APPROACHES TO ASYMMETRIC CATALYSIS MEDIATED BY POLYMER-SUPPORTED AND HOMOGENEOUS ORGANOCATALYSTS

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ICIQ Institut Català d'Investigació Química

DOCTORAL THESIS

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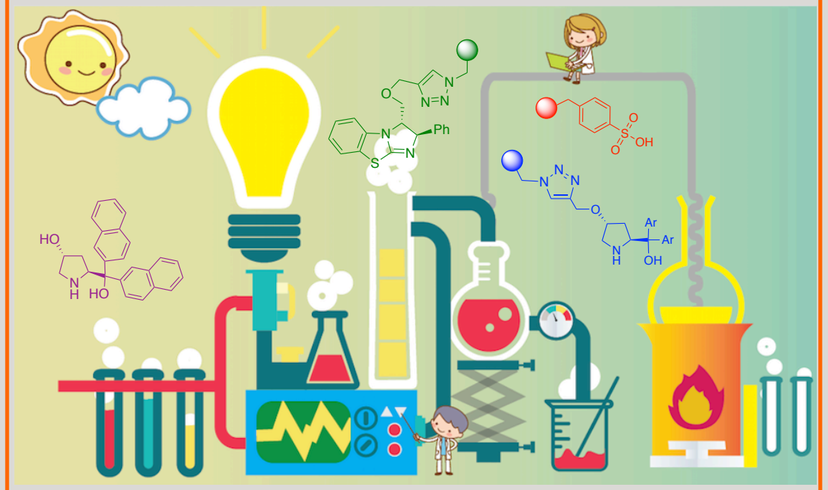

DOCTORAL THESIS
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Approaches to Asymmetric Catalysis Mediated by Polymer-Supported and Homogeneous Organocatalysts

PhD Thesis by

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Tarragona, 2018

Prof. Miquel A. Pericàs Brondo, Group Leader and Director of the Institute of Chemical Research of Catalonia (ICIQ),

CERTIFY that the present Doctoral Thesis entitled: **Approaches to Asymmetric Catalysis Mediated by Polymer-Supported and Homogeneous Organocatalysts**, presented by Shoulei Wang to receive the degree of Doctor, has been carried out under my supervision in the Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, January 2018

PhD Thesis Supervisor

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UNIVERSITAT ROVIRA i VIRGILI

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Abbreviations

In this document the abbreviations and acronyms most commonly used in organic chemistry have been used, according to the recommendations of the ACS "Guidelines for authors":

http://pubs.acs.org/paragonplus/submission/joceah/joceah_authguide.

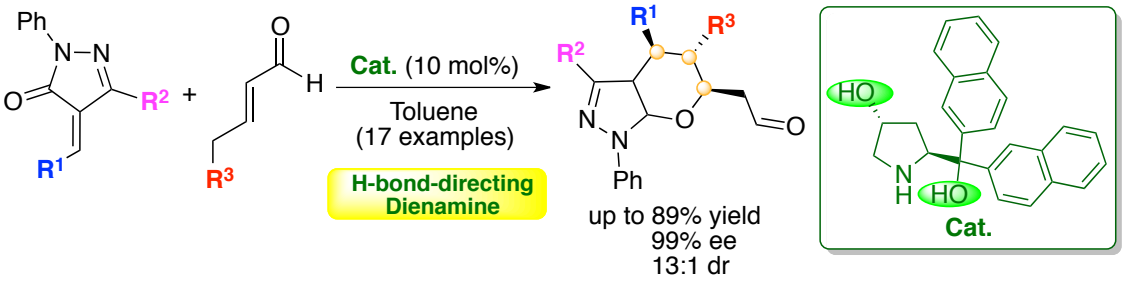
CONTENTS SUMMARY

Thesis Overview

Chapter I. General Introduction

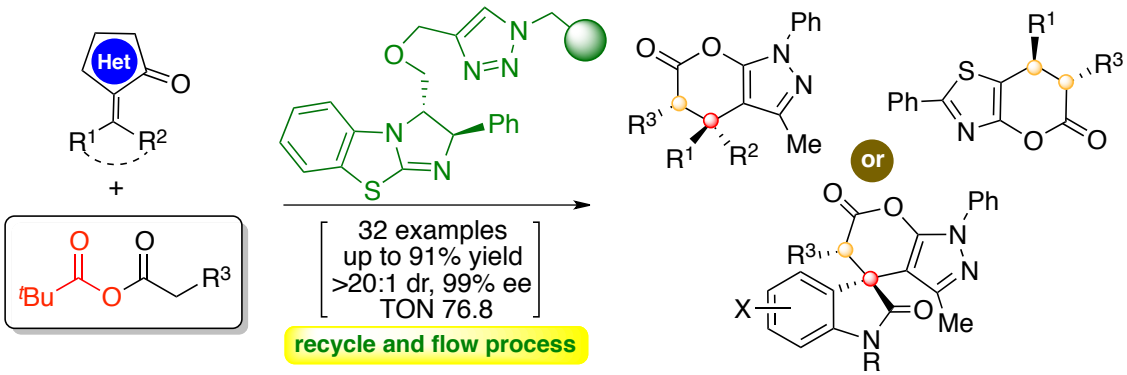
The first chapter is a general introduction of organocatalysis dealing with the concept and mechanisms. The most representative activation modes of aminocatalysis are presented in this chapter, as some of them will be exploited in this thesis. The last part gives a brief introduction of immobilized catalysts and continuous flow chemistry.

Chapter II. H-Bond-Directing Dienamine



In Chapter II, an efficient, highly regio- and stereoselective [4+2] cycloaddition between alkylidene pyrazolones and enals through H-bond-directing dienamine catalysis has been developed. This methodology enables the synthesis of enantioenriched, multifunctionalized tetrahydropyranopyrazole derivatives with three contiguous stereocenters in good yields and excellent enantioselectivities.

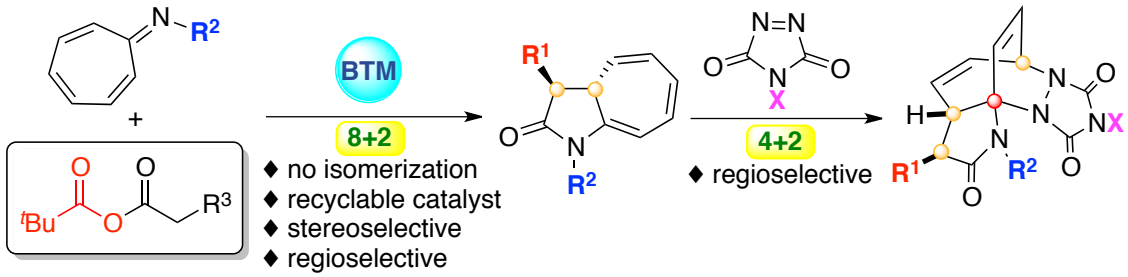
Chapter III. A Robust Immobilized Isothiourea Catalyst



A polystyrene-supported (PS) isothiourea behaves as a robust, highly efficient organocatalyst in a variety of formal [4+2] cycloaddition reactions, that provide an efficient approach to access a series of highly versatile, six-membered heterocycles and spiro-heterocycles bearing an oxindole moiety in high enantiomeric purity and

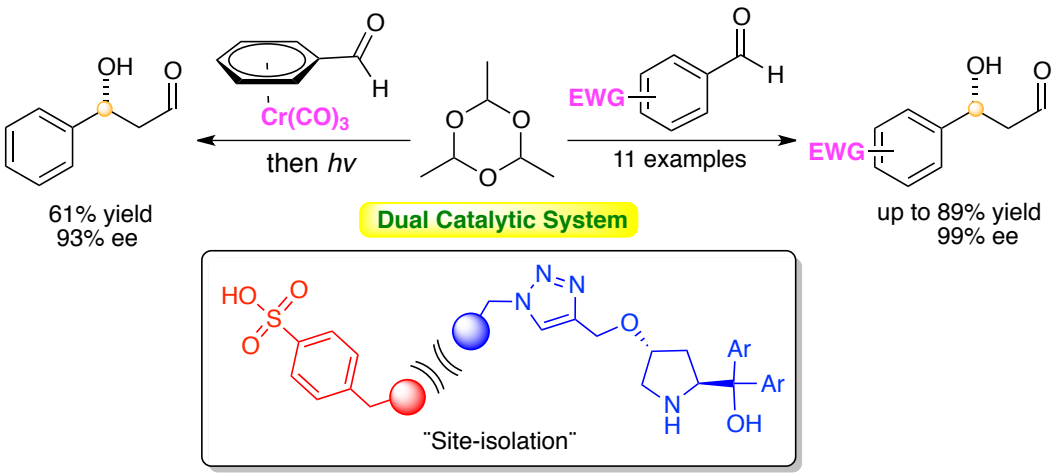
convenient yield. In comparison to its homogeneous counterpart, the immobilized isothiourea catalyst displays higher stereoselectivity and can be recycled for at least 11 runs as well as applied in continuous flow process.

Chapter IV. Catalytic Enantioselective [8+2] Cycloaddition



In this chapter, we report an asymmetric periselective [8+2] higher-order cycloaddition between chiral ammonium enolates and azaheptafulvenes catalyzed by an immobilized isothiourea catalyst. The resulting [8+2] cycloadducts can also undergo completely regioselective [4+2] cycloaddition with active dienophiles to afford bridged polycyclic products in a straightforward manner.

Chapter V. Dual Catalytic System



The cascade deoligomerization/cross-aldol reactions of electron-poor benzaldehydes or η^6-benzaldehyde $Cr(CO)_3$ complex with paraldehyde can be promoted by a dual catalytic system, which operates under site isolation conditions in a recyclable manner. In addition, the obtained products can be easily transferred to medicinal drugs or natural product intermediates.

CHAPTER I

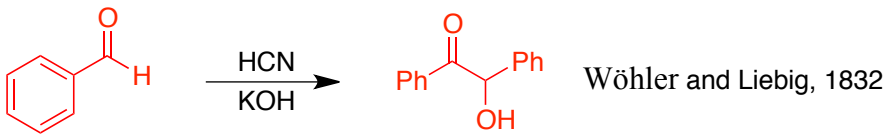
Chapter I

General Introduction

1.1. Organocatalysis

In organic chemistry, chemical reactions that are promoted by substoichiometric amounts of organic molecules are designated as organocatalyzed.[1] In the last twenty years, organocatalysis has become a thriving field, finding broad application in asymmetric transformations. Synthesis of enantiopure molecules having multiple chiral centers is one of the ultimate goals in organic chemistry due to their importance in a pharmaceutical context.[2] As a result, organocatalysts play pivotal roles in the preparation of complex and enantiopure molecular scaffolds owing to their efficient and selective catalytic properties.[3]

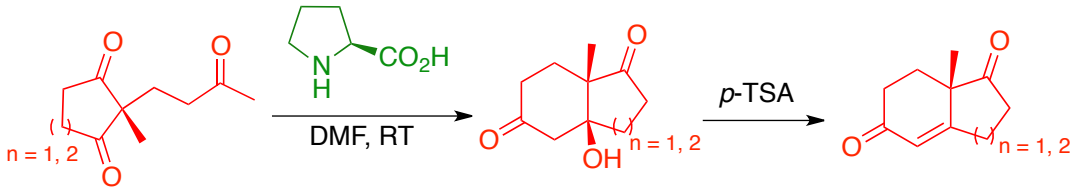
In 1832, Wöhler and Liebig reported the first organocatalyzed benzoin reaction for the construction of α-hydroxyl ketone by employing cyanide as organocatalyst (Scheme 1.1).[4]



Scheme 1.1. First example of organocatalysis

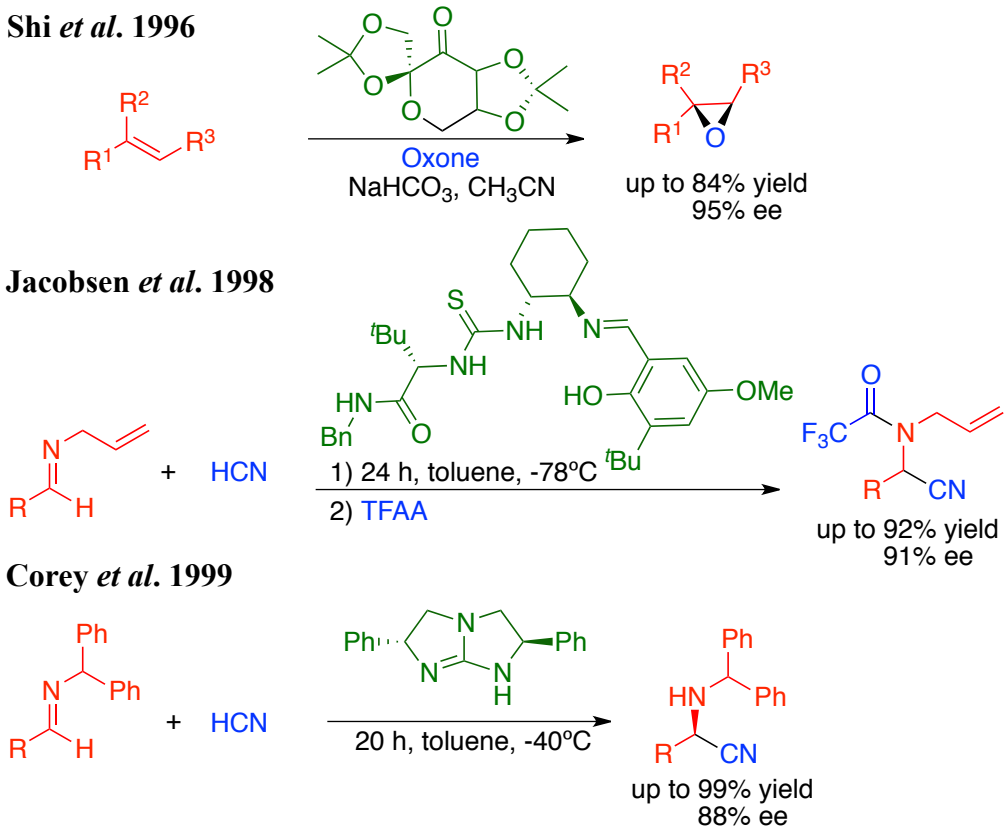
Until the middle of the twentieth century, only sporadic examples of asymmetric organocatalytic reactions appeared. Bredig and Fiske demonstrated the first asymmetric organocatalytic reaction for asymmetric addition of HCN to benzaldehyde, although only poor enantioselectivity could be achieved.[5] In 1960, Pracejus described an organocatalytic methanolysis reaction by using chiral *O*-acetylquinine as catalyst, affording the desired ester product in moderate enantioselectivity (74% ee).[6] In this report, one German terminology "Organische Katalysatoren" employed by the author, is a likely ancestor of what nowadays is termed "organocatalysis" by scientists.

The major breakthrough in the field of organocatalysis was achieved in the 1970s. The transformation, better known as Hajos-Parrish-Eder-Sauer-Wiechert reaction,[7] consists in using L-proline to catalyze the intramolecular aldol condensation reaction, giving the corresponding bicyclic ketones in excellent enantioselectivities (Scheme 1.2).



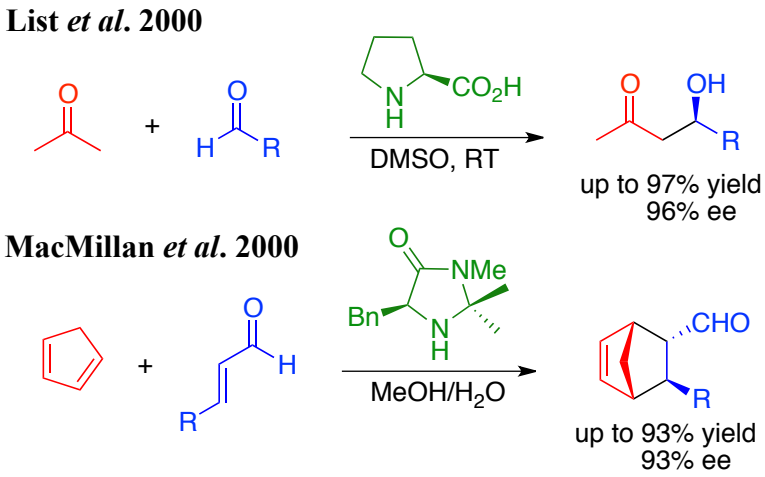
Scheme 1.2. Hajos-Parrish-Eder-Sauer-Wiechert reaction

Subsequently, the potential of organocatalysis was largely neglected in the next twenty years, despite the pioneering efforts achieved by these industrial chemists. Until the late 1990s, a few examples of organocatalysis appeared. Shi and co-workers described an enantiopure ketone-catalyzed highly enantioselective epoxidation reaction of simple olefins.[8] The Jacobsen and Corey groups independently reported the first examples of hydrogen-bonding catalysis for asymmetric Strecker reaction (Scheme 1.3).[9]



Scheme 1.3. Some representative pioneering work of organocatalysis

At the turn of the 21st century, the field of organocatalysis was effectively revived by two seminal studies: one from the List, Barbas and Lerner on intermolecular aldol reactions via enamine catalysis[10] and the other from MacMillan *et al*. on the Diels-Alder reaction via iminium catalysis (Scheme 1.4).[11]



Scheme 1.4. Asymmetric organocatalyzed aldol reaction and Diels-Alder cycloaddition

Since the concept of organocatalysis was firmly established by these pioneering reports, a variety of organocatalysts have been developed in various asymmetric reactions. In general, organocatalysts can be divided into different categories according to the interaction of catalyst with substrate: covalent bond, noncovalent interactions (such as hydrogen bonding) and electrostatic ion pair interactions.[1, 4] Some representative organocatalysts are shown in Figure 1.1.

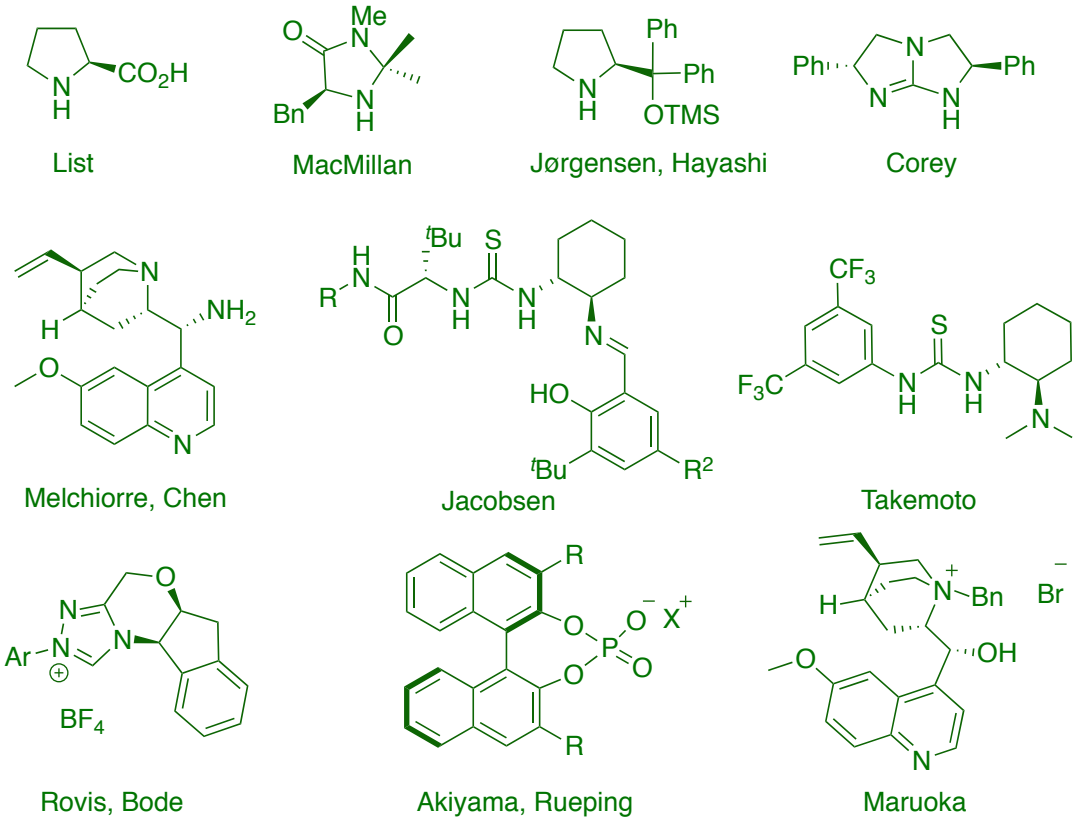


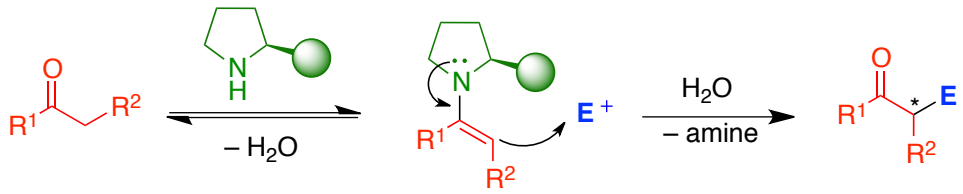
Figure 1.1. Some representative organocatalysts

As one of the most important types of covalent organocatalysts, aminocatalysis is nowadays considered as a powerful synthetic tool for the chemo- and enantioselective functionalization of carbonyl compounds such as aldehydes and ketones. According to the activation mode, aminocatalysts are widely divided in three types, HOMO (highest occupied molecular orbital) activation,[12] LUMO (lowest unoccupied molecular orbital) activation[13] and SOMO (singly occupied molecular orbital) activation.[14]

1.1.1 HOMO Activation

Enamine Catalysis

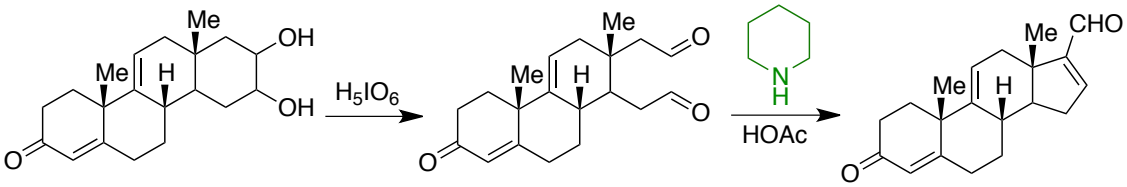
The general strategy of enamine catalysis is based on the condensation between an aminocatalyst and a carbonyl compound.[15] The resulting transient enamine intermediate can attack electrophiles to afford the corresponding α-functionalized carbonyl compounds (Scheme 1.5).



Scheme 1.5. Enamine catalysis

The pioneering research by Woodward, Wieland and Miescher in 1950s on the steroid total synthesis showed the potential of enamine catalysis for activation of carbonyl compounds (Scheme 1.6).[16]

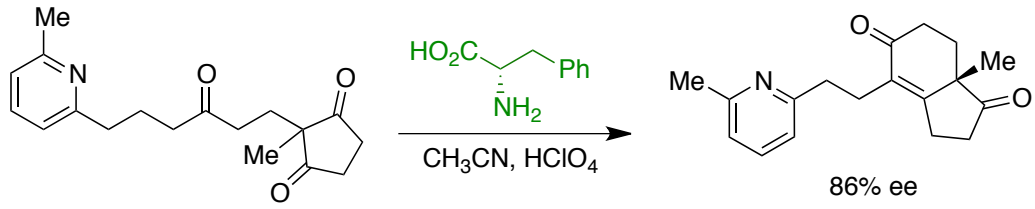
Woodward *et al.* 1952



Scheme 1.6. Woodward-Wieland-Miescher enamine cyclization

Since the first example of asymmetric intramolecular aldol reaction reported by Hajos *et al*. (Scheme 1.2), the application of asymmetric enamine catalysis in natural product synthesis was also explored. In 1976, Danishefsky and co-workers successfully extended the use of chiral amino acids as enamine catalysts in the asymmetric synthesis of estrone and 19-norsteroids (Scheme 1.7).[17]

Danishefsky *et al.* 1976



Scheme 1.7. Asymmetric intramolecular aldol reaction

To understand the mechanism of enamine catalysis in aldol reactions, many groups carried out mechanistic studies, proposing different transition states for the aldol reactions during this period (Figure 1.3).[18]

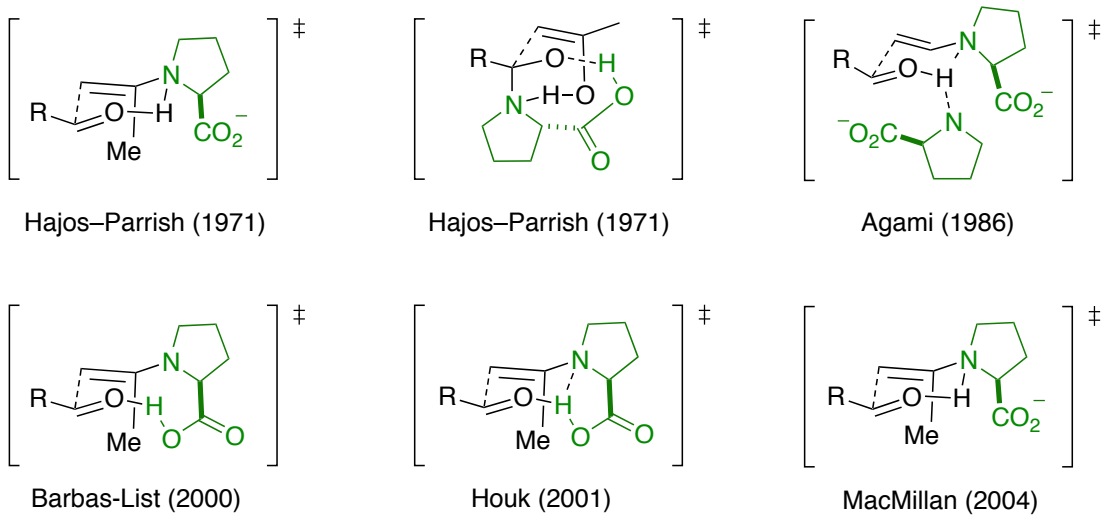
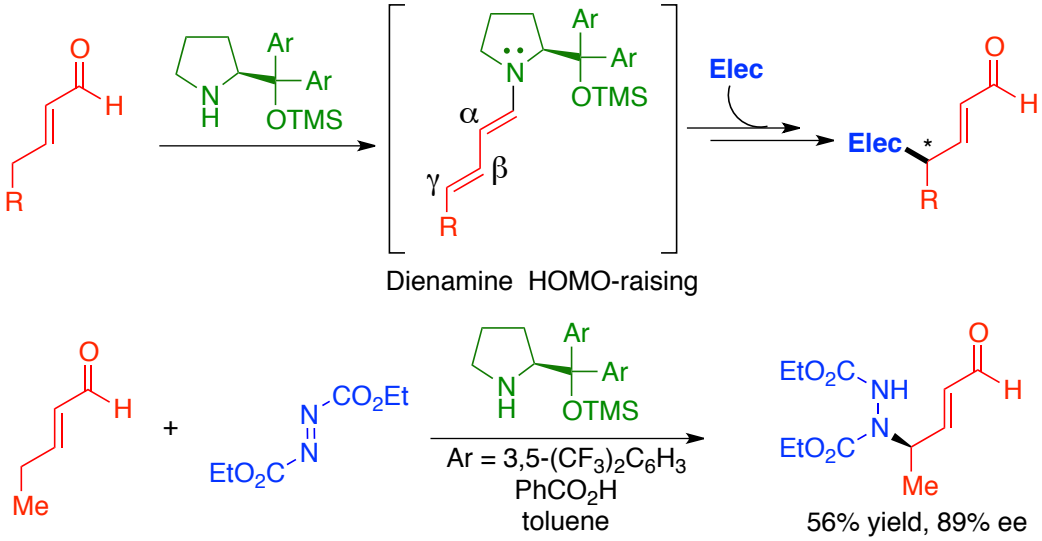


Figure 1.3. Proposed transition states of aldol reaction

Dienamine Catalysis

The concept of dienamine catalysis was first introduced by Jørgensen and co-workers for the direct asymmetric γ-amination of α,β-unsaturated aldehydes in 2006.[19] At the outset of this study, a chiral secondary amine catalyst was shown to activate 2-pentenal in the form of an electron-rich dienamine species which is in equilibrium with the iminium-ion intermediate. The γ-amination reaction proceeded smoothly between the diethyl azodicarboxylate and the chiral dienamine formed in situ with the catalyst, affording the γ-functionalized products in good yields and enantioselectivities. Subsequent investigation by means of computational calculations indicated that γ-amination of α,β-unsaturated aldehydes might proceed through a hetero-Diels-Alder cycloaddition reaction (Scheme 1.8).

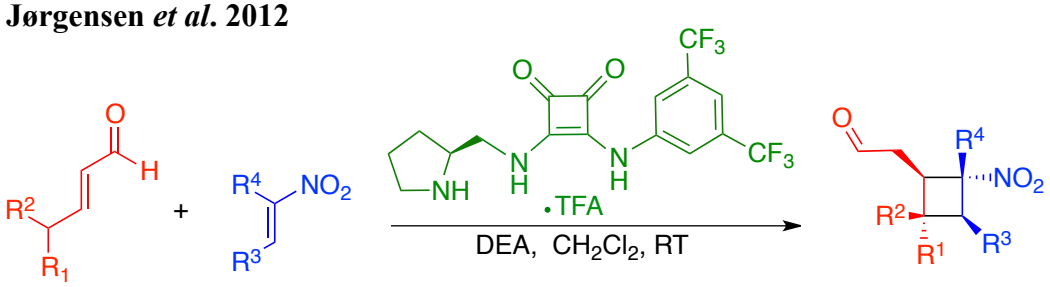
Jørgensen *et al.* 2006



Scheme 1.8. γ-Amination of α,β-unsaturated aldehydes by dienamine catalysis

In 2012, the same group described a novel [2+2] cycloaddition reaction based on the combination of a H-bond-directing and dienamine catalysis (Scheme 1.9).[20] To achieve this dual activation strategy, they designed a new bifunctional squaramide aminocatalyst derived from optically active 2-aminomethylpyrrolidine. The H-bond donor of the dual catalyst could control the electrophilic substrates while the secondary amine of the catalyst simultaneously activated the unsaturated aldehydes via dienamine catalysis, providing the desired product in high yields and excellent diastereo- and enantioselectivities.

Jørgensen *et al.* 2012



Scheme 1.9. H-bond directing and dienamine Catalysis

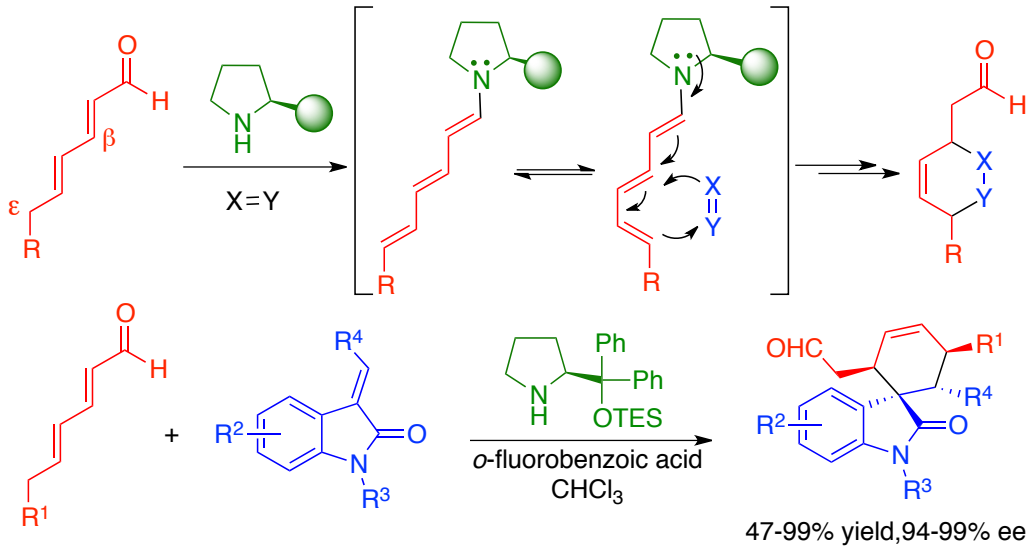
In Chapter II, we report an asymmetric [4+2] cycloaddition catalyzed by a H-bond-directing organocatalyst via dienamine catalysis strategy.

Trienamine Catalysis

The first example of trienamine catalysis was reported by Chen and Jørgensen, when they demonstrated the Diels-Alder reaction of different classes of dienophiles with polyenals

(Scheme 1.10).[21] The reaction employed trienamine intermediates that were in situ generated from optically active secondary amines, affording highly complex molecular structures with excellent stereoselectivities. It should be noted that the trienamine activation showed a perfect stereocontrol relay over a distance of up to eight bonds.

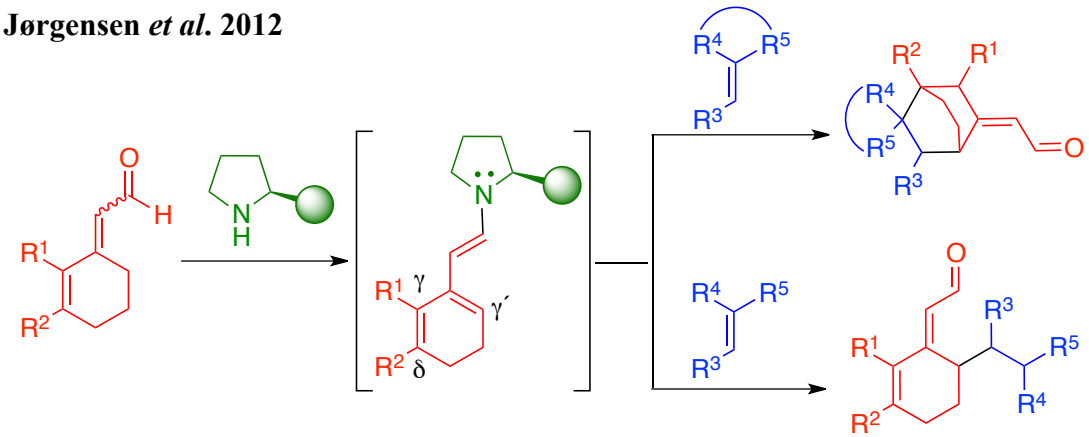
Chen *et al.* 2011



Scheme 1.10. Diels-Alder reaction of trienamine catalysis

Shortly after the linear trienamine catalysis work, the Jørgensen group developed the first cross trienamine catalysis by activation of γ′,δ-carbon centers of cyclic dienals in Diels-Alder reaction (Scheme 1.11).[22] In addition, they also reported highly γ′-selective additions with polarized vinyl bis-sulfones, providing the desired product in a highly stereoselective manner. Further computational calculation and NMR analysis of intermediates suggested that the reaction is thermodynamically driven.

Jørgensen *et al.* 2012

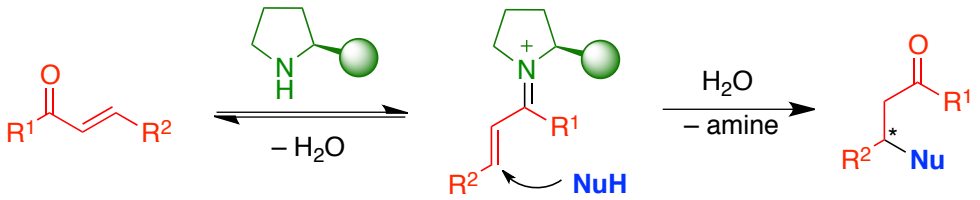


Scheme 1.11. Cross-trienamines in organocatalysis

1.1.2 LUMO Activation

Iminium-ion Catalysis

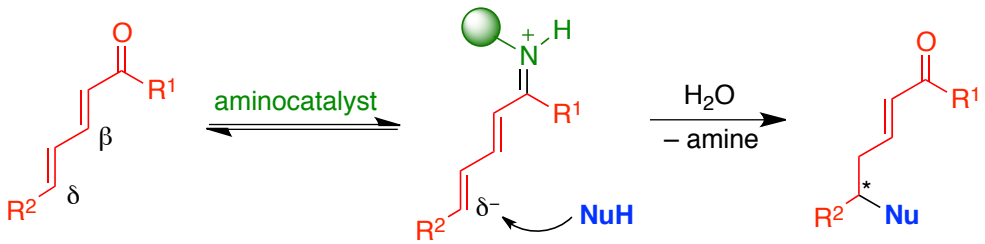
The iminium-ion catalysis was first reported by MacMillan in 2000 for the asymmetric Diels-Alder reaction of unsaturated aldehydes with dienes.[11] The iminium-ion intermediate, generated from the condensation of a chiral amine and an enal, enables the attack of nucleophiles to the β-position of unsaturated carbonyl compounds (Scheme 1.12). Based on this powerful strategy, numerous types of reactions such as Friedel-Crafts, hydride reduction, cyclopropanation, conjugate amination, epoxidation reaction have been achieved in an asymmetric manner.[23]



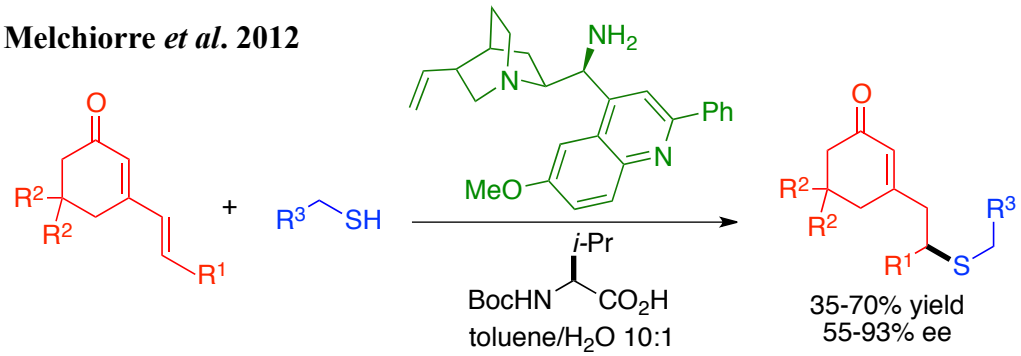
Scheme 1.12. Iminium-ion catalysis

Vinylogous Iminium-ion

In 2012, Melchiorre and co-workers developed the concept of asymmetric vinylogous iminium-ion catalysis in 1,6-addition of alkyl thiols to cyclic dienones.[24] In this strategy, the condensation between a cinchona-based primary amine and 2,4-unsaturated carbonyl compounds led to the formation of an iminium ion intermediate of extended conjugation (Scheme 1.13). The δ-carbon atom of this vinylogous iminium-ion intermediate presents higher electrophilicity than that of the cyclic dienone substrate, providing the 1,6-addition products with high stereocontrol and excellent enantioselectivities (Scheme 1.14).



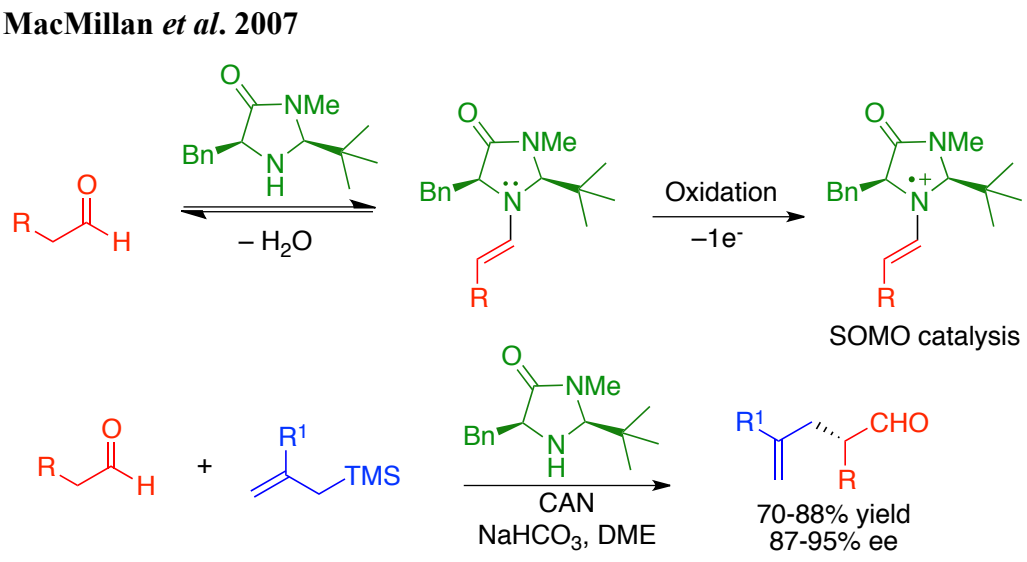
Scheme 1.13. Vinylogous iminium-ion catalysis



Scheme 1.14. 1,6-Addition of alkyl thiols to cyclic dienones via vinylogous iminium-ion catalysis

1.1.3. SOMO Activation

The SOMO (singly occupied molecular orbital) activation mode was first introduced by the MacMillan group in 2007.[25] SOMO catalysis is based on the generation of a three π-electrons radical cation resulting from single electron oxidation of an electron-rich enamine. This highly reactive intermediate can be attacked at the α-carbon of the aldehyde by weak carbon nucleophiles. For example, they demonstrated the direct asymmetric allylic alkylation reaction of different aldehydes by using allyltrimethylsilanes as the SOMO nucleophiles and ceric ammonium nitrate (CAN) as the single-electron-transfer oxidant, affording the corresponding α-allylation products in very good selectivity. Moreover, SOMO catalysis has also been applied in asymmetric α-allylation, α-enolation, α-vinylation and α-heteroarylation transformations (Scheme 1.15).[26]



Scheme 1.15. SOMO catalysis activation mode and α-allylation reaction

1.1.4. Ammonium Enolates

Ammonium enolates, another powerful tool in aminocatalysis, are prepared by the reaction of tertiary amines (R_3N) and various electrophilic substrates including anhydrides, acyl halides α-halocarbonyls, and α,β-unsaturated carbonyls.[27] According to the number of atoms between the enolate oxygen atom and the Lewis base catalyst, ammonium enolates can be divided in C1-, C2- and C3-ammonium enolates (Figure 1.4). This thesis will focus on the C1-ammonium enolates.

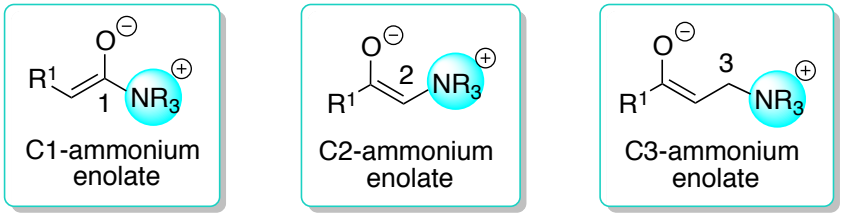
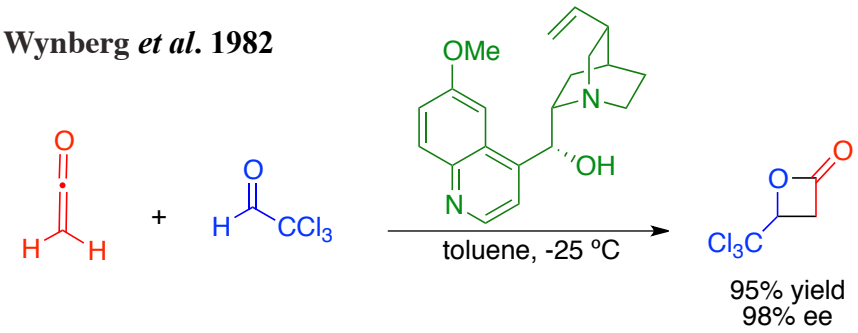


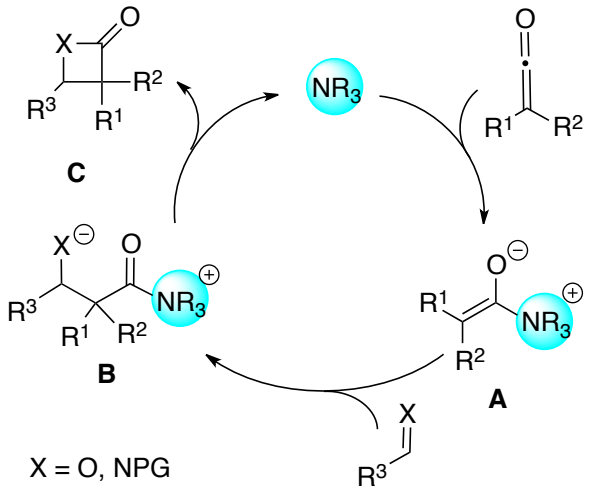
Figure 1.4. Classification of ammonium enolates

Since the earliest work of ammonium enolates carried out by Sauer in 1947,[28] many synthetic efforts have been achieved over the past decades. In 1982, Wynberg and co-workers reported the organocatalytic asymmetric aldol lactonization by using cinchona alkaloid as catalyst, affording the corresponding β-lactone in high yield and enantioselectivity (Scheme 1.16).[29]



Scheme 1.16. β-Lactone synthesis mediated by ammonium enolate

Inspired by the work of Wynberg, many groups have utilized ketenes as precursors for ammonium enolates in the synthesis of β-lactones and β-lactams.[30] The general catalytic cycle for these reactions proceeds through initial attack of the nucleophilic amine catalyst to the ketene electrophile, forming the ammonium enolate species **A**. The resulting zwitterion **A** undergoes conjugate addition (**B**), followed by cyclization, giving the cycloadducts **C** and regenerating the tertiary amine catalyst (Scheme 1.17).



Scheme 1.17. Mechanism of β-lactones and β-lactams formation

Recently, the development of cheap and highly stable alternative precursors to play the role of the unstable ketenes in the in situ generation of ammonium enolates attracted much attention. These alternative precursors include carboxylic acids, esters, acid chlorides and anhydrides, which are easily prepared, bench stable and user friendly.[31] In Chapter III and Chapter IV, we will focus on the use of carboxylic acids as precursors for ammonium enolates in various formal [4+2] and [8+2] cycloadditions.

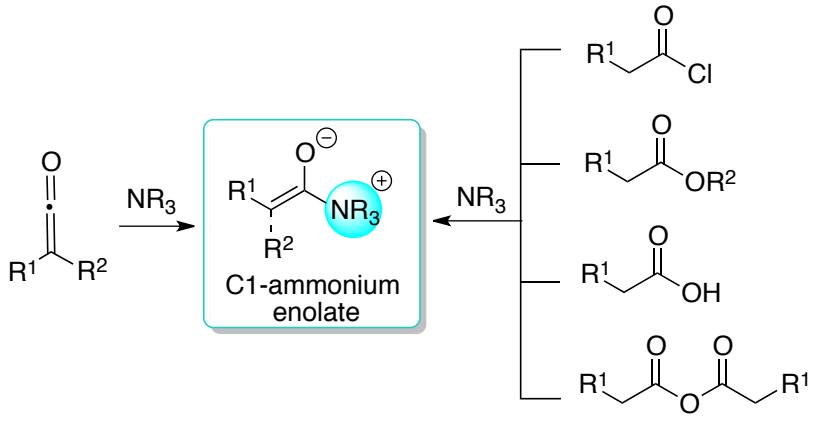


Figure 1.5. Different precursors for generation of C1-ammonium enolates

1.2. Immobilized Catalysts

The sharp increase of the demand for efficient and environmentally acceptable industrial processes has led to the immobilization of homogeneous catalysts.[32] These immobilized catalysts can be separated easily from the reaction mixture and reused several times. In addition, they provide the possibility of continuous flow operation and represent a cost-effective solution. In the ideal situation, an immobilized catalyst should keep a high

activity, compared to its homogeneous counterpart, while having the reusability of a heterogeneous catalyst. In general, the immobilization of homogeneous catalysts can be achieved by two main strategies: covalent binding and non-covalent interactions.[33]

Non-covalent interactions include adsorption (van der Waals forces), electrostatic or ionic interactions, and entrapment.[34] This approach of immobilization does not need re-designing the catalyst but only limited applications can be achieved owing to the weak interactions. For example, immobilization of catalysts through adsorption tends to suffer from catalyst leaching, which leads to reduction in catalytic efficiency.

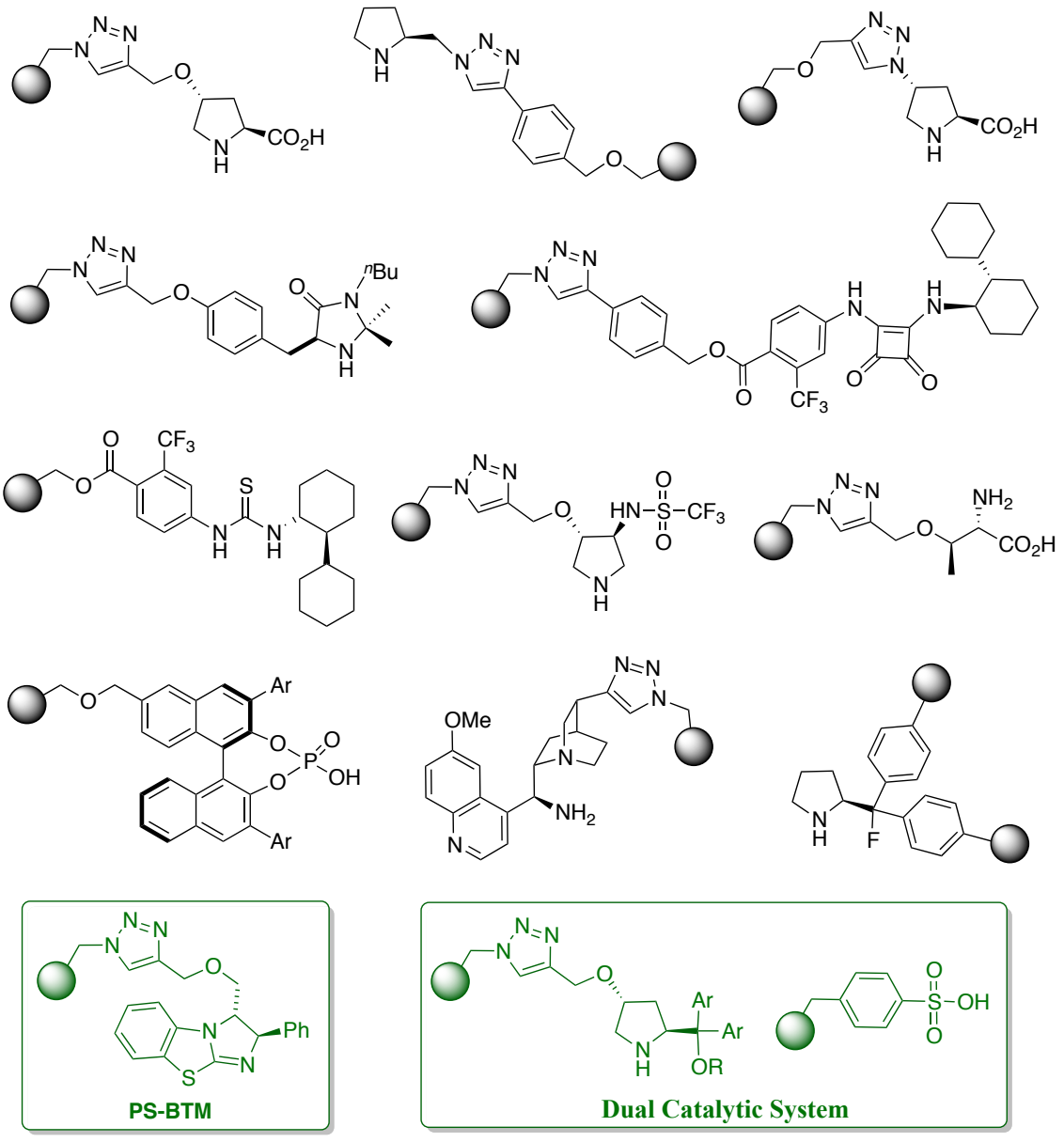


Figure 1.6. Some polystyrene-supported organocatalysts reported by our group

Covalent binding is the most common strategy of immobilization and provides broad applicability due to the stability of the resulting material in many reactions and work-up conditions. This strategy usually requires re-designing the catalyst to link it to a suitable support, commonly silicas, nanotubes, inorganic oxides or organic polymers. Over the past decades, our group has focused on the development of different polystyrene supported (PS) ligands and organocatalysts; some representative supported catalysts are shown in Figure 1.6. Chapters III and Chapters IV of this thesis will show the application of PS-benzotetramisole (BTM) catalyst. On the other hand, a dual catalytic system of two immobilized catalysts will be shown in Chapters V.

1.3. Continuous Flow Methodology

One of the main advantages of using immobilized catalysts is the possibility of implementing continuous flow processes. Compared with conventional batch synthesis, continuous flow features safe operation, cost-effectiveness, easy scale up and precise control of reaction conditions.[35] These advantages make it an attractive solution for industrial operation and large scale preparation.

Continuous flow synthesis is achieved by pumping the initial reactants through the reactor and flowing out the product in a continuous manner. By the use of packed-bed columns for loading immobilized catalyst, the separation and recovery of the catalyst can be easily achieved in a single operation. In addition, no mechanical stirring is required in continuous flow processes, which could increase the service lifetime of the immobilized catalyst. Several applications of continuous flow with various of immobilized catalysts have been achieved in our group.[36] One application of continuous flow is shown in Figure 1.7 and Chapter III, in which an asymmetric formal [4+2] cycloaddition reaction catalyzed by a supported isothiourea catalyst has been successfully set up.

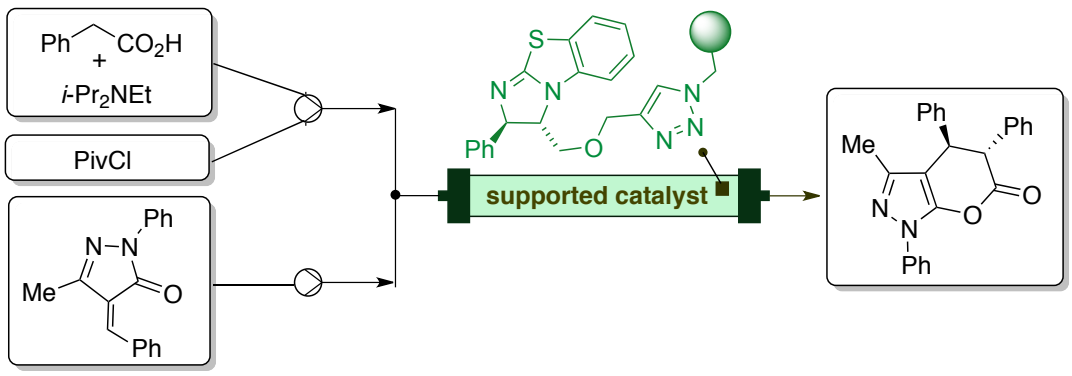


Figure 1.7. Supported isothiourea catalyst in continuous flow process

1.4. Aim of the thesis

The discovery and design of organocatalysts for the efficient preparation of useful enantiopure compounds represents an important goal in organocatalysis. When asymmetric processes are concerned, the recycle and reuse of organocatalysts and implementation of continuous flow processes have attracted more attention due to many advantages.

The aim of the present thesis includes two main sections: (a) studies towards the synthesis of organocatalysts especially polymer-supported ones in asymmetric transformations and their application in recycling experiments and continuous flow processes. (b) the development of new transformations for highly selective bond formations that will enable more rapid and efficient access to potential biologically active compounds and polycyclic scaffold.

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CHAPTER II

Chapter II

H-Bond-Directing Organocatalyst for Asymmetric [4+2] Cycloadditions via Dienamine Catalysis

2.1. Introduction

The synthesis of optically active pyrazolones and their derivatives has attracted a great deal of attention due to their occurrence in many natural products and bioactive compounds. For instance, phenazone **A** and **B** are known as an effective analgesic and antipyretic agent, and the pyrazolone derivative **C** possesses potent activity in inhibiting p38 kinases. In addition, the tetrahydropyranopyrazole (THPP) of the type **D** and the trifluoromethylated analogue **E** are used as fungicide and AMPA receptor activity enhancer, respectively. Compound **F** is well known as a potential inhibitor of human Chk1 kinase (Figure 2.1).[1] As a result, many synthetic efforts have been devoted to the synthesis of functionalized pyrazolones.[2] Nevertheless, the catalytic asymmetric synthesis of fuctionalized tetrahydropyranopyrazoles (THPPs) or dihydropyrano-pyrazolones (DHPPOs) has been less explored.

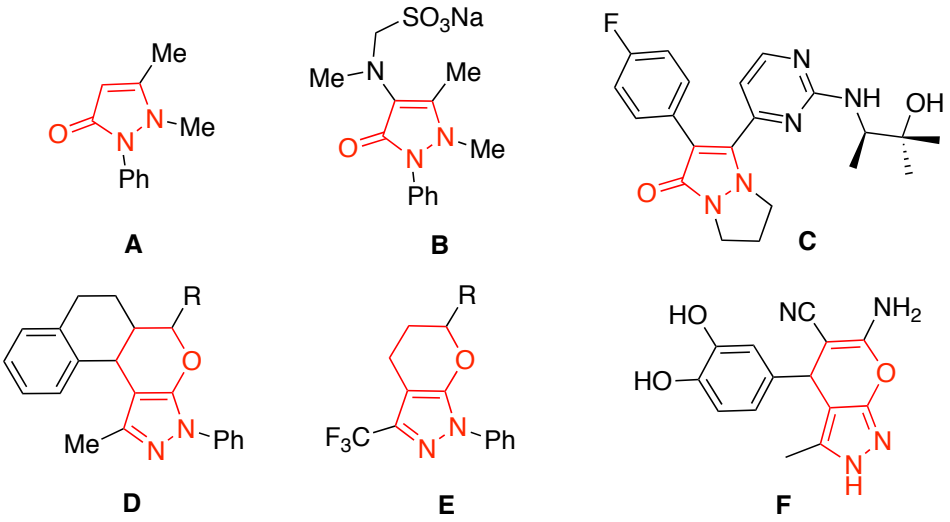
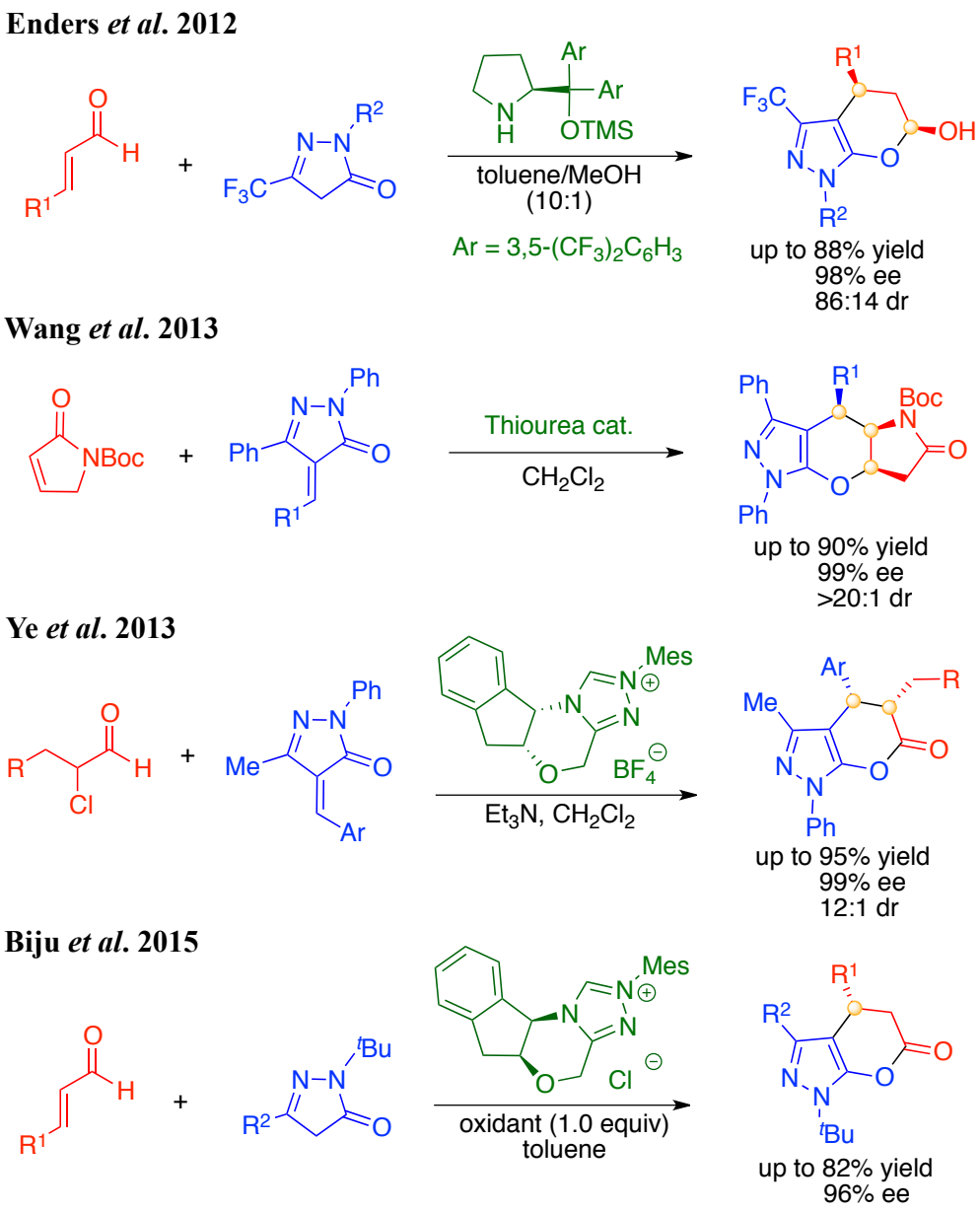


Figure 2.1. Biologically active pyrazoles and pyranopyrazoles

In 2012, Enders and co-workers developed a Michael/Wittig cascade reaction catalyzed by a chiral secondary amine, affording functionalized THPPs in good yields and

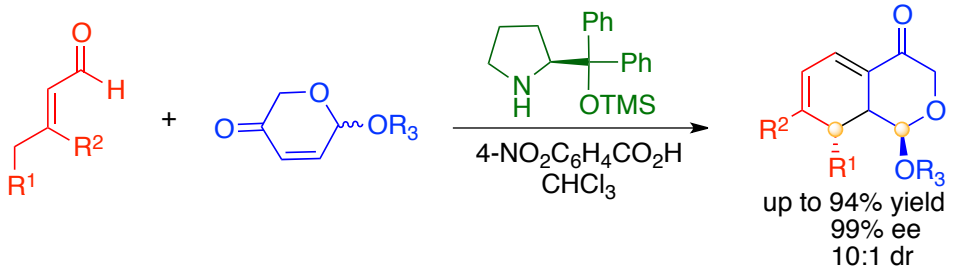
stereoselectivities.[3] Shortly after, Wang and co-workers disclosed an asymmetric β,γ-selective [4+2] cycloaddition for the enantioselective construction of functionalized THPPs.[4] As for the preparation of DHPPOs, the Ye and Biju groups demonstrated *N*-heterocyclic carbene (NHC) catalyzed enantioselective annulations for the synthesis of these scaffolds, respectively (Scheme 2.1).[5] Despite these approaches to chiral THPPs, the development of an efficient methodology to access multifunctionalized and highly enantioenriched THPP frameworks bearing multiple stereocentres is still a challenging endeavor.



Scheme 2.1. Pioneering works for the synthesis of THPPs and DHPPOs

HOMO-raised dienamine species generated upon the condensation of a chiral amine catalyst and α,β-unsaturated aldehyde, have performed as dienophiles or dienes in various cycloaddition reactions. An excellent example of dienamine species playing the role of diene was reported by the Vicario group in 2012[6]. In this case, the dienamine intermediate undergoes a Diels-Alder/elimination cascade reaction and results in a highly efficient dynamic kinetic resolution process.

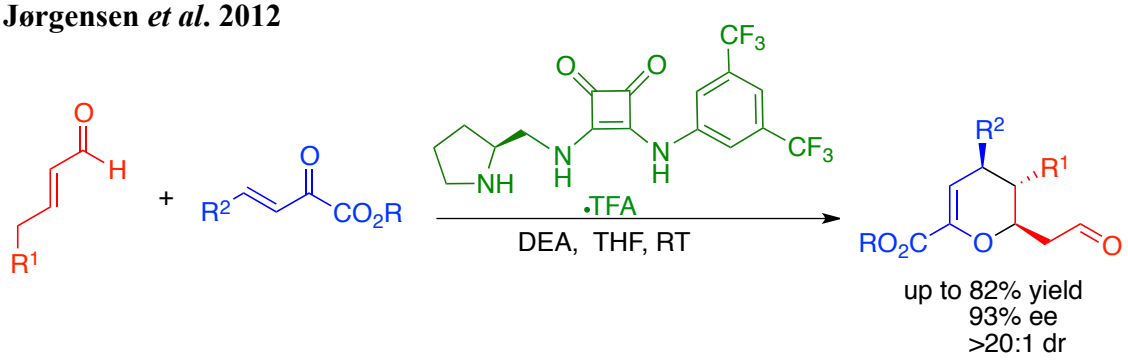
Vicario *et al.* 2012



Scheme 2.2. Dynamic kinetic resolution process of dienamine catalysis

In 2012, the Jørgensen group first reported H-bond-directing dienamine catalysis by inverting the inherent reactivity of α,β-unsaturated aldehydes, which acted as dienophiles for the inverse-electron-demand hetero-Diels–Alder (IEDHDA) reactions.[7] This strategy based on employing a bifunctional H-bond-directing catalyst, which could carry out simultaneous activation of an α,β-unsaturated aldehyde via dienamine formation and recognize the heterodiene system by H-bonding interation (Scheme 2.3).

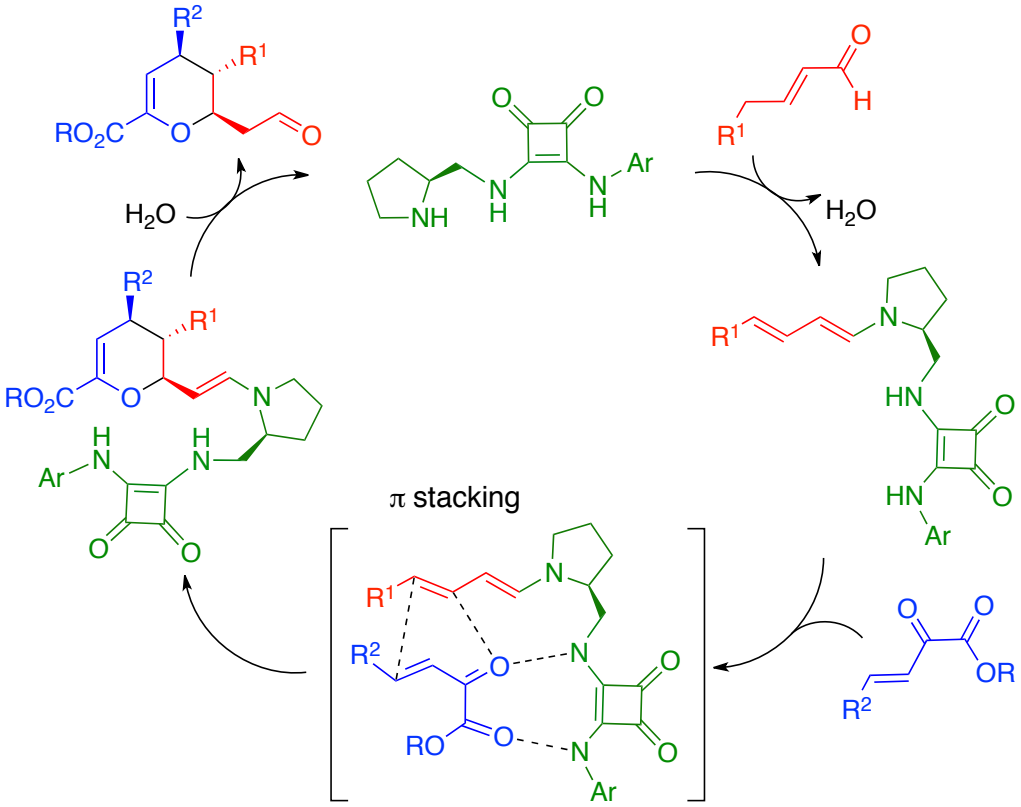
Jørgensen *et al.* 2012



Scheme 2.3. Dienamine-mediated asymmetric [4+2] cycloaddition

To explain the stereochemical outcome, they proposed a transition state model and the plausible reaction mechanism depicted in Scheme 2.4. The two reagents are activated independently: the α,β-unsaturated aldehyde through HOMO activation and the β,γ-unsaturated α-ketoester through LUMO lowering, which in addition fixes the geometry of the approach thanks to the H-bond-directing interaction. Notably, the authors

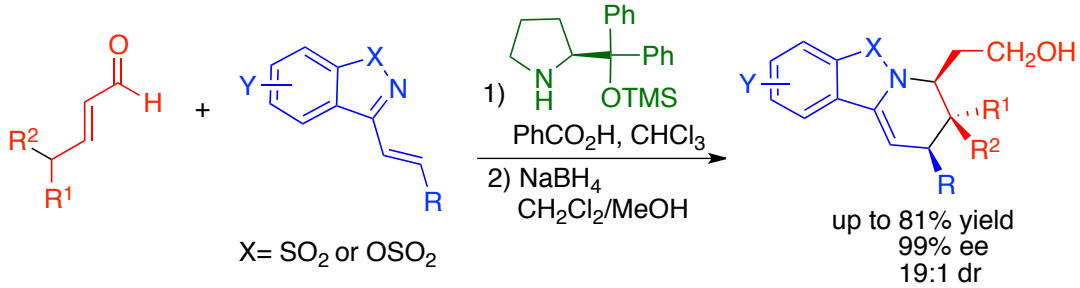
postulated π-stacking interactions between the aromatic moieties of the heterodiene and the dienamine intermediate may play an important role to stabilize the transition state.



Scheme 2.4. Plausible reaction mechanism of dienamine catalysis

Later, the Chen group demostrated the asymmetric IEDHDA reaction of 1-aza-1,3-butadienes with α,β-unsaturated aldehydes by employing dienamine catalysis.[8] The reaction exhibits excellent regioselectivity, producing the fused piperidine derivatives in good yields and high stereoselectivities.

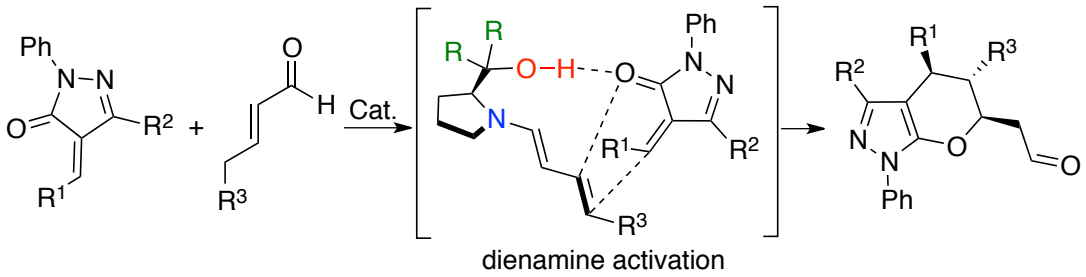
Chen *et al*. 2014



Scheme 2.5. Dienamine mediated IEDHDA reaction

2.2. Aim of the Project

Despite the previous approaches to chiral DHPPOs and THPPs, dienamine catalysis for the conversion of unsaturated pyrazolones has never been reported, although it is a potentially useful approach for the construction of THPPs bearing multiple stereocenters. In this project, we aim to employ a bifunctional H-bond-directing aminocatalyst to activate the α,β-unsaturated aldehydes and alkylidene pyrazolones, affording the fuctionalized THPPs in a highly stereoselectivitive manner (Scheme 2.6).



Scheme 2.6. Dienamine activation strategy for the synthsis of chiral THPPs

With this in mind, we decided to prepare a series of H-bond-directing aminocatalysts for the [4+2] cycloaddition between α,β-unsaturated aldehydes and alkylidene pyrazolones. The bifunctional aminocatalysts for this reaction is shown in Figure 2.2.

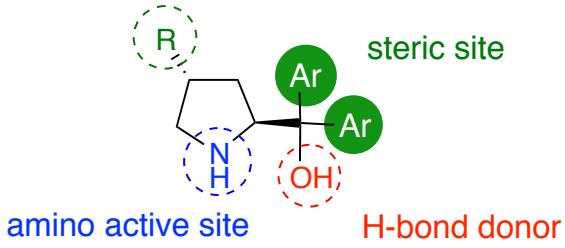


Figure 2.2. H-bond-directing aminocatalyst for [4+2] cycloaddition of alkylidene pyrazolones with enals

2.3. References

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Organic LETTERS

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H-Bond-Directing Organocatalyst for Enantioselective [4 + 2] Cycloadditions via Dienamine Catalysis

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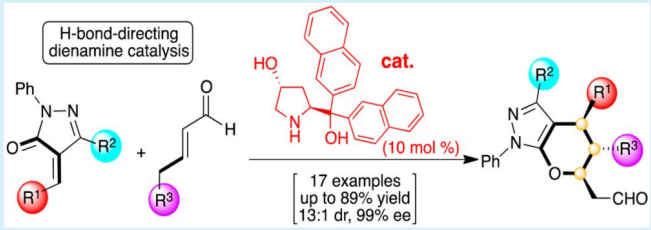
Supporting Information

ABSTRACT: An efficient, highly regio- and stereoselective [4 + 2] cycloaddition reaction to generate tetrahydropyranopyrazole frameworks has been developed. To this end, a dienamine-based catalytic strategy that relies on the H-bond-directing effect of the hydroxy group of a dinaphthylprolinol-type aminocatalyst has been used. This enables the synthesis of multifunctionalized heterocyclic derivatives with three contiguous stereocenters in good yields and excellent enantioselectivities.



Optically active pyrazolones and their derivatives are widely occurring scaffolds that can be found in many natural products and medicinally active molecules.[1] As a consequence, the catalytic asymmetric synthesis of pyrazolones has been the subject of several studies,[2] mainly involving three different strategies: (a) the deprotonation of the relatively acidic α-protons to generate a transient nucleophile;[3] (b) the exploitation of the inherent nucleophilicity of the pyrazole nitrogens;[4] and (c) the use of exocyclic alkylidene pyrazolones as Michael acceptors,[5] which can lead to cascade processes for the construction of spirocycles.

Tetrahydropyranopyrazoles[6] (THPPs) and dihydropyranopirazolones[7] (DHPPOs) are formal derivatives of pyrazolones in which this heterocyclic moiety is fused to a pyran or pyranone ring, respectively. Several members of this subclass present interesting pharmaceutical and biological properties, which make them appealing synthetic targets (Figure 1). Nevertheless, the

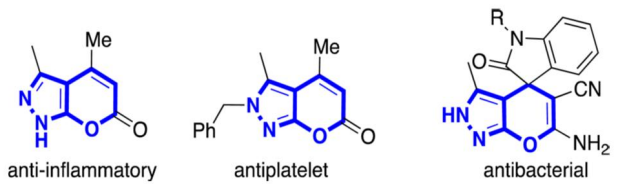
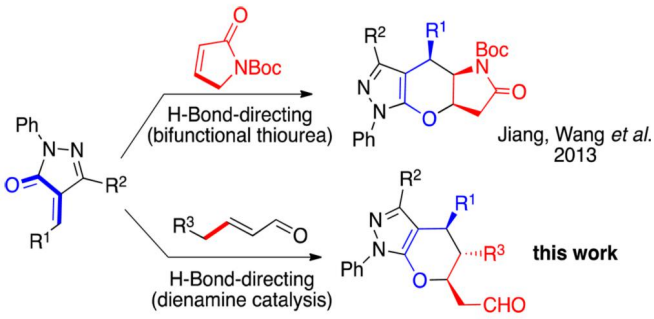


Figure 1. Some biologically active pyranopyrazol(on)es.

catalytic enantioselective transformation of pyrazolone derivatives into functionalized THPPs has received scant attention. In 2012, Enders disclosed an aminocatalytic 3-component reaction that provides THPPs with two stereocenters.[8] One year later, Wang and co-workers reported the bifunctional thiourea-catalyzed asymmetric [4 + 2] cycloaddition of α,β-unsaturated γ-butyrolactams with exocyclic alkylidene pyrazolones (Scheme 1, top).[9] As for the related DHPPOs, the Ye and Biju groups

Scheme 1. [4 + 2] Cycloaddition with Alkylidene Pyrazolones



independently reported NHC-catalyzed enantioselective annulations for the synthesis of these scaffolds.[10] However, the catalytic enantioselective construction of THPP scaffolds bearing three contiguous stereocenters is still a challenging endeavor.

Cycloadditions play a pivotal role in the construction of diverse heterocyclic skeletons.[11] Of special interest is the application of aminocatalytic [4 + 2] processes that involve dienamine intermediates. These can play a dual role as dienes or dienophiles,[12] and their nucleophilicity allows inverse-electron-demand hetero-Diels–Alder (IEDHDA) reactions to be carried out when they are combined with Michael acceptors. In 2012, Jørgensen et al. pioneered the H-bond-directing dienamine strategy in an excellent report showing a distal regio- and stereoselective IEDHDA reaction.[13] More recently, the Chen group developed a [4 + 2] cycloaddition reaction of 1-aza-1,3-butadienes with α,β-unsaturated aldehydes by employing dienamine catalysis.[14] Inspired by previous works on H-bond-directing dienamine-mediated strategies,[13,15] we report herein an

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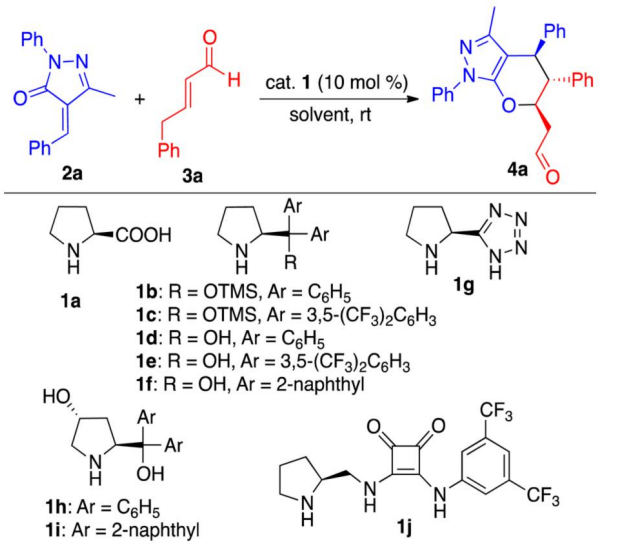
IEDHDA reaction between enals and alkylidene pyrazolones (Scheme 1, bottom). This dienamine-mediated process gives rise to THPPs with three contiguous stereocenters in excellent stereoselectivities. We began to study this reaction with pyrrolidine-derived aminocatalysts, given their success in dienamine-mediated processes.[16] Alkylidene pyrazolone **2a** and α,β-unsaturated aldehyde **3a** were chosen as model substrates, and a range of solvents were screened at room temperature (Table 1).

Table 1. Optimization of Reaction Conditions[a]

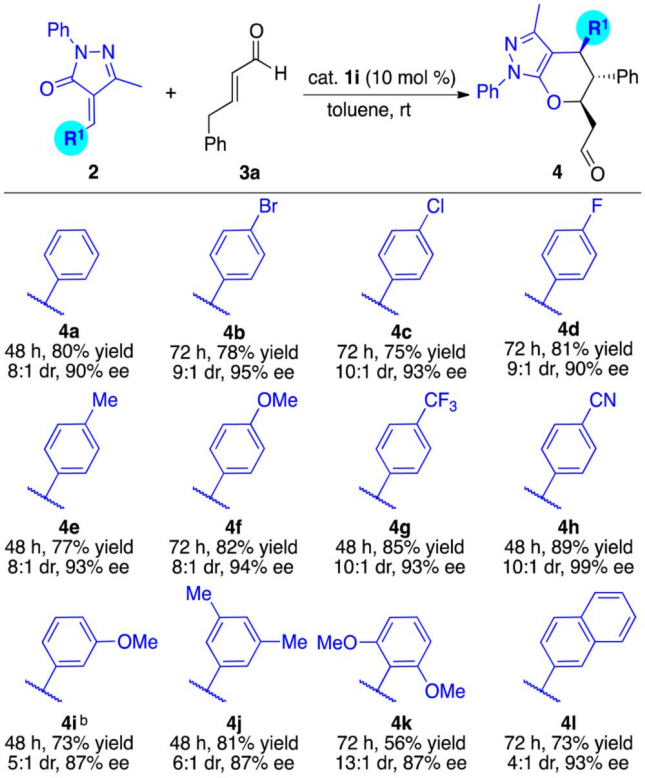


entry	cat.	solvent	t (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	CH_2Cl_2	12	70	1:1	11
2	**1b**	CH_2Cl_2	36	78	4:1	24
3	**1c**	CH_2Cl_2	48	76	4:1	43
4	**1d**	CH_2Cl_2	48	72	6:1	67
5	**1e**	CH_2Cl_2	60	61	6:1	66
6	**1f**	CH_2Cl_2	72	63	6:1	74
7	**1g**	CH_2Cl_2	6	77	4:1	20
8	**1h**	CH_2Cl_2	48	80	7:1	78
9	**1i**	CH_2Cl_2	48	76	7:1	81
10	**1j**	CH_2Cl_2	48	65	4:1	−38
11	**1i**	DCE	48	73	7:1	83
12	**1i**	$CHCl_3$	48	72	7:1	80
13	**1i**	MeCN	48	75	7:1	80
14	**1i**	Et_2O	48	69	6:1	68
15	**1i**	**toluene**	**48**	**80**	**8:1**	**90**
16	**1i**	mesitylene	48	77	8:1	89
17	**1i**	DMF	48	<10	nd	nd

[a]Reactions performed on a 0.1 mmol scale (see Supporting Information). [b]Isolated yield. [c]Determined by ^{1}H NMR spectroscopy. [d]Determined by chiral HPLC after reduction to the corresponding alcohol.

We first examined the [4 + 2] cycloaddition reaction catalyzed by proline, which gave the desired product in excellent regioselectivity and yield, but with poor dr and ee (Table 1, entry 1). When α,α-diarylprolinol silyl ethers were employed, both dr and ee increased slightly (entries 2 and 3). Subsequently, screening of various α,α-diarylprolinols, gave a remarkable increase in stereoselectivity (entries 4−6). We tentatively attribute this to the H-bonding ability of the free hydroxy group. Notably, we found that tetrazole **1g** could enhance the reactivity dramatically (6 h) but without any improvement in ee (entry 7). Pleasingly, compared to **1d**, catalyst **1h** (bearing an extra hydroxy group in C_4[17]) allowed to improve the yield with much higher ee and dr (entry 8). Based on this, we first prepared the more hindered 4-hydroxydinaphthylprolinol catalyst **1i**, which proved beneficial in terms of ee (entry 9). Pyrrolidine-squaramide catalyst **1j** failed to improve the catalytic activity and stereoselectivity (entry 10). Solvent screening (entries 11−17) indicated that toluene was the best option: in these conditions, using catalyst **1i**, the THPP **4a** could be isolated in 80% yield, 90% ee and 8:1 dr (entry 15). With the optimized conditions, the substrate scope of the asymmetric cycloaddition reaction was undertaken and a series of chiral THPPs were synthesized (Scheme 2).

Scheme 2. Scope of Alkylidene Pyrazolones[a]



[a]Reactions performed on a 0.15 mmol scale (see the Supporting Information). [b]Performed at 0 °C.

In general, alkylidene pyrazolones bearing different electron-withdrawing and electron-donating substituents were well tolerated. Specifically, all of the para-substituted substrates (**4b**−**4h**) were obtained in good yields (75−89%), high diastereoselectivities (8:1−10:1 dr), and excellent enantioselectivities (90−99% ee). In contrast to these, the meta-substituted **4i** and **4j** gave a little decrease in the diastereo- and enantioselectivity, while maintaining the high yields. Importantly, the system also admitted introduction of double substitution on the ortho−ortho′ position, providing **4k** in excellent diastereoselectivity (13:1 dr), comparable enantioselectivity (87% ee), and slightly lower yield. Furthermore, **4l** bearing a bulkier 2-naphthyl group was formed in moderate diastereoselectivity (4:1 dr) but with good yield (73%) and excellent enantioselectivity (93% ee).

Next, we set our sights on the performance of various α,β-unsaturated aldehydes. As presented in Scheme 3, the [4 + 2] cycloaddition reactions proceeded smoothly when enals with

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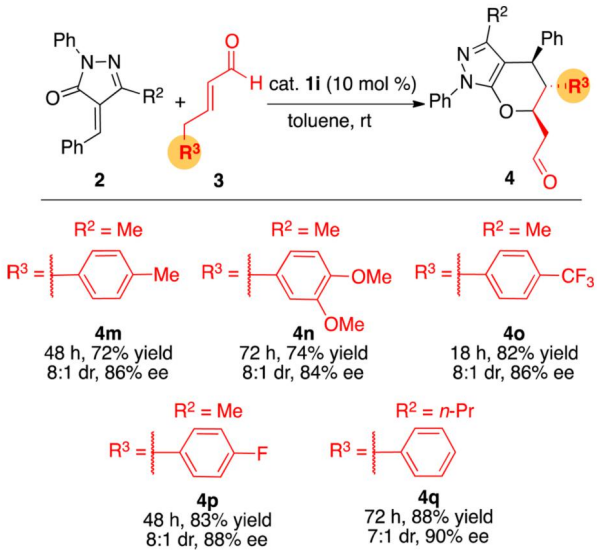
Scheme 3. Scope of Various Enal Reaction Partners[a]

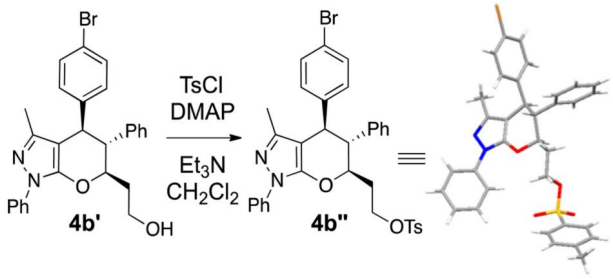


[a]Reactions performed on a 0.15 mmol scale (see Supporting Information).

diverse electronic properties were tested. The corresponding chiral tetrahydropyranopyrazoles **4m**–**4p** were obtained with high enantioselectivities (84–88%), good diastereoselectivities (8:1 dr), and good yields ranging from 72 to 83%. Gratifyingly, an alkylidene pyrazolone bearing a linear aliphatic substituent afforded product **4q** in 88% yield and high stereoselectivity (7:1 dr, 90% ee). As for alkyl-substituted enals, we have only tested crotonaldehyde, which gave good yields but very poor stereoselectivities.

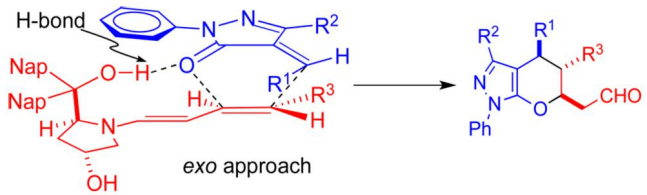
The absolute configuration of tosylate **4b″** (prepared from **4b′** as shown in Scheme 4) was unambiguously determined by X-ray single-crystal analysis.[18] The rest of the cycloadducts have been assigned by analogy to **4b**.

Scheme 4. Synthesis and X-ray Structure of 4b″



The model we propose to account for the formation of the major product is depicted in Scheme 5. The regioselectivity of the attack can be easily inferred from the structure of the final product, and it also matches with the expected course of action given the polarization of the dienamine and the alkylidene pyrazolone. Regarding the stereoselectivity, whereas the pyrazolone geometry is fixed, the dienamine can adopt several conformations. However, as demonstrated by Jørgensen and co-workers on the basis of DFT calculations,[16a] the (*E,s-trans,E*)-dienamine is the most stable conformer. Thus, out of the four possible approaches (see Supporting Information for details) only the one shown in Scheme 5 leads to the major stereoisomer. The preference for such an *exo* approach is justified in terms of (a) H-bonding between the hydroxy group of the diarylprolinol and the carbonyl of the pyrazolone and (b) the repulsion between the aromatic group in the pyrazolone (slightly tilted out-of-plane) and the dienamine, which would take place in an alternative *endo* approach.

Scheme 5. Model Proposed to Explain the Regio- and Stereoselectivity



In summary, we have disclosed the first asymmetric [4 + 2] cycloaddition between alkylidene pyrazolones and enals through H-bond-directing dienamine catalysis. The reaction, promoted by a bifunctional 4-hydroxydinaphthylprolinol species, proceeds smoothly with excellent regioselectivity and high stereoselectivity (up to 89% yield, 13:1 dr, and 99% ee). Thus, we have disclosed a new and efficient protocol for the synthesis of enantioenriched, multifunctionalized tetrahydropyranopyrazole derivatives containing three contiguous stereocenters. Further application of this method and biological evaluation of the THPPs is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03575.

Experimental procedures, characterization data, and copies of NMR spectra and HPLC chromatograms (PDF)

Compound **4b″** (CIF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Karl Anker Jørgensen on his 60th anniversary.

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(18) X-ray structure deposited under CCDC 1438957.

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Supporting Information

A H⁻Bond-Directing Organocatalyst for Enantioselective [4+2] Cycloadditions *via* Dienamine Catalysis

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Table of Contents

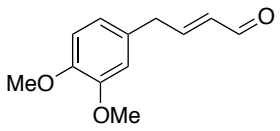
1. General information

Unless otherwise stated, all commercial reagents were used as received. Flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. Thin layer chromatography was carried out using Merck TLC Silicagel 60 F254 aluminum sheets. Components were visualized by UV light (λ = 254 nm) and stained with *p*-anisaldehyde or phosphomolybdic dip. NMR spectra were registered in a Bruker Advance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature, operating at 300 or 400 MHz (^1H) and 75 or 100 MHz (^{13}C). TMS was used as internal standard for ^1H NMR and $CDCl_3$ for ^{13}C NMR. Chemical shifts are reported in ppm referred to TMS. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses of the polystyrene supported catalysts were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid, Spain. High performance liquid chromatography (HPLC) was performed on an Agilent Technologies chromatograph (1100 Series), using Chiralcel columns and guard columns.

2. General procedure for the preparation of α, β-unsaturated aldehydes

Different *α*, *β*-unsaturated aldehydes were prepared according to the literature procedure.[1]

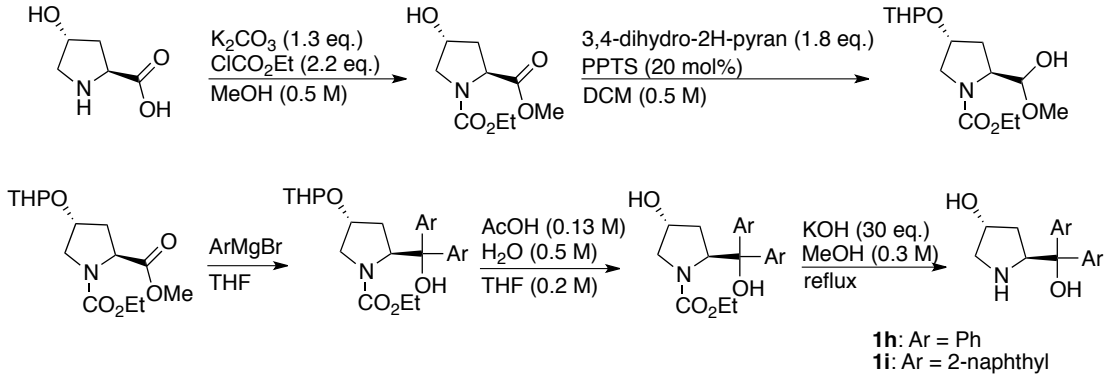
(*E*)-4-(3,4-Dimethoxyphenyl)but-2-enal



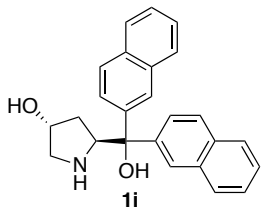
^1H NMR (400 MHz, $CDCl_3$): δ = 3.59 (dd, *J* = 1.6, 6.8 Hz, 2H), 3.87 (s, 6H), 6.08 (tdd, *J* = 1.6, 8.0, 15.6 Hz, 1H), 6.68-6.74 (m, 2H), 6.83-6.85 (m, 1H), 6.94 (td, *J* = 6.8, 15.6 Hz, 1H), 9.54 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.6, 55.9, 56.0, 111.5, 112.0, 120.9, 129.5, 133.3, 148.1, 149.2, 156.7, 193.8.

3. General procedure for the preparation of catalysts 1h and 1i

Catalysts **1h** and **1i** were prepared according to the literature procedure.[2]



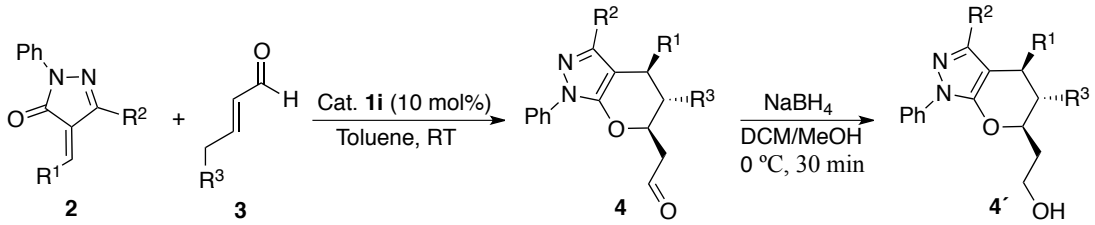
(3*R*,5*S*)-5-(Hydroxydi(naphthalen-2-yl)methyl)pyrrolidin-3-ol



1i

White solid, Melting point: 201-203 ºC. ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ = 1.36-1.41 (m, 1H), 1.74-1.82 (m, 1H), 2.85 (d, *J* = 11.2 Hz, 1H), 3.01 (dd, *J* = 4.0, 11.2 Hz, 1H), 4.18 (s, 1H), 4.84 (dd, *J* = 7.2, 8.8 Hz, 1H), 7.42-7.58 (m, 5H), 7.68 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.77-7.82 (m, 4H), 7.91-7.97 (m, 2H), 8.14 (s, 1H), 8.29 (s, 1H); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ = 36.5, 55.3, 62.6, 70.7, 77.8, 123.5, 124.4, 124.6, 125.7, 125.8, 125.9 (2C), 126.1, 127.2, 127.3 (2C), 127.4, 128.1, 128.2, 131.6, 131.7, 132.7, 132.7, 143.7, 144.7; IR (ATR): ν = 696, 743, 829, 1006, 1095, 1183, 1401, 1485, 1598, 1641, 2946, 3028, 3297, 3049 cm^{-1}; HRMS calcd. for $C_{25}H_{24}NO_2$ $(M + H)^+$: 370.1802, found: 370.1795; $[\alpha]_D^{25}$ = –116.3 (*c* = 0.1, MeOH).

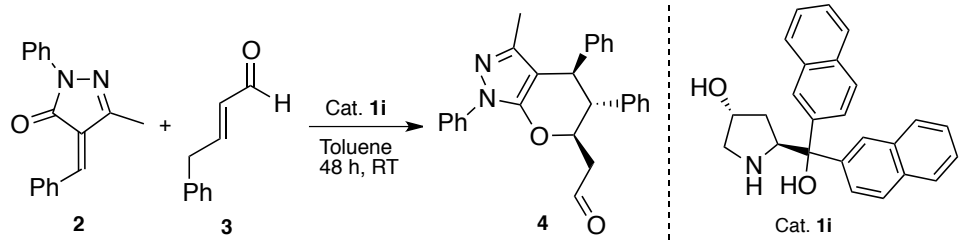
4. General procedure for the [4+2] cycloaddition reaction



To a solution of the (*Z*)-arylidenylpyrazolone[3] **2** (0.15 mmol, 1.0 equiv.) in toluene (1.5 mL) were added the α,β-unsaturated aldehyde **3** (0.3 mmol, 2.0 equiv.) and catalyst **1i** (0.015 mmol, 10 mol%). The reaction mixture was stirred at room temperature and monitored by ^{1}H NMR spectroscopy. After the given reaction time, solvent removal in vacuo gave the crude product **4**, which was directly purified by flash chromatography (FC). The yield of cycloaddition product **4** and diastereomeric ratio were determined at this stage.

To determine the enantiomeric excess, the cycloaddition products **4** were transformed to the corresponding alcohol. To a solution of purified cycloaddition product **4** in DCM/MeOH (2:1, 1.5 mL) was added $NaBH_4$ (11.4 mg, 0.3 mmol) at 0 ºC and the mixture was stirred for 30 minutes. After that, the solvent was removed under vacuum and the residue was diluted with EtOAc (20 mL). The solution was sequentially washed with sat. aq. NH_4Cl (5.0 mL) and water (10.0 mL). The organic phase was dried with anhydrous Na_2SO_4, concentrated under vacuum and subjected to purification by FC to give the corresponding alcohol **4´**. The physical data and the enantiomeric excess of the major diastereoisomer were measured at this stage.

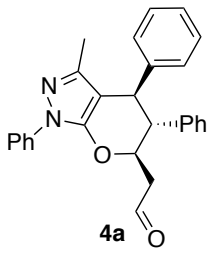
5. Screening of conditions for the [4+2] cycloaddition reaction[a]



Entry	Cat. Loading (mol%)	Concentration (M)	**2**/**3** Ratio	Conv. (%)[b]	ee (%)[c]
1	20	0.1	1:2	>90	88
2	10	0.1	1:2	>90	90
3	5	0.1	1:2	71	86
4	10	0.2	1:2	>90	84
5	10	0.05	1:2	73	90
6	10	0.1	1:1.5	81	87
7	10	0.1	1:1	70	86
8	10	0.1	1.5:1	88	83

[a]Reactions performed on a 0.1 mmol scale. [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by chiral HPLC after transformation into the corresponding alcohol.

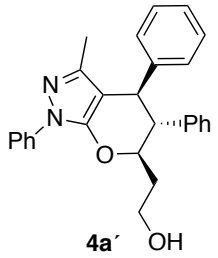
2-((4*R*,5*R*,6*R*)-3-Methyl-1,4,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)-acetaldehyde



White solid, melting point: 149-151 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 3H), 2.46 (ddd, *J* = 1.3, 3.3, 17.0 Hz, 1H), 2.72 (ddd, *J* = 2.5, 8.8, 17.0 Hz, 1H), 2.95 (t, *J* = 10.4 Hz, 1H), 4.12 (d, *J* = 10.4 Hz, 1H), 5.10 (ddd, *J* = 3.3, 8.8, 10.5 Hz, 1H), 6.89-6.96 (m, 4H), 7.13-7.15 (m, 3H), 7.21-7.26 (m, 4H), 7.39-7.43 (m, 2H), 7.74-7.76 (m, 2H), 9.71 (dd, *J* = 1.2, 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 45.7, 47.1, 54.2, 78.7, 100.4, 120.0 (2C), 125.4, 126.8, 127.6, 128.1 (2C), 128.2 (2C), 128.4 (2C), 129.0 (2C), 129.0 (2C), 138.4, 138.6, 141.0, 147.0, 150.0, 198.6; IR (ATR): ν = 691, 755, 928, 1045, 1123, 1391, 1454, 1492, 1515, 1597, 1615, 1721, 2923 cm^{-1}; HRMS calcd. for $C_{27}H_{23}N_2O_2$ $(M - H)^+$: 407.1765, found: 407.1766.

6. Characterization Data

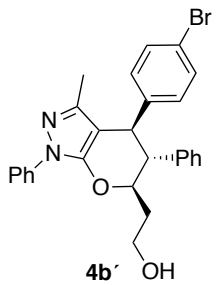
2-((4*R*,5*R*,6*R*)-3-Methyl-1,4,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl) ethanol



4a´

Cycloaddition product **4a** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 10:1) in 80% yield (49.1 mg) as a mixture of diastereoisomers (8:1); the corresponding alcohol **4a´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 6:1) in 83% yield (41.5 mg) as a single diastereoisomer for enantiomeric excess determination. White solid, melting point: 193-195 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62-1.65 (m, 1H), 1.67 (s, 3H), 1.69-1.70 (m, 1H), 1.74-1.83 (m, 1H), 2.87 (t, *J* = 10.4 Hz, 1H), 3.76-3.86 (m, 2H), 4.03 (d, *J* = 10.0 Hz, 1H), 4.73 (td, *J* = 2.4, 10.0 Hz, 1H), 6.88-6.93 (m, 4H), 7.12-7.13 (m, 3H), 7.14-7.25 (m, 4H), 7.42-7.46 (m, 2H), 7.77-7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 36.1, 46.0, 54.8, 59.4, 81.7, 100.5, 120.1 (2C), 125.4, 126.6, 127.1, 128.1 (4C), 128.4 (2C), 128.7 (2C), 129.0 (2C), 138.7, 139.4, 141.3, 147.2, 150.4; IR (ATR): ν = 698, 753, 935, 1044, 1128, 1390, 1455, 1492, 1513, 1598, 1610, 2960, 3341 cm^{-1}; HRMS calcd. for $C_{27}H_{27}N_2O_2$ $(M + H)^+$: 411.2067, found: 411.2064; $[\alpha]_D^{25}$ = –92.0 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 90% ee): t_{major} = 8.4 min, t_{minor} = 10.2 min.

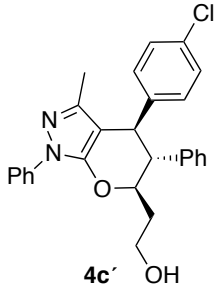
2-((4*R*,5*R*,6*R*)-4-(4-Bromophenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)ethanol



4b´

Cycloaddition product **4b** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 12:1 to 10:1) in 78% yield (56.9 mg) as a mixture of diastereoisomers (9:1); the corresponding alcohol **4b´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 8:1 to 5:1) in 82% yield (47.1 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 190-191 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60-1.67 (m, 2H), 1.69 (s, 3H), 1.73-1.82 (m, 1H), 2.80 (t, *J* = 10.0 Hz, 1H), 3.75-3.85 (m, 2H), 4.02 (d, *J* = 10.4 Hz, 1H), 4.72 (td, *J* = 2.4, 10.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.91-6.92 (m, 2H), 7.21-7.27 (m, 6H), 7.40-7.45 (m, 2H), 7.76-7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 36.0, 45.6, 54.8, 59.3, 81.5, 99.9, 120.1 (2C), 120.5, 125.5, 127.4, 128.4 (2C), 128.9 (2C), 129.1 (2C), 129.8 (2C), 131.3 (2C), 138.6, 139.0, 140.6, 146.8, 150.5; IR (ATR): ν = 692, 754, 934, 1044, 1129, 1391, 1441, 1486, 1514, 1660, 1610, 2923, 3331 cm^{-1}; HRMS calcd. for $C_{27}H_{26}BrN_2O_2$ $(M + H)^+$: 489.1172, found: 489.1152; $[\alpha]_D^{25}$ = –162.9 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 95% ee): t_{major} = 9.8 min, t_{minor} = 12.8 min.

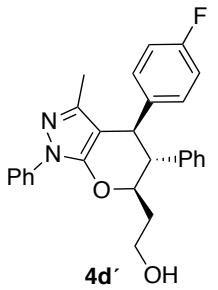
2-((4*R*,5*R*,6*R*)-4-(4-Chlorophenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)ethanol



4c´

Cycloaddition product **4c** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 10:1) in 75% yield (49.8 mg) as a mixture of diastereoisomers (10:1); the corresponding alcohol **4c´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 6:1) in 72% yield (36.5 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 197-198 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60-1.66 (m, 1H), 1.69 (s, 3H), 1.71-1.81 (m, 2H), 2.80 (t, *J* = 10.4 Hz, 1H), 3.74-3.86 (m, 2H), 4.02 (d, *J* = 10.0 Hz, 1H), 4.71 (td, *J* = 2.4, 10.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 6.90-6.91 (m, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.19-7.25 (m, 4H), 7.43 (t, *J* = 8.4 Hz, 2H), 7.76-7.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 36.0, 45.5, 54.8, 59.2, 81.5, 100.0, 120.1 (2C), 125.5, 127.3, 128.4 (4C), 128.8 (2C), 129.1 (2C), 129.4 (2C), 132.3, 138.6, 139.0, 140.0, 146.9, 150.5; IR (ATR): ν = 637, 754, 934, 1045, 1088, 1130, 1391, 1455, 1489, 1515, 1612, 2956, 3323 cm^{-1}; HRMS calcd. for $C_{27}H_{26}ClN_2O_2$ $(M + H)^+$: 445.1677, found: 445.1669; $[\alpha]_D^{25}$ = –140.4 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 92% ee): t_{major} = 9.2 min, t_{minor} = 11.8 min.

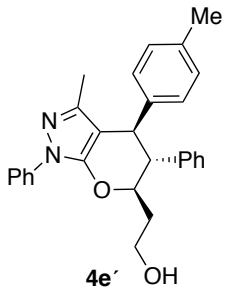
2-((4*R*,5*R*,6*R*)-4-(4-Fluorophenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)ethanol



4d´

Cycloaddition product **4d** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 9:1) in 81% yield (52.3 mg) as a mixture of diastereoisomers (8:1); the corresponding alcohol **4d´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 6:1) in 75% yield (39.9 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 176-178 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61-1.66 (m, 1H), 1.68 (s, 3H), 1.71-1.80 (m, 2H), 2.80 (t, *J* = 10.0 Hz, 1H), 3.72-3.85 (m, 2H), 4.00 (d, *J* = 10.4 Hz, 1H), 4.71 (td, *J* = 2.8, 10.0 Hz, 1H), 6.80-6.91 (m, 6H), 7.17-7.25 (m, 4H), 7.43 (t, *J* = 8.4 Hz, 2H), 7.75-7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 36.0, 45.3, 54.9, 59.1, 81.5, 100.2, 115.0 (d, *J* = 21.3 Hz, 2C), 120.1 (2C), 125.5, 127.2, 128.3 (2C), 128.7 (2C), 129.0 (2C), 129.4 (d, *J* = 7.8 Hz, 2C), 137.0 (d, *J* = 3.1 Hz), 138.6, 139.1, 146.9, 150.4, 161.6 (d, *J* = 244.7 Hz); IR (ATR): ν = 704, 754, 935, 1047, 1131, 1221, 1393, 1455, 1508, 1599, 2924, 2958, 3314 cm^{-1}; HRMS calcd. for $C_{27}H_{26}FN_2O_2$ $(M + H)^+$: 429.1973, found: 429.1985; $[\alpha]_D^{25}$ = –55.6 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 90% ee): t_{major} = 9.2 min, t_{minor} = 11.1 min.

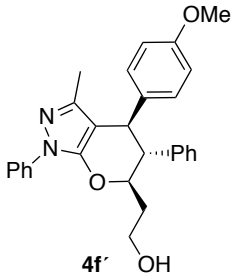
2-((4*R*,5*R*,6*R*)-3-Methyl-1,5-diphenyl-4-(*p*-tolyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)ethanol



4e´

Cycloaddition product **4e** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 10:1) in 77% yield (48.8 mg) as a mixture of diastereoisomers (8:1); the corresponding alcohol **4e´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 6:1) in 78% yield (38.6 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 169-170 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60-1.64 (m, 1H), 1.68 (s, 3H), 1.70-1.82 (m, 2H), 2.25 (s, 3H), 2.84 (t, *J* = 10.2 Hz, 1H), 3.74-3.85 (m, 2H), 3.98 (d, *J* = 10.2 Hz, 1H), 4.70 (m, 1H), 6.74-6.77 (m, 2H), 6.91-6.94 (m, 4H), 7.18-7.26 (m, 4H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.76-7.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 21.1, 36.1, 45.5, 54.8, 59.4, 81.7, 100.7, 120.1 (2C), 125.4, 127.1, 127.9 (2C), 128.5 (2C), 128.7 (2C), 128.8 (2C), 129.1 (2C), 136.0, 138.1, 138.7, 139.5, 147.2, 150.4; IR (ATR): ν = 698, 752, 934, 1045, 1129, 1391, 1455, 1494, 1513, 1599, 2923, 3340 cm^{-1}; HRMS calcd. for $C_{28}H_{29}N_2O_2$ $(M + H)^+$: 425.2224, found: 425.2210; $[\alpha]_D^{25}$ = –134.2 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 92% ee): t_{major} = 7.5 min, t_{minor} = 9.4 min.

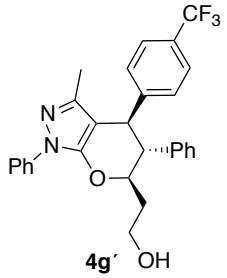
2-((4*R*,5*R*,6*R*)-4-(4-Methoxyphenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano-[2,3-*c*]pyrazol-6-yl)ethanol



4f´

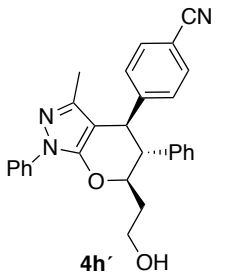
Cycloaddition product **4f** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 10:1) in 82% yield (53.9 mg) as a mixture of diastereoisomers (8:1); the corresponding alcohol **4f´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 6:1) in 81% yield (44.2 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 173-175 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60-1.67 (m, 1H), 1.69 (s, 3H), 1.71-1.80 (m, 2H), 2.82 (t, *J* = 10.4 Hz, 1H), 3.72 (s, 3H), 3.77-3.82 (m, 2H), 3.98 (d, *J* = 10.0 Hz, 1H), 4.70 (td, *J* = 2.4, 10.0 Hz, 1H), 6.65-6.67 (m, 2H), 6.77-6.93 (m, 4H), 7.16-7.24 (m, 4H), 7.42 (t, *J* = 8.4 Hz, 2H), 7.76-7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 36.1, 45.2, 54.9, 55.1, 59.4, 81.7, 100.7, 113.5 (2C), 120.1 (2C), 125.4, 127.1, 128.5 (2C), 128.7 (2C), 129.0 (2C), 129.1 (2C), 133.3, 138.7, 139.6, 147.2, 150.4, 158.2; IR (ATR): ν = 700, 753, 833, 1028, 1133, 1241, 1390, 1455, 1510, 1601, 2924, 3311 cm^{-1}; HRMS calcd. for $C_{28}H_{29}N_2O_3$ $(M + H)^+$: 441.2173, found: 441.2181; $[\alpha]_D^{25}$ = –62.5 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, Hexane/*i*-propanol (93:7), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 94% ee): t_{major} = 17.0 min, t_{minor} = 21.7 min.

2-((4*R*,5*R*,6*R*)-3-Methyl-1,5-diphenyl-4-(4-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)ethanol



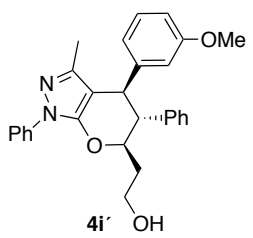
Cycloaddition product **4g** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 10:1) in 85% yield (60.7 mg) as a mixture of diastereoisomers (10:1); the corresponding alcohol **4g´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 6:1) in 77% yield (46.8 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 164-166 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56-1.64 (m, 1H), 1.66 (s, 3H), 1.72-1.80 (m, 1H), 2.13 (br s, 1H), 2.82 (t, *J* = 10.0 Hz, 1H), 3.73-3.85 (m, 2H), 4.08 (d, *J* = 10.0 Hz, 1H), 4.71 (m, 1H), 6.88-6.99 (m, 4H), 7.19-7.26 (m, 4H), 7.38-7.45 (m, 4H), 7.76 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 35.9, 45.8, 54.6, 58.9, 81.3, 99.7, 120.1 (2C), 124.2 (q, *J* = 270.0 Hz), 125.1 (q, *J* = 3.5 Hz, 2C), 125.6, 127.4, 128.3 (2C), 128.4 (2C), 128.9 (2C), 129.0 (q, *J* = 32.0 Hz), 129.1 (2C), 138.4, 138.7, 145.6 (q, *J* = 1.6 Hz), 146.7, 150.6; IR (ATR): ν = 700, 755, 940, 1043, 1121, 1323, 1393, 1455, 1495, 1517, 1601, 2926, 3332 cm^{-1}; HRMS calcd. for $C_{28}H_{26}F_3N_2O_2$ $(M + H)^+$: 479.1941, found: 479.1935; $[\alpha]_D^{25}$ = –52.8 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 93% ee): t_{major} = 7.5 min, t_{minor} = 9.3 min.

4-((4*R*,5*R*,6*R*)-6-(2-Hydroxyethyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-4-yl)benzonitrile



Cycloaddition product **4h** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 10:1) in 89% yield (57.9 mg) as a mixture of diastereoisomers (10:1); the corresponding alcohol **4h´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 6:1) in 74% yield (42.9 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 162-164 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 3H), 1.69-1.81 (m, 3H), 2.81 (t, *J* = 10.0 Hz, 1H), 3.75-3.86 (m, 2H), 4.13 (d, *J* = 10.0 Hz, 1H), 4.71 (td, *J* = 2.4, 10.0 Hz, 1H), 6.89-6.91 (m, 2H), 6.98 (d, *J* = 7.6 Hz, 2H), 7.21-7.25 (m, 4H), 7.42-7.45 (m, 4H), 7.76-7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 35.9, 46.3, 54.7, 59.0, 81.2, 99.2, 110.7, 118.7, 120.1 (2C), 125.7, 127.6, 128.2 (2C), 128.8 (2C), 129.0 (2C), 129.1 (2C), 132.0 (2C), 138.4, 138.5, 146.4, 147.4, 150.6; IR (ATR): ν = 692, 759, 934, 1042, 1125, 1392, 1455, 1492, 1517, 1602, 1664, 2223, 2925, 3375 cm^{-1}; HRMS calcd. for $C_{28}H_{26}N_3O_2$ $(M + H)^+$: 436.2020, found: 436.2014; $[\alpha]_D^{25}$ = –133.9 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, Hexane/*i*-propanol (93:7), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 98% ee): t_{major} = 48.5 min, t_{minor} = 46.9 min.

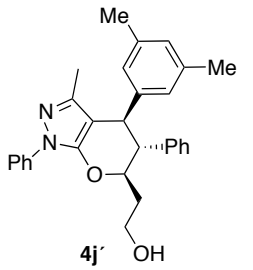
2-((4*R*,5*R*,6*R*)-4-(3-Methoxyphenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano-[2,3-c]pyrazol-6-yl)ethanol



4i´

Cycloaddition product **4i** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 10:1) in 73% yield (48.1 mg) as a mixture of diastereoisomers (5:1); the corresponding alcohol **4i´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 6:1) in 72% yield (35.2 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 208-210 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62-1.68 (m, 2H), 1.73 (s, 3H), 1.75-1.79 (m, 1H), 2.83 (t, *J* = 10.0 Hz, 1H), 3.63 (s, 3H), 3.74-3.88 (m, 2H), 3.90 (d, *J* = 10.4 Hz, 1H), 4.66 (td, *J* = 2.4, 10.0 Hz, 1H), 6.37 (s, 1H), 6.46-6.48 (m, 1H), 6.66-6.68 (m, 1H), 6.88-6.90 (m, 2H), 7.04 (t, *J* = 8.0 Hz, 1H), 7.17-7.25 (m, 4H), 7.45 (t, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 36.1, 46.0, 54.6, 55.1, 59.1, 81.5, 100.4, 112.1, 113.6, 120.0 (2C), 120.5, 125.4, 127.1, 128.4 (2C), 128.7 (2C), 129.1 (3C), 138.7, 139.4, 142.9, 147.2, 150.5, 159.4; IR (ATR): ν = 701, 755, 933, 1042, 1128, 1263, 1391, 1455, 1488, 1513, 1597, 2916, 3325 cm^{-1}; HRMS calcd. for $C_{28}H_{29}N_2O_3$ $(M + H)^+$: 441.2173, found: 441.2191; $[\alpha]_D^{25}$ = –47.8 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 87% ee): t_{major} = 10.4 min, t_{minor} = 11.6 min.

2-((4*R*,5*R*,6*R*)-4-(3,5-Dimethylphenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano-[2,3-c]pyrazol-6-yl)ethanol



4j´

Cycloaddition product **4j** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 10:1) in 81% yield (53.0 mg) as a mixture of diastereoisomers (6:1); the corresponding alcohol **4j´** was isolated by FC on silica (eluting with Cyclohexane/EtOAc from 10:1 to 6:1) in 78% yield (41.8 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 174-175 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54-1.60 (m, 1H), 1.63 (s, 3H), 1.65-1.74 (m, 2H), 2.06 (s, 6H), 2.77 (t, *J* = 10.4 Hz, 1H), 3.67-3.78 (m, 2H), 3.86 (d, *J* = 10.0 Hz, 1H), 4.61 (td, *J* = 2.4, 10.0 Hz, 1H), 6.37 (s, 2H), 6.67 (s, 1H), 6.83-6.85 (m, 2H), 7.09-7.18 (m, 4H), 7.35 (t, *J* = 8.4 Hz, 2H), 7.69-7.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 21.2 (2C), 36.1, 45.7, 54.6, 59.4, 81.7, 100.6, 120.2 (2C), 125.3, 125.9 (2C), 127.0, 128.1, 128.4 (2C), 128.6 (2C), 129.0 (2C), 137.3 (2C), 138.7, 139.6, 141.0, 147.3, 150.4; IR (ATR): ν = 697, 797, 933, 1042, 1127, 1392, 1454, 1494, 1512, 1598, 2869, 2923, 3324 cm^{-1}; HRMS calcd. for $C_{29}H_{31}N_2O_2$ $(M + H)^+$: 439.2380, found: 439.2386; $[\alpha]_D^{25}$ = –60.7 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel OD-H, Hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 87% ee): t_{major} = 9.2 min, t_{minor} = 6.9 min.

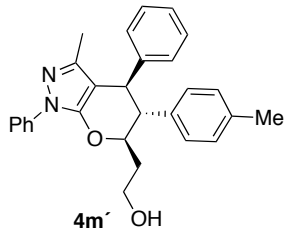
2-((4*R*,5*R*,6*R*)-4-(2,6-Dimethoxyphenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano [2,3-c]pyrazol-6-yl)ethanol

Cycloaddition product **4k** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 10:1) in 56% yield (39.4 mg) as a mixture of diastereoisomers (13:1); the corresponding alcohol **4k´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 6:1) in 88% yield (35.1 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 83-85 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (s, 3H), 1.67-1.72 (m, 2H), 1.79-1.89 (m, 1H), 3.40 (s, 3H), 3.54 (t, *J* = 10.8 Hz, 1H), 3.61 (s, 3H), 3.78-3.88 (m, 2H), 4.69 (td, *J* = 2.4, 10.0 Hz, 1H), 4.87 (d, *J* = 10.8 Hz, 1H), 6.31 (d, *J* = 7.6 Hz, 1H), 6.45-6.48 (m, 1H), 6.98 (d, *J* = 7.6 Hz, 2H), 7.00-7.23 (m, 7H), 7.40-7.44 (m, 2H), 7.76-7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 34.3, 36.1, 48.2, 55.9, 56.0, 59.8, 82.6, 100.9, 104.3, 105.0, 116.8, 119.9 (2C), 125.0, 126.6, 127.8, 128.0 (2C), 128.5 (2C), 129.0 (2C), 139.0, 140.4, 146.4, 149.6, 158.7, 159.4; IR (ATR): ν = 696, 753, 934, 1042, 1106, 1248, 1391, 1454, 1472, 1495, 1513, 1597, 2924, 3322 cm^{-1}; HRMS calcd. for $C_{29}H_{31}N_2O_4$ $(M + H)^+$: 471.2278, found: 471.2270; $[\alpha]_D^{25}$ = +102.0 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, Hexane/*i*-propanol (93:7), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 87% ee): t_{major} = 12.9 min, t_{minor} = 10.5 min.

2-((4*R*,5*R*,6*R*)-3-Methyl-4-(naphthalen-2-yl)-1,5-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)ethanol

Cycloaddition product **4l** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 10:1) in 73% yield (50.2 mg) as a mixture of diastereoisomers (4:1); the corresponding alcohol **4l´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 6:1) in 66% yield (33.6 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 245-247 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63 (s, 3H), 1.65-1.73 (m, 2H), 1.77-1.86 (m, 1H), 2.99 (t, *J* = 10.0 Hz, 1H), 3.77-3.88 (m, 2H), 4.23 (d, *J* = 10.4 Hz, 1H), 4.78 (td, *J* = 2.8, 10.0 Hz, 1H), 6.92-6.94 (m, 2H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.14-7.25 (m, 4H), 7.30 (s, 1H), 7.37-7.47 (m, 4H), 7.60-7.66 (m, 2H), 7.74-7.76 (m, 1H), 7.79-7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 36.1, 46.1, 54.6, 59.4, 81.7, 100.4, 120.1 (2C), 125.4, 125.5, 125.8, 126.0, 127.1, 127.2, 127.6, 127.7, 128.0, 128.4 (2C), 128.8 (2C), 129.1 (2C), 132.5, 133.3, 138.7, 138.8, 139.3, 147.2, 150.5; IR (ATR): ν = 701, 752, 936, 1042, 1128, 1391, 1438, 1455, 1495, 1512, 1596, 2923, 3307 cm^{-1}; HRMS calcd. for $C_{31}H_{29}N_2O_2$ $(M + H)^+$: 461.2224, found: 461.2220; $[\alpha]_D^{25}$ = –174.7 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 92% ee): t_{major} = 11.1 min, t_{minor} = 12.4 min.

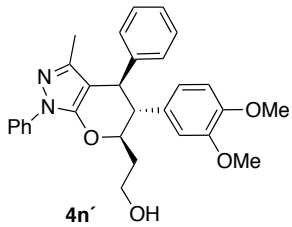
2-((4*R*,5*R*,6*R*)-3-Methyl-1,4-diphenyl-5-(p-tolyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)ethanol



4m´

Cycloaddition product **4m** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 10:1) in 72% yield (45.6 mg) as a mixture of diastereoisomers (8:1); the corresponding alcohol **4m´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 6:1) in 77% yield (35.6 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 149-152 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55-1.64 (m, 1H), 1.66 (s, 3H), 1.71-1.82 (m, 2H), 2.28 (s, 3H), 2.82 (t, *J* = 10.4 Hz, 1H), 3.73-3.85 (m, 2H), 3.98 (d, *J* = 10.4 Hz, 1H), 4.67 (td, *J* = 2.4 Hz, 10.0 Hz, 1H), 6.78-6.80 (m, 2H), 6.88-6.90 (m, 2H), 7.00-7.03 (m, 2H), 7.12-7.13 (m, 3H), 7.20-7.24 (m, 1H), 7.42 (t, *J* = 8.4 Hz, 2H), 7.76-7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 21.1, 36.1, 45.9, 54.3, 59.4, 81.8, 100.6, 120.1 (2C), 125.4, 126.5, 128.1 (2C), 128.2 (2C), 128.2 (2C), 129.1 (2C), 129.4 (2C), 136.2, 136.7, 138.7, 141.5, 147.2, 150.5; IR (ATR): ν = 692, 753, 940, 1054, 1128, 1392, 1453, 1492, 1511, 1599, 2922, 3334 cm^{-1}; HRMS calcd. for $C_{28}H_{29}N_2O_2$ $(M + H)^+$: 425.2224, found: 425.2213; $[\alpha]_D^{25}$ = –133.9 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, Hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 85% ee): t_{major} = 20.2 min, t_{minor} = 16.5 min.

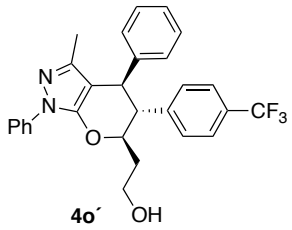
2-((4*R*,5*R*,6*R*)-5-(3,4-Dimethoxyphenyl)-3-methyl-1,4-diphenyl-1,4,5,6-tetrahydropyrano [2,3-c]pyrazol-6-yl)ethanol



4n´

Cycloaddition product **4n** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 8:1) in 74% yield (52.1 mg) as a mixture of diastereoisomers (8:1); the corresponding alcohol **4n´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 8:1 to 5:1) in 83% yield (43.3 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 87-89 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (s, 3H), 1.70-1.83 (m, 3H), 2.78 (t, *J* = 10.2 Hz, 1H), 3.72 (s, 3H), 3.76-3.81 (m, 2H), 3.83 (s, 3H), 3.94 (d, *J* = 10.2 Hz, 1H), 4.67 (td, *J* = 3.2, 9.6 Hz, 1H), 6.34 (s, 1H), 6.46 (dd, *J* = 1.6, 8.4 Hz, 1H), 6.72-6.74 (m, 1H), 6.86-6.90 (m, 2H), 7.11-7.15 (m, 3H), 7.20-7.25 (m, 1H), 7.43 (t, *J* = 8.4 Hz, 2H), 7.76-7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 36.0, 46.2, 54.3, 55.8, 55.9, 59.3, 81.6, 100.5, 111.3, 111.6, 120.1 (2C), 120.3, 125.4, 126.6, 128.2 (4C), 129.1 (2C), 131.8, 138.7, 141.5, 147.2, 147.9, 148.9, 150.5; IR (ATR): ν = 694, 756, 1026, 1141, 1260, 1393, 1454, 1511, 1599, 2850, 2925 cm^{-1}; HRMS calcd. for $C_{29}H_{31}N_2O_4$ $(M + H)^+$: 471.2278, found: 471.2272; $[\alpha]_D^{25}$ = –39.2 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, Hexane/*i*-propanol (70:30), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 84% ee): t_{major} = 11.6 min, t_{minor} = 6.9 min.

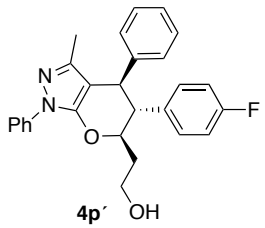
2-((4*R*,5*R*,6*R*)-3-Methyl-1,4-diphenyl-5-(4-(trifluoromethyl)phenyl)-1,4,5,6 tetrahydropyrano[2,3-c]pyrazol-6-yl)ethanol



4o´

Cycloaddition product **4o** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 8:1) in 83% yield (58.6 mg) as a mixture of diastereoisomers (8:1); the corresponding alcohol **4o´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 5:1) in 78% yield (45.7 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 205-206 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57-1.65 (m, 2H), 1.66 (s, 3H), 1.73-1.82 (m, 1H), 2.98 (t, *J* = 10.0 Hz, 1H), 3.78-3.90 (m, 2H), 4.03 (d, *J* = 10.4 Hz, 1H), 4.77 (td, *J* = 2.4 Hz, 10.0 Hz, 1H), 6.83-6.88 (m, 2H), 7.04-7.06 (m, 2H), 7.14-7.16 (m, 3H), 7.22-7.26 (m, 1H), 7.44 (t, *J* = 8.4 Hz, 2H), 7.49-7.51 (m, 2H), 7.76-7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 35.9, 46.2, 54.7, 59.0, 80.9, 100.2, 120.1 (2C), 124.0 (q, *J* = 270.0 Hz), 125.5, 125.7 (q, *J* = 3.7 Hz, 2C), 126.9, 128.0 (2C), 128.4 (2C), 128.7 (2C), 129.1 (2C), 129.2 (q, *J* = 33.0 Hz), 138.6, 140.7, 143.8 (q, *J* = 1.1 Hz), 147.0, 150.2; IR (ATR): ν = 506, 695, 756, 842, 1066, 1115, 1155, 1325, 1456, 1516, 1603, 2926, 3351 cm^{-1}; HRMS calcd. for $C_{28}H_{26}F_3N_2O_2$ $(M + H)^+$: 479.1941, found: 479.1927; $[\alpha]_D^{25}$ = –62.6 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, Hexane/*i*-propanol (93:7), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 86% ee): t_{major} = 10.7 min, t_{minor} = 12.8 min.

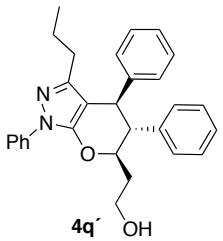
2-((4*R*,5*R*,6*R*)-5-(4-Fluorophenyl)-3-methyl-1,4-diphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)ethanol



4p´

Cycloaddition product **4p** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 8:1) in 82% yield (52.7 mg) as a mixture of diastereoisomers (7:1); the corresponding alcohol **4p´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 4:1) in 77% yield (40.8 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 179-182 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 3H), 1.70-1.80 (m, 2H), 1.82-1.90 (m, 1H), 2.86 (t, *J* = 10.4 Hz, 1H), 3.75-3.87 (m, 2H), 3.94 (d, *J* = 10.0 Hz, 1H), 4.68 (td, *J* = 2.4, 10.0 Hz, 1H), 6.85-6.94 (m, 6H), 7.13-7.15 (m, 3H), 7.21-7.25 (m, 1H), 7.43 (t, *J* = 8.4 Hz, 2H), 7.76-7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 36.0, 46.2, 54.0, 59.1, 81.3, 100.3, 115.6 (d, *J* = 21.3 Hz, 2C), 120.0 (2C), 125.4, 126.7, 128.0 (2C), 128.2 (2C), 129.0 (2C), 129.7 (d, *J* = 8.1 Hz, 2C), 135.1 (d, *J* = 3.3 Hz), 138.6, 141.0, 147.1, 150.4, 161.8 (d, *J* = 245.8 Hz); IR (ATR): ν = 504, 697, 756, 840, 1047, 1134, 1224, 1390, 1455, 1508, 1600, 2923, 3302 cm^{-1}; HRMS calcd. for $C_{27}H_{26}FN_2O_2$ $(M + H)^+$: 429.1973, found: 429.1975; $[\alpha]_D^{25}$ = –52.3 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel OD-H, Hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 87% ee): t_{major} = 31.4 min, t_{minor} = 23.9 min.

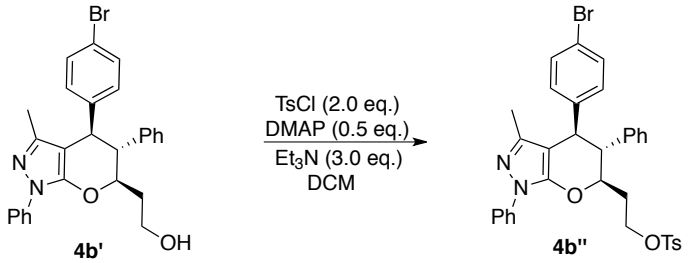
2-((4*R*,5*R*,6*R*)-1,4,5-Triphenyl-3-propyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl) ethanol



4q´

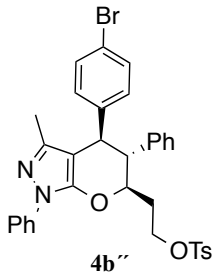
Cycloaddition product **4q** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 10:1) in 88% yield (57.6 mg) as a mixture of diastereoisomers (7:1); the corresponding alcohol **4q´** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 10:1 to 6:1) in 83% yield (47.8 mg) as a single diastereoisomer for structural characterization and enantiomeric excess determination. White solid, melting point: 60-61ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70 (t, *J* = 7.6 Hz, 3H), 1.23-1.40 (m, 2H), 1.61-1.69 (m, 1H), 1.70-1.80 (m, 3H), 2.03-2.13 (m, 1H), 2.88 (t, *J* = 10.4 Hz, 1H), 3.74-3.82 (m, 2H), 4.03 (d, *J* = 10.4 Hz, 1H), 4.73 (td, *J* = 2.4, 10.0 Hz, 1H), 6.88-6.92 (m, 3H), 7.11-7.13 (m, 3H), 7.18-7.24 (m, 3H), 7.26-7.31 (m, 1H), 7.39-7.44 (m, 2H), 7.76-7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 21.7, 30.0, 36.0, 46.3, 54.9, 59.3, 81.4, 99.9, 120.2 (2C), 125.4, 126.6, 127.1, 128.0 (2C), 128.1 (2C), 128.4 (2C), 128.6 (2C), 129.0 (2C), 138.7, 139.4, 141.3, 150.3, 151.2; IR (ATR): ν = 698, 753, 939, 1045, 1134, 1399, 1454, 1492, 1511, 1597, 2876, 2930, 2958, 3341 cm^{-1}; HRMS calcd. for $C_{29}H_{31}N_2O_2$ $(M + H)^+$: 439.2380, found: 439.2369; $[\alpha]_D^{25}$ = –50.2 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, Hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 90% ee): t_{major} = 14.8 min, t_{minor} = 12.9 min.

7. X-Ray analysis data and determination of absolute configuration



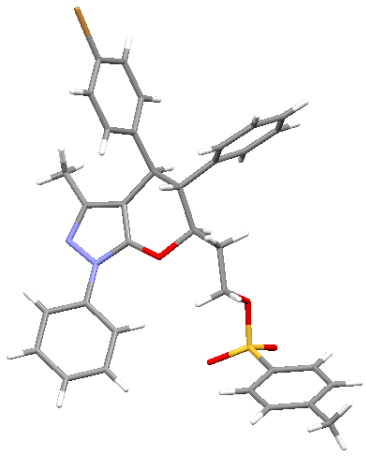
To a solution of **4b´** (0.05 mmol, 24.5 mg, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) were added TsCl (0.1 mmol, 19.0 mg, 2.0 equiv.), DMAP (0.025 mmol, 3.1 mg, 0.5 equiv.) and Et_3N (0.15 mmol, 20.8 µL, 3.0 equiv.). The reaction mixture was stirred overnight at room temperature and monitored by TLC. After the reaction was completed, solvent was removed in vacuo and the crude product was purified by flash chromatography (eluting with cyclohexane/EtOAc from 12:1 to 7:1) to afford **4b´´** in 82% yield (26.3 mg) as a white solid.

