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UNIVERSITY OF HYDERABAD
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PH.D. COURSE WORK RESULTS

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Regn. No.: 16CHPH01

Sl. No.	Course No.	Title of the Course	No. of Credits	Grade
1.	CY801	Research Proposal	3	Pass
2.	CY805	Instrumental Methods-A	3	Pass
3.	CY806	Instrumental Methods-B	3	Pass
4.	CY571	Organometallic Chemistry	3	Pass
5.	CY573	Stereoselective Organic Synthesis	3	Pass

Final Result: Passed

Coordinator
Date: 21/07/2022

Dean
Date: 21/07/2022

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SCHOOL OF CHEMISTRY
University of Hyderabad
Hyderabad-500 046

Direct Organocatalytic Reductive Alkylation / Amination of Chiral Formylcyclopropanes: Scope and Applications

A

Thesis

Submitted for the Degree of

Doctor of Philosophy

By

AKRAM HUSSAIN

School of Chemistry
University of Hyderabad
Hyderabad-500046, India

August 2022

Dedicated to.....

My Parents and My Late Grandparents

My Lord, increase me in knowledge.

(Quran 20:114)

DECLARATION

I hereby declare that the matter embodied in the thesis entitled **"Direct Organocatalytic Reductive Alkylation/Amination of Chiral Formylcyclopropanes: Scope and Applications"** is the result of investigation carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, India, under the supervision of **Prof. Dhevalapally B. Ramachary**.

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CERTIFICATE

Certified that the work contained in the thesis entitled "Direct Organocatalytic Reductive Alkylation/Amination of Chiral Formylcyclopropane: Scope and Applications" has been carried out by Mr. Akram Hussain under my supervision and the same has not been submitted elsewhere for a degree. This thesis is free from plagiarism and has not been submitted previously in part or in full to this or any other University or Institution for award of any degree or diploma.

A. Parts of the thesis have been published in following publications:

1. Swamy Peraka, **Akram Hussain**, and Dhevalapally B. Ramachary. *J. Org. Chem.* **2018**, *83*, 9795.
2. **Akram Hussain**, and Dhevalapally B. Ramachary (*Manuscript under preparation*).
3. **Akram Hussain**, Swamy Peraka, and Dhevalapally B. Ramachary (*Manuscript under preparation*).

B. Presented in the following conferences:
1. J-NOST -XVII- 2022; **2.** ChemFest-2021;

Further the student has passed the following courses towards fulfilment of course work requirement for Ph.D.

Course work	Name	Credits	Pass/Fail
CY-801	Research proposal	3	Pass
CY-805	Instrumental Methods-A	3	Pass
CY-806	Instrumental Methods-B	3	Pass
CY-571	Organometallic Chemistry	3	Pass
CY-573	Stereoselective Organic Synthesis	3	Pass

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CONTENTS

ACKNOWLEDGEMENTS

Firstly, and most I would like to thank my supervisor ***Prof. Dhevalapally B. Ramachary****, for his inspiring guidance and constant encouragement throughout the course of the present investigations. It has been a great privilege and honor to be associated with him.*

I take this opportunity to thank Prof. Ashwini Nangia, Dean, School of Chemistry for providing all the facilities needed for my research. I extend my sincere thanks to former Dean Prof. T. P. Radhakrishnan and all the faculty members of the School of Chemistry for their timely help and cooperation during my Ph. D. program.

It is a great privilege to express my heartfelt regards to all my teachers during the entire tenure of my educational career, especially to Prof. Imran Ali, Prof Nasimul Hoda, Prof. R. P. Mathur, and Dr. K. Anebouselvy for their support and encouragement.

I take this occasion to express my love to the people who are with me under any conditions like Dr. Rizwan Ahmed, Dr. Mohd, Monis Ayyub, Waqar Ahmed, Safa Thayil, and Unalita Phukan.

It gives me great pleasure to thank my well-wishers Dr. Swamy Peraka, Dr. Khalid Naim, and Asif Iqbal during my Ph.D. studies.

I am extremely thankful to my lab seniors and colleagues, Dr. Shruthi, Dr. Rehana, Dr. Suresh Adaveni, Dr. Thirupathi, Dr. Prabhakar, Dr. Surrendra, Dr. Jagjeet, Dr. Anif, Pritam, Gorachand, Ashok, Vamshi, Rajyalaxmi, Sravanti, Shivani, Shyam, Rajkiran, Sharvan, Grace, Ganapati, and Asikul for their friendly cooperation in the lab.

I would like to express my heartfelt thanks to Prof. Periasamy, Prof. Balamurugan, and Prof. P. Ramu Shridhar lab members, Chemistry legends, Chemistry Badminton batch, Welcome party initiators-2016, and Chem-Fest volunteers of 2017 and 2022 for their affection during Ph.D. Studies.

I would like to express my lovable thanks to Dr. Junaid Ali, Dr. Manjoor Pandit, Dr. Shaukat Ali, Dr. Saddam, Dr. Tasnim, Dr. Sneha, Dr. Tanmay, Dr. Ankit Shrivastav, Dr. Mohd, Ishtiyak, Sayyed Basha, Irfan Wazir, Intezar Ali, S. K. Alim, Ishfaqh Ahmed, Mujahid Hussain, Asif Bhai, Noorul, Dr. Arshad, Shadab Bhai, Faisal, Rashid, Abdul Bari Bhai,

Maaz Bhai, Aizan, Abrar, Ehtesam and Pravindra who treated me as a brother during my PhD tenure.

I am very grateful to all my friends and colleagues in the School of Chemistry Dr. Suryanarayan, Dr. Majishankar, Ramesh Anna, Arun Anna, Anji Anna, Dr. Shashi anna, Dr. Shankar anna, Dr. Rajesh, Mou di, Shamita di, Shipra di, Sardamoni, Mamina, Jyotsna, Prachi, Soumya, Kalyani, Shanti, Lata, Ravindra, Jayakrishna, Suman, Narshima, Soutrik, Shubham, Shubham Dutta, Nilanjan, Laxman, Tabbasum, Kamla Laxmi, Sneha, Rina, Ritesh, Arun, Jishu, Sheema, Manas, Manoj, Olivia, Vinay, Vinod, Smruthi, Arun, Sneha, Shabber Ahmed, Ajay, Sachin, Suraj, Satyam, Shampita, Upasna, Moon, Dheeraj, and Liyaqat Ali.

I acknowledge the extreme support provided by the technical and non-teaching staff of the School of Chemistry. I also thank Dr. P. Ragavaiah, Satyanarayana, Vijaya Laxmi, Turab, Durgesh, Mahendra, Venky, Maruthi, and Mahesh for their timely assistance.

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

I would extremely appreciate the role of Hyderabadi food in my Ph.D. tenure especially, Hyderabadi biryani, Arabian mandi, Shawarma, and Irani chai.

Finally, I would like to thank my mother ***Shaira Bano*** *&* *father* ***Maksood Ali,*** *and my uncle* ***Mohd Hussain Ghori*** *&* *aunty* ***Khursida Bano*** *and my brothers Aslam Hussain, Saddam Hussain, Dr. Javed Hussain & sisters Shehnaz, Rehana, and Shabnam for their support, encouragement and deserves great appreciation. The unconditional love of my parents and their blessings made me what I am today and I owe everything to them. Dedicating this thesis to them is a minor recognition for their relentless support and love.*

Most importantly, I would like to thank the ***Almighty****, who gave me this opportunity in my life.*

Akram Hussain

PREFACE

Reductive alkylation/amination is one of the powerful reactions to generate a carbon-carbon/carbon-nitrogen bond in a single step. More importantly, organocatalytic reductive alkylation/amination has become an alternative to metal-mediated reductive alkylation/amination because of its simple operation technique, milder conditions, high efficiency, short reaction time, high regioselectivity, readily available precursors, and potentially greener. The present thesis entitled ***"Direct Organocatalytic Reductive Alkylation/Amination of Chiral Formylcyclopropanes: Scope and Applications"*** *describes the reactions between chiral formylcyclopropanes and active methylene compound or aromatic amines in the presence of secondary amine catalyst or phosphoric acid catalyst for the synthesis of highly functionalized organocatalytic reductive alkylation/amination products which have pharmaceutical and biological importance. In all these 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 superscripts 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 space.*

In the first chapter, an organocatalytic reductive coupling and Lewis acid catalyzed annulative ring-opening strategy is developed, as a two-step protocol for the stereoselective synthesis of dihydropyrans as the major products from the chiral formylcyclopropanes, CH-acids and Hantzsch ester. It is an efficient, catalytic, two-step protocol for the chiral synthesis of dihydropyrans and dihydrofurans. Structurally important and challenging functionally rich cyclopropanes containing cyclic-1,3-diones were synthesized in very good yields with excellent chemo-, enantio- and diastereoselectivities from the readily available starting materials, chiral formylcyclopropanes, cyclic-1,3-diones or CH-acids, and Hantzsch ester through an organocatalytic reductive coupling reaction at ambient conditions, especially without harming the cyclopropane ring. Chiral cyclopropanes containing cyclic-1,3-diones were stereospecifically transformed into dihydropyrans and dihydrofurans found in many bioactive natural products and drugs, through an annulative ring-opening reaction

by using Lewis acid ($BF_3.OEt_2$) or cesium carbonate (Cs_2CO_3)-catalysis. Highly diastereo- and regioselective ring-opening of cyclopropanes was explained through stereospecific intimate ion pair pathway.

In the second chapter, we synthesize a library of chiral dicarbonyl-cyclopropanes which were chemoselectively transformed into reductive alkylation products by using organocatalytic reductive coupling reaction in very good yields with excellent selectivities. These resultant molecules are basic skeletons of important drugs, and natural products and highlight the value of this organocatalytic reductive alkylation as a key protocol.

In the third chapter, we demonstrated the construction of structurally and biologically important chiral cyclopropylamines in good yields with excellent enantio- and diastereoselectivities. In this protocol variety of chiral formylcyclopropanes, achiral aromatic amines, and chiral amines are employed as key starting materials under the phosphoric acid catalysis. Furthermore, these chiral cyclopropylamines are transformed into functionally rich bio-inspired azabicyclo compounds.

LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Ac_2O	acetic anhydride
Anal.	analysis
aq.	aqueous
Ar	aryl
Bn	benzyl
Bp	boiling point
br	broad
Bu	butyl
*t*Bu or ^{t}Bu	*tertiar*y-butyl
n-BuLi	*n*-butyl lithium
calcd.	calculated
cat.	catalytic
cm	centimeter
CS/H	Claisen-Schmidt/Henry
CS/I	Claisen-Schmidt/isomerisation
CSP	chiral stationary phase
CuAAC	copper catalyzed azide-alkyne cycloaddition
DABCO	1,4-Diazabicyclo[2.2.2]octane
dABq	doublet of AB quartet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublet
ddd	doublet of doublet of doublet
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DMAP	dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dt	doublet of triplet
EDG	electron donating group
ee	enantiomeric excess
eq.	equation
equiv.	equivalent(s)
Et	ethyl
EtOH	ethyl alcohol
Et_2O	diethylether
EWG	electron withdrawing group
Fg	functional group
Fig.	figure
gm	gram (s)

h	hour (s)
Hz	hertz
Hex	hexyl
HIV	human immunodeficiency virus
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
^{i}Pr	isopropyl
IR	infrared
$LiAlH_4$	lithium aluminum hydride
lit.	literature
m	multiplet
m-CPBA	*m*-chloro perbenzoic acid
M	molarity
Mp.	melting point
Me	methyl
mg	milligram (s)
mGluR1	metabotropic glutamate receptor 1
mL	milliliter
mmol	millimole
MW	microwave
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidine
OrgAAC	organocatalytic azide-aldehyde cycloaddition
OrgAKC	organocatalytic azide-ketone cycloaddition
OrgRC	organocatalytic reductive coupling
PCC	pyridinium chlorochromate
PET	positron emission tomography
Ph	phenyl
ppm	parts per million
p-TSA	*p*-toluenesulfonic acid
py	pyridine
pr	propyl
q	quartet
RT	room temperature
s	singlet
sec	secondary
t	triplet
TBHP	tertiary-butyl hydroperoxide
*t*BuOK	Potassium tertiarybutoxide
td	triplet of doublet
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulphonyl
UV	ultraviolet

1. Abstract

The cyclopropane ring is unique among all carbocycles due to its unusual bonding and inherent ring strain and has constantly been of great scientific interest to the organic community. In addition to the appealing synthetic transformations that cyclopropanes might present, these smallest carbocycles are part of larger molecular structures that possess a wide range of biological properties spanning from enzyme inhibitions, antibacterial, antimetastatic (anticancer), antifungal, insecticidal, plant growth, and fruit ripening control. The majority of cyclopropane-containing natural compounds have been isolated from plants, fungi, or microorganisms. Many show biological activity and may serve as potential drug leads or provide new ideas for the study of enzyme mechanisms. Here we describe a strategy and extensive synthetic studies for the preparation of a diverse collection of cyclopropane-containing lead-like compounds, fragments, and building blocks.

In the first chapter, an organocatalytic reductive coupling and Lewis acid catalyzed annulative ring-opening strategy is developed, as a two-step protocol for the stereoselective synthesis of dihydropyrans as the major products. It is an efficient, catalytic, two-step protocol for the chiral synthesis of dihydropyrans and dihydrofurans. Structurally important and challenging functionally rich cyclopropanes containing cyclic-1,3-diones were synthesized in very good yields with excellent chemo-, enantio- and diastereoselectivities from the readily available starting materials, chiral formylcyclopropanes, cyclic-1,3-diones or CH-acids, and Hantzsch ester through an organocatalytic reductive coupling reaction at ambient conditions, especially without harming the cyclopropane ring.

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2. Introduction

August Freud described the first cyclopropanation reaction in 1881, using a Wurtz coupling reaction to combine 1,3-dibromopropane with sodium.[1] Gustavson increased the reaction yield by substituting zinc for sodium.[2] The triangular structure of cyclopropane has 60° bond angles between carbon-carbon bonds. Because the carbon-carbon bonds in cyclopropane are weaker than those in a conventional alkane due to ring and torsional strain, cyclopropane becomes a more reactive ring.[3] Despite its high reactivity nature, the cyclopropane scaffold is found in a wide spectrum of natural products and medicines, with a diverse range of biological functions.[4] There are some examples as shown in Figure 1, which act as inhibitors, antagonists, antipsychotic drugs, antibiotics, etc.[5]

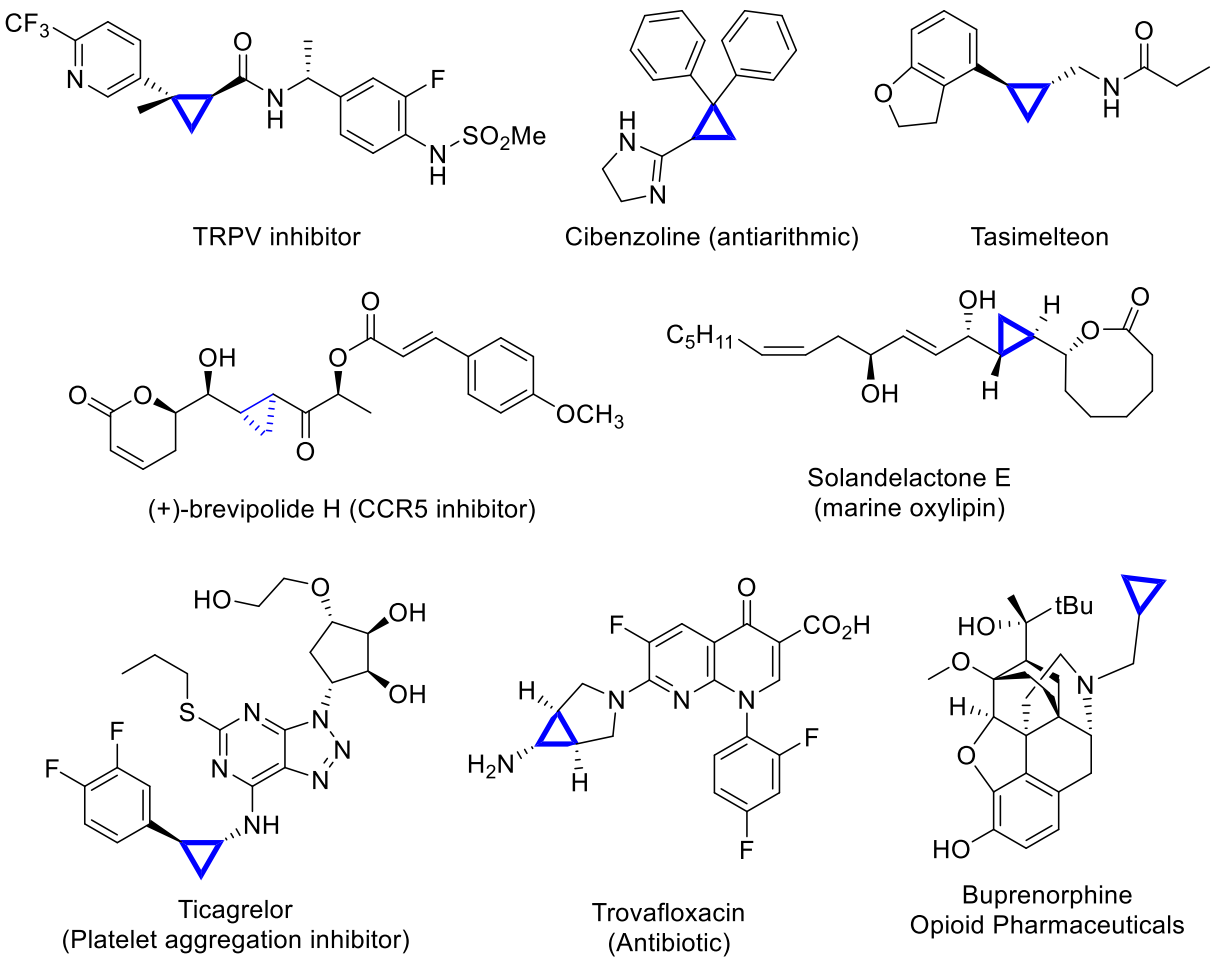
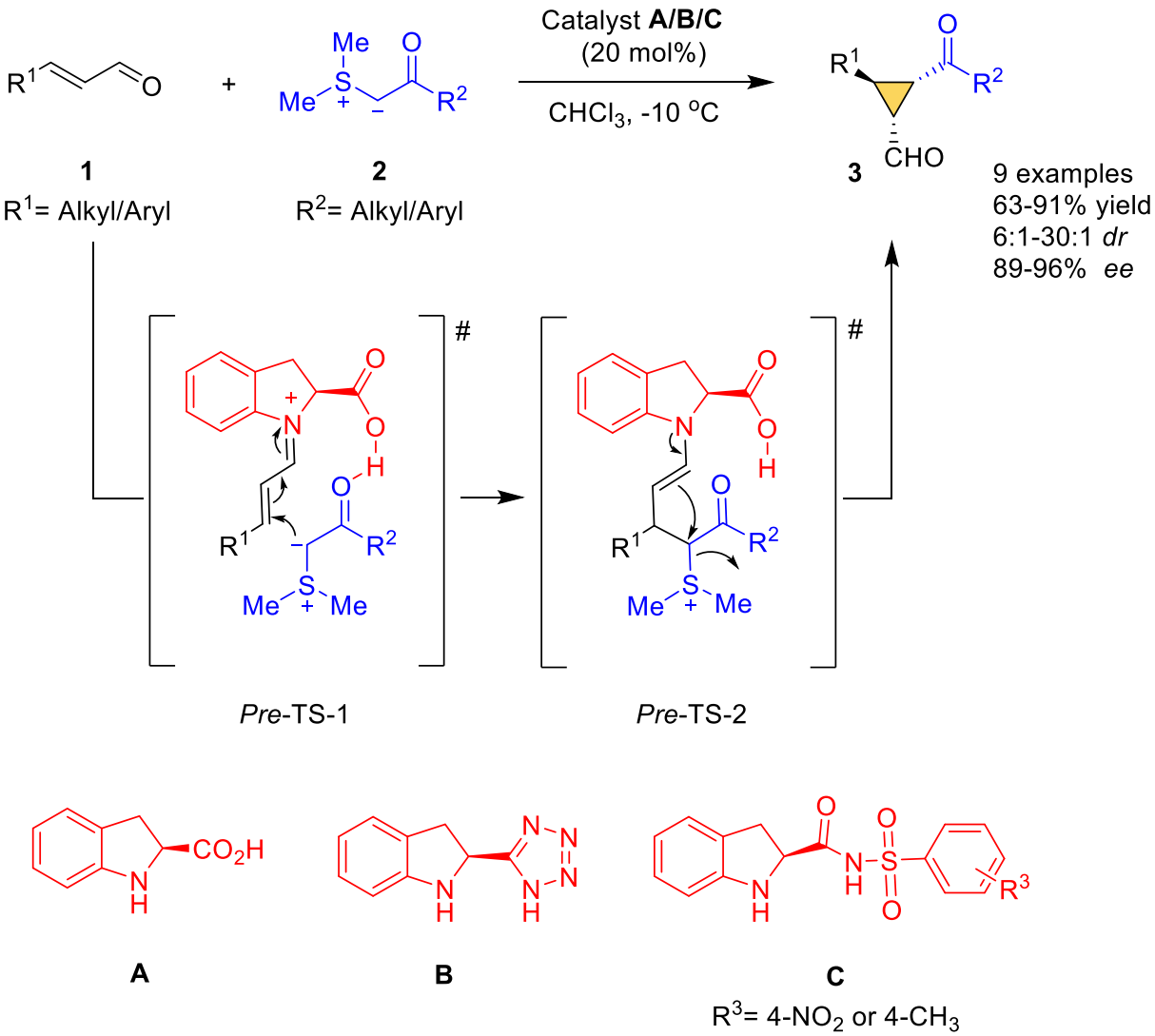


Figure 1. Cyclopropane-containing drug molecules.

Organocatalytic Synthesis of Chiral Formylcyclopropanes:

(1) Cyclopropanation *via* Sulfonium Ylide Addition: [6-8]

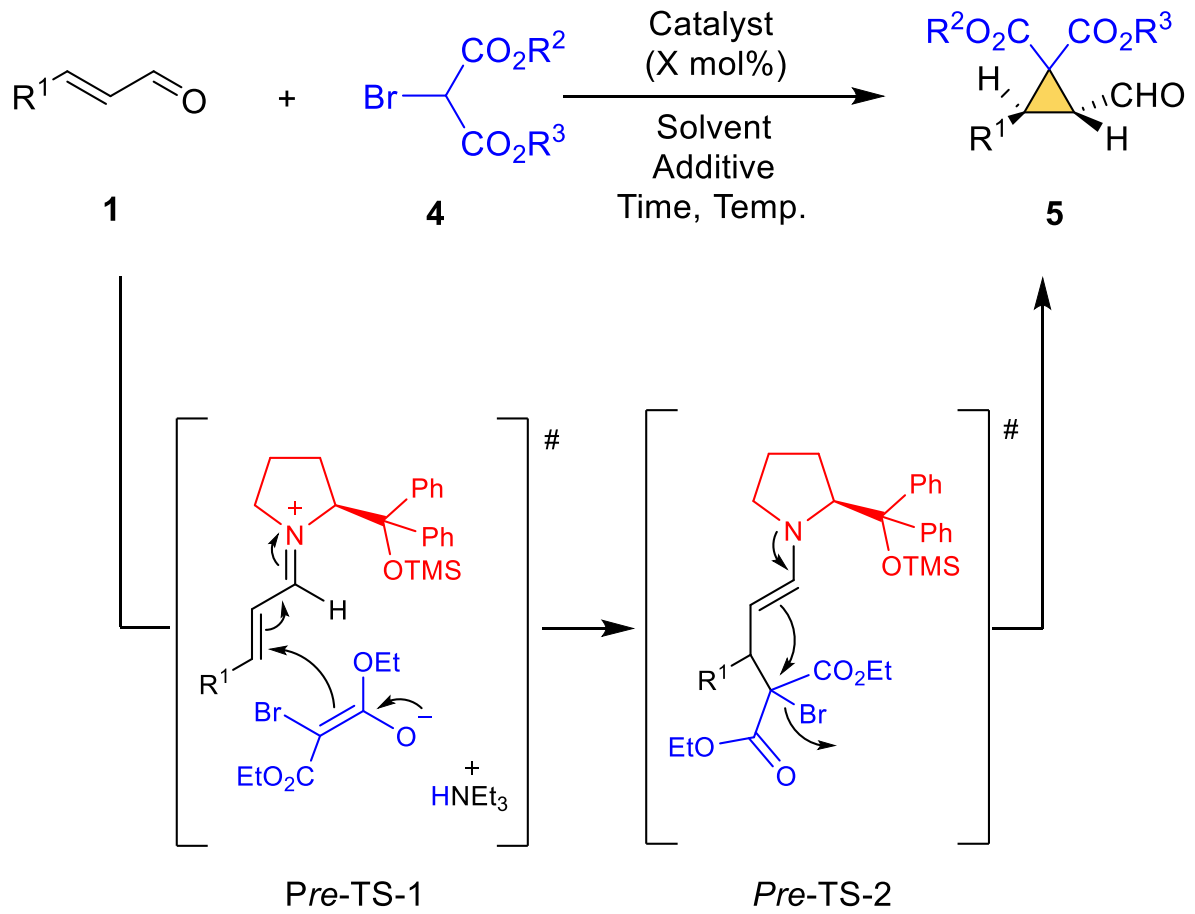
Kunz and MacMillan[6] described enantioselective organocatalytic cyclopropanation in which a direct electrostatic interaction between chiral zwitterionic iminium and sulfonium ylide (*Pre*-TS-1) is the key step in facilitating the formation of a carbon-carbon bond, which is then followed by stereoselective cyclization to yield the cyclopropane (*Pre*-TS-2). In this reaction, α,β-unsaturated aldehyde **1**, and sulfonium ylide **2** were treated in $CHCl_3$ at -10 °C with the chiral 2-carboxylic acid dihydroindole **A** (20 mol%) as a catalyst to create cyclopropane **3** with three stereogenic centers with 63-91% yield and high *ee*'s. Hartikka and Arvidsson[7,8] described organocatalytic cyclopropanation of α,β-unsaturated aldehyde **1** with sulphur ylide **2** by using (-)-indoline-2-yl-1*H*-tetrazole **B** or sulfonamides **C** as a catalyst in these reactions respectively (Scheme 1).



Scheme 1. Cyclopropanation *via* sulfonium ylide addition.

(2) Cyclopropanation *via* Dialkyl Bromomalonate Addition: [9-15]

Stereoselective conjugate addition of dialkyl bromomalonate **4** to α,β-unsaturated aldehydes **1** in the presence of secondary amine **D-H** as a catalyst yielding enantioselectively cyclopropanes **5** with good to excellent yield and high *ee* and *dr*'s. The mechanism can be explained as iminium ion generation from α,β-unsaturated aldehyde, and secondary amine, followed by the attack of the in situ generated anion from the diethyl bromomalonate and triethylamine as shown in *Pre*-TS-1 of the Scheme 2. The first generated Michael adduct intermediate cyclizes by releasing a bromide ion and creating cyclopropane *via* an intramolecular alkylation process (Scheme 2). Full details about these reactions catalyzed by different catalysts **D-H** are discussed in the coming section (see, Figure 2 and Table 1).



Scheme 2. Cyclopropanation via dialkyl bromomalonate addition.

(a) Rios and co-workers[9-11] reported that adding diethyl bromomalonate **4** to α,β-unsaturated aldehyde **1** and chiral secondary amine **D/E** (10 mol%) as a promoter in $CHCl_3$ for 3-14 h at room temperature yielded enantioselectively cyclopropane **5** with 50-88% yield and high *ee*/*dr*'s. The main product was trans-cyclopropane.

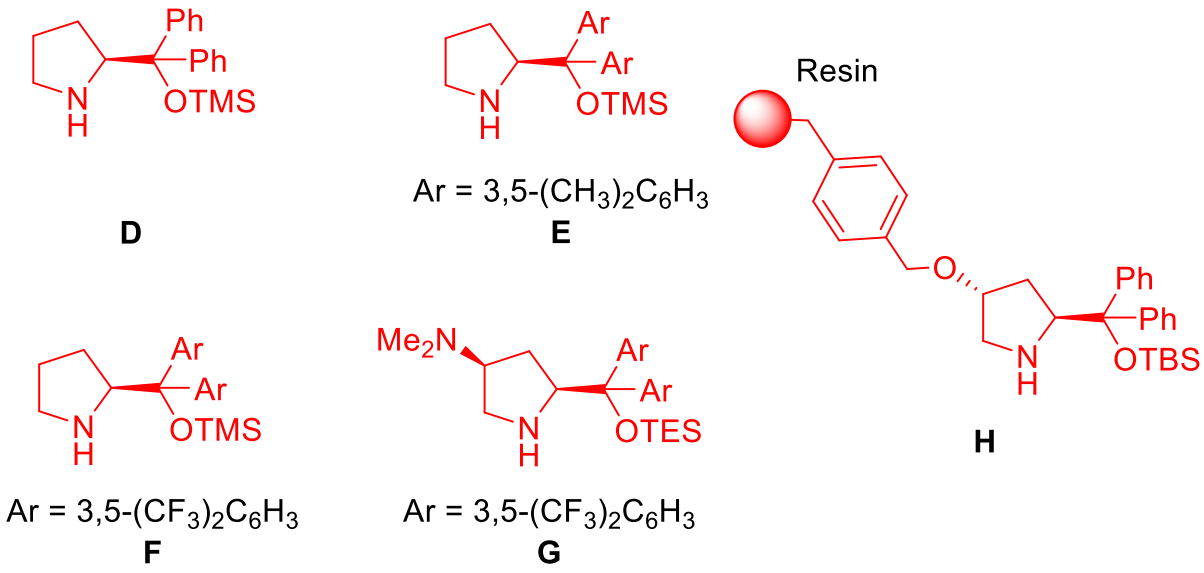


Figure 2. Different types of secondary amine catalysts used in cyclopropanation reaction.

(b) Dialkyl bromomalonate **4** was added to α,β-unsaturated aldehyde **1**, and chiral diphenyl prolinol TMS ether **D** (10 mol%) as a promoter in CH_2Cl_2 at room temperature, yielding enantioselectively cyclopropane **5** with 42-95% yield and high *ee*/*dr*'s, reported by Xie and co-workers.[12] The main product was trans-cyclopropane (Scheme 2, Figure 2, Table 1).

(c) Uria and co-workers[13,14] reported the first organocatalytic enantioselective cyclopropanation reaction of α,β-unsaturated aldehyde **1** with diethyl bromomalonate **4** in the presence of O-TMS-diarylprolinol **F** (20 mol%) and **G** (10 mol%) catalysts in the presence of water as the solvent. The chiral cyclopropane **5** was obtained with 56-84% yield and high *ee*/*dr*'s by stirring the reagents combination at room temperature for 96 h in the absence of a basic additive (Scheme 2, Figure 2, Table 1).

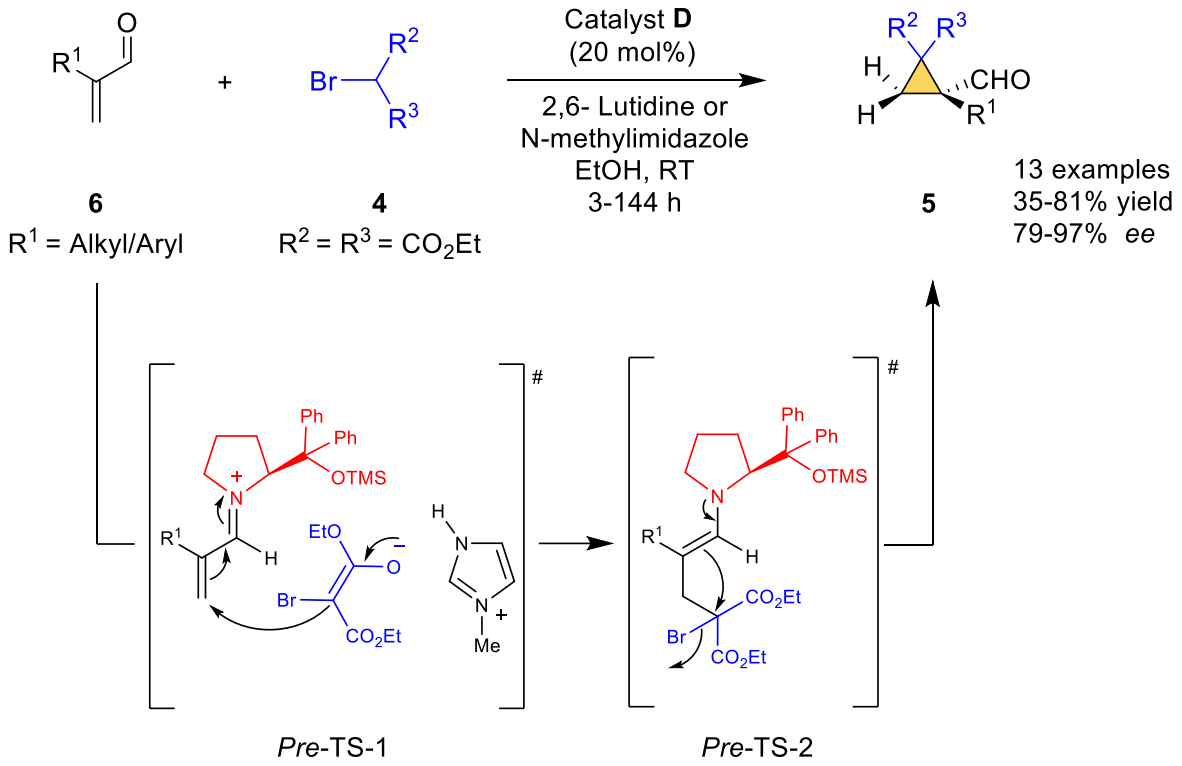
(d) An enantioselective flow technique was used to achieve an organocatalytic enantioselective cyclopropanation reaction,[15] in which a chiral resin **H** was made by mixing chiral vinylbenzyloxy pyrrolidine with styrene in the presence of various additives. Chiral resin was packed in an omnifit glass column with two feed streams, one containing α,β-unsaturated aldehyde **1** and dimethyl bromomalonate **4**, and the other containing N-methylimidazole. The reagent combination flows towards the column, which is assisted by the organocatalyst, promoting the production of chiral cyclopropane **5** with a yield of 23-60% and high *ee*/*dr*'s (Scheme 2, Figure 2, Table 1).

S.N.	R^1	R^2 and R^3	Catalyst (X mol%)	Additive	Solvent	Time, Temp	Products
1[9,10]	Alkyl/Aryl	$R^2 = R^3 =$ Et	**D/E** (20 mol%)	Et_3N	$CHCl_3$	3-14 h, 25 °C	11 examples 50-88% yield 9:1 to >25:1 *dr* 93-99% *ee*
2[11]	Alkyl/Aryl	R^2 = Me/ Et/*t*Bu R^3 = COMe/ CO*t*Bu	**D** (20 mol%)	Et_3N	Toluene	14-72 h, 25 °C	12 examples 68-95% yield 2.4:1 to 25:1 *dr* 63-99% *ee*
3[12]	Alkyl/Aryl/ 2-Furanyl	$R^2 = R^3 =$ Me/Et/*i*Pr/Bn	**D** (10 mol%)	2,6-Lutidine	CH_2Cl_2	5.5-52 h 0 °C	16 examples 42-95% yield >30:1 *dr* 90-98% *ee*
4[13]	Alkyl/Aryl/ 2-Furanyl	$R^2 = R^3 =$ Et	**F** (20 mol%)	No Additive	H_2O	96 h 25 °C	6 examples 56-84% yield >10:1 *dr* 92 to >99% *ee*
5[14]	Aryl/ 2-Furyl	$R^2 = R^3 =$ Et	**G** (10 mol%)	No Additive	H_2O	25 °C	6 examples 60-93% yield >19:1 *dr* 93 to >99% *ee*
6[15]	Aryl/ 2-Furanyl/ 2-Thiophene/ 3-Pyridyl	$R^2 = R^3 =$ Me	**H**	N-methylimidazole	CH_2Cl_2	6 h 25 °C	12 examples 23-60% yield >95:5 *dr* 89-96% *ee*

Table 1. Cyclopropanation *via* dialkyl bromomalonate addition.

(3) Organocatalyzed Cyclopropanation of α-Substituted α,β-Unsaturated Aldehydes:

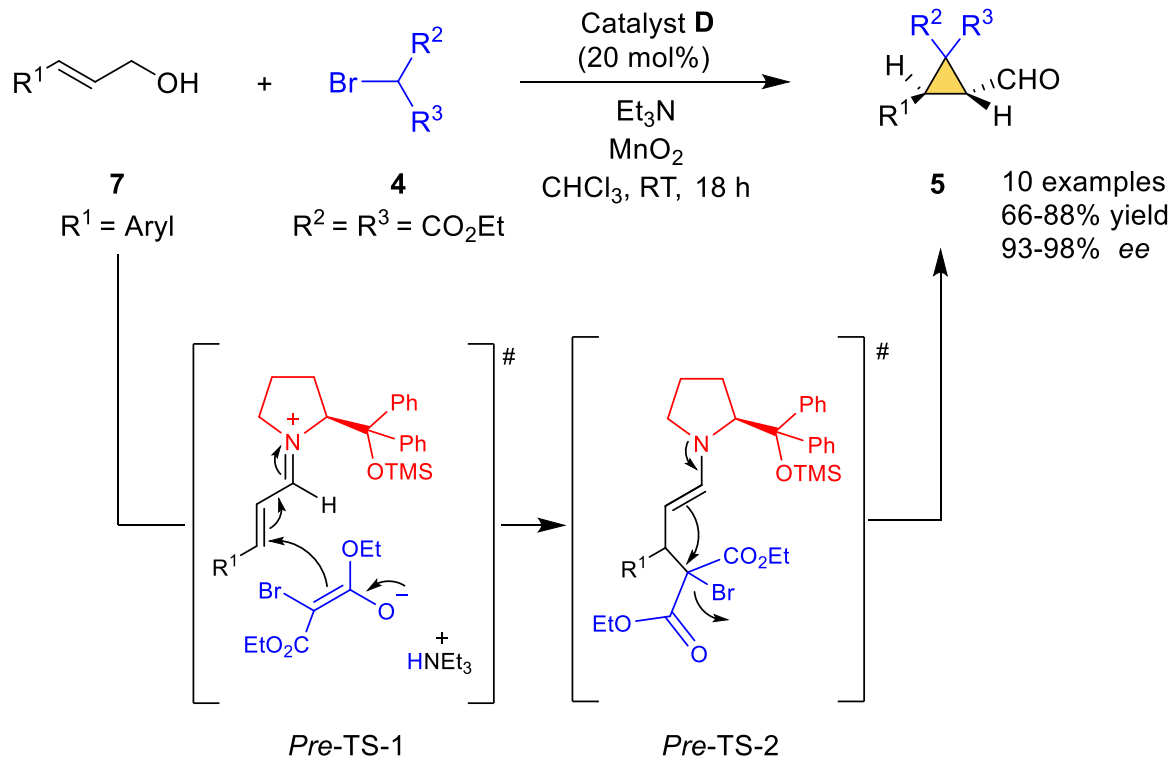
Terrason and co-workers[16] reported the first asymmetric cyclopropane synthesis from α-substituted α,β-unsaturated aldehydes **6**. The key steps in this synthesis were an organocatalytic cascade Michael reaction followed by an intramolecular alkylation to produce chiral cyclopropanes **5** with a quaternary stereogenic centre. Aldehydes **6** were treated with bromomalonate **4** and chiral diphenyl prolinol TMS **D** (20 mol%) as catalyst and 2,6-lutidine or N-methylimidazole as an additive in ethanol at room temperature for 3-144 h to furnish cyclopropanes **5** in high selectivity as described (Scheme 3). Cyclopropane was formed *via* iminium intermediate (*Pre*-TS-1) generation, where Michael addition of bromomalonate was added to iminium ion to generate enamine intermediate, which on further intramolecular alkylation (*Pre*-TS-2) furnished the cyclopropanes with high *ee*/*dr*'s (Scheme 3).



Scheme 3. Cyclopropanation *via* diethyl bromomalonate addition to α-substituted α,β-unsaturated aldehydes.

(4) One-pot Enantioselective Cyclopropanation of Allylic Alcohols:

Rueping and co-workers[17] described the first asymmetric cyclopropane synthesis by using cinnamyl alcohol **7**, diethyl bromomalonate **4**, diphenyl prolinol TMS-ether **D** (20 mol%) as a catalyst, and Et_3N as co-catalyst by using MnO_2 as an oxidant to furnish cyclopropanes **5** in 66-88% yield with high *ee*/*dr*'s in chloroform at room temperature for 18 h. The process began with in situ hydroxyl group oxidation to the corresponding aldehyde by using MnO_2 excess, followed by the in situ generations of the iminium intermediate (*Pre*-TS-1) to which the diethyl malonate was added through Michael addition, and finally, an intramolecular alkylation reaction (*Pre*-TS-2) was taken place to produce cyclopropanes in high *ee*/*dr*'s (Scheme 4).



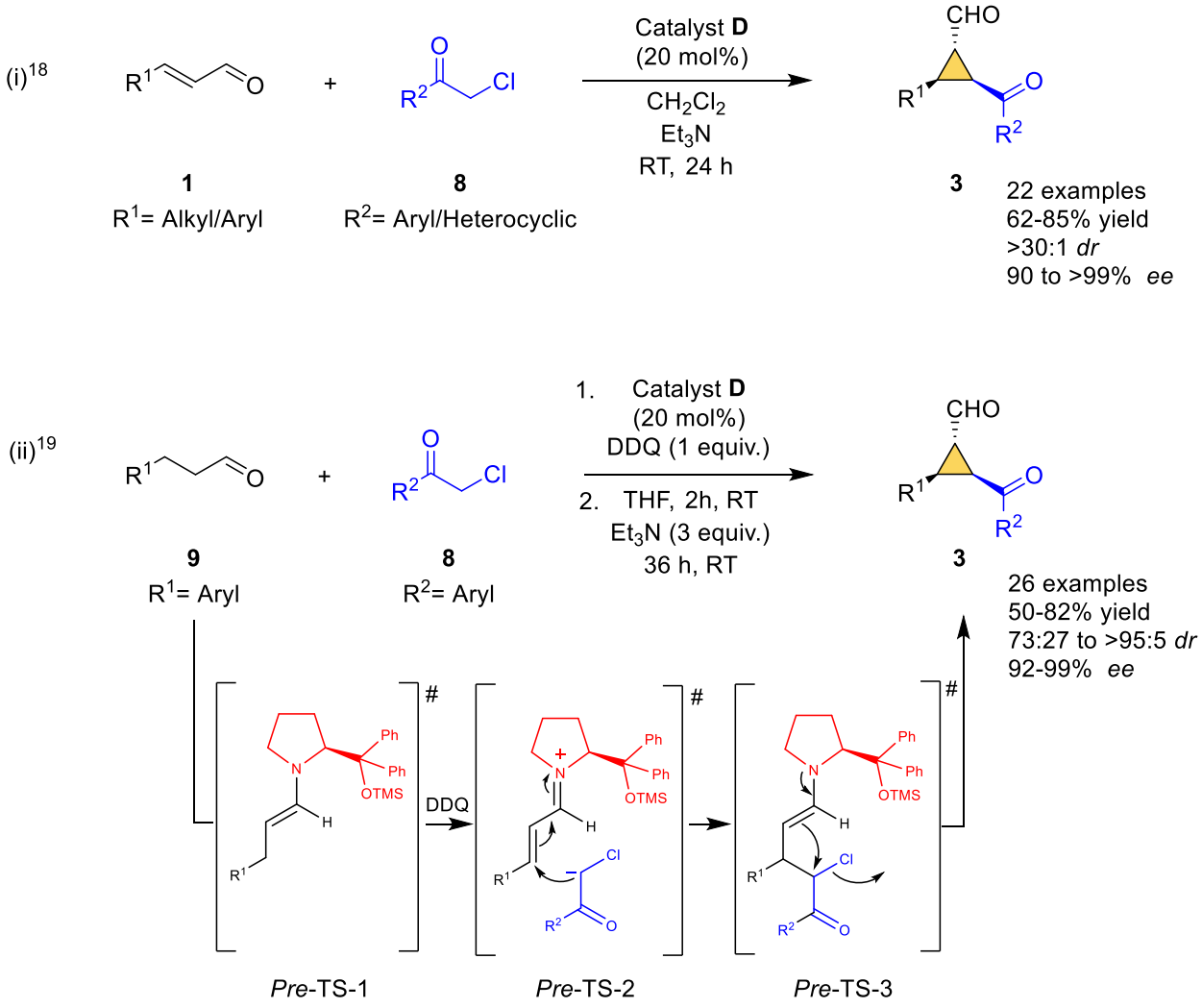
Scheme 4. Cyclopropanation *via* diethyl bromomalonate addition on allylic alcohols.

(5) Cyclopropanation *via* Alkyl Halide Addition:[18,19]

An organocatalytic enantioselective synthesis of cyclopropane was achieved with α,β-unsaturated aldehydes **1** and chloroacetophenone **8** in the presence of diphenyl prolinol TMS-ether **D** (20 mol%) as catalyst and Et_3N as base in CH_2Cl_2 at room temperature for 24 h.[18] The asymmetric reaction proceeded as α,β-unsaturated aldehydes **1** was treated with diphenyl prolinol TMS-ether **D** (20 mol%) in CH_2Cl_2 at room temperature to afford the chiral iminium ion (*Pre*-TS-2), which was attacked by chloroacetophenone **8** *via* Michael addition to produce Michael adduct (*Pre*-TS-3). This intermediate further cyclized to releasing a chloride to furnish cyclopropane **3** in 62-85% yield with high *ee*/*dr*'s as depicted in Scheme 5.

Dzambaski and co-workers[19] described an enantioselective organocatalytic cyclopropane **3** synthesis from saturated aldehyde **9**. This saturated aldehyde **9** in the presence of diphenyl prolinol TMS-ether **D** (20 mol%) catalyst formed enamine intermediate (*Pre*-TS-1), which was *in situ* oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinine (DDQ) in THF at room temperature for 2 h to produce iminium ion. As demonstrated in Scheme 5, a second Michael addition of deprotonated chloroacetophenone **8** to iminium ion (*Pre*-TS-2), followed

by an intramolecular alkylation, yielded chiral cyclopropanes **3** (*Pre*-TS-3) in 50-82% yield with high *ee*/*dr*'s as depicted in Scheme 5.

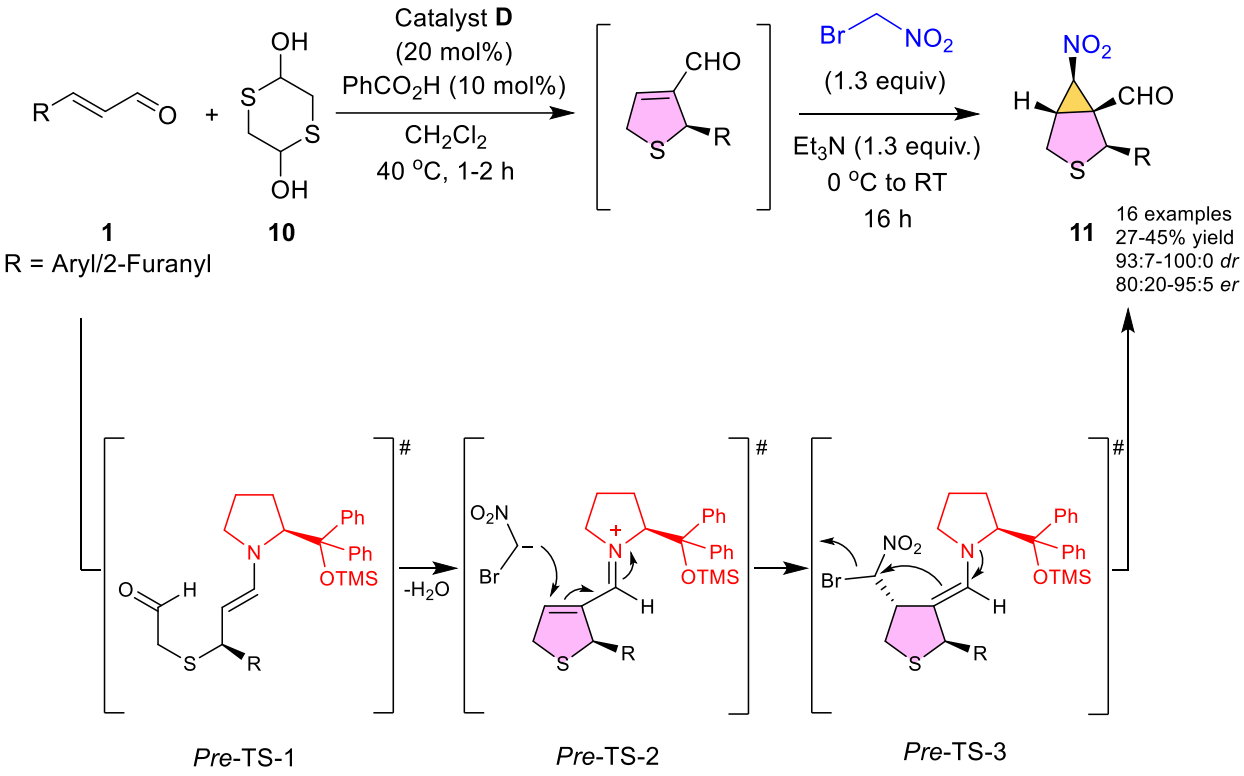


Scheme 5. Cyclopropanation via alkyl halide addition.

(6) Cyclopropanation *via* Bromonitromethane Addition:

A four-step organocatalytic reaction yielded unprecedented bicyclic nitrocyclopropane **11** in one-pot manner.[20] This procedure involved the reaction of α,β-unsaturated aldehyde **1**, and 1,4-dithiane-2,5-diol **10** in CH_2Cl_2 for 2 h at 40 °C in the presence of (*S*)-diphenylprolinolsilyl ether **D** (20 mol%) and benzoic acid as an additive in an inert atmosphere. Then a bromonitromethane/triethylamine mixture is added to furnish the bicyclic nitrocyclopropane **11** with 27-45% yield and high *ee*/*dr*'s. The sulfa-Michael reaction is carried out by adding mercaptoacetaldehyde to the corresponding chiral iminium-ion to produce the enamine intermediate (*Pre*-TS-1) in the asymmetric organocatalytic process. After an

intramolecular aldol reaction and dehydration, an iminium-ion intermediate (*Pre*-TS-2) was obtained, which was then added to bromonitromethane to produce an intermediate (*Pre*-TS-3), in which the bromine atom is displaced through an intramolecular nucleophilic substitution to produce the nitrocyclopropanes (Scheme 6).

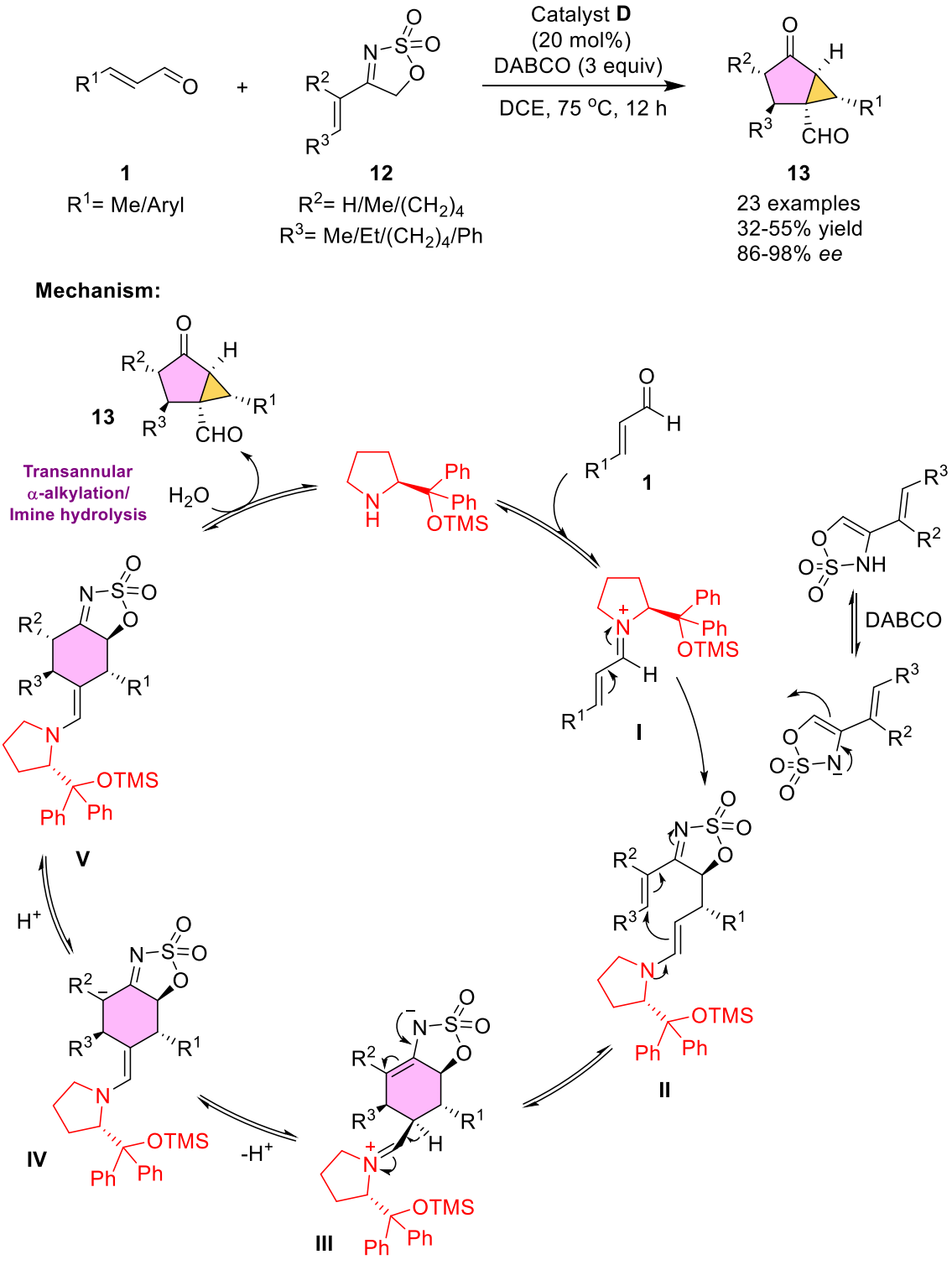


Scheme 6. Cyclopropanation via bromonitromethane addition.

(7) Organocatalytic Transannular Approach to Stereodefined Bicyclo[3.1.0]Hexanes:

Through a transannular alkylation reaction that builds up the bicyclic core and uses asymmetric organocatalysis to install all stereocenters with a diastereodivergent method to construct highly substituted bicyclo[3.1.0]hexanes **13** (Scheme 7)[21]. The substituted bicyclo[3.1.0]hexanes **13** were directly obtained in a single operation from the enals **1** and 4-alkenyl sulfamidate imines **12** *via* a cascade Michael/Michael/transannular alkylation/hydrolysis sequence using successive iminium/enamine/enamine combination of aminocatalytic activation manifolds. In the presence of a diarylprolinol derivative **D** as catalyst, a Michael/Michael cascade reaction under the well-known combination of aminocatalytic iminium/enamine activation mechanisms was responsible for the installation of all stereocenters (**I**), forming an oxathiazole-2,2-dioxide-fused cyclohexane adduct intermediate (**III**/**IV**). This intermediate can continue the cascade process by undergoing a subsequent

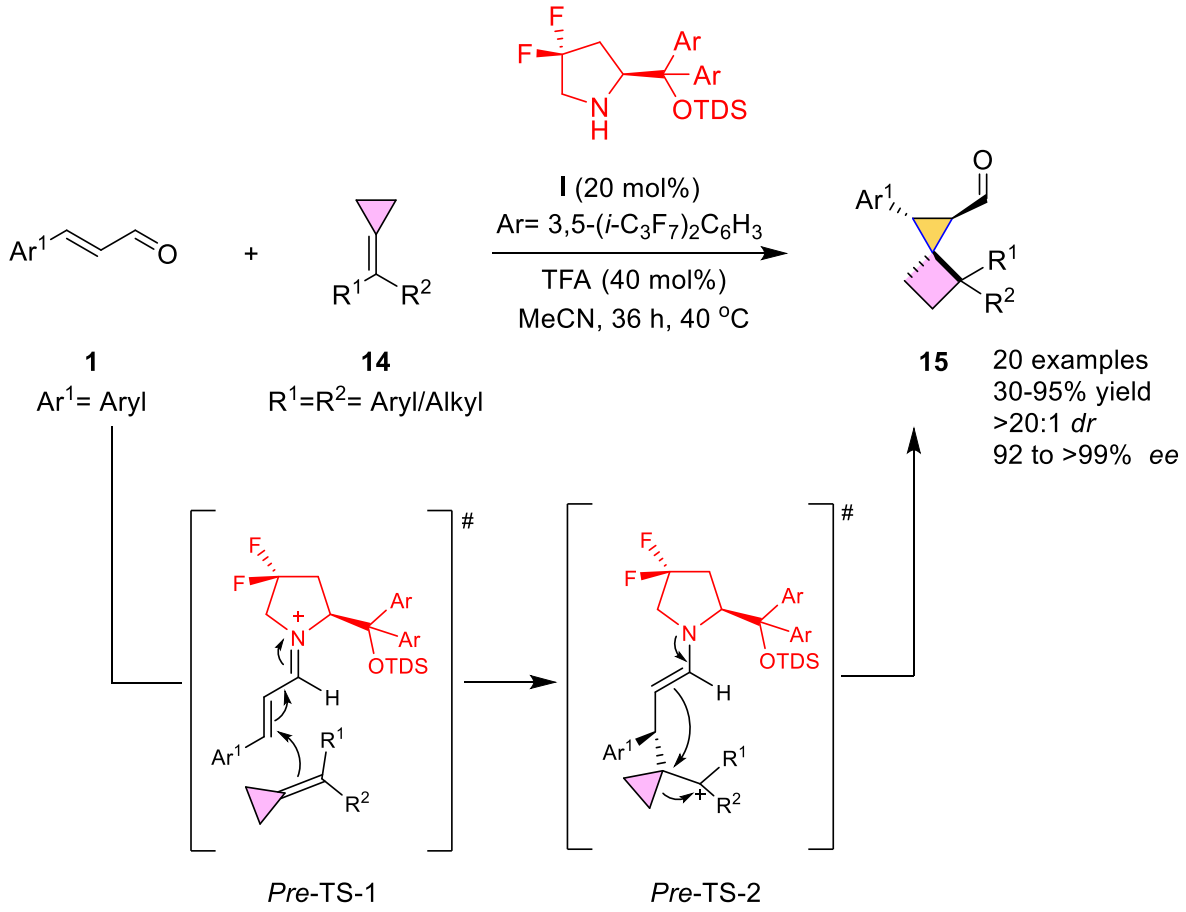
transannular alkylation reaction through an enamine intermediate (**V**) followed by hydrolysis to generate compounds **13** in high yields with *ee* and *dr*'s (Scheme 7).



Scheme 7. Organocatalytic transannular approach to stereodefined bicyclo[3.1.0]hexanes.

(8) Highly Enantioselective Construction of Strained Spiro[2,3]Hexanes Through a Michael Addition/Ring Expansion/Cyclization Cascade:

Zhao and co-workers[22] described a universal organocatalytic enantioselective technique for making highly strained spiro[2,3]hexane **15** skeletons from methylenecyclopropanes **14** and a wide range of α,β-unsaturated aldehydes **1**. To realize the production of spiro[2,3]hexanes **15**, a Michael addition on iminium ion intermediate (*Pre*-TS-1), is followed by ring expansion of methylenecyclopropanes and nucleophilic attack of an enamine (*Pre*-TS-2). The use of an electron-deficient difluoro-substituted secondary amine catalyst **I** and the innate reactivity of methylenecyclopropanes were critical to the success of this method (Scheme 8).

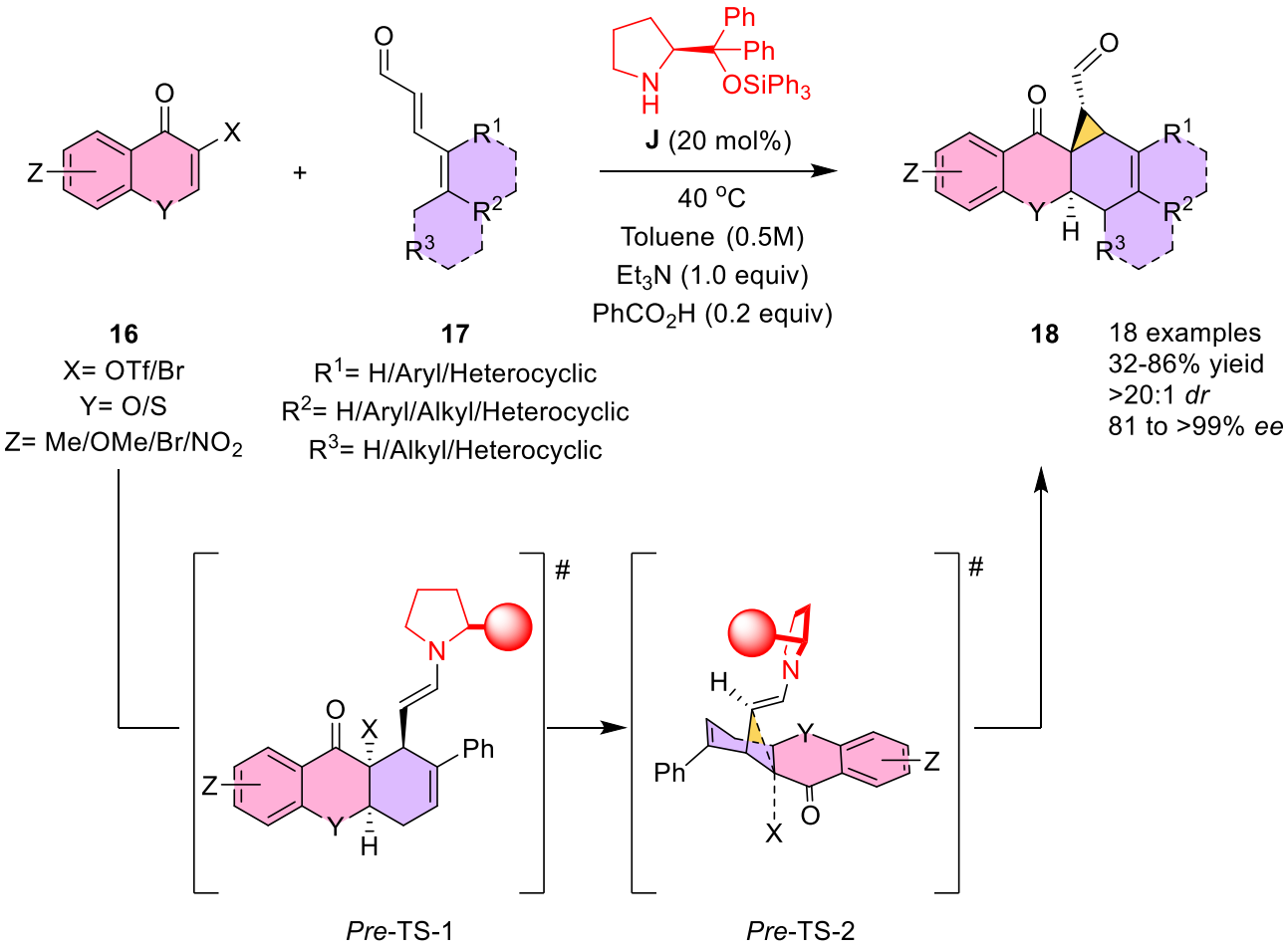


Scheme 8. Highly enantioselective construction of strained spiro[2,3]hexane.

(9) A Direct Organocatalytic Enantioselective Route to Functionalized *trans*-Diels–Alder Products Having the Norcarane Scaffold:

Barlose and co-workers[23] described an enantioselective organocatalytic approach for constructing *trans*-Diels–Alder scaffolds **18** with excellent selectivity, high yield, and up to

five contiguous stereocenters (Scheme 9). The process concept combines the halogen effect with a newly found pseudo-halogen effect to lead to an *endo*-selective secondary-amine catalysed Diels–Alder reaction, resulting in *trans*-Diels–Alder cycloadducts with the norcarane scaffold. The method depends on the formation of a transient *cis*-Diels–Alder intermediate (*Pre*-TS-2) by the reaction of an in situ produced trienamine with an α-brominated or α-pseudo-halogenated enone (*Pre*-TS-1). The endo-transition state-enhanced by the pseudo-halogen effect sets the stereochemistry that allows for a subsequent S_N^2-like reaction at a tertiary center to obtain the *trans*-Diels–Alder scaffold (Scheme 9).



Scheme 9. Direct organocatalytic enantioselective route to functionalized *trans*-Diels-Alder products having the norcarane scaffold.

3. Synthesis of Chiral 2,3-Dihydrofurans and 3,4-Dihydro-2H-pyrans through Organocatalytic Reductive Coupling and Annulative Ring-Opening Reactions

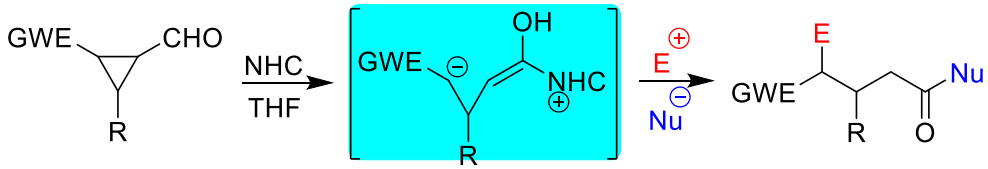
3.1 Introduction

Synthesis and study of cyclopropane ring, which is widely present as key structural motif in many natural and pharmaceutically active compounds, is challenging task due to their stereoelectronic factors and intrinsic ring strain.[24-26] Over the past two decades, the domain of donor-acceptor cyclopropanes (D-A cyclopropanes) has experienced an exponential growth since the seminal work by Wenkert,[27] Danishefsky,[28] and Reissig.[29] The chemist's interest on D-A cyclopropanes increased, as they were predisposed to provide ready access to multi-functionalized intermediates and key building blocks, for the synthesis of natural products and biologically active molecules through various ring-opening strategies.[30-41] The ring-opening has been largely realized through activation by Lewis acid[23,24] and transition-metal catalysis in both achiral[32] and chiral[33] versions. In addition, D-A cyclopropanes are transformed into various cyclic compounds by Brønsted acid[34] and base[35] induced nucleophilic addition, ring-expansion and cycloaddition reactions.

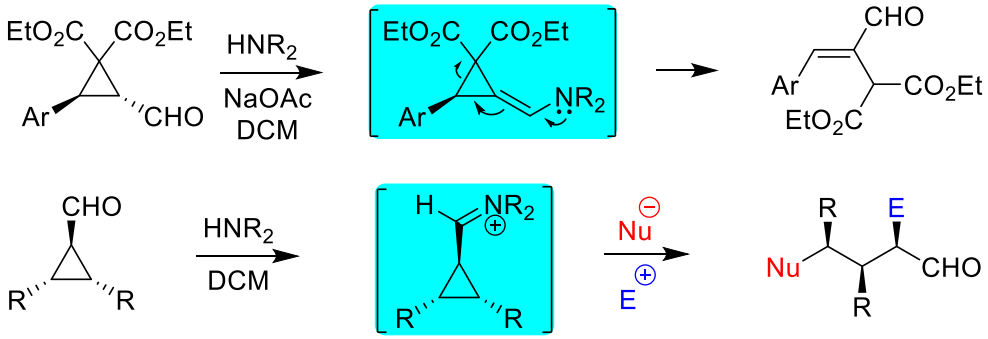
Among D-A cyclopropanes, formylcyclopropanes are of particular interest, as they open up new window for investigation of novel reactions by activation of the formyl group under the newly emerging organocatalysis. In 2006, Bode *et. al.* demonstrated the first NHC-catalyzed redox esterification by ring-opening of chiral formylcyclopropanes (Scheme 10a).[36a] This elegant reaction inspired many organic chemists to use formylcyclopropanes in various ring expansion, annulation and cycloaddition reactions (Scheme 10a).[36b-g] In 2007, Wang and co-workers and in 2008, Cordova and co-workers disclosed the formylcyclopropane ring-opening by secondary amine-catalysis in the presence of base through iminium and enamine formation (Scheme 10b).[12]

Scheme 10. Previous Organocatalytic Methods for Activation of D-A Cyclopropanes.

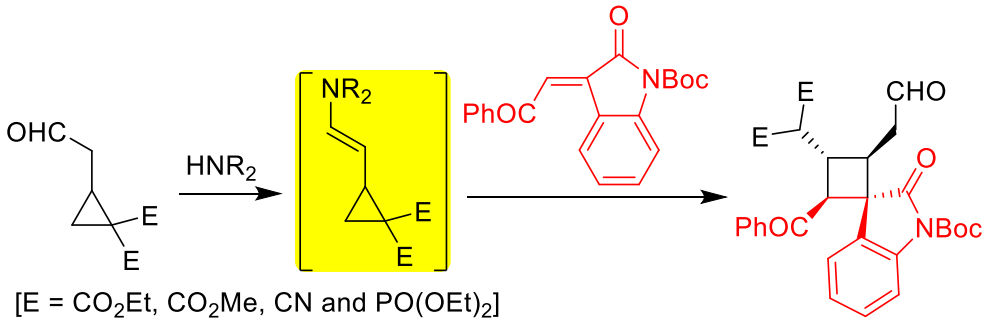
(a) NHC-catalysed cyclopropane ring-opening: Bode, Wang, You, Chi, Reyes[13]



(b) Iminium-mediated cyclopropane ring-opening: Wang, Sparr, Gilmour, Werz[14,15]

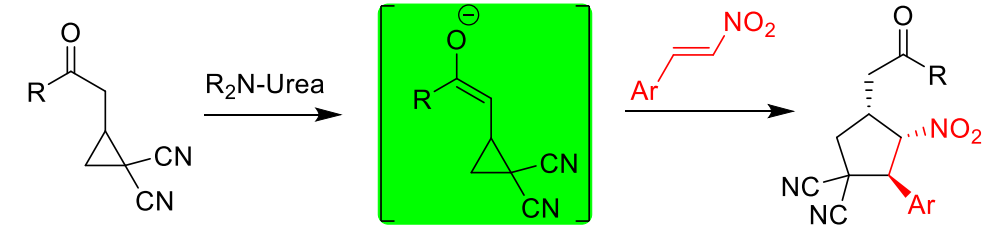


(c) Enamine-mediated cyclopropane ring-opening: Jorgensen[16]



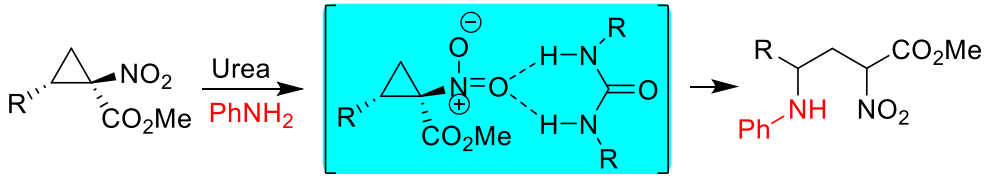
[E = CO_2Et, CO_2Me, CN and $PO(OEt)_2$]

(d) Enolate-mediated cyclopropane ring-opening: Jorgensen[17]



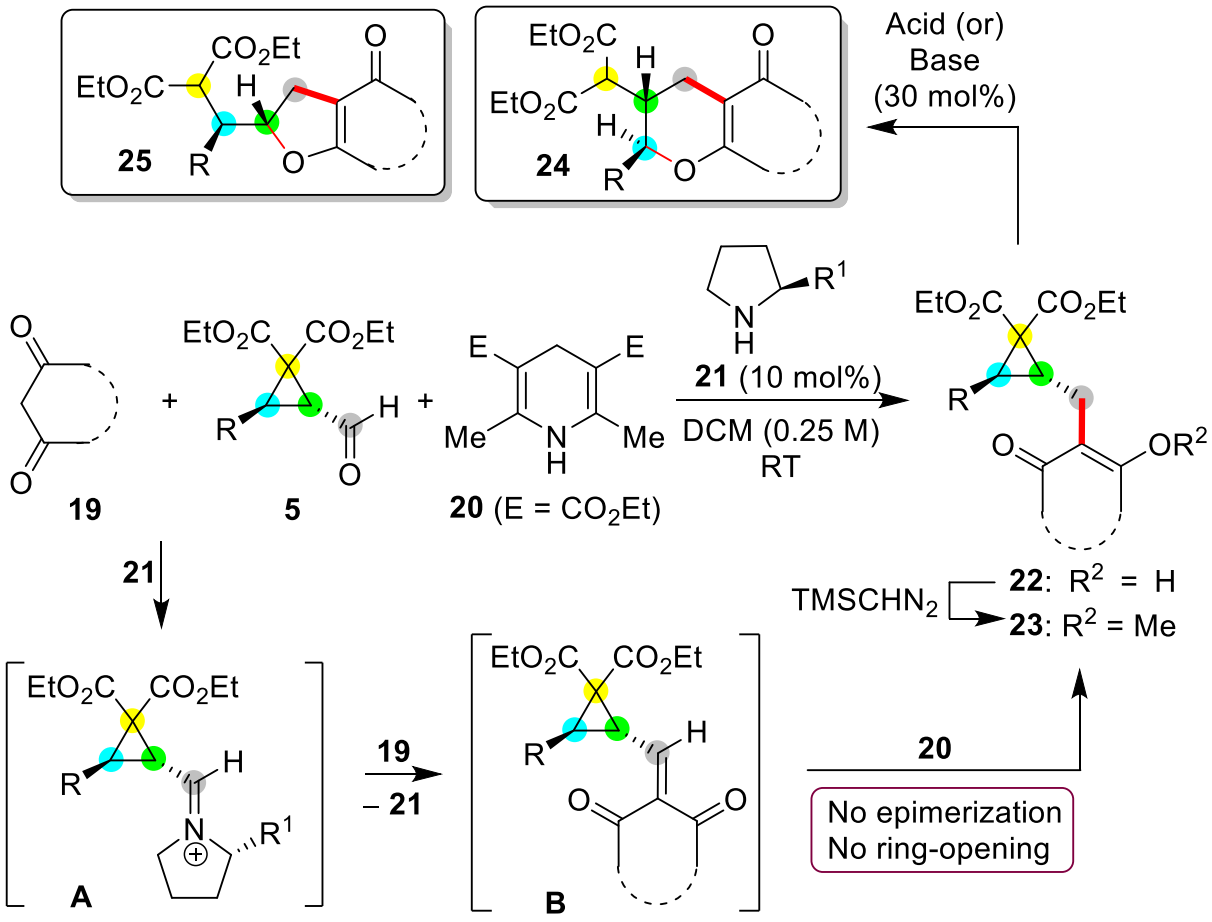
[R = Me, Et, *i*Pr, *t*Bu and Ar]

(e) Urea-catalysed cyclopropane ring-opening: Mattson[18]



Later, Wang, Gilmour and Werz groups realized the synthesis of functionalized cyclic or acyclic molecules through homoconjugate addition of nucleophiles to iminium activated cyclopropanes followed by electrophiles under the organocatalysis (Scheme 10b).[37] Recently, *β*-ketocyclopropanes were utilized as pro D-A cyclopropanes and transformed under the chiral amine-catalysis to generate reactive dipolarophiles through enamine- and enolate-mediated ring-opening processes, and to further employ them in cycloaddition or cascade processes with suitable counter parts (Scheme 10c and 10d).[38,39] Mattson and co-workers reported an urea-mediated ring-opening of nitro-functionalized D-A cyclopropanes through hydrogen bonding catalysis (Scheme 10e).[40] Very recently, Xu *et al.* described DABCO catalyzed ring-expansion of cyclopropyl ketones through Cloke−Wilson rearrangement (not shown in Scheme).[41]

Scheme 11. Reaction Design for the Synthesis of Functionally Rich Chiral Heterocycles through Stereospecific Activation of Formylcyclopropanes.



It is worth mentioning that all the reported organocatalytic approaches which involved activation of formylcyclopropanes through NHC or amine catalysis led to ring-opening of D-A cyclopropanes (Schemes 10a-e). However, the formylcyclopropanes have not been investigated so far under organocatalysis for strategic synthetic transformations without affecting the strained cyclopropane ring.[42,43] To accomplish this synthetic challenge, based on our previous discovery of organocatalytic reductive coupling reaction,[44] we have designed a high-yielding conversion of the formyl group of cyclopropanes into the cyclic-1,3-diketones **22** and **23** containing the methyl group of cyclopropanes, without ring-opening from the cyclic-1,3-diketones or CH-acids **19**, chiral formylcyclopropanes (**5**) and Hantzsch ester (**20**) through the organocatalytic reductive coupling reaction (Scheme 11). Further, the products **22** were converted into 3,4-dihydro-2*H*-pyrans (**24**) and 2,3-dihydrofurans (**25**) by acid/base catalysis (Scheme 11). Nevertheless, the realization of product **22** from **19**, **5** and **20** is a highly challenging task because of the tendency of the cyclopropane to cleave under iminium-catalysis.[12,37] The formation of the product **22** could be possible only upon the selective sequential attack of the carbon nucleophile on the iminium ion intermediate **A** followed by transfer hydrogenation with Hantzsch ester on the activated olefin of the intermediate **B** over multiple addition choices under the iminium activation (Scheme 11).[44] Undoubtedly, this design is a complementary approach to those strategies which demonstrated the ring-opening of formylcyclopropanes under iminium-catalysis (Schemes 10 and 11).

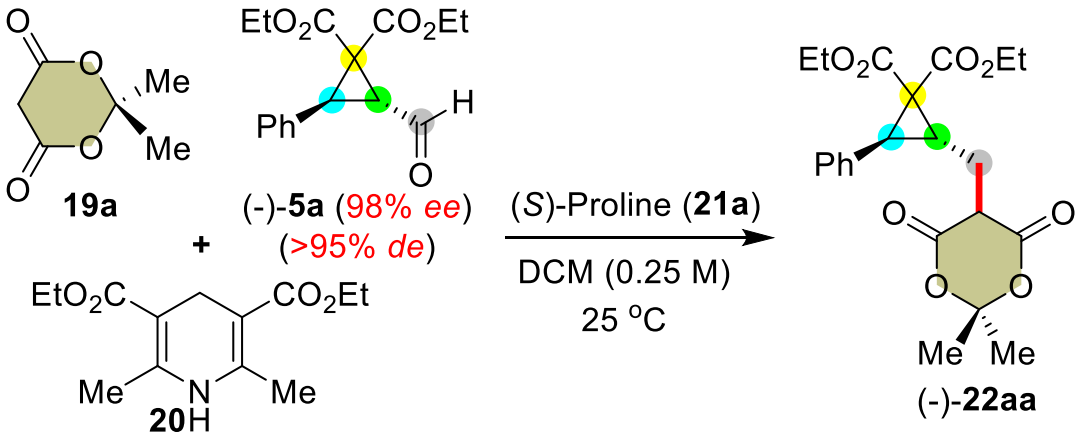
3.2 Results and Discussion

3.2.1 Reaction Optimization:

According to the plan, initially we focused our attention to obtain the chiral cyclopropanes containing cyclic-1,3-diketones **22** from **19** and **5**. First to understand the reactivity of the formylcyclopropanes under iminium-catalysis,[12] the chiral aldehyde (-)-**5a** and Meldrum's acid **19a** were chosen as the substrates and reacted under (*S*)-proline **21a** catalysis in DCM at 25 °C without using any reducing agent. Astonishingly, the reaction provided the corresponding olefin product **Baa** in 61% yield within 20 min without epimerization and ring-opening through Knoevenagel condensation reaction.[44] Then, the olefinic product **Baa** was subjected to hydrogenation using Hantzsch ester (**20**) or H_2 on Pd/C. Intriguingly, the Hantzsch ester (**20**) mediated transfer hydrogenation leads to the desired product (-)-**22aa** in 60% overall yield from

19a and **5a**,[44] whereas the catalytic hydrogenation using H_2 on Pd/C did not afford the desired product (-)-**22aa** instead it gave an inseparable mixture of undesired ring-opened products (results not shown in Table 1).[45] These results clearly indicate the importance of a mild reducing agent along with performing a reaction in one-pot manner as shown in Scheme 11.

Table 2. Investigation of the Proposed Reductive Coupling Reaction of Formylcyclopropane (-)-**5a**[a,b]



entry	**5a** (equiv.)	(*S*)-**21a** (mol%)	*t* (min)	*de* **22aa** (%)	*ee* **22aa** (%)	yield **22aa** (%)
1	1.2	20	20	>98	>99	94
2	1.2	15	20	>98	>99	94
3	1.2	10	24	>98	>99	94
4	1.2	05	40	>98	>99	88
5	1.2	-	240	>98	>99	54
6	1.1	10	20	>98	>99	94
7[c]	1.1	10	20	>98	>99	90
8	1.0	10	24	>98	>99	89
9[d]	1.1	-	20	>98	>99	81
10[e]	1.1	-	20	>98	>99	90
11[f]	1.1	-	20	>98	>99	94
12[g]	1.1	-	15	>98	99	80
13[h]	1.1	-	20	>98	99	85
14[i]	1.1	-	165	>98	99	33

[a]Reactions were carried out in DCM (1.0 mL) with 1.1 equiv. of (-)-**5a** (0.275 mmol) and 1.1 equiv. of **20** (0.275 mmol) relative to the **19a** (0.25 mmol) in the presence of 10 mol% of (*S*)-**21a**

and yield refers to the column-purified product. [b]Enantiomeric excess (*ee*) was determined by chiral HPLC analysis after converting (-)-**22aa** into its dimethyl malonate derivative and diastereomeric excess (*de*) was determined by ^{1}H NMR analysis of crude reaction mixture. [c]1.0 equiv. of **20** used. [d]10 mol% of (*S*)-DPPOTMS (**21b**) was used as catalyst. [e]10 mol% of (*R*)-proline (**21a**) was used as catalyst. [f]10 mol% of (*DL*)-proline (**21a**) was used as catalyst. [g]10 mol% of pyrrolidine (**21c**) was used as catalyst. [h]10 mol% of pyrrolidine/acetic acid (1:1, **21d**) was used as catalyst. [i]10 mol% of $PhCO_2H$ was used as catalyst.

To our delight, the one-pot three-component reductive coupling reaction of **19a**, (-)-**5a** (1.2 equiv., 98% *ee* and >95% *de*) and **20** in the presence of 20 mol% of (*S*)-proline (**21a**) provided only one product (-)-**22aa** in 94% yield with high selectivity (>98% *de* and >99% *ee*) without the formation of any other byproducts through iminium-catalysis (entry 1, Table 2).[44e] Further optimization revealed that 1.1 equiv. of (-)-**5a**, 1.1 equiv. of **20** and 10 mol% of (*S*)-**21a** with respect to **19a** were optimal to obtain (-)-**22aa** in 94% yield with >99% *ee* and >98% *de* at 25 °C in 20 min (entries 2-8, Table 2). Surprisingly, the reductive coupling of **19a** with 1.1 equiv. of (-)-**5a** and 1.1 equiv. of **20** under the catalysis of 10 mol% of (*S*)-2-{diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine [(*S*)-DPPOTMS] (**21b**), (*R*)-proline (**21a**) or (*DL*)-proline (**21a**) at 25 °C for 20 min furnished (-)-**22aa** in 81-94% yield with >99% *ee* and >98% *de* (entries 9-11, Table 2). Notably, the one-pot reductive coupling of **19a** with (-)-**5a** and **20** under the catalysis of 10 mol% of pyrrolidine (**21c**), or pyrrolidine/acetic acid (1:1, **21d**) at 25 °C for 15-20 min furnished the coupling product (-)-**22aa** in reduced (80-85%) yield with 99% *ee* and >98% *de* (entries 12-13, Table 2). In a similar manner, the one-pot reductive coupling reaction of **19a**, (-)-**5a** and **20** under the catalysis of $PhCO_2H$ furnished the expected product (-)-**22aa** in only 33% yield after long reaction time and without affecting the selectivity (entry 14, Table 2). More importantly, the selective formation of (−)-**22aa** with >99% *ee* and >98% *de* from (−)-**5a** (98% *ee* and >95% *de*), **19a** and **20** under (*S*)-**21a**-, (*R*)-**21a**-, (*DL*)-**21a**-, (*S*)-**21b**-, **21c**- or **21d**-catalysis indicates that the iminium ion activation did not epimerize the α- or β-centre of the carbonyl of the cyclopropane ring (Table 2),[24] and that the rate of the Knoevenagel condensation or olefination reaction wasn't affected by catalyst's absolute configuration. This observation may be due to the formation of highly reactive iminium ions **A** as the catalytic intermediates from (-)-**5a** and **21**, which is selectively undergoing Mannich followed by deamination reactions with **19a** to generate (-)-**Baa**. Stereoselective transfer hydrogenation of (-)-**Baa** with **20** furnished the coupling product (-)-**22aa** as a single product without racemization and epimerization. Enantioselectivity of the product (-)-**22aa** was obtained from HPLC analysis

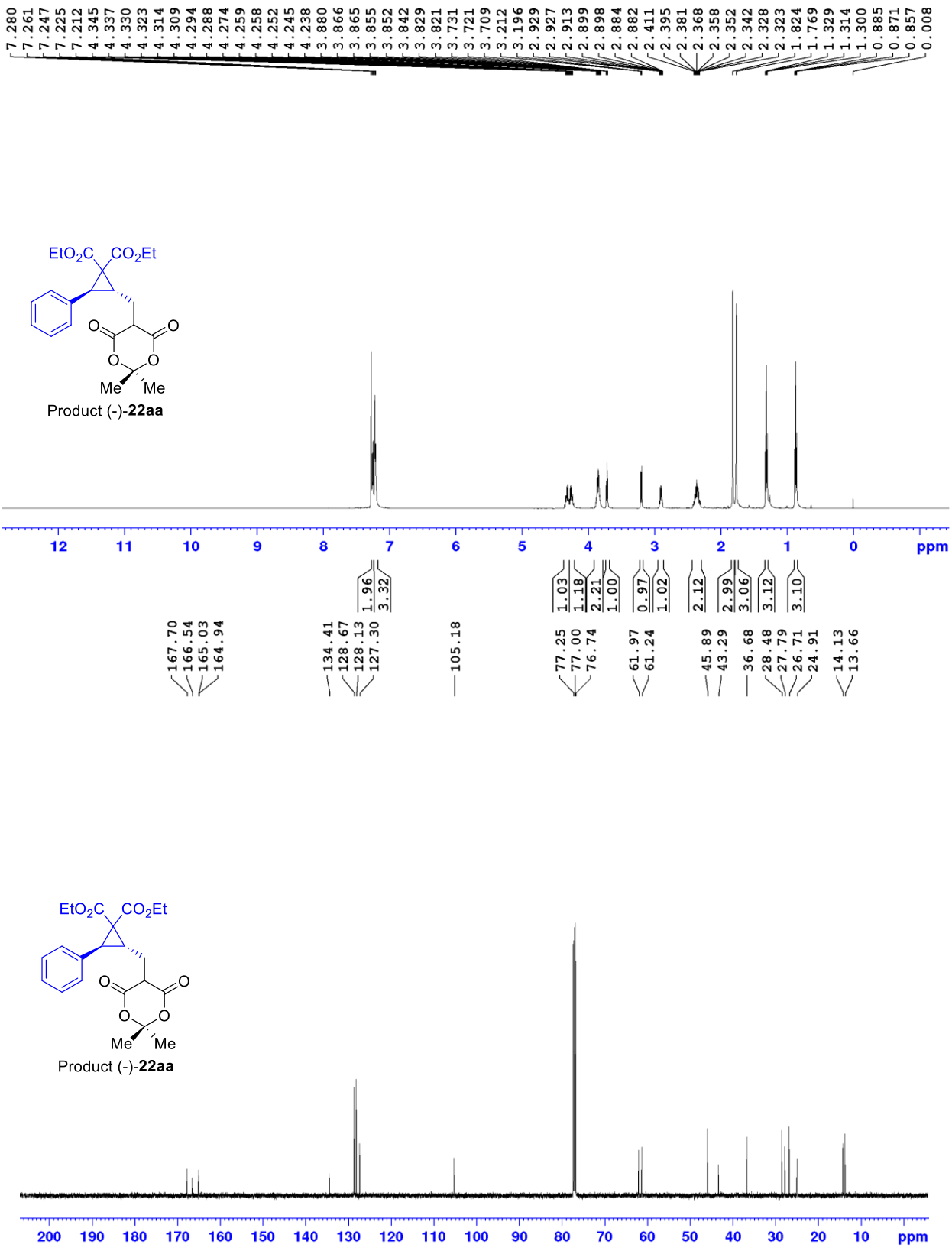
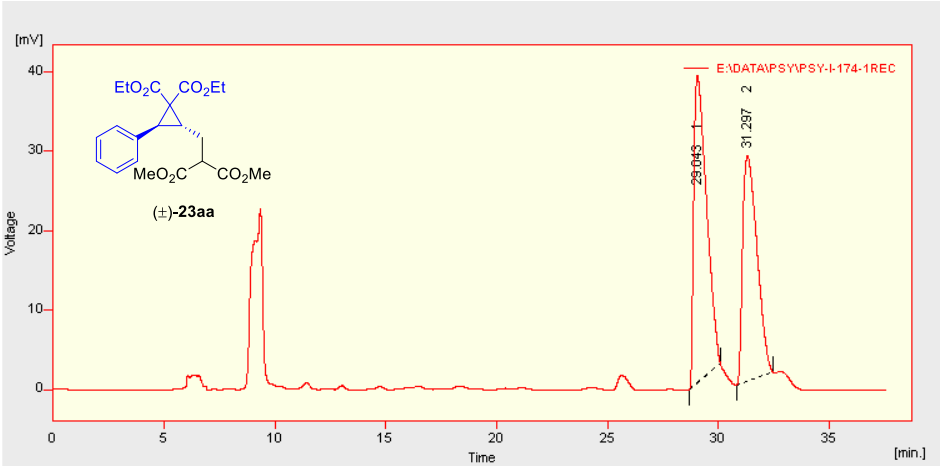


Figure 3. ^{1}H and ^{13}C spectra of the product (-)-**22aa**.

Racemic (±)-**23aa**:

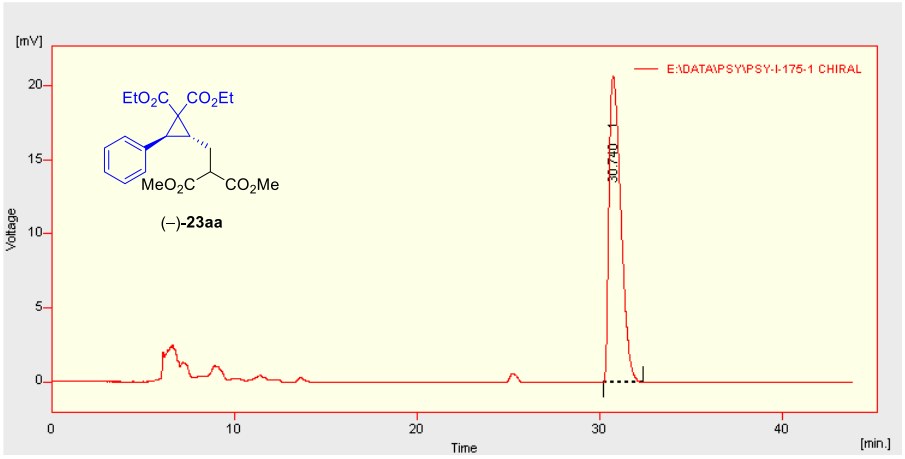


Chiralpak IA-3, Hexane/*i*-PrOH = 95:05, Flow Rate 0.5 mL/min, 254 nm

Result Table (Uncal - E:\DATA\PSY\PSY-I-174-1REC)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	29.043	1539.894	38.591	54.6	57.6	0.67
2	31.297	1278.543	28.364	45.4	42.4	0.75
	Total	2818.437	66.955	100.0	100.0	

Chiral (-)-**23aa** (>99.9% *ee*):



Chiralpak IA-3, Hexane/*i*-PrOH = 95:05, Flow Rate 0.5 mL/min, 254 nm

Result Table (Uncal - E:\DATA\PSY\PSY-I-175-1CHIRAL)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	30.740	933.201	20.637	100.0	100.0	0.73
	Total	933.201	20.637	100.0	100.0	

Figure 4. HPLC spectra of the methylated product (-)-**23aa** of (-)-**22aa**.

on the corresponding dimethyl malonate,[46] which is synthesized through domino *O*-methylation/ketenization/esterification reaction sequence[44c] with ethereal diazomethane solution in methanol and the slight (1-2%) increase in *ee*/*de* of (-)-**22aa** is a consequence of resolution during the five reactions and not because of catalyst optical purity. ^{1}H and ^{13}C spectra of compound (-)-**22aa** and HPLC spectra of methylated product (-)-**23aa** are shown in Figures 3 and 4.

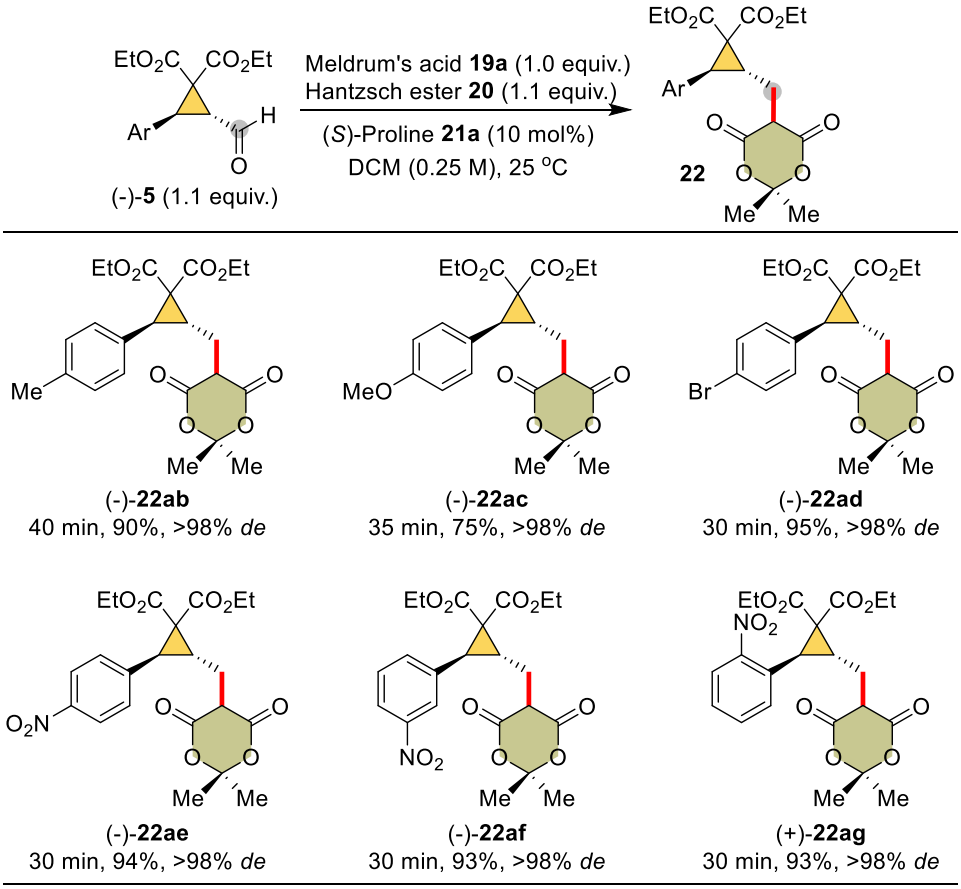
3.2.2 Reaction scope:

We have studied various chiral formylcyclopropanes (-)-**5b-g** and Meldrum's acid **19a** under the optimized reaction conditions to highlight the generality of the organocatalytic reductive coupling reaction (Scheme 12). The formylcyclopropanes containing different aryl groups (-)-**5b** to (-)-**5g** (>95% *de*) were reacted with Meldrum's acid **19a** and **20** under (*S*)-**21a**-catalysis to provide the corresponding reductive coupling products (-)-**22ab** to (+)-**22ag** in good to excellent yields with high selectivity (>98% *de*) at 25 °C in just 30-40 min (Scheme 12). As expected, there is no effect of aryl group substitution (Me, OMe, Br, and NO_2) on the outcome of the reductive coupling reaction rate and selectivity (Scheme 12). ^{1}H and ^{13}C spectra of compound (-)-**22ad** are shown in Figure 5.

Next, the three-component reductive coupling of (–)-**5a** with various cyclic and acyclic CH-acids **19b-o** and **20** were investigated to furnish the corresponding reductive coupling products (-)-**22ba** to (-)-**22oa** in 78-99% yields with >98% *de* at 25 °C in 30-240 min, respectively (Table 3). It is delightful to mention that the chiral formylcyclopropane (–)-**5a** smoothly underwent iminuim-mediated Knoevenagel condensation or olefination with the library of CH-acids **19b-o** followed by in situ transfer hydrogenation with Hantzsch ester **20** to furnish the coupling products (-)-**22ba** to (-)-**22oa** in very good yields with high selectivity at 25 °C in 30-240 min without epimerization and ring-opening reactions (Table 3). The reductive coupling of the formylcyclopropane (–)-**5c** (>95% *de*) with tetronic acid **19e** and cyclopentane-1,3-dione **19j** under the optimal conditions furnished the coupling products (–)-**22ec** and (–)-**22jc** in 87% and 97% yields with enriched *de*'s in 25-30 min, respectively (Table 3). ^{1}H and ^{13}C spectra of compounds (-)-**23ha**, (-)-**22la**, (-)-**22ma**, and (-)-**22oa** are shown in Figures 6-9.

In a similar manner, the reductive coupling of cyclohexane-1,3-dione **19h** with various chiral formylcyclopropanes containing aryl and alkyl groups (-)-**5b** to (-)-**5j** (>95% *de*) and **20** under (*S*)-**21a**-catalysis at 25 °C for 20-50 min furnished the corresponding coupling products (-)-**22hb** to (-)-**22hj** in 80-98% yields with enriched *de*'s (Scheme 13). The aryl or alkyl group substitution on the formylcyclopropanes has no effect on the outcome of the reductive coupling reaction rate and selectivity (Scheme 13). The structures of the reductive coupling products (-)-**22aa** to (-)-**22hj** were established by NMR analysis and the absolute stereochemistry was unambiguously confirmed by X-ray structure analysis of (–)-**22ia** (Figure 16)[47] and also by correlation with previous asymmetric synthesis of formylcyclopropanes (-)-**5a** to (-)-**5j**.[46] ^{1}H and ^{13}C spectra of compounds (-)-**23hh** and (-)-**31hj** are shown in Figures 10 and 11.

Scheme 12. Reductive Coupling Reaction Scope with Respect to Various Formylcyclopropanes (-)-**5**[a,b]



[a]Reactions were carried out in DCM (1.0 mL) with 1.1 equiv. of (-)-**5** (0.275 mmol) and 1.1 equiv. of **20** (0.275 mmol) relative to the Meldrum's acid **19a** (0.25 mmol) in the presence of 10 mol% of (*S*)-**21a** and yield refers to the column-purified product. [b]Diastereomeric excess (*de*) was determined by ^{1}H NMR analysis of crude reaction mixture **22**.

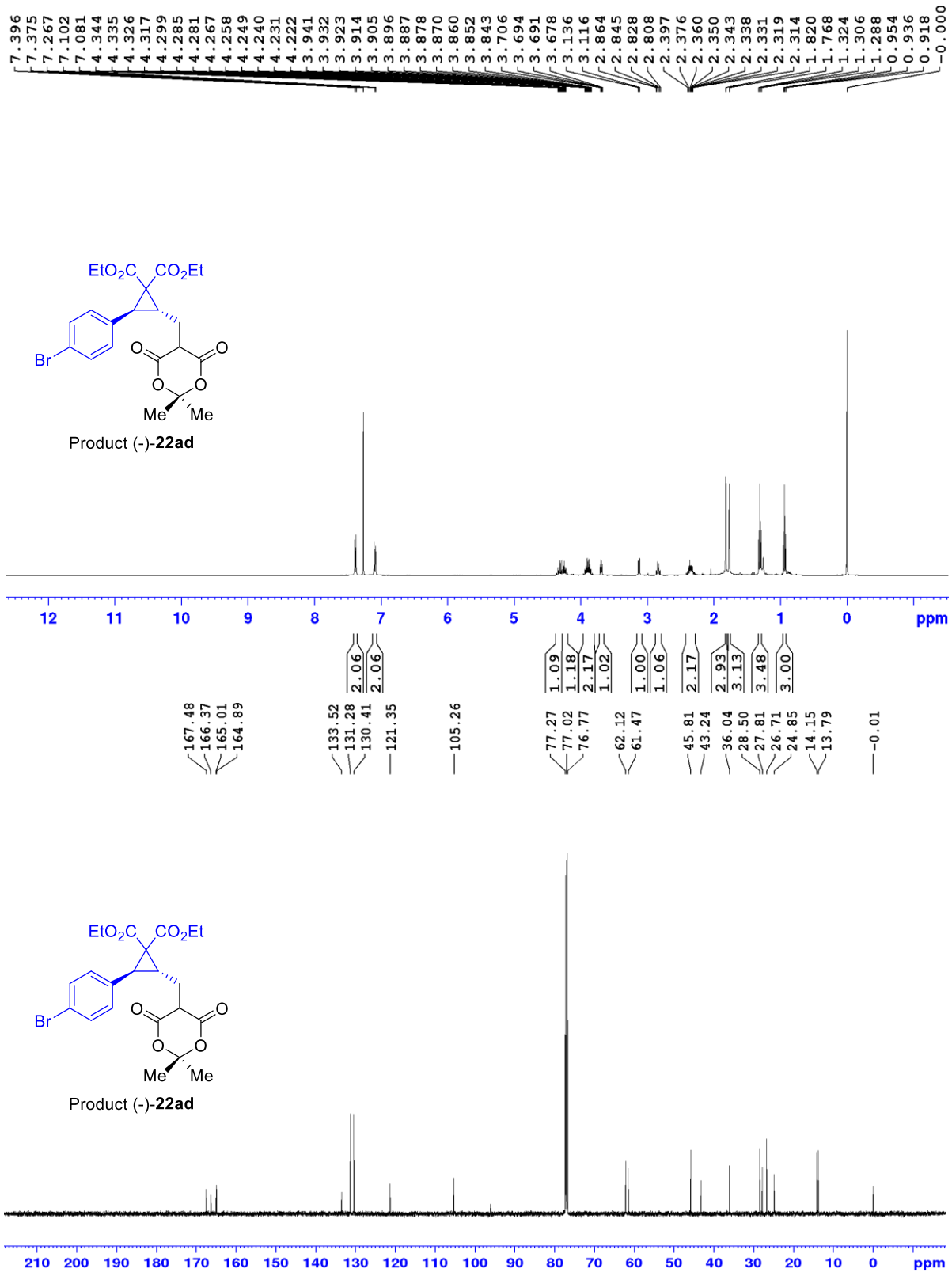
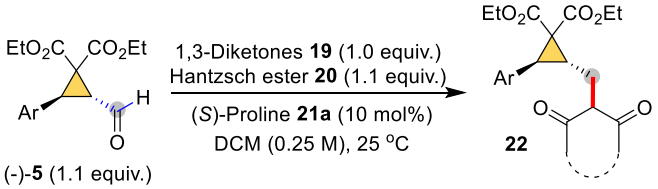
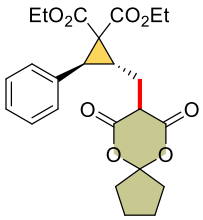


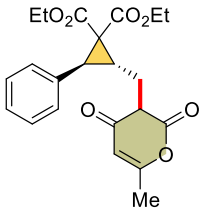
Figure 5. ^{1}H and ^{13}C spectra of the product (-)-**22ad**.

Table 3. Reductive Coupling Reaction Scope with Respect to Various CH-Acids[a,b]

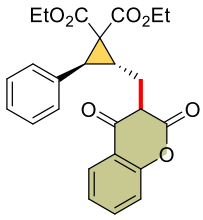




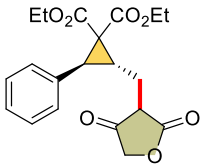
(-)-**22ba:** (30 min, 94%)
(>98% *de*)



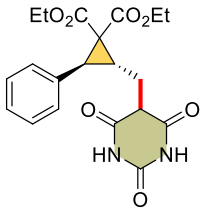
(-)-**22ca:** (120 min, 82%)[c]
(>98% *de*)



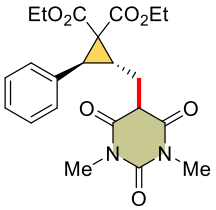
(-)-**22da:** (30 min, 92%)[c]
(>98% *de*)



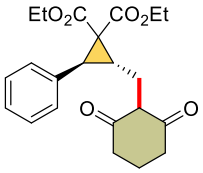
(-)-**22ea:** (30 min, 98%)[c]
(>98% *de*)



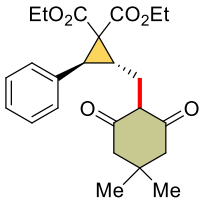
(-)-**22fa:** (120 min, 86%)[c]
(>98% *de*)



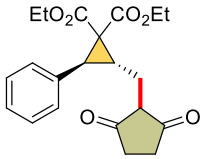
(-)-**22ga:** (45 min, 93%)[c]
(>98% *de*)



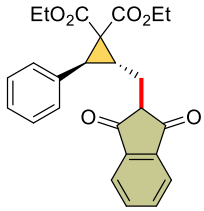
(-)-**22ha:** (45 min, 96%)[c]
(>98% *de*)



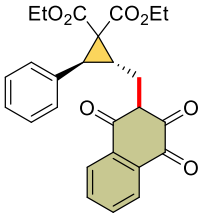
(-)-**22ia:** (45 min, 99%)[c]
(>98% *de*)



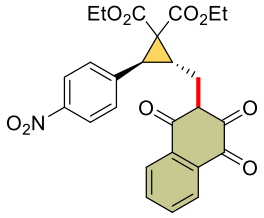
(-)-**22ja:** (45 min, 99%)[c]
(>98% *de*)



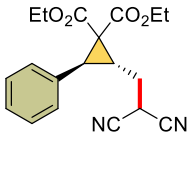
(-)-**22ka:** (45 min, 85%)[c]
(>98% *de*)



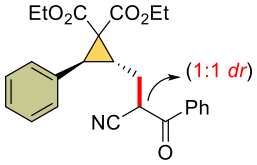
(-)-**22la:** (120 min, 99%)
(>98% *de*)



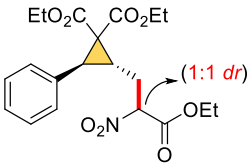
(-)-**22le:** (180 min, 95%)
(>98% *de*)



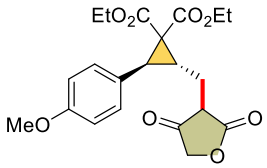
(-)-**22ma:** (45 min, 90%)
(>98% *de*)



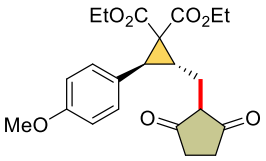
(-)-**22na:** (60 min, 93%)[d]
(>98% *de*)



(-)-**22oa:** (240 min, 78%)[d]
(>98% *de*)



(-)-**22ec:** (30 min, 87%)
(>98% *de*)[c]



(-)-**22jc:** (25 min, 97%)
(>98% *de*)[c]

[a]Reactions were carried out in DCM (1.0 mL) with 1.1 equiv. of (-)-**5** (0.275 mmol) and 1.1 equiv. of **20** (0.275 mmol) relative to the **19** (0.25 mmol) in the presence of 10 mol% of (*S*)-**21a** and yield refers to the column-purified product. [b]Diastereomeric excess (*de*) was determined by ^{1}H NMR analysis of crude reaction mixture **22**. [c]The products **22** were fully characterized by converting them into methyl enol ether **23** and reported yields represent for the column-purified product of **22**. [d]Diastereomeric ratio (*dr*) was determined by ^{1}H NMR analysis of the isolated product of (-)-**22na** and (-)-**22oa**.

