Development of Organocatalytic [3+2]- and [4+2]-Cycloadditions: Scope and Applications

A

Thesis

Submitted for the Degree of

Doctor of Philosophy

By

JAGJEET GUJRAL

School of Chemistry

University of Hyderabad

Hyderabad-500046, India

August 2020

Dedicated to.....

My Parents and my brother Manmeet

||My Ph.D. Research Mantra||

Experiment!

Fail!

Learn!

Repeat!

DECLARATION

I hereby declare that the matter embodied in the thesis entitled "**Development of Organocatalytic [3+2]- and [4+2]-cycloadditions: Scope and Applications**" is the result of investigation carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, India, under the supervision of **Prof. Dhevalapally B. Ramachary**

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made on the basis of the findings of other investigators. Any omission, which might have occurred by oversight or error, is regretted. This research work is free from Plagiarism. I hereby agree that my thesis can be deposited in Shodhganga/INFLIBNET. A report on plagiarism statistics from the University Librarian is enclosed.

Jagjeet Gujral 31/8/2020

University of Hyderabad
August 2020

Jagjeet Gujral
(14CHPH22)

Prof. Dhevalapally B. Ramachary
(Supervisor)

Prof. D.B. Ramachary
School of Chemistry
University of Hyderabad
Hyderabad - 500 046, India.

CERTIFICATE

Certified that the work contained in the thesis entitled **"Development of Organocatalytic [3+2]- and [4+2]-cycloadditions: Scope and Applications"** has been carried out by **Mr. Jagjeet Gujral** under my supervision and the same has not been submitted elsewhere for a degree. This thesis is free from plagiarism and has not been submitted previously in part or in full to this or any other University or Institution for award of any degree or diploma.

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

1. D. B. Ramachary, **Jagjeet Gujral**, S. Peraka, G. S. Reddy, *Eur. J. Org. Chem.* **2017**, 459-464.
2. **Jagjeet Gujral**, T. P. Reddy, B. Gorachand, D. B. Ramachary, *ChemistrySelect* **2018** , *3* , 7900-7905.
3. T. P. Reddy,♣ **Jagjeet. Gujral**,♣ P. Roy, D. B. Ramachary, [♣both contributed equally and manuscript under preparation].

B. Presented in the following conferences:

1. J-NOST -XIV- 2018; **2.** ChemFest-2019;

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

Course work	Name	Credits	Pass/Fail
CY-801	Research proposal	3	Pass
CY-806	Instrumental Methods-B	3	Pass
CY-571	Organometallic Chemistry	2	Pass
CY-573	Stereoselective Organic Synthesis	2	Pass
CY-580	Natural Products and Medicinal Chemistry	2	Pass

Dean
(School of Chemistry)

Dean
SCHOOL OF CHEMISTRY
University of Hyderabad
Hyderabad-500 046

Prof. Dhevalapally B. Ramachary
(Thesis Supervisor)

Prof. D.B. Ramachary
School of Chemistry
University of Hyderabad
Hyderabad - 500 046, India.

CONTENTS

ACKNOWLEDGEMENTS

*I am deeply indebted to **Prof. Dhevalapally B. Ramachary**, my research supervisor, for his inspiring guidance, support and constant encouragement throughout the course of the present investigations. Most importantly, I would like to thank him for his extreme patience in times of disagreements giving way to a healthy two-way discussion as opposed to a one-way lecture. Such an approach has been really instrumental in nurturing positive growth in me, both personally and professionally. Empathetic behavior shown by him in times of the numerous critical health challenges faced by me during my entire research tenure has been the standalone reason for me being able to complete this work. Thus, his supervision is incomparable and it has been a great privilege and honour to be associated with him.*

I take this opportunity to thank Prof. T.P.Radhakrishnan, Former Dean, School of Chemistry for his constant advice and appreciation of my verbal presentations during his period. I am also thankful to present Dean Prof. Anunay Samanta for providing all the facilities needed for our research and regular maintenance of all the instruments. I extend my sincere thanks to former Deans Prof. M. Durga Prasad and Prof. M. Periasamy. I express a deep sense of gratitude to my doctoral committee members Prof. R. Balamurugana and Prof. A. K. Sahoo for the constant positive encouragement and smile on their faces in all our cabin or corridor meets.

I consider it an honour to show my gratitude to my teachers all of whom have laid down the stepping stones for my success. Namely, Mrs. Rashmi Bhasin for instilling the seed of interest in chemistry in me in VIIIth Standard, Mrs. Shefali Shukla and Mrs. Sharda Pasricha for nurturing that seed into a firm tree of interest in Organic Chemistry at BSc. level. My sincere thanks also goes to Prof. Akhilesh Kumar Verma, Prof. Vibha Tondon, Prof. M. Nath and Dr. Komal Aggarwal my Master's teachers for pushing me into this area of research. My special thanks to Dr. Subhas Chandra Pan for introducing me to Organocatalysis during summer project at IIT Guwahati and Dr. Krishanu Show for teaching me my first basics of experimental techniques at CSIR-NCL, Pune.

I am thankful to all my seniors including Dr. M. Kishor, Dr. M. Shiva Prasad, Dr. A. B. Shashank, Dr. P. Srinivasa Reddy, Dr. R. Madhavachary. I render a special thanks to Dr. P. Murali Krishna and Dr. K. S. Shruthi for not only being my mentors but also friends both inside and outside the laboratory. The presence of experienced scholars like Dr. P. Swamy, Dr. G.

Thirupathi, Dr. S. Rehana Anjum and Dr. A. Suresh Kumar has been a great asset for their always being open to discussions on problems both of professional and personal nature, so a heartfelt thanks to them as well. A special thanks to Dr. T. Prabhakar Reddy and Mr. Pritam Roy for steering me clear of the ordeals of PhD. life and being friends in the true sense at workplace. A special mention to Mr. G. Surendra Reddy for his help in my first research project and being cordial with me throughout, in spite of our differences. I am also grateful to Mr. M. Anif Pasha for imparting valuable life lessons that helped me to grow stronger as a person. I would also take an opportunity to thank Mr. Gorachand Badaraita and Mr. Akram Hussain for their lively and loud discussions in lab thus, breaking the monotony of research life. Mr. A. Vamshi Krishna and Mr. E. Ashok are also worthy of praise for their co-operation and help. I would also like to thank the newly joined Ms. P. Rajya Lakshmi for being a nostalgic view of me when I was in my freshmen year of Ph.D.

I acknowledge the help and support provided by the technical and non-teaching staff of the School of Chemistry., Mr. Thurabauddin, Mr. Durgesh Singh and Mr. G. Mahender (for their help in recording NMR immediately whenever I am in need) Bhaskara Rao, Mrs. Asia Perwej, G. S. Maruthi (for helping me in doing HRMS experiments) V. M. Shetty, A. R. Shetty, Deelip, Venkatesh, Aleem (Late), Geetha, Kumar Reddy, Anand, and sathyam for their timely help and support.

My special thanks to Prof. M. Periasamy's research group, Prof. Balamurugan's research group and Prof. Y. Srinivasarao's research group for their generous help and useful discussions. I also thank Anil, Ankit and Junaid for their great help in solving my all crystal data. It gives me immense pleasure to thank my friends of School of Chemistry Showkat, Chandrahas, Ramesh, Nagamaiah, Surya, Rangu Prasad, Umamahesh, Ishfaq, Ali, Isha, Mamina, Daradi, Prachi, Subhabrata, Sneha Paul, Sabari, Sathish, Jyothi, Ranjini dee, Amala dee, Mohan anna, Ramana anna, Saktivelu anna for lending their unconditional help at the needful times.

I would like to express my thanks to my close friends of all times Himanshu Aggarwal, Anurag Sharma (from MSc.), Eishaan, Anuj, Sarang, Parul (from BSc.), Hrishita, Surojit, Moon, Shibendu and Akshay Rastogi (during PhD.) for supporting and encouraging me through the endless conversations and also for being with me at all tough and happy moments.

The word thanks becomes meaningless when it comes to my Family, without their support coming to this stage would have been merely a dream. They are the reason for what I am today

in society. I become wordless to express their support, guidance, service and love towards me. In that my Mother Narinder, Brother Manmeet and Father Amarjeet have been instrumental in setting a solid foundation of moral values that I still carry with me even after a morally degrading PhD. journey. My sister-in-law Maninder and niece Samreen have been a more recent addition to our family but their support and love is now a major part of my life. Therefore, I find that dedicating this thesis to them is a minor recognition of their relentless efforts and unconditional care.

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

Finally, I am deeply indebted to me for still believing in me, even after failing 95% of the times in my research work with just 5% success, which is embodied in this thesis. I have truly grown as a person in which this research journey has served as a means and also without which the end of it would not have been possible.

Jagjeet Gujral

PREFACE

Generating molecular complexities in a single step is a unique property of cycloaddition reactions. Such reactions, if done organocatalytically, far exceed their metal mediated reaction counterparts in selectivity, efficiency and operational simplicity. The present thesis entitled ***"Development of Organocatalytic [3+2]- and [4+2]-cycloadditions: Scope and Applications"*** *is an honest attempt to apply the enolate mediated organocatalytic click strategies to [3+2]-cycloadditions and formal cycloaddition of amidines to ynones in [4+2] manner. A large library of monocyclic, bicyclic and tricyclic heterocycles have been synthesized using these protocols which opens up large prospects for their further biological or material studies. In all these sections, a brief introduction is provided to keep the present work in proper perspective, the compounds are sequentially numbered (bold), and references are marked sequentially as superscript and listed at the end of the thesis. All the figures included in the thesis were obtained by DIRECT PHOTOCOPY OF THE ORIGINAL SPECTRA and in some of them uninformative areas have been cut to save the space.*

The first chapter illustrates an 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) catalyzed enolate-mediated regiospecific synthesis of 1,4,5-trisubstituted N-vinyl-1,2,3-triazoles from simple activated carbonyl compounds and N-vinyl azides through a [3+2]-cycloaddition. Further hydrogenation of these vinyl triazoles led to facile synthesis of, 1,4,5-trisubstituted N-alkyl-1,2,3-triazoles. This work expands the application of such strategies to vinyl azides and not just aryl azides as previously done by many groups. Not only this, it presents a facile method of synthesizing alkyl azide [3+2]-cycloadducts through reduction of final products.

The second chapter describes an enolate mediated click strategy for the synthesis of N,N-bicyclic pyrazolidinones by a [3+2]-cycloaddition between α-enolizable aldehydes and cyclic azomethine imines. All the reactions were carried out under DBU or tBuOK catalysis. This chapter expands the scope of enolate mediate click reactions beyond azides to other 1,3-dipoles like azomethine imines. A large number of bicyclic heterocycles were synthesized using this strategy whose core skeleton has a presence in a number of biologically active compounds.

The third chapter is an attempt to look at amidine bases like 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo(4.3.0)non-5-ene (DBN) and some others in new light not just as a catalysts, as used extensively in organocatalytic click chemistry but as substrates in a catalytic formal [4+2]-cycloaddition with ynones. Theses cycloadditions result in the formation of tricylic heterocycles which may have potential biological or material applications.

LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Ac_2O	acetic anhydride
Ala	Alanine
Anal.	analysis
aq.	aqueous
Ar	aryl
BINOL	1, 1'-Bi-2-naphthol
Bn	benzyl
Bp	boiling point
br	broad
Bu	butyl
*t*Bu or ^{t}Bu	*tertiary*-butyl
n-BuLi	*n*-butyl lithium
calcd.	calculated
cat.	Catalytic
CIF	Crystallographic Information file
cm	centimeter
CSP	chiral stationary phase
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo(4.3.0)non-5-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublet
ddd	doublet of doublet of doublet
dt	doublet of triplet
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DMAP	dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess –Martin Periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dt	doublet of triplet
EDG	electron donating group
ee	enantiomeric excess
Eq.	equation
equiv.	equivalent(s)
Et	ethyl
EWG	electron withdrawing group
ESI	Electrospray ionization
Fg	functional group
Fig.	figure
gm	gram (s)
h	hour (s)

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

Development of Organocatalytic [3+2]- and [4+2]-Cycloadditions: Scope and Applications

1. Abstract

Chapter 1 deals with an 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) catalyzed enolate-mediated regiospecific synthesis of 1,4,5-trisubstituted *N*-vinyl-1,2,3-triazoles from simple activated carbonyl compounds and *N*-vinyl azides through a [3+2]-cycloaddition. Further hydrogenation of these *N*-vinyl-1,2,3-triazoles led to facile synthesis of 1,4,5-trisubstituted *N*-alkyl-1,2,3-triazoles.

Chapter 2 presents an enolate mediated strategy for the synthesis of *N*,*N*-bicyclic pyrazolidinones by a [3+2]-cycloaddition between α-enolizable aldehydes and cyclic azomethine imines. All the reactions were carried out under DBU or *t*BuOK catalysis. This chapter expands the scope of enolate mediate click reactions beyond azides to other 1,3-dipoles like azomethine imines.

Chapter 3 is an attempt to look at amidines like 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo(4.3.0)non-5-ene (DBN) and some others in new light not just as catalysts as used extensively in organocatalytic click chemistry, but as substrates in a Lewis acid or self-catalysed amidine-ynone formal [4+2]-cycloaddition.

2. Introduction

Since time immemorial organic chemists have continuously made an effort to mimic nature and develop tools to synthesize compounds with efficacy as orchestrated by nature. Cycloadditions namely [3+2] and [4+2] are a class of useful reactions that help us in creating moieties of varied complexity in minimum steps. Metal catalysis and organocatalysis both have paved way for facile cycloadditions of such manner. This thesis is a further exploration in this field mainly focusing on an organocatalytic [3+2]- and [4+2]-cycloaddition approach.

The research work presented in this thesis comprises of following parts:

1) Azide-Activated Carbonyl [3+2]-Cycloadditions for *N*-Vinyl-1,2,3-Triazole Synthesis.

2) Aldehyde-Azomethine imine [3+2]-Cycloaddition: *N,N*- Bicyclic Pyrazolidinones Synthesis.

3) Ynone-Amidine [4+2]-Cycloaddition.

A brief introduction of previous works on similar strategies is described further.

2.1 *Previous synthetic methods towards N-vinyl-1,2,3-triazole synthesis:*

N-vinyl-1,2,3-triazoles have attracted a lot of attention owing to certain peculiar properties (Figure 1.) like olefinic appendage for polymer synthesis, free lone pair for hydrogen bonding and a 6-π electron aromatic system rendering both stability and π-π stacking interaction possible. These qualities have attracted chemists to develop methods for their facile synthesis.

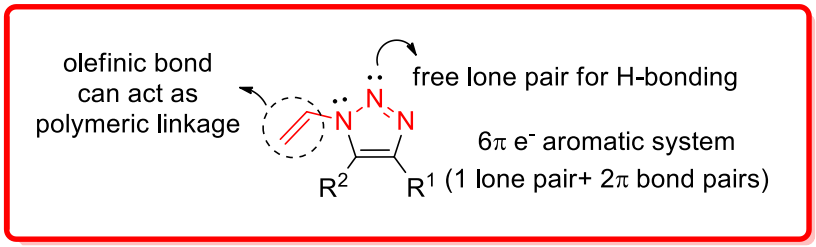
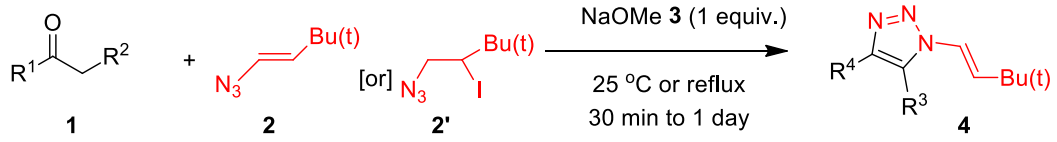


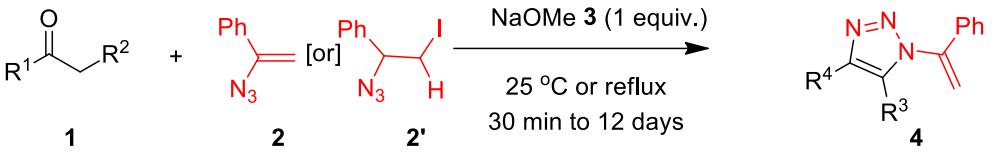
Figure-1: *N*-Vinyl-1,2,3-triazoles as functionally rich moieties.

Few of such strategies have been described here.

Initially, in 1970, L'abbe´ *et al.* devised a method using β-haloalkyl azides or vinyl azides which on treatment with various active methylene compounds in a stoichiometric amount of base NaOMe **3** lead to the formation of *N*-vinyl-1,2,3-triazoles in 62 to 82 % yields. The carbanion generated by base leads to 1,3-dipolar cycloaddition to the azide followed by aromatization to give final products. Both α- and β-vinyl azides were employed in this reaction (Eq.1. and 2.).[1]



R^1, R^2 = Ph, COOEt	R^3, R^4 = Ph, COOH, 74 and 72% yield
R^1, R^2 = Me, COOEt	R^3, R^4 = Me, COOH, 84 and 69% yield
R^1, R^2 = NH_2, CN	R^3, R^4 = NH_2, $CONH_2$, 62 and 72% yield
R^1, R^2 = OMe, CN	R^3, R^4 = NH_2, COOMe, 38 and 31% yield

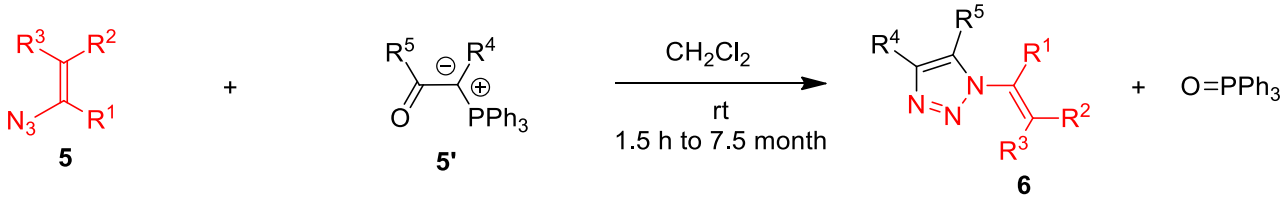


(2)

R^1, R^2 = Ph, COOEt
R^1, R^2 = Me, COOEt
R^1, R^2 = NH_2, CN

R^3, R^4 = Ph, COOH, 69 and 79% yield
R^3, R^4 = Me, COOH, 72 and 74% yield
R^3, R^4 = NH_2, $CONH_2$, 35 and 44% yield

Further, in 1972, Smets *et al.* utilized reactive *α*-keto phosphorus ylides in reaction with *β*-vinyl azides yielding final *N*-vinyl-1,2,3-triazoles **6** just at room temperature in 15-98% yields as shown in Eq.3.[2] This reaction was driven forward by the release of triphenylphosphene oxide.



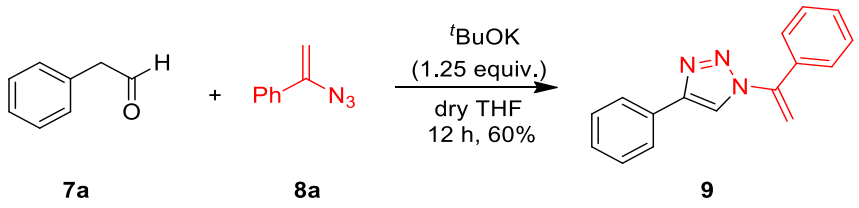
(3)

R^1,R^2,R^3 = Ph, H, H; H, PhCO, H; PhCO, H, Ph; PhCO, H,*m*-$NO_2C_6H_4$; PhCO, H, Ph

R^4, R^5 = Me, Me; H, Me; H, Ph; H, *p*-$NO_2C_6H_4$

15 examples
15-98% yields

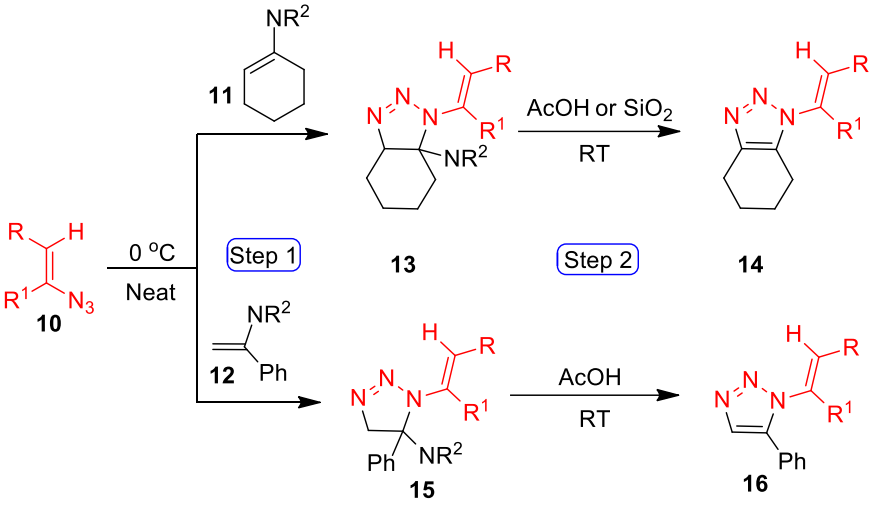
Gilchrist and Rees *et al.* in the year 1975 made a successful attempt of synthesizing *N*-vinyl-1,2,3-triazoles **9** from phenylacetaldehyde **7a** and *β*-azido styrene **8a** in 60% yield by treating with 1.25 equiv. of *t*BuOK in dry THF as depicted in Eq. 4.[3]



(4)

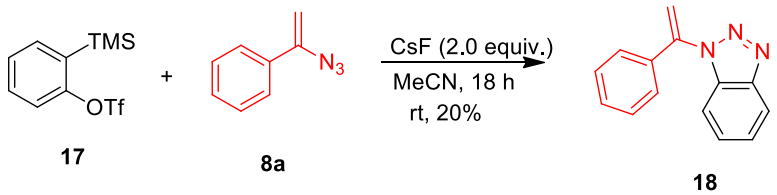
In 1981,[4] Nomura *et al.* reported a procedure for the synthesis of *α*-substituted *N*-vinyl-1,2,3-triazoles from preformed enamines. Under the present protocol *α*-and *β*-azido styrenes on reaction with various preformed enamines in neat condition at 0 °C yielded 4-aminovinyl triazoline

intermediates (**14** and **16**) via [3+2]-Huisgen cycloaddition in 40-86% yields (Step 1). These intermediates on acidification via acetic acid or column silica gel gave vinyl triazoles **14** and **15** in 40-62% yields (Step 2). Equations 5 and 6 describe the aforementioned procedure.

