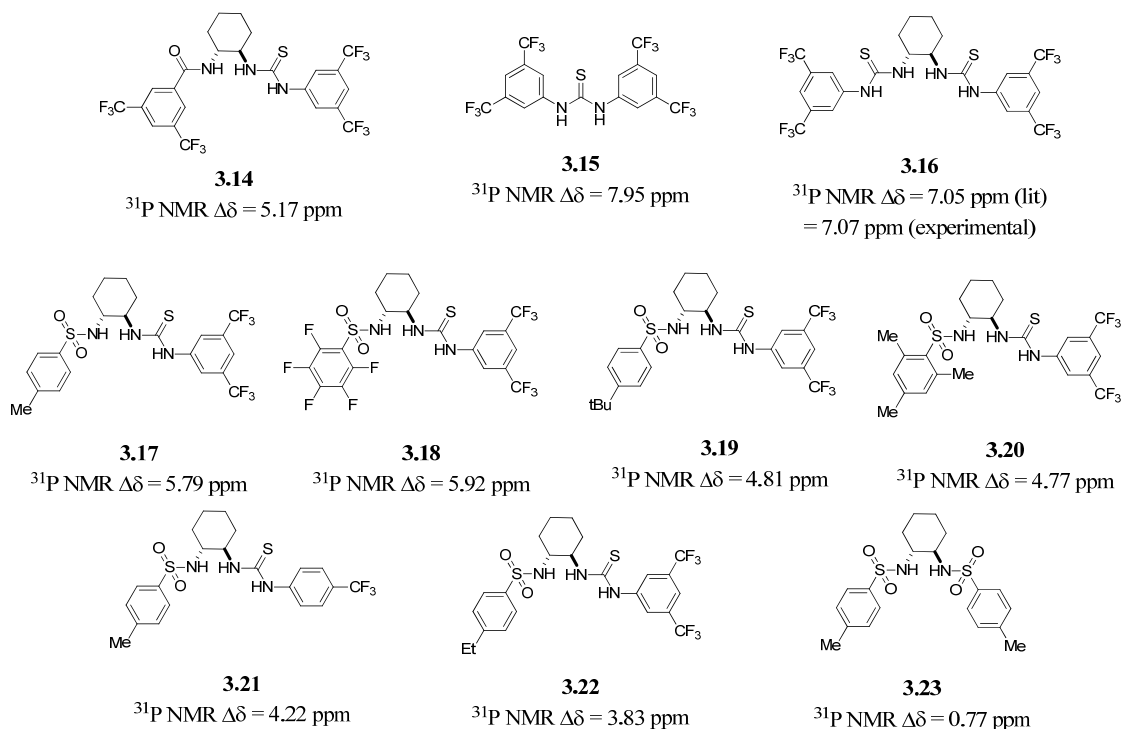
After observing moderate reaction yields we sought to understand the role product inhibition might be playing. Catalyst **3.17** was titrated against the substrates MIC and DHIQ, and lactam product **3.5a** from the reaction, then the proton chemical shift changes of the catalyst NH protons were studied (Figure 3.4). Our hypothesis was that increased binding strength correlated to greater observed chemical shift change. In both toluene and chloroform the product induced a greater chemical shift in the catalyst **3.17** NH protons overall than the starting materials, particularly as the mole ratios of substrate to catalyst increased. Greater catalyst chemical shift change was observed with toluene as the solvent, supported by experimental results showing higher enantioselectivities and stronger product inhibition in toluene than chloroform. These findings supported the hypothesis that product inhibition was occurring.

Figure 3.4 Quantification of product inhibition by ^{1}H NMR binding study
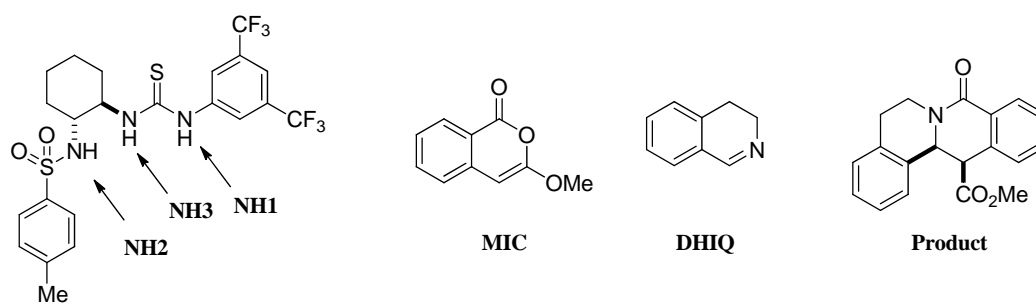
^{1}H NMR binding study proton assignments

NH1 (tol-d8)

NH2 (tol-d8)

NH3 (tol-d8)

NH1 (CDCl₃)

NH2 (CDCl₃)

NH3 (CDCl₃)
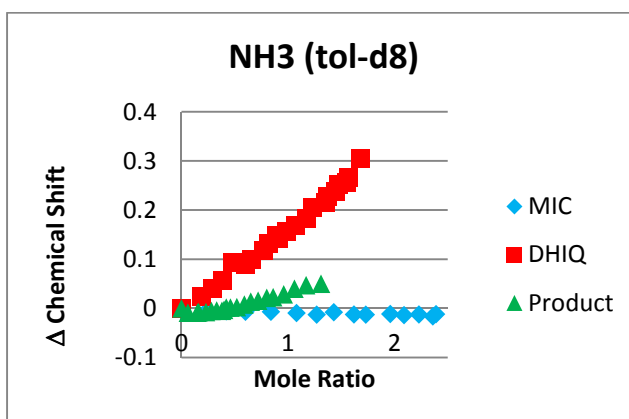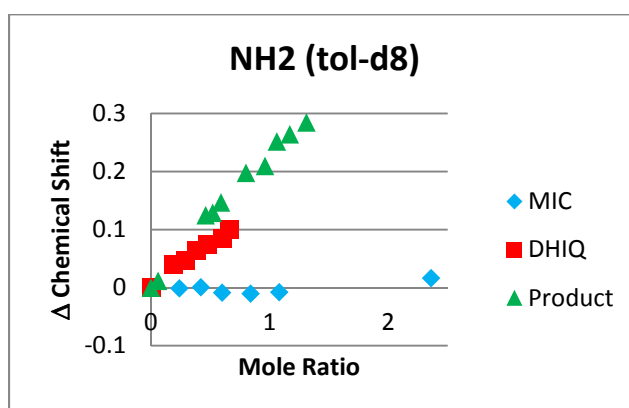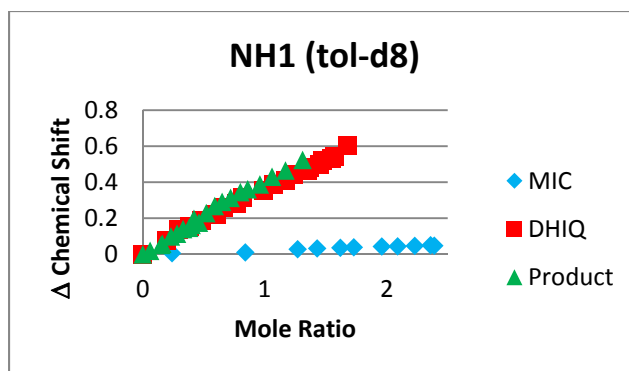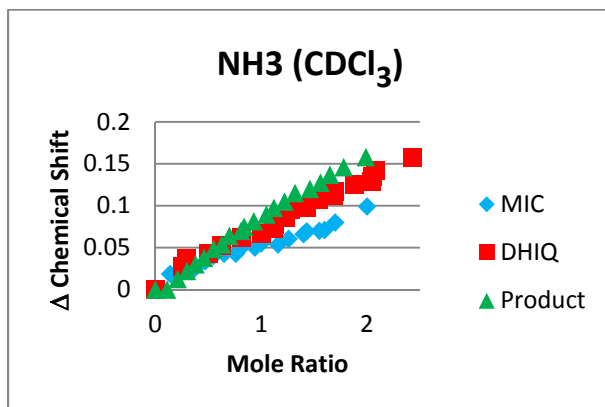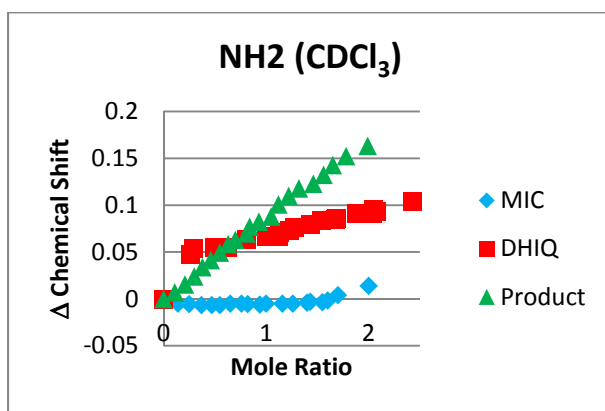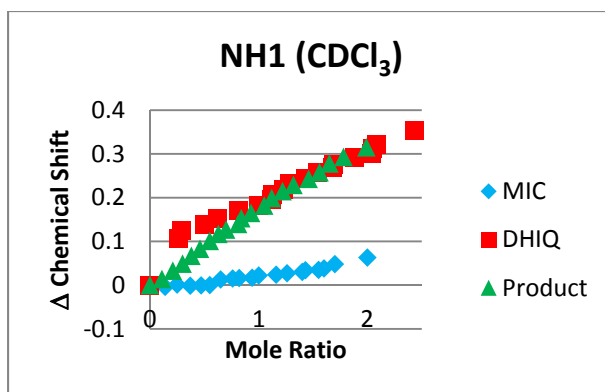
3.4 Summary

In conclusion, we have developed a new catalytic, enantioselective approach to access useful tetrahydroprotoberberine analogues in moderate enantioselectivities up to 84%. A new sulfonamide catalyst was used in conjunction with basic additives to overcome product inhibition. A racemic version of this reaction between MIC and imines was developed, promoted by borontrifluoride diethyletherate. Electron poor imines were tolerated under the reaction conditions, and the *trans* isomers of the products were isolated with high stereoselectivity.

Experimental Section

General Information: Reagents and solvents were purchased from commercial sources and were purified by distillation or recrystallization prior to use. Purification of reaction products was carried out by flash column chromatography using EM Reagent silica gel 60 (230–400 mesh). All reactions were run under a nitrogen atmosphere unless stated otherwise. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, and potassium permanganate, Dragendorff-Munier and anisaldehyde stains, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, ddddd = doublet of doublet of doublet of doublet of doublets, m = multiplet, comp = complex; and coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer or on a Finnigan 2001 Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. HPLC analysis was carried out on an Agilent 1100 series instrument with auto sampler and multiple wavelength detectors. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P–2000 polarimeter at 589 nm and at 20 °C. Racemic products **3.5a-d** were prepared using catalytic 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea.[22] Methoxyisocoumarin,[23] 3,4-dihydroisoquinoline,[24] 6,7-dimethoxy-3,4-dihydroisoquinoline,[25] 1-methyl-3,4-dihydroisoquinoline,[26] 6-methoxy-3,4-dihydroisoquinoline[27] and imine precursors[28] were prepared according to previously published procedures. Catalysts **3.17**[29] was prepared according to previously-reported procedure.

³¹P NMR Probe Study

Following a similar procedure reported by Nödling,[21] aliquots of a solution of catalyst (100 mM) in dichloromethane was added to a solution of phosphine oxide (10 mM) in dichlormethane. ³¹P NMR spectra were then recorded at 25 °C and changes in chemical shift determined.

Product Inhibition Study

Following a similar procedure reported by Mittal,[31] aliquots of a 0.1 M solution of substrate (methoxyisocoumarin, 3,4-dihydroisoquinoline or (13R,13aS)-methyl 8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate) and catalyst (0.1 M) in toluene-*d8* or chloriform-*d3* was titrated against a solution of catalyst (0.1 M) in toluene-*d8* or chloriform-*d3*. ¹H NMR spectra was then recorded at 25 °C and changes in catalyst chemical shift determined.

Synthesis of Starting Materials

3-ethoxy-1H-isochromen-1-one (EIC)
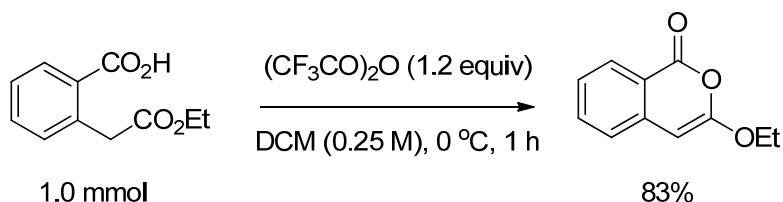
To a solution of 2-(2-ethoxy-2-oxoethyl)benzoic acid[30] (200 mg, 1.0 mmol, 1 equiv) in DCM (3.3 mL, 0.25 M) at 0 °C was added trifluoroacetic anhydride (0.16 mL, 1.15 mmol, 1.2 equiv) in 0.5 mL DCM dropwise. The reaction mixture was stirred at 0 °C for 1 h then concentrated. The crude residue was dissolved in ethyl acetate and washed with water, sat. sodium bicarbonate, brine then dried over sodium sulfate, concentrated to afford EIC in 83% yield; R_f = 0.71 (EtOAc/hexanes 3:7 v/v); mp = 63–65 °C; IR (KBr) 3053, 2987, 2685, 2306, 1741, 1641, 1564, 1484, 1421, 1363, 1312, 1261, 1218, 1186, 1037, 1008, 896, 873, 750 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 8.33–8.08 (m, 1H), 7.68–7.52 (m, 1H), 7.35–7.16 (comp, 2H), 5.56 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.0 Hz, 3H); ¹³C

NMR (125 MHz, CDCl$_3$) δ 161.41, 158.90, 140.21, 135.15, 129.95, 125.49, 124.67, 117.59, 80.03, 65.31, 14.46; *m/z* (ESI–MS) 191.3 [M+H]$^+$.

Synthesis and Characterization of Products

General Procedure A for Lewis Acid Promoted Synthesis of Alkyl Ester:

An oven-dried vial was charged with alkoxyisocoumarin (0.3 mmol, 1 equiv) and imine (0.3 mmol, 1 equiv), powdered 4 A molecular sieves (50 mg) and acetonitrile (0.75 mL, 0.4 M). The reaction was charged with boron trifluoride diethyl etherate (46 μL, 0.33 mmol, 1.1 equiv). The reaction mixture was stirred at rt or 45 °C until the imine could no longer be detected by TLC analysis. The reaction mixture was quenched with sat. sodium bicarbonate (1 mL) and the aqueous layer extracted with diethyl ether. The combined organic layers were dried over sodium sulfate and concentrated.

The crude residue was dissolved in methanol (0.5 mL). Sodium methoxide was added (360 μL, 25% wt. in MeOH, 1.59 mmol, 5.3 equiv) and the reaction mixture stirred for 30 minutes at room temperature. Water (2 mL) was added and the reaction mixture extracted with diethyl ether. The combined organic layers were washed with saturated sodium chloride, dried over sodium sulfate, concentrated and purified by flash column chromatography on silica gel. The resulting product was dried under high vacuum.

General Proecedure B for Asymetric Cycloaddition to Form Alkyl Ester:

An oven-dried vial was charged with alkoxyisocoumarin MIC or EIC (0.24 mmol, 1.2 equiv), catalyst **3.17** (22 mg, 0.04 mmol, 0.2 equiv) and trifluorotoluene (4 mL, 0.05 M). The reaction mixture was cooled to 0 °C-and then charged with imine (0.2 mmol, 1 equiv) and pyridine (4 μL, 0.05 mmol, 0.25 equiv). The reaction mixture was stirred at 0 °C until the imine could no longer be detected by TLC analysis. The reaction was concentrated and purified by flash column chromatography in silica gel. The resulting product was dried under high vacuum.
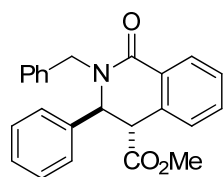
**(±)-(3S,4S)-methyl 1-oxo-2,3-diphenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (3.4a):**
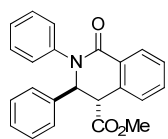
Following the general procedure A, **3.4a** was obtained as a white solid in 63% yield (68 mg, >19:1 dr); R_f = 0.30 (EtOAc/hexanes 3:7 v/v); mp = 150–153 °C; IR (KBr) 3026, 2947, 2871, 1749, 1655, 1619, 1478, 1464, 1402, 1349, 1241, 1133, 992 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.27–8.24 (m, 1H), 7.47–7.42 (comp, 2H), 7.35–7.34 (comp, 2H), 7.34–7.32 (comp, 2H), 7.26–7.14 (comp, 7H), 5.65 (d, J = 1.5 Hz, 1H), 4.04 (d, J = 1.5 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.20, 163.45, 142.45, 139.21, 132.49, 132.30, 129.62, 129.50, 129.12, 128.50, 128.00, 127.10, 126.73, 126.49, 65.00, 53.02, 51.86; m/z (ESI–MS) 358.3 [M+H]$^+$.
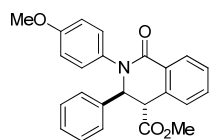
(±)-(3S,4S)-methyl 2-(4-methoxyphenyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (3.4b): Following the general procedure A, compound **3.4b** was obtained as a white solid in 61% yield (71 mg, >19:1 dr); R_f = 0.20 (EtOAc/hexanes 3:7 v/v); mp: 192–194 ºC; IR (KBr) 3467, 3005, 2970, 2949, 1736, 1654, 1426, 1365, 1217, 1092, 898, 528 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.27–8.20 (m, 1H), 7.48–7.39 (comp, 2H), 7.29–7.15 (comp, 6H), 7.16–7.12 (comp, 2H), 6.85 (dd, J = 8.5, 5.5 Hz, 2H), 5.58 (d, J = 4.2 Hz, 1H), 3.99 (d, J = 4.3 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.31, 163.63, 158.44, 139.30, 135.33, 132.42, 132.33, 129.69, 129.56, 128.86, 128.69, 128.54, 128.06, 126.60, 114.44, 65.27, 55.52, 53.06, 51.84; m/z (ESI–MS) 387.4 [M+H]$^+$;

(±)-(3S,4S)-methyl 2-(4-chlorophenyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (3.4c): Following the general procedure A, **3.4c** was obtained as a white solid in 81% yield (95 mg, >19:1); R_f = 0.44 (EtOAc/hexanes 3:7 v/v); mp = 107–108 °C; IR (KBr) 3432, 2860. 2478, 2366, 2345, 1591, 1472, 1332, 1043, 529 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.23 (dd, J = 5.7, 3.5 Hz, 1H), 7.45 (dd, J = 5.7, 3.4 Hz, 2H), 7.32–7.28 (comp, 4H), 7.25–7.19 (comp, 4H), 7.13 (dd, J = 7.5, 2.0 Hz, 2H), 5.67–5.51 (m, 1H), 4.04 (d, J = 1.4 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.11, 163.40, 140.93, 138.82,
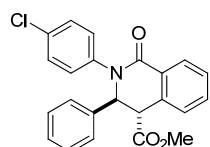
132.69, 132.63, 132.25, 129.63, 129.25, 128.95, 128.74, 128.49, 128.17, 128.13, 126.39, 64.90, 53.05, 51.63; *m/z* (ESI–MS) 392.2 [M+H]⁺.

(±)-(3S,4S)-methyl 1-oxo-3-phenyl-2-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate
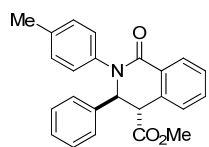
(3.4d): Following the general procedure A, **3.4d** was obtained as a white solid in 72% yield (81 mg, >19:1 dr); R$_f$ = 0.49 (EtOAc/hexanes 3:7 v/v); mp = 169–172 °C; IR (KBr) 3042, 2947, 1736, 1701, 1432, 1325, 1239, 1183, 1002, 855, 723 617, 457 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 8.27–8.23 (m, 1H), 7.46–7.42 (comp, 2H), 7.21 (t, *J* = 8.2 Hz, 6H), 7.18–7.12 (comp, 4H), 5.62 (d, *J* = 1.2 Hz, 1H), 4.02 (d, *J* = 1.4 Hz, 1H), 3.74 (s, 3H), 2.32 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.23, 163.50, 139.85, 139.27, 136.90, 132.39, 132.29, 129.77, 129.69, 129.48, 128.81, 128.64, 128.49, 127.96, 126.55, 126.53, 65.08, 53.01, 51.86, 21.17; *m/z* (ESI–MS) 372.1 [M+H]⁺.

(±)-(3S,4S)-methyl 1-oxo-2-phenyl-3-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate
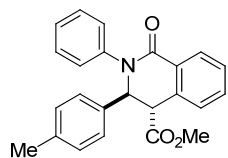
(3.4e): Following the general procedure A, **3.4e** was obtained as a white solid in 73% yield (82 mg, >19:1 dr); R$_f$ = 0.50 (EtOAc/hexanes 3:7 v/v); mp = 144–146 °C; IR (KBr) 3247, 3235, 3029, 2953, 2613, 2534, 1925, 1641, 1495, 1343, 1121, 936, 529 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 8.36 – 8.18 (m, 1H), 7.53–7.41 (comp, 2H), 7.37–7.30 (comp, 4H), 7.26–7.22 (m, 1H), 7.20–7.17 (m, 1H), 7.08-7.01 (comp, 4H), 5.60 (d, *J* = 1.4 Hz, 1H), 4.00 (d, *J* = 1.5 Hz, 1H), 3.74 (s, 3H), 2.25 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.31, 163.51, 142.54, 137.78, 136.23, 132.47, 132.43, 129.72, 129.56, 129.52, 129.13, 128.67, 128.53, 127.10, 126.74, 126.43, 64.86, 53.04, 52.01, 21.10; *m/z* (ESI–MS) 372.2 [M+H]⁺.

(±)-(3S,4S)-methyl **3-(4-chlorophenyl)-1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (3.4f):** Following the general procedure A, **3.4f** was obtained as a white solid in 68% yield (80 mg, >19:1 dr); R_f = 0.45 (EtOAc/hexanes 3:7 v/v); mp = 97–99 °C; IR (KBr) 3457, 3006, 2969, 1736, 1427, 1366, 1216, 899, 528 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.24 (dd, J = 5.6, 3.6 Hz, 1H), 7.46 (dd, J = 5.7, 3.3 Hz, 2H), 7.37–7.29 (comp, 4H), 7.27–7.22 (m, 1H), 7.19 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 5.63 (d, J = 1.2 Hz, 1H), 3.98 (d, J = 1.5 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.93, 163.30, 142.21, 137.78, 133.93, 132.66, 132.03, 129.53, 129.42, 129.21, 129.08, 128.84, 128.57, 127.90, 127.28, 126.70, 64.45, 53.09, 51.69; m/z (ESI–MS) 392.0 [M+H]$^+$.
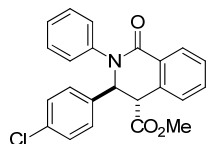
(±)-(3S,4S)-methyl **3-(4-methoxyphenyl)-1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (3.4g):** Following the general procedure A, **3.4g** was obtained as a colorless oil in 45% yield (49 mg, >19:1); R_f = 0.43 (EtOAc/hexanes 3:7 v/v); mp = 112–115 °C; IR (KBr) 3458, 3004, 2973, 1716, 1651, 1366, 1218, 1092, 901, 529 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.27–8.21 (m, 1H), 7.49–7.43 (comp, 2H), 7.37–7.29 (comp, 4H), 7.26–7.21 (m, 1H), 7.21–7.18 (m, 1H), 7.05 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 5.57 (d, J = 1.5 Hz, 1H), 3.99 (d, J = 1.6 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.30, 163.42, 159.28, 142.50, 132.50, 131.18, 129.69, 129.55, 129.14, 128.68, 128.54, 127.72, 127.13, 126.80, 114.22, 64.59, 55.30, 53.02, 52.00; m/z (ESI–MS) 387.9 [M+H]$^+$.
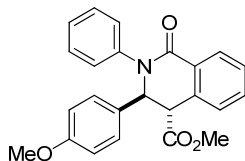
(±)-(3S,4S)-methyl 1-oxo-2-phenyl-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (3.4h): Following the general procedure A, **3.4h** was obtained as a colorless oil in 95% yield (101 mg, >19:1 dr); R_f = 0.33 (EtOAc/hexanes 3:7 v/v); IR (KBr) 3458, 3004, 2946, 1739, 1435, 1365, 1227, 1217, 528 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.50 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.21–8.17 (m, 1H), 7.53 (td, J = 7.8, 1.8 Hz, 1H), 7.47 (dd, J = 8.6, 1.2 Hz, 1H), 7.39 (td, J = 5.8, 2.9 Hz, 1H), 7.35 (d, J = 8.4 Hz,
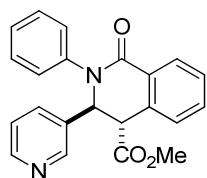
2H), 7.31–7.27 (comp, 2H), 7.25–7.22 (m, 1H), 7.22–7.19 (m, 1H), 7.08 (ddd, J = 7.6, 4.8, 1.0 Hz, 1H), 5.79 (d, J = 1.5 Hz, 1H), 4.53 (d, J = 1.6 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.17, 163.58, 158.43, 149.76, 142.36, 136.95, 132.64, 132.45, 129.49, 129.44, 129.09, 128.53, 126.90, 126.25, 122.59, 120.79, 66.14, 52.94, 49.84; m/z (ESI–MS) 359.5 [M+H]$^+$.

(±)-(3S,4S)-methyl   3-(furan-3-yl)-1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate
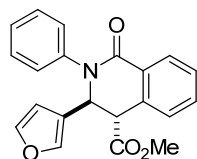
(3.4i): Following the general procedure A, **3.4i** was obtained as a yellow solid in 71% yield (74 mg, >19:1 dr); R$_f$ = 0.47 (EtOAc/hexanes 3:7 v/v); mp = 65–67 °C; IR (KBr) 3072, 3039, 1725, 1631, 1602, 1495, 1388, 1284, 1228, 1174, 1091, 1012 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.20 (dd, J = 7.6, 1.5 Hz, 1H), 7.52 (td, J = 7.4, 1.6 Hz, 1H), 7.47 (td, J = 7.5, 1.4 Hz, 1H), 7.41–7.34 (comp, 4H), 7.32 (dd, J = 7.5, 1.2 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.22 (t, J = 1.7 Hz, 1H), 7.17–7.12 (m, 1H), 5.94 (d, J = 2.8 Hz, 1H), 5.55 (d, J = 1.5 Hz, 1H), 4.00 (d, J = 1.6 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.88, 162.86, 143.59, 142.05, 140.24, 133.15, 132.53, 129.55, 129.39, 129.17, 128.72, 128.67, 127.26, 127.02, 124.50, 108.97, 57.84, 53.03, 50.52; m/z (ESI–MS) 348.1 [M+H]$^+$.

(±)-(3S,4S)-methyl   3-(furan-2-yl)-1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate
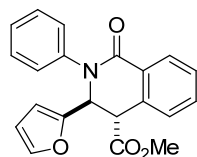
(3.4j): Following the general procedure A, **3.4j** was obtained as a brown oil in 77% yield (80 mg, >19:1 dr); R$_f$ = 0.51 (EtOAc/hexanes 3:7 v/v); IR (KBr) 3493, 3214, 2935, 1749, 16862 1611, 1430, 1371, 1397, 1022, 748, 530 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.19 (dd, J = 7.6, 1.5 Hz, 1H), 7.49 (td, J = 7.5, 1.5 Hz, 1H), 7.47–7.36 (comp, 5H), 7.32 (dd, J = 7.5, 1.3 Hz, 1H), 7.29 (dt, J = 6.5, 1.3 Hz, 2H), 7.23 (dd, J = 1.8, 0.8 Hz, 1H), 6.18 (dd, J = 3.3, 1.8 Hz, 1H), 6.07 (d, J = 3.3 Hz, 1H), 5.68 (d, J = 1.4 Hz, 1H), 4.24 (d, J = 1.7 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.61, 163.10, 151.96, 142.44, 142.07, 132.97, 132.42, 129.35, 129.18, 129.14, 128.65, 128.58, 127.24, 126.81, 59.57, 53.05, 48.68; m/z (ESI–MS) 348.3 [M+H]$^+$.

(±)-(3S,4S)-methyl 1-oxo-2-phenyl-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (3.4k): Following the general procedure A, **3.4k** was obtained as a yellow solid in 66% yield (72 mg, >19:1 dr); R_f = 0.53 (EtOAc/hexanes 3:7 v/v); mp = 61–62 °C; IR (KBr) 3426, 3107, 3020, 2733, 2458, 2337, 1721, 1658, 1510, 1436, 1363, 1194, 702, 529 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.22 (dd, J = 7.5, 1.7 Hz, 1H), 7.54 (td, J = 7.4, 1.7 Hz, 1H), 7.50 (td, J = 7.5, 1.5 Hz, 1H), 7.40–7.31 (comp, 5H), 7.30–7.26 (m, 1H), 5.86 (d, J = 1.6 Hz, 1H), 4.13 (d, J = 1.6 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.69, 162.77, 142.43, 141.92, 132.82, 132.64, 129.93, 129.44, 129.21, 128.91, 128.83, 127.42, 127.20, 126.54, 126.35, 125.44, 61.40, 53.15, 51.62; m/z (ESI–MS) 364.0 [M+H]$^+$.
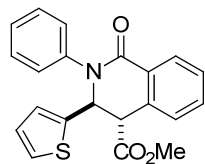
(±)-(3S,4S)-ethyl 1-oxo-2,3-diphenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (3.4l): Following the general procedure A, **3.4l** was obtained as a white solid in 69% yield (77 mg, >19:1 dr), R_f = 0.32 (EtOAc/hexanes 3:7 v/v); mp = 149–151 °C; IR (KBr) 3033, 2955, 1734, 1687, 1503, 1457, 1308, 1233, 1171, 889, 707, 519 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.25 (dd, J = 5.8, 3.3 Hz, 1H), 7.46–7.42 (comp, 2H), 7.38–7.30 (comp, 4H), 7.25–7.15 (comp, 6H), 5.76–5.56 (m, 1H), 4.36–4.09 (comp, 2H), 4.02 (d, J = 1.3 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.69, 163.48, 142.50, 139.33, 132.48, 132.42, 129.58, 129.43, 129.06, 128.81, 128.57, 128.45, 127.96, 127.01, 126.64, 126.48, 64.96, 62.02, 52.00, 14.16; m/z (ESI–MS) 372.2 [M+H]$^+$.
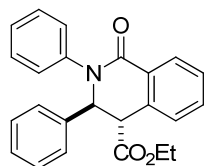
(±)-(3S,4S)-methyl 2-benzyl-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (3.4n): Following the general procedure A, **3.4n** was obtained as a white solid in 34% yield (38 mg, >19:1 dr); R_f = 0.66 (EtOAc/hexanes 3:7 v/v); mp = 77–79 °C; IR (KBr) 3066, 2954, 1737, 1657, 1606, 1453, 1411, 1269, 1237, 1164, 985 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.26 (dd, J = 7.7, 1.6 Hz, 1H), 7.44 (td, J = 7.6, 1.4 Hz, 1H), 7.40 (td, J = 7.5, 1.6 Hz, 1H), 7.34–7.27 (comp, 5H), 7.25–7.20 (comp, 3H), 7.11–7.06 (comp, 2H), 7.03 (dd, J = 7.4, 1.3 Hz, 1H), 5.72 (d, J = 14.6 Hz, 1H), 5.12 (d, J = 1.5 Hz, 1H),

3.87 (d, *J* = 1.4 Hz, 1H), 3.62 (d, *J* = 14.6 Hz, 1H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.01, 164.12, 138.57, 137.14, 132.30, 132.01, 129.43, 129.08, 129.05, 129.01, 128.68, 128.60, 128.35, 128.17, 127.72, 126.44, 60.56, 52.70, 51.65, 48.98; *m/z* (ESI–MS) 372.4 [M+H]$^+$.
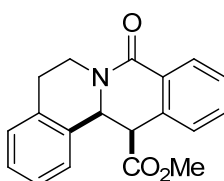
(13R,13aS)-methyl 8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (3.5a): Following the general procedure B, **3.5a** was obtained as a white solid in 72% yield (66 mg, >19:1 dr); R$_f$ = 0.22 (EtOAc/hexanes 3:7 v/v); mp = 163–166 °C; [α]$_D^{20}$ –166.1 (c 0.5, CHCl$_3$, 74% *ee*); IR (KBr) 3501, 3319, 3254, 2919, 2364, 1727, 1644, 1458, 1371, 1525, 998, 912, 746, 531 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.15–8.10 (m, 1H), 7.47–7.36 (comp, 2H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.24 – 7.10 (m, 4H), 5.20 (d, *J* = 4.3 Hz, 1H), 4.96 (dd, *J* = 11.0, 4.8 Hz, 1H), 4.17 (d, *J* = 4.3 Hz, 1H), 3.25 (s, 3H), 3.04–2.86 (comp, 2H), 2.79–2.68 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.45, 163.75, 136.51, 134.63, 133.29, 132.11, 129.28, 128.98, 128.82, 127.61, 127.31, 126.89, 126.23, 124.07, 56.62, 52.04, 51.30, 38.81, 28.98; *m/z* (ESI–MS) 307.8 [M+H]$^+$.

(13R,13aS)-ethyl 8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (3.5b): Following the general procedure B, **3.5b** was obtained as a white solid in 61% yield (39 mg, >19:1 dr); R$_f$ = 0.23 (EtOAc/hexanes 3:7 v/v); mp = 150–153 °C; [α]$_D^{20}$ –176.8 (c 0.5, CHCl$_3$, 84% *ee*); IR (KBr) 2982, 2941, 2903, 2841, 2750, 1752, 1691, 1566, 1494, 1401, 1235, 1150, 1034, 981, 854, 782, 529 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.17 (dd, *J* = 7.1, 1.8 Hz, 1H), 7.51–7.40 (comp, 2H), 7.36–7.31 (m, 1H), 7.27–7.24 (m, 1H), 7.24–7.12 (comp, 3H), 5.25 (d, *J* = 4.4 Hz, 1H), 5.11–4.92 (m, 1H), 4.21 (d, *J* = 4.4 Hz, 1H), 3.74 (q, *J* = 7.1 Hz, 2H), 3.11–2.90 (comp, 2H), 2.77 (d, *J* = 13.3 Hz, 1H), 0.80 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.10, 163.79, 136.56, 134.76, 133.40, 132.08, 129.29, 129.25, 128.95, 128.75, 127.53, 127.27, 126.83, 126.35, 60.98, 56.67, 51.26, 38.78, 28.99, 13.79; *m/z* (ESI–MS) 322.3 [M+H]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t$_R$ = 15.9 min (major) and t$_R$ = 27.3 min (minor).
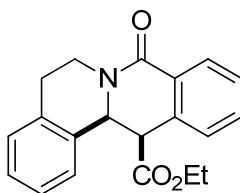
(13R,13aS)-ethyl 2,3-dimethoxy-8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-
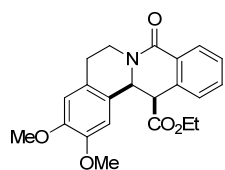
13-carboxylate (3.5c): Following the general procedure B, **3.5c** was obtained as a white solid in 80% yield (61 mg, >19:1 dr); R_f = 0.14 (EtOAc/hexanes 3:7 v/v); mp = 164–165 °C; $[\alpha]_D^{20}$ –316.4 (c 0.5, CHCl₃, 83% *ee*); IR (KBr) 3488, 3125, 3027, 2679, 2368, 2315, 1734, 1531, 1413, 1261, 1109, 739, 528 cm^{-1}; ^{1}H NMR (CDCl₃, 500 MHz) δ 8.19 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.51–7.42 (comp, 2H), 7.35 (d, *J* = 7.3 Hz, 1H), 6.75 (s, 1H), 6.66 (s, 1H), 5.19 (d, *J* = 4.4 Hz, 1H), 5.08–4.94 (m, 1H), 4.20 (d, *J* = 4.4 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.79 (q, *J* = 7.1 Hz, 2H), 3.08–2.89 (comp, 2H), 2.79–2.51 (m, 1H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl₃) δ 169.05, 163.77, 148.09, 134.66, 132.00, 129.31, 129.22, 128.98, 128.69, 127.42, 124.86, 111.40, 109.27, 60.91, 56.38, 56.33, 56.02, 51.16, 38.85, 28.48, 13.86; *m/z* (ESI–MS) 382.2 [M+H]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 13.3 min (major) and t_R = 50.9 min (minor).