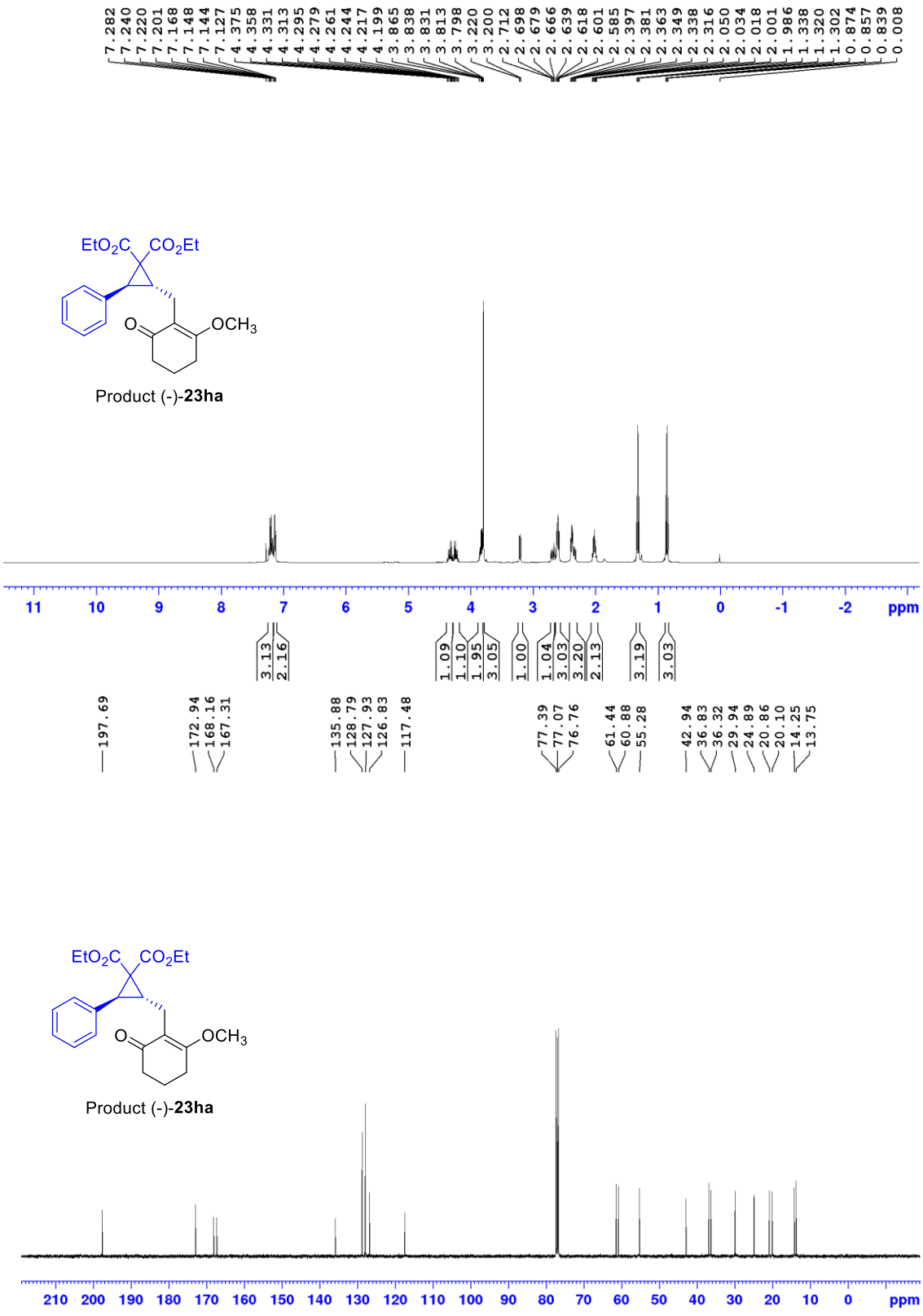


Figure 6. ^{1}H and ^{13}C spectra of the methylated product (-)-**23ha** of (-)-**22ha**.

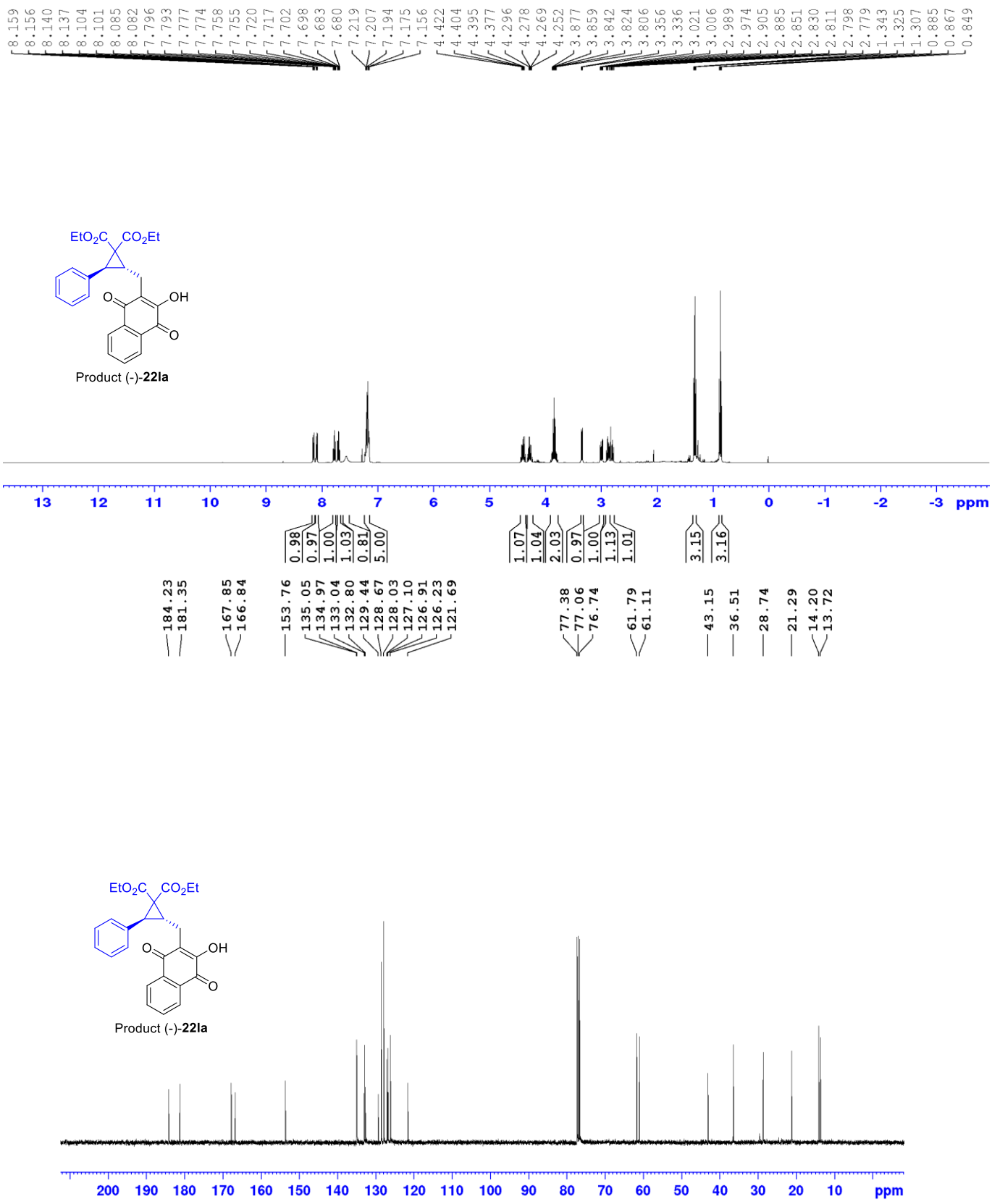


Figure 7. ^{1}H and ^{13}C spectra of the product (-)-**22la**.

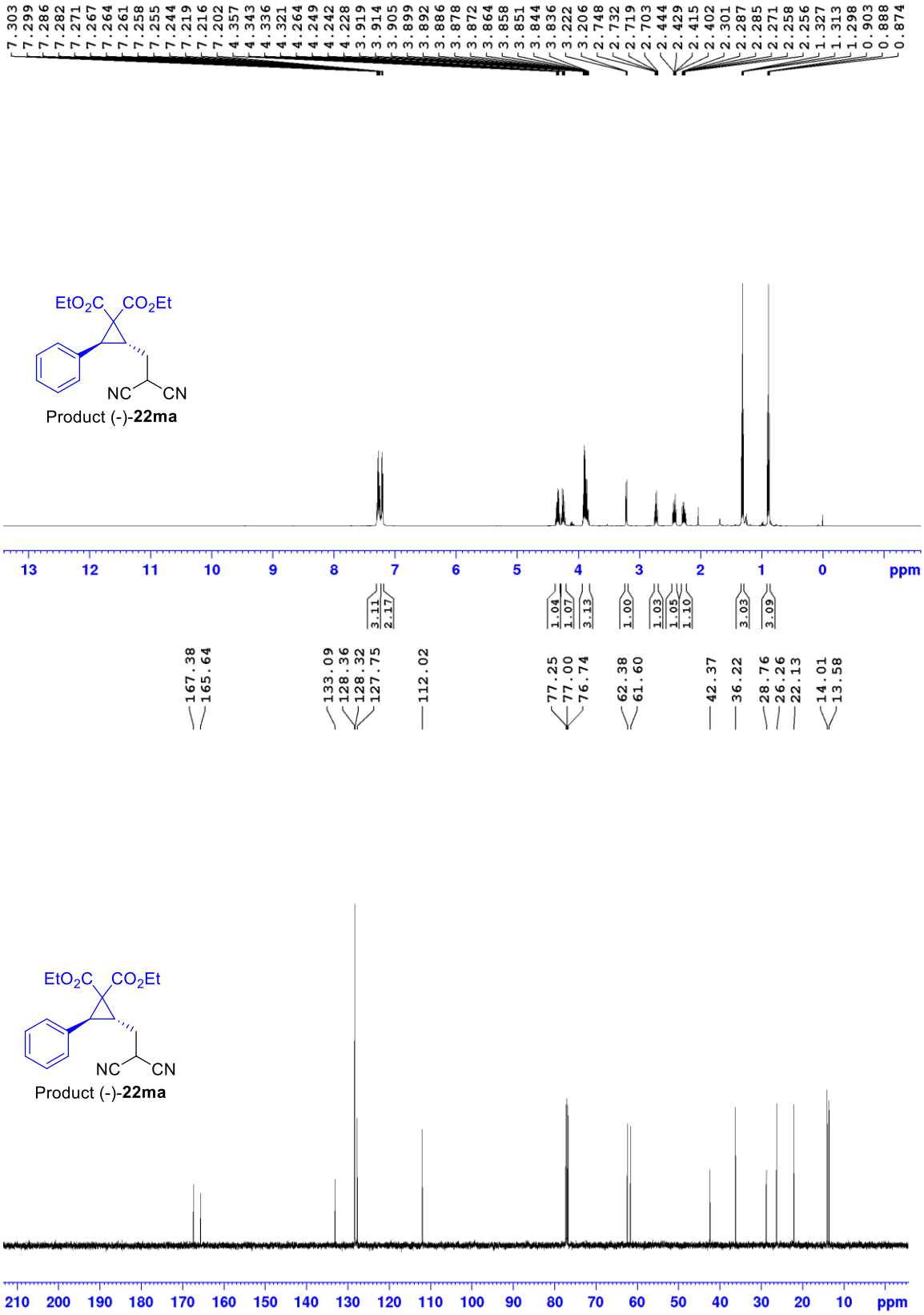


Figure 8. ^{1}H and ^{13}C spectra of the product (-)-**22ma**.

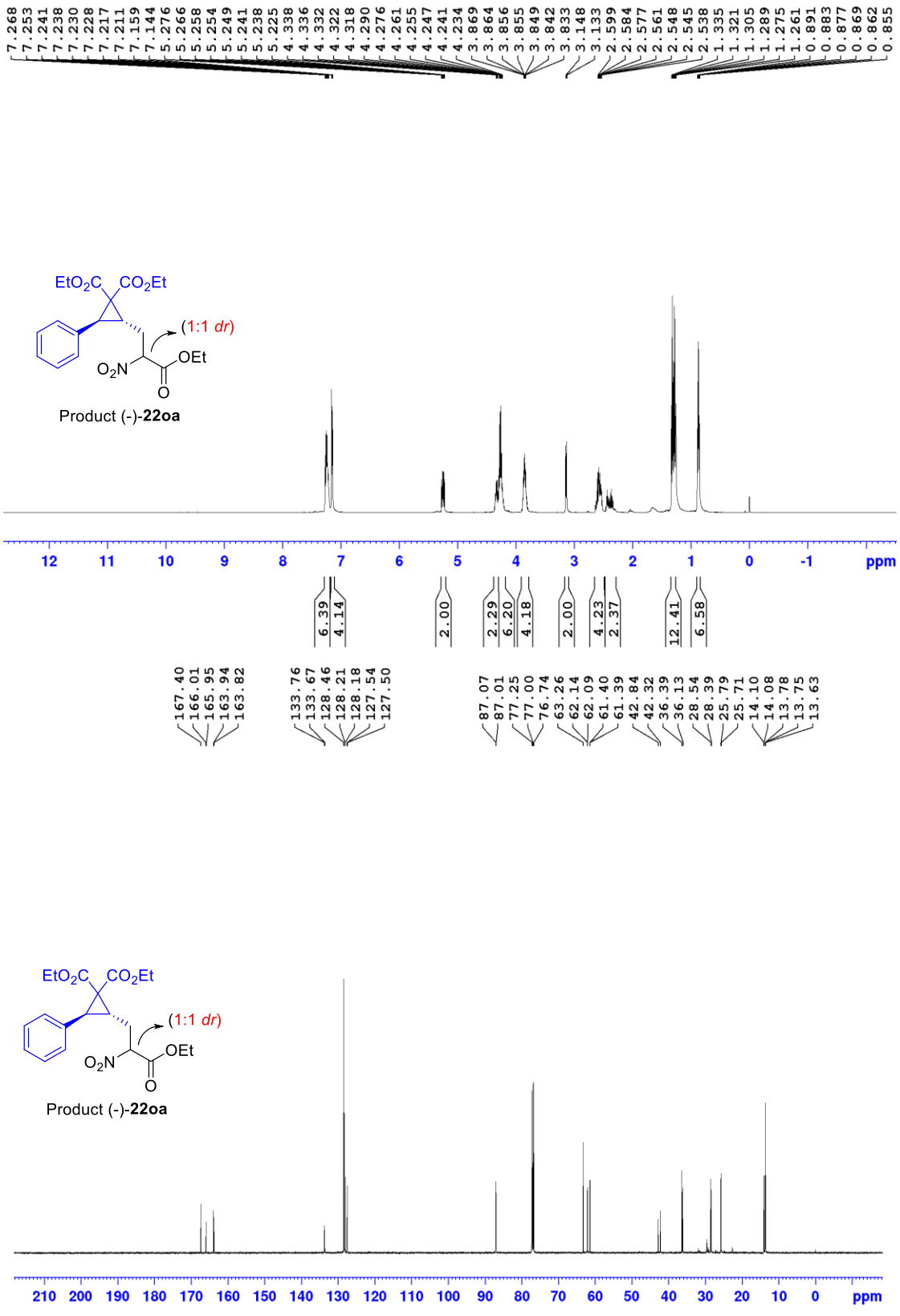
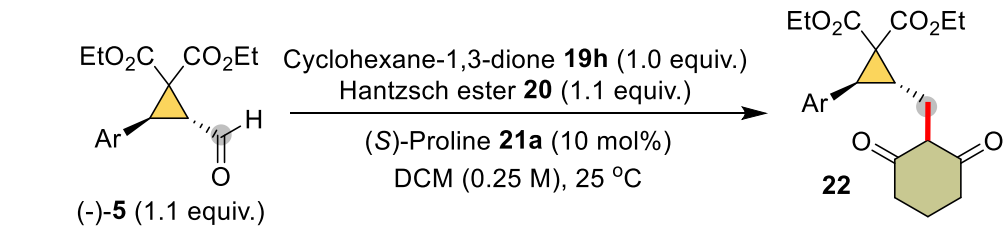
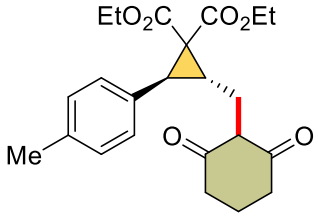


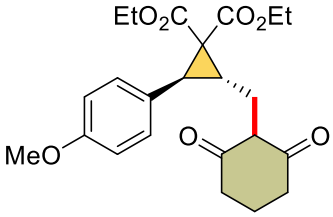
Figure 9. ^{1}H and ^{13}C spectra of the product (-)-**22oa**.

Scheme 13. Reductive Coupling Reaction Scope with Respect to Various Formylcyclopropanes and Cyclohexane-1,3-dione[a,b]

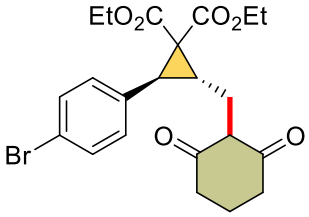




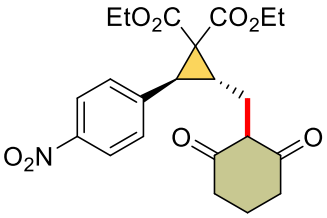
(-)-**22hb**
45 min, 98%, >98% *de*



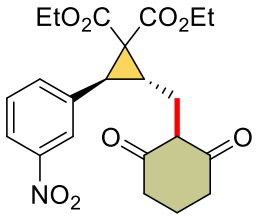
(-)-**22hc**
45 min, 88%, >98% *de*



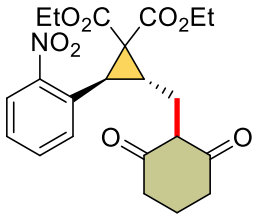
(-)-**22hd**
45 min, 98%, >98% *de*



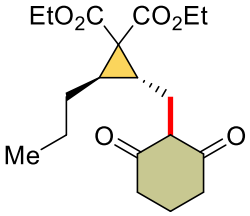
(-)-**22he**
20 min, 97%, >98% *de*



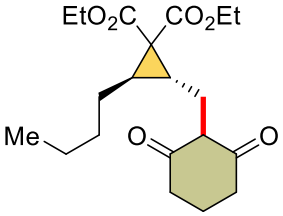
(-)-**22hf**
45 min, 97%, >98% *de*



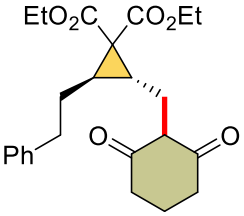
(+)-**22hg**
50 min, 92%, >98% *de*



(-)-**22hh**
30 min, 82%, >98% *de*



(-)-**22hi**
30 min, 82%, >98% *de*



(-)-**22hj**
30 min, 80%, >98% *de*

[a]Reactions were carried out in DCM (1.0 mL) with 1.1 equiv. of (-)-**5** (0.275 mmol) and 1.1 equiv. of **20** (0.275 mmol) relative to the cyclohexane-1,3-dione **19h** (0.25 mmol) in the presence of 10 mol% of (*S*)-**21a** and yield refers to the column-purified product. [b]Diastereomeric excess (*de*) was determined by ^{1}H NMR analysis of crude reaction mixture **22**.

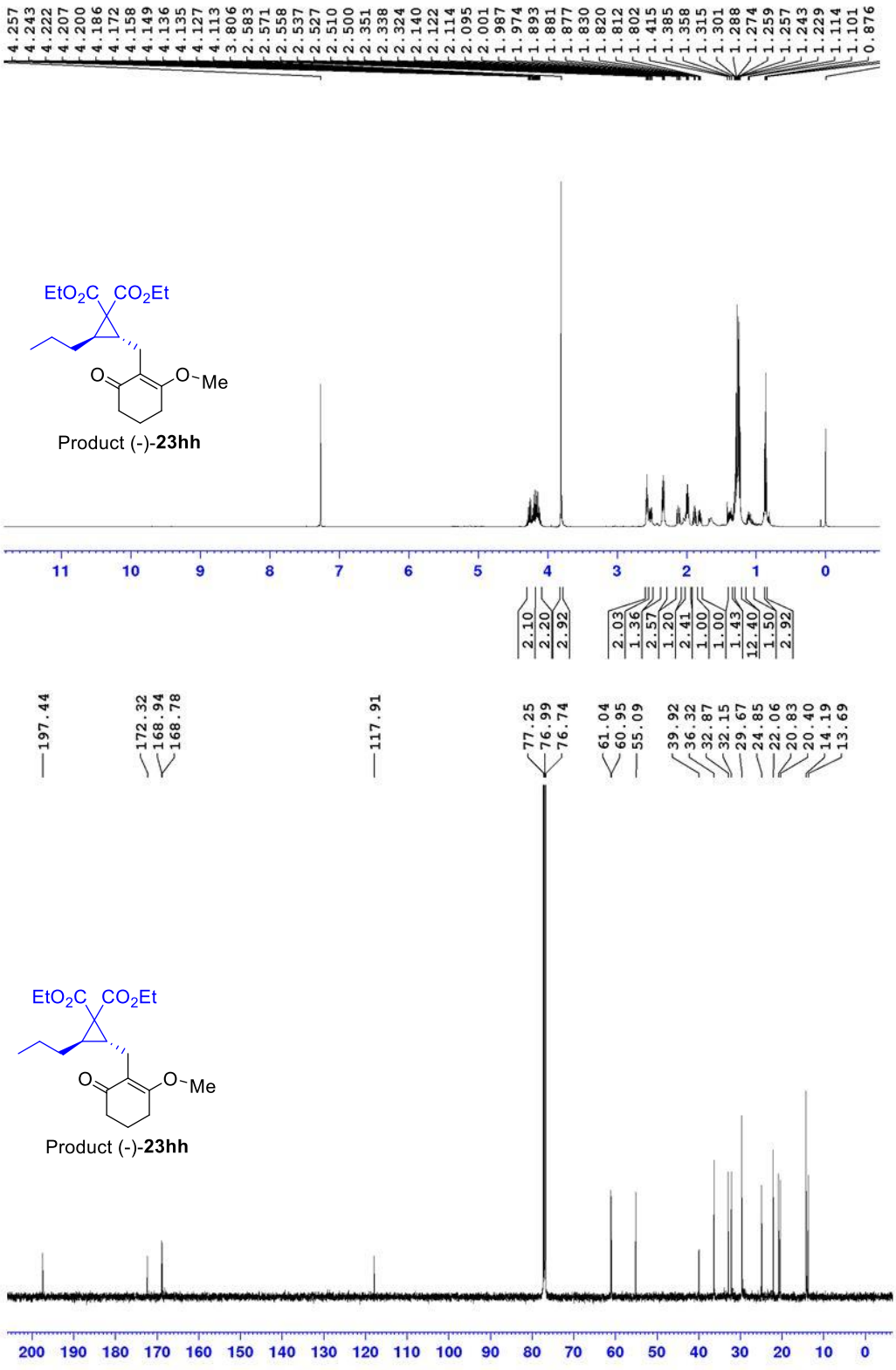


Figure 10. ^{1}H and ^{13}C spectra of the product (-)-**23hh.**

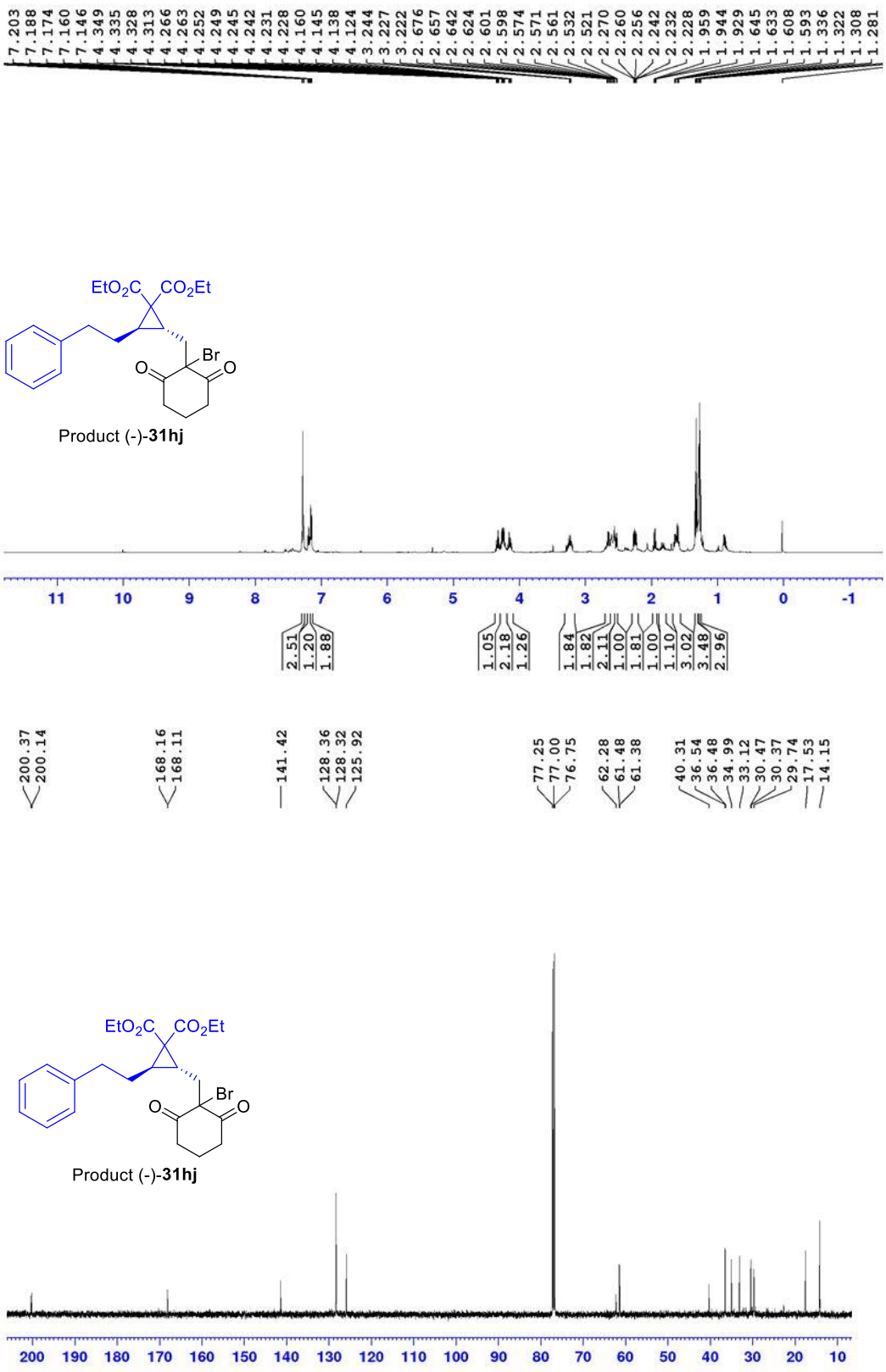
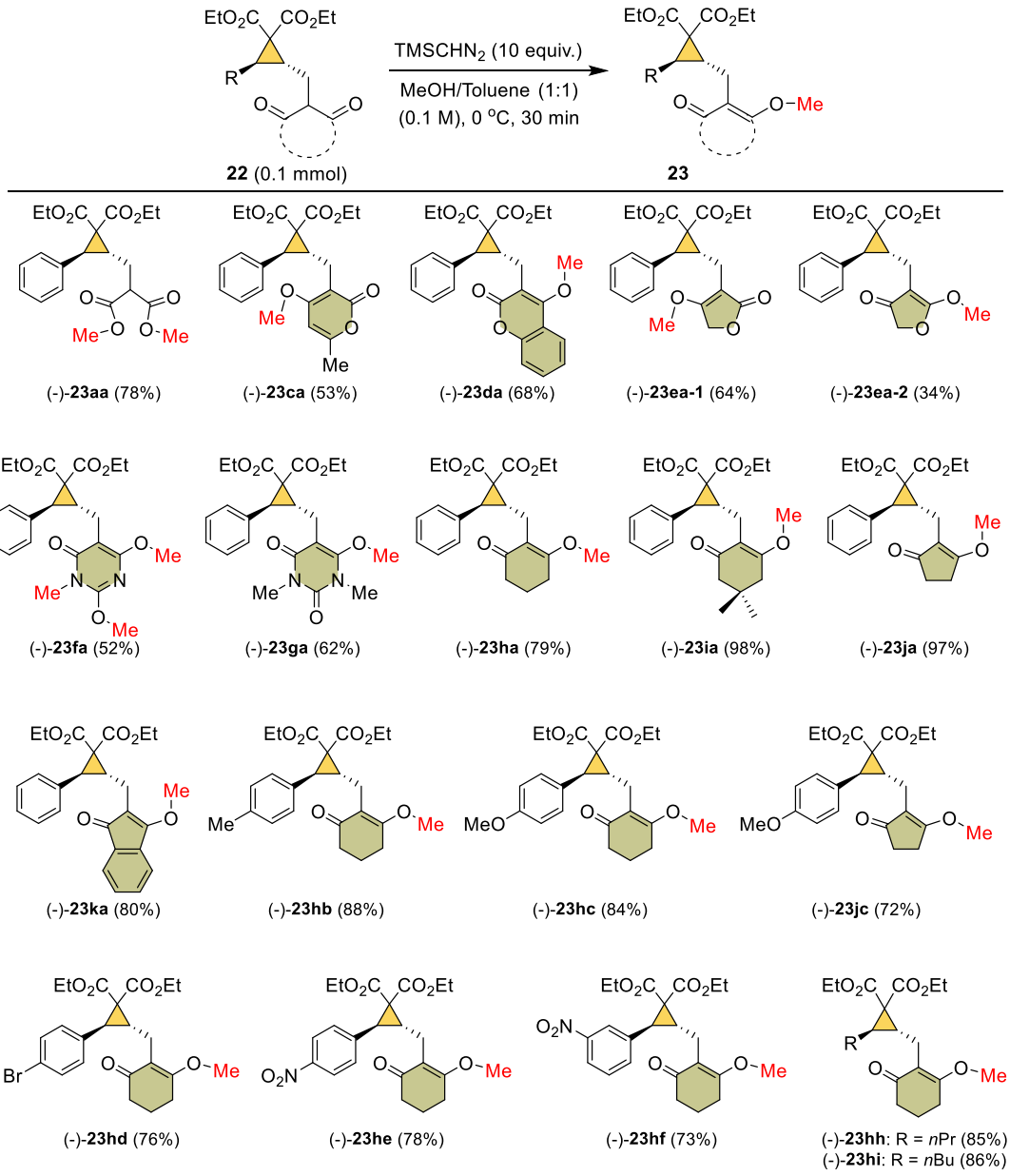


Figure 11. ^{1}H and ^{13}C spectra of the product (-)-**31hj**.

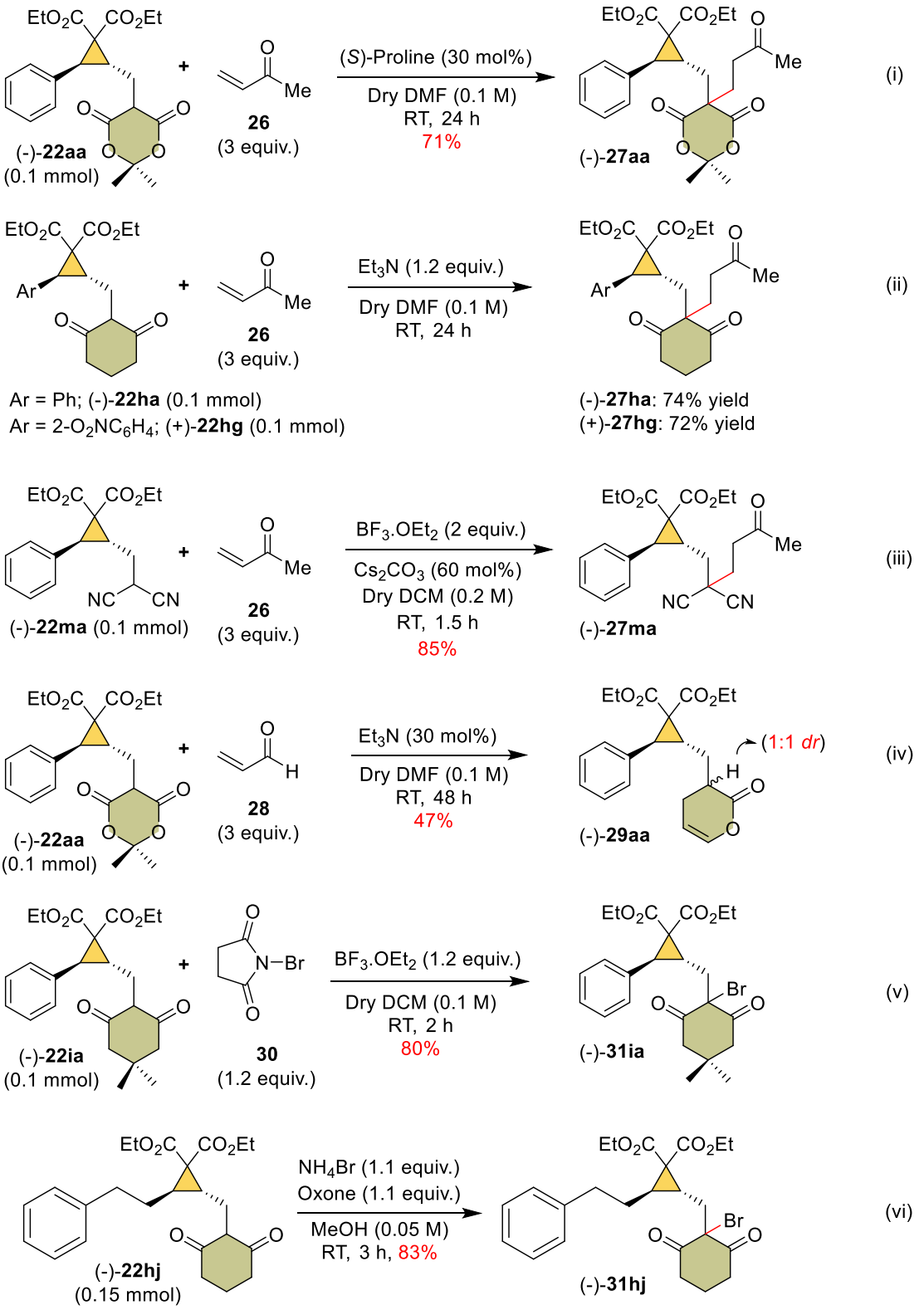
Some of the reductive coupling products **22** were further characterized by converting them into stable methyl etherification products **23** or Michael adducts **27**/**29** or bromination products **31** through simple reaction with $TMSCHN_2$ or methyl vinyl ketone/acrolein or NBS, respectively at room temperature as shown in Table 4 and Scheme 14.

Table 4. Methyl Etherification of TCRA Products **22** for Further Characterization[a,b]



[a]Reactions were carried out in MeOH/toluene (1:1, 1.0 mL) with 10 equiv. of $TMSCHN_2$ relative to the **22** (0.1 mmol) and stirred at 0 °C for 30 min. [b]Yield refers to the column-purified product.

Scheme 14. Synthetic Derivatives of TCRA Products **22** for Further Characterization.



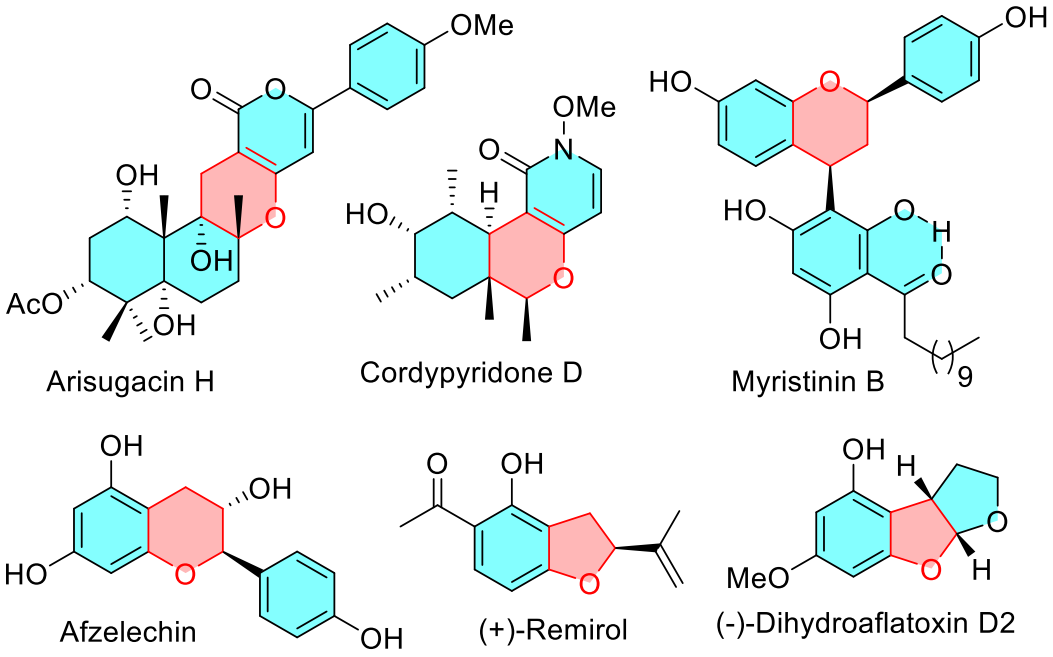
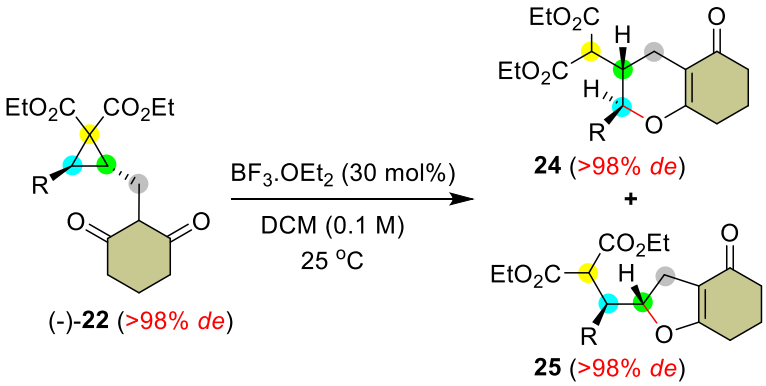
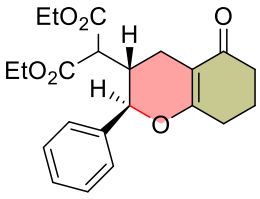


Figure 12. Selected natural products containing pyran and furan as core structure.

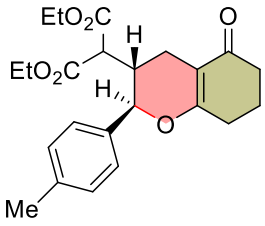
After successfully installing the reactive cyclic-1,3-diketone methyl group in the formylcyclopropanes, we planned to transform **22** into the dihydropyran (**24**) or dihydrofuran (**25**) in a single step. Because, compounds **24** and **25** are prevalent structural motifs found in many natural products and pharmaceuticals with diverse biological activities as shown in Figure 12.[46,48] As both electrophilic and nucleophilic groups are present in the chiral cyclopropanes **22**, it is inspiring to investigate the reactivity and selectivity pattern of these functional groups on the cyclopropane ring under acid/base-catalysis as shown in Scheme 11. We thought that the coordination of $BF_3.OEt_2$ to the carbonyls of tethered diesters of cyclopropane **22** would render this unit more reactive by polarizing the cyclopropane C-C bond and thus facilitate the intramolecular nucleophilic ring-opening by cyclic-1,3-diketone group with inversion at the cyclopropane site.[30] Surprisingly, the treatment of (-)-**22ha** with one equiv. of $BF_3.OEt_2$ in DCM at 25 °C for 2 h gave only one product the dihydropyran (-)-**24ha** in 82% yield and >98% *de* with inversion of configuration at the cyclopropane ring-opening center and similar results were obtained with 30 mol% of catalyst also (Table 5).[30]

Table 5. Scope of Chiral 3,4-Dihydro-2*H*-pyrans Synthesis from Functionally Rich Cyclopropanes (-)-**22ha** to (-)-**22hj**[a,b]

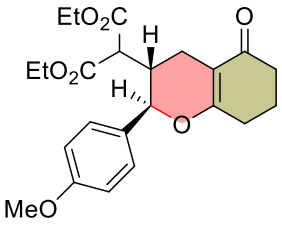




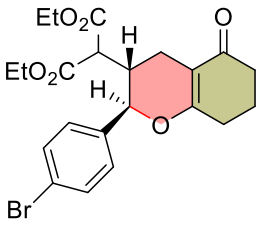
(-)-**24ha**
(3 h, 81%, >98% *de*)



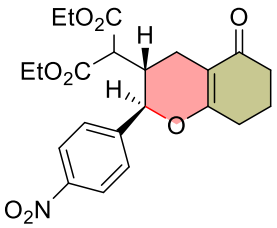
(-)-**24hb**
(1.5 h, 91%, >98% *de*)



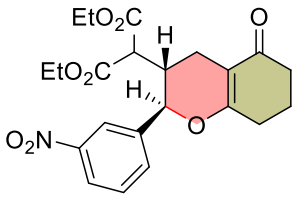
(-)-**24hc**
(1 h, 94%, >98% *de*)



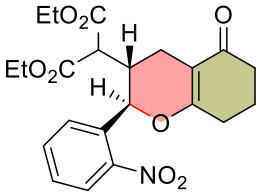
(-)-**24hd**
(2 h, 83%, >98% *de*)[c]



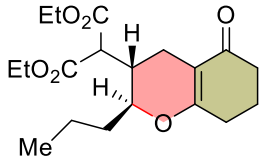
(-)-**24he**
(48 h, 25%, >98% *de*)[d,e]



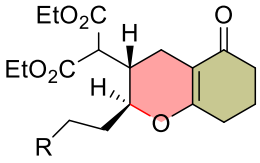
(-)-**24hf**
(30 h, 42%, >98% *de*)[d,f]



(+)-**24hg**
(48 h, 36%, >98% *de*)[d,g]



24hh
(4 h, trace)[h]



24hi: R = Et (4 h, trace)[i]
24hj: R = Ph (2 h, trace)[j]

[a]Reactions were carried out in DCM (1.0 mL) with 0.1 mmol of **22** in the presence of 30 mol% of $BF_3.OEt_2$ at 25 °C and yield refers to the column-purified product. [b]Diastereomeric excess (*de*) of **24** or **25** was determined by ^1H NMR analysis of crude reaction mixture. [c]Isomer (+)-**25hd** formed in 5% yield. [d]$BF_3.OEt_2$ was used in 60 mol%. [e]Isomer (+)-**25he** formed in 49% yield with >98% *de*. [f]Isomer (+)-**25hf** formed in 38% yield with >98% *de*. [g]Isomer (+)-**25hg**

formed in 63% yield with >98% *de*. [h]Isomer (+)-**25hh** formed in 52% yield with >98% *de* and the starting material was completely consumed. [i]Isomer (+)-**25hi** formed in 55% yield with >98% *de* and the starting material was completely consumed. [j]Isomer (+)-**25hj** formed in 72% yield with >98% *de* and the starting material was completely consumed.

Likewise, the reactions of aryl substituted cyclopropanes containing cyclic-1,3-diones (-)-**22ha** to (-)-**22hc** with 30 mol% of $BF_3.OEt_2$ furnished the corresponding annulative ring-opened dihydropyrans (-)-**24ha** to (-)-**24hc** in 81-94% yields with >98% *de* within 1-3 h as single isomers (Table 4). The 4-bromophenyl substituted cyclopropane (–)-**22hd** also reacted smoothly with 30 mol% of $BF_3.OEt_2$ to furnish (–)-**24hd** in 83% yield and >98% *de* along with 5% of the regioisomer (+)-**25hd** (Table 5). Surprisingly, the nitrophenyl substituted cyclopropanes containing cyclic-1,3-diones (-)-**22he** to (+)-**22hg** under 60 mol% of $BF_3.OEt_2$ catalysis in DCM at 25 °C for longer reaction times (30-48 h) furnished the respective annulative ring-opened products in 74-99% yields as mixture of isomers (-)-**24he** to (+)-**24hg** and (+)-**25he** to (+)-**25hg**, respectively (Table 5). In contrast, the aliphatic group substituted cyclopropanes containing cyclic-1,3-diones (–)-**22hh** to (–)-**22hj** under 30 mol% of $BF_3.OEt_2$ catalysis in DCM at 25 °C for 2-4 h furnished the regioisomers of dihydrofurans (+)-**25hh** to (+)-**25hj** as major products (52%, 55% and 72%) and dihydropyrans (–)-**24hh** to (–)-**24hj** in trace amounts, respectively (Table 5). These Lewis acid-catalyzed annulative ring-opening reactions are clearly specifying the fact that the electronic nature of the substituents on aryl group of cyclopropanes **22** controls the outcome of regioselectivity. Electron donating substituents on the aryl group of cyclopropanes **22** are essential for stabilizing or inducing the formation rate of the in situ formed intimate ion pair.[49] On the other hand, electron withdrawing substituents on the aryl group of cyclopropanes **22** decrease the formation rate of the in situ intimate ion pair perhaps due to destabilization.[49] But in the case of aliphatic group substituted cyclopropanes **22**, due to the absence of electronic factors to stabilize or induce the intimate ion pair formation, only kinetics are dominating to guide the product formation rather than thermodynamics (Table 5). ^1H and ^{13}C spectra of compound (-)-**24ha** are shown in Figure 13.

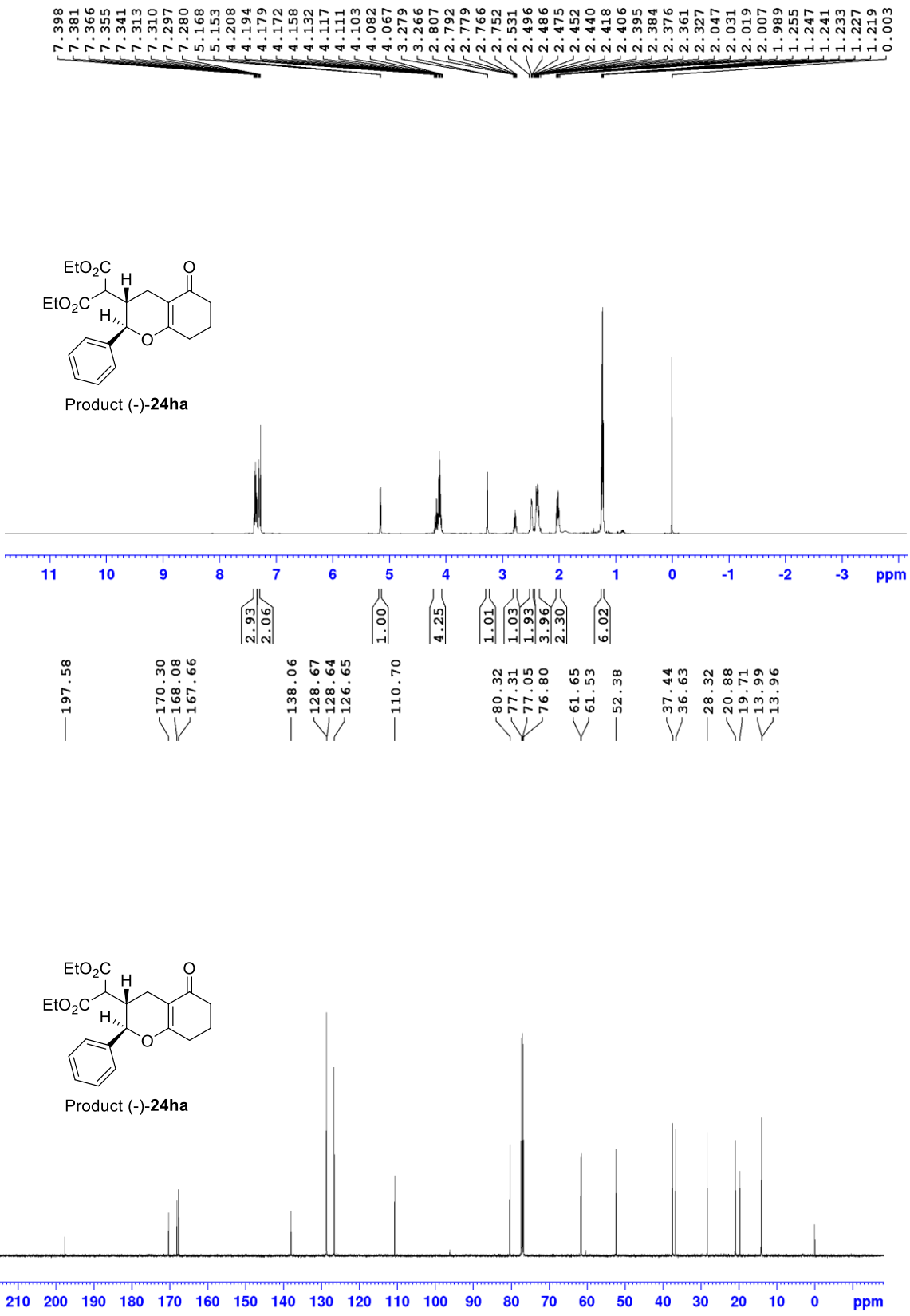
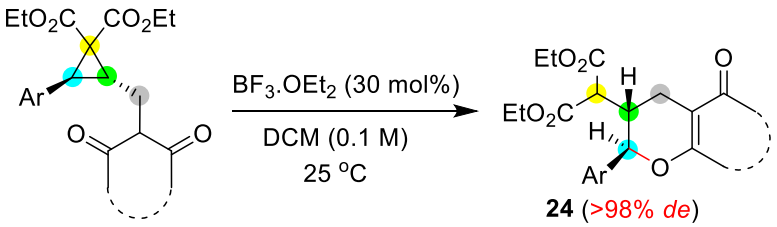
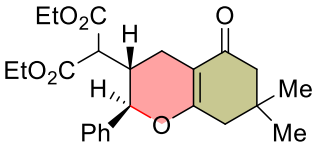


Figure 13. ^{1}H and ^{13}C spectra of the product (-)-**24ha**.

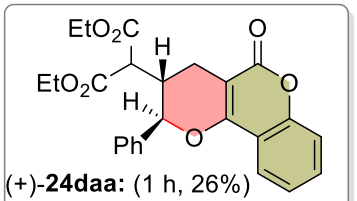
Table 6. Scope of Chiral 3,4-Dihydro-2*H*-pyrans Synthesis from Functionally Rich Cyclopropanes (-)-**22ca** to (-)-**22la**[a,b]



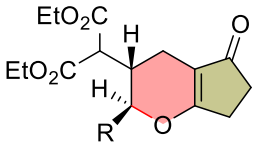
(-)-**22** (>98% *de*) → **24** (>98% *de*)



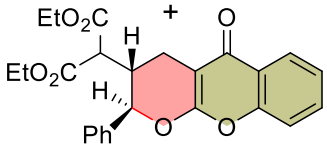
(-)-**24ia:** (2 h, 90%)
(>98% *de*)



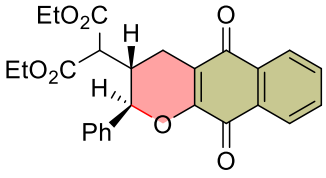
(+)-**24daa:** (1 h, 26%)
(>98% *de*)



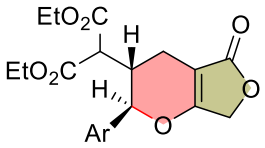
(-)-**24ja:** R = Ph (5 h, 94%)
(>98% *de*);
(-)-**24jc:** R = 4-MeOC$_6$H$_4$ (1 h, 96%)
(>98% *de*)



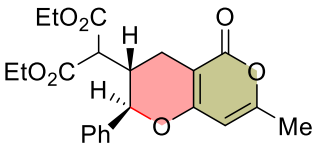
(-)-**24dab:** (1 h, 36%)
(>98% *de*)



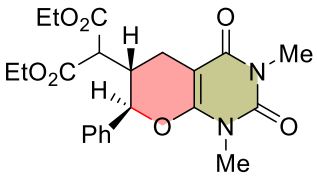
(+)-**24la:** (4 h, 60%)
(>98% *de*)



(-)-**24ea:** Ar = Ph (4 h, 97%)
(>98% *de*);
(-)-**24ec:** Ar = 4-MeOC$_6$H$_4$ (1 h, 83%)
(>98% *de*)



(-)-**24ca:** (22 h, 95%)
(>98% *de*)



(-)-**24ga:** (18 h, 98%)[c]
(>98% *de*)

[a]Reactions were carried out in DCM (1.0 mL) with 0.1 mmol of **22** in the presence of 30 mol% of $BF_3.OEt_2$ at 25 °C and yield refers to the column-purified product. [b]Diastereomeric excess (*de*) of **24** was determined by ^{1}H NMR analysis of crude reaction mixture. [c]$BF_3.OEt_2$ was used in 60 mol%.

The annulative ring-opening reactions of phenyl or 4-methoxyphenyl substituted cyclopropanes containing cyclic-1,3-diones (-)-**22ia**, (-)-**22ja**, (-)-**22jc**, (-)-**22ca**, (-)-**22ea**, (-)-**22ec** and (-)-**22ga** under 30 mol% of $BF_3.OEt_2$-catalysis in DCM at 25 °C for 1-22 h furnished the respective chiral dihydropyrans (-)-**24ia**, (-)-**24ja**, (-)-**24jc**, (-)-**24ca**, (-)-**24ea**, (-)-**24ec** and (-)-**24ga** in 83-98% yields as single isomers (Table 6). Notably, the reaction allowed transfer of absolute stereochemical information with high accuracy. Many of the products (-)-**24** were obtained within 1-5 h from (-)-**22** containing the cyclic-1,3-diones, but formation of the products (-)-**24ca** and (-)-**24ga** took more reaction time (22 and 18 h) from the corresponding cyclopropanes (-)-**22ca** and (-)-**22ga** containing the cyclic β-keto lactone and the cyclic 1,3-diamide respectively (Table 6). This reactivity difference may be explained by the fact that the cyclic-1,3-diones are highly nucleophilic compared to the cyclic β-keto lactone and the cyclic 1,3-diamides. The dihydropyran compound (–)-**24la** was obtained in 60% yield with >98% *de* from the reaction of (–)-**22la** with 30 mol% of $BF_3.OEt_2$ catalysis in DCM at 25 °C in 4 h (Table 6). Surprisingly, the annulative ring-opening reaction of (–)-**22da** under the catalysis of 30 mol% of $BF_3.OEt_2$ furnished a mixture of regioisomers of dihydropyrans (+)-**24daa** and (–)-**24dab** in 26% and 36% yields, respectively (Table 6). ^1H and ^{13}C spectra of compounds (-)-**24ja** and (-)-**24ca** are shown in Figures 14 and 15.

After understanding the stereoselective annulative ring-opening of (-)-**22** through Lewis acid-catalysis, we further showed interest to investigate the same reaction under base-catalysis.[35] In this perspective, few selected functionally rich cyclopropanes **22** were treated with a catalytic amount of Cs_2CO_3 (30-50 mol%) in DMSO at 25 °C for 24-48 h (Table 7). Many of the aryl substituted cyclopropanes containing cyclic-1,3-diones (-)-**22ha** to (+)-**22hg** under 30 mol% of Cs_2CO_3-catalysis in DMSO at 25 °C for 24-48 h furnished a mixture of dihydropyrans (-)-**24ha** to (+)-**24hg** and dihydrofurans (+)-**24ha** to (+)-**24hg** respectively in 57-79% overall yields with >98% *de* (Table 7, entries 1-7). However, the aliphatic group substituted cyclopropanes containing cyclic-1,3-diones (–)-**22hh** to (–)-**22hj** under 30 mol% of Cs_2CO_3-catalysis in DMSO at 25 °C for 24 h furnished the dihydrofurans (+)-**25hh** to (+)-**25hj** as major products (each 50%) and dihydropyrans (–)-**24hh** to (–)-**24hj** in trace amounts, respectively (Table 7, entries 8-10). ^1H and ^{13}C spectra of compound (+)-**25hh** are shown in Figure 16.

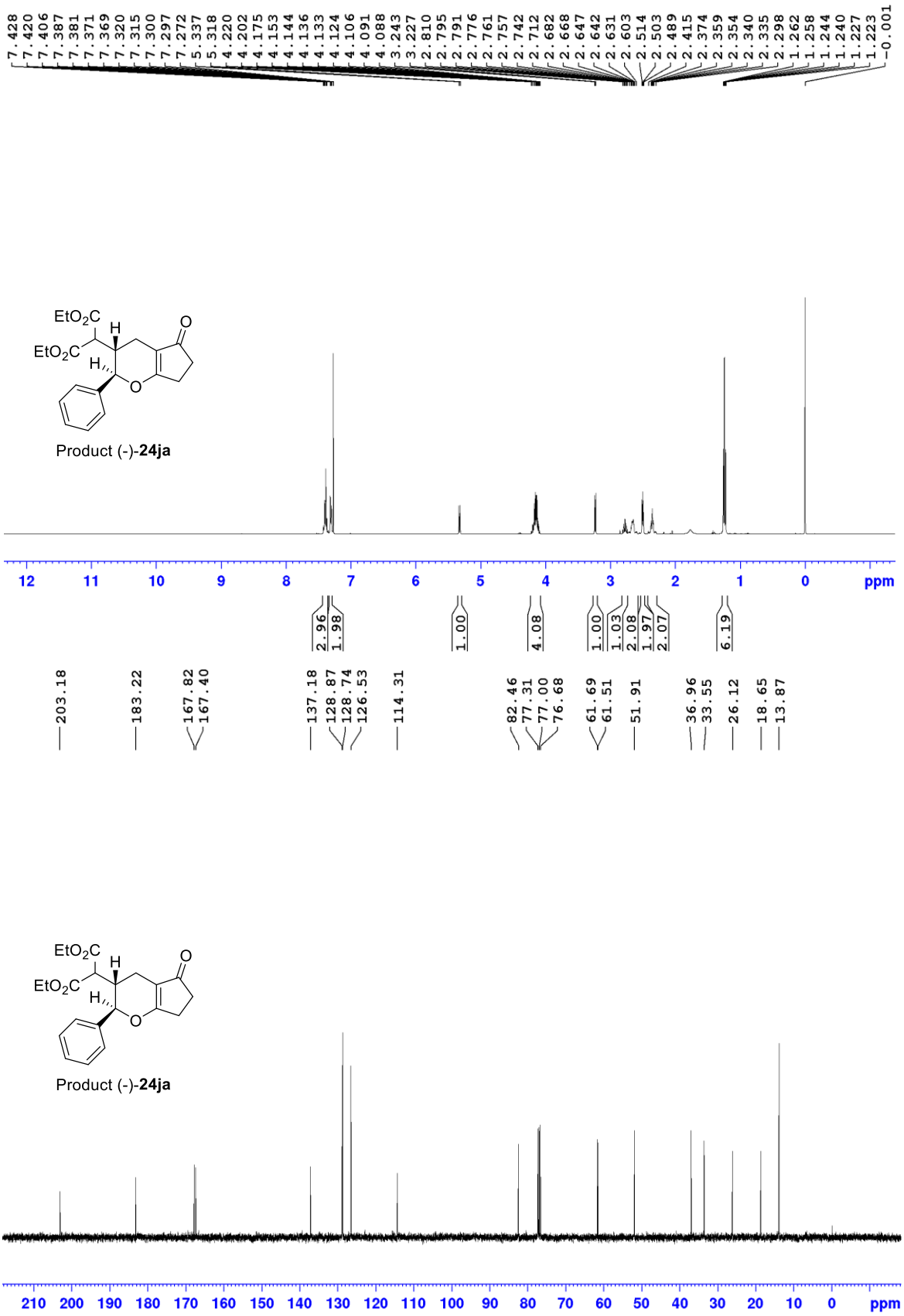


Figure 14. ^{1}H and ^{13}C spectra of the product (-)-**24ja**.

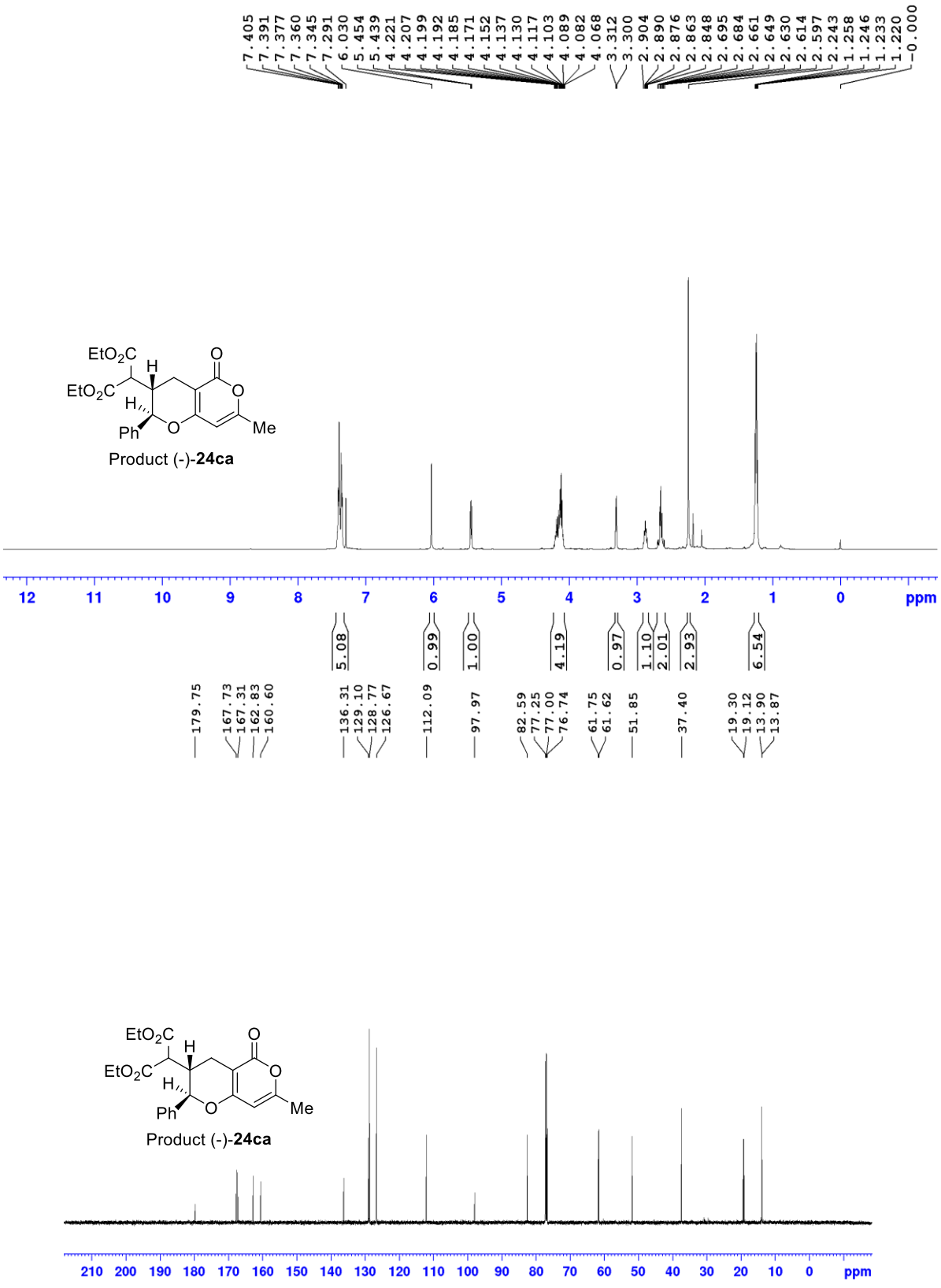
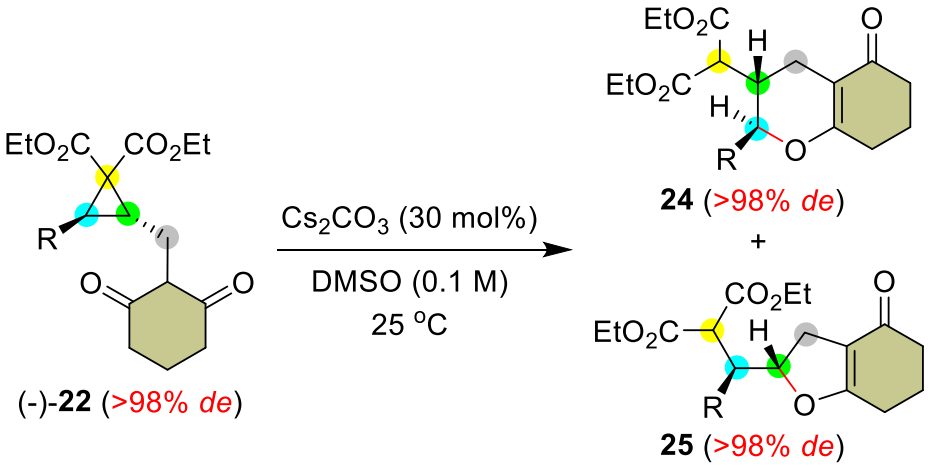


Figure 15. ^{1}H and ^{13}C spectra of the product (-)-**24ca**.

Table 7. Scope of 2,3-Dihydrofurans Synthesis from Functionally Rich Cyclopropanes (-)-**5ha** to (-)-**22hj**[a,b]



entry	**22**	*t* (h)	**24** (%)	**25** (%)	**25** *de* (%)
1	**22ha:** R = Ph	24	(-)-**24ha** (10)	(+)-**25ha** (54)	>98
2	**22hb:** R = 4-MeC_6H_4	40	(-)-**24hb** (23)	(+)-**25hb** (34)	>98
3	**22hc:** R = 4-$MeOC_6H_4$	24	(-)-**24hc** (20)	(+)-**25hc** (40)	>98
4[c]	**22hd:** R = 4-BrC_6H_4	24	(-)-**24hd** (18)	(+)-**25hd** (41)	>98
5[c]	**22he:** R = 4-$O_2NC_6H_4$	48	(-)-**24he** (11)	(+)-**25he** (63)	>98
6[c]	**22hf:** R = 3-$O_2NC_6H_4$	48	(-)-**24hf** (31)	(+)-**25hf** (34)	>98
7[c]	**22hg:** R = 2-$O_2NC_6H_4$	48	(+)-**24hg** (12)	(+)-**25hg** (67)	>98
8	**22hh:** R = *n*-Propyl	24	**24hh** (trace)	(+)-**25hh** (50)	>98
9	**22hi:** R = *n*-Butyl	24	**24hi** (trace)	(+)-**25hi** (50)	>98
10	**22hj:** R = $PhCH_2CH_2$	24	**24hj** (trace)	(+)-**25hj** (50)	>98

[a]Unless otherwise stated, **22** (0.1 mmol), and Cs_2CO_3 (30 mol%) in DMSO (0.1 M) were stirred at 25 °C and yield refers to the column-purified product. [b]Diastereomeric excess (*de*) of **25** was determined by ^1H NMR analysis of crude reaction mixture. [c]The catalyst Cs_2CO_3 was employed in 50 mol%.

Correlation between base-catalysis (Table 7) and Lewis acid-catalysis (Tables 5-6) revealed that the reaction rate and the regioselectivity of the ring-opening are very low in the former case. However, common points in both the cases are requirement of high catalyst loading (50-60 mol%) and longer reaction time (30-48 h) for the annulative ring-opening of cyclopropanes containing electron withdrawing group substituted aryl groups (–)-**22** (Tables 5-7).

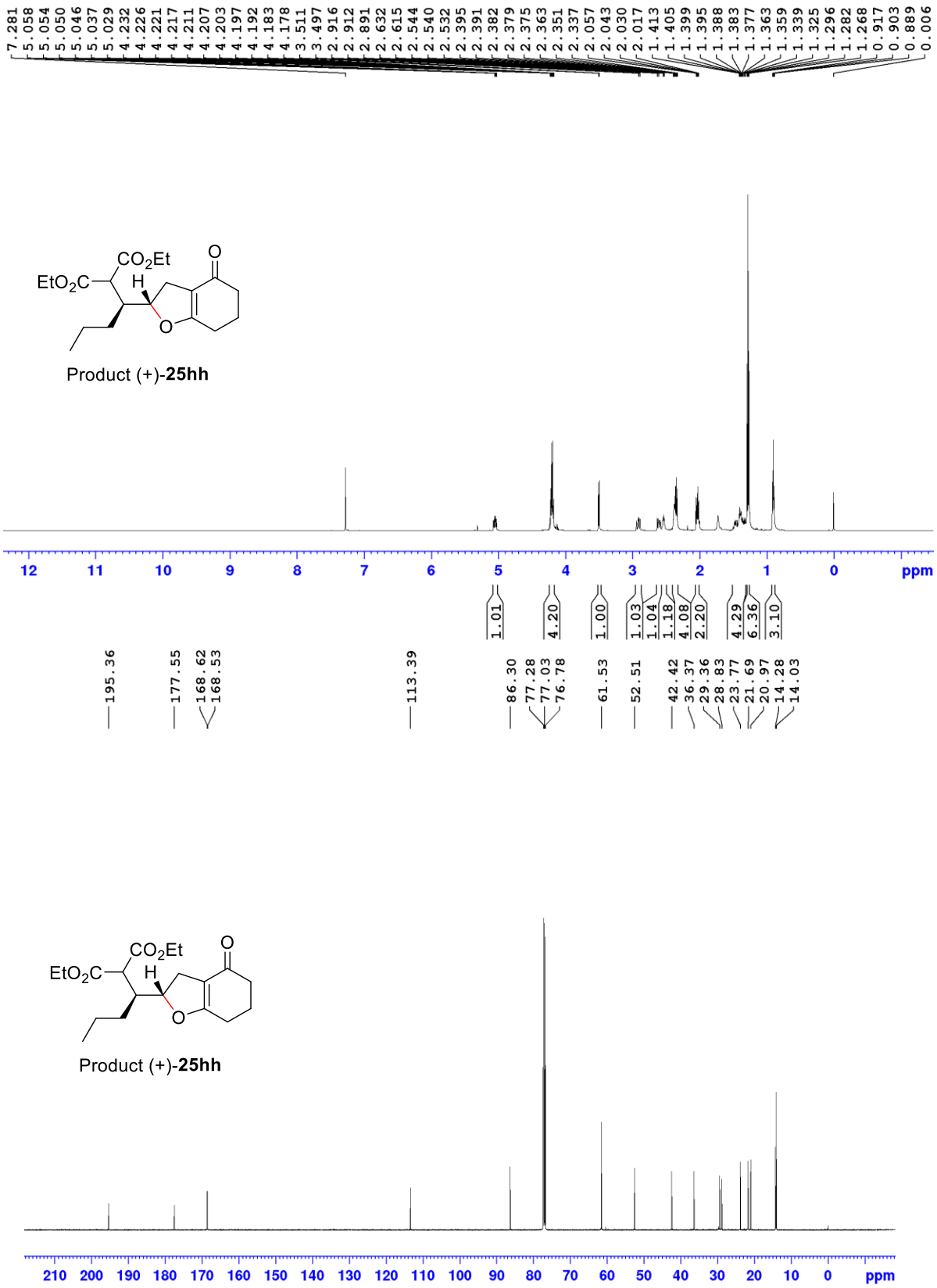
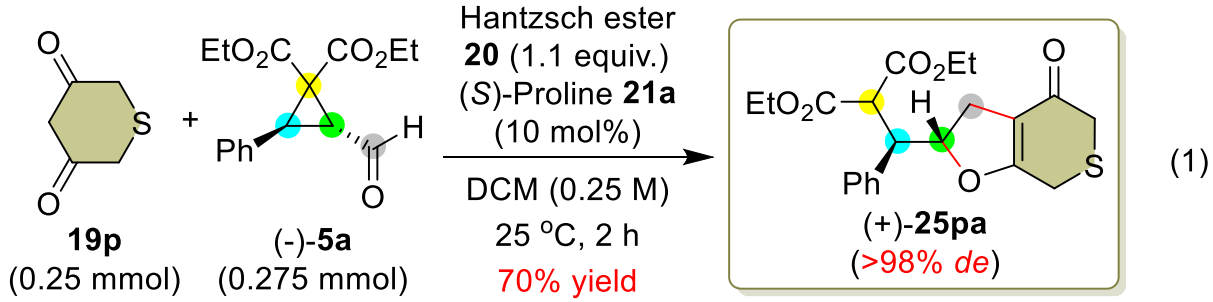


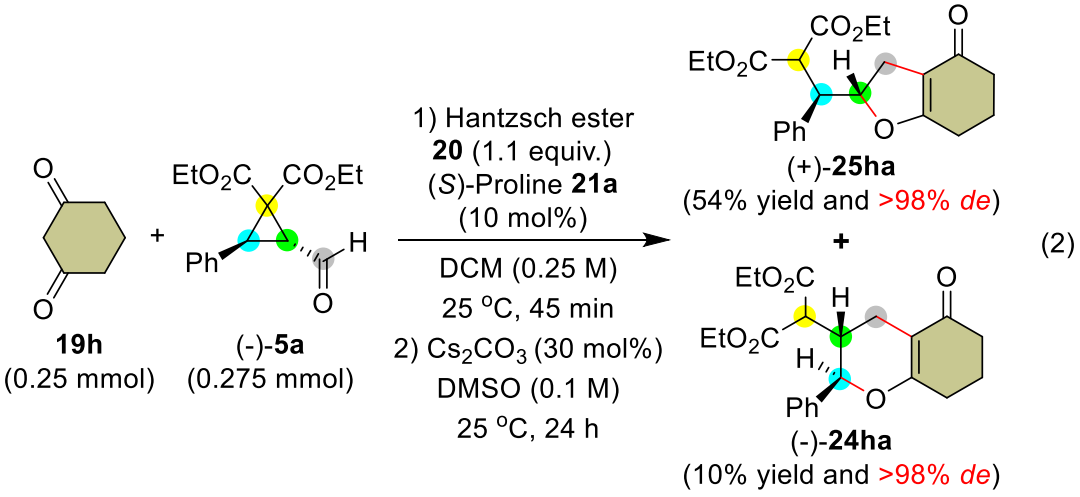
Figure 16. ^{1}H and ^{13}C spectra of the product (+)-**25hh**.

Strikingly, the functionalized chiral dihydrofuran (+)-**25pa** was directly produced in 70% overall yield from the three-component reaction of (−)-**5a**, thiane-3,5-dione **19p** and **20** under (*S*)-**21a**-catalysis in DCM at 25 °C in just 2 h without requiring any inducement from either Lewis acid or base catalysis for the ring-opening annulation (Eq. 1). This reaction is supposed to have gone through unisolable and transient intermediacy of the cyclopropyl containing thiane-3,5-dione **22pa**. This aforementioned shocking result could be explained by the higher nucleophilic nature of the sulfur containing cyclic-1,3-dione fragment of the intermediate **22pa**, which must have exclusively driven the annulative ring-opening reaction in a highly regio- and stereoselective fashion, even in the absence of Lewis acid/base catalysts (Eq. 1). ^{1}H and ^{13}C spectra of compound (+)-**25pa** are shown in Figure 17.



(1)

The sequential one-pot combination of the reductive coupling and the annulative ring-opening of **19h**, (-)-**5a**, and **20** under (*S*)-**21a**/Cs_2CO_3-catalysis at 25 °C for 24 h furnished the products (+)-**25ha** and (−)-**24ha** in 64% overall yield with 5.4:1 ratio (Eq. 2).



(2)

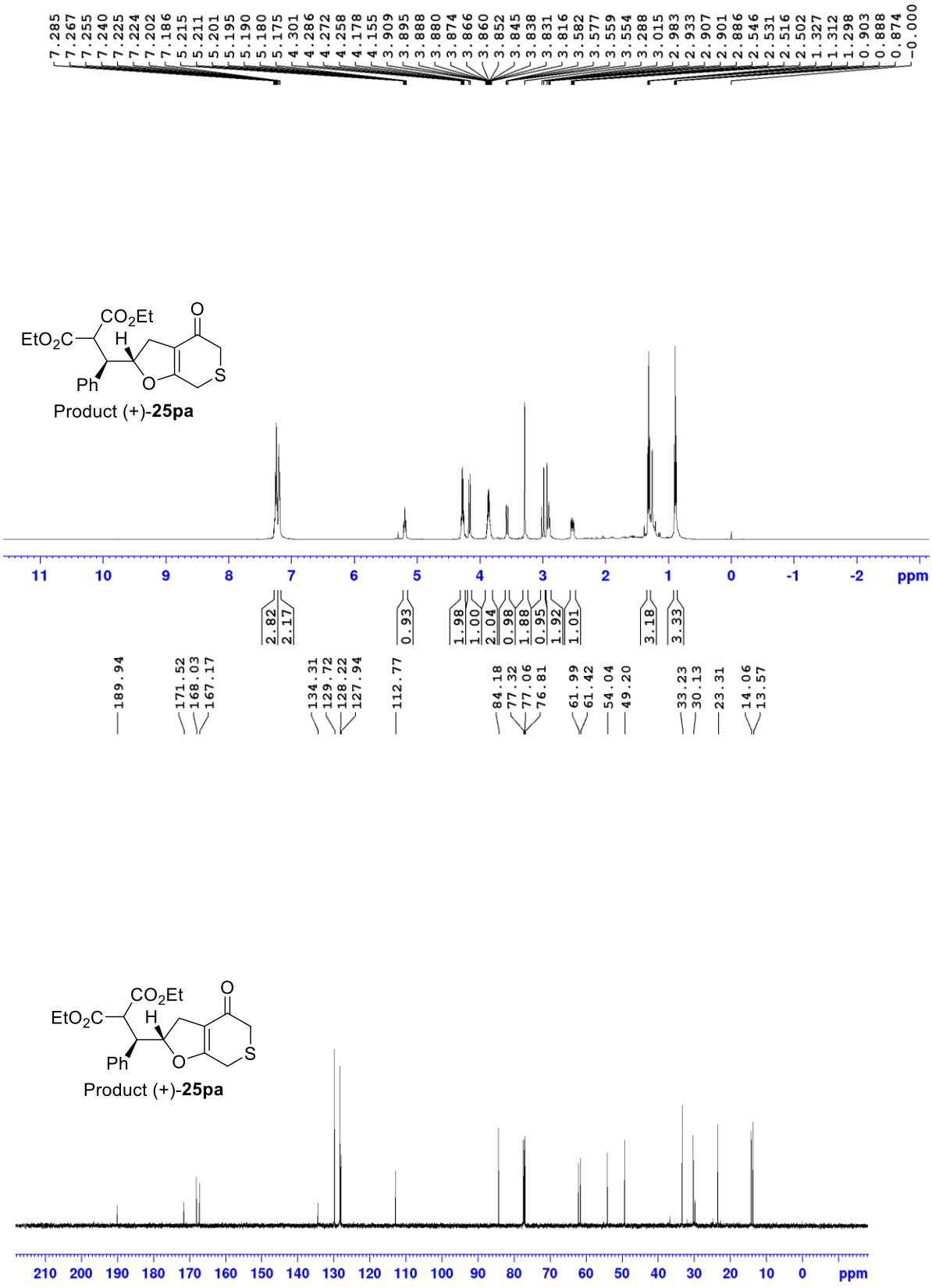
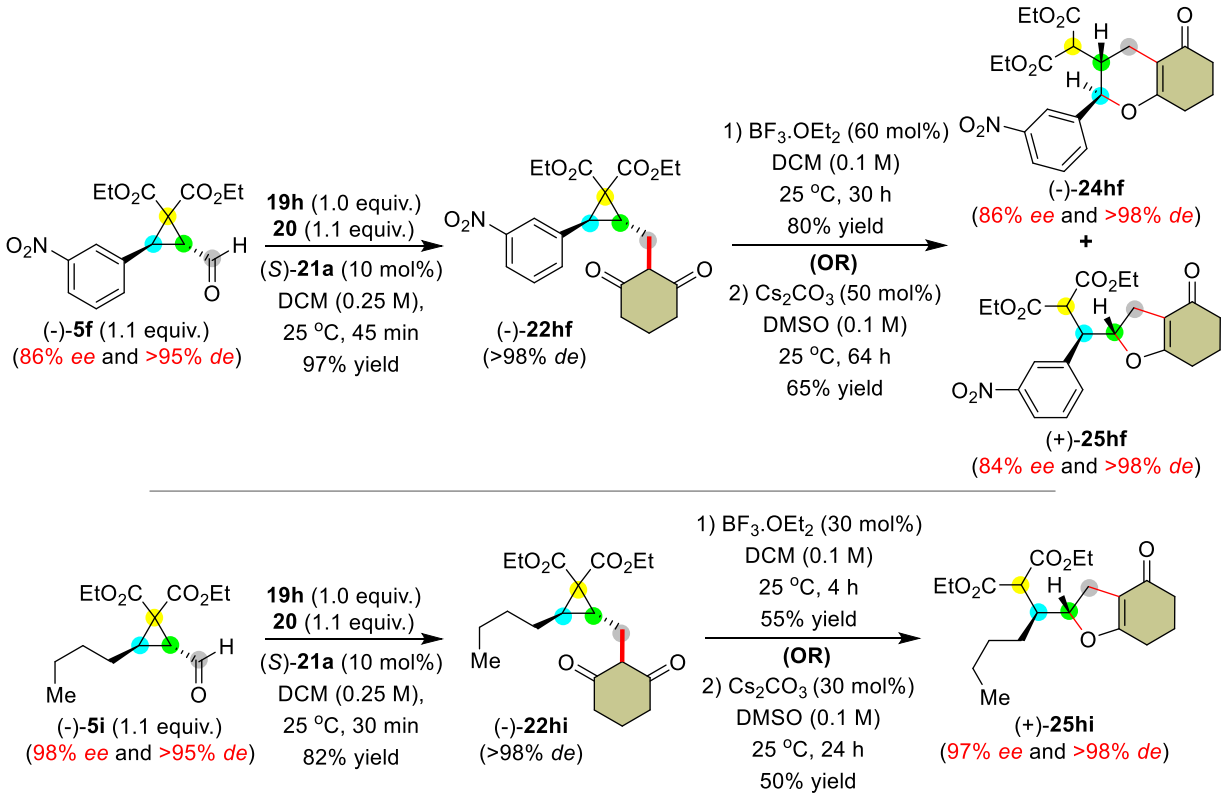


Figure 17. ^{1}H and ^{13}C spectra of the product (+)-**25pa**.

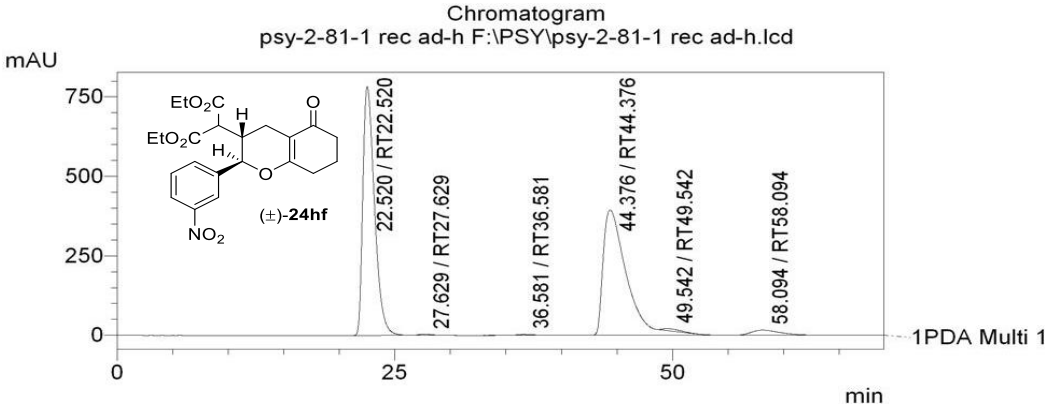
Scheme 15. Non-racemization and Non-epimerization of **22**, **24** and **25** During the Reaction Course.



To investigate the transfer of absolute stereochemical information from the starting materials (-)-**5** to the products (-)-**22** and (-)-**24**/(+)-**25** with high accuracy, we have done HPLC analysis of both the compounds in a sequence of reactions as shown in Scheme 15 (Figure18-20). Chiral HPLC analysis of two reaction sequences of (-)-**5f** → (-)-**22hf** → (-)-**24hf**/(+)-**25hf** and (-)-**5i** → (-)-**22hi** → (+)-**25hi** from both the catalytic methods revealed that there is no loss of chiral information from the starting materials to the products as shown in the Scheme 15.

Slight changes (1-2%) in *ee*/*de* of the products **22-25** compared to the starting materials **5** are consequence of resolution during the reactions, not because of racemization or epimerization of particular chiral centers. By correlation with these results (Scheme 15) we concluded that there is no loss of optical activity (*ee*) in the rest of the chiral molecules **22-25** as compared to their starting materials (-)-**5** studied in this work. HPLC spectra of compounds (-)-**24hf**, (+)-**25hf** and (+)-**25hi** are shown in Figures 18-20.

Racemic **(±)-24hf**:



Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm

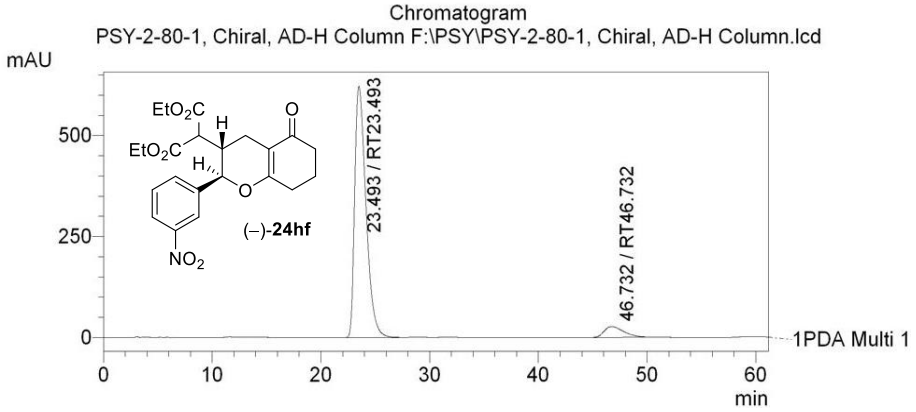
1 PDA Multi 1 / 254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT22.520	22.520	57006872	783471	47.864	64.952
2	RT27.629	27.629	296057	3592	0.249	0.298
3	RT36.581	36.581	278402	2770	0.234	0.230
4	RT44.376	44.376	57991020	394644	48.691	32.717
5	RT49.542	49.542	684758	5858	0.575	0.486
6	RT58.094	58.094	2843581	15903	2.388	1.318
Total			119100690	1206239	100.000	100.000

Chiral **(–)-24hf** (86% *ee*):



Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm

1 PDA Multi 1 / 254nm 4nm

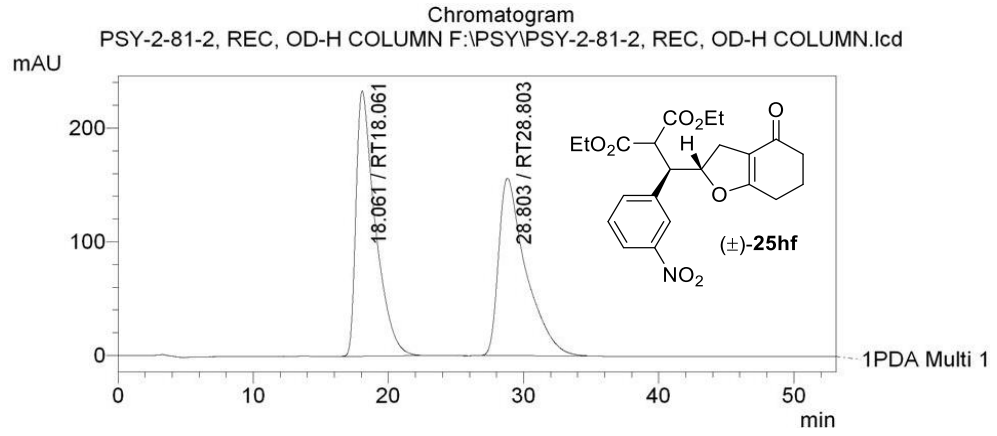
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT23.493	23.493	44677954	621652	92.992	95.847
2	RT46.732	46.732	3366778	26938	7.008	4.153
Total			48044733	648590	100.000	100.000

Figure 18. HPLC spectra of the product (-)-**24hf**.

Racemic **(±)-25hf**:



Chiralpak OD-H, Hexane/*i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm

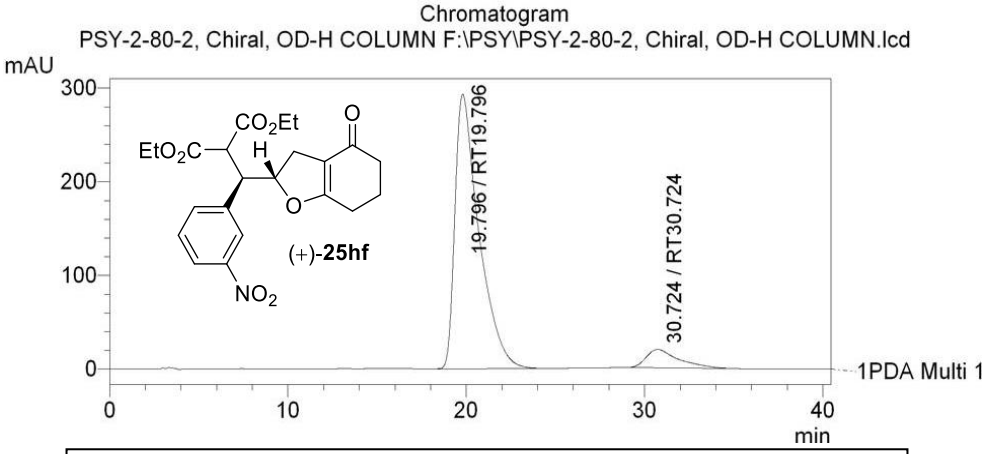
1 PDA Multi 1 / 254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT18.061	18.061	23070126	233145	51.283	59.896
2	RT28.803	28.803	21915446	156104	48.717	40.104
Total			44985572	389249	100.000	100.000

Chiral **(+)-25hf** (84% *ee*):



Chiralpak OD-H, Hexane/*i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm

1 PDA Multi 1 / 254nm 4nm

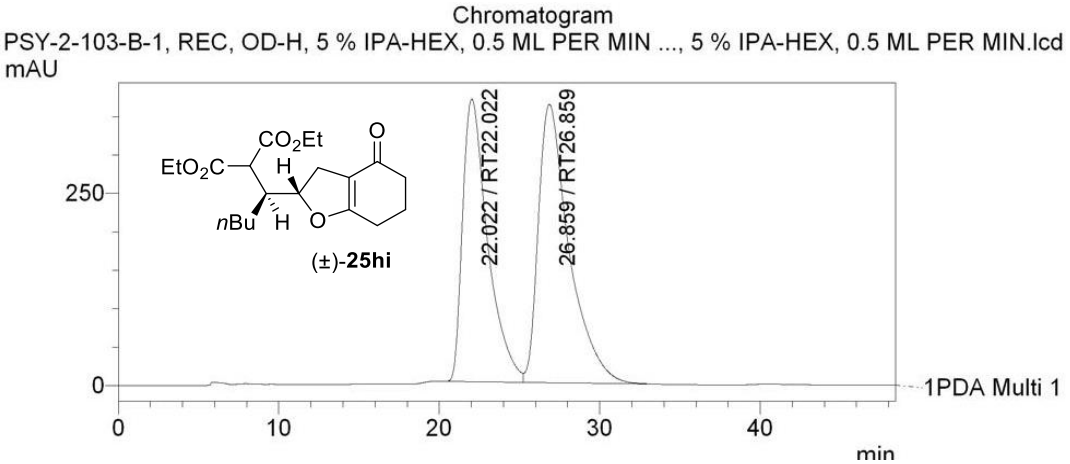
PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT19.796	19.796	27420342	292948	91.876	93.766
2	RT30.724	30.724	2424507	19477	8.124	6.234
Total			29844850	312424	100.000	100.000

Figure 19. HPLC spectra of the product (+)-**25hf**.

Racemic **(±)-25hi**:



Chiralpak OD-H, Hexane/*i*-PrOH = 95:05, Flow Rate 0.5 mL/min, 254 nm

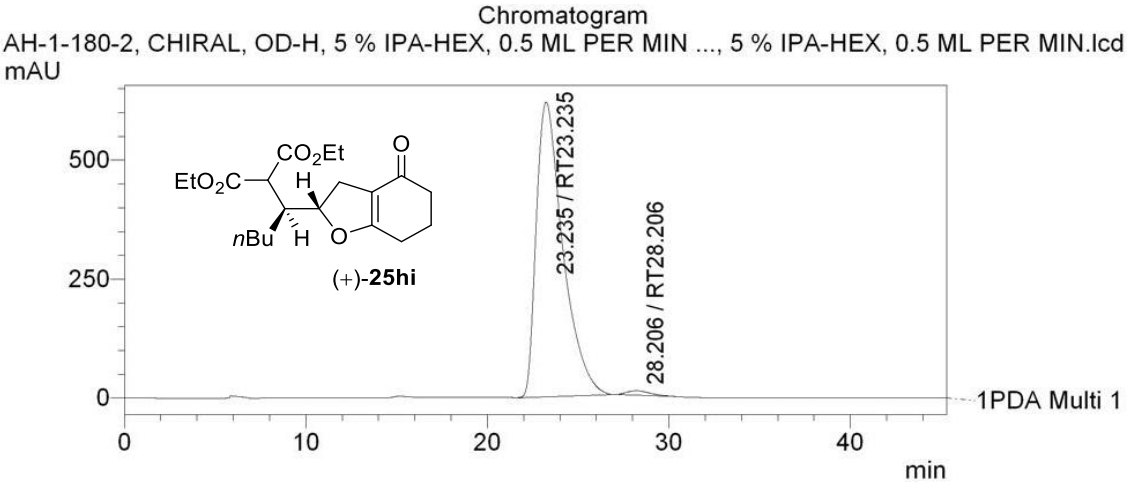
1 PDA Multi 1 / 254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT22.022	22.022	40078108	368154	45.236	50.383
2	RT26.859	26.859	48518793	362552	54.764	49.617
Total			88596901	730706	100.000	100.000

Chiral **(+)-25hi** (97% *ee*):



Chiralpak OD-H, Hexane/*i*-PrOH = 95:05, Flow Rate 0.5 mL/min, 254 nm

1 PDA Multi 1 / 254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT23.235	23.235	63204403	619503	98.589	98.476
2	RT28.206	28.206	904302	9586	1.411	1.524
Total			64108704	629089	100.000	100.000

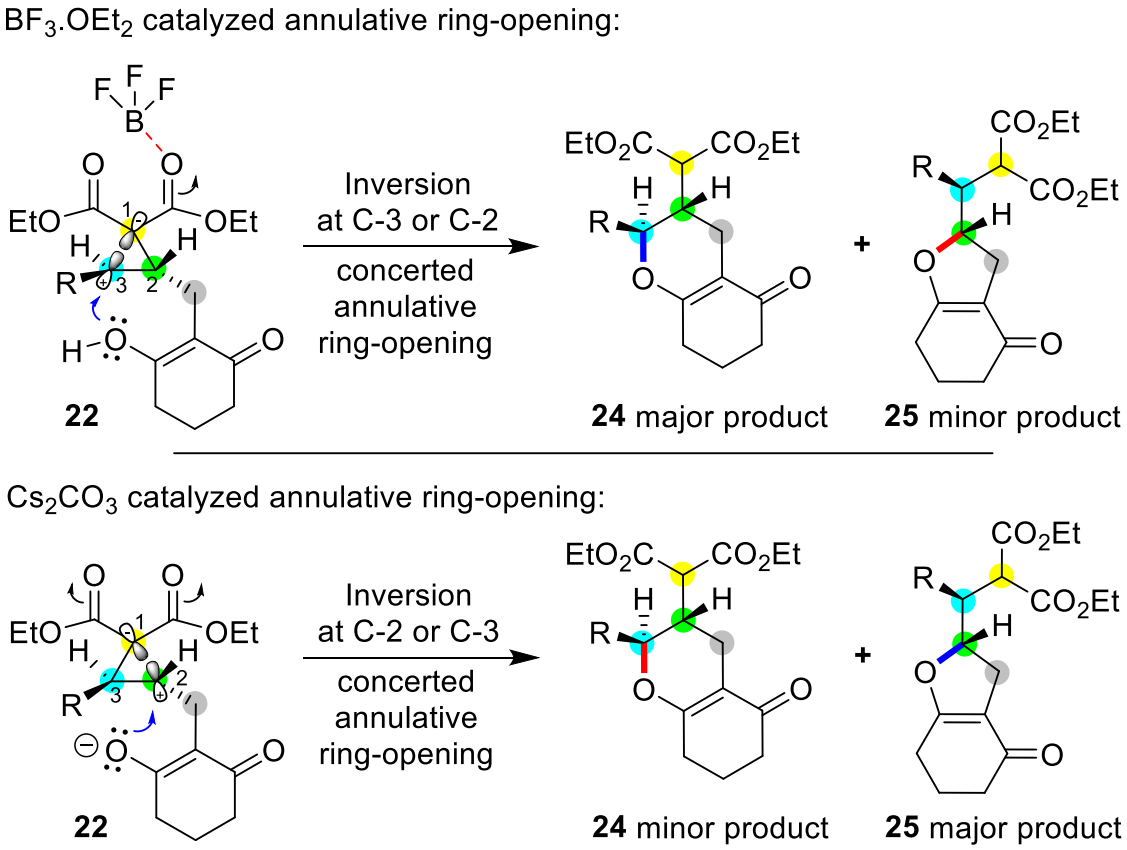
Figure 20. HPLC spectra of the product (+)-**25hi**.

3.2.3 Reaction Mechanism:

Highly diastereo- and regioselective chiral synthesis of dihydropyrans **24** and dihydrofurans **25** through acid-catalysis was explained through stereospecific intimate ion pair pathway and base-catalysis through self-polarization of cyclopropane ring (Scheme 16).[49] The annulative ring-opening products **24/25** were obtained without any significant loss in the stereochemical information from the chiral cyclopropanes **22** as shown in Scheme 15. Mixture of diastereomers would have formed if the reaction proceeded through a ring opened zwitterion, and the results presented in Tables 5-7 suggests that zwitterion was not formed in these annulative ring-opening reactions. Simultaneously, the single crystal X-ray diffraction analysis on the compounds (-)-**24ga** and (+)-**25hc** also revealed that inversion occurred at the cyclopropyl stereocenter (C2 or C3) during the course of the acid/base-catalyzed annulative ring-opening reaction.

Regioselectivity of the acid/base-catalyzed annulative ring-opening can be explained by the stability of the cyclopropane in terms of C1-C3 or C1-C2 σ-bond stability and also by the nature of its close proximity with O-nucleophiles. Reactions of neutral- or electron rich substituted arylcyclopropane containing cyclic-1,3-diones **22** under the Lewis-acid catalysis proceeded with the formation of **24** in high regioselectivities within 1-3 h with 30 mol% catalyst (Tables 5-6). In comparison, the reaction of electron poor substituted arylcyclopropane containing cyclic-1,3-diones **22** under the Lewis-acid catalysis proceeded with low to moderate regioselectivities for 30-48 h and with 60 mol% catalyst loading. In a similar manner, aliphatic group substituted cyclopropane containing cyclic-1,3-diones **22** under the Lewis-acid catalysis for 2-4 h furnished reverse regioselectivities with trace amounts of **24** and 52-72% of **25**. These results can be explained by the ability of the neutral- or electron rich aryl group to stabilize any cationic charge at C3 so as to facilitate the ring-opening of the cyclopropane followed by annulation to dihydropyrans **24** (see Scheme 16). But the electron poor aryl or aliphatic group can't stabilize the cationic charge at C3 and so the entire process of ring-opening followed by annulation will take place in kinetic mode at C2 to furnish the dihydrofurans **25** as the major regioisomers under the Lewis-acid catalysis (Scheme 16).

Scheme 16. Reaction Mechanism for Annulative Ring-Opening of **22**.



Surprisingly, base-catalyzed annulative ring-opening of **22** is less regioselective compared to the Lewis acid-catalyzed, even with neutral- or electron rich substituted aryl groups on cyclopropane ring, without compromising diastereo- and enantioselectivity. This observation may be due to the pre-existence of reactive nucleophiles as enol group in the cyclopropyl containing cyclic-1,3-diones **22** and also the close proximity between intimate cation or self-polarized cationic carbon C2 and the enolate anion nucleophile, which facilitate the reaction kinetics to support the formation of the dihydrofurans **25** as the major regioisomers (Scheme 16).

The structures of the products **22**, **24** and **25** were established by NMR analysis and the absolute stereochemistry was unambiguously confirmed by X-ray structure analysis of (–)-**22ia,** (–)-**24ga** and (+)-**25hc** (Figure 21, 22).[47]

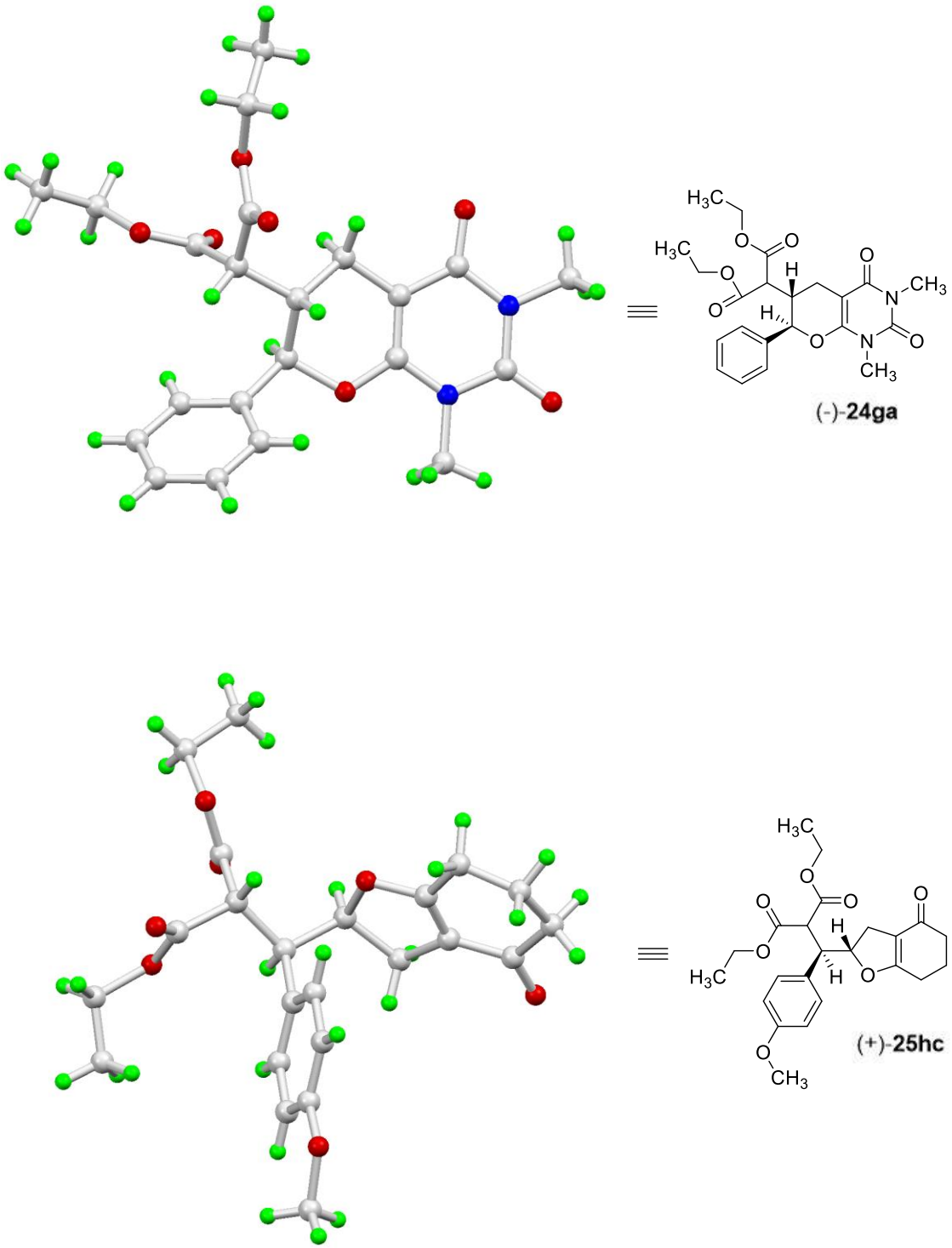


Figure 21. Crystal structures of compounds (-)-**24ga** and (+)-**25hc**.

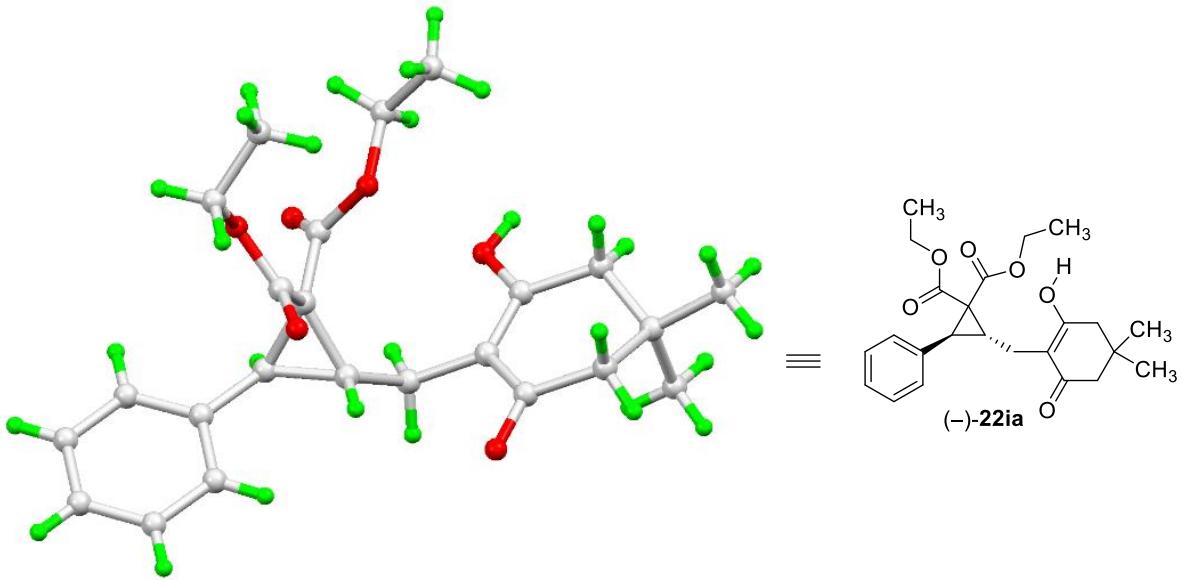


Figure 22. Crystal structure of compound (-)-**22ia**.

3.3 Conclusions

In conclusion, for the first time we have developed an efficient reductive coupling protocol for the activation and utilization of formylcyclopropanes in the presence of various nucleophiles under the iminium-activation and more importantly without cleaving the strained three-membered ring. Using this activation mode, we have synthesized a library of functionally rich chiral cyclopropanes in good to excellent yields with sustained rate and selectivity and further transformed them into chiral dihydropyrans and dihydrofurans in high yields through a novel intramolecular annulative ring-opening reaction. We believe this two-step methodology will be an useful protocol for a large number of applications in medicinal chemistry. Further work is in progress to utilize potential application of this mild activation mode.

4. Organocatalytic Chemoselective Reductive Alkylation of the Chiral Dicarbonyl-Cyclopropanes: Scope and Applications

4.1 Introduction

Cyclopropane plays an essential role in organic synthesis. The importance of cyclopropane is attributed to its ability to transform into various natural products and pharmaceutical compounds through various ring-opening reactions. Cyclopropane is present in many bioactive compounds and natural products, which shows a large spectrum of biological activities such as enzyme inhibition, antimicrobial, insecticidal, and antitumor activity (figure 23).[50-52] Among cyclopropanes, dicarbonyl-cyclopropanes are uniquely positioned because of their ability to transform into valuable compounds through the chemoselective activation of the formyl group with the help of lewis-acid catalysis, transition metal catalysis, and organocatalysis. Organocatalytic activation of dicarbonyl-cyclopropanes can be easily achieved through NHC catalysis, iminium/enamine mediated, enolate mediated, and urea catalyzed reactions.

