Development of Organocatalytic [3+2]- and [3+3]-Cycloadditions and Michael Reactions

A Thesis
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By

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DEDICATED TO

MY PARENTS

DECLARATION

I hereby declare that the entire work embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the guidance of ***Prof. Dhevalapally B. Ramachary*** *and that it has not been submitted elsewhere for any degree or diploma and that all the sources I have used or quoted have been indicated and acknowledged as complete references.*

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CERTIFICATE

*Certified that the entire work contained in the thesis entitled "**Development of Organocatalytic [3+2]- and [3+3]-Cycloadditions and Michael Reactions**" has been carried out by **Mr. Thipparthi Prabhakar** under my supervision and the same has not been submitted elsewhere for a degree.*

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

Course code	Name	Credits	Pass/Fail
1. CY-502	Advanced Organic Synthesis	3	Pass
2. CY-801	Research Proposal	3	Pass
3. CY-802	Chemistry Pedagogy	3	Pass
4. CY-805	Instrumental Methods	3	Pass

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(***Thesis Supervisor***)

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Development of Organocatalytic [3+2]- and [3+3]-Cycloadditions and Michael Reactions

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T. Prabhakar Reddy

Preface and Motivation

Direct organocatalyzed asymmetric reaction along with enamine formation found its discovery after many scientists envisioned the importance of weak interactions involved in antibody catalyzed reactions. The very first utilization and demonstration of the combination of covalent and non-covalent (weak interactions) interactions of organophosphine and amino acid catalyst in the intra-, intermolecular reactions and many cyclization, cycloaddition began the revolution of organocatalysis. The development and growth of asymmetric organocatalysis has become immense in the past decade due to the multi-tasking ability and these are usually cheap to prepare and readily accessible in a range of quantities, suitable for small-scale reactions to industrial-scale reactions. Nevertheless, asymmetric reactions include thiourea activated Michael reactions, amine activated Diels-Alder reactions through iminium or hydrogen bonding activation and nucleophilic phosphine catalyzed cycloadditions through zwitterion formation and many more, discovered based on the construction of covalent and non-covalent interactions from organocatalysts. All these catalysts together to allows the chemical transformations under mild reaction conditions in environmentally friendly and provides straightforward access to enantiopure products and it has been well explored in the past decade.

*The present thesis entitled "**Development of Organocatalytic [3+2]- and [3+3]-Cycloadditions and Michael Reactions**" describes the fully functionalized five membered drug-like molecules synthesis through organophosphinecatalysis. We have designed the syntheses of several biologically active nitrogen heterocycles through 1,3-dipoles and neighbouring group participation in sequential reactions. In all sections, a brief introduction is provided to keep the present work in proper perspective. The compounds are sequentially numbered (bold) and references are marked sequentially as superscript and listed at the end of the thesis. All the figures included in the thesis were obtained by DIRECT PHOTOCOPY OF THE ORIGINAL SPECTRA, and in some of them uninformative areas have been cut to save the space.*

The first chapter demonstrates a novel approach for the synthesis of highly substituted 5-alkylidene-2-cyclopentenones through the triphenyl phosphine-catalyzed

self annulative dimerization of ynones with moderate to good yields and high selectivities. In this protocol, ynone acts as both C2 and C3 synthons, which undergo [3 + 2]-annulative dimerization via in situ generated zwitterion intermediate under mild conditions. Many cyclopentenones have found wide range of applications in biological, medicinal and organic chemistry and also serve as intermediates in many synthetic transformations.

The second chapter demonstrates a novel approach to the one-pot, three component reaction of the amino acid-catalyzed [3+2]-cycloaddition for the synthesis of medicinally/materialistically important poly-functionalized spiroindane-1,3-dione-pyrazolidinones from indane-1,3-diones, aldehydes and N,N-cyclic azomethine imines and also we demonstrated the scope of new two component click reaction of azomethineimine-olefin [3 + 2]-cycloaddition for the synthesis of drug-like spiroindane-1,3-dione-pyrazolidinones by using many examples with high reactivity, selectivity and yields.

The third chapter, fascinating to study the [3+3]-cycloaddition of p-quinols with 1,3-dipoles of azomethine imines to construct six-membered tricyclic oxadiazines molecules. This catalytic [3+3]-cycloaddition afforded the biologically relevant products of tricyclic-oxadiazines in very good to moderate yields with excellent diastereoselectivity under the catalytic amount of brønsted base. The advent of p-quinols brought the prospect of a complementary mode of catalytic [3+3]-cycloaddition for synthesis of heterocyclic molecules, with the potential for savings in cost, time and energy, an easier experimental procedure.

The fourth chapter demonstrates a novel approach for the asymmetric synthesis of highly substituted dihydroquinolines through organocatalysis, where the neighboring ortho-amino group engaged sequential Michael/amination/dehydration reactions on (E)-2-(2-nitrovinyl)anilines with cyclic and acyclic β-keto esters in the presence of a catalytic amount of Rawal's quinidine-NH-benzyl squaramide followed by TFA.

LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
AcONa	sodium acetate
Ac_2O	acetic anhydride
Anal.	analysis
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*t*-butyloxy carbonyl
Bp	boiling point
br	broad
Bu	butyl
*t*Bu or ^{t}Bu	*tertiary*-butyl
n-BuLi	*n*-butyl lithium
BLA	Barbas-List aldol reaction
BzOH	benzoic acid
calcd.	Calculated
cat.	Catalytic
cm	centimeter
COSY	correlation spectroscopy
CSP	chiral stationary phase
dABq	doublet of AB quartet
DABCO	1,4-diazabicyclo[2.2.2]octane
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
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DMAP	dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPP	diphenyl prolinol
DPPP	1,3-Bis(diphenylphosphino)propane
DPP-OTMS	diphenyl prolinol trimethyl silyl ether
dr	diastereomeric ratio
dt	doublet of triplet
ee	enantiomeric excess
eq.	equation
equiv.	equivalent(s)
ESI-HRMS	Electrospray ionization-High resolution mass spectrometry
Et	ethyl
EWG	electron withdrawing group
Fg	functional group
Fig.	figure

gm	gram (s)
h	hour (s)
Hz	hertz
Hex	hexyl
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
i-Pr	isopropyl
IBX	2-Iodoxybenzoic acid
IR	infrared
lit.	literature
LUMO	lowest unoccupied molecular orbital
m	multiplet
m-CPBA	*m*-chloro perbenzoic acid
M	molarity
MCC	Multi-catalysis cascade
Mp.	melting point
Me	methyl
mg	milligram (s)
mL	milliliter
mmol	millimole
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidine
NSAIDs	non-steroidal anti-inflammatory drugs
OM	*oxa*-Michael
PCC	pyridinium chlorochromate
Ph	phenyl
Pg	protecting group
PMHS	Polymethylhydrosiloxane
ppm	parts per million
pre-TS	*pre*-transition state
p-TSA	*p*-toluenesulfonic acid
py	pyridine
pr	propyl
q	quartet
rt	room temperature
s	singlet
sec	secondary
SMA	sequential Michael/acetalization
t	triplet
td	triplet of doublet
tert	tertiary
TBS	*tertiary* butyl dimethyl silyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Thr	Threonine
TLC	thin layer chromatography
TMS	trimethylsilyl
TCRA	three component reductive alkylation
Trp	Tryptophan
TsCl	*p*-toluenesulphonyl chloride
Ts	Toluenesulphonyl
TS	Transition state
UV	ultraviolet

Development of Organocatalytic [3+2]- and [3+3]-Cycloadditions and Michael Reactions

1. ABSTRACT

In chapter 1, we have developed a novel umpolung [3+2]-annulative dimerization of ynones to synthesize functionally rich 5-alkylidene-2-cyclopentenones. There are many biologically active molecules which contains alkylidine cyclopentenone as their core skeleton. It acts as a building block for several natural products due to the possibility of a wide range of functionalizations at the enone motif. There is a need for the development of straightforward, simple and flexible synthetic protocol for accessing 5-alkylidene 2-cyclopentenones. Thus, we have developed a new protocol for the direct synthesis of 5-alkylidene-2 cyclopentenones through the triphenyl phosphine-catalyzed umpolung [3+2]-annulative dimerization of ynones. Herein, ynone acts as both C2 and C3 synthons, which undergo [3+2]-annulative dimerization.

In chapter 2, we explored a new click reaction which is useful in many aspects of organic chemistry. We were interested to know about *N*,*N*-cyclic azomethine imines, stable and quite readily accessible 1,3-dipoles, which have been successfully utilized in 1,3-dipolar [3+2]-cycloaddition reactions for the construction of structurally diverse *N*,*N*-bicyclic pyrazolidinone motifs. Herein, we reported an organocatalytic [3+2] cycloaddition of azomethine imine-olefin with different aldehydes, indane 1,3-diones and *N*,*N*-cyclic azomethine imines through amino acid-catalysis. This organocatalytic reaction excelled itself in terms of reactivity, selectivity and yields. It became one of the versatile click method for the synthesis of drug-like funtionalized spiroindane-1,3-dione-pyrazolidinones from simple precursors through amino acid catalysis.

In chapter 3, we have synthesized agrochemically useful tricyclic-oxadiazines, which are structurally important and functionally rich. Despite of their structural simplicity, *p*-quinols (4-alkyl-4-hydroxy-2,5-cyclohexadienones) and their derivatives always had a vast potential as significant building blocks in the synthesis of several natural products such as cleroindicins C, D, and F, (−)-mesembrine, and clerobungin A. Thus, by choosing *p*-quinols

as our starting material we succeeded in synthesizing functionally rich tricyclic-oxadiazines through straight forward Brønsted base-catalyzed [3+3]-cycloaddition with differently substituted azomethine imines. This catalytic [3+3]-cycloaddition resulted in the biologically relevant products of tricyclic-oxadiazines in very good to moderate yields with excellent diastereoselectivity. The reaction has proven itself in terms of atom economy, chemo- and stereoselectivity.

In chapter 4, we developed an asymmetric method to synthesise highly functionalized 1,4-dihydroquinolines in an optically pure form from *N*-protected-(*E*)-2-(2-nitrovinyl)anilines with *β*-keto esters through enolate-catalysis. This general approach to the asymmetric synthesis of highly substituted 1,4-dihydroquinolines was achieved through neighboring *ortho*-amino group engaged sequential Michael/amination/dehydration reactions on (*E*)-2-(2-nitrovinyl)anilines with cyclic and acyclic *β*-keto esters in the presence of a catalytic amount of Rawal's quinidine-N*H*-benzyl squaramide followed by TFA. We succeeded in synthesizing enantioenriched and highly functionalized 1,4-dihydroquinolines.

2. INTRODUCTION

Asymmetric synthesis is one of the important branch in chemistry. In that, catalytic asymmetric cascade or domino reactions are widely used for the synthesis of valuable natural products which involve the construction of new C-X (X= C, N, O, S, halogen) bonds. As a result, there are many methods available for C-X bond formation, which mainly proceeds through one of the following pathways such as Aldol, Mannich, Michael, aminoxylation, Henry and cycloadditions. However, stereoselective C-C bond formation is of utmost importance in organic chemistry and fascinate synthetic chemists. Over the past few decades, many chemists made their tremendous contributions for stereoselective C-C bond formations through organocatalytic cycloaddition and Michael reactions. Among those reactions, organocatalytic cycloaddition and Michael reactions have drawn special attention in synthetic chemistry community because of their easy handling and advantages in synthesizing various complex molecules in high enantioselective manner which are useful in synthesizing biologically active compounds.

The research work discussed in this thesis deals with three different parts as shown below.

i) [3+2]-Cycloaddition through organophosphine catalysis.

ii) [3+2]- and [3+3]-Cycloadditions through amino acid/base catalysis.

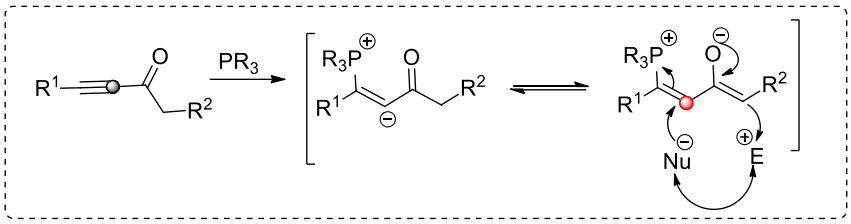
iii) Asymmetric Michael reaction through organocatalysis.

We have given brief introduction on each subdivision of above research areas from the past decade developments in next section.

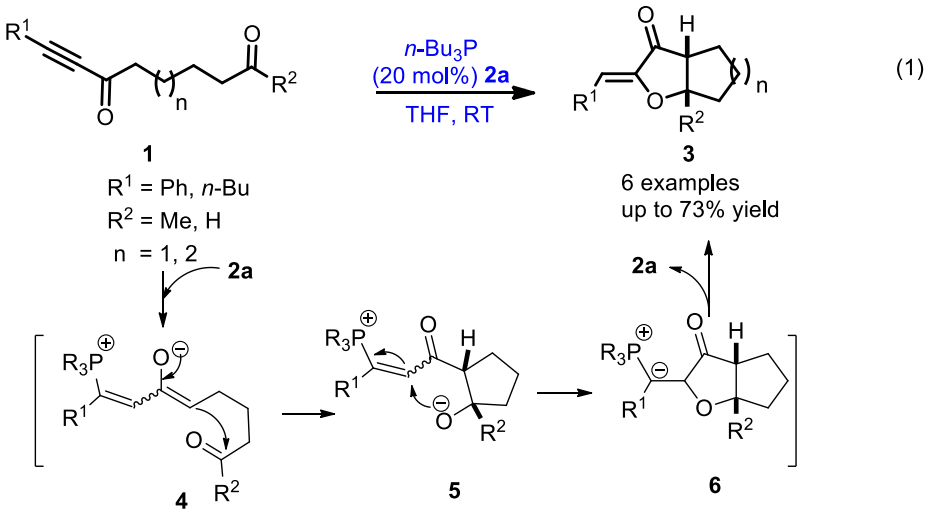
2.1) Brief Introduction for Cycloadditions through Organophosphine Catalysis:

In the last decade, the chemistry community was in a huge need for the synthesis of bioactive compounds by using simple and multi-functionalized/multicomponent starting substrates. In that point of view, enone and ynone analogues are structurally important because they are found in many synthetic and naturally occurring compounds, due to their interesting reactivity's. Therefore, in many reactions such as aldol reaction, Michael/aza-Michael, Diels-Alder and cyclizations, enone and ynone moieties have shown high regio-, chemo-, enantio- and diastereoselectivities due to their versatile reactivities. Traditionally, ynone moieties have proven their worth in enzymatic, metallic and organocatalysis. More recently, organophosphine catalysis has emerged as a useful and eco-friendly strategy for the synthesis of different compounds in many recent competitive research areas. Most importantly, in various asymmetric organophosphinecatalysis, conjugate addition of catalytic amount of phosphorus plays a prominent role. In many cases, addition, non-stabilized zwitterion formation and elimination are well known steps in organophosphine catalysis for the construction of new C-C and C-X (N,O,S,P) bonds in target synthetic molecules. Most importantly under organophosphinecatalysis, ynones have shown unprecedented reactivity, which is famous in many cycloaddition and cyclization for construction of new C-C bond containing highly chemo-, stereoselective five and six member hetero and carbocyclic rings under catalytic conditions.

Reactivity of organophosphine catalysis

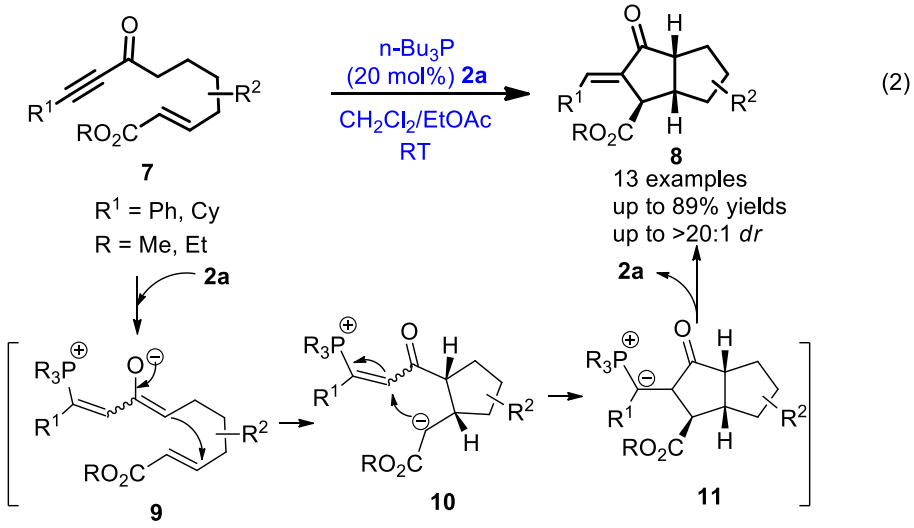


In 2002, Tomita and co-workers synthesized carbocyclic five-, six-membered ring fused motifs from aliphatic diyne-diones and yne-diones through phosphinecatalyzedintramolecularzipper cyclization with high regio- and diastereoselectivity by generating two new stereocenters. Herein, authors designed a novel method of cyclization of diyne monomers by using simple phosphine-catalysis. However, in this tandem reaction, at first phosphine nucleophile attacks ynone **1** (mainly on symmetrical substrates) *via* conjugated addition which results in zwitterionic intermediate**,** which further undergoan intramolecular proton migration from α-methylene to produce the enolate **4**. Subsequently, intermediate enolate **4** nucleophilically adds to the carbonyl group and produces alkoxide intermediate *cis*-**5** and *trans*-**5**. (Based on PM3 molecular orbital calculations of model compounds, in which all *cis*-**5** forms are thermodynamically more stable than *trans*-**5** forms). The *cis*-alkoxide intermediate **5** then undergoes an intramolecular addition to produce *cis*-**6**, which eventually gave bicyclic products **3** *via* intramolecular proton migration and elimination of phosphine **2a** respectively as shown in eq. 1.[1]



(1)

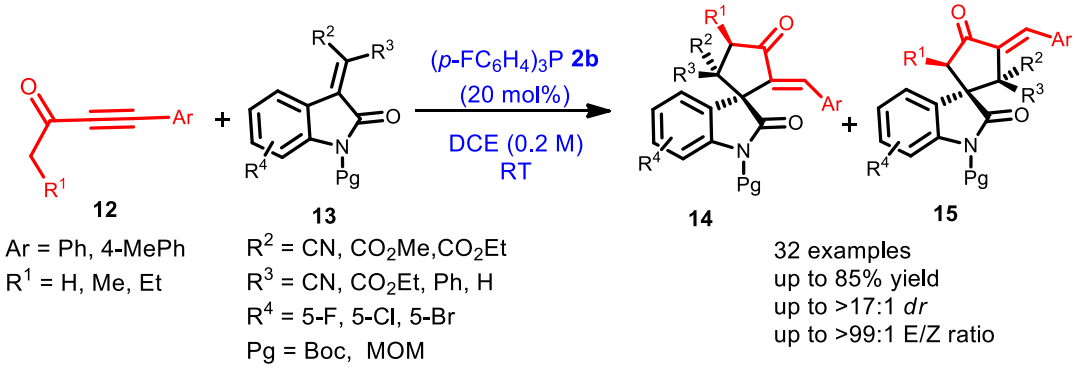
In 2010, Fu and co-workers envisioned the synthesis of an important intermediate *i.e.* functionalized diquinanes moieties, which are biologically and pharmaceutically important from acyclic precursors. In this report, authors used the strategy of Tomita zipper cyclization for the synthesis of diquinanes **8** products from simple ene-yne substrates. However, the yne-enone **7** substrate has undergone Tomita zipper cyclization, and surprisingly gave the enolate intermediate **9**, which further underwent an intramolecular Michael addition rather than an aldol reaction, eventually resulted in a single diastereomer **8** containing two new rings and three new stereo centers with excellent yield. Furthermore, the same strategy was applied for developing five and six membered ring systems with an additional stereocenter promising excellent yields and stereoselectivity as shown in eq. 2.[2]



(2)

In 2013, our laboratory developed an unprecedented [3+2]-cyclization reaction for synthesis of simple and novel functionalized five-membered spiroxindoles analogs through chemo- and stereoselective phosphine catalysis *via* Tomita zipper cyclization (TZC) as a key step. However, the intermolecular Tomita Zipper cyclization between ynone **12** and unmodified olefin **13** is not known for spirocarbocyclic synthesis. Herein, our laboratory performed one-pot synthesis through organophosphinecatalyst, olefin and ynone, which furnished the highly functionalized spirooxindoles **14**/**15** in good yields (up to 85%) and excellent stereoselectivities (up to >17:1*dr*, and up to >99:1E/Z) as shown in eq. 3.[3] Here, zwitterion intermediates **16a**/**16b** were confirmed by ^{31}P NMR analysis under the catalytic

amount of phosphine. Which is treatment with substituted olefins **13** gave highly functionalized regio- and stereoselective spirooxindoles **14** and **15.** The high selectivity of TZC is due to *in situ* generated (*Z,Z*)-enolate, which makes strong electronic (CH-π) interactions with olefins **13**, which was confirmed by the control experiments and also X-ray structure analysis.



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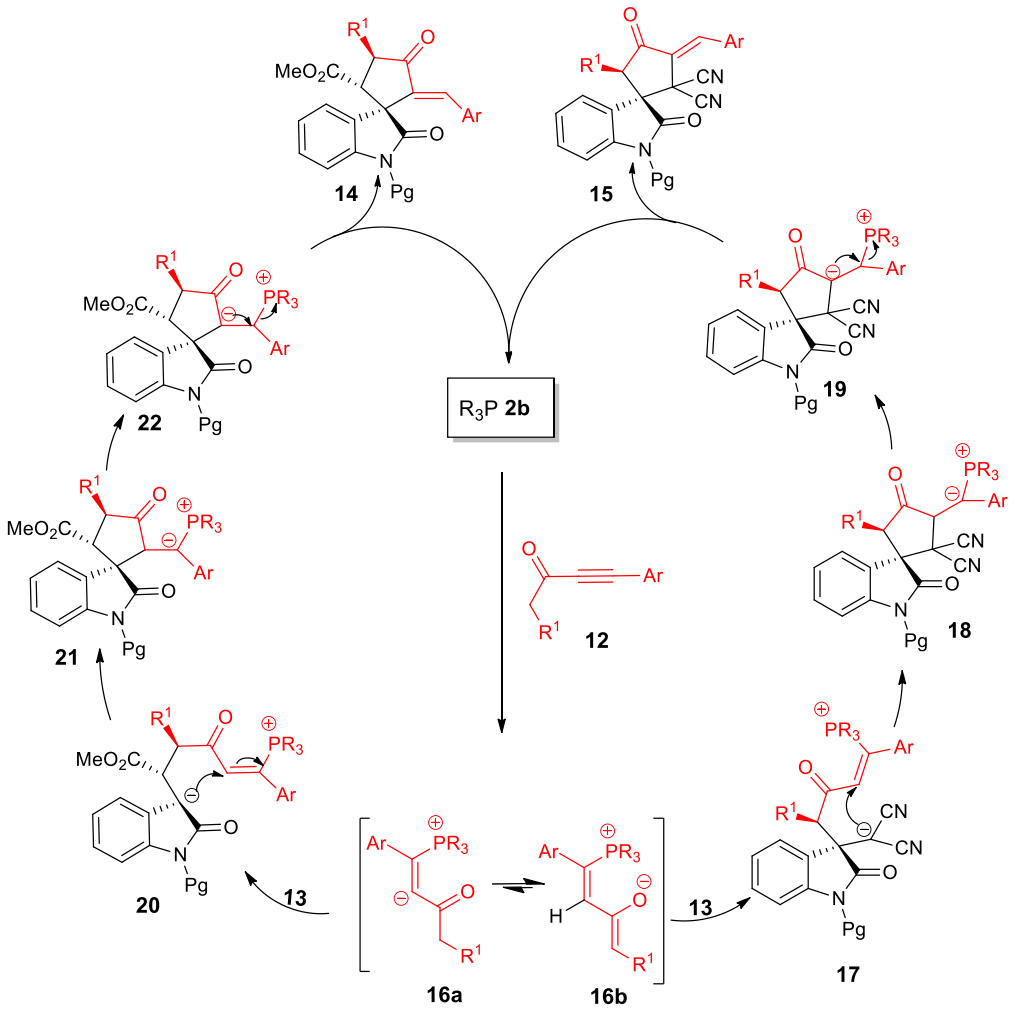
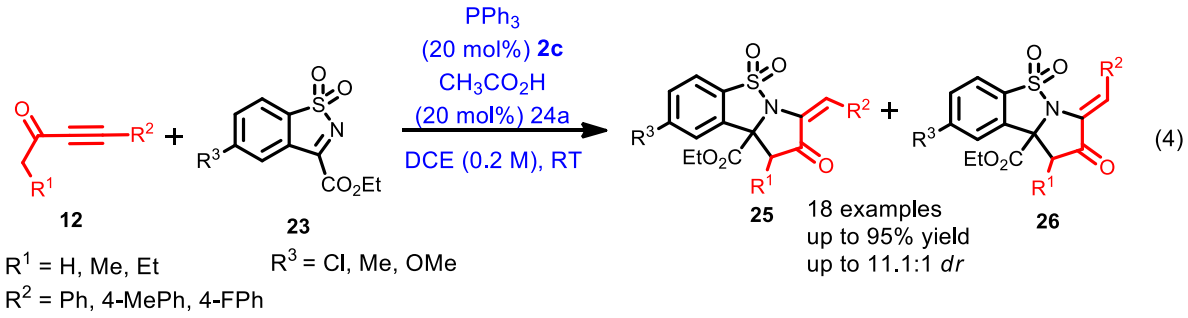


Over the past few years, use of nucleophilic phosphine-catalyzed annulation reactions was attracting the chemistry community for wide spectrum of their biological activities of the products formed. Earlier, from our lab, we developed a highly functionlized five-membered spirooxindoles by using ynones and modified isatin moieties through Tomita zipper-cyclization (TZC) strategy. Further in continuation of our work, In 2016, we reported a metal-free, in expensive, novel and green technology for the synthesis of functionalized drug-like cyclopentanone-fused benzosultams using organophosphinecatalysis. In this report we have utilized the concept of Tomita zipper-cyclization for the synthesis of various benzosultams **25**/**26** products from commercially available ynones **12**, modified cyclic *N*-sulfonyl*α*-iminoesters **23**, PPh_3 **2c** and CH_3CO_2H **24a** as shown in eq. 4.[4]



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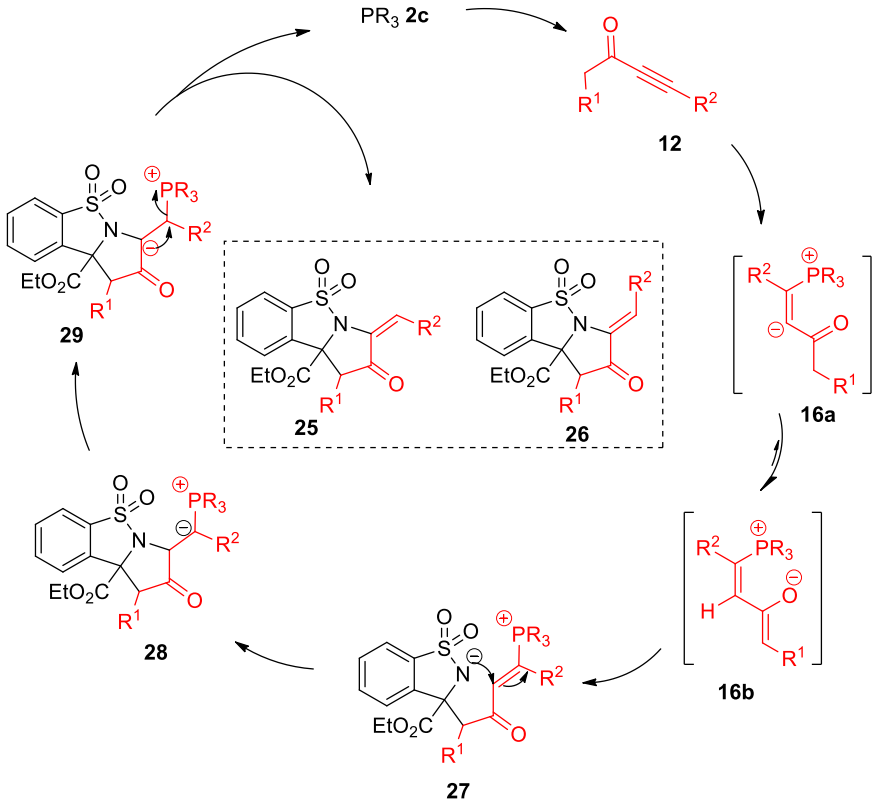
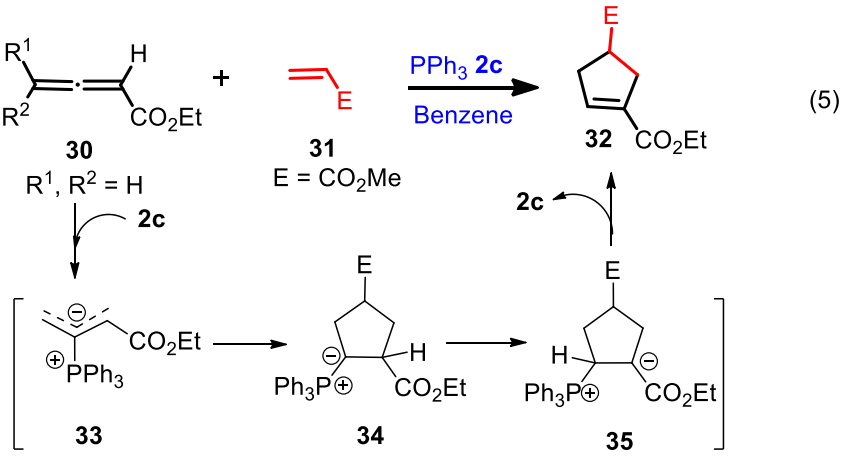
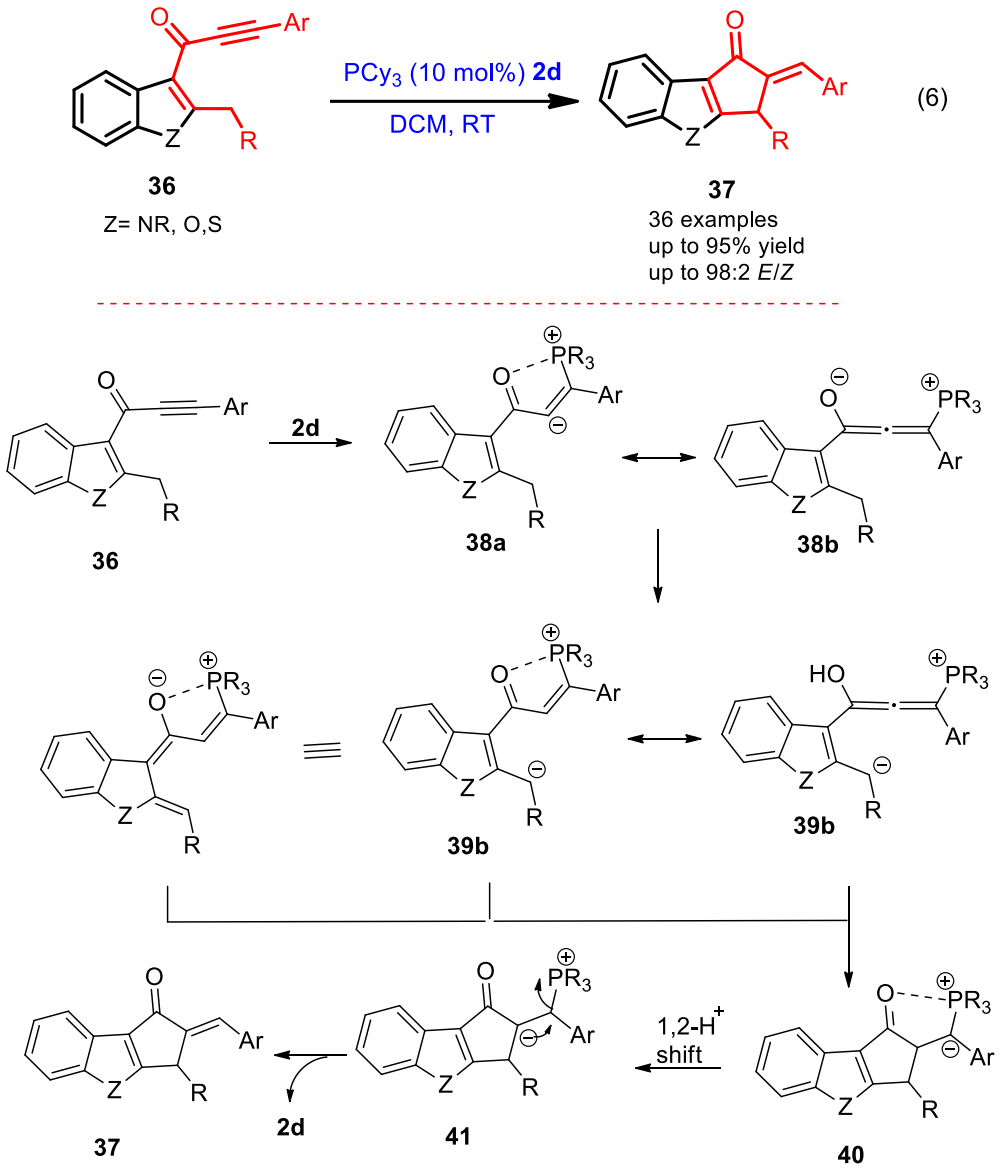


In 2007, Yu and co-workers studied the role of a trace amount of water in phosphinecatalyzed [3+2]-cycloaddition of allenoates **3**0 and alkenes **31**. In this report, authors disclosed the theoretical and experimentally studied an amount of water existing in [3+2]-Cycloaddition system plays an important role in the process of [1,2]-proton shift. However, first in Lu reaction under phosphine catalysis form zwitterionic intermediate of all enoates is slightly exothermic in the gas phase. Which is subsequently react with acrylate to generate ring-closer intermediate *via* Michael addition stepwise process with very close energy in gas and solution phase. The formation of zwitterionic intermediate **34** from **33** which is exothermic by 13.9 kcal/mol. So, the formation of **34** is not favorable thermodynamically. Then intermediate **34** convert to **35** *via* [1,2]-proton transfer and its activation free energy is 39.3 kcal/mol and 39.6 kcal/mol in the gas phase and in benzene solution. Which indicate that the formation of **34** to **35** step is not favorable kinetically. Finally, with these results the Lu [3+2]-cycloaddition are usually performed at rt as shown in eq. 5.[5]



In 2016, Ramasastry and co-workers developed a γ [C(sp^3)-H]-functionalization of ynones for the synthesis of new five–membered contain heteroarenes through organophosphinecatalysis. Which are prevalent in several bioactive natural products and pharmaceutically important. In this report, authors were studied nucleophile phosphine react with designed ynones to generate zwitterionic intermediate **38a/38b** by the activation of

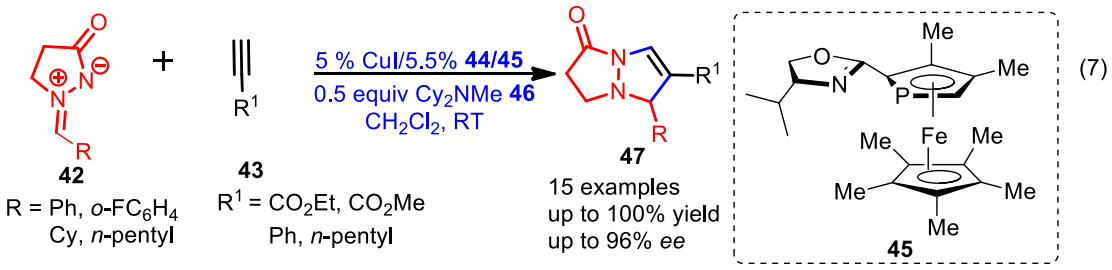
γ [C(sp^3)-H] ynone **36**, which involves intramolecular [1,5]-proton migration to furnish heteroaryl-based *ortho*-quinodimethane (oQDM) **39a/39b**. Which is eventually gave cyclopenta-fused heteroarene product **37** *via* intramolecular cyclization subsequent [1,2]-proton shift and elimination of phosphine **2d** respectively with good yields and excellent stereoselectivities as shown in eq. 6.[6]



(6)

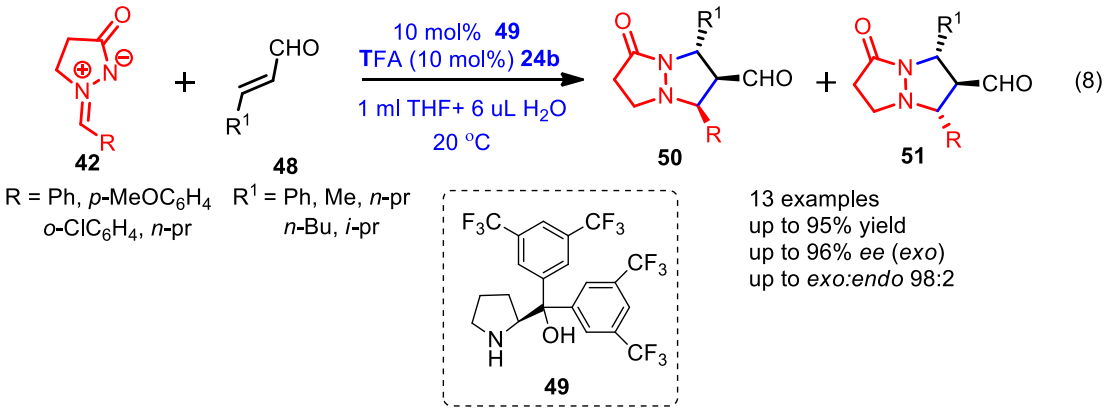
2.2) Brief Introduction for [3+2]- and [3+3]-Cycloadditions through Amino acid/base Catalysis:

In 2003, Fu reported 1,3-dipolar cycloaddition of modified azomethine imines and terminal alkynes in the presence of chiral Cu(I)/ligand **44/45** catalyst, which proceeded highly enantioselective manner to produce nitrogen fused heterocyclic compounds *via in situ* generated Cu(I)-acetylide. As a part of screening, authors investigated the reaction with variety of Cu(I)/ ligands and unfortunately got very poor selectivity. Surprisingly, in case of Cu(I) **44**/**45** catalytic condition, cycloaddition took place smoothly to give corresponding hetero-cyclic products **47** with excellent yields (up to 100%) and high enatioselectivities (up to 96% *ee*) in DCM at rt as shown in eq. 7.[7] In this report, various aromatic, hetero aromatic and aliphatic substrates with respect to the azomethine imine **42** and terminal alkynes **43** were found to be well tolerated by Cu(I)/**45** catalytic condition.

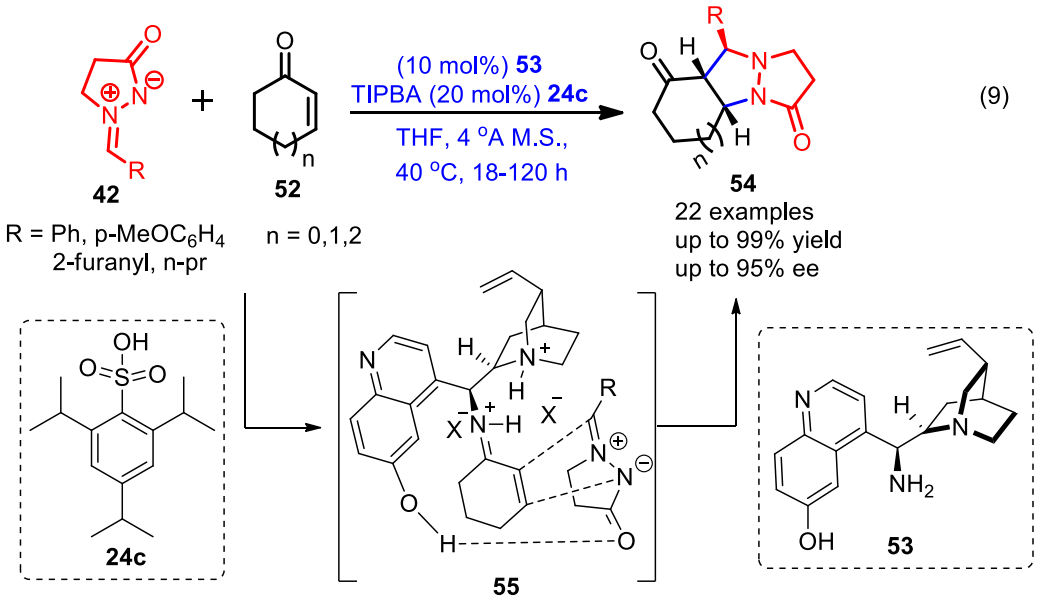


In the past two decades, the number of organocatalyzed reactions increased due to easy availability of catalysts. For example, Chen and co-workers developed an organocatalyzed stereoselective cycloaddition in 2006, which deals with the [3+2]-cycloaddition of *α,β*-unsaturated aldehydes **48** and azomethine imines **42** for the synthesis of enantioselective chiral bicyclic derivatives **50**/**51** under amine **49** catalyst with combination of acid **24b** as a additive. During the mechanistic investigation, they found *α,α*-diarylprolinol catalyst forms (*E*)-iminium or (*Z*)-iminium isomer intermediates with cinnamaldehyde **48**, which then attacks azomethine imine **42** with high selectively to generate bipyrazolidin-3-one derivatives with excellent enantioselectivity (up to 97% *ee*, up to 98:2 *exo:endo*) and

excellent yields (up to 95%) under 10 mol% of TFA **24b** and 10 mol% of **49** in mixture of solvents (THF+H_2O) at rt as shown in eq. 8.[8]

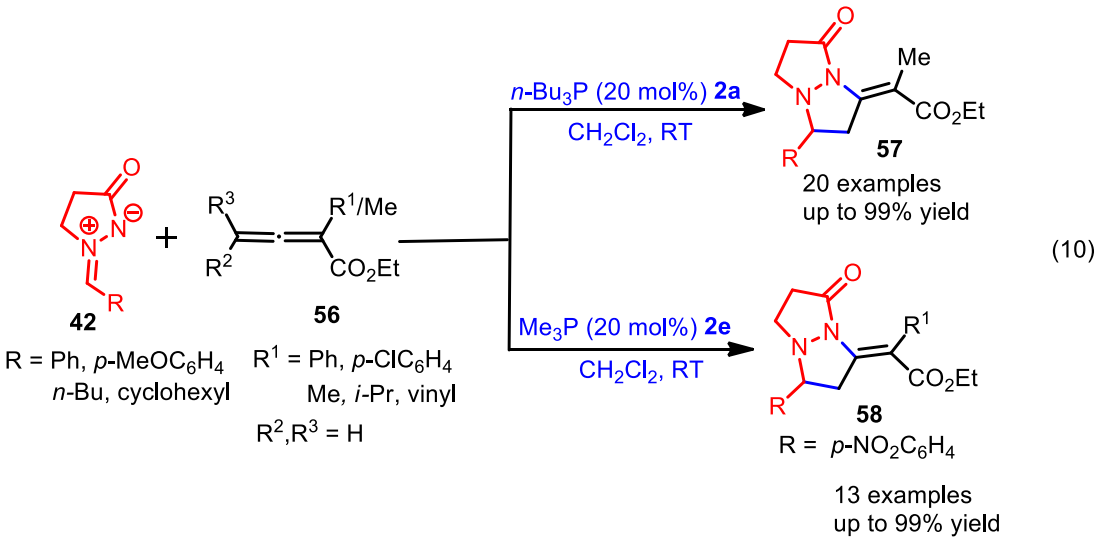


Chen and co-workers recently established the use of bifunctional organocatalysis in [3+2]-cycloaddition for the synthesis of new chiral five-membered fused heterocyclic molecules. Herein, particularly the catalyst has a Bronsted acidic site and Lewis basic site in one molecule which activate starting substrates (electrophile and nucleophile) for the formation of highly selective heterocyclic rings. However, the cycloaddition of 2-cyclohexen-1-one **52** and azomethine imine **42** under primary amine **53** catalysis in combination with TIPBA **24c** resulted in the products **54** with excellent enantioselectity. After these interesting results, authors realized that, primary amine part of the catalyst activated 2-cyclohexen-1-one



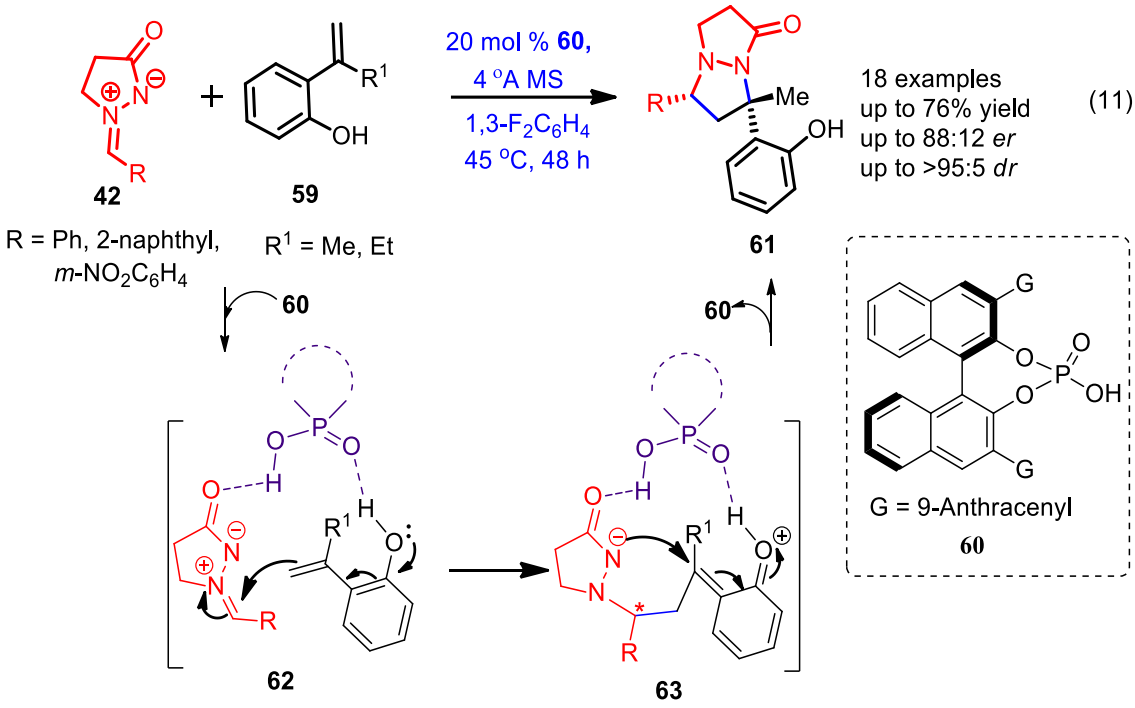
by the formation of ketiminium ion and aromatic hydroxyl group of catalyst activated azomethine imine through hydrogen bonding to leads intermediate **55,** which can judge selectivity and yield of the product. Finally, researchers observed 10 mol% of derived cinchona alkaloid **53** and 20 mol% of TIPBA **24c** additive at 40 °C in THF provided excellent stereoselectivities (>99:1*dr*, up to 95% *ee*), yields (up to 99%) with broad spectrum of substrates in 1,3-dipolar cycloaddition as shown in eq. 9.[9]

In 2011, Risong Na *et al.* described variety of [3+2]- and [3+3]-annulations by active azomethine imines and allenoates through organophosphine catalysis for the synthesis of different *N,N*-fused heterocycles such as tetrahydropyrazolo-pyridazinones, -diazocinones and -diazepinones. All these reaction were performed smoothly under mild nucleophilic phosphinecatalysis. In this communication, 20 mol% of PBu_3 **2a** nucleophilic catalyst actively interacted with substituted azomethine imines **42** and ethyl 2-methyl-buta-2,3dinoate to afford [3+2]-annulation products **57** (tetrahydropyrazolopyrazolones) with moderate to excellent yields (up to 97%) as shown in eq. 10.[10] Upon further investigation, [3+2]-annulation of substituted allenoates **56** with azomethine imine **42** in the presence of 20 mol% of PMe_3 **2e** afforded five membered *N,N*-fused heterocyclic tetrahydropyrazolopyrazolones **58** derivatives in excellent yields (up to 99%) as shown in eq. 10.[10]

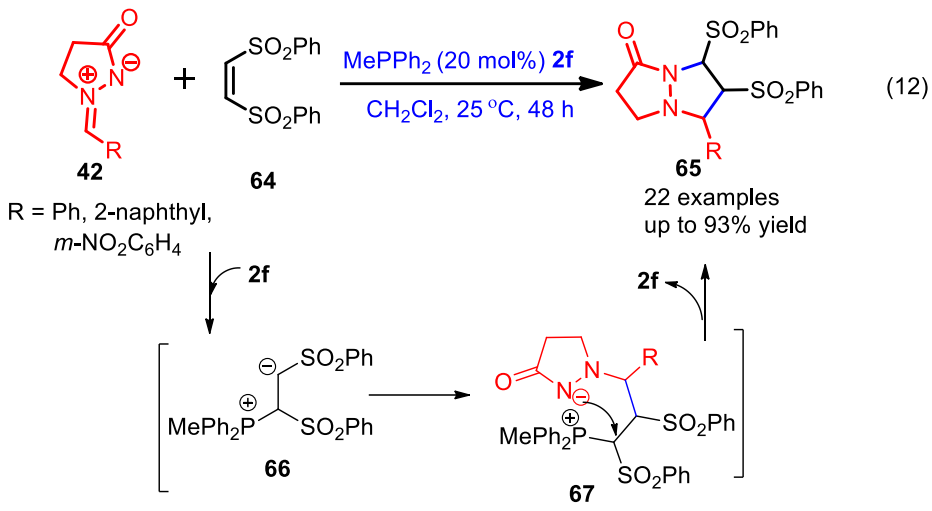


(10)

In the subsequent communication by Shi and co-workers reported the synthesis of chiral *N*,*N*-bicyclic pyrazolidin-3-one derivatives containing four consecutive stereogenic centers by utilizing NGP (Neighbouring group participation) concept in the presence of phosphoric acid. In this communication, the chiral phosphoric acid **60** catalyst form dual hydrogen bonding interacted by azomethine imines **42** and derived *o*-hydroxystyrenes **59**, in which hydroxyl group played important role in the designed asymmetric inverse-electron demand 1,3-dipolar cycloaddition (IED 1,3-DC) for excellent stereoselective synthesis of (up to >95:5 *dr*, 88:12 *er*) of *N*,*N*-fused pyrazolidin-3-one products **61** *via in situ* generated transition intermediates **62** and **63** as shown in eq. 11.[11]

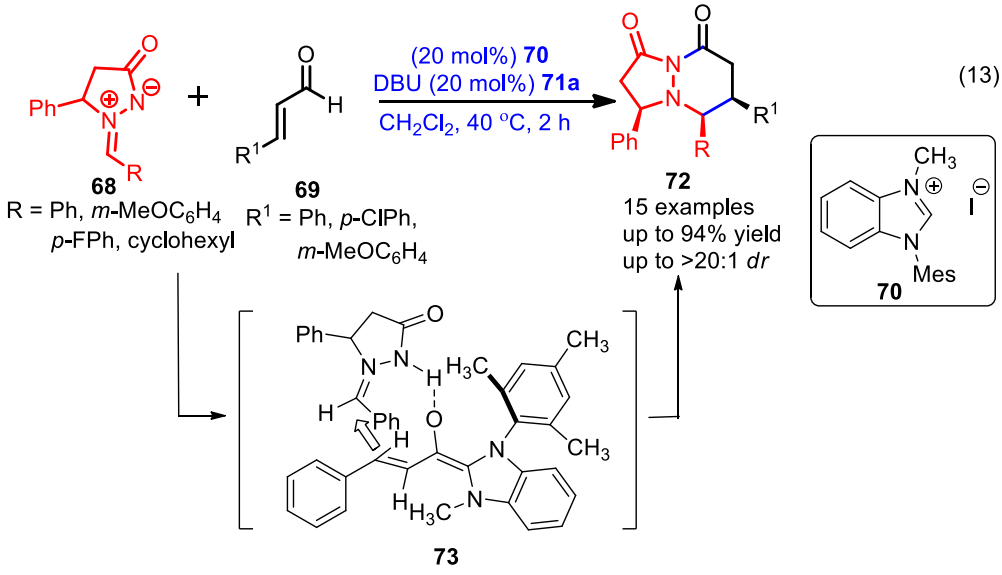


In 2014, Guo and co-workers demonstrated the preparation of new five member *N*,*N*-fused heterocyclic compounds **65** from active azomethine imine **42** and (*Z*)-1,2-bis(phenylsulfonyl)ethylene **64** using a mild organophosphinecatalyst in DCM at rt. By this method, all derivatives such as electron donating, electron withdrawing and different hetero-rings on azomethine imine were successfully tolerated by phosphine catalyst **2f** to afford [3+2]-cycloadduct with excellent yield (up to 93%) as shown in eq. 12.[12] However, these heterocyclic compounds **65** contain two phenylsulfonyl groups which are essential because of the possibility of their easy transformation into variety of functional groups by simple traditional methods with moderate to good yields.



(12)

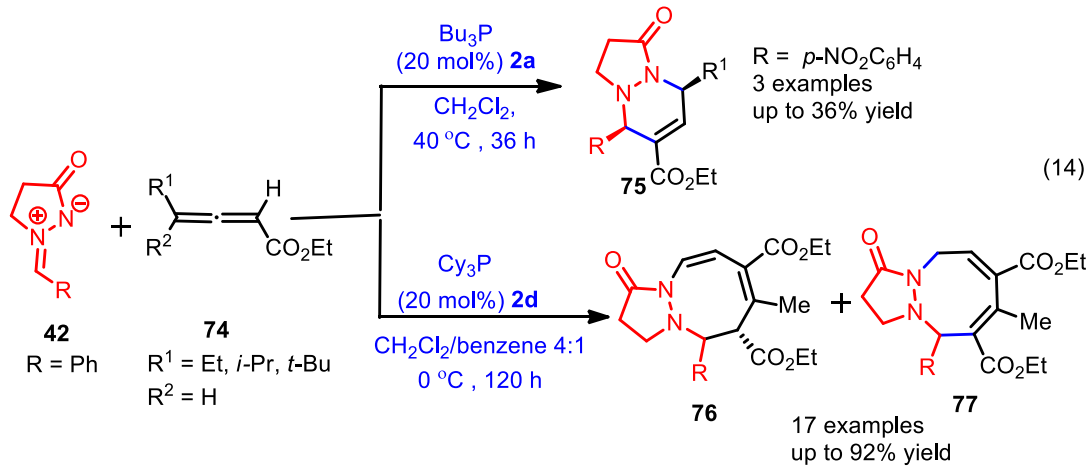
In 2007, Scheidt and co-workers disclosed the intermolecular [3+3]-cycloaddition of **68** and **69** by using N-heterocyclic carbenes **70**. In this report, the *α,β*-unsaturated aldehydes **69** reacted with azomethine imines **68** to afford fused-heterocyclic pyridazinones **72** in excellent yields (up to 94%) and excellent diastereoselectivities (>20:1 *dr*) as shown in eq. 13.[13] However, in NHC catalysis, there will be formation of a carbene in the presence of base **71a** (DBU 20 mol%). This carbene interacts with aldehyde to form Breslow intermediate, Which then adds on to the azomethine imine generating an enol which eventually forms pyridazinone followed by elimination of NHC catalyst through formation of



(13)

enoltautomerization, heteroazolium intermediate and intramolecular acylation reaction sequence as shown in eq. 13.

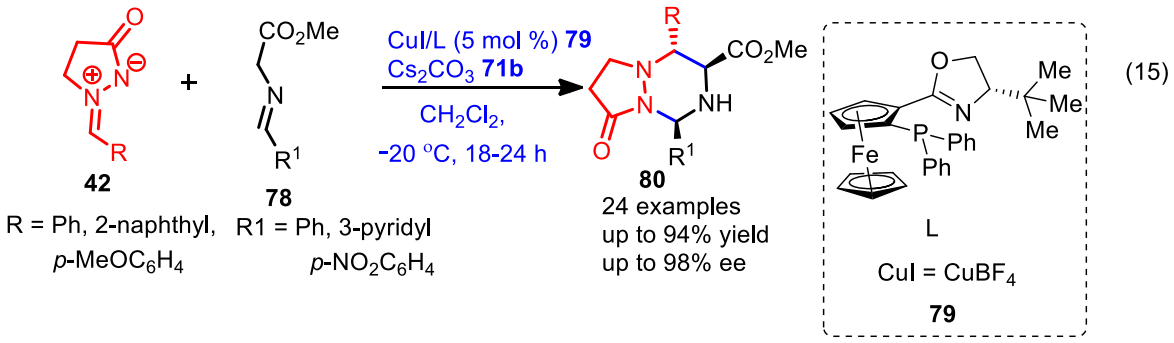
In 2011, Risong Na *et al.* described variety of [3+2]-annulations. Further extension of this work proceeded through the reaction of substituted allenoates **74** (ethyl 2,3-butadinoates) with azomethine imine **42** under 20 mol% of PBu_3 **2a**, which interestingly provided [3+3]-annulation products **75** in moderate yields along with several multiple spots (unknown products) as shown in eq. 14.[10] Later, they showed their interest in solving the multiple spots which formed in the above reaction. Eventually, with the assistance of X-ray crystallography and NMR data, they confirmed the unknown products as the equilibrium mixture of the 1-oxo-2,3,5,6-tetrahydro-1*H*-pyrazolo[1,2-*a*][1,2]-diazocine **76** derivative and the 1-oxo-2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-a][1,2]-diazocine **77** derivatives forms *via* [3+2+3] cycloaddition. In this unprecedented tetrahydropyrazolodiazocinones **76**/**77** provide excellent yield (up to 92%) by 20 mol% of PCy_3 **2d** in mixer of solvents (CH_2Cl_2/benzene 4:1) at 0 °C as shown in eq. 14.



(14)

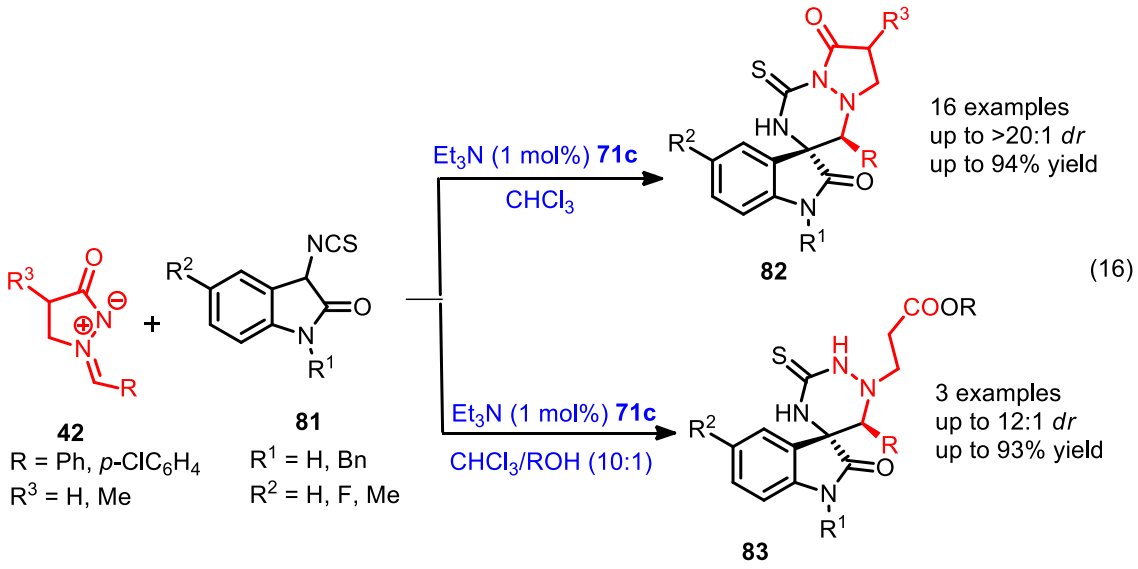
In 2013, Wang and co-workers documented an asymmetric synthesis of substituted 1,2,4-triazinane skeletons by cross 1,3-dipolar cycloaddition. In this report, they have disclosed the first Cu^I/*t*-Bu-Phosferrox complex as a catalyst by cross 1,3-dipolar cycloaddition between azomethine imine ylide **42** and *in situ* generated pyrazolidinium ylide **78** for the construction of pyrazolidinone ring contain *N*,*N*-fused 1,2,4-triazinane **80** frameworks with excellent yields (upto 94%) and enantioselectivity (up to 97% *ee*) in DCM at -20 °C as shown in eq. 15.[14] Herein, they investigated the selectivity of the product with the help of *in situ* formed ylide which coordinated with Cu^I/*t*-Bu-Phosferrox **79** complex

to generate an active species which approaches azomethine imine **42** with *exo* selectivity to form metalloazomethine ylide. Finally chiral 1,2,4-triazinane scaffolds were obtained *via* Mannich addition, *in situ* zwitterionic intermediate formation and intramolecular cyclization sequence respectively.



(15)

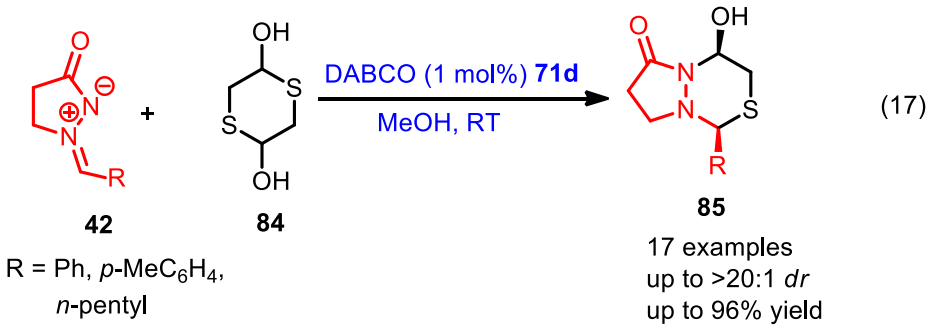
In 2013, Zhu *et al*. developed a novel method for base-catalyzed [3+3]-annulation for the synthesis of spirooxidoles. The annulation of azomethine imines **42** and 3-isothiocyanatooxindoles **81** gave excellent yield (up to 94%) and diastereo selectivities (up to >20:1 *dr*) under mild conditions (1 mol% Et_3N **71c** and $CHCl_3$ at rt) as shown in eq. 16.[15] This interesting result further extended to various synthetic transformations by methylation and ring opening to form interesting products with good yields.



(16)

In the same year, Wang and Co-workers developed DABCO-catalyzed diastereoselective [3+3]-cycloaddition of azomethine imine **42** react with 1,4-dithiane-2,5-diols **84** for the synthesis of *N,N*-fused heterocyclic molecules. Here the dimeric form of

mercaptoacetaldehyde activated by tertiary amine of DABCO **71d**, which leads to attack azomethine imine **42** and subsequent intramolecular cyclization to give highly functionalized sulfur containing six-membered dinitrogen fused heterocycle **85** with good yields (up to 96%) and excellent diastereoselectives (up to 20:1 *dr*) fashion in the presence of DABCO (1mol%) **71d** in MeOH at rt as shown in eq. 17.[16] The cycloadduct further treatment with catalytic amount of *p*-TSA.H_2O and $Et_3SiH/BF_3.Et_2O$ afforded dehydrated and reduction products with excellent yields respectively.



(17)

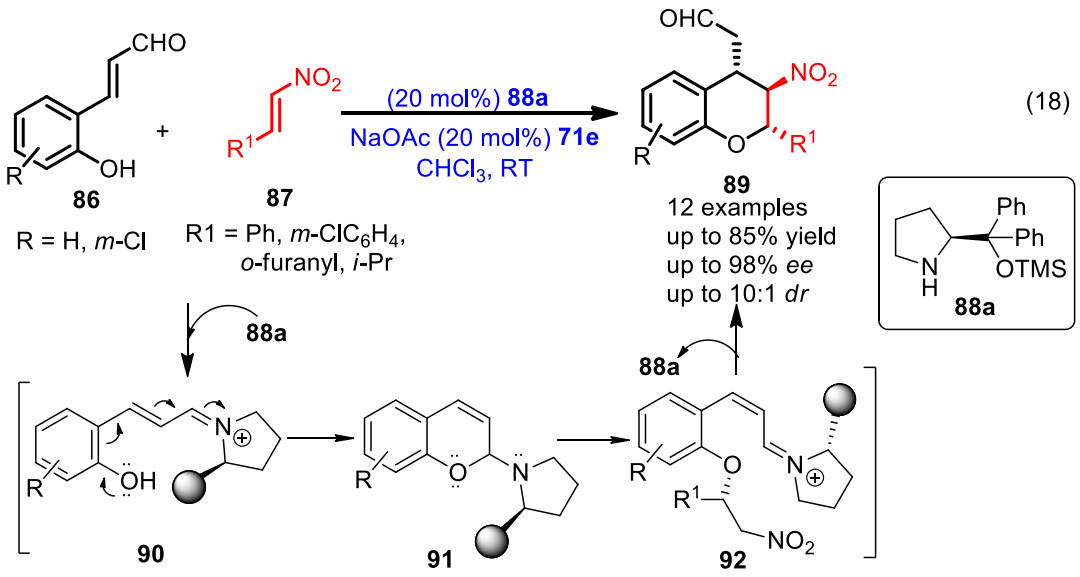
2.3) Brief Introduction for Asymmetric Michael Reactions through Organocatalysis:

Organocatalysts have several advantages as they are robust, inexpensive, readily available, non-toxic, highly chemo-, regio-, diastereo- and enantioselective. As a result of their high stereoselectivity and mild reaction conditions, protective group chemistry which results in byproducts can be avoided. Hence, asymmetric organocatalysis has become a fascinating field in the area of Michael addition reactions.

In recent years, various research groups have been actively involved in developing new synthetic pathways which are much better than the conventional pathways like NGP (Neighboring group participation) in organocatalysis (or) asymmetric supramolecular-organocatalysis by using Michael reactions as key step. In this catalysis, bifunctional hydrogen-bonding catalysts such as urea/thioureas, cinchona alkaloids/their analogues and phosphate-derived Bronsted acids joined the field to facilitate and enhance various asymmetric Michael reactions. Generally, in mechanistic point of view, there will be strong

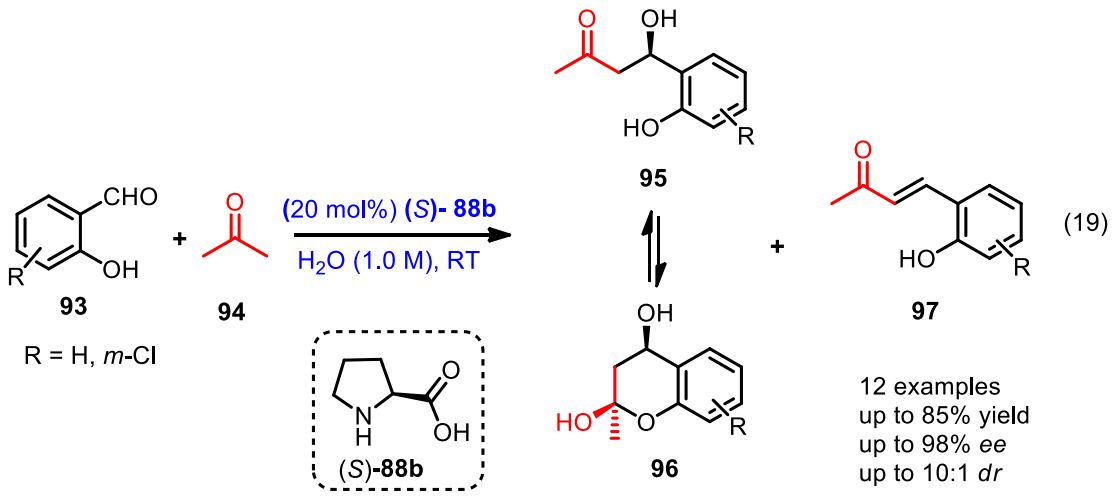
hydrogen bonding interaction between the multifunctional hydrogen bonding catalysts and substrates (nitro, carbonyl, imino, nitrile functionalities). This tendency of hydrogen bonding allows us to study various asymmetric conjugated Michael addition reactions in which bifunctional organocatalysts were used. Significantly, most of the drug molecules are highly enantioselective molecules which can be synthesized by using the recently emerging strategy of supramolecular-organocaralysis.