(13R,13aS)-ethyl 3-methoxy-8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-
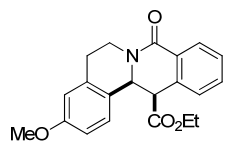
carboxylate (3.5d): Following the general procedure B, **3.5d** was obtained as a white solid in 64% yield (45 mg, >19:1 dr); R_f = 0.17 (EtOAc/hexanes 3:7 v/v); mp = 157–159 °C; $[\alpha]_D^{20}$ –253.7 (c 0.5, CHCl₃, 79% *ee*); IR (KBr) 3522, 3479, 3361, 3293, 2950, 2743, 1709, 1652, 1414, 1376, 1088, 901, 717, 529 cm^{-1}; ^{1}H NMR (CDCl₃, 500 MHz) δ 8.19 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.52–7.42 (comp, 2H), 7.38–7.33 (m, 1H), 7.21 (d, *J* = 8.6 Hz, 1H), 6.85 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.71 (d, *J* = 2.6 Hz, 1H), 5.23 (d, *J* = 4.4 Hz, 1H), 5.01 (dd, *J* = 12.5, 4.2 Hz, 1H), 4.20 (d, *J* = 4.4 Hz, 1H), 3.85–3.74 (comp, 5H), 3.11–2.94 (comp, 2H), 2.75 (d, *J* = 14.8 Hz, 1H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl₃) δ 169.17, 163.78, 158.53, 137.91, 134.73, 132.02, 129.28, 129.21, 128.69, 127.50, 127.47, 125.38, 113.37, 113.18, 60.94, 56.24, 55.42, 51.31, 38.69, 29.25, 13.86; *m/z* (ESI–MS) 552.4 [M+H]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 14.5 min (major) and t_R = 25.0 min (minor).

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Chapter 4. Redox-Neutral α-Sulfenylation of Secondary Amines

4.1   Background

Functionalized secondary and tertiary amines are common structural motifs found in many biologically active compounds.[1] Finding direct and inexpensive ways to build structural complexity is a longstanding challenge in organic synthesis. The most efficient approach involves the direct functionalization of a C–H bond to form a new C–C or C–X bond. The difficulty with this approach is that the C–H bond is relatively inert, unless a nearby functional group can be used to help activate it, such as an amine.[2] There are numerous ways to functionalize an amine in the α-C–H position already reported in the literature.[3] The most common approaches (Figure 4.1) include deprotonation with a strong base to form an anion, oxidation to form an iminium ion, oxidative insertion, and radical generation at the α-position.

Figure 4.1 Functionalization of secondary amines
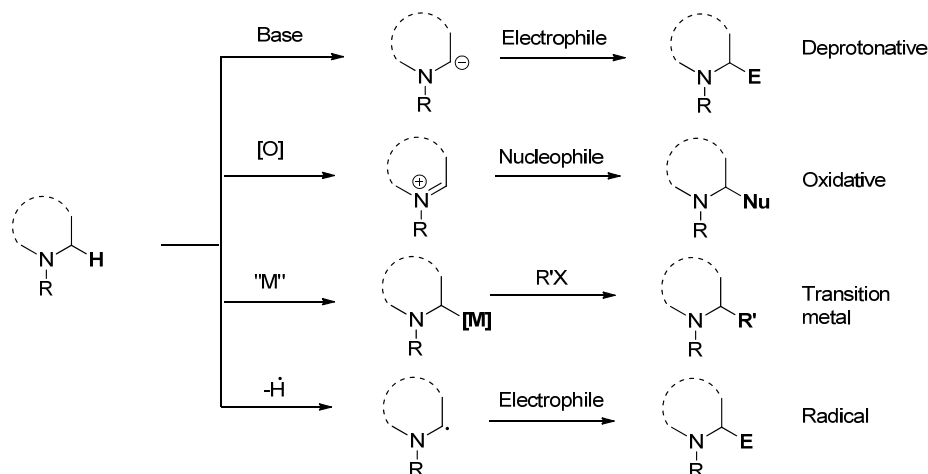
One of the earliest examples of the deprotonation reaction was developed by Beak in 1989,[4] who used sec-butyl lithium as a base to form an anion on piperidine, which was then reacted with trimethylsilyl chloride (Scheme 4.1, eq 1). In 1949, Leonard functionalized an amine at the α-position using iodine as the oxidizing reagent (Scheme 4.1, eq 2).[5] A transmetallation to an unprotected secondary amine was accomplished by Jun in 1998, using a ruthenium carbonyl cluster as a catalyst.[6]

The transmetallated intermediate was then alkylated by hexe-1-ene (Scheme 4.1, eq 3). One of the initial radical functionalization approaches was disclosed by Snieckus and Curran in 1990.[7] An aryl radical was first formed, then transferred to the α-nitrogen position through 1,5-hydride transfer. This α-amino radical intermediate then coupled to a methyl acrylate with high selectivity (Scheme 4.1, eq 4).

Scheme 4.1 The α-functionalization of secondary amines through net oxidation
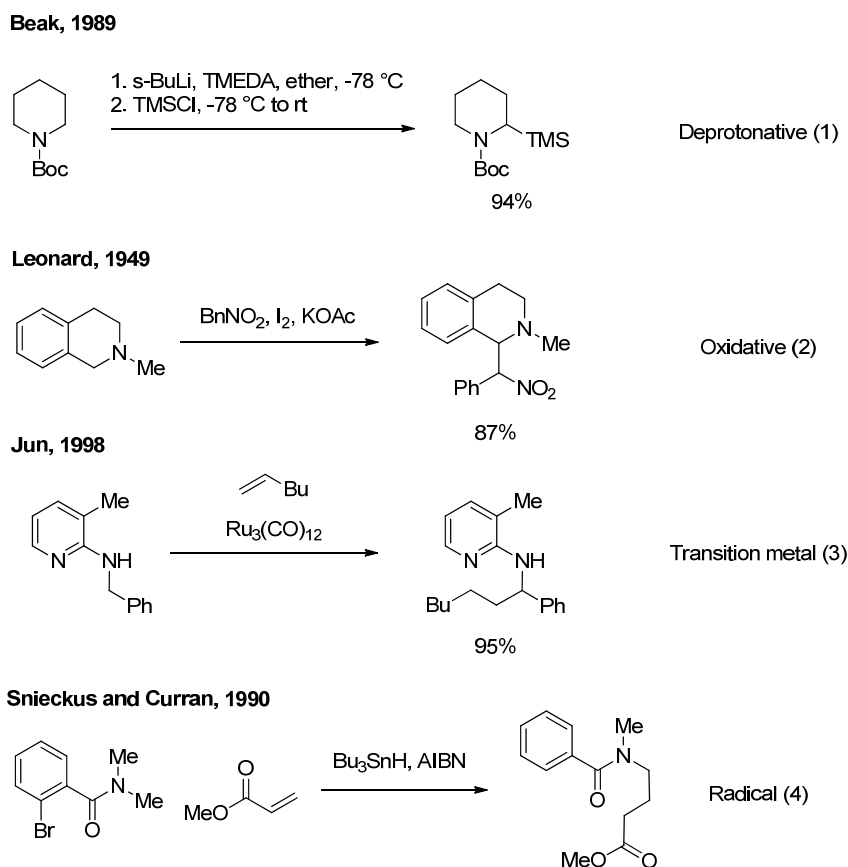
4.1.1 Redox-Neutral Functionalization of Amines

The approaches above usually require use of stoichiometric reagents to functionalize the amines, with the net reaction being an oxidation. Minimizing the number of unnecessary oxidation or reduction steps in a synthesis helps improve its efficiency and avoids additional transformations to "correct" the product's oxidation state. An alternative approach to amine functionalization is when an

oxidation and reduction reaction occur simultaneously, removing the need for an external oxidant and making the reaction net-neutral. This type of transformation is called a redox-neutral reaction.[8,9] One of the first examples of this chemistry is the Tishchenko reaction reported in 1906, where two aldehyde condense to form an ester, promoted by a Lewis acid.[10] One aldehyde molecule is oxidized, the other reduced. In the later variant developed by Evans an aldehyde was shown to couple with a ketone through the same mechanism (Scheme 4.2).[11]

Scheme 4.2 Redox-neutral Tishchenko and Evans-Tishchenko reactions
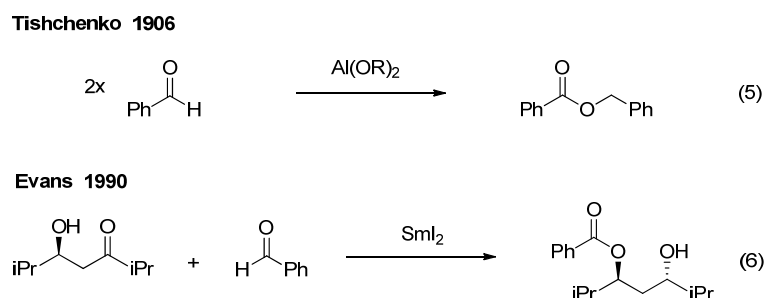
4.1.2   Redox-Neutral Functionalization of Amines via Intramolecular Hydride Transfer

The redox-neutral Evans-Tishchenko reaction occurs through a hydride transfer mechanism.[12] Amines can also be used as substrates in intramolecular hydride transfer/ring closing reactions because the sp^3 C–H bond adjacent to a tertiary amine is a particularly good hydride donor. This is known as the *tert*-amino effect[13] and the first example of an intramolecular 1,6-hydride shift exploiting this reactivity was reported by Meth-Cohn in 1967 (Scheme 4.3, eq 7).[14] The α-proton on the pyrrolidne ring is transferred to the imine, generating an iminium ion intermediate and secondary amine. Subsequent ring closure leads to an aminal product. Reinhoudt provided the first example of a 1,5-hydride shift in 1984, using a dinitrile hydride acceptor (Scheme 4.3, eq 8).[15] The 1,4-hydride transformation is more difficult to accomplish, although several examples exist in the literature.[16]

Scheme 4.3 Intramolecular hydride transfer reactions.

Meth-Cohn 1967

(7)

Reinhoudt 1984

(8)
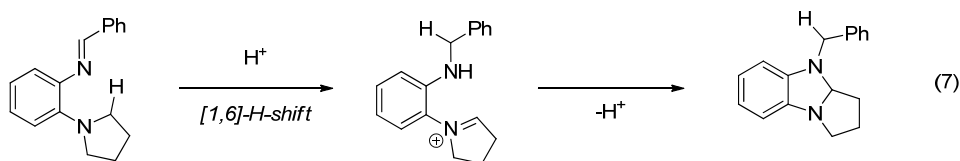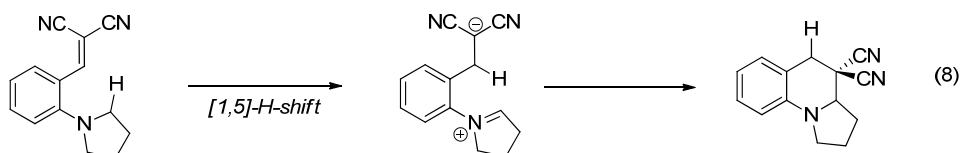
In 2009 the Seidel and Akiyama groups simultaneously[17,18] developed a Brønsted acid-promoted redox process to form cyclic aminals that went through a 1,5-hydride shift and was directed by the *tert*-amino effect (Scheme 4.4, eq 9, 10). In these examples the imine hydride acceptor was formed *in situ* from the condensation of the aldehyde with a primary amine. The Seidel group then developed a variant catalyzed by gadolinium triflate, with dimalonate acting as a hydride acceptor and coordinator to the Lewis acid (Scheme 4.4, eq 11).[19] Unlike previously-reported hydride transfer reactions that required high temperatures to initiate, this transformation could be performed at room temperature and was complete within minutes. The Seidel group modified this approach to give an enantioselective version of the same transformation using a hard Lewis acid catalyst and chiral bisoxazoline ligand (Scheme 4.4, eq 12).[20] This was the first reported example of a catalytic enantioselective hydride-transfer/ring closure reaction. The reaction gave high enantioselectivities even when heated to reflux, although the diastereomeric ratios were poor. The Seidel group later developed a racemic version of the hydride transfer annulation that produced a seven-membered ring.[21] This was the first example of a seven-membered ring annulation using the *tert*-amino effect: previous examples had focused on forming five or six-membered rings.

Scheme 4.4 Examples of the *tert*-amino effect applied to annulation reactions
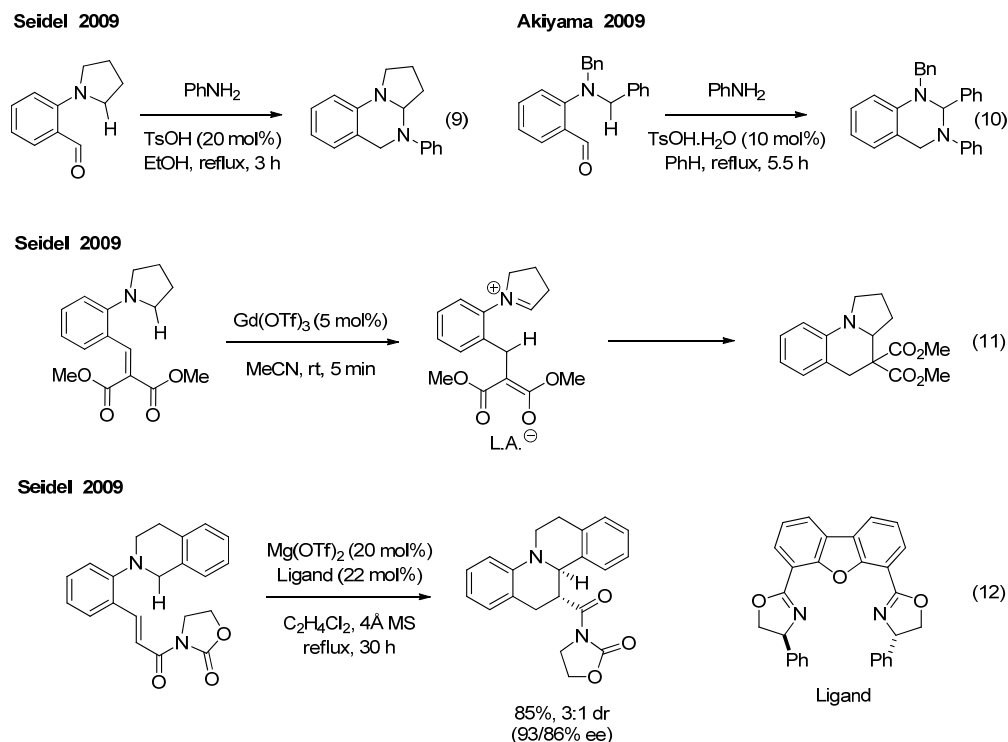
4.1.3 Functionalization of Amines via Azomethine Ylides

The second mechanism for the redox-neutral functionalization of amines involves the generation of an azomethine ylide intermediate. An azomethine ylide is a zwitterion with 4-π electrons spread over a C–N–C bond. The major resonance structure has a positive charge on the nitrogen, and negative charge switching between the two carbons, the charge ratio dependent on their neighboring functional groups. In contrast to the hydride transfer approach which always requires a tertiary amine, an azomethine ylide can be generated from a secondary amine. The classic methods of azomethine ylide generation include ring-opening of an aziridine,[22] deprotonation of an iminium ion pair,[23] or *in situ* imine formation and decarboxylation (Figure 4.2).[24]

Figure 4.2 Formation of azomethine ylides
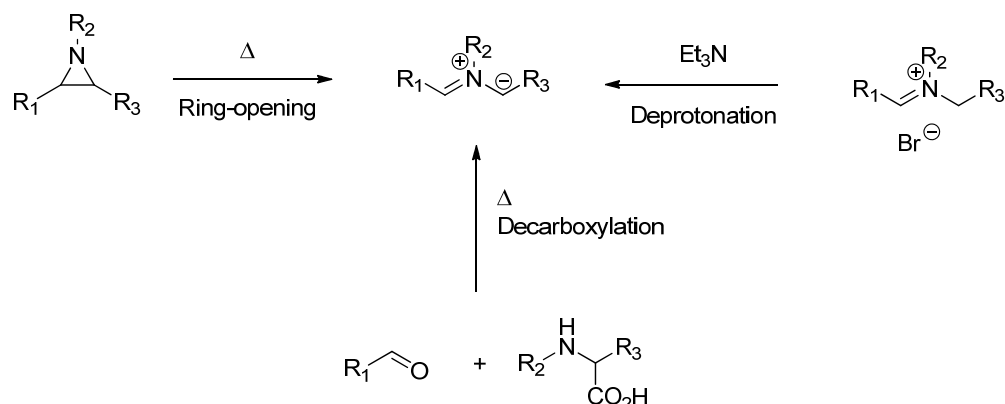
Once generated, azomethine ylides can undergo several transformations. As intermediates they are too reactive to be isolated, but they are frequently used to build up structural complexity and additional ring systems in a molecule. The most common transformations are cycloadditions and electrocyclisations.[25] In 1963 Huisgen provided the first example of a dipolar cycloaddition with dimethylfumarate and a tetrahydroisoquinoline-derived azomethine ylide intermediate (Scheme 4.5, eq 13).[24] In 1992 Grigg showed that an azomethine ylide formed by the condensation of tetrahydroisoquinoline and divinylketone could undergo an 1,5-electrocyclisation and subsequent aromatization in the presence of dibutyltin chloride (Scheme 4.5, eq 14).[26] An 1,7-electrocyclisation and aromatization was developed by Groundwater, where a phenyl ring was functionalized to generate a new C–C bond (Scheme 4.5, eq 15).[27]

Scheme 4.5 Reactions of azomethine ylides

Huisgen 1963

(13)

Grigg 1992

(14)

Groundwater 1999

[1,5]-H shift

(15)
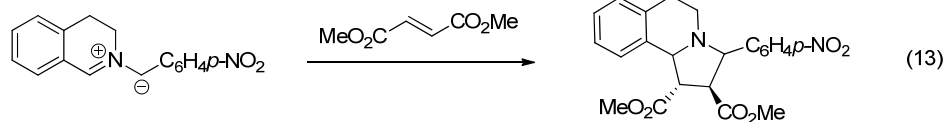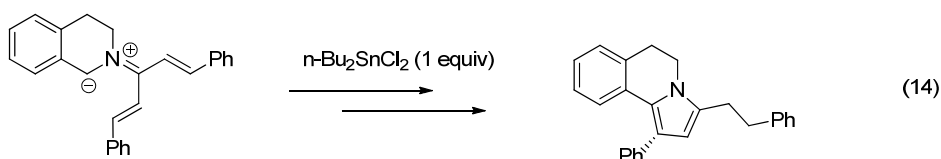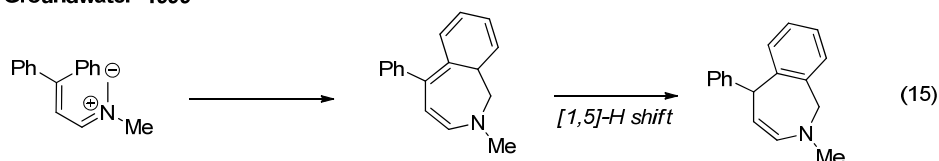
Azomethine ylides can also be protonated and used as electrophiles for nucleophile attack, although that approach is not as common. One of the earliest examples was reported by Cohen and involved the decarboxylation of proline to generate the azomethine ylide, followed with nucleophilic attack by an alcohol to give an *N,O*-acetal (Scheme 4.6, eq 16).[28] In 2008 the Seidel group reported a similar annulation starting from the ortho-aminobenzaldehyde and a secondary amine (Scheme 4.6, eq 17).[29] The aminal product of this reaction was unexpected: pyrrolidine was used as a base in this reaction to catalyze a Friedlander condensation between the ortho-aminobenzaldehyde and a ketone (Scheme 4.6, eq 18). The reaction was later established to go through the azomethine ylide intermediate after combined computational and experimental studies (Scheme 4.6, eq 19).[30,31] In the first step, a hemiaminal is formed. This heminaminal intermediate can form interconverting *cis* and *trans* quinoidal intermediates upon loss of water, although the *cis* quinoidal intermediate is the only one capable of intramolecular proton transfer to form the key azomethine ylide intermediate. Through a second proton transfer mediated by the ethanol solution, the azomethine ylide converts into a zwitterion intermediate, which undergoes ring closure to form the aminal product.

Scheme 4.6 Azomethine ylides in nucleophilic reactions

Cohen 1979 (16)

Seidel 2008 (17)

(18)
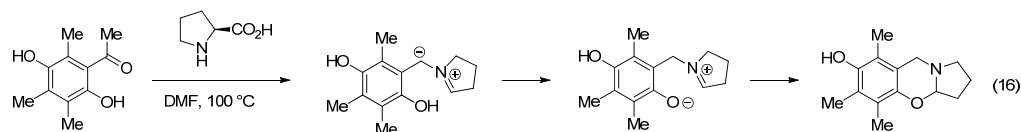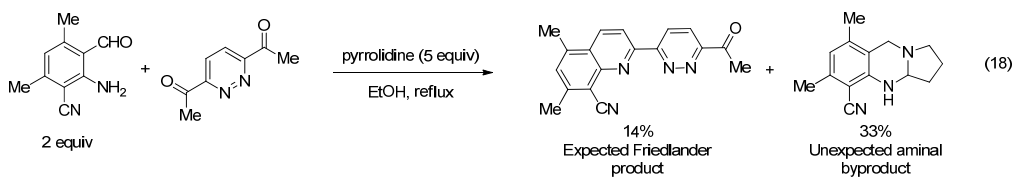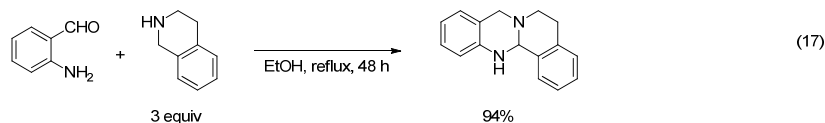
Seidel, 2013 (19)
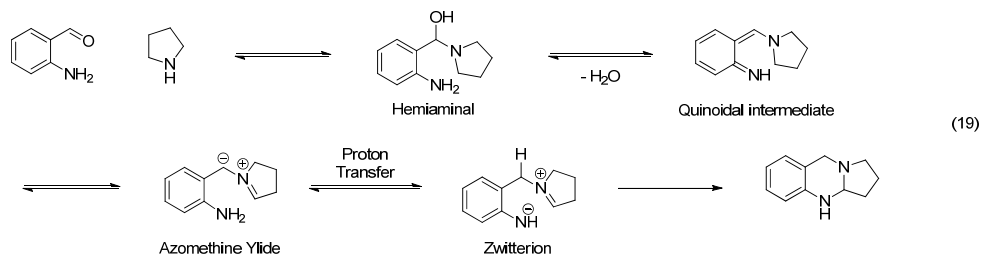
In 2013 the Seidel group reported that a similar transformation could be performed with salicyaldehydes as the annulation partner.[32] Under the same conditions for the aminal reaction none of the desired product was formed, only the an alcohol byproduct and DHIQ were isolated (Scheme 4.7, eq 20). It was hypothesized that the desired *N,O*-acetal product was fragmenting under heating to eliminate DHIQ, and the *o*-quinone methide intermediate could react with another equivalent of THIQ to form the undesired byproduct (Scheme 4.7, eq 21). An alternative set of reaction conditions were developed that allowed the reaction to take place at lower temperatures.

A computational study by Yu in 2011[33] had re-examined a redox-neutral *N*-alkylpyrrole formation first reported by Tunge in 2009.[34] Yu's studies were the first to propose azomethine ylides

as intermediates in these reactions, and argued that Brønsted acids additives worked by facilitating the proton transfers steps.

With toluene as the new solvent, it was found that molecular sieves accelerated the condensation step by absorbing the water molecules, and stoichiometric amounts of acetic acid accelerated the reaction and reduced byproduct formation (Scheme 4.7, eq 22). Experimental and computational studies performed in collaboration with Houk established that the reaction proceeded through a condensation of the hemiacetal to give a zwitterion intermediate. This was followed by two irreversible intramolecular proton transfers. The final zwitterionic intermediate could then ring-close to give the *N,O*-acetal product (Scheme 4.7, eq, 23).

Scheme 4.7 Formation of *N,O*-acetals through azomethine ylide intermediates
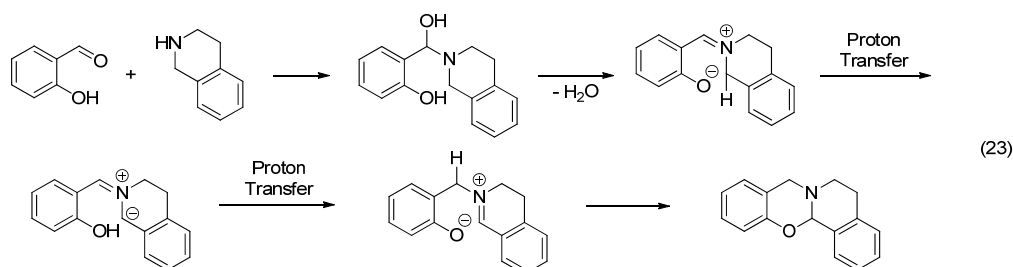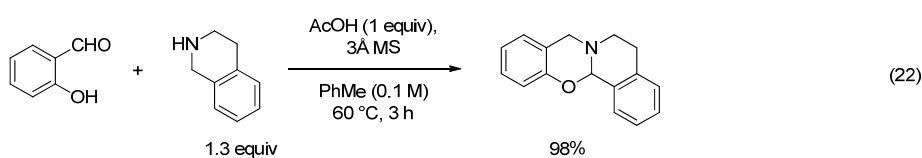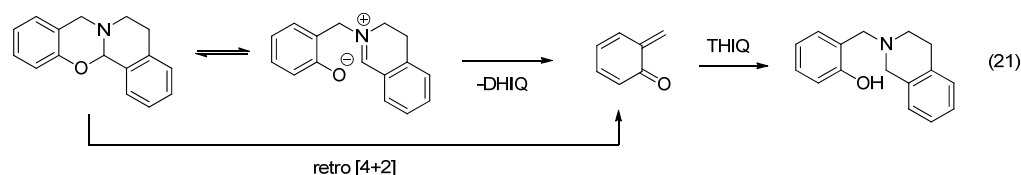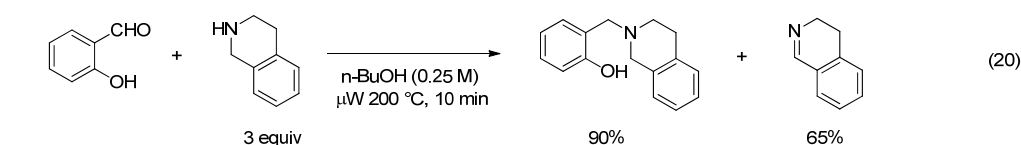
4.1.4 Aims and Significance

The *N,S*-acetal motif is common in nature and present as a key functional group in pharmacologically active compounds (Figure 4.3).[35-43] *N,S*-acetals have been investigated as sedatives (e.g., **4.1** and **4.2**),[35] antibacterials (e.g., **4.3**),[37] and cell growth inhibitors (e.g., **4.4**).[36] Penicillins such as amoxicillin (**4.5**) are widely used as antibacterial medicines.[43]

Figure 4.3 Examples of bioactive *N,S*-acetals
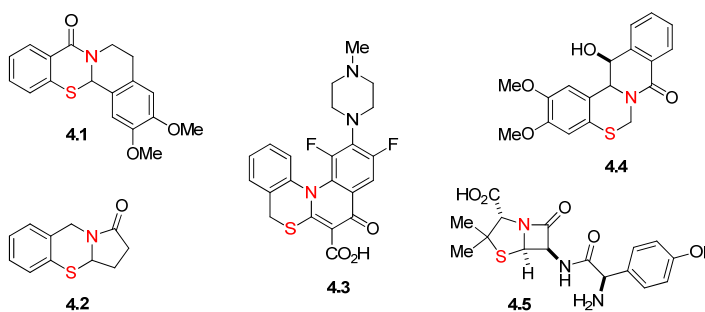
Traditional synthetic approaches to ring-fused *N,S*-acetals include the condensation of preformed imines with thiosalicylic acid, often requiring the addition of a coupling reagent (Scheme 4.8).[35, 44-53] We envisioned a new approach to *N,S*-acetals starting from thiosalicylaldehydes and secondary amines.

Scheme 4.8 Selected approaches to *N,S*-acetals
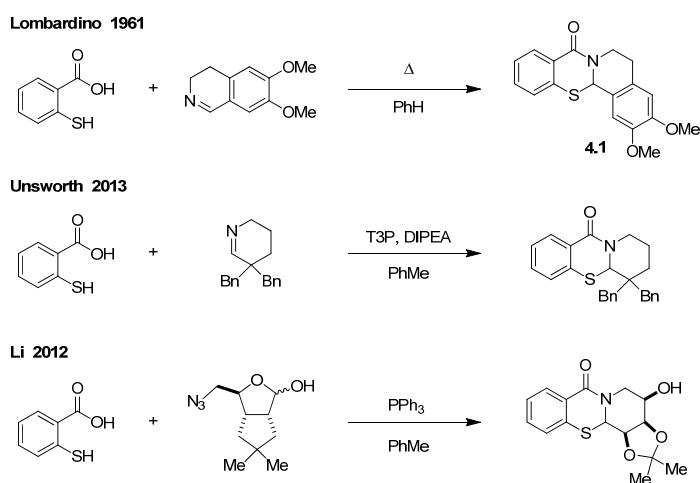
Based upon the analogous α-amination and α-oxygenation reactions, the key feature of this process was proposed to be a redox-neutral amine α-C–H bond functionalization with concurrent *N*-alkylation/α-sulfenylation.[31,32] We recognized that an analogous α-sulfenylation of secondary amines with thiosalicylaldehydes would provide a practical entry to ring-fused *N,S*-acetals not easily accessible by other means. Based on the greater nucleophilicity of thiols compared to alcohols, we speculated that α-sulfenylation might occur with a wider range of substrates.

4.2 Redox-Neutral α-Sulfenylation of Amines

4.2.1 Reaction Optimization

The title reaction was evaluated using thiosalicylaldehyde and 1,2,3,4-tetrahydroisoquinoline (THIQ) as the model substrates. Starting from conditions that were found ideal for the formation of the corresponding aminal and *N,O*-acetal analogues, a brief optimization survey was conducted (Table 4.1). Remarkably, the reaction of thiosalicylaldehyde (**4.6–S**) and THIQ was found to proceed in the absence of any additive at room temperature in ethanol solution to provide product **4.7a** in 40% yield (entry 1). In toluene as the solvent, an increased yield of 51% was observed (entry 2). While higher temperatures served to improve the yield further (entries 3 & 4), the addition of acetic acid was found to have a more dramatic effect. With 10 mol% of acetic acid, **4.7a** was obtained in 90% yield following a reaction time of just two hours at room temperature (entry 6). Raising the reaction temperature to 60 °C in an otherwise identical experiment led to full conversion in only 30 min while allowing for the isolation of **4.7a** in 93%, the highest yield observed (entry 6). As previously noted in the corresponding *N,O*-acetal formation,[32] removal of water from the reaction mixture was crucial in order to achieve rapid conversion. A reaction conducted under otherwise optimal conditions but in the absence of molecular sieves led to the formation of **4.7a** in only 46% after one hour (entry 7). Interestingly, increasing the amount of acetic acid to one equivalent had a detrimental effect on conversion and product yield while leading to an increased formation of disulfides and additional

unidentified byproducts (entries 8-9). This observation is in contrast to what was seen for *N,O*-acetal

formation where an increase in the amount of acid proved highly beneficial.[32]

Table 4.1 Evaluation of reaction conditions for α-sulfenylation of 1,2,3,4-tetrahydroisoquinoline with thiosalicylaldehyde (4.6–S)[a]
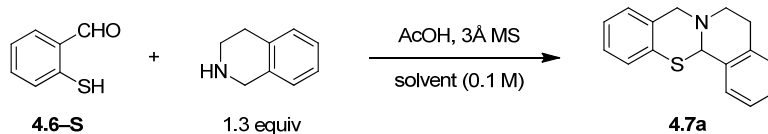
entry	AcOH (equiv)	solvent	T [°C]	time (h)	yield (%)
1	0	EtOH	rt	9	40
2	0	PhMe	rt	18	51
3	0	PhMe	60	0.5	66
4	0	PhMe	120[b]	0.17	60
5	0.1	PhMe	rt	2	90
6	0.1	PhMe	60	0.5	93
7[c]	0.1	PhMe	60	1	46
8	1.0	PhMe	rt	36	trace
9	1.0	PhMe	60	1.5	18

[a] Reactions were conducted on a 1 mmol scale.   Yields correspond to isolated yields of chromatographically purified product. [b] Microwave irradiation in sealed vial. [c] Without molecular sieves.

4.2.2 Substrate Scope

The α-sulfenylation with thiosalicylaldehyde was evaluated with a broad range of secondary amines (Scheme 4.9). A number of cyclic amines such as pyrrolidine, piperidine and azepane underwent reaction with thiosalicylaldehyde at moderate temperatures to give product in generally

good yields. Relatively electron-deficient amines such as morpholine and *N*-phenyl piperazine, substrates that are typically rather reluctant to undergo α-C–H bond functionalization, furnished the corresponding products at elevated temperatures (microwave irradiation at 120–150 °C). Initial attempts to synthesize these *N,S*-acetals at 60–90 °C required longer reaction times to reach complete consumption of the starting materials. In addition, it was found that for these substrates, oxidative dimerization of thiosalicylaldehyde to the corresponding disulfide was a competing process. This undesirable reaction pathway was reduced at elevated temperatures and further minimized by using a larger excess of the amine (3 equivalents). Under these conditions, dibenzylamine, a representative open-chain substrate, generated the corresponding product **7i** in good yield. Several other cyclic amines with benzylic α-C–H bonds, including the sterically demanding 1-phenyl-THIQ, underwent *N,S*-acetal formation under mild conditions. Finally, ring-substitution of thiosalicylaldehyde with either electron-donating or -withdrawing groups was well tolerated.

Scheme 4.9 Substrate scope for the α-sulfenylation[a]

In order to explore the regioselectivity of the *N,S*-acetal formation for substrates with electronically similar α-C–H bonds, **6–S** was allowed to react with 1-methyl pyrrolidine and 1-methyl piperidine (Scheme 4.10). Interestingly, in both cases the product distribution reflects a preference for functionalization of a secondary over an electronically favorable tertiary C–H bond. Apparently, steric issues appear to outweigh electronic effects in these instances. This is in stark contrast to the corresponding aminal formation with 1-methyl pyrrolidine and 1-methyl piperidine that exhibit a pronounced preference for tertiary C–H bond functionalization.[30,31] Interestingly, the major products **4.7r** and **4.7t** were also obtained in higher diastereomeric ratios than their aminal counterparts.