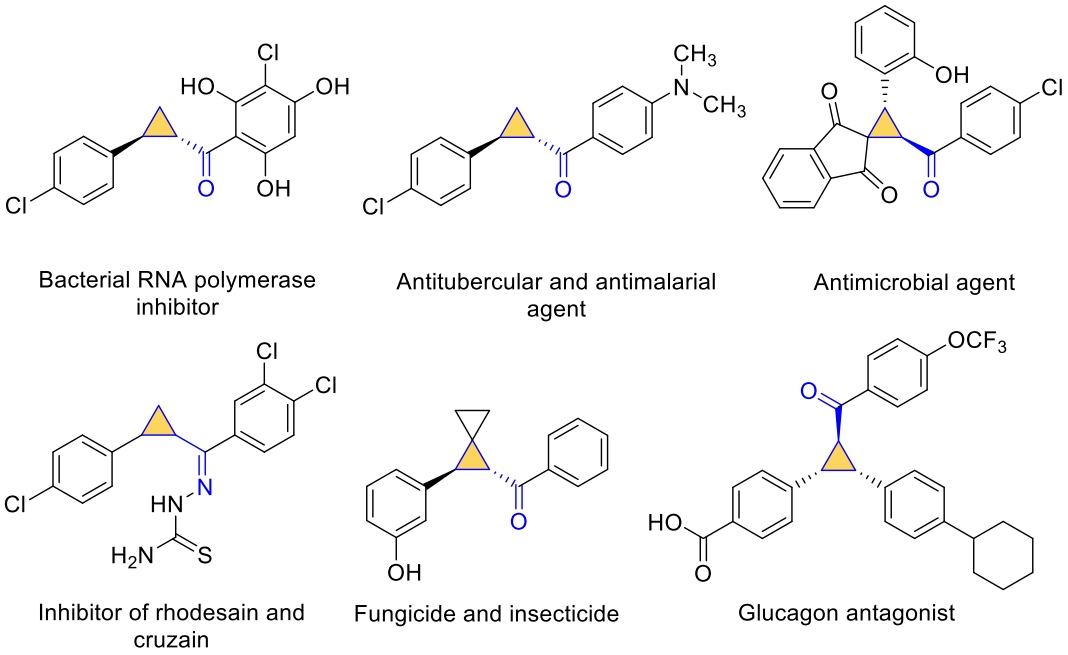
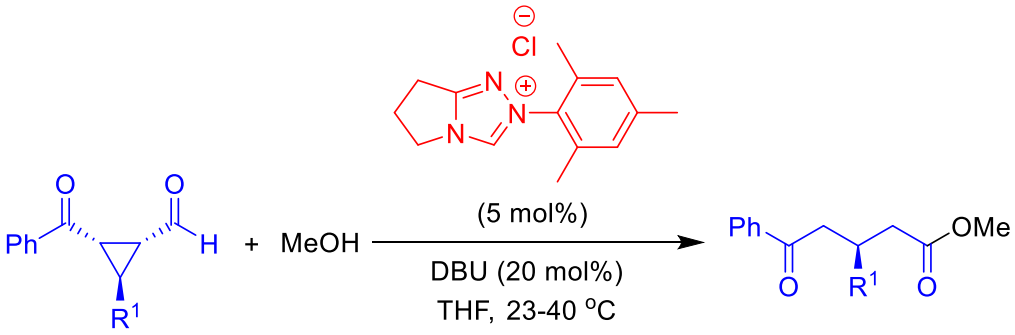


Figure 23. Bioactive drug molecules with cyclopropane scaffold.

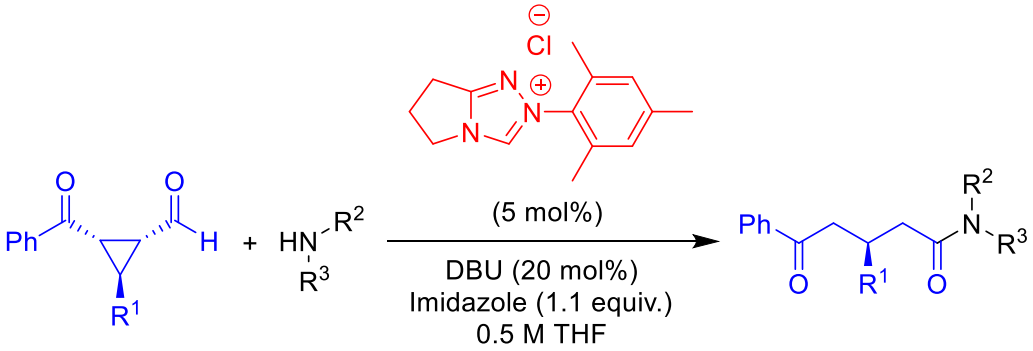
In formylcyclopropanes, particularly dicarbonyl-formylcyclopropanes, are the essential core structures of many bioactive compounds and natural products. In 2005, MacMillan and co-workers[6] described the first enantioselective organocatalytic synthesis of dicarbonyl-cyclopropanes. Later in 2011, Jinxing Ye et al. reported the organocatalytic asymmetric synthesis of dicarbonyl-cyclopropanes.[18] Last year Dzambaski and co-workers[19] also described the organocatalytic synthesis of dicarbonyl-cyclopropanes in a one-pot manner. These synthesis methods of dicarbonyl-cyclopropanes have been described in Schemes 1 and 5.

Scheme 17. Previous Organocatalytic Activation of Dicarbonyl-Cyclopropanes.

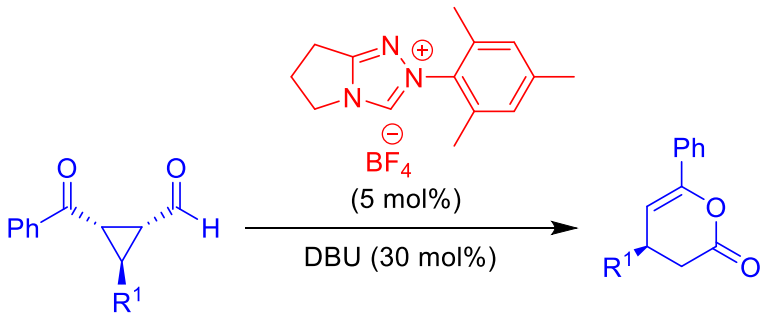
(a) NHC catalysed C-C bond cleavage in redox esterification: Bode[36a]



(b) Amidation reaction of cyclopropane through NHC catalysis: Bode[53]



(c) NHC catalysed ring exapansion cyclopropane: Shu-Li You[36d]

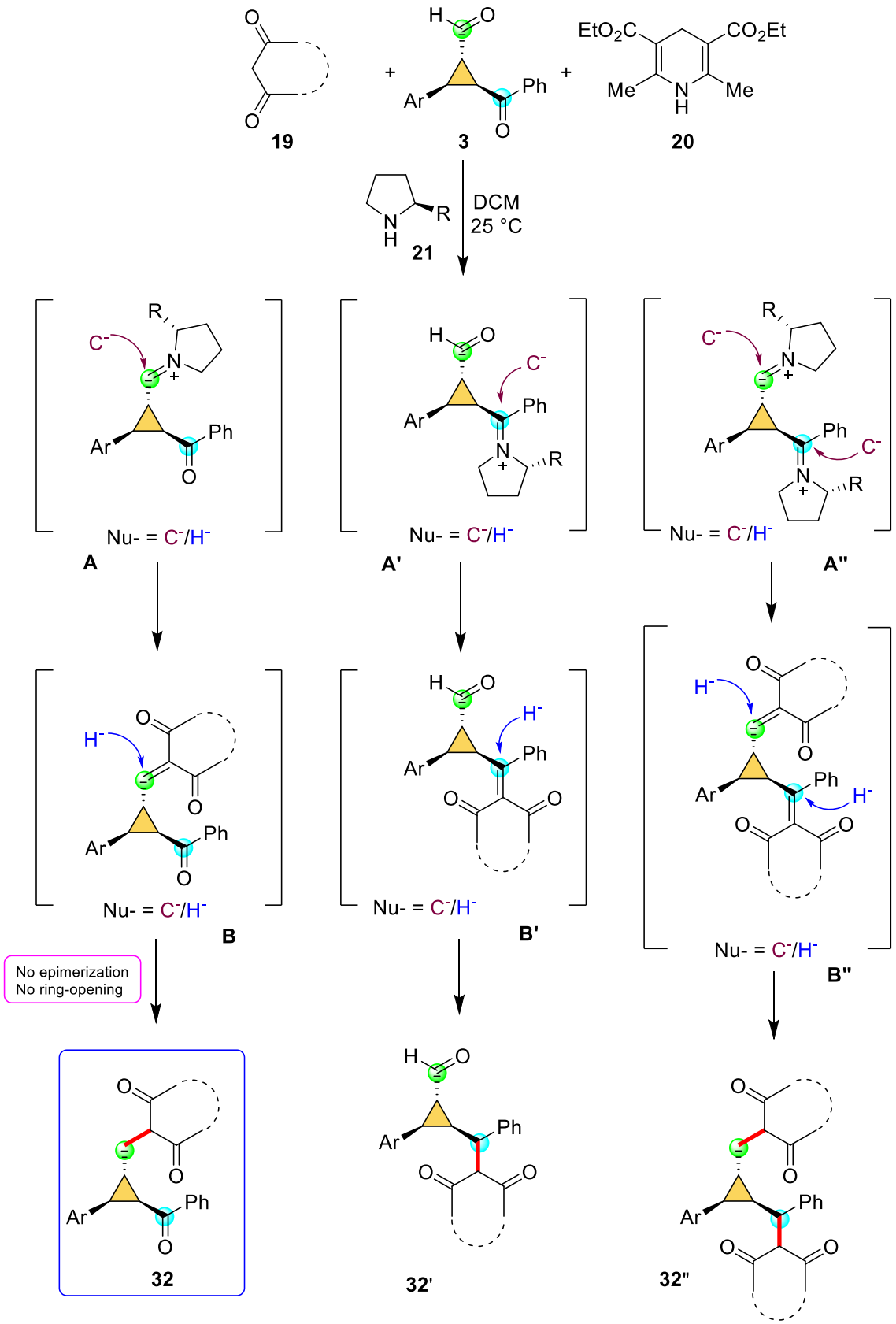


In 2006, Bode and co-workers reported the first organocatalytic activation of dicarbonyl-cyclopropanes by NHC catalyzed C-C bond cleavage in redox esterification.[36a] Again, in 2007, Bode and co-workers described the amidation reaction of dicarbonyl-cyclopropanes through NHC catalysis.[53] In 2009, Shu-Li You et al. also reported NHC catalyzed ring expansion of dicarbonyl-cyclopropanes[36d] (Scheme 17).

The reactivity of these dicarbonyl-cyclopropanes was investigated through NHC catalysis only. It is important to note that all of the described organocatalytic methods involving dicarbonyl-cyclopropanes activated via NHC catalysis resulted in cyclopropane rings being opened. However, the dicarbonyl-cyclopropanes have not been investigated under organocatalysis for strategic synthetic transformations without affecting the strained cyclopropane ring. There is no report on dicarbonyl-cyclopropane activation through iminium ion. To accomplish this synthetic challenge, based on our previous discovery of organocatalytic reductive coupling reaction,[44,54] we have designed a high-yielding conversion of the formyl group of dicarbonyl-cyclopropanes into the cyclic-1,3-diketones **32** without ring-opening from cyclic-1,3-diketones or CH-acids **19**, chiral dicarbonyl-cyclopropanes (-)-**3** and Hantzsch ester **20** through organocatalytic reductive coupling reaction (Scheme 18).

As depicted in Scheme 18, our reaction design suggests that amino acid **21** would catalyze three-component reductive coupling between cyclic 1,3-diones **19**, dicarbonyl-cyclopropanes (-)-**3**, and Hantzsch ester **20** at the ambient conditions in DCM. First, amino acid (*S*)-proline **21a** would selectively react with the formyl group of dicarbonyl-cyclopropanes (-)-**3** to generate the iminium ion **A** by 1,2-addition. Secondly, the in situ generated iminium ion **A** intermediate may undergo reaction with the nucleophiles **19** through 1,2-addition. And the in situ reaction of iminium ion **A** with cyclic 1,3-diones, **19** can produce the intermediate **B** through 1,2-addition (Knoevenagel condensation) (Scheme 18). Thirdly, reduction or transfer hydrogenation of intermediates **B** with Hantzsch ester **20** could result in the formation of products **32**. However, due to the cyclopropane's propensity to cleave under iminium-catalysis, releasing product **32** from **19**, (-)-**3**, and **20** is challenging. Only the selective sequential attack of the carbon nucleophile on the iminium ion intermediate **A** followed by the transfer hydrogenation with Hantzsch ester on the activated olefin of the intermediate **B** over numerous additional options takes place; in contrast, the iminium activation could result in the formation of the product **32**.

Scheme 18. Reaction Design for The Chemoselective Alkylation of CH-Acids.



Similarly, the reaction can also proceed on the ketone group of dicarbonyl-cyclopropane (-)-**3**. First, it will generate iminium ion **A′** by reacting with the ketone group of dicarbonyl-cyclopropane (-)-**3** with (*S*)-proline **21a**. Secondly, the in situ generated iminium ion **A′** intermediate may undergo a reaction with the nucleophiles **19** through 1,2-addition. In situ reaction of iminium ion **A′** with cyclic 1,3-diones, **19** can produce the intermediate **B′** through 1,2-addition (Knoevenagel condensation) (Scheme 18). Thirdly, reduction or transfer hydrogenation of intermediates **B′** with Hantzsch ester **20** could result in the formation of products **32′**.

Another possibility is that both carbonyl groups of dicarbonyl-cyclopropane (-)-**3** can participate in the reaction. First, it will generate di iminium ion **A″** by reacting with both carbonyl groups of dicarbonyl-cyclopropane (-)-**3** with (*S*)-proline **21a**. Secondly, the in situ generated di iminium ion **A″** intermediate may undergo a reaction with the nucleophiles **19** through 1,2-addition. In situ reaction of iminium ion **A″** with cyclic 1,3-diones, **19** can produce the intermediate **B″** through 1,2-addition (Knoevenagel condensation) (Scheme 18). Thirdly, reduction or transfer hydrogenation of intermediates **B″** with Hantzsch ester **20** could result in the formation of reductive coupling products **32″**.

Therefore, it is a challenge to selectively synthesize the desired product in a situation where there is a possibility of forming three different products **32**, **32′**, and **32″** from the three-component reductive alkylation reaction utilizing amino acids as a catalyst.

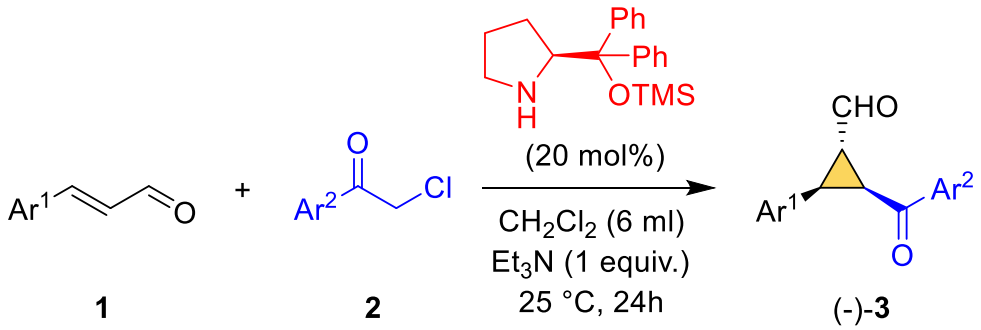
4.2 Results and Discussion

4.2.1 Synthesis of Chiral Dicarbonyl-Cyclopropanes (-)-3:

We synthesize the library of chiral dicarbonyl-cyclopropane (-)-**3** following reported procedure[18]. The asymmetric reaction of α,β-unsaturated aldehydes **1** with diphenyl prolinol TMS-ether **D** (20 mol%) in CH_2Cl_2 at room temperature to afford the chiral iminium ion (*Pre*-TS-2), which was attacked by chloroacetophenone **8** *via* Michael addition to produce the Michael adduct (*Pre*-TS-3). This intermediate further cyclized by releasing a chloride to furnish dicarbonyl-cyclopropane (-)-**3** in 62-85% yield with high *ee*/*dr*'s as depicted in Scheme 5. In Table 8, we showed some of the chiral formylcyclopropanes, which were first synthesized by us. For HPLC analysis, we

converted formylcyclopropane (-)-**3** into corresponding alcohols (-)-**3′** by following procedure **K**.

Table 8. Synthesis of Chiral Dicarbonyl-Cyclopropanes (-)-**3**[a,b]



1 (1 equiv.) (3 mmol) **2** (2 equiv.) (-)-**3**

entry	Ar^1, Ar^2	**3** (%)	**3** *dr*	**3**[c,d] *ee* (%)
1	$Ar^1 = Ar^2 = Ph$	(-)-**3a** (78)	>20:1	>99.9
2	$Ar^1 = p\text{-}CNC_6H_4$, $Ar^2 = Ph$	(-)-**3e** (80)	>20:1	>99.9
3	$Ar^1 = o\text{-}NO_2C_6H_4$, $Ar^2 = Ph$	(-)-**3f** (71)	2:1	99
4	$Ar^1 = o\text{-}CH_3C_6H_4$, $Ar^2 = Ph$	(-)-**3i** (78)	>20:1	>97
5	$Ar^1 = Ph$, $Ar^2 = p\text{-}ClC_6H_4$	(-)-**3l** (72)	>20:1	>99.9

[a]Reaction conditions: α,β-unsaturated aldehydes **1** (3 mmol), chloroacetophenones **8** (6 mmol), **D** (0.6 mmol) and triethylamine (3 mmol) in CH_2Cl_2 (6 mL) were stirred under room temperature for 24 h. [b]Isolated yield. [c]The enantiomer excess was detected on HPLC using the Chiralpak AS-H column. [d]The enantiomer excess was detected on HPLC after conversion to the corresponding alcohols **3′**. Diastereomeric ratio (*dr*) was determined by ^{1}H NMR analysis of crude reaction mixture.

^{1}H and ^{13}C spectra of compounds (-)-**3l**, (-)-**3l′**, and HPLC spectra of compound (-)-**3l′** are shown in Figures 24-26.

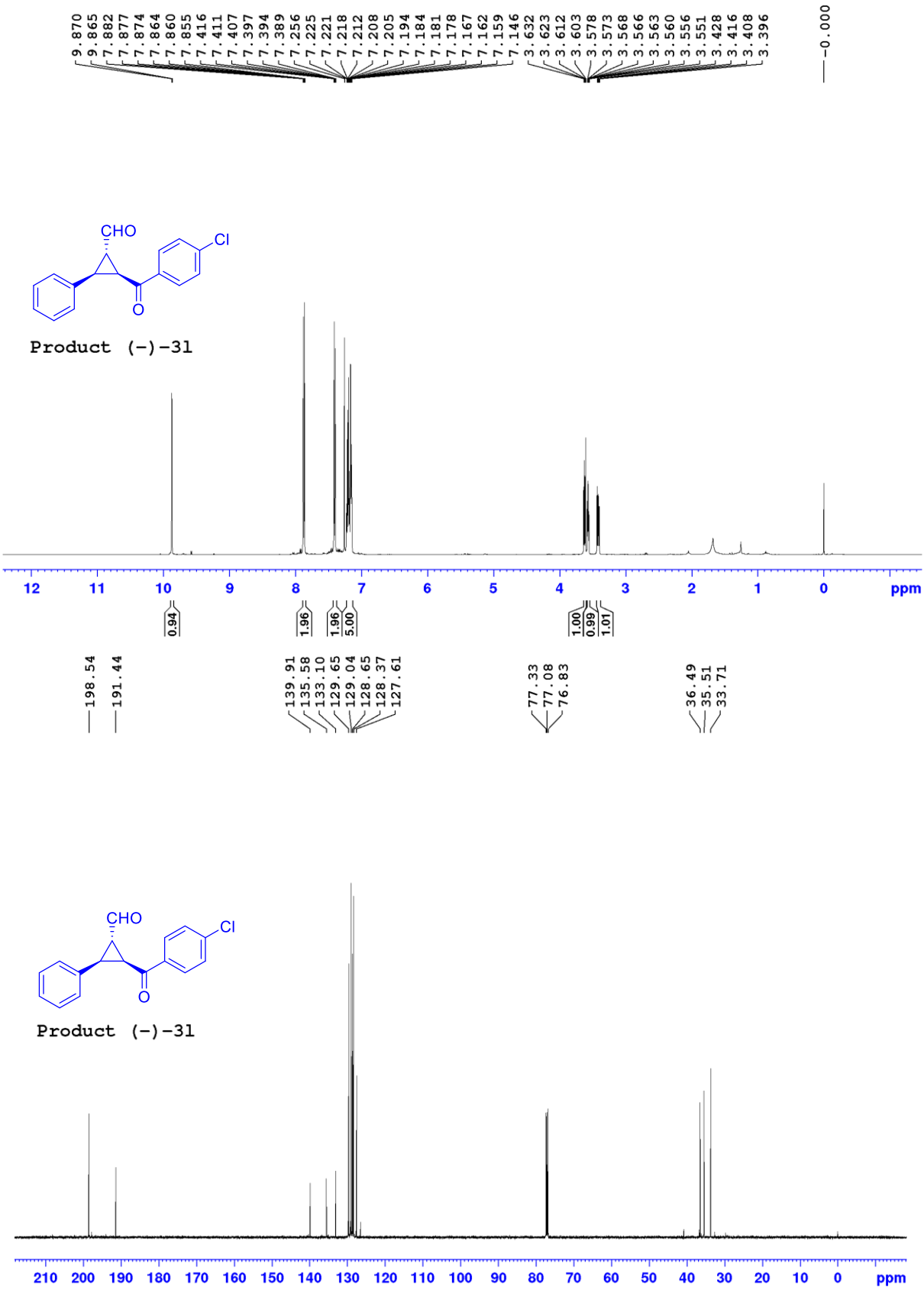


Figure 24. ^{1}H and ^{13}C spectra of the product (-)-**3l**.

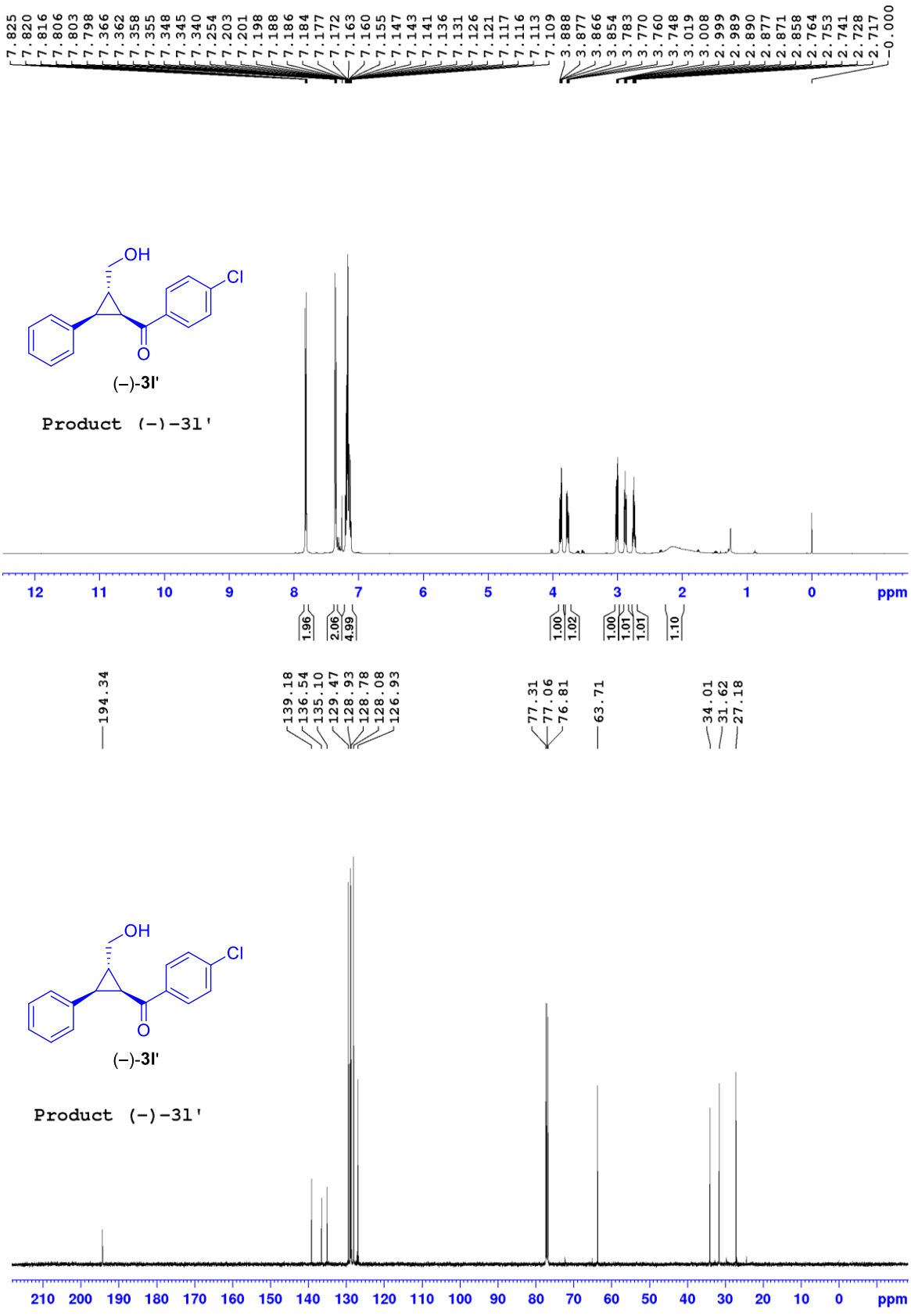
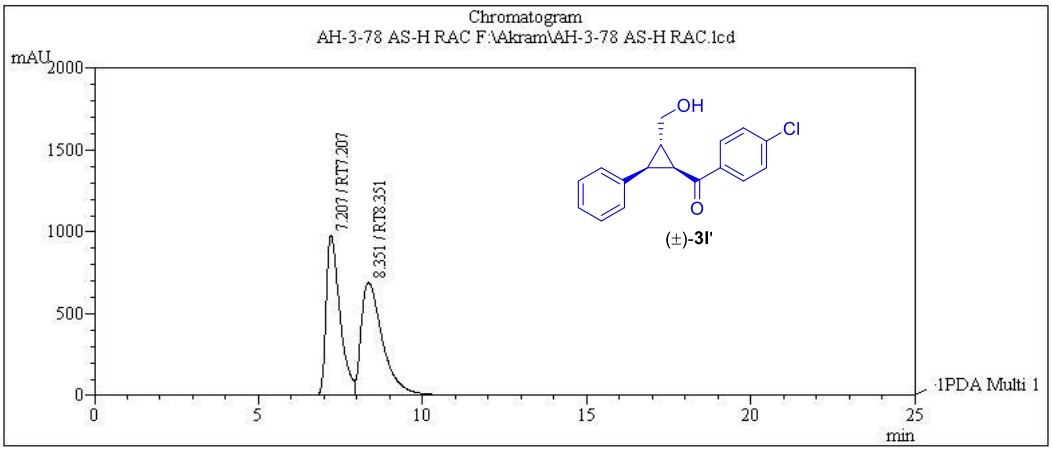


Figure 25. ^{1}H and ^{13}C spectra of the product (-)-**3l′**.

Racemic (±)-**3l′**:



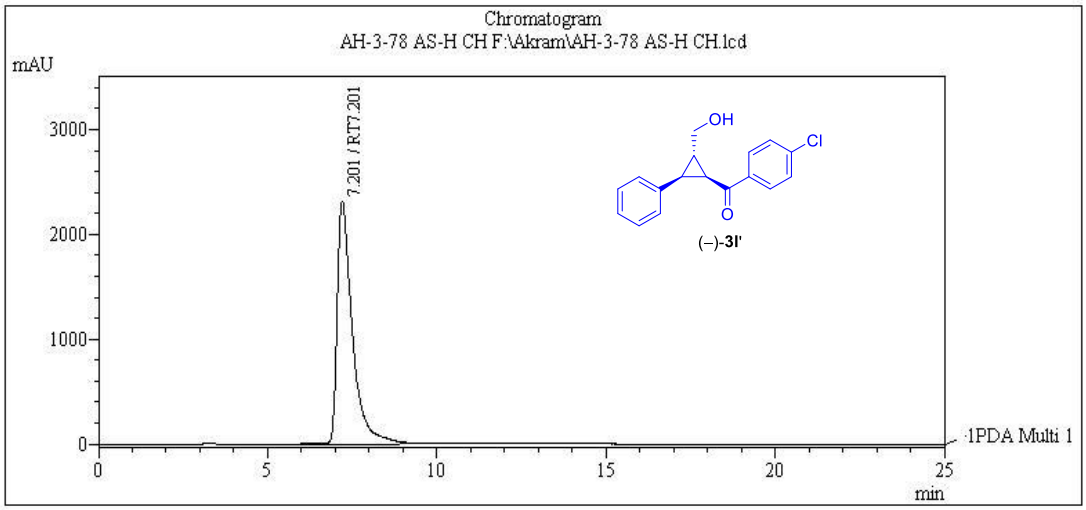
Chiralpak AS-H, Hexane/*i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT7.207	7.207	28488419	977487	47.366	58.619
2	RT8.351	8.351	31657202	690034	52.634	41.381
Total			60145621	1667521	100.000	100.000

Chiral (-)-**3l′** (>99.9% *ee*):



Chiralpak AS-H, Hexane/*i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

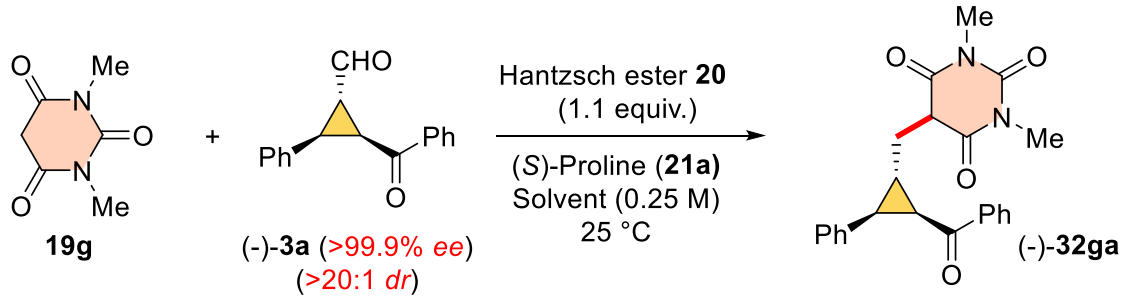
Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT7.201	7.201	72763985	2317922	100.000	100.000
Total			72763985	2317922	100.000	100.000

Figure 26. HPLC spectra of the product (-)-**3l′**.

4.2.2 Reaction Optimization:

Though the application of cyclopropanes in medicinal chemistry is enormous, only a few reports are available for their synthesis. Hence, we decided to investigate the three-component reductive alkylation reaction by choosing 1,3-dimethylbarbituric acid **19g**, dicarbonyl-cyclopropane (-)-**3a**, and Hantzsch ester **20** as our critical substrates. Accordingly, when we treated **19g** (1 equiv.) with (-)-**3a** (1.1 equiv.) under (*S*)-proline **21a** catalyst (10 mol%) and Hantzsch ester **20** (1.1 equiv.) in DCM solvent at room temperature in a one-pot manner. To our surprise, the reaction chemo-selectively proceeded on a formyl group of dicarbonyl-cyclopropanes resulting in a reductive coupling product (-)-**32ga** in 93% yield with >20:1 *dr* and >99.9 *ee* in 30 min (Table 9, entry1). Notably, we did not observe the formation of other possible products **32′**, **32″** in the above reaction.

Table 9. Investigation of The Reductive Alkylation on 1,3-Dimethyl Barbituric Acid **19g** and Dicarbonyl-Cyclopropane (-)-**3a**[a,b]



entry	**19g** (equiv.)	**3a** (equiv.)	**21a** (mol %)	Solvent	*t* (min)	**32ga** (%)	**32ga** *dr*	**32ga** *ee* (%)
1	1	1.1	10	DCM	30	93	>20:1	>99.9
2	1	1.1	5	DCM	60	88	>20:1	>99.9
3	1.1	1	10	DCM	30	88	>20:1	>99.9
4[c]	1	1.1	10	DCM	30	92	>20:1	>99.9
5	1	1.1	10	$CHCl_3$	30	93	>20:1	>99.9
6	1	1.1	10	DCE	60	91	>20:1	>99.9
7	1	1.1	10	EtOH	30	91	>20:1	>99.9
8	1	1.1	10	CH_3CN	30	87	>20:1	>99.9
9	1	1.1	10	DMSO	30	87	>20:1	>99.9

[a]Reactions were carried out in DCM (1.0 mL) with 1.1 equiv of (-)-**3a** (0.275 mmol) and 1.1 equiv of **20** (0.275 mmol) relative to **19g** (0.25 mmol) in the presence of 10 mol % of (*S*)-**21a**, and yield refers to the column-purified product. [b]Enantiomeric excess (*ee*) was determined by chiral HPLC analysis after converting (-)-**32ga** into its dimethyl malonate derivative, and diastereomeric ratio (*dr*) was determined by ^{1}H NMR analysis of crude reaction mixture. [c]A 10 mol % of benzylamine (**21b**) was used as a catalyst.

We proceeded with our further optimization by reducing the catalyst loading to 5 mol%, which resulted in an 88% yield of (-)-**32ga** in 60 minutes of reaction time (Table 9, entry 2). Though there is no discernible effect of the catalyst loading on the reaction yield, it does have a visible effect on the reaction times, which are inversely proportional to the catalyst loadings. Further, we tried to change the equivalents of (-)-**3a** (1.0 equiv.) and **19g** (1.1 equiv.), which resulted in an 88% yield of (-)-**32ga** in 30 minutes of reaction time (Table 9, entry 3).

At the same time, TCRA reaction of (-)-**3a** (0.22 mmol), **19g** (0.2 mmol), and **20** (0.22 mmol) in DCM at 25 °C under the 10 mol% of benzylamine-catalysis for 30 minutes furnished the (-)-**32ga** in 92% yield (Table 9, entry 4) and this result was inferior to (*S*)-**21a** catalysis. Next, we tried TCRA reaction with different solvents such as $CHCl_3$, DCE, EtOH, CH_3CN, and DMSO and in all the cases it furnished lesser yield compared to DCM solvent, which was 93%, 91%, 91%, 87%, and 87%, respectively (Table 9, entry 5-9). Thus, the optimization process ended, inferring entry 1 of Table 9 to be the best-optimized condition. ^{1}H and ^{13}C spectra of compound (-)-**32ga** are shown in Figure 27.

4.2.3 Scope of TCRA Reaction:

With optimized conditions in hand, we continued our studies of three-component reductive alkylation on the chiral dicarbonyl-cyclopropanes (-)-**3** to prove the strength and generality of the coupling reaction. The 1,3-dimethylbarbituric acid **19g** reacted with various dicarbonyl-cyclopropanes (-)-**3b-3i** under the (*S*)-proline **21a** catalysis in the presence of **20** to afford the corresponding reductive alkylation products (-)-**32gb-32gi** with excellent yields (Scheme 19). These coupling reactions were completed within the range of 30 to 60 min.

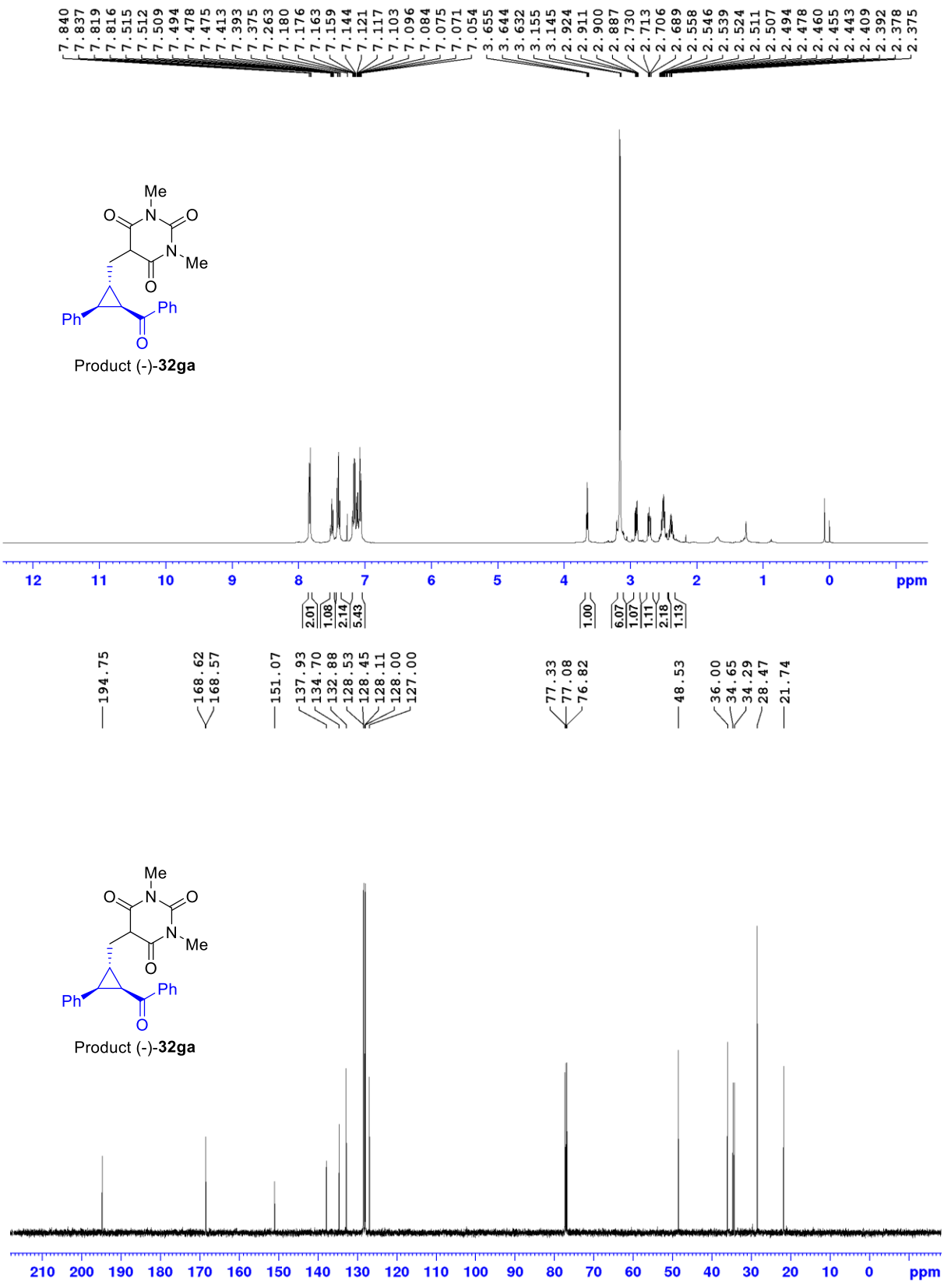
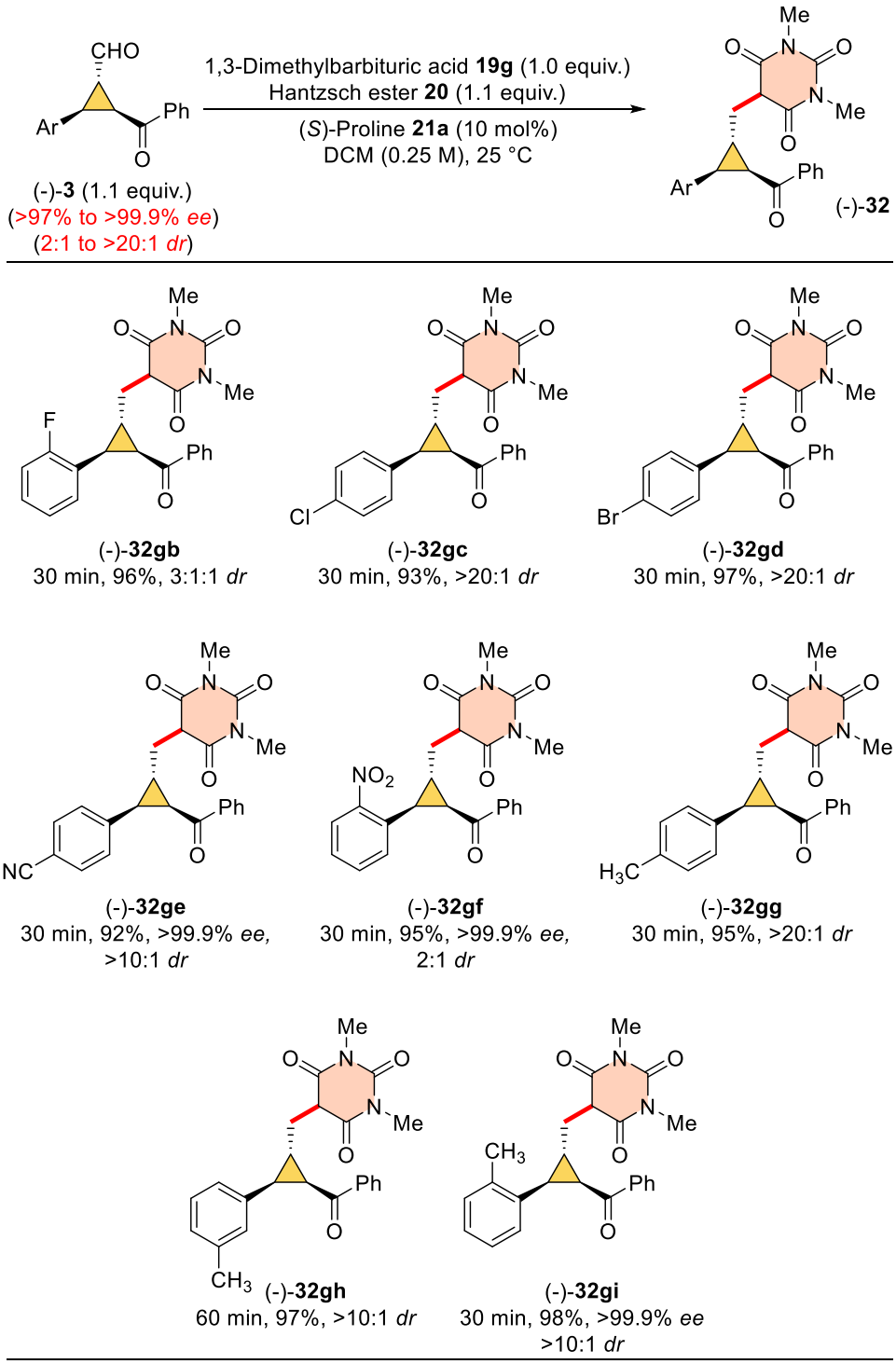


Figure 27. ^{1}H and ^{13}C spectra of the product (-)-**32ga.**

Scheme 19. Reductive Coupling Reaction Scope with Respect to Various Dicarbonyl-Cyclopropanes (-)-**3**[a,b]



[a]Reactions were carried out in DCM (1.0 mL) with 1.1 equiv of (-)-**3** (0.275 mmol) and 1.1 equiv of **20** (0.275 mmol) relative to **19g** (0.25 mmol) in the presence of 10 mol % of (*S*)-**21a**, and yield refers to the column-purified product. [b]Enantiomeric excess (*ee*) was determined by chiral HPLC analysis after converting (-)-**32** into its dimethyl malonate derivative, and diastereomeric ratio (*dr*) was determined by ^{1}H NMR analysis of crude reaction mixture.

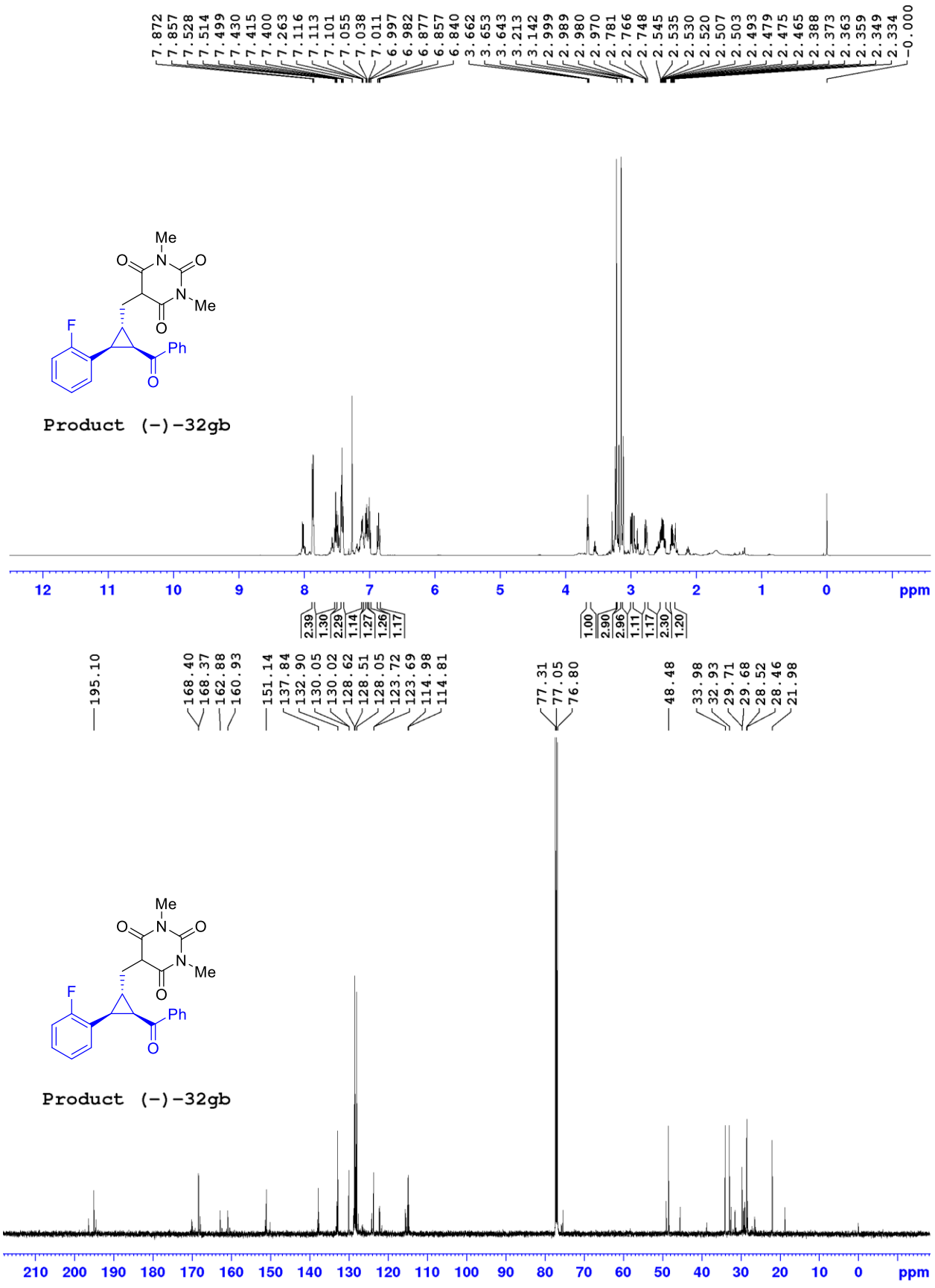


Figure 28. ^{1}H and ^{13}C spectra of the product (-)-**32gb**.

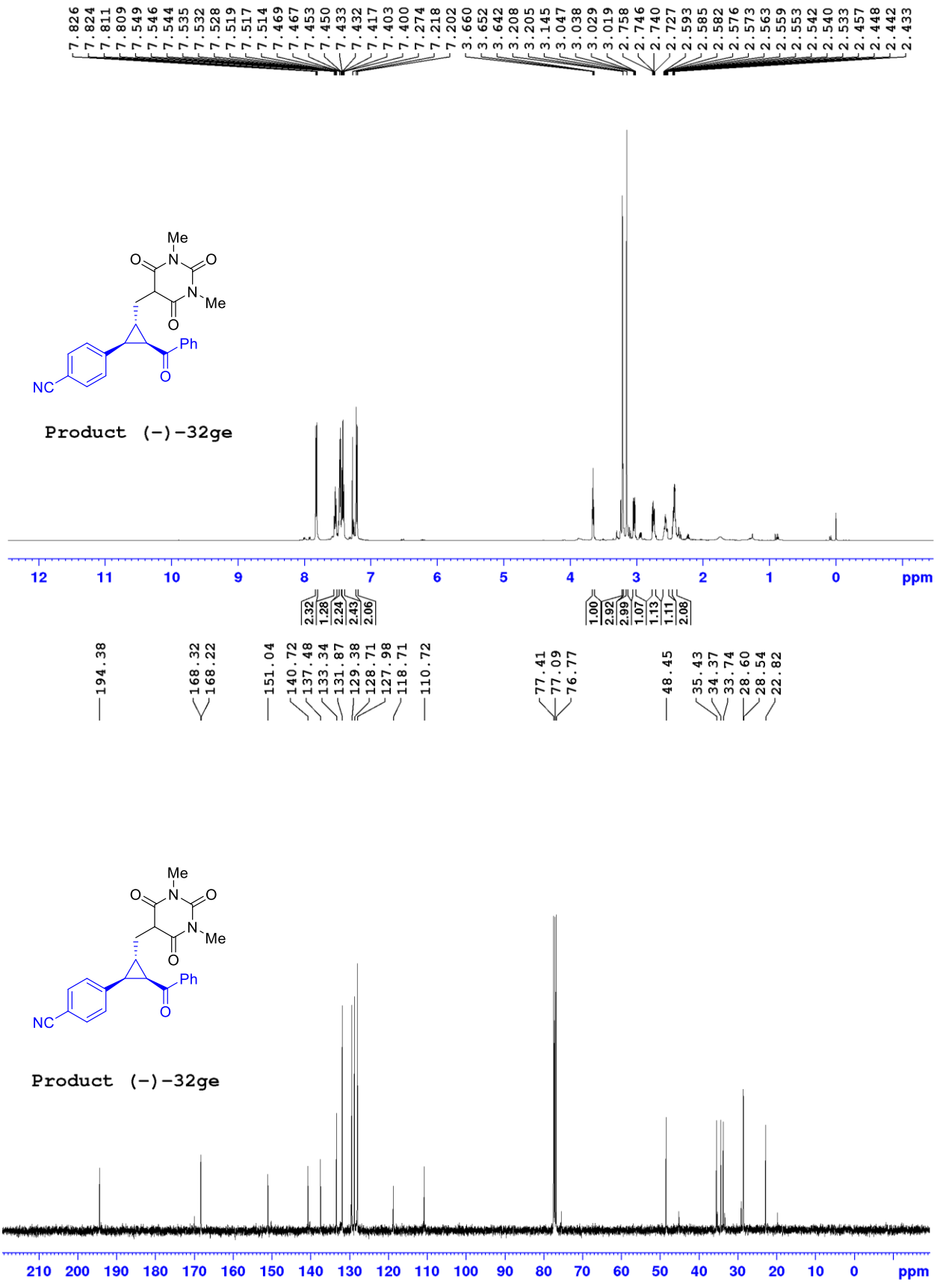
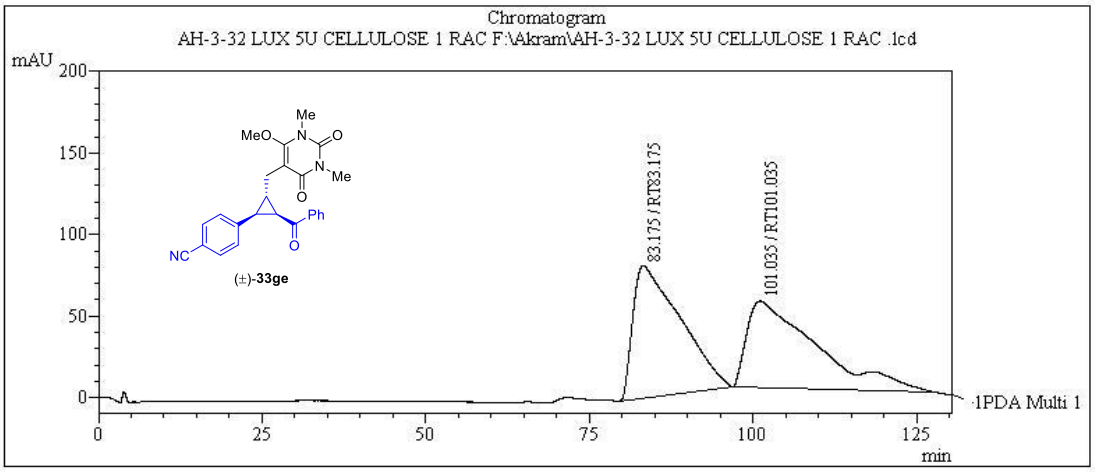


Figure 29. ^{1}H and ^{13}C spectra of the product (-)-**32ge**

Racemic **(±)-33ge**:



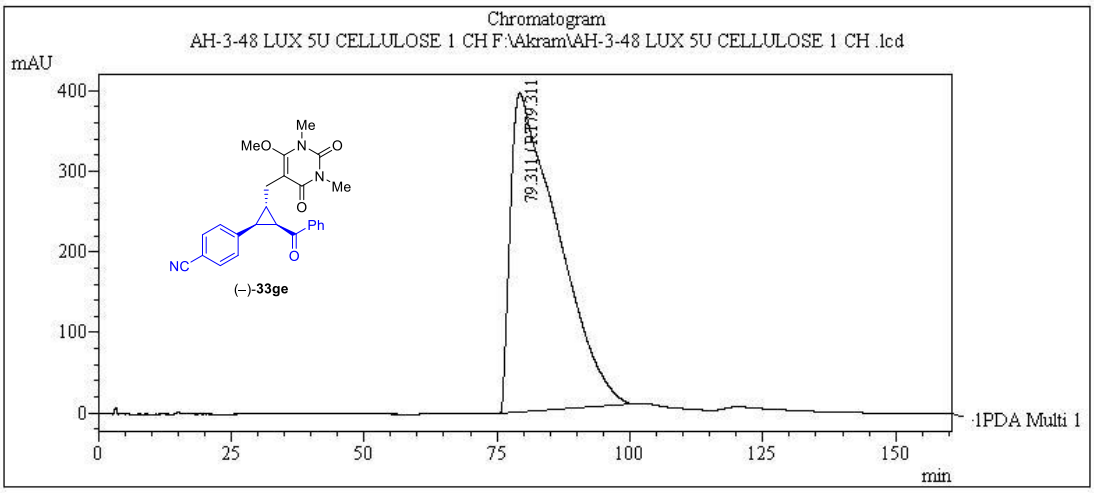
Lux 5u Cellulose-1, Hexane/*i*-PrOH = 95:5, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT83.175	83.175	40584977	81038	50.993	60.441
2	RT101.035	101.035	39004278	53040	49.007	39.559
Total			79589256	134078	100.000	100.000

Chiral **(–)-33ge** (>99.9% *ee*):



Lux 5u Cellulose-1, Hexane/*i*-PrOH = 95:5, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT79.311	79.311	245842717	395837	100.000	100.000
Total			245842717	395837	100.000	100.000

Figure 30. HPLC spectra of the methylated product (-)-**33ge** of (-)-**32ge**.

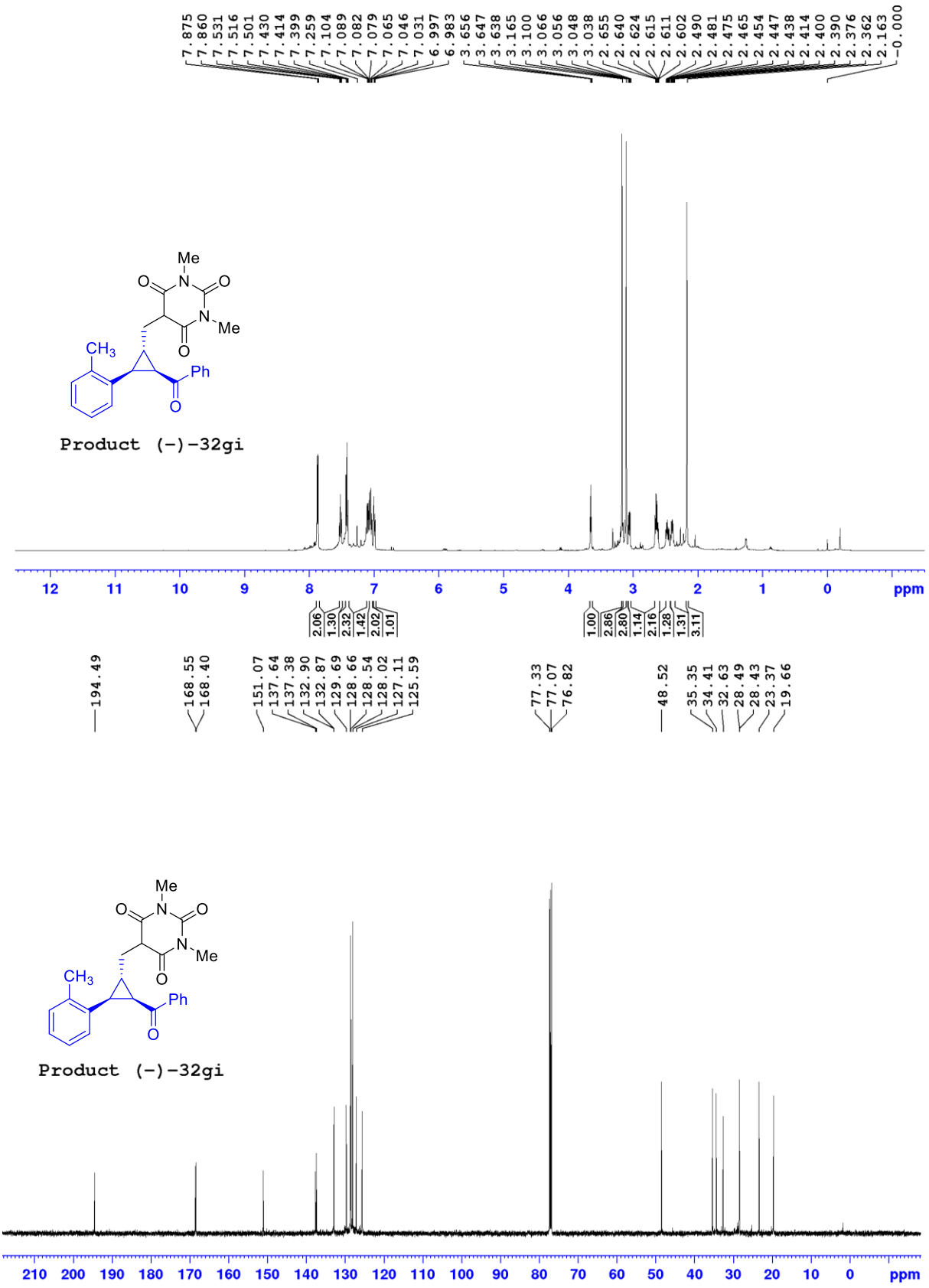
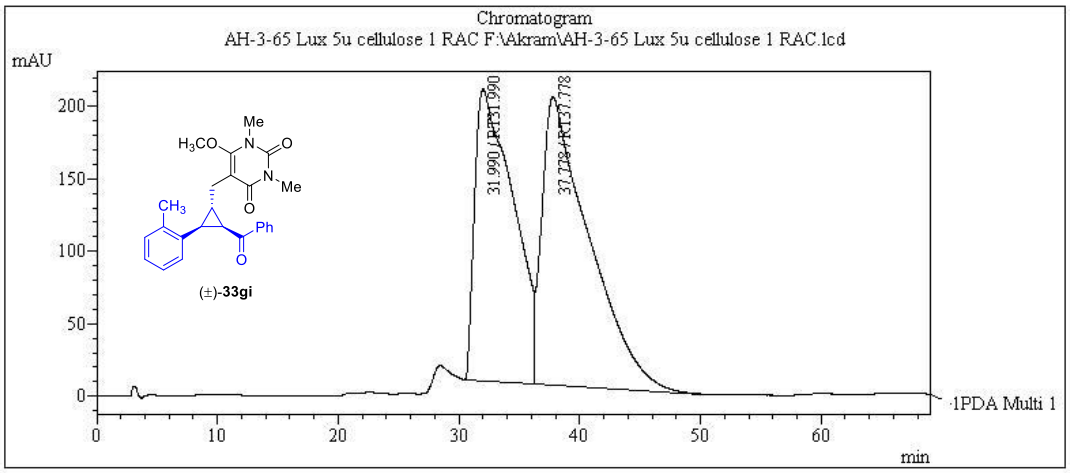


Figure 31. ^{1}H and ^{13}C spectra of the product (-)-**32gi**.

Racemic **(±)-33gi**:



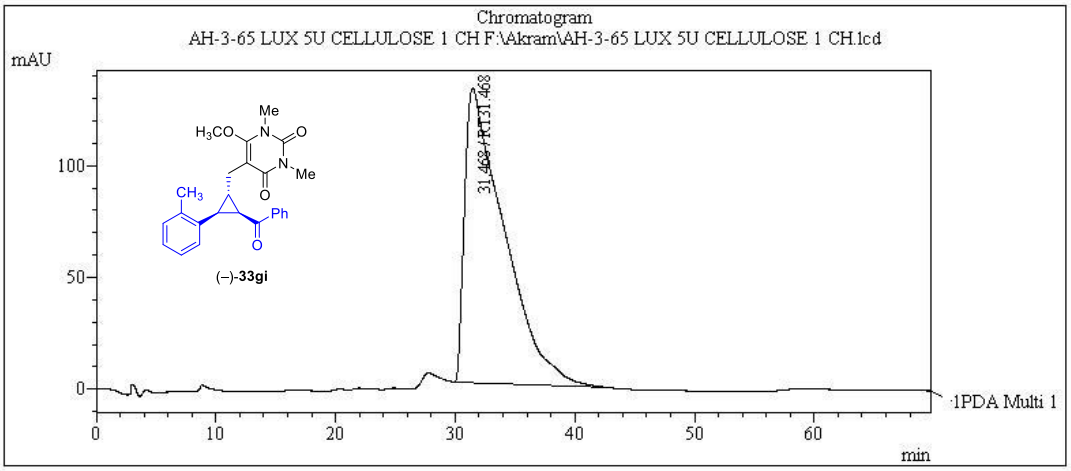
Lux 5u Cellulose-1, Hexane/*i*-PrOH = 95:5, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT31.990	31.990	44644020	201480	45.245	50.282
2	RT37.778	37.778	54027296	199222	54.755	49.718
Total			98671317	400702	100.000	100.000

Chiral **(–)-33gi** (>99.9% *ee*):



Lux 5u Cellulose-1, Hexane/*i*-PrOH = 95:5, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT31.468	31.468	30197738	131624	100.000	100.000
Total			30197738	131624	100.000	100.000

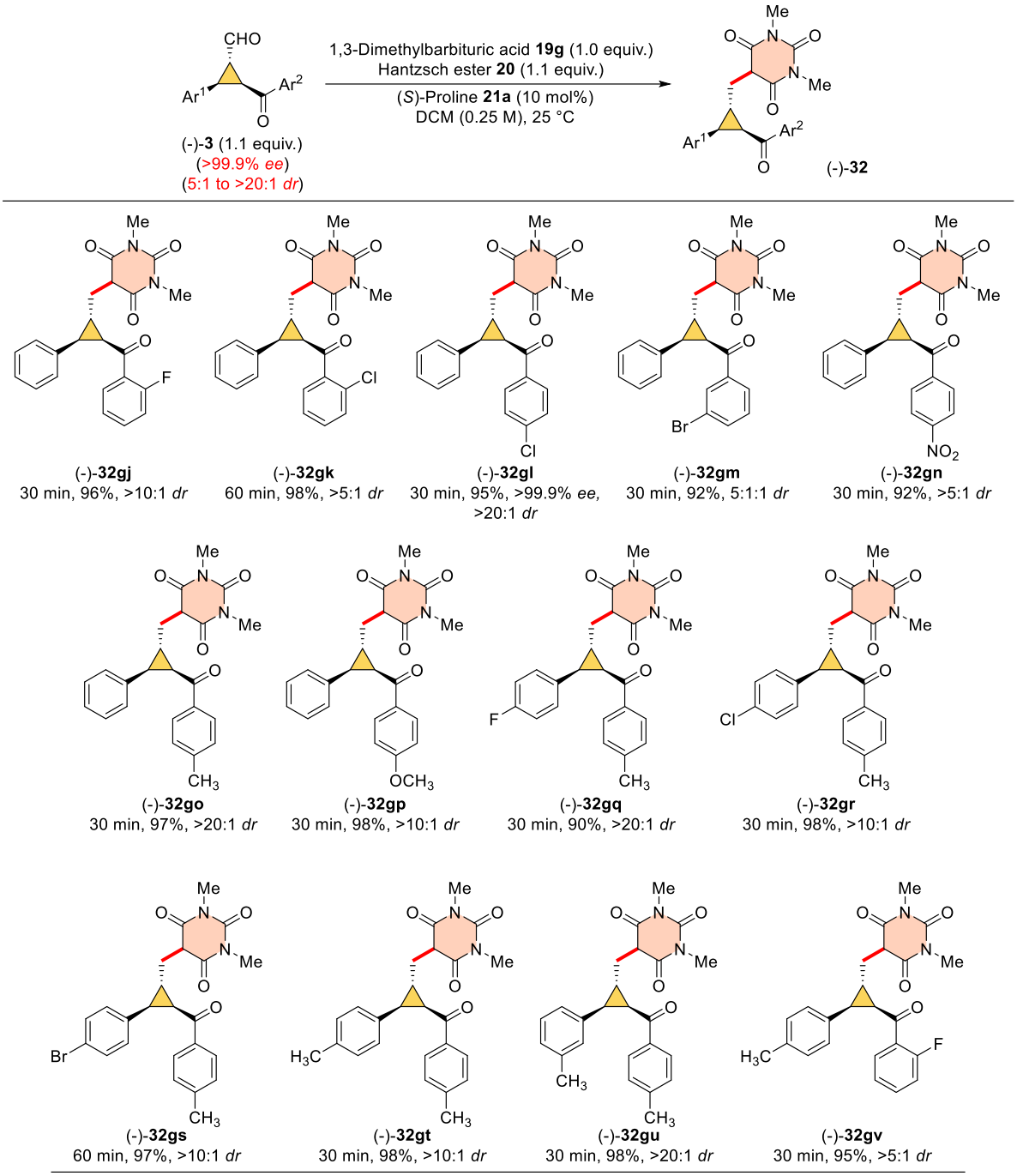
Figure 32. HPLC spectra of the methylated product (-)-**33gi** of (-)-**32gi**.

We have studied various chiral dicarbonyl-cyclopropanes (-)-**3b** to (-)-**3i** and 1,3-dimethylbarbituricacid **19g** under the optimized conditions to highlight the generality of the organocatalytic reductive coupling reaction (Scheme 19). The dicarbonyl-cyclopropanes containing different aryl groups (-)-**3** (>97% to >99.9% *ee*, 2:1 to >20:1 *dr*) reacted with 1,3-dimethylbarbituricacid **19g** and **20** under (*S*)-**21a**-catalysis to provide the corresponding reductive coupling products (-)-**32** in excellent yields with high enantioselectivity (>99.9% *ee*) and diastereo selectivity in the range of 2:1 to >20:1 *dr* at 25 °C in just 30-60 min (Scheme 19). In this coupling reaction, the diastereoselectivity of products was obtained from the starting material dicarbonyl-cyclopropanes (-)-**3**, and hence less diastereoselectivity of products (-)-**32gb** (3:1:1 *dr*) and (-)-**32gf** (2:1 *dr*) were obtained from starting material dicarbonyl-cyclopropanes (-)-**3b** (3:1:1 *dr*) and (-)-**3f** (2:1 *dr*), respectively. As expected, there is no effect of aryl group substitution (F, Cl, Br, CN, NO_2, and Me) on the outcome of the reductive coupling reaction rate and selectivity (Scheme 19). ^{1}H and ^{13}C spectra of compounds (-)-**32gb**, (-)-**32ge**, (-)-**32gi** and HPLC spectra of compounds (-)-**33ge,** (-)-**33gi** are shown in Figures 28-32.

After successfully investigating the organocatalytic reductive alkylation of different dicarbonyl-cyclopropanes (-)-**3b-3i** with 1,3-dimethyl barbituric acid **19g**, we have envisioned synthesizing a library of reductive coupling products (-)-**26** from the corresponding highly substituted chiral dicarbonyl-cyclopropanes (-)-**3j-3v** and 1,3-dimethyl barbituric acid **19g** (Table 10) as there are a numerous synthetic applications starting from the of reductive coupling products (-)-**32**. The reported reductive coupling products (-)-**32** were obtained in excellent yields with high enantio-selectivity (>99.9% *ee*) and diastereoselectivity in the range of 5:1:1 to >20:1 *dr* through a coupling reaction of simple 1,3-dimethylbarbituric acid **19g** with a variety of chiral dicarbonyl-cyclopropanes (-)-**3j-3v** containing halogen atoms, electron-withdrawing, electron-donating, neutral, and both side substituted aryl groups (Table 10). Here, also the diastereoselectivity of the reductive coupling products was obtained from the starting material dicarbonyl-cyclopropanes **3**, and hence less diastereoselectivity of products (-)-**32gk** (>5:1 *dr*), (-)-**32gm** (5:1:1 *dr*), (-)-**32gn** (>5:1 *dr*) and (-)-**32gv** (>5:1 *dr*) were obtained from the starting material dicarbonyl-cyclopropanes (-)-**3k**, (-)-**3m**, (-)-**3n**, (-)-**3v**, respectively. As expected, there is no effect of aryl group substitution containing

halogen atoms, electron-withdrawing, electron-donating, neutral, and di-substituted aryl groups on the outcome of the reductive coupling reaction rate and selectivity (Table 10).

Table 10. Reductive Coupling Reaction Scope with Respect to Various Dicarbonyl-Cyclopropanes (-)-**3**[a,b]



[a]Reactions were carried out in DCM (1.0 mL) with 1.1 equiv of (-)-**3** (0.275 mmol) and 1.1 equiv of **20** (0.275 mmol) relative to **19g** (0.25 mmol) in the presence of 10 mol % of (*S*)-**21a**, and yield refers to the column-purified product. [b]Enantiomeric excess (*ee*) was determined by chiral HPLC analysis after converting (-)-**32** into its dimethyl malonate derivative, and diastereomeric ratio (*dr*) was determined by ^{1}H NMR analysis of crude reaction mixture.

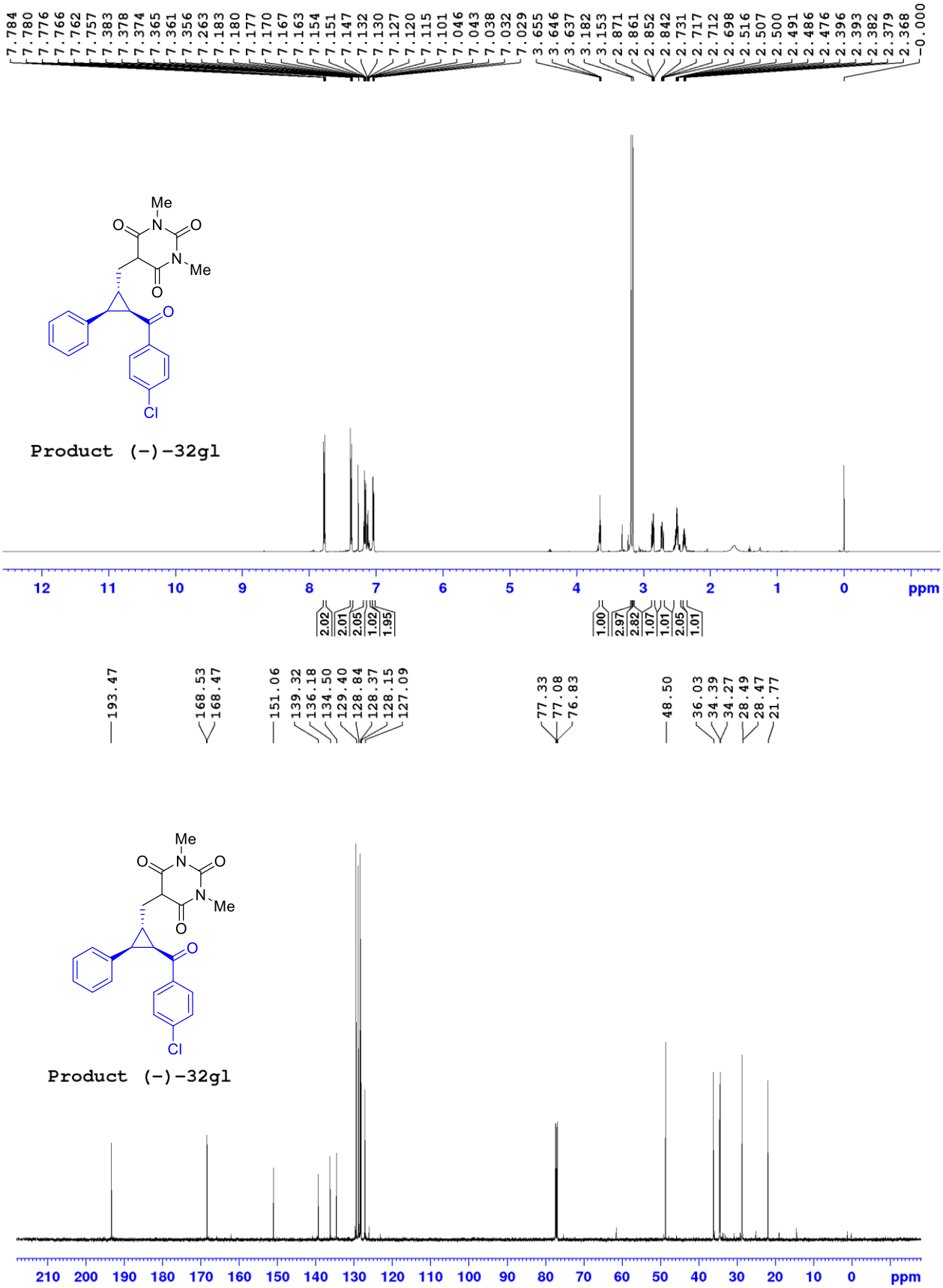
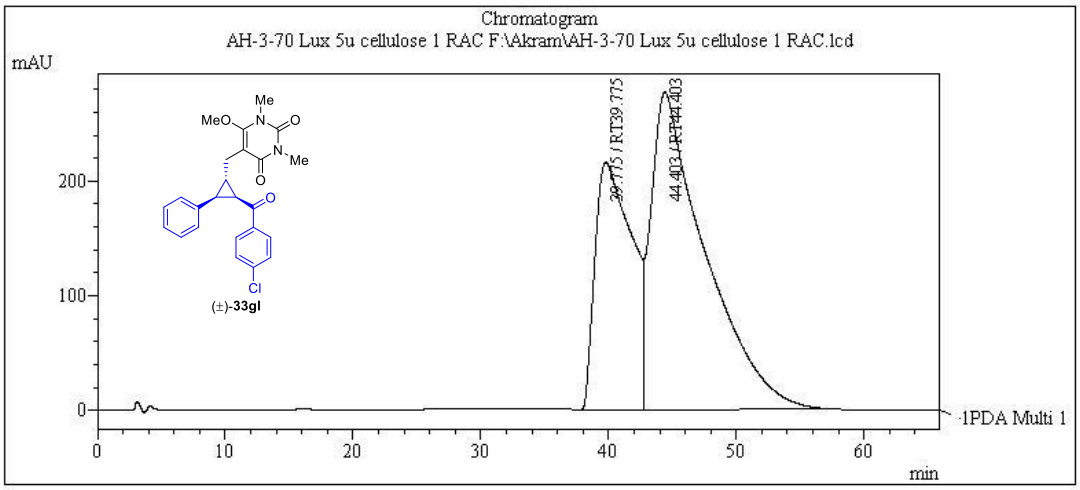


Figure 33. ^{1}H and ^{13}C spectra of the product (-)-**32gl**.

Racemic **(±)-33gl**:



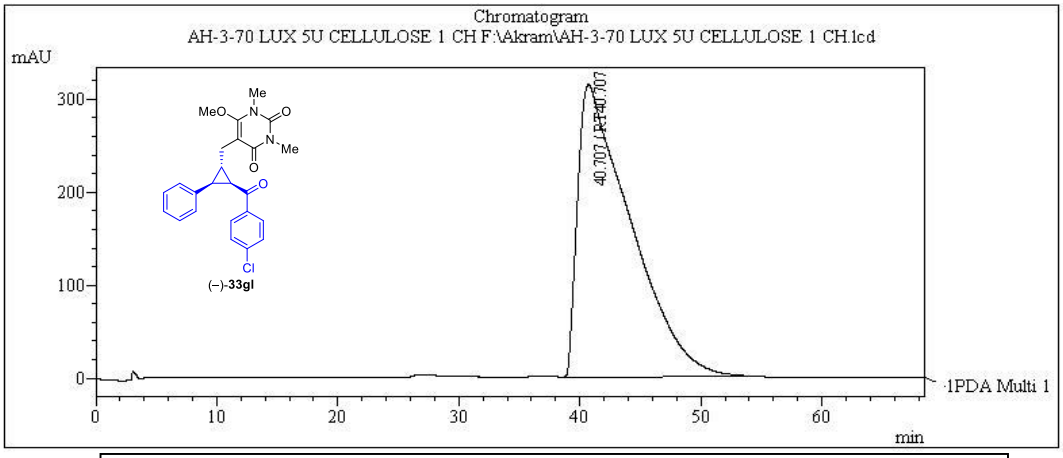
Lux 5u Cellulose-1, Hexane/*i*-PrOH = 95:5, Flow Rate 1.0 mL/min, 254 nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT39.775	39.775	42815060	215418	34.312	43.771
2	RT44.403	44.403	81966453	276733	65.688	56.229
Total			124781512	492151	100.000	100.000

Chiral **(–)-33gl** (>99.9% *ee*):



Lux 5u Cellulose-1, Hexane/*i*-PrOH = 95:5, Flow Rate 1.0 mL/min, 254 nm

PeakTable

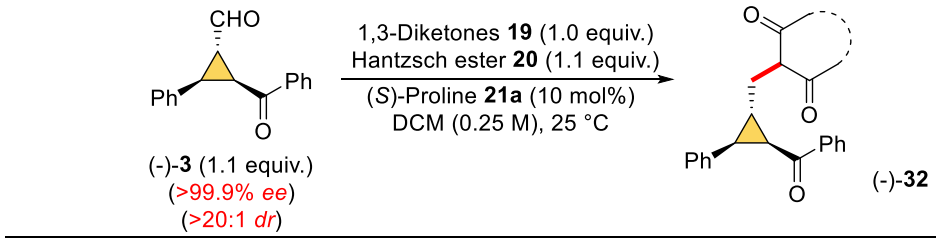
PDA Ch1 254nm 4nm

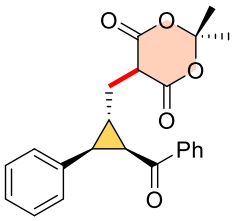
Peak#	Name	Ret. Time	Area	Height	Area %	Height %
1	RT40.707	40.707	95634221	314030	100.000	100.000
Total			95634221	314030	100.000	100.000

Figure 34. HPLC spectra of the methylated product (-)-**33gl** of (-)-**32gl**.

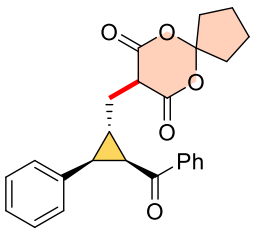
^{1}H and ^{13}C spectra of compound (-)-**32gl** and HPLC spectra of compound (-)-**33gl** are shown in Figures 33 and 34.

Scheme 20. Reductive Coupling Reaction Scope with Respect to Various CH Acids[a,b]

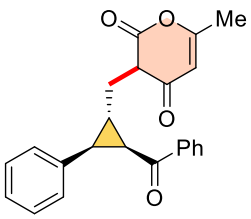




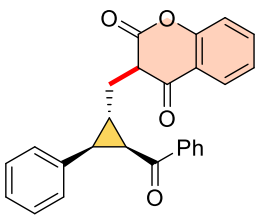
(-)-**32aa**
30 min, 76%, >50:1 *dr*



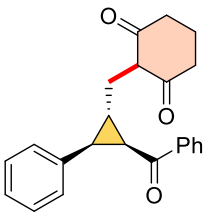
(-)-**32ba**
60 min, 98%, >50:1 *dr*



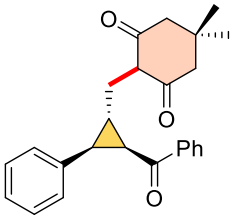
(-)-**32ca**
60 min, 95%, >30:1 *dr*



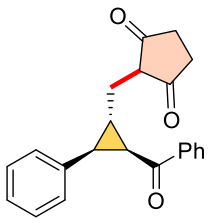
(-)-**32da**
30 min, 94%, >50:1 *dr*



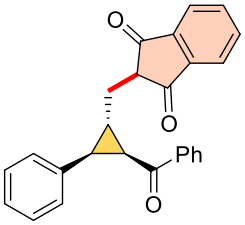
(-)-**32ha**
60 min, 87%, >50:1 *dr*



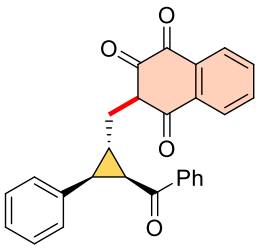
(-)-**32ia**
30 min, 88%, >50:1 *dr*



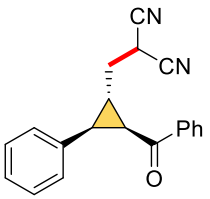
(-)-**32ja**
60 min, 90%, >50:1 *dr*



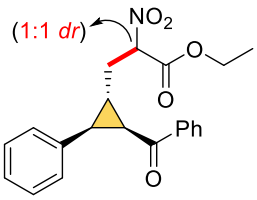
(-)-**32ka**
60 min, 96%, >50:1 *dr*



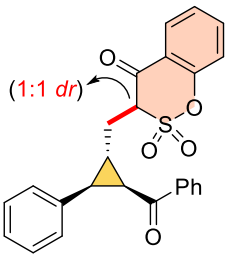
(-)-**32la**
600 min, 91%, >50:1 *dr*



(-)-**32ma**
30 min, 96%, >50:1 *dr*



(-)-**32oa**
240 min, 75%, 1:1 *dr*



(-)-**32qa**
60 min, 98%, 1:1 *dr*

[a]Reactions were carried out in DCM (1.0 mL) with 1.1 equiv of (-)-**3a** (0.275 mmol) and 1.1 equiv of **20** (0.275 mmol) relative to **19** (0.25 mmol) in the presence of 10 mol % of (*S*)-**21a**, and yield refers to the column-purified product. [b]Enantiomeric excess (*ee*) was determined by chiral HPLC analysis after converting (-)-**32** into its dimethyl malonate derivative, and diastereomeric ratio (*dr*) was determined by ^{1}H NMR analysis of crude reaction mixture.

Further, the three-component reductive coupling of (-)-**3a** with various cyclic and acyclic CH-acids **19** was investigated to furnish the corresponding reductive coupling products (-)-**32** with 75-99% yields with >50:1 *dr* at 25 °C in 30-600 min. (Scheme 20). It is delightful to mention that the chiral dicarbonyl-cyclopropane (-)-**3a** smoothly underwent the iminium-mediated Knoevenagel condensation or olefination with the library of CH-acids **19a-19d, 19h-19m, 19o, and 19q** followed by in-situ transfer hydrogenation with Hantzsch ester **20** to furnish the coupling products (-)-**32aa-32da,** (-)-**32ha-32ma,** (-)-**32oa, and** (-)-**32qa** in very good to excellent yields with high diastereoselectivity (>50:1) at 25 °C in 30-600 min without epimerization and ring-opening reactions (Scheme 20). ^{1}H and ^{13}C spectra of compounds (-)-**32aa**, (-)-**33ha**, (-)-**33ja,** and (-)-**32oa** are shown in Figures 35-38.

4.2.4 Methyl Etherification of TCRA Products (-)-32:

Some of the reductive coupling products (-)-**32** were characterized by converting them into stable methyl etherification products (-)-**33** through a simple reaction with $TMSCHN_2$ at 0 °C in MeOH/Toluene (1:1) solvent for HPLC, ^{1}H NMR, and ^{13}C NMR analysis, as shown in Scheme 21. ^{1}H and ^{13}C spectra of compound (-)-**33ga** are shown in Figure 39.

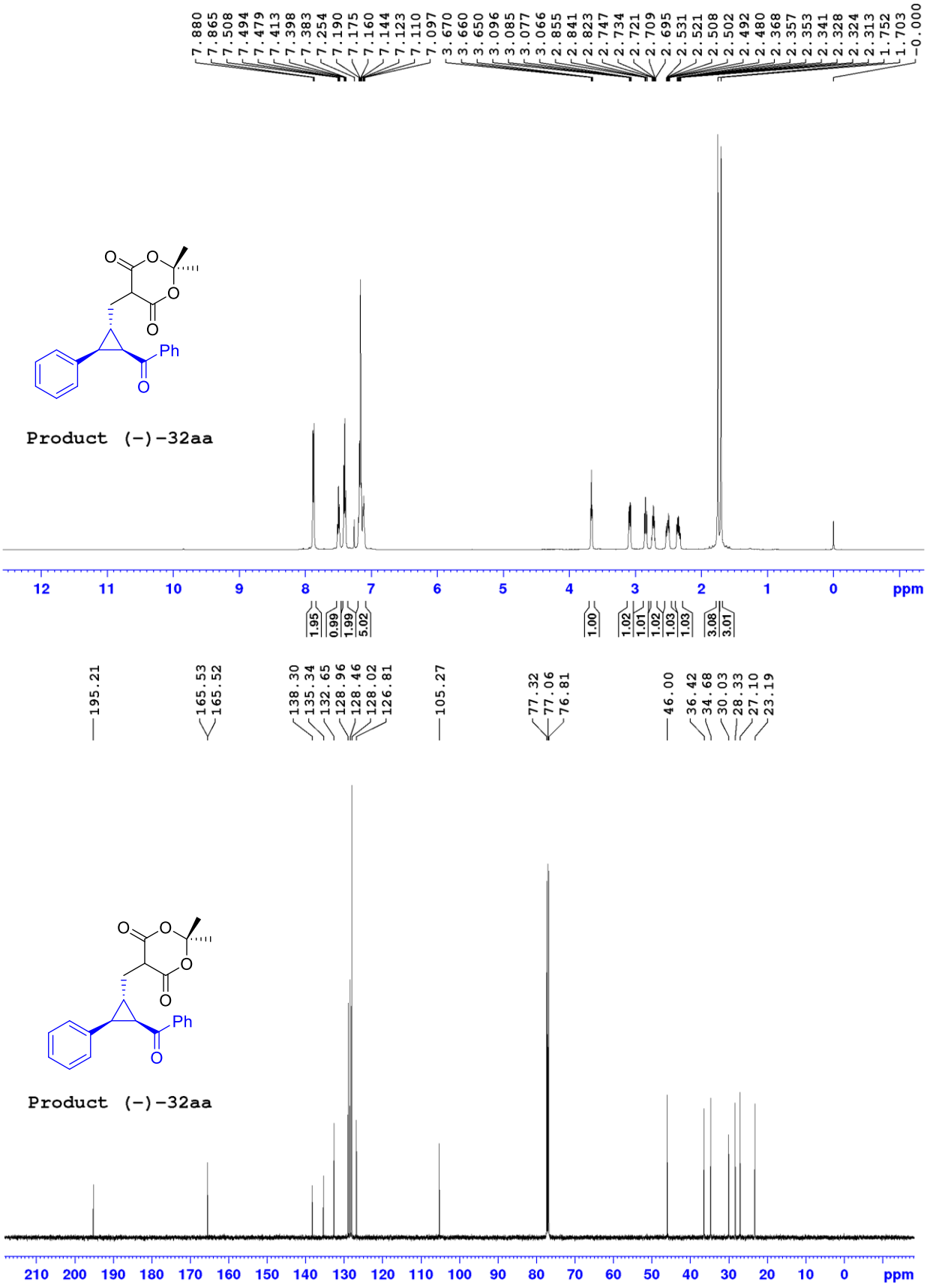


Figure 35. ^{1}H and ^{13}C spectra of the product (-)-**32aa**.

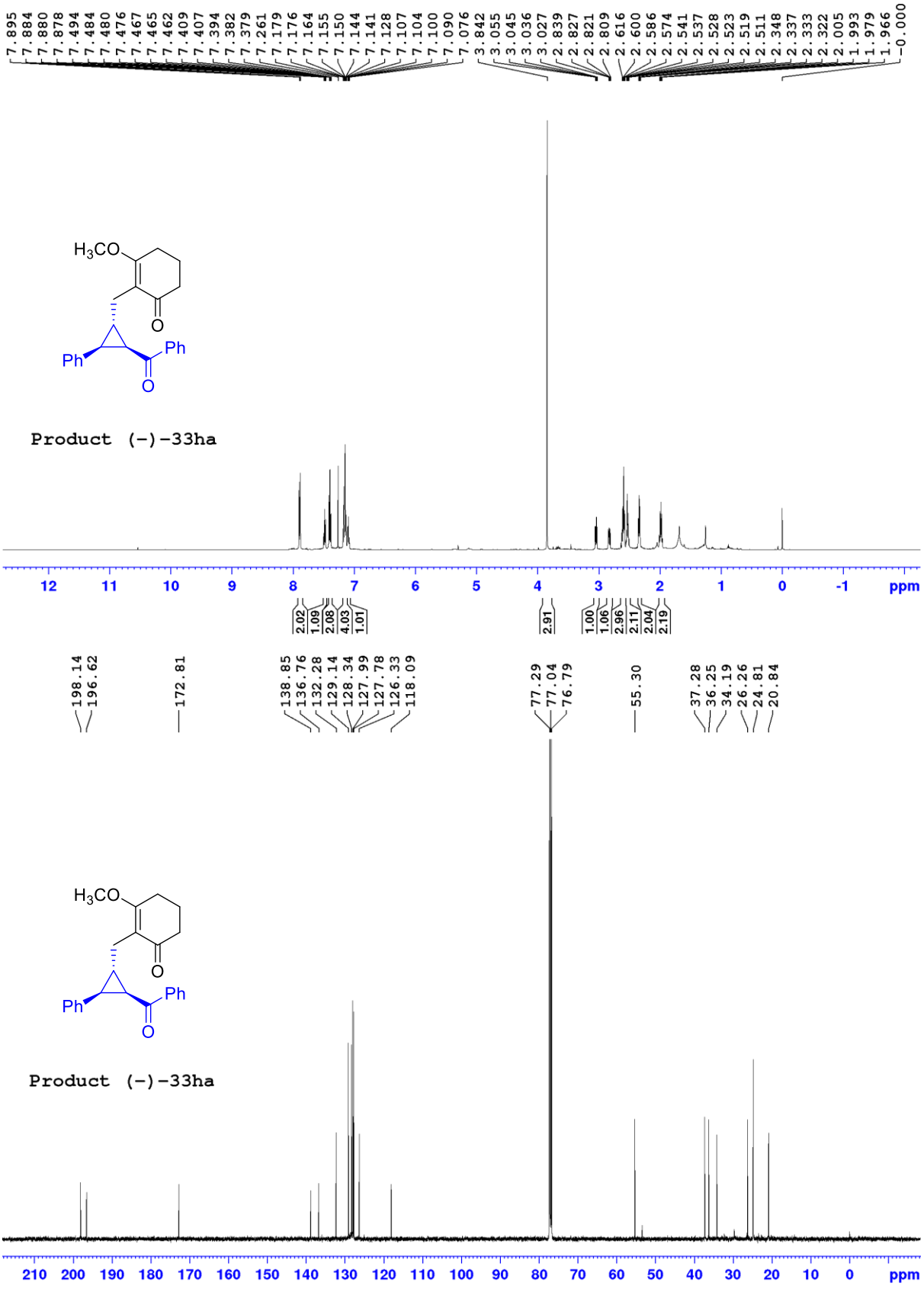


Figure 36. ^{1}H and ^{13}C spectra of the methylated product (-)-**33ha** of (-)-**32ha**.

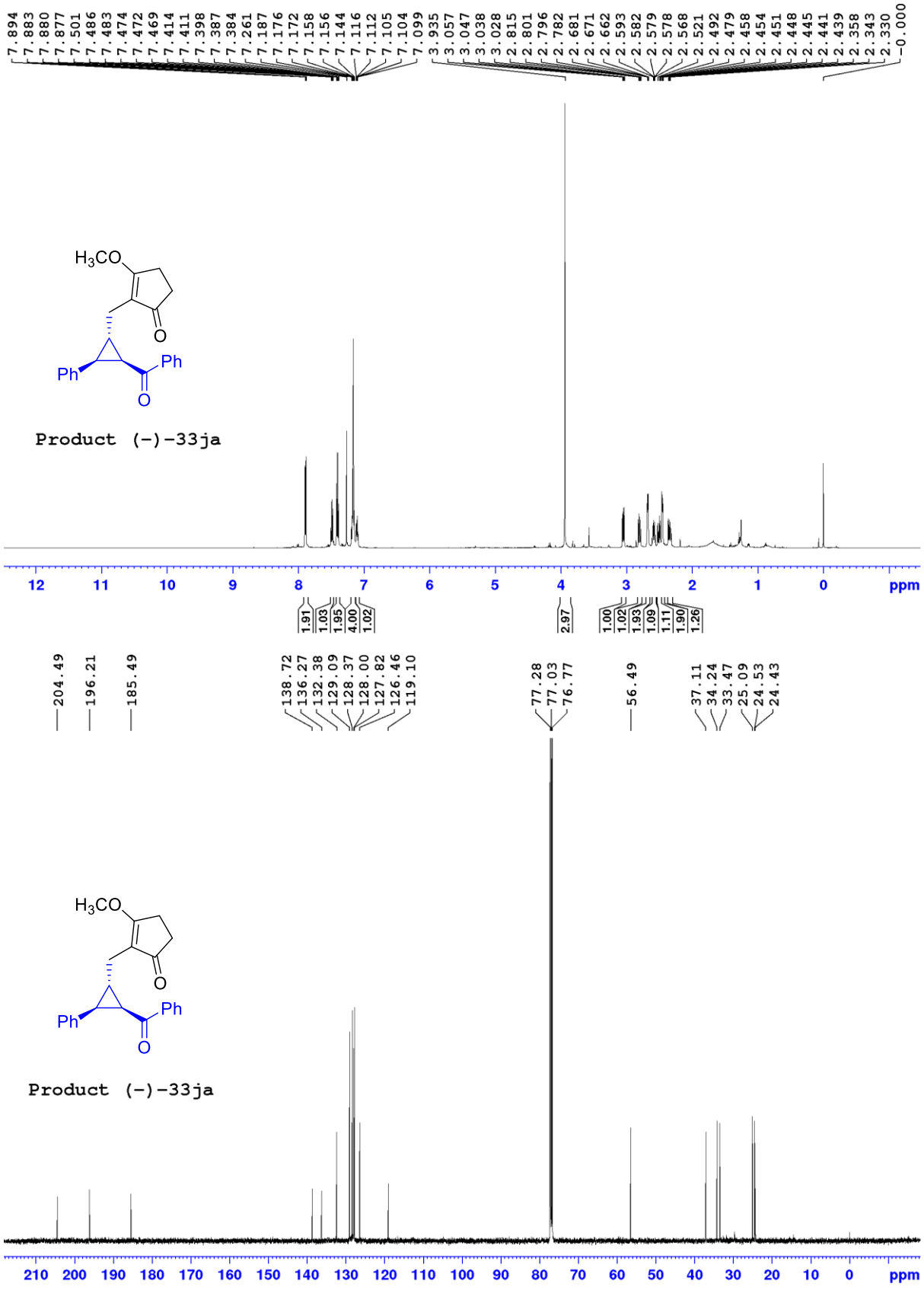


Figure 37. ^{1}H and ^{13}C spectra of the methylated product (-)-**33ja** of (-)-**32ja**.

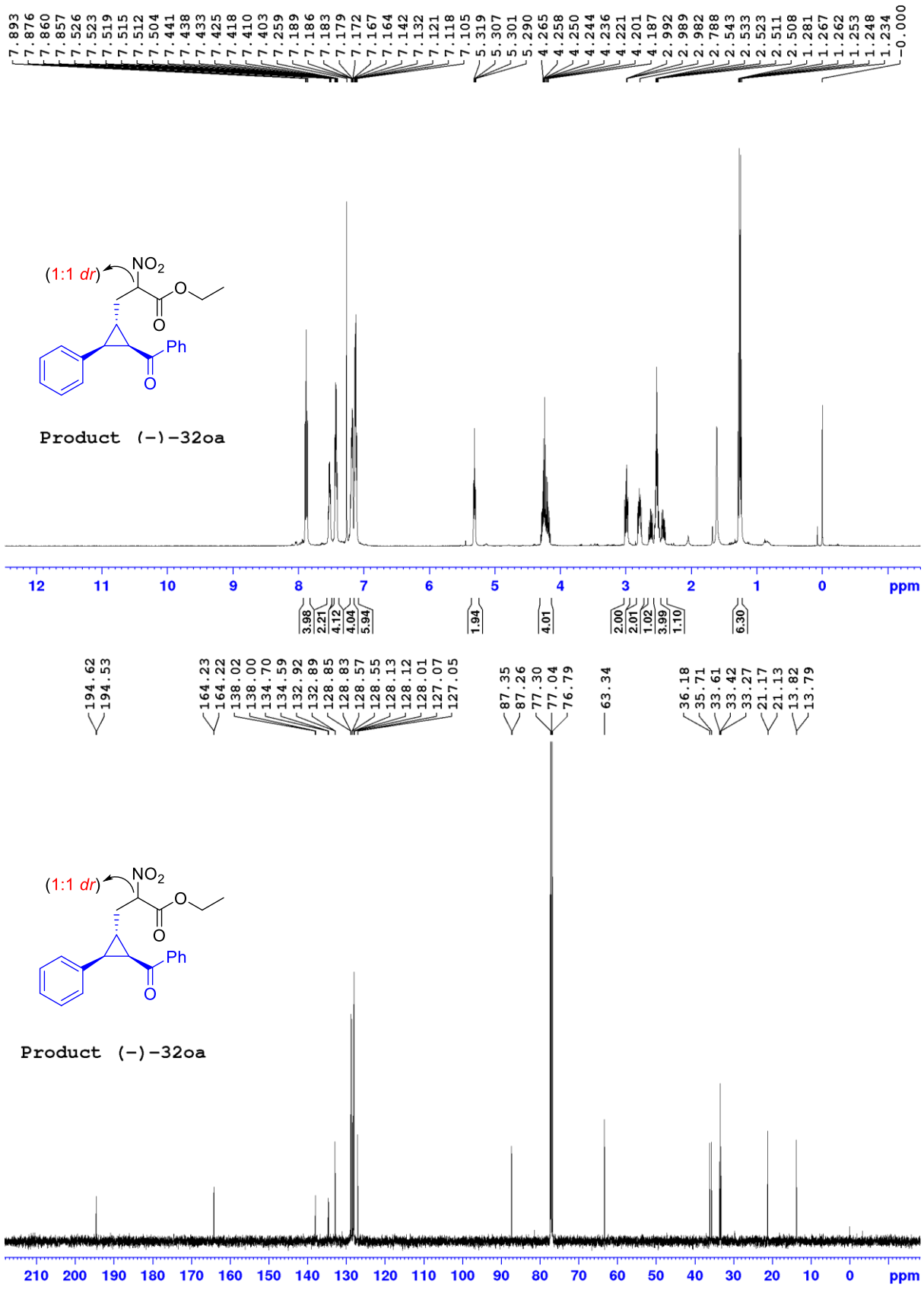
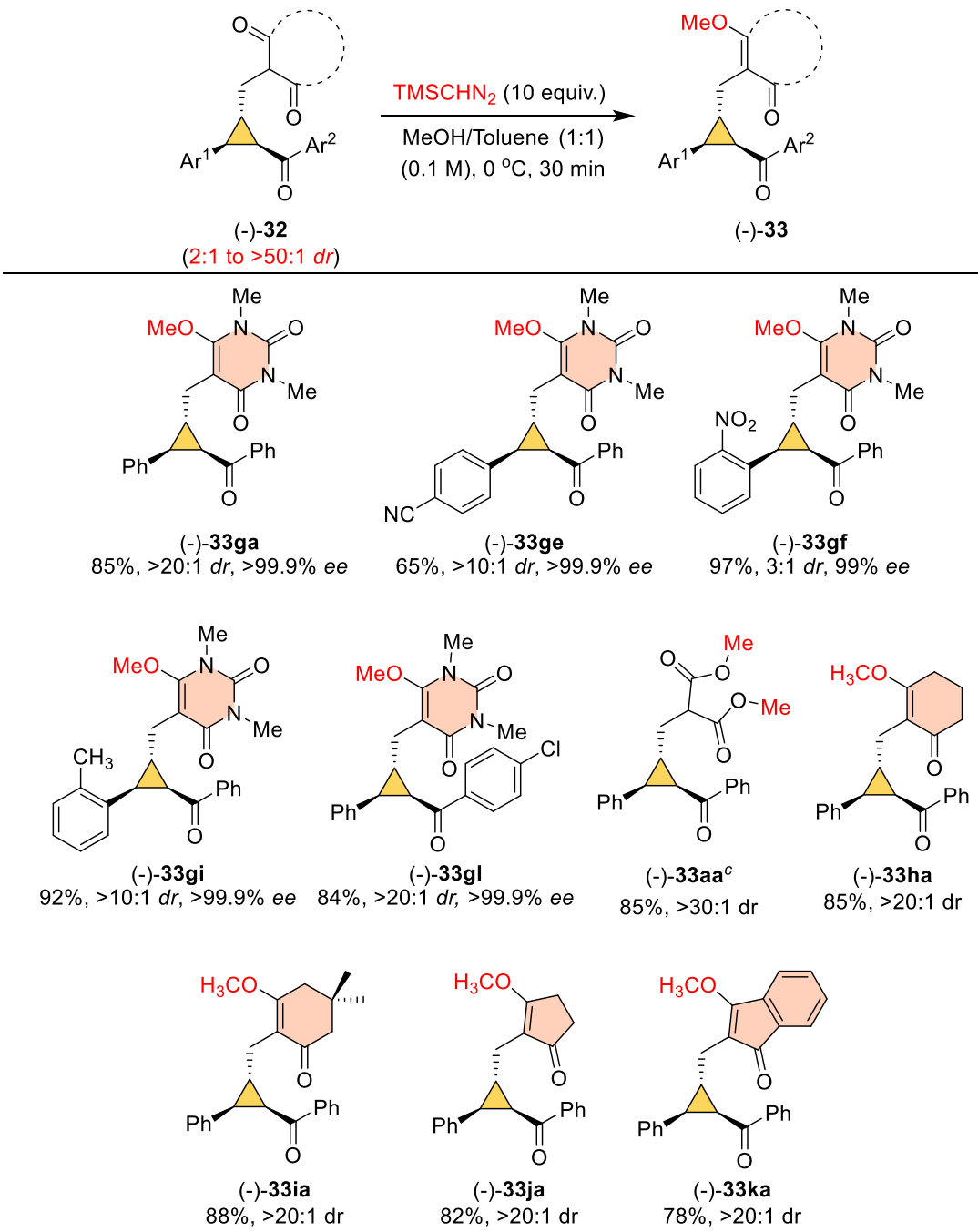


Figure 38. ^{1}H and ^{13}C spectra of the product (-)-**32oa**.

Scheme 21: Methyl Etherification of TCRA Products (-)-**32**[a,b]



[a]Reactions were carried out in MeOH/toluene (1:1, 1.0 mL) with 10 equiv. of $TMSCHN_2$ relative to the **32** (0.1 mmol) and stirred at 0 °C for 30 min. [b]Yield refers to the column-purified product. [C](-)-**33aa** is a methylated product of (-)-**32aa**.

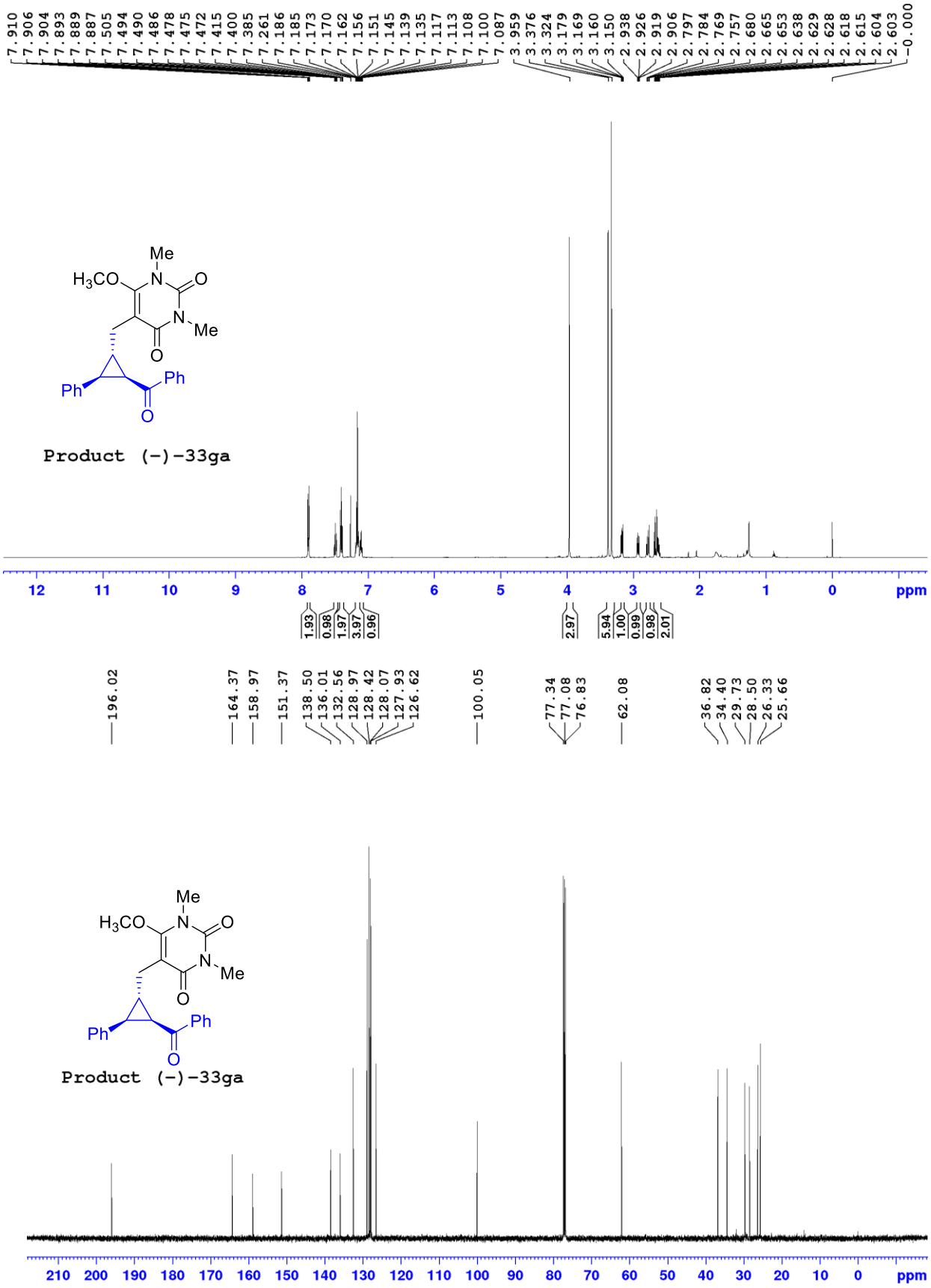
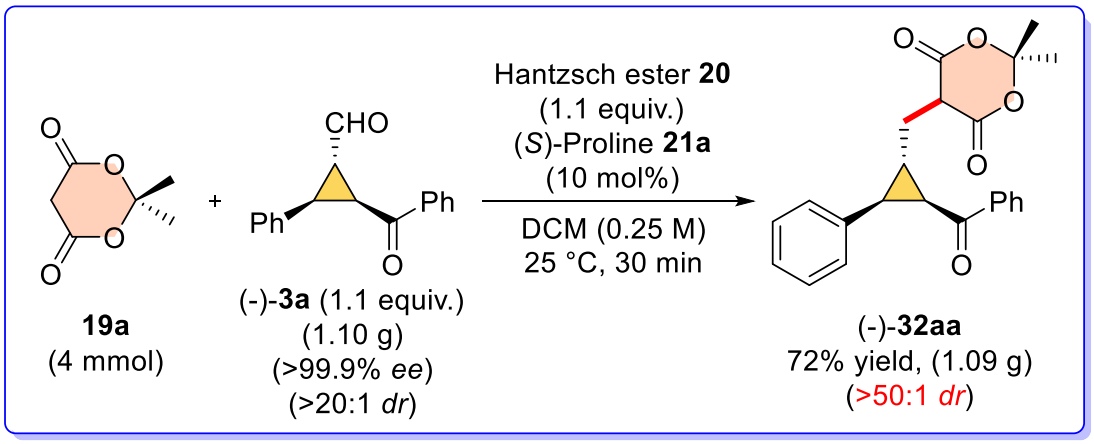


Figure 39. ^{1}H and ^{13}C spectra of the product (-)-**33ga**.