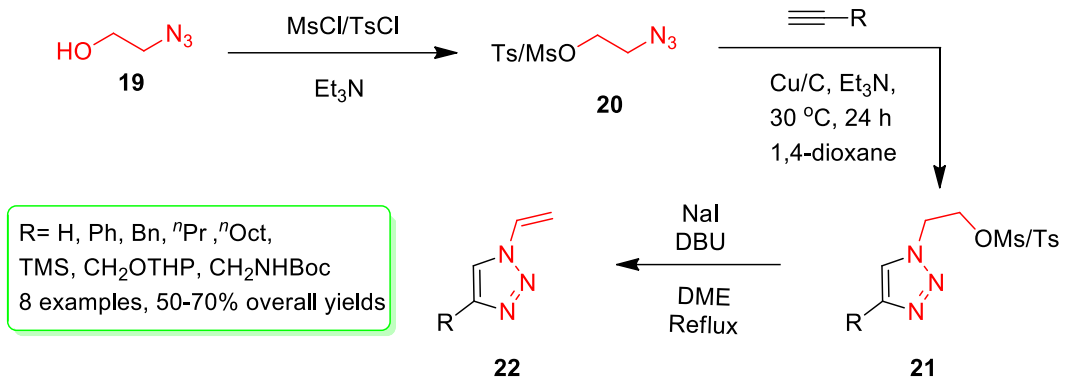


Reaction with **11**		
R, R^1 = H, Ph	NR_2 = 	Step 1: 40% yield; Step 2: 40% yield with SiO_2 elimination
R, R^1 = H, Ph	NR_2 = 	Step 1: 86% yield; Step 2: 40% yield with SiO_2 elimination & Step 1: 86% yield; Step 2: 46% yield with AcOH elimination
R, R^1 = Ph, H	NR_2 = 	Step 1: 62% yield; Step 2: 54% yield with AcOH elimination
Reaction with **12**		
R, R^1 = Ph, H	NR_2 = 	Step 1: 63% yield; Step 2: 62% yield with AcOH elimination

In 2008, Larock *et al.* generated benzyne intermediate *in situ* from *o*-(trimethylsilyl) phenyl triflate by treating with 2.0 equiv. of CsF in MeCN which was made to undergo [3+2]-cycloaddition with *α*-azidostyrene at room temperature for synthesis of 1-styrenyl benzotriazole **18** in 20% yield (Eq.7).[5]

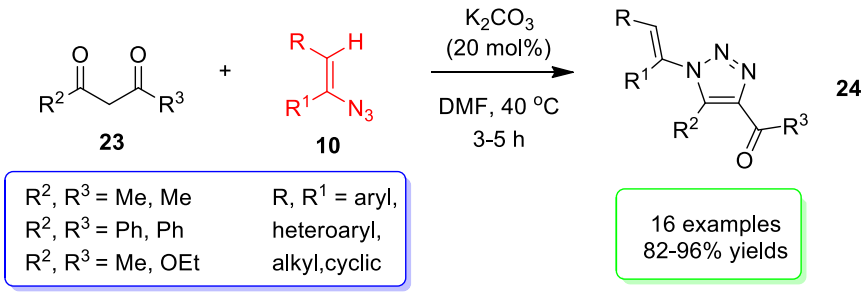


In 2010, Hawker *et al.* developed a strategy where 2-azidoethyl methanesulfonate or azidoethy methylbenzenesulfonate **20** was reacted with varied terminal alkynes in a copper catalysed [3+2]-cycloaddition followed by elimination of the protecting group (mesyl/tosyl) by NaI and DBU generating *N*-vinyl triazoles **22** in 50-70% overall yields (Eq.8.).[6]



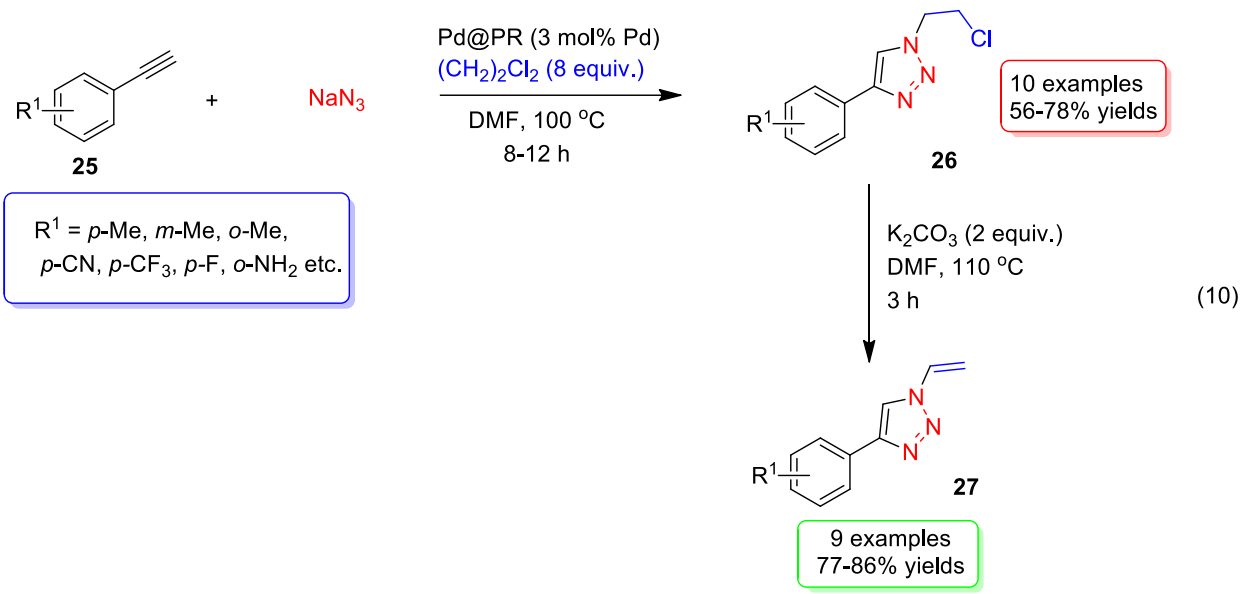
(8)

In 2011, Chiba *et al.* synthesized a variety of *N*-vinyl-1,2,3-triazoles **24** *via* enolate-mediated [3+2]-cycloaddition of 1,3-dicarbonyl compounds with *α*-azidostyrenes **10** in the presence of K_2CO_3 (20 mol%) in DMF at 40 °C in 82-96% yields (Eq.9).[7]



(9)

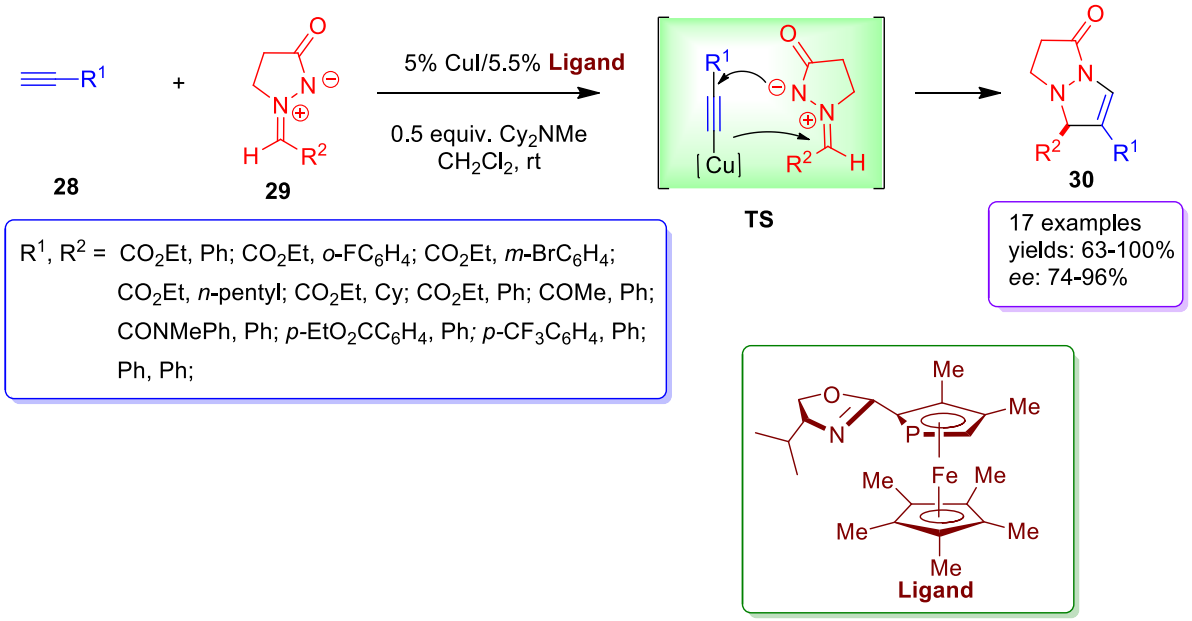
In 2015, Das *et al.* developed a unique polystyrene resin supported palladium(0) (Pd@PR) nanocomposite mediated reaction between terminal alkynes and sodium azide in dichloromethane leading to regioselective synthesis of 4-aryl-1-alkyl/(2-haloalkyl)-1*H*-1,2,3-triazoles **26** which on elimination of HCl by 2 equiv. of K_2CO_3 generated their *N*-vinyl triazoles **27** in 77-86% yields (Eq. 10).[8]



(10)

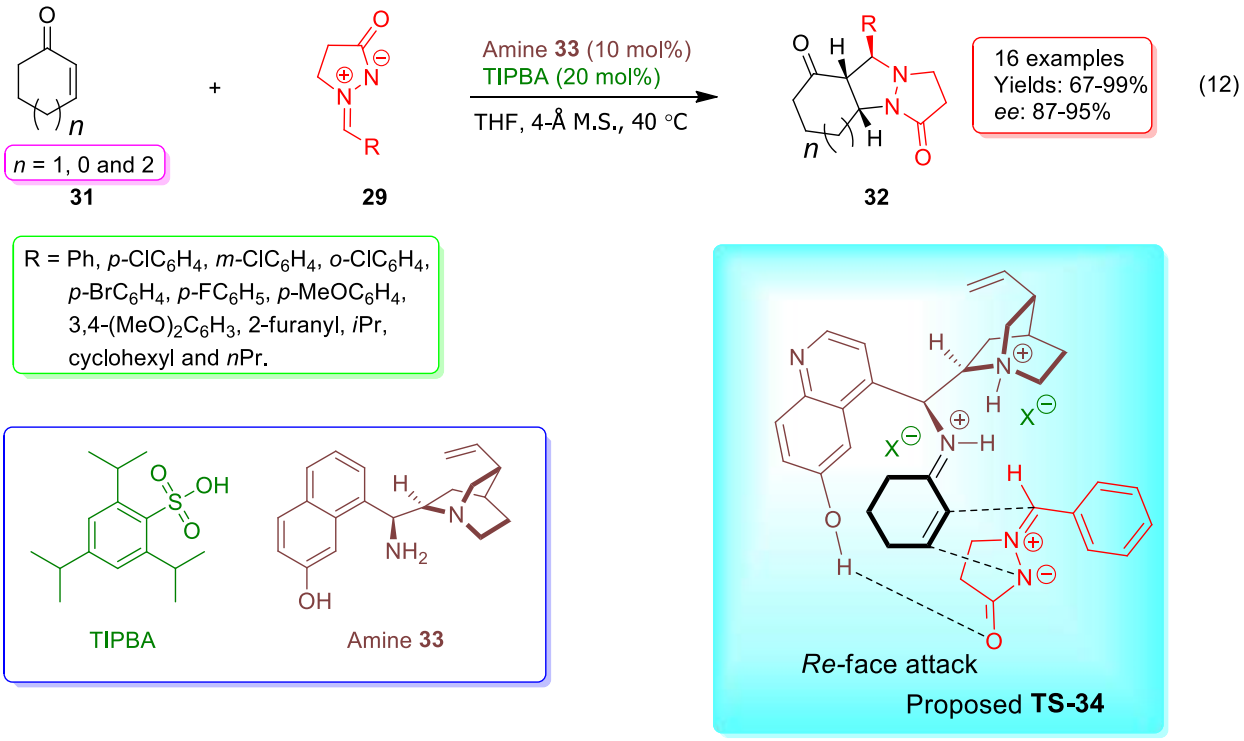
2.2 *Azomethine imine mediated [3+2]-cycloadditions*:

