# Asymmetric Supramolecular-organocatalysis: Design, Scope and Applications

A Thesis
Submitted for the Degree of

*Doctor of Philosophy*


By

**SHRUTHI K. S.**




**SCHOOL OF CHEMISTRY**
**UNIVERSITY OF HYDERABAD**
**HYDERABAD-500 046, INDIA**


**September 2016**

*DEDICATED TO*

*MY GRANDMOTHER*

# *DECLARATION*

*I hereby declare that the entire work embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the guidance of* ***Prof. Dhevalapally B. Ramachary*** *and that it has not been submitted elsewhere for any degree or diploma. In keeping with the general practice, due acknowledgements have been made wherever the work described is based on the findings of other investigators.*

***SHRUTHI K. S.***
***(Candidate)***

**Prof. Dhevalapally B. Ramachary**
**Professor of Chemistry**
**Catalysis Laboratory**
**School of Chemistry**
**University of Hyderabad**
**Gachibowli, Hyderabad-500046, India**
**Work: +91-40-23134816**
**Fax: +91-40-2301246**
**E-mail: ramsc@uohyd.ac.in**

# *Certificate*

*Certified that the work contained in the thesis entitled "**Asymmetric Supramolecular-organocatalysis: Design, Scope and Applications"** has been carried out by **Ms. Shruthi K. S.** under my supervision and the same has not been submitted elsewhere for a degree.*

**Prof. Dhevalapally B. Ramachary**
**(Thesis Supervisor)**

**Dean**
**School of Chemistry**
**University of Hyderabad**

# *CONTENTS*

# *ACKNOWLEDGEMENTS*

*I am greatly indebted to **Prof. Dhevalapally B. Ramachary**, my research supervisor, for his inspiring guidance, support and constant encouragement throughout the course of the present investigations. His enthusiastic supervision is incomparable and it has been a great privilege and honour to be associated with him.*

*I take this opportunity to thank Prof. M. Durga Prasad, Dean, School of Chemistry for providing all the facilities needed for our research. I extend my sincere thanks to former Deans Prof. M. V. Rajasekharan, Prof. D. Basavaiah and Prof. M. Periasamy. My doctoral committee members Dr. R. Balamurugan, Dr. P. Ramu Sridhar and all the faculty members of School of Chemistry for their timely help and co-operation during my Ph. D. program.*

*I consider it as an honor to show my gratitude to my teachers and professors, Mrs Latha Jagadeesh, Mr. Jagadeesh, B. Basavaraju, Loka Prakash Narayan and Prof. Kempegowda. My sincere thanks to Prof. D. Channegowda, for their inspiring classes and their motivational talks which I never wanted to end at any times.*

*My special thanks to Dr. K. Anebouselvy for her care, timely help, and valuable suggestions as and when I approached.*

*I am thankful to all my seniors and labmates, Dr. M. Kishor, Dr. Vijayendar Reddy, Dr. R. Sakthidevi, Dr. Rosy Mallik, Dr .Ch. Venkaiah, Dr. M. Shiva Prasad, Dr. A. B. Shashank, Dr. P. Srinivasa Reddy, Dr. R. Madhavachary, Dr. P. Murali Krishna, Dr. A. Suresh, Dr. Mallikarjun Reddy, Dr. Sreekanth Reddy, Dr. P. Swamy, Dr. G. Thirupathi, Karthik, Shashi, Prabhakar, Jagjeet, Surendra, Anif, Pritam, Akram, Gorachand, Sailalitha, Padhma, Divya, Jyothi, Vijaya, and Mounika for their co-operation and discussions. My special thanks to Dr. Sakthidevi, Dr. Rosy Mallik, Dr. Venkaiah, Dr. Shiva Prasad, Dr. Shashank, Dr. Srinivasa Reddy, Dr. Madhav, Dr. Murali, Anif and Jaggu for their support and useful suggestions and for being available as a friend at all times.*

*I acknowledge the help and support provided by the technical and non-teaching staff of the School of Chemistry. I also thank Dr. P. Raghavaiah (For his great help in solving my all crystal data), Mrs. Vijayalaxmi, Satyanarayana, Thurabauddin, Durgesh Singh (for their help in recording NMR immediately whenever I am in need) Bhaskara Rao, Mrs. Asia Perwej, G. S. Maruthi (for helping me in doing HRMS experiments) V. M. Shetty, A. R. Shetty, Deelip,*

*Venkatesh, Aleem (Late), Geetha, Kumar Reddy, Anand, Sudhakar, Santosh and sathyam for their timely help and support.*

*My special thanks to Dr. Balamurugan's research group for their generous help and useful discussions. It gives me immense pleasure to thank my seniors and friends of School of Chemistry Leela, Harati, Suthanuka, Tamilarasi, Lasiya, Srujana, Dr Sudharani, Thamilarsan, Prasadh, Chandrahash, Ramesh, Basha, Suresh, Satyanarayana, Mohan, Uday, Ramesh, Anand, Harish, Edukondalu, Shanmugam, Lingaiah, Showkat, Junaid, Narasimha, Suman, Satish, Naveen, Nagamaiah, Surya, Dr. Kishore, Dr. Prabhu anna, and Dr Karunakar extending their helping hands at the needful times. I would like to acknowledge the timely help of Dr. Sathish, Dr. Geetha, and Amala for spending their valuable time in solving my x-ray crystal data.*

*I thank my Kannada friend's in HCU Latha, Ashwini and Pushpa for their help, care, support and encouragement.*

*My heartfelt and very special thanks are to my friend Amaleshwari Rasamsetty for her timely help, unconditional care and also being with me at all tough and happy moments. My Special thanks are to my friend Ramakrishna for his care and support. I thank my friends Ranjini, Swati, Ramana, Saktivelu, Dr. Ram kumar, and Krishna for creating a wonderful atmosphere and giving me happy moments.*

*I would like to express my thanks to my close friends of all time Akshatha, Latha, Shubha shree (Late), Divya, Arpitha and Vanitha for supporting and encouraging me also for being with me at all tough and happy moments.*

*My special thanks to my little brother and Sister Vedha Vyash and Logeshwari, they made me to feel like I am staying with family in Hyderabad with their love and affection.*

*The word thanks becomes meaningless when it comes to my Family, without their support coming to this stage would have been merely a dream. They are the reason for what I am today in the society. I become wordless to express their support, guidance, service and love towards me. In that my grandmothers* ***Bommamma*** *(Late), Huchchamma, and Chikkatayamma their support care love is the major Part in my life, I find that dedicating this thesis to them is a minor recognition of their relentless effort and unconditional care.*

*I feel immensely happy to express my love to my mother Prema, father Shivaraju, my sister Spoorthy, brother Yashvanth, nanna atheyandiru Thripuramba, Jayalakshmamma, Prema, Shobha, Anitha, and Nagarathna. Nanna mavandiru, Prakash, Chandru, Raju, Shivanna (late),*

*Appaji Gowda, Krishne Gowda, Sadhashiva, Mahesh and Lokesh. My cousin sisters and their husbands Bharathi, Nagesh, Latha, Krishne Gowda, Saritha, Kumar, My cousin Brothers Suprith, Hemanth and Samarth for their support, care and affection, without which the journey of life would not have been possible.*

*National Single Crystal X-ray Facility, funded by DST (New Delhi) in School of Chemistry is highly acknowledged. I am thankful to the IGM library for providing excellent books and journals. Financial assistance by CSIR (New Delhi) is gratefully acknowledged.*

***Shruthi K. S.***

# *PREFACE*

*Amino acid catalyzed asymmetric reaction found its rediscovery after many scientists envisioned the importance of reactive intermediate formation and weak interactions involved in antibody catalyzed reactions. The first and foremost utilization and demonstration of the covalent and non-covalent interactions of catalyst L-proline with substrate in the intermolecular aldol reactions began the revolution of amino acid catalysis. The development, growth and modification in asymmetric amino acid-catalysis become tremendous in the past decade. Other forms of amines/amino acids catalyzed asymmetric reactions include thiourea activated Michael reactions, chiral amine activated Diels-Alder reactions through enamine, iminium or hydrogen bonding activation and imidazolinium salt catalyzed Michael reactions through π-π interactions and many more, discovered based on the construction of covalent and non-covalent interactions from amines/aminoacids. All these catalysis together shed light on the importance of weak interactions in the transition state for high selectivity in asymmetric reactions and it opens a new paradigm of catalysis called supramolecular-organocatalysis. This catalysis provides one of the ways to catalyze a wide range of reactions, by using the multi-tasking ability and multiple interactions of the substrate and catalyst in the transition state.*

*In this strategy where substrates with active functional group are used, gains the dual advantages of neighboring group participating in the pre-transition state. This in turn, opens a way to understand and to explore the involvement of the active functional group in the pre-transition state to achieve high selectivity and reactivity. This work is one-such result of studies towards utilization of highly functionalized substrates and observing participation of pre-transition state assembly in the supramolecular-organocatalytic asymmetric reactions.*

*The present thesis entitled "**Asymmetric Supramolecular-organocatalysis: Design, Scope and Applications**" describes the asymmetric synthesis of highly functionalized chiral molecules in all sections, a brief introduction is provided to keep the present work in proper perspective. The compounds are sequentially numbered (bold) and references are marked sequentially as superscript and listed at the end of the thesis. All the Figures included in the thesis were obtained by DIRECT PHOTOCOPY OF THE ORIGINAL SPECTRA, and in some of them uninformative areas have been cut to save the space.*

*The first chapter illustrates the involvement of ortho-azido functionality in the transition state and in reaction strategy, 1-azido-2-(2-nitrovinyl)benzenes were reacted with acetone in the presence of L-phenylglycine and quinidine-NH-thiourea catalytic mixture. These results are discussed in this chapter. The Michael reaction yielded the chiral keto azides with high selectivities. Reductive amination of chiral keto azides yielded the chiral tetrahydroquinoline with high enatio- and diastereoselectivities. The Michael reaction proceeded well, through conformationally flexible supramolecular 22-membered pre-transition state intermediate yielding Michael adducts with good yields and excellent enantio-selectivities. Furthermore, evidence for the existence of supramolecular assembly in the pre transition state has been analyzed through on-line ESI-HRMS analysis.*

*The second chapter describes modularly designed supramolecular organocatalyst catalyzed asymmetric Michael addition of ketones to nitro-olefins. The Michael reaction of functionalized N-Cbz-NH-(E)-2-(2-nitrovinyl)anilines with various functionalized cyclic/acyclic ketones catalyzed by presence of D-proline and quinine-NH-thiourea catalytic mixture. The Michael reactions yielded the chiral carbamates with high enatio- and diastereoselectivities. Chiral carbamates on treatment with trifluoroacetic acid undergo aminal formation followed by a dehydration protocol to furnish enantiomerically pure medicinally important tetrahydroacridines with good yields and high selectivities. The Michael reaction proceeded well, through a supramolecular 19-membered pre-transition state intermediate yielding Michael adducts with good yields and excellent enantio-selectivities. Furthermore, evidence for the existence of supramolecular assembly in the pre transition state has been analyzed through on-line ESI-HRMS analysis.*

*In continuation to study the involvement of ortho-azido functionality in the pre-transition state and described for the first time the L-DMTC/ TFA-catalyzed asymmetric LLB-A reaction of cyclohexanones and acetone with less reactive o-azidobenzaldehydes at ambient conditions to furnish the optically active functionalized (2-azidophenyl)alcohols with very good yields, dr, and ee values. These results are discussed in the third chapter. The optically active functionalized (2-azidophenyl)alcohols were transformed into different molecular scaffolds in good yields with high selectivity through Lewis acid mediated $NaBH_4$ reduction, aza-Wittig and Staudinger*

*reaction (azide reduction), followed by oxidative cyclizations, allenone synthesis, and click reaction, respectively. Furthermore, the mechanistic synergy of L-DMTC with TFA to increase the rate and selectivity of LLB-A reaction in DMSO-$d_6$ is explained with the controlled and on-line NMR experiments.*

# *LIST OF ABBREVIATIONS*

| | |
|---|---|
| Ac | acetyl |
| AcOH | acetic acid |
| $Ac_2O$ | acetic anhydride |
| Ala | Alanine |
| Anal. | analysis |
| aq. | aqueous |
| Ar | aryl |
| BINOL | 1, 1'-Bi-2-naphthol |
| Bn | benzyl |
| Boc | butyloxy carbonyl |
| Bp | boiling point |
| br | broad |
| Bu | butyl |
| *t*Bu or $^t$Bu | *tertiary*-butyl |
| *n*-BuLi | *n*-butyl lithium |
| calcd. | calculated |
| cat. | Catalytic |
| CIF | Crystallographic Information file |
| cm | centimeter |
| D-CSA | camphor sulphonic acid |
| CSP | chiral stationary phase |
| Cbz | benzyloxy carbonyl |
| dABq | doublet of AB quartet |
| DCE | 1,2-dichloroethane |
| DCM | dichloromethane |
| dd | doublet of doublet |
| ddd | doublet of doublet of doublet |
| dt | doublet of triplet |
| de | diastereomeric excess |
| DEPT | distortionless enhancement by polarization transfer |
| DMAP | dimethylaminopyridine |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| DPP | diphenyl prolinol |
| DPP-OTMS | diphenyl prolinol silyl ether |
| L-DMTC | (*R*)-5,5-dimethyl thiazolidinium-4-carboxylate |
| DIBAL-H | Diisobutylaluminium hydride |
| dr | diastereomeric ratio |
| dt | doublet of triplet |
| ee | enantiomeric excess |
| Eq. | equation |
| equiv. | equivalent(s) |
| Et | ethyl |
| EWG | electron withdrawing group |
| ESI | Electrospray ionization |

| | |
|---|---|
| Fg | functional group |
| Fig. | figure |
| gm | gram (s) |
| h | hour (s) |
| Hz | hertz |
| Hex | hexyl |
| HPLC | high-performance liquid chromatography |
| HRMS | High resolution mass spectrometry |
| i-Pr | isopropyl |
| IR | infrared |
| IBX | 2-iodoxybenzoic acid |
| lit. | literature |
| LLB-A | List-Lerner-Barbas aldol |
| m | multiplet |
| *m*-CPBA | *m*-chloro perbenzoic acid |
| M | molarity |
| Mp. | melting point |
| Me | methyl |
| mg | milligram (s) |
| mL | milliliter |
| µL | microliter |
| mmol | millimole |
| NMR | nuclear magnetic resonance |
| NMP | *N*-methylpyrrolidine |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| Pg | protecting group |
| ppm | parts per million |
| *p*-TSA | *p*-toluenesulfonic acid |
| py | pyridine |
| pr | propyl |
| q | quartet |
| quin. | quintet |
| rt/RT | room temperature |
| s | singlet |
| sec | secondary |
| t | triplet |
| td | triplet of doublet |
| tert | tertiary |
| TBD | 1,5,7-Triazabicyclo[4.4.0]dec-5-ene |
| TBS | *tertiary* butyl dimethyl silyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| Thr | Threonine |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| *p*TSA | *para* toluenesulphonic acid |
| TsCl | toluenesulphonyl chloride |
| Ts | Toluenesulphonyl |
| TS | Transition state |
| UV | ultraviolate |

# Asymmetric Supramolecular-organocatalysis: Design, Scope and Applications

## 1. ABSTRACT

Functionalized chiral tetrahydroquinolines were synthesized through supramolecular-organocatalysis using quinidine-N*H*-thiourea/L-phenylalanine followed by reductive amination from the simple substrates.

The asymmetric modularly designed supramolecular-organocatalytic Michael addition of a variety of functionally rich nitro-olefins with ketones was explored. The modularly designed supramolecular-organocatalytic Michael reaction is characterized by a high rate, high chemoselectivity, high diastereoselectivity, high enantioselectivity, mild reaction conditions, readily available substrates/catalysts with simple operations, and excellent yields with a broad spectrum of functionally rich substrates. This method constitutes an alternative to previously known organocatalytic Michael reactions.

Herein, for the first time, a combination of L-amino acid, (*R*)-5,5-dimethyl thiazolidinium-4-carboxylate (L-DMTC) with simple Brønsted acid TFA is reported as the suitable synergistic catalyst for the List-Lerner-Barbas aldol (LLB-A) reaction of less reactive 2-azidobenzaldehydes with various ketones at ambient temperature to furnish the optically active functionalized (2-azidophenyl)alcohols with very good yields, *dr* and *ee* values. This method gives first time access to the novel azido-containing multifunctional compounds, which are applicable in material to medicinal chemistry. Chiral functionalized (2-azidophenyl)alcohols were transformed into different molecular scaffolds in good yields with high selectivity through Lewis acid mediated $NaBH_4$ reduction, aza-Wittig and Staudinger reaction (azide reduction), followed by oxidative cyclizations, allenone synthesis, and click reaction, respectively. Chiral LLB-A products might become suitable starting materials for the total synthesis of natural products, ingredients, and inhibitors in medicinal chemistry. The mechanistic synergy of L-DMTC with

TFA to increase the rate and selectivity of LLB-A reaction in DMSO-$d_6$ is explained with the controlled and on-line NMR experiments.

# 2. *INTRODUCTION*

Asymmetric catalysis being the backbone of enantioselective synthesis, where it stands at the crossroads, has many subdivisions namely enzyme catalysis, metal catalysis, organocatalysis and the very recently introduced supramolecular-organocatalysis. Since the beginning researchers have always found ways to activate the substrates using a myriad of chiral catalysts for synthesizing enantiomerically pure organic compounds. Initially, scientists were fascinated by naturally existing and extraordinarily functionalized enzymes, which have greater capability in delivering enantiomerically pure products precisely, from complex starting materials in biochemical reactions. Inspired by these enzyme catalyzed reactions, in order to achieve great reactivity and selectivity for a particular reaction, various catalyst systems were designed and studied. This progressive growth in asymmetric catalysis has blossomed into small-molecule organocatalysis, transition metal catalysis, etc.

In the last few decades, organocatalysis, which uses small organic molecules to catalyze asymmetric organic transformations, has emerged impeccable enough as a powerful tool for enantioselective synthesis, almost mimicking enzyme catalysis. Since the renaissance of this venerable organocatalysis, whose advantages being limitless, like easy availability, cheap, environmental friendly, stable, etc., there has been an avalanche of various organocatalysed asymmetric transformations being endeavored and proved fruitful in providing the desired products with excellent reactivity, selectivity and sustainability. Nevertheless intermittently it failed to cater to certain specially substituted substrates, when single chiral organic compounds were used as organocatalysts. To overcome those limitations researcher developed a catalyst with two or more functional groups in single molecule that is multi functional chiral organocatalysts. These multifunctional chiral organocatalyst able to give the good reactivity and selectivity in some reaction, but the preparation is multi step, time consuming, costly, requires more labor work and library of similar catalyst should be prepared and checked. Certain specially substituted incompatible substrates, limitations of small molecular and multifunctional chiral organocatalyst driven researchers together contributed and paved way for the evolution of a new branch of organocatalysis recognizable as supramolecular-organocatalysis wherein more

than one organic compound are used for catalyzing a particular reaction to furnish the requisite products effectively and selectively. It is remarkable and astonishing to observe the synergistic cooperation of these two or more organocatalysts harnessing various potential weak interactions, serving hand in hand to make possible a conformationally rigid transition state so as to generate the enantiopure products with very high reactivity and selectivity. This domain of supramolecular-organocatalysis, recently emerging and being still in its infancy, also known as modularly designed organocatalysts has a multitude of advantages like rapid access to a vast library of catalyst systems as can be generated by simply mixing two or more single catalysts and uses availability of a maximum number of interactions plausible in the transition state like *H*-bonding, Vander-Waals interaction, electrostatic interaction and covalent interaction between the substrates and the catalysts, making it more rigid so as to deliver best reactivity and selectivity possible for the desired product as shown in Figure-1.

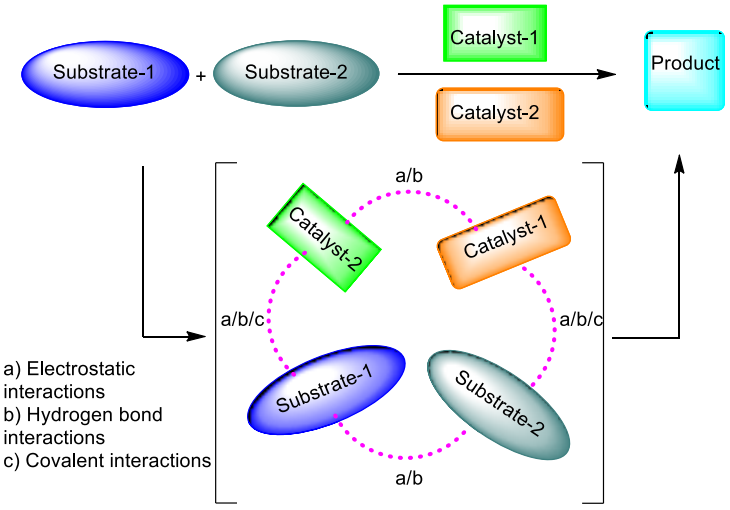


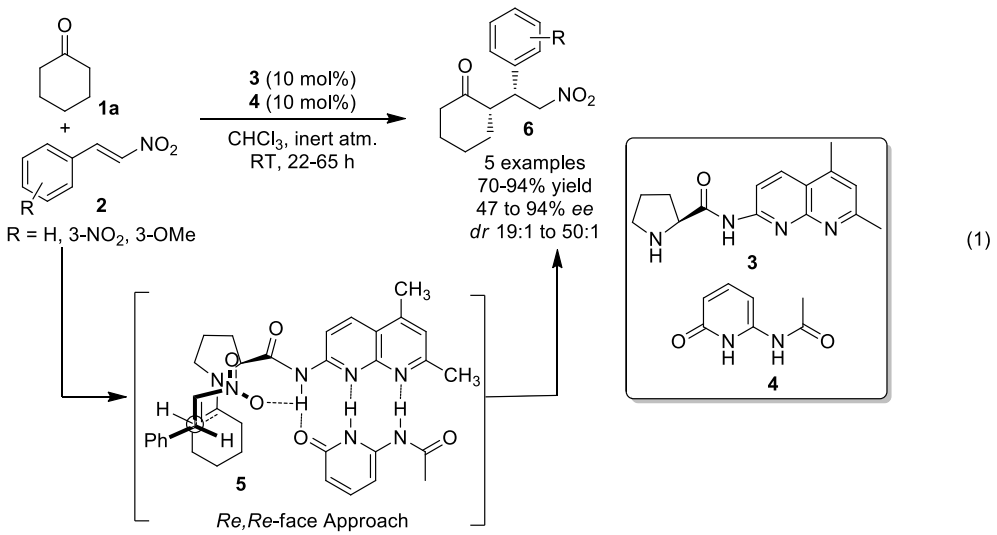

***Figure-1***: Schematic representation of asymmetric supramolecular-organocatalysis.

Supramolecular-organocatalysis is a recently growing as huge area and more and more work is going on. Supramolecular-organocatalysts are used in variety of reactions mainly, Michael, Aldol, Mannich, Diels–Alder reaction etc., In recent years, our research group has been actively involved in engineering reactions which bends under novel supramolecular-organocatalysis for the synthesis of highly functionalized chiral molecules with high selectivity. The strategy utilized for the asymmetric induction includes the utilization of various covalent and non-covalent interactions among the highly functionalised substrates and catalysts in the

transition state to render high asymmetric environment. As the research work described in this thesis deals with supramolecular-organocatalysis in asymmetric Michael reactions.[1] A breif overview of the literature reports on supramolecular-organocatalysis in Michael reactions has been described as follows.

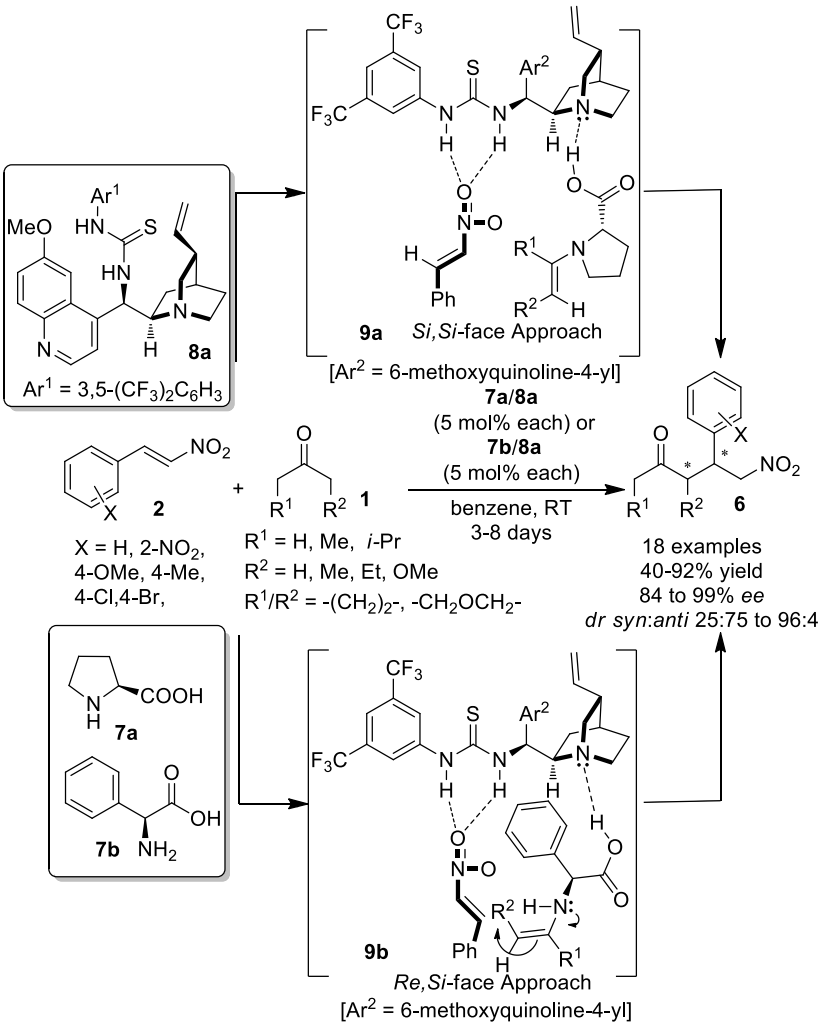
Asymmetric Michael addition of aldehydes or ketones to nitroalkenes is a very familiar and potentially useful organocatalytic reaction for the synthesis of versatile γ-nitrocarbonyl compounds, but is not effectively catalyzed by (*S*)-proline.

In 2007, Matthew L. Clarke and Jose A. Fuentes prepared a novel proline-derived organocatalyst (*S*) ProNap **3** by amide coupling between aminonaphthyridine and (*S*)-proline. When ProNap **3** used alone, gave almost racemic products, albeit with good diastereoselectivity for Michael addition reactions between cyclohexanone **1a** and β-nitrostyrene **2**. The authors also prepared some achiral pyridinones and studied as additives to ProNap found the best combination to be ProNap **3** (10 mol%) with the pyridinone **4** (10 mol%) which provided a high yield of product with excellent diastereo- and enantioselectivity through the transition state **5**, where multiple hydrogen bonding interactions operate among catalyst and substrates as shown in Eq. 1.[2] The additive altered the diastereo- and enantioselectivity as well as the reaction rate in a remarkable and reproducible manner, proving that the addition of achiral additives to a chiral organocatalyst could transform an unselective catalyst into a highly effective one, simply through self-assembly of a new organocatalyst.




(1)

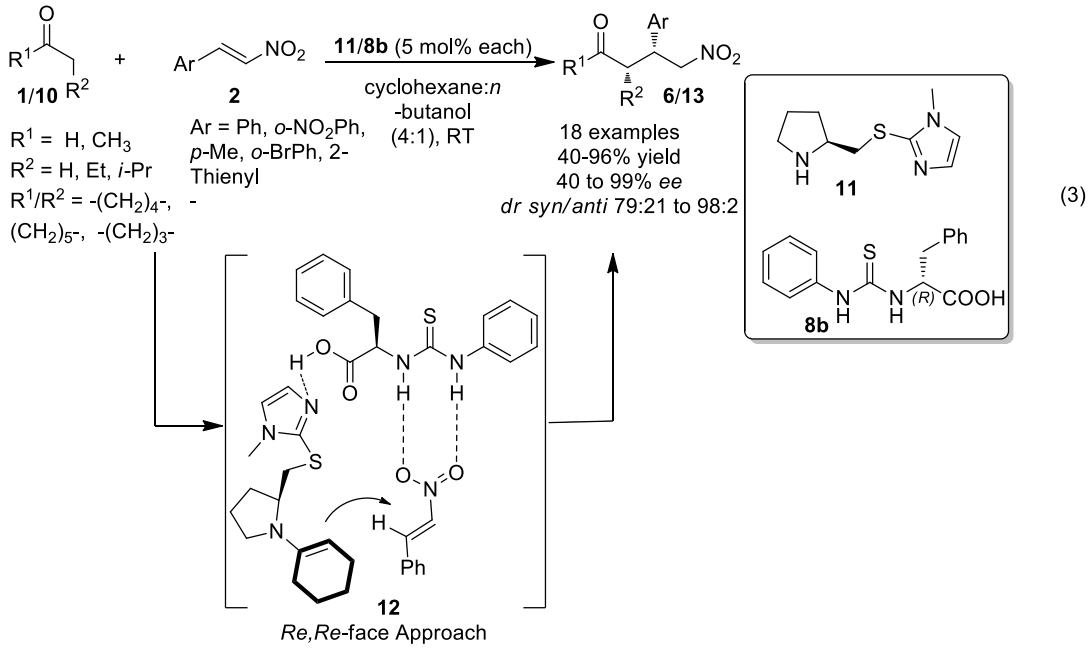
In 2008, Tanmay Mandal and Cong-Gui Zhao expected quinidine thiourea **8a**, to be a good match with L-proline **7a** for the direct Michael addition of ketones **1** to nitroalkenes **2**. The reaction catalyzed by the organocatalyst assembly of quinidine thiourea **8a** and L-proline **7a** yielded the anticipated *S* enantiomer in 86% *ee* at room temperature in benzene. While the assembly of D-proline and quinidine thiourea **8a** was mismatched and delivered poor results. Besides proline, the authors also screened some α-amino acids containing a primary amine group, which led to the finding, the assembly of L-phenylglycine **7b** and quinidine thiourea **8a** as a highly enantioselective catalyst, affording the *R* configured Michael adduct in 95% *ee*. It was concluded that the catalytic activity and directing effects are the result of self-assembled catalysts, instead of synergistic effects as supported by NMR spectroscopy of the L-proline **7a** and quinidine thiourea **8a** mixture. The assembly of L-phenylglycine **7b** and quinidine thiourea **8a** afforded excellent enantioselectivities for the reaction of acetone with β-nitrostyrenes **2**. Nonetheless, this assembly was not very reactive for most other ketone substrates, although, if the reaction occurred, very high enantioselectivity was observed for the product. While the assembly of L-proline **7a** and quinidine thiourea **8a** led to slightly inferior *ee* values for an acetone substrate, it was much more reactive under similar conditions and acted as good catalyst for longer-chain ketones **1**, such as methyl ketones and 3-pentanone and cyclic ketones, such as cyclopentanone and cyclohexanone derivatives. The opposite enantioselectivity and diastereoselectivity obtained for the assemblies of L-proline **7a** and L-phenylglycine **7b** with quinidine thiourea **8a** was rationalized by the proposed transition states **9a** and **9b** as shown in Eq. 2.[3] In the case of L-proline **7a**, the *Si,Si*-attack of the hydrogen-bonded nitrostyrene on the anti rotamer of the *E*-enamine intermediate led to the major *syn* diastereomer **6**. In contrast, in the case of L-phenyglycine **7b**, formation of *Z*-enamine was favored, and the *Re,Si*-attack of the hydrogen-bonded nitrostyrene on this enamine led to the major *anti* product **6**.




(2)

In 2008, Zhen-Yuan Xu *et al*. reported a novel and effective organocatalytic system consisting of pyrrolidinyl-thioimidazole **11** and a chiral thioureido acid **8b**, which efficiently catalyzed the asymmetric Michael reactions of ketones **1** or aldehydes **10** to nitroolefins **2** to afford the product **6**/**13** with high diastereoselectivities (up to 98 : 2) and excellent enantioselectivities (up to 99% *ee*) as shown in Eq. 3.[4] Exhibition of excellent activities by the chiral thioureido acid **8b** as additives indicated their dual role of activating the catalyst (presumably by providing the acidic proton), and also inducing chirality by hydrogen bonding. In polar solvents, the catalyst system exhibited poor activity, indicating solvent interaction with **8b** through hydrogen bonding to weaken the activation ability of **8b** towards the reaction. Though the *ee* of the products **6**/**13** were excellent (99% *ee*) in dioxane and isopropyl ether, the reaction times and yields were disappointing due to the difficulties in dissolution of the polar catalyst

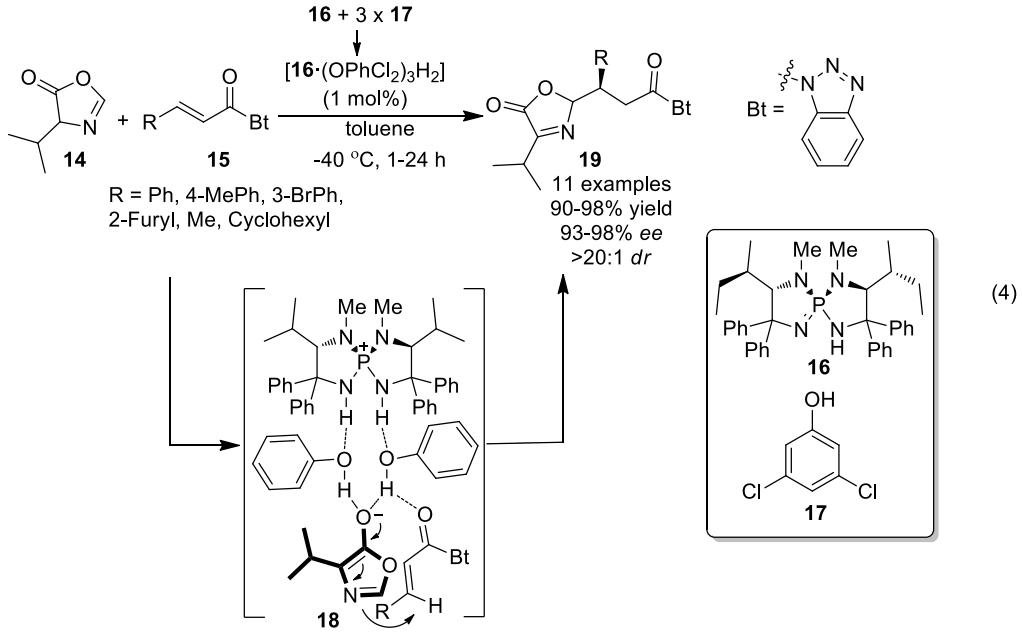
system in such nonpolar solvents and so mixed solvent system cyclohexane–*n*-butanol, was chosen. Different nitro-olefins bearing electron-donating as well as electron-withdrawing aryl groups afforded the desired adducts with high selectivities. 2-(2-nitrovinyl)furan and 2-(2-nitrovinyl)thiophene also worked well. Besides, the asymmetric additions of the aliphatic aldehyde, isovaleraldehyde and various ketones to *trans*-β-nitrostyrene **2** furnished the products in good yields and enantioselectivies. Enamine activation model combined synergistically with the effect of asymmetric counter anion directed catalysis (ACDC) was proposed. While in transition state **12** the thiourea moiety activated the nitro group of the nitro-olefin through hydrogen bonding, and enhancing its electrophilicity, the pyrrolidine activated the ketone by forming an enamine intermediate. Finally the favored *Re*-face attack of the enamine afforded the desired adduct.




(3)

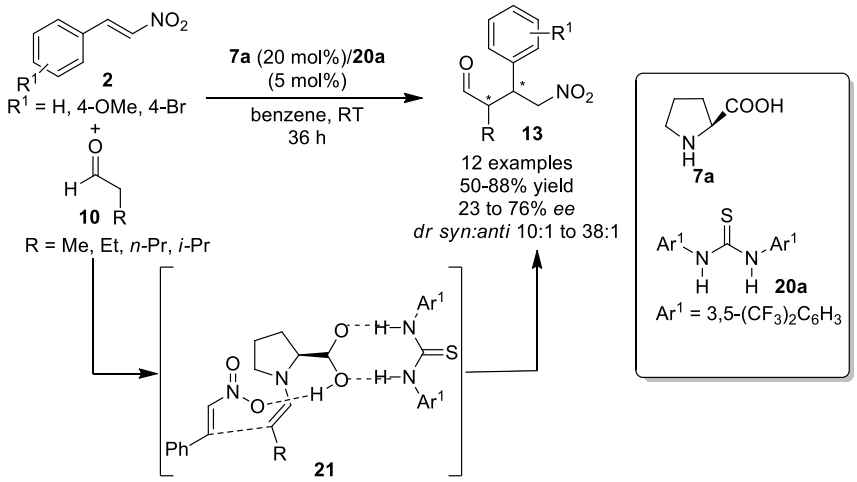
In 2009, Takashi Ooi *et al*. reported that a chiral tetraaminophosphonium cation, two phenols, and a phenoxide anion self-assembled into a catalytically active supramolecular architecture through intermolecular hydrogen bonding and promoted a highly stereoselective conjugate addition of acyl anion equivalents to α,β-unsaturated ester surrogates. The conjugate addition of 2-unsubstituted oxazol-5(4*H*)-one, namely azlactone **14** to α, β-unsaturated acylbenzotriazole **15** was performed in the presence of [**16**·$(OPhCl_2)_3H_2$] in toluene at −40 °C, to

afford essentially diastereomerically pure adduct **19** in a excellent yield, enantioselectivity and diastereoselectivity as shown in Eq. 4.[5]




(4)

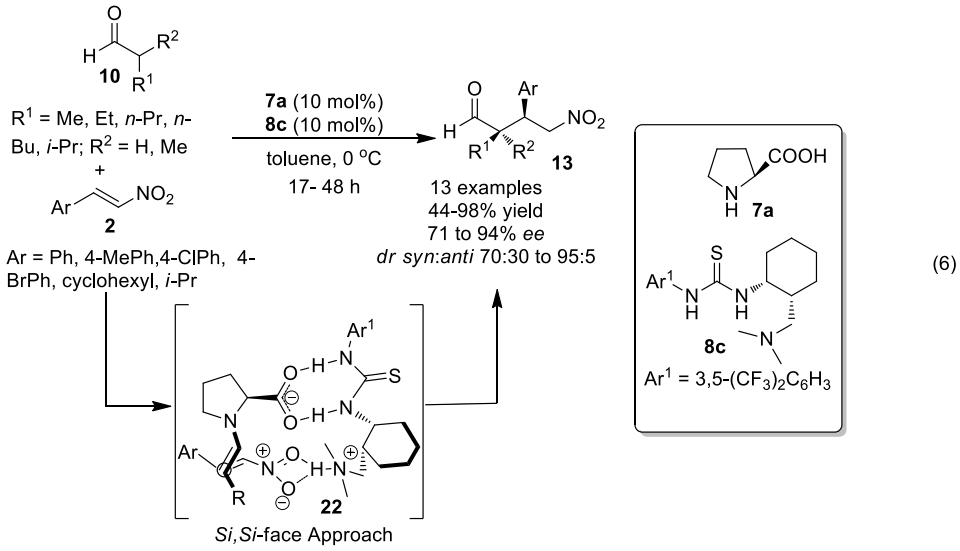
In 2010, Ayhan S. Demir and Serkan Eymur described a proline–thiourea self-assembled organocatalyst for the enantioselective nitro-Michael addition of aldehydes **10** to nitroalkenes **2**. Herein an achiral additive was used in the Michael addition with aldehydes as donors. The reaction was performed between aldehyde **10** and *trans*-β-nitrostyrene **2** at RT for 36 h in the presence of L-proline **7a** and 1,3-bis[3,5-bis(trifluoromethyl)phenyl] thiourea **20a** in benzene solvent furnished the product **13**. The reaction was very slow with a low stereoselectivity in the absence of thiourea **20a** additive, demonstrating its influential effect on the reactivity and selectivity. Unbranched aldehydes as well as α-branched aldehydes gave the 1,4-addition products **13** in good yields and moderate to good enantioselectivities with excellent diastereoselectivities as shown in Eq. 5.[6] The reaction tolerated various nitroalkenes bearing electron-rich and electron-deficient aryl groups efficiently to furnish the products, with a high diastereoselectivity. The mechanism was explained based on the preferential formation of the *anti*-enamine, subsequent reaction with the nitro-olefin *via* an acyclic synclinal transition state 21.




(5)

In the same year, Takuji Hirose *et al*. demonstrated an efficient self-assembled organocatalysts from L-proline **7a** and bifunctional amino thiourea **8c** derived from chiral 1,3-diamines, for the enantioselective Michael addition of aldehydes **10** to nitro-olefins **2** as show in Eq 6.[7] The reaction proceeded very smoothly in toluene to provide excellent yields, moderate diastereoselectivity, and high enantioselectivity. When L-proline **7a** was used alone the reaction took place very slowly and furnished lower enantioselectivity, showing that thiourea not only improved the reaction rate but also enhanced the enantioselectivity. Assessment studies of the catalytic reactivity of different amino thioureas in combination with L-proline proved that the configuration of the amino thiourea had almost no effect on the absolute configuration of the product and that the stereochemistry of the reaction was mainly controlled by the configuration of proline. Linear aldehydes underwent reaction smoothly and gave the products **13** with high yields (80–96%), moderate to high diastereoselectivities (70/30–86/14 *dr*), and high enantioselectivities (90–94% *ee*). The reaction tolerated various substituted *trans*-β-nitrostyrenes **2**, exhibiting moderate effect on the reaction rate, enantioselectivity, and diastereoselectivity to give the desired Michael products **13**. This catalytic system was not effective for ketones as well as β-alkyl nitro-olefins. Interaction between proline and amino thiourea was studied by $^{1}$H NMR experiments and showed that there is hydrogen bonding between thiourea group and the carboxylate of L-proline **7a**. As explained in transition state **26**, the amino thiourea interacted first with proline through two hydrogen bonds to form proline-thiourea complex. L-proline reacts

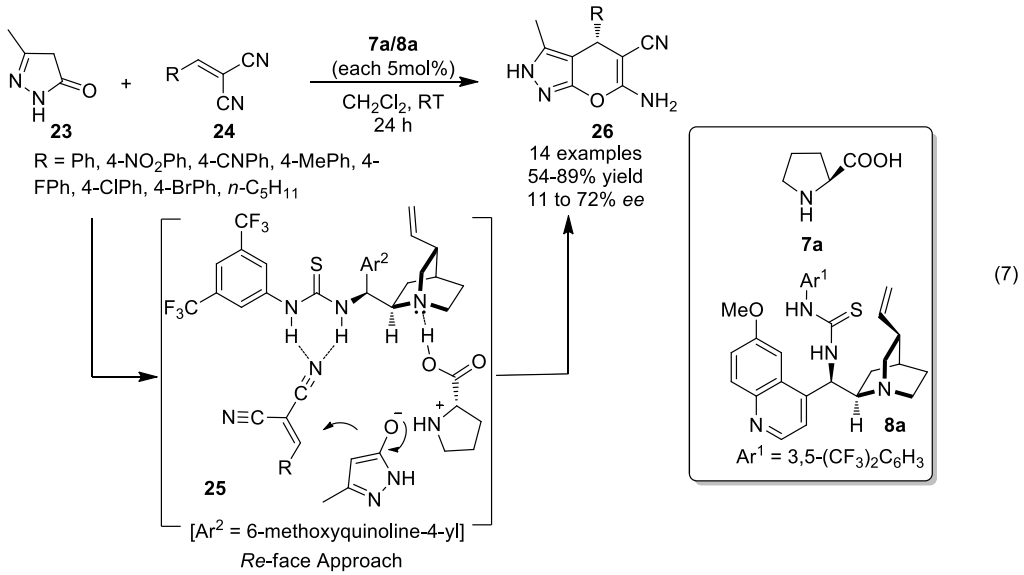
with aldehyde forms enamine intermediate, which on addition to nitro-olefin through *Si,Si*-face attack gave the (2*R*,3*S*)-configured *syn* product.




(6)

In 2011, Cong-Gui Zhao and Savitha Muramulla demonstrated an enantioselective tandem Michael addition–cyclization reaction between 3-methyl-2-pyrazolin-5-one **23** and benzylidenemalononitriles **24** using modularly designed organocatalysts (MDOs) to yield 6-amino-5-cyanodihydropyrano[2,3-*c*]pyrazoles **26** in high yields and moderate to good enantioselectivities as shown in Eq. 7.[8] The amino acids of the MDOs were used as a Lewis base in this base-catalyzed reaction. When L-proline **7a** and quinidine thiourea **8a** were used as the precatalysts in $CH_2Cl_2$ the reaction gave the product **26** in 72% yield and 72% *ee* for the major *R* enantiomer. Although, quinidine thiourea alone was found to catalyze the reaction to furnish the product in 76% yield with 13% *ee* but for the *S* enantiomer, L-proline when used alone no product was obtained. The supramolecular catalytic system and quinidine thiourea **8a** produced the opposite enantiomers with different *ee* values proving that it was certainly the MDO that catalyzed the reaction. It is worth mentioning that opposite enantiomers were obtained in THF and $CH_2Cl_2$ most likely due to the influence of the solvent on the MDO structures. Various benzylidenemalononitrile derivatives with a substituent on the phenyl group were used, and high yields of the products were obtained, with their *ee* values being highly dependent on the nature of the substituents and their positions on the phenyl ring. The observed enantiofacial selectivity of the reaction was rationalized in transition state **25**. Initially, the proline-moiety of the

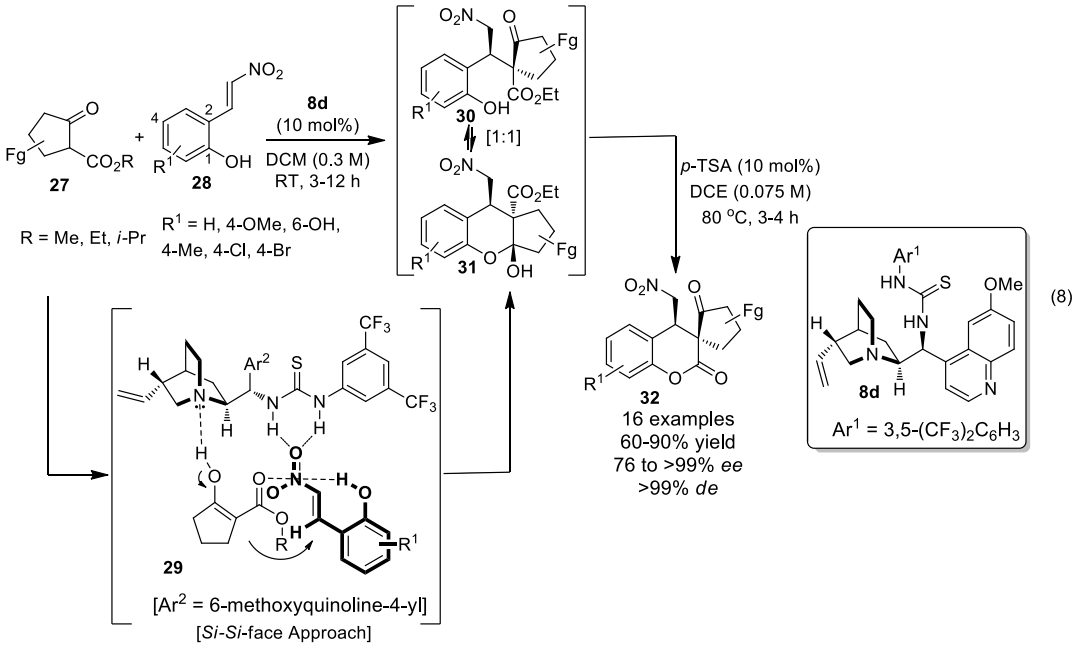
supramolecular-organocatalyst formed from L-proline and quinidine thiourea **8a** deprotonated 3-methyl-2-pyrazolin-5-one **23**. The resulting enol associated with the catalytic system through ionic interactions or hydrogen bonding. Simultaneously, benzylidenemalononitrile **24** interacted with the thiourea moiety through hydrogen bonds. The enol attacked the *Re* face of benzylidenemalononitrile **24** leading to an intermediate, which underwent cyclization and rearrangement to give the observed *R*-enantiomer as the major product.




(7)

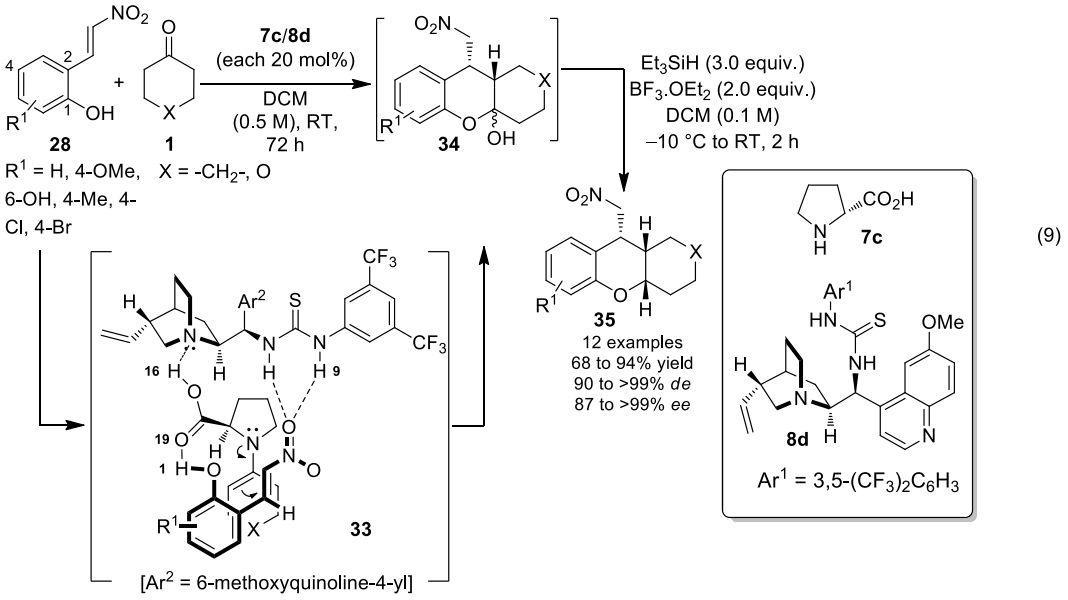
In 2012, Ramachary *et al*. illustrated an extraordinary approach for the asymmetric synthesis of highly substituted spirodihydrocoumarins possessing a quaternary stereocenter, through neighboring *ortho*-hydroxyl group induced sequential Michael–lactonization reactions on 2-(2-nitrovinyl)phenols **28** with alkyl cyclopentanone-2-carboxylates **27** in the presence of a catalytic amount of quinine–N*H*–thiourea **8d**. In this work author used only single catalyst, but the co-operation of two substrates, and one catalyst forming the supramolecular assembly through hydrogenbond interactions, as exhibited in the transition state cluster **29**. Sequential Michael–lactonization reaction of alkyl cyclopentanone-2-carboxylates **27** with 2-(2-nitrovinyl)phenols **28** using 10 mol% of quinine–N*H*–thiourea **8d** as catalyst in DCM at 25 °C for 3 h furnished the products **30**/**31** (which were found to be in fast dynamic equilibrium) in 98% yield, which on further lactonization with *p*-TSA catalyst furnished the product **32** in 75% yield with >99.9% *ee* and >99% *de* as shown in Eq. 8.[9] From the control experiments it was confirmed that the outcome of the product selectivity and reactivity was controlled by neighboring group participation of Ar–O–H through hydrogen-bonding with carbonyl of alkyl

cyclopentanone-2-carboxylates **27** in the transition state along with the catalyst. The reaction proved fruitful for various neutral, electron-withdrawing and electron-donating substituted 2-(2-nitrovinyl)phenols **28** and furnished the products with excellent yields, *ee* and *de* values. In the proposed mechanism, the authors have elucidated the neighboring *ortho*-hydroxyl group involvement in the reaction through a 21 membered supramolecular assembly as shown in the transition state **29** and where the less hindered *Si*-face of 2-(2-nitrovinyl)phenols **28** approached the *Si*-face of the *in situ* generated enol, to furnish the products with excellent yields, *ee*'s and *de* values.




Subsequently, Ramachary *et al*. elegantly demonstrated the application of supramolecular-organocatalysis for the asymmetric Michael reaction of ketone **1** with 2-(2-nitrovinyl)phenols **28**, which were found to be un-reactive under simple organocatalysts, and produced the hexahydroxanthenols **34** with high yield, *ee* and *de* values. The reaction was carried out in the presence of each 5 mol% of D-proline **7c** and quinine-N*H*-thiourea **8d** in dichloromethane at 25 $^{o}$C for 5 h to yield 1:1 ratio of lactol products **34** in quantitative yield with 97% *ee* and 92–95% *de*, which got enriched after the reductive etherification to furnish the product **35** in 90% yield with 94% *de* and >99% *ee* as shown in Eq. 9.[10] Besides, the precatalyst components either **7c** or **8d**, when used alone, were not effective in promoting the reaction. Controlled experiments proved that hydrogen-bonding interaction between *ortho*-phenolic *OH* group of 2-(2-

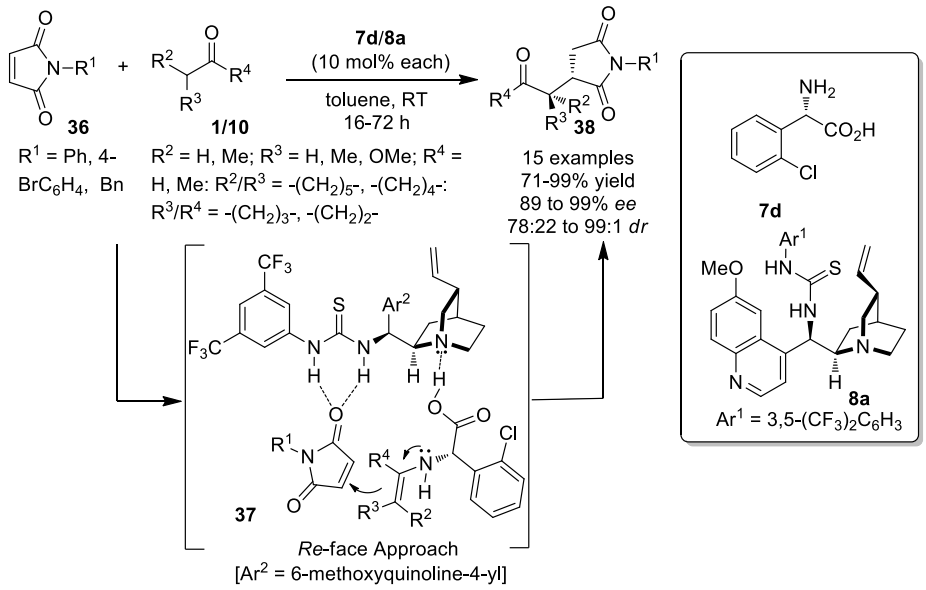
nitrovinyl)phenol **28** and carbonyl group of D-proline **7c** is decisive in determining the magnitude of asymmetric induction for the Michael product. The authors also furnished strong evidence for the existence of the proposed 19-membered cyclic *pre*-TS supramolecular assembly **33**, through electrospray ionization with high-resolution mass spectrometry (ESI-HRMS) technique, thereby establishing the mechanism. Carboxylic group of D-proline **7c** undergoing proton exchange with quinoline moiety of quinine-N*H*-thiourea **8d**, two N*H* groups of quinine-N*H*-thiourea hydrogen bonding with $NO_2$ group of 2-(2-nitrovinyl)phenol **28**, secondary amine group of D-proline forming *syn*-enamine with cyclohexanone and lastly phenolic *OH* group of 2-(2-nitrovinyl)phenol **28** protonating carbonyl group of D-proline, thus closing the rigid 19-membered supramolecular cyclic *pre*-TS **33** to control the facial selectivity.




(9)

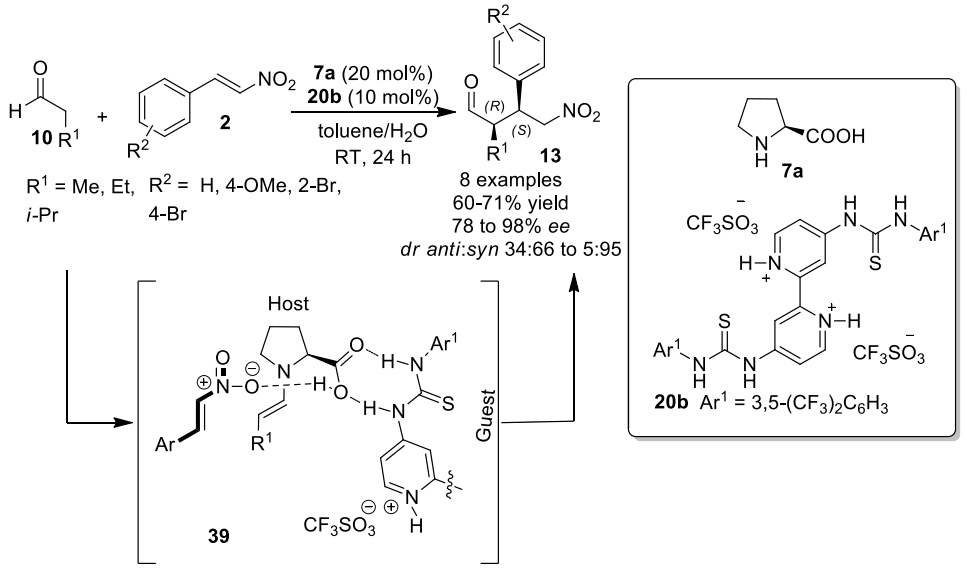
In 2013, Zhao *et al.* efficiently exemplified the application of new self-assembled organocatalysts from primary amino acids and cinchona alkaloid thiourea in the direct Michael addition of both enolizable ketones and aldehydes to maleimides to produce 3-substituted succinimides in high diastereo- and enantioselectivities in toluene. Screening of various substituted L-phenylglycine and cinchona alkaloid thioureas identified L-2-chlorophenylglycine **7d**/quinidine N*H* thiourea **8a** as the best in terms of both the reactivity and enantioselectivity of Michael reaction between enolizable ketones **1** or aldehydes **10** with maleimides **36** to produce 3-substituted succinimides **38** as shown in Eq. 10.[11] In the proposed transition state **37**,

maleimide formed two hydrogen bonding interactions with the thiourea moiety, which not only aided to fix the conformation of maleimide in the transition state, but also to increase the electrophilicity of the maleimide double bond. The enamine, formed between the ketone and L-2-chlorophenylglycine, then attacked the *Re* face of maleimide leading to the formation of the observed major diastereomer.




(10)

In 2013, Ayhan S. Demir and Sinan Basceken used the thiourea bipyridinium trifluoromethanesulfonate salt **20b** and L-proline **7a** for the Michael addition of aldehydes **10** to nitro-olefins **2** was carried out in a mixture of water/toluene solvent as shown in Eq. 11.[12] The Michael product was formed in 98% *ee* and 18:82 *dr*, where as the reaction in the absence of bipyridinium trifluoromethanesulfonate salt **20b** under the same reaction conditions did not furnish the product. It was assumed that the carboxylate moiety of the proline formed an assembly with the thiourea, in turn enhancing the reactivity and selectivity of the catalyst. According to the authors, the *in situ* formed enamine intermediate between aldehydes and the proline–thiourea catalyst presumably adopted the *E*-conformation and subsequently, the proline–thiourea moiety supported the electrophilic substrate orientation and provided the basis for the enantioselective coupling. Finally, the *Re* face of the enamine intermediate attacked the *Re* face of *trans*-β-nitrostyrene **2** show in transition state **39** to give the corresponding preferred *syn* Michael adducts **13**.




(11)

As a part of our on-going research utilization of supramolecular-organocatalyst or modularly designed organocatalyst in the Michael reactions for the synthesis of functionalized chiral molecules, research work was carried out to utilize supramolecular-organocatalytic strategies in Michael reaction of highly functionalised substate for the synthesis of chiral intermediates and building blocks of biologically active compounds and the results are presented in this thesis.

# 3. Asymmetric Synthesis of Tetrahydroquinolines through Supramolecular-organocatalysis

## *3.1 Introduction*

Tetrahydroquinolines are privileged structural moieties found in various natural and biologically active compounds. Some of them have shown a variety of potent biological activities such as antibacterial, antimalarial, antitumor, antiallergic, anticonvulsant, antioxidant and cardiovascular activity.[13] Especially, 2-methyl-1,2,3,4-tetrahydroquinoline is found in the human brain as an endogenous alkaloid. Functionalized chiral 2-alkyltetrahydroquinolines have attracted considerable attention from organic and medicinal chemists due to their many pharmaceutical applications (Figure-2a).

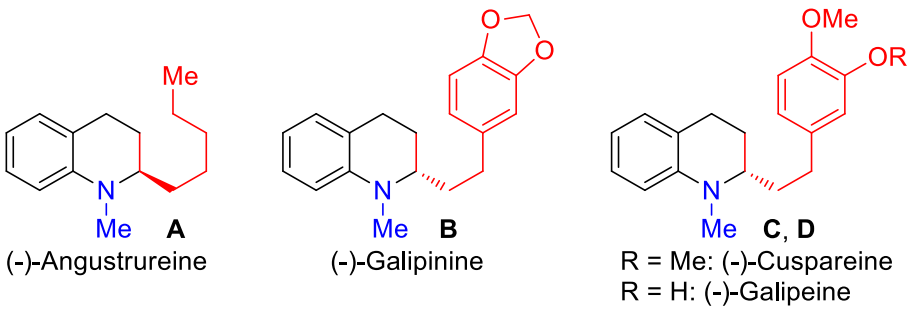



***Figure 2a***: Natural products with tetrahydroquinoline core structure.

For the asymmetric synthesis of chiral tetrahydroquinolines, previous approaches mainly depend on the asymmetric hydrogenation of the corresponding hetero-aromatic compounds,[14] nucleophilic addition of cyclic imines,[15] or the Povarov reaction.[16] Even though a few organocatalytic reactions have been reported,[17] direct and efficient asymmetric methods for their preparation is still remains a challenging task. However to develop a diversity platform for the asymmetric synthesis of 2,4-disubstituted tetrahydroquinolines with high selectivity, we propose herein a synthetic plan based on the enamine induced Michael reaction as the first step (Figure-2b). The organocatalytic asymmetric Michael reaction of functionalized 1-azido-2-(2-nitrovinyl)benzene **40** with ketone **1** followed by reductive amination yields the expected product **42** (Figure-2b).

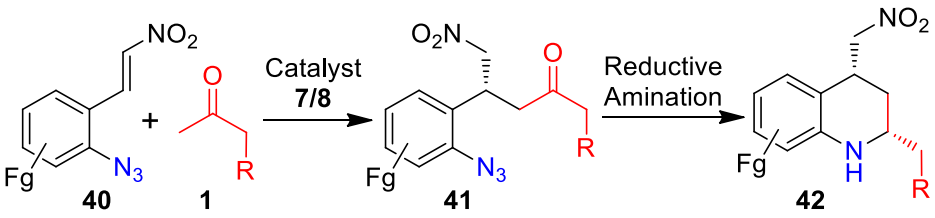



***Figure 2b***: Design plan for the asymmetric synthesis of tetrahydroquinoline scaffold through supramolecular-organocatalysis.

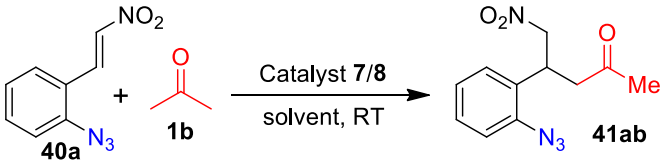
Over the past few years, the organocatalytic asymmetric Michael reaction has become a viable tool for C-C bond formation with good selectivity under mild reaction conditions.[18] The standard organocatalysts for Michael reaction include proline derivatives or cinchona alkaloid-based primary amines and thioureas. To execute the hypothesis of the reaction design, first we propose the asymmetric Michael reaction, for which we have chosen 1-azido-2-(2-nitrovinyl)benzene **40a** and acetone **1b** as the model substrates with **7** and **8** as catalysts. The results of these design reactions are as follows.

## *3.2 Results and Discussions*

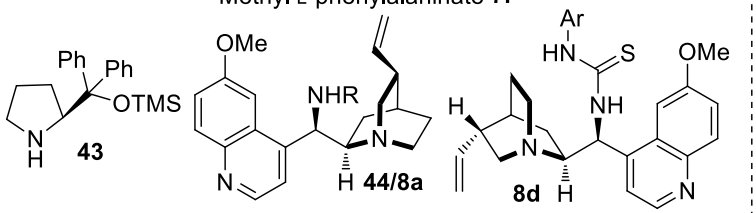
### *3.2.1 Reaction preliminary optimization:*

Studies were initiated on performing the Michael reaction of **40a** with 14 equiv. of **1b** under the standard reaction conditions, the product **41ab** was obtained in moderate to poor yield and *ee*'s (Table 1, entries 1-6). In order to ameliorate the yield and enantioselectivity, instead of screening new catalysts, we initiate of using the emerging chiral supramolecular-organocatalysts,[19] which can be assembled *in situ* from the easily available simple organocatalysts **7** and **8** through weak interactions. As anticipated, treatment of **40a** and **1b** with Zhao's supramolecular-organocatalyst (each 5 mol % of catalysts **7a** and **8a**)[19b] in benzene at 25 °C for 108 h furnished the expected keto azide **41ab** in moderate yield (56%) and promising *ee* (49%) (Table 1, entry 7).

***Table 1***: Reaction Preliminary Optimization.[a]




L-Proline **7a**, L-Phenylglycine **7b**, D-Proline **7c**, *trans*-4-Hydroxy-L-proline **7e**, L-Alanine **7f**, L-Cysteine **7g**, L-Histidine **7h**, L-Isoleucine **7i**, L-Leucine **7j**, L-Phenylalanine **7k**, L-Serine **7l**, L-Threonine **7m**, O-*tert*-Butyl-L-threonine **7n**, L-Tryptophan **7o**, L-Tyrosine **7p**, L-Valine **7q** and Methyl L-phenylalaninate **7r**




**44:** R = H and **8a:** R = CSNHAr; Ar = 3,5-$(CF_3)_2C_6H_3$

| Entry | Catalyst **7**/**8** (each 5 mol%) | Solvent (0.3 M) | Time (h) | Yield (%)[b] **41ab** | *ee* (%)[c] **41ab** |
|---|---|---|---|---|---|
| 1[d] | **43**/$PhCO_2H$ | DCM | 84 | 40 | 43 |
| 2[e] | **44**/$PhCO_2H$ | DCM | 96 | 23 | 18 |
| 3 | **8a** | DCM | 72 | – | – |
| 4[f] | **7a** | DMSO | 6 | 69 | 3 |
| 5[f] | **7a** | DCM | 96 | 16 | 11 |
| 6 | **7k** | DCM | 72 | – | – |
| 7 | **7a**/**8a** | $C_6H_6$ | 108 | 56 | 49 |

[a] Unless otherwise mentioned, all reactions were carried out with (*E*)-1-azido-2-(2-nitrovinyl)benzene **40a** (0.3 mmol), acetone **1b** (4.2 mmol, 14 equiv.), catalysts **7** or **8** (5 mol% ) in DCM at rt. [b] Yield refers to the column purified product. [c] *ee* was determined by CSP HPLC analysis. [d] **43**/$PhCO_2H$ (20 mol % each) was used. [e] **44**/$PhCO_2H$ (10 mol % each) was used. [f] 20 mol% of **7a** was used.

### *3.2.2 Advanced optimization through supramolecular-organocatalysis:*

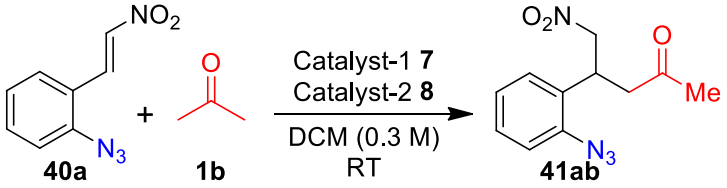
Recently, asymmetric supramolecular-organocatalysis becoming novel tool for the achieving high asymmetric induction, faster reaction rates from the reactions involving highly functionalized starting materials, when compared to organocatalysis.[18] *Disppointingly, when we performed the Michael reaction of **40a** and **1b** with known supramolecular assembly catalysts of*

*Ramachary's* ***7c/8d***[19i] *or* Zhao's ***7b/8a***,[19d] *we obtained with either less yield or ee (Table 2, entries 2, 12 and 13).* To overcome this problem, we thought of screening different supramolecular-catalysts assembled *in situ* from the library of organocatalysts **7** and **8** (Tables 1 and 2). To verify this approach, we examined the Michael reaction of **40a** and 14 equiv. of **1b** in the presence of each 5 mol % of quinidine-*N*H-thiourea **8a** or quinine-*N*H-thiourea **8d** with commercially available amino acids **7a-q** in DCM at 25 °C. After thorough investigation of asymmetric Michael reaction of **40a** and **1b** under the catalysis of supramolecular assembly *in situ* generated from **8a** or **8d** with sixteen amino acids **7a-q**; gave the interesting results that amino acids L-cysteine **7g**, L-isoleucine **7i**, L-phenylglycine **7b**, L-tryptophan **7o** or L-valine **7q** with combination of **8a** furnished the keto azide (–)-**41ab** in moderate to poor yields with high enantioselectivity (Table 2, entries 5, 7, 12, 13, 17 and 19). The same reaction under the combination of **8a** with amino acids L-phenylalanine **7k** or O-*tert*-butyl-L-threonine **7n** gave the keto azide (–)-**41ab** in 90-96% yield with high enantioselectivity within 2-3 days (Table 2, entries 9 and 16). *Interestingly, the pre-catalyst assembly components* ***7k*** *or* ***8a*** *were not effective in promoting the Michael reaction separately (Table 1, entries 3 and 6).*

These results clearly support the hypothesis that highly organized supramolecular assembly is getting involved in the *pre*-transition state of the Michael reaction to achieve high enantioselectivity.[19] To investigate the topology of *pre*-transition state supramolecular assembly, we performed the Michael reaction with shuffled catalysts combination of L-phenylalanine **7k** and quinine-*N*H-thiourea **8d**. The reaction furnished **41ab** in 30% yield with only 9% *ee* which shows there were no weak interactions observed between catalysts (Table 2, entry 11). In the final optimization, asymmetric Michael reaction of **40a** and **1b** through **7k**/**8a**-catalysis in DCM at 25 °C for 72 h furnished the chiral keto-azide (–)-**41ab** in 90% yield with 92% *ee* (Table 2, entry 9).

*Intriguingly, deviating from this optimized condition, by switching the solvent to DMSO (interactions arising from the solvent predominates), or by using the catalyst combination* ***7r/8a*** *(where in* ***7r*** *is methyl ester of* ***7k*** *and so does not have free-acid for weak interactions) was ineffective in promoting the Michael reaction with good reactivity and selectivity (Table 1, entries 20 and 21).*

***Table 2***: Advanced Optimization through Supramolecular-organocatalysis.[a]




**40a** **1b** **41ab**

| Entry | Catalyst **7**/**8** (5 mol%) | Time (h) | Yield (%)[b] **41ab** | *ee* (%)[c] **41ab** |
|---|---|---|---|---|
| 1 | **7c**/**8a** | 48 | 96 | 16 |
| 2 | **7c**/**8d** | 28 | 85 | 24 |
| 3 | **7e**/**8a** | 108 | <5 | – |
| 4 | **7f**/**8a** | 72 | <5 | – |
| 5 | **7g**/**8a** | 60 | 30 | 86 |
| 6 | **7h**/**8a** | 72 | <10 | – |
| 7 | **7i**/**8a** | 108 | 45 | 92 |
| 8 | **7j**/**8a** | 72 | <10 | – |
| **9** | **7k**/**8a** | **72** | **90** | **92** |
| 10[d] | **7k**/**8a** | 72 | 46 | 92 |
| 11 | **7k**/**8d** | 96 | 30 | 9 |
| 12[e] | **7b**/**8a** | 144 | 27 | 94 |
| 13 | **7b**/**8a** | 72 | 17 | 95 |
| 14 | **7l**/**8a** | 60 | <10 | – |
| 15 | **7m**/**8a** | 60 | <10 | – |
| 16 | **7n**/**8a** | 48 | 96 | 80 |
| 17 | **7o**/**8a** | 72 | 22 | 87 |
| 18 | **7p**/**8a** | 60 | <10 | – |
| 19 | **7q**/**8a** | 108 | 20 | 92 |
| 20[f] | **7k**/**8a** | 72 | 52 | 6 |
| 21 | **7r**/**8a** | 72 | 13 | 11 |

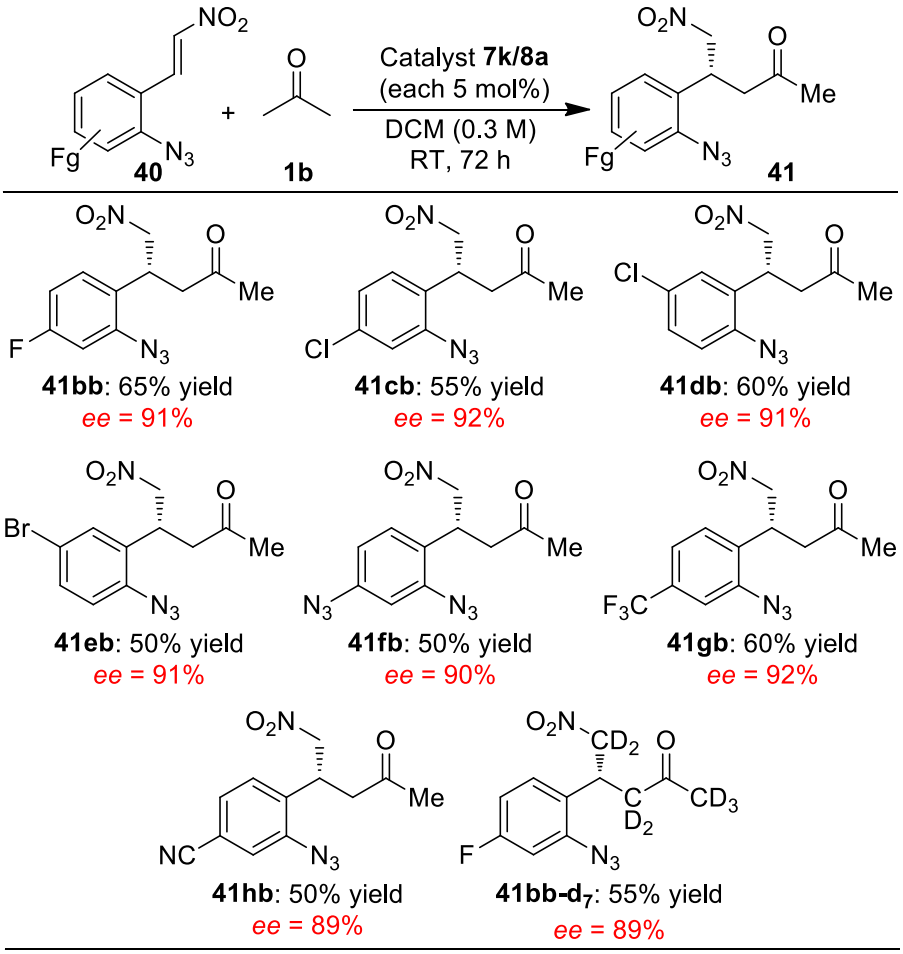
[a] Unless otherwise mentioned, all reactions were carried out with (*E*)-1-azido-2-(2-nitrovinyl)benzene **40a** (0.3 mmol), acetone **1b** (4.2 mmol, 14 equiv.), catalysts **7** and **8** (5 mol% each) in DCM at RT. [b] Yield refers to the column purified product. [c] *ee* was determined by CSP HPLC analysis. [d] Toluene (0.3 M) was used. [e] Benzene (0.3 M) was used. [f] DMSO (0.3 M) was used.

### *3.2.3 Scope of asymmetric supramolecular-organocatalysis:*

The scope of the supramolecular-organocatalysis was further extended by reacting a group of functionalized 1-azido-2-(2-nitrovinyl)benzenes **40b–h** with 14 equiv. of acetone **1b** catalyzed

by each 5 mol % of **7k**/**8a** at 25 °C in DCM for 72 h (Table 3). All the substrates **40b-h** furnished the chiral keto azides **41bb-hb** in good yields and excellent *ee*'s, irrespective of the electronic factors of the substituents present. Treatment of **40b** with deuterated acetone **1b-d$_6$** furnished the expected chiral keto azide **41bb-d$_7$** in 55% yield with 89% *ee* without much alteration in the reaction rate (Table 3).

***Table 3***: Additional Support to the Supramolecular-organocatalysis.[a-c]




[a] Unless otherwise mentioned, all reactions were carried out with (*E*)-1-azido-2-(2-nitrovinyl)benzen **40a** (0.3 mmol), acetone **1b** (4.2 mmol, 14 equiv.), catalysts **7k**/**8a** (5 mol% each) in DCM at RT. [b] Yield refers to the column purified product. [c] *ee* was determined by CSP HPLC analysis.