4.2.5 Gram-scale Synthesis of TCRA Products (-)-32aa:

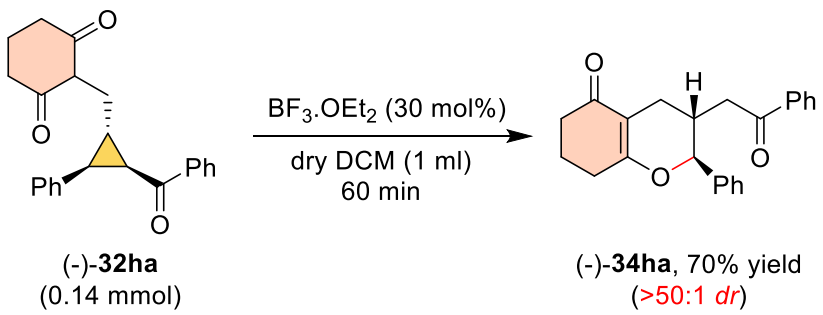
To investigate the sustainability of the reductive coupling reaction on a bulk scale, we planned a gram-scale reaction of Meldrum's acid **19a** (0.58 g, 4 mmol) with chiral dicarbonyl-cyclopropane (-)-**3a** (1.10 g, 4.4 mmol, 1.1 equiv.) and Hantzsch ester **20** (1.11 g, 4.4 mmol) under the catalysis of (*S*)-proline **21a** (46.05 mg, 10 mol%) in DCM (10.0 mL) at 25 °C for 30 min, followed by column chromatography purification furnished the coupling product (-)-**32aa** in 72% (1.09 g) yield with >30:1 *dr* (Equation 3).



(3)

4.2.6 Synthetic Applications of TCRA Products:

As discussed earlier, there are significant potential applications for reductive coupling products**,** and a few of them are shown here. Lewis acid-catalyzed annulative ring-opening reaction of (-)-**32ha** with $BF_3{\cdot}OEt_2$ (30 mol%) in DCM at 25 °C for 60 min furnished the dihydropyran product (-)-**34ha** in 70% yield with >50:1 *dr*. These functionalized dihydropyran compounds are essential biological and medicinal compounds (Equation 4). ^{1}H and ^{13}C spectra of compound (-)-**34ha** are shown in Figure 40.



(4)

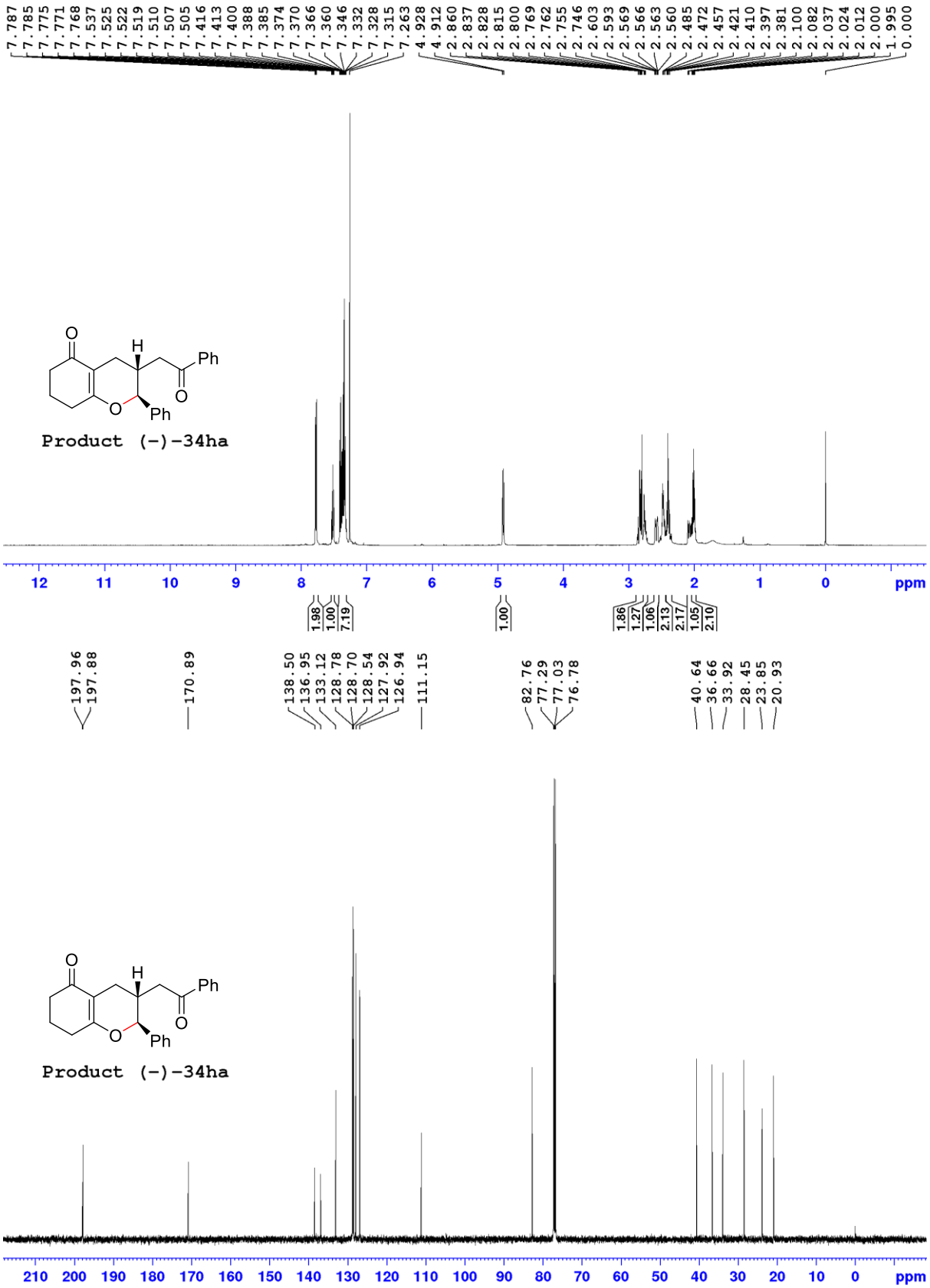
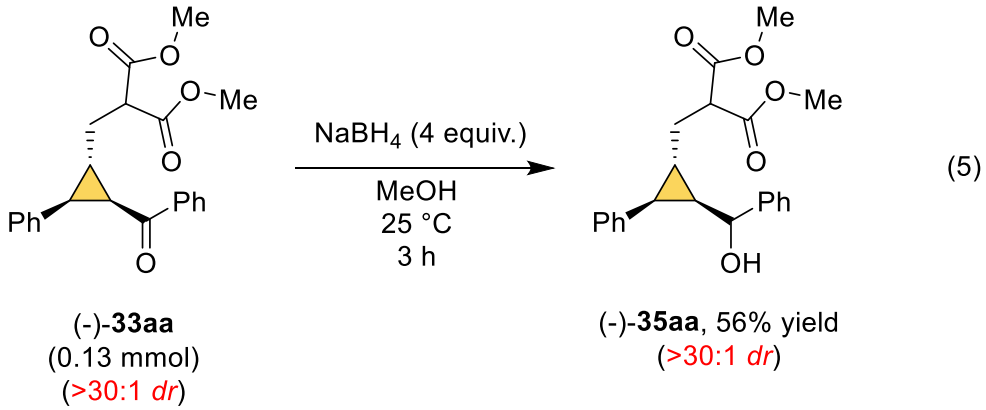


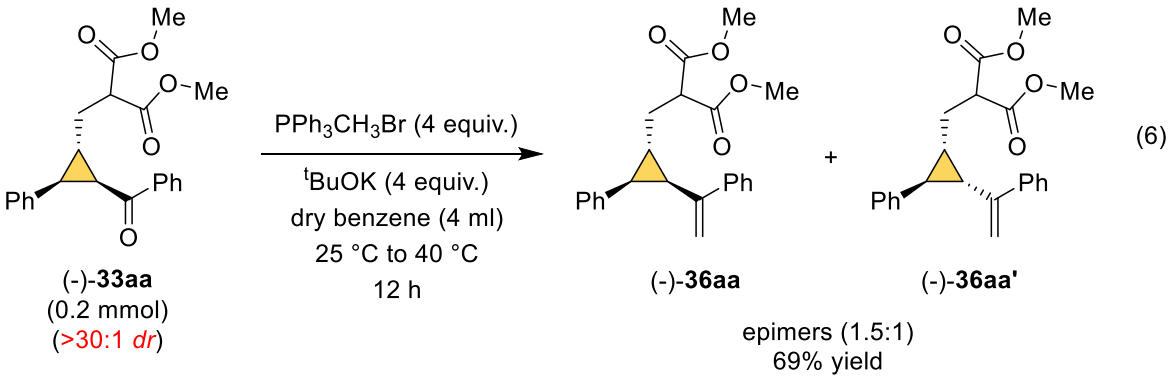
Figure 40. ^{1}H and ^{13}C spectra of the product (-)-**34ha**.

Methylation of the alkylated compound (-)-**32aa** with $TMSCHN_2$ gave product (-)-**33aa**, which is very useful for further synthetic transformation. When we treated compound (-)-**33aa** with $NaBH_4$ in MeOH for 3 h at 25 °C furnished the reduction product (-)-**35aa** in 56% yield with >30:1 *dr* (Equation 5).



(5)

We also performed a Wittig reaction on the compound (-)-**33aa**. First, we generated Wittig salt by treating PPh_3CH_3Br (4 equiv.) with ^{t}BuOK (4 equiv.) in dry benzene solvent. After generating Wittig salt, we added compound (-)-**33aa** at 25 °C; and then we increased the temperature to 40 °C for 12 h, which gave the mixture of epimers (-)-**36aa** and (-)-**36aa′** in 69% yield with a 1.5:1 ratio of epimers (Equation 6). ^{1}H and ^{13}C spectra of compounds (-)-**36aa** and (-)-**36aa′** are shown in Figure 41.



(6)

The structure and relative stereochemistry of the reductive coupling product (-)-**32aa** and its methylated product (-)-**33aa** were established by IR, NMR, and mass analysis and also finally confirmed by correlation with the X-ray crystal structures of (-)-**32aa** and (-)-**33aa** (Figure 42).

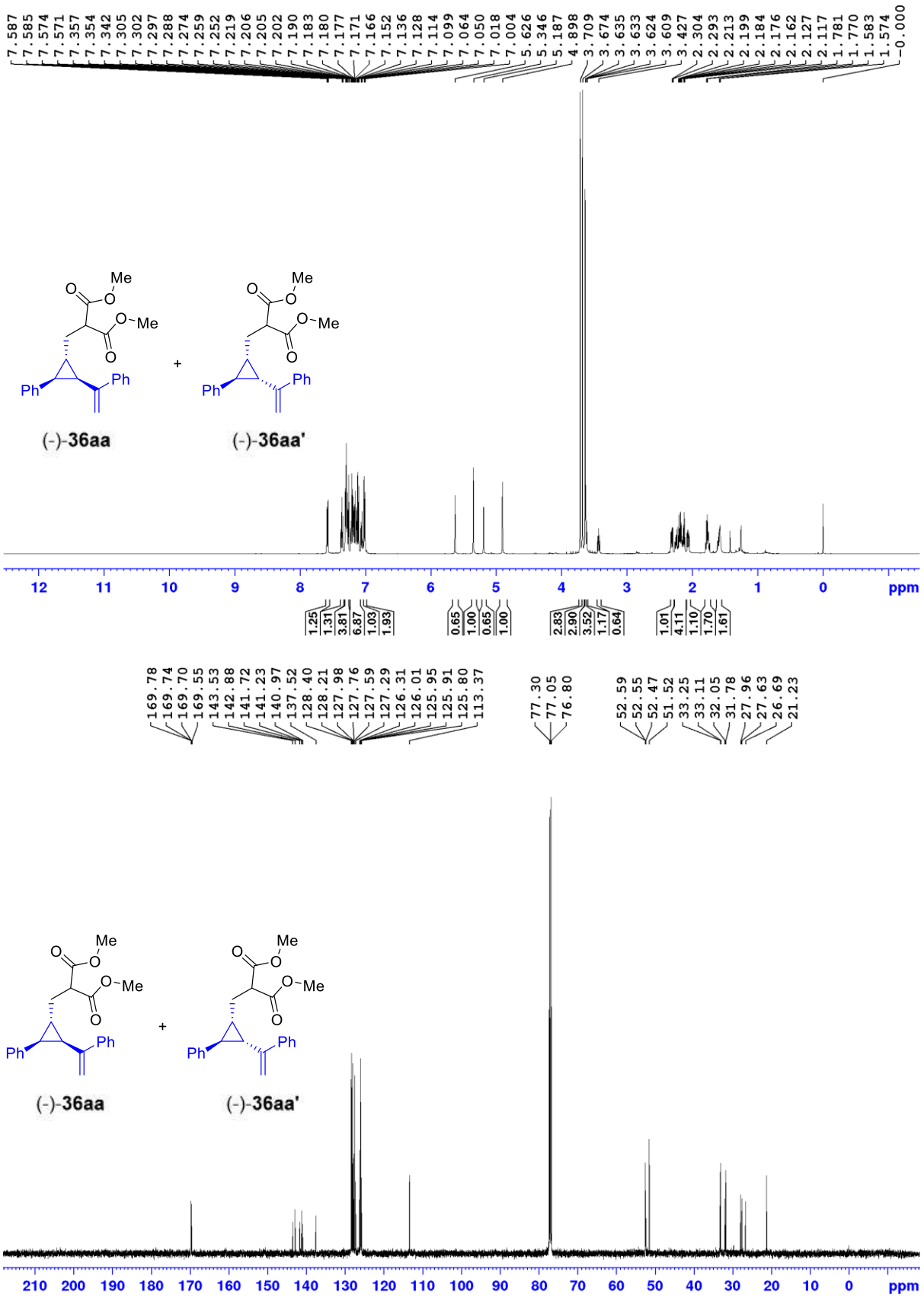


Figure 41. ^{1}H and ^{13}C spectra of the product (-)-**36aa**.

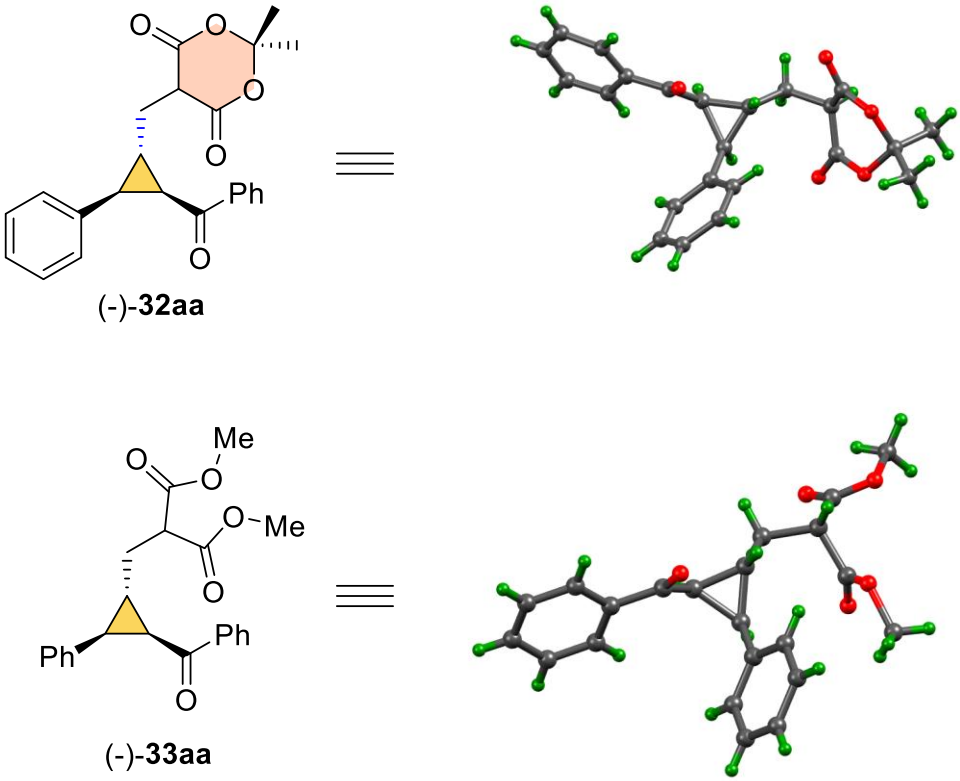


Figure 42. X-ray crystal structures of compounds (-)-**32aa** and (-)-**33aa**.

4.3 Conclusions

In summary, we have effectively established an 'organocatalytic three-component reductive alkylation' for the selective coupling of dicarbonyl-cyclopropane with CH-acids or active methylene compounds under 10 mol% of (*S*)-proline in the presence of Hantzsch ester as a hydrogen source. The metal-free reductive coupling method has wide substrate tolerance in generating mono-alkylated cyclic and acyclic products and has various applications in the total synthesis of natural products, drugs, and designed materials. We have also shown the application of reductive coupling products (-)-**32** into methylation products (-)-**33**, functionally rich dihydropyran compound (-)-**34**, reduction product (-)-**35**, and Wittig product (-)-**36**, which serve as excellent building blocks for many natural products and pharmaceuticals. Further, more applications toward this 'organocatalytic activation of dicarbonyl-cyclopropane' is currently underway.

5. Organocatalytic Reductive Amination of the Chiral Formylcyclopropanes: Scope and Applications

5.1 Introduction

One of the primary purposes of modern science is to improve the quality of human life. Therefore, the drug discovery process mainly requires the development of novel medications as well as the improvement of methods for obtaining existing ones. From a chemical standpoint, this goes hand in hand with efforts to develop new, highly selective techniques to establish chemical bonds with the fewest possible stages in the synthetic process.

Because of the synthetic benefits and the prevalence of amines among biologically active molecules, reductive amination plays a crucial role in pharmaceutical and medicinal chemistry (Figure 43). According to Roughley's research[55], reductive amination applies in a quarter of C-N bond-forming processes in the pharmaceutical sector.

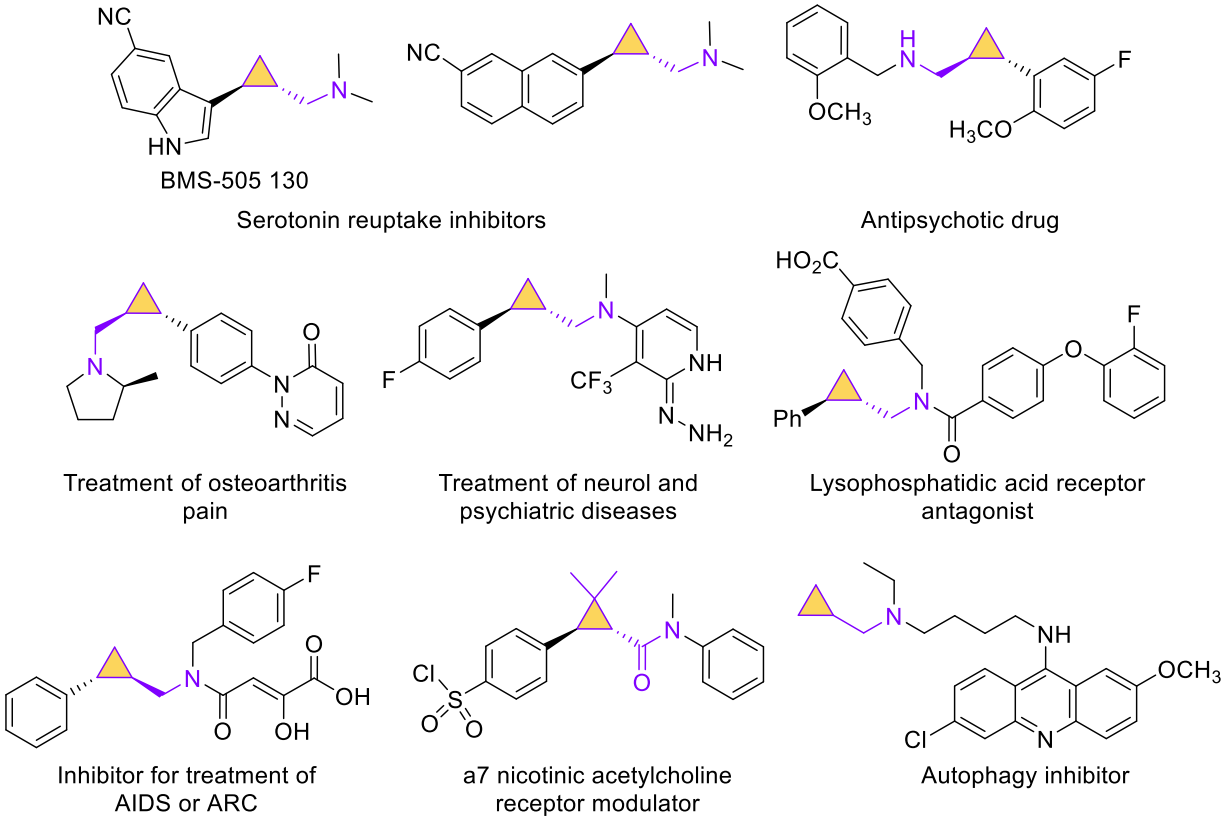


Figure 43. Important cyclopropylamines containing bioactive molecules.

Reductive amination is one of the most effective and adaptable reactions for manufacturing amines and related functional compounds in chemical synthesis and biological systems, which involves treating a mixture of an aldehyde or ketone and an amine with a reductant in one pot[56]. The amines produced in this way are widely used in industry as intermediates in the production of pharmaceuticals, dyes, resins, fine chemicals, solvents, textile additives, disinfectants, rubber stabilizers, corrosion inhibitors, and detergents and plastics. There are some examples, as shown in Figure 43, which act as inhibitors, antagonists, antipsychotic drugs, and others used in the treatment of osteoarthritis pain, etc.[5]

Organocatalysis has become a powerful alternative to metal catalysis since 2000. Various organocatalytic asymmetric reduction systems, particularly for imine reduction, have been developed[57]. Hydrosilanes or Hantzsch esters are the most common hydrogen sources in organocatalytic ARA (Asymmetric Reductive amination), and both require Lewis base and phosphoric acid catalysts to activate.

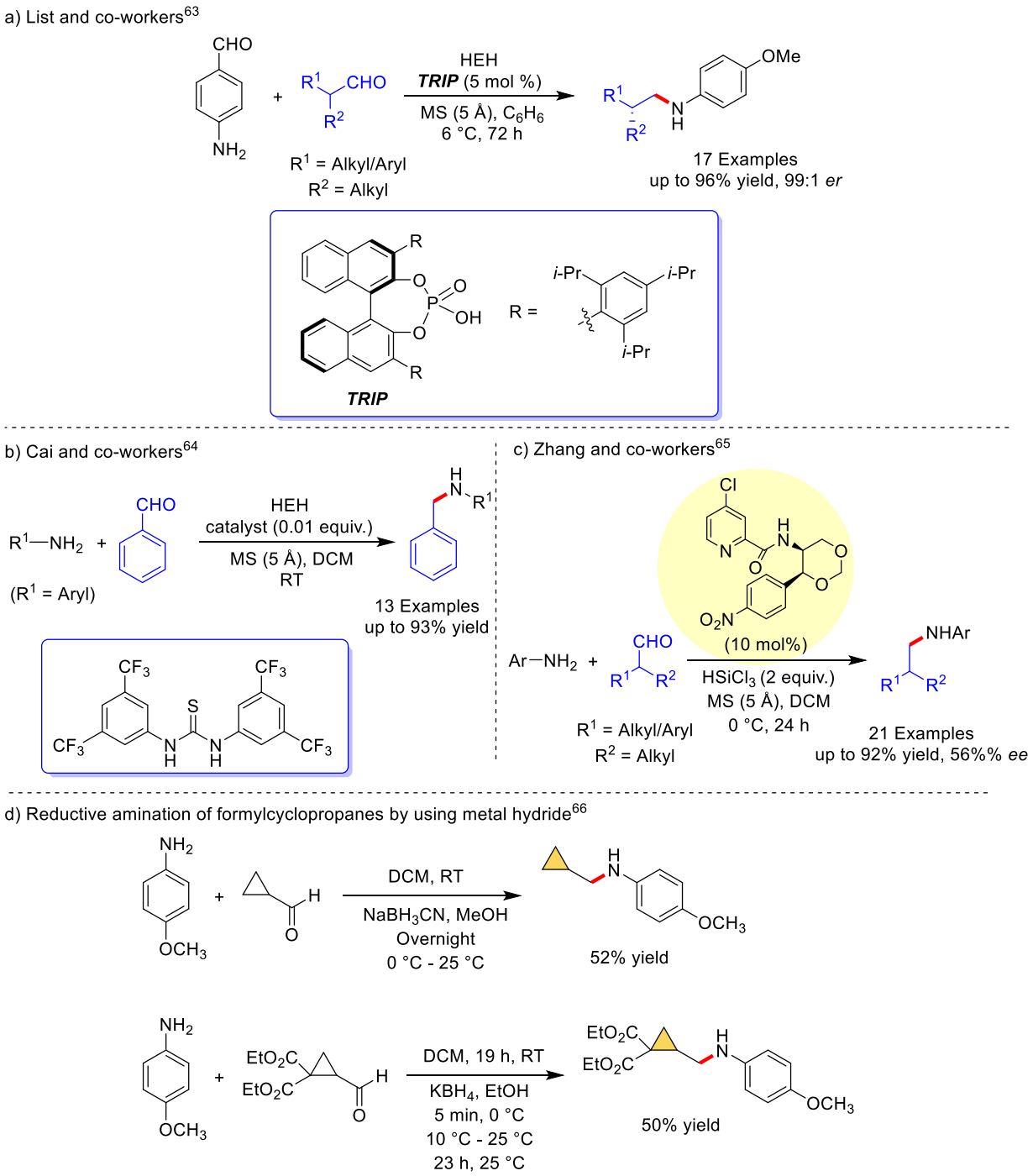
ARA is an essential family of RA reactions, with Hantzsch esters as hydrogen donors and chiral phosphoric acids as catalysts. Hantzsch esters are synthetic versions of NADH, the hydride source required by enzymes in reduction processes. It is thought that the acid activates the imine intermediate in organocatalytic ARA with the chiral phosphoric acid/Hantzsch ester system by hydrogen bonding. Hydrogen bonding between the NH unit of the Hantzsch ester and the P=O group of the phosphoric acid also activates it[58].

The first asymmetric organocatalytic reduction of imines employing Hantzsch ester was published in early 1989[59]. However, until 2005, this reaction recorded no further progress. Several articles on organocatalytic imine reduction and ARA with Hantzsch ester were published simultaneously by the groups of Rueping[60], List[61], and Macmillan[62].

List and co-workers used the chiral phosphoric acid/Hantzsch ester combination. Through a dynamic kinetic resolution process (Scheme 22), α-branched aldehydes were reductively aminated to provide β-branched chiral amines[63]. Cai and co-workers reported the direct reductive amination of aromatic and aliphatic aldehydes in 2009 (Scheme 22). A catalytic quantity of thiourea mediates the reaction[64]. Under *N*, *N*-di-(3',5'-trifluoromethyl) phenyl thiourea catalysis, hydrogen-bonding activation with Hantzsch ester as the hydrogen source reduced a range of aromatic and aliphatic aldimines to get the corresponding amines. The ARA with hydrosilanes catalyzed by chiral Lewis base catalyst was reported by Zhang and co-workers[65] in 2017. At 0 °C for 24 h, amines and α-branched aldehydes reacted in the presence of Lewis base (10 mol%) and Hydrosilanes, furnished the variety of β-branched chiral

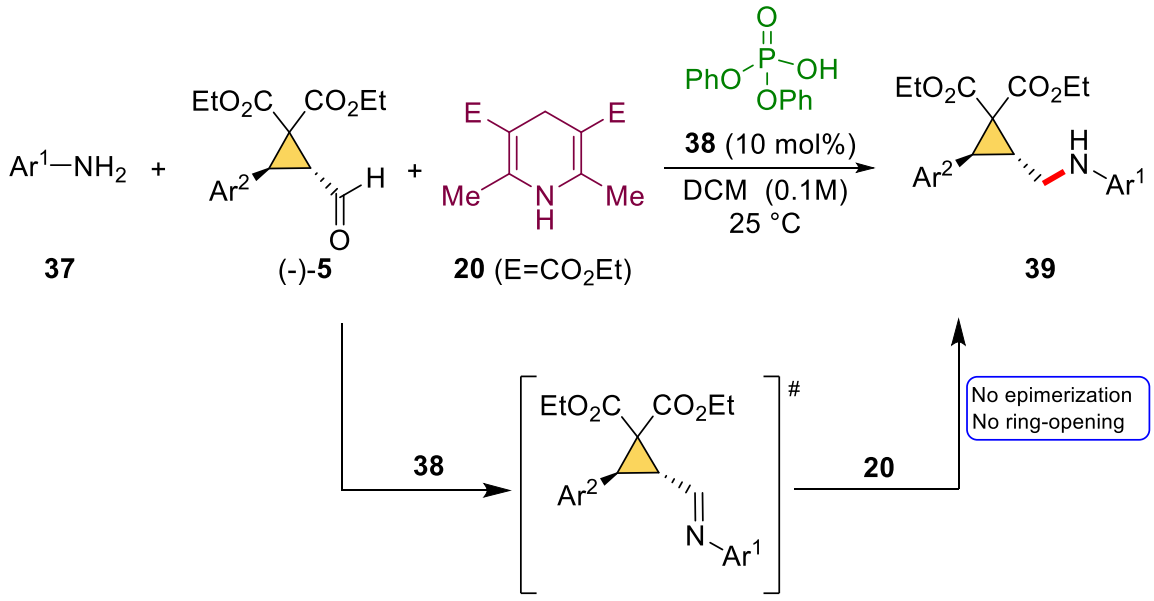
amines in low to moderate enantioselectivities (up to 56 %) and moderate to good yields (up to 92%) (Scheme 22).

Scheme 22: Previous Work on Reductive Amination of Aldehydes.



Cyclopropylamines are a fundamental class of amines which are the core structure of many biologically and medicinally essential compounds (Figure 43). A very few reports are present on synthesize these cyclopropylamines by treating formylcyclopropanes with amines with the help of metal hydride donors such as $NaBH_3CN$, KBH_4, etc.[66] (Scheme 22). First, formylcyclopropane reacts with amine and produce aldimines which subsequently reduces by the hydride donor. Organocatalytic reductive amination of chiral formylcyclopropanes is not reported till date, in which Hantzsch ester is used as a hydride donor in place of the metal hydride. Based on our previous knowledge of developing an organocatalytic reductive alkylation reaction[44,54], we envisioned to accomplish this synthetic challenge by designing a high-yielding conversion of the formyl group of cyclopropanes into the secondary amine compounds **39** without ring-opening from the Aromatic amines **37**, chiral formylcyclopropanes (-)-**5** and Hantzsch ester **20** through the organocatalytic reductive coupling reaction (Scheme 23).

Scheme 23. Reaction Design for The Reductive Amination of Chiral Formylcyclopropane (-)-**5.**

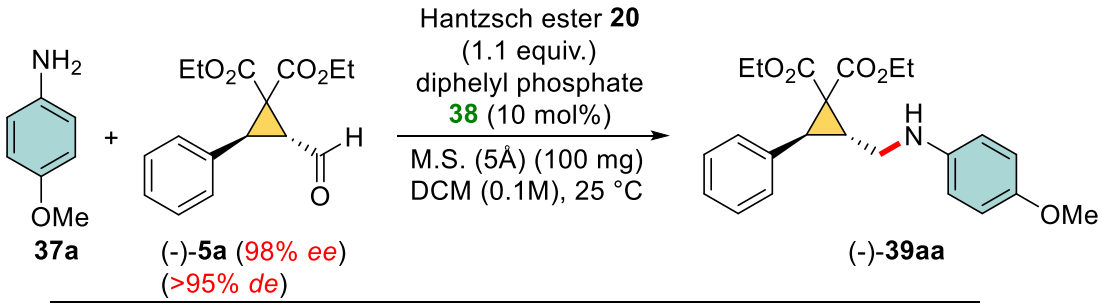


5.2 Results and Discussion

5.2.1 Reaction Optimization:

The initial investigation was carried out with Chiral formylcyclopropane (-)**5a** and *p*-anisidine (**37a**) using Hantzsch ester **20** (HEH) as the reducing reagent in the presence of diphenyl phosphate **38** (10 mol%). The reaction was carried out in DCM at 25 °C with 5 Å MS acting as a water scavenger and furnished the desired product (-)-**39aa** in 93% yield in 240 min with >96% *ee* and >98% *de* (Table11, entry 1). Next, when we stirred the reaction for 30 and 10 min, it gave the product (-)-**39aa** in 98% and 46% yields, respectively (Table11, entry 2,3).

Table 11: Reaction Optimization[a,b]



entry	38 (mol %)	*t* (min)	yield **39aa** (%)	*de* **39aa** (%)	*ee* **39aa** (%)
1	10	240	93	>98	>96
2	10	30	98	>98	>96
3	10	10	46	>98	>96
4[c]	10	30	98	>98	-
5[d]	10	30	94	>98	>96
6[e]	-	300	50	>98	>96
7[f]	10	120	-	>98	>96
8	5	60	98	>98	>96
9[d]	5	60	97	>98	>96

[a]Reactions were carried out in DCM (1.0 mL) with 1.1 equiv of (-)-**5a** (0.11 mmol) and 1.1 equiv of **20** (0.11 mmol) relative to **37a** (0.1 mmol) in the presence of 10 mol % of **38**, and yield refers to the column-purified product. [b]Enantiomeric excess (*ee*) was determined by chiral HPLC analysis, and diastereomeric excess (*de*) was determined by ^{1}H NMR analysis of crude

reaction mixture. [c]Racemic 5a was used. [d]Without molecular sieves. [e]Without acid catalyst. [f]Without Hantzsch ester.

When we used racemic formylcyclopropane **5a** instead of chiral formylcyclopropane, it furnished the Product **39aa** in 98% yield with >98% *de* in 30 min (Table11, entry 4). We also performed a reaction without molecular sieves, which furnished the product (-)-**39aa** in 94% yield with >96% ee and >98% *de* in 30 min (Table11, entry 5). Next, we performed a reaction without acid catalyst, and it furnished the desired product (-)-**39aa** in 50% yield with >96% ee and >98% *de* in 300 min (Table11, entry 6). Acid catalyst forms hydrogen bonds with both imine and Hantzsch ester, which facilitates imine formation. Hence, without an acid catalyst, the reaction rate slows down. In the following condition, we performed a reaction without Hantzsch ester **20**, resulting in no formation of the desired product (-)-**39aa**, only imine was present in the reaction mixture (Table11, entry 7). Next, we changed the catalyst loading from 10 mol% to 5 mol%, which furnished the desired product **39aa** in 98% yield and 97% yield, with and without molecular sieves, respectively, in 60 min. with >96% ee and >98% *de* (Table11, entry 8,9). After analyzing all the conditions, finally, we chose entry 2 as our best-optimized condition for reductive amination reaction. ^{1}H, ^{13}C, and HPLC spectra of compound (-)-**39aa** are shown in Figures 44 and 45.

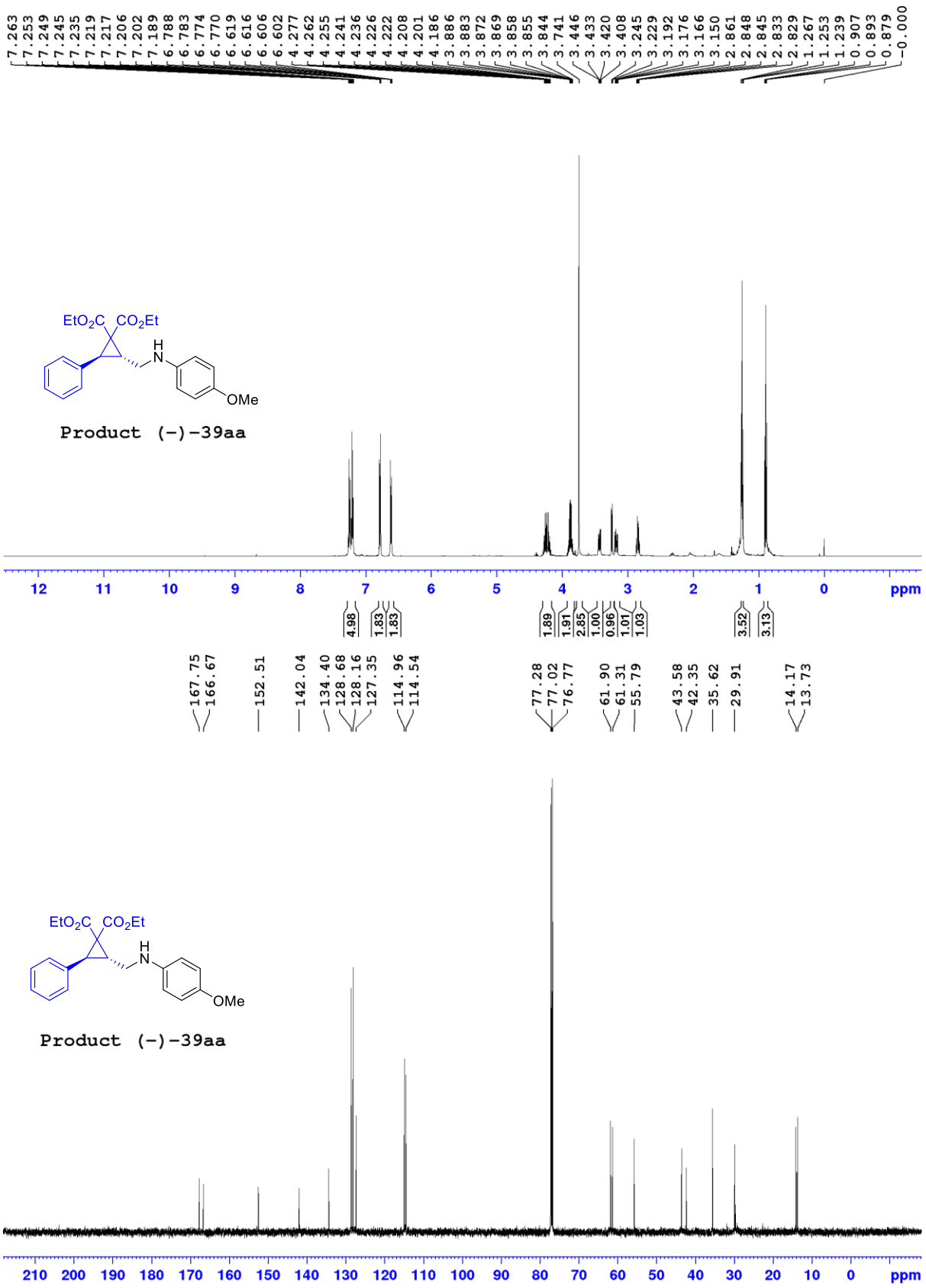
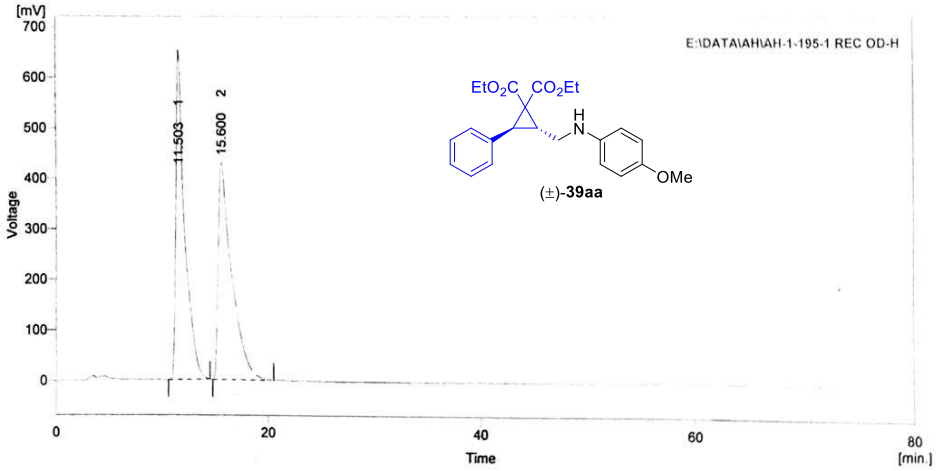


Figure 44. ^{1}H and ^{13}C spectra of the product (-)-**39aa**.

Racemic (±)-**39aa**:

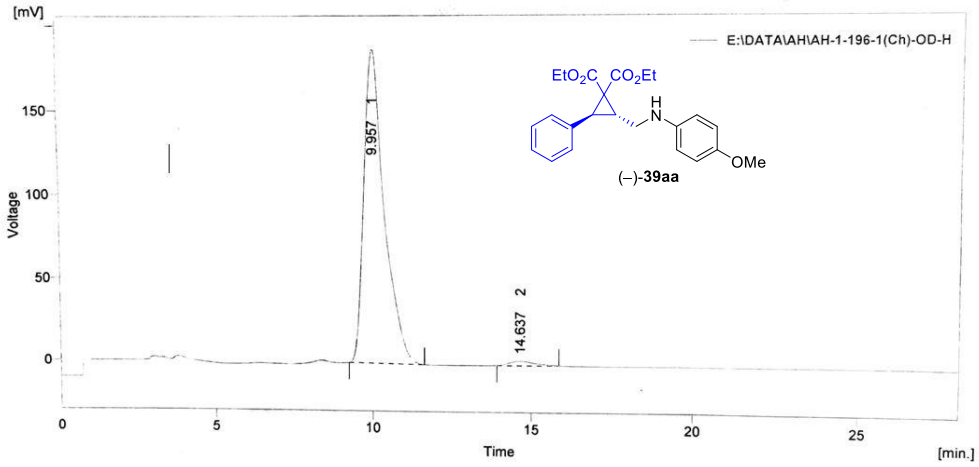


Chiralpak OD-H, Hexane/*i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\AH\AH-1-195-1 REC OD-H)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	11.503	37696.993	653.907	49.8	60.4	0.75
2	15.600	38006.552	428.998	50.2	39.6	1.25
	Total	75703.545	1082.905	100.0	100.0	

Chiral (-)-**39aa** (>96% *ee*):



Chiralpak OD-H, Hexane/*i*-PrOH = 90:10, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\AH\AH-1-196-1(Ch)-OD-H)

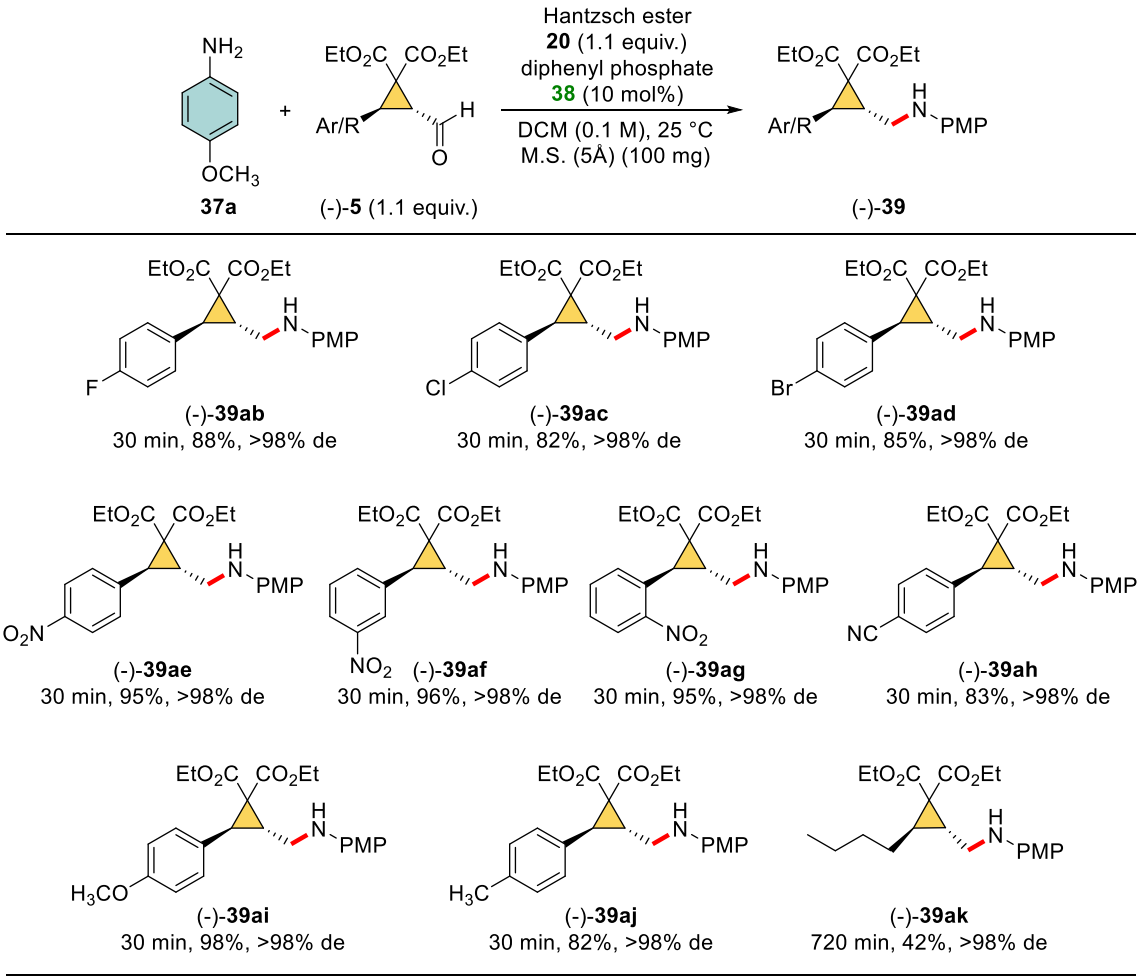
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	9.957	8329.121	186.691	98.3	98.6	0.65
2	14.637	144.119	2.689	1.7	1.4	0.84
	Total	8473.240	189.380	100.0	100.0	

Figure 45. HPLC spectra of the product (-)-**39aa**.

5.2.2 Reaction Scope:

After determining the optimized condition for organocatalytic reductive amination, we looked at the role played by the chiral formylcyclopropane (-)-**5** component in this organocatalytic reduction. As shown in Scheme 24, various substituted chiral formylcyclopropanes (-)-**5** derivatives, including ortho, meta, para-substituted systems as well as electron-rich and electron-deficient systems, are effectively coupled (Scheme 24, 82-98% yield, >98% *de*). We have also tried reductive amination reaction with aliphatic chiral formylcyclopropane (-)-**5k**, which resulted in reductive amination product (-)-**39ak** in 42% yield with >98% *de* (Scheme 24). ^{1}H and ^{13}C spectra of compounds (-)-**39ab**, (-)-**39aj**, (-)-**39ah**, and (-)-**39ak** are shown in Figures 46-49.

Scheme 24. Reductive Amination Reaction Scope with Respect to Various Formylcyclopropanes (-)-**5**[a,b]



[a]Reactions were carried out in DCM (1.0 mL) with 1.1 equiv of (-)-**5** (0.11 mmol) and 1.1 equiv of **20** (0.11 mmol) relative to **37a** (0.1 mmol) in the presence of 10 mol % of **38**, and yield refers to the column-purified product. [b]Diastereomeric excess (*de*) was determined by ^{1}H NMR analysis of crude reaction mixture.

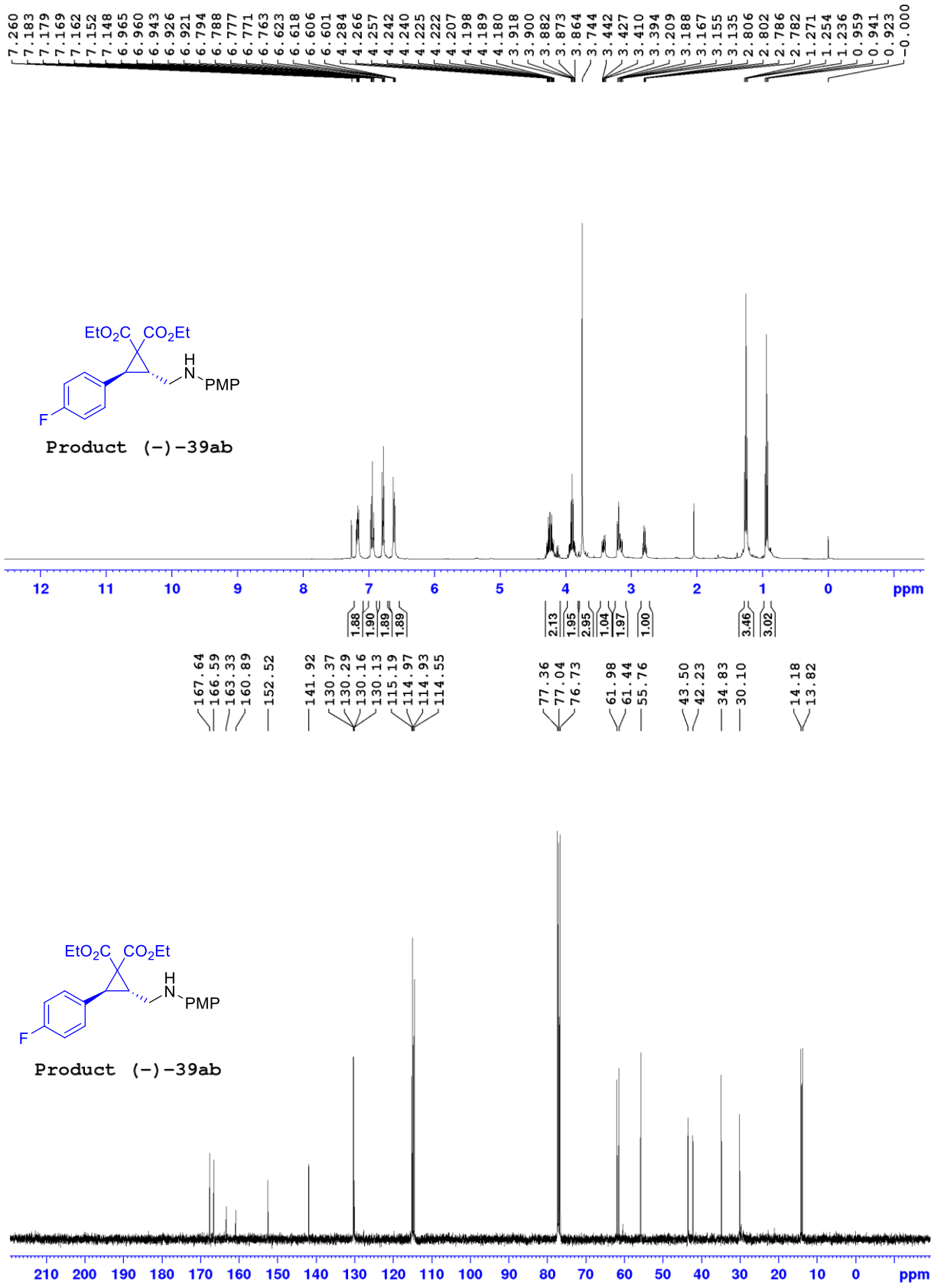


Figure 46. ^{1}H and ^{13}C spectra of the product (-)-**39ab**.

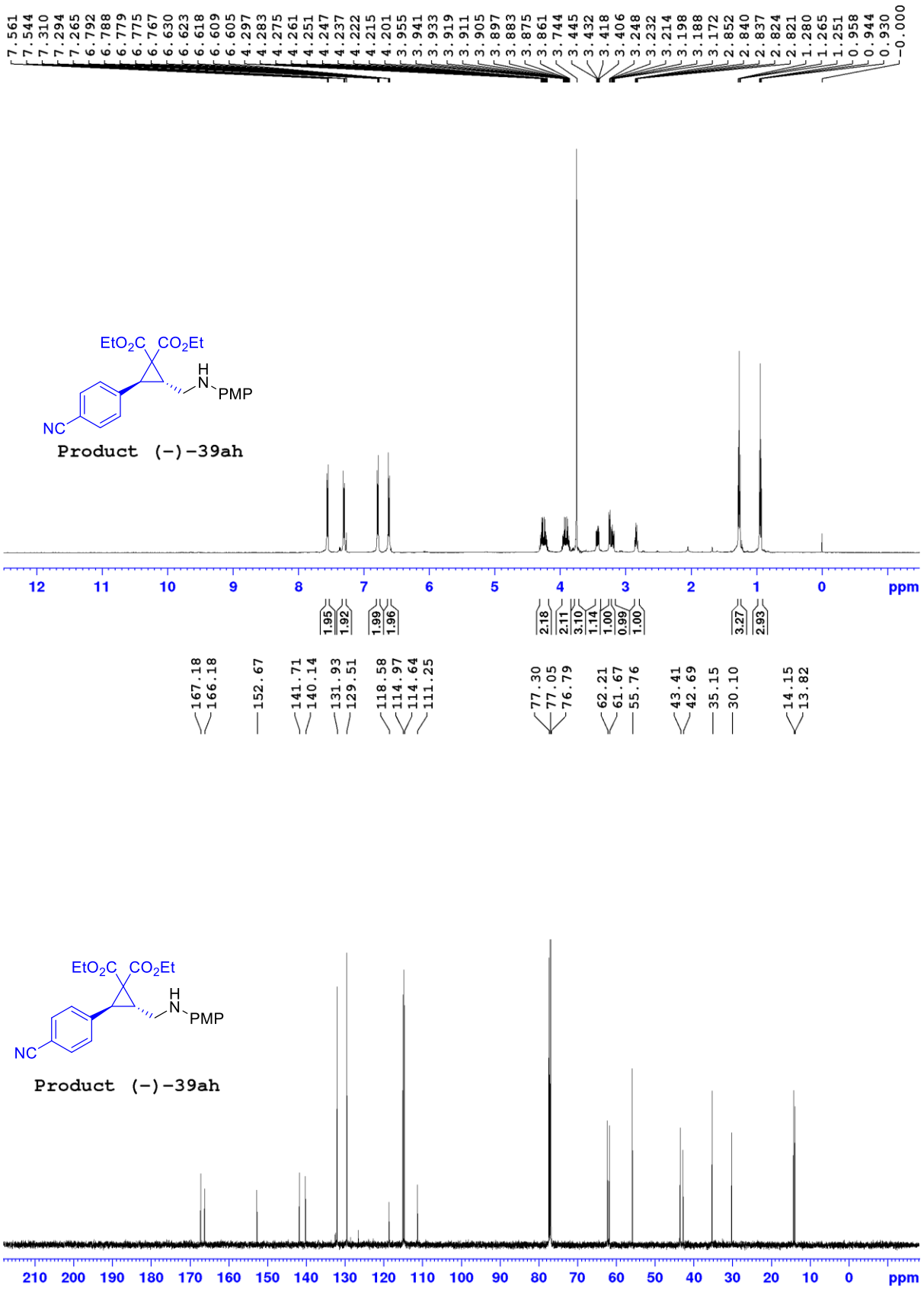


Figure 47. ^{1}H and ^{13}C spectra of the product (-)-**39ah**.

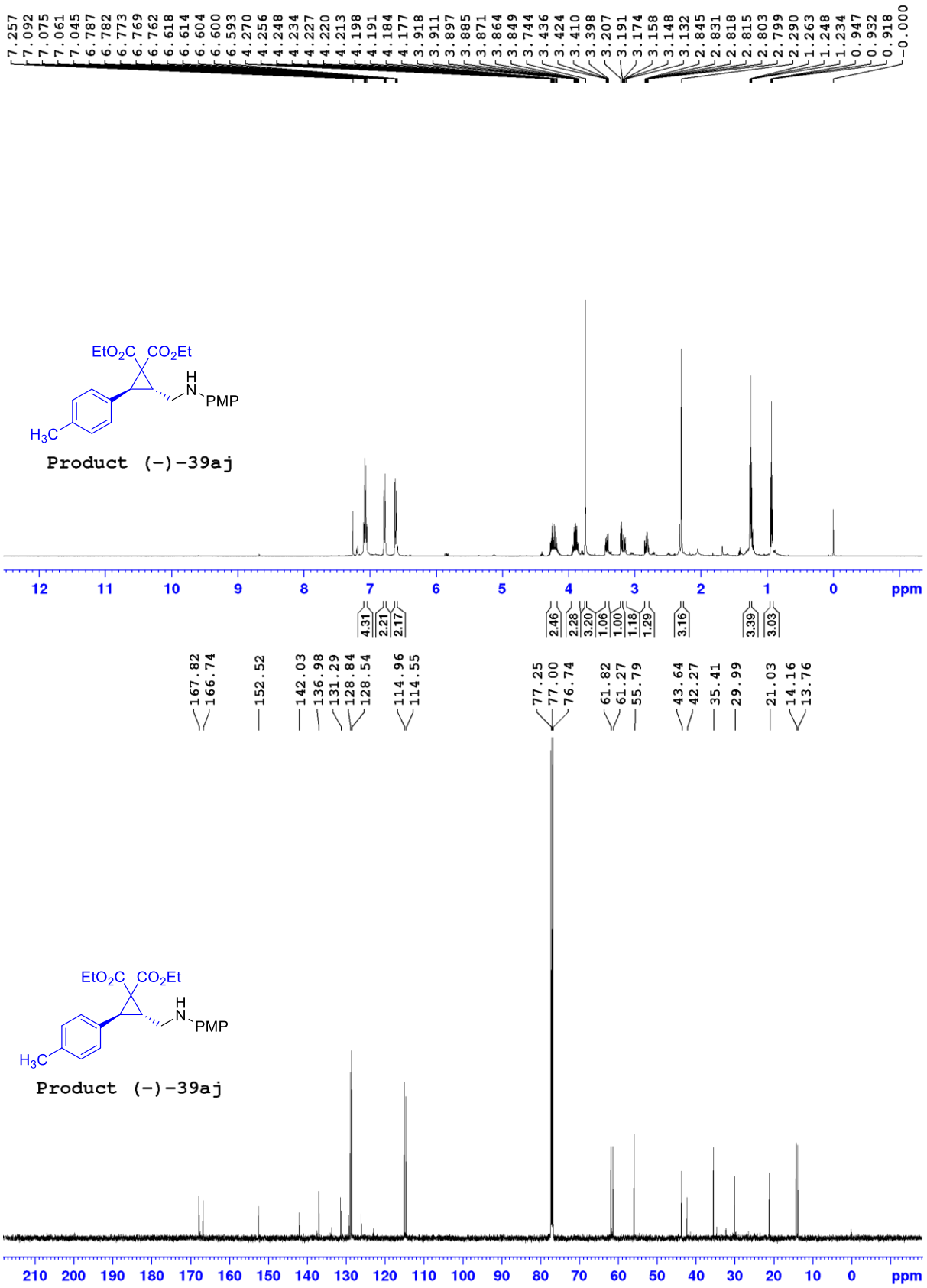


Figure 48. ^{1}H and ^{13}C spectra of the product (-)-**39aj**.

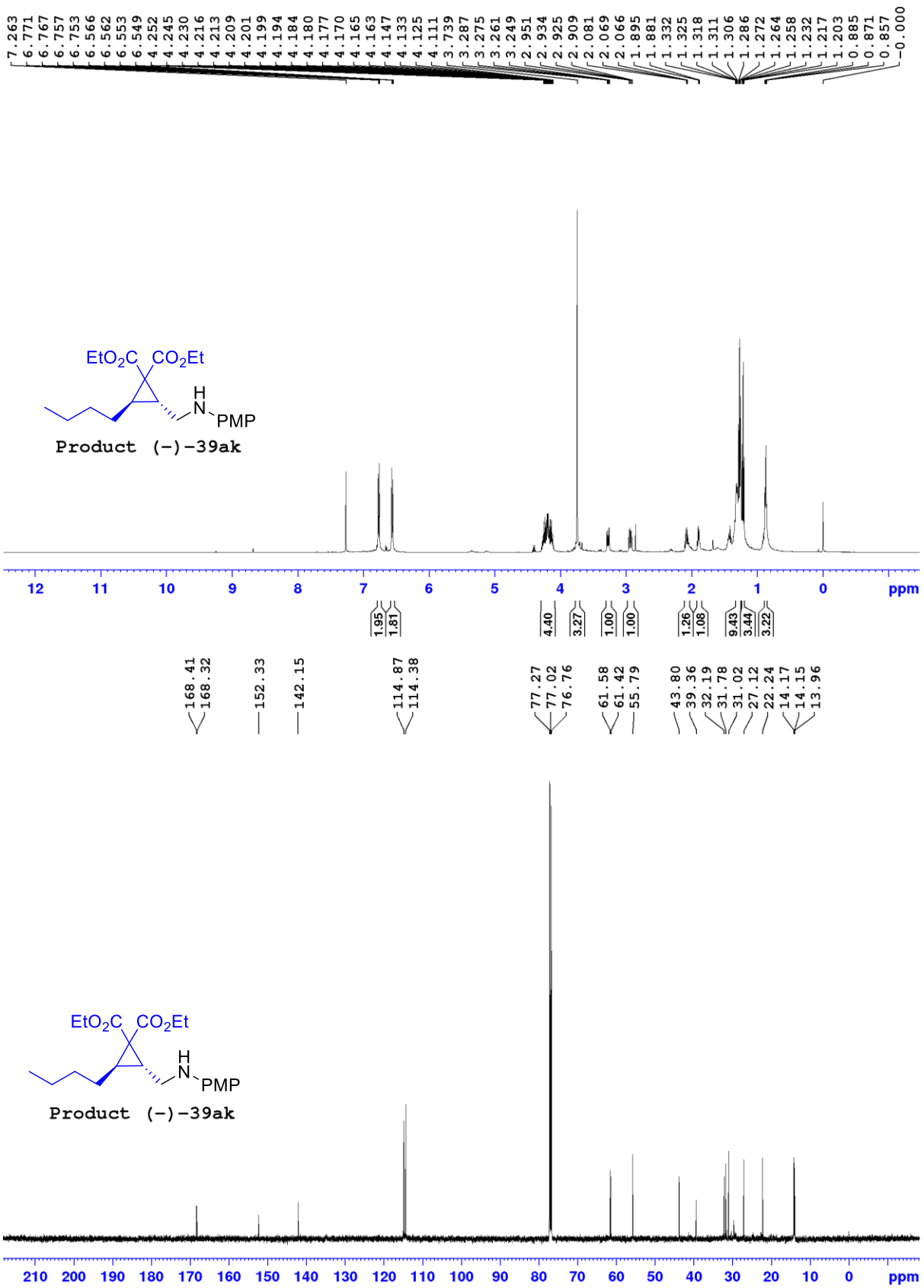


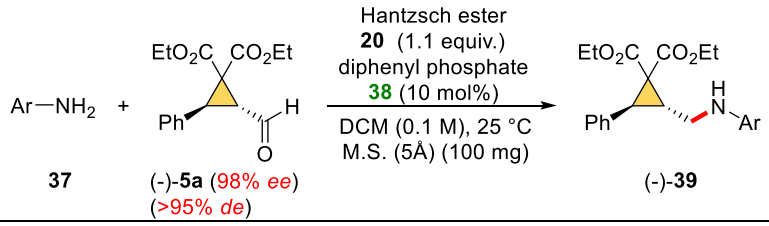
Figure 49. ^{1}H and ^{13}C spectra of the product (-)-**39ak**.

We aimed to investigate the universality of our planned reaction after obtaining acceptable optimal reaction conditions. We assessed the impact of aromatic amines **37.** The reaction expands its scope to several para-, meta-, ortho-, and di-substituted aniline substrates, as indicated in Table 12.

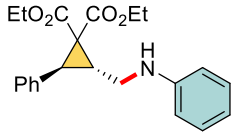
The reactivity and enantiocontrol of the reaction are not significantly affected by various neutral (H), electron-donating (Me), and electron-withdrawing (F, Cl, Br, I, NO_2, CN, OCF_3, ethynyl) groups at the phenyl ring, which resulted in the delivery of the desired reductive amination products (-)-**39** with good to excellent yields (81-98%) and >98% *de*. We also observed the high enantioselectivity (>97% *ee*) for compound (-)-**39ba**. We also tried reactions with ortho-substituted halogen atoms. When we used ortho fluoro and ortho chloro substituted amine compounds, the reaction yielded the reductive amination product in 75% and 23% yields, respectively. With the ortho iodo substituted amine compound, the reaction did not proceed. Because fluoro to iodo atom size is continuously increasing which increases the steric hindrances on ortho position, hence the rate of the reaction decreases.

Regardless of the electronic property and positioning of these functional groups, when two substituents to the phenyl ring of anilines **37**, the corresponding reductive amination products (-)-**39** were also produced in good to excellent yields (75%–97%) and with >98% *de* (Table 12). ^{1}H and ^{13}C spectra of compounds (-)-**39ba**, (-)-**39ca** (-)-**39ha**, (-)-**39pa**, (-)-**39qa** and HPLC spectra of compound (-)-**39ba** are shown in Figures 50-55.

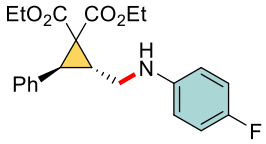
Table 12. Reductive Amination Reaction Scope with Respect to Various Aromatic Amines [a,b]



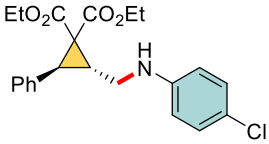
37 (-)-**5a** (98% *ee*) (>95% *de*) (-)-**39**



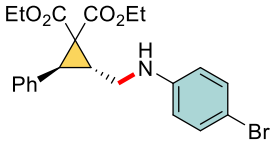
(-)-**39ba**
30 min, 81%, >97% *ee*
>98% *de*



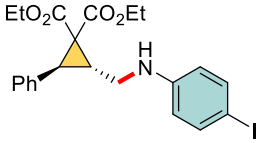
(-)-**39ca**
30 min, 97%, >98% *de*



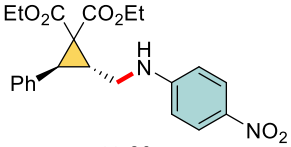
(-)-**39da**
30 min, 85%, >98% *de*



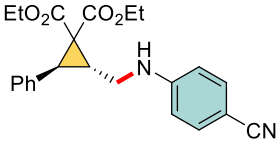
(-)-**39ea**
30 min, 81%, >98% *de*



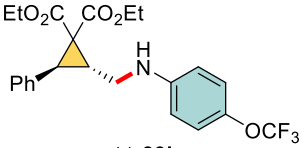
(-)-**39fa**
30 min, 83%, >98% *de*



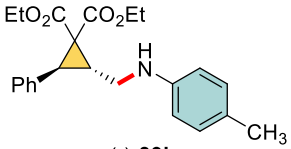
(-)-**39ga**
30 min, 90%, >98% *de*



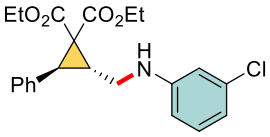
(-)-**39ha**
30 min, 90%, >98% *de*



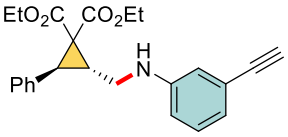
(-)-**39ia**
30 min, 98%, >98% *de*



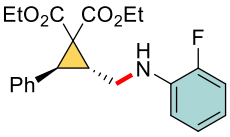
(-)-**39ja**
30 min, 85%, >98% *de*



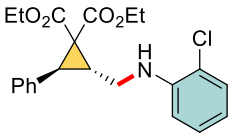
(-)-**39ka**
30 min, 95%, >98% *de*



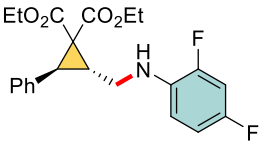
(-)-**39la**
30 min, 97%, >98% *de*



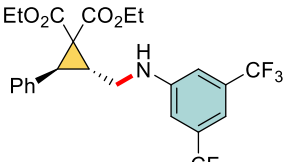
(-)-**39ma**
30 min, 75%, >98% *de*



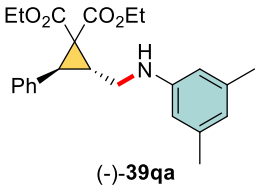
(-)-**39na**
240 min, 23%, >98% *de*



(-)-**39oa**
60 min, 80%, >98% *de*



(-)-**39pa**
60 min, 75%, >98% *de*



(-)-**39qa**
30 min, 97%, >98% *de*

[a]Reactions were carried out in DCM (1.0 mL) with 1.1 equiv of (-)-**5a** (0.11 mmol) and 1.1 equiv of **20** (0.11 mmol) relative to **37** (0.1 mmol) in the presence of 10 mol % of **38**, and yield refers to the column-purified product. [b]Enantiomeric excess (*ee*) was determined by chiral HPLC analysis, and diastereomeric excess (*de*) was determined by ^{1}H NMR analysis of the crude reaction mixture.

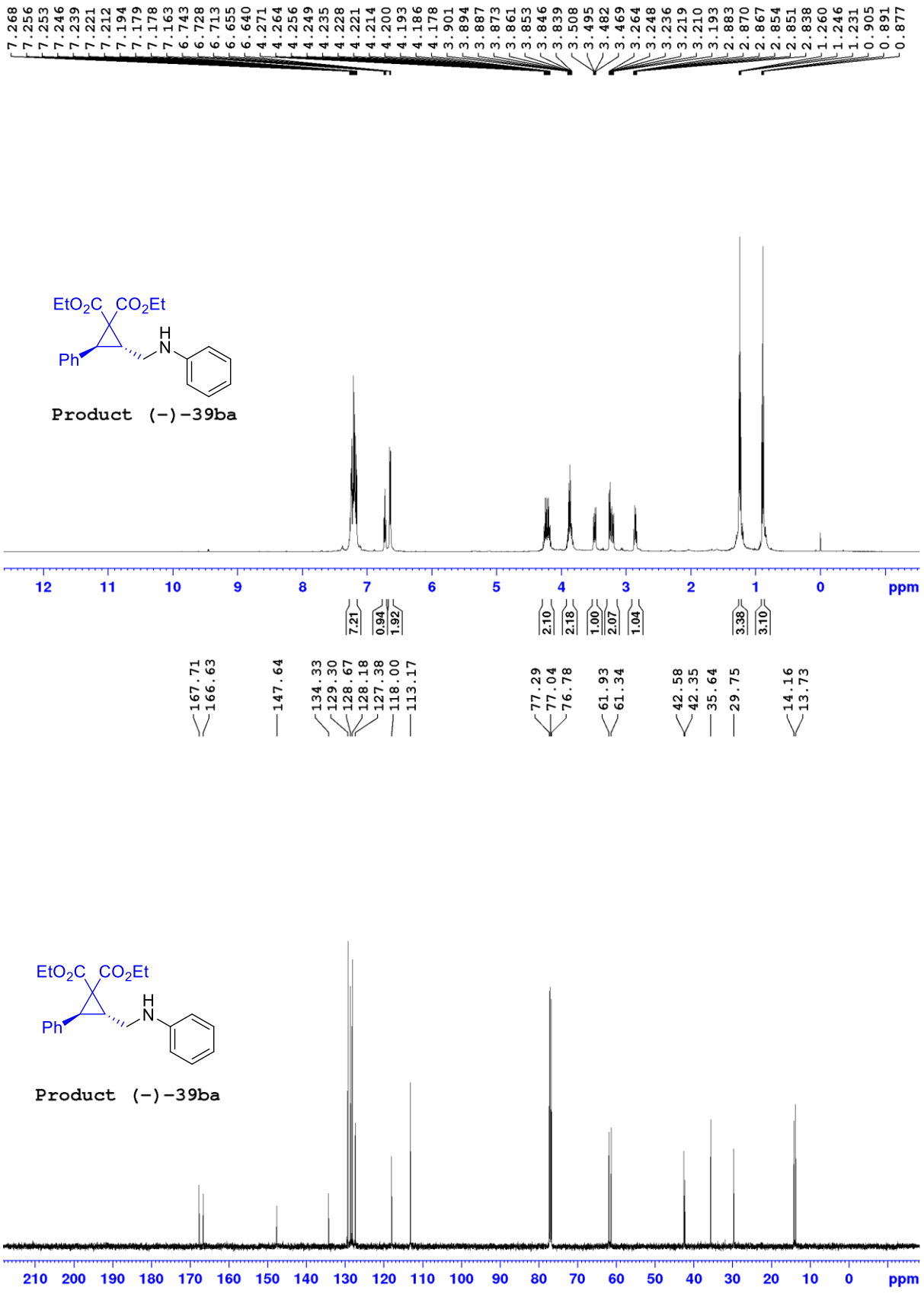
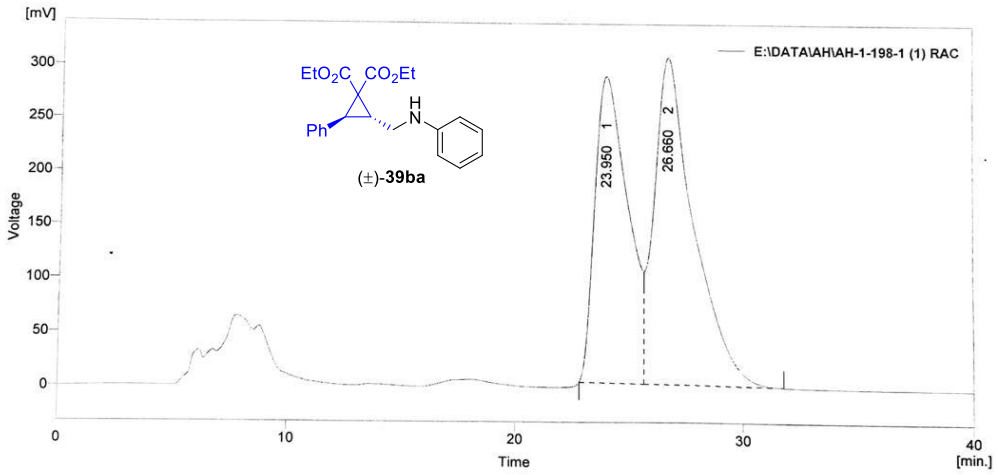


Figure 50. ^{1}H and ^{13}C spectra of the product (-)-**39ba**.

Racemic (±)-3**9ba**:

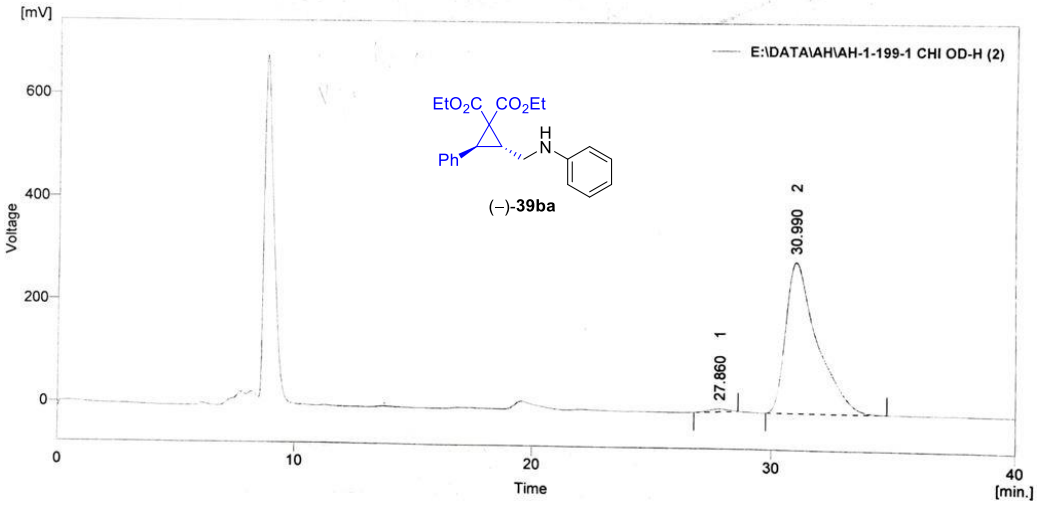


Chiralpak OD-H, Hexane/*i*-PrOH = 95:5, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\AH\AH-1-198-1 (1) RAC)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	23.950	28826.185	287.467	43.9	48.4	1.72
2	26.660	36851.326	306.816	56.1	51.6	1.74
	Total	65677.511	594.283	100.0	100.0	

Chiral (-)-**39ba** (>97% *ee*):



Chiralpak OD-H, Hexane/*i*-PrOH = 95:5, Flow Rate 1.0 mL/min, 254 nm

Result Table (Uncal - E:\DATA\AH\AH-1-199-1 CHI OD-H (2))

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	27.860	282.606	5.316	1.1	1.8	0.90
2	30.990	26195.594	290.961	98.9	98.2	1.28
	Total	26478.199	296.277	100.0	100.0	

Figure 51. HPLC spectra of the product (-)-**39ba**.

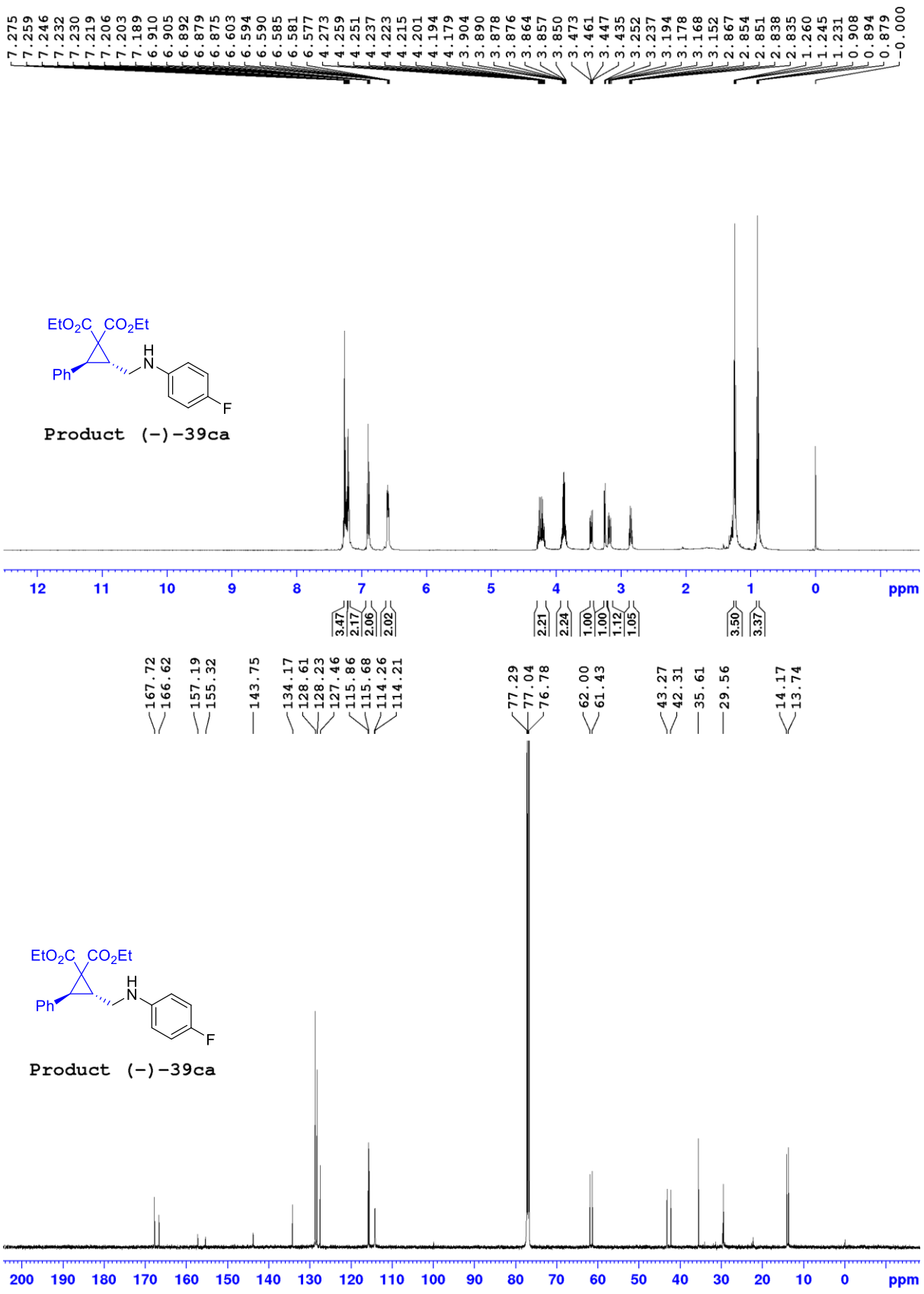


Figure 52. ^{1}H and ^{13}C spectra of the product (-)-**39ca**.

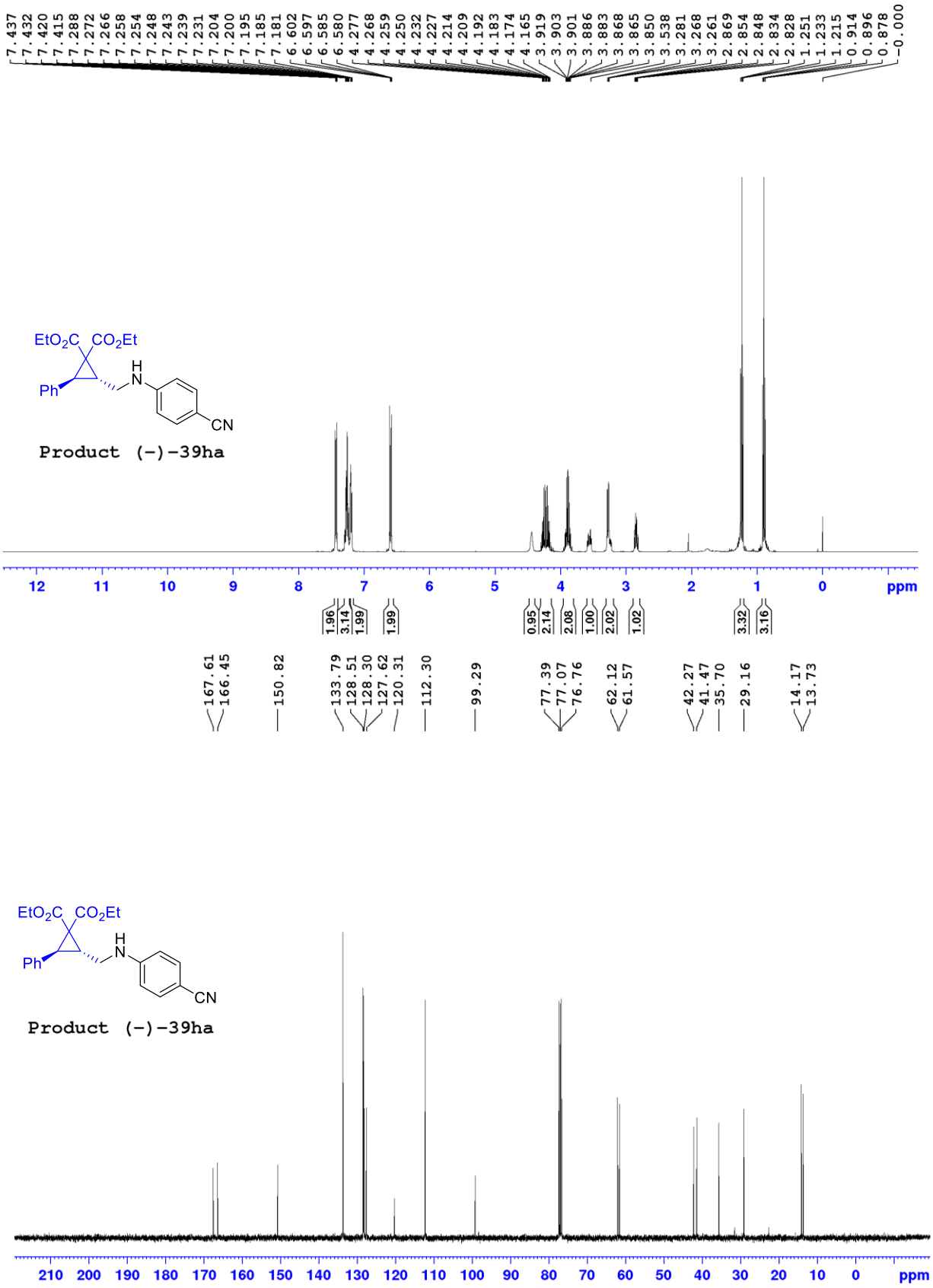


Figure 53. ^{1}H and ^{13}C spectra of the product (-)-**39ha**.

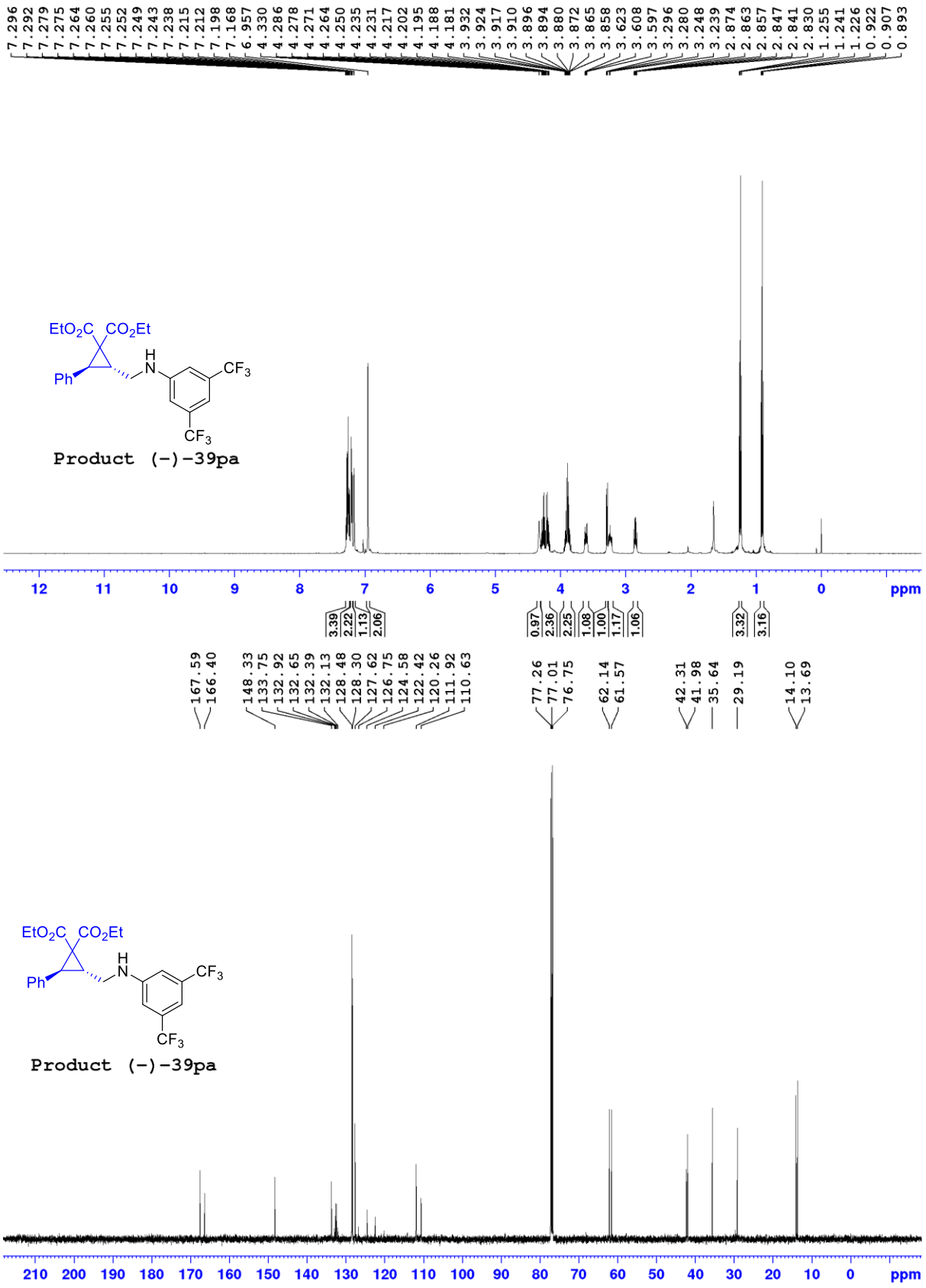


Figure 54. ^{1}H and ^{13}C spectra of the product (-)-**39pa**.

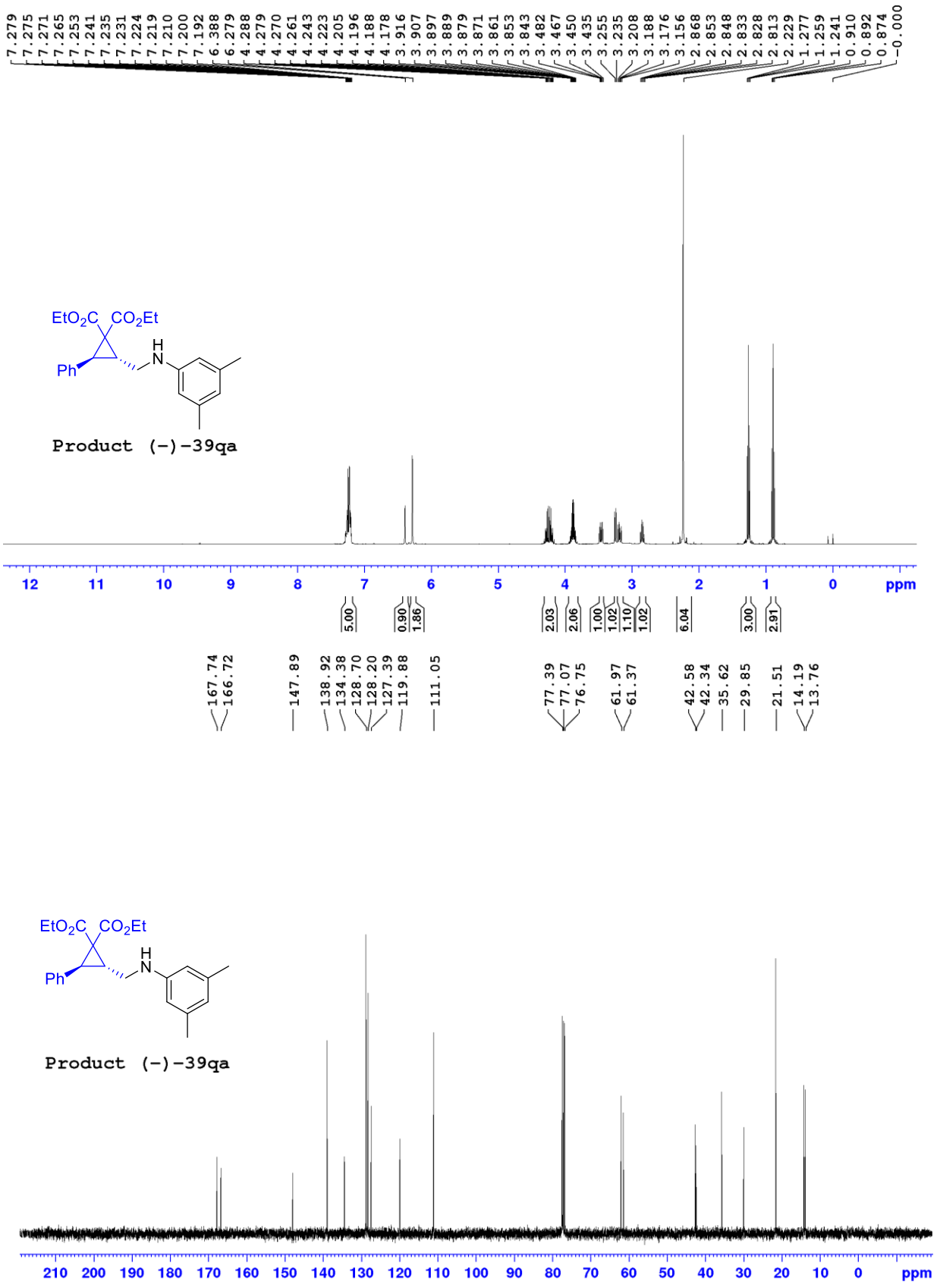
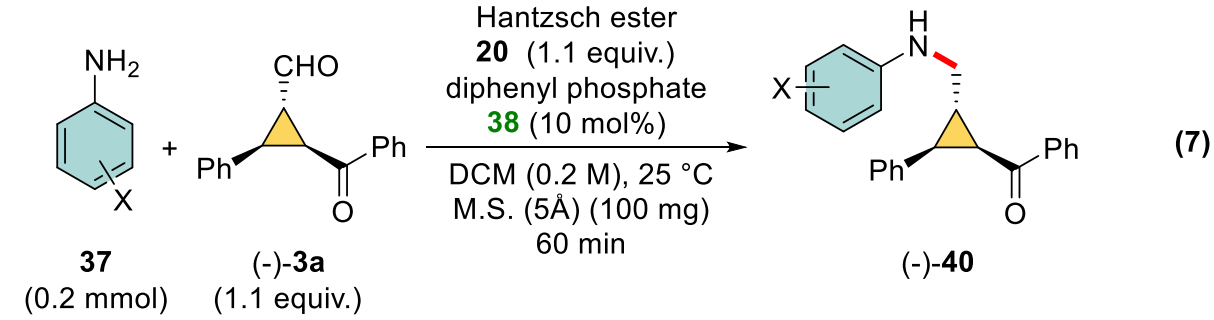


Figure 55. ^{1}H and ^{13}C spectra of the product (-)-**39qa**.

We also performed reactions of dicarbonyl-cyclopropane (-)-**3a** with different substituted anilines such as *p*-OCH_3, *p*-Cl, and *m*-NO_2, which gave the corresponding reductive amination products (-)-**40aa**, (-)-**40fa** and (-)-**40ra** in 92%, 98%, and 94% yields, respectively with >98% *de* in 60 min. To check the chemo-selectivity of this reaction, we tried a reaction between 2 equiv. of (-)-**37a** and reductive amination product (-)-**40aa** for 12 h at 25 °C, after this we increased the temperature up to 50 °C for the next 12 h, resulting in no reaction proceeding and we recovered the total compound (-)-**40aa**, which means the reaction only proceeded on the formyl group of cyclopropane and there was no participation of the keto group in the reaction (Equation 7). ^{1}H and ^{13}C spectra of compound (-)-**40aa** are shown in Figure 56.



(7)

X = *p*-OCH_3 (**37a**)
X = *p*-Cl (**37f**)
X = *m*-NO_2 (**37r**)

(-)-**40aa**, 92%, >98% *de*
(-)-**40fa**, 98%, >98% *de*
(-)-**40ra**, 94%, >98% *de*

After successful reductive amination with aromatic monoamines, we want to elaborate further on this reaction with aromatic diamines such as 4-amino aniline and 3-amino aniline. 4-amino aniline **41** (1 equiv., 0.1 mmol) reacted with chiral formylcyclopropane (-)-**5a** (2.2 equiv.) in the presence of acid catalyst **38** (10 mol%) and Hantzsch ester (2.2 equiv) in DCM at 25 °C for 30 min, furnished the di reductive amination product (-)**42** in 95% yield with >98% *de* (Scheme 25). ^{1}H and ^{13}C spectra of compound (-)-**42** are shown in Figure 57.

Similarly, we tried the reaction of 3-amino aniline **43** (1 equiv., 0.1 mmol) with various chiral formylcyclopropane (-)**5a**, (-)-**5h**, and (-)-**5i** (2.2 equiv.) in the presence of acid catalyst **38** (10 mol%) and Hantzsch ester (2.2 equiv) in DCM at 25 °C in 60 min. Instead of getting di reductive amination products, we got the products (-)-**44a**, (-)-**44h**, and (-)-**44i** in 46%, 45%, and 33% yields, respectively with >98% *de* (Scheme 25). ^{1}H and ^{13}C spectra of compound (-)-**44aa** are shown in Figure 58.

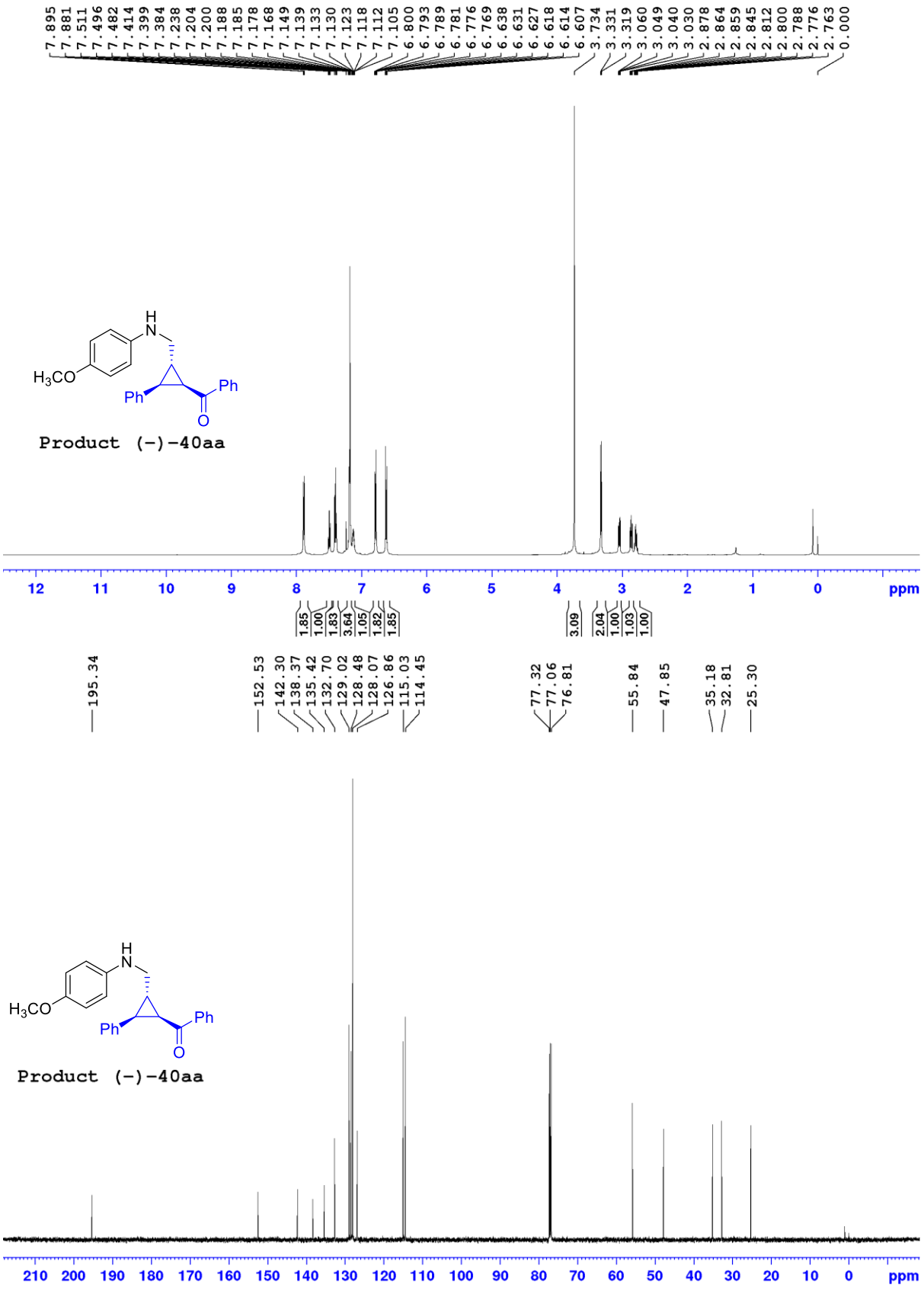
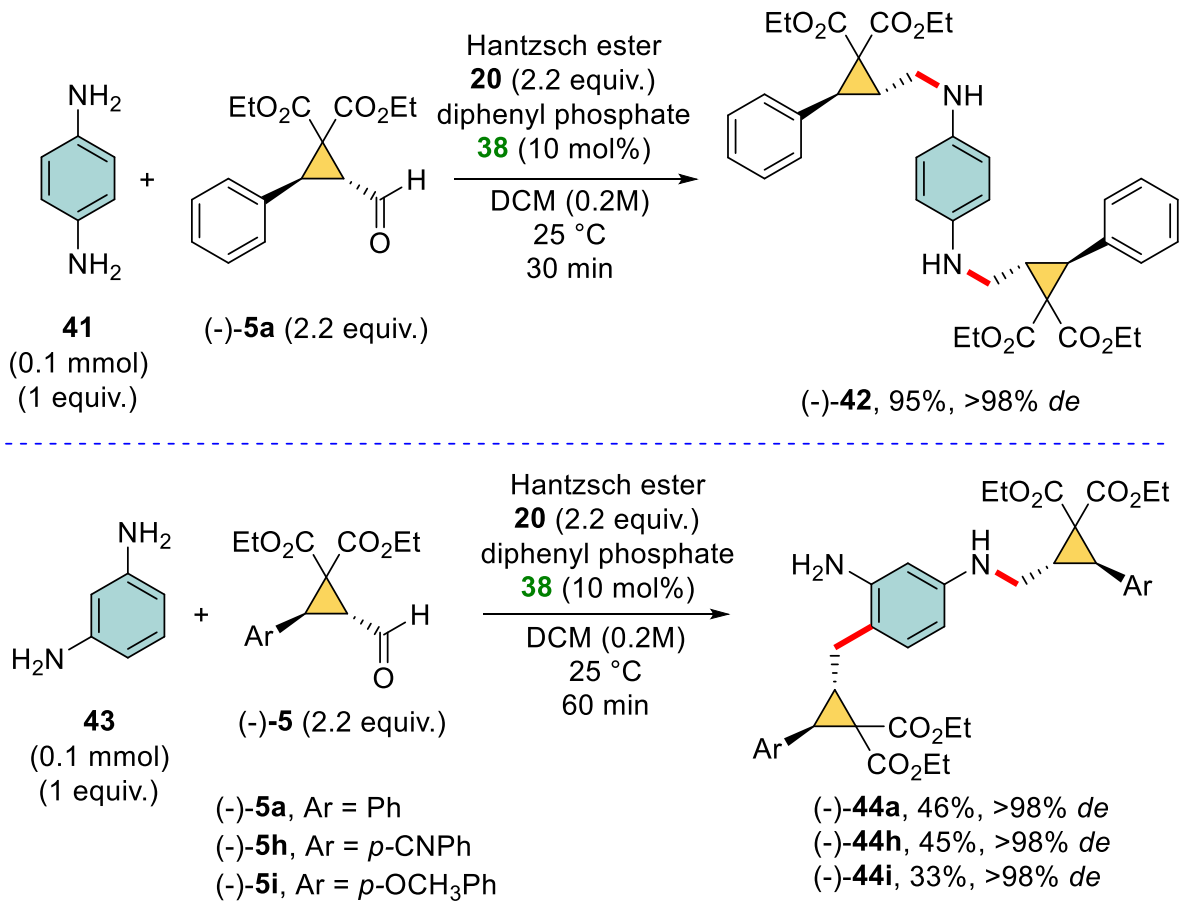


Figure 56. ^{1}H and ^{13}C spectra of the product (-)-**40aa**.

Scheme 25. Reaction Scope with 1,2 and 1,3 Aromatic Diamine[a,b]



[a]Reactions were carried out in DCM (2.0 mL) with 2.2 equiv of (-)-**5** (0.22 mmol) and 2.2 equiv of **20** (0.22 mmol) relative to **41/43** (0.1 mmol) in the presence of 10 mol % of **38**, and yield refers to the column-purified product. [b]Diastereomeric excess (*de*) was determined by ^{1}H NMR analysis of crude reaction mixture.

5.2.3 Formation of (-)-44:

In the first step, chiral formylcyclopropane (-)-**5** is reacted with one of the amine groups and produced a mono reductive amination product. Further, this mono reductive amination product will attack another chiral formylcyclopropane (-)-**5**, and generate intermediate **A**. After this, intermediate **A** will give intermediate **B** by the protonation of anion **O**. After dehydration of intermediate **B,** it will generate intermediate **C**, which will take hydride and proton from Hantzsch ester to form the product (-)-**44** (Figure 2).

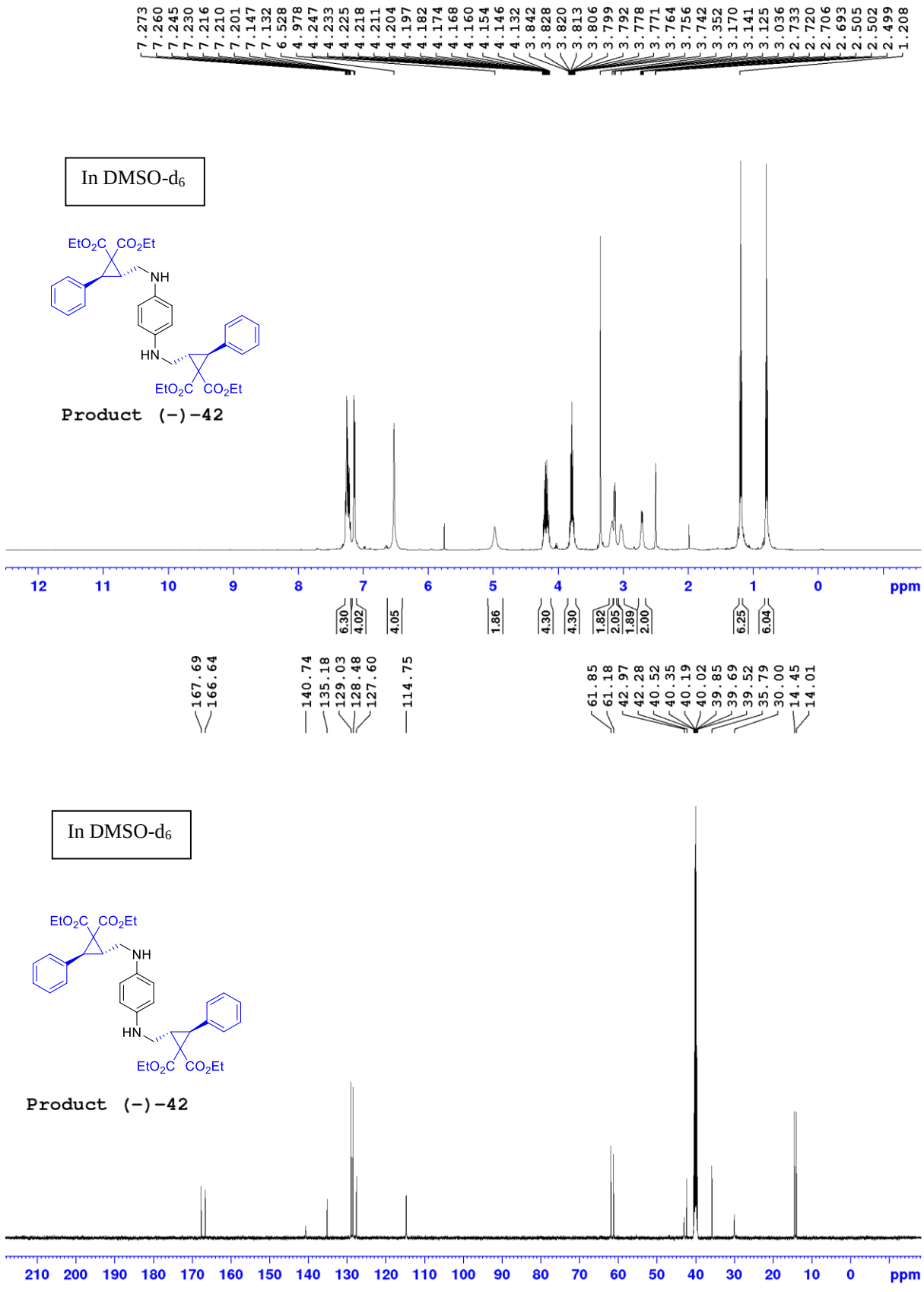


Figure 57. ^{1}H and ^{13}C spectra of the product (-)-**42**.