In 2009, Zu *et al.* reported a novel highly efficient diastereo- and enantioselective oxa-Michael/Michael addition of 2-hydroxy cinnamaldehyde **86** with trans-*β*-nitrostyrene **87** catalyzed by chiral diphenylprolinol-TMS ether **88a**, furnishing a highly useful functionalized chiral chromans with the creation of three new stereogenic centers through NGP of OH. In this paper, the authors found the combination of organocatalyst **88a (**20 mol%) with the additive NaOAc (20 mol%) **71e** to be the best, which proceeded smoothly to afford chiral trisubstituted, highly functionalized chiral chromans **89** with excellent enantiomeric excess (up to 98% *ee*) and diastereoselectivities (up to 10:1*dr*) *via* aminal **91** intermediate**.** The authors have done exploratory study through which they isolated and characterized the aminal intermediate **91,** which acts as an excellent nucleophile, rather than a free phenolic *β*–OH group for the oxa-Michael-Michael reaction in $CHCl_3$ at rt. However, the reactions were applicable to a variety of nitroalkenes **87** bearing electron-withdrawing or electron-donating group's and hetero-aryl and -alkyl groups through organocatalyzed cascade reaction. This



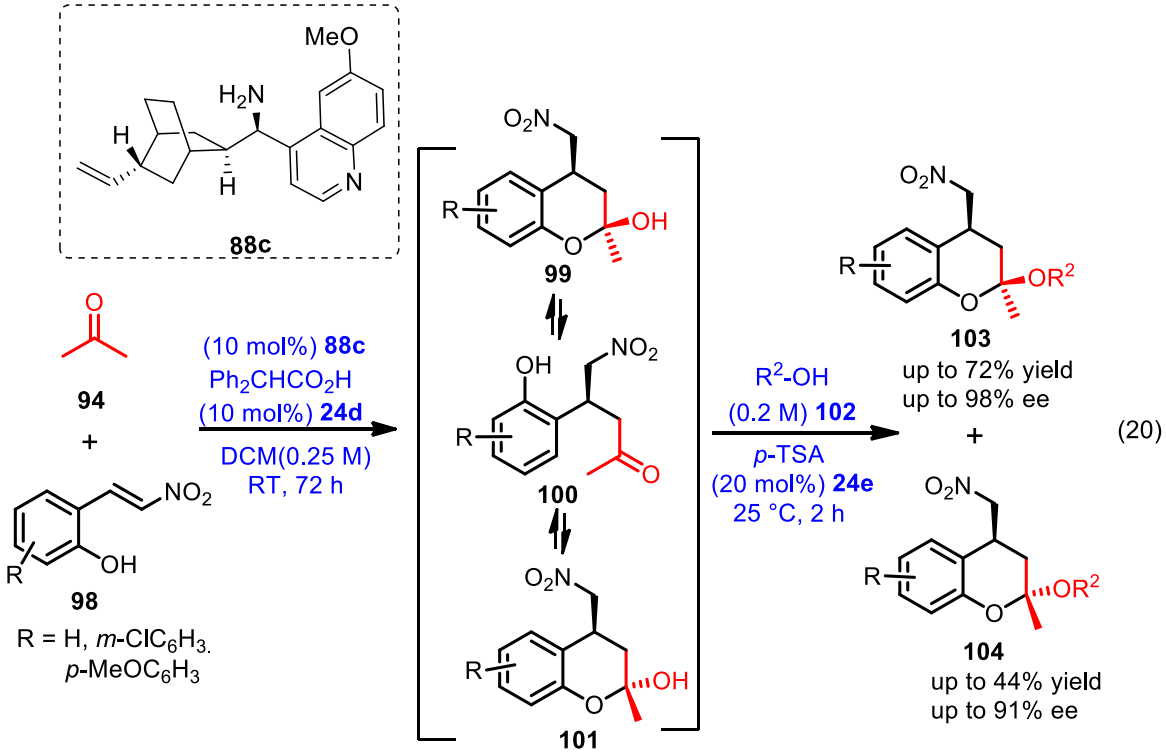
reaction also was shown to have high tolerance towards different substituted 2-hydroxy cinnamaldehydes **86** with high efficiency as shown in eq. 18.[17]

In 2009, our group developed enantioselective highly substituted 2-methylchroman-2,4-diols *via* List-Lerner-Barbas aldol reaction under the simple amino acid catalysis through NGP (Neighbouring group participation) of OH. The chromone moieties had resemblance with the skeleton of various natural products and skeletons important in both medicinal and pharmaceutical industry for the design of many synthetically important compounds with pharmacological properties. Herein, authors have intensively developed the typical route for the synthesis of chiral 2-methylchroman-2,4-diols **96** with excellent enantioselectivity (up to 90% *ee*) and high yields (up to 90%) by using the concept of NGP (Neighbouring group participation) of OH *via* LLB-A/hemiacetalization reactions from commercially available substituted salicylaldehyde **93**, aliphatic ketones **94** and amino acid **88b** under mild conditions as shown in eq. 19.[18]

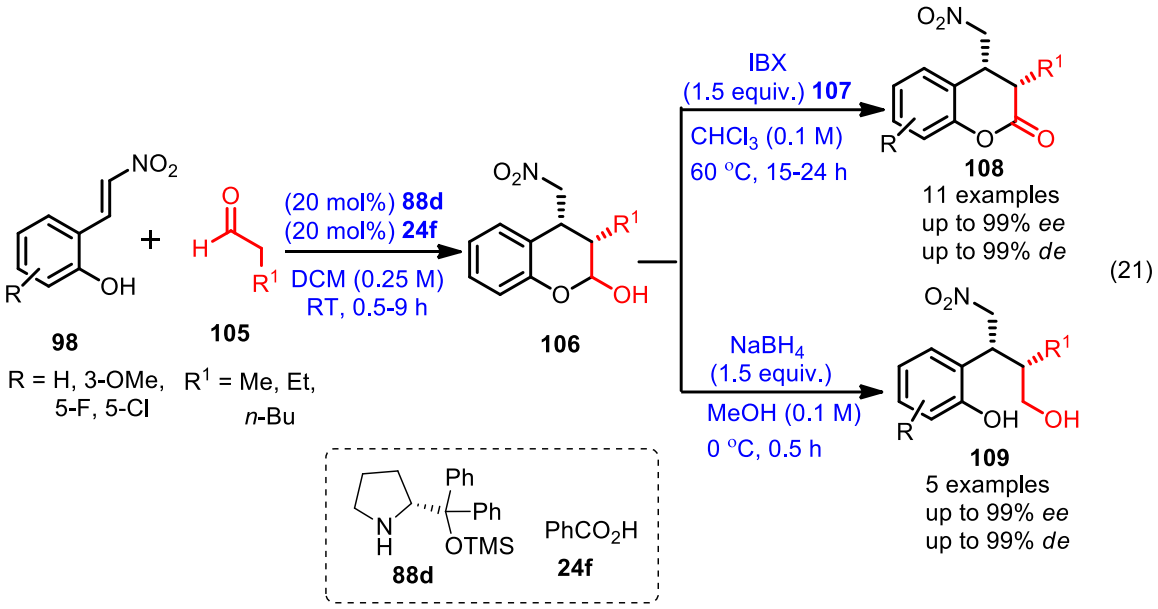


In 2010, Ramachary *et al*. reported the organocatalytic asymmetric synthesis of functionalized 2-alkoxy-2-methyl-4-nitromethyl-chromans *via* sequential Michael/acetalization reactions through NGP (Neighbouring group participation) of OH. This method provides an easy access to novel highly substituted 2-hydroxy-2-methyl-4-nitromethyl-chromans **99/101** and 2-alkoxy-2-methyl-4-nitromethyl-chromans **103/104** compounds *via in situ* generated intermediate 4(2-hydroxy-phenyl)-5-nitro-pentan-2-one **100**

in presence of a catalytic amounts of alkaloid based primary amine like 9-amino-9-deoxyepiquinine **88c** and Ph_2CHCO_2H **24d**. In this work, we studied acetone is activated by the *pre*-catalyst primary amine moiety **88c** through enamine mechanism. This reaction involves sequential Michael and acetalization reactions of acetone with 2-(2-nitro-vinyl)-phenols **98** using 10 mol% of 9-amino-9-deoxyepiquinine **88c** and10 mol% of Ph_2CHCO_2H **24d** as co-catalyst in DCM at 25 °C for 72 h furnishing the product **99/101**containing two or three contiguous stereocenters. In case of Michael adduct **100** it showed the existence of a very fast dynamic equilibrium between *cis*- and *trans*-2-hydroxy-2-methyl-4-nitromethyl-chroman **99/101** under the catalytic reaction conditions. Notably, this fascinating result represents a novel methodology for the development of an enantioselective 2-hydroxy-2-methyl-4-nitromethyl-chroman **99/101** and a new reactivity for amino acid or amine catalysts. This unexpected result **100** and **99/101**, further transformed into two easily separable sequential Michael and acetalization products *cis*-**103** and *trans*-**104** in a 1:1 ratio with high yields (up to 72%) and excellent enantioselectivity (up to 98% *ee*) *via p*-TSA (20 mol%) **24e** catalyzed acetalization reaction in MeOH/EtOH**19** at 25 °C for 2h as shown in eq. 20.[19]



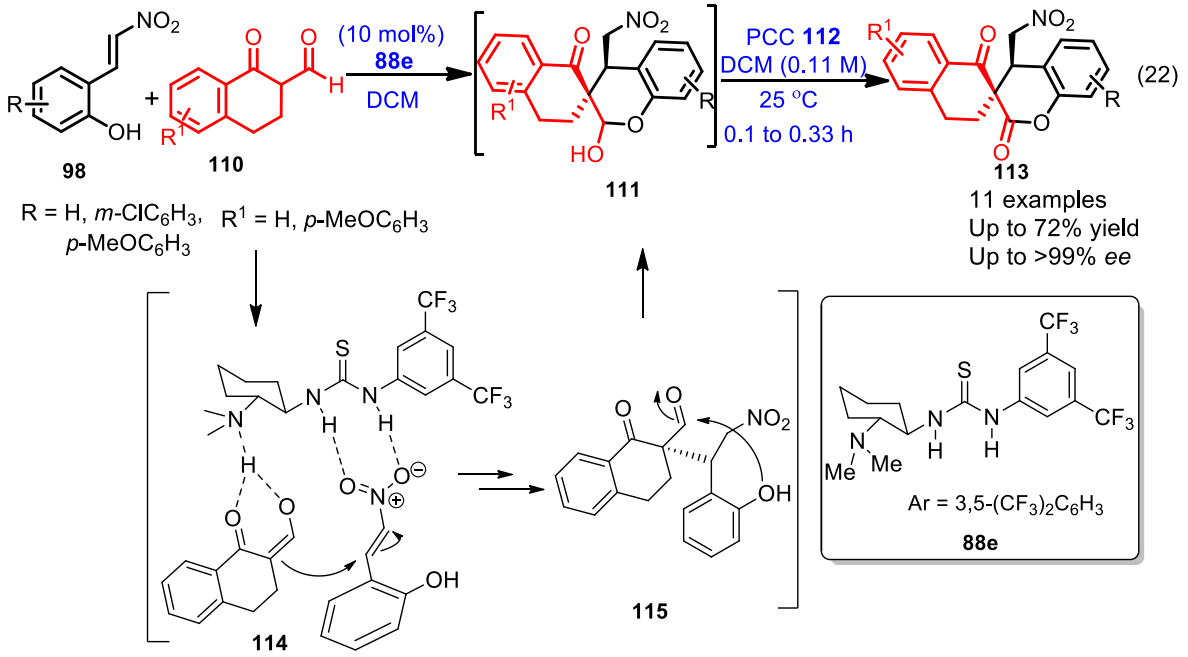
In 2011, Ramachary and co-workers, developed a chiral drug intermediates such as 3-alkyl-4-nitromethylchromans through Barbas-Michael and acetalization (BMA) reaction sequence. Here, authors utilized the concept of NGP (Neighbouring group participation) of OH on trans 2-hydroxy-*β*-nitrostyrene **98** with aldehydes **105** in the presence of derived amino acid **88d** and benzoic acid **24f** to afford the product **106** in high yields (up to 99%), which on further oxidation with IBX **107** or reduction with $NaBH_4$, furnished the products**108** and **109** respectively with excellent yield and enantio-, diastereoselectivity as shown in eq. 21.[20]



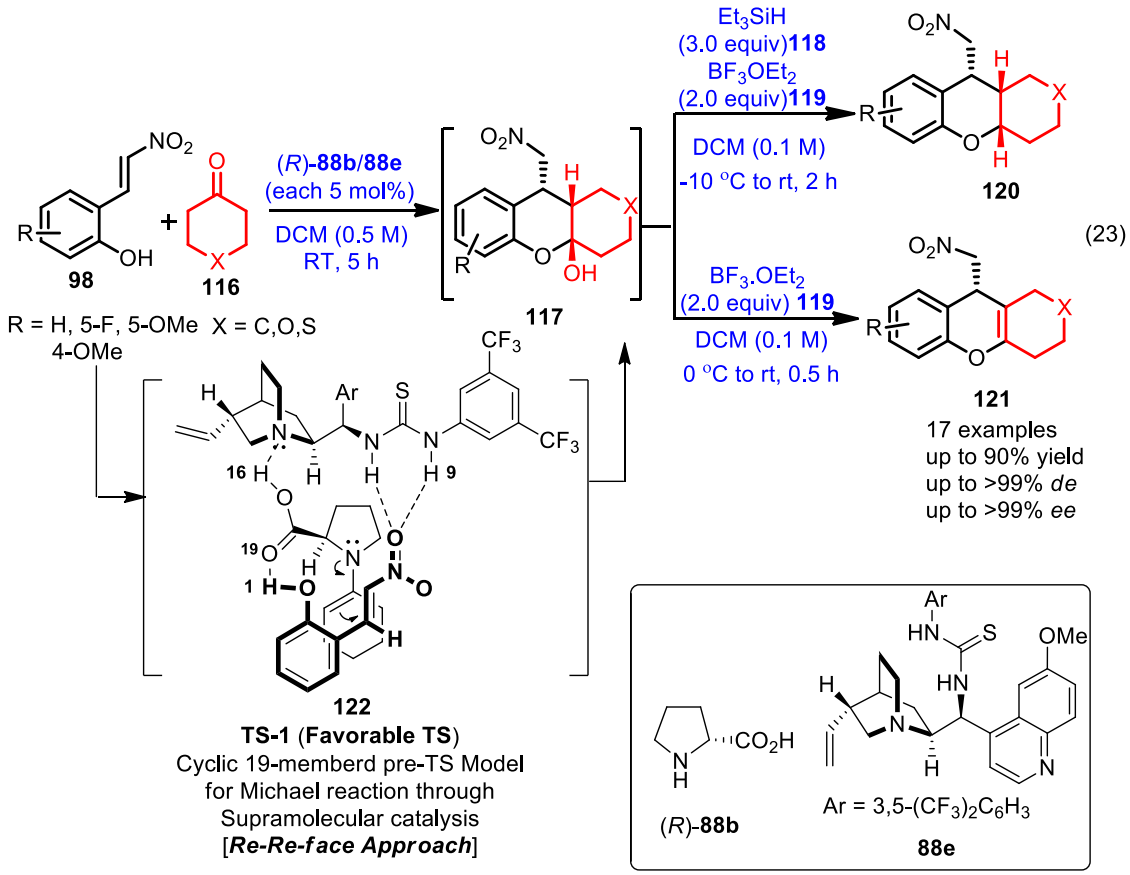
(21)

In 2011, Hong *et al.* demonstrated the use of thiourea assembly as supramolecular-organocatalyst for the highly enantioselective addition of 2-(2-nitroethenyl)phenol **98** to 2-oxocyclohexanecarbaldehyde **110**. Which display a convenient route for construction of chiral 1,3-spiro-2-oxocyclohexan-3,4-dihydrocoumarin **113**. This reaction resulted in multiple quaternary stereocenters and six membered heterocyclic spiro-system, with good yields (up to 72%) and excellent stereoselectivities (up to >20:1*dr*) and (up to 99% *ee*) *via in situ* oxidation of Michael-acetal adduct **111** as shown in eq. 22**.**[21] Herein, the authors used single bifunctional thiourea-tertiary-amine organocatalyst **88e**, which activated two substrates by forming the supramolecular assembly **114** through multiple hydrogen bonding interactions. Neverthless, these interactions are not only enhancing the reaction rate but also improves the enantioselectivity and gives a conventional asymmetric induction during the reaction progression. In this commentary, among the active sites of organocatalyst, thiourea activated

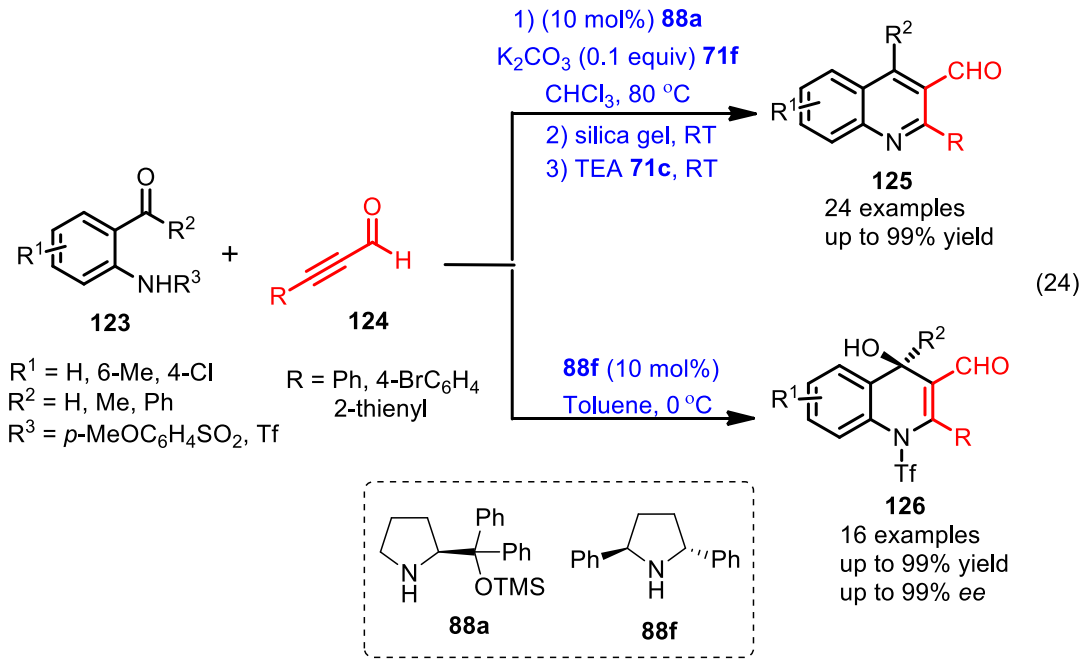
electrophile nitrostyrene **98** and the brønsted base activated enolate of the 2-oxocyclohexanecarbaldehyde triggered the asymmetric domino Michael-addition from the *Re*-face, as shown in eq. 22**.**



In 2012, Ramachary *et al.* developed a striking enamine-based Michael reaction of functionalized 2-hydroxy-*β*-nitrostyren **98** with cyclohexanone **116** under asymmetric supramolecular-organocatalysis for the synthesis of desired hexahydroxanthenols **117**. Which is further treatment with triethylsilane and $BF_3.OEt_2$ to give desired products **120/121** with excellent yields (up to 94%) and good stereoselectivity (>99% *de*, >99% *ee*). Herein, authors based on previous experience demonstrated the importance and use of neighboring multi-functional groups of 2-(2-nitroethenyl)phenol **98**, carbonyl group of proline (*R*)-**88b**. In which nitro and hydroxyl group were activated by bifunctionalthiourea and proline catalyst through multiple hydrogen bonding for the high selectivity of the Michael reaction as shownin eq. 23.[22]

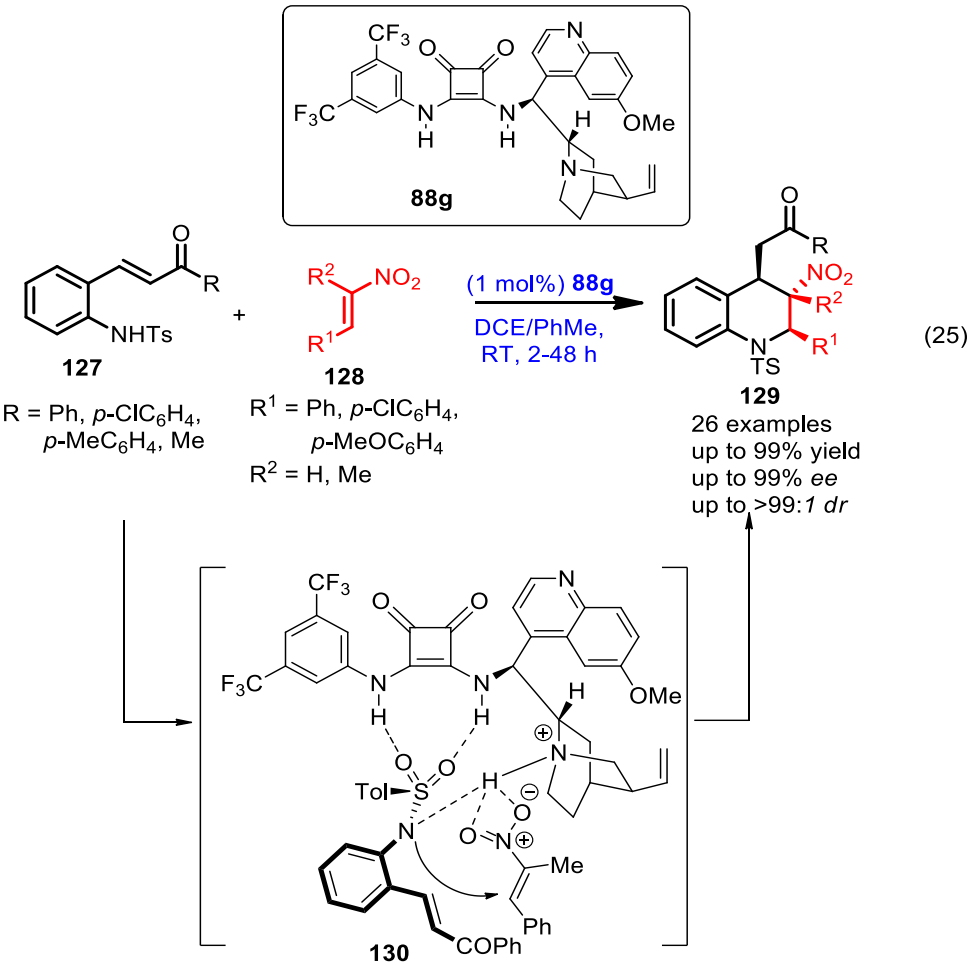


In 2012, Zhang *et al.* demonstrated an unprecedented and useful organocatalytic reaction for the synthesis of quinolones **125** and 1,4-dihydroquinolines **126**. However, this work represents one of the most straightforward method for synthesis of polysubstituted quinolones by reacting *N*-protected 2-aminobezaldehyde **123** with arylpropargyl aldehyde **124** in the presence of modified proline **88a** under basic medium **71f** (K_2CO_3) in $CHCl_3$ at 80 °C. This tandem reaction was found to proceed *via* aza-Michael/aldol/aromatization respectively to yield **125** with excellent yield (up to 99%) as shown in eq. 24.[23] However, the one-pot synthesis of chiral 1,4 -dihydroquinolines by 2'-(trifluoromethanesulfonyl)aminochalcone **123** and substituted ynals **124** under organocatalyst ((2*R*,5*R*)-diphenylpyrrolidine) **88f** in toluene at 0 °C yielded the cycloadduct with excellent yield (up to 99%) and enantioselectivity (up to 99% *ee*) *via* aza-Michael/aldol cascade reaction as shown in eq. 24.



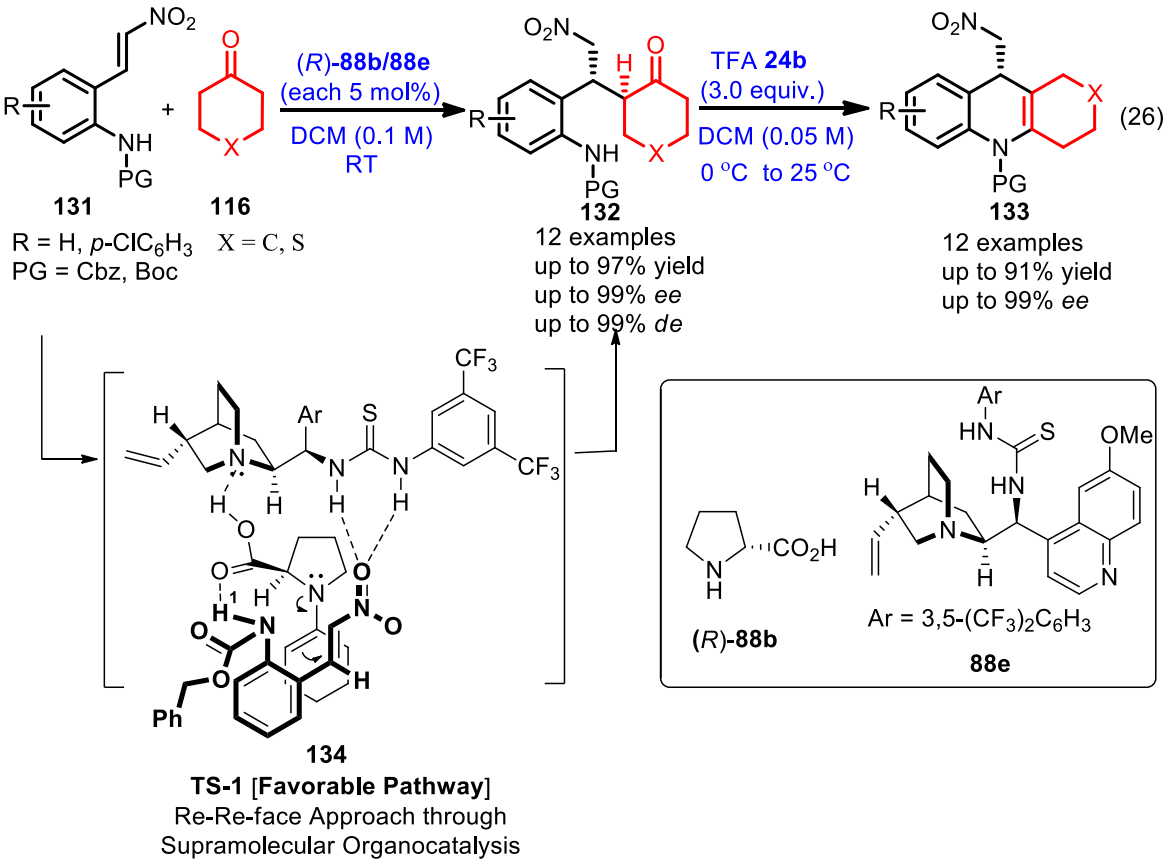
(24)

In 2010, Yang *et al.* developed a highly stereoselective functionalized tetrahydroqunolines **49** and tetrahydrochromanoquiunolines through simple organocatalytic asymmetric cascade aza-Michael/Michael addition reaction sequence. Herein, authors have shown that low catalytic loading of squaramide catalyst **88g** was effective in activating various 2-tosylaminochalcones **127** and *α*-substituted nitroalkenes **128** to yield compounds **129** with excellent yields and stereoselectivities (up to >99:1 *dr*, 99% *ee*) through asymmetrically induced cascade aza-Michael/Michael addition as shown in eq. 25.[24] The basic nitrogen atom of the quinine moiety deprotonated 2-tosylaminochalcone **127**, whereas squaramide moiety coordinated with sulfonamide moiety through hydrogen-bonds forming supramolecular clusters. While *in situ* generated nucleophile attacks on *Re*-face of nitroalkene **128** resulting *R*-configured intermediate, which was further involved in intramolecular Michael addition through the *Re*-face attack, forming three stereocenters including one quaternary center (2*R*,3*S*,4*R*-configured) products **129**.



In 2015, our group developed an efficient Michael addition reaction of *E*-2-(2-nitrovinyl)anilines **131** with cyclic/acyclic ketones **116** to generate chiral functionalized molecules **133** (chiral carbamates) through supramolecular-organocatalysis with excellent yields (up to 99%) and excellent stereoselectivities (up to 99% *de*, >99% *ee*). These fascinating results proceeded through *in situ* formation of a cyclic supramolecular self-assembled 19-membered *pre*-transition state **134** as a result of combination of covalent, hydrogen-bonding, and weak interactions among the effective catalysts and substrates in this Michael reaction. This *pre*-transition state is responsible for high asymmetric induction which was proved by experimental evidence (ESI-HRMS). However, we explored the application of the Michael products in the high-yielding enantio- and diasterioselective synthesis of tetrahydroacridines **133,** through aminal formation/dehydration of chiral carbamate **132** by

using brønsted acid trifluoroacetic acid (TFA) **24b** with excellent yields (up to 91%) and excellent enantioselectivities (up to 99% *ee*) as shown in eq. 26.[25]

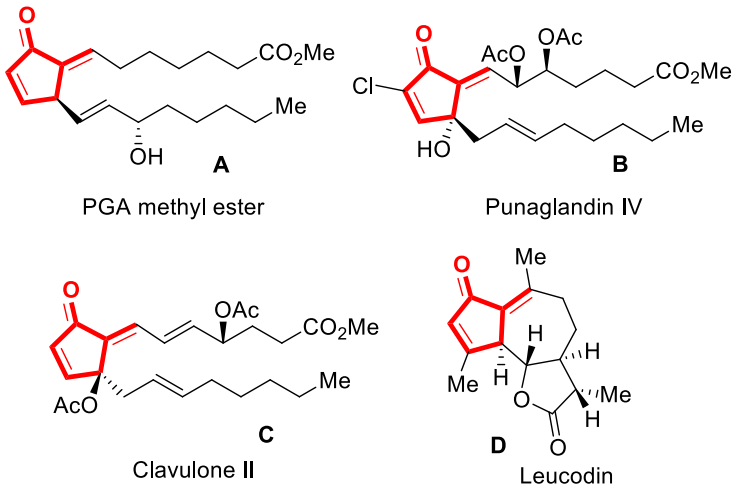


3. Organocatalytic Umpolung Annulative Dimerization of Ynones for the Synthesis of 5-Alkylidene-2-cyclopentenones

3.1 Introduction

The cyclopentenone core is a versatile building block in natural products and bioactive molecules due to the possibility of wide range of functionalizations at the enone motif.[26] Especially, prostaglandins containing cyclopentenone unit display vast biological activities such as anti-tumor, anti-viral, anti-neoplastic and anti-inflammatory activities (Scheme 1).[27]

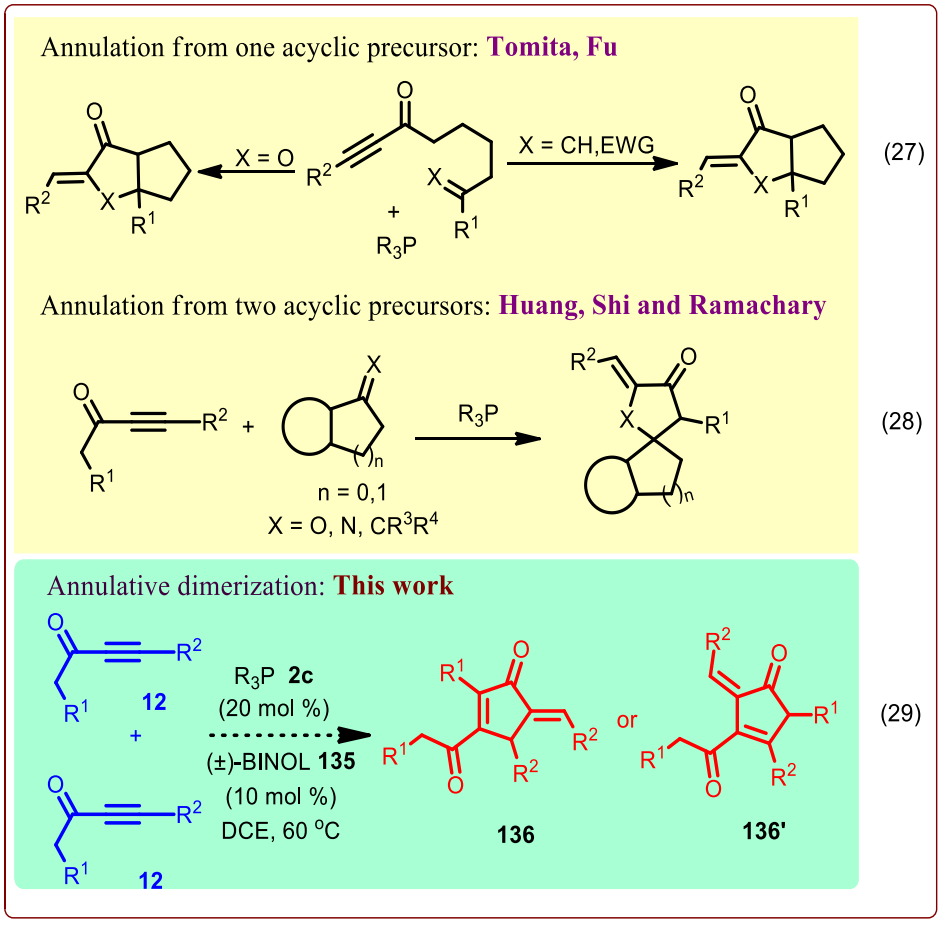
Scheme 1: Biologically active molecules containing alkylidene cyclopentenone scaffold.



Consequently, significant attention has been focused on the synthesis of this structural unit *via* Nazarov cyclization, Pauson-Khand reaction, intramolecular aldol reaction, sulfoxide elimination followed by retro-Diels-Alder reaction, allenic cyclocarbonylation of alkynones and others.[28] However, most of these methods suffer from multistep operations or low efficiency. Therefore, the development of a straightforward, simple and flexible synthetic approach is highly desirable to this class of useful compounds. Recently, Zhai et al. reported a silver-catalyzed ring-contractive rearrangement for the synthesis of 5-alkylidene-2-cyclopentenones.[29]

Over the past few decades, remarkable progress has been made for the construction of carbo- and heterocyclic compounds and natural products through phosphine-catalyzed domino reactions.[30] Overview of the previous methods revealed that activated alkenes and alkynes have been extensively studied under phosphine-catalysis.[30] Recently, the ynone motif, found in many natural products,[31] emerged as a new class of highly reactive Michael acceptor for the construction of carbo-/heterocyclic skeletons. Tomita, Fu and very recently Ramasastry groups exploited elegant phosphine-catalyzed annulation reactions from the single acyclic ynone precursor for the synthesis of carbocycles.[32] Later Shi, Huang, Guo, Yu, Ramachary and other groups studied the annulation reactions using ynone with election deficient alkenes, ketones and azomethine imines.[33] In most of the approaches, ynones acted as three-carbon synthon (C3),[33] while it has been also utilized as four-carbon synthon (C4)[34] in amine-catalysis to furnish annulation reactions.

Scheme 2: Design for the 5-alkylidene-2-cyclopentenones synthesis through umpolung annulative dimerization of ynone.



However, simultaneous generation of three-carbon synthon (C3) and two-carbon synthon (C2) from the same molecule (ynone) under phosphine-catalysis is not known and represents a great challenge for synthetic chemists. In continuation of our research on the reactivity of ynones in phosphine-catalysis, in this chapter, we report the phosphine-catalyzed [3+2]-annulative dimerization of ynones for the synthesis of multi-functionalized 5-alkylidene-2-cyclopentenones **136** or **136'** (Scheme 2).

3.2 Results and Discussions

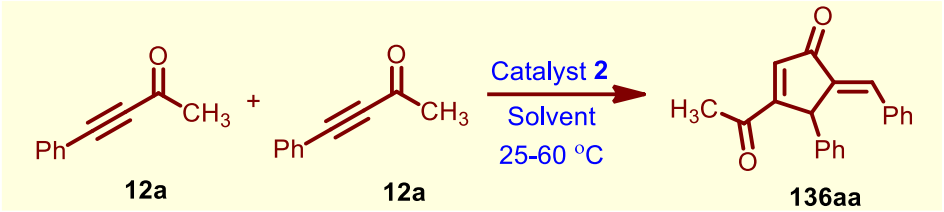
3.2.1 Reaction preliminary optimization:

The investigations were commenced with ynone **12** using 20 mol% of Ph_3P **2c** as the catalyst in HPLC grade solvent of DCE at 25 °C (Table 1, entry 1). Interestingly, we observed formation of unexpected umpolung [3+2]-annulation product **136aa** instead of expected [3+2]-annulation product **136'aa** in 58% yield after 48 h (**136'aa** is expected product based on the previous work,[30-34] see Scheme 2). The molecular structure of **136aa** was unambiguously determined based on NMR and single crystal X-ray structure analysis (Figure 1 and 8 respectively)[35] which clearly indicate the nucleophilic attack at the α-position to keto group of ynone.[36]

Intrigued by these observations, we proceeded to optimize the reaction conditions for improved catalytic system. Next, we carried out the same reaction at 60 °C to afford **136aa** in 65% yield after 13 h (Table 1, entry 2). Reaction with the other phosphine catalysts **2b** and **2g** in DCE afforded **136aa** in 42 and 63% yields, respectively (Table 1, entries 3 and 4). Switching to other HPLC grade solvents such as DCM and $CHCl_3$ gave the annulation product in moderate yields (Table 1, entries 5 and 6). In the case of $CHCl_3$, **2g**-catalysis offered **136aa** in 35% yield within 5 h, while extension of reaction time to 24 h decreased the yield (Table 1, entries 7 and 8). Based on the previous familiarity with this kind of reaction,[37b-d] we suspected that the residual water content in the HPLC grade solvent is influencing the annulation reaction. In order to prove that when we carried out the reaction in dry DCE as solvent, we observed very poor yield of **136aa**, indicating the ability of the residual water either to form hydrogen bond with the carbonyl of the ynone thereby enhancing its electrophilic nature or to act as proton source for the protonation of the in situ formed zwitterionic intermediate (Table 1, entry 9).[37] However, polar protic solvents such as ^{t}BuOH and 2-BuOH as solvent for annulation reaction did not do

well (Table 1, entries 10-12). The controlled experiment carried out under identical conditions and devoid of catalyst failed to furnish the product, despite a prolonged reaction time (Table 1, entry 13).

Table 1: Reaction optimization.[a]



Entry	Solvent (0.4 M)	Catalyst (mol %)	Temp. (°C)	Time (h)	Yield (%)[b] 136aa
1	DCE	**2c**: Ph_3P	25	48	58
2	**DCE**	**2c**	**60**	**13**	**65**
3	DCE	**2b**:(*p*-$FC_6H_4)_3P$	60	13	42
4	DCE	**2g**: (*p*-$OMeC_6H_4)_3P$	60	06	63
5	DCM	**2c**	40	09	56
6	$CHCl_3$	**2c**	60	15	53
7	$CHCl_3$	**2g**	60	05	35
8	$CHCl_3$	**2g**	60	24	28
9[c]	DCE	**2c**	60	13	10
10	^{t}BuOH	**2c**	25	24	-
11	^{t}BuOH	**2c**	60	09	32
12	2-BuOH	**2c**	25	24	-
13	DCE	-	60	48	-

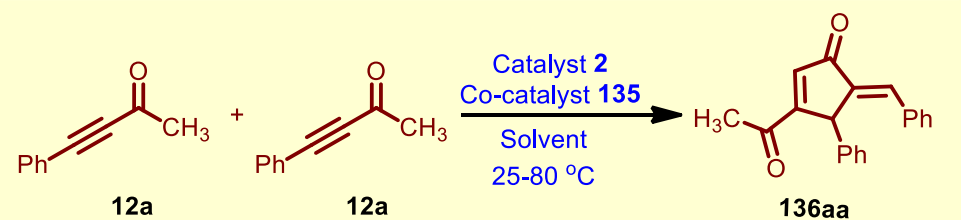
[a] Unless otherwise mentioned, all reactions were carried out with **12a** (0.4 mmol), catalyst **2** (20 mol%, relative to 0.2 mmol of **12a**) in solvent (1 mL). [b] Yield refers to the column-purified product. [c] dry solvent used.

3.2.2 *Reaction optimization with co-catalyst:*

To further improve the reaction rate and yield, we investigated co-catalysts effect on the [3+2]-annulation and the results are summarized in Table 2. Reaction of ynone **12a** with 20 mol% of Ph_3P **2c** as the catalyst and 20 mol% of AcOH **24a** as the co-catalyst in DCE at 25 °C furnished **136aa** in 45% yield after 24 h (Table 2, entry 1). Upon increasing the reaction temperature to 60 °C, a decreased yield was observed (Table 2, entry 2). In the case of reaction with **2g** as catalyst and **135** as co-catalyst, observed **136aa** in 28% yield after 24 h (Table 2,

entry 3). Among other solvents screened, $CHCl_3$ and toluene resulted in 49 and 56% yield, respectively (Table 2, entries 4-8). When 20 mol% of $PhCO_2H$ **24f** was employed as co-catalyst, yield was detected as 43% (Table 2, entry 9). Surprisingly, a promising yield (86%) was obtained on switching to 20 mol% of (±)-BINOL **135** as co-catalyst within 3 h (Table 2, entry 10). By diminishing the co-catalyst loading to 5 and 10 mol% the product was obtained in 85 and 90% yield, respectively, within 4 h (Table 2, entries 11 and 12). In a similar manner, annulative dimerization of **12a** under the catalysis of **2c** with (*R*)-BINOL **135c** or (*S*)-BINOL **135c** as co-catalyst furnished the product **136aa** in 88% and 87% yields, respectively (Table 2, entries 13 and 14). But product **136aa** was obtained with 0% *ee*.

Table 2: Reaction optimization.[a]



12a **12a** **136aa**

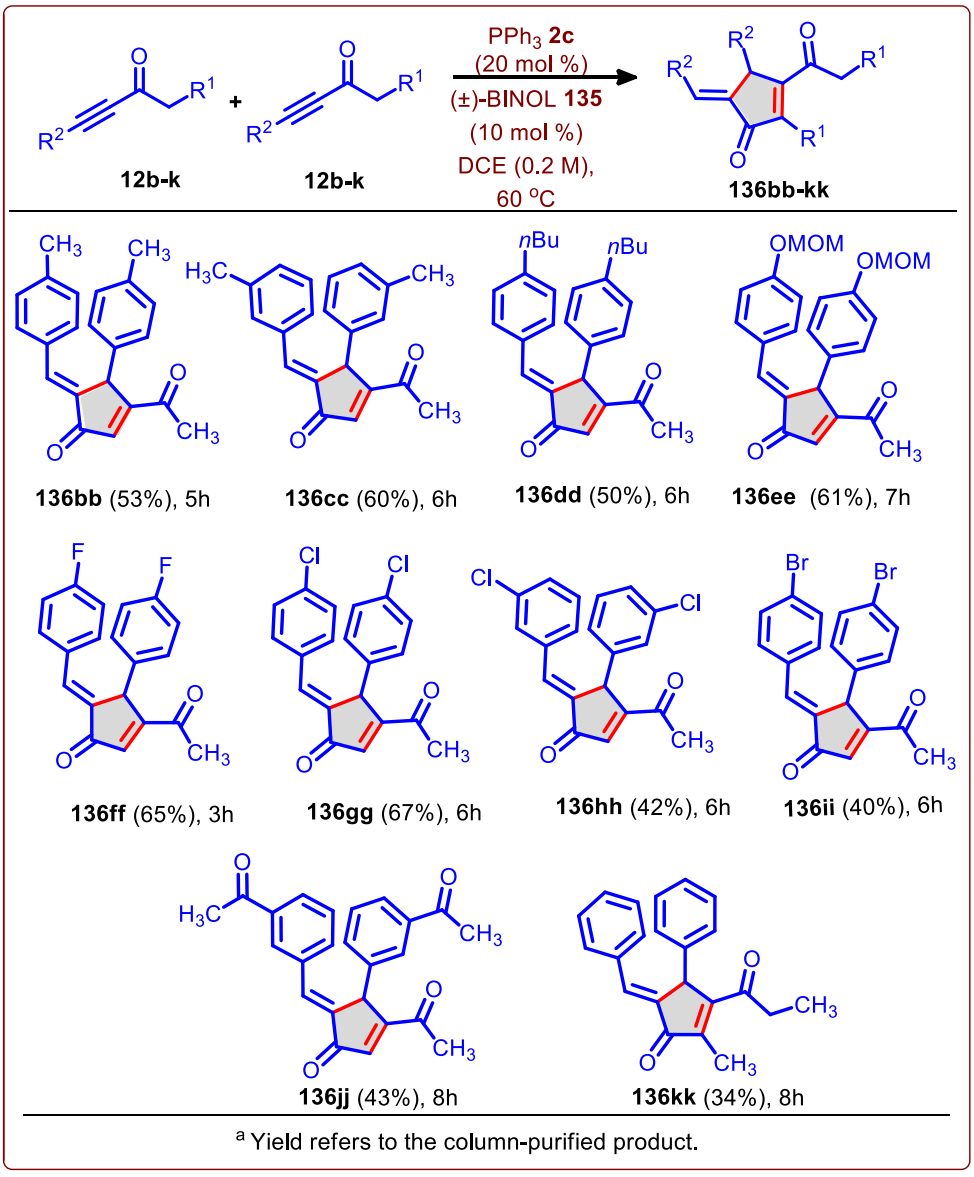
Entry	Solvent (0.4 M)	Catalyst (mol %)	Co-Catalyst (mol %)	Temp. (°C)	Time (h)	Yield (%)[b] **136aa**
1	DCE	**2c**	**24a**: AcOH	25	24	45
2	DCE	**2c**	**24a**	60	10	37
3	DCE	**2g**	**24a**	60	24	28
4	$CHCl_3$	**2c**	**24a**	60	20	49
5	$CHCl_3$	**2b**	**24a**	60	20	34
6	C_6H_6	**2c**	**24a**	60	12	trace
7	C_6F_6	**2c**	**24a**	60	12	Trace
8	Toluene	**2c**	**24a**	80	15	56
9	DCE	**2c**	**24f**:$PhCO_2H$	60	09	43
10	DCE	**2c**	**135**:(±)-BINOL	65	03	86
11[c]	DCE	**2c**	**135**:(±)-BINOL	60	04	85
12[d]	**DCE**	**2c**	**135:(±)-BINOL**	**60**	**04**	**90**
13[d,e]	DCE	**2c**	**135**:(*R*)-BINOL	60	04	88
14[d,e]	DCE	**2c**	**135**:(*S*)-BINOL	60	04	87

[a] Unless otherwise mentioned, all reactions were carried out with **12a** (0.4 mmol), catalyst **2** (20 mol%, relative to 0.2 mmol of **12a**), co-catalyst **135** (20 mol%, relative to 0.2 mmol of **12a**) in solvent (1 mL). [b] Yield refers to the column-purified product. [c] Co-catalyst **135** was taken as 5 mol %. [d] Co-catalyst **135** was taken as 10 mol %. [e] *ee* obtained for the product **136aa** is zero.

3.2.3 Scope of homo-annulation:

With the optimal catalyst and reaction conditions in hand, the substrate scope and generality of the reaction was explored (Table 3). The ynones bearing methyl group at *para*- and *meta*-position afforded the products **136bb-cc** in 53 and 60% yields within 5 and 6 h, respectively (Table 3, entries 1 and 2). Further, the extended alkyl group (*n*Bu) substituted ynone **12d** and MOM protected hydroxy ynone **12e** were also tolerated and gave the products in 50 and 61% yields (Table 3, entries 4 and 5). Halogenated ynones (F, Cl, Br) underwent reactions and resulted the products in 40-67% yields (Table 3, entries 5-8).

Table 3: Reaction scope.[a]



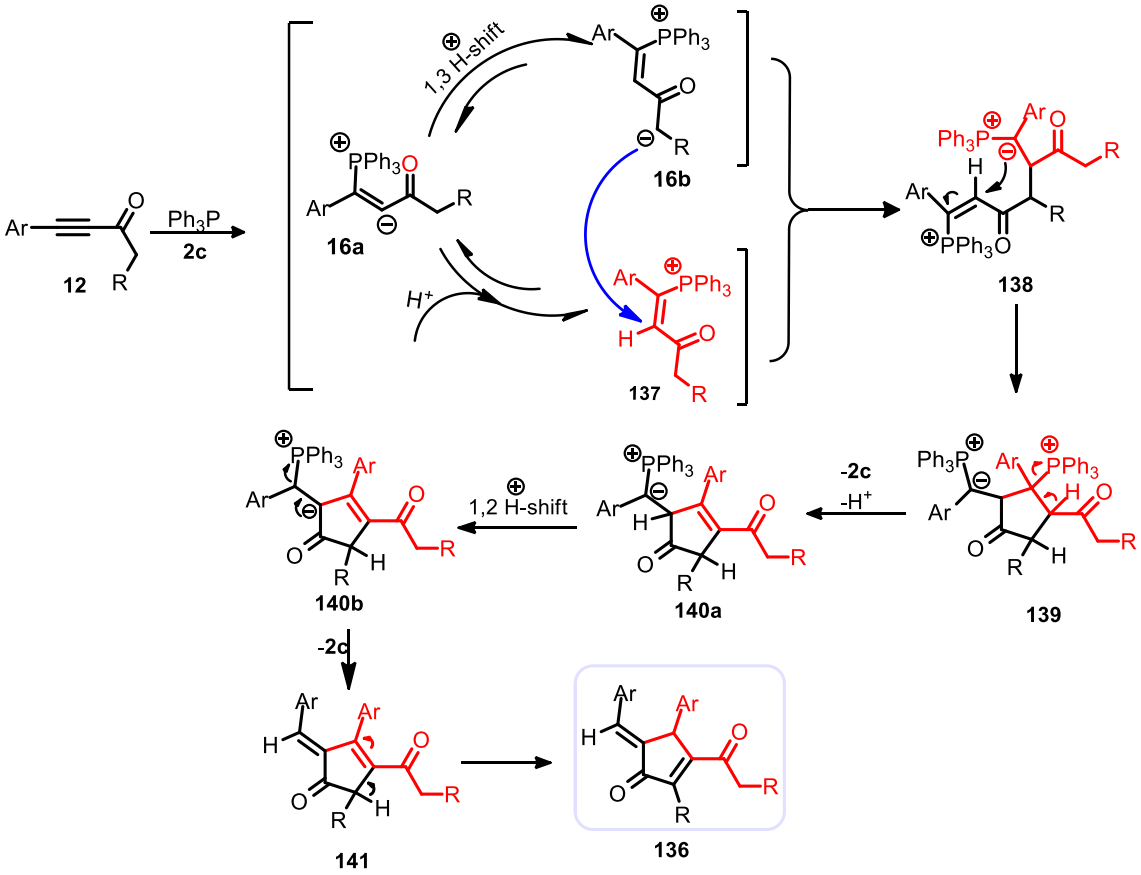
[a] Yield refers to the column-purified product.

Electron-withdrawing substituted ynone **12j** furnished the annulation product **136jj** in 43% yield in 8 h (Table 3, entry 9). Other substituted ynone **12k** also was tolerated and yielded **136kk** in 34% yield in 8 h (Table 3, entry 10).

3.2.4 Reaction mechanism:

A plausible mechanism is proposed as shown in Scheme 3 based on the control experiments. Michael addition of Ph_3P **2c** with ynone **12** generates a zwitterionic intermediate **16a**, which on subsequent intramolecular [1,3]-proton migration produces **16b**. On the other hand, the generated intermediate **16a** quenched with co-catalyst (±)-BINOL **135** (10 mol%) or residual water content (0.01%) in solvent DCE results in another intermediate **137**. A nucleophilic attack of the resulted enolate **16b** on **137** produces phosphonium ion species **138**, which further undergoes an intramolecular cyclization to provide the phosphonium ion **139**. Elimination of proton and Ph_3P **2c** produces the species **140a** from **139**, which on further intramolecular [1,2]-proton migration produces **140b**. On subsequent elimination of Ph_3P **2c** and intramolecular [1,3]-proton migration produces the final annulation product **136**.

Scheme 3: Reaction mechanisum.



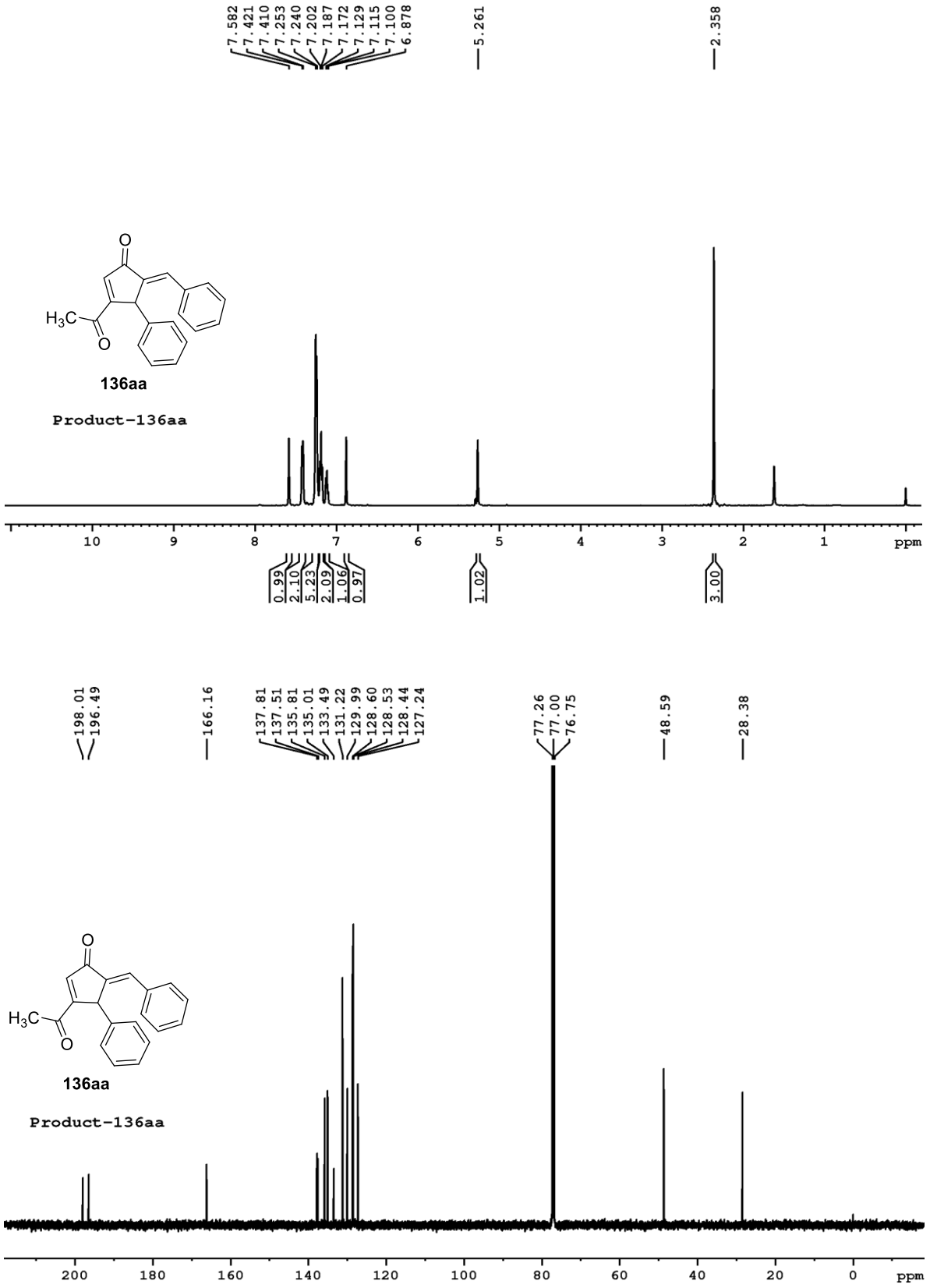


Figure-1: ^{1}H and ^{13}C NMR spectra of the product **136aa.**

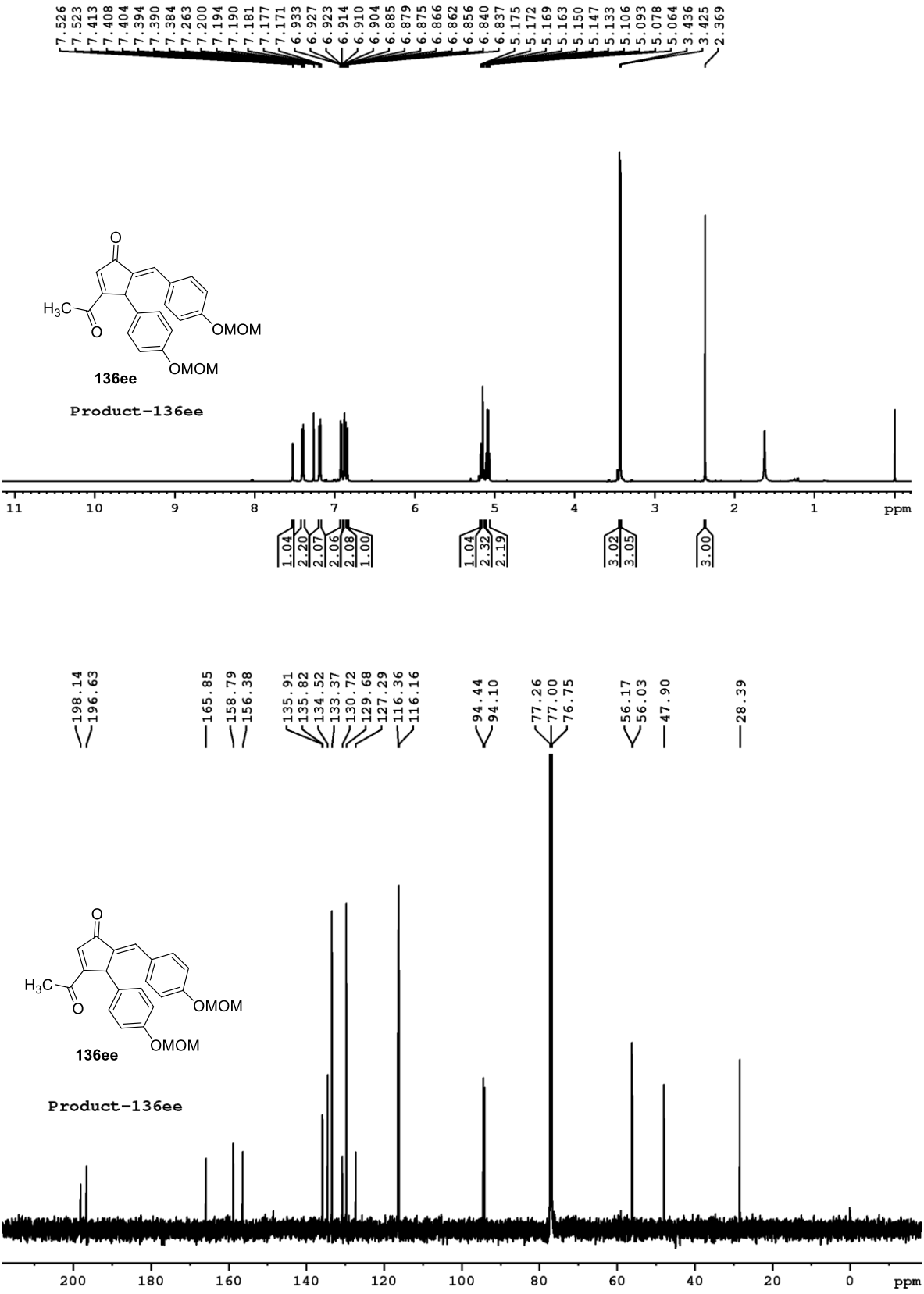


Figure-2: ^{1}H and ^{13}C NMR spectra of the product **136ee.**

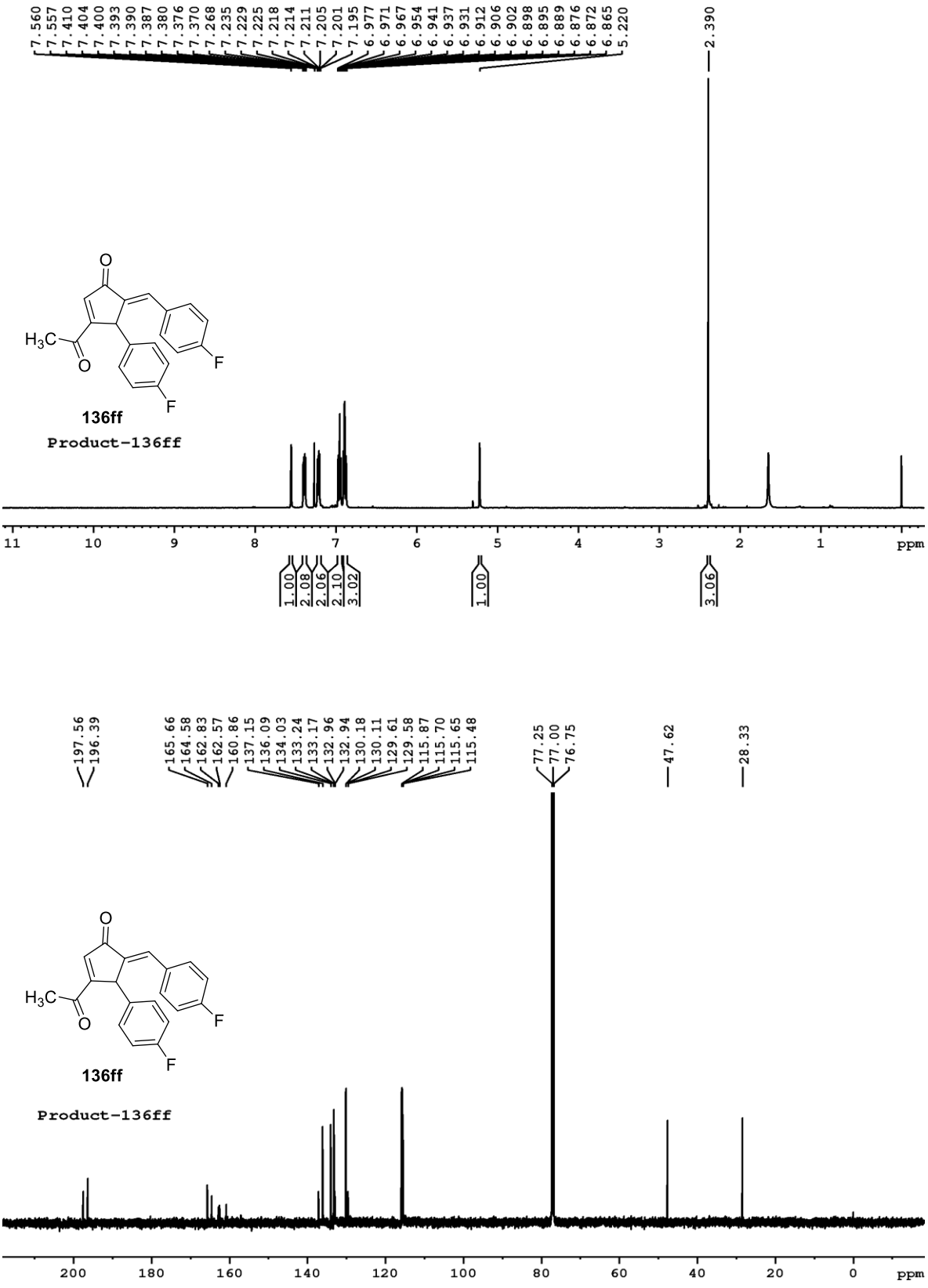


Figure-3: ^{1}H and ^{13}C NMR spectra of the product **136ff.**

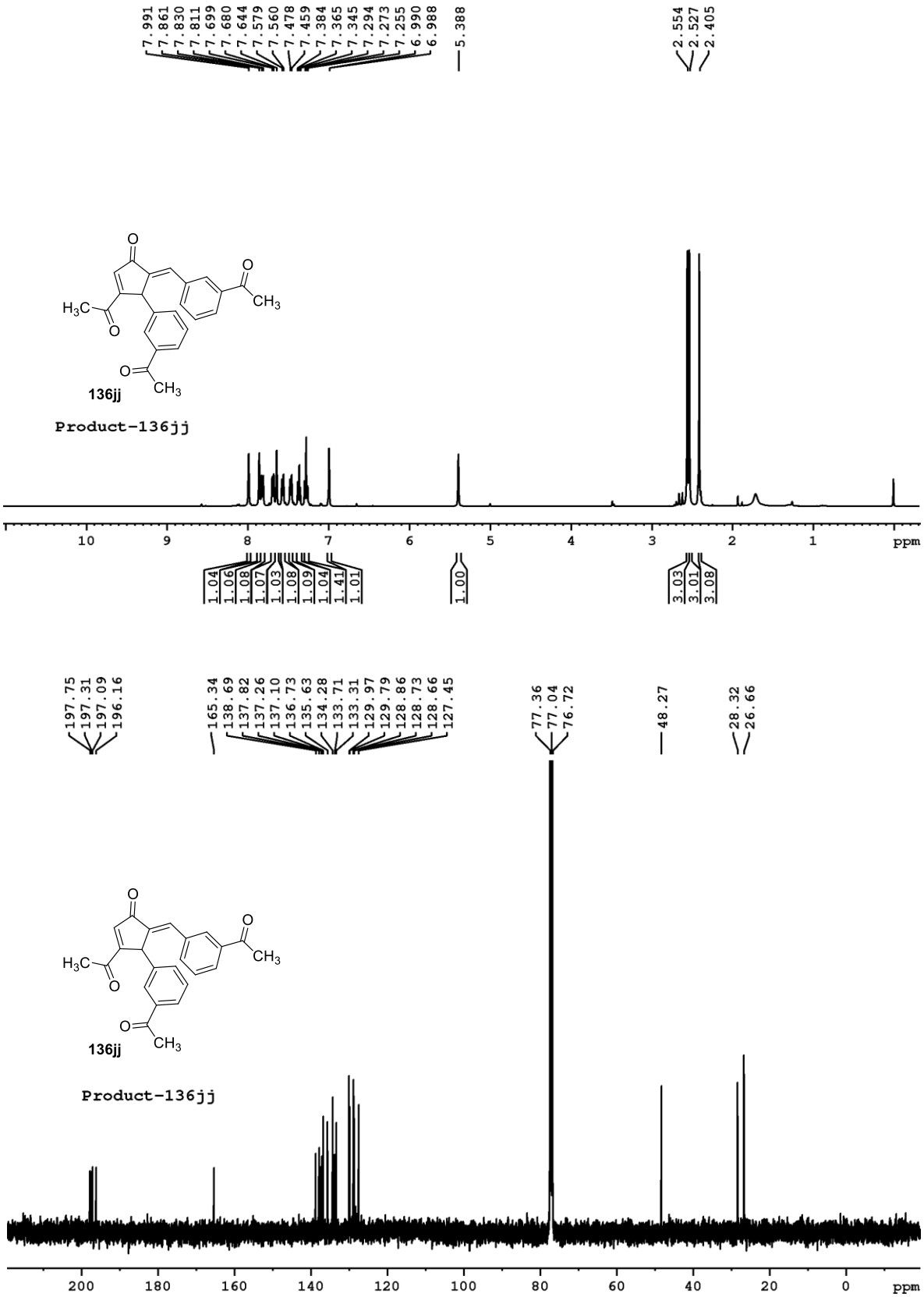


Figure-4: ^{1}H and ^{13}C NMR spectra of the product **136jj.**

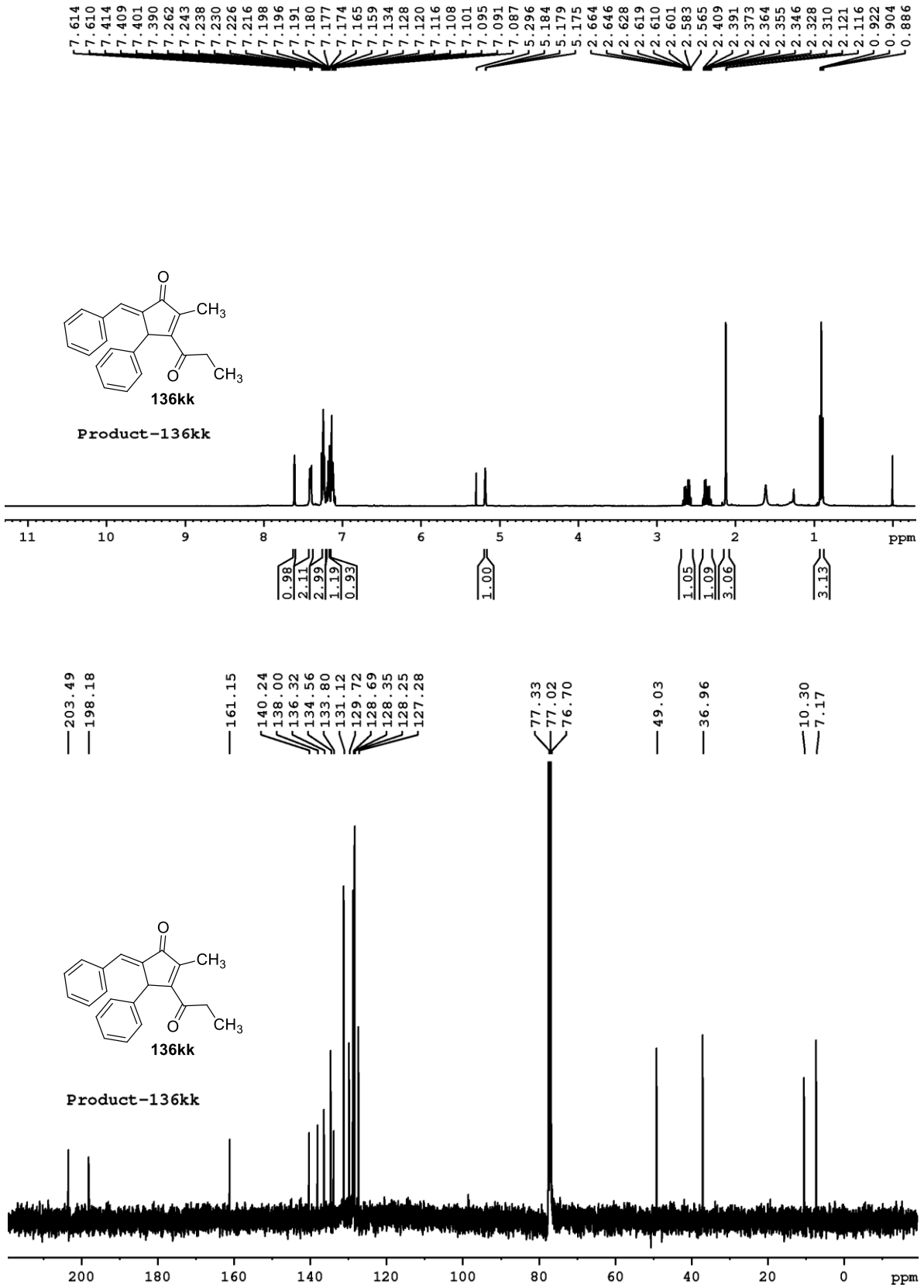
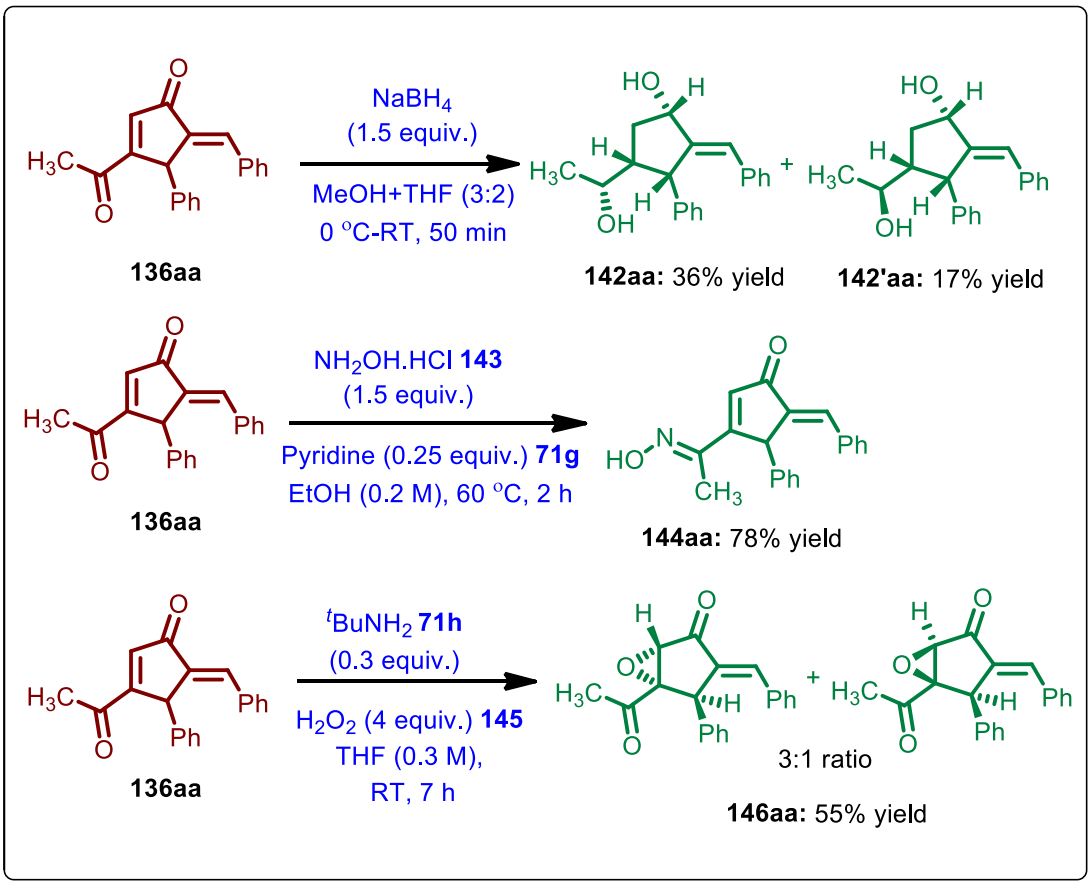


Figure-5: ^{1}H and ^{13}C NMR spectra of the product **136kk.**

3.2.5 Synthetic application of umpolung product 136aa:

With the synthetic applications in mind, we explored the utility of umpolung [3+2]-annulative product **136aa** for various organic transformations (Scheme 4). Reduction of **136aa** with 1.5 equiv. of $NaBH_4$ in MeOH-THF (3:2) at 0-25 °C for 50 min afforded the triple (two carbonyl and one olefin functional groups) reduced alcohols **142aa** and **142'aa** in 36 and 17% yields, respectively. The structure and relative stereochemistry of product **142'aa** was confirmed by NMR analysis and also by NOESY and H, C-COSY experiments as shown in Figures 6,7. The ketoxime **144aa** was synthesized in 78% yield by treating **136aa** with hydroxylamine hydrochloride **143** and pyridine **71g** in EtOH at 60 °C for 2 h. Epoxidation of **136aa** with $^tBuNH_2$ **71h** and H_2O_2 in THF for 7 h delivered **146aa** with preferential oxidation at the cyclic enone position in 55% yield at 25 °C.

Scheme-4. Synthetic Applications of 5-Alkylidene-2-cyclopentenone



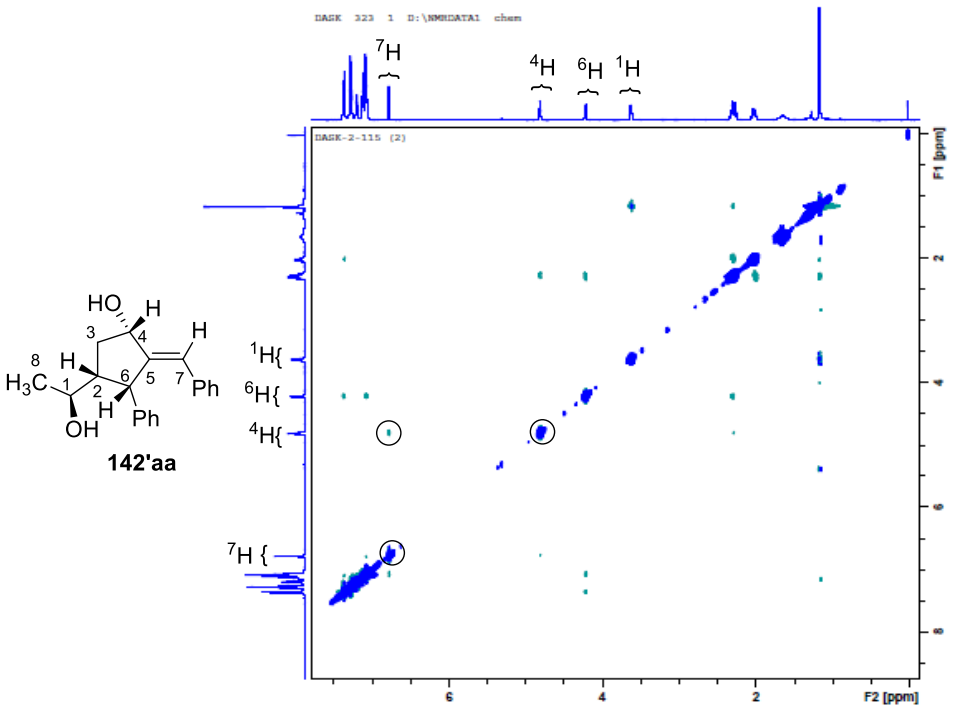


Figure 6: NOESY spectrum of compound **142'aa** (500 MHz, $CDCl_3$ at 25 °C).

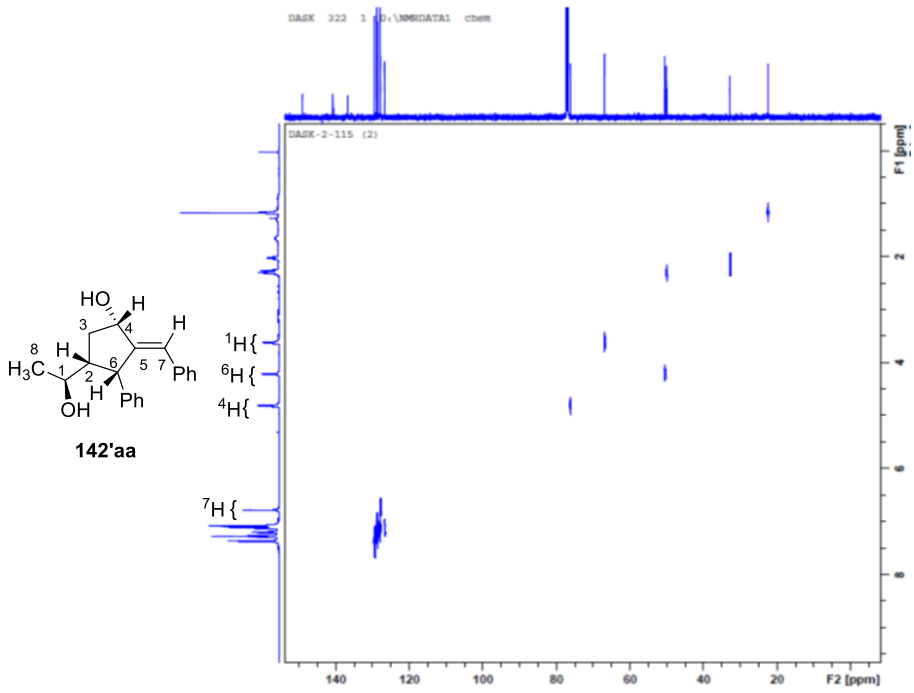


Figure 7: Hetero-COSY spectrum of compound **142'aa** (500 MHz, $CDCl_3$ at 25 °C).

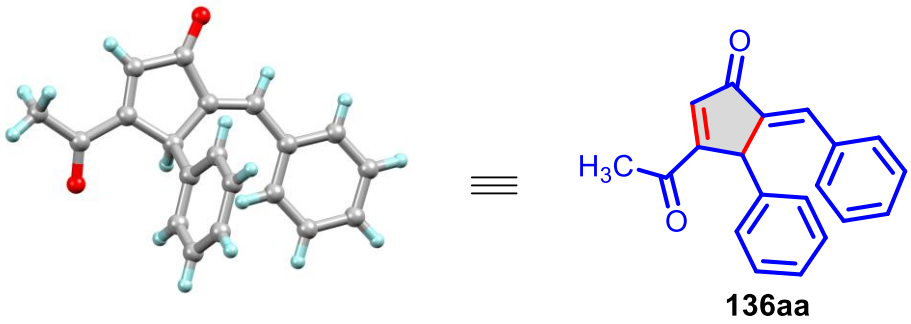
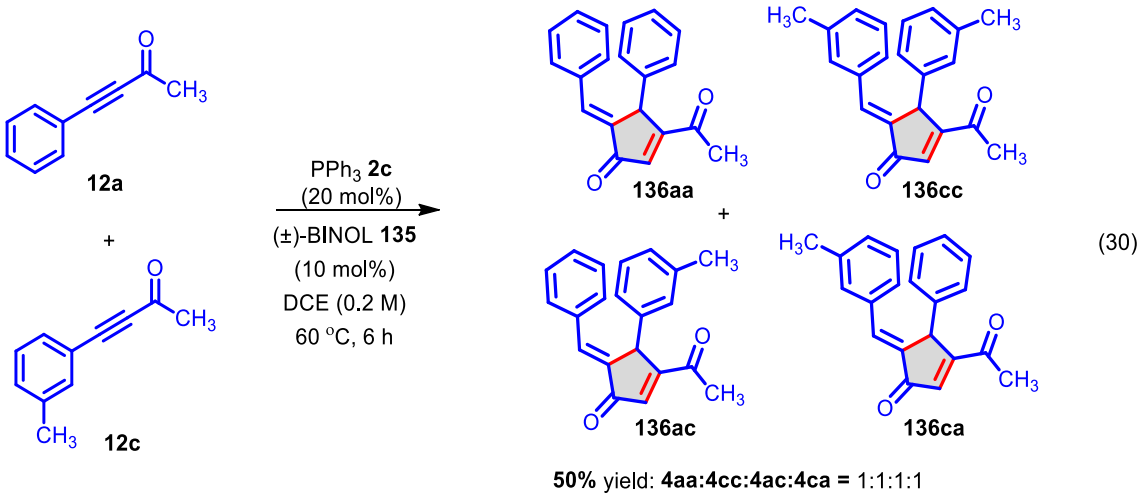


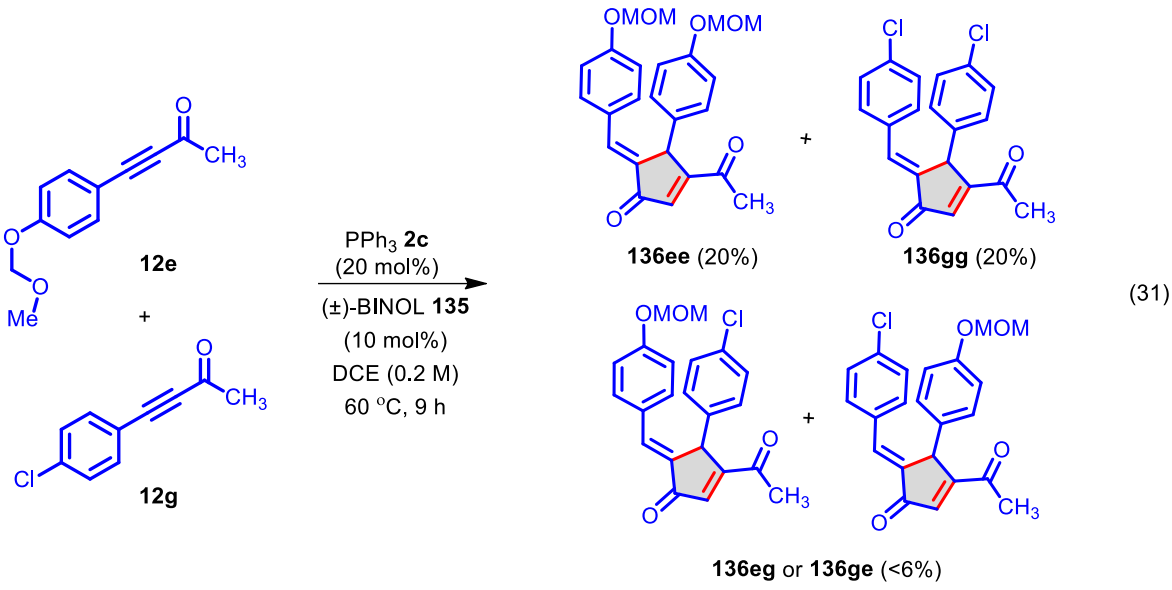
Figure 8: X-Ray crystal structure of (*E*)-3-acetyl-5-benzylidene-4-phenylcyclopent-2-enone (**136aa**).

3.2.6 Scope of hetero-annulation:

Interestingly, phosphine-catalyzed (±)-BINOL **135**-induced umpolung [3+2]-annulative dimerization of two different ynones **12a** and **12c** in DCE at 60 °C for 6 h furnished the four annulation products **136aa/136cc/136ac/136ca** in 50% yield with 1:1:1:1 ratio as shown in eq. 30. Further we investigated the **2c/135**-catalyzed cross annulative dimerization of two different ynones **12e** and **12g** in DCE at 60 °C for 9 h to study electronic factors. Surprisingly, we obtained two self-annulation products **136ee** and **136gg** in each 20% yields and cross-annulation product **136eg** or **136ge** obtained only in <6% yield were also impure as shown in eq. 31. We did not observe any new reaction by treatment of the annulation product **136aa** with catalyst **2c** or **2c/135** in DCE at 25-60 °C for long reaction times.



(30)



(31)

3.3 Conclusion:

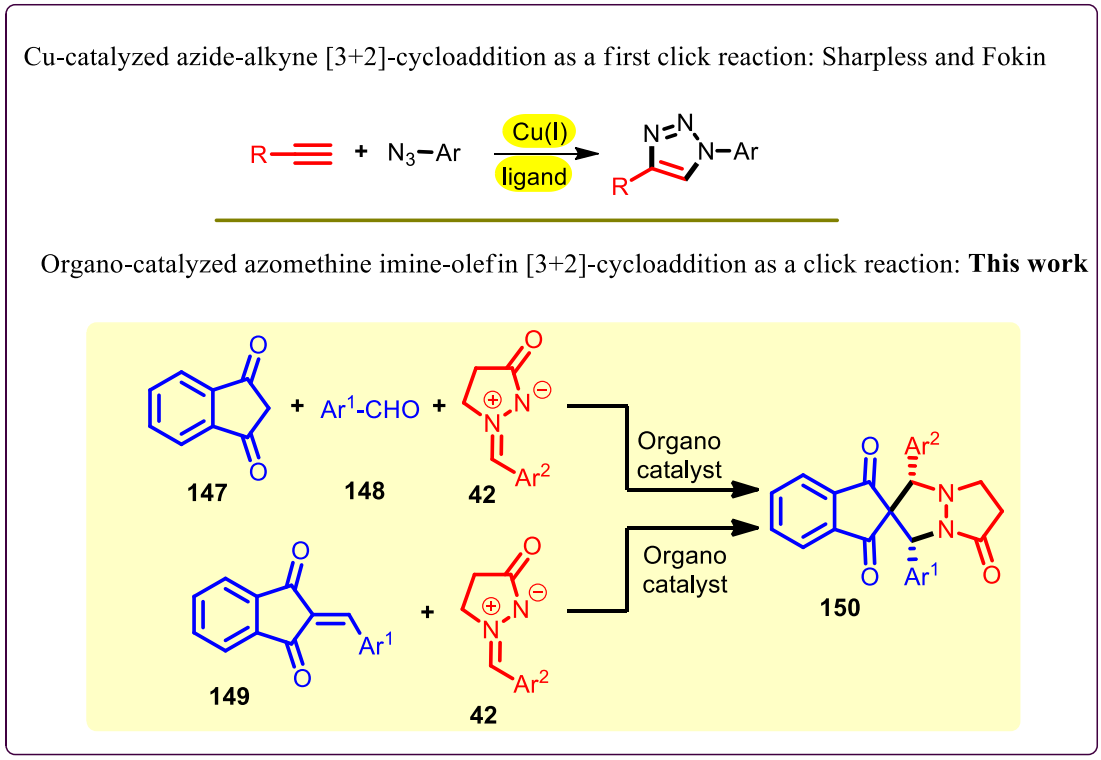
In conclusion, we have developed a new protocol for the direct synthesis of 5-alkylidene-2-cyclopentenones through triphenyl phosphine-catalyzed umpolung [3+2]-annulative dimerization of ynones.

4. Organocatalytic Azomethine Imine-Olefin Click Reaction: High-yielding Stereoselective Synthesis of Spiroindane-1,3-dione-pyrazolidinones

4.1 Introduction

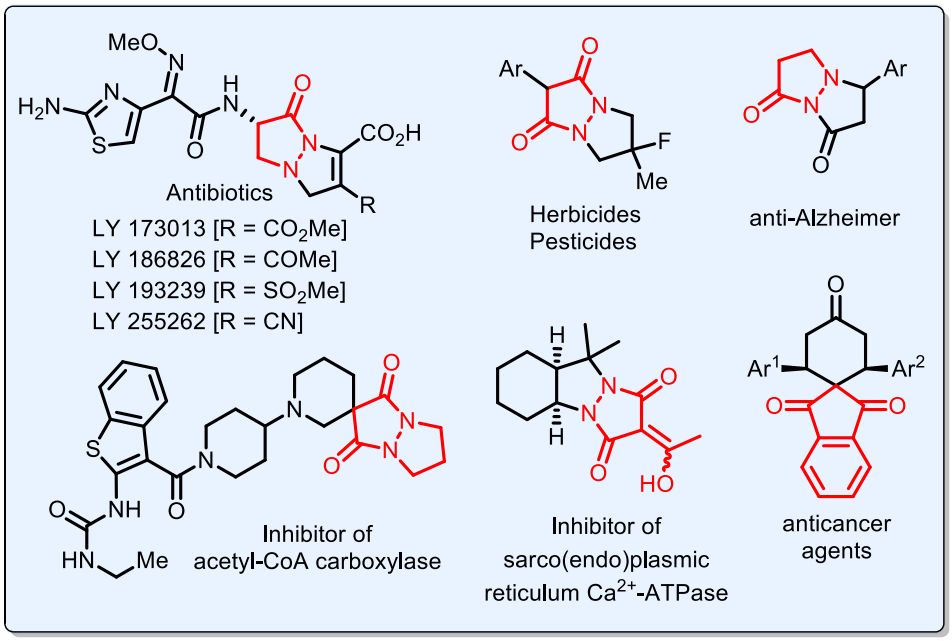
Fascinating "Cu-catalyzed azide/alkyne cycloaddition (CuAAC) or click chemistry"[38] with its distinctiveness and efficacy has given inspiration and driven many scientists into designing a legion of organocatalytic variants of Huisgen, 1,3-dipolar [3+2]-cycloaddition between a α-hydrogen containing carbonyls and an azide, for the synthesis of biologically, medicinally and materialistically important 1,2,3-triazoles (Scheme 5).[39] Delivery of considerable contribution to the field of organocatalytic functionalized 1,2,3-triazole synthesis,[40] prompted us to explore more 'organo-click' concept reactions (Scheme 5).

Scheme 5: Organo-catalyzed azomethine imine-olefin [3+2]-cycloaddition as a new click reaction.