2-((4*R*,5*R*,6*R*)-4-(4-Bromophenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)ethyl 4-methylbenzenesulfonate



4b´´

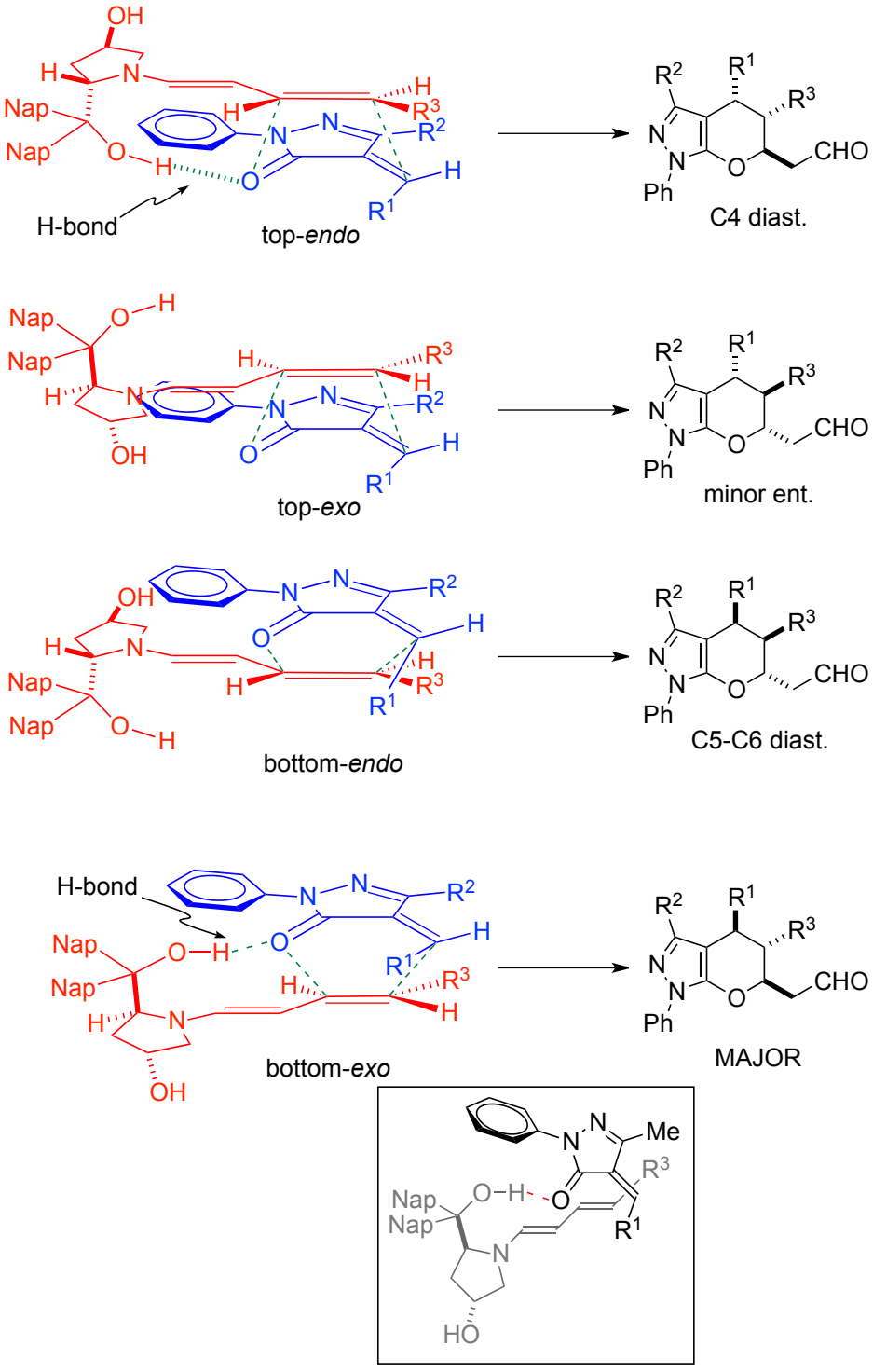
White solid, melting point: 75-76 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (s, 3H), 1.76-1.81 (m, 2H), 2.37 (s, 3H), 2.70 (t, *J* = 10.0 Hz, 1H), 3.98 (d, *J* = 10.4 Hz, 1H), 4.10-4.15 (m, 1H), 4.25-4.31 (m, 1H), 4.51-4.56 (m, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.85-6.86 (m, 2H), 7.19-7.26 (m, 8H), 7.38-7.42 (m, 2H), 7.67-7.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 21.6, 32.7, 45.5, 54.5, 66.2, 79.4, 99.8, 119.9 (2C), 120.5, 125.4, 127.5, 127.7 (2C), 128.2 (2C), 129.0 (2C), 129.0 (2C), 129.7 (2C), 129.8 (2C), 131.3 (2C), 132.8, 138.2, 138.5, 140.2, 144.8, 146.7, 150.1.



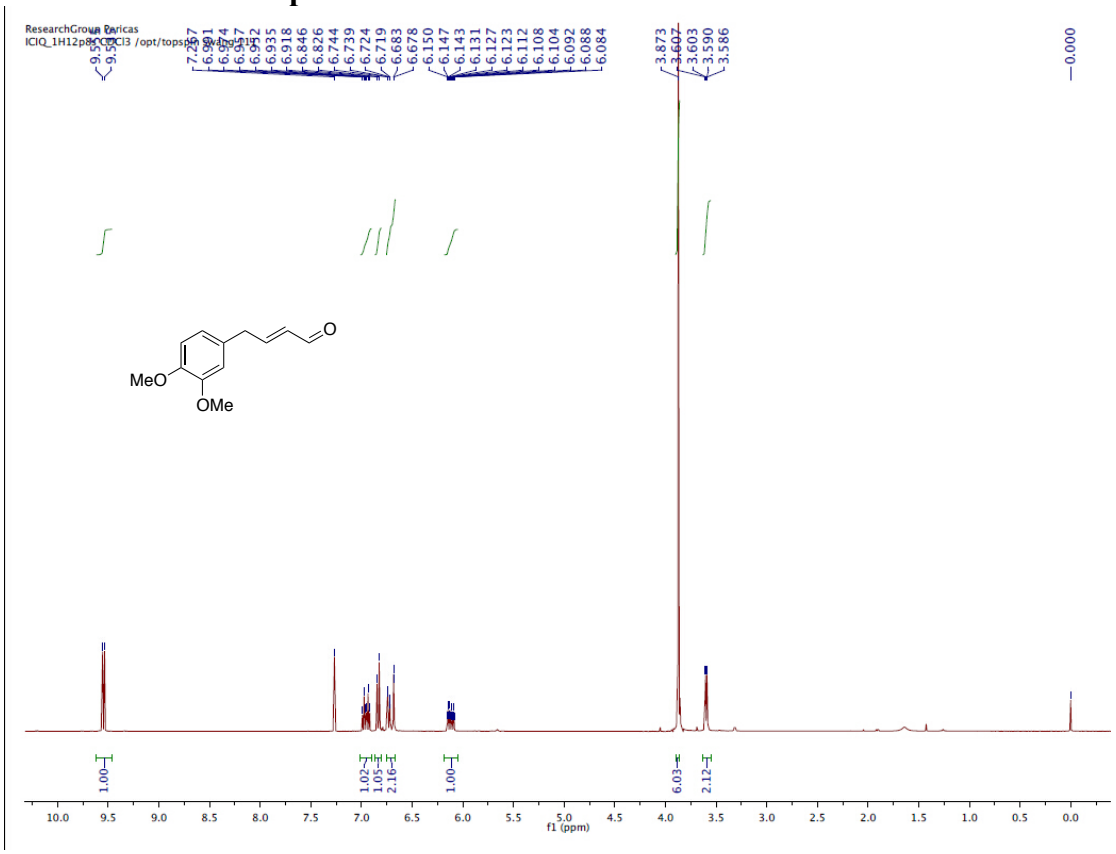
This compound crystallizes as a diethyl ether solvate. The solvent molecule is disordered in two orientations with a ratio of 50:50. This compound crystallizes in the chiral space group C_2. The absolute structure could be determined reliable with a Flack value of -0.003(5) and a Flack value based on Parsons' quotients of 0.003(2).[4] R1 value = 3.43 %.

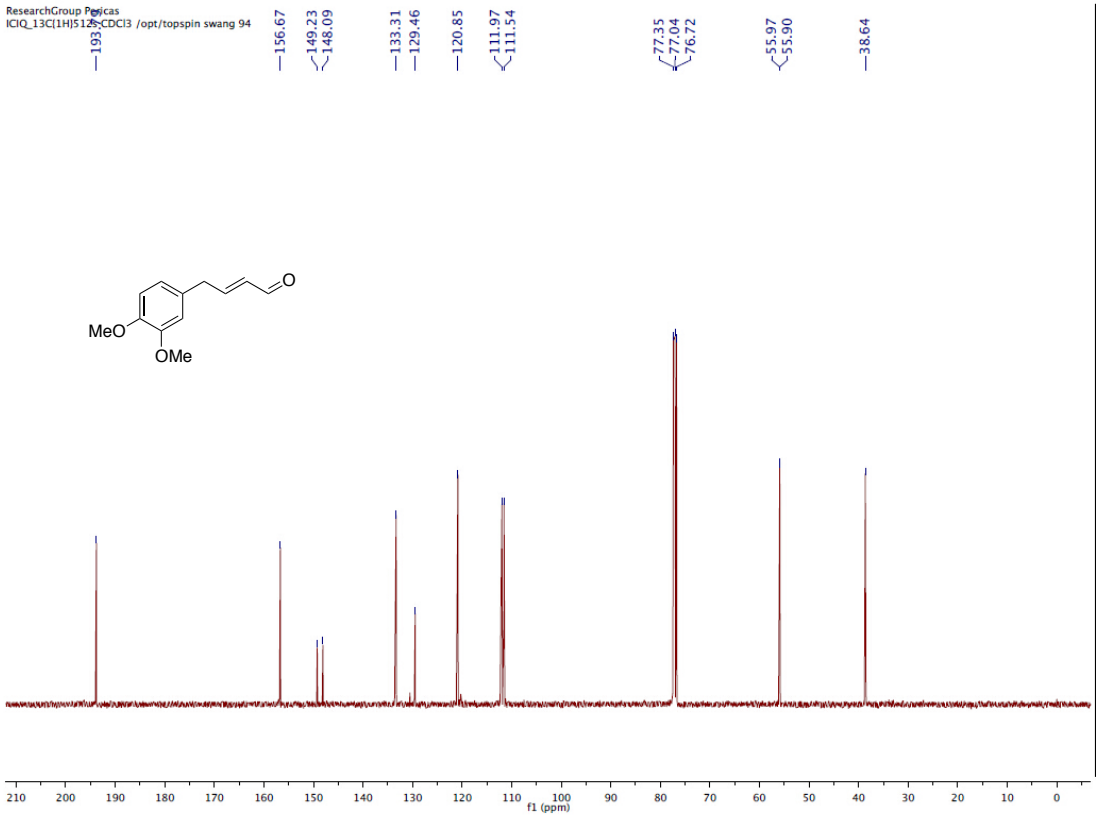
The X-ray structure has been deposited with the **CCDC number 1438957**. The corresponding CIF file has also been uploaded as Supporting Information.

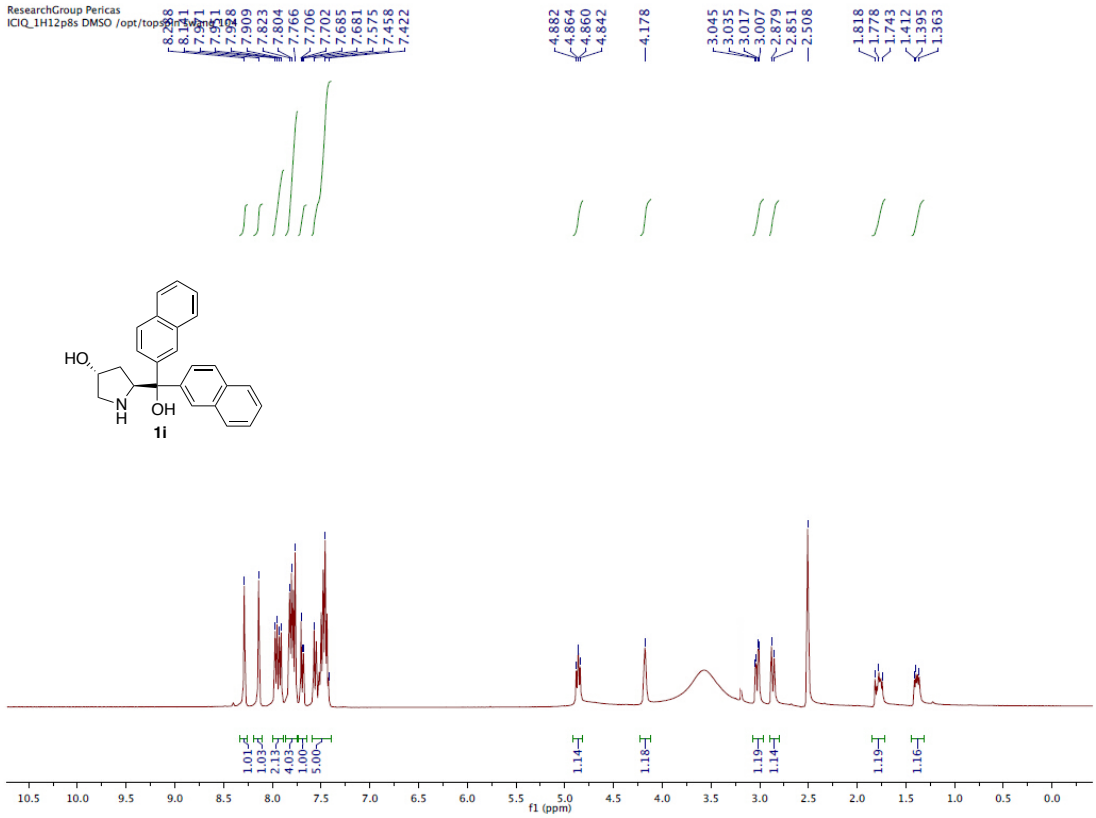
8. Model to account for the observed stereoselectivity



9. ^{1}H and ^{13}C NMR spectra






ResearchGroup Pericas
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7.991
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7.928
7.909
7.823
7.804
7.766
7.706
7.702
7.685
7.681
7.575
7.458
7.422
4.882
4.864
4.860
4.842
4.178
3.045
3.035
3.017
3.007
2.879
2.851
2.508
1.818
1.778
1.743
1.412
1.395
1.363
HO
N
H
OH
1i
1.01
1.03
2.13
4.03
1.00
5.00
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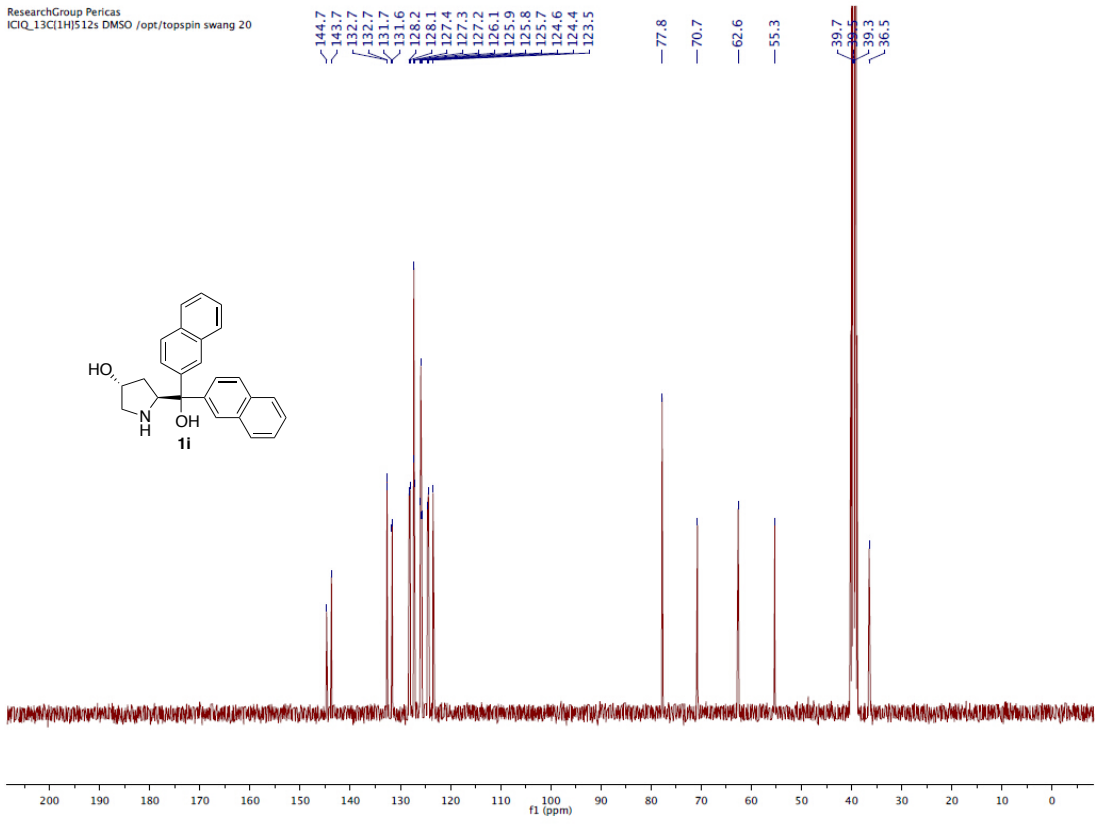
1.19
1.14
1.19
1.16
f1 (ppm)


ResearchGroup Pericas
ICIQ_13C(1H)512s DMSO /opt/topspin swang 20
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143.7
132.7
132.7
131.7
131.6
128.2
128.1
127.4
127.3
127.2
126.1
125.9
125.8
125.7
124.6
124.4
123.5
77.8
70.7
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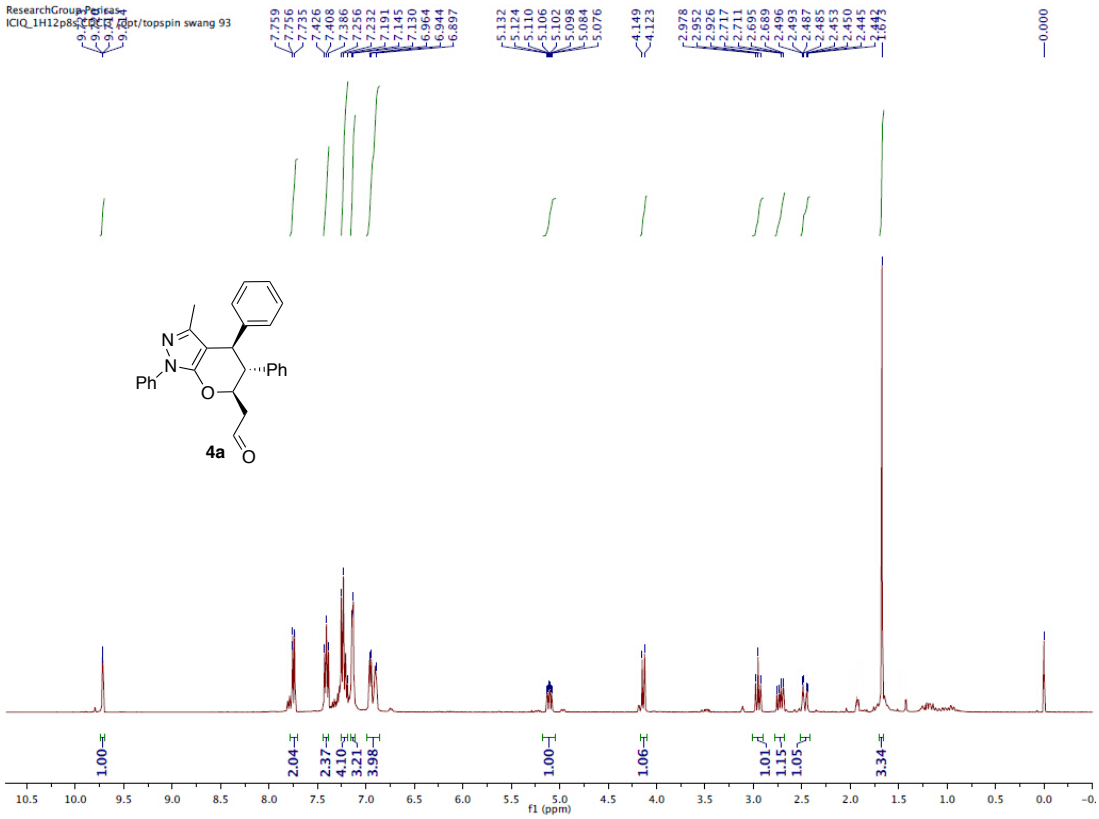
55.3
39.7
39.5
39.3
36.5
HO
N
H
OH
1i
f1 (ppm)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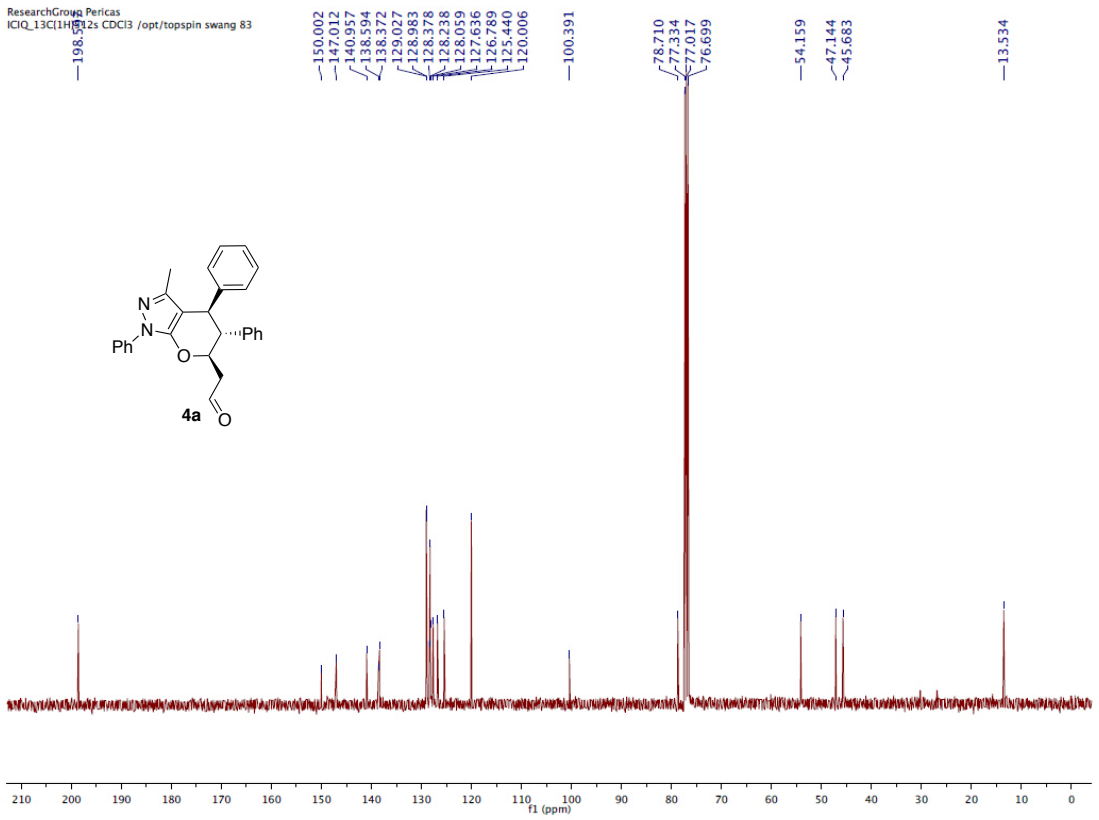
f1 (ppm)


ResearchGroup Pericas
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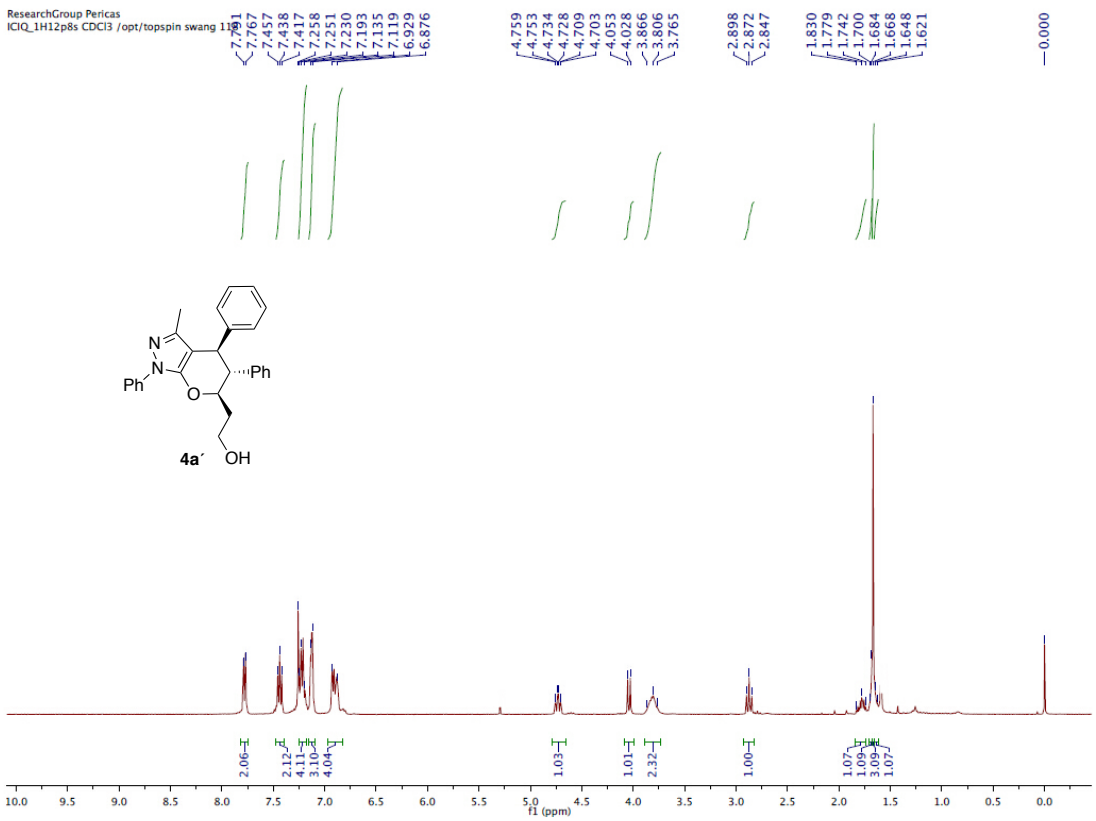
4a
f1 (ppm)


ResearchGroup Pericas
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7.417
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7.251
7.230
7.193
7.135
7.119
6.929
6.876
4.759
4.753
4.734
4.728
4.709
4.703
4.053
4.028
3.866
3.806
3.765
2.898
2.872
2.847
1.830
1.779
1.742
1.700
1.684
1.668
1.648
1.621
0.000
Ph
N
N
O
Ph
OH
4a´
2.06
2.12
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3.10
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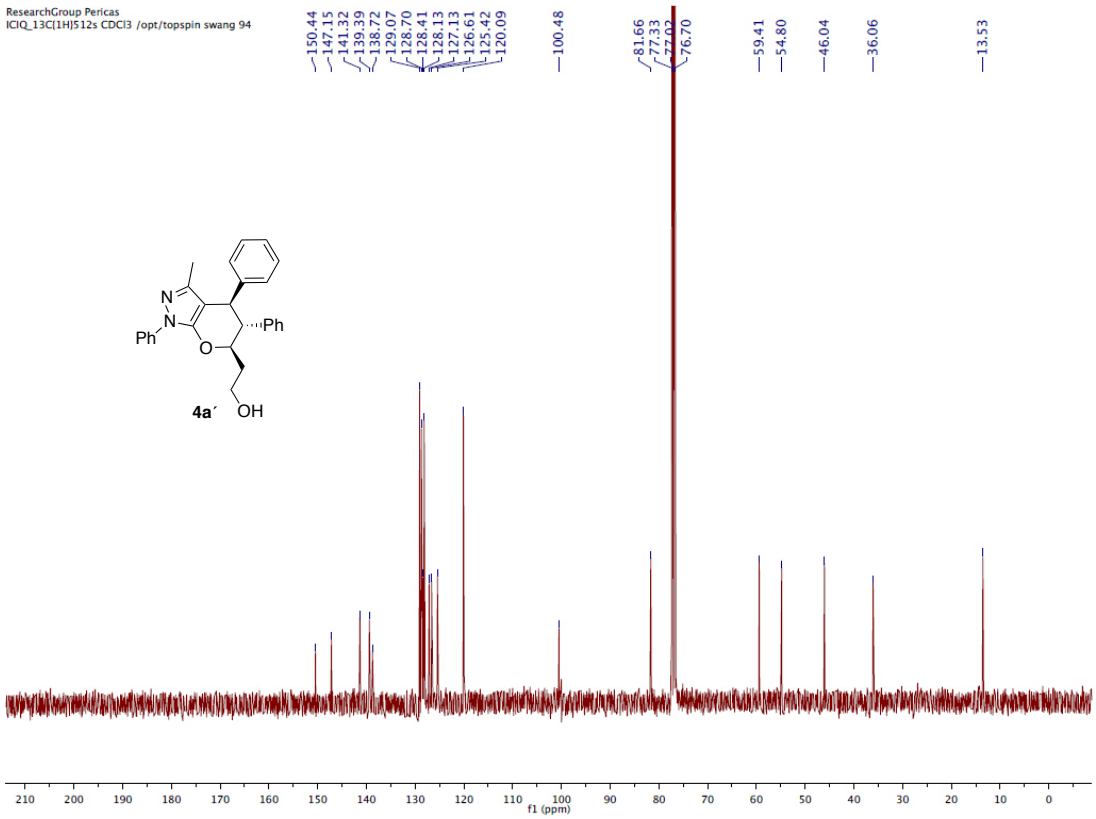
1.03
1.01
2.32
1.00
1.07
1.09
3.09
1.07
f1 (ppm)


ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 94
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128.70
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128.13
127.13
126.61
125.42
120.09
100.48
81.66
77.33
77.02
76.70
59.41
54.80
46.04
36.06
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Ph
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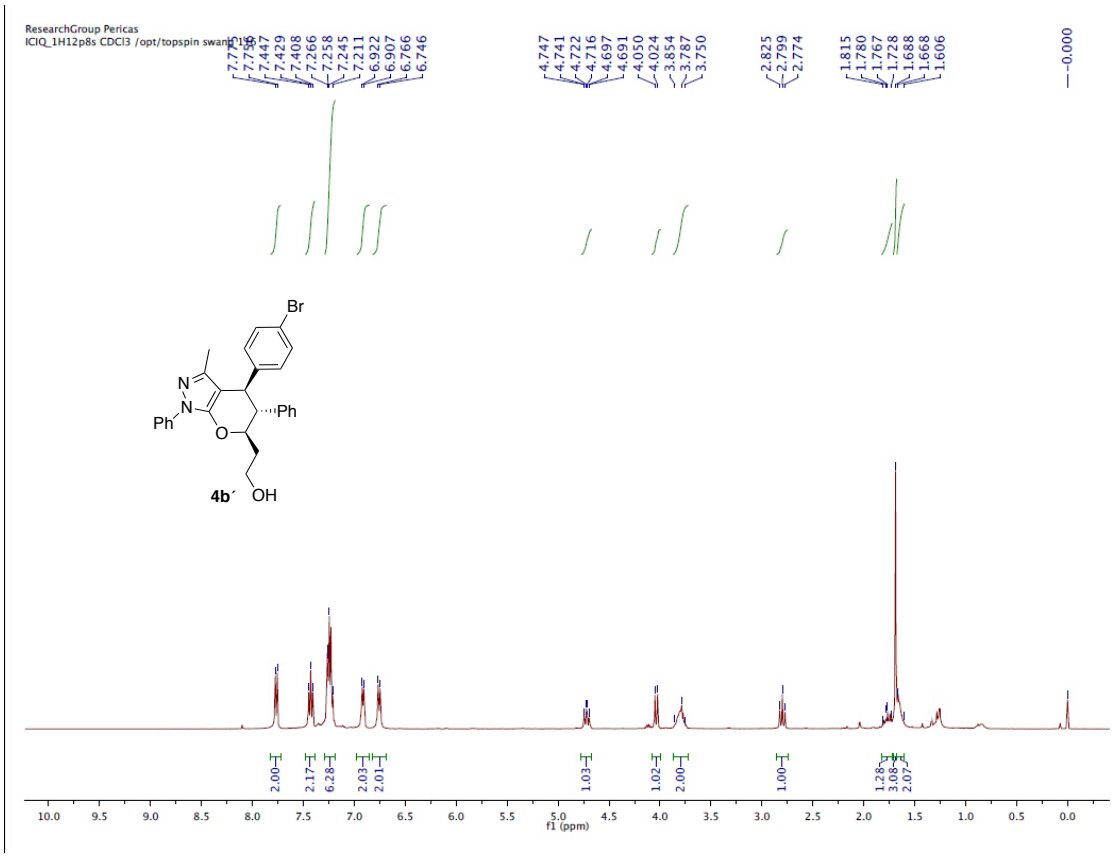
N
O
Ph
OH
4a´
f1 (ppm)


ResearchGroup Pericas
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6.907
6.766
6.746
4.747
4.741
4.722
4.716
4.697
4.691
4.050
4.024
3.854
3.787
3.750
2.825
2.799
2.774
1.815
1.780
1.767
1.728
1.688
1.668
1.606
0.000
Br
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N
Ph
Ph
O
OH
4b´
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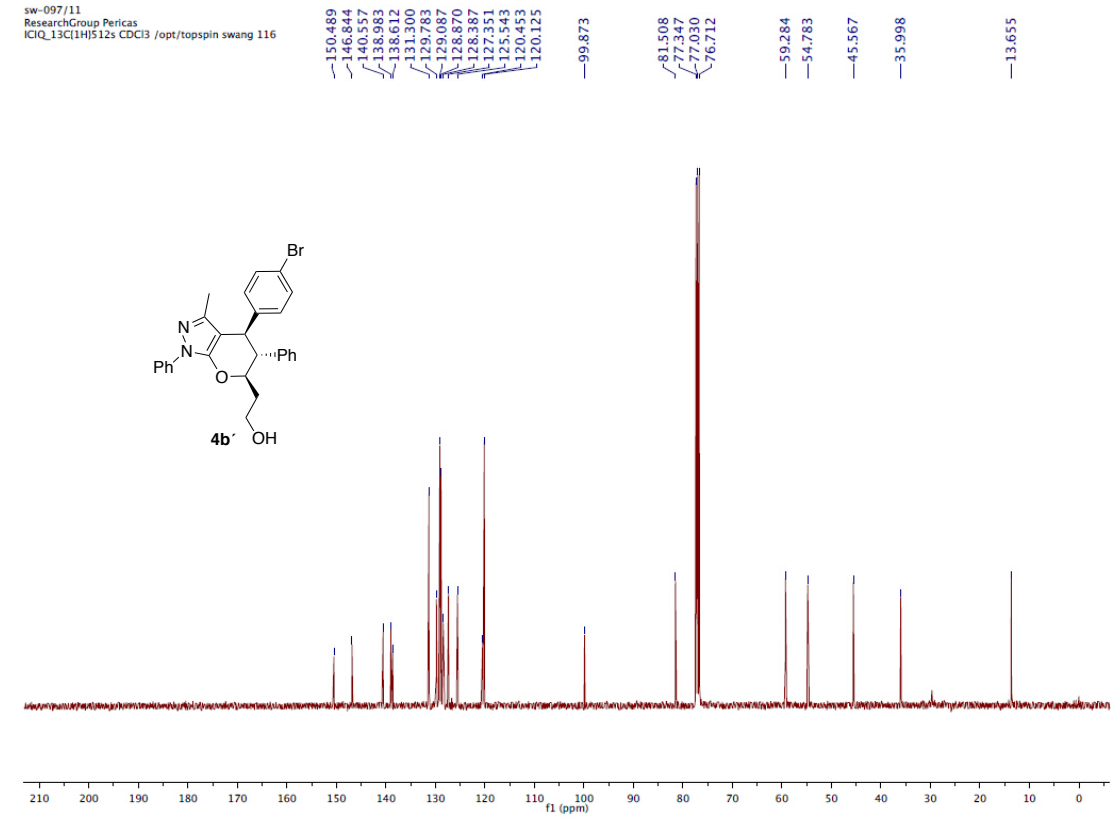
2.01
1.03
1.02
2.00
1.00
1.28
3.08
2.07
f1 (ppm)


sw-097/11
ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 116
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131.300
129.783
129.087
128.870
128.387
127.351
125.543
120.453
120.125
99.873
81.508
77.347
77.030
76.712
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45.567
35.998
13.655
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N
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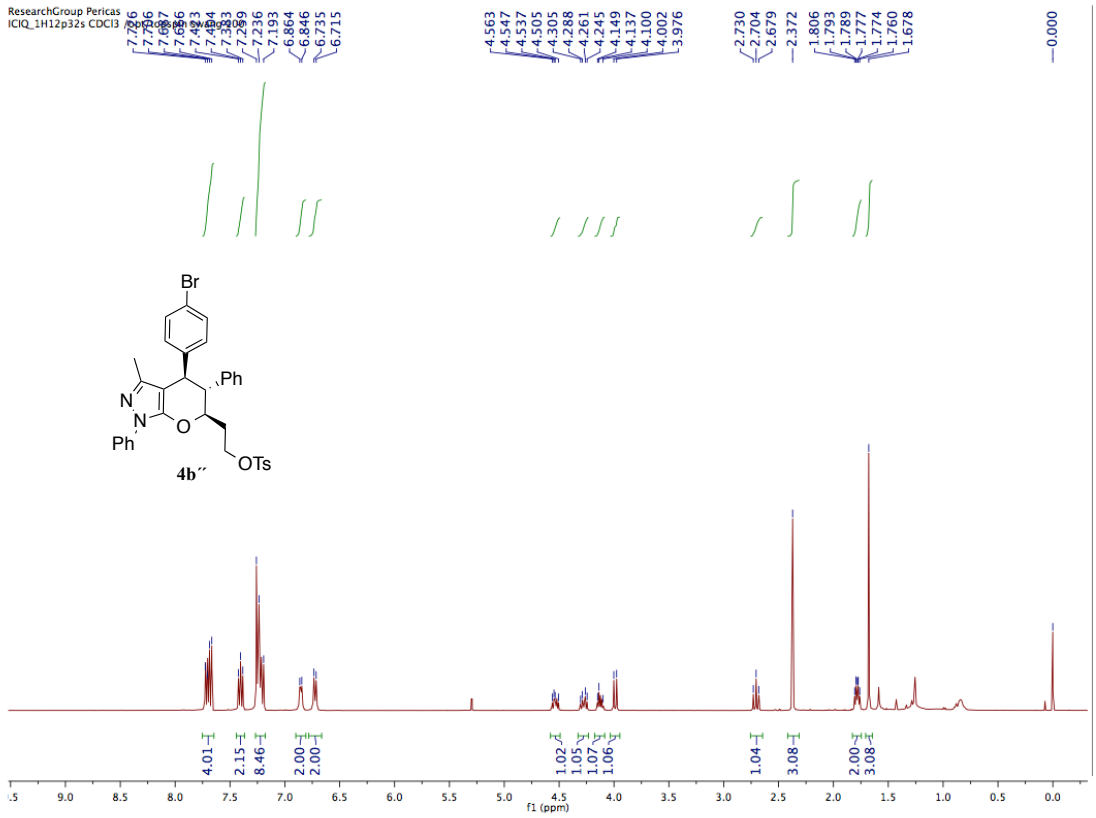
Ph
Ph
O
OH
4b´
f1 (ppm)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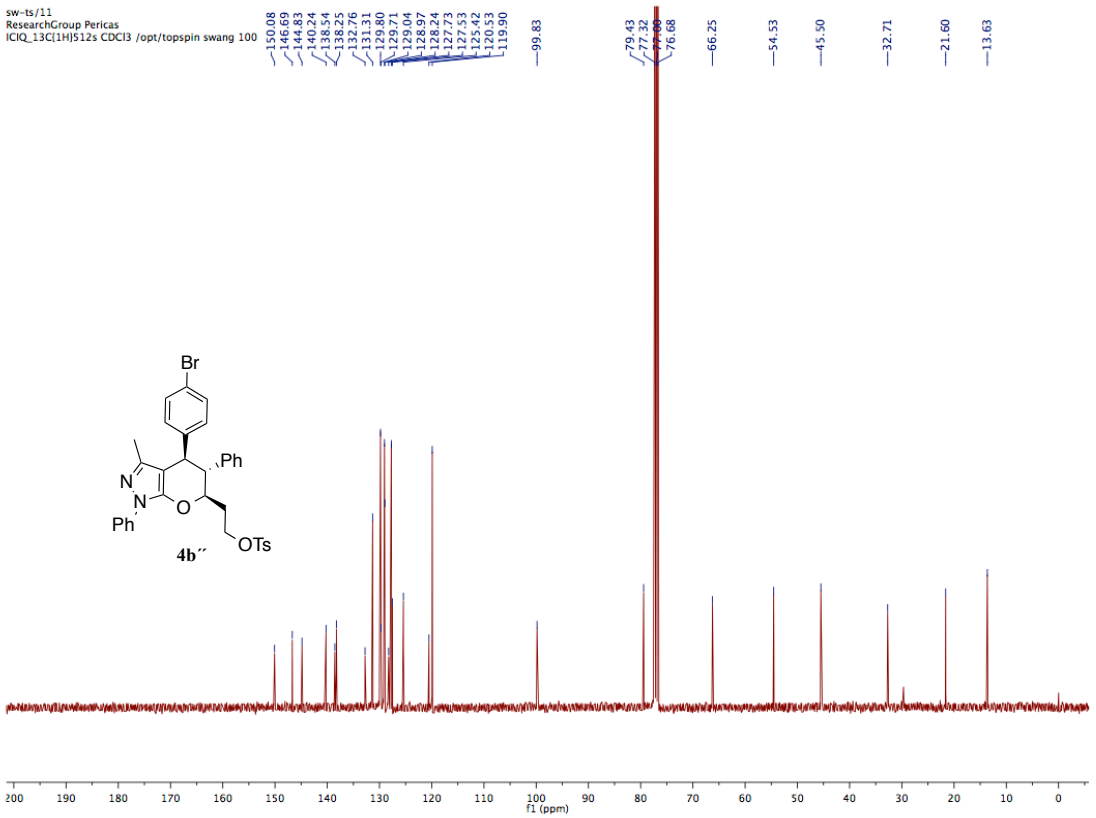
Ph
N
N
O
Ph
OTs
4b''
f1 (ppm)


sw-ts/11
ResearchGroup Pericas
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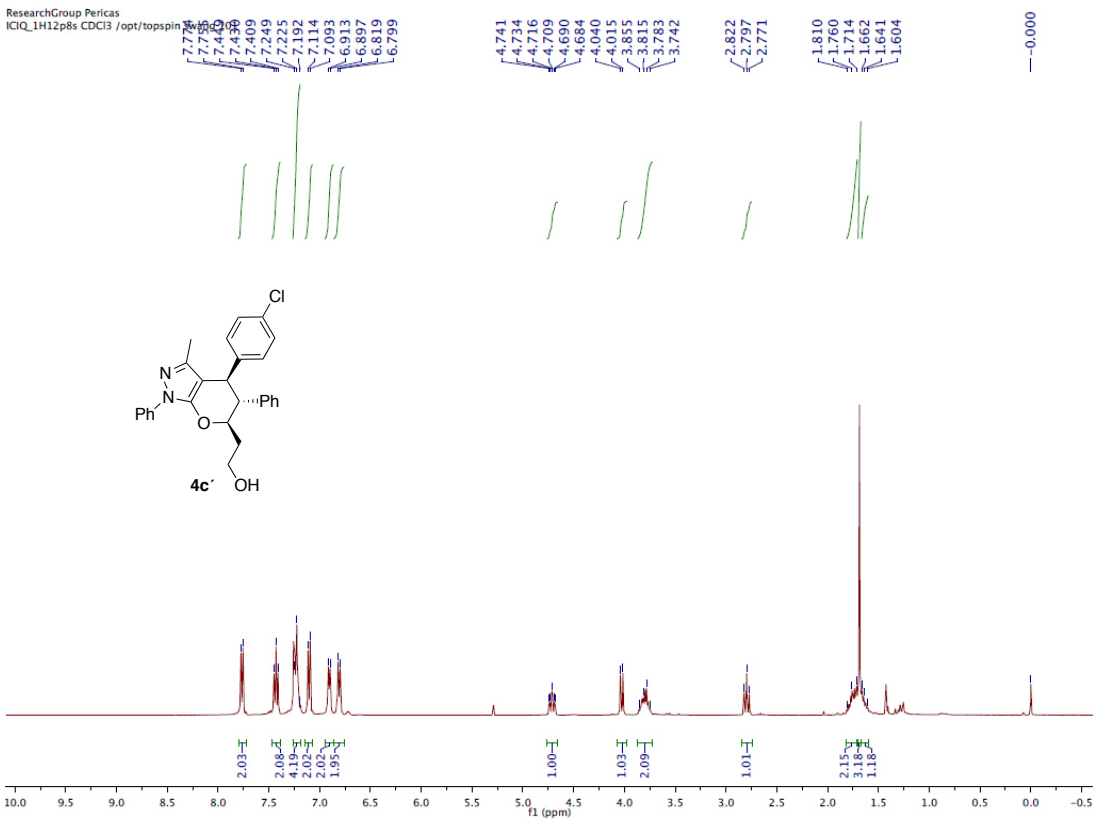
Br
Ph
N
N
O
Ph
OTs
4b''
f1 (ppm)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6.819
6.799
4.741
4.734
4.716
4.709
4.690
4.684
4.040
4.015
3.855
3.815
3.783
3.742
2.822
2.797
2.771
1.810
1.760
1.714
1.662
1.641
1.604
0.000
Cl
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N
Ph
Ph
O
OH
4c´
2.03
2.08
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1.03
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1.01
2.15
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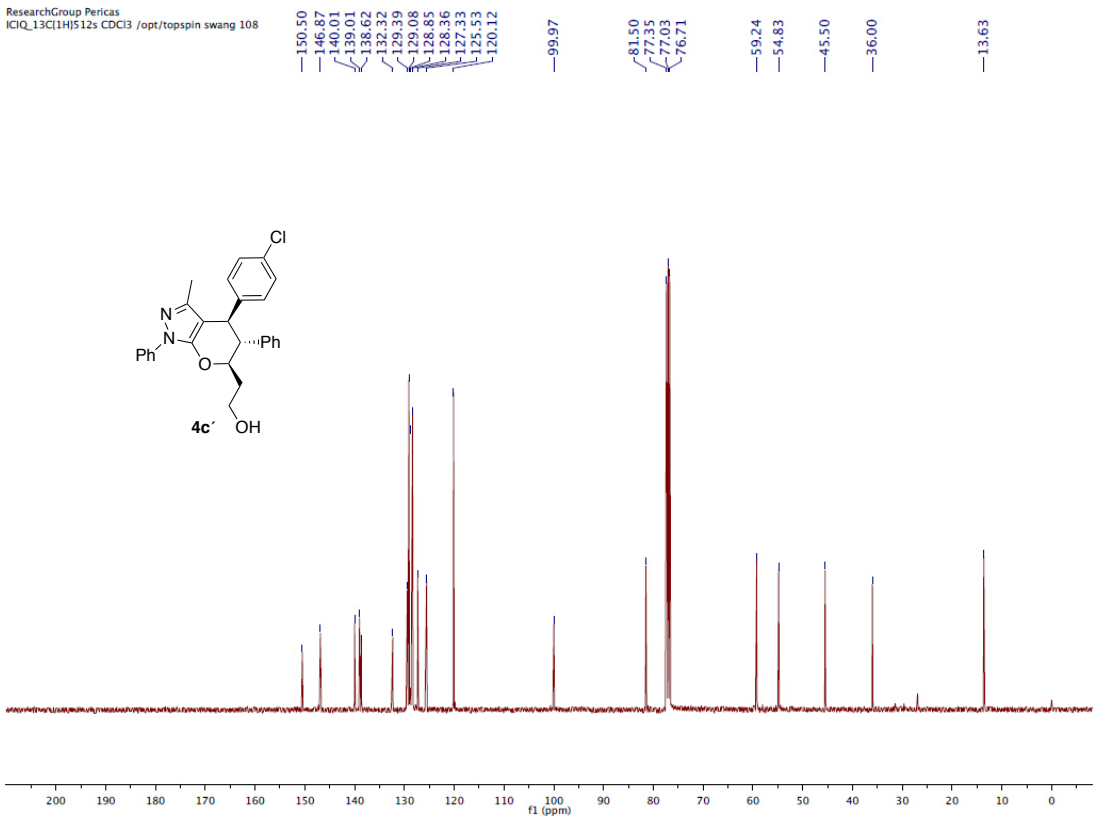
1.18
f1 (ppm)


ResearchGroup Pericas
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129.39
129.08
128.85
128.36
127.33
125.53
120.12
99.97
81.50
77.35
77.03
76.71
59.24
54.83
45.50
36.00
13.63
Cl
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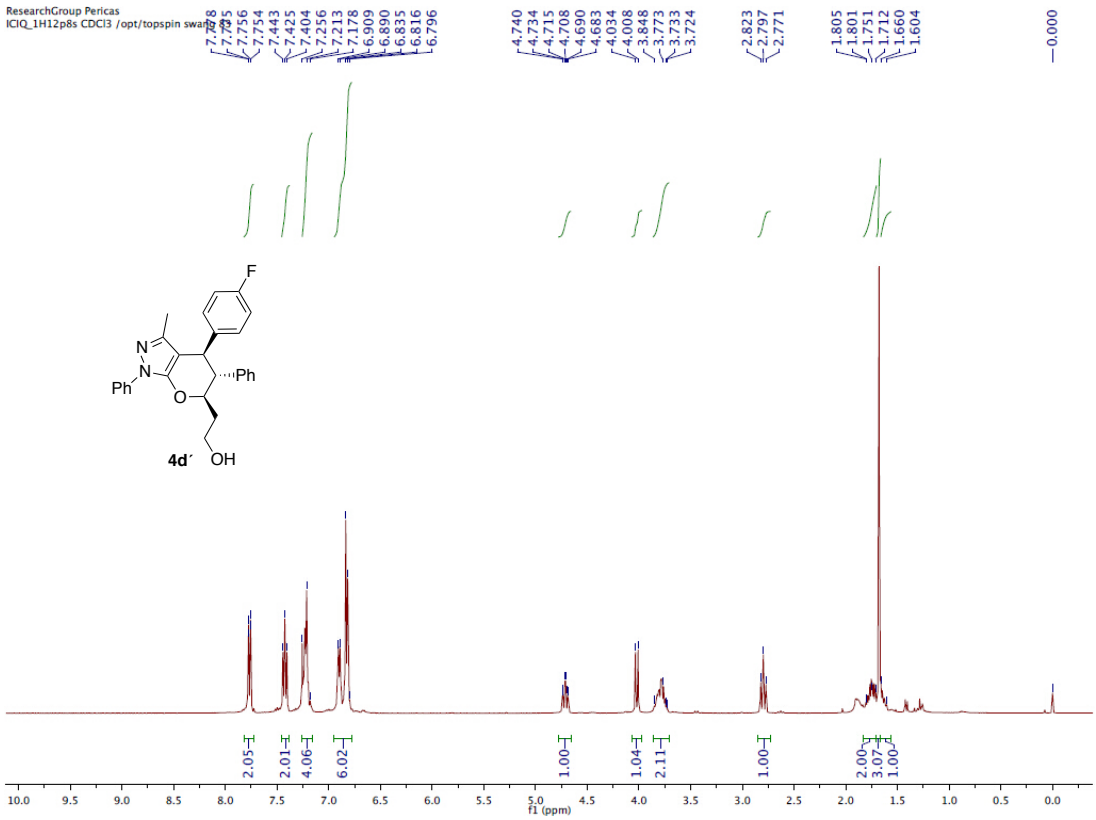
N
Ph
Ph
O
OH
4c´
f1 (ppm)


ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 83
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1.801
1.751
1.712
1.660
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N
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Ph
O
Ph
4d´
OH
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1.04
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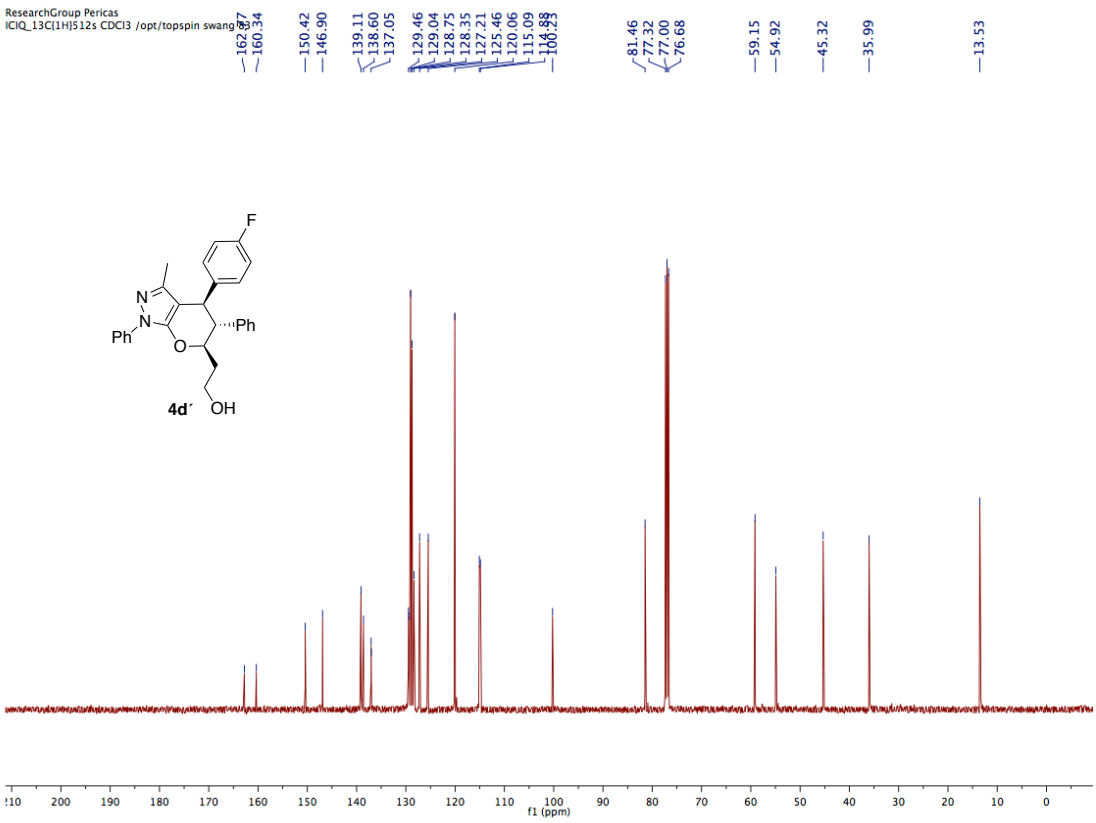
f1 (ppm)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ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 83
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128.35
127.21
125.46
120.06
115.09
114.88
100.23
81.46
77.32
77.00
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35.99
13.53
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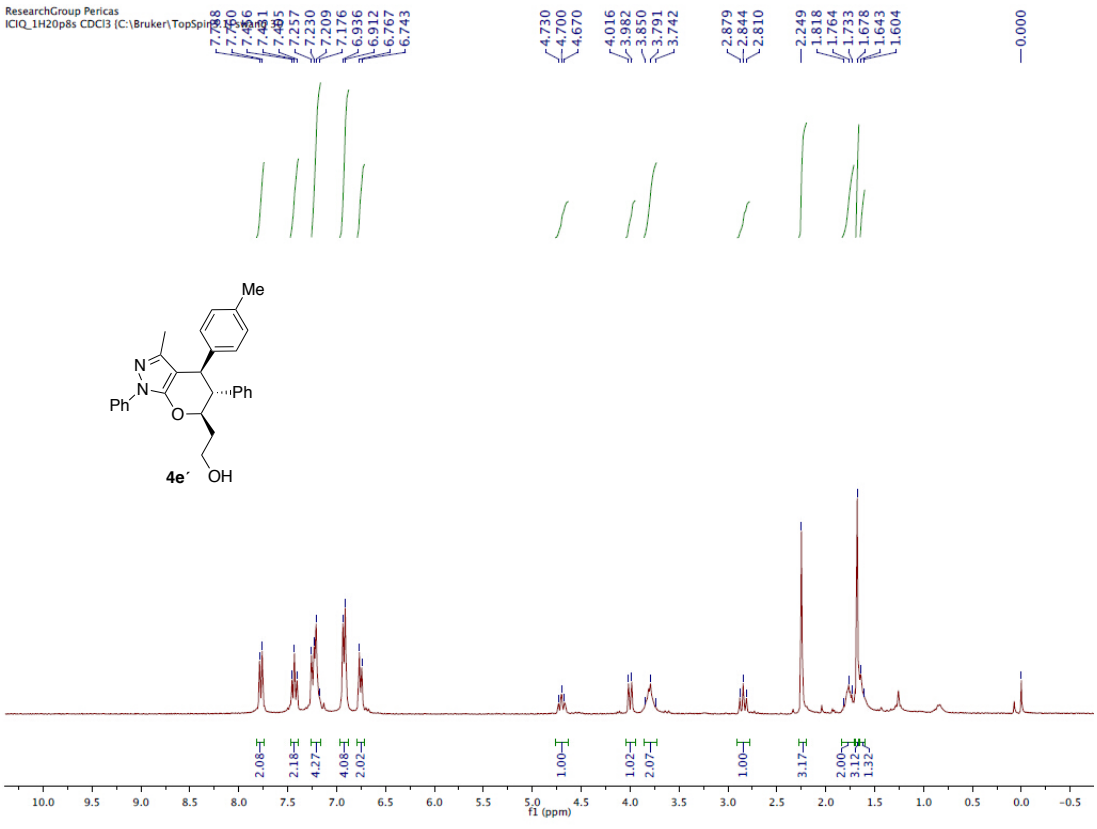
Ph
O
Ph
4d´
OH
f1 (ppm)


ResearchGroup Pericas
ICIQ_1H20p8s CDCl3 (C:\Bruker\TopSpin3.1) swang 31
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7.230
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7.176
6.936
6.912
6.767
6.743
4.730
4.700
4.670
4.016
3.982
3.850
3.791
3.742
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2.844
2.810
2.249
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1.764
1.733
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1.643
1.604
0.000
Me
N
N
Ph
O
Ph
OH
4e´
2.08
2.18
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1.02
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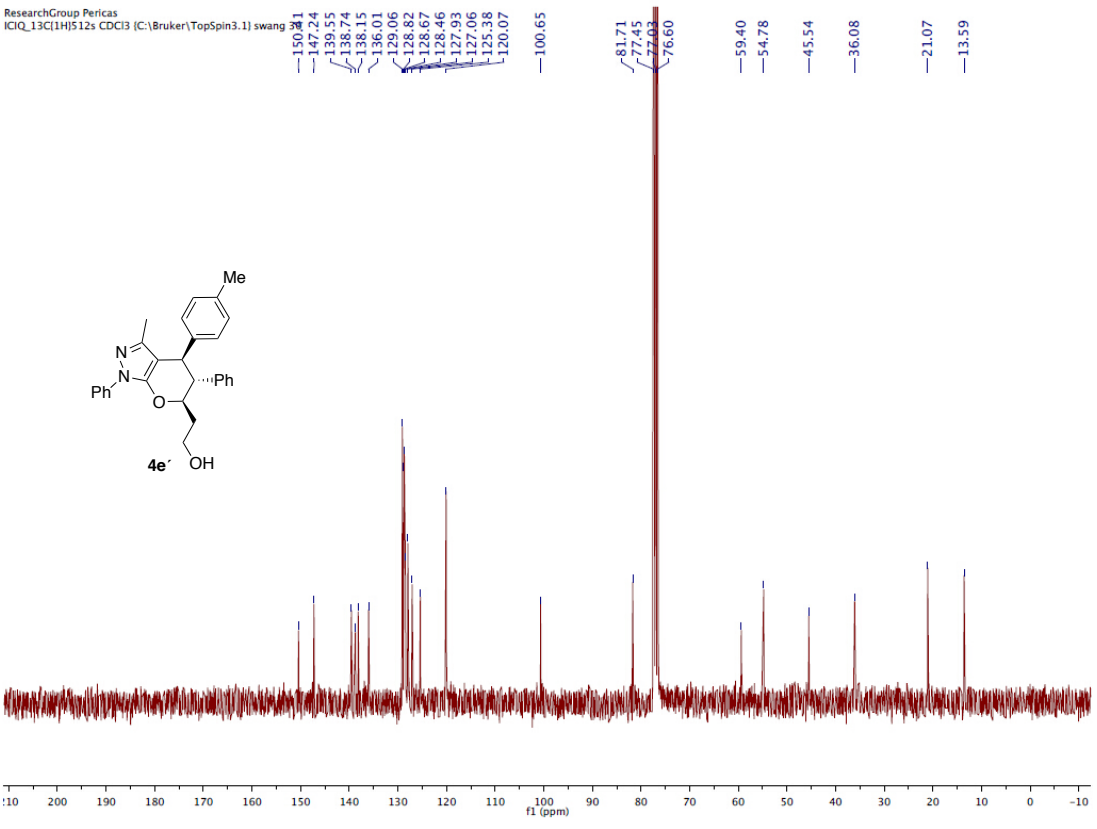
f1 (ppm)


ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 (C:\Bruker\TopSpin3.1) swang 31
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120.07
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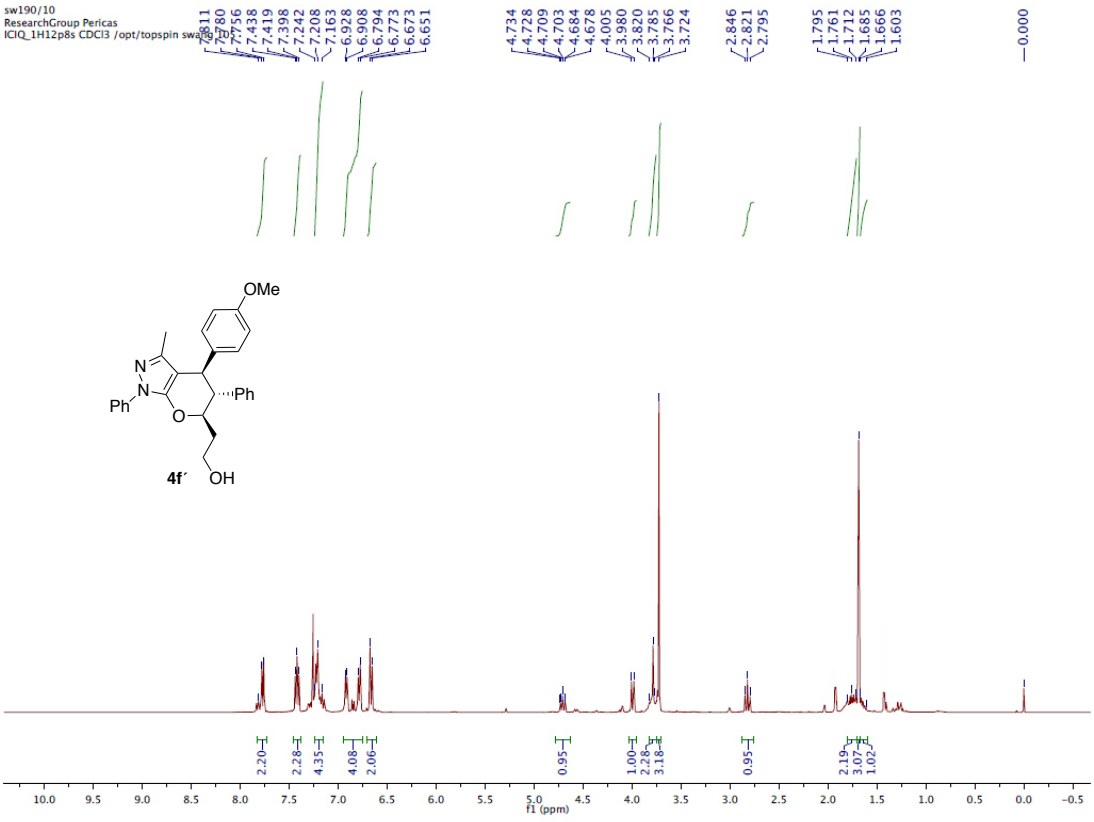
4e´
f1 (ppm)


sw190/10
ResearchGroup Pericas
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Ph
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O
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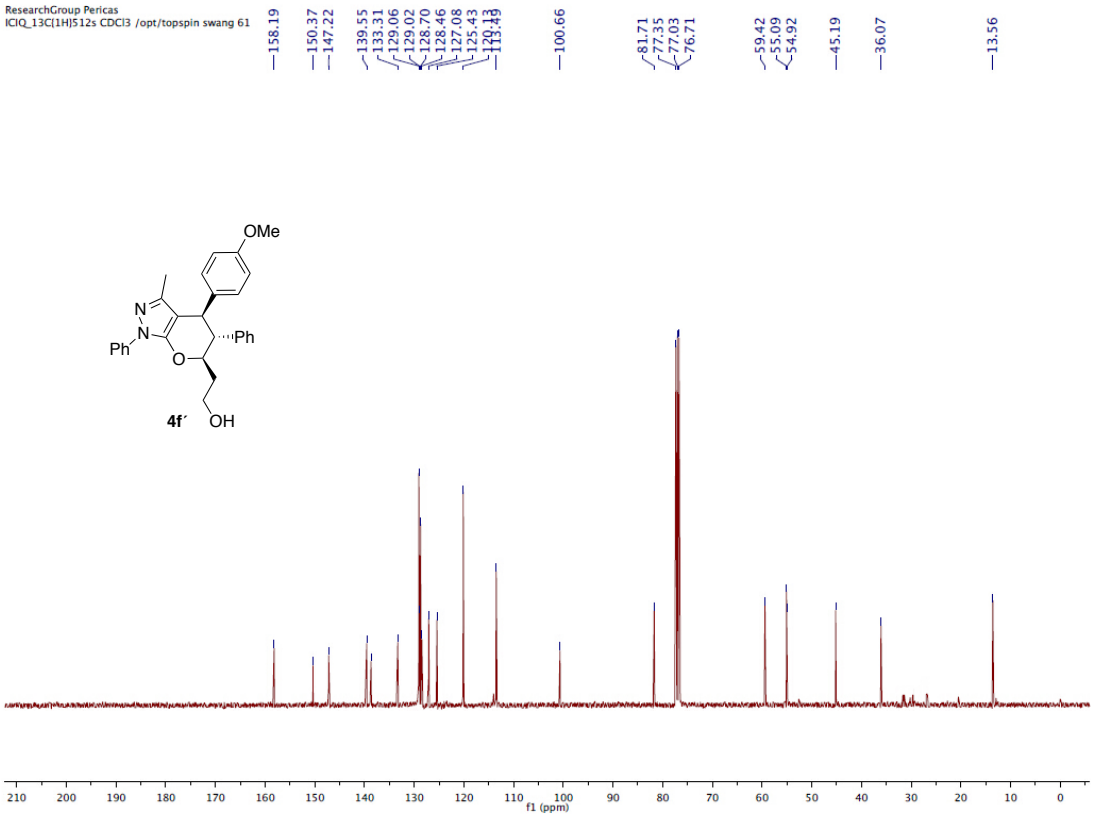
4f´
f1 (ppm)


ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 61
OMe
Ph
Ph
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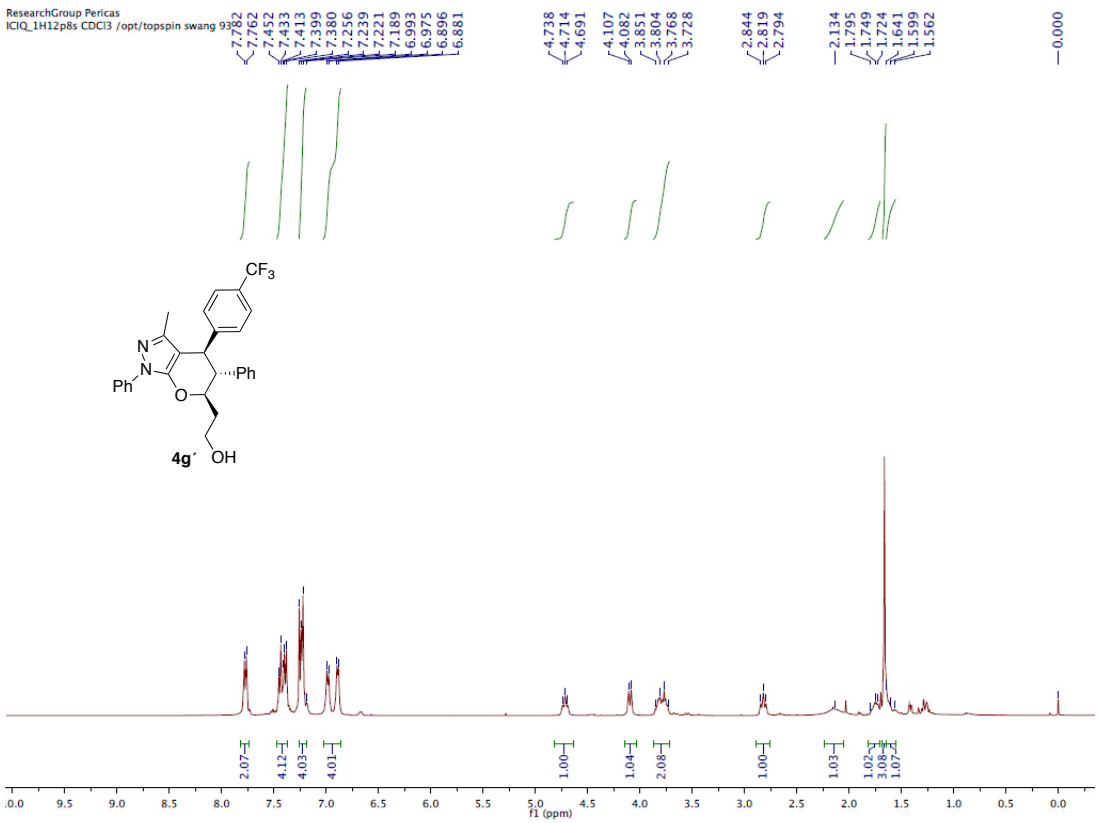
N
OH
4f´
f1 (ppm)


ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 93
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6.975
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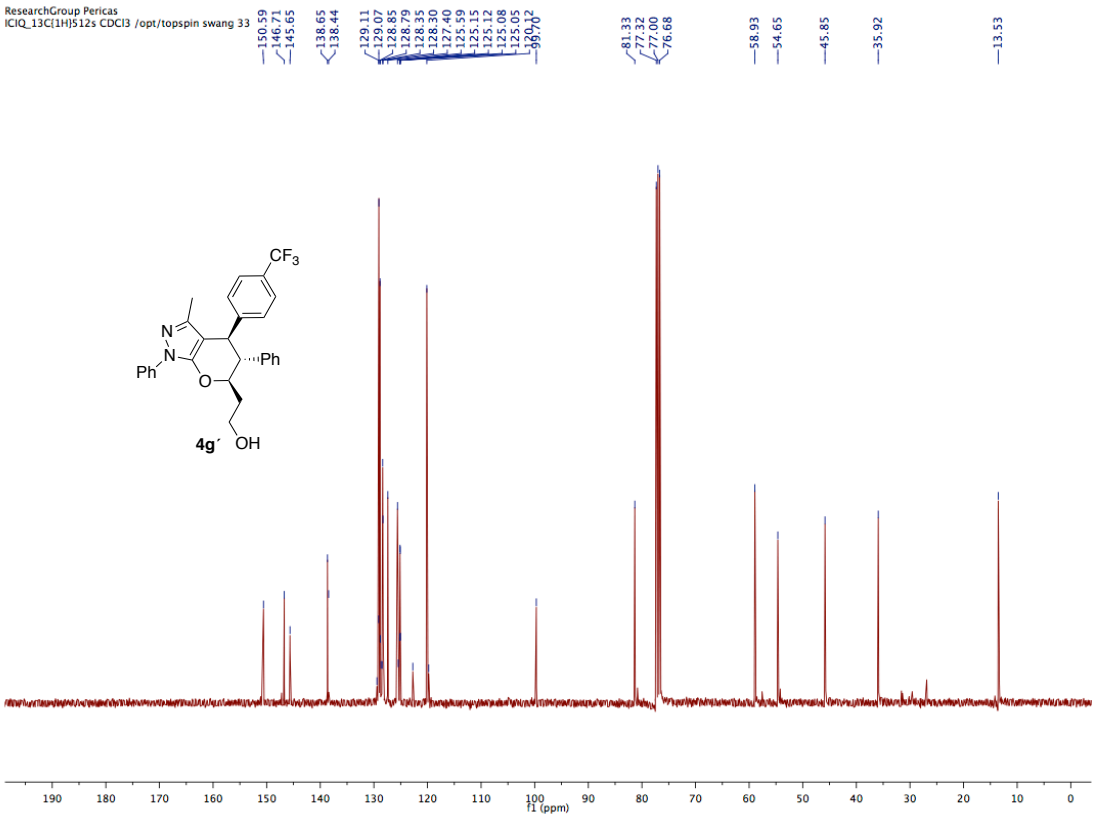
f1 (ppm)


ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 33
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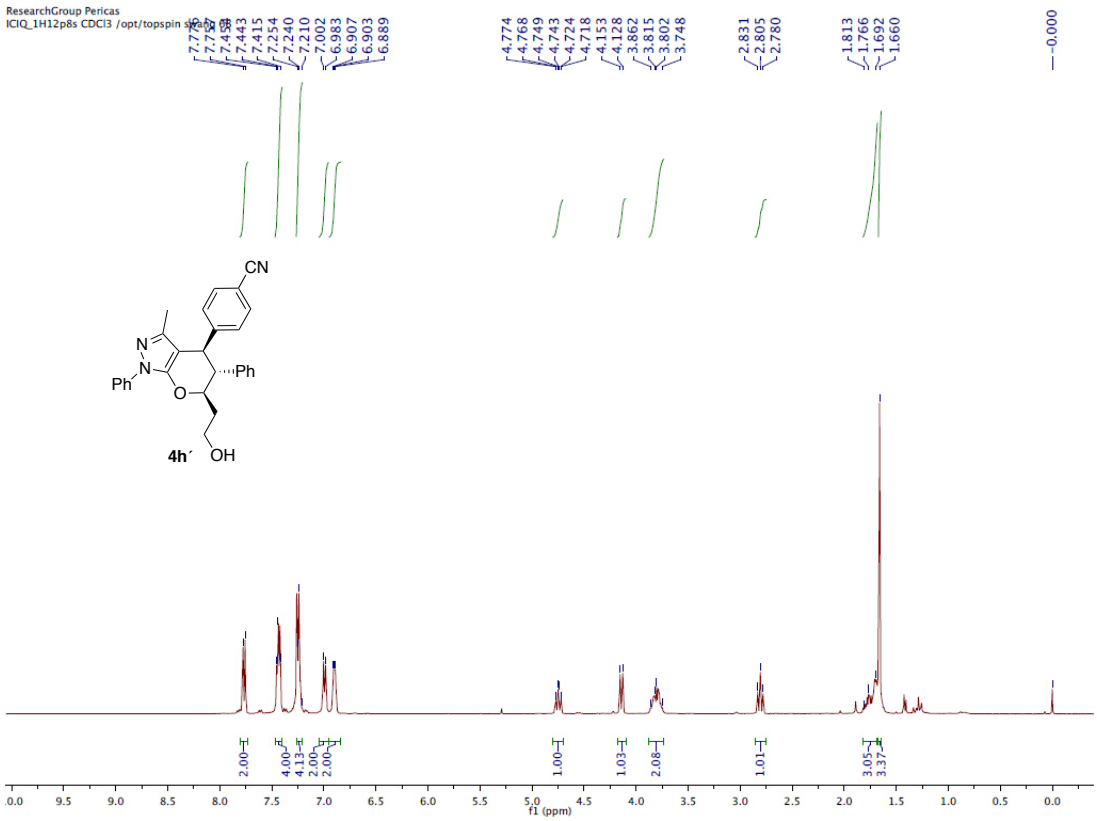
f1 (ppm)


ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin spang
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7.210
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4.749
4.743
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O
Ph
4h´
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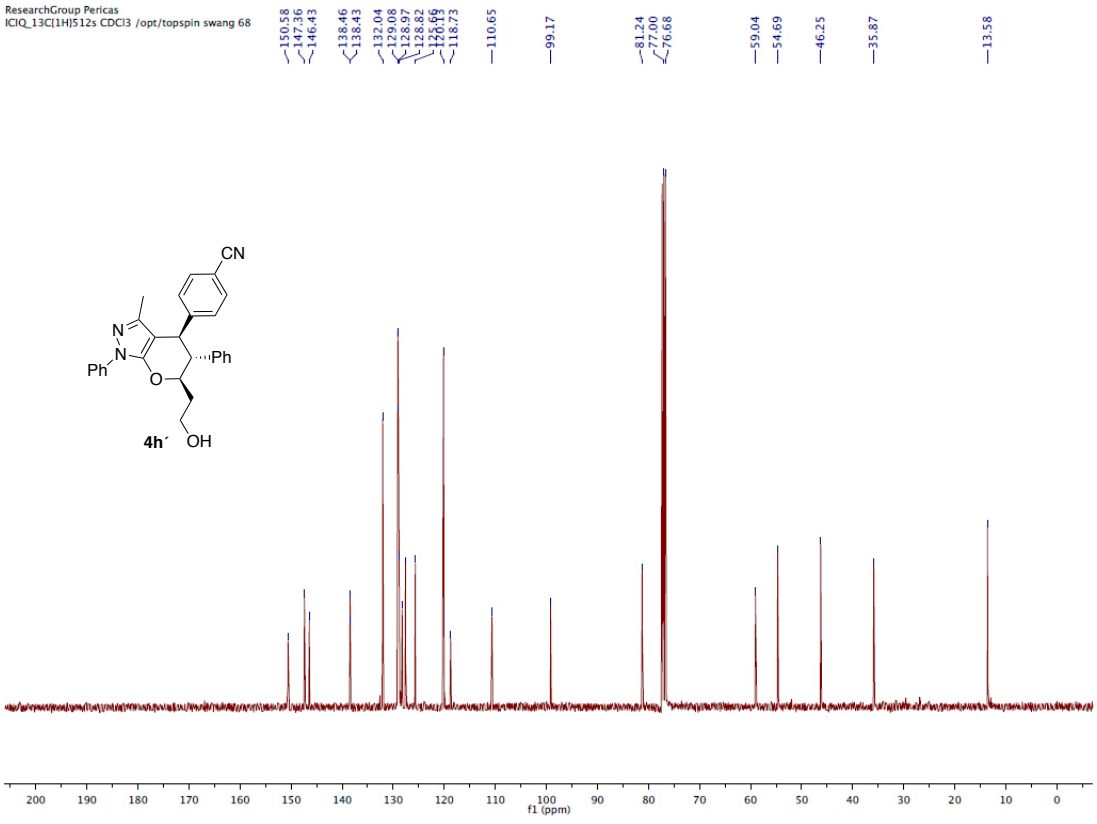
3.37
f1 (ppm)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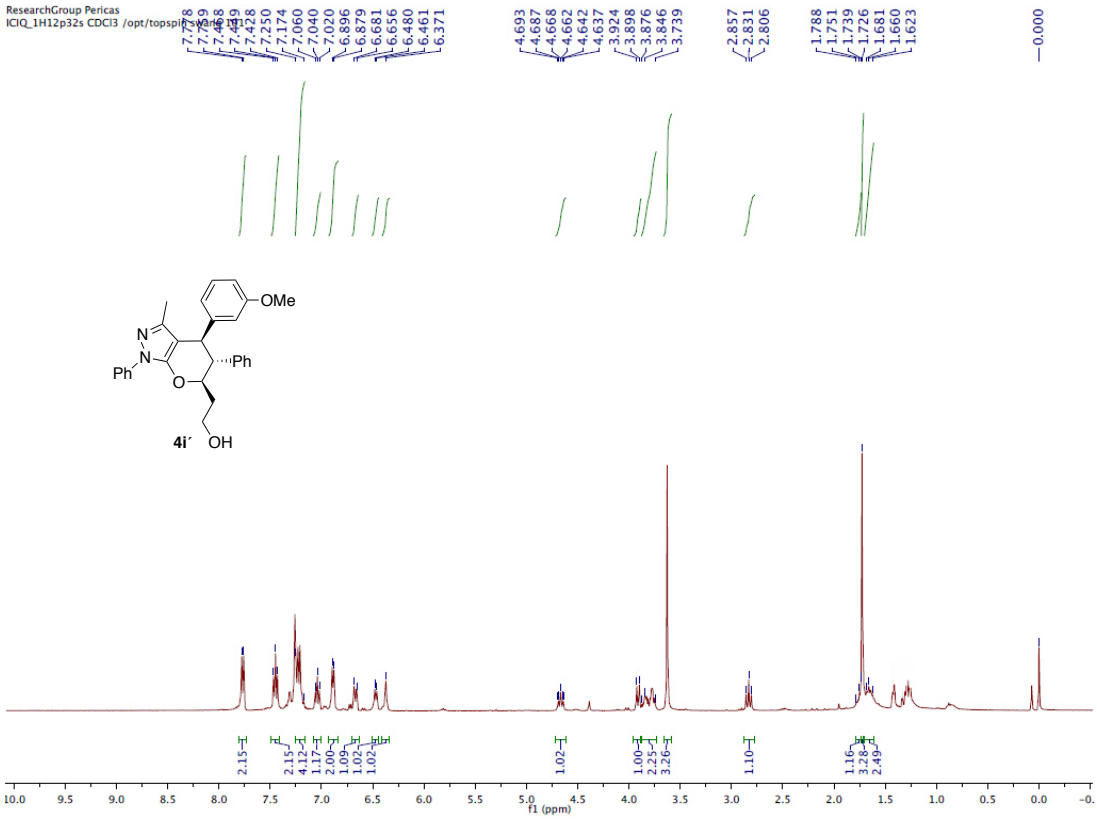
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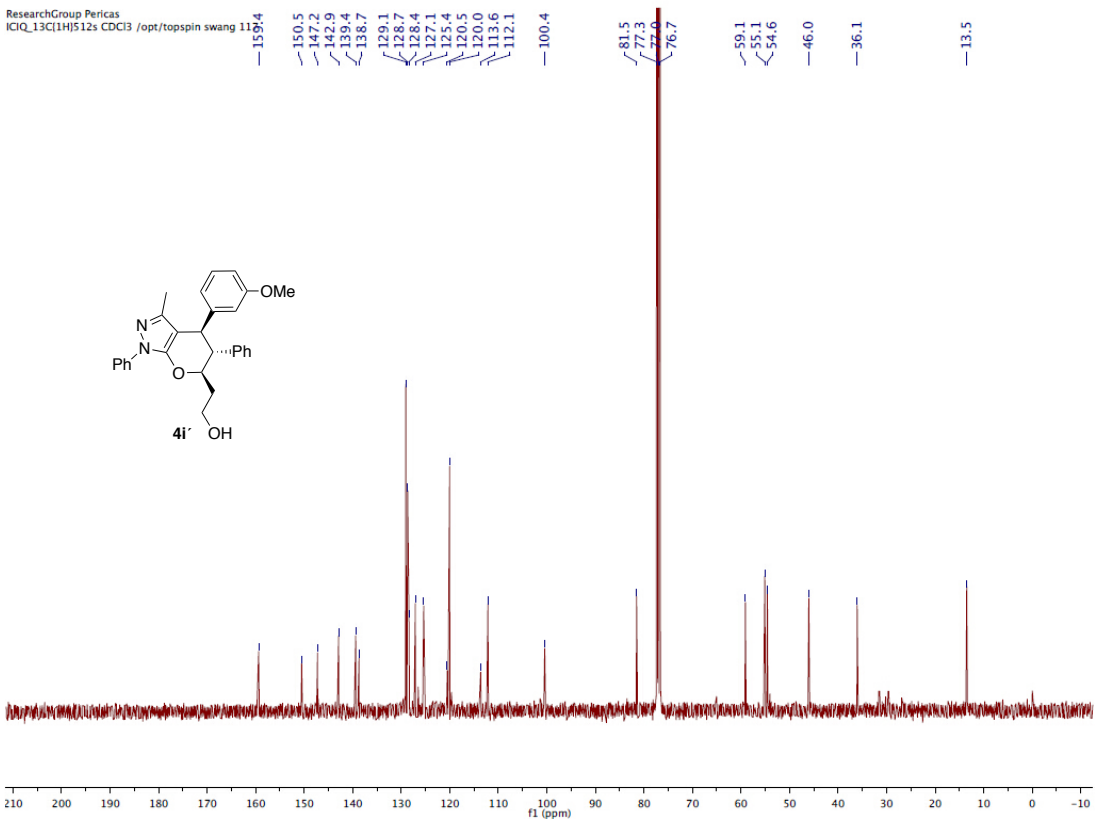
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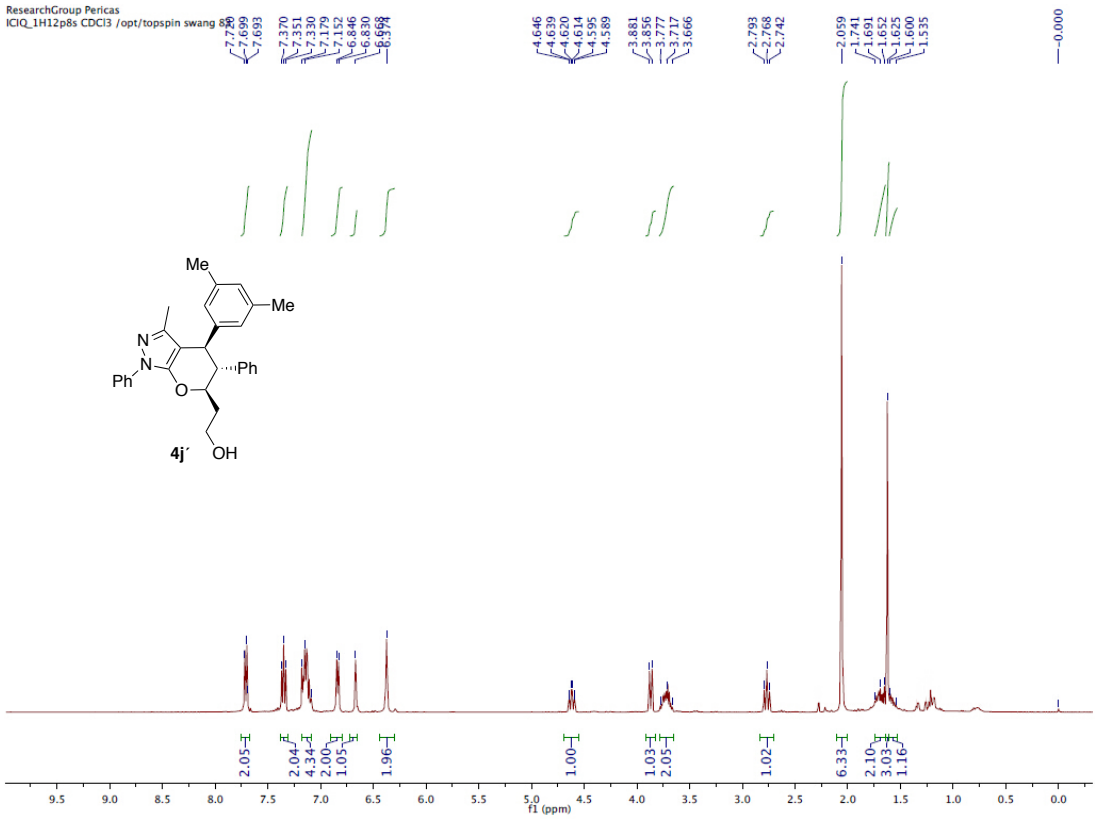
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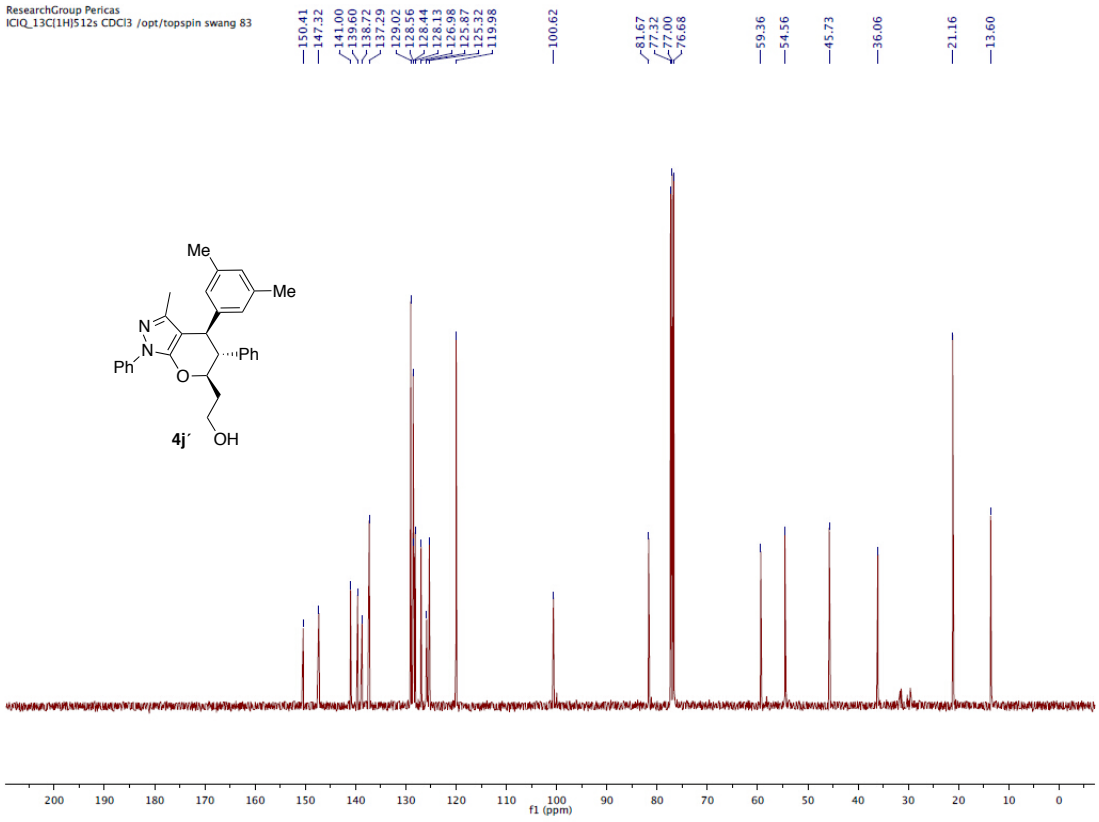
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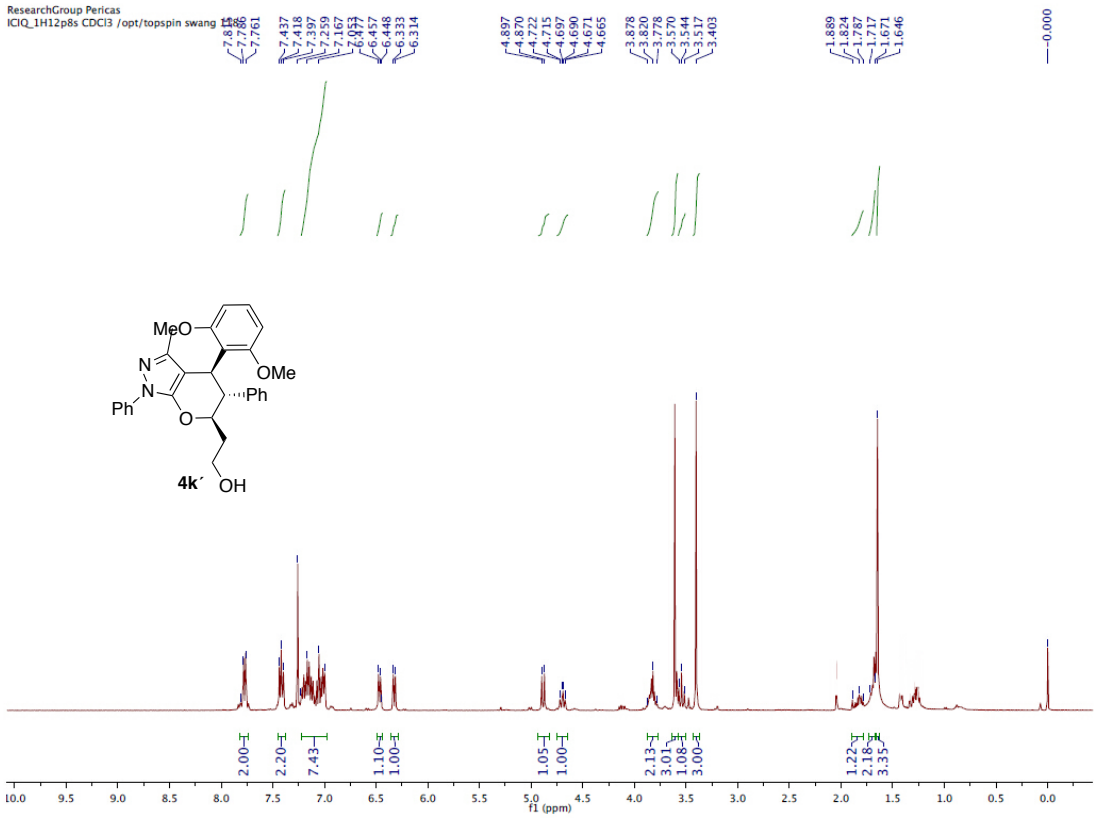
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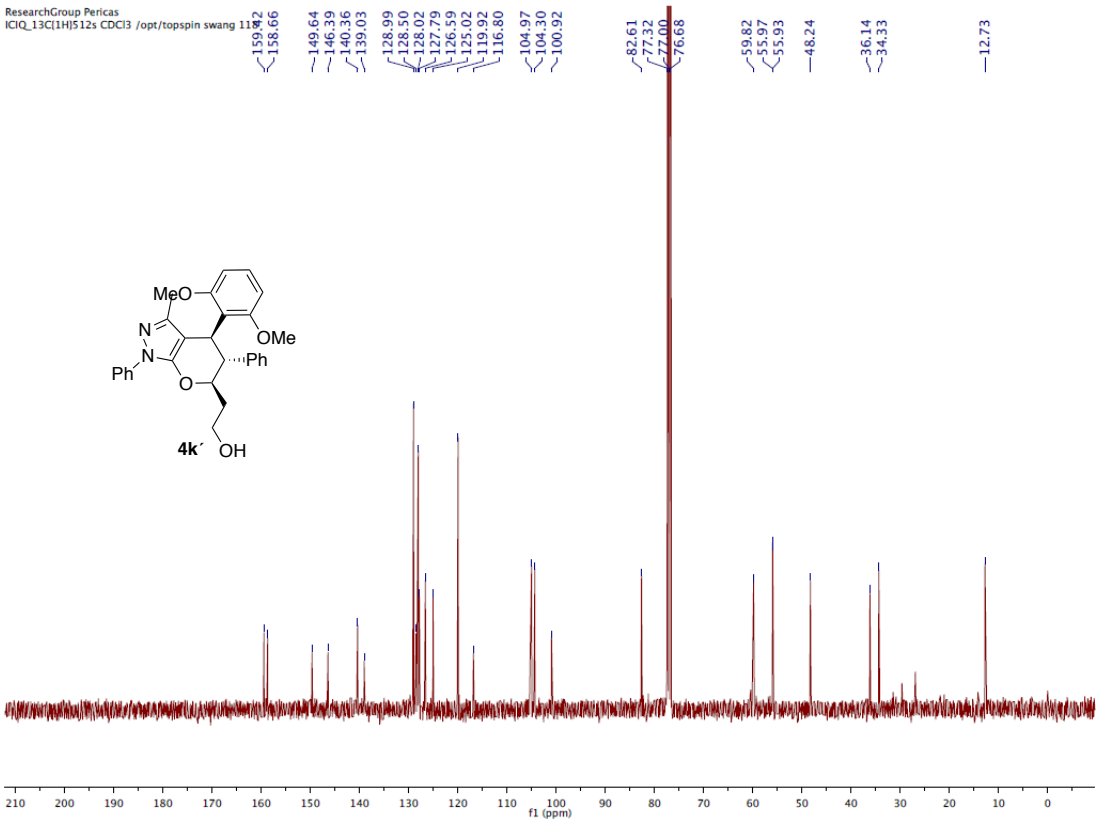
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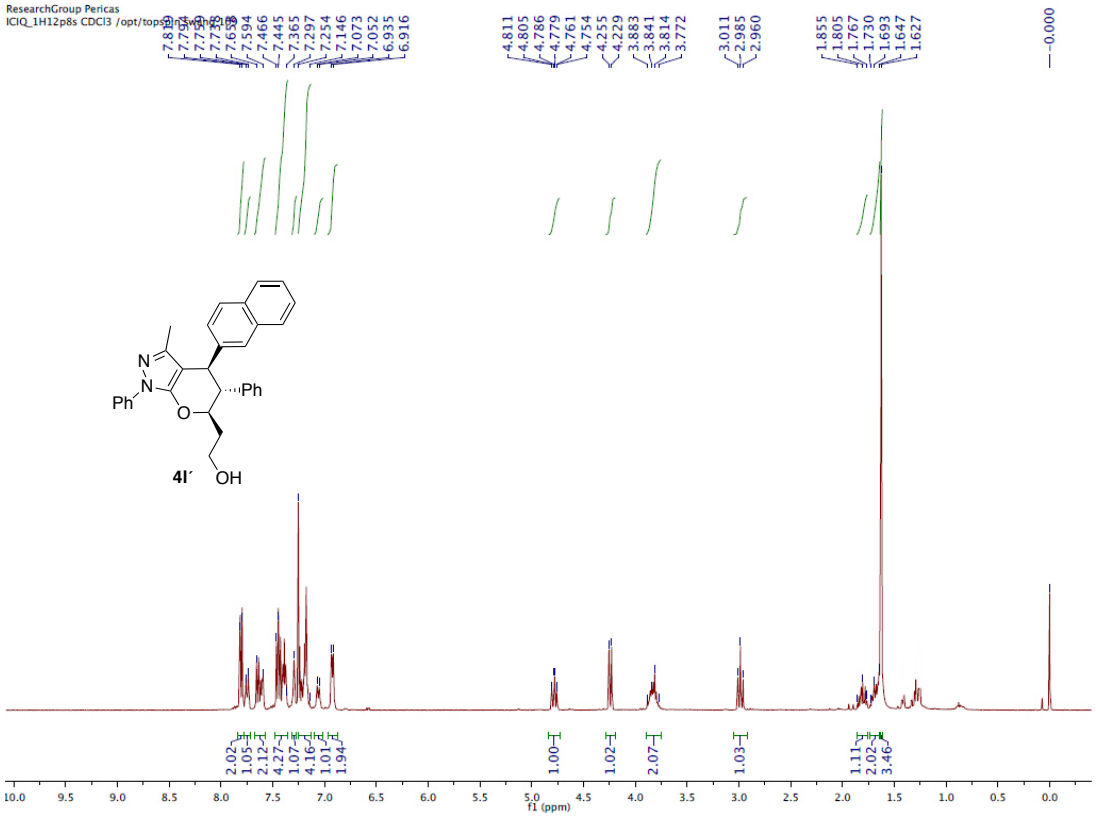
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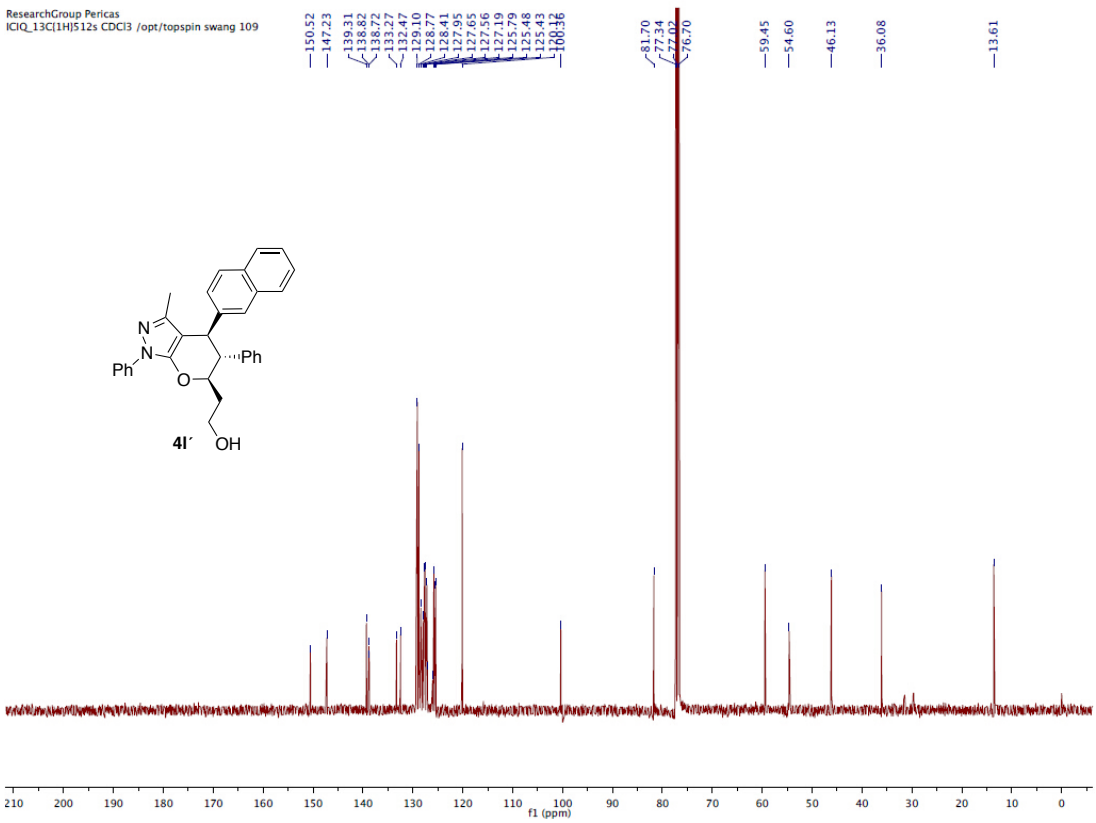
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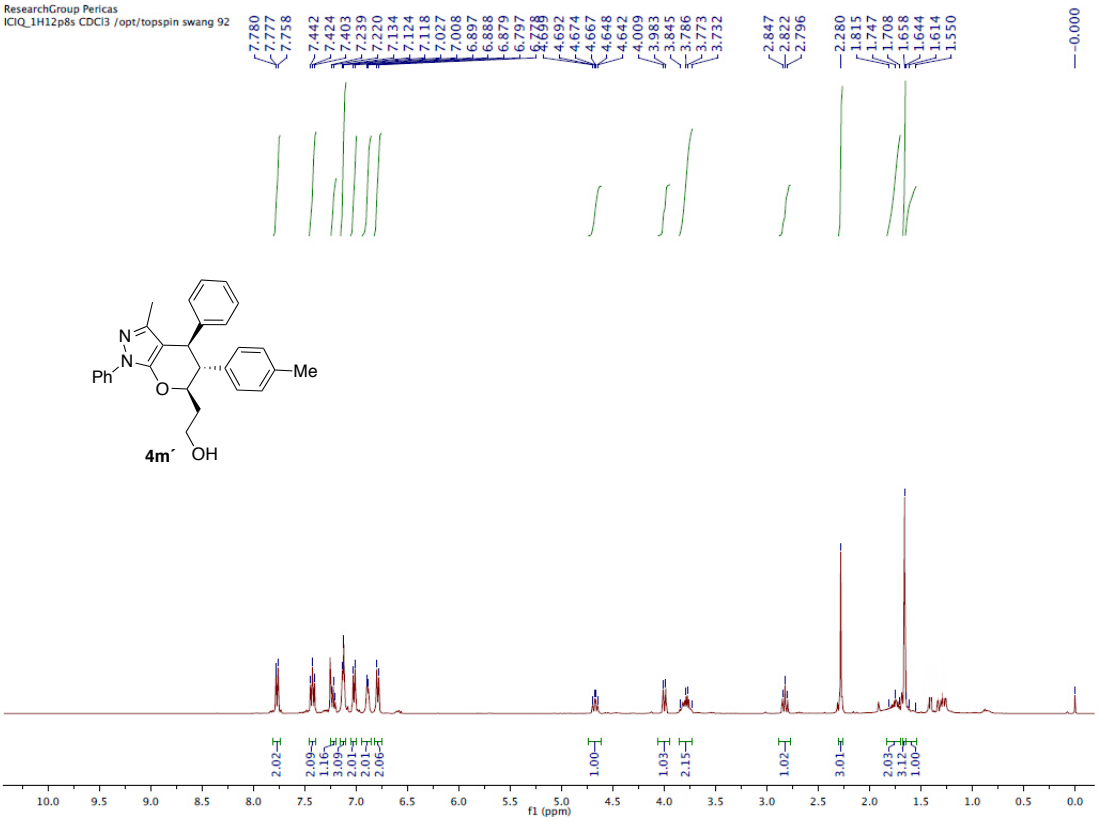
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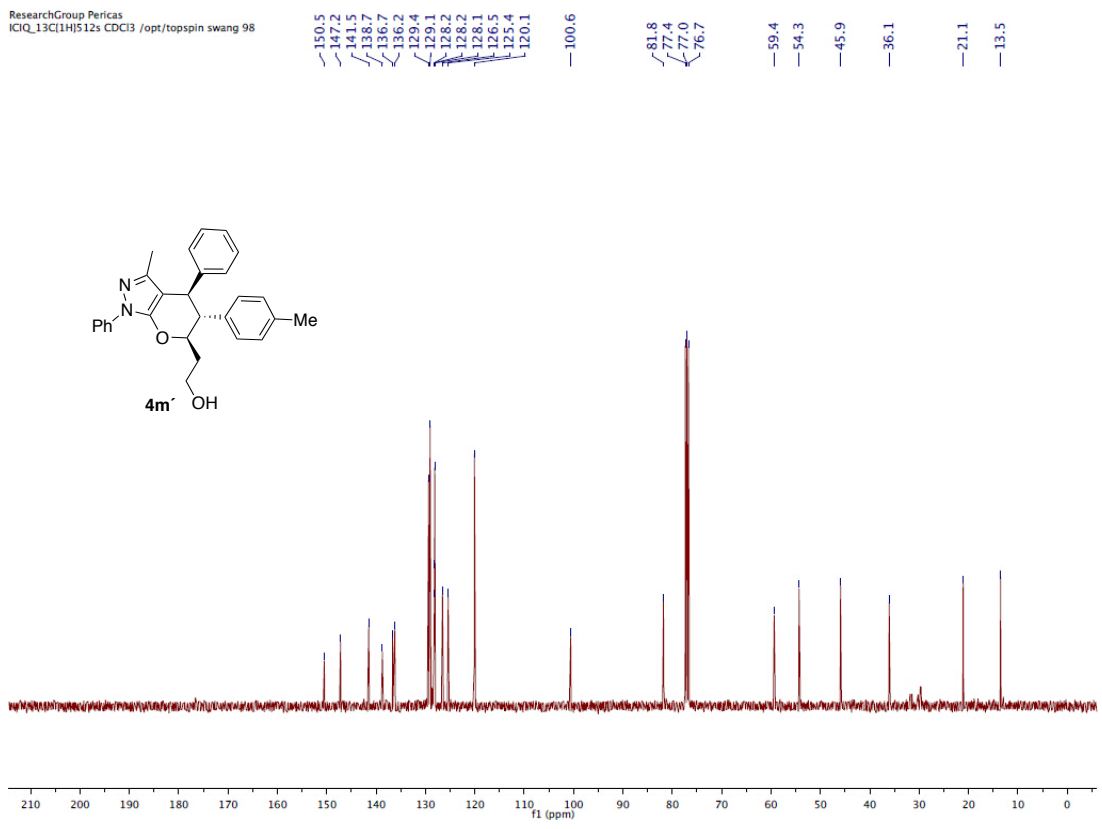
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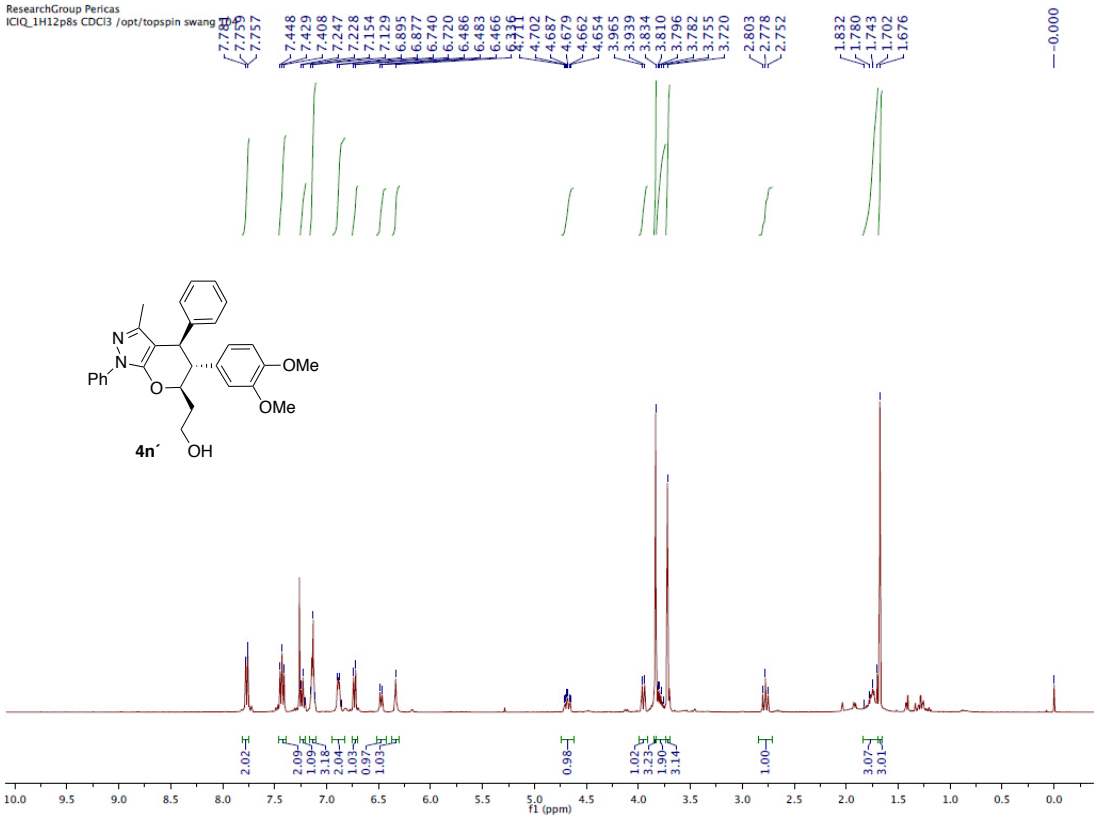
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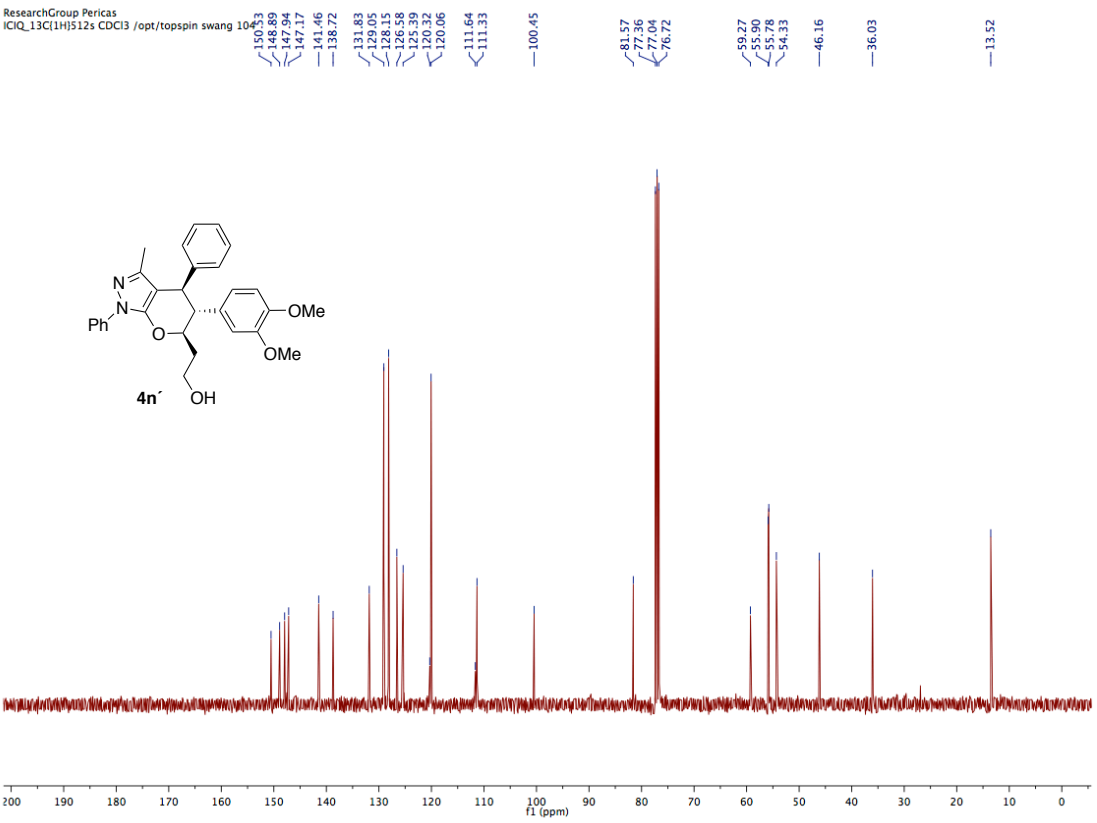
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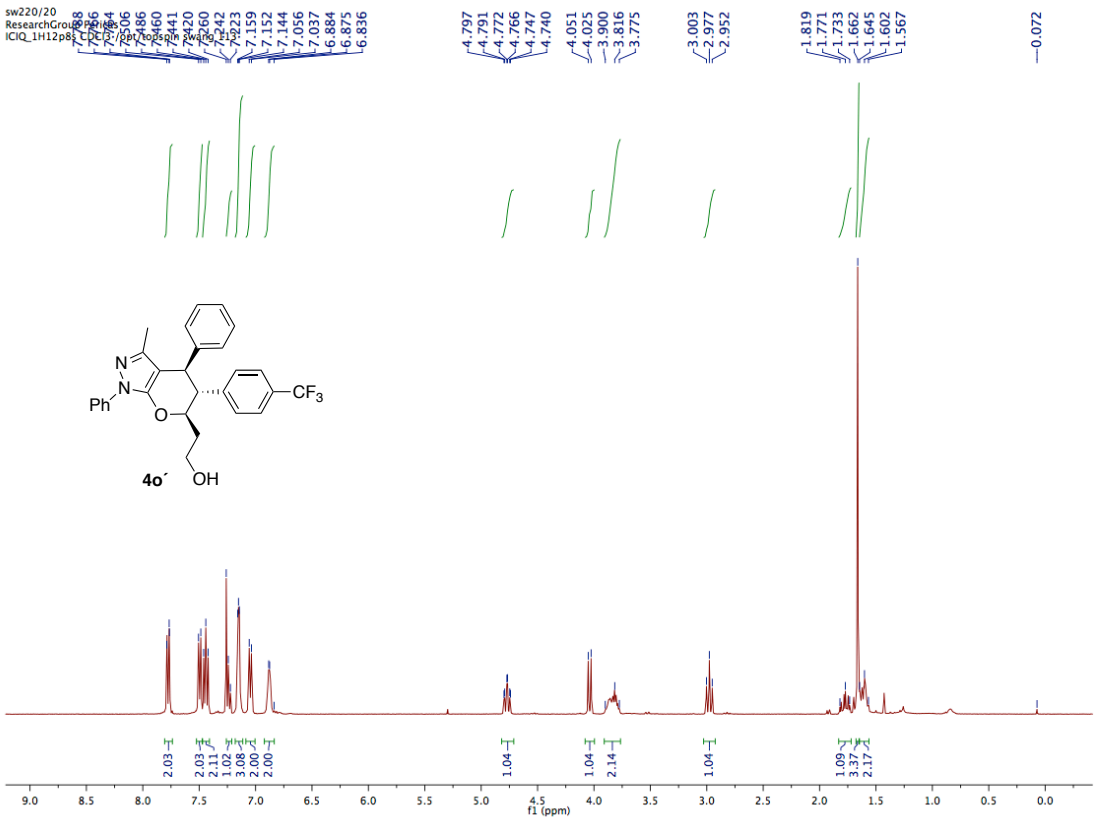
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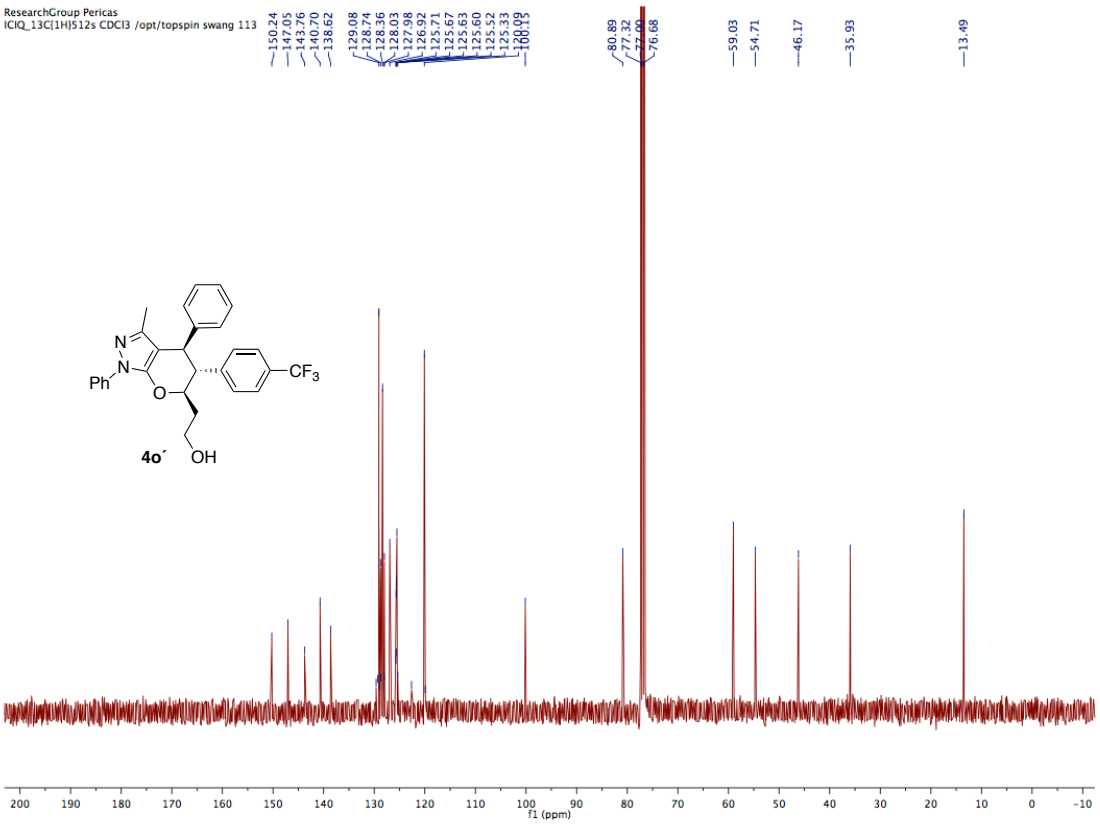
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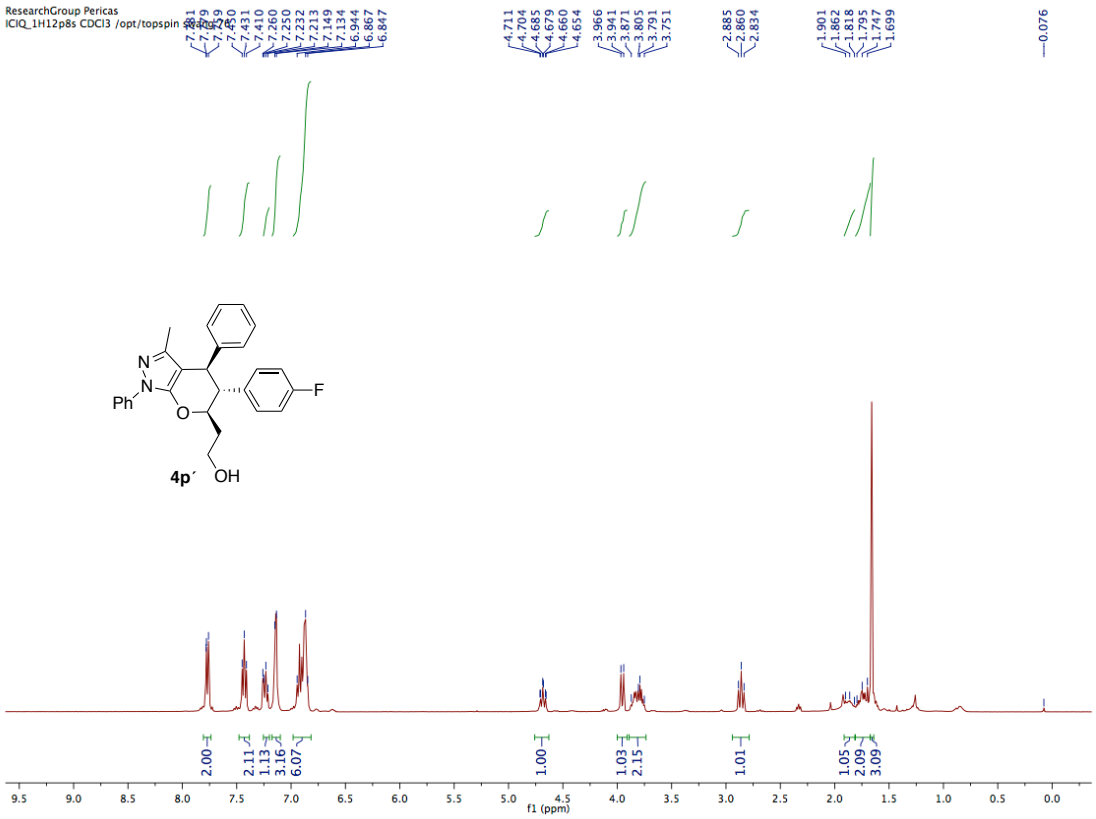
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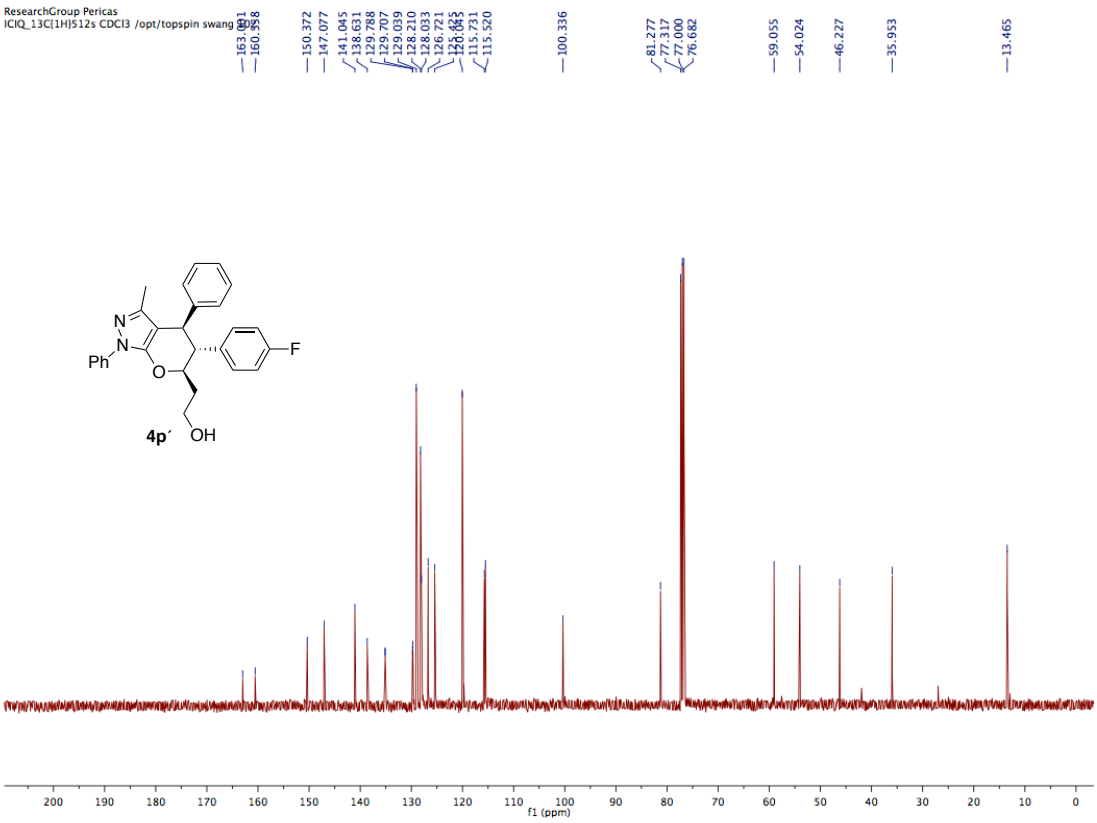
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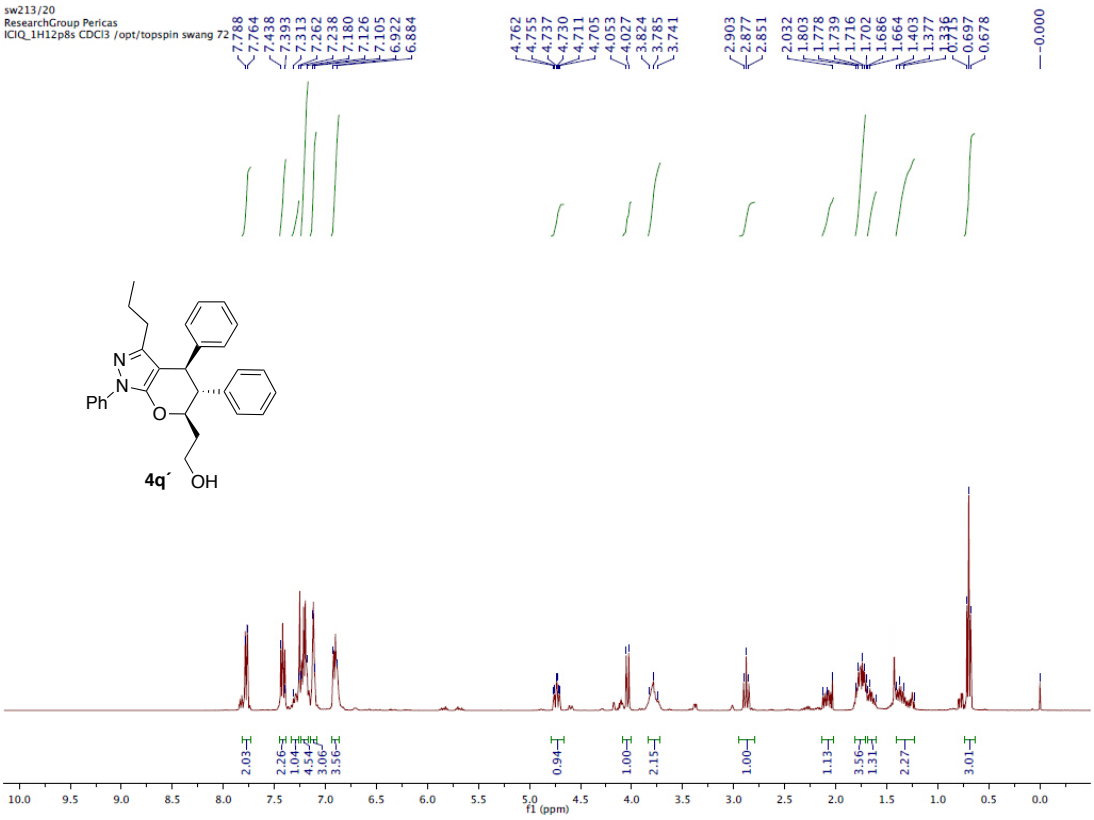
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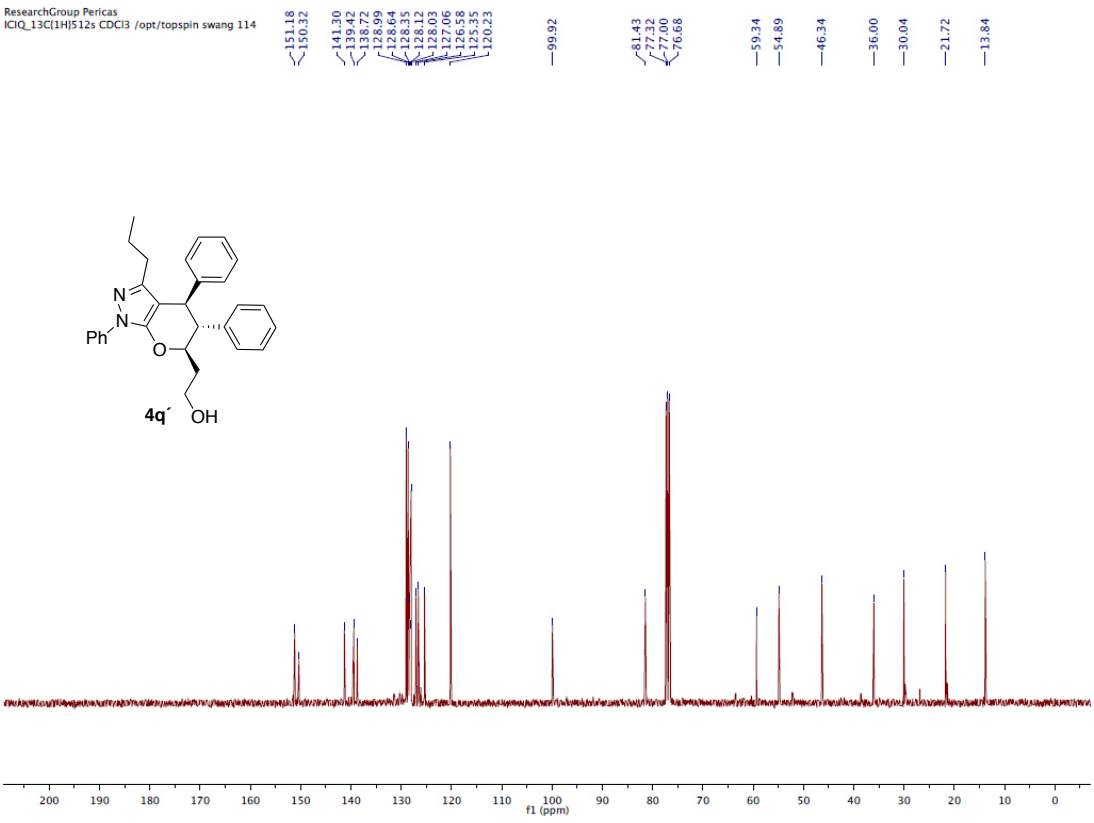
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9. References

1. Ł. Albrecht, G. Dickmeiss, F. C. Acosta, C. Rodríguez-Escrich, R. L. Davis, K. A. Jørgensen *J. Am. Chem. Soc.* **2012**, *134*, 2543-2546.
2. T. Itoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2009**, *11*, 3854-3857.
3. Q. Chen, J. Liang, S. Wang, D. Wang, R. Wang, *Chem. Commun.* **2013**, *49*, 1657-1659.
4. a) H. Flack, *Acta Cryst. A* **1983**, *39*, 876-881; b) S. Parsons, H. Flack, *Acta Cryst. A* **2004**, *60*, s61.

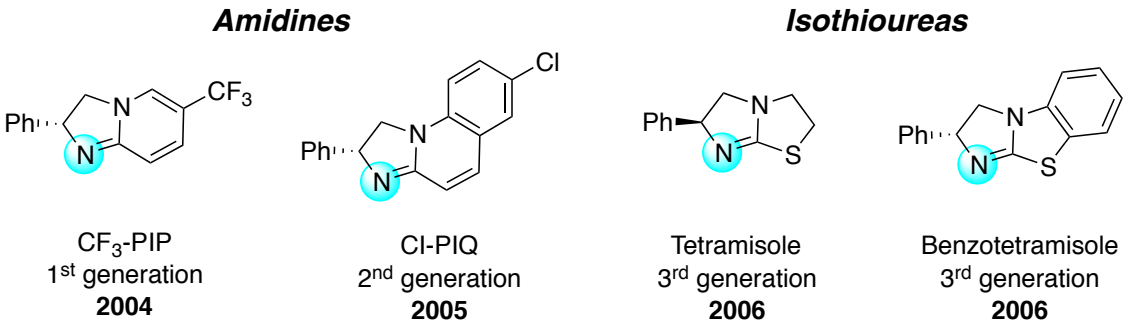
CHAPTER III

Chapter III

Asymmetric [4+2] Annulation Reactions Catalyzed by a Robust, Immobilized Isothiourea

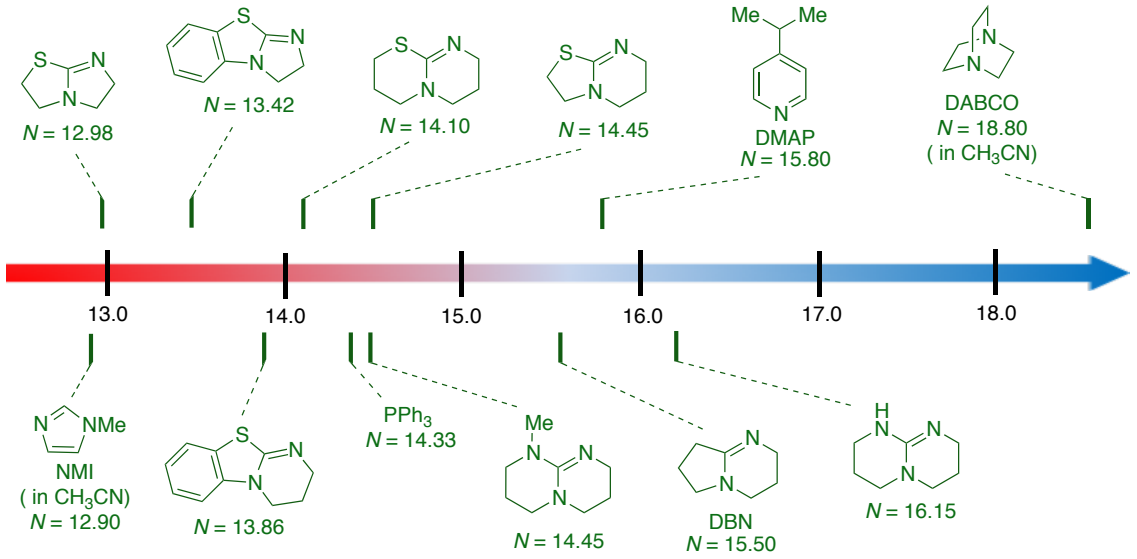
3.1. Introduction to Isothiourea Catalysis

Lewis base organocatalysts have found widespread utility in asymmetric catalysis for useful synthetic transformations. Among them, chiral amidines and isothioureas have proved to be the most commonly used organocatalysts for a large number of enantioselective transformations, particularly in kinetic resolution, formal cycloadditions and domino reactions.[1] In 2004, Birman and co-workers were the first to introduce the chiral amidine-type catalysts CF_3-PIP in enantioselective acyl transfer reactions.[2] Shortly after, the same group reported the second generation amidine-type catalysts Cl-PIQ to increase the reaction rates of acyl transfer via π-stacking effect.[3] One year later, they turned their attention toward the synthesis of chiral isothiourea catalysts (tetramisole and benzotetramisole) in the same type of reaction (Scheme 3.1).[4] After the first efforts on enantioselective kinetic resolution for C-O bond formation, chiral isothiourea catalysts have also been applied to O-Si, C-N and C-C bond formation.



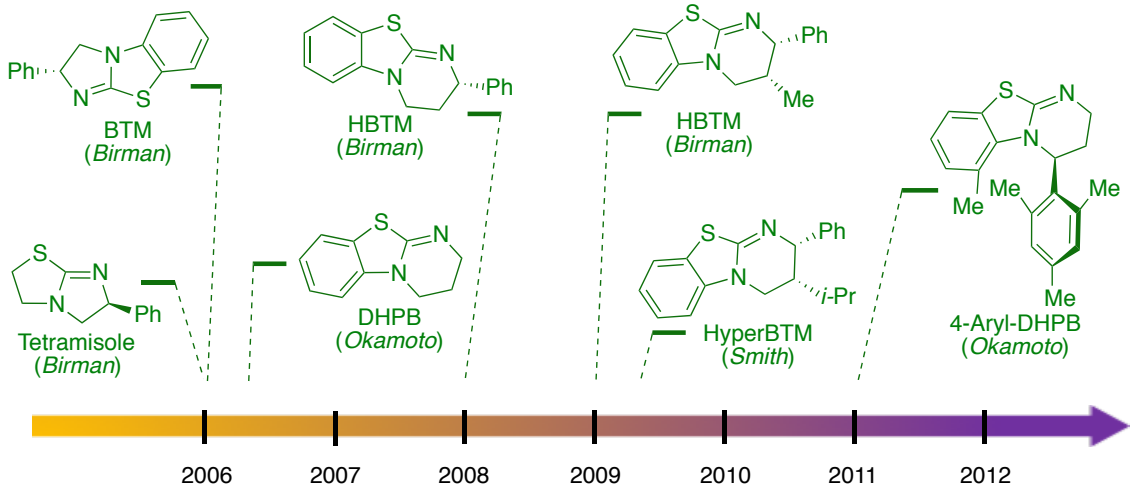
Scheme 3.1. Chiral amidines and isothioureas reported by Birman

The nucleophilicities of nitrogen-based organocatalysts such as isothioureas could be measured by use of benzhydrylium cations as electrophiles. In 2011, Mayr *et al.* determined the nucleophilicities of the isothioureas and compared them with other nitrogen-based organocatalysts.[5] The nucleophilicity values of isothioureas ranged from 12.98 to 14.45, which means they are less nucleophilic than DMAP, amidines, guanidines, and DABCO (Scheme 3.2).