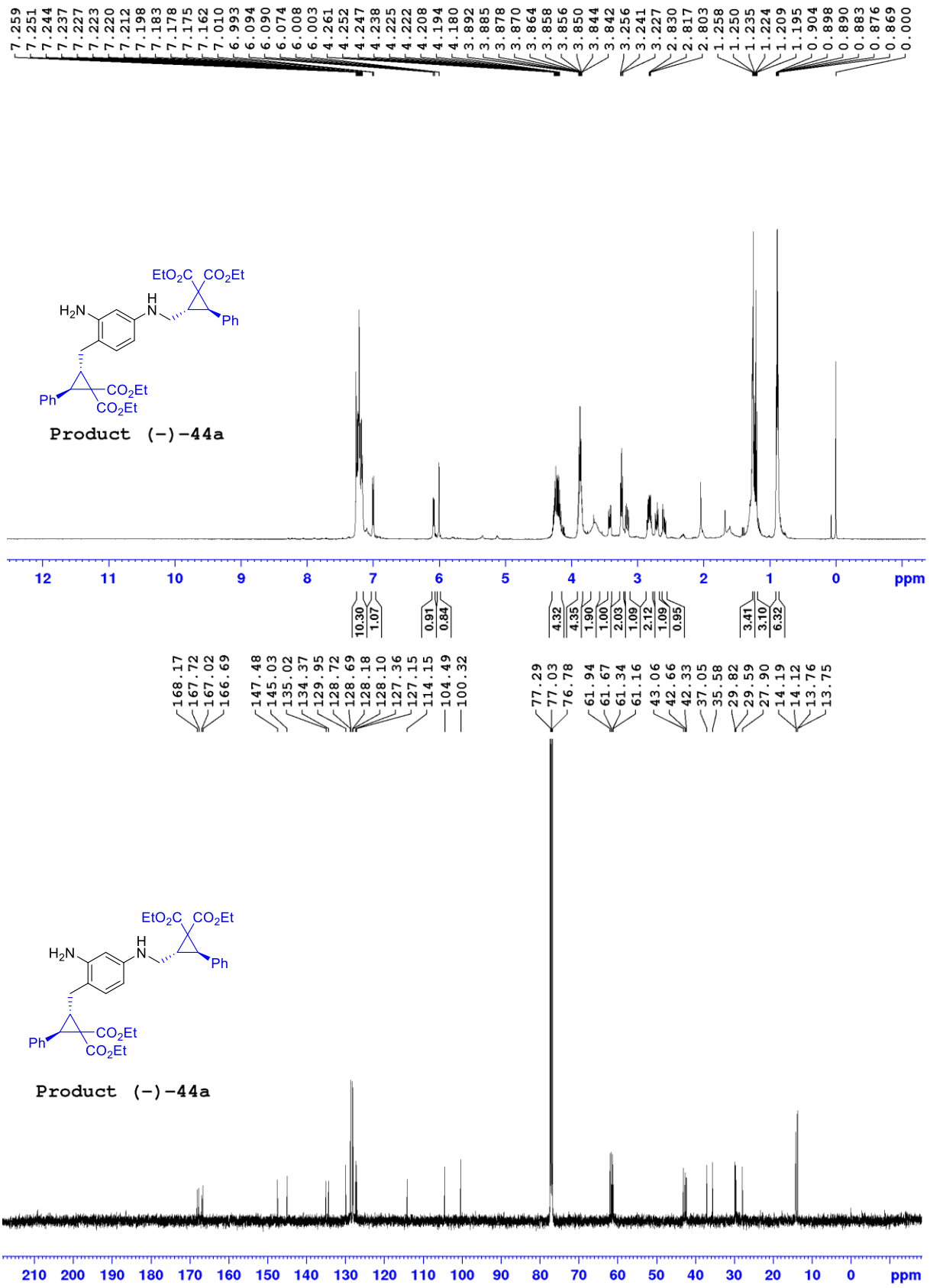
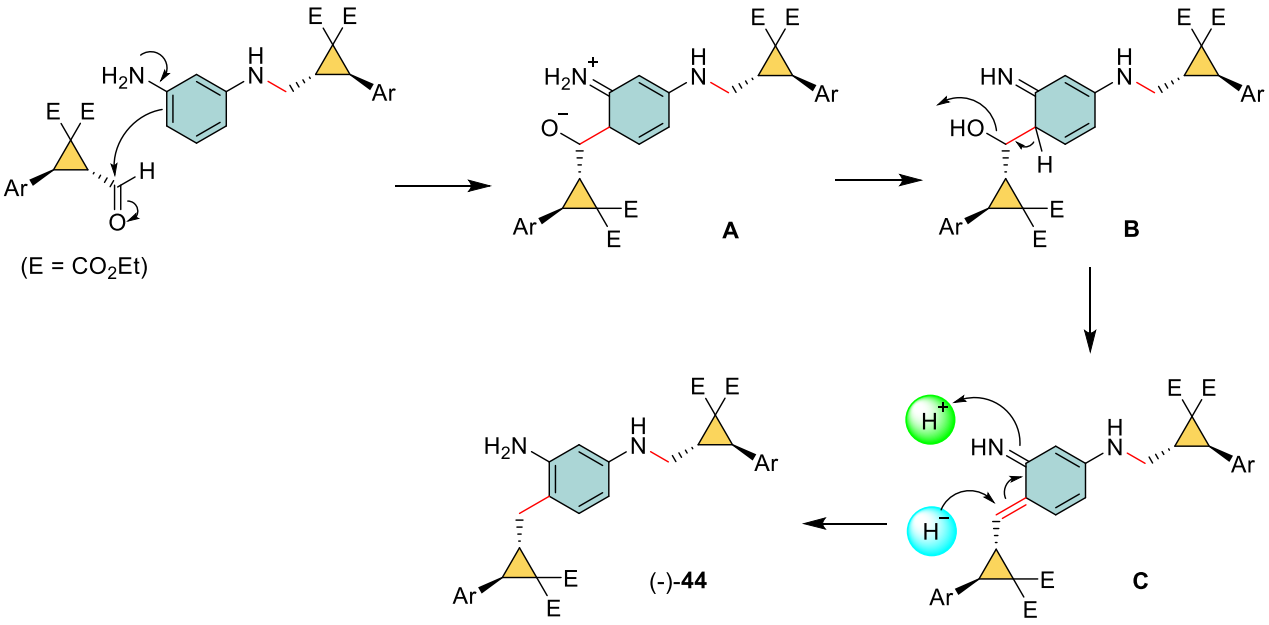
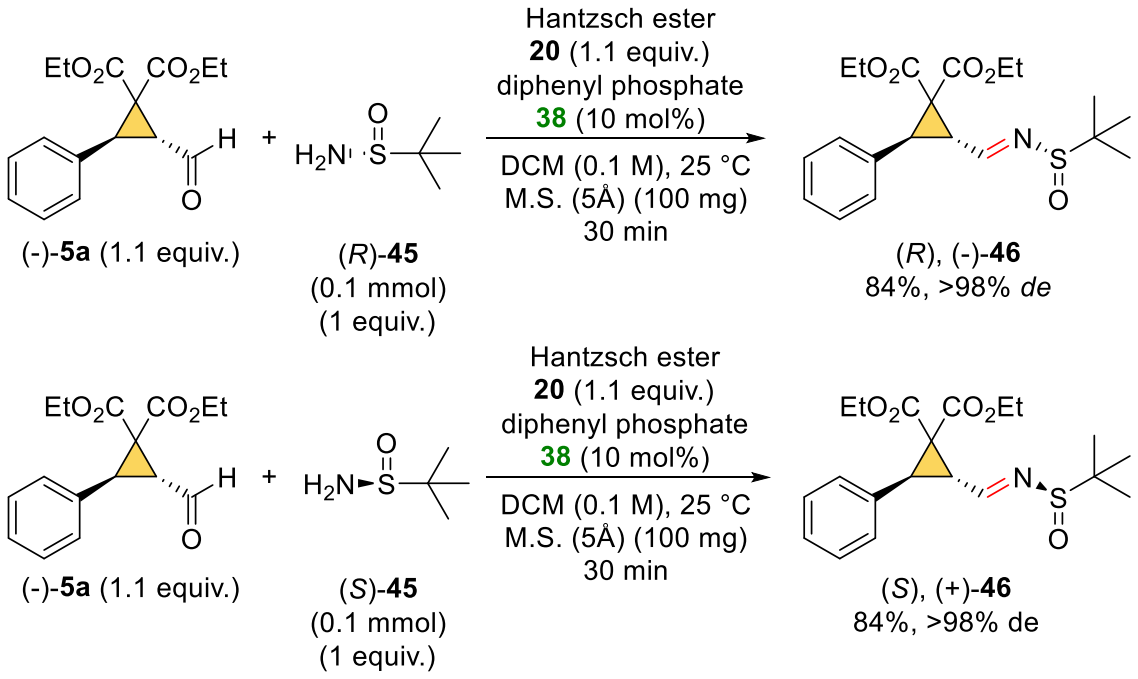


Figure 58. ^{1}H and ^{13}C spectra of the product (-)-**44aa**.

Scheme 26. Mechanism for The Formation of (-)-**44**.



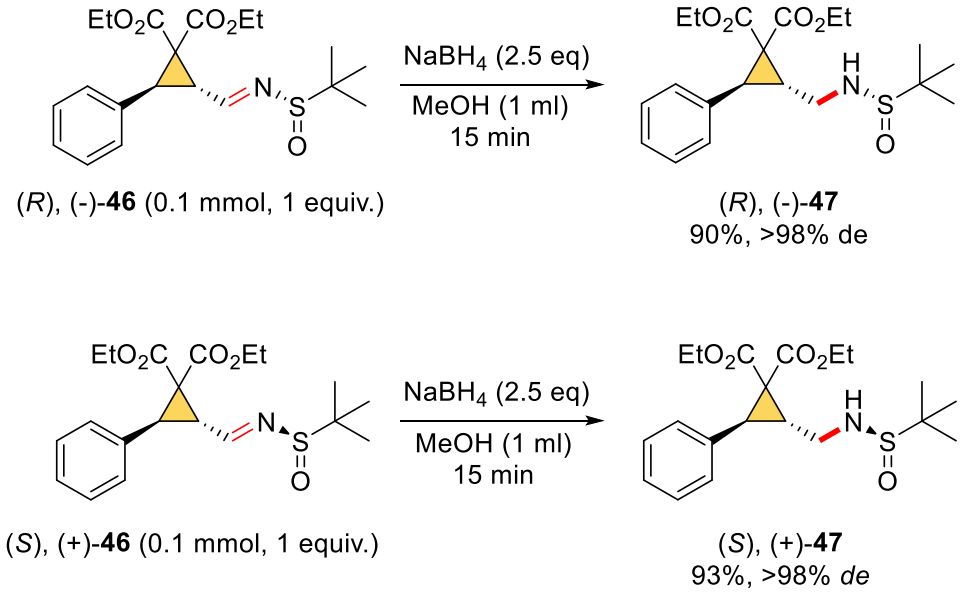
Scheme 27. Reaction Scope with Chiral Amines[a,b]



[a]Reactions were carried out in DCM (1.0 mL) with 1.1 equiv of (-)-**5a** (0.11 mmol) and 1.1 equiv of **20** (0.11 mmol) relative to **39** (0.1 mmol) in the presence of 10 mol % of **32**, and yield refers to the column-purified product. [b]Diastereomeric excess (de) was determined by ^{1}H NMR analysis of the crude reaction mixture.

After the success of a reductive amination reaction with achiral amines, we want to investigate the reactivity towards chiral amines. The reaction of the chiral primary amines (*R*)-(+)-tert-butylsulfinamide **45** and (*S*)-(-)-tert-butylsulfinamide **45** with chiral formylcyclopropane (-)-**5a** in the presence of an acid catalyst and hantzsch ester in DCM at 25 °C for 30 min furnished the imine products (-)-**46** and (+)-**46** in very good yield with >98% *de* (Scheme 2). Notably, here we didn't get the reductive amination product because of the mild nature of Hantzsch ester, which could not reduce this imine product **46** (Scheme 27). ^{1}H and ^{13}C spectra of compound (-)-**46** are shown in Figure 59.

For the reduction of imine product **46**, we treated compounds (-)-**46** and (+)-**46** with $NaBH_4$ (2.5 equiv.) in methanol (1 ml) at 25 °C for 15 min, furnished the reduced product (-)-**47** and (+)-**47** in 90% and 93% yield with >98% *de*, respectively (Equation 8). ^{1}H and ^{13}C spectra of compound (-)-**47** are shown in Figure 60.



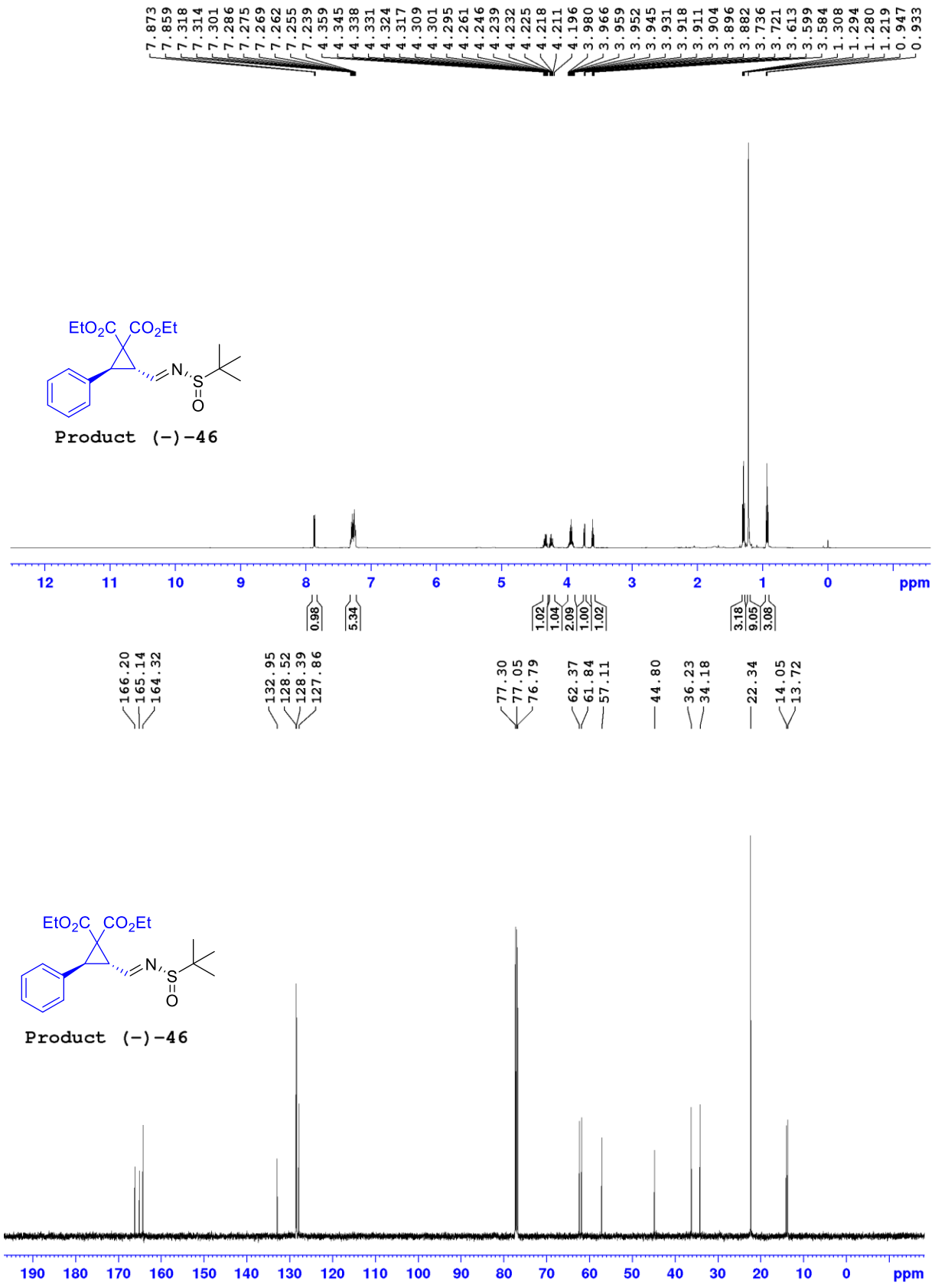


Figure 59. ^{1}H and ^{13}C spectra of the product (-)-**46**.

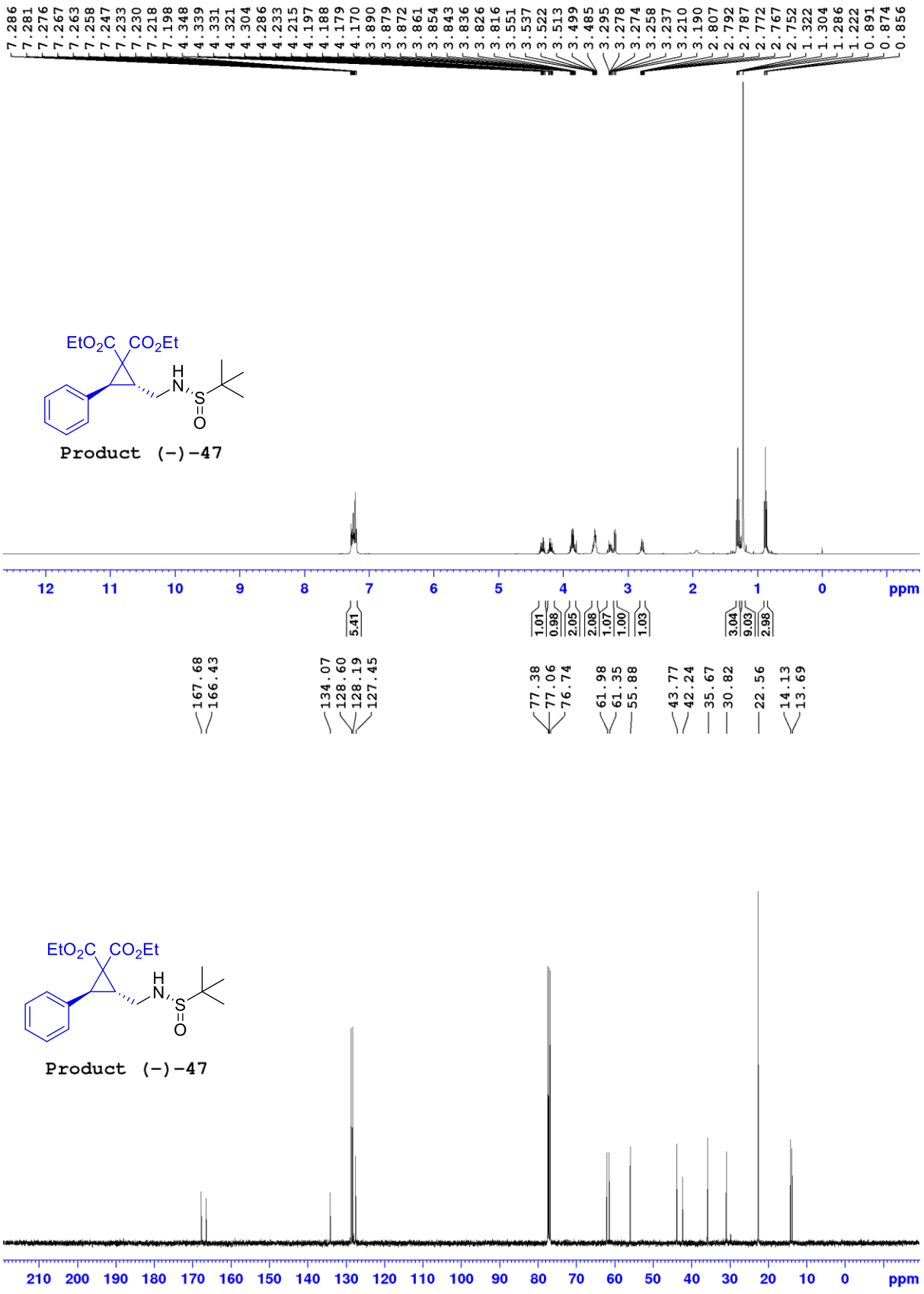
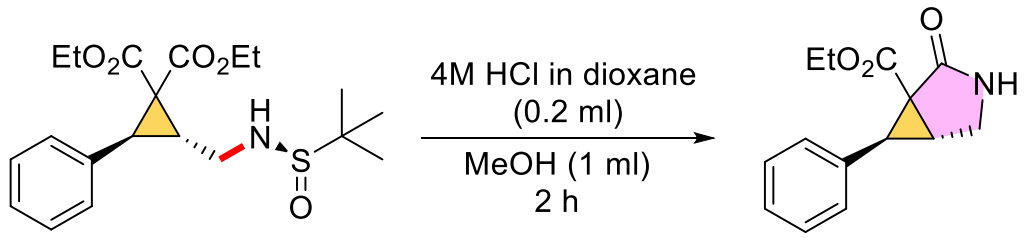


Figure 60. ^{1}H and ^{13}C spectra of the product (-)-**47**.

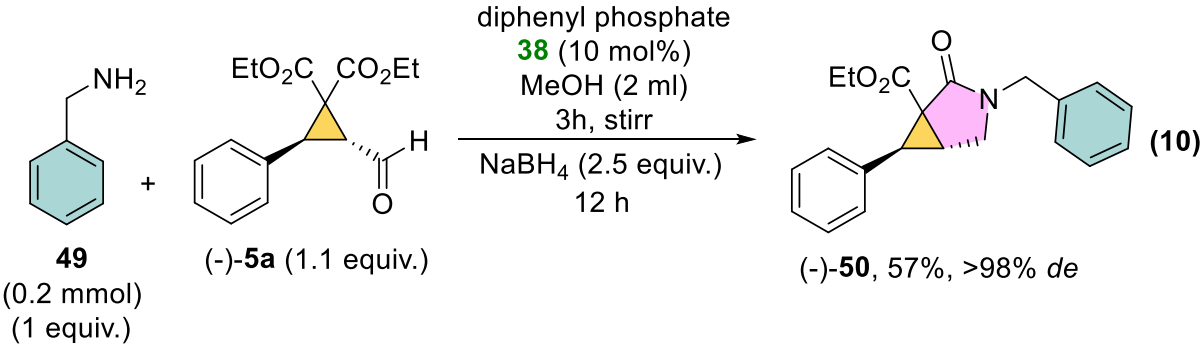
5.2.4 Synthetic Applications of Reductive Amination Reaction:

When we treated the reductive amination product of chiral amine (+)-**47** with 4M hydrochloric acid in dioxane (0.2 ml) in methanol (1 ml) for 2 h, it furnished the azabicyclo product (-)-**48** in 58% yield with >98% *de* (Equation 9). ^{1}H and ^{13}C spectra of compound (-)-**48** are shown in Figure 61.



(+)-**47** (0.2 mmol, 1 equiv.) (-)-**48**, 58%, >98% *de* **(9)**

We also performed a reductive amination reaction with benzylamine **49**. When we treated benzylamine **49** with chiral formylcyclopropane (-)-**5a** in the presence of acid catalyst **38** and Hantzsch ester **20** in DCM solvent then we did not observe the reductive amination product formation. Because of the Hantzsch ester's mild nature, it couldn't reduce the imine product. Further, we tried a reaction between benzylamine **49** and chiral formylcyclopropane (-)-**5a** in the presence of acid catalyst **38** (10 mol%) in methanol for 3 h stirring. After imine formation, we added $NaBH_4$ (2.5 equiv.) in the same reaction mixture. After 12 h of stirring, it furnished the azabicyclo product (-)-**50** instead of the reductive amination product (Equation 10). ^{1}H and ^{13}C spectra of compound (-)-**50** are shown in Figure 62.



49 (0.2 mmol) (1 equiv.) (-)-**5a** (1.1 equiv.) (-)-**50**, 57%, >98% *de* **(10)**

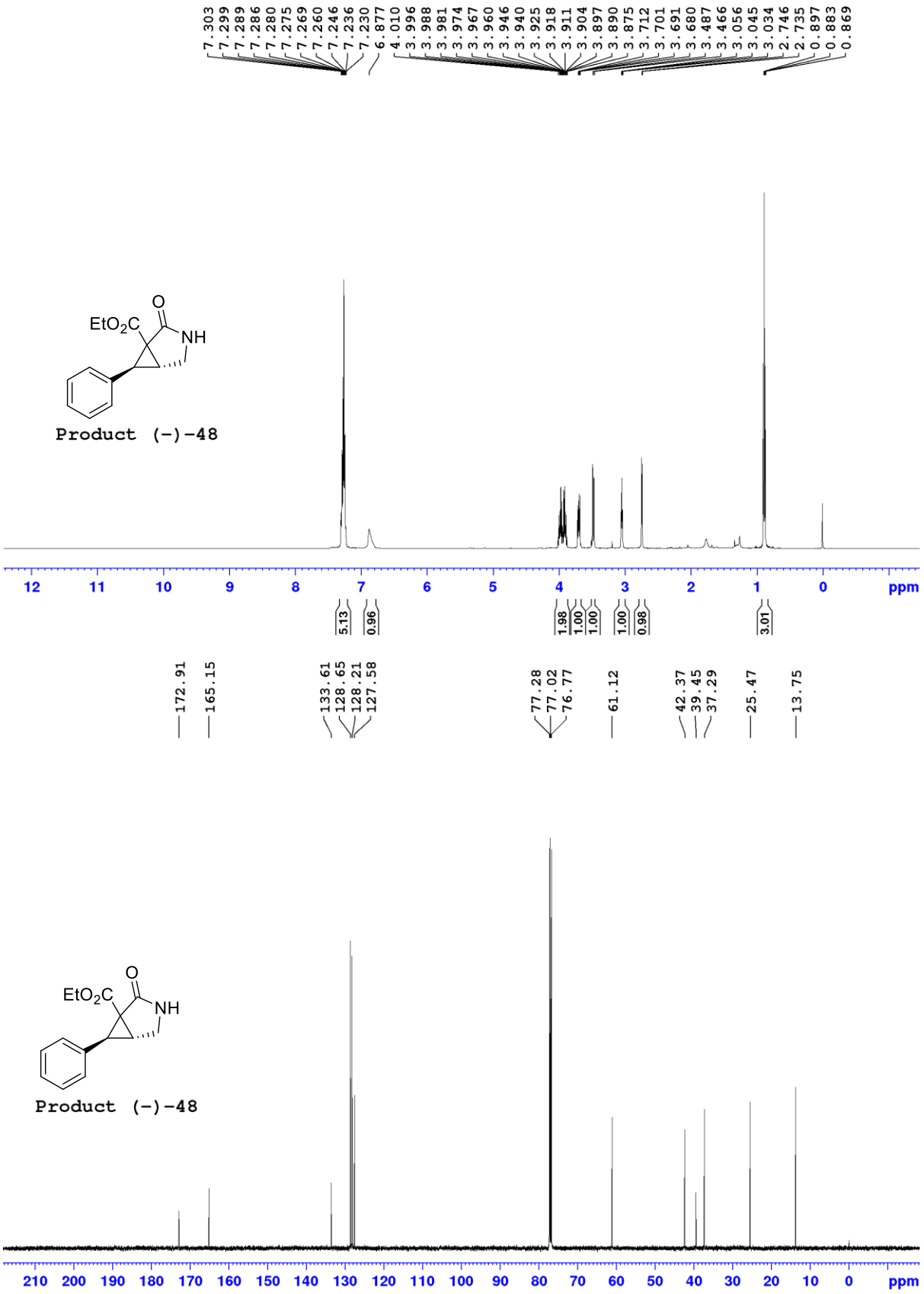
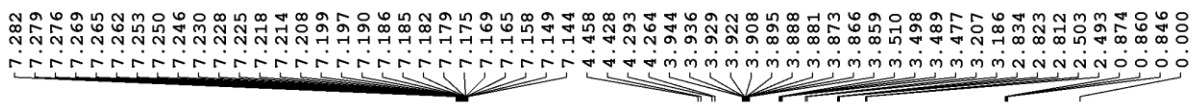
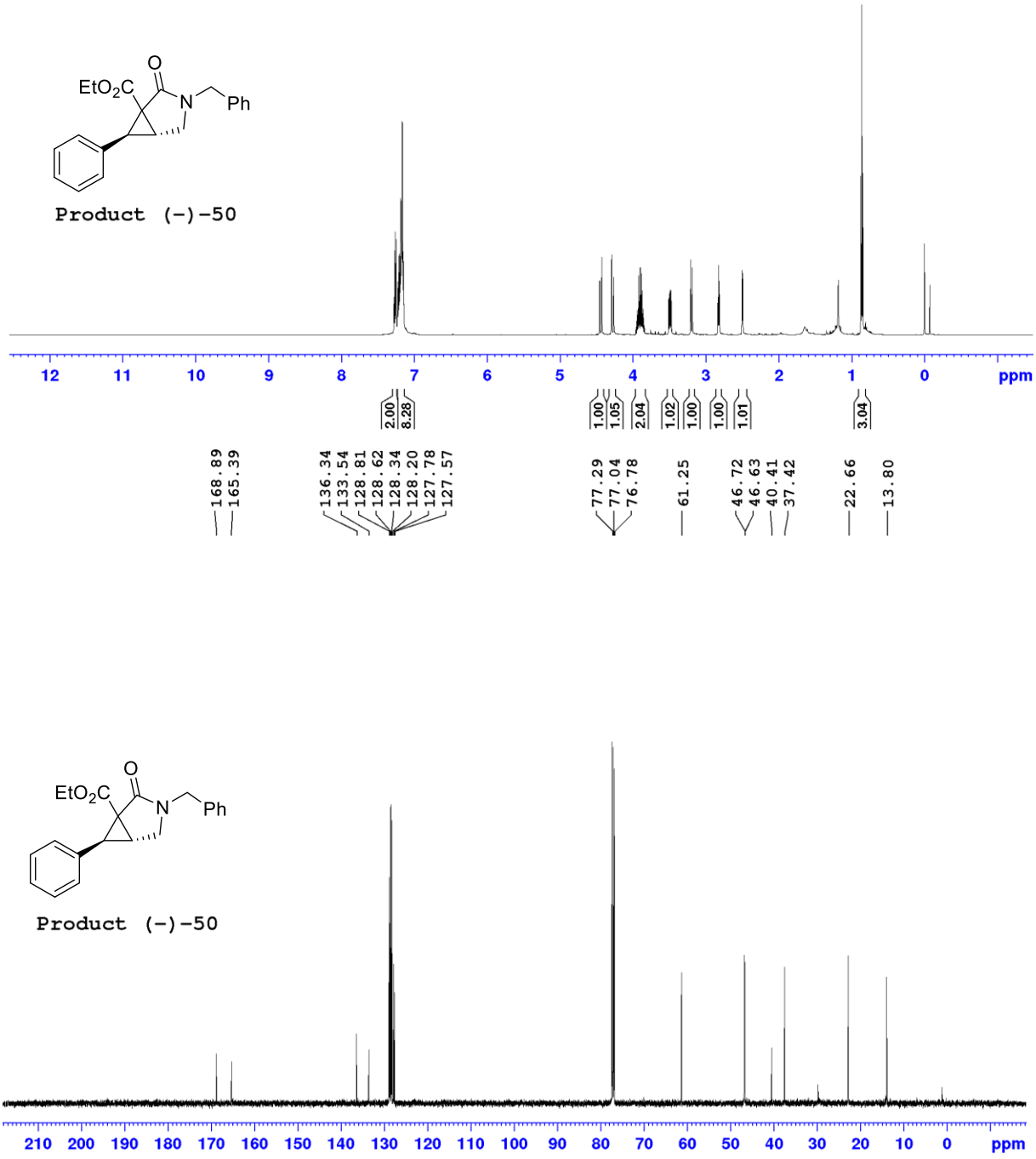


Figure 61. ^{1}H and ^{13}C spectra of the product (-)-**48**.



Figure



62. ^{1}H and ^{13}C spectra of the product (-)-**50**.

The structure and relative stereochemistry of the (-)-**48** was established by IR, NMR, and mass analysis and also finally confirmed by correlation with the X-ray crystal structure of (-)-**48** (Figure 63).

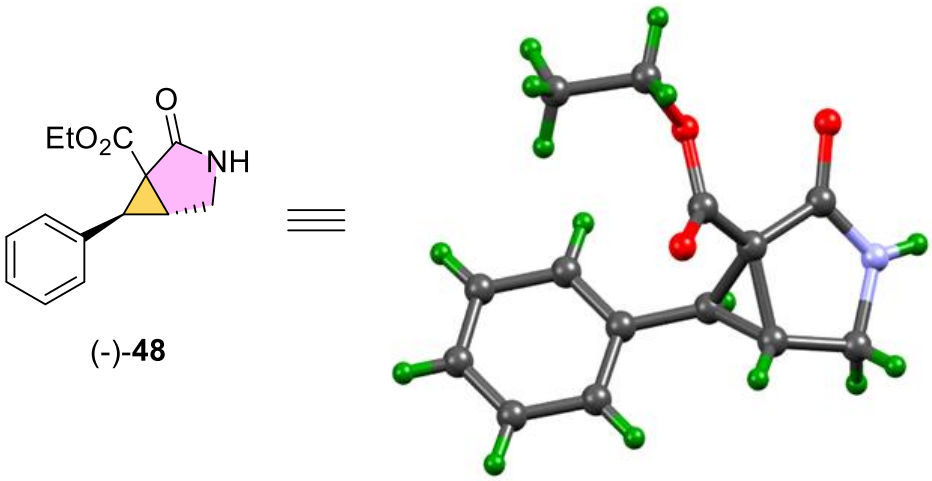


Figure 63. X-ray crystal structure of compound (-)-**48.**

5.3 Conclusions

In conclusion, we have reported the first organocatalytic phosphoric acid-catalyzed reductive amination of chiral formylcyclopropanes for the construction of biologically active and medicinally important chiral formylcyclopropylamines. This protocol could be applied to various formylcyclopropanes, aniline derivatives, and the desired formylcyclopropylamines were obtained in good to excellent yields with high enantioselectivities. Further application of this method to the preparation of other biologically important compounds and detailed mechanistic studies are currently underway in our laboratory and will be reported in due course.

6. Experimental Section

General Experimental Procedures for the Organocatalytic Stereospecific Activation of Donor–Acceptor Cyclopropanes:

General Methods: The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400, 500 MHz and 100, 125 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 were recorded on micromass ESI-TOF MS. IR spectra were recorded on JASCO FT/IR-5300 and Thermo Nicolet FT/IR-5700. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-Kα (λ = 0.71073 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 Mo-Kα fine-focus sealed tube (λ = 0.71073 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.

Materials: All solvents and commercially available chemicals were used as received without further purification unless otherwise stated. The chiral compounds **5**[9,10] and **3**[18] were prepared by following the reported methods.

Olefination of Formylcyclopropane with Meldrum's Acid (Procedure A): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.025 mmol of catalyst (*S*)-proline **21a**, 0.275 mmol of an aldehyde (-)-**5a** and 1.0 mL of anhydrous DCM. Then, 0.25 mmol of Meldrum's acid **19a** was added, and the resulting mixture was allowed to stir for 0.33 h at 25 °C. The olefination product (-)-**Baa** was obtained as a pale yellow liquid in 61% yield after flash column chromatography using short silica gel column packing (eluent: mixture of hexanes/ethyl acetate).

Organocatalytic Reductive Coupling of Formylcyclopropanes with Active Methylene Compounds (Procedure B): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.025 mmol of catalyst **21**, 0.275 mmol of aldehyde (-)-**5**/(-)-**3** and 1.0 mL of anhydrous DCM. Then, 0.275 mmol of Hantzsch ester **20** and 0.25 mmol of active methylene compound **19** were added sequentially to a well-stirred solution and the resulting mixture was allowed to stir for 0.33 to 10.0 h at 25 °C as mentioned in Schemes 12-13/19-20 and Table 3/10. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure coupling products **22/32** were obtained in 75-99% yield (eluent: mixture of hexanes/ethyl acetate).

Derivatization of Reductive Coupling Product 22/32 (Procedure C): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.1 mmol of **22/32**, 0.5 mL of methanol and 0.5 mL of toluene. Then, the reaction mixture was cooled to 0 °C and 1.0 mmol of trimethylsilyldiazomethane ($TMSCHN_2$) was added drop wise for 5 minutes under N_2 atmosphere and the resulting mixture was allowed to stir for 0.5 h. The solvent was evaporated under reduced pressure and the crude reaction mixture was directly loaded onto a silica gel column without aqueous workup, and pure products **23/33** were obtained in 38-98% yield (eluent: mixture of hexanes/ethyl acetate).

$BF_3.OEt_2$-Catalyzed Intramolecular Annulative Ring Opening of Cyclopropanes 22/(-)-**32ha (Procedure D):** To an ordinary glass vial equipped with a magnetic stirring bar were added 0.1 mmol of **22**/(-)-**32ha** and 1.0 mL of anhydrous DCM. Then, 0.03 mmol of $BF_3.OEt_2$ was added and the resulting mixture was allowed to stir for 1.0 to 48.0 h at room temperature as mentioned in Tables 5-6, Equation 4. The pure products **24**/(-)-**33ha** and **25** were obtained by column chromatography by loading the crude reaction mixture directly onto a silica gel column without aqueous workup (eluent: mixture of hexanes/ethyl acetate).

Cs_2CO_3-Catalyzed Intramolecular Annulative Ring Opening of Cyclopropanes 22 (Procedure E): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.1 mmol of **22** and 1.0 mL of DMSO. Then, 0.03 mmol of Cs_2CO_3 was added and the resulting mixture was allowed to stir for 24.0 to 48.0 h at room temperature as mentioned in Table 7. The reaction was quenched with saturated aqueous NH_4Cl and the organic products were extracted three times with Et_2O (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4

and concentrated on rotary evaporator. The pure products **24** and **25** were obtained by column chromatography using mixture of hexanes/ethyl acetate as an eluent.

Michael Reaction of (-)-22aa with MVK (Procedure F): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.03 mmol of (*S*)-proline **21a**, 0.1 mmol of (-)-**22aa** and 1.0 mL of anhydrous DMF. The mixture was stirred for some time and then 0.3 mmol of methyl vinyl ketone (MVK) **26** was added. The resulting mixture was allowed to stir for 24.0 h at room temperature after that the reaction was quenched with saturated aqueous NH_4Cl and the organic products were extracted three times with Et_2O (10 mL). The combined organic layers were washed twice with ice cold water, dried over anhydrous Na_2SO_4 and concentrated on rotary evaporator. The pure product (-)-**27aa** was obtained as a colourless liquid in 71% yield by column chromatography using mixture of hexanes/ethyl acetate as an eluent.

Michael Reactions of (-)-22ha and (+)-22hg with MVK (Procedure G): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.1 mmol of (-)-**22ha** or **(+)-22hg**, 1.0 mL of anhydrous DMF and 0.3 mmol of methyl vinyl ketone (MVK) **26**. The mixture was stirred for some time and then 0.12 mmol of freshly distilled Et_3N was added under N_2 atmosphere. The resulting mixture was allowed to stir for 24.0 h at room temperature under N_2 atmosphere. After completion of the reaction, monitored by TLC, the reaction was quenched with saturated aqueous NH_4Cl and the organic products were extracted three times with Et_2O (10 mL). The combined organic layers were washed twice with ice cold water, dried over anhydrous Na_2SO_4 and concentrated on rotary evaporator. The pure Michael adducts (-)-**27ha** or (+)-**27hg** were obtained as a colourless liquid or pale yellow liquid in 74 and 72% yields, respectively, by column chromatography using mixture of hexanes/ethyl acetate as an eluent.

Michael Reaction of (-)-22ma with MVK (Procedure H): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.06 mmol of Cs_2CO_3, 0.1 mmol of (-)-**22ma** and 0.5 mL of anhydrous DCM. The mixture was stirred for some time and then 0.3 mmol of methyl vinyl ketone (MVK) **26** and 0.2 mmol of $BF_3.OEt_2$ were added sequentially under N_2 atmosphere. The resulting mixture was allowed to stir for 1.5 h at room temperature. After completion of the reaction, monitored by TLC, the reaction was quenched with saturated aqueous NH_4Cl and the organic products were extracted three times with Et_2O (10 mL). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4 and concentrated on rotary evaporator. The pure product (-)-**27ma** was obtained as a pale yellow

liquid in 85% yield by column chromatography using mixture of hexanes/ethyl acetate as an eluent.

Michael Reaction of (-)-22aa with Acrolein (Procedure I): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.1 mmol of (-)-**22aa**, 1.0 mL of anhydrous DMF and 0.3 mmol of acrolein **28**. The mixture was stirred for some time and then 0.03 mmol of freshly distilled Et_3N was added under N_2 atmosphere. The resulting mixture was allowed to stir for 48.0 h at room temperature under N_2 atmosphere. After completion of the reaction, monitored by TLC, the reaction was quenched with saturated aqueous NH_4Cl and the organic products were extracted three times with Et_2O (10 mL). The combined organic layers were washed twice with ice cold water, dried over anhydrous Na_2SO_4 and concentrated on rotary evaporator. The pure product (-)-**29aa** was obtained as a colourless liquid in 47% yield by column chromatography using mixture of hexanes/ethyl acetate as an eluent.

Bromination of 22ia (Procedure J): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.1 mmol of (-)-**22ia**, 0.12 mmol of *N*-bromosuccinimide (**30**) and 1.0 mL of anhydrous DCM. Then, 0.12 mmol of $BF_3.OEt_2$ was added and the resulting mixture was allowed to stir for 0.25 h at room temperature. The pure product (-)-**31ia** was obtained in 80% yield after column chromatography by loading the crude reaction mixture directly onto a silica gel column without aqueous workup (eluent: mixture of hexanes/ethyl acetate).

Reduction of Chiral Formylcyclopropanes (-)-5a, (-)-5f, (-)-3a, (-)-3e, (-)-3f, (-)-3i, and (-)-3l/ Reductive Coupling Product (-)-33aa (Procedure K): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.1 mmol of (-)-**5a**, (-)-**5f**, (-)-**3a**, (-)-**3e**, (-)-**3f**, (-)-**3i**, and (-)-**3l**/(-)-**33aa** and 1.0 mL of methanol. To this solution, 0.25 mmol of $NaBH_4$ was added at 0 °C/25 °C and the resulting mixture was allowed to stir for 10 min at the same temperature. Then, the reaction was quenched with saturated aqueous NH_4Cl and the organic products were extracted three times with Et_2O (10 mL). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4 and concentrated on rotary evaporator. The pure products (-)-**5a′**, (-)-**5f′**, (-)-**3a′**, (-)-**3e′**, (-)-**3f′**, (-)-**3i′**, and (-)-**3l′**/(-)-**35aa** (Equation 5) was obtained as a colourless liquid by column chromatography using mixture of hexanes/ethyl acetate as an eluent.

Wittig Reaction of Formylcyclopropane (-)-5i (Procedure L): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.1 mmol of (-)-**5i** and 1.0 mL of anhydrous DCM. Then, 0.12 mmol of $Ph_3P{=}CHCO_2Et$ was added and the resulting mixture was allowed to

stir for 10 min at room temperature. The pure product (-)-**5i′** was obtained in 85% yield as a colorless liquid after column chromatography by loading the crude reaction mixture directly onto a silica gel column without aqueous workup (eluent: mixture of hexanes/ethyl acetate).

Oxidative Bromination of (-)-22hj (Procedure M): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.15 mmol of (-)-**22hj** and 3.0 mL of methanol. Then, 0.165 mmol of NH_4Br and 0.165 mmol of oxone were added sequentially and the resulting mixture was allowed to stir for 3 h at room temperature. After completion of the reaction, monitored by TLC, the solvent was evaporated under reduced pressure and the product mixture was extracted with ethyl acetate. The combined organic extracts were treated with 5% aqueous $Na_2S_2O_3$ solution and washed with water. The organic components were dried over anhydrous Na_2SO_4 and the pure product (-)-**31hj** was obtained in 83% yield as a colorless liquid after column chromatography (eluent: mixture of hexanes/ethyl acetate).

Wittig Reaction of (-)-33aa (Procedure N): In a 10 mL round-bottom flask equipped with a magnetic stirring bar, methyl triphenylphosphonium bromide (0.8 mmol) and *t*BuOK (0.8 mmol) was added to dry benzene at 25 °C under nitrogen atmosphere and stirred for 30 min. The compound (-)-**33aa** (0.2 mmol) dissolved in dry benzene (1.0 mL) was added dropwise at 25 °C and the reaction mixture was stirred at 40 °C for 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 × 10 mL). The combined organic layers were dried (Na_2SO4) and concentrated. Pure product (-)-**36aa** and (-)-**36aa′** as a mixture of epimers (1.5:1) in 69% yield was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Organocatalytic Reductive Amination of Formylcyclopropanes with Aromatic Amine or Chiral Amine Compounds (Procedure O): To an ordinary glass vial equipped with a magnetic stirring bar was added 0.01 mmol of catalyst **38**, 0.11 mmol of aldehyde (-)-**5** or (-)-**3a** and 1.0 mL of anhydrous DCM. Then, 0.11 mmol of Hantzsch ester **20** and 0.1 mmol of aromatic amines **37**/**41**/**43** or chiral amines **45** were added sequentially to a well-stirred solution and the resulting mixture was allowed to stir for 0.5 to 12 h at 25 °C as mentioned in Scheme 24, 25, 27, Table 12, and Equation 7. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure coupling products **39**/**40**/**42**/**44** or **46** were obtained in 33-98% yield (eluent: mixture of hexanes/ethyl acetate).

Reduction of Imine Product 46 (Procedure P): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.1 mmol of **46** and 1.0 mL of methanol. To this solution, 0.25 mmol of $NaBH_4$ was added at 25 °C and the resulting mixture was allowed to stir for 15 min at the same temperature. Then, the reaction was quenched with saturated aqueous NH_4Cl, and the organic products were extracted three times with Et_2O (10 mL). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The pure Products **47** (Equation 8) were obtained as a colorless liquid in 90%, and 93% yield, respectively by column chromatography using a mixture of hexanes/ethyl acetate as an eluent.

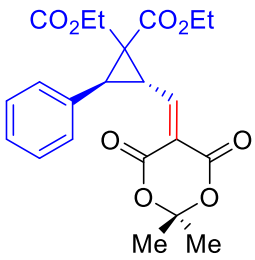
Formation of Azabicyclo Compound (-)-48 (Procedure Q): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.2 mmol of (+)-**47** and 1.0 mL of methanol. To this solution, 0.2 ml 4M HCl in dioxane was added at 25 °C and the resulting mixture was allowed to stir for 2 h at the same temperature. Then, the reaction was quenched with saturated aqueous $NaHCO_3$, and the organic products were extracted with ethyl acetate (10 mL). The combined organic layers were washed with water, and brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The pure Product (-)-**48** (Equation 9) was obtained as a colorless liquid in 58% yield by column chromatography using a mixture of MeOH/$CHCl_3$ as an eluent.

Formation of Azabicyclo Compound (-)-50 (Procedure R): To an ordinary glass vial equipped with a magnetic stirring bar were added 0.2 mmol of **49**, 0.22 mmol of (-)-**5aa**, and 0.02 mmol of catalyst **38** in 2.0 mL of methanol and the resulting mixture was allowed to stir for 3 h at 25 °C. To this reaction solution, 2.5 equivalent $NaBH_4$ was added at 25 °C and the resulting mixture was allowed to stir for 12 h at the same temperature. Then, the reaction was quenched with saturated aqueous NH_4Cl, and the organic products were extracted three times with Et_2O (10 mL). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The pure Product (-)-**50** (Equation 10) was obtained as a colorless liquid in 57% yield by column chromatography using a mixture of hexanes/ethyl acetate as an eluent.

Chapter 3:

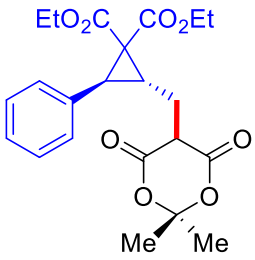
Materials: The chiral compounds **5a** (98% *ee*),[9,10a] **5b** (95% *ee*),[10b] **5c** (90% *ee*),[9,10a] **5d** (98% *ee*),[9,10a] **5e** (98% *ee*),[9,10a] **5f** (86% *ee*),[9,10a] **5g** (95% *ee*),[10b] **5h** (99% *ee*),[9,10a] **5i** (98% *ee*),[9,10a] **5j** (94% *ee*)[9,10a] were prepared by following the reported methods.

Diethyl (2*R*,3*S*)-2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**Baa**): The compound was prepared following the procedure **A** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 61% (63.5 mg); $[\alpha]_D^{25}$ = –41.1° (*c* = 0.7, $CHCl_3$, 98% *ee* and >99:1 *dr*); IR (Neat): ν_{max} 2988, 2927, 2854, 1726, 1620, 1445, 1371, 1275, 1182, 1106, 1020, 926, 860, 798, 743, 697, 641 and 544 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.63 (1H, d, *J* = 11.0 Hz, olefinic-*H*), 7.35-7.26 (5H, m), 4.82 (1H, dd, *J* = 11.0, 7.5 Hz), 4.39-4.34 (1H, m), 4.32-4.26 (1H, m), 3.97-3.87 (2H, m), 3.68 (1H, d, *J* = 7.5 Hz), 1.78 (3H, s), 1.77 (3H, s), 1.31 (3H, t, *J* = 7.0 Hz), 0.91 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.3 (C, O-*C*=O), 164.7 (C, O-*C*=O), 161.1 (C, O-*C*=O), 160.7 (CH), 160.0 (C, O-*C*=O), 132.3 (C), 128.6 (2 x CH), 128.5 (2 x CH), 128.0 (CH), 119.3 (C), 105.1 (C, O-*C*-O), 62.5 (CH_2), 61.9 (CH_2), 47.2 (C), 39.8 (CH), 31.3 (CH), 27.9 (CH_3), 27.7 (CH_3), 14.0 (CH_3), 13.6 (CH_3); LCMS m/z 417.35 (M + H^+), Calcd for $C_{22}H_{24}O_8H$ 417.1549; Anal. Calcd for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.32; H, 5.86. See Supporting Information-I for 2D NMR spectra and analysis for further support[60].



Baa

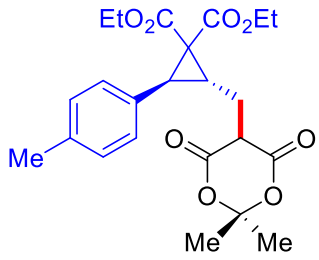
Diethyl (2*R*,3*S*)-2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (22aa): The title compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 94% (98.33 mg); $[\alpha]_D^{25}$ = –45.1° (*c* = 0.1, $CHCl_3$, >99% *ee* and >99:1 *dr*); IR (Neat): ν_{max} 2985, 2936, 1786, 1748, 1598, 1499, 1446, 1373, 1295, 1205, 1122, 1024, 979, 859, 743 and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.26-7.25 (2H, m), 7.23-7.21 (3H, m), 4.36-4.29 (1H, m), 4.29-4.22 (1H, m), 3.89-3.81 (2H, m), 3.72 (1H, t, *J* = 5.0 Hz), 3.20 (1H, d, *J* = 8.0 Hz), 2.90 (1H, br q, *J* = 7.0 Hz), 2.42-2.31 (2H, m), 1.82 (3H, s), 1.77 (3H, s), 1.31 (3H, t, *J* = 7.0 Hz), 0.87 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 166.5 (C, O-*C*=O), 165.0 (C, O-*C*=O), 164.9 (C, O-*C*=O), 134.4 (C), 128.7 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 105.2 (C), 62.0 (CH_2), 61.2 (CH_2), 45.9 (CH), 43.3



(-)-**22aa**

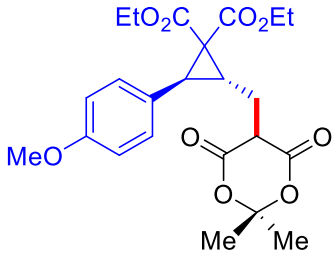
(C), 36.7 (CH), 28.5 (CH_3), 27.8 (CH_3), 26.7 (CH), 24.9 (CH_2), 14.1 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{26}O_8H$ 419.1706; Found 419.1700.

Diethyl (2*R*,3*S*)-2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)-3-(*p*-tolyl)cyclopropane-1,1-dicarboxylate (22ab): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a colorless liquid; Yield: 90% (97.3 mg); $[\alpha]_D^{25}$ = –45.1° (*c* = 0.16, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2982, 2928, 1784, 1743, 1719, 1445, 1369, 1288, 1200, 1180, 1096, 976 and 752 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 7.11 (2H, d, *J* = 8.0 Hz), 7.07 (2H, d, *J* = 8.0 Hz), 4.37-4.29 (1H, m), 4.29-4.21 (1H, m), 3.94-3.82 (2H, m), 3.71 (1H, br t, *J* = 7.0 Hz), 3.17 (1H, d, *J* = 8.0 Hz), 2.88 (1H, br q, *J* = 10 Hz), 2.43-2.33 (2H, m), 2.30 (3H, s, Ar-C*H*$_3$), 1.83 (3H, s), 1.78 (3H, s), 1.32 (3H, t, *J* = 7.2 Hz), 0.92 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.8 (C, O-*C*=O), 166.6 (C, O-*C*=O), 165.0 (C, O-*C*=O), 164.9 (C, O-*C*=O), 136.9 (C), 131.2 (C), 128.8 (2 x CH), 128.5 (2 x CH), 105.1 (C), 61.9 (CH_2), 61.2 (CH_2), 45.9 (CH), 43.1 (C), 36.4 (CH), 28.4 (CH_3), 27.8 (CH_3), 26.6 (CH), 24.8 (CH_2), 21.0 (CH_3), 14.1 (CH_3), 13.7 (CH_3); LCMS m/z 433.30 ($M + H^+$), Calcd for $C_{23}H_{28}O_8H$ 433.1862; Anal. Calcd for $C_{23}H_{28}O_8$: C, 63.88; H, 6.53. Found: C, 63.76; H, 6.58.



(-)-**22ab**

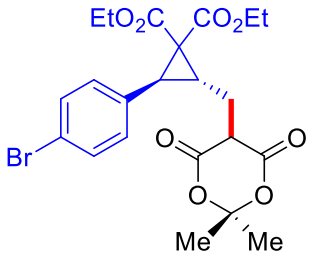
Diethyl (2*R*,3*S*)-2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)-3-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (22ac): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a colorless liquid; Yield: 75% (84.10 mg); $[\alpha]_D^{25}$ = –42.9° (*c* = 0.48, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2982, 2932, 1786, 1720, 1613, 1517, 1442, 1369, 1292, 1248, 1215, 1176, 1123, 1096, 1030, 840, 748 and 667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.15 (2H, d, *J* = 8.5 Hz), 6.80 (2H, d, *J* = 8.5 Hz), 4.36-4.29 (1H, m), 4.29-4.22 (1H, m), 3.94-3.83 (2H, m), 3.78 (3H, s, Ar-OC*H*$_3$), 3.71-3.69 (1H, m), 3.15 (1H, d, *J* = 8.0 Hz), 2.87 (1H, q, *J* = 8.0 Hz), 2.43-2.37 (1H, m), 2.35-2.31 (1H, m), 1.83 (3H, s), 1.78 (3H, s), 1.32 (3H, t, *J* = 7.0 Hz), 0.93 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.8 (C, O-*C*=O), 166.6 (C, O-*C*=O), 165.0 (C, O-*C*=O), 164.9 (C, O-*C*=O), 158.8 (C), 129.7 (2 x CH), 126.3 (C), 113.5 (2 x CH), 105.1 (C), 61.9 (CH_2), 61.2 (CH_2), 55.2 (CH_3, O*C*H$_3$), 45.9 (CH), 43.2 (C), 36.1 (CH), 28.4 (CH_3), 27.9 (CH_3), 26.6 (CH), 24.8



(-)-**22ac**

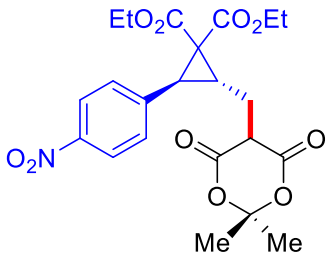
(CH_2), 14.1 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{28}O_9H$ 449.1812; Found 449.1814.

Diethyl (2*S*,3*R*)-2-(4-bromophenyl)-3-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)cyclopropane-1,1-dicarboxylate (22ad): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a colorless liquid; Yield: 95% (118.12 mg); $[\alpha]_D^{25}$ = –37.5° (*c* = 0.11, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2981, 2925, 2853, 1784, 1720, 1491, 1444, 1369, 1289, 1203, 1072, 1010, 979, 841, 751, 667 and 545 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38 (2H, br d, *J* = 8.4 Hz), 7.09 (2H, br d, *J* = 8.4 Hz), 4.36-4.28 (1H, m), 4.28-4.20 (1H, m), 3.96-3.82 (2H, m), 3.71-3.68 (1H, m), 3.13 (1H, d, *J* = 8.0 Hz), 2.84 (1H, q, *J* = 7.4 Hz), 2.41-2.28 (2H, m), 1.82 (3H, s), 1.77 (3H, s), 1.31 (3H, t, *J* = 7.2 Hz), 0.94 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.5 (C, O-*C*=O), 166.4 (C, O-*C*=O), 165.0 (C, O-*C*=O), 164.9 (C, O-*C*=O), 133.5 (C), 131.3 (2 x CH), 130.4 (2 x CH), 121.3 (C), 105.3 (C), 62.1 (CH_2), 61.5 (CH_2), 45.8 (CH), 43.2 (C), 36.0 (CH), 28.5 (CH_3), 27.8 (CH_3), 26.7 (CH), 24.8 (CH_2), 14.1 (CH_3), 13.8 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{25}BrO_8H$ 497.0811; Found 497.0813.



(-)-**22ad**

Diethyl (2*R*,3*S*)-2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)-3-(4-nitrophenyl)cyclopropane-1,1-dicarboxylate (22ae): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 2.5:7.5) and isolated as a pale yellow liquid; Yield: 94% (108.91 mg); $[\alpha]_D^{25}$ = –33.2° (*c* = 0.19, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 3021, 2927, 2855, 1789, 1746, 1602, 1523, 1348, 1294, 1215, 744 and 667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.13 (2H, br d, *J* = 8.8 Hz), 7.39 (2H, br d, *J* = 8.8 Hz), 4.39-4.23 (2H, m), 3.97-3.90 (1H, m), 3.89-3.82 (1H, m), 3.74 (1H, t, *J* = 5.6 Hz), 3.25 (1H, d, *J* = 8.0 Hz), 2.90 (1H, q, *J* = 7.6 Hz), 2.39-2.36 (2H, m), 1.84 (3H, s), 1.78 (3H, s), 1.32 (3H, t, *J* = 7.2 Hz), 0.94 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.1 (C, O-*C*=O), 166.0 (C, O-*C*=O), 164.9 (C, O-*C*=O), 164.8 (C, O-*C*=O), 147.2 (C), 142.2 (C), 129.6 (2 x CH), 123.4 (2 x CH), 105.4 (C), 62.4 (CH_2), 61.7 (CH_2), 45.7 (CH), 43.7 (C), 36.1 (CH), 28.5 (CH_3), 28.1 (CH_3), 26.7



(-)-**22ae**

(CH), 24.8 (CH_2), 14.1 (CH_3), 13.8 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{25}NO_{10}H$ 464.1557; Found 464.1557.

Diethyl (2*R*,3*S*)-2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)-3-(3-nitrophenyl)cyclopropane-1,1-dicarboxylate (22af): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 2.5:7.5) and isolated as a colorless liquid; Yield: 93% (107.74 mg); $[\alpha]_D^{25}$ = –32.3° (*c* = 0.10, $CHCl_3$, 86% *ee* and >99:1 *dr*); IR (Neat): ν_{max} 3021, 2982, 1786, 1741, 1721, 1531, 1445, 1346, 1291, 1200, 1096, 748, 685 and 667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.07 (1H, d, *J* = 6.8 Hz), 8.06 (1H, s), 7.55 (1H, d, *J* = 7.6 Hz), 7.44 (1H, t, *J* = 8.0 Hz), 4.38-4.21 (2H, m), 3.94-3.84 (2H, m), 3.81 (1H, t, *J* = 5.2 Hz), 3.26 (1H, d, *J* = 8.0 Hz), 2.84 (1H, q, *J* = 7.2 Hz), 2.42-2.31 (2H, m), 1.84 (3H, s), 1.78 (3H, s), 1.31 (3H, t, *J* = 7.2 Hz), 0.93 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.0 (C, O-*C*=O), 166.1 (C, O-*C*=O), 164.9 (C, O-*C*=O), 164.8 (C, O-*C*=O), 147.9 (C), 136.8 (C), 134.8 (CH), 129.1 (CH), 123.7 (CH), 122.3 (CH), 105.3 (C), 62.2 (CH_2), 61.6 (CH_2), 45.6 (CH), 43.0 (C), 35.9 (CH), 28.3 (CH_3), 27.9 (CH_3), 26.5 (CH), 24.7 (CH_2), 14.0 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{25}NO_{10}H$ 464.1557; Found 464.1557.

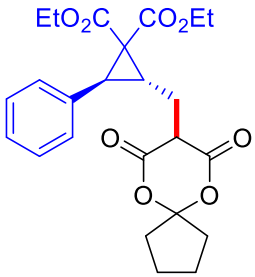
(-)-**22af**

Diethyl (2*R*,3*S*)-2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)-3-(2-nitrophenyl)cyclopropane-1,1-dicarboxylate (22ag): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 2.5:7.5) and isolated as a pale yellow liquid; Yield: 93% (107.8 mg); $[\alpha]_D^{25}$ = +31.7° (*c* = 0.68, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 3025, 2984, 2938, 1784, 1743, 1721, 1525, 1346, 1289, 1205, 1107, 1016, 980, 851, 748, 704 and 667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.96 (1H, dd, *J* = 10.0, 1.0 Hz), 7.55 (1H, dt, *J* = 7.5, 1.0 Hz), 7.44-7.40 (2H, m), 4.38-4.33 (1H, m), 4.32-4.25 (1H, m), 3.92-3.86 (1H, m), 3.84-3.78 (1H, m), 3.79 (1H, t, *J* = 6.0 Hz), 3.67 (1H, d, *J* = 8.5 Hz), 2.81 (1H, q, *J* = 7.5 Hz), 2.43 (2H, t, *J* = 6.0 Hz), 1.86 (3H, s), 1.79 (3H, s), 1.33 (3H, t, *J* = 7.0 Hz), 0.94 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.1 (C, O-*C*=O), 166.6 (C, O-*C*=O), 165.1 (C, O-*C*=O), 165.0 (C, O-*C*=O), 150.0 (C), 133.1 (CH), 131.6 (CH), 130.5 (C), 128.6 (CH), 124.6 (CH), 105.4 (C), 62.1 (CH_2), 61.7 (CH_2), 45.8 (CH), 42.1 (C), 34.8 (CH), 28.8 (CH_3), 28.5 (CH_3), 26.5 (CH), 24.3

(+)-**22ag**

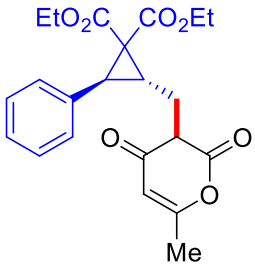
(CH_2), 14.1 (CH_3), 13.6 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{25}NO_{10}H$ 464.1557; Found 464.1557.

Diethyl (2*R*,3*S*)-2-((7,9-dioxo-6,10-dioxaspiro[4.5]decan-8-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (22ba): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 2.5:7.5) and isolated as a colorless liquid; Yield: 94% (104.45 mg); $[\alpha]_D^{25}$ = –37.8° (*c* = 0.54, $CHCl_3$, >99:1 *dr*); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.22 (5H, m), 4.37-4.21 (2H, m), 3.90-3.82 (2H, m), 3.73 (1H, dd, *J* = 6.8, 6.4 Hz), 3.21 (1H, d, *J* = 8.0 Hz), 2.96-2.90 (1H, m), 2.42-2.35 (1H, m), 2.30-2.17 (5H, m), 2.00-1.82 (4H, m), 1.32 (3H, t, *J* = 7.2 Hz), 0.87 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.8 (C, O-*C*=O), 166.6 (C, O-*C*=O), 165.4 (C, O-*C*=O), 165.3 (C, O-*C*=O), 134.4 (C), 128.7 (2 x CH), 128.2 (2 x CH), 127.3 (CH), 114.4 (C), 62.0 (CH_2), 61.3 (CH_2), 47.1 (CH), 43.3 (C), 39.2 (CH_2), 38.0 (CH_2), 36.7 (CH), 27.8 (CH), 24.5 (CH_2), 24.0 (CH_2), 22.5 (CH_2), 14.2 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{28}O_8H$ 445.1862; Found 445.1862.



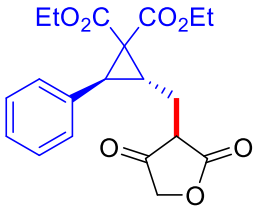
(-)-**22ba**

Diethyl (2*R*,3*S*)-2-((4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (22ca): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (4:6 to 5:5) and isolated as a pale yellow liquid; Yield: 82% (82.04 mg); $[\alpha]_D^{25}$ = –49.4° (*c* = 1.16, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2977, 2925, 1722, 1665, 1582, 1500, 1443, 1412, 1371, 1288, 1252, 1226, 1190, 1112, 1025, 994, 911, 859, 828, 751 and 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.23-7.17 (5H, m), 6.09 (1H, s), 4.41-4.33 (1H, m), 4.31-4.24 (1H, m), 3.88-3.78 (2H, m), 3.22 (1H, d, *J* = 8.0 Hz), 2.94 (1H, q, *J* = 7.5 Hz), 2.84 (1H, dd, *J* = 14.5, 7.0 Hz), 2.63 (1H, dd, *J* = 14.5, 7.0 Hz), 2.16 (3H, s), 1.32 (3H, t, *J* = 7.0 Hz), 0.86 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 169.0 (C), 167.4 (2 x C, O-*C*=O), 167.1 (C, O-*C*=O), 160.8 (C), 135.1 (C), 128.8 (2 x CH), 128.0 (2 x CH), 127.1 (CH), 101.3 (CH), 100.5 (C), 62.1 (CH_2), 61.2 (CH_2), 42.9 (C), 36.9 (CH), 29.4 (CH), 21.0 (CH_2), 19.6 (CH_3), 14.2 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{24}O_7Na$ 423.1420; Found 423.1421.



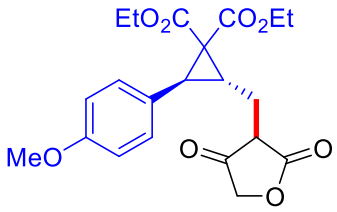
(-)-**22ca**

Diethyl (2*R*,3*S*)-2-((4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (22ea): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (5:5 to 6:4) and isolated as a colorless liquid; Yield: 98% (91.72 mg); $[\alpha]_D^{25}$ = –37.8° (*c* = 0.54, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2977, 2915, 2848, 1722, 1665, 1448, 1407, 1371, 1298, 1221, 1190, 1102, 1040, 864, 740 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.27-7.20 (5H, m), 4.61 (2H, s), 4.37-4.32 (2H, m), 3.91-3.83 (2H, m), 3.07 (1H, d, *J* = 8.0 Hz), 2.74-2.66 (2H, m), 2.35-2.29 (1H, m), 1.34 (3H, t, *J* = 7.0 Hz), 0.87 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 176.0 (C, O-*C*=O), 173.6 (C, O-*C*=O), 170.0 (C, O-*C*=O), 166.9 (C, C=*C*-OH), 134.1 (C), 128.6 (2 x CH), 128.1 (2 x CH), 127.4 (CH), 98.8 (C), 67.2 (CH_2), 62.8 (CH_2), 61.6 (CH_2), 42.9 (C), 36.8 (CH), 28.9 (CH), 20.2 (CH_2), 14.0 (CH_3), 13.6 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{22}O_7Na$ 397.1263; Found 397.1268.



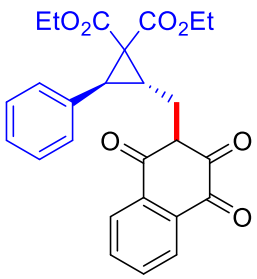
(-)-**22ea**

Diethyl (2*R*,3*S*)-2-((4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)methyl)-3-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (22ec): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (5:5 to 6:4) and isolated as a pale yellow liquid; Yield: 87% (87.96 mg); $[\alpha]_D^{25}$ = –31.0° (*c* = 0.07, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2928, 1720, 1668, 1517, 1412, 1294, 1249, 1218, 1177, 1096, 1032, 747, and 667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.14 (2H, br d, *J* = 8.5 Hz), 6.81 (2H, br d, *J* = 8.5 Hz), 4.59 (2H, d, *J* = 2.0 Hz), 4.35 (2H, q, *J* = 7.0 Hz), 3.93-3.84 (2H, m), 3.77 (3H, s, Ar-OC*H*$_3$), 2.97 (1H, d, *J* = 8.5 Hz), 2.76 (1H, dd, *J* = 16.0, 3.5 Hz), 2.67-2.63 (1H, m), 2.26 (1H, dd, *J* = 16.0, 9.5 Hz), 1.35 (3H, t, *J* = 7.0 Hz), 0.94 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 175.6 (C, C-*C*-OH), 173.2 (C, O-*C*=O), 170.6 (C, O-*C*=O), 167.0 (C, O-*C*=O), 159.0 (C), 129.8 (2 x CH), 125.9 (C), 113.6 (2 x CH), 99.0 (C), 67.2 (CH_2), 63.0 (CH_2), 61.7 (CH_2), 55.3 (CH_3, O*C*H$_3$), 42.9 (C), 36.4 (CH), 29.2 (CH), 20.3 (CH_2), 14.0 (CH_3), 13.7 (CH_3); LCMS m/z 405.40 ($M + H^+$), Calcd for $C_{21}H_{24}O_8H$ 405.1549; Anal. Calcd for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98. Found: C, 62.45; H, 5.94.



(-)-**22ec**

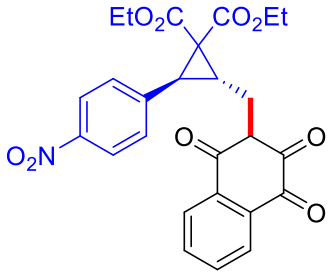
Diethyl (2*R*,3*S*)-2-((3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (22la): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and



(-)-**22la**

isolated as a yellow solid; Mp: 107-109 °C; Yield: 99% (111.0 mg); $[\alpha]_D^{25}$ = –80.9° (*c* = 1.58, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 3323, 2982, 2930, 2853, 1717, 1675, 1644, 1593, 1464, 1371, 1278, 1221, 1112, 1025, 942, 864, 730 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.15 (1H, dd, *J* = 7.6, 1.2 Hz), 8.09 (1H, dd, *J* = 7.6, 1.2 Hz), 7.77 (1H, dt, *J* = 7.6, 1.2 Hz), 7.70 (1H, dt, *J* = 7.6, 1.2 Hz), 7.57 (1H, br s, OH), 7.23-7.16 (5H, m), 4.44-4.36 (1H, m), 4.31-4.23 (1H, m), 3.90-3.78 (2H, m), 3.35 (1H, d, *J* = 8.0 Hz), 3.01 (1H, dd, *J* = 12.8, 6.0 Hz), 2.90-2.85 (1H, m), 2.83-2.81 (1H, m), 1.32 (3H, t, *J* = 7.2 Hz), 0.87 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.2 (C, *C*=O), 181.3 (C, *C*=O), 167.8 (C, O-*C*=O), 166.8 (C, O-*C*=O), 153.8 (C), 135.05 (CH), 134.97 (C), 133.0 (CH), 132.8 (C), 129.4 (C), 128.7 (2 x CH), 128.0 (2 x CH), 127.1 (CH), 126.9 (CH), 126.2 (CH), 121.7 (C), 61.8 (CH_2), 61.1 (CH_2), 43.1 (C), 36.5 (CH), 28.7 (CH), 21.3 (CH_2), 14.2 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{24}O_7Na$ 471.1420; Found 471.1415.

Diethyl (2*R*,3*S*)-2-((3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl)-3-(4-nitrophenyl)cyclopropane-1,1-dicarboxylate (22le): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and

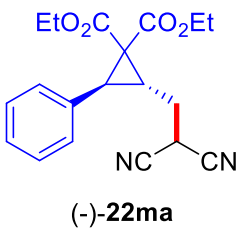


(-)-**22le**

isolated as a yellow solid; Mp: 125-127 °C; Yield: 95% (117.2 mg); $[\alpha]_D^{25}$ = –64.7° (*c* = 0.37, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 3346, 2981, 2929, 1719, 1644, 1594, 1520, 1460, 1369, 1342, 1273, 1215, 1193, 1107, 1024, 986, 944, 851, 753, 725, 694, 667 and 572 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.13 (1H, dd, *J* = 8.0, 1.0 Hz), 8.09 (1H, dd, *J* = 8.0, 1.0 Hz), 8.07 (2H, d, *J* = 8.5 Hz), 7.78 (1H, dt, *J* = 7.5, 1.0 Hz), 7.71 (1H, dt, *J* = 7.5, 1.0 Hz), 7.62 (1H, br s, OH), 7.33 (2H, d, *J* = 9.0 Hz), 4.44-4.38 (1H, m), 4.31-4.24 (1H, m), 3.95-3.89 (1H, m), 3.87-3.81 (1H, m), 3.39 (1H, d, *J* = 8.0 Hz), 3.01 (1H, dd, *J* = 13.5, 6.5 Hz), 2.89 (1H, br dd, *J* = 13.5, 6.5 Hz), 2.78 (1H, dd, *J* = 13.5, 6.5 Hz), 1.32 (3H, t, *J* = 7.0 Hz), 0.94 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 184.2 (C, *C*=O), 181.2 (C, *C*=O), 167.1 (C, O-*C*=O), 166.2 (C, O-*C*=O), 153.8 (C, HO-*C*=C), 147.0 (C), 142.8 (C), 135.1 (CH), 133.1 (CH), 132.7 (C), 129.5 (2 x CH), 129.3 (C), 126.9 (CH), 126.3 (CH), 123.2 (2 x CH), 121.0 (C), 62.1 (CH_2), 61.5 (CH_2), 43.7 (C), 35.9 (CH), 29.1 (CH), 21.3 (CH_2), 14.1 (CH_3), 13.8 (CH_3); LCMS m/z 493.50 (M^+),

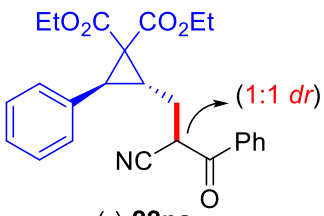
Calcd for $C_{26}H_{23}NO_9$ 493.1373; Anal. Calcd for $C_{26}H_{23}NO_9$: C, 63.28; H, 4.70; N, 2.84. Found: C, 63.21; H, 4.75; N, 2.81.

Diethyl (2*R*,3*S*)-2-(2,2-dicyanoethyl)-3-phenylcyclopropane-1,1-dicarboxylate (22ma): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 90% (76.6 mg); $[\alpha]_D^{25}$ = –40.9° (*c* = 0.40, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2987, 2915, 1722, 1603, 1446, 1371, 1300, 1223, 1190, 1125, 1097, 1024, 854, 745 and 698cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.24 (3H, m), 7.23-7.20 (2H, m), 4.37-4.31 (1H, m), 4.28-4.21 (1H, m), 3.93-3.82 (3H, m), 3.21 (1H, d, *J* = 8.0 Hz), 2.72 (1H, q, *J* = 8.0 Hz), 2.46-2.40 (1H, m), 2.30-2.24 (1H, m), 1.31 (3H, t, *J* = 7.5 Hz), 0.89 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.4 (C, O-*C*=O), 165.6 (C, O-*C*=O), 133.1 (C), 128.4 (2 x CH), 128.3 (2 x CH), 127.7 (CH), 112.0 (2 x C, *C*≡N), 62.4 (CH_2), 61.6 (CH_2), 42.4 (C), 36.2 (CH), 28.7 (CH_2), 26.3 (CH), 22.1 (CH), 14.0 (CH_3), 13.0 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}N_2O_4H$ 341.1501; Found 341.1498.



(-)-**22ma**

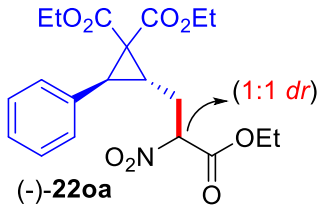
Diethyl (2*R*,3*S*)-2-(2-cyano-3-oxo-3-phenylpropyl)-3-phenylcyclopropane-1,1-dicarboxylate (22na): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a colorless liquid; Yield: 93% (97.53 mg); $[\alpha]_D^{25}$ = –26.7° (*c* = 0.34, $CHCl_3$, 1:1 *dr*); IR (Neat): ν_{max} 3060, 2967, 2915, 2853, 1722, 1603, 1500, 1443, 1371, 1298, 1226, 1117, 1025, 978, 864, 740 and 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, 1:1 diastereomers): δ 8.00-7.96 (2 x 2H, m), 7.66 (2 x 1H, t, *J* = 7.0 Hz), 7.54-7.51 (2 x 2H, m), 7.29-7.21 (2 x 4H, m), 7.20-7.18 (2 x 1H, m), 4.52-4.46 (2 x 1H, m), 4.34-4.18 (2 x 2H, m), 3.91-3.79 (2 x 2H, m), 3.18 (1H, d, *J* = 8.0 Hz), 3.15 (1H, d, *J* = 8.0 Hz), 2.78-2.71 (2 x 1H, m), 2.43-2.37 (1H, m), 2.32-2.29 (2 x 1H, m), 2.25-2.20 (1H, m), 1.31 (3H, t, *J* = 7.0 Hz), 1.27 (3H, t, *J* = 7.0 Hz), 0.88 (3H, t, *J* = 7.0 Hz), 0.85 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 diastereomers) δ 189.76 (C, *C*=O), 189.70 (C, *C*=O), 167.6 (2 x C, O-*C*=O), 166.15 (C, O-*C*=O), 166.07 (C, O-*C*=O), 134.69 (CH), 134.66 (CH), 133.9 (C), 133.87 (2 x C), 133.8 (C), 129.1 (4 x CH), 128.9 (2 x CH), 128.8 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.20 (2 x CH), 128.18 (2 x CH), 127.53 (CH), 127.47 (CH), 116.7 (2 x C, *C*≡N), 62.14 (CH_2), 62.06 (CH_2), 61.42 (CH_2), 61.37 (CH_2), 43.0 (C), 42.5



(-)-**22na**

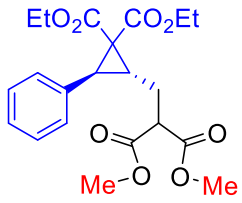
(C), 39.1 (CH), 38.7 (CH), 36.7 (CH), 36.4 (CH), 28.0 (CH_2), 27.6 (CH_2), 27.3 (CH), 27.1 (CH), 14.13 (CH_3), 14.12 (CH_3), 13.65 (CH_3), 13.63 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{25}NO_5Na$ 442.1630; Found 442.1636.

Diethyl (2*R*,3*S*)-2-(3-ethoxy-2-nitro-3-oxopropyl)-3-phenylcyclopropane-1,1-dicarboxylate (22oa): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1:9 to 1.5:8.5) and isolated as a pale yellow liquid; Yield: 78% (79.45 mg); $[\alpha]_D^{25}$ = –33.0° (*c* = 1.19, $CHCl_3$, 1:1 *dr*); IR (Neat): 2982, 2926, 2853, 1724, 1562, 1498, 1446, 1370, 1297, 1221, 1103, 1022, 860, 745 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 1:1 diastereomers): δ 7.27-7.21 (2 x 3H, m), 7.15 (2 x 2H, d, *J* = 7.5 Hz), 5.27-5.22 (2 x 1H, m), 4.36-4.31 (2 x 1H, m), 4.30-4.21 (2 x 3H, m), 3.88-3.81 (2 x 2H, m), 3.14 (2 x 1H, d, *J* = 7.5 Hz), 2.63-2.52 (2 x 2H, m), 2.45-2.33 (2 x 1H, m), 1.33-1.26 (4 x 3H, m), 0.89-0.85 (2 x 3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 diastereomers) δ 167.4 (2 x C, O-*C*=O), 166.0 (C, O-*C*=O), 165.9 (C, O-*C*=O), 163.9 (C, O-*C*=O), 163.8 (C, O-*C*=O), 133.8 (C), 133.7 (C), 128.5 (4 x CH), 128.21 (2 x CH), 128.18 (2 x CH), 127.54 (CH), 127.50 (CH), 87.07 (CH), 87.01 (CH), 63.3 (2 x CH_2), 62.14 (CH_2), 62.09 (CH_2), 61.40 (CH_2), 61.39 (CH_2), 42.8 (C), 42.3 (C), 36.4 (CH), 36.1 (CH), 28.5 (CH_2), 28.4 (CH_2), 25.8 (CH), 25.7 (CH), 14.10 (CH_3), 14.08 (CH_3), 13.8 (CH_3), 13.7 (CH_3), 13.6 (2 x CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{25}NO_8H$ 408.1658; Found 408.1655.



(-)-**22oa**

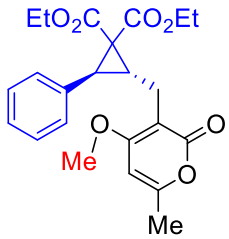
Diethyl (2*R*,3*S*)-2-(3-methoxy-2-(methoxycarbonyl)-3-oxopropyl)-3-phenylcyclopropane-1,1-dicarboxylate (23aa): The compound was prepared from (-)-**22aa** following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1:9 to 1.5:8.5) and isolated as a colorless liquid; Yield: 78% (31.7 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IA-3 column (hexane/2-propanol = 95:05, flow rate 0.5 mL/min, λ = 254 nm), t_R = 29.04 min (minor), t_R = 31.29 min (major); $[\alpha]_D^{25}$ = –30.9° (*c* = 0.37, $CHCl_3$, >99% *ee* and >99:1 *dr*); IR (Neat): ν_{max} 2895, 2951, 1727, 1598, 1439, 1368, 1289, 1220, 1123, 1025, 865, 743 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.25-7.16 (5H, m), 4.36-4.21 (2H, m), 3.89-3.81 (2H, m), 3.74 (3H, s, OC*H*$_3$), 3.69 (3H, s, OC*H*$_3$), 3.57-3.54 (1H, m), 3.11 (1H, d, *J* = 8.0 Hz), 2.58-2.52 (1H, m), 2.26-2.19 (1H, m), 2.14-2.06 (1H, m), 1.31 (3H, t, *J* = 7.2 Hz), 0.87 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ



(-)-**23aa**

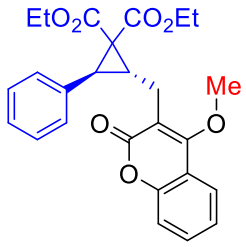
169.2 (C, O-*C*=O), 169.1 (C, O-*C*=O), 167.6 (C, O-*C*=O), 166.5 (C, O-*C*=O), 134.4 (C), 128.6 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 61.9 (CH_2), 61.2 (CH_2), 52.7 (CH_3, O*C*H_3), 52.6 (CH_3, O*C*H_3), 51.0 (CH), 42.8 (C), 36.6 (CH), 27.6 (CH), 27.0 (CH_2), 14.2 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{26}O_8H$ 407.1706; Found 407.1700.

Diethyl (2*R*,3*S*)-2-((4-methoxy-6-methyl-2-oxo-2*H*-pyran-3-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (23ca): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 53% (21.97 mg); $[\alpha]_D^{25}$ = –75.3° (*c* = 0.79, $CHCl_3$, >99:1 *dr*); IR (Neat): 2977, 2925, 2853, 1717, 1644, 1562, 1464, 1365, 1293, 1247, 1221, 1117, 1014, 901, 859, 792, 746 and 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.23-7.13 (5H, m), 6.04 (1H, s), 4.38-4.30 (1H, m), 4.28-4.20 (1H, m), 3.86 (3H, s), 3.84-3.81 (2H, m), 3.25 (1H, d, *J* = 7.6 Hz), 2.82-2.75 (2H, m), 2.57-2.51 (1H, m), 2.62 (3H, s), 1.31 (3H, t, *J* = 7.2 Hz), 0.85 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.1 (C, O-*C*=O), 167.0 (C, O-*C*=O), 166.8 (C, O-*C*=O), 165.1 (C), 162.0 (C), 135.4 (C), 128.7 (2 x CH), 128.0 (2 x CH), 127.0 (CH), 102.7 (C), 95.0 (CH), 61.6 (CH_2), 61.0 (CH_2), 56.4 (CH_3, O*C*H_3), 42.9 (C), 36.7 (CH), 29.0 (CH), 21.4 (CH_2), 20.4 (CH_3), 14.20 (CH_3), 13.70 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{26}O_7H$ 415.1757; Found 415.1762.



(-)-**23ca**

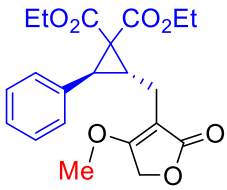
Diethyl (2*R*,3*S*)-2-((4-methoxy-2-oxo-2*H*-chromen-3-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (23da): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1.5:8.5) and isolated as a colorless liquid; Yield: 68% (30.63 mg); $[\alpha]_D^{25}$ = –54.2° (*c* = 0.7, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2972, 2920, 2853, 1722, 1624, 1572, 1453, 1350, 1288, 1226, 1195, 1097, 1045, 962, 911, 859, 756 and 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.69 (1H, dd, *J* = 8.0, 1.0 Hz), 7.54 (1H, br t, *J* = 7.5 Hz), 7.37 (1H, br d, *J* = 8.0 Hz), 7.31 (1H, br t, *J* = 7.5 Hz), 7.24-7.16 (5H, m), 4.42-4.35 (1H, m), 4.30-4.24 (1H, m), 4.02 (3H, s, OC*H*$_3$), 3.87-3.81 (2H, m), 3.32 (1H, d, *J* = 7.5 Hz), 3.00-2.94 (2H, m), 2.87-2.79 (1H, m), 1.31 (3H, t, *J* = 7.5 Hz), 0.86 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.0 (C, O-*C*=O), 166.7 (C, O-*C*=O), 164.6 (C, O-*C*=O), 163.4 (C), 152.9 (C), 134.9 (C), 131.6 (CH), 128.7 (2 x CH), 128.0 (2 x CH), 127.1 (CH), 124.1 (CH), 123.3 (CH), 116.9 (CH), 115.6 (C), 62.2 (CH_3, O*C*H_3), 61.8 (CH_2),



(-)-**23da**

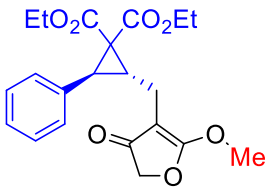
61.1 (CH_2), 43.1 (C), 36.7 (CH), 28.9 (CH), 22.8 (CH_2), 14.1 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{26}O_7H$ 451.1757; Found 451.1754.

Diethyl (2*R*,3*S*)-2-((4-methoxy-2-oxo-2,5-dihydrofuran-3-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (23ea-1): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a pale yellow liquid; Yield: 64% (24.86 mg); $[\alpha]_D^{25} = -57.9°$ (*c* = 0.85, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2987, 2920, 2853, 1748, 1722, 1670, 1458, 1386, 1340, 1288, 1226, 1195, 1102, 1050, 859, 751 and 704 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.25-7.17 (5H, m), 4.72 (2H, s), 4.37-4.29 (1H, m), 4.26-4.18 (1H, m), 3.89 (3H, s, OC*H*$_3$), 3.87-3.79 (2H, m), 3.19 (1H, d, *J* = 8.0 Hz), 2.84 (1H, q, *J* = 7.6 Hz), 2.58 (1H, dd, *J* = 14.8, 6.4 Hz), 2.40 (1H, dd, *J* = 14.8, 8.4 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 0.86 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 174.1 (C), 173.5 (C, O-*C*=O), 167.9 (C, O-*C*=O), 166.7 (C, O-*C*=O), 134.8 (C), 128.7 (2 x CH), 128.1 (2 x CH), 127.2 (CH), 101.5 (C), 65.2 (CH_2), 61.8 (CH_2), 61.1 (CH_2), 57.6 (CH_3, O*C*H$_3$), 42.9 (C), 36.7 (CH), 28.3 (CH), 20.2 (CH_2), 14.2 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{24}O_7Na$ 411.1420; Found 411.1420.



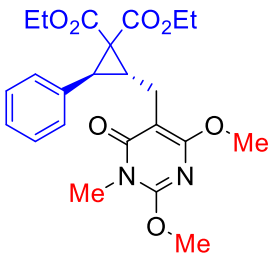
(-)-**23ea-1**

Diethyl (2*R*,3*S*)-2-((2-methoxy-4-oxo-4,5-dihydrofuran-3-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (23ea-2): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 4:6) and isolated as a colorless liquid; Yield: 34% (13.21 mg); $[\alpha]_D^{25} = -62.7°$ (*c* = 0.46, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2925, 2853, 1727, 1603, 1479, 1386, 1288, 1221, 1195, 1138, 1019, 859, 751 and 704 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.25-7.17 (5H, m), 4.60 (2H, s), 4.35-4.28 (1H, m), 4.25-4.19 (1H, m), 4.01 (3H, s, OC*H*$_3$), 3.86-3.81 (2H, m), 3.17 (1H, d, *J* = 8.0 Hz), 2.75 (1H, q, *J* = 8.0 Hz), 2.48 (1H, dd, *J* = 14.8, 6.4 Hz), 2.23 (1H, dd, *J* = 14.8, 8.0 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 0.86 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.6 (C, *C*=O), 181.9 (C, O-*C*-OCH$_3$), 167.9 (C, O-*C*=O), 166.9 (C, O-*C*=O), 135.1 (C), 128.7 (2 x CH), 128.0 (2 x CH), 127.1 (CH), 91.9 (C), 75.0 (CH_2), 61.7 (CH_2), 61.0 (CH_2), 56.2 (CH_3, O*C*H$_3$), 42.9 (C), 36.9 (CH), 28.9 (CH), 17.9 (CH_2), 14.2 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{24}O_7H$ 389.1600; Found 389.1600.



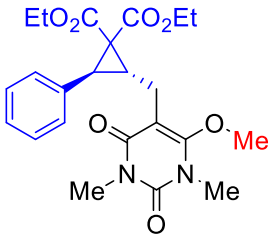
(-)-**23ea-2**

Diethyl (2*R*,3*S*)-2-((2,4-dimethoxy-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (23fa): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a pale yellow solid; Mp 74-76 °C; Yield: 52% (23.11 mg); $[\alpha]_D^{25}$ = –60.4° (*c* = 0.6, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2983, 2951, 2863, 1725, 1669, 1608, 1550, 1459, 1412, 1377, 1292, 1217, 1110, 1029, 917, 859, 787, 741 and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.22-7.14 (5H, m), 4.39-4.31 (1H, m), 4.29-4.21 (1H, m), 4.02 (3H, s, OC*H*$_3$), 3.91 (3H, s, OC*H*$_3$), 3.85-3.78 (2H, m), 3.39 (3H, s, NC*H*$_3$), 2.81 (1H, d, *J* = 7.6 Hz), 2.85-2.79 (2H, m), 2.55-2.49 (1H, m), 1.32 (3H, t, *J* = 7.2 Hz), 0.84 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.1 (C, O-*C*=O), 167.2 (C, O-*C*=O), 165.0 (C, N-*C*-OCH_3), 164.0 (C, N-C=O), 155.2 (C, N-*C*-N), 135.7 (C), 128.8 (2 x CH), 127.9 (2 x CH), 126.8 (CH), 95.6 (C), 61.5 (CH_2), 60.9 (CH_2), 55.4 (CH_3, O*C*H_3), 53.9 (CH_3, O*C*H_3), 43.0 (C), 36.8 (CH), 29.6 (CH_3, N*C*H_3), 28.0 (CH), 21.1 (CH_2), 14.2 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{28}N_2O_7H$ 445.1975; Found 445.1968.

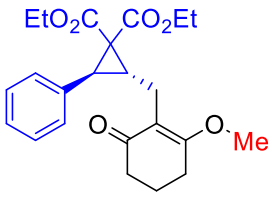


(-)-**23fa**

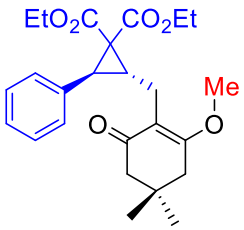
Diethyl (2*R*,3*S*)-2-((6-methoxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (23ga): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (4:6) and isolated as a white solid; Mp: 76-78 °C; Yield: 62% (27.56 mg); $[\alpha]_D^{25}$ = –55.2° (*c* = 0.48, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2981, 2925, 1713, 1650, 1458, 1366, 1291, 1221, 1114, 1028, 980, 862, 747 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.24-7.15 (5H, m), 4.39-4.32 (1H, m), 4.25-4.19 (1H, m), 3.89 (3H, s, OC*H*$_3$), 3.86-3.77 (2H, m), 3.365 (3H, s, NC*H*$_3$), 3.364 (3H, s, NC*H*$_3$), 3.23 (1H, d, *J* = 8.0 Hz), 2.90-2.86 (1H, m), 2.73 (1H, dd, *J* = 14.5, 6.5 Hz), 2.57 (1H, dd, *J* = 14.5, 6.5 Hz), 1.31 (3H, t, *J* = 7.0 Hz), 0.85 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.1 (C, O-*C*=O), 166.8 (C, O-*C*=O), 164.0 (C, N-*C*=O), 159.1 (C, N-*C*-OCH_3), 151.4 (C, N-*C*-N), 135.0 (C), 128.7 (2 x CH), 128.0 (2 x CH), 127.1 (CH), 99.5 (C), 62.2 (CH_3, O*C*H_3), 61.7 (CH_2), 61.0 (CH_2), 43.2 (C), 36.7 (CH), 29.6 (CH_3, N*C*H_3), 29.5 (CH_3, N*C*H_3), 28.4 (CH), 21.6 (CH_2), 14.2 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{28}N_2O_7Na$ 467.1794; Found 467.1788.



(-)-**23ga**

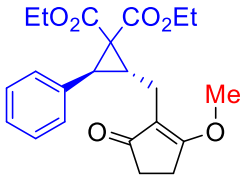
Diethyl (2*R*,3*S*)-2-((2-methoxy-6-oxocyclohex-1-en-1-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (23ha): 
(-)-**23ha**

The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (3:7) and isolated as a colorless liquid; Yield: 79% (31.64 mg); $[\alpha]_D^{25}$ = –62.8° (*c* = 0.37, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2977, 2931, 2853, 1724, 1645, 1611, 1497, 1459, 1370, 1289, 1234, 1189, 1103, 1038, 861, 744 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.24-7.17 (3H, m), 7.16-7.13 (2H, m), 4.37-4.29 (1H, m), 4.28-4.20 (1H, m), 3.86-3.81 (2H, m), 3.80 (3H, s, OC*H*$_3$), 3.21 (1H, d, *J* = 8.0 Hz), 2.69 (1H, dd, *J* = 13.2, 5.6 Hz), 2.64-2.58 (3H, m), 2.40-2.32 (3H, m), 2.02 (2H, quintet, *J* = 6.4 Hz), 1.32 (3H, t, *J* = 7.2 Hz), 0.86 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.7 (C, *C*=O), 172.9 (C, C-*C*-OCH_3), 168.2 (C, O-*C*=O), 167.3 (C, O-*C*=O), 135.9 (C), 128.8 (2 x CH), 127.9 (2 x CH), 126.8 (CH), 117.5 (C), 61.4 (CH_2), 60.9 (CH_2), 55.3 (CH_3, O*C*H_3), 42.9 (C), 36.8 (CH), 36.3 (CH_2), 29.9 (CH), 24.9 (CH_2), 20.9 (CH_2), 20.1 (CH_2), 14.2 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{28}O_6Na$ 423.1784; Found 423.1779.

Diethyl (2*R*,3*S*)-2-((2-methoxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (23ia): 
(-)-**23ia**

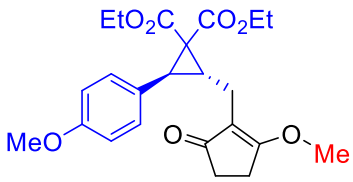
The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a pale yellow liquid; Yield: 98% (42.0 mg); $[\alpha]_D^{25}$ = –53.6° (*c* = 0.49, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2958, 2925, 2863, 1723, 1648, 1617, 1461, 1370, 1293, 1234, 1157, 1102, 1068, 1025, 870, 743 and 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21-7.11 (5H, m), 4.36-4.26 (1H, m), 4.24-4.18 (1H, m), 3.84-3.76 (2H, m), 3.76 (3H, s, OC*H*$_3$), 3.20 (1H, d, *J* = 8.0 Hz), 2.69-2.59 (2H, m), 2.42 (2H, s), 2.33 (1H, dd, *J* = 12.0, 8.0 Hz), 2.24 (2H, s), 1.30 (3H, t, *J* = 8.0 Hz), 1.08 (6H, s, 2 x CH_3), 0.83 (3H, t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.4 (C, *C*=O), 171.0 (C, C-*C*-OCH_3), 168.1 (C, O-*C*=O), 167.2 (C, O-*C*=O), 135.8 (C), 128.7 (2 x CH), 127.9 (2 x CH), 126.8 (CH), 116.3 (C), 61.4 (CH_2), 60.8 (CH_2), 55.2 (CH_3, O*C*H_3), 50.2 (CH_2), 43.0 (C), 38.8 (CH_2), 36.8 (CH), 32.0 (C), 29.8 (CH), 28.53 (CH_3), 28.50 (CH_3), 19.9 (CH_2), 14.2 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{32}O_6H$ 429.2277; Found 429.2273.

Diethyl (2*R*,3*S*)-2-((2-methoxy-5-oxocyclopent-1-en-1-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (23ja): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (4:6) and isolated as a pale yellow liquid; Yield: 97% (37.48 mg); $[\alpha]_D^{25}$ = –59.7° (*c* = 0.78, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2977, 2920, 2858, 1722, 1680, 1629, 1458, 1365, 1293, 1221, 1190, 1097, 895, 859, 782, 740 and 704 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.23-7.20 (2H, m), 7.18-7.15 (3H, m), 4.33-4.28 (1H, m), 4.24-4.19 (1H, m), 3.89 (3H, s, OC*H*$_3$), 3.84-3.79 (2H, m), 3.16 (1H, d, *J* = 8.0 Hz), 2.77-2.72 (1H, m), 2.69-2.67 (2H, m), 2.51-2.45 (3H, m), 2.25 (1H, dd, *J* = 14.5, 8.5 Hz), 1.30 (3H, t, *J* = 7.0 Hz), 0.85 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.9 (C, *C*=O), 185.3 (C, C-*C*-OCH$_3$), 167.9 (C, O-*C*=O), 167.0 (C, O-*C*=O), 135.4 (C), 128.7 (2 x CH), 127.9 (2 x CH), 126.9 (CH), 118.4 (C), 61.5 (CH_2), 60.9 (CH_2), 56.4 (CH_3, O*C*H$_3$), 43.0 (C), 36.9 (CH), 33.4 (CH_2), 28.6 (CH), 24.5 (CH_2), 19.6 (CH_2), 14.2 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{26}O_6Na$ 409.1627; Found 409.1628.



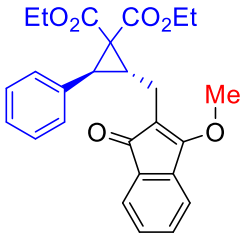
(-)-**23ja**

Diethyl (2*R*,3*S*)-2-((2-methoxy-5-oxocyclopent-1-en-1-yl)methyl)-3-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (23jc): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (4:6) and isolated as a pale yellow liquid; Yield: 72% (29.98 mg); $[\alpha]_D^{25}$ = –71.5° (*c* = 0.14, MeOH, >99:1 *dr*); IR (Neat): ν_{max} 2984, 2935, 2838, 1719, 1686, 1624, 1515, 1462, 1362, 1286, 1246, 1222, 1173, 1115, 1095, 1029, 838, 750, 665, 572 and 548 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.08 (2H, d, *J* = 8.0 Hz), 6.76 (2H, d, *J* = 8.5 Hz), 4.34-4.28 (1H, m), 4.23-4.17 (1H, m), 3.90 (3H, s, OC*H*$_3$), 3.87-3.80 (2H, m), 3.75 (3H, s, OC*H*$_3$), 3.10 (1H, d, *J* = 8.5 Hz), 2.72-2.69 (3H, m), 2.50-2.46 (3H, m), 2.25 (1H, dd, *J* = 14.5, 8.0 Hz), 1.29 (3H, t, *J* = 7.0 Hz), 0.91 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.9 (C, *C*=O), 185.3 (C, C=*C*-OCH$_3$), 168.0 (C, O-*C*=O), 167.0 (C, O-*C*=O), 158.5 (C), 129.7 (2 x CH), 127.3 (C), 118.4 (C), 113.3 (2 x CH), 61.4 (CH_2), 60.8 (CH_2), 56.3 (CH_3, O*C*H$_3$), 55.1 (CH_3, O*C*H$_3$), 42.8 (C), 36.3 (CH), 33.4 (CH_2), 28.7 (CH), 24.4 (CH_2), 19.5 (CH_2), 14.1 (CH_3), 13.7 (CH_3); LCMS m/z 417.35 ($M + H^+$), Calcd for $C_{23}H_{28}O_7H$ 417.1913; Anal. Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.25; H, 6.72.



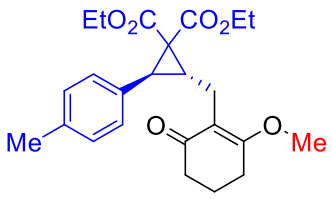
(-)-**23jc**

Diethyl (2*R*,3*S*)-2-((3-methoxy-1-oxo-1H-inden-2-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (23ka): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a yellow liquid; Yield: 80% (34.76 mg); $[\alpha]_D^{25}$ = –92.4° (*c* = 0.25, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2977, 2930, 1727, 1629, 1587, 1500, 1443, 1381, 1334, 1293, 1221, 1190, 1102, 1076, 1024, 973, 932, 864, 777, 798 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.41 (1H, d, *J* = 7.0 Hz), 7.33 (1H, dt, *J* = 7.0, 1.0 Hz), 7.25-7.14 (7H, m), 4.37-4.31 (1H, m), 4.27 (3H, s, OC*H*$_3$), 4.26-4.21 (1H, m), 3.88-3.78 (2H, m), 3.27 (1H, d, *J* = 7.5 Hz), 2.87-2.79 (2H, m), 2.59-2.52 (1H, m), 1.30 (3H, t, *J* = 7.5 Hz), 0.86 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.5 (C, *C*=O), 172.1 (C, C-*C*-OCH$_3$), 168.1 (C, O-*C*=O), 166.7 (C, O-*C*=O), 140.6 (C), 135.0 (C), 132.3 (CH), 132.1 (C), 129.4 (CH), 128.7 (2 x CH), 128.0 (2 x CH), 127.1 (CH), 120.9 (CH), 118.8 (CH), 108.6 (C), 61.7 (CH_2), 61.1 (CH_2), 59.2 (CH_3, O*C*H$_3$), 43.3 (C), 37.1 (CH), 30.3 (CH), 20.3 (CH_2), 14.2 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{26}O_6Na$ 457.1627; Found 457.1629.



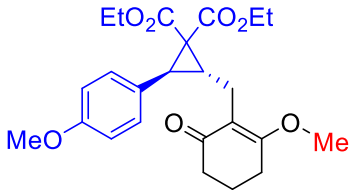
(-)-**23ka**

Diethyl (2*R*,3*S*)-2-((2-methoxy-6-oxocyclohex-1-en-1-yl)methyl)-3-(*p*-tolyl)cyclopropane-1,1-dicarboxylate (23hb): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 88% (36.47 mg); $[\alpha]_D^{25}$ = –74.3° (*c* = 0.23, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2982, 2949, 1718, 1641, 1610, 1461, 1368, 1286, 1226, 1187, 1093, 1042, 748 and 665 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.01 (4H, s), 4.36-4.28 (1H, m), 4.26-4.18 (1H, m), 3.90-3.79 (2H, m), 3.78 (3H, s, OC*H*$_3$), 3.15 (1H, d, *J* = 8.0 Hz), 2.67 (1H, dd, *J* = 13.2, 5.2 Hz), 2.56-2.54 (3H, m), 2.38-2.30 (3H, m), 2.27 (3H, s, ArC*H*$_3$), 2.00 (2H, quintet, *J* = 6.4 Hz), 1.31 (3H, t, *J* = 7.2 Hz), 0.89 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.6 (C, *C*=O), 172.9 (C, C-*C*-OCH$_3$), 168.2 (C, O-*C*=O), 167.3 (C, O-*C*=O), 136.3 (C), 132.7 (C), 128.6 (2 x CH), 128.5 (2 x CH), 117.5 (C), 61.3 (CH_2), 60.8 (CH_2), 55.2 (CH_3, O*C*H$_3$), 42.8 (C), 36.5 (CH), 36.2 (CH_2), 29.9 (CH), 24.8 (CH_2), 21.0 (CH_3), 20.8 (CH_2), 20.0 (CH_2), 14.2 (CH_3), 13.7 (CH_3); LCMS m/z 415.25 ($M + H^+$), Calcd for $C_{24}H_{30}O_6H$ 415.2121; Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.45; H, 7.32.



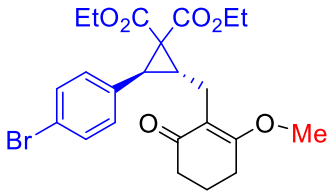
(-)-**23hb**

Diethyl (2*R*,3*S*)-2-((2-methoxy-6-oxocyclohex-1-en-1-yl)methyl)-3-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (23hc): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 84% (36.16 mg); $[\alpha]_D^{25}$ = –77.1° (*c* = 0.10, MeOH, >99:1 *dr*); IR (Neat): ν_{max} 2978, 2949, 1720, 1644, 1610, 1515, 1462, 1368, 1285, 1242, 1172, 1115, 1032, 846 and 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.05 (2H, d, *J* = 8.4 Hz), 6.75 (2H, d, *J* = 8. 4 Hz), 4.36-4.28 (1H, m), 4.26-4.18 (1H, m), 3.90-3.81 (2H, m), 3.79 (3H, s, OC*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 3.14 (1H, d, *J* = 8.0 Hz), 2.66 (1H, dd, *J* = 13.2, 5.2 Hz), 2.60-2.53 (3H, m), 2.39-2.30 (3H, m), 2.00 (2H, quintet, *J* = 6.4 Hz), 1.31 (3H, t, *J* = 7.2 Hz), 0.91 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.7 (C, *C*=O), 172.9 (C, C-*C*-OCH$_3$), 168.2 (C, O-*C*=O), 167.3 (C, O-*C*=O), 158.4 (C), 129.7 (2 x CH), 127.8 (C), 117.5 (C), 113.3 (2 x CH), 61.3 (CH_2), 60.8 (CH_2), 55.2 (CH_3, O*C*H$_3$), 55.1 (CH_3, O*C*H$_3$), 42.8 (C), 36.23 (CH), 36.22 (CH_2), 30.0 (CH), 24.8 (CH_2), 20.8 (CH_2), 20.0 (CH_2), 14.2 (CH_3), 13.8 (CH_3); LCMS m/z 431.10 (M + H^+), Calcd for $C_{24}H_{30}O_7H$ 431.2070; Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 66.85; H, 7.08.



(-)-**23hc**

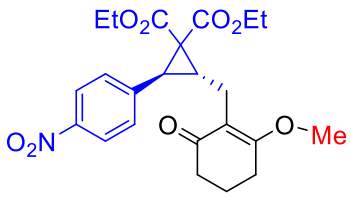
Diethyl (2*S*,3*R*)-2-(4-bromophenyl)-3-((2-methoxy-6-oxocyclohex-1-en-1-yl)methyl)cyclopropane-1,1-dicarboxylate (23hd): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 76% (36.43 mg); $[\alpha]_D^{25}$ = –79.2° (*c* = 0.18, MeOH, >99:1 *dr*); IR (Neat): ν_{max} 2979, 2947, 1719, 1644, 1610, 1367, 1286, 1223, 1186, 1072, 1010, 846 and 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33 (2H, d, *J* = 8.4 Hz), 7.01 (2H, d, *J* = 8.4 Hz), 4.37-4.29 (1H, m), 4.26-4.18 (1H, m), 3.91-3.81 (2H, m), 3.79 (3H, s, OC*H*$_3$), 3.13 (1H, d, *J* = 8.0 Hz), 2.67 (1H, dd, *J* = 13.2, 5.2 Hz), 2.60 (2H, t, *J* = 6.0 Hz), 2.57-2.51 (1H, m), 2.38-2.28 (3H, m), 2.00 (2H, quintet, *J* = 6.4 Hz), 1.31 (3H, t, *J* = 7.2 Hz), 0.92 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.5 (C, *C*=O), 172.8 (C, C-*C*-OCH$_3$), 167.7 (C, O-*C*=O), 167.0 (C, O-*C*=O), 134.9 (C), 130.9 (2 x CH), 130.4 (2 x CH), 120.7 (C), 117.2 (C), 61.4 (CH_2), 60.9 (CH_2), 55.2 (CH_3, O*C*H$_3$), 42.9 (C), 36.2 (CH_2), 36.1 (CH), 29.9 (CH), 24.8 (CH_2), 20.7 (CH_2), 20.0 (CH_2), 14.1 (CH_3), 13.7 (CH_3); LCMS m/z



(-)-**23hd**

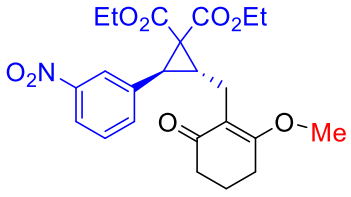
479.25 (M + H^+), Calcd for $C_{23}H_{27}BrO_6H$ 479.1069; Anal. Calcd for $C_{23}H_{27}BrO_6$: C, 57.63; H, 5.68. Found: C, 57.48; H, 5.62.