In 2003, Fu *et al.* reported 1,3-dipolar cycloaddition of modified azomethine imines and terminal alkynes in the presence of a chiral CuI/ligand catalyst, which proceeded in a highly enantioselective manner to produce nitrogen fused heterocyclic compounds **30** via an *in situ* generated Cu(I)-acetylide. Reaction proceeded smoothly in DCM solvent at room temperature to furnish products **30** in 63-100% yields and with good to excellent enantioselectivities (74-96% *ee*) as elucidated in Equation 11.[9]

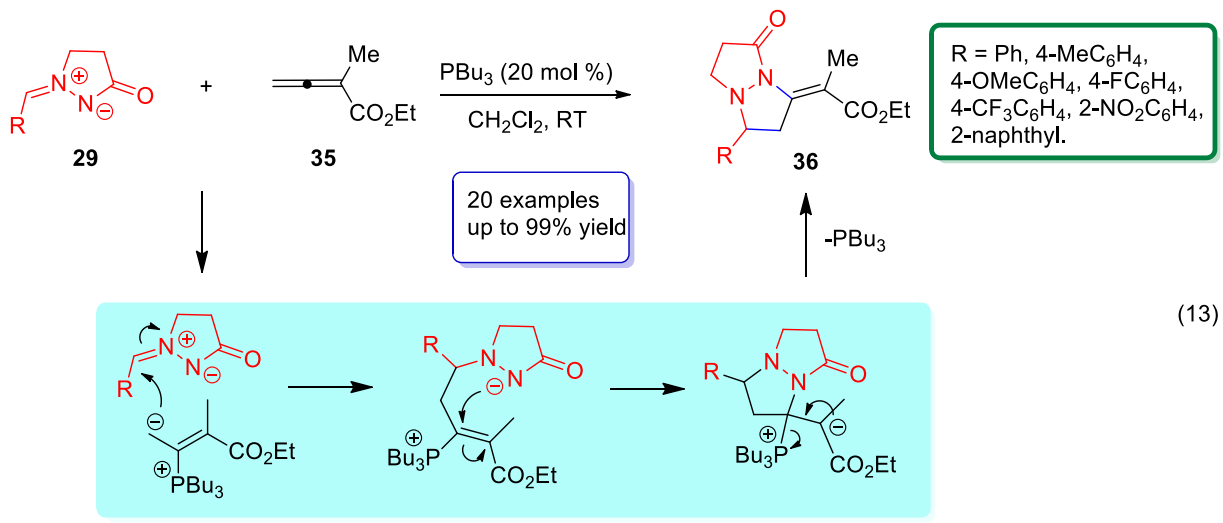


(11)

In 2007, Chen and co-workers exploited bifunctional organocatalyst **33** in presence of 2,4,6-triisopropylbenzenesulfonic acid (TIPBA) in an enantioslective [3+2]-cycloaddition between cyclic enones **31** azomethine imines **29** furnishing tricyclic fused heterocycles **32.** The products were obtained in excellent enantioselectivities (87-95% *ee*) and yields (76-99%). Rationale for this selectivity was presented in the **TS-34** where the ketone is activated through ketiminium ion formation by the primary amine part of **33**. Hydroxyl group on the aromatic ring of **33** brings **29** in close proximity for reaction via hydrogen bonding to amide carbonyl of **29.** Further, ion pair formation between the protonated tertiary amine part and the acid X = TIPBA enhances steric shielding of the *Si* face making *Re* face attack feasible (Eq. 12).[10]

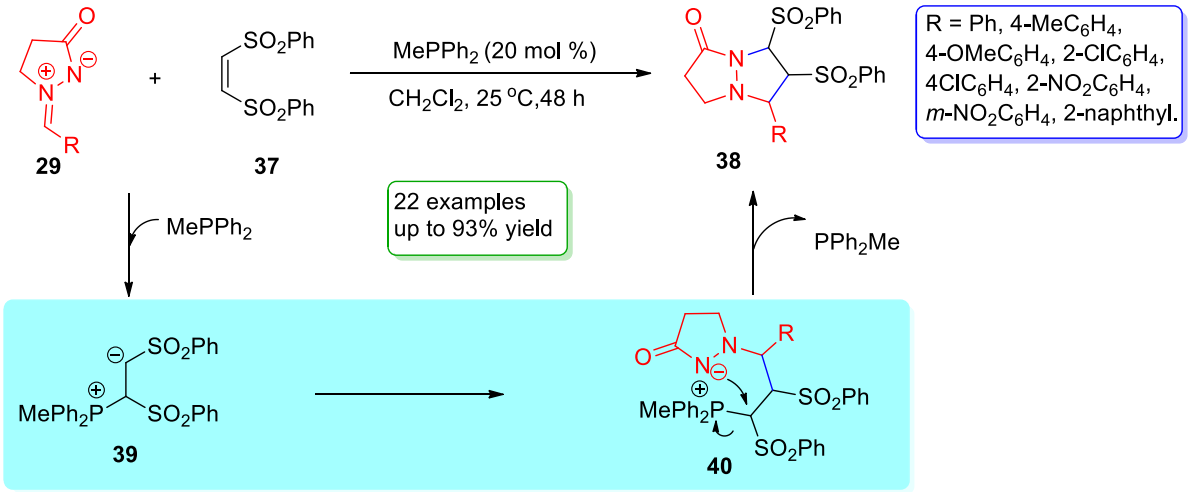


In 2011, Kwon *et al.* formulated a [3+2] annulation between cyclic azomethine imines **29** and allenoates **35** through organophosphine catalysis for the synthesis of different *N*,*N*-fused bicyclic products **36**. Just 20 mol% of trialkylphosphine catalyst like PBu_3 was sufficient to drive a [3+2]-cycloaddition between **29** and **35** at room temperature furnishing products **36** with a maximum yield of 99% as shown in eq. 13.[11] Other phosphine catalysts like PMe_3 also worked well in this protocol.



(13)

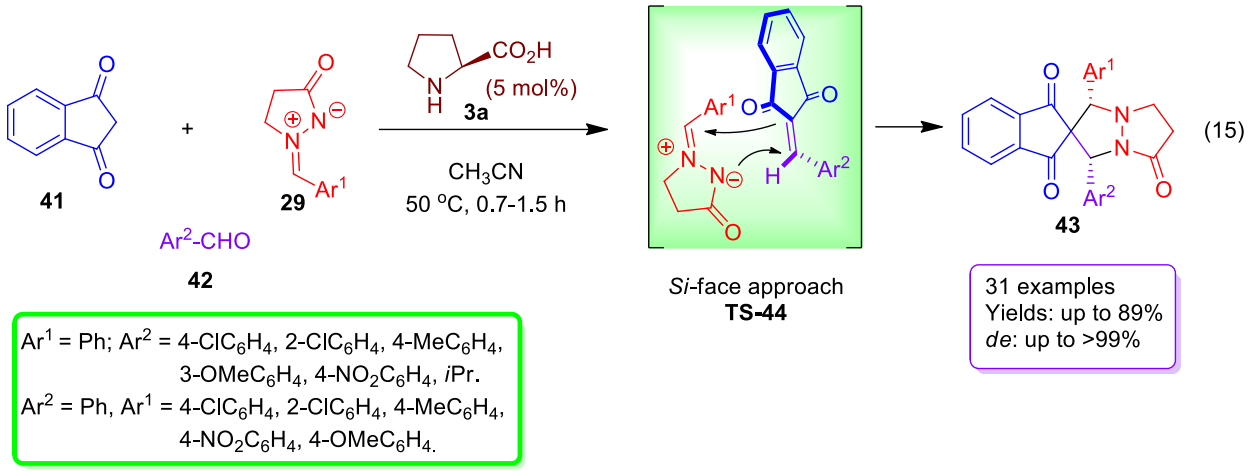
In 2014, Guo and co-workers achieved the synthesis of five *N*,*N*-fused heterocyclic compounds **38** from azomethine imines **29** and (*Z*)-1,2-bis(phenylsulfonyl)ethylene **37** catalysed by $MePPh_2$ organophosphinecatalyst in DCM at 25 ^oC. The reaction proceeded by formation of zwitterionic species **39** to afford [3+2]-cycloadducts with excellent yield (up to 93%) as shown in eq. 14.[12]



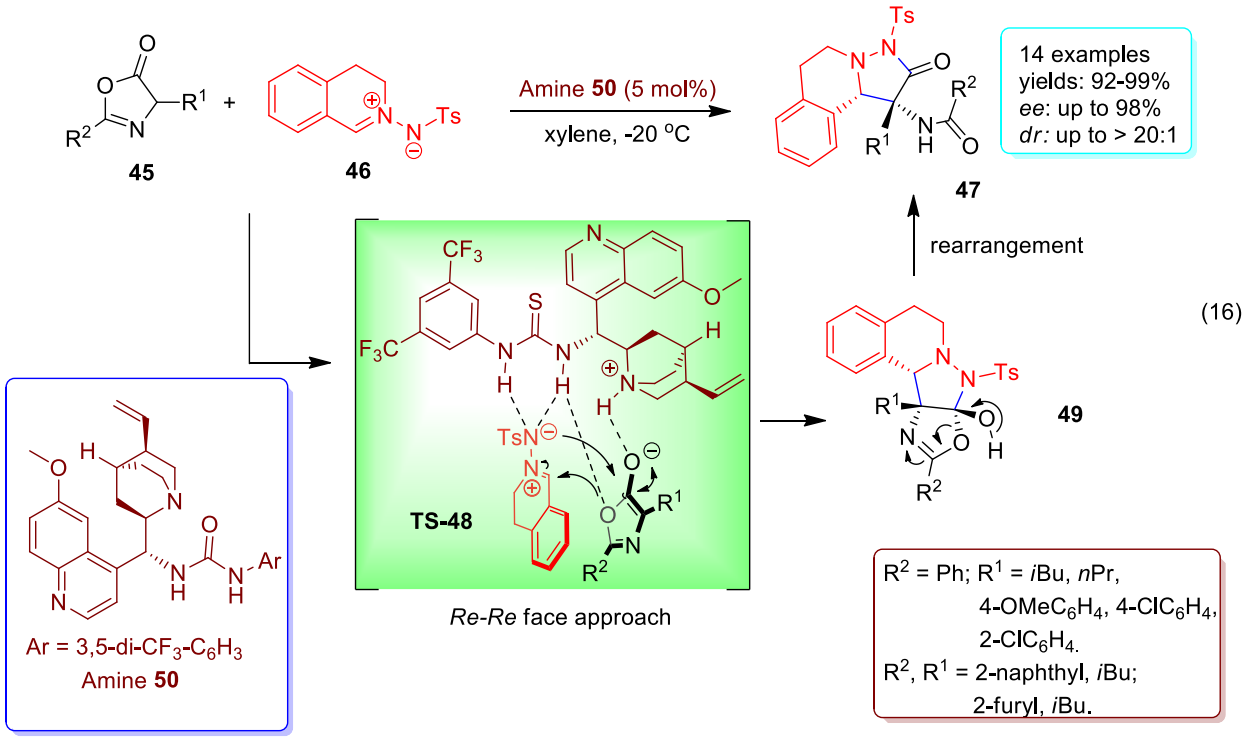
(14)

Ramachary and co-workers in 2016,[13] discovered an organocatalytic azomethine imine-olefin [3+2]-cycloaddition synthesizing spiroindane-1,3-dione-pyrazolidinones **43** from the indane-1,3-dione **41**, aldehydes **42** and *N*,*N*-cyclic azomethine imine **29**. The reaction proceeds initially through a Knoevenagel condensation followed by *si*-face attack of azomethine imine **29**

on the the initial adduct via transition state **TS-44**. This protocol generated the final products up to 89% and *de* up to >99%. Equation 15 elucidates the aforementioned procedure.