We were enticed to know of *N*,*N*-cyclic azomethine imines, stable and quite readily accessible 1,3-dipoles, which have been successfully utilized in 1,3-dipolar [3+2]-cycloaddition reactions for the construction of structurally diverse *N*,*N*-bicyclic pyrazolidinone motifs.[41] The *N*,*N*-bicyclic pyrazolidinone skeletons are not only structurally interesting but also have been investigated as antibiotics, antitumor agents, pesticides, herbicides, calcitonin agonists and potent drugs to relieve Alzheimer's disease (Scheme 6).[42] Simultaneously, spiroindan-1,3-dione scaffolds are essential in medicinal chemistry as they are used as anticancer agents.[43] Medicinally important spiroindan-1,3-dione scaffolds when combined with biologically active *N*,*N*-bicyclic pyrazolidinone skeletons could result in more potential benefits for pharmaceutical chemistry. Accordingly, we envisaged the synthesis of the desired products containing the aforementioned two important bioactive fragments, *via* either an organocatalytic three-component reaction between indane-1,3-dione **147**, aldehyde **148** and *N*,*N*-cyclic azomethine imine **42** or an organocatalytic two-component reaction between 2-arylidene-1,3-indandione **149** and the *N*,*N*-cyclic azomethine imine **42** (Scheme 5).

Scheme 6: Selected examples of biologically active *N*,*N*-bicyclic pyrazolidin-3-one derivatives.



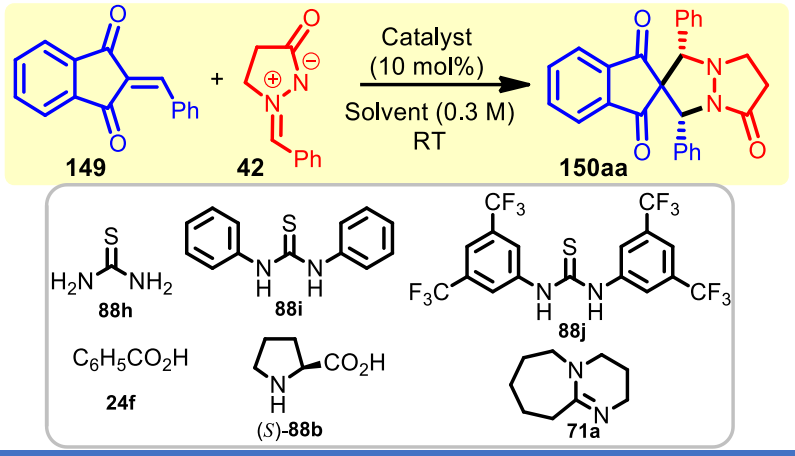
4.2 Results and discussion

4.2.1 Reaction optimization:

As had planned, we embarked on the optimization studies, choosing 2-benzylidene-1,3-indandione **149a** and azomethine imine **42a** as the starting materials (Table 4). Initially, being interested to explore the reactivity of the azomethine imine **42a** towards the reactive olefin **149a**, by solvent and thermal induction under catalyst-free conditions, we carried out the reaction of **149a** with 1.2 equiv. of **42a** in a few solvents like, $CH_3C_6H_5$, DMSO, DCM, EtOH, $CHCl_3$ and CH_3CN at 25-50 °C (Table 1). Gratifyingly, in all the solvents screened, the reaction got over within 6-9 h to furnish the expected spiroindane-1,3-dione-pyrazolidinone **150aa** with up to 81% yield and an extraordinarily steady high diastereoselectivity of >99:1, except that the yield was very less (36%) in toluene solvent (Table 4, entries 1-6). Amid the screened solvents, acetonitrile seemed to promote the azomethine imine-olefin [3+2]-cycloaddition, the best, within 8 h at room temperature (Table 4, entry 6). Reactivity in chloroform is comparable to that in acetonitrile (Table 4, entry 5). With optimized solvent in hand, in order to study the effect of temperature on the reaction, we performed the azomethine imine-olefin [3+2]-cycloaddition reaction in acetonitrile solvent at 50 °C and delighted to know that the temperature enhanced the reaction rate significantly to furnish the product **150aa** within 0.7 h and also without affecting the *dr* of >99:1 (Table 4, entry 7). After getting sufficient enlightenment on the reaction, with the thought of improving the yield further, we focused to comprehend the use of certain H-bonding catalysts like **88h-88j**, benzoic acid **24f**, amino acid (*S*)-**88b** and a tertiary amine catalyst DBU **71a**. Using 10 mol% of thiourea **88h** as catalyst at room temperature reduced the reaction time to 5 h keeping the yield and *dr* the same (Table 4, entry 8). Changing to **88i** reduced the reaction time further providing only marginal increase in yield (Table 4, entry 9). With 10 mol% of Schreiner thiourea **88j** at room temperature, we observed noticeable increase in yield (88%) and the reaction too completed within 1.5 h (Table 4, entry 10). *As expected, apparently the H-bonding catalysts **88h-88j** enhanced the reaction rate by LUMO activation of* benzoic acid **24f**, even though the cycloaddition completed within 3 h, there was a slight drop in the yield (Table 4, entry 11). With 10 mol% of L-proline (*S*)-**88b** at room temperature, we obtained click product **150aa** in 80% yield with >99:1 *dr* under longer reaction

time (8.5 h); and same reaction at 50 °C furnished the click product **150aa** in 86% yield with >99:1 *dr* within

Table 4: Reaction optimization.[a]



Entry	Solvent (0.4 M)	Catalyst (mol %)	Time (h)	Yield (%)[b] 150aa	*dr* (%)[c]
1	Toluene	-	9	36	>99:1
2	DMSO	-	9	61	>99:1
3	DCM	-	6	74	>99:1
4	EtOH	-	9	65	>99:1
5	$CHCl_3$	-	9	80	>99:1
6	CH_3CN	-	8	81	>99:1
7[d]	**CH_3CN**	**-**	**0.7**	**87**	**>99:1**
8	CH_3CN	**88h**	5	81	>99:1
9	CH_3CN	**88i**	3.5	84	>99:1
10	**CH_3CN**	**88j**	**1.5**	**88**	**>99:1**
11	CH_3CN	**24f**	3	76	>99:1
12	CH_3CN	(*S*)-**88b**	8.5	80	>99:1
13[d]	CH_3CN	(*S*)-**88b**	0.75	86	>99:1
14	CH_3CN	**71a**	9	34	>99:1

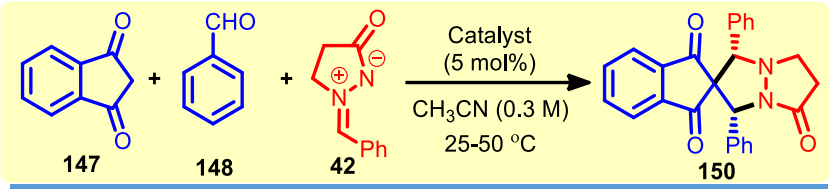
[a] Unless otherwise mentioned, all reactions were carried out with **149a** (0.3 mmol), **42a** (0.36 mmol) in solvent at rt. [b] Yield refers to the column purified product.[c] *dr* was determined by ^{1}H NMR spectroscopy. [d] Reaction performed at 50 °C.

0.75 h (Table 4, entry 12-13). By correlation of these results with entry 6/7, we observed that there is no effect of L-proline (*S*)-**88b** in these two-component reactions. Also we have not seen any enrichment of enantioselectivity in click product **150aa** obtained through (*S*)-**88b**-catalysis at room temperature. Surprisingly, employment of 10 mol% DBU **71a** as catalyst resulted in deactivation of the reaction, thereby producing only 34% yield of the product **150aa**, though the *dr* remained constant throughout (Table 4, entry 14). This result was similar to the recently reported Pengfei Li work of tertiary amine-catalyzed [3+2]-cycloaddition of **42a** and **149a** in DCM solvent at 25 °C.[44] The best optimized condition for this two-component azomethine imine-olefin [3+2]-cycloaddition seems to be treatment of the reactants **149a** and **42a** with 10 mol% of **88j** in acetonitrile at room temperature.

4.2.2 Reaction optimization with three-components:

Alternatively, we were interested to study the performance of the azomethine imine-olefin [3+2]-cycloaddition reaction under a three-component one-pot manner and opted for L-proline (*S*)-**88b** as the catalyst for promoting the initial Knoevenagel condensation or olefination.[45] Reaction of indane-1,3-dione **147** with 1.5 equiv. of benzaldehyde **148a** and 1.2 equiv. of azomethine imine **42a**, in the presence of L-proline (*S*)-**88b** and Schreiner thiourea **88j** each in 5 mol%, in acetonitrile at 25 °C for 1.8 h, furnished the product **150aa** in 78% yield with >99:1 *dr* (Table 5, entry 1).When the reaction temperature was raised to 50 °C, the reaction completed within 0.6 h and the yield increased to 87% (Table 5, entry 2). Astonishingly, even when the reaction of **147**, **148a** and **42a** was performed with just 5 mol% of L-proline (*S*)-**88b**, in the absence of **88j**, the product **150aa** was obtained in 75% yield at 25 °C and in 89% yield at 50 °C, with the *dr* maintained at >99:1 for both the cases (Table 5, entries 3-4). Earlier, we have explained that DBU **71a** is deactivating the cycloaddition, and the same trend followed even in the three-component reaction (Table 5, entry5). To investigate the catalytic power of L-proline (*S*)-**88b**, when the reaction of **147**, **148a** and **42a** was performed in the absence of (l)-**88b**, the product **150aa** was obtained in 72% yield at 25 °C in 9 h and in 75% yield at 50 °C in 5 h, with the *dr* maintained at >99:1 for both the cases under longer reaction times (Table 5, entries 6-7). Results from these one-pot reactions prove that the best optimized condition for the one-pot three-component reaction is utilization of 5 mol% of L-proline (*S*)-**88b** in acetonitrile at 50 °C (Table 5, entry 4).

Table 5: Reaction optimization.[a]



Entry	Catalyst (mol %)	Temp. (°C)	Time (h)	Yield (%)[b] 150aa	*dr* (%)[c]
1	**88j**/(*S*)-**88b**	25	1.8	78	>99:1
2	**88j**/(*S*)-**88b**	50	0.6	87	>99:1
3	(*S*)-**88b**	25	2.2	75	>99:1
4	(*S*)-**88b**	**50**	**0.6**	**89**	>99:1
5	**71a**	50	9	34	>99:1
6	-	25	9	72	>99:1
7	-	50	5	75	>99:1

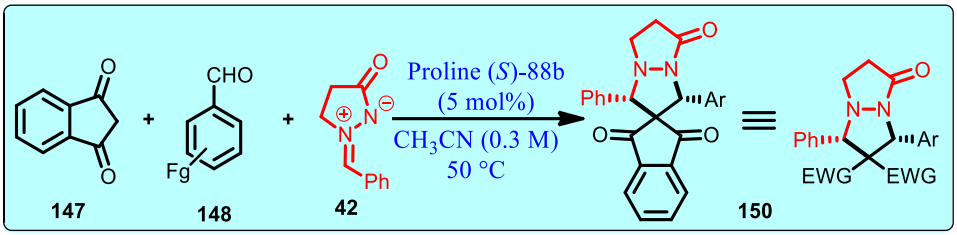
[a] Unless otherwise mentioned, all reactions were carried out with **147** (0.3 mmol), **148a** (0.45 mmol), **42a** (0.36 mmol), catalyst **88** or **71a** (each 5 mol%) in CH_3CN. [b] Yield refers to the column purified product. [c] *dr* was determined by ^1H NMR spectroscopy.

4.2.3 *Scope of the new click reaction:*

Having set the optimization, we directed our attention for establishing the scope of the one-pot reaction, by utilizing various arylaldehydes **148** as shown in Table 6. The reaction tolerated a wide variety of substituents on the phenyl group of the arylaldehyde **148** and comfortably furnished the products in good yields/selectivity. Halogen substituted arylaldehydes **148b-148h** underwent in situ olefination reaction with indane-1,3-dione **147** followed by azomethine imine-olefin [3+2]-cycloaddition reaction to furnish the products, spiroindane-1,3-dione-pyrazolidinones **150ba-150ha** in 60-81% yields with high *dr* (Table 6, entries 1-7). For few cases, especially mono-substituted 4-Cl, 2-Cl, 4-Br and 3-Br arylaldehydes were observed less *dr*. Arylaldehydes containing neutral substituents like 4-Me and 4-^{i}Pr, **150i** and **150l**, on reaction generated the products **150ia** and **150la** in 77% and 68% yields respectively, both in >99:1 *dr* (Table 6, entries 8 and 11). Presence of electron donating substituents 3-OMe and 3-OPh on the arylaldehydes **150j** and **150k** also did not deter the reaction, but smoothly afforded the products**150ja** and **150ka** in 86% and 74% yields correspondingly (Table 6, entries 9-10). Arylaldehydes with electron withdrawing substituents, namely 4-NO_2, 3-NO_2, 4-CN, 3-CN and 4-CF_3, **150m-150q** undergone the one-pot reaction to provide the products **150ma-150qa** in 64-85% yields with moderate to good

dr for all except for **150oa** (Table 6, entries 12-16). Even aliphatic alkylaldehydes **150r-150w** (both straight and branched chain) underwent the reaction to generate the products **150ra-150wa** in 60-80% yields, with all of them having > 99:1 *dr* (Table 6, entries 17-22).[44]

Table 6: Aldehyde substrate scope.[a,b,c]



150ba (81%)[d]
1.2 h, dr = >99:1

150ca (80%)
1.3 h, dr = 8:1

150da (70%)
1 h, dr = 7:1

150ea (64%)
1 h, dr = >99:1

150fa (76%)[d]
1.5 h, dr = 9:1

150ga (68%)
0.8 h, dr = 7:1

150ha (60%)
1 h, dr = >99:1

150ia (77%)[d]
1.4 h, dr = >99:1

150ja (86%)[d]
1.2 h, dr = >99:1

150ka (74%)
1 h, dr = 6:1

150la (68%)
1 h, dr = >99:1

150ma (85%)
0.7 h, dr = 10:1

150na (64%)
1 h, dr = 12:1

150oa (81%)
1.3 h, dr = >99:1

150pa (71%)
1 h, dr = 10:1

150qa (85%)
0.7 h, dr = 25:1

150ra (63%)
1 h, dr = >99:1

150sa (80%)
1 h, dr = >99:1

150ta (61%)
1 h, dr = >99:1

150ua (60%)
1 h, dr = >99:1

150va (68%)
1 h, dr = >99:1

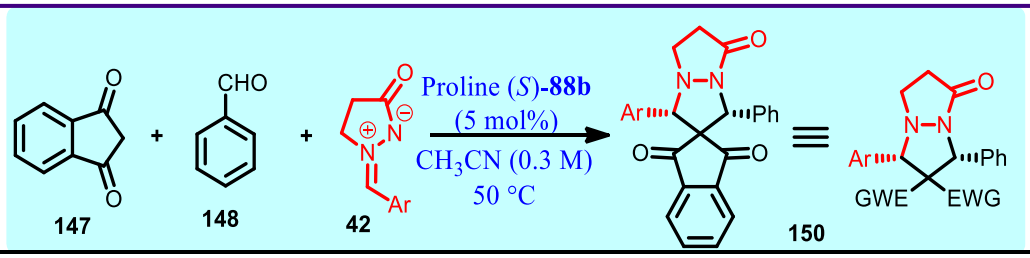
150wa (70%)
1 h, dr = >99:1

[a] Unless otherwise mentioned, all reactions were carried out with **147** (0.3 mmol), **148** (0.45 mmol), **42a** (0.36 mmol), L-proline (l)-**88b** (5 mol%) in CH_3CN. [b] Yield refers to the column purified product. [c] *dr* was determined by ^1H NMR spectroscopy.[d] Reaction performed by two component method.

4.2.4 Scope of three component click reaction:

At this juncture, after demonstrating the scope of the reaction using various substituted arylaldehydes as well as alkylaldehydes, and generating a vast library of spiroindane-1,3-dione-pyrazolidinones, the substrate scope for *N*,*N*-cyclic azomethine imines **42** was explored as shown in Table 7. The *N*,*N*-cyclic azomethine imines **42b**-**42e** containing halogen substituents on the aromatic ring, were subjected to the reaction with indane-1,3-dione **147** and benzaldehyde **148a** to produce the spiroindane-1,3-dione-pyrazolidinones **150ab**-**150ae** in very good yields (74-86%) with diminished *dr* for all, except for **150ad**/**150ab**, where the *dr* remained high (>99:1/20:1) (Table 7, entries 1-4). The electronically almost neutral *p*-Me group containing **42f** afforded the product **150af** in 87% yield with 17:1 *dr*, where as electron donating *p*-OMe group containing **42g** generated the product **150ag** in 81% yield with >99:1 *dr* (Table 7, entries 5-6). Even with *p*-NO_2 and *m*-NO_2 substituents, the yields obtained were good (83% and 63%) with *dr* 4:1 and >99:1 respectively (Table 7, entries 7-8). The structure and relative configuration of the products were determined by NMR analysis and further confirmed unambiguously by X-ray structure analysis of **150ua** (Figure 17).[46]

Table 7: *N*,*N*-Cyclic azomethine imine substrate scope.[a,b,c]



150ab (74%) 1 h, dr = 20:1	**150ac** (79%) 1 h, dr = 3:1	**150ad** (79%) 1.3 h, dr = >99:1	**150ae** (86%) 1 h, dr = 2:1
150af (87%)[d] 1.2 h, dr = 17:1	**150ag** (81%)[d] 1.3 h, dr = >99:1	**150ah** (83%) 1 h, dr = 4:1	**150ai** (63%) 1.2 h, dr = >99:1

[a] Unless otherwise mentioned, all reactions were carried out with **147** (0.3 mmol), **148a** (0.45 mmol), **42** (0.36 mmol), L- proline (*S*)-**88b** (5 mol%) in CH_3CN. [b] Yield refers to the column purified product. [c] *dr* was determined by ^1H NMR spectroscopy. [d] Reaction performed by two component method.

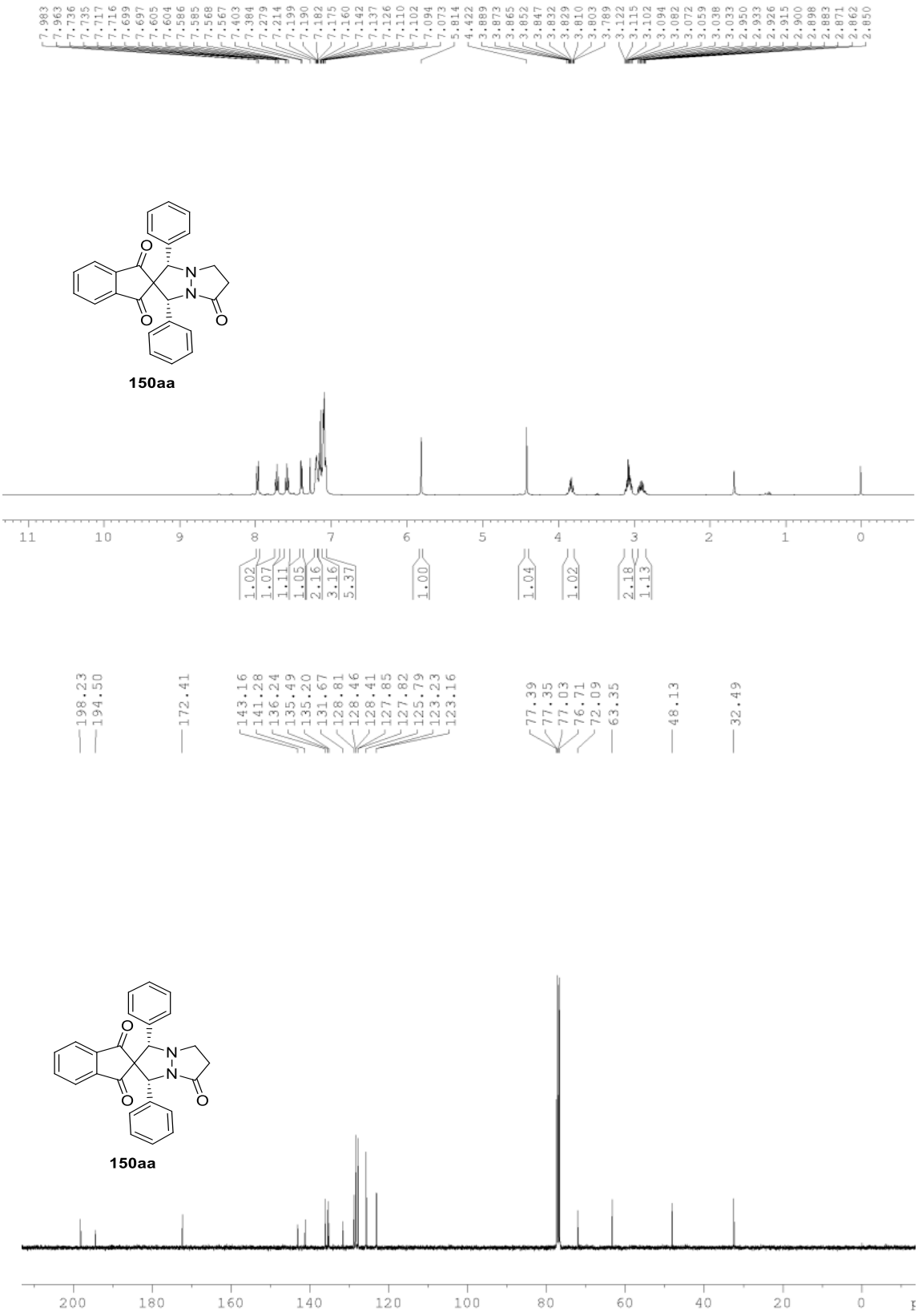


Figure-9: ^{1}H and ^{13}C NMR spectra of the product **150aa.**

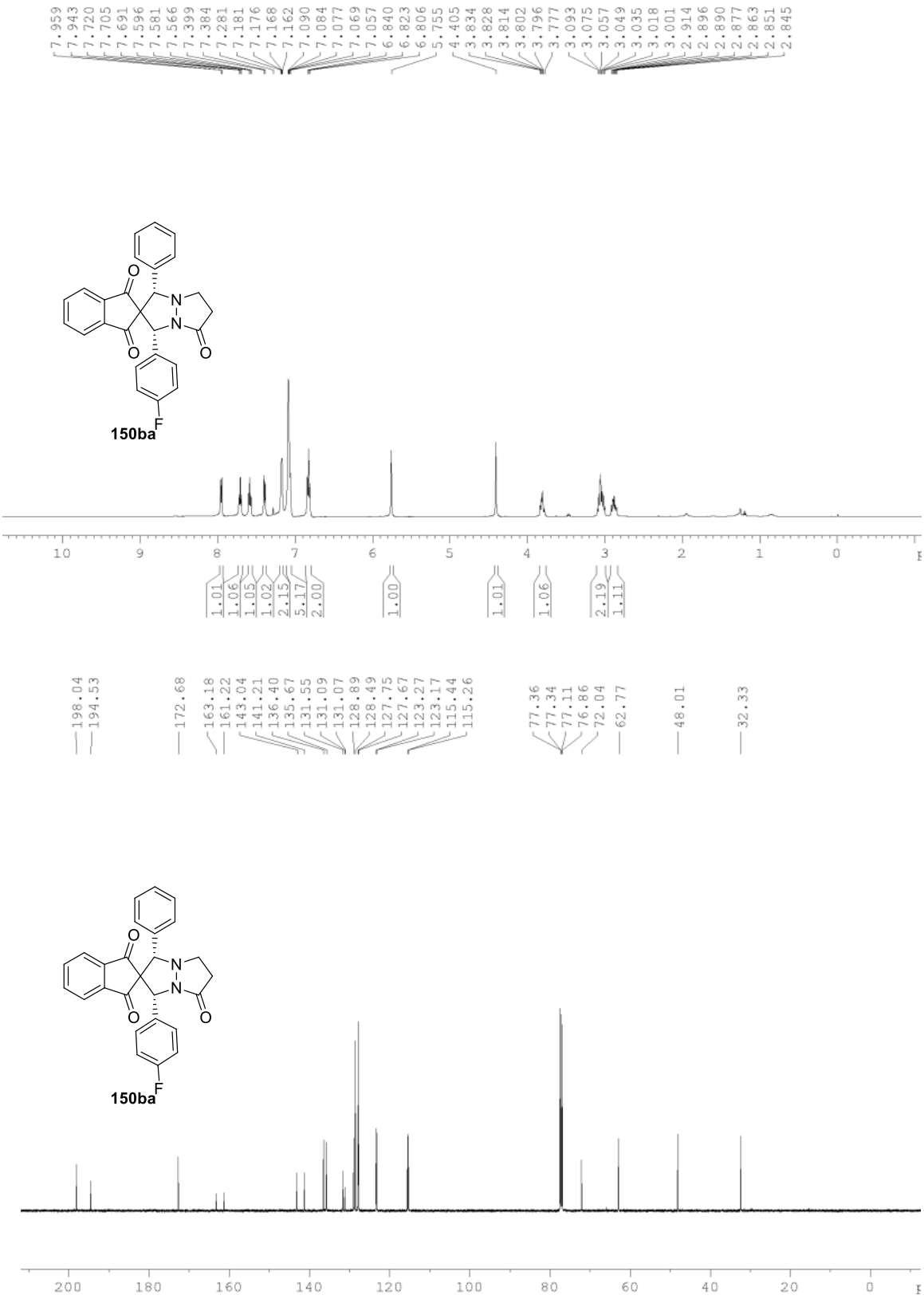


Figure-10: ^{1}H and ^{13}C NMR spectra of the product **150ba.**

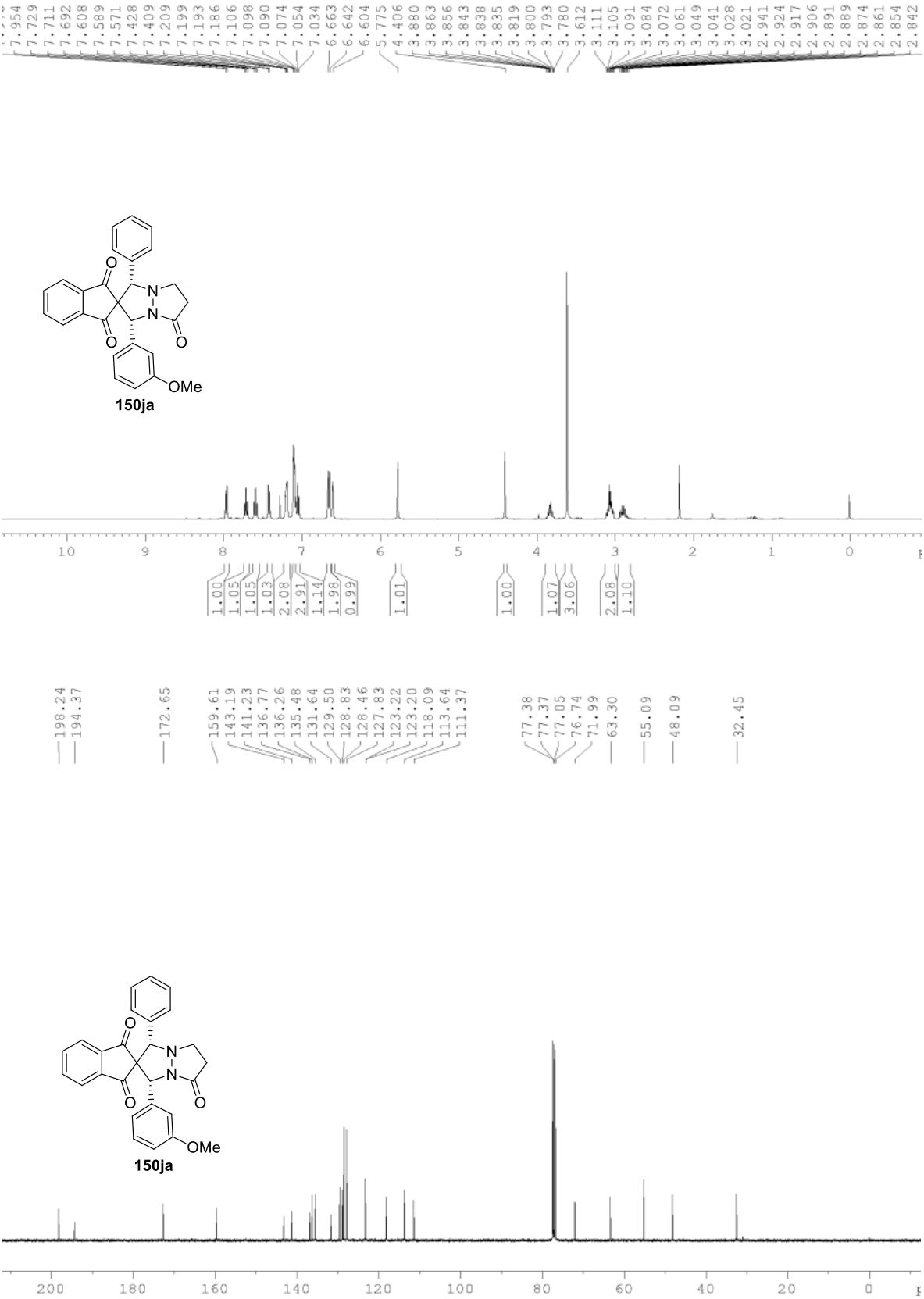


Figure-11: ^{1}H and ^{13}C NMR spectra of the product **150ja.**

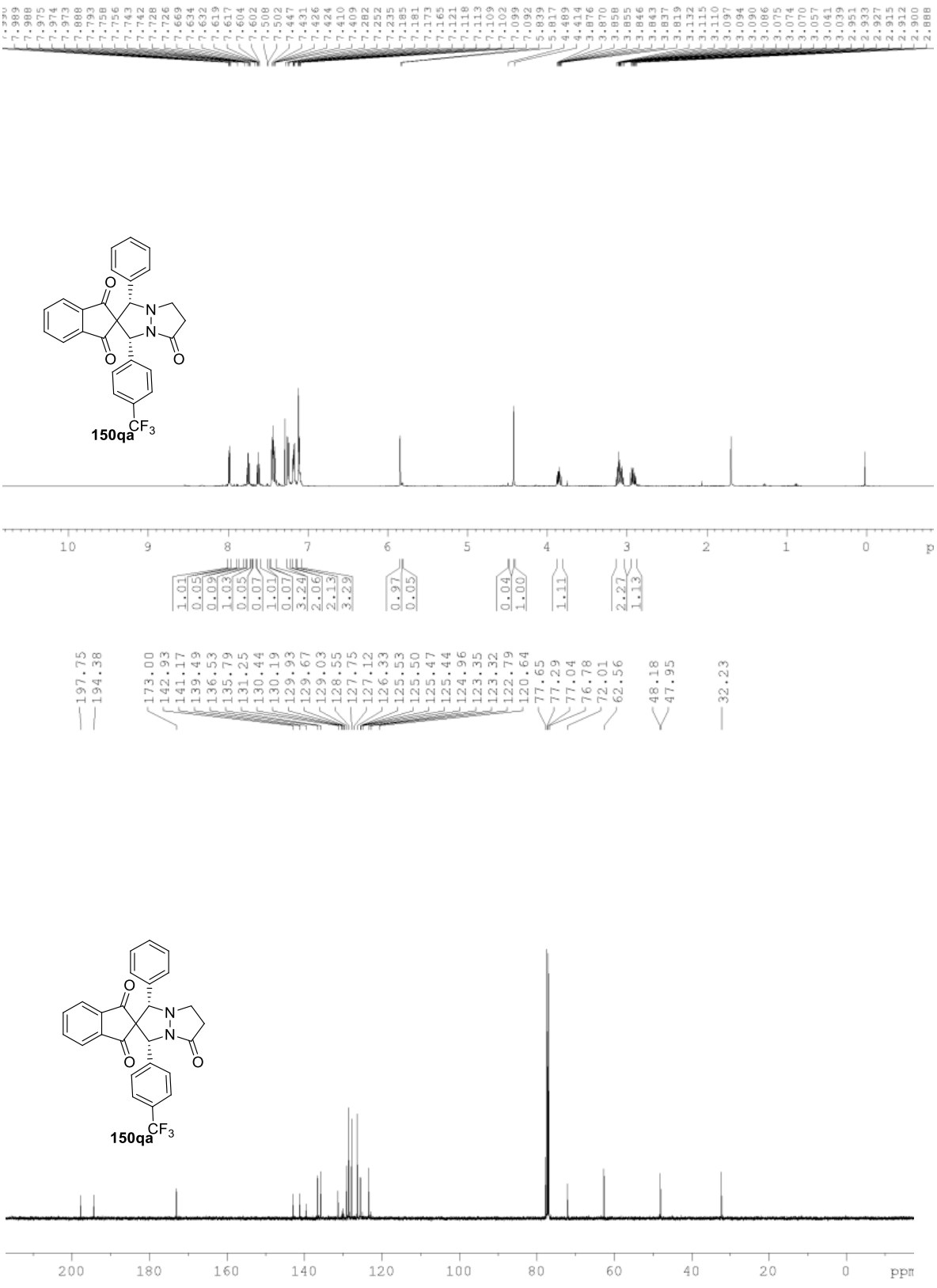


Figure-12: ^{1}H and ^{13}C NMR spectra of the product **150qa.**

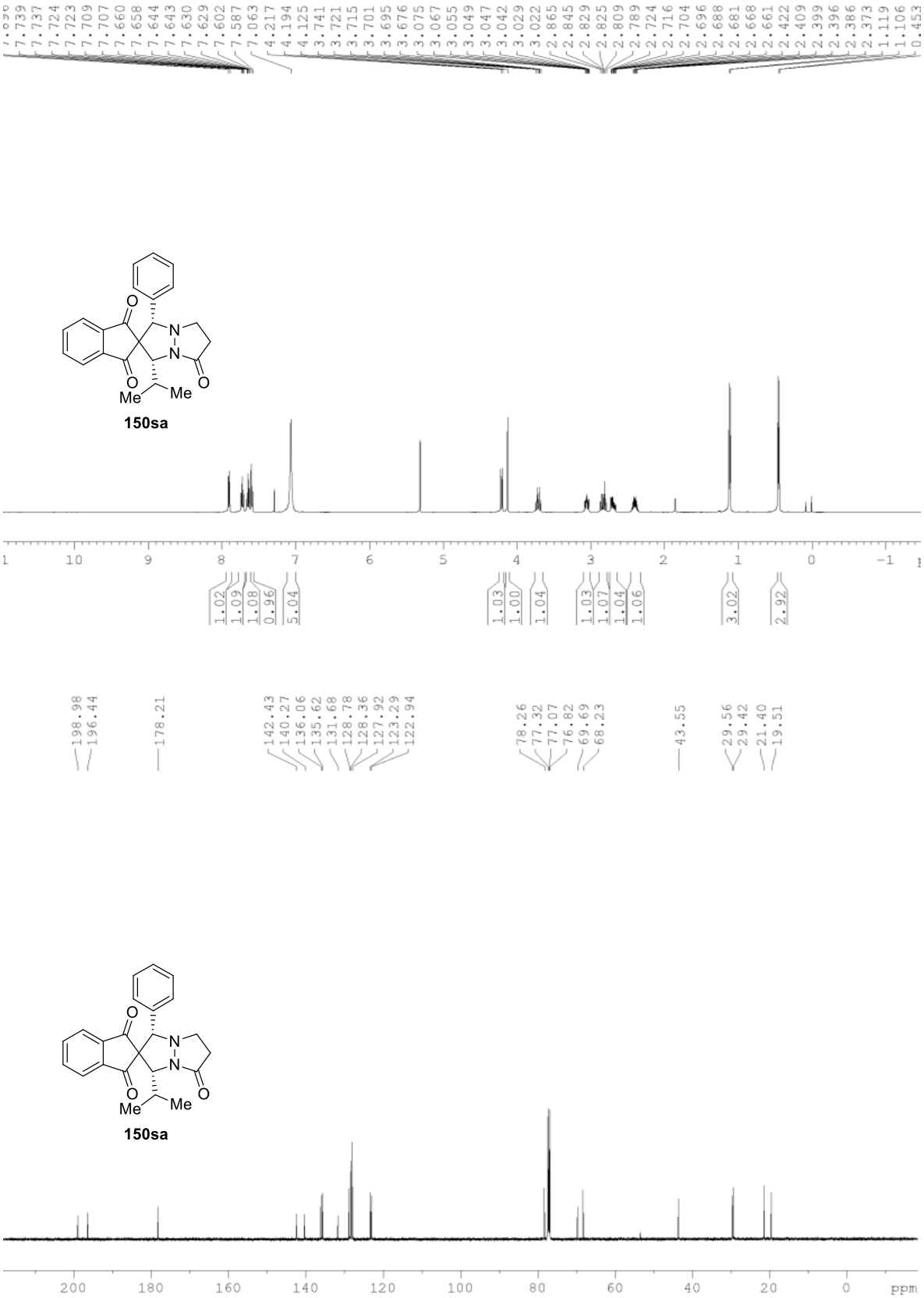


Figure-13: ^{1}H and ^{13}C NMR spectra of the product **150sa.**

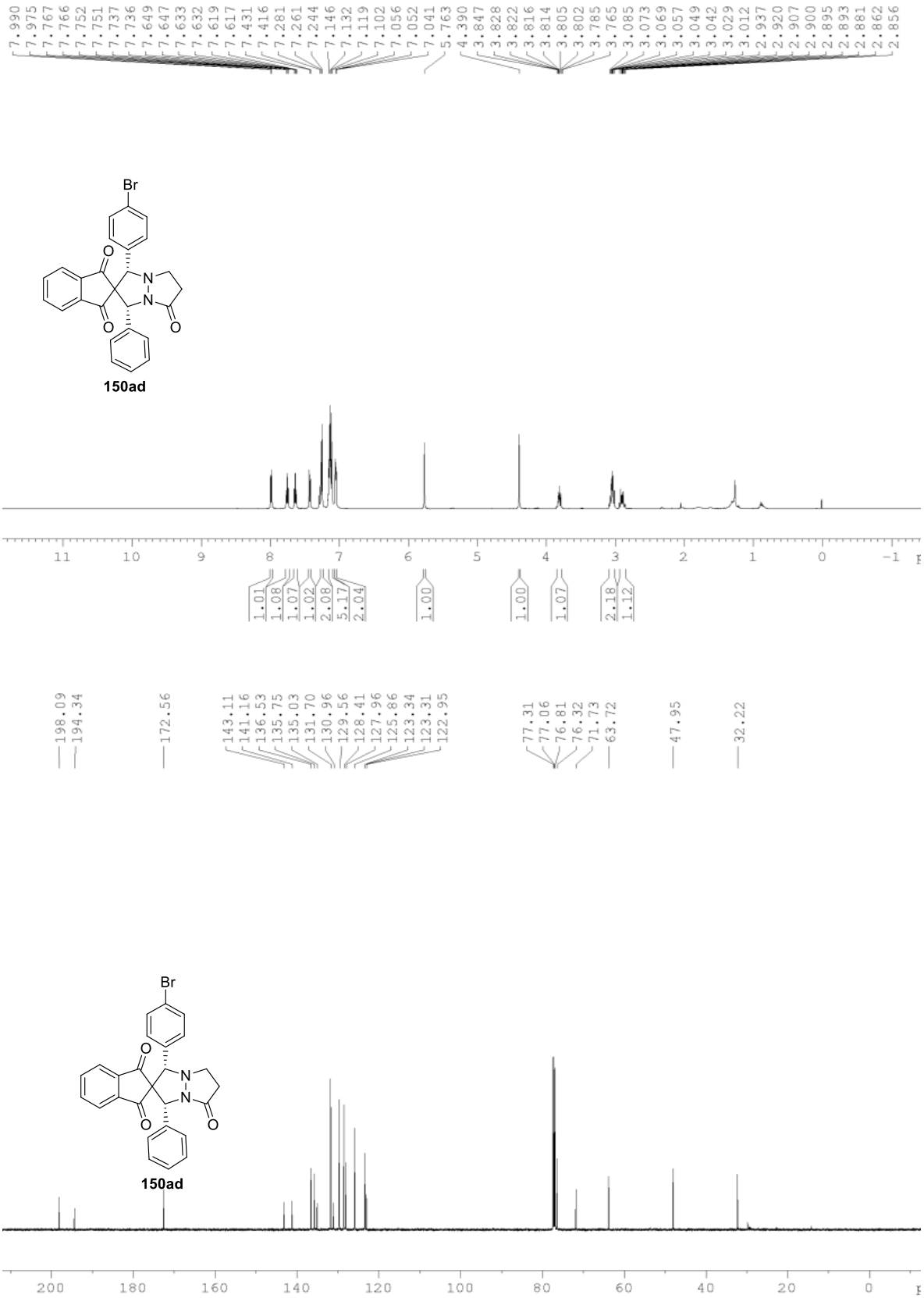


Figure-14: ^{1}H and ^{13}C NMR spectra of the product **150ad.**

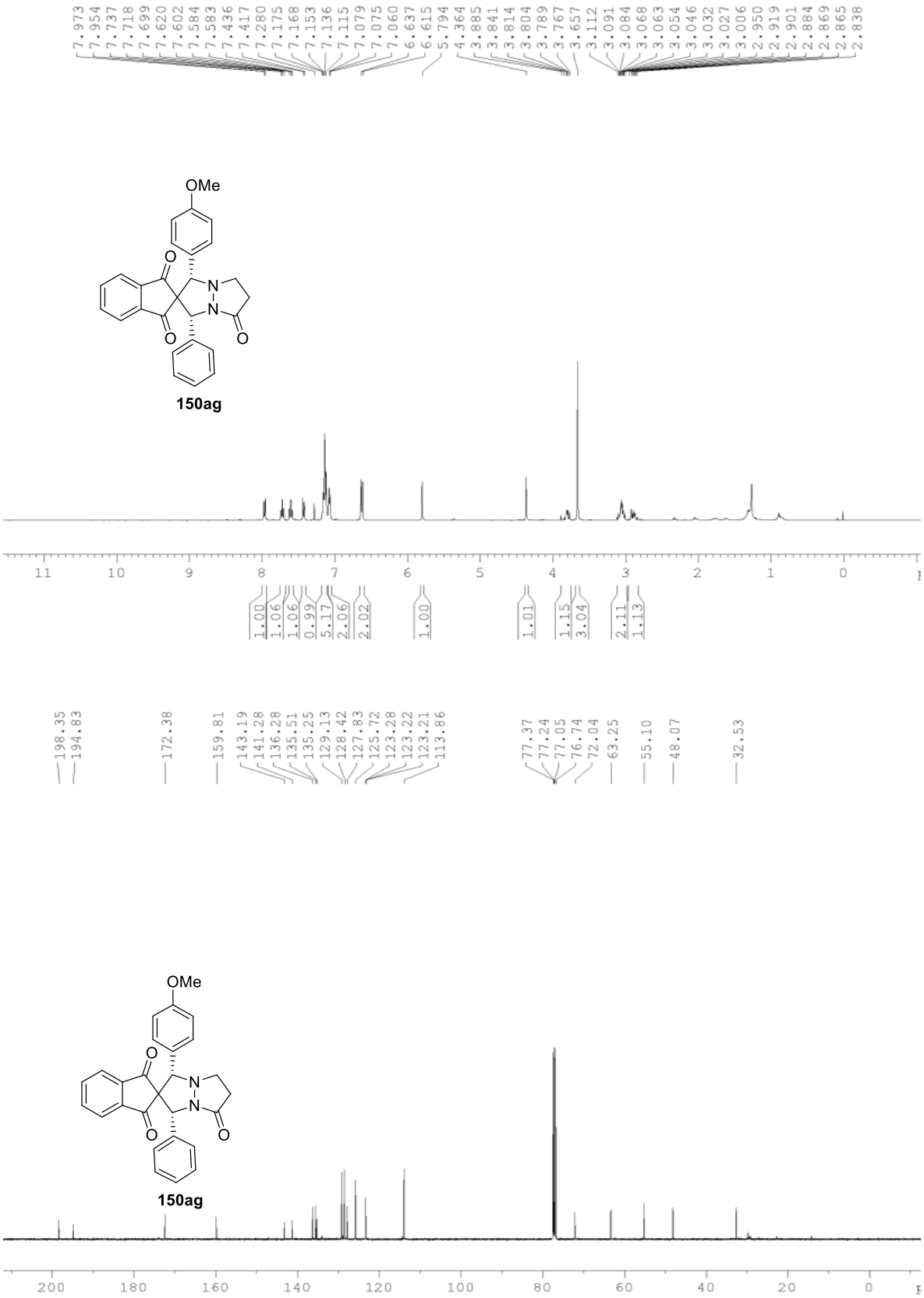


Figure-15: ^{1}H and ^{13}C NMR spectra of the product **150ag.**

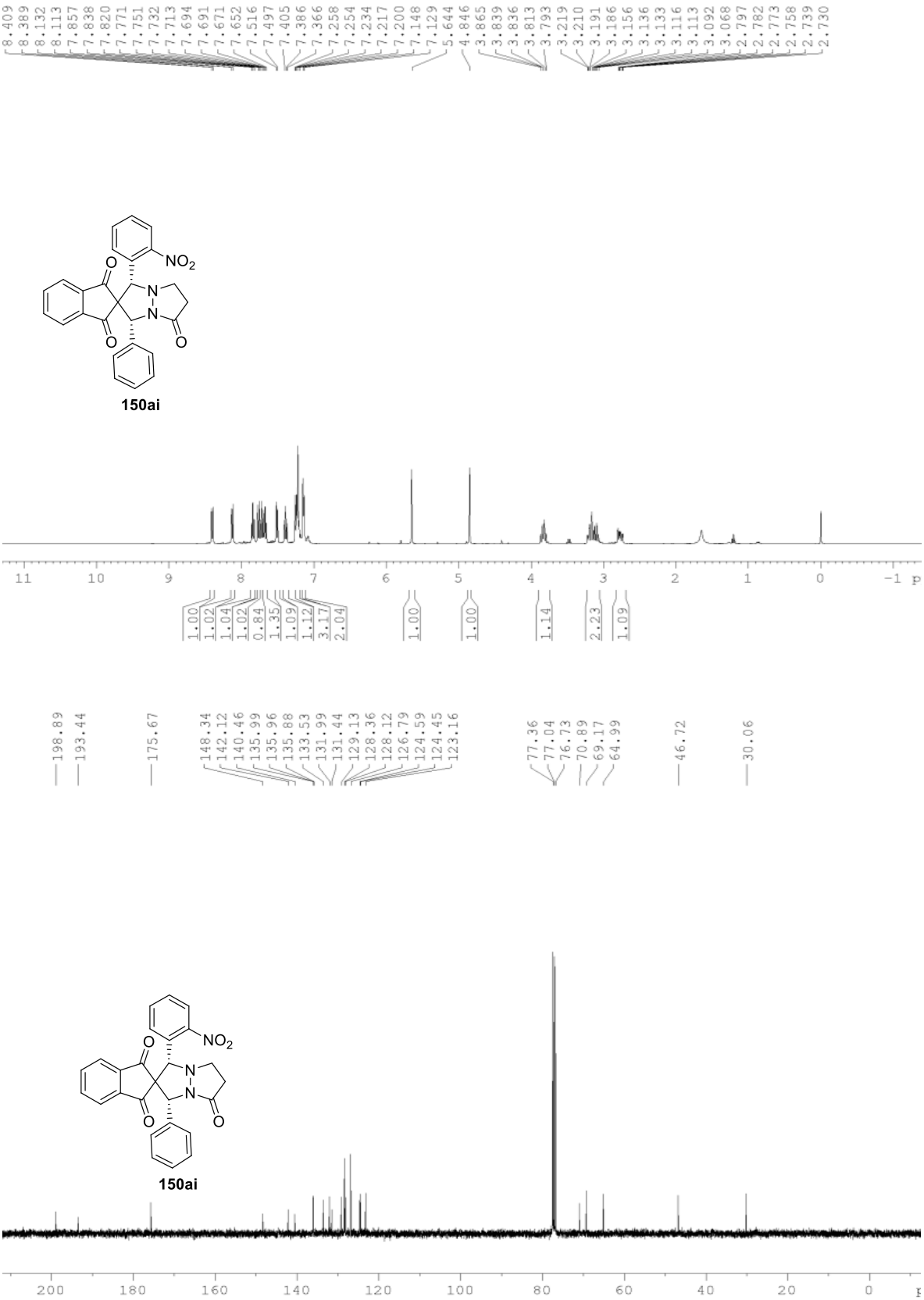


Figure-16: ^{1}H and ^{13}C NMR spectra of the product **150ai.**

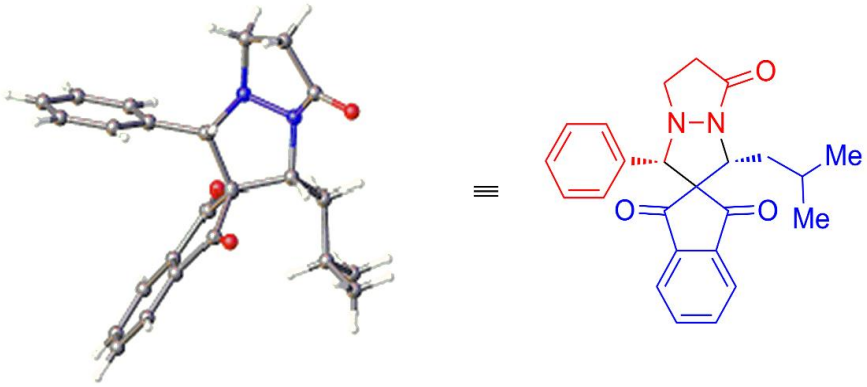
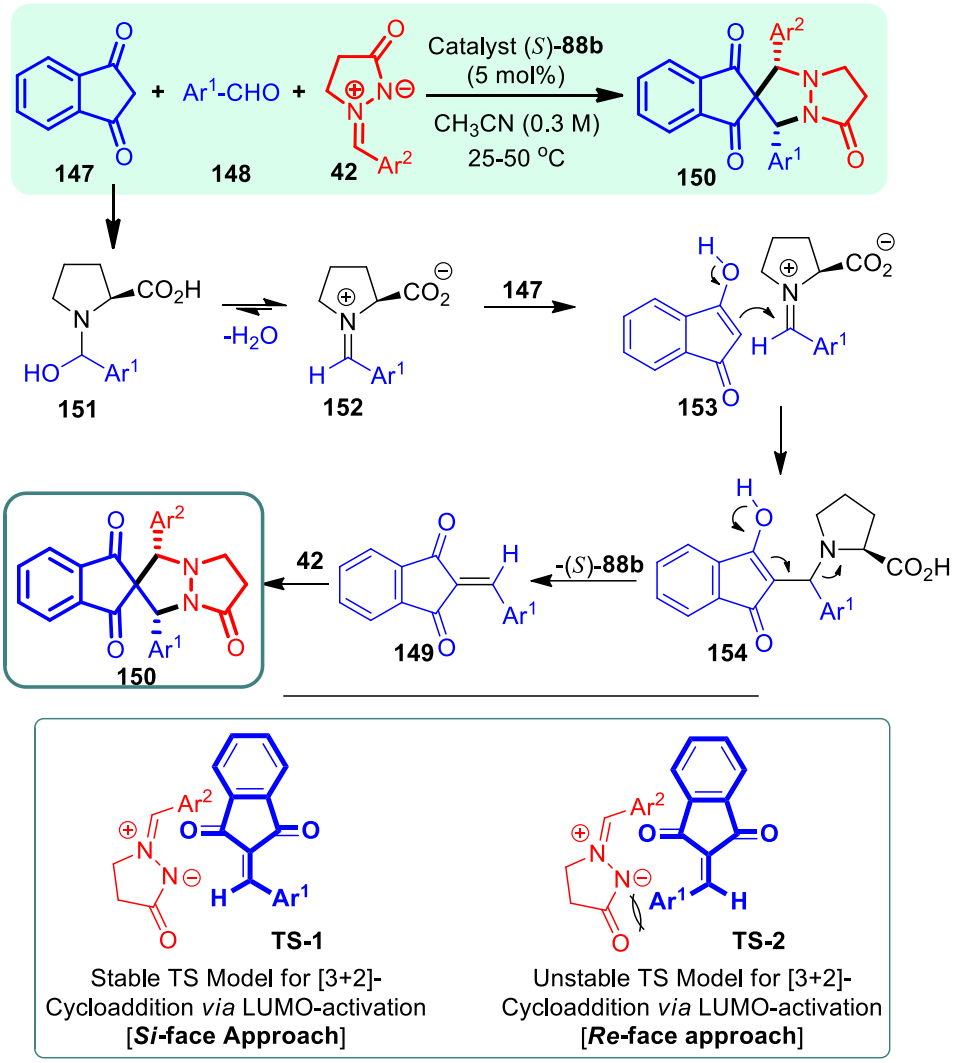


Figure-17: X-ray crystal structure of (1'*S**,3'*R**)-3'-isobutyl-1'-phenyl-6',7'-dihydro-1'H-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'H)-trione **150ua.**

4.2.5 Reaction mechanism:

The mechanism of the organocatalytic three-component azomethine imine-olefin [3+2]-cycloaddition reaction could possibly be explained as shown in the stable TS model as represented in Scheme 7. In the first step, the catalyst proline (*S*)-**88b** activates aldehyde component **148** by most likely iminium ion **152** formation from **151**, which then selectively adds to the indanedione **147** *via* a Mannich and amine elimination type reaction to generate active olefin **149**.[45] In the second step, it is proposed that the azomethine imine **42** approaches and interacts with the in situ generated 2-arylidene-1,3-indandione **149** from the *Si*-face, as the *Re*-face approach would be unstable, due to repulsion from steric hindrance. Firstly, the nitrogen anion of the azomethine imine attacks the less substituted and electronically or hydrogen-bond activated olefinic carbon, allowing the electron-rich other more substituted olefinic carbon to react with the carbon atom of the iminium ion in a concerted manner to generate the spiroindane-1,3-dione-pyrazolidinones in selective manner.

Scheme 7: Reaction mechanism for L-proline-catalyzed three-component [3+2]-cycloaddition.



4.3 Conclusion

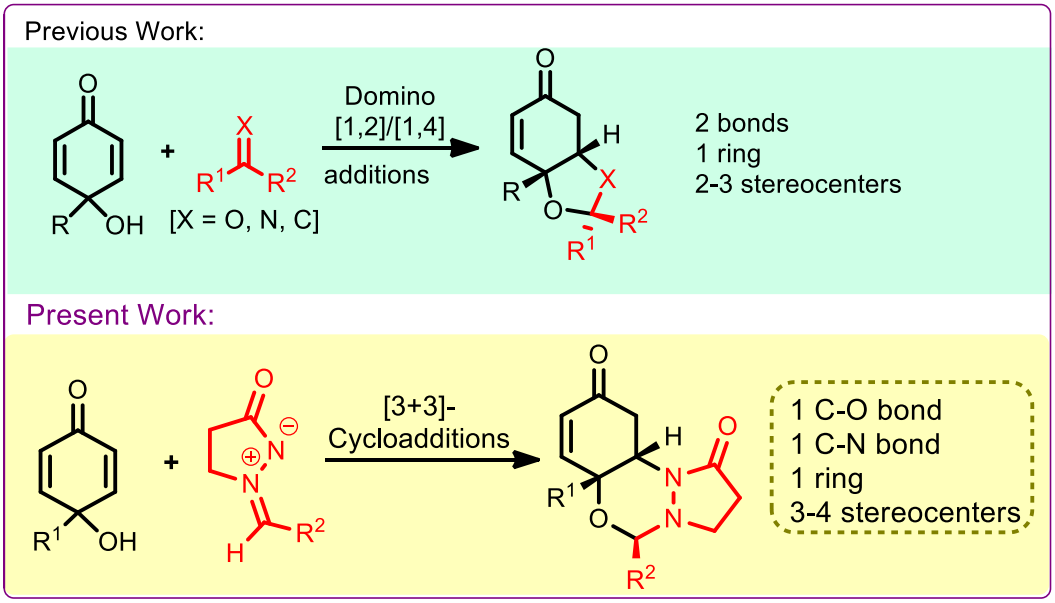
In summary, we have developed a versatile new click method for the synthesis of functionalized spiroindane-1,3-dione-pyrazolidinones **150** from simple precursors through amino acid-catalysis. The products of this click reaction **150** will be useful for the medicinal chemistry. Future investigations within the group will continue to explore the scope of this novel organo-click reaction.

5. Catalytic [3 + 3]-Cycloaddition for Regioselective Preparation of Tricyclic Oxadiazines

5.1 Introduction:

Despite their simplicity, *p*-quinols (4-alkyl-4-hydroxy-2,5-cyclohexadienones) and their derivatives have vast potential as significant building blocks in the synthesis of natural products such as cleroindicins C, D and F, (-)-mesembrine and clerobungin A as well as in reaction engineering, as is evident from past literature (Scheme 8).[47,48] Owing to their versatile reactivity, *p*-quinols are extensively used in various domino reactions, including acetalization/oxa-Michael, hemiaminalization/aza-Michael, reactions (Scheme 8).[49] They are also found to be part of biologically active molecules.

Scheme 8: Reaction Design for the Tricyclic-Oxadiazines.

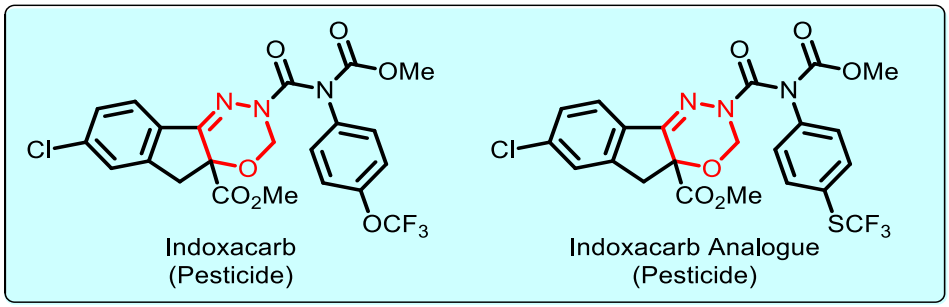


The intriguing facts mentioned below inspired us to utilize *p*-quinols. Firstly, their reactivity is ambident in nature, arising from the nucleophilicity of the tertiary hydroxyl group on one side and the presence of a double Michael acceptor system on the other side. Secondly, they impart a certain degree of intricate sophistication to the core structure of the polycyclic products. Thirdly and more importantly, they are easily and rapidly accessible from oxidative

dearomatization of phenols (Scheme 8).[50] In line with these, we contrived to unravel the uncharted potential of *p*-quinols in atom-economic, chemo- and stereoselective cycloaddition reactions.

We were curious to investigate the reaction of *p*-quinols with azomethine imines as the counterpart, as it would create an aminal through a hemiaminalization step as shown in Scheme 8. At the same time it is fascinating to study the [3+3]-cycloaddition of *p*-quinols with 1,3-dipoles of azomethine imines to construct six-membered heterocyclic rings.[51] Thus, this reaction design would furnish tricyclic-oxadiazine entity, which is not only fascinating, but also functional. For instance, indoxacarb, an oxadiazine pesticide acts against lepidopteran larvae and is the active ingredient in a number of household insecticides (Scheme 9).[52]

Scheme 9: Representative bioactive tricyclic-oxadiazines.



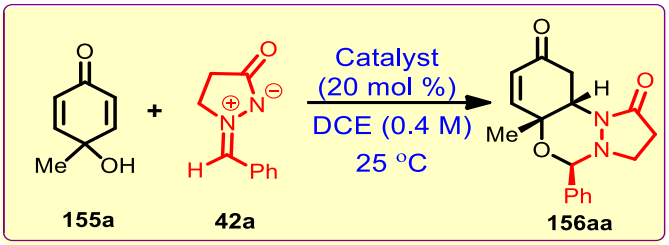
5.2 Results and Discussion

5.2.1 *Reaction Optimization:*

We initiated our study using *p*-quinol **155a** and azomethine imine **42a** as the starting materials and conducted the reaction in the presence of 20 mol % DBU **71a** as catalyst in DCE at 25 °C for 24 h. Even though we observed the formation of the expected product tricyclic-oxadiazine **156aa**, it was disappointing as the yield was very low (<5%, Table 8, entry 1). First, we selected some catalysts belonging to different categories such as tertiary amines, Lewis base, organic base, inorganic base and organic acid (Table 8). Out of the tertiary amine catalysts investigated, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) **71j**, catalyzed the reaction to furnish the product tricyclic- oxadiazine 156aa in 31% yield (with dr 14:1), while DMAP **71i**, DABCO **71d** and quinine **71k** did not catalyze the reaction at all (Table 8, entries 2-5). Alternatively, neither Lewis base triphenylphosphine **2c**, nor inorganic base potassium carbonate **71f** catalyzed the reaction (Table 8, entries 6 and 10). Gratifyingly, organic bases

such as sodium methoxide **71l**, sodium tertiary-butoxide **71m** and potassium tertiary-butoxide **71n** catalyzed the reaction and generated the product **156aa** in 67%, 54% and 70% yields respectively with excellent diastereomeric ratio (*dr* 14:1 to 17:1). *p*-TSA **24e** did not promote the reaction (Table 8, entry 11). In a similar manner, cycloaddition reaction with the treatment of 1.5 equiv of NaH **71o** furnished the product **156aa** in poor (10%) yield (Table 8, entry 12).

Table 8: Reaction Optimization.[a-c]



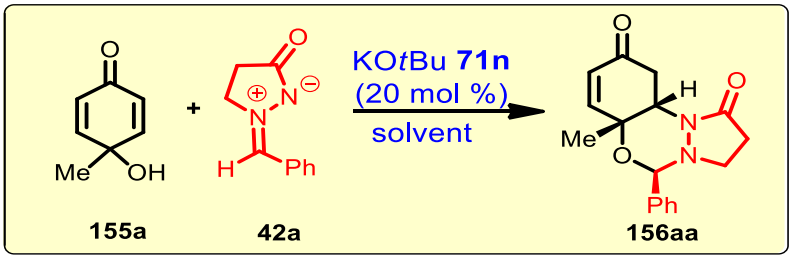
Entry	Catalyst (20 mol %)	Time (h)	Yield **156aa** (%)[b]	*dr*[c]
1	**71a**: DBU	24	<5	
2	**71i**: DMAP	24	nr	-
3	**71d**: DABCO	24	nr	-
4	**71j**: TBD	24	31	14:1
5	**71k**: Quinine	24	nr	-
6	**2c**: PPh_3	24	nr	-
7	**71l**: NaOMe	2	67	14:1
8	**71m**: NaO*t*Bu	2	54	15:1
9	**71n**: KO*t*Bu	1	70	17:1
10	**71f**: K_2CO_3	24	nr	-
11	**24e**: *p*-TSA	24	<5	
12[d]	**71o**: NaH (1.5 equiv)	18	10	

[a] Reactions were carried out in solvent (0.4 M) with 1 equiv of **155a** relative to the **42a** (0.4 mmol) in the presence of 20 mol % of catalyst **71/2c/24e**. [b] Yields refers to the column purified products.[c] *dr* was determined by ^{1}H NMR spectroscopy. [d] Reaction conversion and product purity was very poor. nr = no reaction.

In search of the best solvent for the reaction, an extensive screening of solvents such as DMSO, *t*BuOH, toluene, THF, CH_3CN, $CHCl_3$ and DCM was performed. While the

reaction did not seem to proceed at all in DMSO (Table 9, entry 1), it was very sluggish and the observed yields and *dr*'s were more or less equally inferior in *t*BuOH, toluene, THF and $CHCl_3$ (Table 9, entries 2, 3, 4 and 6). Although, the reaction performed in CH_3CN was complete within 1 h, it produced the product in 46% yield with 25:1 *dr* (Table 9, entry 5). Observation of poor yields and *dr*s in these solvents may be due to the loss of real catalytic nature of KO^{t}Bu **71n** by the interaction with acidic C/O-H bonds of solvents. The product yield decreased slightly in DCM with increased (25:1) *dr* (Table 9, entry 7). In DCE (which was used at the start), on extending the reaction time to 2 h, the product yield and *dr* decreased (Table 9, entry 8). Comparable yields were obtained in DCM and DCE with slight change in *dr*'s at 25 °C for a reaction time of 2 h (Table 9, entries 7 and 8). With the anticipation of improving the product yields, we considered studying the effect of temperature. However, increasing the reaction temperature from 25 °C to 40 °C did not increase the yield significantly in DCE (Table 9, entries 8 and 9). However, performing the reaction at 40 °C in DCM a considerable increase in the yield and *dr* was observed (Table 9, entry 10). Surprisingly, same reaction with 10 mol % of KO^{t}Bu **71n** at 40 °C for 3 h furnished the product **156aa** in reduced yield with 14:1 *dr* (Table 9, entry 11). Under the catalysis of 15 mol % KO^{t}Bu **71n** at 40 °C for 3 h in DCM, the product **156aa** was obtained in 70% yield with 14:1 *dr* (Table 9, entry 12), which is definitely not better than 20 mol % KO^{t}Bu **71n**. On increasing the catalyst loading to 30 mol % KO^{t}Bu **71n** and conducting the reaction for 1 h at 40 °C, the product yield and *dr* reduced to 60% with 3.5:1 *dr* (Table 9, entry 13). Increasing the azomethine imine **42a** equivalents to 1.3 or 1.6 times also did not seem to increase the product yield (Table 9, entries 14, 15 and 16). Swapping the corresponding equivalents of **155a** and **42a** gave surprisingly reduced yield and *dr* (Table 9, entry 17). These results clearly indicate that the [3+3]-cycloaddition yield and *dr* is completely controlled by the solvent nature, temperature, substrate equivalents, catalyst loading and reaction time as shown in Table 9. Consequently, performing the reaction between 1.0 equiv of **155a** and 1.2 equiv of **42a** in the presence of 20 mol % KO^{t}Bu **71n** in DCM at 40 °C for 1 h to furnish the product **156aa** in 76% yield with 50:1 *dr* was found to be the optimized condition (Table 9, entry 16).

Table 9: Reaction Advanced Optimization.[a]



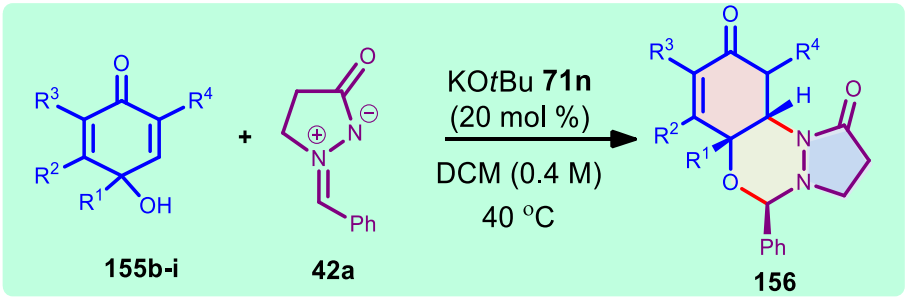
Entry	Solvent (0.4 M)	Time (h)	Temp (°C)	Yield **156aa** (%)[b]	*dr*[c]
1	DMSO	24	25	nr	-
2	*t*BuOH	5	25	17	7:1
3	Toluene	24	25	18	14:1
4	THF	24	25	15	3:1
5	CH_3CN	1	25	46	25:1
6	$CHCl_3$	24	25	20	14:1
7	DCM	2	25	61	25:1
8	DCE	2	25	65	14:1
9	DCE	2	40	67	14:1
10	DCM	1	40	75	50:1
11[d]	DCM	3	40	29	14:1
12[e]	DCM	3	40	70	14:1
13[f]	DCM	1	40	60	3.5:1
14[g]	DCM	1	40	76	50:1
15[h]	DCM	1	40	71	50:1
16[i]	**DCM**	**1**	**40**	**76**	**50:1**
17[j]	DCM	1	40	50	9:1

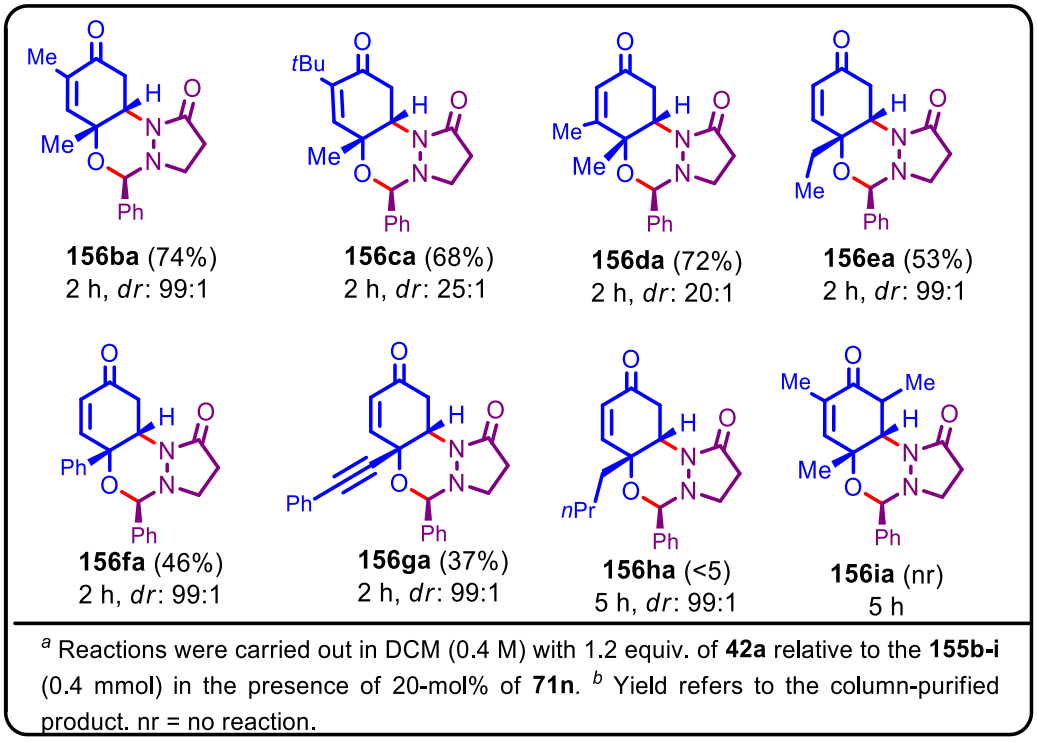
[a] Reactions were carried out in solvent (0.4 M) with 1 equiv of **155a** relative to the **42a** (0.4 mmol) in the presence of 20 mol % of catalyst **71n**. [b] Yields refers to the column purified products. [c] *dr* was determined by ^{1}H NMR spectroscopy.[d] KO^{t}Bu **71n** (10 mol %), [e] **71n** (15 mol %), [f] **71n** (30 mol %), [g] **42a** (1.3 eq), [h] **42a** (1.6 eq), [i] **42a** (1.2 eq), [j] **155a** (1.2 eq), nr = no reaction.

4.2.2 Scope of the new tricyclic reaction with p-Quinols:

After the completion of optimization studies, we decided to further investigate the reaction scope by introducing different alkyl substitutions on the reactant partner *p*-quinol **155a**. It was observed that in most of the cases the product yields were either the same as that of the parent *p*-quinol **155a** or lesser and in few other cases there was negligible yield or no reaction (Table 10). The reaction of *p*-quinol with an additional methyl group at C-2 **155b** furnished the product **156ba** in 74% yield with 99:1 *dr*, whereas *p*-quinol containing an extra tertiary-butyl group at C-2 1c furnished the product **156ca** in 68% yield with diminished *dr* 25:1 (Table 10, entries 1 and 2). Interestingly, substitution of a methyl group at the C-3 position did not appear to have much effect on the yield, whereas the diastereoselectivity reduced to 20:1 (Table 10, entry 3).

Table 10: Reaction Scope with *p*-Quinols.[a,b]





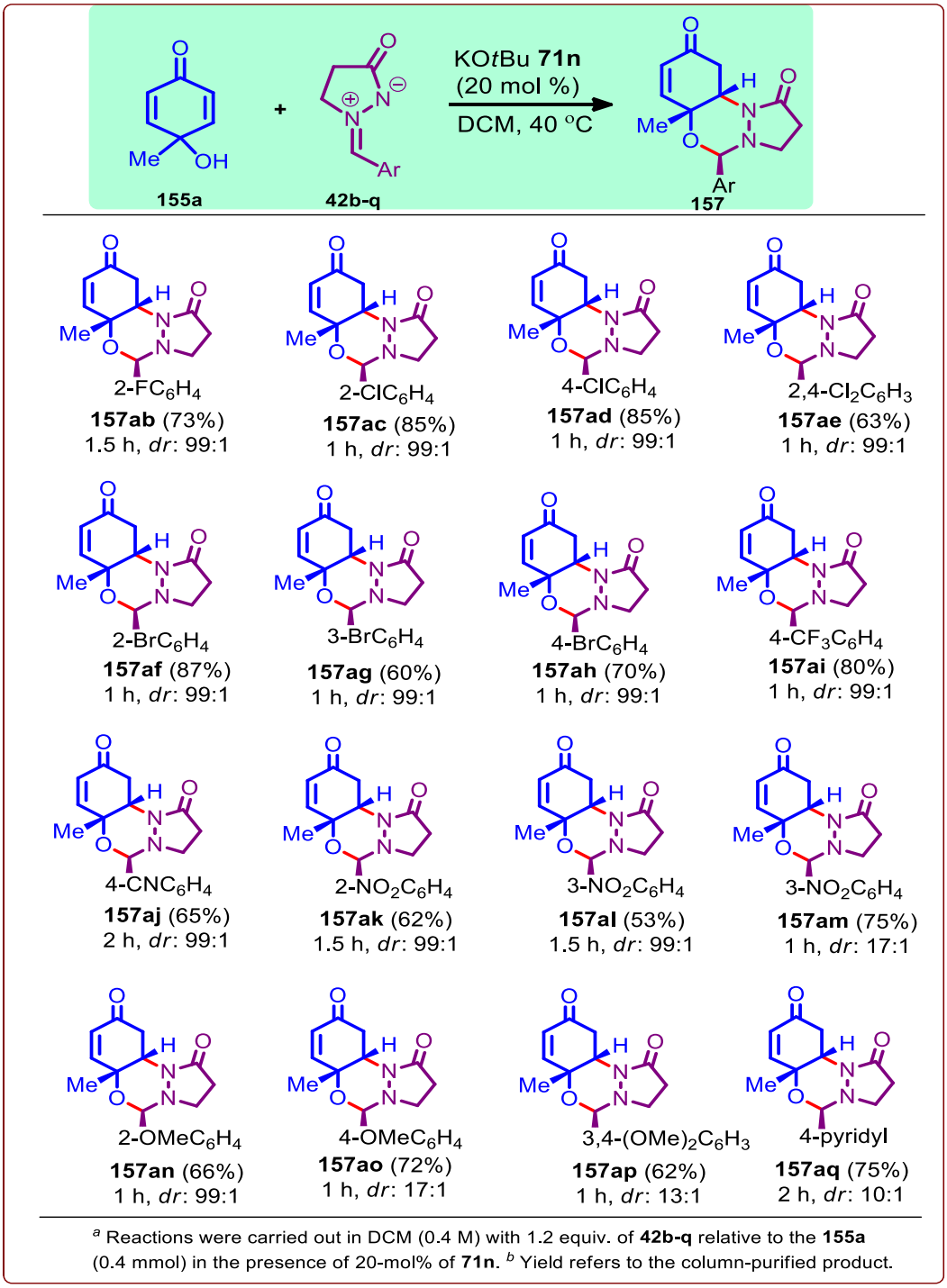
[a] Reactions were carried out in DCM (0.4 M) with 1.2 equiv. of **42a** relative to the **155b-i** (0.4 mmol) in the presence of 20-mol% of **71n**. [b] Yield refers to the column-purified product. nr = no reaction.

By replacing the methyl group at C-4 of *p*-quinol **155a** with either Et, Ph, or phenylethynyl the product yield drops drastically to moderate, but the *dr* remained constant at 99:1 (Table 10, entries 4-6). Disappointingly, introduction of a quite bulky sec-butyl group at C-4 of p-quinol **155a** hindered the reactivity and produced **156ha** only in <5% yield (Table 10, entry 7). It was shocking that when a methyl group each was introduced on either side of the carbonyl carbon (C-2 and C-6) no reaction was observed (Table 10, entry 8).

4.2.3 Scope of the new tricyclic reaction with azomethine imines:

On extending the investigations toward the scope of azomethine imines, we endeavored to study the effect of various substituents at different positions on the phenyl group of **42a** (Table 11). The halogen substituents such as F, Cl, and Br, electron withdrawing groups like CF_3, CN and NO_2, electron donating groups such as Me, and OMe, and heteroatom at the *ortho*-, *meta*- or *para*- or in some cases di-substitutions were all comfortably well-suited for the reaction and the products **157ab**-**157aq** were generated in excellent to reasonable yields with excellent *dr* of 99:1 throughout, except for a few cases (**157am**, **157ao, 157ap** and **157aq**), wherein the *dr* dropped considerably. While *ortho*- or *para*-chloro, *ortho*-bromo and *para*-trifuoromethyl substitutions produced higher yields (80-87%, Table 11, entries 2, 3, 5 and 8) on the contrary, dichloro substitution reduced the yield to 63% (Table 11, entry 4). *Ortho*-fluoro, *para*-bromo, *para*-methyl and *para*-methoxy substitutions appeared to not affect the yield much and the corresponding products formed in 70-75% yields (Table 11, entries 1, 7, 12 and 14). In the cases of *meta*-bromo, *para*-cyano, *ortho*-nitro, *meta*-nitro, *ortho*-methoxy, *meta*-, *para*-dimethoxy and 4-pyridyl substitutions the yields fell to moderate 48-66% (Table 11, entries 6, 9, 10, 11, 13, 15 and 16). We performed gram-scale synthesis of tricyclic-oxadiazine **156aa** in 1.493 g from the **155a** (1.0 g) and **42a** (1.67 g, 1.2 equiv) under the Brønsted base **71n**-catalysis without effecting the reaction selectivity and reactivity.

Table 11: Reaction scope azomethine imines.[a,b]

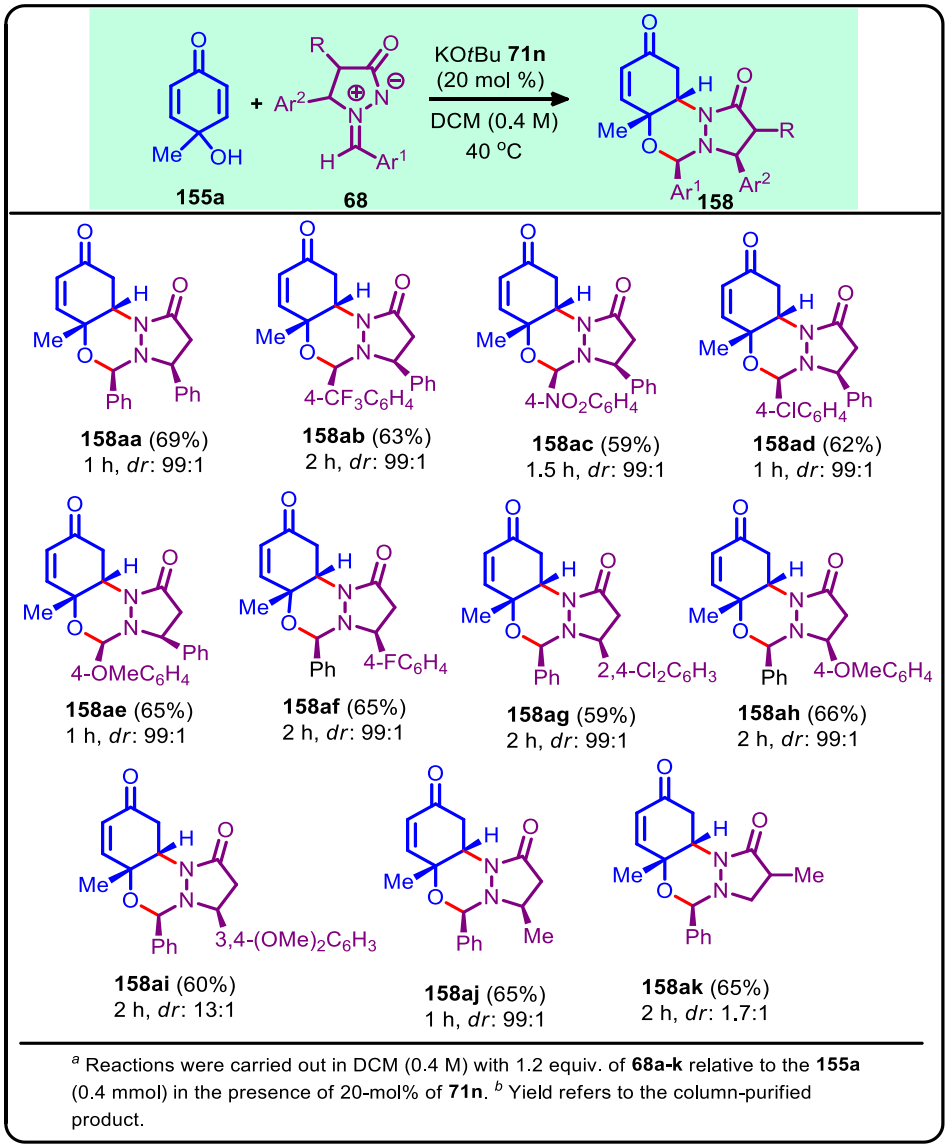


[a] Reactions were carried out in DCM (0.4 M) with 1.2 equiv. of **42b-q** relative to the **155a** (0.4 mmol) in the presence of 20-mol% of **71n**. [b] Yield refers to the column-purified product.