Diethyl (2*R*,3*S*)-2-((2-methoxy-6-oxocyclohex-1-en-1-yl)methyl)-3-(4-nitrophenyl)cyclopropane-1,1-dicarboxylate (23he): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a pale yellow liquid; Yield: 78% (34.75 mg); $[\alpha]_D^{25}$ = –83.7° (*c* = 0.12, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2981, 2927, 2854, 1720, 1643, 1602, 1518, 1462, 1368, 1345, 1286, 1225, 1188, 1107, 1040, 853, 745 and 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.10 (2H, d, *J* = 8.8 Hz), 7.31 (2H, d, *J* = 8.8 Hz), 4.38-4.32 (1H, m), 4.29-4.23 (1H, m), 3.94-3.84 (2H, m), 3.83 (3H, s, OC*H*$_3$), 3.26 (1H, d, *J* = 8.0 Hz), 2.74-2.69 (1H, m), 2.64-2.59 (3H, m), 2.40-2.31 (3H, m), 2.03 (2H, quintet, *J* = 6.4 Hz), 1.33 (3H, t, *J* = 7.2 Hz), 0.94 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.7 (C, *C*=O), 173.1 (C, C-*C*-OCH_3), 167.4 (C, O-*C*=O), 166.8 (C, O-*C*=O), 146.8 (C), 143.9 (C), 129.6 (2 x CH), 123.2 (2 x CH), 117.0 (C), 61.8 (CH_2), 61.3 (CH_2), 55.3 (CH_3, O*C*H_3), 43.6 (C), 36.29 (CH_2), 36.26 (CH), 30.4 (CH), 24.9 (CH_2), 20.8 (CH_2), 20.2 (CH_2), 14.2 (CH_3), 13.9 (CH_3); LCMS m/z 446.35 (M + H^+), Calcd for $C_{23}H_{27}NO_8H$ 446.1815; Anal. Calcd for $C_{23}H_{27}NO_8$: C, 62.01; H, 6.11; N, 3.14. Found: C, 62.12; H, 6.09; N, 3.18.



(-)-**23he**

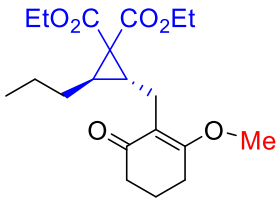
Diethyl (2*R*,3*S*)-2-((2-methoxy-6-oxocyclohex-1-en-1-yl)methyl)-3-(3-nitrophenyl)cyclopropane-1,1-dicarboxylate (23hf): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 73% (32.52 mg); $[\alpha]_D^{25}$ = –68.5° (*c* = 0.10, $CHCl_3$, 86% *ee* and >99:1 *dr*); IR (Neat): ν_{max} 2981, 2927, 2852, 1720, 1643, 1610, 1523, 1462, 1368, 1347, 1288, 1229, 1189, 1097, 1042, 920, 861, 804, 747, 686 and 667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.05 (1H, d, *J* = 8.0 Hz), 7.99 (1H, s), 7.49 (1H, d, *J* = 7.5 Hz), 7.41 (1H, t, *J* = 8.0 Hz), 4.40-4.33 (1H, m), 4.29-4.23 (1H, m), 3.94-3.86 (2H, m), 3.85 (3H, s, OC*H*$_3$), 3.27 (1H, d, *J* = 8.0 Hz), 2.73 (1H, dd, *J* = 13.0, 5.0 Hz), 2.65 (2H, t, *J* = 6.5 Hz), 2.58-2.54 (1H, m), 2.40-2.30 (3H, m), 2.05 (2H, quintet, *J* = 6.4 Hz), 1.34 (3H, t, *J* = 7.0 Hz), 0.96 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.6 (C, *C*=O), 173.1 (C, C-*C*-OCH_3), 167.5 (C, O-*C*=O), 166.9 (C, O-*C*=O), 148.0 (C), 138.4 (C), 135.1 (CH),



(-)-**23hf**

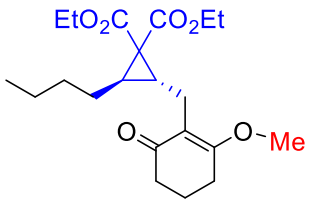
128.9 (CH), 123.9 (CH), 122.0 (CH), 117.1 (C), 61.7 (CH_2), 61.3 (CH_2), 55.3 (CH_3, O*C*H_3), 42.9 (C), 36.3 (CH_2), 36.0 (CH), 30.4 (CH), 24.9 (CH_2), 20.8 (CH_2), 20.2 (CH_2), 14.2 (CH_3), 13.9 (CH_3); LCMS m/z 446.40 (M + H^+), Calcd for $C_{23}H_{27}NO_8H$ 446.1815; Anal. Calcd for $C_{23}H_{27}NO_8$: C, 62.01; H, 6.11; N, 3.14. Found: C, 62.09; H, 6.15; N, 3.10.

(2*R*,3*R*)-Diethyl 2-((2-methoxy-6-oxocyclohex-1-en-1-yl)methyl)-3-propylcyclopropane-1,1-dicarboxylate (23hh): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as oil colour liquid; Yield: 85% (31.15 mg) ; $[\alpha]_D^{25}$ = –23.7° (*c* = 0.06, $CHCl_3$, >95% *de*); IR (Neat): ν_{max} 2957, 2925, 2852, 1720, 1644, 1614, 1462, 1368, 1292, 1241, 1202, 1166, 1123, 1077, 1042, 917, 863 and 753 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.30-4.20 (2H, m), 4.19-4.09 (2H, m), 3.81 (3H, s, OC*H*$_3$), 2.57 (2H, t, *J* = 6.0 Hz), 2.52 (1H, dd, *J* = 13.5, 5.0 Hz), 2.34 (2H, t, *J* = 6.5 Hz), 2.12 (1H, dd, *J* = 18.0, 9.0 Hz), 1.99 (2H, quintet, *J* = 6.5 Hz), 1.89 (1H, br q, *J* = 7.0 Hz), 1.83-1.77 (1H, m), 1.41-1.35 (1H, m), 1.33-1.26 (2H, m), 1.27 (3H, t, *J* = 7.0 Hz), 1.24 (3H, t, *J* = 7.0 Hz), 1.13-1.04 (1H, m), 0.86 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.4 (C, *C*=O), 172.3 (C, C=*C*-OCH$_3$), 168.9 (C, O-*C*=O), 168.8 (C, O-*C*=O), 117.9 (C), 61.0 (CH_2), 60.9 (CH_2), 55.1 (CH_3, O*C*H_3), 39.9 (C), 36.3 (CH_2), 32.9 (CH), 32.1 (CH), 29.7 (CH_2), 24.8 (CH_2), 22.1 (CH_2), 20.8 (CH_2), 20.4 (CH_2), 14.2 (2 x CH_3), 13.7 (CH_3); LCMS m/z 367.30 (M + H^+), Calcd for $C_{20}H_{30}O_6H$ 367.2121; Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.43; H, 8.31.



(-)-**23hh**

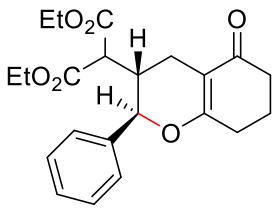
Diethyl (2*R*,3*R*)-2-butyl-3-((2-methoxy-6-oxocyclohex-1-en-1-yl)methyl)cyclopropane-1,1-dicarboxylate (23hi): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a pale yellow liquid; Yield: 86% (32.72 mg); $[\alpha]_D^{25}$ = –28.5° (*c* = 0.10, $CHCl_3$, 98% *ee* and >99:1 *dr*); ^1H NMR ($CDCl_3$, 500 MHz): δ 4.19-4.24 (1H, m), 4.23-4.18 (1H, m), 4.17-4.10 (2H, m), 3.81 (3H, s, OC*H*$_3$), 2.57 (2H, t, *J* = 6.0 Hz), 2.51 (1H, dd, *J* = 13.5, 5.0 Hz), 2.34 (2H, t, *J* = 6.5 Hz), 2.11 (1H, dd, *J* = 13.5, 9.5 Hz), 1.99 (2H, quintet, *J* = 6.5 Hz), 1.87 (1H, q, *J* = 8.0 Hz), 1.83-1.78 (1H, m), 1.43-1.36 (1H, m), 1.29-1.23 (10H, m), 1.15-1.09 (1H, m), 0.85 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.5 (C, *C*=O), 172.4 (C, C-*C*-OCH$_3$), 168.9 (C, O-*C*=O), 168.8 (C, O-*C*=O), 117.9 (C), 61.1 (CH_2), 61.0 (CH_2), 55.1 (CH_3,



(-)-**23hi**

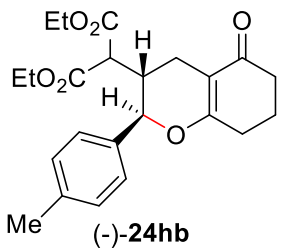
O*C*H$_3$), 39.9 (C), 36.3 (CH$_2$), 33.0 (CH), 32.2 (CH), 31.2 (CH$_2$), 27.2 (CH$_2$), 24.9 (CH$_2$), 22.2 (CH$_2$), 20.8 (CH$_2$), 20.4 (CH$_2$), 14.2 (2 x CH$_3$), 14.1 (CH$_3$); LCMS m/z 381.25 (M + H$^+$), Calcd for $C_{21}H_{32}O_6H$ 381.2277; Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48. Found: C, 66.15; H, 8.52.

Diethyl 2-((2*R*,3*S*)-5-oxo-2-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)malonate (24ha): The compound was prepared following the procedure **D** or procedure **E** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a pale yellow liquid; Yield: 81% (31.3 mg, procedure **D**), 10% (3.86 mg, procedure **E**); $[\alpha]_D^{25}$ = –80.8° (*c* = 1.15, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2981, 2939, 1727, 1626, 1455, 1388, 1369, 1296, 1222, 1175, 1133, 1093, 1027, 861, 751, 700, 649 and 546 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.34 (3H, m), 7.31-7.30 (2H, m), 5.16 (1H, d, *J* = 7.5 Hz), 4.21-4.07 (4H, m), 3.27 (1H, d, *J* = 6.5 Hz), 2.78 (1H, quintet, *J* = 6.5 Hz), 2.53-2.45 (2H, m), 2.44-2.33 (4H, m), 2.05-2.00 (2H, m), 1.24 (3H, t, *J* = 7.0 Hz), 1.23 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.6 (C, *C*=O), 170.3 (C, C-*C*-O), 168.1 (C, O-*C*=O), 167.7 (C, O-*C*=O), 138.1 (C), 128.7 (2 x CH), 128.6 (CH), 126.6 (2 x CH), 110.7 (C, C=*C*-C), 80.3 (CH, C-*C*H-O), 61.6 (CH$_2$), 61.5 (CH$_2$), 52.4 (CH), 37.4 (CH), 36.6 (CH$_2$), 28.3 (CH$_2$), 20.9 (CH$_2$), 19.7 (CH$_2$), 13.99 (CH$_3$), 13.96 (CH$_3$); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{22}H_{26}O_6H$ 387.1808; Found 387.1809.



(-)-**24ha**

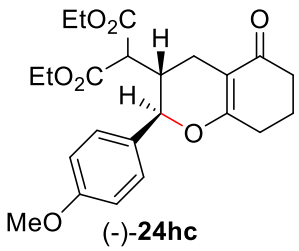
Diethyl 2-((2*R*,3*S*)-5-oxo-2-(*p*-tolyl)-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)malonate (24hb): The compound was prepared following the procedure **D** or procedure **E** and purified by column chromatography using EtOAc/hexanes (3:7) and isolated as a colorless liquid; Yield: 91% (36.44 mg, procedure **D**), 23% (9.21 mg, procedure **E**); $[\alpha]_D^{25}$ = –103.9° (*c* = 0.21, MeOH, >99:1 *dr*); IR (Neat): ν_{max} 2982, 2938, 1727, 1624, 1517, 1447, 1389, 1296, 1222, 1178, 1089, 1027, 817, 748, 667 and 624 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12 (4H, br s), 5.10 (1H, d, *J* = 7.6 Hz), 4.21-4.06 (4H, m), 3.26 (1H, d, *J* = 6.4 Hz), 2.78-2.71 (1H, m), 2.52-2.36 (6H, m), 2.35 (3H, s, ArC*H*$_3$), 2.04-1.97 (2H, m), 1.23 (6H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.6 (C, *C*=O), 170.4 (C, C-*C*-O), 168.1 (C, O-*C*=O), 167.6 (C, O-*C*=O), 138.5 (C), 134.8 (C), 129.3 (2 x CH), 126.6 (2 x CH), 110.6 (C, C=*C*-C), 80.3 (CH, C-*C*H-O), 61.6 (CH$_2$), 61.4 (CH$_2$), 52.2 (CH), 37.4 (CH), 36.6 (CH$_2$), 28.3 (CH$_2$), 21.1 (CH$_3$), 20.8



(-)-**24hb**

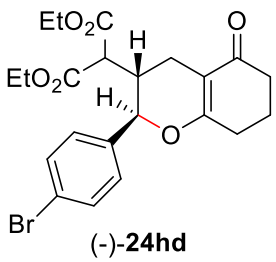
(CH_2), 19.8 (CH_2), 13.92 (CH_3), 13.91 (CH_3); LCMS m/z 401.35 (M + H^+), Calcd for $C_{23}H_{28}O_6H$ 401.1964; Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.92; H, 7.09.

Diethyl 2-((2*R*,3*S*)-2-(4-methoxyphenyl)-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)malonate (24hc): The compound was prepared following the procedure **D** or procedure **E** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a colorless liquid; Yield: 94% (39.15 mg, procedure **D**), 20% (8.33 mg, procedure **E**); $[\alpha]_D^{25}$ = –111.3° (*c* = 0.17, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2982, 2937, 1726, 1623, 1514, 1389, 1296, 1245, 1222, 1173, 1086, 1029, 830, 747, 665 and 624 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.24 (2H, d, *J* = 8.5 Hz), 6.90 (2H, d, *J* = 8.5 Hz), 5.08 (1H, d, *J* = 8.0 Hz), 4.20-4.06 (4H, m), 3.80 (3H, s, OC*H*$_3$), 3.26 (1H, d, *J* = 5.5 Hz), 2.75-2.69 (1H, m), 2.49-2.45 (3H, m), 2.41-2.33 (3H, m), 2.03-1.96 (2H, m), 1.234 (3H, t, *J* = 7.0 Hz), 1.232 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.6 (C, *C*=O), 170.5 (C, C-*C*-O), 168.0 (C, O-*C*=O), 167.6 (C, O-*C*=O), 159.8 (C), 129.8 (C), 128.2 (2 x CH), 114.0 (2 x CH), 110.8 (C, C=*C*-C), 80.3 (CH, C-*C*H-O), 61.5 (CH_2), 61.4 (CH_2), 55.2 (CH_3), 52.3 (CH), 37.6 (CH), 36.6 (CH_2), 28.3 (CH_2), 20.8 (CH_2), 20.1 (CH_2), 13.9 (2 x CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{28}O_7H$ 417.1913; Found 417.1912.



(-)-**24hc**

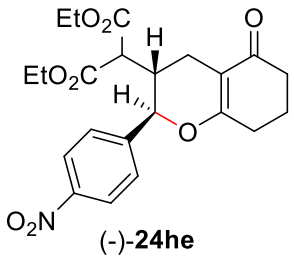
Diethyl 2-((2*R*,3*S*)-2-(4-bromophenyl)-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)malonate (24hd): The compound was prepared following the procedure **D** or procedure **E** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a colorless liquid; Yield: 83% (38.62 mg, procedure **D**), 18% (8.38 mg, procedure **E**); $[\alpha]_D^{25}$ = –105.1° (*c* = 0.17, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2982, 2929, 1727, 1626, 1488, 1387, 1298, 1219, 1175, 1072, 1009, 818, 748, 665 and 548 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51 (2H, d, *J* = 8.4 Hz), 7.20 (2H, d, *J* = 8.4 Hz), 5.14 (1H, d, *J* = 7.2 Hz), 4.23-4.06 (4H, m), 3.26 (1H, d, *J* = 6.8 Hz), 2.76-2.69 (1H, m), 2.49-2.46 (2H, m), 2.44-2.29 (4H, m), 2.05-1.98 (2H, m), 1.25 (3H, t, *J* = 6.8 Hz), 1.23 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.6 (C, *C*=O), 170.1 (C, C-*C*-O), 168.0 (C, O-*C*=O), 167.6 (C, O-*C*=O), 137.1 (C), 131.8 (2 x CH), 128.5 (2 x CH), 122.7 (C), 110.7 (C, C=*C*-C), 79.7 (CH, C-*C*H-O), 61.8 (CH_2), 61.7 (CH_2), 52.3 (CH), 37.4 (CH), 36.6 (CH_2), 28.3 (CH_2), 20.8 (CH_2), 19.9 (CH_2), 14.0 (CH_3),



(-)-**24hd**

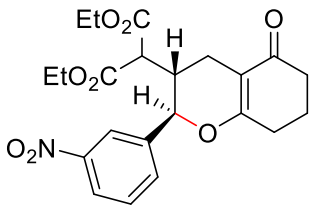
13.97 (CH_3); LCMS m/z 463.05 (M - H^+), Calcd for $C_{22}H_{24}BrO_6$ 463.0762; Anal. Calcd for $C_{22}H_{25}BrO_6$: C, 56.78; H, 5.42. Found: C, 56.65; H, 5.46.

Diethyl 2-((2*R*,3*S*)-2-(4-nitrophenyl)-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)malonate (24he): The compound was prepared following the procedure **D** or procedure **E** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a pale yellow liquid; Yield: 25% (10.79 mg, procedure **D**), 11% (4.74 mg, procedure **E**); $[\alpha]_D^{25}$ = –105.2° (*c* = 0.13, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 3020, 2928, 2855, 1727, 1628, 1525, 1389, 1349, 1215, 1186, 1090, 1027, 851, 745 and 667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.24 (2H, d, *J* = 8.5 Hz), 7.51 (2H, d, *J* = 8.5 Hz), 5.34 (1H, d, *J* = 6.5 Hz), 4.25-4.19 (1H, m), 4.18-4.06 (3H, m), 3.30 (1H, d, *J* = 7.0 Hz), 2.82 (1H, quintet, *J* = 6.5 Hz), 2.57-2.48 (2H, m), 2.46-2.37 (2H, m), 2.34-2.28 (2H, m), 2.07-2.02 (2H, m), 1.26 (3H, t, *J* = 7.0 Hz), 1.24 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.3 (C, *C*=O), 169.5 (C, C-*C*-O), 167.9 (C, O-*C*=O), 167.5 (C, O-*C*=O), 147.9 (C), 145.5 (C), 127.5 (2 x CH), 123.8 (2 x CH), 110.7 (C, C=*C*-C), 78.9 (CH, C-*C*H-O), 61.9 (CH_2), 61.87 (CH_2), 52.3 (CH), 37.2 (CH), 36.5 (CH_2), 28.1 (CH_2), 20.8 (CH_2), 19.4 (CH_2), 14.0 (CH_3), 13.9 (CH_3); LCMS m/z 432.05 (M + H^+), Calcd for $C_{22}H_{25}NO_8H$ 432.1658; Anal. Calcd for $C_{22}H_{25}NO_8$: C, 61.25; H, 5.84; N, 3.25. Found: C, 61.32; H, 5.81; N, 3.28.



(-)-**24he**

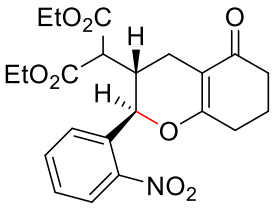
Diethyl 2-((2*R*,3*S*)-2-(3-nitrophenyl)-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)malonate (24hf): The compound was prepared following the procedure **D** or procedure **E** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a colorless liquid; Yield: 42% (18.12 mg, procedure **D**), 31% (13.37 mg, procedure **E**); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel AD-H column (hexane/2-propanol = 90:10, flow rate 1 mL/min, λ = 254 nm), t_R = 23.49 min (major), t_R = 46.73 min (minor); $[\alpha]_D^{25}$ = –66.2° (*c* = 0.07, $CHCl_3$, 86% *ee* and >99:1 *dr*); IR (Neat): ν_{max} 2981, 2941, 2872, 1726, 1627, 1530, 1447, 1388, 1349, 1296, 1222, 1175, 1095, 1024, 860, 810, 754, 691 and 642 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.22 (1H, br d, *J* = 8.0 Hz), 8.19 (1H, br s), 7.70 (1H, br d, *J* = 8.0 Hz), 7.58 (1H, t, *J* = 8.0 Hz), 5.32 (1H, d, *J* = 7.0 Hz), 4.23-4.18 (1H, m), 4.17-4.12 (1H, m), 4.08 (2H, q, *J* = 7.0 Hz), 3.29 (1H, d, *J* = 6.5 Hz), 2.81 (1H, quintet, *J* = 7.0 Hz), 2.58-2.46 (2H, m), 2.42 (2H, q, *J* = 6.5 Hz), 2.34 (2H,



(-)-**24hf**

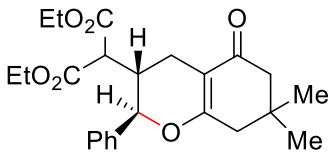
d, *J* = 6.5 Hz), 2.05 (2H, quintet, *J* = 6.0 Hz), 1.26 (3H, t, *J* = 7.5 Hz), 1.22 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.5 (C, *C*=O), 169.6 (C, C=*C*-O), 167.8 (C, O-*C*=O), 167.4 (C, O-*C*=O), 148.3 (C), 140.3 (C), 132.8 (CH), 129.7 (CH), 123.5 (CH), 121.7 (CH), 110.8 (C, C=*C*-C), 78.9 (CH, C-*C*H-O), 61.9 (CH_2), 61.8 (CH_2), 52.2 (CH), 37.3 (CH), 36.5 (CH_2), 28.1 (CH_2), 20.7 (CH_2), 19.7 (CH_2), 13.94 (CH_3), 13.86 (CH_3); LCMS m/z 432.30 (M + H^+), Calcd for $C_{22}H_{25}NO_8H$ 432.1658; Anal. Calcd for $C_{22}H_{25}NO_8$: C, 61.25; H, 5.84; N, 3.25. Found: C, 61.15; H, 5.89; N, 3.18.

Diethyl 2-((2*R*,3*S*)-2-(2-nitrophenyl)-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)malonate (24hg): The title compound was prepared following the procedure **D** or procedure **E** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a pale yellow liquid; Yield: 36% (15.53 mg, procedure **D**), 12% (5.18 mg, procedure **E**); $[\alpha]_D^{25}$ = +13.7° (*c* = 0.14, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 3020, 2928, 1727, 1627, 1533, 1391, 1215, 1186, 1093, 1024, 745 and 667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (1H, dd, *J* = 8.0, 0.8 Hz), 7.66-7.62 (1H, m), 7.55-7.50 (2H, m), 5.76 (1H, d, *J* = 8.0 Hz), 4.13-4.02 (4H, m), 3.33 (1H, d, *J* = 6.4 Hz), 2.96-2.89 (1H, m), 2.53-2.33 (6H, m), 2.05-1.98 (2H, m), 1.22 (3H, t, *J* = 8.0 Hz), 1.21 (3H, t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.6 (C, *C*=O), 170.1 (C, C=*C*-O), 167.63 (C, O-*C*=O), 167.28 (C, O-*C*=O), 149.1 (C), 133.0 (CH), 132.3 (C), 129.7 (CH), 129.4 (CH), 124.8 (CH), 110.8 (C, C=*C*-C), 75.8 (CH, C-*C*H-O), 61.85 (CH_2), 61.81 (CH_2), 52.6 (CH), 36.9 (CH), 36.6 (CH_2), 28.0 (CH_2), 20.8 (CH_2), 20.6 (CH_2), 13.93 (CH_3), 13.91 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{25}NO_8H$ 432.1658; Found 432.1658.



(+)-**24hg**

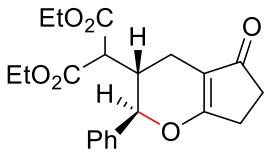
Diethyl 2-((2*R*,3*S*)-7,7-dimethyl-5-oxo-2-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-3-yl)malonate (24ia): The compound was prepared following the procedure **D** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a colorless liquid; Yield: 90% (37.3 mg); $[\alpha]_D^{25}$ = –49.9° (*c* = 1.17, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2958, 2871, 1729, 1630, 1448, 1389, 1368, 1291, 1221, 1163, 1125, 1093, 1027, 987, 906, 861, 751, 698, 658 and 561 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.32 (3H, m), 7.30-7.27 (2H, m), 5.22 (1H, d, *J* = 6.4 Hz), 4.24-4.06 (4H, m), 3.29 (1H, d, *J* = 7.6 Hz), 2.83 (1H, quintet, *J* = 6.4 Hz), 2.43-2.35 (2H, m), 2.33-2.23 (4H, m), 1.25 (3H, t, *J* = 7.2 Hz), 1.22 (3H, t, *J* = 7.2



(-)-**24ia**

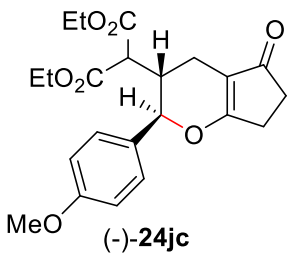
Hz), 1.11 (6H, s, 2 x C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.3 (C, *C*=O), 168.5 (C, C=*C*-O), 168.2 (C, O-*C*=O), 167.8 (C, O-*C*=O), 138.3 (C), 128.6 (2 x CH), 128.5 (CH), 126.2 (2 x CH), 109.1 (C, C=*C*-C), 80.0 (CH, C-*C*H-O), 61.7 (CH_2), 61.6 (CH_2), 52.3 (CH), 50.5 (CH_2), 42.0 (CH_2), 37.0 (CH), 32.2 (C), 28.5 (CH_3), 28.3 (CH_3), 18.7 (CH_2), 14.02 (CH_3), 13.96 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{30}O_6H$ 415.2121; Found 415.2121.

Diethyl 2-((2*R*,3*S*)-5-oxo-2-phenyl-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-3-yl)malonate (24ja): The compound was prepared following the procedure **D** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a colorless liquid; Yield: 94% (35.0 mg); $[\alpha]_D^{25}$ = –58.3° (*c* = 0.24, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2981, 2927, 1727, 1696, 1633, 1444, 1402, 1369, 1289, 1223, 1173, 1029, 986, 943, 906, 750, 701 and 665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.37 (3H, m), 7.31 (2H, d, *J* = 9.2 Hz), 5.33 (1H, d, *J* = 7.6 Hz), 4.22-4.09 (4H, m), 3.23 (1H, d, *J* = 6.4 Hz), 2.81-2.74 (1H, m), 2.73-2.59 (2H, m), 2.51-2.49 (2H, m), 2.42-2.30 (2H, m), 1.244 (3H, t, *J* = 7.2 Hz), 1.240 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.2 (C, *C*=O), 183.2 (C, C=*C*-O), 167.8 (C, O-*C*=O), 167.4 (C, O-*C*=O), 137.2 (C), 128.9 (CH), 128.7 (2 x CH), 126.5 (2 x CH), 114.3 (C, C=*C*-C), 82.5 (CH, C-*C*H-O), 61.7 (CH_2), 61.5 (CH_2), 51.9 (CH), 37.0 (CH), 33.5 (CH_2), 26.1 (CH_2), 18.6 (CH_2), 13.9 (2 x CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{24}O_6H$ 373.1651; Found 373.1652.



(-)-**24ja**

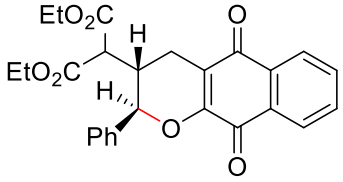
Diethyl 2-((2*R*,3*S*)-2-(4-methoxyphenyl)-5-oxo-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-3-yl)malonate (24jc): The compound was prepared following the procedure **D** and purified by column chromatography using EtOAc/hexanes (3:7) and isolated as a colorless liquid; Yield: 96% (38.63 mg); $[\alpha]_D^{25}$ = –47.8° (*c* = 0.05, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 3017, 2927, 2853, 1727, 1633, 1515, 1402, 1249, 1215, 1176, 1032, 744 and 667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (2H, d, *J* = 8.8 Hz), 6.92 (2H, d, *J* = 8.8 Hz), 5.24 (1H, d, *J* = 8.0 Hz), 4.19-4.10 (4H, m), 3.82 (3H, s), 3.23 (1H, d, *J* = 5.6 Hz), 2.75-2.68 (1H, m), 2.65-2.60 (2H, m), 2.50-2.47 (2H, m), 2.40 (2H, d, *J* = 7.2 Hz), 1.24 (3H, t, *J* = 7.2 Hz), 1.23 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.4 (C, *C*=O), 183.6 (C, C=*C*-O), 168.0 (C, O-*C*=O), 167.5 (C, O-*C*=O), 160.1 (C), 129.1 (C), 128.3 (2 x CH), 114.5 (C, C=*C*-C), 114.2 (2 x CH), 82.6 (CH, C-*C*H-O), 61.8 (CH_2), 61.6 (CH_2), 55.3 (CH_3, O*C*H$_3$), 52.0 (CH), 37.3 (CH),



(-)-**24jc**

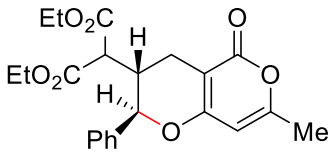
33.7 (CH_2), 26.3 (CH_2), 19.1 (CH_2), 14.0 (2 x CH_3); LCMS m/z 403.30 ($M + H^+$), Calcd for $C_{22}H_{26}O_7H$ 403.1757; Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.52; H, 6.57.

Diethyl 2-((2*R*,3*S*)-5,10-dioxo-2-phenyl-3,4,5,10-tetrahydro-2*H*-benzo[*g*]chromen-3-yl)malonate (24la): The title compound was prepared following the procedure **D** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a deep yellow liquid; Yield: 60% (26.91 mg); $[\alpha]_D^{25}$ = +86.8° (*c* = 0.08, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 3020, 2925, 1727, 1679, 1650, 1626, 1596, 1458, 1385, 1302, 1215, 1092, 1029, 1001, 748, 700 and 667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.14 (1H, dd, *J* = 7.0, 2.0 Hz), 8.08 (1H, dd, *J* = 7.0, 2.0 Hz), 7.75-7.69 (2H, m), 7.39-7.32 (5H, m), 5.46 (1H, d, *J* = 6.0 Hz), 4.26-4.11 (4H, m), 3.37 (1H, d, *J* = 7.5 Hz), 3.00 (1H, quintet, *J* = 6.5 Hz), 2.75 (1H, dd, *J* = 19.0, 6.0 Hz), 2.62 (1H, dd, *J* = 19.0, 5.5 Hz), 1.27 (3H, t, *J* = 7.0 Hz), 1.24 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 183.6 (C, *C*=O), 179.1 (C, *C*=O), 167.9 (C, O-*C*=O), 167.6 (C, O-*C*=O), 154.3 (C, C=*C*-O), 137.5 (C), 134.1 (CH), 133.2 (CH), 132.0 (C), 131.1 (C), 128.9 (2 x CH), 128.7 (CH), 126.4 (CH), 126.2 (CH), 126.1 (2 x CH), 120.6 (C, C=*C*-C), 80.2 (CH, C-*C*H-O), 61.9 (CH_2), 61.8 (CH_2), 52.0 (CH), 36.3 (CH), 19.7 (CH_2), 14.00 (CH_3), 13.97 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{24}O_7H$ 449.1600; Found 449.1598.



(+)-**24la**

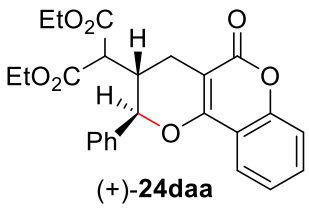
Diethyl 2-((2*R*,3*S*)-7-methyl-5-oxo-2-phenyl-3,4-dihydro-2*H*,5*H*-pyrano[4,3-b]pyran-3-yl)malonate (24ca): The compound was prepared following the procedure **D** and purified by column chromatography using EtOAc/hexanes (5:5 to 6:4) and isolated colorless liquid; Yield: 95% (38.04 mg); $[\alpha]_D^{25}$ = –32.1° (*c* = 0.43, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2982, 2931, 1727, 1670, 1631, 1590, 1425, 1371, 1298, 1243, 1189, 1143, 1102, 1022, 907, 853, 750, 700, 664, 578 and 551 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.34 (5H, m), 6.03 (1H, s, olefinic-*H*), 5.45 (1H, d, *J* = 7.5 Hz), 4.22-4.07 (4H, m), 3.31 (1H, d, *J* = 6.0 Hz), 2.90-2.85 (1H, m), 2.69-2.60 (2H, m), 2.24 (3H, s), 1.25 (3H, t, *J* = 6.0 Hz), 1.23 (3H, t, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 179.7 (C, C=*C*-O), 167.7 (C, O-*C*=O), 167.3 (C, O-*C*=O), 162.8 (C, O-*C*=O), 160.6 (C, C=*C*-CH_3), 136.3 (C), 129.1 (CH), 128.8 (2 x CH), 126.7 (2 x CH), 112.1 (CH), 98.0 (C, C=*C*-CO), 82.6 (CH, C-*C*H-O), 61.7 (CH_2), 61.6 (CH_2), 52.8 (CH),



(-)-**24ca**

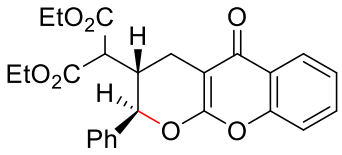
37.4 (CH), 19.3 (CH_2), 19.1 (CH_3), 13.90 (CH_3), 13.87 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}O_7H$ 401.1600; Found 401.1600.

Diethyl 2-((2*R*,3*S*)-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrano[3,2-*c*]chromen-3-yl)malonate (24daa): The compound was prepared following the procedure **D** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a colorless liquid; Yield: 26% (11.35 mg); $[\alpha]_D^{25}$ = +19.2° (*c* = 0.28, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 3020, 2927, 1721, 1704, 1636, 1494, 1404, 1261, 1215, 1169, 1093, 1024, 801, 747, 700 and 667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.80 (1H, dd, *J* = 8.0, 1.6 Hz), 7.56-7.52 (1H, m), 7.43-7.38 (3H, m), 7.36-7.34 (3H, m), 7.29-7.25 (1H, m), 5.50 (1H, d, *J* = 6.8 Hz), 4.26-4.09 (4H, m), 3.37 (1H, d, *J* = 7.2 Hz), 3.04-2.97 (1H, m), 2.72 (1H, dd, *J* = 17.6, 7.2 Hz), 2.66 (1H, dd, *J* = 17.6, 5.6 Hz), 1.26 (6H, 2 x CH_3, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.9 (C, O-*C*=O), 167.6 (C, O-*C*=O), 162.5 (C, O-*C*=O), 159.2 (C, C=*C*-O), 152.4 (C), 137.5 (C), 131.7 (CH), 128.8 (3 x CH), 126.3 (2 x CH), 123.9 (CH), 122.4 (CH), 116.6 (CH), 115.1 (C), 100.2 (C), 80.4 (CH, C-*C*H-O), 61.9 (CH_2), 61.8 (CH_2), 52.1 (CH), 37.0 (CH), 20.8 (CH_2), 13.97 (CH_3), 13.95 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{24}O_7H$ 437.1600; Found 437.1602.



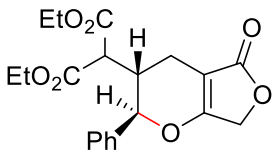
(+)-**24daa**

Diethyl 2-((2*R*,3*S*)-5-oxo-2-phenyl-2,3,4,5-tetrahydropyrano[2,3-*b*]chromen-3-yl)malonate (24dab): The compound was prepared following the procedure **D** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 36% (15.71 mg); $[\alpha]_D^{25}$ = −16.2° (*c* = 0.29, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2982, 2929, 1727, 1621, 1568, 1467, 1419, 1368, 1253, 1175, 1152, 1113, 1029, 992, 937, 860, 753, 694, 665, 624 and 579 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.19 (1H, dd, *J* = 8.0, 1.5 Hz), 7.62 (1H, dt, *J* = 8.0, 1.5 Hz), 7.44-7.37 (7H, m), 5.57 (1H, d, *J* = 7.5 Hz), 4.24-4.09 (4H, m), 3.37 (1H, d, *J* = 6.5 Hz), 2.99-2.94 (1H, m), 2.82-2.73 (2H, m), 1.26 (3H, t, *J* = 7.0 Hz), 1.24 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 177.5 (C, *C*=O), 167.8 (C, O-*C*=O), 167.4 (C, O-*C*=O), 162.8 (C, O-*C*-O), 153.2 (C), 136.5 (C), 132.9 (CH), 129.1 (CH), 128.9 (2 x CH), 126.6 (2 x CH), 125.7 (CH), 125.0 (CH), 122.5 (C), 117.2 (CH), 95.6 (C), 82.9 (CH, C-*C*H-O), 61.8 (CH_2), 61.7 (CH_2), 52.0 (CH), 37.4 (CH), 19.6 (CH_2), 13.97 (CH_3), 13.94 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{24}O_7H$ 437.1600; Found 437.1600.



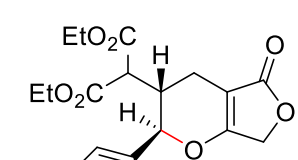
(-)-**24dab**

Diethyl 2-((2*R*,3*S*)-5-oxo-2-phenyl-3,4,5,7-tetrahydro-2*H*-furo[3,4-*b*]pyran-3-yl)malonate (24ea): The compound was prepared following the procedure **D** and purified by column chromatography using EtOAc/hexanes (3:7) and isolated as a colorless liquid; Yield: 97% (36.31 mg); $[\alpha]_D^{25}$ = –64.2° (*c* = 0. 25, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 3019, 2928, 1747, 1727, 1680, 1419, 1263, 1215, 1032, 745 and 667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.38 (3H, m), 7.32-7.30 (2H, m), 5.36 (1H, d, *J* = 8.0 Hz), 4.74 (1H, d, *J* = 16.0 Hz), 4.69 (1H, d, *J* = 16.0 Hz), 4.22-4.10 (4H, m), 3.24 (1H, d, *J* = 6.0 Hz), 2.86-2.80 (1H, m), 2.53 (1H, dd, *J* = 16.5, 8.5 Hz), 2.43 (1H, dd, *J* = 16.5, 5.5 Hz), 1.26 (3H, t, *J* = 7.0 Hz), 1.24 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 173.2 (C, C=*C*-O), 172.2 (C, O-*C*=O), 167.7 (C, O-*C*=O), 167.3 (C, O-*C*=O), 136.4 (C), 129.3 (CH), 128.9 (2 x CH), 126.7 (2 x CH), 100.0 (C), 83.2 (CH, C-*C*H-O), 66.2 (CH_2), 61.88 (CH_2), 61.66 (CH_2), 51.7 (CH), 37.3 (CH), 18.8 (CH_2), 13.9 (2 x CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}O_7H$ 375.1444; Found 375.1444.



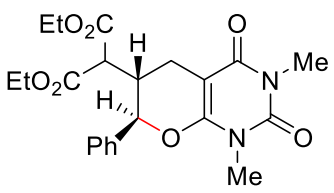
(-)-**24ea**

Diethyl 2-((2*R*,3*S*)-2-(4-methoxyphenyl)-5-oxo-3,4,5,7-tetrahydro-2*H*-furo[3,4-*b*]pyran-3-yl)malonate (24ec): The compound was prepared following the procedure **D** and purified by column chromatography using EtOAc/hexanes (3:7) and isolated as a pale yellow liquid; Yield: 83% (33.57 mg); $[\alpha]_D^{25}$ = –60.0° (*c* = 0.21, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2981, 2932, 1746, 1726, 1677, 1613, 1515, 1414, 1369, 1295, 1246, 1175, 1109, 1026, 904, 830, 748, 695 and 571 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.25 (2H, d, *J* = 8.5 Hz), 6.94 (2H, d, *J* = 8.5 Hz), 5.28 (1H, d, *J* = 8.5 Hz), 4.73-4.64 (2H, m), 4.21-4.12 (4H, m), 3.83 (3H, s, OC*H*$_3$), 3.24 (1H, d, *J* = 5.5 Hz), 2.80-2.74 (1H, m), 2.57 (1H, dd, *J* = 16.5, 9.5 Hz), 2.46 (1H, dd, *J* = 16.5, 5.0 Hz), 1.25 (3H, t, *J* = 7.0 Hz), 1.24 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 173.5 (C, C=*C*-O), 172.3 (C, O-*C*=O), 167.7 (C, O-*C*=O), 167.3 (C, O-*C*=O), 160.3 (C), 128.3 (2 x CH), 128.2 (C), 114.3 (2 x CH), 100.0 (C), 83.2 (CH, C-*C*H-O), 66.2 (CH_2), 61.8 (CH_2), 61.6 (CH_2), 55.3 (CH_3, O*C*H$_3$), 51.7 (CH), 37.5 (CH), 19.0 (CH_2), 13.91 (CH_3), 13.90 (CH_3); LCMS m/z 405.45 ($M + H^+$), Calcd for $C_{21}H_{24}O_8H$ 405.1549; Anal. Calcd for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98. Found: C, 62.45; H, 5.94.



(-)-**24ec**

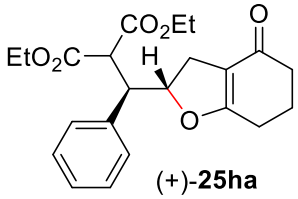
Diethyl 2-((6*S*,7*R*)-1,3-dimethyl-2,4-dioxo-7-phenyl-2,3,4,5,6,7-hexahydro-1*H*-pyrano[2,3-*d*]pyrimidin-6-yl)malonate (24ga): The compound was prepared following the procedure **D** and purified by column chromatography



(-)-**24ga**

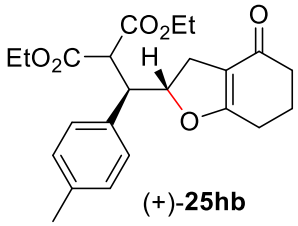
using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a white solid; Mp: 132-134 °C; Yield: 98% (42.18 mg); $[\alpha]_D^{25}$ = –11.6° (*c* = 0.66, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2982, 2931, 1727, 1701, 1637, 1487, 1455, 1371, 1275, 1221, 1173, 1029, 973, 904, 863, 750, 703, 665, 624 and 541 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.37 (3H, m), 7.32-7.30 (2H, m), 5.44 (1H, d, *J* = 7.5 Hz), 4.23-4.16 (1H, m), 4.15-4.08 (3H, m), 3.36 (3H, s, NC*H*$_3$), 3.35 (3H, s, NC*H*$_3$), 3.29 (1H, d, *J* = 6.0 Hz), 2.87-2.82 (1H, m), 2.61 (1H, s), 2.59 (1H, d, *J* = 2.0 Hz), 1.25 (3H, t, *J* = 7.0 Hz), 1.24 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 167.3 (C, O-*C*=O), 162.6 (C, N-*C*=O), 155.1 (C, N-*C*-O), 150.9 (C, N-*C*-N), 136.4 (C), 129.1 (CH), 128.8 (2 x CH), 126.4 (2 x CH), 85.9 (C), 82.6 (CH, C-*C*H-O), 61.7 (CH_2), 61.6 (CH_2), 51.9 (CH), 37.2 (CH), 28.5 (CH_3), 27.9 (CH_3), 19.9 (CH_2), 13.9 (CH_3), 13.8 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{26}N_2O_7H$ 431.1818; Found 431.1819.

Diethyl 2-((*R*)-((*S*)-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)(phenyl)methyl)malonate (25ha): The compound was prepared following the procedure **E** and purified by column chromatography using EtOAc/hexanes (3:7 to 4:6) and isolated as a pale yellow liquid; Yield: 54% (20.86 mg); $[\alpha]_D^{25}$ = +92.7° (*c* = 0.3, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2979, 2939, 1729, 1631, 1454, 1402, 1368, 1301, 1226, 1178, 1148, 1013, 957, 856, 750, 704 and 611 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.23-7.17 (5H, m), 5.18 (1H, ddd, *J* = 9.6, 7.2, 2.4 Hz), 4.27 (2H, q, *J* = 7.2 Hz), 4.18 (1H, d, *J* = 11.6 Hz), 3.88-3.80 (2H, m), 3.54 (1H, dd, *J* = 11.6, 2.0 Hz), 2.83 (1H, t, *J* = 12.0, 1.0 Hz), 2.45 (1H, dd, *J* = 14.4, 7.2 Hz), 2.39-2.22 (2H, m), 2.17-2.10 (1H, m), 2.03-1.96 (1H, m), 1.92-1.83 (1H, m), 1.78-1.69 (1H, m), 1.30 (3H, t, *J* = 7.2 Hz), 0.87 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.0 (C, *C*=O), 177.0 (C, C=*C*-O), 168.1 (C, O-*C*=O), 167.3 (C, O-*C*=O), 134.4 (C), 129.8 (2 x CH), 128.1 (2 x CH), 127.8 (CH), 113.4 (C), 84.4 (CH, C-*C*H-O), 62.0 (CH_2), 61.4 (CH_2), 54.1 (CH), 49.3 (CH), 36.1 (CH_2), 29.3 (CH_2), 23.8 (CH_2), 21.4 (CH_2), 14.1 (CH_3), 13.6 (CH_3); LCMS m/z 387.25 ($M + H^+$), Calcd for $C_{22}H_{26}O_6H$ 387.1808; Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.29; H, 6.81.



(+)-**25ha**

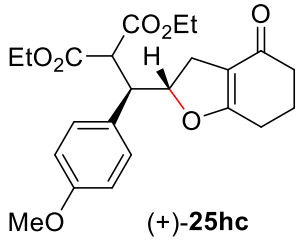
Diethyl 2-((*R*)-((*S*)-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)(*p*-tolyl)methyl)malonate (25hb): The compound was prepared following the procedure **E** and purified by column chromatography using EtOAc/hexanes (3:7 to 4:6) and isolated as a pale yellow liquid; Yield: 34% (13.62 mg); $[\alpha]_D^{25}$ = +98.5° (*c* = 0.07, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2979, 2924, 2852, 1730, 1633, 1454,



(+)-**25hb**

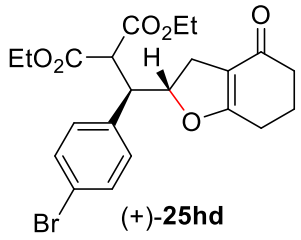
1402, 1368, 1228, 1178, 1146, 1119, 1013, 957, 857, 751 and 611 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.07 (2H, br d, *J* = 8.0 Hz), 7.02 (2H, br d, *J* = 8.0 Hz), 5.17 (1H, ddd, *J* = 9.6, 7.2, 2.4 Hz), 4.27 (2H, dq, *J* = 7.2, 1.6 Hz), 4.16 (1H, d, *J* = 11.6 Hz), 3.87 (2H, dq, *J* = 7.2, 1.6 Hz), 3.52 (1H, dd, *J* = 12.0, 2.4 Hz), 2.86-2.81 (1H, m), 2.45 (1H, dd, *J* = 14.4, 6.8 Hz), 2.39-2.33 (1H, m), 2.31-2.24 (1H, m), 2.27 (3H, s), 2.21-2.13 (1H, m), 2.07-2.00 (1H, m), 1.95-1.85 (1H, m), 1.82-1.72 (1H, m), 1.31 (3H, t, *J* = 6.8 Hz), 0.92 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.1 (C, *C*=O), 177.0 (C, C=*C*-O), 168.2 (C, O-*C*=O), 167.3 (C, O-*C*=O), 137.4 (C), 131.2 (C), 129.6 (2 x CH), 128.7 (2 x CH), 113.5 (C), 84.6 (CH, C-*C*H-O), 61.9 (CH_2), 61.3 (CH_2), 54.3 (CH), 48.9 (CH), 36.1 (CH_2), 29.3 (CH_2), 23.8 (CH_2), 21.4 (CH_2), 21.0 (CH_3), 14.1 (CH_3), 13.6 (CH_3); LCMS m/z 401.35 ($M + H^+$), Calcd for $C_{23}H_{28}O_6H$ 401.1964; Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.85; H, 7.12.

Diethyl 2-((*R*)-(4-methoxyphenyl)((*S*)-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)methyl)malonate (25hc): The compound was prepared following the procedure **E** and purified by column chromatography using EtOAc/hexanes (3:7 to 4:6) and isolated as a white solid; Mp: 105-107 °C; Yield: 40% (16.66 mg); $[\alpha]_D^{25}$ = +124.9° (*c* = 0.04, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 3017, 2959, 2927, 2854, 1729, 1628, 1513, 1404, 1256, 1215, 1180, 1095, 1014, 804, 747, 667 and 611 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.19 (2H, td, *J* = 8.4, 3.2 Hz), 6.96 (2H, td, *J* = 8.4, 3.2 Hz), 5.16 (1H, ddd, *J* = 9.6, 7.2, 2.4 Hz), 4.27 (2H, dq, *J* = 7.2, 1.2 Hz), 4.14 (1H, d, *J* = 11.6 Hz), 3.91-3.84 (2H, m), 3.75 (3H, s, OC*H*$_3$), 3.50 (1H, dd, *J* = 11.6, 2.4 Hz), 2.86-2.80 (1H, m), 2.44 (1H, dd, *J* = 7.2 Hz), 2.38-2.34 (1H, m), 2.32-2.24 (1H, m), 2.21-2.14 (1H, m), 2.10-2.02 (1H, m), 1.96-1.86 (1H, m), 1.83-1.75 (1H, m), 1.31 (3H, t, *J* = 7.2 Hz), 0.93 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.1 (C, *C*=O), 176.9 (C, C=*C*-O), 168.2 (C, O-*C*=O), 167.3 (C, O-*C*=O), 159.0 (C), 130.8 (2 x CH), 126.2 (C), 113.45 (2 x CH), 113.42 (C), 84.6 (CH, C-*C*H-O), 61.9 (CH_2), 61.3 (CH_2), 55.1 (CH_3, O*C*H$_3$), 54.3 (CH), 48.5 (CH), 36.1 (CH_2), 29.3 (CH_2), 23.8 (CH_2), 21.5 (CH_2), 14.0 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{28}O_7H$ 417.1913; Found 417.1915.



(+)-**25hc**

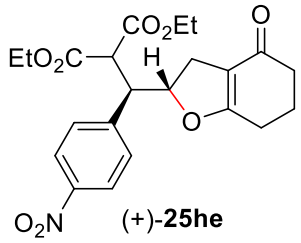
Diethyl 2-((*R*)-(4-bromophenyl)((*S*)-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)methyl)malonate (25hd): The compound was prepared following the procedure **E** and purified by column chromatography using EtOAc/hexanes (3:7 to 4:6) and isolated as a pale yellow liquid; Yield:



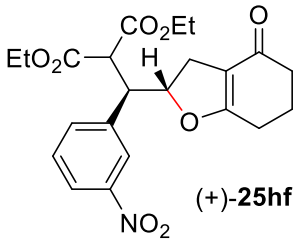
(+)-**25hd**

41% (19.08 mg); $[\alpha]_D^{25}$ = +112.7° (*c* = 0.05, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2978, 2925, 2850, 1730, 1631, 1488, 1402, 1368, 1309, 1228, 1178, 1150, 1115, 1010, 959, 857, 750, 665 and 614 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39 (2H, td, *J* = 8.4, 2.4 Hz), 7.11 (2H, td, *J* = 8.4, 2.4 Hz), 5.23 (1H, ddd, *J* = 9.6, 7.2, 2.4 Hz), 4.32 (2H, dq, *J* = 7.2, 1.2 Hz), 4.15 (1H, d, *J* = 12.0 Hz), 3.93 (2H, dq, *J* = 7.2, 1.2 Hz), 3.55 (1H, dd, *J* = 11.6, 2.4 Hz), 2.91-2.85 (1H, m), 2.45-2.35 (2H, m), 2.31-2.24 (1H, m), 2.23-2.17 (1H, m), 2.13-2.05 (1H, m), 1.98-1.89 (1H, m), 1.85-1.76 (1H, m), 1.33 (3H, t, *J* = 7.2 Hz), 0.97 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.0 (C, *C*=O), 176.7 (C, C=*C*-O), 167.8 (C, O-*C*=O), 167.1 (C, O-*C*=O), 133.6 (C), 131.5 (2 x CH), 131.3 (2 x CH), 122.0 (C), 113.4 (C), 84.1 (CH, C-*C*H-O), 62.1 (CH_2), 61.6 (CH_2), 54.1 (CH), 48.7 (CH), 36.1 (CH_2), 29.4 (CH_2), 23.8 (CH_2), 21.4 (CH_2), 14.0 (CH_3), 13.7 (CH_3); LCMS m/z 465.20 (M + H^+), Calcd for $C_{22}H_{25}BrO_6H$ 465.0913; Anal. Calcd for $C_{22}H_{25}BrO_6$: C, 56.78; H, 5.42. Found: C, 56.71; H, 5.46.

Diethyl 2-((*R*)-(4-nitrophenyl)((*S*)-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)methyl)malonate (25he): The compound was prepared following the procedure **E** and purified by column chromatography using EtOAc/hexanes (3:7 to 4:6) and isolated as a yellow solid; Mp: 109-111 °C; Yield: 63% (27.18 mg); $[\alpha]_D^{25}$ = +125.9° (*c* = 0.20, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2984, 2928, 2869, 1731, 1631, 1604, 1521, 1454, 1401, 1345, 1308, 1256, 1226, 1178, 1110, 1013, 957, 856, 801, 753, 714, 700 and 614 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.14 (2H, br d, *J* = 8.4 Hz), 7.44 (2H, br d, *J* = 8.4 Hz), 5.23 (1H, ddd, *J* = 9.6, 7.2, 2.4 Hz), 4.34-4.26 (2H, m), 4.20 (1H, d, *J* = 11.2 Hz), 3.96-3.84 (2H, m), 3.73 (1H, dd, *J* = 11.6, 2.4 Hz), 2.91 (1H, t, *J* = 12.4 Hz), 2.44-2.35 (2H, m), 2.32-2.24 (1H, m), 2.22-2.15 (1H, m), 2.09-2.02 (1H, m), 1.98-1.89 (1H, m), 1.83-1.73 (1H, m), 1.32 (3H, t, *J* = 7.2 Hz), 0.96 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.8 (C, *C*=O), 176.5 (C, C=*C*-O), 167.4 (C, O-*C*=O), 166.7 (C, O-*C*=O), 147.4 (C), 142.6 (C), 130.7 (2 x CH), 123.1 (2 x CH), 113.2 (C), 83.7 (CH, C-*C*H-O), 62.2 (CH_2), 61.7 (CH_2), 53.8 (CH), 48.8 (CH), 36.0 (CH_2), 29.4 (CH_2), 23.6 (CH_2), 21.3 (CH_2), 13.95 (CH_3), 13.61 (CH_3); LCMS m/z 432.10 (M + H^+), Calcd for $C_{22}H_{25}NO_8H$ 432.1658; Anal. Calcd for $C_{22}H_{25}NO_8$: C, 61.25; H, 5.84; N, 3.25. Found: C, 61.32; H, 5.80; N, 3.31.



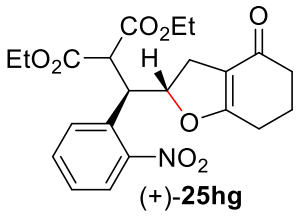
Diethyl 2-((*R*)-(3-nitrophenyl)((*S*)-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)methyl)malonate (25hf): The compound was prepared following the procedure **E** and



(+)-**25hf**

purified by column chromatography using EtOAc/hexanes (3:7 to 4:6) and isolated as oil color liquid; Yield: 34% (14.7 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 mL/min, λ = 254 nm), t_R = 19.79 min (major), t_R = 30.72 min (minor); $[\alpha]_D^{25}$ = +80.7° (*c* = 0.12, $CHCl_3$, 84% *ee* and >99:1 *dr*); IR (Neat): ν_{max} 3015, 2931, 2872, 1729, 1631, 1530, 1404, 1349, 1216, 1180, 1013, 961, 745, 667 and 614 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.17 (1H, t, *J* = 2.0 Hz), 8.13-8.11 (1H, m), 7.59 (1H, br d, *J* = 7.5 Hz), 7.46 (1H, t, *J* = 8.0 Hz), 5.28-5.24 (1H, m), 4.32 (2H, dd, *J* = 7.0, 1.0 Hz), 4.22 (1H, d, *J* = 11.5 Hz), 3.94-3.85 (2H, m), 3.71 (1H, dd, *J* = 11.5, 2.5 Hz), 2.95-2.91 (1H, m), 2.41 (2H, br t, *J* = 6.0 Hz), 2.33 (1H, tdd, *J* = 14.5, 7.0, 1.2 Hz), 2.21-2.15 (1H, m), 2.07-2.01 (1H, m), 1.97-1.89 (1H, m), 1.77-1.71 (1H, m), 1.33 (3H, t, *J* = 7.0 Hz), 0.94 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.9 (C, *C*=O), 176.8 (C, C=*C*-O), 167.5 (C, O-*C*=O), 166.9 (C, O-*C*=O), 148.0 (C), 137.2 (C), 136.8 (CH), 129.1 (CH), 124.0 (CH), 122.9 (CH), 113.2 (C), 83.7 (CH, C-*C*H-O), 62.2 (CH_2), 61.7 (CH_2), 54.0 (CH), 48.8 (CH), 36.1 (CH_2), 29.5 (CH_2), 23.6 (CH_2), 21.4 (CH_2), 14.0 (CH_3), 13.6 (CH_3); LCMS m/z 432.10 ($M + H^+$), Calcd for $C_{22}H_{25}NO_8H$ 432.1658; Anal. Calcd for $C_{22}H_{25}NO_8$: C, 61.25; H, 5.84; N, 3.25. Found: C, 61.18; H, 5.79; N, 3.32.

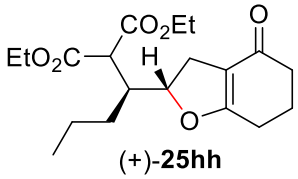
Diethyl 2-((*R*)-(2-nitrophenyl)((*S*)-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)methyl)malonate (25hg): The compound was prepared following the procedure **E** and purified by column chromatography using EtOAc/hexanes (3:7 to 4:6) and isolated as a pale yellow liquid; Yield: 67% (28.91 mg); $[\alpha]_D^{25}$ = +202.2° (*c* = 0.10, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2984, 2942, 1730, 1630, 1527, 1402, 1352, 1226, 1179, 1143, 1011, 956, 854, 748, 711, 665 and 612 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.80 (1H, br d, *J* = 8.0 Hz), 7.53-7.48 (2H, m), 7.43-7.39 (1H, m), 5.32 (1H, ddd, *J* = 9.6, 7.2, 2.4 Hz), 4.48 (1H, dd, *J* = 12.0, 4.0 Hz), 4.27 (2H, dq, *J* = 7.2, 1.2 Hz), 4.15 (1H, d, *J* = 11.2 Hz), 3.96-3.83 (2H, m), 2.98-2.92 (1H, m), 2.57 (1H, tdd, *J* = 16.0, 8.0, 1.2 Hz), 2.49-2.36 (2H, m), 2.30-2.23 (1H, m), 2.21-2.14 (1H, m), 2.04-1.95 (1H, m), 1.94-1.85 (1H, m), 1.30 (3H, t, *J* = 8.0 Hz), 0.97 (3H, t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.1 (C, *C*=O), 176.3 (C, C=*C*-O), 167.2 (C, O-*C*=O), 166.7 (C, O-*C*=O), 151.7 (C), 132.1 (CH), 130.6 (C), 129.9 (CH), 128.6 (CH), 124.7



(+)-**25hg**

(CH), 114.1 (C), 84.7 (CH, C-*C*H-O), 62.2 (CH_2), 61.9 (CH_2), 54.8 (CH), 41.2 (CH), 36.3 (CH_2), 29.4 (CH_2), 23.8 (CH_2), 21.6 (CH_2), 14.0 (CH_3), 13.6 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{25}NO_8H$ 432.1658; Found 432.1658.

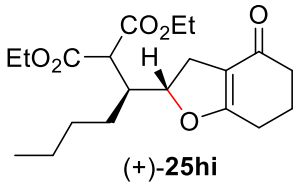
Diethyl 2-((*S*)-1-((*S*)-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)butyl)malonate (25hh):



(+)-**25hh**

The compound was prepared following the procedure **D** or procedure **E** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a colorless liquid; Yield: 52% (18.33 mg, procedure **D**), 50% (17.62 mg, procedure **E**); $[\alpha]_D^{25}$ = +91.4° (*c* = 0.08, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2958, 2937, 2872, 1727, 1633, 1455, 1404, 1369, 1301, 1231, 1180, 1153, 1059, 1032, 946, 858 and 602 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.05 (1H, ddd, *J* = 12.5, 8.5, 4.0 Hz), 4.23-4.18 (4H, m), 3.50 (1H, d, *J* = 7.0 Hz), 2.94-2.89 (1H, m), 2.61 (1H, tdd, *J* = 14.5, 8.5, 1.2 Hz), 2.56-2.54 (1H, m), 2.39-2.34 (4H, m), 2.03 (2H, quintet, *J* = 6.5 Hz), 1.50-1.31 (4H, m), 1.28 (6H, 2 x CH_3, t, *J* = 7.0 Hz), 0.90 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.4 (C, *C*=O), 177.5 (C, C=*C*-O), 168.6 (C, O-*C*=O), 168.5 (C, O-*C*=O), 113.4 (C), 86.3 (CH, C-*C*H-O), 61.5 (2 x CH_2), 52.5 (CH), 42.4 (CH), 36.4 (CH_2), 29.4 (CH_2), 28.8 (CH_2), 23.8 (CH_2), 21.7 (CH_2), 21.0 (CH_2), 14.3 (CH_3), 14.0 (2 x CH_3); LCMS m/z 353.15 ($M + H^+$), Calcd for $C_{19}H_{28}O_6H$ 353.1964; Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.82; H, 8.07.

Diethyl 2-((*S*)-1-((*S*)-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)pentyl)malonate (25hi):

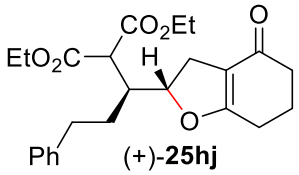


(+)-**25hi**

The compound was prepared following the procedure **D** or procedure **E** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a colorless liquid; Yield: 55% (20.15 mg, procedure **D**), 50% (18.32 mg, procedure **E**); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak OD-H column (hexane/2-propanol = 95:05, flow rate 0.5 mL/min, λ = 254 nm), t_R = 22.0 min (major), t_R = 26.8 min (minor); $[\alpha]_D^{25}$ = +79.0° (*c* = 0.12, $CHCl_3$, 97% *ee* and >99% *de*); IR (KBr): ν_{max} 2954, 2934, 2871, 1727, 1631, 1455, 1402, 1368, 1229, 1176, 1157, 1060, 1030, 943, 858 and 602 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.07-5.02 (1H, m), 4.23-4.17 (4H, m), 3.50 (1H, d, *J* = 6.5 Hz), 2.93-2.89 (1H, m), 2.61 (1H, dd, *J* = 14.5, 9.0 Hz), 2.55-2.50 (1H, m), 2.38-2.33 (4H, m), 2.03 (2H, quintet, *J* = 6.0 Hz), 1.50-1.37 (2H, m), 1.36-1.23 (4H, m), 1.23 (6H, 2 x CH_3, t, *J* = 7.0 Hz), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.2 (C, *C*=O), 177.4 (C, C=*C*-

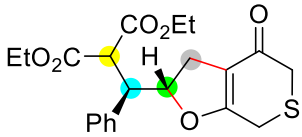
O), 168.54 (C, O-*C*=O), 168.46 (C, O-*C*=O), 113.3 (C, C=*C*-C), 86.3 (CH, C-*C*H-O), 61.4 (2 x CH_2), 52.5 (CH), 42.5 (CH), 36.2 (CH_2), 29.9 (CH_2), 29.3 (CH_2), 26.4 (CH_2), 23.7 (CH_2), 22.8 (CH_2), 21.6 (CH_2), 14.0 (2 x CH_3), 13.8 (CH_3); LCMS m/z 367.30 ($M + H^+$), Calcd for $C_{20}H_{30}O_6H$ 367.2121; Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.48; H, 8.32.

Diethyl 2-((*S*)-1-((*S*)-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)-3-phenylpropyl)malonate (25hj): The compound was prepared following the procedure **D** or procedure **E** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a colourless liquid; Yield: 72% (29.84 mg, procedure **D**), 50% (20.72 mg, procedure **E**); $[\alpha]_D^{25}$ = +110.0° (*c* = 0.06, $CHCl_3$, >99% *de*); IR (KBr): ν_{max} 2981, 2929, 2869, 1727, 1634, 1454, 1402, 1368, 1299, 1229, 1180, 1153, 1115, 1029, 939, 858, 751, 701 and 601 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.29 (2H, br t, *J* = 7.0 Hz), 7.20 (1H, br t, *J* = 7.5 Hz), 7.16 (2H, br d, *J* = 7.5 Hz), 5.08 (1H, ddd, *J* = 13.0, 8.5, 4.0 Hz), 4.26-4.19 (4H, m), 3.59 (1H, d, *J* = 6.0 Hz), 2.96-2.91 (1H, m), 2.76-2.71 (1H, m), 2.66-2.55 (3H, m), 2.38-2.33 (4H, m), 2.02 (2H, quintet, *J* = 6.5 Hz), 1.89-1.83 (1H, m), 1.81-1.73 (1H, m), 1.293 (3H, t, *J* = 7.0 Hz), 1.287 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.2 (C, *C*=O), 177.3 (C, C=*C*-O), 168.41 (C, O-*C*=O), 168.36 (C, O-*C*=O), 141.5 (C), 128.5 (2 x CH), 128.3 (2 x CH), 126.1 (CH), 113.3 (C, C=*C*-C), 86.2 (CH, C-*C*H-O), 61.58 (CH_2), 61.56 (CH_2), 52.4 (CH), 42.3 (CH), 36.3 (CH_2), 34.2 (CH_2), 29.6 (CH_2), 28.9 (CH_2), 23.7 (CH_2), 21.6 (CH_2), 14.1 (2 x CH_3); LCMS m/z 415.25 ($M + H^+$), Calcd for $C_{24}H_{30}O_6H$ 415.2121; Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.55; H, 7.30. Found: C, 69.45; H, 7.26.



(+)-**25hj**

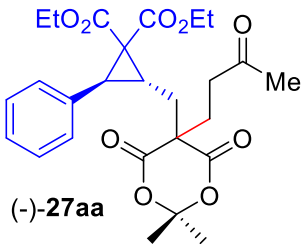
Diethyl 2-((*R*)-((*S*)-4-oxo-3,4,5,7-tetrahydro-2*H*-thiopyrano[3,4-*b*]furan-2-yl)(phenyl)methyl)malonate (25pa): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a colorless liquid; Yield: 70% (28.31 mg); $[\alpha]_D^{25}$ = +41.3° (*c* = 0.92, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2979, 2927, 1729, 1631, 1454, 1388, 1299, 1253, 1179, 1099, 1017, 959, 860, 768, 705 and 612 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.27-7.22 (3H, m), 7.19 (2H, br d, *J* = 8.0 Hz), 5.21-5.17 (1H, m), 4.31-4.23 (2H, m), 4.17 (1H, d, *J* = 11.5 Hz), 3.89-3.82 (2H, m), 3.57 (1H, dd, *J* = 11.5, 2.5 Hz), 3.29 (2H, s), 3.00 (1H, d, *J* = 16 Hz), 2.92 (1H, d, *J* = 16.0 Hz), 2.91-2.89 (1H, m), 2.52 (1H, dd, *J* = 15.0, 7.5 Hz), 1.31 (3H, t, *J* = 7.5 Hz), 0.89 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 189.9 (C, C=O), 171.5 (C, C=*C*-O), 168.0 (C, O-*C*=O), 167.2 (C,



(+)-**25pa**

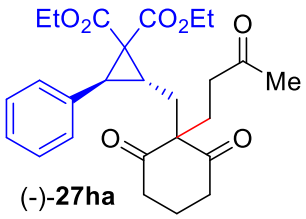
O-*C*=O), 134.3 (C), 129.7 (2 x CH), 128.2 (2 x CH), 127.9 (CH), 112.8 (C), 84.2 (CH, C-*C*H-O), 62.0 (CH_2), 61.4 (CH_2), 54.0 (CH), 49.2 (CH), 33.2 (CH_2), 30.1 (CH_2), 23.3 (CH_2), 14.1 (CH_3), 13.6 (CH_3); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{24}O_6SNa$ 427.1191; Found 427.1191.

Diethyl (2*R*,3*S*)-2-((2,2-dimethyl-4,6-dioxo-5-(3-oxobutyl)-1,3-dioxan-5-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (27aa): The compound was prepared following the procedure **F** and purified by column chromatography using EtOAc/hexanes (2:8) and isolated as a colorless liquid; Yield: 71% (34.7 mg); $[\alpha]_D^{25}$ = –24.1° (*c* = 0.42, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2984, 2924, 2852, 1771, 1717, 1445, 1368, 1285, 1206, 1096, 1059, 1024, 977, 939, 861, 747 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.22-7.15 (3H, m), 7.12 (2H, d, *J* = 7.0 Hz), 4.36-4.29 (1H, m), 4.23-4.17 (1H, m), 3.86-3.75 (2H, m), 3.05 (1H, d, *J* = 7.5 Hz), 2.62 (2H, t, *J* = 7.5 Hz), 2.44-2.40 (2H, m), 2.32-2.29 (2H, m), 2.21 (1H, dd, *J* = 15.5, 9.5 Hz), 2.13 (3H, s), 1.81 (3H, s), 1.58 (3H, s), 1.30 (3H, t, *J* = 7.0 Hz), 0.82 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.0 (C, C=O), 168.7 (C, O-*C*=O), 168.5 (C, O-*C*=O), 167.3 (C, O-*C*=O), 166.2 (C, O-*C*=O), 134.0 (C), 128.3 (2 x CH), 128.1 (2 x CH), 127.4 (CH), 105.9 (C), 61.9 (CH_2), 61.3 (CH_2), 51.8 (C), 43.0 (C), 37.9 (CH_2), 36.1 (CH), 35.0 (CH_2), 31.3 (CH_2), 29.9 (CH_3), 29.5 (CH_3), 28.7 (CH_3), 25.8 (CH), 14.1 (CH_3), 13.6 (CH_3); LCMS m/z 488.65 (M^+), Calcd for $C_{26}H_{32}O_9$ 488.2046; Anal. Calcd for $C_{26}H_{32}O_9$: C, 63.92; H, 6.60. Found: C, 63.85; H, 6.64.



(-)-**27aa**

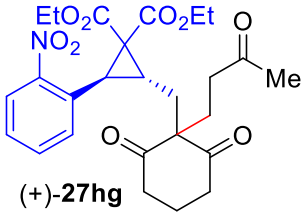
Diethyl (2*R*,3*S*)-2-((2,6-dioxo-1-(3-oxobutyl)cyclohexyl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (27ha): The compound was prepared following the procedure **G** and purified by column chromatography using EtOAc/hexanes (3:7) and isolated as a colorless liquid; Yield: 74% (33.8 mg); $[\alpha]_D^{25}$ = –22.2° (*c* = 0.20, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2932, 1713, 1444, 1368, 1295, 1218, 1135, 1098, 1024, 989, 861, 748, 697 and 667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.26-7.20 (3H, m), 7.12 (2H, d, *J* = 7.0 Hz), 4.37-4.34 (1H, m), 4.27-4.23 (1H, m), 3.86-3.78 (2H, m), 3.02 (1H, d, *J* = 8.5 Hz), 2.71-2.66 (4H, m), 2.36 (2H, t, *J* = 7.0 Hz), 2.29-2.24 (1H, m), 2.15-2.08 (3H, m), 2.10 (3H, s, COC*H*$_3$), 2.04-1.98 (3H, m), 1.33 (3H, t, *J* = 7.0 Hz), 0.84 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.2 (C, C=O), 209.7 (C, C=O), 207.2 (C, C=O), 167.6 (C, O-*C*=O), 166.6 (C, O-*C*=O), 134.4 (C), 128.4 (2 x CH), 128.1 (2 x



(-)-**27ha**

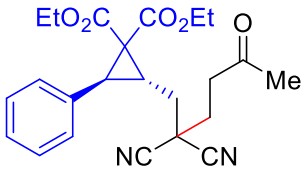
CH), 127.3 (CH), 67.0 (C), 61.9 (CH_2), 61.2 (CH_2), 43.1 (C), 38.95 (CH_2), 38.92 (CH_2), 38.3 (CH_2), 36.7 (CH), 32.2 (CH_2), 29.9 (CH_3), 28.9 (CH_2), 26.4 (CH), 17.0 (CH_2), 14.1 (CH_3), 13.6 (CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{32}O_7H$ 457.2226; Found 457.2226.

Diethyl (2*R*,3*S*)-2-((2,6-dioxo-1-(3-oxobutyl)cyclohexyl)methyl)-3-(2-nitrophenyl)cyclopropane-1,1-dicarboxylate (27hg): The title compound was prepared following the procedure **G** and purified by column chromatography using EtOAc/hexanes (3:7) and isolated as a pale yellow liquid; Yield: 72% (36.11 mg); $[\alpha]_D^{25}$ = +140.2° (*c* = 0.12, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 3020, 2925, 2852, 1717, 1693, 1528, 1444, 1368, 1348, 1296, 1216, 1097, 1024, 875, 748, 704, 667 and 555 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.02 (1H, dd, *J* = 8.0, 1.2 Hz), 7.58 (1H, dt, *J* = 7.6, 1.2 Hz), 7.43 (1H, dt, *J* = 8.0, 1.2 Hz), 7.34 (1H, d, *J* = 7.6 Hz), 4.42-4.34 (1H, m), 4.32-4.24 (1H, m), 3.88-3.80 (1H, m), 3.76-3.68 (1H, m), 3.60 (1H, d, *J* = 7.6 Hz), 2.77-2.69 (4H, m), 2.37 (2H, t, *J* = 7.2 Hz), 2.20-2.13 (5H, m), 2.11 (3H, s, COC*H*$_3$), 2.10-2.02 (2H, m), 1.33 (3H, t, *J* = 7.2 Hz), 0.90 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.2 (C, C=O), 209.1 (C, C=O), 207.3 (C, C=O), 167.0 (C, O-*C*=O), 166.7 (C, O-*C*=O), 149.8 (C), 133.4 (CH), 131.2 (CH), 130.6 (C), 128.6 (CH), 128.4 (CH), 67.6 (C), 62.0 (CH_2), 61.6 (CH_2), 41.5 (C), 38.64 (CH_2), 38.56 (CH_2), 38.2 (CH_2), 34.8 (CH), 31.3 (CH_2), 29.9 (CH_3), 28.1 (CH_2), 27.3 (CH), 17.1 (CH_2), 14.0 (CH_3), 13.5 (CH_3); LCMS m/z 502.45 ($M + H^+$), Calcd for $C_{26}H_{31}NO_9H$ 502.2077; Anal. Calcd for $C_{26}H_{31}NO_9$: C, 62.27; H, 6.23; N, 2.79. Found: C, 62.36; H, 6.19; N, 2.82.



(+)-**27hg**

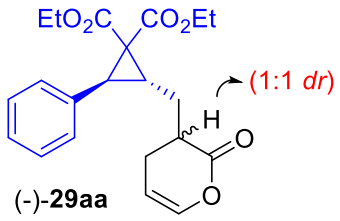
Diethyl (2*R*,3*S*)-2-(2,2-dicyano-5-oxohexyl)-3-phenylcyclopropane-1,1-dicarboxylate (27ma): The compound was prepared following the procedure **H** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 85% (34.9 mg); $[\alpha]_D^{25}$ = –25.1° (*c* = 0.16, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2925, 2854, 1716, 1445, 1368, 1298, 1221, 1192, 1169, 1140, 1097, 1023, 864, 747, 697 and 551 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.32-7.27 (3H, m), 7.25-7.20 (2H, m), 4.39-4.32 (1H, m), 4.27-4.21 (1H, m), 3.94-3.83 (2H, m), 3.29 (1H, d, *J* = 8.0 Hz), 2.89 (2H, t, *J* = 8.0 Hz), 2.82-2.77 (1H, m), 2.50-2.46 (1H, m), 2.36-2.28 (2H, m), 2.25 (3H, s, COC*H*$_3$), 2.19 (1H, dd, *J* = 14.0, 8.5 Hz), 1.32 (3H, t, *J* = 7.5 Hz), 0.90 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 204.3 (C, C=O), 167.6 (C, O-*C*=O), 165.7 (C, O-*C*=O), 133.2 (C), 128.43 (2 x CH), 128.39 (2 x CH), 127.8 (CH),



(-)-**27ma**

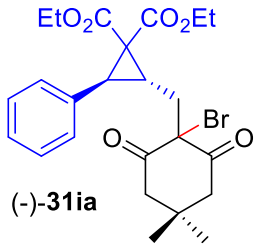
114.7 (2 x C, *C*≡N), 62.4 (CH_2), 61.6 (CH_2), 42.1 (C), 39.2 (CH_2), 36.53 (CH), 36.47 (C), 35.1 (CH_2), 31.5 (CH_2), 30.0 (CH_3), 25.6 (CH), 14.1 (CH_3), 13.6 (CH_3); HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{23}H_{26}N_2O_5$ 410.1842; Found 410.1843.

Diethyl (2*R*,3*S*)-2-((2-oxo-3,4-dihydro-2H-pyran-3-yl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (29aa): The compound was prepared following the procedure **I** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a colorless liquid; Yield: 47% (17.5 mg); $[\alpha]_D^{25}$ = –51.4° (*c* = 0.37, $CHCl_3$, 1:1 *dr*); IR (Neat): ν_{max} 2924, 2854, 1719, 1445, 1369, 1292, 1221, 1192, 1100, 1069, 1025, 861, 744, 697 and 546 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 1:1 diastereomers): δ 7.29-7.26 (4H, 2 x 2H, m), 7.24-7.20 (6H, 2 x 3H, m), 6.510 (1H, d, *J* = 2.5 Hz, olefinic-*H*), 6.497 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 5.32-5.29 (2H, 2 x 1H, m, olefinic-*H*), 4.34-4.29 (2H, 2 x 1H, m), 4.27-4.22 (2H, 2 x 1H, m), 3.90-3.83 (4H, 2 x 2H, m), 3.12 (2H, 2 x 1H, dd, *J* = 8.5, 5.5 Hz), 2.80-2.73 (4H, 2 x 2H, m), 2.68-2.64 (4H, 2 x 2H, m), 2.51-2.46 (2H, 2 x 1H, m), 2.30-2.16 (4H, 2 x 2H, m), 1.84-1.71 (4H, 2 x 2H, m), 1.312 (3H, t, *J* = 7.0 Hz), 1.307 (3H, t, *J* = 7.0 Hz), 0.884 (3H, t, *J* = 7.0 Hz), 0.880 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.2 (2 x C, O-*C*=O), 167.83 (C, O-*C*=O), 167.80 (C, O-*C*=O), 166.72 (C, O-*C*=O), 166.67 (C, O-*C*=O), 141.48 (CH), 141.41 (CH), 134.5 (2 x C), 128.58 (2 x CH), 128.53 (2 x CH), 128.19 (2 x CH), 128.16 (2 x CH), 127.34 (CH), 127.30 (CH), 105.03 (CH), 105.00 (CH), 61.9 (CH_2), 61.8 (CH_2), 61.3 (2 x CH_2), 43.2 (C), 42.9 (C), 38.7 (CH), 38.6 (CH), 36.6 (CH), 36.4 (CH), 28.1 (CH), 27.76 (CH_2), 27.72 (CH), 27.70 (CH_2), 24.3 (CH_2), 24.1 (CH_2), 14.20 (CH_3), 14.17 (CH_3), 13.7 (2 x CH_3); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{24}O_6H$ 373.1651; Found 373.1652.



(-)-**29aa**

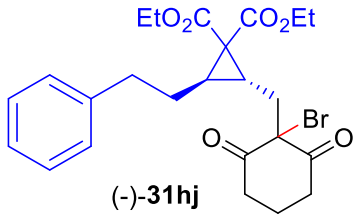
Diethyl (2*R*,3*S*)-2-((1-bromo-4,4-dimethyl-2,6-dioxocyclohexyl)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (31ia): The compound was prepared following the procedure **J** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 80% (39.5 mg); $[\alpha]_D^{25}$ = –36.3° (*c* = 0.25, $CHCl_3$, >99:1 *dr*); IR (Neat): ν_{max} 2959, 2929, 2869, 1720, 1704, 1502, 1464, 1424, 1372, 1292, 1245, 1219, 1190, 1128, 1096, 1023, 863, 745, 697, 618 and 549 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.25-7.21 (2H, m), 7.19-7.16 (3H, m), 4.41-4.35 (1H, m), 4.33-4.27 (1H, m), 3.87-3.77 (2H, m), 3.43 (2H, dd, *J* = 14.0, 7.0 Hz), 3.22 (1H, d, *J* = 7.5 Hz), 2.62-2.58 (2H, m), 2.46-2.41



(-)-**31ia**

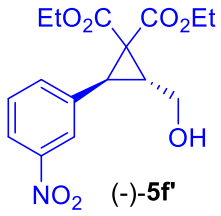
(3H, m), 1.34 (3H, t, J = 7.0 Hz), 1.18 (3H, s, CH_3), 0.84 (3H, t, J = 7.0 Hz), 0.82 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 200.7 (C, C=O), 200.3 (C, C=O), 167.8 (C, O-*C*=O), 166.6 (C, O-*C*=O), 134.6 (C), 128.6 (2 x CH), 128.0 (2 x CH), 127.1 (CH), 61.7 (CH_2), 61.69 (C), 61.7 (CH_2), 49.6 (CH_2), 49.4 (CH_2), 43.5 (C), 37.2 (CH), 30.8 (C), 30.4 (CH), 29.7 (CH_2), 27.5 (CH_3), 25.8 (CH_3), 14.2 (CH_3), 13.7 (CH_3); LCMS m/z 493.00 (M + H^+), Calcd for $C_{24}H_{29}BrO_6H$ 493.1226; Anal. Calcd for $C_{24}H_{29}BrO_6$: C, 58.42; H, 5.92. Found: C, 58.36; H, 5.89.

Diethyl (2*R*,3*R*)-2-((1-bromo-2,6-dioxocyclohexyl)methyl)-3-phenethylcyclopropane-1,1-dicarboxylate (31hj): The compound was prepared following the procedure **M** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a colorless liquid; Yield: 83% (61.43 mg); $[\alpha]_D^{25}$ = –16.5° (*c* = 0.08, $CHCl_3$, >95% *de*); IR (KBr): ν_{max} 2924, 2852, 1716, 1600, 1454, 1369, 1291, 1210, 1176, 1110, 1032, 861, 750, 698, 667 and 568 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28 (2H, br t, J = 7.5 Hz), 7.19 (1H, br t, J = 7.25 Hz), 7.15 (2H, br d, J = 7.0 Hz), 4.32-4.28 (1H, m), 4.27-4.21 (2H, m), 4.17-4.10 (1H, m), 3.29-3.20 (2H, m), 2.70-2.59 (2H, m), 2.58-2.56 (2H, m), 2.56-2.52 (1H, m), 2.27-2.22 (2H, m), 1.95 (1H, q, J = 7.5 Hz), 1.87-1.79 (1H, m), 1.66-1.58 (3H, m), 1.32 (3H, t, J = 7.0 Hz), 1.27 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 200.37 (C, *C*=O), 200.14 (C, *C*=O), 168.16 (C, O-*C*=O), 168.11 (C, O-*C*=O), 141.4 (C), 128.36 (2 x CH), 128.32 (2 x CH), 125.9 (CH), 62.3 (C, *C*-Br), 61.5 (CH_2), 61.4 (CH_2), 40.3 (C), 36.54 (CH_2), 36.48 (CH_2), 35.0 (CH_2), 33.1 (CH), 30.5 (CH_2), 30.4 (CH_2), 29.7 (CH), 17.5 (CH_2), 14.1 (2 x CH_3); LCMS m/z 493.1 (M + H^+), Calcd for $C_{24}H_{29}BrO_6H$ 493.1226; Anal. Calcd for $C_{24}H_{29}BrO_6$: C, 58.42; H, 5.92. Found: C, 58.36; H, 5.87.



(-)-**31hj**

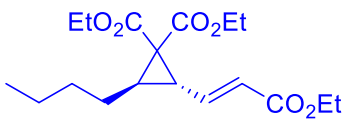
Diethyl (2*R*,3*S*)-2-(hydroxymethyl)-3-(3-nitrophenyl)cyclopropane-1,1-dicarboxylate (5f′): The compound was prepared following the procedure **K** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 2.5:7.5) and isolated as a colorless liquid; Yield: 76% (25.64 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 0.8 mL/min, λ = 254 nm), t_R = 32.71 min (major), t_R = 27.81 min (minor); $[\alpha]_D^{25}$ = –59.1° (*c* = 0.07, $CHCl_3$, 86% *ee* and >99:1 *dr*); IR (Neat): ν_{max} 2981, 2927, 1717, 1523, 1465, 1348, 1291, 1193, 1128, 1027, 805, 734, 687 and 672 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.12 (1H, s), 8.10 (1H, d, J = 8.5 Hz), 7.60 (1H, d,



(-)-**5f'**

J = 8.0 Hz), 7.47 (1H, t, *J* = 8.0 Hz), 4.33-4.27 (2H, m), 4.01 (1H, dd, *J* = 12.0, 6.0 Hz), 3.98-3.86 (2H, m), 3.69 (1H, dd, *J* = 12.0, 8.0 Hz), 3.25 (1H, d, *J* = 8.0 Hz), 2.86 (1H, q, *J* = 7.0 Hz), 2.36 (1H, br s), 1.33 (3H, t, *J* = 7.0 Hz), 0.97 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.6 (C, O-*C*=O), 166.3 (C, O-*C*=O), 148.1 (C), 136.7 (C), 135.0 (CH), 129.2 (CH), 123.8 (CH), 122.5 (CH), 62.3 (CH_2), 61.8 (CH_2), 60.4 (CH_2), 41.9 (C), 33.8 (CH), 32.3 (CH), 14.1 (CH_3), 13.8 (CH_3); LCMS m/z 338.28 ($M + H^+$), Calcd for $C_{16}H_{19}NO_7H$ 338.1240; Anal. Calcd for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68; N, 4.15. Found: C, 56.85; H, 5.62; N, 4.19.

Diethyl (2*R*,3*R*)-2-butyl-3-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)cyclopropane-1,1-dicarboxylate (5i′): The compound was prepared following the procedure **L** and purified by column chromatography using EtOAc/hexanes (0.25:9.75 to 0.5:9.5) and isolated as a colourless liquid; Yield: 85% (28.93 mg); The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel IC-3 column (hexane/2-propanol = 97:03, flow rate 0.5 mL/min, λ = 254 nm), t_R = 21.31 min (minor), t_R = 25.17 min (major); $[\alpha]_D^{25}$ = –32.5° (*c* = 0.13, $CHCl_3$, 98% *ee* and >92% *de*); IR (neat): ν_{max} 2959, 2932, 2872, 1717, 1650, 1465, 1368, 1288, 1201, 1139, 1029, 982, 861 and 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.52 (1H, dd, *J* = 15.5, 10.0 Hz), 6.01 (1H, d, *J* = 15.5 Hz), 4.26-4.21 (2H, m), 4.20-4.17 (2H, m), 4.16 (2H, q, *J* = 7.0 Hz), 2.48 (1H, dd, *J* = 10.0, 7.5 Hz), 2.13 (1H, q, *J* = 7.0 Hz), 1.50-1.45 (1H, m), 1.36-1.27 (5H, m), 1.26 (3H, t, *J* = 7.5 Hz), 1.25 (3H, t, *J* = 7.5 Hz), 1.23 (3H, t, *J* = 7.5 Hz), 0.86 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.3 (C, C=*C*-O), 167.2 (C, C=*C*-O), 165.7 (C, O-*C*=O), 143.6 (CH), 123.6 (CH), 61.69 (CH_2), 61.66 (CH_2), 60.2 (CH_2), 42.6 (C), 34.3 (CH), 33.4 (CH), 30.9 (CH_2), 27.0 (CH_2), 22.1 (CH_2), 14.2 (CH_3), 14.11 (CH_3), 14.07 (CH_3), 13.9 (CH_3); LCMS m/z 341.10 ($M + H^+$), Calcd for $C_{18}H_{28}O_6H$ 341.1964; Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.45; H, 8.23.

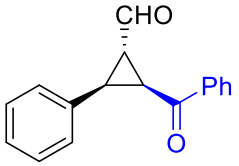


(-)-**5i'**

Chapter 4:

Materials: The chiral dicarbonyl-cyclopropane compounds (-)-**3a-3v** (90 to >99.9% *ee*) were prepared by following the reported method.[18]

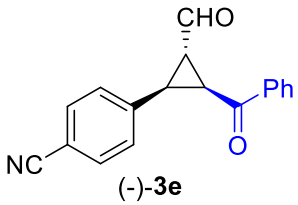
(1*S*,2*S*,3*S*)-2-benzoyl-3-phenylcyclopropane-1-carbaldehyde (3a): The compound was prepared following the reported procedure[18] and purified by column



(-)-**3a**

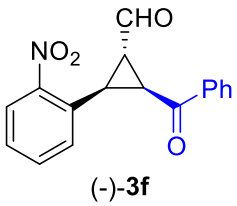
chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow solid (mp = 82-84 °C); Yield: 78% (585 mg); $[\alpha]_D^{25}$ = –111.83° (*c* = 0.093, $CHCl_3$, >99.9% *ee*, >20:1 *dr*); IR (Neat): ν_{max} 3056, 3040, 2837, 2736, 2362, 1704, 1665, 1597, 1446, 1360, 1272, 1216, 1053, 1015, 952, 861, 689 and 643 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.87 (1H, d, *J* = 2.5 Hz), 7.93 (2H, d, *J* = 7.5 Hz), 7.55 (1H, tt, *J* = 7.5 Hz), 7.44 (2H, t, *J* = 8.0 Hz), 7.23-7.14 (5H, m), 3.67 (1H, dd, *J* = 10.0, 4.5 Hz), 3.59-3.54 (1H, m), 3.42 (1H, dd, *J* = 10.5, 6.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 198.7 (C, *C*HO), 192.6 (C, *C*=O), 137.3 (C), 133.4 (CH), 133.3 (C), 128.74 (2 x CH), 128.71 (2 x CH), 128.32 (2 x CH), 128.3 (2 x CH), 127.5 (CH), 36.4 (CH), 35.6 (CH), 33.9 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{17}H_{14}O_2H$ 251.1072; Found 251.1072.

4-((1*S*,2*S*,3*S*)-2-benzoyl-3-formylcyclopropyl)benzonitrile (**3e**): The compound was prepared following the reported procedure[18] and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a brown liquid; Yield: 80% (660 mg); $[\alpha]_D^{25}$ = –96.26° (*c* = 0.107, $CHCl_3$, >99.9% *ee*, >20:1 *dr*); IR (Neat): ν_{max} 3059, 2921, 2854, 2226, 1704, 1670, 1606, 1448, 1279, 1220, 1016, 839 , 691 and 560 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.87 (1H, d, *J* = 2.5 Hz), 7.91 (2H, dd, *J* = 8.5, 1.5 Hz), 7.57 (1H, t, *J* = 7.0 Hz), 7.51-7.43 (4H, m), 7.30 (2H, d, *J* = 8.0 Hz), 3.74 (1H, dd, *J* = 10.5, 5.0 Hz), 3.59-3.54 (1H, m), 3.43 (1H, dd, *J* = 10.0, 6.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 197.8 (C, *C*HO), 192.1 (C, *C*=O), 138.8 (C), 136.7 (C), 133.6 (CH), 131.9 (2 x CH), 129.5 (2 x CH), 128.7 (2 x CH), 128.1 (2 x CH), 118.4 (C, *C*N), 111.1 (C), 35.3 (CH), 35.2 (CH), 33.7 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{18}H_{13}NO_2H$ 276.1025; Found 276.1022.



(-)-**3e**

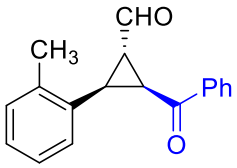
(1*S*,2*S*,3*S*)-2-benzoyl-3-(2-nitrophenyl)cyclopropane-1-carbaldehyde (**3f**): The compound was prepared following the reported procedure[18] and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a red brown liquid; Yield: 71% (628.5 mg); $[\alpha]_D^{25}$ = –101.23° (*c* = 0.101, $CHCl_3$, 99% *ee*, 2:1 *dr*); IR (Neat): ν_{max} 3061, 2849, 2738, 1710, 1666, 1519, 1343, 1216, 1008, 785, 732 , and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): **Major:** δ 9.78 (1H, d, *J* = 3.0 Hz), 8.07 (1H, d, *J* = 7.5 Hz), 7.94 (2H, d, *J* = 7.5 Hz), 7.65-7.38 (6H, m), 3.89 (1H, dd, *J* = 10.0, 4.5 Hz), 3.82-3.72 (1H, m), 3.51-3.41 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 197.6 (C, *C*HO), 193.2 (C, *C*=O), 149.5 (C), 136.7 (C), 133.7 (CH), 133.1 (CH), 132.1 (CH), 129.6



(-)-**3f**

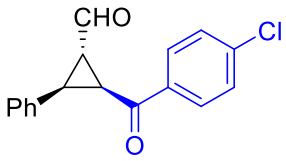
(C), 128.9 (CH), 128.73 (2 x CH), 128.4 (2 x CH), 124.9(CH), 36.1 (CH), 34.1 (CH), 33.7 (CH); **Minor:** δ 9.52 (1H, d, *J* = 2.5 Hz), 7.98 (1H, d, *J* = 8.0 Hz), 7.91 (2H, d, *J* = 8.0 Hz), 7.65-7.38 (6H, m), 3.94 (1H, dd, *J* = 6.5, 5.0 Hz), 3.82-3.72 (1H, m), 3.27-3.21 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 196.2 (C, *C*HO), 195.0 (C, *C*=O), 150.1 (C), 136.5 (C), 134.0 (CH), 133.9 (CH), 132.13 (CH), 129.9 (C), 128.9 (CH), 128.7 (2 x CH), 128.5 (CH), 128.4 (2 x CH), 39.0 (CH), 34.4 (CH), 30.6 (CH); HRMS (ESI-TOF) *m/z*: (M + Na^+) calcd for $C_{17}H_{13}NO_4Na$ 318.0742; Found 318.0742.

(1*S*,2*S*,3*S*)-2-benzoyl-3-(o-tolyl)cyclopropane-1-carbaldehyde (**3i**): The compound was prepared following the reported procedure[18] and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 78% (618 mg); $[\alpha]_D^{25}$ = –111.27° (*c* = 0.142, $CHCl_3$, >97% *ee*, >20:1 *dr*); IR (Neat): ν_{max} 3062, 3027, 2923, 2852, 1712, 1670, 1448, 1217, 841, 704 and 444 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.86 (1H, d, *J* = 2.5 Hz), 7.96 (2H, dd, *J* = 8.5, 1.5 Hz), 7.55 (1H, tt, *J* = 7.0, 1.5 Hz), 7.44 (2H, t, *J* = 8.0 Hz), 7.19-7.16 (1H, m), 7.14-7.11 (2H, m), 7.06-7.02 (1H, m), 3.80 (1H, dd, *J* = 9.5, 4.5 Hz), 3.57-3.52 (1H, m), 3.32 (1H, dd, *J* = 10.0, 6.5 Hz), 2.21 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 198.8 (C, *C*HO), 192.4 (C, *C*=O), 137.5 (C), 137.1 (C), 133.4 (CH), 131.4 (C), 130.0 (CH), 129.0 (CH), 128.7 (2 x CH), 128.3 (2 x CH), 127.6 (CH), 125.7 (CH), 35.6 (CH), 35.0 (CH), 34.1 (CH), 19.8 (CH_3); HRMS (ESI-TOF) *m/z*: (M + Na^+) calcd for $C_{18}H_{16}O_2Na$ 287.1048; Found 287.1049.



(-)-**3i**

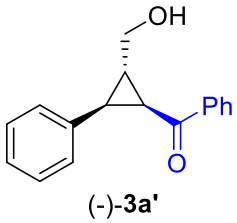
(1*S*,2*S*,3*S*)-2-(4-chlorobenzoyl)-3-phenylcyclopropane-1-carbaldehyde (**3l**): The compound was prepared following the reported procedure[18] and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 72% (613.6 mg); $[\alpha]_D^{25}$ = –155.77° (*c* = 0.104, $CHCl_3$, >99% *ee*, >20:1 *dr*); IR (Neat): ν_{max} 3059, 3034, 2846, 2738, 1711, 1670, 1587, 1400, 1212, 1090, 1008, 732, 696 and 529 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.87 (1H, d, *J* = 2.5 Hz), 7.87 (2H, dt, *J* = 9.5, 2.5 Hz), 7.40 (2H, dt, *J* = 9.5, 2.5 Hz), 7.23-7.13 (5H, m), 3.62 (1H, dd, *J* = 10.0, 4.5 Hz), 3.58-3.54 (1H, m), 3.41 (1H, dd, *J* = 10.0, 6.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 198.5 (C, *C*HO), 191.4 (C, *C*=O), 139.9 (C), 135.6 (C), 133.1 (C), 129.6 (2 x CH), 129.0 (2 x CH), 128.6 (2 x CH), 128.4 (2 x CH), 127.6 (CH), 36.5



(-)-**3l**

(CH), 35.5 (CH), 33.7 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{17}H_{13}ClO_2H$ 285.0682; Found 285.0680.

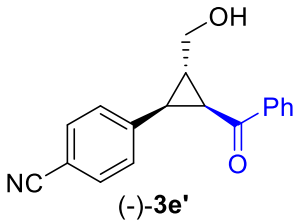
((1*S*,2*S*,3*S*)-2-(hydroxymethyl)-3-phenylcyclopropyl)(phenyl)methanone (**3a′**): The



(-)-**3a'**

compound was prepared following the procedure **K** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a colorless liquid; Yield: 70% (17.65 mg); $[\alpha]_D^{25}$ = –91.0° (*c* = 0.100, $CHCl_3$, >99.9% *ee*, >20:1 *dr*); IR (Neat): ν_{max} 3434, 3057, 3030, 2922, 2872, 2359, 2340, 1661, 446, 1372, 1240, 1219, 1055, 1022, 940, 730, 710 and 534 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.91 (2H, dt, *J* = 8.5, 2.0 Hz), 7.51 (1H, tt, *J* = 8.0, 2.0 Hz), 7.41 (2H, tt, *J* = 8.0, 2.0 Hz), 7.23-7.17 (4H, m), 7.16-7.11 (1H, m), 3.91-3.81 (2H, m), 3.08 (1H, dd, *J* = 9.5, 5.0 Hz), 2.89 (1H, dd, *J* = 10.0, 7.0 Hz), 2.78 (1H, quint, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 195.5 (C, *C*=O), 138.3 (C), 135.3 (C), 132.7 (CH), 129.0 (2 x CH), 128.5 (2 x CH), 128.1 (2 x CH), 128.0 (2 x CH), 126.8 (CH), 64.0 (CH_2), 34.0 (CH), 31.7 (CH), 27.2 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{17}H_{16}O_2H$ 253.1229; Found 253.1229.

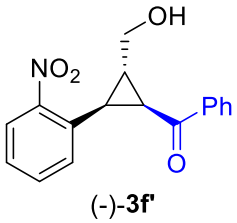
4-((1*S*,2*S*,3*S*)-2-benzoyl-3-(hydroxymethyl)cyclopropyl)benzonitrile (**3e′**): The compound



(-)-**3e'**

was prepared following the procedure **K** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 62% (17.2 mg); $[\alpha]_D^{25}$ = –303.51° (*c* = 0.057, $CHCl_3$, >99.9% *ee*, >20:1 *dr*); IR (Neat): ν_{max} 3446, 3058, 2924, 2876, 2226, 1664, 1606, 1449, 1368, 1216, 1050, 1024, 705 and 560 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.89 (2H, dt, *J* = 8.5, 2.0 Hz), 7.54 (1H, tt, *J* = 7.0, 1.5 Hz), 7.48 (2H, dt, *J* = 8.5, 2.0 Hz), 7.43 (2H, tt, *J* = 8.0, 2.0 Hz), 7.30 (2H, d, *J* = 8.5 Hz), 3.90 (2H, d, *J* = 6.0 Hz), 3.20 (1H, dd, *J* = 10.0, 5.5 Hz), 2.91 (1H, dd, *J* = 9.5, 7.0 Hz), 2.75 (1H, quint, *J* = 6.0 Hz), 1.75 (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 194.9 (C, *C*=O), 141.3 (C), 137.9 (C), 132.2 (CH), 131.8 (2 x CH), 129.8 (2 x CH), 128.7 (2 x CH), 128.0 (2 x CH), 118.9 (C, *C*N), 110.5 (C), 63.1 (CH_2), 33.2 (CH), 31.5 (CH), 27.6 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{18}H_{15}NO_2H$ 278.1181; Found 278.1185.

((1*S*,2*S*,3*S*)-2-(hydroxymethyl)-3-(2-nitrophenyl)cyclopropyl)(phenyl)methanone (**3f′**): The

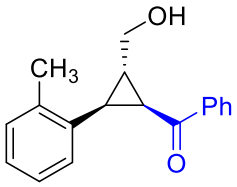


(-)-**3f'**

compound was prepared following the procedure **K** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 59% (17.3 mg); $[\alpha]_D^{25}$ = –80.39° (*c* = 0.102, $CHCl_3$,

99% *ee*, 2:1 *dr*); IR (Neat): ν_{max} 3389, 3062, 2928, 2873, 2360, 2339, 1660, 1519, 1344, 1215, 1023, 785, 731 and 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.92 (2H, d, *J* = 7.5 Hz), 7.56-7.52 (2H, m), 7.48 (1H, d, *J* = 7.0 Hz), 7.42 (2H, t, *J* = 8.0 Hz), 7.37-7.31 (2H, m), 3.87 (2H, d, *J* = 6.0 Hz), 3.30 (1H, dd, *J* = 9.5, 5.0 Hz), 3.20 (1H, t, *J* = 9.0 Hz), 2.72-2.61 (1H, m), 2.04 (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 196.1 (C, *C*=O), 149.9 (C), 137.7 (C), 133.0 (CH), 132.8 (CH), 132.3 (CH), 131.4 (C), 128.5 (2 x CH), 128.2 (2 x CH), 128.0 (CH), 124.5 (CH), 63.6 (CH_2), 32.1 (CH), 30.5 (CH), 30.0 (CH); HRMS (ESI-TOF) *m/z*: ($M + Na^+$) calcd for $C_{17}H_{15}NO_4Na$ 320.0899; Found 320.0898.

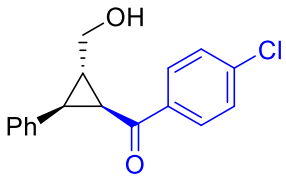
((1*S*,2*S*,3*S*)-2-(hydroxymethyl)-3-(o-tolyl)cyclopropyl)(phenyl)methanone (**3i′**): The



(-)-**3i'**

compound was prepared following the procedure **K** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 94% (25 mg); $[\alpha]_D^{25}$ = –149.62° (*c* = 0.131, $CHCl_3$, >97% *ee*, >20:1 *dr*); IR (Neat): ν_{max} 3388, 3065, 3023, 2922, 2870, 1659, 1448, 1365, 1220, 1042, 1023, 804, 714 and 656 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.92 (2H, dd, *J* = 8.5, 1.0 Hz), 7.50 (1H, tt, *J* = 7.5, 1.0 Hz), 7.40 (2H, t, *J* = 8.0 Hz), 7.24 (1H, d, *J* = 6.5 Hz), 7.16-7.06 (2H, m), 7.01 (1H, d, *J* = 7.5 Hz), 3.92 (1H, dd, *J* = 11.5, 5.0 Hz), 3.79 (1H, dd, *J* = 11.5, 5.5 Hz), 3.20 (1H, dd, *J* = 8.5, 5.5 Hz), 2.80-2.70 (2H, m), 2.19 (3H, s, C*H*$_3$), 1.98 (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 195.3 (C, *C*=O), 137.9 (C), 137.6 (C), 133.5 (C), 132.7 (CH), 129.7 (CH), 129.5 (CH), 128.5 (2 x CH), 128.1 (2 x CH), 127.1 (CH), 125.5 (CH), 64.1 (CH_2), 33.3 (CH), 30.1 (CH), 28.9 (CH), 19.8 (CH_3); HRMS (ESI-TOF) *m/z*: ($M + Na^+$) calcd for $C_{18}H_{18}O_2Na$ 289.1204; Found 289.1204.

(4-chlorophenyl)((1*S*,2*S*,3*S*)-2-(hydroxymethyl)-3-phenylcyclopropyl)methanone (**3l′**): The

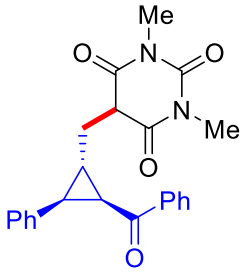


(-)-**3l'**

compound was prepared following the procedure **K** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 89% (25.5 mg); $[\alpha]_D^{25}$ = –200.00° (*c* = 0.101, $CHCl_3$, >99% *ee*, >20:1 *dr*); IR (Neat): ν_{max} 3386, 3062, 3026, 2925, 2873, 2359, 2339, 1662, 1587, 1489, 1400, 1364, 1213, 1089, 1011, 908, 727, 696 and 524 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.81 (2H, dt, *J* = 9.5, 2.5 Hz), 7.35 (2H, dt, *J* = 7.0, 2.0 Hz), 7.22-7.10 (5H, m), 3.87 (1H, dd, *J* = 11.5, 6.0 Hz), 3.76 (1H, dd, *J* = 11.5, 6.5 Hz), 3.00 (1H, dd, *J* = 10.0, 5.5 Hz), 2.87 (1H, dd, *J* = 9.5, 6.5 Hz), 2.74 (1H, quint, *J* = 5.5 Hz), 2.13 (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.3 (C, *C*=O),

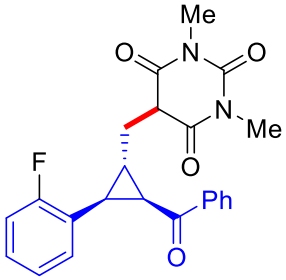
139.2 (C), 136.5 (C), 135.1 (C), 129.5 (2 x CH), 128.9 (2 x CH), 128.8 (2 x CH), 128.1 (2 x CH), 126.9 (CH), 63.7 (CH_2), 34.0 (CH), 31.6 (CH), 27.2 (CH); HRMS (ESI-TOF) *m/z*: (M + Na^+) calcd for $C_{17}H_{15}ClO_2Na$ 309.0658; Found 309.0659.

5-(((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32ga**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 93% (90.5 mg); $[\alpha]_D^{25}$ = –103.97° (*c* = 0.126, $CHCl_3$, >99% *ee*, >20:1 *dr*); IR (Neat): ν_{max} 3056, 2958, 2923, 2853, 1669, 1445, 1374, 1279, 1218, 1076, 730 and 696 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.83 (2H, dd, *J* = 8.4, 1.2 Hz), 7.49 (1H, tt, *J* = 8.4, 1.2 Hz), 7.39 (2H, t, *J* = 8.0 Hz), 7.19-7.04 (5H, m), 3.64 (1H, t, *J* = 4.8 Hz), 3.15(3H, s, C*H*$_3$), 3.14 (3H, s, C*H*$_3$), 2.90 (1H, dd, *J* = 9.6, 5.2 Hz), 2.71 (1H, dd, *J* = 9.6, 6.8 Hz), 2.56-2.44 (2H, m), 2.41-2.34 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.7 (C, *C*=O), 168.62 (C, N-*C*=O), 168.6 (C, N-*C*=O), 151.1 (C, N-*C*=O), 137.9 (C), 134.7 (C), 132.9 (CH), 128.5 (2 x CH), 128.4 (2 x CH), 128.1 (2 x CH), 128.0 (2 x CH), 127.0 (CH), 48.5 (CH), 36.0 (CH), 34.6 (CH_2), 34.3 (CH), 28.5 (2 x CH_3), 21.7 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{22}N_2O_4H$ 391.1658; Found 391.1656.