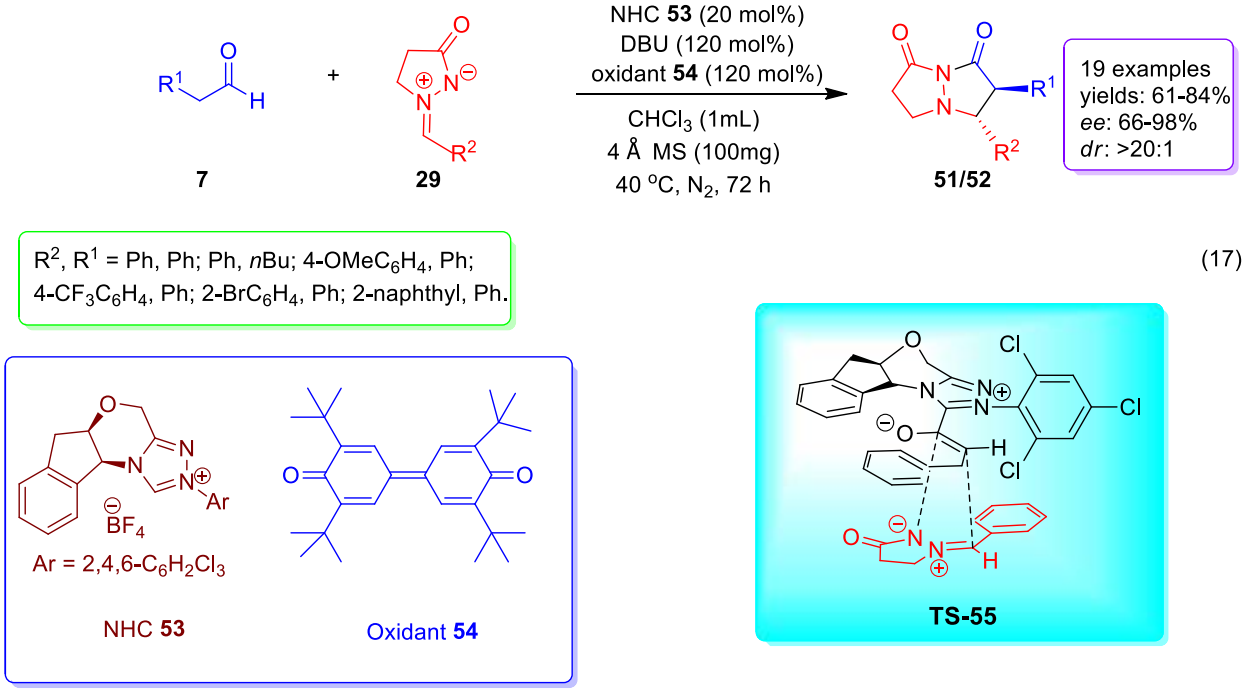
In 2016, Su *et al.* reported an enantioselective 1,3-dipolar cycloaddition between *C,N*-cyclic azomethine imines **46** and azalactones **45** catalysed by thiourea derived amine **50** (Eq. 16.).[14]



Asymmetric induction was achieved through double activation hydrogen bonding between protonated amine **50,** azomethine imine **46** and enolated azalactone **45** resulting in a *re-re*-face

approach as evident in transition state **48.** The species **49** formed from the cycloaddition, being unstable rearranges to the final products **47** in excellent yields ranging from 92 to 99% and *ee* upto 99% with *dr* up to > 20:1.

Ren and Xu *et al.* in 2017 devised a methodology to react *N*,*N*-cyclic azomethine imines **29** with *α*-enolizable aldehydes **7** in an asymmetric [3+2]-cycloaddition utilizing chiral *N*-heterocyclic carbene catalysis under oxidative conditions (Eq. 17.).[15] The cycloadducts **51/52** were produced in moderate to excellent enantioselectivities (66-98% *ee*) and moderate to good yields (61-84%).

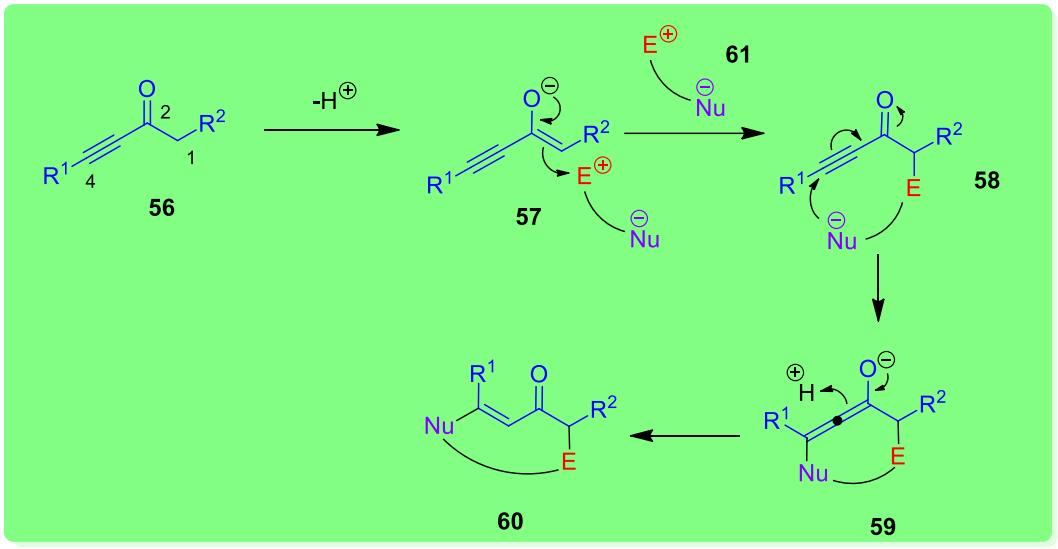


(17)

The reaction was proposed to proceed via the transition state **TS-55** where the NHC-aldehyde intermediate is blocked from one side by bulky groups and the two Ph groups of both reactants point in opposite directions yielding *trans* diastereoselectivity. Finally, the oxidant **54** was used to regenerate the catalyst **53** releasing the products **51/52.**

2.3 *Ynone mediated [4+2]-cycloadditions*:

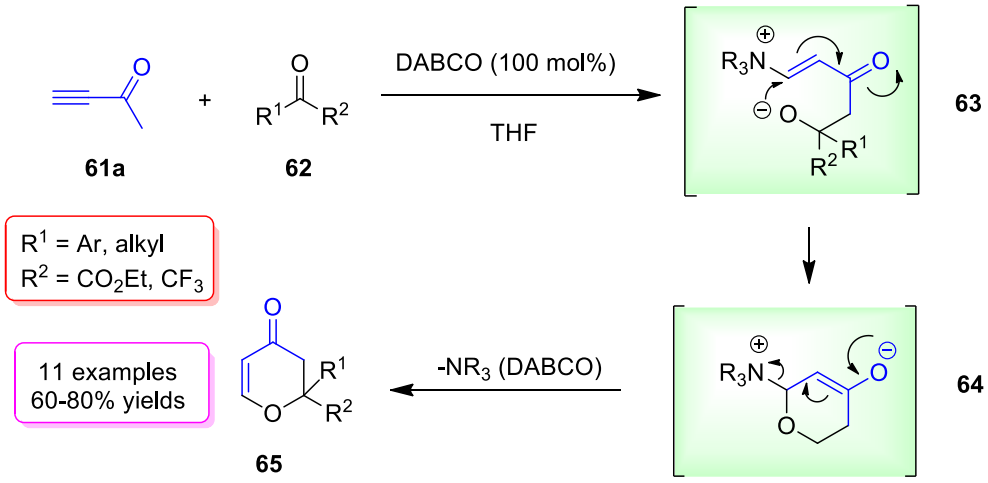
Ynones acting as C-4 synthons in [4+2]-cycloadditions go through a general mechanism as described in equation 18.



(18)

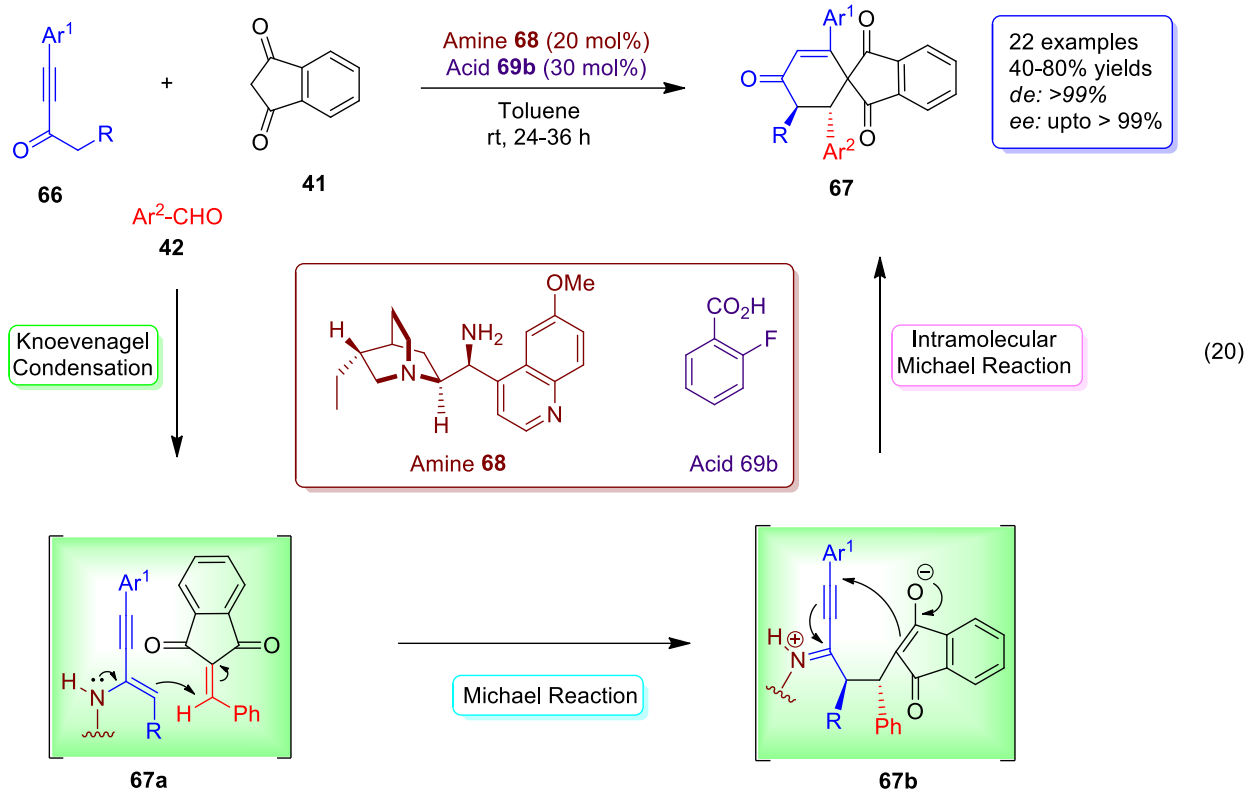
Abstraction of *α*- acidic proton from **56** forms ynolate **57** which is intercepted by the electrophilic end of **61** followed by a Michael attack at C-4 by the nucleophilic end leading to the formation of anionic intermediate **59.** This anion is neutralized by a proton from the system leading to the formation of the final cyclic product **60.** The protocols that would be described herein largely follow this mechanism with little variations from one work to another.