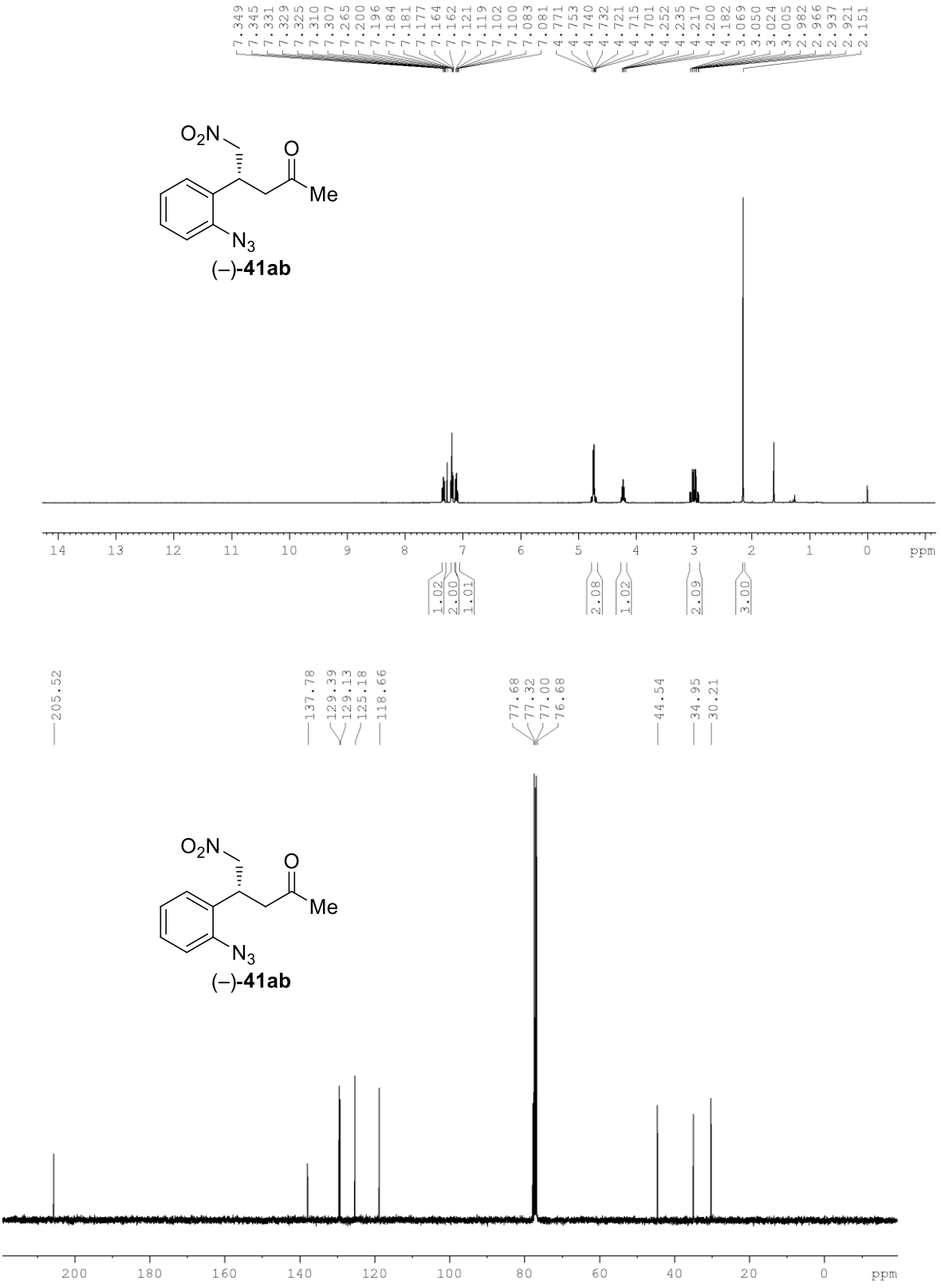



***Figure-3:*** $^{1}$H and $^{13}$C NMR spectra of the product **41ab**.

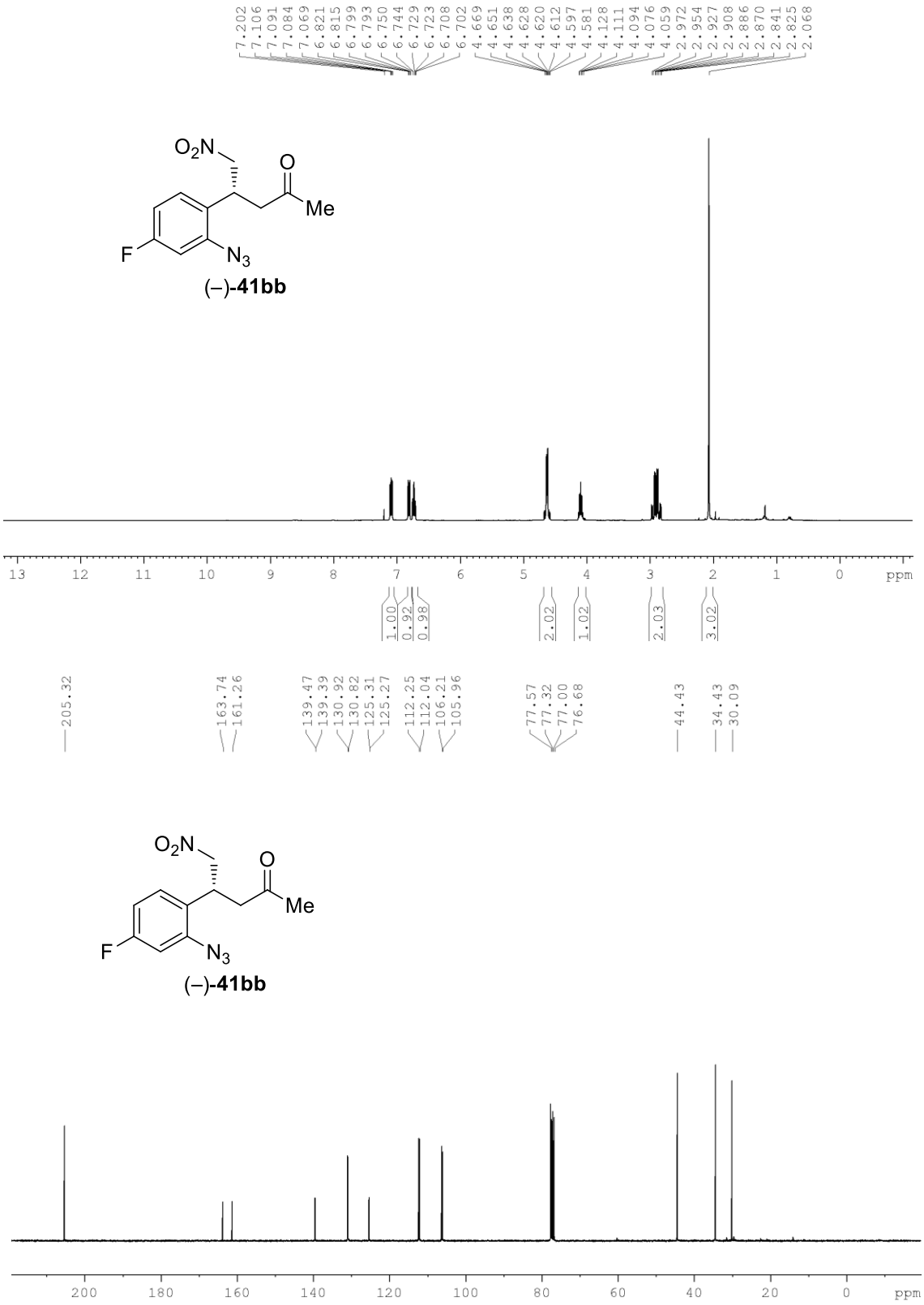



***Figure-4:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **41bb**.

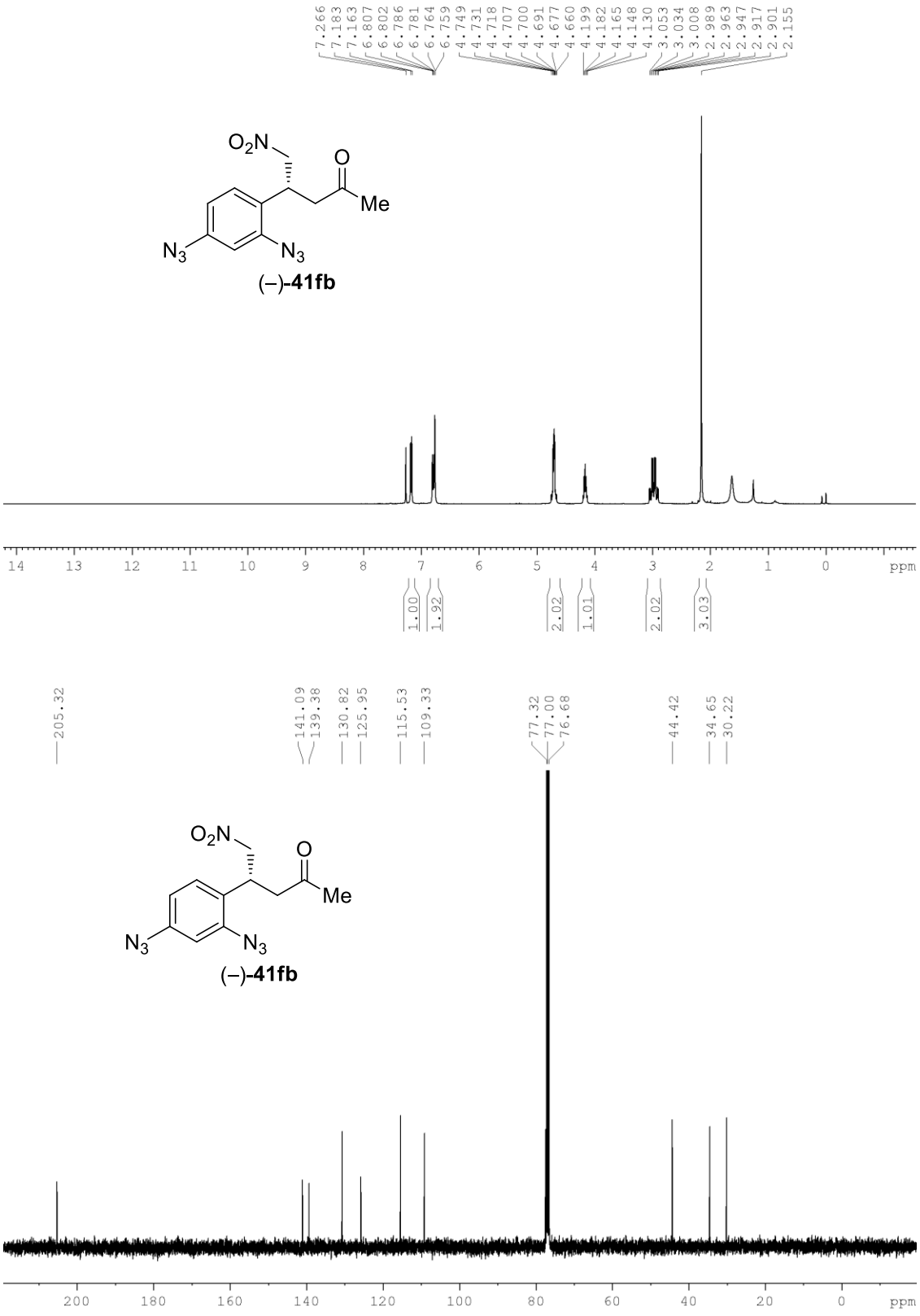



***Figure-5:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **41fb**.

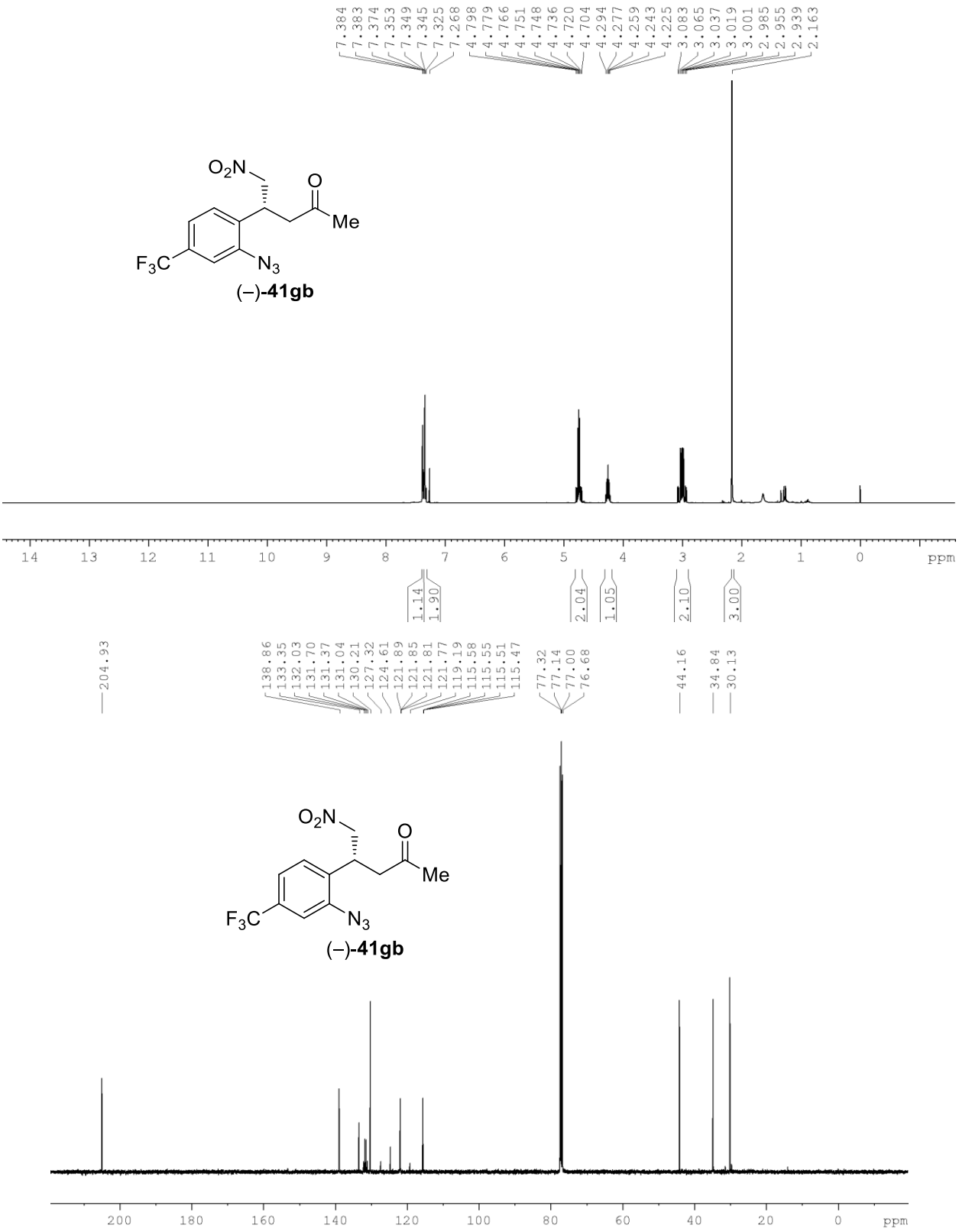



***Figure-6:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **41gb**.

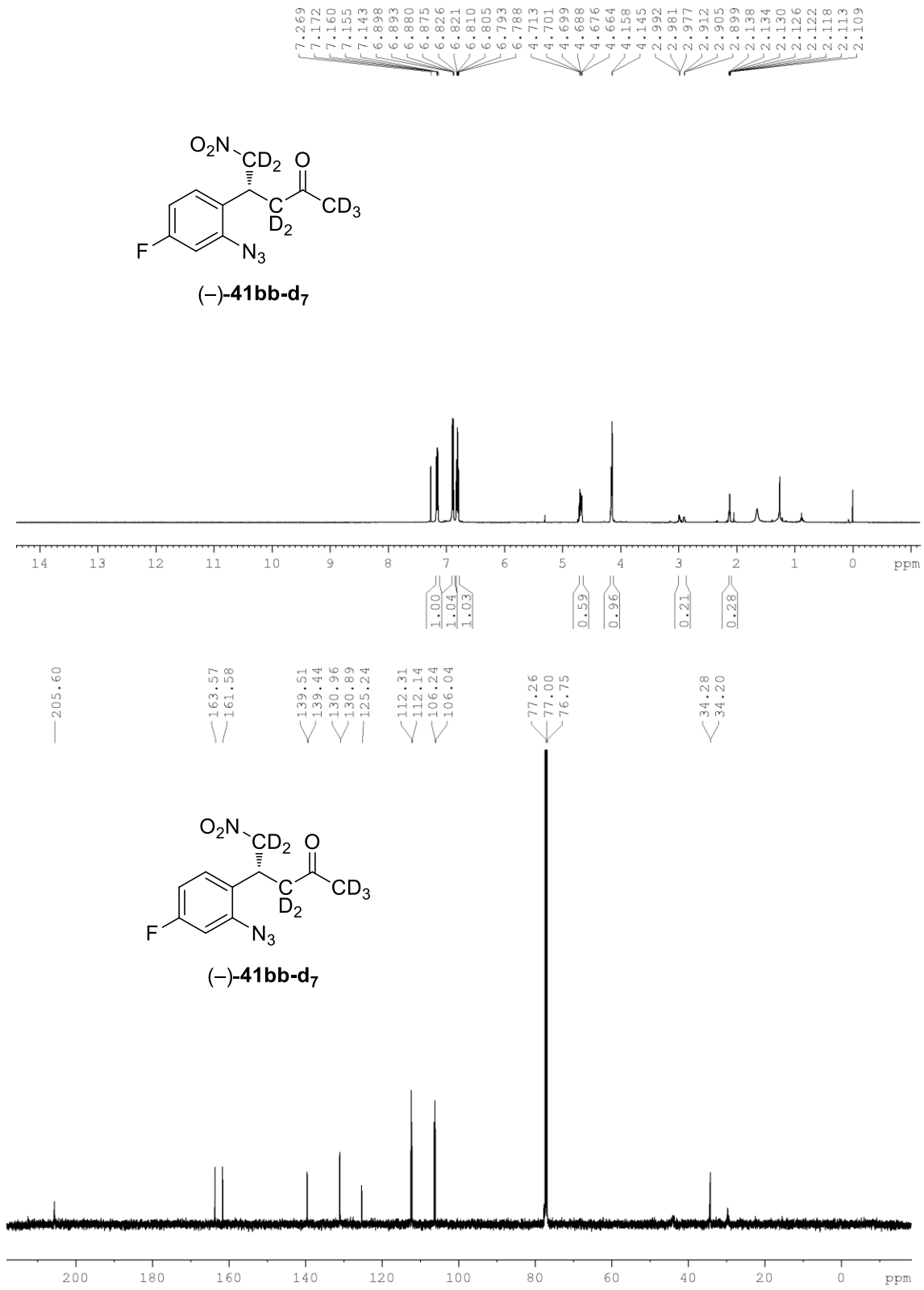



***Figure-7:*** $^{1}$H and $^{13}$C NMR spectra of the product **41bb-d$_7$**.

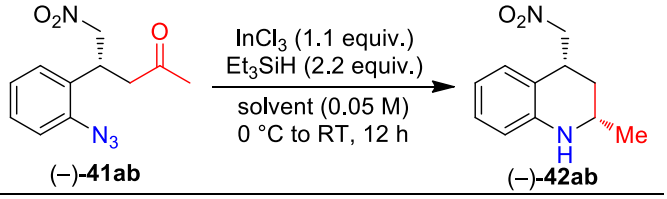
### *3.2.4 Synthetic applications of chiral Michael adducts:*

After synthesizing the optically pure keto azides **41**, we further transformed them into medicinally significant functionalized tetrahydroquinolines **42** through reductive amination by using the Bencivenni-Nanni protocol.[20]

### *3.2.5 Optimization for reductive amination of chiral Michael adducts:*

With the synthetic and medicinal applications in mind, we explored the utilization of the chiral compound **41** in the synthesis of functionalized tetrahydroquinolines **42** through reductive amination reaction (Table 4). When we carried out the reaction of chiral compound (–)-**41ab** with 1.1 equiv. of $InCl_3$ and 2.2 equiv. $Et_3SiH$ in dry $CH_3CN$ at 0 °C for 2 h and brought to room temperature continued stirring at same temperature for 10 h furnish the product (–)-*syn*-**42ab** with 41% yield with 1:2 *dr* ratio without much change in the enantioselectivity. To increase the yield and diastereoselectivity, we carried out the reaction in polar protic solvents like EtOH and MeOH gave the product (–)-*syn*-**42ab** with 45% yield, 1:5 *dr* ratio and 60% yield, 1:6 *dr* ratio respectively. From the Table 4, 1.1 equiv. of InCl3 and 2.2 equiv. $Et_3SiH$ in MeOH at 0-25 °C is the suitable condition for reductive amination.

***Table 4***: Optimization for Reductive Amination of **41ab**.[a]




(–)-**41ab** (–)-**42ab**

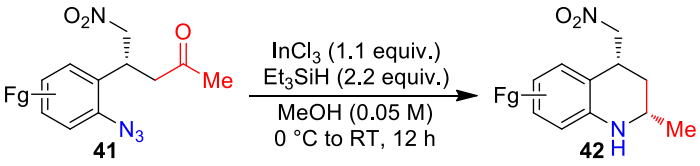
| Entry | Solvent | Yield[b] | *dr*[c] |
|---|---|---|---|
| 1 | $CH_3CN$ | 41 | 1:2 |
| 2 | EtOH | 45 | 1:5 |
| 3 | MeOH | 60 | 1:6 |

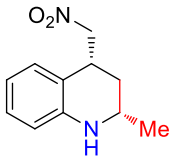
[a] Unless otherwise mentioned, all reactions were carried out with 4-(2-azidophenyl)-5-nitropentan-2-one **41ab** (0.2 mmol), $InCl_3$ (0.22 mmol, 1.1 equiv.), $Et_3SiH$ (0.44 mmol, 2.2 equiv.) in dry MeOH at 0 °C to RT for 12 h. [b] Yield refers to the column-purified product. [c] *dr* was determined based on $^1H$ NMR or HPLC analysis.

### *3.2.6 Reductive amination of chiral keto azides:*

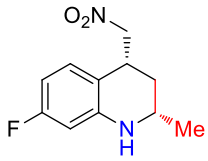
We subjected the optically pure keto azide (–)-**41ab** to reductive amination conditions with triethylsilane and $InCl_3$ at 0-25 °C for 12 h.[20b] To our delight, the reductive amination product (–)-*syn*-**42ab** was isolated in 60% yield with 1:6 *dr* and 90% *ee* (Table 5). The selective reductive amination strategy was demonstrated with five more substrates of **41** containing halogen, $CF_3$ and CN substituents to furnish the *syn*-tetrahydroquinolines **42** in good yields with high *dr*/*ee* (Table 5). The amine compounds, *syn*-**42** are structural analogues of natural products **A**-**D**,[13] which is accentuating the relevance of sequential Michael-reductive amination approach to synthesize these compounds. The structure and absolute stereochemistry of the keto azides **41** and reductive amination products *syn*-**42** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis of (–)-*syn*-**42bb** as shown in Figure-8.[21]

***Table 5***: Reductive Amination of Chiral Keto Azides.[a,b,c,d]

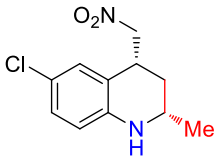


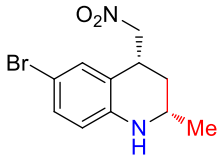

**42ab**: 60% yield
*dr* = 1:6
*ee* = 90% (major)
*ee* = 89% (minor)



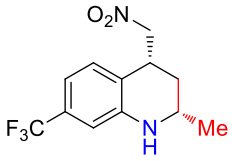

**42bb**: 60% yield
*dr* = 1:5
*ee* = 94% (major)
*ee* = 97% (minor)



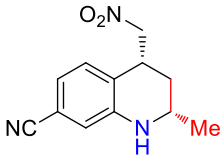

**42db**: 64% yield
*dr* = 1:5
*ee* = 93% (major)
*ee* = 90% (minor)




**42eb**: 65% yield
*dr* = 1:5
*ee* = 90% (major)
*ee* = 89% (minor)




**42gb**: 60% yield
*dr* = 1:5
*ee* = 91% (major)
*ee* = 90% (minor)




**42hb**: 70% yield
*dr* = 1:4
*ee* = 96% (major)
*ee* = 91% (minor)

[a] Unless otherwise mentioned, all reactions were carried out with 4-(2-azidophenyl)-5-nitropentan-2-one **41** (0.2 mmol), $InCl_3$ (0.22 mmol, 1.1 equiv.), $Et_3SiH$ (0.44 mmol, 2.2 equiv.) in dry MeOH at 0 °C to RT for 12 h. [b] Yield refers to the column-purified product. [c] *dr* was determined based on $^1H$ NMR or HPLC analysis. [d] *ee* was determined by CSP HPLC analysis.

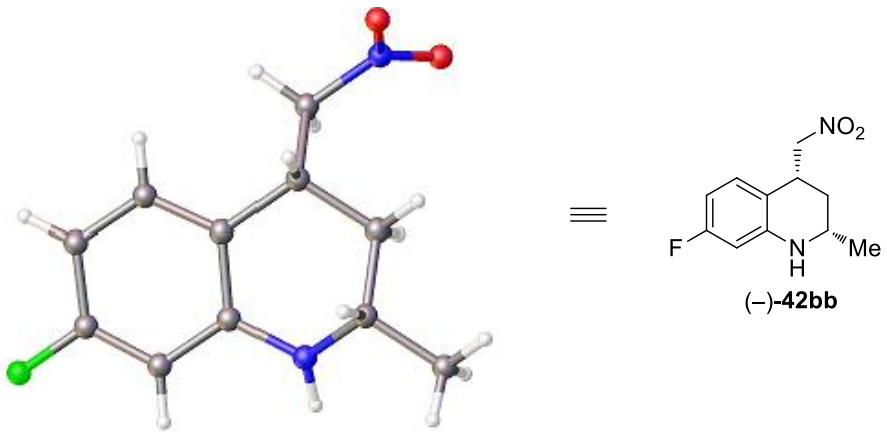
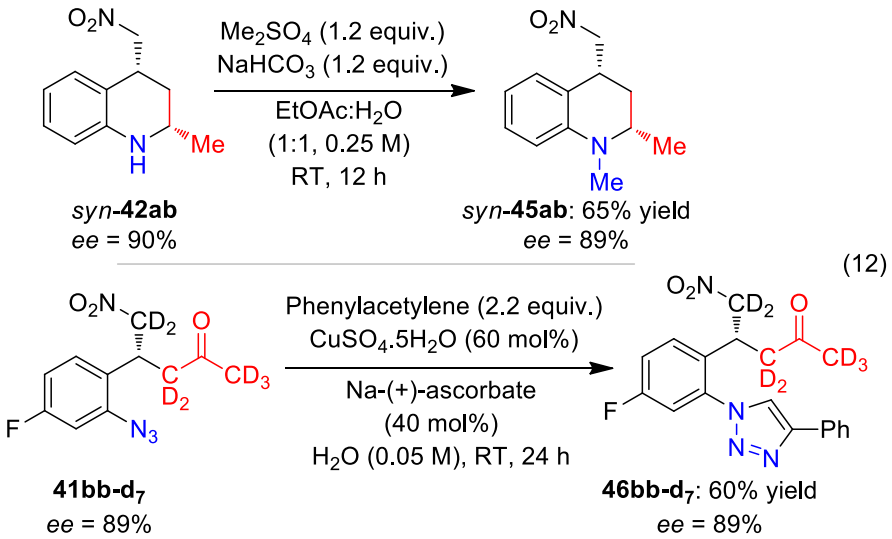



***Figure-8***: X-ray crystal stucture of chiral (2*S*,4*R*)-7-fluoro-2-methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline (**42bb**) [Flack parameter = -0.1].

With applications in mind, we explored the utilization of (–)-*syn*-**42ab** and (–)-**41bb-d$_7$** in the synthesis of functionalized drug-like compounds (+)-*syn*-**45ab** and (+)-**46bb-d$_7$** *via* simple *N*-methylation and a click reaction, respectively (Eq. 12).[22] Compounds of the type (+)-*syn*-**45ab** and (+)-**46bb-d$_7$** are important molecules in medicinal chemistry,[13] which emphasizing the value of the present catalytic approach to the chiral pharmaceuticals.



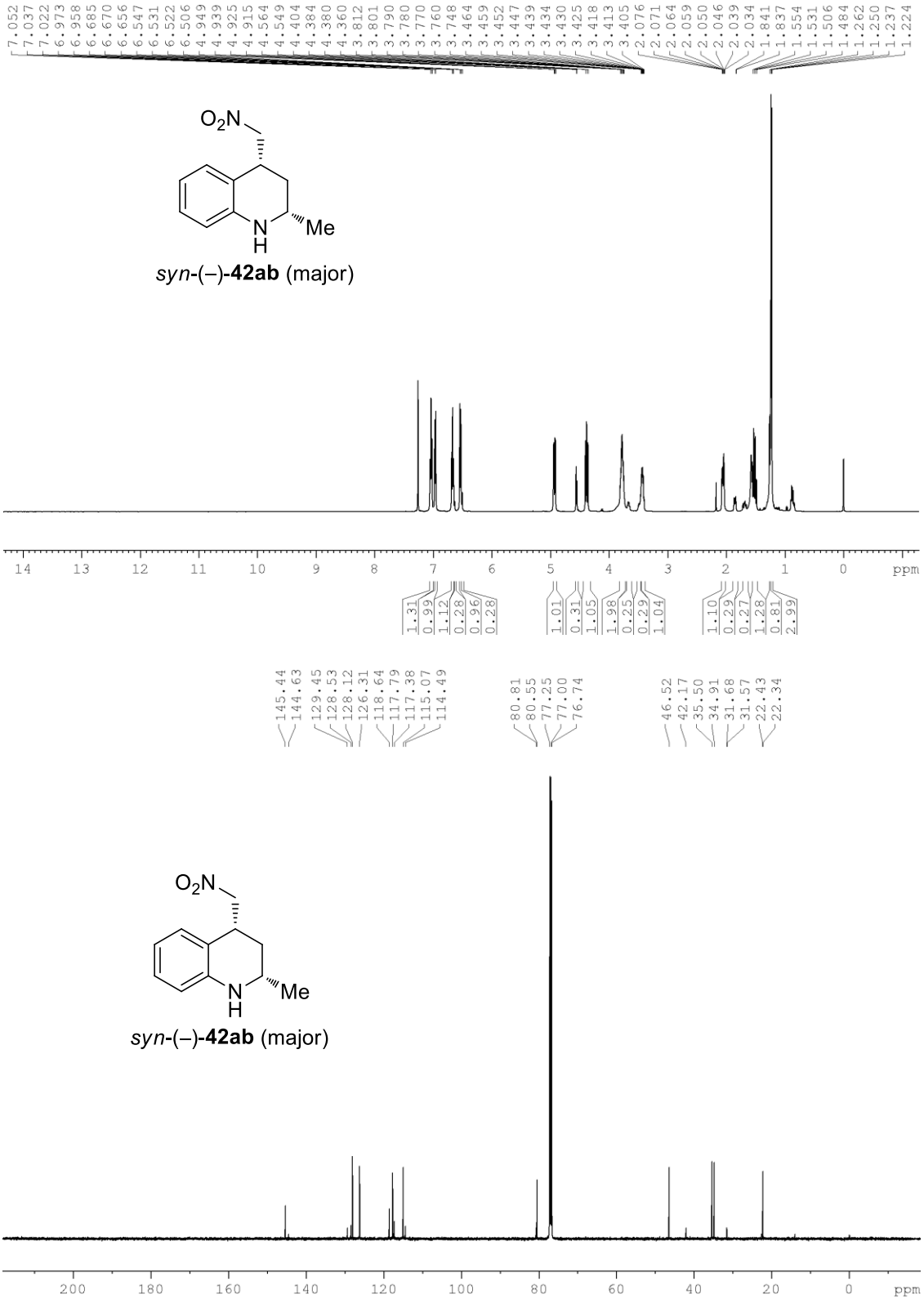



***Figure-9:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **42ab**.


***Figure-10:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **42bb**.

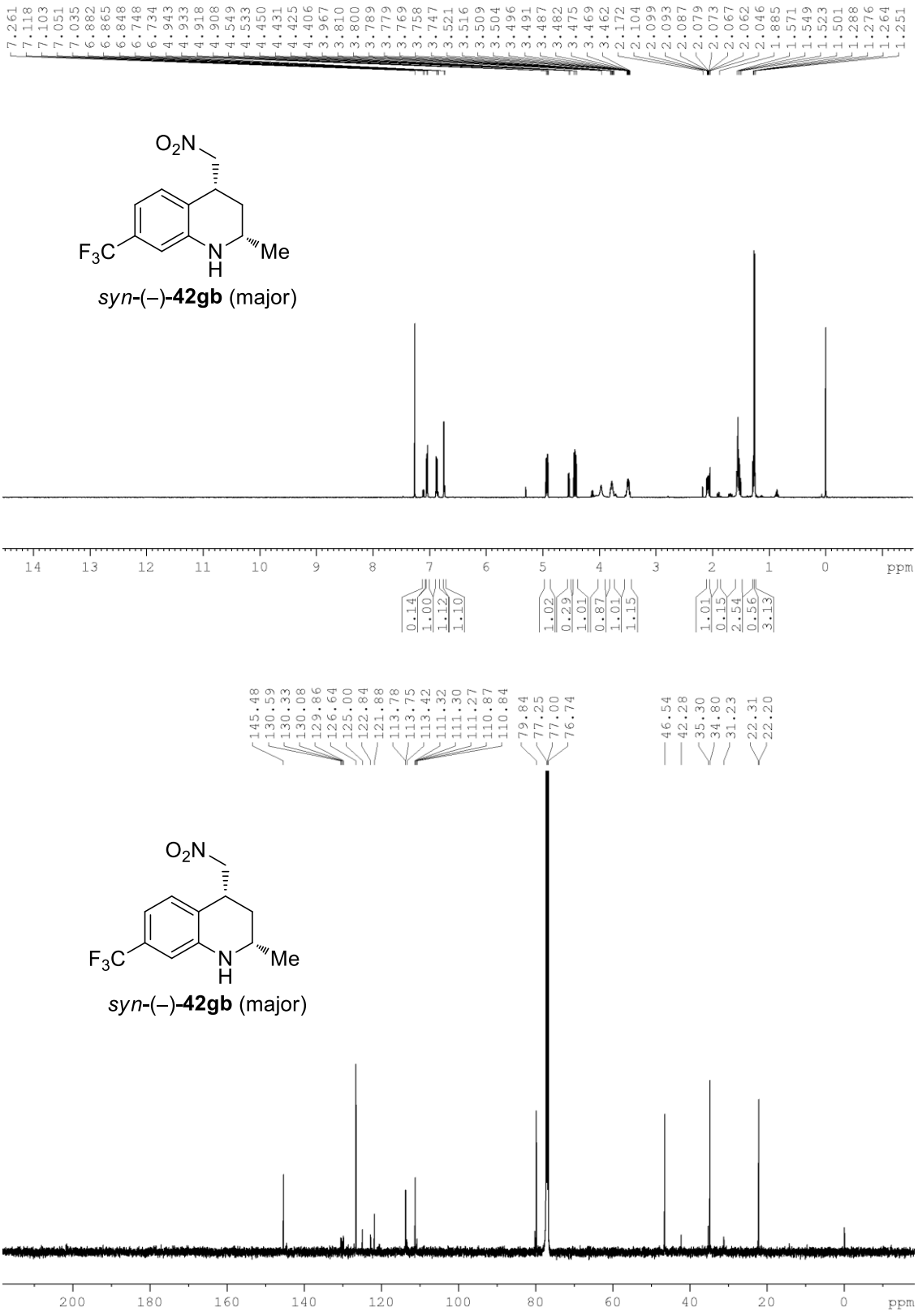



***Figure-11:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **42gb**.

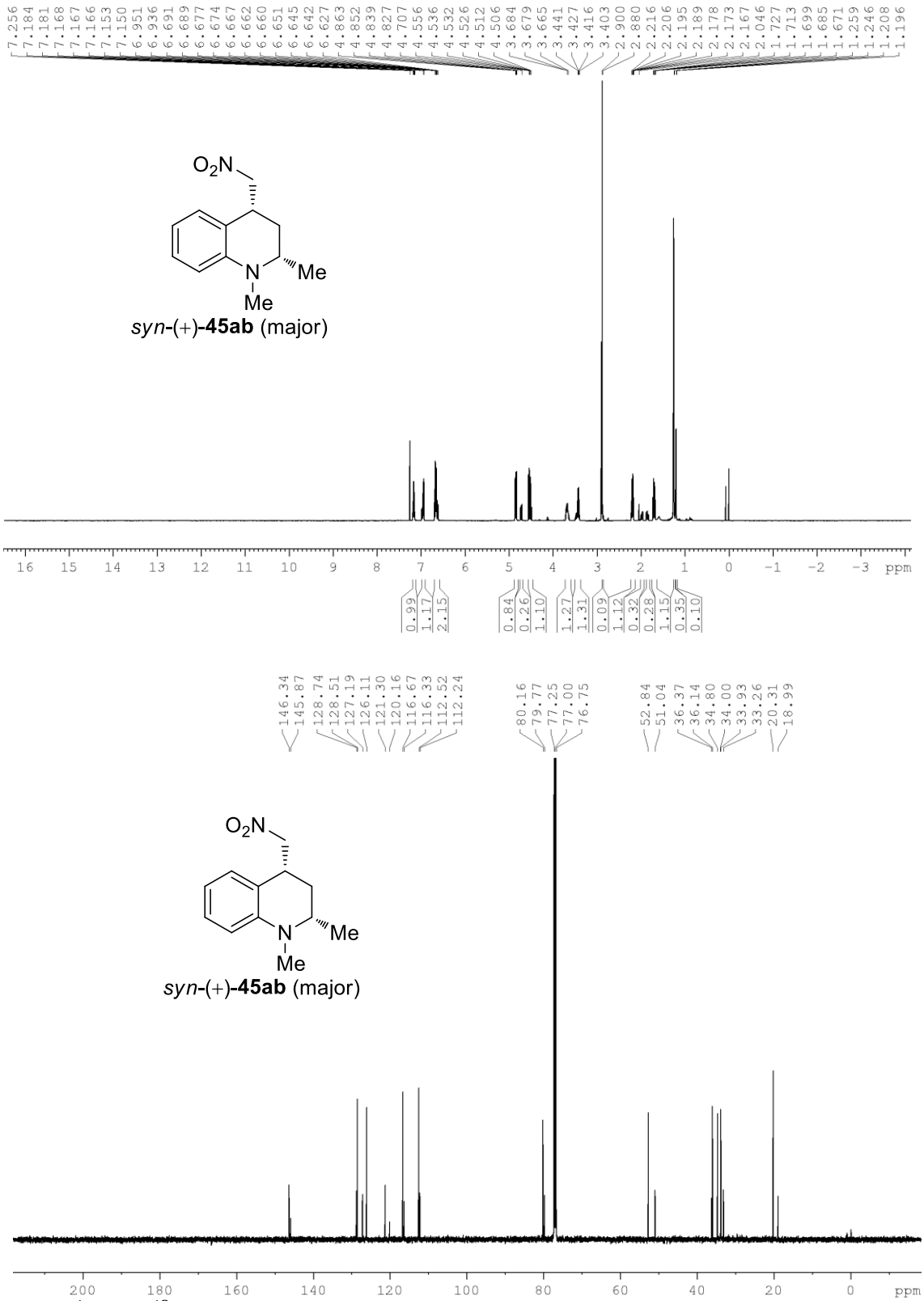
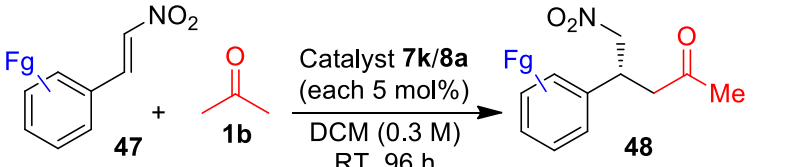



***Figure-12:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **45ab**.

### *3.2.7 Controlled experiments to study the neighboring ortho-azido group participation and formation of supramolecular self-assembly as pre-transition state:*

Furthermore, we performed a few controlled experiments to investigate the involvement of $N_3$, $NO_2$ and other active functional groups of the substrates and the catalysts in the *pre*-transition state of the Michael reaction (Scheme 1). *In addition to $NO_2$, $N_3$ also involves in hydrogen bonding with N-H group of **8a**, due to this reason position of $N_3$ on the aryl is crucial for achieving high rate and selectivity*. This statement was proven by obtaining very poor yields and *ee*'s of Michael products **48ab-48bb** for the longer reaction times from the reaction of **47a-47b** and **1b** with the **7k**/**8a**-catalysis (Scheme 1). To support this, we carried out the reaction of **1b** with $N_3$-free substrates **47c-f**, which gave better results compared to **47a-b** and this confirms that $N_3$ competes for hydrogen bonding with **8a** in addition to $NO_2$ (Scheme 1). Surprisingly, there is no reaction observed between **1b** and *ortho*-NHTs substrate **47g** under the optimized conditions (Scheme 1). It appears that a topological modification in the *pre*-transition state assembly by decreasing single directional hydrogen-bonding between *N*-H group of **8a** and *ortho*-$N_3$/$NO_2$ disturbs the supramolecular assembly and diminishes the rate, yield and *ee* of the reactions (Scheme 1).

***Scheme 1***: Controlled Experiments to Study the $N_3$ Involvement in the *pre* –Transition state (*pre*-TS).




Fg = 3-$N_3$ (**47a**)
Fg = 4-$N_3$ (**47b**)
Fg = H (**47c**)
Fg = 2-OMe (**47d**)
Fg = 2-F (**47e**)
Fg = 2-$NO_2$ (**47f**)
Fg = 2-NHTs (**47g**)

**48ab**: 27% yield, 78% *ee*
**48bb**: 39% yield, 81% *ee*
**48cb**: 75% yield, 90% *ee*
**48db**: 48% yield, 92% *ee*
**48eb**: 74% yield, 93% *ee*
**48fb**: 26% yield, 93% *ee*
**48gb**: no reaction

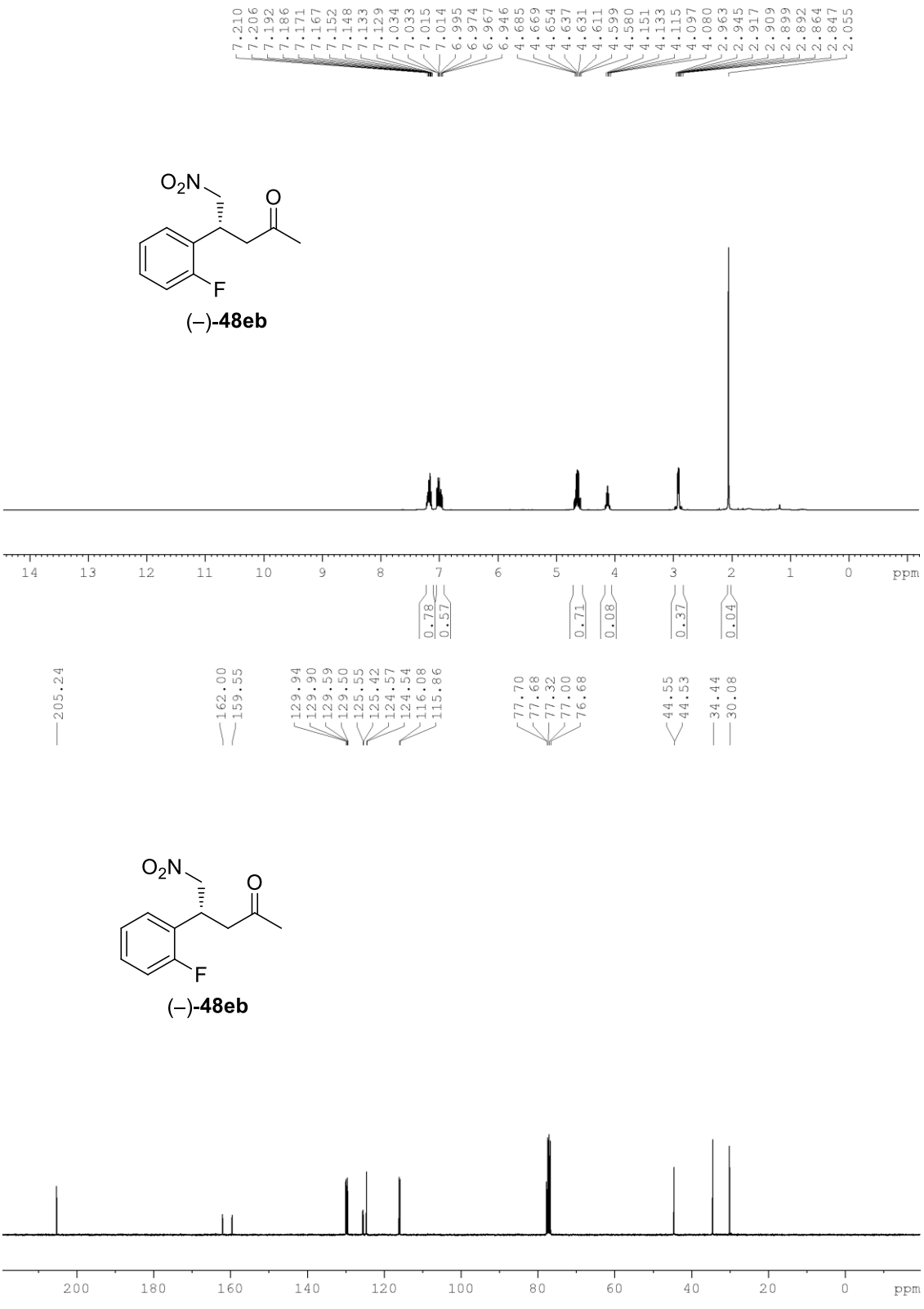
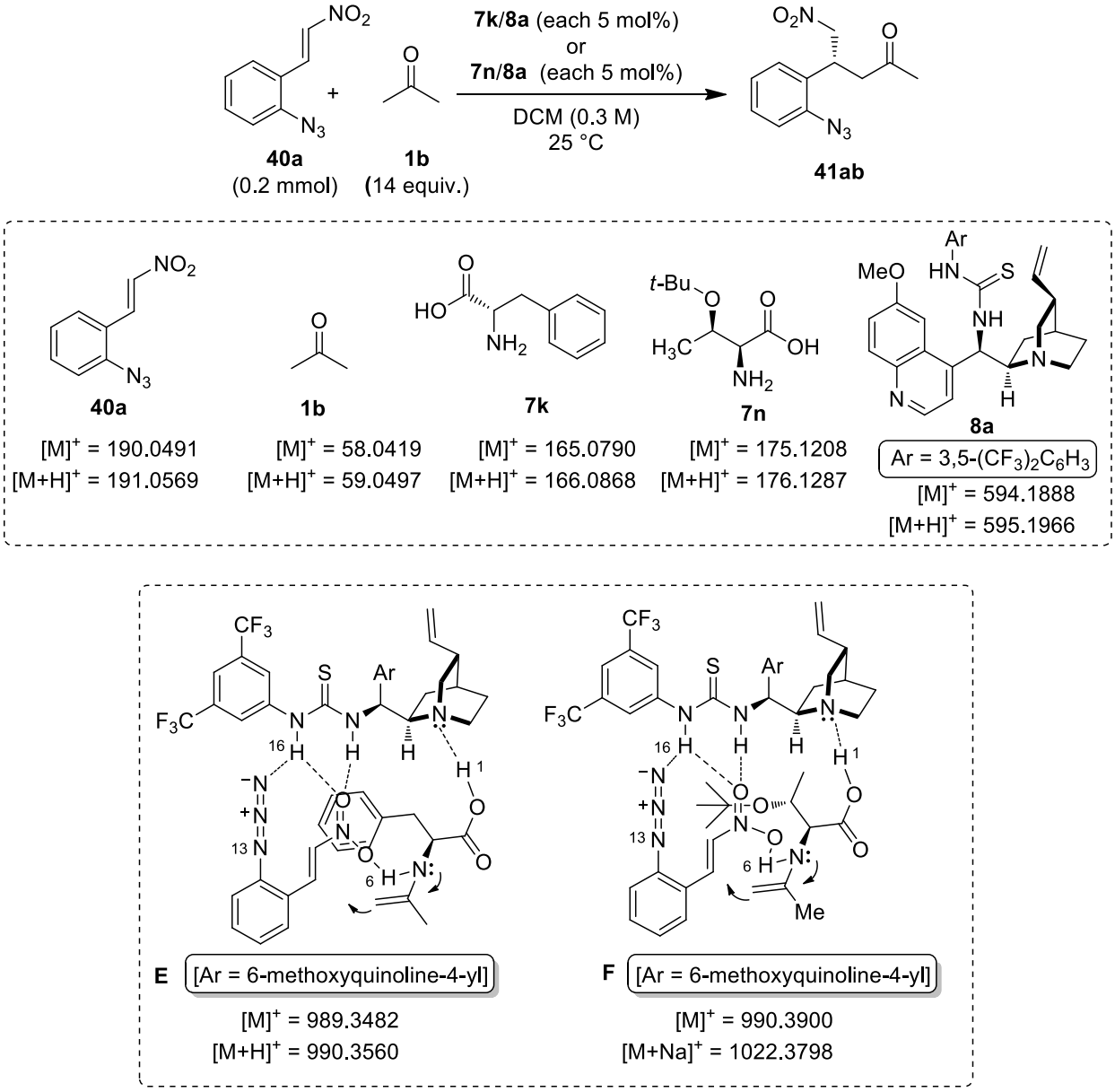



***Figure-13:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **48eb**.

### *3.2.8 Experimental evidence for the formation of supramolecular self-assembly in pre-transition state through on-line ESI-HRMS analysis:*

We gained some more evidence for the involvement of hypothetical *pre*-transition state supramolecular assembly, by careful investigation of the on-going reaction of **40a** and **1b** under the **7k/8a** and **7n/8a**-catalysis using ESI-HRMS technique (Scheme 2), which enabled us to identify the proposed catalytic *pre*-transition state intermediates.[19] The ESI-HRMS spectrum of an on-going reaction of **40a** (0.2 mmol) and **1b** (2.8 mmol, 14 equiv.) in the presence of **7k/8a** (each 5 mol %) in the DCM at 25 °C after 60 minutes, revealed the formation of the *pre*-transition state supramolecular assembly intermediate $[\mathbf{E}+H]^+$ (*m*/*z* 990.3560) [Figure-14-(i)]. In a similar manner, ESI-HRMS spectrum of an on-going reaction of **40a** (0.2 mmol) and **1b** (2.8 mmol, 14 equiv.) in the presence of another catalytic system **7n/8a** (each 5 mol %) in the DCM at 25 °C after 60 minutes also revealed the formation of the key catalytic *pre*-transition state supramolecular assembly intermediate $[\mathbf{F}+Na]^+$ (*m*/*z* 1022.3798) [Figure-14-(ii)]. Catalytic supramolecular assemblies of $[\mathbf{E}+H]^+$ (*m*/*z* 990.3554) and $[\mathbf{F}+Na]^+$ (*m*/*z* 1022.3794) were obtained in very low intensities in ESI-HRMS spectrum, due to this reason we are not able to see the isotopic pattern of both $[\mathbf{E}+H]^+$ (*m*/*z* 990.3554) and $[\mathbf{F}+Na]^+$ (*m*/*z* 1022.3794) in the ESI-HRMS spectrums.

***Scheme 2:*** Experimental Details of the HRMS Experiment: Reaction of **40a** and **1b** in the Presence of **7k**/**8a** and **7n/8a**.



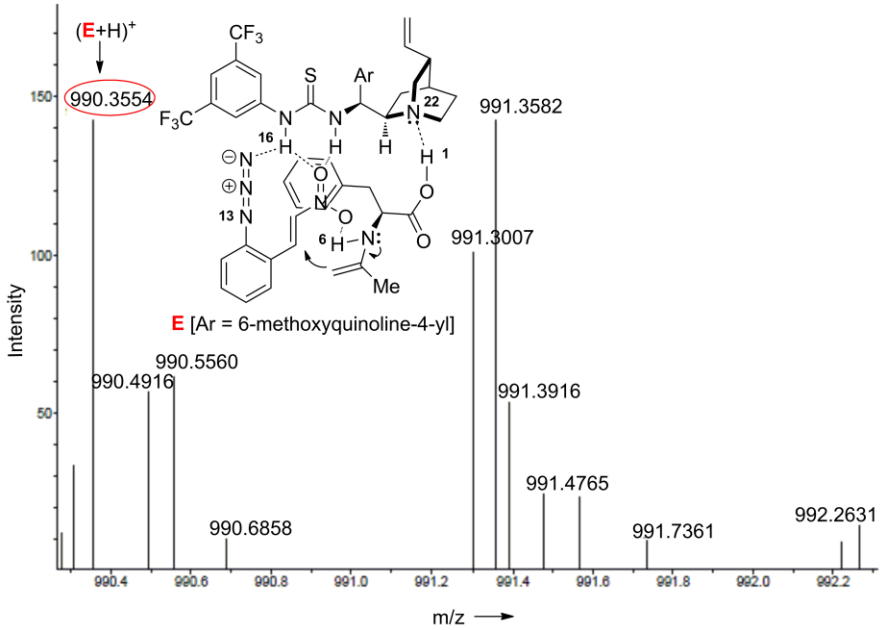



***Figure 14-(i)*:** ESI-HRMS (positive mode) spectrum of the reaction after 60 minutes of **40a** and **1b** catalyzed by **7k/8a** in DCM at 25 °C.

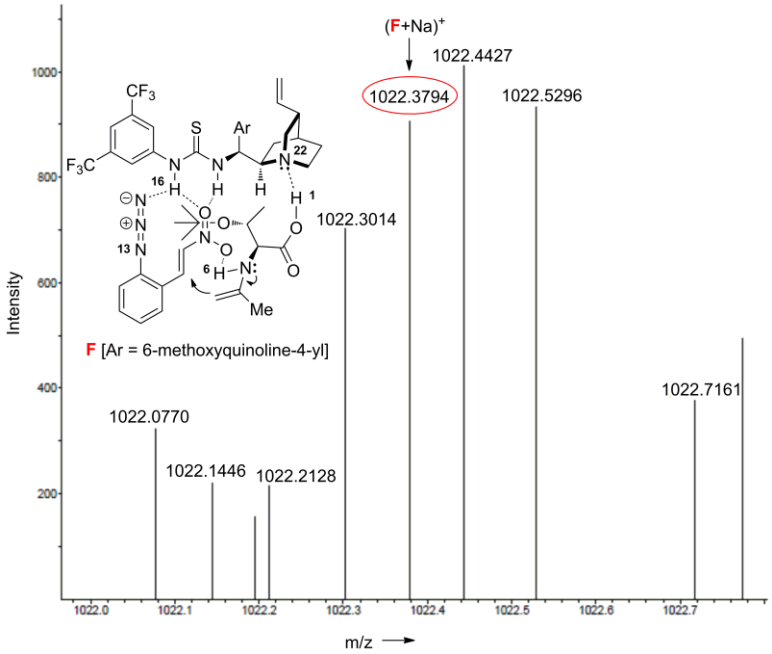
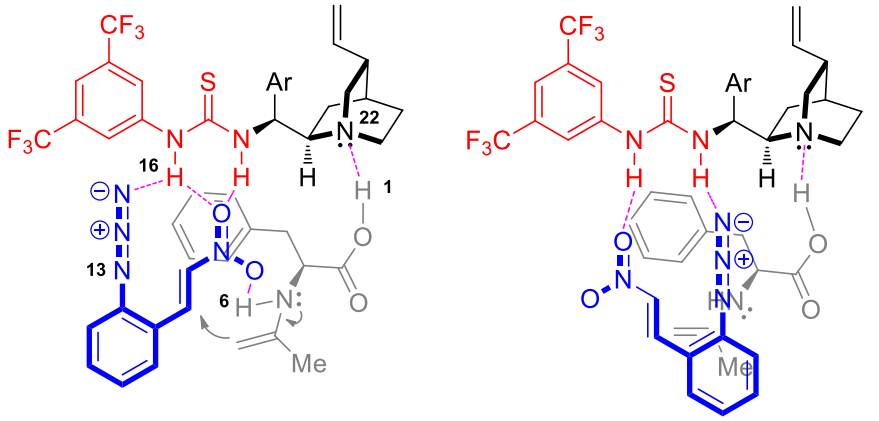



***Figure 14-(ii)*:** ESI-HRMS (positive mode) spectrum of the reaction after 60 minutes of **40a** and **1b** catalyzed by **7n/8a** in DCM at 25 °C.

### *3.2.9 Mechanistic insights:*

With controlled experimental data, herein we securely illustrate the mechanism of the asymmetric Michael reaction through conformationally flexible cyclic 22-membered *pre*-transition state supramolecular assembly by **7k**/**8a**-catalysis and the reaction most probably proceeds through the **TS-1** mechanism (Figure-15). We emphasize five interactions between the substrates and the catalysts to support a cyclic 22-membered *pre*-transition state assembly (**TS-1**) to furnish the chiral keto azides **41** over the less stable **TS-2**. Based on our observations, (i) $CO_2H$ group of L-**7k** undergoes hydrogen bonding with *tert*-amine group of **8a**, which brings the two catalysts closer to the reaction centre; (ii) *N*H groups of **8a** involves the hydrogen-bonding with both $N_3$ and $NO_2$ groups of **40a-h** to activate the electrophilic nature of olefin; (iii) primary amino group of L-**7k** forms enamine with acetone to activate the nucleophilic nature; (iv) finally $NO_2$ group of **40a-h** undergoes hydrogen-bonding with enamine N*H*, thus closing the mobile 22-membered supramolecular cyclic *pre*-transition state to control the enantioselectivity (Figure-15).




**TS-1 (Favorable Activation)**
TS Model for Michael Reaction *via*
Supramolecular-Catalysis
(***Re-face Approach***)

**TS-2 (Unfavorable Activation)**
TS Model for Michael Reaction *via*
Thiourea/Amino acid-Catalysis
(***si-face Approach***)

***Figure-15***: Proposed reaction mechanism.

## *3.3 Conclusions*

In summary, we have demonstrated a novel and efficient *in situ* generated chiral supramolecular assembly as the best catalyst than its synthons for the asymmetric Michael reaction of acetone with (*E*)-1-azido-2-(2-nitrovinyl)benzenes **40** followed by reductive amination to furnish the medicinally important *syn*-2,4-disubstituted tetrahydroquinolines **42** with high yield, *ee* and *de* values. With the help of the ESI-HRMS technique and controlled experiments, we have obtained strong evidence for the *in situ* formation of proposed catalytic supramolecular assembly from the organocatalysts. Readily *in situ* generated chiral supramolecular assembly catalysts would become promising future catalytic systems for more functionalized substrates than organocatalysts.

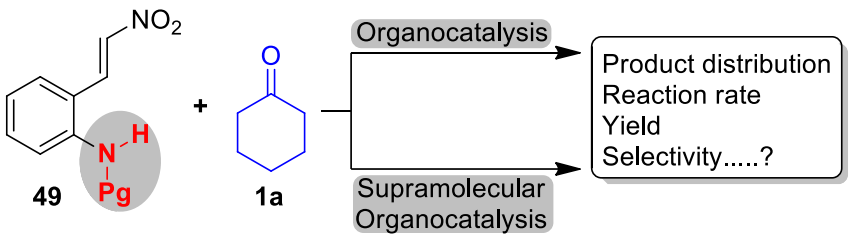
.

# 4. Highly Asymmetric Michael Addition of Ketones to Nitro-olefins through Supramolecular-organocatalysis

## *4.1 Introduction*

The last two decades have witnessed the rediscovery of green asymmetric C-C,[23] C-N,[24] C-O,[25] C-S,[26] C-P,[27] and C-X (X = F, Cl, Br and I)[28] bonds formation through enamine-, enolate-, iminium-, dienamine-, trienamine-, or aminoenyne-activation of simple carbonyl compounds under the catalysis of amine, amino acids and amine thiourea. Surprisingly, these organocatalysts worked well for all substrates other than functionally rich substrates in terms of reactivity and selectivity. To increase the rate and selectivity of known organocatalytic asymmetric reactions, a few research groups have recently started develop the synergistic- and cooperative-catalysis[29] or modularly designed catalysts from organocatalysts.[30] Recently, our group took the challenge to investigate the neighboring group participation in the *pre-* and *post*-transition state of organocatalytic reactions to study the rate/selectivity.[31] In this process, we utilized the new reaction tool called "modularly designed supramolecular-organocatalysis", for which almost all functional groups of substrates and catalysts undergo self-assembly through combination of covalent, hydrogen-bonding and weak interactions.[32] This *in-situ* generated "supramolecular self-assembly" is fully responsible for achieving high rate and selectivity in the designed asymmetric reactions from the functionally rich substrates.[32]

***Scheme 3:*** Proposal for Asymmetric C-C Bond Formation through Modularly Designed Supramolecular-organocatalysis beyond Organocatalysis.



As we were very much interested to synthesizing the highly functionalized chiral products in good yields with high rate/*ee*/*de* through C-C bond formation for the direct synthetic applications, we chose (*E*)-2-(2-nitrovinyl)anilines[33] as the substrates for the asymmetric Michael reaction with cyclic/acyclic ketones (Scheme 3). Notably, upon performing the Michael reaction of functionalized monoprotected (*E*)-2-(2-nitrovinyl)anilines with cyclohexanone under the renowned standard organocatalytic conditions, we ended up with poor results (Table 6). To overcome this problem, we envisioned the use of modularly designed supramolecular-organocatalysts,[30,32] instead of looking for new organocatalysts. Given that massive number of supramolecular-organocatalysts can be assembled *in-situ* from easily available simple organocatalysts through covalent, hydrogen-bonding and weak interactions in a small amount of time, we embarked on this journey. This newly emerging modularly designed self-assembly catalysis seems to be beyond organocatalysis, predicted to be bio-mimetic supramolecular-organocatalysis.[32]

## *4.2 Results and Discussions*

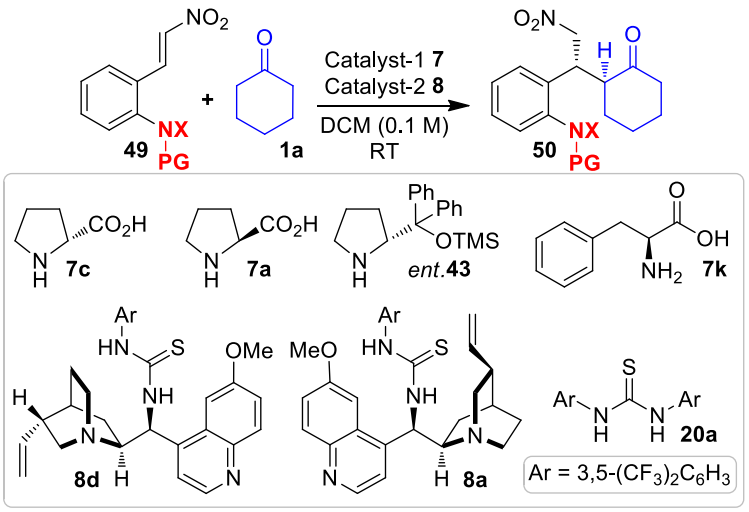
### *4.2.1 Reaction optimization:*

To check the fruition of supramolecular-organocatalysis, we examined the Michael reaction of N-Cbz-N*H*-(*E*)-2-(2-nitrovinyl)aniline **49a** with fifteen equiv. of cyclohexanone **1a** in the presence of catalysts **7** and **8** or (**7**+**8**) in DMSO, MeOH, and DCM at 25 °C. Surprisingly, no Michael reaction was observed in the presence of the well known organocatalysts (*R*)-DPPOTMS *ent*.**43**/$PhCO_2H$, **7c**, **8d** and **7c**/**20a** in DMSO, MeOH or DCM for 24-72 h at 25 °C, and starting materials were recovered (Table 6, entries 1-6). Amazingly, the Michael reaction of **49a** with five equiv. of **1a** under the catalysis of modularly designed supramolecular-organocatalysts (**7c**+**8d**) (each 5 mol%) in DCM (0.5 M) at 25 °C for 5 h furnished the chiral product (–)-**50aa** in 75% yield with 97% *ee* and 93% *de* (Table 6, entry 7). To improve the yield and *ee*/*de* of (–)-**50aa**, we then subjected **49a** with five to fifteen equiv. of **1a** under each 5 mol% of (**7c**+**8d**) in DCM (1.0 to 0.1 M) at 25 °C for 5-16 h (Table 6, entries 8-10). To our delight, the chiral Michael product (–)-**50aa** was isolated in 99% yield with 99% *de* and 98% *ee* from the best optimized conditions (Table 6, entry 10). This result ultimately proves that the reaction yield, rate and selectivity totally depend on the highly organized modularly designed

supramolecular-organocatalysts (**7c**+**8d**) along with reactant equivalents and solvent concentration.

To further understand the role of N*H* and N-protective groups in the self-assembly of the substrates and catalysts in the *pre*-transition state and also to see the scope of modularly designed supramolecular-organocatalysts (**7c**+**8d**), we performed the Michael reaction of cyclohexanone **1a** with different N-protected (*E*)-2-(2-nitrovinyl)anilines **49b-f** through supramolecular-organocatalysis (Table 6, entries 11-17). Reaction of N-Boc-N*H*-(*E*)-2-(2-nitrovinyl)aniline **49b** with **1a** under the (**7c**+**8d**)-catalysis in DCM for 18 h furnished the chiral product (–)-**50ba** in 91% yield with 99% *de* and 97% *ee* (Table 6, entry 11). The same reaction yielded opposite enantiomer (+)-**50ba** in only 57% yield with 99% *de* and 99% *ee* from the catalysts combination of L-proline **7a** and quinidine-*N*H-thiourea **8a** in DCM at 25 °C for longer reaction time (Table 6, entry 12). In the place of L-proline **7a**, when acyclic amino acid (L-phenylalanine **7k**) was used, the reaction did not proceed (Table 6, entry 13).[32b] In a similar manner, Michael reaction of **1a** with N-$CO_2$Et-N*H*-(*E*)-2-(2-nitrovinyl)aniline **49c** and N-Ac-N*H*-(*E*)-2-(2-nitrovinyl)aniline **49d** under (**7c**+**8d**)-catalysis in DCM at 25 °C for 7-5 h, generated chiral products (–)-**50ca** in 82% yield with 99% *de* and 98% *ee* and (–)-**50da** in 89% yield with 92% *de* and 99% *ee*, respectively (Table 6, entries 14 and 15). To investigate the role of N*H* in **49** for the *in-situ* supramolecular self-assembly with **1a** and (**7c**+**8d**) in the *pre*-transition state of the Michael reaction, we performed the reaction with N-Boc-N-Me-(*E*)-2-(2-nitrovinyl)aniline **49e** and N-Cbz-N*H*-(*E*)-3-(2-nitrovinyl)aniline **49f** under the supramolecular-organocatalysis conditions. Distinctly, we acquired the products (+)-**50ea** in 29% yield with 99% *de* and 20% *ee* and **50fa** in <5% yield even after 96/168 h, respectively (Table 6, entries 16 and 17). These observations are in strong support of the hypothetical self-assembly between the active functional groups of substrates and catalysts (Table 6, entries 16 and 17).

***Table 6***: Reaction Optimization.[a]




| Entry | Catalyst **7/8** (5 mol%) | PG, X | *t* (h) | Yield (%)[b] **50** | Selectivity (%)[c] *ee* | *de* |
|---|---|---|---|---|---|---|
| 1[d] | *ent*.**43**/$PhCO_2H$ | **49a**: Cbz, H | 24 | – | – | – |
| 2[d, e] | *ent*.**43**/$PhCO_2H$ | **49a**: Cbz, H | 48 | – | – | – |
| 3[d, f] | *ent*.**43**/$PhCO_2H$ | **49a**: Cbz, H | 48 | – | – | – |
| 4 | **7c** | **49a**: Cbz, H | 24 | – | – | – |
| 5 | **8d** | **49a**: Cbz, H | 24 | – | – | – |
| 6 | **7c/20a** | **49a**: Cbz, H | 72 | – | – | – |
| 7[g] | **7c/8d** | **49a**: Cbz, H | 5 | 75 (**50aa**) | 97 | 93 |
| 8[h] | **7c/8d** | **49a**: Cbz, H | 5 | 90 (**50aa**) | 96 | 94 |
| 9[i] | **7c/8d** | **49a**: Cbz, H | 16 | 98 (**50aa**) | 98 | 99 |
| **10** | **7c/8d** | **49a: Cbz, H** | **10** | **99 (50aa)** | **98** | **99** |
| 11 | **7c/8d** | **49b**: Boc, H | 18 | 91 (**50ba**) | 97 | 99 |
| 12 | **7a/8a** | **49b**: Boc, H | 48 | 57 (**50ba**) | –99 | 99 |
| 13 | **7k/8a** | **49b**: Boc, H | 72 | – | – | – |
| 14 | **7c/8d** | **49c**: $CO_2Et$, H | 7 | 82 (**50ca**) | 98 | 99 |
| 15 | **7c/8d** | **49d**: $COCH_3$, H | 5 | 89 (**50da**) | 99 | 92 |
| 16 | **7c/8d** | **49e**: Boc, Me | 96 | 29 (**50ea**) | 20 | 99 |
| 17[j] | **7c/8d** | **49f**: Cbz, H | 168 | <5 (**50fa**) | nd | – |

[a] Unless stated otherwise, all reactions were carried out with **49** (0.1 mmol), cyclohexanone **1a** (1.5 mmol, 15.0 equiv.), catalysts **7** and **8** (5 mol% each) in DCM (1.0 mL) at 25 °C. [b] Yield refers to the column-purified product. [c] *ee* and *de* were determined by CSP-HPLC analysis. [d] 20 mol% of *ent*.**43**/$PhCO_2H$ was used. [e] DMSO as solvent. [f] MeOH as solvent. [g] **1a** (5.0 equiv.) in DCM (0.5 M). [h] **1a** (5.0 equiv.) in DCM (1.0 M). [i] **1a** (10.0 equiv.) in DCM (0.1 M). [j] (*E*)-benzyl (3-(2-nitrovinyl)phenyl)carbamate **49f** was used.