(-)-**32ga**

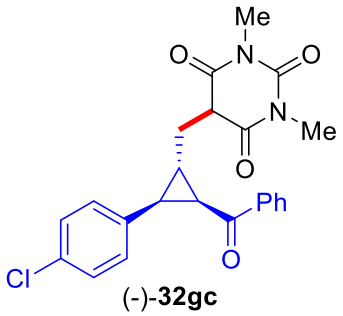
5-(((1*S*,2*R*,3*S*)-2-benzoyl-3-(2-fluorophenyl)cyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gb**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 96% (98 mg); $[\alpha]_D^{25}$ = –106.93° (*c* = 0.101, $CHCl_3$, 3:1:1 *dr*); IR (Neat): ν_{max} 2924, 2853, 1669, 1596, 1580, 1494, 1447, 1375, 1277, 1224, 1077, 1021, 753, 717 and 655 cm^{-1}; Major: ^1H NMR ($CDCl_3$, 500 MHz): δ 7.86 (2H, d, *J* = 7.5 Hz), 7.51 (1H, t, *J* = 7.5 Hz), 7.41 (2H, t, *J* = 7.5 Hz), 7.12-7.09 (1H, m), 7.06-7.03 (1H, m), 7.02-6.98 (1H, m), 6.86 (1H, t, *J* = 10.0 Hz), 3.65 (1H, t, *J* = 5.0 Hz), 3.21 (3H, s, C*H*$_3$), 3.14 (3H, s, C*H*$_3$), 2.98 (1H, dd, *J* = 9.5, 5.0 Hz), 2.76 (1H, dd, *J* = 9.5, 7.5 Hz), 2.55-2.46 (2H, m), 2.39-2.33 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 195.1 (C, *C*=O), 168.40 (C, N-*C*=O), 168.37 (C, N-*C*=O), 161.9 (C, d, *J* = 243.75 Hz), 151.1 (C, N-*C*=O), 137.8 (C), 132.9 (CH), 130.0 (CH, d, *J* = 3.75 Hz), 128.6 (CH), 128.5 (2 x CH), 128.0 (2 x CH), 123.7 (CH, d, *J* = 3.75 Hz), 122.2 (C, d, *J* = 13.75 Hz), 114.9 (CH, d, *J* = 21.25 Hz), 48.5 (CH),



(-)-**32gb**

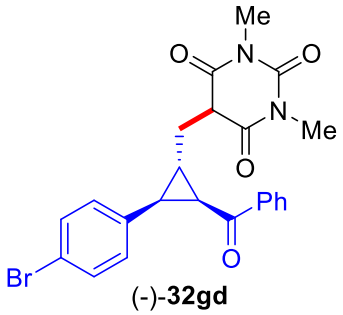
34.0 (CH_2), 32.9 (CH), 29.7 (CH, d, J = 3.75 Hz), 28.5 (CH_3), 28.4 (CH_3), 22.0 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{21}FN_2O_4H$ 409.1564; Found 409.1561.

5-(((1*S*,2*R*,3*S*)-2-benzoyl-3-(4-chlorophenyl)cyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gc**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 93% (98.8 mg); $[\alpha]_D^{25}$ = –134.0° (*c* = 0.100, $CHCl_3$, >20:1 *dr*); IR (Neat): ν_{max} 2925, 2853, 1670, 1596, 1493, 1446, 1374, 1219, 1178, 1076, 1015, 751, 700 and 653 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.82 (2H, d, J = 7.5 Hz), 7.51 (1H, t, J = 7.5 Hz), 7.41 (2H, t, J = 8.0 Hz), 7.13 (2H, d, J = 8.5 Hz), 7.01 (2H, d, J = 8.5 Hz), 3.61 (1H, t, J = 5.0 Hz), 3.18 (3H, s, CH_3), 3.15 (3H, s, CH_3), 2.92 (1H, dd, J = 10.0, 5.5 Hz), 2.67 (1H, dd, J = 9.5, 7.0 Hz), 2.55-2.50 (1H, m), 2.46-2.41 (1H, m), 2.34-2.32 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.6 (C, *C*=O), 168.5 (C, N-*C*=O), 168.4 (C, N-*C*=O), 151.0 (C, N-*C*=O), 137.7 (C), 133.3 (C), 133.0 (CH), 132.8 (C), 129.8 (2 x CH), 128.6 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 48.5 (CH), 35.2 (CH), 34.3 (CH_2), 34.1 (CH), 28.54 (CH_3), 28.49 (CH_3), 22.2 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{21}ClN_2O_4H$ 425.1268; Found 425.1266.



(-)-**32gc**

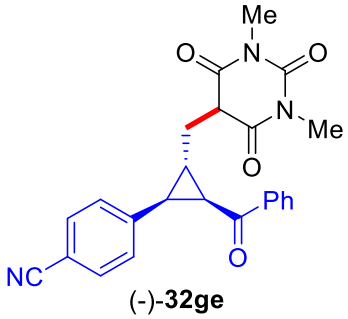
5-(((1*S*,2*R*,3*S*)-2-benzoyl-3-(4-bromophenyl)cyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gd**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 97% (113.81 mg); $[\alpha]_D^{25}$ = –121.30° (*c* = 0.108, $CHCl_3$, >20:1 *dr*); IR (Neat): ν_{max} 2924, 2856, 1676, 1448, 1377, 1275, 1219, 1073, 1009, 750 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.82 (2H, dd, J = 8.5, 1.5 Hz), 7.51 (1H, t, J = 7.5 Hz), 7.41 (2H, t, J = 8.0 Hz), 7.32-7.27 (2H, m), 6.95 (2H, d, J = 8.5 Hz), 3.64 (1H, t, J = 5.0 Hz), 3.18 (3H, s, CH_3), 3.14 (3H, s, CH_3), 2.95-2.91 (1H, m), 2.65 (1H, dd, J = 7.0, 2.5 Hz), 2.56-2.50 (1H, m), 2.47-2.43 (1H, m), 2.38-2.30 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.6 (C, *C*=O), 168.46 (C, N-*C*=O), 168.38 (C, N-*C*=O), 151.0 (C, N-*C*=O), 137.7 (C), 133.9 (C), 133.1 (CH), 131.2 (2 x CH), 130.2 (2 x CH), 128.6 (2 x CH), 128.0 (2 x CH), 120.9 (C), 48.5 (CH), 35.3 (CH), 34.2 (CH_2), 34.0 (CH), 28.55



(-)-**32gd**

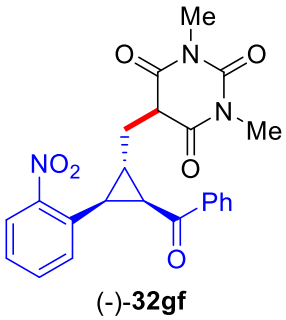
(CH_3), 28.49 (CH_3), 22.1 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{21}BrN_2O_4H$ 469.0763; Found 469.0768.

4-((1*S*,2*R*,3*S*)-2-benzoyl-3-((1,3-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)methyl)cyclopropyl)benzonitrile (**32ge**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 92% (95.5 mg); $[\alpha]_D^{25}$ = –153.92° (*c* = 0.102, $CHCl_3$, >99% *ee*, >10:1 *dr*); IR (Neat): ν_{max} 3005, 2989, 2226, 1678, 1448, 1375, 1275, 1260, 1075, 750 and 560 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.82 (2H, dd, *J* = 7.5, 1.0 Hz), 7.53 (1H, tt, *J* = 7.0, 1.5 Hz), 7.46 (2H, dd, *J* = 8.5, 1.5 Hz), 7.42 (2H, t, *J* = 8.0 Hz), 7.21 (2H, d, *J* = 8.0 Hz), 3.65 (1H, t, *J* = 4.5 Hz), 3.20 (3H, s, C*H*$_3$), 3.14 (3H, s, C*H*$_3$), 3.03 (1H, dd, *J* = 9.5, 5.0 Hz), 2.74 (1H, dd, *J* = 9.5, 6.5 Hz), 2.59-2.53 (1H, m), 2.46-2.41 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 194.4 (C, *C*=O), 168.3 (C, N-*C*=O), 168.2 (C, N-*C*=O), 151.0 (C, N-*C*=O), 140.7 (C), 137.5 (C), 133.3 (CH), 131.9 (2 x CH), 129.4 (2 x CH), 128.7 (2 x CH), 127.9 (2 x CH), 118.7 (C, CN), 110.7 (C), 48.4 (CH), 35.4 (CH), 34.4 (CH), 33.7 (CH_2), 28.6 (CH_3), 28.5 (CH_3), 22.8 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{21}N_3O_4H$ 416.1610; Found 416.1603.



(-)-**32ge**

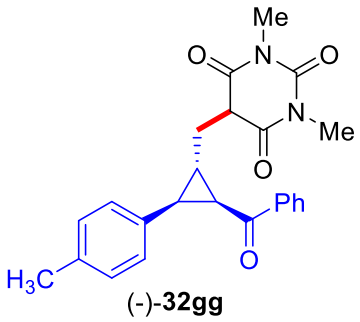
5-(((1*S*,2*R*,3*S*)-2-benzoyl-3-(2-nitrophenyl)cyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gf**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 95% (103.5 mg); $[\alpha]_D^{25}$ = –57.58° (*c* = 0.099, $CHCl_3$, >99% *ee*, 2:1 *dr*); IR (Neat): ν_{max} 2923, 2852, 2359, 1671, 1597, 1577, 1521, 1447, 1377, 1346, 1276, 1221, 1078, 1040, 752, 700 and 657 cm^{-1}; **Major:** ^1H NMR ($CDCl_3$, 500 MHz): δ 7.87-7.82 (3H, m), 7.53 (3H, qd, *J* = 7.5, 0.5 Hz), 7.42 (3H, m), 3.65 (1H, t, *J* = 5.0 Hz), 3.23 (3H, s, C*H*$_3$), 3.18 (1H, dd, *J* = 10.5, 4.5 Hz), 3.11 (1H, dd, *J* = 9.5, 7.0 Hz), 3.07 (3H, s, C*H*$_3$), 2.69-2.62 (1H, m), 2.45-2.38 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 195.5 (C, *C*=O), 168.2 (C, N-*C*=O), 168.1 (C, N-*C*=O), 151.1 (C, N-*C*=O), 149.6 (C), 137.3 (C), 133.2 (CH), 132.9 (CH), 131.8 (CH), 130.9 (C), 128.8 (CH), 128.6 (2 x CH), 128.2 (2 x CH), 124.6 (CH), 48.5 (CH), 34.1 (CH), 33.6 (CH_2), 33.4 (CH), 28.6 (CH_3), 28.4 (CH_3), 25.0 (CH); **Minor:** ^1H NMR ($CDCl_3$, 500 MHz): δ 7.99 (3H, td, *J* = 8.5, 1.5 Hz),



(-)-**32gf**

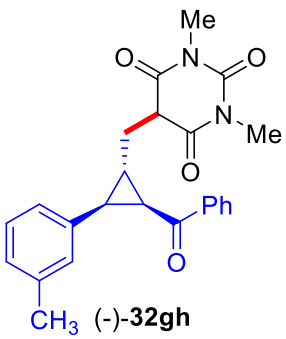
7.62 (2H, t, *J* = 7.5 Hz), 7.49-7.46 (2H, m), 7.34 (2H, td, *J* = 8.5, 1.0 Hz), 3.49 (1H, t, *J* = 5.0 Hz), 3.30 (1H, dd, *J* = 10.0, 5.5 Hz), 3.25 (3H, s, C*H*$_3$), 3.03 (1H, dd, *J* = 10.0, 5.0 Hz), 2.89 (3H, s, C*H*$_3$), 2.50-2.46 (1H, m), 2.12-2.03 (1H, m), 1.68-1.59 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 197.2 (C, *C*=O), 167.9 (C, N-*C*=O), 167.6 (C, N-*C*=O), 150.9 (C, N-*C*=O), 150.8 (C), 136.9 (C), 133.5 (CH), 133.0 (CH), 131.3 (CH), 131.1 (C), 128.1 (CH), 128.2 (2 x CH), 128.1 (2 x CH), 124.9 (CH), 48.1 (CH), 31.6 (CH), 30.4 (CH), 28.8 (CH_2), 28.7 (CH_3), 28.5 (CH_3), 28.3 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{21}N_3O_6H$ 436.1509; Found 436.1507.

5-(((1*S*,2*R*,3*S*)-2-benzoyl-3-(p-tolyl)cyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gg**): The compound was prepared following the procedure **B** and purified by column chromatography using (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 95% (96.1 mg); $[\alpha]_D^{25}$ = –127.27° (*c* = 0.088, $CHCl_3$, >20:1 *dr*); IR (Neat): ν_{max} 2922, 2853, 1669, 1597, 1516, 1446, 1375, 1277, 1219, 1075, 1020, 803, 753, 705 and 652 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.83 (2H, dd, *J* = 8.5, 1.5 Hz), 7.39 (2H, t, *J* = 8.0 Hz), 7.00-6.92 (5H, m), 3.63 (1H, t, *J* = 4.5 Hz), 3.15 (3H, s, C*H*$_3$), 3.14 (3H, s, C*H*$_3$), 2.87 (1H, dd, *J* = 9.5, 5.5 Hz), 2.68 (1H, dd, *J* = 9.5, 6.5 Hz), 2.55-2.34 (2H, m), 2.36-2.33 (1H, m), 2.20 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.9 (C, *C*=O), 168.64 (C, N-*C*=O), 168.59 (C, N-*C*=O), 151.1 (C, N-*C*=O), 138.0 (C), 136.5 (C), 132.8 (CH), 131.5 (C), 128.8 (2 x CH), 128.5 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 48.5 (CH), 35.9 (CH), 34.7 (CH_2), 34.2 (CH), 28.5 (CH_3), 28.4 (CH_3), 21.7 (CH), 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{24}N_2O_4H$ 405.1814; Found 405.1814.



(-)-**32gg**

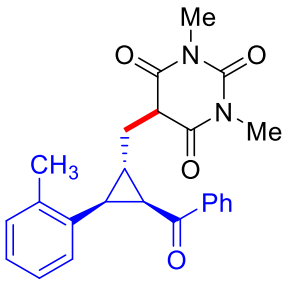
5-(((1*S*,2*R*,3*S*)-2-benzoyl-3-(m-tolyl)cyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gh**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 97% (98.1 mg); $[\alpha]_D^{25}$ = –93.07° (*c* = 0.101, $CHCl_3$, >10:1 *dr*); IR (Neat): ν_{max} 3065, 2954, 2853, 1668 (C=O), 1597, 1445, 1376, 1280, 1076, 1048, 754, 693 and 651 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.83 (2H, dd, *J* = 8.5, 1.5 Hz), 7.50 (1H, tt, *J* = 8.0, 1.5 Hz), 7.40 (2H, t, *J* = 7.5 Hz), 7.04 (1H, t, *J* = 7.5



(-)-**32gh**

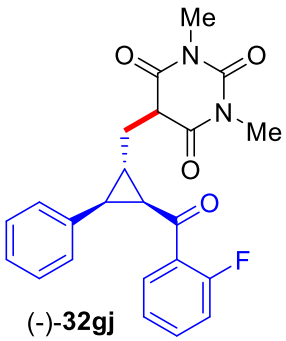
Hz), 6.91 (1H, d, *J* = 7.5 Hz), 6.84 (2H, d, *J* = 9.0 Hz), 3.64 (1H, t, *J* = 4.5 Hz), 3.17 (3H, s, C*H*$_3$), 3.13 (3H, s, C*H*$_3$), 2.88 (1H, dd, *J* = 9.5, 5.0 Hz), 2.66 (1H, dd, *J* = 10.0, 7.0 Hz), 2.49 (2H, dd, *J* = 7.0, 5.0 Hz), 2.37-2.32 (1H, m), 2.23 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.8 (C, *C*=O), 168.64 (C, N-*C*=O), 168.59 (C, N-*C*=O), 151.1 (C, N-*C*=O), 138.0 (C), 137.6 (C), 134.6 (C), 132.8 (CH), 129.2 (CH), 128.5 (2 x CH), 128.0 (2 x CH), 127.9 (CH), 127.8 (CH), 125.5 (CH), 48.5 (CH), 36.0 (CH), 34.7 (CH_2), 34.2 (CH), 28.4 (2 x CH_3), 21.7 (CH_3), 21.5 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{24}N_2O_4H$ 405.1814; Found 405.1813.

5-(((1*S*,2*R*,3*S*)-2-benzoyl-3-(o-tolyl)cyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gi**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 98% (99.1 mg); $[\alpha]_D^{25}$ = –80.51° (*c* = 0.118, $CHCl_3$, >99.9% *ee*, >10:1 *dr*); IR (Neat): ν_{max} 3062, 2956, 2861, 1672, 1597, 1447, 1377, 1285, 1221, 1180, 1079, 911, 756, 730 and 651 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (2H, d, *J* = 7.5 Hz), 7.51 (1H, t, *J* = 7.5 Hz), 7.41 (2H, t, *J* = 8.0 Hz), 7.10-7.03 (3H, m), 6.99(1H, d, *J* = 7.0 Hz), 3.65 (1H, t, *J* = 4.5 Hz), 3.16 (3H, s, C*H*$_3$), 3.10 (3H, s, C*H*$_3$), 3.05 (1H, dd, *J* = 9.0, 5.0 Hz), 2.65-2.60 (2H, m), 2.49-2.44 (1H, m), 2.39-2.16 (1H, m), 2.16 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 135 MHz) δ 194.5 (C, *C*=O), 168.5 (C, N-*C*=O), 168.4 (C, N-*C*=O), 151.1 (C, N-*C*=O), 137.6 (C), 137.4 (C), 132.90 (C), 132.87 (CH), 129.7 (CH), 128.6 (CH), 128.5 (2 x CH), 128.0 (2 x CH), 127.1 (CH), 125.6 (CH), 48.5 (CH), 35.5 (CH), 34.4 (CH_2), 32.6 (CH), 28.5 (CH_3), 28.4 (CH_3), 23.4 (CH_3), 19.6 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{24}N_2O_4H$ 405.1814; Found 405.1814.



(-)-**32gi**

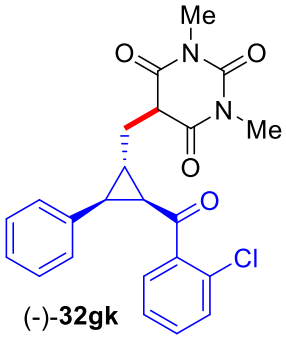
5-(((1*S*,2*R*,3*S*)-2-(2-fluorobenzoyl)-3-phenylcyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gj**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 96% (98 mg); $[\alpha]_D^{25}$ = –82.96° (*c* = 0.135, $CHCl_3$, >10:1 *dr*); IR (Neat): ν_{max} 2926, 2856, 2359, 2339, 1671, 1608, 1450, 1376, 1273, 1209, 1153, 1103, 1078, 1027, 753, 698 and 639 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50 (2H, td, *J* = 7.5, 2.0 Hz)), 7.47-7.41 (1H, m), 7.20 (2H, t, *J* = 7.5 Hz)), 7.15-7.07 (5H,



(-)-**32gj**

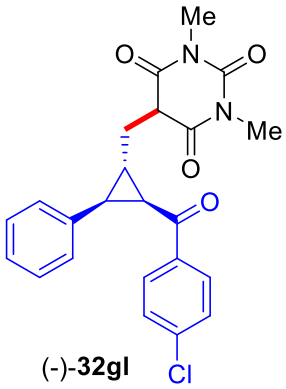
m), 3.64 (1H, t, *J* = 4.5 Hz), 3.21 (3H, s, C*H*$_3$), 3.13 (3H, s, C*H*$_3$), 2.93 (1H, m), 2.77 (1H, dd, *J* = 10.0, 6.5 Hz), 2.55-2.48 (1H, m), 2.48-2.39 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 193.1 (C, *C*=O), 168.52 (C, N-*C*=O), 168.50 (C, N-*C*=O), 162.6 (C, N-*C*=O), 160.6 (C), 151.1 (C), 134.6 (C), 134.2 (CH, d, *J* = 8.75 Hz), 130.4 (CH, d, *J* = 2.5 Hz), 128.7 (2 x CH), 128.1 (2 x CH), 127.0 (CH), 124.3 (CH, d, *J* = 3.75 Hz), 116.5 (CH, d, *J* = 23.75 Hz), 48.5 (CH), 38.3 (CH, d, *J* = 7.5 Hz), 36.7 (CH), 34.5 (CH_2), 28.44 (CH_3), 28.43 (CH_3), 22.3 (CH); ^{19}F NMR ($CDCl_3$, 400 MHz NMR Machine): δ -111.38; HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{21}FN_2O_4H$ 409.1564; Found 409.1562.

5-(((1*S*,2*R*,3*S*)-2-(2-chlorobenzoyl)-3-phenylcyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gk**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 98% (104.1 mg); $[\alpha]_D^{25}$ = –80.0° (*c* = 0.100, $CHCl_3$, >5:1 *dr*); IR (Neat): ν_{max} 3059, 2926, 2856, 2360, 2339, 1674, 1589, 1436, 1377, 1280, 1212, 1075, 1029, 751, 697 and 641 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.31 (2H, m), 7.25-7.21 (4H, m), 7.19-7.15 (3H, m), 3.63 (1H, t, *J* = 5.0 Hz), 3.23 (3H, s, C*H*$_3$), 3.09 (3H, s, C*H*$_3$), 2.89 (1H, dd, *J* = 9.5, 5.0 Hz), 2.75 (1H, dd, *J* = 9.5, 7.0 Hz), 2.57 (1H, dt, *J* = 12.5, 5.0 Hz), 2.47-2.36 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 196.4 (C, *C*=O), 168.4 (2 x C, N-*C*=O), 151.1 (C, N-*C*=O), 139.1 (C), 134.3 (C), 132.0 (CH), 131.6 (C), 130.5 (CH), 129.7 (CH), 128.9 (2 x CH), 128.1 (2 x CH), 127.2 (CH), 126.9 (CH), 48.4 (CH), 38.2 (CH), 37.9 (CH), 34.4 (CH_2), 28.6 (CH_3), 28.5 (CH_3), 23.9 (CH); HRMS (ESI-TOF) *m/z*: (M + Na^+) calcd for $C_{23}H_{21}ClN_2O_4Na$ 447.1088; Found 447.1090.



(-)-**32gk**

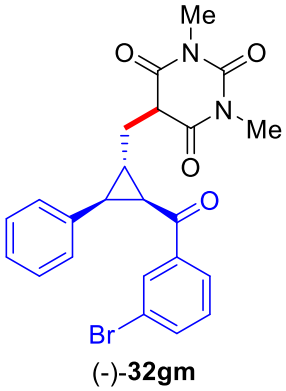
5-(((1*S*,2*R*,3*S*)-2-(4-chlorobenzoyl)-3-phenylcyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gl**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 95% (100.9 mg); $[\alpha]_D^{25}$ = –145.22° (*c* = 0.115, $CHCl_3$, >99.9% *ee*, >20:1 *dr*); IR (Neat): ν_{max} 3004, 1671, 1587, 1440, 1377, 1276, 1217, 1175, 1089, 1046, 1010, 806, 751 and 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (2H, dt, *J* = 9.0, 2.0 Hz), 7.37 (2H, dt, *J* = 9.0, 2.5 Hz), 7.17 (2H, tt, *J* = 8.0, 1.5 Hz), 7.11 (1H, d, *J* = 8.5, 2.5 Hz), 7.03 (2H, d, *J* = 7.0 Hz), 3.64 (1H, t, *J*



(-)-**32gl**

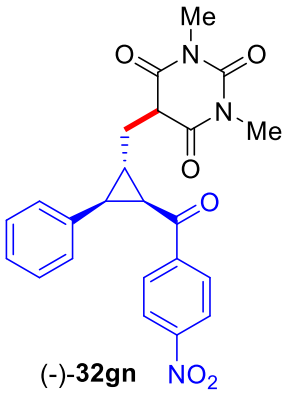
= 4.5 Hz), 3.18 (3H, s, C*H*$_3$), 3.15 (3H, s, C*H*$_3$), 2.85 (1H, dd, *J* = 9.5, 5.0 Hz), 2.71 (1H, dd, *J* = 9.5, 7.0 Hz), 2.54-2.45 (2H, m), 2.47-2.35 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 193.5 (C, *C*=O), 168.53 (C, N-*C*=O), 168.47 (C, N-*C*=O), 151.0 (C, N-*C*=O), 139.3 (C), 136.2 (C), 134.5 (C), 129.4 (2 x CH), 128.8 (2 x CH), 128.4 (2 x CH), 128.1 (2 x CH), 127.1 (CH), 48.5 (CH), 36.0 (CH), 34.4 (CH_2), 34.3 (CH), 28.49 (CH_3), 28.47 (CH_3), 21.8 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{21}ClN_2O_4H$ 425.1268; Found 425.1272.

5-(((1*S*,2*R*,3*S*)-2-(3-bromobenzoyl)-3-phenylcyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gm**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 92% (107.9); $[\alpha]_D^{25}$ = –99.0° (*c* = 0.100, $CHCl_3$, 5:1:1 *dr*); IR (Neat): ν_{max} 3059, 2956, 2849, 1668, 1564, 1420, 1438, 1375, 1277, 1207, 1074, 1000, 749, 695 and 642 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.94 (1H, t, *J* = 2.0 Hz), 7.75 (1H, dd, *J* = 8.0, 1.5 Hz), 7.62 (1H, dq, *J* = 8.0, 1.0 Hz), 7.28 (1H, t, *J* = 8.0 Hz), 7.18 (2H, t, *J* = 7.5 Hz), 7.13 (1H, dt, *J* = 8.5, 2.5 Hz), 7.05 (2H, d, *J* = 7.0 Hz), 3.65 (1H, t, *J* = 5.0 Hz), 3.20 (3H, s, C*H*$_3$), 3.14 (3H, s, C*H*$_3$), 2.87 (1H, dd, *J* = 10.0, 5.0 Hz), 2.74 (1H, dd, *J* = 10.0, 7.0 Hz), 2.49 (2H, dd, *J* = 7.0, 5.0 Hz), 2.42-2.37 (1H, m), ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 193.4 (C, *C*=O), 168.5 (C, N-*C*=O), 168.4 (C, N-*C*=O), 151.0 (C, N-*C*=O), 139.6 (C), 135.7 (CH), 134.4 (C), 131.0 (CH), 130.1 (CH), 128.4 (2 x CH), 128.2 (2 x CH), 127.1 (CH), 126.5 (CH), 122.9 (C), 48.5 (CH), 36.3 (CH), 34.4 (CH), 34.3 (CH_2), 28.53 (CH_3), 28.48 (CH_3), 22.0 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{21}BrN_2O_4H$ 469.0763; Found 469.0762.



(-)-**32gm**

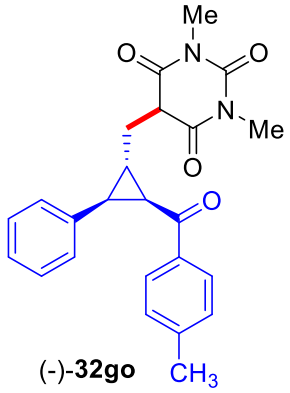
1,3-dimethyl-5-(((1*S*,2*R*,3*S*)-2-(4-nitrobenzoyl)-3-phenylcyclopropyl)methyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gn**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 92% (100.1 mg); $[\alpha]_D^{25}$ = –120.18° (*c* = 0.109, $CHCl_3$, >5:1 *dr*); IR (Neat): ν_{max} 2923, 2853, 2359, 2339, 1671, 1602, 1523, 1440, 1378, 1345, 1277, 1212, 1078, 1047, 846, 752, 698 and 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.24 (2H, d, *J* = 8.5 Hz), 7.97 (2H, d, *J* = 9.0 Hz), 7.18 (2H, t, *J* = 7.5 Hz), 7.14 (1H, t, *J* = 7.5 Hz), 7.05 (2H, d, *J* = 7.0 Hz), 3.67 (1H, t, *J* = 5.0 Hz), 3.22 (3H, s,



(-)-**32gn**

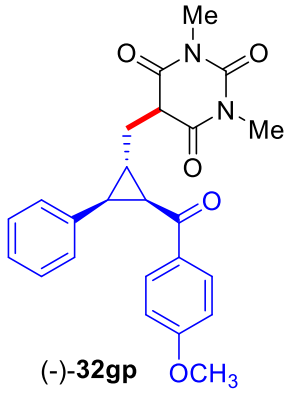
C*H*$_3$), 3.15 (3H, s, C*H*$_3$), 2.94 (1H, dd, *J* = 10.0, 5.0 Hz), 2.83 (1H, dd, *J* = 10.0, 7.0 Hz), 2.56-2.44 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 193.4 (C, *C*=O), 168.34 (C, N-*C*=O), 168.31 (C, N-*C*=O), 151.0 (C, N-*C*=O), 150.1 (C), 142.2 (C), 134.0 (C), 128.9 (2 x CH), 128.36 (2 x CH), 128.28 (2 x CH), 127.4 (CH), 123.8 (2 x CH), 48.4 (CH), 36.8 (CH), 34.9 (CH), 33.9 (CH_2), 28.56 (CH_3), 28.52 (CH_3), 23.4 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{21}N_3O_6H$ 436.1509; Found 436.1506.

1,3-dimethyl-5-(((1*S*,2*R*,3*S*)-2-(4-methylbenzoyl)-3-phenylcyclopropyl)methyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32go**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 97% (98.1); $[\alpha]_D^{25}$ = –165.85° (*c* = 0.082, $CHCl_3$, >20:1 *dr*); IR (Neat): ν_{max} 3027, 2920, 1668, 1605, 1439, 1373, 1277, 1225, 1179, 1076, 1047, 802, 750, 697 and 601 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 (2H, dt, *J* = 8.5, 2.0 Hz), 7.19 (2H, d, *J* = 8.0 Hz), 7.15 (2H, tt, *J* = 7.0, 2.0 Hz), 7.09 (1H, tt, *J* = 7.0, 2.5 Hz), 7.05 (2H, dt, *J* = 7.5, 2.0 Hz), 3.64 (1H, t, *J* = 4.5 Hz), 3.154 (3H, s, C*H*$_3$), 3.147 (3H, s, C*H*$_3$), 2.87 (1H, dd, *J* = 9.5, 5.0 Hz), 2.67 (1H, dd, *J* = 9.5, 7.0 Hz), 2.55-2.44 (2H, m), 2.36 (3H, s, C*H*$_3$), 2.34-2.27 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.2 (C, *C*=O), 168.65 (C, N-*C*=O), 168.60 (C, N-*C*=O), 151.1 (C, N-*C*=O), 143.6 (C), 135.5 (C), 134.8 (C), 129.2 (2 x CH), 128.4 (2 x CH), 128.13 (2 x CH), 128.07 (2 x CH), 126.9 (CH), 48.5 (CH), 35.7 (CH), 34.7 (CH_2), 34.1 (CH), 28.4 (2 x CH_3), 21.6 (CH), 21.5 (CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{24}N_2O_4H$ 405.1814; Found 405.1808.



(-)-**32go**

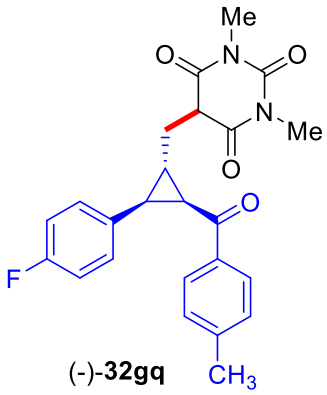
5-(((1*S*,2*R*,3*S*)-2-(4-methoxybenzoyl)-3-phenylcyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gp**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 98% (103 mg); $[\alpha]_D^{25}$ = –227.86° (*c* = 0.140, $CHCl_3$, >10:1 *dr*); IR (Neat): ν_{max} 3062, 2935, 2841, 1671, 1597, 1509, 1438, 1420, 1374, 1237, 1167, 1023, 845, 752, 733, 698 and 603 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.82 (2H, d, *J* = 9.0 Hz), 7.15 (2H, t, *J* = 7.5 Hz), 7.09 (1H, t, *J* = 7.5 Hz), 7.04 (2H, d, *J* = 7.5 Hz), 6.86 (2H, d, *J* = 9.0 Hz), 3.82 (3H, s, OC*H*$_3$), 3.64 (1H, t, *J* =



(-)-**32gp**

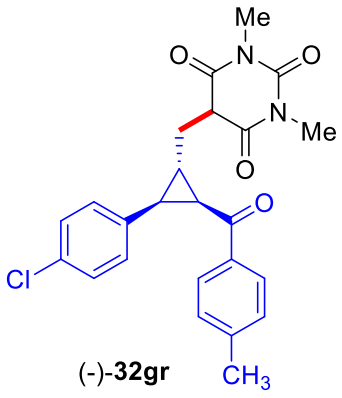
4.5 Hz), 3.15 (3H, s, C*H*$_3$), 3.14 (3H, s, C*H*$_3$), 2.84 (1H, dd, *J* = 9.5, 5.5 Hz), 2.64 (1H, dd, *J* = 9.5, 7.0 Hz), 2.55-2.50 (1H, m), 2.48-2.43 (1H, m) 2.33 (1H, quint, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 193.0 (C, *C*=O), 168.7 (C, N-*C*=O), 168.6 (C, N-*C*=O), 163.3 (C, N-*C*=O), 151.1 (C), 134.9 (C), 131.0 (C), 130.3 (2 x CH), 128.4 (2 x CH), 128.0 (2 x CH), 126.8 (CH), 113.7 (2 x CH), 55.4 (CH_3, *OCH*$_3$), 48.5 (CH), 35.4 (CH), 34.8 (CH_2), 33.9 (CH), 28.4 (2 x CH_3), 21.3 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{24}N_2O_5H$ 421.1763; Found 421.1763.

5-(((1*S*,2*S*,3*R*)-2-(4-fluorophenyl)-3-(4-methylbenzoyl)cyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gq**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 90% (95.1 mg); $[\alpha]_D^{25}$ = –132.58° (*c* = 0.089, $CHCl_3$, >20:1 *dr*); IR (Neat): ν_{max} 2930, 2853, 1669, 1604, 1511, 1442, 1419, 1376, 1277, 1222, 1180, 1047, 825, 754, 744 and 551 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 (2H, d, *J* = 8.5 Hz), 7.20 (2H, d, *J* = 8.0 Hz), 7.03 (2H, dd, *J* = 9.0, 5.5 Hz), 6.84 (2H, tt, *J* = 9.0, 2.0 Hz), 3.64 (1H, t, *J* = 5.0 Hz), 3.18 (3H, s, C*H*$_3$), 3.15 (3H, s, C*H*$_3$), 2.88 (1H, dd, *J* = 9.5, 5.5 Hz), 2.65 (1H, dd, *J* = 9.5, 7.0 Hz), 2.56-2.51 (1H, m), 2.46-2.41 (1H, m), 2.37 (3H, s, C*H*$_3$), 2.34-2.29 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.2 (C, *C*=O), 168.6 (C, N-*C*=O), 168.5 (C, N-*C*=O), 161.7 (C, d, *J* = 243.75 Hz), 151.0 (C, N-*C*=O), 143.8 (C), 135.3 (C), 130.6 (C), 130.0 (CH), 129.9 (CH), 129.3 (2 x CH), 128.1 (2 x CH), 115.1 (CH), 114.9 (CH), 48.5 (CH), 34.9 (CH), 34.5 (CH_2), 33.9 (CH), 28.50 (CH_3), 28.49 (CH_3), 21.9 (CH), 21.6 (CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{23}FN_2O_4H$ 423.1720; Found 423.1720.



(-)-**32gq**

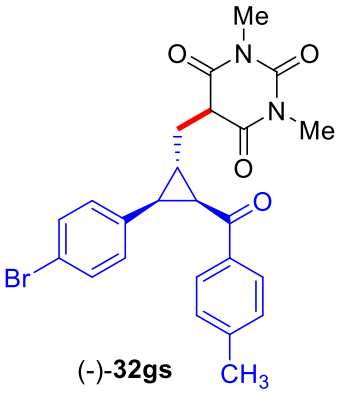
5-(((1*S*,2*S*,3*R*)-2-(4-chlorophenyl)-3-(4-methylbenzoyl)cyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gr**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 98% (107.5 mg); $[\alpha]_D^{25}$ = –142.06° (*c* = 0.107, $CHCl_3$, >10:1 *dr*); IR (Neat): ν_{max} 2924, 2853, 1670, 1605, 1571, 1493, 1442, 1375, 1277, 1226, 1179, 1080, 1047, 1013, 821, 752, 734, 652 and



(-)-**32gr**

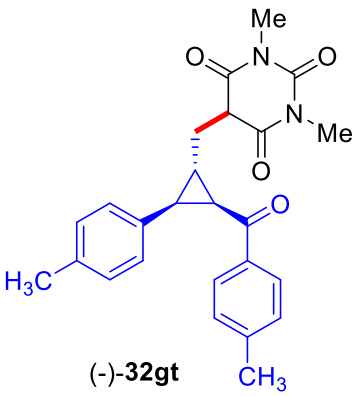
599 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.73 (2H, d, *J* = 8.5 Hz), 7.20 (2H, d, *J* = 8.0 Hz), 7.12 (2H, dt, *J* = 9.5, 1.5 Hz), 6.99 (2H, dt, *J* = 9.5, 2.5 Hz), 3.64 (1H, t, *J* = 5.0 Hz), 3.19 (3H, s, C*H*$_3$), 3.15 (3H, s, C*H*$_3$), 2.89 (1H, dd, *J* = 10.0, 5.5 Hz), 2.64 (1H, dd, *J* = 9.5, 7.0 Hz), 2.56-2.51 (1H, m), 2.45-2.43 (1H, m), 2.37 (3H, s, C*H*$_3$), 2.32-2.29 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 190.1 (C, *C*=O), 168.5 (C, N-*C*=O), 168.4 (C, N-*C*=O), 151.0 (C, N-*C*=O), 143.9 (C), 135.3 (C), 133.5 (C), 132.7 (C), 129.8 (2 x CH), 129.3 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 48.5 (CH), 34.9 (CH), 34.4 (CH_2), 33.9 (CH), 28.52 (CH_3), 28.48 (CH), 21.9 (CH_3), 21.6 (CH_3); HRMS (ESI-TOF) *m/z*: (M + Na^+) calcd for $C_{24}H_{23}ClN_2O_4Na$ 461.1244; Found 461.1244.

5-(((1*S*,2*S*,3*R*)-2-(4-bromophenyl)-3-(4-methylbenzoyl)cyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gs**): The compound was prepared following the procedure **B** and purified by column chromatography using (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 97% (117.2 mg); $[\alpha]_D^{25}$ = –157.84° (*c* = 0.102, $CHCl_3$, >10:1 *dr*); IR (Neat): ν_{max} 2922, 2849, 1670, 1605, 1489, 1441, 1375, 1277, 1226, 1179, 1072, 1047, 1009, 818, 752, 734, 634 and 599 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.73 (2H, d, *J* = 8.0 Hz), 7.27 (2H, d, *J* = 8.0 Hz), 7.20 (2H, d, *J* = 8.0 Hz), 6.94 (2H, d, *J* = 8.0 Hz), 3.64 (1H, t, *J* = 4.5 Hz), 3.18 (3H, s, C*H*$_3$), 3.14 (3H, s, C*H*$_3$), 2.90 (1H, dd, *J* = 9.5, 5.0 Hz), 2.62 (1H, dd, *J* = 9.0, 7.0 Hz), 2.56-2.50 (1H, m), 2.45-2.41 (1H, m), 2.37 (3H, s, C*H*$_3$), 2.34-2.29 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.1 (C, *C*=O), 168.5 (C, N-*C*=O), 168.4 (C, N-*C*=O), 151.0 (C, N-*C*=O), 143.9 (C), 135.3 (C), 134.0 (C), 131.2 (2 x CH), 130.2 (2 x CH), 129.3 (2 x CH), 128.1 (2 x CH), 120.8 (C), 48.5 (CH), 35.0 (CH), 34.3 (CH_2), 33.9 (CH), 28.5 (CH_3), 28.4 (CH_3), 21.9 (CH_3), 21.6 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{23}BrN_2O_4H$ 483.0919; Found 483.0919.



(-)-**32gs**

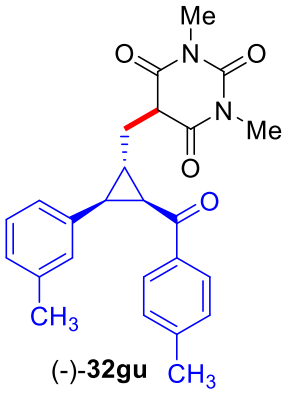
1,3-dimethyl-5-(((1*S*,2*R*,3*S*)-2-(4-methylbenzoyl)-3-(p-tolyl)cyclopropyl)methyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gt**): The compound was prepared following the procedure **B** and purified by column chromatography using (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 98% (102.5); $[\alpha]_D^{25}$ = –167.74° (*c* = 0.090, $CHCl_3$, >10:1 *dr*); IR (Neat): ν_{max} 2921, 2856, 1671, 1605, 1571, 1516, 1443, 1376, 1277, 1226, 1180,



(-)-**32gt**

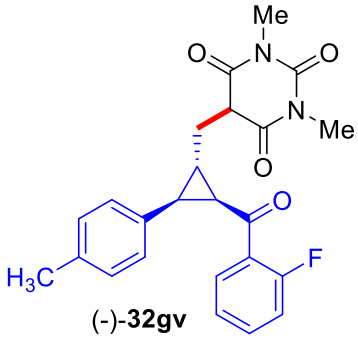
1076, 1048, 812, 752 and 600 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.74 (2H, d, *J* = 8.0 Hz), 7.19 (2H, d, *J* = 7.5 Hz), 6.96-6.92 (4H, m), 3.63 (1H, t, *J* = 5.0 Hz), 3.15 (3H, s, C*H*$_3$), 3.14 (3H, s, C*H*$_3$), 2.84 (1H, dd, *J* = 10.0, 5.5 Hz), 2.65 (1H, dd, *J* = 10.0, 7.0 Hz), 2.53-2.43 (2H, m), 2.36 (3H, s, C*H*$_3$), 2.33-2.29 (1H, m), 2.20 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.4 (C, *C*=O), 168.7 (C, N-*C*=O), 168.6 (C, N-*C*=O), 151.1 (C, N-*C*=O), 143.6 (C), 136.4 (C), 135.5 (C), 131.7 (C), 129.2 (2 x CH), 128.8 (2 x CH), 128.3 (2 x CH), 128.1 (2 x CH), 48.5 (CH), 35.6 (CH), 34.8 (CH_2), 34.1 (CH), 28.4 (2 x CH_3), 21.6 (CH), 21.5 (CH_3), 21.0 (CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{25}H_{26}N_2O_4H$ 419.1971; Found 419.1970.

1,3-dimethyl-5-(((1*S*,2*R*,3*S*)-2-(4-methylbenzoyl)-3-(m-tolyl)cyclopropyl)methyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gu**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 98% (102.5 mg); $[\alpha]_D^{25}$ = 146.74° (*c* = 0.092, $CHCl_3$, >20:1 *dr*); IR (Neat): ν_{max} 2921, 2853, 1669, 1605, 1441, 1376, 1280, 1227, 1178, 1077, 1048, 792, 753, 734, 699 and 598 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.74 (2H, d, *J* = 8.0 Hz), 7.19 (2H, t, *J* = 8.0 Hz), 7.02 (1H, t, *J* = 7.5 Hz), 6.90 (1H, d, *J* = 7.5 Hz), 6.83 (2H, d, *J* = 9.0 Hz), 3.63 (1H, t, *J* = 4.5 Hz), 3.16 (3H, s, C*H*$_3$), 3.13 (3H, s, C*H*$_3$), 2.85 (1H, dd, *J* = 10.0, 5.5 Hz), 2.63 (1H, dd, *J* = 9.5, 7.0 Hz), 2.51-2.47 (2H, m), 2.36 (3H, s, C*H*$_3$), 2.33-2.31 (1H, m), 2.22 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.3 (C, *C*=O), 168.66 (C, N-*C*=O), 168.62 (C, N-*C*=O), 151.1 (C, N-*C*=O), 143.5 (C), 137.6 (C), 135.6 (C), 134.7 (C), 129.20 (CH), 129.17 (2 x CH), 128.1 (2 x CH), 127.9 (CH), 127.7 (CH), 125.5 (CH), 48.5 (CH), 35.8 (CH), 34.8 (CH_2), 34.0 (CH), 28.4 (2 x CH_3), 21.6 (CH_3), 21.5 (CH), 21.3 (CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{25}H_{26}N_2O_4H$ 419.1971; Found 419.1973.



(-)-**32gu**

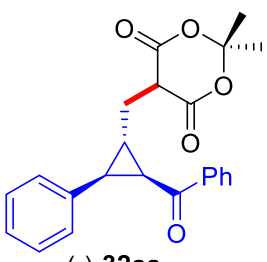
5-(((1*S*,2*R*,3*S*)-2-(2-fluorobenzoyl)-3-(p-tolyl)cyclopropyl)methyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**32gv**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 95% (100.3 mg); $[\alpha]_D^{25}$ = –72.38° (*c* = 0.105, $CHCl_3$, >5:1 *dr*); IR (Neat): ν_{max} 2924, 2859, 2359, 2339, 1674, 1608, 1516, 1451, 1377, 1273, 1211,



(-)-**32gv**

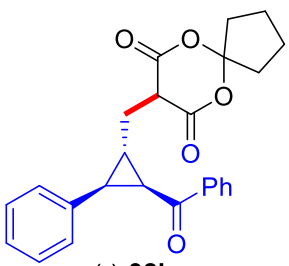
1153, 1103, 1077, 794, 756 and 637 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.51 (1H, td, *J* = 7.5, 1.5 Hz), 7.46-7.42 (1H, m), 7.12 (2H, t, *J* = 7.5 Hz), 7.09 (1H, dd, *J* = 11.0, 8.5 Hz), 6.99 (3H, s), 3.63 (1H, t, *J* = 5.0 Hz), 3.21 (3H, s, C*H*$_3$), 3.13 (3H, s, C*H*$_3$), 2.91-2.88 (1H, m), 2.74 (1H, dd, *J* = 9.5, 6.5 Hz), 2.53-2.47 (1H, m), 2.46-2.37 (2H, m), 2.23 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 193.2 (C, *C*=O), 168.54 (C, N-*C*=O), 168.51 (C, N-*C*=O), 162.6 (C, N-*C*=O), 160.6 (C), 151.1 (C), 136.5 (C), 134.1 (CH, d, *J* = 8.75 Hz), 130.4 (C), 130.4 (CH, d, *J* = 1.25 Hz), 128.8 (2 x CH), 128.6 (2 x CH), 124.3 (CH, d, *J* = 3.75 Hz), 116.5 (CH, d, *J* = 23.75.75 Hz), 48.5 (CH), 38.3 (CH, d, *J* = 6.25 Hz), 36.6 (CH), 34.6 (CH_2), 28.4 (2 x CH_3), 22.4 (CH), 21.0 (CH_3); ^{19}F NMR ($CDCl_3$, 400 MHz NMR Machine): δ -111.39; HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{23}FN_2O_4H$ 423.1720; Found 423.1722.

5-(((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**32aa**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a white solid (MP = 136-138 °C); Yield: 76% (72 mg); $[\alpha]_D^{25}$ = –114.0° (*c* = 0.100, $CHCl_3$, >50:1 *dr*); IR (Neat): ν_{max} 3725, 3627, 3593, 3028, 2933, 2884, 1780, 1742, 1658, 1598, 1448, 1378, 1298, 1220, 1060, 1023, 960, 713, 688 and 576 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (2H, d, *J* = 7.5 Hz), 7.49 (1H, t, *J* = 7.5 Hz), 7.40 (2H, t, *J* = 7.5 Hz), 7.19-7.10 (5H, m), 3.66 (1H, t, *J* = 5.0 Hz), 3.08 (1H, dd, *J* = 9.5, 5.5 Hz), 2.84 (1H, dd, *J* = 9.0, 7.5 Hz), 2.72 (1H, quint, *J* = 6.5 Hz), 2.53-2.48 (1H, m), 2.37-2.31 (1H, m), 1.75 (3H, s), 1.70 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 195.2 (C, *C*=O), 169.53 (C, O-*C*=O), 169.52 (C, O-*C*=O), 138.3 (C), 135.3 (C), 132.6 (CH), 128.9 (2 x CH), 128.4 (2 x CH), 128.0 (4 x CH), 126.8 (CH), 105.3 (C), 46.0 (CH), 36.4 (CH), 34.7 (CH), 30.0 (CH_2), 28.3 (CH_3), 27.1 (CH_3), 23.2 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{22}O_5H$ 379.1545; Found 379.1545.



(-)-**32aa**

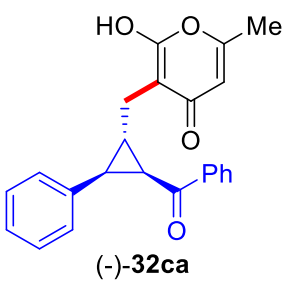
8-(((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)methyl)-6,10-dioxaspiro[4.5]decane-7,9-dione (**32ba**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a white solid (MP = 128-130 °C); Yield: 98% (99.1 mg); $[\alpha]_D^{25}$ = –126.85° (*c* = 0.108, $CHCl_3$, >50:1 *dr*); IR (Neat): ν_{max} 3062, 3031, 2963, 2925, 2870, 2848, 2169, 1787, 1744, 1662, 1597, 1447, 1344, 1218, 1112, 1045, 1022, 980, 759, 695 and 653 cm^{-1}; ^{1}H NMR ($CDCl_3$,



(-)-**32ba**

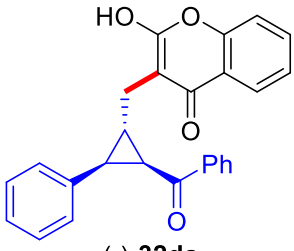
500 MHz): δ 7.89 (2H, dd, *J* = 8.5, 1.5 Hz), 7.50 (1H, dd, *J* = 7.5, 1.5 Hz), 7.41 (2H, t, *J* = 8.0 Hz), 7.20-2.15 (4H, m), 7.13-7.10 (1H, m), 3.65 (1H, t, *J* = 5.5 Hz), 3.10 (1H, dd, *J* = 9.5, 5.5 Hz), 2.85 (1H, dd, *J* = 9.5, 7.0 Hz), 2.76 (1H, quint, *J* = 6.5 Hz), 2.47 (1H, ddd, *J* = 14.5, 6.5, 5.0 Hz), 2.29 (1H, ddd, *J* = 13.5, 7.5, 5.5 Hz), 2.24-2.17 (4H, m), 1.93-1.87 (2H, m), 1.86-1.80 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 195.4 (C, *C*=O), 165.73 (C, O-*C*=O), 165.69 (C, O-*C*=O), 138.3 (C), 135.4 (C), 132.7 (CH), 129.0 (2 x CH), 128.5 (2 x CH), 128.1 (4 x CH), 126.8 (CH), 114.4 (C), 47.4 (CH), 39.1 (CH_2), 38.1 (CH_2), 36.6 (CH), 34.8 (CH), 28.9 (CH_2), 24.4 (CH_2), 23.4 (CH), 22.5 (CH_2); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{25}H_{24}O_5H$ 405.1702; Found 405.1702.

3-(((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)methyl)-2-hydroxy-6-methyl-4*H*-pyran-4-one (**32ca**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a pale yellow liquid; Yield: 95% (85.6 mg); $[\alpha]_D^{25}$ = –113.21° (*c* = 0.106, $CHCl_3$, >30:1 *dr*); IR (Neat): ν_{max} 3060, 3028, 2922, 2851, 2679, 2147, 2030, 1667, 1578, 1497, 1447, 1405, 1374, 1255, 1217, 1177, 1122, 1041, 1023, 993, 946, 826, 762, 727, 696, 652 and 612 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.38 (1H, br s, O*H*), 7.95 (2H, d, *J* = 7.5 Hz), 7.54 (1H, t, *J* = 7.5 Hz), 7.43 (2H, t, *J* = 7.5 Hz), 7.16-7.06 (5H, m), 5.69 (1H, s), 3.24 (1H, dd, *J* = 9.0, 4.5 Hz), 3.09 (1H, t, *J* = 8.5 Hz), 2.90-2.85 (2H, m), 2.70 (1H, q, *J* = 10.5 Hz), 2.05 (3H, s, C*H*$_3$),; ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 199.3 (C, *C*=O), 167.5 (C, O-*C*=O), 166.9 (C), 160.4 (C), 138.3 (C), 136.1 (C), 133.2 (CH), 129.3 (2 x CH), 128.6 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 126.6 (CH), 101.1 (C), 101.0 (CH), 37.6 (CH), 34.3 (CH), 26.1 (CH), 26.1 (CH_2), 19.7 (CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{20}O_4H$ 361.1440; Found 361.1441.



(-)-**32ca**

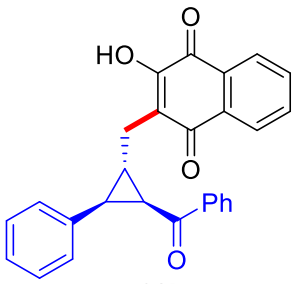
3-(((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)methyl)-2-hydroxy-4*H*-chromen-4-one (**32da**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a yellow liquid; Yield: 94% (93.2 mg); $[\alpha]_D^{25}$ = –114.15° (*c* = 0.106, $CHCl_3$, >50:1 *dr*); IR (Neat): ν_{max} 3303 (OH), 3060, 3031, 2920, 2851, 2144, 1946, 1716, 1668, 1613, 1577, 1449, 1370, 1269, 1217, 1156, 1045, 948, 756, 732 and 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.84



(-)-**32da**

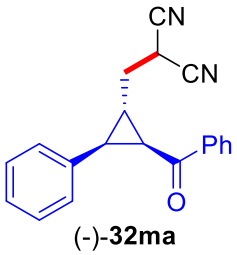
(2H, dd, *J* = 8.5, 1.0 Hz), 7.77 (1H, dd, *J* = 8.0, 1.5 Hz), 7.48-7.44 (2H, m), 7.34 (2H, t, *J* = 8.0 Hz), 7.25 (1H, d, *J* = 6.5 Hz), 7.17 (1H, td, *J* = 8.0, 1.0 Hz), 7.12 (2H, d, *J* = 7.0 Hz), 7.07 (2H, t, *J* = 7.0 Hz), 7.01 (1H, t, *J* = 7.0 Hz), 3.18 (1H, dd, *J* = 9.5, 5.0 Hz), 3.12-3.06 (2H, m), 2.95 (1H, dd, *J* = 14.5, 7.5 Hz), 2.87 (1H, quint, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 198.4 (C, *C*=O), 165.1 (C, O-*C*=O), 161.3 (C), 152.4 (C), 138.1 (C), 135.8 (C), 133.0 (CH), 131.7 (CH), 129.1 (2 x CH), 128.5 (2 x CH), 128.2 (2 x CH), 127.9 (2 x CH), 126.7 (CH), 123.9 (CH), 123.1 (CH), 116.5 (CH), 116.1 (C), 103.6 (C), 37.2 (CH), 34.0 (CH), 26.2 (CH_2), 25.7 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{26}H_{20}O_4H$ 397.1440; Found 397.1440.

2-(((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)methyl)-3-hydroxynaphthalene-1,4-dione (**32la**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a yellow solid (MP = 142-144 °C); Yield: 91% (92.9 mg); $[\alpha]_D^{25}$ = –137.38° (*c* = 0.107, $CHCl_3$, >50:1 *dr*); IR (Neat): ν_{max} 3304 (OH), 2932, 2851, 2200, 2145, 1642, 1593, 1495, 1448, 1365, 1272, 1216, 1082, 1019, 951, 725, 692 and 567 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.11 (1H, d, *J* = 7.5 Hz), 8.06 (1H, d, *J* = 7.5 Hz), 7.88 (2H, d, *J* = 7.0 Hz), 7.73 (1H, td, *J* = 7.5, 1.0 Hz), 7.66 (1H, t, *J* = 7.5 Hz), 7.48 (1H, t, *J* = 7.5 Hz), 7.39 (2H, t, *J* = 8.0 Hz), 7.15-7.13 (4H, m), 7.10-7.06 (1H, m), 3.15 (1H, dd, *J* = 9.5, 5.0 Hz), 3.00-2.92 (2H, m), 2.83 (1H, dd, *J* = 13.0, 7.5 Hz), 2.77 (1H, quint, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 195.8 (C, *C*=O), 184.6 (C, *C*=O), 181.4 (C, *C*=O), 153.6 (C), 138.5 (C), 135.8 (C), 135.9 (CH), 133.0 (CH), 132.8 (C), 132.5 (CH), 129.4 (C), 129.0 (2 x CH), 128.4 (2 x CH), 128.0 (2 x CH), 127.9 (2 x CH), 126.9 (CH), 126.6 (CH), 126.2 (CH), 122.2 (C), 36.8 (CH), 34.3 (CH), 26.2 (CH), 24.5 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{27}H_{20}O_4H$ 409.1440; Found 409.1440.



(-)-**32la**

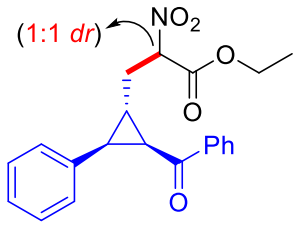
2-(((1S,2R,3S)-2-benzoyl-3-phenylcyclopropyl)methyl)malononitrile (**32ma**): The compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a pale yellow liquid; Yield: 96% (72.1 mg); $[\alpha]_D^{25}$ = –112.26° (*c* = 0.106, $CHCl_3$, >50:1 *dr*); IR (Neat): ν_{max} 3727, 3701, 3625, 3602, 3061, 3028, 2916, 2360, 2339, 1721, 1667, 1597, 1442, 1373, 1241, 1221, 1048, 994, 720, 693 and 653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 (2H, d, *J* = 7.5 Hz), 7.53 (1H, t, *J* = 7.5 Hz), 7.43



(-)-**32ma**

(2H, t, *J* = 7.5 Hz), 7.25-7.14 (5H, m), 3.90 (1H, t, *J* = 7.0 Hz), 3.11 (1H, dd, *J* = 9.5, 5.0 Hz), 2.88 (1H, dd, *J* = 9.5, 5.0 Hz), 2.69 (1H, quint, *J* = 7.0 Hz), 2.40-2.24 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.2 (C, *C*=O), 137.9 (C), 134.2 (C), 133.1 (CH), 128.9 (2 x CH), 128.6 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 127.3 (CH), 112.3 (2 x C, *C*N), 35.4 (CH), 34.1 (CH_2), 33.4 (CH), 22.5 (CH), 21.7 (CH); HRMS (ESI-TOF) *m/z*: (M + Na^+) calcd for $C_{20}H_{16}N_2ONa$ 323.1160; Found 323.1155.

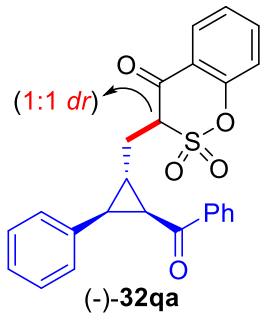
Ethyl (*R*)-3-((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)-2-nitropropanoate (**32oa**): The



(-)-**32oa**

compound was prepared following the procedure **B** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a pale yellow liquid; Yield: 75% (68.9 mg); $[\alpha]_D^{25}$ = –111.21° (*c* = 0.107, $CHCl_3$, 1:1 *dr*); IR (Neat): ν_{max} 3059, 3027, 2981, 2925, 2189, 2038, 2009, 1974, 1746, 1668, 1597, 1558, 1497, 1447, 1367, 1264, 1216, 1022, 943, 858, 760, 728, 694, 596 and 529 cm^{-1}; **Major:** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (2H, t, *J* = 8.5 Hz), 7.54-7.50 (1H, m), 7.44-7.40 (2H, m), 7.20-7.16 (2H, m), 7.14-7.10 (3H, m), 5.32-5.29 (1H, m), 4.29-.15 (2H, m), 3.01-2.96 (1H, m), 2.81-2.75 (1H, m), 2.64-2.58 (1H, m), 2.56-2.48 (2H, m), 1.26 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 500 MHz) δ 194.6 (C, *C*=O), 164.23 (C, O-*C*=O), 138.02 (C), 134.7 (C), 132.92 (CH), 128.85 (2 x CH), 128.6 (2 x CH), 128.13 (2 x CH), 128.0 (2 x CH), 127.1 (CH), 87.3 (CH), 63.3 (CH_2, O*C*H_2CH_3), 36.2 (CH), 33.6 (CH), 33.4 (CH_2), 21.2 (CH), 13.82 (CH_3, OCH_2CH_3); **Minor:** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (2H, t, *J* = 8.5 Hz), 7.54-7.50 (1H, m), 7.44-7.40 (2H, m), 7.20-7.16 (2H, m), 7.14-7.10 (3H, m), 5.32-5.29 (1H, m), 4.29-.15 (2H, m), 3.01-2.96 (1H, m), 2.81-2.75 (1H, m), 2.56-2.48 (2H, m), 2.46-2.39 (1H, m), 1.26 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 500 MHz) δ 194.5 (C, *C*=O), 164.22 (C, O-*C*=O), 138.0 (C), 134.6 (C), 132.89 (CH), 128.83 (2 x CH), 128.5 (2 x CH), 128.12 (2 x CH), 128.0 (2 x CH), 127.0 (CH), 87.2 (CH), 63.3 (CH_2, O*C*H_2CH_3), 35.7 (CH), 33.4 (CH_2), 33.3 (CH), 21.1 (CH), 13.79 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{21}H_{21}NO_5H$ 368.1498; Found 368.1498.

(*S*)-3-(((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)methyl)benzo[e][1,2]oxathiin-4(3*H*)-one 2,2-dioxide (**32qa**): The compound was prepared following the procedure **B** and purified by

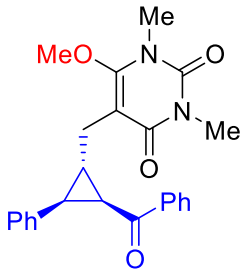


(-)-**32qa**

column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a pale yellow liquid; Yield: 98% (105.9 mg); $[\alpha]_D^{25}$ = –130.41° (*c* = 0.148, $CHCl_3$, 1:1 *dr*); IR (Neat): ν_{max} 3059, 3030, 2921,

2889, 2147, 2003, 1697, 1666, 1606, 1579, 1498, 1454, 1381, 1290, 1218, 1167, 1104, 1045, 1024, 958, 908, 865, 783, 730, 696, 648, 569 and 529 cm^{-1}; **Major:** ^1H NMR ($CDCl_3$, 500 MHz): δ 8.05 (1H, d, *J* = 7.5.0 Hz), 7.85 (2H, d, *J* = 8.0 Hz), 7.65 (1H, t, *J* = 8.0 Hz), 7.49 (1H, q, *J* = 7.0 Hz), 7.41-7.35 (2H, m), 7.34-7.28 (1H, m), 7.20 (1H, t, *J* = 8.5 Hz), 7.18-7.12 (4H, m), 7.12-7.10 (1H, m), 4.45-4.42 (1H, m), 3.05-2.98 (1H, m), 2.84-2.79 (2H, m), 2.75-2.65 (1H, m), 2.46-2.39 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.5 (C, *C*=O), 185.3 (C, *C*=O), 153.66 (C), 138.1 (C), 137.4 (CH), 134.8 (C), 132.76 (CH), 129.3 (CH), 128.93 (2 x CH), 128.5 (2 x CH), 128.0 (4 x CH), 126.95 (CH), 126.5 (CH), 120.5 (C), 119.5 (CH), 69.7 (CH), 36.8 (CH), 34.8 (CH), 29.8 (CH_2), 22.2 (CH); **Minor:** ^1H NMR ($CDCl_3$, 500 MHz): δ 8.01 (1H, d, *J* = 7.5.0 Hz), 7.81 (2H, d, *J* = 7.5 Hz), 7.65 (1H, t, *J* = 8.0 Hz), 7.49 (1H, q, *J* = 7.0 Hz), 7.41-7.35 (2H, m), 7.34-7.28 (1H, m), 7.20 (1H, t, *J* = 8.5 Hz), 7.18-7.12 (4H, m), 7.12-7.10 (1H, m), 4.45-4.42 (1H, m), 3.05-2.98 (1H, m), 2.84-2.79 (1H, m), 2.75-2.65 (1H, m), 2.64-2.56 (1H, m), 2.46-2.39 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 194.3 (C, *C*=O), 185.3 (C, *C*=O), 153.62 (C), 138.0 (C), 137.4 (CH), 134.7 (C), 132.73 (CH), 129.2 (CH), 128.87 (2 x CH), 128.4 (2 x CH), 128.0 (4 x CH), 126.91 (CH), 126.4 (CH), 120.3 (C), 119.4 (CH), 69.6 (CH), 36.5 (CH), 34.6 (CH), 29.6 (CH_2), 22.0 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{25}H_{20}O_5SH$ 433.1110; Found 433.1110.

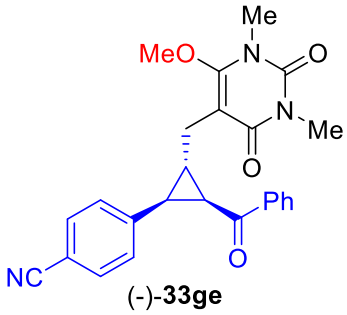
5-(((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)methyl)-6-methoxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (33ga): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 85% (34.4 mg); $[\alpha]_D^{25}$ = –92.73° (*c* = 0.110, $CHCl_3$, >99.9% *ee*, >20:1 *dr*); IR (Neat): ν_{max} 2957, 2923, 2849, 2360, 2340 1692, 1640, 1449, 1215, 1041, 777 and 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.90 (2H, dt, *J* = 8.5, 2.0 Hz), 7.49 (1H, tt, *J* = 8.0, 1.5 Hz), 7.40 (2H, t, *J* = 7.5 Hz), 7.19-7.13 (4H, m), 7.12-7.07 (1H, m), 3.96 (3H, s, O*CH*$_3$), 3.37 (3H, s, N*CH*$_3$), 3.32 (3H, s, N*CH*$_3$), 3.16 (1H, dd, *J* = 9.5, 5.0 Hz), 2.92 (1H, dd, *J* = 10.0, 6.5 Hz), 2.78 (1H, dd, *J* = 14.0, 6.5 Hz), 2.69-2.58 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 196.0 (C, *C*=O), 164.4 (C, N-*C*=O), 159.0 (C), 151.4 (C, N-*C*=O), 138.5 (C), 136.0 (C), 132.5 (CH), 129.0 (2 x CH), 128.4 (2 x CH), 128.1 (2 x CH), 127.9 (2 x CH), 126.6 (CH), 100.0 (C), 62.1 (CH_3, O*CH*3), 36.8 (CH), 34.4 (CH), 29.7 (CH_3), 28.5 (CH_3), 26.3



(-)-**33ga**

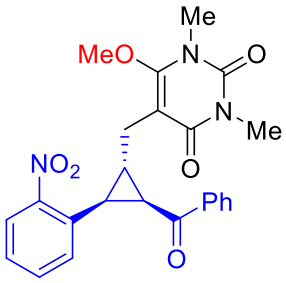
(CH_2), 25.6 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{24}N_2O_4H$ 405.1814; Found 405.1813.

4-((1*S*,2*R*,3*S*)-2-benzoyl-3-((6-methoxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)cyclopropyl)benzonitrile (**33ge**): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 65% (27.9 mg); $[\alpha]_D^{25}$ = –133.33° (*c* = 0.126, $CHCl_3$, >99.9% *ee*, >10:1 *dr*); IR (Neat): ν_{max} 3056, 2957, 2923, 2854, 2360, 2339, 2225, 1700, 1643, 1449, 1419, 1366, 1263, 1218, 1144, 1041, 1022, 980, 870, 754, 703, 653 and 559 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.88 (2H, d, *J* = 7.5 Hz), 7.53 (1H, t, *J* = 7.5 Hz), 7.49-7.39 (4H, m), 7.25 (2H, d, *J* = 8.5 Hz), 3.96 (3H, s, OC*H*$_3$), 3.39 (3H, s, C*H*$_3$), 3.32 (3H, s, C*H*$_3$), 3.28-3.24 (1H, m), 2.93 (1H, dd, *J* = 9.0, 7.0 Hz), 2.77 (1H, dd, *J* = 14.0, 6.5 Hz), 2.67 (1H, dd, *J* = 14.5, 7.5 Hz), 2.59 (1H, quint, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 195.5 (C, *C*=O), 164.4 (C, N-*C*=O), 159.1 (C, N-*C*=O), 151.3 (C), 141.9 (C), 138.0 (C), 133.0 (CH), 131.7 (2 x CH), 129.8 (2 x CH), 128.6 (2 x CH), 128.0 (2 x CH), 119.0 (C, CN), 110.3 (C), 99.6 (C), 62.1 (CH_3, O*C*H$_3$), 36.3 (CH), 34.4 (CH), 29.8 (CH_3), 28.5 (CH_3), 26.4 (CH), 26.2 (CH_2); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{25}H_{23}N_3O_4H$ 430.1767; Found 430.1766.



(-)-**33ge**

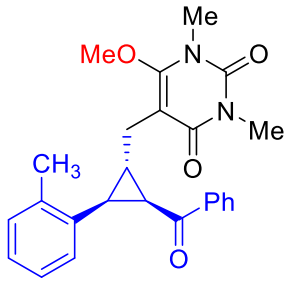
5-(((1*S*,2*R*,3*S*)-2-benzoyl-3-(2-nitrophenyl)cyclopropyl)methyl)-6-methoxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**33gf**): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 97% (43.6 mg); $[\alpha]_D^{25}$ = –90.83° (*c* = 0.120, $CHCl_3$, 99% *ee*, 3:1 *dr*); IR (Neat): ν_{max} 3065, 2952, 2360, 2339, 1700, 1636, 1577, 1520, 1447, 1420, 1345, 1264, 1216, 1144, 1038, 1022, 980, 850, 778, 731, 699 and 657 cm^{-1}; **Major:** ^1H NMR ($CDCl_3$, 500 MHz): δ 7.92 (2H, d, *J* = 7.5 Hz), 7.81 (1H, d, *J* = 8.0 Hz), 7.53-7.45 (3H, m), 7.44-7.38 (3H, m), 3.94 (3H, s, OC*H*$_3$), 3.38 (3H, s, C*H*$_3$), 3.38-3.36 (1 H, m), 3.33 (3H, s, C*H*$_3$), 3.19 (1H, quint, *J* = 8.5 Hz), 2.84 (1H, dd, *J* = 14.5, 6.5 Hz), 2.69 (1H, dd, *J* = 14.5, 7.5 Hz), 2.56-2.48 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 196.4 (C, *C*=O), 164.2 (C, N-*C*=O), 159.0 (C, N-*C*=O), 151.3 (C), 149.9 (C), 137.9 (C), 132.8 (CH), 132.6 (CH), 132.4 (CH), 131.9 (C), 128.4 (2 x CH), 128.1 (2 x CH),



(-)-**33gf**

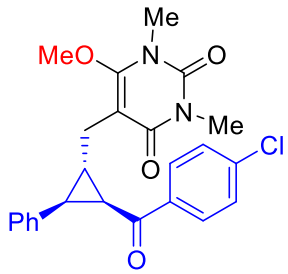
127.7 (CH), 124.3 (CH), 99.7 (C), 62.1 (CH_3, OCH_3), 34.5 (CH), 33.2 (CH), 29.7 (CH), 28.7 (CH_3), 28.4 (CH_3), 26.5 (CH_2); **Minor:** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.12 (2H, d, *J* = 7.5 Hz), 7.99 (1H, d, *J* = 8.0 Hz), 7.62-7.56 (3H, m), 7.32 (3H, t, *J* = 8.0 Hz), 3.89 (3H, s, OCH_3), 3.63 (1H, t, *J* = 5.0 Hz), 3.44 (1H, dd, *J* = 9.5, 5.5 Hz), 3.31 (3H, s, CH_3), 3.29 (3H, s, CH_3), 2.56-2.48 (1H, m), 2.14-2.08 (1H, m), 1.94 (1H, 1H, dd, *J* = 14.0, 11.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 198.2 (C, *C*=O), 164.4 (C, N-*C*=O), 159.2 (C, N-*C*=O), 151.1 (C), 150.8 (C), 137.5 (C), 133.1 (CH), 133.0 (CH), 131.9 (C), 131.7 (CH), 126.6 (2 x CH), 128.4 (2 x CH), 127.9 (CH), 124.7 (CH), 99.3 (C), 62.13 (CH_3, OCH_3), 33.1 (CH), 31.6 (CH), 30.6 (CH), 29.6 (CH_3), 28.3 (CH_3), 22.2 (CH_2); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{23}N_3O_6H$ 450.1665; Found 450.1665.

5-(((1*S*,2*R*,3*S*)-2-benzoyl-3-(o-tolyl)cyclopropyl)methyl)-6-methoxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**33gi**): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 92% (38.5 mg); $[\alpha]_D^{25}$ = –81.03° (*c* = 0.116, $CHCl_3$, >99.9% *ee*, >10:1 *dr*); IR (Neat): ν_{max} 3069, 3021, 2953, 2923, 1824, 1748, 1700, 1643, 1448, 1368, 1262, 1218, 1180, 1144, 1039, 1022, 981, 756, 731, 716 and 656 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.93 (2H, dd, *J* = 8.5, 1.0 Hz), 7.51 (1H, tt, *J* = 7.5, 1.5 Hz), 7.41 (2H, t, *J* = 8.0 Hz), 7.17 (1H, d, *J* = 7.5 Hz), 7.14-7.06 (2H, m), 7.01 (1H, d, *J* = 7.0 Hz), 3.98 (3H, s, OCH_3), 3.38 (3H, s, CH_3), 3.33 (3H, s, CH_3), 3.32 (1H, dd, *J* = 9.0, 4.5 Hz), 2.89-2.77 (2H, m), 2.71-2.67 (1H, m), 2.62-2.58 (1H, m), 2.17 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 195.6 (C, *C*=O), 164.4 (C, N-*C*=O), 158.9 (C, N-*C*=O), 151.3 (C), 138.1 (C), 137.6 (C), 134.2 (C), 132.5 (CH), 129.6 (CH), 129.4 (CH), 128.4 (2 x CH), 128.1 (2 x CH), 126.8 (CH), 125.4 (CH), 100.1 (C), 62.1 (CH_3, OCH_3), 36.1 (CH), 32.7 (CH), 29.7 (CH), 28.5 (CH_3), 27.5 (CH_3), 26.5 (CH_2), 19.8 (CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{25}H_{26}N_2O_4H$ 419.1971; Found 419.1972.



(-)-**33gi**

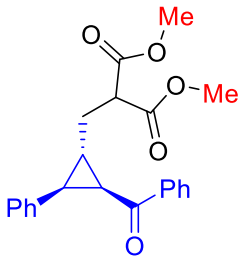
5-(((1*S*,2*R*,3*S*)-2-(4-chlorobenzoyl)-3-phenylcyclopropyl)methyl)-6-methoxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**33gl**): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 84% (36.9 mg); $[\alpha]_D^{25}$ = –125.81° (*c* = 0.124, $CHCl_3$, >99.9% *ee*, >20:1



(-)-**33gl**

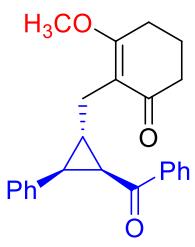
dr); IR (Neat): ν_{max} 3062, 3027, 2952, 2925, 2359, 2342, 1700, 1641, 1587, 1450, 1398, 1361, 1262, 1215, 1090, 1039, 781, 730 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.83 (2H, dt, *J* = 9.0, 2.0 Hz), 7.36 (2H, dt, *J* = 9.5, 2.0 Hz), 7.19-7.16 (2H, m), 7.13-7.09 (3H, m), 3.96 (3H, s, OC*H*$_3$), 3.38 (3H, s, C*H*$_3$), 3.32 (3H, s, C*H*$_3$), 3.12 (1H, dd, *J* = 9.5, 5.0 Hz), 2.92 (1H, dd, *J* = 9.5, 6.5 Hz), 2.78 (1H, dd, *J* = 13.5, 6.0 Hz), 2.66-2.57 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 100 MHz) δ 194.8 (C, *C*=O), 164.4 (C, N-*C*=O), 159.0 (C, N-*C*=O), 151.3 (C), 138.9 (C), 136.8 (C), 135.8 (C), 129.5 (2 x CH), 128.9 (2 x CH), 128.7 (2 x CH), 127.9 (2 x CH), 126.7 (CH), 99.9 (C), 62.1 (CH_3, O*C*H$_3$), 36.9 (CH), 34.3 (CH), 29.7 (CH_3), 28.5 (CH_3), 26.3 (CH_2), 25.8 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{23}ClN_2O_4H$ 439.1425; Found 439.1422.

Dimethyl 2-(((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)methyl)malonate (**33aa**): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1. 5:8.5 to 3:7) and isolated as a white solid (MP = 98-100 °C); Yield: 85% (31.1 mg); $[\alpha]_D^{25}$ = –132.82° (*c* = 0.131, $CHCl_3$, >30:1 *dr*); IR (Neat): ν_{max} 3727, 3701, 3625, 3602, 3034, 3007, 2952, 2926, 2360, 2340, 1730, 1661, 1597, 1499, 1435, 1369, 1337, 1273, 1240, 1218, 1146, 1091, 1021, 943, 869, 731, 714 and 651 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.87 (2H, d, *J* = 7.5 Hz), 7.49 (1H, d, *J* = 7.5 Hz), 7.40 (2H, t, *J* = 7.5 Hz), 7.19-7.09 (5H, m), 3.67 (3H, s), 3.64 (3H, s), 3.62 (1H, t, *J* = 7.5 Hz), 2.94 (1H, dd, *J* = 9.5, 5.0 Hz), 2.74 (1H, dd, *J* = 9.5, 7.5 Hz), 2.46 (1H, quint, *J* = 6.5 Hz), 2.28-2.13 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 195.2 (C, *C*=O), 169.53 (C, O-*C*=O), 169.51 (C, O-*C*=O), 138.3 (C), 135.4 (C), 132.7 (CH), 128.9 (2 x CH), 128.5 (2 x CH), 128.0 (4 x CH), 126.8 (CH), 52.65 (CH_3, COO*C*H$_3$), 52.63 (CH_3, COO*C*H$_3$), 51.3 (CH), 36.7 (CH), 33.9 (CH), 32.2 (CH_2), 23.4 (CH); HRMS (ESI-TOF) *m/z*: (M + Na^+) calcd for $C_{22}H_{22}O_5Na$ 389.1365; Found 389.1361.



(-)-**33aa**

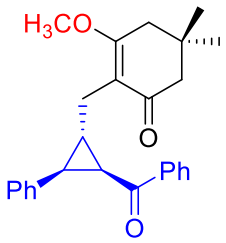
2-(((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)methyl)-3-methoxycyclohex-2-en-1-one (**33ha**): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 85% (30.6 mg); $[\alpha]_D^{25}$ = –149.04° (*c* = 0.104, $CHCl_3$, >20:1 *dr*); IR (Neat): ν_{max} 3056, 3028, 2947, 2920, 2848, 2228, 1733, 1664, 1641, 1608, 1449, 1370, 1240, 1216, 1166, 1097, 1025, 921, 762, 697 and 580 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.89 (2H, dd, *J* = 8.5, 1.0 Hz), 7.48 (1H,



(-)-**33ha**

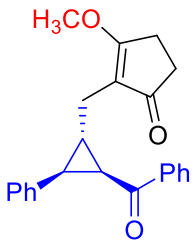
tt, *J* = 8.5, 2.0 Hz), 7.39 (2H, t, *J* = 7.5 Hz), 7.18-7.13 (4H, m), 7.11-7.07 (1H, m), 3.84 (3H, s, OC*H*$_3$), 3.04 (1H, dd, *J* = 9.5, 5.0 Hz), 2.82 (1H, dd, *J* = 9.0, 6.0 Hz), 2.63-2.57 (3H, m), 2.55-2.50 (2H, m), 2.33 (2H, q, *J* = 7.5 Hz), 1.98 (2H, quint, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 198.1 (C, *C*=O), 196.6 (C, *C*=O), 172.8 (C), 138.8 (C), 136.7 (C), 132.3 (CH), 129.1 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 127.8 (2 x CH), 126.3 (CH), 118.1 (C), 55.3 (CH_3, O*C*H$_3$), 37.3 (CH), 36.2 (CH_2), 34.2 (CH), 26.2 (CH), 24.8 (2 x CH_2), 20.8 (CH_2); HRMS (ESI-TOF) *m/z*: (M + H$^+$) calcd for $C_{24}H_{24}O_3H$ 361.1804; Found 361.1804.

2-(((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)methyl)-3-methoxy-5,5-dimethylcyclohex-2-en-1-one (**33ia**): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 88% (34.2 mg); $[\alpha]_D^{25}$ = –112.87° (*c* = 0.101, $CHCl_3$, >20:1 *dr*); IR (Neat): ν_{max} 2955, 2932, 2147, 2008, 1735, 1614, 1449, 1370, 1276, 1236, 1216, 1155, 1111, 1044, 750, 696, 643, 611, 585 and 548 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (2H, dd, *J* = 8.5, 1.0 Hz), 7.47 (1H, tt, *J* = 8.0, 2.0 Hz), 7.39 (2H, t, *J* = 7.5 Hz), 7.18-7.13 (4H, m), 7.10-7.06 (1H, m), 3.82 (3H, s, OC*H*$_3$), 3.02 (1H, dd, *J* = 9.0, 4.5 Hz), 2.83 (1H, dd, *J* = 9.0, 6.0 Hz), 2.62-2.51 (3H, m), 2.42 (2H, s), 2.21 (2H, s), 1.05 (3H, s, C*H*$_3$) 1.03 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 197.9 (C, *C*=O), 196.5 (C, *C*=O), 170.9 (C), 138.8 (C), 136.7 (C), 132.3 (CH), 129.1 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 127.7 (2 x CH), 126.3 (CH), 116.9 (C), 55.3 (CH_3, O*C*H$_3$), 50.1 (CH_2), 38.8 (CH_2), 37.3 (CH), 34.1 (CH), 32.0 (C), 28.5 (2 x CH_3), 26.4 (CH) 24.6 (CH_2); HRMS (ESI-TOF) *m/z*: (M + H$^+$) calcd for $C_{26}H_{28}O_3H$ 389.2117; Found 389.2117.



(-)-**33ia**

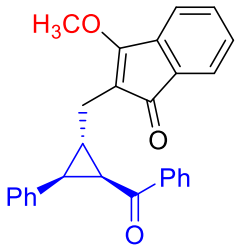
2-(((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)methyl)-3-methoxycyclopent-2-en-1-one (**33ja**): The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 82% (28.4 mg); $[\alpha]_D^{25}$ = –153.64° (*c* = 0.110, $CHCl_3$, >20:1 *dr*); IR (Neat): ν_{max} 3062, 3030, 2919, 2861, 2149, 2024, 1666, 1624, 1497, 1449, 1362, 1257, 1239, 1217, 1177, 1077, 1044, 1022, 938, 868, 761, 732, 698, 651, 612, 591, 570 and 513 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 (2H, dd, *J* = 8.5, 1.5 Hz), 7.48 (1H, tt, *J* = 7.5, 1.5 Hz), 7.40 (2H, t, *J* = 8.0 Hz), 7.19-7.14 (4H, m), 7.11-7.08 (1H, m), 3.93 (3H, s), 3.04 (1H, dd, *J* = 9.5, 5.0 Hz), 2.80 (1H, dd, *J* = 9.5, 7.0 Hz), 2.67 (2H, t, *J* = 5.0 Hz), 2.60-2.55 (1H, m), 2.50 (1H, dd, *J* = 14.5, 6.5 Hz) 2.46-



(-)-**33ja**

2.44 (2H, m), 2.33 (1H, dd, *J* = 14.5, 6.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 204.1 (C, *C*=O), 196.2 (C, *C*=O), 185.5 (C), 138.7 (C), 136.3 (C), 132.3 (CH), 129.1 (2 x CH), 128.4 (2 x CH), 128.0 (2 x CH), 127.4 (2 x CH), 126.4 (CH), 119.1 (C), 56.5 (CH_3, O*C*H_3), 33.1 (CH), 34.2 (CH), 33.5 (CH_2), 25.1 (CH), 24.5 (CH_2), 24.4 (CH_2); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{22}O_3H$ 347.1647; Found 347.1646.

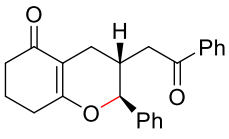
2-(((1*S*,2*R*,3*S*)-2-benzoyl-3-phenylcyclopropyl)methyl)-3-methoxy-1*H*-inden-1-one (**33ka**):



(-)-**33ka**

The compound was prepared following the procedure **C** and purified by column chromatography using EtOAc/hexanes (1. 5:8.5 to 3:7) and isolated as a pale yellow liquid; Yield: 78% (30.8 mg); $[\alpha]_D^{25}$ = –124.37° (*c* = 0.119, $CHCl_3$, >20:1 *dr*); IR (Neat): ν_{max} 3380, 3063, 3028, 2958, 2922, 2853, 2358, 1697, 1665, 1620, 1586, 1496, 1446, 1372, 1310, 1251, 1215, 1180, 1159, 1079, 1044, 1023, 982, 955, 927, 845, 763, 725, 694, 646, 597, and 552 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88 (2H, dd, *J* = 8.5, 3.0 Hz), 7.48 (1H, t, *J* = 7.5 Hz), 7.40-7.36 (3H, m), 7.35-7.29 (1H, m), 7.26-7.18 (2H, m,), 7.18-7.11 (4H, m), 7.11-7.06 (1H, m), 4.34 (3H, s), 3.11 (1H, dd, *J* = 9.5, 5.0 Hz), 2.90 (1H, td, *J* = 9.5, 7.0 Hz), 2.86-2.72 (2H, m), 2.55 (1H, sextet, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 196.1 (C, *C*=O), 195.9 (C, *C*=O), 140.6 (C), 138.5 (C), 135.9 (C), 132.5 (CH), 132.4 (CH), 131.8 (C), 129.4 (CH), 129.0 (2 x CH), 128.4 (2 x CH), 128.1 (2 x CH), 127.9 (2 x CH), 126.6 (CH), 121.0 (CH), 118.8 (CH), 108.3 (C), 59.0 (CH_3, O*CH3*), 36.6 (CH), 39.9 (CH), 26.8 (CH), 24.4 (CH_2); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{27}H_{22}O_3H$ 395.1647; Found 395.1647.

(2*S*,3*R*)-3-(2-oxo-2-phenylethyl)-2-phenyl-2,3,4,6,7,8-hexahydro-5*H*-chromen-5-one (**34ha**):

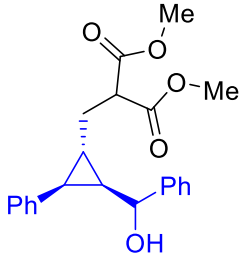


(-)-**34ha**

The compound was prepared following the procedure **D** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 70% (33.8 mg, 0.14 mmol); $[\alpha]_D^{25}$ = –145.19° (*c* = 0.104, $CHCl_3$, >50:1 *dr*); IR (Neat): ν_{max} 3059, 2924, 2852, 2358, 2337, 1724, 1682, 1624, 1448, 1390, 1224, 1186, 1004, 754 and 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78 (2H, dt, *J* = 8.5, 2.0 Hz), 7.52 (1H, tt, *J* = 7.5, 1.5 Hz), 7.43 (7H, m), 4.92 (1H, d, *J* = 8.0 Hz), 2.89-2.78 (2H, m), 2.78-2.72 (1H, m), 2.60 (1H, dd, *J* = 3.5, 1.5 Hz), 2.54-2.44 (2H, m), 2.43-2.34 (2H, m), 2.11-2.06 (1H, m), 2.04-1.98 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 197.96 (C, *C*=O), 197.9 (C, *C*=O), 170.9 (C), 138.5 (C), 136.9 (C), 133.1 (CH), 128.8 (2 x CH), 128.7 (CH), 128.5 (2 x CH), 127.9 (2 x CH), 126.9 (2 x CH), 111.1 (C), 82.7 (CH), 40.6

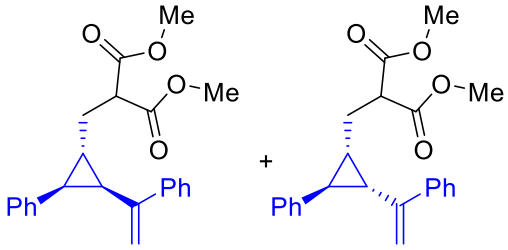
(CH_2), 36.6 (CH_2), 33.9 (CH), 28.4 (CH_2), 23.8 (CH_2), 20.9 (CH_2); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{22}O_3H$ 347.1647; Found 347.1649.

Dimethyl 2-(((1*S*,2*R*,3*S*)-2-((*S*)-hydroxy(phenyl)methyl)-3-phenylcyclopropyl)methyl)malonate (**35aa**): The compound was prepared following the procedure **K** and purified by column chromatography using EtOAc/hexanes (1.5:8.5 to 3:7) and isolated as a colorless liquid; Yield: 56% (26.6 mg, 0.13 mmol); $[\alpha]_D^{25}$ = 200.93° (*c* = 0.108, $CHCl_3$, >30:1 *dr*); IR (Neat): ν_{max} 3412 (OH), 3059, 3026, 2952, 2848, 2032, 1729, 1601, 1495, 1436, 1339, 1193, 1154, 1077, 1027, 963, 914, 844, 823, 759, 699, 649, 612 and 528 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.29 (8H, m), 7.29-7.22 (2H, m), 3.92 (1H, d, *J* = 9.5 Hz), 3.64 (3H, s, C*H*$_3$), 3.58 (3H, s, C*H*$_3$), 3.25 (1H, dd, *J* = 9.0, 6.5 Hz), 2.21 (1H, dd, *J* = 8.5, 6.0 Hz), 2.01-1.87 (2H, m), 1.67 (1H, br s, O*H*), 1.52-1.42 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 169.6 (C, O-*C*=O), 169.4 (C, O-*C*=O), 143.5 (C), 137.4 (C), 128.7 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 127.5 (CH), 126.6 (CH), 125.8 (2 x CH), 73.2 (CH), 52.5 (CH_3), 52.4 (CH_3), 51.2 (CH), 34.8 (CH), 32.5 (CH_2), 29.5 (CH), 19.7 (CH); HRMS (ESI-TOF) *m/z*: (M + Na^+) calcd for $C_{22}H_{24}O_5Na$ 391.1521; Found 391.1524.



(-)-**35aa**

Dimethyl 2-(((1S,2S,3R)-2-phenyl-3-(1-phenylvinyl)cyclopropyl)methyl)malonate (**36aa**) **and Dimethyl 2-(((1S,2S,3S)-2-phenyl-3-(1-phenylvinyl)cyclopropyl)methyl)malonate** (**36aa′**)**:** The compound was prepared following the procedure **N** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a colorless liquid; Yield: 69% (50 mg, 0.2 mmol); $[\alpha]_D^{25}$ = –69.34° (*c* = 0.137, $CHCl_3$, 1.5:1 epimer); IR (Neat): ν_{max} 2954, 2924, 2853, 2170, 2016, 1732 (C=O), 1626, 1495, 1436, 1265, 1155, 1028, 896, 777, 734 and 699 cm^{-1}; **Major epimer 36aa:** ^1H NMR ($CDCl_3$, 500 MHz): δ 7.32-7.26 (4H, m), 7.23-7.08 (4H, m), 7.01 (2H, br d, *J* = 7.0 Hz), 5.34 (1H, s, *vinylic* CH), 4.90 (1H, s, *vinylic* CH), 3.71 (3H, s, COOC*H*$_3$), 3.67 (3H, s, COOC*H*$_3$), 3.62 (1H, t, *J* = 7.5 Hz), 2.31 (1H, dd, *J* = 9.5, 5.5 Hz), 2.27-2.10 (1H, m), 2.06 (1H, dd, *J* = 9.5, 6.0 Hz), 1.81-1.72 (1H, m) 1.63-1.55 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 169.74 (C, O-*C*=O), 169.70 (C, O-*C*=O), 142.9 (C), 141.2 (C), 137.5 (C), 128.4 (2 x CH), 128.2 (2 x CH), 128.0 (2 x CH), 127.7 (CH), 127.6 (2 x CH), 127.3 (CH), 113.4 (CH_2, *vinylic*), 52.6



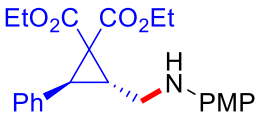
(-)-**36aa** (-)-**36aa'**

(CH), 51.5 (2 x CH_3, COO*C*H_3), 33.2 (CH_2), 33.1 (CH), 31.8 (CH), 21.2 (CH); **Minor epimer 36aa′:** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.58 (2H, d, *J* = 7.0 Hz), 7.36 (2H, t, *J* = 7.5 Hz), 7.23-7.08 (4H, m), 7.08-7.03 (2H, m), 5.62 (1H, s, *vinylic* CH), 5.19 (1H, s, *vinylic* CH), 3.635 (3H, s, COOC*H*$_3$), 3.633 (3H, s, COOC*H*$_3$), 3.42 (1H, t, *J* = 8.0 Hz), 2.27-2.10 (3H, m), 1.81-1.72 (1H, m) 1.63-1.55 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 125 MHz) δ 169.8 (C, O-*C*=O), 169.75 (C, O-*C*=O), 143.5 (C), 141.7 (C), 141.0 (C), 126.3 (2 x CH), 126.0 (4 x CH), 125.95 (2 x CH), 125.91 (CH), 125.8 (CH), 113.4 (CH_2, *vinylic*), 52.55 (2 x CH_3, COO*C*H_3), 52.47 (CH), 32.0 (CH), 27.9 (CH), 27.6 (CH_2), 26.7 (CH); HRMS (ESI-TOF) *m/z*: (M + Na^+) calcd for $C_{23}H_{24}O_4Na$ 387.1572; Found 387.1572.

Chapter 5:

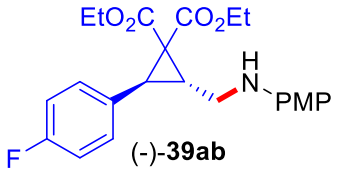
Materials: The chiral compounds **5a-5k** (86-99% *ee*),[9,10] (-)-**3a** (>99.9% *ee*)[18] were prepared by following the reported methods.

Diethyl (2*R*,3*S*)-2-(((4-methoxyphenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**39aa**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 98% (38.95 mg); $[\alpha]_D^{25}$ = –32.4° (*c* = 0.17, $CHCl_3$, >96% *ee*, >98% *de*); IR (Neat): ν_{max} 3389 (NH), 2928, 1718 (O-C=O), 1512, 1464, 1369, 1290, 1232, 1096, 1030, 820, 749, 697, 666 and 521 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25-7.19 (5H, m), 6.78 (2H, td, *J* = 10.0, 3.5 Hz), 6.61 (2H, td, *J* = 10.0, 3.5 Hz), 4.29-4.17 (2H, m, OC*H*$_2$CH$_3$), 3.90-3.84 (2H, m, OC*H*$_2$CH$_3$), 3.74 (3H, s, OC*H*$_3$), 3.42 (1H, dd, *J* = 13.0, 6.5 Hz), 3.24 (1H, d, *J* = 8.0 Hz), 3.17 (1H, dd, *J* = 13.0, 8.0 Hz), 2.84 (1H, td, *J* = 9.5, 6.5 Hz), 1.25 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$), 0.89 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 166.7 (C, O-*C*=O), 152.5 (C), 142.0 (C), 134.4 (C), 128.7 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 114.9 (2 x CH), 114.5 (2 x CH), 61.9 (CH_2, OC*H*$_2$CH$_3$), 61.3 (CH_2, OC*H*$_2$CH$_3$), 55.8 (CH_3, OC*H*$_3$), 43.6 (CH_2), 42.3 (C), 35.6 (CH), 29.9 (CH), 14.2 (CH_3, OCH$_2$C*H*$_3$), 13.7 (CH_3, OC*H*$_2$CH$_3$); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{27}NO_5H$ 398.1967; Found 398.1967.



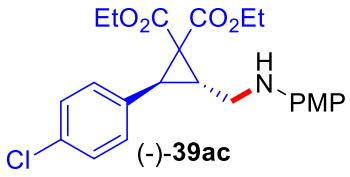
(-)-**39aa**

Diethyl (2*S*,3*R*)-2-(4-fluorophenyl)-3-(((4-methoxyphenyl)amino)methyl)cyclopropane-1,1-dicarboxylate (**39ab**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 88% (36.55 mg); $[\alpha]_D^{25}$ = –27.4° (*c* = 0.102, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3390 (NH), 2981, 2359, 1719 (O-C=O), 1512, 1292, 1219, 1132, 1034, 821, 772 and 617 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.22-7.09 (2H, m), 6.94 (2H, tt, *J* = 8.8, 2.0 Hz), 6.78 (2H, td, *J* = 10.0, 3.2 Hz), 6.61 (2H, td, *J* = 10.4, 3.6 Hz), 4.32-4.09 (2H, m, OCH_2CH_3), 3.99-3.81 (2H, m, OCH_2CH_3), 3.74 (3H, s, OCH_3), 3.42 (1H, dd, *J* = 12.8, 6.0 Hz), 3.21-3.13 (2H, m), 2.79 (1H, td, *J* = 8.0, 8.0 Hz), 1.25 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.94 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.6 (C, O-*C*=O), 166.6 (C, O-*C*=O), 162.1 (C, d, *J* = 244 Hz), 152.5 (C), 141.9 (C), 130.3 (2 x CH, d, *J* = 8.0 Hz), 130.1 (C, d, *J* = 3.0 Hz), 115.1 (2 x CH, d, *J* = 22.0 Hz), 114.9 (2 x CH), 114.5 (2 x CH), 62.0 (CH_2, OCH_2CH_3), 61.4 (CH_2, OCH_2CH_3), 55.7 (CH_3, OCH_3), 43.5 (CH_2), 42.2 (C), 34.8 (CH), 30.1 (CH), 14.2 (CH_3, OCH_2CH_3), 13.8 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: ($M + H^+$) calcd for $C_{23}H_{26}FNO_5H$ 416.1873; Found 416.1878.



(-)-**39ab**

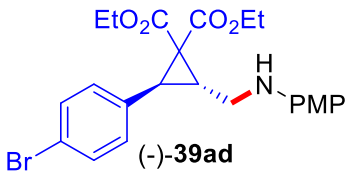
Diethyl (2*S*,3*R*)-2-(4-chlorophenyl)-3-(((4-methoxyphenyl)amino)methyl)cyclopropane-1,1-dicarboxylate (**39ac**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 82% (35.3 mg); $[\alpha]_D^{25}$ = –38.0° (*c* = 0.113, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3386 (NH), 2929, 1719 (O-C=O), 1512, 1464, 1368, 1290, 1233, 1132, 1090, 1034, 1015, 819, 765 and 707 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.25 (2H, td, *J* = 9.2, 2.4 Hz), 7.15 (2H, td, *J* = 9.2, 2.0 Hz), 6.80 (2H, td, *J* = 10.4, 2.4 Hz), 6.63 (2H, td, *J* = 10.4, 2.4 Hz), 4.31-4.20 (2H, m, OCH_2CH_3), 4.01-3.86 (2H, m, OCH_2CH_3), 3.76 (3H, s, OCH_3), 3.44 (1H, dd, *J* = 13.2, 6.4 Hz), 3.24-3.14 (2H, m), 2.81 (1H, td, *J* = 8.0, 7.6 Hz), 1.28 (3H, t, *J* = 7.6 Hz, OCH_2CH_3), 0.98 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.5 (C, O-*C*=O), 166.5 (C, O-*C*=O), 152.5 (C), 141.9 (C), 133.2 (C), 133.0 (C), 130.0 (2 x CH), 128.3 (2 x CH), 114.9 (2 x CH), 114.5 (2 x CH), 62.0 (CH_2, OCH_2CH_3), 61.5 (CH_2, OCH_2CH_3), 55.7 (CH_3, OCH_3), 43.5 (CH_2), 42.3 (C), 34.9 (CH), 30.0 (CH), 14.2 (CH_3, OCH_2CH_3), 13.8 (CH_3,



(-)-**39ac**

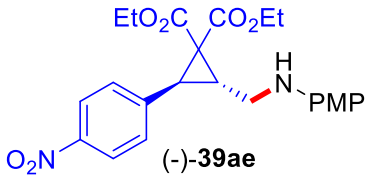
OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{26}ClNO_5H$ 432.1578; Found 432.1578.

Diethyl (2*S*,3*R*)-2-(4-bromophenyl)-3-(((4-methoxyphenyl)amino)methyl)cyclopropane-1,1-dicarboxylate (**39ad**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 85% (40.48 mg); $[\alpha]_D^{25}$ = –36.7° (*c* = 0.090, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3386 (NH), 2923, 2851, 1718 (O-C=O), 1511, 1291, 1233, 1132, 1034, 1010, 820, 733 and 703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37 (2H, td, *J* = 9.2, 2.4 Hz), 7.06 (2H, td, *J* = 8.0, 2.8 Hz), 6.78 (2H, td, *J* = 10.0, 2.4 Hz), 6.61 (2H, td, *J* = 10.0, 2.4 Hz), 4.31-4.15 (2H, m, OCH_2CH_3), 4.00-3.83 (2H, m, OCH_2CH_3), 3.74 (3H, s, OCH_3), 3.41 (1H, dd, *J* = 13.2, 6.4 Hz), 3.21-3.10 (2H, m), 2.78 (1H, td, *J* = 8.0, 7.6 Hz), 1.25 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.95 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.5 (C, O-*C*=O), 166.5 (C, O-*C*=O), 152.5 (C), 141.8 (C), 133.5 (C), 131.3 (2 x CH), 130.4 (2 x CH), 121.4 (C), 114.9 (2 x CH), 114.6 (2 x CH), 62.0 (CH_2, OCH_2CH_3), 61.5 (CH_2, OCH_2CH_3), 55.7 (CH_3, OCH_3), 43.5 (CH_2), 42.2 (C), 34.9 (CH), 29.9 (CH), 14.2 (CH_3, OCH_2CH_3), 13.8 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{26}BrNO_5H$ 476.1073; Found 476.1073.



(-)-**39ad**

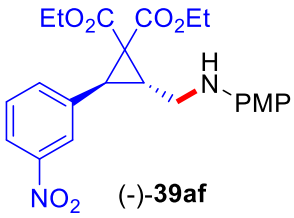
Diethyl (2*R*,3*S*)-2-(((4-methoxyphenyl)amino)methyl)-3-(4-nitrophenyl)cyclopropane-1,1-dicarboxylate (**39ae**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (1:9 to 3:7) and isolated as a pale yellow liquid; Yield: 95% (42 mg); $[\alpha]_D^{25}$ = –25.9° (*c* = 0.091, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3389 (NH), 2982, 1722 (O-C=O), 1601, 1514, 1465, 1368, 1293, 1234, 1133, 1033, 855, 822 and 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.12 (2H, d, *J* = 9.0 Hz), 7.36 (2H, d, *J* = 9.0 Hz), 6.78 (2H, td, *J* = 9.0, 3.5 Hz), 6.62 (2H, td, *J* = 9.0, 3.5 Hz), 4.33-4.19 (2H, m, OCH_2CH_3), 4.00-3.84 (2H, m, OCH_2CH_3), 3.74 (3H, s, OCH_3), 3.44 (1H, dd, *J* = 13.5, 6.5 Hz), 3.27 (1H, d, *J* = 8.0 Hz), 3.21 (1H, dd, *J* = 13.5, 7.5 Hz), 2.86 (1H, td, *J* = 9.5, 8.0 Hz), 1.27 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 0.96 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.1 (C, O-*C*=O), 166.1 (C, O-*C*=O), 152.7 (C), 147.2 (C), 142.2 (C), 141.6 (C), 129.6 (2 x CH), 123.3 (2 x CH), 115.0 (2 x CH), 114.7 (2 x CH), 62.2 (CH_2, OCH_2CH_3), 61.7 (CH_2, OCH_2CH_3), 55.7 (CH_3, OCH_3), 43.4 (CH_2), 42.7 (C), 35.0 (CH), 30.3 (CH), 14.1 (CH_3,



(-)-**39ae**

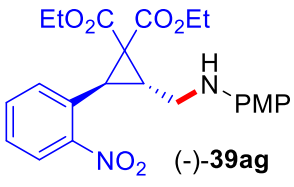
OCH_2CH_3), 13.8 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{26}N_2O_7H$ 443.1818; Found 443.1818.

Diethyl (2*R*,3*S*)-2-(((4-methoxyphenyl)amino)methyl)-3-(3-nitrophenyl)cyclopropane-1,1-dicarboxylate (**39af**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 96% (42.47 mg); $[\alpha]_D^{25}$ = –26.2° (*c* = 0.107, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3393 (NH), 2983, 2928, 1718 (O-C=O), 1718, 1529, 1511, 1464, 1348, 1289, 1231, 1097, 1031, 819, 734 and 687 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.12 (1H, td, *J* = 7.6, 2.0 Hz), 7.95 (1H, t, *J* = 2.0 Hz), 7.69-7.56 (2H, m), 6.74 (2H, td, *J* = 10.0, 3.2 Hz), 6.62 (2H, td, *J* = 10.0, 3.2 Hz), 5.41 (1H, br s, NH), 4.29-4.14 (2H, m, OCH_2CH_3), 3.89-3.76 (2H, m, OCH_2CH_3), 3.64 (3H, s, OCH_3), 3.30 (1H, d, *J* = 8.0 Hz), 3.25 (1H, dd, *J* = 13.2, 6.4 Hz), 3.11 (1H, dd, *J* = 13.2, 7.2 Hz), 2.80 (1H, q, *J* = 6.8 Hz), 1.21 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.81 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.2 (C, O-*C*=O), 166.4 (C, O-*C*=O), 151.6 (C), 147.9 (C), 143.9 (C), 137.5 (C), 136.1 (CH), 130.2 (CH), 123.4 (CH), 122.7 (CH), 115.0 (2 x CH), 114.3 (2 x CH), 62.1 (CH_2, OCH_2CH_3), 61.6 (CH_2, OCH_2CH_3), 55.7 (CH_3, OCH_3), 42.4 (CH_2), 42.3 (C), 34.9 (CH), 30.1 (CH), 14.4 (CH_3, OCH_2CH_3), 14.0 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{26}N_2O_7H$ 443.1818; Found 443.1818.



(-)-**39af**

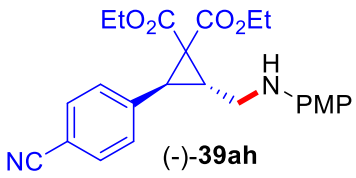
Diethyl (2*R*,3*S*)-2-(((4-methoxyphenyl)amino)methyl)-3-(2-nitrophenyl)cyclopropane-1,1-dicarboxylate (**39ag**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 95% (42.03 mg); $[\alpha]_D^{25}$ = 70.9° (*c* = 0.103, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3393 (NH), 2924, 2360, 1719 (O-C=O), 1512, 1464, 1368, 1346, 1289, 1234, 1133, 1032 and 822 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.97 (1H, dd, *J* = 8.0, 1.0 Hz), 7.51 (1H, dt, *J* = 7.5, 1.0 Hz), 7.41 (1H, t, *J* = 7.5 Hz), 7.30 (1H, d, *J* = 7.5 Hz), 6.79 (2H, td, *J* = 10.5, 3.5 Hz), 6.68 (2H, td, *J* = 10.0, 3.5 Hz), 4.34-4.18 (2H, m, OCH_2CH_3), 3.96-3.87 (1H, m, OCH_2CH_3), 3.85-3.78 (1H, m, OCH_2CH_3), 3.74 (3H, s, OCH_3), 3.71 (1H, d, *J* = 8.5 Hz), 3.52 (1H, dd, *J* = 13.5, 6.5 Hz), 3.29 (1H, dd, *J* = 13.5, 8.0 Hz), 2.75 (1H, td, *J* = 8.0, 8.0 Hz), 1.27 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 0.96 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.0 (C, O-*C*=O), 166.7 (C, O-*C*=O), 152.8 (C), 150.0 (C), 141.2 (C), 133.0 (CH), 131.5 (CH), 130.4 (C), 128.6 (CH),



(-)-**39ag**

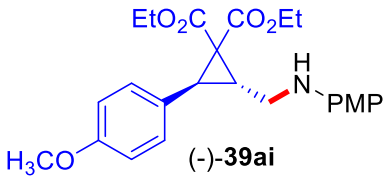
124.7 (CH), 115.0 (2 x CH), 114.9 (2 x CH), 62.0 (CH_2, O*C*H_2CH_3), 61.8 (CH_2, O*C*H_2CH_3), 55.7 (CH_3, *OCH*$_3$), 43.4 (CH_2), 41.1 (C), 34.0 (CH), 30.9 (CH), 14.1 (CH_3, OCH$_2$*C*H_3), 13.6 (CH_3, OCH$_2$*C*H_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{26}N_2O_7H$ 443.1818; Found 443.1819.

Diethyl (2*S*,3*R*)-2-(4-cyanophenyl)-3-(((4-methoxyphenyl)amino)methyl)cyclopropane-1,1-dicarboxylate (**39ah**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 83% (35.04 mg); $[\alpha]_D^{25}$ = –34.1° (*c* = 0.088, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3383 (NH), 2924, 2852, 2227, 1719 (O-C=O), 1608, 1512, 1464, 1369, 1290, 1233, 1132, 1033, 821, 733 and 567 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.55 (2H, d, *J* = 8.5 Hz), 7.30 (2H, d, *J* = 8.0 Hz), 6.78 (2H, td, *J* = 10.5, 2.0 Hz), 6.61 (2H, td, *J* = 10.5, 3.5 Hz), 4.32-4.18 (2H, m, OC*H*$_2$CH$_3$), 3.98-3.84 (2H, m, OC*H*$_2$CH$_3$), 3.74 (3H, s, OC*H*$_3$), 3.42 (1H, dd, *J* = 13.5, 6.5 Hz), 3.24 (1H, d, *J* = 8.0 Hz), 3.19 (1H, dd, *J* = 13.0, 8.0 Hz), 2.83 (1H, td, *J* = 9.5, 8.0 Hz), 1.26 (3H, t, *J* = 7.5 Hz, OCH$_2$C*H*$_3$), 0.94 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.2 (C, O-*C*=O), 166.2 (C, O-*C*=O), 152.6 (C), 141.7 (C), 140.1 (C), 131.9 (2 x CH), 129.5 (2 x CH), 118.6 (C, CN), 114.9 (2 x CH), 114.6 (2 x CH), 111.2 (C), 62.2 (CH_2, O*C*H_2CH_3), 61.6 (CH_2, O*C*H_2CH_3), 55.7 (CH_3, *OCH*$_3$), 43.4 (CH_2), 42.7 (C), 35.1 (CH), 30.1 (CH), 14.1 (CH_3, OCH$_2$*C*H_3), 13.8 (CH_3, OCH$_2$*C*H_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{26}N_2O_5H$ 423.1920; Found 423.1921.