In 2012, Shi and co-workers, synthesized 2,3-dihydropyran-4-ones **65** from activated ketones **62** and but-3-yn-2-one **61a** on treatment with 1 equiv. of DABCO (Eq. 19).[16] The reaction was proposed to occur through an initial attack of the ynolate on the carbonyl carbon followed by Michael attack by tertiary amine at C-4 in turn activating the intermediate **63** towards an intramolecular Michael reaction displacing the base in the process. This strategy furnished the final products **65** in 60-80% yields.



(19)

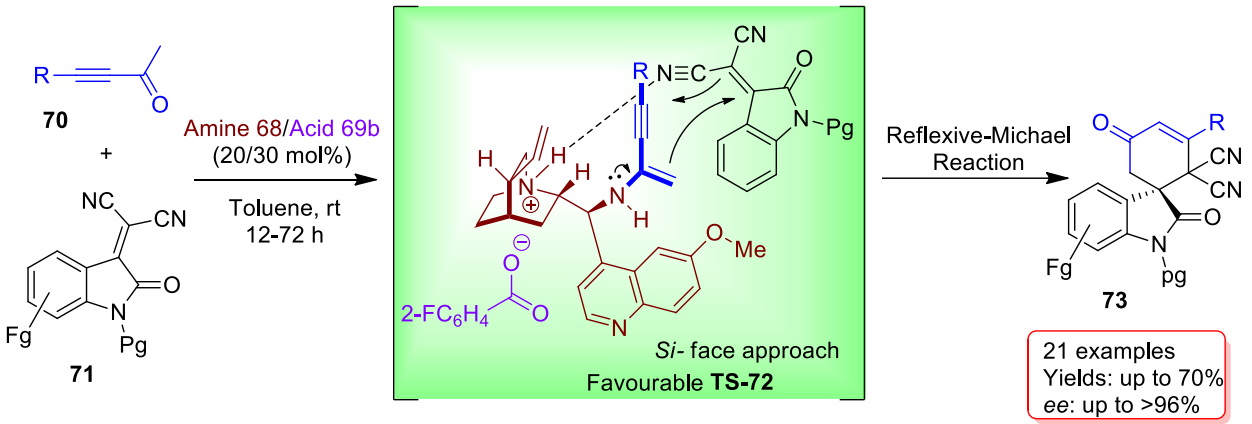
In 2012, Ramachary *et al.* demonstrated a procedure where 2-arylidene-indan-1,3-diones produced *in situ* from 1,3-indanedione **41** and aldehydes **42** by a Knoevenagel condensation reacts with enamine formed from **66** and **68** as depicted in structure **67a** of equation 20.[17]



(20)

The reaction is proposed to proceed through an initial Michael reaction intermolecularly as shown in **67a** and then intramoleculary from **67b** to yield the spiro products **67** in 40-80% yields and up to > 99% *ee*.

The same research group, in the consecutive year, applied a similar strategy to a new set of reactants namely alkynones **70** and 2-(2-oxoindolin-3-ylidene)malononitriles **71** as depicted in Equation 21.[18] The same catalyst **68** and acid **69b** were employed in rendering the reaction enantioselective through the transition state **72.** An asymmetric Reflexive Michael reaction was instrumental in furnishing the final products containing spirooxindole skeletons **73** up to 70% yield and up to >96% enantiomeric excess. This protocol's success establishes the generality of the strategy developed in Eq. 20.

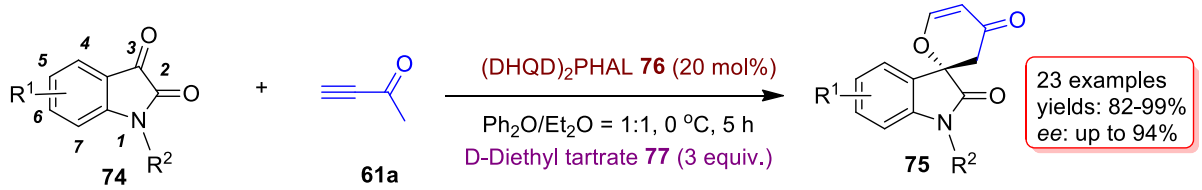


R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$MeOCH_2OC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 2-Thiophenyl and Me_3Si.

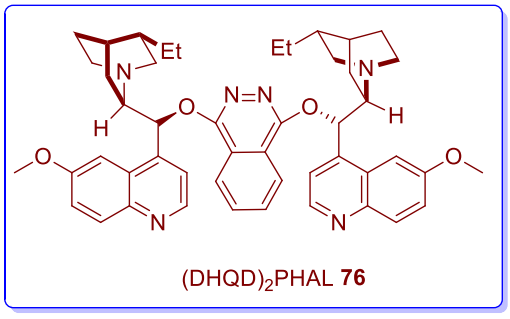
Fg = 5-F, 5-Cl, 5-Br, 5-I, 5-NO_2 and 5,7-Me_2
Pg = H, Me, CH_2OMe, $COCH_3$

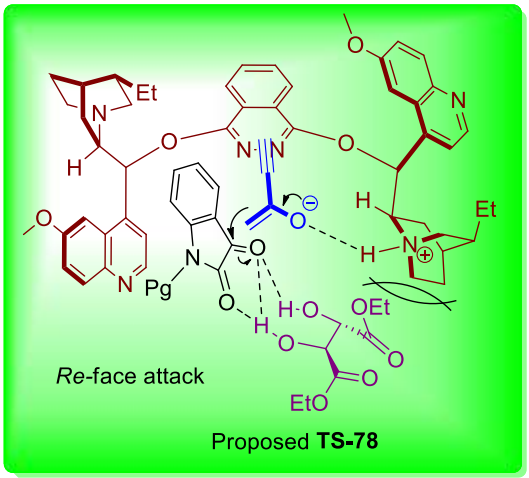
(21)

Shi and Xu *et al.* in july 2013, reported [4+2]-annulations of isatins with but-3-yn-2-one **61** catalyzed by the Cinchona alkaloids-derived organocatalyst $(DHQD)_2PHAL$ **76** in the presence of 3.0 equivalents of D-Diethyl tartrate **77** in a mixed solvent (diphenyl ether:diethyl ether = 1:1), producing substituted spiro[indoline-3,2'-pyran]-2,4'- (3'*H*)-diones **75** in good to excellent yields (82-99%) and high enantioselectivities (up to 94% *ee*) as shown in Eq. 22.[19]



R^1 = H, 4-Me, 4-Cl, 5-F, 5-Cl, 5-Br, 5-Me, 5-OMe, 6-Cl, 6-Me, 6-OMe, 7-F and 7-Cl.
R^2 = Bn, Me, $CH_2CH{=}CH_2$, MOM, CPh_3, $CH_2C_6H_3(3,5\text{-}2CH_3)$, $(CH_2)_3C_6H_5$, Ph and $(CH_2)_2Ph$.

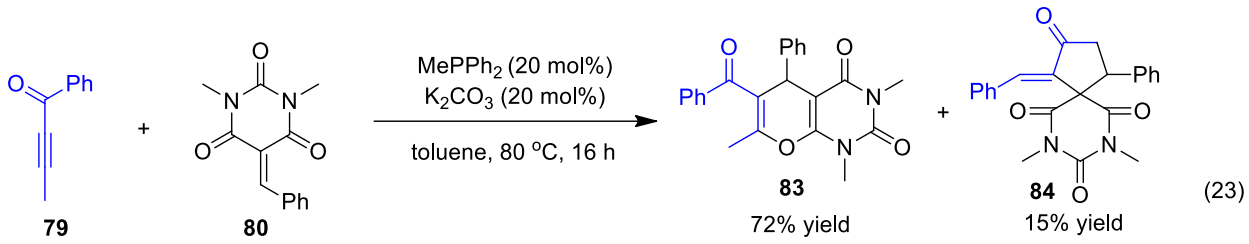




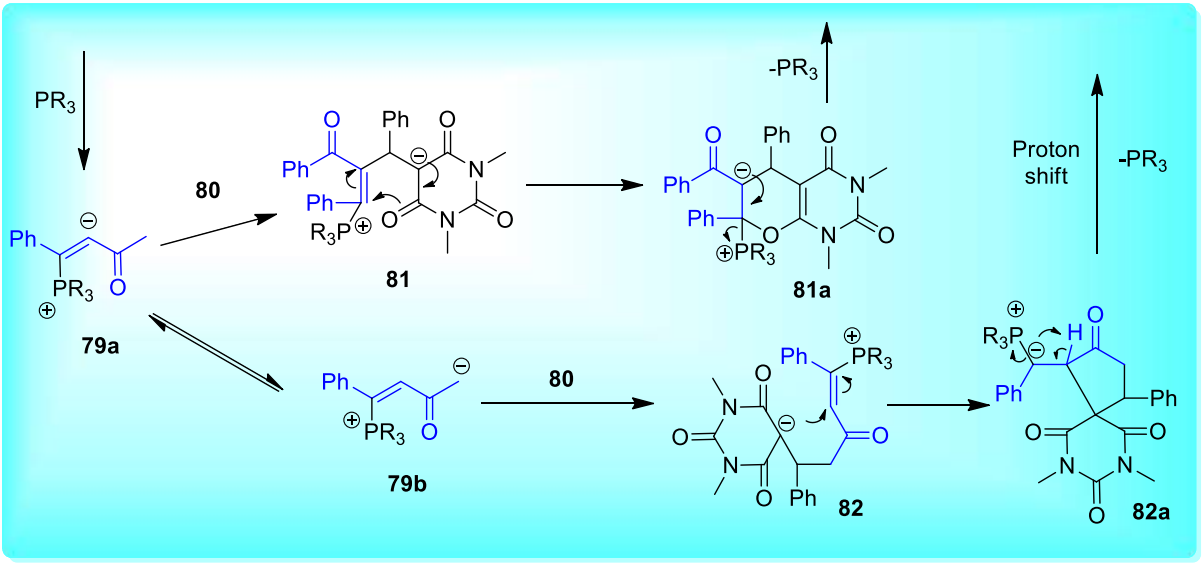
(22)

The reaction was proposed to occur *via* the transition state **78** where the attack on *re*-face of isatin is favoured due to steric interactions between **77** bound to isatin with H-bonding and the catalyst **76.**

Activation of ynones with trialkyl/triaryl phosphines was utilized recently, by Guo and co-workers in [4+2]-annulation of ynone **79** and barbiturate derived alkenes **80** in presence of 20 mol% of $MePPh_2$ and K_2CO_3 at 80 ^oC. This strategy yielded the [4+2]-adduct **83** in 72% yield along with a small amount [3+2]-adduct **84.** This method is illustrated by Equation 23.[20]



(23)



Interaction of **80** with intermediate **79a** led to the desired product **83** through intermediates **81** and **81a.** However, interaction with **79b** intermediate resulted in formation of minor product **84**.