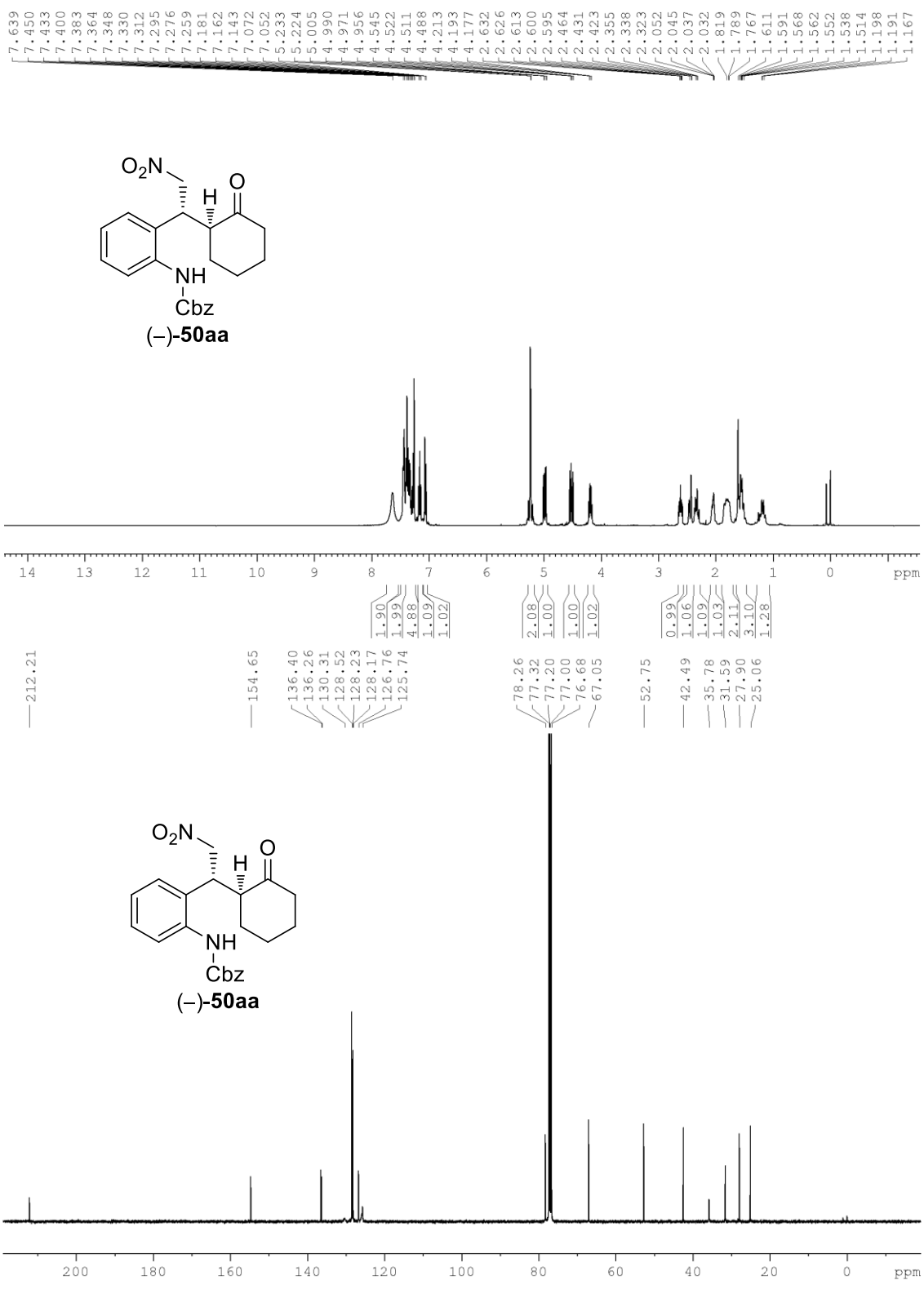



***Figure-16:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **50aa**.

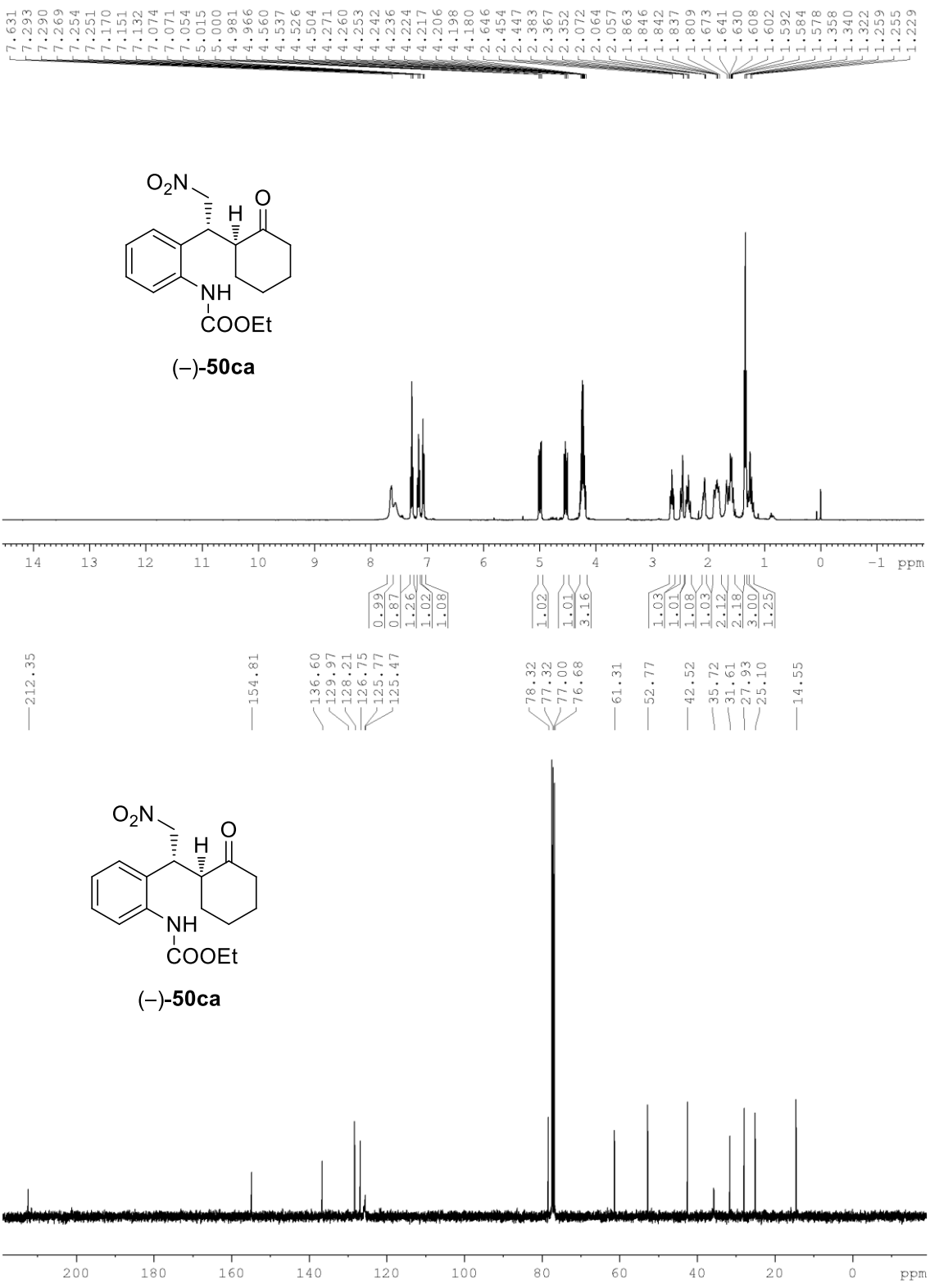


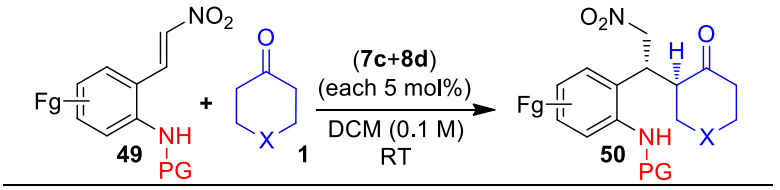

***Figure-17:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **50ca**.

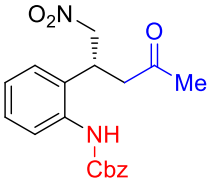
### *4.2.2 Scope of asymmetric supramolecular-organocatalysis:*

Before studying the scope of asymmetric supramolecular-organocatalysis we synthesised a library of racemic compounds *rac*-**50** in excellent yields through DL-proline-catalysis (for details see Annexure-I, Table A1). The universality of the supramolecular-organocatalysis was further supported by treating functionalized N-Cbz-N*H*-(*E*)-2-(2-nitrovinyl)anilines **49a–j** with various functionalized cyclic/acyclic ketones **1a-h** catalyzed by each 5 mol% of (**7c**+**8d**) at 25 °C in DCM for 4-24 h (Table 7). Chiral products **50ab-ja** were isolated in good to excellent yields, good to excellent *de* and *ee* values, and the electronic and steric influence of the substrates were tolerated. Exceptionally, the reaction of simple ketones such as acetone **1b** and butanone **1c** with **49a** or **49b** under (**7c**+**8d**) catalysis furnished expected Michael products **50ab**, **50bb** and **50ac** in good to excellent yields with high selectivity and there was no other regioisomer formed in the later case (Table 7). The Michael reaction of **49a** with different cyclic ketones **1d-h** under (**7c**+**8d**) catalysis at 25 °C for 8-24 h furnished the chiral products **50ad-ah** in good to excellent yields with high *ee* values and moderate *de* values (Table 7). Notably, the ring size and functional groups on cyclic ketones **1d-h** did not show much effect on the outcome of product yield and selectivity (Table 7). In a similar manner, reaction of **1a** with different functionally rich nitro-olefins **49g-j** under the (**7c**+**8d**)-catalysis at 25 °C for 4-7 h furnished the chiral products **50ga-ja** in excellent yields with almost single enantiomer/diastereomer irrespective of the electronic factors of the substrate (Table 7).[34]

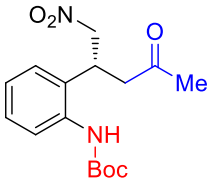
The structures, and relative and absolute stereochemistry of the Michael products **50** were confirmed by NMR spectroscopy and were also confirmed by correlation with previous studies.[32a] The reaction of ketone **1** with 2-(2-nitrovinyl)phenol catalyzed by the same supramolecular-organocatalyst (**7c**+**8d**) was reported to give Michael products with (*R*,*S*) configuration.[32a] It is presumed that the absolute configuration of products **50** can be assigned to be the same by analogy.[32a]

***Table 7***: Reaction Scope.[a-e]

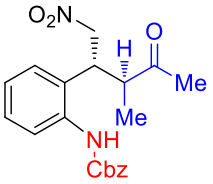


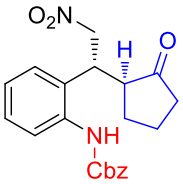

**50ab**: 7 h (90%)
*ee* = 99%



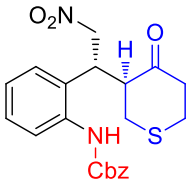

**50bb**: 10 h (93%)
*ee* = 98%



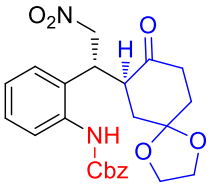

**50ac**: 24 h (50%)
*ee* = 99%; *de* = 85%



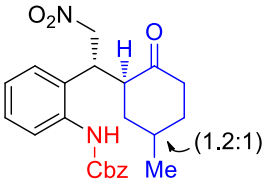

**50ad**: 12 h (66%)
*ee* = 99%; *de* = 57%



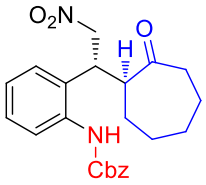

**50ae**: 8 h (88%)
*ee* = 96%; *de* = 70%



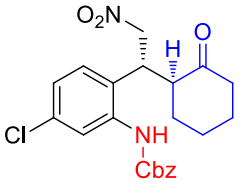

**50af**: 8 h (85%)
*ee* = 89%; *de* = 68%



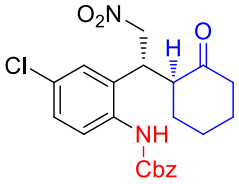

**50ag**: 8 h (97%)
*ee* = 96% (major)
*ee* = 98% (minor)
*de* = 92%



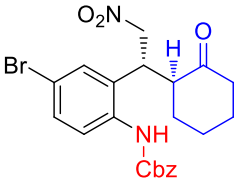

**50ah**: 24 h (40%)
*ee* = 92%; *de* = 82%



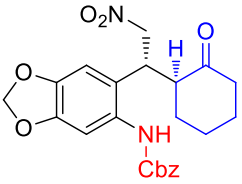

**50ga**: 4 h (90%)
*ee* = 99%; *de* = 99%




**50ha**: 4 h (93%)
*ee* = 99%; *de* = 99%




**50ia**: 5 h (91%)
*ee* = 99%; *de* = 85%




**50ja**: 7 h (80%)
*ee* = 99%; *de* = 85%

[a] Unless stated otherwise, all reactions were carried out with **49** (0.1 mmol), ketone **1** (1.5 mmol, 15.0 equiv.), catalysts **7c** and **8d** (5 mol% each) in DCM at RT. [b] Yield refers to the column-purified product. [c] *de* was determined based on $^1$H NMR or HPLC analysis. [d] *ee* was determined by CSP-HPLC analysis. [e] *ee* mentioned for major isomer.

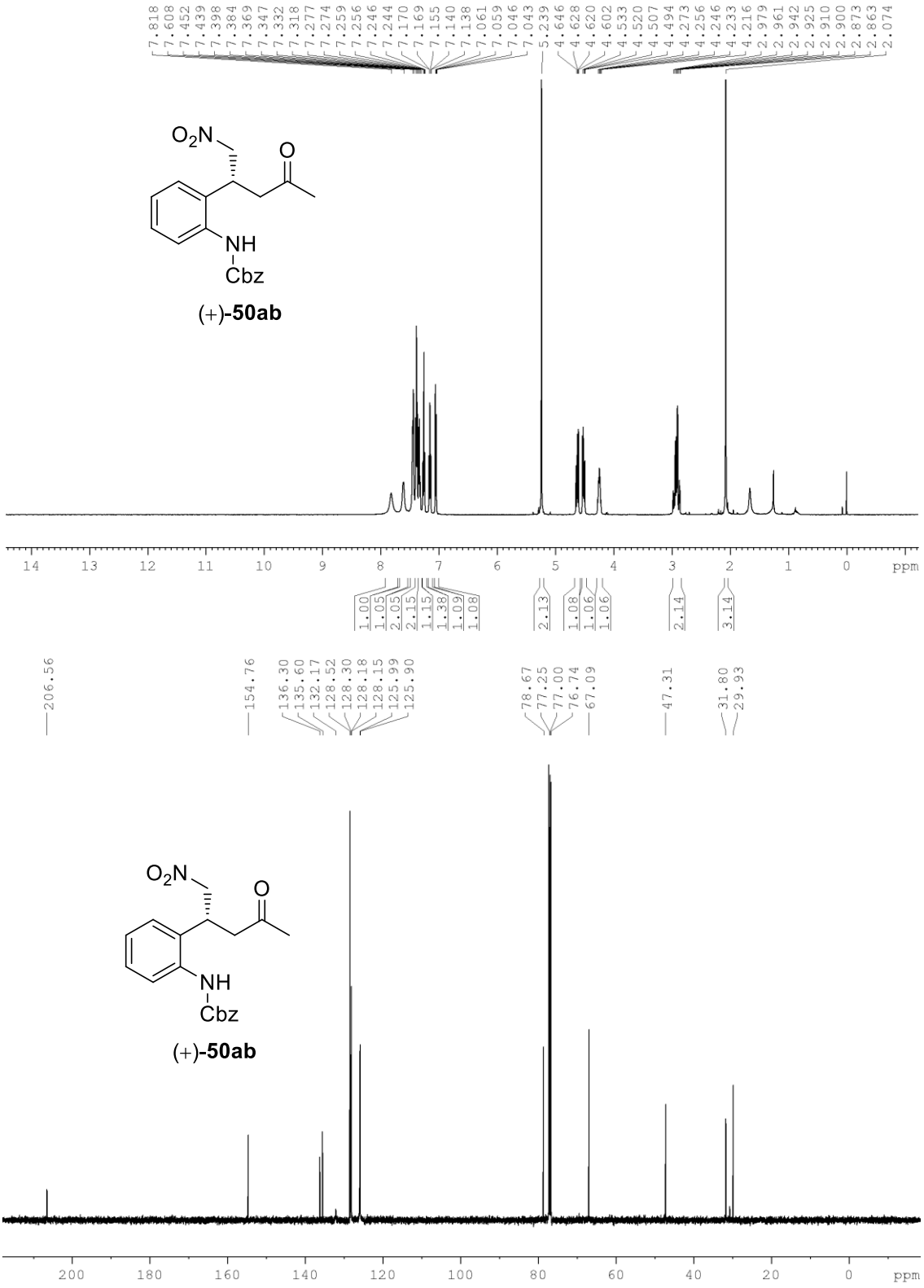



***Figure-18:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **50ab**.

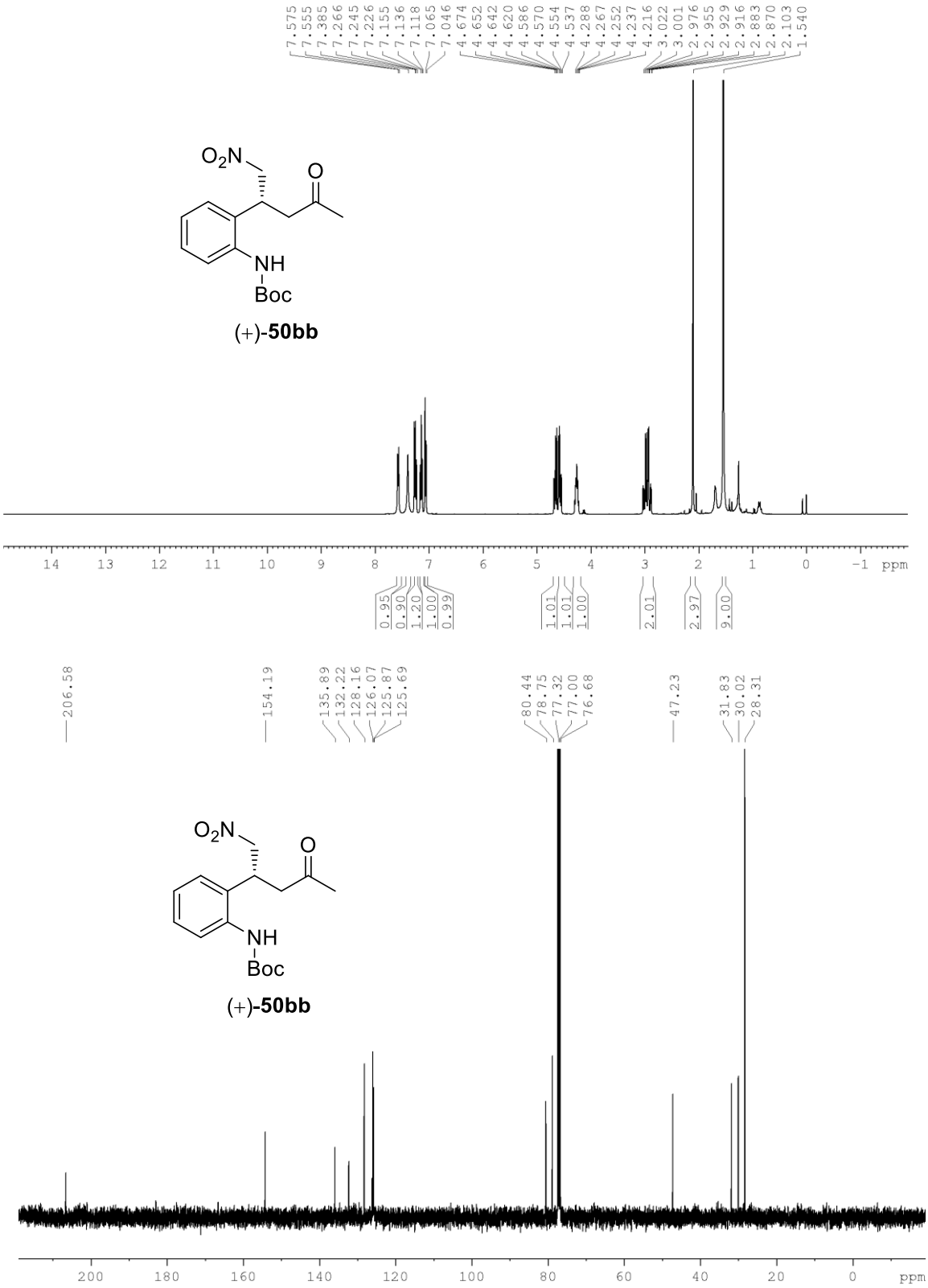



***Figure-19:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **50bb**.

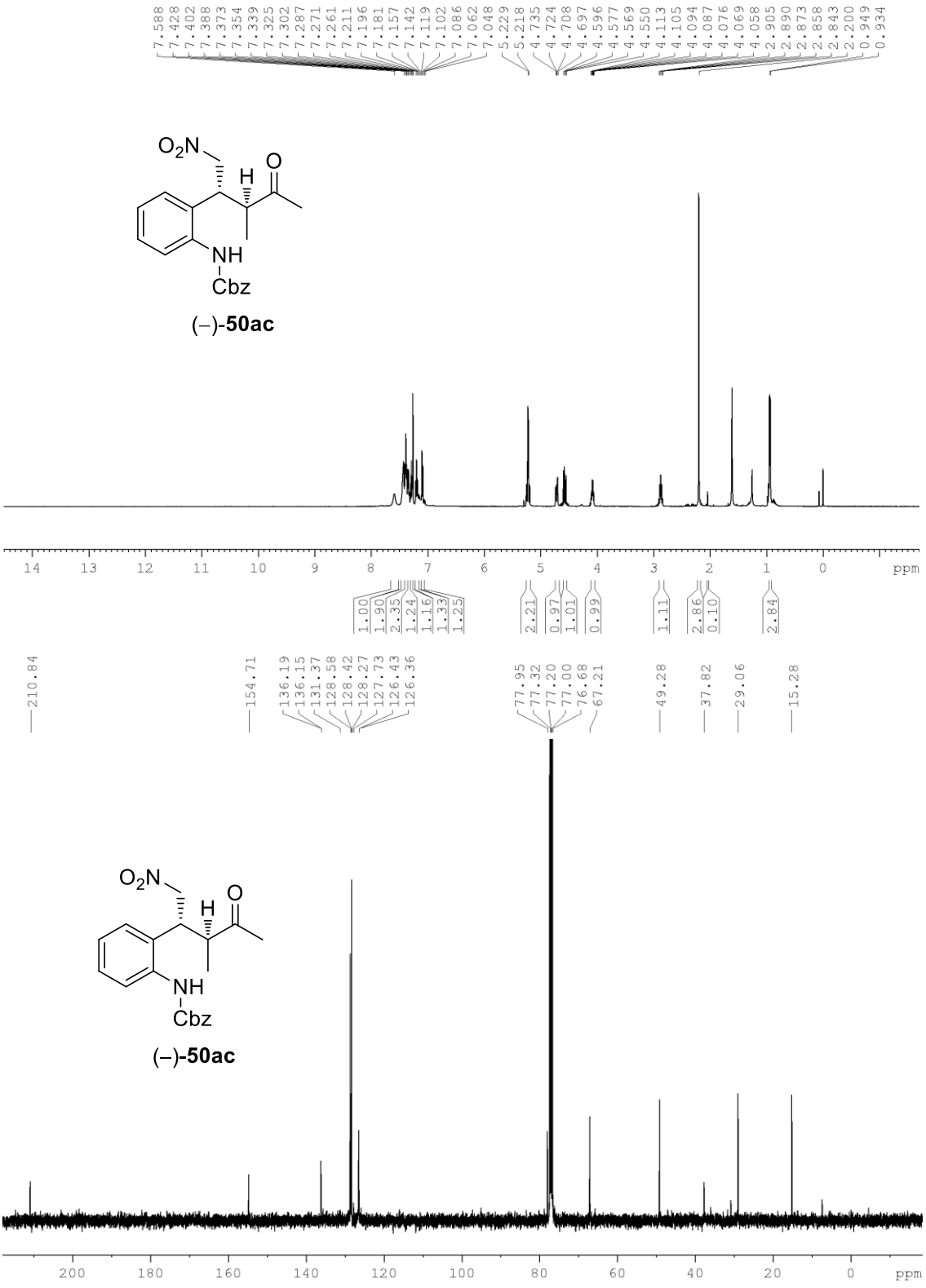



***Figure-20:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **50ac**.

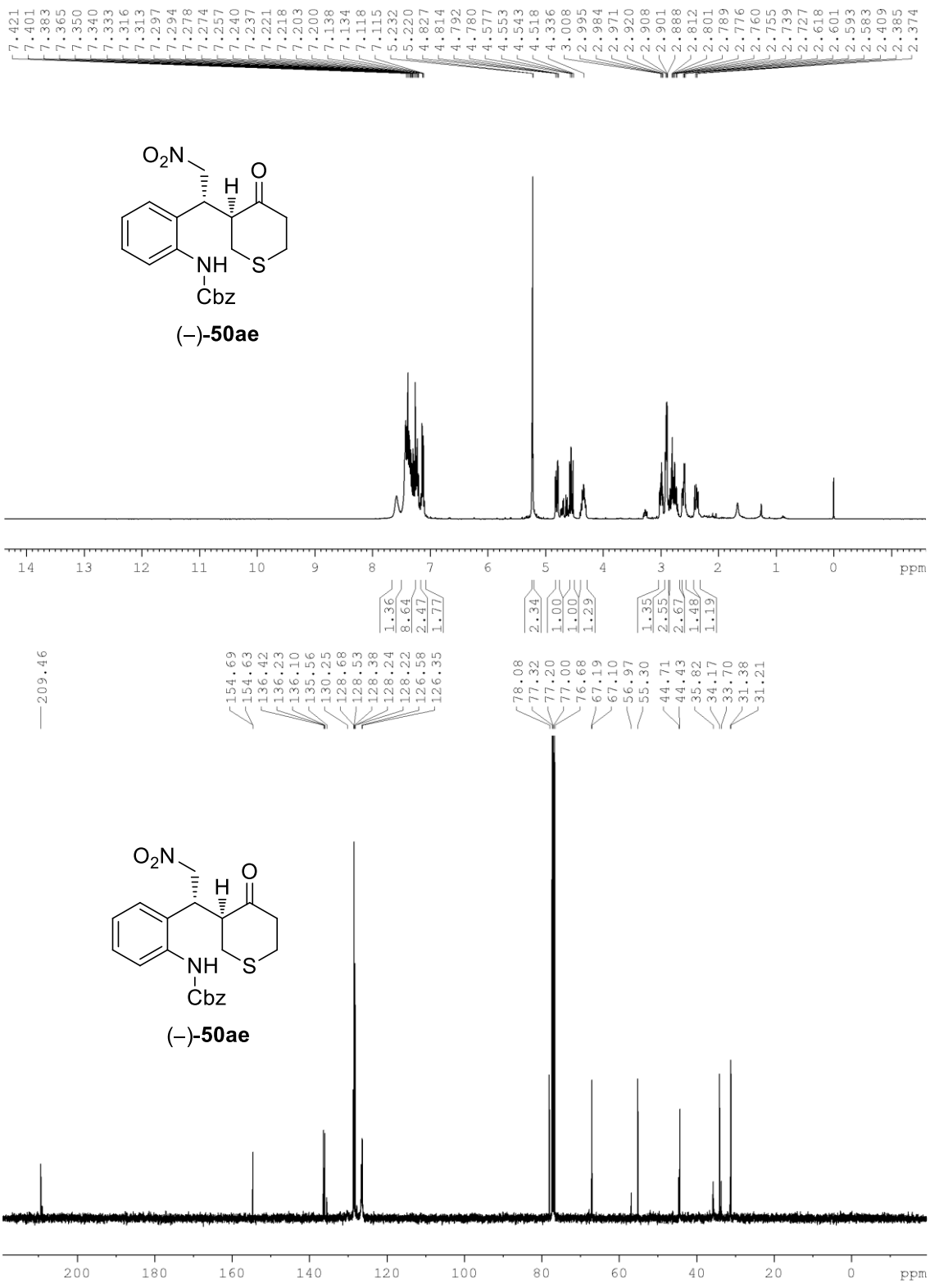



***Figure-21:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **50ae**.

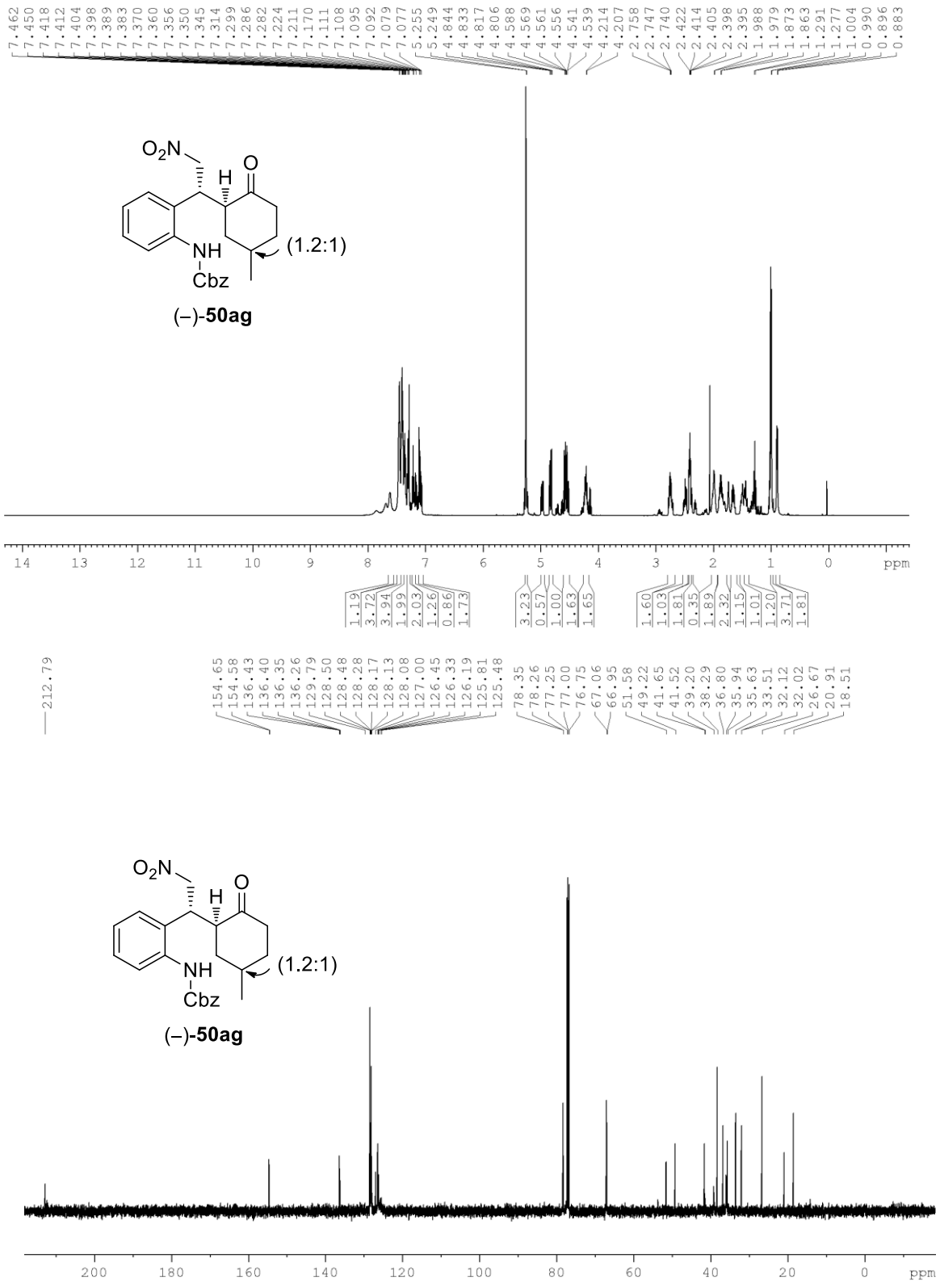



***Figure-22:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **50ag**.

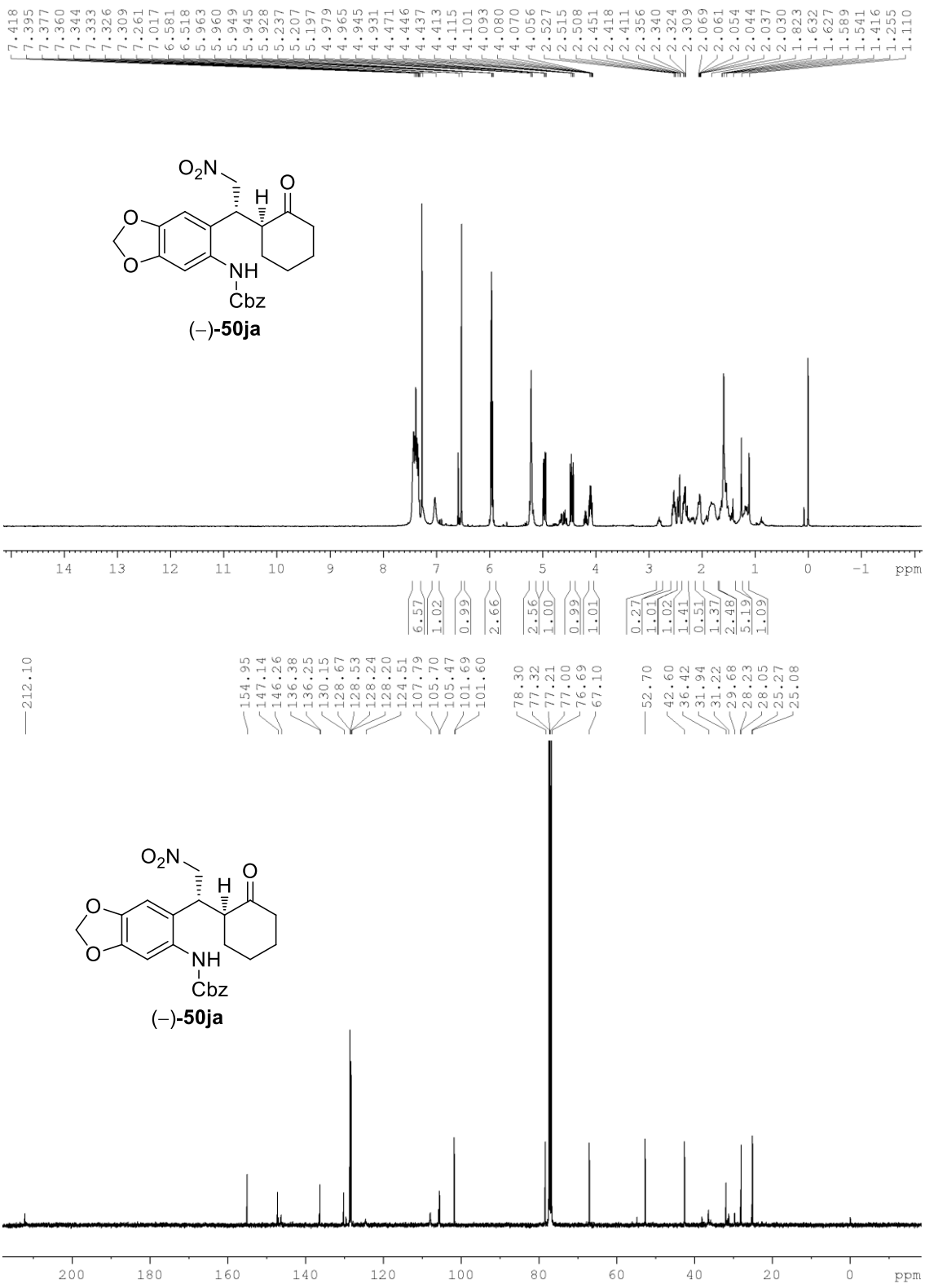


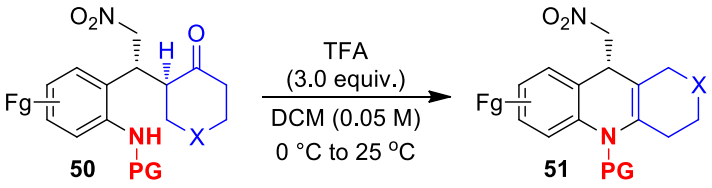

***Figure-23:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **50ja**.

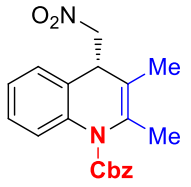
### *4.2.3 Synthetic applications of chiral Michael adducts:*

We explored the utility of both chiral carbamates **50** and racemic carbamates **50** in high-yielding synthesis of chiral tetrahydroquinolines **51** (Table 8) and racemic tetrahydroquinolines *rac*-**51** (for details see Annexure-I, Table A2). Many acridines, such as proflavine have antiseptic properties and related derivatives also bind to DNA and RNA owing to their abilities to intercalate.[34] With these medicinal applications in mind, we subjected different chiral carbamates **50** to simple aminal formation followed by dehydration protocol to furnish the enantiomerically pure tetrahydroacridines **51** (Table 8).[34] Interestingly, Brønsted acid trifluoroacetic acid (TFA)-induced aminal formation/dehydration of chiral carbamate (–)-**50aa** in DCM at 0-25 °C for 3 h furnished the substituted tetrahydroacridine (+)-**51aa** in 90% yield with 98% *ee* (Table 8). Similarly, aminal formation/dehydration of acyclic carbamate (–)-**50ac** in DCM at 0-25 °C for 2 h furnished substituted tetrahydroacridine (+)-**51ac** in 85% yield with 98% *ee* (Table 8). The selective aminal formation/dehydration strategy was further demonstrated with eleven more chiral substrates, and the expected substituted tetrahydroacridines **51ad-ia** were furnished in excellent yields with *ee* values without showing any influence from the electronic and steric factors of the substrates (Table 8).

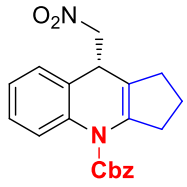
The importance of this protocol is highlighted by the fact that many of the functionalized tetrahydroacridines **51** represent the core structure of antibacterial chromophore,[34] and by the fact that they are easily accessible by this approach. The structure and absolute stereochemistry of the Michael products **50**, and tetrahydroacridines **51** were confirmed by NMR spectroscopy and were also finally confirmed by X-ray structure analysis[35] of (+)-**51da** as shown in Figure-30.

***Table 8***: Reaction Application.[a-d]

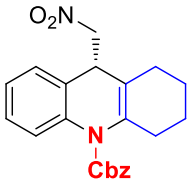


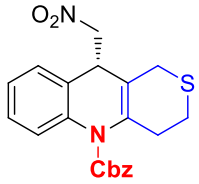

**51ac**: 2 h (85%)
*ee* = 98%



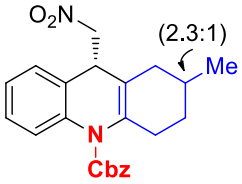

**51ad**: 2 h (90%)
*ee* = 98%



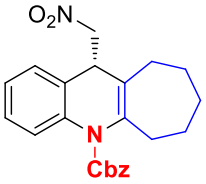

**51aa**: 3 h (90%)
*ee* = 98%



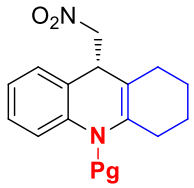

**51ae**: 3 h (90%)
*ee* = 96%



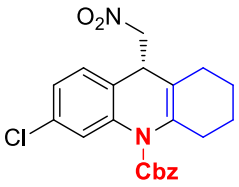

**51ag**[d]: 3 h (90%)
*ee* = 97% (major)
*ee* = 96% (minor)



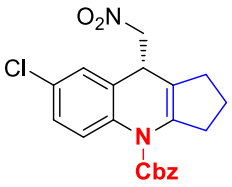

**51ah**: 5 h (82%)
*ee* = 94%



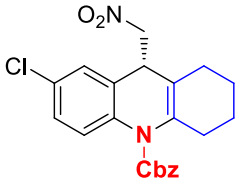

**51ba** (Boc): 3 h (90%), 99% *ee*
**51da** (Ac): 3 h (90%), 98% *ee*



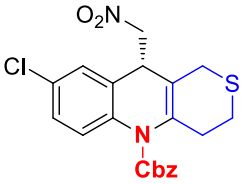

**51ga**: 3 h (89%)
*ee* = 97%



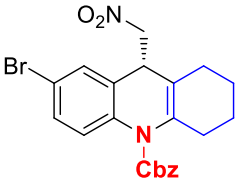

**51hd**: 2 h (90%)
*ee* = 99%




**51ha**: 2 h (91%)
*ee* = 99%




**51he**: 5 h (87%)
*ee* = 96%




**51ia**: 3 h (90%)
*ee* = 99%

[a] Unless stated otherwise, all reactions were carried out with **50** (0.1 mmol), and TFA (0.3 mmol, 3.0 equiv.), DCM at 0 °C to RT.[b] Yield refers to the column-purified product. [c] *ee* was determined by CSP-HPLC analysis. [d] *dr* was determined based on $^1$H NMR or HPLC analysis.

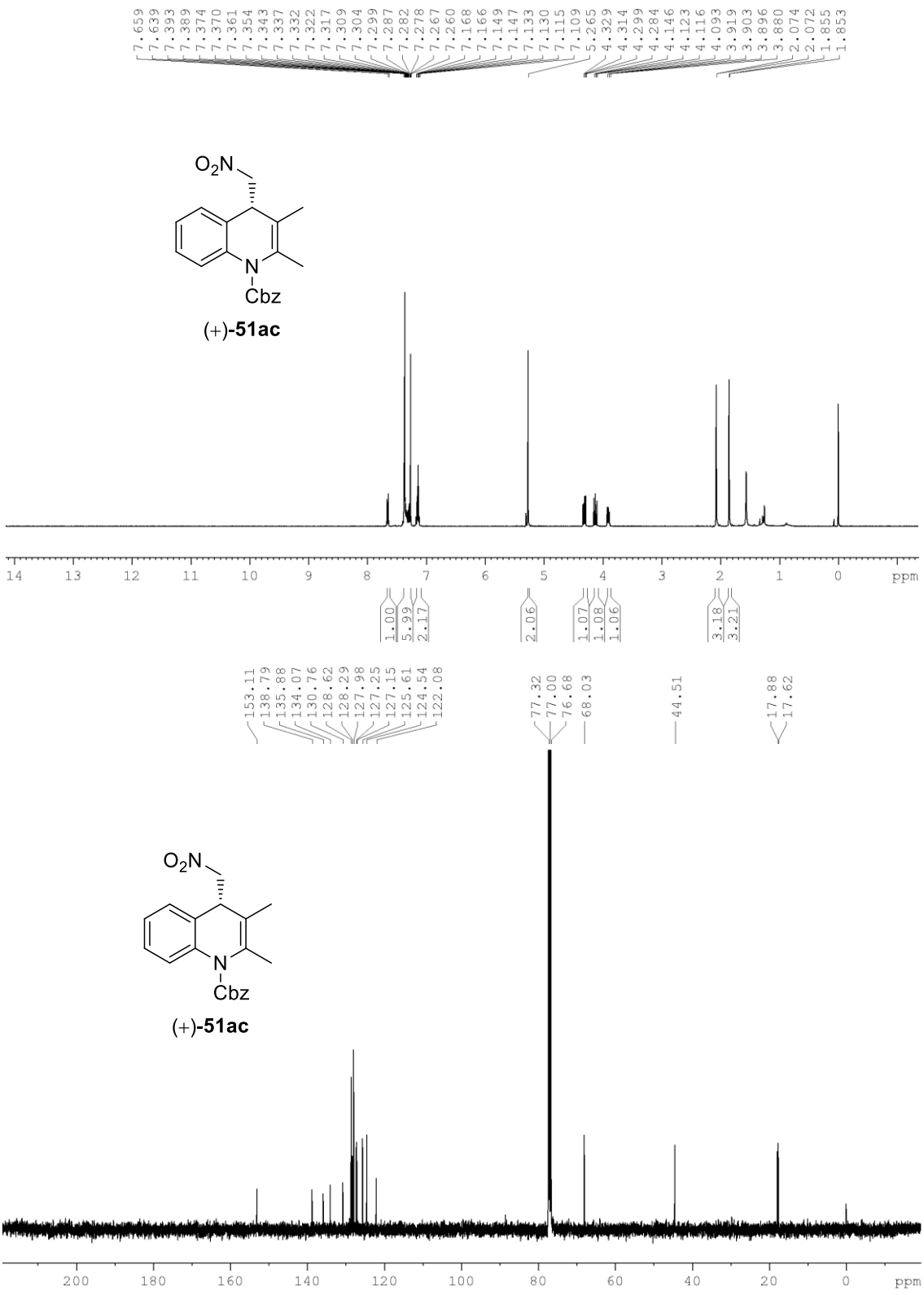



***Figure-24:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **51ac**.

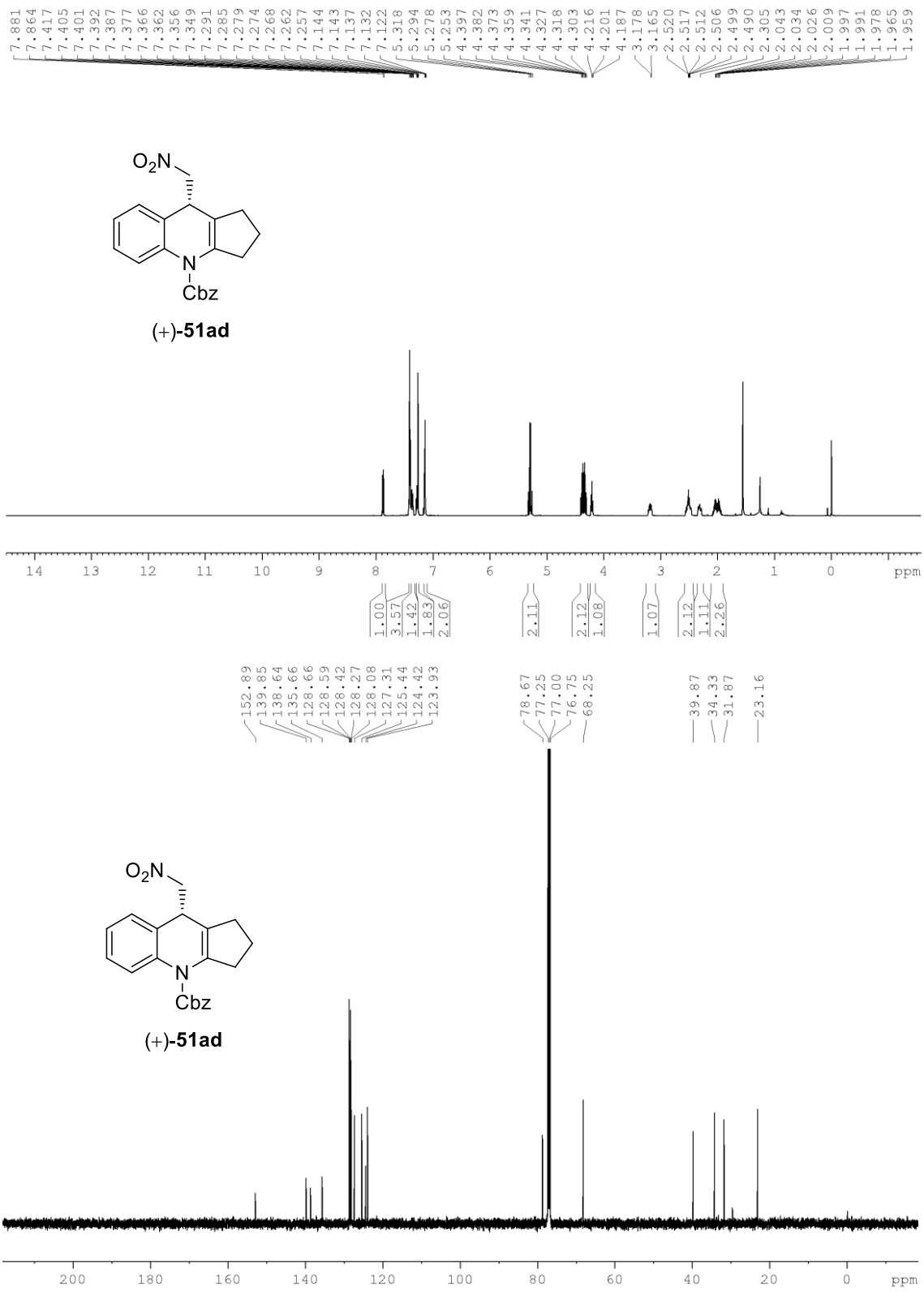



***Figure-25:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **51ad**.

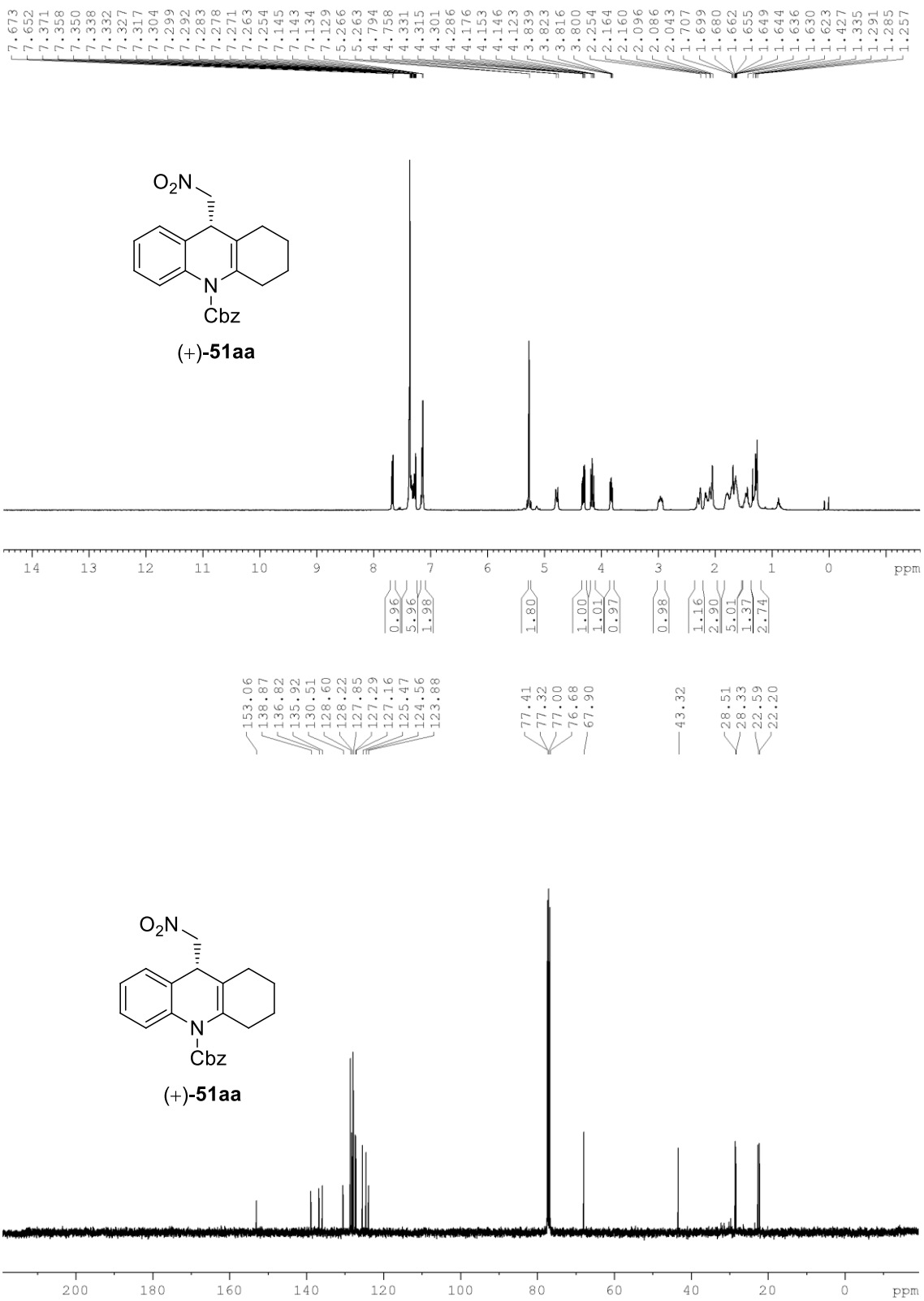



***Figure-26:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **51aa**.

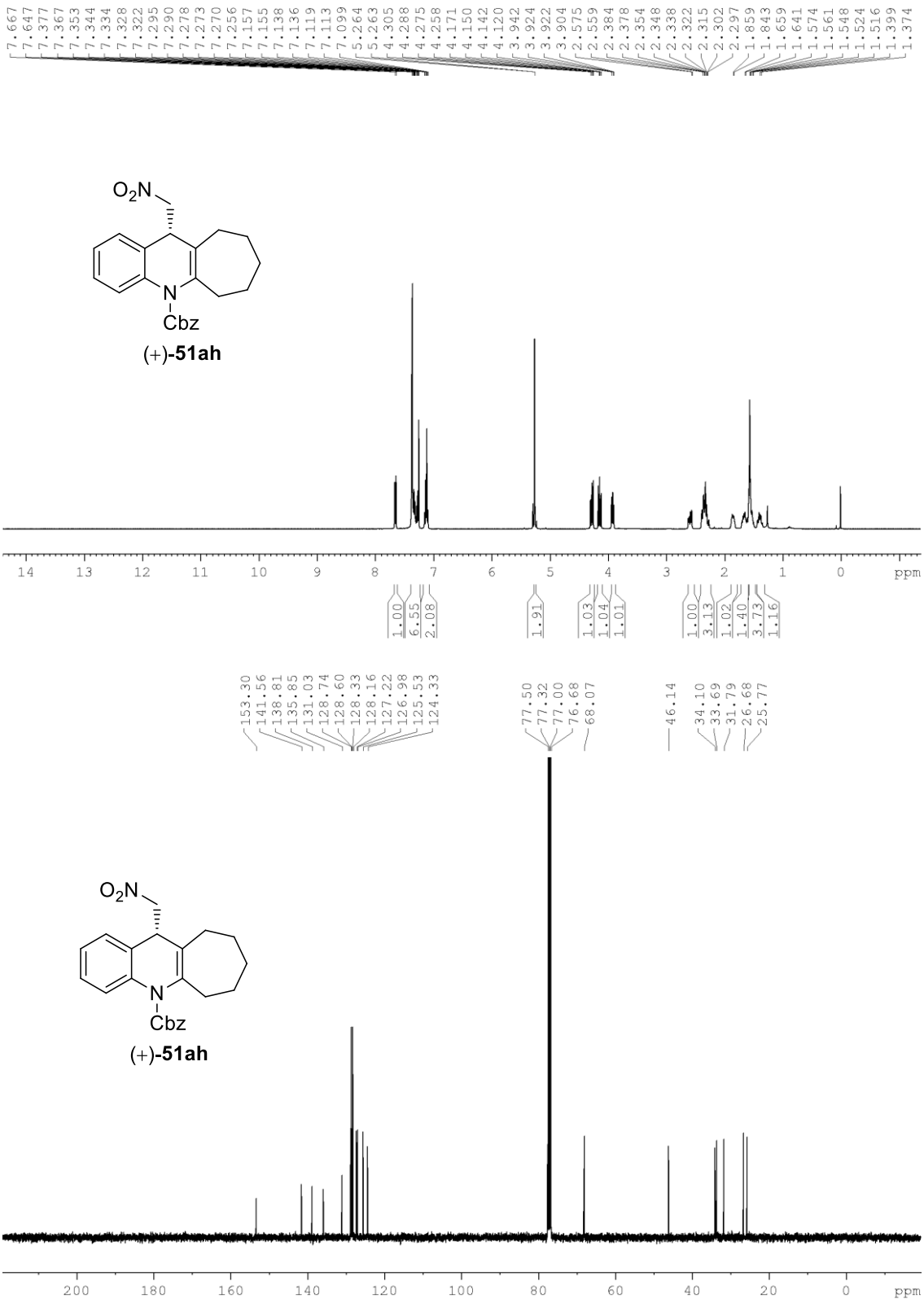



***Figure-27:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **51ah**.

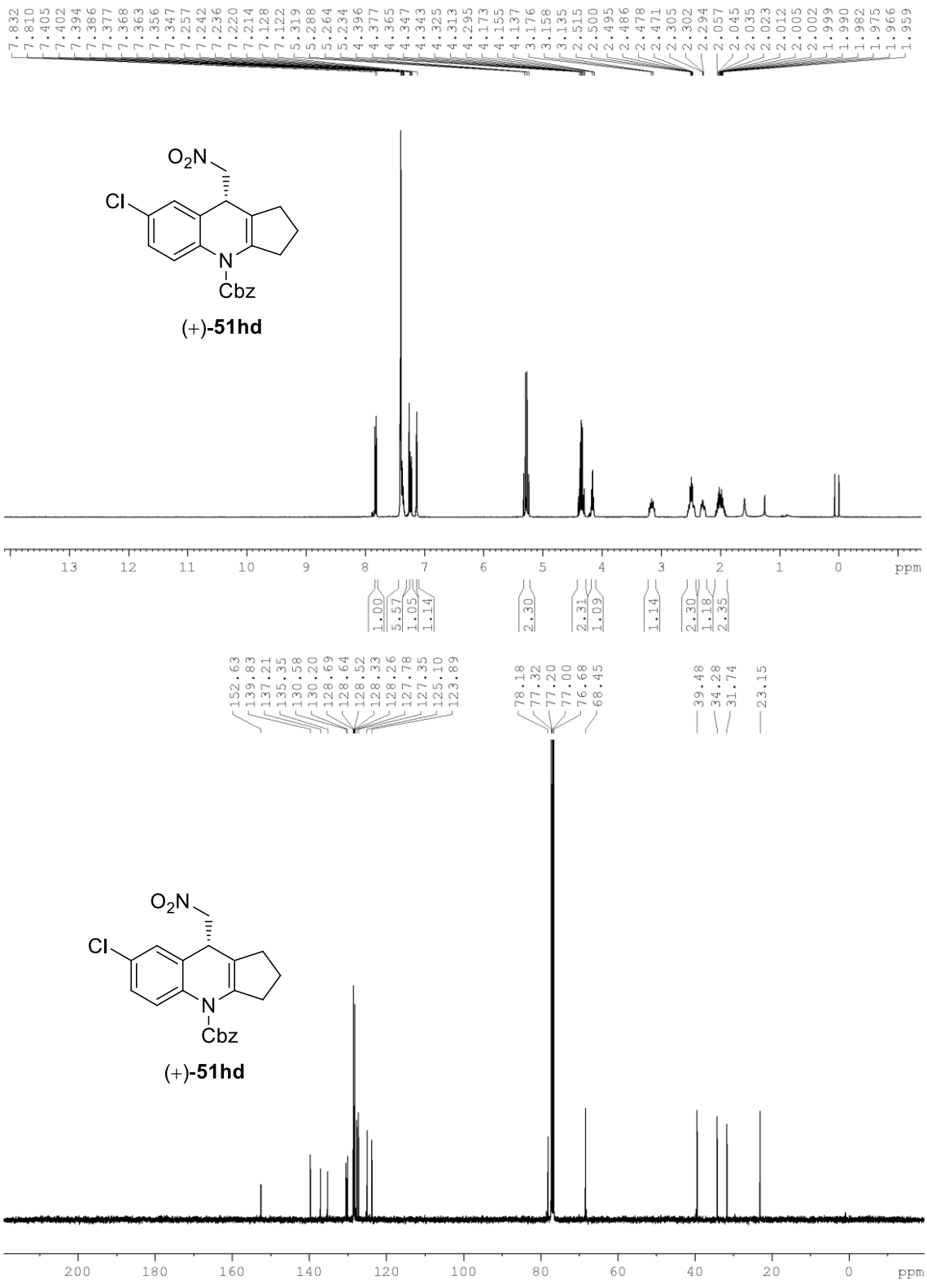



***Figure-28:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **51hd**.

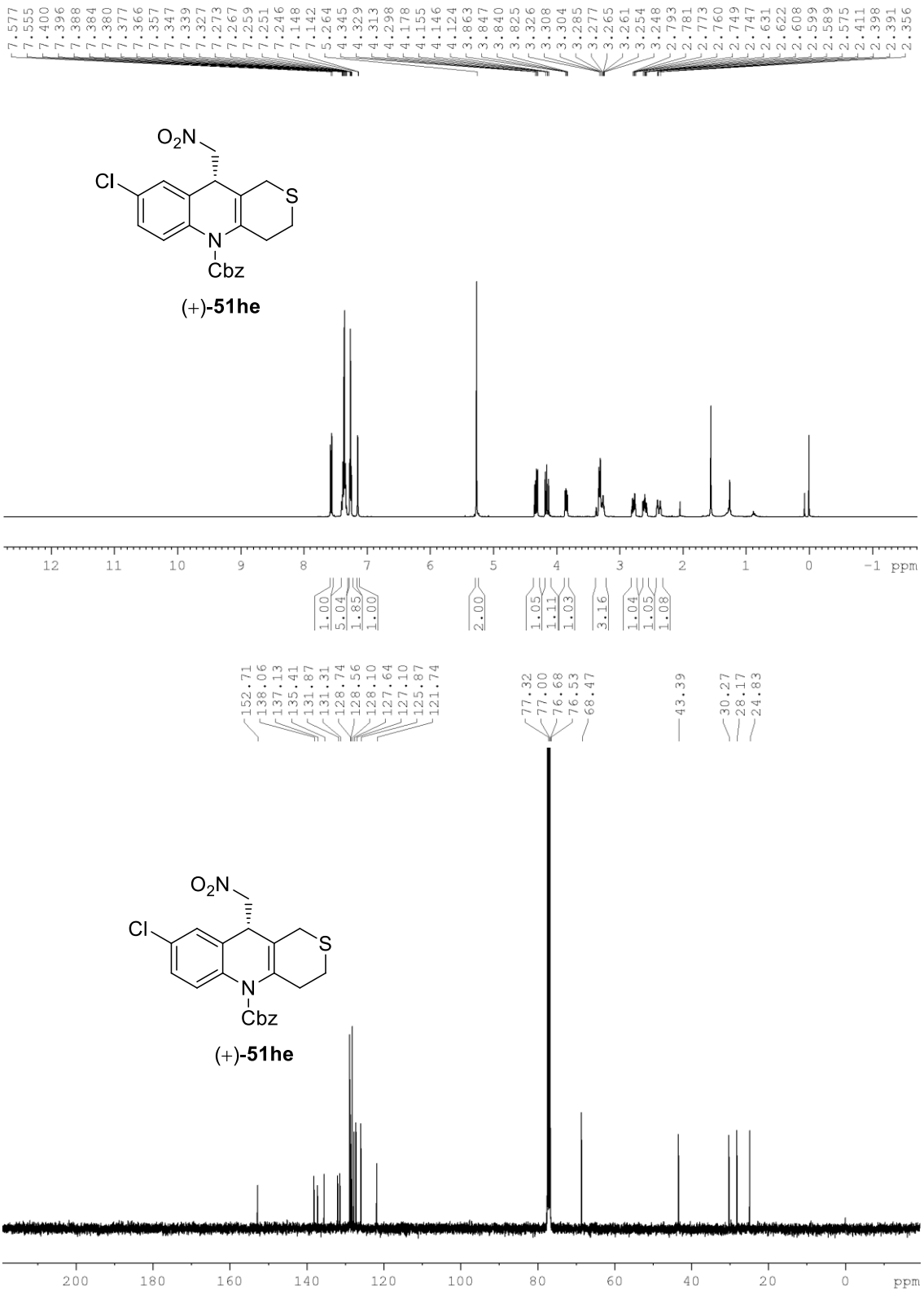



***Figure-29:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **51he**.

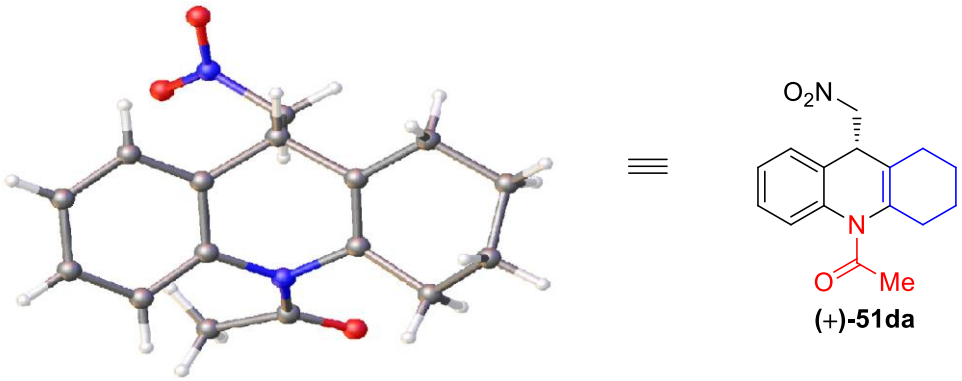
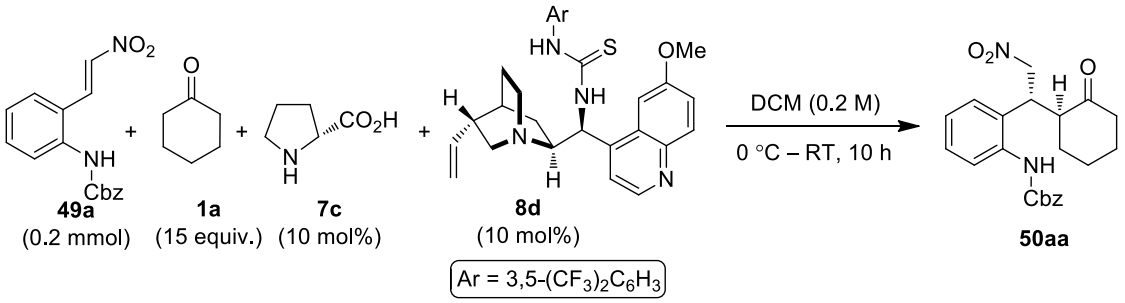


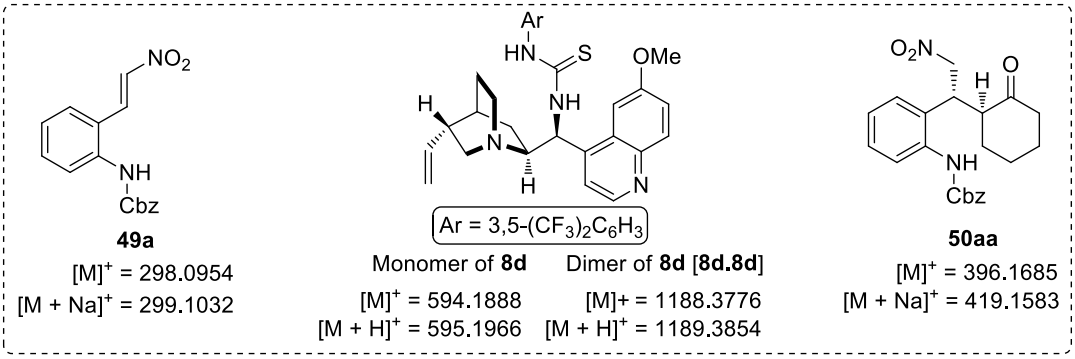

***Figure-30***: X-ray crystal structure of chiral (*R*)-1-(9-(nitromethyl)-1,2,3,4-tetrahydroacridin-10(9*H*)-yl)ethanone (**51da**).

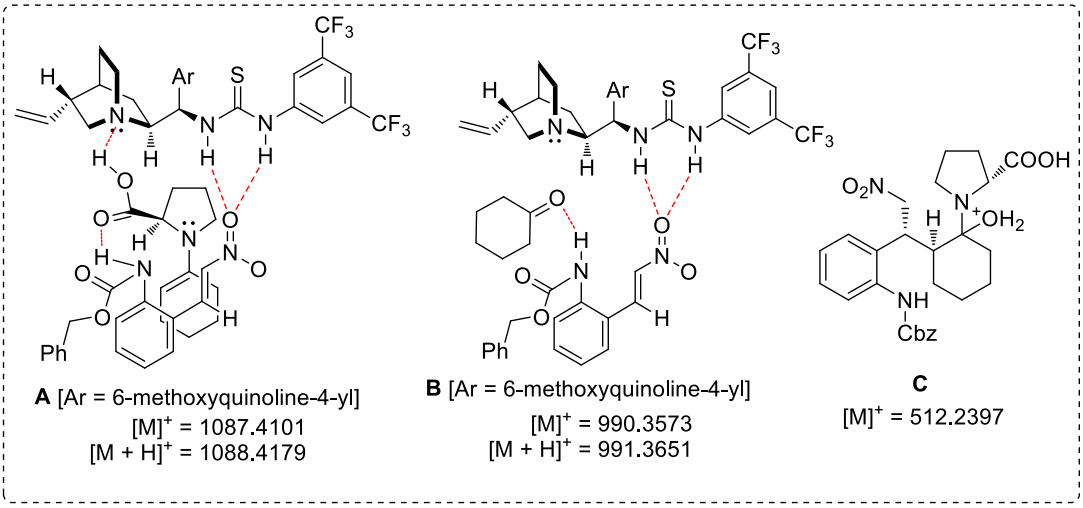
### *4.2.4 Experimental evidence for the formation of supramolecular self-assembly in pre-transition state through on-line ESI-HRMS analysis:*

We have experimental evidence for the hypothetical *in-situ* self-assembled supramolecular 19-membered *pre*-transition state (**TS-1**) through the careful live investigation of the Michael reaction of **49a** with **1a** under (**7c**+**8d**) catalysis using ESI-HRMS technique (Scheme 4, Figure-31). The ESI-HRMS spectrum of an on-going reaction of **49a** and **1a** in the presence of each 10 mol% of (**7c**+**8d**) in DCM at 0-25 °C reveled presence of the product [**50aa**+Na]$^+$ (*m*/*z* 419.1579), and the formation of the key catalytic intermediates such as self-assembled *pre*-transition state ion [**A**+H]$^+$ (*m*/*z* 1088.4177), the dimmer of **8d** [**8d**·**8d**+H]$^+$ (*m*/*z* 1189.3843), [**B**+H]$^+$ (m/z 991.3658) and [**C**]$^+$ (m/z 512.2391) (Figure-31, see annexure-I, Figure A1 and Figure A2 for full details). Interestingly, self-assembled ion [**A**+H]$^+$ is observed from the first moments of the reaction (Figure-31). The stimulated and observed ESI-HRMS isotopic pattern of *pre*-transition state intermediate [**A**+H]$^+$ are shown in Figure-32(a) and Figure-32(b) respectively.

***Scheme 4:*** The Complete Information on the ESI-HRMS Spectrum of an On-going Reaction of **49a** and **1a** (15 equiv.) in the Presence of **7c/8d** (each 10 mol%).



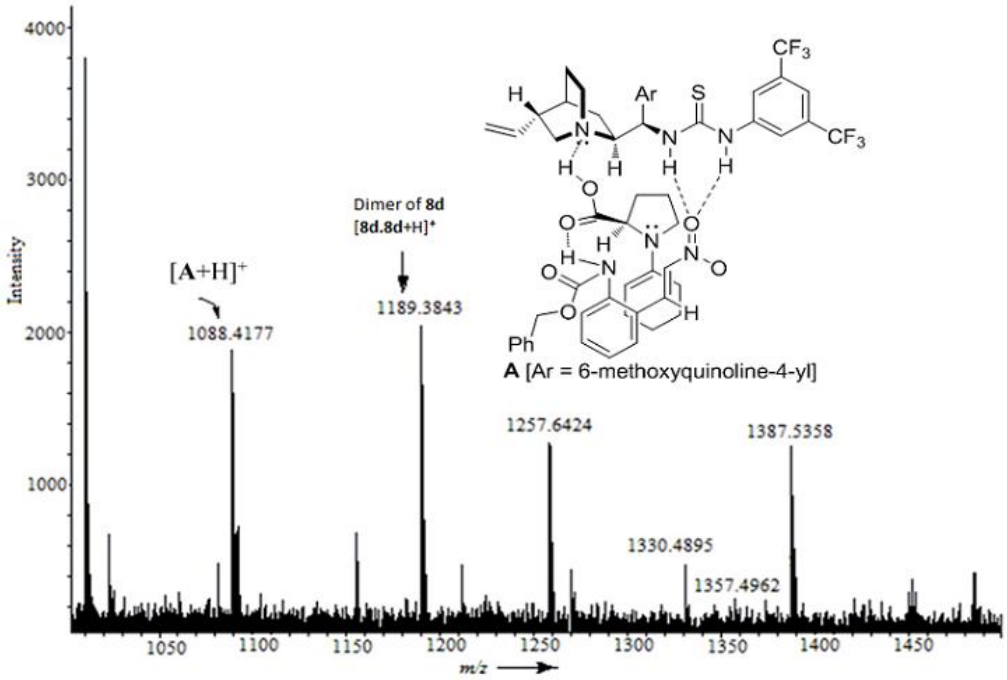
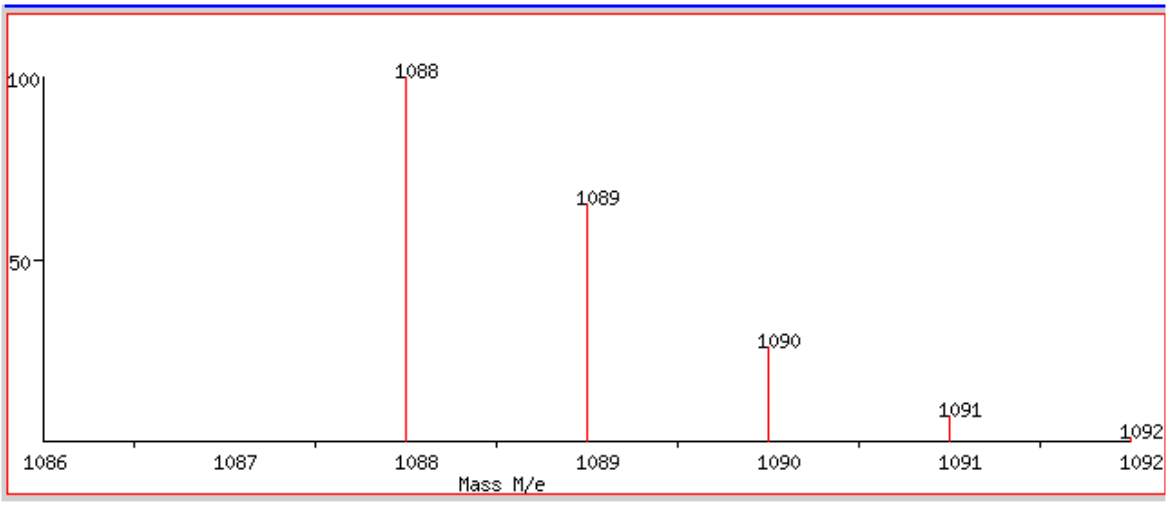



***Figure-31*:** High-resolution mass spectrum (**ESI+**) of the reaction of **49a** with **1a** after 120 min. catalyzed by (**7c**+**8d**) in DCM at 25 °C .

[a] The simulated ESI-HRMS isotopic pattern of *pre*-transition state intermediate [**A**+H]$^+$.



[b] The observed ESI-HRMS isotopic pattern of *pre*-transition state intermediate [**A**+H]$^+$.

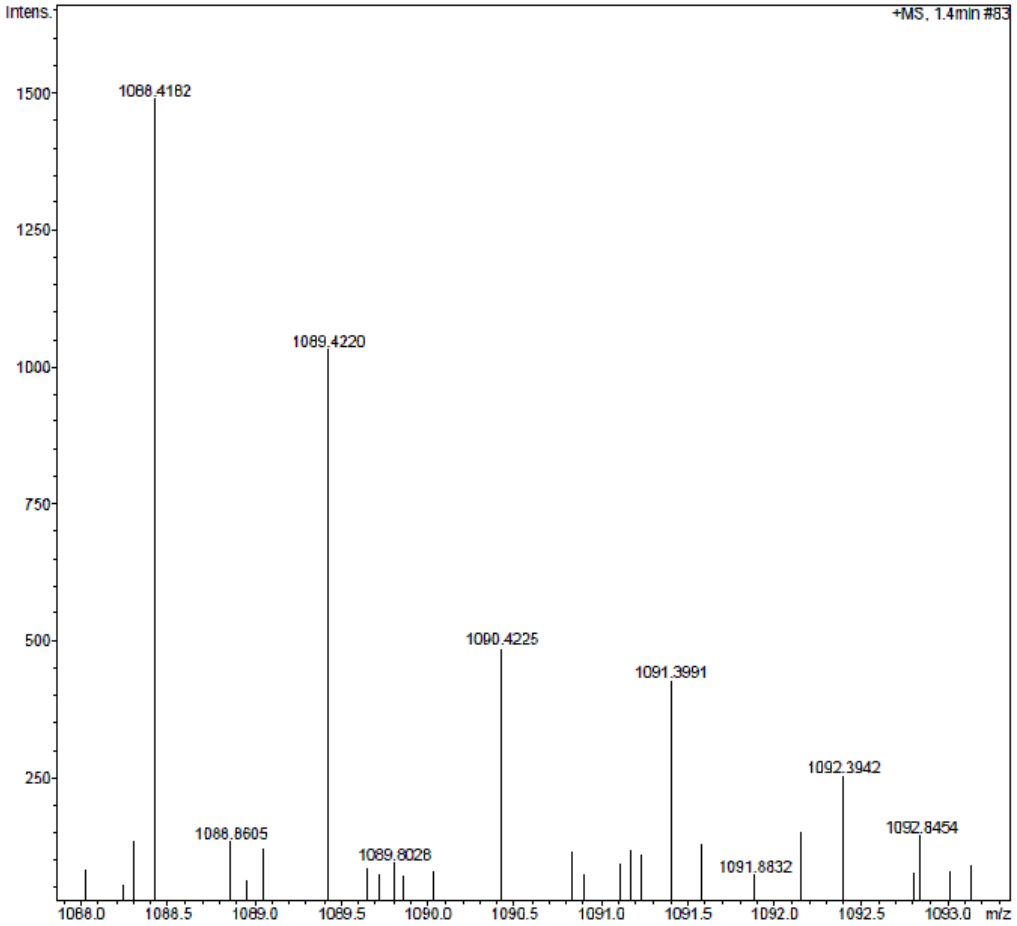
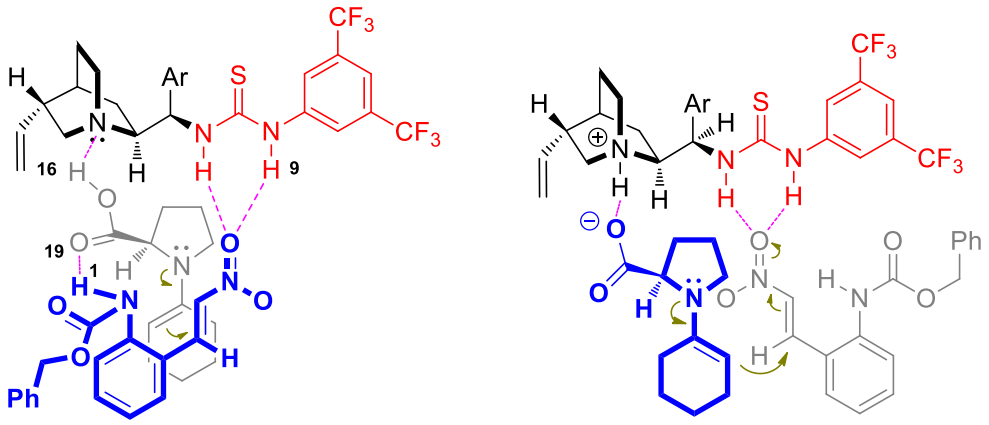



***Figure-32:*** (a) The simulated ESI-HRMS isotopic pattern of *pre*-transition state intermediate [**A**+H]$^+$; (b) The observed ESI-HRMS isotopic pattern of *pre*-transition state intermediate [**A**+H]$^+$.

### *4.2.5 Mechanistic insights:*

With controlled experimental results in hand (see Table 6), we securely explain the mechanism of asymmetric Michael reaction through *in-situ* formation of a cyclic supramolecular self-assembled 19-membered *pre*-transition state by (**7c**+**8d**) catalysis, the reaction most likely proceeds *via* **TS-1** mechanism (Figure-33). In this supramolecular-organocatalysis, we observed four critical interactions among the two substrates and the two catalysts to support a cyclic 19-

membered *pre*-transition state self assembly (i.e., TS-1) to furnish highly enantioselective Michael adduct **50** over the simple acyclic *pre*-transition state (i.e., TS-2) as shown in Figure-33.




**TS-1** [**Favorable Pathway**]
*Re-Re*-face Approach through
Supramolecular-Organocatalysis

**TS-2** [**Unfavorable Pathway**]
*Re-Re*-face Approach through
Organocatalysis

***Figure-33***: Proposed reaction mechanism.

## *4.3 Conclusions*

In summary, we have disclosed a novel and efficient modularly designed supramolecular-organocatalysis for the asymmetric Michael reaction of various cyclic/acyclic ketones with functionally rich N-Cbz-N*H*-(*E*)-2-(2-nitrovinyl)anilines to furnish the desired chiral carbamates **50** in excellent yields, excellent enantioselectivity, diastereoselectivity and chemoselectivity. This protocol showed further applications to the high-yielding chiral synthesis of medicinally important tetrahydroacridines **51**. We proved the reaction mechanism with the help of HRMS and this protocol could become a promising future catalytic system for functionally rich substrates.

.