(-)-**39ah**

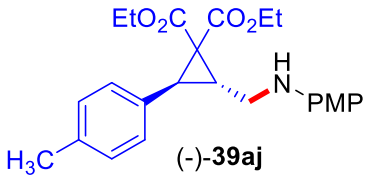
Diethyl (2*S*,3*R*)-2-(4-methoxyphenyl)-3-(((4-methoxyphenyl)amino)methyl)cyclopropane-1,1-dicarboxylate (**39ai**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 98% (41.89 mg); $[\alpha]_D^{25}$ = –40.8° (*c* = 0.103, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3386 (NH), 2934, 2834, 1718 (O-C=O), 1612, 1512, 1463, 1368, 1291, 1234, 1176, 1132, 1094, 1032, 820 and 774 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.12 (2H, br d, *J* = 8.5 Hz), 6.78 (4H, dd, *J* = 8.0, 2.0 Hz), 6.63 (2H, br d, *J* = 8.5 Hz), 4.28-4.15 (2H, m, OC*H*$_2$CH$_3$), 3.95-3.84 (2H, m, OC*H*$_2$CH$_3$), 3.76 (3H, s, OC*H*$_3$), 3.74 (3H, s, OC*H*$_3$), 3.41 (1H, dd, *J* = 13.0, 6.0 Hz), 3.19-3.14 (2H, m), 2.84-2.78 (1H, m), 1.24 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$), 0.94 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.8 (C, O-



(-)-**39ai**

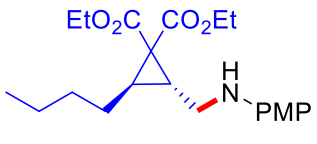
C=O), 166.7 (C, O-*C*=O), 158.9 (C), 152.6 (C), 141.6 (C), 129.8 (2 x CH), 126.3 (C), 114.9 (2 x CH), 114.8 (2 x CH), 113.6 (2 x CH), 61.8 (CH_2, O*C*$H_2$$CH_3$), 61.3 ($CH_2$, O*C*$H_2$$CH_3$), 55.7 ($CH_3$, O*C*$H_3$), 55.2 ($CH_3$, O*C*$H_3$), 43.7 ($CH_2$), 42.2 (C), 35.1 (CH), 29.9 (CH), 14.1 (CH_3, OCH$_2$*C*H_3), 13.8 (CH_3, OCH$_2$*C*H_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{29}NO_6H$ 428.2073; Found 428.2077.

Diethyl (2*R*,3*S*)-2-(((4-methoxyphenyl)amino)methyl)-3-(p-tolyl)cyclopropane-1,1-dicarboxylate (**39aj**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 82% (33.8 mg); $[\alpha]_D^{25}$ = –35.0° (*c* = 0.100, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3389 (NH), 2980, 2928, 1721 (O-C=O), 1513, 1464, 1368, 1291, 1234, 1210, 1181, 1131, 1095, 1035, 820 and 712 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.07 (4H, q, *J* = 8.5 Hz), 6.78 (2H, td, *J* = 10.5, 3.5 Hz), 6.61 (2H, td, *J* = 10.5, 3.5 Hz), 4.27-4.18 (2H, m, OC*H*$_2$CH$_3$), 3.96-3.83 (2H, m, OC*H*$_2$CH$_3$), 3.74 (3H, s, OC*H*$_3$), 3.41 (1H, dd, *J* = 13.0, 6.0 Hz), 3.20 (1H, d, *J* = 8.0 Hz), 3.15 (1H, dd, *J* = 13.0, 8.0 Hz), 2.85-2.78 (1H, m), 2.29 (3H, s, Ar-*CH*$_3$), 1.25 (3H, t, *J* = 7.5 Hz, OCH$_2$C*H*$_3$), 0.93 (3H, t, *J* = 7.5 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.8 (C, O-*C*=O), 166.7 (C, O-*C*=O), 152.5 (C), 142.0 (C), 137.0 (C), 131.3 (C), 128.8 (2 x CH), 128.5 (2 x CH), 114.9 (2 x CH), 114.5 (2 x CH), 61.8 (CH_2, O*C*$H_2$$CH_3$), 61.2 ($CH_2$, O*C*$H_2$$CH_3$), 55.8 ($CH_3$, *OCH*$_3$), 43.6 ($CH_2$), 42.2 (C), 35.4 (CH), 30.0 (CH), 21.0 (CH_3, Ar-CH_3), 14.1 (CH_3, OCH$_2$*C*H_3), 13.7 (CH_3, OCH$_2$*C*H_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{29}NO_5H$ 412.2124; Found 412.2124.



(-)-**39aj**

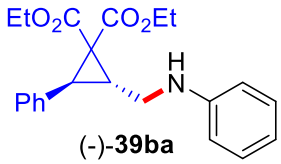
Diethyl (2*R*,3*R*)-2-butyl-3-(((4-methoxyphenyl)amino)methyl)cyclopropane-1,1-dicarboxylate (**39ak**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 42% (16 mg); $[\alpha]_D^{25}$ = –19.0° (*c* = 0.079, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3378 (NH), 2928, 2360, 1721 (O-C=O), 1513, 1464, 1368, 1293, 1219, 820, 772 and 672 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.76 (2H, td, *J* = 10.5, 3.5 Hz), 6.55 (2H, td, *J* = 10.0, 3.5 Hz), 4.29-4.09 (4H, m, OC*H*$_2$CH$_3$), 3.74 (3H, s, OC*H*$_3$), 3.27 (1H, dd, *J* = 13.0, 6.0 Hz), 2.93 (1H, dd, *J* = 13.0, 8.5 Hz), 2.11-2.04 (1H, m), 1.89 (1H, q, *J* = 7.0 Hz), 1.34-1.25 (9H, m), 1.21 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$), 0.87 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.4



(-)-**39ak**

(C, O-*C*=O), 168.3 (C, O-*C*=O), 152.3 (C), 142.1 (C), 114.8 (2 x CH), 114.4 (2 x CH), 61.6 (CH_2, O*C*H_2CH_3), 61.4 (CH_2, O*C*H_2CH_3), 55.8 (CH_3, *OCH*$_3$), 43.8 (CH_2), 39.3 (C), 32.2 (CH), 31.8 (CH), 31.0 (CH_2), 27.1 (CH_2), 22.4 (CH_2), 14.1 (CH_3, OCH_2*C*H_3), 14.1 (CH_3, OCH_2*C*H_3), 13.9 (CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{21}H_{31}NO_5H$ 378.2280; Found 378.2280.

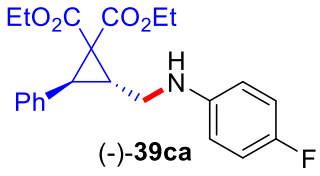
Diethyl (2*S*,3*R*)-2-phenyl-3-((phenylamino)methyl)cyclopropane-1,1-dicarboxylate (39ba):



(-)-**39ba**

The compound was prepared following the procedure **O** and purified by column chromatography using Hexanes/$CHCl_3$ (3:7 to 0:10) and isolated as a pale yellow liquid; Yield: 81% (29.74 mg); $[\alpha]_D^{25}$ = –32.5° (*c* = 0.172, $CHCl_3$, >97% *ee*, >98% *de*); IR (Neat): ν_{max} 3414 (NH), 3020, 2928, 1718 (O-C=O), 1602, 1504, 1370, 1293, 1214, 1133, 1026, 745, 694, 666 and 521 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26-7.16 (7H, m), 6.73 (1H, t, *J* = 7.0 Hz), 6.64 (2H, d, *J* = 8.0 Hz), 4.28-4.16 (2H, m, OC*H*$_2CH_3$), 3.92-3.82 (2H, m, OC*H*$_2CH_3$), 3.48 (1H, dd, *J* = 13.0, 6.0 Hz), 3.26-3.19 (2H, m), 2.86 (1H, td, *J* = 8.0, 6.5 Hz), 1.24 (3H, t, *J* = 7.5 Hz, OCH_2C*H*$_3$), 0.89 (3H, t, *J* = 7.5 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 166.7 (C, O-*C*=O), 147.6 (C), 134.3 (C), 129.3 (2 x CH), 128.6 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 118.0 (CH), 113.1 (2 x CH), 61.9 (CH_2, O*C*H_2CH_3), 61.3 (CH_2, O*C*H_2CH_3), 42.6 (CH_2), 42.3 (C), 35.6 (CH), 29.7 (CH), 14.1 (CH_3, OCH_2*C*H_3), 13.7 (CH_3, OCH_2*C*H_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{22}H_{25}NO_4H$ 368.1862; Found 368.1862.

Diethyl (2*R*,3*S*)-2-(((4-fluorophenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (39ca): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 97% (37.38 mg); $[\alpha]_D^{25}$ = –32.8° (*c* = 0.061, $CHCl_3$, >98% *de*);

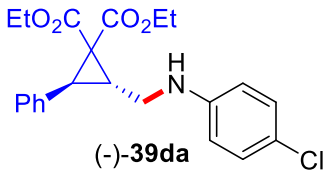


(-)-**39ca**

IR (Neat): ν_{max} 3395 (NH), 2921, 2851, 2572, 1719 (O-C=O), 1510, 1463, 1369, 1290, 1212, 1130, 1097, 1025, 820, 742 and 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28-7.23 (3H, m), 7.21-7.18 (2H, m), 6.93-6.85 (2H, m), 6.64-6.54 (2H, m), 4.29-4.16 (2H, m, OC*H*$_2CH_3$), 3.93-3.83 (2H, m, OC*H*$_2CH_3$), 3.45 (1H, dd, *J* = 13.0, 6.0 Hz), 3.24 (1H, d, *J* = 7.5 Hz), 3.17 (1H, dd, *J* = 13.0, 8.0 Hz), 2.84 (1H, td, *J* = 9.5, 6.5 Hz), 1.24 (3H, t, *J* = 7.0 Hz, OCH_2C*H*$_3$), 0.89 (3H, t, *J* = 7.0 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 166.5 (C, O-*C*=O), 156.2 (C, d, *J* = 233.7 Hz), 143.9 (C), 134.2 (C), 128.6 (2 x CH), 128.2 (2 x CH), 127.4 (CH), 115.7 (2 x CH, d, *J* = 21.2 Hz), 114.1 (2 x CH, d, *J* = 7.5 Hz), 61.9 (CH_2, O*C*H_2CH_3), 61.3

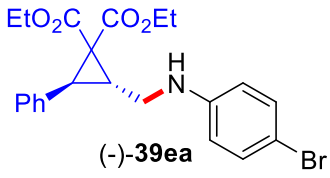
(CH_2, OCH_2CH_3), 43.2 (CH_2), 42.3 (C), 35.6 (CH), 29.6 (CH), 14.1 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{22}H_{24}FNO_4H$ 386.1768; Found 386.1768.

Diethyl (2*R*,3*S*)-2-(((4-chlorophenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**39da**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 85% (34.09 mg); $[\alpha]_D^{25}$ = –37.1° (*c* = 0.097, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3393 (NH), 2980, 2923, 2852, 2575, 1875, 1717 (O-C=O), 1599, 1499, 1368, 1289, 1210, 1094, 815, 742 and 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.23 (3H, m), 7.21-7.18 (2H, m), 7.11 (2H, td, *J* = 10.0, 3.2 Hz), 6.55 (2H, td, *J* = 10.0, 3.2 Hz), 4.28-4.17 (2H, m, OCH_2CH_3), 3.92-3.84 (2H, m, OCH_2CH_3), 3.46 (1H, dd, *J* = 12.8, 6.0 Hz), 3.25 (1H, d, *J* = 8.0 Hz), 3.17 (1H, dd, *J* = 13.2, 8.4 Hz), 2.83 (1H, td, *J* = 8.0, 6.0 Hz), 1.24 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.89 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 166.6 (C, O-*C*=O), 146.3 (C), 134.1 (C), 129.1 (2 x CH), 128.6 (2 x CH), 128.2 (2 x CH), 127.4 (CH), 122.4 (C), 114.0 (2 x CH), 62.0 (CH_2, OCH_2CH_3), 61.4 (CH_2, OCH_2CH_3), 42.5 (CH_2), 42.3 (C), 35.6 (CH), 29.5 (CH), 14.2 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{22}H_{24}ClNO_4H$ 402.1472; Found 402.1472.



(-)-**39da**

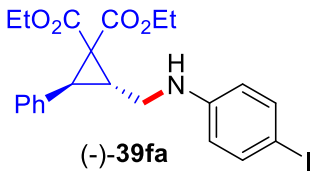
Diethyl (2*R*,3*S*)-2-(((4-bromophenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**39ea**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 81% (36. 05 mg); $[\alpha]_D^{25}$ = –22.9° (*c* = 0.118, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3414 (NH), 2853, 1719 (O-C=O), 1596, 1498, 1369, 1264, 1214, 1026, 814, 733 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.21 (5H, m), 7.21-7.17 (2H, m), 6.50 (2H, td, *J* = 8.8, 3.2 Hz), 4.30-4.15 (2H, m, OCH_2CH_3), 3.95-3.82 (2H, m, OCH_2CH_3), 3.46 (1H, dd, *J* = 13.2, 6.0 Hz), 3.25 (1H, d, *J* = 8.0 Hz), 3.16 (1H, dd, *J* = 13.2, 8.4 Hz), 2.83 (1H, td, *J* = 10.0, 8.0 Hz), 1.24 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.89 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.6 (C, O-*C*=O), 166.5 (C, O-*C*=O), 146.7 (C), 134.1 (C), 132.0 (2 x CH), 128.6 (2 x CH), 128.2 (2 x CH), 127.4 (CH), 114.5 (2 x CH), 109.4 (C), 62.0 (CH_2, OCH_2CH_3), 61.4 (CH_2, OCH_2CH_3), 42.4 (CH_2), 42.3 (C), 35.6 (CH), 29.5 (CH), 14.2 (CH_3,



(-)-**39ea**

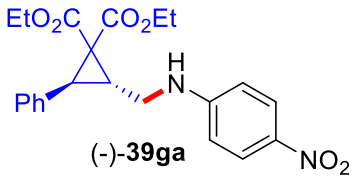
OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{22}H_{24}BrNO_4H$ 446.0967; Found 446.0967.

Diethyl (2*R*,3*S*)-2-(((4-iodophenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**39fa**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 83% (41 mg); $[\alpha]_D^{25}$ = –32.2° (*c* = 0.174, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3414 (NH), 2916, 2848, 2360, 1719 (O-C=O), 1592, 1497, 1369, 1291, 1264, 1097, 812, 735 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.41 (2H, td, *J* = 9.5, 3.0 Hz), 7.27-7.21 (3H, m), 7.20-7.17 (2H, m), 6.41 (2H, td, *J* = 9.5, 3.0 Hz), 4.29-4.15 (2H, m, OCH_2CH_3), 3.91-3.84 (2H, m, OCH_2CH_3), 3.45 (1H, dd, *J* = 13.0, 6.5 Hz), 3.24 (1H, d, *J* = 8.0 Hz), 3.16 (1H, dd, *J* = 12.5, 8.0 Hz), 2.82 (1H, td, *J* = 10.0, 8.0 Hz), 1.24 (3H, t, *J* = 7.5 Hz, OCH_2CH_3), 0.89 (3H, t, *J* = 7.5 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.6 (C, O-*C*=O), 166.5 (C, O-*C*=O), 147.3 (C), 137.8 (2 x CH), 134.1 (C), 128.6 (2 x CH), 128.2 (2 x CH), 127.4 (CH), 115.1 (2 x CH), 78.4 (C), 62.0 (CH_2, OCH_2CH_3), 61.4 (CH_2, OCH_2CH_3), 42.3 (C), 42.2 (CH_2), 35.6 (CH), 29.5 (CH), 14.2 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{22}H_{24}INO_4H$ 494.0828; Found 494.0829.



(-)-**39fa**

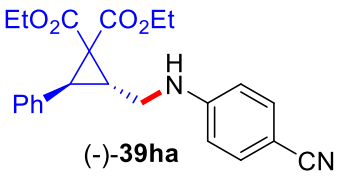
Diethyl (2*R*,3*S*)-2-(((4-nitrophenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**39ga**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 90% (37.12 mg); $[\alpha]_D^{25}$ = –47.8° (*c* = 0.180, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3367 (NH), 2922, 2852, 2365, 2339, 1734 (O-C=O), 1701, 1598, 1502, 1468, 1369, 1300, 1107, 861 and 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.08 (2H, d, *J* = 9.0 Hz), 7.28-7.19 (5H, m), 6.57 (2H, d, *J* = 9.0 Hz), 4.74 (1H, br s), 4.29-4.16 (2H, m, OCH_2CH_3), 3.94-3.83 (2H, m, OCH_2CH_3), 3.67-3.58 (1H, dd, *J* = 13.0, 3.0 Hz), 3.37-3.25 (2H, m), 2.89-2.82 (1H, td, *J* = 8.0, 6.0 Hz), 1.24 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 0.90 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.6 (C, O-*C*=O), 166.4 (C, O-*C*=O), 152.8 (C), 138.5 (C), 133.7 (C), 128.5 (2 x CH), 128.3 (2 x CH), 127.6 (CH), 126.4 (2 x CH), 111.2 (2 x CH), 62.1 (CH_2, OCH_2CH_3), 61.6 (CH_2, OCH_2CH_3), 42.3 (C), 41.6 (CH_2), 35.7 (CH), 29.1 (CH), 14.1 (CH_3,



(-)-**39ga**

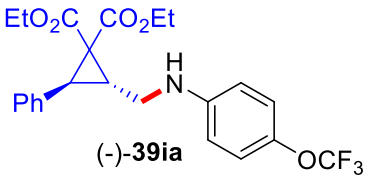
OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + Na^+) calcd for $C_{22}H_{24}N_2O_6Na$ 435.1532; Found 435.1531.

Diethyl (2*R*,3*S*)-2-(((4-cyanophenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**39ha**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 90% (35.32 mg); $[\alpha]_D^{25}$ = –46.2° (*c* = 0.093, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3379 (NH), 2981, 2212, 1718 (O-C=O), 1606, 1526, 1330, 1293, 1213, 1174, 1097, 826 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42 (2H, td, *J* = 9.2, 2.4 Hz), 7.31-7.23 (3H, m), 7.22-7.16 (2H, m), 6.59 (2H, td, *J* = 9.6, 2.4 Hz), 4.43 (1H, br s, NH), 4.31-4.10 (2H, m, OCH_2CH_3), 3.96-3.81 (2H, m, OCH_2CH_3), 3.55 (1H, td, *J* = 13.2, 6.0 Hz), 3.33-3.19 (2H, m), 2.84 (1H, td, *J* = 8.4, 8.0 Hz), 1.23 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.89 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.6 (C, O-*C*=O), 166.4 (C, O-*C*=O), 150.8 (C), 133.8 (C), 133.8 (2 x CH), 128.5 (2 x CH), 128.3 (2 x CH), 127.6 (CH), 120.3 (C, *C*N), 112.3 (2 x CH), 99.3 (C), 62.1 (CH_2, OCH_2CH_3), 61.5 (CH_2, OCH_2CH_3), 42.2 (C), 41.4 (CH_2), 35.7 (CH), 29.1 (CH), 14.1 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{24}N_2O_5H$ 393.1814; Found 393.1815.



(-)-**39ha**

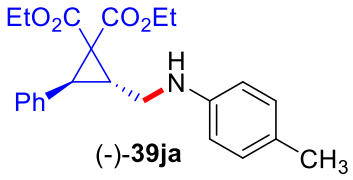
Diethyl (2*S*,3*R*)-2-phenyl-3-(((4-(trifluoromethoxy)phenyl)amino)methyl)cyclopropane-1,1-dicarboxylate (**39ia**): The compound was prepared following the procedure **O** and purified by column chromatography using Hexanes/$CHCl_3$ (3:7 to 0:10) and isolated as a pale yellow liquid; Yield: 98% (44.22 mg); $[\alpha]_D^{25}$ = –34.3° (*c* = 0.105, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3398 (NH), 2982, 1720 (O-C=O), 1612, 1516, 1370, 1252, 1224, 1203, 1161, 1027, 830, 744 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.16 (5H, m), 7.03 (2H, d, *J* = 8.4 Hz), 6.58 (2H, td, *J* = 10.4, 3.2 Hz), 4.31-4.14 (2H, m, OCH_2CH_3), 3.98-3.78 (3H, m), 3.48 (1H, dd, *J* = 12.8, 6.0 Hz), 3.26 (1H, d, *J* = 8.0 Hz), 3.18 (1H, dd, *J* = 12.8, 8.4 Hz), 2.84 (1H, td, *J* = 8.0, 8.0 Hz), 1.23 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.89 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 166.6 (C, O-*C*=O), 146.5 (C), 140.7 (C), 134.1 (C), 128.6 (2 x CH), 128.2 (2 x CH), 127.5 (CH), 122.4 (2 x CH), 120.7 (C, q, *J* = 254 Hz), 113.2 (2 x CH), 62.0 (CH_2, OCH_2CH_3), 61.4 (CH_2, OCH_2CH_3), 42.5 (CH_2), 42.3 (C), 35.6 (CH),



(-)-**39ia**

29.6 (CH), 14.1 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: ($M + H^+$) calcd for $C_{23}H_{24}F_3NO_5H$ 452.1685; Found 452.1665.

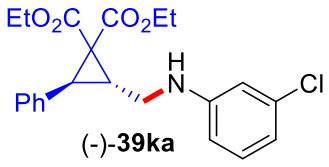
Diethyl (2*S*,3*R*)-2-phenyl-3-((p-tolylamino)methyl)cyclopropane-1,1-dicarboxylate (**39ja**):



(-)-**39ja**

The compound was prepared following the procedure **O** and purified by column chromatography using Hexanes/$CHCl_3$ (3:7 to 0:10) and isolated as a pale yellow liquid; Yield: 85% (32.5 mg); $[\alpha]_D^{25}$ = –32.3° (*c* = 0.102, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3396 (NH), 2980, 2925, 2859, 2360, 1720 (O-C=O), 1616, 1520, 1369, 1290, 1211, 1132, 1098, 808 and 698 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 7.32-7.19 (3H, m), 7.15 (2H, d, *J* = 7.2 Hz), 6.91 (2H, d, *J* = 8.0 Hz), 6.56 (2H, d, *J* = 8.4 Hz), 5.53 (1H, br s, NH), 4.28-4.12 (2H, m, OCH_2CH_3), 3.88-3.72 (2H, m, OCH_2CH_3), 3.28-3.19 (1H, m), 3.18-3.06 (2H, m), 2.73 (1H, q, *J* = 7.2 Hz), 2.15 (3H, s, Ar-CH_3), 1.20 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.80 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.6 (C, O-*C*=O), 166.6 (C, O-*C*=O), 146.7 (C), 135.0 (C), 129.8 (2 x CH), 129.0 (2 x CH), 128.5 (2 x CH), 127.6 (CH), 125.0 (C), 113.0 (2 x CH), 61.9 (CH_2, OCH_2CH_3), 61.2 (CH_2, OCH_2CH_3), 42.3 (C), 41.8 (CH_2), 35.8 (CH), 29.7 (CH), 20.5 (CH_3, *Ar-CH*$_3$), 14.4 (CH_3, OCH_2CH_3), 14.0 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: ($M + H^+$) calcd for $C_{23}H_{27}NO_4H$ 382.2018; Found 382.2011.

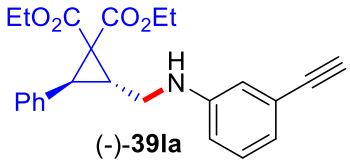
Diethyl (2*R*,3*S*)-2-(((3-chlorophenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**39ka**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 95% (38.18 mg); $[\alpha]_D^{25}$ = –31.6° (*c* = 0.095, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3417 (NH), 3020, 1718 (O-C=O), 1598, 1502, 1370, 1298, 1215, 1134, 1027, 751, 697 and 668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28-7.19 (5H, m), 7.07 (1H, t, *J* = 8.0 Hz), 6.67 (1H, dd, *J* = 8.0, 1.5 Hz), 6.60 (1H, t, *J* = 2.0 Hz), 6.49 (1H, dd, *J* = 8.0, 1.5 Hz), 4.29-4.16 (2H, m, OCH_2CH_3), 3.95-3.82 (2H, m, OCH_2CH_3), 3.48 (1H, dd, *J* = 13.0, 6.0 Hz), 3.25 (1H, d, *J* = 8.0 Hz), 3.17 (1H, dd, *J* = 13.0, 8.5 Hz), 2.83 (1H, td, *J* = 8.0, 8.0 Hz), 1.24 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 0.89 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.6 (C, O-*C*=O), 166.5 (C, O-*C*=O), 149.0 (C), 135.0 (C), 134.1 (C), 130.2 (CH), 128.6 (2 x CH), 128.2 (2 x CH), 127.5 (CH), 117.6 (CH), 112.6 (CH), 111.2 (CH), 62.0 (CH_2, OCH_2CH_3), 61.4 (CH_2, OCH_2CH_3), 42.3 (C), 42.2 (CH_2), 35.6 (CH), 29.5 (CH), 14.1 (CH_3, OCH_2CH_3), 13.7



(-)-**39ka**

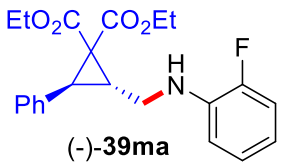
(CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{22}H_{24}ClNO_4H$ 402.1472; Found 402.1473.

Diethyl (2*R*,3*S*)-2-(((3-ethynylphenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**39la**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 97% (37.96 mg); $[\alpha]_D^{25}$ = –28.0° (*c* = 0.100, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3395 (NH), 3286, 2922, 2852, 2574, 2106, 1717 (O-C=O), 1598, 1579, 1465, 1368, 1292, 1211, 1130, 1098, 1025, 859, 780, 743, 696 and 646 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.23 (3H, m), 7.22-7.19 (2H, m), 7.12 (1H, t, *J* = 7.6 Hz), 6.86 (1H, d, *J* = 7.6 Hz), 6.75 (1H, t, *J* = 2.4 Hz), 6.63 (1H, dd, *J* = 8.4, 2.4 Hz), 4.30-4.15 (2H, m, OC*H*$_2$$CH_3$), 3.94-3.82 (2H, m, OC*H*$_2$$CH_3$), 3.49 (1H, dd, *J* = 13.2, 6.0 Hz), 3.25 (1H, d, *J* = 7.6 Hz), 3.19 (1H, dd, *J* = 13.2, 8.4 Hz), 3.01 (1H, s), 2.84 (1H, td, *J* = 10.0, 8.0 Hz), 1.24 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$), 0.89 (3H, t, *J* = 7.2 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 166.6 (C, O-*C*=O), 147.4 (C), 134.1 (C), 129.2 (CH), 128.6 (2 x CH), 128.2 (2 x CH), 127.4 (CH), 122.8 (C), 121.8 (CH), 116.0 (CH), 113.9 (CH), 84.1 (CH), 76.4 (C), 62.0 (CH_2, O*C*H_2CH_3), 61.4 (CH_2, O*C*H_2CH_3), 42.3 (C), 42.3 (CH_2), 35.6 (CH), 29.5 (CH), 14.2 (CH_3, OCH_2C*H*$_3$), 13.7 (CH_3, OCH_2C*H*$_3$); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{25}NO_4H$ 392.1862; Found 392.1865.



(-)-**39la**

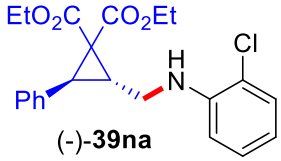
Diethyl (2*R*,3*S*)-2-(((2-fluorophenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**39ma**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.2:9.8 to 0.5:9.5) and isolated as a pale yellow liquid; Yield: 75% (28.9 mg); $[\alpha]_D^{25}$ = –38.3° (*c* = 0.103, CH_3OH, >98% *de*); IR (Neat): ν_{max} 3420 (NH), 2981, 1720 (O-C=O), 1620, 1515, 1450, 1369, 1331, 1293, 1252, 1212, 1189, 1132, 1111, 1028, 742 and 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28-7.24 (2H, m), 7.23-7.19 (3H, m), 7.06-6.91 (2H, m), 6.74 (1H, dt, *J* = 9.0, 1.5 Hz), 6.68-6.60 (1H, m), 4.29-4.18 (2H, m, OC*H*$_2$$CH_3$), 4.07 (1H, br s, NH), 3.93-3.83 (2H, m, OC*H*$_2$$CH_3$), 3.55 (1H, dd, *J* = 13.0, 6.0 Hz), 3.27 (1H, d, *J* = 7.9), 3.23 (1H, dd, *J* = 13.0, 8.5 Hz), 2.88 (1H, td, *J* = 8.0, 6.0 Hz), 1.25 (3H, t, *J* = 7.0 Hz, OCH_2C*H*$_3$), 0.89 (3H, t, *J* = 7.0 Hz, OCH_2C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 166.5 (C, O-*C*=O), 151.6 (C, d, *J* = 237.5 Hz), 136.2 (C, d, *J* = 11.5 Hz), 134.2 (C), 128.6 (2 x CH), 128.2 (2 x CH), 127.4 (CH), 124.6 (CH, d, *J* = 2.5 Hz), 117.1 (CH, d, *J* = 6.2 Hz), 114.5 (CH,



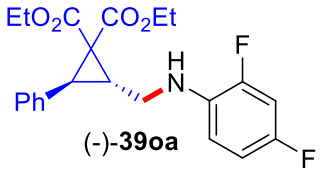
(-)-**39ma**

d, J = 18.7 Hz), 112.4 (CH, d, J = 2.5 Hz), 62.0 (CH_2, OCH_2CH_3), 61.3 (CH_2, OCH_2CH_3), 42.2 (C), 42.2 (CH_2), 35.7 (CH), 29.6 (CH), 14.0 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: ($M + H^+$) calcd for $C_{22}H_{24}FNO_4H$ 386.1768; Found 386.1765.

Diethyl (2*R*,3*S*)-2-(((2-chlorophenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**39na**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.2:9.8 to 0.5:9.5) and isolated as a pale yellow liquid; Yield: 23% (9.24 mg); $[\alpha]_D^{25}$ = –18.4° (*c* = 0.098, CH_3OH, >98% *de*); IR (Neat): ν_{max} 3411 (NH), 2981, 1721 (O-C=O) , 1598, 1512, 1461, 1369, 1292, 1214, 1099, 1033, 965, 752 and 696 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28-7.23 (4H, m), 7.22-7.20 (2H, m), 7.14 (1H, dt, J = 8.5, 1.5 Hz), 6.71 (1H, dd, J = 8.5, 1.5 Hz), 6.65 (1H, dt, J = 8.0, 1.5 Hz), 4.45 (1H, br s, NH), 4.32-4.17 (2H, m, OCH_2CH_3), 3.94-3.83 (2H, m, OCH_2CH_3), 3.58 (1H, dd, J = 13.0, 6.0 Hz), 3.32-3.21 (2H, m), 2.90 (1H, td, J = 8.0, 8.0 Hz), 1.26 (3H, t, J = 7.0 Hz, OCH_2CH_3), 0.90 (3H, t, J = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.8 (C, O-*C*=O), 166.5 (C, O-*C*=O), 143.5 (C), 134.1 (C), 129.2 (CH), 128.6 (2 x CH), 128.2 (2 x CH), 127.9 (CH), 127.4 (CH), 119.2 (C), 117.6 (CH), 111.3 (CH), 62.1 (CH_2, OCH_2CH_3), 61.4 (CH_2, OCH_2CH_3), 42.1 (C), 42.1 (CH_2), 35.7 (CH), 29.5 (CH), 14.1 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: ($M + H^+$) calcd for $C_{22}H_{24}ClNO_4H$ 402.1472; Found 402.1470.

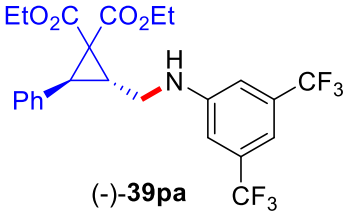


Diethyl (2*R*,3*S*)-2-(((2,4-difluorophenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**39oa**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.2:9.8 to 0.5:9.5) and isolated as a pale yellow liquid; Yield: 80% (32.3 mg); $[\alpha]_D^{25}$ = –32.5° (*c* = 0.117, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3415 (NH), 2926, 2853, 1722 (O-C=O), 1603, 1522, 1465, 1369, 1292, 1217, 1207, 1131, 1108, 1027, 959, 846, 797, 743, 720 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.16 (5H, m), 6.82-6.71 (2H, m), 6.70-6.61 (1H, m), 4.30-4.17 (2H, m, OCH_2CH_3), 3.93-3.83 (2H, m, OCH_2CH_3), 3.52 (1H, dd, J = 13.0, 6.0 Hz), 3.26 (1H, d, J = 7.5 Hz), 3.19 (1H, dd, J = 13.0, 8.5 Hz), 2.86 (1H, td, J = 10.0, 8.0 Hz), 1.25 (3H, t, J = 7.0 Hz, OCH_2CH_3), 0.89 (3H, t, J = 7.5 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 166.5 (C, O-*C*=O), 154.5 (C, dd, J = 236.25, 11.25 Hz), 150.9 (C, dd, J = 240.0, 11.25 Hz), 134.1 (C), 132.7 (C, dd, J = 11.25, 2.5 Hz), 128.6 (2 x CH), 128.2 (2 x CH), 127.5 (CH), 112.4 (CH, dd, J = 8.75, 3.75



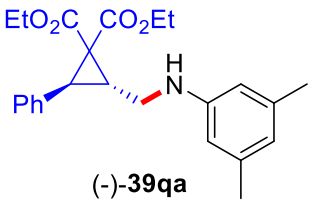
Hz), 110.7 (CH, dd, *J* = 22.5, 3.75 Hz), 103.5 (CH, dd, *J* = 27.5, 23.75 Hz), 62.0 (CH_2, OCH_2CH_3), 61.4 (CH_2, OCH_2CH_3), 42.6 (CH_2), 42.2 (C), 35.7 (CH), 29.5 (CH), 14.0 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{22}H_{23}F_2NO_4H$ 404.1673; Found 404.1673.

Diethyl (2*R*,3*S*)-2-(((3,5-bis(trifluoromethyl)phenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**39pa**): The compound was prepared following the procedure **O** and purified by column chromatography using Hexanes/$CHCl_3$ (3:7 to 0:10) and isolated as a pale yellow liquid; Yield: 75% (37.75 mg); $[\alpha]_D^{25}$ = –25.5° (*c* = 0.133, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3387 (NH), 2984, 2357, 1714 (O-C=O), 1621, 1472, 1438, 1397, 1368, 1274, 1214, 1170, 1122, 860, 699 and 682 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.24 (3H, m), 7.22-7.19 (2H, m), 7.17 (1H, s), 6.95 (2H, s), 4.33 (1H, br s, NH), 4.30-4.17 (2H, m, OCH_2CH_3), 3.96-3.84 (2H, m, OCH_2CH_3), 3.61 (1H, td, *J* = 13.0, 5.5 Hz), 3.29(1H, d, *J* = 8.0 Hz), 3.27-3.21 (1H, m), 2.85 (1H, td, *J* = 8.5, 8.0 Hz), 1.24 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 0.90 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.6 (C, O-*C*=O), 166.4 (C, O-*C*=O), 148.3 (C), 133.7 (C), 132.5 (2 x C, q, *J* = 32.5 Hz), 128.5 (2 x CH), 128.3 (2 x CH), 127.6 (CH), 123.5 (2 x C, q, *J* = 270 Hz), 111.9 (2 x CH), 110.6 (CH), 62.1 (CH_2, OCH_2CH_3), 61.5 (CH_2, OCH_2CH_3), 42.3 (C), 42.0 (CH_2), 35.6 (CH), 29.1 (CH), 14.1 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{23}NO_4F_6H$ 504.1609; Found 504.1609.



(-)-**39pa**

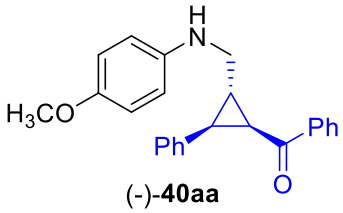
Diethyl (2*R*,3*S*)-2-(((3,5-dimethylphenyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (**39qa**): The compound was prepared following the procedure **O** and purified by column chromatography using Hexanes/$CHCl_3$ (3:7 to 0:10) and isolated as a pale yellow liquid; Yield: 97% (38.3 mg); $[\alpha]_D^{25}$ = –31.1° (*c* = 0.151, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3398 (NH), 2953, 2913, 2846, 1801, 1714 (O-C=O), 1600, 1463, 1368, 1295, 1207, 1186, 1096, 1024, 820, 742 and 693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.19 (5H, m), 6.39 (1H, s), 6.28 (2H, s), 4.31-4.16 (2H, m, OCH_2CH_3), 3.94-3.81 (2H, m, OCH_2CH_3), 3.46 (1H, dd, *J* = 12.8, 6.0 Hz), 3.24 (1H, d, *J* = 8.0 Hz), 3.18 (1H, dd, *J* = 12.8, 8.0 Hz), 2.84 (1H, td, *J* = 10.0, 8.0 Hz), 2.23 (6H, s), 1.26 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.89 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 166.7 (C, O-*C*=O), 147.9 (C), 138.9 (2 x C),



(-)-**39qa**

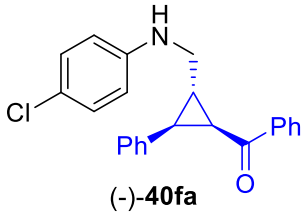
134.4 (C), 128.7 (2 x CH), 128.2 (2 x CH), 127.4 (CH), 119.9 (CH), 111.0 (2 x CH), 61.9 (CH_2, OCH_2CH_3), 61.3 (CH_2, OCH_2CH_3), 42.6 (CH_2), 42.3 (C), 35.6 (CH), 29.8 (CH), 21.5 (2xCH_3), 14.2 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{29}NO_4H$ 396.2174; Found 396.2174.

((1*S*,2*S*,3*S*)-2-(((4-methoxyphenyl)amino)methyl)-3-phenylcyclopropyl)(phenyl)methanone (**40aa**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a brown liquid; Yield: 92% (66 mg, 0.2 mmol); $[\alpha]_D^{25}$ = –93.07° (*c* = 0.101, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3384 (NH), 3062, 2930, 2831, 2359, 2339, 1665 (C=O), 1511, 1448, 1235, 1037, 820 and 695 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.89 (2H, d, *J* = 7.0 Hz), 7.49 (1H, t, *J* = 7.5 Hz), 7.40 (2H, t, *J* = 7.5 Hz), 7.23-7.15 (4H, m), 7.15-7.10 (1H, m), 6.78 (2H, dt, *J* = 10.0, 3.5 Hz), 6.62 (2H, dt, *J* = 10.0, 3.5 Hz), 3.73 (3H, s, OC*H*$_3$), 3.32 (2H, d, *J* = 6.0 Hz), 3.04 (1H, dd, *J* = 10.0, 5.5 Hz), 2.86 (1H, dd, *J* = 9.5, 7.0 Hz), 2.79 (1H, quint, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135) δ 195.3 (C, *C*=O), 151.4 (C), 142.3 (C), 138.4 (C), 135.4 (C), 132.7 (CH), 129.0 (2 x CH), 128.5 (2 x CH), 128.1 (4 x CH), 126.8 (CH), 115.0 (2 x CH), 114.4 (2 x CH), 55.8 (CH_3, O*C*H_3), 47.8 (CH_2), 35.2 (CH), 32.8 (CH), 25.3 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{24}H_{23}NO_2H$ 358.1807; Found 358.1809.



(-)-**40aa**

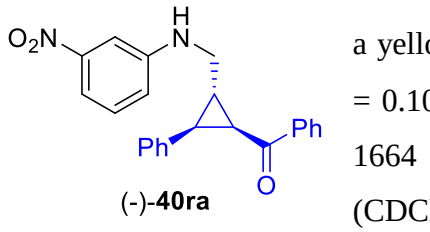
((1*S*,2*S*,3*S*)-2-(((4-chlorophenyl)amino)methyl)-3-phenylcyclopropyl)(phenyl)methanone (**40fa**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a colorless liquid; Yield: 98% (71 mg, 0.2 mmol); $[\alpha]_D^{25}$ = –120° (*c* = 0.100, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3374 (NH), 3062, 3026, 2845, 1663 (C=O), 1597, 1497, 1448, 1367, 1177, 1087, 906, 815, 726 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.89 (2H, dd, *J* = 8.5, 1.5 Hz), 7.51 (1H, tt, *J* = 8.0, 2.0 Hz), 7.40 (2H, t, *J* = 8.0 Hz), 7.22-7.16 (4H, m), 7.15-7.09 (3H, m), 6.55 (2H, dt, *J* = 10.0, 3.0 Hz), 3.92 (1H, br s, N*H*), 3.37-3.29 (2H, m), 3.04 (1H, dd, *J* = 9.5, 5.5 Hz), 2.86 (1H, dd, *J* = 9.5, 7.0 Hz), 2.79 (1H, quint, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135) δ 195.2 (C, *C*=O), 146.6 (C), 138.2 (C), 135.1 (C), 132.8 (CH), 129.2 (2 x CH), 128.9 (2 x CH), 128.5 (2 x CH), 128.1 (2 x CH), 128.0 (2 x CH), 126.9 (CH), 122.4 (C), 114.0 (2 x CH), 46.8 (CH_2), 35.1



(-)-**40fa**

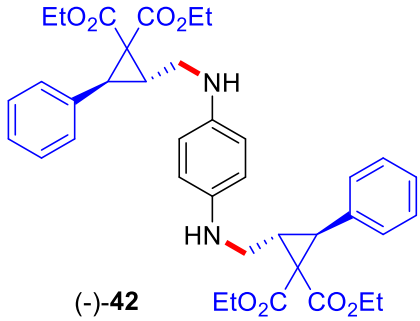
(CH), 32.8 (CH), 24.8 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{20}ClNOH$ 362.1312; Found 362.1311.

((1*S*,2*S*,3*S*)-2-(((3-nitrophenyl)amino)methyl)-3-phenylcyclopropyl)(phenyl)methanone (**40ra**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a yellow liquid; Yield: 94% (70 mg, 0.2 mmol); $[\alpha]_D^{25}$ = –95.37° (*c* = 0.108, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3373 (NH), 3062, 2854, 1664 (C=O), 1525, 1346, 1214, 1044, 733 and 695 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.90 (2H, dt, *J* = 8.5, 1.5 Hz), 7.54 (1H, dd, *J* = 8.0, 1.5 Hz), 7.51 (1H, dt, *J* = 7.0, 1.5 Hz), 7.42 (3H, tt, *J* = 8.0, 2.0 Hz), 7.28 (1H, t, *J* = 8.5 Hz), 7.23-7.17 (4H, m), 7.17-7.12 (1H, m), 6.90 (1H, dd, *J* = 8.5, 2.0 Hz), 4.26 (1H, br s, N*H*), 3.49-3.35 (2H, m), 3.08 (1H, dd, *J* = 10.0, 5.5 Hz), 2.90 (1H, dd, *J* = 9.5, 7.0 Hz), 2.82 (1H, quint, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135) δ 195.1 (C, *C*=O), 149.4 (C), 148.8 (C), 138.1 (C), 134.9 (C), 132.9 (CH), 129.8 (CH), 128.9 (2 x CH), 128.6 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 127.0 (CH), 118.8 (CH), 112.2 (CH), 106.3 (CH), 46.6 (CH_2), 35.1 (CH), 32.9 (CH), 24.5 (CH); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{23}H_{20}N_2O_3H$ 373.1552; Found 373.1552.



(-)-**40ra**

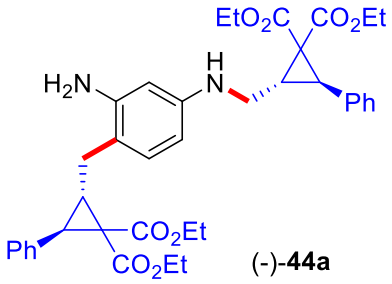
Tetraethyl 3,3'-((1,4-phenylenebis(azanediyl))bis(methylene))(2*S*,2'*S*,3*R*,3'*R*)-bis(2-phenylcyclopropane-1,1-dicarboxylate) (**42**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 95% (62 mg); $[\alpha]_D^{25}$ = –42.5° (*c* = 0.094, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3384 (NH), 2980, 1720 (O-C=O), 1603, 1517, 1464, 1369, 1290, 1211, 1132, 1027, 862, 818, 743 and 698 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ 7.29-7.19 (6H, m), 7.14 (4H, d, *J* = 7.5 Hz), 6.53 (4H, s), 4.98 (2H, br s, NH), 4.27-4.10 (4H, m, OC*H*$_2$CH$_3$), 3.87-3.70 (4H, m, OC*H*$_2$CH$_3$), 3.17 (2H, br s), 3.13 (2H, d, *J* = 8.0 Hz), 3.03 (2H, br s), 2.71 (2H, q, *J* = 7.0 Hz), 1.19 (6H, t, *J* = 7.0 Hz), 0.79 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (2 x C, O-*C*=O), 166.6 (2 x C, O-*C*=O), 140.7 (2 x C), 135.2 (2 x C), 129.0 (4 x CH), 128.5 (4 x CH), 127.6 (2 x CH), 114.7 (4 x CH), 61.8 (2 x CH_2, O*C*H$_2$CH$_3$), 61.2 (2 x CH_2, O*C*H$_2$CH$_3$), 42.9 (2 x CH_2), 42.9 (2 x C), 35.8 (2 x CH), 30.0 (2 x CH), 14.4 (2 x CH_3,



(-)-**42**

OCH_2CH_3), 14.0 (2 x CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{38}H_{44}N_2O_8H$ 657.3176; Found 657.3176.

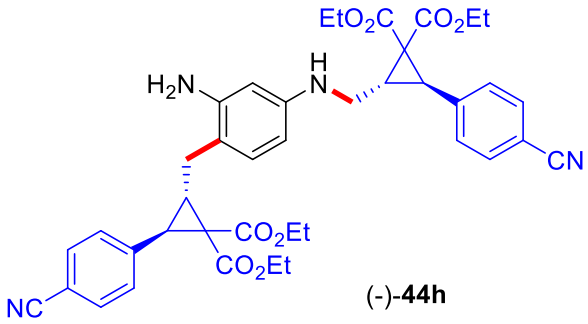
Diethyl (2*S*,3*R*)-2-(2-amino-4-((((1*S*,3*R*)-2,2-bis(ethoxycarbonyl)-3-phenylcyclopropyl)methyl)amino)benzyl)-3-phenylcyclopropane-1,1-dicarboxylate (**44a**):



(-)-**44a**

The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 46% (30.21 mg); $[\alpha]_D^{25}$ = –50.9° (*c* = 0.106, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3379 (NH), 2925, 2853, 2360, 1720 (O-C=O), 1619, 1519, 1462, 1369, 1290, 1222, 1190, 1027, 861, 775, 744 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.27-7.15 (10H, m), 7.00 (1H, d, *J* = 8.5 Hz), 6.08 (1H, dd, *J* = 8.0, 2.0 Hz), 6.00 (1H, d, *J* = 2.5 Hz), 4.29-4.10 (4H, m, OCH_2CH_3), 3.93-3.82 (4H, m, OCH_2CH_3), 3.66 (2H, br s, NH), 3.42 (1H, dd, *J* = 13.0, 6.0 Hz), 3.24 (2H, t, *J* = 7.5 Hz), 3.16 (1H, dd, *J* = 13.0, 8.0 Hz), 2.88-2.77 (2H, m), 2.71 (1H, dd, *J* = 15.5, 6.5 Hz), 2.59 (1H, dd, *J* = 15.5, 8.0 Hz), 1.23 (3H, t, *J* = 7.0 Hz), 1.21 (3H, t, *J* = 7.0 Hz), 0.91-0.86 (6H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.1 (C, O-*C*=O), 167.7 (C, O-*C*=O), 167.0 (C, O-*C*=O), 166.7 (C, O-*C*=O), 147.5 (C), 145.0 (C), 135.0 (C), 134.3 (C), 129.9 (CH), 128.7 (2 x CH), 128.7 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 127.1 (CH), 114.1 (C), 104.5 (CH), 100.3 (CH), 61.9 (CH_2, OCH_2CH_3), 61.6 (CH_2, OCH_2CH_3), 61.3 (CH_2, OCH_2CH_3), 61.1 (CH_2, OCH_2CH_3), 43.0 (C), 42.6 (CH_2), 42.3 (C), 37.0 (CH), 35.6 (CH), 29.8 (CH), 29.6 (CH), 27.9 (CH_2), 14.2 (CH_3, OCH_2CH_3), 14.1 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + Na^+) calcd for $C_{38}H_{44}N_2O_8Na$ 679.2995; Found 679.2996.

Diethyl (2*S*,3*R*)-2-(2-amino-4-((((1*S*,3*R*)-3-(4-cyanophenyl)-2,2-bis(ethoxycarbonyl)cyclopropyl)methyl)amino)benzyl)-3-(4-cyanophenyl)cyclopropane-1,1-dicarboxylate (**44h**):

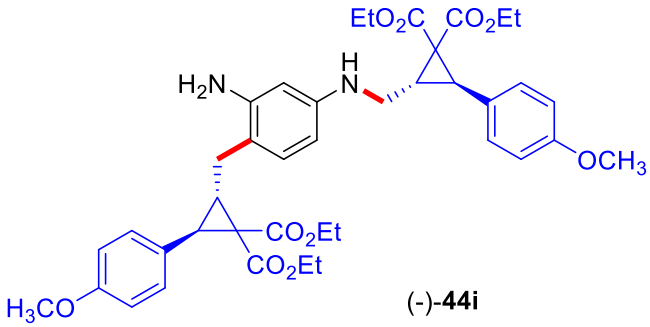


(-)-**44h**

The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a pale yellow liquid; Yield: 45% (31.8 mg); $[\alpha]_D^{25}$ = –43.6° (*c* = 0.110, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3380 (NH), 2981, 2928, 2227, 1720 (O-C=O), 1610, 1519, 1464, 1369, 1293, 1224, 1128,

1023, 853 and 564 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.74 (4H, d, *J* = 8.0 Hz), 7.34 (4H, dd, *J* = 8.0, 6.0 Hz), 6.62 (1H, d, *J* = 8.5 Hz), 5.97 (1H, d, *J* = 2.5 Hz), 5.83 (1H, dd, *J* = 8.0, 2.0 Hz), 5.33 (1H, t, *J* = 6.0 Hz), 4.78 (2H, br s, NH), 4.26-4.10 (4H, m, OC*H*$_2$CH$_3$), 3.87-3.76 (4H, m, OC*H*$_2$CH$_3$), 3.25-3.12 (3H, m), 3.05-2.97 (1H, m), 2.81 (1H, q, *J* = 7.5 Hz), 2.75 (1H, q, *J* = 7.5 Hz), 2.60 (2H, dd, *J* = 15.5, 6.5 Hz), 1.20 (3H, t, *J* = 7.0 Hz), 1.12 (3H, t, *J* = 7.0 Hz), 0.84-0.77 (6H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.4 (C, O-*C*=O), 167.2 (C, O-*C*=O), 166.6 (C, O-*C*=O), 166.3 (C, O-*C*=O), 148.2 (C), 147.1 (C), 141.5 (C), 141.1 (C), 132.4 (4 x CH), 130.1 (2 x CH), 130.0 (2 x CH), 129.7 (CH), 119.1 (C, CN), 119.1 (C, CN), 112.3 (C), 110.4 (C), 110.3 (C), 102.3 (CH), 99.5 (CH), 62.1 (CH$_2$, OC*H*$_2$CH$_3$), 61.9 (CH$_2$, OC*H*$_2$CH$_3$), 61.5 (CH$_2$, OC*H*$_2$CH$_3$), 61.3 (CH$_2$, OC*H*$_2$CH$_3$), 43.7 (C), 42.6 (C), 41.7 (CH$_2$), 36.0 (CH), 35.5 (CH), 30.1 (CH), 30.0 (CH), 28.1 (CH$_2$), 14.4 (CH$_3$, OCH$_2$*C*H$_3$), 14.3 (CH$_3$, OCH$_2$*C*H$_3$), 14.0 (2xCH$_3$, OCH$_2$*C*H$_3$); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{40}H_{42}N_4O_8H$ 707.3081; Found 707.3079.

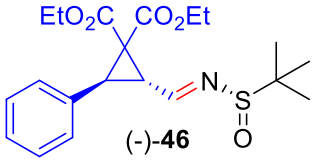
Diethyl (2*S*,3*R*)-2-(2-amino-4-((((1*S*,3*R*)-2,2-bis(ethoxycarbonyl)-3-(4-methoxyphenyl)cyclopropyl)methyl)amino)benzyl)-3-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**44i**): The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a pale yellow liquid; Yield: 33% (23.65 mg); $[\alpha]_D^{25}$ = –49.0° (*c* = 0.100, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3381 (NH), 2979, 2932, 2360, 2339, 1719 (O-C=O), 1614, 1583, 1515, 1463, 1369, 1294, 1248, 1176, 1121, 1031, 838 and 688 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.12 (2H, d, *J* = 8.5 Hz), 7.09 (2H, d, *J* = 8.5 Hz), 6.99 (1H, d, *J* = 8.0 Hz), 6.82-6.74 (4H, m), 6.08 (1H, dd, *J* = 8.0, 2.0 Hz), 6.00 (1H, d, *J* = 2.5 Hz), 4.28-4.15 (4H, m, OC*H*$_2$CH$_3$), 3.96-3.83 (4H, m, OC*H*$_2$CH$_3$), 3.76 (6H, d, *J* = 6.0 Hz), 3.62 (2H, br s, NH), 3.40 (1H, dd, *J* = 13.0, 6.0 Hz), 3.23-3.08 (3H, m), 2.82-2.66 (3H, m), 2.58 (1H, dd, *J* = 15.5, 8.0 Hz), 1.24 (3H, t, *J* = 7.0 Hz), 1.21 (3H, t, *J* = 7.0 Hz), 0.99-0.87 (6H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.2 (C, O-*C*=O), 167.8 (C, O-*C*=O), 167.1 (C, O-*C*=O), 166.7 (C, O-*C*=O), 158.9 (C), 158.7 (C), 147.5 (C), 145.0 (C), 129.9 (CH), 129.8 (4 x CH), 127.0 (C), 126.3 (C), 114.2 (C), 113.6 (2 x CH), 113.5 (2 x CH), 104.5 (CH), 100.3 (CH), 61.8 (CH$_2$, OC*H*$_2$CH$_3$), 61.5 (CH$_2$, OC*H*$_2$CH$_3$),



(-)-**44i**

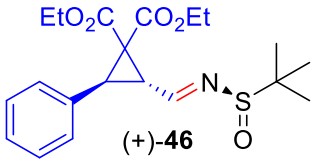
61.2 (CH_2, OCH_2CH_3), 61.0 (CH_2, OCH_2CH_3), 55.2 (2xCH_3, OCH_3), 42.9 (C), 42.7 (CH_2), 42.2 (C), 36.6 (CH), 35.1 (CH), 30.0 (CH), 29.8 (CH), 27.9 (CH_2), 14.1 (CH_3, OCH_2CH_3), 14.0 (CH_3, OCH_2CH_3), 13.8 (2 x CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{40}H_{48}N_2O_{10}H$ 717.3387; Found 717.3387.

Diethyl (2*R*,3*S*)-2-((*E*)-(((*S*)-tert-butylsulfinyl)imino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (-)-**46**: The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (0.5:9.5 to 1:9) and isolated as a pale yellow liquid; Yield: 84% (33.05 mg); $[\alpha]_D^{25}$ = −185.6° (*c* = 0.160, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3015, 1726 (O-C=O), 1615, 1369, 1293, 1215, 1185, 1076, 1022, 747, 696 and 667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.86 (1H, d, *J* = 7.0 Hz), 7.32-7.23 (5H, m), 4.37-4.28 (1H, m, OCH_2CH_3), 4.27-4.19 (1H, m, OCH_2CH_3), 3.99-3.87 (2H, m, OCH_2CH_3), 3.73 (1H, d, *J* = 7.5 Hz), 3.60 (1H, t, *J* = 7.5 Hz), 1.29 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.22 (9H, s), 0.93 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.2 (C, O-*C*=O), 165.1 (C, O-*C*=O), 164.3 (C,CN), 132.9 (C), 128.5 (2 x CH), 128.4 (2 x CH), 127.8 (CH), 62.3 (CH_2, OCH_2CH_3), 61.8 (CH_2, OCH_2CH_3), 57.1 (C), 44.8 (C), 36.2 (CH), 34.2 (CH), 22.3 (3 x CH_3), 14.0 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{20}H_{27}NO_5SH$ 394.1688; Found 394.1688.



(-)-**46**

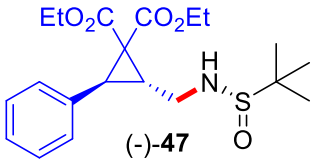
Diethyl (2*R*,3*S*)-2-((*E*)-(((*R*)-tert-butylsulfinyl)imino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (+)-**46**: The compound was prepared following the procedure **O** and purified by column chromatography using EtOAc/hexanes (1:9 to 2:8) and isolated as a pale yellow liquid; Yield: 84% (33.05 mg); $[\alpha]_D^{25}$ = 149.1° (*c* = 0.108, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 2980, 2359, 1730 (O-C=O), 1616, 1450, 1367, 1289, 1219, 1184, 1086, 1023, 772 and 684 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.81 (1H, d, *J* = 7.0 Hz), 7.32-7.25 (5H, m), 4.35-4.27 (1H, m, OCH_2CH_3), 4.26-4.17 (1H, m, OCH_2CH_3), 4.00-3.89 (2H, m, OCH_2CH_3), 3.75 (1H, d, *J* = 7.5 Hz), 3.60 (1H, t, *J* = 7.5 Hz), 1.28 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.20 (9H, s), 0.94 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 166.1 (C, O-*C*=O), 165.2 (C, O-*C*=O), 164.4 (C,CN), 132.8 (C), 128.6 (2 x CH), 128.3 (2 x CH), 127.8 (CH), 62.3 (CH_2, OCH_2CH_3), 61.8 (CH_2, OCH_2CH_3), 57.1 (C), 44.8 (C), 36.4 (CH), 33.9 (CH), 22.2 (3xCH_3), 14.1 (CH_3, OCH_2CH_3), 13.7 (CH_3,



(+)-**46**

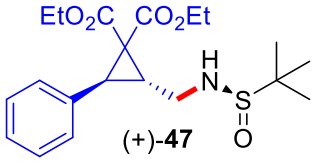
OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{20}H_{27}NO_5SH$ 394.1688; Found 394.1688.

Diethyl (2*R*,3*S*)-2-((((*S*)-tert-butylsulfinyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (-)-**47**: The compound was prepared following the procedure **P** and purified by column chromatography using EtOAc/hexanes (3:7 to 5:5) and isolated as a pale yellow liquid; Yield: 90% (35.6 mg); $[\alpha]_D^{25}$ = –66.6° (*c* = 0.110, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3420 (NH), 3212, 2980, 1720 (O-C=O), 1461, 1368, 1294, 1211, 1132, 1097, 1052, 864, 747, 698 and 597 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.19 (5H, m), 4.38-4.26 (1H, m, OCH_2CH_3), 4.26-4.14 (1H, m, OCH_2CH_3), 3.90-3.81 (2H, m, OCH_2CH_3), 3.57-3.47 (2H, m), 3.33-3.23 (1H, m), 3.20 (1H, d, *J* = 8.0 Hz), 2.78 (1H, td, *J* = 8.0, 8.0 Hz), 1.30 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.22 (9H, s), 0.87 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 166.4 (C, O-*C*=O), 134.0 (C), 128.6 (2 x CH), 128.2 (2 x CH), 127.4 (CH), 62.0 (CH_2, OCH_2CH_3), 61.3 (CH_2, OCH_2CH_3), 55.9 (C), 43.7 (CH_2), 42.2 (C), 35.6 (CH), 30.8 (CH), 22.5 (3 x CH_3), 14.1 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{20}H_{29}NO_5SH$ 396.1845; Found 396.1844.



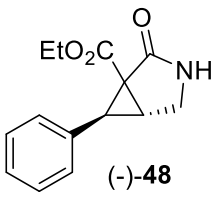
(-)-**47**

Diethyl (2*R*,3*S*)-2-((((*R*)-tert-butylsulfinyl)amino)methyl)-3-phenylcyclopropane-1,1-dicarboxylate (+)-**47**: The compound was prepared following the procedure **P** and purified by column chromatography using EtOAc/hexanes (3:7 to 5:5) and isolated as a pale yellow liquid; Yield: 93% (36.78 mg); $[\alpha]_D^{25}$ = 5.9° (*c* = 0.101, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3420 (NH), 3214, 2979, 1723 (O-C=O), 1461, 1367, 1294, 1211, 1131, 1098, 1055, 863, 773, 744 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.20 (5H, m), 4.39-4.19 (2H, m, OCH_2CH_3), 3.93-3.80 (2H, m, OCH_2CH_3), 3.55-3.42 (2H, m), 3.29-3.16 (2H, m), 2.83 (1H, td, *J* = 10.0, 8.0 Hz), 1.31 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.22 (9H, s), 0.88 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 167.7 (C, O-*C*=O), 166.3 (C, O-*C*=O), 134.0 (C), 128.7 (2 x CH), 128.2 (2 x CH), 127.4 (CH), 62.0 (CH_2, OCH_2CH_3), 61.3 (CH_2, OCH_2CH_3), 55.8 (C), 44.0 (CH_2), 42.2 (C), 35.7 (CH), 30.6 (CH), 22.5 (3 x CH_3), 14.1 (CH_3, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: (M + H^+) calcd for $C_{20}H_{29}NO_5SH$ 396.1845; Found 396.1845.



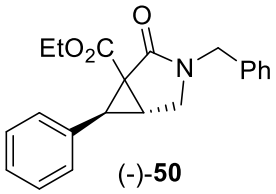
(+)-**47**

Ethyl (5*R*,6*S*)-2-oxo-6-phenyl-3-azabicyclo[3.1.0]hexane-1-carboxylate (**48**): The compound was prepared following the procedure **Q** and purified by column chromatography using MeOH/$CHCl_3$ (0.2:9.8) and isolated as a pale yellow liquid; Yield: 58% (28.43 mg, 0.2 mmol); $[\alpha]_D^{25}$ = –55.5° (*c* = 0.099, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3250 (NH), 2977, 2359, 1718 (O-C=O), 1685 (C=O), 1450, 1372, 1336, 1295, 1242, 1215, 1187, 1131, 1095, 1036, 782, 744, 695, 638 and 573 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.21 (5H, m), 6.87 (1H, br s), 4.04-3.87 (2H, m, OCH_2CH_3), 3.69 (1H, dd, *J* = 10.5, 5.5 Hz), 3.47 (1H, d, *J* = 10.5 Hz), 3.04 (1H, t, *J* = 5.5 Hz), 2.74 (1H, d, *J* = 5.5 Hz), 0.88 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 172.9 (C, HN-*C*=O), 165.1 (C, O-*C*=O), 133.6 (C), 128.6 (2 x CH), 128.2 (2 x CH), 127.6 (CH), 61.1 (CH_2, OCH_2CH_3), 42.3 (CH_2), 39.4 (C), 37.3 (CH), 25.4 (CH), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: ($M + H^+$) calcd for $C_{14}H_{15}NO_3H$ 246.1130; Found 246.1128.



(-)-**48**

Ethyl (5*R*,6*S*)-3-benzyl-2-oxo-6-phenyl-3-azabicyclo[3.1.0]hexane-1-carboxylate (**50**): The compound was prepared following the procedure **R** and purified by column chromatography using EtOAc/hexanes (2:8 to 3:7) and isolated as a pale yellow liquid; Yield: 57% (38.2 mg, 0.2 mmol); $[\alpha]_D^{25}$ = –61.17° (*c* = 0.103, $CHCl_3$, >98% *de*); IR (Neat): ν_{max} 3069, 3030, 2979, 2924, 2359, 2339, 1737 (O-C=O), 1687 (C=O), 1426, 1284, 1183, 1077, 698 and 652 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.27 (2H, tt, *J* = 8.0, 1.5 Hz), 7.24-7.14 (8H, m), 4.44 (1H, d, *J* = 15.0 Hz), 4.28 (1H, d, *J* = 14.5 Hz), 3.97-3.84 (2H, m), 3.49 (1H, dd, *J* = 10.5, 6.0 Hz), 3.19 (1H, d, *J* = 10.5 Hz), 2.82 (1H, t, *J* = 5.5 Hz), 2.50 (1H, d, *J* = 5.0 Hz), 0.86 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135) δ 168.9 (C, *C*=O), 165.4 (C, O-*C*=O), 136.3 (C), 133.5 (C), 128.8 (2 x CH), 128.6 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.8 (CH), 127.6 (CH), 61.1 (CH_2, OCH_2CH_3), 46.7 (CH_2), 46.6 (CH_2), 40.4 (C), 37.4 (CH), 22.6 (CH), 13.7 (CH_3, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: ($M + H^+$) calcd for $C_{21}H_{21}NO_3H$ 336.1600; Found 336.1600.



(-)-**50**

6. References

1. a) Freund, *Journal Für Praktische Chemie* **1881**, *26*, 367-377. b) A. Freund, *Monatshefte Für Chemie* **1882**, *3*, 625-635.
2. G. Gustavson, *Journal Für Praktische Chemie* **1887**, *36*, 300-305.
3. Anslyn, E. V.; Dougherty, D. A. Modern Physical Organic Chemistry. University science books. **2006**, 850-852.
4. Chen, D. Y.-K.; Pouwer, R. H.; Richard, J.-A. Recent Advances in the Total Synthesis of Cyclopropane-containing Natural Products. *Chem. Soc. Rev.* **2012**, *41*, 4631.
5. a) Mattson, R. J.; et al. Conformationally Restricted Homotryptamines. 2. Indole Cyclopropylmethylamines as Selective Serotonin Reuptake Inhibitors. *J. Med. Chem.* **2005**, *48*, 6023. b) King, H. D.; et al. Conformationally restricted homotryptamines. Part 4: Heterocyclic and naphthyl analogs of a potent selective serotonin reuptake inhibitor. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5647. c) Zhang, G.; Cheng, J.; McCorvy J. D.; Lorello, P. J.; Caldarone, B. J.; Roth, B. L.; Kozikowski, A. P. Discovery of *N*-Substituted (2-Phenylcyclopropyl)methylamines as Functionally Selective Serotonin 2C Receptor Agonists for Potential Use as Antipsychotic Medications. *J. Med. Chem.* **2017**, *60*, 6273. d) Wang, T.; Goodall, M. L.; Gonzales, P.; Sepulveda, M.; Martin, K. R.; Gately, S.; MacKeigan, J. P. Synthesis of Improved Lysomotropic Autophagy inhibitors. *J. Med. Chem.* **2015**, *58*, 3025. e) Dian, L.; Marek, I. Asymmetric Preparation of Polysubstituted Cyclopropanes Based on Direct Functionalization of Achiral Three-Membered Carbocycles. *Chem. Rev.* **2018**, *118*, 8415.
6. Kunz, R. K.; MacMillan, D. W. C. Enantioselective Organocatalytic Cyclopropanations. The Identification of a New Class of Iminium Catalyst Based upon Directed Electrostatic Activation *J. Am. Chem. Soc*. **2005**, *127*, 3240.
7. Hartikka, A.; Arvidsson, P. I. Tetrazolic Acid Functionalized Dihydroindol: Rational Design of a Highly Selective Cyclopropanation Organocatalyst. *J. Org. Chem*. **2007**, *72*, 5874.
8. Hartikka, A.; Slosarczyk, A. T.; Arvidsson, P. I. Application of novel sulfonamides in enantioselective organocatalyzed Cyclopropanation. *Tetrahedron Asymmetry* **2007**, *18*, 1403.
9. Rios, R,; Sundén, H.; Vesely, J.; Zhao G.-L.; Dziedzic, P.; Cordova, A. A Simple Organocatalytic Enantioselective Cyclopropanation of α,β-Unsaturated Aldehydes. *Adv. Synth. Catal*. **2007**, *349*, 1028.

10. (a) Ibrahem, I,; Zhao, G.-L.; Rios, R.; Vesely, J.; Sunden, H.; Dziedzic, P.; Cordova, A. One-Pot Organocatalytic Domino Michael/α-Alkylation Reactions: Direct Catalytic Enantioselective Cyclopropanation and Cyclopentanation Reactions. *Chem. Eur. J.* **2008**, *14*, 7867. (b) Rueping, M.; Sunden, H.; Sugiono, E. Unifying Metal- and Organocatalysis for Asymmetric Oxidative Iminium Activation: A Relay Catalytic System Enabling the Combined Allylic Oxidation of Alcohols and Prolinol Ether Catalyzed Iminium Reactions. *Chem. Eur. J.* **2012**, *18*, 3649.
11. Companyó, X.; Alba, A.-N.; Cárdenas, F.; Moyano, A.; Rios, R. Asymmetric Organocatalytic Cyclopropanation-Highly Stereocontrolled Synthesis of Chiral Cyclopropanes with Quaternary Stereocenters. *Eur. J. Org. Chem.* **2009**, 3075-3080.
12. Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. Organocatalytic Enantioselective Cascade Michael-Alkylation Reactions: Synthesis of Chiral Cyclopropanes and Investigation of Unexpected Organocatalyzed Stereoselective Ring Opening of Cyclopropanes. *J. Am. Chem. Soc*. **2007**, *129*, 10886.
13. Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. 'On Water' Iminium/Enamine Catalysis: Organocatalytic Enantioselective Cyclopropanation of α,β-Unsaturated Aldehydes. *Synthesis* **2010**, 701.
14. Martinez, J. I.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. Optimizing the Structure of 4-Dialkylamino-α,α-diarylprolinol Ethers as Catalysts for the Enantioselective Cyclopropanation of α,β-Unsaturated Aldehydes in Water. *ChemCatChem* **2013**, *5*, 2240.
15. Llanes, P.; Rodríguez-Escrich, C.; Sayalero, S.; Pericás, M. A. Organocatalytic Enantioselective Continuous-Flow Cyclopropanation. *Org. Lett*. **2016**, *18*, 6292.
16. Terrason, V.; Lee, A. V. D.; Figueiredo, R. M. D.; Campagne, J. M. Organocatalyzed Cyclopropanation of α-Substituted α,β-Unsaturated Aldehydes: Enantioselective Synthesis of Cyclopropanes Bearing a Chiral Quaternary Center. *Chem. Eur. J.* **2010**, *16*, 7875.
17. Rueping, M., Sundén, H.; Hubener, L.; Sugiono, E. Asymmetric oxidative Lewis base catalysis-unifying iminium and enamine organocatalysis with oxidations. *Chem. Commun*. **2012**, *48*, 2201.
18. Li, W.; Li, X.; Ye, T.; Wu, W.; Liang, X.; Ye, J. Asymmetric organocatalytic Michael/α-alkylation reaction of α,β-unsaturated aldehyde with chloroacetophenone. *Tetrahedron Lett.* **2011**, *52*, 2715.
19. Džambaski, Z.; Bondžić, A. M.; Triandafillidi, I.; Kokotos, C. G.; Bondžić, B. P. Organocatalytic, Organic Oxidant Promoted, Enamine C-H Oxidation/Cyclopropanation Reaction. *Adv. Synth. Catal*. **2021**, *363*, 4002.

20. Zaghi, A.; Bernardi, T.; Bertolasi, V.; Bortolini, O.; Massi, A.; Risi, C. D. One-Pot, Four-Step Organocatalytic Asymmetric Synthesis of Functionalized Nitrocyclopropanes. *J. Org. Chem*. **2015**, *80*, 9176.
21. Riaño, I.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. Organocatalytic Transannular Approach to Stereodefined Bicyclo[3.1.0]hexanes. *J. Org. Chem.* **2018**, *83*, 4180.
22. Zhao, C.-G.; Feng, Z.-T.; Xu, G.-Q.; Gao, A.; Chen, J.-W.; Wang, Z.-Y.; Xu, P.-F. Highly Enantioselective Construction of Strained Spiro[2,3]hexanes through a Michael Addition/Ring Expansion/Cyclization Cascade. *Angew. Chem*. *Int. Ed.* **2020**, *59*, 3058.
23. Barløse, C. L.; Østergaard, N. L.; Bitsch, R. S.; Iversen, M. V.; Jørgensen, K. A Direct Organocatalytic Enantioselective Route to Functionalized trans-Diels–Alder Products Having the Norcarane Scaffold. *Angew. Chem. Int. Ed.* **2021**, *60*, 18318.
24. Perkin, W. H. Ueber die Einwirkung von Aethylenbromid auf Malonsäureäther. *Ber. dtsch. Chem. Ges.* **1884**, *17*, 54.
25. Gordon, M. S. Ring Strain in Cyclopropane, Cyclopropene, Silacyclopropane, and Silacyclopropene. *J. Am. Chem. Soc.* **1980**, *102*, 7419.
26. (a) Gnad, F.; Reiser, O. Synthesis and Applications of *β*-Aminocarboxylic Acids Containing a Cyclopropane Ring. *Chem. Rev.* **2003**, *103*, 1603. (b) Wessjohann, L. A.; Brandt, W.; Thiemann, T. Biosynthesis and Metabolism of Cyclopropane Rings in Natural Compounds. *Chem. Rev.* **2003**, *103*, 1625. (c) Reichelt, A.; Martin, S. F. Synthesis and Properties of Cyclopropane-Derived Peptidomimetics. *Acc. Chem. Res.* **2006**, *39*, 433. (d) Brackmann, F.; de Meijere, A. Natural Occurrence, Syntheses, and Applications of Cyclopropyl-Group-Containing α-Amino Acids. 1. 1-Aminocyclopropanecarboxylic Acid and other 2,3-Methanoamino Acids. *Chem. Rev.* **2007**, *107*, 4493. (e) Ebner, C.; Carreira, E. M. Cyclopropanation Strategies in Recent Total Syntheses. *Chem. Rev.* **2017**, *117*, 11651.
27. Wenkert, E. Oxycyclopropanes in Organochemical Synthesis. *Acc. Chem. Res.* **1980**, *13*, 27.
28. Danishefsky, S. Electrophilic Cyclopropanes in Organic Synthesis. *Acc. Chem. Res.* **1979**, *12*, 66.
29. Reissig, H.-U.; Hirsch, E. Donor-Acceptor Substituted Cyclopropanes: Synthesis and Ring Opening to 1,4-Dicarbonyl Compounds. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 813.
30. For selected reviews, see: (a) Reissig, H.-U.; Zimmer, R. Donor−Acceptor-Substituted Cyclopropane Derivatives and Their Application in Organic Synthesis. *Chem. Rev.* **2003**, *103*, 1151. (b) Carson, C. A.; Kerr, M. A. Heterocycles from Cyclopropanes: Applications in Natural Product Synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3051. (c) Davies, H. M. L.; Denton, J. R. Application of Donor/Acceptor-carbenoids to the Synthesis of Natural Products. *Chem.*

Soc. Rev. **2009**, *38*, 3061. (d) Schneider, T. F.; Kaschel, J.; Werz, D. B. A New Golden Age for Donor–Acceptor Cyclopropanes. *Angew. Chem., Int. Ed.* **2014**, *53*, 5504. (e) Cavitt, M. A.; Phun, L. H.; France, S. Intramolecular Donor–Acceptor Cyclopropane Ring-Opening Cyclizations. *Chem. Soc. Rev.* **2014**, *43*, 804. (f) Gharpure, S. J.; Nanda, L. N. Application of Oxygen/Nitrogen Substituted Donor-Acceptor Cyclopropanes in the Total Synthesis of Natural Products. *Tetrahedron Lett.* **2017**, *58*, 711. For selected papers, see: (g) Selvi, T.; Srinivasan, K. Boron Trifluoride Mediated Ring-Opening Reactions of *trans*-2-Aryl-3-nitro-cyclopropane-1,1-dicarboxylates. Synthesis of Aroylmethylidene Malonates as Potential Building Blocks for Heterocycles. *J. Org. Chem.* **2014**, *79*, 3653. (h) Gupta, A.; Kholiya, R.; Rawat, D. S. $BF_3{\cdot}OEt_2$-Mediated Highly Stereoselective Synthesis of Trisubstituted-Tetrahydrofuran via [3+2] Cycloaddition Reaction of 2-Arylcyclopropyl Ketones with Aldehydes. *Asian. J. Org. Chem.* **2017**, *6*, 993. (i) Sasazawa, K.; Takada, S.; Yubune, T.; Takaki, N.; Ota, R.; Nishii, Y. Stereochemical Courses and Mechanisms of Ring-opening Cyclization of Donor–Acceptor Cyclopropylcarbinols and Cyclization of 7-Benzyloxy Dibenzyl Lignan Lactones. *Chem. Lett.* **2017**, *46*, 524.

31. For recent selected reports, see: (a) Sabbatani, J.; Maulide, N. Temporary Generation of a Cyclopropyl Oxocarbenium Ion Enables Highly Diastereoselective Donor–Acceptor Cyclopropane Cycloaddition. *Angew. Chem., Int. Ed.* **2016**, *55*, 6780. (b) Preindl, J.; Chakrabarty, S.; Waser, J. Dearomatization of Electron Poor Six-membered *N*-Heterocycles through [3 + 2] Annulation with Aminocyclopropanes. *Chem. Sci.* **2017**, *8*, 7112. (c) Garve, L. K. B.; Jones, P. G.; Werz, D. B. Ring-Opening 1-Amino-3-aminomethylation of Donor–Acceptor Cyclopropanes via 1,3-Diazepanes. *Angew. Chem., Int. Ed.* **2017**, *56*, 9226. (d) Lücht, A.; Patalag, L. J.; Augustin, A. U.; Jones, P. G.; Werz, D. B. Reactions of Donor-Acceptor Cyclopropanes with Naphthoquinones: Redox and Lewis Acid Catalysis Working in Concert. *Angew. Chem., Int. Ed.* **2017**, *56*, 10587. (e) Das, S.; Daniliuc, C. G.; Studer, A. Stereospecific 1,3-Aminobromination of Donor–Acceptor Cyclopropanes. *Angew. Chem., Int. Ed.* **2017**, *56*, 11554. (f) Sudhakar, G.; Mahesh, S. K.; Vemulapalli, S. P. B.; Nanubolu, J. B. Nazarov Cyclization and Tandem [4 + 2]-Cycloaddition Reactions of Donor–Acceptor Cyclopropanes. *Org. Lett.* **2017**, *19*, 4500.
32. For selected reviews, see: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. Transition Metal Chemistry of Cyclopropenes and Cyclopropanes. *Chem. Rev.* **2007**, *107*, 3117. (b) Jiao, L.; Yu, Z.-X. Vinylcyclopropane Derivatives in Transition-Metal-Catalyzed Cycloadditions for the Synthesis of Carbocyclic Compounds. *J. Org. Chem.* **2013**, *78*, 6842. (c) Souillart, L.; Cramer, N. Catalytic C–C Bond Activations via Oxidative Addition to Transition Metals.

Chem. Rev. **2015**, *115*, 9410. (d) Fumagalli, G.; Stanton, S.; Bower, J. F. Recent Methodologies That Exploit C–C Single-Bond Cleavage of Strained Ring Systems by Transition Metal Complexes. *Chem. Rev.* **2017**, *117*, 9404.

33. For selected publications, see: (a) Zhou, Y.-Y.; Wang, L.-J.; Li, J.; Sun, X.-L.; Tang, Y. Side-Arm-Promoted Highly Enantioselective Ring-Opening Reactions and Kinetic Resolution of Donor–Acceptor Cyclopropanes with Amines. *J. Am. Chem. Soc.* **2012**, *134*, 9066. (b) Xu, H.; Qu, J.-P.; Liao, S.; Xiong, H.; Tang, Y. Highly Enantioselective [3+2] Annulation of Cyclic Enol Silyl Ethers with Donor–Acceptor Cyclopropanes: Accessing 3*α*-Hydroxy [n.3.0]Carbobicycles. *Angew. Chem., Int. Ed.* **2013**, *52*, 4004. (c) Wales, S. M.; Walker, M. M.; Johnson, J. S. Asymmetric Synthesis of Indole Homo-Michael Adducts via Dynamic Kinetic Friedel–Crafts Alkylation with Cyclopropanes. *Org. Lett.* **2013**, *15*, 2558. (d) de Nanteuil, F.; Serrano, E.; Perrotta, D.; Waser, J. Dynamic Kinetic Asymmetric [3 + 2] Annulation Reactions of Aminocyclopropanes. *J. Am. Chem. Soc.* **2014**, *136*, 6239. (e) Xia, Y.; Liu, X.; Zheng, H.; Lin, L.; Feng, X. Asymmetric Synthesis of 2,3-Dihydropyrroles by Ring-Opening/Cyclization of Cyclopropyl Ketones Using Primary Amines. *Angew. Chem., Int. Ed.* **2015**, *54*, 227. (f) Kang, Q.-K.; Wang, L.; Liu, Q.-J.; Li, J.-F.; Tang, Y. Asymmetric H_2O-Nucleophilic Ring Opening of D–A Cyclopropanes: Catalyst Serves as a Source of Water. *J. Am. Chem. Soc.* **2015**, *137*, 14594. (g) Xia, Y.; Lin, L.; Chang, F.; Liao, Y.; Liu, X.; Feng, X. Asymmetric Ring Opening/Cyclization/Retro-Mannich Reaction of Cyclopropyl Ketones with Aryl 1,2-Diamines for the Synthesis of Benzimidazole Derivatives. *Angew. Chem., Int. Ed.* **2016**, *55*, 12228.
34. (a) Emmett, M. R.; Kerr, M. A. Nucleophilic Ring Opening of Cyclopropane Hemimalonates Using Internal Brønsted Acid Activation. *Org. Lett.* **2011**, *16*, 4180. (b) Nguyen, T. N.; Nguyen, T. S.; May, J. A. Brønsted Acid Catalyzed Homoconjugate Addition of Organotrifluoroborates to Arylated Cyclopropyl Ketones. *Org. Lett.* **2016**, *18*, 3786. (c) Xue, S.; Liu, J.; Qing, X.; Wang, C. Brönsted acid-Mediated Annulations of 1-Cyanocyclopropane-1-carboxylates with Arylhydrazines: Efficient Strategy for the Synthesis of 1,3,5-Trisubstituted Pyrazoles. *RSC Adv.* **2016**, *6*, 67724.
35. (a) Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B. Nucleophilic Addition of Phenol Derivatives to Methyl 1-Nitrocyclopropanecarboxylates. *J. Org. Chem.* **2008**, *73*, 6838. (b) Gladow, D.; Reissig, H.-U. Perfluoroalkyl-Substituted Thiophenes and Pyrroles from Donor–Acceptor Cyclopropanes and Heterocumulenes: Synthesis and Exploration of their Reactivity. *J. Org. Chem.* **2014**, *79*, 4492. (c) Zhu, Y.; Gong, Y. Construction of 2-Pyrone Skeleton via Domino Sequence between 2-Acyl-1-Chlorocyclopropanecarboxylate and

Amines. *J. Org. Chem.* **2015**, *80*, 490. (d) Sasaki, M.; Kondo, Y.; Nishio, T.; Takeda, K. Carbanion-Induced [3 + 2] Annulation of Donor–Acceptor Cyclopropanes. *Org. Lett.* **2016**, *18*, 3858. (e) Saha, A.; Bhattacharyya, A.; Talukdar, R.; Ghorai, M. K. Stereospecific Syntheses of Enaminonitriles and β-Enaminoesters via Domino Ring-Opening Cyclization (DROC) of Activated Cyclopropanes with Pronucleophilic Malononitriles. *J. Org. Chem.* **2018**, *83*, 2131.

36. For NHC-catalyzed ring-opening of formylcyclopropanes, see: (a) Sohn, S. S.; Bode, J. W. *N*-Heterocyclic Carbene Catalyzed C-C Bond Cleavage in Redox Esterifications of Chiral Formylcyclopropanes. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021. (b) Du, D.; Wang, Z. *N*-Heterocyclic Carbene-Catalyzed Domino Reactions of Formylcyclopropane 1,1-Diesters: A New Synthesis of Coumarins. *Eur. J. Org. Chem.* **2008**, 4949. (c) Du, D.; Li, L.; Wang, Z. *N*-Heterocyclic Carbene-Catalyzed Domino Ring-Opening/Redox Amidation/Cyclization Reactions of Formylcyclopropane 1,1-Diesters: Direct Construction of a 6−5−6 Tricyclic Hydropyrido[1,2-*a*]indole Skeleton. *J. Org. Chem.* **2009**, *74*, 4379. (d) Li, G.-Q.; Dai, L.-X.; You, S.-L. *N*-Heterocyclic Carbene Catalyzed Ring Expansion of Formylcyclopropanes: Synthesis of 3,4-Dihydro-*α*-pyrone Derivatives. *Org. Lett.* **2009**, *11*, 1623. (e) Li, L.; Du, D.; Ren, J.; Wang, Z. *N*-Heterocyclic Carbene Catalyzed Domino Reactions of Formylcyclopropane 1,1-Diesters: Construction of a 6-5-5 Tricyclic Pyrrolo[1,2-*a*]indole. *Eur. J. Org. Chem.* **2011**, 614. (f) Lv, H.; Mo, J.; Fang, X.; Chi, Y. R. Formal Diels–Alder Reactions of Chalcones and Formylcyclopropanes Catalyzed by Chiral *N*-Heterocyclic Carbenes. *Org. Lett.* **2011**, *13*, 5366. (g) Prieto, L.; Sánchez-Díez, E.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. Catalytic Generation of Donor-Acceptor Cyclopropanes under *N*-Heterocyclic Carbene Activation and their Stereoselective Reaction with Alkylideneoxindoles. *Adv. Synth. Catal.* **2017**, *359*, 1678.
37. For iminium mediated ring-opening of formylcyclopropanes, see: (a) Li, L.; Li, Z.; Wang, Q. Organocatalytic Nucleophilic Ring Opening of Cyclopropanecarbaldehydes by Benzenethiols: Tandem Synthesis of Benzo[*b*]thiepines. *Synlett* **2009**, 1830. (b) Sparr, C.; Gilmour, R. Cyclopropyl Iminium Activation: Reactivity Umpolung in Enantioselective Organocatalytic Reaction Design. *Angew. Chem., Int. Ed.* **2011**, *50*, 8391. (c) Holland, M. C.; Metternich, J. B.; Daniliuc, C.; Schweizer, W. B.; Gilmour, R. Aromatic Interactions in Organocatalyst Design: Augmenting Selectivity Reversal in Iminium Ion Activation. *Chem. Eur. J.* **2015**, *21*, 10031. (d) Wallbaum, J.; Garve, L. K. B.; Jones, P. G.; Werz, D. B. Ring-Opening Regio-, Diastereo-, and Enantioselective 1,3-Chlorochalcogenation of Cyclopropyl Carbaldehydes. *Chem. Eur. J.* **2016**, *22*, 18756.

38. For enamine-mediated ring-opening of cyclopropanes, see: (a) Halskov, K. S.; Kniep, F.; Lauridsen, V. H.; Iversen, E. H.; Donslund, B. S.; Jørgensen, K. A. Organocatalytic Enamine-Activation of Cyclopropanes for Highly Stereoselective Formation of Cyclobutanes. *J. Am. Chem. Soc.* **2015**, *137*, 1685. (b) Sanchez-Diez, E.; Vesga, D. L.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. Organocatalytically Generated Donor–Acceptor Cyclopropanes in Domino Reactions. One-Step Enantioselective Synthesis of Pyrrolo[1,2-*a*]quinolones. *Org. Lett.* **2016**, *18*, 1270.
39. For enolate-mediated ring-opening of cyclopropanes, see: (a) Dickmeiss, G.; Sio, V. D.; Udmark, J.; Poulsen, T. B.; Marcos, V.; Jørgensen, K. A. Organocatalytic Asymmetric Desymmetrization–Fragmentation of Cyclic Ketones. *Angew. Chem., Int. Ed.* **2009**, *48*, 6650. (b) Blom, J.; Vidal-Albalat, A.; Jørgensen, J.; Barløse, C. L.; Jessen, K. S.; Iversen, M. V.; Jørgensen, K. A. Directing the Activation of Donor–Acceptor Cyclopropanes Towards Stereoselective 1,3-Dipolar Cycloaddition Reactions by Brønsted Base Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 11831.
40. For urea-catalyzed ring-opening, see: (a) So, S. S.; Auvil, T. J.; Garza, V. J.; Mattson, A. E. Boronate Urea Activation of Nitrocyclopropane Carboxylates. *Org. Lett.* **2012**, *14*, 444. (b) Hardman, A. M.; So, S. S.; Mattson, A. E. Urea-catalyzed Construction of Oxazinanes. *Org. Biomol. Chem.* **2013**, *11*, 5793.
41. Zhang, J.; Tang, Y.; Wei, W.; Wu, Y.; Li, Y.; Zhang, J.; Zheng, Y.; Xu, S. Organocatalytic Cloke–Wilson Rearrangement: DABCO-Catalyzed Ring Expansion of Cyclopropyl Ketones to 2,3-Dihydrofurans. *Org. Lett.* **2017**, *19*, 3043.
42. For examples of nucleophilic addition to formylcyclopropanes under Lewis acid conditions, see: (a) Böhm, C.; Schinnerl, M.; Bubert, C.; Zabel, M.; Labahn, T.; Parisini, E.; Reiser, O. A New Strategy for the Stereoselective Synthesis of 1,2,3-Trisubstituted Cyclopropanes. *Eur. J. Org. Chem.* **2000**, 2955. (b) Böhm, C.; Reiser, O. Enantioselective Synthesis of (−)-Roccellaric Acid. *Org. Lett.* **2001**, *3*, 1315.
43. Application of formylcyclopropanes in the total synthesis, see: (a) Barrett, A. G. M.; Doubleday, W. W.; Tustin, G. J.; White, A. J. P.; Williams, D. J. Approaches to the Assembly of the Antifungal Agent FR-900848: Studies on the Asymmetric Synthesis of Bicyclopropanes and an X-ray Crystallographic Analysis of (4*R*,5*R*)-2-[(1*R*,3*S*,4*S*,6*R*)-6-phenyl-1-bicyclopropyl]-1,3-dimethyl-4,5-diphenylimidazolidine. *J. Chem. Soc., Chem. Commun.* **1994**, 1783. (b) Falck, J. R.; Mekonnen, B.; Yu, J.; Lai, J.-Y. Synthesis of the Polycyclopropane Antibiotic FR-900848 via the Horeau Gambit. *J. Am. Chem. Soc.* **1996**, *118*, 6096. (c) Barrett, A. G. M.; Doubleday, W. W.; Tustin, G. J. Asymmetric Synthesis of

Bicyclopropane Derivatives. *Tetrahedron* **1996**, *52*, 15325. (d) Barrett, A. G. M.; Doubleday, W. W.; Hamprecht, D.; Kasdorf, K.; Tustin, G. J.; White, A. J. P.; Williams, D. J. Assembly of the Antifungal Agent FR-900848 and the CETP Inhibitor U-106305: Studies on Remarkable Multicyclopropane Natural Products. *Chem. Commun.* **1997**, 1693.

44. For original papers on the development of organocatalytic reductive coupling reaction through combination of Knoevenagel condensation and transfer hydrogenation in one-pot, see: (a) Ramachary, D. B.; Pasha, Md. A.; Thirupathi, G. Organocatalytic Asymmetric Formal [3+2] Cycloaddition as a Versatile Platform to Access Methanobenzo[7]annulenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 12930. (b) Madhavachary, R.; Ramachary, D. B. High-Yielding Total Synthesis of Sexually Deceptive Chiloglottones and Antimicrobial Dialkylresorcinols through an Organocatalytic Reductive Coupling Reaction. *Eur. J. Org. Chem.* **2014**, 7317. (c) Ramachary, D. B.; Jain, S. Sequential One-pot Combination of Multi-component and Multi-catalysis Cascade Reactions: an Emerging Technology in Organic Synthesis. *Org. Biomol. Chem.* **2011**, *9*, 1277. (d) Ramachary, D. B.; Kishor, M. Direct Catalytic Asymmetric Synthesis of Highly Functionalized Tetronic acids/Tetrahydro-isobenzofuran-1,5-diones via Combination of Cascade Three-component Reductive Alkylations and Michael-aldol Reactions. *Org. Biomol. Chem.* **2010**, *8*, 2859. (e) Ramachary, D. B.; Reddy, Y. V. A General Approach to Chiral Building Blocks via Direct Amino Acid-Catalyzed Cascade Three-Component Reductive Alkylations: Formal Total Synthesis of HIV-1 Protease Inhibitors, Antibiotic Agglomerins, Brefeldin A, and (*R*)-γ-Hexanolide. *J. Org. Chem.* **2010**, *75*, 74. (f) Ramachary, D. B.; Kishor, M.; Reddy, Y. V. Development of Pharmaceutical Drugs, Drug Intermediates and Ingredients by Using Direct Organo-Click Reactions. *Eur. J. Org. Chem.* **2008**, 975. (g) Ramachary, D. B.; Kishor, M. Organocatalytic Sequential One-Pot Double Cascade Asymmetric Synthesis of Wieland−Miescher Ketone Analogues from a Knoevenagel/Hydrogenation/Robinson Annulation Sequence: Scope and Applications of Organocatalytic Biomimetic Reductions. *J. Org. Chem.* **2007**, *72*, 5056. (h) Ramachary, D. B.; Kishor, M.; Babul Reddy, G. Development of Drug Intermediates by using Direct Organocatalytic Multi-component Reactions. *Org. Biomol. Chem.* **2006**, *4*, 1641. (i) Ramachary, D. B.; Kishor, M.; Ramakumar, K. A Novel and Green Protocol for Two-carbon Homologation: A Direct Amino Acid/K_2CO_3-catalyzed Four-component Reaction of Aldehydes, Active Methylenes, Hantzsch esters and Alkyl Halides. *Tetrahedron Lett.* **2006**, *47*, 651.

45. For hydrogenolysis of cyclopropanes using H_2 on Pd/C, see: Sone, Y.; Kimura, Y.; Ota, R.; Mochizuki, T.; Ito, J.; Nishii, Y. Catalytic Hydrogenolysis of Enantioenriched Donor–

Acceptor Cyclopropanes Using H_2 and Palladium on Charcoal. *Eur. J. Org. Chem.* **2017**, 2842 and references cited therein.

46. See Supporting Information[54] for more details.
47. CCDC-1821780 [(-)-**22ia**], CCDC-1821658 [(-)-**24ga**] and CCDC-1821659 [(+)-**25hc**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
48. For dihydropyran as a structural motif found in many bioactive natural products and drugs, see: (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. Natural Product-like Combinatorial Libraries Based on Privileged Structures. 1. General Principles and Solid-Phase Synthesis of Benzopyrans. *J. Am. Chem. Soc.* **2000**, *122*, 9939. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. The Combinatorial Synthesis of Bicyclic Privileged Structures or Privileged Substructures. *Chem. Rev.* **2003**, *103*, 893. (c) Pratap, R.; Ram, V. J. Natural and Synthetic Chromenes, Fused Chromenes, and Versatility of Dihydrobenzo[*h*]chromenes in Organic Synthesis. *Chem. Rev.* **2014**, *114*, 10476. (d) Robert, S.; Bertolla, C.; Masereel, B.; Dogné, J. M.; Pochet, L. Novel 3-Carboxamide-coumarins as Potent and Selective FXIIa Inhibitors. *J. Med. Chem.* **2008**, *51*, 3077. (e) Mahadevan, A.; Siegel, C.; Martin, B. R.; Abood, M. E.; Beletskaya, I.; Razdan, R. K. Novel Cannabinol Probes for CB1 and CB2 Cannabinoid Receptors. *J. Med. Chem.* **2000**, *43*, 3778. For dihydrofurans as a structural motif found in natural products and drugs, see: (f) Bowen, D. M.; DeGraw Jr., J. I.; Shah, V. R.; Bonner, W. A. The Synthesis and Pharmacological Action of Tremetone. *J. Med. Chem.* **1963**, *6*, 315. (g) Bonner, W. A.; Burke, N. I.; Fleck, W. E.; Hill, R. K.; Joule, J. A.; Sjöberg, B.; Zalkow, J. H. The Absolute Configurations of Tremetone and Toxol. *Tetrahedron* **1964**, *20*, 1419. (h) Banskota, A. H.; Tezuka, Y.; Prasain, J. K.; Matsushige, K.; Saiki, I.; Kadota, S. Chemical Constituents of Brazilian Propolis and Their Cytotoxic Activities. *J. Nat. Prod.* **1998**, *61*, 896. (i) Yamaguchi, S.; Muro, S.; Kobayashi, M.; Miyazawa, M.; Hirai, Y. Absolute Structures of Some Naturally Occurring Isopropenyldihydrobenzofurans, Remirol, Remiridiol, Angenomalin, and Isoangenomalin. *J. Org. Chem.* **2003**, *68*, 6274.
49. (a) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. Scope and Mechanism for Lewis Acid-Catalyzed Cycloadditions of Aldehydes and Donor−Acceptor Cyclopropanes: Evidence for a Stereospecific Intimate Ion Pair Pathway. *J. Am. Chem. Soc.* **2008**, *130*, 8642. (b) Smith, A. G.; Slade, M. C.; Johnson, J. S. Cyclopropane−Aldehyde Annulations at Quaternary Donor Sites: Stereoselective Access to Highly Substituted Tetrahydrofurans. *Org. Lett.* **2011**, *13*, 1996.

50. Fujii, N.; Mallari, J. P.; Hansell, E. J.; Mackey, Z.; Doyle, P.; Zhou, Y. M.; Gut, J,; Rosenthal, P. J.; McKerrowc, J. H.; Guy, R. K. Discovery of potent thiosemicarbazone inhibitors of rhodesain and cruzain. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 121.
51. Ajay, A.; Singh, V.; Singh, S.; Pandey, S.; Gunjan, S.; Dubey, D.; Sinha, S. K.; Singh, B. N.; Chaturvedi, V.; Tripathi, R.; Ramchandran, R.; Tripathi, R. P. Synthesis and bio-evaluation of alkylaminoaryl phenyl cyclopropyl methanones as antitubercular and antimalarial agents. *Bioorg. Med. Chem.* **2010**, *18*, 8289.
52. Banothu, J.; Basavoju, S.; Bavantula, R. Pyridinium Ylide Assisted Highly Stereoselective One-Pot Synthesis of trans -2-(4-Chlorobenzoyl)-3-aryl-spiro[cyclopropane-1,2′-inden]-1′,3′-diones and Their Antimicrobial and Nematicidal Activities. *Journal of Heterocyclic Chemistry* **2015**, *52*, 853.
53. Bode, J. W.; Sohn, S. S. N-Heterocyclic Carbene-Catalyzed Redox Amidations of α-Functionalized Aldehydes with Amines. *J. Am. Chem. Soc.* **2007,** *129*, 13798.
54. Peraka, S.; Hussain, A.; Ramachary, D. B. Modular Access to Chiral 2,3-Dihydrofurans and 3,4-Dihydro-2H-pyrans by Stereospecific Activation of Formylcyclopropanes through Combination of Organocatalytic Reductive Coupling and Lewis-Acid-Catalyzed Annulative Ring- Opening Reactions. *J. Org. Chem.* **2018**, *83*, 9795.
55. Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54*, 3451.
56. (a) Robichaud, A.; Ajjou, A. N. First example of direct reductive amination of aldehydes with primary and secondary amines catalyzed by water-soluble transition metal catalysts. *Tetrahedron Lett.,* **2006**, *47*, 3633. (b) Ohkuma, T.; Noyori, R.; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. E. Springer: New York, **2004**. (c) Tararov, V. I.; Borner, A. Approaching Highly Enantioselective Reductive Amination. *Synlett,* **2005**, 203. (d) Gomez, S.; Peters, J. A.; Maschmeyer, T. The Reductive Amination of Aldehydes and Ketones and the Hydrogenation of Nitriles: Mechanistic Aspects and Selectivity Control. *Adv. Synth. Catal.,* **2002**, *344*, 1037.
57. (a) You, S. L. Recent Developments in Asymmetric Transfer Hydrogenation with Hantzsch Esters: A Biomimetic Approach. *Chem. Asian J.* **2007**, *2*, 820. (b) Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. Enantioselective Organocatalytic Transfer Hydrogenation Reactions using Hantzsch Esters. *Acc. Chem. Res.* **2007**, *40*, 1327.
58. Wang, C.; Xiao, J. Asymmetric Reductive Amination. *Top. Curr. Chem.* **2014**, *343*, 261.
59. Singh, S.; Batra, U. K. Asymmetric Reductions of Imines using NADH Models. *Indian J. Chem., Sect. B* **1989**, *28*, 1.

60. Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. Enantioselective Brønsted Acid Catalyzed Transfer Hydrogenation: Organocatalytic Reduction of Imines. *Org. Lett.* **2005**, *7*, 3781.
61. Hoffmann, S.; Seayad, A. M.; List, B. A Powerful Brønsted Acid Catalyst for the Organocatalytic Asymmetric Transfer Hydrogenation of Imines. *Angew. Chem. Int. Ed.* **2005**, *44*,7424.
62. Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. Enantioselective Organocatalytic Reductive Amination. *J. Am. Chem. Soc.* **2006**, *128*, 84.
63. Hoffmann, S.; Nicoletti, M.; List, B. Catalytic Asymmetric Reductive Amination of Aldehydes via Dynamic Kinetic Resolution. *J. Am. Chem. Soc.* **2006**, *128*, 13074.
64. Huang, Y.-B.; Cai, C. Direct reductive amination of aldehydes and ketones mediated by a thiourea derivative as an organocatalyst. *Journal of Chemical Research* **2009**, *11*, 686.
65. Hu, F. Z.; Chen, H.; Xu, X. Y.; Yuan, W. C.; Zhang, X. M. Dynamic Kinetic Resolution in Enantioselective Reductive Amination of α -Branched Aldehydes by Lewis Base Organocatalyzed Hydrosilylation. *Chemistry Select* **2017**, *2*, 4076.
66. (a) Kuznetsov, D. M.; Kutateladze, A. G. Step-Economical Photoassisted Diversity-Oriented Synthesis: Sustaining Cascade Photoreactions in Oxalyl Anilides to Access Complex Polyheterocyclic Molecular Architectures. *J. Am. Chem. Soc.* **2017**, *139*, 16584. (b) Maximiano, A. P.; Ramos, G. S.; Marques, M. V.; Sá, M. M. Functionalized Cyclopropanes as Versatile Intermediates for the Diversity-Oriented Synthesis of γ-Lactones, γ-Lactams and δ-Lactams. *Synthesis* **2021**, *53*, 2408.

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LIST OF PUBLICATIONS

1. Modular Access to Chiral 2,3-Dihydrofurans and 3,4-Dihydro-2H-pyrans by Stereospecific Activation of Formylcyclopropanes through Combination of Organocatalytic Reductive Coupling and Lewis-Acid-Catalyzed Annulative Ring-Opening Reactions. Swamy Peraka, Akram Hussain, and Dhevalapally B. Ramachary. *J. Org. Chem.* **2018**, *83*, 9795.

2. Organocatalytic One-pot Synthesis of Pseudo-Terpenoids. Swamy Peraka, Badaraita Gorachand, Akram Hussain, Revoju Sravanthi, and Dhevalapally B. Ramachary. *Eur. J. Org. Chem.* **2022**, DOI: 10.1002/ejoc.202200674.

3. Organocatalytic Chemoselective Reductive Alkylation of Chiral Formylcyclopropanes. Akram Hussain, and Dhevalapally B. Ramachary (*Manuscript under preparation*).

4. Organocatalytic Reductive Amination of Chiral Formylcyclopropanes. Akram Hussain, Swamy Peraka, and Dhevalapally B. Ramachary (*Manuscript under preparation*).

Oral Presentations and Conferences

1. Talk in XVII J-NOST 2022 "Synthesis of Chiral Dihydropyrans and Dihydrofurans through Organocatalytic Reductive Coupling" organized by the School of Chemistry, University of Hyderabad.

2. Talk in CHEMFEST 2021 "Synthesis of Chiral Dihydropyrans and Dihydrofurans through Organocatalytic Reductive Coupling" organized by the School of Chemistry, University of Hyderabad.

3. Attended 9th Asian Network of Natural & Unnatural Materials (ANNUM-2022) International Conference organized by the Department of Chemistry, University of Delhi.

4. Attended Prof. A. Srikrishna memorial Lecture Series in 2017, 2019, and 2021 at the University of Hyderabad.

5. Attended CHEMFEST 2017, 2018, 2019, 2021, and 2022 organized by the School of Chemistry, University of Hyderabad.

6. Attended Nobel Symposium 2021 organized by the University of Hyderabad.

Direct Organocatalytic Reductive Alkylation/Amination of Chiral Formylcyclopropane: Scope and Applications

by Akram Hussain

Direct Organocatalytic Reductive Alkylation/Amination of Chiral Formylcyclopropane: Scope and Applications

ORIGINALITY REPORT

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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Swamy Peraka, Akram Hussain, Dhevalapally B. Ramachary. " Modular Access to Chiral 2,3-Dihydrofurans and 3,4-Dihydro-2 -pyrans by Stereospecific Activation of Formylcyclopropanes through Combination of Organocatalytic Reductive Coupling and Lewis-Acid-Catalyzed Annulative Ring-Opening Reactions ", The Journal of Organic Chemistry, 2018 Publication	24%
2	Swamy Peraka, Akram Hussain, Dhevalapally Buchi Ramachary. "Modular Access to Chiral 2,3-Dihydrofurans and 3,4-Dihydro-2H-pyrans by Stereospecific Activation of Formylcyclopropanes through Combination of Organocatalytic Reductive Coupling and Lewis acid-catalyzed Annulative Ring-Opening Reactions", The Journal of Organic Chemistry, 2018 Publication	13%

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3	Mohammed Anif Pasha, A. Vamshi Krishna, Etikala Ashok, Dhevalapally B. Ramachary. "Organocatalytic Reductive Propargylation: Scope and Applications", The Journal of Organic Chemistry, 2019 Publication	1 %
4	Topics in Current Chemistry, 2014. Publication	1 %
5	www.pubfacts.com Internet Source	1 %
6	Iker Riaño, Uxue Uria, Efraím Reyes, Luisa Carrillo, Jose L. Vicario. "Organocatalytic Transannular Approach to Stereodefined Bicyclo[3.1.0]hexanes", The Journal of Organic Chemistry, 2018 Publication	<1 %
7	Albert Moyano, Ramon Rios. "Asymmetric Organocatalytic Cyclization and Cycloaddition Reactions", Chemical Reviews, 2011 Publication	<1 %
8	Casper Larsen Barløse, Niklas Lawaetz Østergaard, René Slot Bitsch, Marc Vejlgaard Iversen, Karl Anker Jørgensen. "A Direct Organocatalytic Enantioselective Route to Functionalized trans - Diels - Alder Products Having the Norcarane Scaffold", Angewandte Chemie International Edition, 2021 Publication	<1 %

9	Jia-Lu Zhang, Wen-Long Ye, Jie Zhang, Xiu-Qin Hu, Peng-Fei Xu. "Enantioselective Construction of Polycyclic Indazole Skeletons Bearing Five Consecutive Chiral Centers through an Asymmetric Triple-Reaction Sequence", Organic Letters, 2021 Publication	<1 %
10	Fang-Zhi Hu, Hui Chen, Xiao-Ying Xu, Wei-Cheng Yuan, Xiao-Mei Zhang. " Dynamic Kinetic Resolution in Enantioselective Reductive Amination of -Branched Aldehydes by Lewis Base Organocatalyzed Hydrosilylation ", ChemistrySelect, 2017 Publication	<1 %
11	Meazza, Marta, Maria Ashe, Hun Yi Shin, Hye Sung Yang, Andrea Mazzanti, Jung Woon Yang, and Ramon Rios. "Enantioselective Organocatalytic Cyclopropanation of Enals using Benzyl Chlorides", The Journal of Organic Chemistry Publication	<1 %
12	Yamamoto, Yoshihiko, Shota Mori, and Masatoshi Shibuya. "Ruthenium-Catalyzed Transfer-Hydrogenative Cyclization of 1,6-Diynes with Hantzsch 1,4-Dihydropyridine as a H 2 Surrogate", Chemistry - A European Journal, 2013. Publication	<1 %

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