Scheme 4.10 Regioselectivity of the α-sulfenylation[a]
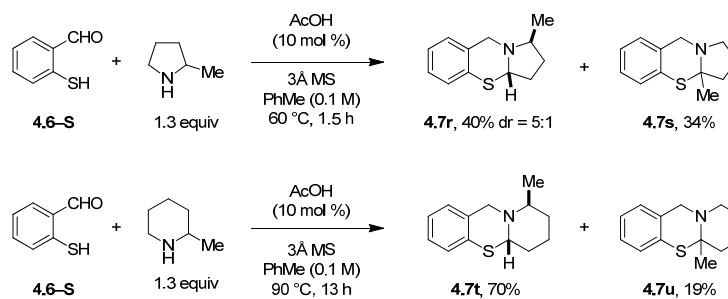
a) Reactions were performed on a 1 mmol scale.

4.2.3   Mechanistic Considerations

To rationalize the enhanced reactivities in the *N,S*-acetal series compared to the corresponding *N,O*-acetals, we analyzed the model reaction between thiosalicylaldehyde (**4.6–S**) and THIQ by the same computational method described previously (M06-2X-D3/def2-TZVPP/IEFPCM(toluene)//TPSS-D2/6-31+G(d,p)/IEFPCM(toluene).[32]

For the uncatalyzed reactions without acetic acid, the calculated free energy profiles for the oxo- and thio pathways are summarized in Figure 4.4. The hemiaminals **4.8–O** and **4.8–S** as well as the transition states for the dehydration (**TS1–O/S**) are very similar for both systems. In contrast, a substantial difference was calculated for all other intermediates and transition states. While the sulfur-compound of **4.9**, **TS2**, and **4.10** is 4–5 kcal mol^{-1} more stable than the oxygen analog, differences of more than 10 kcal mol^{-1} were calculated for **TS3**, **4.11**, and **4.7a**. This stability difference can also be rationalized with the higher acidity of thiophenol compared to phenol in both DMSO ($\Delta pK_a \approx 8$) and aqueous solution ($\Delta pK_a \approx 3$).[56,57] This difference in acidity might also be responsible for the fact that no thiosalicylaldehyde-mediated proton transfer (e.g., the thio-analogue of **TS3-O-Sali**)[32] could be located.

Figure 4.4 Free energy profile [in kcal·mol^{-1}, M06-2X-D3/def2-TZVPP/IEFPCM//TPSS-D2/6-31+G(d,p)/IEFPCM] for uncatalyzed transformation of **4.6–O** (black) and **4.6–S** (red) and **THIQ** in toluene.
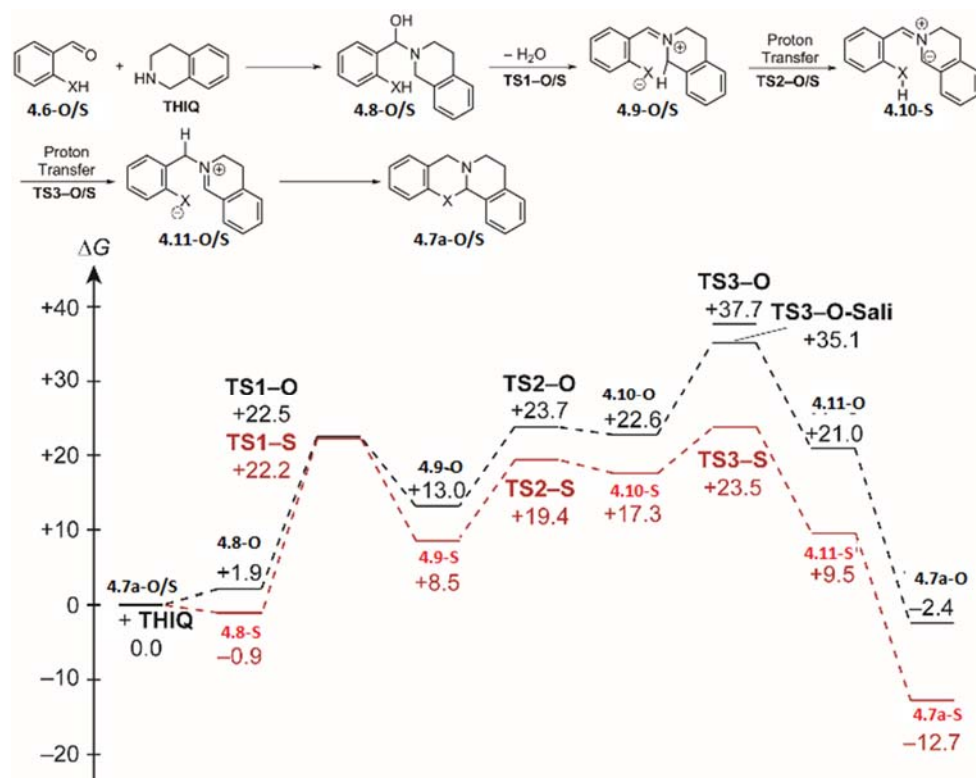
Next, we analyzed whether acetic acid has the same catalytic effect for the synthesis of *N,S*-acetals as previously described for the corresponding *N,O*-acetals.[32] Figure 4.5 summarizes the calculated transition states for the uncatalyzed and acetic-acid-catalyzed *N,S*-acetal formation. Similar to the formation of *N,O*-acetals, acetic acid stabilizes the transition states **TS1–S** ($\Delta\Delta G^{\ddagger} = -1.5$ kcal mol^{-1}) and **TS3–S** ($\Delta\Delta G^{\ddagger} = -2.6$ kcal mol^{-1}). As previously reported for the formation of *N,O*-acetals,[32] transition state **TS2–S** for the endergonic transformation of **4.9–S** to **4.10–S** is actually destabilized by acetic acid ($\Delta\Delta G^{\ddagger} = +10.9$ kcal mol^{-1}). Again, a small barrier (with respect to **4.10–S**) and the entropic penalty ($-T\Delta S$) render **TS2–S-HOAc** less favorable than **TS2–S** and are responsible for the preference of the intramolecular proton transfer over the intermolecular process for this step.

Due to the higher acidities of thiols, the rate-determining step (**TS3–S**) is lowered to a much smaller extent than in the *N,O*-acetal series. These computational findings are also reflected in the experimental data of Table 4.1, as acetic acid is not necessarily required for the formation of *N,S*-acetals but is ultimately needed in the *N,O*-acetal series.

Figure 4.5 Calculated transition state structures [M06-2X-D3/def2-TZVPP/IEFPCM//TPSS-D2/6-31+G(d,p)/IEFPCM], relative free energies (in kcal·mol^{-1}), and selected bond lengths (in Å) for the uncatalyzed and acetic-acid-catalyzed transformation of **4.6–S** and **THIQ**.
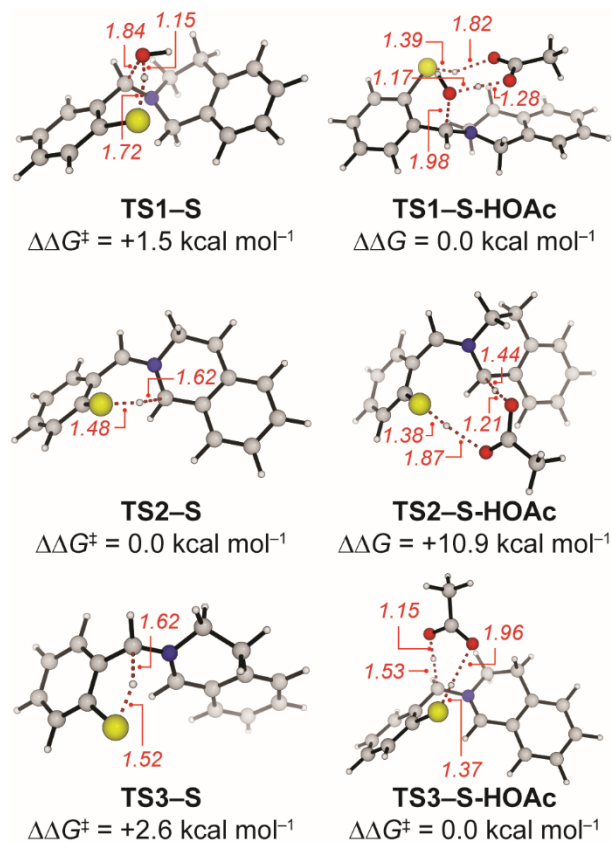
4.3 Summary

In conclusion, a relatively mild and effective approach to ring-fused *N,S*-acetals has been developed. This reaction expands upon our previously reported azomethine ylide chemistry and corresponding α-amination and α-oxygenation reactions. Using computational studies we gained a better understanding of the differences between the α-sulfenylation and α-oxygenation reactions, including reaction rates and importance of acetic acid as a promoter.

Experimental Section

General Information: Secondary amines were purchased from commercial sources unless otherwise stated and were distilled prior to use. Glacial acetic acid was purchased from EMD and was used as received. 3Å powdered molecular sieves were purchased from Alfa Aesar and were activated before use by heating in a furnace to 300 °C for 2 h and were stored in a desiccator. Reagent grade toluene was purchased from Sigma-Aldrich and distilled over sodium. Microwave reactions were carried out in a CEM Discover S reactor. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F254 plates. Visualization was accomplished with UV light. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (1H-NMR) were recorded on a Varian VNMRS-500 MHz and are reported in ppm using chloroform as the internal standard (7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad; and coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (13C-NMR) were recorded on a Varian VNMRS-300 MHz and are reported in ppm using chloroform as the internal standard (77.0 ppm). Mass spectra were recorded on a Finnigan LCQ- DUO mass spectrometer.

General Procedure A: To a solution of aldehyde (1.0 mmol) in toluene (10 mL) was added 3 Å molecular sieves (200 mg), amine (1.3 mmol) and glacial acetic acid (0.1 mmol). The mixture was heated to 60 °C until the aldehyde was consumed. Subsequently, the reaction mixture was cooled to room temperature, filtered through a plug of celite and washed with 50 mL dichloromethane. The crude product was concentrated in vacuo and purified by silica gel chromatography.

General Procedure B: A solution of aldehyde (1.0 mmol) in toluene (10 mL) was added to a 35 mL

microwave vial equipped with a magnetic stir bar and 3 Å molecular sieves (200 mg). To the solution

was added amine (3.0 mmol) and glacial acetic acid (0.1 mmol). The mixture was irradiated in the

microwave until the aldehyde was consumed. Subsequently, the reaction mixture was cooled to room

temperature, filtered through a plug of celite and washed with 50 mL dichloromethane. The crude

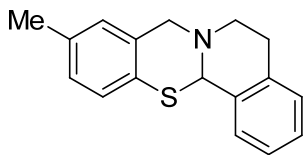product was concentrated in vacuo and purified by silica gel chromatography.

(±)-5,6,8,13a-Tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline (4.7a):   Following general
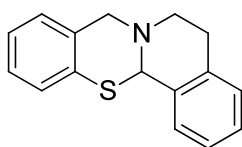
procedure A, compound **4.7a** was obtained from the reaction between

thiosalicylaldehyde[1] and 1,2,3,4-tetrahydroisoquinoline at 60 °C for 30 min.

The reaction mixture was purified via silica gel chromatography in 89:10:1

hexanes/EtOAc/Et$_3$N, resulting in the isolation of 236 mg of **4.7a** as a tan solid (93% yield) (R$_f$ = 0.34

in hexanes/EtOAc 90:10 v/v); mp: 175-176 ºC; IR (KBr) 2980, 2841, 2407, 1948, 1917, 1587, 1567,

1470, 1431, 1263, 1221, 1175, 1138, 933, 774, 754 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.26–7.15

(comp., 4H), 7.12–6.96 (comp., 4H), 6.16 (s, 1H), 4.55 (d, J = 16.6 Hz, 1H), 3.94 (d, J = 16.6 Hz, 1H),

3.31–3.15 (comp., 2H), 2.90–2.77 (comp, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 134.9, 134.8, 133.1,

129.2, 128.0, 127.9, 127.0, 126.6, 126.4, 126.2, 126.1, 124.2, 67.1, 57.8, 43.7, 28.8; m/z (ESI–MS)

254.2 [M+H]$^+$.

(±)-2,3,3a,9-Tetrahydro-1H-benzo[e]pyrrolo[2,1-b][1,3]thiazine (4.7b):   Following general
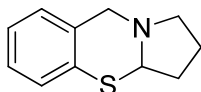
procedure A, compound **4.7b** was obtained from the reaction between

thiosalicylaldehyde[1] and pyrrolidine at 60 ºC for 3.5 h. The reaction mixture was

purified via silica gel chromatography in 89:10:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of

122 mg of **4.7b** as an orange solid (64% yield) (R$_f$ = 0.38 in hexanes/EtOAc 85:15 v/v); mp: IR (KBr)

3289, 3958, 2929, 2838, 1586, 1566, 1468, 1468, 1432, 1344, 1259, 1230, 1135, 1063, 991, 919, 873,

742, 609 cm^{-1}; 51-53 ºC; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.20–6.91 (comp, 4H), 5.10–4.84 (m, 1H),

4.27 (d, J = 15.9 Hz, 1H), 3.88 (d, J = 16.0 Hz, 1H), 2.97–2.86 (m, 1H), 2.78 (app q, J = 8.4 Hz, 1H),

2.39–2.26 (m, 1H), 2.16–2.00 (m, 1H), 2.00–1.86 (comp, 2H); ^{13}C NMR (75 MHz, CDCl₃) δ 134.8, 128.1, 127.5, 126.8, 124.1, 67.2, 51.6, 49.1, 32.5, 21.8; *m/z* (ESI–MS) 192.0 [M+H]⁺.

(±)-5a,6,7,8,9,11-Hexahydrobenzo[e]pyrido[2,1-b][1,3]thiazine (4.7c): Following general procedure A, compound **4.7c** was obtained from the reaction between thiosalicylaldehyde[1] and piperidine at 90 °C for 32 h. The reaction mixture was purified via silica gel chromatography in 89:10:1 hexanes/EtOAc/Et₃N, resulting in the isolation of 118 mg of **4.7c** as a yellow solid (58% yield) (R$_f$ = 0.28 in hexanes/EtOAc 90:10 v:v); mp: 106-107 °C; IR (KBr) 3269, 2941, 2412, 1586, 1564, 1465, 1431, 1279, 1188, 1123, 1037, 829, 742, 679, 650, 566 cm⁻¹; ^{1}H NMR (500 MHz, CDCl₃) δ 7.12–6.88 (comp, 4H), 5.29–5.22 (m, 1H), 4.29 (d, *J* = 16.4 Hz, 1H), 3.74 (d, *J* = 16.4 Hz, 1H), 2.76 (app td, *J* = 11.2, 3.9 Hz, 1H), 2.51 (app dt, *J* = 11.2, 3.7 Hz, 1H), 2.03 (app tt, *J* = 13.3, 4.1 Hz, 1H), 1.95–1.50 (comp., 5H); ^{13}C NMR (75 MHz, CDCl₃) δ 133.8, 127.9, 127.0, 126.7, 126.4, 123.7, 64.8, 58.4, 45.9, 29.9, 25.2, 18.1; *m/z* (ESI–MS) 206.2 [M+H]⁺.
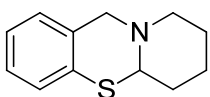
(±)-6,7,8,9,10,12-Hexahydro-5aH-benzo[5,6][1,3]thiazino[3,2-a]azepine (4.7d): Following general procedure A, compound **4.7d** was obtained from the reaction between thiosalicylaldehyde[1] and azepane at 60 °C for 14 h. The reaction mixture was purified via silica gel chromatography in 89:10:1 hexanes/EtOAc/Et₃N, resulting in the isolation of 154 mg of **4.7d** as a brown oil (70% yield) (R$_f$ = 0.51 in hexanes/EtOAc 80:10 v/v); IR (KBr) 3058, 2930, 2850, 1714, 1587, 1566, 1438, 1354, 1260, 1203, 1145, 1085, 955, 745, 673, 581 cm⁻¹; ^{1}H NMR (500 MHz, CDCl₃) δ 7.14–6.91 (comp, 4H), 5.20 (app t, *J* = 7.3 Hz, 1H), 4.22 (d, *J* = 16.2 Hz, 1H), 3.83 (d, *J* = 16.2 Hz, 1H), 3.04–2.88 (m, 1H), 2.45 (app dt, *J* = 14.3, 4.0 Hz, 1H), 2.41–2.25 (m, 1H), 1.94–1.83 (m, 1H), 1.83–1.59 (comp, 5H), 1.47–1.27 (m, 1H); ^{13}C NMR (75 MHz, CDCl₃) δ 135.4, 128.1, 127.7, 127.1, 126.7, 123.5, 69.4, 59.6, 47.6, 36.0, 29.6, 29.4, 23.2; *m/z* (ESI–MS) 220.2 [M+H]⁺.
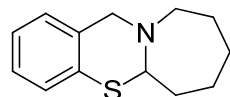
(±)-3,4,6,11a-Tetrahydro-1H-benzo[5,6][1,3]thiazino[2,3-c][1,4]oxazine (4.7e): Following general
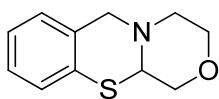
procedure B, compound **4.7e** was obtained from the reaction between thiosalicylaldehyde[1] and morpholine at 120 °C for 10 min. The reaction mixture was purified via silica gel chromatography in 74:25:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 120 mg of **4.7e** as a white solid (58% yield) (R_f = 0.14 in hexanes/EtOAc 85:15 v/v); mp: 140-142 °C; IR (KBr) 3853, 3675, 3649, 3628, 2889, 2849, 2360, 2340, 1558, 1540, 1521, 1506, 1456, 1436, 1142, 1122, 1098, 1007, 746, 657 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.14–6.93 (comp, 4H), 4.95 (s, 1H), 4.28 (d, J = 16.5 Hz, 1H), 3.98–3.91 (comp, 2H), 3.83–3.65 (comp, 3H), 3.04 (app td, J = 11.3, 3.4 Hz, 1H), 2.43–2.36 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 133.0, 128.0, 127.2, 127.1, 125.9, 124.2, 68.7, 66.7, 63.1, 57.6, 45.8; m/z (ESI–MS) 207.3 [M+H]$^+$.

(±)-3,4,6,11a-Tetrahydro-1H-benzo[e][1,4]thiazino[3,4-b][1,3]thiazine (4.7f): Following general
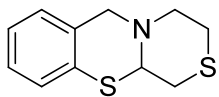
procedure B, compound **4.7f** was obtained from the reaction between thiosalicylaldehyde[1] and thiomorpholine at 150 °C for 15 min. The reaction mixture was purified via silica gel chromatography in 79:20:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 152 mg of **4.7f** as a white solid (68% yield) (R_f = 0.28 in hexanes/EtOAc 80:20 v/v); mp: 158-159 °C; IR (KBr) 3267, 3057, 2948, 2841, 2432, 1712, 1588, 1467, 1423, 1377, 1283, 1257, 1228, 1185, 1110, 951, 744, 737, 648 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.14–7.04 (comp, 2H), 7.06–6.91 (comp, 2H), 5.33–5.29 (m, 1H), 4.31 (d, J = 16.6 Hz, 1H), 3.71 (d, J = 16.6 Hz, 1H), 3.44–3.34 (m, 1H), 3.17–3.08 (m, 1H), 3.05–2.93 (m, 1H), 2.78–2.70 (m, 1H), 2.67–2.60 (m, 1H), 2.57–2.50 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 133.0, 127.9, 127.4, 127.0, 126.1, 124.1, 63.0, 59.5, 46.5, 32.1, 27.7; m/z (ESI–MS) 224.9 [M+H]$^+$.

(±)-2-Phenyl-1,2,3,4,6,11a-hexahydrobenzo[e]pyrazino[2,1-b][1,3]thiazine **(4.7g):** Following general procedure B, compound **4.7g** was obtained from the reaction between thiosalicylaldehyde[1] and 1-phenylpiperazine at 120 °C for 10 min. The reactio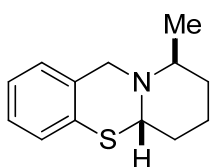n mixture was purified via silica gel chromatography in 84:15:1 hexanes/EtOAc/Et$_3$N, resulting in isolation of 117 mg of **4.7g** as a brown solid (41 % yield) (R$_f$ = 0.25 in hexanes/EtOAc 85:15 v/v); mp: 117–119 °C; IR (KBr) 3053, 2824, 1597, 1501, 1437, 1247, 1225, 1173, 1074, 1037, 1013, 923, 825, 741, 688, 523, 514 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37–7.17 (comp, 2H), 7.16–6.78 (comp, 7H), 5.23–5.15 (m, 1H), 4.36 (d, J = 16.5 Hz, 1H), 3.85 (d, J = 16.5 Hz, 1H), 3.63–3.58 (comp., 2H), 3.32 (dd, J = 12.9, 3.0 Hz, 1H), 3.18 (app td, J = 11.0, 3.1 Hz, 1H), 3.05 (app td, J = 11.2, 3.1 Hz, 1H), 2.70–2.62 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 150.7, 133.3, 129.0, 128.8, 127.8, 127.0, 126.8, 125.9, 123.8, 119.8, 116.2, 63.2, 57.3, 52.8, 48.1, 45.9;. m/z (ESI–MS) 282.8 [M+H]$^+$.
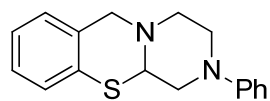
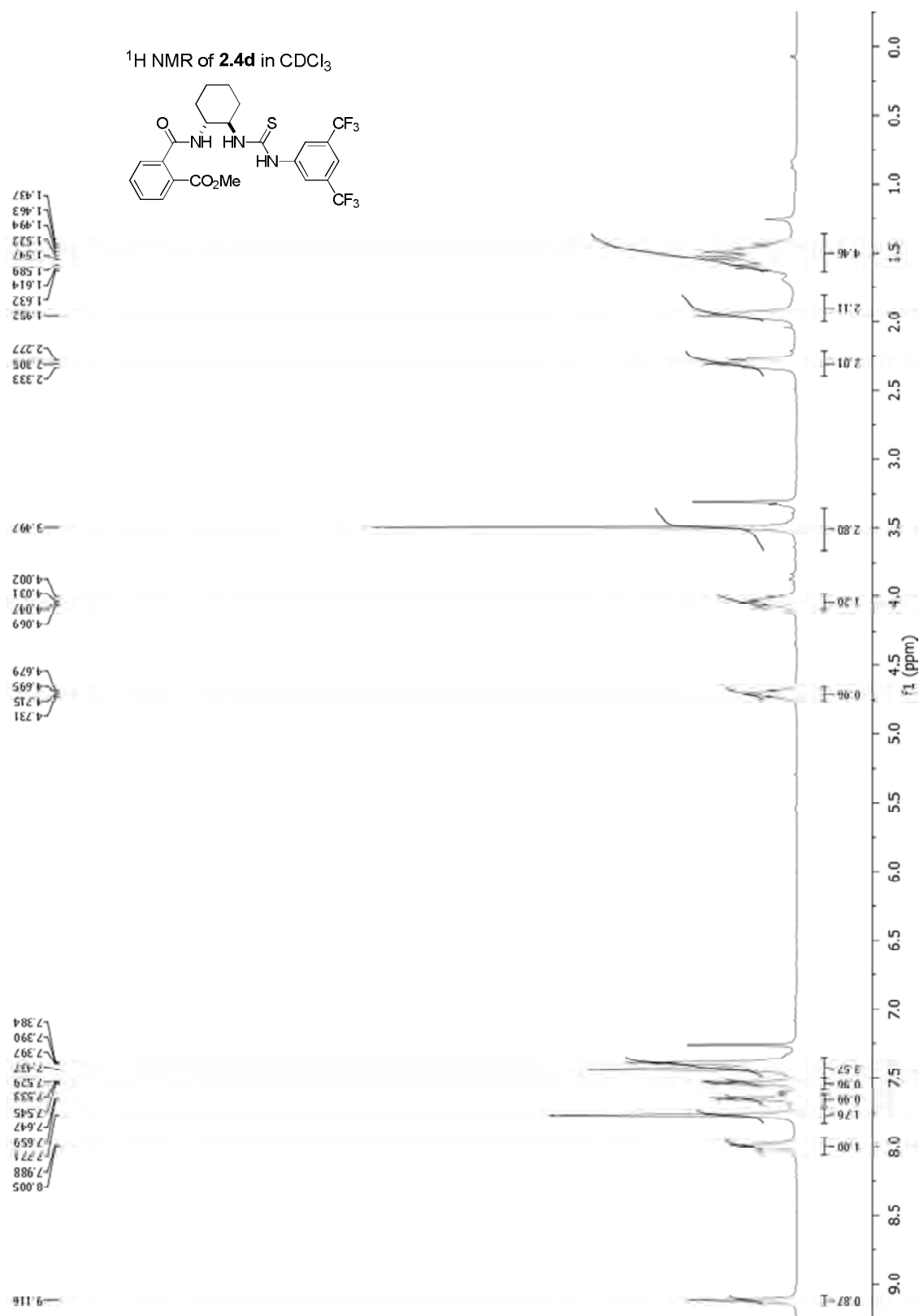**(±)-2-Methyl-1,2,3,4,6,11a-hexahydrobenzo[e]pyrazino[2,1-b][1,3]thiazine** **(4.7h):** Following general procedure B, compound **4.7h** was obtained from the reaction between thiosalicylaldehyde[1] and N-methyl piperazine at 150 °C for 15 min. The reaction mixture was purified by silica gel chromatography in 29:70:1 hexanes/EtOAc/Et$_3$N, resulting in isolation of 172 mg of **4.7h** as an orange solid (78% yield) (R$_f$ = 0.17 in hexanes/EtOAc 30:70 v/v); mp: 92–93 °C; IR (KBr) 3854, 3822, 3736, 3651, 3054, 2974, 2935, 2854, 2781, 1712, 1587, 1458, 1437, 1340, 1315, 1279, 1162, 1072, 1018, 658 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.07–6.98 (comp, 2H), 6.97–6.88 (comp, 2H), 5.02 (s, 1H), 4.24 (d, J = 16.4 Hz, 1H), 3.73 (d, J = 16.4 Hz, 1H), 3.00 (app td, J = 11.2, 2.9 Hz, 1H), 2.82–2.72 (comp, 2H), 2.57–2.41 (comp, 2H), 2.35–2.21 (comp, 4H).; ^{13}C NMR (75 MHz, CDCl$_3$) δ 133.5, 127.7, 127.0, 126.7, 125.9, 123.7, 62.9, 58.1, 57.2, 54.5, 45.9, 45.8; m/z (ESI–MS) 222.1 [M+H]$^+$.
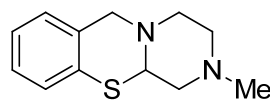
(±)-3-Benzyl-2-phenyl-3,4-dihydro-2H-benzo[e][1,3]thiazine (4.7i): Following general procedure B, compound **4.7i** was obtained from the reaction between thiosalicylaldehyde[1] and dibenzylamine at 150 ºC for 15 min. The reaction mixture was purified by silica gel chromatography in 94:5;1 hexanes/EtOAc/Et₃N, resulting in isolation of 242 mg of **7i** as a yellow solid (76% yield) (R$_f$ = 0.39 in hexanes/EtOAc 95:5 v/v); mp: 98-100 ºC; IR (KBr) 3855, 3753, 3676, 3085, 3028, 2926, 2773, 1948, 1870, 1069, 975, 905, 862, 714, 965 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.64 (app d, J = 7.6 Hz, 2H), 7.40–7.21 (comp, 9H), 7.20–7.15 (m, 1H), 7.08–7.01 (m, 1H), 6.92 (app d, J = 7.3 Hz, 1H), 5.75 (s, 1H), 3.92–3.72 (comp, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 140.3, 138.3, 133.0, 129.0, 128.5, 128.4, 128.3, 127.9, 127.8, 127.2(7), 127.2(5), 126.9, 124.3, 69.4, 54.6, 50.1; m/z (ESI–MS) 318.8 [M+H]⁺.
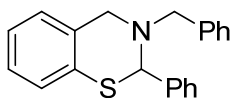
(±)-2,3-Dimethoxy-5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline **(4.7j):** Following the general procedure A, compound **4.7j** was obtained from the reaction between thiosalicylaldehyde[1] and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[2] at 60 °C for 30 min. The reaction mixture was purified via silica gel chromatography in 78:20:2 hexanes/EtOAc/Et₃N, resulting in the isolation of 301.6 mg of **4.7j** as a white solid (96% yield) (R$_f$ = 0.25 in hexanes/EtOAc 60:40 v/v); mp: 163–164 ºC; IR (KBr) 3056, 2995, 2926, 2840, 1609, 1519, 1459, 1327, 1271, 1259, 1144, 1100, 1036, 1014, 740, 639 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.09 (app td, J = 7.3, 2.1 Hz, 1H), 7.06–6.97 (comp, 3H), 6.68–6.62 (comp, 2H), 6.09 (s, 1H), 4.68–4.40 (m, 1H), 4.05–3.92 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.35–3.01 (comp, 2H), 2.95–2.60 (comp, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 148.7, 147.5, 134.9, 128.0, 127.0, 126.8, 126.6, 126.5, 125.2, 124.1, 111.6, 109.0, 67.1, 57.8, 56.0, 55.9, 43.8, 28.5; m/z (ESI–MS) 314.1 [M+H]⁺.
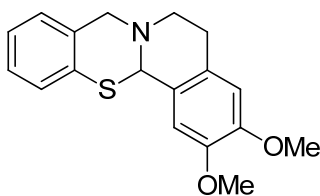
(±)-3-Methoxy-5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline (4.7k): Following the general procedure A, compound **4.7k** was obtained from the reaction between thiosalicylaldehyde[1] and 6-methoxy-1,2,3,4-tetrahydro-isoquinoline[3] at 60 °C for 30 min. The reaction mixture was purified via silica gel chromatography in 79:20:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of 262.9 mg of **4.7k** as a white solid (93% yield) (R_f = 0.29 in hexanes/EtOAc 80:20 v/v); mp: 130–131 ºC; IR (KBr) 2999, 2944, 2906, 2850, 1607, 1560, 1502, 1468, 1431, 1383, 1323, 1265, 1249, 1067, 1035, 905, 860, 821, 763, 663 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.13–7.05 (comp, 2H), 7.05–6.95 (comp, 3H), 6.74 (dd, J = 8.4, 2.7 Hz, 1H), 6.69 (d, J = 2.6 Hz, 1H), 6.12 (s, 1H), 4.74–4.26 (comp, 2H), 3.79 (s, 3H), 3.36–3.04 (comp, 2H), 3.00–2.71 (comp, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 158.89, 134.91, 134.39, 127.78, 127.18, 127.14, 126.75, 126.38, 126.33, 123.90, 113.69, 112.06, 66.77, 57.64, 55.01, 43.38, 28.91.; *m/z* (ESI–MS) 284.2 [M+H]$^+$.
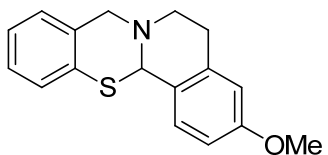
(±)-6,7,9,14a-Tetrahydro-5H-benzo[c]benzo[5,6][1,3]thiazino[3,2-a]azepine (4.7l): Following general procedure A, compound **4.7l** was obtained from the reaction between thiosalicylaldehyde[1] and 2,3,4,5-tetrahydro-1H-benzo[c]azepine[4] at 60 ºC for 1 h. The reaction mixture was purified via silica gel chromatography in 84:15:1 hexanes/EtOAc/Et$_3$N, resulting in isolation of 219 mg of **4.7l** as a brown solid (82% yield) (R_f = 0.31 in hexanes/EtOAc 95:15 v/v); mp: 110 – 113 ºC; IR (KBr) 3048, 2917, 2846,1587, 1560, 1465, 1316, 1108, 1105, 1068, 1035, 980, 871, 848, 769, 738, 662, 612 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.18–6.86 (comp, 8H), 6.06 (s, 1H), 4.55 (d, *J* = 16.7 Hz, 1H), 3.79 (d, *J* = 16.7 Hz, 1H), 3.45–3.27 (comp, 2H), 2.91–2.78 (m, 1H), 2.70 (app dd, *J* = 14.9, 6.9 Hz, 1H), 2.00–1.88 (m, 1H), 1.76 (app q, *J* = 12.1 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 142.78, 136.55, 134.14, 130.26, 130.15, 128.44, 128.30, 127.27, 126.84, 126.59, 126.14, 124.33, 74.55, 61.38, 52.25, 34.73, 28.80; *m/z* (ESI–MS) 268.8 [M+H]$^+$.
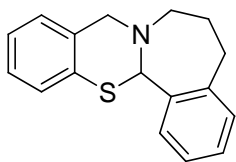
(±)-7,8,13,13b-Tetrahydro-5H-benzo[5',6'][1,3]thiazino[3',2':1,2]pyrido[3,4-b]indole **(4.7m):**
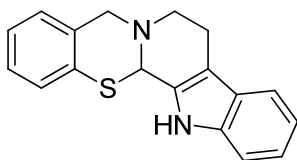
Following the general procedure, compound **4.7m** was obtained from the reaction between thiosalicylaldehyde[1] and triptoline at 60 °C for 6 h. The reaction mixture was purified via silica gel chromatography in 78:20:2 hexanes/EtOAc/Et₃N, resulting in the isolation of 234.4 mg of **4.7m** as a yellow solid (80% yield) (R_f = 0.21 in hexanes/EtOAc 80:20 v/v); mp: 197–199 ºC; IR (KBr) 3397, 2151, 3056, 2919, 2843, 1478, 1466, 1449, 1437, 1367, 1338, 1319, 1186, 1165, 1109, 1067, 748, 731 cm^{-1}; ^{1}H NMR (500 MHz, CDCl₃) δ 7.86 (s, 1H), 7.51 (app d, J = 7.9 Hz, 1H), 7.34 (app d, J = 8.1 Hz, 1H), 7.23–7.17 (m, 1H), 7.16–7.03 (comp, 5H), 6.10 (s, 1H), 4.49 (d, J = 16.2 Hz, 1H), 3.97 (d, J = 16.2 Hz, 1H), 3.26–3.12 (m, 1H), 3.06–2.79 (comp, 3H); ^{13}C NMR (125 MHz, CDCl₃) δ 136.4, 134.4, 131.5, 128.4, 128.2, 127.2, 127.1, 126.6, 124.6, 122.5, 119.8, 118.8, 111.2, 109.1, 62.7, 57.6, 45.5, 21.6; *m/z* (ESI–MS) 293.2 [M+H]$^+$.