## *ANNEXURE-I: Experimental ESI-HRMS spectra; High-yielding synthesis of racemic products 50 and 51.*

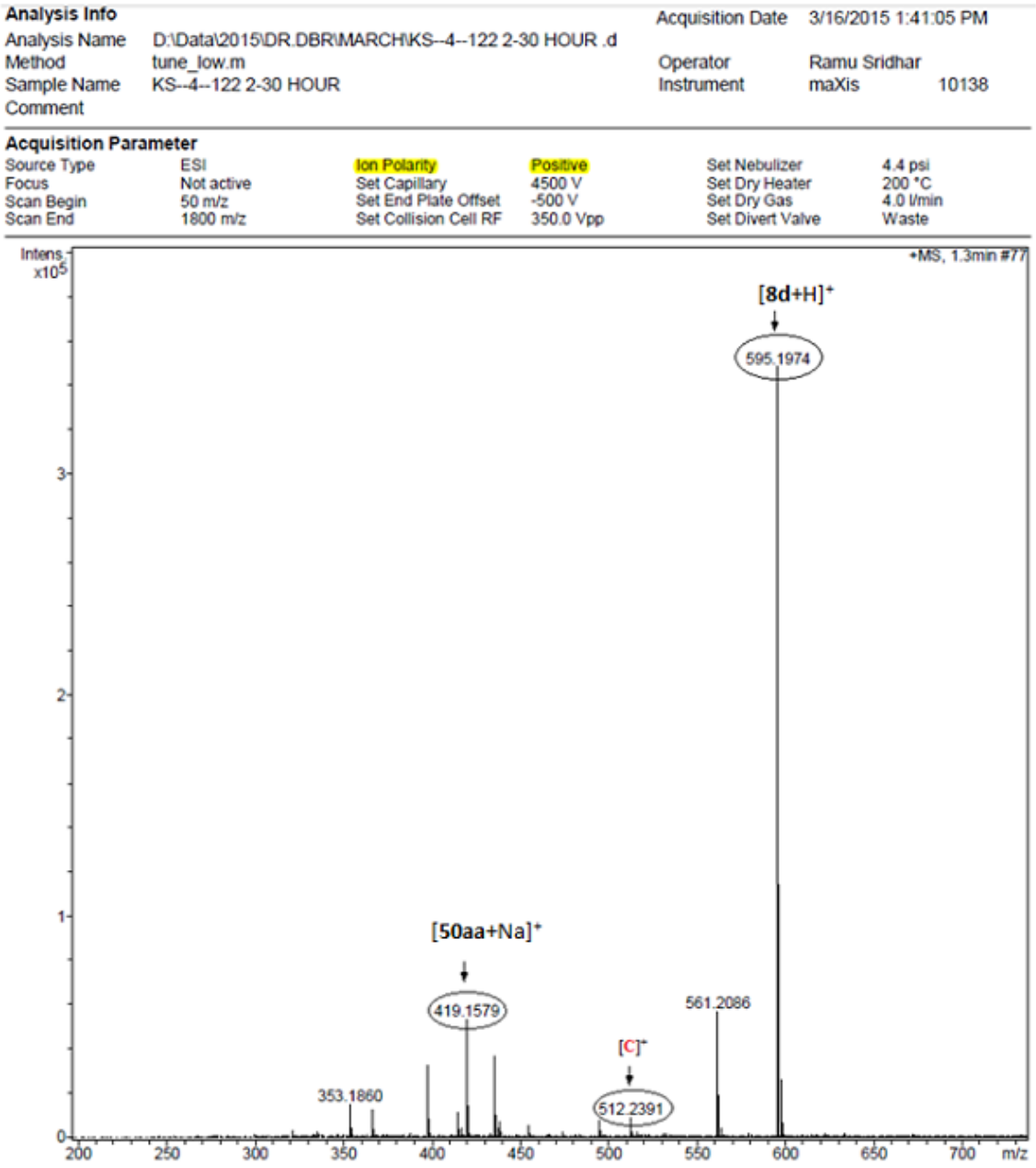



***Figure-A1*:** High-resolution mass spectrum (**ESI+**) of the reaction of **49a** with **1a** after 150 min. catalyzed by (**7c**+**8d**) in DCM at 25 °C.

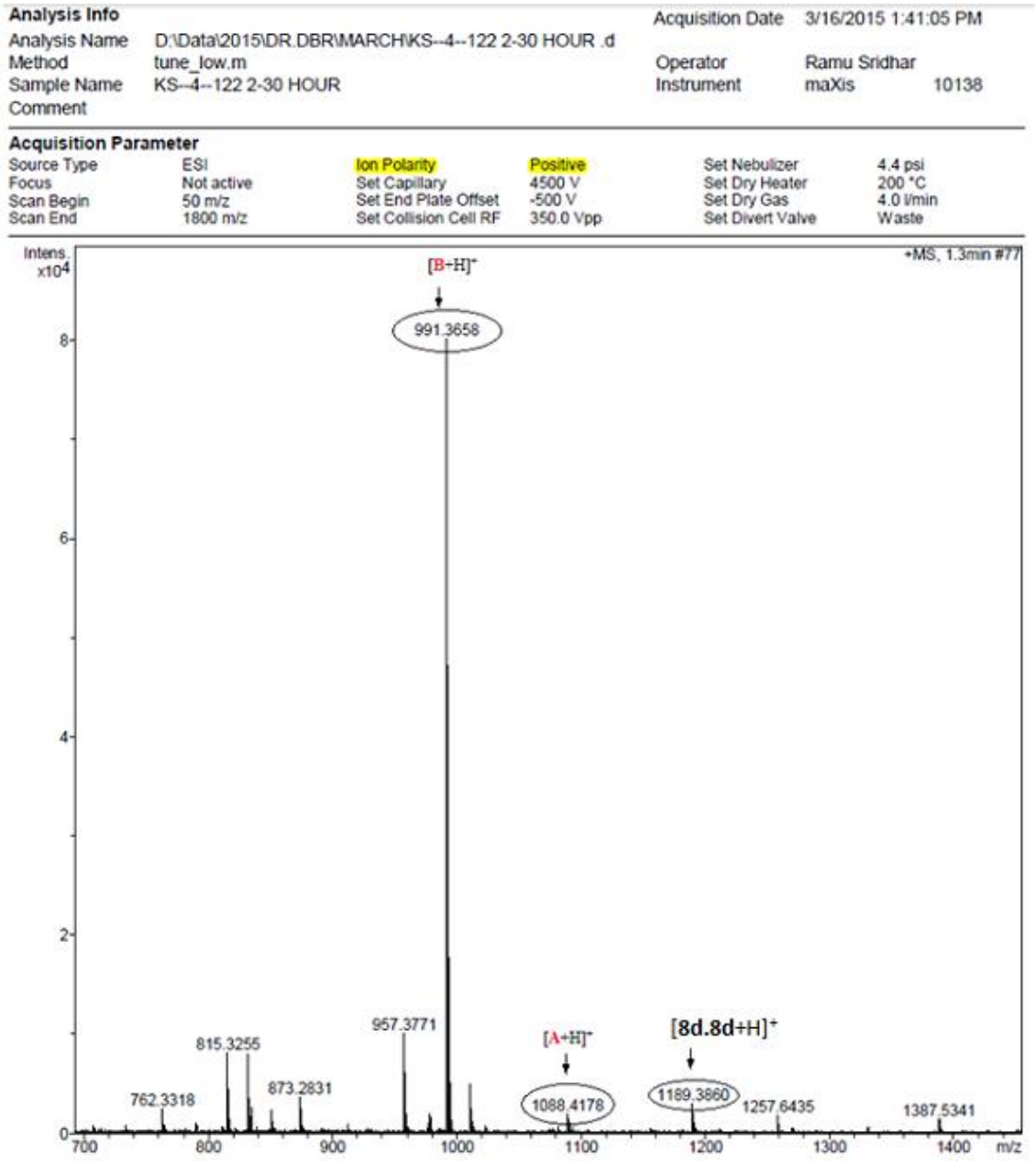
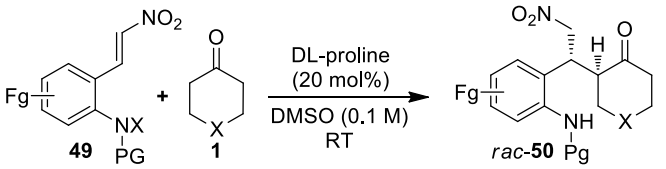


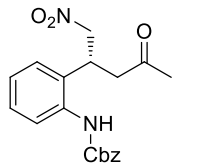

***Figure-A2*:** High-resolution mass spectrum (**ESI+**) of the reaction of **49a** with **1a** after 150 min. catalyzed by (**7c**+**8d**) in DCM at 25 °C.

## *Synthesis of racemic products 50:*

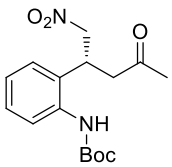
To synthesize the racemic products **50**, ketones **1a-h** were reacted with functionalized monoprotected (*E*)-2-(2-nitrovinyl)anilines **49a**–**j** in DMSO in the presence of 20 mol% of DL-proline at room temperature. This in turn, generated a library of racemic compounds **50** in excellent yields. The results are presented in Table A1.

***Table A1***: Synthesis of Racemic Products **50**.[a-c]

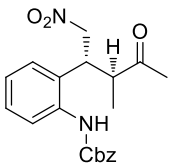


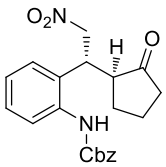

*rac*-**50ab**: 5 h (90%)



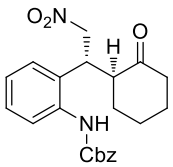

*rac*-**50bb**: 5 h (90%)



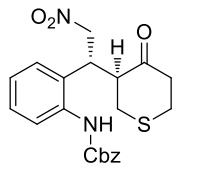

*rac*-**50ac**: 8 h (70%) *de* = 23%



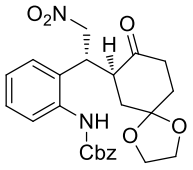

*rac*-**50ad**: 8 h (57%) *de* = 60%



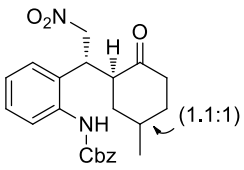

*rac*-**50aa**: 5 h (98%) *de* = 99%



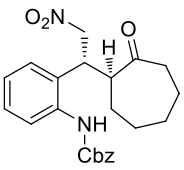

*rac*-**50ae**: 6 h (80%) *de* = 51%



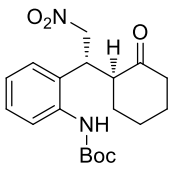

*rac*-**50af**: 7 h (75%) *de* = 64%



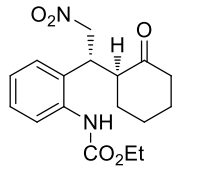

*rac*-**50ag**: 8 h (90%) *de* = 76%



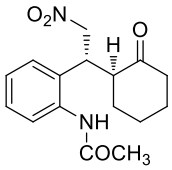

*rac*-**50ah**: 24 h (49%) *de* = 61%



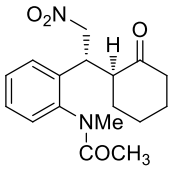

*rac*-**50ba**: 5 h (95%) *de* = 99%



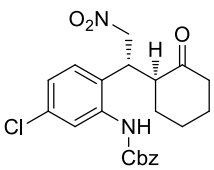

*rac*-**50ca**: 5 h (90%) *de* = 99%



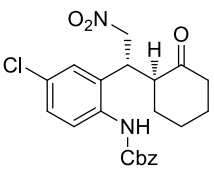

*rac*-**50da**: 4 h (90%) *de* = 71%



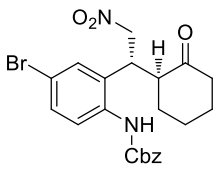

*rac*-**50ea**: 4 h (78%) *de* = 99%



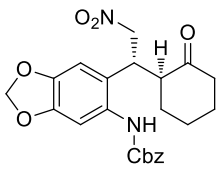

*rac*-**50ga**: 3 h (53%) *de* = 89%




*rac*-**50ha**: 3 h (88%) *de* = 99%




*rac*-**50ia**: 5 h (85%) *de* = 91%



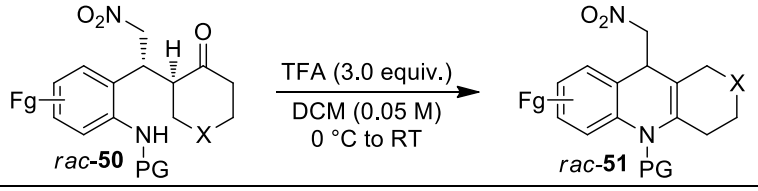

*rac*-**50ja**: 7 h (80%) *de* = 85%

[a] Unless otherwise mentioned, all reactions were carried out with **49** (0.1 mmol), ketone **1** (1.5 mmol, 15.0 equv.) and DL-proline (20 mol%) in DMSO at RT. [b] Yield refers to the column-purified product. [c] *de* was determined based on $^1$H NMR or HPLC analysis.

## *Synthesis of racemic products 51:*

To synthesize the racemic products **51**, the racemic carbamates **50** in dichloromethane were treated with trifluoroacetic acid (3.0 equiv.) at 0 ºC then brought to room temperature. This in turn, generated a library of racemic compounds **51** in excellent yields. The results are presented in Table A2.

***Table A2***: Synthesis of Racemic Products **51**.[a-c]




*rac*-**50** *rac*-**51**

*rac*-**51ac**: 5 h (85%) | *rac*-**51ad**: 2 h (90%) | *rac*-**51aa**: 3 h (89%) | *rac*-**51ae**: 3 h (90%)

*rac*-**51ag**: 3 h (88%) | *rac*-**51ah**: 5 h (80%) | *rac*-**51ba** (Boc): 3 h (90%), *rac*-**51da** (Ac): 3 h (90%) | *rac*-**51ga**: 3 h (89%)

*rac*-**51hd**: 2 h (85%) | *rac*-**51ha**: 2 h (88%) | *rac*-**51he**: 5 h (87%) | *rac*-**51ia**: 3 h (90%)

[a] Unless otherwise mentioned, all reactions were carried out with *rac*-**50** (0.1 mmol), TFA (0.3 mmol, 3.0 equiv.), DCM at 0 °C to RT. [b] Yield refers to the column-purified product. [c] dr was determined based on $^1$H NMR or HPLC analysis.

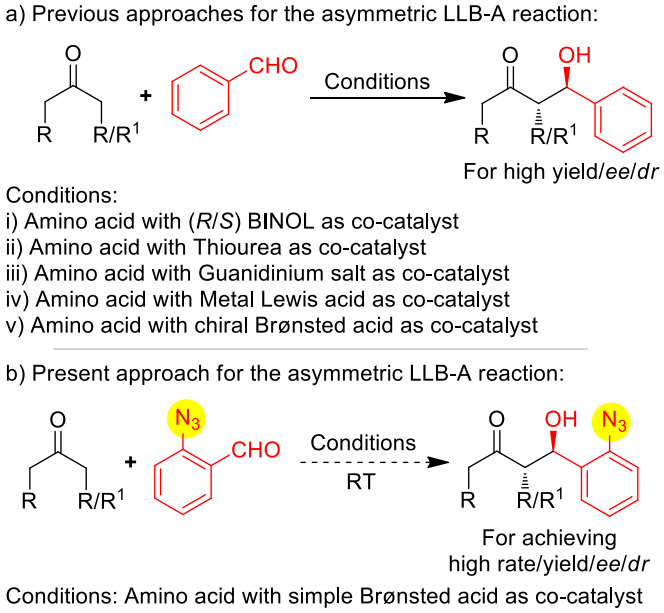
# 5. A Brønsted Acid-Amino Acid as a Synergistic-catalyst for Asymmetric List-Lerner-Barbas Aldol Reactions

## *5.1 Introduction*

In 2000, List, Lerner and Barbas discovered the L-proline-catalysed enamine-mediated asymmetric intermolecular aldol reaction, which has created a new realm in organic chemistry called as *organocatalysis*.[36] After this preliminary exploration, many chemists entered in this field to investigate the reaction scope by changing the catalysts along with co-catalysts and the different substrates of aldehydes and ketones.[37] In this connection, in order to increase the rate and selectivity of List-Lerner-Barbas aldol (LLB-A) reaction, (*S*)-BINOL,[38] Schreiner's thiourea,[39] TBD salt,[40] $ZnCl_2$/$CoCl_2$,[41] and chiral Brønsted acid, D-CSA[42] are used as promoters along with L-amino acid,[36,37] (*S*)-(–)-5-(2-pyrrolidinyl)-1*H*-tetrazole,[43] or Singh's prolinamide[44] as catalysts (Scheme 5a). Even though various combination of catalysts/co-catalysts were used to achieve best rate and selectivity for LLB-A reaction, at ambient conditions, so far it was not successful, either rate or selectivity is compromised (Scheme 5a).

In continuation of our recent interest in the development of supramolecular-organocatalysis and understanding the neighbouring group participation in the *pre*- or *post*-transition state of organocatalytic reactions,[45] herein, we have chosen less reactive, functionalized 2-azidobenzaldehydes as the substrate with different ketones to study the enhancement in reaction rate and selectivity of LLB-A reaction under the catalysis of different L-amino acids along with known/unknown co-catalysts (Scheme 5b). Our main focus in this study to develop the chiral poly functionalized products, which contain a medicinally/materialistically important *ortho*-azido group under simple ambient catalytic conditions.[46] For this design, we have chosen sterically and electronically challenging *ortho*-azidobenzaldehydes as the electrophile with cyclic/acyclic ketone as the pro-nucleophile with synergistic-catalysis of L-amino acid and simple Brønsted acid (Scheme 5 and Figure-34).

***Scheme 5*: Summary of Previous Work and the Design Plan of this Work.**



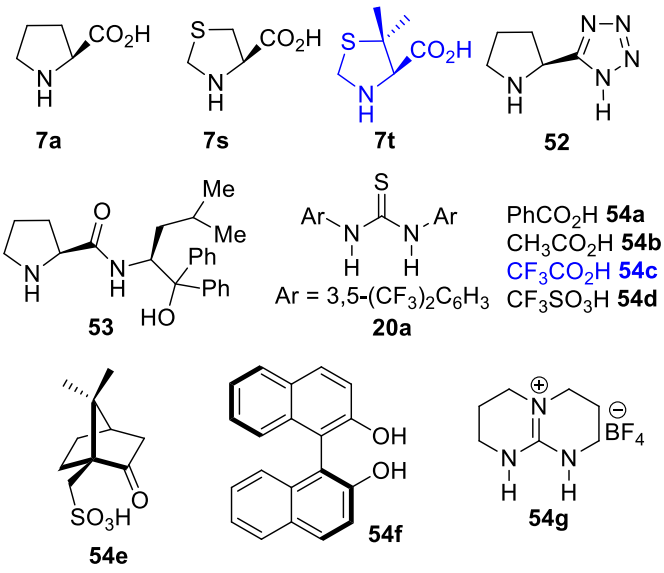




***Figure 34***: Library of catalyst and co-catalyst screened in this study.

## *5.2 Results and Discussions*

### *5.2.1 Reaction optimization with cyclic ketones:*

In the preliminary optimization, we have chosen LLB-A conditions of L-proline (**7a**) (20 mol%) as catalyst in DMSO for the reaction of *o*-azidobezaldehyde (**55a**) with cyclohexanone (**1a**) at room temperature for 24 h, which furnished the expected LLB-A product *anti*-(–)-**56aa** in only 16% yield with 91% *ee* in 4:1 *dr* (Table 9, entry 1). On obtaining very low yield, we further tested other amino acids such as L-thioproline (**7s**), (*R*)-5,5-dimethyl thiazolidinium-4-carboxylate (L-DMTC)[47] (**7t**) and (*S*)-(–)-5-(2-pyrrolidinyl)-1*H*-tetrazole[43] (**52**) in DMSO at room temperature for 24-48 h, which also furnished low to good yields but with good *ee* and moderate *dr* (Table 9, entries 2-7). Among the tested amino acids, L-DMTC[47] (**7t**) gave promising results in terms of *ee* (99%) and *dr* (6:1) (Table 9, entry 3). The designed LLB-A reaction under the catalysis of Singh's prolinamide[44] (**53**) with benzoic acid (5**4a**) as the co-catalyst under neat conditions at –35 °C for 24 h furnished the *anti*-(–)-**56aa** in 91% yield with 98% *ee* and 99:1 *dr* (Table 9, entry 8). However, the same neat reaction at 25 °C for 2 h furnished the *anti*-(–)-**56aa** in 95% yield with decreased *ee* and *dr* (Table 9, entry 9). Even though the Singh's catalyst **53** furnished good yield and selectivity, the reaction temperature was too low to be applicable universally, which is deviating from the main goal that we are on the lookout for reactions at ambient conditions. When we performed the reaction at room temperature, the results were not appreciable (Table 9, entry 9).

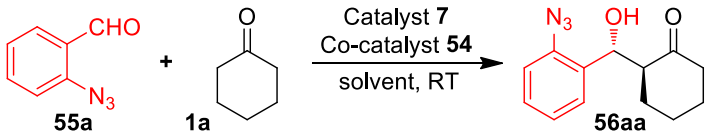
In this regard, as mentioned earlier, since L-DMTC (**7t**) gave good selectivity but low yield/rate, we extended our investigations further to check whether the yield/rate of the reaction could be increased by using L-DMTC (p$K_a$ = ~9.76) (**7t**) in combination with Brønsted acid co-catalysts such as benzoic acid (p$K_a$ = 11.1) (**54a**), acetic acid (p$K_a$ = 12.3) (**54b**), trifluoroacetic acid (p$K_a$ = 3.45) (**54c**) and trifluoromethane sulfonic acid (p$K_a$ = 0.3) (**54d**) (Table 9, entries 10-14). Among these Brønsted acid co-catalysts, when used in pair with L-DMTC (**7t**) (20 mol%), trifluoroacetic acid (**54c**) (40 mol%) seems to be ideal in providing good yield/rate as well as excellent *ee* and *dr* (Table 9, entry 13). The same combination of catalysts **7t**/**54c** when used in a different solvent acetonitrile furnished a low yield with low selectivity, whereas in DMSO-$d_6$ only yield was reduced (Table 9, entries 15 and 16). Synergistic combination of **7t** (20 mol%)

with 20 or 30 mol% of **54c** also in DMSO at 25 °C for 24 h furnished **56aa** with reduced yield (76-78%) but the selectivity remained unchanged (results not shown in Table 9). There is no LLB-A reaction observed even after 48 h at 25 °C under only TFA (**54c**)-catalysis in DMSO (not shown in Table 9).

After realizing the importance of the role played by TFA (p$K_a$ = 3.45) (**54c**) in boosting the yield/rate, we were curious to know how well it works when used along with L-proline (**7a**) (p$K_a$ = 12.3) and L-thioproline (p$K_a$ = ~9.33) (**7s**) (Table 9, entries 17 and 18) and disappointed to find that even though there was an unsatisfactory increase in yield, there was also noticeable drop in *ee*. In a similar manner, TFA (**54c**) with proline-tetrazole (p$K_a$ = 11.26) **52**-catalysis also gave disappointing results with decreased yield and slightly increased *ee*/*dr* (Table 9, entry 19). Switching back to L-DMTC (**7t**), we also wanted to check the contribution to yield and selectivity by a chiral Brønsted acid, D-CSA (p$K_a$ = 5.61) (**54e**) as co-catalyst, but it furnished only poor yield with moderate selectivity (Table 9, entry 20). Simultaneously, we were interested in screening hydrogen-bond donating compounds such as (*S*)-BINOL (p$K_a$ = 13.22) (**54f**), Schreiner's thiourea (p$K_a$ = 8.5) (**20a**) and TBD salt (p$K_a$ = 25.98) (**54g**) as the co-catalysts along with L-proline (p$K_a$ = 12.3) (**7a**), as they were recently reported in the literature to be better co-catalysts when used in combination with amino acids. Utilization of Schreiner's thiourea (**20a**) as co-catalyst in hexane solvent provided only moderate yield with excellent *ee* and *dr*, whereas (*S*)-BINOL (**54f**) furnished moderate yield and excellent *dr* but with little lower *ee*, while TBD salt (**54g**) under neat reaction condition resulted in comparable yield and *ee* with catalyst **7t**/**54c** system but with lesser *dr* (Table 9, entries 21-25).

Finally, the best optimized reaction conditions were found to be the combination of catalysts **7t** (20 mol%) and **54c** (40 mol%) in DMSO at room temperature. The acidity of the Brønsted acid co-catalysts, structure of the amino acid and solvent nature seem to be playing essential role in controlling the rate and selectivity, which will be discussed elaborately in mechanistic section.

***Table 9***: Optimization of LLB-A Reaction with Cyclic Ketones.[a]




| Entry | Catalyst **7** | Co-cat. **54** | Solvent | *t* (h) | Yield (%)[b] **56aa** | *ee* (%)[c] | *dr*[d] |
|---|---|---|---|---|---|---|---|
| 1 | **7a** | - | DMSO | 24 | 16 | 91 | 4:1 |
| 2 | **7s** | - | DMSO | 24 | 16 | 98 | 8:1 |
| 3 | **7t** | - | DMSO | 48 | 25 | 99 | 6:1 |
| 4 | **7t** | - | NMP | 48 | 15 | 98 | 6:1 |
| 5 | **7t** | - | $CH_3CN$ | 48 | 17 | 90 | 6:1 |
| 6 | **7t** | - | Neat | 48 | 20 | 92 | 6:1 |
| 7 | **52** | - | DMSO | 24 | 90 | 91(96) | 1:2 |
| 8[e] | **53** | **54a** | Neat | 24 | 91 | 98 | 99:1 |
| 9 | **53** | **54a** | Neat | 2 | 95 | 83 | 5:1 |
| 10 | **7t** | **54a** | DMSO | 48 | 28 | 96 | 6:1 |
| 11 | **7t** | **54a** | $CH_3CN$ | 96 | 16 | 79 | 6:1 |
| 12 | **7t** | **54b** | DMSO | 24 | 20 | 96 | 6:1 |
| **13** | **7t** | **54c** | **DMSO** | **24** | **88** | **99** | **17:1** |
| 14 | **7t** | **54d** | DMSO | 24 | 16 | 67 | 18:1 |
| 15 | **7t** | **54c** | $CH_3CN$ | 24 | 47 | 92 | 17:1 |
| 16 | **7t** | **54c** | DMSO-$D_6$ | 24 | 74 | 99 | 17:1 |
| 17 | **7a** | **54c** | DMSO | 24 | 29 | 80 | 7:1 |
| 18 | **7s** | **54c** | DMSO | 24 | 58 | 91 | 18:1 |
| 19 | **52** | **54c** | DMSO | 24 | 88 | 95(82) | 3.5:1 |
| 20 | **7t** | **54e** | DMSO | 48 | 13 | 85 | 30:1 |
| 21[f] | **7a** | **20a** | Hexane | 24 | 53 | >99 | 99:1 |
| 22[g,h] | **7a** | **54f** | DMSO | 24 | 72 | 97 | 99:1 |
| 23[g] | **7a** | **54f** | DMSO | 10 | 76 | 95 | 99:1 |
| 24[i,h] | **7a** | **54g** | Neat | 24 | 60 | >99 | 8:1 |
| **25**[i] | **7a** | **54g** | **Neat** | **24** | **88** | **99** | **7.7:1** |

[a] Unless otherwise mentioned, all reactions were carried out with **55a** (0.3 mmol), cyclohexanone **1a** (4.2 mmol, 14 equiv.), catalysts **7** (20 mol%) and 5**4** (40 mol%) in DMSO (0.3 M) at RT. [b] Yield refers to the column-purified product of both the isomer. [c] *ee* was determined by CSP HPLC analysis the values in the paranthesis refers to the *syn* isomer *ee* values. [d] *dr* was determined based on $^1$H NMR or HPLC analysis. [e] Reaction was carried out using **53** (10 mol%) and **54a** (10 mol%) under neat condition at -35 °C. [f] **7a** and **20a** (each 10 mol %) were used in hexane (0.14 M). [g] 7**a** (30 mol%) and **54f** (1 mol%) were used in DMSO (1.25 M). [h] Reaction was carried out at 0 °C. [i] **7a** (15 mol%) and **54g** (10 mol%) were used under neat condition at RT.

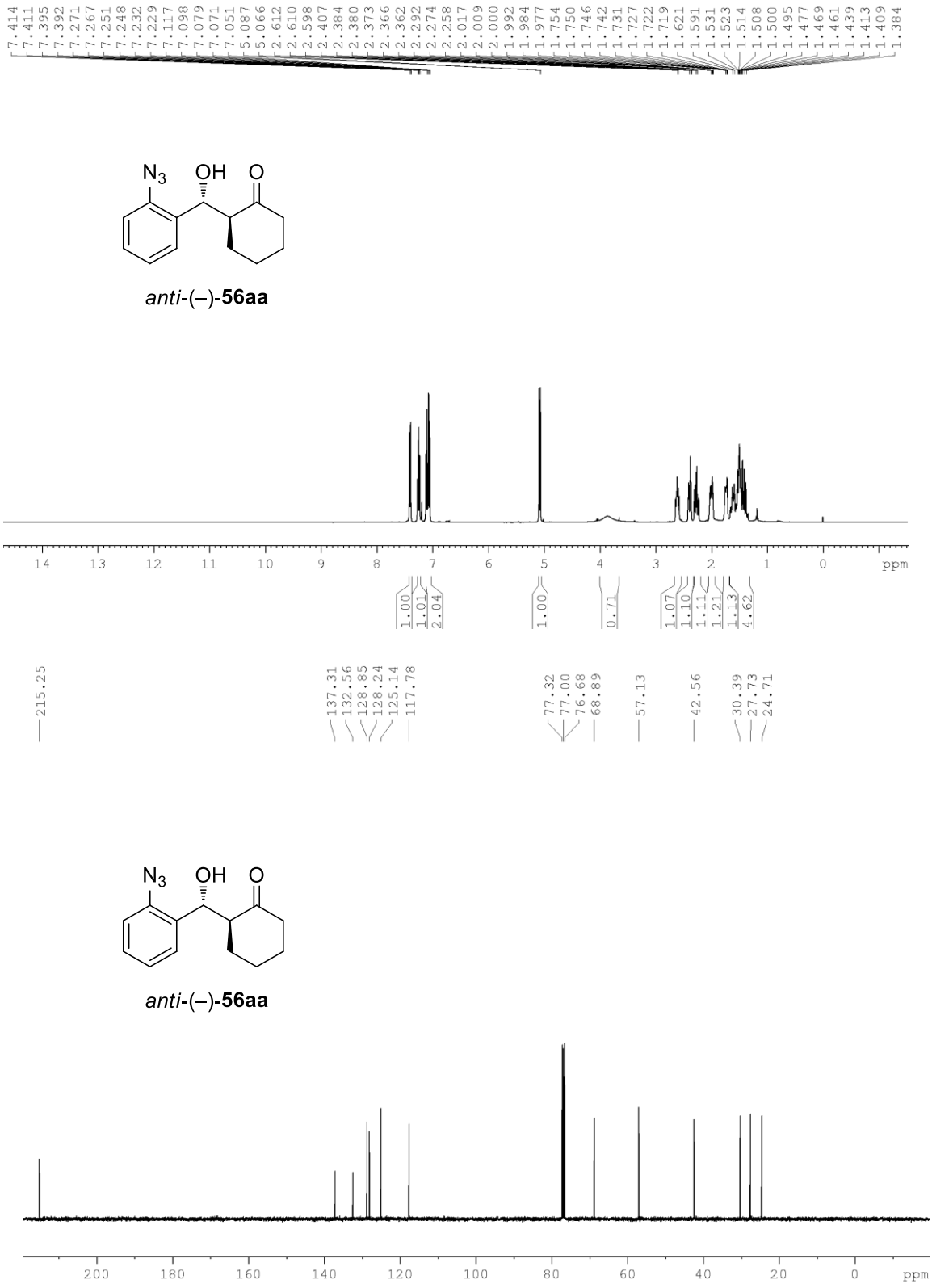
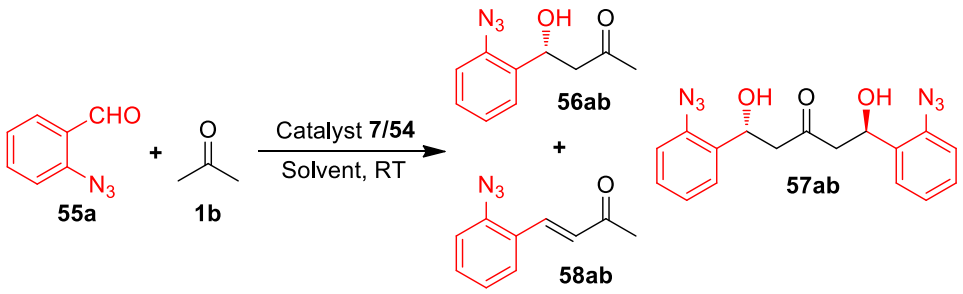



***Figure-35:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **56aa**.

### *5.2.2 Reaction optimization with acyclic ketones:*

After completing the optimization studies and arriving at the above said best optimization conditions for the cyclohexanone, we shifted our attention onto the acyclic ketone acetone (**1b**). The LLB-A reaction on acetone (**1b**) using the best optimization conditions of **7t**/**54c** (Table 9 entry13) revealed that the expected aldol product (+)-**56ab** was obtained only in 21% yield and 85% *ee*, along with 21% of the elimination product **58ab** (Table 10, entry 1). The reason behind the formation of the elimination product **58ab** might be due to the acidity of the Brønsted acid co-catalyst **54c**. Even the second best optimized conditions, namely, **7a** with **54g** under neat reaction condition, furnished the aldol product (+)-**56ab** in moderate yield and *ee* along with the elimination product **58ab** (Table 10, entry 2). The catalyst system **53**/**54a** under neat reaction condition at room temperature generated the aldol product (+)-**56ab** in good yield but with moderate *ee* (Table 10, entry 3). The same reaction even in the absence of **54a** also furnished the product in more or less the same yield with a slight increase in *ee*, along with a negligible amount of the bis-aldol product **57ab** (Table 10, entry 4).[48] The very same reaction at low temperature using the catalyst **53** either in the absence or presence of **54a** produced the aldol product in low yield with moderate *ee*, but with increased yield of the bis-aldol product (+)-**57ab** with 98-99% *ee* (Table 10, entries 5-6). With these unsatisfactory results for the acetone under the combination catalyst system, we shifted our focus back to the conventional usage of just the amino acids instead. The aldol reaction of acetone (**1b**) with *o*-azidobenzaldehyde (**55a**) under L-proline (**7a**) catalysis in DMSO, furnished the product in 88% yield with 72% *ee* (Table 10, entry 7). The results were almost same even in the other two solvents DMF and NMP (Table 10, entries 8-9). Under L-DMTC (**7t**) catalysis in DMSO solvent, the product was obtained in 65% yield with 87% *ee* and also the results were comparable in acetonitrile solvent, whereas the same catalyst in NMP as solvent, furnished the product in poor yield but with same *ee* (Table 10, entries 10-12). L-Proline based tetrazole (**52**) also catalyzed the reaction in a similar manner (Table 10, entry 13). At the end, it is obvious from Table 10, that L-DMTC (**7t**) catalysis in DMSO solvent is the best optimized condition for the acetone.

***Table10***: Optimization of LLB-A Reaction with Acyclic Ketones.[a]




| Entry | Catalyst **7** | Co-cat. **54** | Solvent | *t* (h) | Yield (%)[b] **56ab** | *ee* (%)[c] **56ab** | Yield (%)[b] **58ab** | Yield (%)[b,d] **57ab** | *ee* (%)[c] **57ab** |
|---|---|---|---|---|---|---|---|---|---|
| 1[e] | **7t** | **54c** | DMSO | 24 | 21 | 85 | 21 | - | - |
| 2[f] | **7a** | **54g** | Neat | 24 | 57 | 64 | 20 | - | - |
| 3[g] | **53** | **54a** | Neat | 4 | 79 | 59 | - | - | - |
| 4[h] | **53** | - | Neat | 5 | 85 | 70 | - | <3 | - |
| 5[g,i] | **53** | **54a** | Neat | 24 | 29 | 61 | - | 21 | >99 |
| 6[h,i] | **53** | - | Neat | 24 | 32 | 79 | - | 23 | 98 |
| 7 | **7a** | - | DMSO | 3 | 88 | 72 | 12 | - | - |
| 8 | **7a** | - | DMF | 6 | 64 | 66 | 14 | - | - |
| 9 | **7a** | - | NMP | 6 | 88 | 73 | 7 | - | - |
| 10 | **7t** | - | DMSO | 12 | 65 | 87 | 6 | - | - |
| 11[j] | **7t** | - | NMP | 24 | 12 | 88 | - | - | - |
| 12 | **7t** | - | $CH_3CN$ | 9 | 69 | 86 | 3 | - | - |
| 13 | **52** | - | DMSO | 3 | 86 | 73 | 12 | - | - |

[a] Unless otherwise mentioned, all reactions were carried out with **55a** (0.3 mmol), acetone **1b** (1.5 mmol, 14 equiv.), catalysts **7** (20 mol%) in DMSO (0.25 M) at RT. [b] Yield refers to the column-purified product. [c] *ee* was determined by CSP HPLC analysis. [d] *dr* was determined based on $^1$H NMR or HPLC analysis. [e] **7t** (20 mol %) and **54c** (40 mol %) were used. [f] **7a** (15 mol%) and **54g** (10 mol%) were used. [g] **53** (10 mol %) and **54a** (10 mol %) were used. [h] **53** (10 mol%) was used. [i] Reaction was carried out at –35 °C. [j] Reaction was carried out at 4 °C.

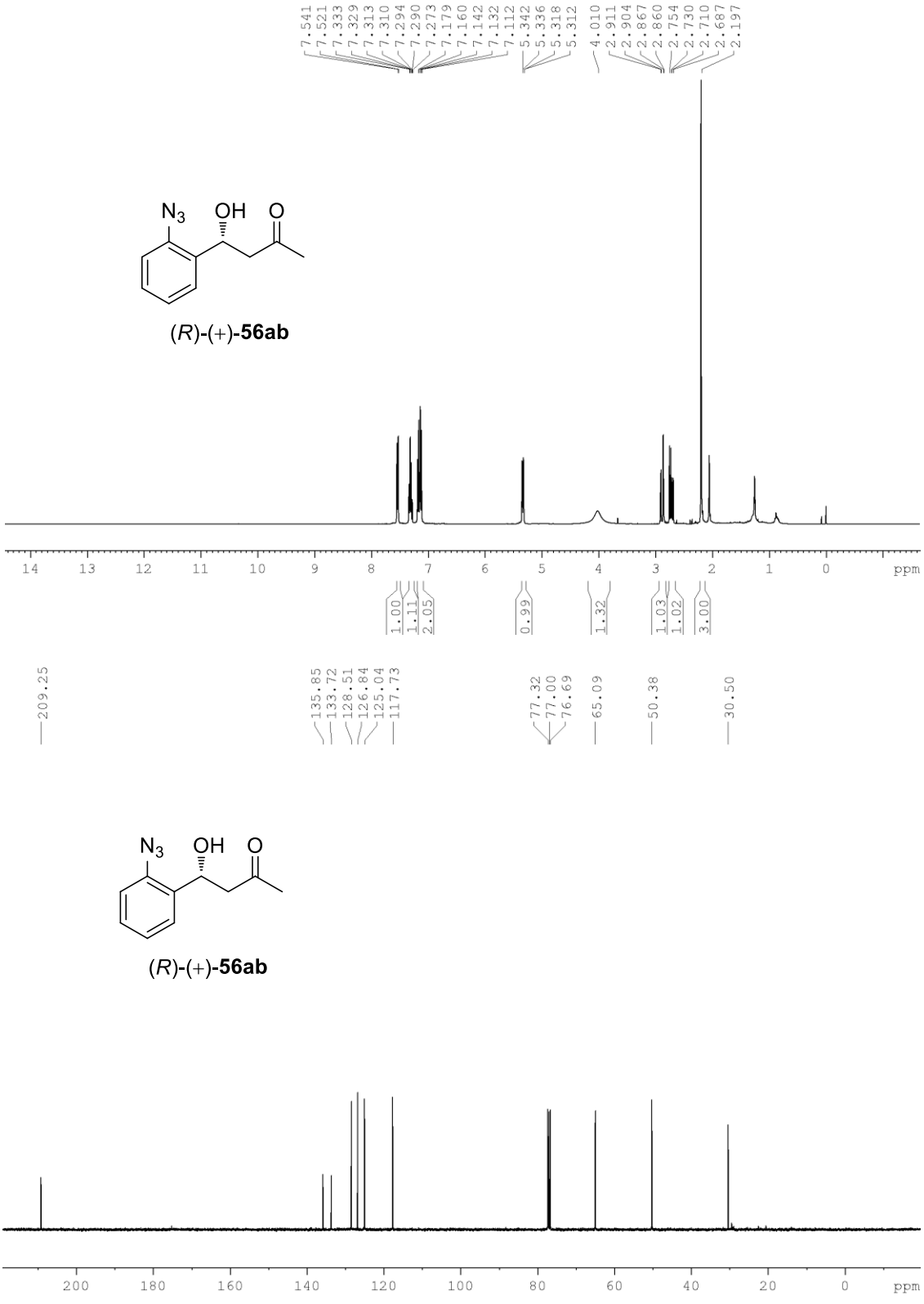



***Figure-36:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **56ab**.

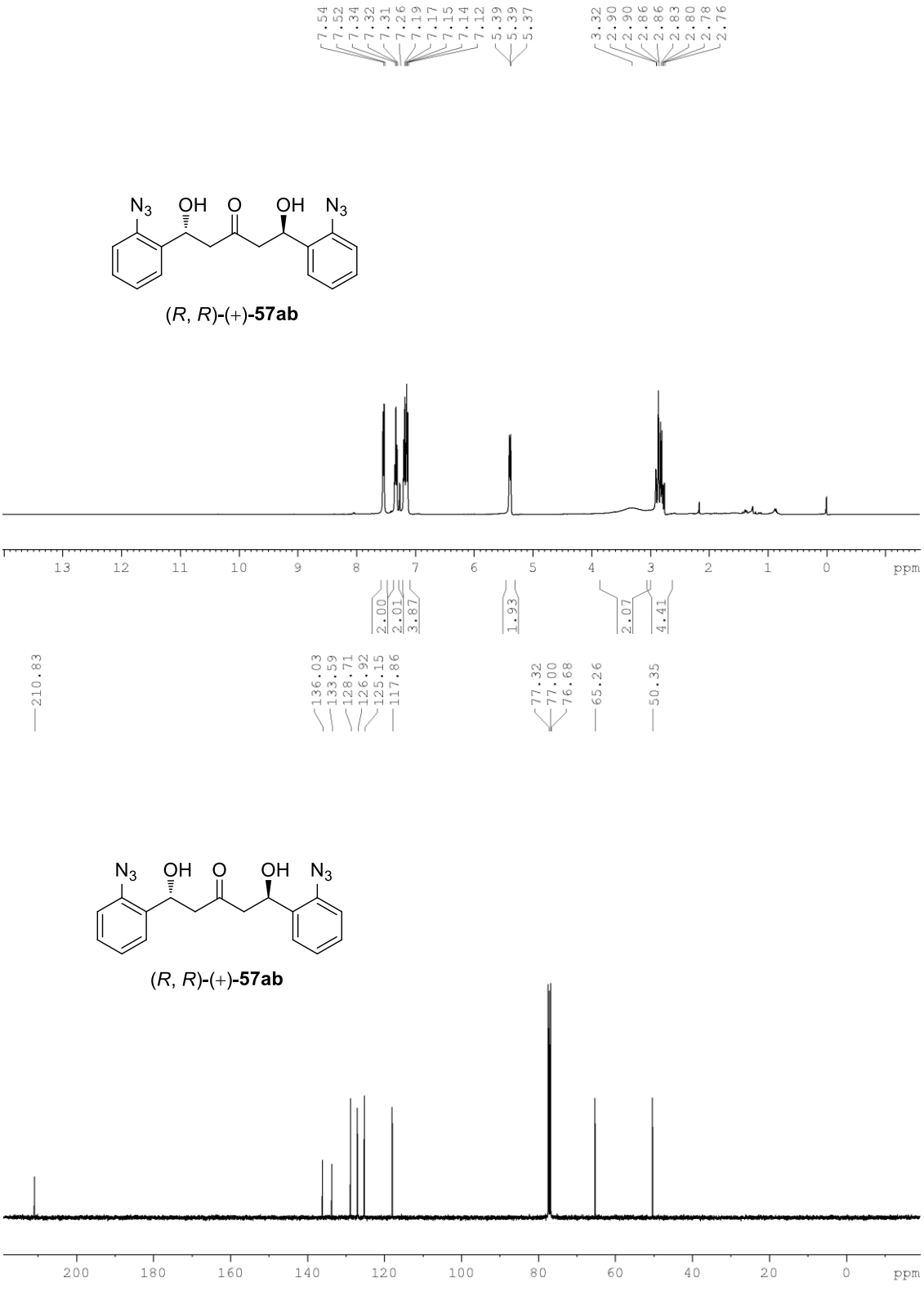


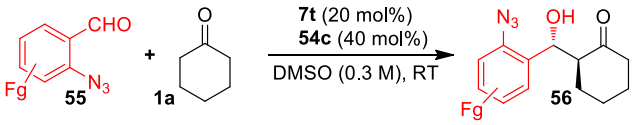

***Figure-37:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **57ab**.

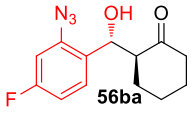
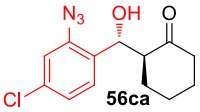
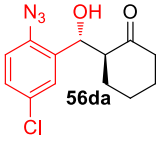
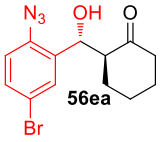
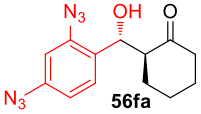
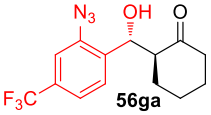
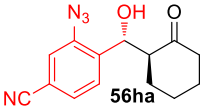
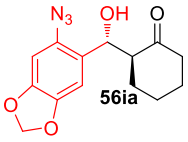
### *5.2.3 Scope of asymmetric LLB-A reaction:*

After testing the applicability of the LLB-A reaction on the acyclic ketone, acetone (**1b**), we focused our attention to study the scope of the reaction, utilizing various functionalized *o*-azidobenzaldehydes. Initially, the reaction was carried out on halo-substituted *o*-azidobenzaldehydes **55b-e** with cyclohexanone (**1a**) using the best optimized catalyst **7t/54c** system to furnish the products *anti*-(–)-**56ba-ea** in very good yields with good *dr* and excellent *ee* (Table 11, entries 1-4). The LLB-A reaction of 2,4-diazidobenzaldehyde (**55f**) with **1a** resulted in the product *anti*-(–)-**56fa** with less yield but with increased *dr* and 98% *ee* (Table 11, entry 5). *o*-Azidobenzaldehydes possessing electron withdrawing group such as *p*-(trifluoromethyl) and *p*-cyano groups **55g** and **55h** also underwent the reaction to provide the products *anti*-(+)-**56ga** and *anti*-(–)-**56ha** in good yields with good *dr* and excellent *ee* (Table 11, entries 6 and 7). Presence of an electron donating substituent like dioxymethylene group on *o*-azidobenzaldehyde, **55i** also did not deter the reaction, but produced the product *anti*-(–)-**56ia** in somewhat lesser yield but with good *dr* and 97% *ee* (Table 11, entry 8).

In this particular exercise, wherever we observed reduced yield, the reactions were also performed with the other catalyst system, **7a**/**54g**, under neat conditions and found to furnish the products with better yields but with reduced *dr* in few cases (Table 11, entries 1, 5 and 8).

***Table 11***: Scope of the L-DMTC (**7t**) and TFA (**54c**) Catalyzed LLB-A Reactions.[a]




| Entry | Product **56** | *t* (h) | Yield (%)[b] | *dr*[c] | *ee*[d,e] |
|---|---|---|---|---|---|
| 1 |  **56ba** | 24 | 75 | 17:1 | 99 |
| | | 24[f] | 91 | 17:1 | >99 |
| 2 |  **56ca** | 36 | 89 | 17:1 | 98 |
| 3 |  **56da** | 18 | 90 | 51:1 | 99 |
| 4 |  **56ea** | 24 | 79 | 17:1 | >99 |
| 5 |  **56fa** | 48 | 41 | 99:1 | 98 |
| | | 36[f] | 93 | 13:1 | 99 |
| 6 |  **56ga** | 16 | 85 | 17:1 | >99 |
| 7 |  **56ha** | 18 | 90 | 21:1 | >99 |
| 8 |  **56ia** | 120 | 46 | 17:1 | 97 |
| | | 120[f] | 51 | 2.4:1 | 99 |

[a] Unless otherwise mentioned, all reactions were carried out with **55** (0.3 mmol), cyclohexanone **1a** (4.2 mmol, 14.0 equiv.), catalysts **7t** (20 mol%) and **54c** (40 mol%) in DMSO (0.3 M) at RT. [b] Yield refers to the column-purified product. [c] *dr* was determined based on $^1$H NMR or HPLC analysis. [d] *ee* was determined by CSP HPLC analysis. [e] *ee* mentioned for major isomer. [f] Reactions were carried out with **55** (0.3 mmol), cyclohexanone **1a** (3 mmol, 10.0 equiv.) with catalysts **7a** (15 mol%) and **54g** (10 mol%) under neat condition at RT.

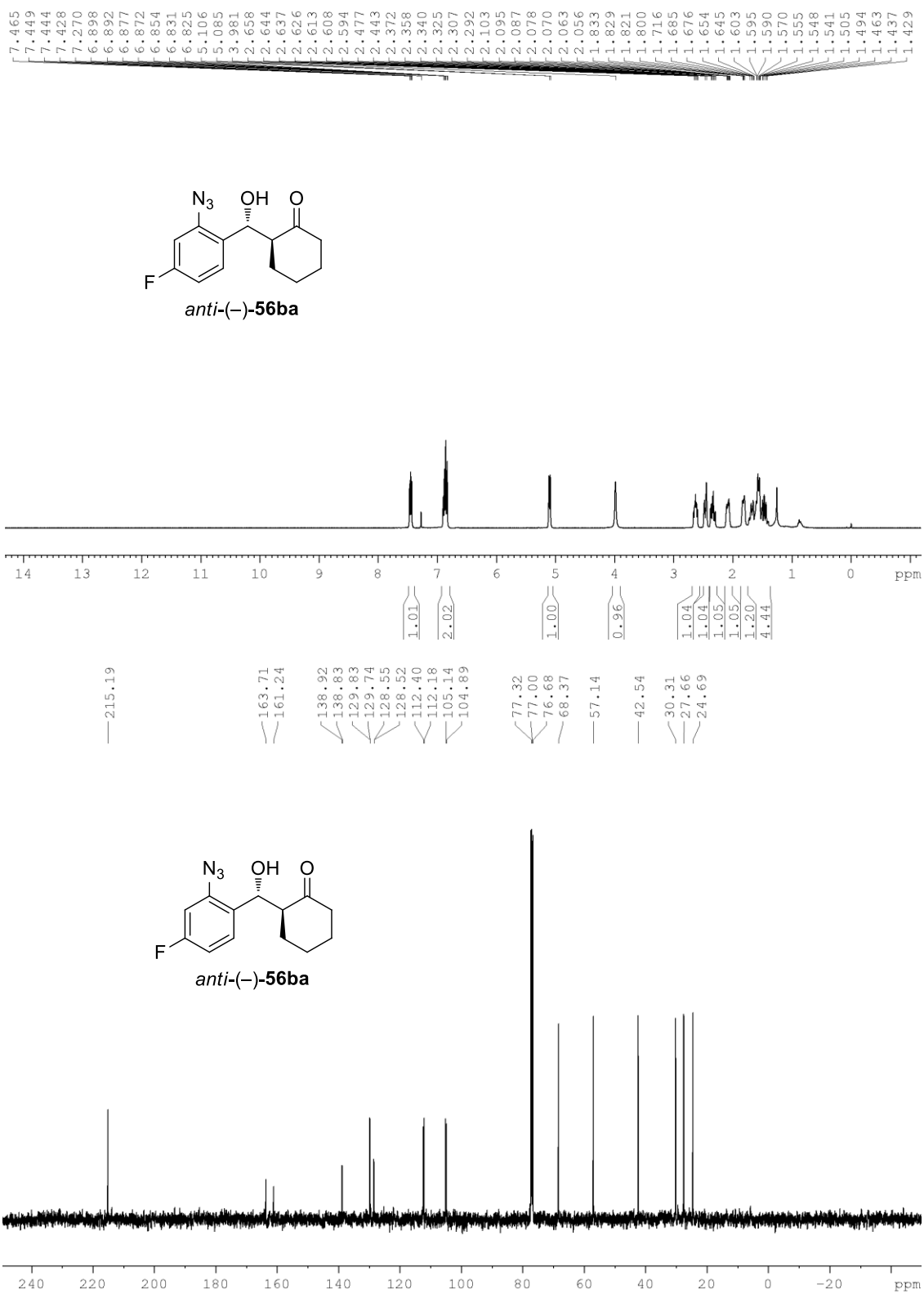



***Figure-38:*** $^{1}$H and $^{13}$C NMR spectra of the product **56ba**.

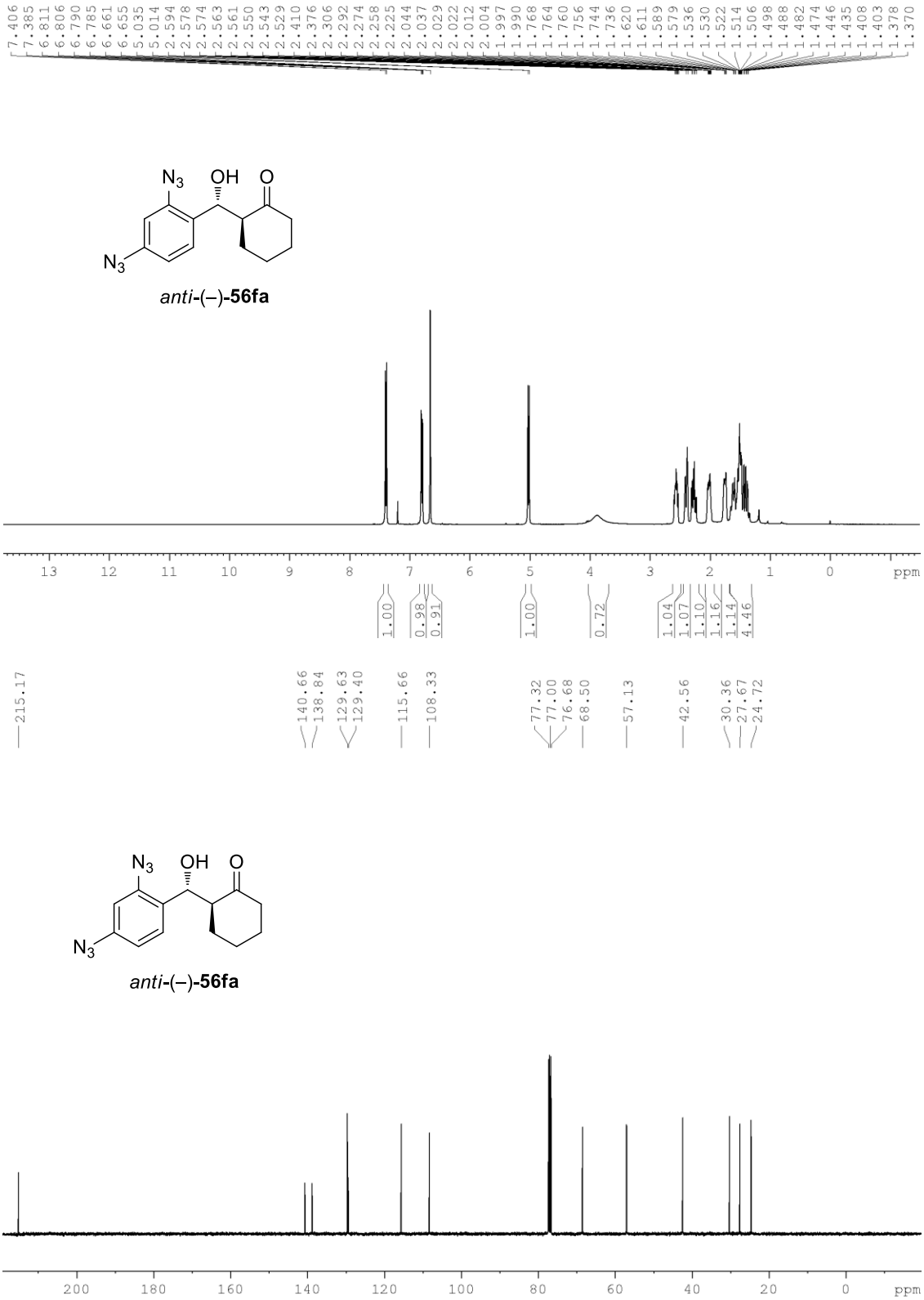



***Figure-39:*** $^{1}$H and $^{13}$C NMR spectra of the product **56fa**.

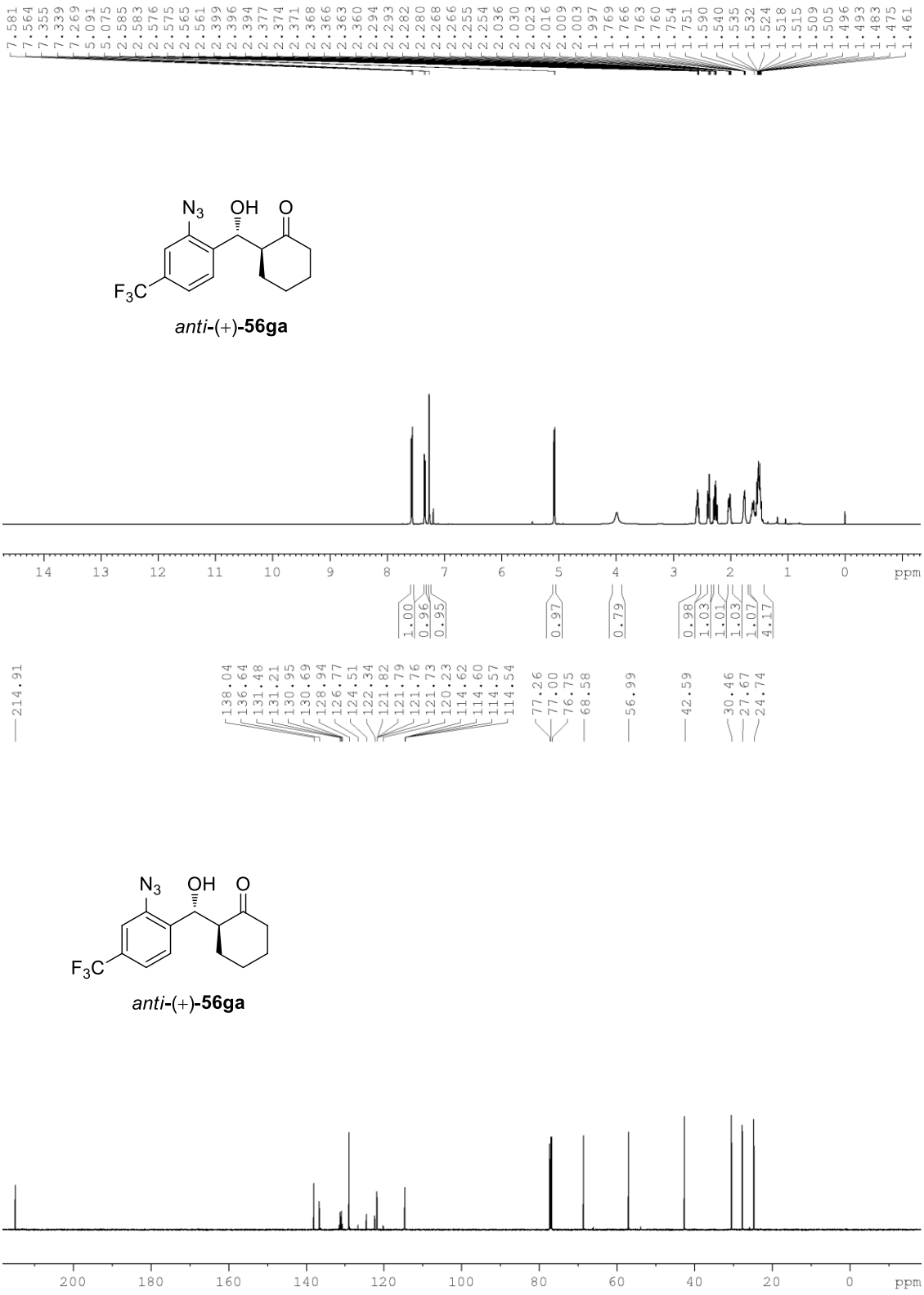



***Figure-40:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **56ga**.

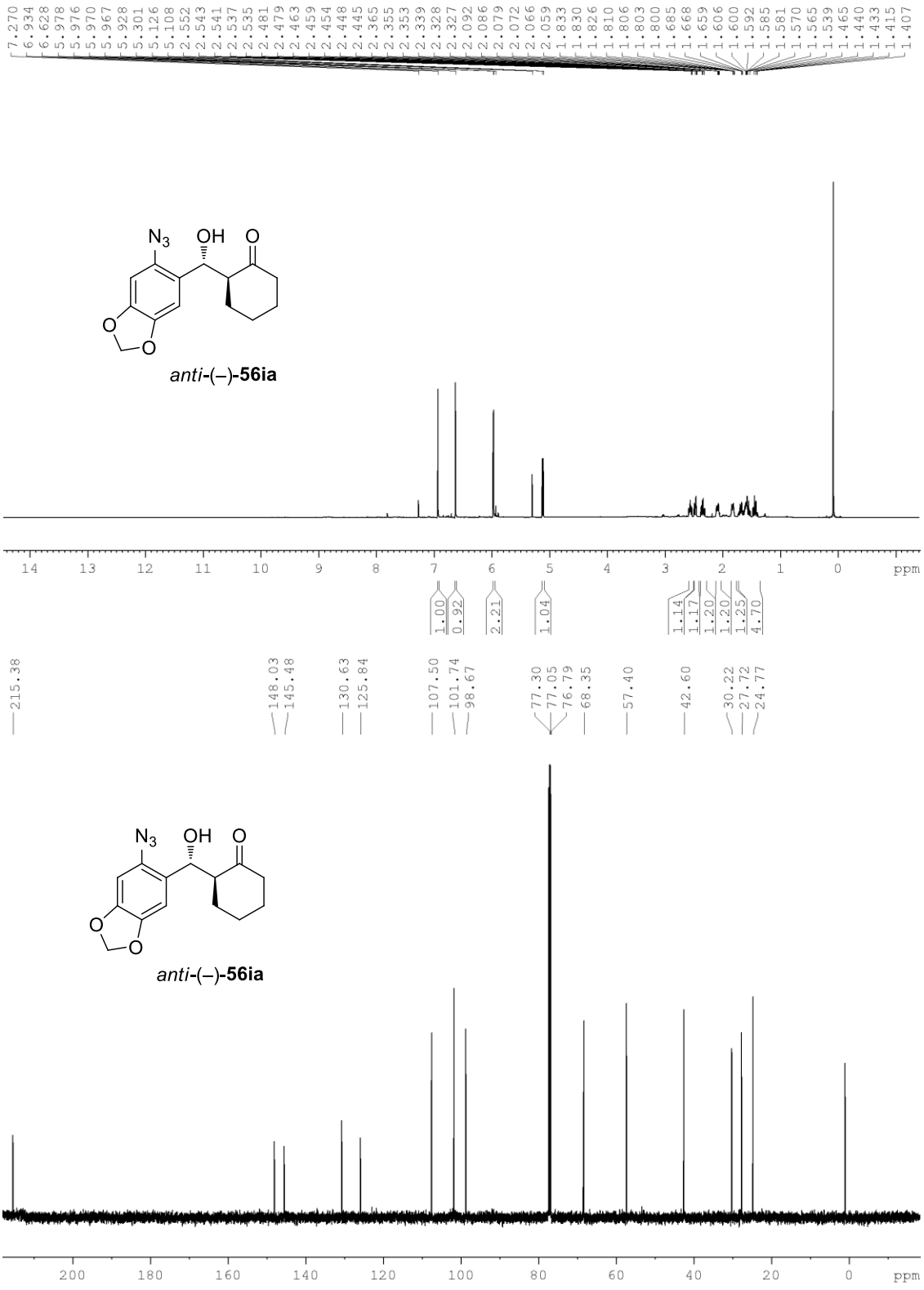



***Figure-41:*** $^{1}$H and $^{13}$C NMR spectra of the product **56ia**.

### *5.2.4 Asymmetric desymmetrization of 4-substituted cyclohexanone via LLB-A reactions:*

After studying the scope of the LLB-A reaction with various functionalized *o*-azidobenzaldehydes **55a-i**, we extended our studies further in order to check the generality of the reaction on various 4-substituted cyclohexanones **1g-l**. The 4-alkyl substituted cyclohexanones **1g-l** on subjecting to LLB-A reaction with *o*-azidobenzaldehyde (**55a**) using the optimized condition resulted in the products *anti*-(–)-**56ag** to *anti*-(–)-**56al** in 55-95% yields with good *dr* and 99% *ee* (Table 12, entries 1-5). Our choice of 4-substituted cyclohexanone substrates revealed itself the intriguing contribution imparted by the size and bulkiness of the 4-alkyl substituent in controlling the *dr* of the products in the LLB-A reaction. The size of the 4-alkyl substituent worked as a steric handle in controlling the *dr* of the product, as the size of the 4-substituent increased, the *dr* of the product increased too. Another fascinating element of surprise in this scenario was that we observed the exclusive formation of a single enantiomer, resulting in asymmetric desymmetrization[49] of the 4-substituted cyclohexanone substrates under the given reaction conditions. The structure, regioselectivity and absolute stereochemistry of the LLB-A products **56** and **57** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (–)-**56ca** and (–)-**56ag** as shown in Figure-42 and 45.[50]

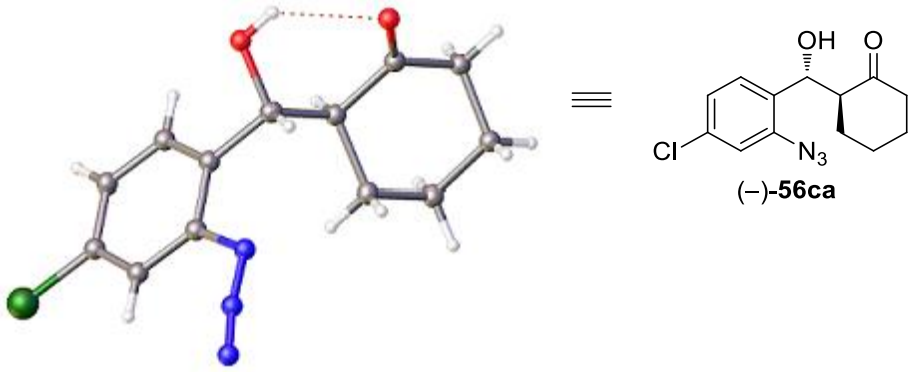
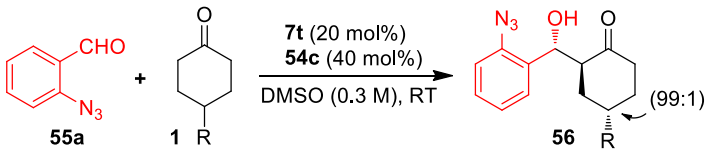
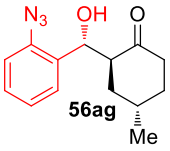
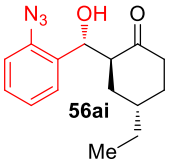
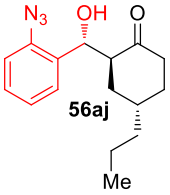
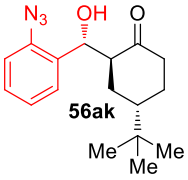
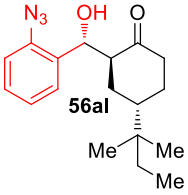



***Figure-42***: X-Ray crystal structure of chiral (*S*)-2-((*R*)-(2-azido-4-chlorophenyl)(hydroxy)methyl)cyclohexanone (**56ca**).

***Table 12***: Asymmetric Desymmetrization of 4-Substituted Cyclohexanone through L-DMTC (**7t**) and TFA (**54c**) Catalyzed LLB-A Reactions.[a]




| Entry | Product **56** | *t* (h) | Yield (%)[b] | *dr*[c] | *ee*[d,e] |
|---|---|---|---|---|---|
| 1 |  **56ag** | 36 | 80 | 6.2:1 | >99 |
| 2 |  **56ai** | 48 | 88 | 13.6:1 | 99 |
| 3 |  **56aj** | 24 | 75 | 10.7:1 | >99 |
| 4 |  **56ak** | 48 | 55 | 99:1 | 99 |
| 5 |  **56al** | 36 | 95 | 18:1 | 99 |

[a] Unless otherwise mentioned, all reactions were carried out with **55a** (0.3 mmol), cyclohexanone **1** (4.2 mmol, 14.0 equiv.), catalysts **7t** (20 mol%) and **54c** (40 mol%) in DMSO (0.3 M) at RT. [b] Yield refers to the column-purified product. [c] *dr* was determined based on $^1$H NMR or HPLC analysis. [d] *ee* was determined by CSP-HPLC analysis. [e] *ee* mentioned for major isomer.

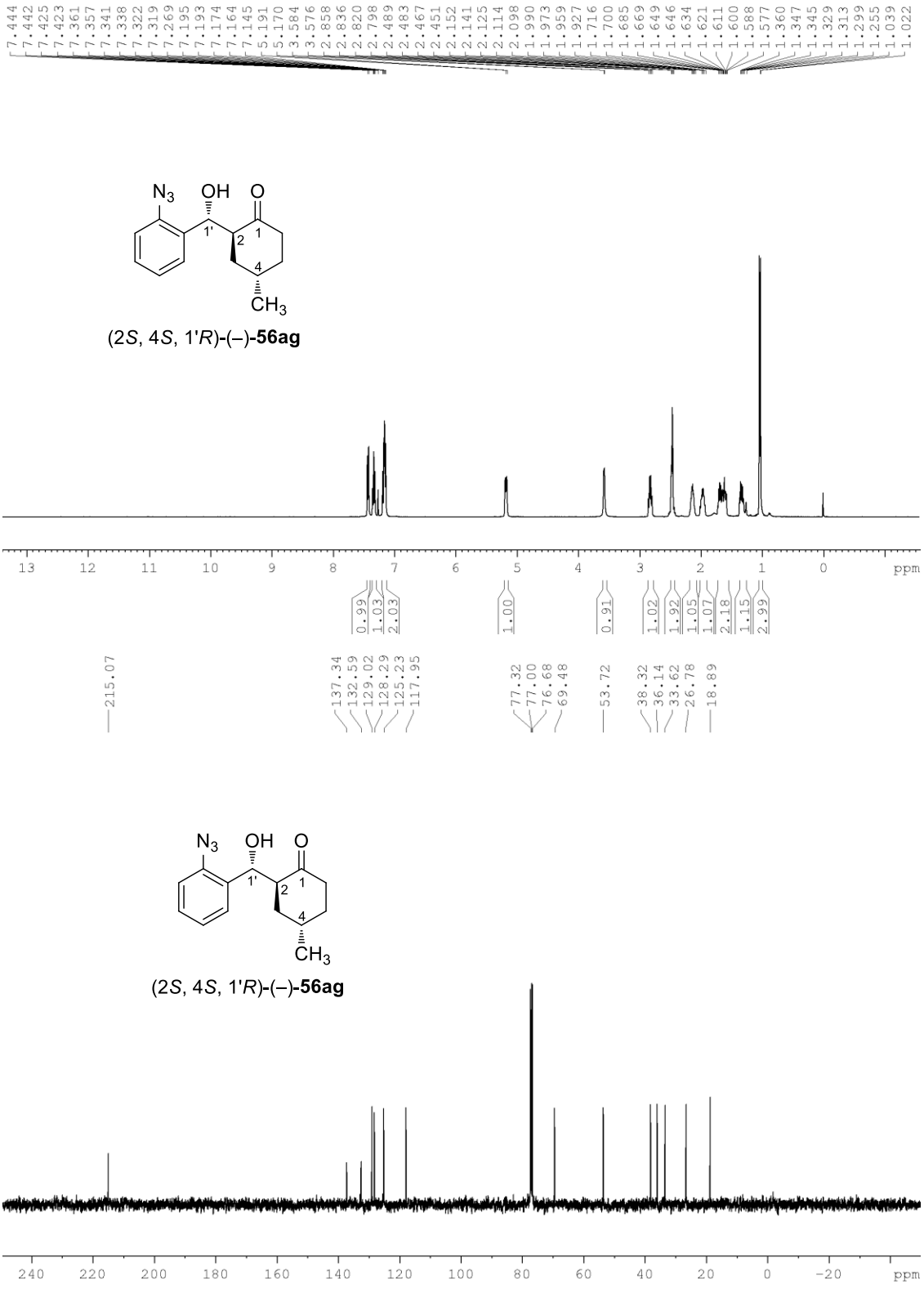



***Figure-43:*** $^{1}$H and $^{13}$C NMR spectra of the product **56ag**.

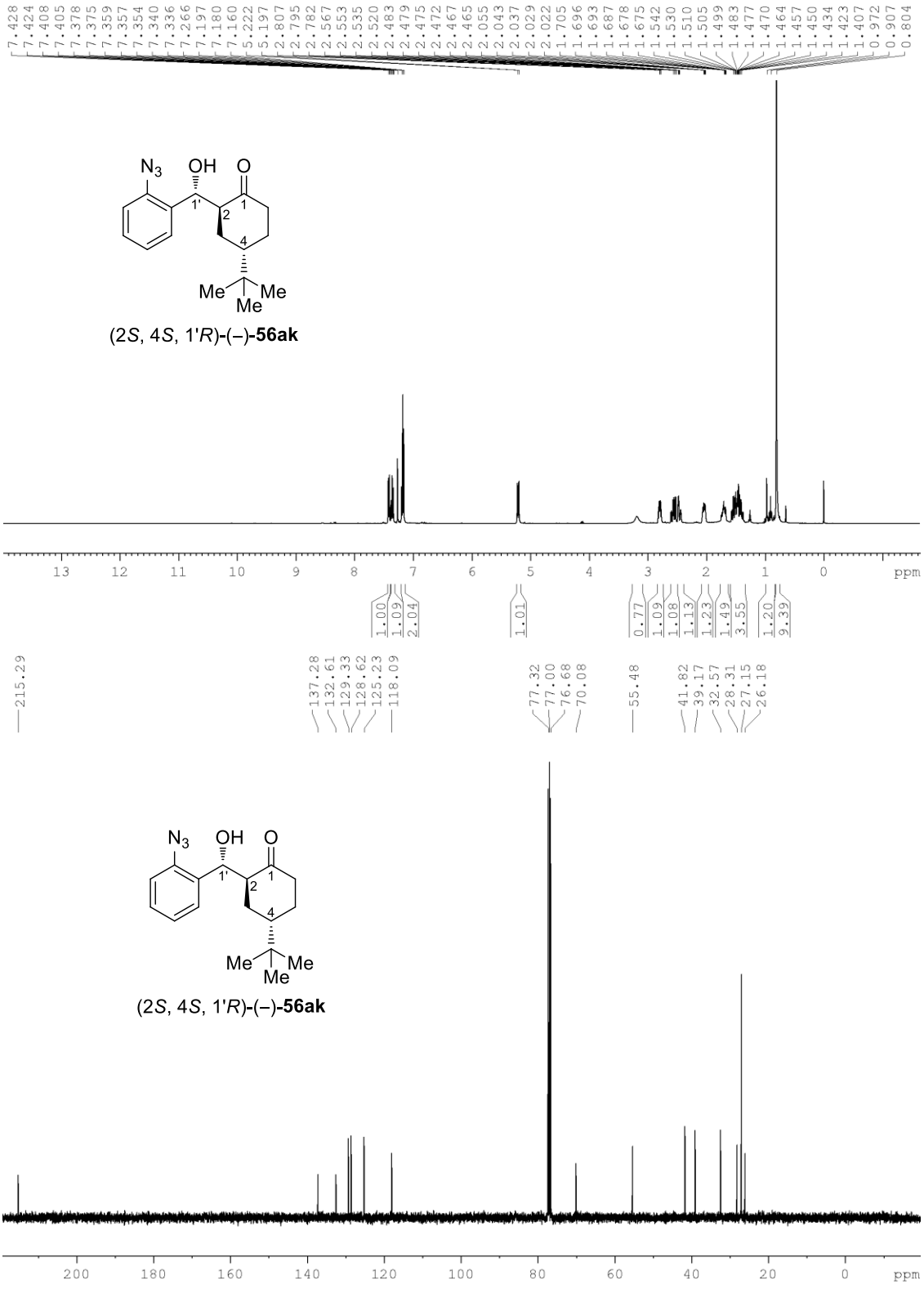



***Figure-44:*** $^{1}$H and $^{13}$C NMR spectra of the product **56ak**.

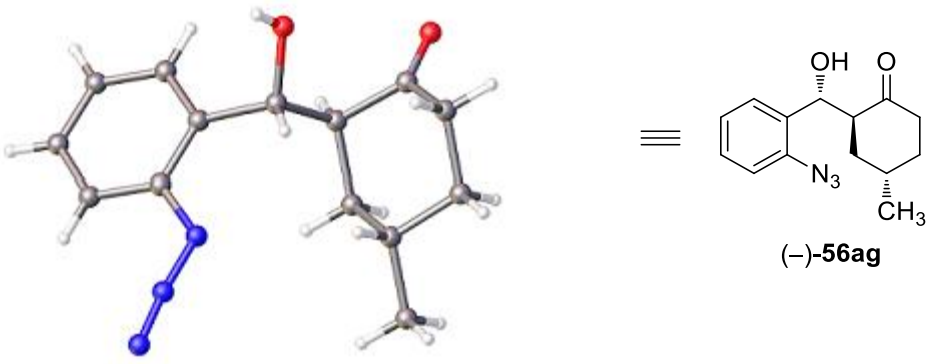


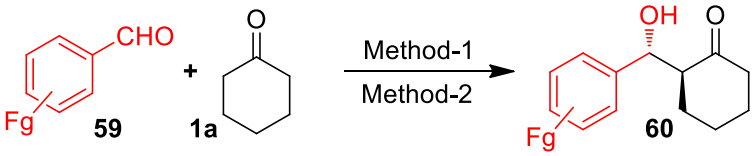

***Figure-45***: X-Ray crystal structure of chiral (2*S*,4*S*)-2-((*R*)-(2-azidophenyl)(hydroxy)methyl)-4-methylcyclohexanone (**56ag**).