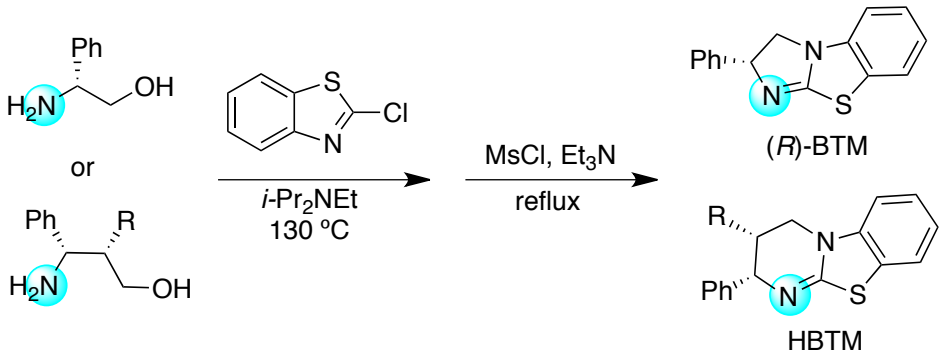
Scheme 3.2. Nucleophilicity scale of different nitrogen-based organocatalysts

Since the first chiral isothiourea catalyst reported by Birman, several new types of isothiourea catalysts were designed and employed in a large variety of asymmetric transformations (Scheme 3.3). In 2006, the group of Okamoto developed an achiral six-membered ring isothiourea named dihydrobenzothiazolo-pyrimidine (DHPB) as an acyl transfer catalyst, which exhibited extremely high activity compare to benzotetramisole (BTM).[6] Inspired by Okamoto´s work, Birman developed a chiral analogue of six-membered ring isothiourea catalyst, named homobenzotetramisole (HBTM).[7] In 2009, Birman and Smith explored the second generation of HBTM catalysts by adding a methyl group and an isopropyl group on the ring, respectively.[8] This additional stereocenter plays a key role on both reactivity and steroselectivity. In 2011, Okamoto synthesized a chiral analogue of previous DHPBs and explored them in the kinetic resolution as well as in the Steglich rearrangement reactions, which showed the possibility for remote stereocontrol by an additional substituent at the 4-position of DHPB.[9]



Scheme 3.3. Chronological development of significant isothiourea catalysts

The general procedure for the preparation of chiral isothioureas starts from the chiral β-amino alcohols or γ-amino alcohols. Coupling of these with chlorobenzothiazole can be performed through an aromatic nucleophilic substitution.[10] The final cyclization is promoted by methanesulfonyl chloride as activating reagent for the hydroxy group (Scheme 3.4). Notably, isothiourea catalysts such as BTM and HBTM can be synthesized on a multi-gram scale without any need for chromatographic purification.



Scheme 3.4. General procedure for the synthesis of BTM and HBTM

3.2. Different Transformations Catalyzed by Isothioureas

To date, isothioureas have been explored in a large variety of asymmetric transformations, including kinetic resolution, rearrangements, silylations, formal cycloadditions and domino reactions (Figure 3.1). This thesis mainly focuses on the formal cycloaddition reaction, which is an important type of reaction catalyzed by isothiourea catalysis.

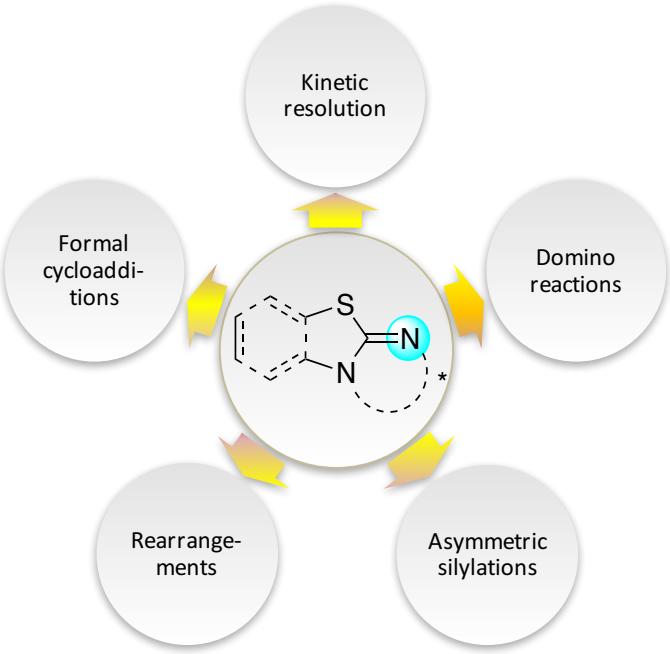


Figure 3.1. Examples of enantioselective transformations catalyzed by isothioureas

In general, isothioureas can react with various anhydrides, acyl chlorides, or triarylsilyl chlorides, and form the corresponding activated intermediates. The main types of activated intermediates can be classified into four types, which are shown in Figure 3.2

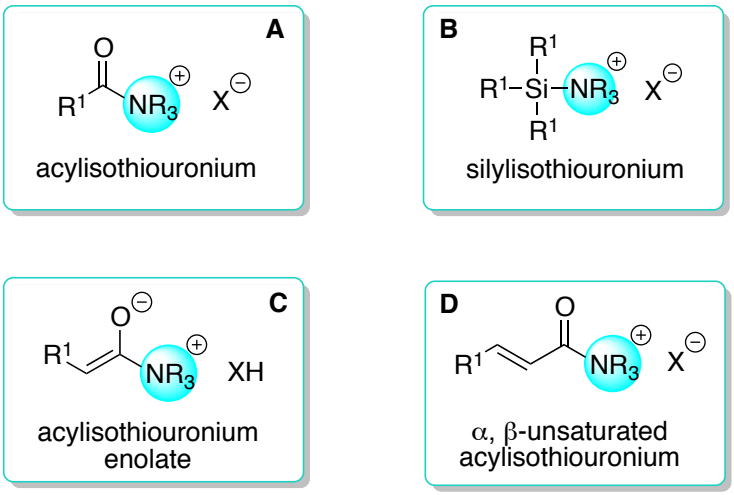


Figure 3.2. Different activated intermediates derived from isothiourea catalysts

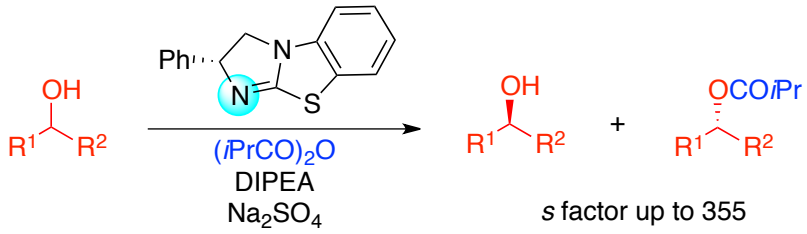
The acylisothiouronium intermediates **A** present one reactive site on the acyl group, which can be well applied in kinetic resolutions and rearrangement reactions. The silylisothiouronium intermediates **B** are employed in asymmetric silylations due to the fact that they have one single reactive site on the silicon atom. The acylisothiouronium enolate intermediates **C** are formed from the deprotonation of the acylisothiouronium species, which could serve as 2π components in various formal [2+n] cycloaddition

reactions. The α,β-unsaturated acylisothiouronium intermediates **D** involved two electrophilic centers and one nucleophilic center, which could react as a Michael acceptor or bis-electrophile intermediates in formal [3+n] cycloaddition reactions.

3.2.1. Kinetic Resolution

The seminal work of Birman demonstrated the potential of chiral isothiourea catalysts for the kinetic resolution of secondary benzylic alcohols through acyl transfer (Scheme 3.5).[4] Comparison of tetramisole and BTM on various substrates suggested that an extended π-system in the structure of BTM is beneficial for the chiral recognition of the substrates.

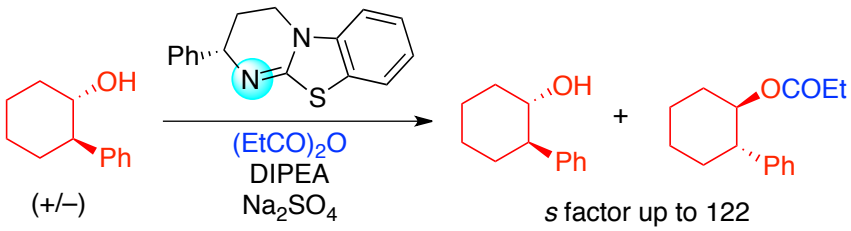
Birman *et al.* 2006



Scheme 3.5. Kinetic resolution of benzylic alcohols

In 2008, Birman reported the first HBTM catalyst, which is a ring expanded analogue of the BTM, proving that it displays higher catalytic reactivity in kinetic resolution processes (Scheme 3.6).[7] This HBTM catalyst led not only to high levels of selectivity in kinetic resolution of benzylic alcohols, but also to efficient kinetic resolution of aryl-substituted cycloalkanols.

Birman *et al.* 2008



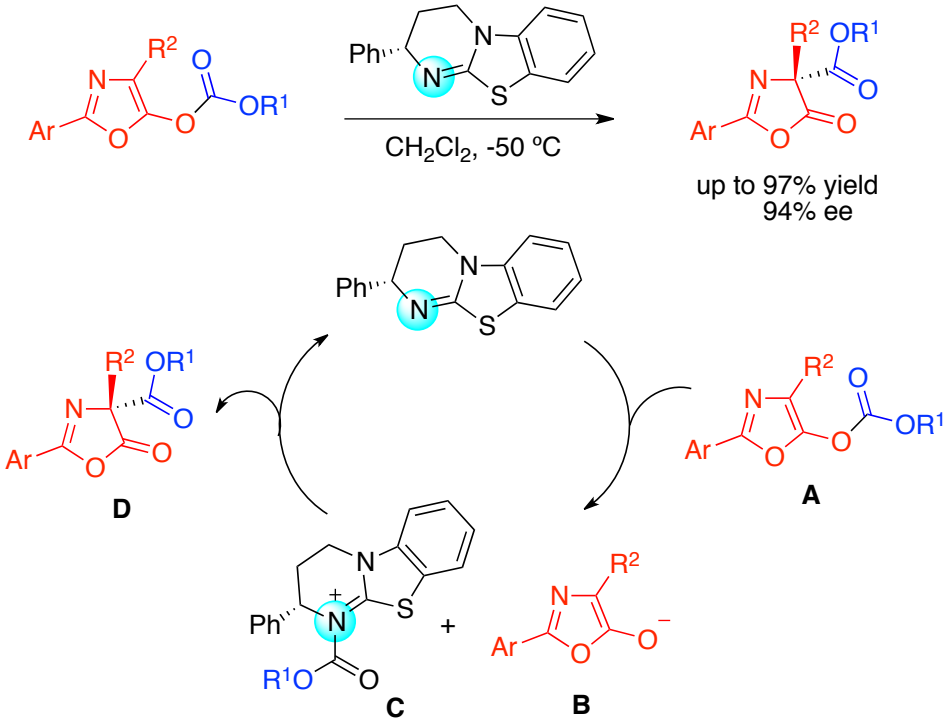
Scheme 3.6. Kinetic resolution of 2-aryl-substituted cycloalkanols

3.2.2. Rearrangement

Since the first rearrangement reaction of acylated azlactones by acyl shift introduced by Höfle and Steglich in 1960s,[11] many efforts to achieve this transformation have been described. In 2009, the Smith group employed HBTM catalyst for the Steglich

rearrangement reaction with excellent levels of enantiocontrol (Scheme 3.7).[8b] To understand the factors that lead to high stereocontrol in this process, they performed calculations on the rearrangement of oxazolyl carbonate **A** and proposed the catalytic cycle for this transformation. It was assumed that the formation of final product is initiated through nucleophilic attack of oxazolyl carbonate **A** to form the corresponding tetrahedral intermediate. Subsequently, enolate addition of azlactone **B** onto the *N*-carboxyl intermediate **C** gives *C*-carboxylazlactone **D** with concomitant release of the catalyst.

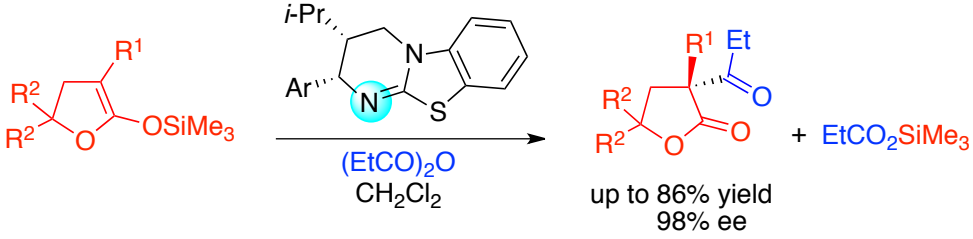
Smith *et al*. 2009



Scheme 3.7. Steglich rearrangement of oxazolyl carbonate

In 2011, the same group reported a similar asymmetric acylation reaction between silyl ketene acetals and anhydrides, the desired *C*-acyl products could be obtained in good yields with high enantiocontrol (up to 98% ee) by employing of a range of chiral isothiourea catalysts (Scheme 3.8).[12]

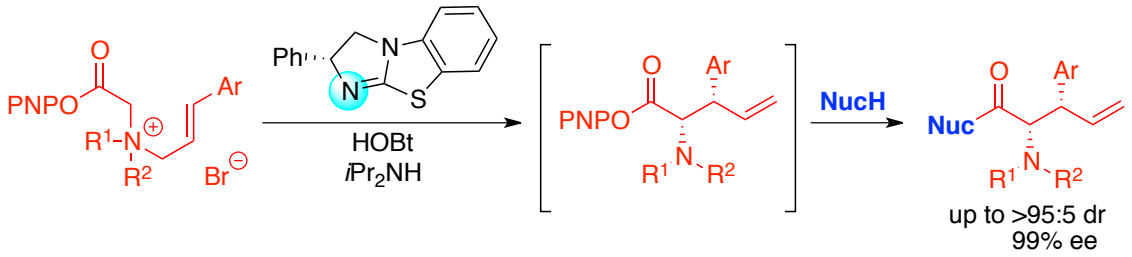
Smith *et al*. 2010



Scheme 3.8. Enantioselective acylation of silyl ketene acetals

The Smith group developed the first catalytic asymmetric sigmatropic rearrangement of allylic ammonium ylides in 2014.[13] They used BTM to activate *para*-nitrophenyl esters, which in the presence of diisopropylamine as a base, provided the *syn*-configured α-amino acid derivatives with excellent stereoselectivities. The resulting intermediate could be activated by HOBt as a nucleophilic co-catalyst and converted into amides or ester by use of amines or alcohols as nucleophiles (Scheme 3.9).

Smith *et al.* 2014

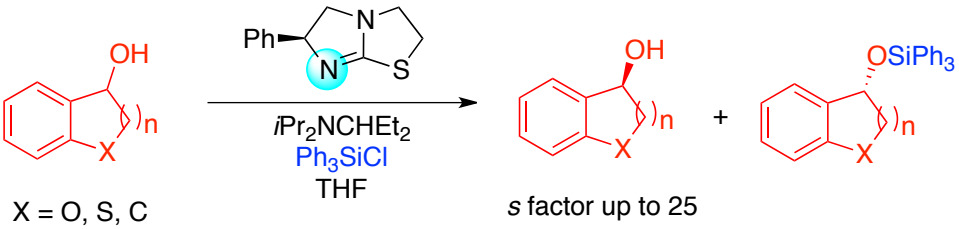


Scheme 3.9. Sigmatropic rearrangement of ammonium ylides

3.2.3. Asymmetric Silylation

Silylation is one of the most common methods for present kinetic resolution due to the fact that silyl groups have a broad tolerance for other functional groups and have many advantages compare to other protecting groups. In 2011, the Wiskur group demonstrated the aymmetric silylation reaction by using tetramisole to activate the electrophilicity of triphenylsilyl chloride, resulting in high levels of selectivity for monofunctional bicyclic alcohols (Scheme 3.10).[14]

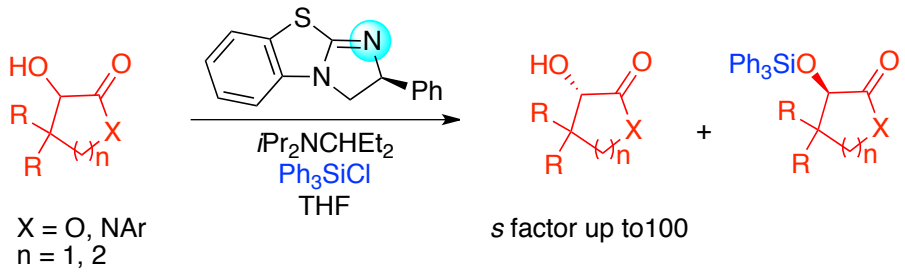
Wiskur *et al.* 2011



Scheme 3.10. Tetramisole catalyzed silylation of secondary alcohols

The same group also expanded the silylation-based kinetic resolutions for α-hydroxy lactones and α-hydroxy lactams, and selectivity factors up to 100 can be achieved utilizing BTM as catalyst.[15] Particularly, this transformation can be well applied in spiro-containing lactones and lactams (Scheme 3.11).

Wiskur *et al.* 2013



Scheme 3.11. BTM catalyzed silylation of α-hydroxy lactones and lactams

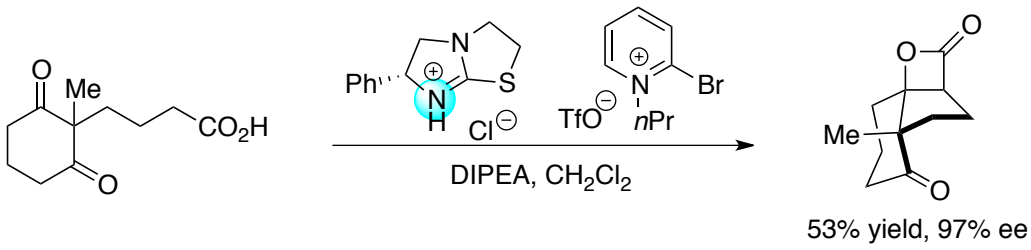
3.2.4. Formal Cycloadditions

Formal cycloadditions are important transformations that can be catalyzed by isothioureas catalysis. To date, these catalysts have been well explored and widely used in various formal [2+2], [3+2], [3+3], [4+2] and [4+3] cycloadditions.

Formal [2+2] Cycloadditions

The first study of formal [2+2] cycloaddition was carried out by the Romo group in 2008.[16] Using a stoichiometric amount of chiral tetramisole for the desymmetrization of prochiral diketoacids, they produced the complex tricyclic β-lactones shown in Scheme 3.12 with high enantioselectivity (Scheme 3.12).

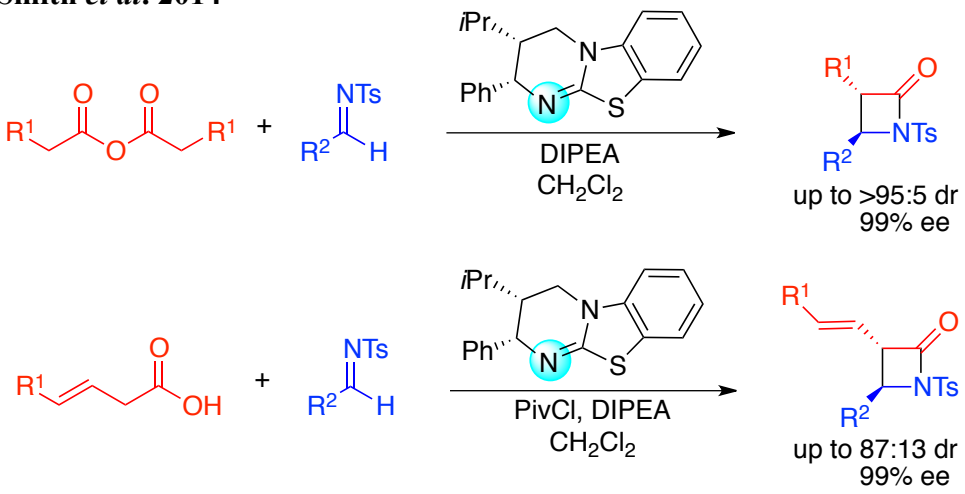
Romo *et al.* 2008



Scheme 3.12. Stoichiometric enantioselective synthesis of tricyclic β-lactones

Smith and co-workers described a formal [2+2] cycloaddition by using *N*-sulfonylimines as electrophilic partners to react with arylacetic anhydrides or arylacetic acids, generating the corresponding four-membered ring lactam products in high stereoselectivities.[17] This cascade reaction involves a Mannich reaction followed by a lactamization. Another similar transformation of [2+2] cycloaddition was also reported by the same group. In this case, they used β,γ-unsaturated carboxylic acids instead of arylacetic acids as partners to react with *N*-sulfonylimines, providing the desired products in comparable stereoselectivities (Scheme 3.13).

Smith *et al.* 2014

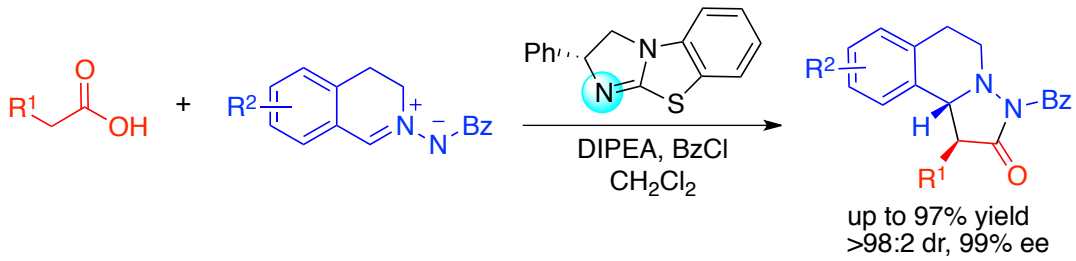


Scheme 3.13. Formal [2+2] cycloaddition catalyzed by HBTM

Formal [3+2] Cycloadditions

Studer *et al.* presented a highly stereoselective 1,3-dipolar cycloaddition of azomethine imines with active esters by using BTM as catalyst (Scheme 3.14).[18] Theoretical studies of the formal [3+2] cycloadditions reveal that a stepwise mechanism is operative. The first step is the formation of the C–C bond which determines the rate and stereocontrol. The second one consists in the C–N bond formation with a low barrier.

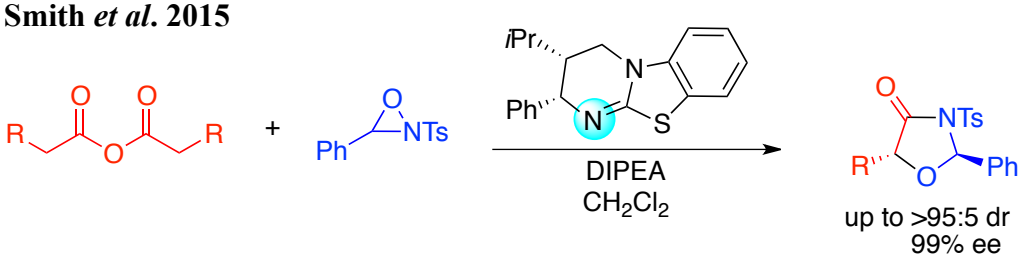
Studer *et al.* 2015



Scheme 3.14. 1,3-Dipolar cycloaddition catalyzed by BTM

Smith and co-workers developed a formal [3+2] cycloaddition of ammonium enolates with racemic oxaziridines, giving oxazolidin-4-ones in high yield and excellent enantioselectivities (Scheme 3.15).[19]

Smith *et al.* 2015

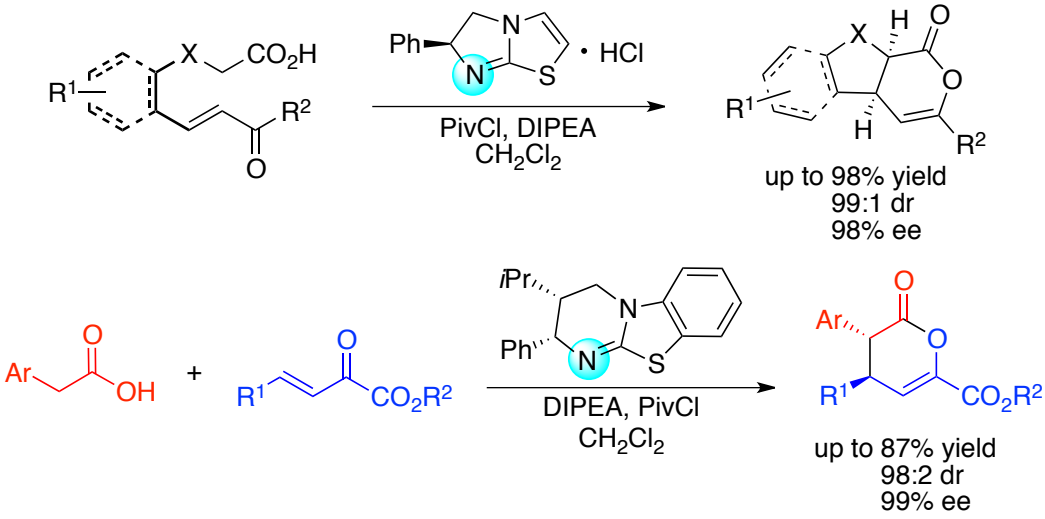


Scheme 3.15. Synthesis of oxazolidinones via formal [3+2] cycloaddition

Formal [4+2] Cycloadditions

The first example of intra- and intermolecular Michael addition-lactonization was explored by the Smith group in 2011.[20] In this study, tetramisole promoted the intramolecular Michael addition-lactonization of a variety of enone acids and HBTM promoted the intermolecular Michael addition-lactonization of arylacetic acids with α-keto-β,γ-unsaturated esters (Scheme 3.16). The same group also demonstrated a similar intermolecular process by using trifluoromethylenones, trichloromethylenones and α-ketophosphonates as Michael acceptors.

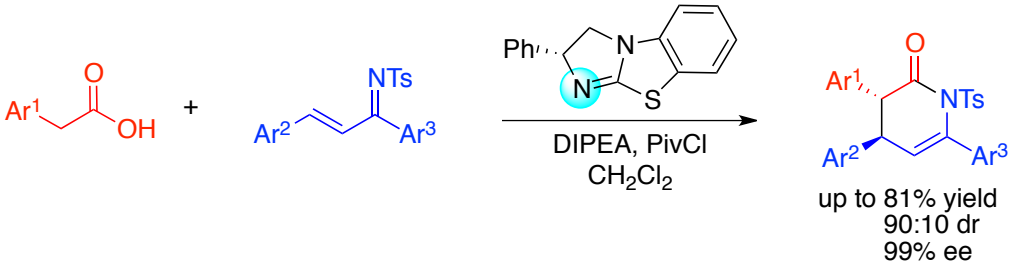
Smith *et al.* 2011



Scheme 3.16. Isothiourea catalyzed intramolecular and intermolecular Michael addition-lactonization

This Michael/lactamization process could also be applied to *N*-tosylenimines under BTM catalysis, affording the dihydropyridones with high diastereo- and excellent enantioselectivities.[21] The dihydropyridone products can be readily derivatized to a range of synthetic building blocks via *N*- to *C*-sulfonyl transfer, *N*-deprotection and reduction (Scheme 3.17).

Smith *et al.* 2012

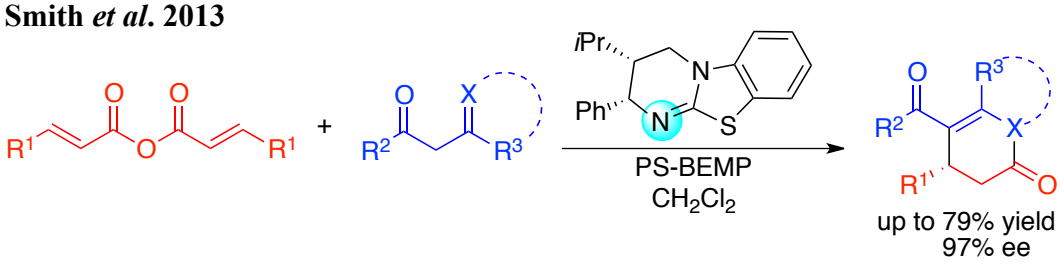


Scheme 3.17. Synthesis of oxazolidinones via formal [4+2] cycloaddition

Formal [3+3] Cycloadditions

One year later, the same group presented the formal [3+3] cycloadditions of 1,3-diketones β-ketoesters or azaaryl ketones with anhydrides, giving the functionalized esters, dihydropyranones, or dihydropyridone in good yields and high enantioselectivities (Scheme 3.18).[22]

Smith *et al.* 2013

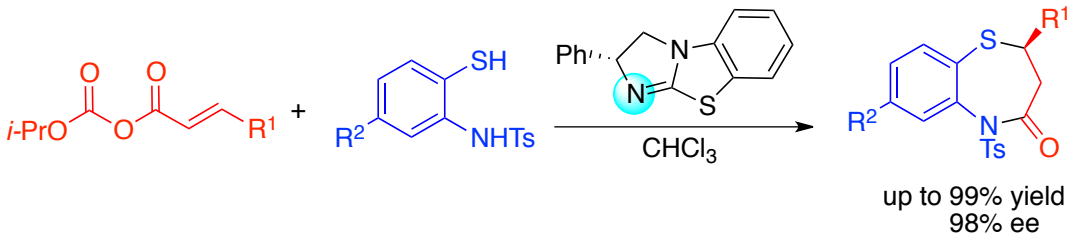


Scheme 3.18. Formal [3+3] cycloaddition catalyzed by HBTM

Formal [4+3] Cycloadditions

More recently, Matsubara and co-workers reported the first example of asymmetric formal [4 + 3] cycloaddition to afford 1,5-benzothiazepines by utilizing α,β-unsaturated acylammonium as bis-electrophile intermediates (Scheme 3.19).[23] This formal [4+3] cycloaddition was promoted by chiral BTM and the intermediate underwent two sequential chemoselective nucleophilic attacks by 2-aminothiophenols. The mechanism of the net [4+3] cycloaddition suggested that the reversibility of the sulfa-Michael addition dictates the high regio- and enantioselectivity of the transformation.

Matsubara *et al.* 2015



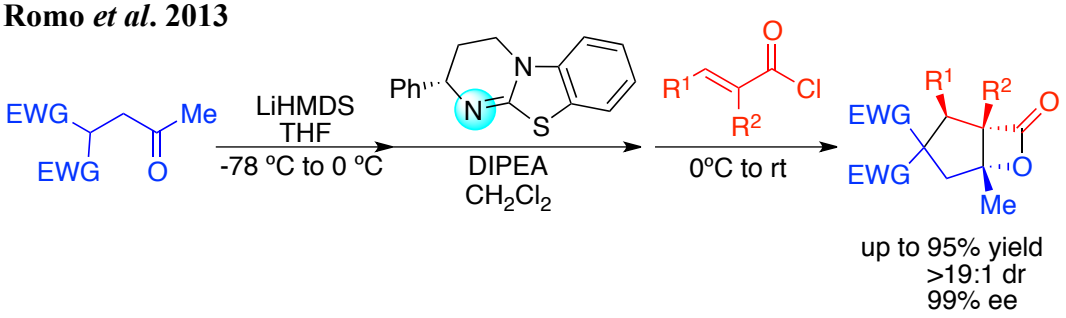
Scheme 3.19. Formal [4+3] cycloaddition catalyzed by BTM

Domino Reactions

The group of Romo described a Michael-aldol-β-lactonization and Michael-Michael-aldol-β-lactonization organocascade processes for the synthesis of complex cyclopentanes by utilizing chiral isothiourea as catalysts (Scheme 3.20).[24] This tandem reaction enables the construction of two C–C bonds, one C–O bond, two rings and three

contiguous stereocentres, providing the complex cyclopentanes with high stereoselectivities.

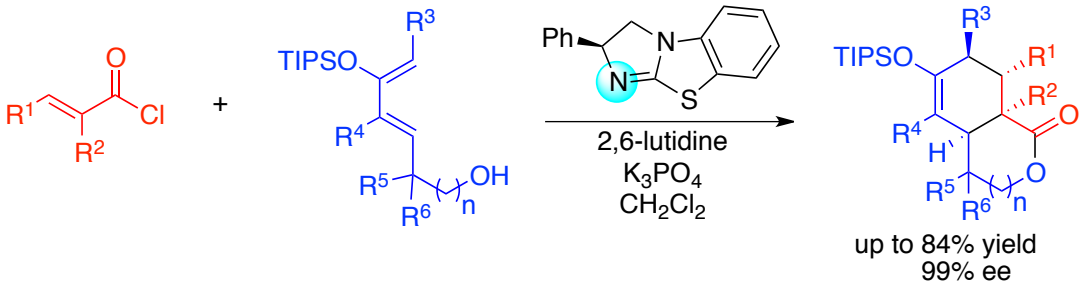
Romo *et al*. 2013



Scheme 3.20. Isothiourea catalyzed Michael-aldol-lactonization sequence

Later, the same group demonstrated a highly stereoselective Diels−Alder-lactonization organocascade for the synthesis of bicyclic lactones utilizing chiral α,β-unsaturated acylammonium species, which are readily generated in situ from unsaturated acid chlorides with chiral BTM catalyst (Scheme 3.21).[25] The utility of this cascade protocol was demonstrated by transformation of the chiral bicyclic products to several core structures of natural products.

Romo *et al*. 2014



Scheme 3.21. Isothiourea catalyzed Diels−Alder-lactonization sequence

3.3. Immobilization of Isothiourea Organocatalyst

Considering the importance of the chiral isothiourea catalysts in organic synthesis and our continuing interest toward the immobilization of homogeneous catalytic species, we considered that BTM was an optimal candidate for immobilization due to its widespread use. An analysis of the BTM structure suggested that the γ position could be ideal for immobilization purposes, since an additional substituent at this carbon would occupy a spatially remote position with respect to the catalytic site (Figure 3.3).

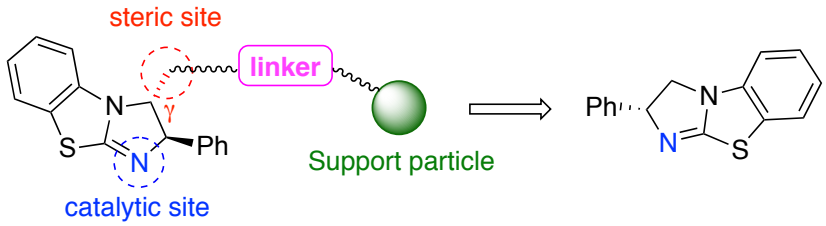
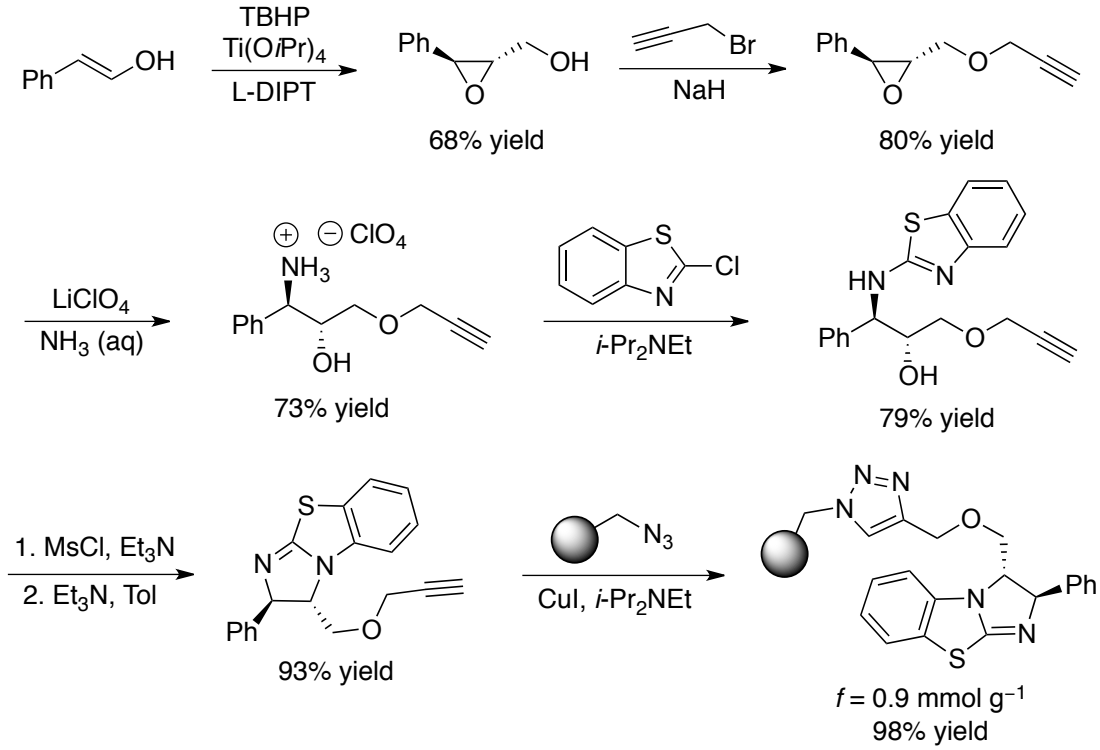


Figure 3.3. Design for immobilization of BTM catalyst

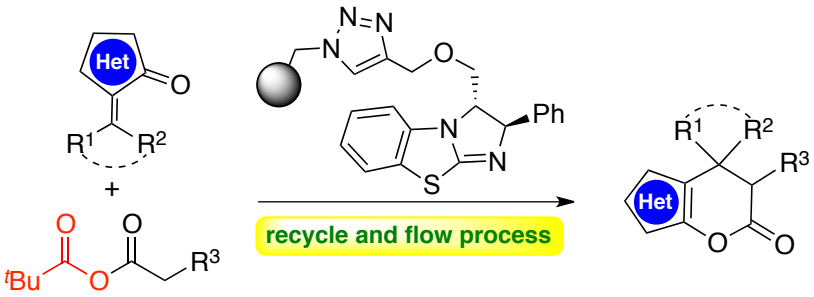
The retrosynthetic introduction of a functional group in γ position ultimately leads to phenylglycidol, a material readily available in enantiopure form by catalytic asymmetric Sharpless epoxidation, as the chiral aducts for the preparation of the immobilized BTM analogue. The general procedure for the preparation of PS-BTM catalyst is shown in Scheme 3.23.



Scheme 3.23. Synthesis of the PS-supported BTM analogue

3.4. Aim of the Project

As an initial assessment of the performance of the immobilized isothiourea, it was tested in the Michael addition/cyclization reaction previously reported by Smith and co-workers (see Scheme 3.17).[26] Immobilized isothiourea displayed a high level of recyclability in batch and flow in these processes. However, applications of this immobilized isothiourea catalyst in new transformations have not been investigated in depth. Herein, we aim to demonstrate a new application of immobilized isothiourea in asymmetric formal [4+2] cycloadditions.



Scheme 3.24. Formal [4+2] cycloaddition of unsaturated heterocycles with in situ generated anhydrides

Heterocyclic compounds containing nitrogen-nitrogen and nitrogen-sulfur arrays are frequently encountered as privileged structural frameworks in numerous bioactive natural products and pharmaceuticals. Given the manifold interest in heterocycles of these classes, we wish to report an asymmetric formal [4+2] cycloadditions of the ammonium enolate with unsaturated heterocycles catalyzed by immobilized isothiourea, affording a variety of optically pure, functionalized six-membered heterocycles bearing a tertiary or quaternary stereocenter (Scheme 3.24). From a practical perspective, another goal of this project is to test the recyclability and continuous flow application.

3.5. References

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Asymmetric [4 + 2] Annulation Reactions Catalyzed by a Robust, Immobilized Isothiourea

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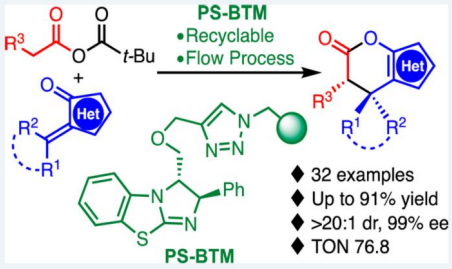
Supporting Information

ABSTRACT: A polystyrene-supported isothiourea (**1a**) behaves as a highly efficient organocatalyst in a variety of formal [4 + 2] cycloaddition reactions. The catalytic system has proven to be highly versatile, leading to six-membered heterocycles and spiro-heterocycles bearing an oxindole moiety in high yields and very high enantioselectivities (32 examples, including the previously unreported oxindole spiropyranopyrazolones **8**; 97% mean ee). The notable chemical stability of **1a** under operation conditions results in high recyclability (11 cycles, accumulated TON of 76.8) and allows the implementation of an extended-operation continuous flow process (no decrease in yield or ee after 18 h).



KEYWORDS: *isothioureas, enantioselective catalysis, solid-supported catalysts, spirocyclic compounds*

1. INTRODUCTION

Since their introduction by Birman and Okamoto in the past decade,[1] chiral isothioureas have become an important class of enantioselective organocatalysts.[2] As chiral Lewis base catalysts, isothioureas have been explored in a large variety of asymmetric transformations, including acyl transfer,[3] silyl transfer,[4] formal pericyclic,[5] and domino reactions.[6] Considering the importance of this type of catalyst in organic synthesis and our continuing interest toward the immobilization of homogeneous catalytic species,[7] we recently synthesized a polystyrene-supported isothiourea organocatalyst that was successfully applied in the Michael addition/cyclization reaction with tosylimine derivatives.[8] However, applications of this new immobilized isothiourea catalyst in new transformations have not been investigated in depth. Herein, we report the first enantioselective formal [4 + 2] cycloaddition reactions between several types of unsaturated heterocycles and in situ activated arylacetic acids in a process catalyzed by an immobilized isothiourea catalyst that can be operated in batch and flow.

Heterocyclic compounds containing nitrogen−nitrogen and nitrogen−sulfur arrays are frequently encountered as privileged structural frameworks in numerous bioactive natural products and pharmaceuticals.[9] Indeed, the pyrazolone, thiazolone, or spiro-oxindole pyrazolone scaffolds can be found in antiplatelet,[10] anti-inflammatory,[11] anticancer,[12] kinase-inhibitor,[13] and antibacterial[14] compounds (Figure 1). In particular, chiral spirocyclic pyrazolones bearing a quaternary stereocenter (promising subsets of the spirocyclic family) are very interesting, albeit hardly available from a synthetic perspective.[15] Indeed, despite some synthetic efforts devoted to the synthesis of functionalized pyranopyrazolone derivatives,[16] the development of an efficient methodology for the catalytic asymmetric construction of pyranothiazolones[17] and spiro-pyranopyrazolones bearing a quaternary stereocenter is still a challenging endeavor.

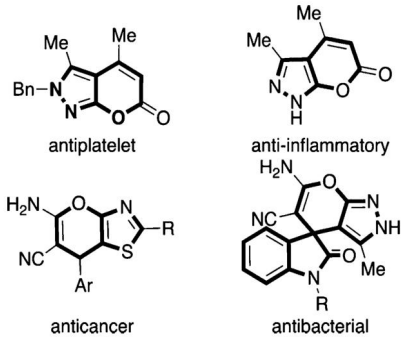


Figure 1. Examples of biologically active pyrazolone and thiazolone derivatives.

The exploitation of chiral isothioureas in asymmetric transformations via asymmetric ammonium enolate addition is a well-developed and powerful synthetic strategy.[18] Romo et al. have pioneered the in situ generation of ammonium enolates from carboxylic acids and their application to a range of aldol-lactonization reactions.[19] Building upon this work, Smith et al. have recently utilized chiral isothioureas to promote the intra- and intermolecular asymmetric functionalization of carboxylic acids through a Michael−lactonization cascade reaction.[20] It is worth noting that procedures for the asymmetric Michael−lactonization sequence in the presence of isothiourea catalysts to create a quaternary stereocenter remain rare due to the low

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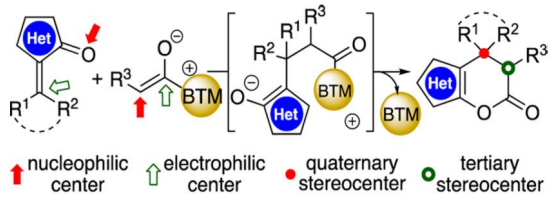
reactivity of most substrates. Given the manifold interest in heterocycles of these classes, we wish to report a highly enantioselective version of the ammonium enolate addition involving unsaturated heterocycles, thus leading to a variety of optically pure, functionalized six-membered heterocycles bearing a tertiary or quaternary stereocenter (Scheme 1).

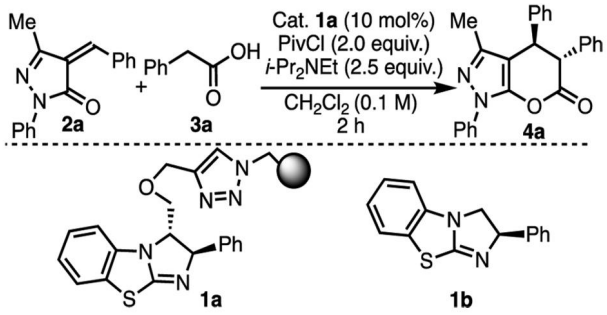
Scheme 1. Formal [4 + 2] Cycloaddition with Unsaturated Heterocycles



2. RESULTS AND DISCUSSION

We initiated our study by investigating the reaction of alkylidene pyrazolone **2a** with phenylacetic acid **3a**, using pivaloyl chloride as a reagent to activate in situ the carboxylic acid (Table 1).

Table 1. Optimization of Reaction Conditions[a]



entry	modification of std conditions	conversn (%)[b]	dr[b]	ee (%)[c]
1	std conditions	>95	8:1	98
2	**1b** as the catalyst	>95	3:1	98
3	Et_3N as the base	>95	5:1	98
4	PhCOCl instead of PivCl	55	5:1	98
5	TsCl instead of PivCl	76	7:1	98
6	THF instead of CH_2Cl_2	90	3:1	98
7	toluene instead of CH_2Cl_2	60	6:1	96
8	**2.0 equiv *i*-Pr_2NEt**	**>95**	**9:1**	**99**
9	5 mol % catalyst	81	5:1	98

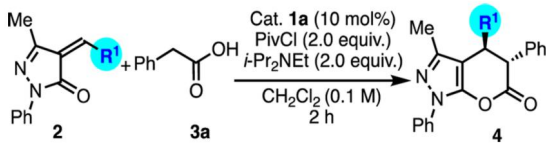
[a]Reactions performed on a 0.1 mmol scale (see the Supporting Information). [b]Determined by ^1H NMR spectroscopy. [c]Determined by chiral HPLC.

Inspired by previous works, a protocol based on immobilized isothiourea **1a**, PivCl, and *i*-Pr_2NEt in CH_2Cl_2 at room temperature led to full conversion and provided the desired product in good diastereoselectivity and almost complete enantioselectivity (entry 1). In contrast, when homogeneous benzotetramisole (BTM, **1b**) was employed, only moderate diastereoselectivity was observed, although the conversion and enantioselectivity remained the same (entry 2). This points to an intimate interplay of steric effects that takes place due to the additional stereocenter present in **1a** (the *handle* for immobilization).

Evaluation of the effect of the base employed showed that Et_3N led to lower diastereoselectivity (entry 3). Changing the activating reagent to PhCOCl and TsCl (entries 4 and 5) did not improve the results. Subsequently, solvent screening showed negative effects on either reactivity or selectivity (entries 6 and 7). We next studied the effect of the relative amounts of the different reactants (see the Supporting Information for details) and found that reducing the amount of *i*-Pr_2NEt to 2.0 equiv afforded the best result in terms of diastereo- and enantioselectivity (entry 8). On the other hand, decreasing the catalyst loading to 5 mol % resulted in lower stereoselectivity (entry 9).

With the reaction conditions optimized for **2a**, we investigated the substrate scope for this asymmetric cycloaddition reaction. As shown in Table 2, the course of the reaction was insensitive to

Table 2. Scope of the [4 + 2] Cycloaddition: Alkylidene Pyrazolones[a]



entry	R^1 (2)	yield (%) (4)[b]	dr[c]	ee (%)[d]
1	Ph (**2a**)	83 (**4a**)	9:1	99
2	4-Br-C_6H_4 (**2b**)	83 (**4b**)	9:1	99
3	4-Cl-C_6H_4 (**2c**)	81 (**4c**)	7:1	98
4	4-F-C_6H_4 (**2d**)	82 (**4d**)	8:1	98
5	4-Me-C_6H_4 (**2e**)	72 (**4e**)	5:1	99
6	3-Cl-C_6H_4 (**2f**)	84 (**4f**)	7:1	97
7	3-Me-C_6H_4 (**2g**)	71 (**4g**)	7:1	99
8	2-MeO-C_6H_4 (**2h**)	68 (**4h**)[e]	>20:1	99
9	2-thienyl (**2i**)	81 (**4i**)	6:1	96

[a]Reactions performed on a 0.1 mmol scale (see the Supporting Information). [b]Isolated yield. [c]Determined by ^1H NMR spectroscopy. [d]Determined by chiral HPLC. [e]Reaction time: 6 h.

electronic changes at the meta and para positions of the aromatic substituent R^1 on alkylidenepyrazolones. Specifically, substrates with these substitution patterns (**2b**–**g**) underwent reaction in good yields (71–84%), high diastereoselectivities (5:1 to 9:1 dr), and almost complete enantioselectivities (97–99% ee), for both electron-withdrawing and electron-donating meta or para substituents. The ortho-substituted derivative **2h** required longer reaction times (6 h) but gave the desired product **4h** in very high diastereoselectivity (>20:1 dr), comparable enantioselectivity (99% ee), and good yield (68%). Furthermore, **4i** bearing a heteroaromatic 2-thienyl group (entry 9) was also formed in good yield and diastereoselectivity with a comparable ee (96%).

Next, the [4 + 2] cycloaddition with a variety of arylacetic acids was investigated under the optimized conditions (Scheme 2). A range of arylacetic acids with diverse electronic and steric properties worked well, giving rise to cycloadducts **4j**–**n** in good yields (73–86%), very high ee values (96–99%), and good diastereoselectivities (5:1 to 13:1 dr). Acid **3o**, bearing an *N*-methylindole substituent, showed no decrease in yield or stereoselectivity.

Dihydropyranothiazolones are another class of nitrogen–sulfur heterocycles present in several drug candidates. This encouraged us to study their ability to be engaged as substrates in an analogous transformation. Gratifyingly, cycloadducts **6** could be accessed under similar reaction conditions. Following a brief screening of reaction conditions, the reaction of alkylidenethiazolone **5a** with substituted arylacetic acids furnished dihydropyranothiazolones **6a**–**e** (Scheme 3) in excellent enantio (99%)-

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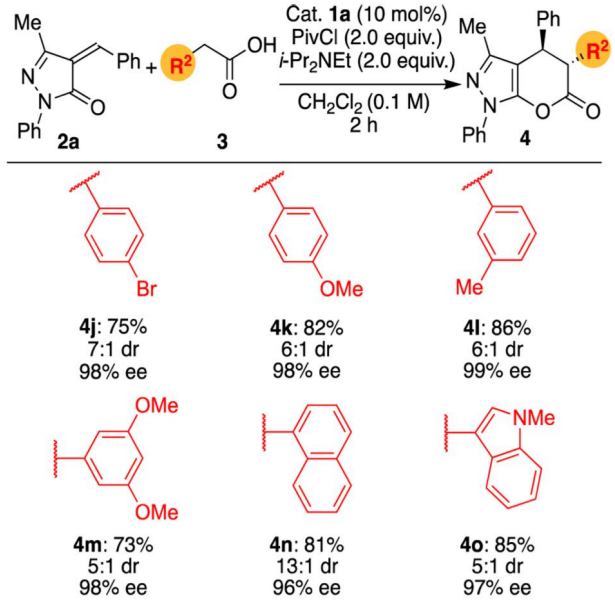
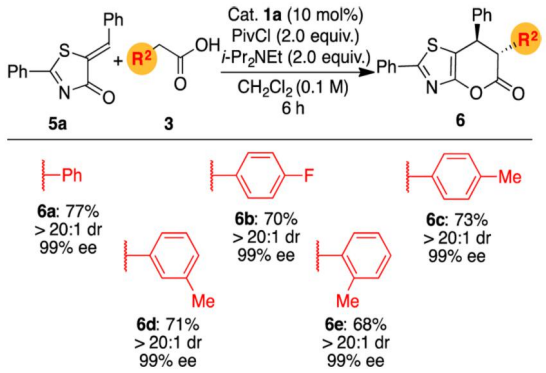
Scheme 2. Scope of the [4 + 2] Cycloaddition: Arylacetic Acids



and diastereoselectivities (>20:1 dr), with yields ranging from 68 to 77%.

Scheme 3. Scope of Substituted Arylacetic Acids with a 5-Alkylidene Thiazolone



With the aim of probing the versatility of this strategy, we prepared different disubstituted alkylidenepyrazolones, which would afford the corresponding cycloadducts bearing an all-carbon quaternary stereocenter (see Scheme 4 and the Supporting Information). While most disubstituted alkylidene-pyrazolones did not engage in the reaction, the isopropylidene derivative afforded the desired product **8a** in poor yield but very high enantioselectivity (96% ee). On the basis of this observation, we wondered whether an isatin derivative of the pyrazolone would undergo the annulation reaction thanks to the less sterically demanding nature of the substrate. This would give rise to functionalized dihydropyranopyrazolones bearing a spirocyclic quaternary stereocenter. With this in mind, we first synthesized an *N*-methylisatin-derived pyrazolone and performed the cascade [4 + 2] reaction at 0 °C. To our delight, the corresponding spiropyranopyrazolone **8b** was obtained in 88% yield with very high enantioselectivity (96% ee) in a very short reaction time (30 min). The minor, anti diastereoisomer was also isolated with high ee values. It is worth mentioning that, to the best of our knowledge, this is the first synthesis of optically pure spirocyclic oxindole-pyranopyrazolone scaffolds.[21] Biological studies to assess the therapeutic potential of these unique structures are currently underway.

Subsequent studies showed the generality of this approach to assemble a range of optically active substituted spiropyranopyrazolones under the established optimal reaction conditions. As indicated in Scheme 4, variations in the electronic properties of the substituents on the benzene ring of the arylacetic acid **3** were investigated and the corresponding spirocyclic adducts **8b–g** were isolated in good yields (81–91%) with high ee values and moderate diastereoselectivities. To emphasize the generality of our approach, various N-substituted isatin-derived pyrazolones were also tested and participated equally well in the reaction (**8h–j**). Furthermore, the extension of the substrate range to electron-poor or electron-rich substituted *N*-methylisatin-derived pyrazolones was well tolerated, providing the [4 + 2] annulation products in good yields and 93–96% ee (**8k–l**).

The absolute configuration given for all of the dihydropyranopyrazolones **4**, dihydropyranothiazolones **6**, and spiropyranopyrazolones **8** is based on the X-ray analysis of the major diastereoisomers **4b**, **6a**, **8c** and minor diastereoisomer **8c′** (see Figure 2 and the Supporting Information).

From a practical perspective, the use of an immobilized isothiourea catalyst offers the inherent advantages of easy recovery and reuse. Under the standard conditions, we explored the recyclability of catalyst **1a** in the reaction of alkylidene pyrazolone **2a** with phenylacetic acid **3a** as model substrates. After each run, the catalyst could be recovered by simple filtration and reused in the next cycle by adding fresh reactants. With the reaction time kept constant, nine consecutive reaction cycles were performed with 10 mol % of resin **1a**, affording the cycloadducts with constant stereoselectivity and only marginal erosion in the yield (Scheme 5). To gain insight into the recyclability profile of **1a**, the same catalyst was used in two more cycles (reaching a total of 11), increasing the reaction time to 24 h. Under these conditions, product **4a** was obtained in higher yields and slightly lower enantioselectivities. The accumulated TON for the whole recycling experiment was 76.8. Indeed, the robustness of this catalytic system was further proven by implementing an 18 h continuous flow experiment, which provided 2.74 g of **4a** (67% yield and 99% ee) as a single diastereomer (see section 7 in the Supporting Information for details).

The proposed catalytic cycle for these transformations (Scheme 6) proceeds through initial in situ formation of the mixed anhydride **A** from the arylacetic acid, followed by formation of the corresponding acyl ammonium species **B**. This is deprotonated by pivalate (the amine is just a shuttle base)[22] to generate an enolate (**C**) which undergoes stereoselective conjugate addition (**D**), followed by lactonization, giving the cycloadduct product **E** and regenerating the immobilized isothiourea. The proposed approaches of dihydropyranopyrazolone **4** and dihydropyranothiazolone **6** are in accordance with previous reports and configurational analysis. Our current working hypothesis involves an epimerization of the stereocenter α to the lactone C=O, a situation that has been observed for related systems[20e] (see section 9 in the Supporting Information for details).

3. CONCLUSIONS

In summary, we have disclosed an asymmetric polystyrene-supported isothiourea catalyzed formal [4 + 2] cycloaddition of unsaturated heterocycles with in situ activated arylacetic acids. The annulation strategy described represents an efficient

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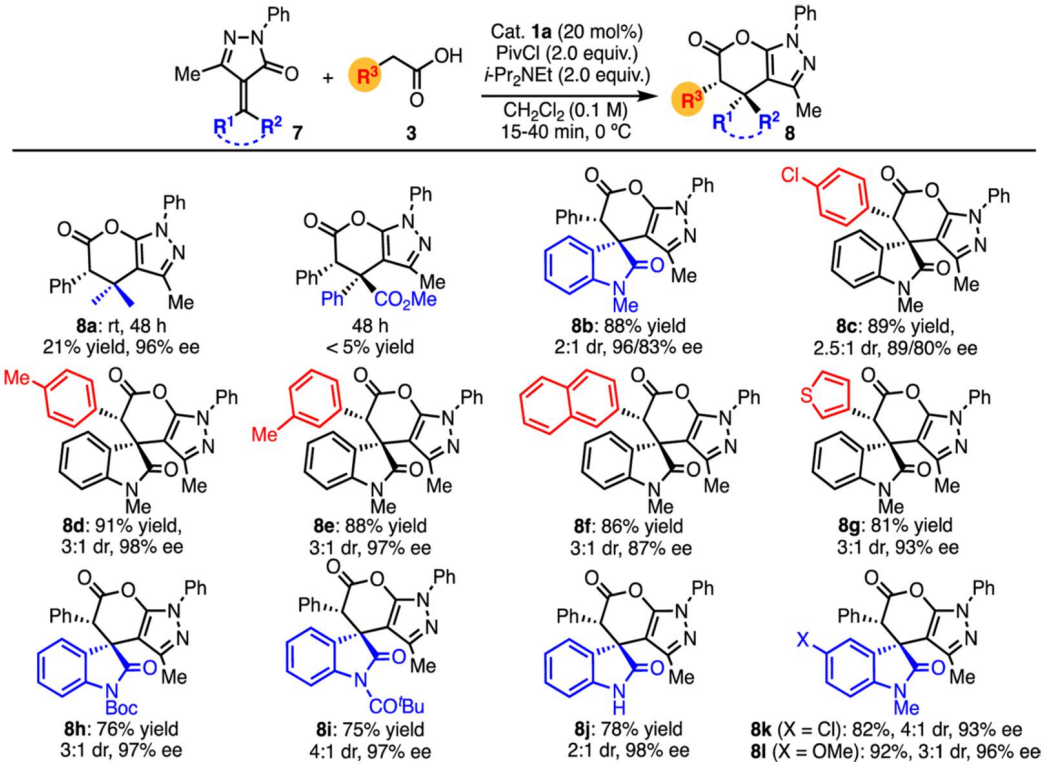
Scheme 4. Scope of the Reaction between Different Disubstituted Alkylidene Pyrazolones and Arylacetic Acids



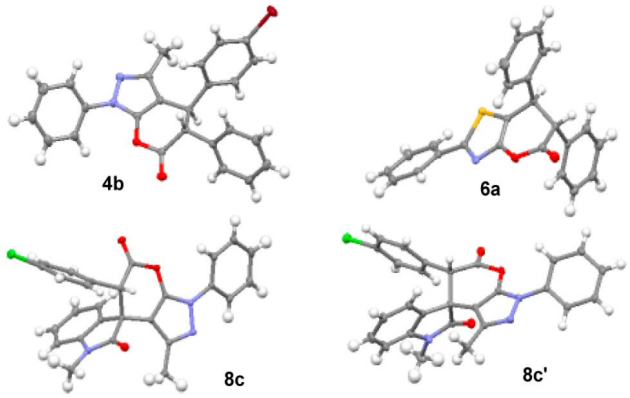
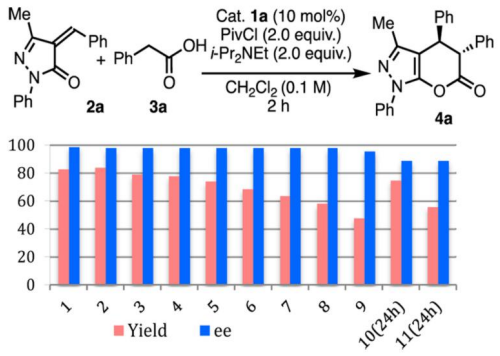


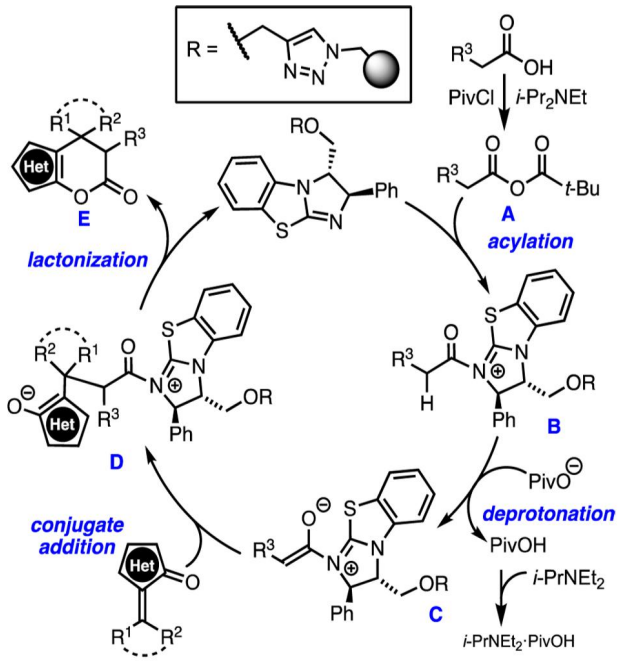
Figure 2. X-ray structures: **4b**, CCDC 1519361; **6a**, CCDC 1519360; **8c**, CCDC 1519359; **8c′**, CCDC 1519358.

Scheme 5. Recyclability Test



approach to access a series of dihydropyranopyrazolone and dihydropyranothiazolone derivatives, as well as spiropyranopyrazolones bearing a quaternary stereocenter, with very high enantiomeric purity and convenient yields. In comparison to its homogeneous counterpart, **1a** displays higher stereoselectivity

Scheme 6. Proposed Catalytic Pathway



and the same reactivity. In addition, it can be recycled at least 11 times by simple filtration of the reaction mixture. Finally, the implementation of a continuous flow process with this catalytic resin illustrates the benefits of this approach. Further application of the polystyrene-supported isothiourea catalyst and biological evaluation of the heterocycles prepared is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b00360.

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Synthetic procedures, characterization data, NMR spectra, and HPLC chromatograms (PDF)
Crystallographic data (CIF)
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Notes

The authors declare no competing financial interest.

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Supporting Information

Asymmetric [4+2] Annulation Reactions Catalyzed by a Robust, Immobilized Isothiourea

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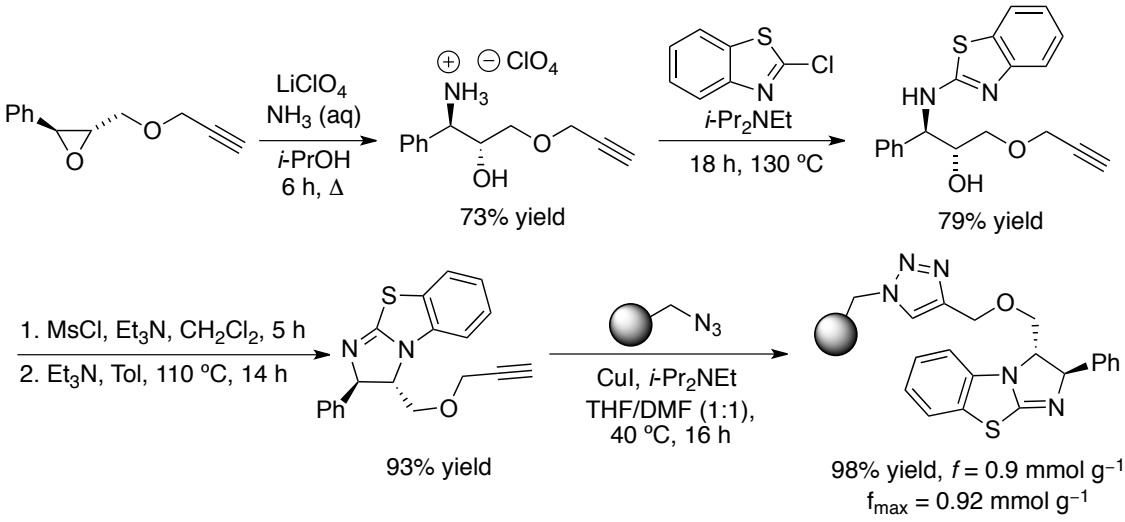
1. General information

Unless otherwise stated, all commercial reagents were used as received. Flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. Thin layer chromatography was carried out using Merck TLC Silicagel 60 F254 aluminum sheets. Components were visualized by UV light (λ = 254 nm) and stained with *p*-anisaldehyde or phosphomolybdic dip. NMR spectra were registered in a Bruker Advance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature, operating at 300 or 400 MHz (^1H) and 75 or 100 MHz (^{13}C). TMS was used as internal standard for ^1H NMR and $CDCl_3$ for ^{13}C NMR. Chemical shifts are reported in ppm referred to TMS. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses of the polystyrene supported catalysts were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid, Spain. High performance liquid chromatography (HPLC) was performed on an Agilent Technologies chromatograph (1100 Series), using Chiralcel columns and guard columns. The continuous flow experiments were carried out using P4.1S Azura pump developed by Knauer and a Legato 270 push/pull syringe pump developed by KD scientific. Racemic reference samples were prepared using 20-40 mol% DMAP instead of the PS-BTM, following the same conditions used for the asymmetric reaction.

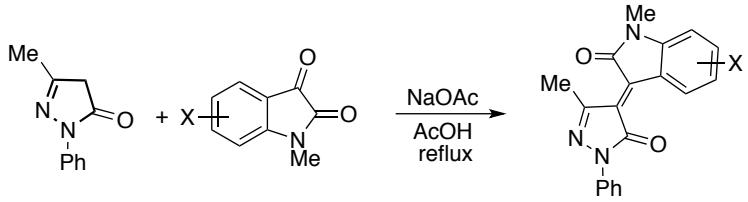
2. General procedure for the preparation of PS-BTM catalyst

Polymer-supported benzotetramisole catalyst was prepared according to our previously reported procedure.[1]



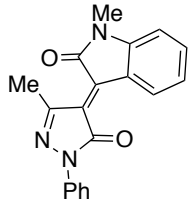
3. General procedure for the preparation of oxoindolylidene pyrazolones

Different methyloxoindolylidene pyrazolones were prepared according to the literature procedure[2] or the following method.[3]



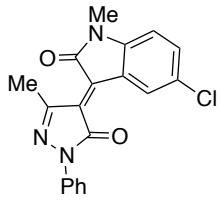
To a mixture of methyl isatin (5 mmol, 1 equiv.), sodium acetate (7.5 mmol, 1.5 equiv.) and the pyrazolone (6 mmol, 1.2 equiv.) were added 15 mL of glacial acetic acid. The resulting mixture was refluxed for 24 h. After that, the reaction mixture was diluted with EtOAc (40 mL) and washed with water (3 × 20 mL). The organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the desired product.

(*E*)-1-Methyl-3-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)indolin-2-one



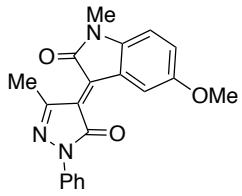
Dark red solid, melting point: 168-170 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.66 (s, 3H), 3.21 (s, 3H), 6.75 (d, *J* = 7.6 Hz, 1H), 7.03-7.08 (m, 1H), 7.20-7.23 (m, 1H), 7.41-7.46 (m, 3H), 7.93-7.95 (m, 2H), 9.29 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 26.2, 108.2, 119.2 (2C), 121.2, 123.0, 125.2, 128.8 (2C), 129.9, 131.7, 135.6, 137.7, 139.1, 147.4, 148.6, 164.0, 166.1; IR (ATR): ν = 538, 584, 690, 757, 1009, 1097, 1185, 1288, 1338, 1366, 1475, 1595, 1687, 1719, 2925 cm^{-1}; HRMS calcd. for $C_{19}H_{16}N_3O_2$ $[M + H]^+$: 318.1237, found: 318.1236.

(*E*)-5-Chloro-1-methyl-3-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)indolin-2-one



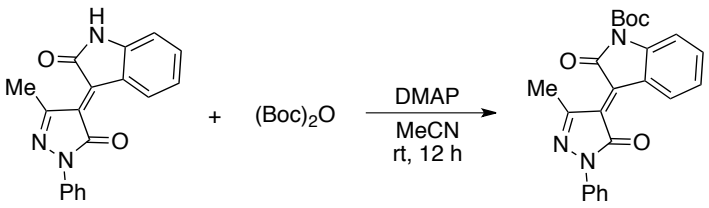
Dark purple solid, melting point: 160-161 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.65 (s, 3H), 3.19 (s, 3H), 6.68 (d, *J* = 8.4 Hz, 1H), 7.21-7.24 (m, 1H), 7.39-7.46 (m, 3H), 7.91-7.94 (m, 2H), 9.37 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 26.3, 109.0, 119.2 (2C), 122.0, 125.4, 128.3, 128.9 (2C), 131.0, 131.2, 134.8, 137.5, 137.7, 145.7, 148.4, 163.8, 165.6; IR (ATR): ν = 590, 688, 729, 757, 901, 1157, 1286, 1366, 1456, 1595, 1683, 1716, 2926 cm^{-1}; HRMS calcd. for $C_{19}H_{15}ClN_3O_2$ $[M + H]^+$: 352.0847, found: 352.0847.

(*E*)-5-Methoxy-1-methyl-3-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)indolin-2-one

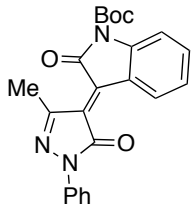


Dark blue solid, melting point: 181-183 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.65 (s, 3H), 3.16 (s, 3H), 3.85 (s, 3H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.99-7.02 (m, 1H), 7.19-7.23 (m, 1H), 7.41-7.45 (m, 2H), 7.93-7.95 (m, 2H), 9.04 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 26.2, 56.0, 108.6, 116.4, 119.2 (2C), 121.7, 122.3, 125.2, 128.8 (2C), 129.9, 137.7, 139.6, 141.6, 148.6, 155.6, 164.0, 165.9; IR (ATR): ν = 643, 693, 755, 811, 935, 1033, 1169, 1255, 1287, 1366, 1455, 1565, 1587, 1685, 1709, 2923 cm^{-1}; HRMS calcd. for $C_{20}H_{18}N_3O_3$ $[M + H]^+$: 348.1343, found: 348.1346.

(*E*)-*tert*-Butyl-3-(3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)-2-oxoindoline-1-carboxylate

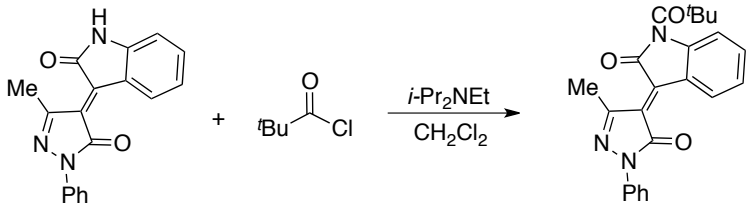


A 25 mL round-bottom flask containing a magnetic stirring bar was charged with oxoindolylidene pyrazolone (303 mg, 1.0 mmol, 1.0 equiv.), DMAP (12.2 mg, 10 mol%, 0.1 equiv.) and acetonitrile (5 mL) was added via syringe. A solution of $(Boc)_2O$ (261 mg, 1.2 mmol, 1.0 equiv.) in acetonitrile (5 mL) was added to the mixture via syringe over 10 min, and the reaction was allowed to stir at room temperature for 12 h. The solvent was then removed in vacuo and the residue was purified by flash column chromatography (eluting with cyclohexane/EtOAc from 20:1 to 5:1) to give the desired product (370 mg, 92% yield) as a red solid.

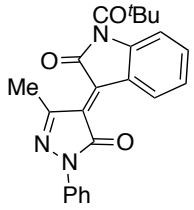


Dark red solid, melting point: 174-175 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 9H), 2.62 (s, 3H), 7.19-7.24 (m, 2H), 7.41-7.45 (m, 2H), 7.51-7.55 (m, 1H), 7.84-7.86 (m, 1H), 7.91-7.94 (m, 2H), 9.40 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 28.1 (3C), 85.2, 114.7, 119.2 (2C), 121.5, 124.6, 125.4, 128.9 (2C), 130.2, 130.8, 135.9, 137.5, 137.6, 143.2, 148.3, 148.5, 163.6, 164.2; IR (ATR): ν = 650, 689, 750, 903, 1011, 1100, 1158, 1251, 1298, 1342, 1396, 1461, 1684, 1730, 1765, 2967 cm^{-1}; HRMS calcd. for $C_{23}H_{22}N_3O_4$ $[M + H]^+$: 404.1605, found: 404.1599.

(*E*)-3-(3-Methyl-5-oxo-1-phenyl-1*H*-pyrazol-4(5*H*)-ylidene)-1-pivaloylindolin-2-one

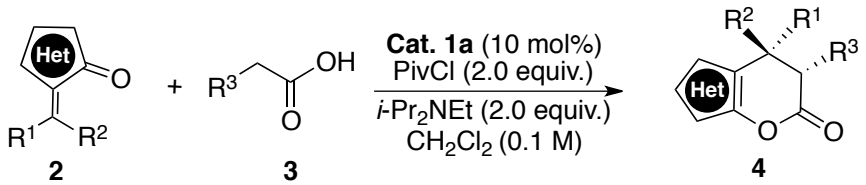


A solution of oxoindolylidene pyrazolone (303 mg, 1.0 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (10 mL) was cooled to 0 °C in an ice bath and treated with pivaloyl chloride (148 µL, 1.2 mmol, 1.2 equiv.) followed by *i*-Pr_2NEt (261 µL, 1.5 mmol, 1.5 equiv.). The mixture was stirred at 0 °C for 20 min and then warmed up to room temperature for 3 hours. After that, aqueous NH_4Cl (5 mL) was added and it was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was then washed with brine (5 mL), dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (eluting with cyclohexane/EtOAc from 20:1 to 5:1) to give the desired product (352 mg, 91% yield) as a red solid.

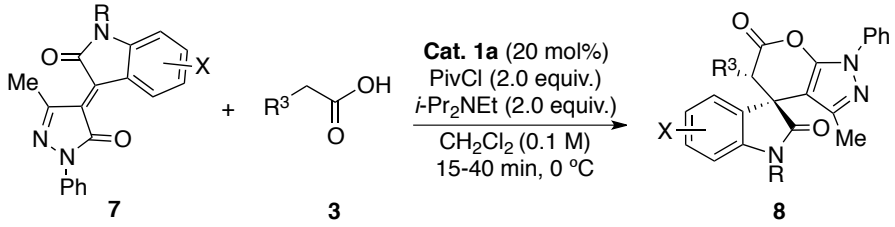


Dark red solid, melting point: 164-166 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9H), 2.59 (s, 3H), 7.17-7.25 (m, 2H), 7.41-7.46 (m, 3H), 7.48-7.52 (m, 1H), 7.92-7.94 (m, 2H), 9.39 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 27.1 (3C), 43.6, 113.9, 119.2 (2C), 122.4, 124.6, 125.4, 128.9 (2C), 130.2, 131.0, 135.8, 137.6, 137.9, 144.5, 148.1, 163.6, 165.7, 182.1; IR (ATR): ν = 580, 651, 690, 748, 898, 986, 1084, 1118, 1279, 1332, 1458, 1572, 1596, 1683, 1709, 1738, 2929 cm^{-1}; HRMS calcd. for $C_{23}H_{22}N_3O_3$ $[M + H]^+$: 388.1656, found: 388.1667.

4. General procedure for the [4+2] cycloaddition reaction



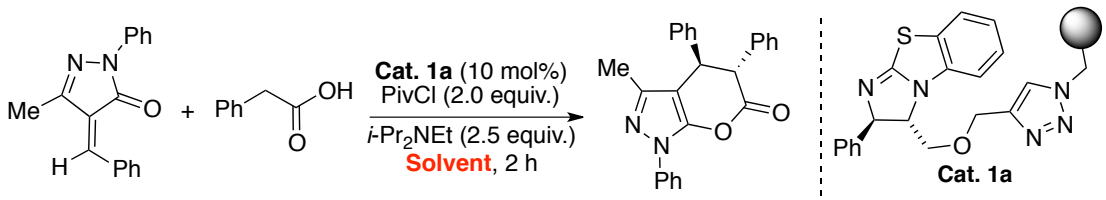
To a solution of **2** (0.10 mmol, 1.0 equiv.) in CH_2Cl_2 (1.0 mL) were added the phenylacetic acid derivative **3** (0.20 mmol, 2.0 equiv.) and polymer-supported BTM (0.010 mmol, 11.2 mg, 10 mol%). The mixture was shaken at 0 ºC in an ice bath and *i*-Pr_2NEt (0.20 mmol, 34.8 µL, 2.0 equiv.) and pivaloyl chloride (0.20 mmol, 24.5 µL, 2.0 equiv.) were added dropwise. The reaction was shaken from 0 ºC to r.t. for the given reaction time. After that the resin was filtered off, washed with CH_2Cl_2 (3 × 1 mL) and the combined organic layers were concentrated under reduced pressure. Crude products **4** were directly purified by flash chromatography (FC).



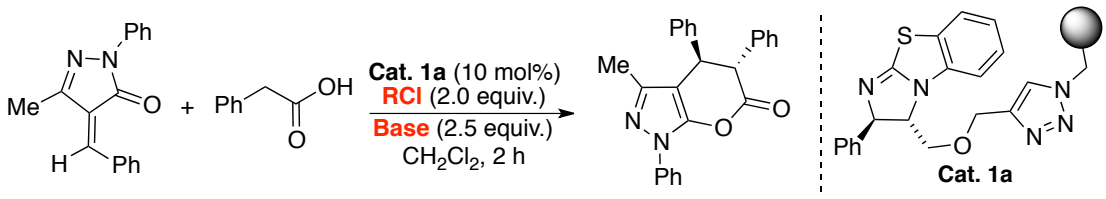
7 3 8

To a solution of oxoindolylidene pyrazolone **7** (0.10 mmol, 1.0 equiv.) in CH_2Cl_2 (1.0 mL) were added the phenylacetic acid derivative **3** (0.20 mmol, 2.0 equiv.), polymer-supported BTM (0.010 mmol, 22.4 mg, 20 mol%) and the mixture was shaken at 0 ºC in an ice bath. Then, *i*-Pr_2NEt (0.20 mmol, 2.0 equiv.) and pivaloyl chloride (0.20 mmol, 2.0 equiv.) were added dropwise. The reaction was shaken at 0 ºC for 15-40 min and monitored by TLC. After that the resin was filtered off, washed with CH_2Cl_2 (3 × 1 mL) and the combined organic layers were concentrated under reduced pressure. Crude products **8** were directly purified by flash chromatography (FC).

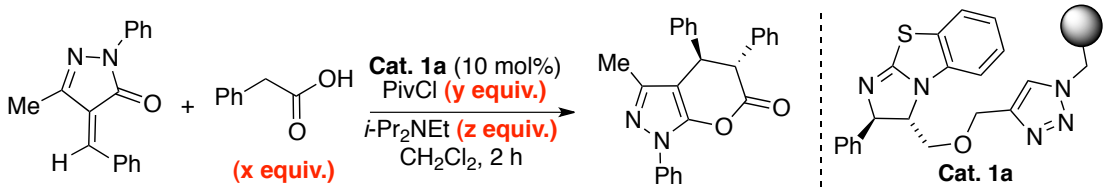
5. Screening of conditions for the [4+2] cycloaddition reaction[a]



Entry	Solvent	Conv. (%)[b]	dr[b]	ee (%)[c]
1	CH_2Cl_2	>95	8:1	98/93
2	THF	90	3:1	98/93
3	$CHCl_3$	>95	5:1	98/93
4	toluene	60	6:1	96/–
5	Et_2O	31	4:1	–/–



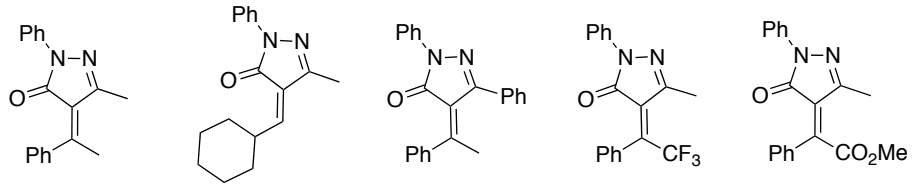
Entry	RCl	Base	Conv. (%)[b]	dr[b]	ee (%)[c]
1	PivCl	Et_3N	>95	5:1	98
2	PivCl	*i*-Pr_2NEt	>95	8:1	98
3	TsCl	*i*-Pr_2NEt	76	7:1	98
4	PhCOCl	*i*-Pr_2NEt	55	5:1	98



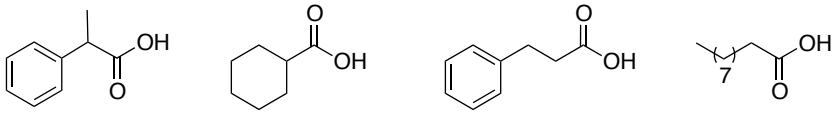
Entry	x	y	z	Conv. (%)[b]	dr[b]	ee (%)[c]
1	2.0	2.0	2.5	>95	8:1	98
2	2.0	2.0	2.0	>95	9:1	99
3	1.5	1.5	2.0	>95	6:1	99

[a] Reactions performed on a 0.1 mmol scale. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC.

The following unsaturated pyrazolones afforded only traces (<5%) of the desired cycloaddition product.

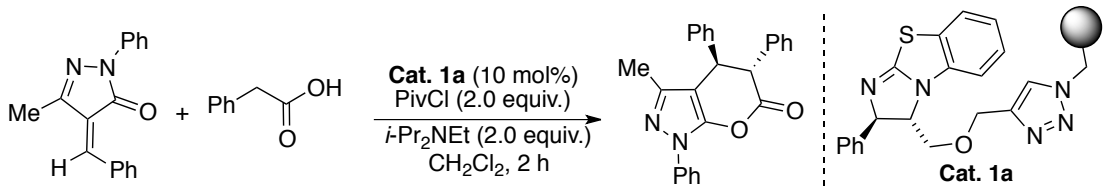


The following acids afforded only traces (<5%) of the desired cycloaddition product.



6. General procedure for the recycling experiments

To a solution of (*Z*)-4-benzylidene-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **2a** (0.15 mmol, 39.3 mg, 1.0 equiv.) in CH_2Cl_2 (1.5 mL) were added phenylacetic acid **3a** (0.30 mmol, 40.8 mg, 2.0 equiv.) and polymer-supported BTM **1** (0.015 mmol, 16.8 mg, 10 mol%). The mixture was shaken at 0 ºC in an ice bath. Then, *i*-Pr_2NEt (0.30 mmol, 52.2 µL, 2.0 equiv.) and pivaloyl chloride (0.30 mmol, 36.8 µL, 2.0 equiv.) were added dropwise. The reaction was shaken from 0 ºC to r.t. for 2 hours and the resin was filtered off and washed with freshly distilled CH_2Cl_2 (3 × 1 mL). The recovered catalyst was gently dried under vacuum at 30 ºC for 2-3 h. The dried catalyst was directly used in the next recycling run.



[a]

Cycle	Yield. (%)[a]	ee (%)[b]	Cycle	Yield (%)[a]	ee (%)[b]
1	83	99	7	64	98
2	84	98	8	58	98
3	79	98	9	48	96
4	78	98	10	75	89[c]
5	74	98	11	56	89[c]
6	69	98			

Isolated yield. [b] Determined by chiral HPLC. [c] Reactions run for 24 h.

7. General procedure for the continuous flow process

The packed-bed reactor consisted of a vertically mounted Omnifit glass chromatography column (10 mm pore size and up to maximal 70 mm of adjustable bed height) loaded with the PS-BTM **1a** (600 mg, 0.54 mmol; f = 0.9 mmol·g^{-1}). The resin was swollen by pumping freshly distilled CH_2Cl_2 at 100 µL min^{-1} for 30 min. The three streams used to introduce reagents in the system were (see diagram below):

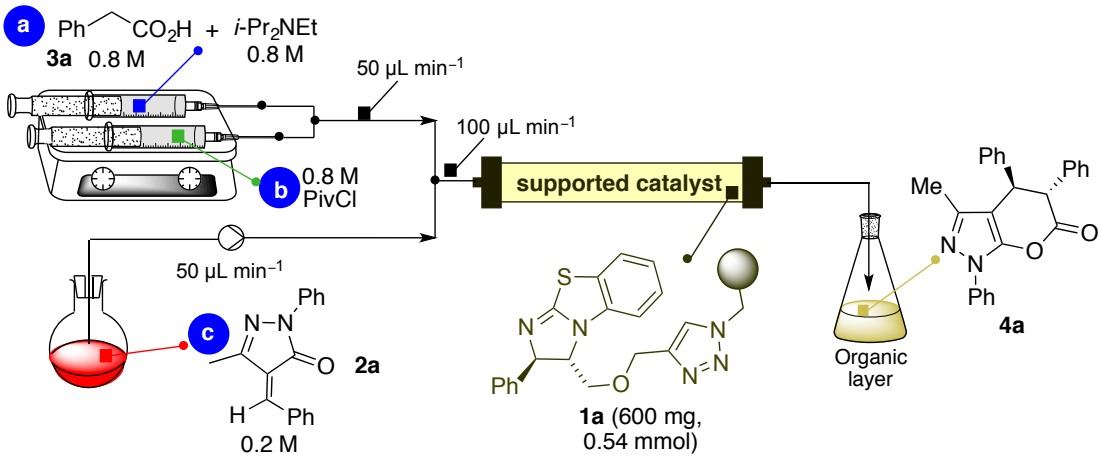
(a) A mixture of *i*-Pr_2NEt and phenylacetic acid in CH_2Cl_2 (0.8 M each).

(b) A solution of pivaloyl chloride (0.8 M in CH_2Cl_2).

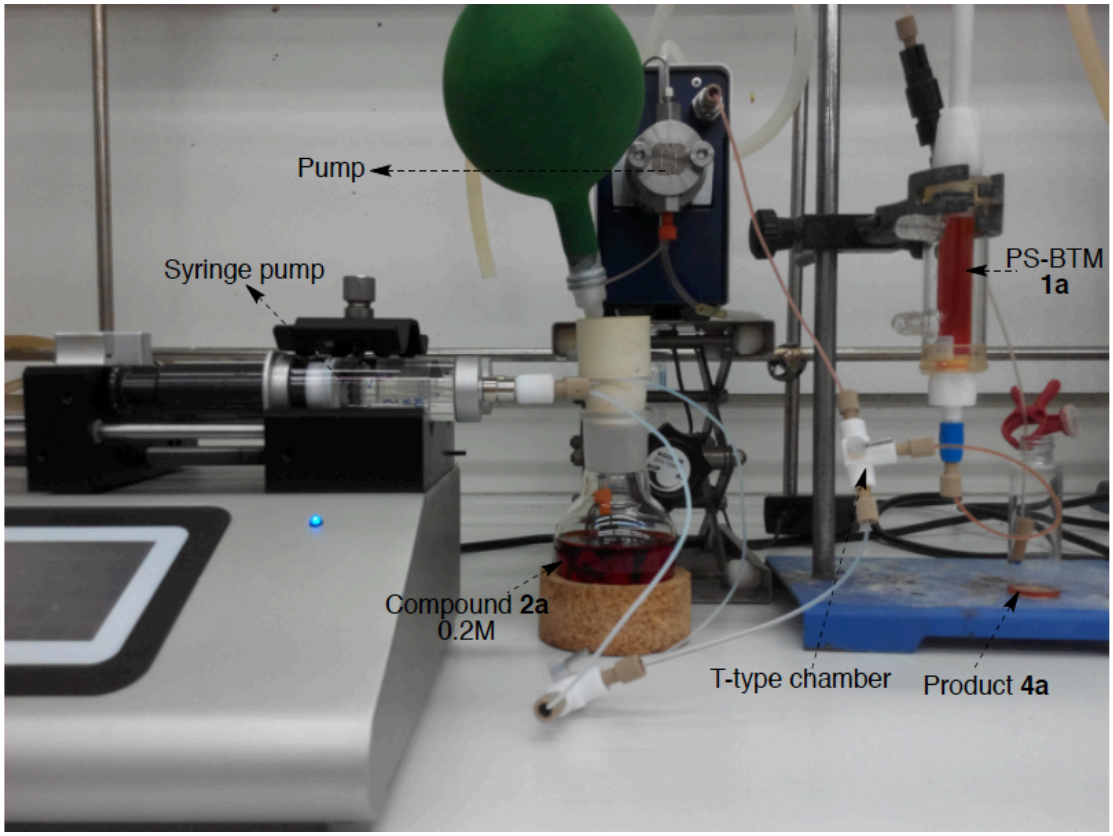
(c) A solution of **2a** (0.2 M) in freshly distilled CH_2Cl_2 through a P 4.1S Azura pump developed by Knauer at 50 µL min^{-1}.

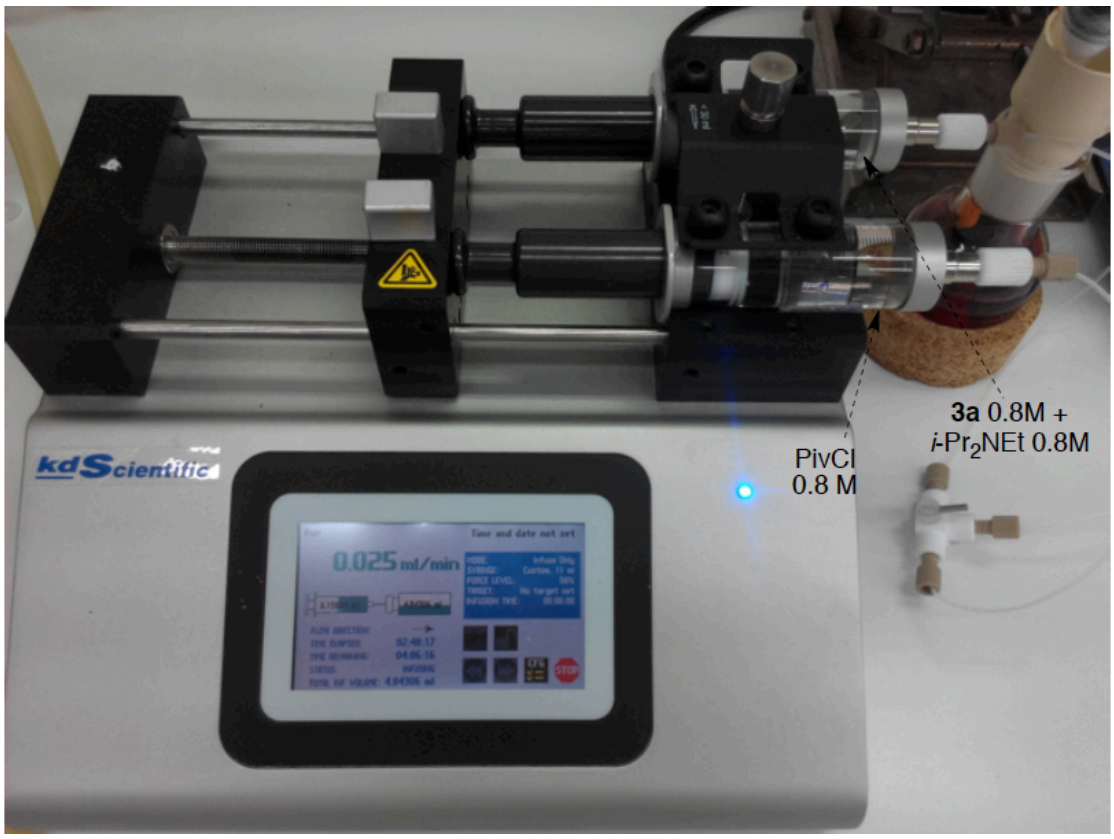
Solutions (a) and (b) were pumped through a Legato 270 push/pull dual syringe pump developed by KD scientific in 2 different syringes with a flow of 25.0 µL min^{-1} for each of them (50 µL min^{-1} combined flow rate a + b).

A T-type mixing chamber mixed current (a+b) with (c) before the combined stream reached the reactor (total flow rate: 100 µL min^{-1}). Conversion and enantiomeric ratio of the final product were determined by ^{1}H NMR spectroscopy and HPLC analysis respectively of periodically collected samples. The experiment was run for 18 h and was stopped when a slight deactivation of the catalyst was detected. All of the final crude products were combined, washed with water and the aqueous layer was extracted with CH_2Cl_2. Combined organic layers were dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude residue was recrystallized to give pure **4a** as single diastereoisomer in 67% yield (2.74 g) and 99% ee.



Entry	Time	Period	Conv. (%)[a]	ee (%)[b]
1	1 h	1 h	>99	97
2	2 h	1 h	>99	98
3	3 h	1 h	>99	98
4	5 h	2 h	>99	98
5	7 h	2 h	>99	98
6	12 h	5 h	99	98
7	14 h	2 h	98	98
8	16 h	2 h	96	98
9	18 h	2 h	94	98

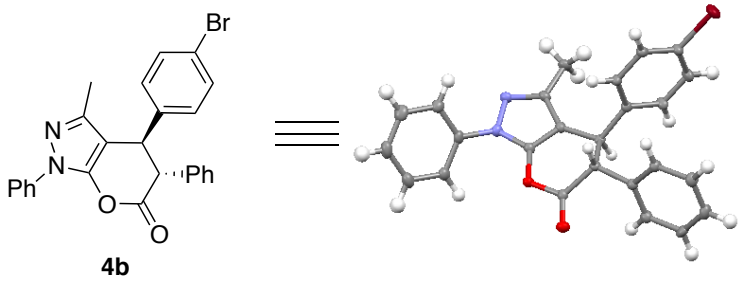

Pump
Syringe pump
PS-BTM
1a
Compound 2a
0.2M
T-type chamber
Product 4a


kdScientific
0.025 ml/min
3a 0.8M +
i-Pr2NEt 0.8M
PivCl
0.8 M

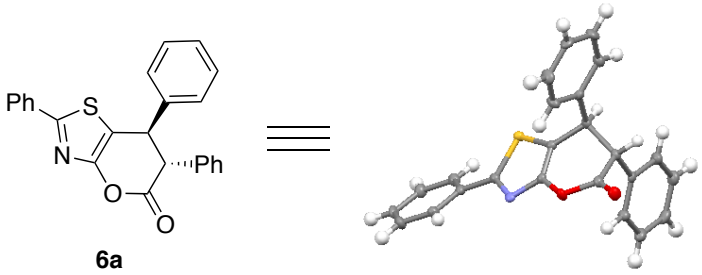
8. Configuration and X-Ray structures

The structures depicted below have been deposited in the Cambridge Crystallographic Data Centre with the following CCDC Numbers:

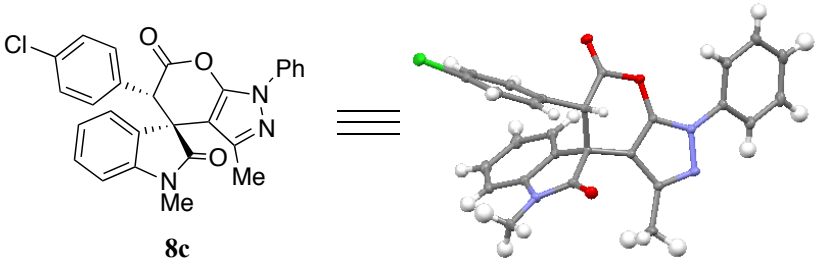
4b – CCDC 1519361
6a – CCDC 1519360
8c – CCDC 1519359
8c´ – CCDC 1519358



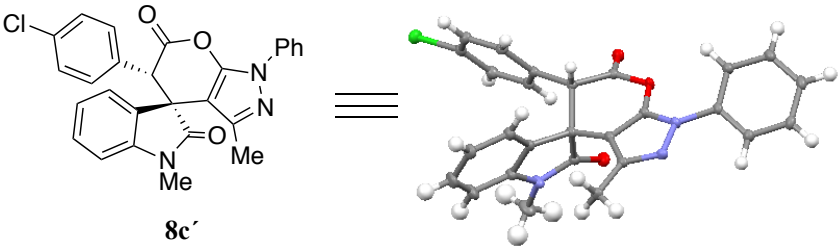
4b



6a



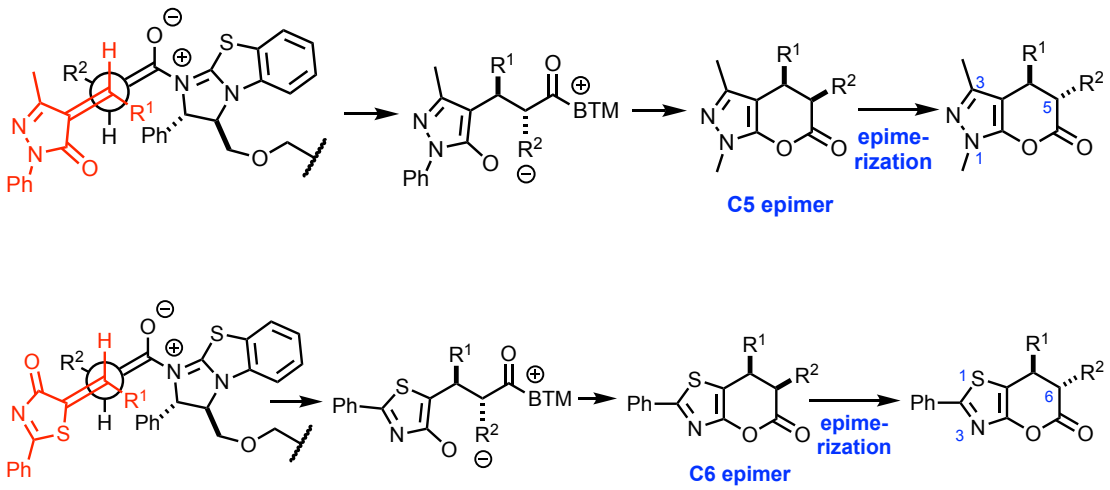
8c



8c´

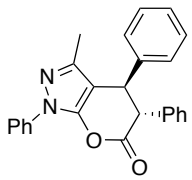
9. Stereochemical models

The following stereochemical models for the pyrazolone and the thiazolone have been proposed according to the X-ray structures and literature precedents. The depicted attack minimizes undesired gauche interactions between R^1 and R^2, but leads to the C_5-epimer of the observed compound (C_6 in the second case, due to the different numbering of the heterocyclic moiety). Subsequently, an epimerization of the relatively acidic stereocentre takes place to lead to the observed major diastereomer. Such an epimerization has been previously described by Smith *et al.*[4] for related systems. In the same paper, going from (*E*) to (*Z*)-Michael acceptors entailed a change in the major diastereomer obtained (before epimerization). In our case, however, given that the electrophile is trisubstituted and no chelation is expected, we postulate that the *E*/*Z* stereochemistry of the electrophile does not have an impact in the stereochemical outcome of the reaction.



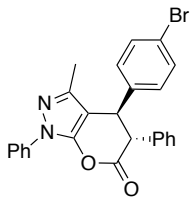
10. Compound characterization

(4*R*,5*R*)-3-Methyl-1,4,5-triphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



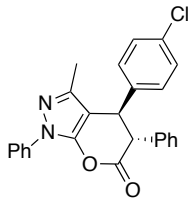
Cycloaddition product **4a** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 12:1 to 7:1) in 83% yield (9:1 dr) and the major diastereoisomer was isolated in 74% yield (28.0 mg). White solid, melting point: 160-162 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.87 (s, 3H), 4.13 (d, *J* = 6.8 Hz, 1H), 4.33 (d, *J* = 6.8 Hz, 1H), 7.09-7.14 (m, 4H), 7.24-7.32 (m, 7H), 7.44-7.48 (m, 2H), 7.77-7.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 43.2, 54.8, 99.1, 120.9 (2C), 126.6, 127.5 (2C), 127.6, 128.0, 128.2 (2C), 128.9 (2C), 129.0 (2C), 129.2 (2C), 135.8, 137.6, 140.2, 146.3, 146.3, 166.6; IR (ATR): ν = 506, 693, 938, 1066, 1094, 1309, 1454, 1485, 1594, 1687, 1784, 2925 cm^{-1}; HRMS calcd. for $C_{25}H_{20}N_2NaO_2$ $[M + Na]^+$: 403.1417, found: 403.1409; $[\alpha]_D^{25}$ = –109.7 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (98:2), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 99% ee): t_{major} = 15.6 min, t_{minor} = 12.9 min.

(4*R*,5*R*)-4-(4-Bromophenyl)-3-methyl-1,5-diphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



Cycloaddition product **4b** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 12:1 to 7:1) in 83% yield (9:1 dr) and the major diastereoisomer was isolated in 72% yield (32.8 mg). White solid, melting point: 154-155 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86 (s, 3H), 4.03 (d, *J* = 7.6 Hz, 1H), 4.30 (d, *J* = 7.6 Hz, 1H), 6.96-6.98 (m, 2H), 7.09-7.11 (m, 2H), 7.29-7.32 (m, 4H), 7.40-7.42 (m, 2H), 7.45-7.49 (m, 2H), 7.76-7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.2, 42.8, 54.7, 98.6, 120.9 (2C), 121.6, 126.7, 128.2, 128.3 (2C), 129.0 (2C), 129.3 (2C), 129.3 (2C), 132.1 (2C), 135.3, 137.5, 139.2, 146.0, 146.3, 166.3; IR (ATR): ν = 699, 732, 932, 1010, 1066, 1100, 1396, 1452, 1487, 1513, 1617, 1787, 2923 cm^{-1}; HRMS calcd. for $C_{25}H_{20}BrN_2O_2$ $[M + H]^+$: 459.0703, found: 459.0708; $[\alpha]_D^{25}$ = –99.2 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 99% ee): t_{major} = 14.1 min, t_{minor} = 10.6 min.

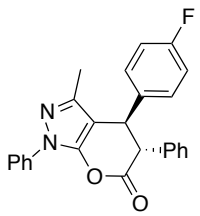
(4*R*,5*R*)-4-(4-Chlorophenyl)-3-methyl-1,5-diphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



Cycloaddition product **4c** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 14:1 to 6:1) in 81% yield (7:1 dr) and the major diastereoisomer was isolated in 70% yield (29.0 mg). White solid, melting point: 120-121 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85 (s, 3H), 4.03 (d, *J* = 7.8 Hz, 1H), 4.31 (d, *J* = 7.8 Hz, 1H), 7.01-7.04 (m, 2H), 7.08-7.11 (m, 2H), 7.24-7.32 (m, 6H), 7.44-7.48 (m, 2H), 7.76-7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.2,

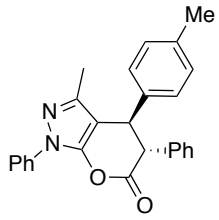
42.8, 54.8, 98.7, 120.9 (2C), 126.7, 128.2, 128.3 (2C), 128.9 (2C), 129.0 (2C), 129.2 (2C), 129.3 (2C), 133.5, 135.3, 137.5, 138.6, 146.1, 146.3, 166.3; IR (ATR): ν = 693, 753, 824, 1014, 1089, 1409, 1454, 1491, 1596, 1703, 1790, 2924 cm^{-1}; HRMS calcd. for $C_{25}H_{20}ClN_2O_2$ $[M + H]^+$: 415.1208, found: 415.1201; $[\alpha]_D^{25}$ = –116.2 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 98% ee): t_{major} = 13.2 min, t_{minor} = 10.0 min.

(4*R*,5*R*)-4-(4-Fluorophenyl)-3-methyl-1,5-diphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



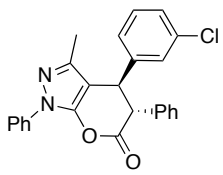
Cycloaddition product **4d** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 12:1 to 7:1) in 82% yield (8:1 dr) and the major diastereoisomer was isolated in 72% yield (28.7 mg). White solid, melting point: 121-123 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85 (s, 3H), 4.04 (d, *J* = 7.6 Hz, 1H), 4.32 (d, *J* = 7.6 Hz, 1H), 6.95-6.99 (m, 2H), 7.04-7.11 (m, 4H), 7.28-7.32 (m, 4H), 7.44-7.48 (m, 2H), 7.76-7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 42.6, 55.0, 99.0, 115.9 (d, *J* = 21.6 Hz, 2C), 120.9 (2C), 126.7, 128.1, 128.3 (2C), 128.9 (2C), 129.2 (d, *J* = 8.2 Hz, 2C), 129.3 (2C), 135.5, 135.9 (d, *J* = 3.2 Hz), 137.6, 146.1, 146.3, 162.1 (d, *J* = 246.8 Hz), 166.4; IR (ATR): ν = 511, 693, 735, 759, 840, 930, 1096, 1224, 1453, 1508, 1598, 1783, 2925 cm^{-1}; HRMS calcd. for $C_{25}H_{19}FN_2NaO_2$ $[M + Na]^+$: 421.1323, found: 421.1310; $[\alpha]_D^{25}$ = –46.5 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 98% ee): t_{major} = 12.0 min, t_{minor} = 9.7 min.

(4*R*,5*R*)-3-Methyl-1,5-diphenyl-4-(*p*-tolyl)-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



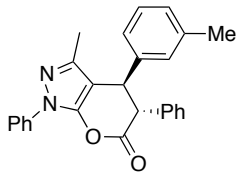
Cycloaddition product **4e** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 12:1 to 7:1) in 72% yield (5:1 dr) and the major diastereoisomer was isolated in 60% yield (23.7 mg). White solid, melting point: 127-128 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88 (s, 3H), 2.31 (s, 3H), 4.11 (d, *J* = 6.8 Hz, 1H), 4.29 (d, *J* = 6.8 Hz, 1H), 6.97-6.99 (m, 2H), 7.07-7.15 (m, 4H), 7.26-7.31 (m, 4H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 21.0, 42.7, 54.9, 99.3, 120.9 (2C), 126.5, 127.4 (2C), 128.0, 128.2 (2C), 128.9 (2C), 129.2 (2C), 129.6 (2C), 136.0, 137.3, 137.3, 137.7, 146.3, 146.3, 166.7; IR (ATR): ν = 510, 665, 694, 735, 757, 931, 1060, 1099, 1452, 1487, 1616, 1787, 2923 cm^{-1}; HRMS calcd. for $C_{26}H_{22}N_2NaO_2$ $[M + Na]^+$: 417.1573, found: 417.1560; $[\alpha]_D^{25}$ = –89.7 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 99% ee): t_{major} = 9.8 min, t_{minor} = 7.7 min.

(4*R*,5*R*)-4-(3-Chlorophenyl)-3-methyl-1,5-diphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



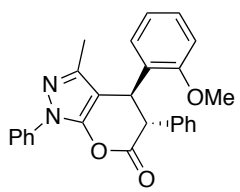
Cycloaddition product **4f** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 14:1 to 7:1) in 84% yield (7:1 dr) and the major diastereoisomer was isolated in 74% yield (30.6 mg). White solid, melting point: 128-130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3H), 4.08 (d, *J* = 6.4 Hz, 1H), 4.31 (d, *J* = 6.4 Hz, 1H), 6.95-6.98 (m, 1H), 7.11-7.13 (m, 3H), 7.20-7.25 (m, 2H), 7.29-7.33 (m, 4H), 7.45-7.49 (m, 2H), 7.77-7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 42.9, 54.6, 98.3, 120.9 (2C), 125.8, 126.7, 127.7, 128.0, 128.2 (2C), 128.2, 129.0 (2C), 129.3 (2C), 130.3, 134.9, 135.4, 137.5, 142.3, 146.1, 146.4, 166.2; IR (ATR): ν = 513, 663, 695, 734, 942, 1065, 1095, 1385, 1433, 1485, 1620, 1786, 2924 cm^{-1}; HRMS calcd. for $C_{25}H_{20}ClN_2O_2$ [M + H]$^+$: 415.1208, found: 415.1199; $[\alpha]_D^{25}$ = –79.8 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 97% ee): t_{major} = 10.9 min, t_{minor} = 8.6 min.

(4*R*,5*R*)-3-Methyl-1,5-diphenyl-4-(*m*-tolyl)-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one:



Cycloaddition product **4g** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 12:1 to 7:1) in 71% yield (7:1 dr) and the major diastereoisomer was isolated in 62% yield (24.5 mg). White solid, melting point: 178-179 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (s, 3H), 2.29 (s, 3H), 4.13 (d, *J* = 6.4 Hz, 1H), 4.29 (d, *J* = 6.4 Hz, 1H), 6.88-6.91 (m, 2H), 7.04-7.06 (m, 1H), 7.13-7.18 (m, 3H), 7.25-7.31 (m, 4H), 7.43-7.48 (m, 2H), 7.78-7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 21.4, 42.9, 54.7, 99.0, 120.8 (2C), 124.5, 126.5, 128.0 (2C), 128.1 (2C), 128.4, 128.8, 128.9 (2C), 129.2 (2C), 136.0, 137.7, 138.7, 140.3, 146.3, 146.3, 166.7; IR (ATR): ν = 506, 696, 729, 782, 944, 1062, 1091, 1388, 1484, 1513, 1612, 1784, 2923 cm^{-1}; HRMS calcd. for $C_{26}H_{22}N_2NaO_2$ [M + Na]$^+$: 417.1573, found: 417.1559; $[\alpha]_D^{25}$ = –108.9 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 99% ee): t_{major} = 7.9 min, t_{minor} = 6.9 min.

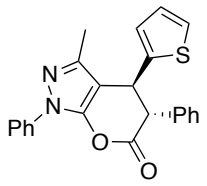
(4*R*,5*R*)-4-(2-Methoxyphenyl)-3-methyl-1,5-diphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1H)-one



Cycloaddition product **4h** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 12:1 to 7:1) in 68% yield (28.0 mg, >20:1 dr). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (s, 3H), 3.79 (s, 3H), 4.25 (d, *J* = 2.0 Hz, 1H), 4.41 (d, *J* = 2.0 Hz, 1H), 6.88-6.93 (m, 2H), 7.07-7.10 (m, 1H), 7.25-7.34 (m, 7H), 7.43-7.47 (m, 2H), 7.79-7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 39.8, 52.0, 54.6, 97.2, 111.0, 120.7 (3C), 126.3, 127.3 (2C), 128.0, 128.6, 128.9, 129.1 (2C), 129.2 (2C), 129.4, 137.8, 138.0, 146.5, 146.6, 156.8, 166.7; IR (ATR): ν = 698, 755,

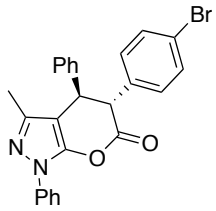
943, 1125, 1217, 1365, 1456, 1490, 1508, 1598, 1738, 1791, 2970 cm^{-1}; HRMS calcd. for $C_{26}H_{23}N_2O_3$ $[M + H]^+$: 411.1703, found: 411.1698; $[\alpha]_D^{25}$ = –121.3 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 99% ee): t_{major} = 7.7 min, t_{minor} = 12.9 min.

(4*S*,5*R*)-3-Methyl-1,5-diphenyl-4-(thiophen-2-yl)-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



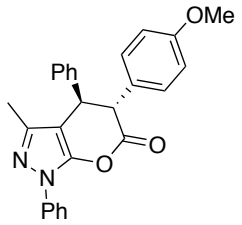
Cycloaddition product **4i** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 12:1 to 7:1) in 81% yield (6:1 dr) and the major diastereoisomer was isolated in 69% yield. White solid, melting point: 152-153 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (s, 3H), 4.27 (d, *J* = 6.0 Hz, 1H), 4.63 (d, *J* = 6.0 Hz, 1H), 6.77-6.78 (m, 1H), 6.88-6.91 (m, 1H), 7.17-7.22 (m, 3H), 7.28-7.34 (m, 4H), 7.44-7.48 (m, 2H), 7.76-7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 38.2, 55.4, 99.2, 120.9 (2C), 125.0, 125.4, 126.7, 127.1, 127.9 (2C), 128.2, 129.0 (2C), 129.2 (2C), 135.4, 137.5, 144.3, 145.9, 146.2, 166.1; IR (ATR): ν = 505, 665, 691, 908, 930, 1060, 1092, 1386, 1453, 1485, 1618, 1787, 2924 cm^{-1}; HRMS calcd. for $C_{23}H_{19}N_2O_2S$ $[M + H]^+$: 387.1162, found: 387.1156; $[\alpha]_D^{25}$ = –35.7 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 96% ee): t_{major} = 10.4 min, t_{minor} = 8.9 min.

(4*R*,5*R*)-5-(4-Bromophenyl)-3-methyl-1,4-diphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



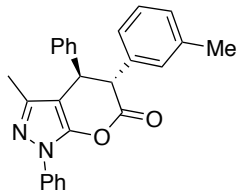
Cycloaddition product **4j** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 12:1 to 7:1) in 75% yield (7:1 dr) and the major diastereoisomer was isolated in 64% yield (29.3 mg). White solid, melting point: 138-139 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80 (s, 3H), 4.06 (d, *J* = 8.4 Hz, 1H), 4.27 (d, *J* = 8.4 Hz, 1H), 6.95-6.98 (m, 2H), 7.06-7.09 (m, 2H), 7.25-7.32 (m, 4H), 7.38-7.42 (m, 2H), 7.44-7.49 (m, 2H), 7.75-7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 43.4, 54.4, 99.1, 120.9 (2C), 122.1, 126.7, 127.7 (2C), 127.8, 129.0 (2C), 129.3 (2C), 130.2 (2C), 131.9 (2C), 134.6, 137.5, 139.5, 146.1, 146.2, 166.3; IR (ATR): ν = 506, 666, 697, 757, 934, 1066, 1099, 1394, 1454, 1488, 1595, 1786, 2924 cm^{-1}; HRMS calcd. for $C_{25}H_{20}BrN_2O_2$ $[M + H]^+$: 459.0703, found: 459.0706; $[\alpha]_D^{25}$ = –68.0 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (98:2), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 98% ee): t_{major} = 18.1 min, t_{minor} = 20.5 min.

(4*R*,5*R*)-5-(4-Methoxyphenyl)-3-methyl-1,4-diphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



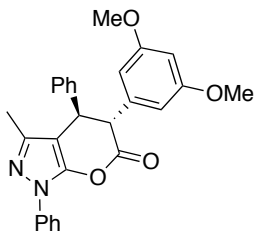
Cycloaddition product **4k** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 5:1) in 82% yield (6:1 dr) and the major diastereoisomer was isolated in 70% yield (28.7 mg). White solid, melting point: 89-90 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.87 (s, 3H), 3.76 (s, 3H), 4.08 (d, *J* = 6.8 Hz, 1H), 4.29 (d, *J* = 6.8 Hz, 1H), 6.79-6.83 (m, 2H), 7.03-7.05 (m, 2H), 7.09-7.11 (m, 2H), 7.22-7.31 (m, 4H), 7.43-7.47 (m, 2H), 7.77-7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 43.1, 54.0, 55.2, 99.2, 114.3 (2C), 120.8 (2C), 126.5, 127.5 (2C), 127.6, 127.7, 129.0 (2C), 129.2 (2C), 129.3 (2C), 137.6, 140.3, 146.3, 146.3, 159.2, 166.9; IR (ATR): ν = 694, 753, 834, 943, 1031, 1066, 1097, 1178, 1245, 1454, 1510, 1612, 1788, 2924 cm^{-1}; HRMS calcd. for $C_{26}H_{23}N_2O_3$ $[M + H]^+$: 411.1703, found: 411.1708; $[\alpha]_D^{25}$ = –87.8 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (98:2), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 98% ee): t_{major} = 18.7 min, t_{minor} = 21.5 min.

(4*R*,5*R*)-3-Methyl-1,4-diphenyl-5-(*m*-tolyl)-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



Cycloaddition product **4l** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 12:1 to 7:1) in 86% yield (6:1 dr) and the major diastereoisomer was isolated in 73% yield (28.8 mg). White solid, melting point: 112-114 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89 (s, 3H), 2.29 (s, 3H), 4.09 (d, *J* = 6.4 Hz, 1H), 4.33 (d, *J* = 6.8 Hz, 1H), 6.91-6.96 (m, 2H), 7.07-7.19 (m, 4H), 7.23-7.31 (m, 4H), 7.44-7.48 (m, 2H), 7.77-7.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 21.4, 43.0, 54.7, 99.0, 120.9 (2C), 125.0, 126.5, 127.5 (2C), 127.6, 128.8, 128.8, 129.0 (2C), 129.0, 129.2 (2C), 135.8, 137.7, 138.6, 140.5, 146.3, 146.3, 166.7; IR (ATR): ν = 697, 749, 1094, 1397, 1454, 1491, 1599, 1702, 1788, 2923 cm^{-1}; HRMS calcd. for $C_{26}H_{23}N_2O_2$ $[M + H]^+$: 395.1754, found: 395.1757; $[\alpha]_D^{25}$ = –115.4 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 99% ee): t_{major} = 10.6 min, t_{minor} = 8.4 min.

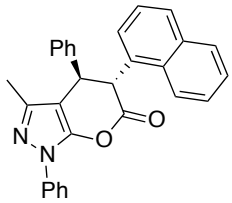
(4*R*,5*R*)-5-(3,5-Dimethoxyphenyl)-3-methyl-1,4-diphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



Cycloaddition product **4m** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 12:1 to 7:1) in 73% yield (5:1 dr) and the major diastereoisomer was isolated in 61% yield (26.9 mg). White solid, melting point: 93-95 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89 (s, 3H), 3.70 (s, 6H), 4.06 (d, *J* = 6.4 Hz, 1H), 4.33 (d, *J* = 6.4 Hz, 1H), 6.28-6.29 (m, 2H), 6.35-6.37 (m, 1H), 7.11-7.14 (m, 2H), 7.25-7.32 (m, 4H), 7.44-7.48 (m, 2H), 7.76-7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 42.8, 54.8, 55.3 (2C), 99.0, 99.8, 106.5 (2C),

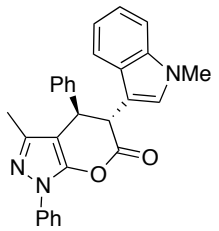
120.9 (2C), 126.6, 127.5 (2C), 127.7, 129.0 (2C), 129.2 (2C), 137.6, 137.9, 140.3, 146.3, 146.3, 160.9 (2C), 166.4; IR (ATR): ν = 692, 754, 834, 1063, 1151, 1203, 1455, 1594, 1716, 1790, 2924 cm^{-1}; HRMS calcd. for $C_{27}H_{25}N_2O_4$ $[M + H]^+$: 441.1816, found: 411.1819; $[\alpha]_D^{25}$ = –177.6 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 98% ee): t_{major} = 19.3 min, t_{minor} = 13.9 min.

(4*R*,5*R*)-3-Methyl-5-(naphthalen-1-yl)-1,4-diphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



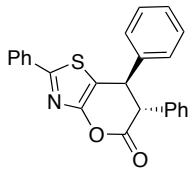
Cycloaddition product **4n** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 12:1 to 7:1) in 81% yield (13:1 dr) and the major diastereoisomer was isolated in 75% yield (32.3 mg). White solid, melting point: 124-126 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (s, 3H), 4.50 (d, *J* = 6.8 Hz, 1H), 4.77 (d, *J* = 6.8 Hz, 1H), 7.08-7.14 (m, 3H), 7.23-7.34 (m, 5H), 7.47-7.57 (m, 4H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.84-7.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 43.0, 51.8, 99.0, 120.9 (2C), 123.2, 125.2, 125.9, 126.4, 126.6, 126.7, 127.4 (2C), 127.7, 129.0 (3C), 129.3 (2C), 129.4, 130.5, 132.2, 134.2, 137.7, 140.9, 146.2, 146.5, 166.4; IR (ATR): ν = 691, 754, 793, 934, 1026, 1070, 1102, 1393, 1486, 1510, 1596, 1776, 2922 cm^{-1}; HRMS calcd. for $C_{29}H_{23}N_2O_2$ $[M + H]^+$: 431.1754, found: 431.1742; $[\alpha]_D^{25}$ = –58.4 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 96% ee): t_{major} = 13.8 min, t_{minor} = 9.1 min.

(4*R*,5*R*)-3-Methyl-5-(1-methyl-1*H*-indol-3-yl)-1,4-diphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



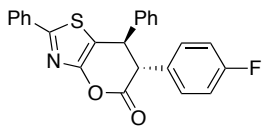
Cycloaddition product **4o** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 12:1 to 5:1) in 85% yield (5:1 dr) and the major diastereoisomer was isolated in 70% yield (30.2 mg). White solid, melting point: 93-94 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 3.68 (s, 3H), 4.45 (d, *J* = 3.6 Hz, 1H), 4.48 (d, *J* = 3.6 Hz, 1H), 6.73 (s, 1H), 7.16-7.19 (m, 3H), 7.26-7.35 (m, 6H), 7.42-7.46 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.79-7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 32.9, 41.9, 46.4, 99.0, 109.4, 109.6, 118.9, 119.9, 120.6 (2C), 122.4, 126.4 (3C), 127.0 (2C), 127.6, 129.1 (2C), 129.2 (2C), 136.8, 137.8, 141.4, 146.4, 146.7, 165.8; IR (ATR): ν = 690, 739, 926, 1059, 1122, 1332, 1390, 1440, 1509, 1596, 1784, 2849, 2923 cm^{-1}; HRMS calcd. for $C_{28}H_{23}N_3NaO_2$ $[M + Na]^+$: 456.1682, found: 456.1686; $[\alpha]_D^{25}$ = –146.0 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IC, hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 97% ee): t_{major} = 15.1 min, t_{minor} = 17.9 min.

(6*R*,7*R*)-2,6,7-Triphenyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]thiazol-5-one



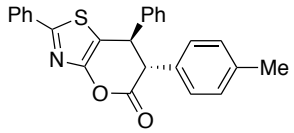
Cycloaddition product **6a** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 7:1) in 77% yield (29.5 mg, >20:1 dr). White solid, melting point: 179-180 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.20 (d, *J* = 7.8 Hz, 1H), 4.53 (d, *J* = 7.8 Hz, 1H), 7.11-7.15 (m, 4H), 7.25-7.32 (m, 6H), 7.41-7.45 (m, 3H), 7.87-7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.7, 54.7, 110.1, 125.8 (2C), 127.4 (2C), 128.0, 128.2, 128.3 (2C), 128.9 (2C), 129.0 (2C), 129.1 (2C), 130.7, 132.8, 135.5, 140.3, 155.8, 165.7, 167.1; IR (ATR): ν = 696, 763, 902, 998, 1129, 1242, 1364, 1454, 1496, 1560, 1774, 2923 cm^{-1}; HRMS calcd. for $C_{24}H_{17}NNaO_2S$ $[M + Na]^+$: 406.0872, found: 406.0865; $[\alpha]_D^{25}$ = –19.3 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IC, hexane/*i*-propanol (75:25), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 99% ee): t_{major} = 61.7 min, t_{minor} = 75.0 min.

(6*R*,7*R*)-6-(4-Fluorophenyl)-2,7-diphenyl-6,7-dihydro-5*H*-pyrano[2,3-*d*]thiazol-5-one



Cycloaddition product **6b** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 7:1) in 70% yield (>20:1 dr). White solid, melting point: 180-181 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (d, *J* = 8.4 Hz, 1H), 4.47 (d, *J* = 8.4 Hz, 1H), 6.94-6.98 (m, 2H), 7.05-7.11 (m, 4H), 7.26-7.31 (m, 3H), 7.40-7.44 (m, 3H), 7.87-7.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.9, 54.1, 110.3, 115.8 (d, *J* = 21.7 Hz, 2C), 125.8 (2C), 127.5 (2C), 128.3, 129.0 (2C), 129.1 (2C), 130.2 (d, *J* = 8.2 Hz, 2C), 130.8, 131.0 (d, *J* = 3.4 Hz), 132.7, 139.9, 155.7, 162.3 (d, *J* = 247.4 Hz), 165.7, 167.0; IR (ATR): ν = 499, 524, 643, 680, 763, 782, 827, 945, 1113, 1228, 1351, 1456, 1509, 1561, 1603, 1769, 2923 cm^{-1}; HRMS calcd. for $C_{24}H_{17}FNO_2S$ $[M + H]^+$: 402.0959, found: 402.0952; $[\alpha]_D^{25}$ = –31.6 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IC, hexane/*i*-propanol (75:25), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 99% ee): t_{major} = 57.9 min, t_{minor} = 78.9 min.

(6*R*,7*R*)-2,7-Diphenyl-6-(*p*-tolyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]thiazol-5-one Cycloaddition

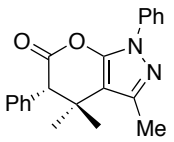


product **6c** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 7:1) in 73% yield (28.9 mg, >20:1 dr). White solid, melting point: 181-182 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 4.17 (d, *J* = 7.6 Hz, 1H), 4.50 (d, *J* = 7.6 Hz, 1H), 7.01-7.09 (m, 4H), 7.11-7.14 (m, 2H), 7.26-7.32 (m, 3H), 7.39-7.45 (m, 3H), 7.87-7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 44.6, 54.3, 110.1, 125.8 (2C), 127.3 (2C), 128.0 (2C), 128.1, 129.0 (2C), 129.1 (2C), 129.6 (2C), 130.7, 132.4, 132.8, 137.8, 140.4, 155.8, 165.6, 167.2; IR (ATR): ν = 500, 636, 674, 754, 775, 814, 931, 1100, 1238, 1308, 1352, 1456, 1518, 1564, 1772, 2917 cm^{-1}; HRMS calcd. for $C_{25}H_{20}NO_2S$ $[M + H]^+$: 398.1209, found: 398.1218; $[\alpha]_D^{25}$ = –70.3 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IC, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 99% ee): t_{major} = 80.0 min, t_{minor} = 85.9 min.

(6*R*,7*R*)-2,7-Diphenyl-6-(*m*-tolyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]thiazol-5-one Cycloaddition product **6d** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 7:1) in 71% yield (28.2 mg, >20:1 dr). White solid, melting point: 184-185 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3H), 4.17 (d, *J* = 7.6 Hz, 1H), 4.52 (d, *J* = 7.6 Hz, 1H), 6.92-6.97 (m, 2H), 7.06-7.07 (m, 1H), 7.12-7.18 (m, 3H), 7.27-7.33 (m, 3H), 7.40-7.45 (m, 3H), 7.88-7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 44.6, 54.6, 110.0, 125.0, 125.8 (2C), 127.3 (2C), 128.1, 128.7, 128.8, 128.9, 129.0 (2C), 129.1 (2C), 130.7, 132.8, 135.4, 138.6, 140.4, 155.8, 165.6, 167.1; IR (ATR): ν = 680, 731, 762, 955, 1106, 1243, 1349, 1455, 1490, 1562, 1770, 2922 cm^{-1}; HRMS calcd. for $C_{25}H_{20}NO_2S$ $[M + H]^+$: 398.1209, found: 398.1209; $[\alpha]_D^{25}$ = –105.6 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 99% ee): t_{major} = 20.6 min, t_{minor} = 13.5 min.

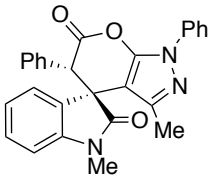
(6*R*,7*R*)-2,7-Diphenyl-6-(*o*-tolyl)-6,7-dihydro-5*H*-pyrano[2,3-*d*]thiazol-5-one Cycloaddition product **6e** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 7:1) in 68% yield (27.0 mg, >20:1 dr). White solid, melting point: 88-89 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (s, 3H), 4.39 (d, *J* = 8.8 Hz, 1H), 4.49 (d, *J* = 8.8 Hz, 1H), 7.08-7.18 (m, 6H), 7.26-7.29 (m, 3H), 7.40-7.45 (m, 3H), 7.87-7.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 44.6, 51.0, 110.4, 125.8 (2C), 126.6, 127.5 (2C), 128.0, 128.0, 128.2, 129.0 (2C), 129.0 (2C), 130.7, 130.8, 132.8, 134.3, 136.4, 140.4, 155.9, 165.6, 167.1; IR (ATR): ν = 681, 740, 934, 969, 1103, 1236, 1352, 1455, 1494, 1562, 1777, 2924 cm^{-1}; HRMS calcd. for $C_{25}H_{19}NNaO_2S$ $[M + Na]^+$: 420.1029, found: 420.1032; $[\alpha]_D^{25}$ = –8.9 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel AD-H, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 99% ee): t_{major} = 18.3 min, t_{minor} = 11.1 min.

(*S*)-3,4,4-Trimethyl-1,5-diphenyl-4,5-dihydropyrano[2,3-*c*]pyrazol-6(1*H*)-one



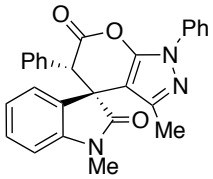
Cycloaddition product **8a** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 10:1) as a colorless oil in 21% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (s, 3H), 1.35 (s, 3H), 2.36 (s, 3H), 3.84 (s, 1H), 7.19-7.21 (m, 2H), 7.27-7.31 (m, 1H), 7.33-7.36 (m, 3H), 7.43-7.47 (m, 2H), 7.75-7.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 24.5, 28.2, 35.2, 59.1, 105.7, 121.0 (2C), 126.5, 128.1, 128.4 (2C), 129.2 (2C), 130.2 (2C), 133.3, 137.6, 144.8, 144.9, 167.3; IR (ATR): ν = 667, 693, 755, 901, 1058, 1110, 1392, 1454, 1510, 1599, 1787, 2971 cm^{-1}; HRMS calcd. for $C_{21}H_{21}N_2O_2$ $[M + H]^+$: 333.1598, found: 333.1600; $[\alpha]_D^{25}$ = +34.0 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (98:2), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 96% ee): t_{major} = 10.0 min, t_{minor} = 8.8 min.

(3*R*,5'*S*)-1,3'-Dimethyl-1',5'-diphenyl-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-2,6'(5'*H*)-dione



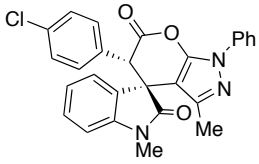
Cycloaddition product **8b** was isolated by FC on silica (eluting from CH_2Cl_2 to CH_2Cl_2/EtOAc 20:1) in 88% yield (2:1 dr), the major diastereoisomer was isolated in 58% yield (25.2 mg) and the minor diastereoisomer was isolated in 29% yield (12.6 mg). Major diastereoisomer: white solid, melting point: 190-191 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (s, 3H), 3.01 (s, 3H), 4.56 (s, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.86-6.88 (m, 2H), 6.95-6.97 (m, 1H), 7.01-7.05 (m, 1H), 7.09-7.13 (m, 2H), 7.18-7.22 (m, 1H), 7.26-7.35 (m, 2H), 7.47-7.51 (m, 2H), 7.78-7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 26.4, 51.7, 53.3, 97.8, 108.5, 121.2 (2C), 123.1, 124.7, 126.9, 127.1, 127.8 (2C), 128.4, 129.3 (2C), 129.6, 130.0 (2C), 130.6, 137.4, 142.9, 144.6, 147.4, 165.5, 174.8; IR (ATR): ν = 538, 685, 740, 969, 1057, 1092, 1368, 1489, 1511, 1609, 1706, 1787, 2925 cm^{-1}; HRMS calcd. for $C_{27}H_{22}N_3O_3$ $[M + H]^+$: 436.1656, found: 436.1649; $[\alpha]_D^{25}$ = +254.5 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 96% ee): t_{major} = 25.2 min, t_{minor} = 11.4 min.

(3*S*,5'*S*)-1,3'-Dimethyl-1',5'-diphenyl-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-2,6'(5'*H*)-dione



Minor diastereoisomer **8b´**: white solid, melting point: 182-183 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (s, 3H), 2.97 (s, 3H), 4.37 (s, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 7.01-7.03 (m, 2H), 7.09-7.17 (m, 4H), 7.23-7.27 (m, 1H), 7.29-7.33 (m, 1H), 7.38-7.40 (m, 1H), 7.45-7.49 (m, 2H), 7.78-7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 26.1, 52.2, 53.8, 97.4, 108.6, 121.3 (2C), 123.0, 124.1, 126.7, 126.8, 127.7 (2C), 128.2, 129.2 (2C), 129.6, 130.2 (2C), 130.5, 137.5, 144.0, 144.7, 147.8, 165.2, 175.0; IR (ATR): ν = 696, 726, 751, 967, 1063, 1098, 1350, 1372, 1455, 1491, 1517, 1610, 1712, 1791, 2923 cm^{-1}; HRMS calcd. for $C_{27}H_{22}N_3O_3$ $[M + H]^+$: 436.1656, found: 436.1663; $[\alpha]_D^{25}$ = –63.6 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 83% ee): t_{major} = 17.2 min, t_{minor} = 8.1 min.

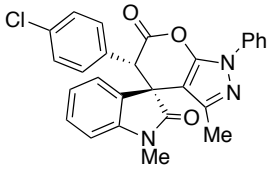
(3*R*,5'*S*)-5'-(4-Chlorophenyl)-1,3'-dimethyl-1'-phenyl-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-2,6'(5'*H*)-dione



Cycloaddition product **8c** was isolated by FC on silica (eluting from CH_2Cl_2 to CH_2Cl_2/EtOAc 20:1) in 89% yield (2.5:1 dr), the major diastereoisomer was isolated in 62% yield (29.0 mg) and the minor diastereoisomer was isolated in 27% yield (12.7 mg). Major diastereoisomer: white solid, melting point: 166-167 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86

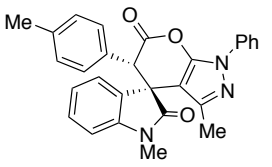
(s, 3H), 3.03 (s, 3H), 4.61 (s, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.79-6.82 (m, 2H), 7.05-7.10 (m, 4H), 7.27-7.35 (m, 2H), 7.46-7.50 (m, 2H), 7.76-7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 26.4, 51.7, 52.7, 97.9, 108.7, 121.1 (2C), 123.3, 124.4, 126.9 (2C), 128.0 (2C), 129.0, 129.3 (2C), 129.8, 131.4 (2C), 134.5, 137.4, 142.7, 144.4, 147.1, 165.3, 174.4; IR (ATR): ν = 538, 687, 756, 850, 915, 971, 1015, 1056, 1087, 1371, 1491, 1510, 1610, 1715, 1792, 3068 cm^{-1}; HRMS calcd. for $C_{27}H_{21}ClN_3O_3$ $[M + H]^+$: 470.1266, found: 470.1254; $[\alpha]_D^{25}$ = +305.1 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 89% ee): t_{major} = 34.1 min, t_{minor} = 10.3 min.