(±)-13a-Phenyl-5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline (4.7n): Following the general procedure, compound **4.7n** was obtained from the reaction between thiosalicylaldehyde[1] and 1-phenyl-1,2,3,4-tetrahydroisoquinoline[5] at 60 °C for 1 h. The reaction mixture was purified via silica gel chromatography in 94:5:1 hexanes/EtOAc/Et₃N, resulting in the isolation of 242.5 mg of **4.7n** as a white solid (75% yield) (R_f = 0.55 in hexanes/EtOAc 80:20 v/v); mp: 146–148 ºC; IR (KBr) 3060, 2948, 2892, 1589, 1569, 1486, 1468, 1431, 1320, 1260, 1194, 1147, 1120, 1068, 1035, 827, 740, 700, 674 cm^{-1}; ^{1}H NMR (500 MHz, CDCl₃) δ 7.74 (app d, J = 6.8 Hz, 2H), 7.36–7.20 (comp, 3H), 7.20–7.06 (comp, 4H), 7.06–6.95 (comp, 2H), 6.92 (app d, J = 7.4 Hz, 1H), 6.64 (app d, J = 7.8 Hz, 1H), 3.97 (d, J = 17.2 Hz, 1H), 3.61 (d, J = 17.2 Hz, 1H), 3.49–3.36 (comp, 2H), 3.10–2.97 (m, 1H), 2.94–2.82 (m, 1H); ^{13}C NMR (125 MHz, CDCl₃) δ 145.3, 140.5, 134.2, 132.2, 129.5, 128.7, 128.1, 127.9, 127.8, 127.6, 127.0, 126.9, 126.8, 126.2, 126.0, 124.0, 80.0, 53.6, 47.1, 29.5; *m/z* (ESI–MS) 330.2 [M+H]$^+$.
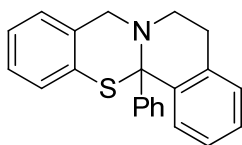
(±)-10-Methyl-5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline (4.7o): Following general procedure A, compound **4.7o** was obtained from the reaction between 5-methylthiosalicylaldehyde[6] and 1,2,3,4-tetrahydroisoquinoline at 60 °C for 30 min. The reaction was purified by silica gel chromatography in 89:10:1 hexanes/EtOAc /Et$_3$N, resulting in isolation of 232 mg of **4.7o** as a tan solid (87% yield) (R$_f$ = 0.32 in hexanes/EtOAc 90:10 v/v); mp: 167-169 °C; IR (KBr) 3448, 3034, 2957, 2928, 2887, 2848, 1629, 1483, 1474, 1383, 1321, 1144, 1125, 947, 814, 725, 685, 661, 629, 614 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30–7.12 (comp, 4H), 7.00–6.86 (comp, 3H), 6.14 (s, 1H), 4.53 (d, J = 16.6 Hz, 1H), 3.91 (d, J = 16.6 Hz, 1H), 3.34–3.13 (comp, 2H), 2.85–2.27 (comp., 2H), 2.29 (s, 3H);. ^{13}C NMR (75 MHz, CDCl$_3$) δ 134.9, 133.8, 133.0, 131.1, 129.2, 128.6, 127.9, 127.8, 126.4, 126.2, 126.1, 126.0, 66.9, 57.8, 43.7, 28.8, 20.9; m/z (ESI–MS) 268.6 [M+H]$^+$.

(±)-11-Methoxy-5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline (4.7p): Following general procedure A, compound **4.7p** was obtained from the reaction between 4-methoxythiosalicylaldehyde[7] and 1,2,3,4-tetrahydroisoquinoline at 60 °C for 30 min. The reaction was purified by silica gel chromatography in 89:10:1 hexanes/EtOAc /Et$_3$N, resulting in isolation of 175 mg of **7p** as a tan solid (62% yield) (R$_f$ = 0.29 in hexanes/EtOAc 90:10 v/v); mp: 145–146 °C; IR (KBr) 2996, 2962, 2929, 2840, 1594, 1488, 1359, 1344, 1263, 1233, 1119, 1006, 836, 814, 747, 659 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.29–7.11 (comp, 4H), 6.95 (d, J = 8.3 Hz, 1H), 6.71–6.53 (comp, 2H), 6.15 (s, 1H), 4.55–4.42 (m, 1H), 3.98–3.83 (m, 1H), 3.74 (s, 3H), 3.30–3.10 (comp, 2H), 2.93–2.74 (comp, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 158.3, 135.9, 134.6, 133.1, 129.2, 128.9, 127.9, 126.3, 126.1, 118.4, 111.0, 110.9, 67.2, 57.2, 55.3, 43.6, 28.7; m/z (ESI–MS) 284.7 [M+H]$^+$.
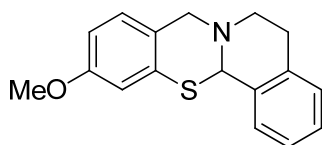
(±)-10-Nitro-5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline (4.7q): Following general procedure A, compound **4.7q** was obtained from the reaction between 5-nitrothiosalicylaldehyde[8] and 1,2,3,4-tetrahydroisoquinoline at 60 °C for 30 min. The reaction was purified by silica gel chromatography in 84:15:1 hexanes/EtOAc /Et₃N, resulting in isolation of 173 mg of **4.7q** as a tan solid (57% yield) (R_f = 0.45 in hexanes/EtOAc 85:15 v/v); mp: 193–195 °C; IR (KBr) 3081, 2953, 2848, 1596, 1571, 1330, 1301, 1128, 954, 936, 911, 862, 808, 756, 743, 718, 655, 537 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.98–7.88 (comp, 2H), 7.31–7.07 (comp, 5H), 6.27 (s, 1H), 4.31 (br s, 2H), 2.98 (br s, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 145.8, 143.95, 133.7, 132.9, 129.3, 128.4, 127.0, 126.5, 126.4, 126.1, 122.9, 122.0, 68.6, 57.6, 43.7, 28.6; *m/z* (ESI–MS) 299.3 [M+H]⁺.
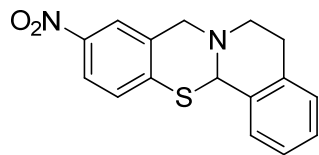
(±)-1-Methyl-2,3,3a,9-tetrahydro-1H-benzo[e]pyrrolo[2,1-b][1,3]thiazine (4.7r): Following general procedure A, compound **4.7r** was obtained from the reaction between thiosalicylaldehyde[1] and 2-methyl pyrrolidine at 60 °C for 1.5 h. The reaction mixture was purified by silica gel chromatography in 89:10:1 hexanes/EtOAc/Et₃N, resulting in isolation of 83 mg of **4.7r** as a yellow oil (40% yield). Relative stereochemistry was determined by GCOSY and NOESY NMR. (R_f = 0.44 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3463, 2962, 1705, 1647, 1439, 1373, 1232, 1136, 1068, 1038, 954, 912, 744, 668, 580, 502 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.19–6.95 (comp, 4H), 5.17 (app d, *J* = 5.9, 1H), 4.23 (d, *J* = 16.0 Hz, 1H), 3.83 (d, *J* = 16.0 Hz, 1H), 2.96–2.83 (m, 1H), 2.39–2.29 (app ddt, m, 1H), 2.26–2.17 (m, 1H), 1.93–1.80 (m, 1H), 1.50 (dddd, *J* = 12.3, 10.3, 7.3, 4.5 Hz, 1H), 1.14 (d, *J* = 6.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 135.8, 128.4, 128.1, 127.5, 126.9, 124.1, 68.9, 53.7, 49.4, 30.8, 30.7, 18.9; *m/z* (ESI–MS) 206.4 [M+H]⁺.
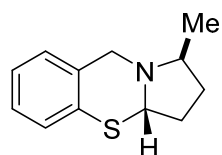
In addition, 70 mg of **4.7s** was isolated as a yellow oil (34% yield) (R_f = 0.32 in hexanes/EtOAc 90:10
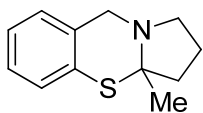
v/v); IR (KBr) 3057, 2968, 2925, 2846, 1590, 1567, 1476, 1438, 1371, 1341, 1317, 1188, 1069, 1028, 936, 744, 668, 555 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.16–6.92 (comp, 4H), 4.43–4.19 (m, 1H), 4.01–3.79 (m, 1H), 3.08–2.91 (m, 1H), 2.83–2.63 (m, 1H), 2.18–1.97 (comp, 2H), 1.95–1.84 (comp, 2H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 134.5, 128.1, 127.6, 126.7, 126.4, 123.7, 74.8, 50.7, 47.6, 40.9, 29.2, 19.8; *m/z* (ESI–MS) 206.8 [M+H]$^+$.

(±)-9-Methyl-5a,6,7,8,9,11-hexahydrobenzo[e]pyrido[2,1-b][1,3]thiazine (4.7t): Following general

procedure A, compound **4.7t** was obtained from the reaction between thiosalicylaldehyde[1] and 2-methyl piperidine at 90 ºC for 13 h. The reaction mixture was purified by silica gel chromatography in 89:10:1 hexanes/EtOAc/Et$_3$N, resulting in the isolation of a mixture of 153 mg of **7t** (70% yield) and 42 mg of **4.6u** (19% yield) as a yellow solid. Relative stereochemistry of **7t** was determined by GCOSY and NOESY NMR. Characterization data for **7t**: (R_f = 0.28 in hexanes/EtOAc 90:10 v/v); mp: 74–77 ºC; IR (KBr) 3433, 3068, 2976, 2939, 2837, 1571, 1563, 1432, 1372, 1257, 1207, 1157, 1134, 1083, 1070, 741, 677 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.13–6.87 (comp, 4H), 5.46–5.39 (m, 1H), 4.15 (d, *J* = 16.4 Hz, 1H), 4.02 (d, *J* = 16.5 Hz, 1H), 2.69–2.58 (m, 1H), 2.01 (dddd, *J* = 26.0, 16.7, 13.1, 9.4 Hz, 2H), 1.81–1.70 (m, 1H), 1.68–1.54 (comp, 2H), 1.41–1.24 (m, 1H), 1.05 (d, *J* = 6.5, Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 135.5, 127.9, 126.9, 126.8(4), 126.8(2), 126.0, 123.6(9), 123.6(7), 66.7, 54.4, 47.1, 34.1, 31.5, 30.4, 19.8, 19.2, 14.1; *m/z* (ESI–MS) 220.2 [M+H]$^+$.

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¹H NMR of **2.4d** in CDCl₃

^{13}C NMR of **2.4d** in CDCl$_3$

^{1}H NMR of 2.4**e** in CDCl$_3$

^{13}C NMR of **2.4e** in CDCl$_3$

24.997
25.207

34.434
32.608

55.944
56.851

67.760

110.154

117.302
122.427
124.244
127.204
128.090
128.526
129.042
129.918
130.034
131.495
132.026
134.804
136.328
140.939

167.753
170.230

181.585

f1 (ppm)

^{1}H NMR of **2.4f** in CDCl$_3$

^{13}C NMR of **2.4f** in CDCl$_3$

34.944
25.323

32.378
32.513

56.090
56.824
60.916
61.210
61.503
61.797

117.560
121.607
122.025
122.172
123.813
124.195
126.010
126.366
127.424
127.746
130.400
131.016
131.310
131.472
131.743
132.000
133.003
136.969
140.244

166.878

170.009

181.503

^{1}H NMR of **2.4g** in CDCl$_3$

^{13}C NMR of **2.4g** in CDCl$_3$

24.769
25.092

32.158
32.870

55.535
56.960

117.524
121.844
122.339
122.692
124.014
124.517
126.761
126.815
126.833
126.890
127.015
127.631
130.755
130.872
131.198
131.404
133.629
137.140
134.221
140.402

169.224

181.591

F1 (ppm)

^{1}H NMR of **2.4h** in CDCl$_3$

149

^{13}C NMR of **2.4h** in CDCl$_3$

^{1}H NMR of **2.4i** in CDCl$_3$

1.412
1.432
1.459
1.527
1.554
1.580
1.618
1.976
1.991
2.044
2.284
2.298
2.302
2.413

3.911
3.923
3.940
3.958

4.649
4.663
4.677
4.701

7.351
7.366
7.526
7.571

7.864
7.881

8.298
8.311
8.492
8.511
8.587
8.731

^{13}C NMR of **2.4i** in CDCl$_3$

^{1}H NMR of **2.4j** in CDCl$_3$

1.380
1.407
1.432
1.457
1.476
1.496
1.514
1.539
1.566
1.590
1.960
1.971
1.990
2.265
2.290
2.314
2.333

3.945
3.953
3.968
3.975
3.985
3.991
4.006
4.014
4.696
4.715
4.735
4.755

7.415
7.514
7.626
7.722
7.739

8.379
8.400
8.482
8.789

f1 (ppm)

^{13}C NMR of **2.4j** in CDCl$_3$

^{1}H NMR of **2.4k** in CDCl$_3$

^{13}C NMR of **2.4k** in CDCl$_3$

24.722
24.702

32.425
32.346

65.790
57.005

116.000
116.319
121.627
121.764
122.515
123.702
123.011
123.833
129.999
127.578
127.609
127.636
127.657
127.727
127.969
127.802
127.643
131.670
131.396
131.003
134.536
134.808
135.220
139.084

167.022

181.402

^{1}H NMR of **2.4l** in CDCl$_3$

Peak labels (right side, rotated):
1.366, 1.397, 1.425, 1.461, 1.477, 1.491, 1.514, 1.892, 1.935, 1.955, 2.286, 2.311, 2.350, 2.374

3.926, 3.946, 3.962, 3.984

4.015, 4.639, 4.655, 4.675

7.481, 7.534, 7.571, 7.587, 7.609, 7.619, 7.773, 7.789, 7.844, 7.860, 7.888

8.900

Integration (ppm axis): 4.32 (~1.5), 2.44 (~2.0), 2.31 (~2.5), 1.15 (~4.0), 1.07 (~4.5), 1.00, 3.83, 1.00, 1.94 (~7.5–8.0), 1.08 (~9.0)

f1 (ppm)

^{13}C NMR of **2.4l** in CDCl$_3$

29.484
24.641

31.266
32.407

55.675
57.409

118.082
121.828
123.570
123.992
124.103
128.526
128.032
130.011
130.234
130.426
131.092
131.358
131.629
131.891
132.790
140.035

165.607

181.939

^{1}H NMR of **2.4n** in CDCl$_3$

1.192
1.224
1.246
1.254
1.283
1.361
1.390
1.418
1.703
1.733
1.758
1.782

2.194
2.216

3.259
3.267
3.282
3.289
3.304
3.313

4.444
4.460
4.465
4.502

6.460
6.477

6.755

7.675
7.825

8.007

8.298

4.60
1.47
1.05
1.06
1.10
1.03
0.84
1.00
1.91
1.01
2.20

^{13}C NMR of **2.4n** in CDCl$_3$

24.239
24.434

31.994
32.518

57.790
59.342

119.823
119.880
121.360
121.615
123.439
123.702
124.968
126.168
130.036
132.689
132.822
133.096

138.279

141.354

181.460

^{1}H NMR of **2.5a** in CDCl$_3$

MeO

N

O

CO$_2$Me

^{13}C NMR of **2.5a** in CDCl$_3$

50.014
52.140
55.502

66.002

114.413
126.593
127.852
128.044
128.169
128.369
128.584
128.698
128.861
129.396
132.333
132.787
134.669
136.967

160.404

163.890

169.680

f1 (ppm)

¹H NMR of **2.5b** in CDCl₃

^{13}C NMR of **2.5b** in CDCl$_3$

21.333

51.921
53.087

65.140

130.587
128.030
128.061
130.535
129.734
129.886
132.595
137.962
136.996
139.311
139.872

163.601

171.300

f1 (ppm)

^{1}H NMR of **2.5c** in CDCl$_3$

3.642

4.853
4.865

5.327
5.339

6.975
6.989
7.077
7.094
7.162
7.176
7.192
7.316
7.331
7.344
7.474
7.487
7.503
7.528
7.540
7.558

8.280
8.296

^{13}C NMR of **2.5c** in CDCl$_3$

99.976
52.081

65.532

110.181
126.316
127.030
127.555
128.022
128.192
128.413
128.609
128.742
128.819
128.846
128.904
129.113
129.185
132.689
136.734
137.777
138.463
140.089

163.602

169.300

^{1}H NMR of **2.5ca** in $(CD_3)_2SO$

^{13}C NMR of **2.5ca** in (CD$_3$)$_2$SO

49.183

64.108

127.579
127.070
127.299
127.404
127.040
128.090
128.429
128.883
129.172
130.231
132.350
134.542
137.024
140.357

162.093

170.365

^{1}H NMR of **2.5d** in CDCl$_3$

^{1}H NMR of **2.5e** in CDCl$_3$

^{13}C NMR of **2.5e** in CDCl$_3$

49.654
52.096
55.888

60.747

65.075

104.581

126.709
127.788
127.820
128.082
128.996
128.474
129.207
129.409
132.130
132.605
137.155
137.390

159.206

161.707

169.439

^{1}H NMR of **2.5f** in CDCl$_3$

^{13}C NMR of **2.5f** in CDCl$_3$

49.979
51.956
52.683

60.563

126.741
127.309
127.424
128.161
128.332
128.589
128.462
128.709
128.906
128.996
129.053
132.222
137.106
138.599

164.096

170.981

^{1}H NMR of **2.5g** in CDCl$_3$

^{13}C NMR of **2.5g** in CDCl$_3$

29.002

51.098
52.072

59.534

127.385
127.743
127.886
128.099
128.320
128.418
131.392
131.487
131.888
138.070

164.537

170.106

^{1}H NMR of **2.5ga** in CDCl$_3$

13C NMR of **2.5ga** in CDCl$_3$

29.044

50.628

58.709
59.807

127.344
128.140
128.204
128.667
129.293
131.180
131.239
133.350
134.309
136.363

164.916

173.483

^{1}H NMR of **2.5gb** in CDCl$_3$

^{13}C NMR of **2.5gb** in CDCl$_3$

^{1}H NMR of **2.5gc** in CDCl$_3$

3.462

4.046
4.056

5.185
5.196

5.970

7.297
7.311
7.337
7.354
7.398
7.415
7.486
7.500
7.514
7.516
7.520
7.524
7.536
7.538
7.550
8.210
8.224

2.91

1.02

1.00

1.06

1.10
1.91
1.87
2.03

1.02

^{13}C NMR of **2.5gc** in CDCl$_3$

^{1}H NMR of **2.5h** in CDCl$_3$

3.657
3.710
3.768

4.976
4.888

5.236
5.248

6.669
6.686
6.810
6.828
6.870
6.904
7.020
7.046
7.467
7.470
7.472
7.484
7.489
7.515
7.518
7.531
8.280
8.296

^{13}C NMR of **2.5h** in CDCl$_3$

^{1}H NMR of **2.5i** in CDCl$_3$

^{13}C NMR of **2.5i** in CDCl$_3$

^{1}H NMR of **2.5j** in CDCl$_3$

2.242

3.661
3.700

4.887
4.899

5.256
5.268

6.805
6.822
6.848
6.862
6.879
6.966
7.041
7.058
7.461
7.464
7.467
7.483
7.504
7.507
7.520

8.280
8.296

^{13}C NMR of **2.5j** in CDCl$_3$

50.030
52.134
55.506

65.294

114.398

127.678
127.861
128.114
128.332
128.815
129.318
129.454
132.611
132.828
133.842
134.766
138.425

158.455

163.920

169.733

^{1}H NMR of **2.5k** in CDCl$_3$

2.187

3.649
3.749

4.890
4.902

5.257
5.269

6.763
6.775
6.790
6.808
7.023
7.038
7.046
7.056
7.457
7.469
7.472
7.488
7.506
7.507
7.511
7.526

8.277
8.294

3.34

3.07
3.19

1.07

1.14

4.00

3.66

3.20

1.00

f1 (ppm)

^{13}C NMR of **2.5k** in CDCl$_3$

21.377

49.871
51.930
55.300

65.833

114.233
124.699
127.752
128.003
128.143
128.306
128.384
128.590
129.179
129.329
132.552
132.750
134.454
136.543
137.964

158.332

164.006

169.527

f1 (ppm)

^{1}H NMR of **2.5l** in CDCl$_3$

3.660
3.685
3.755

4.848
4.859

5.908
5.919
6.716
6.730
6.747
6.764
6.795
6.813
7.016
7.032
7.084
7.102
7.155
7.172
7.181
7.218
7.234
7.442
7.455
7.470
7.474

8.264
8.281

8.89
1.00
1.10
2.07
1.95
1.01
2.00
1.13
1.15
2.13
1.07

^{13}C NMR of **2.5l** in CDCl$_3$

49.777
51.807
55.325
57.746

110.074
114.099
120.475
124.623
127.034
127.831
127.897
128.541
128.639
129.288
129.368
132.389
133.393
134.714

156.620
158.081

164.324

169.922

^{1}H NMR of **2.5m** in CDCl$_3$

3.725
3.788

4.910
4.921

5.542
5.553

6.669
6.672
6.676
6.679
6.778
6.785
6.788
6.796
6.852
6.870
7.077
7.090
7.096
7.505
7.517
7.561
7.573
7.576
7.681
7.697

8.255
8.274

2.80
3.06

0.99

1.00

0.98
1.05
1.99
2.83

1.33
1.20
1.09

1.16

^{13}C NMR of **2.5m** in CDCl$_3$

49.594
52.206
55.404

62.005

114.382
126.030
126.196
127.579
127.855
128.205
128.286
128.941
132.618
132.692

139.358

158.600

163.435

169.117

^{1}H NMR of **2.5n** in CDCl$_3$

3.760
3.792

4.763
4.774

5.365
5.376

5.954
5.960
6.169
6.173
6.176
6.179

6.860
6.878
7.109
7.127
7.205
7.457
7.459
7.529
7.531
7.542
7.545
7.549

8.231
8.248

2.91
2.94

1.00

1.01

0.93
1.07

1.99

1.99
0.93
1.39
2.13

0.99

f1 (ppm)

^{13}C NMR of **2.5n** in CDCl$_3$

^{1}H NMR of **2.5o** in CDCl$_3$

^{13}C NMR of **2.5o** in CDCl$_3$

28.883

40.180
51.367
52.070

58.837

109.788

123.428
127.090
127.777
128.112
131.299
131.730
132.143

140.362
142.493

164.849

169.852

^{1}H NMR of **2.5oa** in CDCl$_3$

¹³C NMR of **2.5oa** in CDCl₃

49.902
50.753
52.315

108.869

123.022
127.063
128.893
128.910
132.299
135.210
137.391
190.114
141.164

165.658

169.815

^{1}H NMR of **2.5p** in CDCl$_3$

3.766
3.803

4.550
4.560
4.838
4.848
4.855
4.866

6.150
6.167
6.181
6.199
6.379
6.410

6.903
6.920
7.186
7.198
7.201
7.211
7.229
7.233
7.250
7.268
7.509

8.206
8.223

6.28

1.15
1.00

1.09
1.07

2.06
2.28
1.48
1.75
1.06
2.02
1.23

1.00

f1 (ppm)

^{13}C NMR of **2.5p** in CDCl$_3$

49.668
52.259
55.430

64.005

114.365
124.517
126.659
127.405
128.130
128.514
128.763
129.039
129.190
132.333
133.659
133.893
134.331
135.883

158.436

163.692

169.840

^{1}H NMR of **2.5pa** in CDCl$_3$

^{13}C NMR of **2.5pa** in CDCl$_3$

47.606
51.752
52.035
55.534

105.055

114.898
117.604

127.051
127.671
127.825
128.294
128.775
131.923
134.066
134.895
136.811
140.461
144.631

155.990

171.809

186.359

f1 (ppm)

^{1}H NMR of **2.5q** in CDCl$_3$

0.906
0.930
0.935
0.954
0.961
0.969
0.976
0.998
1.023
1.257
1.296
1.315
1.344
1.354
1.498
1.540
1.655
1.669

3.800
3.829

4.266
4.275
4.284

4.638
4.648

6.892
6.910
7.339
7.357
7.412
7.510
7.513
7.526
7.730
7.745

8.089
8.092
8.104
8.107

5.22
2.88
2.09
1.40

6.00

1.00

1.05

2.02

2.11
1.44
1.28
1.08

1.03

^{13}C NMR of **2.5q** in CDCl$_3$

^{1}H NMR of **2.5r** in CDCl$_3$

0.720
0.730
0.734
0.743

2.006
2.022
2.035
2.037
2.044
2.049
2.058
2.062
2.072
2.085

3.812
3.817

4.314
4.323
4.333
4.589
4.599

6.917
6.935
7.340
7.358
7.405
7.420
7.511
7.513
7.696
7.711

8.101
8.116

^{13}C NMR of **2.5r** in CDCl$_3$

19.971
20.921

31.174

42.397

52.205
55.544

66.388

114.180

126.783
128.909
129.556
132.817
134.582

158.156

164.331

170.842

f1 (ppm)

¹H NMR of **2.6a** in CDCl₃

^{13}C NMR of **2.6a** in CDCl$_3$

^{1}H NMR of **2.6b** in CDCl$_3$
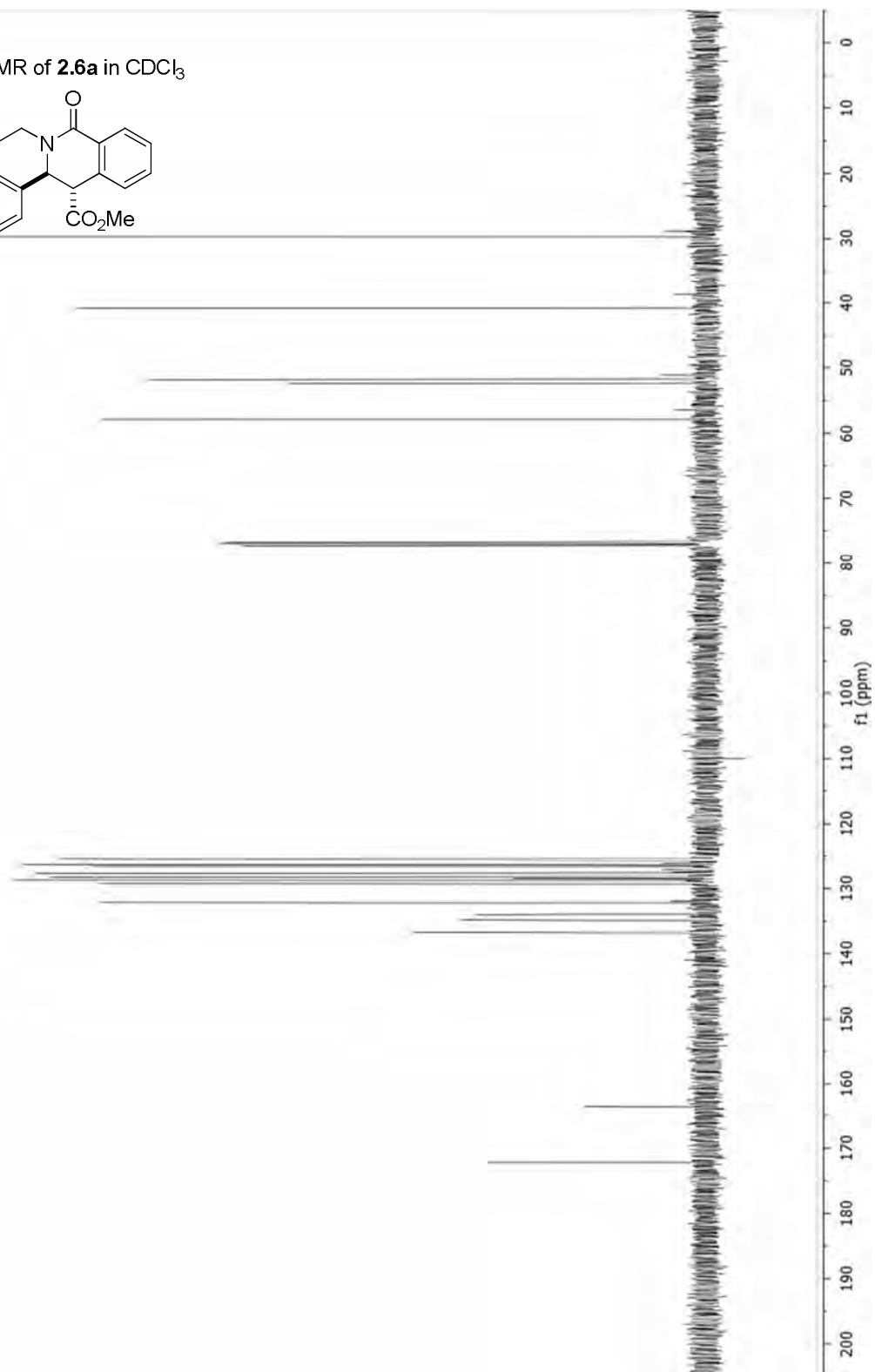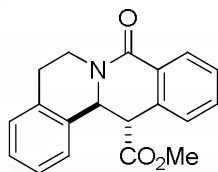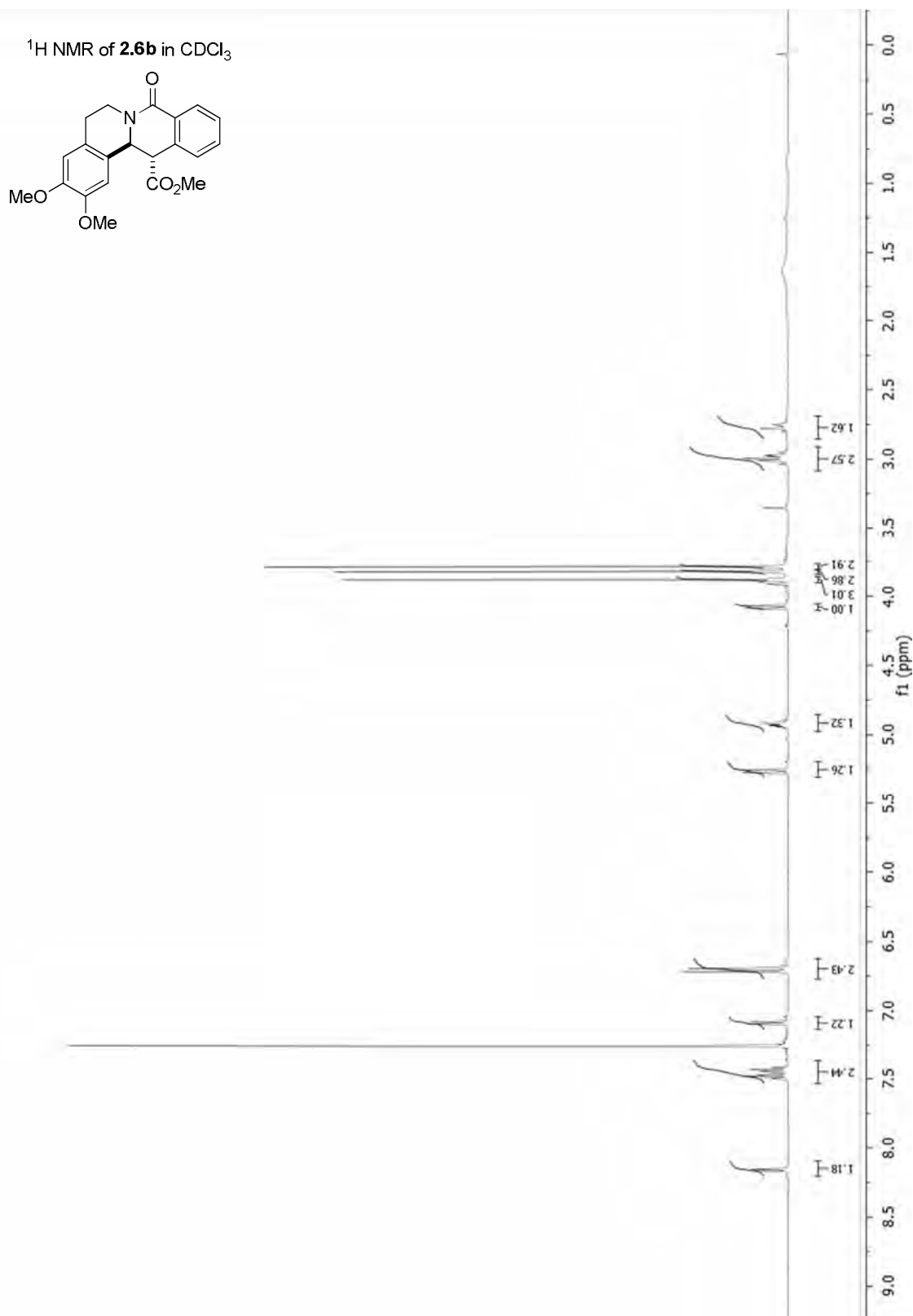
^{13}C NMR of **2.6b** in CDCl$_3$

^{1}H NMR of **2.6c** in CDCl$_3$
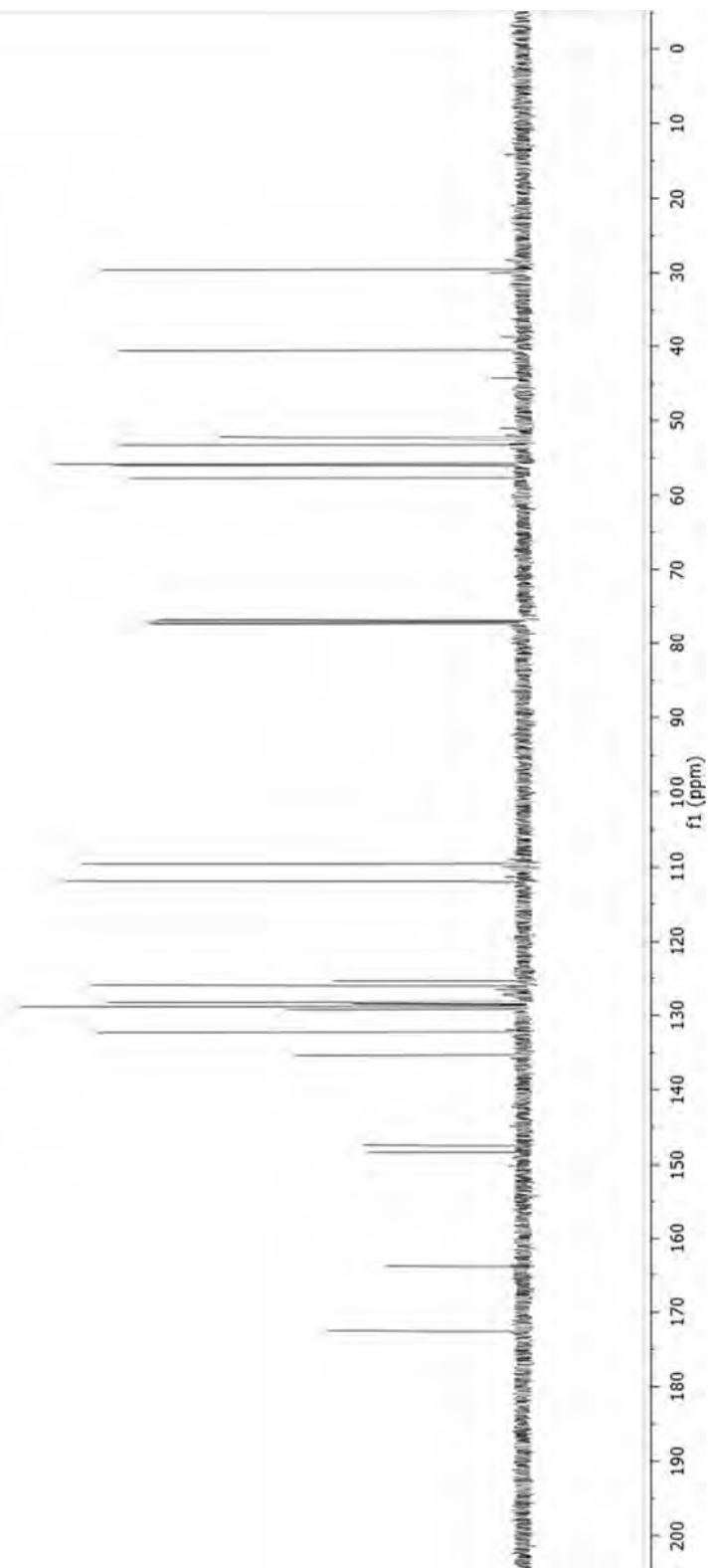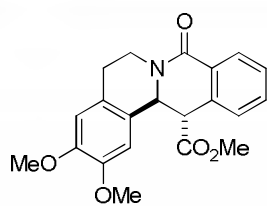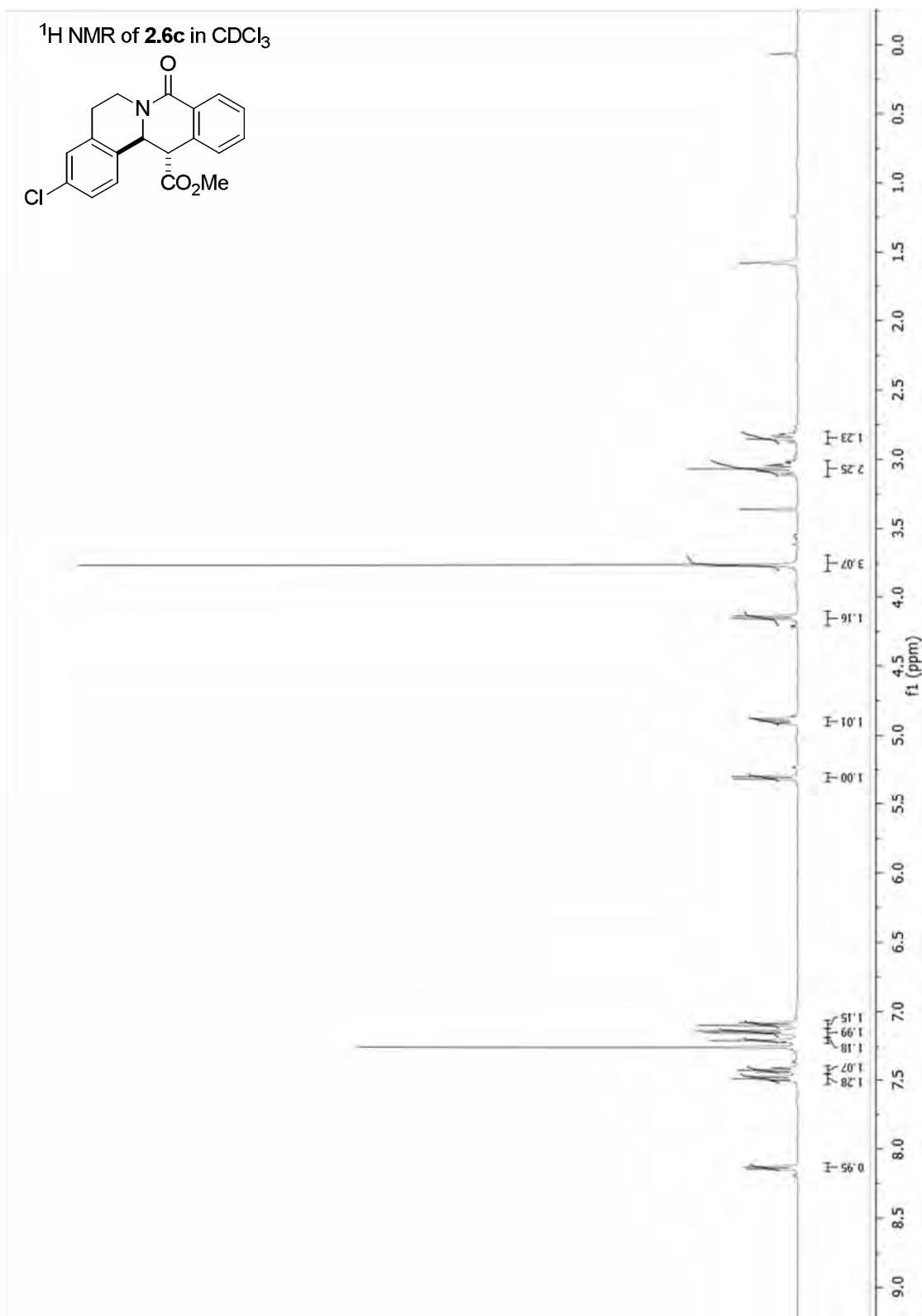
^{13}C NMR of **2.6c** in CDCl$_3$