To increase the resourcefulness further and to examine the adaptability of the reaction for another different substitution pattern on the azomethine imines, we selected some more azomethine imines of the form **68** and tested their reactivity and selectivity (Table 12). All the tested (*Z*)-2-arylidene-3-aryl/alkyl-5-oxopyrazolidin-2-ium-1-ides **68** containing halogen,

electron-withdrawing or donating groups on either of the two phenyl rings of **68** were quite well compatible to furnish the products **158aa**-**158ai** in good yields with excellent *dr* (99:1), except for **158ai**, whose *dr* was 13:1 (Table 12, entries 1-9). Notably, swapping of a phenyl group in **68** with a methyl group was also tolerable and the corresponding product **158aj** was generated in 65% yield with *dr* 99:1 (Table 12, entry 10). Surprisingly, reaction of **155a** with (*Z*)-2-benzylidene-4-methyl-5-oxopyrazolidin-2-ium-1-ide **68k** under the similar conditions furnished the tricyclic-oxadiazine **158ak** in 65% yield with poor *dr* 1.7:1 as shown in Table 12, entry 11. Observation of poor *dr* in product **158ak** formation may be due to the loss of steric hindrance in the pre-transition state of **155a**+**68k**.

Table 12: Reaction scope with functionally rich azomethine imines.[a,b]



[a] Reactions were carried out in DCM (0.4 M) with 1.2 equiv. of **68a-k** relative to the **155a** (0.4 mmol) in the presence of 20-mol% of **71n**. [b] Yield refers to the column-purified product.

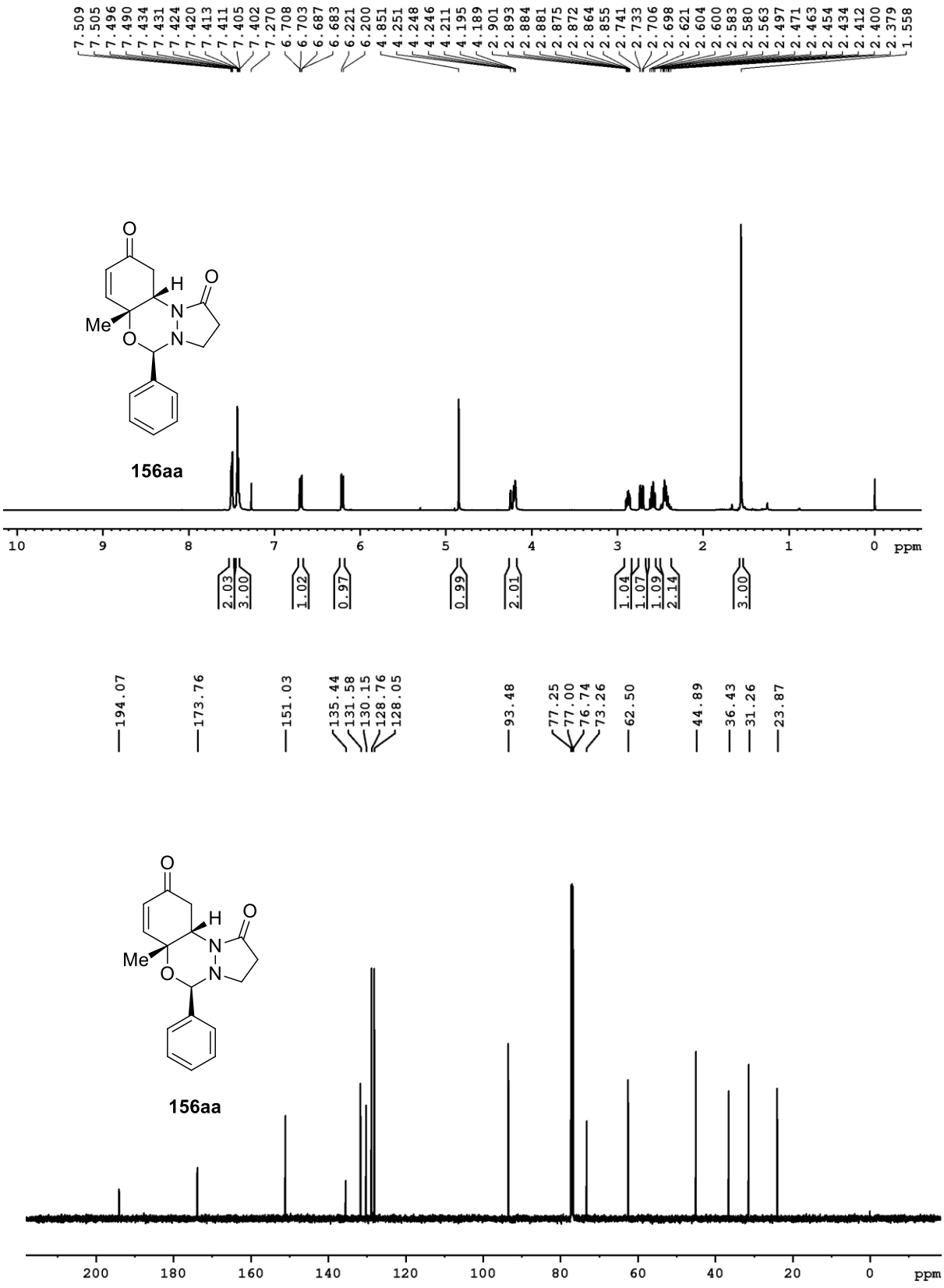


Figure-18: ^{1}H and ^{13}C NMR spectra of the product **156aa.**

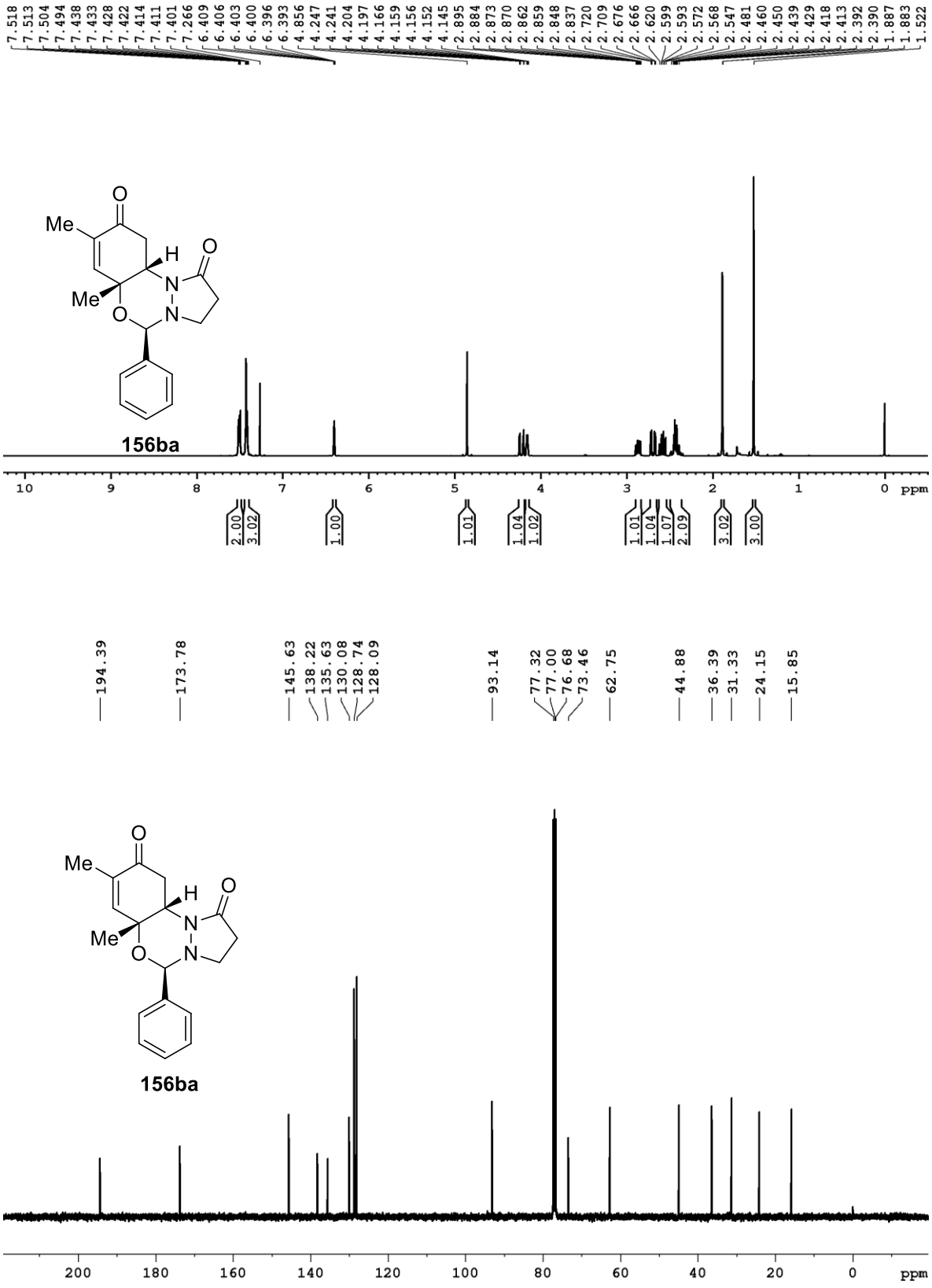


Figure-19: ^{1}H and ^{13}C NMR spectra of the product **156ba**

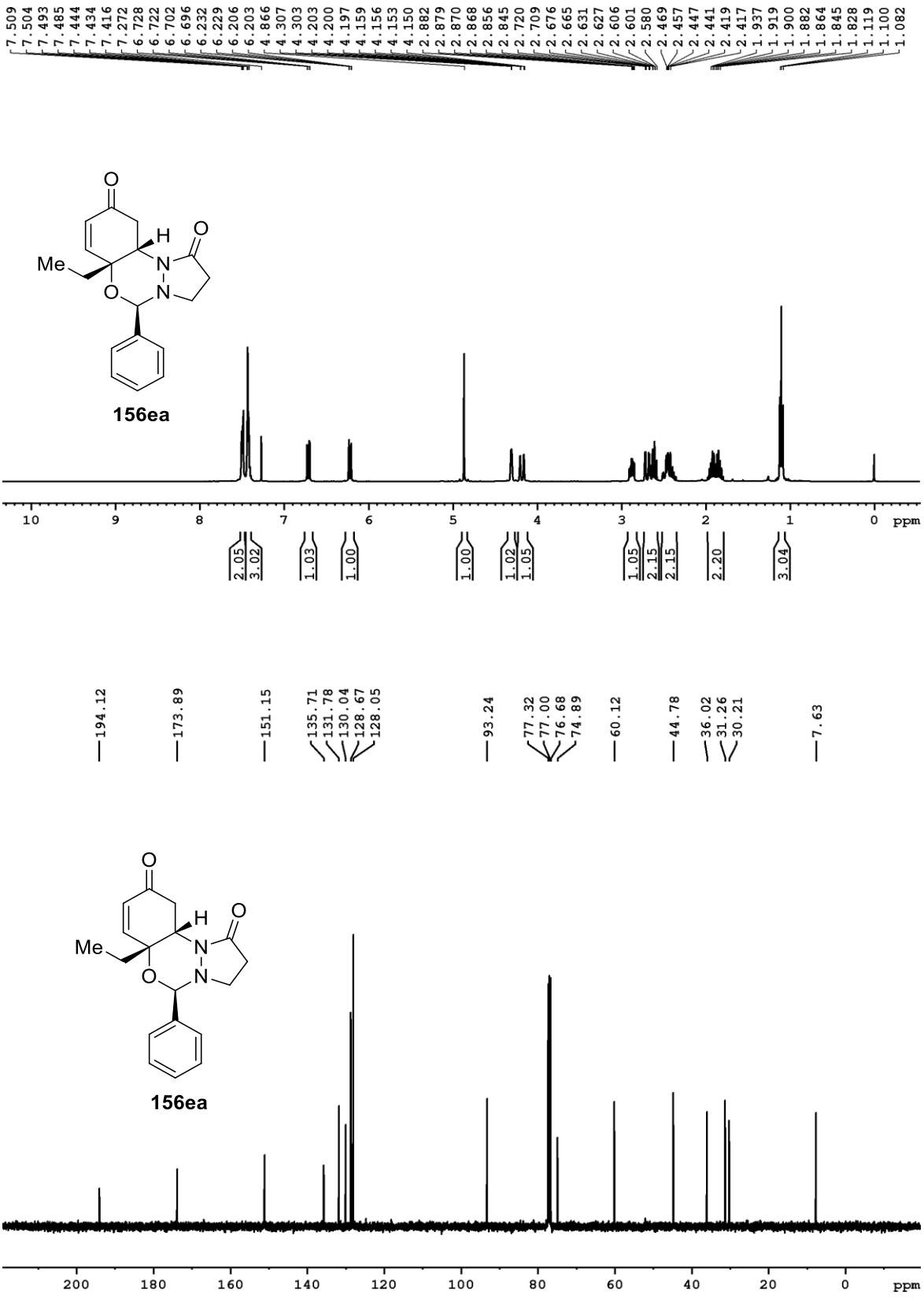


Figure-20: ^{1}H and ^{13}C NMR spectra of the product **156ea**

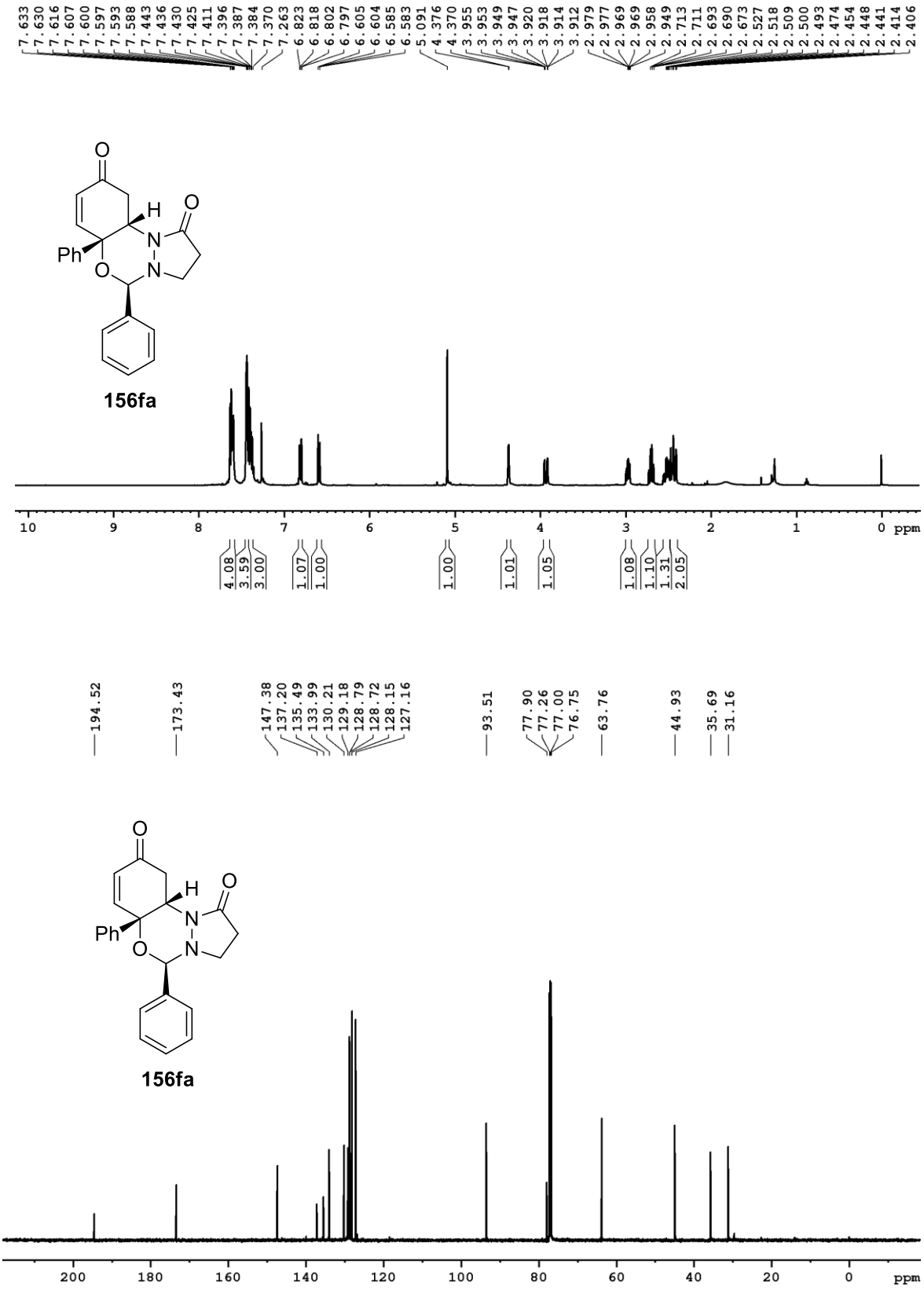


Figure-21: ^{1}H and ^{13}C NMR spectra of the product **156fa**

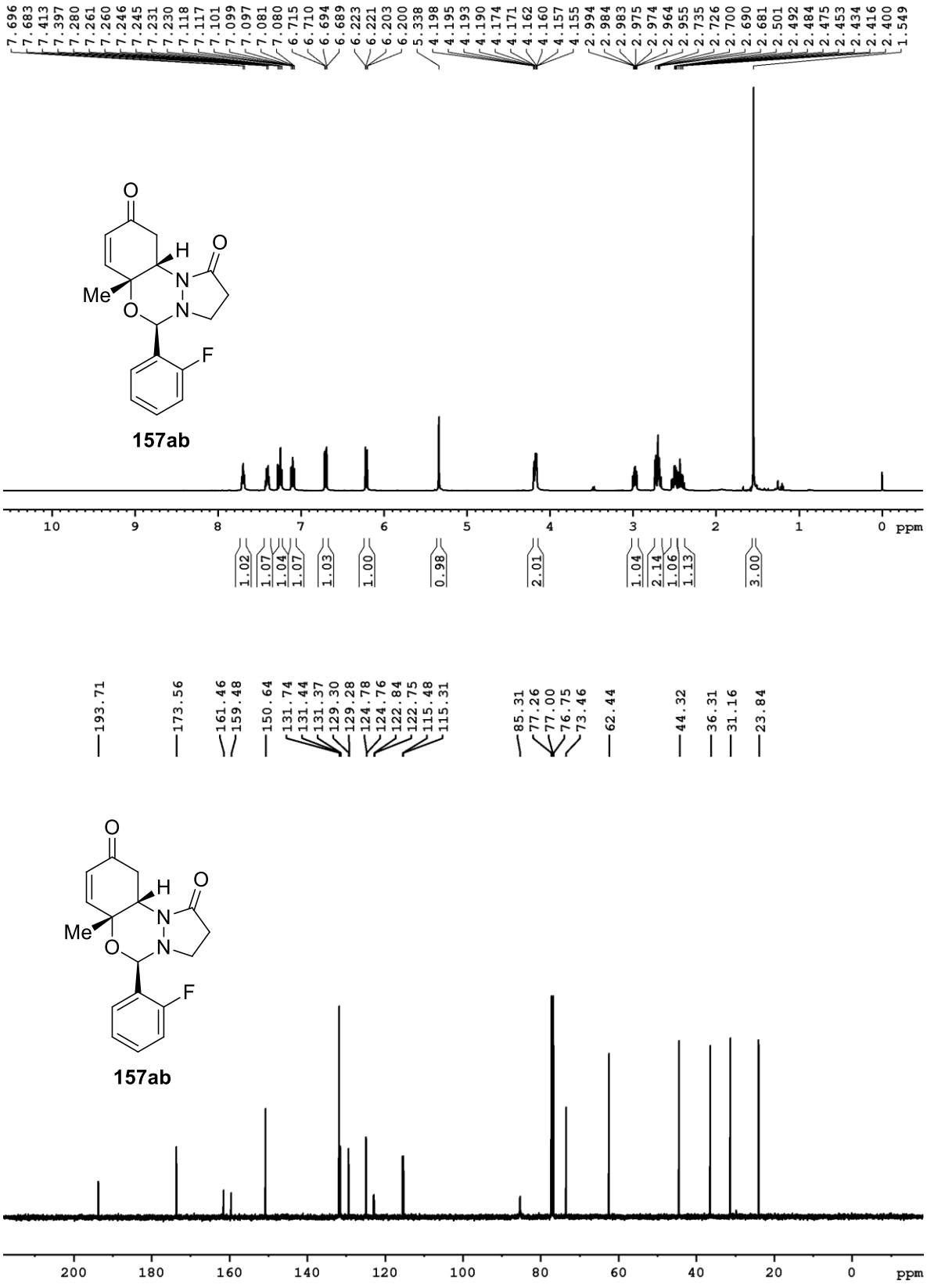


Figure-22: ^{1}H and ^{13}C NMR spectra of the product **157ab**

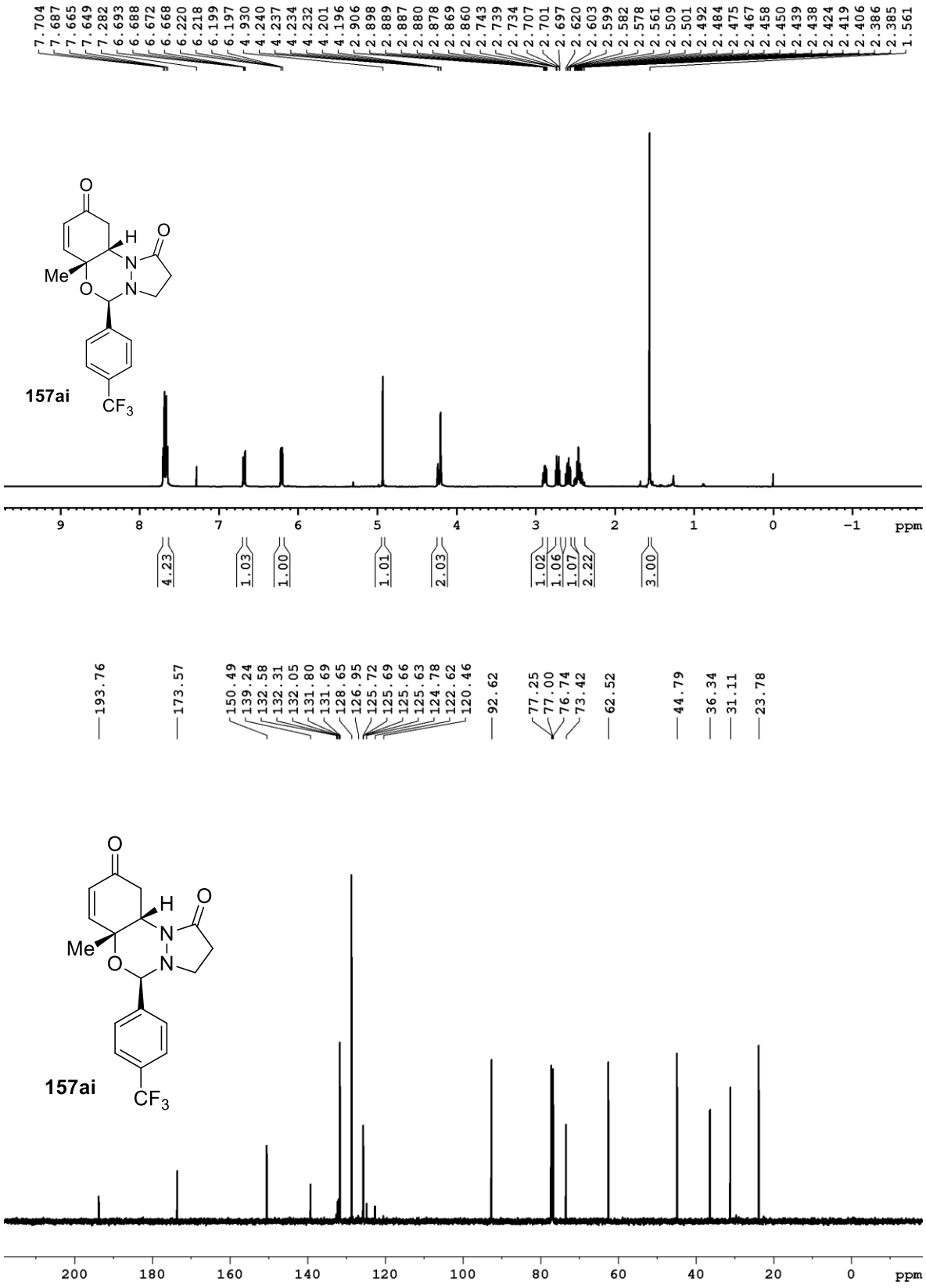


Figure-23: ^{1}H and ^{13}C NMR spectra of the product **157ai**

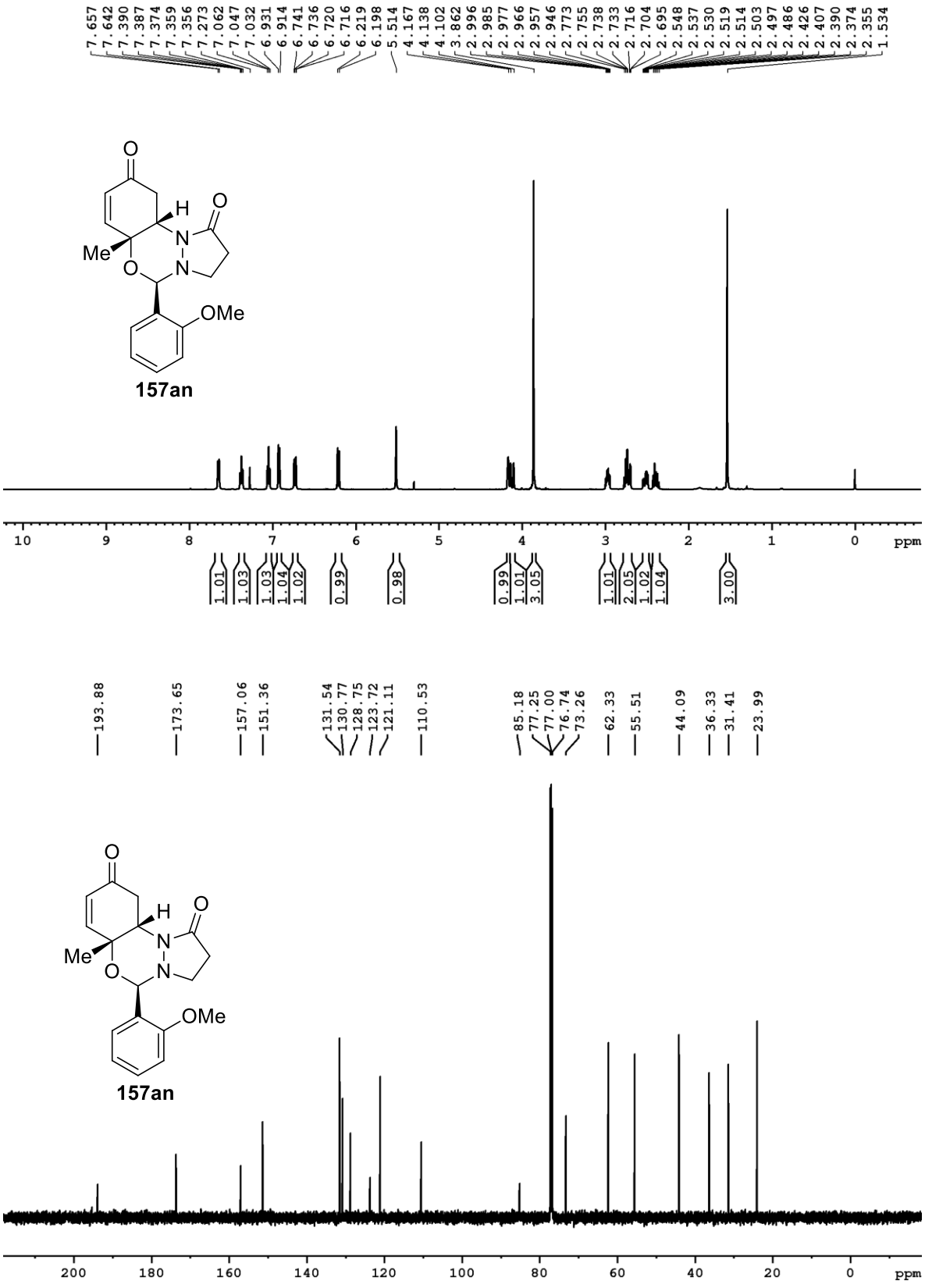


Figure-24: ^{1}H and ^{13}C NMR spectra of the product **157an**

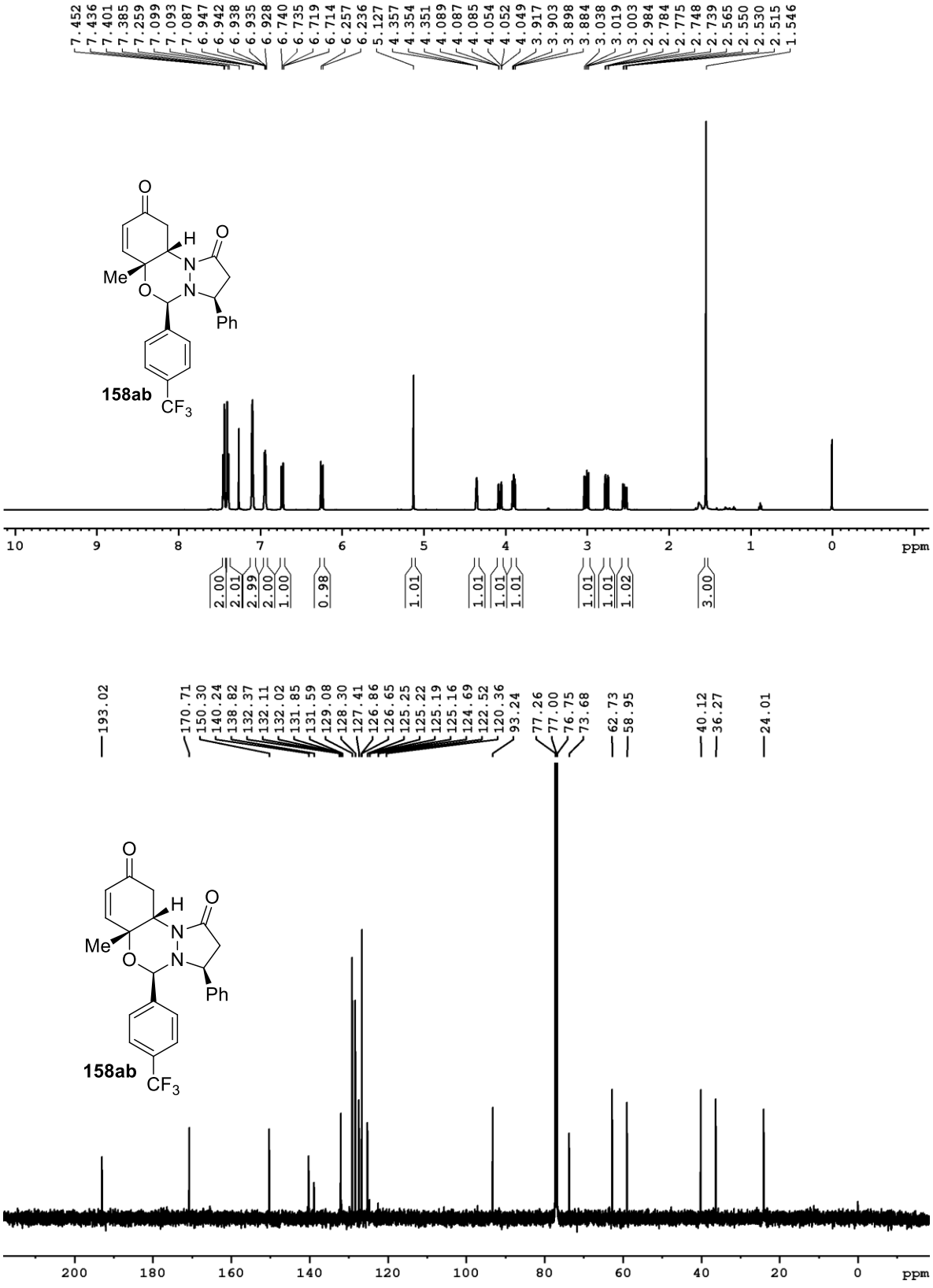


Figure-25: ^{1}H and ^{13}C NMR spectra of the product **158ab**

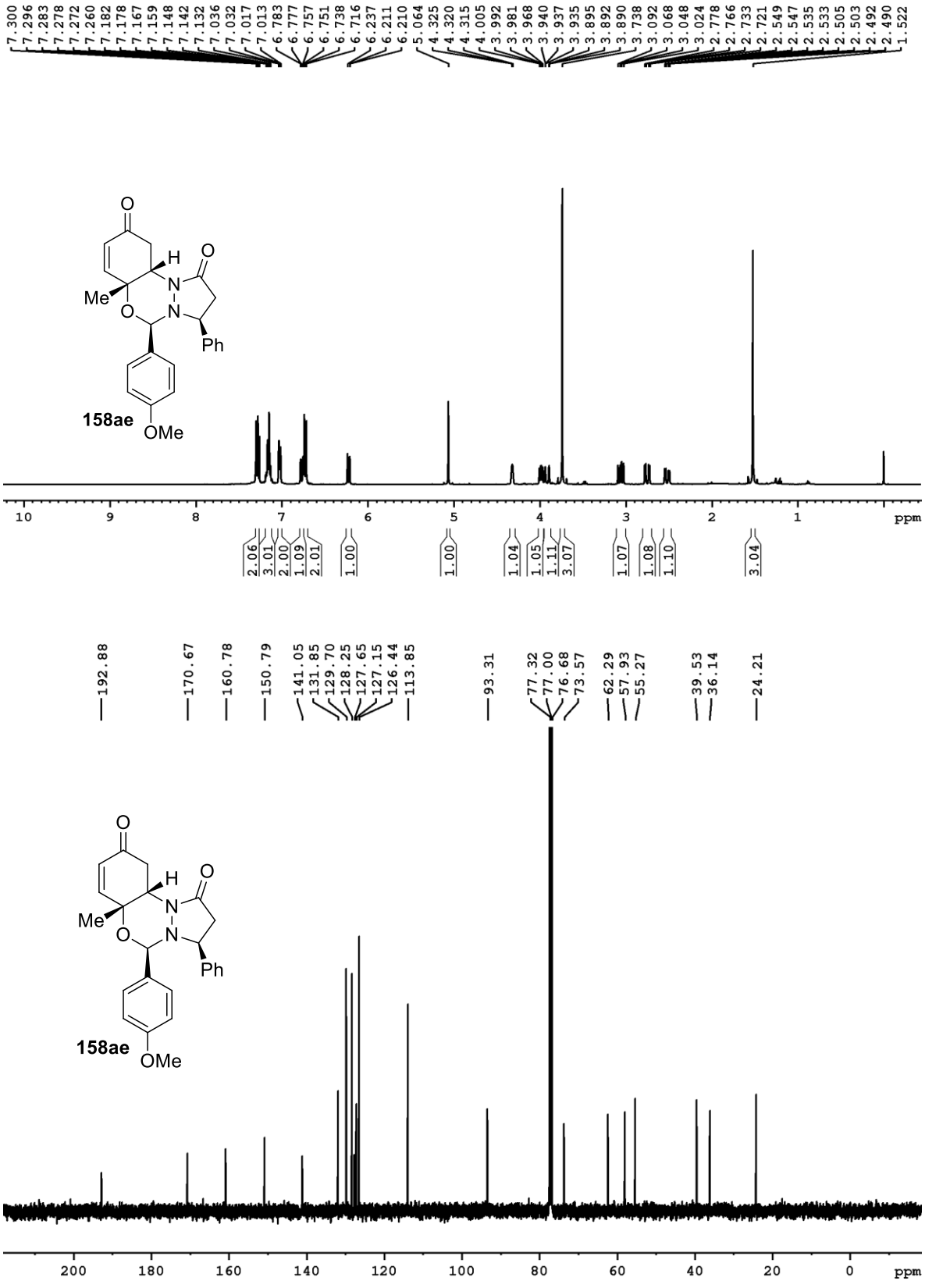


Figure-25: ^{1}H and ^{13}C NMR spectra of the product **158ae**

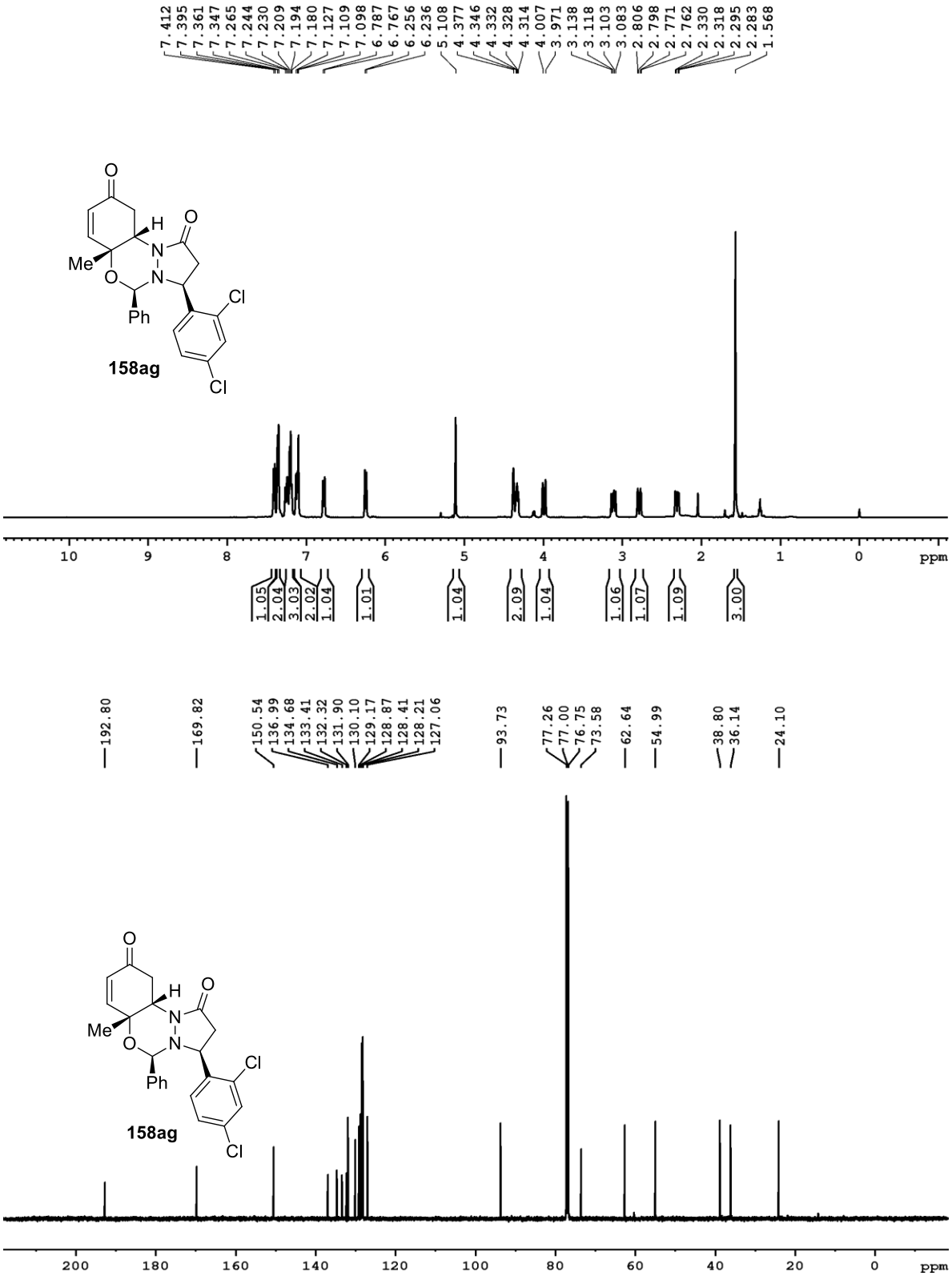


Figure-26: ^{1}H and ^{13}C NMR spectra of the product **158ag**

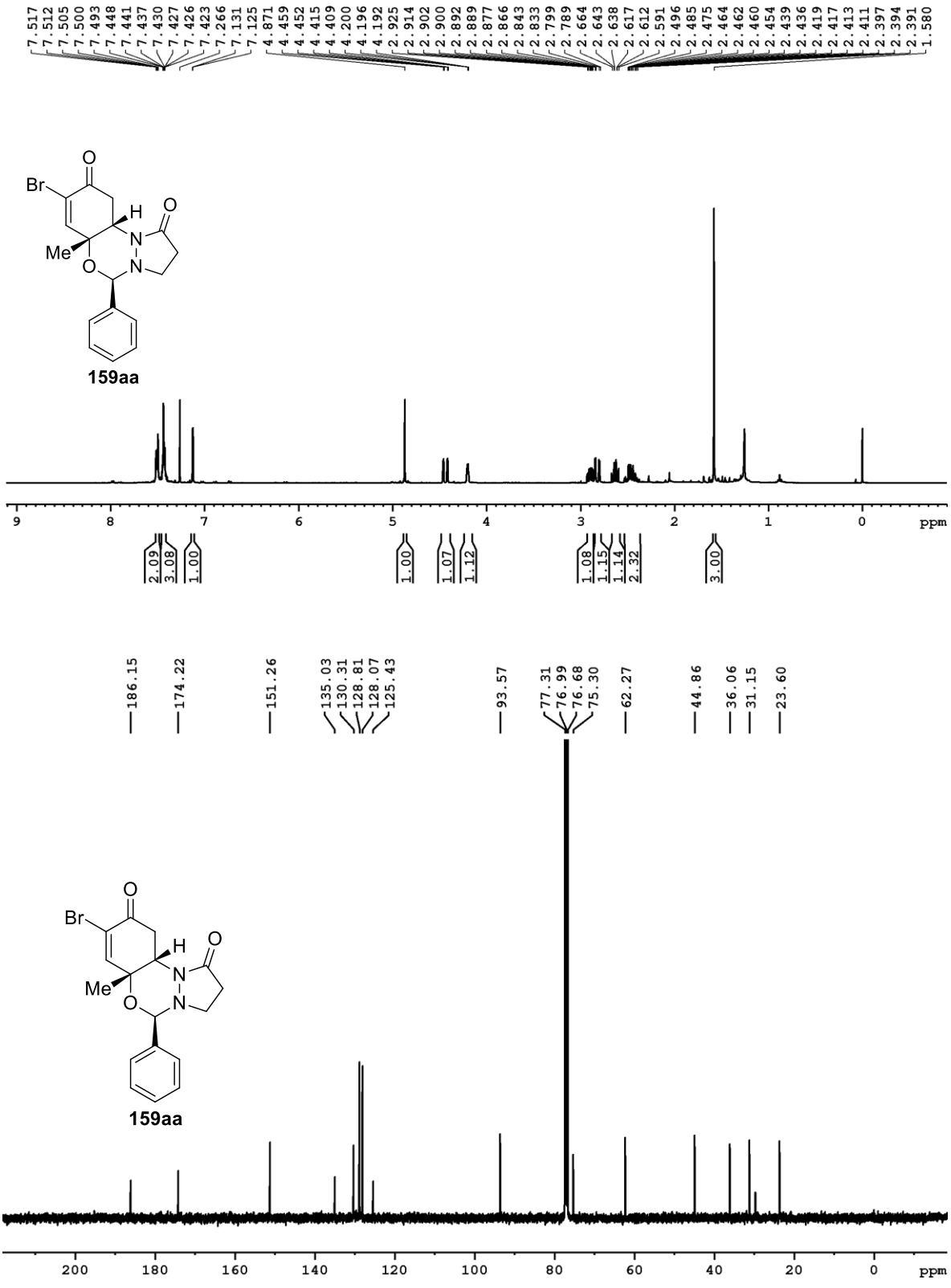
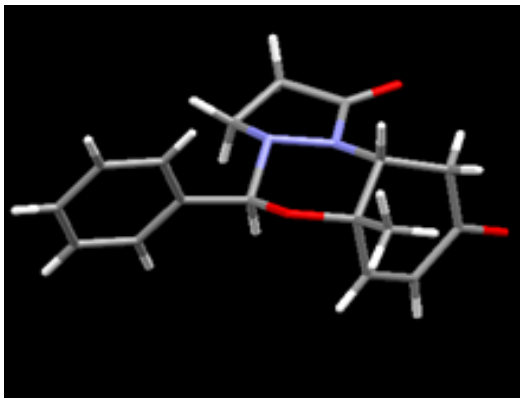
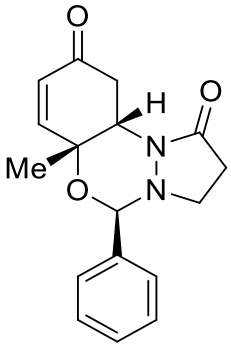


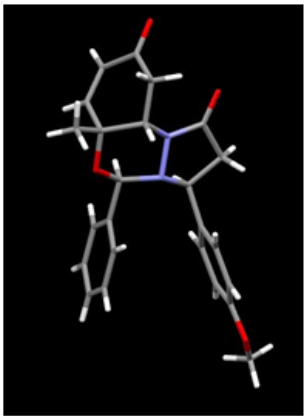
Figure-27: ^{1}H and ^{13}C NMR spectra of the product **159aa**

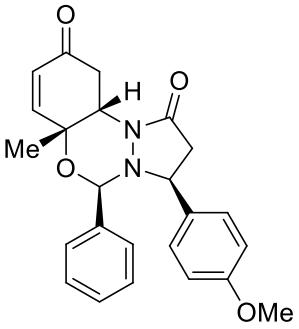




156aa

Figure 28. Crystal structure of (5*R**,6a*R**,10a*S**)-6a-methyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[*e*]pyrazolo[1,2-*c*][1,3,4]oxadiazine-1,9(5*H*,6a*H*)-dione (**156aa**).



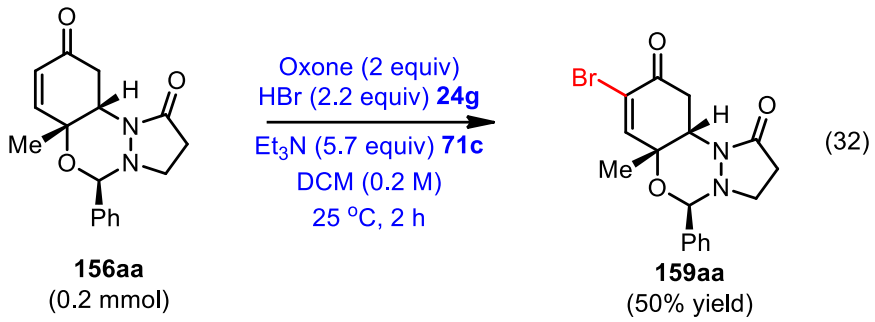


158ah

Figure 29. Crystal structure of (3*S**,5*R**,6a*R**,10a*S**)-3-(4-methoxyphenyl)-6a-methyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[*e*]pyrazolo[1,2-*c*][1,3,4]oxadiazine-1,9(5*H*,6a*H*)-dione (**158ah**).

3.2.4 *Synthetic application of product 155aa:*

As part of synthetic applications, reaction of **156aa** with oxone and HBr in the presence of Et_3N in DCM at 25 °C for 2 h furnished the brominated tricyclic-oxadiazine **159aa** in 50% yield, and which can be a precursor for a variety of coupling reactions (Eq.32). The structure and stereochemistry of the products, tricyclic-oxadiazines **156**, **157** and **158** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on **156aa** and **158ah** as shown in Figures 28 and 29.[53]

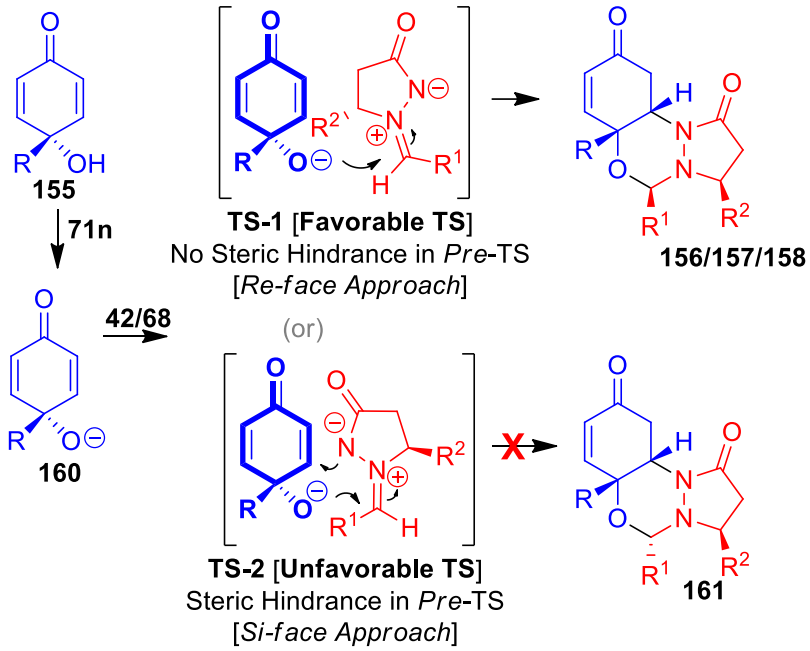


(32)

3.2.5 *Reaction mechanism:*

According to the plausible reaction mechanism depicted in Scheme 10, first the Brønsted base abstracts the proton of the tertiary hydroxyl group of *p*-quinol **155a** to generate the potassium dienolate **160**, which subsequently adds to the azomethine imine **42**/**68** dipole in a highly selective mode to produce the nitrogen anion through **TS-1** instead of **TS-2** due to the steric hindrance and electrostatic repulsions. Final in situ chemoselective intramolecular addition of the nitrogen anion to the Michael acceptor system would take place instantaneously in a highly diastereoselective 1,4-fashion to furnish the product tricyclic-oxadiazines **156**, **157** or **158**. At present we have no evidence of knowing if it is a stepwise or a concerted one, but we believe it is going through concerted path as we did not observe intermediates during the reaction.

Scheme-10: Reaction Mechanism:



5.3 Conclusions

In summary, a straightforward, atom-economical, chemoselective, stereoselective and elegant Brønsted base-catalyzed [3+3]-cycloaddition route for accessing functionally rich tricyclic-oxadiazines has been accomplished. This catalytic [3+3]-cycloaddition afforded the biologically relevant products of tricyclic-oxadiazines in very good to moderate yields with excellent diastereoselectivity.

6. Rawal's Catalyst as an Effective Stimulant for the Highly Asymmetric Michael Addition of β-Keto Esters to Functionally Rich Nitro-olefins

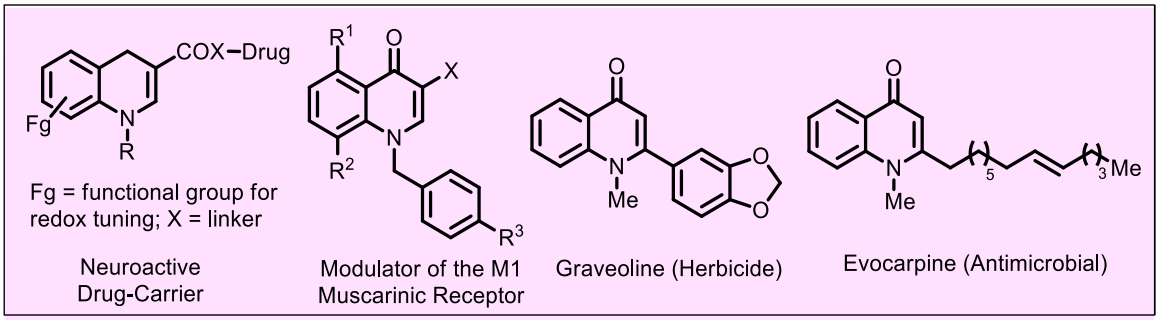
6.1 Introduction:

Recently organocatalytic domino/cascade reactions have emerged as powerful strategy for the complex molecular synthesis by employing simple and readily available precursors in a simple operational manner.[54] In this scenario, one of the important protocol for the C–C bond formation is asymmetric Michael reaction, which has been extensively used in cascade reactions.[55] Wherein, the Michael reaction of *β*-keto esters to nitro-olefins is a fully atom-economic transformation with prominent synthetic potential as the resulting functional groups will be in high demand.[56] To control the reactivity and selectivity of this Michael reaction, in 2003 Takemoto and co-workers identified the bifunctional thiourea–tertiary amine as an efficient catalyst.[57] A milestone report by Rawal's group showed that replacement of the thiourea function by a squaramide catalyst as the hydrogen-bond donor allows a dramatic decrease in the catalyst loading and also increase in the reaction rate/selectivity.[58,59] The pioneering work of Rawal's and other groups from the past few years has shown the importance of chiral hydrogen-bonding catalysis through squaramide catalyst.[58,59]

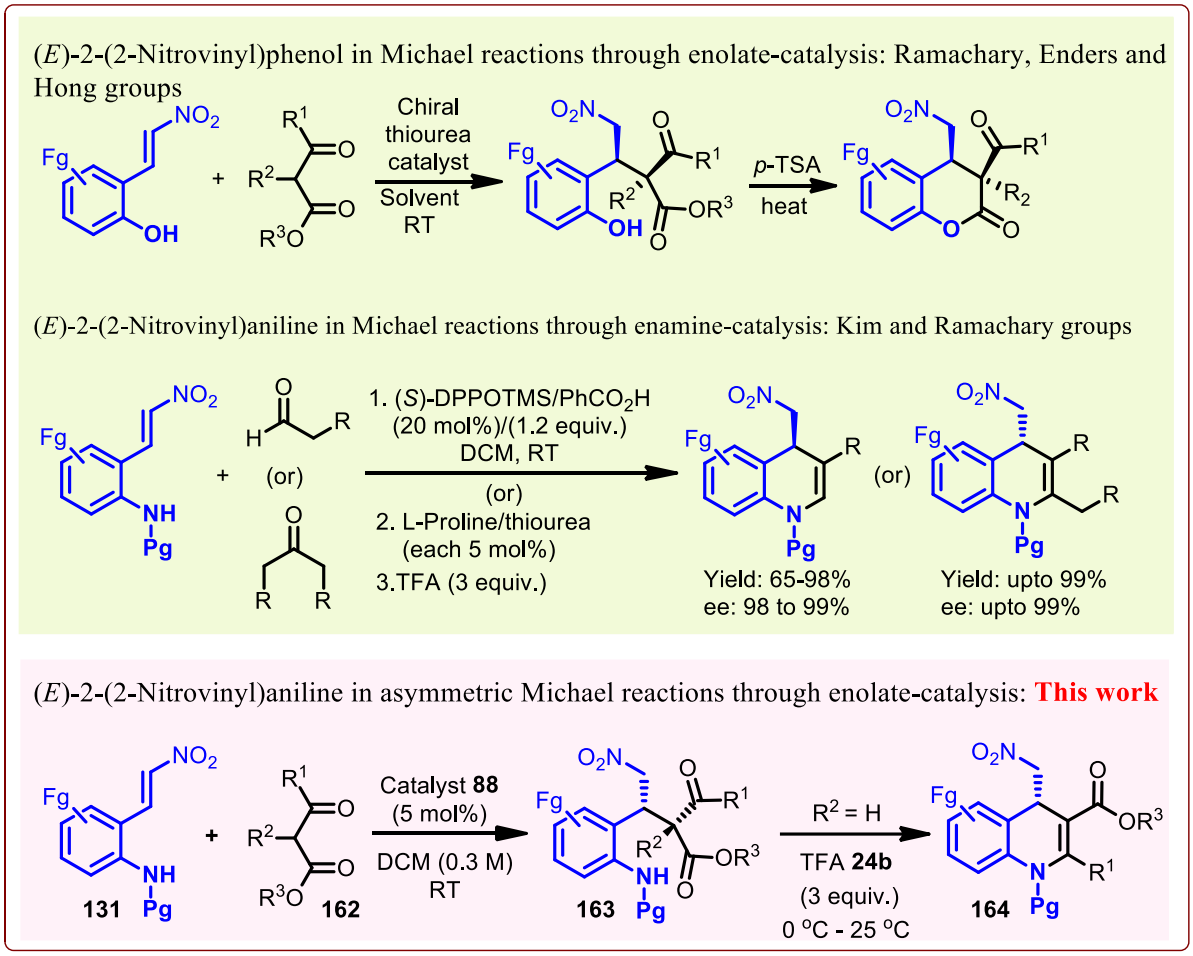
Nowadays, bio-mimetic one-pot synthesis of the highly functionalized chiral Michael adducts for synthetic applications are in high demand. Recently, we and others have reported the natural products inspired dihydrocoumarins synthesis through a Michael addition of 1,3-dicarbonyls to 2-(2-nitrovinyl)phenol and subsequent intramolecular hemiacetalization.[60] In this reaction, the *ortho*-hydroxyl group participates as neighboring group both during and after the reaction and makes this sequence as a powerful tool among the existing annulation methods. With this inspiration, herein we describe an unusual efficient neighboring *ortho*-amino group engaged asymmetric organocatalytic sequential one-pot reaction for the synthesis of drug-like chiral dihydroquinolines from simple substrates and catalysts by using sequential Michael/amination/dehydration reactions. Hydroquinolines are versatile synthetic intermediates in organic synthesis and also prevalent unit in biological and pharmaceutical substances (Scheme 11).[61] Even though numerous synthetic methods have been known for their

synthesis, there is an urgent requirement to develop an efficient asymmetric protocol due to their many applications.[62]

Scheme 11: Biological Activity molecules containing 1,4-dihydroquinoline moiety.



Scheme 12: Reaction design for the 1,4-dihydroquinoline synthesis.



Recently, we and Kim group independently reported the asymmetric synthesis of 2,3,4-trisubstituted 1,4-dihydroquinolines by the cascade Michael/amination/dehydration reaction of aldehydes or ketones with (*E*)-2-(2-nitrovinyl)anilines through enamine-catalysis with excellent selectivity.[63] However, there is no suitable asymmetric method to synthesise highly functionalized 1,4-dihydroquinolines in optically pure form from (*E*)-2-(2-nitrovinyl)anilines with β-keto esters through enolate-catalysis.[64] In continuation of our research interest in this area, we envisaged functionally rich (*E*)-2-(2-nitrovinyl)anilines and *β*-keto esters as the potential substrates for the newly designed Michael/amination/dehydration reaction sequence (Scheme 12).

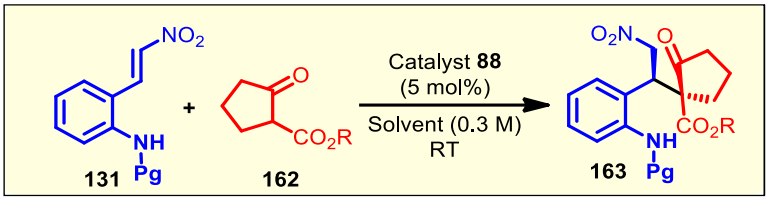
6.2 Results and Discussion

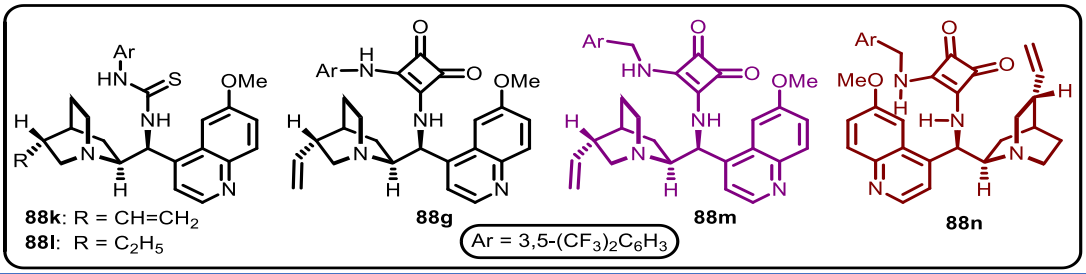
6.2.1 Reaction Optimization:

To find the best catalytic conditions, we screened a number of emerging hydrogen-bond-donating organocatalysts for the reaction of *N*-Boc-(*E*)-2-(2-nitrovinyl)aniline **131a** with 1.3 equiv. of ethyl 2-oxocyclopentanecarboxylate **162a** (Table 13). Reaction of **131a** with 1.3 equiv. of **162a** under 10 mol% of quinine-*N*H-thiourea **88k**-catalysis in toluene at 25 °C for 4 h furnished the **163aa** in 70% yield with 58% *ee* and >99% *de* (Table 13, entry 1). The same reaction in DCM for 4 h furnished the product **163aa** with *ee* increased to 75% with 68% yield and >99% *de* (Table 13, entry 2). Reaction under the hydroquinine-*N*H-thiourea **88l**-catalysis furnished **163aa** with increased yield (82%) and no change in *ee* and *de* (Table 13, entry 3). With these moderate results, we moved to investigate this reaction with other set of hydrogen-bond-donating catalysts **88g/88m/88n** based on the chiral squaramide derivatives discovered by Rawal's group. Recently Rawal's squaramide catalysts have been found to be more powerful hydrogen-bond-donating catalysts compared to their corresponding thiourea analogues in both catalytic activity and selectivity.[58,59] Therefore, herein we shown interest to investigate Rawal's catalysts **88g/88m/88n** for the high asymmetric induction. Unfortunately, reaction of **131a** with **162a** under 5 mol% of quinine-*N*H-squaramide **88g** in DCM at 25 °C for 6 h gave the product **163aa** in 71% yield with poor *ee* (18%) and good *de* (Table 13, entry 4). After this poor selectivity, we shown interest to investigate the electronic and steric factors of *N*-aryl group in the squaramide catalyst, we used quinine-*N*H-benzyl squaramide catalyst **88m** for the high selectivity. Surprisingly, the Michael reaction of **131a** with **162a** under 5 mol% of **88m**-

catalysis furnished the product (-)-**163aa** in 71% yield with 97% *ee* and >99% *de* within 5 h (Table 13, entry 5). This result is indicating that the presence of benzyl group in the squaramide catalyst has significant effect on the outcome of selectivity. In a similar manner, the Michael reaction of **131a** with **162a** under the 5 mol% of quinidine-*N*H-benzyl squaramide **88n**-catalysis furnished the opposite enantiomer (+)-**163aa** in 77% yield with 98% *ee* and >99% *de* within 5 h (Table 13, entry 6). Whereas 10 mol% of **88n**-catalysis furnished the product (+)-**163aa** in 77% yield with decreased *ee* of 83% (entry 7), which indicates that the catalyst loading has a significant effect on the selectivity of the reaction. Use of brine instead of DCM as solvent with 2 mol% of catalyst **88n** the aforesaid product was obtained in 48% yield with 91% *ee* and >99% *de* in 16 h (Table 13, entry 8). To obtain the highest selectivity of the product **163aa**, we thought of using sterically hindered isopropyl 2-oxocyclopentanecarboxylate **162b** with **131a** under **88m/88n**-catalysis. Surprisingly, the reaction of **131a** with **162b** under 5 mol% of **88n**-catalysis in DCM at RT for 6 h furnished the product (+)-**163ab** in 80% yield with >99% *ee* and *de* (Table 13, entry 10). Similar reaction under **88m**-catalysis furnished the opposite enantiomer (-)-**163ab** in 75% yield with >99% *ee* and *de* (Table 13, entry 11). To further investigate the reaction conditions, we carried out the Michael reactions of other *N*-protected-(*E*)-2-(2-nitrovinyl)anilines **131b**/**131c** with **162b** under **88m**- or **88n**-catalysis in DCM at RT. It has shown that other carbamate protecting groups (Cbz and CO_2Et) were tolerated and the desired products were obtained in moderate yields (42−65%) with excellent *ee*'s (96 to >99%) and *de*'s (97 to >99%) within 8 h (Table 13, entries 12-14). Finally we envisioned the optimized condition to be 25 °C in DCM under 5 mol% of Rawal's catalysts **88m** or **88n** to furnish the Michael adduct **163ab** in 75-80% yield with >99% *ee* and >99% *de* (Table 13, entry 10-11).

Table 13: Reaction Optimization.[a,b]





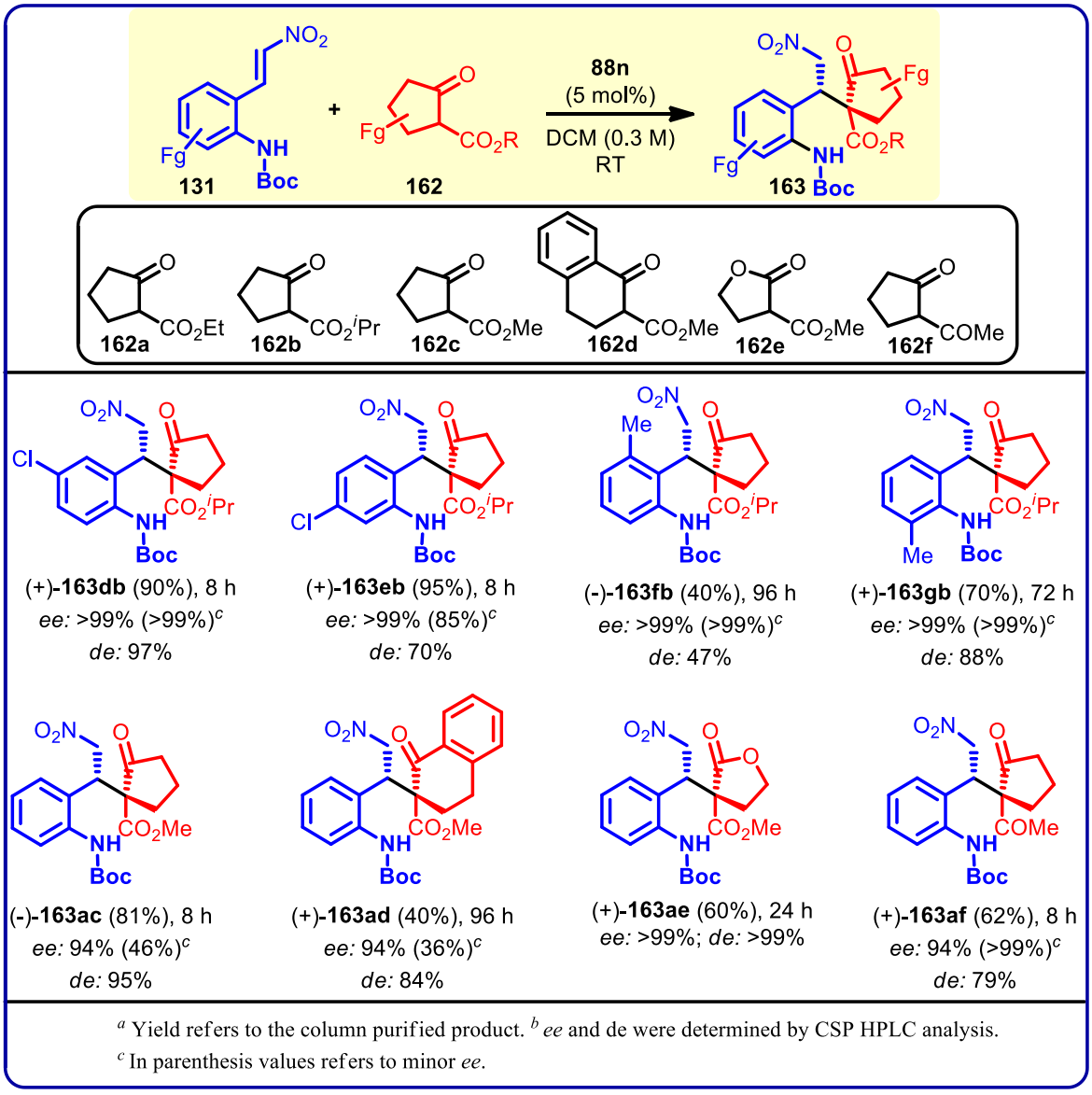
Entry	Pg	R	Catalyst (5 mol%)	Solvent (0.3 M)	Time (h)	Yield (%)[b]	*ee* (%)[c]	*de* (%)[c]
1[d]	**131a**: Boc	**162a**: Et	**88k**	Toluene	4	**163aa** (70)	58	>99
2[d]	**131a**: Boc	**162a**: Et	**88k**	DCM	4	**163aa** (68)	75	>99
3[d]	**131a**: Boc	**162a**: Et	**88l**	DCM	4	**163aa** (82)	74	>99
4	**131a**: Boc	**162a**: Et	**88g**	DCM	6	**163aa** (71)	18	>99
5	**131a**: Boc	**162a**: Et	**88m**	DCM	5	**163aa** (71)	97	>99
6	**131a**: Boc	**162a**: Et	**88n**	DCM	5	**163aa** (77)	-98	>99
7[d]	**131a**: Boc	**162a**: Et	**88n**	DCM	5	**163aa** (77)	-83	>99
8[e]	**131a**: Boc	**162a**: Et	**88n**	Brine	16	**163aa** (48)	-91	>99
9[d]	**131a**: Boc	**162b**: ^{i}Pr	**88n**	DCM	6	**163ab** (75)	-95	>99
10	**131a**: Boc	**162b**: ^{i}Pr	**88n**	DCM	6	**163ab** (80)	->99	>99
11	**131a**: Boc	**162b**: ^{i}Pr	**88m**	DCM	6	**163ab** (75)	>99	>99
12	**131b**: Cbz	**162b**: ^{i}Pr	**88n**	DCM	8	**163bb** (65)	->99	>99
13	**131b**: Cbz	**162b**: ^{i}Pr	**88m**	DCM	8	**163bb** (63)	98	97
14	**131c**:CO_2Et	**162b**: ^{i}Pr	**88n**	DCM	8	**163cb** (42)	-96	>99

[a] Unless otherwise mentioned, all reactions were carried out with **131** (0.2 mmol), **162** (0.26 mmol), catalyst **88** (5 mol%) in DCM (0.3 M) at rt. [b] Yield refers to the column purified product. [c] *ee* and *de* were determined by CSP HPLC analysis. [d] 10 mol% of catalyst **88** was used. [e] Reaction performed with 2 mol% of **88n**.

6.2.2 Scope of asymmetric Michael reaction:

With the optimized conditions in hand, the scope of the Rawal's quinidine-*N*H-benzyl squaramide **88n**-catalyzed asymmetric Michael reaction was investigated. A series of substituted *N*-Boc-(*E*)-2-(2-nitrovinyl)anilines **131d-g** were reacted with 1.3 equiv. of cyclic β-keto esters **162a-f** catalyzed by 5 mol% of **88n** at 25 °C in DCM for 8-96 h to furnish the highly substituted chiral Michael adducts **163db-af** in 40-95% yields with excellent *ee*'s and *de*'s (Table 14). Electronic and steric nature of the *N*-Boc-(*E*)-2-(2-nitrovinyl)anilines were investigated with *β*-keto ester **162b**. Halogen substituted *N*-Boc-(*E*)-2-(2-nitrovinyl)anilines **131d-e** reacted well with **162b** and furnished the products (+)-**163db** and (+)-**163eb** in excellent yields (90 and 95%) and *ee*'s (99%) with good to moderate *de*'s (97 and 70%) within 8 h respectively. Methyl substituted *N*-Boc-(*E*)-2-(2-nitrovinyl)anilines **131f-g** gave the desired products (-)-**163fb** and (+)-**163gb** in moderate to good yields (40 and 70%) with excellent *ee*'s (>99%) and moderate *de*'s (47 and 88%) through **88n**-catalysis for 96 and 72 h, respectively. We also tested the other cyclic β-keto esters to investigate the generality of this asymmetric reaction. Methyl 2-oxocyclopentanecarboxylate **162c** with **131a** under the **88n**-catalysis furnished the product (-)-**163ac** in 81% yield with 94% *ee* and 95% *de* within 8 h. Intriguingly, six-membered cyclic *β*-keto ester **162d** gave the product (+)-**163ad** only in 40% yield with 94% *ee* and 84% *de* for 96 h; but simple ethyl 2-oxocyclohexanecarboxylate **162d'** gave the Michael product (+)-**163ad'** in 65% yield with >99% *ee* and >99% *de* for within 40 h (Table 14). Heterocyclic *β*-keto ester **162e** with **131a** under **88n**-catalysis furnished the product (+)-**163ae** in 60% yield with >99% *ee* and *de* for 24 h. In a similar manner, 2-acetylcyclopentanone **162f** with **131a** under **88n**-catalysis furnished the product (+)-**163af** in 62% yield with 94% *ee* and 79% *de* within 8 h. It was observed that compared to five membered cyclic *β*-keto esters, six-membered cyclic *β*-keto esters gave the corresponding products in low yield. The structure and absolute stereochemistry of the Michael products **163** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (+)-**163ae** as shown in Figure 37.[65]

Table 14: Reaction Scope with cyclic *β*-keto esters [a,b]



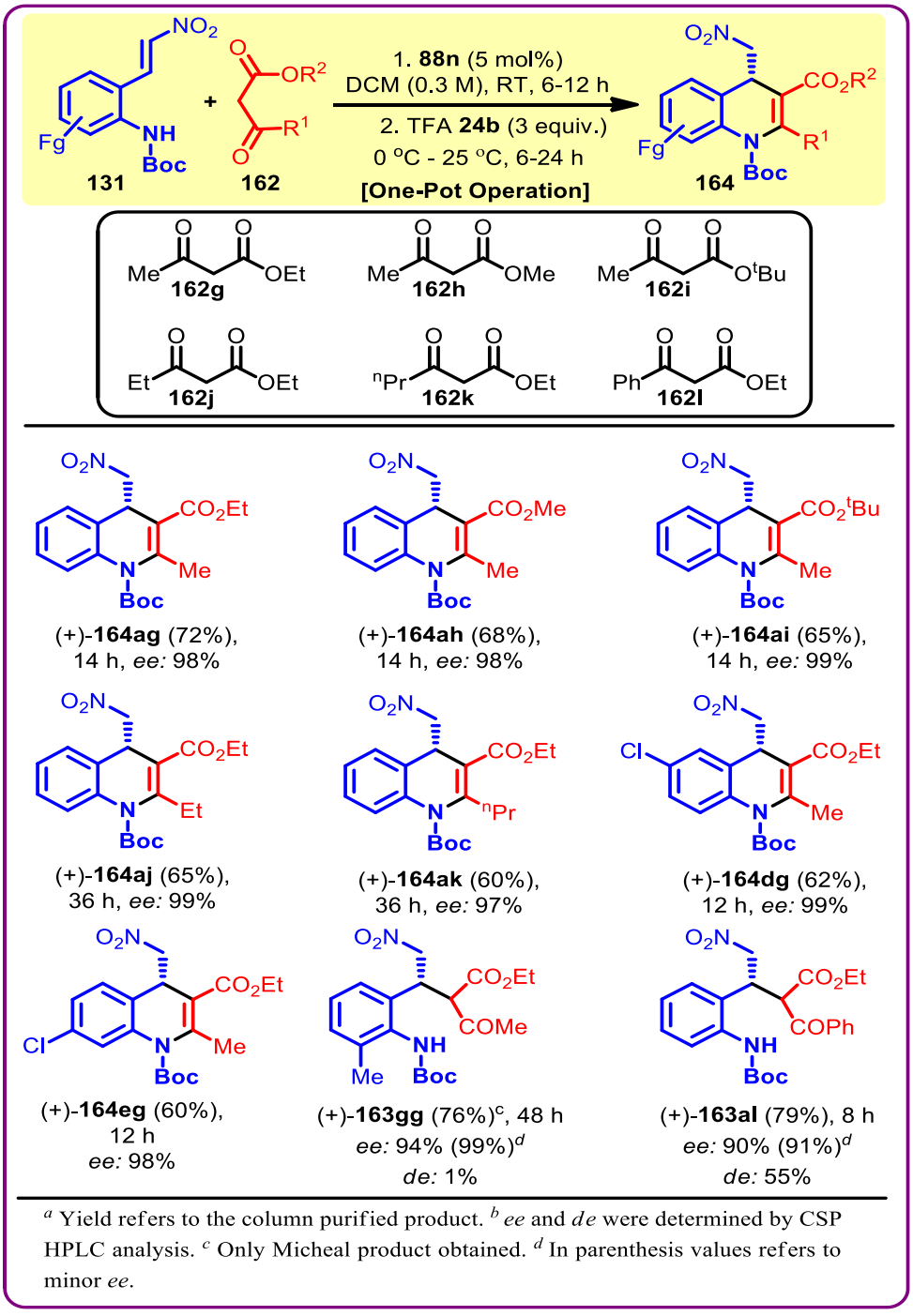
[a] Yield refers to the column purified product. [b] *ee* and de were determined by CSP HPLC analysis.
[c] In parenthesis values refers to minor *ee*.

6.2.3 Synthetic application of Michael adducts:

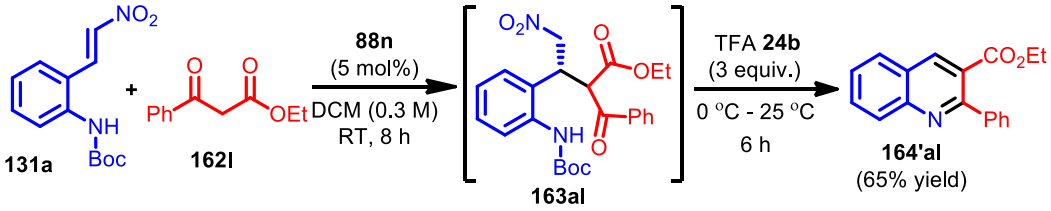
In order to expand the reaction scope, we explored the utilization of different acyclic β-keto esters **162g-l**. First the reaction of **131a** with 1.3 equiv. of ethyl acetoacetate **162g** under the catalysis of **88n** at 25 °C for 8 h in DCM furnished the product **163ag** in 76% yield with 1:1 *dr*. For the clear understanding of selectivity and also for the HPLC separation, we transformed the product **163ag** in situ into easily separable and also very important 1,4-

dihydroquinoline (+)-**5ag** in 72% yield with 98% *ee* through TFA **24b**-mediated cascade amination/dehydration in DCM at 0-25 °C for 6 h in one-pot manner (Table 15). We further investigated the substrate scope for Rawal's quinidine-*N*H-benzyl squaramide **88n**-catalyzed and TFA **24b**-promoted asymmetric Michael/amination/dehydration reaction sequence with **131a-g** and **162h-l** for the synthesis of chiral 1,4-dihydroquinolines (Table 15). Methyl and ^{t}butyl-3-oxobutanoates **162h-i** with **131a** under in DCM followed by TFA-mediated one-pot amination/dehydration reaction generated the cyclised products (+)-**164ah-ai** in 68% and 65% yields with 98% and 99% *ee*, respectively (Table 15). Likewise, ethyl 3-oxopentanoate and 3-oxohexanoate **162j-k** generated the expected cyclised products (+)-**164aj** and (+)-**164ak** in 65% and 60% yields with excellent *ee*'s (99% and 97%) after 36 h respectively (Table 15). In the case of ethyl 3-oxo-3-phenylpropanoate **162l**, the Michael product (+)-**163al** was obtained in 79% yield with 90% *ee* and 55% *de* at 25 °C for 8 h; but when in-situ treatment of (+)-**163al** with TFA **24b** at 0-25 °C for 24 h furnished the unexpected by-product ethyl 2-phenylquinoline-3-carboxylate in 65% yield may be due to the electronic/steric hindrance of phenyl group (eq 32). Reaction of substituted *N*-Boc-(*E*)-2-(2-nitrovinyl)anilines **131d-e** with **162g** under **88n**-catalysis followed by in situ treatment with TFA **24b** furnished the cyclised products (+)-**164dg** and (+)-**164eg** in good yields (62 and 60%) with excellent *ee*'s (99 and 98%) at 25 °C for 12 h, respectively (Table 15). Surprisingly, the reaction of methyl substituted *N*-Boc-(*E*)-2-(2-nitrovinyl)aniline **131g** with **162g** under **88n**-catalysis followed by in situ treatment with TFA **24b** furnished the only Michael product (+)-**163gg** in 76% yield with 94/99% *ee* and 1:1 *dr* at 25 °C for 48 h without cyclization may be due to the steric hindrance of methyl groups (Table 15).[66] After these interesting results, TFA **24b**-mediated cascade amination/dehydration protocol was applied to the many of Table 14 compounds in DCM at 0-25 °C; for within 1 h compounds were decomposed.