### *5.2.5 Controlled experiments to study the ortho-$N_3$ involvement in the pre-transition State:*

After conducting studies towards the scope and generality of the LLB-A reaction with differently substituted *o*-azidobenzaldehydes and 4-substituted cyclohexanone substrates, at this juncture, we turned our attention to examine the involvement of the azido group of the *o*-azidobenzaldehydes in the *pre*-transition state, for which we performed some controlled experiments (Table 13). In the absence of the *o*-azido group, meaning simple benzaldehyde (**59a**) underwent LLB-A reaction under the catalysis of **7t**/**54c** (Method-1) with cyclohexanone (**1a**) to furnish the product *anti*-(+)-**60aa** in reduced (45%) yield with 97% *ee* and 4.4:1 *dr* (Table 13, entry 1). Likewise, 3-azidobenzaldehyde (**59b**) gave the product *anti*-(+)-**60ba** in almost similar yield and *ee* with slightly better *dr*, while 4-azidobenzaldehyde (**59c**) provided the product *anti*-(+)-**60ca** in low yield with a noticeable decrease in *ee*, though there was an increase in *dr* (Table 13, entries 2 and 3). *These results on comparison with that of o-azidobenzaldehyde (**55a**) (Table 9, entry 13) provide insight into the fact that indeed the o-azido group plays a vital role in the pre-transition state to control the product formation.*[45] Moreover, these controlled experiments were also conducted *via* Method-2 (Table 13) using **7a**/**54g** under neat conditions, which provided the products *anti*-(+)-**60aa** to *anti*-(+)-**60ca** in more or less similar yields but with deteriorated *ee* and *dr* when compared with result for *o*-azidobenzaldehyde (**55a**) (Table 9, entry 25), which is again in accordance with our explanation. More detailed description of the participation from the *o*-azido group will be provided later during the mechanistic studies.

Structure and regioselectivity of LLB-A products **60** were obtained based on the NMR analysis and also by correlation with previous L-proline catalyzed LLB-A reactions (Scheme 6).[37]

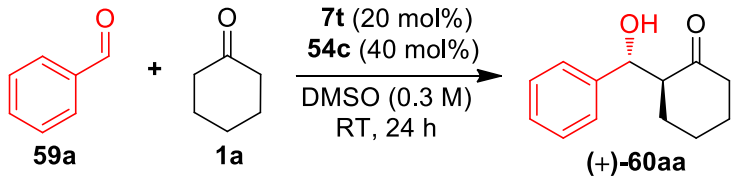
***Table 13:*** Controlled Experiments to Study the Effect of Azido Group in LLB-A Reactions.[a]




| Entry | Fg | Method-1 | | | Method-2 | | |
|---|---|---|---|---|---|---|---|
| | | Yield (%)[b] | *ee* (%)[c,d] | *dr*[e] | Yield (%)[b] | *ee* (%)[c,d] | *dr*[e] |
| 1 | H (**59a**) | 45 (**60aa**) | 97 | 4.4:1 | 88 (**60aa**) | 90 | 2.2:1 |
| 2 | 3-$N_3$ (**59b**) | 47 (**60ba**) | 96 | 6.3:1 | 90 (**60ba**) | 93 | 3.4:1 |
| 3 | 4-$N_3$ (**59c**) | 16 (**60ca**) | 88 | 15.6:1 | 81 (**60ca**) | 93 | 4.5:1 |

[a] Unless otherwise mentiod all the reaction was carried out under Method-1: **7t** (20 mol%) and **54c** (40 mol%) DMSO (0.3 M), RT, 24 h; Method-2: **7a** (15 mol%) and **54g** (10 mol%) Neat, RT, 24 h. [b] Yield refers to the column-purified product. [c] *ee* was determined by CSP-HPLC analysis. [d] *ee* mentioned for major isomer. [e] *dr* was determined based on $^1$H NMR or HPLC analysis.

***Scheme 6:*** Determination of Absolute Configuration by Comparison with Reported Optical Rotation.




**(+)-60aa**

97% *ee* and 4.4:1 *dr*

$[\alpha]_D^{25}$ = +**14.1**° (*c* = 0.37, $CHCl_3$)

---

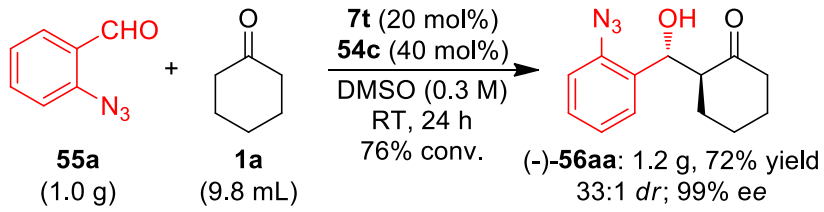
93 % *ee* and 61:1 *dr*

Lit.[51] $[\alpha]_D^{24}$ = –**24.2**° (*c* = 1.03, $CHCl_3$)

### *5.2.6 Gram scale synthesis of LLB-A product (-)-56aa:*[a]

With industrial applications in mind, herein, we have demonstrated the gram-scale synthesis of LLB-A product (–)-**56aa** (Scheme 7). By scaling up milligrams to 1.0 gram of *o*-azidobenzaldehyde (**55a**) with 9.8 mL of cyclohexanone (**1a**) in 22.6 mL of DMSO at 25 °C for 24 h under the **7t**/**54c**-catalysis furnished the LLB-A product (–)-**56aa** in 76% conversion with 72% yield, 33:1 *dr* and 99% *ee*. Reaction rate slightly decreased and *dr* improved in gram-scale synthesis compared to milligram-scale (Table 9, entry 13), may be due to the slight change in reaction volume (Scheme 7).

***Scheme 7:*** Gram Scale Synthesis of LLB-A Product (–)-**56aa.**[a]




[a]Reaction conditions: **55a** (1.0 g, 6.8 mmol), **1a** (9.8 mL, 95.2 mmol), **7t** (219.2 mg, 20 mol%), **54c** (208 μL, 40 mol%), DMSO (22.6 mL, 0.3 M), RT, 24 h, 76% conversion and 72% yield [90% yield based on the starting material consumed].

## *5.3 Synthetic applications of chiral LLB-A products:*

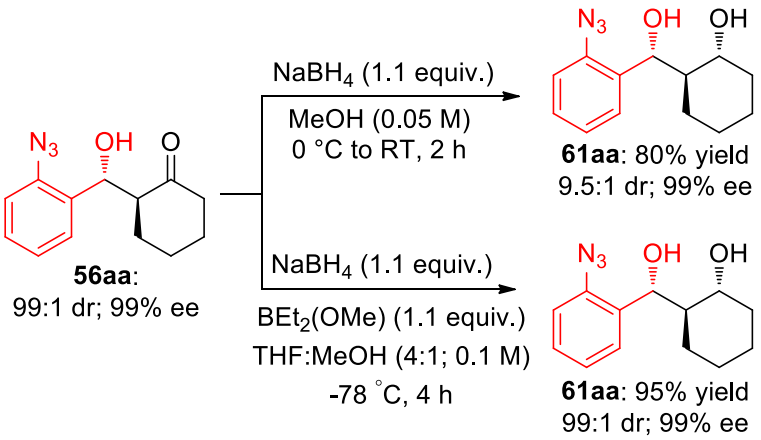
As organic chemists, we felt that our investigation would be incomplete and futile without applications. Subsequently, we sought after some application oriented studies on the derived LLB-A products.

### *5.3.1 Asymmetric synthesis of syn-(+)-1,3-Diols:*

First, we wanted to reduce the LLB-A product, keto-alcohol *anti*-(–)-**56aa,** to the dihydroxy compound (+)-**61aa**, as chiral *syn*-diols are important as chiral ligands for many asymmetric reactions. Simple sodium borohydride reduction at 0 °C to 25 °C on the keto-alcohol *anti*-(–)-**56aa** furnished the *syn*-diol (+)-**61aa** in 80% yield with 99% *ee*, but with reduced 9.5:1

*dr* (Scheme 8). On contrary, when the same sodium borohydride reduction was carried out in the presence of 1.1 equiv. of Lewis acid $BEt_2OMe$ at -78 °C, the product was formed in 95% yield, absolutely as a single isomer with an optical purity of 99%, the reason being interaction of the Lewis acid with both keto and hydroxy group, resulting in the transfer of hydride from the face opposite to that of the hydroxy group so as to produce the *syn*-diol (+)-**61aa** extraordinarily (Scheme 8). The *syn*-diol (+)-**61aa** possessing an azido group could be easily converted to a chiral amino-diol, which could serve as potent chiral ligand (Scheme 8).

***Scheme 8:*** Asymmetric Synthesis of *syn*-(+)-1,3-Diol **61aa** from *anti*-(–)-**56aa.**




### *5.3.2 Asymmetric synthesis of functionalized tetrahydroacridines from LLB-A products:*

Second, the LLB-A products *anti*-(–)-**56ai-56ak** were converted to alkyl substituted tetrahydroacridines (–)-**62ai-62ak**, by treating them with 1.1 equiv. of tributylphosphine in toluene at RT for 1 h. In this cascade reaction, tributylphosphine initially reacted with the azido group to generate iminophosphorane intermediate, which underwent an *in-situ* intramolecular aza-Wittig reaction with the keto group, followed by *in-situ* elimination of the hydroxyl group as water resulted in aromatization to furnish the alkyl substituted chiral (–)-tetrahydroacridines in very good yields, which were found to be materialistically and medicinally important compounds (Scheme 9).[52] Three different tetrahydroacridines (–)-**62ai-62ak** were furnished in good yields with high *ee*'s, but the *ee*'s of (–)-**62ai-62ak**were slightly decreased compared to starting LLB-A compounds, may be due to the epimerization because of basic nature of reaction with tributylphosphine and tributylphosphine oxide. It is worth mentioning here that the crude LLB-A

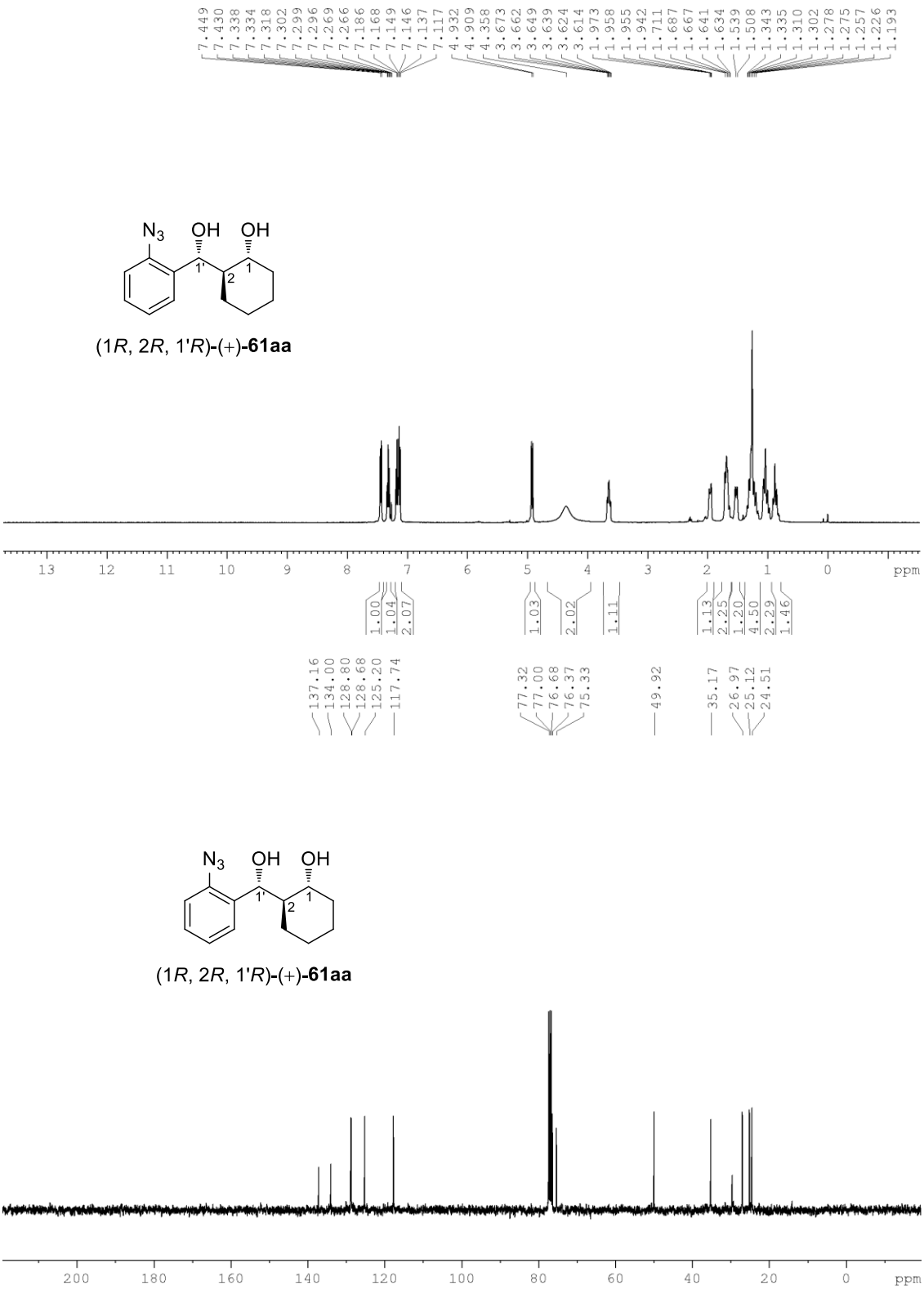
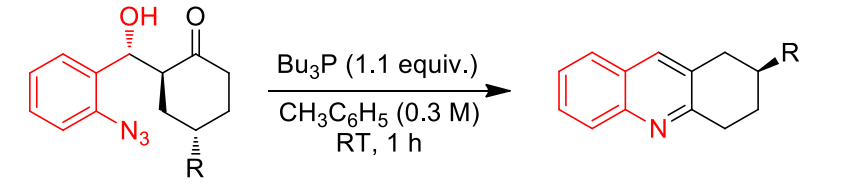



***Figure-46:*** $^{1}$H and $^{13}$C NMR spectra of the product **61aa**.

products, *anti*-(–)-**56ai-56ak** gave better yields of tetrahydroacridines (–)-**62ai-62ak** than the corresponding purified products (Scheme 9).

***Scheme 9*:** Asymmetric Synthesis of Functionalized Tetrahydroacridines **62.**




**56ai**: R = Et, 99% ee
**56aj**: R = *n*-Pr, 99% ee
**56ak**: R = *t*-Bu, 99% ee

**62ai**: R = Et, 85% yield; 94% ee
**62aj:** R = *n*-Pr, 73% yield; 96% ee
**62ak**: R = *t*-Bu, 90% yield; 98% ee

### *5.3.3 Asymmetric synthesis of structurally rigid 10-membered lactams:*

Third, we decided to convert the chiral LLB-A products into functionally rich and structurally rigid 10-membered lactams, which could prove to be effective chelating ligands for different metal ions (Scheme 10).[53] Consequently, Baeyer-Villiger oxidation of *anti*-(–)-**56aa** with *m*-CPBA furnished the selective lactone (+)-**63aa** in 67% yield, which on hydrolysis of the lactone followed by protection of the resulting diol as acetonide and esterification of the carboxylic acid with ethereal diazomethane solution, generated the azido-ester (–)-**64aa** in 70% yield. Reduction of the azido group to amino group was effected with either indium chloride and triethylsilane or tributylphosphine to furnish the compound (–)-**65aa**, which, on reaction with potassium tertiary butoxide in dry THF, produced the 10-membered lactam (–)-**66aa** in 57% yield (Scheme 10).

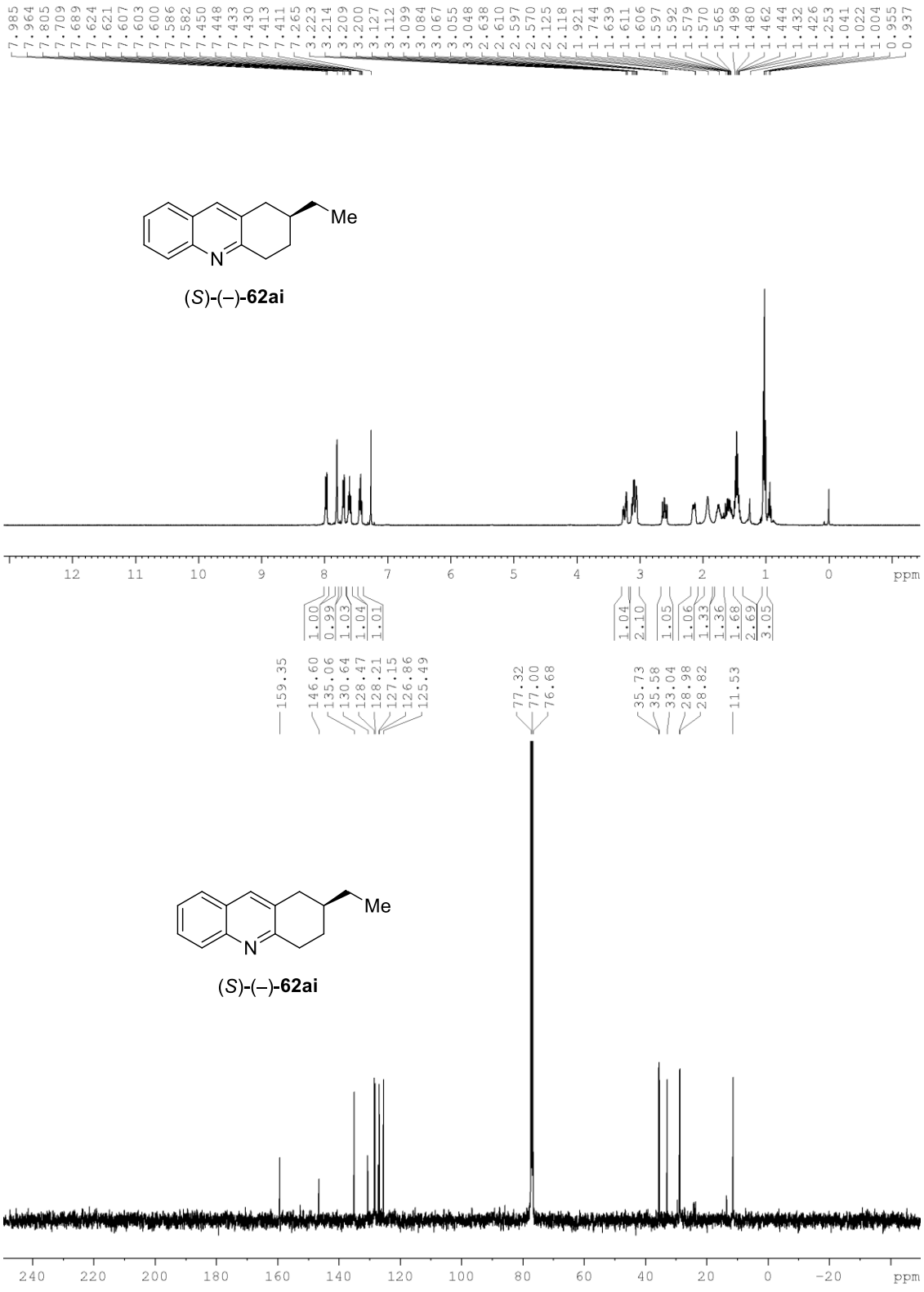



***Figure-47:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **62ai**.

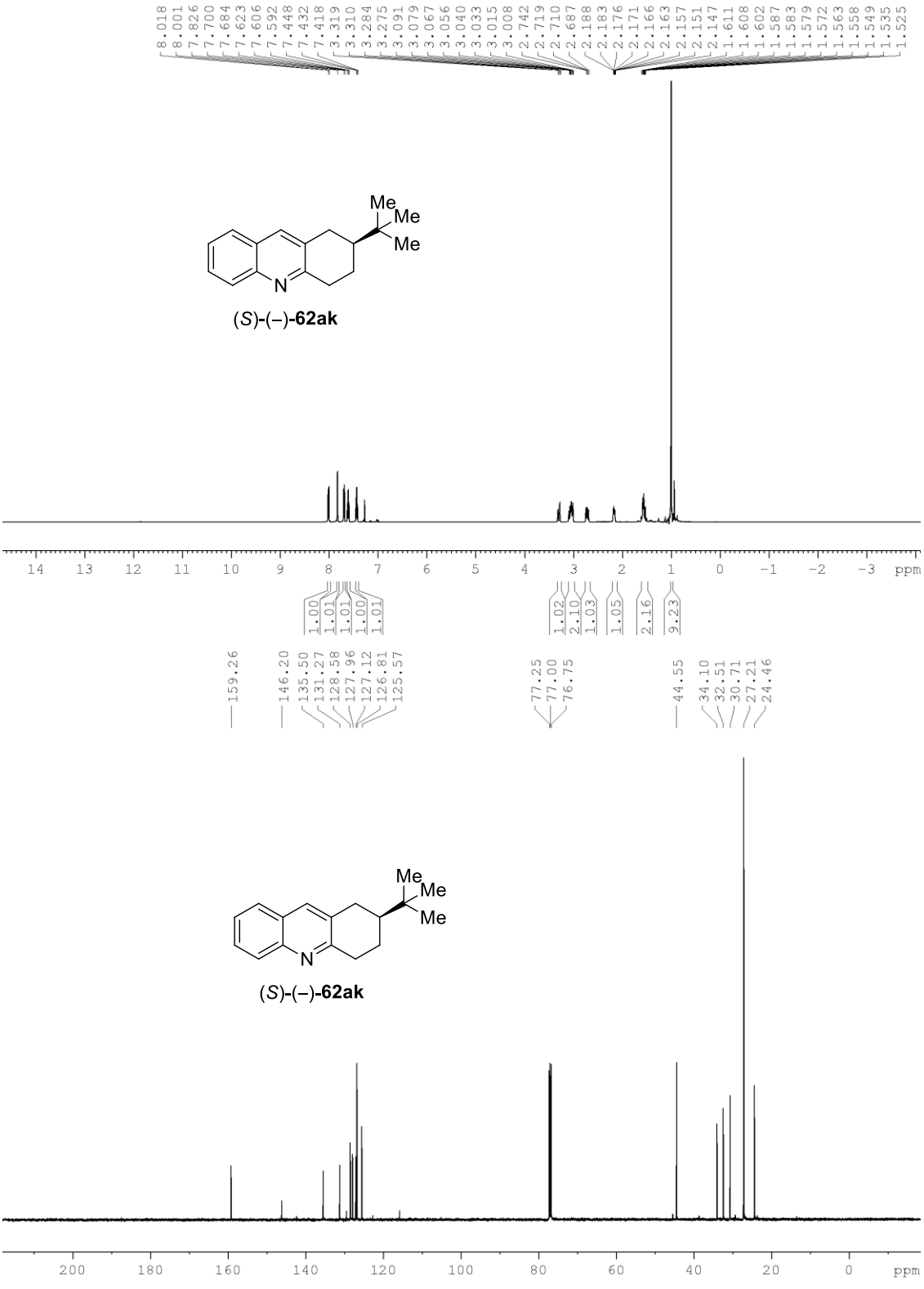
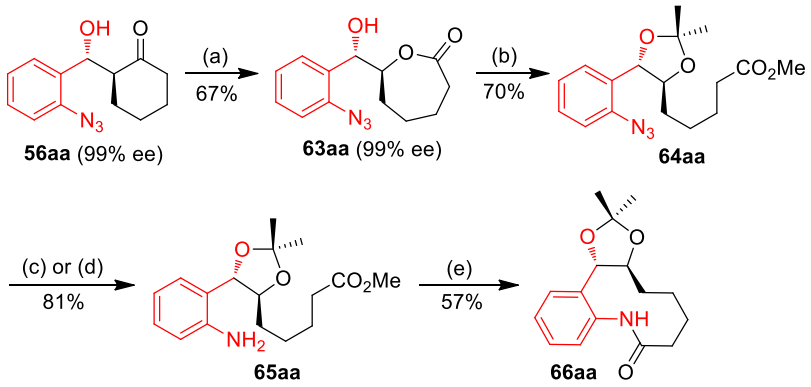



***Figure-48:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **62ak**.

***Scheme 10:*** Asymmetric Synthesis of 10-Membered (–)-Lactam **66aa.**[a]




[a] Reaction conditions: (a) *m*CPBA (3 equiv.), $NaHCO_3$ (2 equiv.), $CH_2Cl_2$ (0.1 M), RT, 5 h, 67%; (b) (i) 5% aq. NaOH, MeOH:$H_2O$ (1:1), 80 °C, 1 h; (ii) 2,2-dimethoxypropane (1.4 equiv.), *p*TSA (0.01 equiv.), $MgSO_4$ (0.007 equiv.), Acetone (0.1 M), RT, 4 h; (iii) $CH_2N_2$, $Et_2O$, 0-5 °C, 0.5 h, 70% for 3 steps; (c) $InCl_3$ (1.1 equiv.), $Et_3SiH$ (2.2 equiv.), MeOH (0.05 M), 0 °C to RT, 2 h, 81%; (d) $Bu_3P$ (3 equiv.), dry $CH_3C_6H_5$ (0.1 M), RT, 1 h, 71%; (e) *t*BuOK (1.5 equiv.), dry THF (0.03 M), RT, 24 h, 57%.

### *5.3.4 Asymmetric synthesis of functionalized allenone:*

After opening the doors to few applications for the LLB-A products, still unsatisfied, we wanted to exploit more from the lactone (+)-**63aa**. As a result, the lactone (+)-**63aa** was subjected to DIBAL-H reduction to furnish the triol (+)-**67aa**, which was converted to the alcohol (+)-**68aa** by protection of two of the hydroxy groups as acetonide. The propargylic alcohol (+)-**70aa**, prepared from the acetonide-alcohol (+)-**68aa** through IBX oxidation and Grignard addition, which, on one-pot oxidation, followed by subsequent isomerisation by treatment with PCC, furnished the functionalized allenone (+)-**71aa** in good yield (Scheme 11), which could be an impending substrate for diverse organocatalytic reactions.[54]

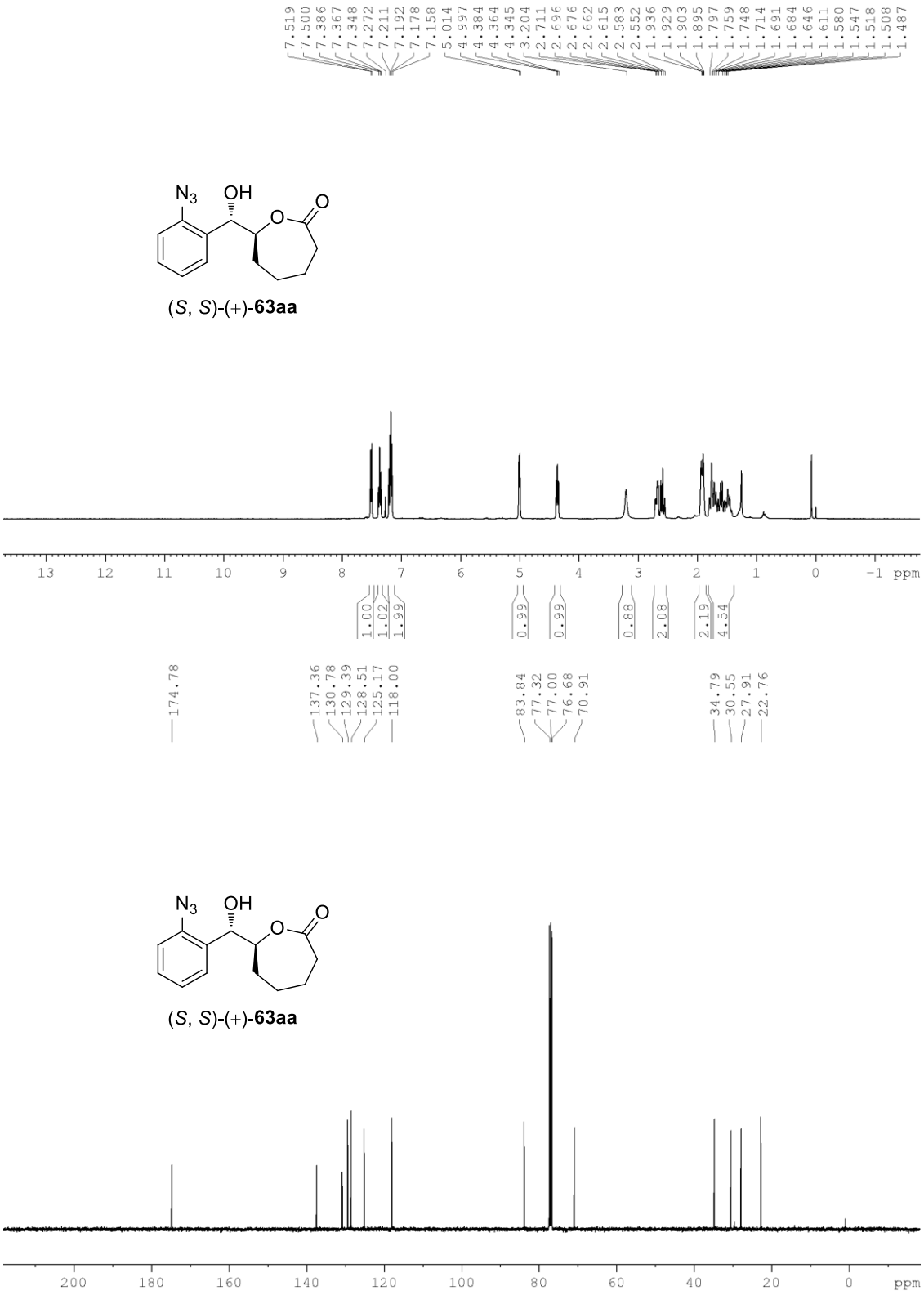



***Figure-49:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **63aa**.

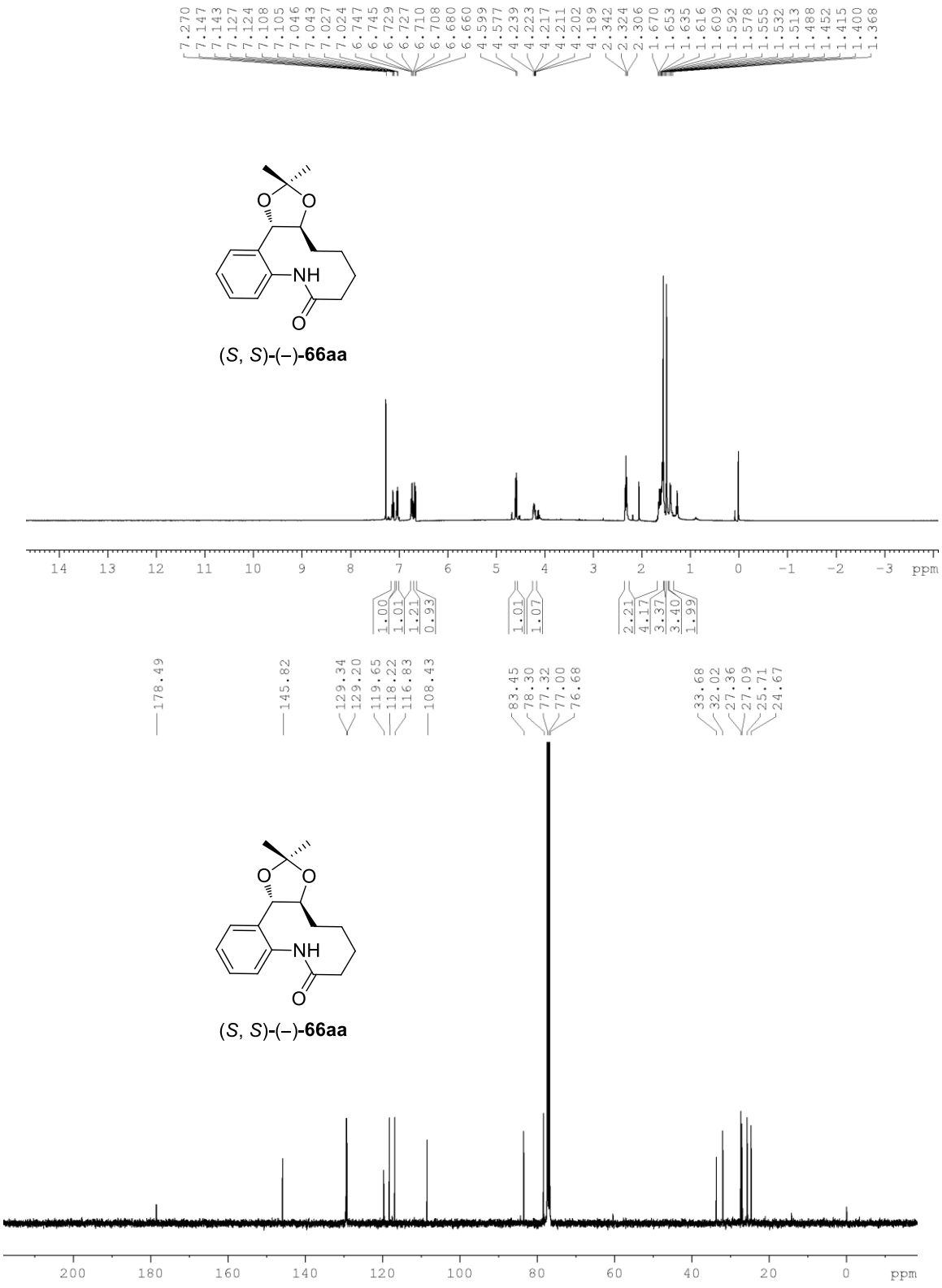
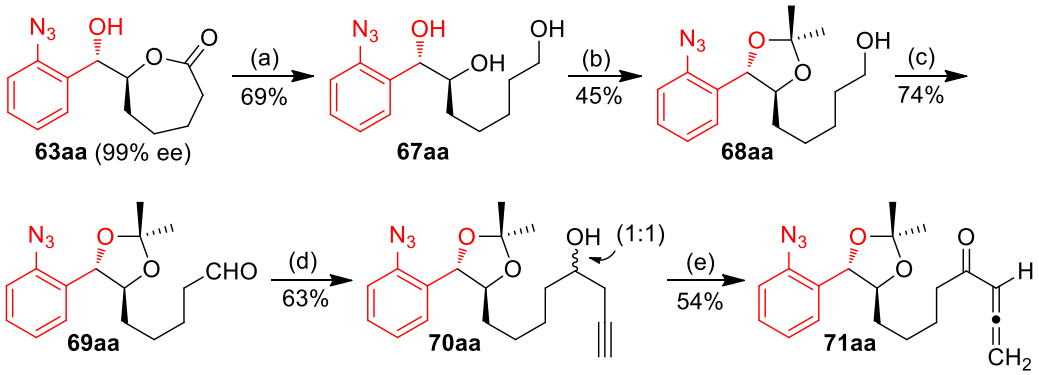



***Figure-50:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **66aa**.

***Scheme 11:*** Asymmetric Synthesis of Functionalized (+)-Allenone **71aa.**[a]




[a] Reaction conditions: (a) DIBAL-H (4 equiv.), $CH_3C_6H_5$ (0.5 M), RT, 4 h, 69%; (b) 2,2-dimethoxypropane (1.4 equiv.), *p*TSA (0.01 equiv.), $MgSO_4$ (0.007 equiv.), Acetone (0.15 M), RT, 4 h, 45%; (c) IBX (3 equiv.), $CH_3CN$ (0.16 M), 80 °C, 3 h, 74%; (d) prop-2-yn-1-ylmagnesium bromide (1.5 equiv.), dry THF (0.03 M), -10 °C to RT, 12 h, 63%; (e) PCC (2 equiv.), $CH_2Cl_2$ (0.04 M), 0 °C to RT, 2 h, 54%.

### *5.3.5 Asymmetric Synthesis of Functionalized 1,2,3-Triazoles:*

In another direction, the lactone (+)-**63aa**, possessing the functionally important azido group, on treatment with ethyl acetylene dicarboxylate underwent click reaction in water for 5 h to furnish the 1,2,3-triazole (+)-**72aa** in 55% yield,[55] whereas prolonged reaction time (24 h) resulted in the formation of the 1,2,3-triazole as well as the hydrolysis of the lactone ring to give a carboxylic acid, which was esterified with ethereal diazomethane solution to furnish the 1,2,3-triazole diol-ester (+)-**73aa** with increased yield, 80% (Scheme 12).[55]

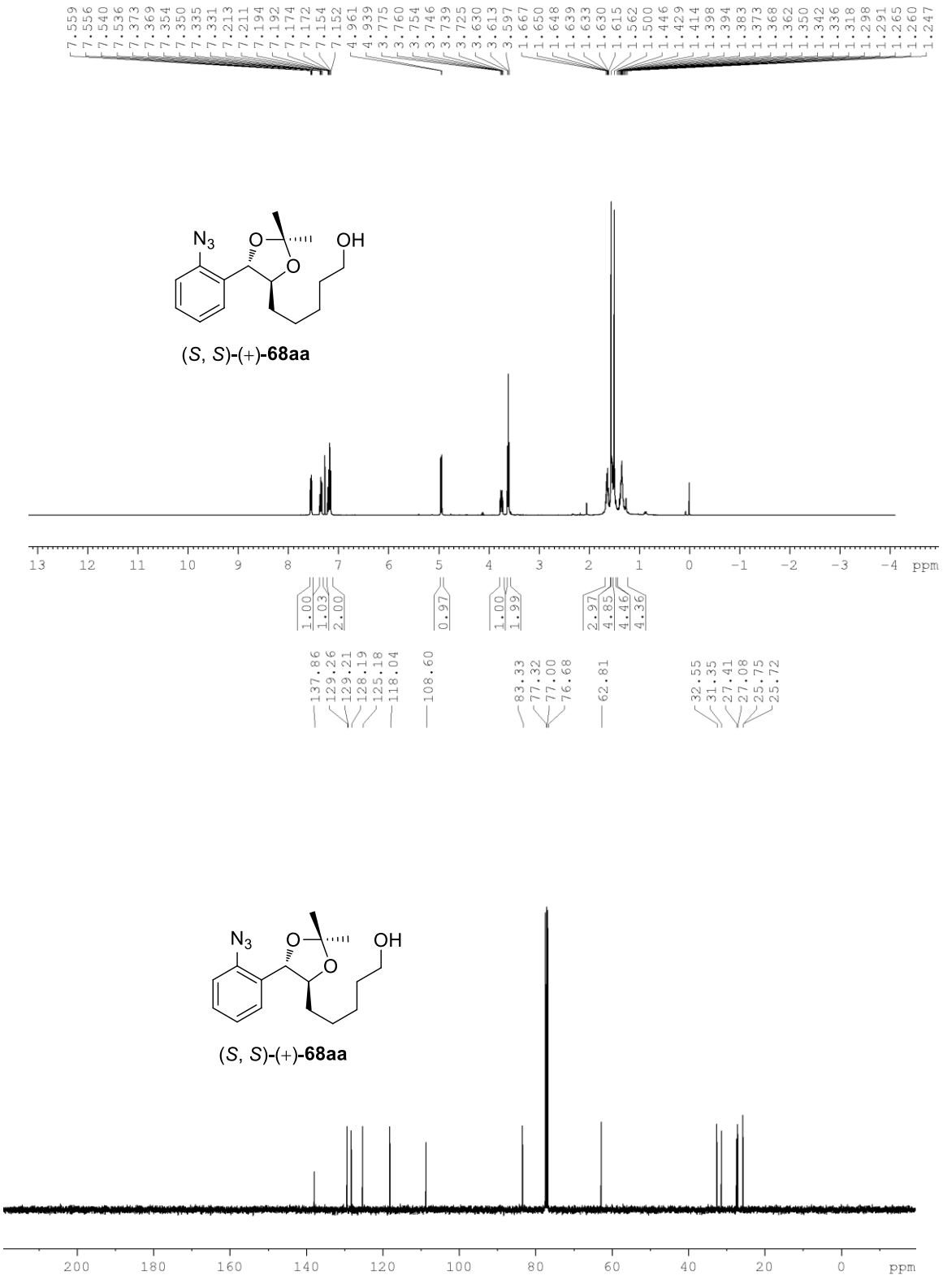



***Figure-51:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **68aa**.

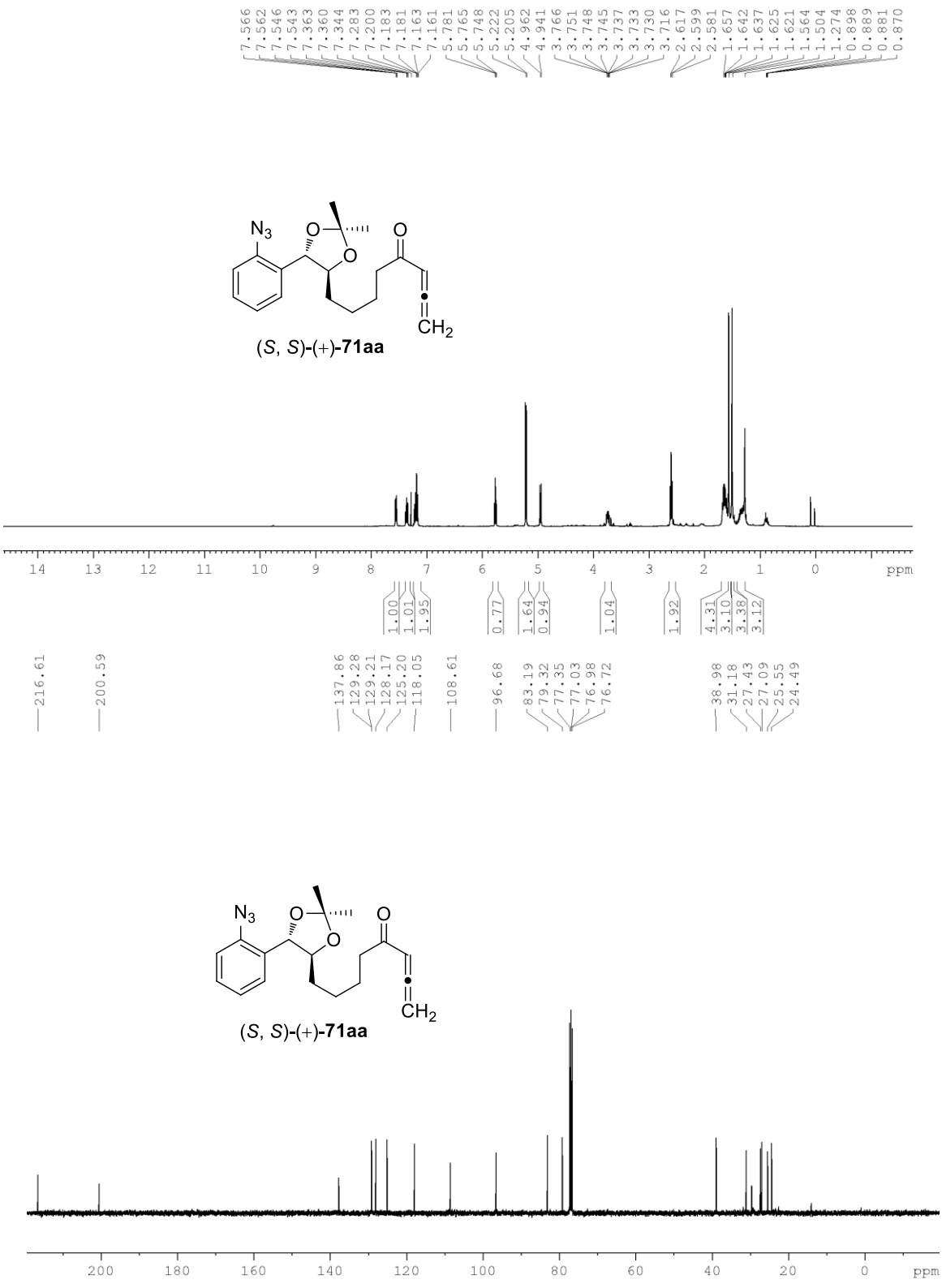
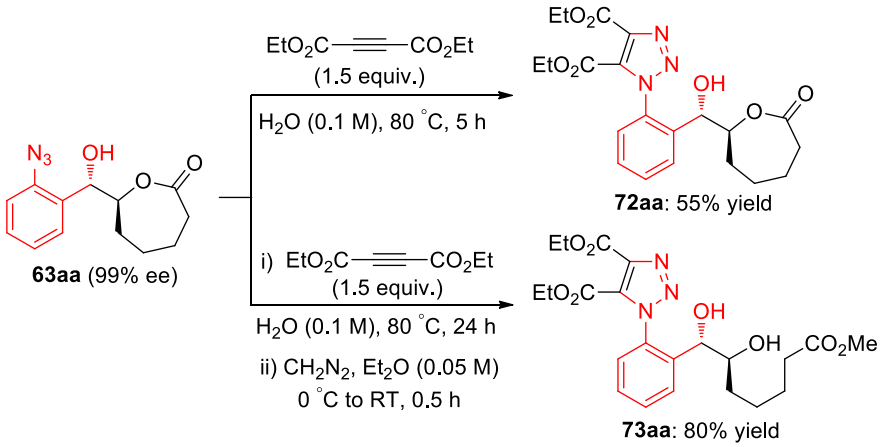



***Figure-52:*** $^{1}$H and $^{13}$C NMR spectra of the product **71aa**.

***Scheme 12:*** Application of Click Reaction on LLB-A Compound **63aa**.




### *5.3.6 Reaction mechanism:*

Herein, we attempted to explain the mechanistic aspects of the synergistic L-DMTC/TFA catalyzed LLB-A reaction based on the few controlled and NMR experiments (Scheme 13). We gathered substantial evidence from the NMR studies of catalyst combination **7t** and **54c** in DMSO-$d_6$ that the catalyst L-DMTC (**7t**) coordinates with two molecules of TFA (**54c**) and exists in the ionic cluster form **74a** which is in equilibrium with **74b** (Scheme 13). As entire signals in $^{1}H$ and $^{13}C$ NMR spectrums of **7t** with **54c** are shifted compared to only **7t,** which is due to the strong interaction of both the functional groups of NH and $CO_2H$ with TFA (For spectral details see Annexure-II, Figure-A1-A3). We have also done **7t**-catalyzed LLB-A reactions of **55a** and **1a** in DMSO-$d_6$ with and without TFA (**54c**) in NMR tube to know the reaction relative rates (Figure-54, $^{1}H$ spectral details are given in Annexure-II, Figure-A4 and Figure-A5). From the optimization studies, we came to know that DMSO facilitates the LLB-A reaction, most probably due to the stabilization of synergistic catalyst cluster by interaction of the solvent molecules. From the above experiments, we are proposing that the cyclohexanone **1a** reacts sharply with the catalyst cluster **74a** to form the enamine **75a**, which exists in equilibrium with **75b**. The *o*-azidobenzaldehyde (**55a**) approaches the enamine **75a** from its *Re*-face in such a way that it can anchor by interaction *via* electrostatic interactions and hydrogen bonding of the azido group and the aldehyde group with the sulphur and carboxylic acid of L-DMTC (**7t**)

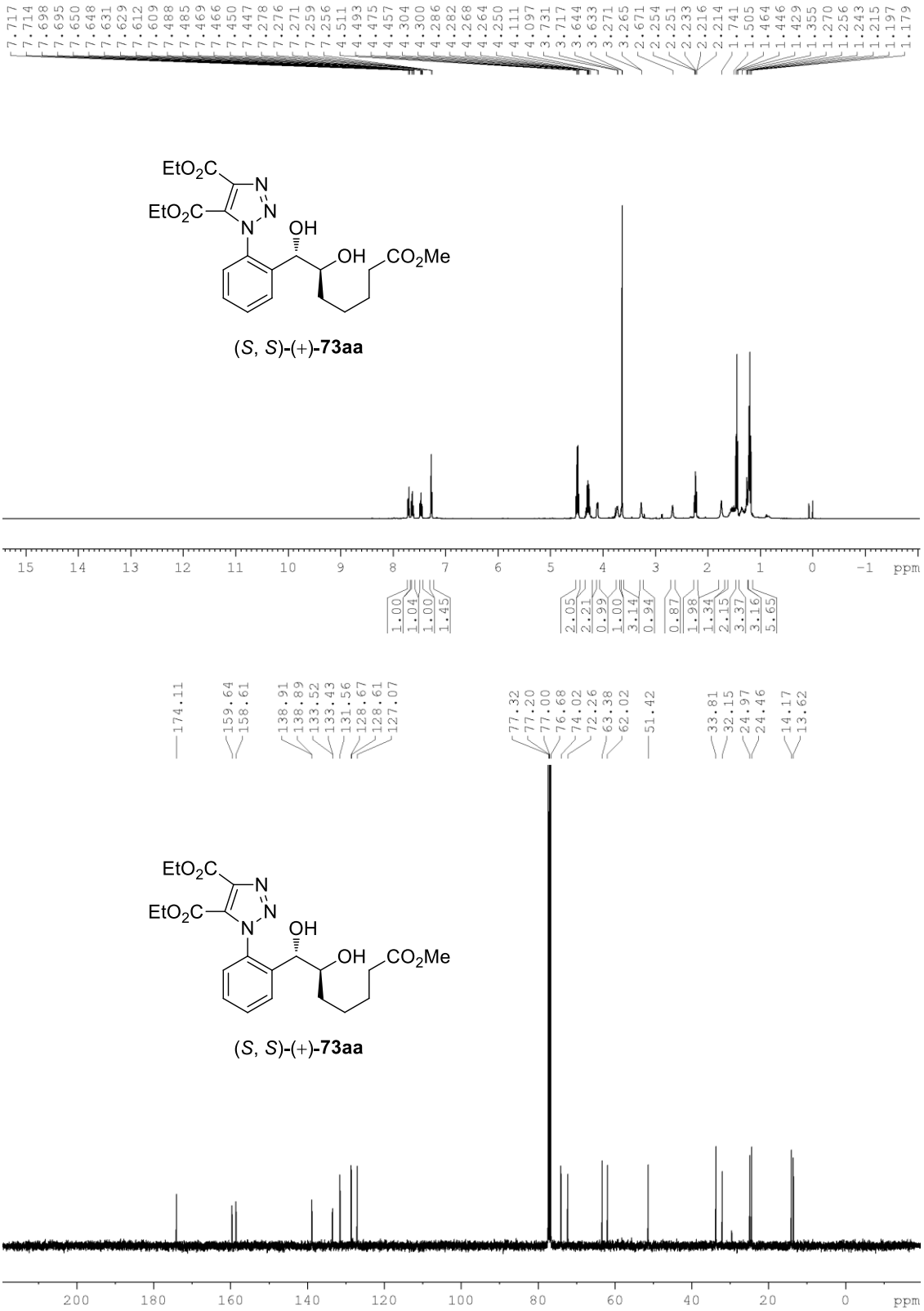
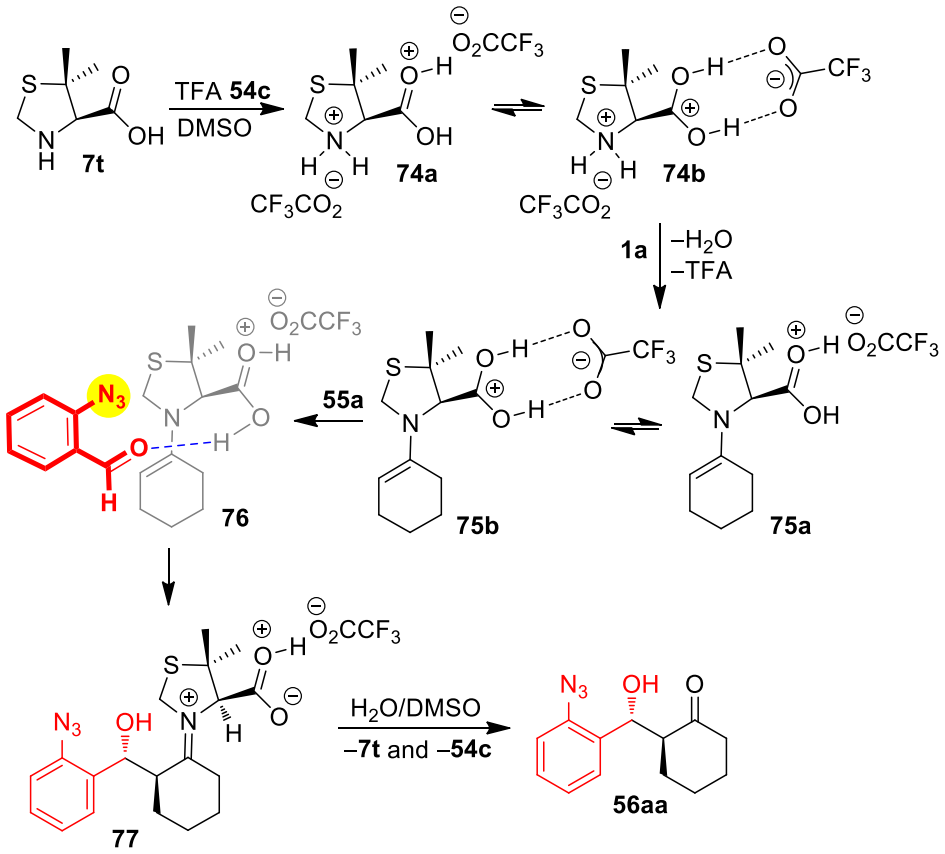



***Figure-53:*** $^{1}H$ and $^{13}C$ NMR spectra of the product **73aa**.

respectively, so that the *Re*-face of the *o*-azidobenzaldehyde (**55a**) is facing the *Re*-face of the enamine **75a** for the aldol reaction.[37] Accordingly, this results in the formation of the iminium intermediate **77**, which, on hydrolysis, furnishes the product *anti*-(−)-**56aa**, regenerating the synergistic catalyst L-DMTC (**7t**) and TFA (**54c**). This LLB-A reaction rate and selectivity is completely controlled by catalysts **7t** (p$K_a$ = ~9.76) and **54c** (p$K_a$ = 3.45) structure and their dense interactions based on the p$K_a$ values synergestic in DMSO, which is thoroughly utilized by *o*-azido group interactions.[56]

***Scheme 13:*** Proposed Reaction Mechanism.



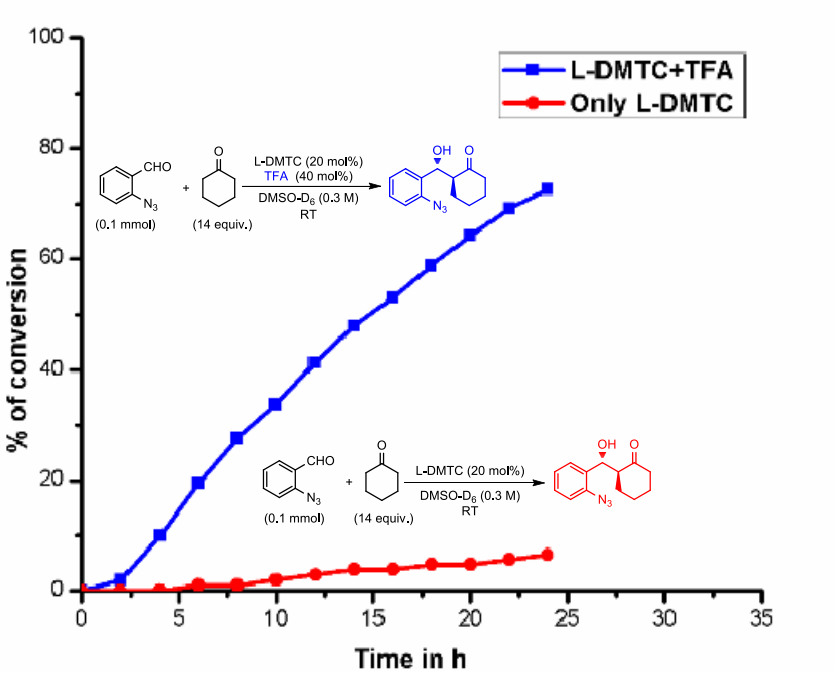



***Figure-54:*** NMR experiments to find the relative rate of LLB-A reaction under the **7t**- and **7t**/**54c** catalysis.

## *5.4 Conclusions:*

In summary, we have described for the first time the L-DMTC/TFA-catalyzed asymmetric LLB-A reaction of cyclohexanones and acetone with less reactive *o*-azidobenzaldehydes at ambient conditions. The LLB-A reaction proceeds in very good yields with high selectivity using a synergistic combination of L-amino acid, L-DMTC with simple Brønsted acid TFA. Furthermore, we have demonstrated the application of chiral LLB-A products *anti*-(–)-**56** in the synthesis of highly functionalized azido-containing molecular scaffolds **60**-**73**. We explained the mechanistic synergy of L-DMTC with TFA to increase the rate and selectivity of LLB-A reaction of **55** and **1** in DMSO-$d_6$ with the controlled and on-line NMR experiments. Further work is in progress to utilize chiral LLB-A products, *anti*-(–)-**56** as intermediates for the bioactive molecules synthesis.

## *ANNEXURE-II: NMR Experiment to Study the L-DMTC 7t and TFA 54c Interactions in DMSO-$d_6$; Details of NMR Experiment to Study relative rate of LLB-A reaction catalyzed by 7t/54c in DMSO-$d_6$ at 25 °C.*

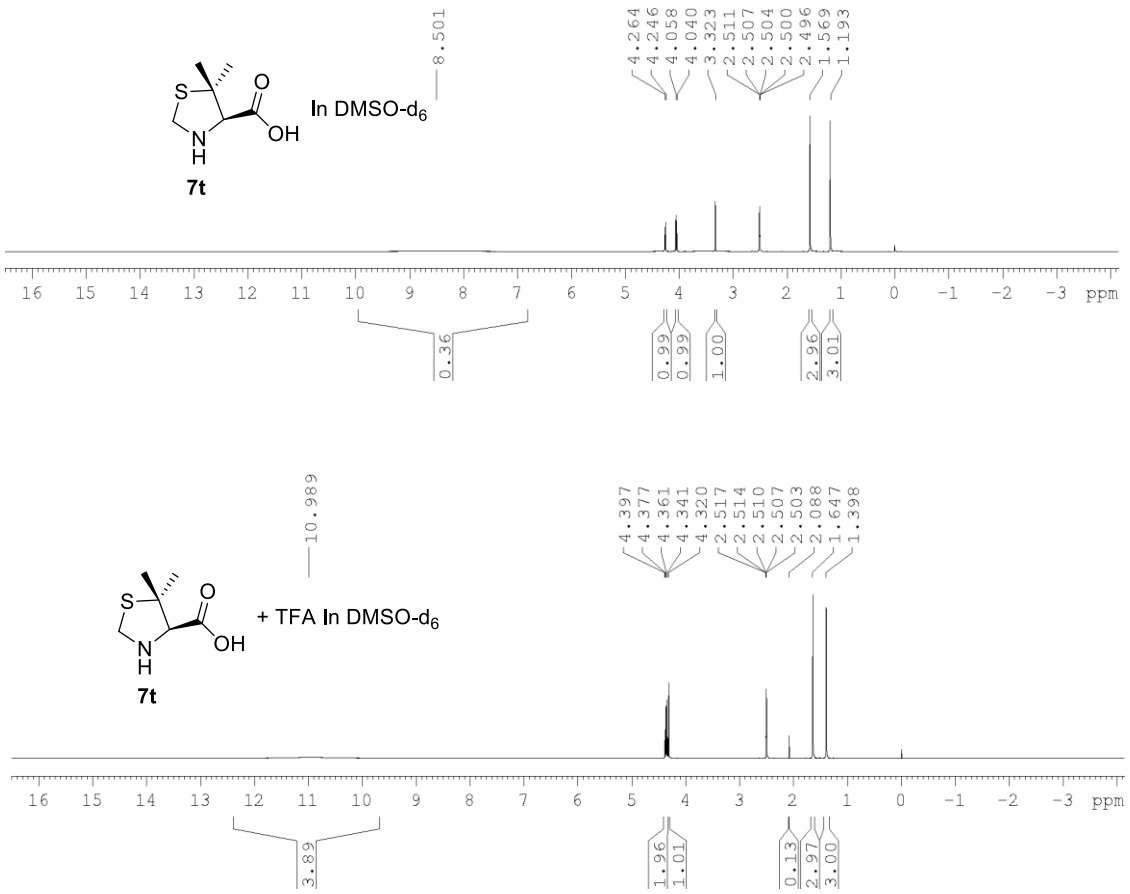



***Figure-A1:*** $^1$H NMR spectra of **7t** and **7t**+**54c** in DMSO-$d_6$.

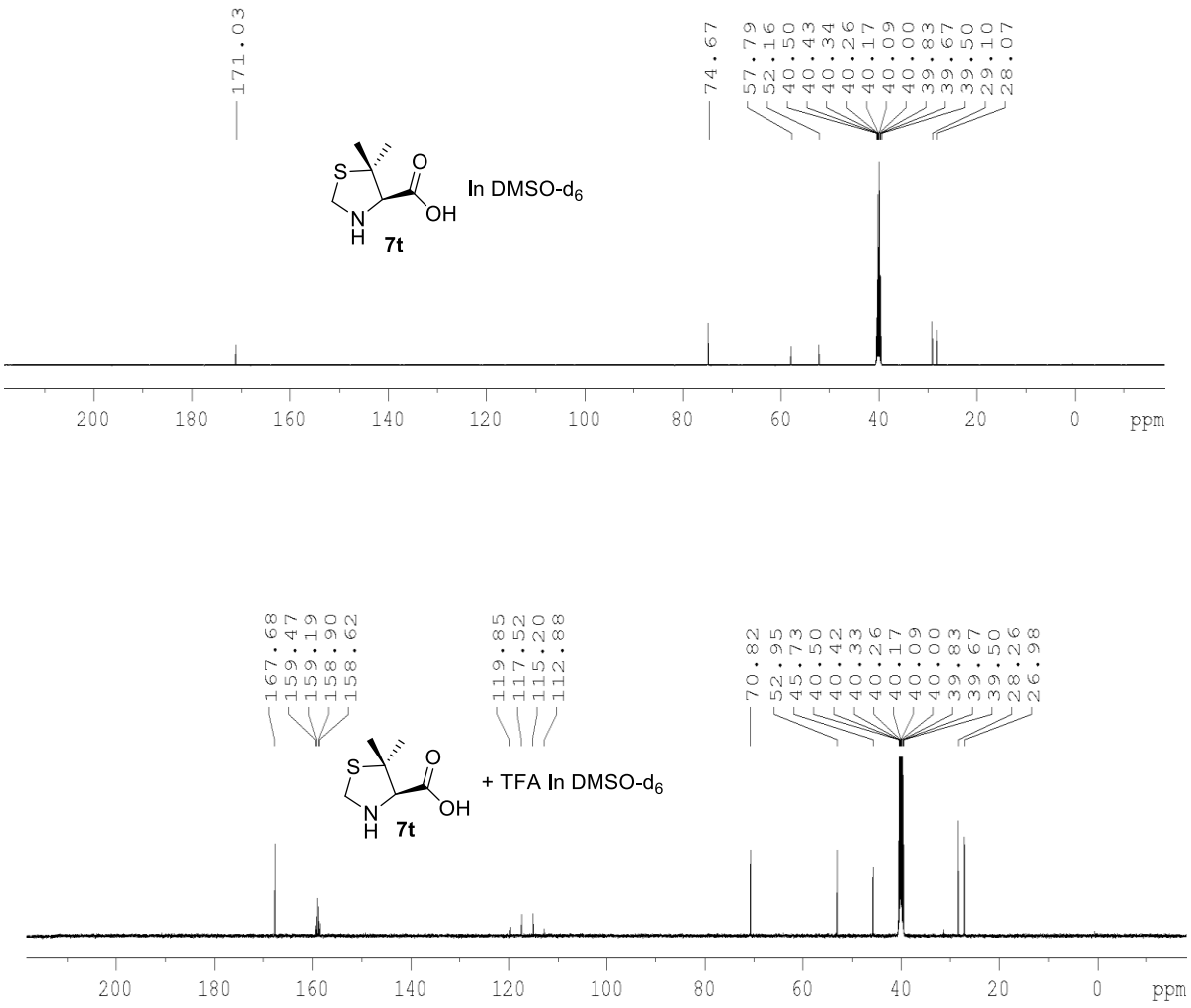



***Figure-A2:*** $^{13}$C NMR spectra of **7t** and **7t**+**54c** in DMSO-$d_6$.

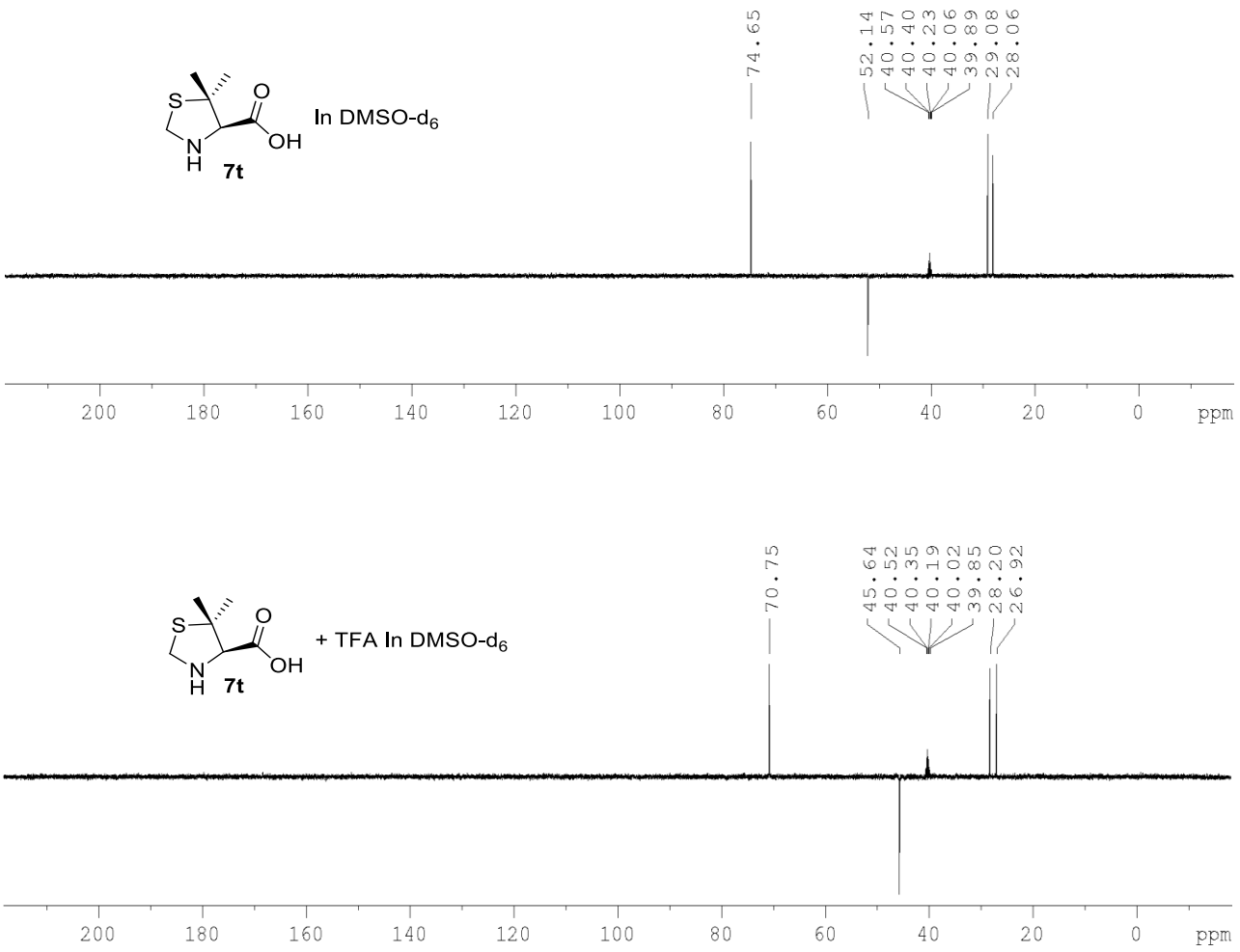
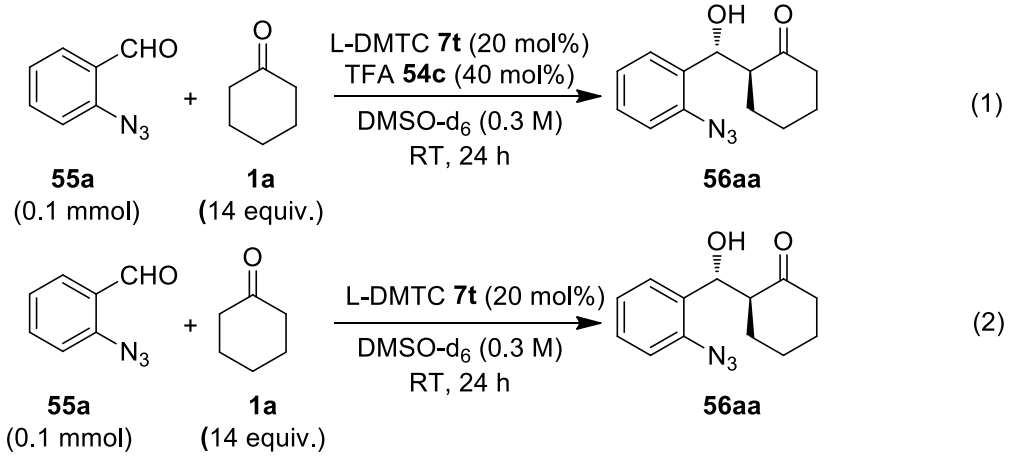



***Figure-A3:*** DEPT NMR spectra of **7t** and **7t**+**54c** in DMSO-$d_6$.

***Procedure for the NMR experiment to study effect of TFA 54c on L-DMTC 7t catalyzed LLB-A reaction:***

The $^{1}$H NMR spectra of both the ongoing reactions of **55a**[57] (0.1 mmol) and **1a** (1.4 mmol, 14 equiv.) in the presence of L-DMTC **7t** (20 mol%), and TFA **54c** (40 mol%) (Eq. A1); and in presence of only L-DMTC **7t** (20 mol%) (Eq. A2) in DMSO-$d_6$ at 25 °C were reported in Figure-A4 and Figure-A5, respectively. Spectra were recorded for every 2 h intervals for both the reactions, and shown that in the presence of TFA reactivity of the reaction is very high as compared to in the absence of TFA.



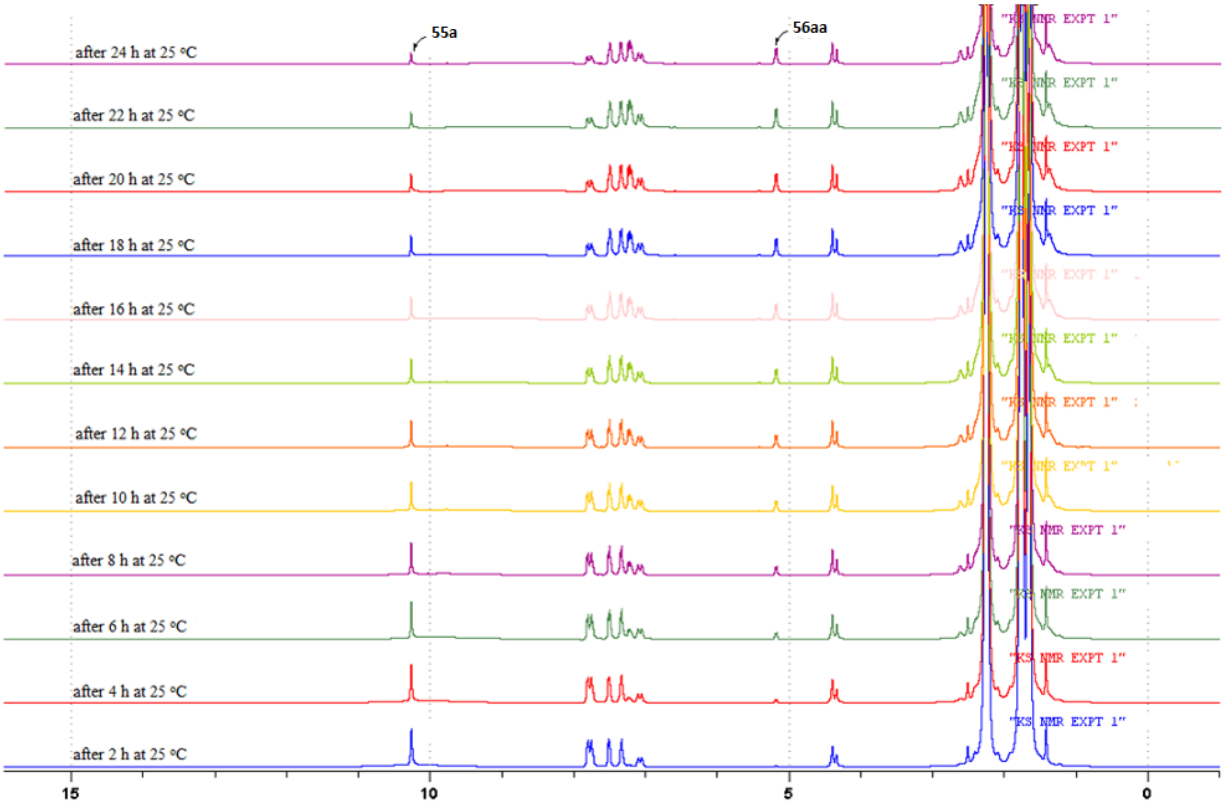



***Figure-A4*:** $^{1}$H NMR spectra (recorded at intervals of 2 h up to 24 h) of the reaction of **55a** and **1a** catalyzed by **7t**/5**4c** in DMSO-$d_6$ at 25 °C.

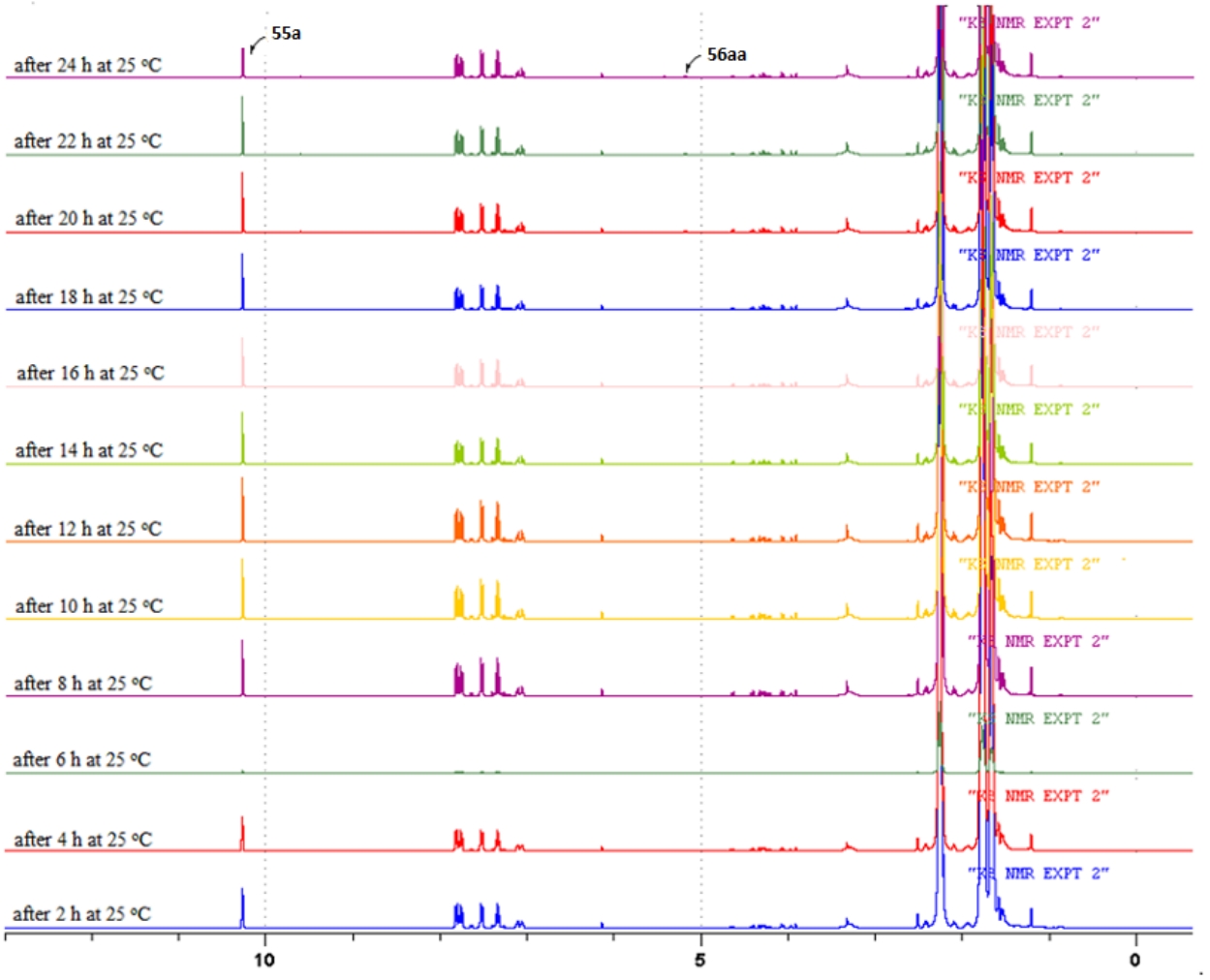



***Figure-A5:*** $^{1}$H NMR spectra (recorded at intervals of 2 h up to 24 h) of the reaction of **55a** and **1a** catalyzed by **7t** in DMSO-$d_6$ at 25 °C.