(3*S*,5'*S*)-5'-(4-Chlorophenyl)-1,3'-dimethyl-1'-phenyl-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-2,6'(5'*H*)-dione



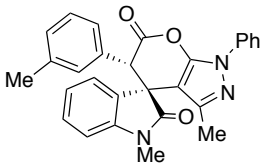
Minor diastereoisomer **8c´**: white solid, melting point: 143-145 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55 (s, 3H), 3.00 (s, 3H), 4.36 (s, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.96-6.98 (m, 2H), 7.08-7.11 (m, 2H), 7.13-7.17 (m, 1H), 7.27-7.34 (m, 2H), 7.37-7.39 (m, 1H), 7.45-7.49 (m, 2H), 7.77-7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 26.2, 52.2, 53.1, 97.2, 108.9, 121.3 (2C), 123.2, 124.0, 126.4, 126.9, 128.0 (2C), 129.2, 129.2 (2C), 129.8, 131.6 (2C), 134.3, 137.4, 143.9, 144.6, 147.7, 164.9, 174.8; IR (ATR): ν = 537, 691, 752, 855, 968, 1060, 1087, 1372, 1492, 1516, 1610, 1706, 1797, 2925 cm^{-1}; HRMS calcd. for $C_{27}H_{21}ClN_3O_3$ $[M + H]^+$: 470.1266, found: 470.1262; $[\alpha]_D^{25}$ = –24.0 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 80% ee): t_{major} = 14.8 min, t_{minor} = 9.0 min.

(3*R*,5'*S*)-1,3'-Dimethyl-1'-phenyl-5'-(*p*-tolyl)-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-2,6'(5'*H*)-dione



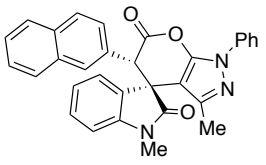
Cycloaddition product **8d** was isolated by FC on silica (eluting from CH_2Cl_2 to CH_2Cl_2/EtOAc 20:1) in 91% yield (3:1 dr) and the major diastereoisomer was isolated in 67% yield (29.9 mg). White solid, melting point: 182-184 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (s, 3H), 2.24 (s, 3H), 3.03 (s, 3H), 4.51 (s, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.74-6.76 (m, 2H), 6.90-6.95 (m, 3H), 7.01-7.05 (m, 1H), 7.26-7.34 (m, 2H), 7.46-7.50 (m, 2H), 7.78-7.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 21.1, 26.4, 51.6, 52.9, 97.9, 108.5, 121.1 (2C), 123.0, 124.8, 126.8, 127.1, 127.6, 128.6 (2C), 129.3 (2C), 129.5, 129.8 (2C), 137.5, 138.2, 143.0, 144.6, 147.4, 165.7, 174.9; IR (ATR): ν = 539, 688, 755, 913, 1054, 1087, 1371, 1492, 1509, 1609, 1713, 1799, 2923 cm^{-1}; HRMS calcd. for $C_{28}H_{24}N_3O_3$ $[M + H]^+$: 450.1812, found: 450.1809; $[\alpha]_D^{25}$ = +246.7 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 98% ee): t_{major} = 19.0 min, t_{minor} = 9.9 min.

(3*R*,5'*S*)-1,3'-Dimethyl-1'-phenyl-5'-(*m*-tolyl)-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-2,6'(5'*H*)-dione



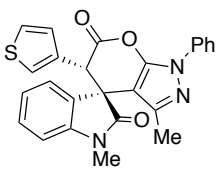
Cycloaddition product **8e** was isolated by FC on silica (eluting from CH_2Cl_2 to CH_2Cl_2/EtOAc 20:1) in 88% yield (3:1 dr) and the major diastereoisomer was isolated in 65% yield (29.0 mg). White solid, melting point: 156-158 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (s, 3H), 2.14 (s, 3H), 3.01 (s, 3H), 4.49 (s, 1H), 6.63-6.69 (m, 3H), 6.93-6.95 (m, 1H), 6.98-7.05 (m, 3H), 7.25-7.34 (m, 2H), 7.47-7.51 (m, 2H), 7.78-7.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 21.2, 26.3, 51.6, 53.3, 97.7, 108.4, 121.2 (2C), 123.0, 124.8, 126.9 (2C), 127.2, 127.7, 129.1, 129.3 (2C), 129.5, 130.5, 130.7, 137.5, 137.5, 143.0, 144.7, 147.4, 165.5, 174.9; IR (ATR): ν = 687, 749, 1060, 1096, 1371, 1489, 1514, 1611, 1713, 1790, 2921 cm^{-1}; HRMS calcd. for $C_{28}H_{24}N_3O_3$ [M + H]$^+$: 450.1812, found: 450.1801; $[\alpha]_D^{25}$ = +233.1 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 97% ee): t_{major} = 26.2 min, t_{minor} = 9.4 min.

(3*R*,5'*S*)-1,3'-Dimethyl-5'-(naphthalen-2-yl)-1'-phenyl-1'*H*-spiro[indoline-3,4'-pyrano [2,3-*c*]pyrazole]-2,6'(5'*H*)-dione



Cycloaddition product **8f** was isolated by FC on silica (eluting from CH_2Cl_2 to CH_2Cl_2/EtOAc 20:1) in 86% yield (3:1 dr) and the major diastereoisomer was isolated in 63% yield (30.2 mg). White solid, melting point: 125-127 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85 (s, 3H), 2.92 (s, 3H), 4.77 (s, 1H), 6.58 (d, *J* = 7.6 Hz, 1H), 6.90-6.92 (m, 1H), 7.02-7.07 (m, 2H), 7.22-7.27 (m, 1H), 7.31-7.35 (m, 1H), 7.38-7.46 (m, 3H), 7.47-7.51 (m, 2H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.64-7.66 (m, 1H), 7.70-7.73 (m, 1H), 7.80-7.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 26.4, 51.8, 53.4, 98.0, 108.6, 121.2 (2C), 123.1, 124.7, 126.0, 126.5, 126.9, 127.0, 127.1, 127.3, 127.4, 128.0, 128.1, 129.3 (2C), 129.6, 129.8, 132.6, 132.8, 137.4, 142.8, 144.6, 147.3, 165.6, 174.8; IR (ATR): ν = 479, 541, 662, 689, 748, 975, 1057, 1091, 1371, 1490, 1511, 1610, 1715, 1791, 2924 cm^{-1}; HRMS calcd. for $C_{31}H_{24}N_3O_3$ [M + H]$^+$: 486.1812, found: 486.1793; $[\alpha]_D^{25}$ = +206.5 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (75:25), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 87% ee): t_{major} = 49.7 min, t_{minor} = 10.6 min.

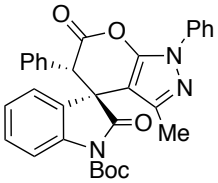
(3*R*,5'*R*)-1,3'-Dimethyl-1'-phenyl-5'-(thiophen-3-yl)-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-2,6'(5'*H*)-dione



Cycloaddition product **8g** was isolated by FC on silica (eluting from CH_2Cl_2 to CH_2Cl_2/EtOAc 20:1) in 81% yield (3:1 dr) and the major diastereoisomer was isolated in 59% yield (25.9 mg). White solid, melting point: 187-188 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (s, 3H), 3.09 (s, 3H), 4.70 (s, 1H),

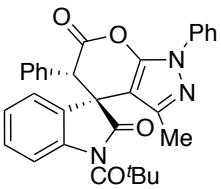
6.51 (dd, *J* = 1.2, 4.2 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.92-6.94 (m, 2H), 7.02-7.08 (m, 2H), 7.28-7.34 (m, 2H), 7.46-7.50 (m, 2H), 7.77-7.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 26.5, 48.9, 51.4, 97.7, 108.6, 121.1 (2C), 123.2, 124.4, 125.1, 125.6, 126.9, 127.2, 127.9, 129.3 (2C), 129.7, 130.5, 137.4, 143.0, 144.6, 147.4, 165.2, 174.9; IR (ATR): ν = 507, 661, 690, 751, 979, 1058, 1107, 1443, 1492, 1512, 1611, 1712, 1787, 2923 cm^{-1}; HRMS calcd. for $C_{25}H_{19}N_3NaO_3S$ $[M + Na]^+$: 464.1039, found: 464.1026; $[\alpha]_D^{25}$ = +187.3 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 93% ee): t_{major} = 24.3 min, t_{minor} = 11.9 min.

(3*R*,5'*S*)-*tert*-Butyl 3'-methyl-2,6'-dioxo-1',5'-diphenyl-5',6'-dihydro-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-1-carboxylate



Cycloaddition product **8h** was isolated by FC on silica (eluting from CH_2Cl_2 to CH_2Cl_2/EtOAc 50:1) in 76% yield (3:1 dr) and the major diastereoisomer was isolated in 57% yield. White solid, melting point: 99-101 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58 (s, 9H), 1.82 (s, 3H), 4.51 (s, 1H), 6.77-6.79 (m, 1H), 6.85-6.87 (m, 2H), 7.07-7.17 (m, 3H), 7.23-7.36 (m, 3H), 7.47-7.51 (m, 2H), 7.67-7.69 (m, 1H), 7.79-7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 28.0 (3C), 52.2, 54.1, 85.0, 97.7, 115.3, 121.2 (2C), 124.7, 124.8, 125.5, 127.0, 128.2 (2C), 128.7, 129.3 (2C), 129.9, 129.9 (2C), 130.4, 137.3, 139.3, 144.9, 147.3, 148.3, 164.7, 174.0; IR (ATR): ν = 692, 753, 840, 1146, 1249, 1287, 1343, 1370, 1455, 1605, 1732, 2926 cm^{-1}; HRMS calcd. for $C_{31}H_{28}N_3O_5$ $[M + H]^+$: 522.2023, found: 522.2015; $[\alpha]_D^{25}$ = –104.8 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 97% ee): t_{major} = 16.2 min, t_{minor} = 7.4 min.

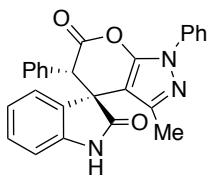
(3*R*,5'*S*)-3'-Methyl-1',5'-diphenyl-1-pivaloyl-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-2,6'(5'*H*)-dione



Cycloaddition product **8i** was isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 10:1) in 75% yield (4:1 dr) and the major diastereoisomer was isolated in 60% yield. White solid, melting point: 133-135 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 9H), 1.84 (s, 3H), 4.54 (s, 1H), 6.86-6.88 (m, 3H), 7.08-7.12 (m, 1H), 7.14-7.17 (m, 2H), 7.26-7.31 (m, 3H), 7.32-7.36 (m, 1H), 7.48-7.52 (m, 2H), 7.80-7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 26.4 (3C), 43.3, 52.3, 54.0, 98.3, 114.8, 121.1 (2C), 124.7, 124.8, 126.9, 127.0, 128.4 (2C), 128.9, 129.3 (2C), 129.8, 130.0 (2C), 130.4, 137.4, 140.6, 144.6, 147.1, 165.0, 174.4, 181.5; IR (ATR): ν = 595, 698, 752, 1022, 1075, 1179, 1302, 1398, 1456, 1472, 1617, 1700, 1798, 2925 cm^{-1}; HRMS calcd. for $C_{31}H_{28}N_3O_4$ $[M + H]^+$: 506.2074, found: 506.2078; $[\alpha]_D^{25}$ = –119.6 (*c* = 0.1, $CHCl_3$);

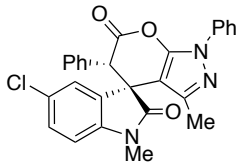
HPLC (Chiralcel IA, hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 97% ee): t_{major} = 15.8 min, t_{minor} = 7.0 min.

(3*R*,5'*S*)-3'-Methyl-1',5'-diphenyl-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-2,6'(5'*H*)-dione



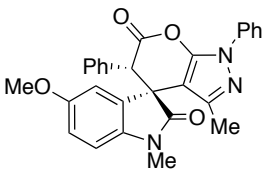
Cycloaddition product **8j** was isolated by FC on silica (eluting with CH_2Cl_2/EtOAc from 100:1 to 10:1) in 78% yield (2:1 dr) and the major diastereoisomer was isolated in 53% yield. White solid, melting point: 218-220 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86 (s, 3H), 4.51 (s, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.84-6.86 (m, 1H), 6.91-6.93 (m, 2H), 6.97-7.01 (m, 1H), 7.13-7.16 (m, 2H), 7.19-7.27 (m, 2H), 7.31-7.35 (m, 1H), 7.47-7.51 (m, 2H), 7.78-7.81 (m, 2H), 8.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 51.9, 53.1, 97.6, 110.4, 121.2 (2C), 123.1, 125.2, 126.9, 127.3, 128.1 (2C), 128.6, 129.3 (2C), 129.7, 130.1 (2C), 130.8, 137.4, 140.0, 144.7, 147.3, 165.3, 177.0; IR (ATR): ν = 695, 741, 926, 1075, 1097, 1212, 1395, 1455, 1471, 1489, 1513, 1614, 1722, 1792, 3063 cm^{-1}; HRMS calcd. for $C_{26}H_{20}N_3O_3$ $[M + H]^+$: 422.1499, found: 422.1499; $[\alpha]_D^{25}$ = +285.9 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 98% ee): t_{major} = 24.2 min, t_{minor} = 11.6 min.

(3*R*,5'*S*)-5-Chloro-1,3'-dimethyl-1',5'-diphenyl-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-2,6'(5'*H*)-dione



Cycloaddition product **8k** was isolated by FC on silica (eluting from CH_2Cl_2 to CH_2Cl_2/EtOAc 50:1) in 82% yield (4:1 dr) and the major diastereoisomer was isolated in 65% yield. White solid, melting point: 113-115 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 3H), 2.99 (s, 3H), 4.56 (s, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 6.88-6.92 (m, 3H), 7.14-7.17 (m, 2H), 7.22-7.27 (m, 2H), 7.32-7.36 (m, 1H), 7.48-7.52 (m, 2H), 7.78-7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 26.5, 51.8, 53.2, 97.1, 109.4, 121.2 (2C), 125.1, 127.0, 128.0 (2C), 128.6, 128.6, 128.8, 129.3 (2C), 129.6, 129.9 (2C), 130.3, 137.3, 141.4, 144.5, 147.3, 165.0, 174.4; IR (ATR): ν = 692, 754, 813, 1101, 1361, 1454, 1487, 1514, 1609, 1717, 1793, 2924 cm^{-1}; HRMS calcd. for $C_{27}H_{21}ClN_3O_3$ $[M + H]^+$: 470.1266, found: 470.1263; $[\alpha]_D^{25}$ = +141.3 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 93% ee): t_{major} = 29.2 min, t_{minor} = 26.1 min.

(3*R*,5'*S*)-5-Methoxy-1,3'-dimethyl-1',5'-diphenyl-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-2,6'(5'*H*)-dione

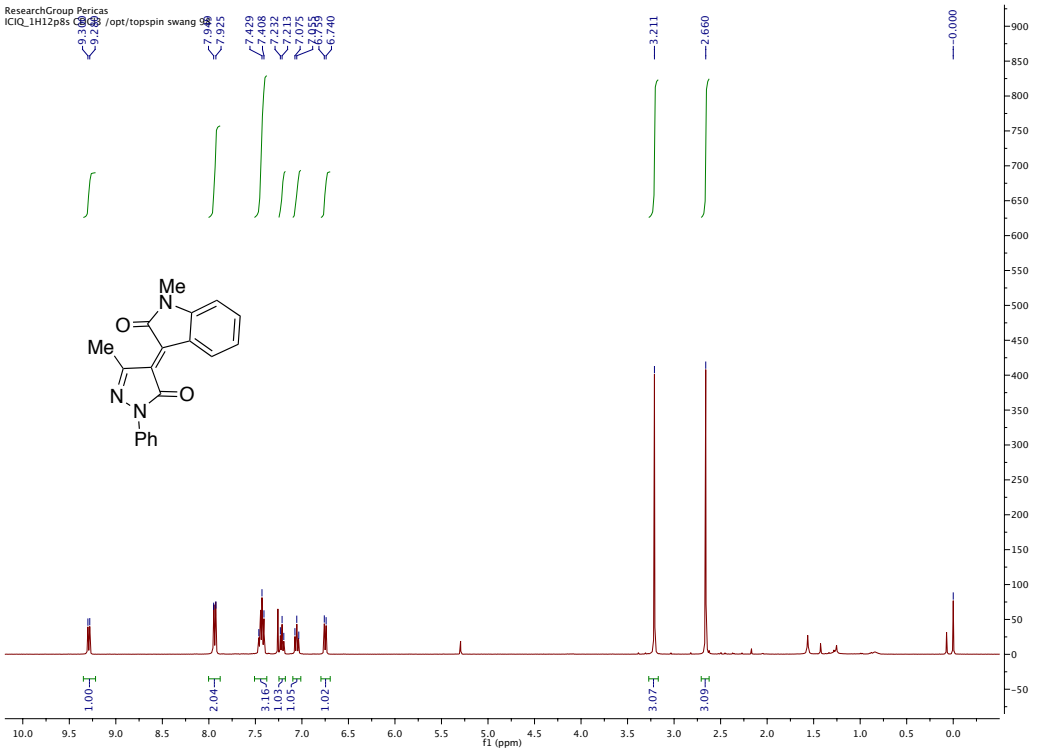


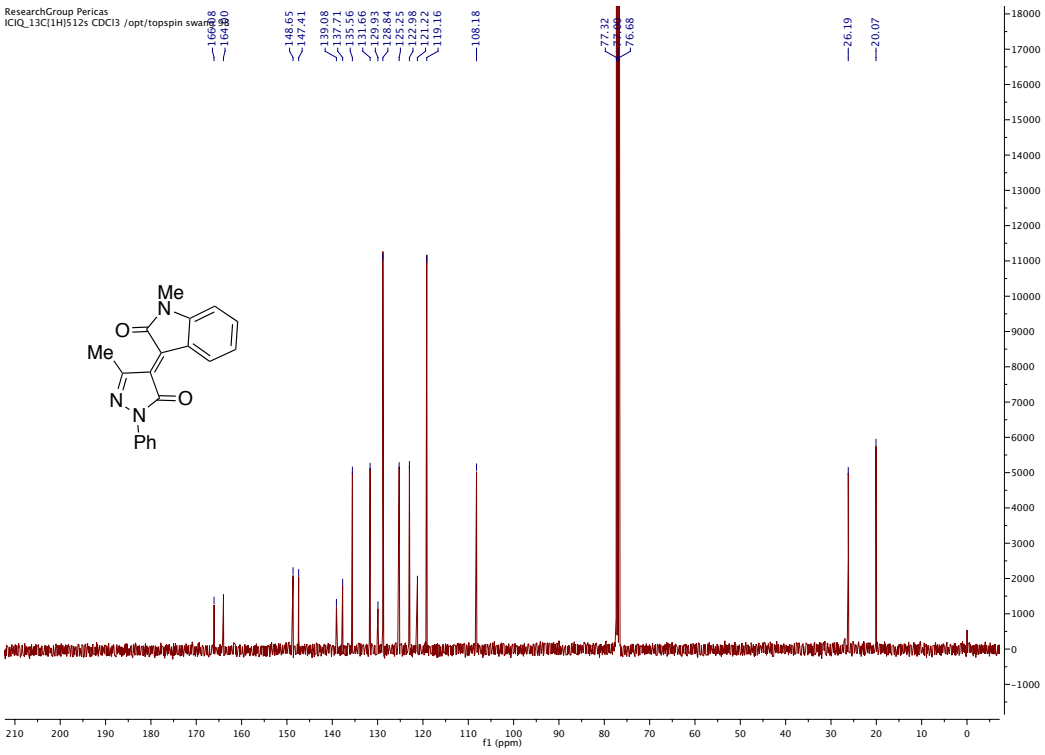
Cycloaddition product **8l** was isolated by FC on silica (eluting from CH_2Cl_2 to CH_2Cl_2/EtOAc 50:1) in 92% yield (3:1 dr) and the major diastereoisomer was isolated in 69% yield. White solid, melting point: 93-95 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (s, 3H), 3.00 (s, 3H), 3.68 (s, 3H), 4.53 (s, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.78-6.81 (m, 1H), 6.91-6.93 (m, 2H), 7.13-7.16 (m, 2H), 7.20-7.24 (m, 1H), 7.31-7.35 (m, 1H), 7.47-7.51 (m, 2H), 7.78-7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 26.4, 52.0, 53.2, 55.8, 97.7, 109.0, 111.7, 114.3, 121.2 (2C), 126.9, 127.9 (2C), 128.1, 128.5, 129.3 (2C), 130.0 (2C), 130.8, 136.4, 137.4, 144.7, 147.4, 156.2, 165.4, 174.6; IR (ATR): ν = 692, 739, 1098, 1233, 1289, 1363, 1454, 1495, 1599, 1712, 1792, 2850, 2925 cm^{-1}; HRMS calcd. for $C_{28}H_{24}N_3O_4$ $[M + H]^+$: 466.1761, found: 466.1764; $[\alpha]_D^{25}$ = +172.0 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 254 nm, 96% ee): t_{major} = 18.9 min, t_{minor} = 13.1 min.

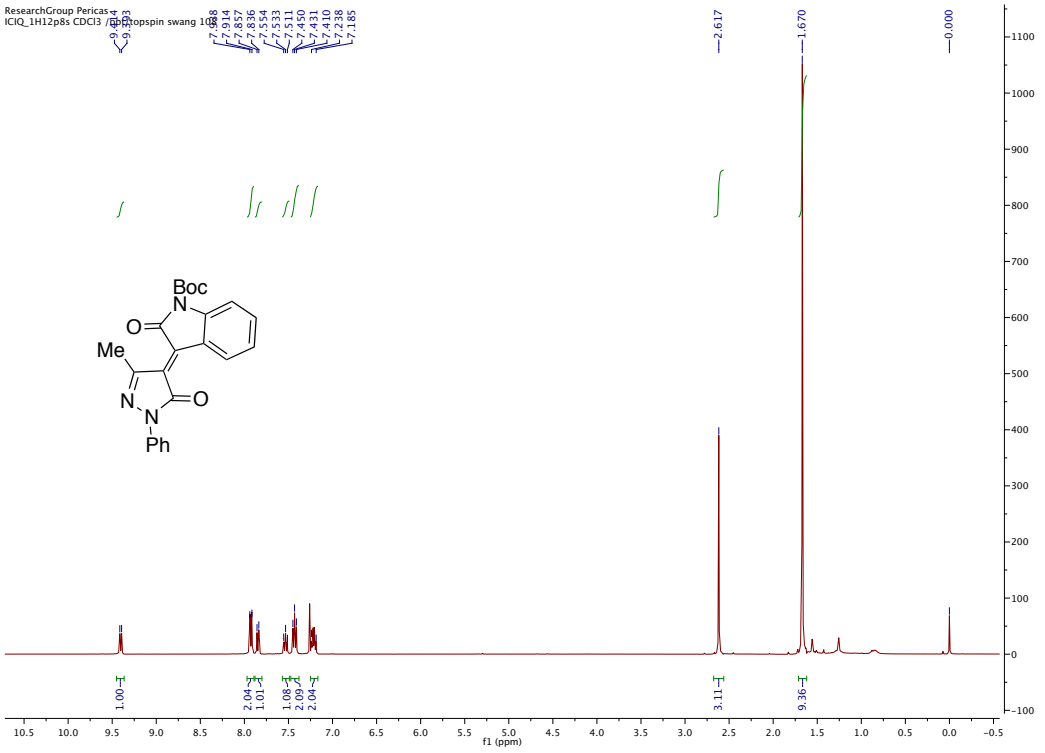
11. References

[1] J. Izquierdo, M. A. Pericàs, *ACS Catal.* **2016**, *6*, 348-356.
[2] Y. A. El-Ossaily, R. M. Zaki, S. A. Metwally, *J. Sci. Res.* **2014**, *6*, 293-307.
[3] Q. Chen, J. Liang, S. Wang, D. Wang, R. Wang, *Chem. Commun.* **2013**, *49*, 1657-1659.
[4] L. C. Morrill, J. Douglas, T. Lebl, A. M. Z. Slawin, D. J. Fox, A. D. Smith, *Chem. Sci.* **2013**, *4*, 4146-4155.

12. ^{1}H and ^{13}C NMR spectra



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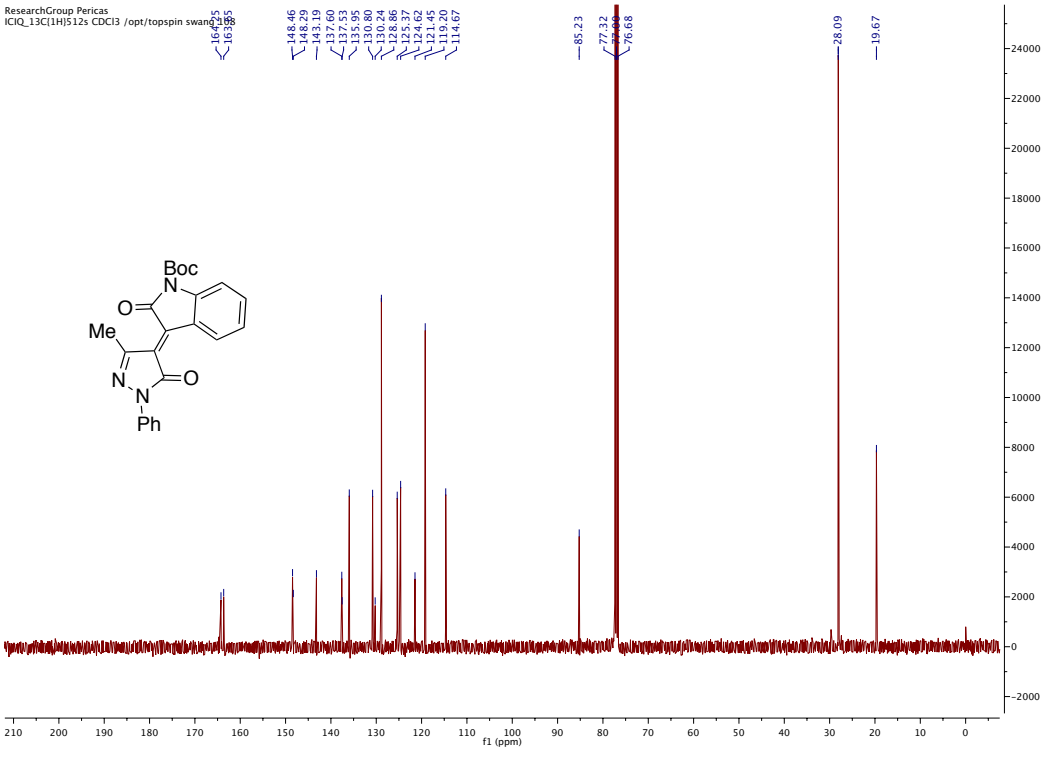
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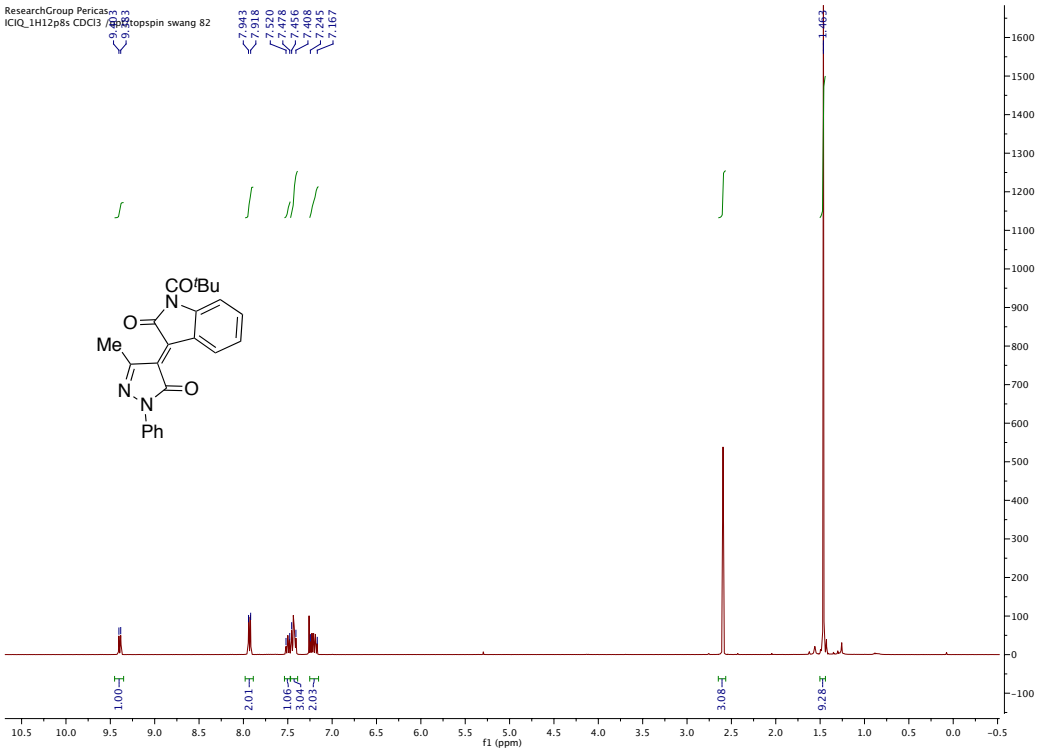
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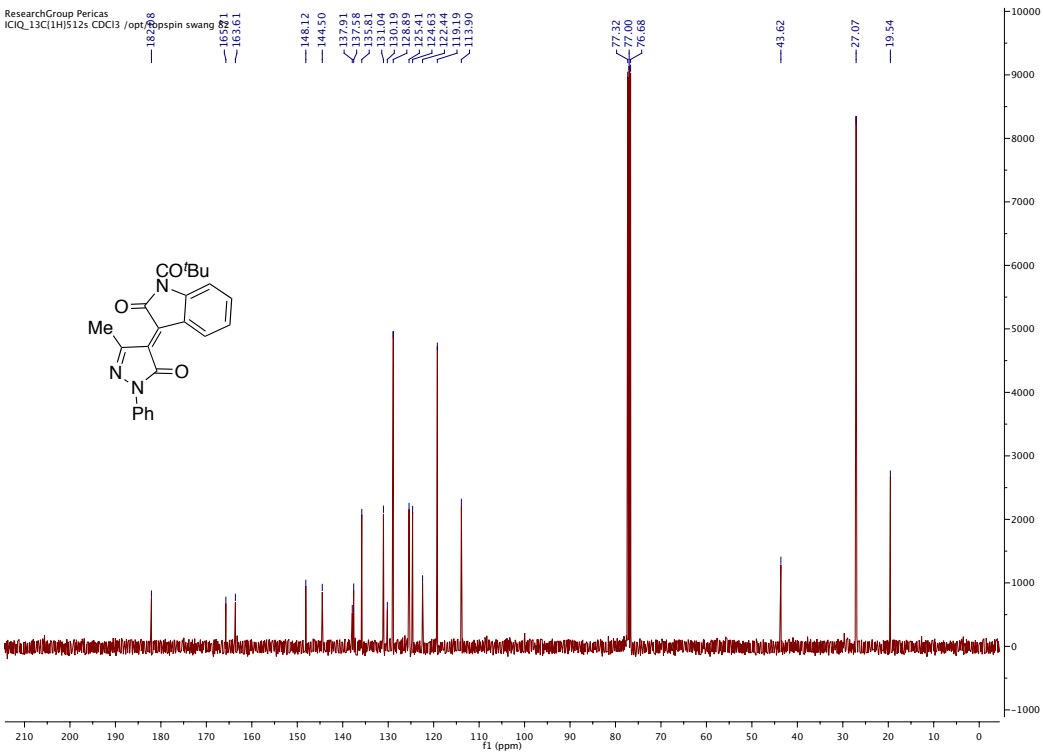
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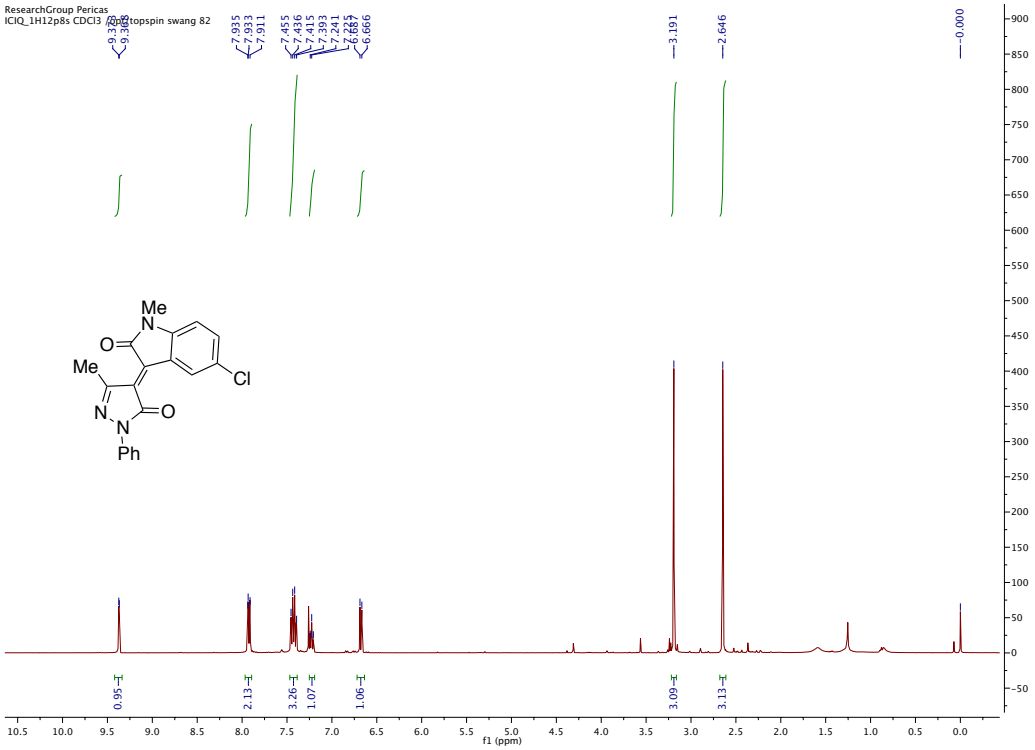
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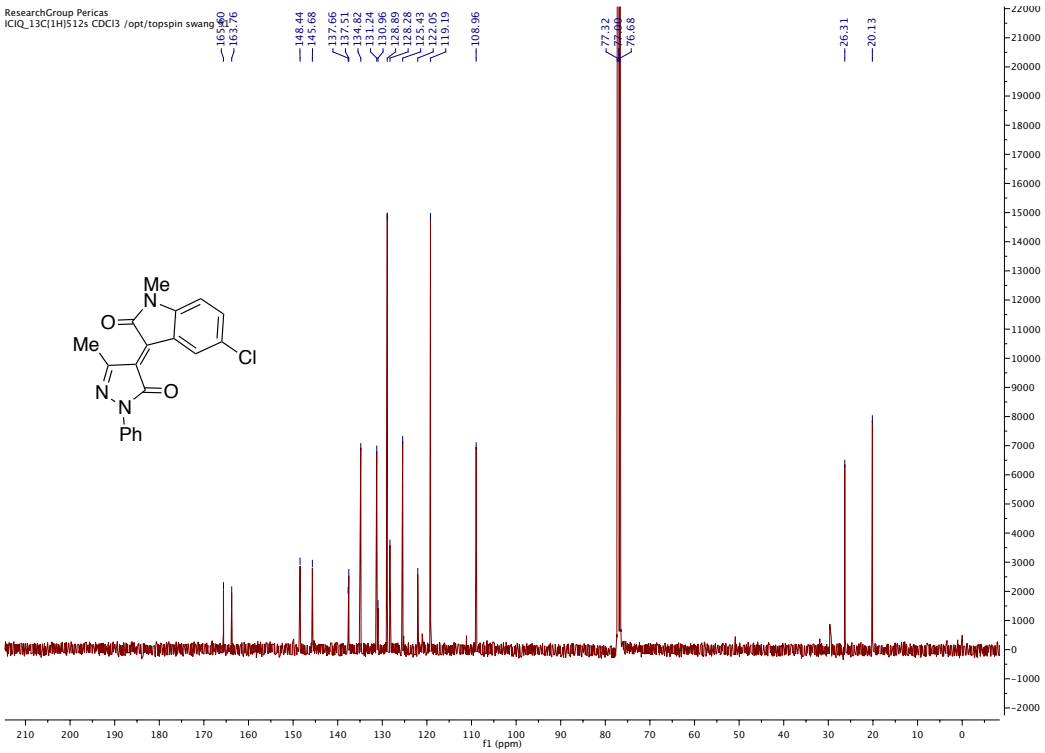
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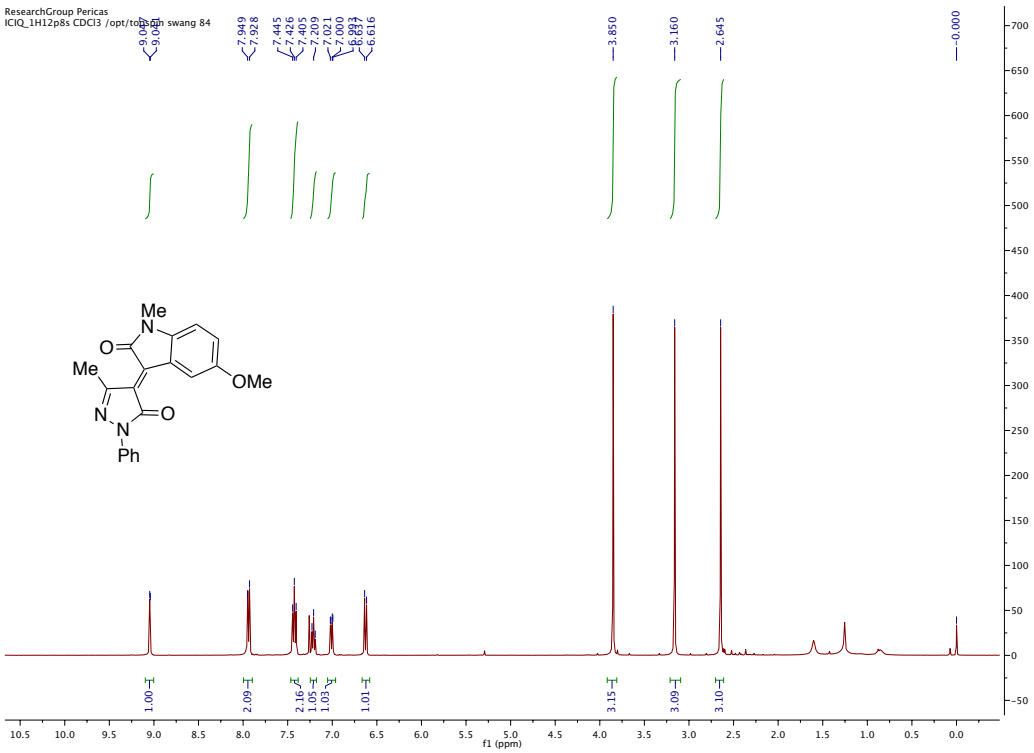
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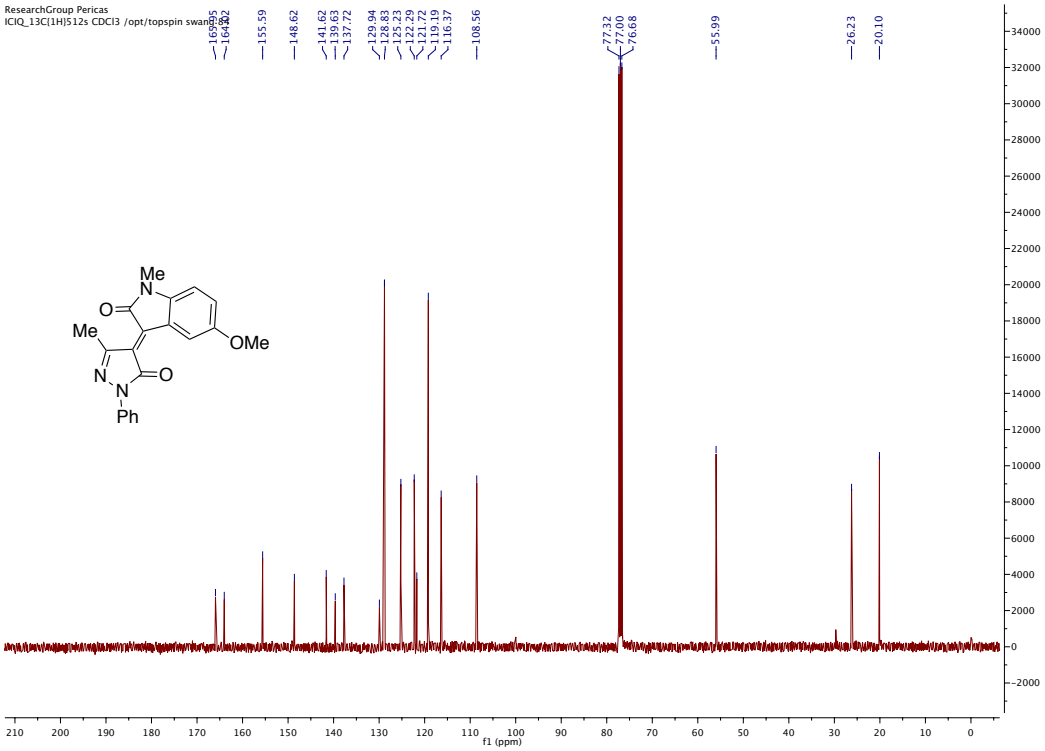
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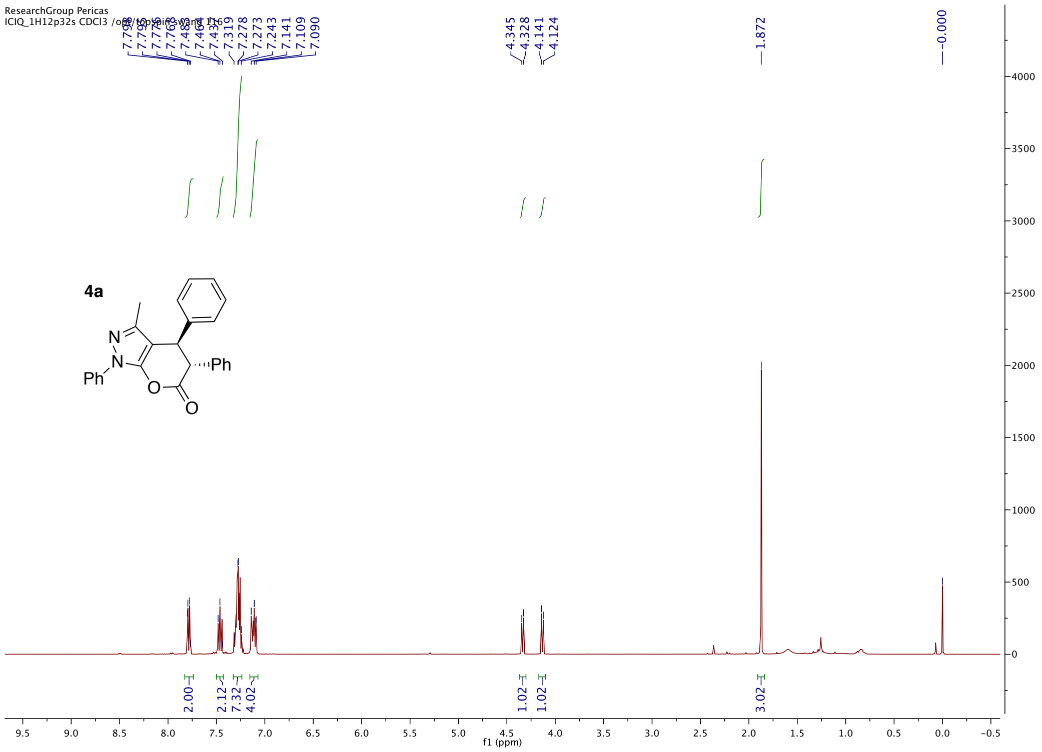
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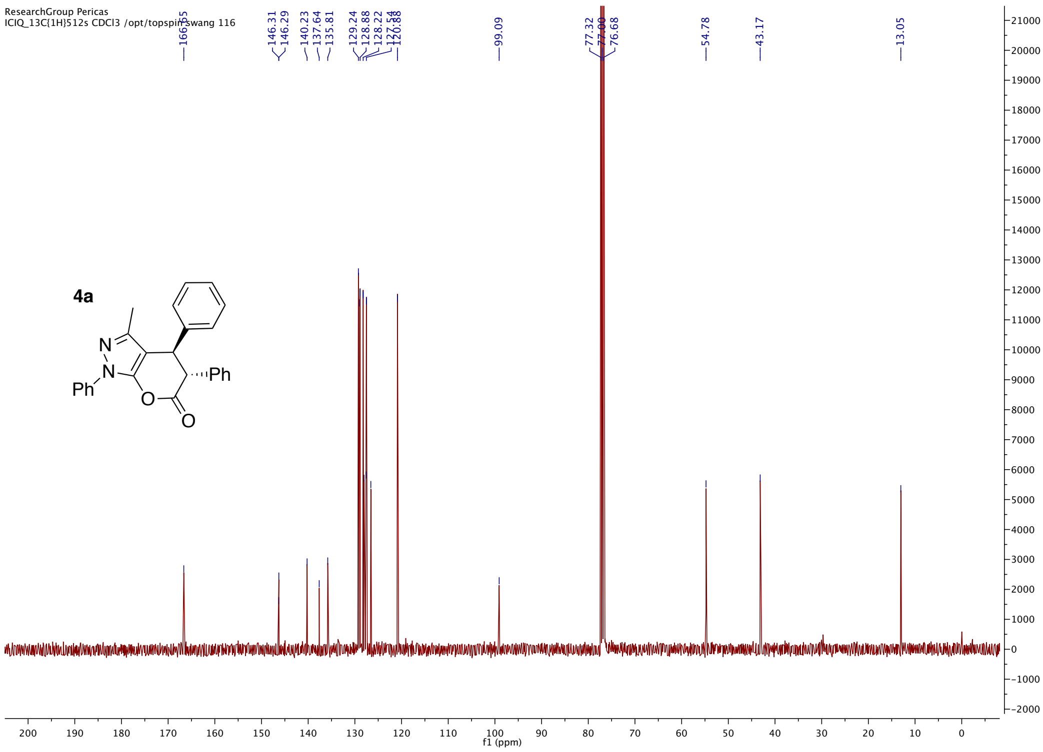
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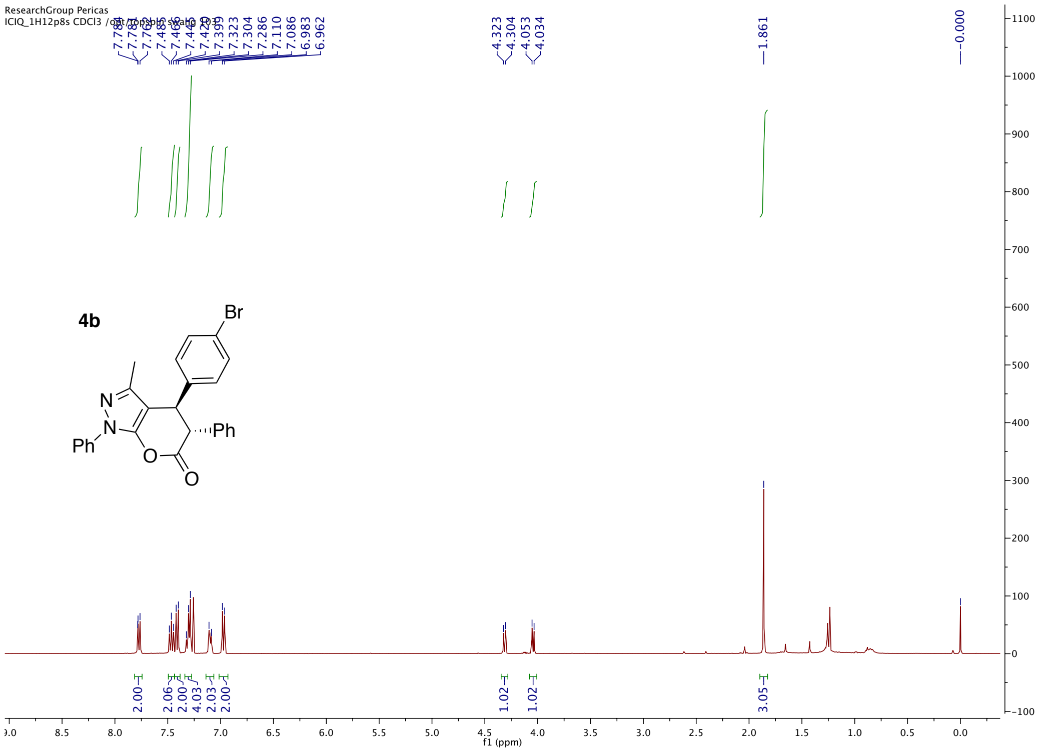
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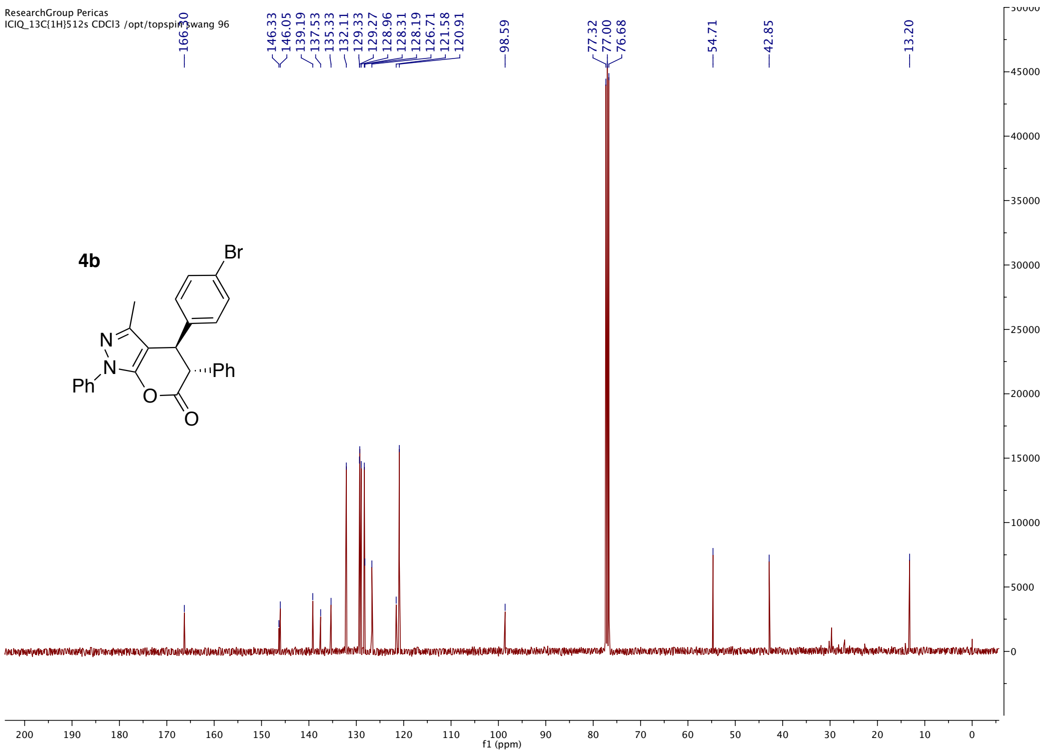
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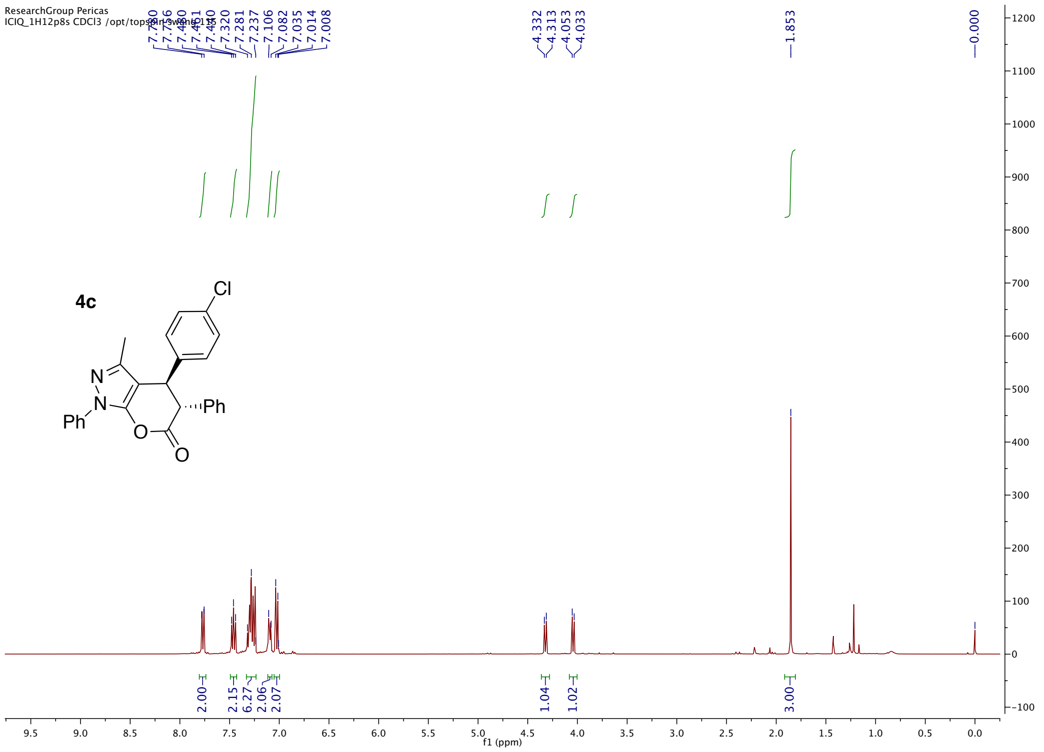
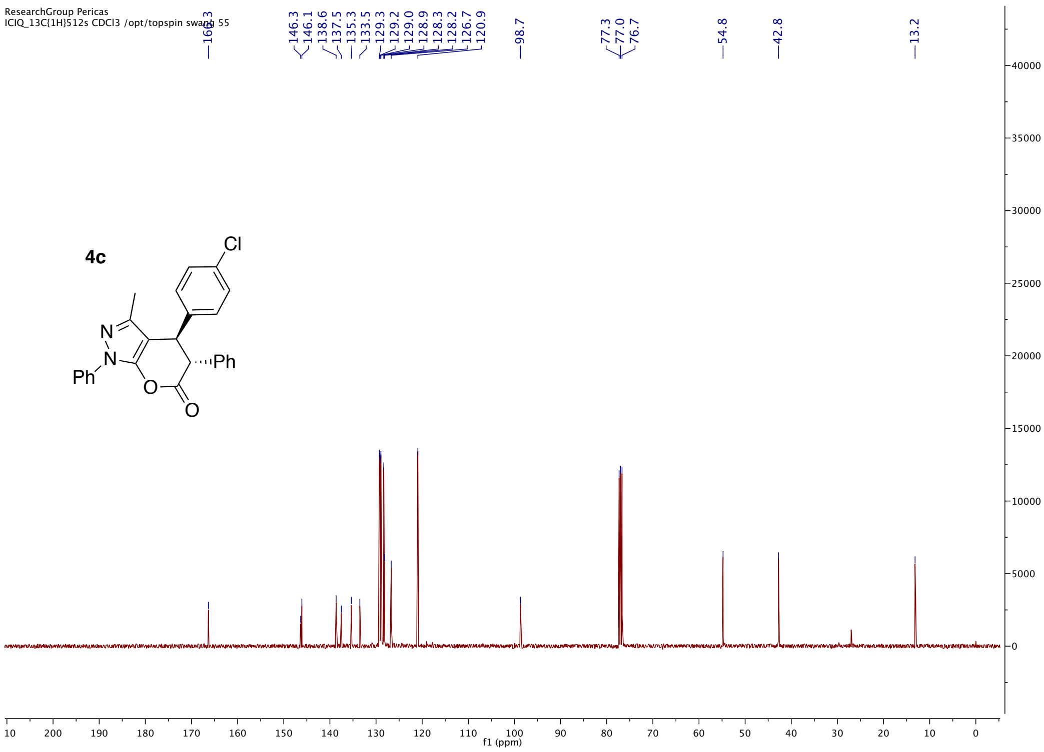
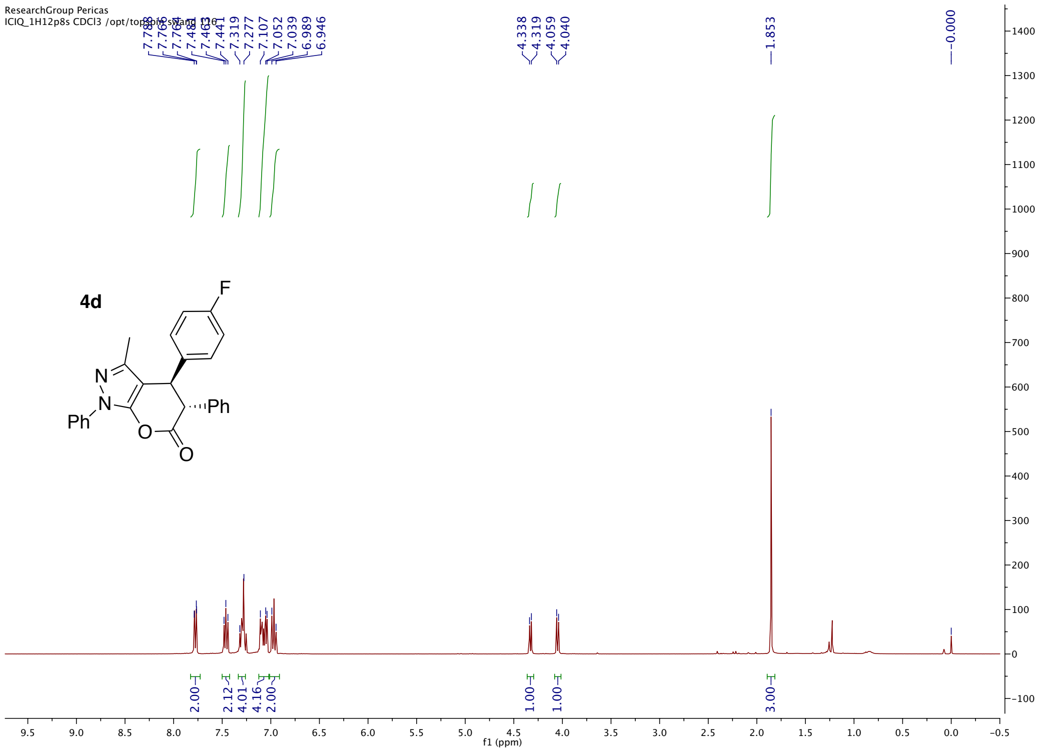
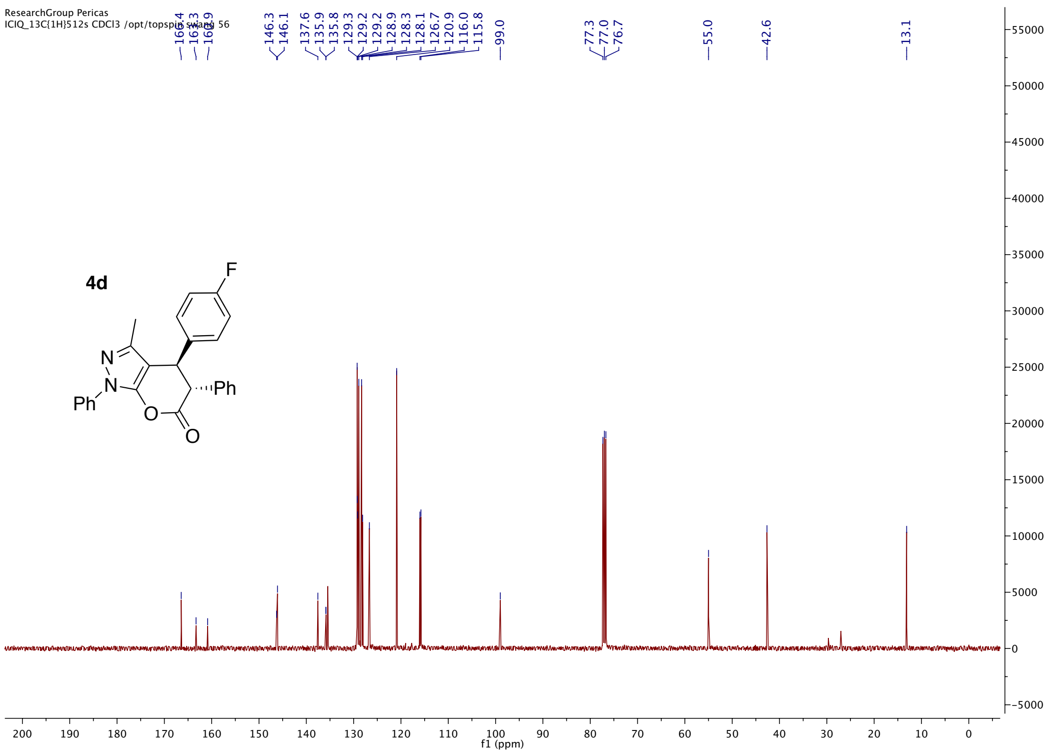
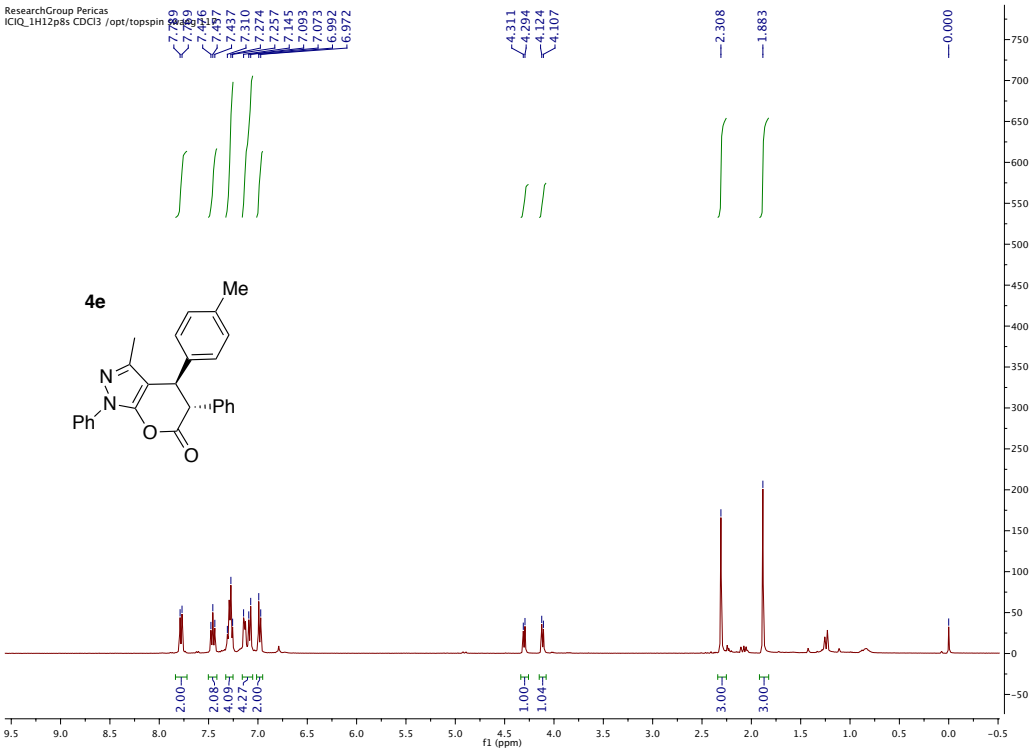
128.31
128.19
126.71
121.58
120.91
98.59
77.32
77.00
76.68
54.71
42.85
13.20
4b
Br
N
N
Ph
O
O
Ph
f1 (ppm)

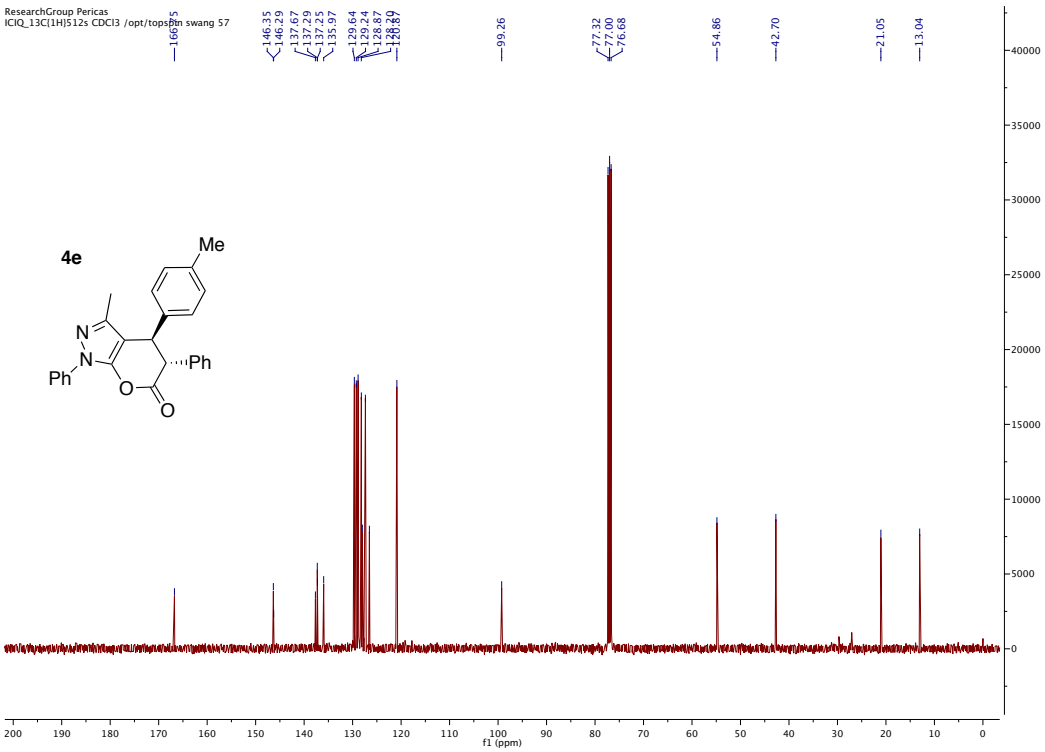

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 15
4c
f1 (ppm)

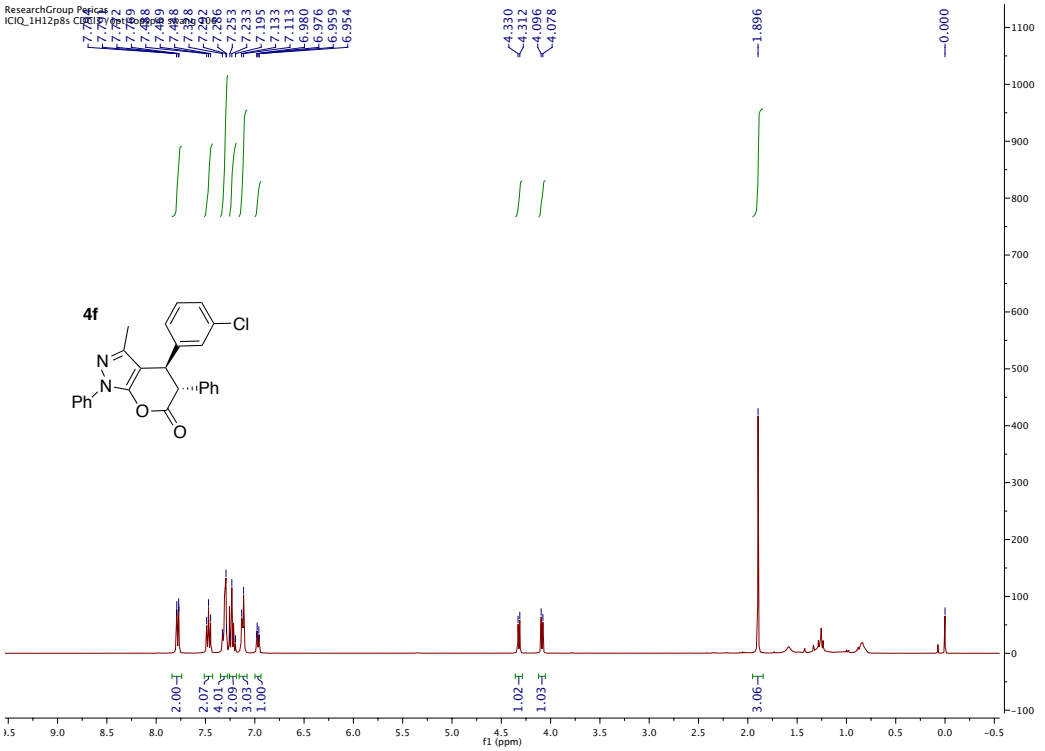

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 55
4c
f1 (ppm)

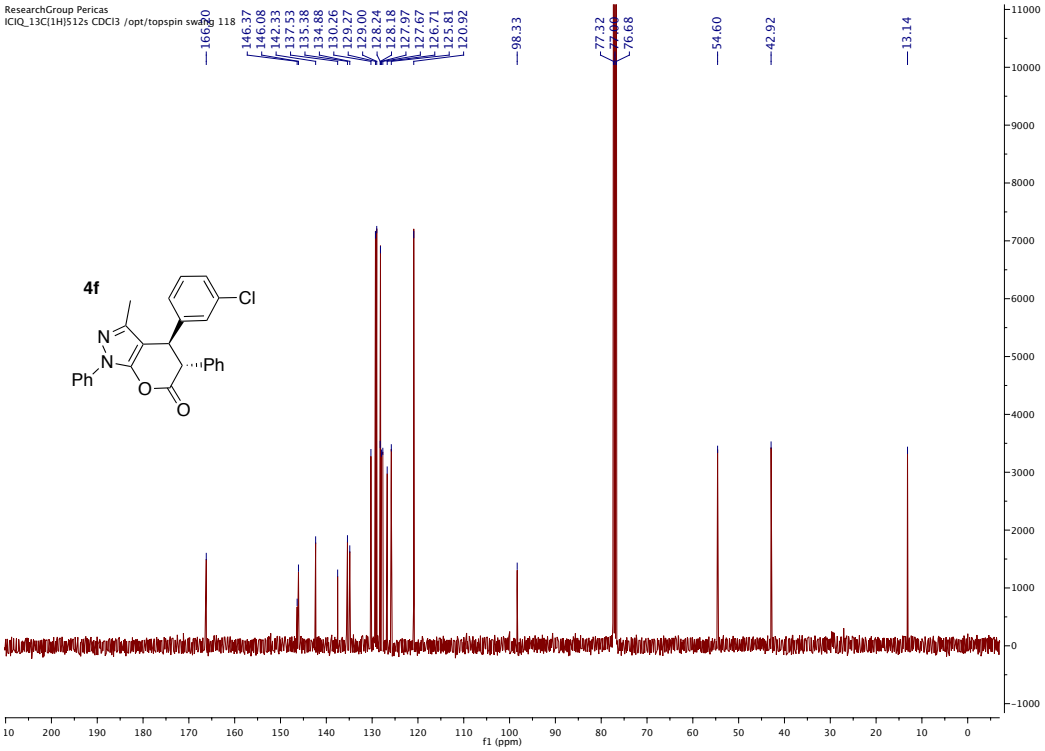


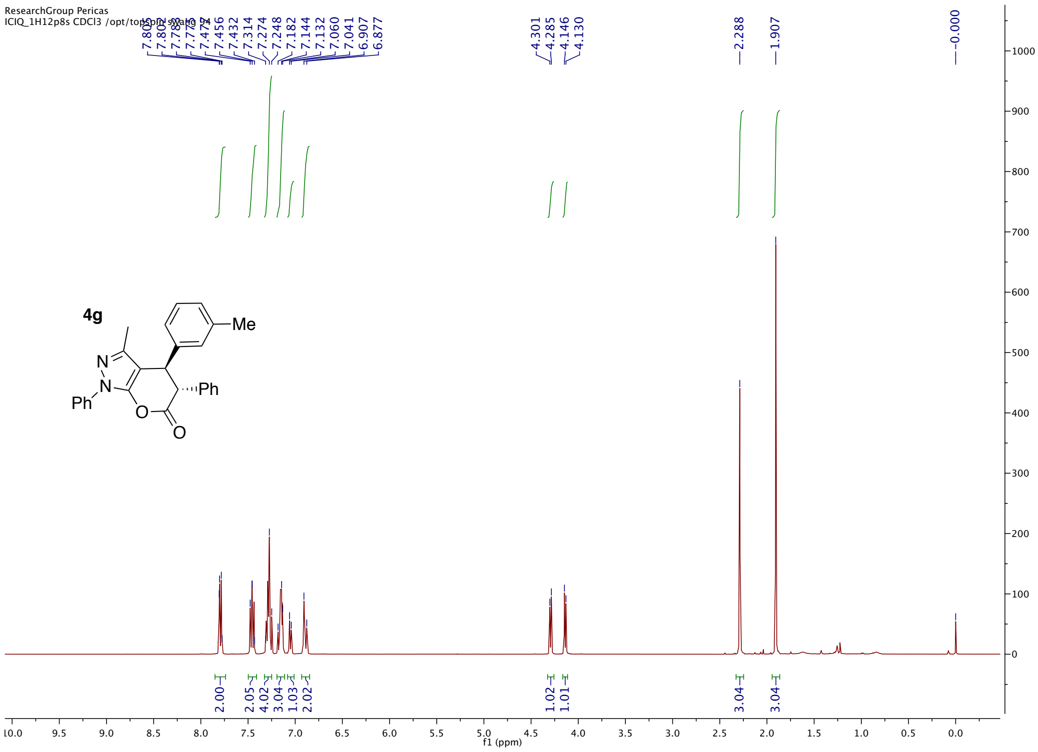


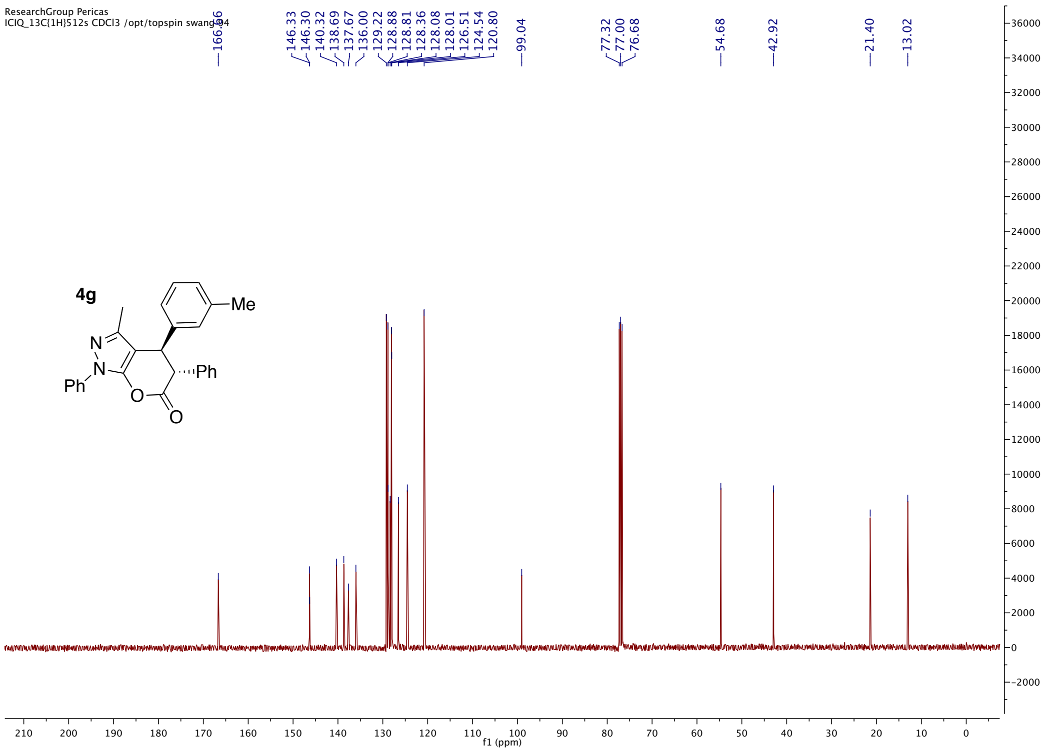

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin
7.789
7.769
7.456
7.437
7.310
7.274
7.257
7.145
7.093
7.073
6.992
6.972
4.311
4.294
4.124
4.107
2.308
1.883
0.000
4e
Me
N
N
Ph
O
Ph
O
2.00
2.08
4.09
4.27
2.00
1.00
1.04
3.00
3.00
f1 (ppm)

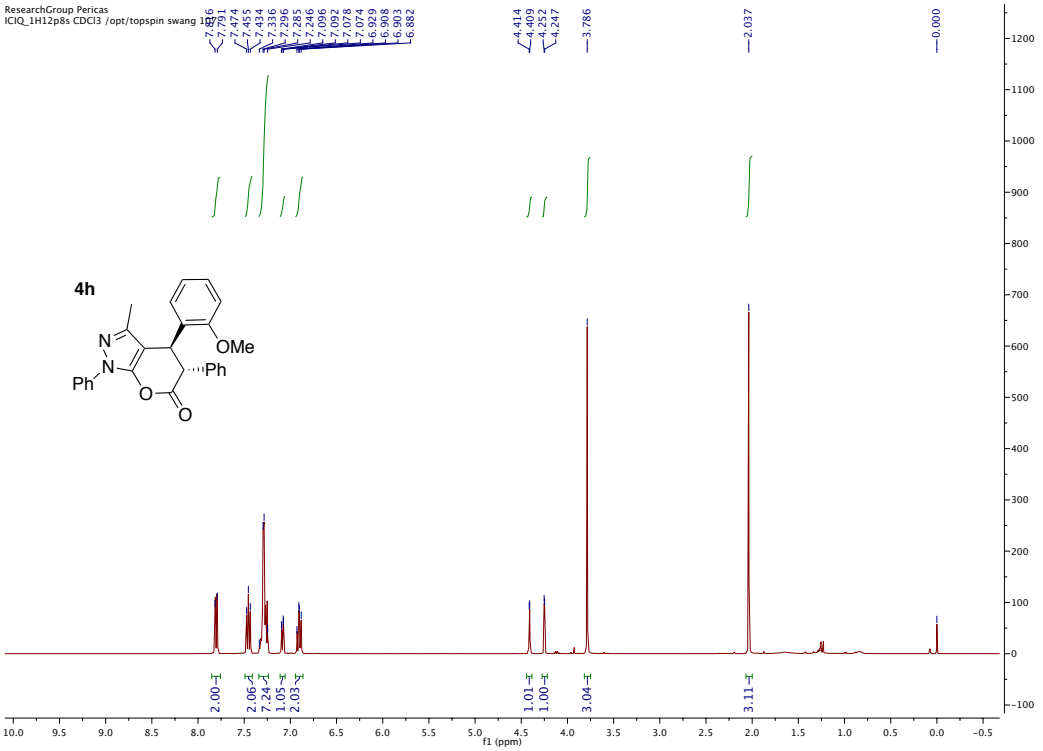

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 57
166.35
146.35
146.29
137.67
137.29
137.25
133.97
129.64
129.24
128.87
99.26
77.32
77.00
76.68
54.86
42.70
21.05
13.04
4e
Me
N
N
Ph
O
Ph
O
f1 (ppm)

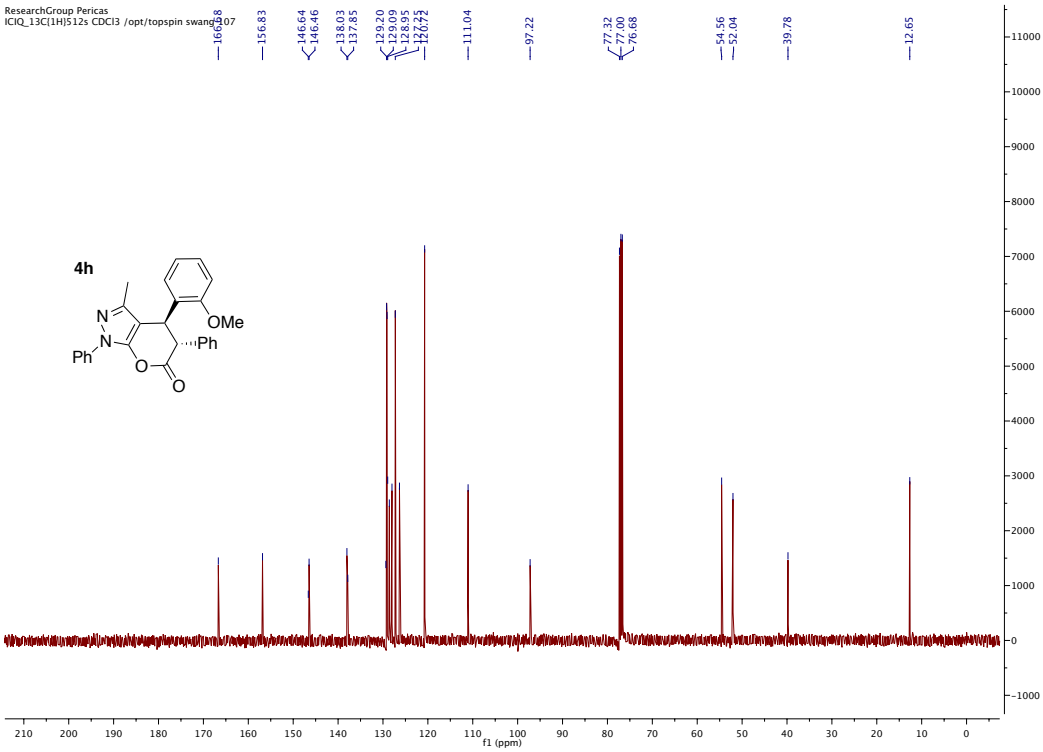

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 118
4f
Cl
Ph
Ph
N
N
O
O
f1 (ppm)

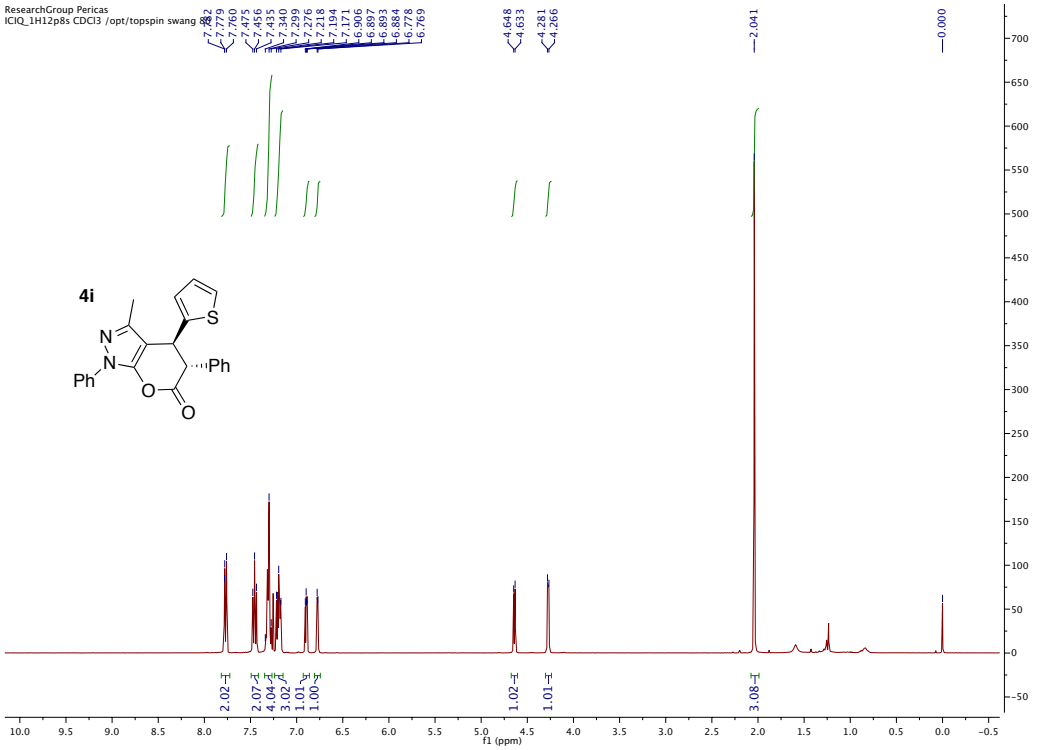

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 118
4f
Cl
Ph
Ph
N
N
O
O
f1 (ppm)

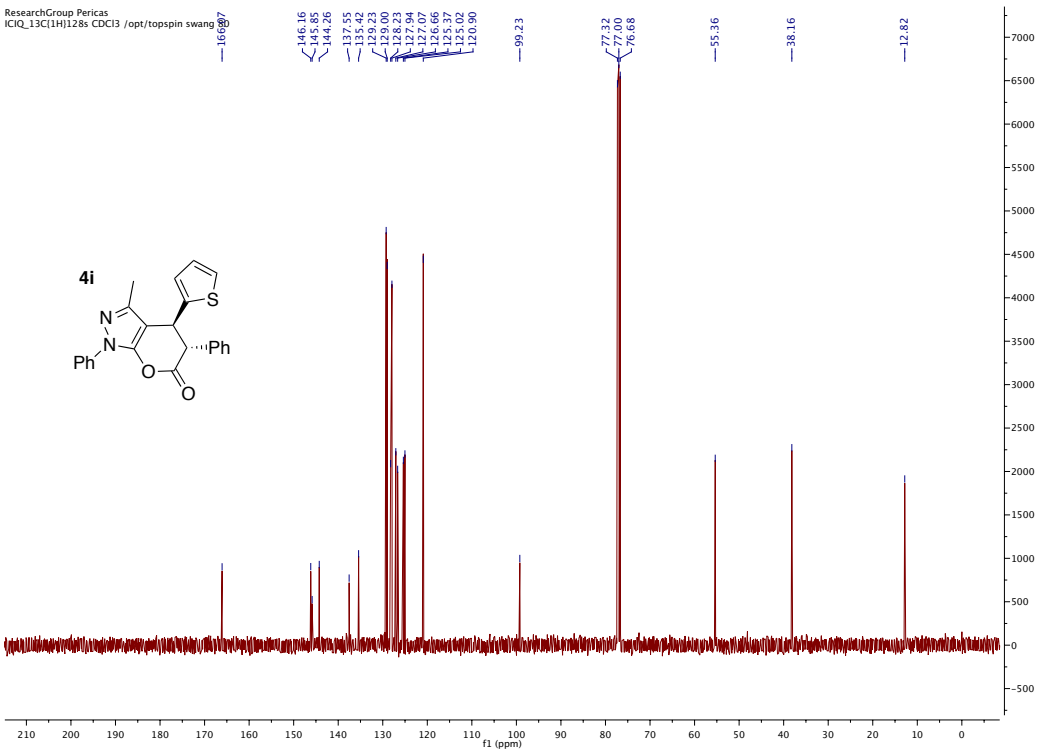

ResearchGroup Pericas
4g
Me
Ph
f1 (ppm)

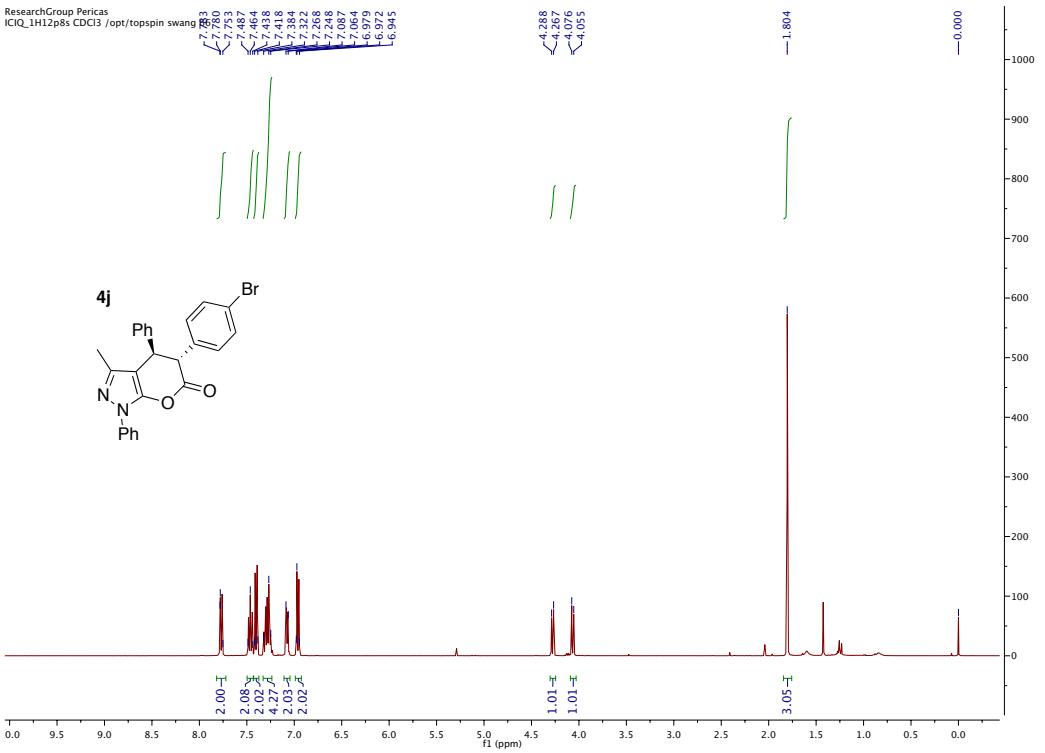

ResearchGroup Pericas
4g
Me
Ph
f1 (ppm)

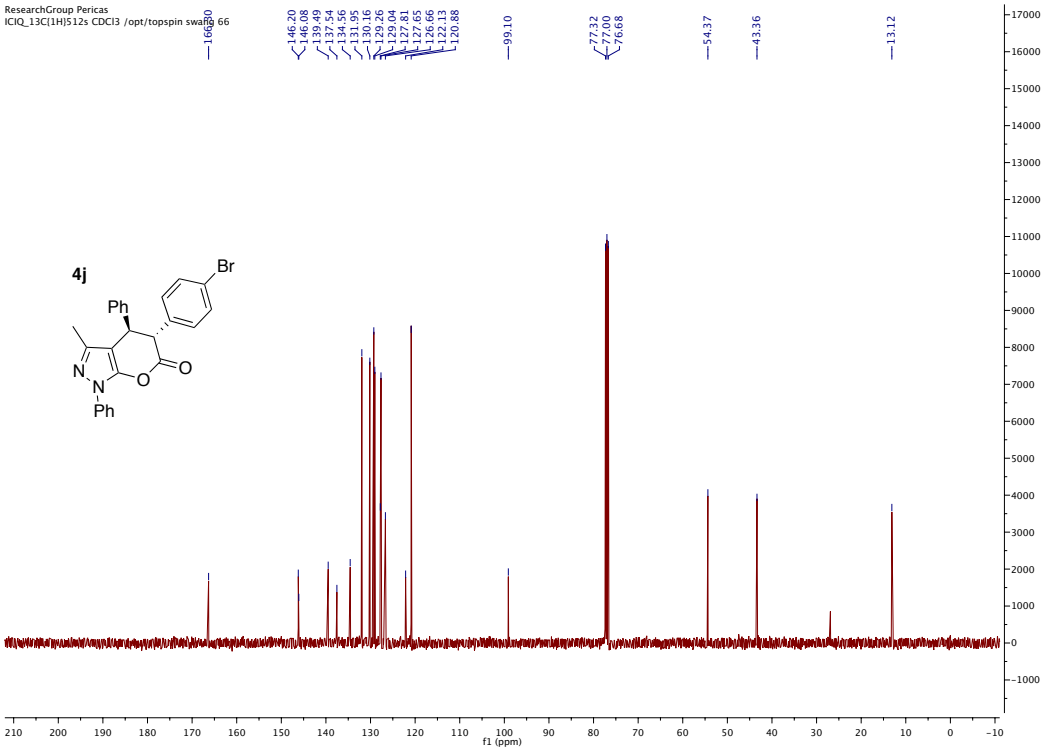

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 1
7.816
7.791
7.774
7.455
7.434
7.336
7.296
7.285
7.246
7.096
7.092
7.078
7.074
6.929
6.908
6.903
6.882
4.414
4.409
4.252
4.247
3.786
2.037
0.000
4h
N
N
Ph
O
O
OMe
Ph
2.00
2.06
7.24
1.05
2.03
1.01
1.00
3.04
3.11
f1 (ppm)

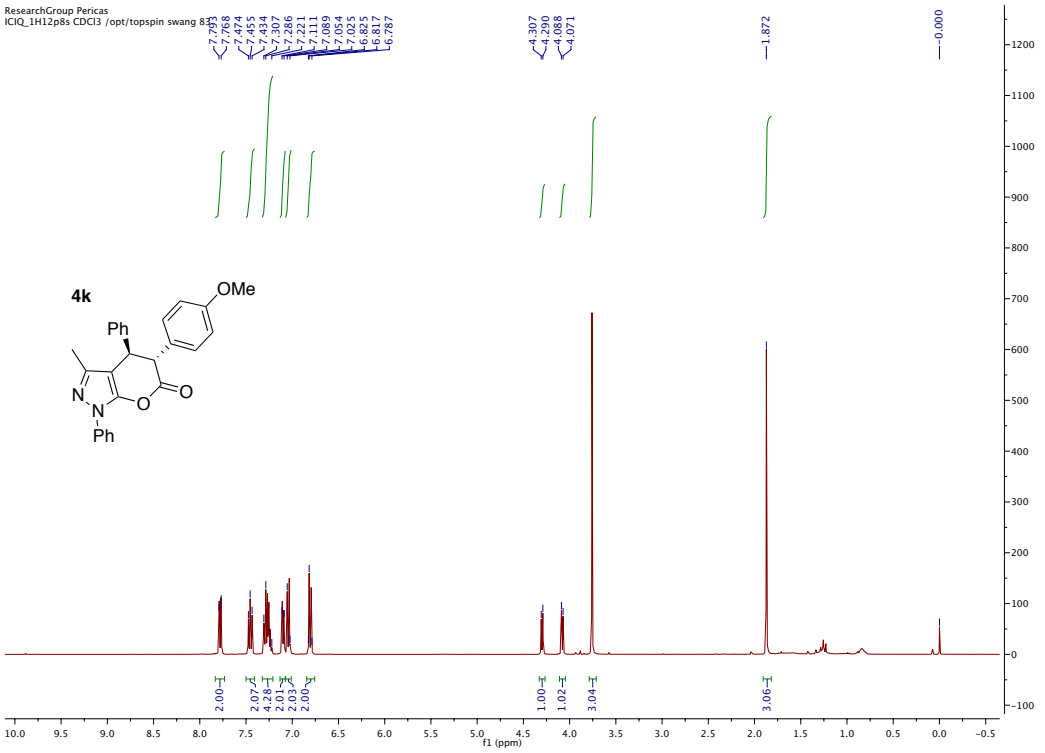

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 107
168.68
156.83
146.64
146.46
138.03
137.85
129.20
129.09
128.95
120.73
120.53
111.04
97.22
77.32
77.00
76.68
54.56
52.04
39.78
12.65
4h
N
N
Ph
O
O
OMe
Ph
f1 (ppm)

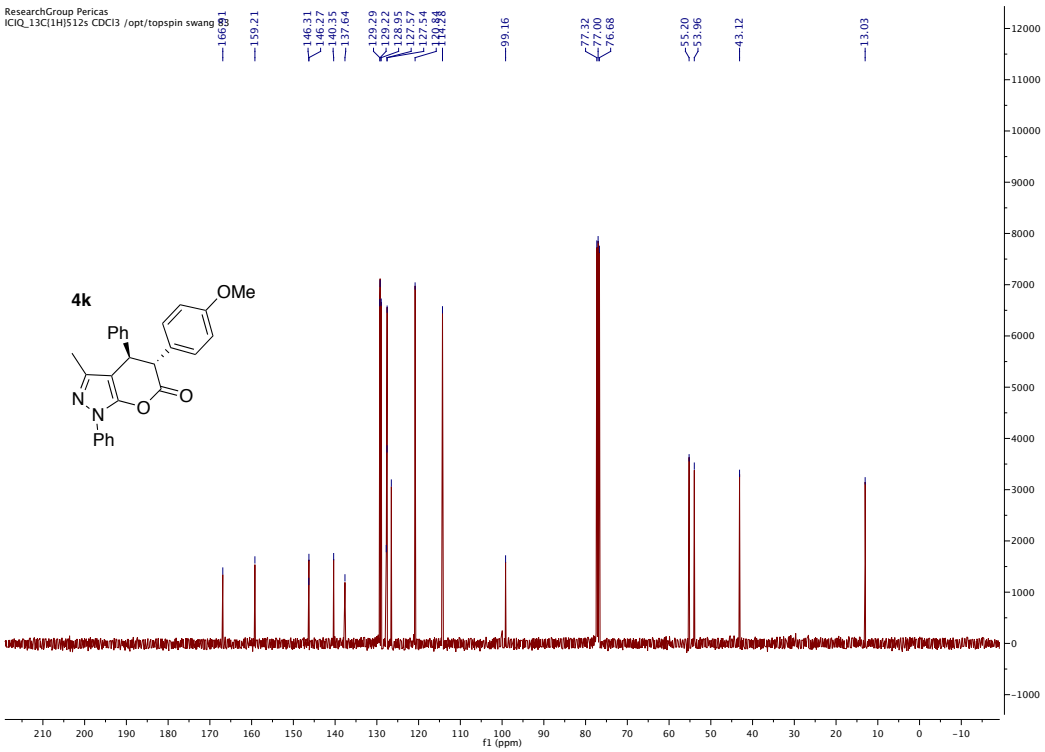

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang
4i
f1 (ppm)

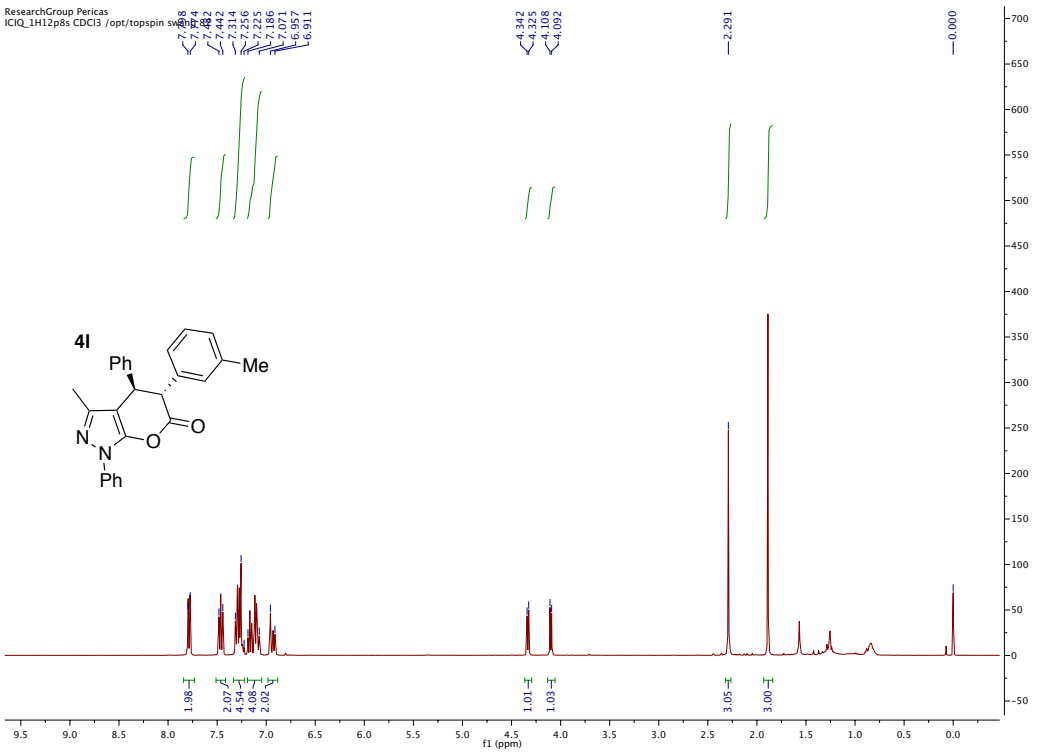

ResearchGroup Pericas
ICIQ_13C{1H}128s CDCl3 /opt/topspin swang
4i
f1 (ppm)

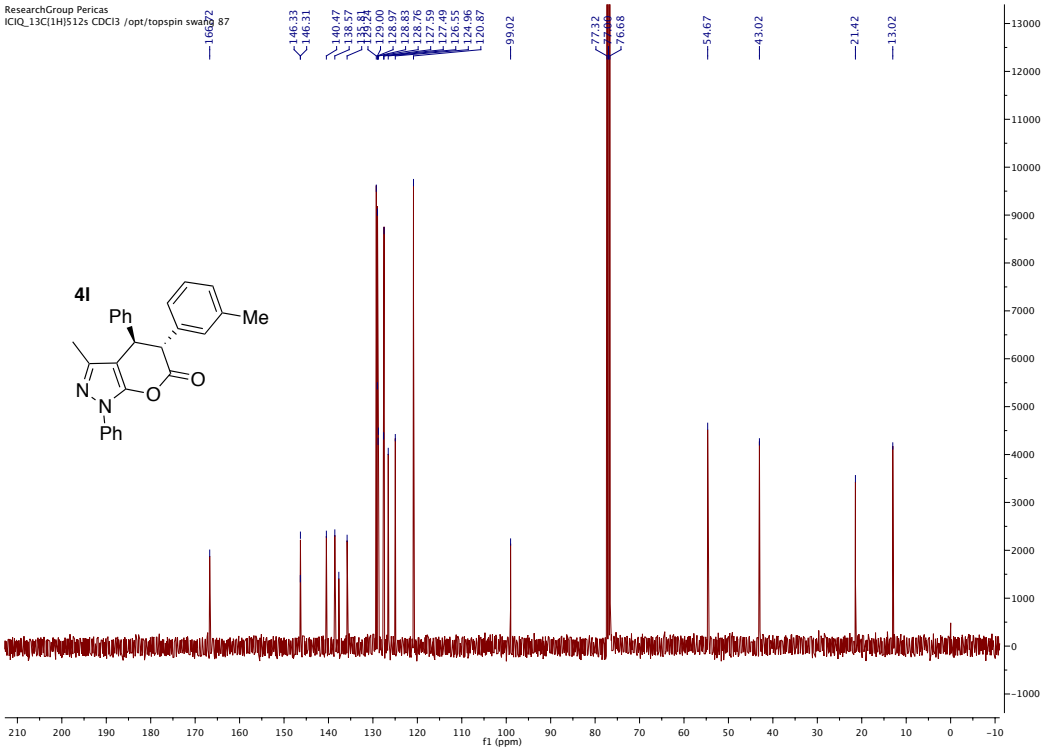

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 33
7.793
7.780
7.753
7.487
7.464
7.438
7.418
7.384
7.332
7.268
7.248
7.087
7.064
6.979
6.972
6.945
4.288
4.267
4.076
4.055
1.804
0.000
4j
Br
Ph
N
N
O
O
Ph
2.00
2.08
2.02
4.27
2.03
2.02
1.01
1.01
3.05
f1 (ppm)

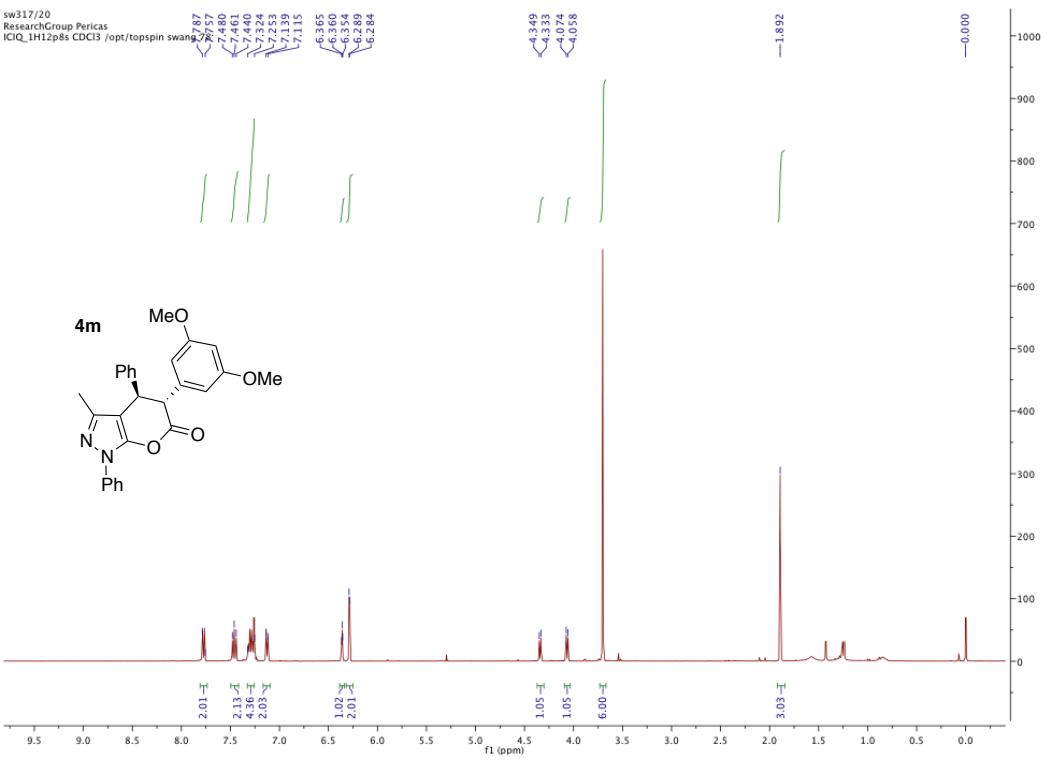

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 66
166.80
146.20
146.08
139.49
137.54
134.56
131.95
130.16
129.26
129.04
127.81
127.65
126.66
122.13
120.88
99.10
77.32
77.00
76.68
54.37
43.36
13.12
4j
Br
Ph
N
N
O
O
Ph
f1 (ppm)

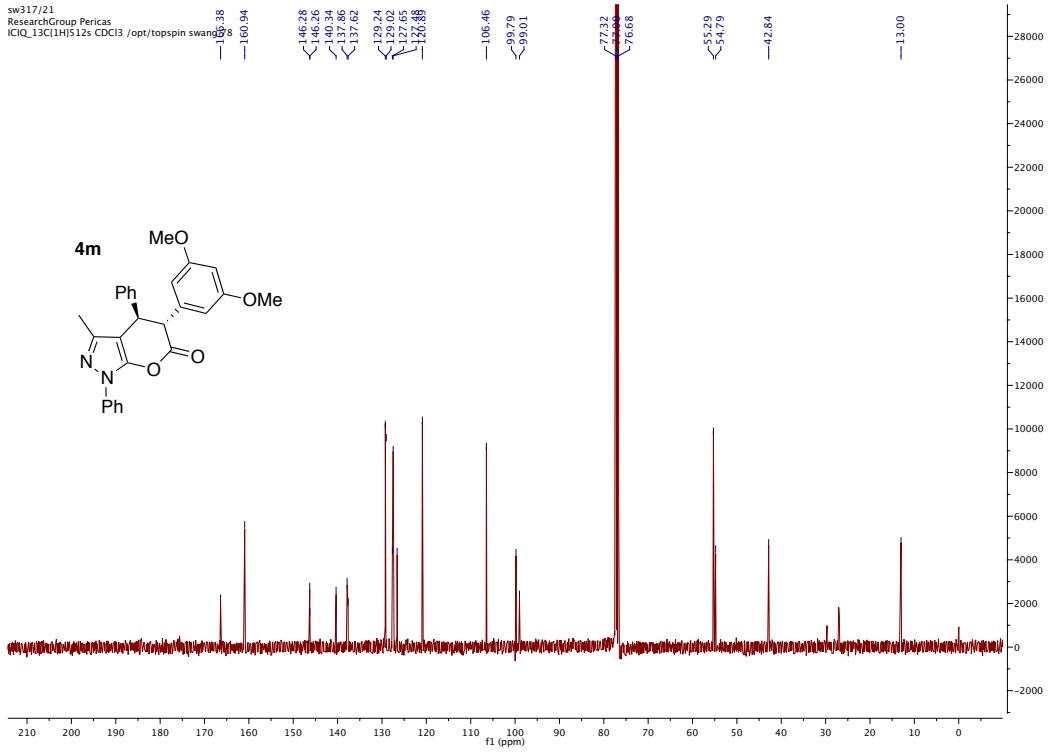

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 83
7.793
7.768
7.474
7.455
7.434
7.307
7.286
7.221
7.111
7.089
7.054
7.025
6.825
6.817
6.787
4.307
4.290
4.088
4.071
1.872
0.000
4k
OMe
Ph
N
N
O
O
Ph
2.00
2.07
4.28
2.01
2.03
2.00
1.00
1.02
3.04
3.06
f1 (ppm)

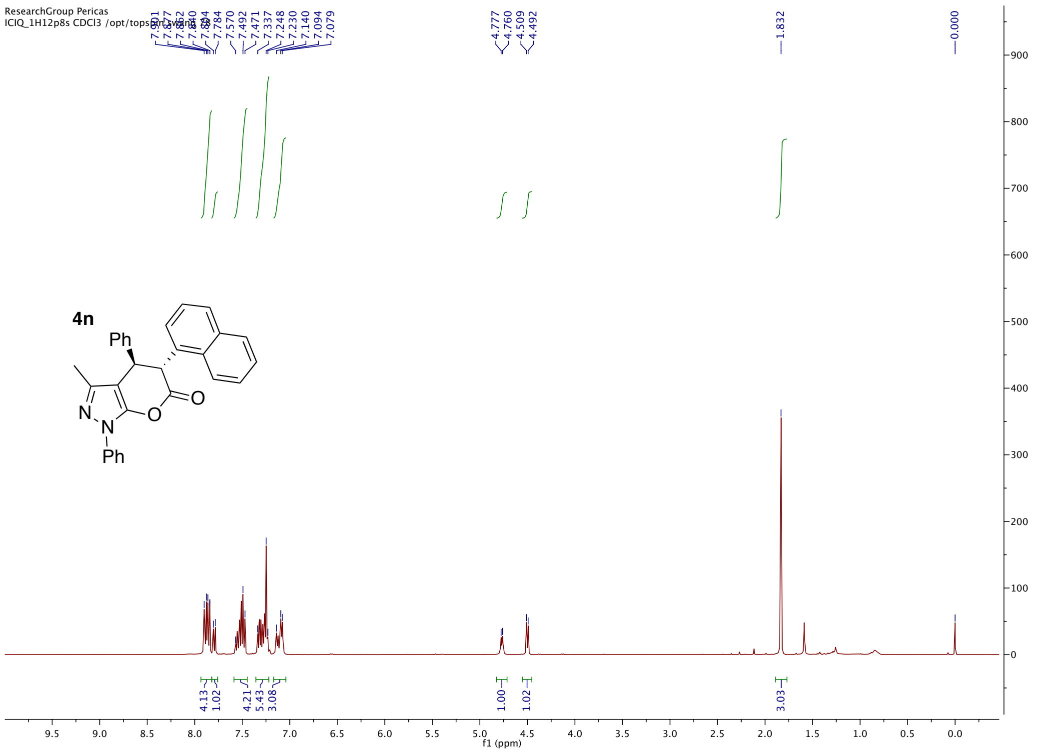

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 83
166.31
159.21
146.31
146.27
140.35
137.64
129.29
129.22
128.95
127.57
127.54
99.16
77.32
77.00
76.68
55.20
53.96
43.12
13.03
4k
OMe
Ph
N
N
O
O
Ph
f1 (ppm)

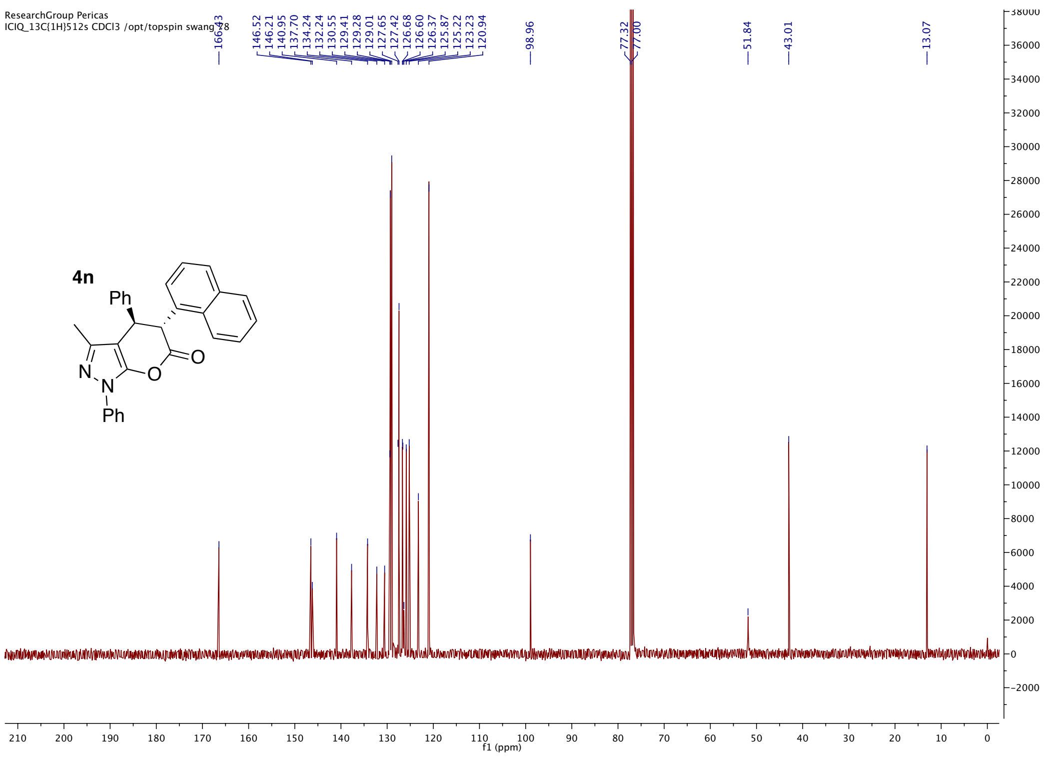

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swans 87
4I
Ph
Me
N
N
O
O
Ph
f1 (ppm)

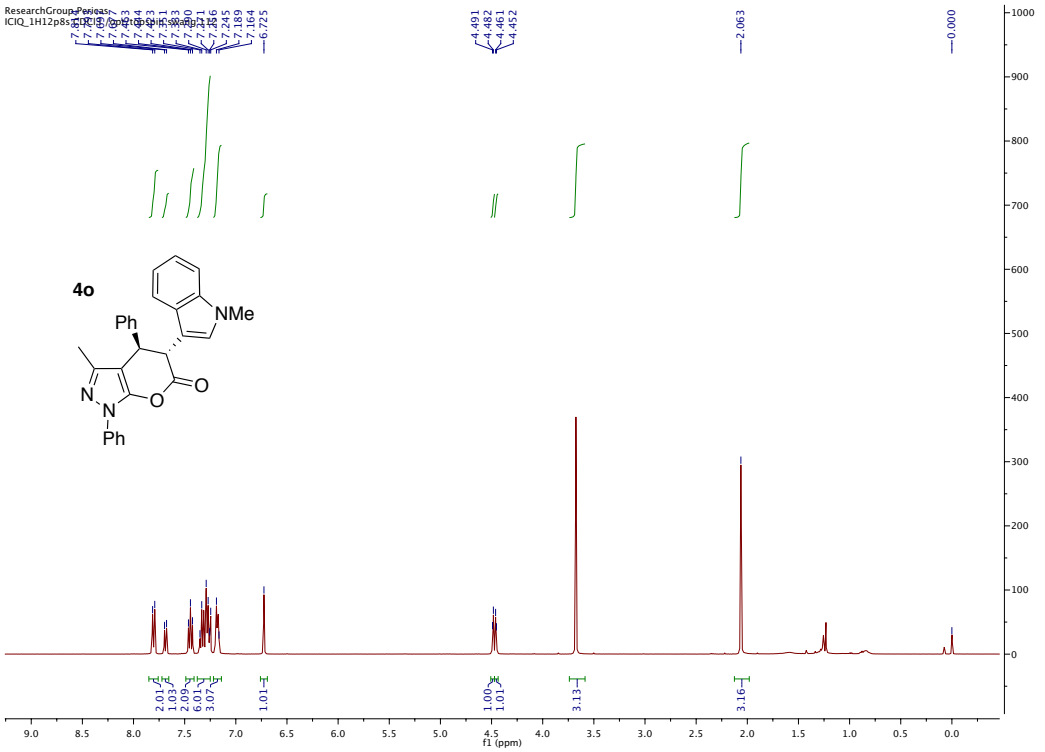

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swans 87
4I
Ph
Me
N
N
O
O
Ph
f1 (ppm)

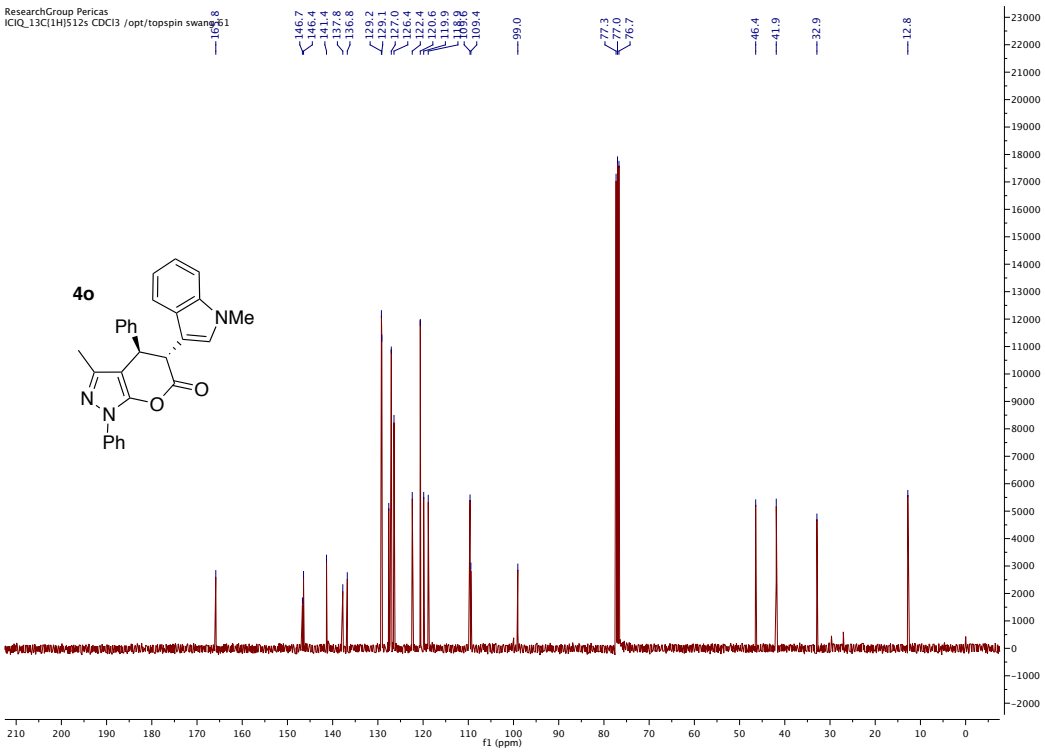

sw317/20
ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 78
4m
MeO
OMe
Ph
N
N
O
O
Ph
f1 (ppm)

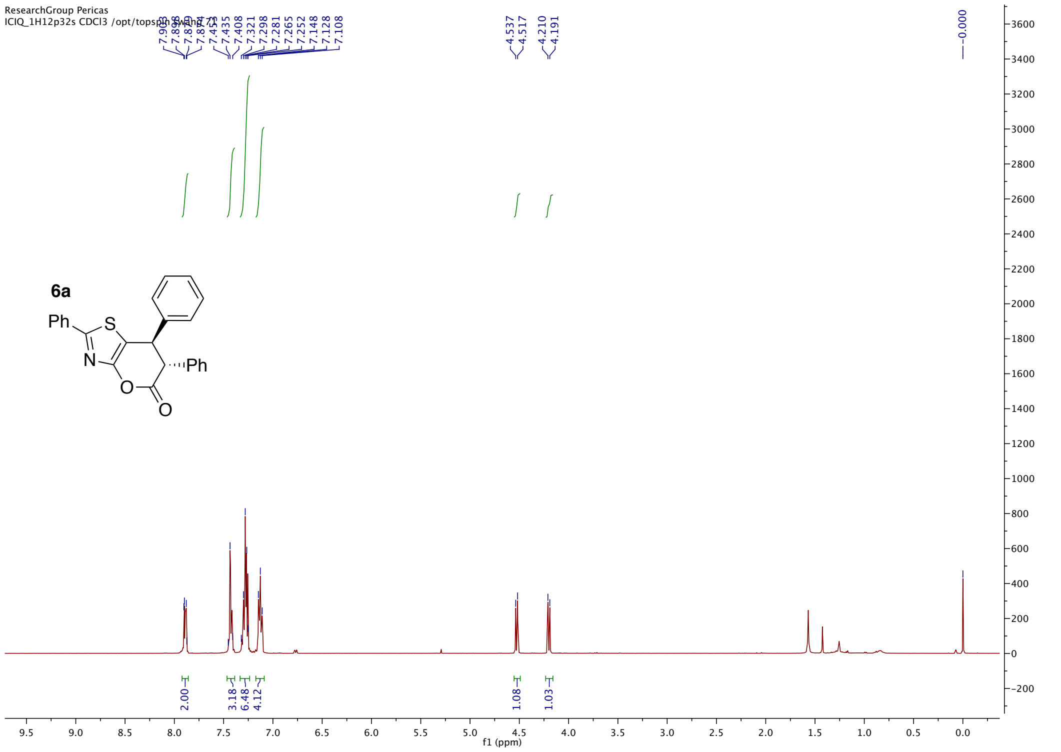

sw317/21
ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 78
4m
MeO
OMe
Ph
N
N
O
O
Ph
f1 (ppm)

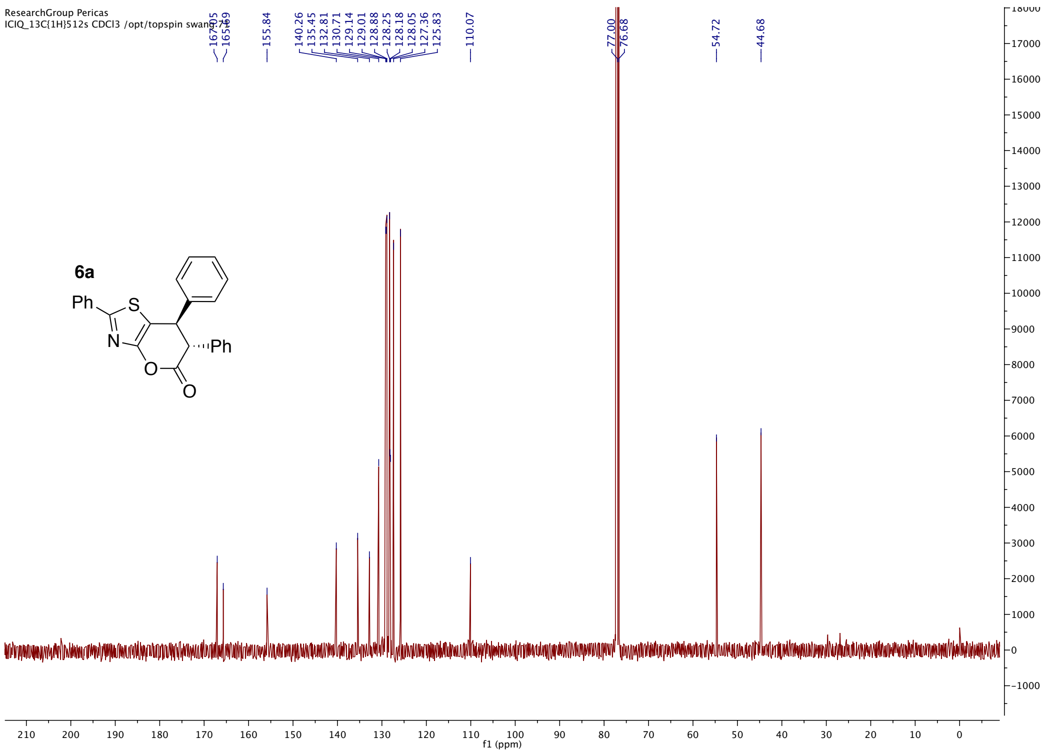

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang
4n
Ph
N
N
O
O
Ph
4.777
4.760
4.509
4.492
1.832
0.000
4.13
1.02
4.21
5.43
3.08
1.00
1.02
3.03
f1 (ppm)

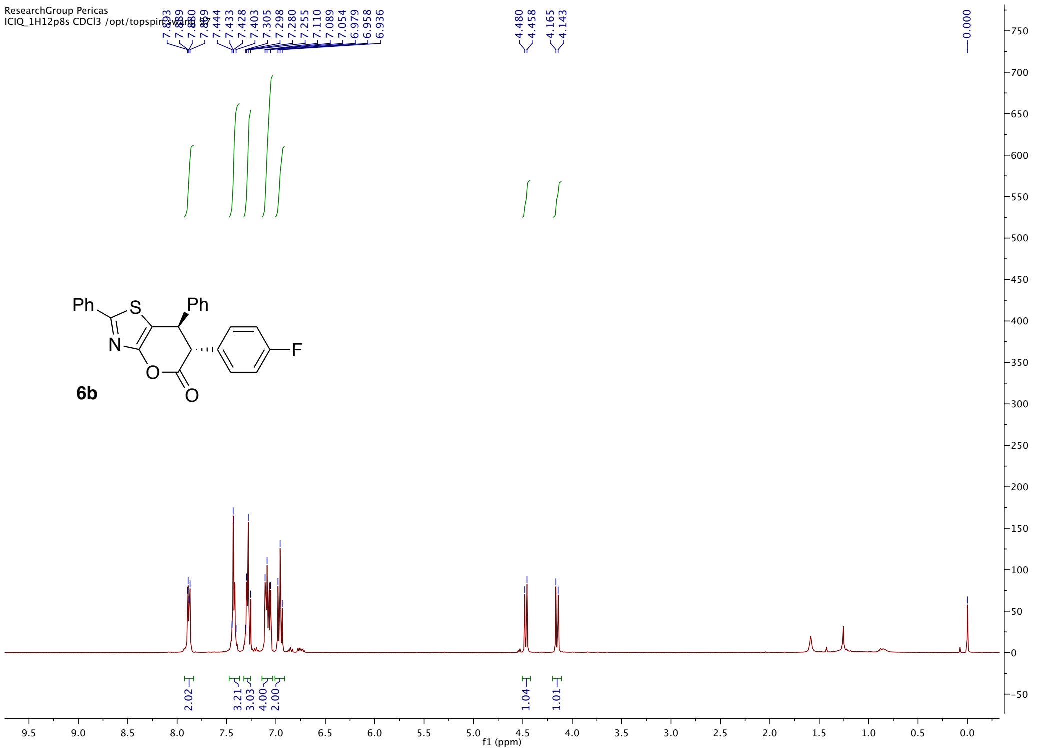

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 78
166.43
146.52
146.21
140.95
137.70
134.24
132.24
130.55
129.41
129.28
129.01
127.65
127.42
126.68
126.60
126.37
125.87
125.22
123.23
120.94
98.96
77.32
77.00
51.84
43.01
13.07
4n
Ph
N
N
O
O
Ph
f1 (ppm)

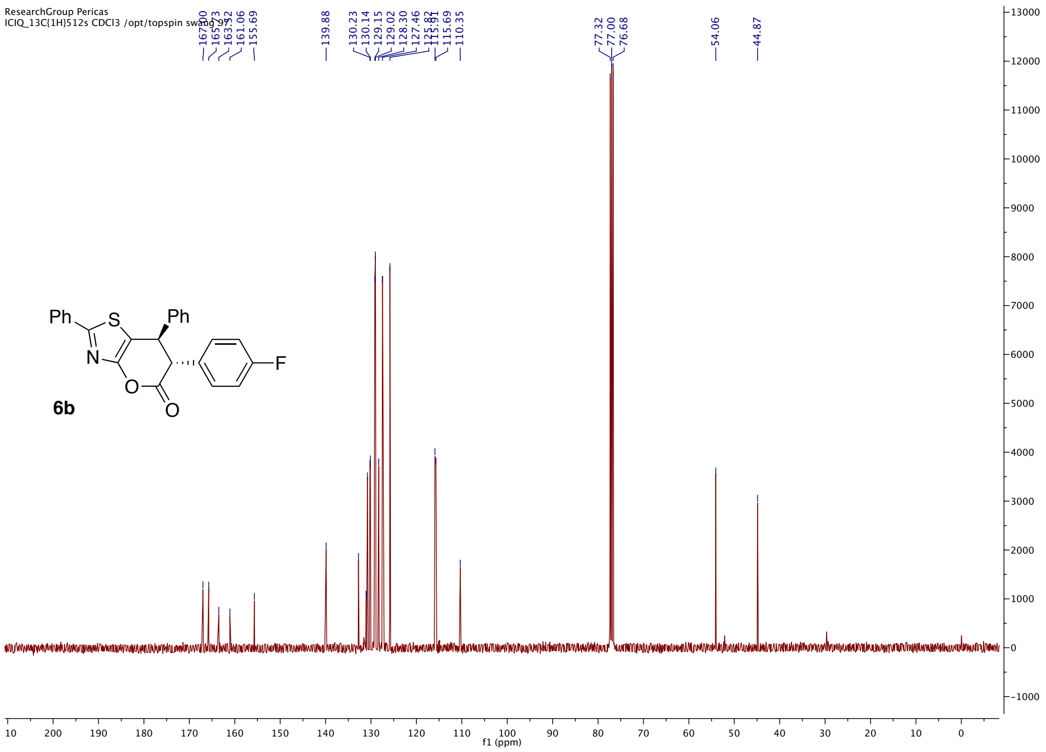

4o
Ph
NMe
N
N
O
O
Ph
f1 (ppm)

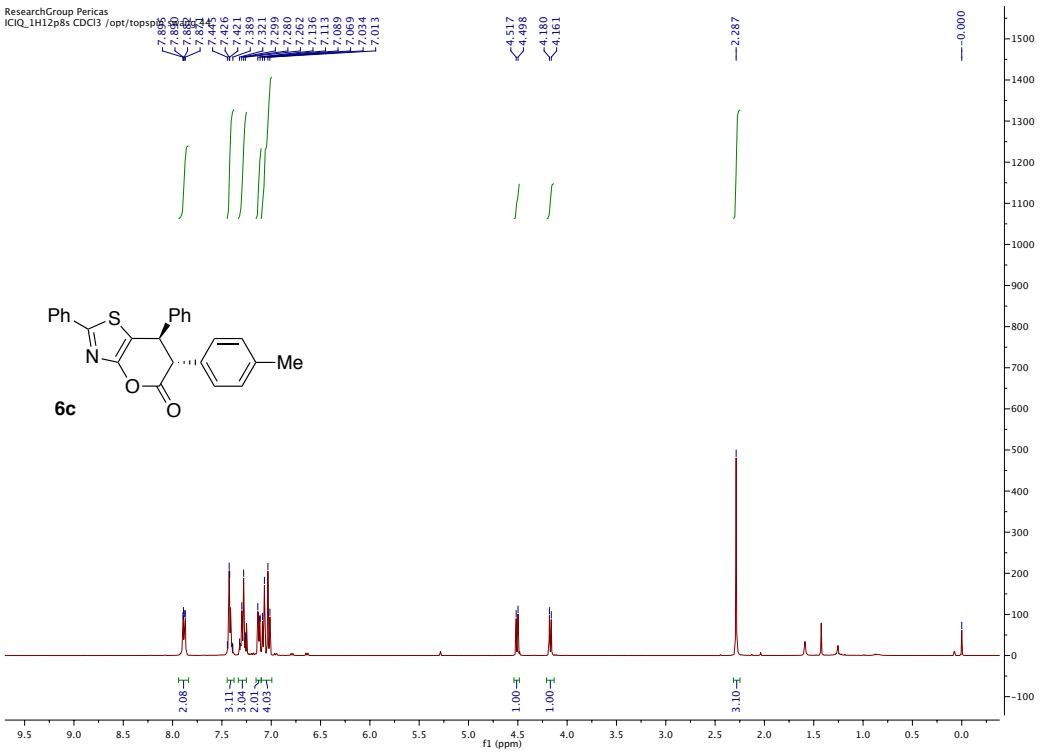

4o
Ph
NMe
N
N
O
O
Ph
f1 (ppm)

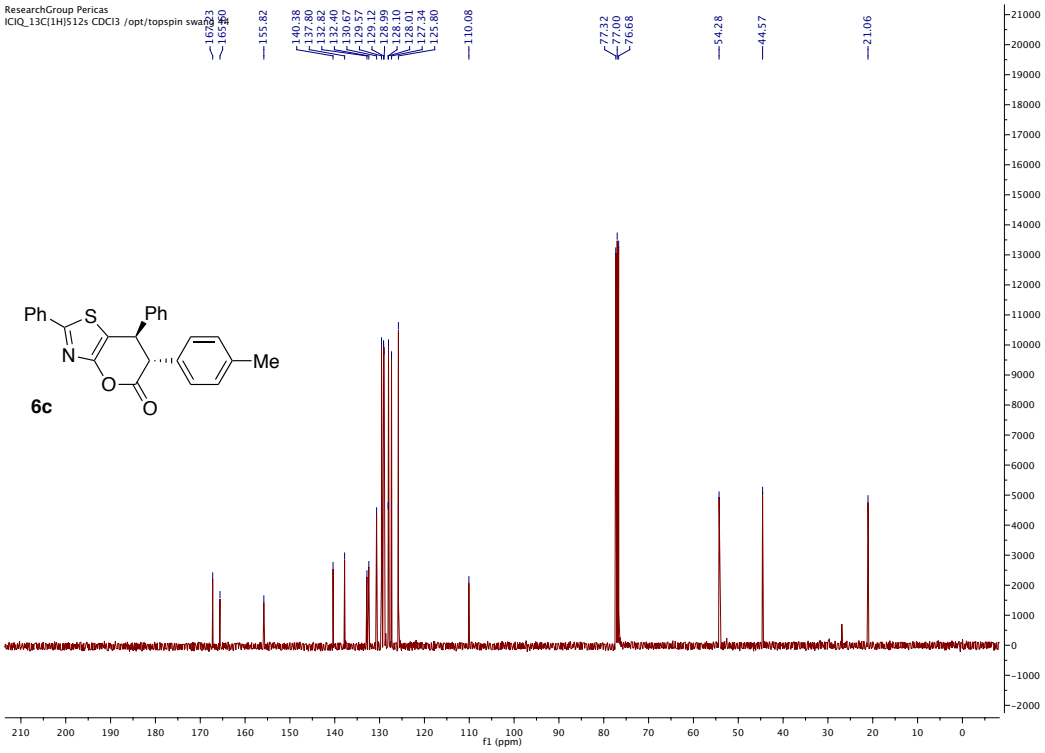

ResearchGroup Pericas
ICIQ_1H12p32s CDCl3 /opt/topspin swan
6a
Ph
S
N
O
O
Ph
f1 (ppm)