Table 15: Reaction Application[a,b]



[a] Yield refers to the column purified product. [b] *ee* and *de* were determined by CSP HPLC analysis. [c] Only Micheal product obtained. [d] In parenthesis values refers to minor *ee*.



(32)

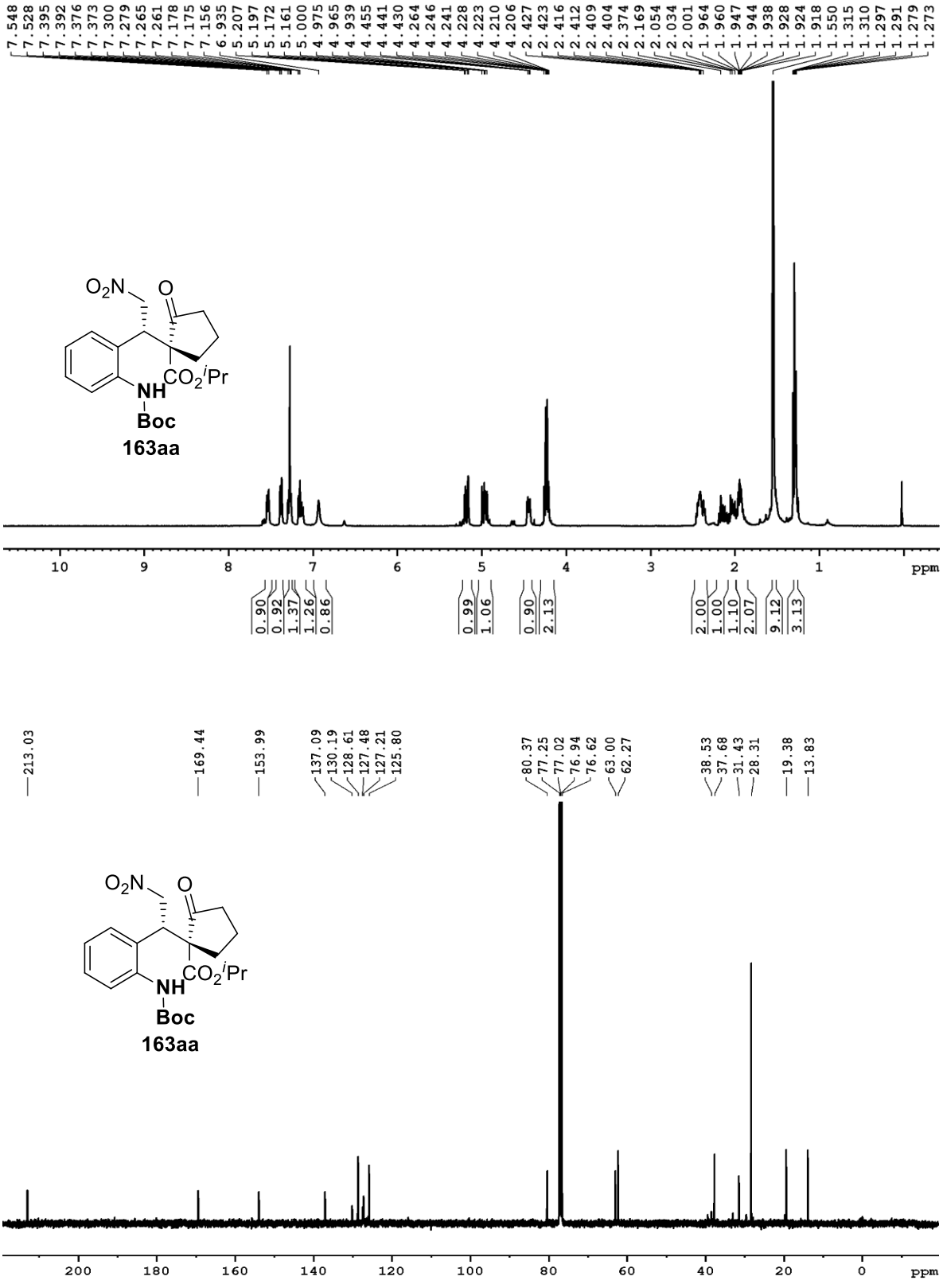


Figure-30: ^{1}H and ^{13}C NMR spectra of the product **163aa**

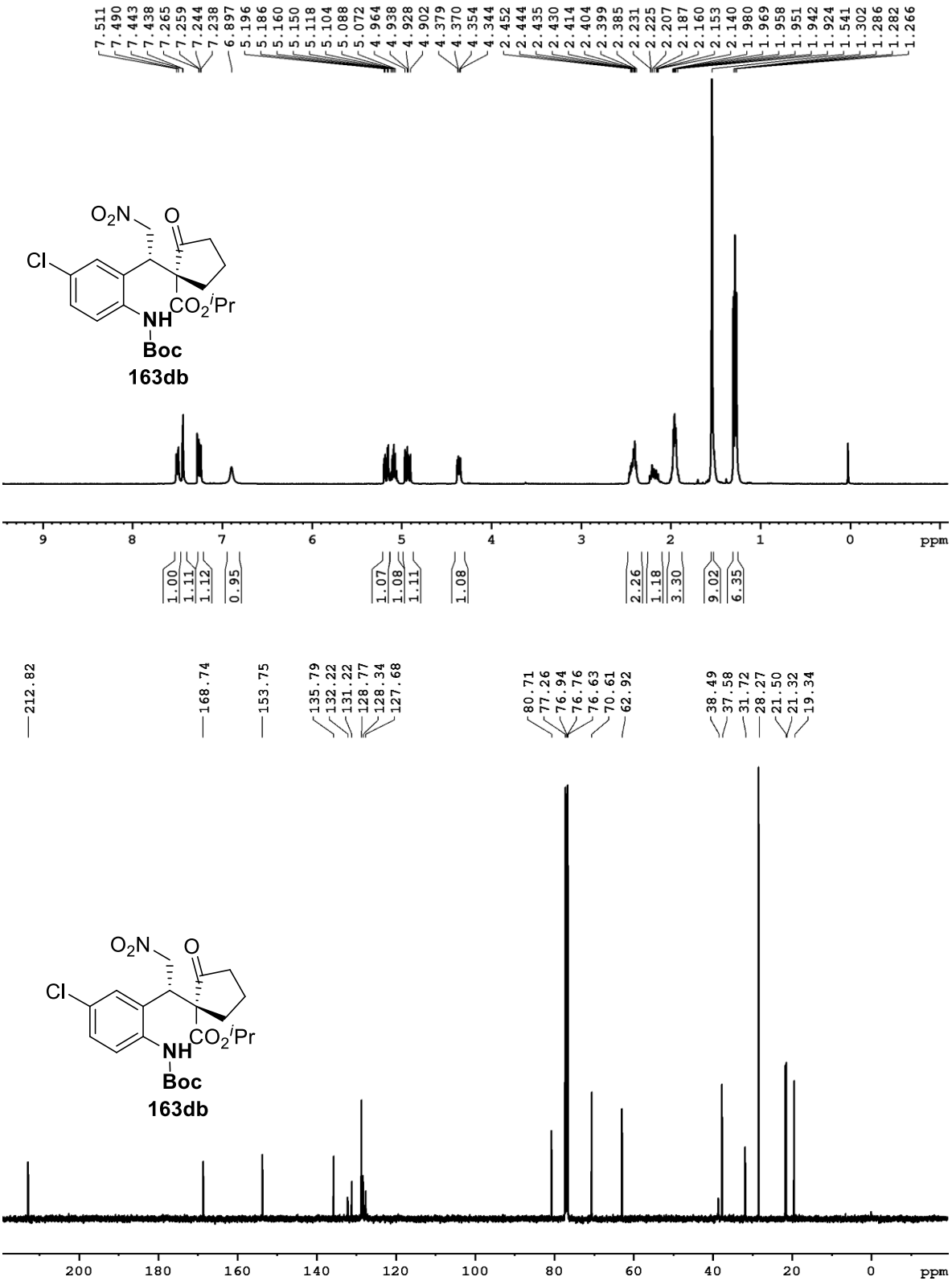


Figure-31: ^{1}H and ^{13}C NMR spectra of the product **163db**

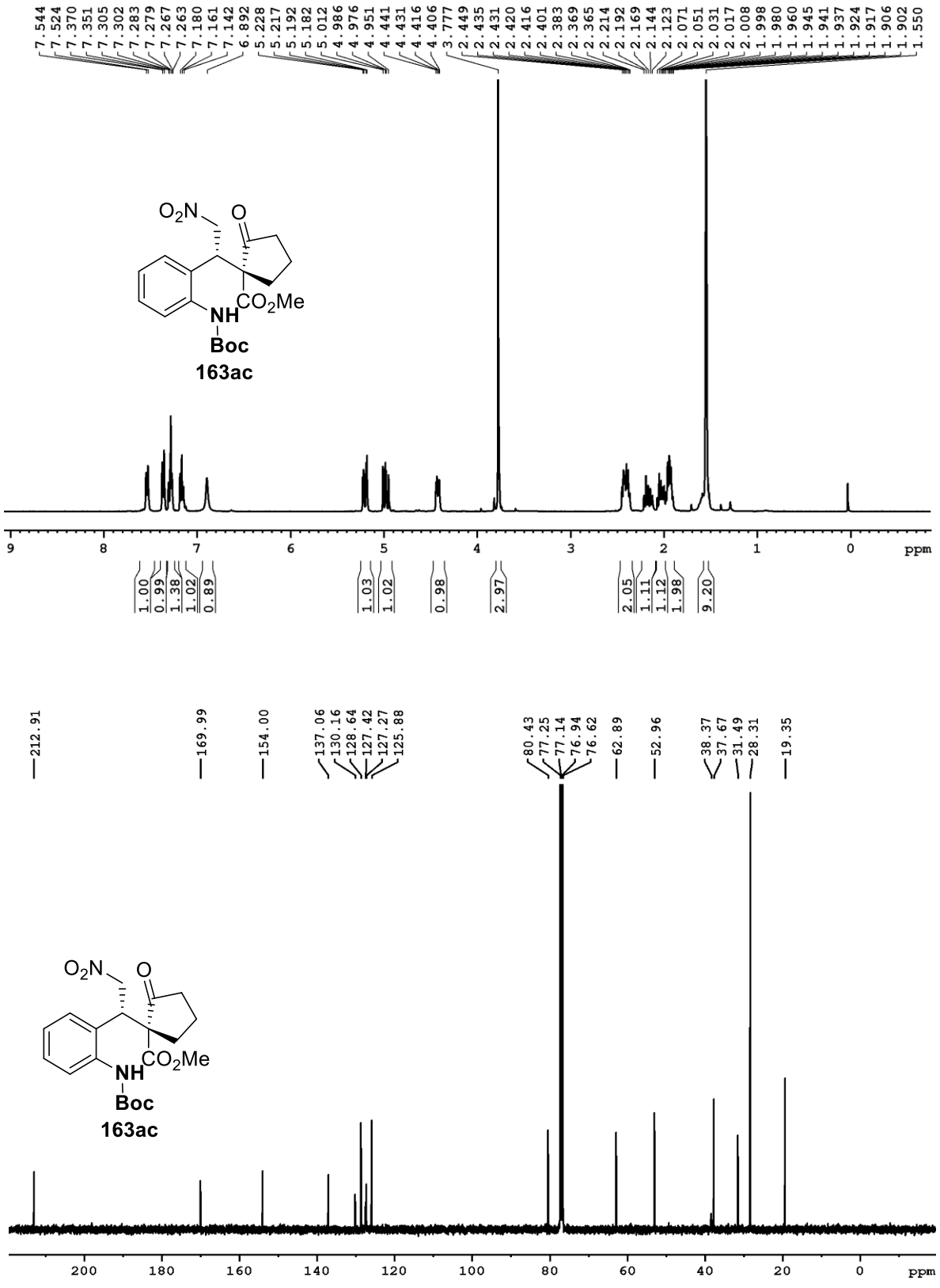


Figure-32: ^{1}H and ^{13}C NMR spectra of the product **163ac**

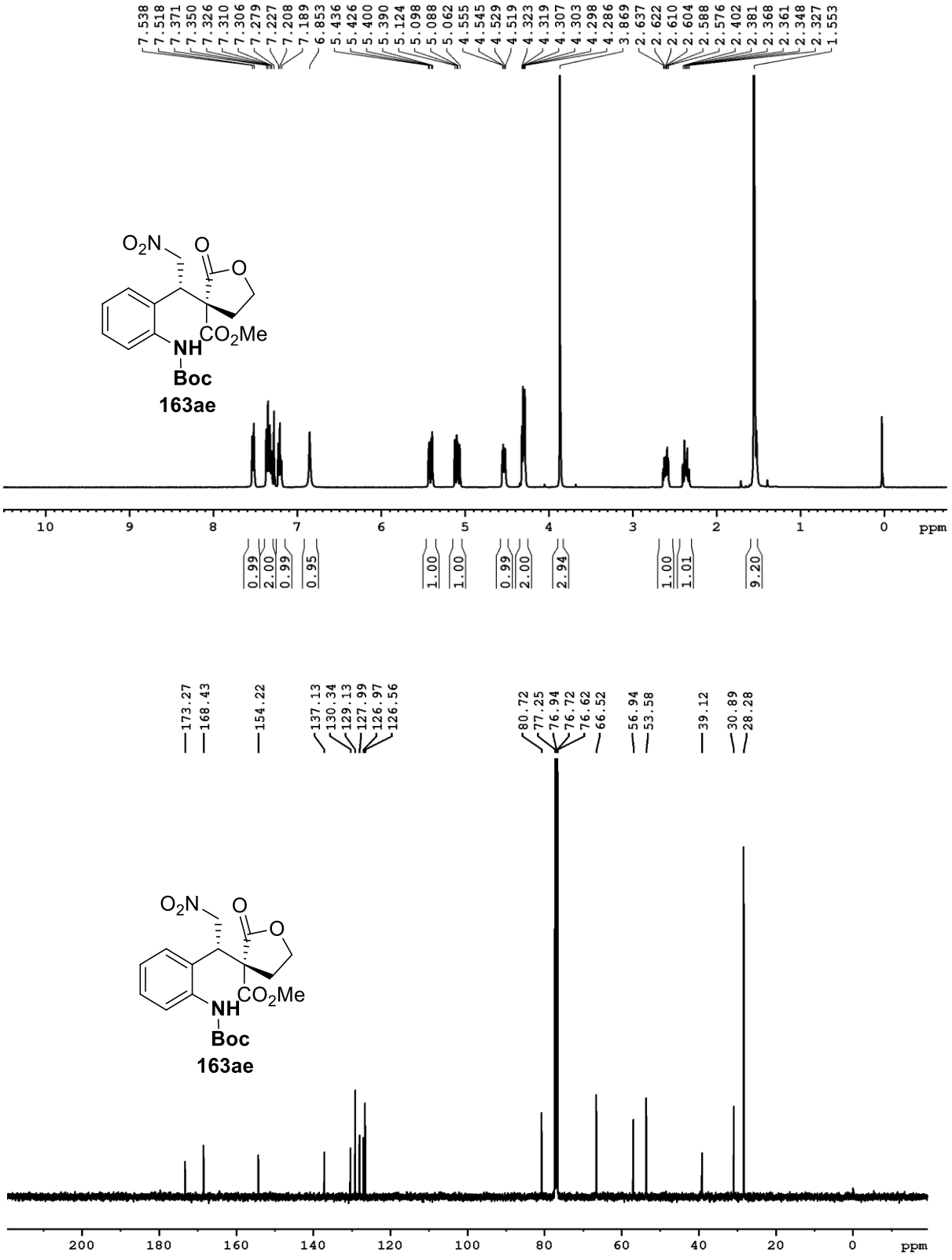


Figure-33: ^{1}H and ^{13}C NMR spectra of the product **163ae**

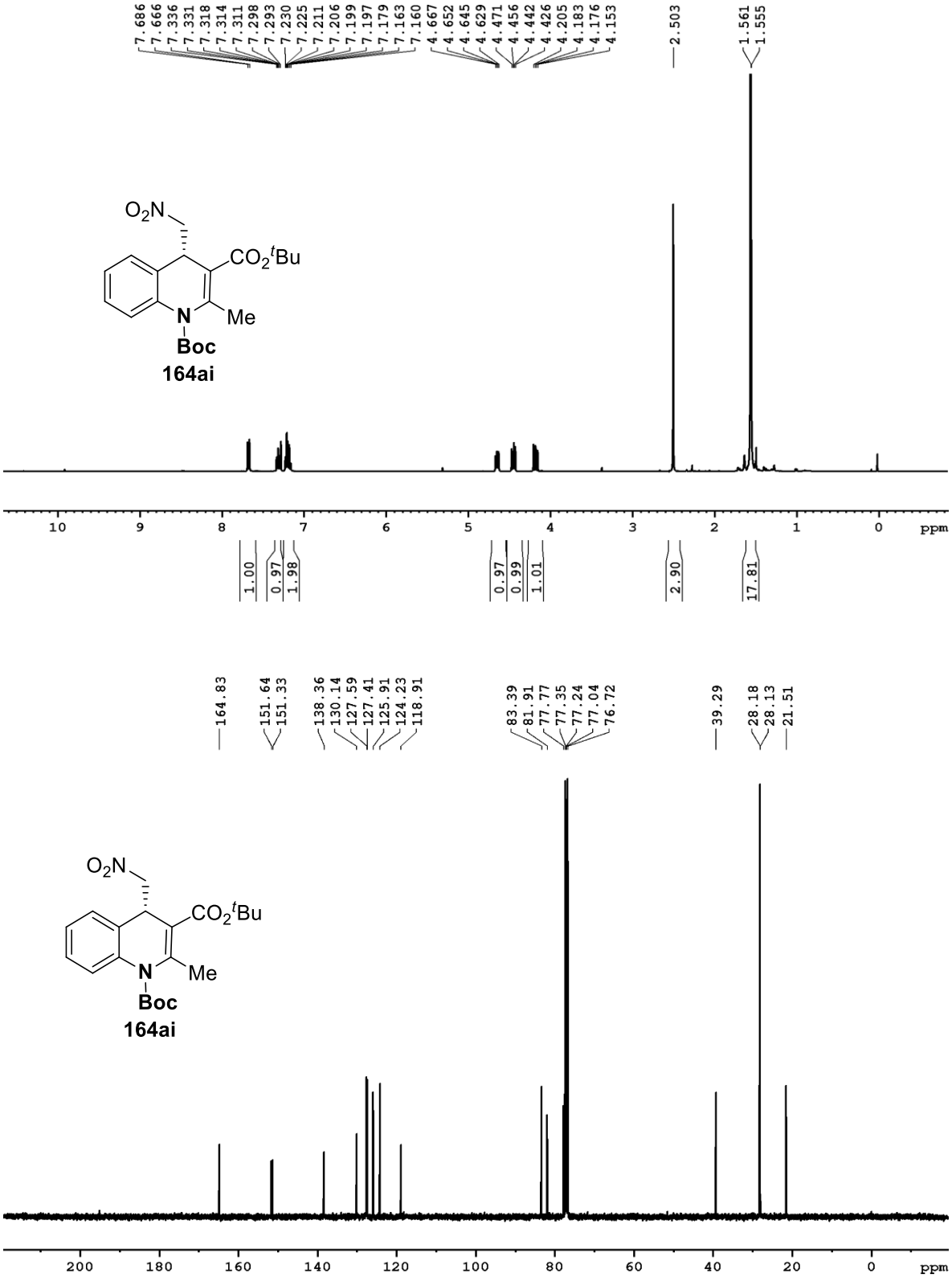


Figure-34: ^{1}H and ^{13}C NMR spectra of the product **164ai**

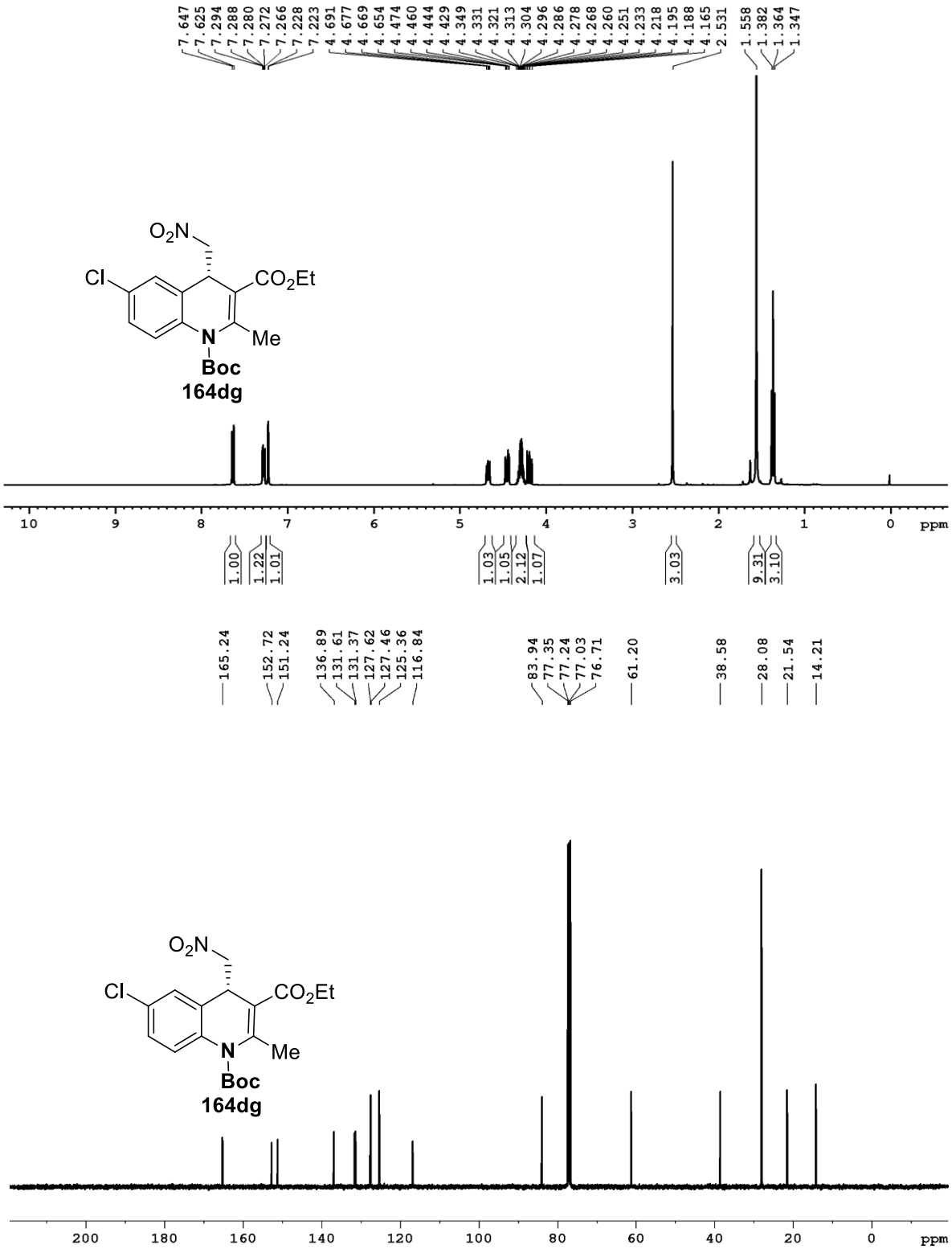


Figure-35: ^{1}H and ^{13}C NMR spectra of the product **164dg**

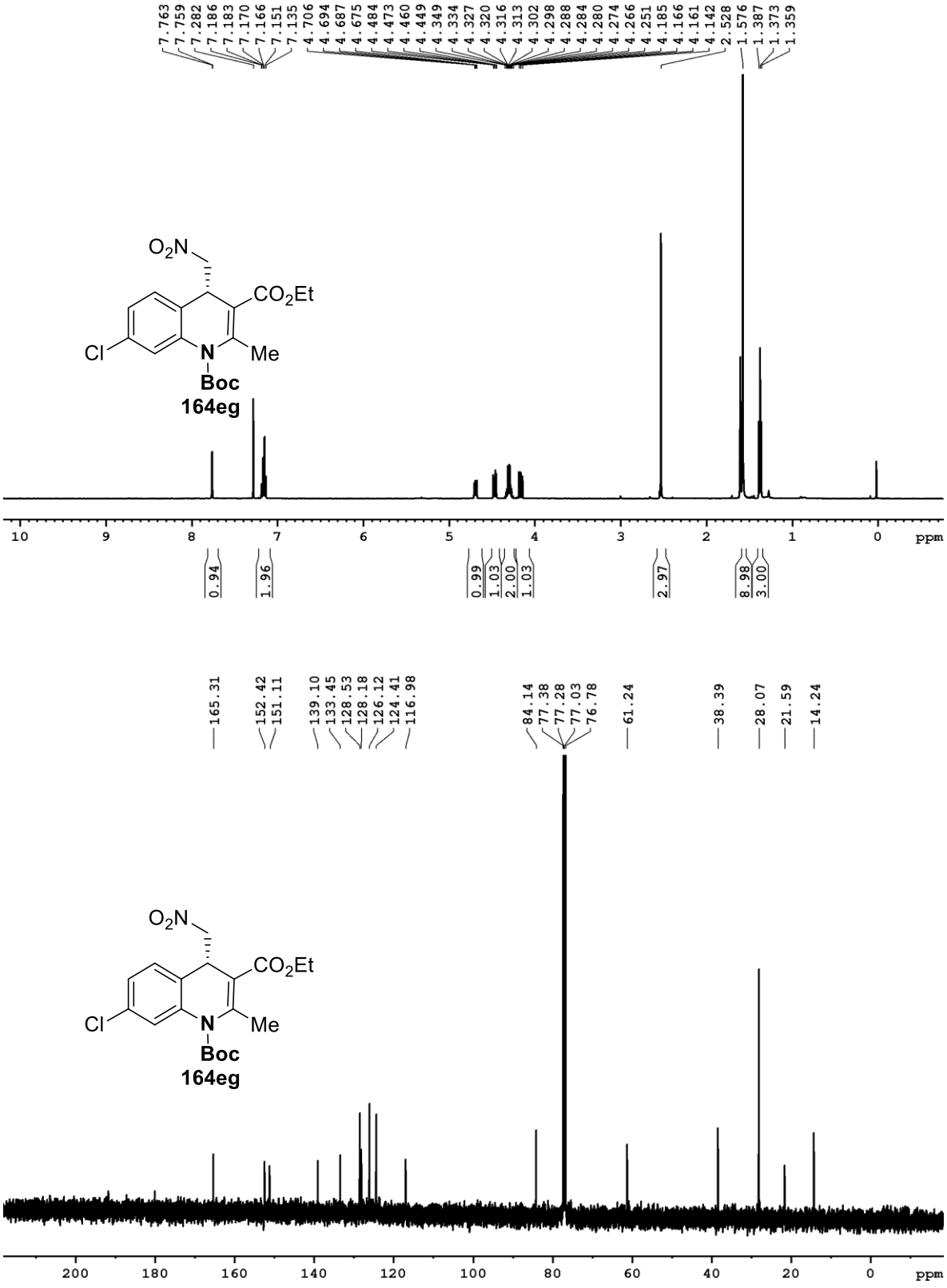


Figure-36: ^{1}H and ^{13}C NMR spectra of the product **164eg**

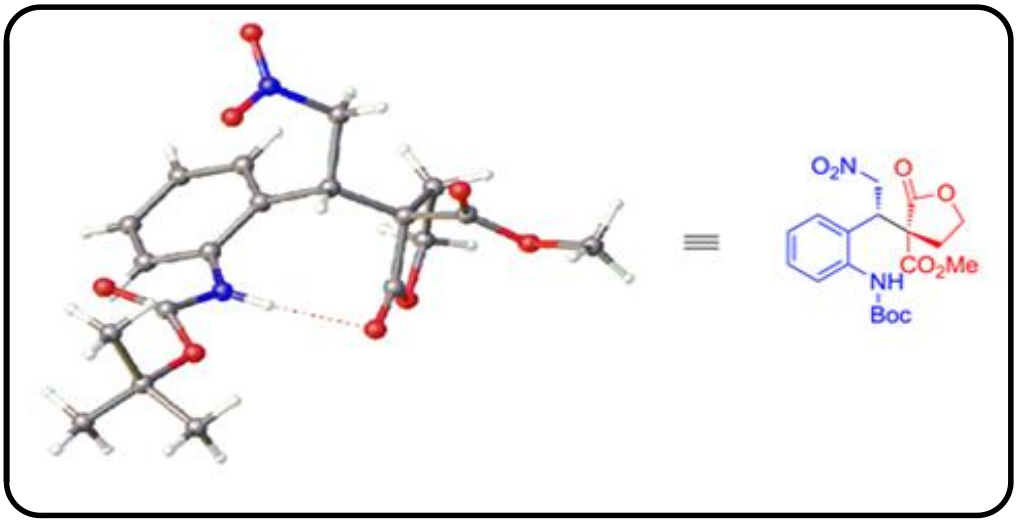
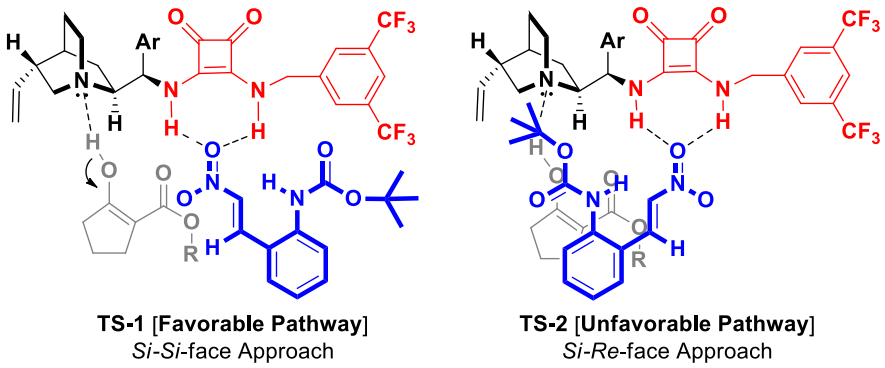


Figure-37: X-ray crystal structure of chiral(*S*)-methyl 3-((*S*)-1-(2-((tert-butoxycarbonyl)amino)phenyl)-2-nitroethyl)-2-oxotetrahydrofuran-3-carboxylate **163ae**.

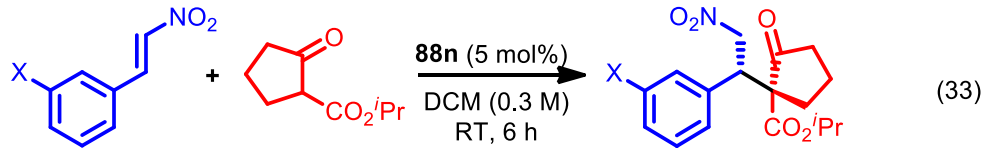
6.2.4 Mechanistic insights:

With controlled experimental data in hand, herein we firmly elucidate the mechanism of the asymmetric Michael reaction through double hydrogen-bonding assembly by **88n**-catalysis, and propose that the reaction most likely proceeds *via* **TS-1** mechanism (Scheme 13). In the case of the addition of *β*-keto-esters **131** to substituted 2-(2-nitrovinyl)anilines **162** *via* Rawal's **88n**-catalysis, we can rationalize the observed stereochemistries through a favoured double hydrogen-bonding assembly transition state where the less hindered *si*-face of **162** approaches the *si*-face of the *in situ* generated enol as shown in **TS-1**. Outcome of decent selectivity and reactivity for the *β*-keto-ester **131** addition to the 2-(2-nitrovinyl)anilines **162** could be explained by soft involvement due to the steric hindrance of neighboring group Ar-**NHBoc** as shown in Scheme 13.

Scheme 13: Proposed transition state for the asymmetric Michael reactions.



Fascinatingly, the Michael reaction of simple (*E*)-(2-nitrovinyl)benzene **131h** and *N*-Boc-(*E*)-3-(2-nitrovinyl)aniline **131i** with **162b** *via* **88n**-catalysis in DCM at 25 °C for 6 h furnished the expected products (-)-**163hb** in 63% yield with 98% *ee* and >99% *de*; and (-)-**163ib** in 71% yield with 99% *ee* and >99% *de* respectively as shown in eq. (33). This result gives evident for the fact that there is not much of neighboring *ortho*-amino group participation in the reaction pre-transition state and also Rawal's catalyst **88n** is sufficient enough to activating both the substrates in the pre-transition state along with steric hindrance of neighboring group Ar-**NHBoc** to control the selectivity.



131h: X = H
131i: X = NH-Boc

162b

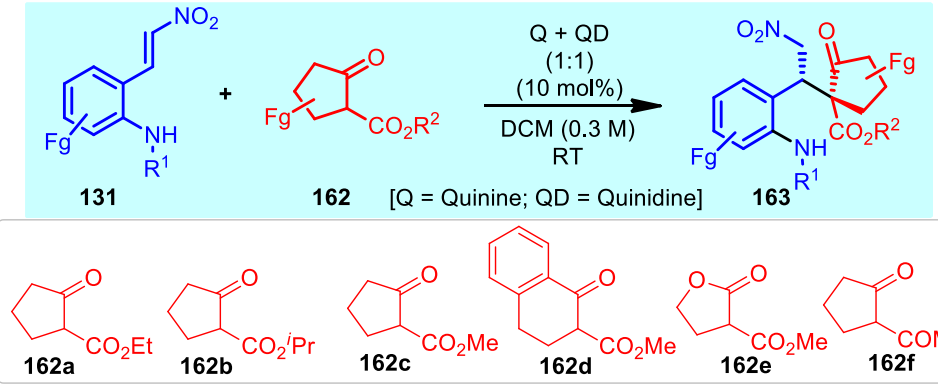
X = H: (-)-**163hb** (63% yield)
ee: 98% and *de:* >99%
X = NH-Boc: (-)-**163ib** (71% yield)
ee: 99% and *de:* >99%

(33)

6.2.5 Synthesis of racemic products 163:

To synthesize the racemic products **163**, (*E*)-2-(2-nitrovinyl)anilines **131a-g** were reacted with *β*-keto esters **162a-f** in DCM (1.0 mL), in the presence of 1:1 mixture of quinine and quinidine (each 5 mol%) at rt. This in turn, generated a library of racemic compounds **163** in excellent yields. The results are presented in Table 16

Table 16: Synthesis of racemic Michael products **163**.[a,b]



(±)-**163aa** (70%)
12 h, *de*: 59%

(±)-**163ab** (73%)
12 h, *de*: 35%

(±)-**163bb** (74%)
12 h, *de*: 59%

(±)-**163cb** (40%)
12 h, *de*: 77%

(±)-**163db** (64%)
12 h, *de*: 48%

(±)-**163eb** (64%)
12 h, *de*: 56%

(±)-**163fb** (47%)
36 h, *de*: 58%

(±)-**163gb** (64%)
24 h, *de*: 75%

(±)-**163ac** (83%)
15 h, *de*: 58%

(±)-**163ad** (20%)
48 h, *de*: 3%

(±)-**163ae** (43%)
24 h, *de*: 44%

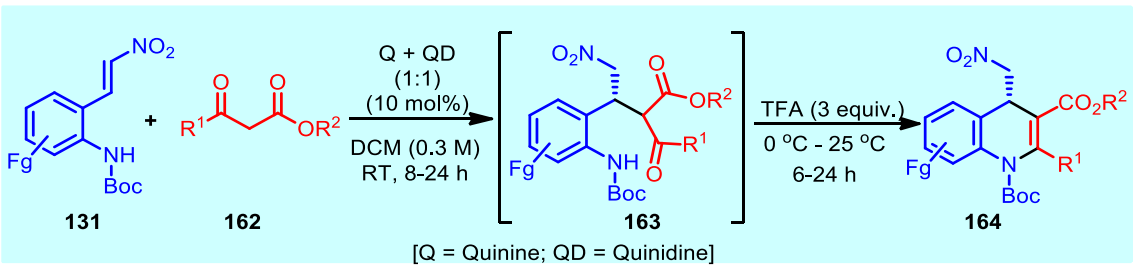
(±)-**163af** (36%)
20 h, *de*: 17%

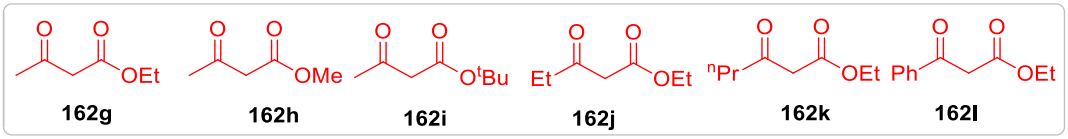
[a] Yield refers to the column purified product. [b] de was determined by CSP HPLC analysis.

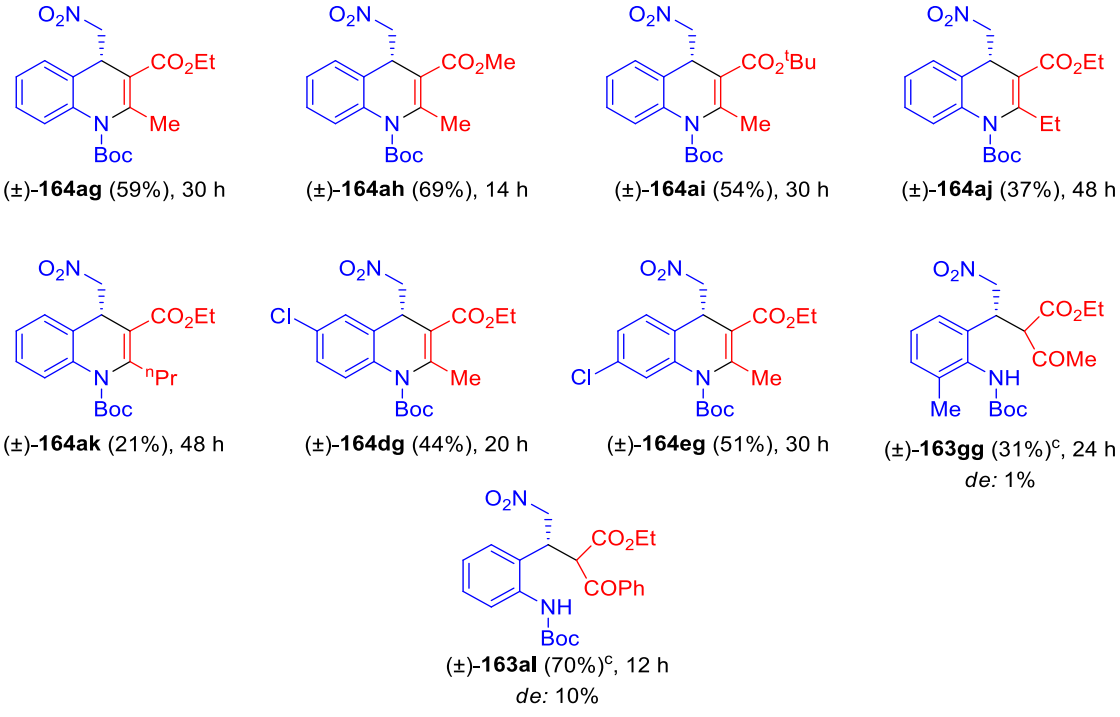
6.2.6 Synthesis of racemic 1,4-dihydroquinolines 164:

To synthesize the racemic products **164**, (*E*)-2-(2-nitrovinyl)anilines **131a-g** were reacted with *β*-keto esters **162g-l** in DCM (1.0 mL), in the presence of 1:1 mixture of quinine and quinidine (each 5 mol%) at 25 °C until complete consumption of (*E*)-2-(2-nitrovinyl)anilines **131**. then slowly added trifluoroacetic acid (TFA)(3.0 equiv) at room temperature. This in turn, generated a library of racemic compounds **164** in excellent yields. The results are presented in Table 17.

Table 17: Synthesis of racemic 1,4-dihydroquinolines **164:**[a-c]







[a] Yield refers to the column purified product. [b] de were determined by CSP HPLC analysis. [c] Only Micheal product obtained.

6.4 Conclusions

In summary, we have developed Rawal's quinidine-*N*H-benzyl squaramide **88n**-catalyzed and TFA-promoted asymmetric sequential Michael/amination/dehydration reaction of *N*-protected-(*E*)-2-(2-nitrovinyl)anilines **131** with *β*-keto esters **162** for the synthesis of enantioenriched and highly functionalized 1,4-dihydroquinolines **164**. Further work is in progress to utilize 1,4-dihydroquinoline derivatives for biological studies.

7. Experimental Section

General Methods:

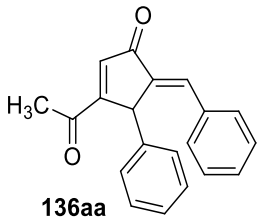
The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. *In the ^{13}C NMR spectra, the nature of the 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. GCMS mass spectrometry was performed on Shimadzu GCMS-QP2010 mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010 A mass spectrometer. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, 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. Ynones **12a-k** [67] were prepared according to the literature procedure.

Procedure 1a: General Procedure for the Phosphine-Catalyzed Intermolecular Self-TZC Reaction: In an ordinary glass vial equipped with a magnetic stirring bar was taken a mixture 0.4 mmol of ynone **12** and phosphine catalyst **2c** (20 mol%, relative to 0.2

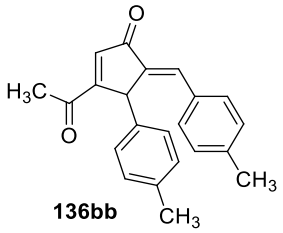
mmol of **12**) in dichloroethane (1.0 mL). Then (±)-BINOL **135** (10 mol%, relative to 0.2 mmol of **12**) were added sequentially to the reaction mixture and stirred at temperature indicated in each case until total disappearance of the starting material (monitored by TLC). The reaction mixture was concentrated and pure products **136** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(*E*)-3-Acetyl-5-benzylidene-4-phenylcyclopent-2-enone (136aa): Prepared by following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp.: 178-180 °C; IR (Neat): ν_{max} 3059, 2915, 1688, 1623, 1592, 1492, 1448, 1356, 1174, 1024, 878, 757, 695 and 601 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.58 (1H, s), 7.41 (2H, d, *J* = 5.5 Hz), 7.25-7.24 (5H, m), 7.19 (2H, t, *J* = 7.5 Hz), 7.11 (1H, t, *J* = 7.5 Hz), 6.88 (1H, s), 5.26 (1H, s), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.0 (C, *C*=O), 196.5 (C, *C*=O), 166.2 (C), 137.8 (C), 137.5 (C), 135.8 (CH), 135.0 (CH), 133.5 (C), 131.2 (2 x CH), 130.0 (CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.2 (CH), 48.6 (CH), 28.4 (CH_3, CO*C*H_3); HRMS m/z 311.1049 ($M + Na^+$), calcd for $C_{20}H_{16}O_2Na$ 311.1048.



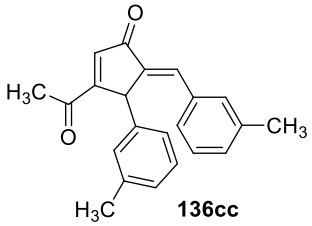
136aa

(*E*)-3-Acetyl-5-(4-methylbenzylidene)-4-(*p*-tolyl)cyclopent-2-enone (136bb): Prepared by following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp.: 160-162 °C; IR (Neat): ν_{max} 2920, 1676, 1624, 1593, 1505, 1361, 1257, 1164, 870 and 803 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.55 (1H, s), 7.37 (2H, d, *J* = 8.0 Hz), 7.17 (2H, d, *J* = 8.0 Hz), 7.09 (2H, d, *J* = 8.0 Hz), 7.02 (2H, d, *J* = 8.0 Hz), 6.86 (1H, d, *J* = 1.2 Hz), 5.22 (1H, s), 2.37 (3H, s), 2.31 (3H, s), 2.24 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.3 (C, *C*=O), 196.7 (C, *C*=O), 166.1 (C), 140.7 (C), 136.8 (2 x C), 135.8 (CH), 134.9 (CH), 134.5 (C), 131.6 (2 x CH), 130.8 (C), 129.35 (2 x CH), 129.31 (2 x CH), 128.5 (2 x CH), 48.3 (CH), 28.4 (CH_3, CO*C*H_3), 21.5 (CH_3), 21.0 (CH_3); HRMS m/z 317.1542 ($M + H^+$), calcd for $C_{22}H_{21}O_2$ 317.1542.

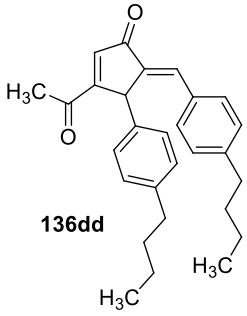


136bb

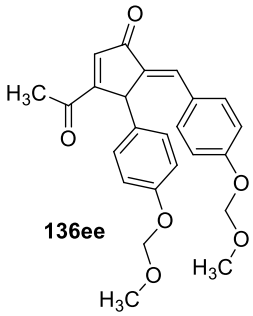
(*E*)-3-Acetyl-5-(3-methylbenzylidene)-4-(*m*-tolyl)cyclopent-2-enone (136cc): Prepared by following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp.: 122-124 °C; IR (Neat): ν_{max} 3059, 1681, 1621, 1595, 1511, 1465, 1271, 1212, 1175, 1144, 959, 819, 751, 702 and 666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.53 (1H, d, *J* = 1.5 Hz), 7.27 (1H, br s), 7.24 (1H, br d, *J* = 7.5 Hz), 7.15 (1H, t, *J* = 7.5 Hz), 7.11-7.05 (3H, m), 7.04 (1H, br s), 6.93 (1H, br d, *J* = 7.0 Hz), 6.88 (1H, d, *J* = 1.5 Hz), 5.21 (1H, s), 2.37 (3H, s), 2.25 (3H, s), 2.24 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.2 (C, *C*=O), 196.5 (C, *C*=O), 166.1 (C), 138.1 (C), 138.0 (C), 137.7 (C), 137.5 (C), 135.8 (CH), 135.0 (CH), 133.4 (C), 131.7 (CH), 130.8 (CH), 129.3 (CH), 128.9 (CH), 128.32 (CH), 128.30 (CH), 128.0 (CH), 125.8 (CH), 48.7 (CH), 28.4 (CH_3, CO*C*H_3), 21.3 (CH_3), 21.1 (CH_3); HRMS m/z 317.1542 ($M + H^+$), calcd for $C_{22}H_{21}O_2$ 317.1542.



(*E*)-3-Acetyl-5-(4-butylbenzylidene)-4-(4-butylphenyl)cyclopent-2-enone (136dd): Prepared by following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp.: 106-108 °C; IR (Neat): ν_{max} 2956, 2923, 2858, 1694, 1627, 1604, 1511, 1420, 1254, 1206, 1168, 959, 879, 736 and 662 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.55 (1H, d, *J* = 1.0 Hz), 7.34 (2H, br d, *J* = 8.0 Hz), 7.15 (2H, br d, *J* = 8.0 Hz), 7.07 (2H, br d, *J* = 8.0 Hz), 7.00 (2H, br d, *J* = 8.0 Hz), 6.85 (1H, d, *J* = 1.5 Hz), 5.20 (1H, br s), 2.54 (2H, t, *J* = 8.0 Hz), 2.48 (2H, t, *J* = 8.0 Hz), 2.36 (3H, s), 1.54-1.48 (4H, m), 1.32-1.24 (4H, m), 0.89 (3H, t, *J* = 7.5 Hz), 0.87 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.3 (C, *C*=O), 196.7 (C, *C*=O), 166.2 (C), 145.6 (C), 141.8 (C), 137.0 (C), 135.7 (CH), 134.9 (CH), 134.7 (C), 131.5 (2 x CH), 131.1 (C), 128.6 (4 x CH), 128.4 (2 x CH), 48.4 (CH), 35.5 (CH_2), 35.1 (CH_2), 33.3 (CH_2), 33.2 (CH_2), 28.4 (CH_3, CO*C*H_3), 22.3 (2 x CH_2), 13.89 (CH_3), 13.86 (CH_3); HRMS m/z 401.2481 ($M + H^+$), calcd for $C_{28}H_{33}O_2$ 401.2481.



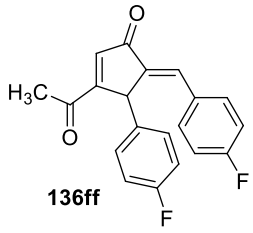
(*E*)-3-Acetyl-5-(4-(methoxymethoxy)benzylidene)-4-(4-(methoxymethoxy)phenyl)cyclopent-2-enone (136ee): Prepared by following the procedure



136ee

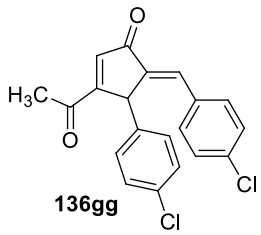
1a and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp.: 108-110 °C; IR (Neat): ν_{max} 2957, 2920, 2848, 1743, 1686, 1598, 1505, 1459, 1366, 1241, 1154, 1077, 999, 849 and 803 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (1H, d, *J* = 1.5 Hz), 7.40 (2H, td, *J* = 9.0, 2.0 Hz), 7.18 (2H, td, *J* = 9.0, 2.0 Hz), 6.91 (2H, td, *J* = 9.0, 2.0 Hz), 6.87 (2H, td, *J* = 9.0, 2.0 Hz), 6.84 (1H, d, *J* = 1.5 Hz), 5.17 (1H, br t, *J* = 1.5 Hz), 5.15 (2H, ABq, *J* = 8.0 Hz), 5.08 (2H, ABq, *J* = 7.0 Hz), 3.44 (3H, s), 3.42 (3H, s), 2.37 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.1 (C, *C*=O), 196.6 (C, *C*=O), 165.8 (C), 158.8 (C), 156.4 (C), 135.9 (C), 135.8 (CH), 134.5 (CH), 133.4 (2 x CH), 130.7 (C), 129.7 (2 x CH), 127.3 (C), 116.4 (2 x CH), 116.2 (2 x CH), 94.4 (CH_2), 94.1 (CH_2), 56.2 (CH_3, O*C*H_3), 56.0 (CH_3, O*C*H_3), 47.9 (CH), 28.4 (CH_3, CO*C*H_3); HRMS m/z 431.1474 ($M + Na^+$), calcd for $C_{24}H_{24}O_6Na$ 431.1471.

(*E*)-3-Acetyl-5-(4-fluorobenzylidene)-4-(4-fluorophenyl)cyclopent-2-enone (136ff): Prepared by following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp.: 126-128 °C; IR (Neat): ν_{max} 3065, 1681, 1624, 1593, 1505, 1412, 1366, 1221, 1159, 1025, 963, 880, 818 and 736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (1H, d, *J* = 1.5 Hz), 7.41-7.37 (2H, m), 7.23-7.19 (2H, m), 6.95 (2H, tt, *J* = 8.5, 2.0 Hz), 6.91-6.86 (3H, m), 5.22 (1H, s), 2.39 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.6 (C, *C*=O), 196.4 (C, *C*=O), 165.7 (C), 163.7 (C, d, *J* = 218.7 Hz, *C*-F), 161.7 (C, d, *J* = 213.7 Hz, *C*-F), 137.1 (C), 136.1 (CH), 134.0 (CH), 133.2 (2 x CH, d, *J* = 8.7 Hz), 132.9 (C, d, *J* = 2.5 Hz), 130.1 (2 x CH, d, *J* = 8.7 Hz), 129.6 (C, d, *J* = 3.7 Hz), 115.8 (2 x CH, d, *J* = 21.2 Hz), 115.6 (2 x CH, d, *J* = 21.2 Hz), 47.6 (CH), 28.3 (CH_3, CO*C*H_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –108.5, –114.5; HRMS m/z 325.1040 ($M + H^+$), calcd for $C_{20}H_{15}F_2O_2$ 325.1040.



136ff

(*E*)-3-Acetyl-5-(4-chlorobenzylidene)-4-(4-chlorophenyl)cyclopent-2-enone (136gg):

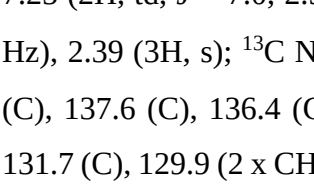


136gg

Prepared by following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp.: 104-106 °C; IR (Neat): ν_{max} 2951, 2926, 2853, 1681, 1629, 1588, 1485, 1247, 1164, 1087, 1009, 803 and 684 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (1H, d, *J* = 1.5 Hz), 7.33 (2H, td, *J* = 7.0, 2.5 Hz), 7.25 (2H, td, *J* = 7.0, 2.5 Hz), 7.17 (4H, br s), 6.90 (1H, d, *J* = 2.0 Hz), 5.21 (1H, t, *J* = 1.5 Hz), 2.39 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.4 (C, *C*=O), 196.2 (C, *C*=O), 165.4 (C), 137.6 (C), 136.4 (C), 136.2 (CH), 135.8 (C), 133.9 (CH), 133.3 (C), 132.3 (2 x CH), 131.7 (C), 129.9 (2 x CH), 128.91 (2 x CH), 128.86 (2 x CH), 47.7 (CH), 28.3 (CH_3, $CO\mathit{C}H_3$); HRMS m/z 357.0449 ($M + H^+$), calcd for $C_{20}H_{15}Cl_2O_2$ 357.0449.

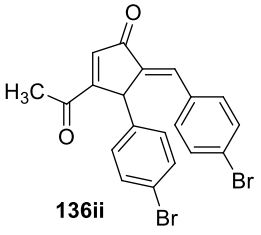
(*E*)-3-Acetyl-5-(3-chlorobenzylidene)-4-(3-chlorophenyl)cyclopent-2-enone (136hh):

Prepared by following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp.: 122-124 °C; IR (Neat): ν_{max} 2925, 2848, 1691, 1629, 1592, 1489, 1401, 1365, 1257, 1164, 1086, 1009, 874 and 812 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (1H, br d, *J* = 0.8 Hz), 7.39 (1H, br s), 7.25-7.22 (2H, m), 7.21-7.19 (1H, m), 7.17-7.15 (3H, m), 7.13-7.10 (1H, m), 6.94 (1H, br d, *J* = 1.2 Hz), 5.21 (1H, s), 2.41 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.3 (C, *C*=O), 196.1 (C, *C*=O), 165.3 (C), 139.3 (C), 138.6 (C), 136.5 (CH), 134.9 (C), 134.54 (C), 134.46 (C), 133.9 (CH), 130.5 (CH), 130.0 (CH), 129.8 (2 x CH), 129.2 (CH), 128.4 (CH), 127.7 (CH), 127.2 (CH), 48.0 (CH), 28.3 (CH_3, $CO\mathit{C}H_3$); HRMS m/z 395.0003 ($M + K^+$), calcd for $C_{20}H_{14}Cl_2O_2K$ 395.0008.



136hh

(*E*)-3-Acetyl-5-(4-bromobenzylidene)-4-(4-bromophenyl)cyclopent-2-enone (136ii):

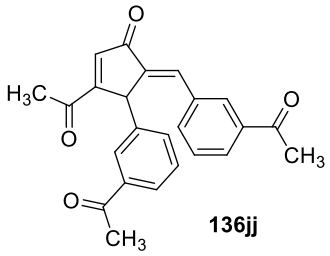


136ii

Prepared by following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp.: 134-136 °C; IR (Neat): ν_{max} 2957, 2915, 2848, 1681, 1619, 1583, 1479, 1366, 1262, 1071, 1009, 818 and 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (1H, br d, *J* = 1.2 Hz), 7.42 (2H, td, *J* = 8.5, 1.6 Hz), 7.34 (2H, td, *J* = 8.5, 1.6 Hz), 7.26 (2H, td, *J* = 8.5, 1.6 Hz), 7.13 (2H, td, *J* = 8.5, 1.6 Hz),

6.91 (1H, d, *J* = 1.6 Hz), 5.20 (1H, s), 2.40 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.4 (C, *C*=O), 196.2 (C, *C*=O), 165.3 (C), 137.7 (C), 136.3 (C), 136.2 (CH), 134.0 (CH), 132.4 (2 x CH), 132.1 (C), 131.9 (2 x CH), 131.8 (2 x CH), 130.2 (2 x CH), 125.0 (C), 121.5 (C), 47.8 (CH), 28.3 (CH_3, CO*C*H_3); HRMS m/z 444.9437 ($M + H^+$), calcd for $C_{20}H_{15}Br_2O_2$ 444.9439.

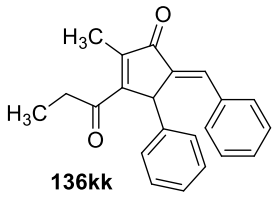
(*E*)-3-Acetyl-5-(3-acetylbenzylidene)-4-(3-acetylphenyl)cyclopent-2-enone (136jj):



136jj

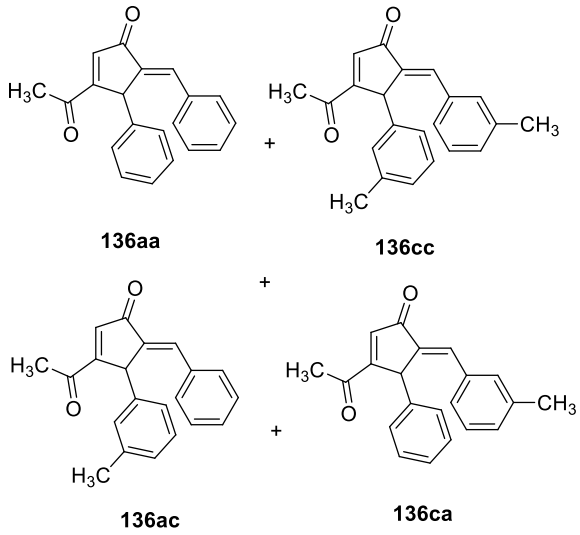
Prepared by following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp.: 132-134 °C; IR (Neat): ν_{max} 3008, 2920, 2853, 1748, 1686, 1593, 1428, 1361, 1268, 1159, 798, 730 and 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (1H, br s), 7.86 (1H, br s), 7.82 (1H, br d, *J* = 7.6 Hz), 7.69 (1H, br d, *J* = 7.6 Hz), 7.64 (1H, br s), 7.57 (1H, br d, *J* = 7.6 Hz), 7.47 (1H, br d, *J* = 7.6 Hz), 7.36 (1H, t, *J* = 7.6 Hz), 7.27 (1H, t, *J* = 7.2 Hz), 6.99 (1H, d, *J* = 0.8 Hz), 5.39 (1H, br s), 2.55 (3H, s), 2.53 (3H, s), 2.40 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.7 (C, *C*=O), 197.3 (C, *C*=O), 197.1 (C, *C*=O), 196.2 (C, *C*=O), 165.3 (C), 138.7 (C), 137.8 (C), 137.3 (C), 137.1 (C), 136.7 (CH), 135.6 (CH), 134.3 (CH), 133.7 (C), 133.3 (CH), 130.0 (CH), 129.8 (CH), 128.9 (CH), 128.73 (CH), 128.66 (CH), 127.4 (CH), 48.3 (CH), 28.3 (CH_3), 26.7 (2 x CH_3); HRMS m/z 395.1259 ($M + Na^+$), calcd for $C_{24}H_{20}O_4Na$ 395.1259.

(*E*)-5-Benzylidene-2-methyl-4-phenyl-3-propionylcyclopent-2-enone (136kk): Prepared by following the procedure **1a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp.: 128-130 °C; IR (Neat): ν_{max} 3008, 2920, 2853, 1738, 1681, 1624, 1593, 1464, 1376, 1211, 1138, 813, 777 and 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (1H, d, *J* = 1.6 Hz), 7.41-7.39 (2H, m), 7.24-7.22 (3H, m), 7.20-7.16 (2H, m), 7.13-7.09 (3H, m), 5.18 (1H, t, *J* = 1.6 Hz), 2.61 (1H, qd, *J* = 14.4, 7.2 Hz), 2.36 (1H, qd, *J* = 14.4, 7.2 Hz), 2.12 (3H, d, *J* = 2.0 Hz, olefinic-C*H*$_3$), 0.90 (3H, t, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.5 (C, *C*=O), 198.2 (C, *C*=O), 161.1 (C), 140.2 (C), 138.0 (C), 136.3 (C), 134.6 (CH), 133.8 (C), 131.1 (2 x CH), 129.7 (CH), 128.7 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.3 (CH), 49.0 (CH), 37.0 (CH_2, *C*H_2CH$_3$), 10.3 (CH_3), 7.2 (CH_3, CH_2*C*H_3); HRMS m/z 339.1360 ($M + Na^+$), calcd for $C_{22}H_{20}O_2Na$ 339.1361.



136kk

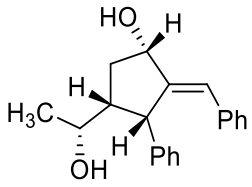
(*E*)-3-Acetyl-5-benzylidene-4-phenylcyclopent-2-enone (136aa), (*E*)-3-Acetyl-5-(3-methylbenzylidene)-4-(*m-tolyl*)cyclopent-2-enone (136cc), (*E*)-3-Acetyl-5-benzylidene-4-(*m-tolyl*)cyclopent-2-enone (136ac) and (*E*)-3-Acetyl-5-(3-methylbenzylidene)-4-phenylcyclopent-2-enone (136ca) [1:1:1:1]: Prepared by following the procedure **1a** and



purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp.: 170-172 °C; IR (Neat): ν_{max} 1696, 1685, 1627, 1589, 1491, 1447, 1402, 1364, 1323, 1293, 1252, 1205, 1045, 956, 879, 855, 785, 764, 716, 702 and 637 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, mixture of 1:1:1:1 ratio) δ 7.58-7.53 (4H, m), 7.44-7.41 (4H, m), 7.26-7.23 (12H, m), 7.22-7.16 (5H, m), 7.15-7.10 (5H, m), 7.09-7.07 (6H, m), 7.04-7.00 (2H, m), 6.93-6.92 (2H, m), 6.88-6.87 (4H, m), 5.26-5.25 (2H, m), 5.22-5.20 (2H, m), 2.363-2.360 (12H, m), 2.25 (3H, s), 2.24 (6H, s), 2.22 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135, mixture of 1:1:1:1 ratio) δ 198.2 (C, *C*=O), 198.1 (C, *C*=O), 198.00 (C, *C*=O), 197.98 (C, *C*=O), 196.51 (C, *C*=O), 196.49 (2 x C, *C*=O), 196.47 (C, *C*=O), 166.3 (C), 166.2 (2 x C), 166.1 (C), 138.13 (C), 138.06 (C), 138.0 (2 x C), 137.9 (C), 137.81 (C), 137.79 (C), 137.7 (C), 137.59 (C), 137.58 (C), 137.5 (C), 137.4 (C), 135.9 (CH), 135.79 (CH), 135.77 (CH), 135.7 (CH), 135.2 (CH), 135.01 (CH), 134.99 (CH), 134.81 (CH), 133.6 (C), 133.5 (C), 133.45 (C), 133.37 (C), 131.75 (CH), 131.68 (CH), 131.23 (2 x CH), 131.20 (2 x CH), 130.84 (CH), 130.79 (CH), 130.0 (CH), 129.9 (CH), 129.3 (CH), 129.0 (CH), 128.8 (CH), 128.7 (3 x CH), 128.6 (2 x CH), 128.51 (2 x CH), 128.46 (2 x CH), 128.42 (2 x CH), 128.40 (2 x CH), 128.34 (CH), 128.31 (3 x CH), 128.01 (CH), 127.97 (CH), 127.22 (CH), 127.19 (CH), 125.9 (CH), 125.8 (CH), 48.71 (CH), 48.68 (CH), 48.6 (CH), 48.5 (CH), 28.4 (2 x CH_3), 28.3 (2 x CH_3), 21.3 (2 x CH_3), 21.1 (2 x CH_3); HRMS m/z 289.1225 ($M + H^+$), calcd for $C_{20}H_{17}O_2$ 289.1229 (**136aa**); 303.1364 ($M + H^+$), calcd for $C_{21}H_{19}O_2$ 303.1385 (**136ac** or **136ca**); 317.1527 ($M + H^+$), calcd for $C_{22}H_{21}O_2$ 317.1542 (**136cc**).

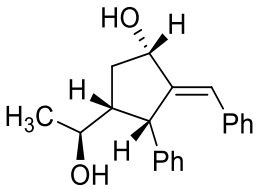
Procedure 1b: General Procedure for the Reduction of Product 136aa: In an oven dried round bottom flask, $NaBH_4$ (0.3 mmol) was added to the stirred solution of product **136aa** (0.2 mmol) in dry MeOH-THF (3:2) at 0 °C. Reaction mixture was stirred for 50 min at 25 °C. The crude reaction mixture was treated with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. Pure products **142aa** and **142'aa** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(1*S,3*S**,4*R**,*E*)-2-Benzylidene-4-((*R**)-1-hydroxyethyl)-3-phenylcyclopentanol (142aa):** Prepared by following the procedure **1b** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp.: 158-160 °C; IR (Neat): ν_{max} 3390, 1593, 1485, 1438, 1335, 1149, 1113, 1077, 1035, 922, 865 and 746 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.47 (2H, br d, *J* = 7.0 Hz), 7.29 (2H, br t, *J* = 7.0 Hz), 7.21-7.18 (1H, m), 7.17-7.10 (5H, m), 6.70 (1H, s), 4.89 (1H, dt, *J* = 7.5, 1.5 Hz), 4.33 (1H, d, *J* = 6.0 Hz), 3.20-3.15 (1H, m), 2.13-2.03 (3H, m), 1.66-1.61 (1H, m), 1.41 (1H, br s), 1.09 (3H, d, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 149.7 (C), 141.2 (C), 136.7 (C), 129.9 (2 x CH), 128.6 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 127.7 (CH), 126.8 (CH), 126.3 (CH), 75.8 (CH), 67.8 (CH), 50.8 (CH), 49.8 (CH), 34.9 (CH_2), 22.7 (CH_3); HRMS m/z 317.1513 ($M + Na^+$), calcd for $C_{20}H_{22}O_2Na$ 317.1517.



142aa

(1*S,3*S**,4*R**,*E*)-2-Benzylidene-4-((*S**)-1-hydroxyethyl)-3-phenylcyclopentanol (142'aa):** Prepared by following the procedure **1b** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp.: 156-158 °C; IR (Neat): ν_{max} 3344, 3019, 2967, 1593, 1495, 1448, 1371, 1268, 1118, 1030, 916, 751 and 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.35 (2H, d, *J* = 7.0 Hz), 7.26 (2H, t, *J* = 7.0 Hz), 7.17 (1H, t, *J* = 7.0 Hz), 7.10-7.05 (5H, m), 6.76 (1H, br s), 4.80 (1H, t, *J* = 6.0 Hz), 4.20 (1H, d, *J* = 6.5 Hz), 3.60 (1H, m), 2.30-2.23 (2H, m), 2.01-1.97 (1H, m), 1.66 (2H, br s), 1.15 (3H, d, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 149.0 (C), 140.7 (C), 136.6 (C), 129.3 (2 x CH), 128.7 (2 x CH), 128.6 (2 x CH), 127.9 (2 x CH), 127.7 (CH), 126.7 (CH), 126.6 (CH), 76.2 (CH),

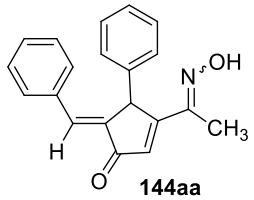


142'aa

66.7 (CH), 50.5 (CH), 50.0 (CH), 32.8 (CH_2), 22.4 (CH_3); HRMS m/z 317.1516 ($M + Na^+$), calcd for $C_{20}H_{22}O_2Na$ 317.1517.

Procedure 1c: General Procedure for the Synthesis of (*E*)-5-Benzylidene-3-((*E*)-1 (hydroxyimino)ethyl)-4-phenylcyclopent-2-enone (144aa): In an oven dried round bottom flask, a mixture of hydroxylamine hydrochloric acid (1.5 equiv.), pyridine (0.25 equiv.) and compound **136aa** (0.3 mmol) in 95% ethanol (1 ml) was stirred at 60 °C temperature and the progress of the reaction was monitored by TLC. The crude reaction mixture was treated with brine solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. Pure product **144aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(*E*)-5-Benzylidene-3-((*E*)-1-(hydroxyimino)ethyl)-4-phenylcyclopent-2-enone (144aa):



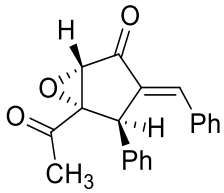
144aa

Prepared by following the procedure **1c** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp.: 124-126 °C; IR (Neat): ν_{max} 3282, 3050, 2926, 2853, 1671, 1619, 1583, 1443, 1268, 1190, 1020, 870, 761 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.21 (1H, br s), 7.47 (1H, d, *J* = 1.2 Hz), 7.43-7.40 (2H, m), 7.24-7.21 (5H, m), 7.15 (2H, br t, *J* = 7.2 Hz), 7.08 (1H, t, *J* = 7.2 Hz), 6.68 (1H, d, *J* = 0.8 Hz), 5.32 (1H, s), 2.05 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.2 (C, *C*=O), 168.1 (C), 152.3 (C), 139.5 (C), 139.0 (C), 134.0 (C), 132.5 (CH), 131.5 (CH), 130.8 (2 x CH), 129.4 (CH), 128.8 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 126.8 (CH), 48.9 (CH), 11.7 (CH_3); HRMS m/z 304.1335 ($M + H^+$), calcd for $C_{20}H_{18}NO_2$ 304.1338.

Procedure 1d: General Procedure for the Epoxidation of Product 136aa: In an oven dried round bottom flask, aqueous H_2O_2 solution (30%, 1.2 mmol) was added to the stirred solution of product **136aa** (0.3 mmol) and *tert*-$BuNH_2$ **71h** (0.09 mmol) in THF (1.0 mL) at 25 °C and stirred for 7 h. The crude reaction mixture was treated with brine solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic

layers were dried (Na_2SO_4), and concentrated. Pure product **146aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(1*S,4*R**,5*S**,*E*)-5-Acetyl-3-benzylidene-4-phenyl-6-oxabicyclo[3.1.0]hexan-2-one (146aa):** Prepared by following the procedure **1d** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp.: 100-102 °C; IR (Neat): ν_{max} 3060, 3029, 2926, 1712, 1619, 1490, 1454, 1361, 1216, 1175, 1025, 844, 767 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 3:1 *dr*, for major isomer) δ 7.57 (1H, s), 7.39-7.38 (2H, m), 7.33-7.26 (5H, m), 7.23-7.20 (3H, m), 4.83 (1H, s), 4.09 (1H, s), 2.03 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135, 3:1 *dr*, for major isomer) δ 198.7 (C, *C*=O), 195.5 (C, *C*=O), 138.4 (CH), 137.6 (C), 136.1 (C), 133.4 (C), 130.7 (2 x CH), 130.2 (CH), 128.8 (2 x CH), 128.7 (2 x CH), 128.6 (2 x CH), 127.7 (CH), 68.3 (C), 59.1 (CH), 46.4 (CH), 26.6 (CH_3); ^1H NMR ($CDCl_3$, 500 MHz, 3:1 *dr*, for minor isomer) δ 7.72 (2H, m), 7.33-7.26 (5H, m), 7.18-7.16 (3H, m), 6.72 (1H, s), 4.43 (1H, s), 4.16 (1H, s), 2.06 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135, 3:1 *dr*, for minor isomer) δ 198.8 (C, *C*=O), 194.3 (C, *C*=O), 144.1 (CH), 140.3 (C), 136.3 (C), 133.9 (C), 130.5 (2 x CH), 130.3 (CH), 129.1 (2 x CH), 128.1 (2 x CH), 127.6 (2 x CH), 127.5 (CH), 66.8 (C), 61.9 (CH), 50.1 (CH), 26.0 (CH_3); HRMS m/z 327.0998 ($M + Na^+$), calcd for $C_{20}H_{16}O_3Na$ 327.0997.



146aa

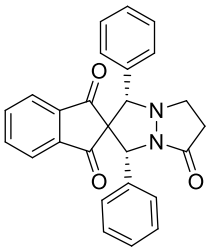
Materials: All solvents and commercially available chemicals were used as received. *N*,*N*-Cyclic azomethine imines **42a-i**[68] and 2-arylidene-1,3-indandiones **149** (**149a**, **149b**, **149f**, **149i** and **149j**)[69] were prepared according to the literature procedure.

Procedure 2a: General procedure for L-proline catalyzed three-component synthesis of spiroindane-1,3-dione-pyrazolidinones: In an ordinary glass vial equipped with a magnetic stirring bar, to L-proline (***S***)-**88b** (5 mol%) in CH_3CN (0.5 mL), were added 1,3-indandione **147** (0.3 mmol) and aldehyde **148** (0.45 mmol, 1.5 equiv.) and the reaction mixture was stirred at ambient temperature for 15 to 20 minutes. When the reaction mixture solidified, more solvent (0.5 mL) was added. To the reaction mixture azomethine imine **42** (0.36 mmol, 1.2 equiv.) was added and stirred at 50 °C for 0.6-1.5 h. The reaction mixture was treated with saturated aqueous ammonium chloride solution and the aqueous layer was

extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, and concentrated. Pure products **150** were obtained by quick filtration (silica gel, mixture of hexane/ethyl acetate).

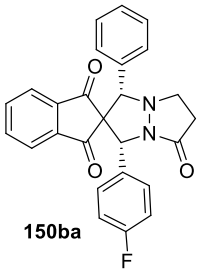
Procedure 2b: General procedure for the two-component synthesis of spiroindane-1,3-dione-pyrazolidinones: In an ordinary glass vial equipped with a magnetic stirring bar, to 2-arylideneindane-1,3-dione **149** (0.3 mmol) and azomethine imine **42** (0.36 mmol, 1.2 equiv.) were added in CH_3CN (1.0 mL) and stirred at 50 °C for 1.2-1.5 h. The reaction mixture was treated with saturated aqueous ammonium chloride solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, and concentrated. Pure products **150** were obtained by quick filtration (silica gel, mixture of hexane/ethyl acetate).

(1'*S,3'*R**)-1',3'-Diphenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*) trione (150aa):** Prepared by following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 160-162 °C; *dr* = >99:1; IR (KBr): ν_{max} 3032, 2935, 1752, 1714, 1584, 1455, 1346, 1265, 1109, 920, 768, 698 and 617 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97 (1H, d, *J* = 8.0 Hz), 7.72 (1H, dt, *J* = 7.6, 0.4 Hz), 7.58 (1H, dt, *J* = 7.6, 0.4 Hz), 7.39 (1H, d, *J* = 7.6 Hz), 7.21-7.17 (2H, m), 7.16-7.13 (3H, m), 7.11-7.07 (5H, m), 5.81 (1H, s), 4.42 (1H, s), 3.89-3.79 (1H, m), 3.12-3.03 (2H, m), 2.93-2.85 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.2 (C, *C*=O), 194.5 (C, *C*=O), 172.4 (C, *C*=O), 143.2 (C), 141.3 (C), 136.2 (CH), 135.5 (CH), 135.2 (C), 131.7 (C), 128.8 (CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.85 (CH), 127.82 (2 x CH), 125.8 (2 x CH), 123.23 (CH), 123.16 (CH), 77.4 (CH), 72.1 (C), 63.3 (CH), 48.1 (CH_2), 32.5 (CH_2); LCMS m/z 409.15 ($M + H^+$), calcd for $C_{26}H_{21}N_2O_3$ 409.1552; HRMS m/z 431.1373 ($M + Na^+$), calcd for $C_{26}H_{20}N_2O_3Na$ 431.1372; Anal. calcd for $C_{26}H_{20}N_2O_3$ (408.1474): C, 76.45; H, 4.94; N, 6.86. Found: C, 76.32; H, 4.98; N, 6.79%.



150aa

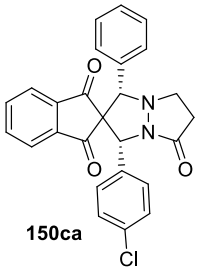
(1'*S,3'*R**)-3'-(4-Fluorophenyl)-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2a] pyrazole]-1,3,5'(3'*H*)-trione (150ba):** Prepared by following the procedure



150ba

2b and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 150-152 °C; *dr* = >99:1; IR (KBr): ν_{max} 2357, 2335, 1752, 1708, 1514, 1341, 1260, 1233, 1168, 763 and 703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.95 (1H, d, *J* = 8.0 Hz), 7.70 (1H, t, *J* = 7.5 Hz), 7.58 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 7.5 Hz), 7.18-7.16 (2H, m), 7.09-7.06 (5H, m), 6.82 (2H, t, *J* = 8.5 Hz), 5.75 (1H, s), 4.40 (1H, s), 3.83-3.78 (1H, m), 3.09-3.00 (2H, m), 2.91-2.84 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.0 (C, *C*=O), 194.5 (C, *C*=O), 172.7 (C, *C*=O), 162.2 (C, d, *J* = 245.0 Hz, *C*-F), 143.0 (C), 141.2 (C), 136.4 (CH), 135.7 (CH), 131.5 (C), 131.1 (C, d, *J* = 2.5 Hz), 128.9 (CH), 128.5 (2 x CH), 127.75 (3 x CH), 127.67 (CH), 123.2 (2 x CH, d, *J* = 12.5 Hz), 115.3 (2 x CH, d, *J* = 22.5 Hz), 77.3 (CH), 72.0 (C), 62.8 (CH), 48.0 (CH_2), 32.3 (CH_2); LCMS m/z 427.40 ($M + H^+$), calcd for $C_{26}H_{20}FN_2O_3$ 427.1458; HRMS m/z 449.1272 ($M + Na^+$), calcd for $C_{26}H_{19}FN_2O_3Na$ 449.1277; Anal. calcd for $C_{26}H_{19}FN_2O_3$ (426.1380): C, 73.23; H, 4.49; N, 6.57. Found: C, 73.15; H, 4.53; N, 6.49%.