^{1}H NMR of **2.6d** in CDCl$_3$

^{13}C NMR of **2.6d** in CDCl$_3$

^{1}H NMR of **2.7** in CDCl$_3$

^{13}C NMR of **2.7** in CDCl$_3$

51.691
51.938
57.539

126.315
127.383
128.665
128.711
128.890
129.009
132.660
135.072
137.563

165.778
169.367

^{1}H NMR of **2.8** in CDCl$_3$

^{13}C NMR of **2.8** in CDCl$_3$

57.535
57.741
57.693

126.473
126.337
127.734
128.354
128.623
128.087
130.093
130.095
134.282
139.706

165.151

171.249

220

¹H NMR of **2.9** in CDCl₃

^{13}C NMR of **2.9** in CDCl$_3$

51.678
52.899
55.364

65.108

114.283

126.443
127.889
128.387
128.530
128.797
129.392
129.533
132.173
137.363
139.170
139.137

159.377

163.471

171.150

^{1}H NMR of **3.4a** in CDCl$_3$

3.743

4.034
4.037

5.648
5.651
7.123
7.177
7.210
7.215
7.216
7.219
7.228
7.231
7.237
7.335
7.343
7.435
7.438
7.440
7.445
7.453
7.456

8.244
8.248
8.252
8.253
8.254
8.257
8.262

3.01

1.03

1.00

2.14
1.93
1.87
2.14

0.97

^{13}C NMR of **3.4a** in CDCl$_3$

52.053
53.024

65.003

126.490
126.778
127.105
128.009
128.501
129.118
129.496
129.619
132.599
132.988
139.202
142.918

163.454

171.106

^{1}H NMR of **3.4b** in CDCl$_3$

^{13}C NMR of **3.4b** in CDCl$_3$

57.678
52.099
55.364

66.108

114.283

126.443
127.809
128.307
128.528
128.647
129.307
129.533
132.173
132.262
135.170
139.137

150.277

163.471

171.150

^{1}H NMR of **3.4c** in CDCl$_3$

^{13}C NMR of **3.4c** in CDCl$_3$

^{1}H NMR of **3.4d** in CDCl$_3$

2.316

3.745

4.018
4.021

5.621
5.623

7.131
7.148
7.152
7.164
7.168
7.174
7.189
7.192
7.196
7.208
7.225
7.429
7.433
7.440
7.447
7.451
8.239
8.243
8.252
8.257

^{13}C NMR of **3.4d** in CDCl$_3$

21.172

51.860
53.012

65.076

126.526
126.554
127.965
128.406
128.659
128.806
129.485
129.691
129.765
133.293
137.305
136.899
139.268
139.848

163.500

171.235

^{1}H NMR of **3.4e** in CDCl$_3$

2.254

3.242

4.001
4.004

5.597
5.600
7.032
7.036
7.175
7.183
7.193
7.221
7.228
7.233
7.244
7.326
7.332
7.337
7.435
7.437
7.440
7.445
7.450
7.455

8.232
8.236
8.242
8.244
8.250

231

^{13}C NMR of **3.4e** in CDCl$_3$

^{1}H NMR of **3.4f** in CDCl$_3$

^{13}C NMR of **3.4f** in CDCl$_3$

^{1}H NMR of **3.4g** in CDCl$_3$

^{13}C NMR of **3.4g** in CDCl$_3$

^{1}H NMR of **3.4h** in CDCl$_3$

^{13}C NMR of **3.4h** in CDCl$_3$

49.836
52.943

66.139

126.789
127.591
128.748
128.866
128.526
129.040
129.436
129.487
132.449
132.645
136.949
142.363

149.755

158.934

163.578

171.474

^{1}H NMR of **3.4i** in CDCl$_3$

^{13}C NMR of **3.4i** in CDCl$_3$

^{1}H NMR of **3.4j** in CDCl$_3$

3.737

4.236
4.240

5.682
5.694
6.065
6.071
6.170
6.174
6.177
6.180
7.222
7.229
7.231
7.232
7.235
7.409
7.418
7.420
7.422
7.441
7.496

8.178
8.181
8.193
8.196

2.98

1.00

0.99

0.95
0.97

0.60
0.83
1.05
4.99
1.08

0.97

^{13}C NMR of **3.4j** in CDCl$_3$

91.671
53.055
59.567

120.812
122.226
128.575
128.652
129.144
129.180
129.348
132.423
134.574
142.060
142.436

151.964

163.100

170.610

^{1}H NMR of **3.4k** in CDCl$_3$

3.754

4.128
4.131

5.862
5.603
6.220
6.771
6.773
6.793
6.800
6.808
6.810

7.076
7.078
7.326
7.329
7.342
7.346
7.365
7.379

8.209
8.212
8.224
8.227

^{13}C NMR of **3.4k** in CDCl$_3$

Peak labels (rotated):

51.619
53.197

61.403

125.441
126.350
126.540
127.101
127.424
128.829
128.907
129.211
129.428
129.535
132.644
132.819
141.910
142.426

162.762

170.692

^{1}H NMR of **3.4l** in CDCl$_3$

1.196
1.211
1.225

4.019
4.021
4.164
4.172
4.186
4.200
4.213
4.222
4.235
4.242
4.249

5.644
5.648
5.720
7.183
7.193
7.198
7.203
7.215
7.229
7.241
7.313
7.330
7.340
7.344
7.356
7.429
7.435
7.440
7.443
7.447

8.243
8.248
8.253
8.262

^{13}C NMR of **3.4l** in CDCl$_3$

14.159

52.005

62.017
64.956

126.479
126.641
127.013
127.955
128.451
128.500
128.815
129.052
129.431
129.584
132.416
132.481
139.332
142.093

163.477

170.692

¹H NMR of **3.4n** in CDCl₃

^{13}C NMR of **3.4n** in CDCl$_3$

¹H NMR of **3.5b** in CDCl₃

^{13}C NMR of **3.5b** in CDCl$_3$

29.983

38.811

51.303
52.042
56.622

124.074
126.333
126.891
127.311
127.610
128.848
128.929
129.202
132.109
133.202
134.628
136.309

163.747

169.440

f1 (ppm)

^{1}H NMR of **3.5a** in CDCl$_3$

^{13}C NMR of **3.5a** in CDCl$_3$

13.790
28.902
38.283
51.263
56.670
60.978

126.342
126.832
127.271
127.528
128.750
128.955
129.254
129.290
132.079
133.403
134.758
136.560

163.793
169.101

^{1}H NMR of **3.5c** in CDCl$_3$

^{13}C NMR of **3.5c** in CDCl$_3$

^{1}H NMR of **3.5d** in CDCl$_3$

^{13}C NMR of **3.5d** in CDCl$_3$

¹H NMR of **4.7a** in CDCl₃

^{13}C NMR of **4.7a** in CDCl$_3$

¹H NMR of **4.7b** in CDCl₃
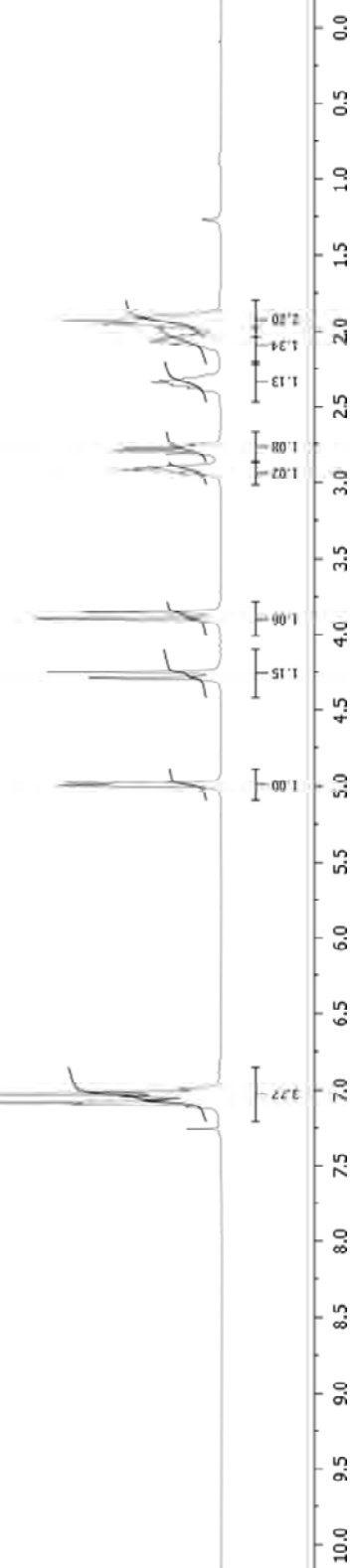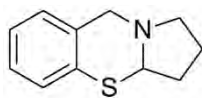
¹³C NMR of **4.7b** in CDCl₃
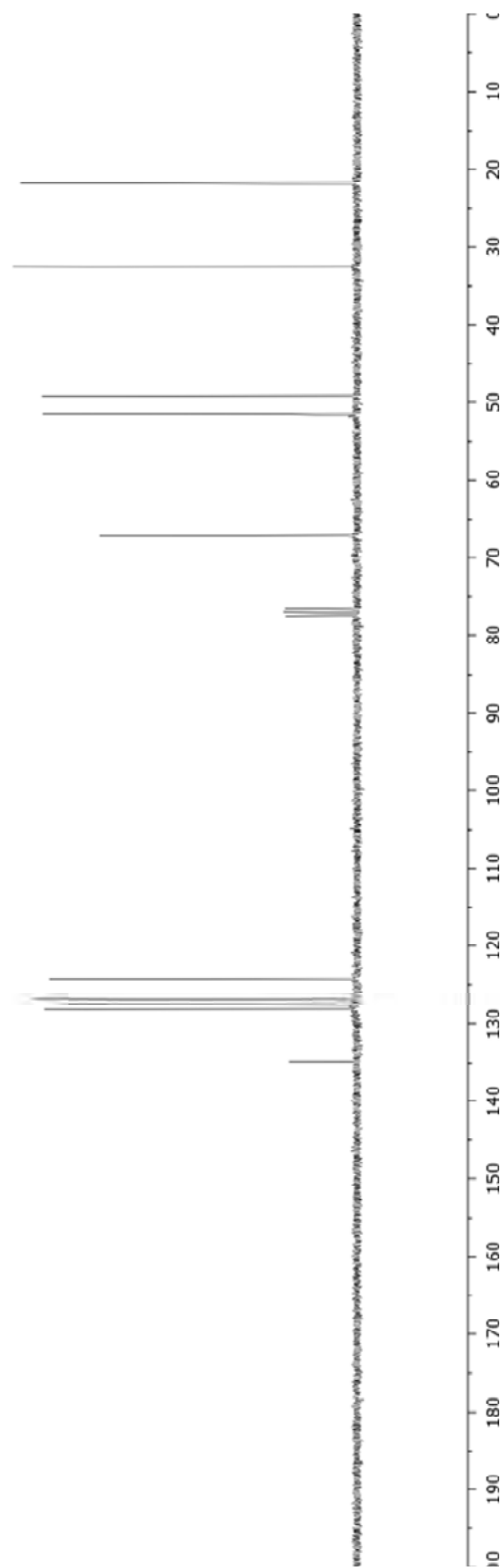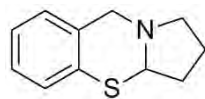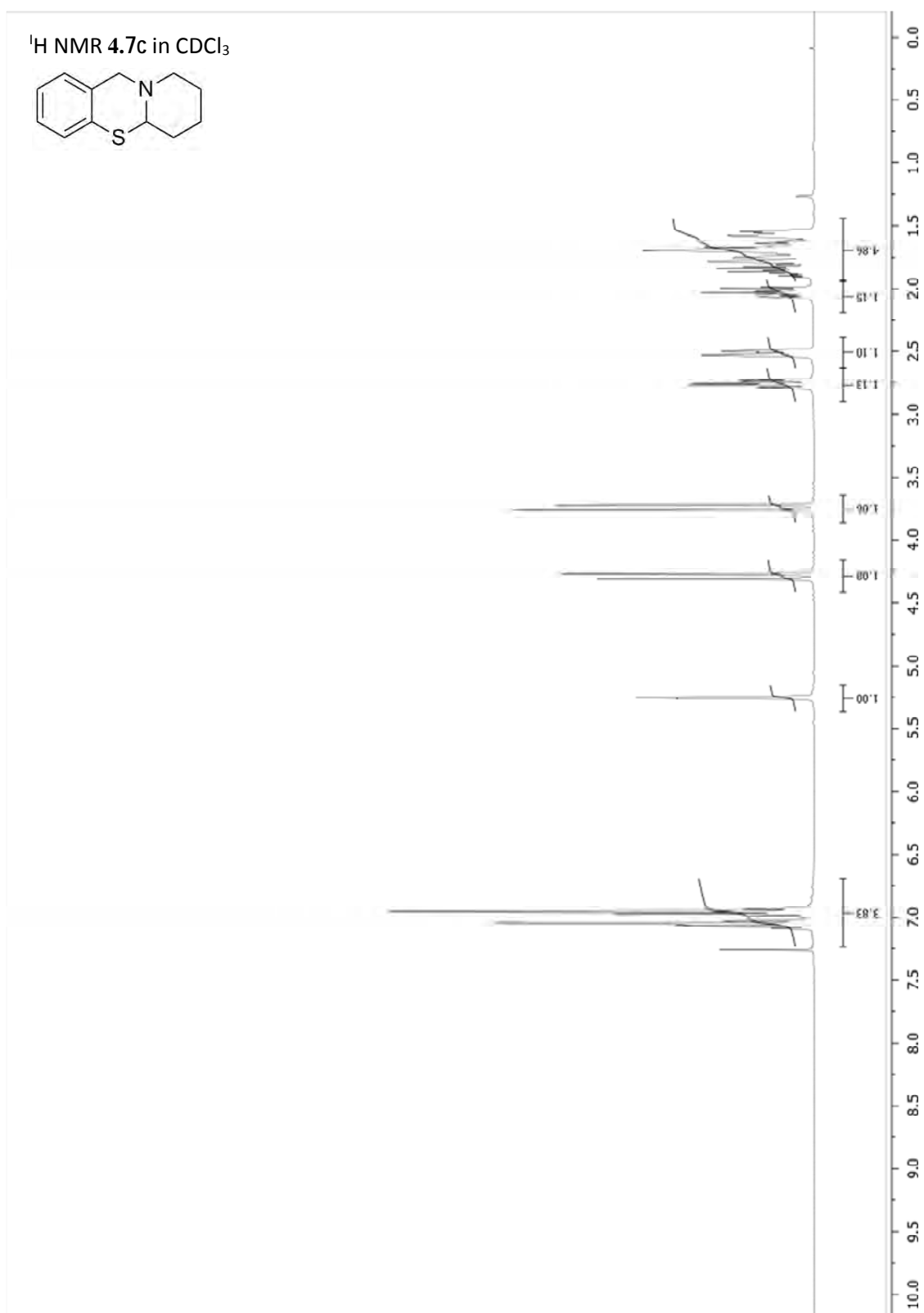
^IH NMR **4.7c** in CDCl₃

^{13}C NMR of **4.7c** in CDCl$_3$
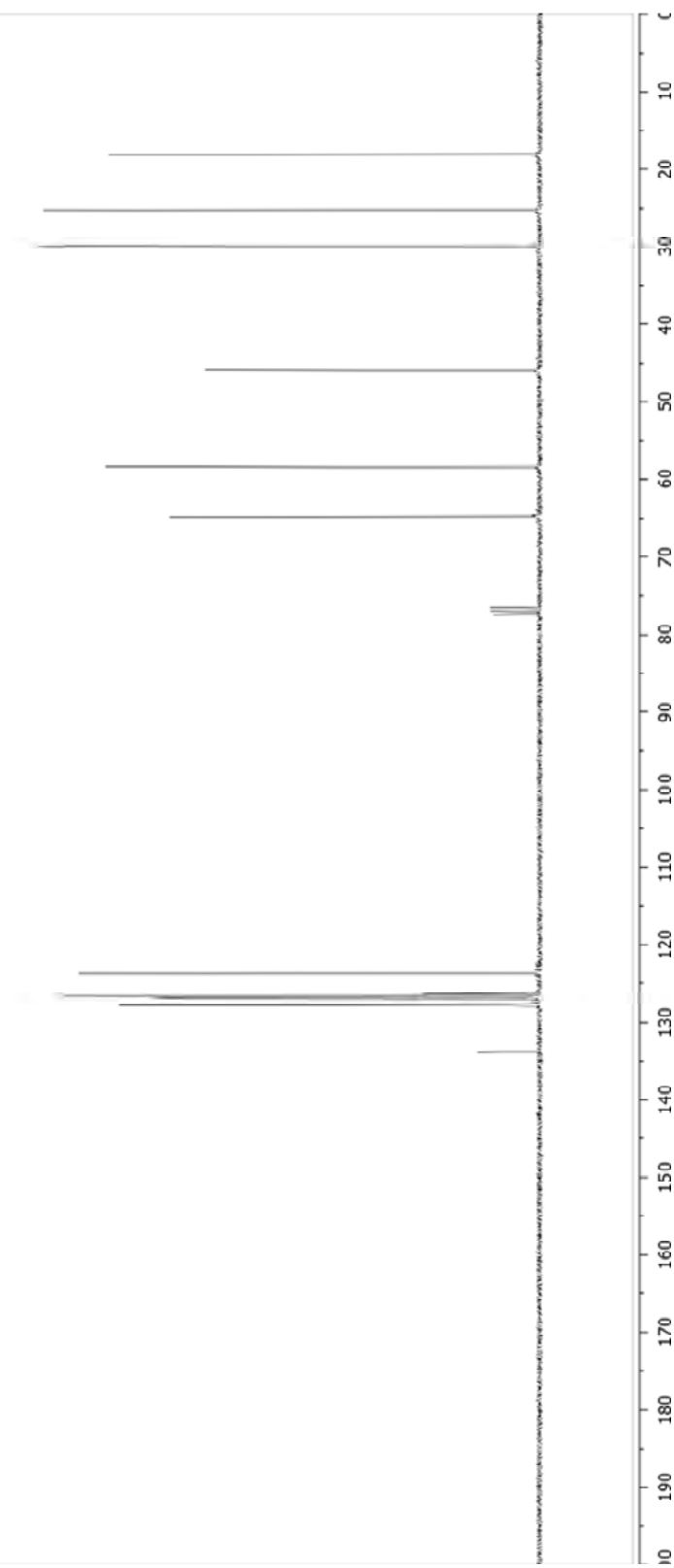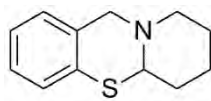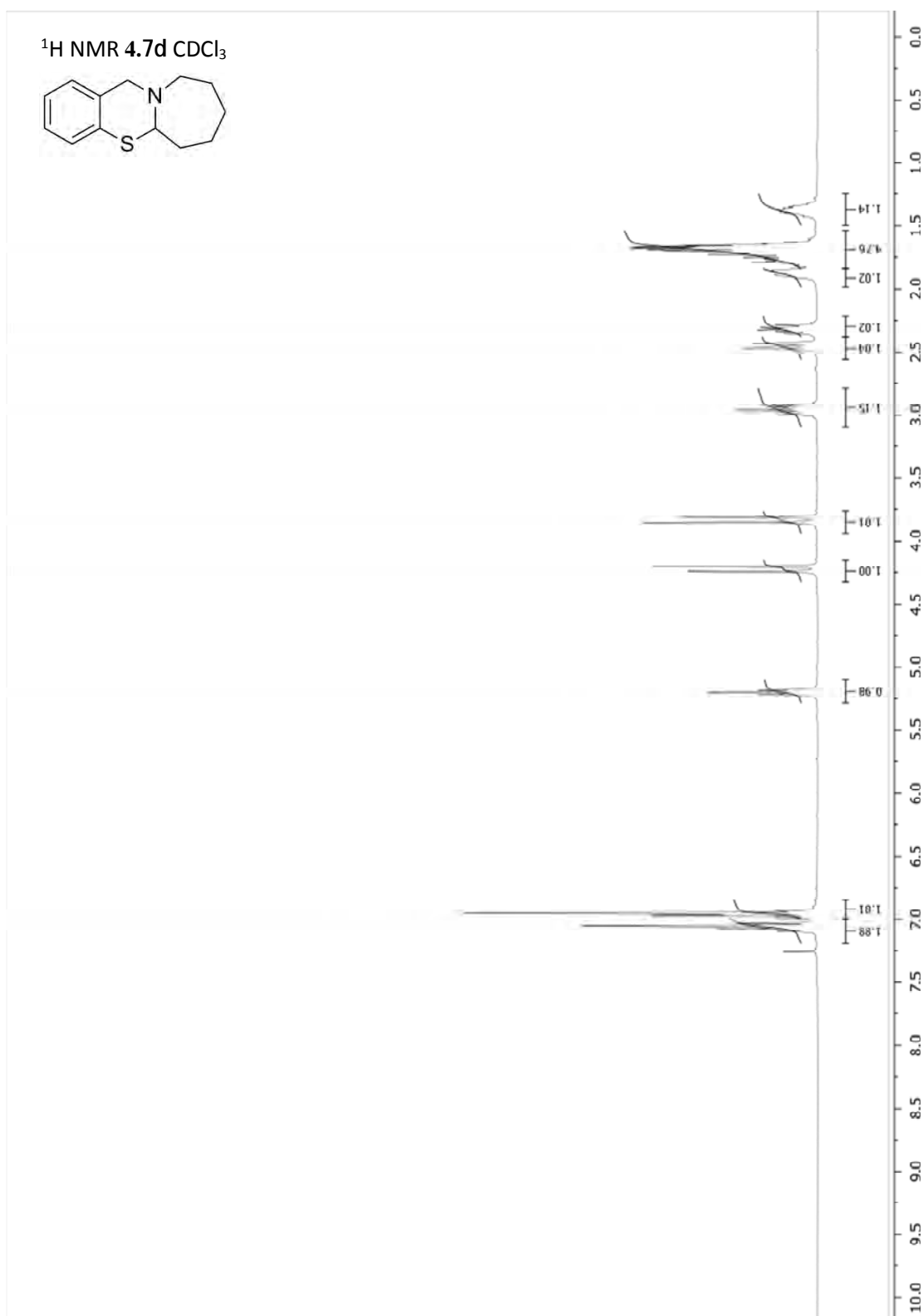
^{1}H NMR **4.7d** CDCl$_3$

¹³C NMR of **4.7d** in CDCl₃
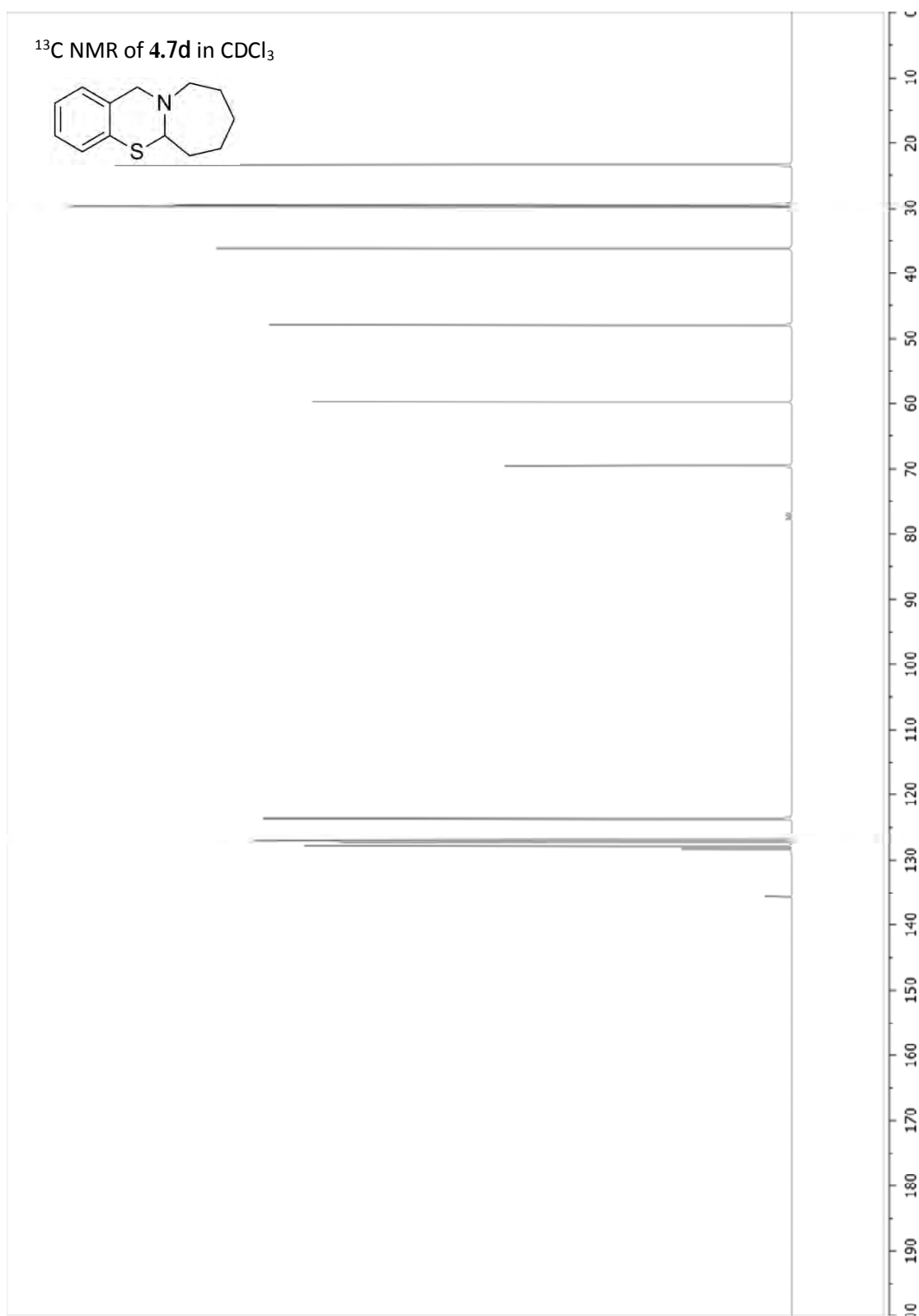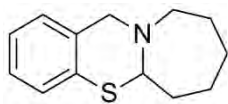
¹H NMR **4.7**e in CDCl₃
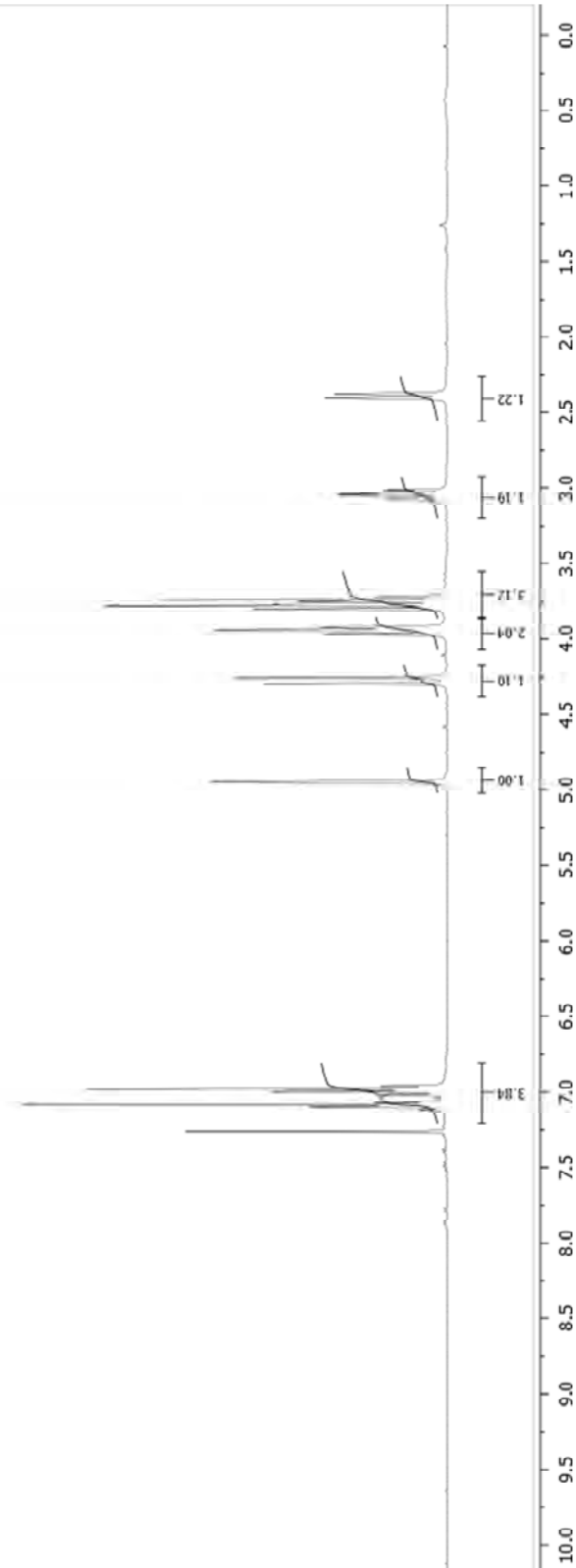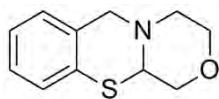
^{13}C NMR of **4.7e** in CDCl$_3$
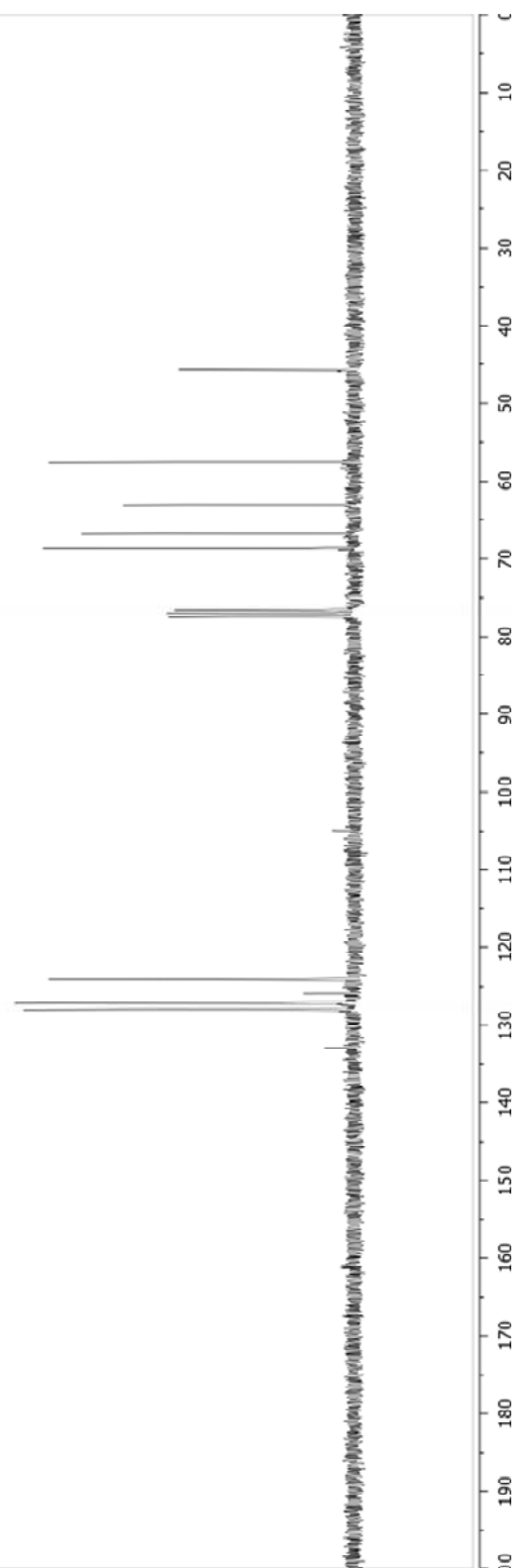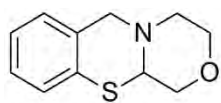
¹H NMR **4.7f** in CDCl₃
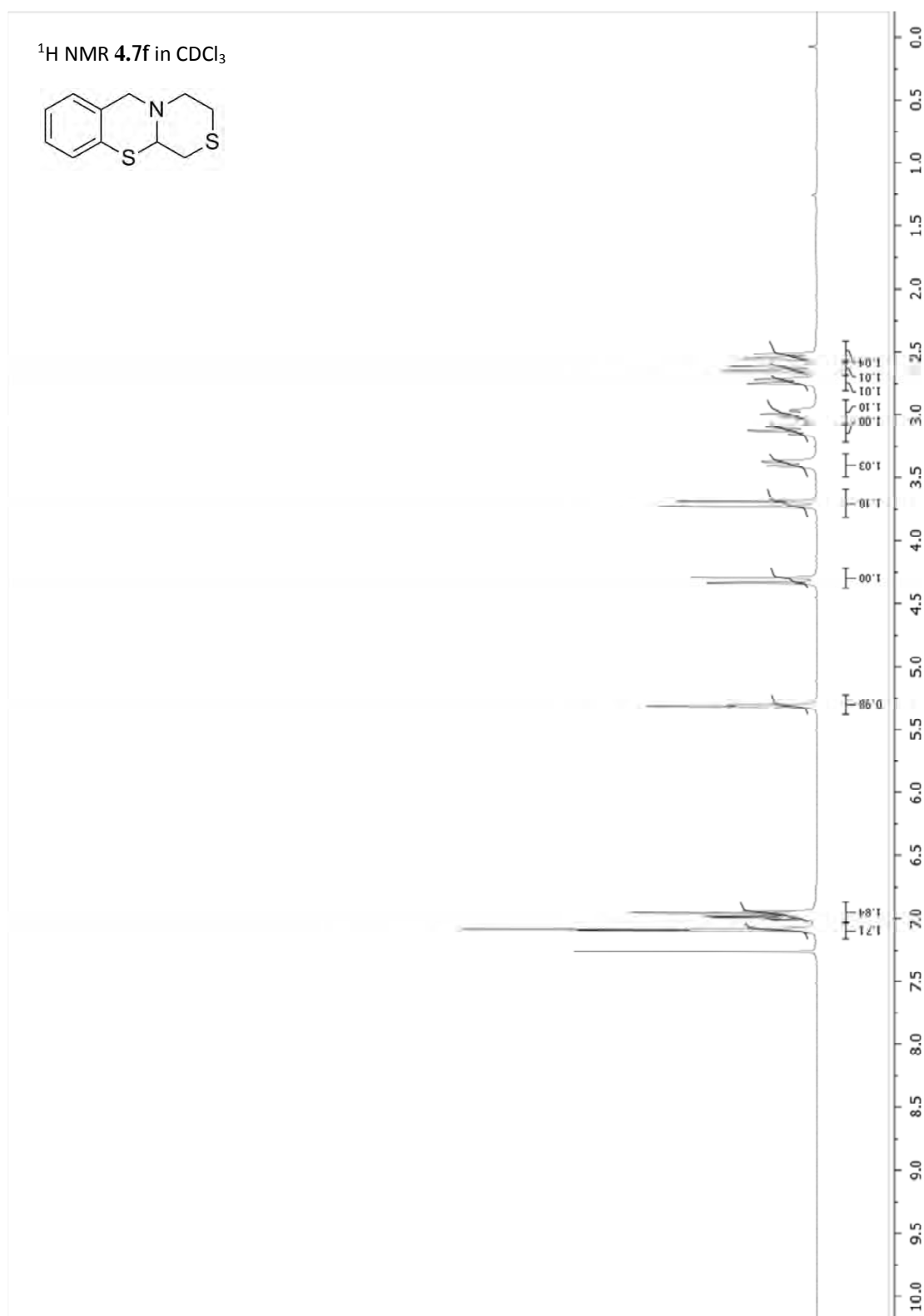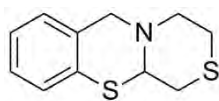
^{13}C NMR of **4.7f** in CDCl$_3$
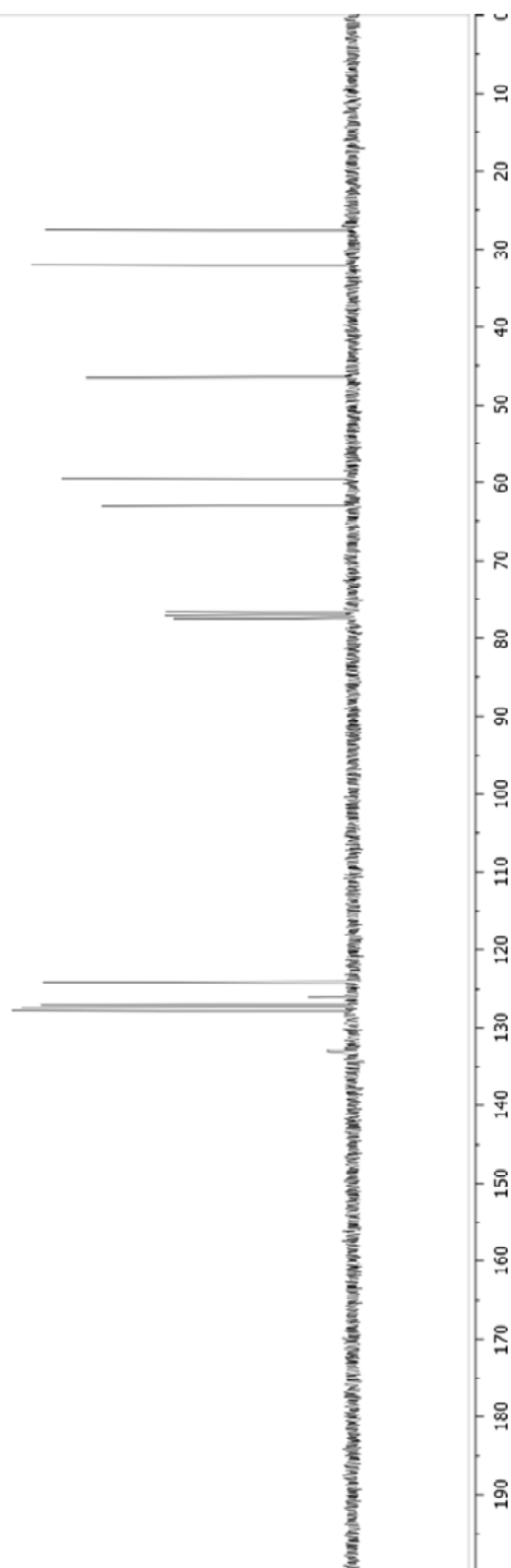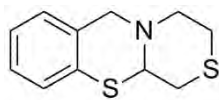
¹H NMR **4.7g** in CDCl₃