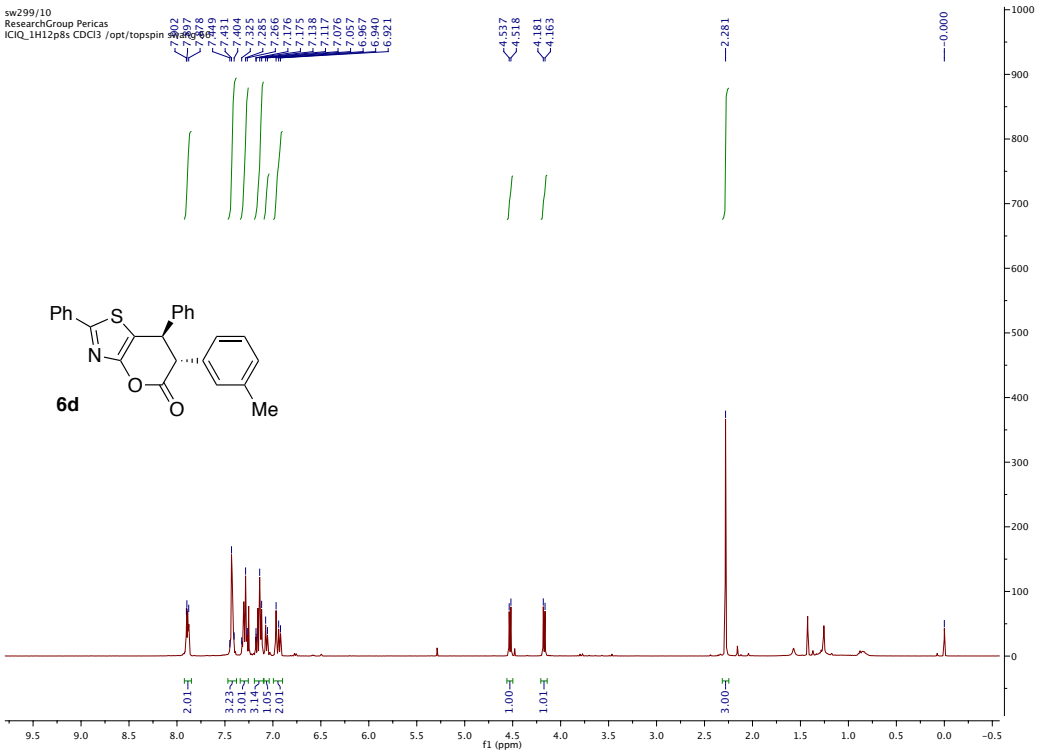

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swan
6a
Ph
S
N
O
O
Ph
f1 (ppm)

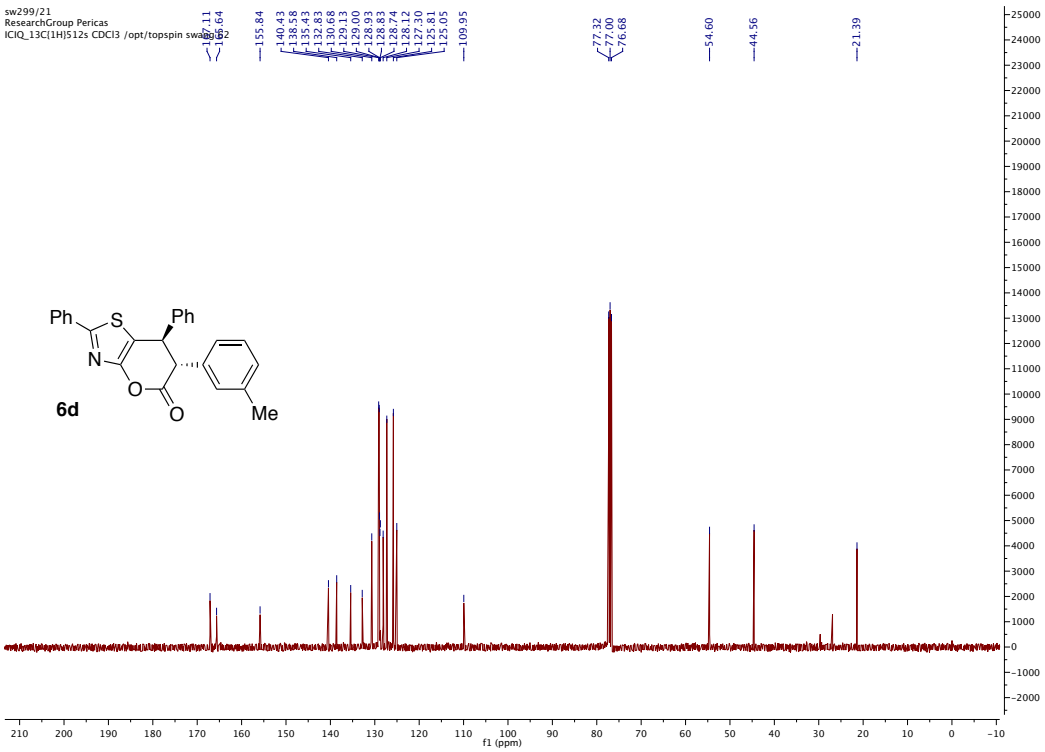

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 97
6b
f1 (ppm)

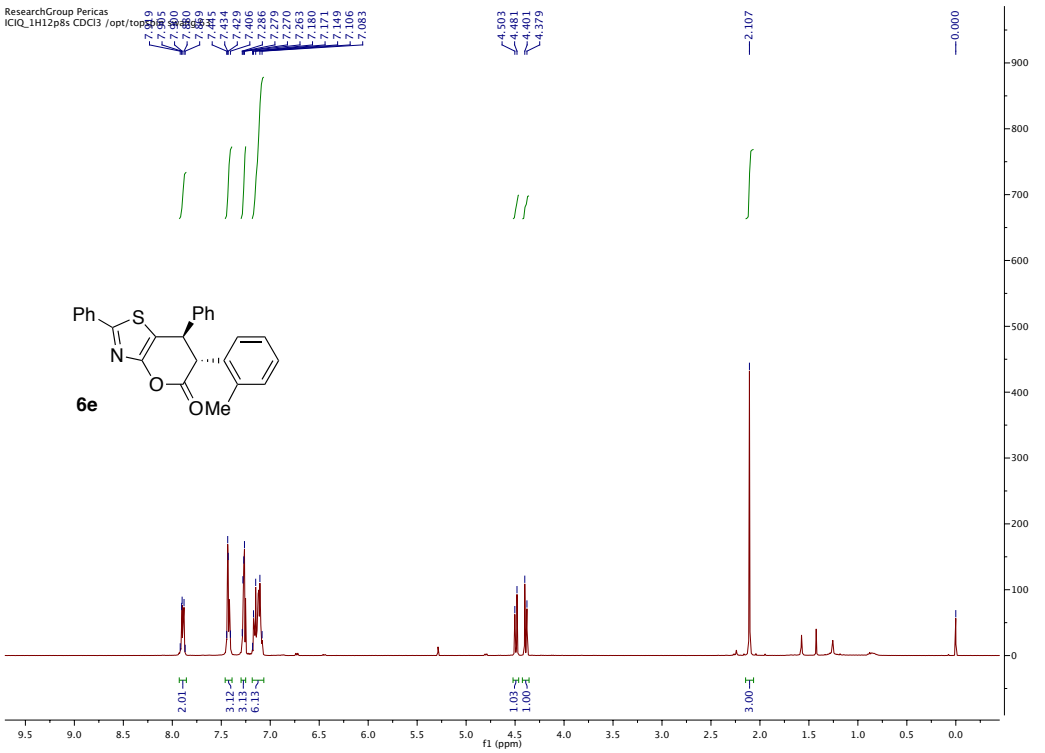

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 97
6b
f1 (ppm)

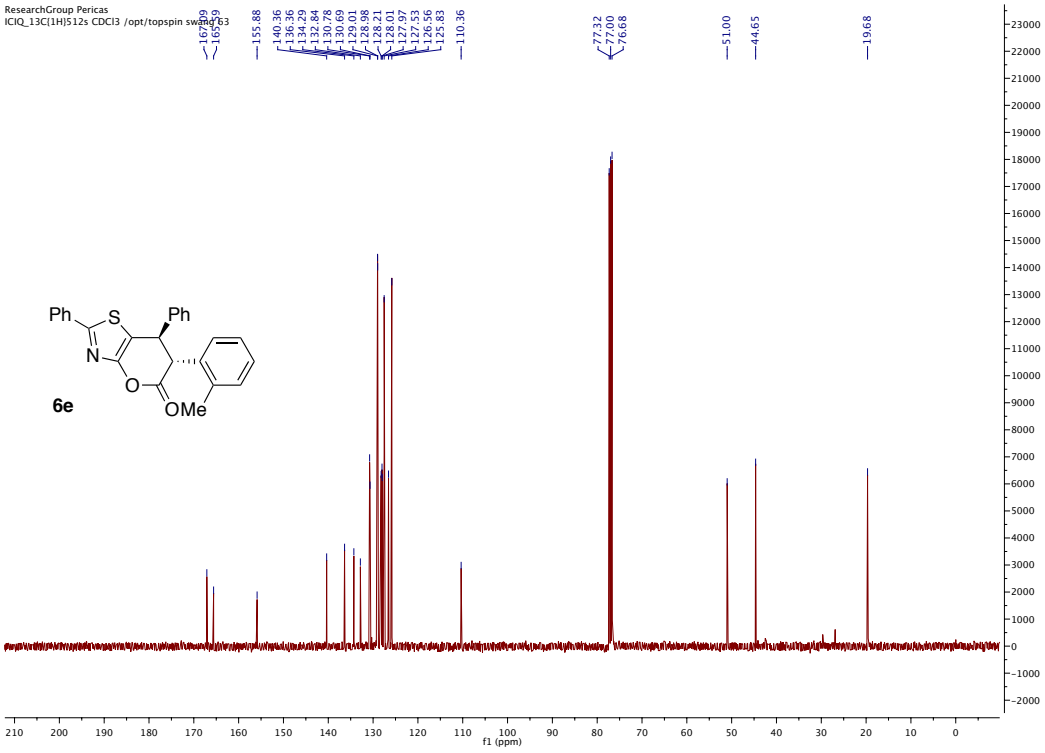

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin
7.895
7.880
7.862
7.844
7.445
7.426
7.421
7.389
7.321
7.299
7.280
7.262
7.136
7.113
7.089
7.069
7.034
7.013
4.517
4.498
4.180
4.161
2.287
0.000
Ph
S
Ph
N
O
O
Me
6c
2.08
3.11
3.04
2.01
4.03
1.00
1.00
3.10
f1 (ppm)


ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin
167.23
165.40
155.82
140.38
137.80
132.82
132.40
130.67
129.57
129.12
128.99
128.10
128.01
127.34
125.80
110.08
77.32
77.00
76.68
54.28
44.57
21.06
Ph
S
Ph
N
O
O
Me
6c
f1 (ppm)


sw299/10
ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang48
7.902
7.897
7.878
7.449
7.431
7.404
7.285
7.266
7.176
7.175
7.138
7.117
7.076
7.057
6.967
6.940
6.921
4.537
4.518
4.181
4.163
2.281
0.000
Ph
S
Ph
N
O
O
Me
6d
2.01
3.23
3.01
3.14
1.05
2.01
1.00
1.01
3.00
f1 (ppm)


sw299/21
ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang52
167.11
163.64
155.84
140.43
138.58
133.43
132.83
130.68
129.13
129.00
128.93
128.83
128.74
128.12
127.30
125.81
125.05
109.95
77.32
77.00
76.68
54.60
44.56
21.39
Ph
S
Ph
N
O
O
Me
6d
f1 (ppm)


ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 63
7.919
7.905
7.900
7.880
7.859
7.445
7.434
7.429
7.406
7.286
7.279
7.270
7.263
7.180
7.171
7.149
7.106
7.083
4.503
4.481
4.401
4.379
2.107
0.000
Ph
S
Ph
N
O
OMe
6e
2.01
3.12
3.13
6.13
1.03
1.00
3.00
f1 (ppm)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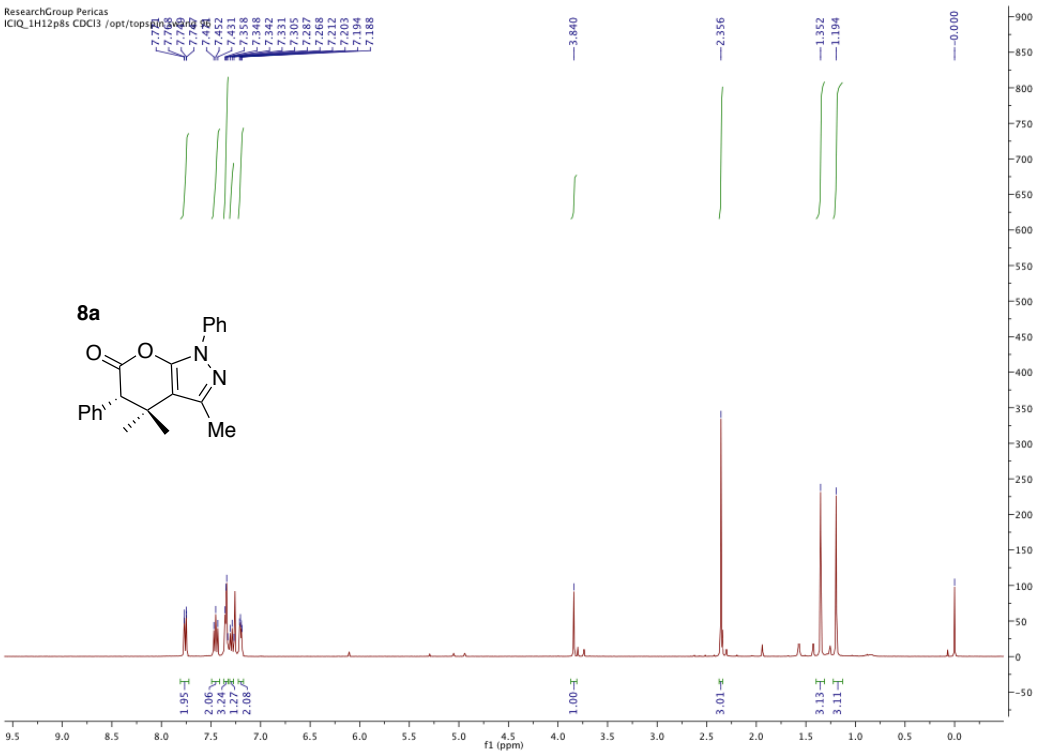
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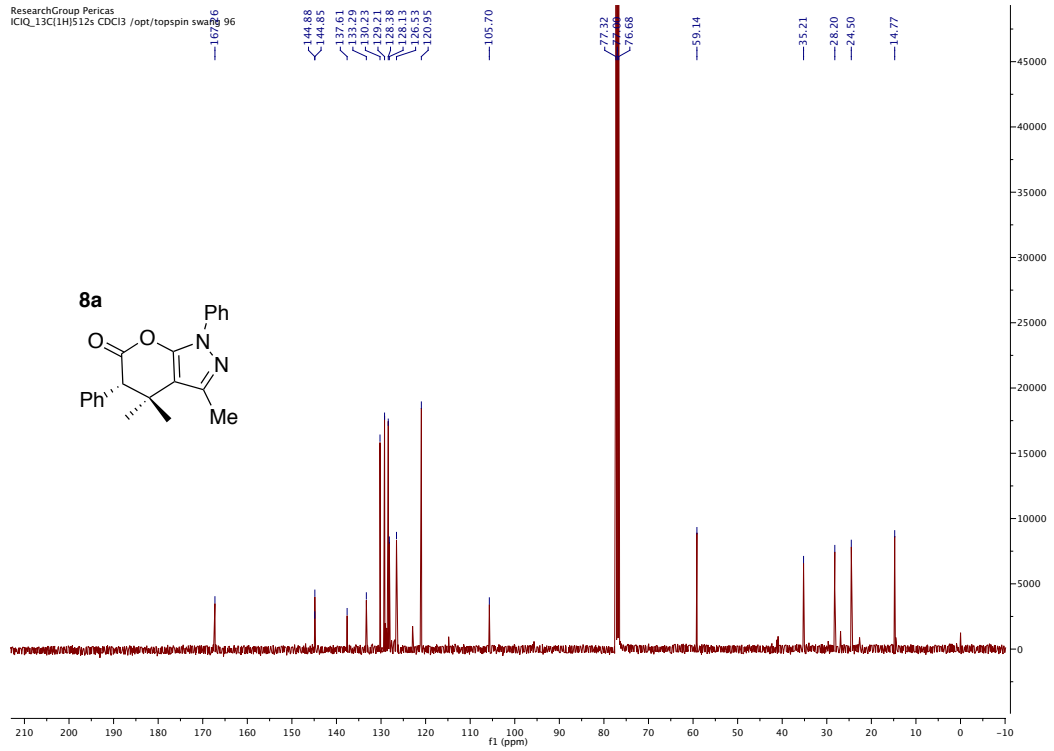
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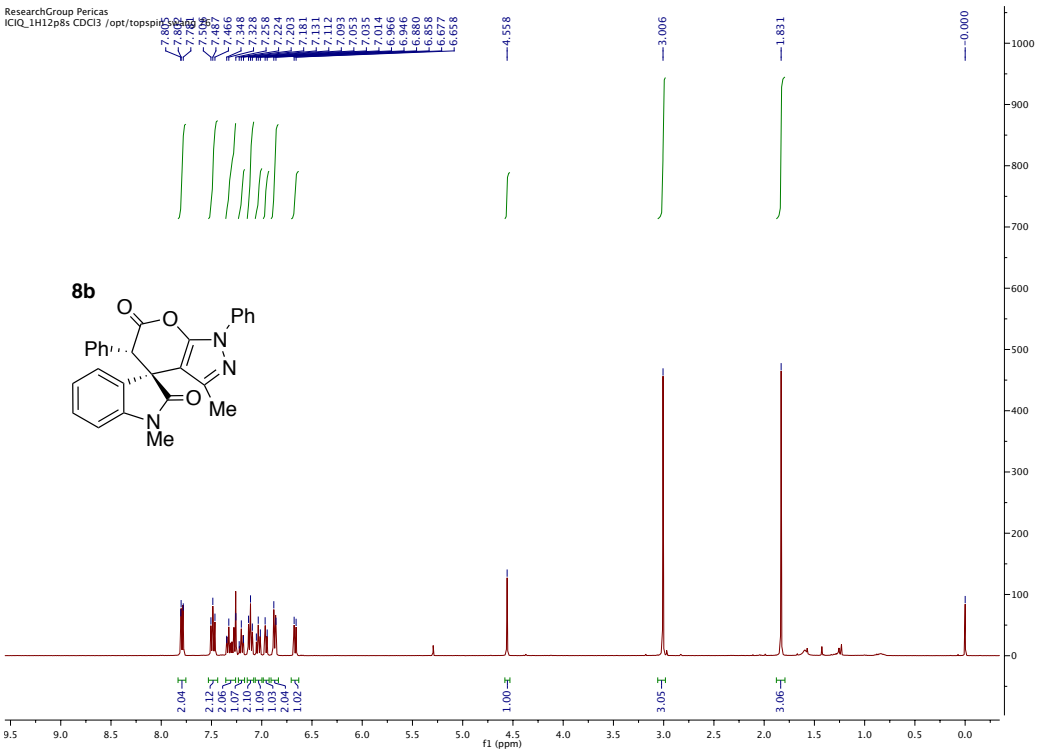
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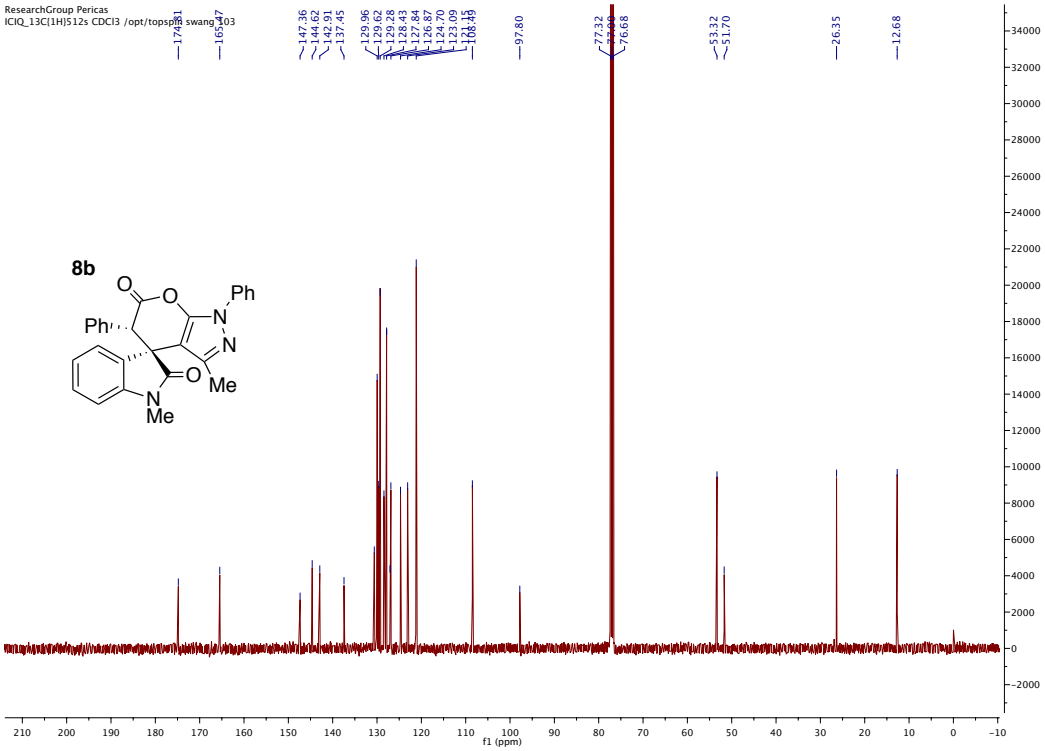
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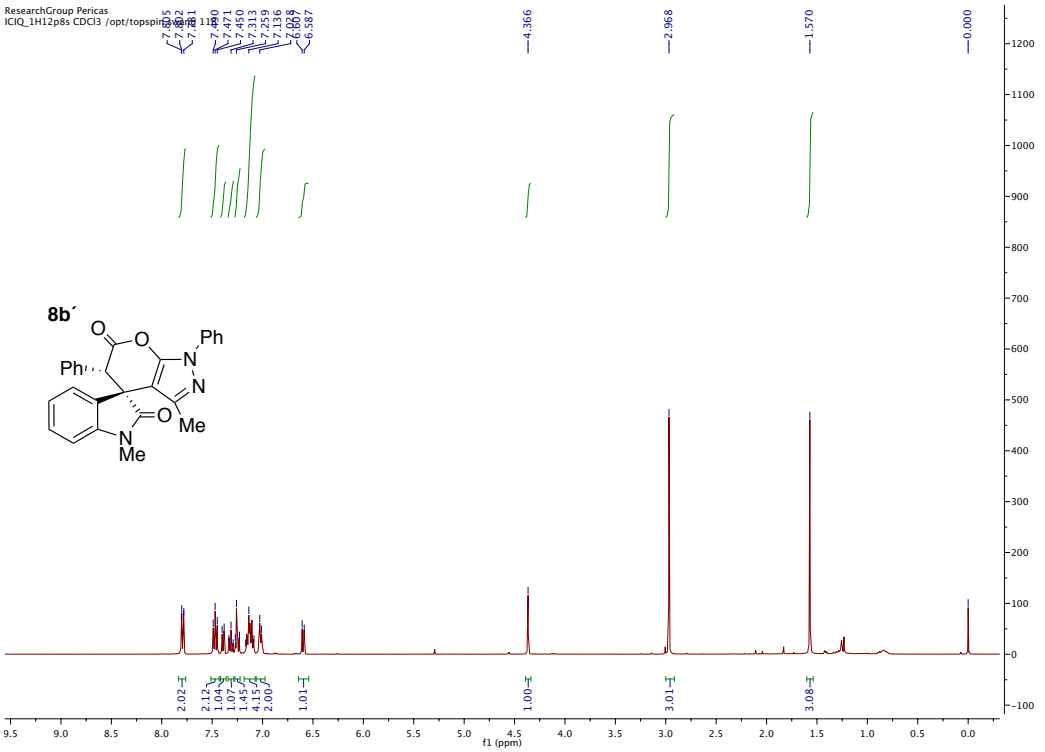
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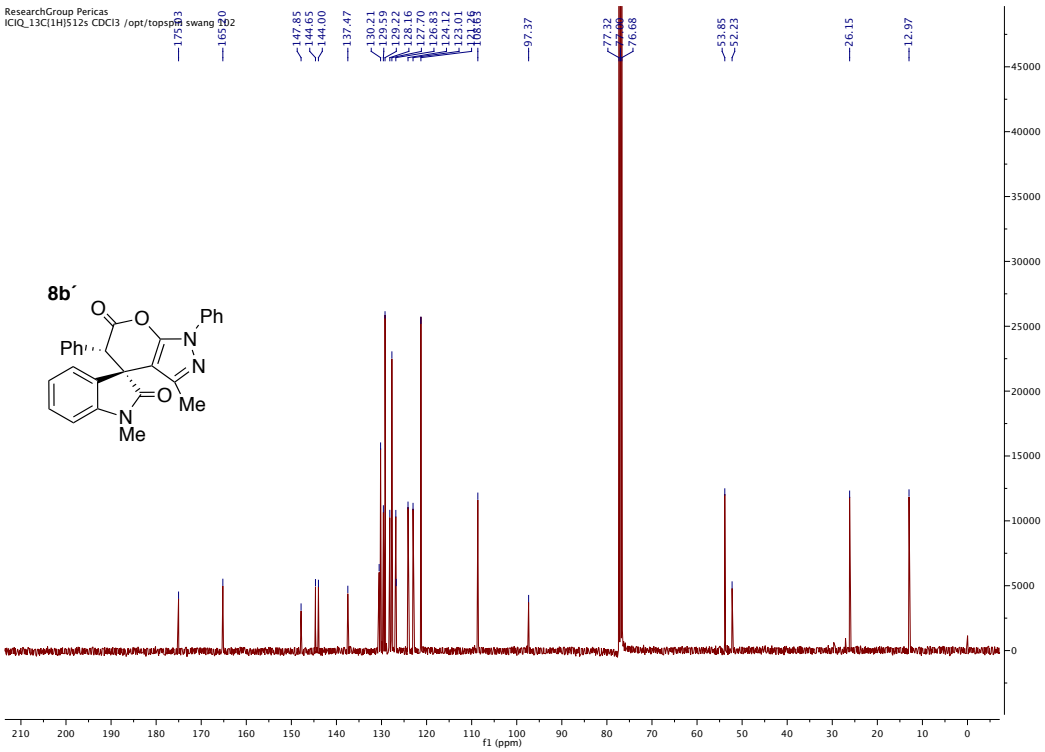
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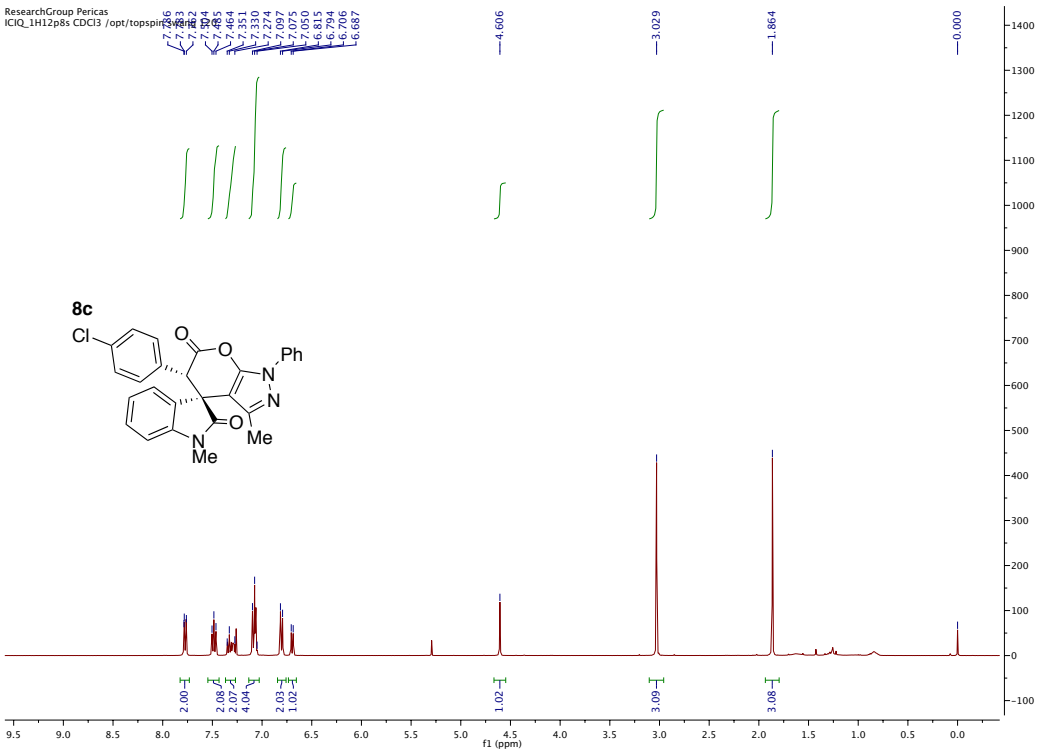
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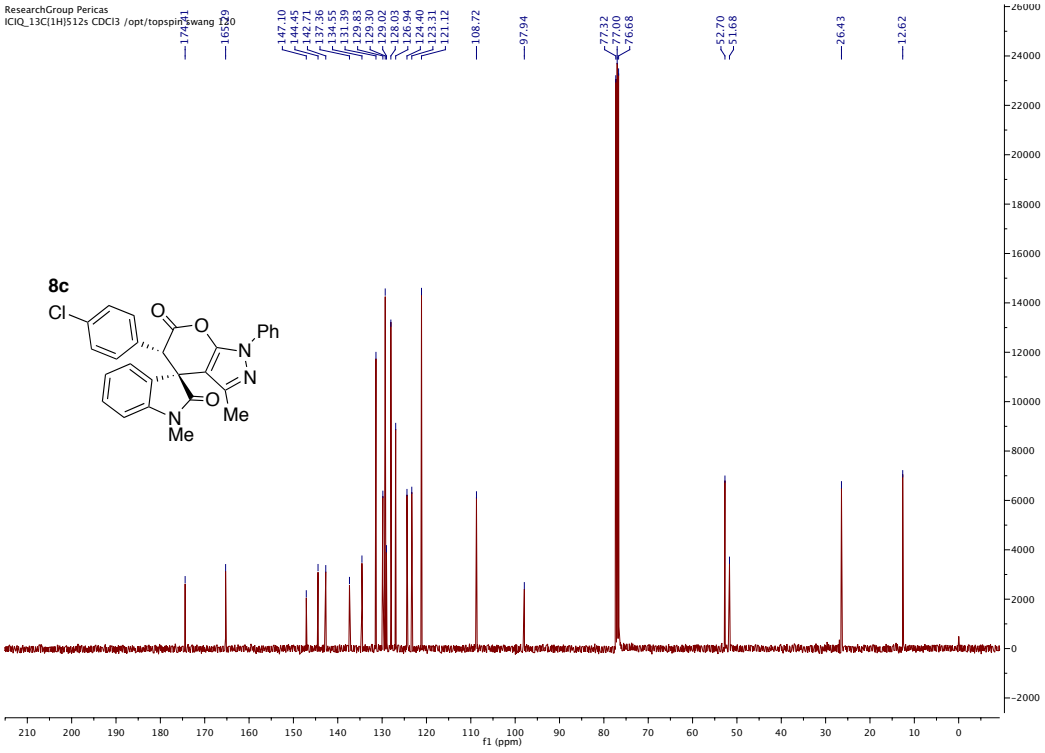
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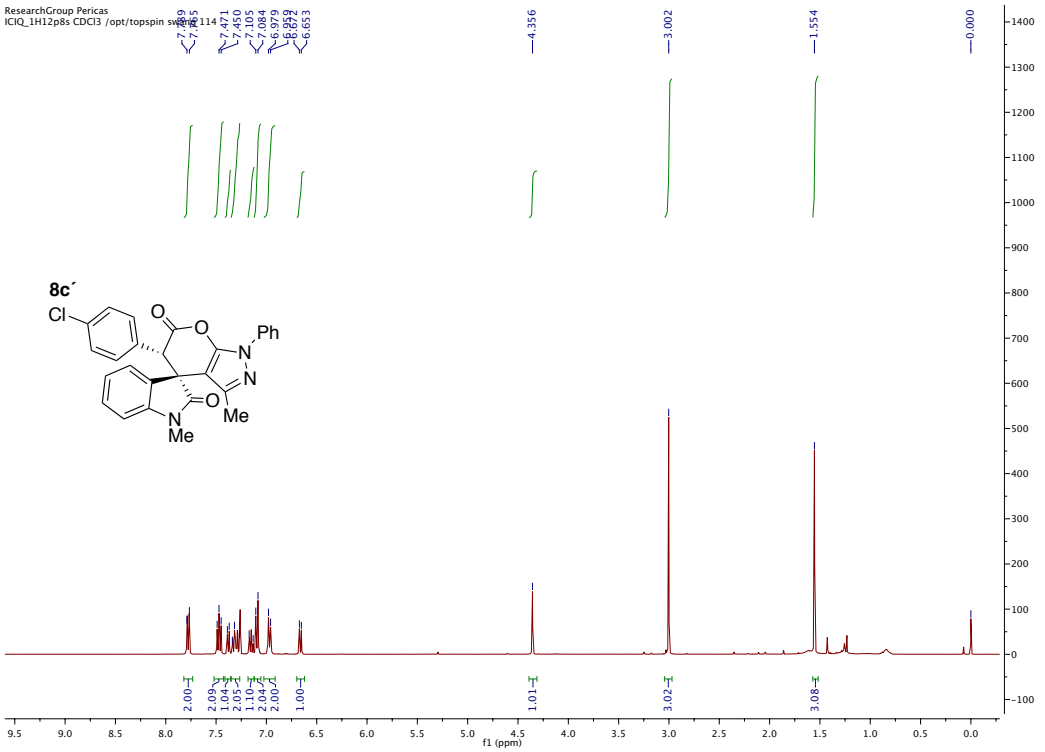
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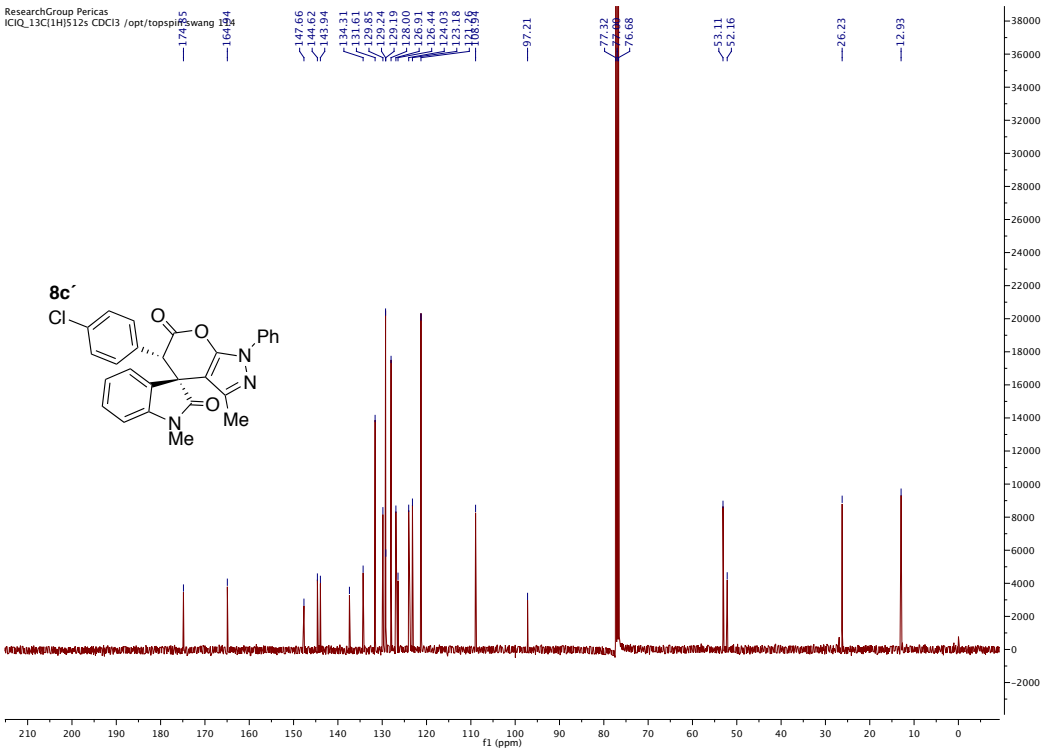
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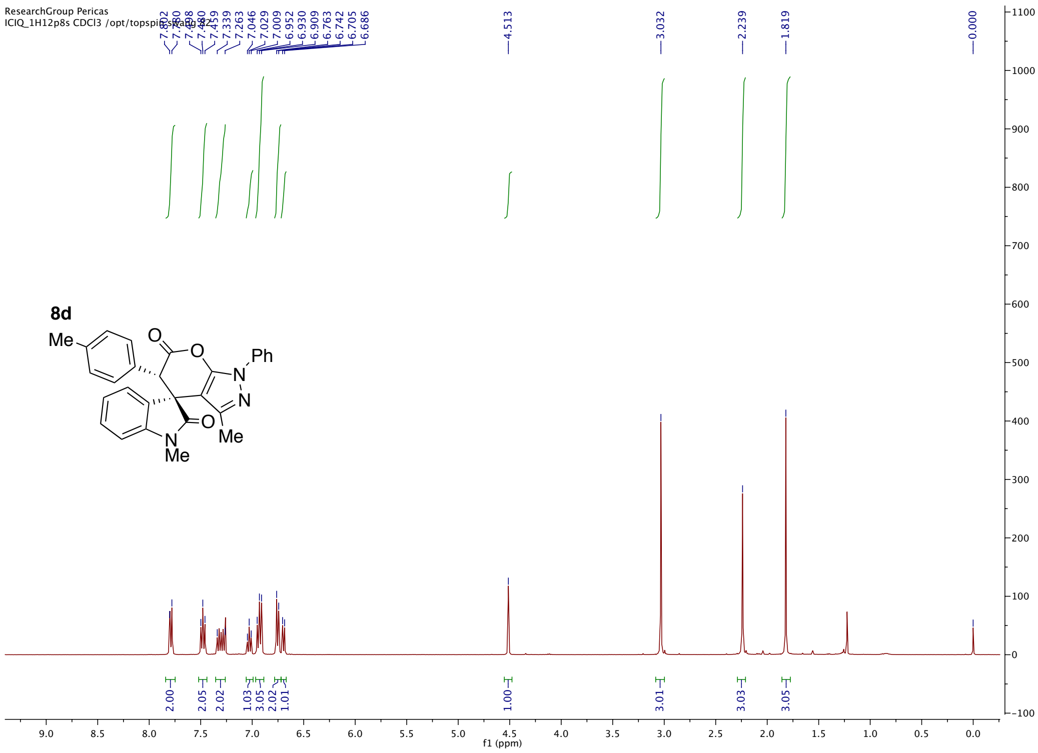

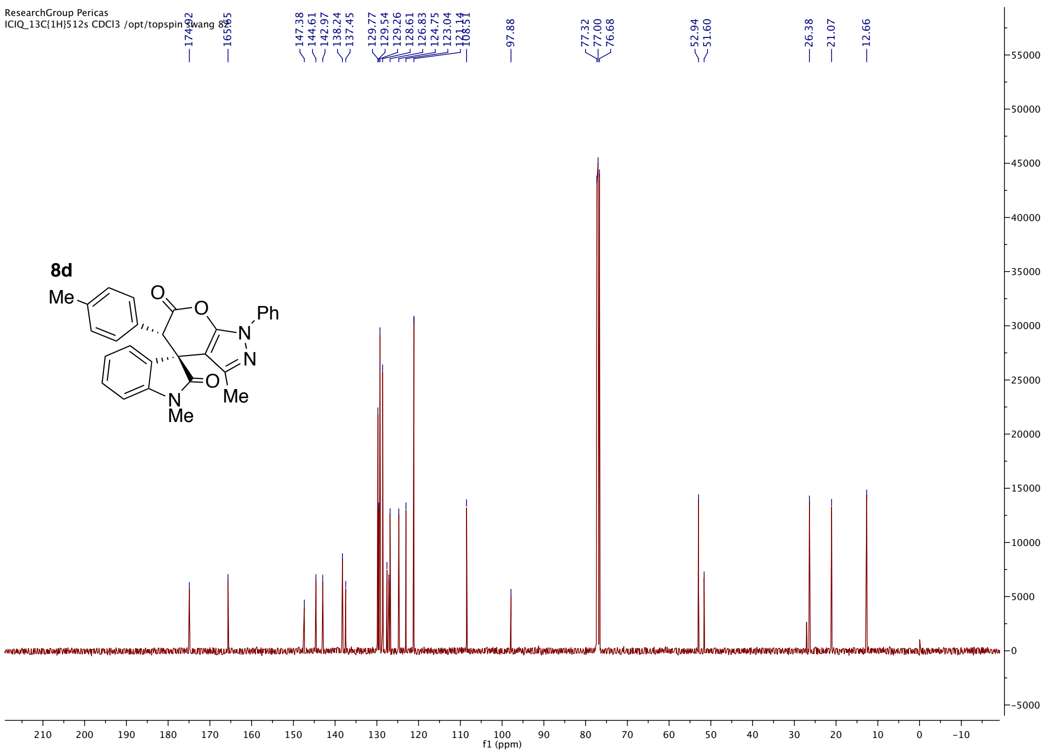

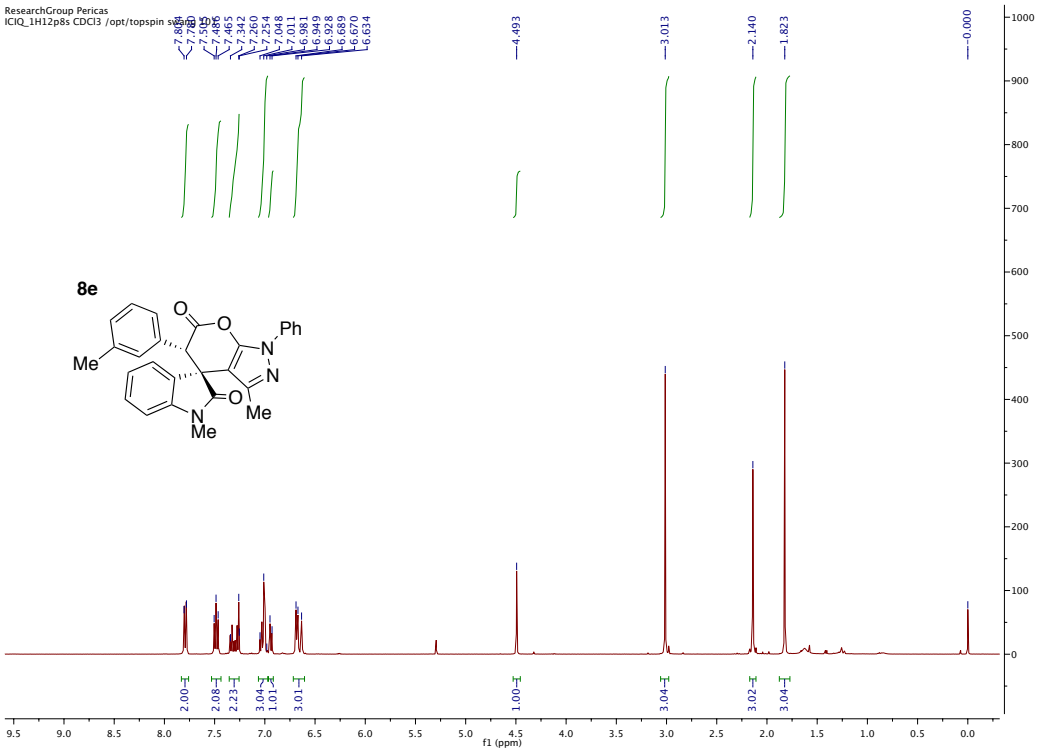
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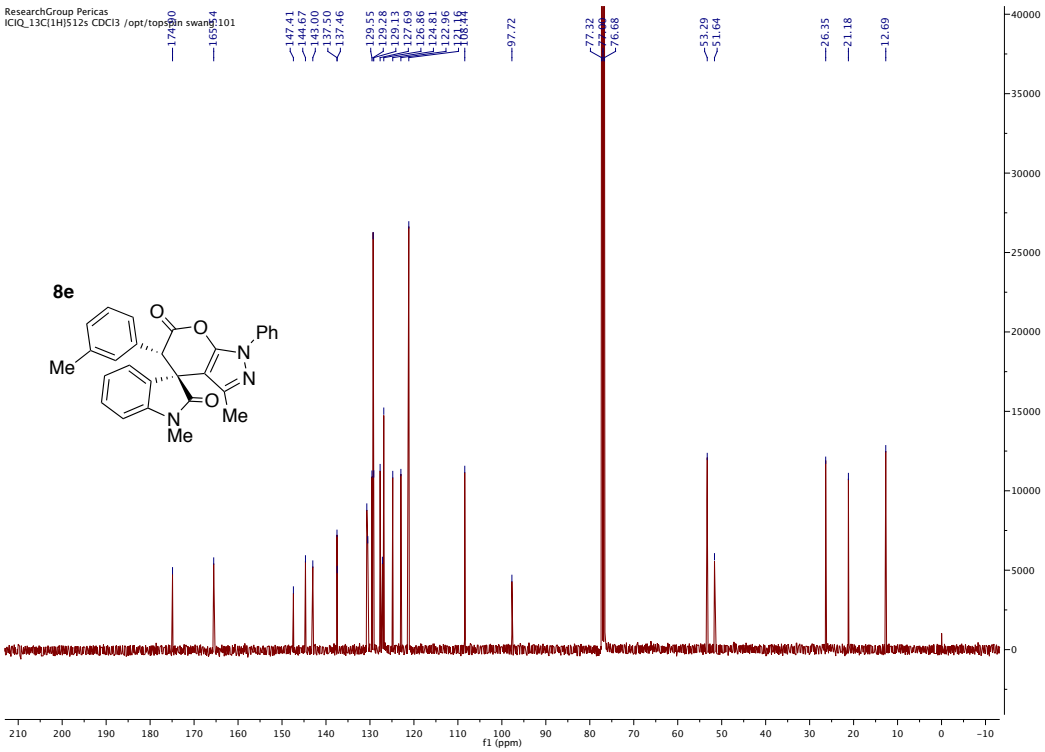
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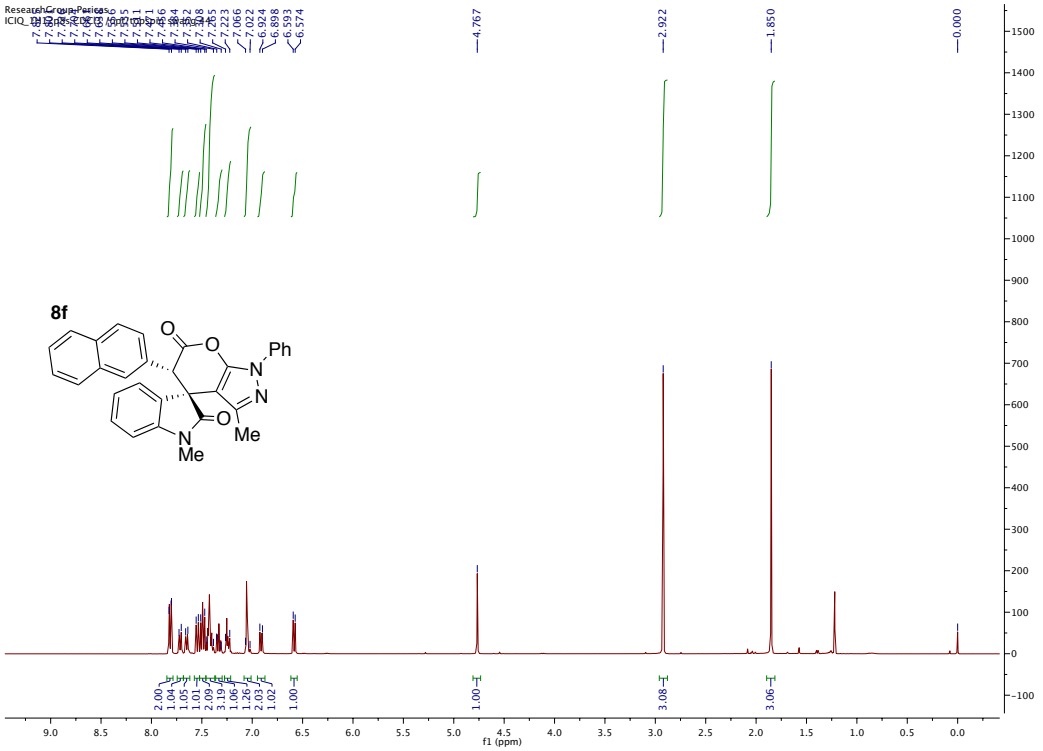
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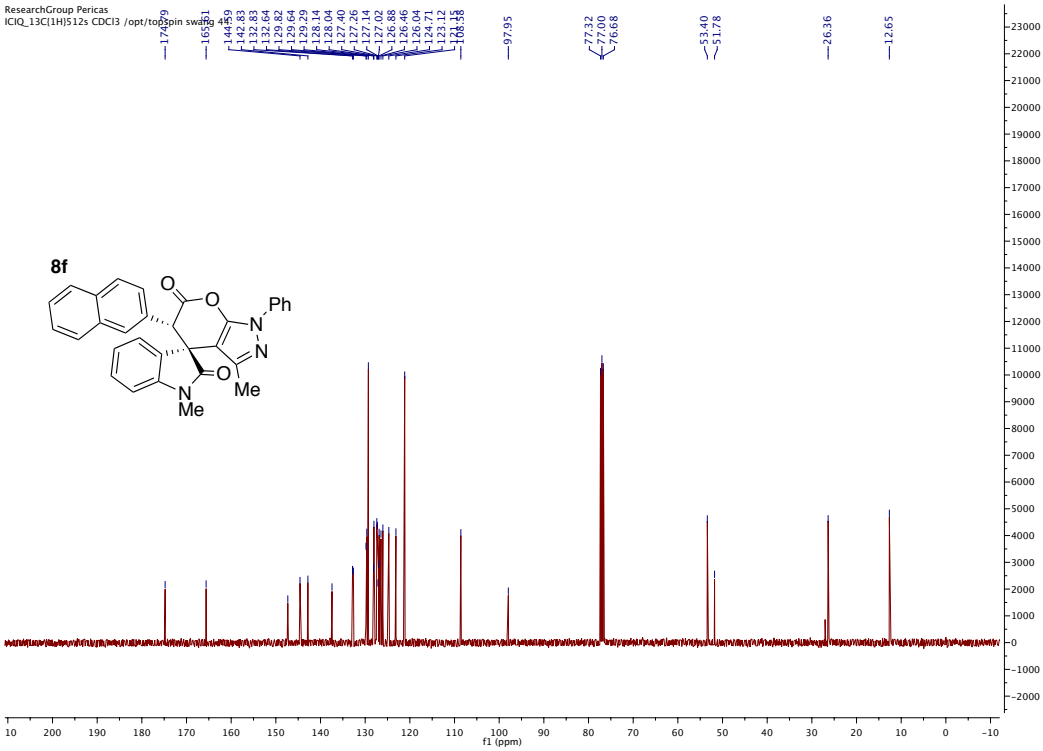
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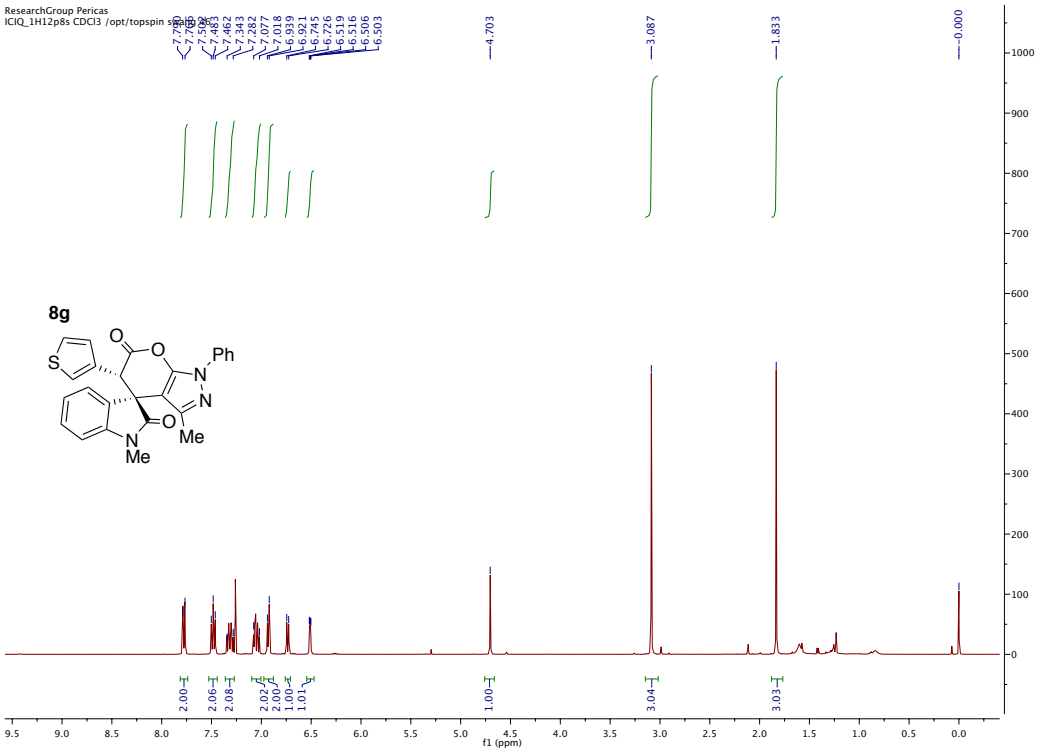
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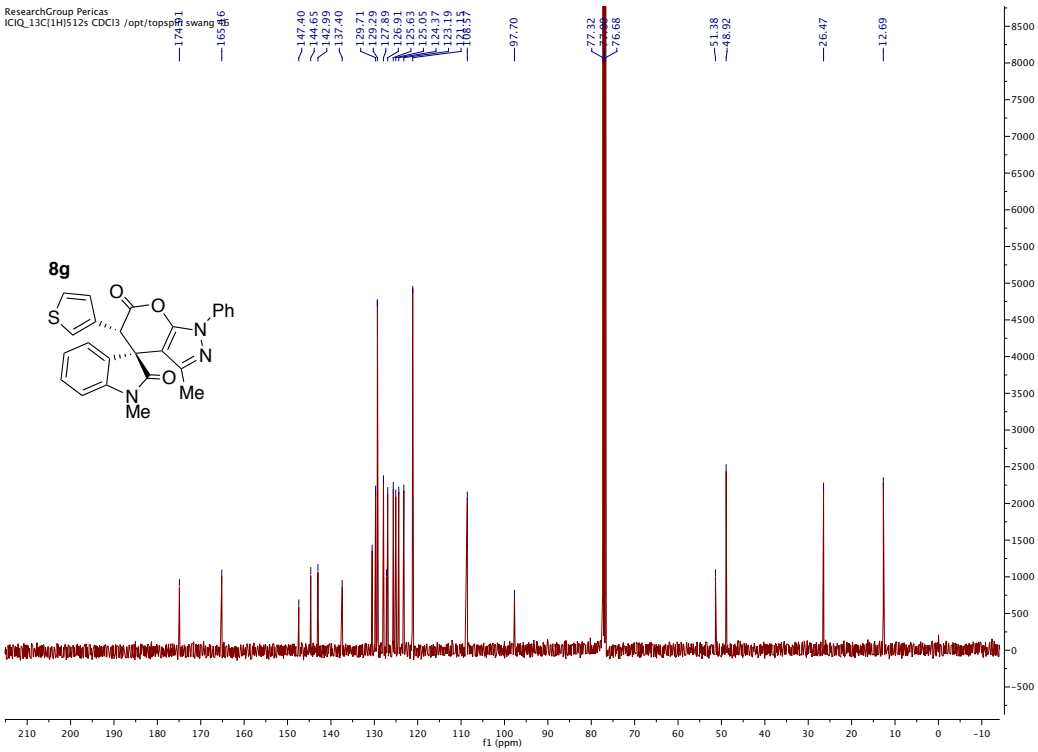
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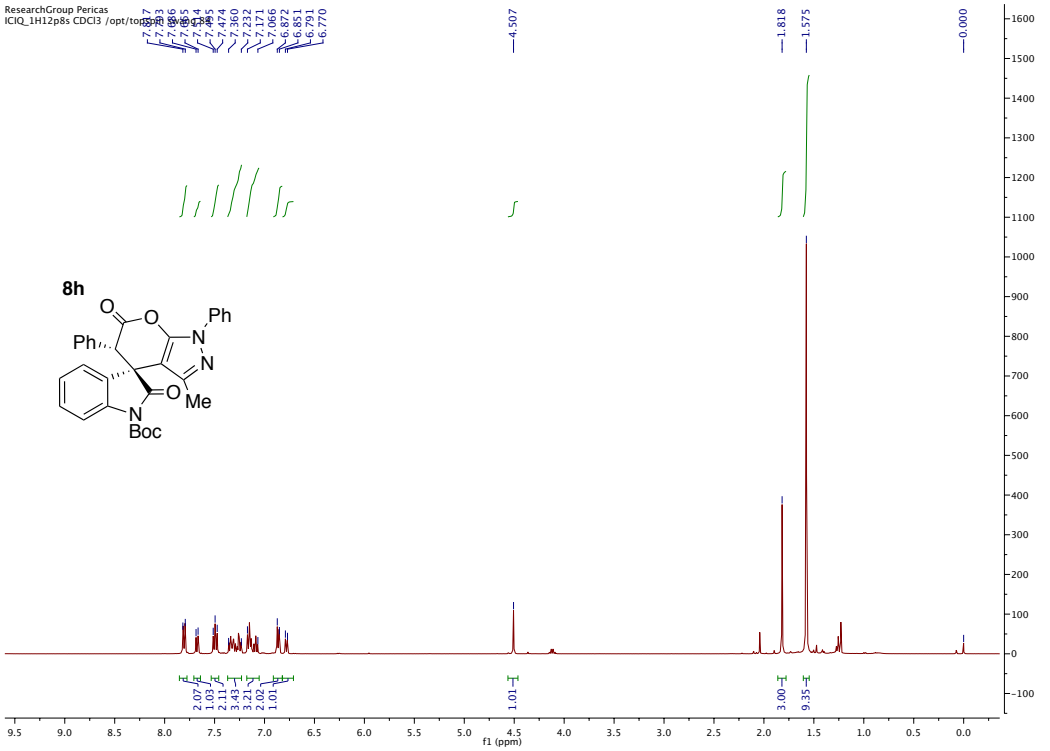
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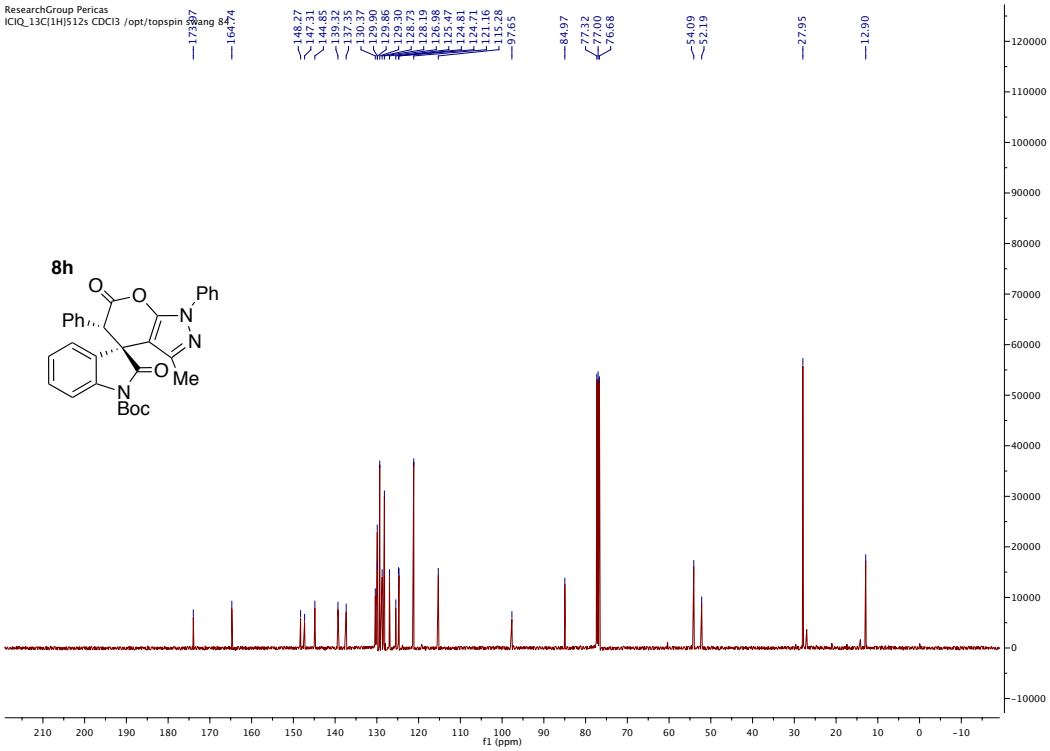
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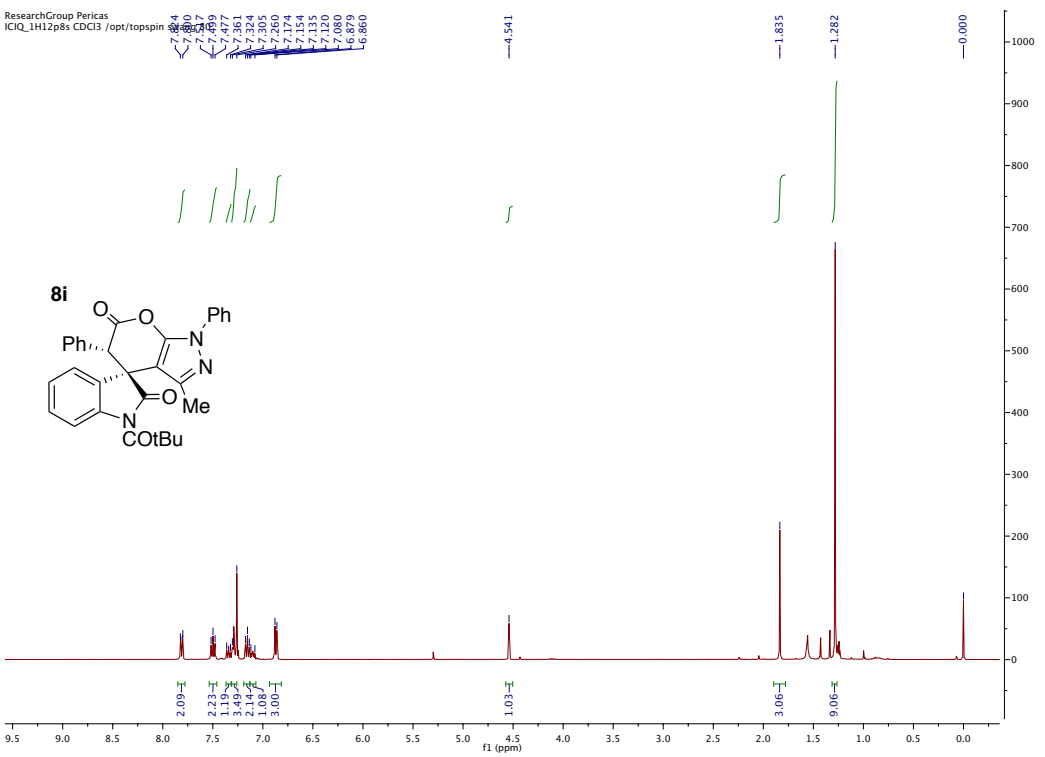
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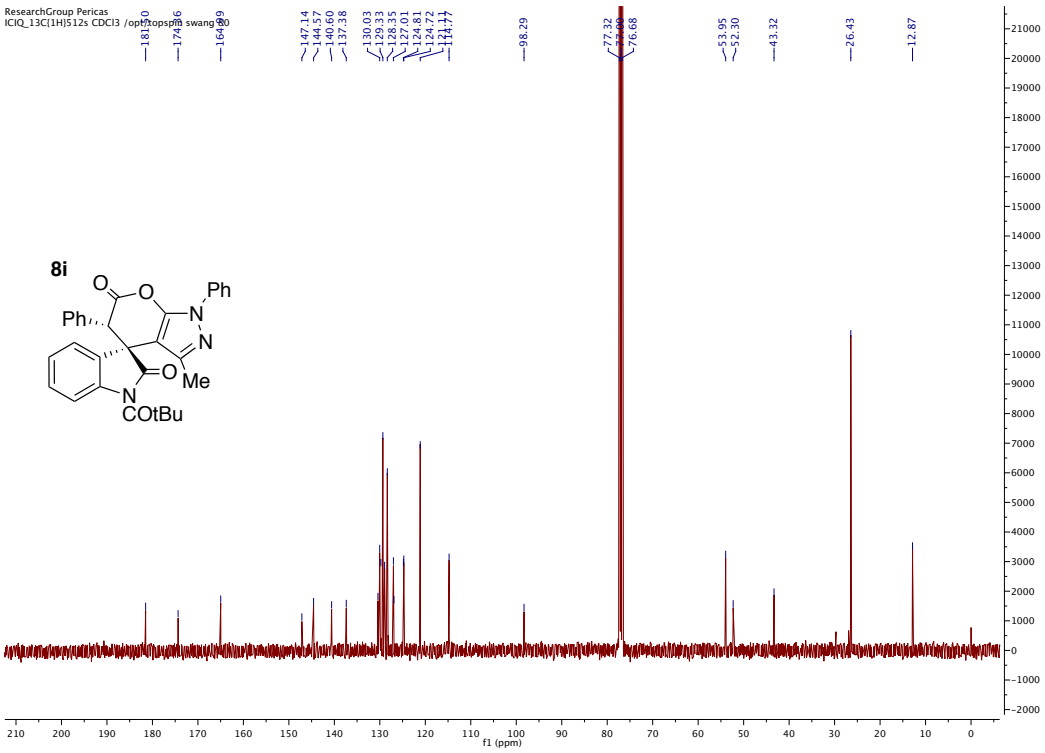
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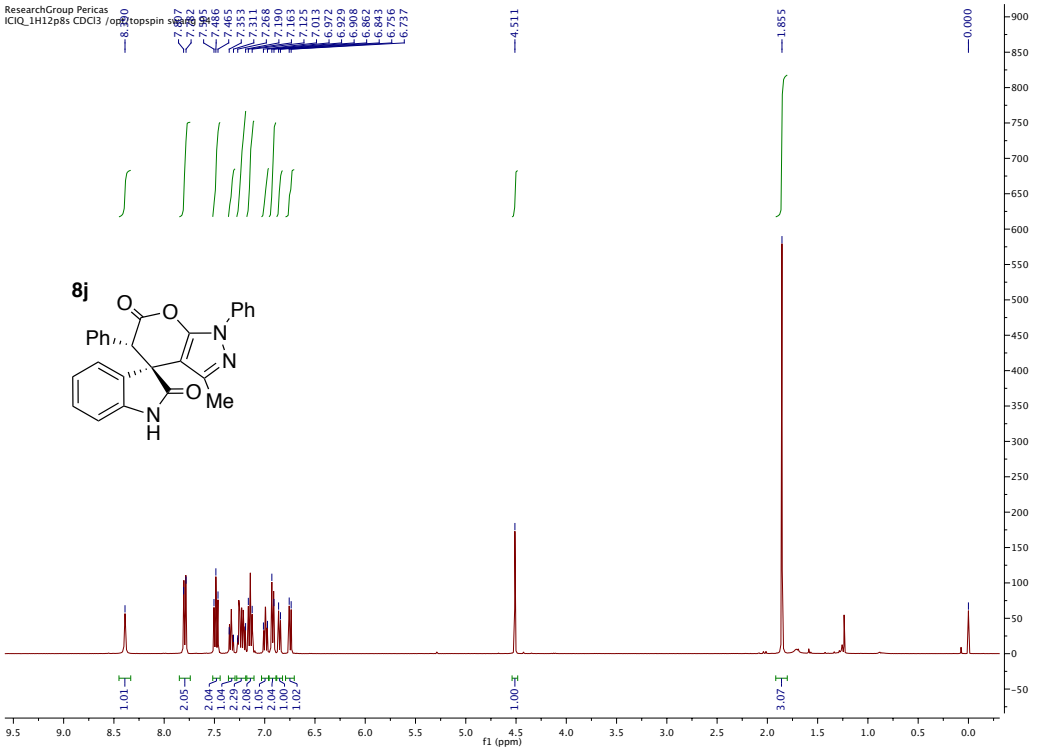
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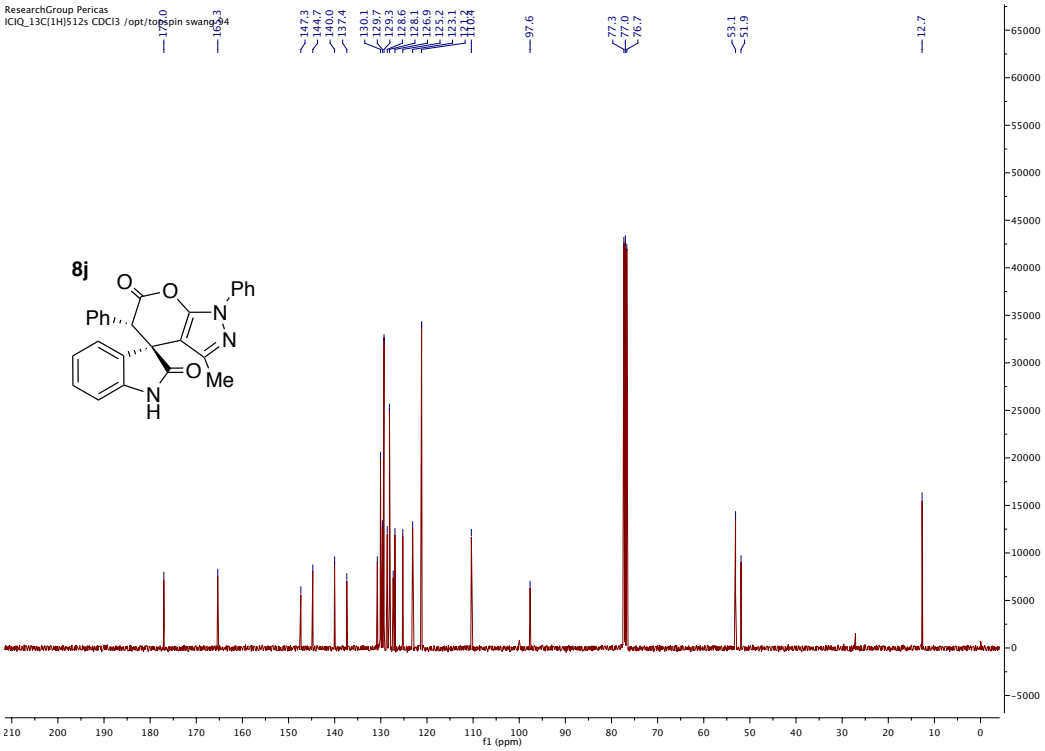
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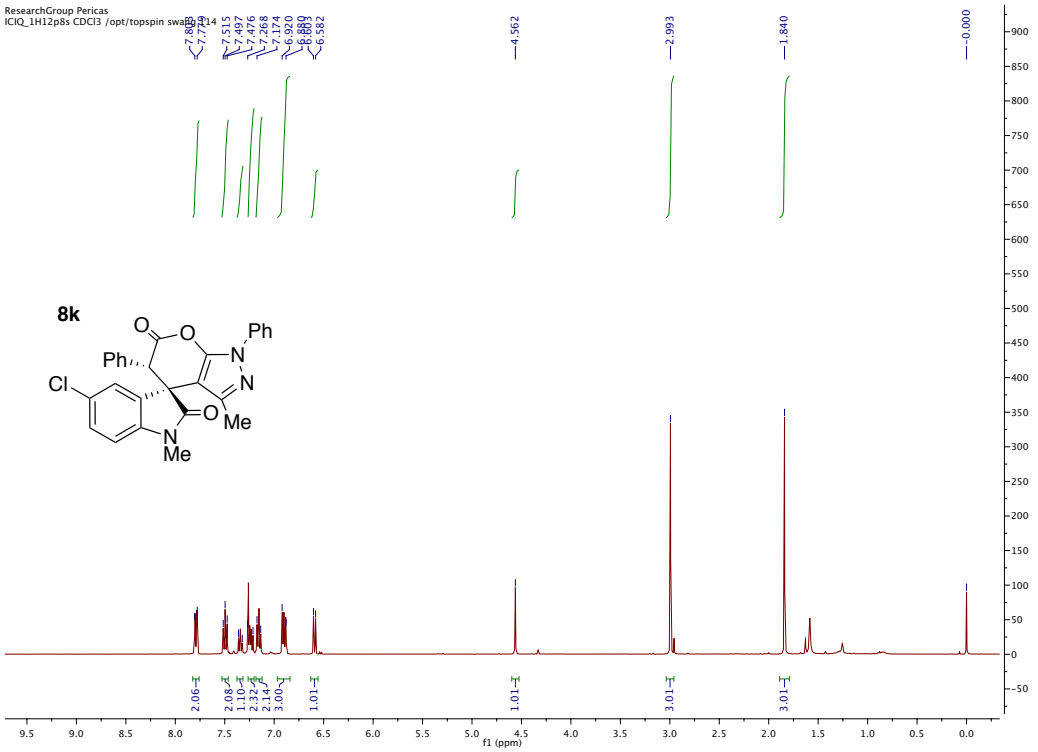
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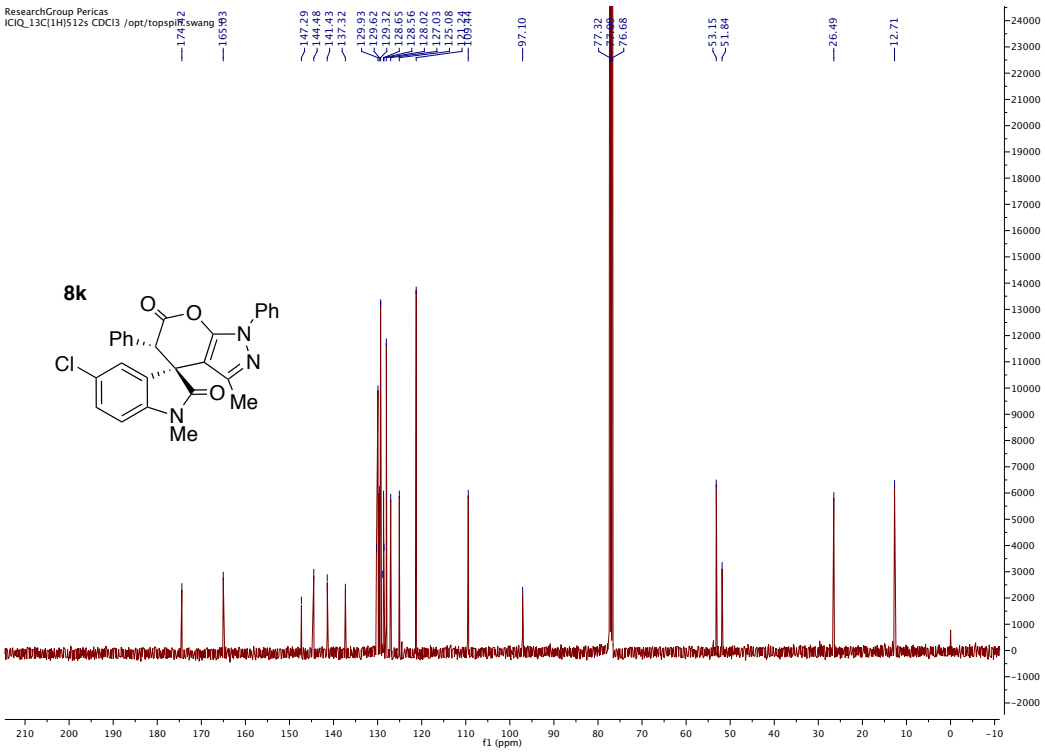
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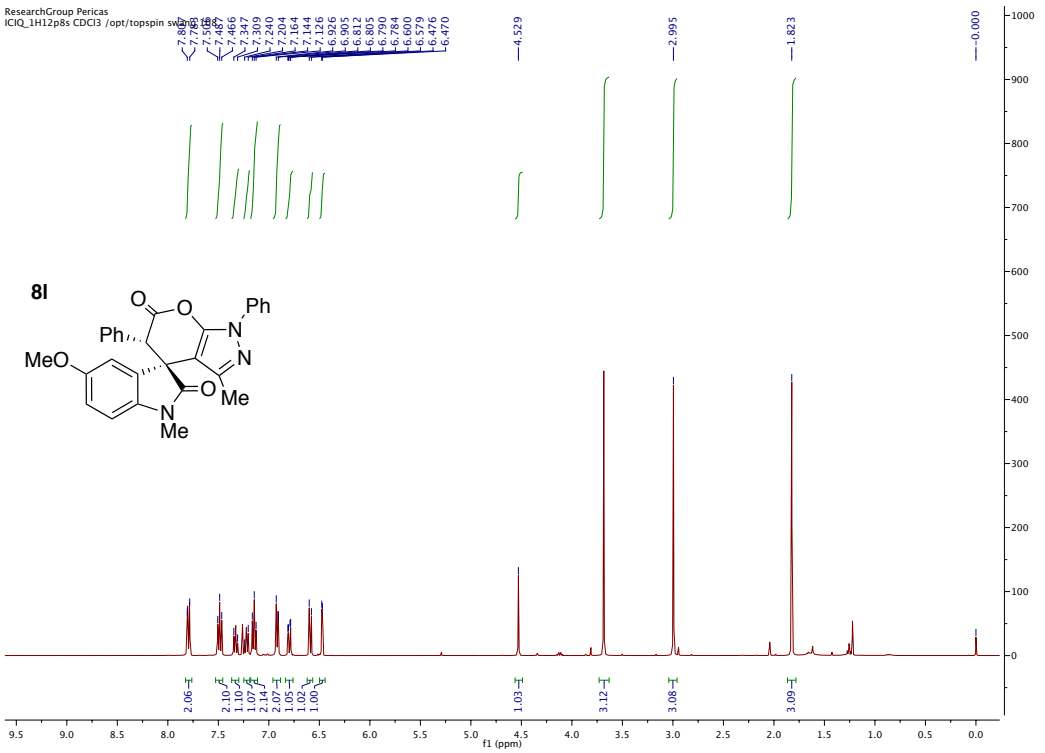
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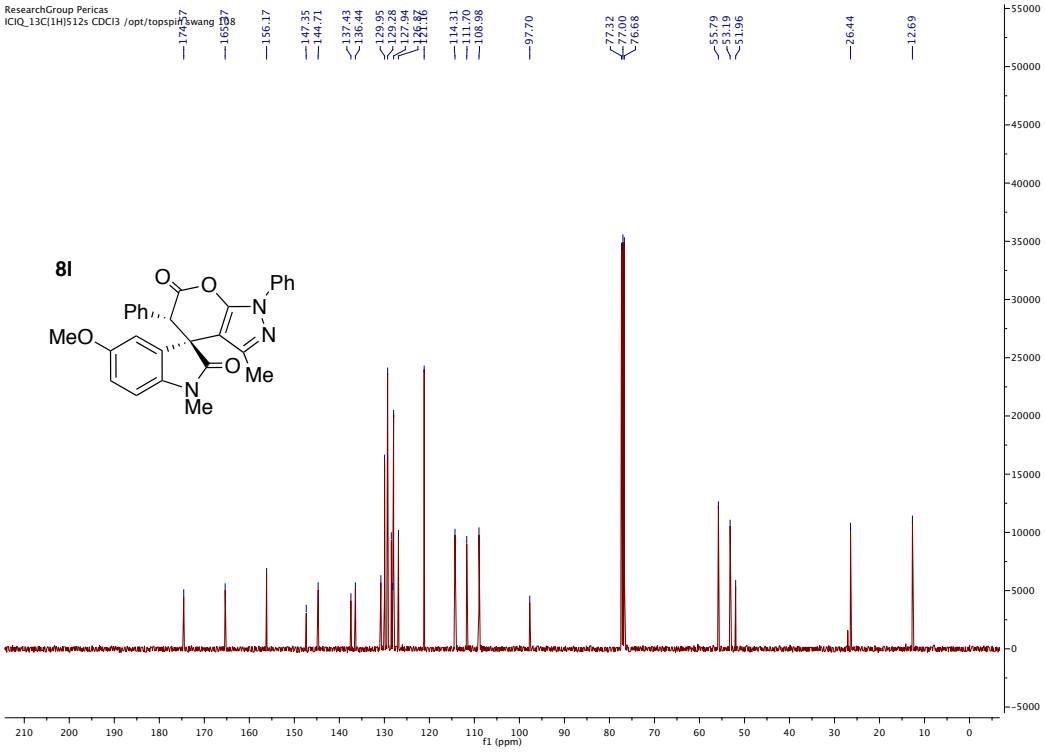
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CHAPTER IV

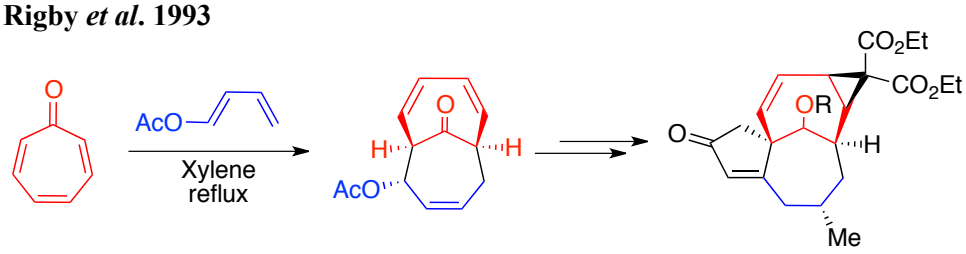
Chapter IV

Catalytic Asymmetric [8+2] Annulation Reactions Promoted by a Recyclable Immobilized Isothiourea

4.1. Introduction

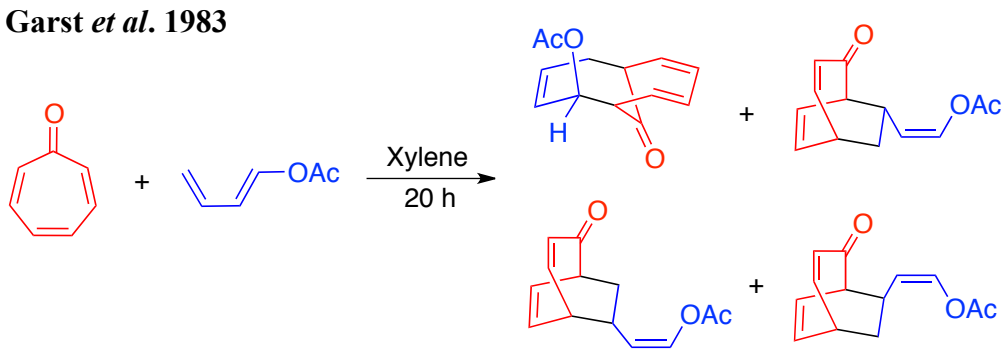
Cycloaddition reactions that involve more than six π electrons can be regarded as higher-order cycloadditions and represent an efficient approach to synthesize medium and large rings. These ring systems are core scaffolds in numerous natural products and have been applied in total synthesis. For instance, the thermally allowed [6+4] cycloaddition of tropone with 1,3-butadienyl acetate was employed by Rigby *et al*. in the synthesis of tetracyclic isoingenane system (Scheme 4.1).[1]

Rigby *et al*. 1993



Scheme 4.1. Higher-order cycloaddition for the synthesis of a tetracyclic isoingenane system

General examples of higher-order cycloaddition include [8π + 2π], [6π + 4π], [4π + 4π], and [6π + 2π] cycloaddition reactions. Although higher-order cycloaddition reactions exhibit characteristics similar to the Diels-Alder reaction, most of them only proceed with modest chemical efficiency. This can be attributed to the fact that the extended π system exhibits a broader reactivity spectrum depending on the substrate and conditions, thus leading to poor periselectivities. For example, the reaction between tropone and 1,3-butadienyl acetate under mild conditions gave rise to four products, none of which predominated (Scheme 4.2).[2]



Scheme 4.2. Higher-order cycloadditions of tropone with 1,3-butadienyl acetate

Heptafulvenes and their heteroanalogues (tropone, tropothione, and azaheptafulvenes), a subclass of the family of "non-benzenoid aromatic compounds", have been recognized as important synthons for higher-order cycloaddition owing to their conjugated cyclic polyolefin systems. These compounds can be applied as 2π, 4π, 6π, or 8π components in various cycloadditions to provide the corresponding annulated products (Figure 4.1).

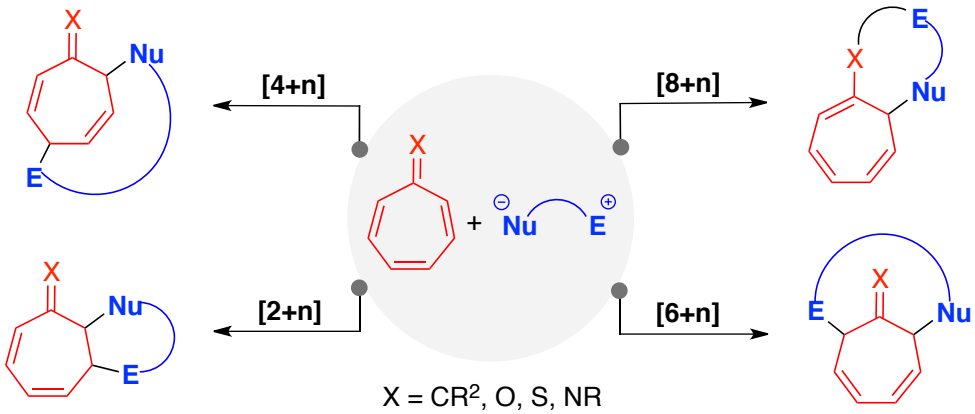


Figure 4.1. Different types of cycloadditions with heptafulvenes and their heteroanalogues

4.2. [8+2] Cycloaddition

As the most important category of higher-order cycloadditions, [8+2] cycloadditions provide a direct approach to highly functionalized bicyclic [5.3.0] rings, which represent a framework that can be found in numerous biologically active molecules. As mentioned before, heptafulvenes and their heteroanalogues can act as 8π components and are thus widely employed in various [8+2] cycloadditions. In addition, a few other rigidly fused systems containing four π bonds like dienylisobenzofurans and indolizines have also been found undergo [8+2] processes (Figure 4.2).

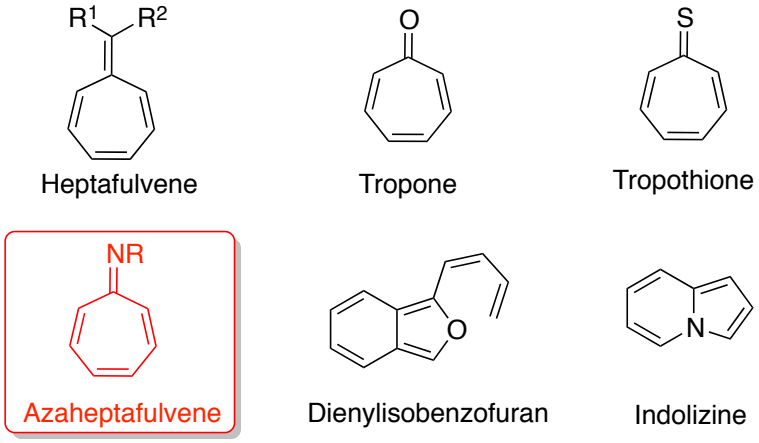
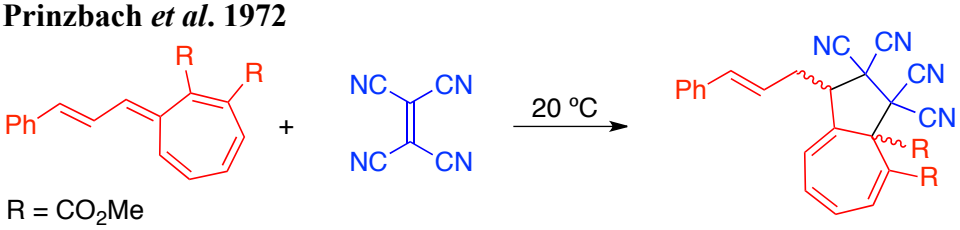


Figure 4.2. Reported 8π components in various [8+2] cycloadditions

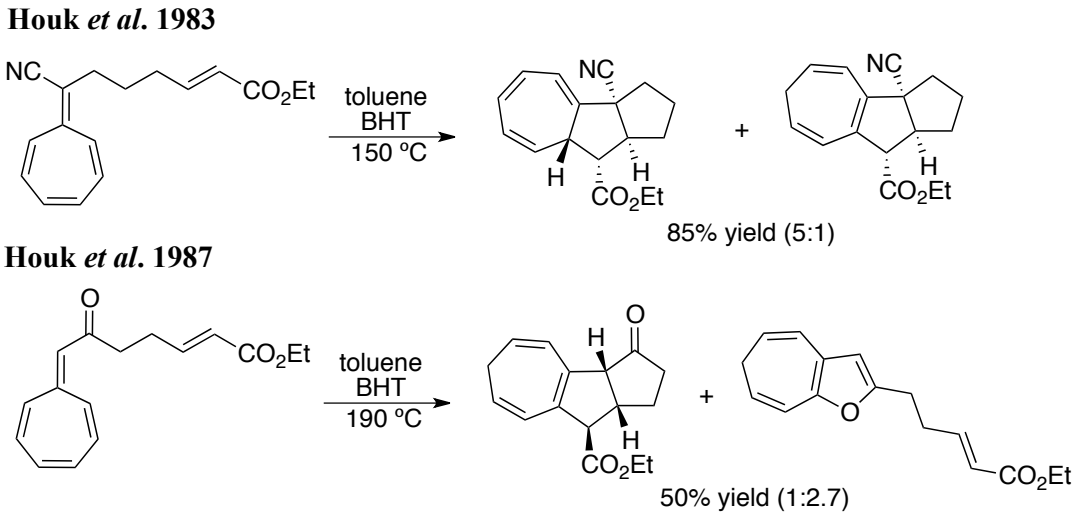
4.2.1 [8+2] Cycloadditions with Heptafulvenes

The first [8+2] cycloaddition was introduced by Doering and Wiley in 1960, who employed methylenecycloheptatriene as 8π component and dimethyl acetylene-dicarboxylate as 2π component.[3] In general, the electron-rich heptafulvenes tend to react as 8π partners and electron-deficient heptafulvenes exhibit multiple reactivity profiles. In 1972, Prinzbach and co-workers described a highly efficient [8+2] cycloaddition reaction between vinyl heptafulvene and tetracyanoethylene (TCNE), affording the [8+2] product in quantitative yield (Scheme 4.3).[4]



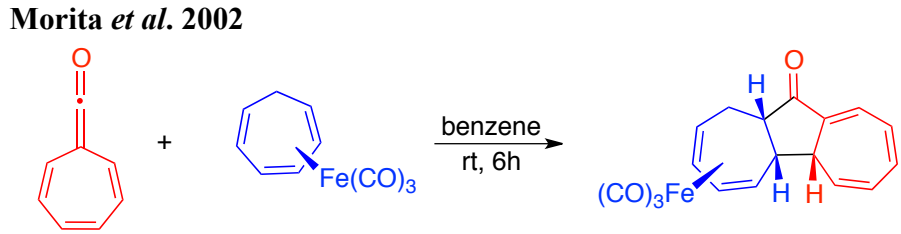
Scheme 4.3. [8+2] Cycloaddition of vinyl heptafulvene with TCNE

Intramolecular [8+2] cycloadditions were well established by Houk and co-workers utilizing heptafulvenes with tethered enophiles to afford the corresponding tricyclic systems in good yields (Scheme 4.4).[5]



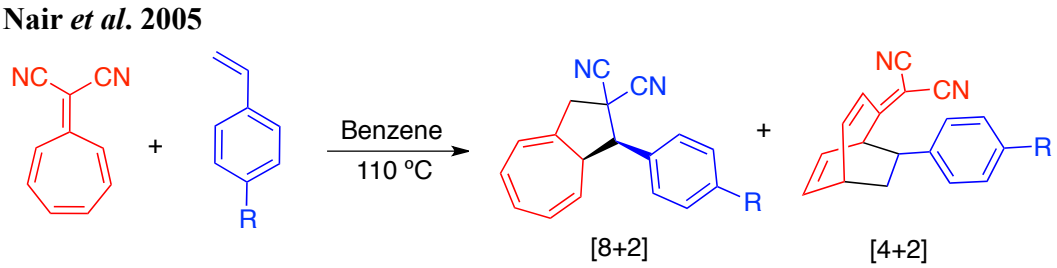
Scheme 4.4. Intramolecular [8+2] cycloadditions

Morita *et al*. employed a special kind of ketene, 8-oxoheptafulvene, as 8π component with cycloheptatriene iron carbonyl for the [8+2] cycloaddition (Scheme 4.5).[6] Although the reaction afforded a mixture of products, the [8+2] derivative was the major one.



Scheme 4.5. [8+2] Cycloaddition of 8-oxoheptafulvene with cycloheptatriene iron carbonyl

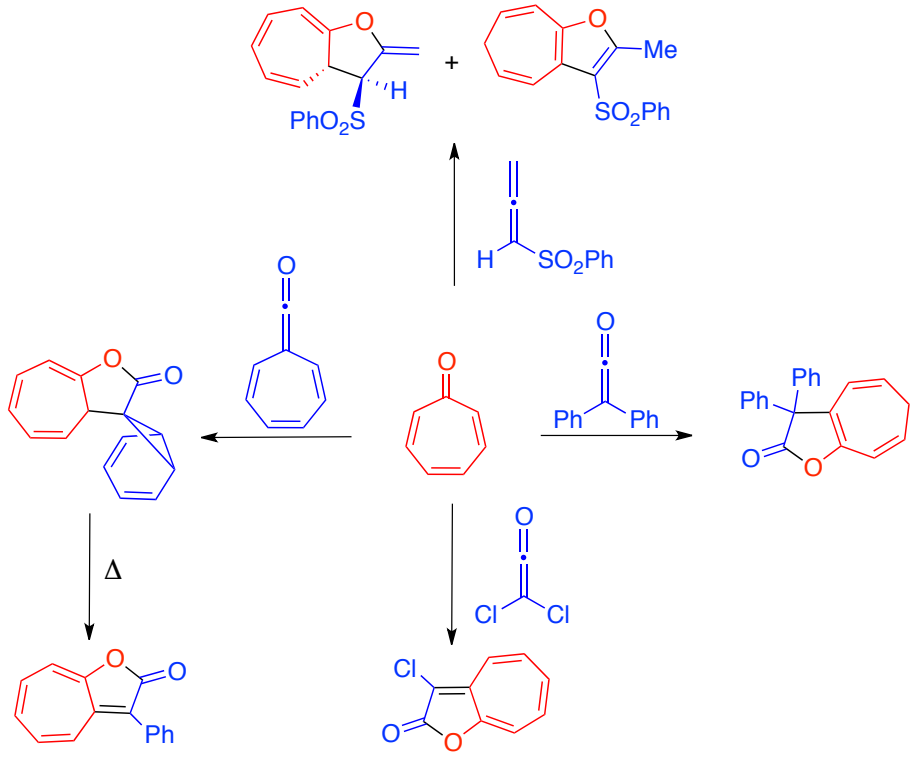
Dicyanoheptafulvenes are another type of heptafulvenes that have been applied in [8+2] cycloaddition reactions. In 2005, Nair *et al*. reported that dicyanoheptafulvene undergoes efficient cycloaddition reaction with styrenes.[7] The product was isolated as 1:1 ratio of the [8+2] and [4+2] cycloaddition product (Scheme 4.6).



Scheme 4.6. [8+2] Cycloaddition of dicyanoheptafulvene with styrenes

4.2.2. [8+2] Cycloadditions with Tropones

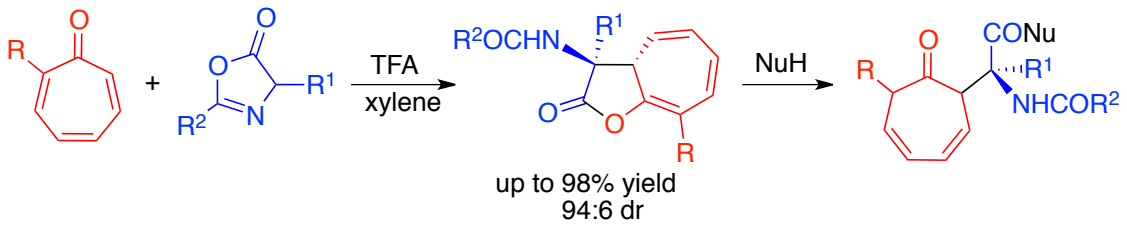
Tropone is well-explored to serve as 4π component in [4+2] cycloadditions and as 6π component in [6+3] and [6+4] cycloadditions. There are only a few examples in which tropone serves as an 8π component. For many of these reactions, tropone was shown to react with various ketenes, such as dichloroketene,[8] 8-oxoheptafulvene,[9] diphenylketene,[8] phenyl sulfonyl allene[10] (Scheme 4.7).



Scheme 4.7. [8+2] Cycloaddition of tropone with ketenes

Recently, Alemán and co-workers reported a formal [8+2] cycloaddition of tropones with azlactones under Brønsted acid catalysis.[11] The cycloaddition products obtained in this transformation can easily be opened by nucleophiles to form α,α-disubstituted amino acids (or dipeptides) bearing seven-membered rings at the quaternary position (Scheme 4.8).

Alemán *et al.* 2014

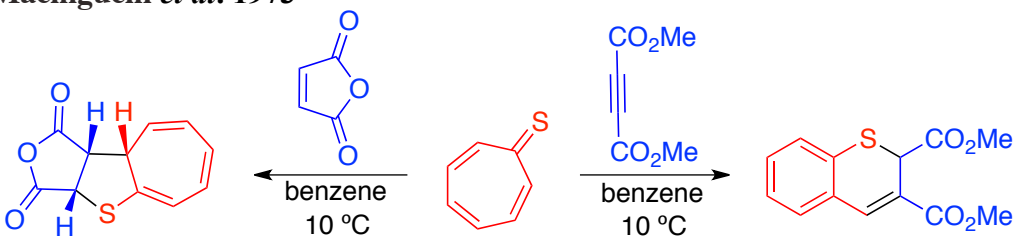


Scheme 4.8. [8+2] Cycloaddition of tropone with azlactones

4.2.3. [8+2] Cycloadditions with Tropothione

The first [8+2] cycloaddition of tropothione was reported by Machiguchi and co-workers in 1973.[12] The reaction of tropothione with maleic anhydride afforded the [8+2] cycloadduct in quantitative yield, while the addition of dimethyl acetylene dicarboxylate (DMAD) provided the rearrangement product in moderate yield.

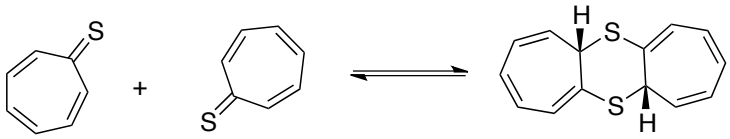
Machiguchi *et al.* 1973



Scheme 4.9. [8+2] Cycloadditions of tropothione with maleic anhydride and DMAD

In contrast to tropone, tropothione is not very stable and prefers to serve as an 8π component in cycloaddition reactions. Indeed, whereas it is stable at –78 ºC under nitrogen, it dimerizes readily at 0 ºC. This dimerization of tropothione was found to give a head-to-tail [8+8] type dimer (Scheme 4.10).[13]

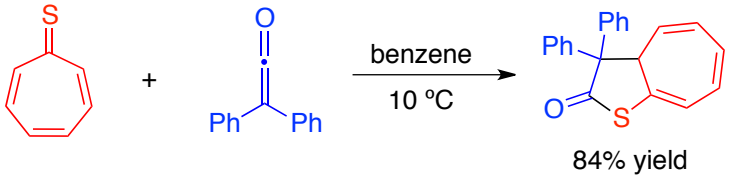
Machiguchi *et al.* 1989



Scheme 4.10. Dimerization of tropothione

The same group reported that tropothione could undergo an efficient [8+2] cycloaddition with diphenyl ketene yielding the corresponding cycloaddition product in good yield (Scheme 4.11).[14]

Machiguchi *et al.* 1990

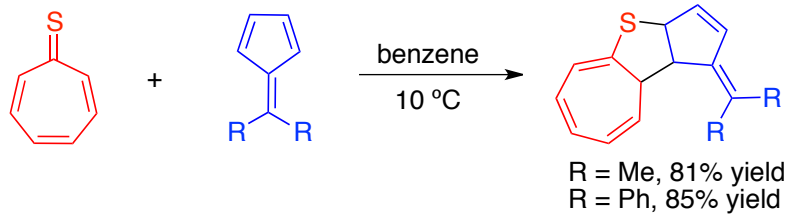


Scheme 4.11. [8+2] Cycloadditions of tropothione with diphenylketene

In contrast to the [6+4] cycloaddition between tropone and dimethylfulvene, Machiguchi *et al*. found that tropothione reacts with dimethyl and diphenyl pentafulvenes via an [8+2] cycloaddition pathway.[15] They performed theoretical investigation that seems to indicate

that the large lobe of the HOMO on the sulfur atom is responsible for the selective [8+2] cycloaddition, while the secondary orbital interactions in the course of the intrinsic reaction coordinate account for the *endo* configuration observed.

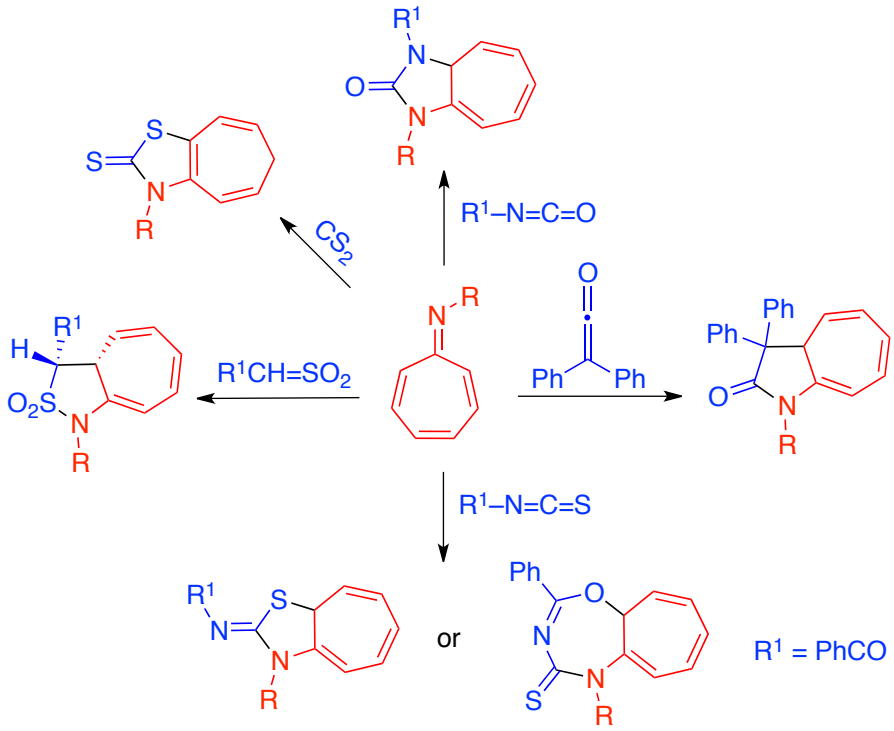
Machiguchi *et al*. 1993



Scheme 4.12. [8+2] Cycloaddition of tropothione with pentafulvenes

4.2.4. [8+2] Cycloadditions with Azaheptafulvenes

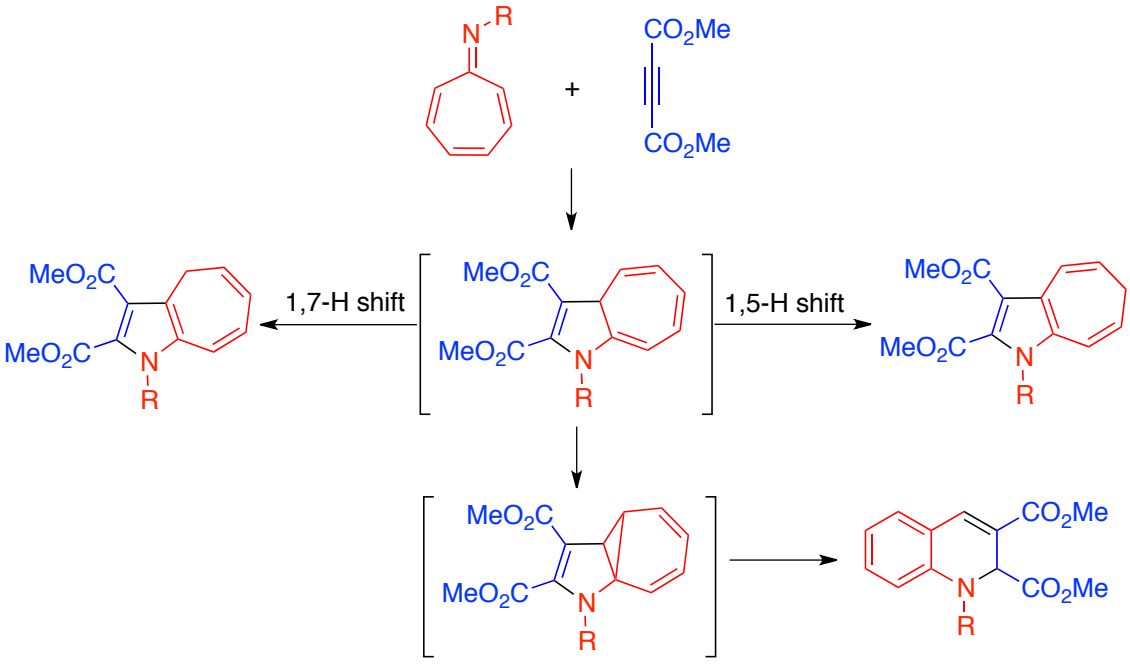
Azaheptafulvenes are very appealing reagents because they can serve as excellent 8π components in various [8+n] cycloadditions. Moreover, they are stable and easy prepare. In 1977, Kanemasa and co-workers developed the first efficient method for the synthesis of azaheptafulvenes.[16] Since then, they have been mainly used with electron-deficient 2π systems, such as isocyanates,[17] isothiocyanates,[17] carbon disulfide, sulfenes[18] and ketenes,[19] providing the corresponding [8+2] adducts in good yields (Scheme 4.13).



Scheme 4.13. [8+2] Cycloadditions of azaheptafulvenes with 2π systems

Kanemasa and co-workers reported that the reaction of azaheptafulvene with dimethyl acetylene dicarboxylate (DMAD) delivered three different products.[20] The ratio of these three products depends on the polarity of the solvent. In a polar solvent like methanol 1,7-H shift was the major product, whereas in a non-polar solvent such as benzene, 1,5-H shift predominated. The initially formed [8+2] product could also undergo ring contraction and hydrogen shift to yield a dihydroquinoline derivertive (Scheme 4.14).

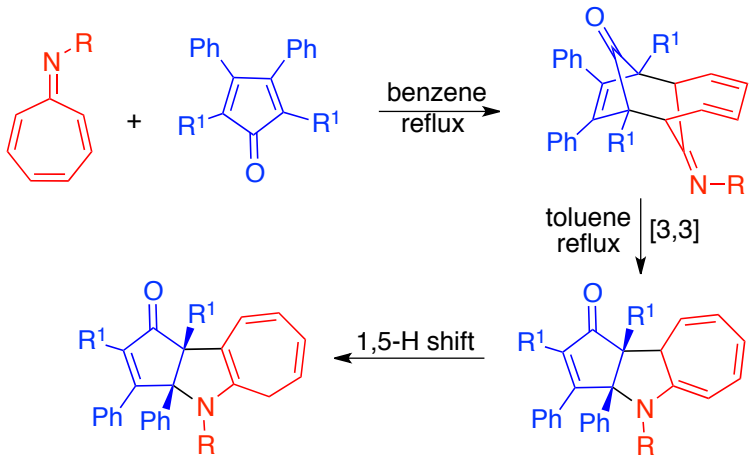
Kanemasa *et al*. 1977



Scheme 4.14. [8+2] Cycloaddition of azaheptafulvenes with DMAD

Gandolfi and co-workers demonstrated the cycloaddition reactions of azaheptafulvenes with cyclopentadienones, giving the major *exo* [6+4] cycloaddition products with minor quantities of *endo* [4+2] and [8+2] cycloaddition products.[21] They observed that the [6+4] cycloaddition adducts could undergo [3,3] sigmatropic rearrangement to afford the [8+2] products at higher temperatures (Scheme 4.15).

Gandolfi *et al*. 1993

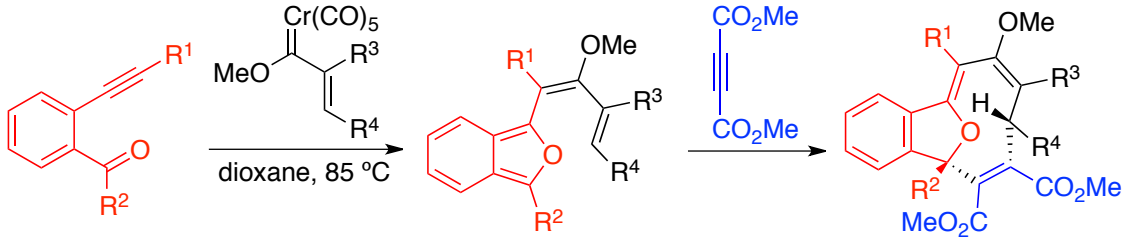


Scheme 4.15. Cycloaddition of azaheptafulvenes with cyclopentadienones

4.2.5. [8+2] Cycloadditions with Other Systems

Herndon and co-workers described an efficient [8+2] cycloaddition by utilizing dienyl isobenzofurans with dimethyl acetylene dicarboxylate for the synthesis of oxa-bridged macrocycles (Scheme 4.16).[22] The dienyl isobenzofurans were generated through the coupling of α,β-unsaturated Fischer carbene complexes with 2-alkynylbenzophenone derivatives. The macrocyclic system is a key scaffold of many biologically active compounds, such as 2,11-cyclized cembranoids or cladiellanes.

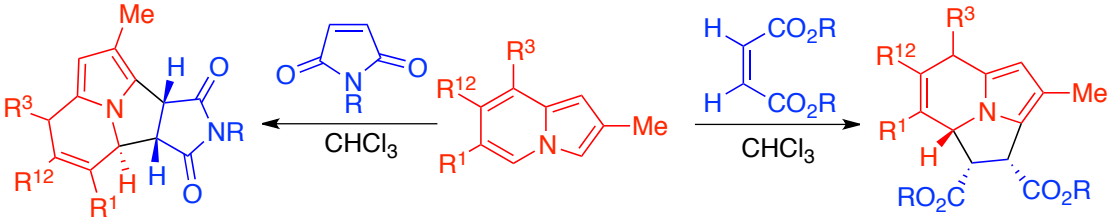
Herndon *et al*. 2003



Scheme 4.16. [8+2] Cycloaddition of dienyl isobenzofurans with DMAD

Indolizines are another class of heterocycles which contain eight π electrons in the perimeter and have been widely used in cycloaddition reactions. Kanemasa and co-workers reported the reaction of indolizines with maleates and acrylates yielding the corresponding [8+2] products (Scheme 4.17).[23] They proposed a stepwise mechanism and the reaction proceeded via [8+2] cycloaddition followed by [1,5]-sigmatropic H-shift.

Kanemasa *et al*. 1976

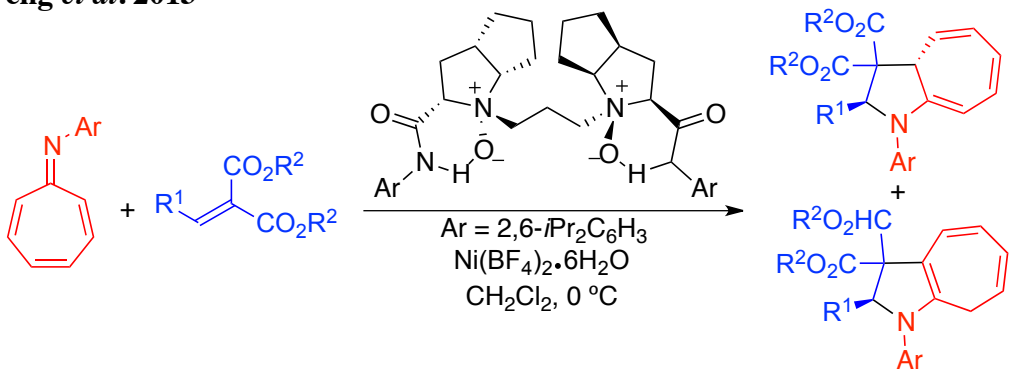


Scheme 4.17. [8+2] Cycloaddition of indolizines with maleates and acrylates

4.3. Asymmetric [8+2] Cycloaddition

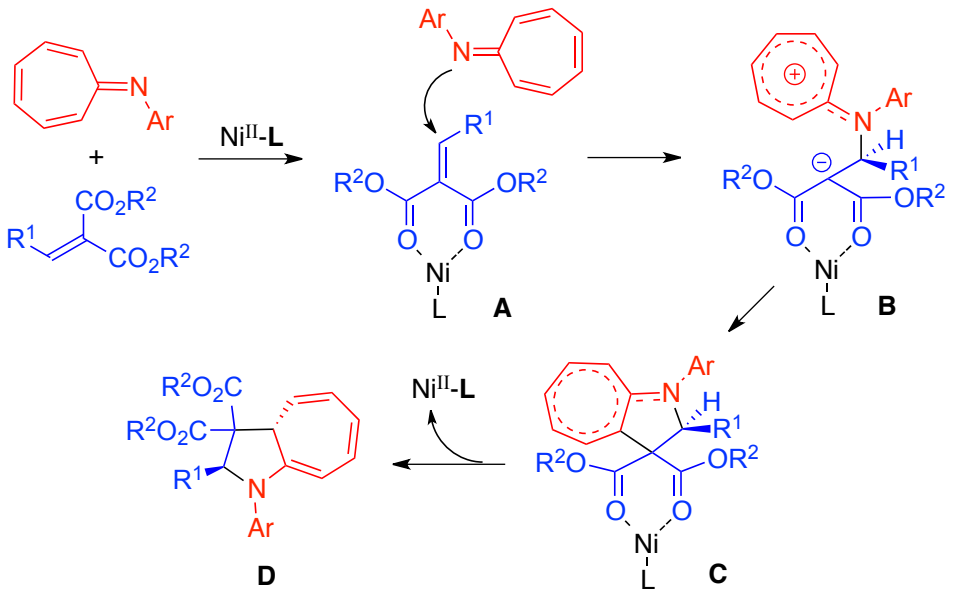
As described above, numerous methodologies to carry out [8+2] cycloaddition have been reported, but enantioselective versions remain scarce. Feng and co-workers developed the first asymmetric [8+2] cycloaddition reaction of azaheptafulvenes with alkylidene malonates mediated by a chiral *N*,*N*′-dioxide nickel complex (Scheme 4.18).[24] They found that the allylic rearrangement products are promoted by silica gel, which could be avoided by using basic Al_2O_3 for flash chromatography.

Feng *et al*. 2013



Scheme 4.18. Enantioselective [8+2] cycloaddition of azaheptafulvenes with alkylidene malonates

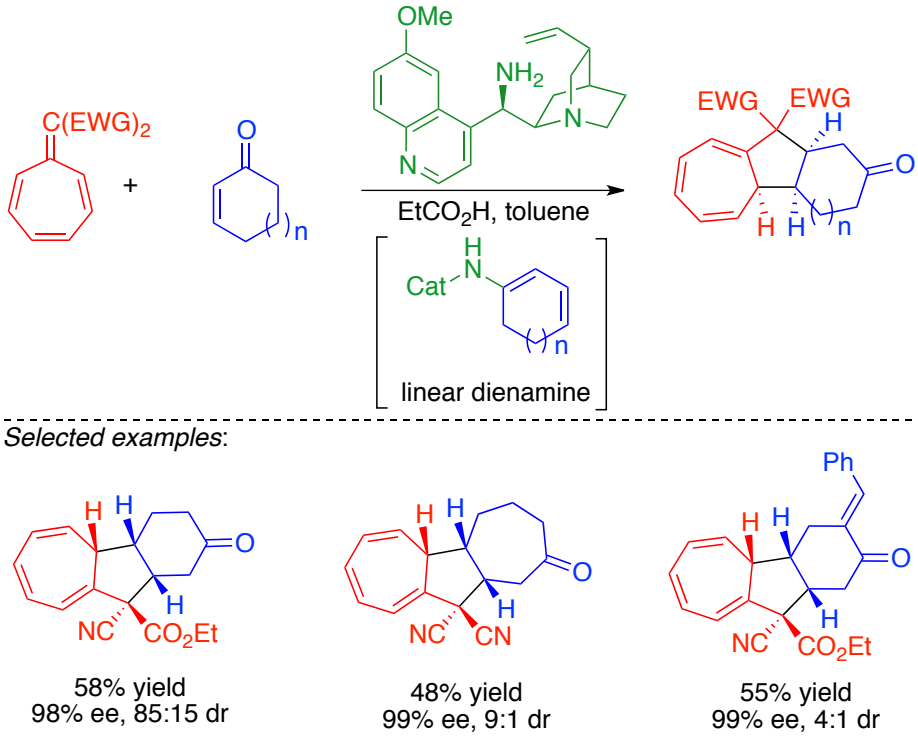
From the mechanistic point of view, the authors propose that the [8+2] cycloadditions proceed via a stepwise pathway (Scheme 4.19). First, the *N*,*N*′-dioxide and the alkylidene malonates coordinate with Ni^{II} to form an octahedral complex **A** as the intermediate. Then the azaheptafulvenes attack from the *Si* face to generate the zwitterionic intermediate **B**. Last, the ring closure occurs to afford intermediate **C**, followed by release of the catalyst and generation of the cycloaddition product **D**.



Scheme 4.19. Proposed reaction pathway for the asymmetric [8+2] cycloaddition of azaheptafulvenes with alkylidene malonates

Very recently, the Jørgensen group reported the organocatalytic asymmetric [8+2] cycloaddition reactions of 2-cycloalkenones with heptafulvenes in the presence of cinchona alkaloid primary amines as catalysts (Scheme 4.20).[25] In this study, the linear dienamine generated upon condensation of the 2-cycloalkenones with the aminocatalyst served as the 2π component in [8+2] or [4+2] cycloadditions whereas a cross-dienamine intermediate could serve as 4π component in [6+4] cycloadditions. The periselectivities of these cycloadditions depended on the ring size of the 2-cycloalkenones and the substitution pattern of the heptafulvenes. In addition, the products of the [8+2] cycloaddition reactions can undergo simple one-step transformations with triazolinedione to give access to all-carbon polycyclic compounds.

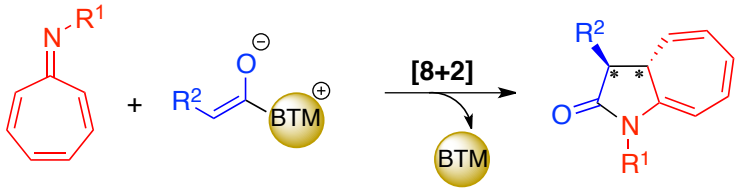
Jørgensen *et al*. 2017



Scheme 4.20. Enantioselective [8+2] cycloaddition of 2-cycloalkenones with heptafulvenes

4.4. Aim of the Project

Considering the importance of [8+2] cycloadditions in organic synthesis and the limited examples of asymmetric [8+2] cycloadditions, we aim to develop a general and efficient approach for peri-, regio-, and stereoselective [8+2] cycloaddition. On the basis of our previous project on formal [4+2] cycloaddition reactions promoted by an immobilized isothiourea, we envisioned that chiral ammonium enolates (derived from activated carboxylic acids and isothioureas) could be suitable reaction partners for catalytic [8+2] cycloaddition with azaheptafulvenes, which would play the role of 8π dipolarophiles.



Scheme 4.21. Enantioselective [8+2] cycloaddition of azaheptafulvenes with ammonium enolates

In order to further explore the synthetic potential of this methodology, we aim to test a Diels–Alder reaction of the resulting [8+2] cycloadducts with highly active dienophiles, which may sereve as 4π components due to the generated cycloheptatriene unit.

4.5. References

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Organocatalysis

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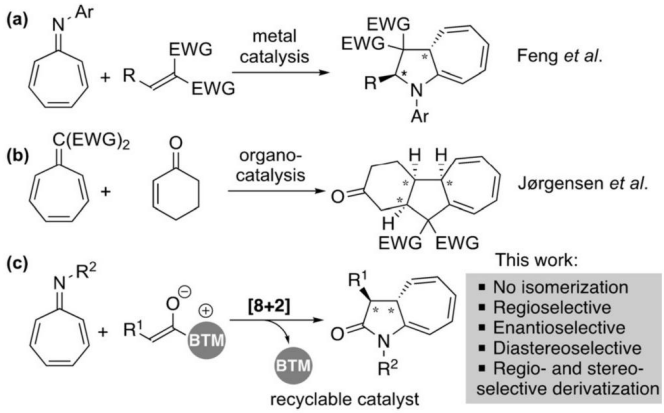
Catalytic Asymmetric [8+2] Annulation Reactions Promoted by a Recyclable Immobilized Isothiourea

*Shoulei Wang, Carles Rodríguez-Escrich, and Miquel A. Pericàs**

Abstract: *Higher-order cycloaddition reactions constitute an efficient approach towards the construction of medium to large ring systems. However, enantioselective versions of these transformations remain scarce, which hampers their deployment in medicinal chemistry, or any other discipline in which homochirality is deemed crucial. Herein, we report a novel method for the production of enantiomerically enriched cycloheptatrienes fused to a pyrrolidone ring on the basis of an isothiourea-catalyzed periselective [8+2] cycloaddition reaction between chiral ammonium enolates (generated in situ from carboxylic acids) and azaheptafulvenes. The resulting bicyclic compounds can be hydrogenated, but, most remarkably, they can also undergo completely regioselective [4+2] cycloaddition with active dienophiles to give architecturally complex polycyclic compounds in a straightforward manner.*

Cyclic structures are ubiquitous in natural products and pharmaceutical compounds. Among the myriad strategies devised to construct such architectures,[1] cycloaddition reactions constitute one of the most efficient approaches in terms of atom economy and overall reaction selectivity.[2] Indeed, the synthesis of rings with up to six members by either thermal or photochemical [2+2],[3] [3+2],[4] and [4+2][5] processes is well established. On the other hand, the synthesis of medium and large rings through reactions involving more than six π electrons (so-called higher-order cycloaddition reactions[6]) is an interesting approach to build complex polycyclic compounds and bridge-containing carbocyclic products. However, this alternative[7] is often hampered by lack of periselectivity and other competing side reactions,[8] which, along with the extra challenge of transferring stereochemical information across a number of bonds, can explain the lack of general methods to produce enantiomerically enriched compounds through higher-order cycloaddition reactions.[9]

Heptafulvenes[10] and their heteroanalogues (tropone,[11] tropothione,[12] and the azaheptafulvenes[13]), a subclass of the family of "non-benzenoid aromatic compounds", have been recognized as important synthons for higher-order cycloaddition reactions owing to their conjugated cyclic polyolefin systems. Among all the possible reaction pathways of heptafulvene derivatives, the [8+2] cycloaddition provides a direct approach to highly functionalized bicyclic [5.3.0] rings, which are core scaffolds in numerous natural products.[14] Since the first [8+2] cycloaddition introduced by Doering and Wiley in 1960,[15] various methodologies to carry out this process have been described,[16] but enantioselective versions remain scarce: To the best of our knowledge, a metal-mediated cycloaddition reported by Feng and co-workers[17] (Scheme 1a) and an organocatalytic cycloaddition described by Jørgensen and co-workers[18] (Scheme 1b) are the only catalytic enantioselective [8+2] reactions reported to date. Therefore, the development of a general and efficient approach for peri-, regio-, and stereoselective [8+2] cycloaddition remains a highly attractive and challenging goal.



Scheme 1. Enantioselective versions of [8+2] cycloaddition. EWG = electron-withdrawing group.

We envisioned that chiral ammonium enolates[19] (derived from activated carboxylic acids and isothioureas) could be suitable reaction partners for catalytic [8+2] cycloaddition with azaheptafulvenes, which would play the role of 8π dipolarophiles. Herein, we present the implementation of this strategy, which leads to enantiomerically enriched 7,5-fused heterocyclic compounds (Scheme 1c). The cycloheptatrienes generated can be either hydrogenated or derivatized in a Diels–Alder reaction to afford bridged polycyclic products in a highly regioselective manner.

On the basis of our previous studies on formal hetero-[4+2] cycloaddition reactions promoted by an immobilized isothiourea of the benzotetramisole (BTM) type,[19e,g] we investigated a model reaction of the azaheptafulvene **2a** with phenylacetic acid (**3a**) in the presence of a polystyrene-

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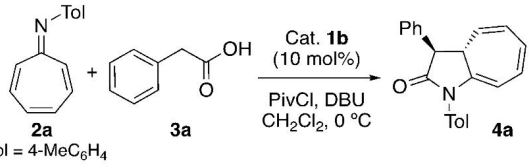
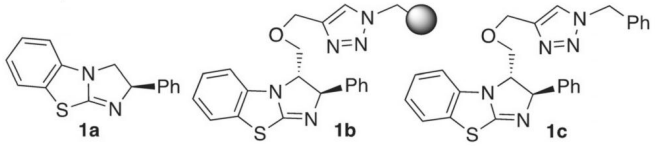
Table 1: Optimization of the reaction conditions.[a]



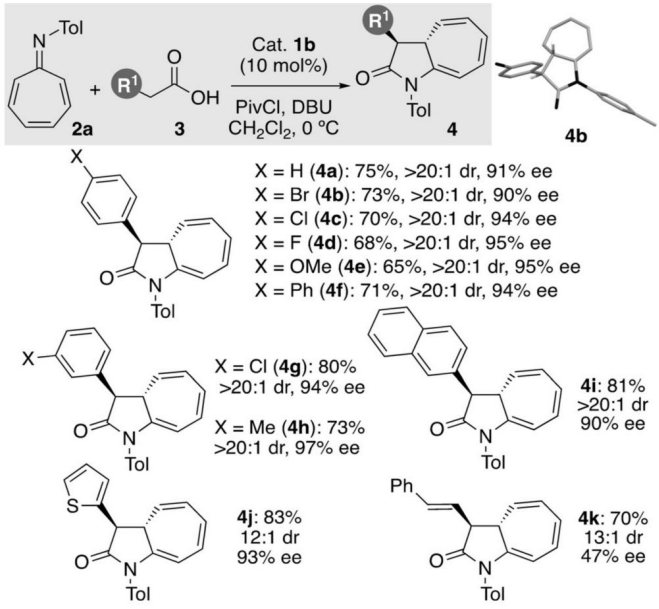
Entry	Modification of the standard conditions	Conv. [%]	dr[b]	*ee*[c] [%]
1	none	>95	96:4	91
2	**1a** as the catalyst	>95	75:25	91
3	**1c** as the catalyst	>95	96:4	90
4	^{i}Pr$_2$NEt as the base	>95	96:4	87
5	Et$_3$N as the base	>95	96:4	70
6	TsCl instead of PivCl	65	97:3	90
7	BnCOCl instead of PivCl	55	96:4	91
8	THF instead of CH_2Cl_2	88	98:2	20
9	Et$_2$O instead of CH_2Cl_2	20	76:24	–
10	$CHCl_3$ instead of CH_2Cl_2	>95	97:3	88
11	5 mol% catalyst	78	97:3	84

[a] Reactions were performed on a 0.1 mmol scale. [b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [c] The *ee* value was determined by HPLC on a chiral stationary phase. Bn = benzyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Tol = *p*-tolyl, Ts = *p*-toluenesulfonyl.



supported BTM catalyst (Table 1). After a preliminary study, we established a standard protocol based on the use of immobilized isothiourea **1b**, pivaloyl chloride (PivCl), and DBU in CH_2Cl_2 at 0 °C. Under these conditions, azaheptafulvene **2a** was fully consumed and the desired [8+2] product **4a** was obtained with high stereoselectivity (96:4 dr, 91% *ee*; Table 1, entry 1). Previously reported possible side products,[17] such as those derived from isomerization of the cycloheptatriene unit, were not detected. For the sake of comparison, we also tested the homogeneous isothiourea catalyst **1a**, but only moderate diastereoselectivity was observed (entry 2). This result suggested that the additional stereocenter present in **1b** was critical, as confirmed by the results obtained with the homogeneous analogue **1c** (entry 3). Likewise, other bases, such as ^{i}Pr$_2$NEt and Et$_3$N, resulted in lower enantioselectivity, although conversion and diastereoselectivity remained the same (entries 4 and 5). Substitution of the activating reagent (PivCl) for BnCOCl or TsCl (entries 6 and 7) did not improve the results either, whereas other solvents screened had a negative impact on reactivity and stereoselectivity (entries 8–10). Furthermore, a decrease in the catalyst loading to 5 mol% resulted in lower reactivity and stereoselectivity (entry 11).

After the preliminary optimized reaction conditions passed the stress tests summarized in Table 1, we turned our attention to validating the generality of this [8+2] annulation reaction. A broad range of substituted phenylacetic acids bearing electron-withdrawing and electron-donating substituents were tolerated, giving rise to the cycloadducts **4a–h** in



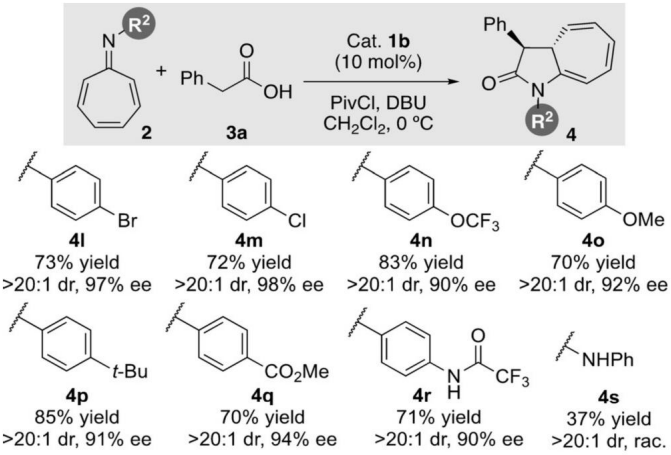
Scheme 2. Scope of the reaction with respect to the aryl acetic acid substrate. Reactions were performed on a 0.1 mmol scale (see the Supporting Information).

good yields (65–80%) with high enantioselectivity (90–97% *ee*) and diastereoselectivity (>20:1 dr; Scheme 2). Bulkier 2-naphthylacetic acid also proved to be a good substrate, delivering the desired product **4i** with comparable yield and stereoselectivity (>20:1 dr, 90% *ee*). A heteroaromatic moiety could also be accommodated in **3**, as shown by the synthesis of the corresponding 2-thienyl derivative (product **4j**, 83% yield, 93% *ee*); although the diastereomeric ratio decreased, the result was still more than satisfactory (12:1). The system also worked with unsaturated carboxylic acids, providing **4k** in good yield and diastereoselectivity (13:1 dr) but moderate enantioselectivity; however, the use of purely aliphatic acids resulted in no conversion. The absolute configuration of **4b** could be ascertained by X-ray diffraction analysis,[20] and that of **4a**,**c–k** was assigned by analogy.

Next, we set our sights on the evaluation of various *N*-aryl-substituted 8-azaheptafulvenes in this cycloaddition. In general, the [8+2] annulation reactions were insensitive to the electronic nature of the aromatic N-substituent on the azaheptafulvene (R^2). A series of cycloheptatriene-fused pyrrolidone derivatives **4l–r** were synthesized in good yields (70–85%) with high stereoselectivity (90–98% *ee*, >20:1 dr in all cases; Scheme 3).

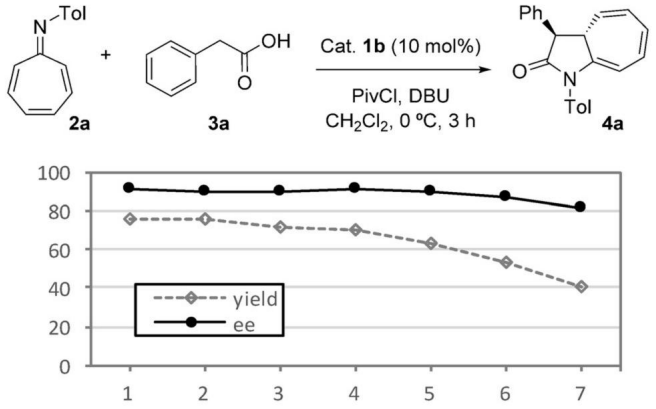
Further attempts to explore the scope of the reaction by using tropone phenylhydrazone as a substrate gave the expected product **4s** in low yield in racemic form, but with high diastereoselectivity. Disappointingly, no [8+2] product was observed with a tropolone derivative bearing a methoxy substituent on C2 of the 8-azaheptafulvene.

From a practical perspective, the possibility of recycling the immobilized isothiourea catalyst **1b** is appealing owing to the inherent reduction of costs and increase in overall efficiency. To this end, the reaction between **2a** and **3a** was



Scheme 3. Scope of the reaction with respect to the azaheptafulvene. Reactions were performed on a 0.1 mmol scale (see the Supporting Information).

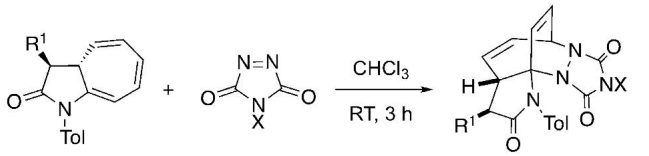
carried out in a series of experiments in which catalyst **1b** was recovered by simple filtration and reused by adding fresh reactants after each run. No significant decrease in stereoselectivity was observed, and only marginal erosion of the yield took place over the first four runs (Scheme 4). The accumulated turnover number (TON) for these recycling experiments was 44.7, which shows the advantage of this strategy over the usual approach, for which a maximum TON of 10 can be achieved with a catalyst loading of 10 mol%.



Scheme 4. Recyclability tests.