3. Triazabicyclodecene as an Organocatalyst for Regiospecific Synthesis of 1,4,5-Trisubstituted *N*-Vinyl-1,2,3-Triazoles

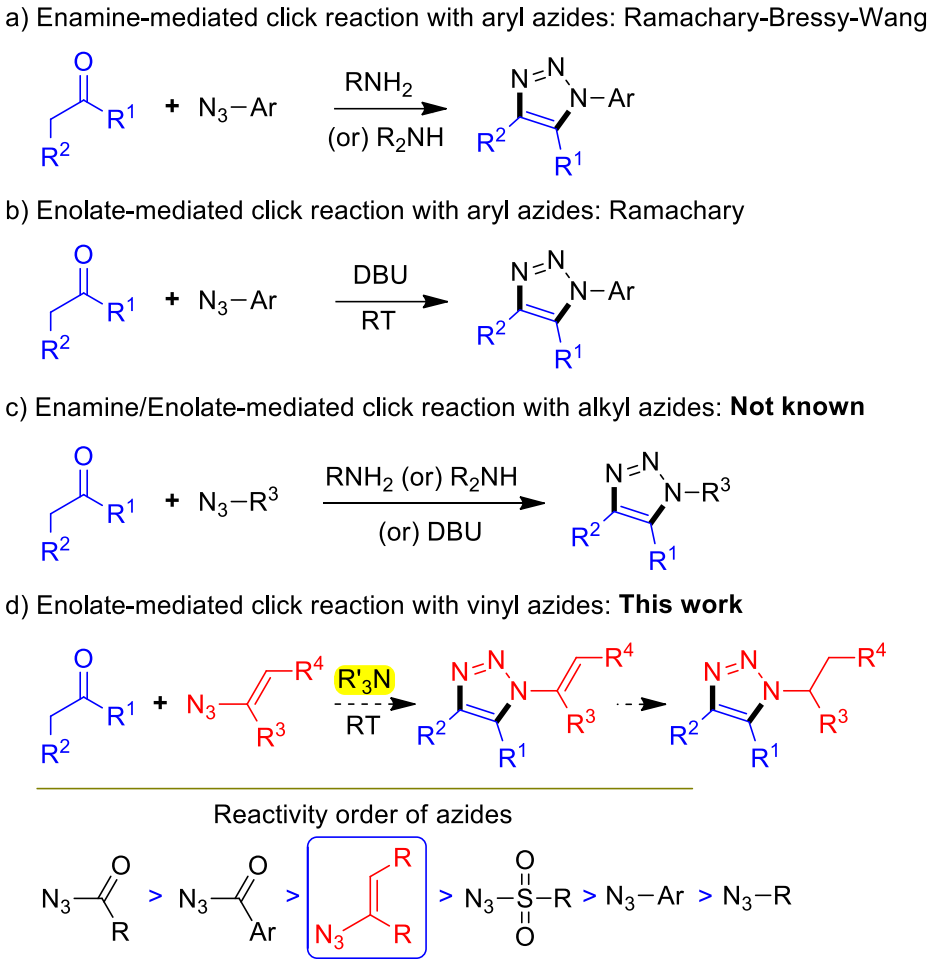
3.1 Introduction

1,2,3-Triazoles have emerged as a core of considerable interest for chemists/biologists in the past few decades. This interest stems from their wide applicability in the fields of medicinal, organic, polymer and material chemistry.[21] 1,2,3-Triazoles are also capable of playing an important role as "amide isosteres" due to their bio-similarity with amide bonds in properties like relative planarity, dipole moment and amphihydrogen-bonding capability.[22] Considering these applications, high-yielding selective synthesis of variety of functionalized 1,2,3-triazoles becomes a challenge for synthetic chemists.

With the advent of the concept of "click chemistry" there has been an explosion in the number of reactions leading to the synthesis of functionalized 1,2,3-triazoles beginning from the copper-catalysed click reaction reported by Sharpless.[23] Amino acid- or amine-catalysed [3+2]-cycloaddition entering into this field has given rise to an "organocatalytic click strategy" for the synthesis of substituted 1,2,3-triazoles,[24-26] which has proved itself at par and in many cases ahead of similar metal mediated transformations in terms of atom-economy and selectivity (eq. a, Scheme 1).[24-26]

The realm of organocatalytic 1,2,3-triazole synthesis initiated by our group in 2008 was further enriched by the groups of Pons-Bressy, Wang, Dehaen, Paixão, Alves, Li and many other groups. In early years, this field witnessed a surge in enamine-mediated 1,2,3-triazole formation from different carbonyl compounds like enones, β-ketoesters, ketones and enals with tosyl/aryl azides.[24] In the year 2014, an approach complimentary to the enamine based strategy, an enolate-mediated functionally rich 1,2,3-triazole formation was reported by our group (eq. b, Scheme 1).[25a,b,g,h,l]

Scheme 1: Previous and Present Reaction design.



In all the previous organocatalytic reports, though a wide range of activated carbonyls substrates have been employed for the 1,2,3-triazole synthesis, the variability of the reacting partner azide has been limited to simple aryl azides and tosyl azide.

Till now these organocatalytic [3+2]-cycloadditions have been limited to thermally stable aryl azides [decomposition temperature 140-170 °C]. Moving towards the thermally less stable azides, the observance of the interplay between reactivity and stability is a worthy goal to pursue. Step towards our vision was initiated by choosing substituted vinyl azides as the click

partners (eq. d, Scheme 1).[27a] Rationale for this choice has been the fact that vinyl azides are of medium thermal stability [decomposition temperature 60-70 °C] and are more reactive towards such transformations than tosyl, aryl or alkyl azides as shown in Scheme 1. Respective vinyl substituted 1,2,3-triazoles could also occupy major role in medicinal to material chemistry. According to the earlier reports,[27b-c,24f] the physicochemical or electronic factors which need to be considered for reactivity were the existence of more number of dipolar mesomeric or resonance structures from the azido moiety with attached group and it has been shown that more the number of dipolar mesomeric or resonance structures more is the reactivity of the azide partner. Due to this double-bond character between N^1-N^2 in R-N^1-N^2≡N^3 is decreased by introducing an acyl, ester or sulfonyl group in conjugation with the triazo group. Therefore acyl or sulfonyl azides are less stable than alkyl/aryl azides. This factor renders aliphatic azides though thermally highly stable, less reactive in these [3+2]-cycloaddition reactions. A fine balance of electronic and thermal factors is achieved in choosing vinyl azides as click partners. If such a transformation could be achieved this would be a very simple way of introducing an olefinic functionality directly into the 1,2,3-triazole moiety of which previous reports have been scarce.[1,3,28]

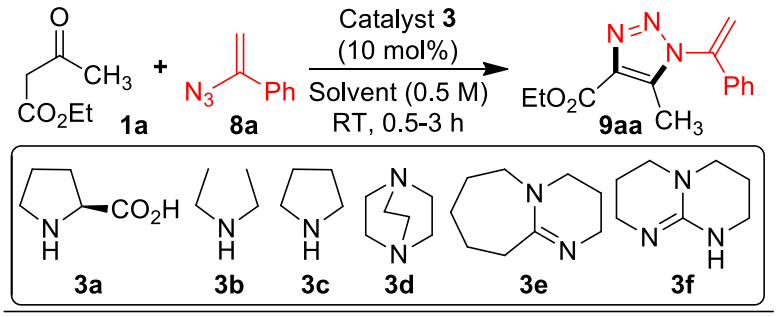
3.2 Results and Discussion

3.2.1 Reaction preliminary optimization:

We optimized the designed organo-click reaction by screening simple organocatalysts for the [3+2]-cycloaddition of ethyl acetoacetate **1a** with 1.5 equiv. of *α*-azidostyrene **8a** under ambient conditions (Table 1). The reaction of **1a** with 1.5 equiv. of *α*-azidostyrene **8a** in DMSO under 10-mol% of proline **3a**-catalysis did not furnished the expected product **9aa** even after 24 h at 25 °C (Table 1, entry 1). The same reaction under 10-mol% of diethyl amine **3b**-catalysis furnished the 1-vinyl-1*H*-1,2,3-triazole **9aa** in only 35% yield with complete consumption of starting materials (Table 1, entry 2). The click reaction of **1a** with 1.5 equiv. of **8a** in DMSO under 10-mol% of pyrrolidine **3c**-catalysis did not furnished the expected product **9aa**; but ethyl acetoacetate **1a** is consumed totally (Table 1, entry 3). After obtaining discouraging results with

the catalysts **3a-c** through enamine-mediated reaction,[24] we thought of investigating the click reaction through the in situ enolate formation,[25] for which we tested some *tert*-amines **3d-f** and base **3g-h** as the catalysts for the organo-click reaction. Organo-click reaction of **1a** with **8a** under 1,4-diazabicyclo[2.2.2]octane (DABCO) **3d**-catalysis didn't furnish the expected product **9aa** (Table 1, entry 4). Intriguingly, the reaction of **1a** with 1.5 equiv. of **8a** in DMSO under 10-mol% of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) **3e**-catalysis at 25 °C for 3.0 h furnished **9aa** in 88% yield (Table 1, entry 5).

Table 1: Reaction Preliminary Optimization.[a]



Entry	Catalyst **3**	Solvent	*t* [h]	Yield **9aa** [%][b]
1	**3a**	DMSO	24	–
2	**3b**	DMSO	3.0	35
3[c]	**3c**	DMSO	3.0	–
4	**3d**	DMSO	3.0	–
5	**3e**	DMSO	3.0	88
6	**3e**	DMF	3.0	85
7	**3e**	$CHCl_3$	3.0	11
8	**3e**	CH_3CN	3.0	37
9	**3f**	DMSO	3.0	98
10	K_2CO_3 **3j**	DMSO	1.5	83
11	*t*BuOK **3k**	DMSO	1.5	84
12	–	DMSO	24	–

[a] Reactions were carried out in solvent (0.5 M) with 1.5 equiv. of **8a** relative to the **1a** (0.5 mmol) in the presence of 10-mol% of catalyst **3**. *b* Yield refers to the column-purified product. [c] EAA **1a** was consumed totally.

Deviating from this condition, by switching the solvent to DMF, $CHCl_3$ or CH_3CN by using 10-mol% of DBU **3e** as the catalyst was not so successful in promoting the high-yielding click reaction (Table 1, entries 6, 7, and 8).[25l] These solvent studies clearly support our hypothesis of involvement of reactive enolate formation and their stability. With these moderate results, we thought of using a strong organic base, the commercially available guanidine 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD) **3f** as the catalyst for [3+2]-cycloaddition. Because, the p*K*a value of the conjugate acid of TBD **3f** in acetonitrile is close to 26 and also TBD **3f** has been applied as a suitable catalyst for a variety of reactions, including Michael, Wittig, Henry, Strecker, transesterification and acyl transfer reactions.[29] Fascinatingly, the click reaction of **1a** with 1.5 equiv. of **2a** in DMSO under 10-mol% of TBD **3f**-catalysis at 25 °C for 3.0 h furnished the 1-vinyl-1*H*-1,2,3-triazole **4aa** in 98% yield (Table 1, entry 9). Relatively less basic *tert*-amines like DABCO [p*K*a 8.8] **3d**, and DBU [p*K*a 12.0] **3e** catalysts furnished the 1-vinyl-1*H*-1,2,3-triazole **9aa** with poor to good yields compared to TBD [p*K*a 26.0] **3f** (Table 1, entries 4 to 9), also no reaction was observed without the catalyst in DMSO for 24 h at 25 °C (Table 1, entry 12). The same click reaction under 10-mol% of non-amine bases K_2CO_3 [p*K*a 10.33] **3j** and *t*BuOK [p*K*a 29.4] **3k**-catalysis also furnished the 1-vinyl-1*H*-1,2,3-triazole **9aa** in good yields within 1.5 h at 25 °C; but which is inferior to TBD **3f**-catalysis (Table 1, entries 10-11). We finally envisioned the optimized condition to be 25 °C in DMSO under 10-mol% of TBD **3f**-catalysis which furnished the 1-vinyl-1*H*-1,2,3-triazole **9aa** in 98% yield from **1a** and **8a** (Table 1,entry 9).