# 6. *Experimental Section*

***General Methods*:**

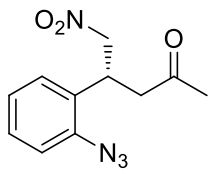
The $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded at 400 MHz and 500 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for $^{1}H$ NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for $^{13}C$ NMR. *In the $^{13}C$ NMR spectra, the nature of the carbons (C, CH, $CH_2$ or $CH_3$) was determined by recording the DEPT-135 experiment, and is given in parentheses.* The coupling constants *J* are given in Hz. Column chromatography was performed using Acme's silica gel (particle size 0.063-0.200 mm). High-resolution mass spectra (HRMS) were recorded on ESI-TOF maXis. GCMS mass spectrometry was performed on Shimadzu GCMS-QP2010 mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010 A mass spectrometer. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Cu-Kα (λ = 1.540 Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Cu-Kα fine-focus sealed tube (λ = 1.540 Å). For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. $H_2SO_4$ (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

## 1. General experimental procedures for Asymmetric synthesis of tetrahydroquinolines through supramolecular organocatalysis

**1a. General procedure for asymmetric Michael reaction of acetone 1b with 1-azido-2-(2-nitrovinyl)benzene 40 or (*E*)-β-nitrostyrene 47 through supramolecular-organocatalysis:** In an ordinary glass vial equipped with a magnetic stirring bar was taken a mixture of quinidine-N*H*-thiourea **8a** (8.9 mg, 0.015 mmol) and L-phenylalanine **7k** (2.5 mg, 0.015 mmol) in DCM (1.0 mL, 0.3 M) and was added 1-azido-2-(2-nitrovinyl)benzene **40** or (*E*)-β-nitrostyrene **47** (0.3 mmol). After stirring for a minute, acetone **1b** (4.2 mmol) was added and the reaction mixture was stirred at 25 °C for 3 days. To the crude reaction mixture, aqueous $NH_4Cl$ solution was

added and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure products **41** or **48** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

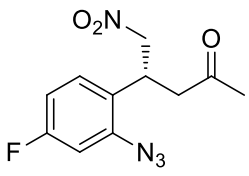
**(*R*)-4-(2-azidophenyl)-5-nitropentan-2-one** (**41ab**): Prepared following the procedure **1a** and



**41ab**

purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u amylose-2 column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 34.10 min (major), $t_R$ = 43.43 min (minor); **$[\alpha]_D^{25}$ = –12.4 (*c* = 0.98 g/100 mL, $CHCl_3$, 92% *ee*);** IR (Neat): $\nu_{max}$ 2952, 2124 ($N_3$), 1713 (C=O), 1550 ($NO_2$), 1490, 1376, 1285, 1163 and 752 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.33 (1H, dt, *J* = 8.0, 1.6 Hz), 7.20-7.16 (2H, m), 7.10 (1H, dt, *J* = 7.6, 0.8 Hz), 4.74 (1H, dd, *J* = 12.4, 7.2 Hz), 4.71 (1H, dd, *J* = 12.4, 6.8 Hz), 4.22 (1H, quintet, *J* = 6.8 Hz), 3.03 (1H, dd, *J* = 18.4, 8.0 Hz), 2.95 (1H, dd, *J* = 18.0, 6.4 Hz), 2.15 (3H, s, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 205.5 (C, *C*=O), 137.8 (C), 129.4 (CH), 129.1 (CH), 125.2 (C, CH), 118.7 (CH), 77.7 ($CH_2$), 44.5 ($CH_2$), 34.9 (CH), 30.2 ($CH_3$); HRMS m/z 271.0807 (M + Na), calcd for $C_{11}H_{12}N_4O_3Na$ 271.0802.

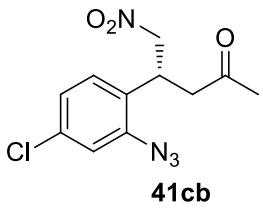
**(*R*)-4-(2-azido-4-fluorophenyl)-5-nitropentan-2-one** (**41bb**): Prepared following the procedure



**41bb**

**1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u amylose-2 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 15.04 min (major), $t_R$ = 18.84 min (minor); **$[\alpha]_D^{25}$ = –11.2 (*c* = 0.35 g/100 mL, $CHCl_3$, 91% *ee*);** IR (Neat): $\nu_{max}$ 2933, 2115 ($N_3$), 1714 (C=O), 1594, 1546 ($NO_2$), 1500, 1359, 1294, 1211, 1163, 957 and 844 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.09 (1H, dd, *J* = 8.8, 6.0 Hz), 6.81 (1H, dd, *J* = 8.8, 2.4 Hz), 6.73 (1H, dt, *J* = 8.4, 2.4 Hz), 4.64 (1H, dd, *J* = 12.4, 7.2 Hz), 4.61 (1H, dd, *J* = 12.4, 6.4 Hz), 4.09 (1H, quintet, *J* = 6.8 Hz), 2.94 (1H, dd, *J* = 18.0, 7.2 Hz), 2.85 (1H, dd, *J* = 18.0, 6.4 Hz), 2.07 (3H, s, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 205.3 (C, *C*=O), 162.5 (C, d, *J* = 248.0 Hz, *C*-F), 139.4 (C, d, *J* = 8.0 Hz), 130.9 (CH, d, *J* = 10.0 Hz), 125.3 (C, d, *J* = 4.0 Hz), 112.1 (CH, d, *J* = 21.0 Hz), 106.1 (CH, d, *J* = 25.0 Hz), 77.6 ($CH_2$), 44.4 ($CH_2$), 34.4 (CH), 30.1 ($CH_3$); HRMS m/z 289.0707 (M + Na), calcd for $C_{11}H_{11}FN_4O_3Na$ 289.0707.

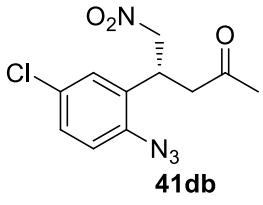
**(*R*)-4-(2-azido-4-chlorophenyl)-5-nitropentan-2-one** (**41cb**): Prepared following the procedure



**41cb**

**1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u amylose-2 column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 37.33 min (major), $t_R$ = 44.84 min (minor); **$[\alpha]_D^{25}$ = –29.6 (*c* = 0.15 g/100 mL, $CHCl_3$, 92% *ee*);** IR (Neat): $\nu_{max}$ 2923, 2113 ($N_3$), 1715 (C=O), 1575, 1548 ($NO_2$), 1499, 1375, 1312, 1259, 1162 and 837 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.18 (1H, d, *J* = 8.5 Hz), 6.79 (1H, dd, *J* = 8.5, 2.5 Hz), 6.76 (1H, d, *J* = 2.0 Hz), 4.72 (1H, dd, *J* = 12.0, 7.0 Hz), 4.68 (1H, dd, *J* = 12.5, 6.5 Hz), 4.17 (1H, quintet, *J* = 7.0 Hz), 3.02 (1H, dd, *J* = 18.0, 7.5 Hz), 2.93 (1H, dd, *J* = 18.0, 6.5 Hz), 2.15 (3H, s, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 205.2 (C, *C*=O), 141.1 (C), 139.4 (C), 130.8 (CH), 126.1 (C), 115.6 (CH), 109.3 (CH), 77.6 ($CH_2$), 44.5 ($CH_2$), 34.7 (CH), 30.2 ($CH_3$); HRMS m/z 305.0417 (M + Na), calcd for $C_{11}H_{11}ClN_4O_3Na$ 305.0412.

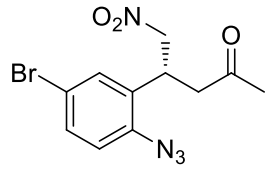
**(*R*)-4-(2-azido-5-chlorophenyl)-5-nitropentan-2-one** (**41db**): Prepared following the



**41db**

procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u amylose-2 column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 28.57 min (major), $t_R$ = 42.43 min (minor); **$[\alpha]_D^{25}$ = –15.1 (*c* = 0.28 g/100 mL, $CHCl_3$, 91% *ee*);** IR (Neat): $\nu_{max}$ 2922, 2117 ($N_3$), 1715 (C=O), 1548 ($NO_2$), 1486, 1375, 1291, 1153, 1117 and 812 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.21 (1H, dd, *J* = 8.4, 2.4 Hz), 7.10 (1H, d, *J* = 2.4 Hz), 7.02 (1H, d, *J* = 8.4 Hz), 4.63 (2H, m), 4.10 (1H, quintet, *J* = 6.8 Hz), 2.95 (1H, dd, *J* = 18.4, 7.6 Hz), 2.85 (1H, dd, *J* = 18.0, 6.4 Hz), 2.09 (3H, s, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 205.0 (C, *C*=O), 136.4 (C), 131.2 (C), 130.4 (C), 129.4 (CH), 129.0 (CH), 119.8 (CH), 77.2 ($CH_2$), 44.2 ($CH_2$), 34.6 (CH), 30.1 ($CH_3$); HRMS m/z 305.0416 (M + Na), calcd for $C_{11}H_{11}ClN_4O_3Na$ 305.0412.

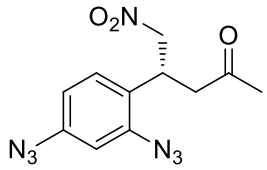
**(*R*)-4-(2-azido-5-bromophenyl)-5-nitropentan 2-one** (**41eb**): Prepared following the procedure



**41eb**

**1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u amylose-2 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 20.43 min (major), $t_R$ = 29.10 min (minor); **$[\alpha]_D^{25}$ = –2.0 (*c* = 0.25 g/100 mL, $CHCl_3$, 91% *ee*);** IR (Neat): $\nu_{max}$ 2918, 2115 ($N_3$), 1714 (C=O), 1547 ($NO_2$), 1482, 1357, 1291, 1163, 1111 and 810 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.36 (1H, dd, *J* = 8.8, 2.4 Hz), 7.24 (1H, d, *J* = 2.4 Hz), 6.97 (1H, d, *J* = 8.4 Hz), 4.63 (2H, d, *J* = 6.8 Hz), 4.09 (1H, quintet, *J* = 6.8 Hz), 2.95 (1H, dd, *J* = 18.4, 7.6 Hz), 2.86 (1H, dd, *J* = 18.4, 6.4 Hz), 2.09 (3H, s, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 205.0 (C, *C*=O), 137.1 (C), 132.3 (CH), 132.0 (CH), 131.5 (C), 120.2 (CH), 118.0 (C), 77.2 ($CH_2$), 44.2 ($CH_2$), 34.6 (CH), 30.2 ($CH_3$); HRMS m/z 348.9913 (M + Na), calcd for $C_{11}H_{11}BrN_4O_3Na$ 348.9907.

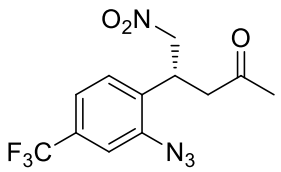
**(*R*)-4-(2,4-diazidophenyl)-5-nitropentan-2-one** (**41fb**): Prepared following the procedure **1a**



**41fb**

and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u amylose-2 column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 57.57 min (major), $t_R$ = 68.51 min (minor); **$[\alpha]_D^{25}$ = –24.0 (*c* = 0.07 g/100 mL, $CHCl_3$, 90% *ee*);** IR (Neat): $\nu_{max}$ 2919, 2111 (2 x $N_3$), 1714 (C=O), 1547 ($NO_2$), 1499, 1375, 1312, 1286, 1259, 1162 and 837 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.17 (1H, d, *J* = 8.4 Hz), 6.79 (1H, dd, *J* = 8.0, 2.0 Hz), 6.76 (1H, d, *J* = 1.6 Hz), 4.72 (1H, dd, *J* = 12.4, 7.6 Hz), 4.68 (1H, dd, *J* = 12.4, 6.4 Hz), 4.16 (1H, quintet, *J* = 6.8 Hz), 3.02 (1H, dd, *J* = 18.4, 7.6 Hz), 2.93 (1H, dd, *J* = 18.0, 6.4 Hz), 2.15 (3H, s, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 205.3 (C, *C*=O), 141.1 (C), 139.4 (C), 130.8 (CH), 125.9 (C), 115.5 (CH), 109.3 (CH), 77.6 ($CH_2$), 44.4 ($CH_2$), 34.6 (CH), 30.2 ($CH_3$); HRMS m/z 312.0818 (M + Na), calcd for $C_{11}H_{11}N_7O_3Na$ 312.0816.

**(*R*)-4-(2-azido-4-(trifluoromethyl)phenyl)-5-nitropentan-2-one** (**41gb**): Prepared following

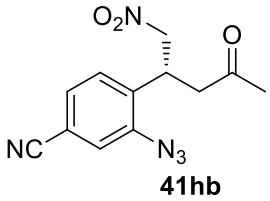


**41gb**

the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u amylose-

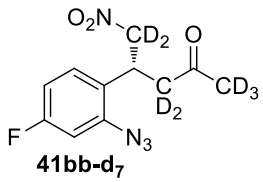
2 column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 20.33 min (major), $t_R$ = 23.78 min (minor); **$[\alpha]_D^{25}$ = –17.3 (*c* = 0.69 g/100 mL, $CHCl_3$, 92% *ee*);** IR (Neat): $\nu_{max}$ 2923, 2853, 2116 ($N_3$), 1718 (C=O), 1551 ($NO_2$), 1421, 1376, 1329, 1276, 1153, 1123, 1086 and 896 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.38-7.37 (1H, m), 7.35-7.32 (2H, m), 4.77 (1H, dd, *J* = 12.8, 7.2 Hz), 4.73 (1H, dd, *J* = 12.8, 6.4 Hz), 4.26 (1H, quintet, *J* = 6.4 Hz), 3.06 (1H, dd, *J* = 18.4, 7.6 Hz), 2.97 (1H, dd, *J* = 18.4, 6.4 Hz), 2.17 (3H, s, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 204.9 (C, *C*=O), 138.9 (C), 133.3 (C), 131.5 (C, q, *J* = 33.0 Hz), 130.2 (CH), 123.2 (C, q, *J* = 271.0 Hz, *C*$F_3$), 121.8 (CH, q, *J* = 4.0 Hz), 115.5 (CH, q, *J* = 3.0 Hz), 77.1 ($CH_2$), 44.2 ($CH_2$), 34.8 (CH), 30.1 ($CH_3$); HRMS m/z 339.0680 (M + Na), calcd for $C_{12}H_{11}F_3N_4O_3Na$ 339.0675.

**(*R*)-3-azido-4-(1-nitro-4-oxopentan-2-yl)benzonitrile** (**41hb**): Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u amylose-2 column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 36.63 min (major), $t_R$ = 51.43 min (minor); **$[\alpha]_D^{25}$ = –19.7 (*c* = 0.25 g/100 mL, $CHCl_3$, 89% *ee*);** IR (Neat): $\nu_{max}$ 2924, 2232, 2114 ($N_3$), 1715 (C=O), 1548 ($NO_2$), 1501, 1408, 1374, 1294, 1220, 1164, 867 and 771 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.35 (1H, s), 7.33 (1H, d, *J* = 8.0 Hz), 7.26 (1H, d, *J* = 8.0 Hz), 4.70 (1H, dd, *J* = 12.8, 7.6 Hz), 4.65 (1H, dd, *J* = 12.8, 6.4 Hz), 4.17 (1H, quintet, *J* = 6.4 Hz), 2.98 (1H, dd, *J* = 18.4, 7.2 Hz), 2.90 (1H, dd, *J* = 18.4, 6.4 Hz), 2.10 (3H, s, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 204.8 (C, *C*=O), 139.3 (C), 134.8 (C), 130.6 (CH), 128.5 (CH), 121.7 (CH), 117.4 (C), 113.1 (C, *C*≡N), 76.9 ($CH_2$), 43.9 ($CH_2$), 34.9 (CH), 30.2 ($CH_3$); HRMS m/z 296.0760 (M + Na), calcd for $C_{12}H_{11}N_5O_3Na$ 296.0754.



**41hb**

**(*R*)-4-(2-azido-4-fluorophenyl)-5-nitropentan-2-one (41bb-$d_7$):** Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u amylose-2 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 31.29 min (major), $t_R$ = 41.41 min (minor); **$[\alpha]_D^{25}$ = –10.2 (*c* = 0.31 g/100 mL, $CHCl_3$, 89% *ee*);** IR (Neat): $\nu_{max}$ 2920, 2117 ($N_3$), 1710 (C=O), 1594, 1536 ($NO_2$), 1501, 1296, 1211 and 958

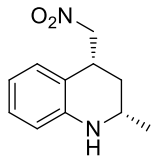


**41bb-$d_7$**

$cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.16 (1H, dd, *J* = 9.0, 6.0 Hz), 6.89 (1H, dd, *J* = 9.0, 2.5 Hz), 6.81 (1H, dt, *J* = 8.0, 2.5 Hz), 4.70 (2H, 70% D-atom, m), 4.15(1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 205.6 (C, *C*=O), 162.6 (C, d, *J* = 247.5 Hz, *C*-F), 139.5 (C, d, *J* = 8.7 Hz), 130.9 (CH, d, *J* = 8.7 Hz), 125.2 (C), 112.2 (CH, d, *J* = 21.2 Hz), 106.1 (CH, d, *J* = 25.0 Hz), 34.2 (CH); HRMS m/z 296.1144 (M + Na), calcd for $C_{11}H_4D_7FN_4O_3Na$ 296.1147.

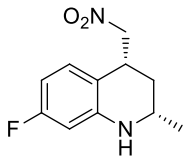
**1b. General procedure for the reductive cyclization of Michael products 41:** In an oven dried round bottom flask, containing $InCl_3$ (0.22 mmol) and triethylsilane (0.07 mL, 0.44 mmol) in MeOH (2 mL, 0.05 M) at 0 °C was added the Michael product **41** (0.2 mmol) dissolved in MeOH. The mixture was stirred at the same temperature for 2 h and then brought to room temperature and stirred for another 10 h. To the crude reaction mixture was added water and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure tetrahydroquinolines **42** were purified by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**(2*S*,4*R*)-2-methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline** (*syn*-**42ab**): Prepared following the procedure **1b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 50 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 16.81 min (minor), $t_R$ = 21.37 min (major) [for minor *anti*-isomer], $t_R$ = 23.79 min (minor), $t_R$ = 34.64 min (major) [for major *syn*-isomer]; **$[\alpha]_D^{25}$ = −21.1** (***c* = 0.28 g/100 mL, $CHCl_3$, 90% *ee*** for major *syn*-isomer; **89% *ee*** for minor *anti*-isomer and *dr* = 6:1); IR (neat): $\nu_{max}$ 3396 (NH), 2925, 2853, 1709, 1608, 1546 ($NO_2$), 1490, 1376, 1314, 1259, 1159 and 746 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, major *syn*-isomer) δ 7.04 (1H, t, *J* = 7.5 Hz), 6.96 (1H, d, *J* = 7.5 Hz), 6.67 (1H, dt, *J* = 7.5, 0.8 Hz), 6.54 (1H, dd, *J* = 8.0, 0.8 Hz), 4.93 (1H, dd, *J* = 12.0, 5.0 Hz), 4.38 (1H, dd, *J* = 12.0, 10.5 Hz), 3.81-3.75 (2H, m), 3.46-3.40 (1H, m), 2.05 (1H, ddd, *J* = 12.5, 6.0, 2.5 Hz), 1.52 (1H, q, *J* = 11.5 Hz), 1.23 (3H, d, *J* = 6.5 Hz, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135, major *syn*-isomer) δ 145.4 (C), 128.1 (CH), 126.3 (CH), 118.6 (C), 117.8 (CH), 115.1 (CH), 80.5 ($CH_2$), 46.5 (CH), 35.5 ($CH_2$), 34.9 (CH), 22.3 ($CH_3$); HRMS m/z 207.1133 (M + H), calcd for $C_{11}H_{15}N_2O_2$ 207.1128.



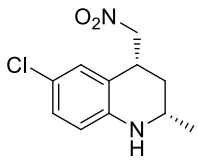
*syn*-**42ab**

**(2*S*,4*R*)-7-fluoro-2-methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline** (*syn*-**42bb**): Prepared following the procedure **1b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 83 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 20.32 min (minor), $t_R$ = 25.69 min (major) [for minor *anti*-isomer], $t_R$ = 29.27 min (minor), $t_R$ = 43.49 min (major) [for major *syn*-isomer]; **$[\alpha]_D^{25}$ = −11.4 [*c* = 0.07 g/100 mL, $CHCl_3$, 94% *ee*** (major *syn*-isomer), **97% *ee*** (minor *anti*-isomer) and *dr* = 5:1]; IR (neat): $\nu_{max}$ 3391 (NH), 2921, 2853, 1616, 1542 ($NO_2$), 1490, 1378, 1334, 1196, 1179, 1150 and 837 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, major *syn*-isomer) δ 6.90-6.86 (1H, m), 6.35 (1H, dt, *J* = 8.4, 2.4 Hz), 6.22 (1H, dd, *J* = 10.4, 2.8 Hz), 4.89 (1H, dd, *J* = 12.0, 4.8 Hz), 4.38 (1H, dd, *J* = 12.0, 9.6 Hz), 3.87 (1H, br s, *N*H), 3.73-3.68 (1H, m), 3.49-3.41 (1H, m), 2.04 (1H, ddd, *J* = 12.8, 6.0, 2.8 Hz), 1.50 (1H, q, *J* = 11.2 Hz), 1.23 (3H, d, *J* = 6.0 Hz, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135, major *syn*-isomer) δ 162.6 (C, d, *J* = 242.0 Hz, *C*-F), 146.8 (C, d, *J* = 11.0 Hz), 127.5 (CH, d, *J* = 10.0 Hz), 114.3 (C), 104.3 (CH, d, *J* = 22.0 Hz), 101.1 (CH, d, *J* = 24.0 Hz), 80.3 ($CH_2$), 46.5 (CH), 35.2 ($CH_2$), 34.4 (CH), 22.2 ($CH_3$); HRMS m/z 225.1036 (M + H), calcd for $C_{11}H_{14}FN_2O_2$ 225.1034.



*syn*-**42bb**

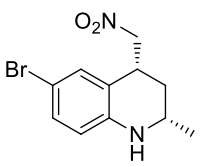
**(2*S*,4*R*)-6-chloro-2-methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline** (*syn*-**42db**): Prepared following the procedure **1b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 64 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 19.56 min (minor), $t_R$ = 23.63 min (major) [for minor *anti*-isomer], $t_R$ = 25.45 min (minor), $t_R$ = 36.45 min (major) [for major *syn*-isomer]; **$[\alpha]_D^{25}$ = −34.1** [***c* = 0.20 g/100 mL, $CHCl_3$, 93% *ee*** (major *syn*-isomer), **90% *ee*** (minor *anti*-isomer) and *dr* = 5:1]; IR (neat): $\nu_{max}$ 3405 (NH), 2965, 2925, 1718, 1546 ($NO_2$), 1491, 1376, 1298, 1252, 1192, 1104 and 811 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, major *syn*-isomer) δ 7.01-6.97 (1H, m), 6.94-6.93 (1H, m), 6.47 (1H, d, *J* = 8.4 Hz), 4.89 (1H, dd, *J* = 12.4, 4.8 Hz), 4.38 (1H, dd, *J* = 12.0, 10.0 Hz), 3.78-3.70 (1H, m), 3.46-3.39 (1H, m), 2.05 (1H, ddd, *J* = 12.8, 5.6, 2.4 Hz), 1.50 (1H, q, *J* = 11.2 Hz), 1.23 (3H, d, *J* = 6.4 Hz, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135, major *syn*-isomer) δ 144.0 (C), 128.0 (CH), 126.2 (CH), 122.1



*syn*-**42db**

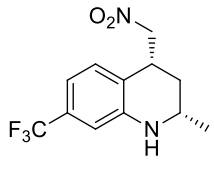
(C), 120.0 (C), 116.1 (CH), 80.1 ($CH_2$), 46.5 (CH), 35.0 ($CH_2$), 34.8 (CH), 22.2 ($CH_3$); HRMS m/z 241.0737 (M + H), calcd for $C_{11}H_{14}ClN_2O_2$ 241.0738.

**(2*S*,4*R*)-6-bromo-2-methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline** (*syn*-**42eb**): Prepared following the procedure **1b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 54 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 22.07 min (minor), $t_R$ = 26.18 min (major) [for minor *anti*-isomer], $t_R$ = 28.77 min (minor), $t_R$ = 42.55 min (major) [for major *syn*-isomer]; **$[\alpha]_D^{25}$ = −22.8** [***c* = 0.18 g/100 mL, $CHCl_3$, 90% *ee*** (major *syn*- isomer), **89% *ee*** (minor *anti*-isomer) and *dr* = 5:1]; IR (neat): $\nu_{max}$ 3400 (NH), 2923, 1598, 1547 ($NO_2$), 1488, 1376, 1299, 1190, 877 and 809 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, major *syn*-isomer) δ 7.11 (1H, dd, *J* = 8.5, 1.5 Hz), 7.06 (1H, br s), 6.42 (1H, d, *J* = 9.0 Hz), 4.89 (1H, dd, *J* = 12.0, 4.5 Hz), 4.38 (1H, dd, *J* = 12.0, 10.0 Hz), 3.79 (1H, br s, *N*H), 3.77-3.71 (1H, m), 3.43-3.39 (1H, m), 2.04 (1H, ddd, *J* = 13.0, 6.0, 2.5 Hz), 1.49 (1H, q, *J* = 11.5 Hz), 1.23 (3H, d, *J* = 6.5 Hz, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135, major *syn*-isomer) δ 144.4 (C), 130.9 (CH), 129.0 (CH), 120.6 (C), 116.5 (CH), 109.1 (C), 80.1 ($CH_2$), 46.5 (CH), 35.0 ($CH_2$), 34.8 (CH), 22.2 ($CH_3$); HRMS m/z 285.0235 (M + H), calcd for $C_{11}H_{14}BrN_2O_2$ 285.0233.



*syn*-**42eb**

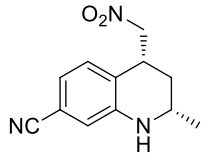
**(2*S*,4*R*)-2-methyl-4-(nitromethyl)-7-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline** (*syn*-**42gb**): Prepared following the procedure **1b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 91 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 4.47 min (minor), $t_R$ = 5.08 min (major) [for minor *anti*-isomer], $t_R$ = 5.61 min (minor), $t_R$ = 6.30 min (major) [for major *syn*-isomer]; **$[\alpha]_D^{25}$ = −15.7** [***c* = 0.12 g/100 mL, $CHCl_3$, 91% *ee*** (major *syn*-isomer), **90% *ee*** (minor *anti*-isomer) and *dr* = 5:1]; IR (neat): $\nu_{max}$ 3419 (NH), 2927, 2856, 1724, 1622, 1550 ($NO_2$), 1494, 1376, 1328, 1138, 1076, 978 and 856 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, major *syn*-isomer) δ 7.04 (1H, d, *J* = 8.0 Hz), 6.87 (1H, d, *J* = 8.5 Hz), 6.75 (1H, br s), 4.92 (1H, dd, *J* = 12.0, 5.0 Hz), 4.43 (1H, dd, *J* = 12.0, 9.5 Hz), 3.97 (1H, br s, *N*H), 3.81-3.75 (1H, m), 3.52-3.46 (1H, m), 2.08 (1H, ddd, *J* = 13.0, 6.0, 2.5 Hz), 1.55 (1H, q, *J* = 11.0 Hz), 1.26 (3H, d, *J* = 6.0 Hz, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$,



*syn*-**42gb**

DEPT-135, major *syn*-isomer) δ 145.5 (C), 130.2 (C, q, *J* = 32.5 Hz), 126.4 (CH), 123.9 (C, *C*$F_3$, q, *J* = 271.2 Hz), 121.9 (C), 113.8 (CH, q, *J* = 3.7 Hz), 111.3 (CH, q, *J* = 3.7 Hz), 79.8 ($CH_2$), 46.5 (CH), 34.82 (CH), 34.80 ($CH_2$), 22.2 ($CH_3$); HRMS m/z 275.1002 (M + H), calcd for $C_{12}H_{14}F_3N_2O_2$ 275.1002.

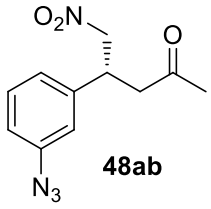
**(2*S*,4*R*)-2-methyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline-7-carbonitrile** (*syn*-**42hb**):



*syn*-**42hb**

Prepared following the procedure **1b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 138 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 85:15, flow rate 0.8 mL/min, λ = 254 nm), $t_R$ = 11.28 min (minor), $t_R$ = 14.94 min (major) [for minor *anti*-isomer], $t_R$ = 16.28 min (minor), $t_R$ = 21.90 min (major) [for major *syn*-isomer]; **$[\alpha]_D^{25}$ = −11.8** [***c* = 0.08 g/100 mL, $CHCl_3$, 96% *ee*** (major *syn*-isomer), **91% *ee*** (minor *anti*-isomer) and *dr* = 4:1]; IR (neat): $\nu_{max}$ 3371 (NH), 2921, 2852, 2227, 1544 ($NO_2$), 1493, 1379, 1320, 1186, 1154, 1084, 1015, 854 and 804 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, major *syn*-isomer) δ 7.02 (1H, dd, *J* = 8.0, 1.0 Hz), 6.90 (1H, dd, *J* = 8.0, 1.5 Hz), 6.75 (1H, d, *J* = 1.5 Hz), 4.90 (1H, dd, *J* = 12.5, 5.0 Hz), 4.45 (1H, dd, *J* = 12.5, 9.0 Hz), 4.01 (1H, br s, *N*H), 3.79-3.73 (1H, m), 3.53-3.46 (1H, m), 2.08 (1H, ddd, *J* = 13.0, 6.0, 3.0 Hz), 1.53 (1H, q, *J* = 12.0 Hz), 1.26 (3H, d, *J* = 6.5 Hz, C$H_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135, major *syn*-isomer) δ 145.6 (C), 126.9 (CH), 123.4 (C), 120.5 (CH), 118.8 (C), 117.4 (CH), 111.7 (C,*C*≡N), 79.4 ($CH_2$), 46.5 (CH), 34.9 (CH), 34.4 ($CH_2$), 22.1 ($CH_3$); HRMS m/z 232.1082 (M + H), calcd for $C_{12}H_{14}N_3O_2$ 232.1081.

**(*R*)-4-(3-azidophenyl)-5-nitropentan-2-one** (**48ab**):♣ Prepared following the procedure **1a** and

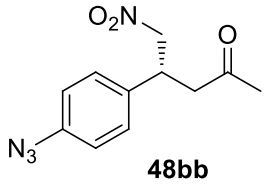


**48ab**

purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u amylase-2 column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 44.02 min (major), $t_R$ = 51.99 min (minor); **$[\alpha]_D^{25}$ = –3.8 (*c* = 0.10 g/100 mL, $CHCl_3$, 78% *ee*);** IR (Neat): $\nu_{max}$ 2922, 2853, 2106 ($N_3$), 1714 (C=O), 1547 ($NO_2$), 1376, 1287, 1163 and 786 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.32 (1H, t, *J* = 8.0 Hz), 7.00 (1H, br d, *J* = 8.0 Hz), 6.96 (1H, br ddd, *J* = 8.0, 2.4, 0.8 Hz), 6.85 (1H, t, *J* = 1.6 Hz), 4.69 (1H, dd, *J* = 12.8, 6.8 Hz), 4.59 (1H, dd, *J* = 12.4, 8.0 Hz), 4.00 (1H, quin, *J* = 7.2 Hz), 2.91 (2H, d, *J* = 7.2 Hz) 2.14 (3H, s, C$H_3$); $^{13}C$ NMR ($CDCl_3$,

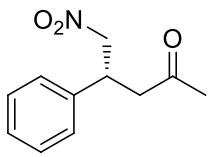
DEPT-135) δ 205.0 (C, *C*=O), 140.9 (C), 140.8 (C), 130.4 (CH), 123.8 (CH), 118.4 (CH), 118.2 (CH), 79.1 ($CH_2$), 45.9 ($CH_2$), 38.7 (CH), 30.3 ($CH_3$); HRMS m/z 271.0808 (M + Na), calcd for $C_{11}H_{12}N_4O_3Na$ 271.0802.

**(*R*)-4-(4-azidophenyl)-5-nitropentan-2-one** (**48bb**):♣ Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 22.60 min (minor), $t_R$ = 27.25 min (major); **$[\alpha]_D^{25}$ = –1.5 (*c* = 0.26 g/100 mL, $CHCl_3$, 81% *ee*);** IR (Neat): $\nu_{max}$ 2922, 2097 ($N_3$), 1714 (C=O), 1550 ($NO_2$), 1508, 1376, 1285, 1163,1130, 1117 and 832 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.21 (2H, d, *J* = 8.4 Hz), 6.99 (2H, d, *J* = 8.4 Hz), 4.68 (1H, dd, *J* = 12.4, 6.8 Hz), 4.57 (1H, dd, *J* = 12.4, 8.0 Hz), 3.99 (1H, quin, *J* = 6.8 Hz), 2.90 (2H, d, *J* = 7.2 Hz) 2.13 (3H, s, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 205.1 (C, *C*=O), 139.6 (C), 135.4 (C), 128.8 (2 x CH), 119.6 (2 x CH), 79.3 ($CH_2$), 46.0 ($CH_2$), 38.4 (CH), 30.3 ($CH_3$); HRMS m/z 271.0805 (M + Na), calcd for $C_{11}H_{12}N_4O_3Na$ 271.0802.



**48bb**

**(*R*)-5-nitro-4-phenylpentan-2-one** (**48cb**):♣ Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 110 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 220 nm), $t_R$ = 16.44 min (minor), $t_R$ = 17.54 min (major); **$[\alpha]_D^{25}$ = –1.5 (*c* = 0.20 g/100 mL, $CHCl_3$, 90% *ee*) ;** IR (Neat): $\nu_{max}$ 3044, 2968, 2917, 1710 (C=O), 1547 ($NO_2$), 1536, 1360, 1324,1184, 1161 and 751 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.35-7.31 (2H, m), 7.29-7.25 (1H, m), 7.23-7.21 (2H, m) 4.69 (1H, dd, *J* = 12.4, 6.8 Hz), 4.60 (1H, dd, *J* = 12.4, 7.6 Hz), 4.01 (1H, quin, *J* = 7.2 Hz), 2.92 (2H, d, *J* = 7.2 Hz), 2.12 (3H, s, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 205.4 (C, *C*=O), 138.8 (C), 129.0 (2 x CH), 127.9 (CH), 127.3 (2 x CH), 79.4 ($CH_2$), 46.1 ($CH_2$), 39.0 (CH), 30.4 ($CH_3$); HRMS m/z 230.0788 (M + Na), calcd for $C_{11}H_{13}NO_3Na$ 230.0788.

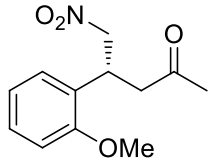


**48cb**

♣ The absolute configuration of chiral products **48ab-fb** were established by comparison of (–)-**48cb** with the same chiral product synthesized from direct asymmetric Michael reaction (see Fei

Xue et. al. *Adv. Synth. Catal.*, **2008**, *350*, 2194-2198; E. N. Jacobsen et. al. *J. Am. Chem. Soc*. **2006**, *128*, 7170 and W. Wang et. al. *Org. Lett*. **2009,** *11*, 2864).

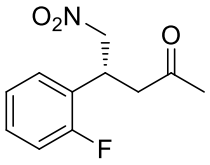
**(*R*)-4-(2-methoxyphenyl)-5-nitropentan-2-one (48db):♠** Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak AS-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 210 nm), $t_R$ = 11.96 min (minor), $t_R$ = 13.38 min (major). **$[\alpha]_D^{25}$ = –27.8 (*c* = 0.31 g/100 mL, $CHCl_3$, 92% *ee*);** IR (Neat): $\nu_{max}$ 3003, 2970, 2942, 2915, 2844, 1709 (C=O), 1600, 1551 ($NO_2$), 1501, 1441, 1381, 1244, 1167, 1129, 1025 and 762 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.20-7.15 (1H, m), 7.06 (1H, dd, *J* = 7.6, 1.6 Hz), 6.85-6.80 (2H, m), 4.67 (1H, dd, *J* = 12.0, 7.2 Hz), 4.63 (1H, dd, *J* = 12.0, 6.8 Hz), 4.14 (1H, quin, *J* = 6.8 Hz), 3.78 (3H, s, O-C$H_3$), 2.95 (1H, dd, *J* = 17.6, 7.6 Hz), 2.88 (1H, dd, *J* = 17.6, 6.8 Hz), 2.05 (3H, s, C$H_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 206.1 (C, *C*=O), 157.0 (C), 129.2 (CH), 128.9 (CH), 126.4 (C), 120.9 (CH), 110.9 (CH), 77.8 ($CH_2$), 55.3 ($CH_3$, O-*C*$H_3$), 44.5 ($CH_2$), 35.3 (CH), 30.2 ($CH_3$); HRMS m/z 260.0894 (M + Na), calcd for $C_{12}H_{15}NO_4Na$ 260.0893.



**48db**

♠ The absolute configuration of chiral products **41ab-hb,** and **48ab-fb** were established by comparison of (–)-**48db** with the same chiral product synthesized from direct asymmetric Michael reaction (see F. Xue et. al. *Adv. Synth. catal*. **2008**, *350*, 2194; and Ramachary et. al. *Org. Biomol. Chem.* **2010**, *8*, 4259).

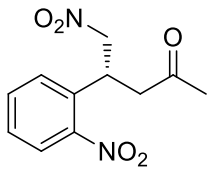
**(*R*)-4-(2-fluorophenyl)-5-nitropentan-2-one (48eb):** Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as solid Mp: 74 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak AS-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 210 nm), $t_R$ = 11.43 min (minor), $t_R$ = 13.14 min (major). **$[\alpha]_D^{25}$ = –5.2 (*c* = 0.48 g/100 mL, $CHCl_3$, 93% *ee*);** IR (Neat): $\nu_{max}$ 2920, 2855, 1715 (C=O), 1556 ($NO_2$), 1501, 1436, 1386, 1233, 1156, 1112, 827 and 756 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.21-7.13 (2H, m), 7.03-6.95 (2H, m), 4.66 (1H, dd, *J* = 12.4, 6.8 Hz), 4.60 (1H, dd, *J* = 12.4, 7.6 Hz), 4.11 (1H, quin, *J* = 6.8 Hz), 2.93 (1H, dd, *J* = 18.4, 7.6 Hz), 2.87 (1H, dd, *J* = 18.4, 6.4 Hz), 2.05 (3H, s, C$H_3$). $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 205.2 (C, *C*=O), 160.8 (C, d, *J* = 244.0 Hz), 129.9 (CH, d, *J* = 4.0 Hz), 129.5 (CH, d, *J* = 9.0 Hz),



**48eb**

125.5 (C, d, *J* = 13.0 Hz), 124.5 (CH, d, *J* = 3.0 Hz), 116.0 (CH, d, *J* = 22.0 Hz), 77.7 ($CH_2$, d, *J* = 2.0 Hz), 44.5 ($CH_2$, d, *J* = 2.0 Hz), 34.4 (CH), 30.1 ($CH_3$); HRMS m/z 248.0693 (M + Na), calcd for $C_{11}H_{12}FNO_3Na$ 248.0693.

**(*R*)-5-nitro-4-(2-nitrophenyl)pentan-2-one (48fb):♥** Prepared following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 18.22 min (minor), $t_R$ = 20.31 min (major). **$[\alpha]_D^{25}$ = +28.6 (*c* = 0.41 g/100 mL, $CHCl_3$, 93% *ee*);** IR (Neat): $\nu_{max}$ 3019, 1720 (C=O), 1551 ($NO_2$), 1518, 1359, 1211 and 756 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.81 (1H, d, *J* = 8.4 Hz), 7.52 (1H, t, *J* = 7.6 Hz), 7.37 (1H, t, *J* = 8.0 Hz), 7.31 (1H, d, *J* = 8.0 Hz), 4.77 (1H, dd, *J* = 13.2, 6.4 Hz), 4.73 (1H, dd, *J* = 13.2, 7.2 Hz), 4.45 (1H, quin, *J* = 6.8 Hz), 2.97 (2H, d, *J* = 6.8 Hz), 2.08 (3H, s, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 204.8 (C, *C*=O), 149.8 (C), 133.5 (C), 133.2 (CH), 128.7 (CH), 128.5 (CH), 125.1 (CH), 77.9 ($CH_2$), 45.2 ($CH_2$), 33.8 (CH), 30.0 ($CH_3$); HRMS m/z 275.0638 (M + Na), calcd for $C_{11}H_{12}N_2O_5Na$ 275.0638.

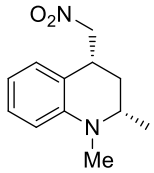


**48fb**

♥ The absolute configuration of chiral products **41ab-hb, and 48ab-fb** were also established by comparison of (+)-**48fb** with the same chiral product synthesized from direct asymmetric Michael reaction (see W. Wang et. al. *Org. Lett*. **2009,** *11*, 2864 and L. –X. Wang et. al. *Eur. J. Org. Chem.* **2010**, 1849).

**1c. General procedure for the preparation of *N*-methyl-tetrahydroquinoline 45ab from 42ab:** Pure tetrahydroquinoline **42ab** (20 mg, 0.1 mmol) was taken in a 1:1 ratio of $H_2O$ and EtOAc (1.0 mL, 0.1 M). To this solution was added sodium bicarbonate (10 mg, 0.12 mmol), and then dimethyl sulfate (0.01 mL, 0.12 mmol) was added drop wise. The mixture was stirred at 25 °C for 13 h. To the crude reaction mixture was added saturated $NaHCO_3$ solution and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure product **45ab** was purified by column chromatography (silica gel, mixture of hexane/ethyl acetate).

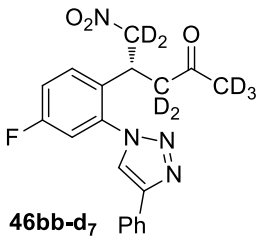
**(2*S*,4*R*)-1,2-dimethyl-4-(nitromethyl)-1,2,3,4-tetrahydroquinoline** (*syn*-**45ab**): Prepared following the procedure **1c** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 20.56 min (minor), $t_R$ = 34.60 min (major) [for minor *anti*-isomer], $t_R$ = 22.75 min (major), $t_R$ = 26.02 min (minor) [for major *syn*-isomer]; **$[\alpha]_D^{25}$ = +45.3 [*c* = 0.16 g/100 mL, $CHCl_3$, 89% *ee*** (major *syn*-isomer), **88% *ee*** (minor *anti*-isomer) and *dr* = 6:1]; IR (neat): $\nu_{max}$ 2959, 2926, 1605, 1545 ($NO_2$), 1501, 1375, 1326, 1047 and 751 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, major *syn*-isomer) δ 7.18-7.15 (1H, m), 6.94 (1H, d, *J* = 7.5 Hz), 6.69-6.64 (2H, m), 4.84 (1H, dd, *J* = 12.0, 6.0 Hz), 4.53 (1H, dd, *J* = 12.0, 10.0 Hz), 3.71-3.65 (1H, m), 3.45-3.40 (1H, m), 2.88 (3H, s, NC$H_3$), 2.22-2.17 (1H, m), 1.73-1.67 (1H, m), 1.25 (3H, d, *J* = 6.5 Hz, C$H_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135, major *syn*-isomer) δ 146.3 (C), 128.5 (CH), 126.1 (CH), 121.3 (C), 116.7 (CH), 112.5 (CH), 80.2 ($CH_2$), 52.8 (CH), 36.4 (CH), 34.8 ($CH_3$), 33.9 ($CH_2$), 20.3 ($CH_3$); HRMS m/z 243.1102 (M + Na), calcd for $C_{12}H_{16}N_2O_2Na$ 243.1104.



*syn*-**45ab**

**1d. General procedure for the preparation of chiral triazole 46bb-$d_7$ from the Michael product 41bb-$d_7$:** To the pure Michael product **41bb-$d_7$** (20 mg, 0.07 mmol) in $H_2O$ (1.0 mL, 0.07 M), were added phenyl acetylene (0.02 mL, 0.15 mmol), $CuSO_4.5H_2O$ (6.7 mg, 60 mol-%) and Na-(+)-ascorbate (5.5 mg, 40 mol-%) and stirred at 25 °C for 24 h. To the crude reaction mixture was added aqueous $NH_4Cl$ solution and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure chiral triazole product **46bb-$d_7$** was purified by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**(*R*)-4-(4-fluoro-2-(4-phenyl-1H-1,2,3-triazol-1-yl)phenyl)-5-nitropentan-2-one** (**46bb-$d_7$**): Prepared following the procedure **1d** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u cellulose 2 column (hexane/EtOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 17.36 min (major), $t_R$ = 21.37 min (minor); **$[\alpha]_D^{25}$ = +7.8 (*c* = 0.10 g/100 mL, $CHCl_3$, 89% *ee*);** IR (Neat): $\nu_{max}$ 3140, 2926, 2860,



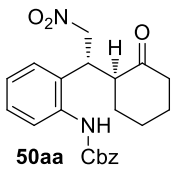
**46bb-$d_7$**

1710 (C=O), 1605, 1545 ($NO_2$), 1507, 1381, 1249, 1178 and 773 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 8.19 (1H, s), 7.93 (2H, d, *J* = 7.6 Hz), 7.48 (2H, t, *J* = 7.6 Hz), 7.40 (2H, m) 7.28-7.24 (1H, m), 7.15 (1H, dd, *J* = 8.8, 3.6 Hz), 3.79 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 205.3 (C, *C*=O), 161.4 (C, d, *J* = 249.0 Hz, *C*-F), 148.3 (C), 137.2 (C, d, *J* = 9.0 Hz), 131.4 (C), 129.8 (C), 129.2 (CH, d, *J* = 9.0 Hz), 129.0 (2 x CH), 128.7 (CH), 125.9 (2 x CH), 121.9 (CH), 117.8 (CH, d, *J* = 20.0 Hz), 114.6 (CH, d, *J* = 24.0 Hz), 32.9 (CH); HRMS m/z 376.1798 (M + H), calcd for $C_{19}H_{11}D_7FN_4O_3$ 376.1797.

## 2. General experimental procedures for Asymmetric Supramolecular Organocatalysis

**2a. General procedure for asymmetric Michael reaction of ketone 1 with 2-amino-*β*-nitrostyrenes 49 through supramolecular-organocatalysis:** In an ordinary glass vial equipped with a magnetic stirring bar, to a mixture of 9-amino-9-deoxyepiquinine thiourea **8d** (2.97 mg, 0.005 mmol) and D-proline **7c** (0.57 mg, 0.005 mmol) in DCM (1.0 mL, 0.1 M), was added 2-amino-*β*-nitrostyrenes **49** (0.1 mmol). After stirring for a minute, was added ketone **1** (1.5 mmol) and the reaction mixture was stirred at 25 °C, then the reaction was monitored using TLC. The crude reaction mixture was then worked up with aqueous $NH_4Cl$ solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure products **50** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

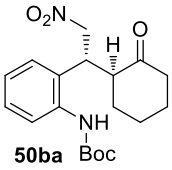
**benzyl (2-((*R*)-2-nitro-1-((*S*)-2-oxocyclohexyl)ethyl)phenyl)carbamate (50aa):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 220 nm), $t_R$ = 21.92 min (major), $t_R$ = 28.96 min (minor) [for minor isomer]; $t_R$ = 32.74 min (minor), $t_R$ = 44.69 min (major) [for major isomer]; **$[\alpha]_D^{25}$ = –9.2° (*c* = 0.47 g/100 mL, $CHCl_3$, 98% *ee*);** IR (Neat): $\nu_{max}$ 3298 (NH), 2945, 1702 (C=O), 1550 ($NO_2$), 1450, 1377, 1216, 1044, and 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.64 (2H, br s, N*H* and Ar-*H*), 7.45-7.43 (2H, m), 7.40-7.26 (4H, m), 7.16 (1H, t, *J* = 7.6 Hz), 7.06 (1H, d, *J* = 8.0 Hz), 5.29-5.19 (2H, m, OC$H_2$Ph), 4.98 (1H, dd, *J* = 13.6, 6.0 Hz), 4.52 (1H, dd, *J* = 13.6, 9.2 Hz), 4.15 (1H, br q, *J* = 8.0 Hz), 2.64-2.58 (1H, m), 2.46-2.42



**50aa**

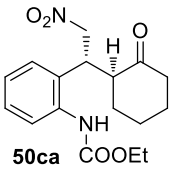
(1H, m), 2.37-2.29 (1H, m), 2.07-2.02 (1H, m), 1.85-1.76 (2H, m), 1.59-1.51 (2H, m), 1.23-1.14 (1H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 212.2 (C, *C*=O), 154.6 (C), 136.4 (C), 136.3 (C), 130.3 (C), 128.5 (2 x CH), 128.2 (3 x CH), 128.17 (2 x CH), 126.8 (CH), 125.7 (CH), 78.3 ($CH_2$), 67.0 ($CH_2$), 52.7 (CH), 42.5 ($CH_2$), 35.8 (CH), 31.6 ($CH_2$), 27.9 ($CH_2$), 25.1 ($CH_2$); HRMS m/z 419.1578 (M + Na), calcd for $C_{22}H_{24}N_2O_5Na$ 419.1583.

***tert*-butyl (2-((*R*)-2-nitro-1-((*S*)-2-oxocyclohexyl)ethyl)phenyl)carbamate (50ba):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 9.12 min (minor), $t_R$ = 10.16 min (major); **$[\alpha]_D^{25}$ = –18.9° (*c* = 0.43 g/100 mL, $CHCl_3$, 97% *ee*);** IR (Neat): $\nu_{max}$ 3306 (NH), 2939, 1702 (C=O), 1552 ($NO_2$), 1448, 1367, 1276, 1156, 1048, 1023 and 751 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.60 (1H, d, *J* = 8.0 Hz), 7.27-7.22 (1H, m), 7.21 (1H, br s, N*H*), 7.13 (1H, dt, *J* = 7.6, 1.2 Hz), 7.06 (1H, dd, *J* = 7.6, 1.2 Hz), 5.00 (1H, dd, *J* = 13.2, 5.6 Hz), 4.55 (1H, dd, *J* = 13.2, 9.2 Hz), 4.17 (1H, td, *J* = 8.4, 5.6 Hz), 2.68-2.62 (1H, m), 2.48-2.44 (1H, m), 2.39-2.30 (1H, m), 2.09-2.04 (1H, m), 1.87-1.79 (2H, m), 1.68-1.59 (2H, m), 1.53 (9H, s, 3 x C*H*$_3$), 1.26-1.21 (1H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 212.3 (C, *C*=O), 154.0 (C), 136.8 (C), 130.4 (C), 128.0 (CH), 126.6 (CH), 126.1 (CH), 125.4 (CH), 80.3 (C), 78.3 ($CH_2$), 52.8 (CH), 42.6 ($CH_2$), 36.0 (CH), 31.9 ($CH_2$), 28.3 (3 x $CH_3$), 28.1 ($CH_2$), 25.1 ($CH_2$); HRMS m/z 385.1734 (M + Na), calcd for $C_{19}H_{26}N_2O_5Na$ 385.1739.



**50ba**

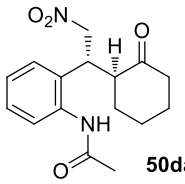
**ethyl (2-((*R*)-2-nitro-1-((*S*)-2-oxocyclohexyl)ethyl)phenyl)carbamate (50ca):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 22.12 min (minor), $t_R$ = 26.56 min (major**);** **$[\alpha]_D^{25}$ = –18.7° (*c* = 0.38 g/100 mL, $CHCl_3$, 98% *ee***); IR (Neat): $\nu_{max}$ 3355 (N*H*), 2937, 2862, 1703 (C=O), 1550 ($NO_2$), 1514, 1449, 1377, 1299, 1218, 1060 and 734 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.64 (1H, d, *J* = 6.8 Hz), 7.56 (1H, br s, N*H*), 7.27 (1H, t, *J* = 9.0 Hz), 7.15 (1H, t, *J* = 7.6 Hz), 7.07 (1H, d, *J* = 7.4 Hz), 4.99 (1H, dd, *J* = 13.6, 6.0 Hz), 4.53 (1H, dd, *J* = 13.6, 9.2 Hz), 4.30-4.22 (3H, m), 2.68-2.61 (1H, m), 2.49-2.45 (1H, m), 2.40-



**50ca**

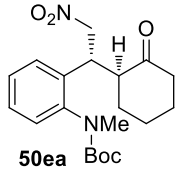
2.32 (1H, m), 2.09-2.05 (1H, m), 1.89-1.81 (2H, m), 1.67-1.52 (2H, m), 1.34 (3H, t, *J* = 7.2 Hz), 1.31-1.20 (1H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 212.3 (C, *C*=O), 154.8 (C), 136.6 (C), 130.0 (C), 128.2 (2 x CH), 126.7 (CH), 125.5 (CH), 78.3 ($CH_2$), 61.3 ($CH_2$), 52.8 (CH), 42.5 ($CH_2$), 35.7 (CH), 31.6 ($CH_2$), 27.9 ($CH_2$), 25.1 ($CH_2$), 14.5 ($CH_3$); HRMS m/z 357.1422 (M + Na), calcd for $C_{17}H_{22}N_2O_5Na$ 357.1426.

***N*-(2-((*R*)-2-nitro-1-((*S*)-2-oxocyclohexyl)ethyl)phenyl)acetamide (50da):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a chiralpak ID-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 22.32 min (major), $t_R$ = 34.91 min (minor) [for major isomer]; 43.01 min (major), 56.79 min (minor) [for minor isomer]; **$[\alpha]_D^{25}$ = –6.9° (*c* = 0.49 g/100 mL, $CHCl_3$, 99% *ee*);** IR (Neat): $\nu_{max}$ 3277 (N*H*), 2943, 1702 (C=O), 1668, 1549 ($NO_2$), 1448, 1376, 1295 and 731 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 8.47 (1H, s, N*H*), 7.66 (1H, d, *J* = 8.0 Hz), 7.29 (1H, t, *J* = 7.2 Hz), 7.18 (1H, t, *J* = 7.6 Hz), 7.07 (1H, d, *J* = 8.0 Hz), 4.97 (1H, dd, *J* = 13.6, 6.8 Hz), 4.52 (1H, dd, *J* = 13.2, 8.4 Hz), 4.22 (1H, q, *J* = 7.2 Hz), 2.65 (1H, quin, *J* = 6.0 Hz), 2.48-2.45 (1H, m), 2.40-2.32 (1H, m), 2.28 (3H, s, NCOC*H*$_3$), 2.09-2.07 (1H, m) 1.96-1.92 (1H, m), 1.85-1.83 (1H, m), 1.65-1.54 (2H, m), 1.26-1.17 (1H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 212.7 (C, *C*=O), 169.2 (C), 136.2 (C), 130.3 (C), 128.2 (CH), 127.0 (CH), 126.9 (CH), 126.0 (CH), 78.4 ($CH_2$), 52.6 (CH), 42.5 ($CH_2$), 35.6 (CH), 31.4 ($CH_2$), 27.8 ($CH_2$), 25.1 ($CH_2$), 24.1 ($CH_3$); HRMS m/z 327.1319 (M + Na), calcd for $C_{16}H_{20}N_2O_4Na$ 327.1321.



**50da**

***tert*-butyl methyl(2-((*R*)-2-nitro-1-((*S*)-2-oxocyclohexyl)ethyl)phenyl)carbamate (50ea):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 220 nm), $t_R$ = 6.50 min (major), $t_R$ = 7.21 min (minor); **$[\alpha]_D^{25}$ = +9.2° (*c* = 0.19 g/100 mL, $CHCl_3$, 20% *ee*);** IR (Neat): $\nu_{max}$ 2977, 2933, 2863, 1693 (C=O), 1549 ($NO_2$), 1494, 1448, 1365, 1267, 1152, 1130 and 736 cm$^{-1}$; $^1$H NMR ($CDCl_3$, major rotamer at 50 °C): δ 7.37-7.10 (4H, m), 5.04 (1H, q, *J* = 12.4 Hz), 4.77-4.74 (1H, m), 3.89-3.75 (1H, m), 3.14 (3H, s), 2.90 (1H, br s), 2.47-2.28 (2H, m), 2.14-2.06

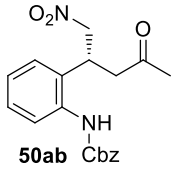


**50ea**

(1H, m), 1.91-1.80 (2H, m), 1.73-1.53 (2H, m), 1.42 (9H, br s, 3 x C$H_3$), 1.26-1.18 (1H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135, major rotamer at 50 °C): δ 212.0 (C, *C*=O), 155.5 (C), 143.4 (C), 136.1 (C), 128.6 (CH), 128.0 (2 x CH), 127.7 (CH), 80.2 (C), 77.7 ($CH_2$), 53.7 (CH), 43.0 ($CH_2$), 38.1 (CH), 34.1 ($CH_2$), 28.5 ($CH_2$), 28.3 (3 x $CH_3$), 28.3 ($CH_3$), 25.4 ($CH_2$); HRMS m/z 399.1895 (M + Na), calcd for $C_{20}H_{28}N_2O_5Na$ 399.1896.

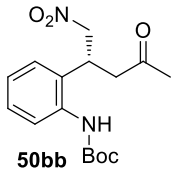
**Note:** Some of the peaks of minor rotamer overlap with the major rotamer.

**(*R*)-benzyl (2-(1-nitro-4-oxopentan-2-yl)phenyl)carbamate (50ab):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u cellulose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 18.64 min (major), $t_R$ = 29.83 min (minor); **$[\alpha]_D^{25}$ = +55.0° (*c* = 0.27 g/100 mL, $CHCl_3$, 99% *ee*);** IR (Neat): $\nu_{max}$ 3400 (N*H*), 1713 (C=O), 1549 ($NO_2$), 1520, 1220, 1018 and 752 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.82 (1H, br s, N*H*), 7.61 (1H, br s), 7.45-7.44 (2H, m), 7.38 (2H, t, *J* = 7.0 Hz), 7.35-7.32 (1H, m), 7.25 (1H, dt, *J* = 9.0, 1.5 Hz), 7.15 (1H, dt, *J* = 7.5, 0.5 Hz), 7.05 (1H, dd, *J* = 7.5, 1.0 Hz), 5.24 (2H, s, OC$H_2$Ph), 4.62 (1H, dd, *J* = 13.0, 9.0 Hz), 4.51 (1H, dd, *J* = 13.0, 6.5 Hz), 4.25 (1H, quin, *J* = 8.5 Hz), 2.95 (1H, dd, *J* = 18.5, 9.0 Hz), 2.89 (1H, dd, *J* = 18.5, 5.0 Hz), 2.07 (3H, s, COC$H_3$); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 206.6 (C, *C*=O), 154.8 (C), 136.3 (C), 135.6 (C), 132.2 (C), 128.5 (3 x CH), 128.3 (CH), 128.2 (2 x CH), 128.1 (CH), 126.0 (CH), 125.9 (CH), 78.7 ($CH_2$), 67.1 ($CH_2$), 47.3 ($CH_2$), 31.8 (CH), 29.9 ($CH_3$); HRMS m/z 379.1264 (M + Na), calcd for $C_{19}H_{20}N_2O_5Na$ 379.1270.



**50ab**

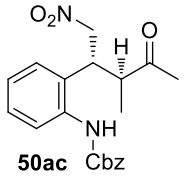
**(*R*)-*tert*-butyl (2-(1-nitro-4-oxopentan-2-yl)phenyl)carbamate (50bb):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a chiral pak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 9.87 min (major), $t_R$ = 11.84 min (minor); **$[\alpha]_D^{25}$ = +44.2° (*c* = 0.29 g/100 mL, $CHCl_3$, 98% *ee*);** IR (Neat): $\nu_{max}$ 3329 (N*H*), 2981, 2876, 1710 (C=O), 1555 ($NO_2$), 1509, 1475, 1365, 1157, 1046 and 842 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.56 (1H, d, *J* = 8.0 Hz), 7.38 (1H, br s, N*H*), 7.23 (1H, t, *J* = 7.6 Hz), 7.14 (1H, t, *J* = 7.6 Hz), 7.05 (1H, d, *J* = 7.6 Hz), 4.65 (1H, dd, *J* = 12.8, 8.8 Hz), 4.56 (1H, dd, *J* = 13.2, 6.8 Hz),



**50bb**

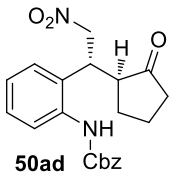
4.25 (1H, quintet, *J* = 8.0 Hz), 2.99 (1H, dd, *J* = 18.4, 8.4 Hz), 2.90 (1H, dd, *J* = 18.4, 5.2 Hz), 2.10 (3H, s, COC*H*$_3$), 1.54 (9H, s, 3 x C*H*$_3$); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 206.6 (C, *C*=O), 154.2 (C), 135.9 (C), 132.2 (C), 128.2 (CH), 126.1 (CH), 125.9 (CH), 125.7 (CH) 80.4 (C), 78.7 ($CH_2$), 47.2 ($CH_2$), 31.8 (CH), 30.0 ($CH_3$), 28.3 (3 x $CH_3$); HRMS m/z 345.1426 (M + Na), calcd for $C_{16}H_{22}N_2O_5Na$ 345.1426.

**benzyl (2-((2*R*,3*S*)-3-methyl-1-nitro-4-oxopentan-2-yl)phenyl)carbamate (50ac):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a chiralpak ID-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 220 nm), $t_R$ = 16.87 min (major), $t_R$ = 19.16 min (minor) [for major isomer]; $t_R$ = 21.92 min (major), $t_R$ = 39.81 min (minor) [for minor isomer]; **$[\alpha]_D^{25}$ = –39.2° (*c* = 0.14 g/100 mL, $CHCl_3$, 99% *ee*);** IR (Neat): $\nu_{max}$ 3308 (N*H*), 2925, 1709 (C=O), 1552 ($NO_2$), 1518, 1454, 1218 and 1045 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.59 (1H, br s, N*H*), 7.45-7.43 (2H, m), 7.39 (2H, t, *J* = 7.0 Hz ), 7.35-7.32 (2H, m), 7.29 (1H, t, *J* = 7.5 Hz), 7.20 (1H, t, *J* = 7.5 Hz), 7.09 (1H, d, *J* = 8.0 Hz), 5.22-5.21 (2H, m), 4.72 (1H, dd, *J* = 13.5, 5.5 Hz), 4.57 (1H, dd, *J* = 13.5, 9.5 Hz), 4.08 (1H, dt, *J* = 9.0, 5.5 Hz), 2.87 (1H, quin, *J* = 7.5 Hz), 2.20 (3H, s, COC*H*$_3$), 0.94 (3H, d, *J* = 7.5 Hz); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 210.8 (C, *C*=O), 154.7 (C), 136.2 (C), 136.1 (C), 131.2 (C), 128.6 (3 x CH), 128.4 (CH), 128.3 (3 x CH), 126.43 (CH), 126.36 (CH), 77.9 ($CH_2$), 67.2 ($CH_2$), 49.3 (CH), 37.8 (CH), 29.1 ($CH_3$), 15.3 ($CH_3$); HRMS m/z 393.1426 (M + Na), calcd for $C_{20}H_{22}N_2O_5Na$ 393.1426.



**50ac**

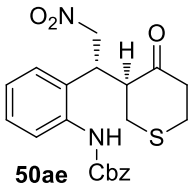
**benzyl (2-((*R*)-2-nitro-1-((*S*)-2-oxocyclopentyl)ethyl)phenyl)carbamate (50ad):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 31.52 min (major), $t_R$ = 62.81 min (minor) [for major isomer]; $t_R$ = 42.67 min (major), $t_R$ = 55.95 (minor) [for minor isomer]; **$[\alpha]_D^{25}$ = –22.9° (*c* = 0.28 g/100 mL, $CHCl_3$, 99% *ee*);** IR (Neat): $\nu_{max}$ 3307 (N*H*), 2965, 1723 (C=O), 1550 ($NO_2$), 1517, 1476, 1452, 1377, 1298, 1214, 1042 and 752 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.61 (1H, br s), 7.53-7.51 (2H, m), 7.45-7.31 (4H, m), 7.29-7.25 (1H, m), 7.19-7.13 (1H, m), 7.08 (1H, dd, *J* = 8.0, 1.6 Hz), 5.23 (2H, s), 5.19 (1H, dd, *J* = 13.6,



**50ad**

5.2 Hz), 4.61 (1H, dd, *J* = 13.6, 8.8 Hz), 4.12 (1H, q, *J* = 7.2 Hz), 2.52-2.40 (1H, m), 2.35-2.26 (1H, m), 2.10-1.85 (3H, m), 1.76-1.64 (1H, m), 1.57-1.42 (1H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 219.6 (C, *C*=O), 154.6 (C), 136.2 (C), 135.9 (C), 130.1 (C), 128.57 (2 x CH), 128.4 (CH), 128.27 (2 x CH), 128.23 (CH), 127.1 (CH), 126.7 (CH), 125.7 (CH), 77.9 ($CH_2$), 67.0 ($CH_2$), 51.5 (CH), 38.1 ($CH_2$), 35.7 (CH), 26.8 ($CH_2$), 20.2 ($CH_2$); HRMS m/z 405.1422 (M + Na), calcd for $C_{21}H_{22}N_2O_5Na$ 405.1426.

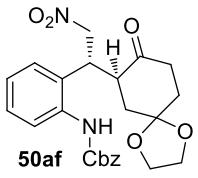
**benzyl (2-((*R*)-2-nitro-1-((*S*)-4-oxotetrahydro-2*H*-thiopyran-3-yl)ethyl)phenyl)carbamate**



**50ae**

**(50ae):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 220 nm), $t_R$ = 19.67 min (minor), $t_R$ = 53.76 min (major) [for major isomer]; $t_R$ = 27.76 min (minor), $t_R$ = 41.97 min (major) [for minor isomer]; **$[\alpha]_D^{25}$ = –18.8° (*c* = 0.86 g/100 mL, $CHCl_3$, 96% *ee*);** IR (Neat): $\nu_{max}$ 3312 (N*H*), 2921, 1703 (C=O), 1551 ($NO_2$), 1512, 1452, 1378, 1215, 1044, 910 and 732 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.56 (1H, br s, N*H*), 7.42-7.28 (6H, m), 7.26-7.17 (2H, m), 7.16-7.10 (1H, m), 5.22 (2H, s), 4.80 (1H, dd, *J* = 14.0, 5.2 Hz), 4.55 (1H, dd, *J* = 13.6, 9.6 Hz), 4.40-4.36 (1H, m), 2.99 (1H, dt, *J* = 9.6, 4.4 Hz), 2.92-2.86 (2H, m), 2.84-2.70 (2H, m), 2.63-2.56 (1H, m), 2.38 (1H, dd, *J* = 14.0, 9.6 Hz); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 209.5 (C, *C*=O), 154.6 (C), 136.4 (C), 136.2 (C), 130.2 (C), 128.7 (CH), 128.5 (3 x CH), 128.24 (CH), 127.22 (2 x CH), 126.6 (CH), 126.3 (CH), 78.1 ($CH_2$), 67.2 ($CH_2$), 55.3 (CH), 44.4 ($CH_2$), 35.8 (CH), 34.2 ($CH_2$), 31.2 ($CH_2$); HRMS m/z 437.1148 (M + Na), calcd for $C_{21}H_{22}N_2O_5SNa$ 437.1147.

**benzyl (2-((*R*)-2-nitro-1-((*S*)-8-oxo-1,4-dioxaspiro[4.5]decan-7-yl)ethyl)phenyl)carbamate**

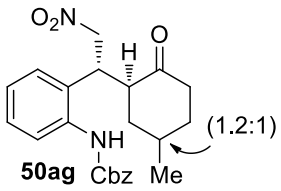


**50af**

**(50af):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 41.68 min (major), $t_R$ = 45.53 min (minor) [for major isomer]; $t_R$ = 53.30 min (major), $t_R$ = 65.44 min (minor) [for minor isomer]; **$[\alpha]_D^{25}$ = +23.9° (*c* = 0.34 g/100 mL, $CHCl_3$,**

**89% *ee*);** IR (Neat): $\nu_{max}$ 3294 (N*H*), 2960, 2891, 1710 (C=O), 1589, 1552 ($NO_2$), 1517, 1476, 1452, 1378, 1302, 1217, 1121, 1046 and 734 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.86 (1H, br s), 7.68 (1H, br s), 7.45-7.28 (6H, m), 7.16-7.13 (1H, m), 7.04 (1H, dd, *J* = 8.0, 1.2 Hz), 5.23 (2H, s), 4.87 (1H, dd, *J* = 13.2, 6.4 Hz), 4.50 (1H, dd, *J* = 13.6, 8.8 Hz), 4.25 (1H, q, *J* =7.6 Hz), 4.05-3.96 (2H, m), 3.93-3.88 (2H, m), 3.04-2.98 (1H, m), 2.69-2.53 (1H, m), 2.50-2.44 (1H, m), 2.12-1.70 (3H, m), 1.59 (1H, t, *J* = 12.4 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 210.8 (C, *C*=O), 154.5 (C), 136.5 (C), 136.3 (C), 129.1 (C), 128.5 (3 x CH), 128.4 (CH), 128.2 (2 x CH), 128.1 (CH), 126.8 (CH), 125.5 (CH), 106.8 (C), 78.2 ($CH_2$), 67.0 ($CH_2$), 64.8 ($CH_2$), 64.5 ($CH_2$), 48.8 (CH), 38.1 ($CH_2$), 37.4 ($CH_2$), 35.2 (CH), 34.3 ($CH_2$); HRMS m/z 477.1639 (M + Na), calcd for $C_{24}H_{26}N_2O_7Na$ 477.1638.

**benzyl (2-((1*R*)-1-((1*S*)-5-methyl-2-oxocyclohexyl)-2-nitroethyl)phenyl)carbamate (50ag):**

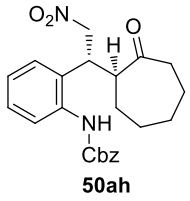


**50ag**

Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 220 nm), $t_R$ = 46.54 min (major), $t_R$ = 51.12 min (minor) [for major isomer]; $t_R$ = 39.14 min (minor), $t_R$ = 41.57 min (major) [for minor isomer]; **$[\alpha]_D^{25}$ = –5.7° (*c* = 1.0 g/100 mL, $CHCl_3$, 96% *ee*);** IR (Neat): $\nu_{max}$ 3313 (N*H*), 2956, 1702 (C=O), 1551 ($NO_2$), 1514, 1452, 1377, 1213, 1044, 911 and 733 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 1.2:1 ratio of isomers) δ 7.85 (2H, br s, 2 x N*H*), 7.68 (1H, br s), 7.61 (1H, br s), 7.46-7.45 (2H, m), 7.46-7.45 (2H, m), 7.42-7.38 (2H, m), 7.42-7.38 (2H, m), 7.37-7.33 (1H, m), 7.37-7.33 (1H, m), 7.32-7.25 (1H, m), 7.32-7.25 (1H, m), 7.24-7.20 (1H, m), 7.19-7.13 (1H, m), 7.10 (1H, dd, *J* = 8.0, 1.5 Hz), 7.07 (1H, dd, *J* = 7.5, 1.0 Hz), 5.25 (2H, s), 5.24 (2H, s), 4.97 (1H, dd, *J* = 13.5, 6.5 Hz), 4.82 (1H, dd, *J* = 13.5, 5.5 Hz), 4.56 (1H, dd, *J* = 13.5, 9.5 Hz), 4.53 (1H, dd, *J* = 13.0, 7.5 Hz), 4.29-4.18 (1H, m), 4.29-4.18 (1H, m), 2.78-2.70 (1H, m), 2.78-2.70 (1H, m), 2.52-2.46 (1H, m), 2.42-2.37 (1H, m), 2.42-2.37 (1H, m), 2.32-2.29 (1H, m), 2.03-1.98 (1H, m), 2.03-1.98 (1H, m), 1.90-1.80 (1H, m), 1.90-1.80 (1H, m), 1.75 (1H, m), 1.53-1.48 (1H, m), 1.46-1.42 (2H, m), 1.41-1.16 (2H, m), 1.00 (3H, d, *J* = 7.0 Hz), 0.89 (3H, d, *J* = 6.5 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135, 1.2:1 ratio of isomers) δ 212.8 (C, *C*=O), 212.79 (C, *C*=O), 154.65 (C), 154.58 (C), 136.43 (C), 136.40 (C), 136.35 (C), 136.26 (C), 129.8 (C), 129.8 (C), 128.50 (2 x CH), 128.48 (2 x CH), 128.3

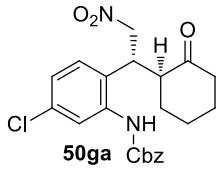
(CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 128.13 (CH), 128.13 (CH), 128.08 (CH), 128.08 (CH), 127.0 (CH), 127.0 (CH), 126.4 (CH), 126.3 (CH), 126.2 (CH), 126.2 (CH), 78.35 ($CH_2$), 78.26 ($CH_2$), 67.1 ($CH_2$), 66.9 ($CH_2$), 51.6 (CH), 49.2 (CH), 41.6 ($CH_2$), 39.2 ($CH_2$), 38.3 ($CH_2$), 36.8 ($CH_2$), 35.9 (CH), 35.5 (CH), 35.6 ($CH_2$), 33.5 ($CH_2$), 32.0 (CH), 26.7 (CH), 20.9 ($CH_3$), 18.5 ($CH_3$); HRMS m/z 411.1925 (M + Na), calcd for $C_{23}H_{26}N_2O_5Na$ 411.1920.

**benzyl (2-((*R*)-2-nitro-1-((*S*)-2-oxocycloheptyl)ethyl)phenyl)carbamate (50ah):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 27.78 min (minor), $t_R$ = 35.39 min (major) [for major isomer]; $t_R$ = 37.74 min (minor), $t_R$ = 47.51 min (major) [for minor isomer]; **$[\alpha]_D^{25}$ = –17.4° (*c* = 0.23 g/100 mL, $CHCl_3$, 92% *ee*)**; IR (Neat): $\nu_{max}$ 3306 (N*H*), 2926, 2856, 1697 (C=O), 1551 ($NO_2$), 1515, 1452, 1377, 1298, 1215, 1044, 752 and 734 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.58 (1H, br s), 7.43-7.22 (6H, m), 7.21 (1H, t, *J* = 7.2 Hz), 7.15-7.05 (2H, m), 5.22 (2H, s), 4.73 (1H, dd, *J* = 12.0, 5.6 Hz) 4.56 (1H, dd, *J* = 13.6, 9.6 Hz), 4.07 (1H, dt, *J* = 10.4, 6.4 Hz), 2.91 (1H, dt, *J* = 10.0, 3.6 Hz), 2.72-2.43 (1H, m), 2.13-1.79 (2H, m), 1.73-1.50 (3H, m), 1.42-1.08 (4H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 214.6 (C, *C*=O), 154.7 (C), 136.2 (C), 136.1 (C), 131.6 (C), 128.5 (3 x CH), 128.3 (CH), 128.3 (2 x CH), 128.2 (2 x CH), 126.4 (CH), 78.2 ($CH_2$), 67.2 ($CH_2$), 53.9 (CH), 43.4 ($CH_2$), 37.5 (CH), 29.0 ($CH_2$), 28.5 ($CH_2$), 28.49 ($CH_2$), 23.7 ($CH_2$); HRMS m/z 433.1741 (M + Na), calcd for $C_{23}H_{26}N_2O_5Na$ 433.1739.



**50ah**

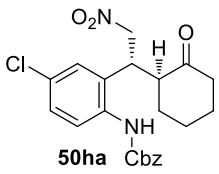
**benzyl (5-chloro-2-((*R*)-2-nitro-1-((*S*)-2-oxocyclohexyl)ethyl)phenyl)carbamate (50ga):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u cellulose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 220 nm), $t_R$ = 18.77 min (major), $t_R$ = 32.59 min (minor) [for major isomer]; $t_R$ = 20.69 min (major), $t_R$ = 22.82 min (minor) [for minor isomer]; **$[\alpha]_D^{25}$ = –6.1° (*c* = 0.44 g/100 mL, $CHCl_3$, 99% *ee*);** IR (Neat): $\nu_{max}$ 3298 (N*H*), 2969, 2929, 2858, 1737 (C=O), 1697, 1577, 1553 ($NO_2$), 1513, 1473, 1445, 1414, 1260, 1211, 1085, 1060, 903, 811 and 734 $cm^{-1}$; $^1H$ NMR



**50ga**

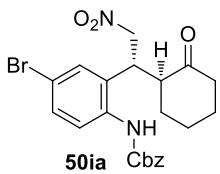
($CDCl_3$) δ 7.89 (1H, br s, N*H*), 7.77 (1H, br s), 7.44 (2H, d, *J* = 7.5 Hz), 7.38 (2H, br t, *J* = 7.5 Hz), 7.35-7.32 (1H, m), 7.11 (1H, dd, *J* = 8.5, 2.0 Hz), 6.97 (1H, d, *J* = 8.5 Hz), 5.23 (2H, q, *J* = 12 Hz), 4.92 (1H, dd, *J* = 13.5, 6.0 Hz), 4.48 (1H, dd, *J* = 13.5, 8.5 Hz), 4.15 (1H, q, *J* = 6.5 Hz), 2.62-2.57 (1H, m), 2.46-2.43 (1H, m), 2.35-2.29 (1H, m), 2.07-2.03 (1H, m), 1.88-1.80 (2H, m), 1.57-1.50 (2H, m), 1.26-1.13 (1H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 212.1 (C, *C*=O), 154.2 (C), 137.7 (C), 136.0 (C), 133.8 (C), 130.1 (C), 128.5 (2 x CH), 128.3 (3 x CH), 128.0 (CH), 125.4 (CH), 125.2 (CH), 78.0 ($CH_2$), 67.2 ($CH_2$), 52.6 (CH), 42.4 ($CH_2$), 35.3 (CH), 31.3 ($CH_2$), 27.7 ($CH_2$), 25.0 ($CH_2$); HRMS m/z 453.1192 (M + Na), calcd for $C_{22}H_{23}ClN_2O_5Na$ 453.1193.