To demonstrate the synthetic potential of this methodology, we decided to test the behavior of the [8+2] cycloadducts **4** as 4π components in a Diels–Alder reaction. Thus, cycloheptatriene-fused pyrrolidone **4a** was treated with *N*-phenyltriazolinedione (**5a**) in $CHCl_3$ at room temperature. To our delight, the [4+2] product **6a** was obtained as a single regioisomer in good yield with high stereoselectivity (>20:1 dr, 87% *ee*). The general applicability of the Diels–Alder reaction between cycloadducts **4** and N-substituted triazolinediones **5** was subsequently investigated. As shown in Table 2, structurally unique bridged polycyclic products **6** containing one quaternary and three tertiary stereocenters

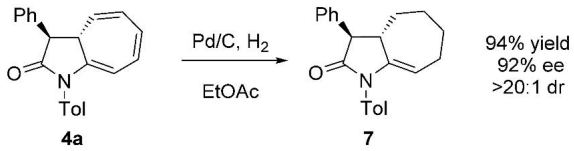
Table 2: Diels–Alder reactions of **4** with different substituted triazolinediones.[a]



Entry	X	R^1	dr	Yield [%]
1	Ph (**6a**)	Ph	>20:1	75[b]
2	Ph (**6b**)	4-BrC_6H_4	>20:1	80
3	Et (**6c**)	Ph	>20:1	70
4	^{n}Bu (**6d**)	Ph	>20:1	77

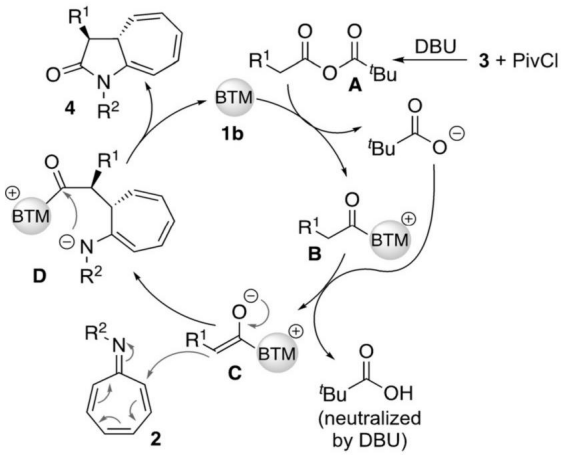
[a] Reactions were performed on a 0.1 mmol scale (see the Supporting Information). [b] The product was formed with 87% *ee*, as determined by HPLC on a chiral stationary phase.

could be efficiently prepared in a highly regio- and stereoselective manner through a [8+2]/[4+2] reaction sequence. The structure and absolute configuration of compounds **6** were confirmed by X-ray diffraction analysis of **6b**.[20] To further demonstrate the versatility of these cycloadducts, we showed that the cycloheptatriene-fused pyrrolidone **4a** could be hydrogenated in the presence of a catalytic amount of Pd/C to provide compound **7** in good yield while retaining the stereochemical information in **4a** (Scheme 5).



Scheme 5. Catalytic hydrogenation of **4a**.

We propose the following catalytic cycle for this transformation on the basis of previous reports of isothiourea-mediated cyclization reactions (Scheme 6):[21] The mixed anhydride **A** formed in situ from **3** and pivaloyl chloride



Scheme 6. Proposed catalytic pathway.

reacts with the isothiourea **1b** to form the corresponding acyl ammonium species **B**, which is deprotonated by the pivalate to generate the corresponding enolate **C** (DBU acts as a shuttle base to deprotonate the pivalic acid generated[22]). Subsequently, 1,8-conjugate addition of **C** onto the azaheptafulvene **2** gives rise to **D**, which readily cyclizes to generate the desired cycloadduct **4** with concomitant release of the catalyst, which can then participate in the next cycle. At present we cannot rule out a concerted mechanism, but literature precedent suggests[16d] that a stepwise mechanism is operative with highly polarized substrates.

In conclusion, we have developed the first asymmetric organocatalytic [8+2] annulation reaction between azaheptafulvenes and aryl acetic acids activated in situ for the direct synthesis of enantiomerically enriched cycloheptatriene-fused pyrrolidone derivatives. The transformation is promoted by a supported isothiourea catalyst that can be recycled at least seven times by simple filtration. Moreover, we have studied the derivatization of the resulting [8+2] cycloadducts by means of [4+2] cycloaddition to give bridged polycyclic products in a regioselective manner. The [8+2]/[4+2] cycloaddition sequence reported herein represents an efficient stereoselective synthetic approach to polycyclic compounds. Further synthetic application of this methodology is currently under way.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · [8+2] cycloaddition · higher-order cycloaddition reactions · immobilized catalysts · isothioureas

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[20] CCDC 1562521 (**4b**) and 1562520 (**6b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Supporting Information

Catalytic Asymmetric [8+2] Annulation Reacions Promoted by a Recyclable Immobilized Isothiourea

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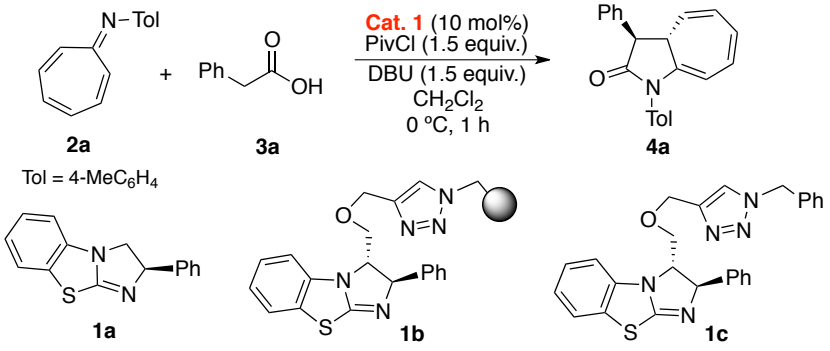
Table of Contents

1. General information

Unless otherwise stated, all commercial reagents were used as received. Flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. Thin layer chromatography was carried out using Merck TLC Silicagel 60 F254 aluminum sheets. Components were visualized by UV light (λ = 254 nm) and stained with *p*-anisaldehyde or phosphomolybdic dip. NMR spectra were registered in a Bruker Advance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature, operating at 400 MHz (^1H) and 100 MHz (^{13}C). TMS was used as internal standard for ^1H NMR and $CDCl_3$ for ^{13}C NMR. Chemical shifts are reported in ppm referred to TMS. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses of the polystyrene supported catalysts were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid, Spain. High performance liquid chromatography (HPLC) was performed on an Agilent Technologies chromatograph (1100 Series), using Chiralcel columns and guard columns. Racemic samples were prepared using 20-40 mol% DMAP instead of the polymer-supported benzotetramisole (PS-BTM), following the same conditions used for the asymmetric reaction. Azaheptafulvenes were prepared according to the literature procedure.[1] PS-BTM catalyst was prepared according to our previously reported procedure.[2]

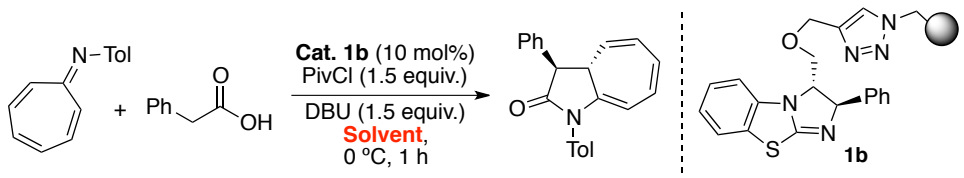
2. Screening of conditions for the [8+2] cycloaddition reaction[a]

Table S1. Catalysts screening



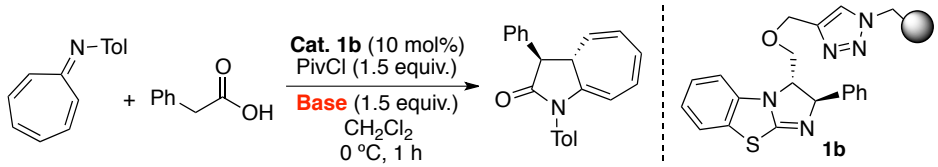
Entry	Cat.	Conv. (%)[b]	dr[b]	ee (%)[c]
1	**1a**	>95	75:25	91
2	**1b**	>95	96:4	91
3	**1c**	>95	96:4	90

Table S2. Solvents screening



Entry	Solvent	Conv. (%)[b]	dr[b]	ee (%)[c]
1	CH_2Cl_2	>95	96:4	91
2	THF	88	98:2	20
3	$CHCl_3$	>95	97:3	88
4	toluene	67	97:3	10
5	Et_2O	<15	76:24	-

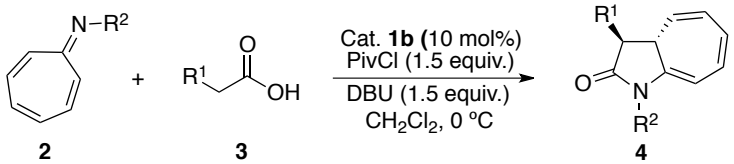
Table S3. Bases screening



Entry	Base	Conv. (%)[b]	dr[b]	ee (%)[c]
1	*i*-Pr_2NEt	>95	96:4	87
2	DBU	>95	96:4	91
3	Et_3N	>95	96:4	70

[a] Reactions performed on a 0.1 mmol scale. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC.

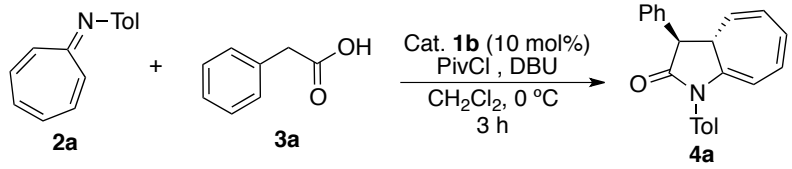
3. General procedure for the [8+2] cycloaddition reaction



To a solution of acid **3** (0.15 mmol, 1.5 equiv.) in CH_2Cl_2 (0.5 mL) at 0 ºC was added polymer-supported BTM **1b** (0.010 mmol, f = 0.9 mmol/g, 11.2 mg, 10 mol%). Pivaloyl chloride (0.15 mmol, 18.4 µL, 1.5 equiv.) and DBU (0.15 mmol, 22.4 µL, 1.5 equiv.) were added dropwise to the mixture, which was shaken at 0 ºC for 10 min. Then **2** (0.10 mmol, 1.0 equiv.) was added to the reaction mixture and it was shaken at the same temperature until **2** was consumed (determined by TLC). After that, the resin was filtered off, washed with CH_2Cl_2 (4 × 1 mL) and the combined organic layers were concentrated under reduced pressure. Crude products **4** were directly purified by flash chromatography (FC).

4. General procedure for the recycling experiments

To a solution of phenylacetic acid **3a** (0.15 mmol, 20.4 mg, 1.5 equiv.) in CH_2Cl_2 (0.5 mL) at 0 ºC was added polymer-supported BTM **1b** (0.010 mmol, f = 0.9 mmol/g, 11.2 mg, 10 mol%). Pivaloyl chloride (0.15 mmol, 18.4 µL, 1.5 equiv.) and DBU (0.15 mmol, 22.4 µL, 1.5 equiv.) were added dropwise to the mixture, which was shaken at 0 ºC for 10 min. Then **2a** (0.10 mmol, 19.5mg, 1.0 equiv.) was added and the reaction mixture and it was shaken at the same temperature for 3 hours. After that the resin was filtered off and washed with dry CH_2Cl_2 (4 × 1 mL). The recovered catalyst was dried under vacuum at 30 ºC for 2-3 h. The dried catalyst was directly used in the next recycling run.



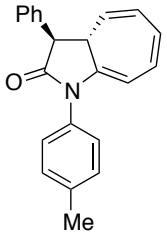
2a **3a** **4a**

Cycle	Yield (%)[a]	dr[b]	ee (%)[c]
1	75	>95:5	91
2	75	>95:5	90
3	71	>95:5	90
4	70	>95:5	91
5	63	>95:5	90
6	53	>95:5	87
7	40	>95:5	81

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC.

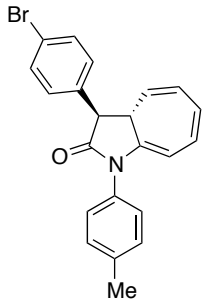
5. Compound characterization

(3*R*,3a*S*)-3-Phenyl-1-(*p*-tolyl)-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



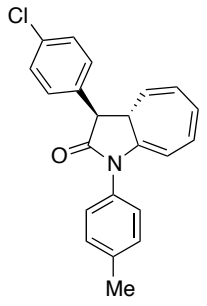
Cycloaddition product **4a** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 7:1) in 75% yield (23.4 mg, >20:1 dr). White solid, melting point: 118-119 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 3.11-3.13 (m, 1H), 4.02 (d, *J* = 4.8 Hz, 1H), 5.37-5.41 (m, 1H), 5.45 (d, *J* = 6.4 Hz, 1H), 6.20-6.26 (m, 2H), 6.38-6.43 (m, 1H), 7.18-7.20 (m, 2H), 7.28-7.32 (m, 3H), 7.35-7.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 44.7, 54.7, 100.0, 122.8, 125.4, 127.0 (2C), 127.5, 127.5 (2C), 127.9, 129.0 (2C), 129.4, 130.2 (2C), 132.2, 138.5, 139.1, 139.2, 175.5; IR (ATR): ν = 515, 571, 678, 706, 825, 1205, 1246, 1364, 1397, 1513, 1631, 1717, 3021 cm^{-1}; HRMS calcd. for $C_{22}H_{19}NNaO$ $[M + Na]^+$: 336.1359, found: 336.1357; $[\alpha]_D^{25}$ = +45.1 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 91% ee): t_{major} = 6.7 min, t_{minor} = 11.0 min.

(3*R*,3a*S*)-3-(4-Bromophenyl)-1-(*p*-tolyl)-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



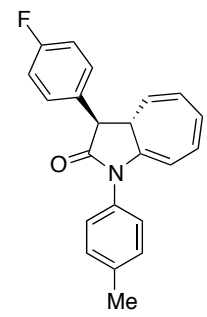
Cycloaddition product **4b** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 7:1) in 73% yield (28.5 mg, >20:1 dr). White solid, melting point: 135-137 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3H), 3.09-3.11 (m, 1H), 4.00 (d, *J* = 5.2 Hz, 1H), 5.37-5.40 (m, 1H), 5.48 (d, *J* = 6.4 Hz, 1H), 6.23-6.29 (m, 2H), 6.40-6.45 (m, 1H), 7.18-7.20 (m, 2H), 7.26-7.32 (m, 4H), 7.51-7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 44.4, 54.1, 100.3, 121.5, 122.5, 125.5, 127.0 (2C), 128.1, 129.3 (2C), 129.4, 130.3 (2C), 132.0, 132.1 (2C), 137.9, 138.6, 138.9, 174.9; IR (ATR): ν = 510, 557, 701, 812, 1008, 1215, 1248, 1399, 1513, 1619, 1636, 1716, 2961, 3023 cm^{-1}; HRMS calcd. for $C_{22}H_{18}BrNNaO$ $[M + Na]^+$: 414.0464, found: 414.0462; $[\alpha]_D^{25}$ = –13.2 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 90% ee): t_{major} = 6.8 min, t_{minor} = 12.3 min.

(3*R*,3a*S*)-3-(4-Chlorophenyl)-1-(*p*-tolyl)-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



Cycloaddition product **4c** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 7:1) in 70% yield (24.3 mg, >20:1 dr). White solid, melting point: 119-121 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 3.06-3.09 (m, 1H), 3.99 (d, *J* = 5.2 Hz, 1H), 5.34-5.38 (m, 1H), 5.45 (dd, *J* = 1.6, 6.4 Hz, 1H), 6.20-6.26 (m, 2H), 6.38-6.43 (m, 1H), 7.15-7.18 (m, 2H), 7.27-7.36 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 44.4, 54.0, 100.3, 122.5, 125.5, 127.0 (2C), 128.1, 128.9 (2C), 129.1 (2C), 129.4, 130.3 (2C), 132.0, 133.5, 137.4, 138.6, 138.9, 174.9; IR (ATR): ν = 512, 561, 689, 818, 1014, 1090, 1205, 1255, 1364, 1398, 1515, 1627, 1716, 2922 cm^{-1}; HRMS calcd. for $C_{22}H_{18}ClNNaO$ $[M + Na]^+$: 370.0969, found: 370.0971; $[\alpha]_D^{25}$ = –7.5 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 94% ee): t_{major} = 6.4 min, t_{minor} = 10.8 min.

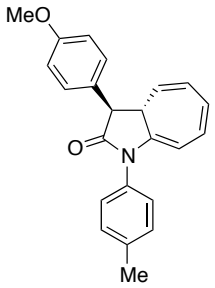
(3*R*,3a*S*)-3-(4-Fluorophenyl)-1-(*p*-tolyl)-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



Cycloaddition product **4d** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from from 20:1 to 7:1) in 68% yield (22.5 mg, >20:1 dr). White solid, melting point: 99-101 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 3.06-3.09 (m, 1H), 3.99 (d, *J* = 4.8 Hz, 1H), 5.35-5.39 (m, 1H), 5.45 (dd, *J* = 1.2, 6.4 Hz, 1H), 6.20-6.26 (m, 2H), 6.38-6.42 (m, 1H), 7.04-7.08 (m, 2H), 7.16-7.18 (m, 2H), 7.27-7.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 44.6, 53.9, 100.2, 115.9 (d, *J* = 21.5 Hz, 2C), 122.6, 125.5, 127.0 (2C), 128.1, 129.2 (d, *J* = 8.1 Hz, 2C), 129.4, 130.2 (2C), 132.1,

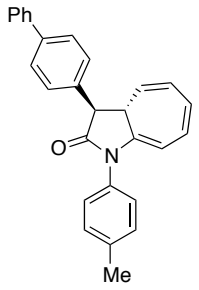
134.8 (d, *J* = 3.3 Hz), 138.6, 139.0, 162.2 (d, *J* = 246.2 Hz), 175.2; IR (ATR): ν = 504, 568, 696, 806, 1158, 1219, 1268, 1369, 1400, 1509, 1546, 1635, 1718, 2856, 2921 cm^{-1}; HRMS calcd. for $C_{22}H_{18}FNNaO$ $[M + Na]^+$: 354.1265, found: 354.1267; $[\alpha]_D^{25}$ = +8.6 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 95% ee): t_{major} = 6.1 min, t_{minor} = 9.8 min.

(3*R*,3a*S*)-3-(4-Methoxyphenyl)-1-(*p*-tolyl)-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



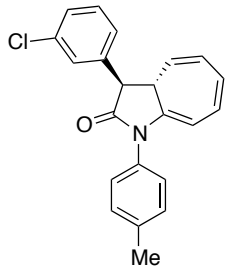
Cycloaddition product **4e** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 7:1) in 65% yield (22.3 mg, >20:1 dr). White solid, melting point: 115-116 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 3.07-3.09 (m, 1H), 3.80 (s, 3H), 3.95 (d, *J* = 5.2 Hz, 1H), 5.35-5.39 (m, 1H), 5.43 (dd, *J* = 1.6, 6.4 Hz, 1H), 6.19-6.24 (m, 2H), 6.37-6.41 (m, 1H), 6.88-6.92 (m, 2H), 6.16-6.18 (m, 2H), 7.27-7.29 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 44.7, 53.9, 55.3, 100.0, 114.4 (2C), 122.9, 125.4, 127.0 (2C), 127.9, 128.6 (2C), 129.4, 130.2 (2C), 131.2, 132.2, 138.4, 139.3, 159.0, 175.7; IR (ATR): ν = 527, 697, 811, 1027, 1180, 1210, 1244, 1400, 1513, 1623, 1642, 1715, 2917 cm^{-1}; HRMS calcd. for $C_{23}H_{21}NNaO_2$ $[M + Na]^+$: 366.1464, found: 366.1463; $[\alpha]_D^{25}$ = –10.1 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 230 nm, 95% ee): t_{major} = 10.7 min, t_{minor} = 19.5 min.

(3*R*,3a*S*)-3-([1,1'-Biphenyl]-4-yl)-1-(*p*-tolyl)-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



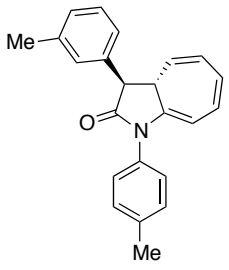
Cycloaddition product **4f** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 5:1) in 71% yield (27.6 mg, >20:1 dr). White solid, melting point: 155-156 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 3.16-3.19 (m, 1H), 4.07 (d, *J* = 5.2 Hz, 1H), 5.40-5.43 (m, 1H), 5.47 (dd, *J* = 1.6, 6.4 Hz, 1H), 6.21-6.27 (m, 2H), 6.40-6.44 (m, 1H), 7.20-7.22 (m, 2H), 7.29-7.31 (m, 2H), 7.33-7.37 (m, 1H), 7.43-7.46 (m, 4H), 7.57-7.61 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 44.6, 54.4, 100.1, 122.8, 125.4, 127.0 (2C), 127.1 (2C), 127.3, 127.8 (2C), 128.0 (3C), 128.8 (2C), 129.4, 130.2 (2C), 132.2, 138.1, 138.5, 139.2, 140.6, 140.7, 175.4; IR (ATR): ν = 513, 696, 756, 816, 1215, 1262, 1366, 1396, 1512, 1541, 1633, 1721, 2918, 3012 cm^{-1}; HRMS calcd. for $C_{28}H_{23}NNaO$ $[M + Na]^+$: 412.1672, found: 412.1674; $[\alpha]_D^{25}$ = –20.5 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 94% ee): t_{major} = 7.9 min, t_{minor} = 11.7 min.

(3*R*,3a*S*)-3-(3-Chlorophenyl)-1-(*p*-tolyl)-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



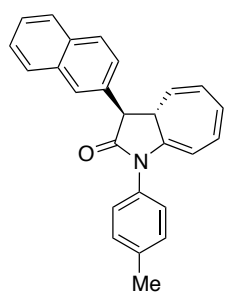
Cycloaddition product **4g** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 7:1) in 80% yield (27.8 mg, >20:1 dr). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 3.07-3.10 (m, 1H), 3.98 (d, *J* = 5.2 Hz, 1H), 5.34-5.38 (m, 1H), 5.45 (dd, *J* = 1.6, 6.4 Hz, 1H), 6.20-6.26 (m, 2H), 6.38-6.42 (m, 1H), 7.17-7.19 (m, 2H), 7.24-7.31 (m, 5H), 7.34-7.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 44.4, 54.3, 100.3, 122.4, 125.6, 125.9, 127.0 (2C), 127.8, 127.8, 128.1, 129.4, 130.3 (3C), 132.0, 134.8, 138.6, 138.8, 140.9, 174.7; IR (ATR): ν = 512, 687, 797, 1081, 1210, 1252, 1366, 1398, 1478, 1513, 1633, 1720, 2922 cm^{-1}; HRMS calcd. for $C_{22}H_{18}ClNNaO$ $[M + Na]^+$: 370.0969, found: 370.0968; $[\alpha]_D^{25}$ = +10.9 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 230 nm, 94% ee): t_{major} = 6.5 min, t_{minor} = 11.9 min.

(3*R*,3a*S*)-3-(*m*-Tolyl)-1-(*p*-tolyl)-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



Cycloaddition product **4h** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 7:1) in 73% yield (23.9 mg, >20:1 dr). Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 2.39 (s, 3H), 3.09-3.11 (m, 1H), 3.96 (d, *J* = 5.2 Hz, 1H), 5.36-5.39 (m, 1H), 5.44 (dd, *J* = 1.6, 6.4 Hz, 1H), 6.18-6.24 (m, 2H), 6.37-6.42 (m, 1H), 7.09-7.20 (m, 5H), 7.25-7.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.5, 44.8, 54.7, 100.0, 122.9, 124.5, 125.4, 127.0 (2C), 127.9, 128.3, 128.3, 128.9, 129.4, 130.2 (2C), 132.2, 138.4, 138.7, 139.0, 139.3, 175.6; IR (ATR): ν = 512, 706, 745, 1211, 1253, 1366, 1398, 1513, 1634, 1726, 2923, 3019 cm^{-1}; HRMS calcd. for $C_{23}H_{21}NNaO$ $[M + Na]^+$: 350.1515, found: 350.1508; $[\alpha]_D^{25}$ = +11.8 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 97% ee): t_{major} = 6.3 min, t_{minor} = 15.1 min.

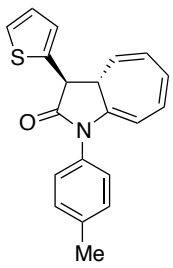
(3*R*,3a*S*)-3-(Naphthalen-2-yl)-1-(*p*-tolyl)-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



Cycloaddition product **4i** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 7:1) in 81% yield (29.4 mg, >20:1 dr). White solid, melting point: 137-139 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 3.20-3.22 (m, 1H), 4.17 (d, *J* = 5.2 Hz, 1H), 5.42-5-45 (m, 1H), 5.48 (dd, *J* = 1.2, 6.8 Hz, 1H), 6.20-6.25 (m, 2H), 6.38-6.43 (m, 1H), 7.20-7.24 (m, 2H), 7.28-7.30 (m, 2H), 7.42-7.50 (m, 3H), 7.79-7.86 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 44.6, 54.9, 100.1, 122.8, 125.2, 125.5, 126.0, 126.3, 126.6, 127.1 (2C), 127.6, 127.8, 128.0, 129.0, 129.4, 130.2 (2C), 132.2, 132.7, 133.4,

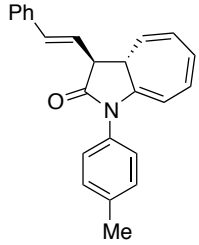
136.3, 138.5, 139.2, 175.4; IR (ATR): ν = 478, 506, 568, 699, 735, 817, 1214, 1267, 1366, 1399, 1512, 1630, 1721, 2922 cm^{-1}; HRMS calcd. for $C_{26}H_{21}NNaO$ $[M + Na]^+$: 386.1515, found: 386.1517; $[\alpha]_D^{25}$ = –19.2 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, hexane/*i*-propanol (75:25), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 90% ee): t_{major} = 7.8 min, t_{minor} = 21.4 min.

(3*S*,3a*S*)-3-(Thiophen-2-yl)-1-(*p*-tolyl)-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



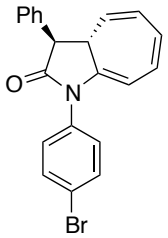
Cycloaddition product **4j** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 5:1) in 83% yield (26.4 mg, 12:1 dr). White solid, melting point: 153-155 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3H), 3.20-3.23 (m, 1H), 4.19 (d, *J* = 6.4 Hz, 1H), 5.29-5.32 (m, 1H), 5.35 (dd, *J* = 1.6, 6.4 Hz, 1H), 6.14-6.20 (m, 2H), 6.29-6.34 (m, 1H), 6.92-6.94 (m, 1H), 7.02-7.03 (m, 1H), 7.08-7.10 (m, 2H), 7.17-7.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 44.6, 49.8, 100.4, 122.5, 124.9, 125.2, 125.5, 127.0, 127.0 (2C), 128.2, 129.4, 130.2 (2C), 132.0, 138.6, 138.8, 140.1, 173.9; IR (ATR): ν = 514, 703, 821, 1021, 1219, 1243, 1362, 1397, 1514, 1630, 1716, 2924 cm^{-1}; HRMS calcd. for $C_{20}H_{17}NNaOS$ $[M + Na]^+$: 342.0923, found: 342.0921; $[\alpha]_D^{25}$ = –26.3 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 93% ee): t_{major} = 11.7 min, t_{minor} = 20.7 min.

(3*S*,3a*S*)-3-((*E*)-Styryl)-1-(*p*-tolyl)-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



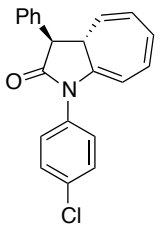
Cycloaddition product **4k** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 25:1 to 10:1) in 70% yield (23.7 mg, 13:1 dr). Light yellow solid, melting point: 61-62 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 3.08-3.11 (m, 1H), 3.64 (t, *J* = 7.2 Hz, 1H), 5.30-5.33 (m, 1H), 5.40 (dd, *J* = 1.2, 6.4 Hz, 1H), 6.23-6.27 (m, 2H), 6.36-6.42 (m, 2H), 6.68 (d, *J* = 16.8 Hz, 1H), 7.15-7.17 (m, 2H), 7.25-7.33 (m, 5H), 7.39-7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 41.8, 52.0, 100.3, 122.7, 125.2, 125.4, 126.5 (2C), 127.1 (2C), 127.8, 128.2, 128.5 (2C), 129.3, 130.2 (2C), 132.1, 132.8, 136.5, 138.5, 139.5, 175.1; IR (ATR): ν = 510, 691, 733, 817, 963, 1208, 1254, 1366, 1398, 1512, 1632, 1721, 2922, 3020 cm^{-1}; HRMS calcd. for $C_{24}H_{21}NNaO$ $[M + Na]^+$: 362.1515, found: 362.1517; $[\alpha]_D^{25}$ = –20.7 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 47% ee): t_{major} = 7.4 min, t_{minor} = 13.0 min.

(3*R*,3a*S*)-1-(4-Bromophenyl)-3-phenyl-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



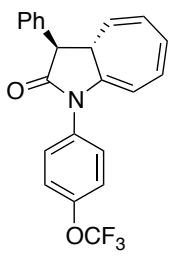
Cycloaddition product **4l** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 7:1) in 73% yield (27.6 mg, >20:1 dr). White solid, melting point: 93-95 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.09-3.12 (m, 1H), 4.01 (d, *J* = 4.8 Hz, 1H), 5.38 (dd, *J* = 4.0, 9.2 Hz, 1H), 5.47 (dd, *J* = 1.2, 6.4 Hz, 1H), 6.20-6.29 (m, 2H), 6.39-6.43 (m, 1H), 7.20-7.24 (m, 2H), 7.28-7.41 (m, 5H), 7.60-7.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.6, 54.6, 100.1, 122.2, 122.8, 125.9, 127.5 (2C), 127.7, 128.0, 128.9 (2C), 129.1 (2C), 129.2, 132.8 (2C), 133.8, 138.2, 138.8, 175.3; IR (ATR): ν = 510, 695, 783, 1011, 1069, 1253, 1365, 1487, 1540, 1633, 1723, 2849, 2922 cm^{-1}; HRMS calcd. for $C_{21}H_{16}BrNNaO$ [M + Na]$^{+}$: 400.0307, found: 400.0294; $[\alpha]_D^{25}$ = +32.9 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 230 nm, 97% ee): t_{major} = 10.8 min, t_{minor} = 20.2 min.

(3*R*,3a*S*)-1-(4-Chlorophenyl)-3-phenyl-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



Cycloaddition product **4m** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 7:1) in 72% yield (24.0 mg, >20:1 dr). White solid, melting point: 53-55 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.10-3.12 (m, 1H), 4.01 (d, *J* = 4.8 Hz, 1H), 5.38 (dd, *J* = 4.0, 9.2 Hz, 1H), 5.47 (d, *J* = 6.0 Hz, 1H), 6.20-6.28 (m, 2H), 6.39-6.43 (m, 1H), 7.25-7.27 (m, 2H), 7.30-7.39 (m, 5H), 7.44-7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.6, 54.6, 100.1, 122.8, 125.9, 127.5 (2C), 127.6, 128.0, 128.6 (2C), 129.1 (2C), 129.2, 129.8 (2C), 133.3, 134.2, 138.3, 138.8, 175.3; IR (ATR): ν = 515, 696, 938, 783, 830, 1015, 1088, 1205, 1365, 1491, 1632, 1723, 2923, 3016 cm^{-1}; HRMS calcd. for $C_{21}H_{16}ClNNaO$ [M + Na]$^{+}$: 356.0813, found: 356.0811; $[\alpha]_D^{25}$ = +30.8 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 98% ee): t_{major} = 10.2 min, t_{minor} = 18.3 min.

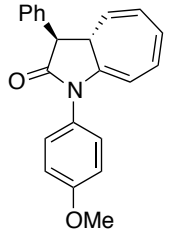
(3*R*,3a*S*)-3-Phenyl-1-(4-(trifluoromethoxy)phenyl)-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



Cycloaddition product **4n** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 7:1) in 83% yield (31.8 mg, >20:1 dr). White solid, melting point: 106-107 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.12-3.15 (m, 1H), 4.04 (d, *J* = 4.8 Hz, 1H), 5.40 (dd, *J* = 3.6, 9.2 Hz, 1H), 5.49 (dd, *J* = 1.2, 6.4 Hz, 1H), 6.22-6.31 (m, 2H), 6.41-6.45 (m, 1H), 7.30-7.41 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.6, 54.6, 100.1, 120.4 (q, *J* = 256.5 Hz) 122.0 (2C), 122.9, 125.9, 127.5 (2C), 127.7, 128.0, 128.8 (2C), 129.1, 129.2 (2C), 133.2, 138.2, 138.7, 148.7, 175.3; IR (ATR): ν = 518, 705, 782, 1155, 1203,

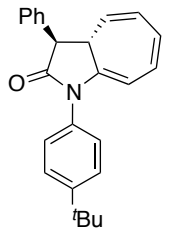
1264, 1400, 1508, 1542, 1635, 1717, 3028 cm^{-1}; HRMS calcd. for $C_{22}H_{16}F_3NNaO_2$ $[M + Na]^+$: 406.1025, found: 406.1030; $[\alpha]_D^{25}$ = –24.1 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 90% ee): t_{major} = 8.9 min, t_{minor} = 13.9 min.

(3*R*,3a*S*)-1-(4-Methoxyphenyl)-3-phenyl-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



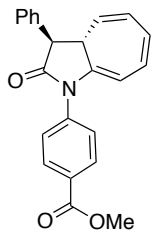
Cycloaddition product **4o** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 7:1) in 70% yield (23.0 mg, >20:1 dr). White solid, melting point: 144-145 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.10-3.13 (m, 1H), 3.83 (s, 3H), 4.00 (d, *J* = 4.8 Hz, 1H), 5.36-5.40 (m, 1H), 5.43 (dd, *J* = 1.2, 6.4 Hz, 1H), 6.18-6.24 (m, 2H), 6.37-6.42 (m, 1H), 6.97-6.99 (m, 2H), 7.20-7.23 (m, 2H), 7.26-7.31 (m, 1H), 7.34-7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.7, 54.7, 55.5, 99.9, 114.8 (2C), 122.8, 125.4, 127.4, 127.5 (2C), 127.5, 127.9, 128.4 (2C), 129.0 (2C), 129.4, 139.1, 139.5, 159.4, 175.6; IR (ATR): ν = 529, 711, 779, 1021, 1156, 1218, 1247, 1371, 1402, 1512, 1632, 1713, 2930 cm^{-1}; HRMS calcd. for $C_{22}H_{19}NNaO_2$ $[M + Na]^+$: 352.1308, found: 352.1309; $[\alpha]_D^{25}$ = +10.6 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 92% ee): t_{major} = 12.6 min, t_{minor} = 25.1 min.

(3*R*,3a*S*)-1-(4-(*tert*-Butyl) phenyl)-3-phenyl-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



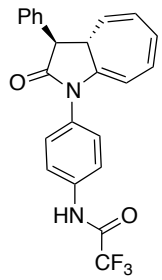
Cycloaddition product **4p** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 7:1) in 85% yield (30.2 mg, >20:1 dr). White solid, melting point: 63-64 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9H), 3.09-3.12 (m, 1H), 4.02 (d, *J* = 5.2 Hz, 1H), 5.37-5.40 (m, 1H), 5.49 (dd, *J* = 1.2, 6.4 Hz, 1H), 6.19-6.24 (m, 2H), 6.37-6.42 (m, 1H), 7.21-7.24 (m, 2H), 7.27-7.30 (m, 1H), 7.36-7.37 (m, 4H), 7.47-7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.3 (3C), 34.7, 44.7, 54.7, 100.0, 122.8, 125.4, 126.5 (2C), 126.6 (2C), 127.5, 127.5 (2C), 127.9, 129.0 (2C), 129.4, 132.0, 139.1, 139.1, 151.4, 175.5; IR (ATR): ν = 582, 702, 1021, 1217, 1250, 1367, 1401, 1453, 1513, 1631, 1714, 2962 cm^{-1}; HRMS calcd. for $C_{25}H_{26}NO$ $[M + H]^+$: 356.2009, found: 356.2005; $[\alpha]_D^{25}$ = +29.8 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 91% ee): t_{major} = 10.0 min, t_{minor} = 12.7 min.

Methyl 4-((3*R*,3a*S*)-2-oxo-3-phenyl-3,3a-dihydrocyclohepta[*b*]pyrrol-1(2*H*)-yl) benzoate



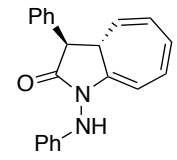
Cycloaddition product **4q** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 20:1 to 7:1) in 70% yield (25.0 mg, >20:1 dr). White solid, melting point: 134-135 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.09-3.12 (m, 1H), 3.94 (s, 3H), 4.03 (d, *J* = 5.2 Hz, 1H), 5.39 (dd, *J* = 4.0, 9.2 Hz, 1H), 5.52 (dd, *J* = 1.2, 6.8 Hz, 1H), 6.22-6.31 (m, 2H), 6.40-6.45 (m, 1H), 7.28-7.33 (m, 1H), 7.35-7.38 (m, 4H), 7.41-7.43 (m, 2H), 8.14-8.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.5, 52.3, 54.6, 100.3, 122.9, 126.0, 127.0 (2C), 127.5 (2C), 127.7, 128.0, 129.1 (2C), 129.2, 129.9, 130.9 (2C), 137.7, 138.7, 138.8, 166.2, 175.2; IR (ATR): ν = 501, 694, 762, 1019, 1109, 1276, 1370, 1401, 1431, 1551, 1639, 1715, 3025 cm^{-1}; HRMS calcd. for $C_{23}H_{19}NNaO_3$ $[M + Na]^+$: 380.1257, found: 380.1246; $[\alpha]_D^{25}$ = +87.0 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 230 nm, 94% ee): t_{major} = 9.4 min, t_{minor} = 13.7 min.

2,2,2-Trifluoro-*N*-(4-((3*R*,3a*S*)-2-oxo-3-phenyl-3,3a-dihydrocyclohepta[*b*]pyrrol-1(2*H*)-yl)phenyl)acetamide



Cycloaddition product **4r** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 3:1) in 71% yield (29.1 mg, >20:1 dr). White solid, melting point: 162-164 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.16-3.19 (m, 1H), 4.02 (d, *J* = 5.2 Hz, 1H), 5.38.5.41 (m, 2H), 6.20-6.28 (m, 2H), 6.37-6.41 (m, 1H), 7.17-7.19 (m, 2H), 7.33-7.43 (m, 5H), 7.52-7.54 (m, 2H), 8.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.6, 55.0, 100.8, 115.6 (d, *J* = 286.8 Hz), 121.7 (2C), 122.8, 126.1, 127.5 (2C), 127.8, 128.0 (2C), 128.1, 129.1, 129.1 (2C), 131.8, 135.7, 138.3, 138.5, 154.8 (d, *J* = 37.5 Hz), 176.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –75.67 (s, 3F); IR (ATR): ν = 516, 696, 836, 1146, 1246, 1368, 1402, 1511, 1538, 1612, 1632, 1698, 2923, 3086, 3267 cm^{-1}; HRMS calcd. for $C_{23}H_{17}F_3N_2NaO_2$ $[M + Na]^+$: 433.1134, found: 433.1120; $[\alpha]_D^{25}$ = +38.5 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IA, hexane/*i*-propanol (80:20), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 90% ee): t_{major} = 8.4 min, t_{minor} = 12.0 min.

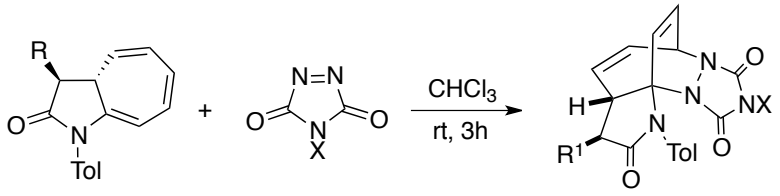
(3*R*,3a*S*)-3-Phenyl-1-(phenylamino)-3,3a-dihydrocyclohepta[*b*]pyrrol-2(1*H*)-one



Cycloaddition product **4s** was prepared as described in section 3 and isolated by FC on silica (eluting with cyclohexane/EtOAc from 15:1 to 5:1) in 37% yield (11.6 mg, >20:1 dr). White solid, melting point: 147-148 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.20-3.23 (m, 1H), 3.90 (d, *J* = 5.2 Hz, 1H), 5.33 (dd, *J* = 3.2, 9.2 Hz, 1H), 5.87 (dd, *J* = 1.6, 6.8 Hz, 1H), 6.18-6.26 (m, 2H), 6.36 (s, 1H), 6.44-6.48 (m, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 1H), 7.22-7.26 (m, 2H), 7.29-7.31 (m, 3H), 7.34-7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.7, 53.0, 99.5, 113.9 (2C), 122.0, 125.4, 125.7, 127.5

(2C), 127.7, 128.3, 129.1 (2C), 129.2, 129.3 (2C), 135.8, 138.2, 145.3, 173.3; IR (ATR): ν = 498, 579, 749, 1224, 1280, 1447, 1494, 1541, 1602, 1640, 1712, 3020, 3254 cm^{-1}; HRMS calcd. for $C_{21}H_{18}N_2NaO$ $[M + Na]^+$: 337.1311, found: 337.1306.

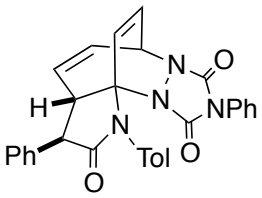
6. General procedure for the [4+2] cycloaddition reaction



4 **5** **6**

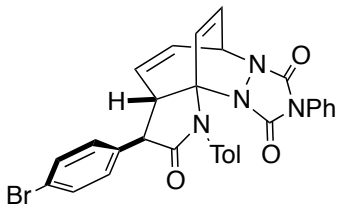
To a solution of the **4b** (0.10 mmol, 1.0 equiv.) in $CHCl_3$ (1.0 mL) were added the triazolinedione **5** (0.15 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 3 hours and monitored by TLC. After the reaction completed, solvent removal in vacuo and the crude product **6** were directly purified by flash chromatography (FC).

(3*R*,3a*S*,6*S*,11a*S*)-3,9-Diphenyl-1-(*p*-tolyl)-3,3a-dihydro-6,11a-ethenopyrrolo[2,3-c][1,2,4] triazolo[1,2-a][1,2]diazepine-2,8,10(1*H*,6*H*,9*H*)-trione



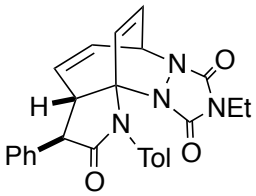
Cycloaddition product **6a** was prepared as described in section 6 and isolated by FC on silica (eluting with CH_2Cl_2/EtOAc from 100:1 to 40:1) in 75% yield (36.6 mg, >20:1 dr). White solid, melting point: 203-205 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 3.52 (dt, *J* = 2.4, 12.0 Hz, 1H), 4.16 (d, *J* = 12.0 Hz, 1H), 5.16 (t, *J* = 6.8 Hz, 1H), 5.86 (dd, *J* = 2.0, 11.2 Hz, 1H), 6.02-6.07 (m, 1H), 6.41 (d, *J* = 9.2 Hz, 1H), 6.64 (dd, *J* = 7.2, 9.2 Hz, 1H), 7.22-7.26 (m, 2H), 7.30-7.41 (m, 6H), 7.44-7.48 (m, 4H), 7.58-7.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 50.1, 50.7, 56.6, 79.7, 122.8, 124.4 (2C), 125.3 (2C), 127.9, 128.2, 128.9 (2C), 129.0 (2C), 129.0 (2C), 129.9 (2C), 130.1, 130.2, 130.2, 131.3, 132.8, 135.9, 137.0, 150.5, 151.6, 173.4; IR (ATR): ν = 521, 704, 732, 815, 1132, 1214, 1349, 1394, 1511, 1704, 1727, 2918 cm^{-1}; HRMS calcd. for $C_{30}H_{24}N_4NaO_3$ $[M + Na]^+$: 511.1741, found: 511.1744; $[\alpha]_D^{25}$ = +54.3 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, hexane/*i*-propanol (85:15), flow rate = 1.0 mL min^{-1}, λ = 210 nm, 87% ee): t_{major} = 43.8 min, t_{minor} = 50.5 min.

(3*R*,3a*S*,6*S*,11a*S*)-3-(4-Bromophenyl)-9-phenyl-1-(p-tolyl)-3,3a-dihydro-6,11a ethenopyrrolo[2,3-c][1,2,4]triazolo[1,2-a][1,2]diazepine-2,8,10(1*H*,6*H*,9*H*)-trione



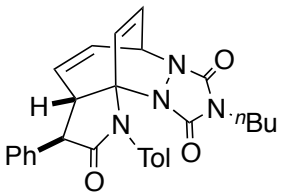
Cycloaddition product **6b** was prepared as described in section 6 and isolated by FC on silica (eluting with CH_2Cl_2/EtOAc from 100:1 to 40:1) in 80% yield (45.2 mg, >20:1 dr). White solid, melting point: 207-208 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 3.48 (dt, *J* = 2.4, 12.4 Hz, 1H), 4.14 (d, *J* = 12.4 Hz, 1H), 5.17 (t, *J* = 7.2 Hz, 1H), 5.83 (dd, *J* = 2.0, 11.2 Hz, 1H), 6.04-6.09 (m, 1H), 6.40 (d, *J* = 9.2 Hz, 1H), 6.64 (dd, *J* = 7.2, 9.2 Hz, 1H), 7.18-7.26 (m, 4H), 7.35-7.39 (m, 1H), 7.44-7.59 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 50.1, 50.2, 56.3, 79.6, 122.0, 123.1, 124.5 (2C), 125.3 (2C), 128.2, 129.0 (2C), 129.8, 130.0 (3C), 130.4, 130.6 (2C), 131.2, 132.1 (2C), 132.6, 134.8, 137.2, 150.6, 151.6, 172.9; IR (ATR): ν = 518, 718, 759, 806, 1072, 1260, 1366, 1491, 1698, 1758, 2924 cm^{-1}; HRMS calcd. for $C_{30}H_{23}BrN_4NaO_3$ $[M + Na]^+$: 589.0846, found: 589.0830; $[\alpha]_D^{25}$ = +112.0 (*c* = 0.1, $CHCl_3$).

(3*R*,3a*S*,6*S*,11a*S*)-9-Ethyl-3-phenyl-1-(*p*-tolyl)-3,3a-dihydro-6,11a-ethenopyrrolo[2,3-*c*][1,2,4]triazolo[1,2-*a*][1,2]diazepine-2,8,10(1*H*,6*H*,9*H*)-trione



Cycloaddition product **6c** was prepared as described in section 6 and isolated by FC on silica (eluting with CH_2Cl_2/EtOAc from 40:1 to 10:1) in 70% yield (30.8 mg, >20:1 dr). White solid, melting point: 194-196 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3H), 2.35 (s, 3H), 3.47 (dt, *J* = 2.4, 12.4 Hz, 1H), 3.65 (q, *J* = 7.2 Hz, 2H), 4.09 (d, *J* = 12.4 Hz, 1H), 5.03 (t, *J* = 7.2 Hz, 1H), 5.79 (dd, *J* = 2.0, 11.2 Hz, 1H), 5.92-5.97 (m, 1H), 6.34 (d, *J* = 9.2 Hz, 1H), 5.57 (dd, *J* = 7.2, 9.2 Hz, 1H), 7.20-7.22 (m, 2H), 7.28-7.33 (m, 3H), 7.37-7.43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 21.0, 34.6, 49.9, 50.8, 56.5, 79.2, 122.6, 124.4 (2C), 127.8, 128.8 (2C), 128.9 (2C), 129.8 (3C), 130.1, 130.2, 132.8, 135.9, 136.9, 151.8, 153.2, 173.4; IR (ATR): ν = 588, 608, 700, 727, 820, 1013, 1211, 1346, 1420, 1451, 1515, 1693, 1718, 1758, 2924 cm^{-1}; HRMS calcd. for $C_{26}H_{24}N_4NaO_3$ $[M + Na]^+$: 463.1741, found: 463.1729; $[\alpha]_D^{25}$ = +121.9 (*c* = 0.1, $CHCl_3$).

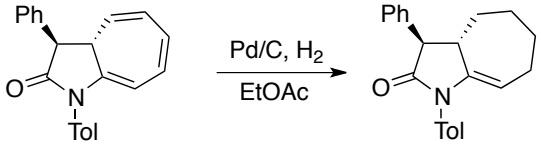
(3*R*,3a*S*,6*S*,11a*S*)-9-Butyl-3-phenyl-1-(*p*-tolyl)-3,3a-dihydro-6,11a-ethenopyrrolo[2,3-*c*][1,2,4]triazolo[1,2-*a*][1,2]diazepine-2,8,10(1*H*,6*H*,9*H*)-trione



Cycloaddition product **6d** was prepared as described in section 6 and isolated by FC on silica (eluting with CH_2Cl_2/EtOAc from 100:1 to 40:1) in 77% yield (36.0 mg, >20:1 dr). White solid, melting point: 192-193 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.6 Hz, 3H), 1.33-1.39 (m, 2H), 1.65-1.72 (m, 2H), 2.35 (s, 3H), 3.47 (dt, *J* = 2.4,

12.4 Hz, 1H), 3.59 (t, *J* = 7.2 Hz, 2H), 4.09 (d, *J* = 12.4 Hz, 1H), 5.03(t, *J* = 7.2 Hz, 1H), 5.78 (dd, *J* = 2.0, 10.8 Hz, 1H), 5.92-5.97 (m, 1H), 6.34 (d, *J* = 9.2 Hz, 1H), 6.57 (dd, *J* = 6.8, 9.2 Hz, 1H), 7.20-7.22 (m, 2H), 7.28-7.33 (m, 3H), 7.37-7.43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 19.7, 21.0, 29.8, 39.3, 50.0, 50.8, 56.5, 79.2, 122.7, 124.5 (2C), 127.8, 128.8 (2C), 128.9 (2C), 129.8 (3C), 130.0, 130.2, 132.8, 136.0, 136.9, 152.0, 153.4, 173.4; IR (ATR): ν = 534, 586, 694, 727, 1016, 1219, 1366, 1418, 1446, 1516, 1688, 1711, 1754, 2957 cm^{-1}; HRMS calcd. for $C_{28}H_{28}N_4NaO_3$ $[M + Na]^+$: 491.2054, found: 491.2047; $[\alpha]_D^{25}$ = +29.2 (*c* = 0.1, $CHCl_3$).

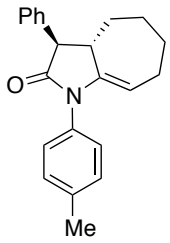
7. Hydrogenation of 4a



4a **7**

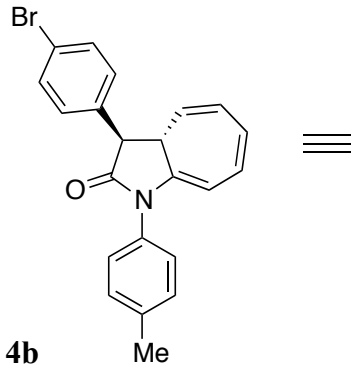
A suspension of Pd/C (10 wt.%, 10 mg) and **4a** (31.3 mg, 0.1 mmol) in ethyl acetate (3.0 mL) was stirred at room temperature under 1 atm hydrogen atmosphere. After being stirred 3 hours, the mixture was filtrated through a pad of Celite and the filtration was concentrated in vacuo, the residue was purified by column chromatography on silica gel (eluting with cyclohexane/EtOAc from 20:1 to 5:1) to afford the desired the product **7** in 94% yield (29.8 mg, >20:1 dr).

(3*R*,3a*S*)-3-Phenyl-1-(*p*-tolyl)-3,3a,4,5,6,7-hexahydrocyclohepta[*b*]pyrrol-2(1*H*)-one:



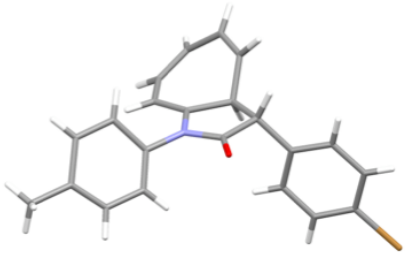
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19-1.30 (m, 1H), 1.39-1.45 (m, 1H), 1.53-1.59 (m, 1H), 1.70-1.75 (m, 1H), 1.93-2.00 (m, 3H), 2.04-2.12 (m, 1H), 2.31 (s, 3H), 2.96-3.01 (m, 1H), 3.43 (d, *J* = 7.2 Hz, 1H), 4.80-4.84 (m, 1H), 7.07-7.09 (m, 2H), 7.18-7.23 (m, 5H), 7.28-7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 26.5, 28.1, 30.8, 33.3, 47.7, 55.6, 103.3, 127.2, 127.9 (2C), 128.2 (2C), 128.8 (2C), 130.1 (2C), 132.9, 138.0, 139.6, 147.3, 174.4; IR (ATR): ν = 513, 697, 728, 770, 809, 1217, 1396, 1451, 1513, 1667, 2921, 3030 cm^{-1}; HRMS calcd. for $C_{22}H_{24}NO$ $[M + H]^+$: 318.1852, found: 318.1848; $[\alpha]_D^{25}$ = –27.7 (*c* = 0.1, $CHCl_3$); HPLC (Chiralcel IB, hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 230 nm, 92% ee): t_{major} = 11.7 min, t_{minor} = 17.5 min.

8. Configuration and X-Ray structures of 4b and 6b



4b

≡



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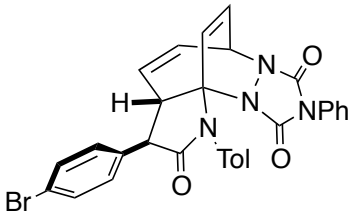
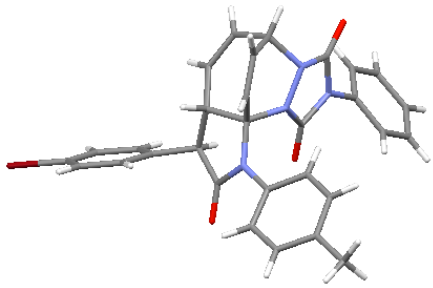


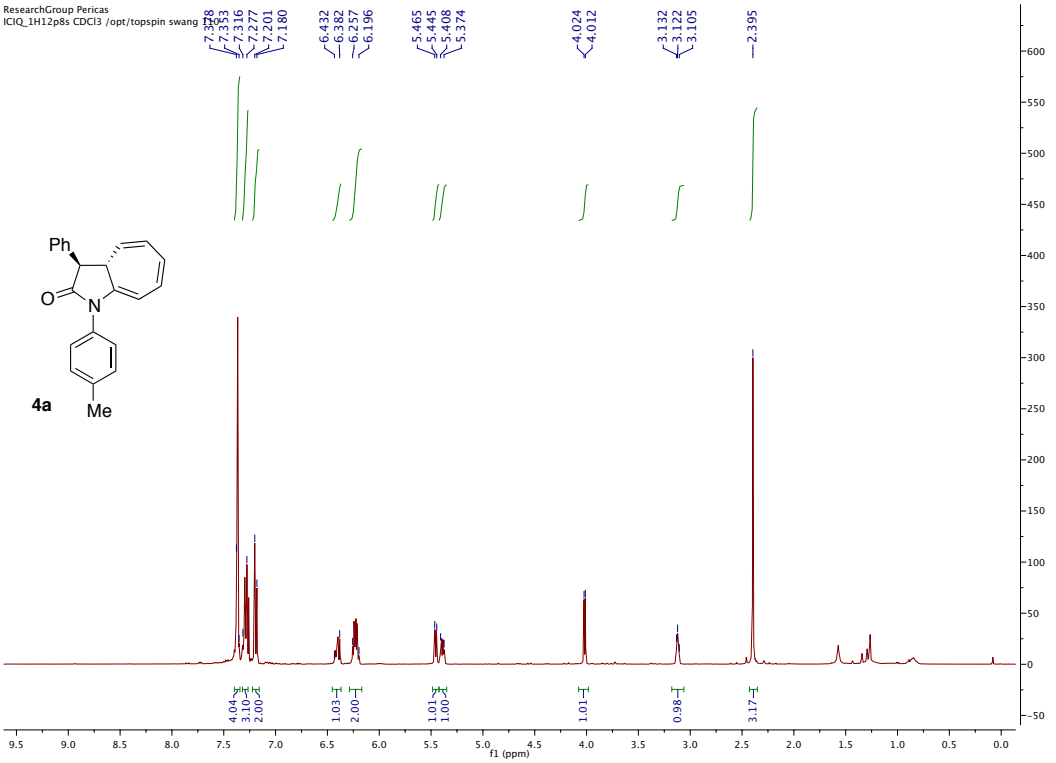
6b

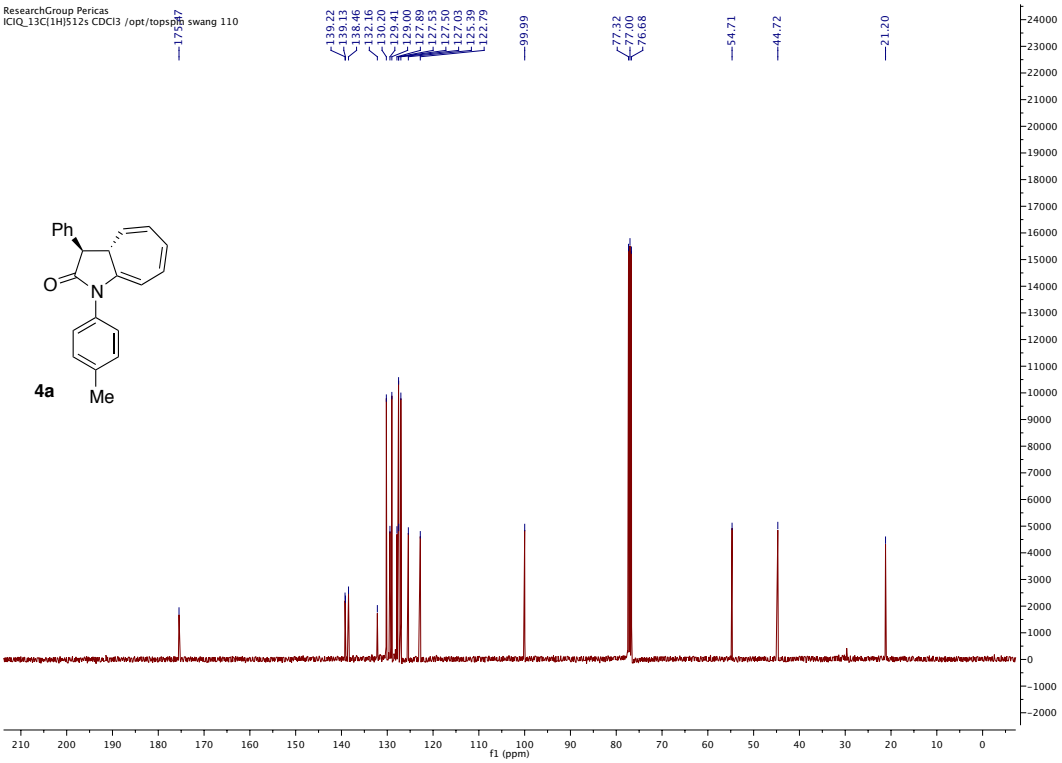
≡

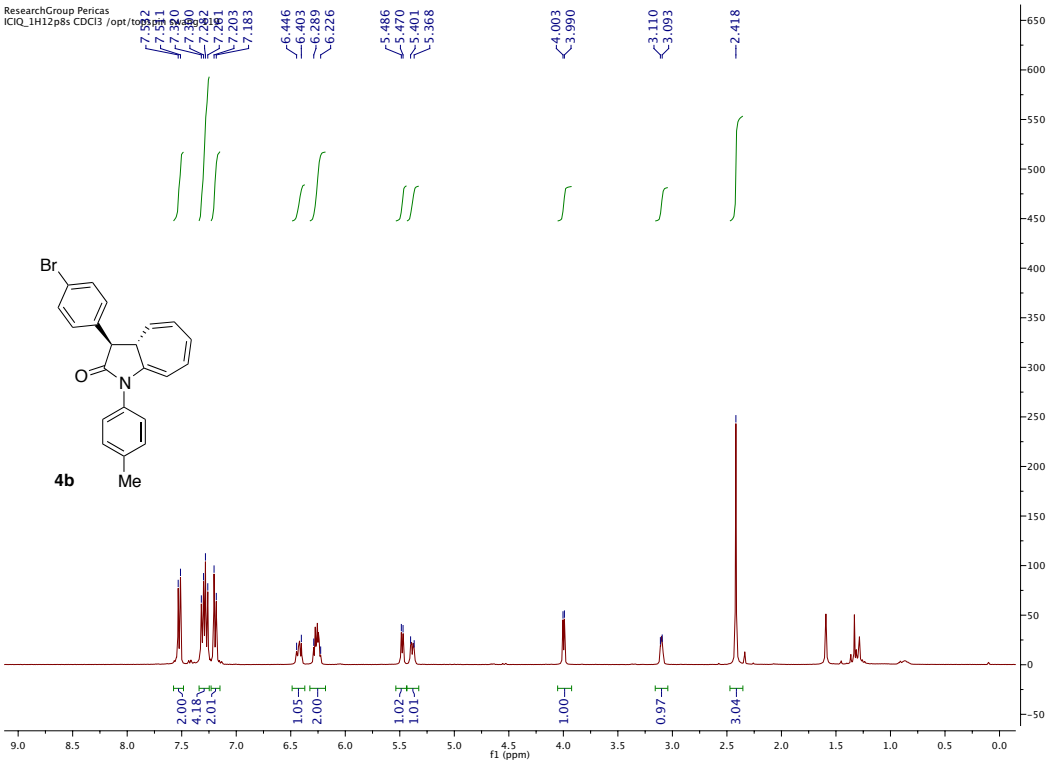


CCDC 1562520

9. ^{1}H and ^{13}C NMR spectra






ResearchGroup Pericas
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7.261
7.203
7.183
6.446
6.403
6.289
6.226
5.486
5.470
5.401
5.368
4.003
3.990
3.110
3.093
2.418
Br
O
N
Me
4b
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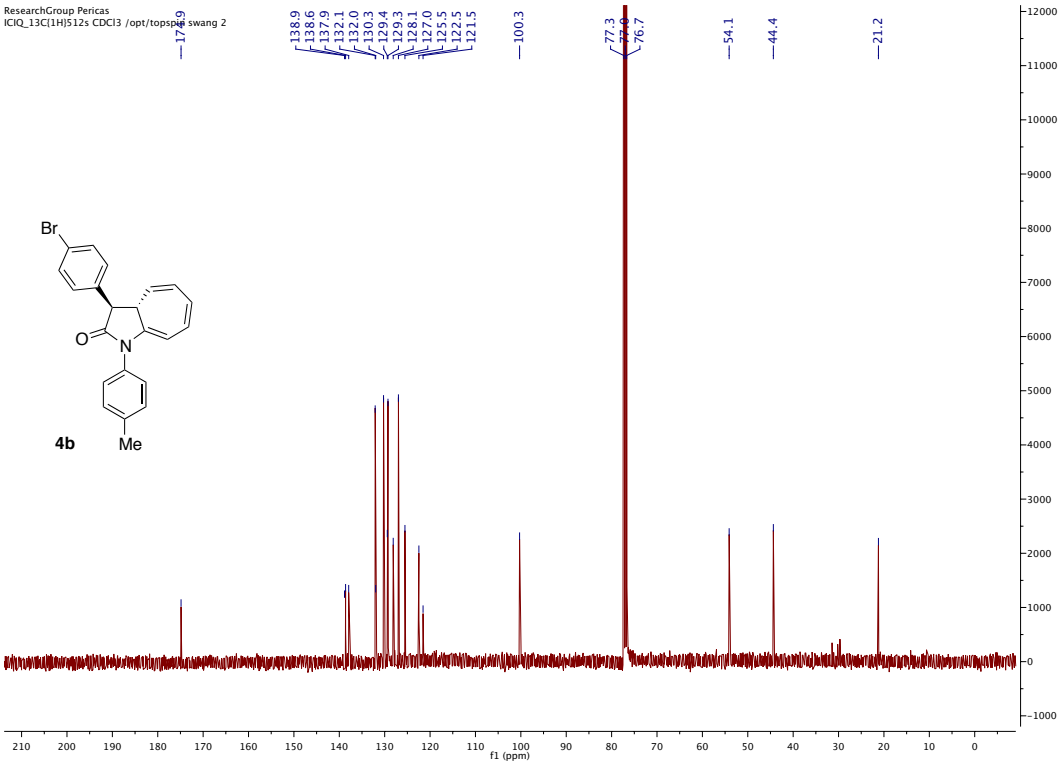
4.18
2.01
1.05
2.00
1.02
1.01
1.00
0.97
3.04
f1 (ppm)


ResearchGroup Pericas
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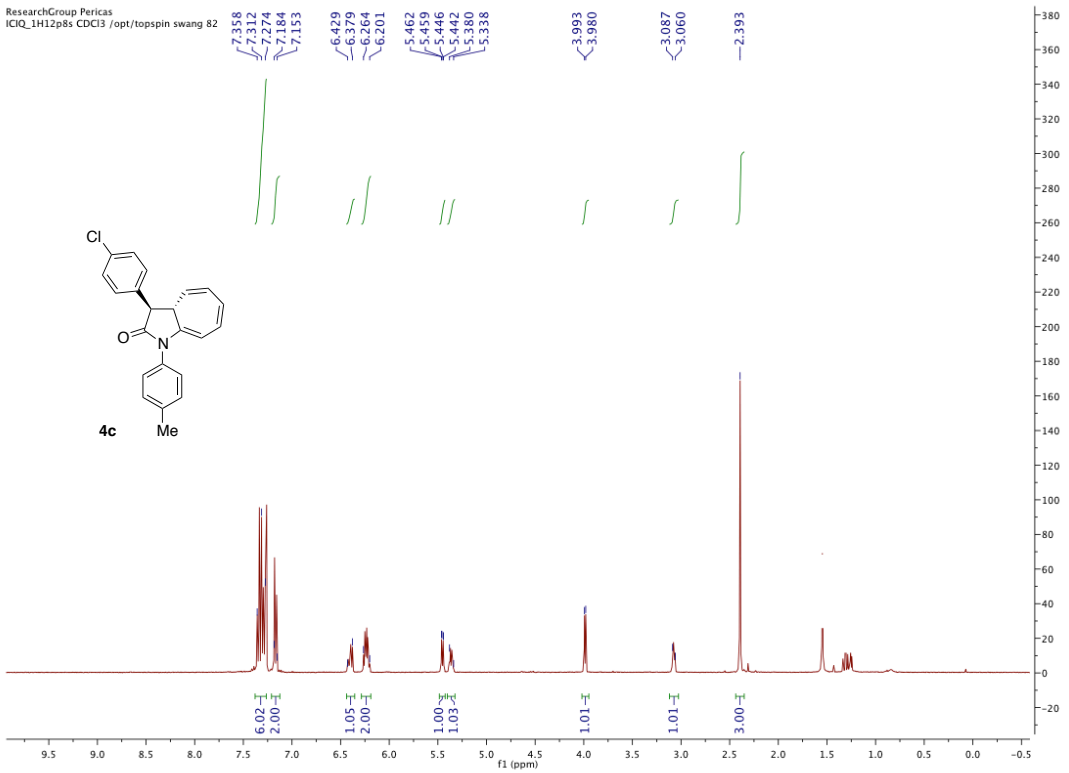
138.9
138.6
137.9
132.1
132.0
130.3
129.4
129.3
128.1
127.0
125.5
122.5
121.5
100.3
77.3
77.0
76.7
54.1
44.4
21.2
Br
O
N
Me
4b
f1 (ppm)


ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 82
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7.184
7.153
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6.379
6.264
6.201
5.462
5.459
5.446
5.442
5.380
5.338
3.993
3.980
3.087
3.060
2.393
Cl
O
N
Me
4c
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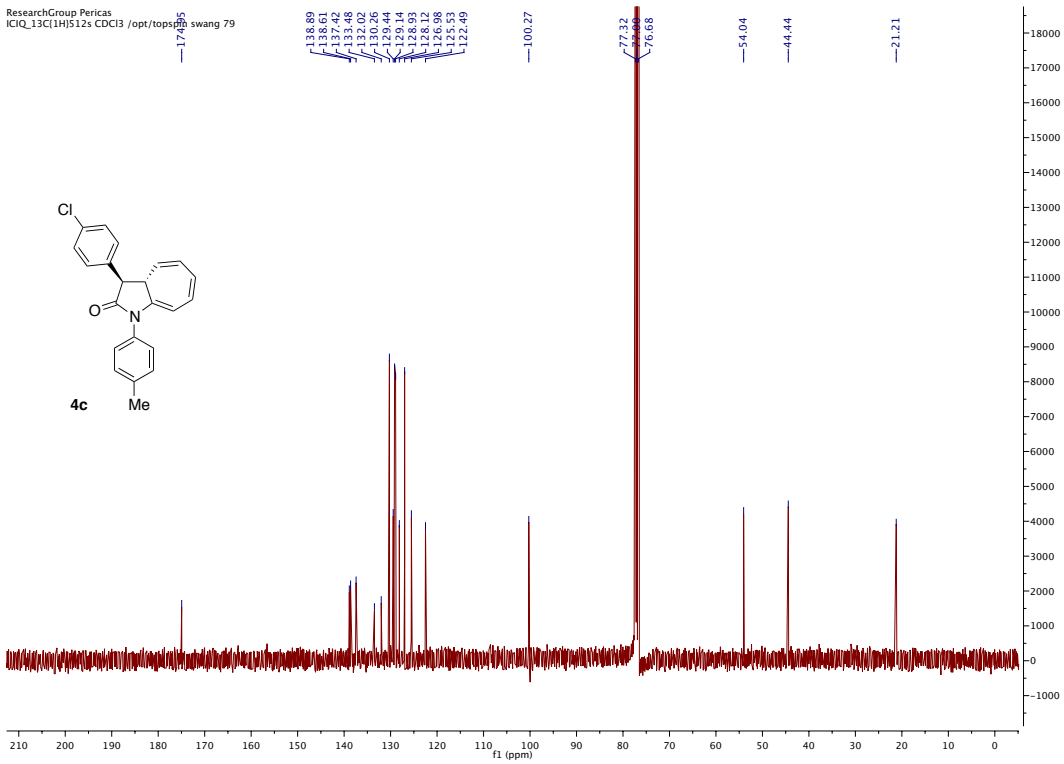
2.00
1.05
2.00
1.00
1.03
1.01
1.01
3.00
f1 (ppm)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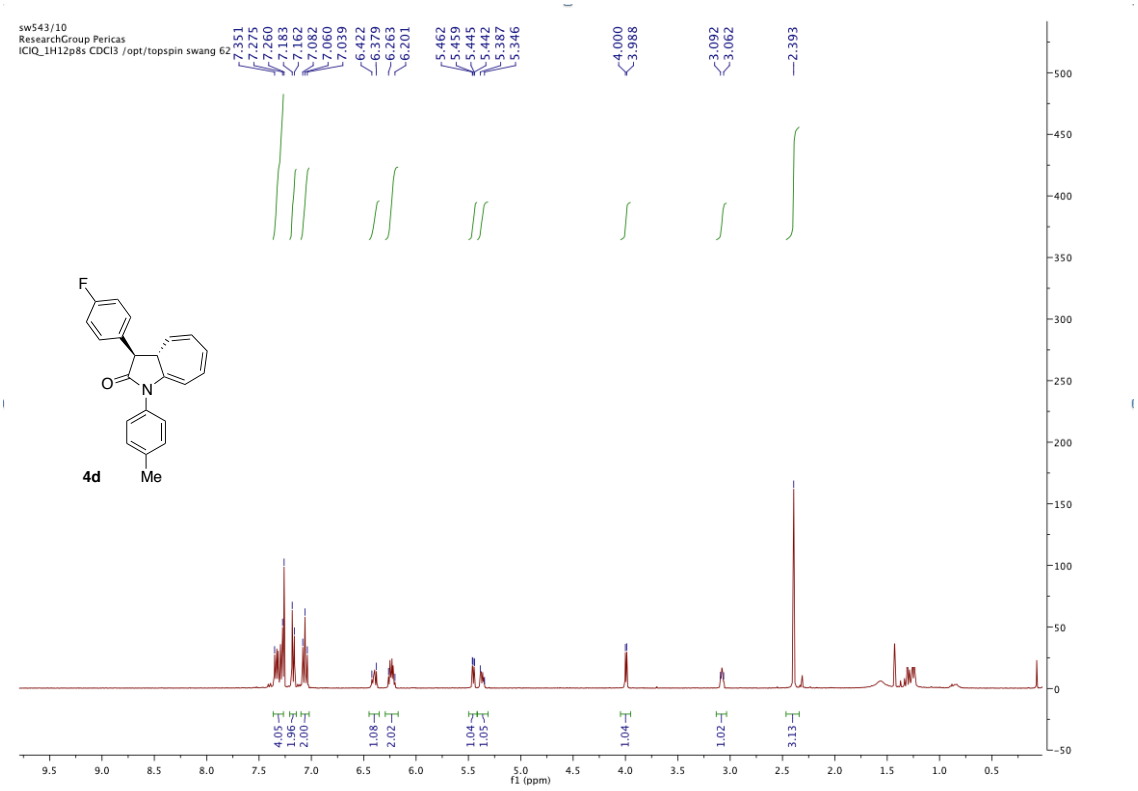
132.02
130.26
129.44
129.14
128.93
128.12
126.98
125.53
122.49
100.27
77.32
77.06
76.68
54.04
44.44
21.21
Cl
O
N
Me
4c
f1 (ppm)


sw543/10
ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 62
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7.060
7.039
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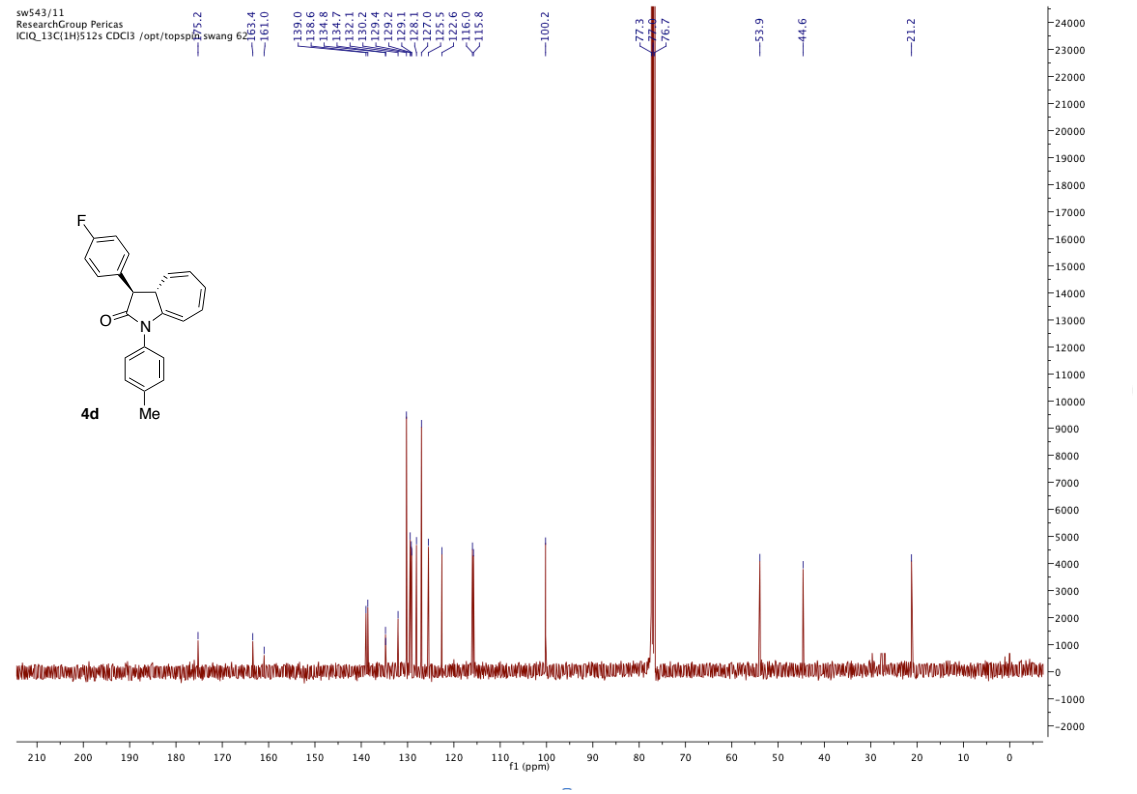
6.263
6.201
5.462
5.459
5.445
5.442
5.387
5.346
4.000
3.988
3.092
3.062
2.393
F
O
N
4d
Me
4.05
1.96
2.00
1.08
2.02
1.04
1.05
1.04
1.02
3.13
f1 (ppm)


sw543/11
ResearchGroup Pericas
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138.6
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134.7
132.1
130.2
129.4
129.2
129.1
128.1
127.0
125.5
122.6
116.0
115.8
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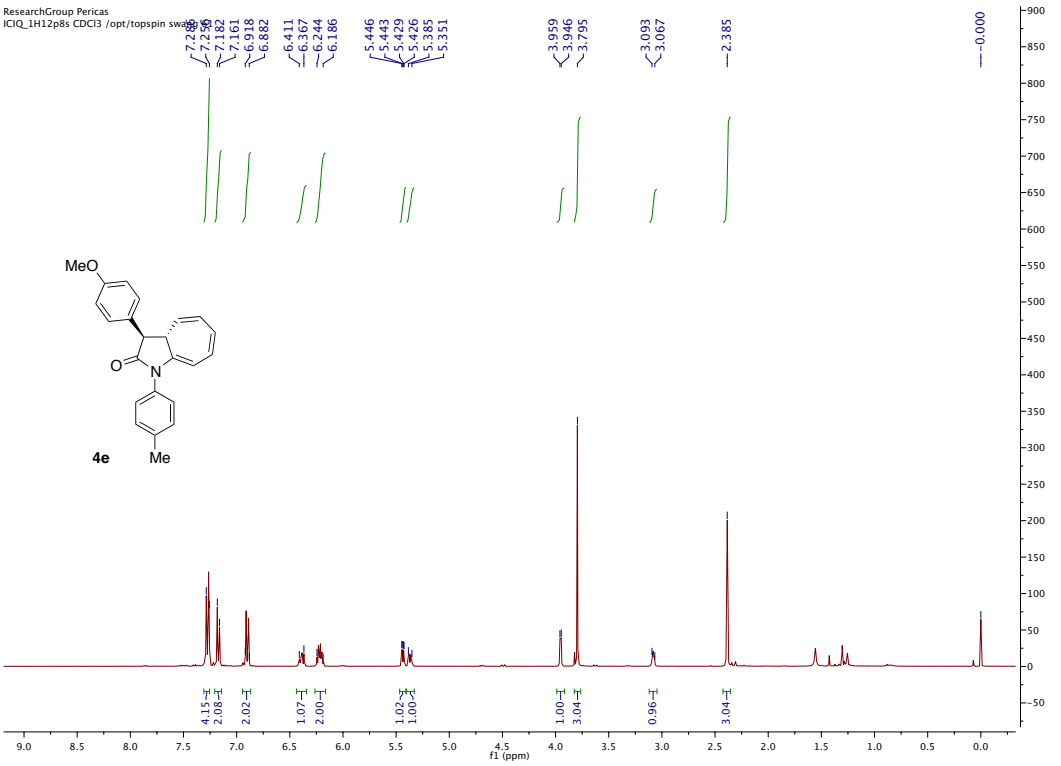
77.3
76.7
53.9
44.6
21.2
F
O
N
4d
Me
f1 (ppm)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5.446
5.443
5.429
5.426
5.385
5.351
3.959
3.946
3.795
3.093
3.067
2.385
0.000
MeO
O
N
4e
Me
4.15
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1.07
2.00
1.02
1.00
1.00
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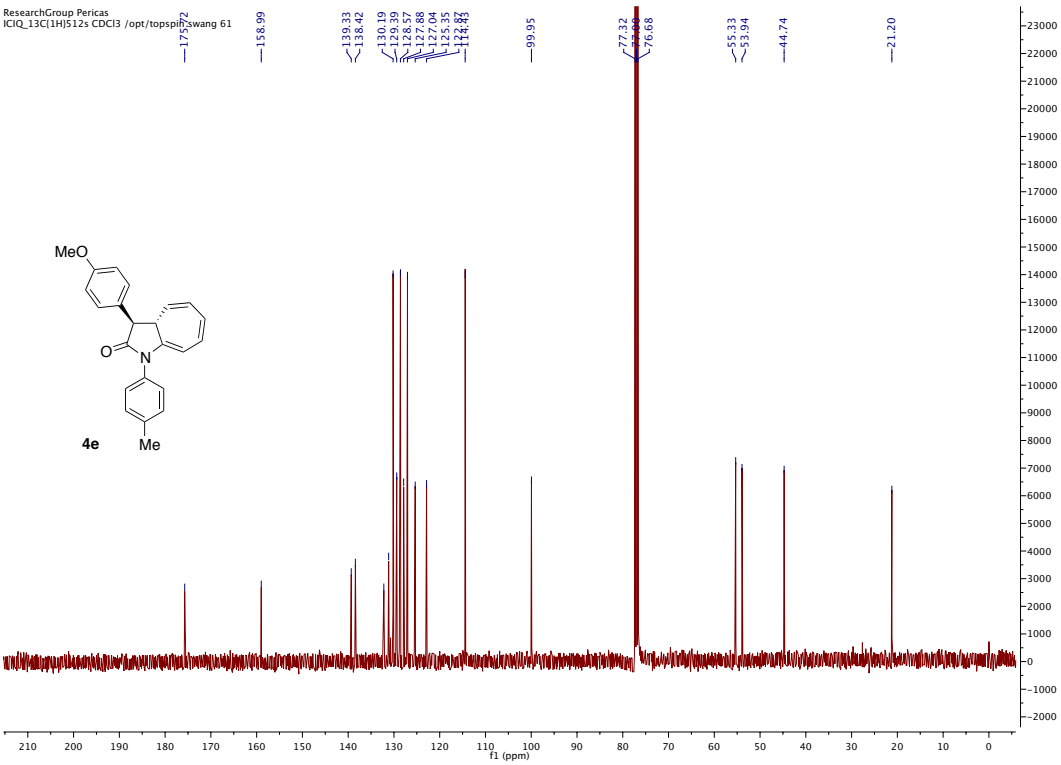
0.96
3.04
f1 (ppm)


ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 61
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130.19
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127.88
127.04
125.35
114.83
99.95
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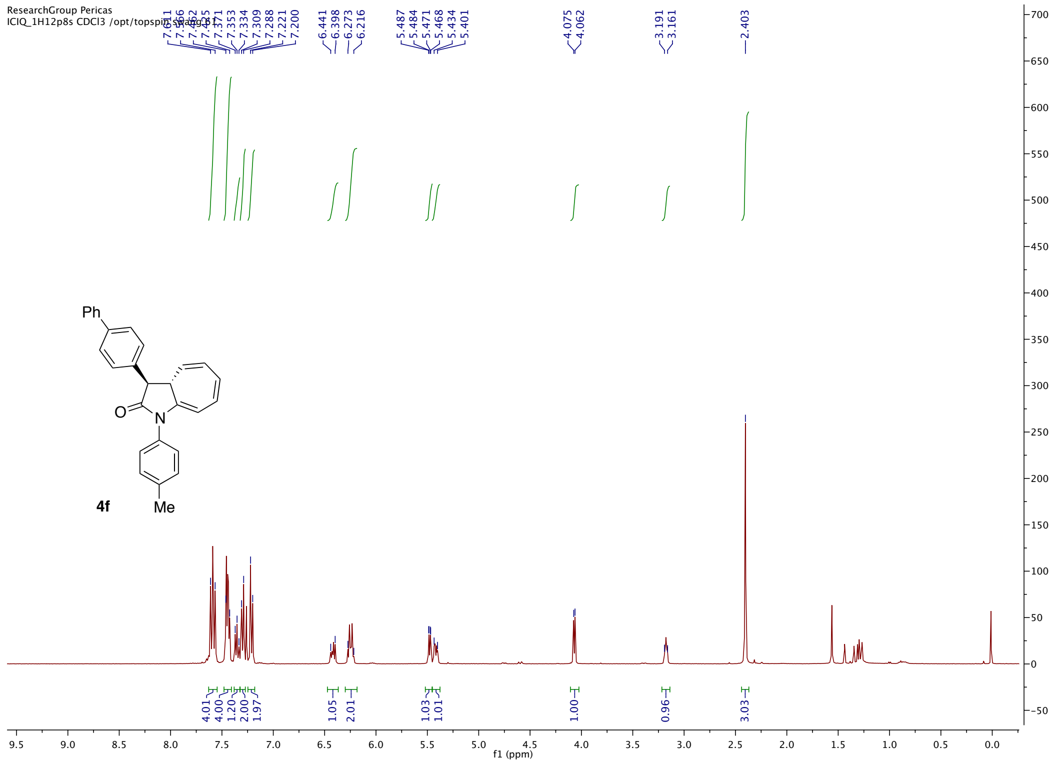
76.68
55.33
53.94
44.74
21.20
MeO
O
N
4e
Me
f1 (ppm)


ResearchGroup Pericas
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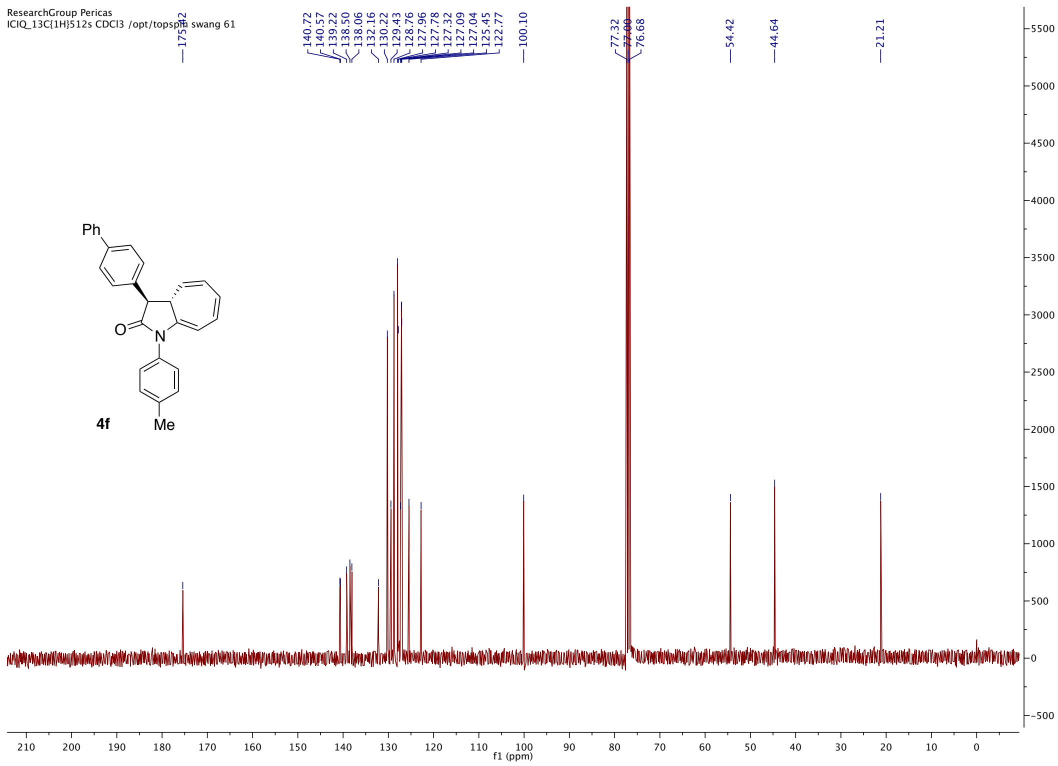
Ph
O
N
4f
Me
f1 (ppm)


ResearchGroup Pericas
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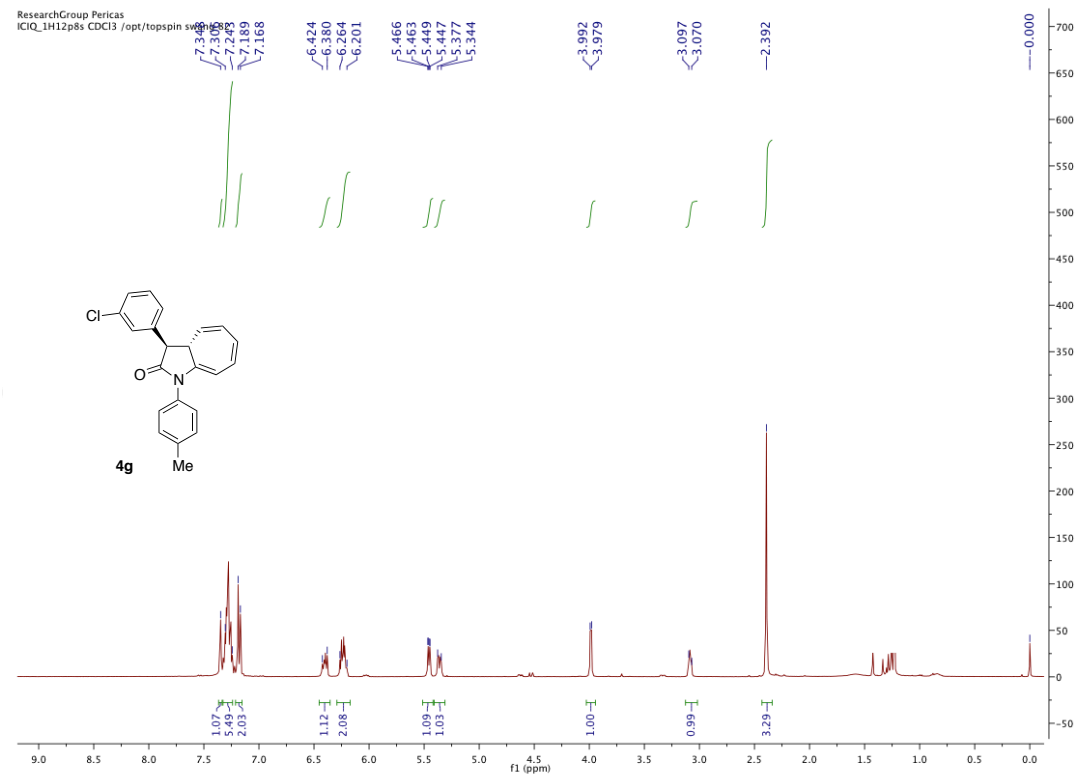
Ph
O
N
4f
Me
f1 (ppm)


ResearchGroup Pericas
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6.201
5.466
5.463
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5.447
5.377
5.344
3.992
3.979
3.097
3.070
2.392
0.000
Cl
O
N
4g
Me
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1.09
1.03
1.00
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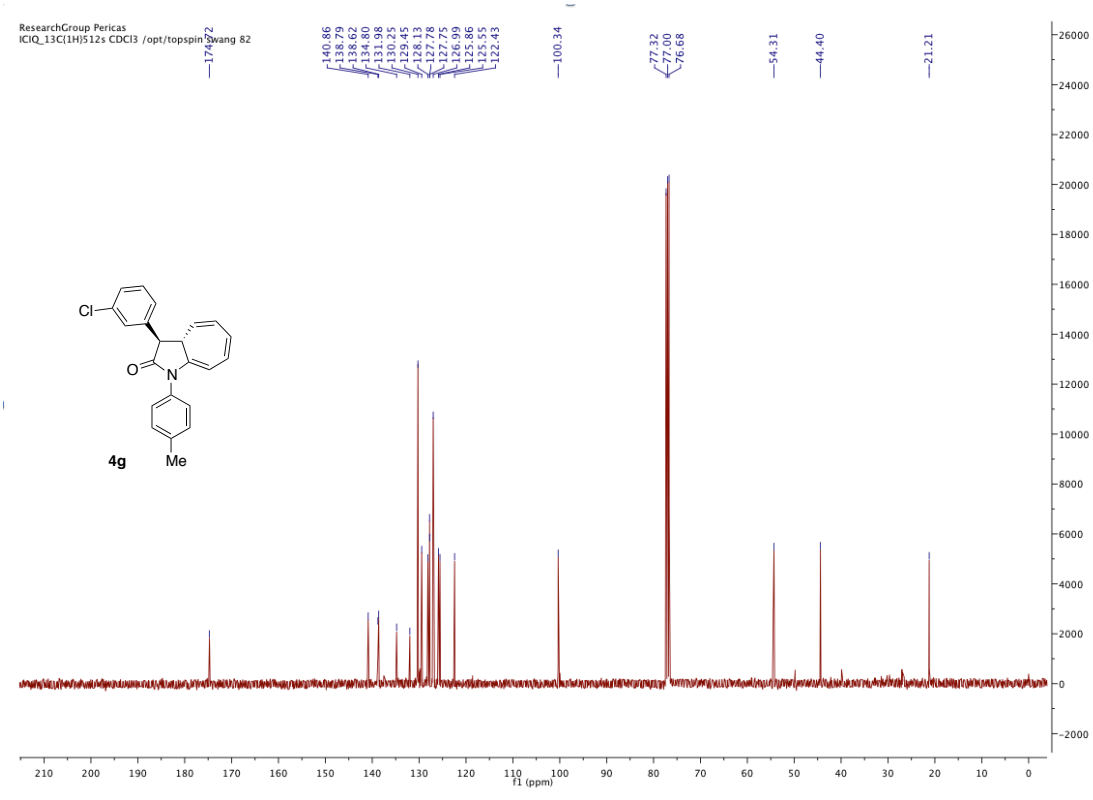
3.29
f1 (ppm)


ResearchGroup Pericas
ICIQ_13C(1H)512s CDCl3 /opt/topspin2 swang 82
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130.35
129.45
128.13
127.78
127.75
126.99
125.86
125.55
122.43
100.34
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77.00
76.68
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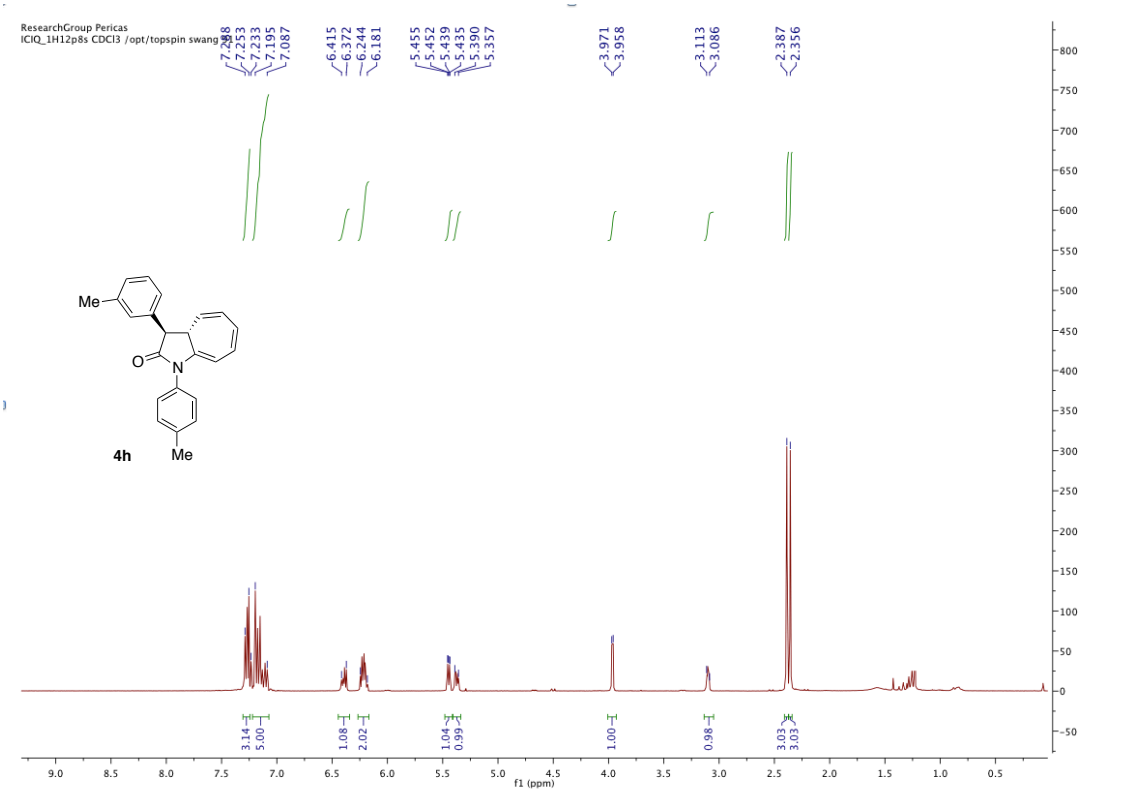
21.21
Cl
O
N
4g
Me
f1 (ppm)


ResearchGroup Pericas
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6.372
6.244
6.181
5.455
5.452
5.439
5.435
5.390
5.357
3.971
3.958
3.113
3.086
2.387
2.356
Me
O
N
4h
Me
3.14
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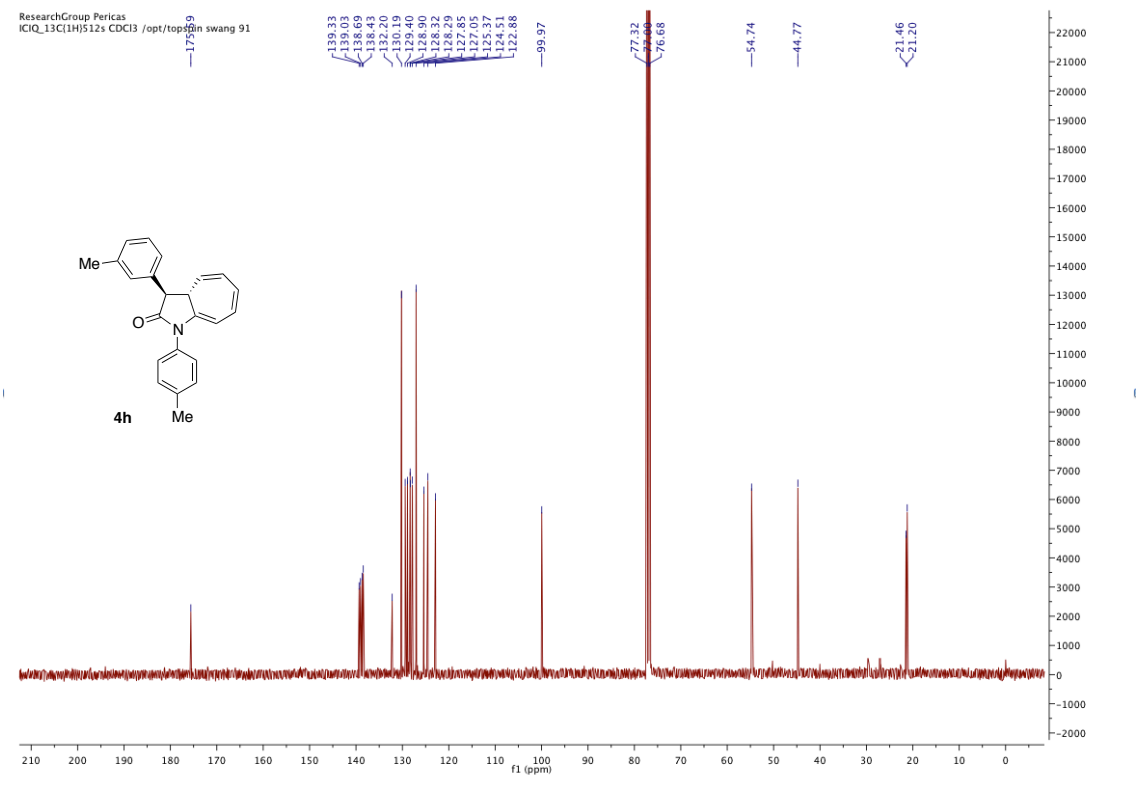
1.08
2.02
1.04
0.99
1.00
0.98
3.03
3.03
f1 (ppm)


ResearchGroup Pericas
ICIQ_13C(1H)512s CDCl3 /opt/topspin swang 91
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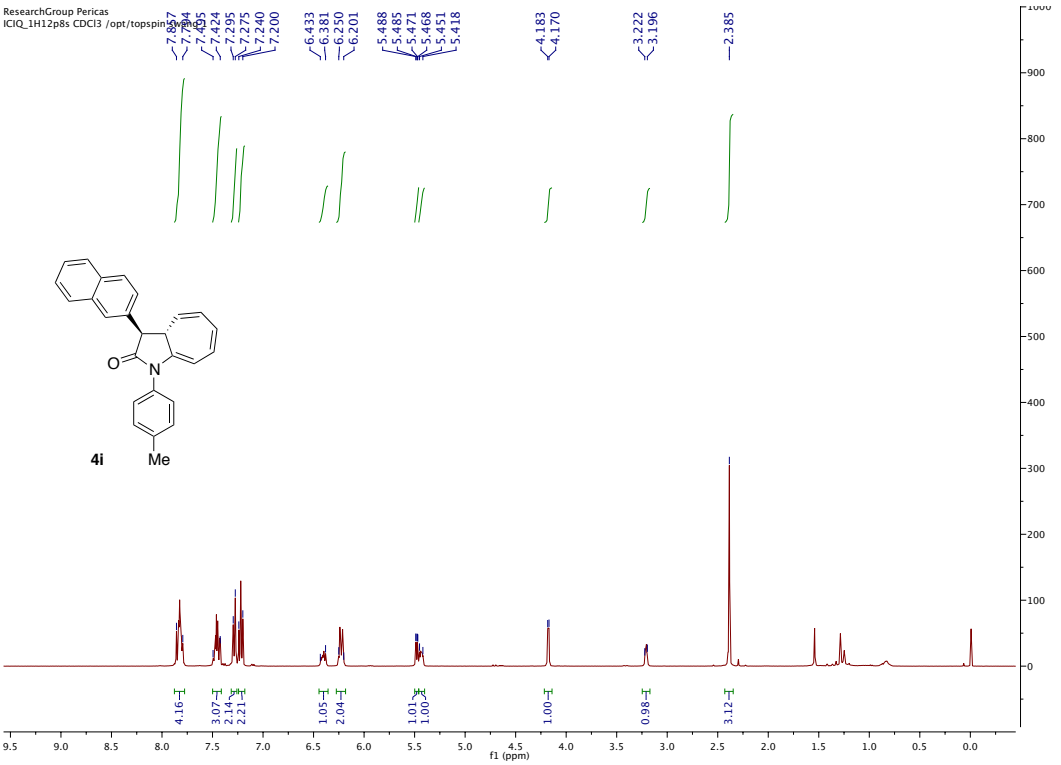
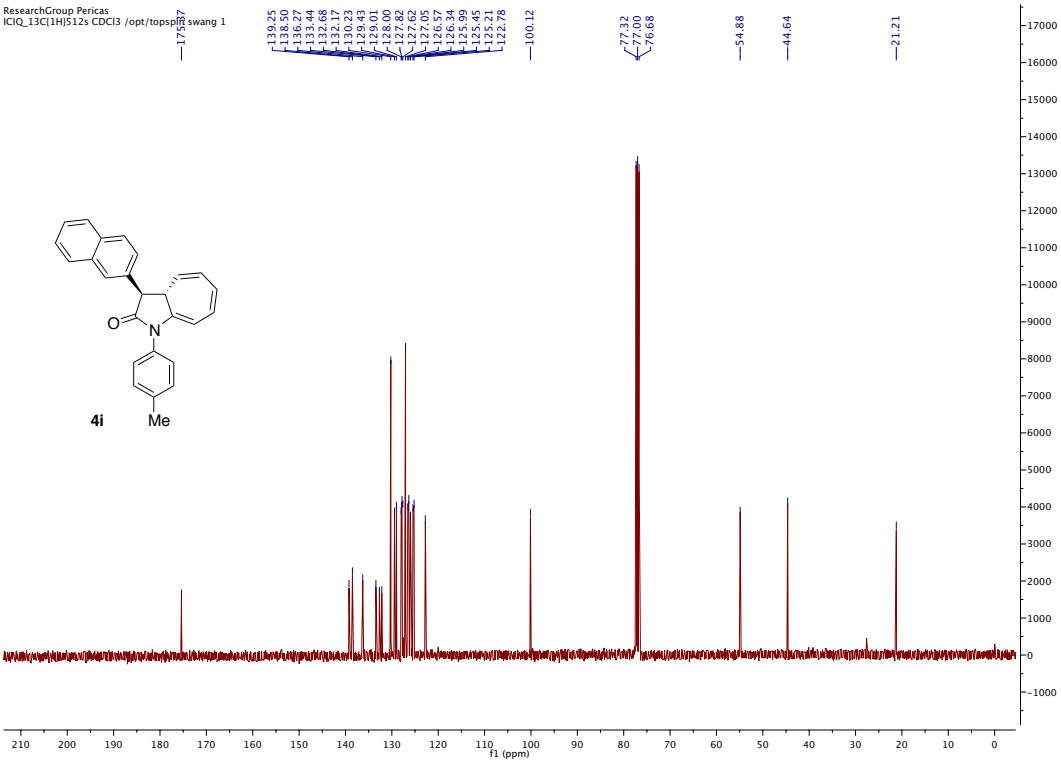
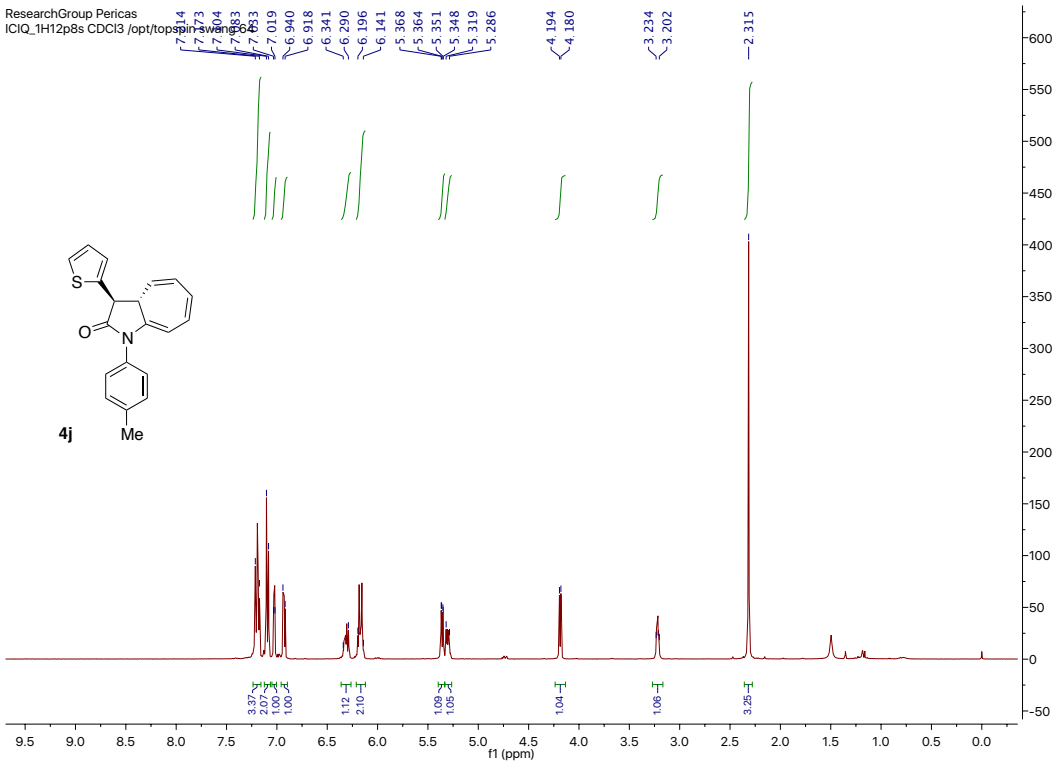
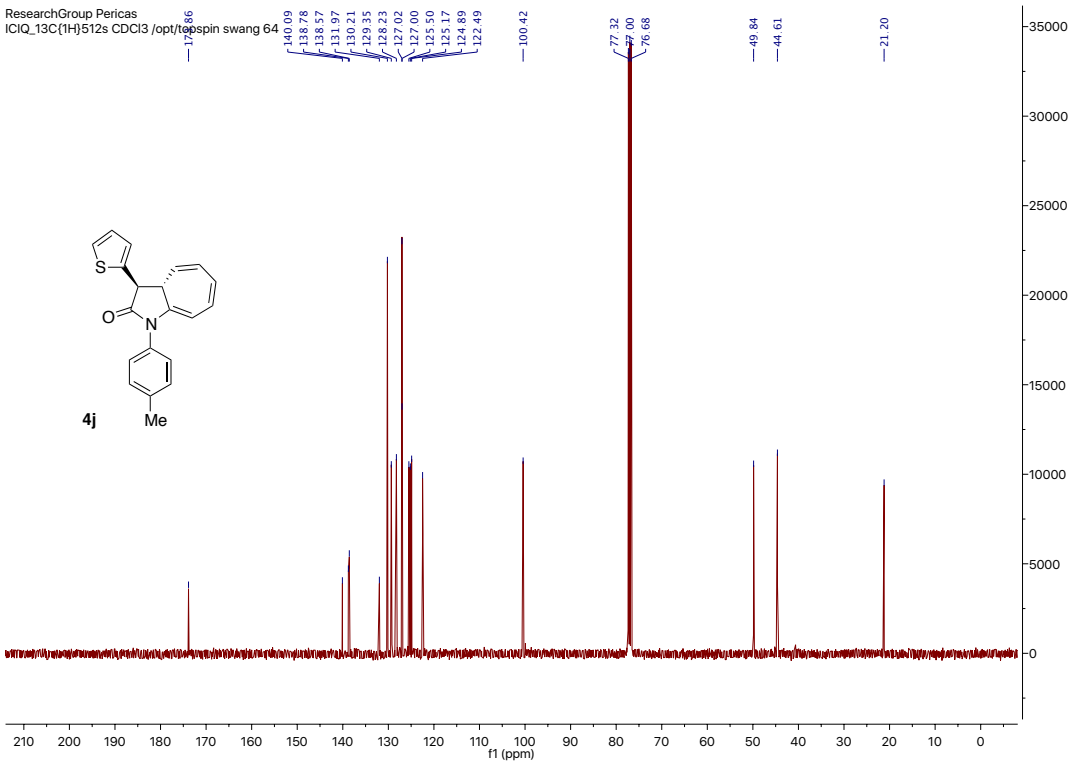
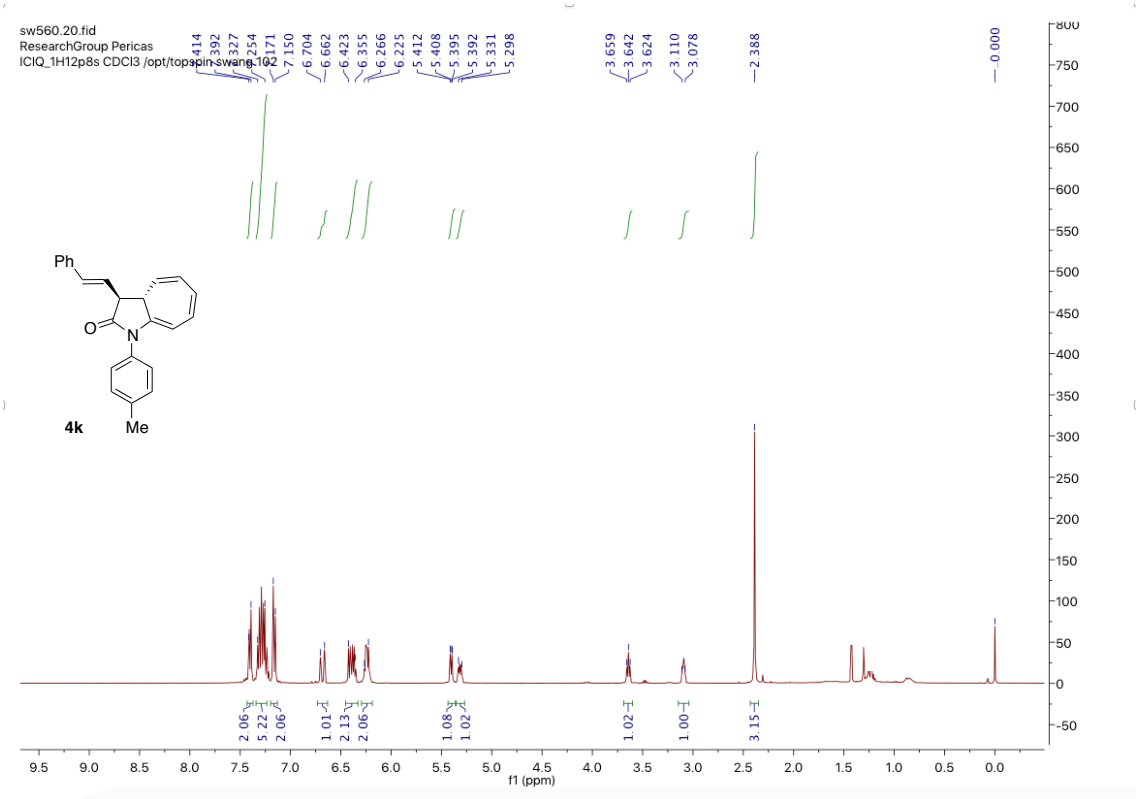
138.43
132.20
130.19
129.40
128.90
128.32
127.85
127.05
125.37
124.51
122.88
99.97
77.32
77.00
76.68
54.74
44.77
21.46
21.20
Me
O
N
4h
Me
f1 (ppm)

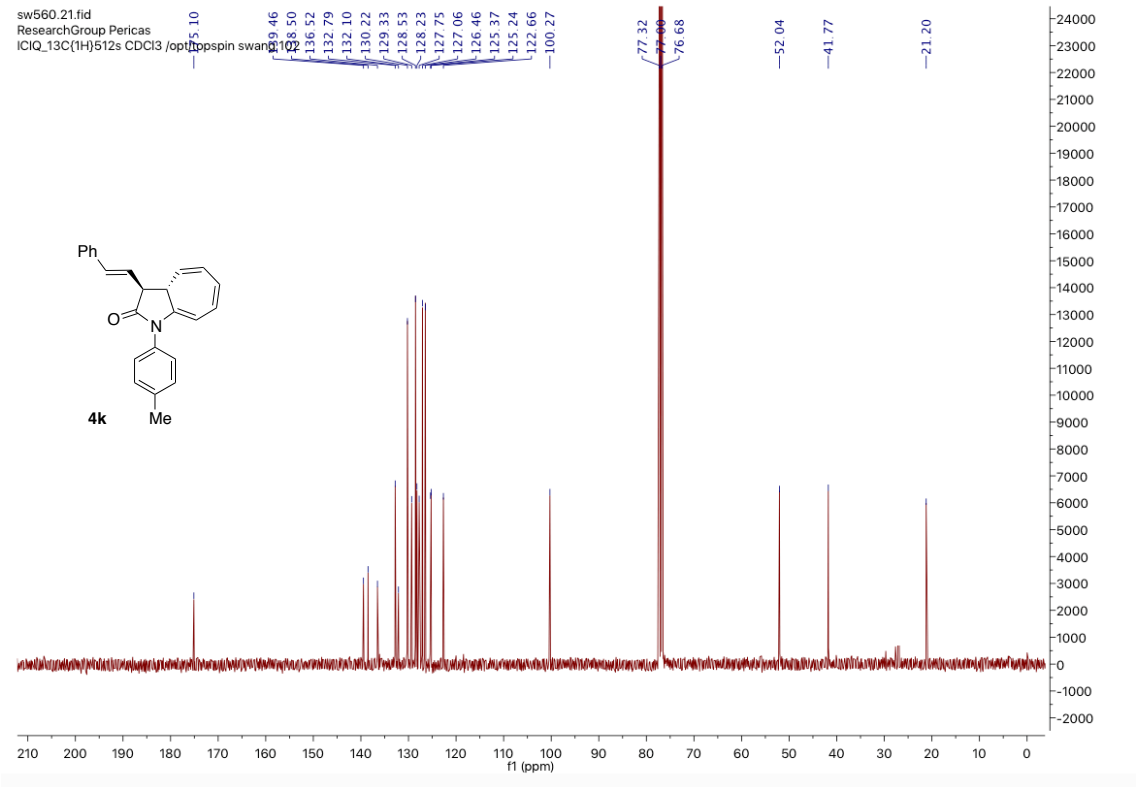

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin3.5pl6
7.857
7.784
7.495
7.424
7.295
7.275
7.240
7.200
6.433
6.381
6.250
6.201
5.488
5.485
5.471
5.468
5.451
5.418
4.183
4.170
3.222
3.196
2.385
4i
Me
4.16
3.07
2.14
2.21
1.05
2.04
1.01
1.00
1.00
0.98
3.12
f1 (ppm)

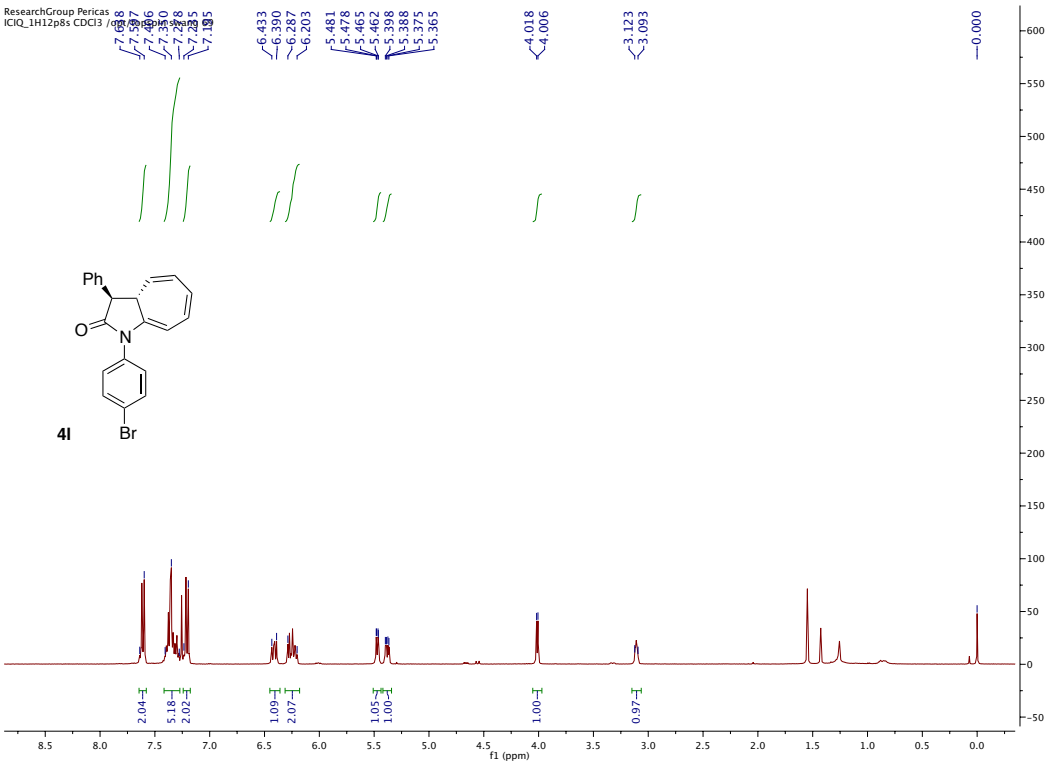

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin3.5pl6 swang 1
175.87
139.25
138.59
136.27
133.44
132.68
132.17
130.23
129.43
129.01
128.00
127.82
127.62
127.55
126.67
126.34
125.99
125.45
125.21
122.78
100.12
77.32
77.00
76.68
54.88
44.64
21.21
4i
Me
f1 (ppm)

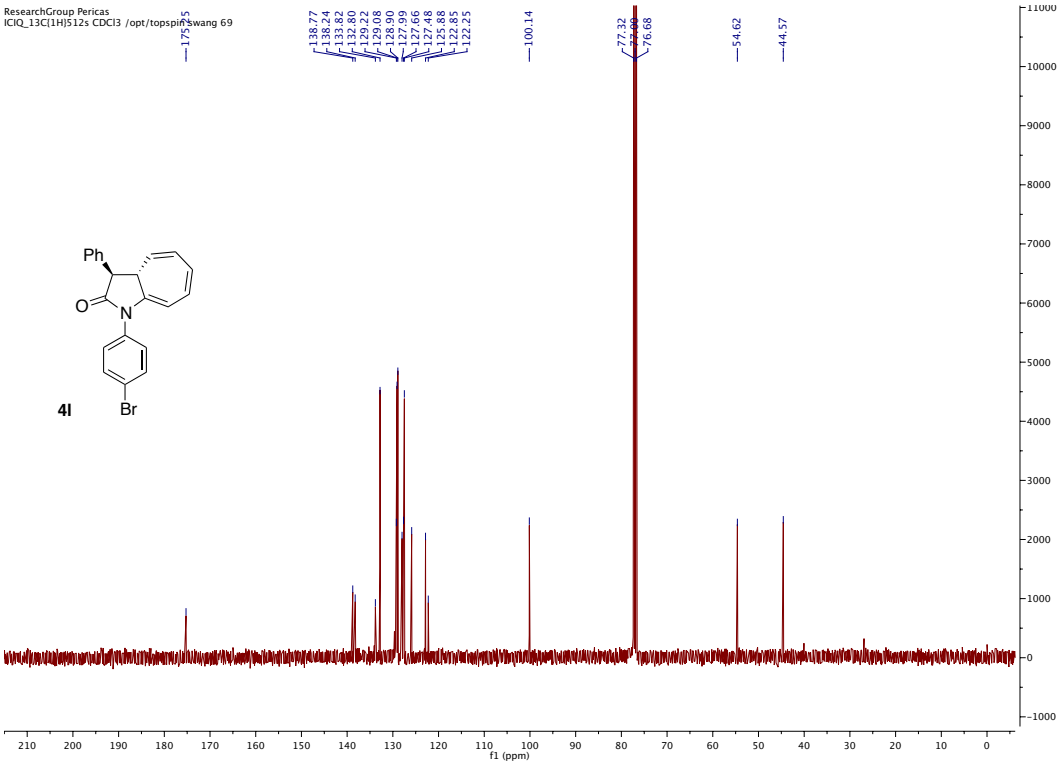

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 64
7.114
7.073
7.004
6.983
6.933
7.019
6.940
6.918
6.341
6.290
6.196
6.141
5.368
5.364
5.351
5.348
5.319
5.286
4.194
4.180
3.234
3.202
2.315
S
O
N
4j
Me
3.37
2.07
1.00
1.00
1.12
2.10
1.09
1.05
1.04
1.06
3.25
f1 (ppm)

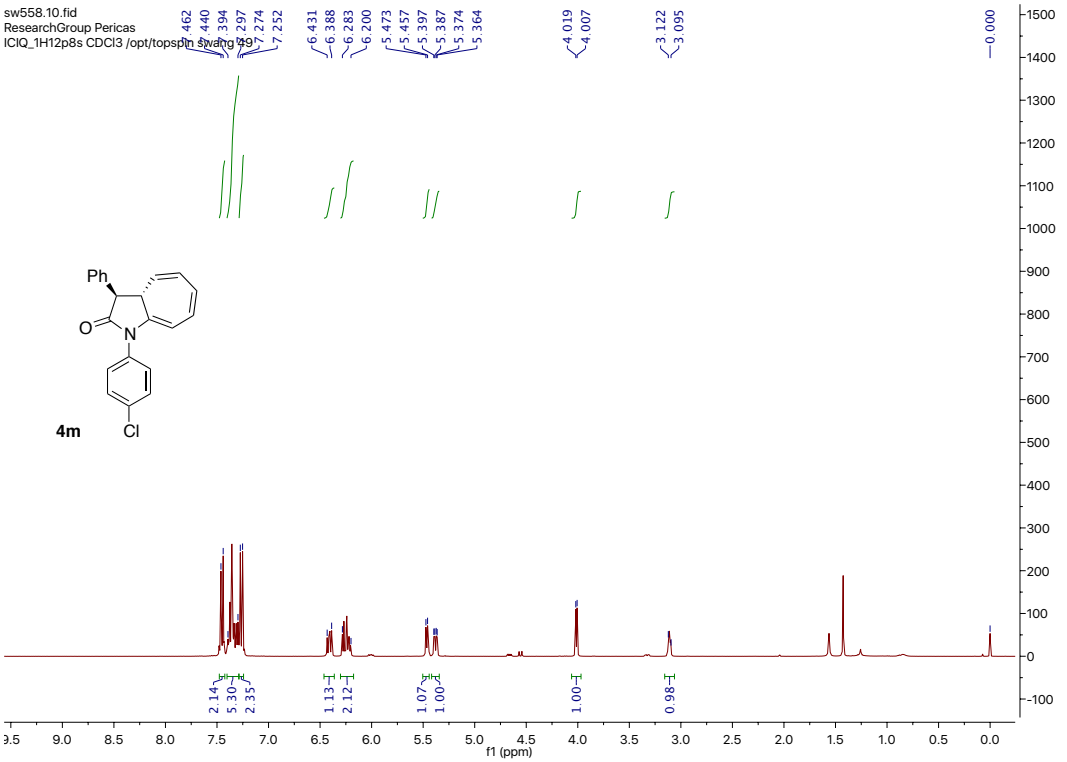

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 64
172.86
140.09
138.78
138.57
131.97
130.21
129.35
128.23
127.02
127.00
125.50
125.17
124.89
122.49
100.42
77.32
77.00
76.68
49.84
44.61
21.20
S
O
N
4j
Me
f1 (ppm)

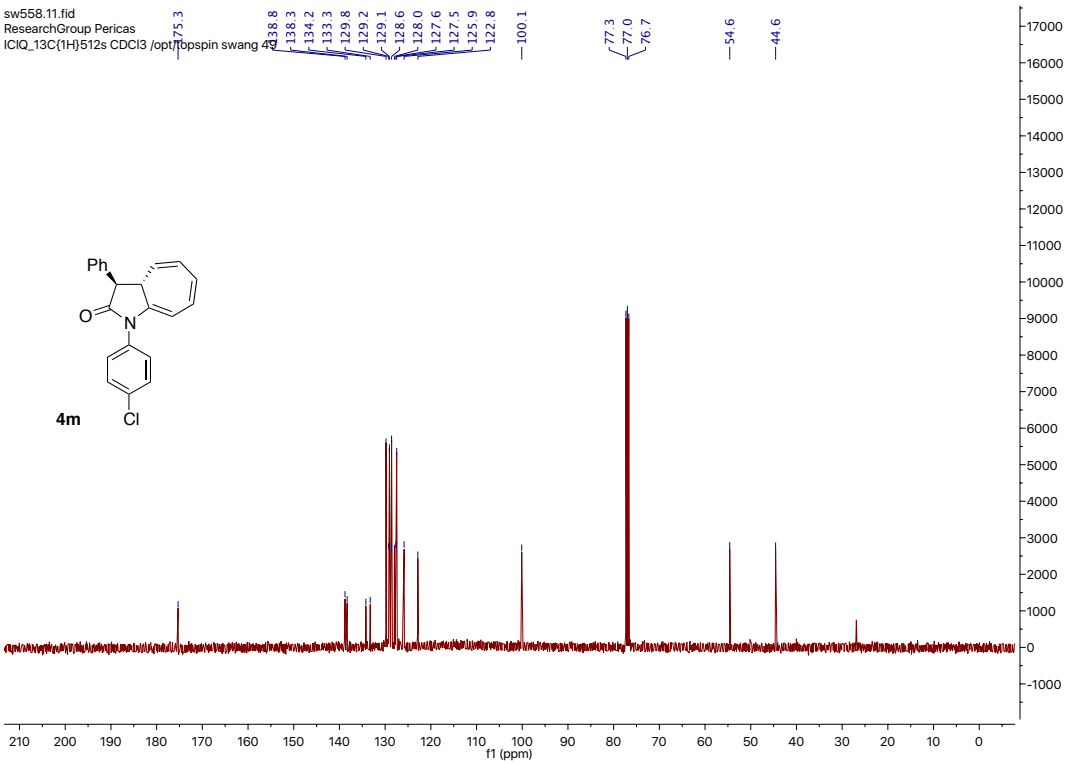

sw560.20.fid
ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 102
7.414
7.392
7.327
7.254
7.171
7.150
6.704
6.662
6.423
6.355
6.266
6.225
5.412
5.408
5.395
5.392
5.331
5.298
3.659
3.642
3.624
3.110
3.078
2.388
0.000
Ph
O
N
4k
Me
2.06
5.22
2.06
1.01
2.13
2.06
1.08
1.02
1.02
1.00
3.15
f1 (ppm)

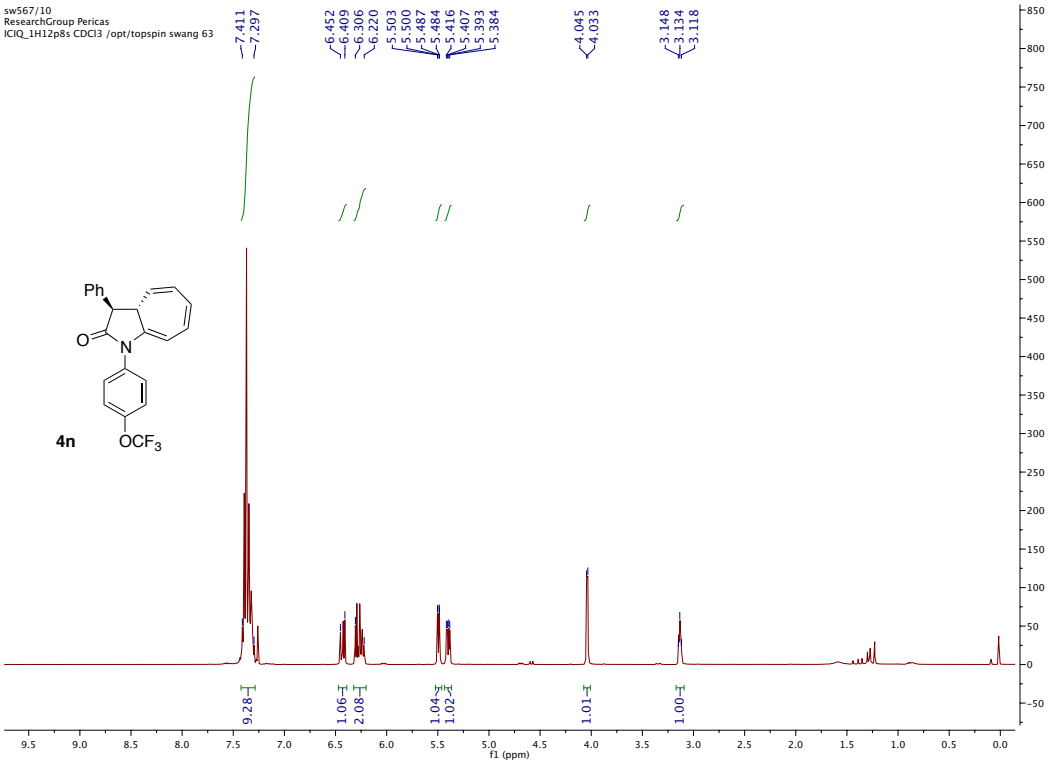

sw560.21.fid
ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 103
165.10
139.46
138.50
136.52
132.79
132.10
130.22
129.33
128.53
128.23
127.75
127.06
126.46
125.37
125.24
122.66
100.27
77.32
77.00
76.68
52.04
41.77
21.20
Ph
O
N
4k
Me
f1 (ppm)

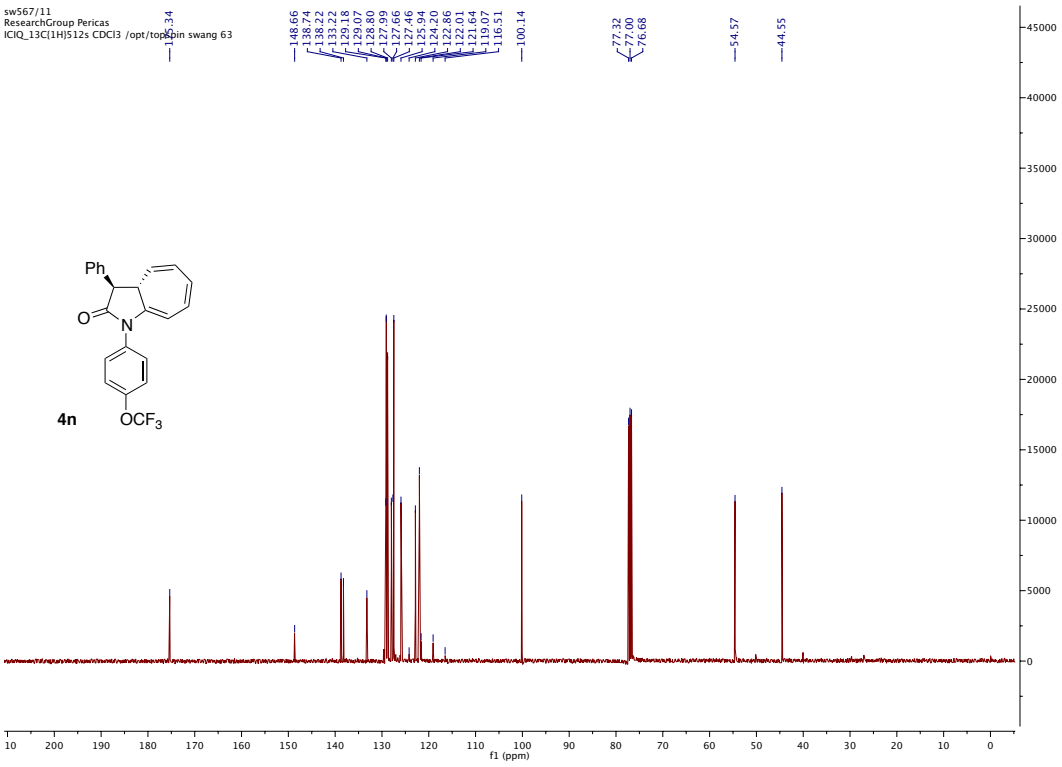

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin/swang 69
7.688
7.597
7.486
7.350
7.278
7.235
7.195
6.433
6.390
6.287
6.203
5.481
5.478
5.465
5.462
5.398
5.388
5.375
5.365
4.018
4.006
3.123
3.093
0.000
Ph
O
N
Br
4l
2.04
5.18
2.02
1.09
2.07
1.05
1.00
1.00
0.97
f1 (ppm)