^{13}C NMR of **4.7g** in CDCl$_3$
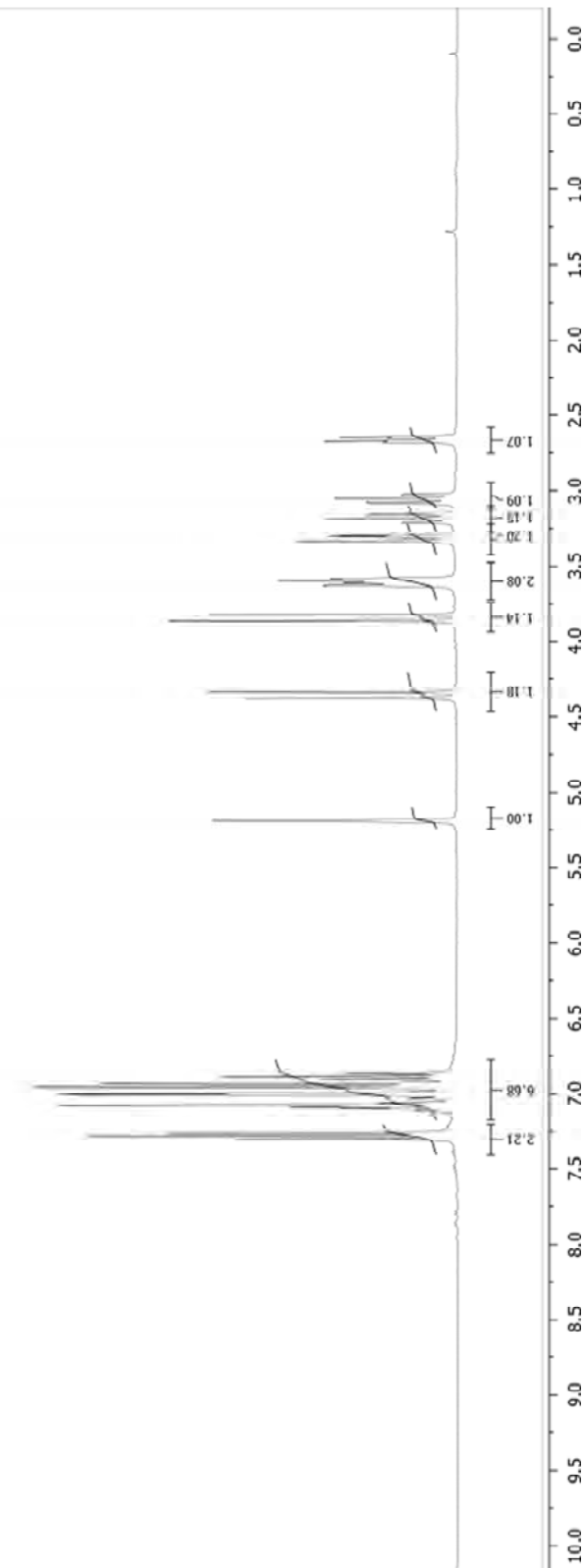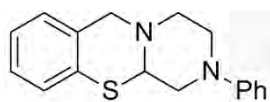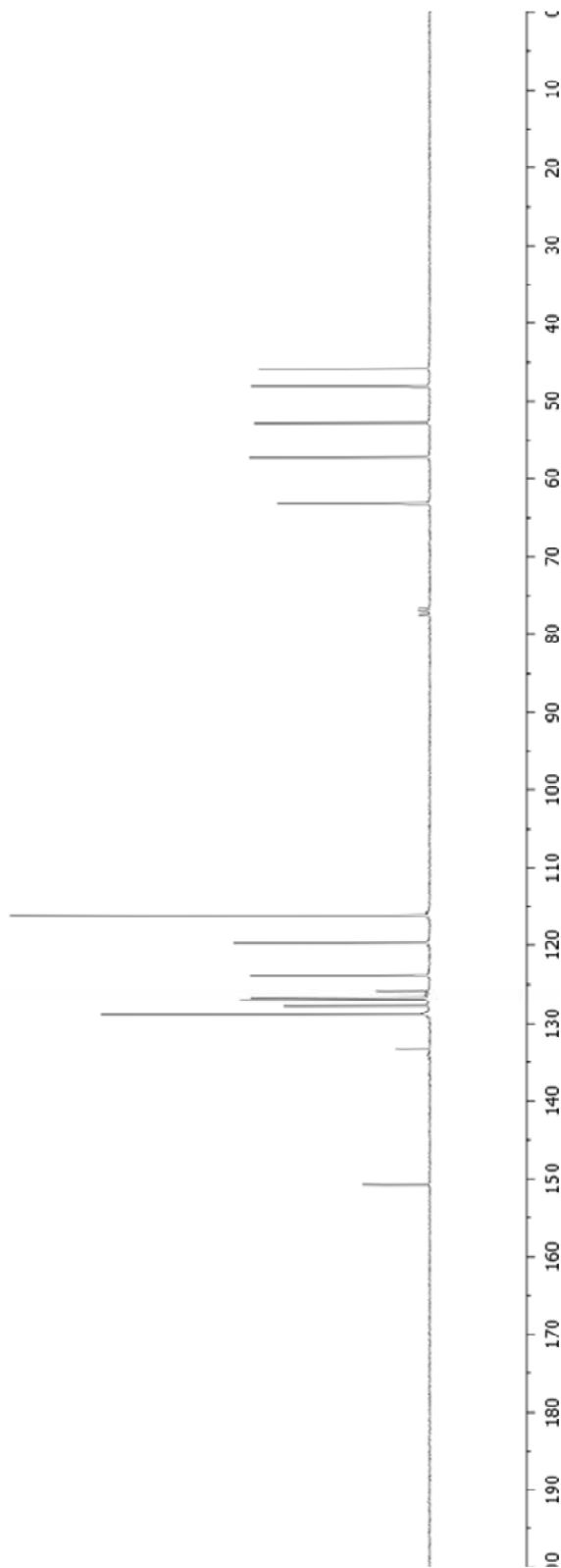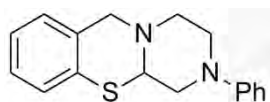
^{1}H NMR **4.7h** in CDCl$_3$
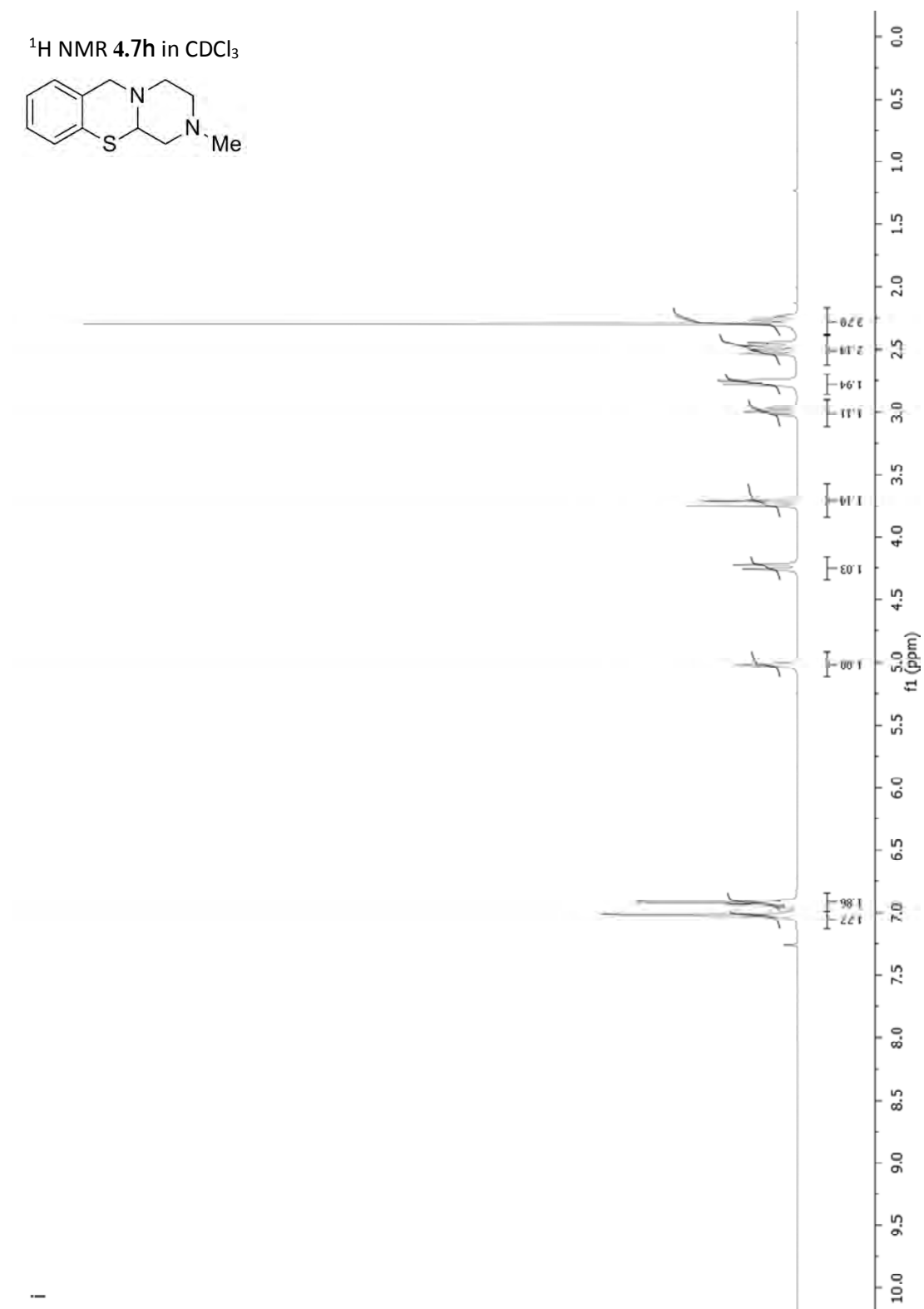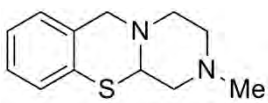
^{13}C NMR of **4.7h** in CDCl$_3$
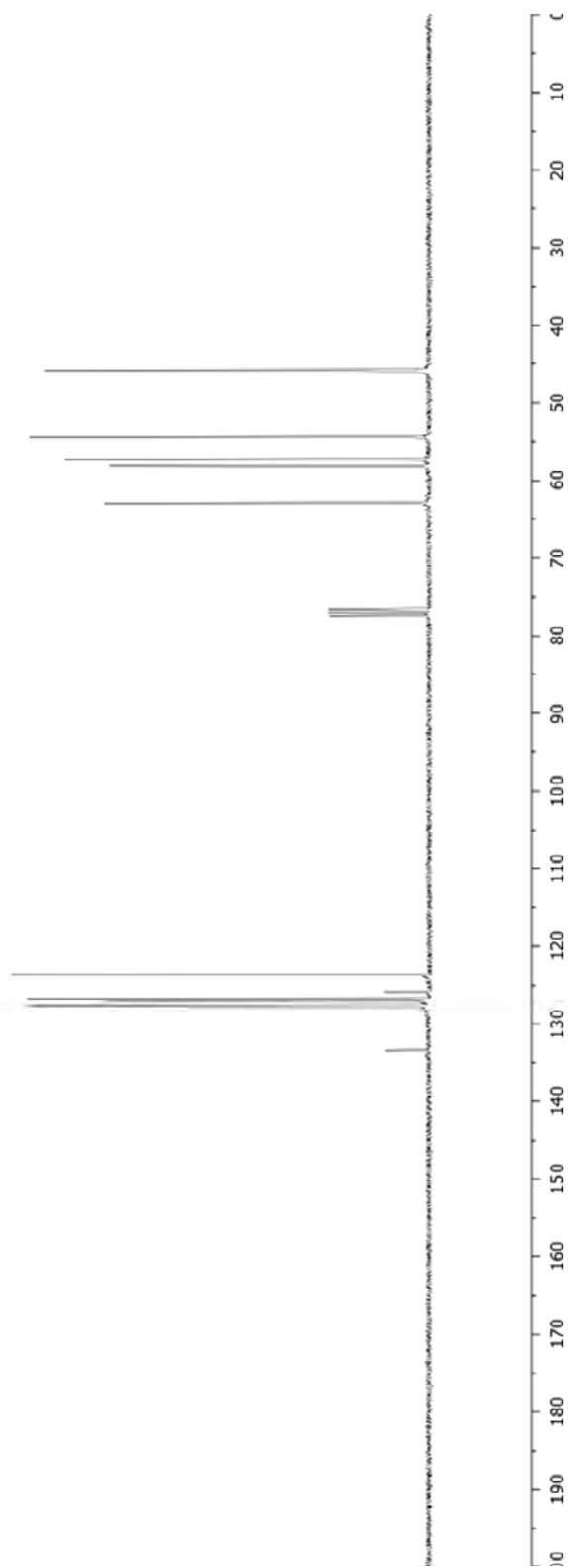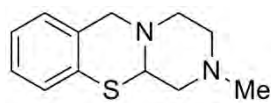
^{1}H NMR of **4.7i** in CDCl$_3$
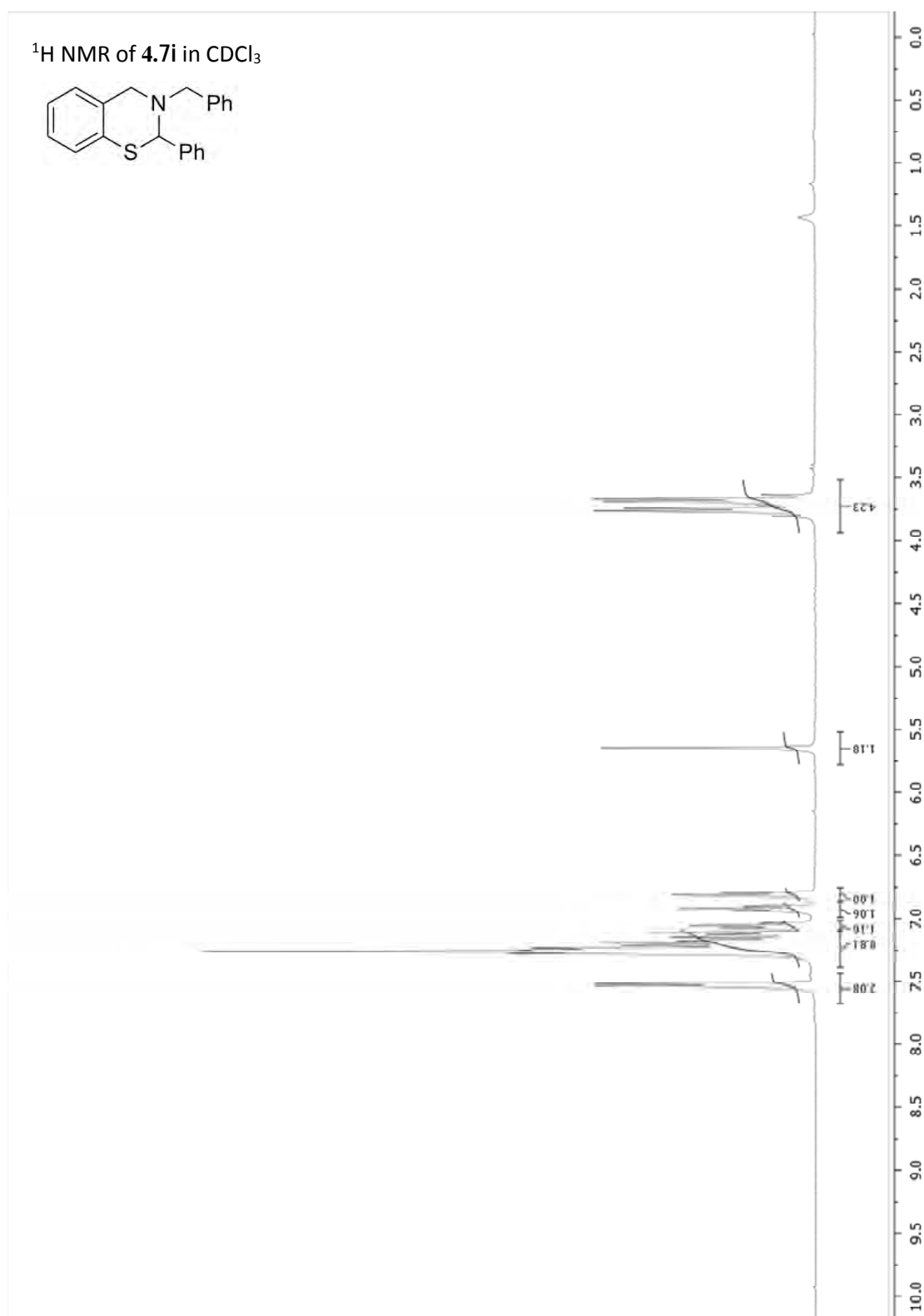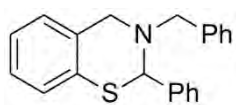
^{13}C NMR of **4.7i** in CDCl$_3$

¹H NMR of **4.7j** in CDCl₃

^{13}C NMR of **4.7j** in CDCl$_3$
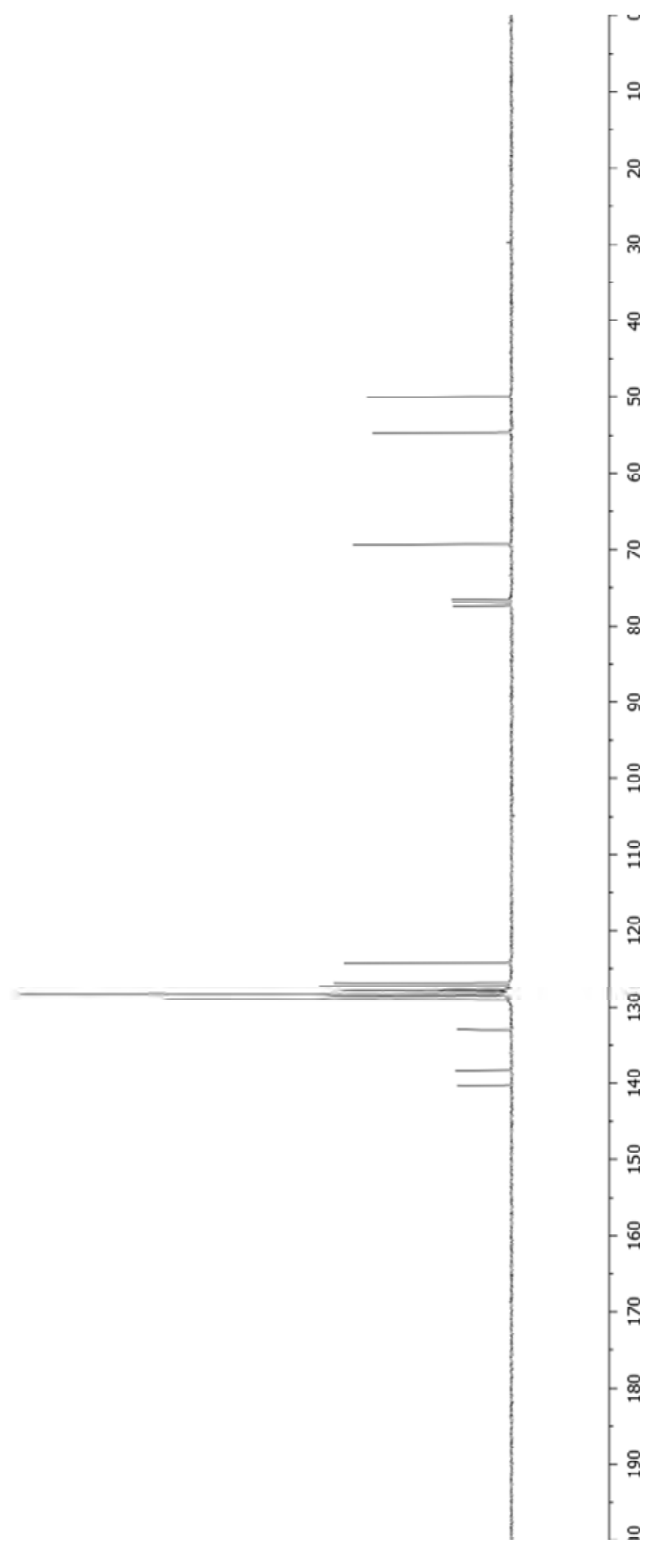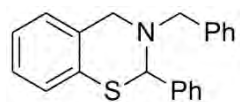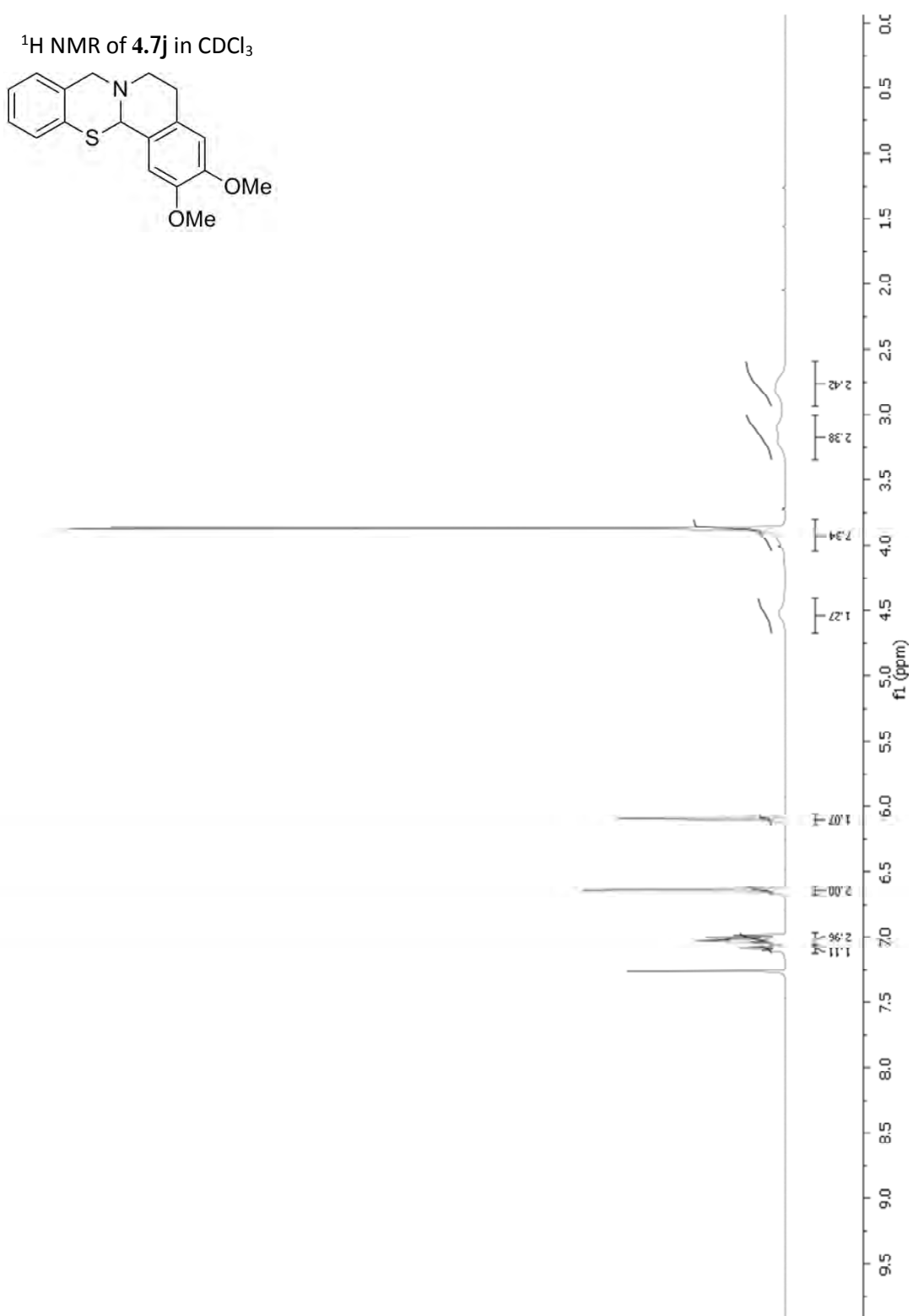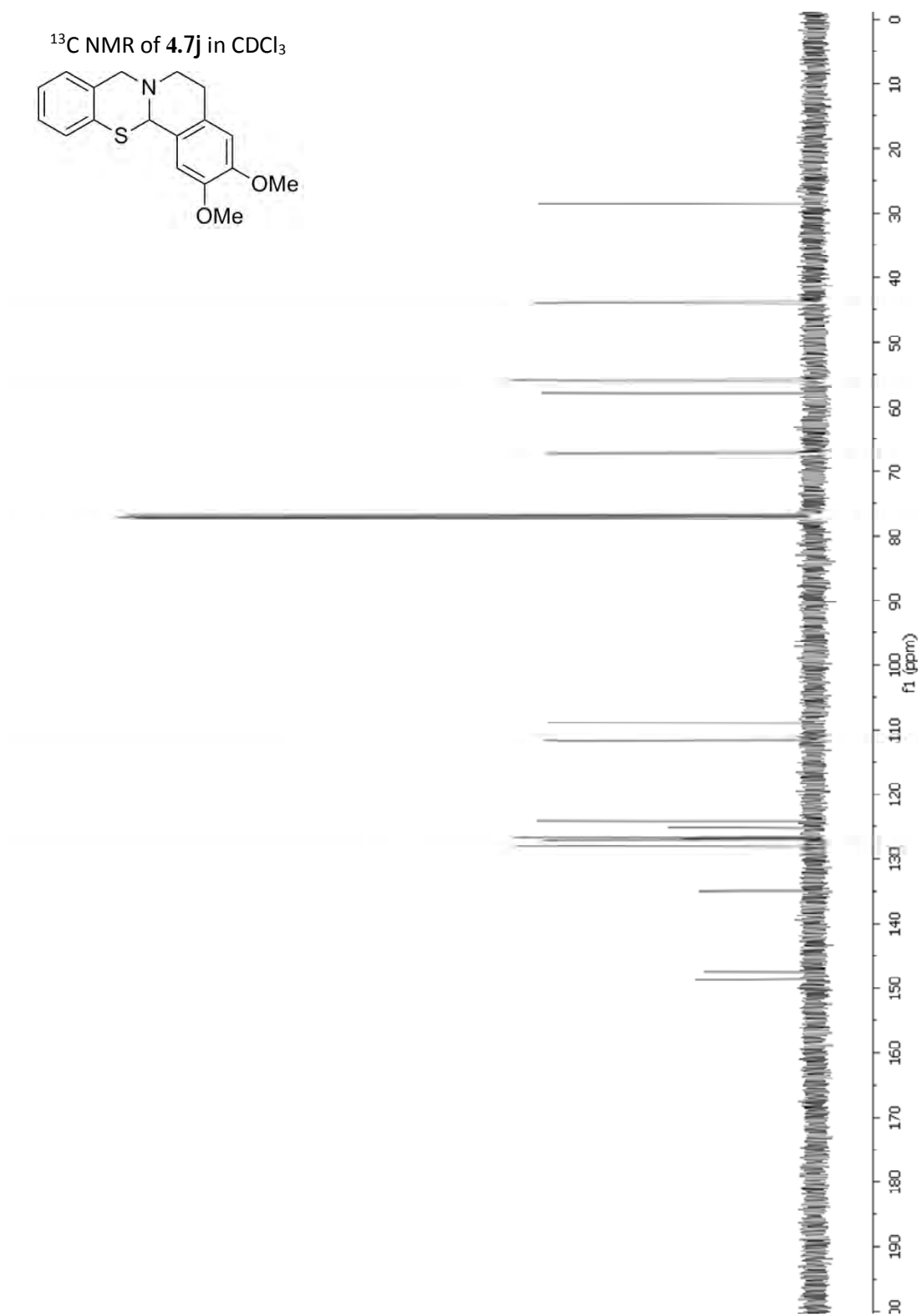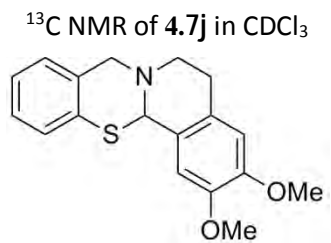
^{13}C NMR of **4.7k** in CDCl$_3$
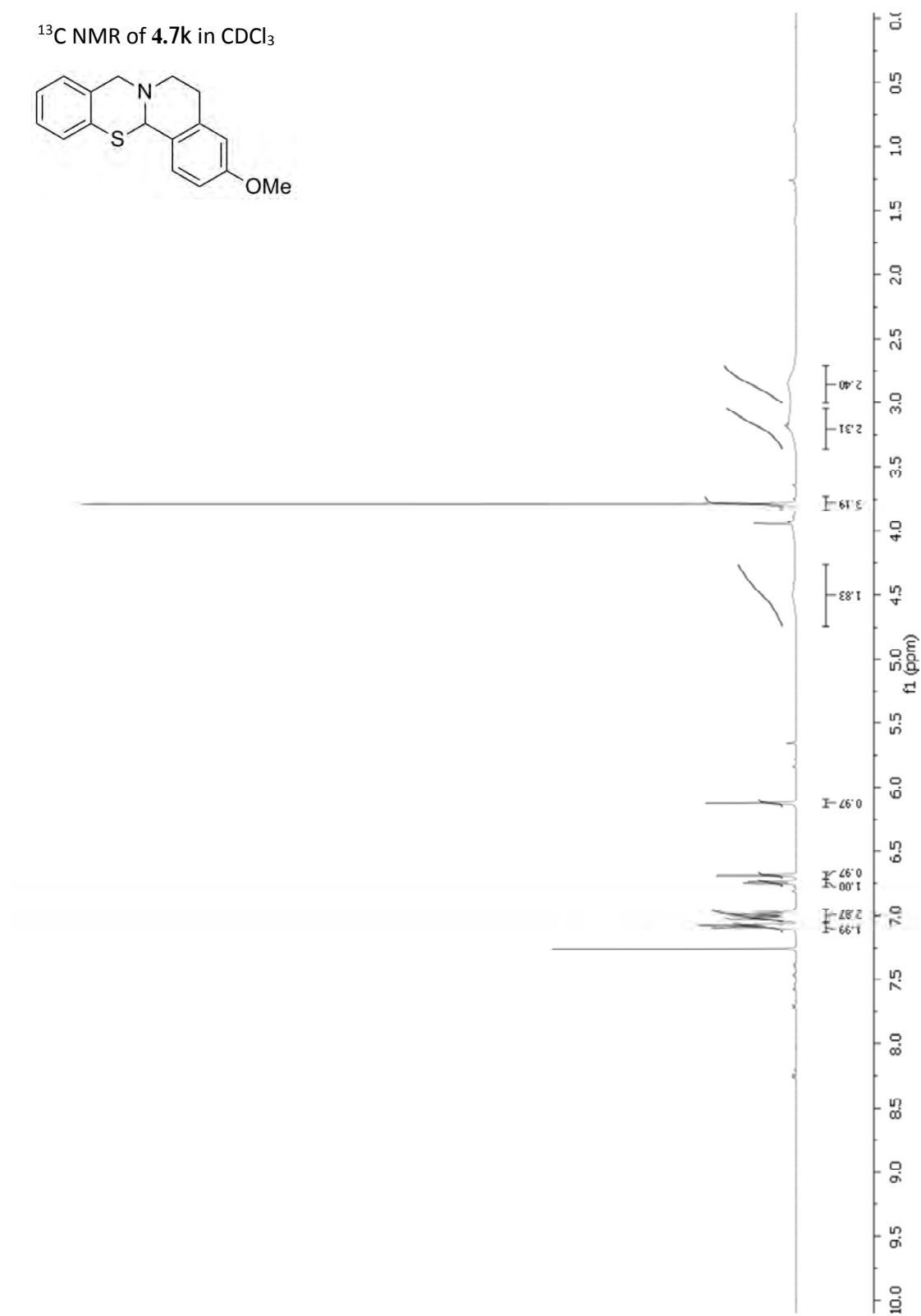
^{13}C NMR of **4.7k** in CDCl$_3$
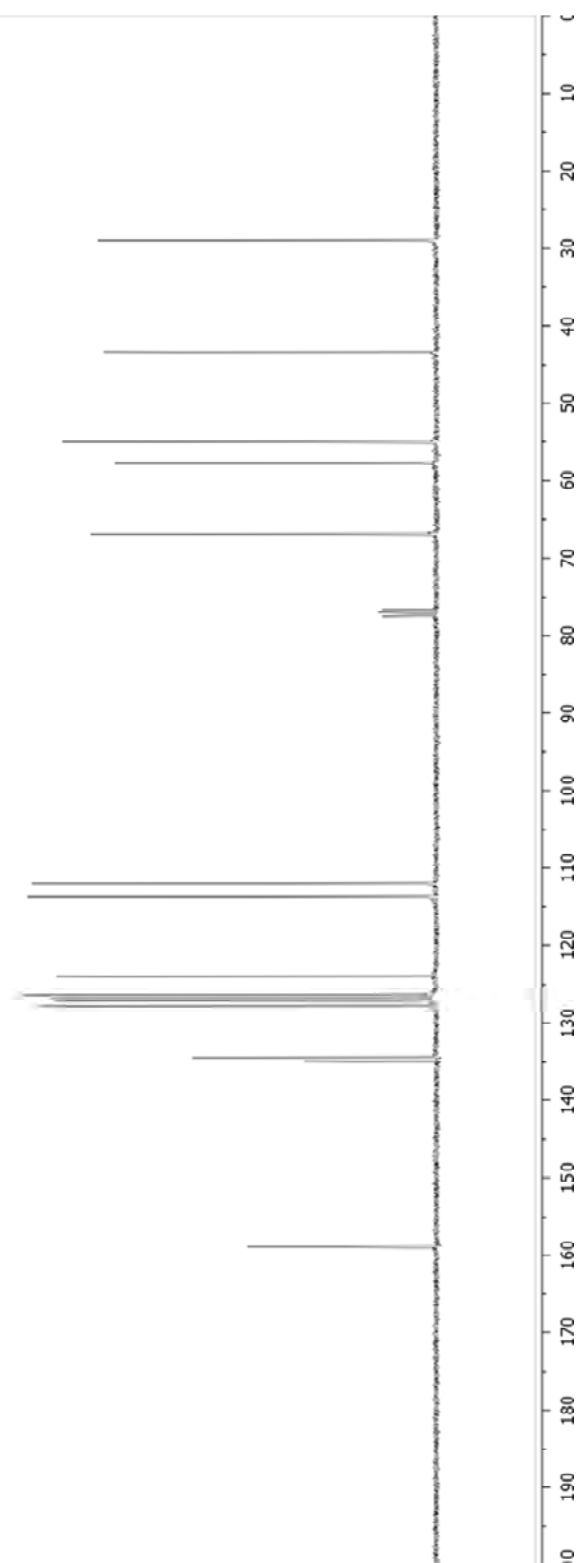
^{1}H NMR of **4.7l** in CDCl$_3$