**benzyl (4-chloro-2-((*R*)-2-nitro-1-((*S*)-2-oxocyclohexyl)ethyl)phenyl)carbamate (50ha):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u cellulose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 18.91 min (major), $t_R$ = 26.06 min (minor); **$[\alpha]_D^{25}$ = –0.3° (*c* = 0.40 g/100 mL, $CHCl_3$, 99% *ee*);** IR (Neat): $\nu_{max}$ 3299 (N*H*), 2942, 2866, 1703 (C=O), 1552 ($NO_2$), 1509, 1453, 1377, 1290, 1218, 1132, 1046, 907, 825 and 733 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.70 (1H, br s), 7.62 (1H, br s), 7.42-7.32 (5H, m), 7.26-7.23 (1H, m), 7.06-7.02 (1H, m), 5.26-5.18 (2H, m), 4.95 (1H, dd, *J* = 14.0, 6.4 Hz), 4.48 (1H, dd, *J* = 13.6, 8.8 Hz), 4.16 (1H, q, *J* = 6.8 Hz), 2.62-2.56 (1H, m), 2.47-2.44 (1H, m), 2.37-2.29 (1H, m), 2.07-2.04 (1H, m), 1.89-1.82 (2H, m), 1.65-1.52 (2H, m), 1.27-1.17 (1H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 211.9 (C, *C*=O), 154.4 (C), 136.0 (C), 135.1 (C), 132.1 (C), 130.9 (C), 128.5 (2 x CH), 128.4 (CH), 128.3 (3 x CH), 127.1 (CH), 126.8 (CH), 77.9 ($CH_2$), 67.2 ($CH_2$), 52.5 (CH), 42.4 ($CH_2$), 35.8 (CH), 31.5 ($CH_2$), 27.8 ($CH_2$), 25.0 ($CH_2$); HRMS m/z 453.1193 (M + Na), calcd for $C_{22}H_{23}ClN_2O_5Na$ 453.1193.



**50ha**

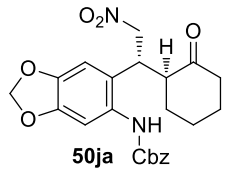
**benzyl (4-bromo-2-((*R*)-2-nitro-1-((*S*)-2-oxocyclohexyl)ethyl)phenyl)carbamate (50ia):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 220 nm), $t_R$ = 12.35 min (major), $t_R$ = 83.36 min (minor) [for major isomer]; $t_R$ = 15.77 min (major), $t_R$ = 34.13 min (minor) [for minor isomer]; **$[\alpha]_D^{25}$ = –8.2° (*c* = 0.50 g/100 mL, $CHCl_3$, 99% *ee*);** IR (Neat):



**50ia**

$\nu_{max}$ 3305 (N*H*), 2953, 2920, 2850, 1703 (C=O), 1552 ($NO_2$), 1508, 1454, 1377, 1291, 1218, 1045, 734 and 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.72 (1H, br s), 7.56 (1H, br s), 7.42-7.30 (6H, m), 7.17 (1H, s), 5.22 (2H, s), 4.94 (1H, dd, *J* = 13.6, 6.0 Hz), 4.47 (1H, dd, *J* = 14.4, 9.6 Hz), 4.14 (1H, q, *J* = 6.8 Hz), 2.61-2.57 (1H, m), 2.46-2.43 (1H, m), 2.36-2.28 (1H, m), 2.08-2.05 (1H, m), 1.87-1.80 (2H, m), 1.56 (2H, t, *J* = 10.8 Hz), 0.97-0.83 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 211.9 (C, *C*=O), 154.4 (C), 136.0 (C), 135.7 (C), 132.3 (C), 131.4 (CH), 129.8 (CH), 128.5 (2 x CH), 128.3 (3 x CH), 127.4 (CH), 118.6 (C), 77.9 ($CH_2$), 67.2 ($CH_2$), 52.6 (CH), 42.4 ($CH_2$), 35.7 (CH), 31.4 ($CH_2$), 27.8 ($CH_2$), 25.0 ($CH_2$); HRMS m/z 497.0683 (M + Na), calcd for $C_{22}H_{23}BrN_2O_5Na$ 497.0688.

**benzyl (6-((*R*)-2-nitro-1-((*S*)-2-oxocyclohexyl)ethyl)benzo[*d*][1,3]dioxol-5-yl)carbamate (50ja):** Prepared following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u cellulose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 220 nm), $t_R$ = 39.31min (major), $t_R$ = 45.36 min (minor); **$[\alpha]_D^{25}$ = –2.0° (*c* = 0.20 g/100 mL, $CHCl_3$, 99% *ee*)**; IR (Neat): $\nu_{max}$ 3366 (N*H*), 2931, 2863, 1705 (C=O), 1552 ($NO_2$), 1506, 1487, 1379, 1216 and 1036 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.42-7.31 (6H, m), 7.02 (1H, br s), 6.52 (1H, s), 5.96-5.93 (2H, m), 5.24-5.16 (2H, m), 4.95 (1H, dd, *J* = 13.6, 5.6 Hz), 4.44 (1H, dd, *J* = 13.6, 10.0 Hz), 4.09 (1H, dt, *J* = 8.8, 5.6 Hz), 2.56-2.49 (1H, m), 2.45-2.41 (1H, m), 2.36-2.23 (1H, m), 2.10-2.03 (1H, m), 1.94-1.79 (2H, m), 1.68-1.37 (2H, m), 1.21-1.15 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 212.1 (C, *C*=O), 154.9 (C), 147.1 (C), 146.2 (C), 136.2 (C), 130.1 (C), 128.5 (3 x CH), 128.2 (2 x CH), 128.2 (CH), 107.8 (C), 105.5 (CH), 101.7 ($CH_2$), 78.3 ($CH_2$), 67.1 ($CH_2$), 52.7 (CH), 42.6 ($CH_2$), 36.4 (CH), 31.9 ($CH_2$), 28.0 ($CH_2$), 25.1 ($CH_2$); HRMS m/z 463.1479 (M + Na), calcd for $C_{23}H_{24}N_2O_7Na$ 463.1481.

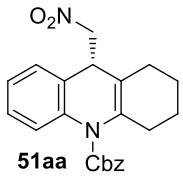


**50ja**

**Note:** In $^{13}C$ NMR spectrum of compounds **50aa**, **50ba**, **50ca**, **50ea**, **50ac**, **50ad**, **50ae**, **50af**, **50ag**, **50ah**, **50ga**, **50ha**, **50ia** and **50ja**; aromatic quaternary carbon attached to the nitrogen atom (*C*-N) shows poor resolution even after more than 10000 scans in the solvent system of $CDCl_3$.

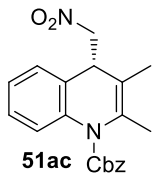
**2b. General procedure for the acid catalyzed cyclization:** In an ordinary glass vial equipped with a magnetic stirring bar, to a solution of compound **50** (0.1 mmol, 1.0 equiv) in DCM (2.0 mL) was added trifluoroacetic acid (0.3 mmol, 3.0 equiv) at 0 °C then brought to room temperature, then the reaction was monitored using TLC. After completion the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $NaSO_4$, and concentrated. Pure products **51** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

**(*R*)-benzyl 9-(nitromethyl)-1,2,3,4-tetrahydroacridine-10(9*H*)-carboxylate (51aa):** Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 18.45 min (minor), $t_R$ = 22.82 min (major); **$[\alpha]_D^{25}$ = +79.7° (*c* = 0.24 g/100 mL, $CHCl_3$, 98% *ee*);** IR (Neat): $\nu_{max}$ 2940, 1710 (C=O), 1550 ($NO_2$), 1488, 1378, 1316, 1275, 1260 and 1236 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.66 (1H, d, *J* = 8.0 Hz), 7.37-7.25 (6H, m), 7.16-7.12 (2H, m), 5.26 (2H, ABq, *J* = 12.4 Hz), 4.31 (1H, dd, *J* = 12.0, 6.0 Hz), 4.15 (1H, dd, *J* = 12.0, 9.2 Hz), 3.82 (1H, dd, *J* = 8.8, 6.0 Hz), 2.97-2.93 (1H, m), 2.30-2.25 (1H, m), 2.17-2.04 (2H, m), 1.80-1.59 (3H, m), 1.47-1.41 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 153.1 (C), 138.9 (C), 136.8 (C), 135.9 (C), 130.5 (C), 128.6 (2 x CH), 128.2 (CH), 127.8 (2 x CH), 127.3 (CH), 127.2 (CH), 125.5 (CH), 124.6 (CH), 123.9 (C), 77.4 ($CH_2$), 67.9 ($CH_2$), 43.3 (CH), 28.5 ($CH_2$), 28.3 ($CH_2$), 22.6 ($CH_2$), 22.2 ($CH_2$); HRMS m/z 401.1476 (M + Na), calcd for $C_{22}H_{22}N_2O_4Na$ 401.1477.



**51aa**

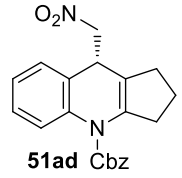
**(*R*)-benzyl 2,3-dimethyl-4-(nitromethyl)quinoline-1(4*H*)-carboxylate (51ac):** Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 8.68 min (minor), $t_R$ = 10.54 min (major); **$[\alpha]_D^{25}$ = +165.2° (*c* = 0.06 g/100 mL, $CHCl_3$, 98% *ee*)**; IR (Neat): $\nu_{max}$ 3034, 2927, 2847, 1708 (C=O), 1549 ($NO_2$), 1488, 1376, 1319, 1251, 1217,



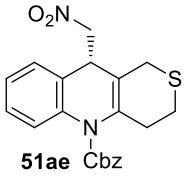
**51ac**

1057 and 765 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.65 (1H, d, *J* = 8.0 Hz), 7.39-7.27 (6H, m), 7.17-7.11 (2H, m), 5.26 (2H, br s), 4.31 (1H, dd, *J* = 12.0, 6.0 Hz), 4.12 (1H, dd, *J* = 12.0, 9.2 Hz), 3.90 (1H, dd, *J* = 9.2, 6.4 Hz), 2.07 (3H, d, *J* = 0.8 Hz, olefinic-C*H*$_3$), 1.85 (3H, d, *J* = 0.8 Hz, olefinic-C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 153.1 (C), 138.8 (C), 135.9 (C), 134.1 (C), 130.8 (C), 128.6 (2 x CH), 128.3 (CH), 128.0 (2 x CH), 127.2 (CH), 127.1 (CH), 125.6 (CH), 124.5 (CH), 122.1 (C), 77.0 ($CH_2$), 68.0 ($CH_2$), 44.5 (CH), 17.9 ($CH_3$), 17.6 ($CH_3$); HRMS m/z 375.1312 (M + Na), calcd for $C_{20}H_{20}N_2O_4Na$ 375.1321.

**(*R*)-benzyl 2,3-dimethyl-4-(nitromethyl)quinoline-1(4*H*)-carboxylate (51ad):** Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 7.86 min (minor), $t_R$ = 10.38 min (major); **$[\alpha]_D^{25}$ = +112.2° (*c* = 0.3 g/100 mL, $CHCl_3$, 98% *ee*)**; IR (Neat): $\nu_{max}$ 2962, 1715 (C=O), 1551 ($NO_2$), 1487, 1456, 1327, 1301, 1264, 1221, 1133, 1076 and 1024 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.87 (1H, d, *J* = 8.5 Hz), 7.42-7.39 (4H, m), 7.38-7.33 (1H, m), 7.29-7.26 (1H, m), 7.16-7.12 (2H, m), 5.29 (2H, q, *J* = 12.0 Hz), 4.38 (1H, dd, *J* = 12.0, 7.5 Hz), 4.32 (1H, dd, *J* = 11.5, 7.0 Hz), 4.20 (1H, t, *J* = 7.5 Hz), 3.20-3.16 (1H, m), 2.54-2.47 (2H, m), 2.33-2.28 (1H, m), 2.05-1.95 (2H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 152.9 (C), 139.8 (C), 138.6 (C), 135.7 (C), 128.7 (2 x CH), 128.6 (C), 128.4 (CH), 128.3 (2 x CH), 128.1 (CH), 127.3 (CH), 125.4 (CH), 124.4 (C), 123.9 (CH), 78.7 ($CH_2$), 68.2 ($CH_2$), 39.9 (CH), 34.3 ($CH_2$), 31.9 ($CH_2$), 23.2 ($CH_2$); HRMS m/z 387.1321 (M + Na), calcd for $C_{21}H_{20}N_2O_4Na$ 387.1321.

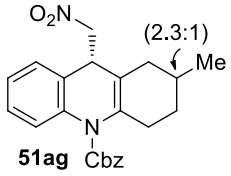



**(*S*)-benzyl 10-(nitromethyl)-3,4-dihydro-1*H*-thiopyrano[4,3-b]quinoline-5(10*H*)-carboxylate (51ae):** Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 15.31 min (minor), $t_R$ = 17.44 min (major); **$[\alpha]_D^{25}$ = +42.5° (*c* = 0.46 g/100 mL, $CHCl_3$, 96% *ee*)**; IR (Neat): $\nu_{max}$ 2920, 1708 (C=O), 1548 ($NO_2$), 1487, 1422, 1377, 1321, 1290, 1236, 1143, 1023, 909 and 729 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ



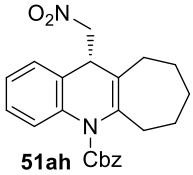
7.64 (1H, d, *J* = 8.0 Hz), 7.42-7.25 (6H, m), 7.19-7.12 (2H, m), 5.27 (2H, s), 4.33 (1H, dd, *J* = 12.0, 6.0 Hz), 4.16 (1H, dd, *J* = 12.4, 9.2 Hz), 3.88 (1H, dd, *J* = 9.2, 6.4 Hz), 3.38-3.27 (3H, m), 2.80-2.74 (1H, m), 2.63-2.57 (1H, m), 2.42-2.36 (1H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 152.9 (C), 138.5 (C), 137.9 (C), 135.6 (C), 130.2 (C), 128.6 (2 x CH), 128.4 (CH), 128.0 (2 x CH), 127.5 (CH), 127.2 (CH), 125.9 (CH), 124.6 (CH), 122.0 (C), 76.9 ($CH_2$), 68.2 ($CH_2$), 43.7 (CH), 30.2 ($CH_2$), 28.2 ($CH_2$), 24.8 ($CH_2$); HRMS m/z 419.1041 (M + Na), calcd for $C_{21}H_{20}N_2O_4SNa$ 419.1041.

**(9*R*)-benzyl 2-methyl-9-(nitromethyl)-1,2,3,4-tetrahydroacridine-10(9*H*)-carboxylate (51ag):** Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 220 nm), $t_R$ = 8.88 min (minor), $t_R$ = 9.88 min (major) [for minor isomer]; $t_R$ = 9.45 min (minor), $t_R$ = 10.77 min (major) [for major isomer]; **$[\alpha]_D^{25}$ = +57.5° (*c* = 0.89 g/100 mL, $CHCl_3$, 97% *ee*)**; IR (Neat): $\nu_{max}$ 2952, 2918, 2876, 1709 (C=O), 1549 ($NO_2$), 1487, 1455, 1377, 1320, 1295, 1234, 1189, 1143, 1062, 1021, and 908 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 2.3:1 ratio) δ 7.67 (1H, d, *J* = 8.0 Hz), 7.64 (1H, d, *J* = 8.0 Hz), 7.38-7.29 (6H, m), 7.29-7.24 (6H, m), 7.14-7.11 (4H, m), 5.27 (2H, m), 5.26 (2H, m), 4.30 (1H, dd, *J* = 12.0, 6.0 Hz), 4.27 (1H, dd, *J* = 12.0, 6.5 Hz), 4.16 (1H, dd, *J* = 12.0, 9.0 Hz), 4.13 (1H, dd, *J* = 12.0, 9.0 Hz), 3.81 (1H, t, *J* = 8.0 Hz), 3.80 (1H, t, *J* = 6.5 Hz), 3.11-3.08 (1H, m), 3.01-2.94 (1H, m), 2.30-2.27 (1H, m), 2.23-2.18 (1H, m), 2.14-2.10 (1H, m), 2.04-1.97 (1H, m), 1.80-1.72 (4H, m), 1.68-1.61 (1H, m), 1.47-1.44 (1H, m), 1.12-1.07 (2H, m), 0.99 (3H, d, *J* = 5.2 Hz), 0.98 (3H, d, *J* = 4.8 Hz); $^{13}$C NMR ($CDCl_3$, DEPT-135, 2.3:1 ratio) δ 153.2 (C), 153.0 (C), 139.0 (C), 138.9 (C), 136.6 (C), 136.4 (C), 135.93 (C), 135.91 (C), 131.0 (C), 130.2 (C), 128.6 (4 x CH), 128.2 (CH), 128.19 (CH), 127.9 (2 x CH), 127.7 (2 x CH), 127.3 (CH), 127.2 (CH), 127.1 (2 x CH), 125.5 (CH), 125.4 (CH), 124.8 (CH), 124.4 (CH), 123.7 (C), 123.6 (C), 77.45 ($CH_2$), 77.41 ($CH_2$), 67.9 (2 x $CH_2$), 43.8 (CH), 43.0 (CH), 36.9 ($CH_2$), 36.7 ($CH_2$), 31.2 ($CH_2$), 30.0 ($CH_2$), 29.2 ($CH_2$), 28.6 (CH), 27.9 (CH), 26.4 ($CH_2$), 21.6 ($CH_3$), 20.4 ($CH_3$); HRMS m/z 415.1630 (M + Na), calcd for $C_{23}H_{24}N_2O_4Na$ 415.1634.



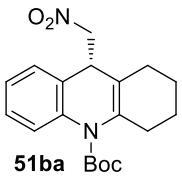
**51ag**

**(*R*)-benzyl 11-(nitromethyl)-6,7,8,9,10,11-hexahydro-5*H*-cyclohepta[*b*]quinoline-5-carboxylate (51ah):** Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 7.88 min (minor), $t_R$ = 10.20 min (major); **$[\alpha]_D^{25}$ = +140.2° (*c* = 0.06 g/100 mL, $CHCl_3$, 94% *ee*)**; IR (Neat): $\nu_{max}$ 2920, 2849, 1713 (C=O), 1551 ($NO_2$), 1488, 1456, 1378, 1316, 1275, 1257, 1223, 1081, 1026, 909 and 750 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.66 (1H, d, *J* = 8.0 Hz), 7.37-7.26 (6H, m), 7.16-7.09 (2H, m), 5.26 (2H, br s), 4.28 (1H, dd, *J* = 12.0, 6.8 Hz), 4.15 (1H, dd, *J* = 11.6, 8.4 Hz), 3.92 (1H, dd, *J* = 8.0, 7.2 Hz), 2.61-2.56 (1H, m), 2.38-2.26 (3H, m), 1.87-1.81 (1H, m), 1.69-1.64 (1H, m), 1.62-1.48 (3H, m), 1.43-1.34 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 153.3 (C), 141.6 (C), 138.8 (C), 135.8 (C), 131.0 (C), 128.7 (C), 128.6 (2 x CH), 128.3 (CH), 128.2 (2 x CH), 127.2 (CH), 127.0 (CH), 125.5 (CH), 124.3 (CH), 77.5 ($CH_2$), 68.1 ($CH_2$), 46.1 (CH), 34.1 ($CH_2$), 33.7 ($CH_2$), 31.8 ($CH_2$), 26.7 ($CH_2$), 25.8 ($CH_2$); HRMS m/z 415.1632 (M + Na), calcd for $C_{23}H_{24}N_2O_4Na$ 415.1634.



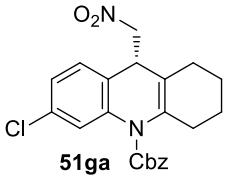
**51ah**

**(*R*)-*tert*-butyl 9-(nitromethyl)-1,2,3,4-tetrahydroacridine-10(9*H*)-carboxylate (51ba):** Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 99:1, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 13.78 min (minor), $t_R$ = 21.43 min (major); **$[\alpha]_D^{25}$ = +99.1° (*c* = 0.19 g/100 mL, $CHCl_3$, 99% *ee*)**; IR (Neat): $\nu_{max}$ 2977, 2938, 1704 (C=O), 1551 ($NO_2$), 1485, 1367, 1319, 1274, 1238, 1165, 1145, 1019, 858 and 754 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.64 (1H, d, *J* = 8.4 Hz), 7.29-7.24 (1H, m), 7.12 (2H, d, *J* = 4.4 Hz), 4.34 (1H, dd, *J* = 12.0, 6.4 Hz), 4.18 (1H, dd, *J* = 12.0, 9.2 Hz), 3.81 (1H, dd, *J* = 8.8, 6.4 Hz), 2.96-2.88 (1H, m), 2.30-2.26 (1H, m), 2.18-2.04 (2H, m), 1.83-1.76 (1H, m), 1.75-1.62 (2H, m), 1.52 (9H, s), 1.51-1.42 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 152.3 (C), 139.4 (C), 137.1 (C), 130.6 (C), 127.1 (CH), 127.0 (CH), 125.1 (CH), 124.7 (CH), 123.2 (C), 82.0 (C), 77.6 ($CH_2$), 43.4 (CH), 28.7 ($CH_2$), 28.4 ($CH_2$), 28.2 (3 x $CH_3$), 22.7 ($CH_2$), 22.3 ($CH_2$); HRMS m/z 367.1635 (M + Na), calcd for $C_{19}H_{24}N_2O_4Na$ 367.1634.



**51ba**

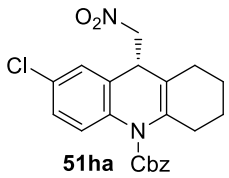
**(*R*)-benzyl 6-chloro-9-(nitromethyl)-1,2,3,4-tetrahydroacridine-10(9*H*)-carboxylate (51ga):**



**51ga**

Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 7.63 min (minor), $t_R$ = 8.42 min (major); **$[\alpha]_D^{25}$ = +92.7° (*c* = 0.34 g/100 mL, $CHCl_3$, 97% *ee*)**; IR (Neat): $\nu_{max}$ 2938, 2861, 1711 (C=O), 1679, 1548 ($NO_2$), 1456, 1420, 1376, 1312, 1233, 1194, 1038, 907, 874 and 761 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.71 (1H, d, *J* = 2.0 Hz), 7.41-7.31 (5H, m), 7.12 (1H, dd, *J* = 8.4, 2.0 Hz), 7.04 (1H, d, *J* = 8.0 Hz), 5.27 (2H, ABq, *J* = 12.4 Hz), 4.30 (1H, dd, *J* = 12.4, 6.0 Hz), 4.11 (1H, dd, *J* = 12.4, 9.6 Hz), 3.79 (1H, dd, *J* = 9.2, 5.6 Hz), 2.96-2.88 (1H, m), 2.29-2.25 (1H, m), 2.17-2.11 (1H, m), 2.06-2.02 (1H, m), 1.80-1.59 (3H, m), 1.46-1.41 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 152.7 (C), 139.7 (C), 136.6 (C), 135.6 (C), 133.0 (C), 128.8 (C), 128.7 (2 x CH), 128.4 (CH), 128.2 (CH), 127.9 (2 x CH), 125.6 (CH), 124.8 (CH), 123.6 (C), 77.0 ($CH_2$), 68.2 ($CH_2$), 42.7 (CH), 28.5 ($CH_2$), 28.2 ($CH_2$), 22.6 ($CH_2$), 22.1 ($CH_2$); HRMS m/z 435.1087 (M + Na), calcd for $C_{22}H_{21}ClN_2O_4Na$ 435.1088.

**(*R*)-benzyl 7-chloro-9-(nitromethyl)-1,2,3,4-tetrahydroacridine-10(9*H*)-carboxylate (51ha):**

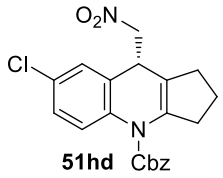


**51ha**

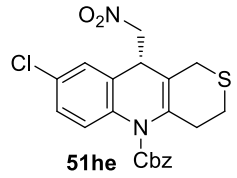
Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 8.54 min (minor), $t_R$ = 18.72 min (major); **$[\alpha]_D^{25}$ = +35.7° (*c* = 0.31 g/100 mL, $CHCl_3$, 99% *ee*)**; IR (Neat): $\nu_{max}$ 2939, 2851, 1713 (C=O), 1678, 1551 ($NO_2$), 1484, 1377, 1312, 1235, 1202, 1151, 1027, 824 and 762 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.59 (1H, d, *J* = 8.8 Hz), 7.40-7.31 (5H, m), 7.23 (1H, dd, *J* = 8.8, 2.4 Hz), 7.13 (1H, d, *J* = 2.4 Hz), 5.26 (2H, s), 4.29 (1H, dd, *J* = 12.4, 6.0 Hz), 4.14 (1H, dd, *J* = 12.4, 9.2 Hz), 3.77 (1H, dd, *J* = 9.2, 6.4 Hz), 2.96-2.89 (1H, m), 2.29-2.24 (1H, m), 2.17-2.03 (2H, m), 1.80-1.73 (1H, m), 1.71-1.70 (1H, m), 1.67-1.57 (1H, m), 1.47-1.41 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 152.8 (C), 137.5 (C), 136.9 (C), 135.7 (C), 132.2 (C), 130.8 (C), 128.7 (2 x CH), 128.4 (CH), 128.0 (2 x CH), 127.3 (CH), 127.2 (CH), 125.7 (CH), 123.5 (C), 77.0 ($CH_2$), 68.1 ($CH_2$), 42.9 (CH), 28.5 ($CH_2$), 28.3

($CH_2$), 22.6 ($CH_2$), 22.1 ($CH_2$); HRMS m/z 435.1087 (M + Na), calcd for $C_{22}H_{21}ClN_2O_4Na$ 435.1088.

**(*R*)-benzyl 7-chloro-9-(nitromethyl)-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-4(9*H*)-carboxylate (51hd):** Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 9.33 min (minor), $t_R$ = 30.86 min (major); **$[\alpha]_D^{25}$ = +41.8° (*c* = 0.46 g/100 mL, $CHCl_3$, 99% *ee*)**; IR (Neat): $\nu_{max}$ 2955, 2851, 1715 (C=O), 1681, 1548 ($NO_2$), 1373, 1321, 1299, 1246, 1220, 1099, 1022, 820 and 749 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.82 (1H, d, *J* = 8.8 Hz), 7.40-7.35 (5H, m), 7.23 (1H, dd, *J* = 8.8, 2.4 Hz), 7.12 (1H, d, *J* = 2.4 Hz), 5.28 (2H, q, *J* = 12.4 Hz), 4.37 (1H, dd, *J* = 12.4, 7.6 Hz), 4.32 (1H, dd, *J* = 12.0, 7.2 Hz), 4.15 (1H, t, *J* = 7.2 Hz), 3.20-3.12 (1H, m), 2.54-2.44 (2H, m), 2.34-2.26 (1H, m), 2.07-1.93 (2H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 152.6 (C), 139.8 (C), 137.2 (C), 135.3 (C), 130.6 (C), 130.2 (C), 128.7 (2 x CH), 128.5 (CH), 128.3 (2 x CH), 127.8 (CH), 127.3 (CH), 125.1 (CH), 123.9 (C), 78.2 ($CH_2$), 68.4 ($CH_2$), 39.5 (CH), 34.3 ($CH_2$), 31.7 ($CH_2$), 23.1 ($CH_2$); HRMS m/z 421.0931 (M + Na), calcd for $C_{21}H_{19}ClN_2O_4Na$ 421.0931.

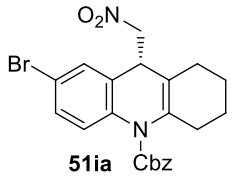



**(*S*)-benzyl 8-chloro-10-(nitromethyl)-3,4-dihydro-1*H*-thiopyrano[4,3-*b*]quinoline-5(10*H*)-carboxylate (51he):** Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 12.67 min (minor), $t_R$ = 22.20 min (major); **$[\alpha]_D^{25}$ = +68.4° (*c* = 0.16 g/100 mL, $CHCl_3$, 96% *ee*)**; IR (Neat): $\nu_{max}$ 2971, 2918, 2857, 1713 (C=O), 1679, 1550 ($NO_2$), 1483, 1376, 1284, 1235, 1193, 1147, 1103, 1025 and 732 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.57 (1H, d, *J* = 8.8 Hz), 7.41-7.32 (5H, m), 7.26 (1H, dd, *J* = 8.8, 2.4 Hz), 7.14 (1H, d, *J* = 2.4 Hz), 5.26 (2H, s), 4.32 (1H, dd, *J* = 12.8, 6.4 Hz), 4.15 (1H, dd, *J* = 12.8, 9.2 Hz), 3.84 (1H, dd, *J* = 9.2, 6.4 Hz), 3.37-3.24 (3H, m), 2.81-2.75 (1H, m), 2.63-2.57 (1H, m), 2.41-2.34 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 152.7 (C), 138.1 (C), 137.1 (C), 135.4 (C), 131.9 (C), 131.3 (C),



128.7 (2 x CH), 128.6 (CH), 128.1 (2 x CH), 127.6 (CH), 127.1 (CH), 125.9 (CH), 121.7 (C), 76.5 ($CH_2$), 68.5 ($CH_2$), 43.4 (CH), 30.3 ($CH_2$), 28.2 ($CH_2$), 24.8 ($CH_2$); HRMS m/z 453.0651 (M + Na), calcd for $C_{22}H_{19}ClN_2O_4SNa$ 453.0652.

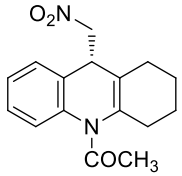
**(*R*)-benzyl 7-bromo-9-(nitromethyl)-1,2,3,4-tetrahydroacridine-10(9*H*)-carboxylate (51ia):**



**51ia**

Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 8.21 min (minor), $t_R$ = 16.76 min (major); **$[\alpha]_D^{25}$ = +28.4° (*c* = 0.36 g/100 mL, $CHCl_3$, 99% *ee*)**; IR (Neat): $\nu_{max}$ 2928, 2858, 1712 (C=O), 1679, 1550 ($NO_2$), 1481, 1377, 1311, 1284, 1235, 1152, 1111, 1027, 823 and 785 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.53 (1H, d, *J* = 8.4 Hz), 7.40-7.31 (6H, m), 7.28 (1H, d, *J* = 2.4 Hz), 5.26 (2H, s), 4.29 (1H, dd, *J* = 12.4, 6.0 Hz), 4.14 (1H, dd, *J* = 12.0, 9.2 Hz), 3.78 (1H, dd, *J* = 8.8, 6.0 Hz), 2.97-2.89 (1H, m), 2.28-2.24 (1H, m), 2.16-2.02 (2H, m), 1.80-1.70 (2H, m), 1.66-1.59 (1H, m), 1.46-1.41 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 152.8 (C), 138.0 (C), 136.9 (C), 135.7 (C), 132.5 (C), 130.2 (CH), 130.1 (CH), 128.7 (2 x CH), 128.4 (CH), 128.0 (2 x CH), 126.1 (CH), 123.5 (C), 118.5 (C), 76.9 ($CH_2$), 68.2 ($CH_2$), 42.8 (CH), 28.5 ($CH_2$), 28.3 ($CH_2$), 22.6 ($CH_2$), 22.1 ($CH_2$); HRMS m/z 479.0580 (M + Na), calcd for $C_{22}H_{21}BrN_2O_4Na$ 479.0582.

**(*R*)-1-(9-(nitromethyl)-1,2,3,4-tetrahydroacridin-10(9*H*)-yl)ethanone (51da):** Prepared following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 98-100 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 17.50 min (minor), $t_R$ = 18.77 min (major); **$[\alpha]_D^{25}$ = +37.2° (*c* = 0.07 g/100 mL, $CHCl_3$, 98% *ee*);** IR (Neat): $\nu_{max}$ 2940, 1707 (C=O), 1550 ($NO_2$), 1488, 1378, 1316, 1275, 1260 and 1236 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.39 (1H, d, *J* = 7.5 Hz), 7.31 (1H, dt, *J* = 7.0, 2.0 Hz), 7.19 (1H, dt, *J* = 7.5, 1.0 Hz), 7.16 (1H, dd, *J* = 7.5, 2.0 Hz), 4.41 (1H, dd, *J* = 12.0, 6.0 Hz), 4.14 (1H, dd, *J* = 12.0, 10.0 Hz), 3.81 (1H, dd, *J* = 10.0, 6.0 Hz), 3.07-3.00 (1H, m), 2.33-2.30 (1H, m), 2.28 (3H, s), 2.19-2.08 (2H, m), 1.86-1.80 (1H, m), 1.76-1.63 (2H, m), 1.50-1.41 (1H, m); $^{13}C$ NMR



**51da**

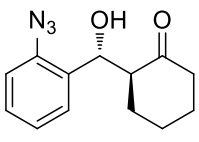
($CDCl_3$, DEPT-135) δ 169.3 (C, *C*=O), 140.2 (C), 139.3 (C), 132.2 (C), 127.9 (CH), 127.3 (CH), 126.1 (CH), 125.7 (C), 124.5 (CH), 77.0 ($CH_2$), 43.8 (CH), 28.8 ($CH_2$), 28.2 ($CH_2$), 24.1 ($CH_3$), 22.5 ($CH_2$), 22.2 ($CH_2$); HRMS m/z 309.1214 (M + Na), calcd for $C_{16}H_{18}N_2O_3Na$ 309.1215.

**3. General experimental procedures for the asymmetric List-Lerner-Barbas Aldol Reactions.**

**3a. General Procedure for L-DMTC and TFA Catalyzed LLB-A Reaction of Cyclohexanones 1a with 2-Azidobenzaldehydes 55:** In an ordinary glass vial equipped with a magnetic stirring bar, containing L-DMTC (**7t**) (9.7 mg, 0.06 mmol) in DMSO (1.0 mL, 0.3 M), was added TFA (**54c**) (9.2 µL, 0.12 mmol). After stirring for a minute, 2-azidobenzaldehyde (**55**) (0.3 mmol) and cyclohexanone (**1a**) (4.2 mmol) were added and the reaction mixture was stirred at 25 °C. Completion of the reaction was monitored using TLC. The crude reaction mixture was then worked up with aqueous $NH_4Cl$ solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure LLB-A products **56** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

**3b. General Procedure for L-Proline and Guanidinium Tetrafluoroborate Catalyzed LLB-A Reaction of Cyclohexanone 2 with 2-Azidobenzaldehyde 55:** In an ordinary glass vial equipped with a magnetic stirring bar, guanidinium tetrafluoroborate (**54g**) (6.2 mg, 0.03 mmol) and L-proline (**7a**) (5.2 mg, 0.045 mmol) were weighed together. Cyclohexanone (**1a**) (3.0 mmol) was added to the solid mixture followed by addition of 2-azidobenzaldehydes (**55**) (0.3 mmol) and the reaction mixture was stirred at 25 °C. Completion of the reaction was monitored using TLC. The crude reaction mixture was then worked up with aqueous $NH_4Cl$ solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure LLB-A products **56** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

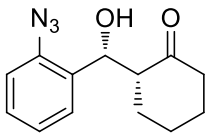
**(*S*)-2-((*R*)-(2-Azidophenyl)(hydroxy)methyl)cyclohexanone (56aa):** Prepared following the procedure **3a** and **3b** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as liquid.; Yield: 88% (64.7 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 95:5, flow rate



*anti*-(–)-**56aa**

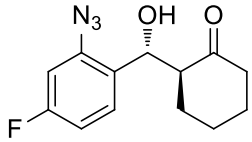
0.5 mL/min, λ = 254 nm), $t_R$ = 18.13 min (major), $t_R$ = 25.32 min (minor); $[\alpha]_D^{25}$ = –4.3° (*c* = 0.44, $CHCl_3$, 99% ee/de); IR (Neat): $\nu_{max}$ 3507 (OH), 2931, 2855, 2126 ($N_3$), 1699 (C=O), 1584, 1490, 1447, 1310 and 751 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.40 (1H, dd, *J* = 7.6, 1.2 Hz), 7.25 (1H, dt, *J* = 8.0, 1.6 Hz), 7.10 (1H, t, *J* = 7.6 Hz), 7.06 (1H, d, *J* = 8.0 Hz), 5.08 (1H, d, *J* = 8.4 Hz), 3.87 (1H, br s, O*H*), 2.64-2.58 (1H, m), 2.42-2.36 (1H, m), 2.27 (1H, dt, *J* = 12.8, 5.6 Hz), 2.02-1.97 (1H, m), 1.75-1.72 (1H, m), 1.63-1.37 (4H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 215.2 (C, *C*=O), 137.3 (C), 132.6 (C), 128.8 (CH), 128.2 (CH), 125.1 (CH), 117.8 (CH), 68.9 (CH), 57.1 (CH), 42.6 ($CH_2$), 30.4 ($CH_2$), 27.7 ($CH_2$), 24.7 ($CH_2$); HRMS m/z 268.1061 (M + Na), calcd for $C_{13}H_{15}N_3O_2Na$ 268.1062.

**(*R*)-2-((*R*)-(2-Azidophenyl)(hydroxy)methyl)cyclohexanone (56aa):** Prepared following the procedure **3a** and **3b** and purified by column chromatography using EtOAc/hexane (1:9) and isolated as solid.; Yield: 60% (44.2 mg); Mp 74-78 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 17.07 min (minor), $t_R$ = 19.64 min (major); $[\alpha]_D^{25}$ = –144.5° (*c* = 0.29, $CHCl_3$, 96% ee); IR (Neat): $\nu_{max}$ 3496 (OH), 2937, 2860, 2115 ($N_3$), 1699 (C=O), 1584, 1490, 1452, 1293, 1129, 1074, 981 and 751 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.52 (1H, dd, *J* = 8.0, 0.5 Hz), 7.30 (1H, dt, *J* = 7.5, 1.5 Hz), 7.16 (1H, dt, *J* = 7.5, 0.5 Hz), 7.12 (1H, dd, *J* = 7.5, 1.0 Hz), 5.53 (1H, d, *J* = 1.0 Hz), 3.16 (1H, s, O*H*), 2.75 (1H, m), 2.48-2.37 (2H, m), 2.11-2.06 (1H, m), 1.86-1.82 (1H, m), 1.76-1.50 (4H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 214.9 (C, *C*=O), 135.5 (C), 132.4 (C), 128.07 (CH), 128.06 (CH), 124.6 (CH), 117.6 (CH), 66.3 (CH), 54.3 (CH), 42.6 ($CH_2$), 27.9 ($CH_2$), 26.0 ($CH_2$), 24.8 ($CH_2$); HRMS m/z 268.1061 (M + Na), calcd for $C_{13}H_{15}N_3O_2Na$ 268.1062.



*syn*-(–)-**56aa**

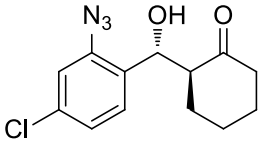
**(*S*)-2-((*R*)-(2-Azido-4-fluorophenyl)(hydroxy)methyl)cyclohexanone (56ba):** Prepared following the procedure **3a** and **3b** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as solid.; Yield: 75% (59.0 mg); Mp 64-66 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 7.27 min (major), $t_R$ = 12.40 min (minor); $[\alpha]_D^{25}$ = –0.7° (*c* = 0.86, $CHCl_3$, 99% ee, 17:1 dr);



*anti*-(–)-**56ba**

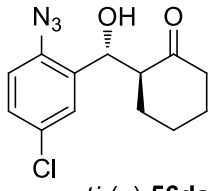
IR (Neat): $\nu_{max}$ 3457 (OH), 2959, 2920, 2849, 2120 ($N_3$), 1704 (C=O), 1594, 1457, 1375, 1299 and 959 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.45 (1H, dd, *J* = 8.4, 6.4 Hz), 6.87 (1H, dt, *J* = 8.4, 2.4 Hz), 6.84 (1H, dd, *J* = 11.6, 2.4 Hz), 5.09 (1H, d, *J* = 8.4 Hz), 3.98 (1H, s, O*H*), 2.66-2.59 (1H, m), 2.48-2.44 (1H, m), 2.33 (1H, dt, *J* = 12.8, 5.6 Hz), 2.10-2.06 (1H, m), 1.83-1.80 (1H, m), 1.72-1.39 (4H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 215.2 (C, *C*=O), 162.5 (C, d, *J* = 247.0 Hz), 138.9 (C, d, *J* = 9.0 Hz), 129.8 (CH, d, *J* = 9.0 Hz), 128.5 (C, d, *J* = 3.0 Hz), 112.3 (CH, d, *J* = 22.0 Hz), 105.0 (CH, d, *J* = 25.0 Hz), 68.4 (CH), 57.1 (CH), 42.5 ($CH_2$), 30.3 ($CH_2$), 27.7 ($CH_2$), 24.7 ($CH_2$); HRMS m/z 286.0968 (M + Na), calcd for $C_{13}H_{14}FN_3O_2Na$ 286.0968.

**(*S*)-2-((*R*)-(2-Azido-4-chlorophenyl)(hydroxy)methyl)cyclohexanone (56ca):** Prepared following the procedure **3a** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as solid.; Yield: 89% (75.0 mg); Mp 63-65 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 7.45 min (major), $t_R$ = 10.30 min (minor); $[\alpha]_D^{25}$ = –5.3° (*c* = 0.87, $CHCl_3$, 98% ee, 17:1 dr); IR (Neat): $\nu_{max}$ 3523 (OH), 2959, 2942, 2866, 2126 ($N_3$), 1688 (C=O), 1573, 1490, 1408, 1304, 1266, 1096, 1047 and 871 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.42 (1H, d, *J* = 8.4 Hz), 7.15 (1H, d, *J* = 8.0 Hz), 7.11 (1H, s), 5.09 (1H, br d, *J* = 5.6 Hz), 3.96 (1H, br d, *J* = 2.4 Hz), 2.65-2.59 (1H, m), 2.48-2.45 (1H, m), 2.33 (1H, dt, *J* = 12.8, 5.6 Hz), 2.10-2.08 (1H, m), 1.84-1.81 (1H, m), 1.72-1.47 (4H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 215.2 (C, *C*=O), 138.6 (C), 134.3 (C), 131.3 (C), 129.5 (CH), 125.4 (CH), 117.9 (CH), 68.5 (CH), 57.1 (CH), 42.6 ($CH_2$), 30.4 ($CH_2$), 27.7 ($CH_2$), 24.8 ($CH_2$); HRMS m/z 302.0673 (M + Na), calcd for $C_{13}H_{14}ClN_3O_2Na$ 302.0672.



*anti*-(–)-**56ca**

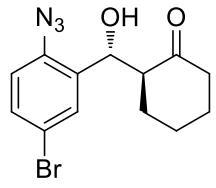
**(*S*)-2-((*R*)-(2-Azido-5-chlorophenyl)(hydroxy)methyl)cyclohexanone (56da):** Prepared following the procedure **3a** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as liquid.; Yield: 90% (76.0 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 6.53 min (major), $t_R$ = 7.72 min (minor) [for minor *syn*-isomer], $t_R$ = 10.36 min (major), $t_R$ = 12.35 min (minor) [for major *anti*-isomer]; $[\alpha]_D^{25}$ = –11.2° (*c* = 0.93, $CHCl_3$, 99% ee and 51:1 dr); IR (Neat): $\nu_{max}$ 3512 (OH), 2937, 2860,



*anti*-(–)-**56da**

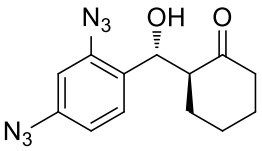
2120 ($N_3$), 2088, 1699 (C=O), 1479, 1408, 1293, 1112, 1036, 899 and 811 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.41 (1H, d, *J* = 2.4 Hz), 7.20 (1H, dd, *J* = 8.8, 2.4 Hz), 6.98 (1H, d, *J* = 8.4 Hz), 5.03 (1H, d, *J* = 8.4 Hz), 3.93 (1H, br s O*H*), 2.56-2.50 (1H, m), 2.40-2.34 (1H, m), 2.26 (1H, dt, *J* = 12.8, 6.0 Hz), 2.03-1.96 (1H, m), 1.76-1.73 (1H, m), 1.64-1.37 (4H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 214.9 (C, *C*=O), 135.8 (C), 134.4 (C), 130.6 (C), 128.7 (CH), 128.3 (CH), 118.9 (CH), 68.4 (CH), 57.1 (CH), 42.5 ($CH_2$), 30.2 ($CH_2$), 27.6 ($CH_2$), 24.6 ($CH_2$); HRMS m/z 302.0674 (M + Na), calcd for $C_{13}H_{14}ClN_3O_2Na$ 302.0672.

**(*S*)-2-((*R*)-(2-Azido-5-bromophenyl)(hydroxy)methyl)cyclohexanone (56ea):** Prepared following the procedure **3a** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as solid.; Yield: 79% (77.0 mg); Mp 99-102 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 15.44 min (major), $t_R$ = 17.93 min (minor); $[\alpha]_D^{25}$ = –13.1° (*c* = 0.60, $CHCl_3$, >99% ee, 17:1 dr); IR (Neat): $\nu_{max}$ 3457 (OH), 2937, 2866, 2126 ($N_3$), 1688 (C=O), 1474, 1293 and 1096 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.62 (1H, d, *J* = 1.6 Hz), 7.42 (1H, dd, *J* = 8.4, 2.0 Hz), 7.00 (1H, d, *J* = 8.4 Hz), 5.10 (1H, d, *J* = 8.4 Hz), 4.00 (1H, br s, O*H*), 2.63-2.57 (1H, m), 2.48-2.45 (1H, m), 2.33 (1H, dt, *J* = 12.8, 6.0 Hz), 2.11-2.07 (1H, m), 1.83-1.81 (1H, m), 1.72-1.47 (4H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 215.0 (C, *C*=O), 136.4 (C), 134.7 (C), 131.7 (CH), 131.3 (CH), 119.3 (CH), 118.3 (C), 68.4 (CH), 57.2 (CH), 42.6 ($CH_2$), 30.3 ($CH_2$), 27.6 ($CH_2$), 24.7 ($CH_2$); HRMS m/z 346.0167 (M + Na), calcd for $C_{13}H_{14}BrN_3O_2Na$ 346.0167.



*anti*-(–)-**56ea**

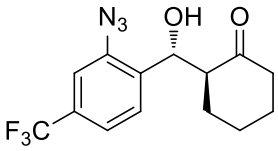
**(*S*)-2-((*R*)-(2,4-Diazidophenyl)(hydroxy)methyl)cyclohexanone (56fa):** Prepared following the procedure **3a** and **3b**. Purified by column chromatography using EtOAc/hexane (1:5) and isolated as liquid.; Yield: 41% (35.0 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 5.99 min (minor), $t_R$ = 6.55 min (major) [for minor *syn*-isomer], $t_R$ = 9.37 min (major), $t_R$ = 10.60 min (minor) [for major *anti*-isomer]; $[\alpha]_D^{25}$ = –26.5° (*c* = 0.50, $CHCl_3$, 98% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 3457 (OH), 2981, 2937, 2904, 2115 ($N_3$), 1748 (C=O), 1447, 1370, 1244, 1047, and 844 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.39 (1H, d, *J* =



*anti*-(–)-**56fa**

8.4 Hz), 6.80 (1H, dd, *J* = 8.4, 2.0 Hz), 6.66 (1H, d, *J* = 2.0 Hz), 5.02 (1H, d, *J* = 8.4 Hz), 3.88 (1H, br s, O*H*), 2.59-2.53 (1H, m), 2.41-2.38 (1H, m), 2.27 (1H, dt, *J* = 12.8, 5.6 Hz), 2.04-1.99 (1H, m), 1.77-1.74 (1H, m), 1.66-1.37 (4H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 215.2 (C, *C*=O), 140.7 (C), 138.8 (C), 129.6 (CH), 129.4 (C), 115.7 (CH), 108.3 (CH), 68.5 (CH), 57.1 (CH), 42.6 ($CH_2$), 30.4 ($CH_2$), 27.7 ($CH_2$), 24.7 ($CH_2$); HRMS m/z 309.1072 (M + Na), calcd for $C_{13}H_{14}N_6O_2Na$ 309.1076.

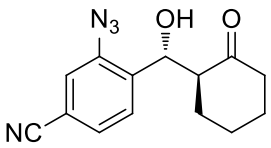
**(*S*)-2-((*R*)-(2-Azido-4-(trifluoromethyl)phenyl)(hydroxy)methyl)cyclohexanone (56ga):**




*anti*-(+)-**56ga**

Prepared following the procedure **3a** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as solid.; Yield: 85% (80.0 mg); Mp 70-72 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 9.82 min (major), $t_R$ = 12.32 min (minor); $[\alpha]_D^{25}$ = +4.5° (*c* = 1.01, $CHCl_3$, >99% ee, 17:1 dr); IR (Neat): $\nu_{max}$ 3468 (OH), 2959, 2871, 2120 ($N_3$), 1693 (C=O), 1589, 1425, 1331, 1293, 1123 and 866 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.57 (1H, d, *J* = 8.0 Hz), 7.35 (1H, br d, *J* = 8.0 Hz), 7.27 (1H, s), 5.08 (1H, d, *J* = 8.0 Hz), 4.00 (1H, br s, O*H*), 2.58-2.56 (1H, m), 2.40-2.36 (1H, m), 2.26 (1H, ddt, *J* = 13.0, 6.0, 0.5 Hz), 2.04-2.00 (1H, m), 1.77-1.75 (1H, m), 1.62-1.45 (4H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 214.9 (C, *C*=O), 138.0 (C), 136.6 (C), 131.1 (C, q, *J* = 33.7 Hz), 128.9 (CH), 123.4 (C, q, *J* = 282.5 Hz), 121.8 (CH, q, *J* = 3.7 Hz), 114.6 (CH, q, *J* = 2.5 Hz), 68.6 (CH), 57.0 (CH), 42.6 ($CH_2$), 30.5 ($CH_2$), 27.7 ($CH_2$), 24.7 ($CH_2$); HRMS m/z 336.0929 (M + Na), calcd for $C_{14}H_{14}F_3N_3O_2Na$ 336.0936.

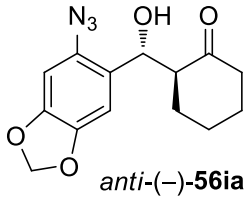
**3-Azido-4-((*R*)-hydroxy((*S*)-2-oxocyclohexyl)methyl)benzonitrile (56ha):** Prepared following the procedure **3a** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as solid.; Yield: 90% (73.0 mg); Mp 78-80 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 9.37 min (major), $t_R$ = 11.57 min (minor) [for minor *syn*-isomer], $t_R$ = 12.71 min (major), $t_R$ = 17.12 min (minor) [for major *anti*-isomer]; $[\alpha]_D^{25}$ = –1.5° (*c* = 0.96, $CHCl_3$, 99% ee, 21:1 dr); IR (Neat): $\nu_{max}$ 3425 (OH), 2942, 2866, 2236 (CN), 2110 ($N_3$), 1688 (C=O), 1567, 1501, 1414, 1293, 1041 and 888 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.63




*anti*-(–)-**56ha**

(1H, d, *J* = 8.0 Hz), 7.44 (1H, dd, *J* = 8.0, 0.8 Hz), 7.36 (1H, d, *J* = 1.2 Hz), 5.11 (1H, d, *J* = 7.2 Hz), 4.06 (1H, d, *J* = 2.4 Hz), 2.64-2.58 (1H, m), 2.44-2.41 (1H, m), 2.31 (1H, dt, *J* = 12.8, 5.6 Hz), 2.10-2.06 (1H, m), 1.83 (1H, br s), 1.71-1.49 (4H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 214.6 (C, *C*=O), 138.4 (C), 138.2 (C), 129.2 (CH), 128.4 (CH), 120.8 (CH), 117.6 (C), 112.4 (C), 68.5 (CH), 56.7 (CH), 42.5 ($CH_2$), 30.4 ($CH_2$), 27.6 ($CH_2$), 24.6 ($CH_2$); HRMS m/z 293.1014 (M + Na), calcd for $C_{14}H_{14}N_4O_2Na$ 293.1014.

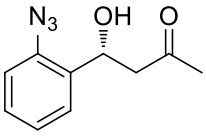
**(*S*)-2-((*R*)-(6-Azidobenzo[*d*][1,3]dioxol-5-yl)(hydroxy)methyl)cyclohexanone (56ia):**



*anti*-(–)-**56ia**

Prepared following the procedure **3a** and **3b**. Purified by column chromatography using EtOAc/hexane (1:5) and isolated as liquid.; Yield: 46% (40.0 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 16.50 min (minor), $t_R$ = 19.07 min (major); $[\alpha]_D^{25}$ = –9.0° (*c* = 0.20, $CHCl_3$, 97% ee, 17:1 dr); IR (Neat): $\nu_{max}$ 3512 (OH), 2920, 2855, 2110 ($N_3$), 1688 (C=O), 1479, 1233, 1123, 1047 and 926 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 6.93 (1H, s), 6.63 (1H, s), 5.97 (2H, dd, *J* = 4.0, 1.0 Hz), 5.12 (1H, d, *J* = 9.0 Hz), 2.58-2.52 (1H, m), 2.49-2.44 (1H, m), 2.33(1H, ddt, *J* = 14.0, 6.0, 1.0 Hz), 2.09-2.04 (1H, m), 1.83-1.80 (1H, m), 1.72-1.37 (4H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 215.4 (C, *C*=O), 148.0 (C), 145.5 (C), 130.6 (C), 125.8 (C), 107.5 (CH), 101.7 ($CH_2$), 98.7 (CH), 68.3 (CH), 57.4 (CH), 42.6 ($CH_2$), 30.2 ($CH_2$), 27.7 ($CH_2$), 24.8 ($CH_2$); HRMS m/z 312.0955 (M + Na), calcd for $C_{14}H_{15}N_3O_4Na$ 312.0960.

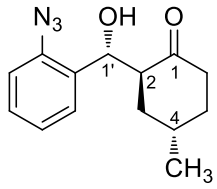
**(*R*)-4-(2-Azidophenyl)-4-hydroxybutan-2-one (56ab):**[57d] Prepared following the procedure **3a** and **3b**. Purified by column chromatography using EtOAc/hexane (1:9) and isolated as liquid.; Yield: 21% (13.0 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 85:15, flow rate 0.8 mL/min, λ = 254 nm), $t_R$ = 7.90 min (major), $t_R$ = 8.76 min (minor); $[\alpha]_D^{25}$ = +26.8° (*c* = 0.07, $CHCl_3$, 85% ee); IR (Neat): $\nu_{max}$ 3427 (OH), 2961, 2923, 2122 ($N_3$), 1704 (C=O), 1489, 1299, 1062 and 755 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.53 (1H, d, *J* = 8.0 Hz), 7.31 (1H, dt, *J* = 8.0, 1.6 Hz), 7.16 (1H, t, *J* = 7.6 Hz), 7.12 (1H, d, *J* = 8.0 Hz), 5.33 (1H, dd, *J* = 9.6, 2.4 Hz), 4.01 (1H, br s, O*H*), 2.88 (1H, dd, *J* = 17.6, 2.8 Hz), 2.72 (1H, dd, *J* = 17.6, 9.6 Hz), 2.20 (3H, s, C*H*$_3$); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ



(*R*)-(+)-**56ab**

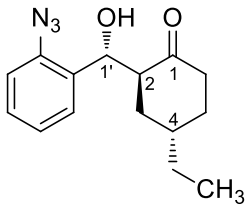
209.2 (C, *C*=O), 135.8 (C), 133.7 (C), 128.5 (CH), 126.8 (CH), 125.0 (CH), 117.7 (CH), 65.1 (CH), 50.4 ($CH_2$), 30.5 ($CH_3$); HRMS m/z 228.0752 (M + Na), calcd for $C_{10}H_{11}N_3O_2Na$ 228.0749.

**(2*S*,4*S*)-2-((*R*)-(2-Azidophenyl)(hydroxy)methyl)-4-methylcyclohexanone (56ag):** Prepared following the procedure **3a** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as solid.; Yield: 80% (62.0 mg); Mp 62-64 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 28.76 min (major), $t_R$ = 36.47 min (minor); $[\alpha]_D^{25}$ = –27.4° (*c* = 0.71, $CHCl_3$, 99% ee, 6:1 dr); IR (Neat): $\nu_{max}$ 3392 (OH), 2964, 2926, 2849 2120 ($N_3$), 1699 (C=O), 1589, 1496, 1452, 1304, and 756 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.43 (1H, dd, *J* = 7.6, 0.8 Hz), 7.34 (1H, dt, *J* = 8.0, 1.6 Hz), 7.19-7.14 (2H, m), 5.18 (1H, d, *J* = 8.4 Hz), 3.58 (1H, d, *J* = 3.2 Hz), 2.83 (1H, q, *J* = 8.8 Hz), 2.49-2.45 (2H, m), 2.17-2.10 (1H, m), 2.01-1.93 (1H, m), 1.72-1.58 (2H, m), 1.36-1.25 (1H, m), 1.03 (3H, d, *J* = 6.8 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 215.1 (C, *C*=O), 137.3 (C), 132.6 (C), 129.0 (CH), 128.3 (CH), 125.2 (CH), 117.9 (CH), 69.5 (CH), 53.7 (CH), 38.3 ($CH_2$), 36.1 ($CH_2$), 33.6 ($CH_2$), 26.8 (CH), 18.9 ($CH_3$); HRMS m/z 282.1218 (M + Na), calcd for $C_{14}H_{17}N_3O_2Na$ 282.1218.



(2*S*, 4*S*, 1'*R*)-(–)-**56ag**

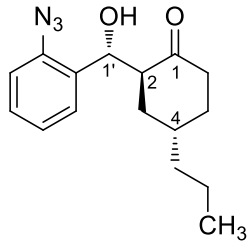
**(2*S*,4*S*)-2-((*R*)-(2-Azidophenyl)(hydroxy)methyl)-4-ethylcyclohexanone (56ai):** Prepared following the procedure **3a** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as solid.; Yield: 88% (72.0 mg); Mp 85-89 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 8.95 min (major), $t_R$ = 10.22 min (minor); $[\alpha]_D^{25}$ = –36.3° (*c* = 0.74, $CHCl_3$, 99% ee, 14:1 dr); IR (Neat): $\nu_{max}$ 3402 (OH), 2969, 2915, 2849, 2131 ($N_3$), 1709 (C=O), 1577, 1490, 1446, 1287, 1106, 1035, 766 and 679 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.44 (1H, br d, *J* = 8.0 Hz), 7.34 (1H, br t, *J* = 8.0 Hz), 7.18 (1H, t, *J* = 7.6 Hz), 7.06 (1H, d, *J* = 8.0 Hz), 5.18 (1H, d, *J* = 8.8 Hz), 3.57 (1H, d, *J* = 2.8 Hz), 2.78 (1H, q, *J* = 5.6 Hz), 2.45 (2H, t, *J* = 6.8 Hz), 1.99-1.92 (1H, m), 1.83-1.68 (2H, m), 1.62-1.55 (1H, m), 1.48-1.30 (3H, m), 0.84 (3H, t, *J* = 7.2 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-



(2*S*, 4*S*, 1'*R*)-(–)-**56ai**

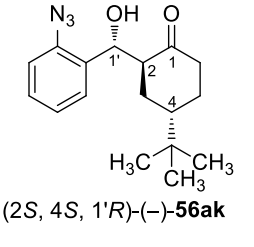
135) δ 215.2 (C, *C*=O), 137.3 (C), 132.6 (C), 129.1 (CH), 128.3 (CH), 125.2 (CH), 117.9 (CH), 69.5 (CH), 53.8 (CH), 38.5 ($CH_2$), 33.7 (CH), 33.6 ($CH_2$), 31.4 ($CH_2$), 25.6 ($CH_2$), 11.9 ($CH_3$); HRMS m/z 296.1378 (M + Na), calcd for $C_{15}H_{19}N_3O_2Na$ 296.1375.

**(2*S*,4*S*)-2-((*R*)-(2-Azidophenyl)(hydroxy)methyl)-4-propylcyclohexanone (56aj):** Prepared following the procedure **3a** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as solid.; Yield: 75% (64.6 mg); Mp 78-81 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 16.69 min (major), $t_R$ = 18.57 min (minor); $[\alpha]_D^{25}$ = –20.8° (*c* = 0.88, $CHCl_3$, >99% ee, 11:1 dr); IR (Neat): $\nu_{max}$ 3402 (OH), 2959, 2926, 2843, 2127 ($N_3$), 2098, 1707 (C=O), 1577, 1484, 1296, 1172, 1035, 759 and 684 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.43 (1H, d, *J* = 7.6 Hz), 7.34 (1H, t, *J* = 7.2 Hz), 7.19-7.14 (2H, m), 5.18 (1H, d, *J* = 8.8 Hz), 3.60 (1H, s, O*H*), 2.78 (1H, q, *J* = 8.8 Hz), 2.45 (2H, t, *J* = 6.4 Hz), 1.98-1.91 (2H, m), 1.71-1.67 (1H, m), 1.60-1.54 (1H, m), 1.42-1.16 (5H, m), 0.88 (3H, t, *J* = 7.2 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 215.2 (C, *C*=O), 137.3 (C), 132.6 (C), 129.0 (CH), 128.3 (CH), 125.2 (CH), 117.9 (CH), 69.4 (CH), 54.0 (CH), 38.5 ($CH_2$), 35.2 ($CH_2$), 34.1 ($CH_2$), 31.7 ($CH_2$), 31.6 (CH), 20.4 ($CH_2$), 14.1 ($CH_3$); HRMS m/z 288.1712 (M + H), calcd for $C_{16}H_{21}N_3O_2H$ 288.1712.



(2*S*, 4*S*, 1'*R*)-(–)-**56aj**

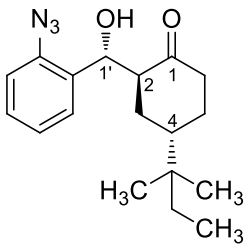
**(2*S*,4*S*)-2-((*R*)-(2-Azidophenyl)(hydroxy)methyl)-4-(*tert*-butyl)cyclohexanone (56ak):** Prepared following the procedure **3a** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as solid.; Yield: 55% (50.0 mg); Mp 145-148 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 7.33 min (minor), $t_R$ = 23.30 min (major); $[\alpha]_D^{25}$ = –73.6° (*c* = 0.23, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 3436 (OH), 2959, 2926, 2849, 2126 ($N_3$), 1720 (C=O), 1468, 1375, 1288 and 756 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.42 (1H, dd, *J* = 8.0, 1.6 Hz), 7.36 (1H, dt, *J* = 7.6, 1.2 Hz), 7.20-7.16 (2H, m), 5.21 (1H, d, *J* = 10.0 Hz), 3.18 (1H, br s, O*H*), 2.82-2.77 (1H, m), 2.61-2.52 (1H, m), 2.48-2.43 (1H, m), 2.08-2.01 (1H, m), 1.07-1.67 (1H, m), 1.57-1.37 (3H, m), 0.80 (9H, s, 3 x C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 215.3 (C, *C*=O), 137.3 (C), 132.6 (C), 129.3



(2*S*, 4*S*, 1'*R*)-(–)-**56ak**

(CH), 128.6 (CH), 125.2 (CH), 118.1 (CH), 70.1 (CH), 55.5 (CH), 41.8 (CH), 39.2 ($CH_2$), 32.6 (C), 28.3 ($CH_2$), 27.1 (3 x $CH_3$), 26.2 ($CH_2$); HRMS m/z 324.1688 (M + Na), calcd for $C_{17}H_{23}N_3O_2Na$ 324.1688.

**(2*S*,4*S*)-2-((*R*)-(2-Azidophenyl)(hydroxy)methyl)-4-(*tert*-pentyl)cyclohexanone (56al):**

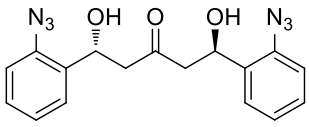



(2*S*, 4*S*, 1'*R*)-(–)-**56al**

Prepared following the procedure **3a** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as solid.; Yield: 95% (90.0 mg); Mp 116-120 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 7.47 min (minor), $t_R$ = 20.75 min (major); $[\alpha]_D^{25}$ = –48.4° (*c* = 0.29, $CHCl_3$, 99% ee, 18:1 dr); IR (Neat): $\nu_{max}$ 3386 (OH), 2970, 2926, 2877, 2120 ($N_3$), 2098, 1680 (C=O), 1496, 1310, 1041 and 767 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.42 (1H, d, *J* = 7.6 Hz), 7.37 (1H, t, *J* = 7.6 Hz), 7.21-7.17 (2H, m), 5.21 (1H, dd, *J* = 9.5, 5.2 Hz), 3.17 (1H, d, *J* = 5.6 Hz), 2.86-2.80 (1H, m), 2.59-2.50 (2H, m), 2.00-1.97 (1H, m), 1.81-1.74 (1H, m), 1.61-1.43 (3H, m), 1.29-1.11 (2H, m), 0.81 (3H, t, *J* = 7.6 Hz), 0.73 (3H, s, C*H*$_3$), 0.71 (3H, s, C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 215.5 (C, *C*=O), 137.3 (C), 132.5 (C), 129.3 (CH), 128.6 (CH), 125.2 (CH), 118.1 (CH), 70.1 (CH), 55.1 (CH), 39.5 (CH), 39.3 ($CH_2$), 35.0 (C), 32.3 ($CH_2$), 27.7 ($CH_2$), 25.4 ($CH_2$), 23.7 ($CH_3$), 23.6 ($CH_3$), 8.0 ($CH_3$); HRMS m/z 338.1845 (M + Na), calcd for $C_{18}H_{25}N_3O_2Na$ 338.1844.

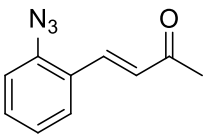
**3c. General Procedure for the Preparation of Double Aldol Product 57ab:** In a 10 mL round bottomed flask equipped with a magnetic stirring bar, prolinamide catalyst **53** (11.0 mg, 0.03 mmol), $PhCO_2H$ (3.6 mg, 0.03 mmol) were added followed by addition of acetone (**1b**) (1 mL, 0.3 M). The reaction mixture was cooled to –35 °C. After stirring the reaction mixture at –35 °C for 0.5 h, 2-azidobenzaldehyde (**55a**) (44.1 mg, 0.3 mmol) was added to it and stirring was continued at the same temperature for 24 h. The crude reaction mixture was worked up with aqueous $NH_4Cl$ solution and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure LLB-A products **56ab** and double-aldol addition product **57ab** were obtained by column chromatography (silica gel, mixture of hexane/ ethylacetate).

**(1*R*,5*R*)-1,5-bis(2-Azidophenyl)-1,5-dihydroxypentan-3-one (57ab):** Prepared following the procedure **3c** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as solid.; Yield: 21% (22.2 mg); Mp 58-62 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 85:15, flow rate 0.8 mL/min, λ = 254 nm), $t_R$ = 20.14 min (major), $t_R$ = 23.48 min (minor); $[\alpha]_D^{25}$ = +57.8° (*c* = 0.34, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 3403 (OH), 2126 ($N_3$), 1715 (C=O), 1584, 1490, 1446, 1293 and 745 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.54 (2H, dd, *J* = 7.6, 1.2 Hz), 7.33 (2H, dt, *J* = 7.6, 1.6 Hz), 7.18 (2H, dt, *J* = 7.6, 1.2 Hz), 7.14 (2H, dd, *J* = 8.0, 0.8 Hz), 5.40 (1H, d, *J* = 2.8 Hz), 5.37 (1H, d, *J* = 2.8 Hz), 3.33 (2H, br s, OH), 2.89 (2H, dd, *J* = 17.6, 2.8 Hz), 2.80 (2H, dd, *J* = 17.2, 2.8 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 210.8 (C, *C*=O), 136.0 (2 x C), 133.6 (2 x C), 128.7 (2 x CH), 126.9 (2 x CH), 125.1 (2 x CH), 117.9 (2 x CH), 65.3 (2 x CH), 50.3 (2 x $CH_2$); HRMS m/z 375.1182 (M + Na), calcd for $C_{17}H_{16}N_6O_3Na$ 375.1182.



(*R*, *R*)-(+)-**57ab**

**(*E*)-4-(2-Azidophenyl)but-3-en-2-one (58ab):**[57b] Prepared following the procedure **3a** and **3b**. purified by column chromatography using EtOAc/hexane (1:18) and isolated as solid.; Yield: 21% (11.8 mg); Mp 88-92 °C; IR (Neat): $\nu_{max}$ 2126 ($N_3$), 2077, 1666 (C=O), 1644, 1622, 1479, 1293, 1260, 986 and 762 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.77 (1H, d, *J* = 16.4 Hz), 7.60 (1H, d, *J* = 7.6 Hz), 7.43 (1H, t, *J* = 7.6 Hz), 7.21 (1H, d, *J* = 8.0 Hz), 7.16 (1H, t, *J* = 7.6 Hz), 6.70 (1H, d, *J* = 9.6 Hz), 2.40 (3H, s); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 198.6 (C, *C*=O), 139.3 (C), 137.6 (CH), 131.5 (CH), 128.6 (CH), 127.8 (CH), 126.0 (C), 125.0 (CH), 118.8 (CH), 27.1 ($CH_3$); HRMS m/z 210.0642 (M + Na), calcd for $C_{10}H_9N_3ONa$ 210.0643.



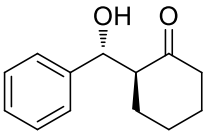
**58ab**

**3d. General Procedure for L-DMTC and TFA Catalyzed LLB-A Reaction of 1a with 59:** In an ordinary glass vial equipped with a magnetic stirring bar, containing L-DMTC (**7t**) (9.7 mg, 0.06 mmol) in DMSO (1.0 mL, 0.3 M), was added TFA (**54c**) (9.2 µL, 0.12 mmol). After stirring for a minute, aldehyde **59** (0.3 mmol) and cyclohexanone (**1a**) (4.2 mmol) were added and the reaction mixture was stirred at 25 °C. Completion of the reaction was monitored using TLC. The crude reaction mixture was then worked up with aqueous $NH_4Cl$ solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$),

filtered and concentrated. Pure LLB-A products **60** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

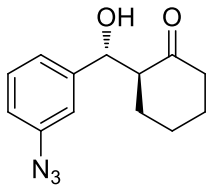
**3e. General Procedure for L-Proline and Guanidinium tetrafluoroborate Catalyzed LLB-A Reaction of 1a with 59:** In an ordinary glass vial equipped with a magnetic stirring bar, guanidinium tetrafluoroborate (**54g**) (6.2 mg, 0.03 mmol) and L-proline (**7a**) (5.2 mg, 0.045 mmol) were weighed together. Cyclohexanone (**1a**) (3.0 mmol) was added to the solid mixture followed by addition of aldehydes **59** (0.3 mmol) and the reaction mixture was stirred at 25 °C. Completion of the reaction was monitored using TLC. The crude reaction mixture was then worked up with aqueous $NH_4Cl$ solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure LLB-A products **60** were obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

**(*S*)-2-((*R*)-Hydroxy(phenyl)methyl)cyclohexanone (60aa):**[44e] Prepared following the procedure **3d** and **3e**. Purified by column chromatography using EtOAc/hexane (1:5) and isolated as liquid.; Yield: 45% (27.6 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 220 nm), $t_R$ = 16.72 min (major), $t_R$ = 20.79 min (minor); $[\alpha]_D^{25}$ = +14.1° (*c* = 0.37, $CHCl_3$, 97% ee, 4.4:1 dr); IR (Neat): $\nu_{max}$ 3501 (OH), 2926, 2860, 1693 (C=O), 1452, 1299, 1129 and 1041; $^1$H NMR ($CDCl_3$) δ 7.36-7.26 (5H, m), 4.78 (1H, d, *J* = 8.8 Hz), 3.97 (1H, s, OH), 2.65-2.58 (1H, m), 2.50-2.46 (1H, m), 2.36 (1H, dt, *J* = 13.2, 6.0 Hz), 2.10-2.06 (1H, m), 1.80-1.76 (1H, m), 1.69-1.27 (4H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 215.5 (C, *C*=O), 140.9 (C), 128.3 (2 x CH), 127.8 (CH), 127.0 (2 x CH), 74.7 (CH), 57.4 (CH), 42.6 ($CH_2$), 30.8 ($CH_2$), 27.8 ($CH_2$), 24.7 ($CH_2$); HRMS m/z 227.1048 (M + Na), calcd for $C_{13}H_{16}O_2Na$ 227.1048.



*anti*-(+)-**60aa**

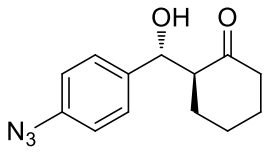
**(*S*)-2-((*R*)-(3-Azidophenyl)(hydroxy)methyl)cyclohexanone (60ba):** Prepared following the procedure **3d** and **3e**. Purified by column chromatography using EtOAc/hexane (1:5) and isolated as liquid.; Yield: 47% (34.6 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 13.67 min (major), $t_R$ = 16.73 min



*anti*-(+)-**60ba**

(minor); $[\alpha]_D^{25}$ = +7.3° (*c* = 0.44, $CHCl_3$, 96% ee, 6:1 dr); IR (Neat): $\nu_{max}$ 3485 (OH), 2937, 2860, 2400, 2110 ($N_3$), 1688 (C=O), 1600, 1490, 1441, 1288, 1224, 882 and 690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.32 (1H, t, *J* = 8.0 Hz), 7.07 (1H, d, *J* = 7.5 Hz), 7.02 (1H, s), 6.96 (1H, dd, *J* = 7.5, 1.0 Hz), 4.77 (1H, dd, *J* = 8.5, 1.5 Hz), 4.03 (1H, d, *J* = 2.0 Hz), 2.61-2.56 (1H, m), 2.49-2.45 (1H, m), 2.35 (1H, dt, *J* = 13.0, 5.5 Hz), 2.11-2.07 (1H, m), 1.82-1.79 (1H, m), 1.71-1.52 (3H, m), 1.35-1.25 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 215.2 (C, *C*=O), 143.0 (C), 140.1 (C), 129.6 (CH), 123.7 (CH), 118.5 (CH), 117.4 (CH), 74.3 (CH), 57.2 (CH), 42.6 ($CH_2$), 30.7 ($CH_2$), 27.7 ($CH_2$), 24.6 ($CH_2$); HRMS m/z 268.1063 (M + Na), calcd for $C_{13}H_{15}N_3O_2Na$ 268.1062.

**(*S*)-2-((*R*)-(4-Azidophenyl)(hydroxy)methyl)cyclohexanone (60ca):** Prepared following the procedure **3d** and **3e**. Purified by column chromatography using EtOAc/hexane (1:5) and isolated as liquid.; Yield: 16% (12.0 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 7.91 min (major), $t_R$ = 9.54 min (minor); $[\alpha]_D^{25}$ = +13.1° (*c* = 0.13, $CHCl_3$, 88% ee, 16:1 dr); IR (Neat): $\nu_{max}$ 3429 (OH), 2934, 2864, 2101 ($N_3$), 1703 (C=O), 1692, 1606, 1510, 1503, 1284, 1128, 1039 and 834 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.31 (2H, d, *J* = 8.4 Hz), 7.01 (2H, d, *J* = 8.4 Hz), 4.77 (1H, d, *J* = 8.8 Hz), 4.00 (1H, s, OH), 2.62-2.54 (1H, m), 2.51-2.46 (1H, m), 2.36 (1H, dt, *J* = 13.2, 6.0 Hz), 2.13-2.05 (1H, m), 1.82-1.78 (1H, m), 1.72-1.49 (4H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 215.4 (C, *C*=O), 139.5 (C), 137.8 (C), 128.5 (2 x CH), 119.0 (2 x CH), 74.2 (CH), 57.4 (CH), 42.6 ($CH_2$), 30.7 ($CH_2$), 27.7 ($CH_2$), 24.7 ($CH_2$); HRMS m/z 268.1062 (M + Na), calcd for $C_{13}H_{15}N_3O_2Na$ 268.1062.