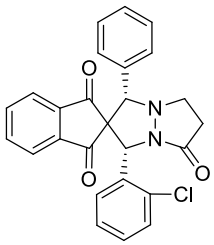
(1'*S,3'*R**)-3'-(4-Chlorophenyl)-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2a] pyrazole]-1,3,5'(3'*H*)-trione (150ca):** Prepared by following the procedure



150ca

2a and purified by column chromatography using EtOAc/hexane and isolated as off-white solid. Mp 160-162 °C; *dr* = 8:1; IR (KBr): ν_{max} 2849, 2816, 1746, 1719, 1590, 1487, 1336, 1292, 1265, 1179, 1098, 1028, 768 and 703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, for major isomer) δ 7.96 (1H, d, *J* = 7.5 Hz), 7.73 (1H, t, *J* = 7.5 Hz), 7.61 (1H, t, *J* = 7.5 Hz), 7.42 (1H, d, *J* = 8.0 Hz), 7.18-7.17 (2H, m), 7.13 (2H, d, *J* = 8.0 Hz), 7.11-7.10 (3H, m), 7.06-7.01 (2H, m), 5.76 (1H, s), 4.40 (1H, s), 3.85-3.79 (1H, m), 3.10-3.02 (2H, m), 2.93-2.86 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for major isomer) δ 197.9 (C, *C*=O), 194.4 (C, *C*=O), 172.7 (C, *C*=O), 143.0 (C), 141.2 (C), 136.4 (CH), 135.7 (CH), 133.9 (C), 133.7 (C), 131.5 (C), 128.9 (CH), 128.6 (2 x CH), 128.5 (2 x CH), 127.8 (2 x CH), 127.4 (2 x CH), 123.3 (2 x CH), 77.4 (CH), 72.0 (C), 62.7 (CH), 48.0 (CH_2), 32.3 (CH_2); HRMS m/z 465.0982 ($M + Na^+$), calcd for $C_{26}H_{19}ClN_2O_3Na$ 465.0982.

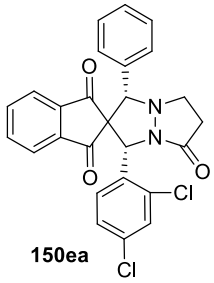
(1'*S,3'*S**)-3'-(2-Chlorophenyl)-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2a] pyrazole]-1,3,5'(3'*H*)-trione (150da):** Prepared by following the procedure



150da

2a and purified by column chromatography using EtOAc/hexane and isolated as light brown solid. Mp 156-158 °C; *dr* = 7:1; IR (KBr): ν_{max} 2964, 2849, 1742, 1715, 1594, 1386, 1255, 1085, 888 and 756 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, for major isomer) δ 7.96 (1H, d, *J* = 8.0 Hz), 7.79 (1H, dd, *J* = 8.0, 0.8 Hz), 7.71 (1H, dt, *J* = 7.6, 0.8 Hz), 7.57 (1H, dt, *J* = 7.6, 0.4 Hz), 7.34 (2H, d, *J* = 9.5 Hz), 7.16-7.12 (3H, m,), 7.10-7.05 (4H, m), 5.99 (1H, s), 4.36 (1H, s), 3.81 (1H, ddd, *J* = 11.6, 9.2, 8.0 Hz), 3.12 (1H, ddd, *J* = 11.6, 9.2, 6.8 Hz), 2.96-2.89 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for major isomer) δ 198.6 (C, *C*=O), 194.5 (C, *C*=O), 173.9 (C, *C*=O), 141.8 (C), 141.5 (C), 135.9 (CH), 135.5 (CH), 134.2 (C), 131.7 (C), 131.5 (C), 129.3 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.3 (2 x CH), 128.1 (2 x CH), 126.9 (CH), 123.04 (CH), 122.99 (CH), 78.1 (CH), 70.9 (C), 60.5 (CH), 45.9 (CH_2), 30.8 (CH_2); LCMS m/z 443.35 ($M + H^+$), calcd for $C_{26}H_{20}ClN_2O_3$ 443.1162; HRMS m/z 465.0986 ($M + Na^+$), calcd for $C_{26}H_{19}ClN_2O_3Na$ 465.0982; Anal. calcd for $C_{26}H_{19}ClN_2O_3$ (442.1084): C, 70.51; H, 4.32; N, 6.33. Found: C, 70.42; H, 4.28; N, 6.41%.

(1'*S,3'*S**)-3'-(2,4-Dichlorophenyl)-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a] pyrazole]-1,3,5'(3'*H*)-trione (150ea):** Prepared by following the procedure

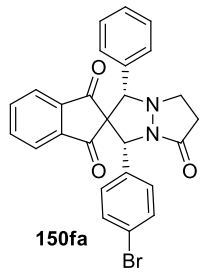


150ea

2a and purified by column chromatography using EtOAc/hexane and isolated as light brown solid. Mp 174-176 °C; *dr* = >99:1; IR (KBr): ν_{max} 2919, 2849, 1746, 1708, 1649, 1590, 1471, 1341, 1255, 812, 763 and 709 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.95 (1H, d, *J* = 7.5 Hz), 7.73-7.70 (2H, m), 7.59 (1H, dt, *J* = 7.5,0.5 Hz), 7.36 (1H, d, *J* = 7.5 Hz), 7.32 (1H, dd, *J* = 8.5, 2.0 Hz), 7.12-7.10 (3H, m), 7.09-7.05 (3H, m), 5.92 (1H, s), 4.34 (1H, s), 3.83-3.77 (1H, m), 3.15-3.10 (1H, m), 2.98-2.84 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.3 (C, *C*=O), 194.5 (C, *C*=O), 174.3 (C, *C*=O), 141.8 (C), 141.4 (C), 136.0 (CH), 135.7 (CH), 134.2 (C), 133.1 (C), 132.1 (C), 131.5 (C), 130.5 (CH), 128.9 (CH), 128.7 (CH), 128.4 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 123.11 (CH), 123.08 (CH), 78.1 (CH), 70.8 (C), 60.1 (CH), 45.8 (CH_2), 30.5 (CH_2); LCMS m/z 475.45 ($M + H^+$), calcd for $C_{26}H_{17}Cl_2N_2O_3$ 475.0616; HRMS m/z 499.0587 ($M + Na^+$), calcd for $C_{26}H_{18}Cl_2N_2O_3Na$

499.0592; Anal. calcd for $C_{26}H_{18}Cl_2N_2O_3$ (476.0694): C, 65.42; H, 3.80; N, 5.87. Found: C, 65.34; H, 3.86; N, 5.81%.

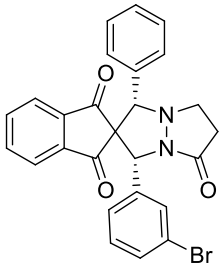
(1'*S,3'*R**)-3'-(4-Bromophenyl)-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150fa):** Prepared by following the procedure



150fa

2b and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 152-154 °C; *dr* = 9:1; IR (KBr): ν_{max} 2926, 1742, 1704, 1589, 1485, 1408, 1342, 1255, 1129, 1074, 1014 and 761 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, for major isomer) δ 7.96 (1H, d, *J* = 7.6 Hz), 7.73 (1H, dt, *J* = 7.6, 0.8 Hz), 7.61 (1H, dt, *J* = 7.6, 0.8 Hz), 7.43 (1H, d, *J* = 7.6 Hz), 7.29 (2H, d, *J* = 8.4 Hz), 7.19-7.16 (2H, m), 7.11-7.09 (3H, m), 6.99 (2H, d, *J* = 8.4 Hz), 5.74 (1H, s), 4.40 (1H, s), 3.85-3.78 (1H, m), 3.11-3.01 (2H, m), 2.93-2.85 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for major isomer) δ 197.9 (C, *C*=O), 194.4 (C, *C*=O), 172.7 (C, *C*=O), 143.0 (C), 141.2 (C), 136.4 (CH), 135.7 (CH), 134.4 (C), 131.5 (2 x CH), 131.4 (C), 128.9 (CH), 128.5 (2 x CH), 127.8 (2 x CH), 127.7 (2 x CH), 123.3 (2 x CH), 121.9 (C), 77.5 (CH), 71.9 (C), 62.7 (CH), 48.0 (CH_2), 32.3 (CH_2); HRMS m/z 487.0655 ($M + H^+$), calcd for $C_{26}H_{20}BrN_2O_3$ 487.0657.

(1'*S,3'*R**)-3'-(3-Bromophenyl)-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ga):** Prepared by following the procedure

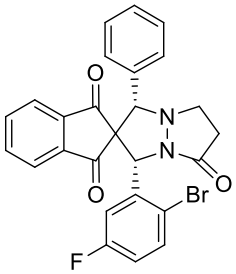


150ga

2a and purified by column chromatography using EtOAc/hexane and isolated as off-white solid. Mp 170-172 °C; *dr* = 7:1; IR (KBr): ν_{max} 2926, 1741, 1709, 1594, 1419, 1330, 1254, 1068, 1024 and 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, for major isomer) δ 7.98 (1H, d, *J* = 7.5 Hz), 7.74 (1H, t, *J* = 7.5 Hz), 7.62 (1H, dt, *J* = 7.5, 0.5 Hz), 7.43(1H, d, *J* = 8.0 Hz), 7.31 (1H, br s), 7.28-7.27 (1H, m), 7.19-7.17 (2H, m), 7.11-7.09 (3H, m), 7.02 (1H, t, *J* = 7.5 Hz), 6.98 (1H, d, *J* = 7.5 Hz), 5.75 (1H, s), 4.39 (1H, s), 3.87-3.81 (1H, m), 3.12-3.02 (2H, m), 2.94-2.87 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for major isomer) δ 197.9 (C, *C*=O), 194.3 (C, *C*=O), 173.2 (C, *C*=O), 143.1 (C), 141.2 (C), 137.8 (C), 136.4 (CH), 135.7 (CH), 131.4 (C), 131.1 (CH), 129.9 (CH) , 129.1 (CH), 128.9 (CH), 128.5 (2 x CH), 127.8 (2 x CH), 124.5 (CH), 123.34 (CH), 123.26 (CH), 122.7 (C), 77.5 (CH), 72.0 (C), 62.6 (CH), 47.7 (CH_2), 32.0 (CH_2); LCMS m/z 487.30 ($M + H^+$), calcd for $C_{26}H_{20}BrN_2O_3$

487.0657; HRMS m/z 509.0485 ($M + Na^+$), calcd for $C_{26}H_{19}BrN_2O_3Na$ 509.0477; Anal. calcd for $C_{26}H_{19}BrN_2O_3$ (486.0579): C, 64.08; H, 3.93; N, 5.75. Found: C, 64.15; H, 3.89; N, 5.82%.

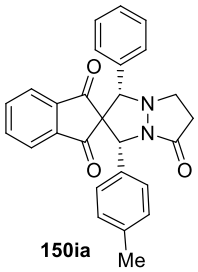
(1'*S,3'*S**)-3'-(2-Bromo-5-fluorophenyl)-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ha):** Prepared by following the procedure



150ha

2a and purified by column chromatography using EtOAc/hexane and isolated as light brown solid. Mp 160-162 °C; *dr* = >99:1; IR (KBr): ν_{max} 2931, 1753, 1698, 1594, 1468, 1342, 1249, 1129, 1041 and 778 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97 (1H, d, *J* = 7.6 Hz), 7.73 (1H, dt, *J* = 7.6, 0.8 Hz), 7.61 (1H, dd, *J* = 7.6, 0.8 Hz), 7.58-7.55 (1H, m), 7.36 (1H, d, *J* = 7.6 Hz), 7.22 (1H, dd, *J* = 8.8, 5.2 Hz), 7.13-7.07 (5H, m), 6.84 (1H, dt, *J* = 8.0, 2.8 Hz), 5.90 (1H, s), 4.33 (1H, s), 3.86-3.78 (1H, m), 3.15 (1H, ddd, *J* = 12.0, 9.6, 5.2 Hz), 3.01-2.92 (1H, m), 2.85 (1H, ddd, *J* = 17.6, 9.6, 4.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.7 (C, *C*=O), 194.2 (C, *C*=O), 174.8 (C, *C*=O), 162.1 (C, d, *J* = 245.0 Hz, *C*-F), 142.0 (C), 141.5 (C), 138.7 (C, d, *J* = 8.0 Hz), 135.9 (CH), 135.6 (CH), 133.3 (CH, d, *J* = 8.0 Hz), 131.7 (C), 128.9 (CH), 128.3 (2 x CH), 128.2 (2 x CH), 123.1 (CH), 123.0 (CH), 117.5 (CH, d, *J* = 25.0 Hz), 116.8 (CH, d, *J* = 23.0 Hz), 115.8 (C, d, *J* = 3.0 Hz), 78.3 (CH), 70.6 (C), 62.2 (CH), 45.3 (CH_2), 30.0 (CH_2); LCMS m/z 504.45 (M^+), calcd for $C_{26}H_{18}BrFN_2O_3$ 504.0485; HRMS m/z 505.0569 ($M + H^+$), calcd for $C_{26}H_{19}BrFN_2O_3$ 505.0563; Anal. calcd for $C_{26}H_{18}BrFN_2O_3$ (504.0485): C, 61.80; H, 3.59; N, 5.54. Found: C, 61.92; H, 3.52; N, 5.48%.

(1'*S,3'*R**)-1'-Phenyl-3'-(*p*-tolyl)-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ia):** Prepared by following the procedure **2b** and purified

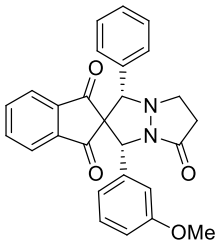


150ia

by column chromatography using EtOAc/hexane and isolated as white solid. Mp 154-156 °C; *dr* = >99:1; IR (KBr): ν_{max} 2962, 1752, 1714, 1590, 1514, 1455, 1341, 1292, 1260, 1184, 1093, 768 and 628 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.96 (1H, d, *J* = 8.0 Hz), 7.71 (1H, dt, *J* = 7.6, 0.8 Hz), 7.58 (1H, dt, *J* = 7.6, 0.8 Hz), 7.41 (1H, d, *J* = 7.6 Hz), 7.21-7.19 (2H, m), 7.11-7.09 (3H, m), 6.98-6.93 (4H, m), 5.78 (1H, s), 4.41 (1H, s), 3.87-3.79 (1H, m), 3.13-3.02 (2H, m), 2.95-2.83 (1H, m), 2.20 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.3 (C, *C*=O), 194.6 (C, *C*=O), 171.9 (C, *C*=O), 143.2 (C), 141.3 (C), 137.5 (C), 136.2 (CH), 135.5 (CH),

132.0 (C), 131.7 (C), 129.1 (2 x CH), 128.8 (CH), 128.4 (2 x CH), 127.8 (2 x CH), 125.7 (2 x CH), 123.2 (2 x CH), 77.4 (CH), 72.1 (C), 63.2 (CH), 48.4 (CH_2), 32.7 (CH_2), 21.1 (CH_3); HRMS m/z 423.1711 ($M + H^+$), calcd for $C_{27}H_{23}N_2O_3$ 423.1709.

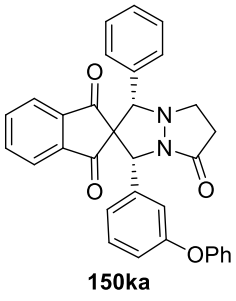
(1'*S,3'*R**)-3'-(3-Methoxyphenyl)-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ja):** Prepared by following the procedure



150ja

2b and purified by column chromatography using EtOAc/hexane and isolated as off-white solid. Mp 152-154 °C; *dr* = >99:1; IR (KBr): ν_{max} 2940, 1746, 1698, 1606, 1584, 1498, 1384, 1260, 1038, 768 and 644 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.96 (1H, d, *J* = 7.6 Hz), 7.71 (1H, t, *J* = 7.6 Hz), 7.59 (1H, t, *J* = 7.6 Hz), 7.42 (1H, d, *J* = 7.6 Hz), 7.21-7.19 (2H, m), 7.11-7.07 (3H, m), 7.05 (1H, t, *J* = 8.0 Hz), 6.65 (2H, d, *J* = 8.4 Hz), 6.60 (1H, br s), 5.77 (1H, s), 4.41 (1H, s), 3.88-3.78 (1H, m), 3.61 (3H, s, OC*H*$_3$), 3.11-3.02 (2H, m), 2.94-2.82 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.2 (C, *C*=O), 194.4 (C, *C*=O), 172.6 (C, *C*=O), 159.6 (C), 143.2 (C), 141.2 (C), 136.8 (C), 136.3 (CH), 135.5 (CH), 131.6 (C), 129.5 (CH), 128.8 (CH), 128.5 (2 x CH), 127.8 (2 x CH), 123.22 (CH), 123.20 (CH), 118.1 (CH), 113.6 (CH), 111.4 (CH), 77.4 (CH), 72.0 (C), 63.3 (CH), 55.1 (CH_3, O*C*H_3), 48.1 (CH_2), 32.4 (CH_2); LCMS m/z 439.40 ($M + H^+$), calcd for $C_{27}H_{23}N_2O_4$ 439.1658; HRMS m/z 461.1477 ($M + Na^+$), calcd for $C_{27}H_{22}N_2O_4Na$ 461.1477; Anal. calcd for $C_{27}H_{22}N_2O_4$ (438.1580): C, 73.96; H, 5.06; N, 6.39. Found: C, 73.85; H, 5.10; N, 6.31%.

(1'*S,3'*R**)-3'-(3-Phenoxyphenyl)-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ka):** Prepared by following the procedure

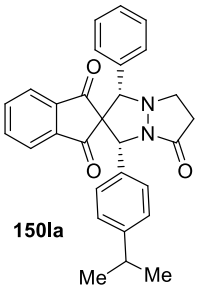


150ka

2a and purified by column chromatography using EtOAc/hexane and isolated as off-white solid. Mp 138-140 °C; *dr* = 6:1; IR (KBr): ν_{max} 2957, 1741, 1708, 1584, 1487, 1249, 1217, 1109, 763 and 703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, for major isomer) δ 7.93 (1H, d, *J* = 7.6 Hz), 7.73 (1H, t, *J* = 7.6 Hz), 7.63 (1H, t, *J* = 7.6 Hz), 7.46 (1H, d, *J* = 7.6 Hz), 7.20-7.14 (5H, m), 7.11-7.10 (3H, m), 7.03 (1H, t, *J* = 7.6 Hz), 6.90 (1H, d, *J* = 7.6 Hz), 6.78-6.76 (3H, m), 6.69-6.65 (1H, m), 5.76 (1H, s), 4.39 (1H, s), 3.84-3.77 (1H, m), 3.10-2.98 (2H, m), 2.93-2.82 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for major isomer) δ 198.1 (C, *C*=O), 194.3 (C, *C*=O), 172.9 (C, *C*=O), 157.1 (C), 156.9 (C), 143.2 (C),

141.2 (C), 137.4 (C), 136.3 (CH), 135.5 (CH), 131.6 (C), 129.9 (CH), 129.6 (2 x CH), 128.8 (CH), 128.5 (2 x CH), 127.8 (2 x CH), 123.4 (CH), 123.1 (CH), 123.0 (CH), 120.8 (CH), 118.6 (2 x CH), 118.4 (CH), 116.4 (CH), 77.3 (CH), 71.9 (C), 63.0 (CH), 47.8 (CH_2), 32.2 (CH_2); LCMS m/z 501.30 ($M + H^+$), calcd for $C_{32}H_{25}N_2O_4$ 501.1814; HRMS m/z 523.1636 ($M + Na^+$), calcd for $C_{32}H_{24}N_2O_4Na$ 523.1634; Anal. calcd for $C_{32}H_{24}N_2O_4$ (500.1736): C, 76.78; H, 4.83; N, 5.60. Found: C, 76.65; H, 4.79; N, 5.68%.

(1'*S,3'*R**)-3'-(4-Isopropylphenyl)-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150la):** Prepared by following the procedure

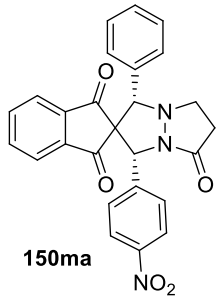


150la

2a and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Mp 120-122 °C; *dr* = >99:1; IR (KBr): ν_{max} 2953, 2909, 1742, 1709, 1589, 1457, 1266, 1194, 1090, 899 and 767 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.97 (1H, d, *J* = 8.0 Hz), 7.72 (1H, t, *J* = 7.6 Hz), 7.59 (1H, t, *J* = 7.6 Hz), 7.41 (1H, d, *J* = 7.6 Hz), 7.22-7.20 (2H, m), 7.11-7.10 (3H, m), 7.00 (4H, br s), 5.78 (1H, s), 4.42 (1H, s), 3.88-3.80 (1H, m), 3.14-3.02 (2H, m), 2.93-2.87 (1H, m), 2.77 (1H, heptate, *J* = 6.8 Hz, C*H*(CH_3)$_2$), 1.13 (6H, t, *J* = 6.4 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.3 (C, *C*=O), 194.6 (C, *C*=O), 171.9 (C, *C*=O), 148.3 (C), 143.2 (C), 141.3 (C), 136.2 (CH), 135.4 (CH), 132.2 (C), 131.7 (C), 128.8 (CH), 128.4 (2 x CH), 127.8 (2 x CH), 126.5 (2 x CH), 125.7 (2 x CH), 123.20 (CH), 123.16 (CH), 77.3 (CH), 72.2 (C), 63.3 (CH), 48.5 (CH_2), 33.6 (CH, *C*H(CH_3)$_2$), 32.8 (CH_2), 23.8 (CH_3, CH(*C*H$_3$)$_2$), 23.7 (CH_3, CH(*C*H$_3$)$_2$); LCMS m/z 451.55 ($M + H^+$), calcd for $C_{29}H_{27}N_2O_3$ 451.2022; HRMS m/z 451.2027 ($M + H^+$), calcd for $C_{29}H_{27}N_2O_4$ 451.2022; Anal. calcd for $C_{29}H_{26}N_2O_3$ (450.1943): C, 77.31; H, 5.82; N, 6.22. Found: C, 77.23; H, 5.78; N, 6.31%.

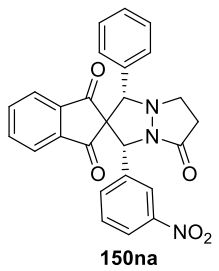
(1'*S,3'*R**)-3'-(4-Nitrophenyl)-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ma):** Prepared by following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp 132-134 °C; *dr* = 10:1; IR (KBr): ν_{max} 3054, 2989, 1752, 1714, 1676, 1525, 1487, 1357, 1260, 1238, 1114, 936, 860, and 774 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, for major isomer) δ 8.06 (2H, d, *J* = 8.0 Hz), 8.00 (1H, d, *J* = 7.2 Hz), 7.77 (1H, t, *J* = 7.2 Hz), 7.64 (1H, t, *J* = 7.2 Hz), 7.41 (1H, d, *J* = 7.6 Hz), 7.33-7.29 (2H, m), 7.17-7.10 (5H, m), 5.87 (1H, s), 4.41

(1H, s), 3.90-3.83 (1H, m), 3.17-3.02 (2H, m), 2.99-2.89 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for major isomer) δ 197.5 (C, *C*=O), 194.4 (C, *C*=O), 173.7 (C, *C*=O), 147.5 (C), 143.1 (C), 142.8 (C), 141.1 (C), 136.7 (CH), 136.0 (CH), 131.0 (C), 129.1 (CH), 128.6 (2 x CH), 127.7 (2 x CH), 126.9 (2 x CH), 123.7 (2 x CH), 123.5 (CH), 123.3 (CH), 77.7 (CH), 72.1 (C), 62.3 (CH), 47.5 (CH_2), 31.8 (CH_2); HRMS m/z 454.1401 (M + H^+), calcd for $C_{26}H_{20}N_3O_5$ 454.1403.



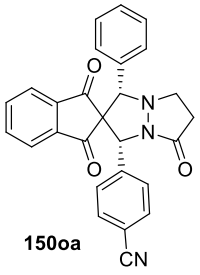
150ma

(1'*S,3'*R**)-3'-(3-Nitrophenyl)-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150na):** Prepared by following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated yellow solid. Mp 164-166 °C; *dr* = 12:1; IR (KBr): ν_{max} 2926, 2855, 1748, 1704, 1594, 1534, 1348, 1255, 1178, 1019, 767 and 729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, for major isomer) δ 8.04-7.98 (3H, m), 7.74 (1H, dt, *J* = 7.5, 0.5 Hz), 7.60 (1H, dt, *J* = 7.5, 1.0 Hz), 7.46 (1H, d, *J* = 7.5 Hz), 7.39-7.35 (2H, m), 7.16-7.14 (2H, m), 7.11-7.09 (3H, m), 5.84 (1H, s), 4.40 (1H, s), 3.86 (1H, ddd, *J* = 11.5, 9.5, 7.0 Hz), 3.15-3.09 (1H, m), 3.07-3.00 (1H, m), 2.95-2.88 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for major isomer) δ 197.6 (C, *C*=O), 194.4 (C, *C*=O), 173.9 (C, *C*=O), 148.2 (C), 142.9 (C), 141.1 (C), 138.0 (C), 136.6 (CH), 136.0 (CH), 132.2 (CH), 131.2 (C), 129.4 (CH), 129.1 (CH), 128.6 (2 x CH), 127.8 (2 x CH), 123.5 (CH), 123.2 (CH), 123.1 (CH), 121.3 (CH), 77.7 (CH), 71.9 (C), 62.2 (CH), 47.3 (CH_2), 31.7 (CH_2); LCMS m/z 452.35 (M + H^+), calcd for $C_{26}H_{18}N_3O_5$ 452.1246; HRMS m/z 454.1403 (M + H^+), calcd for $C_{26}H_{20}N_3O_5$ 454.1403; Anal. calcd for $C_{26}H_{19}N_3O_5$ (453.1325): C, 68.87; H, 4.22; N, 9.27. Found: C, 68.73; H, 4.26; N, 9.19%.



150na

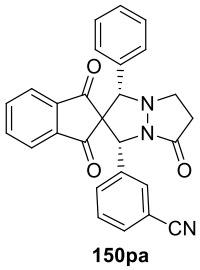
4-((1'*S,3'*R**)-1,3,5'-Trioxo-1'-phenyl-1,3,3',5',6',7'-hexahydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazol]-3'-yl)benzonitrile (150oa):** Prepared by following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as light brown solid. Mp 124-126 °C; *dr* = >99:1; IR (KBr): ν_{max} 2926, 2838, 2230, 1742, 1709, 1687, 1589, 1490, 1336, 1265, 1156, 1063, 871 and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (1H, d, *J* = 7.6 Hz), 7.76 (1H, t, *J* = 7.6 Hz), 7.63 (1H, t, *J* = 7.6 Hz), 7.49 (2H, d, *J* = 8.4 Hz),



150oa

7.41 (1H, d, *J* = 8.0 Hz), 7.24 (2H, d, *J* = 8.0 Hz), 7.17-7.14 (2H, m), 7.12-7.09 (3H, m), 5.82 (1H, s), 4.39 (1H, s), 3.88-3.80 (1H, m), 3.15-3.00 (2H, m), 2.97-2.87 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.5 (C, *C*=O), 194.3 (C, *C*=O), 173.5 (C, *C*=O), 142.8 (C), 141.12 (C), 141.06 (C), 136.6 (CH), 135.9 (CH), 132.3 (2 x CH), 131.1 (C), 129.1 (CH), 128.6 (2 x CH), 127.7 (2 x CH), 126.7 (2 x CH), 123.4 (CH), 123.3 (CH), 118.5 (C, *C*≡N), 111.8 (C), 77.7 (CH), 72.0 (C), 62.5 (CH), 47.6 (CH_2), 31.9 (CH_2); LCMS m/z 434.20 (M + H^+), calcd for $C_{27}H_{20}N_3O_3$ 434.1505; HRMS m/z 434.1500 (M + H^+), calcd for $C_{27}H_{20}N_3O_3$ 434.1505; Anal. calcd for $C_{27}H_{19}N_3O_3$ (433.1426): C, 74.81; H, 4.42; N, 9.69. Found: C, 74.89; H, 4.38; N, 9.75%.

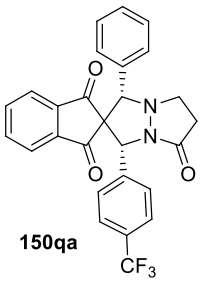
3-((1'*S,3'*R**)-1,3,5'-Trioxo-1'-phenyl-1,3,3',5',6',7'-hexahydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazol]-3'-yl)benzonitrile (150pa):** Prepared by following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as light brown solid. Mp 180-182 °C; *dr* = 10:1; IR (KBr): ν_{max} 2964, 2860, 1698, 1594, 1293, 1260, 1118, 1074, 909 and 822 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, for major isomer) δ 7.99 (1H, d, *J* = 8.0 Hz), 7.76 (1H, dt, *J* = 7.5, 1.0 Hz), 7.63 (1H, dt, *J* = 7.5, 0.5 Hz), 7.49-7.46 (2H, m), 7.40 (1H, d, *J* = 7.5 Hz), 7.35-7.30 (2H, m), 7.16-7.15 (2H, m), 7.11-7.10 (3H, m), 5.79 (1H, s), 4.39 (1H, s), 3.85 (1H, ddd, *J* = 11.0, 9.5, 7.0 Hz), 3.12 (1H, ddd, *J* = 11.5, 9.5, 7.5 Hz), 3.08-3.01 (1H, m), 2.92 (1H, ddd, *J* = 16.5, 9.5, 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, for major isomer) δ 197.6 (C, *C*=O), 194.3 (C, *C*=O), 173.7 (C, *C*=O), 142.9 (C), 141.1 (C), 137.4 (C), 136.6 (CH), 135.9 (CH), 131.6 (CH), 131.2 (C), 130.4 (CH), 129.8 (CH), 129.2 (CH), 129.1 (CH), 128.6 (2 x CH), 127.8 (2 x CH), 123.5 (CH), 123.2 (CH), 118.4 (C, *C*≡N), 112.7 (C), 77.7 (CH), 71.9 (C), 62.2 (CH), 47.4 (CH_2), 31.7 (CH_2); LCMS m/z 434.20 (M + H^+), calcd for $C_{27}H_{20}N_3O_3$ 434.1505; HRMS m/z 456.1329 (M + Na^+), calcd for $C_{27}H_{19}N_3O_3Na$ 456.1324; Anal. calcd for $C_{27}H_{19}N_3O_3$ (433.1426): C, 74.81; H, 4.42; N, 9.69. Found: C, 74.68; H, 4.48; N, 9.61%.



150pa

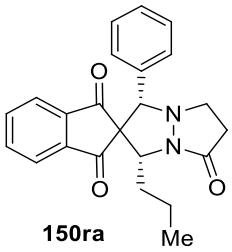
(1'*S,3'*R**)-1'-Phenyl-3'-(4-(trifluoromethyl)phenyl)-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150qa):** Prepared by following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as off-white solid. Mp 132-134 °C; *dr* = 25:1; IR (KBr): ν_{max} 2924, 1757, 1714, 1622, 1595,

1492, 1455, 1325, 1260, 1125, 1017, 768 and 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, for major isomer) δ 7.98 (1H, td, *J* = 7.5, 0.5 Hz), 7.74 (1H, dt, *J* = 7.5, 1.0 Hz), 7.62 (1H, dt, *J* = 7.5, 1.0 Hz), 7.45-7.41 (3H, m), 7.24 (2H, d, *J* = 8.5 Hz), 7.18-7.16 (2H, m), 7.12-7.09 (3H, m), 5.84 (1H, s), 4.41 (1H, s), 3.88-3.82 (1H, m), 3.13-3.04 (2H, m), 2.95-2.88 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for major isomer) δ 197.7 (C, *C*=O), 194.4 (C, *C*=O), 173.0 (C, *C*=O), 142.9 (C), 141.2 (C), 139.5 (C), 136.5 (CH), 135.8 (CH), 131.2 (C), 131.1 (C, q, *J* = 32.5 Hz), 129.0 (CH), 128.5 (2 x CH), 127.7 (2 x CH), 126.3 (2 x CH), 125.5 (2 x CH, q, *J* = 3.7 Hz), 123.9 (C, q, *J* = 270.0 Hz, *C*F_3), 123.35 (CH), 123.32 (CH), 77.6 (CH), 72.0 (C), 62.6 (CH), 47.9 (CH_2), 32.2 (CH_2); LCMS m/z 475.45 ($M + H^+$), calcd for $C_{27}H_{18}F_3N_2O_3$ 475.1270; HRMS m/z 477.1429 ($M + H^+$), calcd for $C_{27}H_{20}F_3N_2O_3$ 477.1426; Anal. calcd for $C_{27}H_{19}F_3N_2O_3$ (476.1348): C, 68.06; H, 4.02; N, 5.88. Found: C, 68.15; H, 4.08; N, 5.81%.



150qa

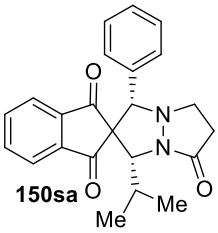
(1'*S,3'*R**)-1'-Phenyl-3'-propyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ra):** Prepared by following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Mp 136-138 °C; *dr* = >99:1; IR (KBr): ν_{max} 3065, 2957, 2924, 2881, 1741, 1708, 1595, 1498, 1460, 1336, 1255, 1179, 1071, 768, 736 and 693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.91 (1H, d, *J* = 7.6 Hz), 7.74 (1H, dt, *J* = 7.6, 1.6 Hz), 7.69-7.67 (1H, m), 7.65-7.63 (1H, m), 7.12-7.06 (5H m), 4.53 (1H, t, *J* = 7.6 Hz), 4.18 (1H, s), 3.66 (1H, ddd, *J* = 11.2, 9.2, 7.2 Hz), 2.96 (1H, ddd, *J* = 11.2, 10.0, 7.2 Hz), 2.89-2.74 (2H, m), 2.10-2.01 (1H, m), 1.51-1.43 (1H, m), 1.29-1.17 (1H, m), 1.03-0.90 (1H, m), 0.78 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.7 (C, *C*=O), 195.9 (C, *C*=O), 173.4 (C, *C*=O), 142.5 (C), 140.9 (C), 136.2 (CH), 135.7 (CH), 131.8 (C), 128.7 (CH), 128.4 (2 x CH), 127.8 (2 x CH), 123.3 (CH), 123.1 (CH), 77.4 (CH), 69.9 (C), 60.6 (CH), 46.6 (CH_2), 33.2 (CH_2), 31.8 (CH_2), 20.3 (CH_2), 13.6 (CH_3); LCMS m/z 375.15 ($M + H^+$), calcd for $C_{23}H_{23}N_2O_3$ 375.1709; HRMS m/z 375.1708 ($M + H^+$), calcd for $C_{23}H_{23}N_2O_3$ 375.1709; Anal. calcd for $C_{23}H_{22}N_2O_3$ (374.1630): C, 73.78; H, 5.92; N, 7.48. Found: C, 73.89; H, 5.86; N, 7.41%.



150ra

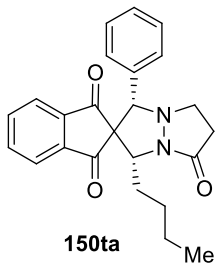
(1'*S,3'*R**)-3'-Isopropyl-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150sa):** Prepared by following the procedure **2a** and purified

by column chromatography using EtOAc/hexane and isolated as white solid. Mp 180-182 °C; *dr* = >99:1; IR (KBr): ν_{max} 2959, 2871, 1742, 1704, 1594, 1457, 1337, 1238, 1183, 1068, 942, 866 and 763 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.90 (1H, d, *J* = 7.5 Hz), 7.72 (1H, dt, *J* = 7.5, 1.0 Hz), 7.64 (1H, dt, *J* = 7.5, 1.0 Hz), 7.59 (1H, d, *J* = 7.5 Hz), 7.06 (5H, br s), 4.20 (1H, d, *J* = 11.5 Hz), 4.12 (1H, s), 3.74-3.68 (1H, m), 3.05 (1H, ddd, *J* = 13.0, 10.0, 4.0 Hz), 2.86-2.79 (1H, m,), 2.69 (1H, ddd, *J* = 18.0, 10.0, 4.0 Hz), 2.39 (1H, ddd, *J* = 18.0, 13.0, 6.5 Hz), 1.11 (3H, d, *J* = 6.5 Hz, $CH(CH_3)_2$), 0.45 (3H, d, *J* = 6.5 Hz, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 199.0 (C, *C*=O), 196.4 (C, *C*=O), 178.2 (C, *C*=O), 142.4 (C), 140.3 (C), 136.1 (CH), 135.6 (CH), 131.7 (C), 128.8 (CH), 128.4 (2 x CH), 127.9 (2 x CH), 123.3 (CH), 122.9 (CH), 78.3 (CH), 69.7 (C), 68.2 (CH), 43.5 (CH_2), 29.6 (CH_2), 29.4 (CH, $CH(CH_3)_2$), 21.4 (CH_3, $CH(CH_3)_2$), 19.5 (CH_3, $CH(CH_3)_2$); LCMS m/z 375.30 ($M + H^+$), calcd for $C_{23}H_{23}N_2O_3$ 375.1709; HRMS m/z 375.1714 ($M + H^+$), calcd for $C_{23}H_{23}N_2O_3$ 375.1709; Anal. calcd for $C_{23}H_{22}N_2O_3$ (374.1630): C, 73.78; H, 5.92; N, 7.48. Found: C, 73.65; H, 5.87; N, 7.53%.



150sa

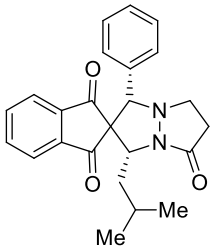
(1'*S,3'*R**)-3'-Butyl-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ta):** Prepared by following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as light brown solid. Mp 166-168 °C; *dr* = >99:1; IR (KBr): ν_{max} 2959, 2855, 1742, 1715, 1594, 1457, 1331, 1255, 1184, 1024, 937 and 767 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.93 (1H, td, *J* = 7.6, 0.8 Hz), 7.75 (1H, dt, *J* = 7.6, 1.6 Hz), 7.71-7.65 (2H, m), 7.14-7.09 (5H, m), 4.54 (1H, t, *J* = 7.6 Hz), 4.20 (1H, s), 3.69 (1H, ddd, *J* = 11.2, 9.6, 7.2 Hz,), 2.98 (1H, ddd, *J* = 11.6, 9.6, 7.2 Hz), 2.90-2.76 (2H, m), 2.14-2.04 (1H, m), 1.57-1.48 (1H, m), 1.26-1.17 (3H, m), 0.96-0.86 (1H, m), 0.74 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.8 (C, *C*=O), 196.0 (C, *C*=O), 173.4 (C, *C*=O), 142.6 (C), 140.9 (C), 136.2 (CH), 135.7 (CH), 131.9 (C), 128.7 (CH), 128.4 (2 x CH), 127.8 (2 x CH), 123.3 (CH), 123.1 (CH), 77.5 (CH), 69.9 (C), 60.8 (CH), 46.7 (CH_2), 31.8 (CH_2), 30.8 (CH_2), 29.0 (CH_2), 22.2 (CH_2), 13.7 (CH_3); LCMS m/z 389.35 ($M + H^+$), calcd for $C_{24}H_{25}N_2O_3$ 389.1865; HRMS m/z 389.1868 ($M + H^+$), calcd for $C_{24}H_{25}N_2O_3$



150ta

389.1865; Anal. calcd for $C_{24}H_{24}N_2O_3$ (388.1787): C, 74.21; H, 6.23; N, 7.21. Found: C, 74.32; H, 6.19; N, 7.28%.

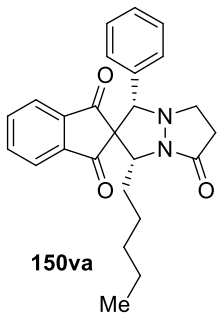
(1'*S,3'*R**)-3'-Isobutyl-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ua):** Prepared by following the procedure **2a** and purified



150ua

by column chromatography using EtOAc/hexane and isolated as light brown solid. Mp 132-134 °C; *dr* = >99:1; IR (KBr): ν_{max} 2957, 2930, 1741, 1709, 1590, 1455, 1363, 1250, 1098, 1017 and 763 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.93 (1H, d, *J* = 7.6 Hz), 7.76 (1H, dt, *J* = 7.2, 1.6 Hz), 7.71-7.65 (2H, m), 7.14-7.10 (5H, m), 4.64 (1H, dd, *J* = 8.8, 6.4 Hz), 4.20 (1H, s), 3.72-3.65 (1H, m,), 2.99 (1H, ddd, *J* = 12.0, 8.4, 7.6 Hz), 2.82 (2H, t, *J* = 8.4 Hz), 2.02 (1H, ddd, *J* = 13.6, 8.8, 6.4 Hz), 1.36 (1H, heptate, *J* = 6.4 Hz, C*H*$(CH_3)_2$), 1.28-1.21 (1H, m), 0.85 (3H, d, *J* = 2.8 Hz, CH(C*H*$_3)_2$), 0.83 (3H, d, *J* = 2.8 Hz, CH(C*H*$_3)_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.9 (C, *C*=O), 196.0 (C, *C*=O), 174.1 (C, *C*=O), 142.6 (C), 140.9 (C), 136.2 (CH), 135.7 (CH), 132.0 (C), 128.7 (CH), 128.4 (2 x CH), 127.8 (2 x CH), 123.3 (CH), 123.1 (CH), 77.4 (CH), 70.0 (C), 59.1 (CH), 46.2 (CH_2), 40.2 (CH_2), 31.5 (CH_2, *C*H_2CH$(CH_3)_2$), 25.9 (CH, *C*H$(CH_3)_2$), 22.5 (CH_3, CH(*C*$H_3)_2$), 22.2 (CH_3, CH(*C*$H_3)_2$); LCMS m/z 387.20 (M + H^+), calcd for $C_{24}H_{23}N_2O_3$ 387.1709; HRMS m/z 389.1872 (M + H^+), calcd for $C_{24}H_{25}N_2O_3$ 389.1865; Anal. calcd for $C_{24}H_{24}N_2O_3$ (388.1787): C, 74.21; H, 6.23; N, 7.21. Found: C, 74.15; H, 6.29; N, 7.18%.

(1'*S,3'*R**)-3'-Pentyl-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150va):** Prepared by following the procedure **2a** and purified

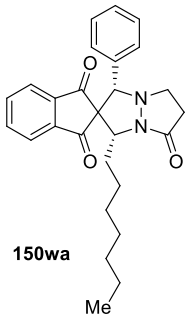


150va

by column chromatography using EtOAc/hexane and isolated as light brown solid. Mp 109-121 °C; *dr* = >99:1; IR (KBr): ν_{max} 2930, 2849, 1741, 1703, 1460, 1336, 1250, 1174, 1098, 936 and 769 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.91 (1H, d, *J* = 7.6 Hz), 7.74 (1H, dt, *J* = 7.6, 1.6 Hz), 7.70-7.64 (2H, m), 7.12-7.08 (5H, m), 4.52 (1H, t, *J* = 7.6 Hz), 4.18 (1H, s), 3.67 (1H, ddd, *J* = 11.2, 9.2, 7.2 Hz,), 2.96 (1H, ddd, *J* = 11.2, 10.0, 7.2 Hz), 2.90-2.75 (2H, m), 2.11-2.02 (1H, m), 1.56-1.47 (1H, m), 1.20-1.06 (5H, m), 0.94-0.85 (1H, m), 0.70 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.8 (C, *C*=O), 196.0 (C, *C*=O), 173.3 (C, *C*=O), 142.5 (C), 140.9 (C), 136.2 (CH), 135.7 (CH), 131.8 (C),

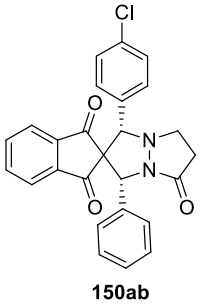
128.7 (CH), 128.4 (2 x CH), 127.8 (2 x CH), 123.3 (CH), 123.1 (CH), 77.5 (CH), 69.9 (C), 60.8 (CH), 46.7 (CH_2), 31.9 (CH_2), 31.2 (CH_2), 31.1 (CH_2), 26.5 (CH_2), 22.2 (CH_2), 13.7 (CH_3); LCMS m/z 403.25 ($M + H^+$), calcd for $C_{25}H_{27}N_2O_3$ 403.2022; HRMS m/z 425.1841 ($M + Na^+$), calcd for : $C_{25}H_{26}N_2O_3Na$ 425.1841; Anal. calcd for $C_{25}H_{26}N_2O_3$ (402.1943): C, 74.60; H, 6.51; N, 6.96. Found: C, 74.58; H, 6.57; N, 6.89%.

(1'*S,3'*R**)-3'-Heptyl-1'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150wa):** Prepared by following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as brown semi solid. *dr* = >99:1; IR (Neat): ν_{max} 2926, 2849, 1742, 1709, 1594, 1452, 1386, 1266, 1183, 1014, 888, 767 and 696 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (1H, d, *J* = 7.6 Hz), 7.74 (1H, dt, *J* = 6.8, 1.6 Hz), 7.70-7.64 (2H, m), 7.12-7.10 (5H, m), 4.53 (1H, t, *J* = 7.6 Hz), 4.19 (1H, s), 3.67 (1H, ddd, *J* = 11.2, 9.2, 7.2 Hz), 3.00-2.91 (1H, m), 2.89-2.75 (2H, m), 2.11-2.03 (1H, m), 1.57-1.48 (1H, m), 1.20-1.14 (5H, m), 1.10-1.07 (4H, m), 0.92-0.86 (1H, m), 0.78 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.8 (C, *C*=O), 195.9 (C, *C*=O), 173.2 (C, *C*=O), 142.6 (C), 140.9 (C), 136.2 (CH), 135.7 (CH), 131.8 (C), 128.7 (CH), 128.4 (2 x CH), 127.8 (2 x CH), 123.3 (CH), 123.1 (CH), 77.5 (CH), 70.0 (C), 60.8 (CH), 46.8 (CH_2), 31.9 (CH_2), 31.5 (CH_2), 31.1 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 26.8 (CH_2), 22.4 (CH_2), 14.0 (CH_3); LCMS m/z 431.10 ($M + H^+$), calcd for $C_{27}H_{31}N_2O_3$ 431.2335; HRMS m/z 431.2334 ($M + H^+$), calcd for $C_{27}H_{31}N_2O_3$ 431.2335; Anal. calcd for $C_{27}H_{30}N_2O_3$ (430.2256): C, 75.32; H, 7.02; N, 6.51. Found: C, 75.23; H, 7.08; N, 6.61%.



150wa

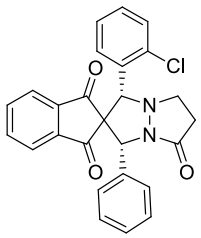
(1'*S,3'*R**)-1'-(4-Chlorophenyl)-3'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ab):** Prepared by following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Mp 150-152 °C; *dr* = 20:1; IR (KBr): ν_{max} 2920, 2843, 1747, 1704, 1588, 1490, 1347, 1254, 1090, 882, 761 and 695 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, for major isomer) δ 7.98 (1H, d, *J* = 7.6 Hz), 7.75 (1H, dt, *J* = 7.6, 0.8 Hz), 7.64 (1H, dt, *J* = 7.6, 0.8 Hz), 7.43 (1H, d, *J* = 8.0 Hz), 7.19-7.13 (5H m), 7.12-7.09 (2H, m), 7.06-7.04 (2H, m), 5.77 (1H, s), 4.40 (1H, s), 3.86-3.79 (1H, m), 3.11-3.01 (2H, m), 2.96-2.85 (1H, m); ^{13}C NMR



150ab

($CDCl_3$, DEPT-135, for major isomer) δ 193.3 (C, *C*=O), 189.7 (C, *C*=O), 167.7 (C, *C*=O), 138.3 (C), 136.4 (C), 131.8 (CH), 131.0 (CH), 130.2 (C), 130.0 (C), 125.6 (C), 124.5 (2 x CH), 124.0 (2 x CH), 123.7 (2 x CH), 123.2 (CH), 121.1 (2 x CH), 118.59 (CH), 118.57 (CH), 71.6 (CH), 67.0 (C), 58.9 (CH), 43.3 (CH_2), 27.6 (CH_2); LCMS m/z 443.35 ($M + H^+$), calcd for $C_{26}H_{20}ClN_2O_3$ 443.1162; HRMS m/z 443.1163 ($M + H^+$), calcd for $C_{26}H_{20}ClN_2O_3$ 443.1162; Anal. calcd for $C_{26}H_{19}ClN_2O_3$ (442.1084): C, 70.51; H, 4.32; N, 6.33. Found: C, 70.42; H, 4.36; N, 6.27%.

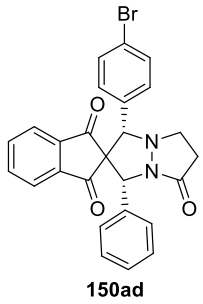
(1'*R,3'*R**)-1'-(2-Chlorophenyl)-3'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ac):** Prepared by following the procedure



150ac

2a and purified by column chromatography using EtOAc/hexane and isolated as light brown solid. Mp 142-144 °C; *dr* = 3:1; IR (KBr): ν_{max} 2964, 2909, 1753, 1709, 1671, 1265, 1243, 1073, 882, 761, and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, for major isomer) δ 8.05 (1H, d, *J* = 7.6 Hz), 7.85 (1H, d, *J* = 7.6 Hz), 7.79 (1H, t, *J* = 7.6 Hz), 7.64 (1H, t, *J* = 7.6 Hz), 7.41 (1H, d, *J* = 7.6 Hz), 7.29-7.17 (4H, m), 7.15-7.08 (4H, m), 5.88 (1H, s), 4.84 (1H, s), 3.87-3.77 (1H, m), 3.14-3.07 (1H, m), 3.05-2.89 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for major isomer) δ 198.1 (C, *C*=O), 193.9 (C, *C*=O), 173.9 (C, *C*=O), 142.3 (C), 141.3 (C), 136.1 (CH), 135.8 (C), 135.7 (CH), 133.6 (C), 131.0 (CH), 130.8 (C), 129.6 (CH), 129.2 (CH), 128.4 (2 x CH), 127.9 (CH), 127.0 (CH), 126.1 (2 x CH), 123.7 (CH), 123.0 (CH), 72.0 (CH), 71.0 (C), 63.9 (CH), 46.9 (CH_2), 31.2 (CH_2); ^1H NMR ($CDCl_3$, 400 MHz, for minor isomer) δ 7.98 (1H, d, *J* = 7.6 Hz), 7.23 (1H, t, *J* = 7.6 Hz), 7.62-7.58 (1H, m), 7.41 (1H, d, *J* = 7.6 Hz), 7.29 (1H, br s), 7.26-7.17 (4H, m), 7.15-7.03 (4H, m), 5.83 (1H, s), 4.43 (1H, s), 3.87-3.77 (1H, m), 3.14-3.07 (1H, m), 3.05-2.89 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for minor isomer) δ 198.2 (C, *C*=O), 193.5 (C, *C*=O), 172.4 (C, *C*=O), 143.1 (C), 141.26 (C), 136.3 (CH), 135.7 (C), 135.6 (CH), 134.2 (C), 131.0 (CH), 130.8 (C), 129.5 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.0 (CH), 125.7 (2 x CH), 123.3 (CH), 123.2 (CH), 72.1 (CH), 71.1 (C), 63.3 (CH), 48.2 (CH_2), 32.6 (CH_2); HRMS m/z 465.0981 ($M + Na^+$), calcd for $C_{26}H_{19}ClN_2O_3Na$ 465.0982.

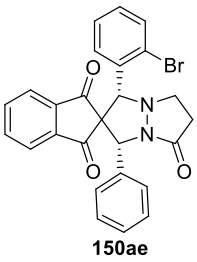
(1'*S,3'*R**)-1'-(4-Bromophenyl)-3'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ad):** Prepared by following the procedure



150ad

2a and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 162-164 °C; *dr* = >99:1; IR (KBr): ν_{max} 2962, 2854, 1742, 1709, 1643, 1589, 1463, 1353, 1227, 1079, 887 and 767 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (1H, d, *J* = 7.5 Hz), 7.75 (1H, dt, *J* = 7.5, 0.5 Hz), 7.63 (1H, dt, *J* = 7.5, 1.0 Hz), 7.42 (1H, d, *J* = 7.5 Hz), 7.25 (2H, d, *J* = 8.5 Hz), 7.15-7.10 (5H, m), 7.06-7.04 (2H, m), 5.76 (1H, s), 4.39 (1H, s), 3.85-3.76 (1H, m), 3.08-3.01 (2H, m), 2.94-2.86 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.1 (C, *C*=O), 194.3 (C, *C*=O), 172.6 (C, *C*=O), 143.1 (C), 141.2 (C), 136.5 (CH), 135.7 (CH), 135.0 (C), 131.7 (2 x CH), 131.0 (C), 129.6 (2 x CH), 128.4 (2 x CH), 128.0 (CH), 125.9 (2 x CH), 123.34 (CH), 123.31 (CH), 122.9 (C), 76.3 (CH), 71.7 (C), 63.7 (CH), 47.9 (CH_2), 32.2 (CH_2); HRMS m/z 487.0655 ($M + H^+$), calcd for $C_{26}H_{20}BrN_2O_3$ 487.0657.

(1'*R,3'*R**)-1'-(2-Bromophenyl)-3'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ae):** Prepared by following the procedure

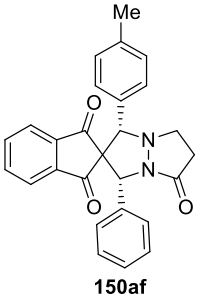


150ae

2a and purified by column chromatography using EtOAc/hexane and isolated as light brown solid. Mp 138-140 °C; *dr* = 2:1; IR (KBr): ν_{max} 3024, 2969, 2909, 1742, 1709, 1583, 1534, 1473, 1271, 1178, 1024, 871, 761 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, for major isomer) δ 8.02 (1H, d, *J* = 7.6 Hz), 7.82 (1H, d, *J* = 7.6 Hz), 7.75 (1H, t, *J* = 7.6 Hz), 7.62 (1H, t, *J* = 7.6 Hz), 7.39 (1H, d, *J* = 8.0 Hz), 7.23-7.16 (4H, m), 7.12-7.05 (4H, m), 5.85 (1H, s), 4.82 (1H, s), 3.84-3.71 (1H, m), 3.11-3.01 (2H, m), 2.94-2.84 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for major isomer) δ 198.2 (C, *C*=O), 193.8 (C, *C*=O), 174.1 (C, *C*=O), 142.4 (C), 141.3 (C), 136.1 (CH), 135.9 (C), 135.7 (CH), 132.6 (CH), 132.4 (C), 131.7 (CH), 129.9 (CH), 128.4 (2 x CH), 127.9 (CH), 127.5 (CH), 126.1 (2 x CH), 124.0 (C), 123.8 (CH), 123.0 (CH), 74.0 (CH), 71.1 (C), 63.9 (CH), 46.8 (CH_2), 31.1 (CH_2); ^1H NMR ($CDCl_3$, 400 MHz, for minor isomer) δ 7.95 (1H, d, *J* = 7.6 Hz), 7.69 (1H, d, *J* = 7.6 Hz), 7.56 (1H, t, *J* = 7.6 Hz), 7.40-7.36 (1H, m), 7.27 (1H, br s), 7.23-7.14 (4H, m), 7.12-6.92 (4H, m), 5.79 (1H, s), 4.40 (1H, s), 3.84-3.81 (1H, m), 3.01-2.96 (2H, m), 2.94-2.84 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for minor isomer) δ 198.2 (C, *C*=O), 194.6 (C, *C*=O), 172.4 (C, *C*=O), 142.1 (C),

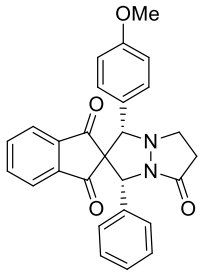
141.3 (C), 136.3 (CH), 135.9 (C), 135.5 (CH), 132.1 (CH), 132.0 (C), 131.6 (CH), 129.6 (CH), 128.5 (CH), 128.46 (CH), 127.8 (CH), 127.5 (CH), 125.7 (2 x CH), 123.3 (C), 123.2 (2 x CH), 74.02 (CH), 72.2 (C), 63.3 (CH), 48.2 (CH_2), 32.8 (CH_2); HRMS m/z 487.0656 ($M + H^+$), calcd for $C_{26}H_{20}BrN_2O_3$ 487.0657.

(1'*S,3'*R**)-3'-Phenyl-1'-(*p*-tolyl)-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150af):** Prepared by following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 144-146 °C; *dr* = 17:1; IR (KBr): ν_{max} 2947, 2931, 2854, 1742, 1709, 1682, 1583, 1484, 1353, 1260, 1178, 1095, 756, 613 and 586 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, for major isomer) δ 7.97 (1H, d, *J* = 7.5 Hz), 7.72 (1H, t, *J* = 7.5 Hz), 7.60 (1H, t, *J* = 7.5 Hz), 7.42 (1H, d, *J* = 7.5 Hz), 7.17-7.12 (3H, m), 7.10-7.07 (4H, m), 6.91 (2H, d, *J* = 7.5 Hz), 5.80 (1H, s), 4.39 (1H, s), 3.85-3.79 (1H, m), 3.11-3.03 (2H, m), 2.94-2.81 (1H, m), 2.16 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, for major isomer) δ 198.3 (C, *C*=O), 194.6 (C, *C*=O), 172.3 (C, *C*=O), 143.2 (C), 141.3 (C), 138.7 (C), 136.2 (CH), 135.4 (CH), 135.2 (C), 129.1 (2 x CH), 128.5 (C), 128.4 (2 x CH), 127.8 (CH), 127.7 (2 x CH), 125.8 (2 x CH), 123.2 (2 x CH), 77.3 (CH), 72.0 (C), 63.4 (CH), 48.1 (CH_2), 32.5 (CH_2), 21.0 (CH_3); LCMS m/z 423.45 ($M + H^+$), calcd for $C_{27}H_{23}N_2O_3$ 423.1709; HRMS m/z 445.1528 ($M + Na^+$), calcd for : $C_{27}H_{22}N_2O_3Na$ 445.1528; Anal. calcd for $C_{27}H_{22}N_2O_3$ (422.1630): C, 76.76; H, 5.25; N, 6.63. Found: C, 76.85; H, 5.21; N, 6.58%.



150af

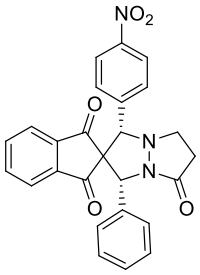
(1'*S,3'*R**)-1'-(4-Methoxyphenyl)-3'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ag):** Prepared by following the procedure **2b** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 140-142 °C; *dr* = >99:1; IR (KBr): ν_{max} 2962, 2919, 1708, 1611, 1579, 1519, 1460, 1309, 1265, 1179, 1033, 839, 774 and 703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.96 (1H, d, *J* = 7.6 Hz), 7.72 (1H, t, *J* = 7.6 Hz), 7.60 (1H, t, *J* = 7.2 Hz), 7.43 (1H, d, *J* = 7.6 Hz), 7.17-7.11 (5H, m), 7.08-7.06 (2H, m), 6.63 (2H, d, *J* = 8.8 Hz), 5.79 (1H, s), 4.36 (1H, s), 3.88-3.77 (1H, m), 3.66 (3H, s, OC*H*$_3$), 3.11-3.01 (2H, m), 2.95-2.84 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.3 (C, *C*=O), 194.8 (C, *C*=O), 172.4 (C, *C*=O), 159.8 (C),



150ag

143.2 (C), 141.3 (C), 136.3 (CH), 135.5 (CH), 135.2 (C), 129.1 (2 x CH), 128.4 (2 x CH), 127.8 (CH), 125.7 (2 x CH), 123.3 (C), 123.22 (CH), 123.21 (CH), 113.9 (2 x CH), 77.2 (CH), 72.0 (C), 63.2 (CH), 55.1 (CH_3, OCH_3), 48.1 (CH_2), 32.5 (CH_2); HRMS m/z 439.1653 ($M + H^+$), calcd for $C_{27}H_{23}N_2O_4$ 439.1658.

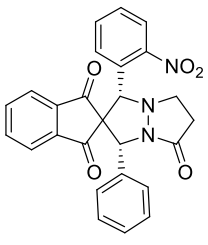
(1'*S,3'*R**)-1'-(4-Nitrophenyl)-3'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ah):** Prepared by following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid.



150ah

Mp 158-160 °C; *dr* = 4:1; IR (KBr): ν_{max} 2953, 2920, 1747, 1709, 1528, 1462, 1358, 1265, 767 and 706 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, for major isomer) δ 8.07-7.96 (3H, m), 7.79 (1H, t, *J* = 7.6 Hz), 7.66 (1H, t, *J* = 7.6 Hz), 7.46 (2H, d, *J* = 8.4 Hz), 7.41 (1H, d, *J* = 7.6 Hz), 7.19-7.15 (3H, m), 7.06-7.04 (2H, m), 5.76 (1H, s), 4.55 (1H, s), 3.93-3.81 (1H, m), 3.12-3.03 (2H, m), 2.98-2.89 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for major isomer) δ 197.8 (C, *C*=O), 194.0 (C, *C*=O), 172.7 (C, *C*=O), 148.0 (C), 143.0 (C), 141.0 (C), 139.6 (C), 136.8 (CH), 136.1 (CH), 134.7 (C), 128.9 (2 x CH), 128.5 (2 x CH), 128.2 (CH), 126.0 (2 x CH), 123.7 (2 x CH), 123.6 (CH), 123.4 (CH), 75.4 (CH), 71.7 (C), 64.1 (CH), 48.0 (CH_2), 32.0 (CH_2); ^1H NMR ($CDCl_3$, 400 MHz, for minor isomer) δ 8.07-7.96 (3H, m), 7.72 (1H, t, *J* = 7.6 Hz), 7.59 (1H, t, *J* = 7.6 Hz), 7.47-7.40 (3H, m), 7.19-7.15 (3H, m), 7.10-7.09 (2H, m), 5.82 (1H, s), 4.42 (1H, s), 3.93-3.81 (1H, m), 3.12-3.03 (2H, m), 2.98-2.89 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, for minor isomer) δ 196.3 (C, *C*=O), 191.5 (C, *C*=O), 172.4 (C, *C*=O), 148.1 (C), 143.1 (C), 141.3 (C), 140.3 (C), 137.3 (CH), 136.3 (CH), 135.2 (C), 128.8 (CH), 128.78 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.1 (CH), 125.8 (CH), 123.8 (CH), 123.77 (CH), 123.2 (CH), 123.19 (CH), 75.8 (CH), 71.5 (C), 63.0 (CH), 48.2 (CH_2), 32.5 (CH_2); HRMS m/z 454.1401 ($M + H^+$), calcd for $C_{26}H_{20}N_3O_5$ 454.1403.

(1'*S,3'*R**)-1'-(2-Nitrophenyl)-3'-phenyl-6',7'-dihydro-1'*H*-spiro[indene-2,2'-pyrazolo[1,2-a]pyrazole]-1,3,5'(3'*H*)-trione (150ai):** Prepared by following the procedure **2a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Mp 148-150 °C; *dr* = >99:1; IR (KBr): ν_{max} 2958, 2909, 2882, 1715, 1594, 1523, 1462, 1347, 1260, 1183, 767 and 723 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.40 (1H, d,



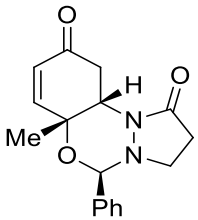
150ai

J = 8.0 Hz), 8.12 (1H, d, *J* = 7.6 Hz), 7.84 (1H, t, *J* = 7.6 Hz), 7.76 (1H, d, *J* = 8.0 Hz), 7.73-7.65 (2H, m), 7.51 (1H, d, *J* = 7.6 Hz), 7.39 (1H, t, *J* = 7.6 Hz), 7.26-7.20 (3H, m), 7.14 (2H, d, *J* = 7.6 Hz), 5.64 (1H, s), 4.85 (1H, s), 3.86-3.79 (1H, m), 3.22-3.07 (2H, m), 2.80-2.73 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.9 (C, *C*=O), 193.4 (C, *C*=O), 175.7 (C, *C*=O), 148.3 (C), 142.1 (C), 140.5 (C), 136.0 (C), 135.96 (CH), 135.88 (CH), 133.5 (CH), 132.0 (CH), 131.4 (C), 129.1 (CH), 128.4 (2 x CH), 128.1 (CH), 126.8 (2 x CH), 124.6 (CH), 124.4 (CH), 123.2 (CH), 70.9 (C), 69.2 (CH), 65.0 (CH), 46.7 (CH_2), 30.1 (CH_2); HRMS m/z 454.1406 (M + H^+), calcd for $C_{26}H_{20}N_3O_5$ 454.1403.

Materials: All solvents and commercially available chemicals were used as received. *p*-Quinols **155a-i**[70] and azomethine imines **42a-q/68a-k**[71] were prepared according to the literature procedure.

Procedure 3a: General Procedure for Base-Catalyzed [3+3]-Cycloaddition Reaction: In an oven dried glass vial equipped with a magnetic stirring bar was taken a mixture of *p*-quinol **155 (**0.4 mmol, 1.0 equiv.) and azomethine imine **42/68** (0.48 mmol, 1.2 equiv.) in dry dichloromethane (1.0 mL) under inert atmosphere. Allow the reaction mixture to stir for 1-2 minutes and then KO^{t}Bu (20 mol %, relative to 0.4 mmol of **155**) **71n** were added sequentially to the reaction mixture and stirred at 40 °C for time indicated in the Tables. The reaction mixture was concentrated and pure products **156/157/158** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

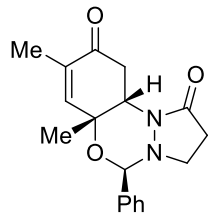
(5*R,6a*R**,10a*S**)-6a-methyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5*H*,6a*H*)-dione (156aa):** Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Yield: 76% (90.69 mg); Mp.: 162-164 °C; *dr* = 50:1; IR (Neat): ν_{max} 2920, 2851, 1696, 1529, 1350, 1258, 1114, 1069, 791 and 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51-7.49 (2H, m), 7.43-7.40 (3H, m), 6.69 (1H, dd, *J* = 10.5, 2.5 Hz), 6.21 (1H, br d, *J* = 10.5 Hz), 4.85 (1H, s), 4.25-4.19 (2H, m), 2.88 (1H, ddd, *J* = 14.5, 8.5, 4.5 Hz), 2.72 (1H, dd, *J* = 17.5, 4.0 Hz), 2.59 (1H, dt, *J* = 10.5, 8.5 Hz), 2.50-2.38 (2H, m), 1.56 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.1 (C, *C*=O), 173.8 (C, *C*=O), 151.0 (CH), 135.4 (C), 131.6 (CH),



156aa

130.1 (CH), 128.8 (2 x CH), 128.0 (2 x CH), 93.5 (CH), 73.3 (C), 62.5 (CH), 44.9 (CH_2), 36.4 (CH_2), 31.3 (CH_2), 23.9 (CH_3); HRMS m/z 299.1399 ($M + H^+$), calcd for $C_{17}H_{18}N_2O_3H$ 299.1396.

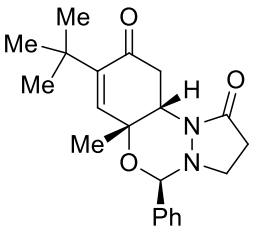
(5*R,6a*R**,10a*S**)-6a,8-dimethyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5*H*,6a*H*)-dione (156ba):** Prepared by following the procedure **3a**



156ba

and purified by column chromatography using EtOAc/hexane and isolated as white solid. Yield: 74% (92.4 mg); Mp 124-126 °C; *dr* = 99:1; IR (Neat): ν_{max} 2925, 1693, 1495, 1408, 1249, 1116, 1067, 1025, 756 and 678 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.52-7.49 (2H, m), 7.44-7.40 (3H, m), 6.4 (1H, sextet, *J* = 1.2 Hz), 4.86 (1H, s), 4.22 (1H, dd, *J* = 17.6, 2.8 Hz), 4.17-4.14 (1H, m), 2.87 (1H, ddd, *J* = 14.4, 8.8, 4.4 Hz), 2.69 (1H, dd, *J* = 17.6, 4.4 Hz), 2.58 (1H, dt, *J* = 10.8, 8.4 Hz), 2.49-2.37 (2H, m), 1.88 (3H, d, *J* = 1.6 Hz), 1.52 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.4 (C, *C*=O), 173.8 (C, *C*=O), 145.6 (CH), 138.2 (C), 135.6 (C), 130.1 (CH), 128.7 (2 x CH), 128.1 (2 x CH), 93.1 (CH), 73.5 (C), 62.7 (CH), 44.9 (CH_2), 36.4 (CH_2), 31.3 (CH_2), 24.1 (CH_3), 15.8 (CH_3); HRMS m/z 313.1556 ($M + H^+$), calcd for $C_{18}H_{20}N_2O_3H$ 313.1552.

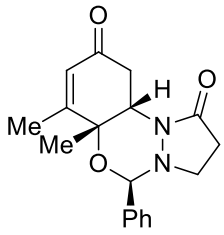
(5*R,6a*R**,10a*S**)-8-(*tert*-butyl)-6a-methyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5*H*,6a*H*)-dione (156ca):**



156ca

Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Yield: 68% (95.88 mg); Mp 138-140 °C; *dr* = 25:1; IR (Neat): ν_{max} 2957, 2868, 1694, 1456, 1318, 1119, 1069, and 703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.51-7.49 (2H, m), 7.44-7.41 (3H, m), 6.39 (1H, d, *J* = 2.0 Hz), 4.82 (1H, s), 4.15-4.09 (2H, m), 2.88 (1H, ddd, *J* = 14.5, 9.5, 4.5 Hz), 2.66 (1H, dd, *J* = 17.0, 3.5 Hz), 2.56 (1H, dt, *J* = 10.0, 8.5 Hz), 2.48-2.35 (2H, m), 1.51 (3H, s), 1.23 (9H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.4 (C, *C*=O), 173.4 (C, *C*=O), 149.1 (C), 143.2 (CH), 135.5 (C), 130.0 (CH), 128.7 (2 x CH), 128.0 (2 x CH), 93.0 (CH), 73.5 (C), 61.8 (CH), 44.8 (CH_2), 37.8 (CH_2), 34.6 (C), 31.1 (CH_2), 29.2 (3 x CH_3), 24.2 (CH_3); HRMS m/z 355.2022 ($M + H^+$), calcd for $C_{21}H_{26}N_2O_3H$ 355.2022.

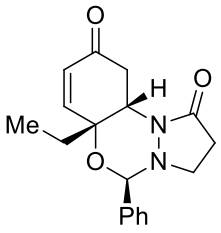
(5*R,6a*R**,10a*S**)-6a,7-dimethyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (156da):** Prepared by following the procedure **3a**



156da

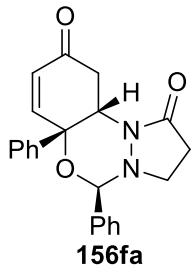
and purified by column chromatography using EtOAc/hexane and isolated as light white solid. Yield: 72% (89.95 mg); Mp 170-172 °C; *dr* = 20:1; IR (Neat): ν_{max} 2924, 2852, 1689, 1410, 1251, 1066, 754 and 701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.51-7.49 (2H, m), 7.43-7.40 (3H, m), 6.10 (1H, s), 4.54 (1H, s), 4.21-4.15 (2H, m), 2.90-2.86 (1H, m), 2.69 (1H, dd, *J* = 17.5, 4.0 Hz), 2.55 (1H, br q, *J* = 10.5 Hz), 2.44-2.40 (2H, m), 1.96 (3H, s), 1.52 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.6 (C, *C*=O), 173.3 (C, *C*=O), 158.9 (C), 135.3 (C), 130.2 (CH), 130.1 (CH), 128.7 (2 x CH), 128.0 (2 x CH), 93.7 (CH), 75.1 (C), 62.8 (CH), 44.8 (CH_2), 36.3 (CH_2), 31.2 (CH_2), 23.2 (CH_3), 17.9 (CH_3); HRMS m/z 335.1374 ($M + Na^+$), calcd for $C_{18}H_{20}N_2O_3Na$ 335.1372.

(5*R,6a*R**,10a*S**)-6a-ethyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (156ea):** Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Yield: 53% (65.78 mg); Mp.: 172-174 °C; *dr* = 99:1; IR (Neat): ν_{max} 2979, 2934, 1696, 1407, 1319, 1256, 1227, 1114, 1063, 1026, 927, 750 and 707 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.51-7.48 (2H, m), 7.44-7.40 (3H, m), 6.71 (1H, dd, *J* = 10.4, 2.4 Hz), 6.22 (1H, dd, *J* = 10.4, 1.2 Hz), 4.87 (1H, s), 4.31-4.29 (1H, m), 4.20-4.15 (1H, m), 2.90-2.84 (1H, m), 2.72-2.58 (2H, m), 2.51-2.35 (2H, m), 1.97-1.79 (2H, m), 1.10 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.1 (C, *C*=O), 173.9 (C, *C*=O), 151.1 (CH), 135.7 (C), 131.8 (CH), 130.0 (CH), 128.7 (2 x CH), 128.0 (2 x CH), 93.2 (CH), 74.9 (C), 62.1 (CH), 44.8 (CH_2), 36.0 (CH_2), 31.3 (CH_2), 30.2 (CH_2), 7.6 (CH_3); HRMS m/z 313.1554 ($M + H^+$), calcd for $C_{18}H_{20}N_2O_3H$ 313.1552.



156ea

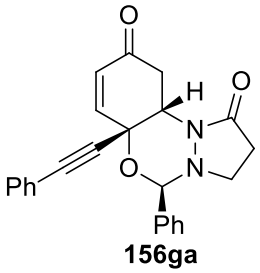
(5*R,6a*S**,10a*S**)-5,6a-diphenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (156fa):** Prepared by following the procedure **3a**



156fa

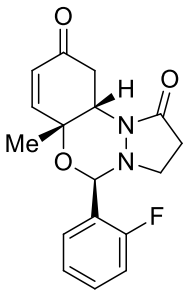
and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Yield: 46% (66.31 mg); Mp.: 162-164 °C; *dr* = 99:1; IR (Neat): ν_{max} 3029, 2925, 1698, 1621, 1315, 1448, 1315, 1183, 1058, 749, and 699 cm^{-1}; ^{1}H NMR (**(**$CDCl_3$, 400 MHz) δ 7.63-7.58 (4H, m), 7.44-7.26 (6H, m), 6.81 (1H, dd, *J* = 10.4, 2.4 Hz), 6.59 (1H, dd, *J* = 10.4, 1.2 Hz), 5.09 (1H, s), 4.37 (1H, q, *J* = 2.8 Hz), 3.96-3.91 (1H, m), 3.00-2.94 (1H, m), 2.70 (1H, dt, *J* = 10.4, 8.8 Hz), 2.53-2.40 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.6 (C, *C*=O), 173.4 (C, *C*=O), 147.4 (CH), 137.1 (C), 135.4 (C), 134.0 (CH), 130.2 (CH), 129.2 (CH), 128.8 (2 x CH), 128.7 (2 x CH), 128.1 (2 x CH), 127.1 (2 x CH), 93.5 (CH), 77.9 (C), 63.7 (CH), 44.9 (CH_2), 35.7 (CH_2), 31.1 (CH_2); HRMS m/z 361.1552 (M + H^+), calcd for $C_{22}H_{20}N_2O_3H$ 361.1552.

(5*R,6a*S**,10a*S**)-5-phenyl-6a-(phenylethynyl)-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5*H*,6a*H*)-dione (156ga):** Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Yield: 37% (56.89 mg); Mp.: 158-160 °C; *dr* = 99:1; IR (Neat): ν_{max} 2923, 2843, 2220, 1668, 1626, 1442, 1390, 1321, 1258, 1113, 1055, 926, 860, 757, and 693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56-7.54 (2H, m), 7.45-7.41 (5H, m), 7.36-7.29 (3H, m), 6.80 (1H, dd, *J* = 10.4, 2.8 Hz), 6.30 (1H, dd, *J* = 10.4, 0.8 Hz), 4.92 (1H, s), 4.56 (1H, q, *J* = 3.2 Hz), 4.19-4.14 (1H, m), 3.16 (1H, dd, *J* = 17.2, 4.0 Hz), 2.94 (1H, ddd, *J* = 13.2, 8.0, 5.2 Hz), 2.61 (1H, dt, *J* = 10.0, 8.4 Hz), 2.50-2.42 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.8 (C, *C*=O), 173.7 (C, *C*=O), 146.1 (CH), 134.7 (C), 132.0 (2 x CH), 131.9 (CH), 130.4 (CH), 129.4 (CH), 128.8 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 121.0 (C), 93.0 (CH), 88.1 (C), 83.3 (C), 70.5 (C), 62.0 (CH), 45.1 (CH_2), 37.2 (CH_2), 31.1 (CH_2); HRMS m/z 385.1552 (M + H^+), calcd for $C_{24}H_{20}N_2O_3H$ 385.1552.



156ga

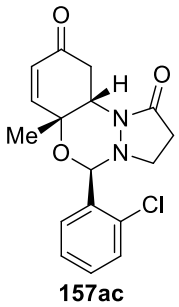
(5*R,6a*R**,10a*S**)-5-(2-fluorophenyl)-6a-methyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (157ab):**



157ab

Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light white solid. Yield: 73% (92.36 mg); Mp.: 146-148 °C; *dr* = 99:1; IR (Neat): ν_{max} 2922, 2852, 1698, 1493, 1324, 1116, 1068, and 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (1H, dt, *J* = 8.0, 1.5 Hz), 7.43-7.38 (1H, m), 7.24 (1H, dt, *J* = 7.5, 0.5 Hz), 7.10 (1H, dt, *J* = 8.5, 0.5 Hz), 6.70 (1H, dd, *J* = 10.5, 2.5 Hz), 6.21 (1H, dd, *J* = 10.5, 1.5 Hz), 5.34 (1H, s), 4.20-4.15 (2H, m), 2.98 (1H, ddd, *J* = 14.5, 9.5, 4.5 Hz), 2.73-2.66 (2H, m), 2.53-2.47 (1H, m), 2.45-2.38 (1H, m), 1.55 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.7 (C, *C*=O), 173.6 (C, *C*=O), 160.5 (C, d, *J* = 247.5 Hz, *C*-F), 150.6 (CH), 131.7 (CH), 131.4 (CH, d, *J* = 8.7 Hz), 129.3 (CH, d, *J* = 2.5 Hz), 124.8 (CH, d, *J* = 2.5 Hz), 122.8 (C, d, *J* = 11.2 Hz), 115.4 (CH, d, *J* = 21.2 Hz), 85.3 (CH), 73.5 (C), 62.4 (CH), 44.3 (CH_2), 36.3 (CH_2), 31.2 (CH_2), 23.8 (CH_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –119.4; HRMS m/z 317.1302 ($M + H^+$), calcd for $C_{17}H_{17}FN_2O_3H$ 317.1301.

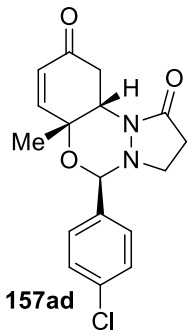
(5*R,6a*R**,10a*S**)-5-(2-chlorophenyl)-6a-methyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (157ac):**



157ac

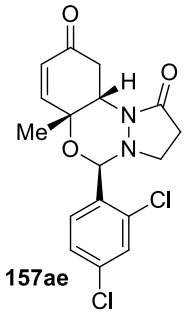
Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light white solid. Yield: 85% (113.14 mg); Mp.: 180-182 °C; *dr* = 99:1; IR (Neat): ν_{max} 2986, 2923, 1694, 1407, 1321, 1111, 1075, 1027, and 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76-7.74 (1H, m), 7.43-7.40 (1H, m), 7.39-7.35 (2H, m), 6.75 (1H, dd, *J* = 10.4, 2.4 Hz), 6.22 (1H, dd, *J* = 10.4, 1.2 Hz), 5.52 (1H, s), 4.18-4.10 (2H, m), 3.00 (1H, ddd, *J* = 15.6, 9.2, 5.2 Hz), 2.75-2.67 (2H, m), 2.58-2.50 (1H, m), 2.47-2.38 (1H, m), 1.53 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.6 (C, *C*=O), 173.4 (C, *C*=O), 150.6 (CH), 133.7 (C), 133.0 (C), 131.7 (CH), 130.9 (CH), 129.8 (CH), 129.4 (CH), 127.5 (CH), 88.2 (CH), 73.4 (C), 62.3 (CH), 44.2 (CH_2), 36.2 (CH_2), 31.3 (CH_2), 23.8 (CH_3); HRMS m/z 333.1005 ($M + H^+$), calcd for $C_{17}H_{17}ClN_2O_3H$ 333.1006.