^{13}C NMR of **4.7l** in CDCl$_3$
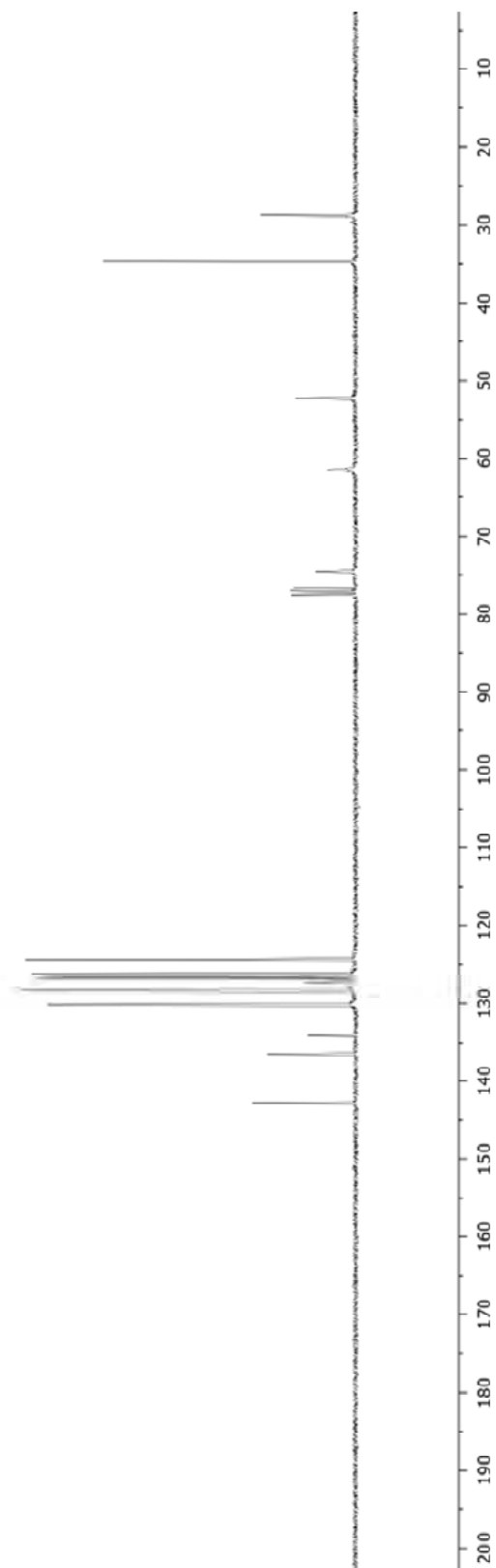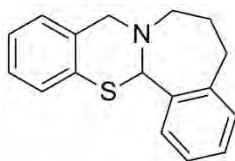
^{1}H NMR of **4.7m** in CDCl$_3$
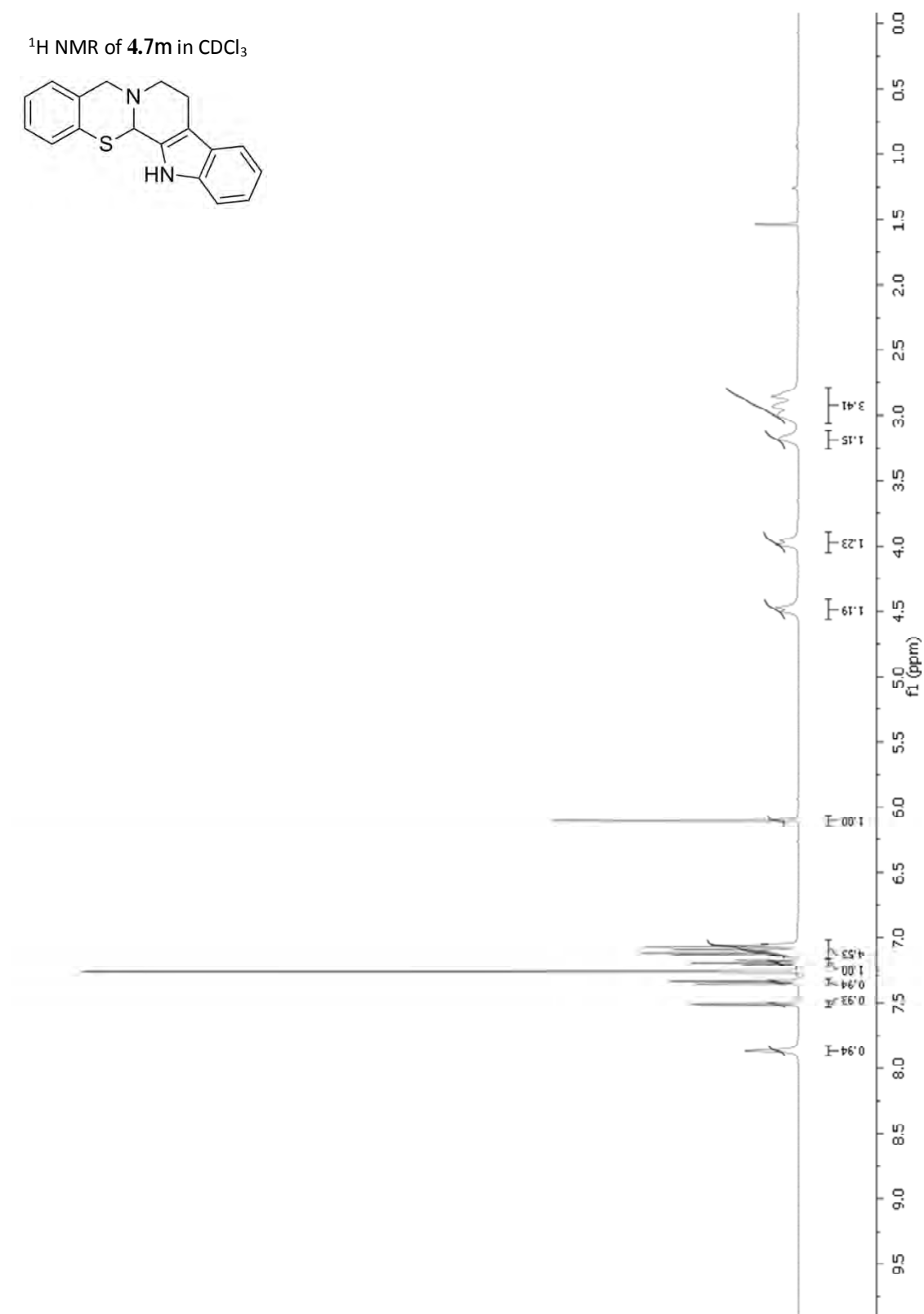
^{13}C NMR of **4.7m** in CDCl$_3$
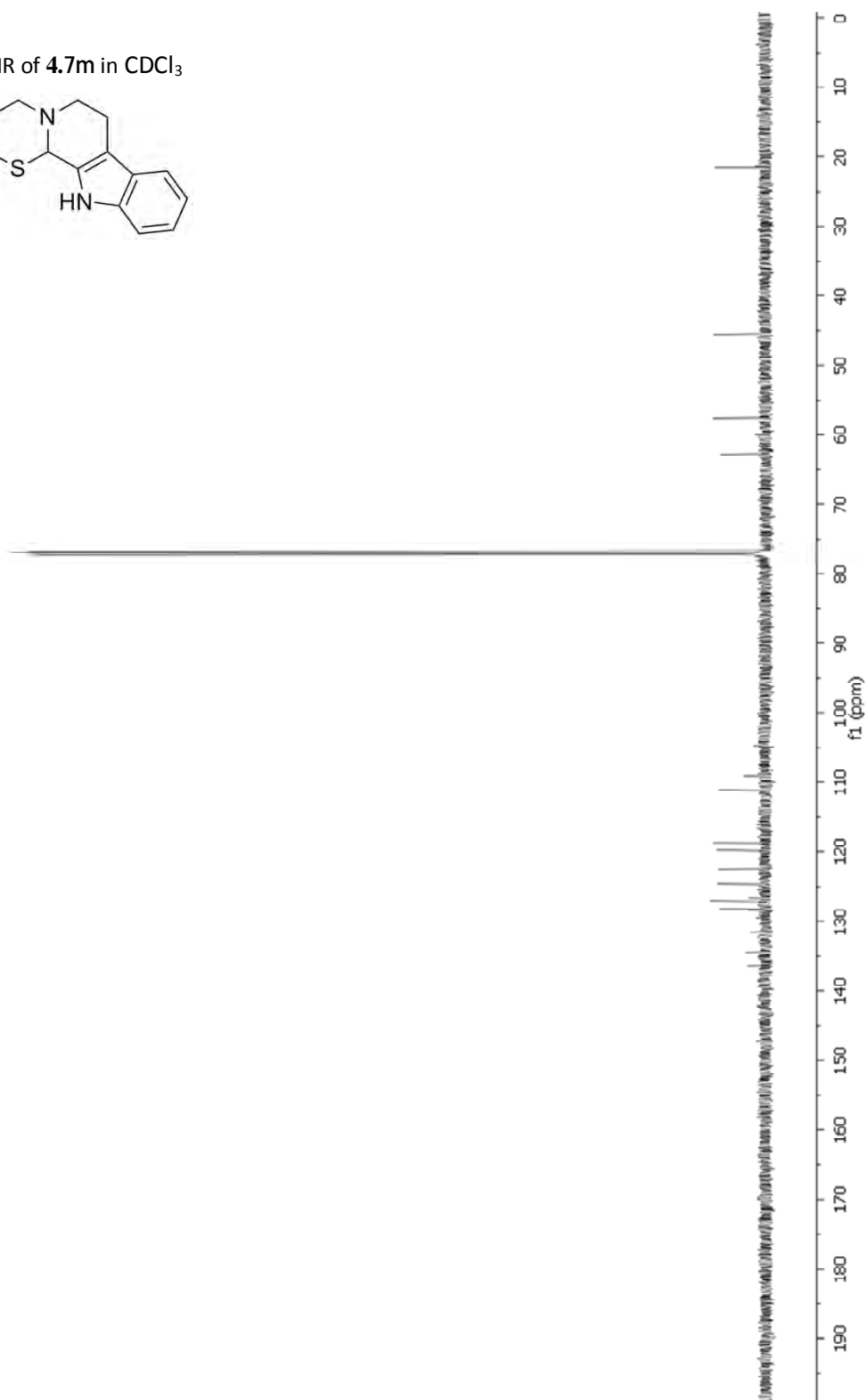
^{1}H NMR of **4.7n** in CDCl$_3$
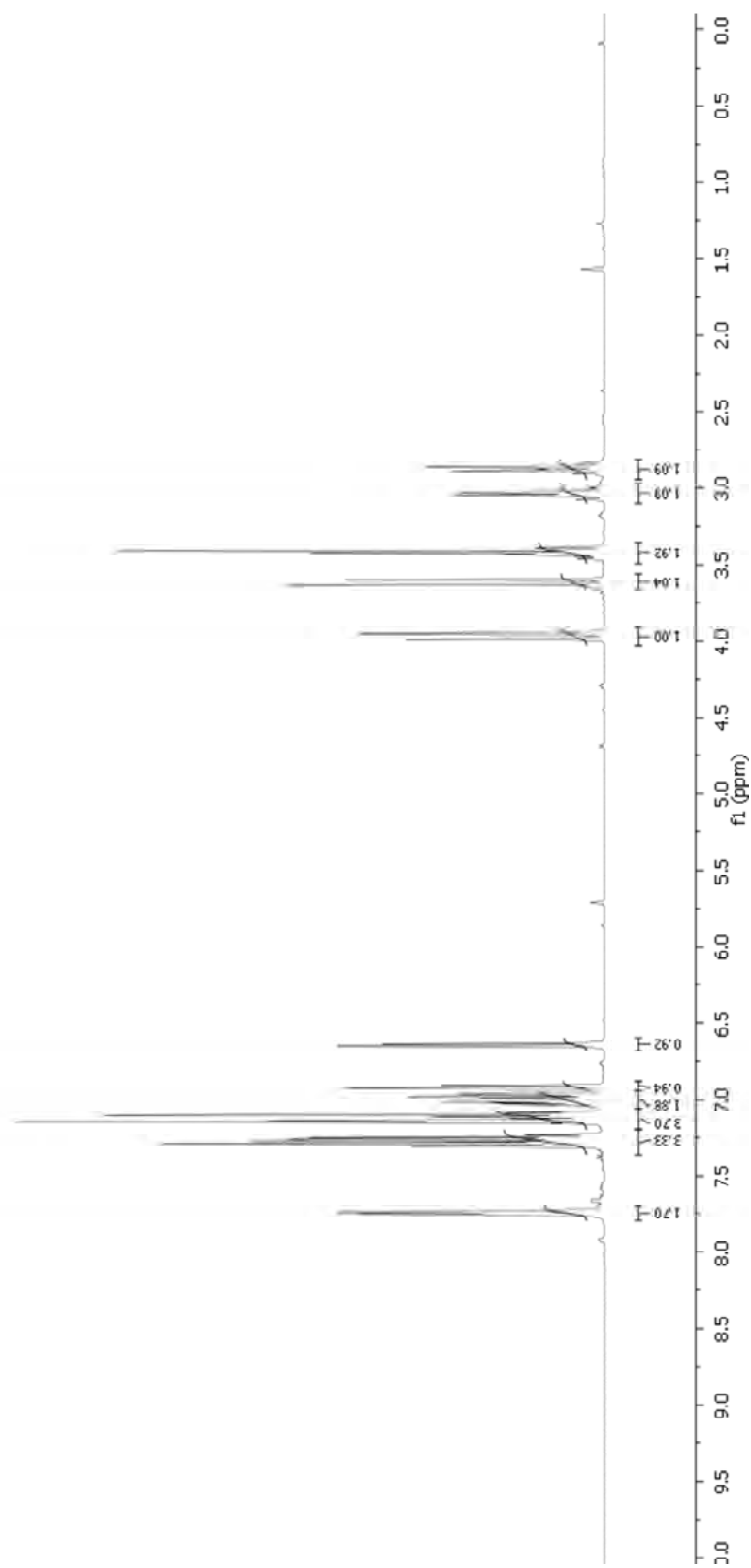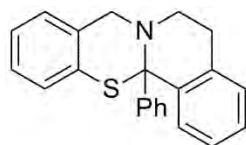
^{13}C NMR of **4.7n** in CDCl$_3$
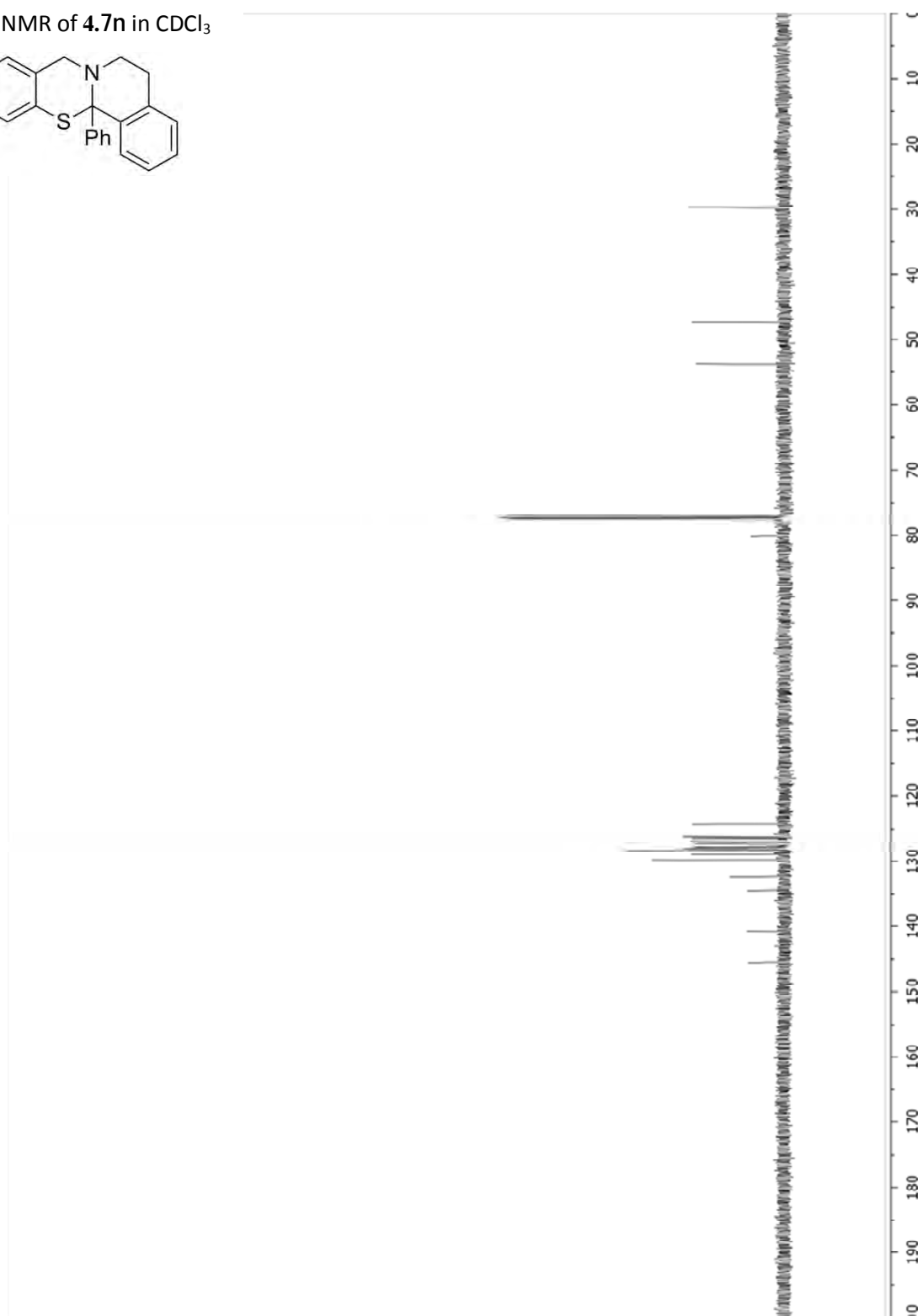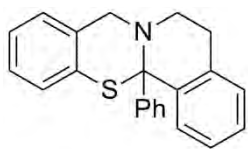
^{1}H NMR of **4.7o** in CDCl$_3$
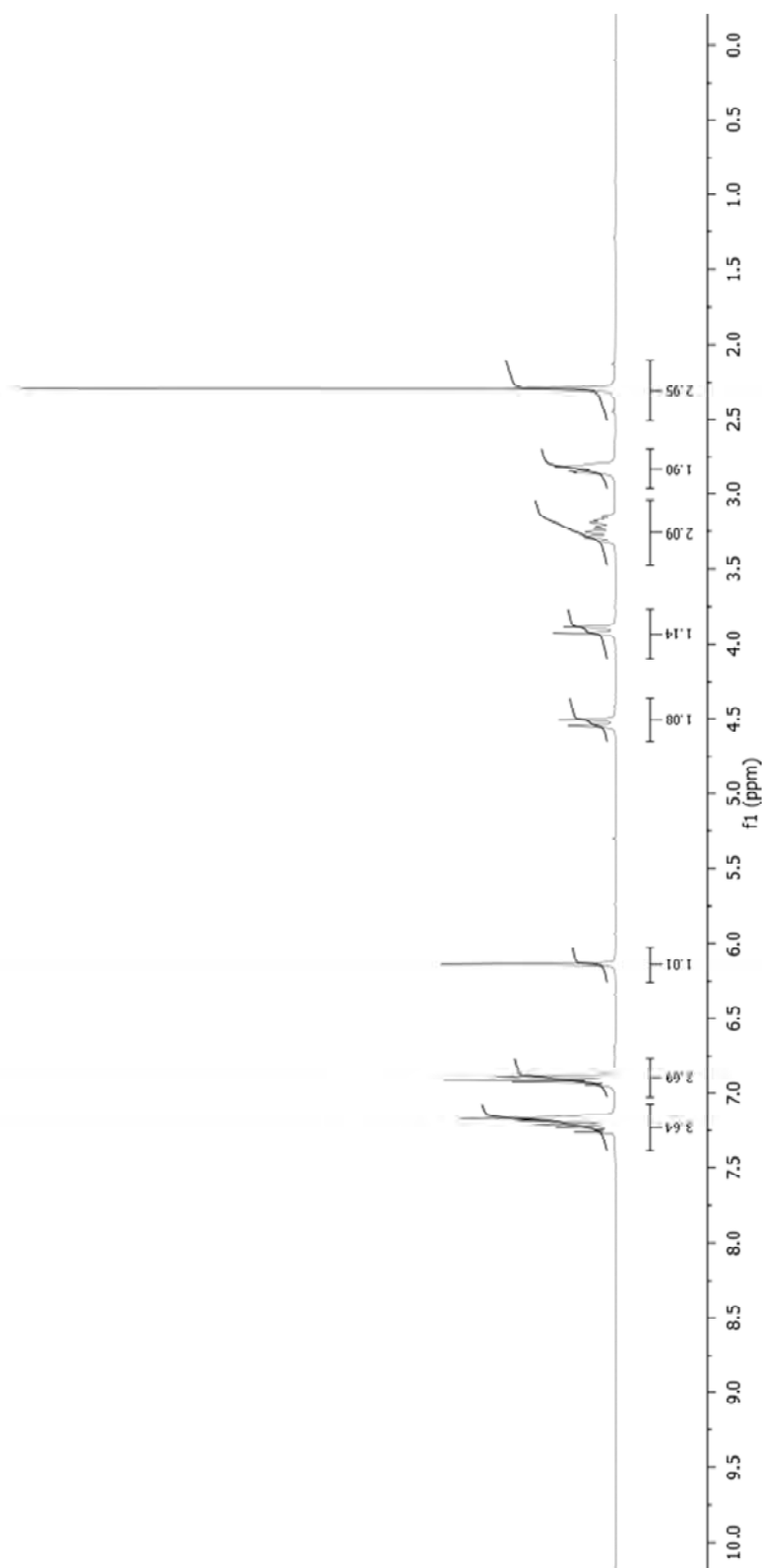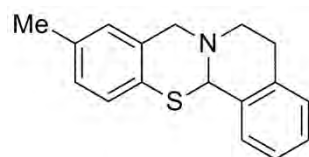
^{13}C NMR of **4.7o** in CDCl$_3$
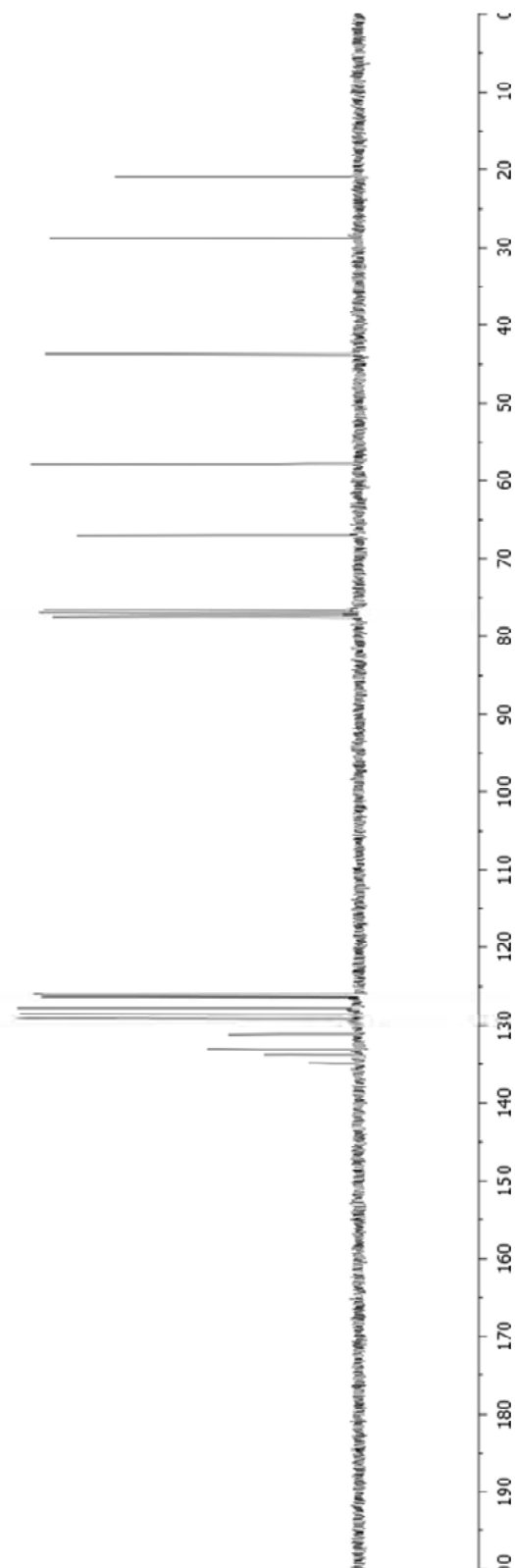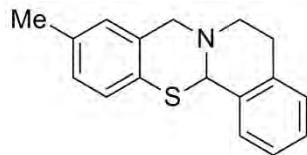
^{1}H NMR of **4.7p** in CDCl$_3$
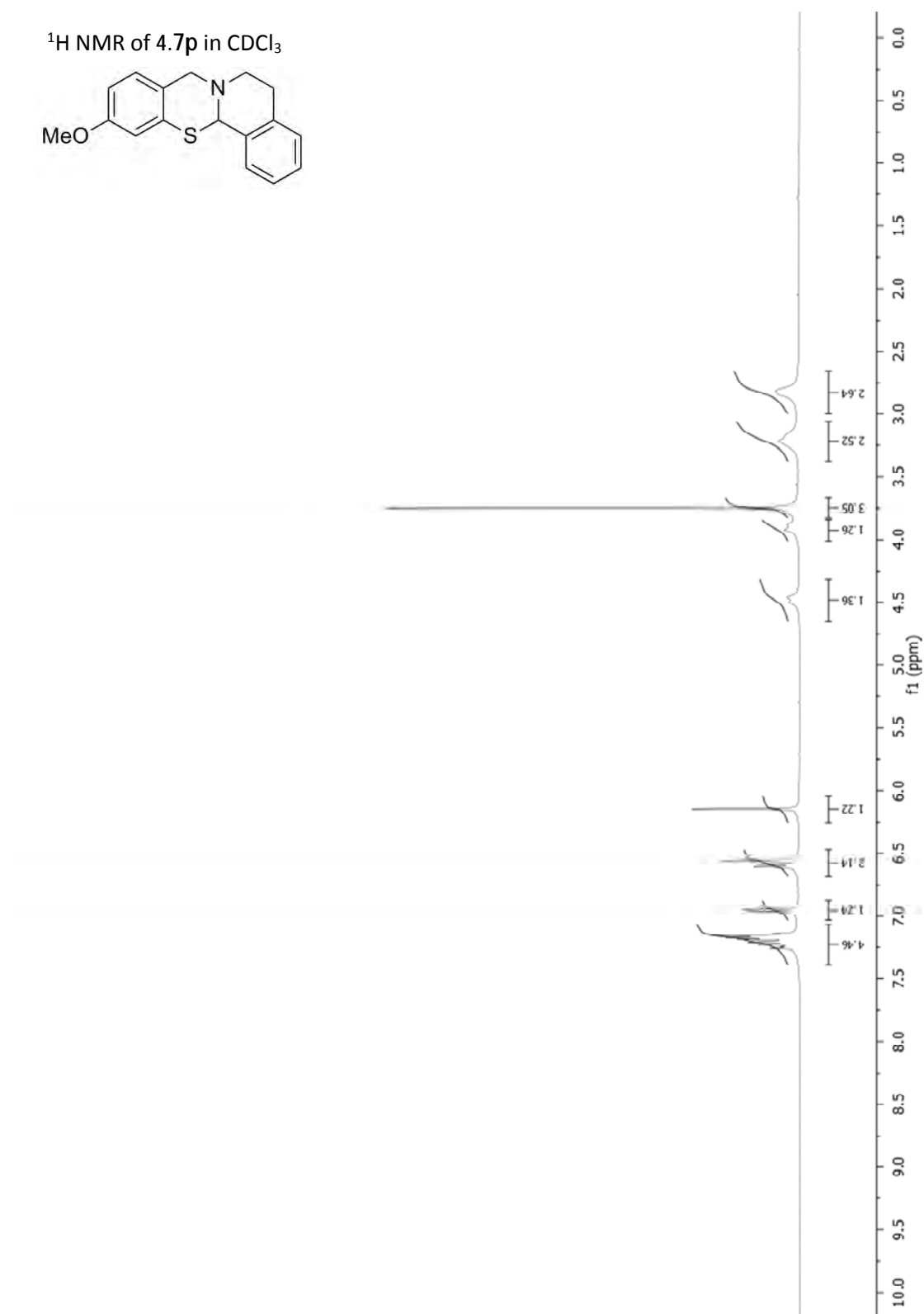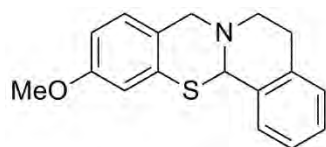
^{13}C NMR of **4.7p** in CDCl$_3$
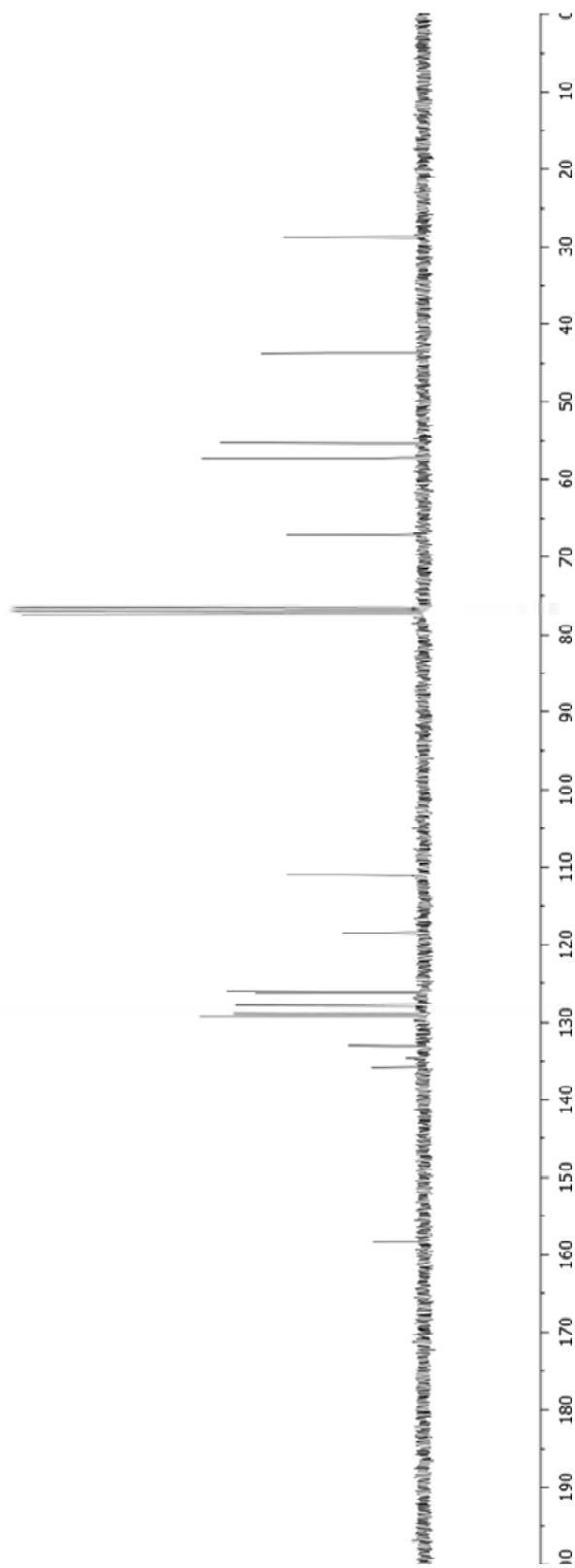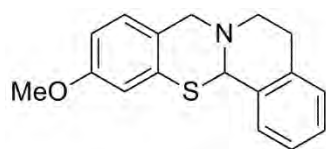
^{1}H NMR of **4.7q** in CDCl$_3$