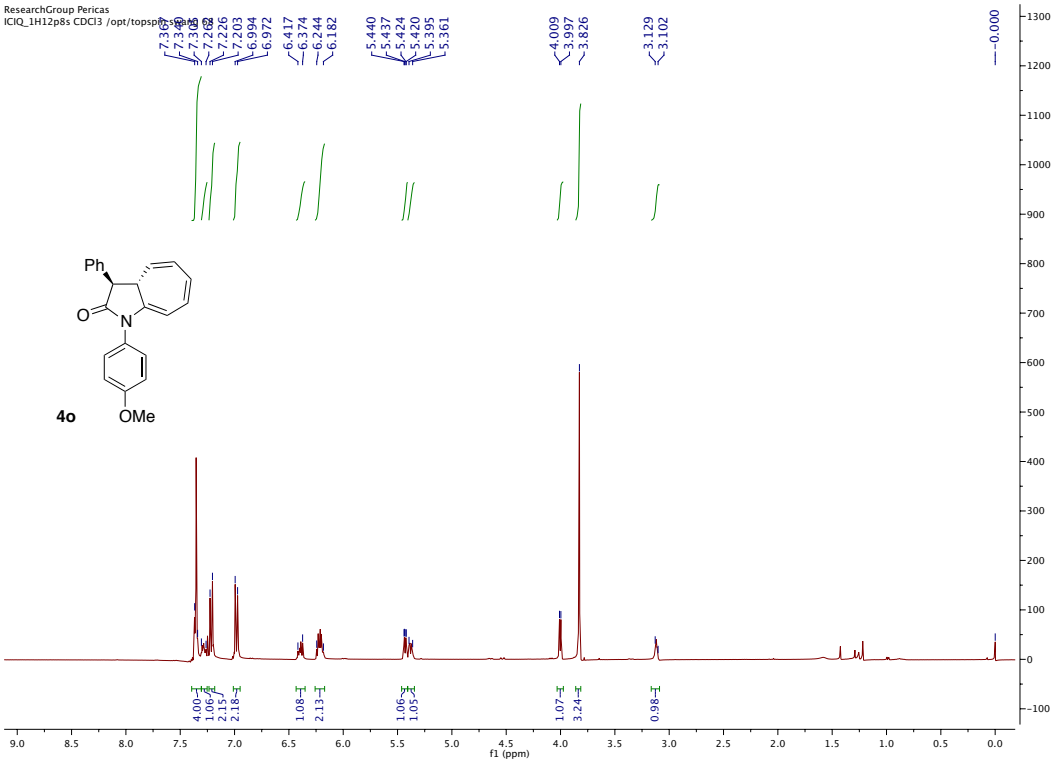

ResearchGroup Pericas
ICIQ_13C(1H)512s CDCl3 /opt/topspin/swang 69
175.55
138.77
138.74
133.82
132.80
129.22
129.08
128.90
127.99
127.66
127.48
125.88
122.85
122.25
100.14
77.32
77.00
76.68
54.62
44.57
Ph
O
N
Br
4l
f1 (ppm)

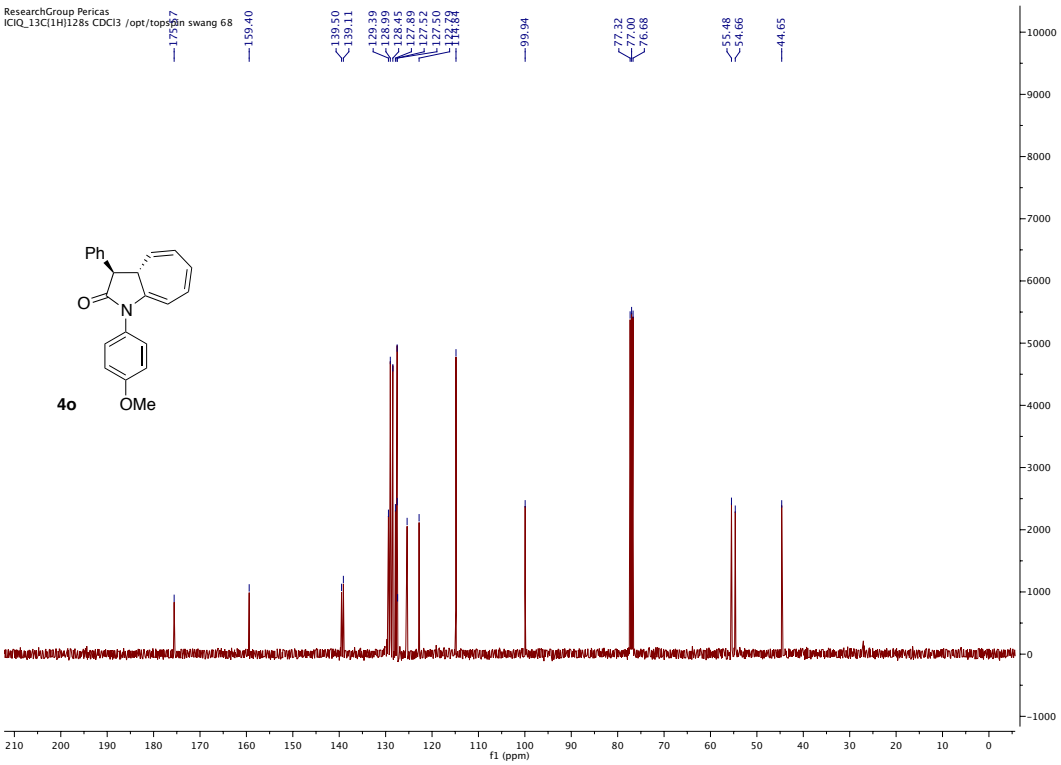

sw558.10.fid
ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 491
7.462
7.440
7.394
7.297
7.274
7.252
6.431
6.388
6.283
6.200
5.473
5.457
5.397
5.387
5.374
5.364
4.019
4.007
3.122
3.095
0.000
Ph
O
N
Cl
4m
2.14
5.30
2.35
1.13
2.12
1.07
1.00
1.00
0.98
f1 (ppm)

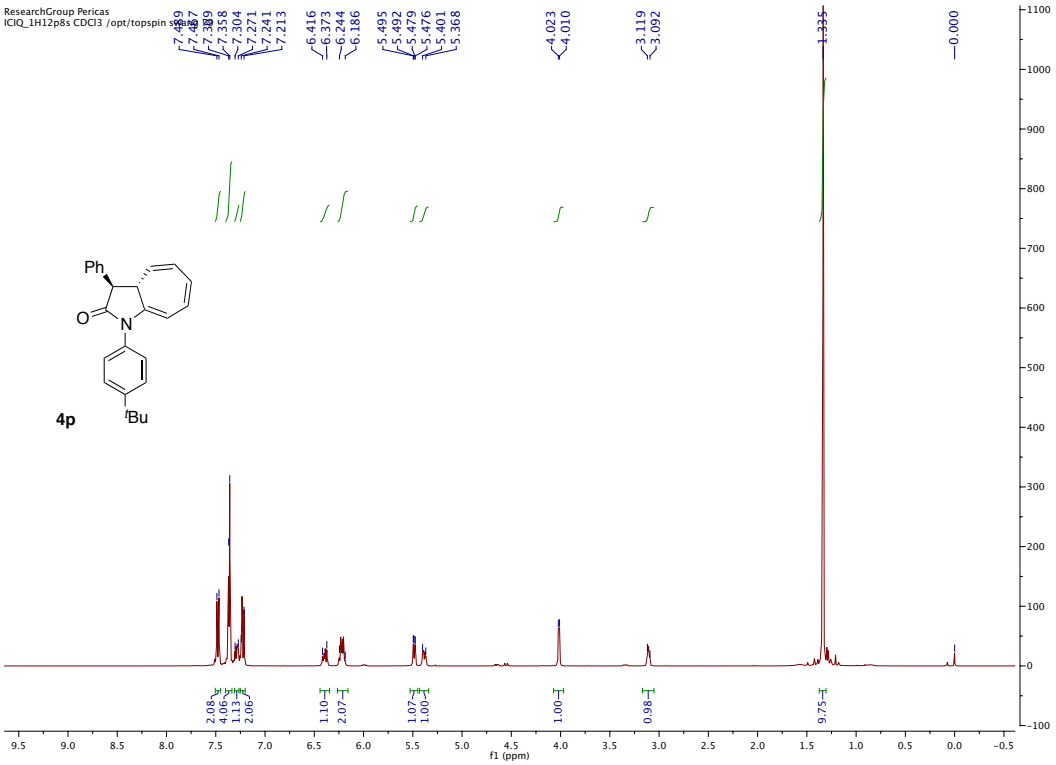

sw558.11.fid
ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 492
175.3
138.8
138.3
134.2
133.3
129.8
129.2
129.1
128.6
128.0
127.6
127.5
125.9
122.8
100.1
77.3
77.0
76.7
54.6
44.6
Ph
O
N
Cl
4m
f1 (ppm)

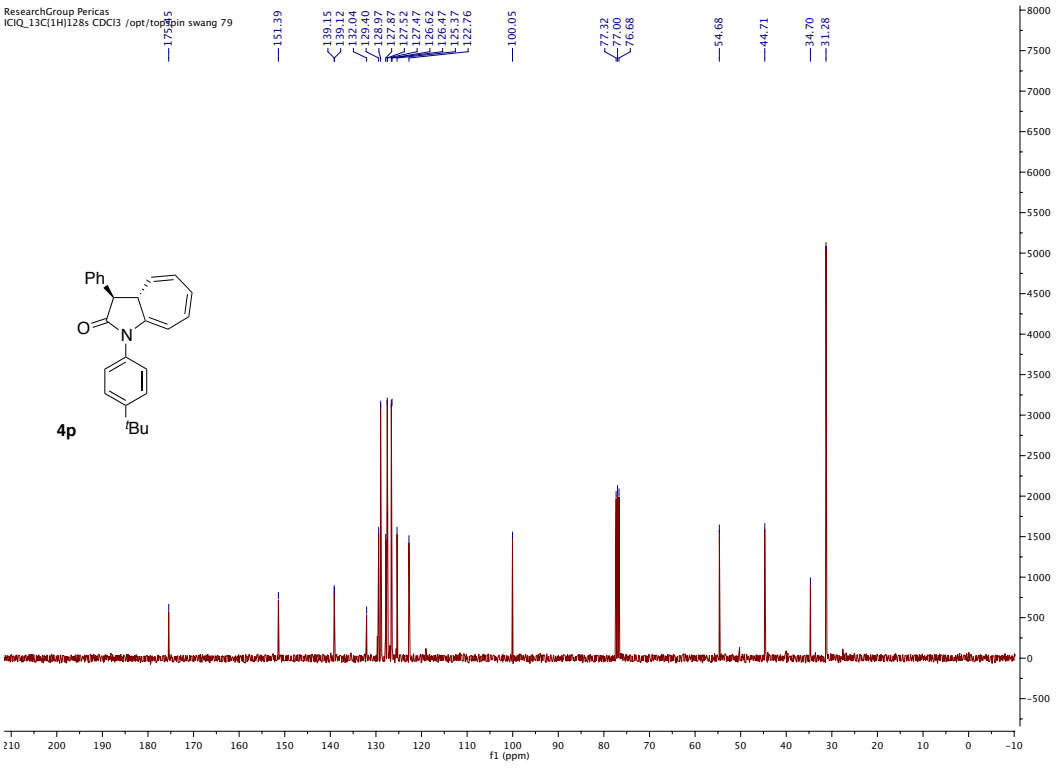

sw567/10
ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 63
7.411
7.297
6.452
6.409
6.306
6.220
5.503
5.500
5.487
5.484
5.416
5.407
5.393
5.384
4.045
4.033
3.148
3.134
3.118
Ph
O
N
4n
OCF3
9.28
1.06
2.08
1.04
1.02
1.01
1.00
f1 (ppm)

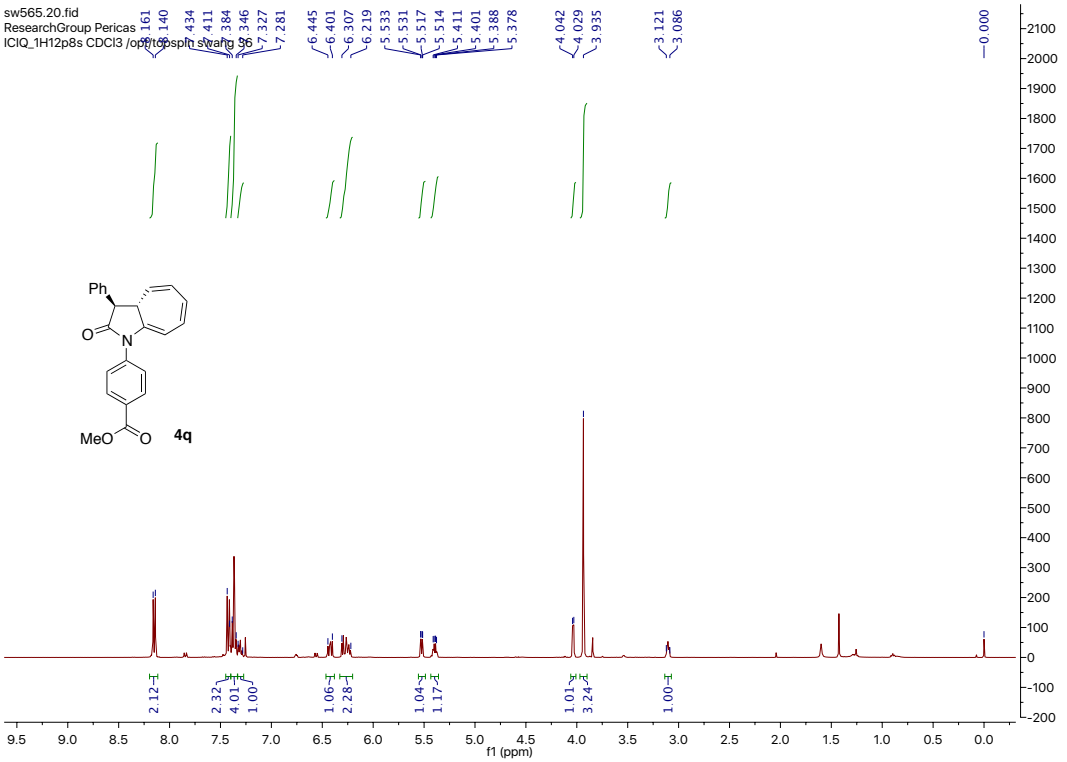

sw567/11
ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 63
170.34
148.66
138.74
138.22
133.22
129.18
129.07
128.80
127.99
127.66
127.46
125.94
124.20
122.86
122.01
121.64
119.07
116.51
100.14
77.32
77.00
76.68
54.57
44.55
Ph
O
N
4n
OCF3
f1 (ppm)

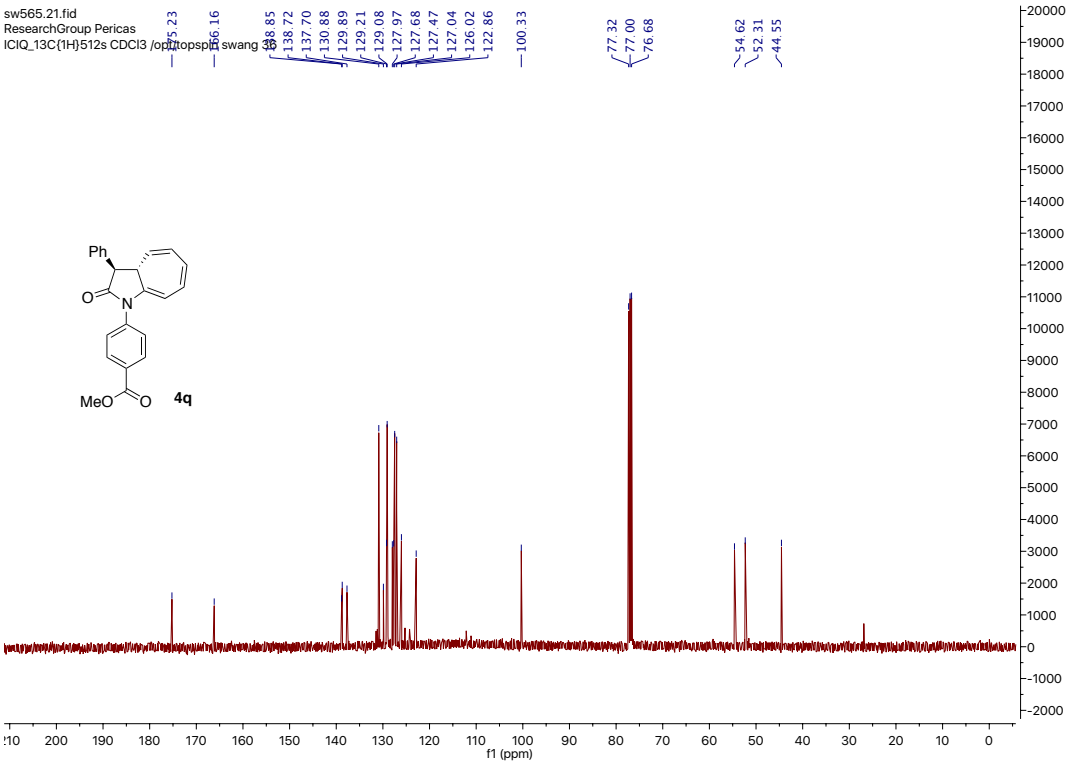

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 68
7.366
7.344
7.302
7.282
7.226
7.203
6.994
6.972
6.417
6.374
6.244
6.182
5.440
5.437
5.424
5.420
5.395
5.361
4.009
3.997
3.826
3.129
3.102
0.000
Ph
O
N
4o
OMe
4.00
1.06
2.15
2.18
1.08
2.13
1.06
1.05
1.07
3.24
0.98
f1 (ppm)

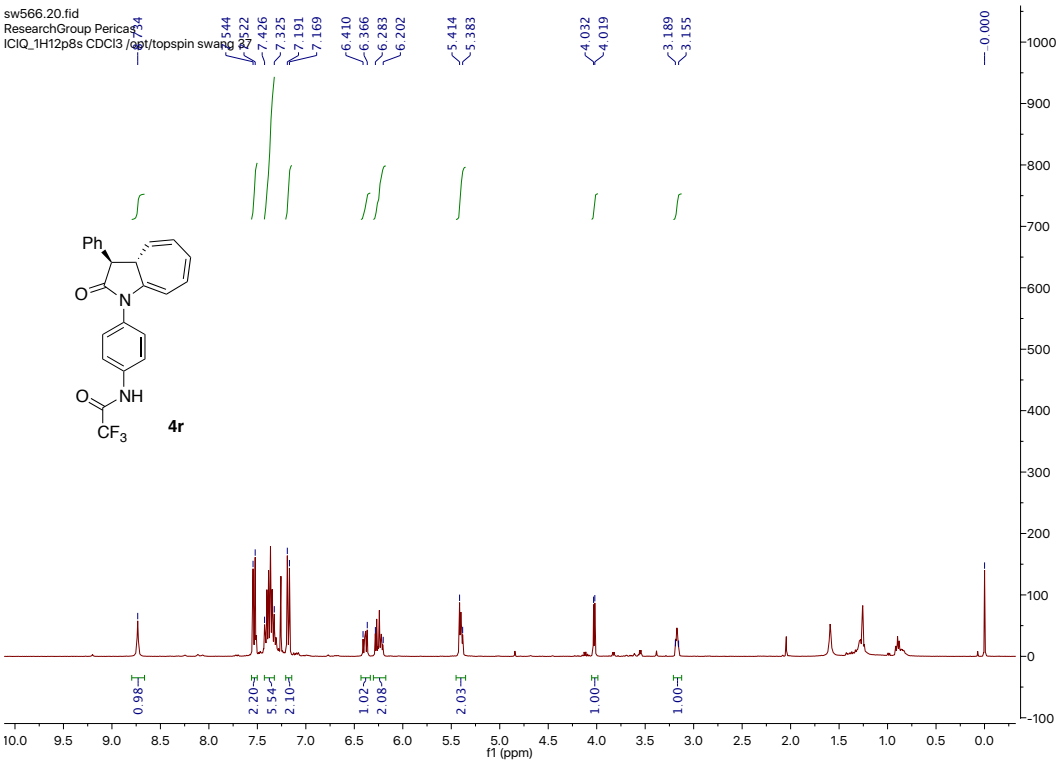

ResearchGroup Pericas
ICIQ_13C[1H]128s CDCl3 /opt/topspin swang 68
175.77
159.40
139.50
139.11
129.39
128.99
128.45
127.89
127.52
127.50
114.84
99.94
77.32
77.00
76.68
55.48
54.66
44.65
Ph
O
N
4o
OMe
f1 (ppm)

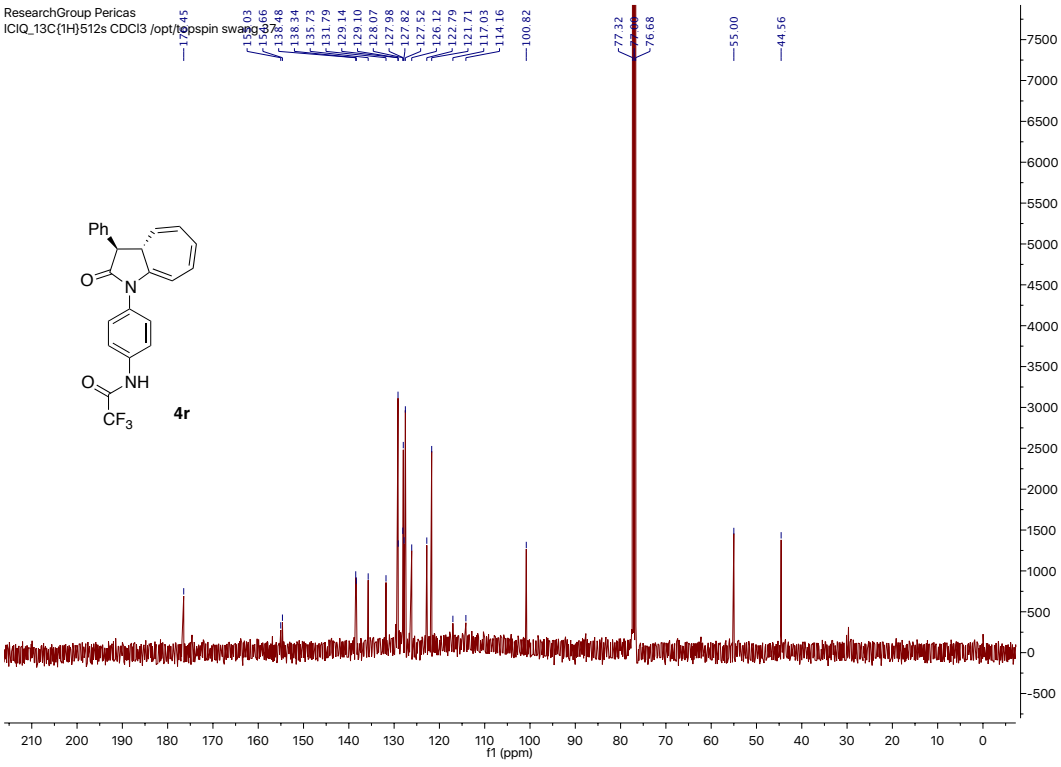

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang
7.489
7.487
7.389
7.358
7.304
7.271
7.241
7.213
6.416
6.373
6.244
6.166
5.495
5.492
5.479
5.476
5.401
5.368
4.023
4.010
3.119
3.092
1.335
0.000
Ph
O
N
tBu
4p
2.08
4.06
1.13
2.06
1.10
2.07
1.07
1.00
1.00
0.98
9.75
f1 (ppm)

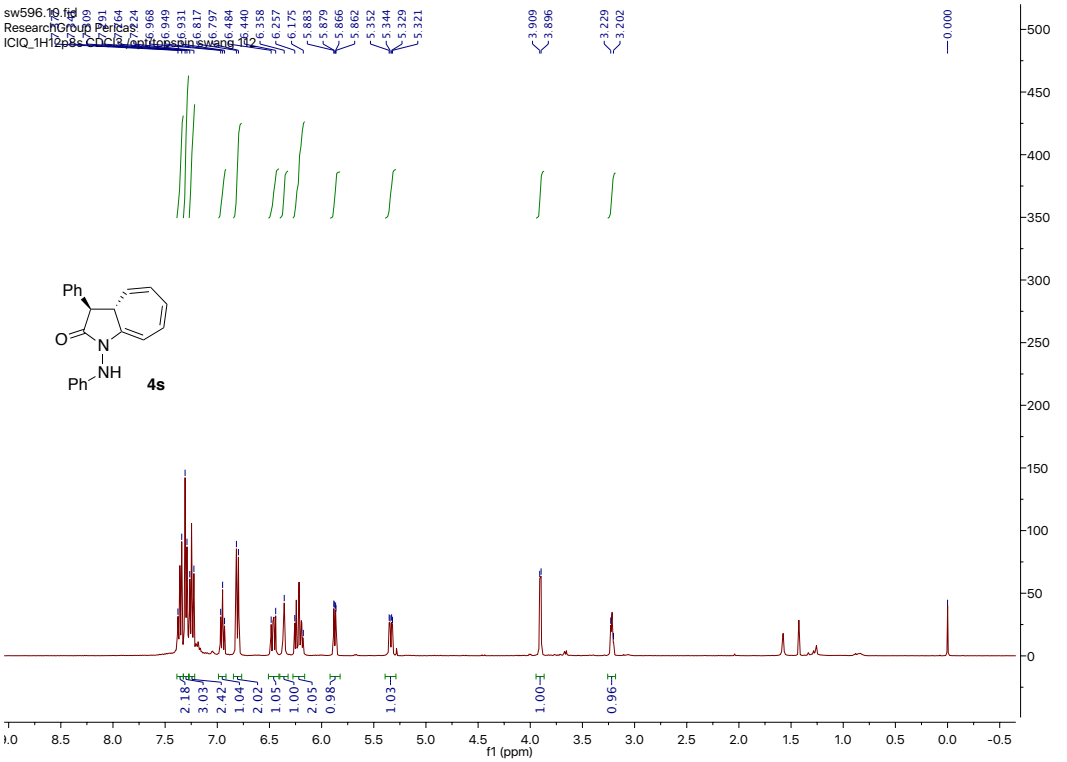

ResearchGroup Pericas
ICIQ_13C(1H)128s CDCl3 /opt/topspin swang 79
175.95
151.39
139.15
139.12
132.04
129.40
128.97
127.87
127.52
127.47
126.62
126.47
125.37
122.76
100.05
77.32
77.00
76.68
54.68
44.71
34.70
31.28
Ph
O
N
tBu
4p
f1 (ppm)

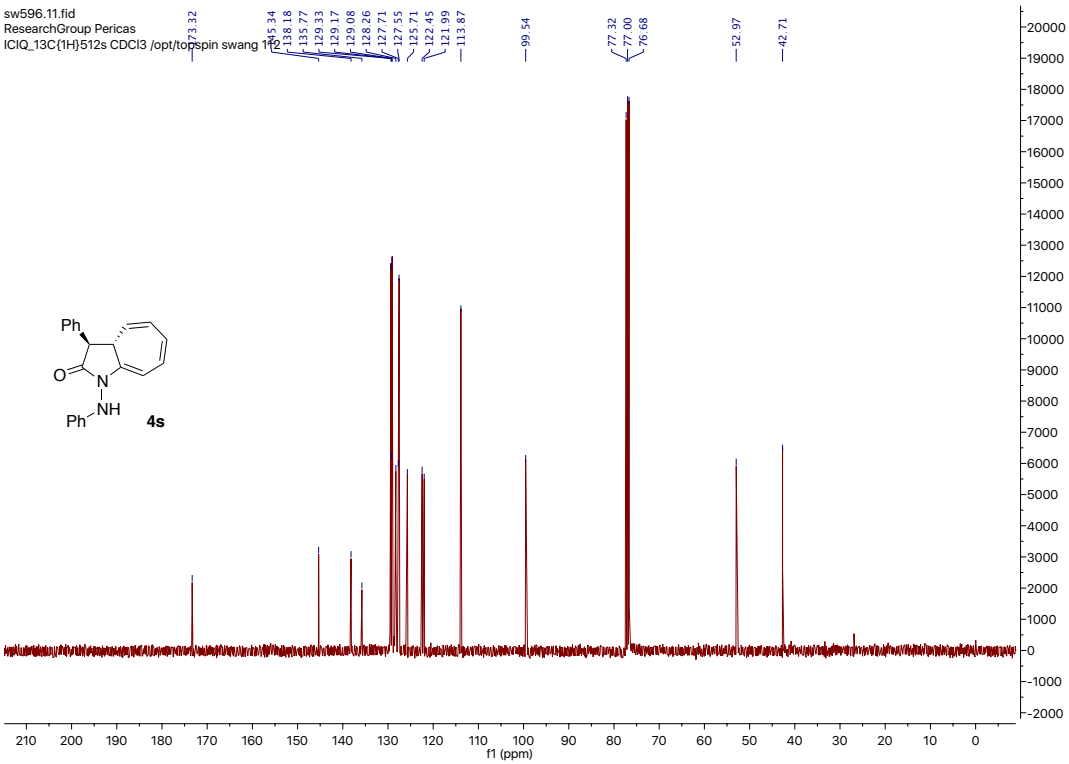

sw565.20.fid
ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 56
7.161
7.140
7.434
7.411
7.384
7.346
7.327
7.281
6.445
6.401
6.307
6.219
5.533
5.531
5.517
5.514
5.411
5.401
5.388
5.378
4.042
4.029
3.935
3.121
3.086
0.000
Ph
O
N
MeO
O
4q
2.12
2.32
4.01
1.00
1.06
2.28
1.04
1.17
1.01
3.24
1.00
f1 (ppm)

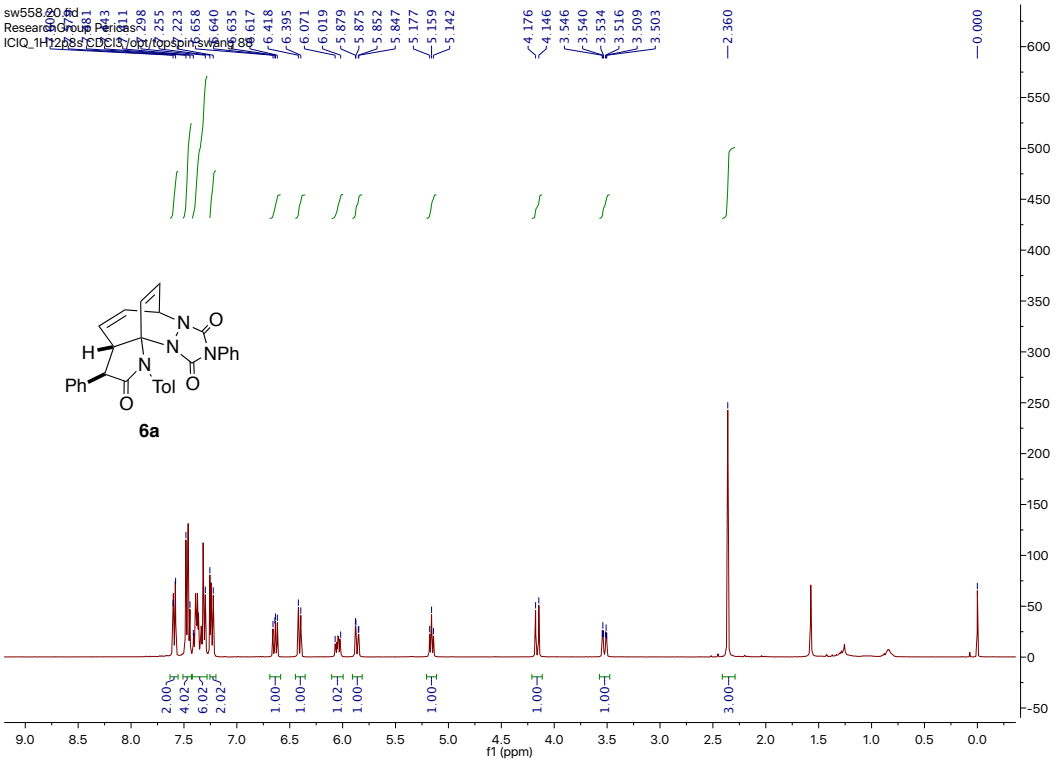

sw565.21.fid
ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 56
165.23
136.16
138.85
138.72
137.70
130.88
129.89
129.21
129.08
127.97
127.68
127.47
127.04
126.02
122.86
100.33
77.32
77.00
76.68
54.62
52.31
44.55
Ph
O
N
MeO
O
4q
f1 (ppm)

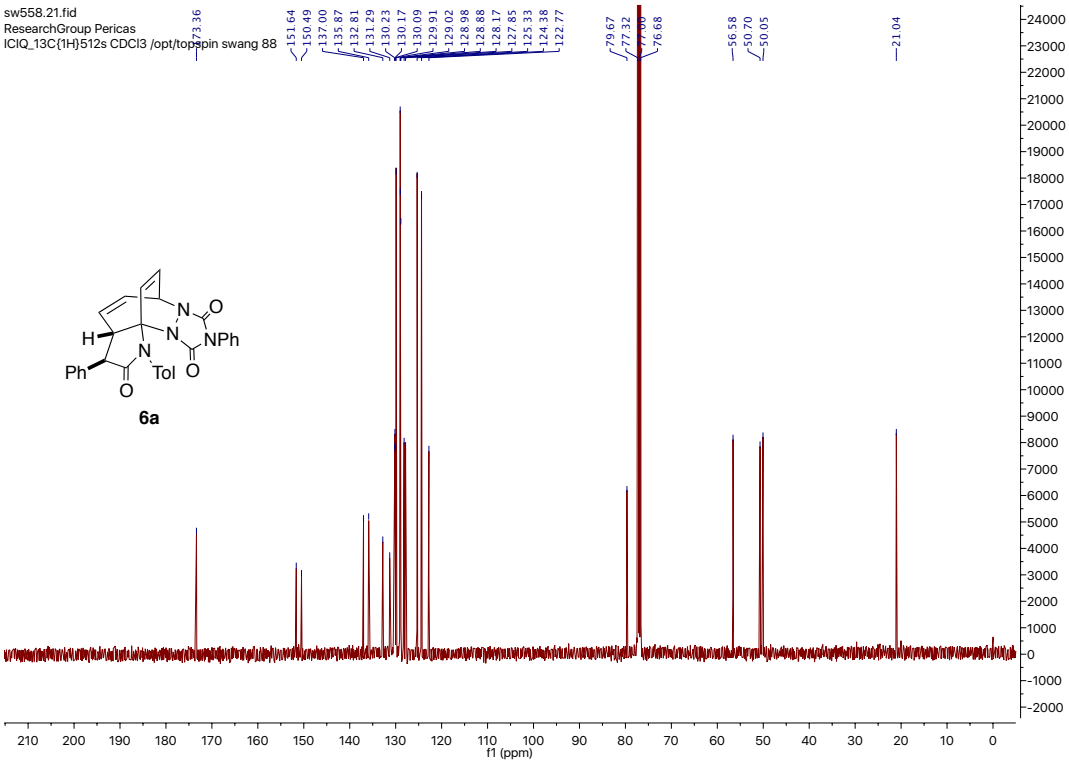

sw566.20.fid
ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 27
7.434
7.544
7.522
7.426
7.325
7.191
7.169
6.410
6.366
6.283
6.202
5.414
5.383
4.032
4.019
3.189
3.155
0.000
Ph
O
N
O
NH
CF3
4r
0.98
2.20
5.54
2.10
1.02
2.08
2.03
1.00
1.00
f1 (ppm)

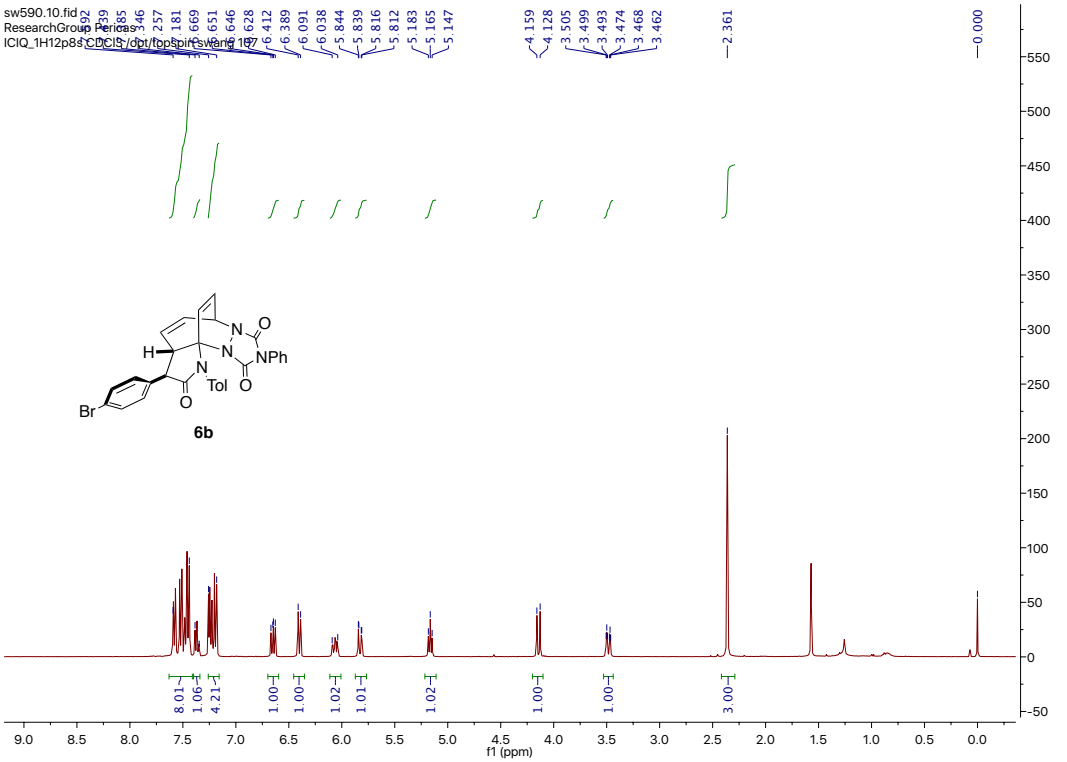

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 36
170.45
153.03
150.66
138.48
138.34
135.73
131.79
129.14
129.10
128.07
127.98
127.82
127.52
126.12
122.79
121.71
117.03
114.16
100.82
77.32
77.00
76.68
55.00
44.56
Ph
O
N
O
NH
CF3
4r
f1 (ppm)


sw596.10.fid
ResearchGroup Pericas
ICIQ_1H12ps CDCl3 /opt/topspin swang 1h2
Ph
O
N
NH
Ph
4s
f1 (ppm)


sw596.11.fid
ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 1h2
Ph
O
N
NH
Ph
4s
f1 (ppm)


sw558.20.fid
ResearchGroup Pericas
ICIQ_1H1268s CDCl3 /opt/topspin swang 88
7.881
7.843
7.811
7.798
7.255
7.223
6.658
6.640
6.635
6.617
6.418
6.395
6.071
6.019
5.879
5.875
5.852
5.847
5.177
5.159
5.142
4.176
4.146
3.546
3.540
3.534
3.516
3.509
3.503
2.360
0.000
N
O
N
NPh
H
N
Ph
Tol
O
O
6a
2.00
4.02
6.02
2.02
1.00
1.00
1.02
1.00
1.00
1.00
1.00
3.00
f1 (ppm)


sw558.21.fid
ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin swang 88
173.36
151.64
150.49
137.00
135.87
132.81
131.29
130.23
130.17
130.09
129.91
129.02
128.98
128.88
128.17
127.85
125.33
124.38
122.77
79.67
77.32
77.00
76.68
56.58
50.70
50.05
21.04
N
O
N
NPh
H
N
Ph
Tol
O
O
6a
f1 (ppm)


sw590.10.fid
ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin swang 107
7.92
7.39
7.85
7.46
7.257
7.181
6.669
6.651
6.646
6.628
6.412
6.389
6.091
6.038
5.844
5.839
5.816
5.812
5.183
5.165
5.147
4.159
4.128
3.505
3.499
3.493
3.474
3.468
3.462
2.361
0.000
8.01
1.06
4.21
1.00
1.00
1.02
1.01
1.02
1.00
1.00
3.00
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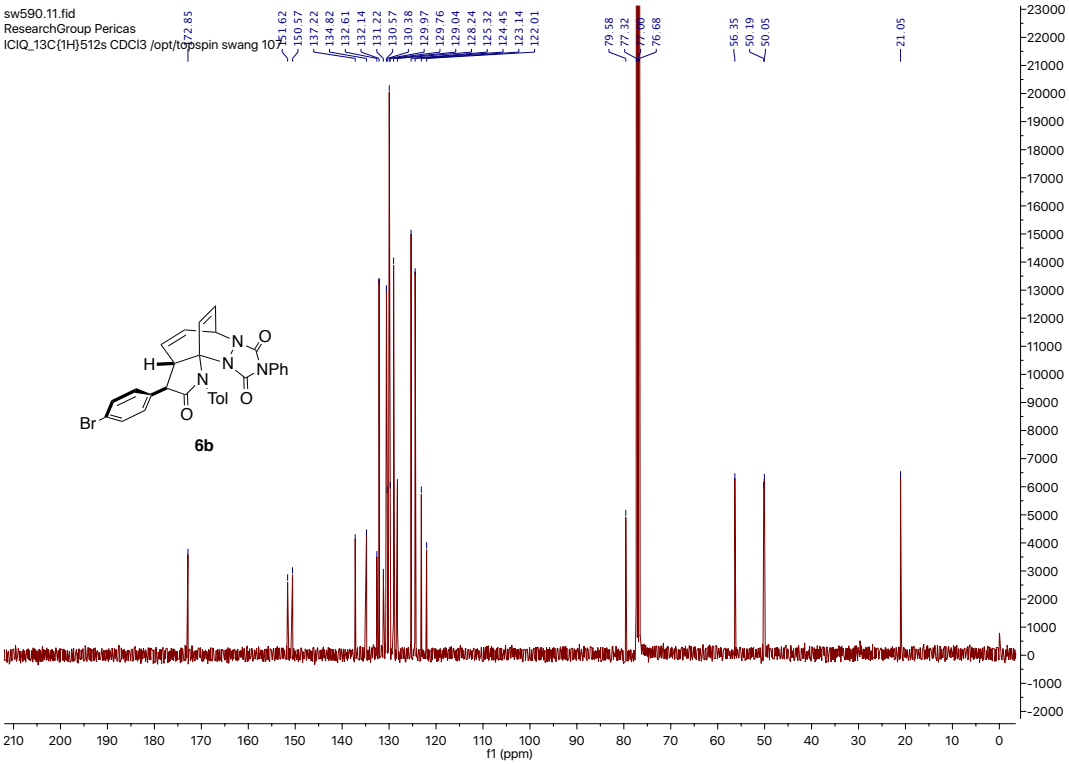
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128.24
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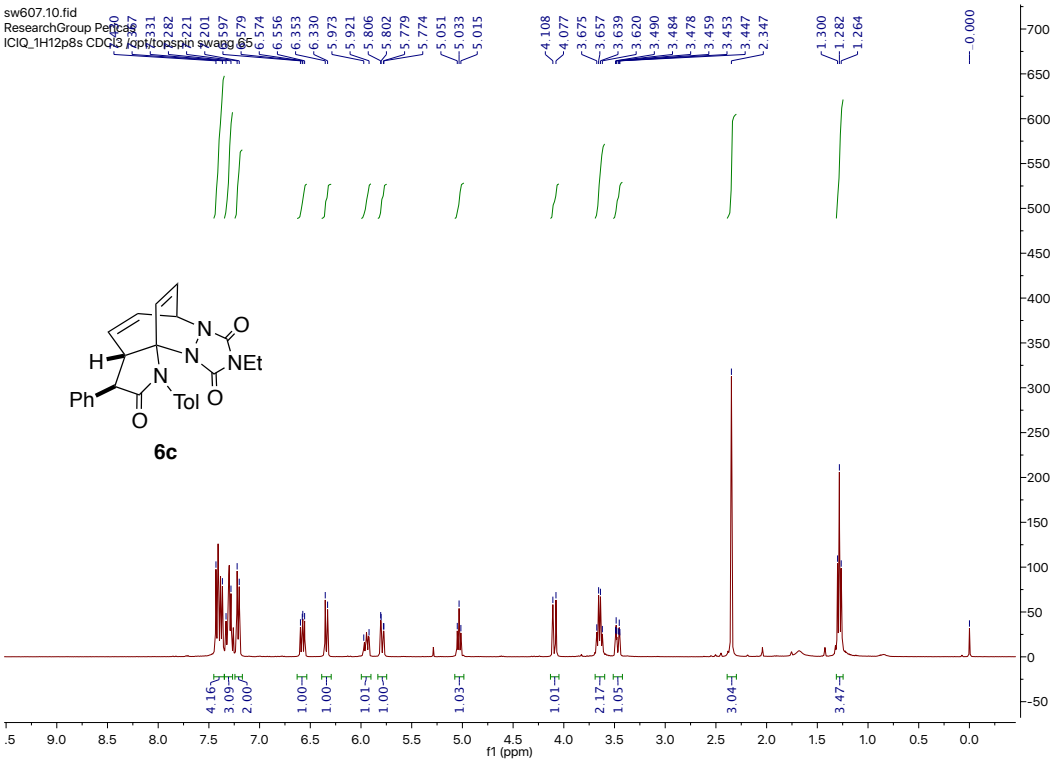
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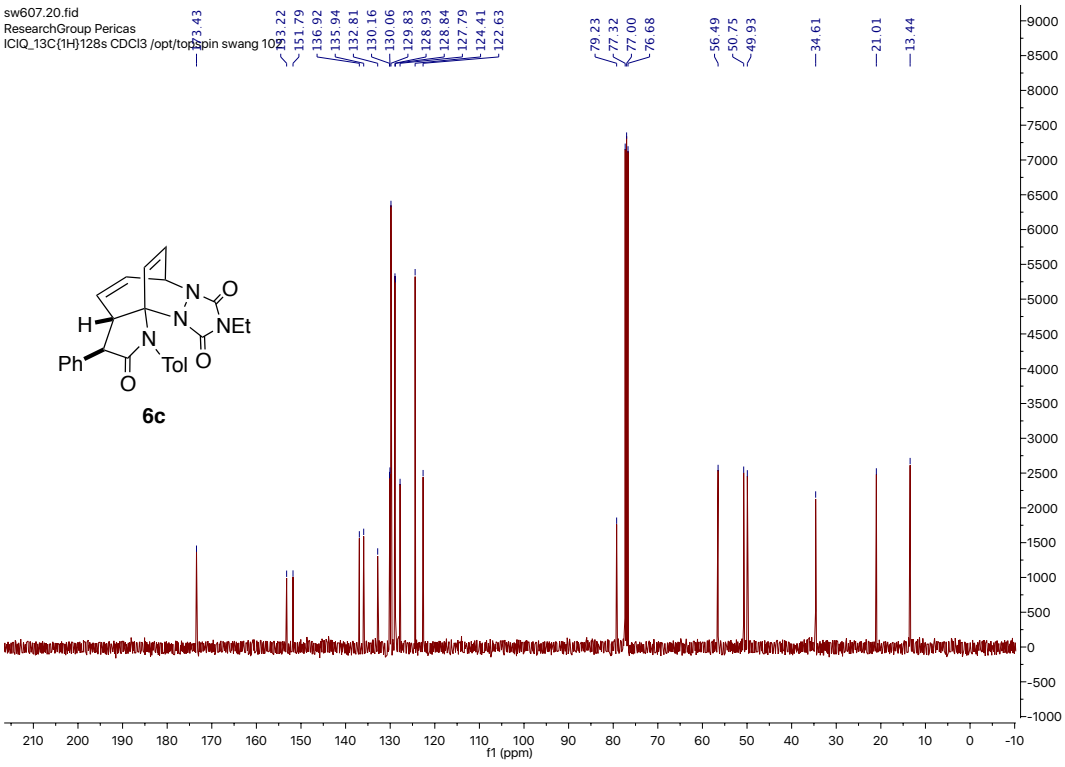
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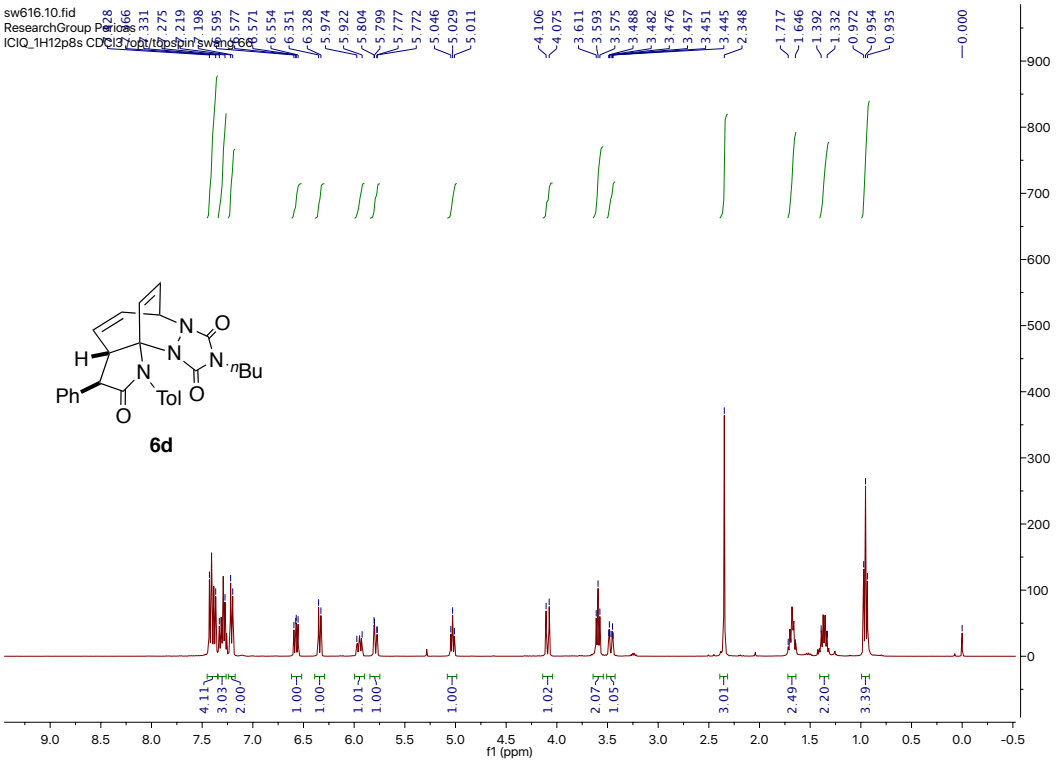
f1 (ppm)
6c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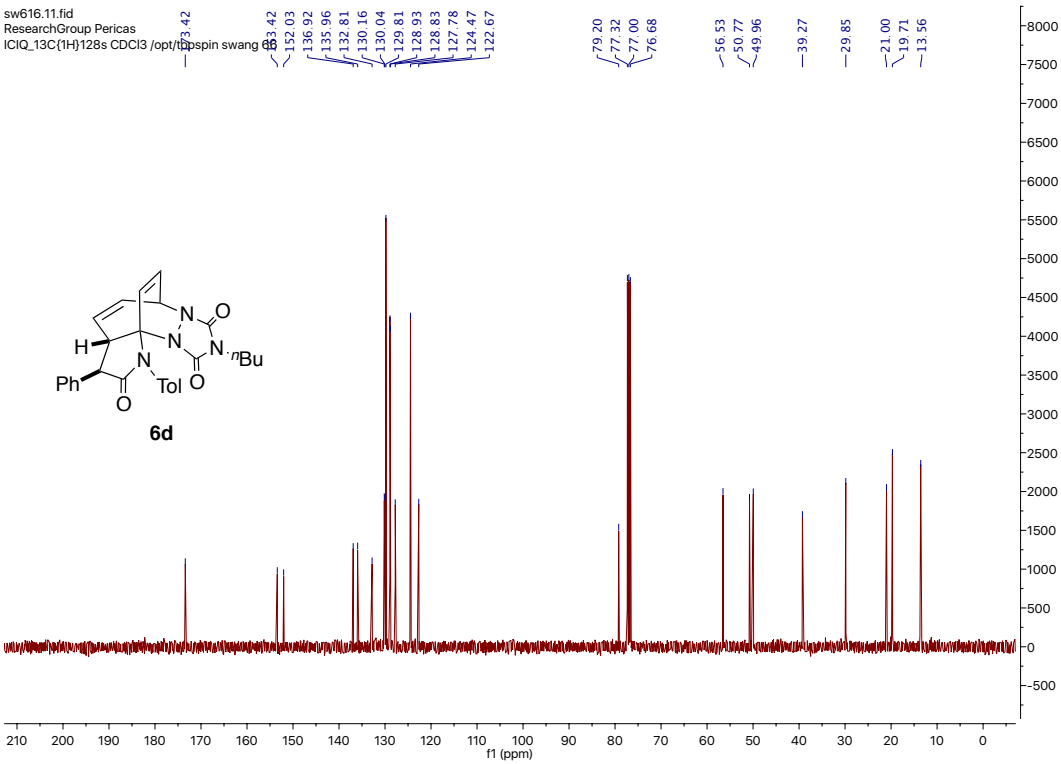
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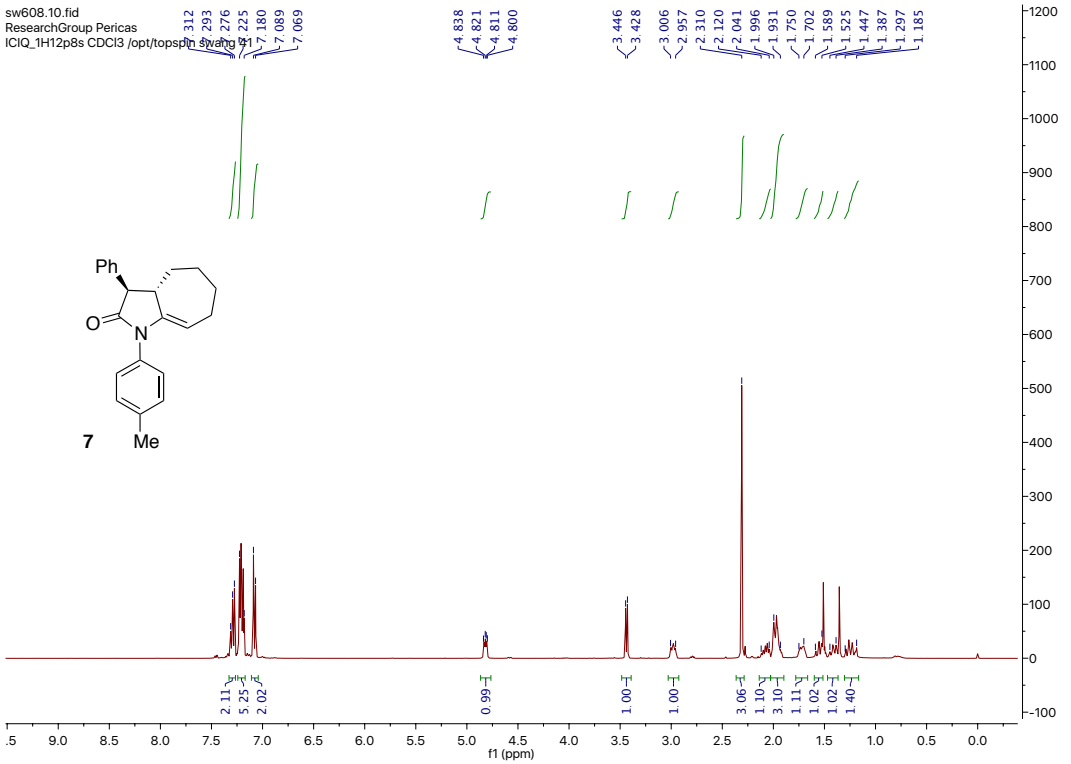
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1.589
1.525
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1.387
1.297
1.185
Ph
O
N
7
Me
2.11
5.25
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1.10
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1.02
1.40
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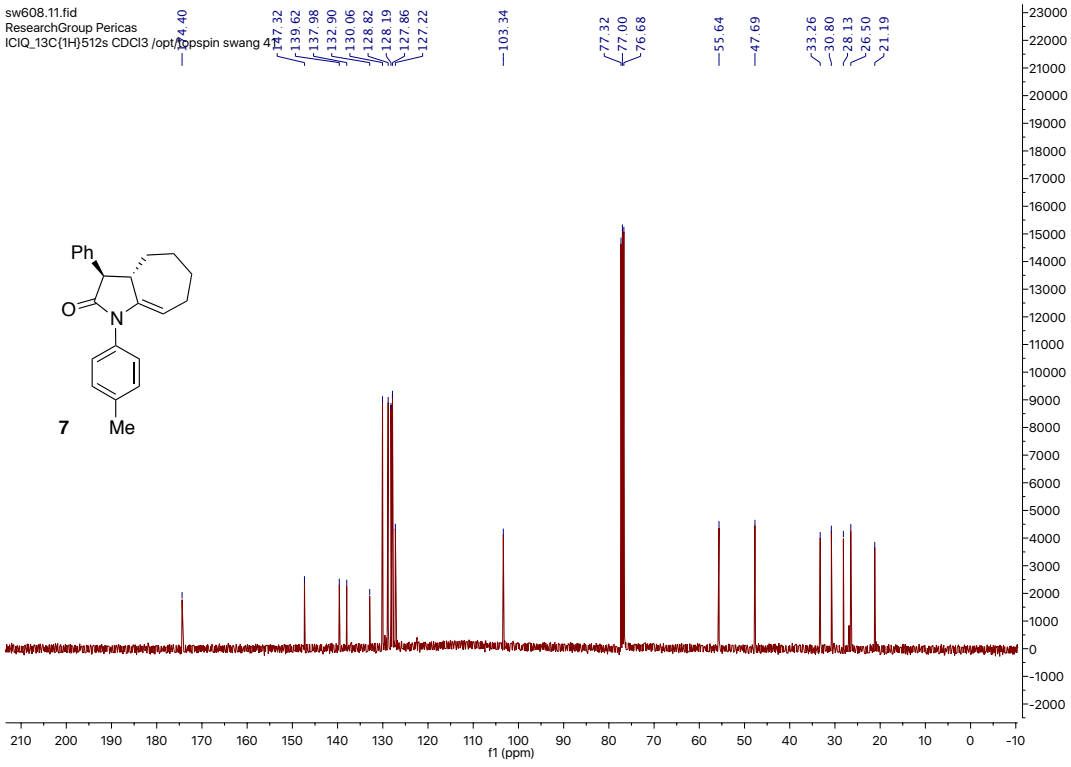
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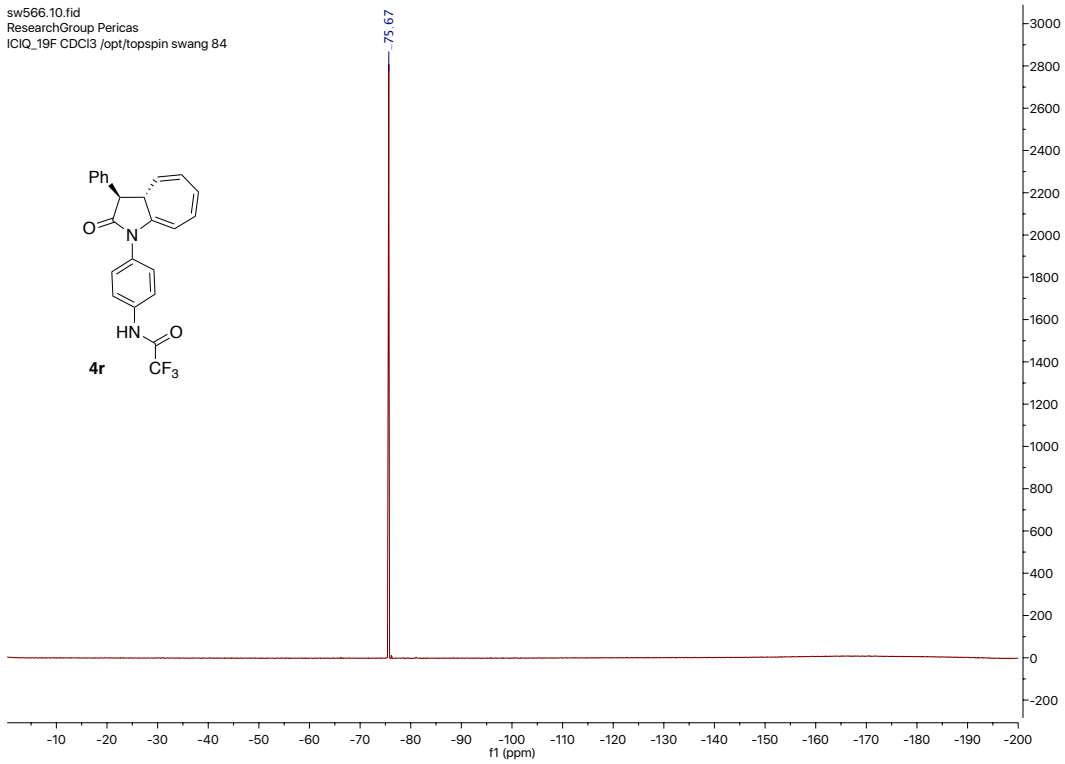
10. ^{19}F NMR spectra



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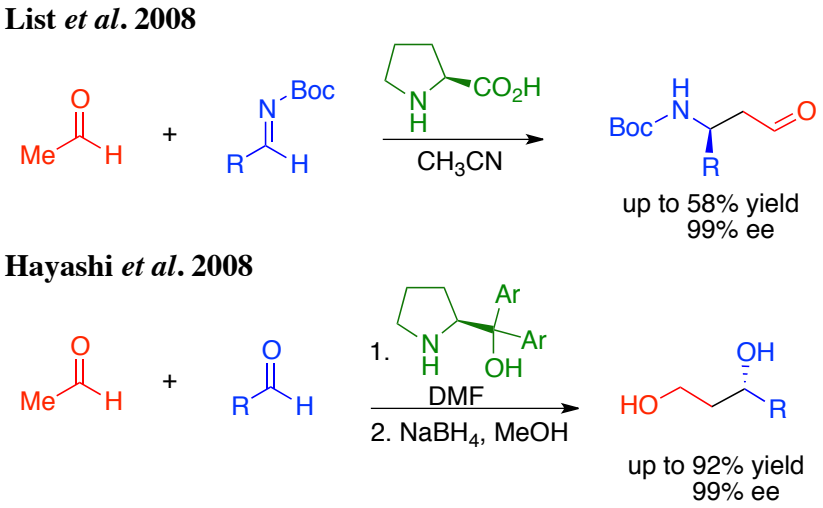
CHAPTER V

Chapter V

Asymmetric Cross-Aldol Reaction of Paraldehyde Promoted by Site-Isolated Incompatible Catalysts

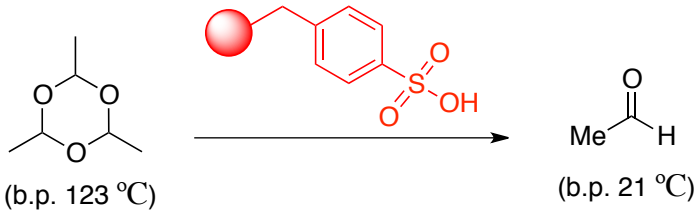
5.1. Introduction

As the smallest enolizable aldehyde, acetaldehyde is the most challenging substrate in α-functionalization reactions owing to its high reactivity and the formation of undesired by-products due to its inherent tendency towards oligomerization and aldolization. Pioneering works dealing with the organocatalytic activation of acetaldehyde were reported by the List group[1] and the Hayashi group[2] in 2008 (Scheme 5.1).



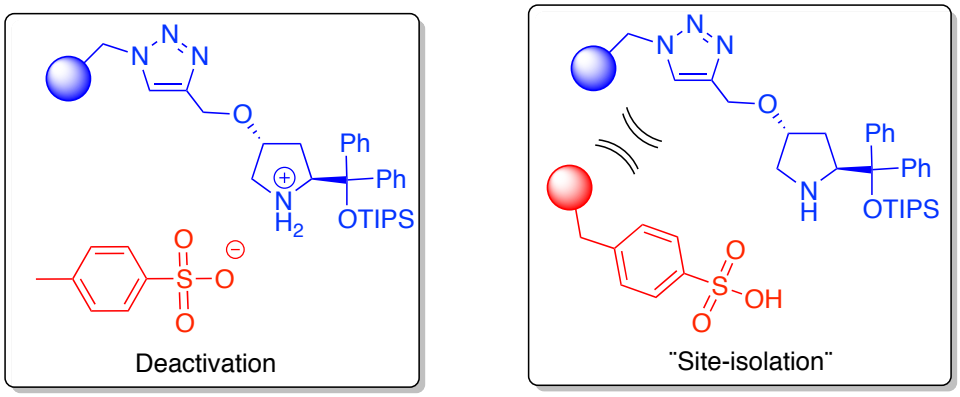
Scheme 5.1. Pioneering works of organocatalytic acetaldehyde activation

Despite these excellent previous results, some problems remain unsolved.[3] For instance, the low boiling point of acetaldehyde seriously hampers its transportation, storage, and handling. The oligomerization of acetaldehyde causes quick consumption and leads to poor reaction yields. In order to solve these problems, we postulated the use of paraldehyde as a more convenient alternative to acetaldehyde, which can be depolymerized into three molecules of acetaldehyde under Brønsted acid catalysis.[4] Moreover, paraldehyde is less expensive, easier to handle and can be deoligomerized by a supported sulfonic acid, which opens the possibility of site isolation (Scheme 5.2).



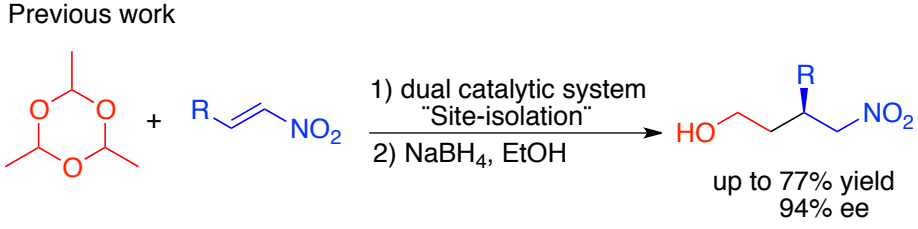
Scheme 5.2. Deoligomerization of paraldehyde catalyzed by supported sulfonic acid

Aminocatalysts such as proline and its derivatives have been well explored in asymmetric α-functionalization of acetaldehyde.[5] However, these aminocatalysts can react with strong acids, thus leading to the deactivation of the catalytic system. In order to avoid this, we proposed to exploit the dual immobilized catalytic system due to the fact that their inherent properties are site-isolated upon immobilization. Under this principle, two incompatible catalysts can work together in the same media after immobilization. Accordingly, we successfully applied the dual immobilized catalytic system to the asymmetric Michael reaction with paraldehyde as acetaldehyde surrogate (Scheme 5.4).[6]



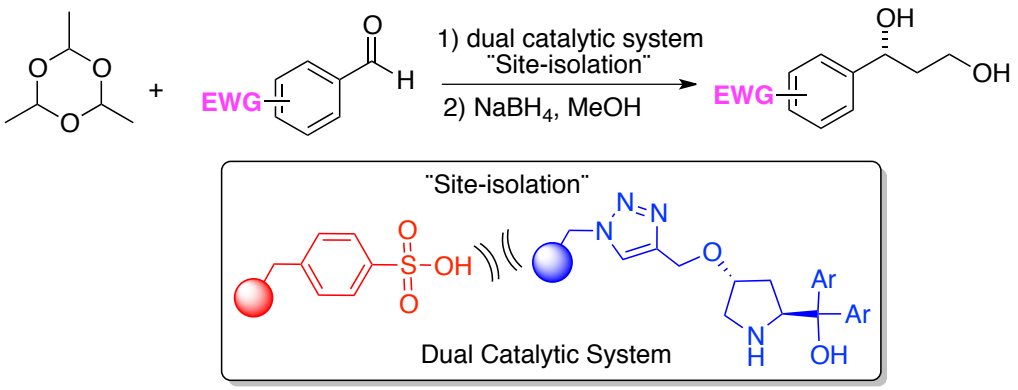
Scheme 5.3. Deactivation mode and compatibilization by site-isolation

In our previous work, polystyrene supported (PS) sulfonic acid catalyst was enclosed in a teabag, thus being isolated from the PS-diphenylprolinol TIPS ether catalyst to prevent mutual deactivation. This dual catalytic system worked compatibly in cascade Michael reactions with paraldehyde, providing Michael products in good yields with excellent enantioselectivities (Scheme 5.4).



Scheme 5.4. Asymmetric Michael reaction promoted by dual site-isolated catalysts

However, this site-isolated catalytic system could not be recycled and proved sensitive to moisture and oxygen. For further development of this site-isolated system, we speculated with the application of this concept to the asymmetric cross-aldol reactions of acetaldehyde, as well as studies concerning the recyclability (Scheme 5.5). The results of asymmetric cross-aldol reactions are presented in the section 5.3 and article D.

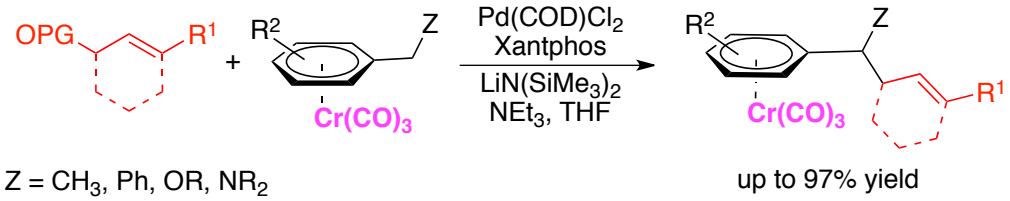


Scheme 5.5. Asymmetric aldol reaction promoted by dual site-isolated catalysts

This methodology granted access to enantioenriched 1-arylpropane-1,3-diols, a privileged core structure occurring in a variety of drugs and natural products. However, the main drawback of this method was the fact that only electron-poor benzaldehydes could be used as effective substrates. The phenyl substituted diols cannot be obtained via this strategy, despite the fact that the corresponding product is a key building block in the synthesis of many active pharmaceutical ingredients. Thus, we assumed that the cross-aldol reaction of benzaldehyde with paraldehyde could be facilitated by a reversible electronic modification.

η^6-Arene-$Cr(CO)_3$ complexes are easily formed upon reaction of $Cr(CO)_3$ with aromatic substrates and can be removed in quantitative yield by exposure to visible light. Owing to the electron-withdrawing properties of the chromium tricarbonyl group, the electron density of η^6-arene decreases, consequently increasing its reactivity in some transformations. For instance, Walsh and co-workers reported a palladium catalyzed allylic substitution reaction of toluene derived pronucleophiles activated by the aromatic η^6-coordination of $Cr(CO)_3$ (Scheme 5.6).[7] A variety of cyclic and acyclic allylic electrophiles can be employed with benzylic nucleophiles for the synthesis of allylation products that are otherwise difficult to prepare.

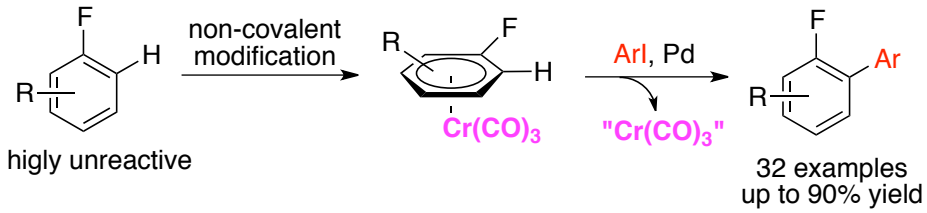
Walsh *et al.* 2011



Scheme 5.6. Allylic substitution with (η^6-arene-CH_2Z) $Cr(CO)_3$

General methods to facilitate C−H arylation of arenes are exclusively limited to the use of strongly electron-withdrawing substituents or directing groups. Larrosa and co-workers explored η^6-coordination of the $Cr(CO)_3$ unit on arene for dramatically promoting the reactivity of C−H bonds in arylation reaction (Scheme 5.7).[8] This strategy provided an efficient approach for the direct arylation of highly unreactive monofluorobenzenes, affording the *ortho*-substituted biaryls with good yields and high selectivity.

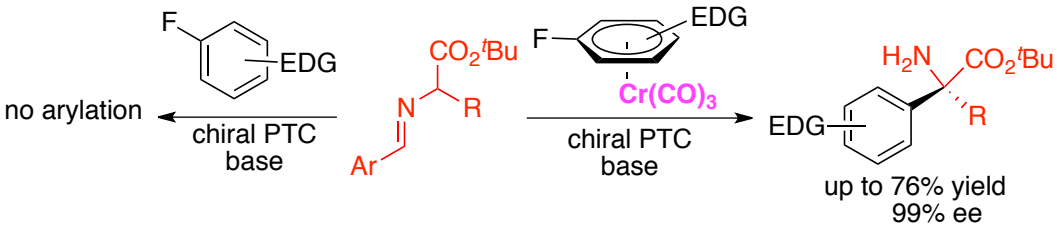
Larrosa *et al.* 2013



Scheme 5.7. C−H Arylation of η^6-arenes-$Cr(CO)_3$

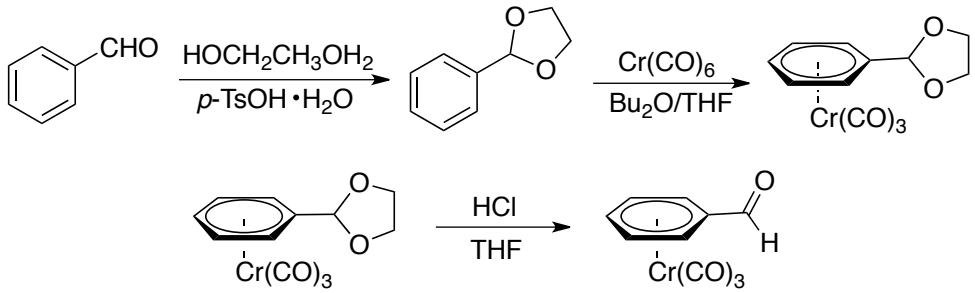
Chiral phase-transfer catalyzed (PTC) nucleophilic aromatic substitution (S_NAr) reaction provide an efficient approach to the enantioselective α-arylation of carbonyl compounds. The drawback of this method is that electrophiles are limited to electron-deficient arenes, such as those bearing a nitro group. To overcome this limitation, the Maruoka group employed chromium complexes coordinated with electron-rich fluoroarenes for asymmetric S_NAr reactions (Scheme 5.8).[9] This strategy efficiently enhanced the reactivity towards S_NAr reaction, giving the corresponding α,α-disubstituted α-amino acids containing various electron-donating substituents with high enantioselectivities.

Maruoka *et al.* 2014



Scheme 5.8. S_NAr reaction of α-amino acid derivatives with η^6-arenes-$Cr(CO)_3$

η^6-Benzaldehyde $Cr(CO)_3$ complex could be prepared in three steps starting from the benzaldehyde. The general procedure for the synthesis of this compound is shown in Scheme 5.9.[10]



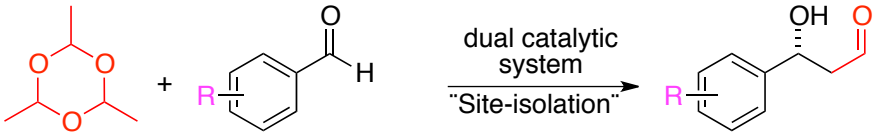
Scheme 5.9. General procedure for the synthesis of η^6-benzaldehyde $Cr(CO)_3$

5.2. Aim of the Project

Article D

To overcome the drawbacks of acetaldehyde, we postulated the use of paraldehyde as a more convenient alternative to acetaldehyde in asymmetric transformations. We have already introduced a "wolf-and-lamb" reaction system for the asymmetric Michael reaction of acetaldehyde (Scheme 5.4). However, the dual catalytic system required strict operation to avoid their mutual deactivation.

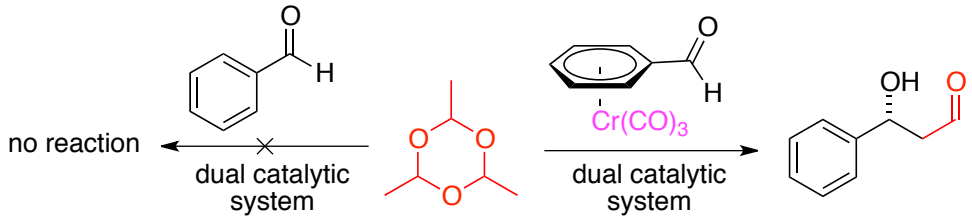
In order to develop the site-isolated system and user-friendly system, we aim to identify a supported dual catalytic system to promote the cascade cross-aldol reactions of paraldehyde with various substituted benzaldehydes, as well as studies concerning the recyclability (Scheme5.10).



Scheme 5.10. Strategy for cross-aldol reaction catalyzed by dual catalytic system

Article E

Inspired by previous works on reversible electronic modification using $Cr(CO)_3$ complex, we assumed that the η^6-benzaldehyde $Cr(CO)_3$ complex could be used as an activated benzaldehyde surrogate in the cross-aldol reaction with paraldehyde mediated by the dual catalytic system (Scheme 5.10). Once the cross-aldol reaction by using η^6-benzaldehyde $Cr(CO)_3$ had been achieved, we aimed to use the resulting phenyl substituted diols for further transformations.



Scheme 5.10. Strategy for cross-aldol reaction by using η^6-benzaldehyde $Cr(CO)_3$

5.3. References

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CHEMISTRY A European Journal Communication

Site Isolation

Highly Enantioselective Cross-Aldol Reactions of Acetaldehyde Mediated by a Dual Catalytic System Operating under Site Isolation

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Abstract: Polystyrene-supported (PS) diarylprolinol catalysts **1a** (Ar = phenyl) and **1b** (Ar = 3,5-bis(trifluoromethyl)-phenyl) have been developed. Operating under site-isolation conditions, PS-**1a**/**1b** worked compatibly with PS-bound sulfonic acid catalyst **2** to promote deoligomerization of paraldehyde and subsequent cross-aldol reactions of the resulting acetaldehyde in one pot, affording aldol products in high yields with excellent enantioselectivities. The effect of water on the performance of the catalytic system has been studied and its optimal amount (0.5 equiv) has been determined. The dual catalytic system (**1**/**2**) allows repeated recycling and reuse (10 cycles). The potential of this methodology is demonstrated by a two-step synthesis of a phenoperidine analogue (68% overall yield; 98% *ee*) and by the preparation of highly enantioenriched 1,3-diols **4** and 3-methylamino-1-arylpropanols **5**, key intermediates in the synthesis of a variety of druglike structures.

The aldol reaction has attracted plenty of interest due to its pivotal role in organic synthesis.[1] Among the various methods available to carry out this reaction enantioselectively, the organocatalytic methods stand out for several reasons: 1) under extremely mild reaction conditions excellent stereocontrol can be achieved in up to two newly formed stereocenters, 2) no prefunctionalization of any of the reactants is required, and 3) the reactions take place in a metal-free environment, which avoids product contamination with toxic metal derivatives.[2] Therefore, important developments have been achieved since the first report on the direct asymmetric intermolecular aldol reaction catalyzed by proline in 2000.[3] The use of acetaldehyde (the simplest enolizable aldehyde), however, has been a great challenge due to its high reactivity and its inherent tendency to oligomerize.[4] In 2008, Hayashi and co-workers reported the first asymmetric aldol reaction of acetaldehyde with good yields and excellent enantioselectivities by using diaryprolinol as the catalyst.[5] Shortly after, the same reaction was tested with a diamine catalyst to afford aldol products with varying yields (34–99%) and enantioselectivities (69–92%).[6] Recently, a water compatible diarylprolinol derivative has been reported to promote this reaction in brine, affording aldol products in good yields and *ee*'s.[7]

Despite the excellent results in these reports, some problems remain unsolved in this reaction, especially from the practical point of view. For instance, the low boiling point of acetaldehyde (21 °C) seriously hampers its transportation, storage, and handling, therefore increasing cost and energy consumption. From the reaction perspective, the tendency to oligomerization and high reactivity of acetaldehyde is detrimental, since side reactions are common. To overcome these drawbacks, an interesting example was reported recently using vinyl acetate as acetaldehyde precursor in cross-aldol reactions. The recorded enantioselectivities, however, were very low (10–20% *ee*).[8] On the other hand, the high catalyst loading required for the reaction to take place in a reasonable time makes desirable the development of a recyclable catalytic system.[9]

We have recently introduced a "wolf-and-lamb" reaction system[10] for the asymmetric Michael reaction of acetaldehyde. In our approach,[11] cheap and easy-to-handle paraldehyde (3.7 € per mol; b.p. 123 °C) is employed as a convenient source of acetaldehyde, which is slowly generated by acid-catalyzed deoligomerization (polystyrene-bound sulfonic acid). In this way, the concentration of the reactive species in the reaction media remains low and the problems mentioned above are avoided. Acetaldehyde generated in this way is able to undergo a Michael reaction mediated by a polystyrene-supported (PS)-supported diphenylprolinol TIPS (triisopropylsilyl) ether, furnishing the addition products in good yield with excellent enantioselectivity. The implementation of this approach required the operation of the two catalysts under strict site isolation[12] conditions (tea bag) to avoid their mutual deactivation. In light of these results, we speculated that application of this concept could provide a convenient solution for the asymmetric cross-aldol reactions of acetaldehyde (Scheme 1).

In view of precedents with homogeneous catalysts,[5] we selected and prepared the new PS-diarylprolinols **1a**–**b** (Figure 1) to mediate the cross-aldol reaction in combination with the

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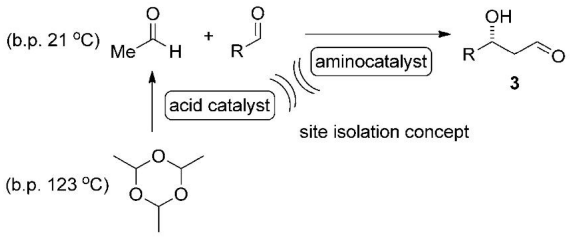
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201404215.



Scheme 1. Cascade deoligomerization plus cross-aldol reaction mediated by two incompatible catalysts operating under site isolation.

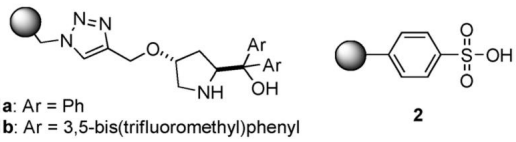
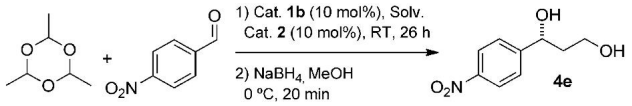


Figure 1. Catalysts used in this study.

same PS-bound sulfonic acid **2**, already used to deoligomerize paraldehyde for Michael additions.[11] For the optimization of reaction conditions, the cascade deoligomerization plus cross-aldol reaction between 4-nitrobenzaldehyde and paraldehyde leading after reduction to **4e** was selected (Table 1). The dual catalytic system **1a**/**2** was rather inefficient in CH_2Cl_2, with low conversion and moderate *ee* recorded after 26 h (Table 1, entry 1). In contrast, **1b** provided much higher enantioselectivities in this solvent, although conversion remained low (entry 2). The use of **1b** was adopted and, to improve conversion, several solvents were screened. Surprisingly, no conversion was observed in DMF, which was the optimal solvent in the analogous homogeneous catalytic reaction (entry 3).[5a] However, increased conversion and *ee* were recorded in THF, MeCN, and THF/MeCN or even under neat conditions (entries 4–8). Particularly in MeCN, 64% conversion and 98% *ee* were achieved. In full agreement with our working hypothesis, no conversion was observed when the reaction was carried out with a soluble acid, in this case *p*TsOH, instead of catalyst **2**, due to salt formation with **1b** (entry 6). Higher conversions could be achieved when increasing the temperature in MeCN, but at the cost of lowering the enantioselectivity of the reaction (entry 9). Water (entry 10) and brine (entry 11) were also tested, but almost no conversion was observed in both cases.

Table 1. Cascade paraldehyde deoligomerization and asymmetric cross-aldol reaction of 4-nitrobenzaldehyde with paraldehyde mediated by **1b**/**2**.[a]



Entry	Solvent	Water content	Conv. [%][b]	*ee* [%][c]
1[d]	CH_2Cl_2	–	19	73
2	CH_2Cl_2	–	15	94
3	DMF	–	0	–
4	Neat	–	47	94
5	THF	–	59	98
6[e]	THF	–	0	n.d.
7	MeCN	–	64	98
8	THF/MeCN	–	59	98
9[f]	MeCN	–	88	78
10	H_2O	–	4	–
11	brine	–	0	–
12[g]	MeCN	0	8	n.d.
13	MeCN	0.5	74	98
14	MeCN	1.0	71	98
15	MeCN	5.0	65	98
16[h]	**MeCN**	**0.5**	**91**	**98**

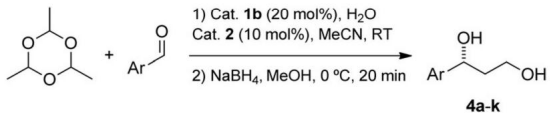
[a] The reaction was carried out with 4-nitrobenzaldehyde (0.1 mmol), paraldehyde (0.2 mmol), **1b** (10 mol%), and **2** (10 mol%) in 0.1 mL solvent. [b] By ^{1}H NMR spectroscopy. [c] By HPLC analysis. [d] Compound **1a** was used instead of **1b**. [e] *p*TsOH was used instead of **2**. [f] At 50 °C. [g] In the glovebox. [h] 20 mol% of **1b** was used.

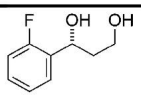
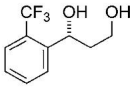
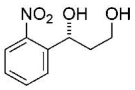
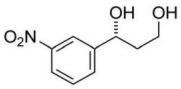
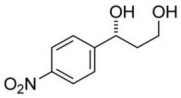
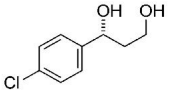
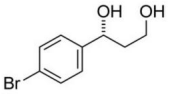
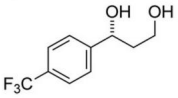
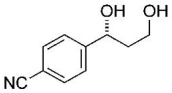
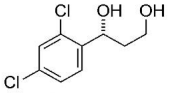
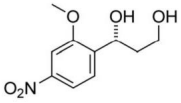
To evaluate the impact of moisture on the performance of the dual catalytic system, the reaction was carried out in strictly anhydrous media (glovebox, dry MeCN), but only 8% conversion was observed (compare entries 12 and 7). These results encouraged us to quantify the influence of added water to the reaction media on the performance of the reaction.[13] While its presence in small amounts entailed an increase in conversion (entries 13, 14), larger quantities were found to slow down the process (entry 15), albeit enantioselectivity remained unchanged. It was eventually found (entry 16) that excellent conversion (91%) and enantioselectivity (98%) could be achieved with 20 mol% of **1b** and 0.5 equivalents of water as an additive. Most likely, water is required to reactivate catalyst **1b**, which might be deactivated by slow oxazolidine formation with any of the aldehydes present in the reaction mixture (vide infra). Noteworthy, the combined use of **1b**/**2** under these conditions does not require the physical separation of the two resins, as was the case for the combined use of the silyl ether of **1a** and **2** in Michael additions of acetaldehyde.[11]

The scope of the cross-aldol reaction was studied next under the optimized reaction conditions, and the results are listed in Table 2. It was established that benzaldehydes with either *ortho*, *meta*, or *para* electron-withdrawing substituents afforded the desired cross-aldol products with generally good yields and excellent enantioselectivities (Table 2, entries 1–9). In addition, disubstituted aromatic aldehydes, such as 2,4-dichlorobenzaldehyde and 2-methoxy-4-nitro-benzaldehyde, were also tolerated (entries 10 and 11). Benzaldehyde and aromatic aldehydes bearing electron-donating substituents, in turn, are not reactive when using this method.

From the mechanistic point of view, the whole procedure involves two separate reactions that take place in a cascade manner. First, paraldehyde is deoligomerized into acetaldehyde, a process catalyzed by the supported Brønsted acid **2**. Then acetaldehyde condenses with catalyst **1b** to generate the enamine intermediate, which reacts with the corresponding aldehyde to afford the product. A catalyst off-cycle, regulated by the addition of water to the reaction media also needs to be considered. In Scheme 2, oxazolidine formation is shown for the aldol product **3e**, but similar parasitic species can also be proposed with acetaldehyde or the aromatic aldehyde involved in the cross-aldol reaction.

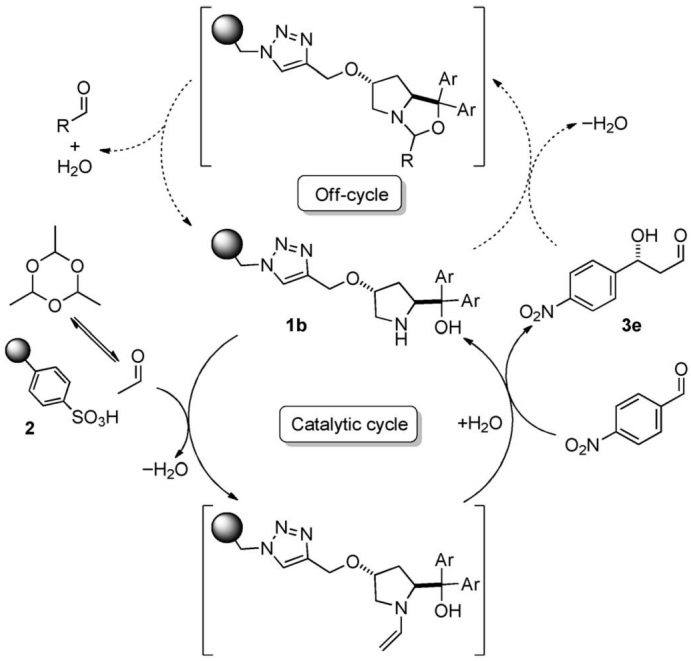
Table 2. Asymmetric cross-aldol reaction of acetaldehyde.[a]



Entry	Product	*t* [h]	4	Yield [%][b]	*ee* [%][c]
1		52	**4a**	62	97
2		52	**4b**	40	99
3		28	**4c**	77	99
4		72	**4d**	78	99
5		26	**4e**	80	98
6		52	**4f**	28	97
7		72	**4g**	47	97
8		72	**4h**	68	97
9		28	**4i**	61	98
10		52	**4j**	63	98
11		28	**4k**	89	96

[a] Reactions were carried out with aldehyde (0.2 mmol), paraldehyde (0.4 mmol), H_2O (0.1 mmol), **1b** (20 mol%), and **2** (10 mol%) in 0.2 mL MeCN. [b] Isolated yield. [c] *ee* was measured by HPLC analysis.

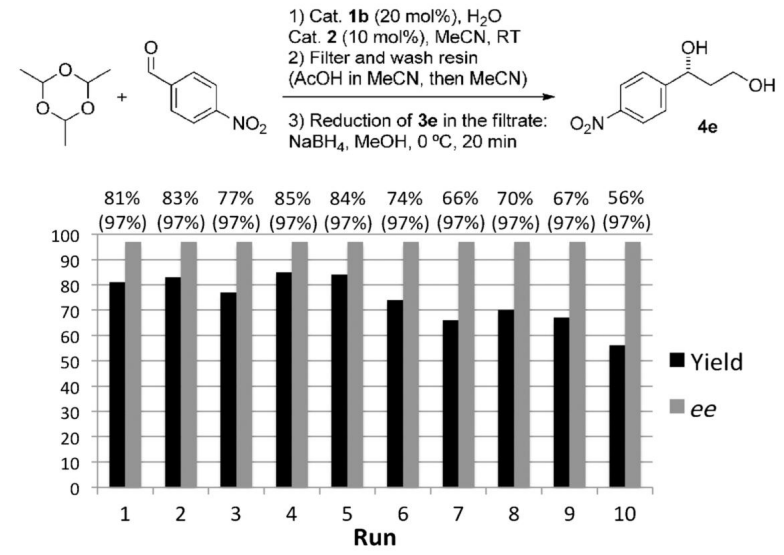
From a practical perspective, one of the main advantages offered by heterogenized catalysts is their easy recovery by simple filtration and the consequent possibility of reusing. In this respect, the fact of recycling two different polystyrene-supported catalysts without having to separate them is of particular interest. Therefore, the recyclability of the **1b**/**2** dual catalyst system was tested in the cross-aldol reaction with 4-nitrobenzaldehyde using different protocols. It was found that thoroughly drying the resin between cycles improved the performance on the forthcoming runs. However, the system was still suffering from a gradual deactivation. We then hypothesized that an oxazolidine off-cycle species might be responsible for sequestering part of the catalytically active species **1b**



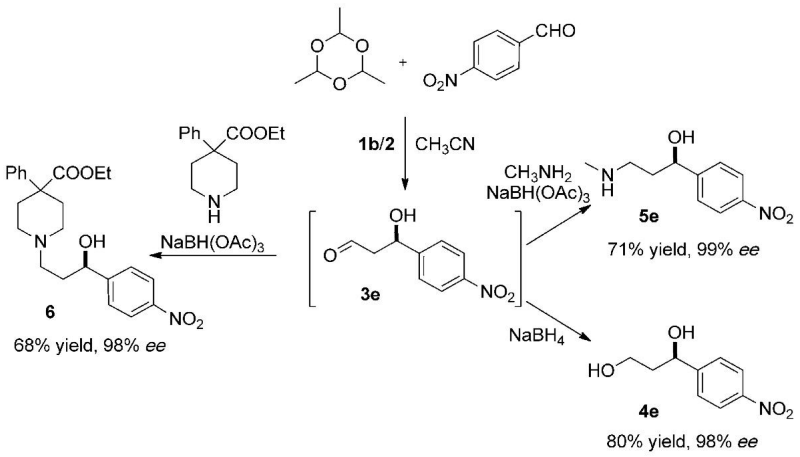
Scheme 2. Schematic mechanistic picture of the paraldehyde deoligomerization plus cross-aldol cascade process mediated by **1b**/**2**.

(see Scheme 2 and the Supporting Information). To circumvent this problem, after each cycle, the combined resins were washed with AcOH in moist MeCN with the goal of hydrolyzing this parasitic species, thus setting the aminocatalyst free again (see the Supporting Information for details). To our delight, this strategy proved to have a tremendous impact on the reusability of the **1b**/**2** combination. Keeping the reaction time constant (26 h) we could achieve roughly the same results for the first 5 runs. After that, the isolated yield decreased, albeit in a very mild manner. For instance, in the tenth run, the aldol product was still isolated in 56% yield. Even more remarkably, the enantioselectivity remained constant at 97% throughout the ten runs (Scheme 3).

Enantioenriched diols with the general structure **4** are key intermediates in the synthesis of a variety of marketed drugs (Tolterodine,[14] Dapoxetine[15]) and natural products (Diospongins A and B[16]). Amino alcohols **5**, in turn, are intermediates in the synthesis of important drugs (Atomoxetine,[17] Fluoxetine,[18] Nisoxetine,[18d] and Duloxetine.[18a,d,e]) Traditional methods for the preparation of enantioenriched **4** normally involve Sharpless epoxidation of allylic alcohols,[19] and a cross-aldol, organocatalytic approach would represent important advantages.[20] Enantiopure amino alcohols **5** have been synthesized from **4** in two steps,[19] but could also be acceded by simple reductive amination from cross-aldol products **3**. Taking the cross-aldol reaction of *p*-nitrobenzaldehyde as an example, we show in Scheme 4 how crude **3e** can be directly converted to amino alcohol **5e** by reductive amination with $MeNH_2$ in good overall yield (71%) and excellent *ee* (99%). In a further application, the phenoperidine[21] analogue **6** has been prepared (68% overall yield, 98% *ee*) by reductive amination of crude **3e** with ethyl 4-phenylpiperidine-4-carboxylate and NaBH-



Scheme 3. Recycling tests of the dual catalytic system.



Scheme 4. Synthesis of drug analogues and intermediates from crude cross-aldol adducts **3**.

$(OAc)_3$. Polymer-supported **1b**, which could act as a competitive aminating reagent, is conveniently removed by filtration (together with **2**) before the reductive amination step.[22]

In summary, two polymer-supported catalytic species that would mutually deactivate in solution, define a "wolf-and-lamb" catalytic system suitable for performing, in a sequential manner and in a single reaction pot, the acid-catalyzed deoligomerization of paraldehyde and the highly enantioselective, amine-catalyzed cross-aldol reaction of acetaldehyde with aromatic aldehydes. This dual catalytic system, which exploits the site isolation principle in heterogeneous catalysis, simply relies in the absence of chemical communication between individual polymer beads and does not require any additional permeable barrier. Catalytic activity can be regulated by the addition of small amounts of water to the reaction media, and the whole catalytic system can be recycled and reused at least ten times by simple filtration of the polymer mixture and mild acidic washing to recover full performance. The suitability of the crude cross-aldol products for the straightforward preparation of enantiopure drug analogues highlights the potential of the present methodology in medicinal chemistry.

Experimental Section

General procedure for the aldol reaction

Catalyst **1b** (0.04 mmol, 20 mol%), Catalyst **2** (0.02 mmol, 10 mol%) and the aldehyde (0.2 mmol) were mixed in a vial with acetonitrile (0.2 mL). Then paraldehyde (0.4 mmol) and deionized water (0.1 mmol) were added and the vial was capped and shaken at room temperature. After reaction completion (see Table 2), the mixture was filtered and the resin was washed with methanol (3×0.5 mL). The filtrates were combined and cooled to 0 °C. Then $NaBH_4$ (0.6 mmol) was added and the mixture was stirred for 20 min. The reaction was quenched with aqueous NH_4Cl (3 mL), and extracted with ethyl acetate (3×5 mL). The organic phases were combined, washed with brine (2 mL), and dried over Na_2SO_4. After solvent removal, products were purified by flash chromatography on silica gel, with hexanes/ethyl acetate mixtures as the eluent.

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Keywords: acetaldehyde · cross-aldol · recycling · site-isolation · wolf and lamb

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[22] An attempt to purify **3e** by chromatography failed, probably due to decomposition of this hydroxy aldehyde on silica gel.

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Supporting Information

Highly Enantioselective Cross-Aldol Reactions of Acetaldehyde Mediated by a Dual Catalytic System Operating under Site Isolation

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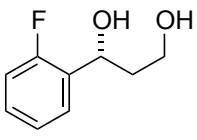
1. General information

Unless otherwise stated, all commercial reagents were used as received. Flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. Thin layer chromatography was carried out using Merck TLC Silicagel 60 F254 aluminum sheets. Components were visualized by UV light (λ = 254 nm) and stained with *p*-anisaldehyde or phosphomolybdic dip. NMR spectra were registered in a Bruker Advance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature, operating at 400 or 500 MHz (^1H) and 100 or 126 MHz ($^{13}C\{^1H\}$). TMS was used as internal standard for ^1H NMR and $CDCl_3$ for ^{13}C NMR. Chemical shifts are reported in ppm referred to TMS. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses of the polystyrene supported catalysts were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid, Spain. High performance liquid chromatography (HPLC) was performed on an Agilent Technologies chromatograph (1100 Series), using Chiralcel columns and guard columns. The absolute configuration of the reaction products was confirmed by HPLC, by comparison with reported data.[1] Catalyst **2** was purchased from Novabiochem®.

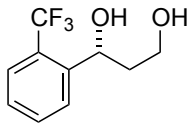
2. General procedure for cross-aldol reaction

Catalyst **1b** (20 mol%, 0.04 mmol), Catalyst **2** (10 mol%, 0.02 mmol) and the corresponding aldehyde (0.2 mmol) were mixed in a vial with acetonitrile (0.4 mL). Then paraldehyde (54.8 μL, 0.4 mmol) and deionized water (1.8 μL, 0.1 mmol) were added and the vial was sealed and shaken at room temperature. After completion, the mixture was filtered and washed with methanol (3 × 0.5 mL). The filtrates were combined and cooled to 0 °C. Then $NaBH_4$ (22.7 mg, 0.6 mmol) was added and the mixture was stirred for 20 minutes. The reaction was quenched with aqueous NH_4Cl (3 mL), and extracted with ethyl acetate (3 × 5 mL). The organic phases were combined, washed with brine (2 mL) and dried over Na_2SO_4. After solvent removal, products were purified by flash chromatography on silica gel, with hexanes/ethyl acetate mixtures as eluent.

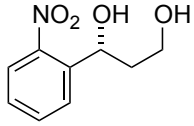
3. Characterization data for products 4[2]



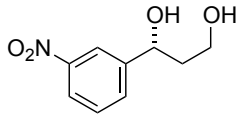
4a. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.05 - 1.95 (m, 2H), 2.42 (brs, 1H), 3.17 (brs, 1H), 3.93 - 3.83 (m, 2H), 5.28 (t, *J* = 6.1 Hz, 1H), 7.06 - 6.96 (m, 1H), 7.16 (dt, *J* = 7.5, 1.1 Hz, 1H), 7.30 - 7.20 (m, 1H), 7.54 (dt, *J* = 7.6, 1.7 Hz, 1H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ = 39.2, 61.7, 68.5, 115.4 (d, *J* = 21.7 Hz), 124.4, 127.3, 129.0 (d, *J* = 8.2 Hz), 131.3 (d, *J* = 13.1 Hz), 159.6 (d, *J* = 245.2 Hz); HPLC (Chiralcel IC, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 270 nm): t_{major} = 13.3 min, t_{minor} = 10.4 min.



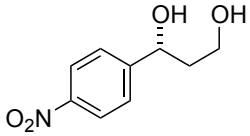
4b. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 - 1.77 (m, 2H), 2.44 (s, 1H), 3.20 (s, 1H), 4.06 - 3.77 (m, 2H), 5.38 (d, *J* = 9.1 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.68 - 7.53 (m, 2H), 7.85 (d, *J* = 7.8 Hz, 1H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ = 40.8, 62.2, 70.3, 124.5 (q, *J* = 272.0 Hz), 125.6 (q, *J* = 5.8 Hz), 126.5 (q, *J* = 30.1 Hz), 127.6, 127.9, 132.5, 143.6; HPLC (Chiralcel AD-H, Hexane/*i*-propanol (97:3), flow rate = 0.8 mL min^{-1}, λ = 270 nm): t_{major} = 31.6 min, t_{minor} = 29.6 min.



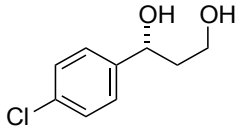
4c. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 - 2.03 (m, 1H), 2.04 - 2.16 (m, 1H), 3.77 (brs, 1H), 3.88 - 4.03 (m, 2H), 5.50 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.34 - 7.51 (m, 1H), 7.66 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.91 (m, 2H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ = 39.7, 62.0, 69.9, 124.5, 128.3, 128.3, 133.8, 140.0, 147.6; HPLC (Chiralcel IC, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 270 nm): t_{major} = 20.4 min, t_{minor} = 32.3 min.



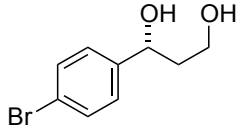
4d. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.05 - 1.92 (m, 2H), 2.40 (brs, 1H), 3.67 (brs, 1H), 3.92 (t, *J* = 5.5 Hz, 2H), 5.10 (t, *J* = 6.1 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 8.12 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 8.25 (t, *J* = 1.9 Hz, 1H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ = 40.4, 61.4, 73.4, 120.8, 122.5, 129.6, 131.9, 146.7, 148.5; HPLC (Chiralcel IC, Hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 270 nm): t_{major} = 75.2 min, t_{minor} = 68.1 min.



4e. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 - 1.95 (m, 2H), 2.11 (t, *J* = 3.9 Hz, 1H), 3.45 (d, *J* = 3.0 Hz, 1H), 3.93 (dt, *J* = 4.9, 2.3 Hz, 2H), 5.11 (dt, *J* = 6.1, 2.0 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 2H), 8.22 (d, *J* = 8.6 Hz, 2H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ = 40.4, 61.5, 73.6, 123.9 (×2), 126.6 (×2), 147.4, 151.8; HPLC (Chiralcel OJ, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 270 nm): t_{major} = 23.7 min, t_{minor} = 31.5 min.

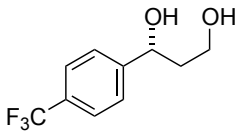


4f. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 - 1.85 (m, 2H), 2.21 (s, 1H), 2.97 (d, *J* = 2.6 Hz, 1H), 3.93 - 3.80 (m, 2H), 4.96 (dt, *J* = 8.3, 3.0 Hz, 1H), 7.32 (m, 4H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ = 40.6, 61.6, 73.8, 127.2 (×2), 128.8 (×2), 133.3, 143.0; HPLC (Chiralcel AS-H, Hexane/i-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 210 nm): t_{major} = 13.4 min, t_{minor} = 12.0 min.

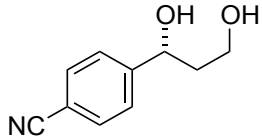


4g. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86 - 2.04 (m, 2H), 2.31 (s, 1H), 3.08 (s, 1H), 3.80 - 3.91 (m, 2H), 4.94 (dd, *J* = 8.4, 3.6 Hz, 1H), 7.21 - 7.29 (m, 2H), 7.45 - 7.52 (m, 2H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ = 40.5, 61.5,

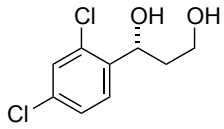
73.8, 121.4, 127.5 (×2), 131.7 (×2), 143.5; HPLC (Chiralcel IC, Hexane/i-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 270 nm): t_{major} = 23.4 min, t_{minor} = 20.4 min.



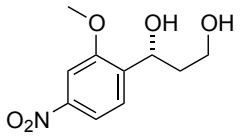
4h.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86 - 2.09 (m, 2H), 2.44 (s, 1H), 3.41 (s, 1H), 3.88 (t, *J* = 5.5 Hz, 2H), 4.98 - 5.09 (m, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ = 40.5, 61.5, 73.8, 124.3 (q, *J* = 272.0 Hz), 125.6 (q, *J* = 3.8 Hz, ×2), 126.1 (×2), 129.8 (q, *J* = 32.4 Hz), 148.4; HPLC (Chiralcel IC, Hexane/*i*-propanol (95:5), flow rate = 1.0 mL min^{-1}, λ = 270 nm): t_{major} = 12.9 min, t_{minor} = 11.6 min.



4i. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 - 2.00 (m, 2H), 3.46 (brs, 1H), 3.90 (t, *J* = 5.3 Hz, 2H), 5.04 (t, *J* = 6.1 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J*= 8.2 Hz, 2H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ = 40.4, 61.5, 73.7, 111.3, 119.0, 126.5 (×2), 132.5 (×2), 149.9; HPLC (Chiralcel IC, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 270 nm): t_{major} = 24.2 min, t_{minor} = 21.6 min.



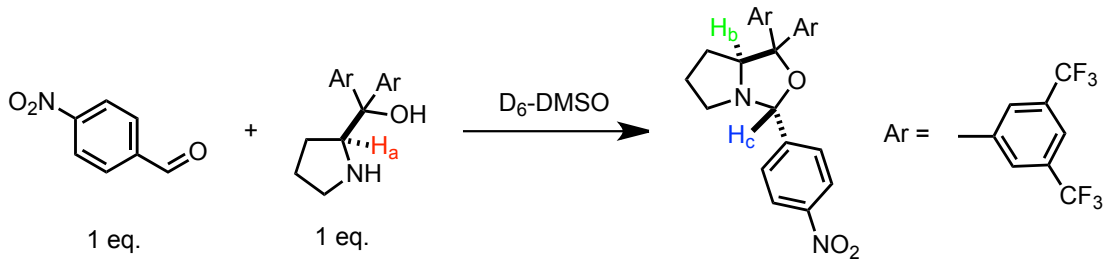
4j.[4] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80 - 1.91 (m, 1H), 1.97 - 2.07 (m, 1H), 2.48 (brs, 1H), 3.54 (brs, 1H), 3.84 - 3.96 (m, 2H), 5.29 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.25 - 7.32 (m, 1H), 7.33 (d, *J* = 2.1 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ = 38.4, 61.8, 70.89, 127.6, 128.2, 129.2, 132.0, 133.6, 140.4; HPLC (Chiralcel OD-H, Hexane/*i*-propanol (96:4), flow rate = 1.0 mL min^{-1}, λ = 270 nm): t_{major} = 22.3 min, t_{minor} = 21.2 min.



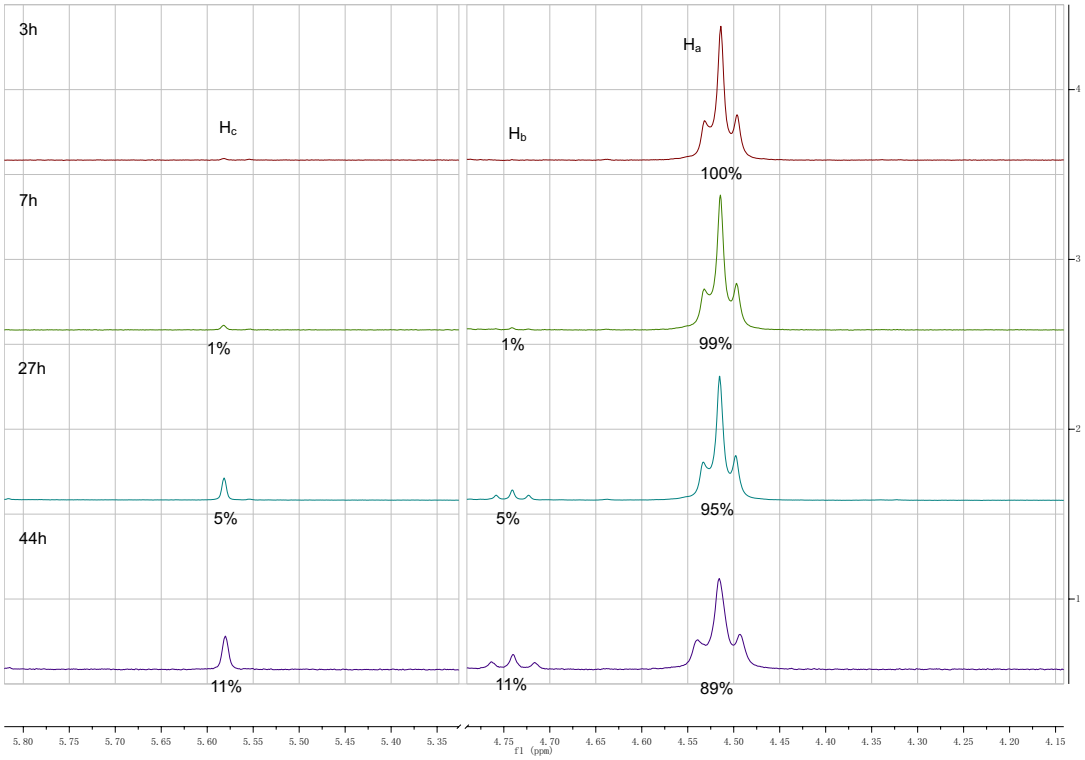
4k. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.86 - 1.97 (m, 1H), 1.98 - 2.11 (m, 1H), 2.46 (brs, 1H), 3.57 (brs, 1H), 3.84 - 3.91 (m, 2H), 3.93 (s, 3H), 5.28 (dd, *J* = 8.6, 3.2 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 2.1 Hz, 1H), 7.87 (dd, *J* = 8.4, 2.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 38.2, 56.1, 61.8, 69.3, 105.4, 116.3, 127.0, 140.1, 148.1, 156.2; IR (ATR): ν = 521.4, 739.5, 802.8, 868.1, 1021.2, 1049.5, 1069.3, 1247.6, 1307.9, 1344.6, 1512.5, 2929.1, 3357.1 cm^{-1}; HPLC (Chiralcel IC, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 270 nm): t_{major} = 27.6 min, t_{minor} = 25.9 min; HRMS calcd for $C_{10}H_{12}NO_5$ $(M - H)^-$: 226.0721, found: 226.0721; $[\alpha]_D^{25}$ = +56.2 (*c* 0.9, MeOH).

4. Catalysts recycling

4.1. NMR study on catalyst deactivation[5]



To determine the oxazolidine formed from catalyst **1** and aldehyde, diarylprolinol (Ar = 3,5-bis(trifluoromethyl)phenyl, 1.0 eq.) was mixed with 4-nitrobenzaldehyde (1.0 eq.) in D_6-DMSO and checked by ^{1}H NMR. The appearance of a singlet at 5.58 ppm (assigned as H_c) and a triplet at 4.74 ppm (assigned as H_b, J = 7.1 Hz), whose chemical shifts, peak shapes and integrations matched with the reported similar compounds, indicated the formation of oxazolidine as a parasitic species which could account for the decrease in catalytic activity observed upon recycling. The amount of oxazolidine was slowly increasing, 11% of oxazolidine was observed after 44 hours.



4.2. Different procedures of catalysts recycling

Catalyst **1b** (20 mol%, 0.04 mmol), Catalyst **2** (10 mol%, 0.02 mmol) and 4-nitrobenzaldehyde (30.2 mg, 0.2 mmol) were mixed in a vial with acetonitrile (0.4 mL). Then paraldehyde (54.8 μL,

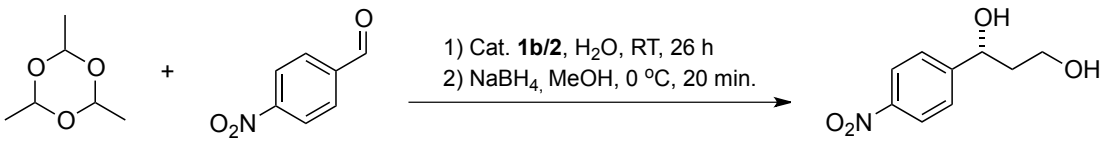
0.4 mmol) and deionized water (1.8 μL, 0.1 mmol) were added and the vial was sealed and shaken at room temperature.

Procedure A: After 26 h, the mixture was filtered and washed with acetonitrile (3 × 0.5 mL). The filtrates were worked up as abovementioned (see Section 2). The mixed catalysts were washed with acetonitrile (3 × 3 mL) and then used in the next reaction directly.

Procedure B: After 26 h, the mixture was filtered and washed with acetonitrile (3 × 0.5 mL). The filtrates were worked up as abovementioned (see Section 2). The mixed catalysts were washed with acetonitrile (3 × 3 mL) and dried at 40 °C under vacuum for 3 h, and then used in the next reaction.

Procedure C: After 26 h, the mixture was filtered and washed with acetonitrile (3 × 0.5 mL). The filtrates were worked up as abovementioned (see Section 2). The mixed catalysts were washed with acetic acid solution in acetonitrile (10%, 4 × 1 mL), acetonitrile (4 × 1 mL), dried at 40 °C under vacuum for 3 h and then used in the next reaction.

Table S1 Results of recycling tests using different work up procedure.[a]

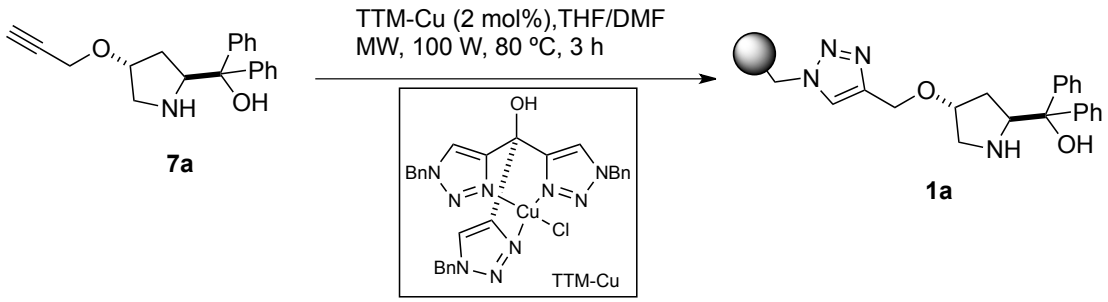


Cycle	Procedure A		Procedure B		Procedure C	
	Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]
1	80	98	80	97	81	97
2	45	97	66	98	83	97
3	48	98	57	97	77	97
4	41	98	60	98	85	97
5			54	97	84	97
6			50	97	74	97
7			43	96	66	97
8			38	96	70	97
9					67	97
10					56	97

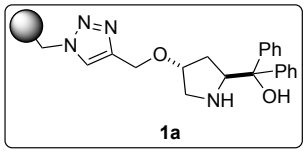
[a] Each reaction was carried out with 4-nitrobenzaldehyde (0.2 mmol), paraldehyde (0.4 mmol), H_2O (0.1 mmol), **1b** (20 mol%) and **2** (10 mol%) in 0.4 mL MeCN for 26 h. [b] Isolated yield. [c] Determined by HPLC.

5. Synthesis and characterization of 1a, 1b, 5 and 6

5.1 Synthesis and characterization of 1a



7a and azidomethylpolystyrene resin were synthesized according to our previously reported procedure.[6]

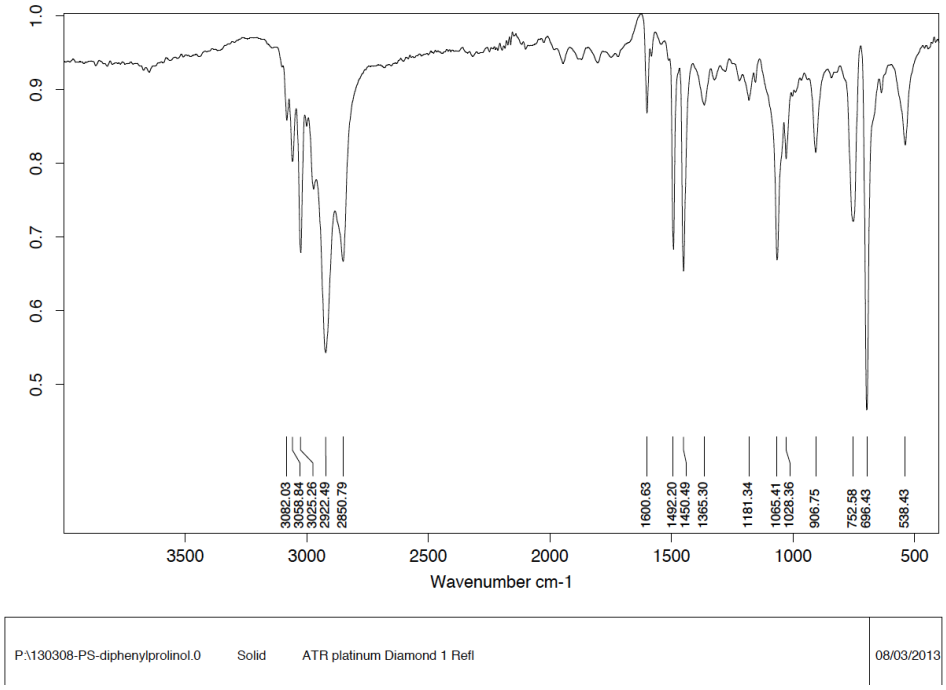


A mixture of azidomethylpolystyrene (f = 0.53 mmol g^{-1}, 0.25 mmol, 0.47 g), **7a** (0.375 mmol, 0.12 g) and tris(triazolyl)methyl copper (TTM-Cu) complex (2 mol%, 0.005 mmol) in THF/DMF 1:1 (6 mL) were placed in a tube for microwave reactions.[7] The reaction mixture was heated at 80 ºC (set temperature) under microwave irradiation of 100 W without stirring and monitored by IR. After the cycloaddition reaction was completed (ca. 3 h), the resin was filtered and washed with CH_2Cl_2 (20 mL), MeOH (20 mL), water (20 mL), MeOH (20 mL) and THF (20 mL) and was dried overnight under vacuum at 40 ºC.

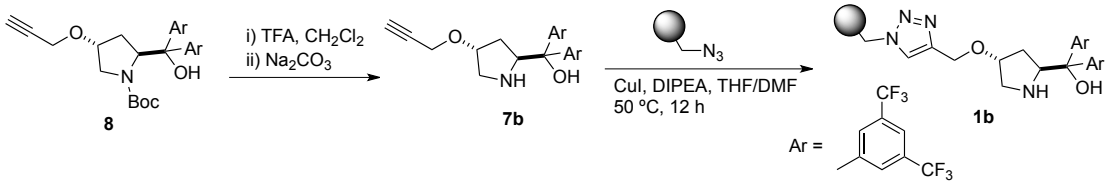
IR (ATR): ν = 538.4, 696.4, 752.6, 906.8, 1028.4, 1065.4, 1181.3, 1365.3, 1450.5, 1492.2, 1600.6, 2850.8, 2922.5, 3025.3, 3058.8 cm^{-1}

A 99% yield of functionalization was calculated on the basis of nitrogen elemental analysis.

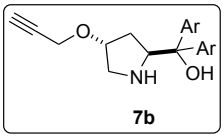
Calcd: N(%) 2.55; found: N(%) 2.58, C(%) 85.51, H(%) 7.80, Cu(%) 0.06; f = 0.46 mmol g^{-1}.



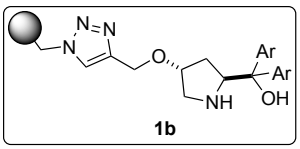
5.2 Synthesis and characterization of 1b



8 was synthesized according to our previously reported procedure.[8]



8 (0.3 g, 0.44 mmol) was dissolved in 4 mL CH_2Cl_2 and TFA (10 eq., 4.4 mmol) was added slowly. The mixture was stirred at room temperature overnight. Then, it was cooled to 0 ºC and the pH value was adjusted slowly to 8.0 using sat. aqueous Na_2CO_3 solution. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phase was washed with brine and dried ($MgSO_4$). Solvent removal under reduced pressure afforded 0.2 g of **7b** (0.34 mmol, 78% yield), which was directly used in the next step.

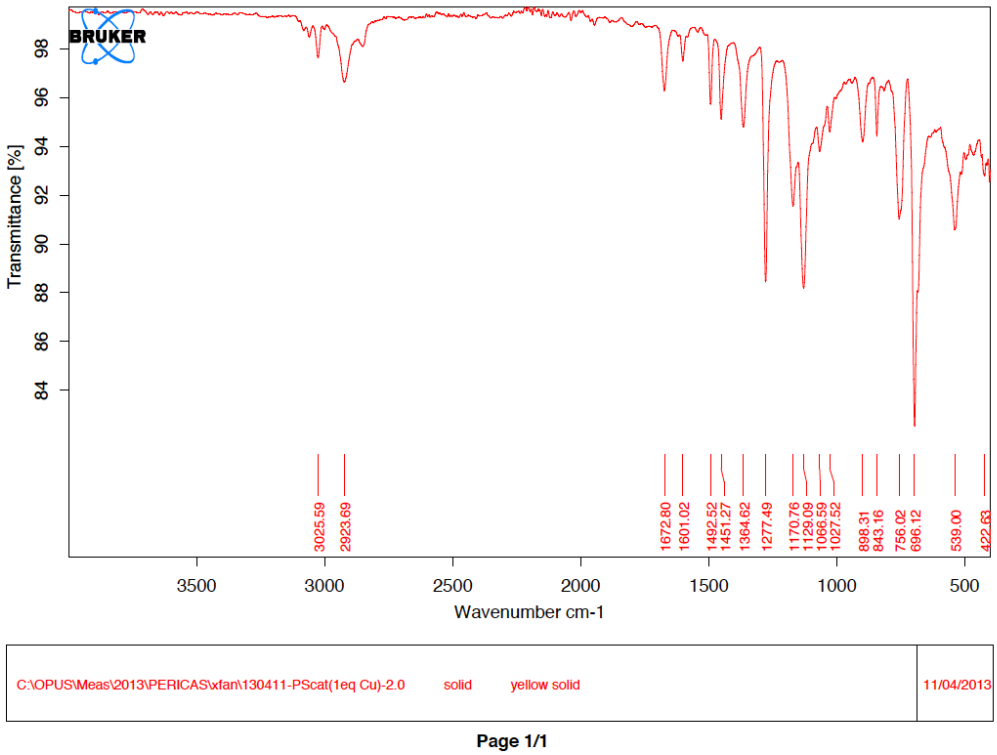


A mixture of azidomethylpolystyrene (f = 0.53 mmol g^{-1}, 0.25 mmol, 0.47 g), **7b** (0.38 mmol, 0.22 g), CuI (1.0 eq., 0.25 mmol) and DIPEA (10.0 eq., 2.5 mmol) in THF/DMF 1:1 (6 mL) were placed in a flask under orbital shaking in an oil bath at 50 ºC. The reaction was monitored by IR. After the cycloaddition reaction was completed (12 h), the resin was filtered and washed with ethylenediamine (5 × 5 mL), CH_2Cl_2 (20 mL), MeOH (20 mL), water (20 mL), MeOH (20 mL) and THF (20 mL) and was dried overnight under vacuum at 40 ºC.

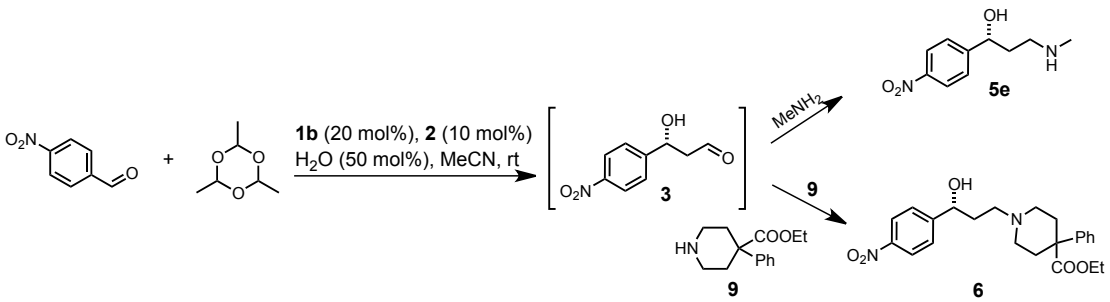
IR (ATR): ν = 539.0, 696.1, 756.0, 898.3, 1129.1, 1277.5, 1364.6, 1451.3, 1492.5, 1672.8, 2923.7, 3025.6 cm^{-1}

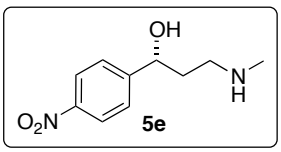
A 95% yield of functionalization was calculated on the basis of fluorine elemental analysis.

Calcd.: F(%) 9.37; found: F(%) 8.87, N(%) 2.39, C(%) 79.55, H(%) 5.77, Cu(%) 0.06; f = 0.39 mmol g^{-1}.



5.3 Synthesis and characterization of 5e and 6



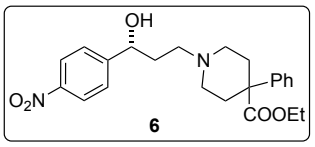


Catalyst **1b** (20 mol%, 0.04 mmol), Catalyst **2** (10 mol%, 0.02 mmol) and 4-nitrobenzaldehyde (1.0 eq., 0.2 mmol) were mixed in a vial with acetonitrile (0.4 mL). Then paraldehyde (2.0 eq., 0.4 mmol) and deionized water (0.5 eq., 0.1 mmol) were added and the vial was sealed and shaken at room temperature. After 26 h, the mixture was filtered and washed with AcOH in THF (10%, 2 × 2 mL). The filtrates were combined. Crude product **3** was obtained after removal of volatile materials under reduced pressure.

Crude **3** was dissolved in anhydrous THF (1 mL), methylamine (33 wt% in EtOH, 1.0 mmol) and anhydrous Na_2SO_4 (0.2 g) were added. The mixture was stirred for 1 hour and then $NaBH(OAc)_3$ (1.0 mmol) was added. After stirring overnight, the reaction was quenched with saturated aqueous NH_4Cl (3 mL), and extracted with ethyl acetate (3 × 5 mL). The organic phases were combined,

washed with brine (2 mL) and dried over Na_2SO_4. After solvent removal, products were purified by fast flash chromatography on silica gel, with CH_2Cl_2/MeOH/NH_4OH mixtures as eluent. 30 mg of **5e** (0.14 mmol, 71% overall yield for two steps) were obtained with 99% ee (measured by chiral HPLC).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.66 - 1.78 (m, 1H), 1.88 - 1.93 (m, 1H), 2.47 (s, 3H), 2.89 - 2.95 (m, 2H), 4.21 (brs, 2H), 5.05 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.47 - 7.72 (m, 2H), 8.19 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 36.0, 36.4, 50.5, 75.1, 123.6 (×2), 126.4 (×2), 147.0, 152.8; HPLC (Chiralcel IC, Hexane /*i*-propanol (95:5, 0.05% Diethylamine used as additive), flow rate = 1.0 mL min^{-1}, λ = 280 nm): t_{major} = 49.7 min, t_{minor} = 42.8 min; HRMS calcd for $C_{10}H_{15}N_2O_3$ $(M + H)^+$: 211.1077, found: 211.1083; $[\alpha]_D^{25}$ = +48.1 (*c* 1.0, MeOH); IR (ATR): ν = 426.1, 547.7, 698.6, 753.4, 829.1, 852.4, 1017.4, 1099.3, 1342.8, 1524.1, 1604.5, 2793.1, 2845.4, 2923.8, 3105.3, 3309.6 cm^{-1}.



6

Catalyst **1b** (20 mol%, 0.04 mmol), Catalyst **2** (10 mol%, 0.02 mmol) and 4-nitrobenzaldehyde (1.0 eq., 0.2 mmol) were mixed in a vial with acetonitrile (0.4 mL). Then paraldehyde (2.0 eq., 0.4 mmol) and deionized water (0.5 eq., 0.1 mmol) were added and the vial was sealed and shaken at room temperature. After 26 h, the mixture was filtered and washed with AcOH in THF (10%, 2 × 2 mL). The filtrates were combined. Crude product **3** was obtained after removal of volatile materials under reduced pressure. Then it was dissolved in anhydrous THF (1 mL), and **9** (3.0 eq., 0.6 mmol) and anhydrous Na_2SO_4 (0.2 g) were added. The mixture was stirred for 1 hour and then $NaBH(OAc)_3$ (3.0 eq., 0.6 mmol) was added. After stirring for 5 h, the reaction was quenched with saturated aqueous NH_4Cl (3 mL), and extracted with ethyl acetate (3 × 5 mL). The organic phases were combined, washed with brine (2 mL) and dried over Na_2SO_4. After solvent removal, products were purified by fast flash chromatography on silica gel, with CH_2Cl_2/MeOH/NH_4OH mixtures as eluent. 56 mg of **6** (0.14 mmol, 68% overall yield for two steps) were obtained with 98% ee (measured by chiral HPLC) as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.18 (t, *J* = 7.1 Hz, 3H), 1.75 - 1.92 (m, 2H), 1.93 - 2.42 (m, 4H), 2.51 - 2.79 (m, 4H), 2.85 - 3.20 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 5.03 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.24 - 7.29 (m, 1H), 7.31 - 7.41 (m, 4H), 7.52 - 7.57 (m, 2H), 8.20 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 14.2, 33.6, 33.9, 34.2, 49.1, 50.9, 52.5, 57.3, 61.1, 75.1, 123.7 (×2), 125.9 (×2), 126.4 (×2), 127.3, 128.2, 128.7 (×2), 147.1, 152.7, 174.2; HPLC (Chiralcel IA, Hexane /*i*-propanol (90:10, 0.1% Diethylamine used as additive), flow rate = 1.0 mL min^{-1}, λ = 280 nm): t_{major} = 17.3 min, t_{minor} = 14.2 min; HRMS calcd for $C_{23}H_{29}N_2O_5$ $(M + H)^+$: 413.2071, found: 413.2081; $[\alpha]_D^{25}$ = +60.1 (*c* 1.35, $CHCl_3$); IR (ATR): ν = 440.9, 697.6, 767.8, 862.1, 1024.3,

1048.5, 1127.4, 1227.1, 1344.6, 1516.7, 1600.9, 1717.8, 2839.1, 2922.1, 2969.6 cm^{-1}; Melting point: 152.8–153.2 ºC.