(5*R,6a*R**,10a*S**)-5-(4-chlorophenyl)-6a-methyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (157ad):**



Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Yield: 85% (112.9 mg); Mp.: 148-150 °C; *dr* = 99:1; IR (Neat): ν_{max} 2982, 2846, 1689, 1589, 1412, 1389, 1261, 1112, 1075, 1030, 826, 792 and 766 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45 (2H, td, *J* = 8.4, 2.0 Hz), 7.41 (2H, td, *J* = 8.4, 2.0 Hz), 6.67 (1H, dd, *J* = 10.4, 2.4 Hz), 6.21 (1H, dd, *J* = 10.4, 1.2 Hz), 4.84 (1H, s), 4.25-4.20 (1H, m), 4.18 (1H, m), 2.91-2.85 (1H, m), 2.71 (1H, dd, *J* = 17.6, 4.0 Hz), 2.61-2.53 (1H, m), 2.51-2.37 (2H, m), 1.55 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.0 (C, *C*=O), 173.7 (C, *C*=O), 150.7 (C), 136.1 (C), 133.9 (C), 131.7 (CH), 129.4 (2 x CH), 129.0 (2 x CH), 92.7 (CH), 73.4 (C), 62.5 (CH), 44.8 (CH_2), 36.4 (CH_2), 31.2 (CH_2), 23.8 (CH_3); HRMS m/z 333.1006 ($M + H^+$), calcd for $C_{17}H_{17}ClN_2O_3H$ 333.1006.

(5*R,6a*R**,10a*S**)-5-(2,4-dichlorophenyl)-6a-methyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5*H*,6a*H*)-dione (157ae):**

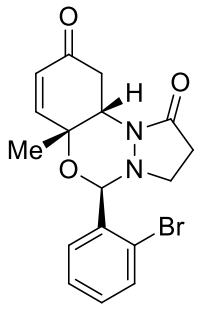


Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Yield: 63% (92.53 mg); Mp.: 142-144 °C; *dr* = 99:1; IR (Neat): ν_{max} 3013, 2918, 1693, 1590, 1476, 1384, 1255, 1112, 1077, 747 and 666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70 (1H, d, *J* = 8.4 Hz), 7.44 (1H, d, *J* = 2.0 Hz), 7.36 (1H, dd, *J* = 8.4, 2.0 Hz), 6.73 (1H, dd, *J* = 10.4, 2.4 Hz), 6.22 (1H, d, *J* = 10.4 Hz), 5.46 (1H, s), 4.17-4.11 (2H, m), 3.0 (1H, dt, *J* = 9.6, 5.2 Hz), 2.74-2.65 (2H, m), 2.58-2.50 (1H, m), 2.48-2.39 (1H, m), 1.53 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.5 (C, *C*=O), 173.3 (C, *C*=O), 150.3 (CH), 136.1 (C), 134.4 (C), 131.8 (CH), 131.6 (C), 130.8 (CH), 129.2 (CH), 127.9 (CH), 87.7 (CH), 73.5 (C), 62.3 (CH), 44.2 (CH_2), 36.2 (CH_2), 31.2 (CH_2), 23.8 (CH_3); HRMS m/z 367.0618 ($M + H^+$), calcd for $C_{17}H_{16}Cl_2N_2O_3H$ 367.0616.

(5*R,6a*R**,10a*S**)-5-(2-bromophenyl)-6a-methyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5*H*,6a*H*)-dione (157af):**

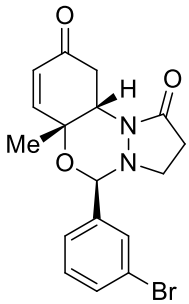
Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Yield: 87% (131.27 mg); Mp.: 189-191 °C;

dr = 99:1; IR (Neat): ν_{max} 2985, 2924, 1699, 1407, 1322, 1257, 1117, 1073, 1025 and 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (1H, br d, *J* = 7.0 Hz), 7.60 (1H, dd, *J* = 8.0, 1.0 Hz), 7.41 (1H, br t, *J* = 7.0 Hz), 7.28 (1H, dt, *J* = 7.5, 1.5 Hz), 6.78 (1H, dd, *J* = 10.5, 2.5 Hz), 6.23 (1H, dd, *J* = 10.5, 1.0 Hz), 5.50 (1H, s), 4.18-4.17 (1H, m), 4.15-4.10 (1H, m), 3.00 (1H, ddd, *J* = 14.5, 9.5, 5.5 Hz), 2.74-2.68 (2H, m), 2.59-2.52 (1H, m), 2.46-2.39 (1H, m), 1.53 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.5 (C, *C*=O), 173.3 (C, *C*=O), 150.6 (CH), 134.6 (C), 132.8 (CH), 131.8 (CH), 131.2 (CH), 130.2 (CH), 128.1 (CH), 124.0 (C), 90.9 (CH), 73.5 (C), 62.4 (CH), 44.3 (CH_2), 36.3 (CH_2), 31.4 (CH_2), 23.9 (CH_3); HRMS m/z 377.0507 ($M + H^+$), calcd for $C_{17}H_{17}BrN_2O_3H$ 377.0501.



157af

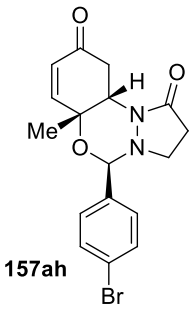
(5*R,6a*R**,10a*S**)-5-(3-bromophenyl)-6a-methyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (157ag):**



157ag

Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Yield: 60% (90.53 mg); Mp.: 156-158 °C; *dr* = 99:1; IR (Neat): ν_{max} 2923, 2852, 1698, 1408, 1321, 1259, 1114, 1070, 752 and 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (1H, t, *J* = 1.6 Hz), 7.57 (1H, br d, *J* = 8.0 Hz), 7.42 (1H, br d, *J* = 7.6 Hz), 7.30 (1H, t, *J* = 7.6 Hz), 6.66 (1H, dd, *J* = 10.0, 2.0 Hz), 6.20 (1H, br d, *J* = 10.0 Hz), 4.82 (1H, s), 4.24-4.17 (2H, m), 2.90 (1H, ddd, *J* = 14.4, 8.4, 4.4 Hz), 2.71 (1H, dd, *J* = 17.2, 3.6 Hz), 2.58 (1H, dt, *J* = 10.4, 8.4 Hz), 2.51-2.39 (2H, m), 1.55 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.8 (C, *C*=O), 173.6 (C, *C*=O), 150.6 (CH), 137.6 (C), 133.2 (CH), 131.7 (CH), 131.2 (CH), 130.2 (CH), 126.8 (CH), 122.8 (C), 92.6 (CH), 73.4 (C), 62.5 (CH), 44.9 (CH_2), 36.4 (CH_2), 31.2 (CH_2), 23.8 (CH_3); HRMS m/z 377.0502 ($M + H^+$), calcd for $C_{17}H_{17}BrN_2O_3H$ 377.0501.

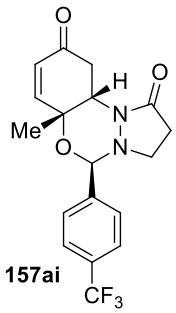
(5*R,6a*R**,10a*S**)-5-(4-bromophenyl)-6a-methyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5*H*,6a*H*)-dione (157ah):**



157ah

Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Yield: 70% (105.62 mg); Mp.: 162-164 °C; *dr* = 99:1; IR (Neat): ν_{max} 2981, 2894, 1689, 1391, 1262, 1111, 1063, 1012, 824 and 765 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.56 (2H, br d, *J* = 8.0 Hz), 7.38 (2H, br d, *J* = 8.5 Hz), 6.66 (1H, dd, *J* = 10.5, 2.5 Hz), 6.20 (1H, br d, *J* = 10.5 Hz), 4.81 (1H, s), 4.24-4.20 (1H, m), 4.17-4.16 (1H, m), 2.90-2.85 (1H, m), 2.71 (1H, dd, *J* = 17.5, 4.0 Hz), 2.59-2.53 (1H, m), 2.47-2.38 (2H,m), 1.54 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.9 (C, *C*=O), 173.7 (C, *C*=O), 150.7 (CH), 134.5 (C), 132.0 (2 x CH), 131.7 (CH), 129.8 (2 x CH), 124.3 (C), 92.8 (CH), 73.4 (C), 62.5 (CH), 44.9 (CH_2), 36.4 (CH_2), 31.2 (CH_2), 23.9 (CH_3); HRMS m/z 377.0504 ($M + H^+$), calcd for $C_{17}H_{17}BrN_2O_3H$ 377.0501.

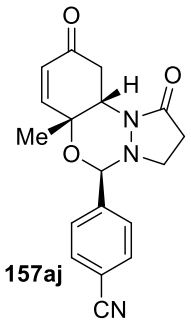
(5*R,6a*R**,10a*S**)-6a-methyl-5-(4-(trifluoromethyl)phenyl)-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (157ai):**



157ai

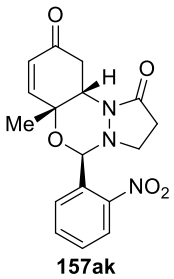
Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Yield: 80% (117.22 mg); Mp.: 188-190 °C; *dr* = 99:1; IR (Neat): ν_{max} 2923, 1694, 1409, 1321, 1257, 1164, 1119, 1064, 1018, 750 and 665 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.69 (2H, d, *J* = 8.5 Hz), 7.65 (2H, d, *J* = 8.5 Hz), 6.68 (1H, dd, *J* = 10.5, 2.5 Hz), 6.21 (1H, dd, *J* = 10.5, 1.0 Hz), 4.93 (1H, s), 4.24-4.19 (2H, m), 2.88 (1H, ddd, *J* = 14.5, 9.0, 4.5 Hz), 2.73-2.70 (1H, m), 2.59 (1H, dt, *J* = 10.5, 8.5 Hz), 2.51-2.38 (2H, m), 1.56 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.8 (C, *C*=O), 173.6 (C, *C*=O), 150.5 (CH), 139.2 (C), 132.2 (C, q, *J* = 32.5 Hz), 131.7 (CH), 128.6 (2 x CH), 125.7 (2 x CH, q, *J* = 3.7 Hz), 123.7 (C, q, *J* = 270.0 Hz, *C*F_3), 92.6 (CH), 73.4 (C), 62.5 (CH), 44.8 (CH_2), 36.3 (CH_2), 31.1 (CH_2), 23.8 (CH_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –62.8; HRMS m/z 367.1270 ($M + H^+$), calcd for $C_{18}H_{17}F_3N_2O_3H$ 367.1270.

4-((5*R,6a*R**,10a*S**)-6a-methyl-1,9-dioxo-1,2,3,5,6a,9,10,10a-octahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazin-5-yl)benzonitrile (157aj):** Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Yield: 65% (84.06 mg); Mp.: 156-158 °C; *dr* = 99:1; IR (Neat): ν_{max} 2923, 2851, 2230, 1694, 1409, 1255, 1117, 1076, 1022, 835, and 756 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.73 (2H, d, *J* = 8.0 Hz), 7.64 (2H, d, *J* = 8.0 Hz), 6.66 (1H, dd, *J* = 10.5, 2.5 Hz), 6.21 (1H, d, *J* = 10.5 Hz), 4.91 (1H, s), 4.23-4.18 (2H, m), 2.86 (1H, dt, *J* = 9.5, 4.5 Hz), 2.74-2.70 (1H, m), 2.57 (1H, dt, *J* = 10.5, 8.5 Hz), 2.49-2.39 (2H, m), 1.56 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.7 (C, *C*=O), 173.5 (C, *C*=O), 150.2 (CH), 140.3 (C), 132.5 (2 x CH), 131.8 (CH), 129.0 (2 x CH), 118.1 (C), 114.1 (C), 92.5 (CH), 73.5 (C), 62.6 (CH), 44.8 (CH_2), 36.3 (CH_2), 31.1 (CH_2), 23.8 (CH_3); HRMS m/z 324.1348 ($M + H^+$), calcd for $C_{18}H_{17}N_3O_3H$ 324.1348.



157aj

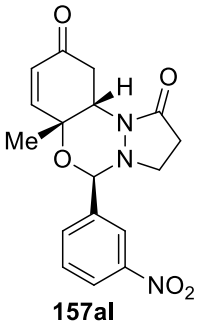
(5*R,6a*R**,10a*S**)-6a-methyl-5-(2-nitrophenyl)-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (157ak):** Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Yield: 62% (85.14 mg); Mp.: 190-192 °C; *dr* = 99:1; IR (Neat): ν_{max} 2918, 2850, 1694, 1529, 1350, 1258, 1114, 1069, 791 and 755 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.03 (1H, dd, *J* = 8.0, 1.0 Hz), 7.92 (1H, dd, *J* = 8.0, 1.0 Hz), 7.74 (1H, t, *J* = 8.0 Hz), 7.60 (1H, dt, *J* = 8.5, 1.5 Hz), 6.77 (1H, dd, *J* = 10.0, 2.5 Hz), 6.21 (1H, d, *J* = 10.5 Hz), 5.57 (1H, s), 4.193-4.187 (1H, m), 4.10 (1H, br d, *J* = 18.0 Hz), 3.01 (1H, dt, *J* = 10.0, 5.5 Hz), 2.74-2.66 (2H, m), 2.62-2.55 (1H, m), 2.46-2.39 (1H, m), 1.52 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.3 (C, *C*=O), 173.2 (C, *C*=O), 150.0 (CH), 149.3 (C), 133.5 (CH), 131.9 (CH), 130.6 (CH), 130.5 (CH), 129.8 (C), 124.1 (CH), 86.6 (CH), 73.8 (C), 62.4 (CH), 44.5 (CH_2), 36.2 (CH_2), 31.1 (CH_2), 23.9 (CH_3); HRMS m/z 344.1246 ($M + H^+$), calcd for $C_{17}H_{17}N_3O_5H$ 344.1246.



157ak

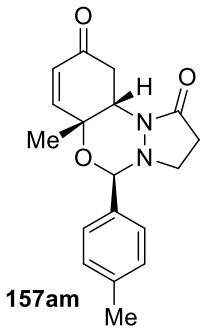
(5*R,6a*R**,10a*S**)-6a-methyl-5-(3-nitrophenyl)-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (157al):** Prepared by following the procedure **3a** and purified by column chromatography using

EtOAc/hexane and isolated as white solid. Yield: 53% (72.78 mg); Mp.: 198-200 °C; *dr* = 99:1; IR (Neat): ν_{max} 2989, 2923, 1694, 1409, 1321, 1164, 1119, 1064, 1018, 836, 750 and 665 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.40 (1H, t, *J* = 1.5 Hz), 8.32-8.30 (1H, m), 7.87 (1H, br d, *J* = 8.0 Hz), 7.64 (1H, t, *J* = 8.0 Hz), 6.69 (1H, dd, *J* = 10.5, 2.5 Hz), 6.22 (1H, dd, *J* = 10.5, 1.0 Hz), 4.99 (1H, s), 4.25-4.21 (2H, m), 2.92-2.87 (1H, m), 2.73 (1H, dd, *J* = 18.0, 4.5 Hz), 2.61 (1H, dt, *J* = 10.5, 8.5 Hz), 2.53-2.41 (2H, m), 1.57 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.7 (C, *C*=O), 173.5 (C, *C*=O), 150.2 (CH), 148.4 (C), 137.6 (C), 134.2 (CH), 131.8 (CH), 129.8 (CH), 125.0 (CH), 123.4 (CH), 92.2 (CH), 73.6 (C), 62.5 (CH), 44.9 (CH_2), 36.3 (CH_2), 31.1 (CH_2), 23.8 (CH_3); HRMS m/z 344.1245 ($M + H^+$), calcd for $C_{17}H_{17}N_3O_5H$ 344.1246.



157al

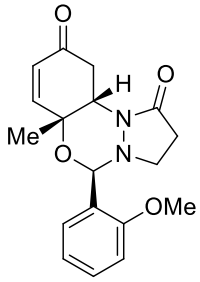
(5*R,6a*R**,10a*S**)-6a-methyl-5-(p-tolyl)-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (157am):** Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Yield: 75% (93.7 mg); Mp.: 148-150 °C; *dr* = 17:1; IR (Neat): ν_{max} 2920, 2851, 1694, 1408, 1321, 1257, 1226, 1027 and 751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38 (2H, d, *J* = 8.0 Hz), 7.22 (2H, d, *J* = 8.0 Hz), 6.68 (1H, dd, *J* = 10.4, 2.4 Hz), 6.20 (1H, dd, *J* = 10.4, 1.2 Hz), 4.81 (1H, s), 4.25-4.17 (2H, m), 2.89 (1H, ddd, *J* = 14.0, 8.4, 4.4 Hz), 2.71 (1H, dd, *J* = 17.2, 4.0 Hz), 2.58 (1H, dt, *J* = 10.8, 8.4 Hz), 2.50-2.40 (2H, m), 2.38 (3H, s), 1.54 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.2 (C, *C*=O), 173.8 (C, *C*=O), 151.2 (CH), 140.2 (C), 132.5 (C), 131.5 (CH), 129.4 (2 x CH), 127.9 (2 x CH), 93.4 (CH), 73.2 (C), 62.5 (CH), 44.9 (CH_2), 36.5 (CH_2), 31.3 (CH_2), 23.9 (CH_3), 21.3 (CH_3); HRMS m/z 313.1555 ($M + H^+$), calcd for $C_{18}H_{20}N_2O_3H$ 313.1552.



157am

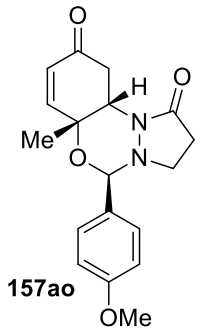
(5*R,6a*R**,10a*S**)-5-(2-methoxyphenyl)-6a-methyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (157an):** Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Yield: 66% (86.68 mg); Mp.: 166-168 °C; *dr* = 99:1; IR (Neat): ν_{max} 2925, 1693, 1495, 1408, 1249, 1116, 1067, 1025 and 756 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.65 (1H, d, *J* = 7.5 Hz), 7.37 (1H, dt, *J* = 8.0, 1.5 Hz), 7.05 (1H,

t, *J* = 7.5 Hz), 6.92 (1H, d, *J* = 8.5 Hz), 6.73 (1H, dd, *J* = 10.5, 2.0 Hz), 6.21 (1H, d, *J* = 10.5 Hz), 5.51 (1H, s), 4.17 (1H, m), 4.12 (1H, d, *J* = 18.0 Hz), 3.86 (3H, s), 2.97 (1H, dt, *J* = 10.0, 5.5 Hz), 2.77-2.69 (2H, m), 2.55-2.49 (1H, m), 2.43-2.35 (1H, m), 1.53 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.9 (C, *C*=O), 173.6 (C, *C*=O), 157.1 (C), 151.4 (CH), 131.5 (CH), 130.8 (CH), 128.7 (CH), 123.7 (C), 121.1 (CH), 110.5 (CH), 85.2 (CH), 73.3 (C), 62.3 (CH), 55.5 (CH_3), 44.1 (CH_2), 36.3 (CH_2), 31.4 (CH_2), 24.0 (CH_3); HRMS m/z 329.1500 (M + H^+), calcd for $C_{18}H_{20}N_2O_4H$ 329.1501.



157an

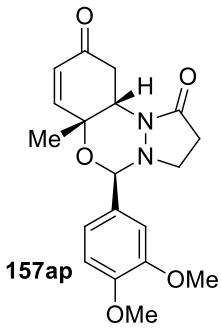
(5*R,6a*R**,10a*S**)-5-(4-methoxyphenyl)-6a-methyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (157ao):**



157ao

Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Yield: 72% (94.56 mg); Mp.: 136-138 °C; *dr* = 17:1; IR (Neat): ν_{max} 2924, 2850, 1692, 1613, 1515, 1407, 1320, 1248, 1172, 1115, 1027, 833 and 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (2H, td, *J* = 9.0, 2.5 Hz), 6.92 (2H, td, *J* = 9.0, 2.5 Hz), 6.68 (1H, dd, *J* = 10.5, 2.5 Hz), 6.19 (1H, dd, *J* = 10.5, 1.0 Hz), 4.80 (1H, s), 4.25-4.15 (2H, m), 3.83 (3H, s), 2.88 (1H, ddd, *J* = 14.5, 8.5, 4.5 Hz), 2.70 (1H, dd, *J* = 17.5, 4.5 Hz), 2.57 (1H, dt, *J* = 10.5, 8.5 Hz), 2.48-2.37 (2H, m), 1.54 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.2 (C, *C*=O), 173.8 (C, *C*=O), 160.9 (C), 151.2 (CH), 131.5 (CH), 129.3 (2 x CH), 127.7 (C), 114.1 (2 x CH), 93.1 (CH), 73.2 (C), 62.5 (CH), 55.3 (CH_3), 44.9 (CH_2), 36.4 (CH_2), 31.3 (CH_2), 23.9 (CH_3); HRMS m/z 329.1501 (M + H^+), calcd for $C_{18}H_{20}N_2O_4H$ 329.1501.

(5*R,6a*R**,10a*S**)-5-(3,4-dimethoxyphenyl)-6a-methyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (157ap):**

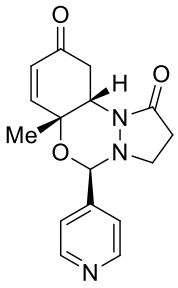


157ap

Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Yield: 62% (81.43 mg); Mp 150-152 °C; *dr* = 13:1; IR (Neat): ν_{max} 2935, 2838, 1695, 1517, 1464, 1407, 1262, 1262, 1236, 1026, and 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.06 (1H, d, *J* = 1.5 Hz), 7.00 (1H, dd, *J* = 8.5, 1.5 Hz), 6.87 (1H, d, *J* = 8.5 Hz), 6.70 (1H, dd, *J* = 10.0, 2.5

Hz), 6.20 (1H, dd, *J* = 10.5, 1.0 Hz), 4.79 (1H, s), 4.25-4.18 (2H, m), 3.94 (3H, s), 3.90 (3H, s), 2.90 (1H, ddd, *J* = 13.5, 9.0, 4.5 Hz), 2.71 (1H, dd, *J* = 17.5, 4.0 Hz), 2.58 (1H, dt, *J* = 10.5, 8.5 Hz), 2.47-2.40 (2H, m), 1.56 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.1 (C, *C*=O), 173.7 (C, *C*=O), 151.1 (CH), 150.5 (C), 149.4 (C), 131.5 (CH), 128.0 (C), 120.9 (CH), 110.8 (CH), 110.3 (CH), 93.3 (CH), 73.3 (C), 62.4 (CH), 56.0 (CH_3), 55.9 (CH_3), 44.9 (CH_2), 36.4 (CH_2), 31.2 (CH_2), 23.9 (CH_3); HRMS m/z 359.1608 (M + H^+), calcd for $C_{19}H_{22}N_2O_5H$ 359.1607.

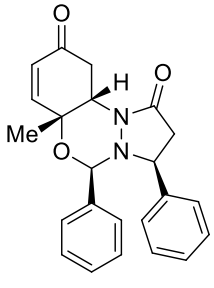
(5*R,6a*R**,10a*S**)-6a-methyl-5-(pyridin-4-yl)-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5*H*,6a*H*)-dione (157aq):**



157aq

Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Mp 150-152 °C; Yield: 48% (57.46 mg); *dr*: 10:1; IR (Neat): ν_{max} 2983, 1688, 1603, 1567, 1411, 1319, 1283, 1112, 1068, 916, 727 and 643 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.70 (2H, dd, *J* = 4.5, 1.5 Hz), 7.44 (2H, dd, *J* = 4.5, 1.5 Hz), 6.66 (1H, dd, *J* = 10.5, 2.5 Hz), 6.21 (1H, dd, *J* = 10.0, 1.0 Hz), 4.85 (1H, s), 4.23-4.19 (2H, m), 2.90 (1H, ddd, *J* = 9.5, 9.0, 4.5 Hz), 2.72 (1H, dd, *J* = 18.0, 5.0 Hz), 2.59 (1H, td, *J* = 10.5, 8.5 Hz), 2.46-2.40 (2H, m), 1.56 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.8 (C, *C*=O), 173.5 (C, N-*C*=O), 150.4 (2 x CH), 150.26 (CH), 143.6 (C), 131.8 (CH), 122.8 (2 x CH), 92.07 (CH), 73.4 (C), 62.5 (CH), 44.8 (CH_2), 36.3 (CH_2), 31.1 (CH_2), 23.7 (CH_3); HRMS m/z 300.1340 (M + H^+), calcd for $C_{16}H_{17}N_3O_3H$ 300.1348; Anal. calcd for $C_{16}H_{17}N_3O_3$ (299.1269): C, 64.20; H, 5.72; N, 14.04. Found: C, 64.15; H, 5.68; N, 14.12%.

(3*S,5*R**,6a*R**,10a*S**)-6a-methyl-3,5-diphenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (158aa):**

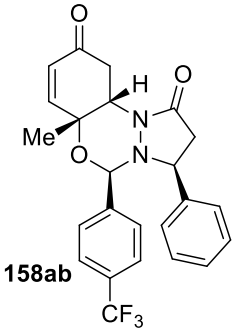


158aa

Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as half white solid. Yield: 69% (103.34 mg); Mp.: 166-168 °C; *dr* = 99:1; IR (Neat): ν_{max} 2921, 2851, 1698, 1457, 1410, 1325, 1116, 1068, 1026, 756 and 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.36 (2H, m), 7.29-7.18 (3H, m), 7.17-7.10 (3H, m), 7.02-7.00 (2H, m), 6.77 (1H, dd, *J* = 10.4, 2.8 Hz),

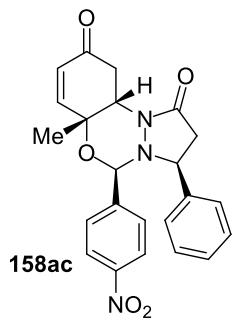
6.23 (1H, dd, *J* = 10.4, 0.8 Hz), 5.11 (1H, s), 4.35-4.34 (1H, m), 3.99 (1H, dd, *J* = 9.6, 5.6 Hz), 3.92 (1H, ddd, *J* = 18.0, 2.4, 1.2 Hz), 3.07 (1H, dd, *J* = 17.2, 9.6 Hz), 2.76 (1H, dd, *J* = 18.0, 5.2 Hz), 2.53 (1H, ddd, *J* = 17.4, 5.6, 0.8 Hz), 1.53 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 192.9 (C, *C*=O), 170.7 (C, *C*=O), 150.7 (CH), 140.9 (C), 135.3 (C), 131.9 (CH), 130.0 (CH), 128.4 (4 x CH), 128.2 (2 x CH), 127.2 (CH), 126.4 (2 x CH), 93.7 (CH), 73.6 (C), 62.3 (CH), 57.9 (CH), 39.5 (CH_2), 36.1 (CH_2), 24.2 (CH_3); HRMS m/z 375.1710 (M + H^+), calcd for $C_{23}H_{22}N_2O_3H$ 375.1709.

(3*S,5*R**,6a*R**,10a*S**)-6a-methyl-3-phenyl-5-(4-(trifluoromethyl)phenyl)-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (158ab):**



Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Yield: 63% (111.49 mg); Mp.: 172-174 °C; *dr* = 99:1; IR (Neat): ν_{max} 3021, 1731, 1374, 1325, 1247, 1215, 1046, 751 and 667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (2H, d, *J* = 8.0 Hz), 7.39 (2H, d, *J* = 8.0 Hz), 7.10-7.09 (3H, m), 6.95-6.93 (2H, m), 6.73 (1H, dd, *J* = 10.5, 2.5 Hz), 6.25 (1H, br d, *J* = 10.5 Hz), 5.13 (1H, s), 4.35 (1H, m), 4.07 (1H, ddd, *J* = 17.5, 1.6, 1.0 Hz), 3.90 (1H, dd, *J* = 9.5, 7.0 Hz), 3.01 (1H, dd, *J* = 17.5, 9.5 Hz), 2.76 (1H, dd, *J* = 18.0, 4.5 Hz), 2.54 (1H, dd, *J* = 17.5, 7.5 Hz), 1.55 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.0 (C, *C*=O), 170.7 (C, *C*=O), 150.3 (CH), 140.2 (C), 138.8 (C), 132.02 (CH), 132.0 (C, q, *J* = 32.5 Hz), 129.1 (2 x CH), 128.3 (2 x CH), 127.4 (CH), 126.6 (2 x CH), 125.2 (2 x CH, q, *J* = 3.75 Hz), 123.6 (C, q, *J* = 271.2 Hz, *C*F_3), 93.2 (CH), 73.7 (C), 62.7 (CH), 58.9 (CH), 40.1 (CH_2), 36.3 (CH_2), 24.0 (CH_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ –63.04; HRMS m/z 443.1582 (M + H^+), calcd for $C_{24}H_{21}F_3N_2O_3H$ 443.1582.

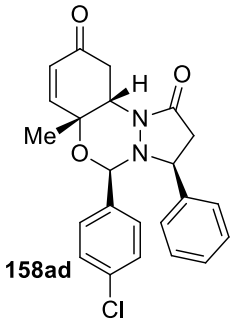
(3*S,5*R**,6a*R**,10a*S**)-6a-methyl-5-(4-nitrophenyl)-3-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (158ac):**



Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Yield: 59% (98.98 mg); Mp.: 218-220 °C; *dr* = 99:1; IR (Neat): ν_{max} 2925, 2854, 1690, 1521, 1346, 1281, 1111, 1074, 858, 757, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (2H, d, *J* = 8.4 Hz),

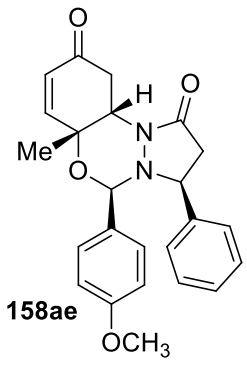
7.52 (2H, d, *J* = 8.4 Hz), 7.09-7.08 (3H, m), 6.95 (2H, br d, *J* = 3.6 Hz), 6.74 (1H, dd, *J* = 10.4, 2.0 Hz), 6.26 (1H, d, *J* = 10.4 Hz), 5.18 (1H, s), 4.37 (1H, br s), 4.09 (1H, d, *J* = 17.2 Hz), 3.91 (1H, t, *J* = 8.4 Hz), 3.02 (1H, dd, *J* = 17.6, 9.6 Hz), 2.78 (1H, dd, *J* = 17.6, 4.4 Hz), 2.54 (1H, dd, *J* = 17.6, 7.6 Hz), 1.56 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.0 (C, *C*=O), 170.6 (C, *C*=O), 150.1 (CH), 148.6 (C), 141.6 (C), 140.0 (C), 132.0 (CH), 129.7 (2 x CH), 128.3 (2 x CH), 127.5 (CH), 126.6 (2 x CH), 123.2 (2 x CH), 92.7 (CH), 73.8 (C), 62.8 (CH), 59.1 (CH), 40.2 (CH_2), 36.3 (CH_2), 23.9 (CH_3); HRMS m/z 420.1566 (M + H^+), calcd for $C_{23}H_{21}N_3O_5H$ 420.1559.

(3*S,5*R**,6a*R**,10a*S**)-5-(4-chlorophenyl)-6a-methyl-3-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (158ad):**



Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid. Yield: 62% (101.39 mg); Mp.: 164-166 °C; *dr* = 99:1; IR (Neat): ν_{max} 2923, 2852, 1694, 1408, 1256, 1118, 1071, 1030, 757 and 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.26 (2H, m), 7.16-7.14 (5H, m), 7.00-6.97 (2H, m), 6.74 (1H, dd, *J* = 10.4, 2.8 Hz), 6.24 (1H, dd, *J* = 10.4, 1.2 Hz), 5.07 (1H, s), 4.34-4.33 (1H, m), 3.98 (1H, ddd, *J* = 18.0, 2.4, 1.2 Hz), 3.92 (1H, dd, *J* = 9.6, 6.4 Hz), 3.04 (1H, dd, *J* = 17.2, 9.6 Hz), 2.76 (1H, dd, *J* = 18.0, 4.8 Hz), 2.53 (1H, ddd, *J* = 17.4, 6.4, 0.8 Hz), 1.53 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 192.9 (C, *C*=O), 170.7 (C, *C*=O), 150.4 (CH), 140.6 (C), 135.9 (C), 133.8 (C), 132.0 (CH), 129.9 (2 x CH), 128.6 (2 x CH), 128.3 (2 x CH), 127.3 (CH), 126.5 (2 x CH), 93.1 (CH), 73.6 (C), 62.5 (CH), 58.4 (CH), 39.8 (CH_2), 36.2 (CH_2), 24.1 (CH_3); HRMS m/z 409.1318 (M + H^+), calcd for $C_{23}H_{21}ClN_2O_3H$ 409.1319.

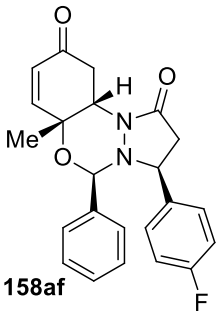
(3*S,5*R**,6a*R**,10a*S**)-5-(4-methoxyphenyl)-6a-methyl-3-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (158ae):**



Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light brown solid. Yield: 65% (105.15 mg); Mp.: 174-176 °C; *dr* = 99:1; IR (Neat): ν_{max} 2983, 2928, 1732, 1697, 1613, 1516, 1373, 1248, 1115, 1046, 752, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (2H, td, *J*

= 8.8, 1.6 Hz), 7.19-7.13 (3H, m), 7.04-7.01 (2H, m), 6.77 (1H, dd, *J* = 10.4, 2.4 Hz), 6.73 (2H, td, *J* = 8.8, 1.6 Hz), 6.22 (1H, br d, *J* = 10.4 Hz), 5.06 (1H, s), 4.32 (1H, m), 3.99 (1H, dd, *J* = 9.6, 5.2 Hz), 3.94-3.89 (1H, m), 3.74 (3H, s), 3.06 (1H, dd, *J* = 17.6, 9.6 Hz), 2.75 (1H, dd, *J* = 18.0, 4.8 Hz), 2.52 (1H, ddd, *J* = 17.4, 5.6, 0.8 Hz), 1.52 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 192.9 (C, *C*=O), 170.7 (C, *C*=O), 160.8 (C), 150.8 (CH), 141.0 (C), 131.8 (CH), 129.7 (2 x CH), 128.2 (2 x CH), 127.6 (C), 127.1 (CH), 126.4 (2 x CH), 113.8 (2 x CH), 93.3 (CH), 73.6 (C), 62.3 (CH), 57.9 (CH), 55.3 (CH_3), 39.5 (CH_2), 36.1 (CH_2), 24.2 (CH_3); HRMS m/z 405.1815 (M + H^+), calcd for $C_{24}H_{24}N_2O_4H$ 405.1814.

(3*S,5*R**,6a*R**,10a*S**)-3-(4-fluorophenyl)-6a-methyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (158af):**



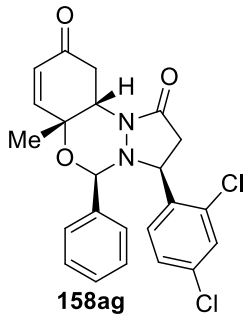
158af

Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Yield: 65% (102.02 mg); Mp.: 208-210 °C; *dr* = 99:1; IR (Neat): ν_{max} 3012, 1697, 1509, 1409, 1322, 1224, 1115, 1068, 1026, 837, 751, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.33 (2H, m), 7.26-7.25 (1H, m), 7.23-7.19 (2H, m), 6.97-6.94 (2H, m), 6.84-6.79 (2H, m), 6.76 (1H, dd, *J* = 10.4, 2.4 Hz), 6.23 (1H, dd, *J* = 10.4, 1.2 Hz), 5.08 (1H, s), 4.34-4.32 (1H, m), 3.99-3.94 (2H, m), 3.04 (1H, dd, *J* = 17.2, 9.6 Hz), 2.76 (1H, dd, *J* = 17.6, 4.4 Hz), 2.47 (1H, ddd, *J* = 17.4, 6.0, 1.2 Hz), 1.54 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.0 (C, *C*=O), 170.5 (C, *C*=O), 161.8 (C, d, *J* = 244.0 Hz, *C*-F), 150.7 (CH), 136.6 (C, d, *J* = 4.0 Hz), 135.2 (C), 131.9 (CH), 130.1 (CH), 128.4 (4 x CH), 128.1 (2 x CH, d, *J* = 8.0 Hz), 115.1 (2 x CH, d, *J* = 21.0 Hz), 93.8 (CH), 73.6 (C), 62.5 (CH), 57.6 (CH), 39.8 (CH_2), 36.2 (CH_2), 24.1 (CH_3); ^{19}F NMR ($CDCl_3$, 375 MHz): δ −115.14; HRMS m/z 393.1615 (M + H^+), calcd for $C_{23}H_{21}FN_2O_3H$ 393.1614.

(3*S,5*R**,6a*R**,10a*S**)-3-(2,4-dichlorophenyl)-6a-methyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (158ag):**

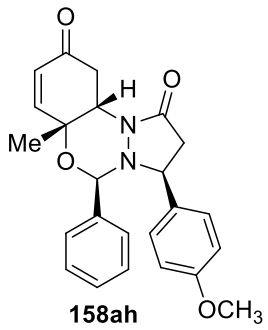
Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Yield: 59% (104.62 mg); Mp.: 202-204 °C; *dr* = 99:1; IR (Neat): ν_{max} 2922, 2851, 1699, 1469, 1410, 1322, 1115, 1069, 1051, 755, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (1H, d, *J* = 8.5 Hz), 7.35 (2H, d, *J* = 7.0 Hz), 7.24-

7.18 (3H, m), 7.13-7.10 (2H, m), 6.78 (1H, d, *J* = 10.0 Hz), 6.25 (1H, d, *J* = 10.0 Hz), 5.11 (1H, s), 4.38-4.31 (2H, m), 3.99 (1H, br d, *J* = 18.0 Hz), 3.11 (1H, dd, *J* = 17.5, 10.0 Hz), 2.78 (1H, dd, *J* = 17.5, 4.5 Hz), 2.31 (1H, dd, *J* = 17.5, 6.0 Hz), 1.57 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 192.8 (C, *C*=O), 169.8 (C, *C*=O), 150.5 (CH), 137.0 (C), 134.7 (C), 133.4 (C), 132.3 (C), 131.9 (CH), 130.1 (CH), 129.2 (CH), 128.9 (CH), 128.4 (2 x CH), 128.2 (2 x CH), 127.1 (CH), 93.7 (CH), 73.6 (C), 62.6 (CH), 55.0 (CH), 38.8 (CH_2), 36.1 (CH_2), 24.1 (CH_3); HRMS m/z 443.0928 (M + H^+), calcd for $C_{23}H_{20}Cl_2N_2O_3H$ 443.0929.



158ag

(3*S,5*R**,6a*R**,10a*S**)-3-(4-methoxyphenyl)-6a-methyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (158ah):**



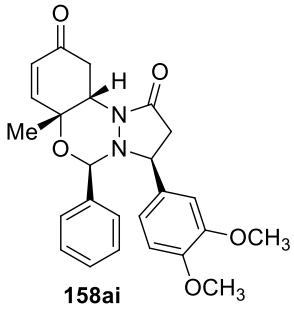
158ah

Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as light yellow solid. Yield: 66% (106.77 mg); Mp.: 220-222 °C; *dr* = 99:1; IR (Neat): ν_{max} 2924, 1697, 1513, 1410, 1325, 1249, 1177, 1115, 1067, 1028, and 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (2H, d, *J* = 6.5 Hz), 7.26-7.22 (3H, m), 6.91 (2H, d, *J* = 8.5 Hz), 6.77 (1H, dd, *J* = 10.0, 1.5 Hz), 6.68 (2H, d, *J* = 8.5 Hz), 6.23 (1H, d, *J* = 10.0 Hz), 5.09 (1H, s), 4.31 (1H, s), 3.96-3.89 (2H, m), 3.73 (3H, s), 3.03 (1H, dd, *J* = 17.5, 9.5 Hz), 2.75 (1H, dd, *J* = 18.0, 4.5 Hz), 2.50 (1H, dd, *J* = 17.5, 5.0 Hz), 1.52 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 192.8 (C, *C*=O), 170.8 (C, *C*=O), 158.7 (C), 150.6 (CH), 135.5 (C), 133.0 (C), 131.9 (CH), 130.0 (CH), 128.45 (2 x CH), 128.41 (2 x CH), 127.5 (2 x CH), 113.7 (2 x CH), 93.7 (CH), 73.5 (C), 62.3 (CH), 57.4 (CH_3), 55.2 (CH), 39.4 (CH_2), 36.1 (CH_2), 24.2 (CH_3); HRMS m/z 405.1815 (M + H^+), calcd for $C_{24}H_{24}N_2O_4H$ 405.1814.

(3*S,5*R**,6a*R**,10a*S**)-3-(3,4-dimethoxyphenyl)-6a-methyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (158ai):**

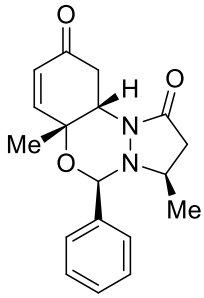
Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Yield: 60% (104.27 mg); Mp 178-180 °C; *dr* = 13:1; IR (Neat): ν_{max} 3017, 1696, 1516, 1412, 1262, 1215, 1026, 752 and 667 cm^{-1}; ^{1}H NMRS ($CDCl_3$, 500 MHz) δ 7.38 (2H, br d, *J* = 6.5 Hz), 7.29-7.22 (3H, m), 6.77 (1H, dd, *J* = 10.5,

2.5 Hz), 6.63 (1H, d, *J* = 8.5 Hz), 6.56 (1H, dd, *J* = 8.5, 1.5 Hz), 6.42 (1H, d, *J* = 1.5 Hz), 6.23 (1H, d, *J* = 10.5 Hz), 5.08 (1H, s), 4.32-4.31 (1H, m), 3.97-3.91 (2H, m), 3.80 (3H, s), 3.76 (3H, s), 3.02 (1H, dd, *J* = 17.5, 9.5 Hz), 2.76 (1H, dd, *J* = 17.5, 5.0 Hz), 2.55 (1H, dd, *J* = 17.5, 5.5 Hz), 1.53 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 192.9 (C, *C*=O), 170.8 (C, *C*=O), 150.7 (CH), 148.7 (C), 148.2 (C), 135.5 (C), 133.4 (C), 131.8 (CH), 130.0 (CH), 128.6 (2 x CH), 128.3 (2 x CH), 118.7 (CH), 111.0 (CH), 110.1 (CH), 93.9 (CH), 73.5 (C), 62.5 (CH), 57.9 (CH), 55.9 (CH_3), 55.8 (CH_3), 39.3 (CH_2), 36.2 (CH_2), 24.1 (CH_3); HRMS m/z 435.1921 ($M + H^+$), calcd for $C_{25}H_{26}N_2O_5H$ 435.1920.



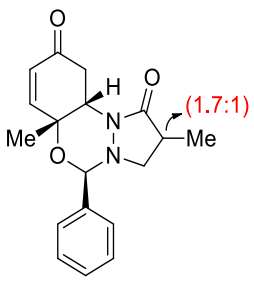
158ai

(3*R,5*R**,6a*R**,10a*S**)-3,6a-dimethyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5H,6aH)-dione (158aj):** Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as yellow gel; Yield: 65% (81.21 mg); *dr* = 99:1; IR (Neat): ν_{max} 2981, 1682, 1606, 1454, 1402, 1288, 1084, 938, 752 and 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52-7.48 (2H, m), 7.45-7.41 (3H, m), 6.73 (1H, dd, *J* = 10.4, 2.8 Hz), 6.19 (1H, dd, *J* = 10.4, 1.2 Hz), 4.94 (1H, s), 4.22-4.21 (1H, m), 3.85 (1H, ddd, *J* = 18.0, 2.0, 1.2 Hz), 3.08-3.00 (1H, m), 2.81-2.70 (2H, m), 2.07 (1H, ddd, *J* = 17.2, 4.8, 1.2 Hz), 1.50 (3H, s), 0.83 (3H, d, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 192.8 (C, *C*=O), 171.2 (C, *C*=O), 150.6 (CH), 136.2 (C), 131.8 (CH), 130.1 (CH), 128.7 (2 x CH), 128.2 (2 x CH), 93.1 (CH), 73.5 (C), 62.0 (CH), 50.1 (CH), 38.2 (CH_2), 36.1 (CH_2), 24.2 (CH_3), 21.1 (CH_3); HRMS m/z 313.1556 ($M + H^+$), calcd for $C_{18}H_{20}N_2O_3H$ 313.1552.



158aj

(5*R,6a*R**,10a*S**)-2,6a-dimethyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5*H*,6a*H*)-dione (158ak):** Prepared by following the procedure **3a** and purified by column chromatography using EtOAc/hexane and isolated as semi solid; Yield: 65% (81.21 mg); *dr* = 1.7:1; IR (Neat): ν_{max} 2977, 2925, 1695, 1455, 1406, 1323, 1114, 1063, 750 and 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, 1.7:1 mixture of isomers) δ 7.52-7.50 (4H, m), 7.44-7.41 (6H, m), 6.73

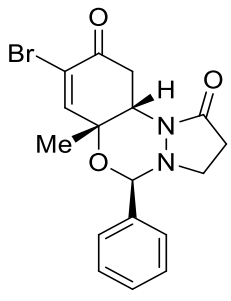


158ak

(1H, dd, *J* = 10.0, 2.0 Hz), 6.68 (1H, dd, *J* = 10.0, 2.0 Hz), 6.21 (1H, d, *J* = 10.0 Hz), 6.19 (1H, d, *J* = 10.0 Hz), 4.97 (1H, s), 4.76 (1H, s), 4.40-4.36 (1H, m), 4.24-4.19 (2H, m), 3.93 (1H, br d, *J* = 18.0 Hz), 2.96-2.91 (2H, m), 2.77-2.65 (4H, m), 2.53-2.46 (1H, m), 2.15 (1H, dd, *J* = 12.0, 9.0 Hz), 1.58 (3H, s), 1.53 (3H, s), 1.13 (6H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, 1.7:1 mixture of isomers) δ 194.5 (C, *C*=O), 193.0 (C, *C*=O), 176.6 (C, *C*=O), 175.5 (C, *C*=O), 151.3 (CH), 150.7 (CH), 136.0 (C), 135.3 (C), 131.9 (CH), 131.5 (CH), 130.2 (CH), 130.1 (CH), 128.8 (2 x CH), 128.77 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 94.1 (CH), 92.8 (CH), 73.5 (C), 73.2 (C), 62.8 (CH), 62.1 (CH), 53.1 (CH_2), 51.9 (CH_2), 37.2 (CH), 36.6 (CH_2), 36.2 (CH_2), 36.0 (CH), 24.3 (CH_3), 23.8 (CH_3), 14.7 (CH_3), 13.4 (CH_3); HRMS m/z 313.1551 ($M + H^+$), calcd for $C_{18}H_{20}N_2O_3H$ 313.1552.

Procedure 3b: General Procedure for the Bromination of Product 156aa: In an oven dried round bottom flask was taken the mixture of product **156aa** (0.2 mmol) and oxone (0.4 mmol) in dry DCM (1 mL). To this mixture 2N HBr (0.44 mmol) was added which resulted in dark red coloured solution. After allowing it to stir for 2 h at r.t., Et_3N (0.16 mL) was added. Then, the reaction mixture was allowed to stir for another 12 h and usual work-up was done using EtOAc. The combined organic layers were dried (Na_2SO_4), and concentrated. Pure product **159aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(5*R,6a*R**,10a*S**)-8-bromo-6a-methyl-5-phenyl-2,3,10,10a-tetrahydrobenzo[e]pyrazolo[1,2-c][1,3,4]oxadiazine-1,9(5*H*,6a*H*)-dione (159aa):**



159aa

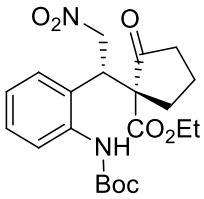
Prepared by following the procedure **3b** and purified by column chromatography using EtOAc/hexane and isolated as yellow gel; Yield: 50% (37.72 mg); *dr* = 99:1; IR (Neat): ν_{max} 3009, 2981, 1687, 1572, 1405, 1355, 1258, 1111, 1068, 796 and 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52-7.49 (2H, m), 7.45-7.42 (3H, m), 7.13 (1H, d, *J* = 2.4 Hz), 4.87 (1H, s), 4.43 (1H, dd, *J* = 17.6, 2.4 Hz), 4.20 (1H, m), 2.90 (1H, ddd, *J* = 10.0, 9.2, 4.4 Hz), 2.82 (1H, dd, *J* = 17.6, 4.0 Hz), 2.63 (1H, dt, *J* = 10.4, 8.4 Hz), 2.53-2.37 (2H, m), 1.58 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 186.1 (C, *C*=O), 174.2 (C, *C*=O), 151.3 (CH), 135.0 (C), 130.3 (CH), 128.8 (2 x CH), 128.0 (2 x CH),

125.4 (C), 93.6 (CH), 75.3 (C), 62.3 (CH), 44.9 (CH_2), 36.0 (CH_2), 31.1 (CH_2), 23.6 (CH_3); HRMS m/z 377.0500 ($M + H^+$), calcd for $C_{17}H_{17}BrN_2O_3H$ 377.0501.

Materials: All solvents and commercially available chemicals were used as received. Functionalized 2-amino-β-nitrostyrenes **131a-j**[72] was prepared according to the literature procedure.

Procedure 4a: General procedure for quinidine-squaramide catalyzed asymmetric Michael reaction of (*E*)-2-(2-nitrovinyl)anilines 131 with β-keto esters 162: In an ordinary glass vial equipped with a magnetic stirring bar, to the **88m** or **88n** (5 mol%) in DCM (1.0 mL), were added (*E*)-2-(2-nitrovinyl)anilines **131a-i** (0.3 mmol) and *β*-keto esters **162a-l** (0.4 mmol, 1.33 equiv.). After stirring the reaction mixture at 25 °C as shown in Tables 13-15, the crude reaction mixture was concentrated and pure chiral products **163** were obtained by quick filtration (silica gel, mixture of hexane/ethyl acetate).

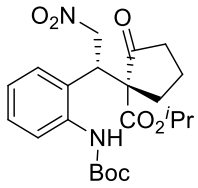
(*R*)-Ethyl 1-((*S*)-1-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-nitroethyl)-2-oxocyclopentane carboxylate (163aa): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 107-109 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u Cellulose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 9.55 min (minor), t_R = 14.92 min (major); **$[\alpha]_D^{25}$ = +3.4° (*c* = 0.17 g/100 mL, $CHCl_3$, 98% *ee* and >99% *de*)**; IR (KBr): ν_{max} 3408 (N-*H*), 2980, 1720 (C=O), 1555 (NO_2), 1450, 1367 (NO_2), 1229, 1154, 1023 and 855 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, at 50 °C) δ 7.54 (1H, d, *J* = 8.0 Hz), 7.38 (1H, dd, *J* = 7.6, 1.2 Hz), 7.30-7.26 (1H, m), 7.18-7.12 (1H, m), 6.93 (1H, br s, N*H*), 5.18 (1H, dd, *J* = 14.4, 4.4 Hz), 4.97 (1H, dd, *J* = 14.4, 10.0 Hz), 4.45 (1H, dd, *J* = 10.4, 4.4 Hz), 4.23 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.44-2.36 (2H, m), 2.19-2.10 (1H, m), 2.07-1.99 (1H, m), 1.98-1.88 (2H, m), 1.55 (9H, s, OC(C*H*$_3$)$_3$), 1.29 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, at 50 °C) δ 213.0 (C, *C*=O), 169.4 (C, O–*C*=O), 154.0 (C, O–*C*=O), 137.0 (C), 130.2 (C), 128.6 (CH), 127.5 (CH), 127.2 (CH), 125.8 (CH), 80.4 (C), 77.0 (CH_2), 63.0 (C), 62.3 (CH_2, O*C*H$_2$CH$_3$), 38.5 (CH), 37.7 (CH_2),



(+)-163aa

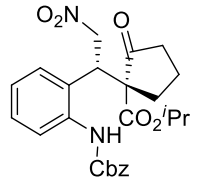
31.4 (CH_2), 28.3 (3 x CH_3, OC(CH_3)$_3$), 19.4 (CH_2), 13.8 (CH_3, OCH_2CH_3); HRMS m/z 443.1795 (M + Na), calcd for $C_{21}H_{28}N_2O_7Na$ 443.1795.

(*R*)-Isopropyl 1-((*S*)-1-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate (163ab): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 108-110 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 0.8 mL/min, λ = 254 nm), t_R = 14.72 min (major), t_R = 23.55 min (minor); **[α]$_D^{25}$ = +12.1° (*c* = 0.07 g/100 mL, $CHCl_3$, >99% *ee* and >99% *de*)**; IR (KBr): ν_{max} 3383 (N-*H*), 2980, 1717 (C=O), 1556 (NO_2), 1451, 1368 (NO_2), 1230, 1155, 1047 and 906 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, at 50 °C) δ 7.54 (1H, d, *J* = 8.0 Hz), 7.41 (1H, d, *J* = 7.6 Hz), 7.28 (1H, dt, *J* = 7.6, 1.2 Hz), 7.16 (1H, t, *J* = 7.6 Hz), 6.96 (1H, br s, N*H*), 5.15 (1H, dd, *J* = 14.0, 4.4 Hz), 5.08 (1H, septet, *J* = 6.4 Hz), 4.96 (1H, dd, *J* = 14.0, 10.0 Hz), 4.46 (1H, dd, *J* = 10.0, 4.0 Hz), 2.45-2.35 (2H, m), 2.19-2.07 (1H, m), 2.05-1.98 (1H, m), 1.96-1.90 (2H, m), 1.55 (9H, s, OC(C*H*$_3$)$_3$), 1.28 (6H, d, *J* = 6.0 Hz, OCH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135, at 50 °C) δ 213.1 (C, *C*=O), 168.9 (C, O–*C*=O), 154.0 (C, O–*C*=O), 137.0 (C), 130.2 (C), 128.6 (CH), 127.5 (CH), 127.2 (CH), 125.7 (CH), 80.3 (C), 77.0 (CH_2), 70.3 (CH, O*C*H(CH$_3$)$_2$), 63.1 (C), 38.5 (CH), 37.7 (CH_2), 31.4 (CH_2), 28.3 (3 x CH_3, OC(*C*H$_3$)$_3$), 21.5 (CH_3, OCH(*C*H$_3$)$_2$), 21.3 (CH_3, OCH(*C*H$_3$)$_2$), 19.4 (CH_2); HRMS m/z 457.1951 (M + Na), calcd for $C_{22}H_{30}N_2O_7Na$ 457.1951.



(+)-**163ab**

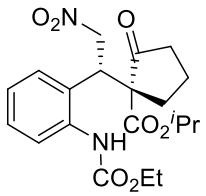
(*R*)-Isopropyl 1-((*S*)-1-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate (163bb): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 77-79 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.13 min (major), t_R = 33.06 min (minor); **[α]$_D^{25}$ = +18.7° (*c* = 0.14 g/100 mL, $CHCl_3$, >99% *ee* and >99% *de*)**; IR (KBr): ν_{max} 3402 (N-*H*), 2987, 1719 (C=O), 1555 (NO_2), 1471, 1376 (NO_2), 1215, 1183, 1043, 906 and 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, at 50 °C) δ 7.59 (1H, d, *J* = 7.6 Hz), 7.46-7.44 (2H, m), 7.42-7.37 (3H, m), 7.35-7.28 (3H, m), 7.18 (1H, t, *J* = 7.6 Hz),



(+)-**163bb**

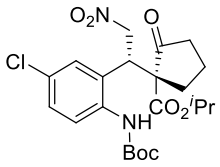
5.26 (2H, s, OC*H*$_2$Ph), 5.12 (1H, dd, *J* = 14.0, 4.0 Hz), 5.06 (1H, septet, *J* = 6.4 Hz), 4.93 (1H, dd, *J* = 14.0, 10.4 Hz), 4.46 (1H, dd, *J* = 10.0, 4.0 Hz), 2.44-2.30 (2H, m), 2.06-1.94 (2H, m), 1.92-1.80 (2H, m), 1.25 (3H, d, *J* = 6.4 Hz, OCH(C*H*$_3$)$_2$), 1.23 (3H, d, *J* = 6.4 Hz, OCH(C*H*$_3$)$_2$); ^{13}C NMR (CDCl$_3$, DEPT-135, at 50 °C) δ 213.2 (C, *C*=O), 168.8 (C, O–*C*=O), 154.6 (C, O–*C*=O), 136.7 (C), 136.5 (C), 130.0 (C), 128.8 (CH), 128.5 (2 x CH), 128.1 (2 x CH), 128.1 (CH), 127.6 (CH), 126.9 (CH), 126.0 (CH), 76.9 (CH$_2$), 70.4 (CH, O*C*H(CH$_3$)$_2$), 67.0 (CH$_2$, O*C*H$_2$Ph), 63.2 (C), 38.5 (CH), 37.6 (CH$_2$), 31.3 (CH$_2$), 21.4 (CH$_3$, OCH(*C*H$_3$)$_2$), 21.3 (CH$_3$, OCH(*C*H$_3$)$_2$), 19.3 (CH$_2$); HRMS m/z 491.1795 (M + Na), calcd for $C_{25}H_{28}N_2O_7Na$ 491.1795.

(*R*)-Isopropyl 1-((*S*)-1-(2-((ethoxycarbonyl)amino)phenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate (163cb): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 110-112 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 17.7 min (major), t_R = 55.8 min (minor) [for minor isomer], t_R = 20.7 min (major), t_R = 27.6 min (minor) [for major isomer]; **[α]$_D^{25}$ = +20.9° (*c* = 0.07 g/100 mL, CHCl$_3$, 96% *ee* and >99% *de*)**; IR (KBr): ν_{max} 3386 (N-*H*), 2986, 1719 (C=O), 1555 (NO$_2$), 1470, 1376 (NO$_2$), 1219, 1147, 1098 and 906 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz, at 50 °C) δ 7.58 (1H, d, *J* = 8.0 Hz), 7.39 (1H, dd, *J* = 7.6, 1.2 Hz), 7.28 (1H, dt, *J* = 7.6, 1.2 Hz), 7.20 (1H, br s, N*H*), 7.16 (1H, dt, *J* = 7.6, 1.2 Hz), 5.10 (1H, dd, *J* = 14.0, 4.0 Hz), 5.06 (1H, septet, *J* = 6.4 Hz), 4.91 (1H, dd, *J* = 14.0, 10.0 Hz), 4.49 (1H, dd, *J* = 10.0, 4.4 Hz), 4.25 (2H, dq, *J* = 7.2, 1.6 Hz, OC*H*$_2$CH$_3$), 2.45-2.32 (2H, m), 2.10-1.99 (2H, m), 1.97-1.88 (2H, m), 1.34 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.27 (3H, d, *J* = 6.4 Hz, OCH(C*H*$_3$)$_2$), 1.25 (3H, d, *J* = 6.4 Hz, OCH(C*H*$_3$)$_2$); ^{13}C NMR (CDCl$_3$, DEPT-135, at 50 °C) δ 213.2 (C, *C*=O), 168.9 (C, O–*C*=O), 154.8 (C, O–*C*=O), 136.9 (C), 129.7 (C), 128.7 (CH), 127.6 (CH), 126.7 (CH), 125.7 (CH), 76.9 (CH$_2$), 70.4 (CH, O*C*H(CH$_3$)$_2$), 63.2 (C), 61.3 (CH$_2$, O*C*H$_2$CH$_3$), 38.4 (CH), 37.6 (CH$_2$), 31.1 (CH$_2$), 21.4 (CH$_3$, OCH(*C*H$_3$)$_2$), 21.3 (CH$_3$, OCH(*C*H$_3$)$_2$), 19.4 (CH$_2$), 14.5 (CH$_3$, OCH$_2$*C*H$_3$); HRMS m/z 429.1633 (M + Na), calcd for $C_{20}H_{26}N_2O_7Na$ 429.1638.



(+)-**163cb**

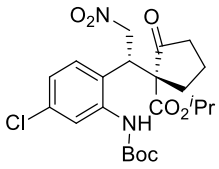
(*R*)-Isopropyl 1-((*S*)-1-(2-((*tert*-butoxycarbonyl)amino)-5-chlorophenyl)-2-nitroethyl)-2 oxocyclopentanecarboxylate (163db): Prepared by following the procedure **4a** and purified



(+)-**163db**

by column chromatography using EtOAc/hexane and isolated as white solid. Mp 78-80 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 16.3 min (minor), t_R = 21.4 min (major) [for minor isomer], t_R = 18.9 min (major), t_R = 38.3 min (minor) [for major isomer]; **$[\alpha]_D^{25}$ = +2.6° (*c* = 0.27 g/100 mL, $CHCl_3$, >99% *ee* and 97% *de*)**; IR (KBr): ν_{max} 3381 (N-*H*), 2980, 1716 (C=O), 1556 (NO_2), 1456, 1368 (NO_2), 1231, 1155, 1098 and 906 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, at 50 °C) δ 7.50 (1H, d, *J* = 8.4 Hz), 7.44 (1H, d, *J* = 2.0 Hz), 7.25 (1H, dd, *J* = 8.4, 2.4 Hz), 6.89 (1H, br s, N*H*), 5.17 (1H, dd, *J* = 14.4, 4.0 Hz), 5.09 (1H, septet, *J* = 6.4 Hz), 4.93 (1H, dd, *J* = 14.4, 10.4 Hz), 4.36 (1H, dd, *J* = 10.4, 4.0 Hz), 2.45-2.38 (2H, m), 2.23-2.14 (1H, m), 1.98-1.92 (3H, m), 1.54 (9H, s, OC(CH_3)$_3$), 1.29 (3H, d, *J* = 6.4 Hz, OCH(CH_3)$_2$), 1.27 (3H, d, *J* = 6.4 Hz, OCH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135, at 50 °C) δ 212.8 (C, *C*=O), 168.7 (C, O–*C*=O), 153.7 (C, O–*C*=O), 135.8 (C), 132.2 (C), 131.2 (C), 128.8 (CH), 128.3 (CH), 127.7 (CH), 80.7 (C), 76.8 (CH_2), 70.6 (CH, O*C*H(CH_3)$_2$), 62.9 (C), 38.5 (CH), 37.6 (CH_2), 31.7 (CH_2), 28.3 (3 x CH_3, OC(CH_3)$_3$), 21.5 (CH_3, OCH(CH_3)$_2$), 21.3 (CH_3, OCH(CH_3)$_2$), 19.3 (CH_2); HRMS m/z 491.1560 (M + Na), calcd for $C_{22}H_{29}N_2O_7ClNa$ 491.1561.

(*R*)-Isopropyl 1-((*S*)-1-(2-((*tert*-butoxycarbonyl)amino)-4-chlorophenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate (163eb): Prepared by following the procedure **4a** and

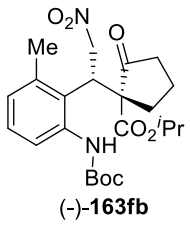


(+)-**163eb**

purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 102-104 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OJ-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 15.1 min (minor), t_R = 54.0 min (major) [for minor isomer], t_R = 19.4 min (minor), t_R = 26.8 min (major) [for major isomer]; **$[\alpha]_D^{25}$ = +6.9° (*c* = 0.18 g/100mL, $CHCl_3$, 99% *ee* for major isomer, 85% *ee* for minor isomer and 70% *de*)**; IR (KBr): ν_{max} 3376 (N-*H*), 2981, 1717 (C=O), 1556 (NO_2), 1456, 1368 (NO_2), 1230, 1154, 1098 and 938 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, at 50 °C) δ 7.65 (1H, br d, *J* = 2.0 Hz), 7.36 (1H, d, *J* = 8.4 Hz), 7.12 (1H,

dd, *J* = 8.4, 2.0 Hz), 7.06 (1H, br s, N*H*), 5.11-5.05 (2H, m), 4.90 (1H, dd, *J* = 14.4, 10.4 Hz), 4.38 (1H, dd, *J* = 10.4, 4.0 Hz), 2.44-2.37 (2H, m), 2.17-2.07 (1H, m), 2.03-1.90 (3H, m), 1.55 (9H, s, OC(C*H*$_3$)$_3$), 1.27 (3H, d, *J* = 6.4 Hz, OCH(C*H*$_3$)$_2$), 1.26 (3H, d, *J* = 6.4 Hz, OCH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135, at 50 °C) δ 213.0 (C, *C*=O), 168.8 (C, O–*C*=O), 153.4 (C, O–*C*=O), 138.5 (C), 134.4 (C), 128.8 (CH), 127.8 (C), 126.4 (CH), 125.5 (CH), 80.8 (C), 76.7 (CH_2), 70.5 (CH, O*C*H(CH$_3$)$_2$), 63.1 (C), 38.1 (CH), 37.6 (CH_2), 31.4 (CH_2), 28.3 (3 x CH_3, OC(*C*H$_3$)$_3$), 21.4 (CH_3, OCH(*C*H$_3$)$_2$), 21.3 (CH_3, OCH(*C*H$_3$)$_2$), 19.4 (CH_2); HRMS m/z 491.1558 (M + Na), calcd for $C_{22}H_{29}N_2O_7ClNa$ 491.1561.

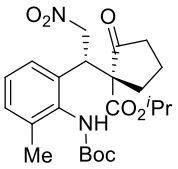
(*R*)-Isopropyl 1-((*S*)-1-(2-((*tert*-butoxycarbonyl)amino)-6-methylphenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate (163fb): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 0.8 mL/min, λ = 254 nm), t_R = 7.8 min (minor), t_R = 12.2 min (major) [for major isomer]; t_R = 11.2 min (minor), t_R = 13.5 min (major) [for minor isomer]; **$[\alpha]_D^{25}$ = –15.0° (*c* = 0.12 g/100 mL, $CHCl_3$, >99% *ee* for major, >99% *ee* for minor and dr = 3:1);** IR (Neat): ν_{max} 3285 (N-*H*), 2978, 1720 (C=O), 1556 (NO_2), 1454, 1367 (NO_2), 1232, 1157, 1099 and 905 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, at 50 °C, major isomer) δ 8.35 (1H, br s, N*H*), 7.54 (1H, d, *J* = 8.0 Hz), 7.19-7.14 (1H, m), 6.92 (1H, d, *J* = 7.6 Hz), 5.04-4.94 (2H, m), 4.85-4.75 (1H, m), 4.56-4.53 (1H, m), 2.66-2.62 (1H, m), 2.56-2.48 (1H, m), 2.38 (3H, s, C*H*$_3$), 2.03-1.96 (1H, m), 1.88-1.78 (3H, m), 1.57 (9H, s, OC(C*H*$_3$)$_3$), 1.11 (3H, d, *J* = 6.4 Hz, OCH(C*H*$_3$)$_2$), 1.04 (3H, d, *J* = 6.4 Hz, OCH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135, at 50 °C, major isomer) δ 213.8 (C, *C*=O), 174.2 (C, O–*C*=O), 169.2 (C, O–*C*=O), 154.0 (C), 139.0 (C), 137.5 (C), 128.4 (CH), 127.1 (CH), 124.2 (CH), 80.1 (C), 75.2 (CH_2), 71.1 (CH, O*C*H(CH$_3$)$_2$), 64.3 (C), 40.3 (CH), 37.0 (CH_2), 35.7 (CH_2), 28.4 (3 x CH_3, OC(*C*H$_3$)$_3$), 21.5 (CH_3, OCH(*C*H$_3$)$_2$), 21.2 (CH_3, OCH(*C*H$_3$)$_2$), 20.9 (CH_3), 19.1 (CH_2); HRMS m/z 471.2100 (M + Na), calcd for $C_{23}H_{32}N_2O_7Na$ 471.2108.



(-)-**163fb**

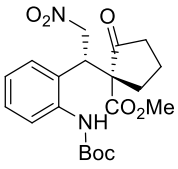
(*R*)-Isopropyl 1-((*S*)-1-(2-((*tert*-butoxycarbonyl)amino)-3-methylphenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate (163gb): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as oil. The

enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 7.5 min (major), t_R = 8.7 min (minor) [for minor isomer]; t_R = 10.1 min (major), t_R = 14.5 min (minor) [for major isomer]; **$[\alpha]_D^{25}$ = +2.6° (*c* = 0.52 g/100 mL, $CHCl_3$, >99% *ee*, >99% *ee*** and **dr = 15:1)**; IR (Neat): ν_{max} 3380 (N-*H*), 2979, 1716 (C=O), 1555 (NO_2), 1488, 1375 (NO_2), 1231, 1185, 1100, 907 and 777 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.32 (1H, m), 7.18-7.15 (2H, m), 6.57 (1H, br s, N*H*), 5.23 (1H, d, *J* = 11.6 Hz), 5.13-4.98 (2H, m), 4.47 (1H, br s), 2.47-2.32 (2H, m), 2.29 (3H, s, CH_3), 2.24-2.10 (1H, m), 2.06-1.98 (1H, m), 1.95-1.84 (2H, m), 1.54 (9H, s, OC(CH_3)$_3$), 1.28 (3H, d, *J* = 6.4 Hz, OCH(CH_3)$_2$), 1.27 (3H, d, *J* = 6.4 Hz, OCH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 213.7 (C, *C*=O), 169.1 (C, O–*C*=O), 153.8 (C, O–*C*=O), 138.1 (C), 135.1 (C), 134.6 (C), 130.7 (CH), 127.6 (CH), 125.1 (CH), 80.1 (C), 77.6 (CH_2), 70.1 (CH, OC*H*(CH$_3$)$_2$), 62.7 (C), 39.1 (CH), 37.9 (CH_2), 32.0 (CH_2), 28.3 (3 x CH_3, OC(*C*H$_3$)$_3$), 21.6 (CH_3, OCH(*C*H$_3$)$_2$), 21.5 (CH_3, OCH(*C*H$_3$)$_2$), 19.5 (CH_2), 18.7 (CH_3); HRMS m/z 471.2103 (M + Na), calcd for $C_{23}H_{32}N_2O_7Na$ 471.2108.



(+)-**163gb**

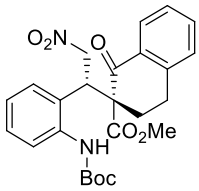
(*R*)-Methyl 1-((*S*)-1-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate (163ac): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as semisolid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u Cellulose-2 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 8.19 min (minor), t_R = 10.12 min (major) [for minor isomer]; t_R = 14.60 min (minor), t_R = 16.13 min (major) [for major isomer]; **$[\alpha]_D^{25}$ = –7.6° (*c* = 0.60 g/100 mL, $CHCl_3$, 94% *ee* for major, 46% *ee* for minor** and **dr = 39:1)**; IR (Neat): ν_{max} 3393 (N-*H*), 2981, 1720 (C=O), 1556 (NO_2), 1450, 1367 (NO_2), 1230, 1154, 1048, 985 and 751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, at 50 °C) δ 7.53 (1H, d, *J* = 8.0 Hz), 7.36 (1H, br d, *J* = 7.6 Hz), 7.28 (1H, dt, *J* = 7.6, 1.6 Hz), 7.16 (1H, br t, *J* = 7.6 Hz), 6.89 (1H, br s, N*H*), 5.20 (1H, dd, *J* = 14.0, 4.0 Hz), 4.98 (1H, dd, *J* = 14.0, 10.0 Hz), 4.42 (1H, dd, *J* = 10.0, 4.0 Hz), 3.78 (3H, s, CO_2CH_3), 2.45-2.36 (2H, m), 2.21-2.12 (1H, m), 2.07-1.98 (1H, m), 1.96-1.90 (2H, m), 1.55 (9H, s, OC(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, at 50 °C) δ 212.9 (C, *C*=O), 170.0 (C, O–*C*=O), 154.0 (C, O–*C*=O), 137.1 (C), 130.2 (C), 128.6



(-)-**163ac**

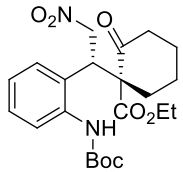
(CH), 127.4 (CH), 127.3 (CH), 125.9 (CH), 80.4 (C), 76.9 (CH_2), 62.9 (C), 53.0 (CH_3, CO_2CH_3), 38.4 (CH), 37.7 (CH_2), 31.5 (CH_2), 28.3 (3 x CH_3, $OC(CH_3)_3$), 19.3 (CH_2); HRMS m/z 429.1632 (M + Na), calcd for $C_{20}H_{26}N_2O_7Na$ 429.1638.

(*R*)-Methyl 2-((*S*)-1-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-nitroethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (163ad): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 21.20 min (major), t_R = 24.11 min (minor) [for major isomer]; t_R = 33.09 min (major), t_R = 38.81 min (minor) [for minor isomer]; **$[\alpha]_D^{25}$ = +100.7° (*c* = 0.33 g/100 mL, $CHCl_3$, 94% *ee* for major, 36% *ee* for minor** and **dr = 12:1)**; IR (Neat): ν_{max} 3370 (N-*H*), 2979, 1724 (C=O), 1555 (NO_2), 1451, 1367 (NO_2), 1233, 1155, 1052, 906 and 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, at 50 °C) δ 8.04 (1H, d, *J* = 7.6 Hz), 7.57 (1H, d, *J* = 8.0 Hz), 7.49-7.43 (2H, m), 7.34-7.29 (1H, m), 7.28-7.24 (1H, m), 7.20-7.14 (3H, m), 5.23 (1H, dd, *J* = 14.4, 4.0 Hz), 4.95 (1H, dd, *J* = 14.4, 10.0 Hz), 4.66 (1H, dd, *J* = 10.0, 4.0 Hz), 3.65 (3H, s, OCH_3), 3.08-3.00 (1H, m), 2.94-2.87 (1H, m), 2.50-2.45 (1H, m), 2.19-2.10 (1H, m), 1.51 (9H, s, $OC(CH_3)_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, at 50 °C) δ 194.4 (C, *C*=O), 170.2 (C, O–*C*=O), 154.0 (C, O–*C*=O), 142.7 (C), 137.3 (C), 134.1 (CH), 131.6 (C), 129.8 (C), 128.6 (CH), 128.5 (CH), 128.4 (2 x CH), 126.9 (CH), 126.8 (CH), 125.4 (CH), 80.3 (C), 77.8 (CH_2), 60.1 (C), 52.8 (CH_3, CO_2CH_3), 39.3 (CH), 30.3 (CH_2), 28.3 (3 x CH_3, $OC(CH_3)_3$), 25.7 (CH_2); HRMS m/z 491.1794 (M + Na), calcd for $C_{25}H_{28}N_2O_7Na$ 491.1795.



(+)-**163ad**

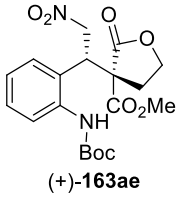
(*R*)-Ethyl 1-((*S*)-1-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-nitroethyl)-2-oxocyclohexanecarboxylate (163ad'): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 0.5 mL/min, λ = 254 nm), t_R = 29.9 min (major), t_R = 36.8 min (minor); **$[\alpha]_D^{25}$ = +42.8° (*c* = 0.30 g/100 mL, $CHCl_3$, >99% *ee* and >99% *de*)**; IR (Neat): ν_{max} 3364 (N-*H*), 2970, 1709 (C=O), 1556 (NO_2), 1463, 1375 (NO_2), 1227, 1156, 1019 and 762 cm^{-1};



(+)-**163ad'**

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (1H, br s), 7.27 (1H, t, *J* = 8.0 Hz), 7.13 (1H, t, *J* = 8.0 Hz), 7.07 (1H, br d, *J* = 7.5 Hz), 6.73 (1H, br s, N*H*), 5.14 (1H, dd, *J* = 14.5, 3.0 Hz), 4.70 (1H, dd, *J* = 14.5, 11.0 Hz), 4.46 (1H, dd, *J* = 11.0, 3.0 Hz), 4.26 (2H, q, *J* = 7.0 Hz, OC*H*$_2$CH$_3$), 2.53-2.50 (1H, m), 2.44-2.38 (1H, m), 2.14 (1H, dd, *J* = 14.0, 2.0 Hz), 2.03-2.01 (1H, m), 1.70-1.68 (1H, m), 1.64-1.57 (2H, m), 1.52 (9H, s, OC(C*H*$_3$)$_3$), 1.42-1.37 (1H, m), 1.28 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.2 (C, *C*=O), 169.7 (C, O–*C*=O), 154.0 (C, O–*C*=O), 137.0 (C), 129.5 (C), 128.5 (CH), 127.4 (CH), 126.9 (CH), 125.6 (CH), 80.4 (C), 77.5 (CH$_2$), 63.0 (C), 62.2 (CH$_2$, O*C*H$_2$CH$_3$), 41.4 (CH$_2$), 39.3 (CH), 35.9 (CH$_2$), 28.3 (3 x CH$_3$, OC(*C*H$_3$)$_3$), 27.9 (CH$_2$), 22.3 (CH$_2$), 14.0 (CH$_3$, OCH$_2$*C*H$_3$); HRMS m/z 452.2397 (M + NH_4^+), calcd for $C_{22}H_{34}N_3O_7$ 452.2397.

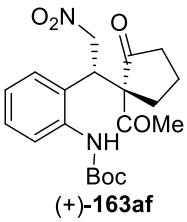
(*S*)-Methyl 3-((*S*)-1-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-nitroethyl)-2-oxotetrahydrofuran-3-carboxylate (163ae): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 153-155 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 220 nm), t_R = 18.6 min (minor), t_R = 20.4 min (major) [for minor isomer], t_R = 25.6 min (major), t_R = 35.9 min (minor) [for major isomer]; **[α]$_D^{25}$ = +23.3° (*c* = 0.17 g/100 mL, CHCl$_3$, >99% *ee* and >99% *de*)**; IR (KBr): ν_{max} 3378 (N-*H*), 2983, 1763 (C=O), 1556 (NO_2), 1450, 1368 (NO_2), 1236, 1157, 1025 and 909 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, at 50 °C) δ 7.53 (1H, d, *J* = 8.0 Hz), 7.37-7.31 (2H, m), 7.21 (1H, t, *J* = 7.6 Hz), 6.85 (1H, br s, N*H*), 5.41 (1H, dd, *J* = 14.4, 4.0 Hz), 5.09 (1H, dd, *J* = 14.4, 10.4 Hz), 4.54 (1H, dd, *J* = 10.4, 4.0 Hz), 4.32-4.29 (2H, m), 3.87 (3H, s, OC*H*$_3$), 2.64-2.58 (1H, m), 2.40-2.33 (1H, m), 1.55 (9H, s, OC(C*H*$_3$)$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, at 50 °C) δ 173.3 (C, O-*C*=O), 168.4 (C, O–*C*=O), 154.2 (C, O–*C*=O), 137.1 (C), 130.3 (C), 129.1 (CH), 128.0 (CH), 127.0 (CH), 126.6 (CH), 80.7 (C), 76.7 (CH$_2$), 66.5 (CH$_2$), 56.9 (C), 53.6 (CH$_3$, CO$_2$*C*H$_3$), 39.1 (CH), 30.9 (CH$_2$), 28.3 (3 x CH$_3$, OC(*C*H$_3$)$_3$); HRMS m/z 426.1877 (M + NH_4), calcd for $C_{19}H_{28}N_3O_8$ 426.1877.