^{13}C NMR of **4.7q** in CDCl$_3$
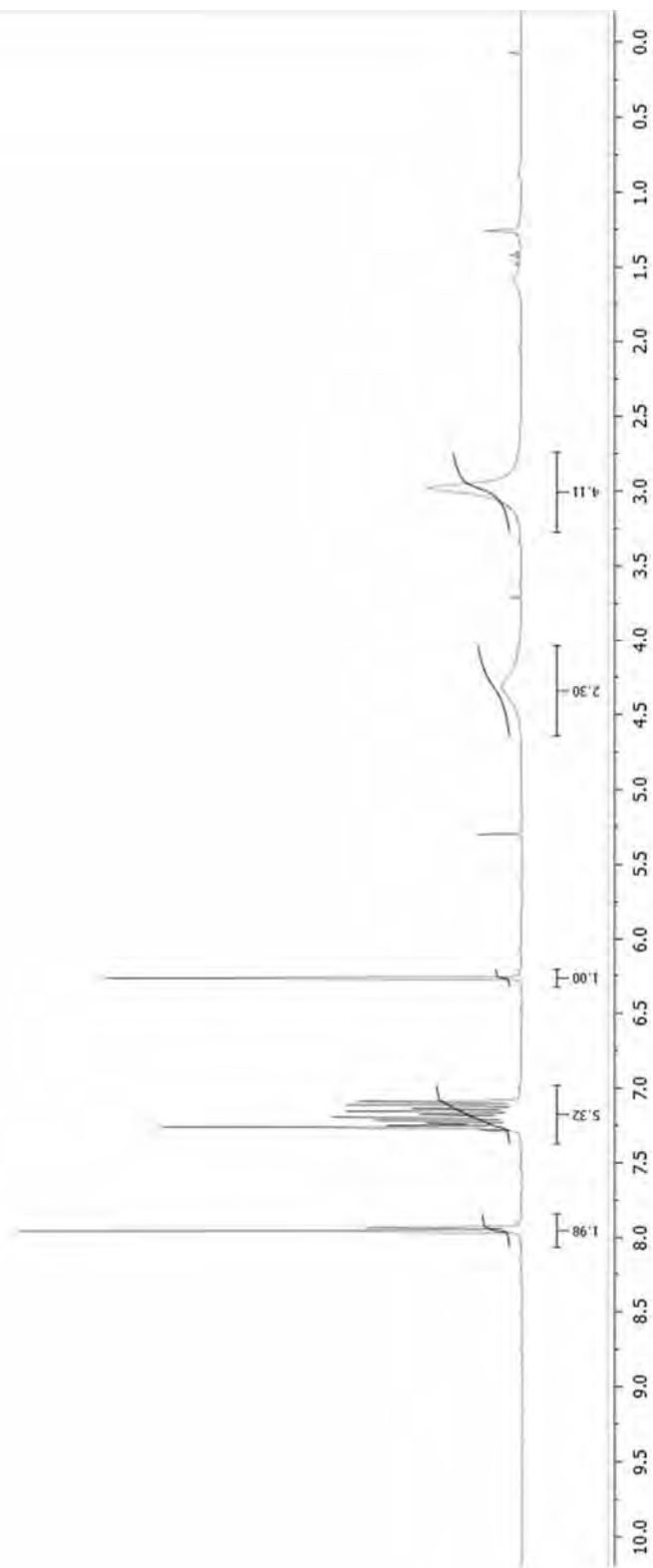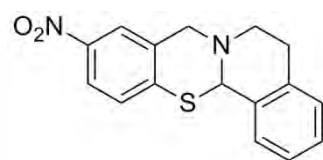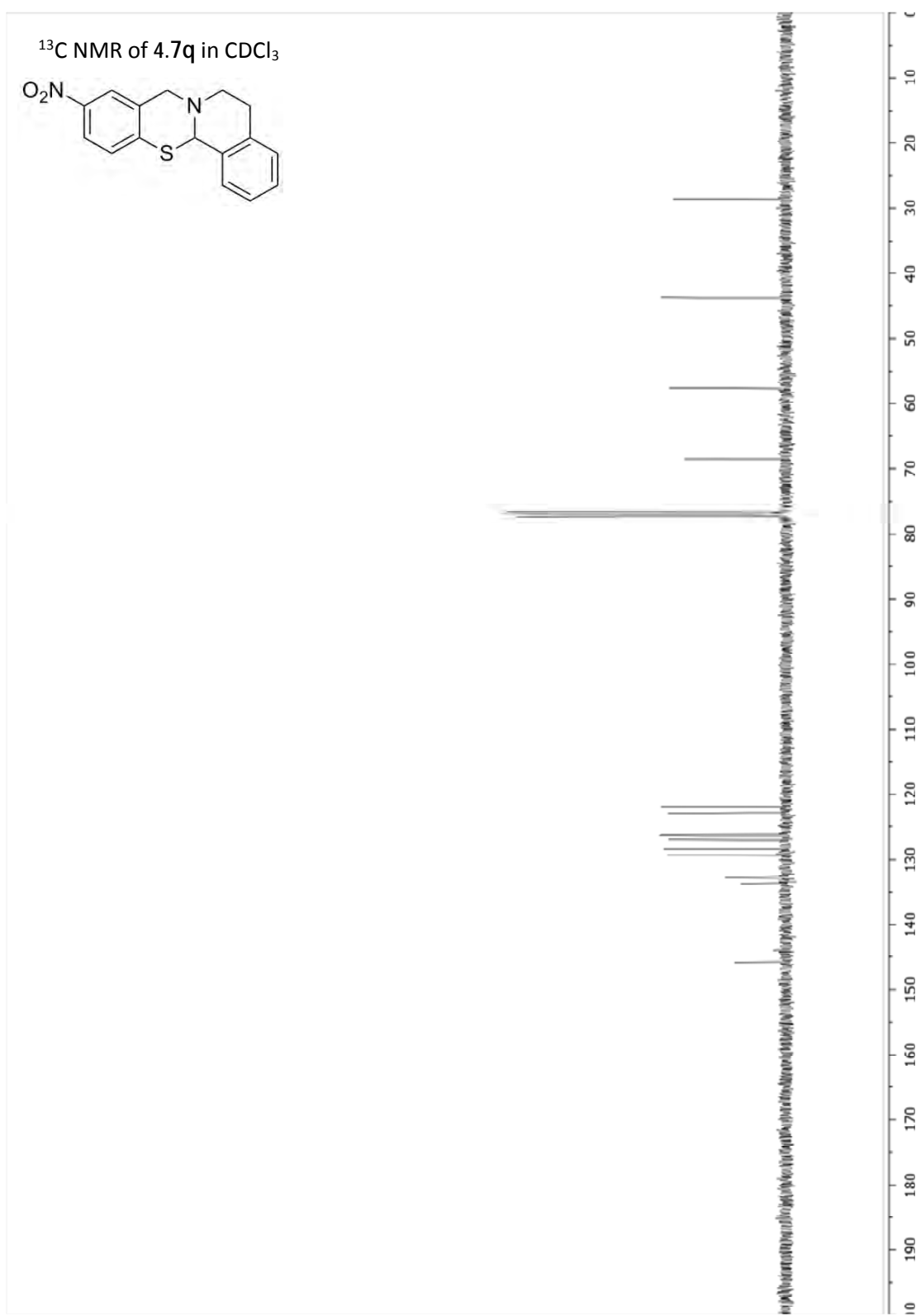
¹H NMR of **4.7r** in CDCl₃
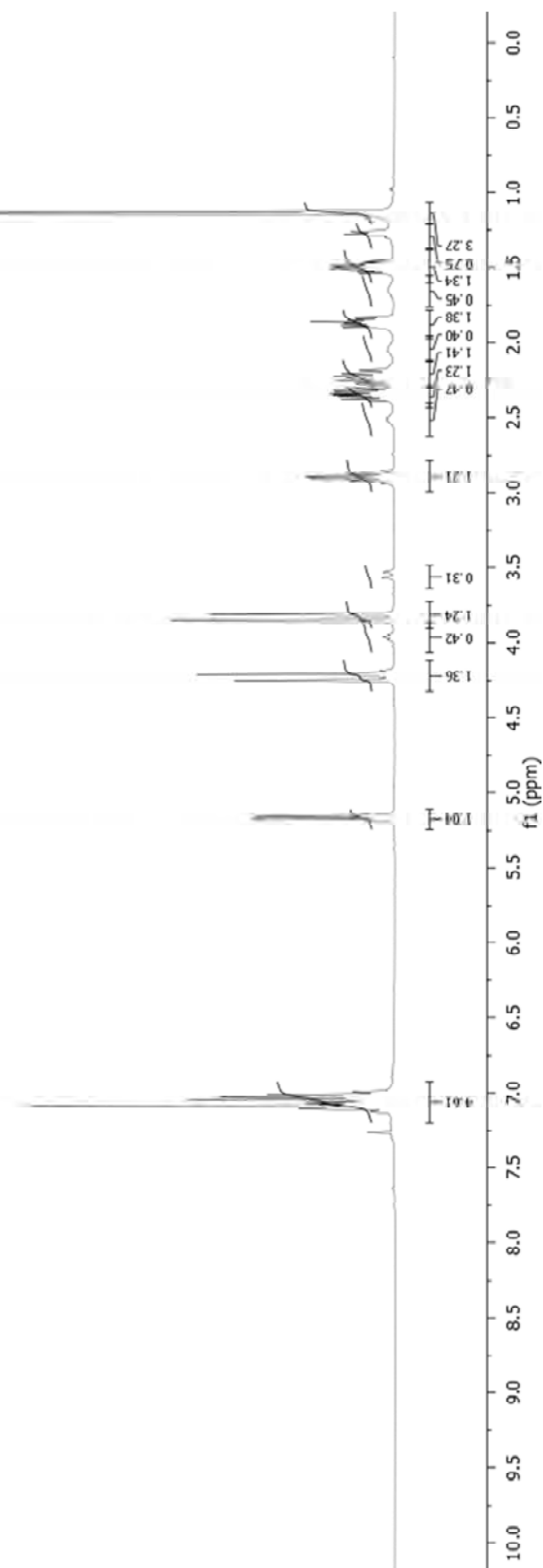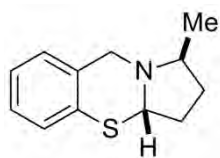
^{13}C NMR of **4.7r** in CDCl$_3$
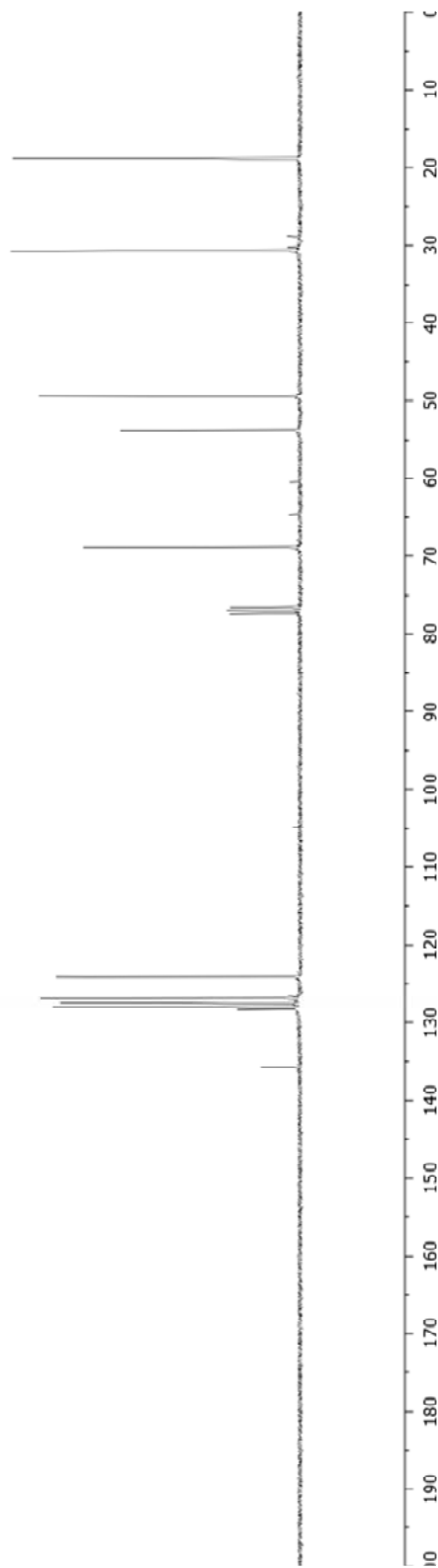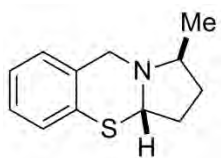
GCOSY NMR of **4.7r** in CDCl$_3$
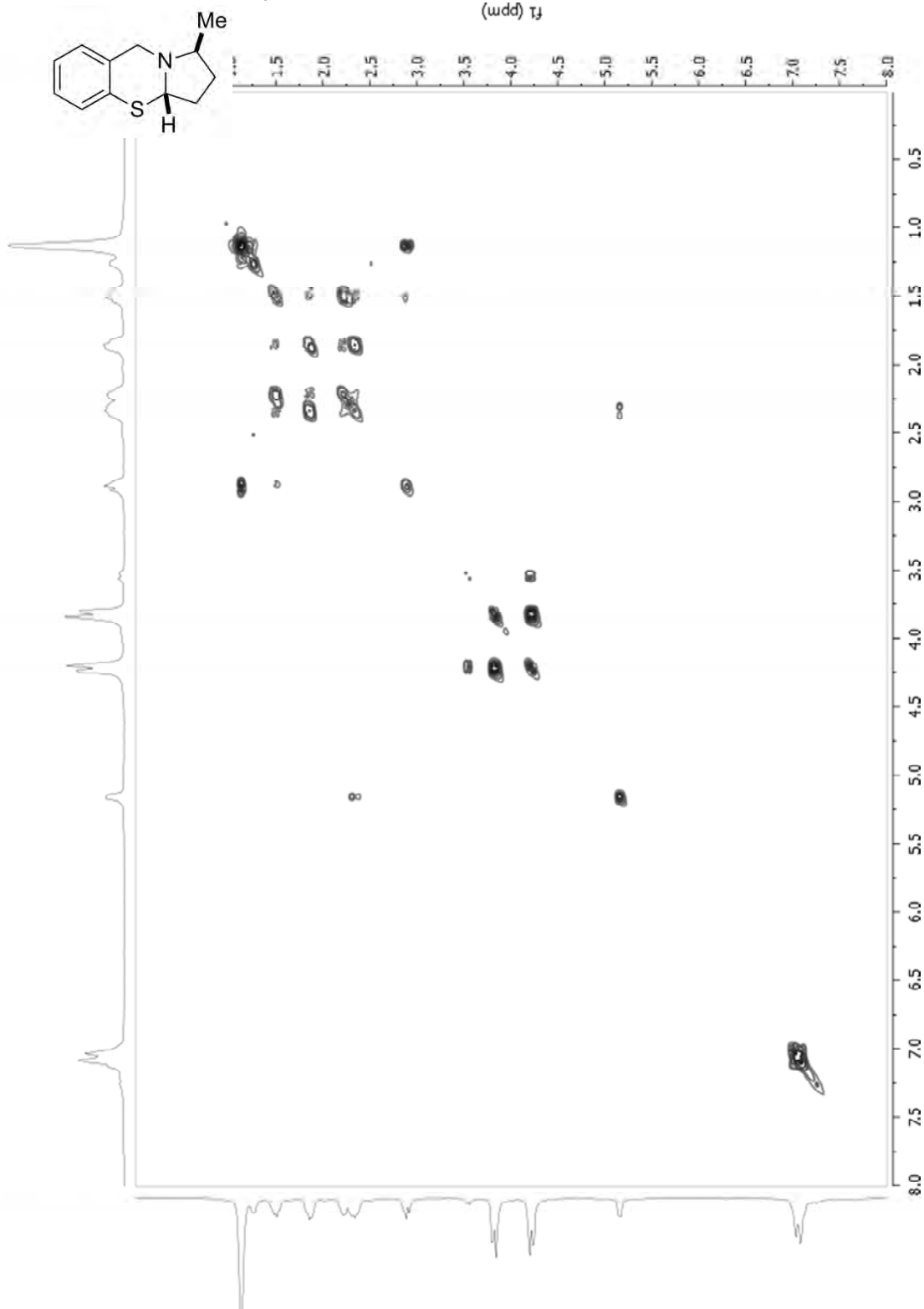
NOESY NMR of **4.7r** in CDCl$_3$
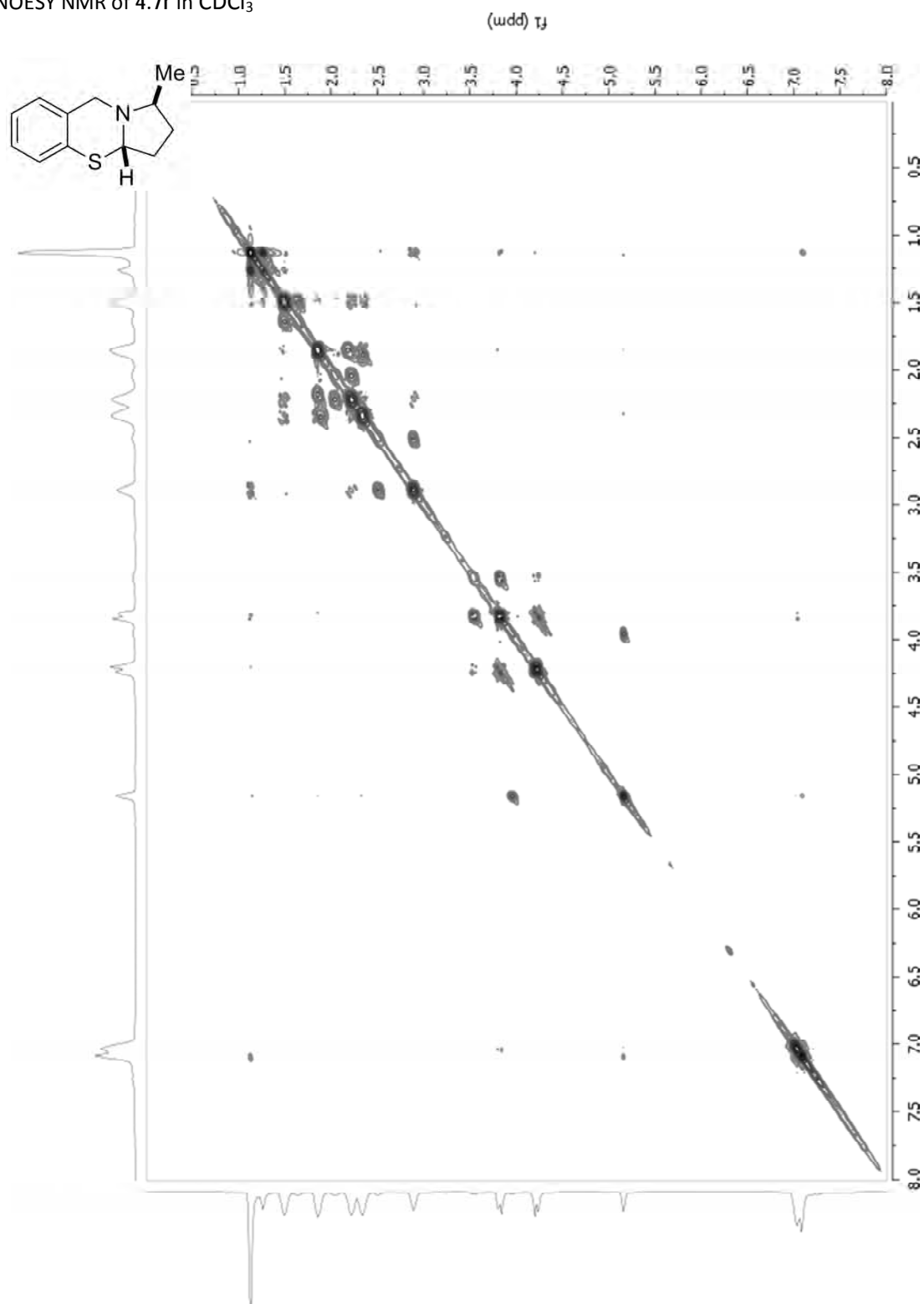
¹H NMR **4.7s** in CDCl₃
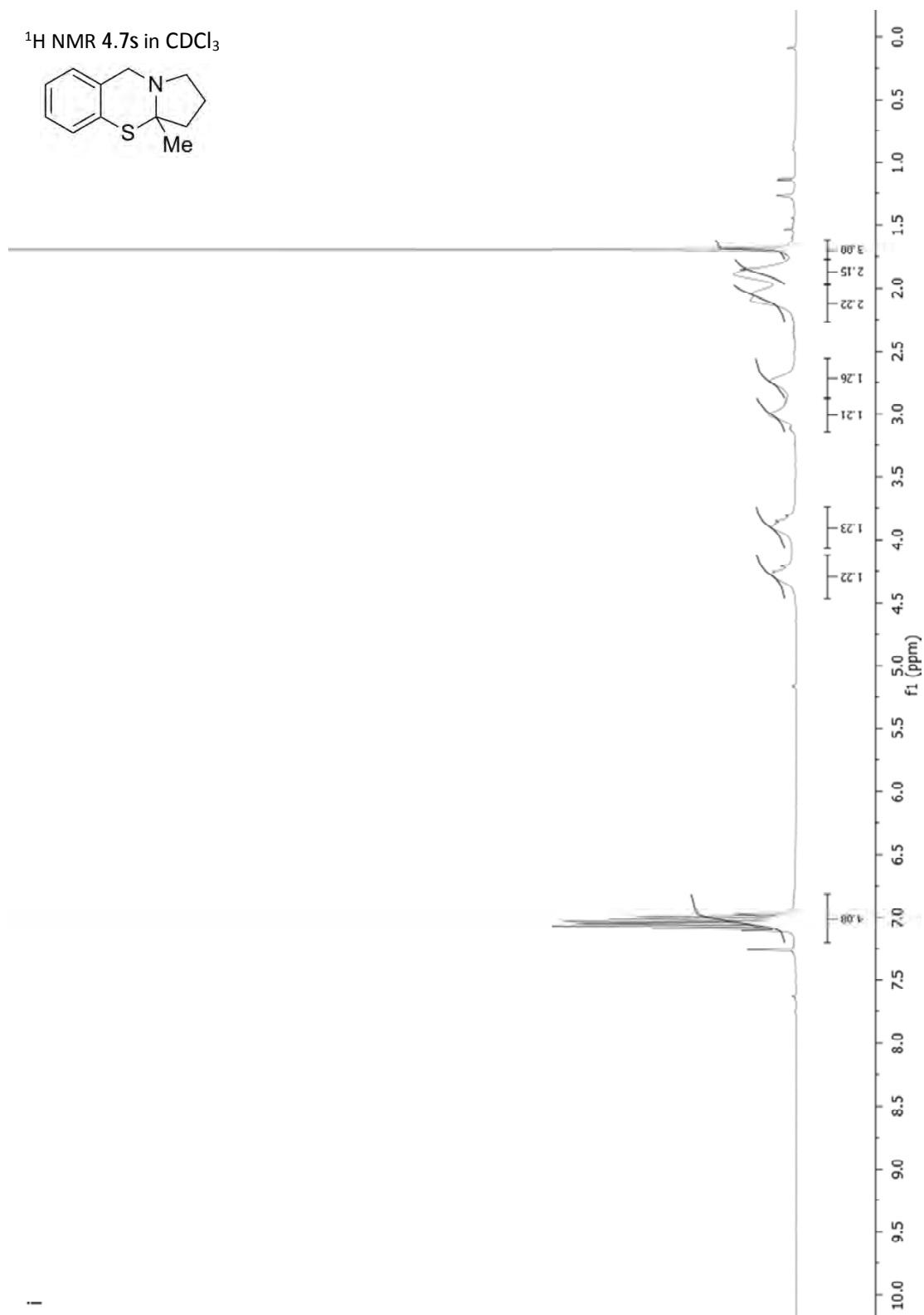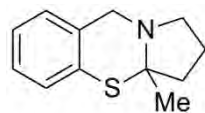
¹³C NMR 4.7s in CDCl₃
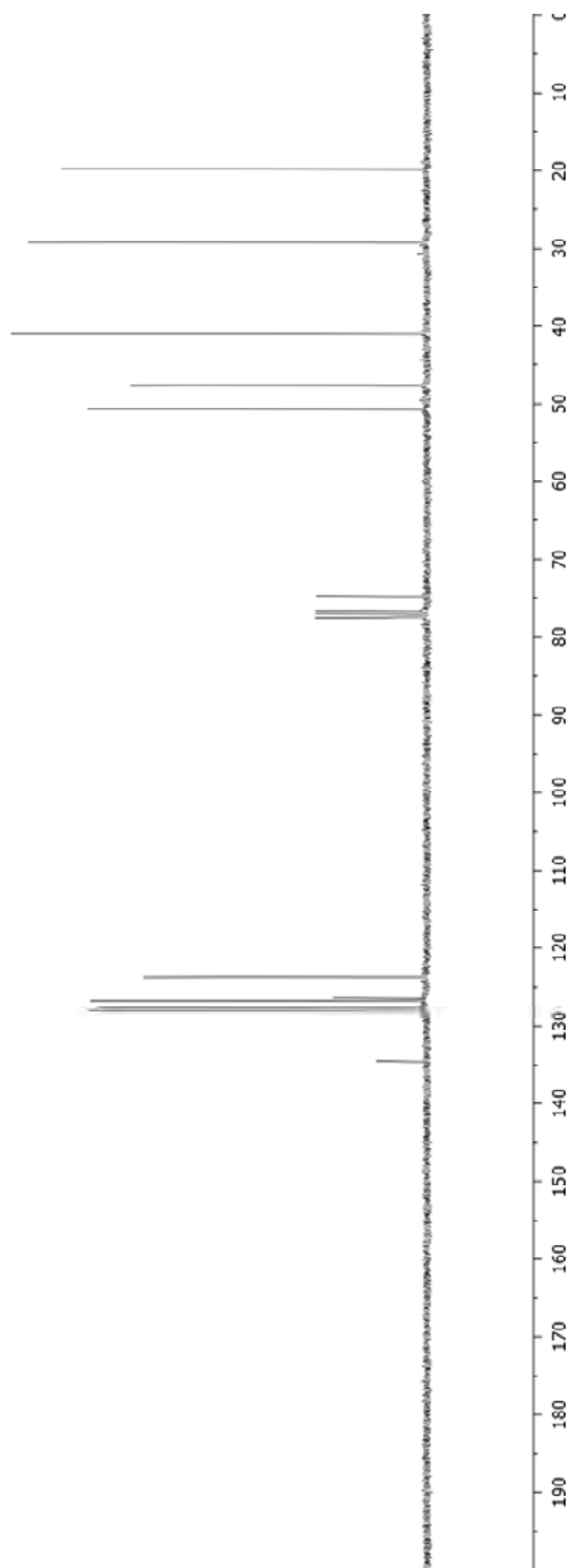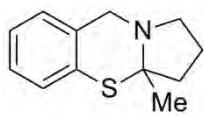
¹H NMR of **4.7t** in CDCl₃
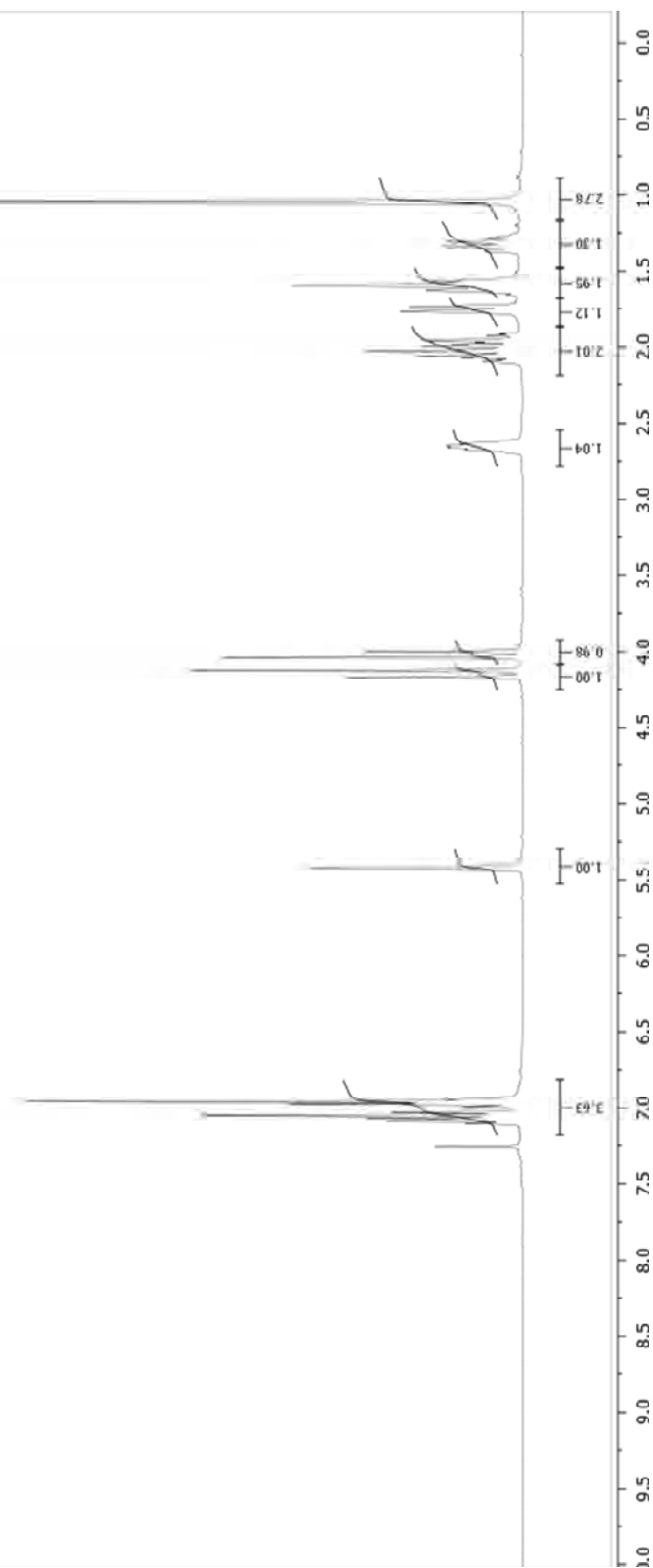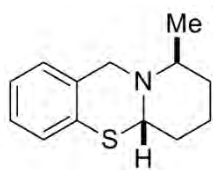
^{13}C NMR of **4.7t** in CDCl$_3$
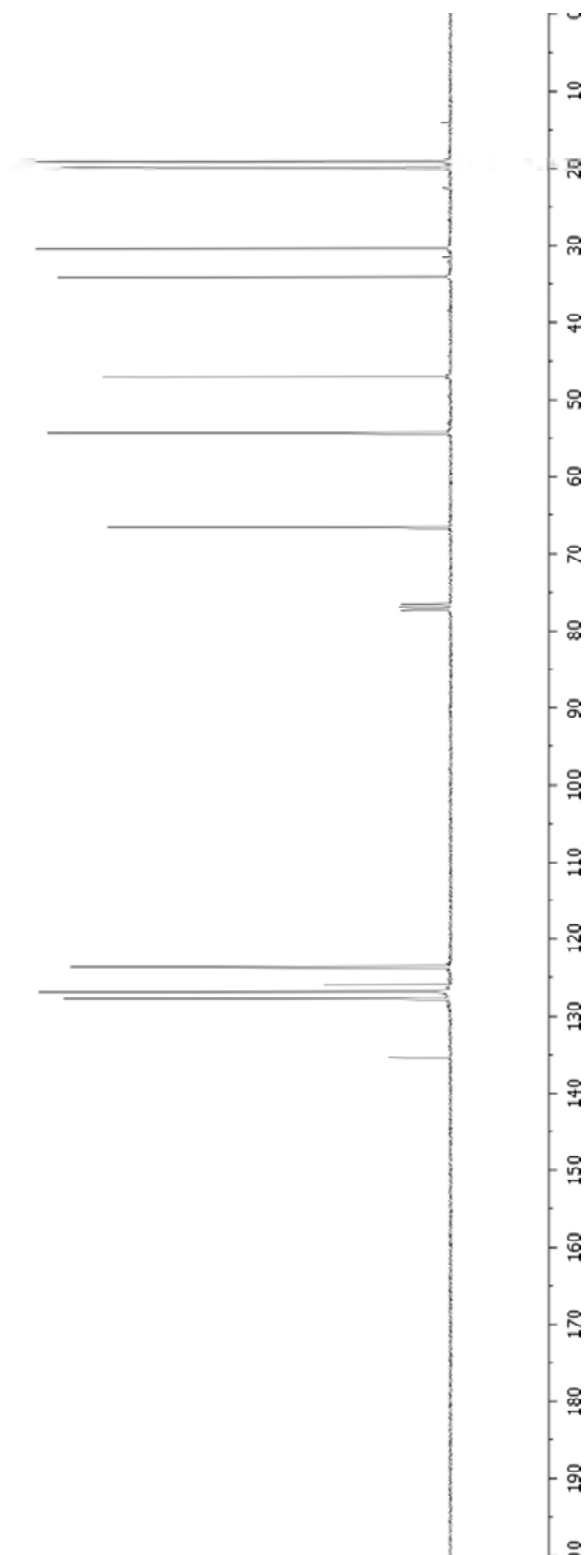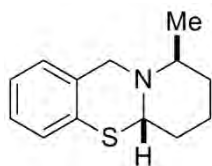
GCOSY NMR of 4.7t in DMSO

NOESY NMR of **4.7t** in DMSO