7. References

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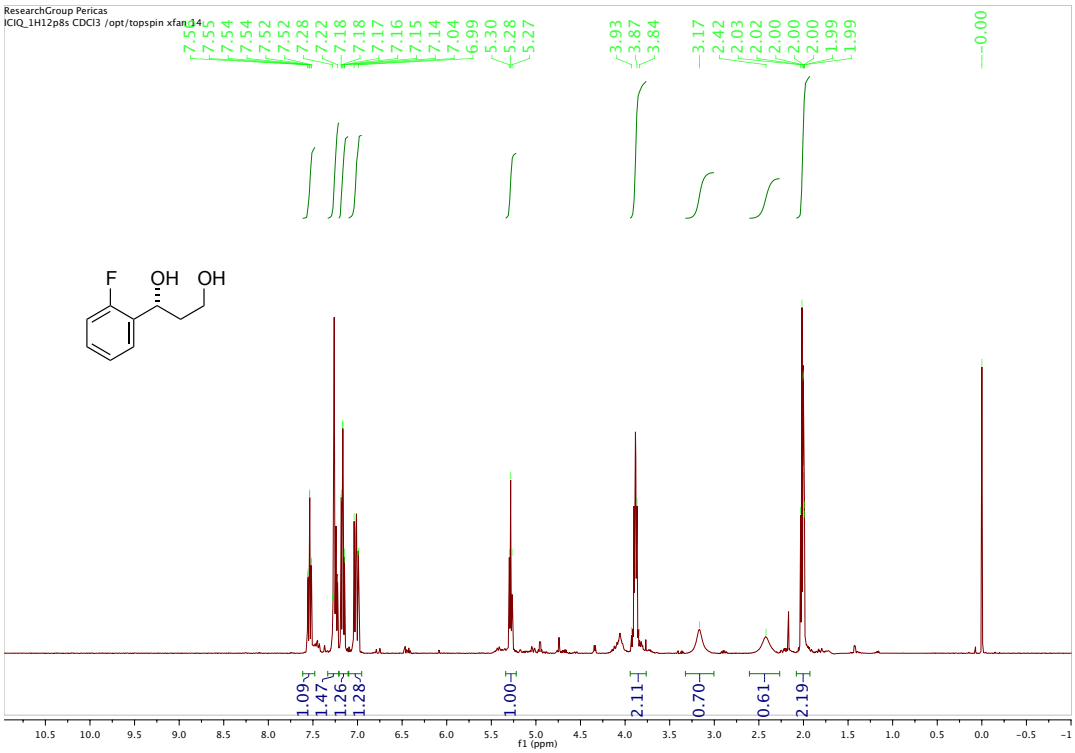
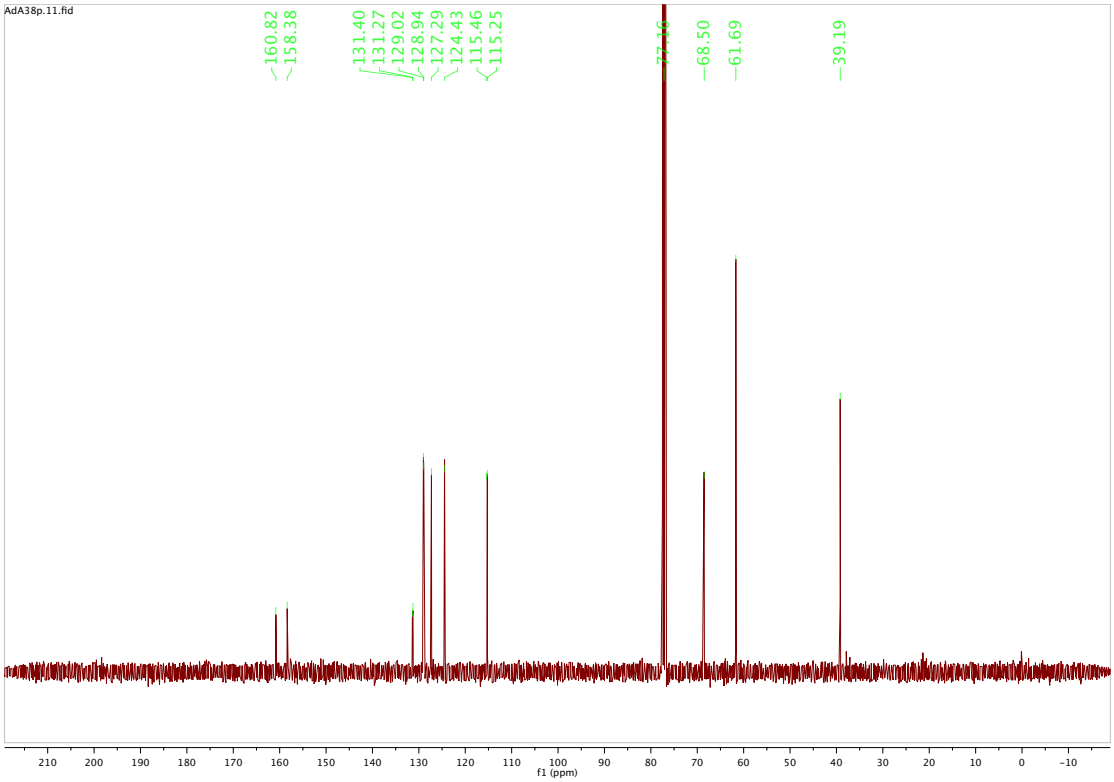
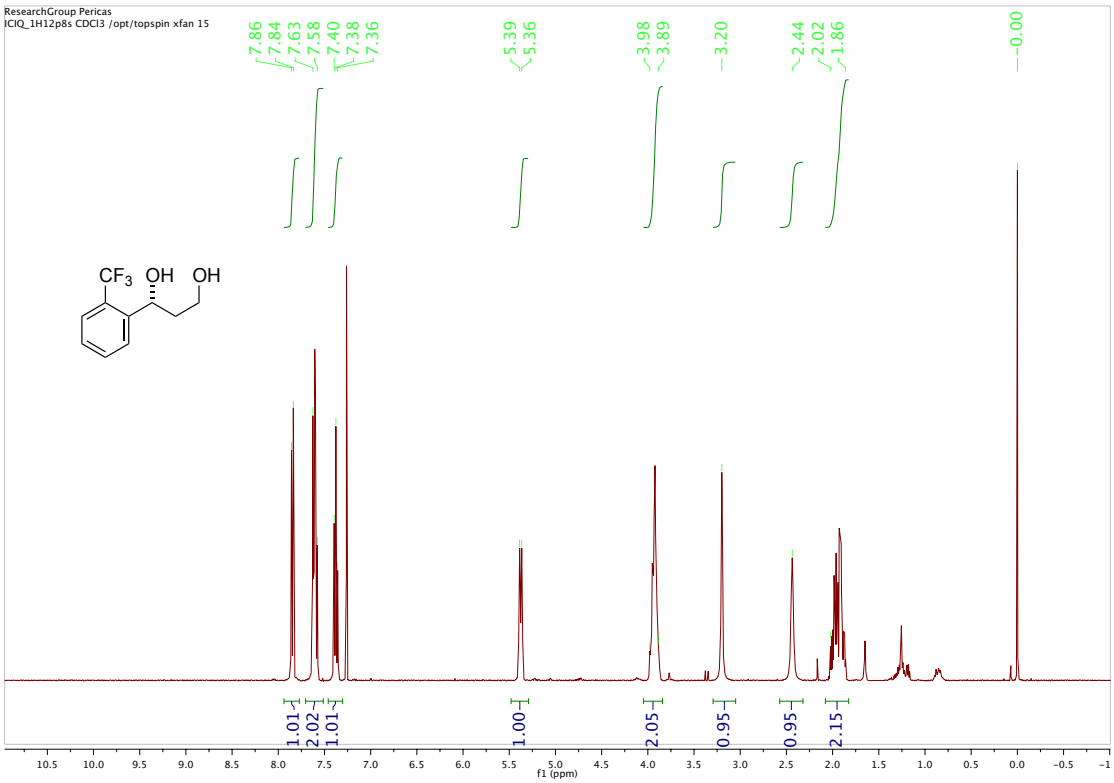
6. ^{1}H and ^{13}C NMR spectra



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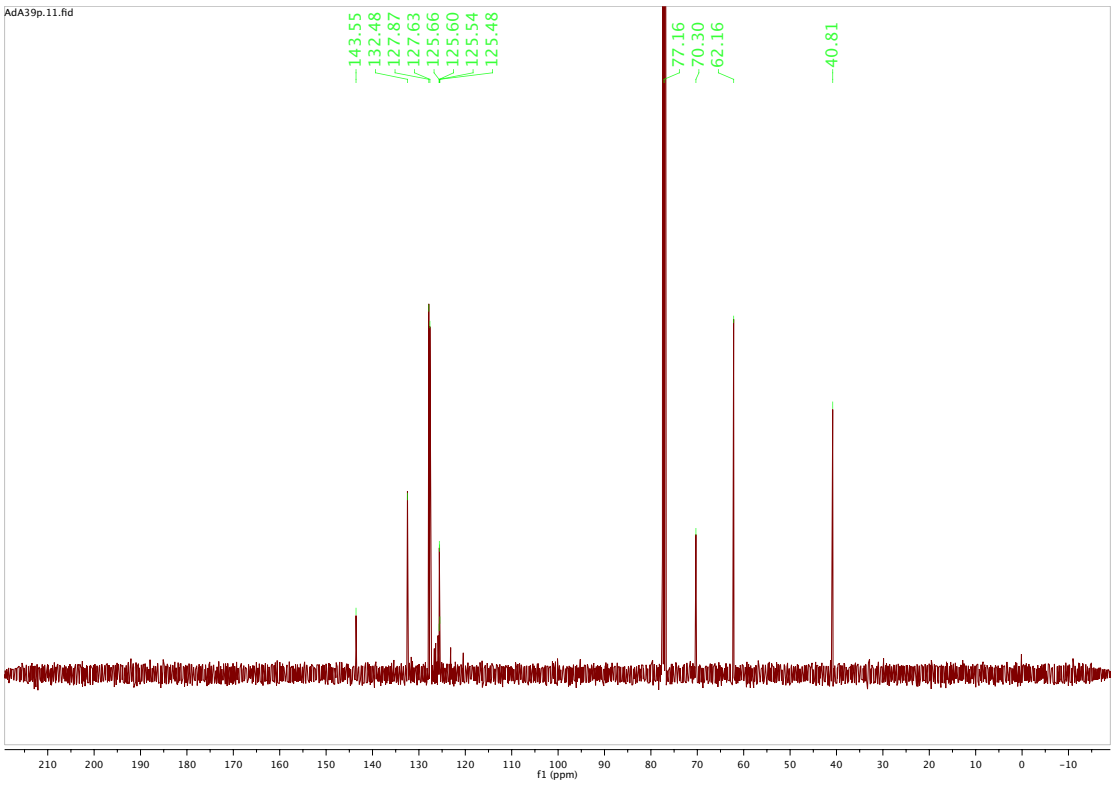
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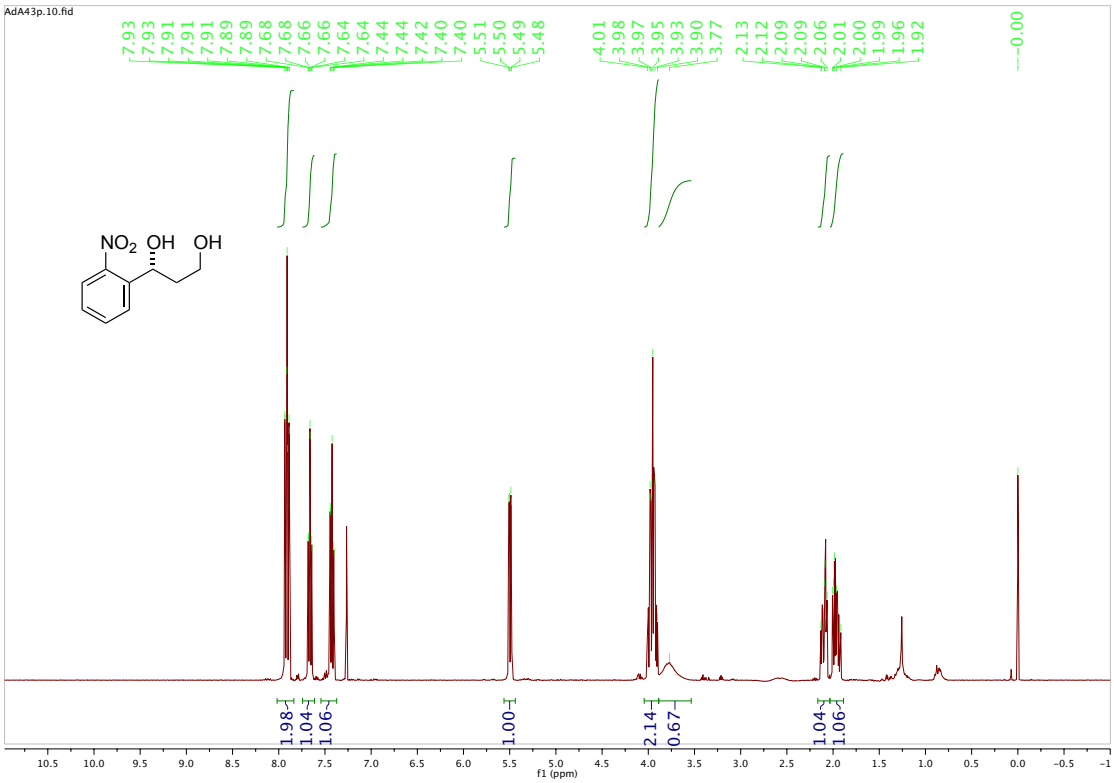
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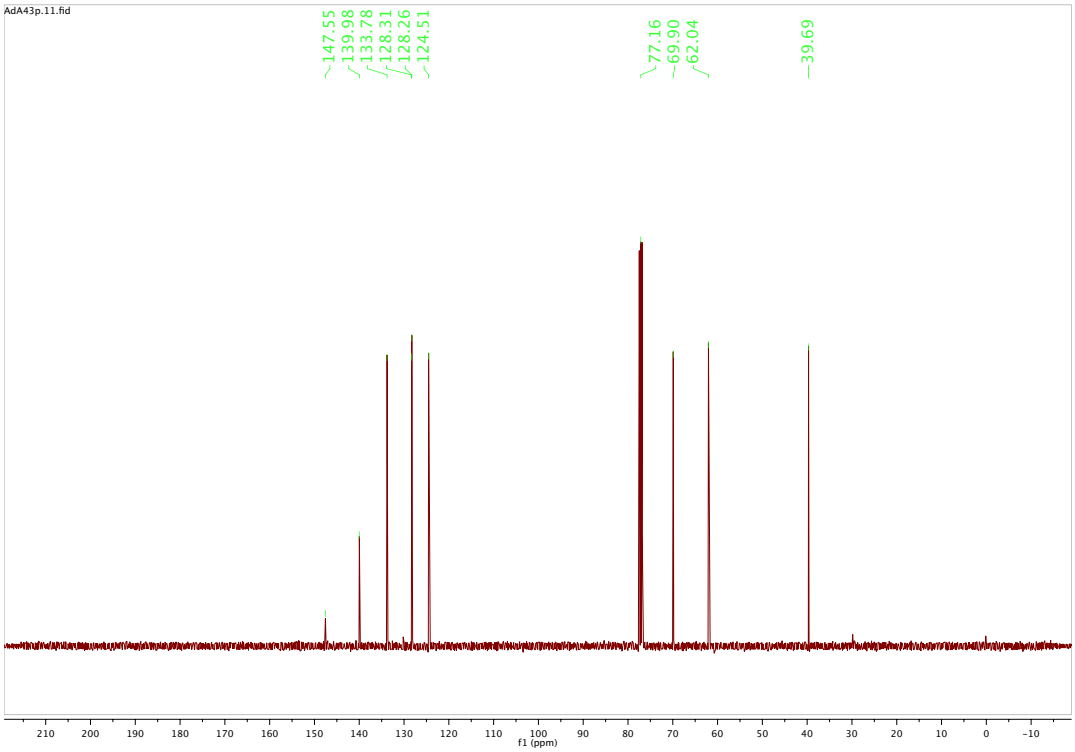
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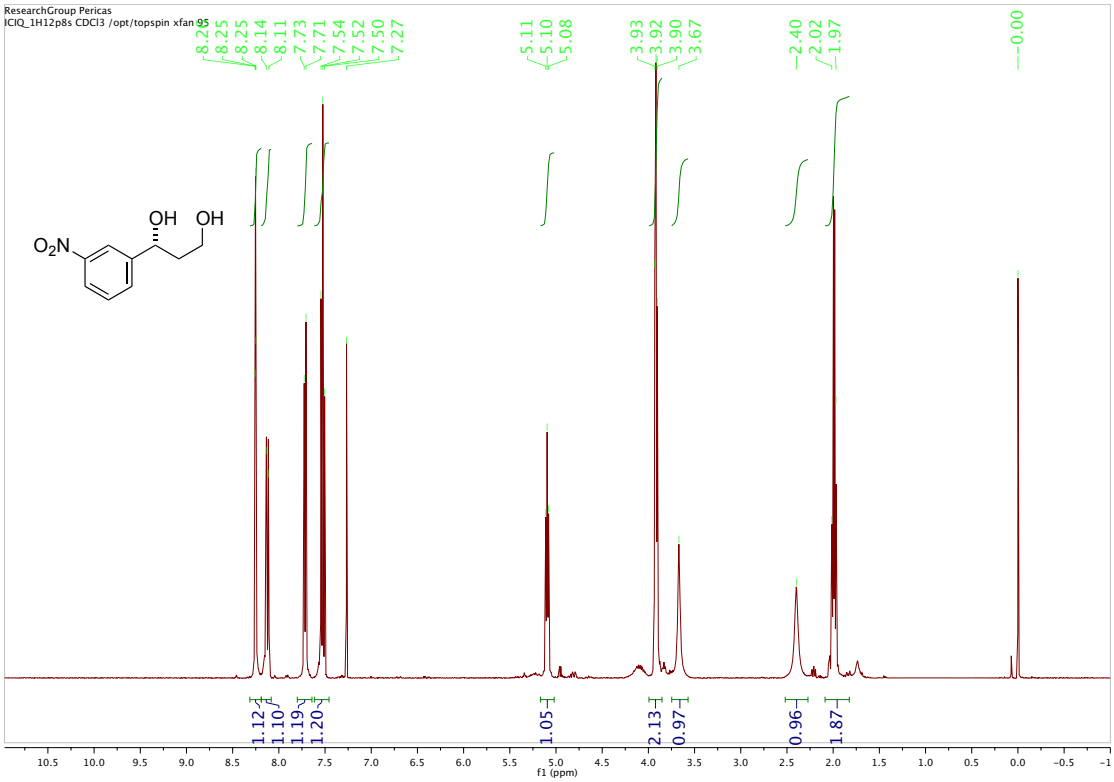
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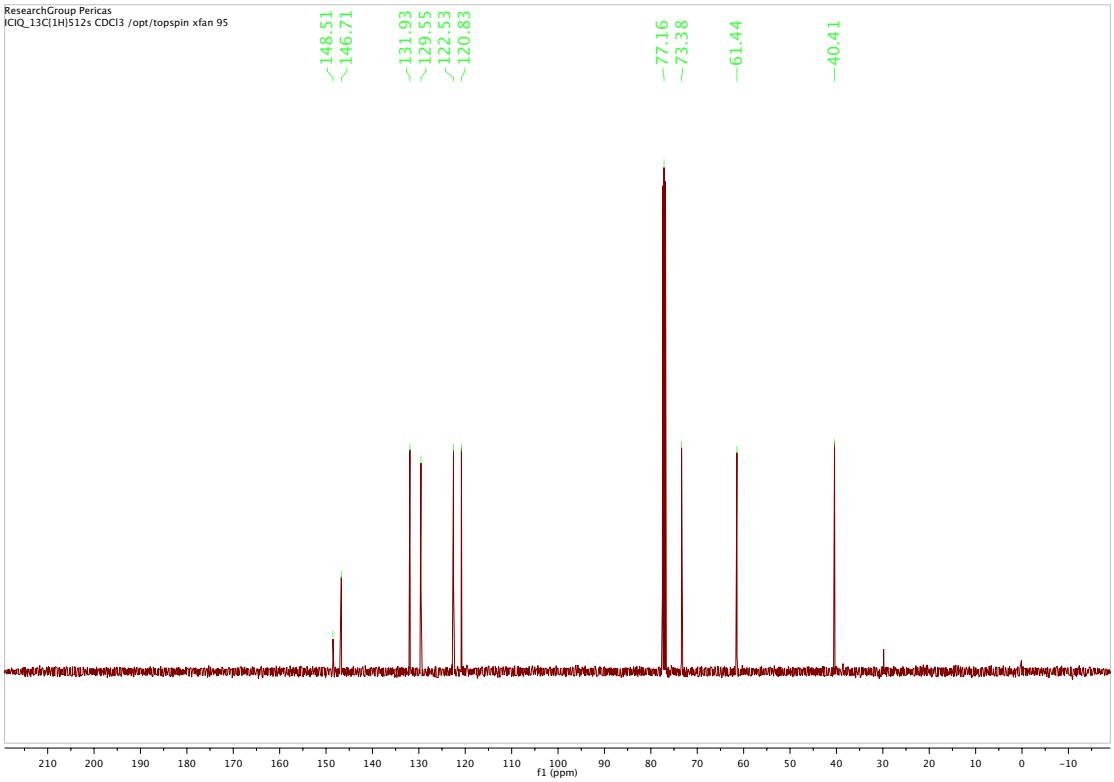
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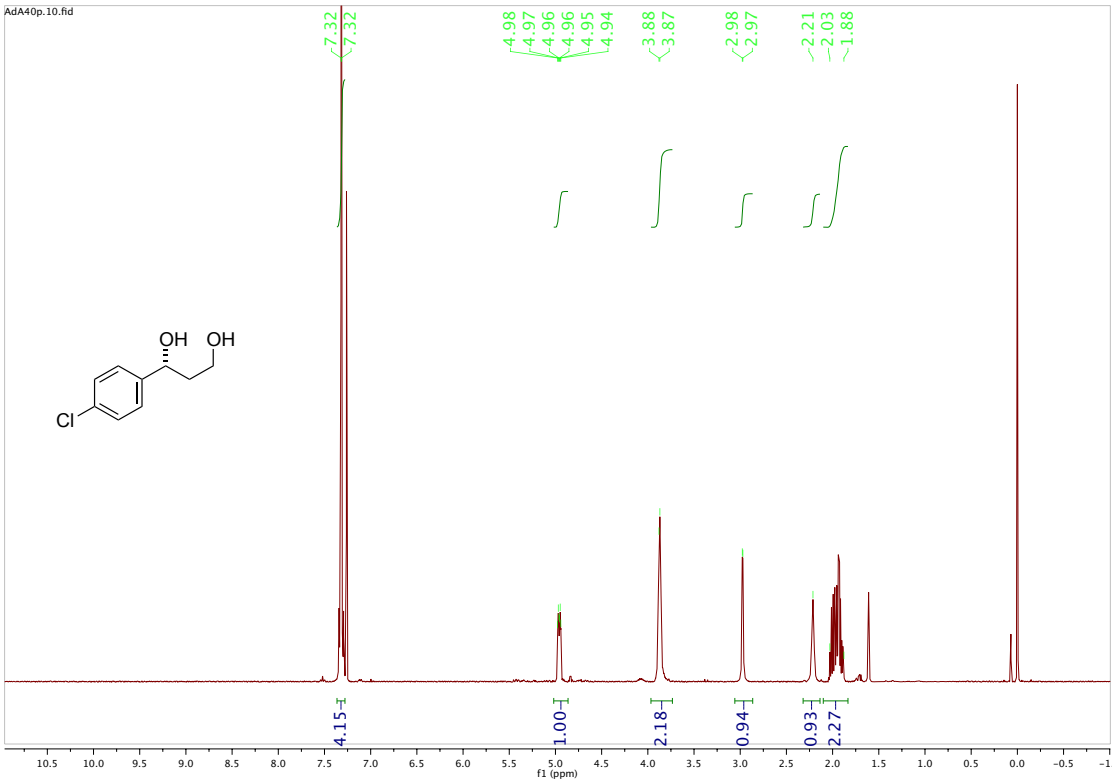
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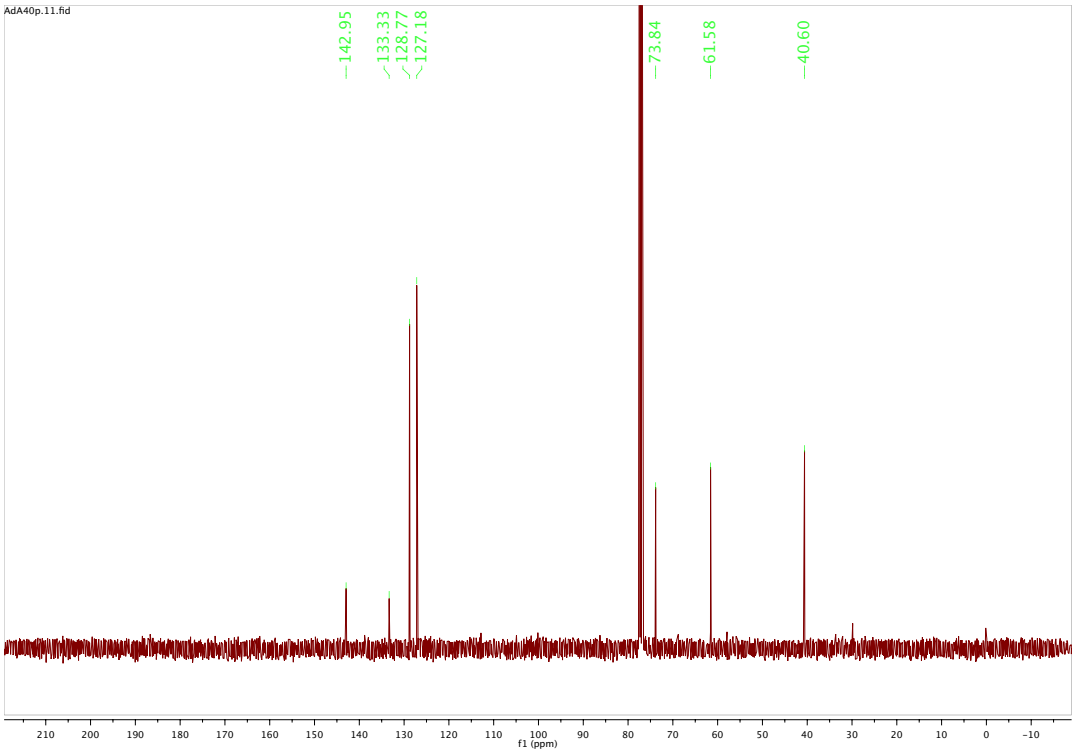
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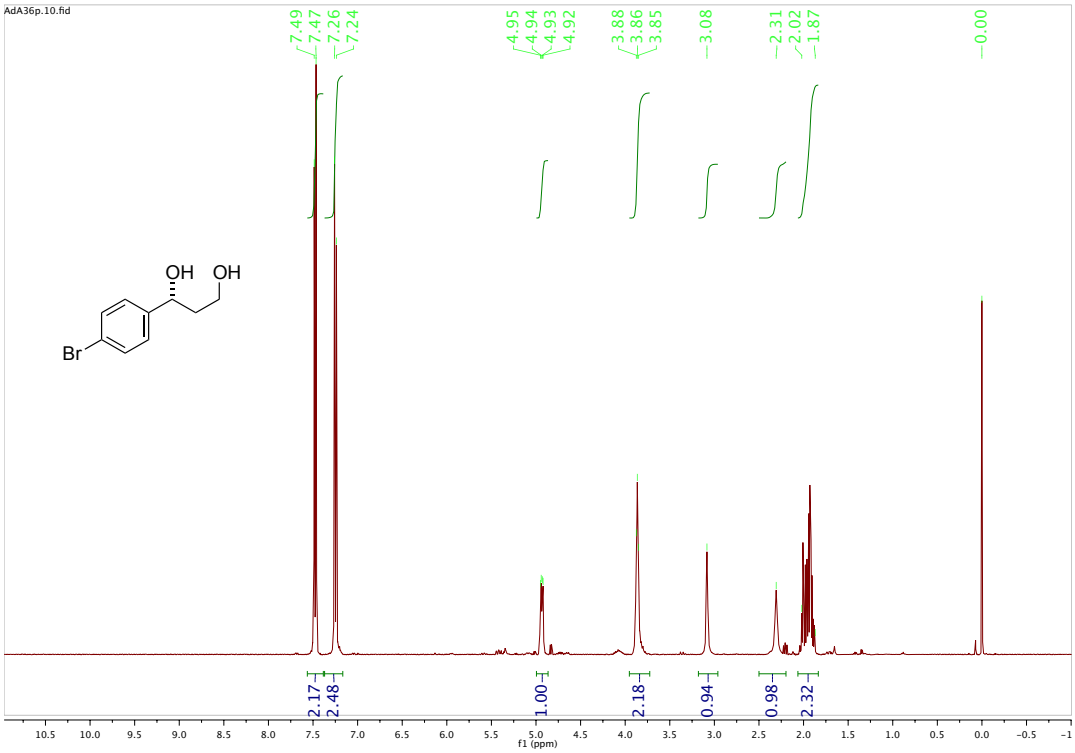
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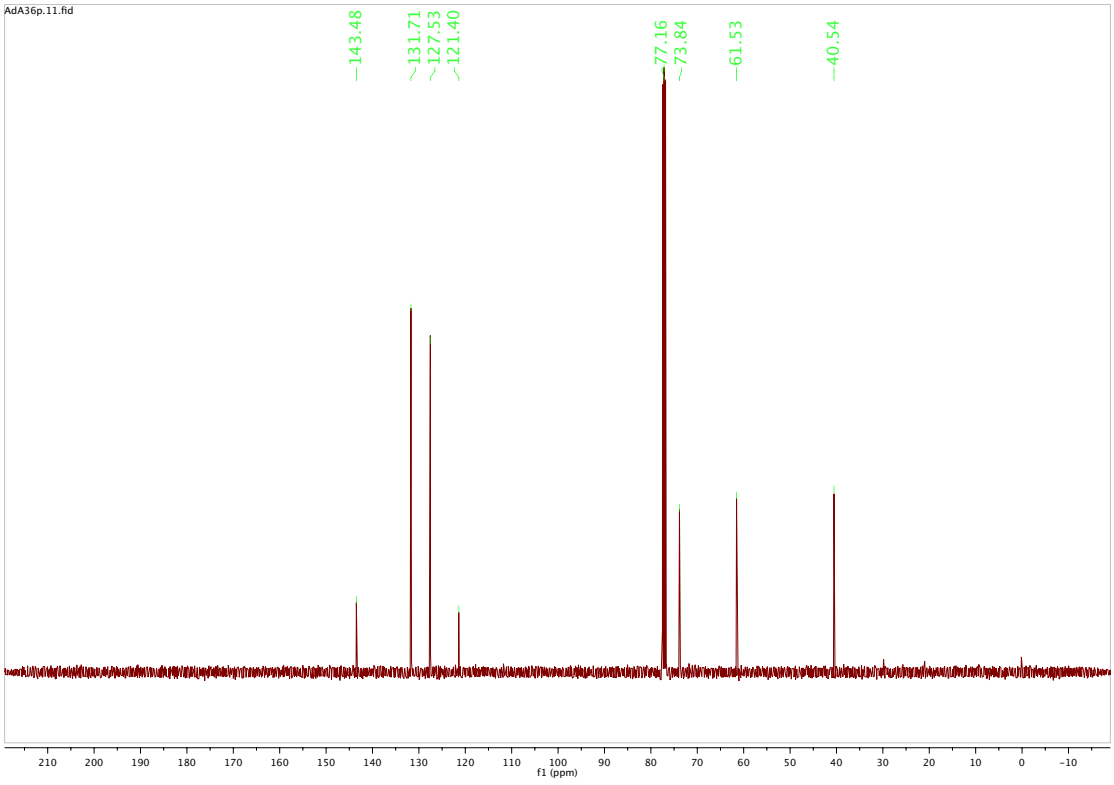
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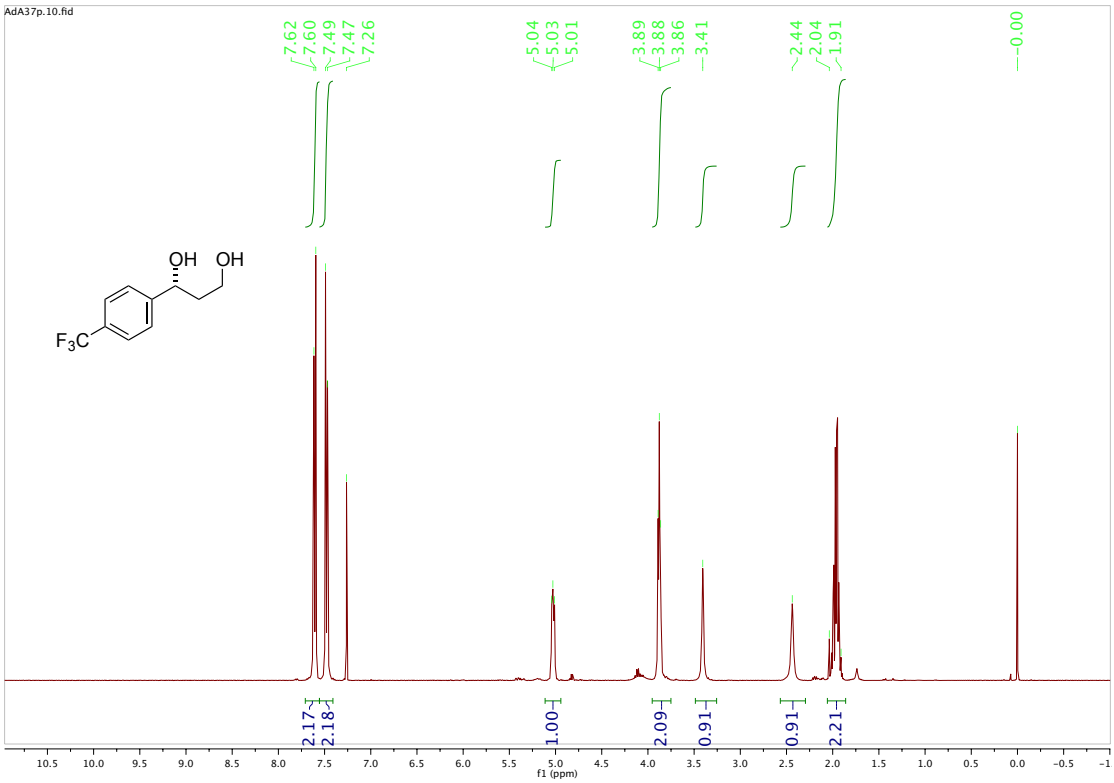
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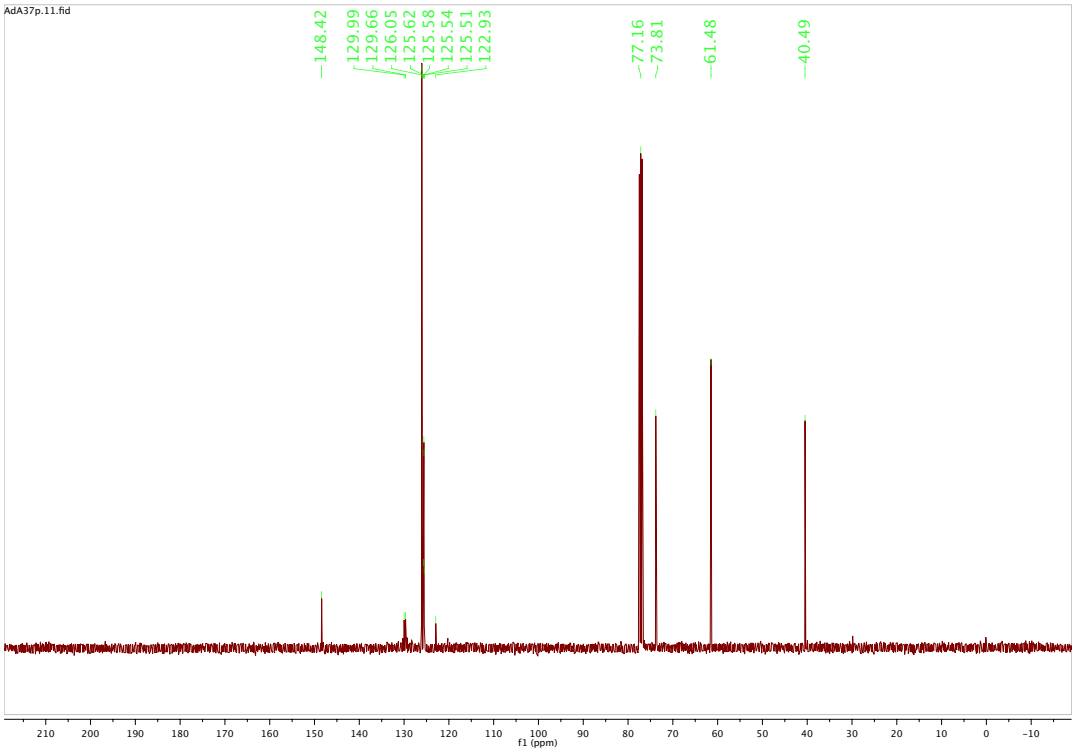
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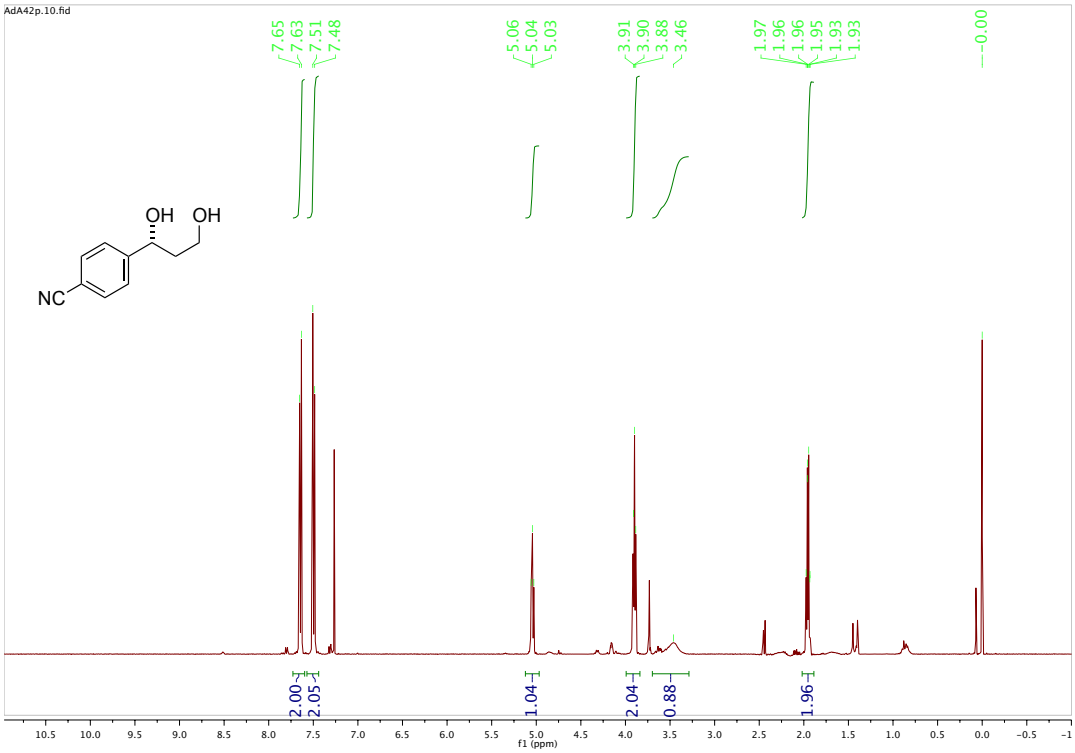
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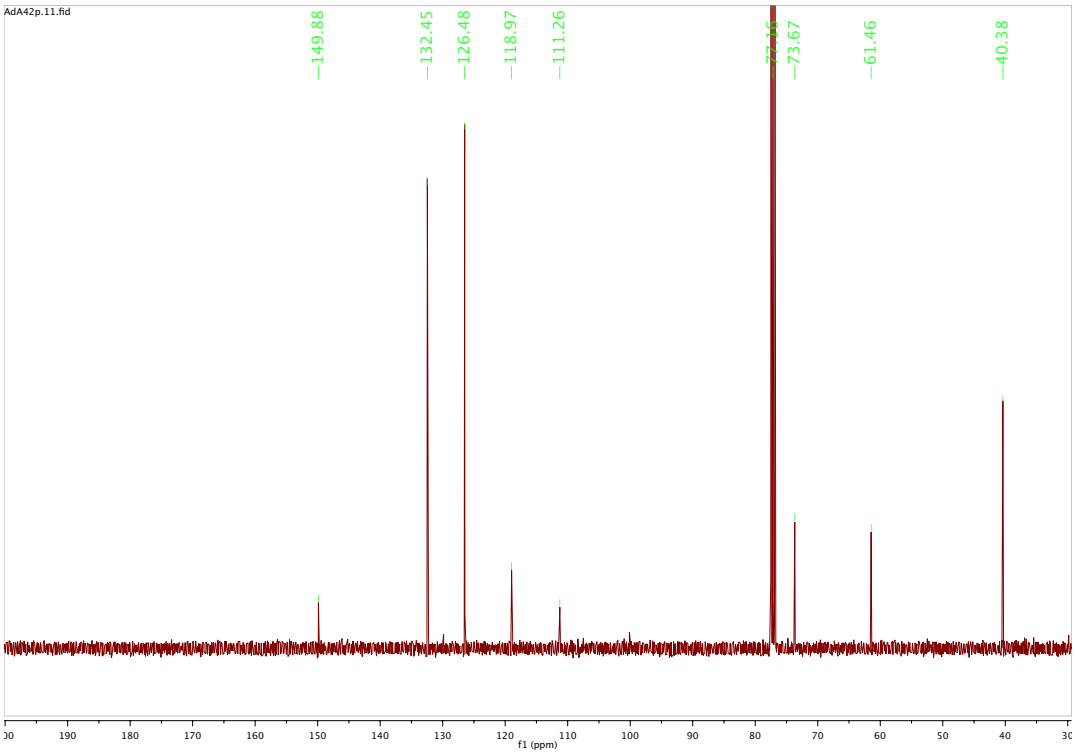
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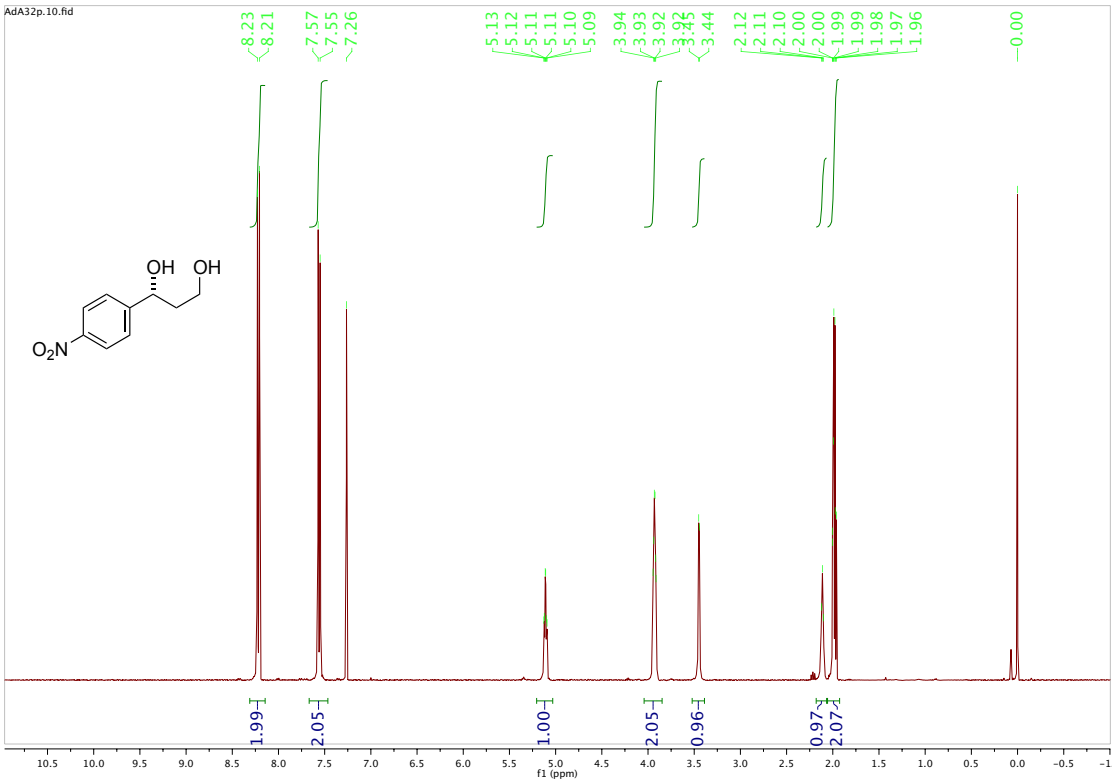
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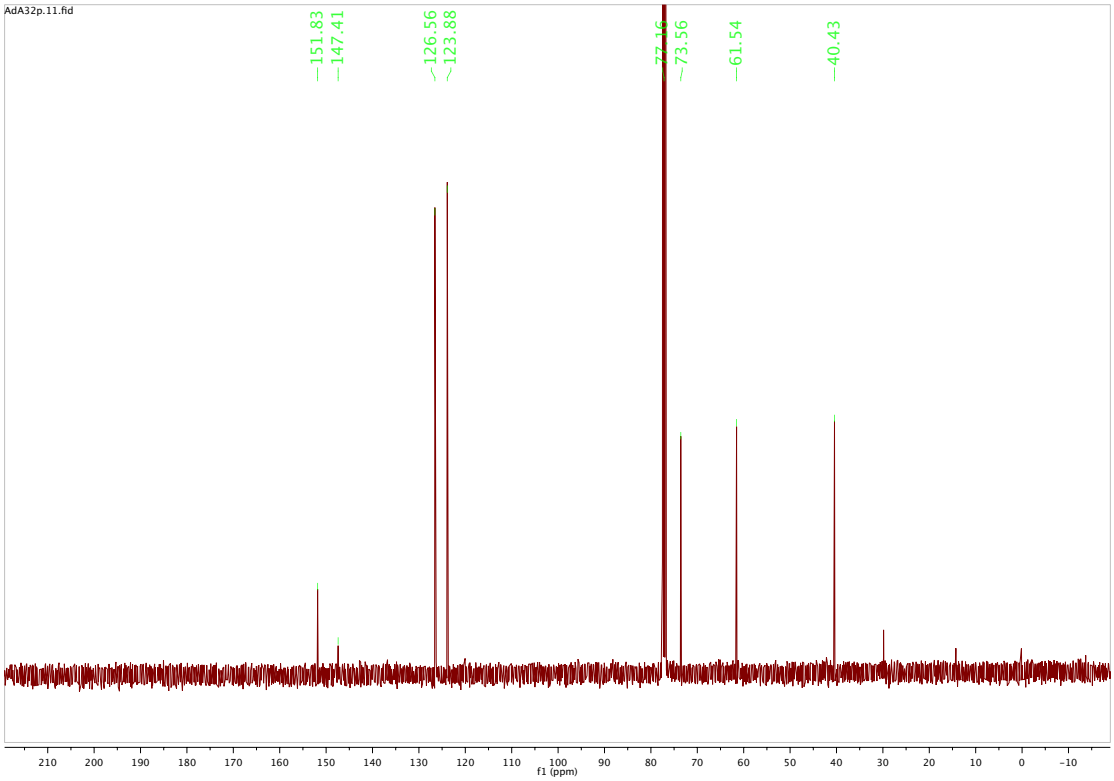
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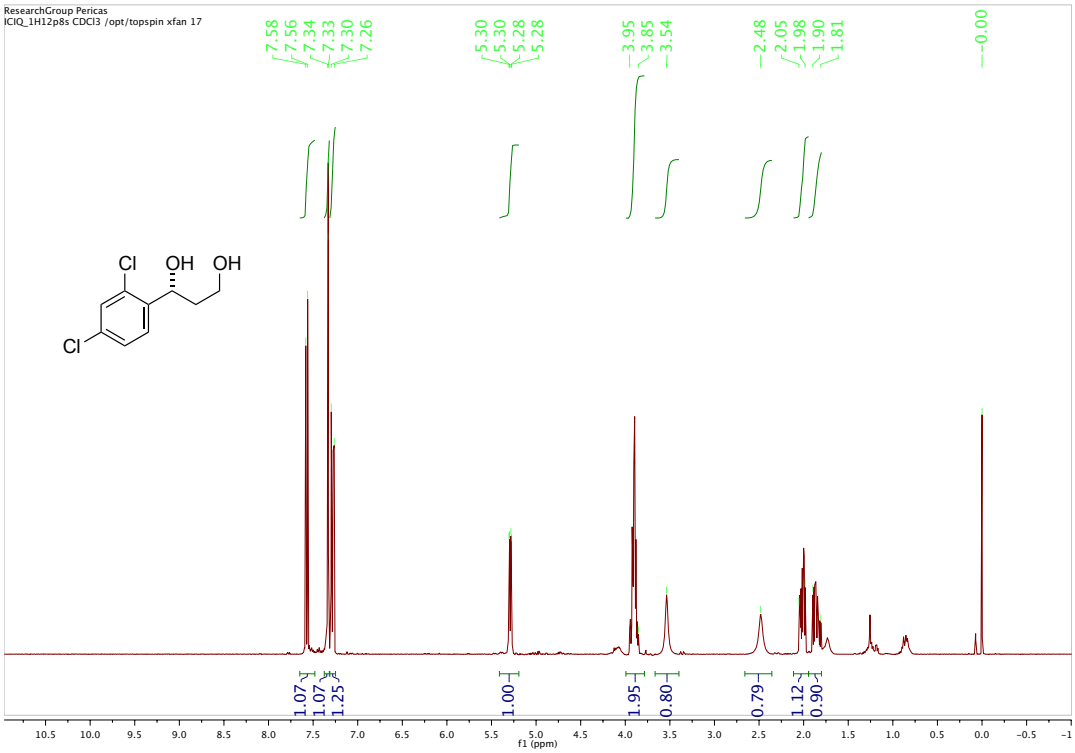
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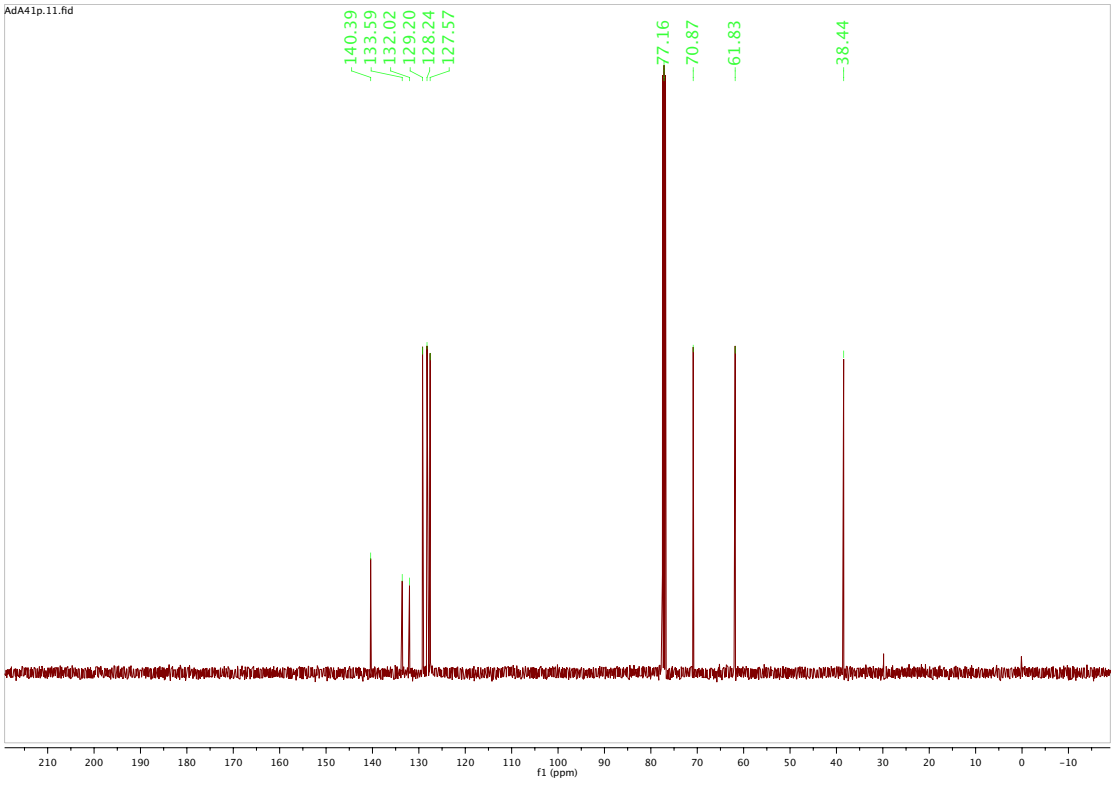
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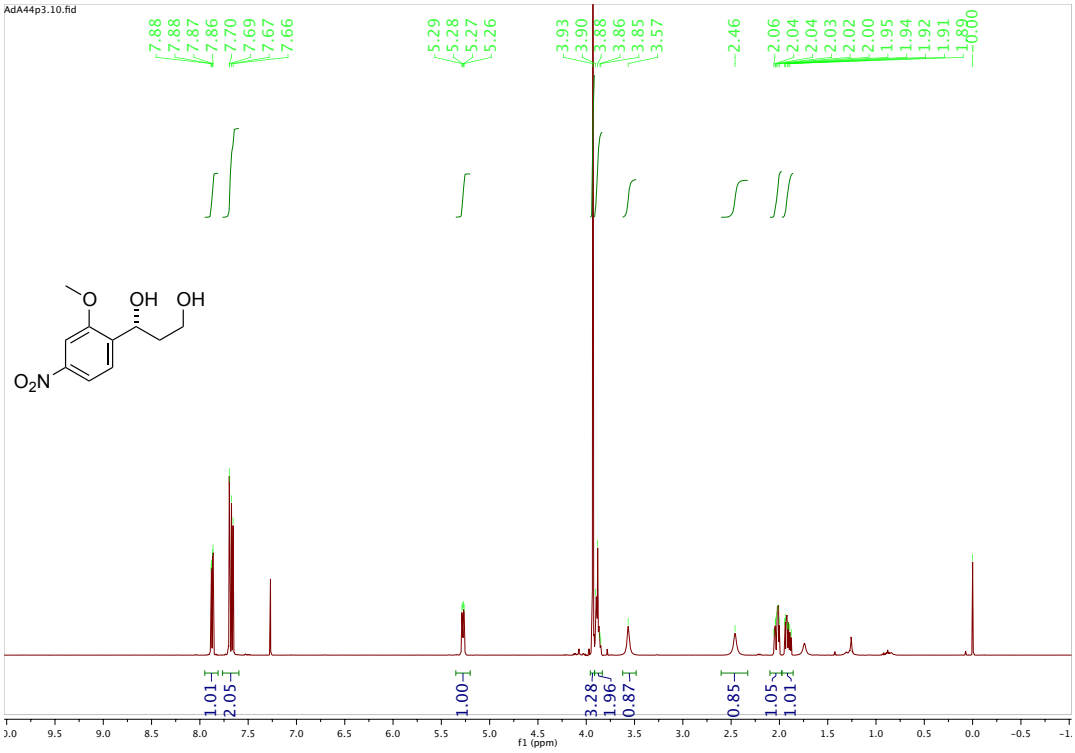
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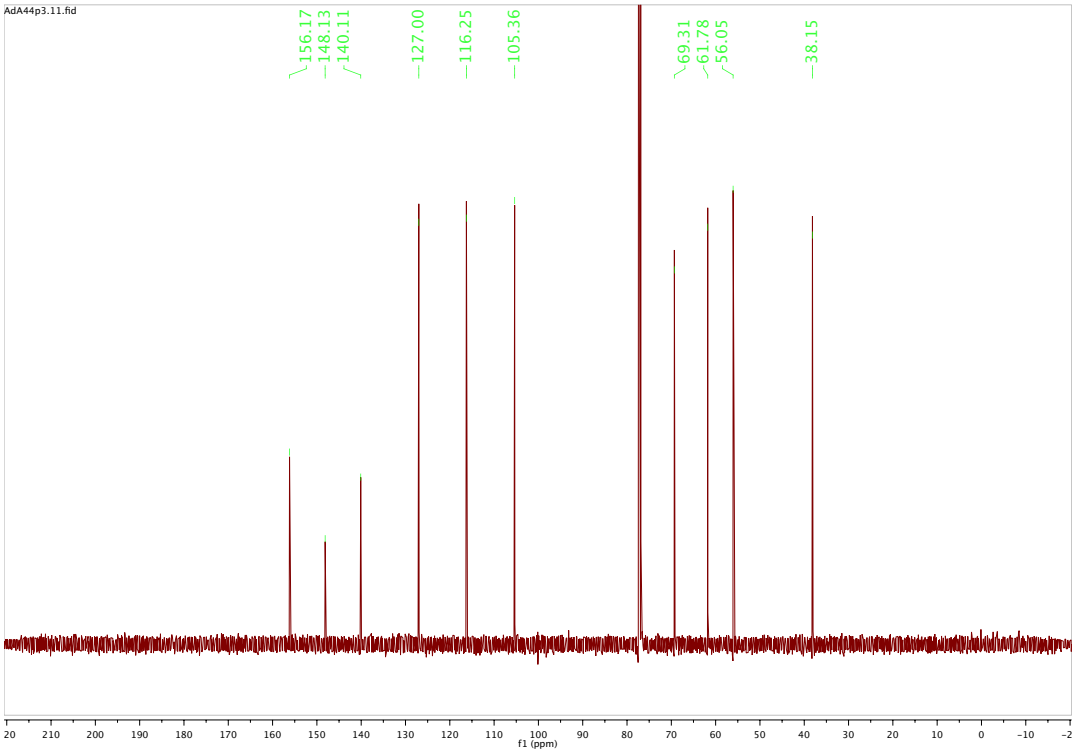
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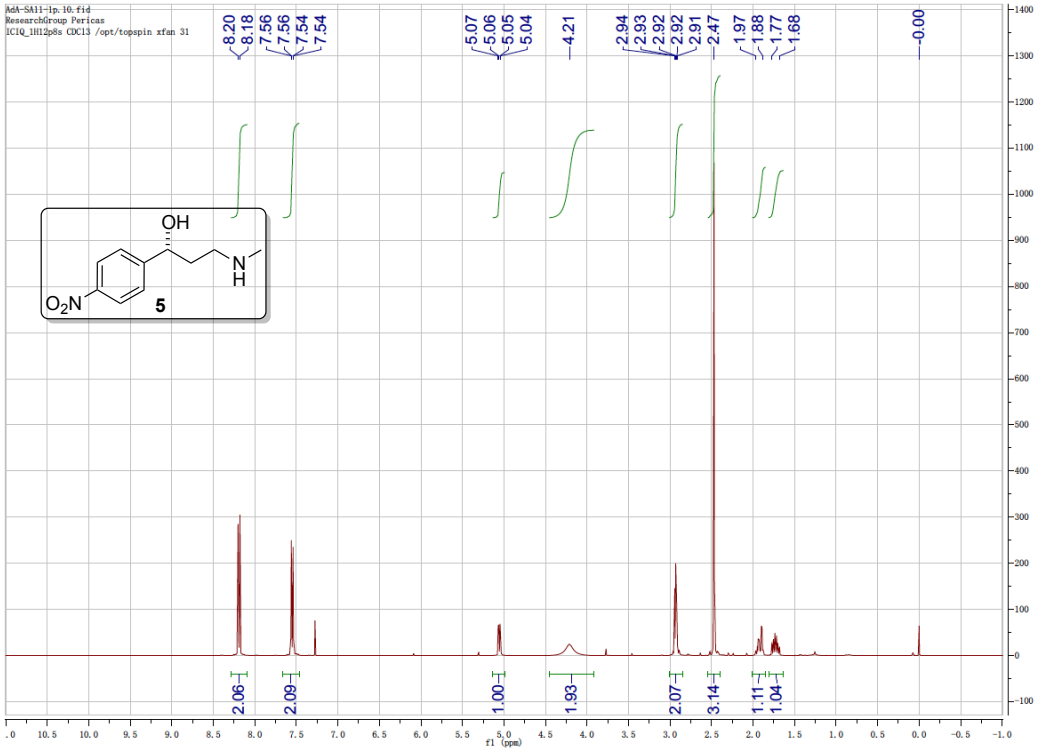
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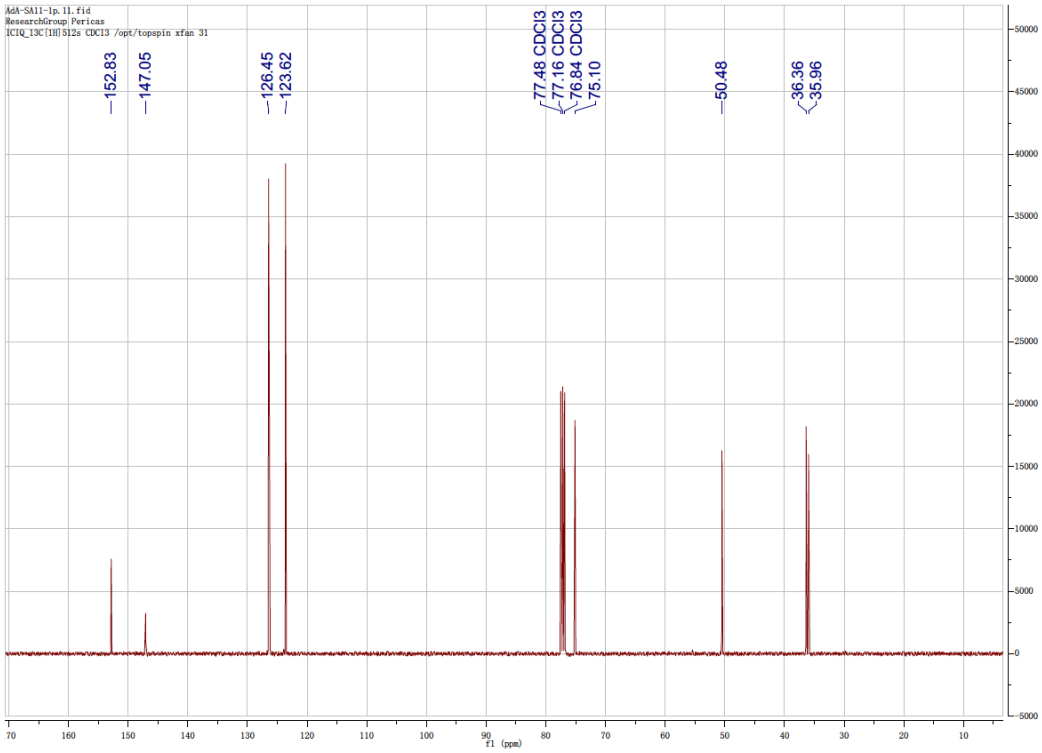
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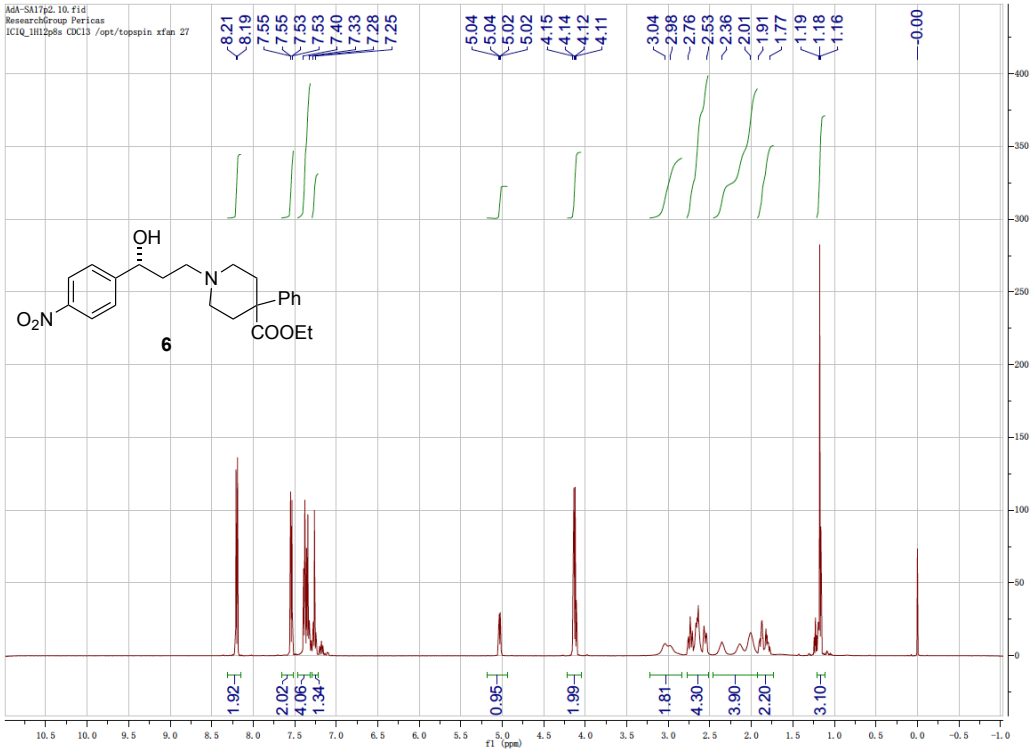
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5.02
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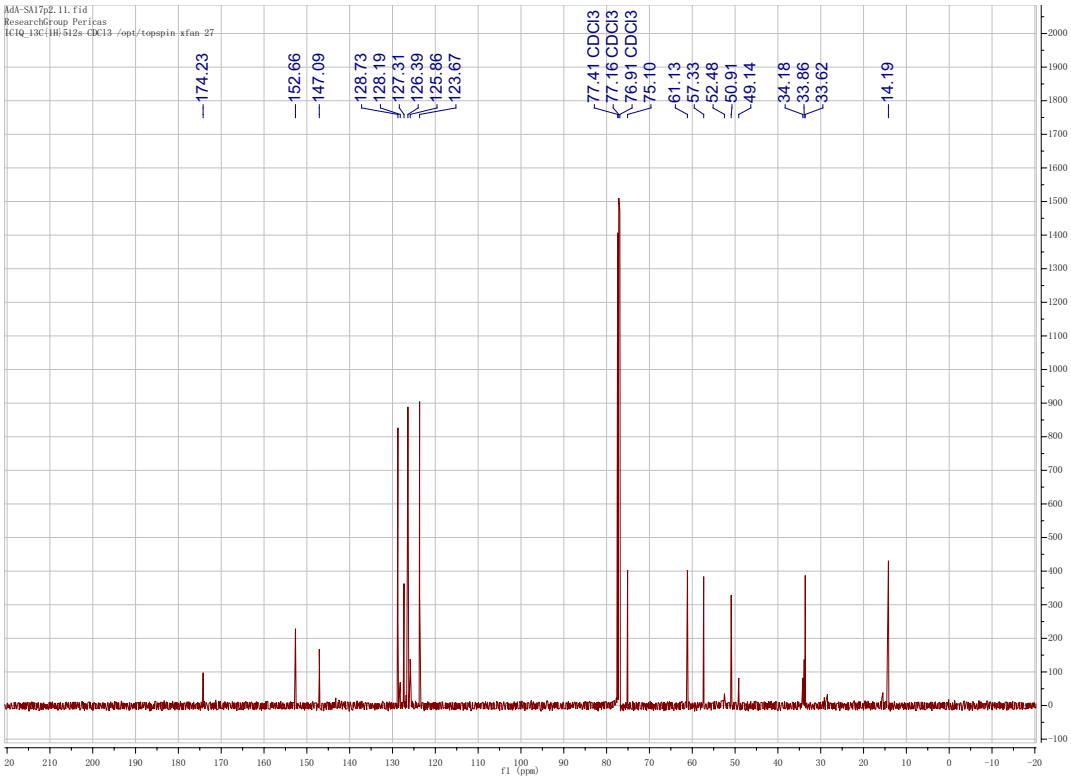
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33.86
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14.19
f1 (ppm)

Article E

A Site Isolation Enabled Organocatalytic Approach to Enantiopure γ-Amino Alcohol Drugs

Shoulei Wang, Carles Rodríguez-Escrich, Xinyuan Fan, and Miquel A. Pericàs*

Abstract: *Solid support-enabled site isolation has previously allowed to use paraldehyde as an acetaldehyde surrrogate in aldol reactions. However, only electron-poor aldehydes were tolerated by the system. Herein, we show that the temporary conversion of benzaldehyde into η^6-benzaldehyde $Cr(CO)_3$ circumvents this limitation. Asymmetric synthesis of (R)-Phenoperidine, as well as formal syntheses of (R)-Fluoxetine and (R)-Atomoxetine, illustrate the benefits of this strategy.*

The direct cross-aldol reaction represents one of the most important carbon-carbon bond forming processes since it can provide an efficient approach to both naturally occurring and synthetically important building blocks.[1] During the past decade, a variety of enamine-mediated aminocatalytic processes have been developed and successfully applied in asymmetric cross-aldol reaction.[2] However, most of these examples are not efficient with acetaldehyde as the donor due to its high reactivity unavoidably leading to a variety of by-products arising from its oligomerization and self-aldolization.[3] Recently, the Hayashi group reported the first organocatalytic direct cross-aldol reaction of acetaldehyde with aromatic aldehydes using a diarylprolinol as the catalyst.[4] Later, the use in the same reactions of chiral primary amine catalysts under neat conditions[5] and of suitably modified diarylprolinol catalysts in aqueous media,[6] have also been reported. More recently, we have disclosed a highly enantioselective version of the reaction promoted by a dual catalytic system (polystyrene-bound sulfonic acid **1** and polystyrene-supported diarylprolinol catalyst **2**, Figure 1) which enabled the use of paraldehyde as a convenient source of acetaldehyde.[7] Compared to acetaldehyde, paraldehyde is less expensive, easier to handle (b.p. 123 ºC) and can be deoligomerized in situ by polystyrene-bound sulfonic acid **1**. The site isolation scenario generated under these conditions[8] enabled catalyst **1** to work compatibly with **2** in one pot in a highly recyclable manner, furnishing the aldol products in good yields and excellent enantioselectivities.

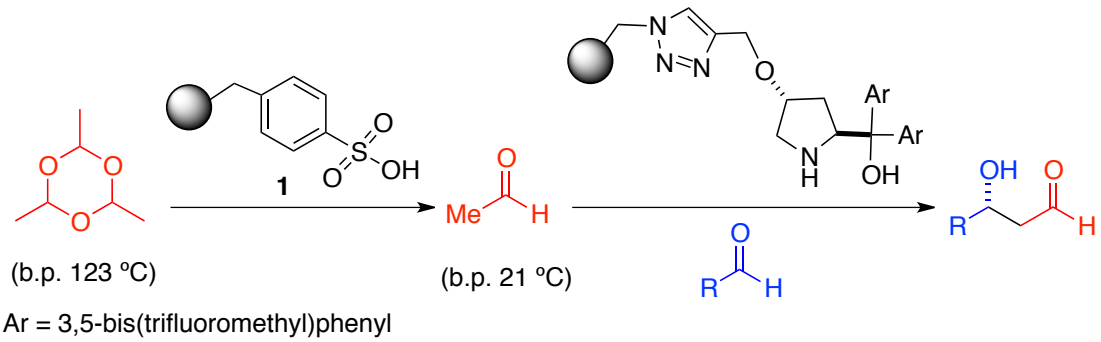
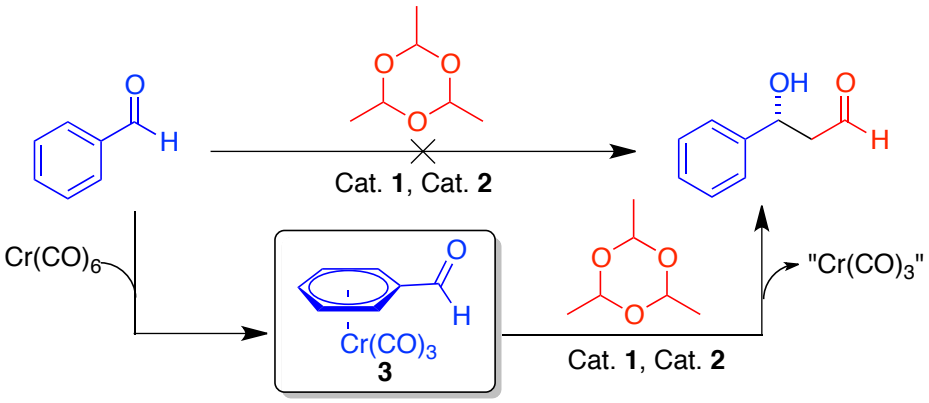


Figure 1. Cascade deoligomerization and cross-aldol reaction mediated by **1**/**2** operating under site isolation.

This methodology granted access to enantioenriched 1-arylpropane-1,3-diols, a privileged core structure occurring in a variety of drugs and natural products.[9] However, the drawback of this method was the fact that only electron-poor benzaldehydes could be used as effective substrates (Scheme 1, top). Considering the importance of 3-phenyl-3-hydroxypropanal as a key building block in the synthesis of many active pharmaceutical ingredients, we analyzed methods allowing the reversible electronic modification of benzaldehyde that could favor its participation in the cross-aldol reaction.

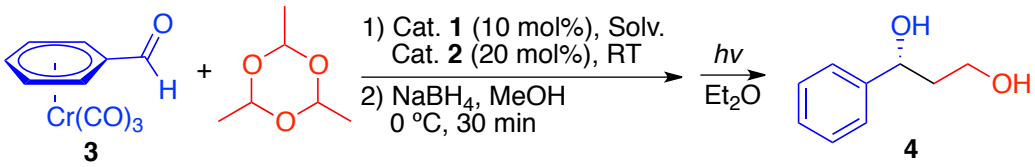
It is known that the formation of η^6-arene-$Cr(CO)_3$ complexes importantly decreases the electron density of the parent arene and modifies accordingly its reactivity.[10] From a practical perspective, these complexes are easily formed upon reaction of $Cr(CO)_6$ with aromatic substrates, and the metal moiety can be later removed in quantitative yield by exposure to sunlight.[11] Thus, the complexation/decomplexation process has normally low impact on the efficiency of the overall process. In 2011, Walsh *et al.* exploited this approach to favor the generation of nucleophiles for allylic substitution reaction,[12] and the same strategy has been recently applied by Larrosa *et al.* for enhancing the reactivity of C-H bonds in arylation reactions.[13] With these precedents in mind, we assumed that the η^6-benzaldehyde complex **3** could be used as an activated benzaldehyde surrogate in the cross-aldol reaction with paraldehyde mediated by the **1**/**2** dual catalytic system (Scheme 1, bottom).



Scheme 1. Deoligomerization/cross-aldol reaction of paraldehyde with complex **3** mediated by the **1**/**2** dual catalytic system.

Initially, we investigated the cross-aldol reaction of the tricarbonyl (η^6-benzaldehyde) chromium (0) with paraldehyde mediated by the dual catalytic system **1**/**2** in DMF (Table 1, entry 1) but the target aldol product was not formed at all in this solvent. A subsequent solvent screening showed that when acetonitrile was employed the product can be isolated in 18% yield and 93% ee (entries 3). A screening of additives including benzoic acid, *p*-nitrobenzoic acid and water revealed the latter as the most convenient one (entries 4-6). When raising the temperature, either with conventional heating or using the microwave, the enantioselectivity was maintained but the yield slightly decreased (entries 7 and 8). In order to evaluate the effect of different reaction times on the yield and enantioselectivity, we carried out a series of comparative experiments (see supporting information) which showed that after 72 hours the reduced aldol product **4** could be obtained in 38% yield and 93% ee (entry 9). Subsequently, the use of different amounts of paraldehyde was examined (entries 10-12), but the improvement was not significant (entry 10). Finally, increasing the loading of polystyrene-supported catalyst **2** led to a major yield improvement (up to 61%) when 40 mol% of this catalyst was used (entry 15).

Table 1. Tandem deoligomerization plus cross-aldol reaction of tricarbonyl (η^6-benzaldehyde) chromium (0) with paraldehyde catalyzed by **1**/**2**.[a]

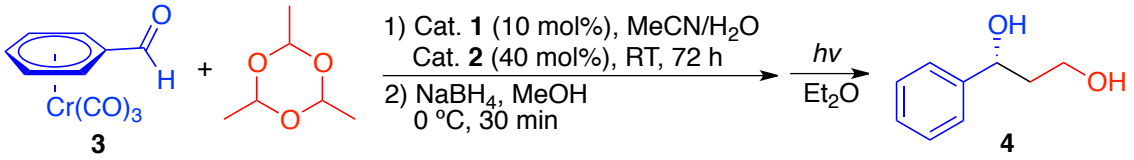


Entry	Time (h)	Solvent	Paraldehyde (equiv.)	Yield (%)[b]	ee (%)[c]
1	24	DMF	2	0	–
2	24	CH_3NO_2	2	15	92
3	24	MeCN	2	18	93
4[a]	24	MeCN	2	12	92
5[e]	24	MeCN	2	17	93
6	24	MeCN/H_2O	2	20	93
7[i]	24	MeCN/H_2O	2	17	93
8[g]	24	MeCN/H_2O	2	19	93
9	72	MeCN/H_2O	2	38	93
10	72	MeCN/H_2O	5	41	93
11	72	MeCN/H_2O	10	33	93
12	72	MeCN/H_2O	20	30	92
13	72	Paradehyde	–	20	92
14[n]	72	MeCN/H_2O	5	49	93
15[i]	72	MeCN/H_2O	5	61	93

[a]The reaction was carried out with **3** (0.1 mmol), paraldehyde, **1** (10 mol%), **2** (20 mol%) and H_2O (0.5 mmol) in 0.3 mL solvent. [b]Determined by ^{1}H NMR using mesitylene as internal standard. [c]By HPLC. [d]0.01 mmol $PhCO_2H$ added. [e]0.01 mmol *p*-$NO_2C_6H_4CO_2H$ added. [f]At 40 °C. [g]Using microwave at 40 °C. [h]30 mol% of **2** was used. [i]40 mol% of **2** was used.

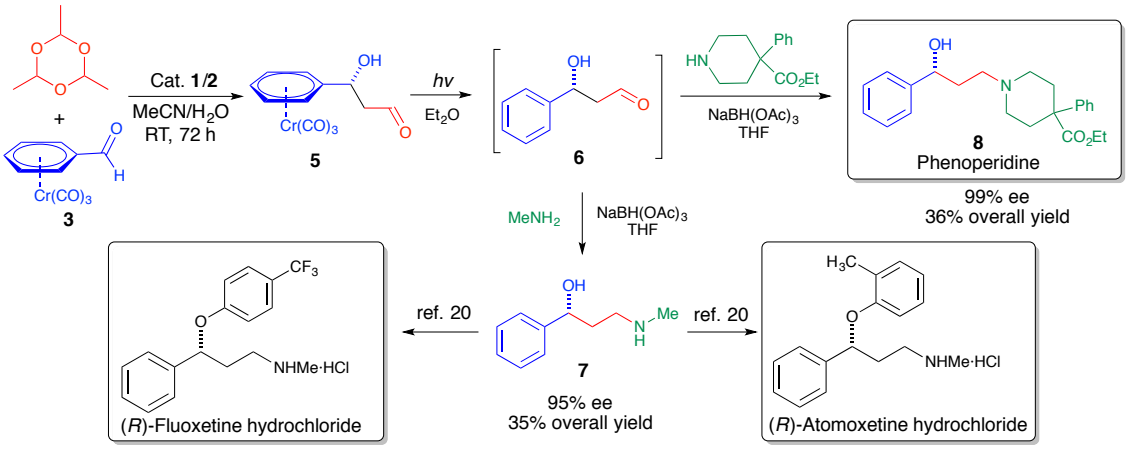
It is to be noted that such a high catalyst loading can only be justified if the dual catalytic system is amenable to recycling.[14] In this regard, it is worth mentioning that the recovery of the two different polystyrene-supported catalysts can be achieved by simple filtration without separating the two resins. Gratifyingly, the mixture of the two catalysts can be reactivated by briefly washing with AcOH after each reaction cycle. The role of the acid is presumably to hydrolise the parasite oxazolidine formed by catalyst **2** and acetaldehyde, thus increasing the effective amount of catalytic species.[7] Using this strategy, the **1**/**2** dual catalytic system could be reused for five cycles with essentially the same results. On the sixth cycle, the aldol product was still obtained in high enantioselectivity (90% ee), albeit with slightly decreased yield.

Table 2. Recycling in the tandem deoligomerization plus cross-aldol reaction of tricarbonyl (η^6-benzaldehyde) chromium (0) with paraldehyde catalyzed by **1**/**2**.



Cycle	Yield (%)	ee (%)
1	58	93
2	60	93
3	54	92
4	53	93
5	50	92
6	38	90

As already mentioned, enantiomerically enriched 1,3-diols and β-hydroxyaldehydes are versatile building blocks for the synthesis of a wide variety of natural products and commercially important drugs.[15] For instance, enantioenriched diol **4** is a key intermediate in the preparation of the selective serotonin reuptake inhibitor (*R*)-fluoxetine (Prozac®) and the norepinephrine reuptake inhibitor (*R*)-atomoxetine (Strattera®), which are important drugs for the treatment of important psychiatric disorders.[9, 16] According to previous literature procedures, the reduced cross-aldol product **4** can be converted into amino alcohol **7**, a common precursor to both drugs, in four steps and 36% overall yield.[9] We have now found (Scheme 2) that crude aldol **6**, obtained by decomplexation of **5** in ether solution on exposure to sunlight, can be converted into **7** (95% ee) in a single step by reductive amination with $MeNH_2$ (35% overall yield). Bearing in mind that **6** can be converted into **4** by simple aldehyde reduction, the improvement over previous approaches ultimately relying on the asymmetric Sharpless epoxidation[9] becomes evident. Phenoperidine **8**,[17] another well-known drug can also be synthesized in a single step from crude **6** upon treatment with ethyl 4-phenylpiperidine-4-carboxylate and $NaBH(OAc)_3$ in 36% overall yield and 99% ee.



Scheme 2 Synthesis of drugs and intermediates with the present methodology

In conclusion, we have developed an efficient approach for enhancing the reactivity of benzaldehyde in the cross-aldol reaction with acetaldehyde resulting from the deoligomerization of paraldehyde in a tandem process mediated by the dual polymer-supported catalytic system **1**/**2** operating under site isolation conditions in a recyclable manner. The strategy reported herein, involving η^6-coordination to $Cr(CO)_3$, has been applied to overcome the challenges and limitation of cross-aldol reaction of acetaldehyde with benzaldehyde, affording 1-phenylpropane-1,3-diol in high yield and excellent enantioselectivity. The crude, enantioenriched aldol **6** has been applied to the development of very short formal syntheses of the important drugs (R)-Fluoxetine and (R)-Atomoxetine.

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Supporting Information

A Site Isolation Enabled Organocatalytic Approach to Enantiopure γ-Amino Alcohol Drugs

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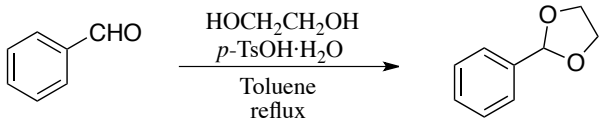
Table of Contents

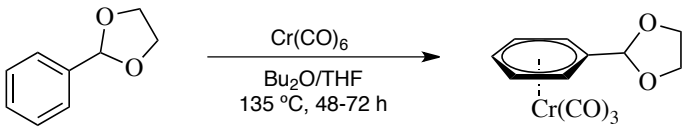
1. General information

Unless otherwise stated, all commercial reagents were used as received. Flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. Thin layer chromatography was carried out using Merck TLC Silicagel 60 F254 aluminum sheets. Components were visualized by UV light (λ = 254 nm) and stained with *p*-anisaldehyde or phosphomolybdic dip. NMR spectra were registered in a Bruker Advance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature, operating at 300 or 400 MHz (^1H) and 75 or 100 MHz (^{13}C[1]). TMS was used as internal standard for ^1H NMR and $CDCl_3$ for ^{13}C NMR. Chemical shifts are reported in ppm referred to TMS. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses of the polystyrene supported catalysts were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid, Spain. High performance liquid chromatography (HPLC) was performed on an Agilent Technologies chromatograph (1100 Series), using Chiralcel columns and guard columns. The absolute configuration of the reaction products was confirmed by HPLC, by comparison with reported data.[2] Catalyst **1** was purchased from Novabiochem®. Catalyst **2** was prepared according to a previously reported procedure.[1]

2. General procedure for the preparation of tricarbonyl (η^6-benzaldehyde) chromium (0) – Compound 3

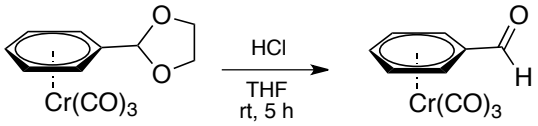


2-Phenyl-1,3-dioxolane: A mixture of benzaldehyde (20.0 mmol) and ethane-1,2-diol (22.0 mmol) in toluene (20 mL), containing a catalytic quantity of *p*-TsOH·H_2O (0.4 mmol) was refluxed in a Dean-Stark trap until water ceased to be removed (4 h). Evaporation of the solvent followed by distillation gave the product as a colorless oil (14.6 mmol, 2.19 g, 73% yield), which was directly used in the next step without any purification.[3]



Tricarbonyl (η^6-2-phenyl-1,3-dioxolane) chromium (0): A 10:1 mixture of Bu_2O/THF (22 ml), hexcarbonylchromium (0) (10.0 mmol, 2.2 g) and 2-phenyl-1,3-dioxolane (8.3 mmol, 1.25 g) was heated to 135 ºC under argon atmosphere. The mixture was stirred at this temperature for 48-72 hours until the formation of the first trace of green precipitate was observed. The cooled solution was filtered through celite and the solvent evaporated to give the crude complex which, after flash column chromatography on silica gel, gave the title compound as a yellow solid (5.9 mmol, 1.78 g, 71% yield).[3]

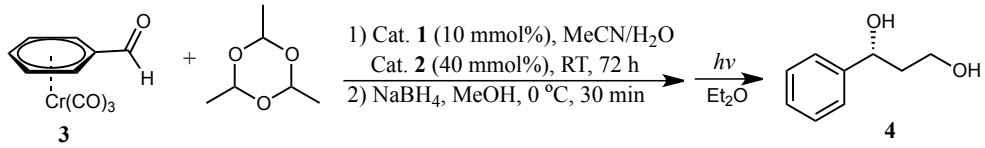
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.00-4.18 (m, 4H), 5.27-5.36 (m, 3H), 5.52-5.56 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.8(×2), 90.9 (×2), 91.2 (×2), 92.9, 101.4, 232.2; It is a known compound.[3]



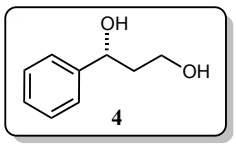
3

Tricarbonyl (η^6-benzaldehyde) chromium (0): Tricarbonyl (η^6-2-phenyl-1,3-dioxolane) chromium (0) (2.0 mmol, 0.6 g) was dissolved in THF (10 mL) and aqueous HCl (2.5 M, 5 mL) was added. The solution was stirred 5 hours and slowly turned to red. Then the mixture was extracted with ethyl acetate (3 × 5 mL) and the organic phases were combined and dried with anhydrous Na_2SO_4. After removal of the solvent, the crude products were purified by chromatography on silica gel to give a red solid (1.90 mmol, 488 mg, 95% yield).[3] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.31 (t, J = 6.2 Hz, 2H), 5.71 (t, J = 6.2 Hz, 1H), 5.95 (d, J = 6.5 Hz, 2H), 9.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 89.0 (×2), 94.6 (×2), 95.4, 187.6, 229.8; It is a known compound.[4]

3. General procedure for the cross-aldol reaction[5]

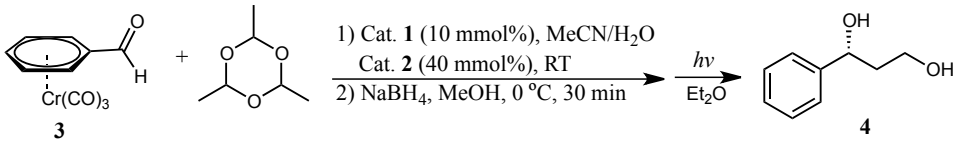


Catalyst **1** (10 mol%, 0.02 mmol, 6.7 mg), catalyst **2** (40 mol%, 0.08 mmol, 170.4 mg) and tricarbonyl (η^6-benzaldehyde) chromium (0) (0.2 mmol, 51.4 mg) were mixed in a brown vial with acetonitrile (0.6 mL). Then paraldehyde (137 μL, 5.0 eq., 1.0 mmol) and deionized water (1.8 μL, 0.1 mmol) were added and the brown vial was sealed and shaken at room temperature for 72 hours. After that the reaction mixture was filtered and washed with methanol (3 × 0.8 mL). The filtrates were combined and cooled to 0 ºC, then $NaBH_4$ (37.8 mg, 1.0 mmol) was added and the mixture was stirred for 20 minutes. After that, the reaction was quenched with aqueous NH_4Cl (2 mL) and extracted with ethyl acetate (3 × 5 mL). The organic layer was then washed with brine (2 mL), dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (5 mL) and this solution was exposed to air and light until a colorless solution with a green or brown precipitate resulted. Filtration through celite, concentration and purification of the crude product by column chromatography on silica gel (hexane/ethyl acetate 1:1), provided the pure product **4**[2] (0.11 mmol, 18 mg) as a colorless oil in 58% yield and 93% ee.



(*R*)-1-phenylpropane-1,3-diol (4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85-2.04 (m, 2H), 2.88 (brs, 1H), 3.34 (brs, 1H), 3.81 (t, *J* = 5.4 Hz, 2H), 4.92 (dd, *J* = 3.9, 8.4 Hz, 1H), 7.23-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.5, 61.5, 74.4, 125.6 (×2), 127.6, 128.5 (×2), 144.3; HPLC (Chiralcel AD-H, Hexane/*i*-propanol (97:3), flow rate = 1.0 mL min^{-1}, λ = 210 nm): t_{major} = 35.0 min, t_{minor} = 37.2 min.

4. Optimization of the reaction time [a]



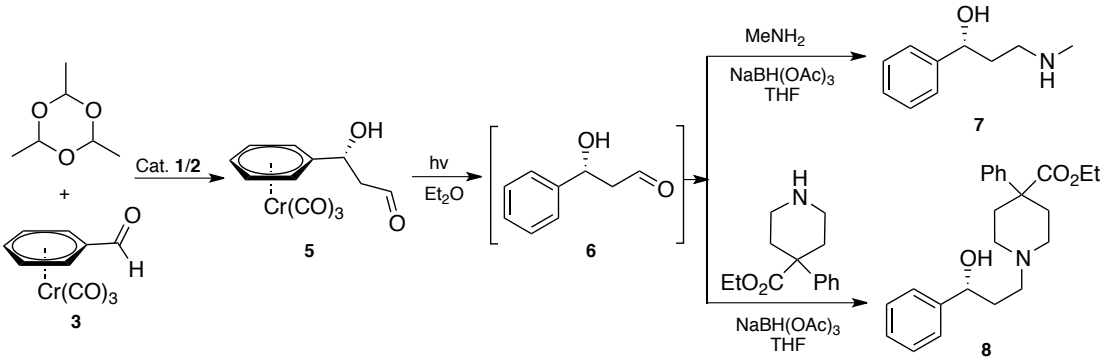
Entry	Time	Yield (%)[b]	ee (%)[c]
1	6	10	93
2	12	19	93
3	24	33	93
4	48	48	93
5	72	60	93
6	96	63	93

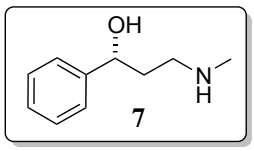
[a] Each reaction was carried out with tricarbonyl (η^6-benzaldehyde) chromium(0) (0.2 mmol), paraldehyde (1.0 mmol), H_2O (0.1 mmol), **1** (10 mol%) and **2** (40 mol%) in 0.6 mL MeCN at room temperature. [b] Yields estimated by ^{1}H NMR. [c] Determined by HPLC.

5. General procedure for catalyst recycling

Catalyst **1** (10 mol%, 0.02 mmol, 6.7 mg), catalyst **2** (40 mol%, 0.08 mmol, 170.4 mg) and tricarbonyl (η^6-benzaldehyde) chromium (0) (0.2 mmol, 51.4 mg) were mixed in a brown vial with acetonitrile (0.6 mL). Then paraldehyde (137 μL, 5.0 eq., 1.0 mmol) and deionized water (1.8 μL, 0.1 mmol) were added and the brown vial was sealed and shaken at room temperature. After 72 h, the mixture was filtered and washed with acetonitrile (3 × 1 mL), the filtrate being treated as described above to isolate the desired compound. As for the mixed catalysts recovered, they were washed with acetic acid (0.5 mL) and acetonitrile (4 × 1 mL), repeating this procedure several times until the solvent was colorless. After that, the mixed catalysts were dried at 40 ºC under vacuum for 6 h and then used in the next reaction.

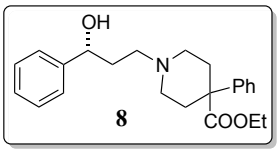
6. Synthesis and characterization of 7 and 8[1]





Catalyst **2** (40 mol%, 0.12 mmol, 255.6 mg), catalyst **1** (10 mol%, 0.03 mmol, 10.1 mg) and the tricarbonyl (η^6-benzaldehyde) chromium (0) (0.3 mmol, 77 mg) were mixed in a brown vial with acetonitrile (0.9 mL). Then, paraldehyde (5.0 eq., 206 μL, 1.5 mmol) and deionized water (2.7 μL, 0.15 mmol) were added and the brown vial was sealed and shaken at room temperature for 72 hours. After that, the reaction mixture was filtered and washed with acetonitrile (3 × 1.2 mL) and AcOH (15% in THF, 3 × 1.2 mL). The filtrates were combined and crude product **5** was obtained after removal of the solvent under vacuum. Then, this was dissolved in Et_2O (25 mL) and the resulting solution was exposed to air and light until a colorless solution with a green or brown precipitate resulted. Filtration through celite and concentration gave the crude product **6**.

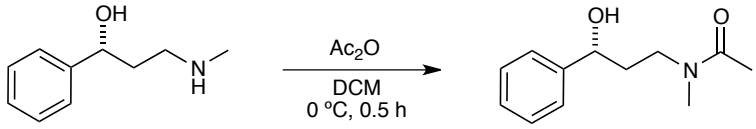
Crude product **6** was dissolved in anhydrous THF (3 mL) and methylamine (33 wt% in EtOH, 1.5 mmol, 140 mg) and anhydrous Na_2SO_4 (2.1 mmol, 0.3 g) were added. The mixture was stirred for 5 hours and then $NaBH(OAc)_3$ (2.0 eq., 0.6 mmol, 127 mg) was added in portions. After stirring overnight, the solution was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 8 mL). The organic layer was washed with brine (2 mL) and dried with anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude mixture, which was purified by fast column chromatography on silica gel, with CH_2Cl_2/MeOH/NH_4OH mixtures as eluent. In this manner, 20 mg of **7** (0.12 mmol, 35% overall yield for three steps) were obtained as a colorless oil with 95% ee (determined by chiral HPLC analysis of their *N*-acyl derivative according to a reported procedure[6]).
^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.72-1.96 (m, 2H), 2.45 (s, 3H), 2.81-2.95 (m, 2H), 4.03 (brs, 2H), 4.93 (dd, *J* = 3.1, 8.7 Hz, 1H), 7.21-7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 36.0, 36.8, 50.4, 75.5, 125.6 (×2), 126.9, 128.2 (×2), 145.1. $[\alpha]_D^{25}$ = +45.8 (*c* = 0.1, $CHCl_3$). It is a known compound.[7]



The crude **6** (see above) was dissolved in anhydrous THF (3 mL) and ethyl 4-phenylpiperidine-4-carboxylate (2.0 eq., 0.6 mmol, 140 mg) and anhydrous Na_2SO_4 (2.1 mmol, 0.3 g) were added. The mixture was stirred for 5 hours and then $NaBH(OAc)_3$ (2.0 eq., 0.6 mmol, 127 mg) was added in portions. After stirring overnight, the solution was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 8 mL). The organic layer was washed with brine (2 mL) and dried with anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue which was purified by fast column chromatography on silica gel, with CH_2Cl_2/MeOH/NH_4OH mixtures as eluent. In this manner, 40 mg of **8** (0.11 mmol, 36% overall yield for three steps) were obtained as a yellow oil with 99% ee (determined by chiral HPLC).

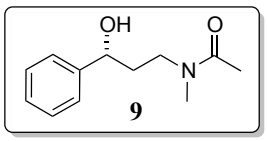
^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.17 (t, *J* = 7.1 Hz, 3H), 1.47-1.53 (m, 1H), 1.67-1.73 (m, 1H), 1.80-1.88 (m, 1H), 1.97-2.08 (m, 2H), 2.34 (t, *J* = 11.7 Hz, 1H), 2.55-2.67 (m, 4H), 2.87-2.88 (m, 1H), 3.10-3.13 (m, 1H), 4.09-4.16 (q, *J* = 7.1 Hz, 2H), 4.97 (dd, *J* = 2.7, 9.9 Hz, 1H), 7.20 - 7.40 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.1, 31.7, 33.5, 34.1, 46.4, 49.0, 50.5, 57.6, 61.0, 74.7, 125.7 (×2), 127.1 (×2), 127.2 (×2), 128.3 (×2), 128.6, 128.6 (×2), 144.9, 174.1. HPLC (Chiralcel IA, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 215 nm): t_{major} = 20.4 min, t_{minor} = 17.0 min. HRMS calcd for $C_{23}H_{29}NO_3$ $(M + H)^+$: 368.2220, found: 368.2213. $[\alpha]_D^{25}$ = +21.5 (*c* = 0.1, $CHCl_3$). IR (ATR): ν = 539, 698, 761, 858, 1022, 1106, 1177, 1214, 1447, 1496, 1601, 1721, 2586, 2937 cm^{-1}.

7. Preparation of the acetylated compound 9[6]



7 **9**

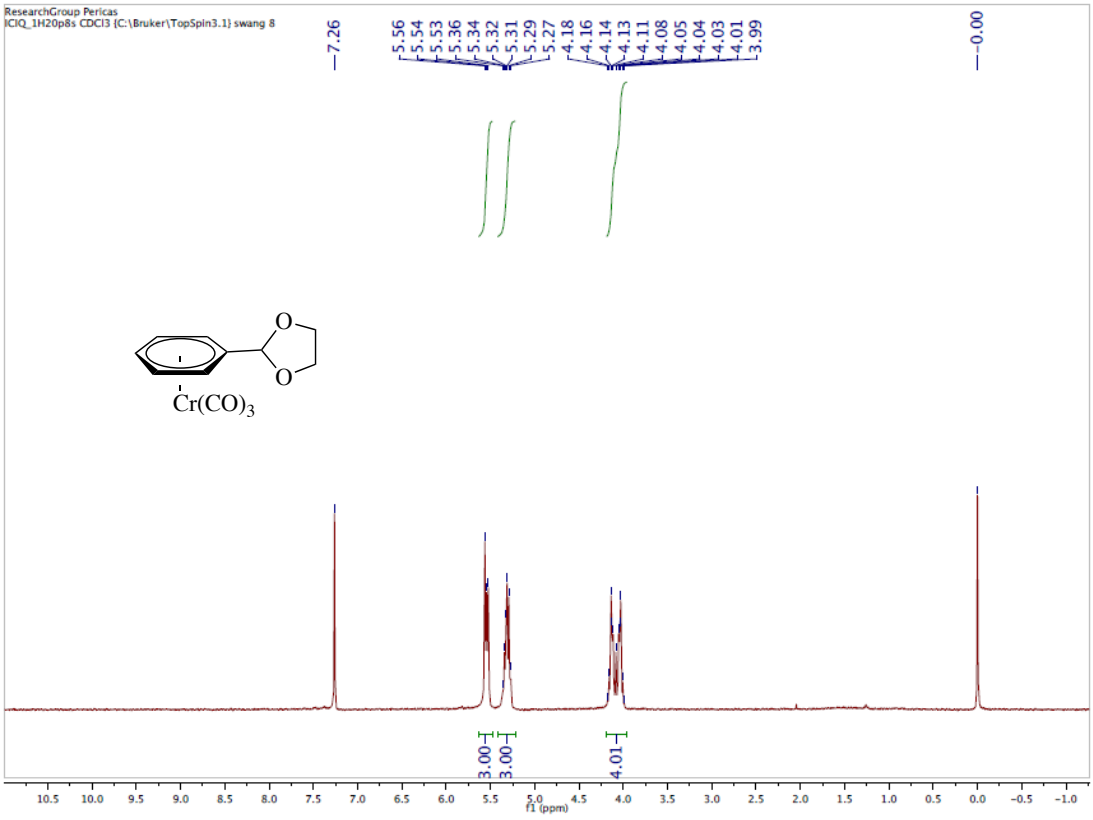
To a solution of **7** (0.20 mmol, 33 mg) in CH_2Cl_2 (3 mL) at 0 °C was added acetic anhydride (0.20 mmol, 20 μL). The resulting reaction mixture was stirred vigorously at this temperature for 30 min. After removal of the solvent, the crude product was purified by column chromatography on silica gel (eluting with CH_2Cl_2/MeOH, 10:1) to afford the desired *N*-acyl derivative **9** as a mixture of rotamers.

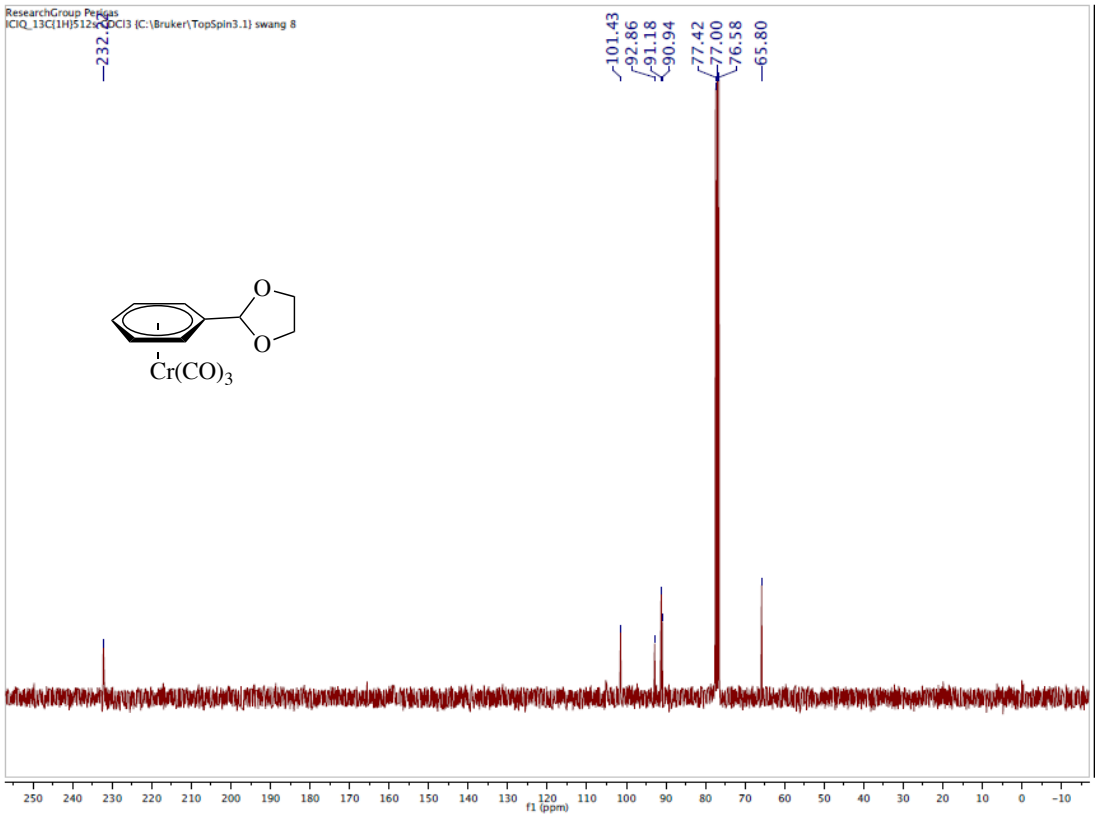


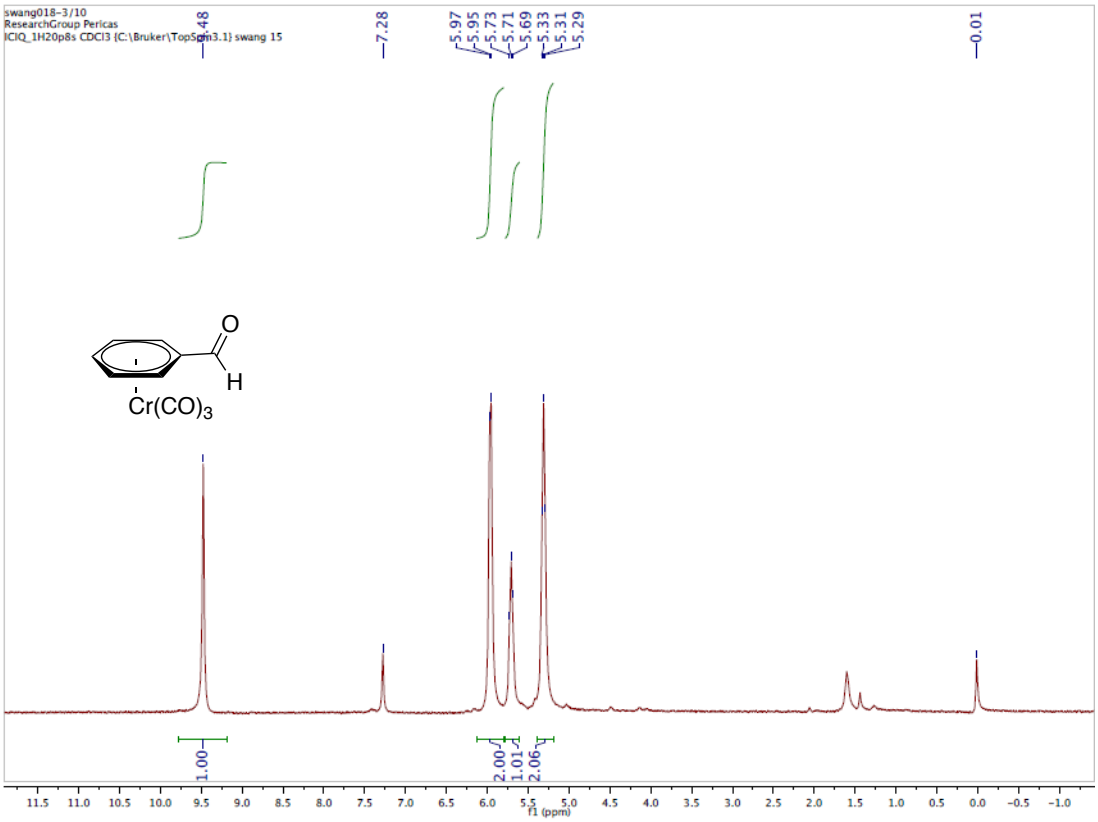
9

(*R*)-*N*-(3-Hydroxy-3-phenylpropyl)-*N*-methylacetamide (9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77-1.85 (m, 1H), 1.91-1.99 (m, 1H), 2.07 (s, 0.7H), 2.09 (s, 2.2H), 2.90 (s, 0.7H), 3.00 (s, 2.3H), 3.07-3.13 (m, 0.8H), 3.35-3.52 (m, 0.5H), 4.05-4.15 (m, 0.8H), 4.50-4.56 (m, 1.4H), 4.68 (t, *J* = 6.5 Hz, 0.2H), 7.22-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.6, 33.1, 36.3, 36.7, 37.3, 44.5, 47.4, 69.9, 71.5, 125.6, 127.1, 127.9, 128.3, 128.7, 144.0, 170.7, 172.1; HPLC (Chiralcel OD-H, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 222 nm): t_{major} = 22.5 min, t_{minor} = 17.7 min. It is a known compound.[6]

8. ^{1}H and ^{13}C NMR spectra






swang018-3/10
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5.97
5.95
5.73
5.71
5.69
5.33
5.31
5.29
0.01
O
H
Cr(CO)3
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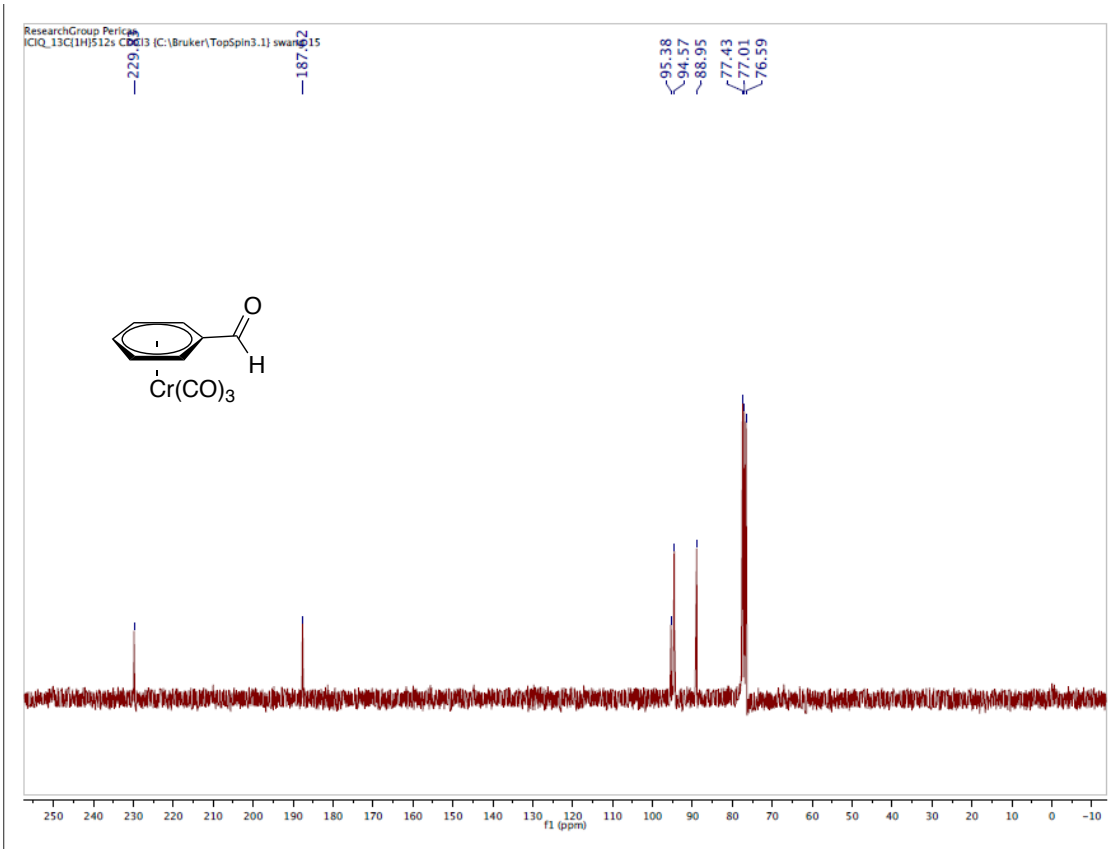
2.00
1.01
2.06
f1 (ppm)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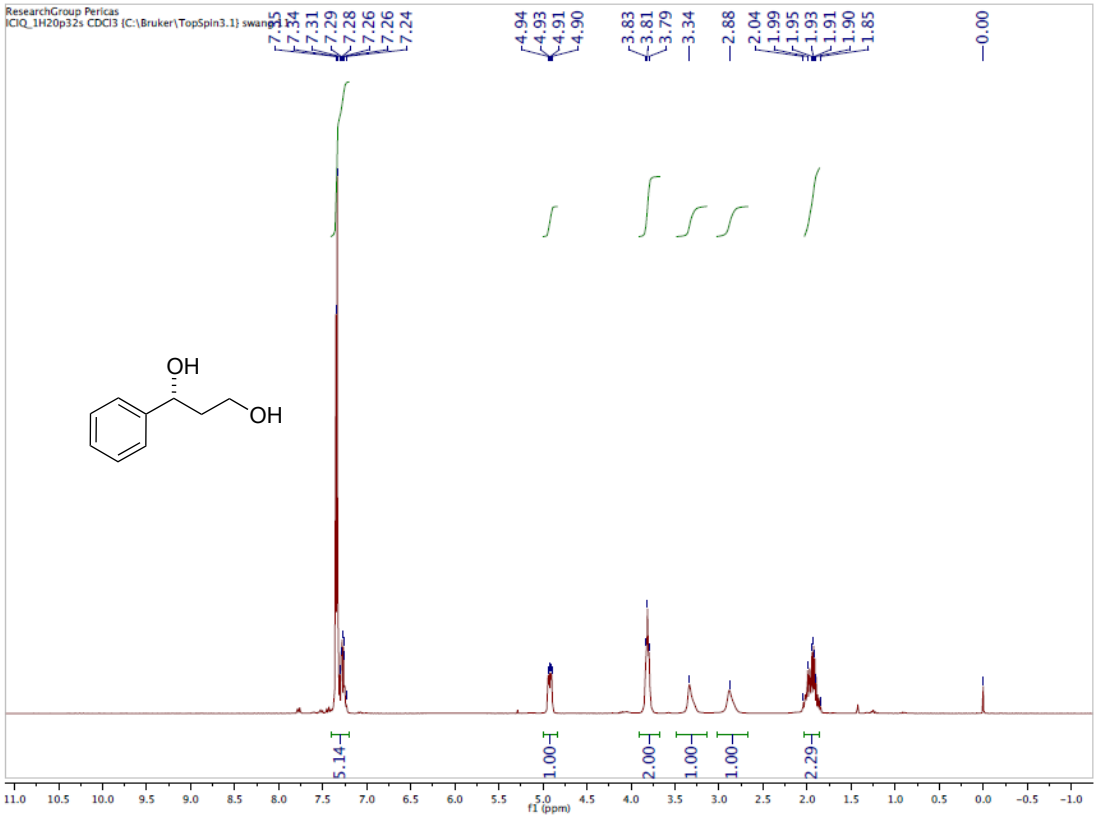
Cr(CO)3
f1 (ppm)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3.83
3.81
3.79
3.34
2.88
2.04
1.99
1.95
1.93
1.91
1.90
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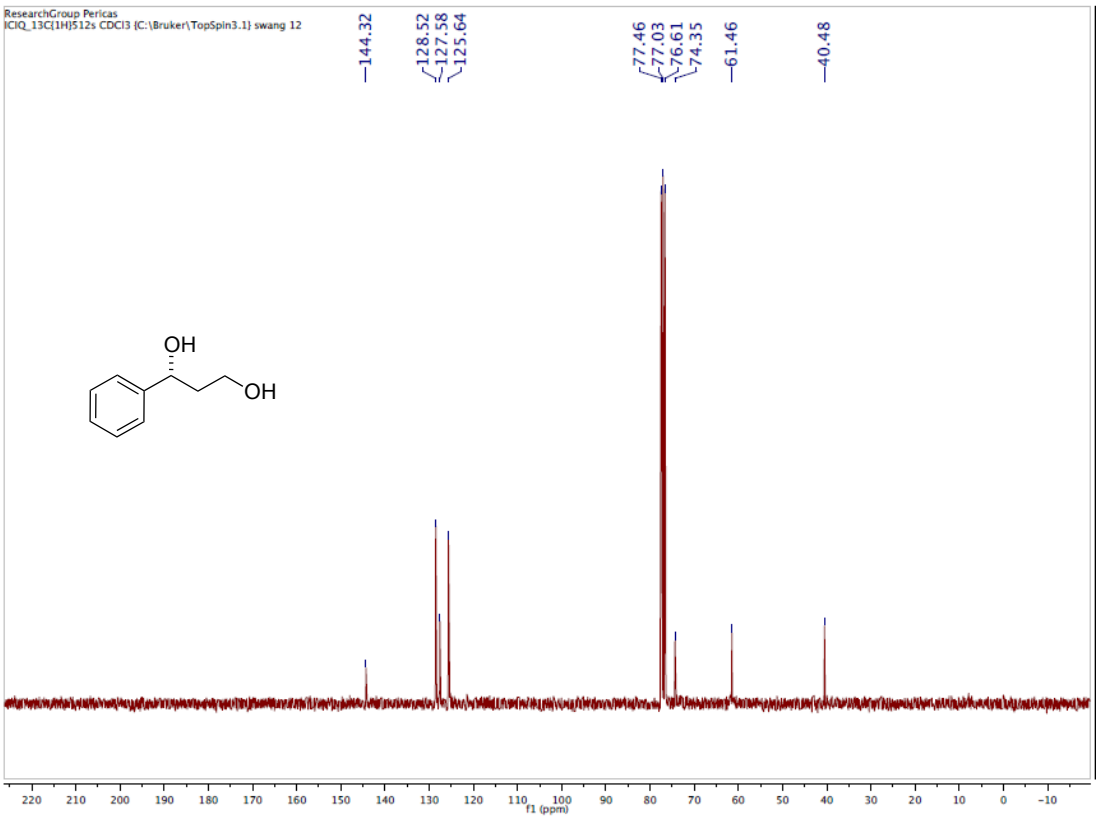
2.00
1.00
1.00
2.29
f1 (ppm)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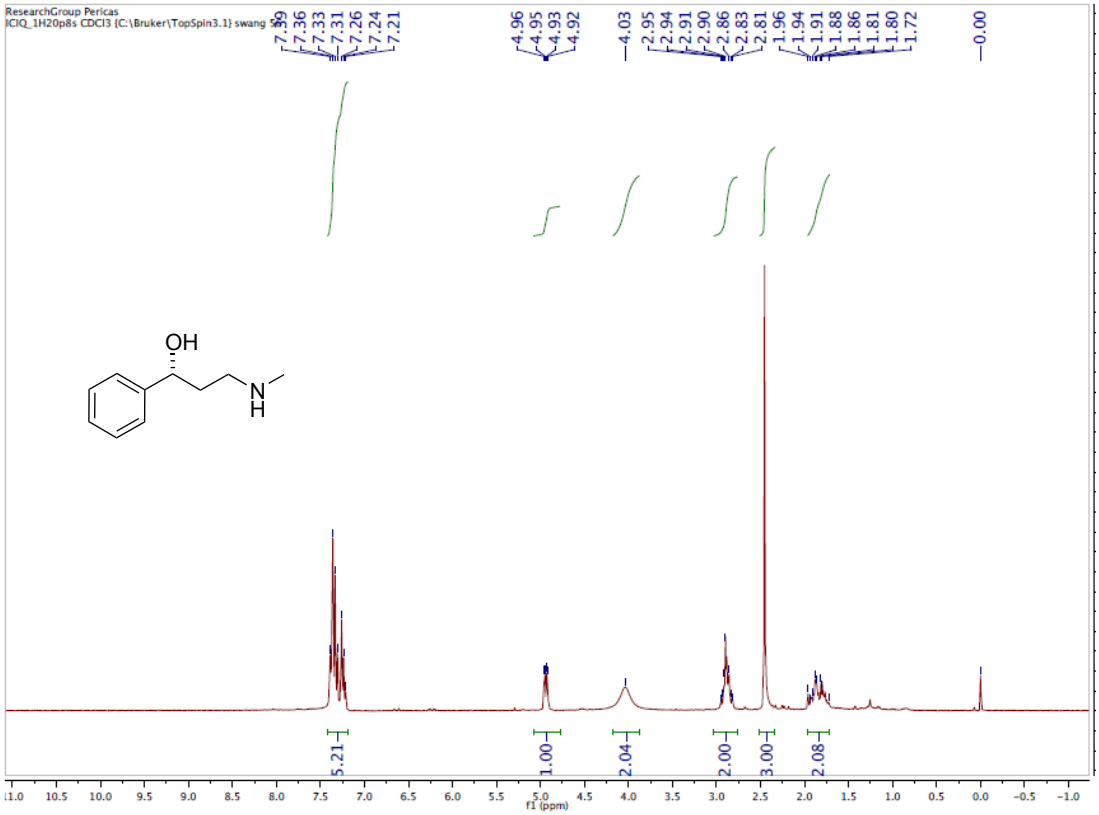
76.61
74.35
61.46
40.48
OH
OH
f1 (ppm)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2.91
2.90
2.86
2.83
2.81
1.96
1.94
1.91
1.88
1.86
1.81
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H
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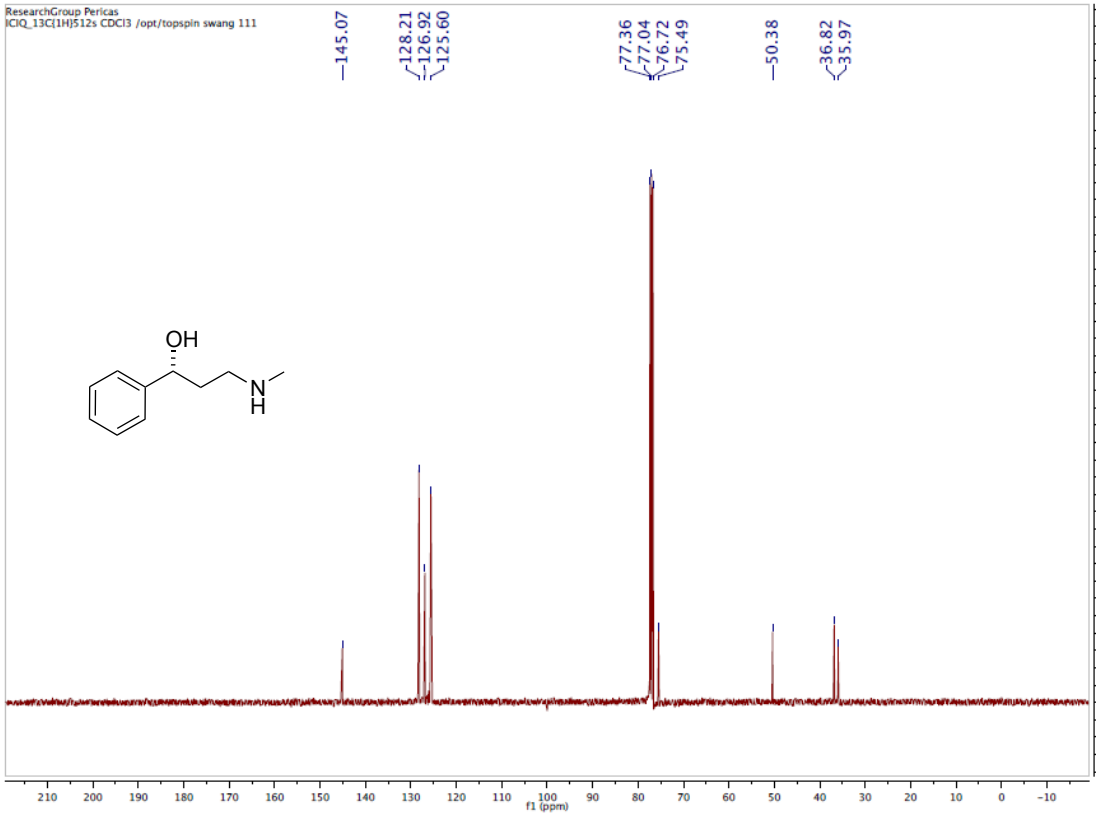
2.04
2.00
3.00
2.08
f1 (ppm)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35.97
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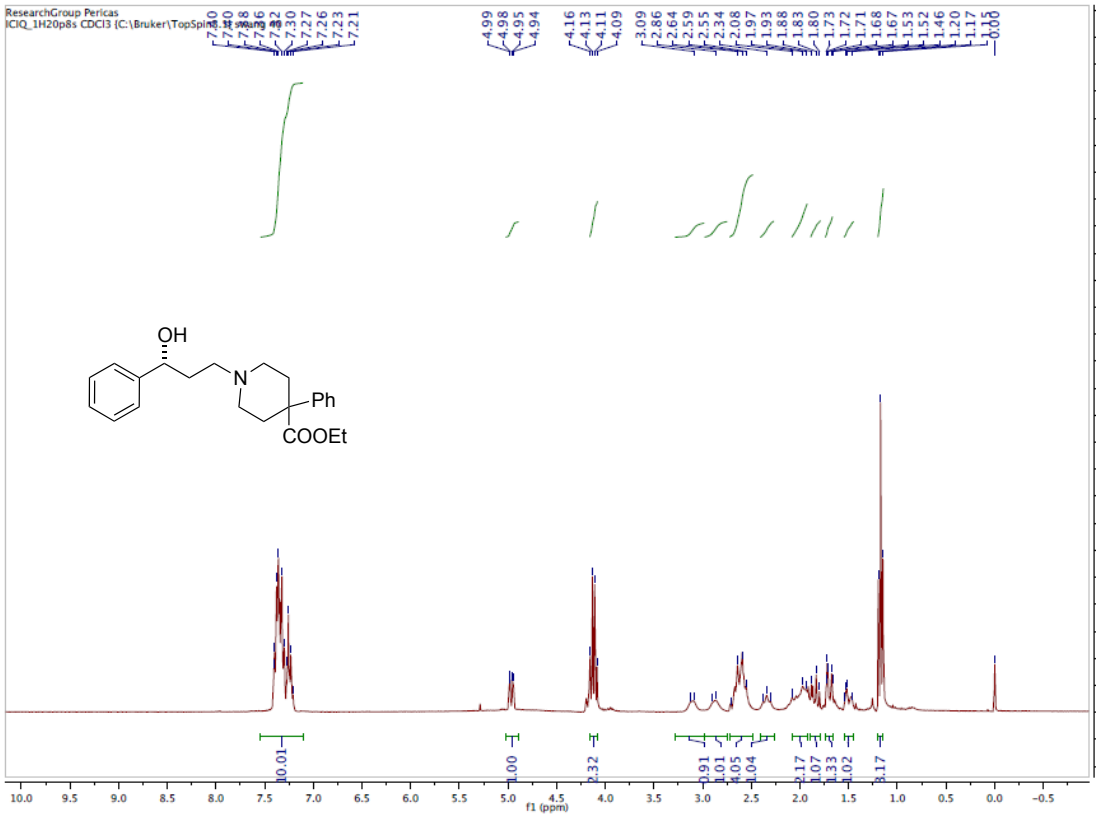
N
H
f1 (ppm)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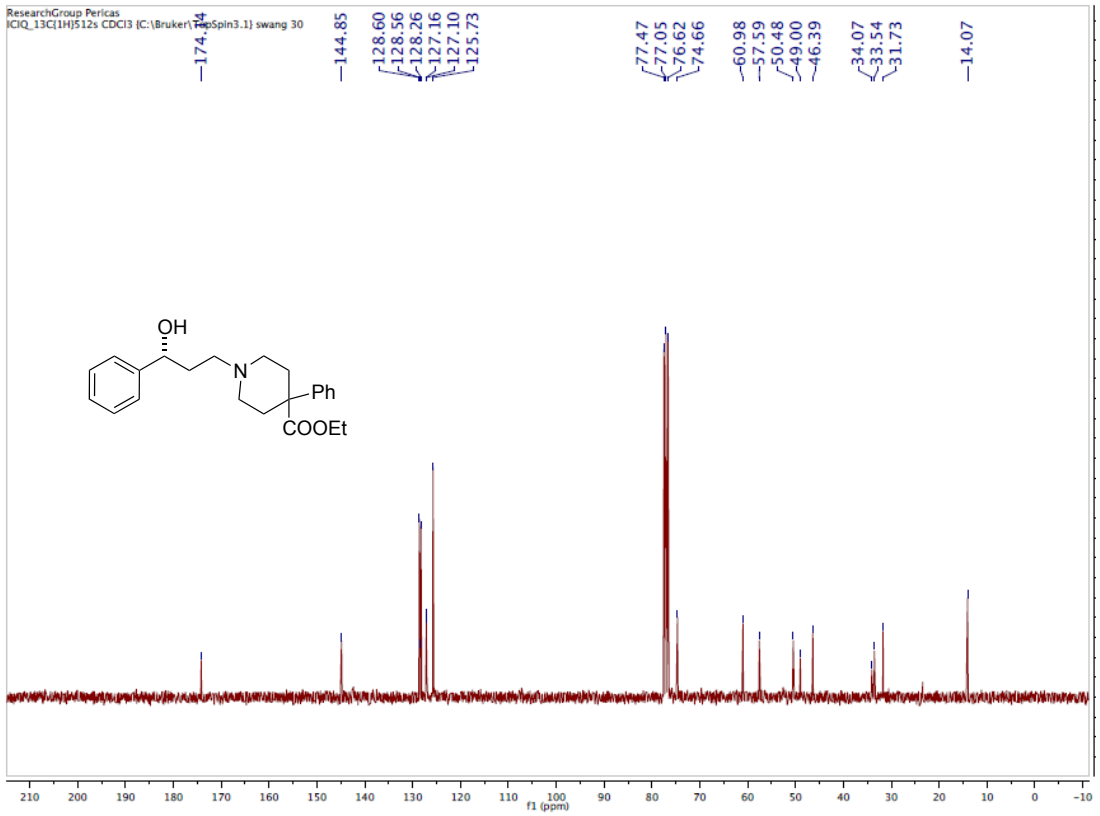
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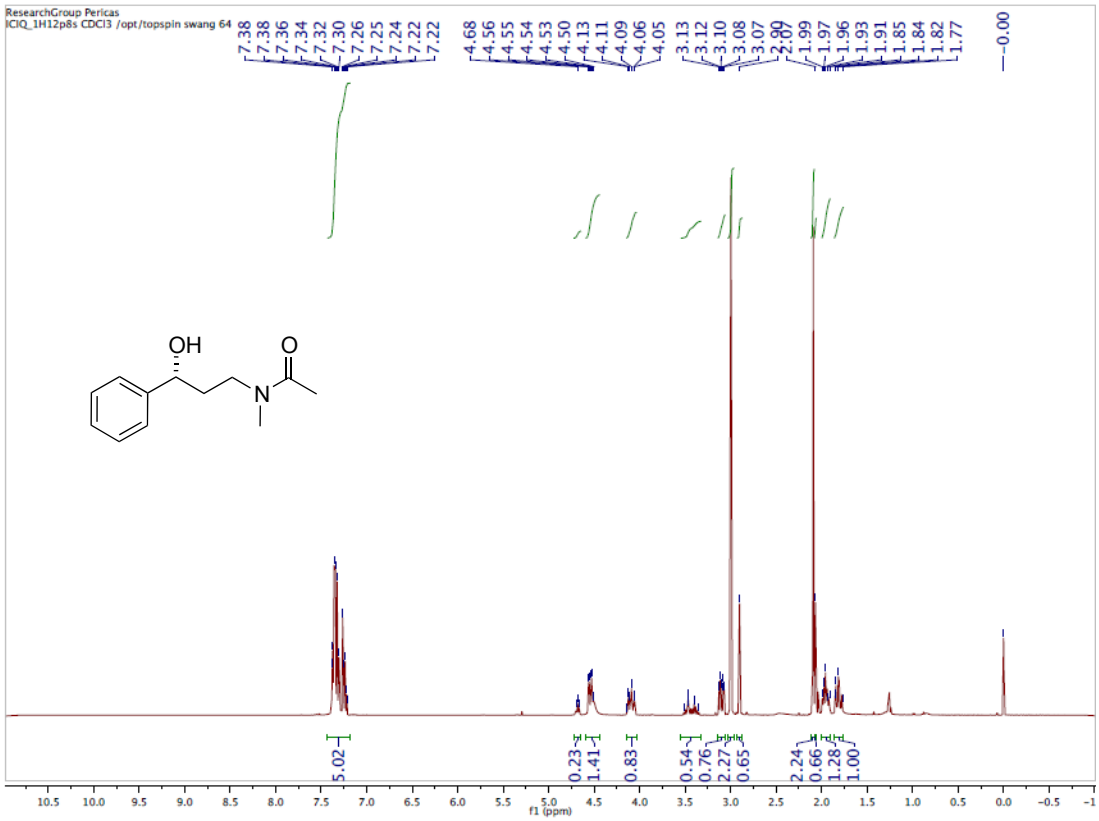
Ph
COOEt
f1 (ppm)


ResearchGroup Pericas
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4.54
4.53
4.50
4.13
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4.06
4.05
3.13
3.12
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OH
O
N
5.02
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0.66
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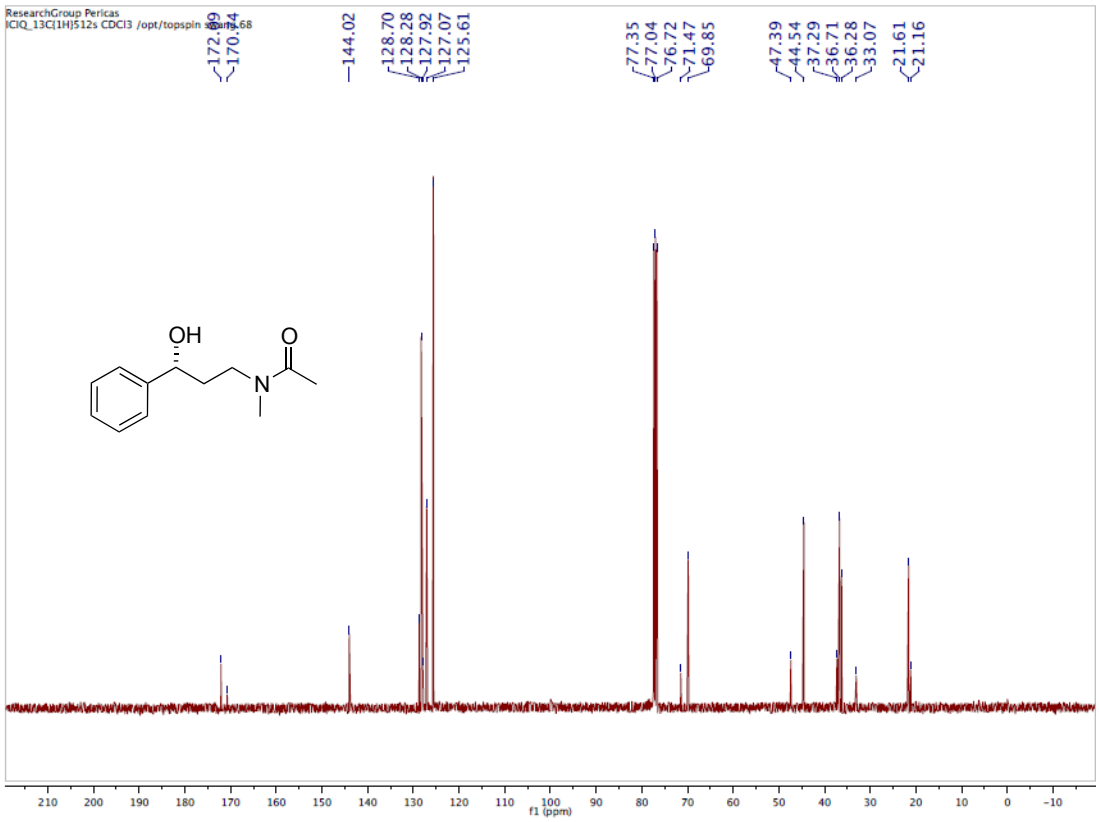
1.00
f1 (ppm)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69.85
47.39
44.54
37.29
36.71
36.28
33.07
21.61
21.16
OH
O
N
f1 (ppm)

9. References

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Conclusions

The discovery and design of organocatalysts with better efficiency, able to promote new transformations and reaching higher turnover numbers has attracted a lot of attention in organocatalysis. This thesis focuses on the synthesis of organocatalysts, especially polymer-supported ones and their application in various asymmetric transformations.

Chapter II describes the development of a H-bond-directing aminocatalyst for the asymmetric [4+2] cycloaddition reactions of alkylidene pyrazolones with enals. The more hindered 4-hydroxy dinaphthylprolinol catalyst has been prepared and displayed higher reactivities and enantioselectivities in the [4+2] cycloadditions, affording the tetrahydropyranopyrazole derivatives containing three contiguous stereocenters with good results (up to 89% yield, 13:1 dr, and 99% ee).

Chapter III summarizes a formal [4+2] cycloadditions of unsaturated heterocycles with in situ activated arylacetic acids catalyzed by a robust, immobilized isothiourea. This annulation strategy represents an efficient approach to access a series of six-membered heterocycles and spiro-heterocycles in high yields and very high enantioselectivities (32 examples, 97% mean ee). In addition, recyclability of the immobilized isothiourea catalyst (11 cycles, accumulated TON of 76.8) and its application in continuous flow process (no decrease in yield or ee after 18 h) are also demonstrated.

In order to explore new transformations by utilizing this immobilized isothiourea catalyst, **Chapter IV** investigates a periselective asymmetric [8+2] annulation reaction between chiral ammonium enolates (generated in situ from carboxylic acids) and azaheptafulvenes. The [8+2] annulation reactions proceeds smoothly catalyzed by the immobilized isothiourea, yielding the cycloheptatriene-fused pyrrolidone derivatives in high yields and excellent stereoselectivities (up to 85% yield, >20:1 dr, and 98% ee). Moreover, we have demonstrated the derivatization of the resulting [8+2] cycloadducts to give bridged-polycyclic products via [4+2] cycloaddition, which represents an efficient stereoselective synthetic approach to polycyclic compounds.

Finally, **Chapter V** focuses on the cascade deoligomerization/cross-aldol reactions of electron-poor benzaldehydes with paraldehyde promoted by a dual catalytic system (PS-diarylprolinol catalyst and PS-sufonic acid catalyst). The dual catalytic system can be recycled ten times by simple filtration of the polymer mixture and mild acidic washing to recover full performance. To overcome the limitation of the deoligomerization/cross-aldol reaction with benzaldehyde, we synthesized η^6-benzaldehyde $Cr(CO)_3$ as an alternative and successfully applied it in this cascade process. The application of the resulting diol product was proven by reductive amination reaction, affording the well-known drug (*R*)-phenoperidine or intermediates of (*R*)-fluoxetine and (*R*)-atomoxetine.

List of Publications

1. "Highly Enantioselective Cross-Aldol Reactions of Acetaldehyde Mediated by a Dual Catalytic System Operating under Site Isolation"
   Xinyuan Fan, Carles Rodríguez-Escrich, **Shoulei Wang**, Sonia Sayalero, and Miquel A. Pericàs, *Chem. Eur. J*. **2014**, 20, 13089−13093.

2. "H-Bond-Directing Organocatalyst for Enantioselective [4+2] Cycloadditions via Dienamine Catalysis"
   Shoulei Wang, Carles Rodríguez-Escrich, and Miquel A. Pericàs, *Org. Lett*. **2016**, 18, 556−559.

3. "Asymmetric [4 + 2] Annulation Reactions Catalyzed by a Robust, Immobilized Isothiourea"
   Shoulei Wang, Javier Izquierdo, Carles Rodríguez-Escrich, and Miquel A. Pericàs, *ACS Catal.* **2017**, 7, 2780−2785.

4. "Catalytic Asymmetric [8+2] Annulation Reactions Promoted by a Recyclable Immobilized Isothiourea"
   Shoulei Wang, Carles Rodríguez-Escrich, and Miquel A. Pericàs, *Angew. Chem. Int. Ed.* **2017**, 56, 15068−15072.

5. "Synthesis of Diverse 11- and 12-Membered Macrolactones from a Common Linear Substrate Using a Single Biocatalyst"
   Michael M. Gilbert, Matthew D. DeMars, Song Yang, Jessica M. Grandner, **Shoulei Wang**, Hengbin Wang, Alison R. H. Narayan, David H. Sherman, K. N. Houk, and John Montgomery, *ACS Cent. Sci.* **2017**, 3, 1304−1310.

6. "A Site Isolation Enabled Organocatalytic Approach to Enantiopure γ-Amino Alcohol Drugs"
   Shoulei Wang, Carles Rodríguez-Escrich, Xinyuan Fan, and Miquel A. Pericàs, *Submitted*.