(+)-**163ae**

***tert*-Buty (2-((*S*)-1-((*S*)-1-acetyl-2-oxocyclopentyl)-2-nitroethyl)phenyl)carbamate (163af):** Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by

chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 16.85 min (major), t_R = 39.48 min (minor) [for major isomer]; t_R = 18.25 min (major), t_R = 19.0 min (minor) [for minor isomer]; **$[\alpha]_D^{25}$ = +20.0° (*c* = 0.10 g/100 mL, $CHCl_3$, >99% *ee*, 94% *ee*** and **dr = 8:1)**; IR (Neat): ν_{max} 3376 (N-*H*), 2920, 1704 (C=O), 1556 (*NO_2*), 1453, 1367 (*NO_2*), 1234, 1156, 1024 and 756 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, at 50 °C, major isomer) δ 7.54 (1H, d, *J* = 7.6 Hz), 7.29 (2H, m), 7.18-7.09 (2H, m), 4.83-4.77 (1H, m), 4.66-4.63 (2H, m), 2.62-2.60 (1H, m), 2.31 (3H, s, COC*H*$_3$), 2.26-2.23 (1H, m), 2.18-2.11 (1H, m), 2.01-1.94 (2H, m), 1.84-1.78 (1H, m), 1.55 (9H, s, OC(C*H*$_3$)$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135, at 50 °C, major isomer) δ 215.0 (C, *C*=O), 202.4 (C, *C*=O), 154.0 (C, O–*C*=O), 137.2 (C), 129.3 (C), 128.8 (CH), 127.6 (CH), 127.58 (CH), 125.7 (CH), 80.4 (C), 76.5 (CH_2), 71.7 (C), 38.5 (CH), 38.4 (CH_2), 28.4 (CH_2), 28.3 (3 x CH_3, OC(*C*H$_3$)$_3$), 26.6 (CH_3, COC*H*$_3$), 19.5 (CH_2); HRMS m/z 413.1684 (M + Na), calcd for $C_{20}H_{26}N_2O_6Na$ 413.1689.

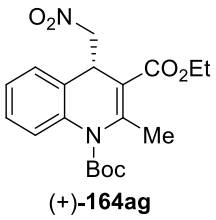


(+)-**163af**

Procedure 4b: General procedure for quinidine-squaramide catalyzed one-pot synthesis of 1,4-dihydroquinolines 164 from (*E*)-2-(2-nitrovinyl)anilines 131 and *β*-keto esters 162: In an ordinary glass vial equipped with a magnetic stirring bar, to the **88n** (5 mol%) in DCM (1.0 mL), were added (*E*)-2-(2-nitrovinyl)anilines **131a-i** (0.3 mmol) and *β*-keto esters **162a-l** (0.4 mmol, 1.33 equiv.). The resulting mixture was stirred at 25 °C until complete consumption of (*E*)-2-(2-nitrovinyl)anilines **131a-i** and added trifluoroacetic acid (3.0 equiv.) at room temperature. After stirring at 25 °C as shown in Table 15, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified using silica gel column chromatography using ethyl acetate and hexane as eluents to afford the desired 1,4-dihydroquinoline compounds **164**.

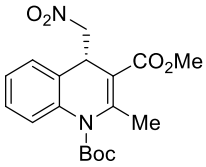
(*S*)-1-*tert*-Butyl 3-ethyl 2-methyl-4-(nitromethyl)quinoline-1,3(4*H*)-dicarboxylate (164ag): Prepared by following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak ID-H column (hexane/2-propanol =

90:10, flow rate 0.8 mL/min, λ = 254 nm), t_R = 6.80 min (minor), t_R = 7.41 min (major); **$[\alpha]_D^{25}$ = +212.1° (*c* = 0.17 g/100 mL, $CHCl_3$, 98% *ee*)**; IR (Neat): ν_{max} 2979, 1716 (C=O), 1587 (NO_2), 1487, 1370 (NO_2), 1232, 1151, 1076 and 917 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70 (1H, d, *J* = 8.0 Hz), 7.34-7.30 (1H, m), 7.24-7.16 (2H, m), 4.72 (1H, dd, *J* = 9.2, 6.0 Hz), 4.46 (1H, dd, *J* = 11.6, 6.0 Hz), 4.35-4.23 (2H, m, OCH_2CH_3), 4.20 (1H, dd, *J* = 11.6, 9.2 Hz), 2.54 (3H, s, CH_3), 1.56 (9H, s, $OC(CH_3)_3$), 1.37 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.5 (C, O–*C*=O), 152.7 (C), 151.5 (C, O–*C*=O), 138.3 (C), 129.9 (C), 127.6 (CH), 127.5 (CH), 126.0 (CH), 124.1 (CH), 117.3 (C), 83.5 (C), 77.6 (CH_2), 61.1 (CH_2, OCH_2CH_3), 38.9 (CH), 28.1 (3 x CH_3, $OC(CH_3)_3$), 21.6 (CH_3), 14.2 (CH_3, OCH_2CH_3); HRMS m/z 399.1529 (M + Na), calcd for $C_{19}H_{24}N_2O_6Na$ 399.1532.



(+)-**164ag**

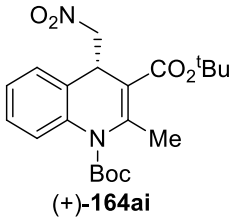
(*S*)-1-*tert*-Butyl 3-methyl-2-methyl-4-(nitromethyl)quinoline-1,3(4*H*)-dicarboxylate (164ah): Prepared by following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 10.60 min (minor), t_R = 12.06 min (major); **$[\alpha]_D^{25}$ = +208.9° (*c* = 0.21 g/100 mL, $CHCl_3$, 98% *ee*)**; IR (Neat): ν_{max} 2930, 1720 (C=O), 1552 (NO_2), 1484, 1369 (NO_2), 1222, 1153, 1078 and 998 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.71 (1H, d, *J* = 8.0 Hz), 7.35-7.33 (1H, m), 7.22-7.19 (2H, m), 4.73 (1H, dd, *J* = 9.2, 6.0 Hz), 4.48 (1H, dd, *J* = 12.0, 6.0 Hz), 4.20 (1H, dd, *J* = 12.0, 9.2 Hz), 3.84 (3H, s, OCH_3), 2.55 (3H, s, CH_3), 1.57 (9H, s, $OC(CH_3)_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.9 (C, O–*C*=O), 153.2 (C), 151.5 (C, O–*C*=O), 138.2 (C), 129.8 (C), 127.6 (CH), 127.5 (CH), 126.0 (CH), 124.1 (CH), 116.9 (C), 83.6 (C), 77.5 (CH_2), 52.0 (OCH_3, $COOCH_3$), 38.9 (CH), 28.1 (3 x CH_3, $OC(CH_3)_3$), 21.7 (CH_3); HRMS m/z 385.1314 (M + Na), calcd for $C_{18}H_{22}N_2O_6Na$ 385.1376.



(+)-**164ah**

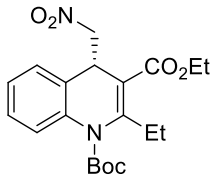
(*S*)-di-*tert*-Butyl 2-methyl-4-(nitromethyl)quinoline-1,3(4*H*)-dicarboxylate (164ai): Prepared by following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 95:5,

flow rate 0.5 mL/min, λ = 254 nm), t_R = 8.28 min (minor), t_R = 10.70 min (major); **$[\alpha]_D^{25}$ = +226.9° (*c* = 0.32 g/100 mL, $CHCl_3$, >99% *ee*)**; IR (Neat): ν_{max} 2979, 1716 (C=O), 1552 (NO_2), 1487, 1370 (NO_2), 1217, 1151, 1076 and 917 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (1H, d, *J* = 8.0 Hz), 7.34-7.29 (1H, m), 7.23-7.16 (2H, m), 4.65 (1H, dd, *J* = 9.2, 6.4 Hz), 4.45 (1H, dd, *J* = 11.6, 6.4 Hz), 4.18 (1H, dd, *J* = 11.6, 9.2 Hz), 2.50 (3H, s, C*H*$_3$), 1.56 (9H, s, OC(C*H*$_3$)$_3$), 1.55 (9H, s, OC(C*H*$_3$)$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 164.8 (C, O–*C*=O), 151.6 (C), 151.3 (C, O–*C*=O), 138.4 (C), 130.1 (C), 127.6 (CH), 127.4 (CH), 125.9 (CH), 124.2 (CH), 118.9 (C), 83.4 (C), 81.9 (C), 77.8 (CH_2), 39.3 (CH), 28.2 (3 x CH_3, OC(*C*H$_3$)$_3$), 28.1 (3 x CH_3, OC(*C*H$_3$)$_3$), 21.5 (CH_3); HRMS m/z 427.1844 (M + Na), calcd for $C_{21}H_{28}N_2O_6Na$ 427.1845.



(+)-**164ai**

(*S*)-1-*tert*-Butyl 3-ethyl-2-ethyl-4-(nitromethyl)quinoline-1,3(4*H*)-dicarboxylate (164aj):

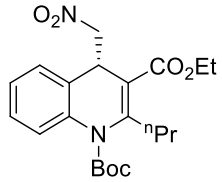


(+)-**164aj**

Prepared by following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 9.32 min (minor), t_R = 11.71 min (major); **$[\alpha]_D^{25}$ = +225.7° (*c* = 0.13 g/100 mL, $CHCl_3$, >99% *ee*)**; IR (Neat): ν_{max} 2978, 1717 (C=O), 1553 (NO_2), 1487, 1369 (NO_2), 1224, 1151, 1080 and 894 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.64 (1H, d, *J* = 8.0 Hz), 7.34-7.29 (1H, m), 7.22-7.16 (2H, m), 4.65 (1H, dd, *J* = 9.6, 6.4 Hz), 4.52 (1H, dd, *J* = 12.0, 6.0 Hz), 4.36-4.24 (2H, m, OC*H*$_2$CH$_3$), 4.18 (1H, dd, *J* = 12.0, 9.6 Hz), 3.34 (1H, sextet, *J* = 7.2 Hz), 2.90 (1H, sextet, *J* = 7.6 Hz), 1.56 (9H, s, OC(C*H*$_3$)$_3$), 1.37 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.09 (3H, t, *J* = 7.6 Hz, CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.5 (C, O–*C*=O), 158.2 (C), 151.7 (C, O–*C*=O), 139.0 (C), 130.7 (C), 127.6 (CH), 127.5 (CH), 126.0 (CH), 124.3 (CH), 118.1 (C), 83.4 (C), 77.5 (CH_2), 61.1 (CH_2, O*C*H$_2$CH$_3$), 39.4 (CH), 28.1 (3 x CH_3, OC(*C*H$_3$)$_3$), 25.7 (CH_2, *C*H$_2$CH$_3$), 14.1 (CH_3, OCH$_2$*C*H$_3$), 12.7 (CH_3, CH$_2$*C*H$_3$); HRMS m/z 413.1681 (M + Na), calcd for $C_{20}H_{26}N_2O_6Na$ 413.1689.

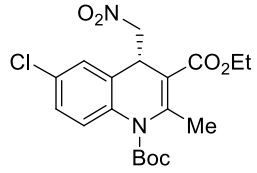
(*S*)-1-*tert*-Butyl 3-ethyl-4-(nitromethyl)-2-propylquinoline-1,3(4*H*)-dicarboxylate (164ak): Prepared by following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by

chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 97:3, flow rate 0.5 mL/min, λ = 254 nm), t_R = 10.79 min (minor), t_R = 13.62 min (major); **$[\alpha]_D^{25}$ = +159.5° (*c* = 0.14 g/100 mL, $CHCl_3$, 97% *ee*)**; IR (Neat): ν_{max} 2964, 1714 (C=O), 1553 (NO_2), 1487, 1369 (NO_2), 1219, 1151, 1078 and 919 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.63 (1H, d, *J* = 8.0 Hz), 7.33-7.28 (1H, m), 7.22-7.16 (2H, m), 4.66 (1H, dd, *J* = 9.6, 6.0 Hz), 4.52 (1H, dd, *J* = 12.0, 6.0 Hz), 4.35-4.24 (2H, m, OCH_2CH_3), 4.18 (1H, dd, *J* = 12.0, 9.6 Hz), 3.38-3.30 (1H, m), 2.89-2.82 (1H, m), 1.55 (9H, s, $OC(CH_3)_3$), 1.37 (3H, t, *J* = 6.8 Hz, OCH_2CH_3), 0.89-0.85 (5H, m, CH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.5 (C, O–*C*=O), 157.1 (C), 151.7 (C, O–*C*=O), 138.8 (C), 130.7 (C), 127.6 (CH), 127.5 (CH), 126.0 (CH), 124.4 (CH), 118.7 (C), 83.4 (C), 77.5 (CH_2), 61.1 (CH_2, OCH_2CH_3), 39.4 (CH), 34.0 (CH_2), 28.1 (3 x CH_3, $OC(CH_3)_3$), 21.9 (CH_2), 14.2 (CH_3, OCH_2CH_3), 13.9 (CH_3, $CH_2CH_2CH_3$); HRMS m/z 427.1842 (M + Na), calcd for $C_{21}H_{28}N_2O_6Na$ 427.1845.



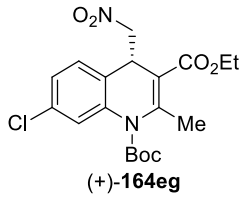
(+)-**164ak**

(*S*)-1-*tert*-Butyl 3-ethyl-6-chloro-2-methyl-4-(nitromethyl)quinoline-1,3(4*H*)-dicarboxylate (164dg): Prepared by following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 9.66 min (minor), t_R = 11.31 min (major); **$[\alpha]_D^{25}$ = +199.2° (*c* = 0.18 g/100 mL, $CHCl_3$, 99% *ee*)**; IR (Neat): ν_{max} 2980, 1717 (C=O), 1552 (NO_2), 1483, 1370 (NO_2), 1232, 1152, 1093 and 987 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.64 (1H, d, *J* = 8.8 Hz), 7.28 (1H, dd, *J* = 8.8, 2.4 Hz), 7.22 (1H, d, *J* = 2.0 Hz), 4.67 (1H, dd, *J* = 9.2, 5.6 Hz), 4.45 (1H, dd, *J* = 12.0, 5.6 Hz), 4.35-4.23 (2H, m, OCH_2CH_3), 4.19 (1H, dd, *J* = 12.0, 9.2 Hz), 2.53 (3H, s, CH_3), 1.56 (9H, s, $OC(CH_3)_3$), 1.36 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.2 (C, O–*C*=O), 152.7 (C), 151.2 (C, O–*C*=O), 136.9 (C), 131.6 (C), 131.4 (C), 127.6 (CH), 127.4 (CH), 125.4 (CH), 116.8 (C), 83.9 (C), 77.2 (CH_2), 61.2 (CH_2, OCH_2CH_3), 38.6 (CH), 28.1 (3 x CH_3, $OC(CH_3)_3$), 21.5 (CH_3), 14.2 (CH_3, OCH_2CH_3); HRMS m/z 433.1141 (M + Na), calcd for $C_{19}H_{23}N_2O_6ClNa$ 433.1143.



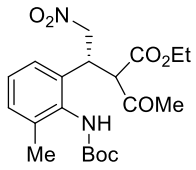
(+)-**164dg**

(*S*)-1-*tert*-Butyl 3-ethyl-7-chloro-2-methyl-4-(nitromethyl)quinoline-1,3(4*H*)-dicarboxylate (164eg): Prepared by following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 9.06 min (minor), t_R = 10.27 min (major); **$[\alpha]_D^{25}$ = +229.8° (*c* = 0.18 g/100 mL, $CHCl_3$, 98% *ee*)**; IR (Neat): ν_{max} 2980, 1717 (C=O), 1553 (NO_2), 1484, 1370 (NO_2), 1238, 1151, 1094 and 921 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.76 (1H, d, *J* = 2.0 Hz), 7.19-7.13 (2H, m), 4.69 (1H, dd, *J* = 9.5, 6.0 Hz), 4.47 (1H, dd, *J* = 12.0, 5.5 Hz), 4.35-4.25 (2H, m, OCH_2CH_3), 4.16 (1H, dd, *J* = 12.0, 9.5 Hz), 2.53 (3H, s, CH_3), 1.58 (9H, s, $OC(CH_3)_3$), 1.37 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.3 (C, O–*C*=O), 152.4 (C), 151.1 (C, O–*C*=O), 139.1 (C), 133.4 (C), 128.5 (CH), 128.1 (C), 126.1 (CH), 124.4 (CH), 117.0 (C), 84.1 (C), 77.4 (CH_2), 61.2 (CH_2, OCH_2CH_3), 38.4 (CH), 28.1 (3 x CH_3, $OC(CH_3)_3$), 21.6 (CH_3), 14.2 (CH_3, OCH_2CH_3); HRMS m/z 433.1136 (M + Na), calcd for $C_{19}H_{23}N_2O_6ClNa$ 433.1143.



(+)-**164eg**

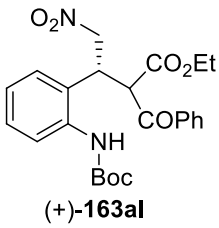
(3*R*)-Ethyl 2-acetyl-3-(2-((*tert*-butoxycarbonyl)amino)-3-methylphenyl)-4-nitrobutanoate (163gg): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 220 nm), t_R = 20.55 min (major), t_R = 27.96 min (minor); t_R = 34.92 min (minor), t_R = 40.41 min (major); **$[\alpha]_D^{25}$ = +4.3° (*c* = 0.19 g/100 mL, $CHCl_3$, 99% *ee*, 94% *ee* and dr = 1:1)**; IR (Neat): ν_{max} 3392 (N-*H*), 2981, 1710 (C=O), 1555 (NO_2), 1489, 1367 (NO_2), 1244, 1159, 1052, 955 and 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, at 50 °C, *dr* = 1.5:1.0) δ 7.18-7.12 (3H, m), 7.06-7.00 (3H, m), 6.22 (2H, br s, N*H*), 4.91-4.87 (3H, m), 4.67-4.60 (2H, m), 4.25 (4H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.17 (1H, br d, *J* = 7.6 Hz), 4.05 (2H, br q, *J* = 7.2 Hz), 2.29 (6H, br s, 2 x CH_3), 2.13 (6H, br s, 2 x CH_3), 1.52 (18H, s, 2 x $OC(CH_3)_3$), 1.30 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.10 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, at 50 °C, *dr* = 1.5:1.0) δ 200.74 (C, *C*=O), 200.67 (C, *C*=O), 167.8 (C, O–*C*=O), 167.5 (C, O–*C*=O), 154.4 (2 x C, O–*C*=O), 137.96 (C), 137.90 (C), 134.2 (2 x



(+)-**163gg**

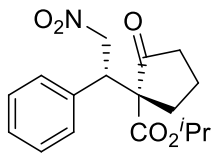
C), 131.9 (C), 131.78 (C), 130.41 (CH), 130.37 (CH), 127.65 (CH), 127.62 (CH), 124.3 (2 x CH), 80.4 (2 x C), 77.1 (CH_2), 76.95 (CH_2), 61.9 (2 x CH), 61.86 (2 x CH_2, O*C*H_2CH_3), 36.3 (2 x CH), 29.6 (2 x CH_3), 28.2 (6 x CH_3, 2 x OC(*C*H_3)$_3$), 18.46 (CH_3), 18.42 (CH_3), 13.89 (CH_3, OCH_2CH_3), 13.68 (CH_3, OCH_2CH_3); HRMS m/z 431.1797 (M + Na), calcd for $C_{20}H_{28}N_2O_7Na$ 431.1795.

(3*R*)-Ethyl 2-benzoyl-3-(2-((*tert*-butoxycarbonyl)amino)phenyl)-4-nitrobutanoate (163al): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm), t_R = 31.90 min (major), t_R = 41.18 min (minor) [for major isomer]; t_R = 45.22 min (major), t_R = 51.52 min (minor) [for minor isomer]; **$[\alpha]_D^{25}$ = +69.2° [*c* = 0.37 g/100 mL, $CHCl_3$, 90% *ee*, 91% *ee*** and **dr = 3.7:1]**; IR (Neat): ν_{max} 3412 (N-*H*), 2980, 1726(C=O), 1554 (NO_2), 1473, 1367 (NO_2), 1230, 1154, 1023, 976 and 729 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, major isomer) δ 8.05 (2H, dd, *J* = 8.0, 0.8 Hz), 7.65-7.54 (2H, m), 7.52-7.48 (2H, m), 7.29-7.25 (1H, m), 7.20-7.17 (1H, m), 7.15-7.09 (1H, m), 6.99 (1H, br s, N*H*), 5.05-4.7 (4H, m), 3.97-3.84 (2H, m, OC*H*$_2$CH$_3$), 1.57 (9H, s, OC(C*H*$_3$)$_3$), 0.92 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 193.5 (C, *C*=O), 167.4 (C, O–*C*=O), 154.2 (C, O–*C*=O), 136.3 (C), 135.8 (C), 134.3 (CH), 130.0 (C), 129.0 (2 x CH), 128.9 (2 x CH), 128.7 (CH), 126.9 (CH), 126.5 (CH), 125.7 (CH), 80.6 (C), 77.3 (CH_2), 62.2 (CH_2, OCH_2CH_3), 56.7 (CH), 35.9 (CH), 28.3 (3 x CH_3, OC(*C*H_3)$_3$), 13.5 (CH_3, OCH_2CH_3); HRMS m/z 479.1796 (M + Na), calcd for $C_{24}H_{28}N_2O_7Na$ 479.1795.



(+)-**163al**

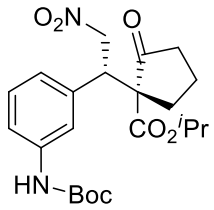
(*R*)-Isopropyl 1-((*S*)-2-nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate (163hb): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as oil. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Lux 5u Cellulose-2 column (hexane/2-propanol = 95:5, flow rate 0.5 mL/min, λ = 220 nm), t_R = 29.91 min (minor), t_R = 39.68 min (major); **$[\alpha]_D^{25}$ = –25.4° (*c* = 0.33 g/100 mL, $CHCl_3$, 98% *ee*)**; IR (Neat): ν_{max} 2975, 1715 (C=O), 1551 (NO_2),



(-)-**163hb**

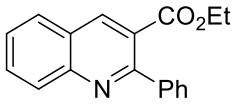
1457, 1375 (NO_2), 1227, 1101, 1036 and 904 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.33-7.26 (5H, m), 5.19 (1H, dd, *J* = 13.5, 4.0 Hz), 5.09-5.00 (2H, m), 4.07 (1H, dd, *J* = 11.0, 4.0 Hz), 2.39-2.33 (2H, m), 2.05-1.87 (4H, m), 1.26 (3H, d, *J* = 6.0 Hz, OCH(CH_3)$_2$), 1.25 (3H, d, *J* = 6.0 Hz, OCH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.3 (C, *C*=O), 168.8 (C, O–*C*=O), 135.5 (C), 129.4 (2 x CH), 128.8 (2 x CH), 128.2 (CH), 76.5 (CH_2), 70.1 (CH, O*C*H(CH_3)$_2$), 62.5 (C), 46.3 (CH), 37.8 (CH_2), 31.4 (CH_2), 21.6 (CH_3, OCH(*C*H_3)$_2$), 21.4 (CH_3, OCH(*C*H_3)$_2$), 19.3 (CH_2); HRMS m/z 342.1319 (M + Na), calcd for $C_{17}H_{21}NO_5Na$ 342.1318.

(*R*)-Isopropyl 1-((*S*)-1-(3-((*tert*-butoxycarbonyl)amino)phenyl)-2-nitroethyl)-2-oxocyclopentanecarboxylate (163ib): Prepared by following the procedure **4a** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 103-105 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 0.8 mL/min, λ = 254 nm), t_R = 10.76 min (minor), t_R = 12.40 min (major); **$[\alpha]_D^{25}$ = –18.5°(*c* = 0.28 g/100 mL, $CHCl_3$, 99% *ee*)**; IR (KBr): ν_{max} 3397 (N-*H*), 2981, 1731 (C=O), 1540 (NO_2), 1441, 1381 (NO_2), 1238, 1156, 1041 and 860 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37 (1H, br d, *J* = 7.5 Hz), 7.25 (1H, s), 7.23 (1H, t, *J* = 8.0 Hz), 6.95 (1H, d, *J* = 7.5 Hz), 6.50 (1H, br s, N*H*), 5.18 (1H, dd, *J* = 13.5, 3.5 Hz), 5.08 (1H, septet, *J* = 6.5 Hz), 5.01 (1H, dd, *J* = 13.5, 11.0 Hz), 4.02 (1H, dd, *J* = 11.0, 3.5 Hz), 2.41-2.36 (2H, m), 2.09 (1H, dd, *J* = 18.5, 9.5 Hz), 2.05-1.97 (1H, m), 1.96-1.92 (1H, m), 1.91-1.82 (1H, m), 1.53 (9H, s, OC(C*H*$_3$)$_3$), 1.27 (3H, d, *J* = 6.5 Hz, OCH(C*H*$_3$)$_2$), 1.26 (3H, d, *J* = 6.5 Hz, OCH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 212.4 (C, *C*=O), 168.8 (C, O–*C*=O), 152.5 (C, O–*C*=O), 138.8 (C), 136.6 (C), 129.4 (CH), 123.7 (CH), 119.4 (CH), 118.2 (CH), 80.7 (C), 76.5 (CH_2), 70.1 (CH, O*C*H(CH_3)$_2$), 62.4 (C), 46.2 (CH), 37.8 (CH_2), 31.5 (CH_2), 28.3 (3 x CH_3, OC(*C*H_3)$_3$), 21.6 (CH_3, OCH(*C*H_3)$_2$), 21.4 (CH_3, OCH(*C*H_3)$_2$), 19.4 (CH_2); HRMS m/z 457.1952 (M + Na), calcd for $C_{22}H_{30}N_2O_7Na$ 457.1951.



(-)-163ib

Ethyl 2-phenylquinoline-3-carboxylate (164al): Prepared by following the procedure **4b** and purified by column chromatography using EtOAc/hexane and isolated as oil. IR (Neat): ν_{max} 2926, 1715 (C=O), 1594, 1485, 1370, 1101, 1036, 767 and 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.68 (1H, s), 8.21 (1H, d, *J* = 8.5 Hz), 7.95 (1H, d, *J* = 8.0 Hz), 7.86-7.82 (1H, m), 7.66-7.61 (3H, m), 7.51-7.46 (3H, m), 4.21 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 1.10 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.0 (C, O-*C*=O), 158.2 (C), 148.4 (C), 140.8 (C), 139.1 (CH), 131.6 (CH), 129.5 (CH), 128.6 (3 x CH), 128.25 (CH), 128.22 (2 x CH), 127.3 (CH), 125.9 (C), 125.5 (C), 61.6 (CH_2, OCH_2CH_3), 13.7 (CH_3, OCH_2CH_3); LRMS m/z 278.15 (M + H+), calcd for $C_{18}H_{15}NO_2$ 277.1103.



164al

8. REFERENCES

1. H. Kuroda, I. Tomita and T. Endo, *Org. Lett.*, 2003, **5**, 129.
2. J. E. Wilson, J. Sun and G. C. Fu, *Angew. Chem. Int. Ed.*, 2010, **49**, 161-163.
3. D. B. Ramachary, C. Venkaiah and P. M. Krishna, *Org. Lett.*, 2013, **15**, 4714-4717.
4. D. B. Ramachary, P. M. Krishna and T. P. Reddy, *Org. Biomol. Chem.*, 2016, **14**, 6413.
5. Y. Xia, Y. Liang, Y. Chen, M. Wang, L. Jiao, F. Huang, S. Liu, Y. Li and Z. -X. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 3470.
6. M. Raghu, J. Grover, and S. S. V. Ramasastry, *Chem. Eur. J.*, 2016, **22**, 18316 -18321.
7. R. Shintani and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 10778-10779.
8. W. Chen, X. -H. Yuan, R. Li, W. Du, Y. Wu, L. -S. Ding and Y. –C. Chena, *Adv. Synth. Catal.*, 2006, **348**, 1818-1822.
9. W. Chen, W. Du, Y. -Z. Duan, Y. Wu, S. -Y. Yang and Y. -C. Chen, *Angew. Chem. Int. Ed.*, 2007, **46**, 7667-7670.
10. R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, J. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard, H. Guo and O. Kwon, *J. Am. Chem. Soc*., 2011, **133**, 13337-13348.
11. R. -Y. Zhu, C. -S. Wang, J. Zheng, F. Shi and S. -J. Tu, *J. Org. Chem.*, 2014, **79**, 9305-9312
12. Z. Li, H. Yu, H. Liu, L. Zhang, H. Jiang, B. Wang and H. Guo, *Chem. Eur. J.*, 2014, **20**, 1731-1736.
13. A. Chan and K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 5335.
14. M. -C. Tong, X. Chen, H. -Y. Tao and C. -J. Wang, *Angew. Chem. Int. Ed.*, 2013, **52**, 12377-12380.
15. G. Zhu, W. Sun, C. Wu, G. Li, L. Hong and R. Wang, *Org. Lett.*, 2013, **15**, 4988-4991.
16. X. Fang, J. Li, H. -Y. Tao and C. -J. Wang, *Org. Lett.*, 2013, **15**, 5554-5557.
17. L. Zu, S. Zhang, H. Xie and W. Wang, *Org. Lett.*, **2009,** 11, 1627–1630.
18. D. B. Ramachary and R. Sakthidevi, *Chem. Eur. J.*, 2009, **15**, 4516-4522.
19. D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.*, 2010, **8**, 4259-4265.

20. D. B. Ramachary, M. S. Prasad and R. Madhavachary, *Org. Biomol. Chem.*, 2011, **9**, 2715-2721.
21. B. -C. Hong, P. Kotame and G. -H. Lee, *Org. Lett.*, 2011, **13**, 5758–5761
22. D. B. Ramachary, R. Sakthidevi and K. S. Shruthi, *Chem. Eur. J.*, 2012, **18**, 8008-8012.
23. X. Zhang, X. Song, H. Li, S. Zhang, X. Chen, X. Yu and W. Wang, *Angew. Chem. Int. Ed.*, 2012, 51, 7282.
24. W. Yang, H. –X. He, Y. Gao and D. –M. Du, *Adv. Synth. Catal.*, 2013, **355**, 3670-3678.
25. D. B. Ramachary, K. S. Shruthi and R. Madhavachary, *Eur. J. Org. Chem.*, 2015, 6413-6418.
26. (a) D. J. Aitken, H. Eijsberg, A. Frongia, J. Ollivier and P. P. Piras, *synthesis* 2014, **46**, 1; (b) S. P. Simeonov, J. P. M. Nunes, K. Guerra, V. B. Kurteva and C. A. M. Afonso, *Chem. Rev*., 2016, **116**, 5744.
27. (a) M. Suzuki, Y. Morita, A. Yanagisawa, B. J. Baker, P. J. Scheuer and R. Noyori, *J. Org. Chem*., 1988, **53**, 286; (b) B. J. Baker and P. J. Scheuer, *J. Nat. Prod*., 1994, **57**, 1346; (c) M. Suzuki, M. Mori, T. Niwa, R. Hirata, K. Furuta, T. Ishikawa and R. Noyori, *J. Am. Chem. Soc*., 1997, **119**, 2376; (d) T. Ishikawa, M. T. Kuo, K. Furuta and M. Suzuki, *Cytotechnology*, 1998, **27**, 81; (e) D. S. Straus and C. K. Glass, *Med. Res. Rev.*, 2001, **21**, 185; (f) S. M. Roberts, M. G. Santorob and E. S. Sickle, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1735; (g) J.-W. d. Kraker, M. C. R. Franssen, M. Joerink, A. d. Groot and H. Bouwmeester, *J. Plant Physiol*., 2002, **129**, 257; (h) C. Kuhn, E. Roulland, J.-C. Madelmont, C. Monneret and J.-C. Florent, *Org. Biomol. Chem*., 2004, **2**, 2028.
28. (a) E. Block and A. Wall, *J. Org. Chem*., 1987, **52**, 809; (b) L. A. Paquette and G. Ladouceur, *J. Org. Chem*., 1989, **54**, 4278; (c) J. W. Herndon, J. Zhu and D. Sampedro, *Tetrahedron*, 2000, **56**, 4985; (d) M. A. Tius, *Acc. Chem. Res*., 2003, **36**, 284; (e) J. P. Eddolls, M. Iqbal, S. M. Roberts and M. G. Santoro, *Tetrahedron*, 2004, **60**, 2539; (f) C. Kuhn, E. Roulland, J.-C. Madelmont, C. Monneret and J.-C. Florent, *Org. Biomol. Chem*., 2004, **2**, 2028; (g) M. Pohmakotr, S. Thamapipol, P. Tuchinda, S. Prabpai, P. Kongsaeree and V. Reutrakul, *J. Org. Chem*., 2007, **72**, 5418; (h) K. Furuta, M. Maeda, Y. Hirata, S. Shibata, K. Kiuchi and M. Suzuki, *Bioorg. Med. Chem. Lett*., 2007, **17**, 5487; (i) N. Shimada, C. Stewart and M. A. Tius, *Tetrahedron*, 2011, **67**, 5851; (j) K. C. Nicolaou, P. Heretsch, A. ElMarrouni, C. R. H. Hale, K. K. Pulukuri, A. K. Kudva,

V. Narayan and K. S. Prabhu, *Angew. Chem., Int. Ed*., 2014, **53**, 10443; (k) K. M. Brummond and D. Chen, *Org. Lett.*, 2008, **10**, 705.

29. L. Zhao, J. Wang, H. Zheng, Y. Li, K. Yang, B. Cheng, X. Jin, X. Yao and H. Zhai, *Org. Lett*., 2014, **16**, 6378.
30. Selected reviews on phosphine catalysis: (a) X. Lu, C. Zhang and Z. Xu, *Acc. Chem. Res*., 2001, **34**, 535; (b) D. H. Valentine and J. H. Hillhouse, *Synthesis*, 2003, 317. (c) J. L. Methot and W. R. Roush, *Adv. Synth. Catal*., 2004, **346**, 1035; (d) X. Lu, Y. Du and C. Lu, *Pure Appl. Chem*., 2005, **77**, 1985; (e) V. Nair, R. S. Menon, A. R. Sreekanth, N. Abhilash and A. T. Biju, *Acc. Chem. Res*., 2006, **39**, 520; (f) L. W. Ye, J. Zhou and Y. Tang, *Chem. Soc. Rev*., 2008, **37**, 1140. (g) L.-G. Meng, P. Cai, Q. Guo and S. Xue, *J. Org. Chem*., 2008, **73**, 8491; (h) V. Sriramurthy and O. Kwon, *Org. Lett*., 2010, **12**, 1084; (i) S. S. Kinderman, J. H. van Maarseveen and H. Hiemstra, *Synlett*, 2011, 1693; (j) Y. Xiao, Z. Sun, H. Guo and O. Kwon, *Beilstein J. Org. Chem*., 2014, **10**, 2089; (k) E. Li, P. Jia, L. Liang and Y. Huang, *ACS Catal*., 2014, **4**, 600. (l) P. Xie and Y. Huang, *Org. Biomol. Chem*., 2015, **13**, 8578; (m) Y. Gu, P. Hu, C. Ni and X. Tong, *J. Am. Chem. Soc*., 2015, **137**, 6400; (n) T. Wang, X. Han, F. Zhong, W. Yao and Y. Lu, *Acc. Chem. Res*., 2016, **49**, 1369.
31. (a) K. Imai, *J. Pharm. Soc. Jpn*., 1956, **76**, 405; (b) C. H. Fawcett, R. D. Firu and D. M. Spencer, *Physiol. Plant. Pathol*., 1971, **1,** 163; (c) C. Chowdhury and N. G. Kundu, *Tetrahedron*, 1999, **55**, 7011; (d) C. A. Quesnelle, P. Gill, M. Dodier, D. St. Laurent, M. Serrano-Wu, A. Marinier, A. Martel, C. E. Mazzucco, T. M. Stickle, J. F. Barret, D. M. Vyas and B. N. Balasubramanian, *Bioorg. Med. Chem. Lett*., 2003, **13**, 519; (e) D. V. Kuklev, A. J. Domb and V. M. Dembitsky, *Phytomedicine*, 2013, **20**, 1145.
32. (a) H. Kuroda, I. Tomita and T. Endo, *Org. Lett*., 2003, **5**, 129; (b) J. E. Wilson, J. Sun and G. C. Fu, *Angew. Chem., Int. Ed*., 2010, **49**, 161; (c) M. Raghu, J. Grover and S. S. V. Ramasastry, *Chem. Eur. J*., 2016, **22**, 18316.
33. (a) Z. Lian and M. Shi, *Eur. J. Org. Chem*., 2012, **2012**, 581; (b) Z. Lian and M. Shi, *Org. Biomol. Chem*., 2012, **10**, 8048; (c) L. Yang, P. Xie, E. Li, X. Li, Y. Huang and R. Chen, *Org. Biomol. Chem*., 2012, **10**, 7628; (d) D. B. Ramachary, C. Venkaiah and P. M. Krishna, *Org. Lett*., 2013, **15**, 4714; (e) L. Liang, E. Li, P. Xie and Y. Huang, *Chem. - Asian J*., 2014, **9**, 1270; (f) L. Liang and Y. Huang, *Org. Lett*., 2016, **18**, 2604; (g) D. B.

Ramachary, P. M. Krishna and T. P. Reddy, *Org. Biomol. Chem*., 2016, **14**, 6413; (h) X. Gao, Z. Li, W. Yang, Y. Liu, W. Chen, C. Zhang, L. Zheng and H. Guo, *Org. Biomol. Chem*., 2017, **15**, 5298.

34. (a) Z. Lian, Q.-Y. Zhao, Y. Wei and M. Shi, *Eur. J. Org. Chem*., 2012, **2012**, 3338; (b) D. B. Ramachary, C. Venkaiah and P. M. Krishna, *Chem. Commun*., 2012, **48**, 2252; (c) Q. Wang, Z. Lian, Q. Xu and M. Shi, *Adv. Synth. Catal*., 2013, **355**, 3344; (d) Y. Liu, T.-R. Kang, Q.-Z. Liu, L.-M. Chen, Y.-C. Wang, J. Liu, Y.-M. Xie, J.-L. Yang and L. He, *Org. Lett*., 2013, **15**, 6090; (e) D. B. Ramachary, C. Venkaiah and R. Madhavachary, *Org. Lett*., 2013, **15**, 3042; (f) Q. Wang, Q. Xu and M. Shi, *Org. Chem. Front*., 2015, **2**, 211; (g) L. Liang, E. Li, X. Dong and Y. Huang, *Org. Lett*., 2015, **17**, 4914.
35. CCDC-1561066 for **136aa** contains the supplementary crystallographic data for this paper.
36. (a) C. Lu and X. Lu, *Org. Lett*., 2002, **4**, 4677; (b) L.-G. Meng, K. Tang, H.-F. Liu, J. Xiao and S. Xue, *Synlett*, 2010, **12**, 905; (c) X. Bugaut and F. Glorius, *Chem. Soc. Rev*., 2012, **41**, 3511.
37. (a) Y. Huang and V. H. Rawal, *J. Am. Chem. Soc*., 2002, **124**, 9662; (b) Y. Xia, Y. Liang, Y. Chen, M. Wang, L. Jiao, F. Huang, S. Liu, Y. Li and Z.-X. Yu, *J. Am. Chem. Soc*., 2007, **129**, 3470; (c) Y. Liang, S. Liu, Y. Xia, Y. Li and Z.-X. Yu, *Chem. Eur. J*., 2008, **14**, 4361; (d) Y. Liang, S. Liu and Z.-X. Yu, *Synlett*, 2009, 905.
38. *a*) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem. Int. Ed*., 2001, **40**, 2004; (*b*) H. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128; (*c*) J. C. Jewett and C. R. Bertozzi, *Chem. Soc. Rev*., 2010, **39**, 1272.
39. (*a*) D. B. Ramachary, K. Ramakumar and V. V. Narayana, *Chem. Eur. J*., 2008, **14**, 9143; (*b*) D. B. Ramachary and A. B. Shashank, *Chem. Eur. J*., 2013, **19**, 13175; (*c*) D. B. Ramachary, A. B. Shashank and S. Karthik, *Angew. Chem. Int. Ed*., 2014, **53**, 10420; (*d*) A. B. Shashank, S. Karthik, R. Madhavachary and D. B. Ramachary, *Chem. Eur. J*., 2014, **20**, 16877; (*e*) D. B. Ramachary, P. M. Krishna, G. Jagjeet and G. S. Reddy, *Chem. Eur. J*., 2015, **21**, 16775; (*f*) P. M. Krishna, D. B. Ramachary and S. Peesapati, *RSC Adv.*, 2015, **5**, 62062.
40. (*a*) M. Belkheira, D. E. Abed, J.-M. Pons and C. Bressy, *Chem. Eur. J*., 2011, **17**, 12917; (*b*) L. J. T. Danence, Y. Gao, M. Li, Y. Huang and J. Wang, *Chem. Eur. J.*, 2011, **17**,

3584; (*c*) L. Wang, S. Peng, L. J. T. Danence, Y. Gao and J. Wang, *Chem. Eur. J.*, 2012, **18**, 6088; (*d*) W. Li, Q. Jia, Z. Du and J. Wang, *Chem. Commun*., 2013, **49**, 10187; (*e*) W. Li and J. Wang, *Angew. Chem. Int. Ed*., 2014, **53**, 14186; (*f*) S. S. V. Ramasastry, *Angew. Chem. Int. Ed*., 2014, **53**, 14310; (*g*) C. G. S. Lima, A. Ali, S. S. van Berkel, B. Westermann and M. W. Paixão, *Chem. Commun*., 2015, **51**, 10784; (*h*) J. John, J. Thomas and W. Dehaen, *Chem. Commun*., 2015, **51**, 10797.

41. (*a*) W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang and Y.-C. Chen, *Angew. Chem., Int. Ed*., 2007, **46**, 7667; (*b*) J. Li, X. Lian, X. Liu, L. Lin and X. Feng, *Chem. -Eur. J*., 2013, **19**, 5134; (*c*) Y. Qian, P. J. Zavalij, W. Hu and M. P Doyle, *Org. Lett*., 2013, **15**, 1564; (*d*) Z. Li, H. Yu, L. H. Liu, L. Zhang, H. Jiang, B. Wang and H. C. Guo, *Chem. -Eur. J*., 2014, **20**, 1731; (*e*) R.-Y. Zhu, C.-S. Wang, J. Zheng, F. Shi and S.-J. Tu, *J. Org.Chem*., 2014, **79**, 9305; (*f*) C. Yin, L. Lin, D. Zhang, J. Feng, X. Liu and X. Feng, *J. Org. Chem*., 2015, **80**, 9691.
42. (*a*) E. M. Kosower, A. E. Radkowsky, A. H. Fairlamb, S. L. Croft and R. A. Nea, *Eur. J. Med. Chem*., 1995, **30**, 659; (*b*) S. Hanessian, G. McNaughton-Smith, H.-G. Lombart and W. D. Lubell, *Tetrahedron*, 1997, **53**, 12789; (*c*) L. Pezdirc, V. Jovanovski, D. Bevk, R. Jakše, S. Pirc, A. Meden, B. Stanovnik and J. Svete, *Tetrahedron*, 2005, **61**, 3977; (*d*) L. Pezdirc, D. Bevk, U. Grošelj, A. Meden, B. Stanovnik and J. Svete, *J. Comb. Chem*., 2007, **9**, 717; (*e*) Y. Sheng, G. Daniel, W. Katharina, L. Bettina, S. Michael and S. Juergen, *Bioorg. Med. Chem*., 2011, **19**, 4669.
43. (*a*) D. Pizzirani, M. Roberti, S. Grimaudo, A. D. Cristina, R. M. Pipitone, M. Tolomeo and M. Recanatini, *J. Med. Chem*., 2009, **52**, 6936; (*b*) D. B. Ramachary, Ch. Venkaiah and P. M. Krishna, *Chem. Commun*., 2012, **48**, 2252.
44. During the preparation of this manuscript, Pengfei Li group reported Et_3N-catalyzed two-component synthesis of spiroindane-1,3-dione-pyrazolidinones with lower reaction rate, selectivity and less substrate scope, see: J. Duan, J. Cheng, Y. Cheng and P. Li, *Asian J. Org. Chem.*, 2016, **5**, 477-480 [DOI: 10.1002/ajoc.201500529].
45. For organocatalytic olefinations, see: (*a*) D. B. Ramachary and Y. V. Reddy, *J. Org. Chem.*, 2010, **75**, 74; (*b*) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.*, 2010, **8**, 2859; (*c*) D. B. Ramachary, Ch. Venkaiah, Y. V. Reddy and M. Kishor, *Org. Biomol. Chem.*, 2009, **7**, 2053; (*d*) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.*, 2008,

6, 4176; (*e*) D. B. Ramachary, Y. V. Reddy and M. Kishor, *Org. Biomol. Chem.*, 2008, **6**, 4188; (*f*) D. B. Ramachary, M. Kishor and Y. V. Reddy, *Eur. J. Org. Chem.*, 2008, 975; (*g*) D. B. Ramachary and M. Kishor, *J. Org. Chem.*, 2007, **72**, 5056; (*h*) D. B. Ramachary and G. Babul Reddy, *Org. Biomol. Chem.*, 2006, **4**, 4463; (*i*) D. B. Ramachary, M. Kishor and G. Babul Reddy, *Org. Biomol. Chem.*, 2006, **4**, 1641; (*j*) D. B. Ramachary and C. F. Barbas III, *Chem. Eur. J.*, 2004, **10**, 5323.

46. CCDC-1465133 for **150ua** contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

47. (a) J. Mease, K. P. Reber, *J. Org. Chem.,* 2016, **81**, 12006; (b) P. D. Brown, A. C. Willis, M. S. Sherburn and A. L. Lawrence, *Org. Lett*., 2012, **14**, 4537; (c) K. Zhao, G. -J. Cheng, H. Yang, H. Shang, X. Zhang, Y. -D. Wu and Y. Tang, *Org. Lett*., 2012, **14**, 4878; (d) Q. Gu and S. -L. You, *Chem. Sci.,* 2011, **2**, 1519; (e) S. Barradas, M. C. Carreno, M. González-López, A. Latorre and A. Urbano, *Org. Lett.,* 2007, **9**, 5019.

48. (a) K. Kishi, S. Takizawa, H. Sasai, *ACS Catal.,* 2018, **8**, 5228; (b) N. J. Green, C, A. Connolly, K. P. W. Rietdijk, G. S. Nichol, F. Duarte and A. L. Lawrence, *Angew. Chem. Int. Ed*., 2018, **57**, 6198; (c) C. Martín-Santos, C. Jarava-Barrera, S. del Pozo, A. Parra, S. Díaz-Tendero, R. Mas-Ballesté, S. Cabrera and J. Aleman, *Angew. Chem. Int. Ed*., 2014, **53**, 8184; (d) P. H. Bos, M. T. Antalek, J. A. Jr. Porco, C. R. J. Stephenson, *J. Am. Chem. Soc.,* 2013, **135**, 17978; (e) M. C. Carreno and M. Ribagorda, *Org. Lett.,* 2003, **5**, 2425.

49. (a) W. Yao, X. Dou, S. Wen, J. Wu, J. J. Vittal and Y. Lu, *Nat. Commun*., 2016, 7, 13024, doi: 10.1038/ncomms13024; (b) S. Takizawa, K. Kishi, Y. Yoshida, S. Mader, F. A. Arteaga, S. Lee, M. Hoshino, M. Rueping, M. Fujita and H. Sasai, *Angew. Chem. Int. Ed.,* 2015, **54**, 15511; (c) J. Zhao, J. Liu, X. Xie, S. Li and Y. Liu, *Org. Lett*., 2015, **17**, 5926; (d) M. T. Corbett and J. S. Johnson, *Chem. Sci.,* 2013, **4**, 2828; (e) W. Wu, X. Li, H. Huang, X. Yuan, J. Lu, K. Zhu and J. Ye, *Angew. Chem. Int. Ed.,* 2013, **52**, 1743; (f) J. Zhang, J. Wu, Z. Yin, H. Zeng, K. Khanna, C. Hu and S. Zheng, *Org. Biomol. Chem.,* 2013, **11**, 2939; (g) D. M. Rubush, M. A. Morges, B. J. Rose, D. H. Thamm, T. Rovis, *J. Am. Chem. Soc.,* 2012, **134**, 13554; (h) Q. Gu and S. -L. You, *Org. Lett.,* 2011, **13**, 5192; (i) Q. Gu, Z. -Q. Rong, C. Zheng and S. -L. You, *J. Am. Chem. Soc.,*

2010, **132**, 4056; (j) Y. Hayashi, H. Gotoh, T. Tamura, H. Yamaguchi, R. Masui and M. Shoj, *J. Am. Chem. Soc.,* 2005, **127**, 16028.

50. (a) R. R. Reddy, S. S. Gudup and P. Ghorai, *Angew. Chem. Int. Ed.,* 2016, **55**, 15115; (b) N. T. Vo, R. D. M. Pace, F. O'Har, M. J. Gaunt, *J. Am. Chem. Soc.,* 2008, **130**, 404; (c) M. C. Carreño, M. González-López, A. Urbano, *Angew. Chem. Int. Ed.,* 2006, **45**, 2737.
51. For examples of [3+3]-cycloadditions with azomethine imine, see: (a) X. -X. Sun, C. Li, Y. –Y. He, Z. –Q. Zhu, G. –J. Mei and F. Shi, *Adv. Synth. Catal.,* 2017, **359**, 2660; (b) L. Liang and Y. Huang, *Org. Lett.,* 2016, **18,** 2604; (c) W. –L. Yang, C. –Y. Li, W. –J. Qin, F. –F. Tang, X. Yu and W. –P. Deng, *ACS Catal*., 2016, **6**, 5685; (d) X. –X. Sun, H. –H. Zhang, G. –H. Li, Y. –Y. He and F. Shi, *Chem. Eur. J.,* 2016, **22**, 17526; (e) C. –S. Wang, R. –Y. Zhu, Y. –C. Zhang and F. Shi, *Chem. Commun.,* 2015, **51**, 11798; (f) C. Yuan, H. Liu, Z. Gao, L. Zhou, Y. Feng, Y. Xiao and H. Guo, *Org. Lett.,* 2015, **17**, 26. (g) L. Zhang, H. Liu, G. Qiao, Z. Hou, Y. Liu, Y. Xiao and H. Guo, *J. Am. Chem. Soc.,* 2015, **137**, 4316; (h) W. Dai, H. Lu, X. Li, F. Shi and S. –J. Tu, *Chem. Eur. J.,* 2014, **20**, 11382; (i) F. Shi, R. –Y. Zhu, W. Dai, C. –S Wang and S. –J. Tu, *Chem. Eur. J.*, 2014, **20**, 2597; (j) J. Du, X. Xu, Y. Li, L. Pan and Q. Liu, *Org. Lett.,* 2014, **16**, 4004; (k) H. Guo, H. Liu, F. –L. Zhu, R. Na, H. Jiang, Y. Wu, L. Zhang, Z. Li, H. Yu, B. Wang, Y. Xiao, X. –P. Hu and M. Wang, *Angew. Chem. Int. Ed.,* 2013, **52**, 12641; (l) M. –C. Tong, X. Chen, H. –Y. Tao and C. –J. Wang, *Angew. Chem. Int. Ed.,* 2013, **52**, 12377; (m) G. Zhu, W. Sun, C. Wu, G. Li, L. Hong and R. Wang, *Org. Lett.,* 2013, **15**, 4988.
52. a) S. F. McCann, G. D. Annis, R. Shapiro, D. W. Piotrowski, G. P. Lahm, J. K. Long, K. C. Lee, M. M. Hughes, B. J. Myers, S. M. Griswold, B. M. Reeves, R. W. March, P. L. Sharpe, P. Lowder, W. E. Barnette and K. D. Wing, *Pest. Manag. Sci.,* 2001, 57, 153; (b) D. Xu, X. Cai and S. Gong, *Curr. Bioact. Compd.,* 2018, 14, 9.
53. CCDC-1861916 (**156aa**) and CCDC-1861917 (**158ah**) contains the supplementary crystallographic data for this paper.
54. For selected reviews on asymmetric organocatalytic sequential one-pot reactions, see: (a) D. Enders, C. Grondal and M. R. M. Huettl, *Angew. Chem. Int. Ed.*, 2007, **46**, 1570-1581; (b) A. Erkkilä, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416-5470; (c) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178-2189; (d) B. Westermann, M. Ayaz and S. S. van Berkel, *Angew. Chem. Int. Ed.*, 2010, **49**, 846-849;

(e) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167-178; (f) D. B. Ramachary and S. Jain, *Org. Biomol. Chem.*, 2011, **9**, 1277-1300; (g) M. Rueping, J. Dufour and F. R. Schoepke, *Green Chem.*, 2011, **13**, 1084-1105; (h) D. B. Ramachary and Y. V. Reddy, *Eur. J. Org. Chem.*, 2012, 865-887; (i) J. Yu, F. Shi and L. –Z. Gong, *Acc. Chem. Res.*, 2011, **44**, 1156-1171; For selected papers on asymmetric organocatalytic sequential one-pot reactions, see: (j) N. S. Chowdari, D. B. Ramachary and C. F. Barbas III, *Org. Lett.*, 2003, **5**, 1685-1688; (k) D. B. Ramachary and C. F. Barbas III, *Chem. Eur. J.*, 2004, **10**, 5323-5331; (l) J. W. Yang, M. T. Hechavarria Fonseca and B. List, *J. Am. Chem. Soc.*, 2005, **127**, 15036-15037; (m) Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 15051-15053; (n) M. Marigo, S. Bertelsen, A. Landa and K. A. Jorgensen, *J. Am. Chem. Soc.*, 2006, **128**, 5475-5479; (o) D. Enders, M. R. M. Huettl, C. Grondal and G. Raabe, *Nature* 2006, **441**, 861-863; (p) W. Wang, H. Li, J. Wang and L. Zu, *J. Am. Chem. Soc.*, 2006, **128**, 10354-10355; (q) M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem. Int. Ed.*, 2006, **45**, 3683-3686; (r) J. Wang, H. Li, H. Xie, L. Zu, X. Shen and W. Wang, *Angew. Chem. Int. Ed.*, 2007, **46**, 9050-9053; (s) A. Carlone, S. Cabrera, M. Marigo and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2007, **46**, 1101-1104; (t) J. Zhou and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 7498-7499; (u) O. Penon, A. Carlone, A. Mazzanti, M. Locatelli, L. Sambri, G. Bartoli and P. Melchiorre, *Chem. Eur. J.*, 2008, **14**, 4788-4791; (v) D. Enders, C. Wang and J. W. Bats, *Angew. Chem. Int. Ed.*, 2008, **47**, 7539-7542; (w) D. Zhu, M. Lu, P. J. Chua, B. Tan, F. Wang, X. Yang and G. Zhong, *Org. Lett.*, 2008, **10**, 4585-4588; (x) H. Ishikawa, T. Suzuki and Y. Hayashi, *Angew. Chem. Int. Ed.*, 2009, **48**, 1304-1307; (y) M. Rueping, A. Kuenkel, F. Tato and J. W. Bats, *Angew. Chem. Int. Ed.*, 2009, **48**, 3699-3702; (z) R. Imashiro, H. Uehara and C. F. Barbas III, *Org. Lett.*, 2010, **12**, 5250-5253; (aa) K. Jiang, Z. –J. Jia, L. Wu and Y. –C. Chen, *Org. Lett.*, 2010, **12**, 2766-2769; (ab) H. Ishikawa, M. Honma and Y. Hayashi, *Angew. Chem. Int. Ed.*, 2011, **50**, 2824-2827.

55. (*a*) C. Min, X. Han, Z. Liao, X. Wu, H.-B. Zhou and C. Dong, *Adv. Synth. Catal*., 2011, **353**, 2715; (*b*) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed*., 2008, **47**, 4638; (*c*) D. W. C. MacMillan, *Nature*, 2008, **455**, 304; (*d*) C. F. Nising and S. Bräse, *Chem. Soc. Rev*., 2008, **37**, 1218; (*e*) S. S. Mossé and A. Alexakis, *Chem. Commun*., 2007, 3123; (*f*)

D. Almaşi, D. A. Alonso and C. Nájera, *Tetrahedron: Asymmetry*, 2007, **18**, 299; (*g*) S. B. Tsogoeva, *Eur. J. Org. Chem*., 2007, 1701; (*h*) B. List and J. W. Yang, *Science*, 2006, **313**, 1584; (*i*) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri and M. Petrini, *Chem. Rev*., 2005, **105**, 933; (*j*) L.-W. Xu and C.-G. Xia, *Eur. J. Org. Chem*., 2005, 633; (*k*) W. Notz, F. Tanaka and C. F. Barbas III, *Acc. Chem. Res*., 2004, **37**, 580; (*l*) J. Christoffers and A. Baro, *Angew. Chem., Int. Ed*., 2003, **42**, 1688; (*m*) O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem*., 2002, 1877.

56. (*a*) Z. Dong, X. Jin, P. C. Wang, C. Min, J. Zhang, Z. Chen, H.-B. Zhou and C. Dong, *ARKIVOC*, 2011, **9**, 367; (*b*) R. Manzano, J. M. Andrés, M. D. Muruzábal and R. Pedrosa, *Adv. Synth. Catal*., 2010, **352**, 3364; (*c*) S. Ban, D.-M. Du, H. Liu and W. Yang, *Eur. J. Org. Chem*., 2010, 5160; (*d*) T. Tsubogo, Y. Yamashita and S. Kobayashi, *Angew. Chem. Int. Ed*., 2009, **48**, 9117; (*e*) B. Tan, X. Zhang, P. J. Chua and G. F. Zhong, *Chem. Commun*., 2009, 779; (*f*) W.-M. Zhou, H. Liu and D.-M. Du, *Org. Lett*., 2008, **10**, 2817; (*g*) P. Gao, C. Wang, Y. Wu, Z. Zhou and C. Tang, *Eur. J. Org. Chem*., 2008, 4563; (*h*) N. Mase, K. Watanabe, H. Yoda, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc*., 2006, **128**, 4966; (*i*) W. Wang, J. Wang and H. Li, *Angew. Chem., Int. Ed*., 2005, **44**, 1369; (*j*) C. Czekelius and E. M. Carreira, *Angew. Chem., Int. Ed*., 2005, **44**, 612; (*k*) N. Mase, R. Thayumanavan, F. Tanaka and C. F. Barbas III, *Org. Lett*., 2004, **6**, 2527; (*l*) T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc*., 2003, **125**, 12672.

57. (*a*) T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc*., 2005, **127**, 119; (*b*) T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc*., 2003, **125**, 12672.

58. (*a*) K. S. Yang, A. E. Nibbs, Y. E. Turkmen and V. H. Rawal, *J. Am. Chem. Soc*., 2013, **135**, 16050; (*b*) Y. Zhu, J. P. Malerich and V. H. Rawal, *Angew. Chem., Int. Ed*., 2010, **49**, 153; (*c*) Y. Qian, G. Ma, A. Lv, H.-L. Zhu, J. Zhao and V. H. Rawal, *Chem. Commun*., 2010, **46**, 3004; (*d*) H. Konishi, T. Y. Lam, J. P. Malerich and V. H. Rawal, *Org. Lett*., 2010, **12**, 2028; (*e*) J. P. Malerich, K. Hagihara and V. H. Rawal, *J. Am. Chem. Soc*., 2008, **130**, 14416.

59. (*a*) H. Y. Bae and C. E. Song, *ACS Catal*., 2015, **5**, 3613; (*b*) P. Chauhan, S. Mahajan, U. Kaya, D. Hack and D. Enders, *Adv. Synth. Catal*., 2015, **357**, 253; (*c*) D.-F. Chen, F. Zhao, Y. Hu and L.-Z. Gong, *Angew. Chem., Int. Ed*., 2014, **53**, 10763; (*d*) Ł. Albrecht,

G. Dickmeiss, F. C. Acosta, C. R. Escrich, R. L. Davis and K. A. Jørgensen, *J. Am. Chem. Soc*., 2012, **134**, 2543; (*e*) R. I. Storer, C. Aciro and L. H. Jones, *Chem. Soc. Rev*., 2011, **40**, 2330; (*f*) H.-L. Song, K. Yuan and X.-Y. Wu, *Chem. Commun*., 2011, **47**, 1012; (*g*) H. Y. Bae, S. Some, J. H. Lee, J.-Y. Kim, M. J. Song, S. Lee, Y. J. Zhang and C. E. Song, *Adv. Synth. Catal*., 2011, **353**, 3196; (*h*) J. Alemn, A. Parra, H. Jiang and K. A. Jørgensen, *Chem. Eur. J*., 2011, **17**, 6890; (*i*) H. Jiang, M. W. Paixão, D. Monge and K. A. Jørgensen, *J. Am. Chem. Soc*., 2010, **132**, 2775; (*j*) L. Dai, S.-X. Wang and F.-E. Chen, *Adv. Synth. Catal*., 2010, **352**, 2137; (*k*) J. W. Lee, T. H. Ryu, J. S. Oh, H. Y. Bae, H. B. Jang and C. E. Song, *Chem. Commun*., 2009, 7224.

60. For selected examples of organocatalytic asymmetric syntheses of chromans and 3,4-dihydrocoumarins, see: (a) P. Kotame, B. –C. Hong and J. –H. Liao, *Tetrahedron Lett.*, 2009, **50**, 704-707; (b) L. Zu, S. Zhang, H. Xie and W. Wang, *Org. Lett.*, 2009, **11**, 1627-1630; (c) A. E. Nibbs, A. –L. Baize, R. M. Herter and K. A. Scheidt, *Org. Lett.*, 2009, **11**, 4010-4013; (d) H. Lv, L. You and S. Ye, *Adv. Synth. Catal.*, 2009, **351**, 2822-2826; (e) D. B. Ramachary and R. Sakthidevi, *Chem. Eur. J.*, 2009, **15**, 4516-4522; (f) B. –C. Hong, P. Kotame, C. –W. Tsai and J. –H. Liao, *Org. Lett.*, 2010, **12**, 776-779; (g) J. –L. Li, S. –L. Zhou, B. Han, L. Wu and Y. –C. Chen, *Chem. Commun.*, 2010, **46**, 2665-2667; (h) K. –S. Choi and S. –G. Kim, *Tetrahedron Lett.*, 2010, **51**, 5203-5206; (i) X. –F. Wang, Q. –L. Hua, Y. Cheng, A. –L. An, Q. –Q. Yang, J. –R. Chen and W. –J. Xiao, *Angew. Chem. Int. Ed.*, 2010, **49**, 8379-8383; (j) D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.*, 2010, **8**, 4259-4265; (k) D. Enders, C. Wang, X. Yang and G. Raabe, *Adv. Synth. Catal.*, 2010, **352**, 2869-2874; (l) D. Lu, Y. Li and Y. Gong, *J. Org. Chem.*, 2010, **75**, 6900-6907; (m) B. –C. Hong, P. Kotame and J. –H. Liao, *Org. Biomol. Chem.*, 2011, **9**, 382-386; (n) D. B. Ramachary, M. S. Prasad and R. Madhavachary, *Org. Biomol. Chem.*, 2011, **9**, 2715-2721; (o) Q. –L. Hua, C. Li, X. –F. Wang, L. –Q. Lu and J. –R. Chen, *ACS Catal.*, 2011, **1**, 221-226; (p) D. Enders, X. Yang, C. Wang, G. Raabe and J. Runsik, *Chem. Asian. J.*, 2011, **6**, 2255-2259; (q) B. –C. Hong, P. Kotame and G. –H. Lee, *Org. Lett.*, 2011, **13**, 5758-5761.

61. (*a*) J. D. Shields, D. T. Ahneman, T. J. A. Graham and A. G. Doyle, *Org. Lett*., 2014, **16**, 142; (*b*) C. Luo and Y. Huang, *J. Am. Chem. Soc*., 2013, **135**, 8193; (*c*) W. Yang, H.-X. He, Y. Gao and D.-M. Du, *Adv. Synth. Catal*., 2013, **355**, 3670; (*d*) S. N. Mistry, C.

Valant, P. M. Sexton, B. Capuano, A. Christopoulos and P. J. Scammells, *J. Med. Chem*., 2013, **56**, 5151; (*e*) V. Sridharan, P. A. Suryavanshi and J. C Menéndez, *Chem. Rev.*, 2011, **111**, 7157; (*f*) S. Heeb, M. P. Fletcher, S. R. Chhabra, S. P. Diggle, P. Williams and M. Cámara, *FEMS Microbiol Rev*, 2011, **35**, 247; (*g*) J. Fotie, M. Kaiser, D. A. Delfin, J. Manley, C. S. Reid, J.-M. Paris, T. Wenzler, L. Maes, K. V. Mahasenan, C. Li and K. A. Werbovetz, *J. Med. Chem*., 2010, **53**, 966; (*h*) X. Liu and Y. Lu, *Org. Biomol. Chem*., 2010, **8**, 4063; (*i*) L. Foucout, F. Gourand, M. Dhilly, P. Bohn, G. Dupas, J. Costentin, A. Abbas, F. Marsais, L. Barré and V. Levacher, *Org. Biomol. Chem*., 2009, **7**, 3666; (*j*) J. P. Michael, *Nat. Prod. Rep*., 2008, **25**, 166.

62. For selected synthesis of chiral 1,4-dihydroquinolines, see: (*a*) X. Zhang, X. Song, H. Li, S. Zhang, X. Chen, X. Yu and W. Wang, *Angew. Chem., Int. Ed*., 2012, **51**, 7282; (*b*) F. Rezgui, P. Mangeney and A. Alexakis, *Tetrahedron Lett*., 1999, **40**, 6241; (*c*) X. Liu and Y. Lu, *Org. Lett.*, 2010, **12**, 5592.
63. (*a*) D. B. Ramachary, K. S. Shruthi and R. Madhavachary, *Eur. J. Org. Chem*., 2015, 6413; (*b*) Y. Lee and S.-G. Kim, *J. Org. Chem*., 2014, **79**, 8234.
64. During the preparation of this manuscript, Kim group reported asymmetric synthesis of 1,4-dihydroquinolines with lower selectivity (<90% *ee*) and more catalyst loading, see: H. Kim and S.-G. Kim, *Tetrahedron Lett*., 2015, **56**, 4819.
65. CCDC-1432348 for (+)-**163ae** contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or mailto:deposit@ccdc.cam.ac.uk. See supporting information for crystal structure.
66. For organocatalytic high-yielding synthesis of racemic products **163** and **164** from **131** and **162** through [Q + QD]-catalysis followed by TFA, see Table **16** and **17.** We have also done racemic products **163** synthesis from **131** and **162** through DBU or DABCO-catalysis, but reaction conversions are very low even after 24 h at 25 °C.
67. (a) S. R.Gagne, C. Curutchet, F. Grenier and G. D. Scholes, *Tetrahedron.*, 2010, **66**, 4230-4242; b) A. Zanka, *Organic Process Research & Development*., 1998, **2**, 60-62; c) H. Liu, G. Dou and D. Shi, *J. Comb. Chem.*, 2010, **12**, 292-294.

68. C. Yin, L. Lin, D. Zhang, J. Feng, X. Liu and X. Feng, *J. Org. Chem*., 2015, **80**, 9691.

69. C.-J. Lee, C.-N. Sheu, C.-C. Tsai, Z.-Z. Wu and W. Lin, *Chem. Commun*., 2014, **50**, 5304.

70. (a) M. C. Carreno, M. Gonzalez-Lopez and A. Urbano, *Angew. Chem. Int. Ed*., 2006, **45**, 2737–2741; b) M. Novak and S. A. Glover, *J. Am. Chem. Soc.* 2004, **126**, 7748-7749; c) J. Zhao, J. Liu, X. Xie, S. Li and Y. Liu, *Org. Lett.*, 2015, **17**, 5926-5929.

71. (a) J. B. Grimm, K. J. Wilson and D. J. Witter, *J. Org. Chem.*, 2009, **74**, 6390-6393; b) S. E. Winterton, J. M. Ready, *Org. Lett.*, 2016, **18**, 2608-2611.

72. For the synthesis of substituted 2-(2-nitrovinyl)anilines **131a-j**, see: Y. Lee and S. -G. Kim, *J. Org. Chem.*, 2014, **79**, 8234-8243.

ABOUT THE AUTHOR

The author, **Mr. T. Prabhakar Reddy** was born on 5th February 1989 in Parkal, Telangana. After his initial schooling in Narsakkapally, he obtained his B.Sc. degree in 2010 from Chaitanya Degree College Autonomous, Hanamkonda and he obtained his M.Sc. degree with Drugs and Pharmaceuticals specialization in 2012 from Jawaharlal Nehru Technological University, Hyderabad. He continued as a research scholar in the School of Chemistry, University of Hyderabad for the Ph.D. programme from July 2014 onwards.

LIST OF PUBLICATIONS

1. **T. Prabhakar Reddy**, A. V. Krishna and D. B. Ramachary, "Catalytic [3+3]-Cycloaddition for Regioselective Preparation of Tricyclic Oxadiazines" *Org. Lett.*, **2018**, *20*, 6979−6983. *Most accessed article in November 2018.*

2. J. Gujral, **T. Prabhakar Reddy**, B. Gorachand, and D. B. Ramachary, "An Aldehyde-Azomethine Imine [3+2]-Cycloaddition: High-Yielding Regioselective Synthesis of Substituted *N*,*N*-Bicyclic Pyrazolidinones", *Chemistry Select* **2018**, *3*, 7900–7905.

3. D. B. Ramachary, **T. Prabhakar Reddy** and A. S. Kumar, "Organocatalytic Umpolung Annulative Dimerization of Ynones for the Synthesis of 5-Alkylidene-2-cyclopentenones", *Org. Biomol. Chem.*, **2017**, *15*, 9785–9789.
   Featured as a Hot Article in the Organic and Biomolecular Chemistry.

4. D. B. Ramachary, P. M. Krishna and **T. Prabhakar Reddy**, **"**Stereoselective synthesis of cyclopentanone-fused benzosultams through Tomita zipper cyclization", *Org. Biomol. Chem.*, **2016**, *14*, 6413–6416.

5. D. B. Ramachary, **T. Prabhakar Reddy** and A. S. Kumar, "Organocatalytic Azomethine Imine-olefin Click Reaction: High-yielding Stereoselective Synthesis of Spiroindane-1,3-dione-pyrazolidinones", *Org. Biomol. Chem.*, **2016**, *14*, 6517–6522.,
   Featured as a Hot Article in the Organic and Biomolecular Chemistry.

6. A. S. Kumar, **T. Prabhakar Reddy**, R. Madhavachary and D. B. Ramachary, "Rawal's Catalyst as an Effective Stimulant for the Highly Asymmetric Michael Addition of *β*-Keto esters to Functionally Rich Nitro-olefins", *Org. Biomol. Chem.*, **2016**, *14*, 5494–5499. *Highlighted as new talent in Organic and Biomolecular Chemistry themed issue.*

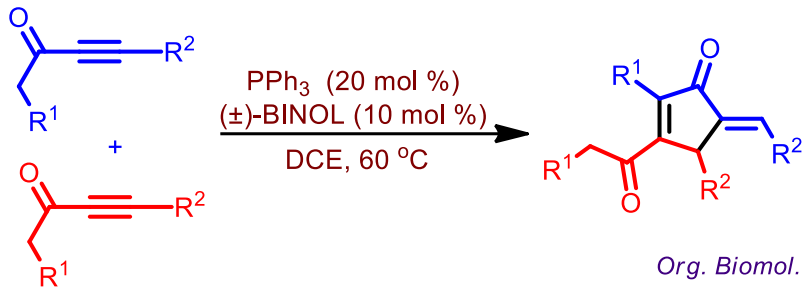
7. A. V. Krishna, **T. Prabhakar Reddy** and D. B. Ramachary, "Development of Organocatalytic Stereoselective Double Aza-Michael Reaction". [Manuscript under preparation]

8. **T. Prabhakar Reddy**, J. Gujral and D. B. Ramachary "DBU as an Effective Nucleophile in [4+2]-Cycloaddition for the Synthesis of Heterocyclic Compounds" [To be communicate]

Poster and Oral Presentations

1. **Poster Presentation:** 6th INDIGO Research Conference" (Indian- German graduate school advanced organic synthesis for a sustainable future), November 2018, Hyderabad, India.
2. **Oral Presentation**: "CHEM-FEST 2018", School of Chemistry, Hyderabad, India. Organizer: University of Hyderabad, INDIA
3. **Poster Presentation**: "CHEM-FEST 2018", School of Chemistry, Hyderabad, India. Organizer: University of Hyderabad, INDIA
4. **Oral Presentation:** "13th J-National Organic Symposium Trust (J-NOST) Conference, Banaras Hindu University, Varanasi, India. Organizer: NOST
5. **Poster Presentation:** "CHEM-FEST 2017", School of Chemistry, Hyderabad, India. Organizer: University of Hyderabad, INDIA
6. **Participation**: 1st Indo-Taiwan Symposium on "Recent Trends in Chemical Sciences", November 2014, University of Hyderabad, INDIA. Organizer: Academica Sinica, Taiwan and School of Chemistry, University of Hyderabad.
7. **Participation:** National Seminor on Recent Advances in Hetero-cyclic Chemistry on 4th & 5th of Nov, 2011 at JNTU Hyderabad; Organizer: NSRAHC.

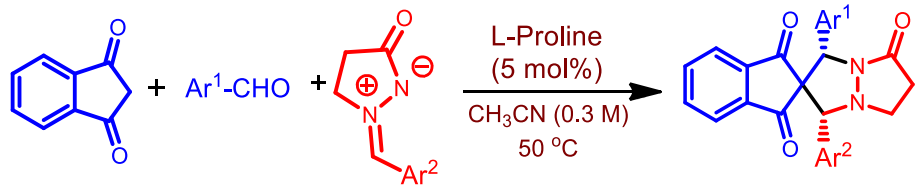
1. **Organocatalytic azomethine imine-olefin click reaction: high-yielding stereoselective synthesis of spiroindane-1,3-dione-pyrazolidinones.**



Examples: **11**
Yields: up to **90%**
Selectivity: up to **>99%**

Org. Biomol. Chem., **2017**, *15*, 9785-9789

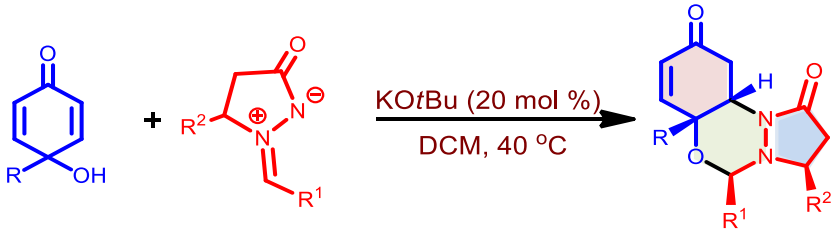
2. **Organocatalytic azomethine imine-olefin click reaction: high-yielding stereoselective synthesis of spiroindane-1,3-dione-pyrazolidinones.**



Examples: **31**
Yields: up to **89%**
dr: up to **>99:1**

Org. Biomol. Chem., **2016**, *14*, 6517-6522

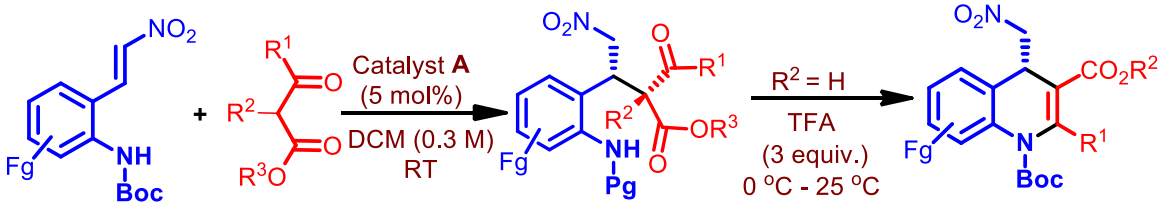
3. **Catalytic [3+3]-cycloaddition for regioselective preparation of tricyclic oxadiazines.**

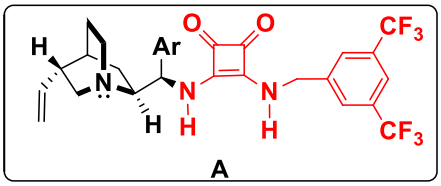


Examples: **37**
Yields up to: **87%**
dr: up to **99:1**

Org. Lett., **2018**, *20*, 6979-6983.

4. **Rawal's catalyst as an effective stimulant for the highly asymmetric Michael addition of *β*-keto esters to functionally rich nitro-olefins.**





Examples: **9**
Yields: up to **90%**
ee: up to **>99%**
de: up to **>99%**

Examples: **7**
Yields: up to **72%**
ee: up to **99%**

Org. Biomol. Chem., **2016**, *14*, 5494-5499.

Development of Organocatalytic [3+2]- and [3+3] -Cycloadditions and Michael Reactions

by Thipparthi Prabhakar Reddy

Development of Organocatalytic [3+2]- and [3+3] - Cycloadditions and Michael Reactions

ORIGINALITY REPORT

58%	5%	59%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Suresh Kumar, A., T. Prabhakar Reddy, R. Madhavachary, and Dhevalapally B. Ramachary. "Rawal's catalyst as an effective stimulant for the highly asymmetric Michael addition of β-keto esters to functionally rich nitro-olefins", Organic & Biomolecular Chemistry, 2016. Publication	15%
2	T. Prabhakar Reddy, A. Vamshi Krishna, Dhevalapally B. Ramachary. "Catalytic [3 + 3]-Cycloaddition for Regioselective Preparation of Tricyclic Oxadiazines", Organic Letters, 2018 Publication	15%
3	Ramachary, Dhevalapally B., T. Prabhakar Reddy, and A. Suresh Kumar. "Organocatalytic azomethine imine-olefin click reaction: high-yielding stereoselective synthesis of spiroindane-1,3-dione-pyrazolidinones", Organic & Biomolecular Chemistry, 2016. Publication	12%

4	Dhevalapally B. Ramachary, T. Prabhakar Reddy, A. Suresh Kumar. "Organocatalytic umpolung annulative dimerization of ynones for the synthesis of 5-alkylidene-2-cyclopentenones", Organic & Biomolecular Chemistry, 2017 Publication	11%
5	Hongchao Guo, Yi Chiao Fan, Zhanhu Sun, Yang Wu, Ohyun Kwon. "Phosphine Organocatalysis", Chemical Reviews, 2018 Publication	1%
6	Dhevalapally B. Ramachary, Rajasekar Sakthidevi. "Sequential combination of Michael and acetalization reactions: direct catalytic asymmetric synthesis of functionalized 4-nitromethyl-chromans as drug intermediates", Organic & Biomolecular Chemistry, 2010 Publication	<1%
7	baadalsg.inflibnet.ac.in Internet Source	<1%
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9	Dixit Parmar, Erli Sugiono, Sadiya Raja, Magnus Rueping. "Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and	<1%

Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates", Chemical Reviews, 2014
Publication

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10 Yuanzhi Xia, Yong Liang, Yuanyuan Chen, Ming Wang, Lei Jiao, Feng Huang, Song Liu, Yahong Li, Zhi-Xiang Yu. "An Unexpected Role of a Trace Amount of Water in Catalyzing Proton Transfer in Phosphine-Catalyzed (3 + 2) Cycloaddition of Allenoates and Alkenes", Journal of the American Chemical Society, 2007 <1%
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12 Ramachary, Dhevalapally B., M. Shiva Prasad, and R. Madhavachary. "A general approach to high-yielding asymmetric synthesis of chiral 3-alkyl-4-nitromethylchromans via cascade Barbasâ€“Michael and acetalization reactions", Organic & Biomolecular Chemistry, 2011. <1%
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---

13 Albert Moyano, Ramon Rios. "Asymmetric Organocatalytic Cyclization and Cycloaddition Reactions", Chemical Reviews, 2011 <1%
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---

14 Dhevalapally B. Ramachary, Kodambahalli S.

Shruthi, R. Madhavachary. "A Modularly Designed Supramolecular Organocatalyst as an Effective Stimulant for the Highly Asymmetric Michael Addition of Ketones to Nitro Olefins", European Journal of Organic Chemistry, 2015
Publication

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15 Junjun Feng, Xin Li. "Enantioselective Vinylogous Michael–Michael Cascade Reactions of 3-Alkylidene Oxindoles and Nitroolefin Enoates", The Journal of Organic Chemistry, 2017
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---

16 Ren-Yi Zhu, Cong-Shuai Wang, Jian Zheng, Feng Shi, Shu-Jiang Tu. " Organocatalytic Asymmetric Inverse-Electron-Demand 1,3-Dipolar Cycloaddition of , ′-Cyclic Azomethine Imines ", The Journal of Organic Chemistry, 2014
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---

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Publication

---

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Publication

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