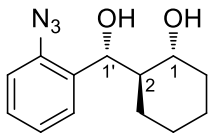


*anti*-(+)-**60ca**

**3f. General Procedure for the Reduction of LLB-A Products 56:** In a 10 mL round bottomed flask equipped with a magnetic stirring bar, compound *anti*-(–)-**56aa** (0.18 mmol) was dissolved in dry MeOH (3.6 ml, 0.05 M) and then cooled to ice salt temperature, followed by addition of $NaBH_4$ (7.5 mg, 0.20 mmol) under nitrogen atmosphere. Stirred the reaction mixture at same temperature for 0.5 h and then at RT 1.5 h, the crude reaction mixture was worked up with aqueous $NH_4Cl$ solution and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure product (+)-**61aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**3g. Lewis acid Mediated *syn*-Selective Reduction of LLB-A Products 56:** In a 10 mL round bottomed flask equipped with a magnetic stirring bar, compound *anti*-(–)-**56aa** (0.18 mmol) was dissolved in dry THF:MeOH (4:1, 0.1 M) and then cooled to –78 °C, $BEt_2OMe$ (19.8 mg, 0.20 mmol), and $NaBH_4$ (7.5 mg, 0.20 mmol) were added to it under nitrogen atmosphere. After stirring the reaction mixture at same temperature for 4 h, the crude reaction mixture was worked up with slow addition of $H_2O_2$ solution and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure product (+)-**61aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

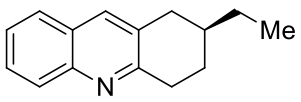
**(1*R*,2*R*)-2-((*R*)-(2-Azidophenyl)(hydroxy)methyl)cyclohexanol (61aa):** Prepared following the procedure **3f** and **3g**. Purified by column chromatography using EtOAc/hexane (1:4) and isolated as liquid.; Yield: 95% (46.8 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 95:5, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 9.92 min (major), $t_R$ = 13.58 min (minor); $[\alpha]_D^{25}$ = +4.6° (*c* = 0.71, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 3273 (OH), 2928, 2856, 2121 ($N_3$), 1583, 1489, 1449, 1290, 1128, 1076, 1006, 907 and 731 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.44 (1H, br d, *J* = 7.6 Hz), 7.32 (1H, tt, *J* = 8.0, 1.2 Hz), 7.17 (1H, t, *J* = 7.2 Hz), 7.13 (1H, d, *J* = 8.0 Hz), 4.92 (1H, d, *J* = 9.2 Hz), 4.36 (2H, br s, O*H*), 3.64 (1H, dt, *J* = 9.6, 4.4 Hz), 1.97-1.94 (1H, m), 1.71-1.63 (2H, m), 1.54-1.51 (1H, m), 1.34-1.16 (3H, m), 1.07-0.91 (2H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 137.2 (C), 134.0 (C), 128.8 (CH), 128.7 (CH), 125.2 (CH), 117.7 (CH), 76.4 (CH), 75.3 (CH), 49.9 (CH), 35.2 ($CH_2$), 27.0 ($CH_2$), 25.1 ($CH_2$), 24.5 ($CH_2$); HRMS m/z 270.1216 (M + Na), calcd for $C_{13}H_{17}N_3O_2Na$ 270.1218.



(1*R*, 2*R*, 1'*R*)-(+)-**61aa**

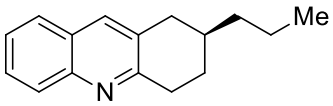
**3h. General Procedure for the Preparation of Chiral 1,2,3,4-Tetrahydroacridine 62:** Crude LLB-A product **56** (0.3 mmol) was dissolved in toluene (1 mL, 0.3 M) followed by addition of $Bu_3P$ (82 µL, 0.33 mmol). The reaction mixture was stirred at 25 °C for 1 h. The crude reaction mixture was then worked up with aqueous $NH_4Cl$ solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure products **62** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**(*S*)-2-Ethyl-1,2,3,4-tetrahydroacridine (62ai):** Prepared following the procedure **3h** and purified by column chromatography using EtOAc/hexane (1:18) and isolated as liquid.; Yield: 85% (54.0 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), $t_R$ = 5.80 min (major), $t_R$ = 7.14 min (minor); $[\alpha]_D^{25}$ = –75.2° (*c* = 0.16, $CHCl_3$, 94% ee); IR (Neat): $\nu_{max}$ 2958, 2924, 2874, 2855, 1622, 1493, 1235, 1155, 857 and 750 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.97 (1H, d, *J* = 8.4 Hz), 7.80 (1H, s), 7.70 (1H, d, *J* = 8.0 Hz), 7.60 (1H, dt, *J* = 6.8, 1.6 Hz), 7.43 (1H, dt, *J* = 6.8, 0.8 Hz), 3.23 (1H, ddd, *J* = 18.0, 5.6, 3.6 Hz), 3.13-3.05 (2H, m), 2.60 (1H, dd, *J* = 16.4, 11.2 Hz), 2.17-2.12 (1H, m), 1.79-1.68 (1H, m), 1.67-1.51 (1H, m), 1.46 (2H, quin, *J* = 7.2 Hz), 1.02 (3H, t, *J* = 7.6 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 159.3 (C), 146.6 (C), 135.1 (CH), 130.6 (C), 128.5 (CH), 128.2 (CH), 127.1 (C), 126.9 (CH), 125.5 (CH), 35.7 (CH), 35.6 ($CH_2$), 33.0 ($CH_2$), 29.0 ($CH_2$), 28.8 ($CH_2$), 11.5 ($CH_3$); HRMS m/z 212.1439 (M + H), calcd for $C_{15}H_{18}N$ 212.1439.



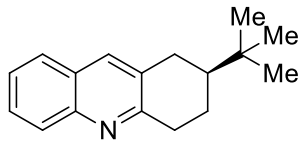
(*S*)-(–)-**62ai**

**(*S*)-2-Propyl-1,2,3,4-tetrahydroacridine (62aj):**[52d,c] Prepared following the procedure **3h** and purified by column chromatography using EtOAc/hexane (1:18) and isolated as liquid.; Yield: 73% (49.3 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 16.00 min (major), $t_R$ = 18.39 min (minor); $[\alpha]_D^{25}$ = –33.4° (*c* = 0.33, $CHCl_3$, 96% ee); IR (Neat): $\nu_{max}$ 2957, 2926, 2871, 2854, 1716 and 1456 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.90 (1H, d, *J* = 8.8 Hz), 7.66 (1H, s), 7.57 (1H, d, *J* = 8.4 Hz), 7.49 (1H, dt, *J* = 6.8, 0.8 Hz), 7.31 (1H, dt, *J* = 6.8, 0.8 Hz), 3.13 (1H, ddd, *J* = 18.0, 5.6, 4.0 Hz), 3.02-2.89 (2H, m), 2.46 (1H, dd, *J* = 16.4, 10.4 Hz), 2.05-1.94 (1H, m), 1.75-1.68 (1H, m), 1.51-1.41 (1H, m), 1.40-1.25 (4H, m), 0.85 (3H, t, *J* = 6.8 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 159.1 (C), 146.3 (C), 135.1 (CH), 130.5 (C), 128.4 (CH), 128.0 (CH), 127.0 (C), 126.8 (CH), 125.4 (CH), 38.3 ($CH_2$), 35.7 ($CH_2$), 33.6 (CH), 32.8 ($CH_2$), 29.2 ($CH_2$), 20.0 ($CH_2$), 14.2 ($CH_3$); HRMS m/z 226.1596 (M + H), calcd for $C_{16}H_{20}N$ 226.1596.



(*S*)-(–)-**62aj**

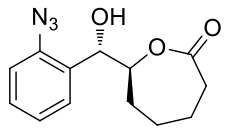
**(*S*)-2-(*tert*-Butyl)-1,2,3,4-tetrahydroacridine (62ak):**[52c] Prepared following the procedure **3h** and purified by column chromatography using EtOAc/hexane (1:18) and isolated as liquid.; Yield: 90% (64.6 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), $t_R$ = 13.63 min (minor), $t_R$ = 17.78 min (major); $[\alpha]_D^{25}$ = –101.5° (*c* = 0.36, $CHCl_3$, 98% ee); IR (Neat): $\nu_{max}$ 2942, 2860, 1495, 1429, 1366, 1277 and 1261 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 8.01 (1H, d, *J* = 6.8 Hz), 7.83 (1H, s), 7.69 (1H, d, *J* = 6.4 Hz), 7.61 (1H, t, *J* = 6.8 Hz), 7.43 (1H, t, *J* = 6.4 Hz), 3.32-3.27 (1H, m), 3.09-3.01 (2H, m), 2.71 (1H, dd, *J* = 12.8, 9.2 Hz), 2.19-2.15 (1H, m), 1.61-1.50 (2H, m), 1.00 (9H, s, 3 x C*H*$_3$); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 159.3 (C), 146.2 (C), 135.5 (CH), 131.3 (C), 128.6 (CH), 128.0 (CH), 127.1 (C), 126.8 (CH), 125.6 (CH), 44.5 (CH), 34.1 ($CH_2$), 32.5 (C), 30.7 ($CH_2$), 27.2 (3 x $CH_3$), 24.5 ($CH_2$); HRMS m/z 240.1752 (M + H), calcd for $C_{17}H_{21}NH$ 240.1752.



(*S*)-(–)-**62ak**

**3i. General Procedure for the Preparation of 63aa:** To a solution of chiral product *anti*-(-)-**56aa** (170 mg, 0.7 mmol) in dry DCM (7 mL, 0.1 M) were added successively $NaHCO_3$ (117 mg, 1.4 mmol) and *m*CPBA (362 mg, 2.1 mmol). The reaction mixture was stirred at 25 °C for 5 h. The reaction mixture was worked up with aqueous $NaHCO_3$ and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure product (+)-**63aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**(*S*)-7-((*S*)-(2-Azidophenyl)(hydroxy)methyl)oxepan-2-one (63aa):** Prepared following the procedure **3i** and purified by column chromatography using EtOAc/hexane (1:3) and isolated as liquid.; Yield: 67% (122.5 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 85:15, flow rate 0.8 mL/min, λ = 254 nm), $t_R$ = 14.38 min (minor), $t_R$ = 19.84 min (major); $[\alpha]_D^{25}$ = +68.5° (*c* = 0.86, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 3386 (OH), 2953, 2920, 2866, 2126 ($N_3$), 2093, 1726 (C=O), 1584, 1496, 1457, 1304, 1178, 1052 and 756 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.51 (1H, d, *J* = 7.6 Hz), 7.37 (1H, t, *J* = 7.6 Hz), 7.19 (1H, t, *J* = 7.6 Hz), 7.16 (1H, d, *J* = 7.6 Hz), 5.00 (1H, d, *J* = 6.4 Hz), 4.36 (1H, t, *J* = 8.0 Hz), 3.20 (1H, br s, O*H*), 2.71-2.66 (1H, m), 2.58 (1H, t, *J* = 12.8 Hz),

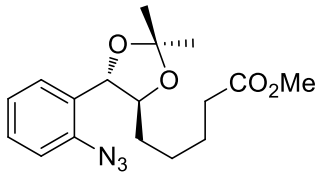


(*S*, *S*)-(+)-**63aa**

1.94-1.89 (2H, m), 1.80-1.45 (4H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 174.8 (C, *C*=O), 137.4 (C), 130.8 (C), 129.4 (CH), 128.5 (CH), 125.2 (CH), 118.0 (CH), 83.8 (CH), 70.9 (CH), 34.8 ($CH_2$), 30.5 ($CH_2$), 27.9 ($CH_2$), 22.8 ($CH_2$); HRMS m/z 284.1011 (M + Na), calcd for $C_{13}H_{15}N_3O_3Na$ 284.1011.

**3j. General Procedure for the Preparation of 64aa:** To a solution of chiral product *anti*-(+)-**63aa** (300 mg, 1.1 mmol) in MeOH (6 mL) was added aqueous 5% NaOH solution (6 mL). The reaction mixture was heated to reflux at 80 °C for 1 h. The reaction mixture was worked up with aqueous 2N HCl and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. To the crude hydrolyzed compound was dissolved in acetone (11 mL 0.1 M), $MgSO_4$ (1.0 mg, 0.008 mmol), *p*-TSA.$H_2O$ (1.89 mg, 0.011 mmol), and 2,3-dimethoxypropane (0.19 mL, 1.54 mmol) were added. The reaction mixture was stirred at 25 °C for 4 h. Anhydrous $Na_2CO_3$ (254 mg, 2.4 mmol) was added to the reaction mixture, then filtered and concentrated. To the crude reaction mixture dissolved in diethyl ether (10 mL, 0.05 M), diazomethane in ether solution was added at 0-5 °C for 30 min. Ether was evaporated. Pure product (-)-**64aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**Methyl 5-((4*S*,5*S*)-5-(2-azidophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentanoate (64aa):**



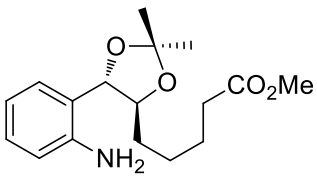
(*S*, *S*)-(–)-**64aa**

Prepared following the procedure **3j** and purified by column chromatography using EtOAc/hexane (1:10) and isolated as liquid.; Yield: 70% (256.7 mg); $[\alpha]_D^{25}$ = –3.3° (*c* = 0.18, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 2981, 2931, 2866, 2131 ($N_3$), 1742 (C=O), 1584, 1485, 1457, 1381, 1299, 1233, 1162, 1090 and 1047 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.54 (1H, dd, *J* = 7.6, 1.6 Hz), 7.34 (1H, dt, *J* = 8.0, 1.6 Hz), 7.20-7.14 (2H, m), 4.94 (1H, d, *J* = 8.4 Hz), 3.75-3.70 (1H, m), 3.65 (3H, s, OC*H*$_3$), 2.30 (2H, t, *J* = 7.6 Hz), 1.66-1.61 (5H, m), 1.55 (3H, s, C*H*$_3$), 1.49 (3H, s, C*H*$_3$), 1.42-1.26 (1H, m); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 174.0 (C, *C*=O), 137.8 (C), 129.3 (CH), 129.1 (C), 128.1 (CH), 125.2 (CH), 118.0 (CH), 108.6 (C), 83.1 (CH), 77.0 (CH), 51.4 (O*C*H$_3$), 33.9 ($CH_2$), 31.0 ($CH_2$), 27.4 ($CH_3$), 27.1 ($CH_3$), 25.5 ($CH_2$), 24.9 ($CH_2$); HRMS m/z 356.1581 (M + Na), calcd for $C_{17}H_{23}N_3O_4Na$ 356.1586.

**3k. General Procedure for the Preparation of 65aa: Method-1:** To a solution of chiral product (–)-**64aa** (33 mg, 0.1 mmol) in dry toluene (1 mL, 0.1 M), $Bu_3P$ (75 µL, 0.3 mmol) was

added and the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was worked up with aqueous $NH_4Cl$ solution and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure product (−)-**65aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate); **Method-2:** In an oven dried round bottom flask, equipped with magnetic stirring bar, containing $InCl_3$ (15 mg, 0.066 mmol) and triethylsilane (20 µL, 0.13 mmol) in MeOH (2 mL, 0.05 M) at 0 °C was added (−)-**64aa** (0.06 mmol) dissolved in MeOH drop wise. The mixture was stirred at the same temperature for 2 h. The crude reaction mixture was then worked up with water and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure product (−)-**65aa** was by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**Methyl 5-((4*S*,5*S*)-5-(2-aminophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentanoate (65aa):**




(*S*, *S*)-(−)-**65aa**

Prepared following the procedure **3k** and purified by column chromatography using EtOAc/hexane (1:9) and isolated as liquid.; Yield: 81% (15.0 mg); $[\alpha]_D^{25}$ = −10.6° (*c* = 0.17, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 3454 ($NH_2$), 3367 ($NH_2$), 2933, 1734 (C=O), 1618, 1499, 1460, 1436, 1378, 1305, 1228, 1168, 1089, 1036, 902 and 866 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.11 (1H, dt, *J* = 7.5, 1.5 Hz), 7.02 (1H, dd, *J* = 7.5, 1.5 Hz), 6.71 (1H, dt, *J* = 7.5, 1.0 Hz), 6.65 (1H, dd, *J* = 8.0, 1.0 Hz), 4.57 (1H, d, *J* = 8.5 Hz), 4.29 (2H, br s, N*H*$_2$), 4.22-4.18 (1H, m), 3.64 (3H, s, OC*H*$_3$), 2.28 (2H, t, *J* = 7.0 Hz), 1.65-1.55 (5H, m), 1.54 (3H, s, C*H*$_3$), 1.46 (3H, s, C*H*$_3$), 1.40-1.35 (1H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 174.0 (C, *C*=O), 145.9 (C), 129.3 (CH), 129.2 (CH), 119.6 (C), 118.1 (CH), 116.7 (CH), 108.4 (C), 83.4 (CH), 78.3 (CH), 51.4 (O*C*H$_3$), 33.9 ($CH_2$), 32.1 ($CH_2$), 27.3 ($CH_3$), 27.1 ($CH_3$), 25.8 ($CH_2$), 25.0 ($CH_2$); HRMS m/z 330.1681 (M + Na), calcd for $C_{17}H_{25}NO_4Na$ 330.1681.

**3l. General Procedure for the Preparation of 66aa:** To a solution of chiral product (−)-**65aa** (20 mg, 0.06 mmol) in dry THF (2 mL, 0.03 M) was added KO*t*Bu (10 mg, 0.09 mmol), and the reaction mixture was stirred at 25 °C for 24 h. The crude reaction mixture was treated with saturated aqueous $NH_4Cl$ solution, and then the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), and

concentrated. Pure product (–)-**66aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**(3a*S*,13b*S*)-2,2-Dimethyl-4,5,6,7,9,13b-hexahydrobenzo[*b*][1,3]dioxolo[4,5-*d*]azecin-8(3a*H*)-one (66aa):** Prepared following the procedure **3l** and purified by column chromatography using EtOAc/hexane (1:8) and isolated as liquid.; Yield: 57% (9.4 mg); $[\alpha]_D^{25}$ = –5.0° (*c* = 0.14, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 3452, 3370 (NH), 2983, 2926, 2855, 1708 (C=O), 1617, 1499, 1460, 1379, 1233, 1169, 1087, 1037, 889, and 751 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.12 (1H, dt, *J* = 8.0, 1.6 Hz), 7.03 (1H, dd, *J* = 7.6, 1.2 Hz), 6.73 (1H, dt, *J* = 7.2, 0.8 Hz), 6.67 (1H, d, *J* = 8.0 Hz), 4.59 (1H, d, *J* = 8.8 Hz), 4.24-4.19 (1H, m), 2.32 (2H, t, *J* = 7.2 Hz), 1.67-1.56 (5H, m), 1.55 (3H, s, C*H*$_3$), 1.49 (3H, s, C*H*$_3$), 1.46-1.37 (2H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 178.5 (C, *C*=O), 145.8 (C), 129.3 (CH), 129.2 (CH), 119.6 (C), 118.2 (CH), 116.8 (CH), 108.4 (C), 83.4 (CH), 78.3 (CH), 33.7 ($CH_2$), 32.0 ($CH_2$), 27.4 ($CH_3$), 27.1 ($CH_3$), 25.7 ($CH_2$), 24.7 ($CH_2$); HRMS m/z 276.1594 (M + H), calcd for $C_{16}H_{22}NO_3$ 276.1599.

(*S*, *S*)-(–)-**66aa**

**3m. General Procedure for the Preparation of 67aa:** To a solution of chiral product (+)-**63aa** (655 mg, 2.5 mmol) in dry toluene (5 ml, 0.5 M) was added DIBAL-H (25% solution in toluene, 6.8 mL, 10.0 mmol), and the reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was quenched with $H_2O$ (10 mL), sodium potassium (+)-tartrate tetrahydrate (7 g), and ethyl acetate (10 mL) were added. This mixture was stirred vigorously for 1 h was again diluted with $H_2O$. Aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried ($Na_2SO_4$), and concentrated. Pure product (+)-**67aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

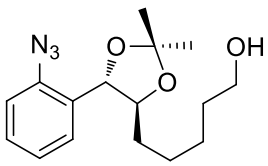
**(1*S*,2*S*)-1-(2-Azidophenyl)heptane-1,2,7-triol (67aa):** Prepared following the procedure **3m** and purified by column chromatography using EtOAc/hexane (1:2) and isolated as liquid.; Yield: 69% (457.7 mg); $[\alpha]_D^{25}$ = +97.5° (*c* = 0.36, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 3360 (OH), 2930, 2857, 2122 ($N_3$), 1713 (C=O), 1583, 1488, 1450, 1284, 1046 and 752 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.42 (1H, d, *J* = 9.2 Hz), 7.34 (1H, dt, *J* = 7.6, 1.6 Hz), 7.18-7.14 (2H, m), 4.72 (1H, d, *J* = 5.6 Hz), 3.74-3.70 (1H, m), 3.59 (2H, t, *J* = 6.4 Hz), 3.22 (1H, br s, O*H*), 2.78 (1H, br s, O*H*), 1.94 (1H, br s, O*H*), 1.56-1.44 (4H, m), 1.39-1.24 (4H, m); $^{13}C$

(*S*, *S*)-(+)-**67aa**

NMR ($CDCl_3$, DEPT-135) δ 137.0 (C), 132.6 (C), 128.9 (CH), 128.3 (CH), 125.0 (CH), 118.0 (CH), 74.8 (CH), 72.5 (CH), 62.7 ($CH_2$), 32.7 ($CH_2$), 32.4 ($CH_2$), 25.5 ($CH_2$), 25.4 ($CH_2$); HRMS m/z 288.1323 (M + Na), calcd for $C_{13}H_{19}N_3O_3$ 288.1324.

**3n. General Procedure for the Preparation of 68aa:** To a solution of chiral product (+)-**67aa** (360 mg, 1.35 mmol) in acetone (9 mL 0.15 M), $MgSO_4$ (1.0 mg, 0.009 mmol), *p*-TSA.$H_2O$ (2.3 mg, 0.013 mmol), and 2,3-dimethoxypropane (0.23 mL, 1.89 mmol) were added. The reaction was stirred at 25 °C for 4 h. Anhydrous $Na_2CO_3$ (254 mg, 2.4 mmol) was added to the reaction mixture. The mixture was filtered and concentrated. Pure product (+)-**68aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

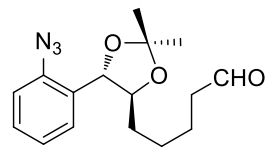
**5-((4*S*,5*S*)-5-(2-Azidophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-1-ol (68aa):** Prepared following the procedure **3n** and purified by column chromatography using EtOAc/hexane (1:5) and isolated as liquid.; Yield: 45% (185.5 mg); $[\alpha]_D^{25}$ = +100.3° (*c* = 0.28, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 3370 (OH), 2935, 2125 ($N_3$), and 1377 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.54 (1H, dd, *J* = 7.6, 1.6 Hz), 7.35 (1H, dt, *J* = 7.6, 1.6 Hz), 7.19 (1H, dt, *J* = 7.6, 0.8 Hz), 7.16 (1H, dd, *J* = 8.0, 0.8 Hz), 4.94 (1H, d, *J* = 8.4 Hz), 3.77-3.72 (1H, m), 3.61 (2H, t, *J* = 6.8 Hz), 1.66-1.57 (4H, m), 1.56 (3H, s, C*H*$_3$), 1.49 (3H, s, C*H*$_3$),1.41-1.24 (4H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 137.9 (C), 129.3 (CH), 129.2 (C), 128.2 (CH), 125.2 (CH), 118.0 (CH), 108.6 (C), 83.3 (CH), 77.0 (CH), 62.8 ($CH_2$), 32.5 ($CH_2$), 31.3 ($CH_2$), 27.4 ($CH_3$), 27.1 ($CH_3$), 25.75 ($CH_2$), 25.72 ($CH_2$); HRMS m/z 328.1636 (M + Na), calcd for $C_{16}H_{23}N_3O_3Na$ 328.1637.



(*S*, *S*)-(+)-**68aa**

**3o. General Procedure for the Preparation of 69aa:** To a solution of chiral product (+)-**68aa** (240 mg, 0.8 mmol) in $CH_3CN$ (5 mL 0.16 M), IBX (672 mg, 2.4 mmol) was added, and the reaction was heated to reflux for 3 h. Reaction mixture was filtered and concentrated. Pure product (+)-**69aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**5-((4*S*,5*S*)-5-(2-Azidophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentanal (69aa):** Prepared following the procedure **3o** and purified by column chromatography using EtOAc/hexane (1:12) and isolated as liquid.; Yield: 74% (179.5 mg); $[\alpha]_D^{25}$ = +53.3° (*c* = 0.20, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 2929, 2858, 2123 ($N_3$), 1723 (C=O), 1585, 1489, 1453, 1370, 1292,



(*S*, *S*)-(+)-**69aa**

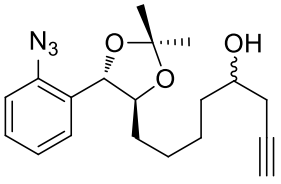
1236, 1164, 1100, 1050, 886 and 753 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 9.74 (1H, s, C*H*O), 7.54 (1H, d, *J* = 6.8 Hz), 7.35 (1H, t, *J* = 6.4 Hz), 7.21-7.15 (2H, m), 4.94 (1H, d, *J* = 8.0 Hz), 3.73 (1H, q, *J* = 8.4 Hz), 2.42 (2H, t, *J* = 6.4 Hz), 1.66-1.64 (4H, m), 1.55 (3H, s), 1.49 (3H, s),1.40-1.26 (2H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 202.4 (CH, *C*HO), 137.8 (C), 129.3 (CH), 129.1 (C), 128.1 (CH), 125.2 (CH), 118.0 (CH), 108.6 (C), 83.1 (CH), 77.0 (CH), 43.7 ($CH_2$), 31.1 ($CH_2$), 27.4 ($CH_3$), 27.0 ($CH_3$), 25.5 ($CH_2$), 22.0 ($CH_2$); HRMS m/z 326.1469 (M + Na), calcd for $C_{16}H_{21}N_3O_3Na$ 326.1481.

**3p. General Procedure for the Preparation of 70aa:**

**Step 1:** To a flame-dried flask was added 1.0 g of Mg, 24 mg of $HgCl_2$, and 4 mL of diethyl ether. Propargyl bromide (0.1 mL, 80% in toluene) was added, and the reaction was initiated by heating with a heat gun. The mixture was cooled to 0 °C, and a solution of 1.4 mL of propargyl bromide (80% in toluene) in 8 mL of ether was slowly added over 1 h. The reaction was stirred at 0 °C for 0.5 h and allowed to settle at 0 °C for 0.5 h to give a ~1 M solution.

**Step 2:** To a solution of chiral product (+)-**69aa** (250 mg, 0.82 mmol) in dry THF (26 ml 0.03 M), at −10 °C was added propargyl magnesium bromide (1.2 mL, 1 M solution in ether, 1.2 mmol). The reaction mixture was stirred at the same temperature for 30 min and then brought to room temperature and stirred for another 12 h. The crude reaction mixture was treated with saturated aqueous $NH_4Cl$ solution, and then the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), and concentrated. Pure products (+)-**70aa** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**8-((4*S*,5*S*)-5-(2-Azidophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)oct-1-yn-4-ol (70aa):** Prepared following the procedure **3p** and purified by column chromatography using EtOAc/hexane (1:7) and isolated as liquid.; Yield: 63% (177.0 mg); $[\alpha]_D^{25}$ = +3.9° (*c* = 0.26, $CHCl_3$); IR (Neat): $\nu_{max}$ 3436 (OH), 3307, 2990, 2933, 2863, 2246, 2122 ($N_3$), 2084, 1584, 1492, 1454, 1372, 1299, 1230, 1169, 1103, 1046, and 884 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.54 (1H, br d, *J* = 7.6 Hz), 7.35 (1H, br t, *J* = 7.6 Hz), 7.19 (1H, br t, *J* = 7.6 Hz), 7.16 (1H, br d, *J* = 8.0 Hz), 4.95 (1H, d, *J* = 8.0 Hz), 3.75-3.73 (2H, m), 2.42-2.26 (2H, m), 2.04 (1H, br s), 1.99 (1H, br s), 1.74-1.60 (3H, m), 1.56 (3H, s, C*H*$_3$), 1.50 (3H, s, C*H*$_3$), 1.52-1.26 (5H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 137.9 (C), 129.3 (CH), 129.2 (C), 128.2 (CH), 125.1 (CH), 118.1 (CH), 108.6 (C), 83.3 (CH),

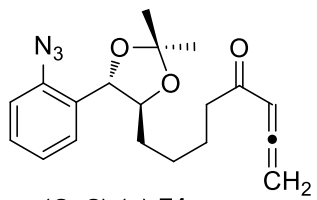


(*S*, *S*)-(+)-**70aa**

80.9 (C), 77.0 (CH), 70.8 (CH), 69.7 (CH), 36.0 ($CH_2$), 31.3 ($CH_2$), 27.4 ($CH_3$), 27.3 ($CH_2$), 27.1 ($CH_3$), 25.8 ($CH_2$), 25.6 ($CH_2$); HRMS m/z 366.1787 (M + Na), calcd for $C_{19}H_{25}N_3O_3Na$ 366.1794.

**3q. General Procedure for the Preparation of 71aa:** To a solution of chiral product (+)-**70aa** (70 mg, 0.2 mmol) in DCM (5 mL 0.04 M), at 0 °C was added PCC (86.2 mg, 0.4 mmol). The reaction mixture after stirred at the same temperature for 30 min was brought to room temperature and stirred for an additional 2 h. The crude reaction mixture was passed through a pad of celite and concentrated to dryness. Pure chiral products (+)-**71aa** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**8-((4*S*,5*S*)-5-(2-Azidophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)octa-1,2-dien-4-one (71aa):**



(*S*, *S*)-(+)-**71aa**

Prepared following the procedure **3q** and purified by column chromatography using EtOAc/hexane (1:17) and isolated as liquid.; Yield: 54% (37.0 mg); $[\alpha]_D^{25}$ = +10.3° (*c* = 0.37, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 2987, 2930, 2856, 2125 ($N_3$), 1933, 1681 (C=O), 1585, 1490, 1452, 1370, 1293, 1237, 1171, 1041 and 754 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.53 (1H, dd, *J* = 7.6, 1.6 Hz), 7.34 (1H, dt, *J* = 7.6 1.6 Hz), 7.18 (1H, dt, *J* = 7.6, 0.8 Hz), 7.15 (1H, dd, *J* = 8.0, 0.8 Hz), 5.75 (1H, t, *J* = 6.8 Hz), 5.19 (2H, d, *J* = 6.4 Hz), 4.93 (1H, d, *J* = 8.8 Hz), 3.75-3.67 (1H, m), 2.58 (2H, t, *J* = 7.2 Hz), 1.66-1.56 (4H, m), 1.54 (3H, s, C*H*$_3$), 1.49 (3H, s, C*H*$_3$), 1.36-1.30 (2H, m); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 216.6 (C, HC=*C*=$CH_2$), 200.6 (C, *C*=O), 137.8 (C), 129.25 (CH), 129.18 (C), 128.1 (CH), 125.2 (CH),118.0 (CH), 108.6 (C), 96.6 (CH), 83.2 (CH), 79.3 ($CH_2$), 77.0 (CH), 38.9 ($CH_2$), 31.1 ($CH_2$), 27.4 ($CH_3$), 27.1 ($CH_3$), 25.5 ($CH_2$), 24.5 ($CH_2$); HRMS m/z 364.1633 (M + Na), calcd for $C_{19}H_{23}N_3O_3Na$ 364.1637.

**3r. General Procedure for the Preparation of 72aa:** To a solution of chiral product (+)-**63aa** (25 mg, 0.1 mmol) in $H_2O$ (1 mL, 0.1 M), was added diethyl acetylenedicarboxylate (25.5 mg, 0.15 mmol) and the reaction was stirred at 70 °C for 5 h. The crude reaction mixture was diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), and concentrated. Pure products (+)-**72aa** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**Diethyl 1-(2-((*S*)-hydroxy((*S*)-7-oxooxepan-2-yl)methyl)phenyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (72aa):** Prepared following the procedure **3r** and purified by column chromatography using EtOAc/hexane (1:3) and isolated as liquid.; Yield: 55% (23.7 mg); $[\alpha]_D^{25}$ = +17.2° (*c* = 0.28, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 3496 (OH), 2984, 2940, 2864, 1733 (C=O), 1558, 1498, 1444, 1376, 1348, 1285, 1254, 1226, 1189, 1087, 1016, and 771 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.72 (1H, br d, *J* = 6.8 Hz), 7.65 (1H, br t, *J* = 6.8 Hz), 7.51 (1H, dt, *J* = 7.6, 1.2 Hz), 7.31 (1H, br d, *J* = 7.6 Hz), 4.49 (2H, q, *J* = 6.8 Hz), 4.41 (1H, br d, *J* = 6.0 Hz), 4.31-4.23 (1H, m), 4.26 (2H, q, *J* = 6.8 Hz), 3.00 (1H, br s, OH), 2.67-2.62 (1H, m), 2.56-2.48 (1H, m), 1.89-1.86 (2H, m), 1.74-1.67 (2H, m), 1.61-1.49 (2H, m), 1.45 (3H, t, *J* = 7.2 Hz), 1.16 (3H, t, *J* = 7.2 Hz); $^{13}C$ NMR ($CDCl_3$, DEPT-135) δ 174.4 (C, *C*=O), 159.6 (C, *C*=O), 158.0 (C, *C*=O), 139.0 (C), 137.0 (C), 133.9 (C), 133.6 (C), 131.5 (CH), 129.2 (CH), 129.0 (CH), 127.5 (CH), 82.8 (CH), 72.3 (CH), 63.2 ($CH_2$), 62.0 ($CH_2$), 34.7 ($CH_2$), 30.9 ($CH_2$), 27.7 ($CH_2$), 22.7 ($CH_2$), 14.2 ($CH_3$), 13.6 ($CH_3$); HRMS m/z 454.1585 (M + Na), calcd for $C_{21}H_{25}N_3O_7Na$ 454.1590.

(*S*, *S*)-(+)-**72aa**

**3s. General Procedure for the Preparation of 73aa :** To a solution of chiral product (+)-**63aa** (25 mg, 0.1 mmol) in $H_2O$ (1 mL, 0.1 M), was added diethyl acetylenedicarboxylate (25.5 mg, 0.15 mmol) and the reaction was stirred at 70 °C for 12 h. The crude reaction mixture was diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$), and concentrated. To the crude reaction mixture dissolved in diethyl ether (10 mL, 0.05 M), diazomethane in ether solution was added at 0-5 °C for 0.5 h. Ether was evaporated in fume wood. Pure products (+)-**73aa** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

**Diethyl 1-(2-((1*S*,2*S*)-1,2-dihydroxy-7-methoxy-7-oxoheptyl)phenyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (73aa):** Prepared following the procedure **3s** and purified by column chromatography using EtOAc/hexane (1:2) and isolated as liquid.; Yield: 80% (37.0 mg); $[\alpha]_D^{25}$ = +23.0° (*c* = 0.17, $CHCl_3$, 99% ee, 99:1 dr); IR (Neat): $\nu_{max}$ 3481 (OH), 2982, 2941, 2864, 1731 (C=O), 1557, 1496, 1438, 1376, 1285, 1252, 1195, 1082, 1013, and 766 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.71 (1H, dd, *J* = 7.6, 1.2

(*S*, *S*)-(+) **73aa**

Hz), 7.63 (1H, dt, *J* = 7.6, 0.8 Hz), 7.47 (1H, dt, *J* = 7.6, 1.2 Hz), 7.27 (1H, dd, *J* = 7.6, 0.8 Hz), 4.48 (2H, q, *J* = 7.2 Hz), 4.34-4.22 (2H, m), 4.10 (1H, d, *J* = 5.6 Hz), 3.79-3.72 (1H, m), 3.63 (3H, s, OC*H*$_3$), 3.27 (1H, br s), 2.67 (1H, br s), 2.23 (2H, dt, *J* = 7.6, 1.2 Hz), 1.59-1.48 (2H, m), 1.45 (3H, t, *J* = 7.2 Hz), 1.41-1.30 (4H, m), 1.26 (3H, t, *J* = 5.6 Hz); $^{13}$C NMR ($CDCl_3$, DEPT-135) δ 174.1 (C, *C*=O), 159.6 (C, *C*=O), 158.6 (C, *C*=O), 138.91 (C), 138.89 (C), 133.5 (C), 133.4 (C), 131.6 (CH), 128.7 (CH), 128.6 (CH), 127.1 (CH), 74.0 (CH), 72.3 (CH), 63.4 ($CH_2$), 62.0 ($CH_2$), 51.4 ($CH_3$), 33.8 ($CH_2$), 32.1 ($CH_2$), 25.0 ($CH_2$), 24.5 ($CH_2$), 14.2 ($CH_3$), 13.6 ($CH_3$); HRMS m/z 486.1847 (M + Na), calcd for $C_{22}H_{29}N_3O_8Na$ 486.1852.

**3t. General Procedure for the Gram Scale Synthesis of (-)-56aa:** In an 100 mL round bottomed flask equipped with a magnetic stirring bar, containing L-DMTC (**7t**) (219.2 mg, 1.36 mmol, 20 mol%) in DMSO (22.6 mL, 0.3 M), was added TFA (**54c**) (208 µL, 2.72 mmol, 40 mol%). After stirring for a minute, 2-azidobenzaldehyde (**55a**) (1.0 g, 6.8 mmol) and cyclohexanone (**1a**) (9.8 mL, 95.2 mmol) were added and the reaction mixture was stirred at 25 °C for 24 h. The crude reaction mixture was then worked up with aqueous $NH_4Cl$ solution and the aqueous layer was extracted with ethyl acetate (3 x 60 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure LLB-A product (–)-**56aa** (1.2 g, 72%) and starting material **55a** (200 mg, 20%) was obtained through column chromatography (silica gel, mixture of hexane/ethyl acetate).

# *7. REFERENCES*


1. a) D. B. Ramachary, K. S. Shruthi, *Org. Biomol. Chem.* **2014**, *12*, 4300-4304; b) D. B. Ramachary, K. S. Shruthi, R. Madhavachary, *Eur. J. Org. Chem.* **2015**, 6413-6418.
2. a) M. L. Clarke, J. A. Fuentes, *Angew. Chem. Int. Ed*. **2007**, *46*, 930-933; b) J. A. Fuentes, T. Lebl, A. M. Z. Slawin, M. L. Clarke, *Chem. Sci*. **2011**, *2*, 1997-2005.
3. T. Mandal, C.-G. Zhao, *Angew. Chem. Int. Ed.* **2008**, *47*, 7714-7717.
4. D.-Q. Xu, H.-D. Yue, S.-P. Luo, A.-B. Xia, S. Zhang, Z.-Y. Xu, *Org. Biomol. Chem.* **2008**, *6*, 2054-2057.
5. D. Uraguchi, Y. Ueki, T. Ooi, *Science* **2009**, *326*, 120-123.
6. A. S. Demir, S. Eymur, *Tetrahedron: Asymmetry* **2010**, *21*, 112-115.
7. W.-H. Wang, T. Abe, X.-B. Wang, K. Kodama, T. Hirose, G.-Y. Zhang, *Tetrahedron: Asymmetry 21*, 2010, 2925-2933.
8. S. Muramulla, C.-G. Zhao, *Tetrahedron Lett*. **2011,** *52*, 3905-3908.
9. D. B. Ramachary, R. Madhavachary, M. S. Prasad, *Org. Biomol. Chem*. **2012**, *10*, 5825-5829.
10. D. B. Ramachary, R. Sakthidevi, K. S. Shruthi, *Chem. Eur. J.* **2012**, *18*, 8008-8012.
11. S. Muramulla, J.-A. Ma, J. C.-G. Zhao, *Adv. Synth. Catal*. **2013**, *355*, 1260-1264.
12. A. S. Demir, S. Basceken, *Tetrahedron Lett*. **2013**, *54*, 5677-5681.
13. a) J. H. Rakotoson, N. Fabre, I. Jacquemond-Collet, S. Hannedouche, I. Fouraste, C. Moulis, *Planta Med.* **1998**, *64*, 762-763; b) I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fouraste, C. Moulis, *Phytochemistry* **1999**, *51*, 1167-1169; c) P. J. Houghton, T. Z. Woldemariam, Y. Watanabe, M. Yates, *Planta Med.* **1999**, *65*, 250-254; d) I. Jacquemond-Collet, J. M. Bessiere, S. Hannedouche, C. Bertrand, I. Fouraste, C. Moulis, *Phytochem. Anal.* **2001**, *12*, 312-319.
14. a) W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1998-2007; b) R. Noyori, *Angew. Chem. Int. Ed*. **2002**, *41*, 2008-2022; c) W. -B. Wang, S. -M. Lu, P. -Y. Yang, X. -W. Han, Y. -G. Zhou, *J. Am. Chem. Soc*. **2003**, *125*, 10536-10537; d) W. Tang, X. Zhang, *Chem. Rev*. **2003**, *103*, 3029-3069; e) C. Moessner, C. Bolm, *Angew. Chem. Int. Ed*. **2005**, *44*, 7564-7567; f) S. -M. Lu, Y. -Q. Wang, X. -W. Han, Y. -G. Zhou, *Angew. Chem. Int. Ed*. **2006**, *45*, 2260-2263. Mihel, I.; Orlović, M.; Polla, E.; Borčić, S. *J. Org. Chem.* **1979**, *44*, 4086–4090.
15. a) K. B. Jensen, M. Roberson, K. A. Jørgensen, *J. Org. Chem.* **2000**, *65*, 9080-9084; b) K. Funabashi, H. Ratni, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001,** *123*, 10784-10785; c)

Z. Li, C. -J. Li, *Org. Lett*. **2004**, *6*, 4997-4999; d) S. Wang, C. T. Seto, *Org. Lett*. **2006**, *8*, 3979-3982; e) C. Dubs, Y. Hamashima, N. Sasamoto, T. M. Seidel, S. Suzuki, D. Hashizume, M. Sodeoka, *J. Org. Chem.* **2008**, *73*, 5859-5871.

16. a) P. Buonora, J. -C. Olsen, T. Oh, *Tetrahedron* **2001**, *57*, 6099-6138; b) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc*. **2006**, *128*, 13070-13071; c) V. V. Kouznetsov, *Tetrahedron* **2009**, *65*, 2721-2750; d) G. Dagousset, J. Zhu, G. Masson, *J. Am. Chem. Soc*. **2011**, *133*, 14804-14813.
17. a) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem. Int. Ed*. **2006**, *45*, 3683-3686; b) Q. -S. Guo, D. -M. Du, J. Xu, *Angew. Chem. Int. Ed*. **2008**, *47*, 759-762; c) Z. -X. Jia, Y. -C. Luo, P. -F. Xu, *Org. Lett*. **2011**, *13*, 832-835; d) Z. -X. Jia, Y. -C. Luo, Y. Wang, L. Chen, P. -F. Xu, B. Wang, *Chem. Eur. J*. **2012**, *18*, 12958-12961.
18. For the selected recent reviews on enamine-based Michael reaction, see: a) B. Bradshaw, J. Bonjoch, *Synlett* **2012**, *23*, 337-356; b) Y. Zhang, W. Wang, *Catal. Sci. Technol.* **2012**, *2*, 42-53. For the selected recent papers, see: c) D. B. Ramachary, M. S. Prasad, R. Madhavachary, *Org. Biomol. Chem.* **2011**, *9*, 2715-2721; d) B. –C. Hong, P. Kotame, J. –H. Liao, *Org. Biomol. Chem.* **2011**, *9*, 382-386; e) D. Enders, X. Yang, C. Wang, G. Raabe, J. Runsik, *Chem. Asian. J.* **2011**, *6*, 2255-2259; f) D. B. Ramachary, R. Sakthidevi, *Org. Biomol. Chem.* **2010**, *8*, 4259-4265; g) D. Enders, C. Wang, X. Yang, G. Raabe, *Adv. Synth. Catal.* **2010**, *352*, 2869-2874; h) D. Lu, Y. Li, Y. Gong, *J. Org. Chem.* **2010**, *75*, 6900-6907; i) H. Uehara, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2009**, *48*, 9848-9852; j) X. Zhu, F. Tanaka, R. A. Lerner, C. F. Barbas III, I. A. Wilson, *J. Am. Chem. Soc.* **2009**, *131*, 18206-18207; k) P. Dinér, A. Kjærsgaard, M. A. Lie, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 122-127; l) P. García-García, A. Ladépêche, R. Halder, B. List, *Angew. Chem. Int. Ed.* **2008**, *47*, 4719-4721; m) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861-863
19. For the excellent reviews on supramolecular assembly in catalysis, see: a) L. A. Joyce, S. H. Shabbir, E. V. Anslyn, *Chem. Soc. Rev.* **2010**, *39*, 3621-3632; b) J. Meeuwissen, J. N. H. Reek, *Nature Chem*. **2010**, *2*, 615-621. For early work on self assembly approach to asymmetric catalysis, see: c) M. L. Clarke, J. A. Fuentes, *Angew. Chem. Int. Ed*. **2007**, *46*, 930-933; d) T. Mandal, C. -G. Zhao, *Angew. Chem., Int. Ed.* **2008**, *47*, 7714-7717; e) D.

Uraguchi, Y. Ueki, T. Ooi, *Science* **2009**, *326*, 120-123; f) A. -B. Xia, D. -Q. Xu, S. -P. Luo, J. -R. Jiang, J. Tang, Y. -F. Wang, Z. -Y. Xu, *Chem. Eur. J*. **2010**, *16*, 801-804; g) J. A. Fuentes, T. Lebl, A. M. Z. Slawin, M. L. Clarke, *Chem. Sci*. **2011**, *2*, 1997-2005; h) D. B. Ramachary, R. Madhavachary, M. S. Prasad, *Org. Biomol. Chem*. **2012**, *10*, 5825-5829; i) D. B. Ramachary, R. Sakthidevi, K. S. Shruthi, *Chem. Eur. J.* **2012**, *18*, 8008-8012; j) D. Sinha, S. Perera, J. C. -G. Zhao, *Chem. Eur. J.* **2013**, *19*, 6976-6979.

20. a) N. Hayashi, I. Shibata, A. Baba, *Org. Lett.* **2004**, *6*, 4981-4983; b) L. Benati, G. Bencivenni, R. Leardini, D. Nanni, M. Minozzi, P. Spagnolo, R. Scialpi, G. Zanardi, *Org. Lett*. **2006**, *8*, 2499-2502; c) O. –Y. Lee, K. –L. Law, C. –Y. Ho, D. Yang, *J. Org. Chem.* **2008**, *73*, 8829-8837; d) O. –Y. Lee, K. –L. Law, D. Yang, *Org. Lett.* **2009**, *11*, 3302-3305.
21. CCDC-955384 for (–)-**42bb** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
22. a) D. B. Ramachary, R. Mondal, R. Madhavachary, *Org. Biomol. Chem.* **2012**, *10*, 5094; b) D. B. Ramachary, R. Mondal, Ch. Venkaiah, *Eur. J. Org. Chem.* **2010**, 3205; c) D. B. Ramachary, G. B. Reddy, R. Mondal, *Tetrahedron Lett.* 2007, **48**, 7618; d) D. B. Ramachary, G. B. Reddy, *Org. Biomol. Chem.* **2006**, *4*, 4463; e) D. B. Ramachary, C. F. Barbas III, *Chem. Eur. J*. **2004**, *10*, 5323; f) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.*, **2001**, *40*, 2004.
23. a) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res*. **2004**, *37*, 580-591; b) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79-87; c) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev*. **2007**, *107*, 5471-5569; d) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470; e) D. Enders, C. Grondal, M. R. M. Huttl, *Angew. Chem. Int. Ed*. **2007**, *46*, 1570–1581; f) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev*. **2009**, *38*, 2178–2189; g) M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Paixao, K. A. Jørgensen, *Angew. Chem. Int. Ed*. **2010**, *49*, 2668–2679; h) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010,** *2*, 167-178; i) D. B. Ramachary, S. Jain, *Org. Biomol. Chem.* **2011**, *9*, 1277-1300; j) V. Bisai, A. Bisai, V. K. Singh, *Tetrahedron* **2012**, *68*, 4541-4580; k) K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248-264; l) D.

B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, 865–888; m) I. Atodiresei, C. Vila, M. Rueping, *ACS Catal*. **2015**, *5*, 1972−1985.

24. a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336-9337; b) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1842−1843; c) A. Córdova, S. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866−1867; d) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827–833; e) W. Notz, S. Watanabe, N. S. Chowdari, G. Zhong, J. M. Betancort, F. Tanaka, C. F. Barbas III, *Adv. Synth. Catal.* **2004**, *346*, 1131–1140; f) A. Co´rdova, *Chem. Eur. J.* **2004**, *10*, 1987–1997; g) C. M. Kleiner, P. R. Schreiner, *Chem. Commun*. **2006**, 4315–4317; h) D. Perdicchia, K. A. Jørgensen, *J. Org. Chem*. **2007**, *72*, 3565-3568; i) E. Reyes, H. Jiang, A. Milelli, P. Elsner, R. G. Hazell, K. A. Jørgensen, *Angew. Chem. Int. Ed*. **2007**, *46*, 9202–9205; j) X. Lu, L. Deng, *Angew. Chem. Int. Ed*. **2008**, *47*, 7710–7713; k) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan, G. Zhong, *Angew. Chem. Int. Ed.* **2008**, *47*, 10187–10191; l) H. Li, L. Zu, H. Xie, J. Wang, W. Wang, *Chem. Commun*. **2008**, 5636–5638; m) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29–41; n) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J*. **2009**, *15*, 11058–11076; o) D. Enders, A. Greb, K. Deckers, P. Selig, C. Merkens, *Chem. Eur. J*. **2012**, *18*, 10226–10229; p) M. Sanchez-Rosello, J. L. Acena, A. Simon-Fuentes, C. del Pozo, *Chem. Soc. Rev*. **2014**, *43*, 7430-7453; q) M. Rueping, J. Dufour, L. Bui, *ACS Catal*. **2014**, *4*, 1021−1025; r) Y. Lee, S. Heo, S. –G. Kim, *Adv*. *Synth*. *Catal*. **2015**, *357*, 1545–1550.

25. a) M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc*. **2005**, *127*, 6964-6965; b) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc*. **2008**, *130*, 6070–6071; c) B. –C. Hong, P. Kotame, C. –W. Tsai, J. –H. Liao, *Org. Lett*. **2010,** *12*, 776-779; d) C, F. Nising, S, Brase, *Chem. Soc. Rev*. **2012**, *41*, 988-999; e) Y. Kobayashi, Y. Taniguchi, N. Hayama, T. Inokuma, Y. Takemoto, *Angew. Chem. Int. Ed*. **2013**, *52*, 11114-11118; f) R. L. Davis, K. L. Jensen, B. Gschwend, K. A. Jørgensen, *Chem. Eur. J*. **2014**, *20*, 64-67.

26. a) M. Marigo, T. Schulte, J. Franzen, K. A. Jørgensen, *J. Am. Chem. Soc*. **2005**, *127*, 15710-15711; b) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed*. **2005**, *44*, 794–797; c) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc*. **2006**, *128*, 10354-

10355; d) N. K. Rana, S. Selvakumar, V. K. Singh, *J. Org. Chem.* **2010**, *75*, 2089–2091; e) P. Chauhan, S. Mahajan, D. Enders, *Chem. Rev*. **2014**, *114*, 8807−8864.

27. a) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, A. Mazzanti, L. Sambri, P. Melchiorre, *Chem. Commun*. **2007**, 722-724; b) X. Fu, Z. Jiang, C. –H. Tan, *Chem. Commun*. **2007**, 5058-5060; c) A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Angew. Chem. Int. Ed.* **2007**, *46*, 4504-4506; d) I. Ibrahem, R. Rios, J. Vesely, P. Hammar, L. Eriksson, F. Himo, A. Cordova, *Angew. Chem. Int. Ed.* **2007**, *46*, 4507-4510; e) L. Albrecht, A. Albrecht, H. Krawczyk, K. A. Jorgensen, *Chem. Eur. J.* **2010**, *16*, 28-48.
28. a) J.-A. Ma, D. Cahard, *Chem. Rev*. **2008**, *108*, PR1-PR43; b) M. Marigo, D. Fielenbach, A. Braunton, A. Kjaersgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed*. **2005**, *44*, 3703–3706; c) D. D. Steiner, N. Mase, C. F. Barbas III, *Angew. Chem. Int. Ed*. **2005**, *44*, 3706–3710; d) N. Halland, A. Braunton, S. Bachmann, M. Marigo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004,** *126*, 4790-4791; e) M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004,** *126*, 4108-4109.
29. reviews on synergistic- or cooperative-catalysis, see: a) D. –F. Chen, Z. –Y. Han, X. –L. Zhou, L. –Z. Gong, *Acc. Chem. Res*. **2014**, *47*, 2365−2377; b) A. E. Allen, D. W. C. MacMillan, *Chem. Sci*. **2012**, *3*, 633–658; c) J. –F. Brière, S. Oudeyer, V. Dallab, V. Levacher, *Chem. Soc. Rev.* **2012**, *41*, 1696–1707; d) S. Piovesana, D. M. S. Schietroma, M. Bella, *Angew. Chem. Int. Ed.* **2011**, *50*, 6216–6232; e) D. H. Paull, C. J. Abraham, M. T. Scerba, E. Alden-Danforth, T. Lectka, *Acc. Chem. Res.* **2008**, *41*, 655–663; f) J. –A. Ma, D. Cahard, *Angew. Chem. Int. Ed.* **2004**, *43*, 4566–4583; For recent papers on synergistic- or cooperative-catalysis, see: g) I. Ibrahem, G. Ma, S. Afewerki, A. Cordova, *Angew. Chem. Int. Ed*. **2013**, *52*, 878–882; h) B. M. Trost, X. Luan, Y. Miller, *J. Am. Chem. Soc*. **2011**, *133*, 12824–12833; i) H. Rahaman, Á. Madarász, I. Pápai, P. M. Pihko, *Angew. Chem. Int. Ed.* **2011**, *50*, 6123–6127; j) A. Peschiulli, B. Procuranti, C. J. O' Connor, S. J. Connon, *Nat. Chem.* **2010,** *2*, 380-384; k) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science* **2010**, *327*, 986-990; l) G. Bergonzini, S. Vera, P. Melchiorre, *Angew. Chem. Int. Ed.* **2010**, *49*, 9685–9688; m) A. –B. Xia, D. –Q. Xu, S. –P. Luo, J. –R. Jiang, J. Tang, Y. –F. Wang, Z. –Y. Xu, *Chem. Eur. J.* **2010**, *16*, 801–804; n) Y. Chi, S. T. Scroggins, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2008**, *130*, 6322–6323.

30. a) M. L. Clarke, J. A. Fuentes, *Angew. Chem. Int. Ed*. **2007**, *46*, 930-933; b) T. Mandal, C. –G. Zhao, *Angew. Chem. Int. Ed*. **2008**, *47*, 7714-7717; c) D. Uraguchi, Y. Ueki, T. Ooi, *Science* **2009**, *326*, 120-123; d) A. S. Demir, S. Eymur, *Tetrahedron: Asymmetry* **2010**, *21*, 112–115; e) W. –H. Wanga, T. Abe, X. –B. Wang, K. Kodama, T. Hirose, G. –Y. Zhang, *Tetrahedron: Asymmetry* **2010**, *21*, 2925–2933; f) D. Sinha, T. Mandal, S. Gogoi, J. J. Goldman, J. C. –G. Zhao, *Chin. J. Chem.* **2012**, *30*, 2624-2630; g) S. Perera, D. Sinha, N. K. Rana, V. Trieu-Do, J. C. –G. Zhao, *J. Org. Chem*. **2013**, *78*, 10947-10953; h) S. Muramulla, J. –A. Ma, J. C. –G. Zhao, *Adv. Synth. Catal*. **2013**, *355*, 1260-1264; i) D. Sinha, S. Perera, J. C. –G. Zhao, *Chem. Eur. J*. **2013**, *19*, 6976-6979; j) N. K. Rana, H. Huang, J. C. –G. Zhao, *Angew. Chem. Int. Ed.* **2014**, *53*, 7619-7623.

31. a) L. Zu, S. Zhang, H. Xiz, W. Wang, *Org. Lett*. **2009**, *11*, 1627–1630; b) A. E. Nibbs, A. –L. Baize, R. M. Herter, K. A. Scheidt, *Org. Lett*. **2009**, *11*, 4010–4013; c) S. Chandrasekhar, K. Mallikarjun, G. Pavankumarreddy, K. V. Rao, B. Jagadeesh, *Chem. Commun.* **2009**, 4985–4987; d) D. B. Ramachary, R. Sakthidevi, *Chem. Eur. J*. **2009**, *15*, 4516–4522; e) J. –L. Li, S. –L. Zhou, B. Han, L. Wu, Y. –C. Chen, *Chem. Commun*. **2010**, *46*, 2665–2667; f) K. –S. Choi, S. –G. Kim, *Tetrahedron Lett*. **2010**, *51*, 5203–5206; g) X. –F. Wang, Q. –L. Hua, Y. Cheng, A. –L. An, Q. –Q. Yang, J. –R. Chen, W. –J. Xiao, *Angew. Chem., Int. Ed*. **2010**, *49*, 8379–8383; h) D. B. Ramachary, R. Sakthidevi, *Org. Biomol. Chem*. **2010**, *8*, 4259–4265; i) D. Enders, C. Wang, X. Yang, G. Raabe, *Adv. Synth. Catal*. **2010**, *352*, 2869–2874; j) D. Lu, Y. Li, Y. Gong, *J. Org. Chem*. **2010**, *75*, 6900–6907; k) B. –C. Hong, P. Kotame, J. –H. Liao, *Org. Biomol. Chem*. **2011**, *9*, 382–386; l) D. B. Ramachary, M. S. Prasad, R. Madhavachary, *Org. Biomol. Chem*. **2011**, *9*, 2715–2721; m) D. Enders, X. Yang, C. Wang, G. Raabe, J. Runsik, *Chem. Asian J*. **2011**, *6*, 2255–2259; n) B. –C. Hong, P. Kotame, G. –H. Lee, *Org. Lett*. **2011**, *13*, 5758–5761. o) D. B. Ramachary, R. Madhavachary, M. S. Prasad, *Org. Biomol. Chem*. **2012**, *10*, 5825-5829; p) D. B. Ramachary, P. S. Reddy, M. S. Prasad, *Eur. J. Org. Chem.* **2014**, 3076–3081; q) D. B. Ramachary, M. S. Prasad, S. Vijaya Laxmi, R. Madhavachary, *Org. Biomol. Chem*. **2014**, *12*, 574–580.

32. a) D. B. Ramachary, R. Sakthidevi, K. S. Shruthi, *Chem. Eur. J*. **2012**, *18*, 8008–8012; b) D. B. Ramachary, K. S. Shruthi, *Org. Biomol. Chem.* **2014**, *12*, 4300-4304.

33. a) H. Mao, A. Lin, Y. Tang, Y. Shi, H. Hu, Y. Cheng, C. Zhu, *Org. Lett*. **2013**, *15*, 4062-4065; b) Y. Lee, S. –G. Kim, *J. Org. Chem*. **2014**, *79*, 8234−8243; c) O. D. Engl, S. P. Fritz, A. Kaslin, H. Wennemers, *Org. Lett*. **2014**, *16*, 5454−5457; d) M. Yu, S. –G. Kim, *Tetrahedron Lett*. **2015,** *56*, 4159-4162.
34. W. A. Denny, *Curr. Med. Chem.* **2002**, *9*, 1655-1665.
35. CCDC-1411306 for (+)-**51da** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
36. Early references for BLA reaction, see: a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc*. **2000**, *122*, 2395–2396; d) W. Notz, B. List, *J. Am. Chem. Soc*. **2000**, *122*, 7386–7387.
37. For the development of BLA reactions, see: a) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc*. **2001**, *123*, 5260–5267; b) B. List, P. Pojarliev, C. Castello, *Org. Lett*. **2001**, *3*, 573–575; c) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc*. **2001**, *123*, 11273–11283; d) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc*. **2001**, *123*, 12911–12912; e) A. Cordova, W. Notz, C. F. Barbas III, *J. Org. Chem*. **2002**, *67*, 301–303; f) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2002**, *124*, 6798–6799; g) A. Bogevig, K. Juhl, N. Kumaragurubaran, K. A. Jorgensen, *Chem. Commun*. **2002**, 620–621; h) M. Nakadai, S. Saito, H. Yamamoto, *Tetrahedron* **2002**, *58*, 8167–8177; i) P. Kotrusz, I. Kmentova, B. Gotov, S. Toma, E. Solcaniova, *Chem. Commun*. **2002**, 2510–2511; j) T. Darbre, M. Machuqueiro, *Chem. Commun*. **2003**, 1090–1091; k) L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc*. **2003**, *125*, 16–17; l) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc*. **2003**, *125*, 2475–2479; m) B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5839–5842; n) C. Allemann, R. Gordillo, F. R. Clemente, P. H-Y. Cheong, K. N. Houk, *Acc. Chem. Res*. **2004**, *37*, 558–569; o) S. Chandrasekhar, C. Narsihmulu, N. R. Reddy, S. S. Sultana, *Chem. Commun*. **2004**, 2450–2451; p) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem*. **2004**, *116*, 2474–2477; *Angew. Chem. Int. Ed*. **2004**, *43*, 2420–2423; q) J. T. Suri, D. B. Ramachary, C. F. Barbas III, *Org. Lett*. **2005**, *7*, 1383–1385; r) S. Kallstrom, A. Erkkila, P. M. Pihko, R. Sjoholm, R. Sillanpaa, R. Leino, *Synlett* **2005**, 751–756; s) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C.

F. Barbas III, *J. Am. Chem. Soc*. **2006**, *128*, 734–735; t) Y. Zhou, Z. Shan, *J. Org. Chem*. **2006**, *71*, 9510–9512; u) M. Raj, V. Maya, S. K. Ginotra, V. K. Singh, *Org. Lett.* **2006**, *8*, 4097–4099; v) V. Maya, M. Raj, V. K. Singh, *Org. Lett*. **2007**, *9*, 2593–2595; w) J. Huang, X. Zhang, D. W. Armstrong, *Angew. Chem*. **2007**, *119*, 9231–9235; *Angew. Chem. Int. Ed*. **2007**, *46*, 9073–9077; x) D. Enders, A. A. Narine, *J. Org. Chem*. **2008**, *73*, 7857–7870; y) C. L. Chandler, B. List, *J. Am. Chem. Soc*. **2008**, *130*, 6737–6739; z) R. Pedrosa, J. M. Andres, R. Manzano, D. Roman, S. Tellez, *Org. Biomol. Chem*. **2011**, *9*, 935–940; aa) S. S. V. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2007**, *129*, 288-289; ab) S. S. V. Ramasastry, K. Albertshofer, F. Tanaka, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2007**, *46*, 5572-5575; ac) S. S. V. Ramasastry, K. Albertshofer, N. Utsumi, C. F. Barbas III, *Org. Lett.* **2008**, *10*, 1621-1624.

38. (*S*)-BINOL as additive for BLA reactions, see: a) Y. Zhou, Z. Shan, *J. Org. Chem.* **2006**, *71*, 9510-9512; b) Y. Zhou, Z. Shan, *Tetrahedron: Asymmetry* **2006**, *17*, 1671–1677; c) D. Deng, P. Liu, B. Ji, W. Fu, L. Li, *Catal. Lett*. **2010**, *137*, 163–170; d) R. L. Sutar, N. N. Joshi, *Synth. Commun*. **2014**, *44*, 352–360.
39. Schreiner's thiourea as additive for BLA reactions, see: a) O. Reis, S. Eymur, B. Reis, A. S. Demir, *Chem. Commun*. **2009**, 1088–1090; b) X. Companyo, G. Valero, L. Crovetto, A. Moyano, R. Rios, *Chem. Eur. J*. **2009**, *15*, 6564–6568; c) N. El-Hamdouni, X. Companyo, R. Rios, A. Moyano, *Chem. Eur. J*. **2010**, *16*, 1142–1148; d) X.-S. Xue, C. Yang, X. Li, J.-P. Cheng, *J. Org. Chem.* **2014**, *79*, 1166−1173.
40. TBD's salt as additive for BLA reactions, see: a) A. Martínez-Castañeda, B. Poladura, H. Rodriguez-Solla, C. Concellón, V. del Amo, *Org. Lett*. **2011**, *13*, 3032-3035; b) Á. Martínez-Castañeda, B. Poladura, H. Rodriguez-Solla, C. Concellón, V. del Amo, *Chem. Eur. J*. **2012**, *18*, 5188–5190; c) Á. Martínez-Castañeda, H. Rodríguez-Solla, C. Concellón, V. del Amo, *J. Org. Chem*. **2012**, *77*, 10375−10381; d) A. Martinez-Castaneda, K. Kedziora, I. Lavandera, H. Rodriguez-Solla, C. Concellon, V. del Amo, *Chem. Commun.* **2014**, *50*, 2598-2600.
41. Metal Lewis acid $ZnCl_2$/$CoCl_2$ as additive for BLA reactions, see: a) M. Z. Gao, J. Gao, B. S. Lane, R. A. Zingaro, *Chem. Lett.* **2003**, *32*, 524-525; b) T. Darbre, M. Machuqueiro, *Chem. Commun.* **2003**, 1090–1091; c) J. Kofoed, M. Machuqueiro, J.-L. Reymond, T. Darbre, *Chem*

. *Commun.* **2004**, 1540–1541; d) K. Shen, X. Liu, K. Zheng, W. Li, X. Hu, L. Lin, X. Feng, *Chem. Eur. J*. **2010**, *16*, 3736–3742.

42. Chiral Brønsted acid D-CSA as additive for BLA reactions, see: a) Y. -S. Wu, Y. Chen, D. –S. Deng, J. Cai, *Synlett* **2005**, *10*, 1627–1629; b) P. M. Pihko, K. M. Laurikainen, A. Usano, A. I. Nyberg, J. A. Kaavi, *Tetrahedron* **2006**, *62*, 317–328; c) S. Bhowmick, S. S. Kunte, K. C. Bhowmick, *Tetrahedron: Asymmetry* **2014**, *25*, 1292–1297.
43. For the (*S*)-(–)-5-(2-pyrrolidinyl)-1*H*-tetrazole **3d**-catalyzed asymmetric reactions, see: a) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, *43*, 1983 –1986; b) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962-5963; c) V. Wascholowski, K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Eur. J*. **2008**, *14*, 6155-6165; d) B. Maji, H. Yamamoto, *Angew. Chem. Int. Ed*. **2014**, *53*, 8714 –8717.
44. For the prolinamide catalyzed asymmetric BLA reactions, see: a) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L. -Z. Gong, A. Qiao, Y. -Z. Jiang, Y. -D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263; b) Z. Tang, F. Jiang, X. Cui, L. -Z. Gong, A. -Q. Mi, Y. -Z. Jiang, Y. -D. Wu, *Proc. Natl. Acad. Sci. USA*. **2004**, *101*, 5755–5760; c) Z. Tang, Z. -H. Yang, X. -H. Chen, L. -F. Cun, A. -Q. Mi, Y. -Z. Jiang, L. -Z. Gong, *J. Am. Chem. Soc*. **2005**, *127*, 9285–9289; d) M. Raj, V. Maya, S. K. Ginotra, V. K. Singh, *Org. Lett*. **2006**, *8*, 4097–4099; d) V. Maya, M. Raj, V. K. Singh, *Org. Lett*. **2007**, *9*, 2593–2595.
45. For supramolecular-organocatalysis or neighboring group participation in organocatalytic reactions, see: a) D. B. Ramachary, R. Sakthidevi, *Chem. Eur. J*. **2009**, *15*, 4516–4522; b) D. B. Ramachary, R. Sakthidevi, *Org. Biomol. Chem*. **2010**, *8*, 4259–4265; c) D. B. Ramachary, R. Sakthidevi, K. S. Shruthi, *Chem. Eur. J.* **2012**, *18*, 8008–8012; d) D. B. Ramachary, R. Madhavachary, M. S. Prasad, *Org. Biomol. Chem*. **2012**, *10*, 5825-5829; e) D. B. Ramachary, P. S. Reddy, M. S. Prasad, *Eur. J. Org. Chem.* **2014**, 3076–3081; f) D. B. Ramachary, M. S. Prasad, S. Vijaya Laxmi, R. Madhavachary, *Org. Biomol. Chem*. **2014**, *12*, 574–580; g) D. B. Ramachary, K. S. Shruthi, *Org. Biomol. Chem.* **2014**, *12*, 4300-4304; h) D. B. Ramachary, K. S. Shruthi, R. Madhavachary, *Eur. J. Org. Chem.* **2015**, 6413–6418; from other research group, see: i) A. Martínez, M. van Gemmeren, B. List, *Synlett* **2014**, 961-964; j) M. L.Clarke, J. A. Fuentes, *Angew. Chem. Int. Ed.* **2007**, *46*, 930-933; k) T. Mandal, C.-G. Zhao, *Angew.*

*Chem. Int. Ed*. **2008**, *47*, 7714-7717; l) D. Uraguchi, Y. Ueki, T. Ooi, *Science* **2009**, *326*, 120-123; m) D. Sinha, S. Perera, J. C.-G. Zhao, *Chem. Eur. J*. **2013**, *19*, 6976-6979.

46. a) J. H. Rakotoson, N. Fabre, I. Jacquemond-Collet, S. Hannedouche, I. Fouraste, C. Moulis, *Planta Med.* **1998**, *64*, 762-763; b) I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fouraste, C. Moulis, *Phytochemistry* **1999**, *51*, 1167-1169; c) P. J. Houghton, T. Z. Woldemariam, Y. Watanabe, M. Yates, *Planta Med.* **1999**, *65*, 250-254; d) I. Jacquemond-Collet, J. M. Bessiere, S. Hannedouche, C. Bertrand, I. Fouraste, C. Moulis, *Phytochem. Anal.* **2001**, *12*, 312-319.
47. For L-DMTC **3c**-catalyzed reactions, see: a) W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199–201; b) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc*. **2002**, *124*, 827-833; c) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem. Int. Ed*. **2003**, *42*, 4233–4237; d) D. B. Ramachary, C. F. Barbas III, *Chem. Eur. J*. **2004**, *10*, 5323–5331; e) D. D. Steiner, N. Mase, C. F. Barbas III, *Angew. Chem. Int. Ed*. **2005**, *44*, 3706–3710.
48. D. B. Ramachary, R. Mondal, R. Madhavachary, *Org. Biomol. Chem*. **2012**, *10*, 5094–5101.
49. a) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem*. **2004**, *116*, 1132–1132; *Angew. Chem. Int. Ed.* **2004**, *43*, 1112–1112; b) D. B. Ramachary, C. F. Barbas III, *Org. Lett*. **2005**, *7*, 1577–1580; c) S. Luo, H. Xu, J. Li, L. Zhang, X. Mi, X. Zheng, J. -P. Cheng, *Tetrahedron* **2007**, *63* 11307–11314; d) J. Jiang, L. He, S. -W. Luo, L. -F. Cun, L. -Z. Gong, *Chem. Commun*. **2007**, 736–738; e) S. Luo, L. Zhang, X. Mi, Y. Qiao, J. -P. Cheng, *J. Org. Chem.* **2007**, *72*, 9350-9352; f) J. Joseph, D. B. Ramachary, E. D. Jemmis, *Org. Biomol. Chem.* **2006**, *4*, 2685–2689.
50. CCDC-1438716 for (−)-**56ca** and CCDC-1438717 for (−)-**56ag** contains the supplementary crystallographic data for this paper.
51. a) S. E. Denmark, R. A. Stavenger, K.-T. Wong, X. Su, *J. Am. Chem. Soc*. 1**999**, *121*, 4982-4991. b) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.* **2006**, *118*, 972-975.
52. For the applications of functionalized tetrahydroacridines, see: a) D. Basavaiah, J. S. Rao, R. J. Reddy, *J. Org. Chem.* **2004**, *69*, 7379-7382 and references cited therein; b) L. Ren, T. Lei, L. -Z. Gong, *Chem. Commun*. **2011**, *47*, 11683–11685; c) A. Bañón-Caballero, G. Guillena,

C. Nájera, *J. Org. Chem*. **2013**, *78*, 5349−5356; d) L. Li, D. Seidel, *Org. Lett*. **2010**, *12*, 5064−5067.

53. a) R. L. Augustine, W. G. Pierson, *J. Org. Chem*. **1969**, *34*, 1070−1075; b) M. Bartra, V. Bou, J. Garcia, F. Urpi, J. Vilarrasa, *J. Chem. Soc. Chem. Commun.* **1988**, 270-272; c) C. Pascal, F. Gueritte-Voegelein, C. Thal, D. Guenard, *Synth. Commun*. **1997**, *27*, 1501-1507.
54. a) X. Cong, K. -G. Liu, Q. -J. Liao, Z. -J. Yao, *Tetrahedron Lett.* **2005**, *46*, 8567–8571; b) J. Liu, S. Ma, *Tetrahedron* **2013**, *69*, 10161-10167; c) S. Ma, Y. -C. Yang, P. H. Toy, *Synlett* **2015**, 1732-1736; d) Y. Xiao, Z. Sun, H. Guo, O. Kwon, *Beilstein J. Org. Chem.* **2014**, *10*, 2089–2121 and references cited therein; e) W. Yao, X. Dou, Y. Lu, *J. Am. Chem. Soc.* **2015**, *137*, 54−57.
55. H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed*. **2001**, *40*, 2004-2021.
56. All p$K_a$ values used in this manuscript were reported in DMSO. L-Thioproline (p$K_a$ = ~9.33) **3b** and L-DMTC (p$K_a$ = ~9.76) **3c** p$K_a$ values are estimated approximately in DMSO from their reported values in water in comparison with that of L-proline **3a** in water and DMSO.
57. For synthesis of substituted 2-azidobenzaldehydes **55a-i**, see: a) B. J. Stokes, C. V. Vogel, L. K. Pan, M. Urnezis, T. G. Driver, *Org. Lett.* **2010**, *12*, 2884-2887; b) B. J. Stokes, S. Liu, T. G. Driver, *J. Am. Chem. Soc*. **2011**, *133*, 4702-4705; c) J. Hu, Y. Cheng, Y. Yang, Y. Rao, *Chem. Commun*. **2011**, *47*, 10133-10135; d) J. M. Muchowski, M, L. Maddox, *Can. J. Chem.* **2004**, *82*, 461–478; e) X. Huang, P. Li, X.-S. Li, D.-C. Xu, J.-W. Xie, *Org. Biomol. Chem.* **2010**, *8*, 4527–4529; f) W.-J. Li, Q. Li, D.-L. Liu, M.-W. Ding, *J. Agric. Food Chem.* **2013**, *61*, 1419−1426.

# *ABOUT THE AUTHOR*

The author, **Ms. Shruthi K. S.** was born on 16th November 1986 in Kodambahalli, Karnataka. After her initial schooling in Thaggahalli, she obtained her B.Sc. degree in 2007 from Bharathi College, affiliated to University of Mysore Bharathi Nagara and she obtained her M.Sc. degree with general chemistry in 2009 from University of Mysore, Mysore. She worked at HIKAL R & D Ltd. Bangalore during 2010-2011. She continued as a research scholar in the School of Chemistry, University of Hyderabad for the Ph. D. programme from July 2011 onwards.

# *LIST OF PUBLICATIONS*


1. D. B. Ramachary, R. Sakthidevi and **K. S. Shruthi**, "Asymmetric Supramolecular catalysis: A bio-inspired tool for the high asymmetric induction in the enamine-based Michael reactions". ***Chem. Eur. J.*** **2012**, *18*, 8008-8012.

2. D. B. Ramachary and **K. S. Shruthi**, "Asymmetric Synthesis of Tetrahydroquinolines through Supramolecular Organocatalysis", ***Org. Biomol. Chem.*** **2014,** *12,* 4300-4304.

3. D. B. Ramachary, **K. S. Shruthi** and R. Madhavachary, "A Modularly Designed Supramolecular Organocatalyst as an Effective Stimulant for the Highly Asymmetric Michael Addition of Ketones to Nitro Olefins", ***Eur. J. Org. Chem.*** **2015,** 6413–6418.

4. D. B. Ramachary, and **K. S. Shruthi** "A Brønsted Acid-Amino Acid as a Synergistic Catalyst for Asymmetric List-Lerner-Barbas Aldol Reactions". ***J. Org. Chem.*** **2016,** *81*, 2405–2419.

5. D. B. Ramachary, P. Sreekanth Reddy, **K. S. Shruthi**, R. Madhavachary and P. V. Govardhana Reddy "A Brønsted Acid-Primary Amine as a Synergistic-catalyst for Stereoselective Asymmetric Diels-Alder Reactions", ***Eur. J. Org. Chem.*** **2016,** 0000–0000 (DOI: 10.1002/ejoc.201601011).

## *Posters and Presentations*

1. **Poster presentation:** "Indo-German Conference on Bio Inspired Chemistry 2014" September 10 - 12, 2014 IISC, Bangalore, India**.**
   **Organizers:** IISC, Bangalore.
2. **Poster presentation:** The First Indo-Taiwan Symposium on "Recent Trends in Chemical Sciences (RTCS-2014)" November 17 - 18, 2014, HCU, Hyderabad, INDIA**.**
   **Organizers:** University of Hyderabad, Hyderabad.
3. **Poster presentation**: "MedChem India 2015" Hotel Radisson Hitec City, Hyderabad, India on 10-11 September 2015.
   **Organizers:** Select Bio
4. **Oral prasenatation: "**ChemFest -2016" (13$^{th}$ Annual In-House Symposium), School of Chemistry, University of Hyderabad.
   **Organizers:** University of Hyderabad, Hyderabad.