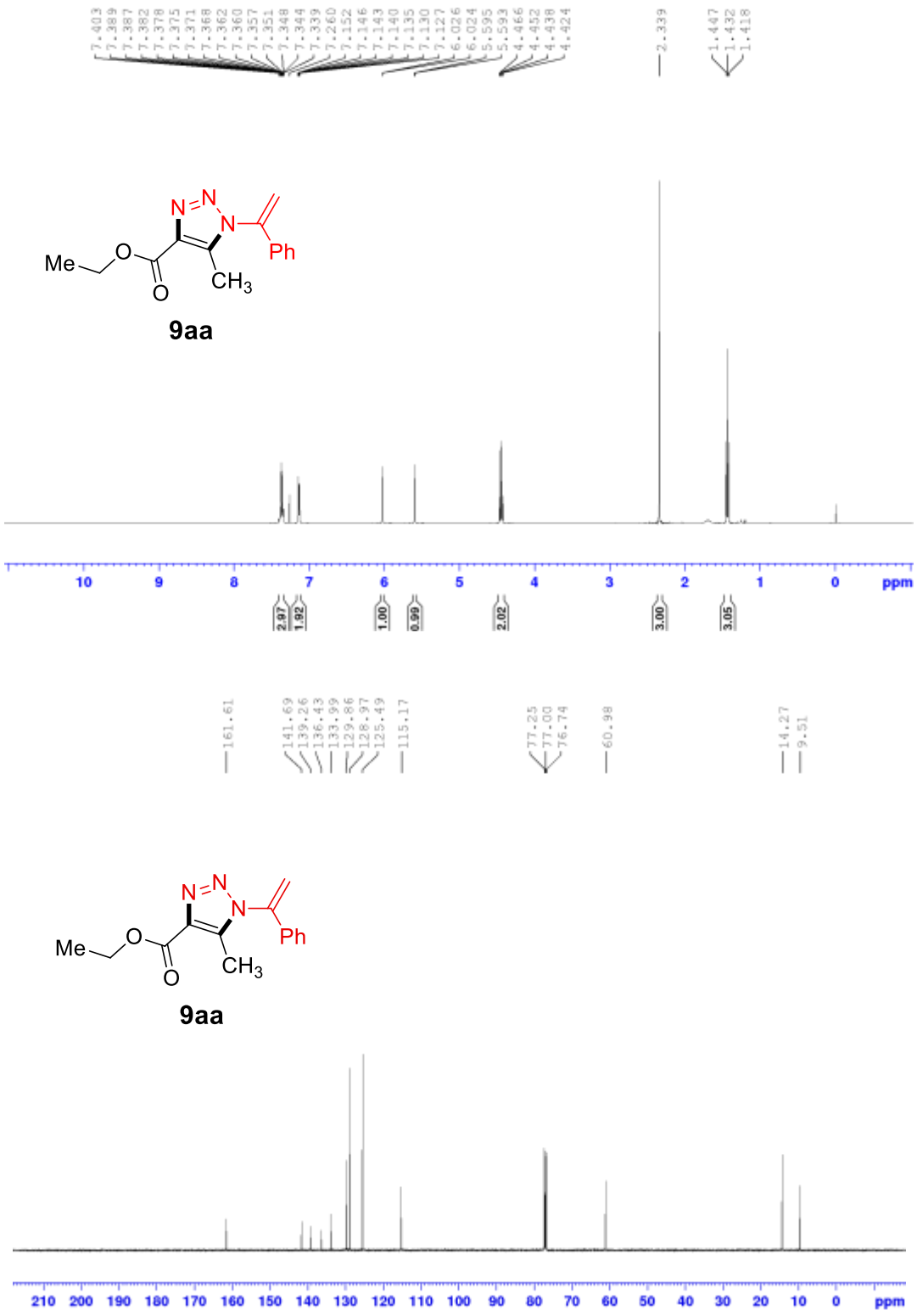
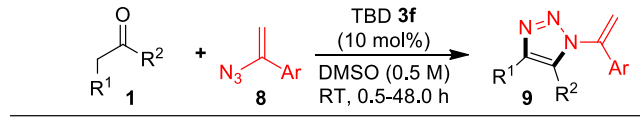


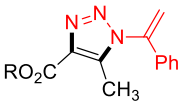
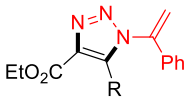
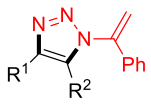
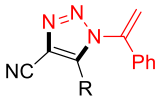
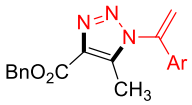
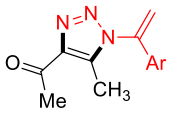
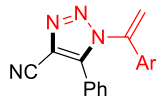
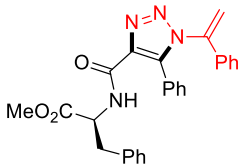
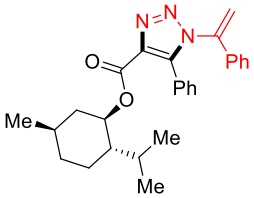
Figure-2: ^{1}H NMR and ^{13}C NMR spectrum of product **9aa**.

3.2.2 Substrate Scope of the Organocatalysed Click Reaction:

With the best conditions in hand, the wider scope and the generality of the novel TBD-catalysed click reactions were investigated. A variety of functionalized activated carbonyls such as alkyl acetoacetates **1b-e**, ethyl 3-oxo-3-alkyl/aryl-propanoates **1f-k**, alkyl/aryl substituted 1,3-diketones **1l-o**, 3-oxo-3-alkyl/aryl-propanenitriles **1p-r**, chiral *N*-alkyl-3-oxo-3-phenylpropanamide **1s** and chiral alkyl 3-oxo-3-phenylpropanoate **1t** were reacted with substituted *α*-azidostyrenes **8a-g**, or ((2-azidoallyl)oxy)benzenes **8h-i** catalysed by 10-mol% of TBD **3f** at 25 °C in DMSO for 0.5-48 h as shown in Table 2. Interestingly, the click reaction of alkyl acetoacetates **1b-e** containing different alkyl groups like methyl, allyl, propargyl, and benzyl with *α*-azidostyrene **8a** under **3f**-catalysis furnished the expected 1-vinyl-1*H*-1,2,3-triazoles **9ba-ea** in excellent to good yields within 1.0-3.0 h (Table 2). In a similar manner, the TBD **3f**-catalyzed click reaction of **8a** with ethyl 3-oxo-3-alkyl/aryl-propanoates **1f-k** containing ethyl, *n*-propyl, trifluoromethyl, phenyl, 4-nitrophenyl and 4-methoxyphenyl furnished the expected functionalized 1-vinyl-1*H*-1,2,3-triazoles **9fa-ka** in excellent to moderate yields from 2.5-48.0 h (Table 2). Yields of the 1-vinyl-1*H*-1,2,3-triazole products **9fa-ga** were sustained with 93-94%, but the yields slightly decreased by increasing the reaction time with electron withdrawing groups such as trifluoromethyl, phenyl, 4-nitrophenyl and 4-methoxyphenyl compared to methyl group (Table 2). For example, instead of 10 mol% of TBD **3f**, 1.2 equiv. of DBU-catalysed click reaction of the ethyl 4,4,4-trifluoro-3-oxobutanoate **1h** with **8a** in DMSO at 25 °C for 48 h furnished the 1,2,3-triazole **9ha** in only 50% yield (Table 2). Click reaction of symmetric 1,3-diketones like pentane-2,4-dione **1l** and 1,3-diphenylpropane-1,3-dione **1m** with **8a** under 10-mol% of **3f**-catalysis furnished the selective products **9la** in 77% yield in 2.0 h and **9ma** in 70% yield in 7.0 h, respectively (Table 2).

Table 2: Substrate Scope.[a]



	**9ba:** R = Me (2.5 h; 92%) **9ca:** R = allyl (3.0 h; 82%) **9da:** R = propargyl (1.5 h; 97%) **9ea:** R = benzyl (1.0 h; 92%)
	**9fa:** R = CH_3CH_2 (2.5 h; 94%) **9ga:** R = $CH_3CH_2CH_2$ (3.0 h; 93%) **9ha:** R = CF_3 (48 h; 50%)[b] **9ia:** R = Ph (7.0 h; 82%) **9ja:** R = 4-$NO_2C_6H_4$ (16.0 h; 90%) **9ka:** R = 4-$OMeC_6H_4$ (8.0 h; 70%)
	**9la:** R^1 = Ac, R^2 = Me (2.0 h; 77%) **9ma:** R^1 = Bz, R^2 = Ph (7.0 h; 70%) **9na:** R^1 = Ac, R^2 = Ph (32%) **+** **9'na:** R^1 = Bz, R^2 = Me (21%); *t* (7.0 h) **9oa:** R^1 = 3,4,5-$(OMe)_3C_6H_2CO$, R^2 = Ph (21%) **+** **9'oa:** R^1 = Bz, R^2 = 3,4,5-$(OMe)_3C_6H_2$ (21%); *t* (5.5 h)
	**9pa:** R = Ph (7.0 h; 82%) **9qa:** R = 4-MeC_6H_4 (7.0 h; 87%) **9ra:** R = *t*-Bu (7.5 h; 70%)
	**9eb:** Ar = 4-FC_6H_4 (1.0 h; 96%) **9ec:** Ar = 4-ClC_6H_4 (1.5 h; 90%) **9ed:** Ar = 4-MeC_6H_4 (4.0 h; 80%)[c] **9ee:** Ar = 2-MeC_6H_4 (2.0 h; 82%)[c] **9ef:** Ar = 4-$OMeC_6H_4$ (5.0 h; 30%)[c] **9eg:** Ar = 2-naphthyl (4.0 h; 80%) **9eh:** Ar = 4-$PhC_6H_4OCH_2$ (0.85 h; 85%) **9ai:** Ar = 4-$NO_2C_6H_4OCH_2$ (0.75 h; 90%)[d]
	**9lb:** Ar = 4-FC_6H_4 (0.5 h; 91%) **9lc:** Ar = 4-ClC_6H_4 (0.5 h; 90%)
	**9pb:** Ar = 4-FC_6H_4 (4.0 h; 90%) **9pc:** Ar = 4-ClC_6H_4 (4.0 h; 85%)
	(+)-**9sa:** *t* (12 h); 87%
	(–)-**9ta:** *t* (3 h); 80%

[a] Reactions were carried out in DMSO (0.5 M) with 1.5 equiv. of **8** relative to the **1** (0.5 mmol) in the presence of 10-mol% of **3f** and yield refers to the column-purified product. [b] 1.2 equiv. of DBU **3e** was used as catalyst. [c] Reaction performed in neat with 30 mol% of **3f**. [d] Ethyl acetoacetate **1a** was used.

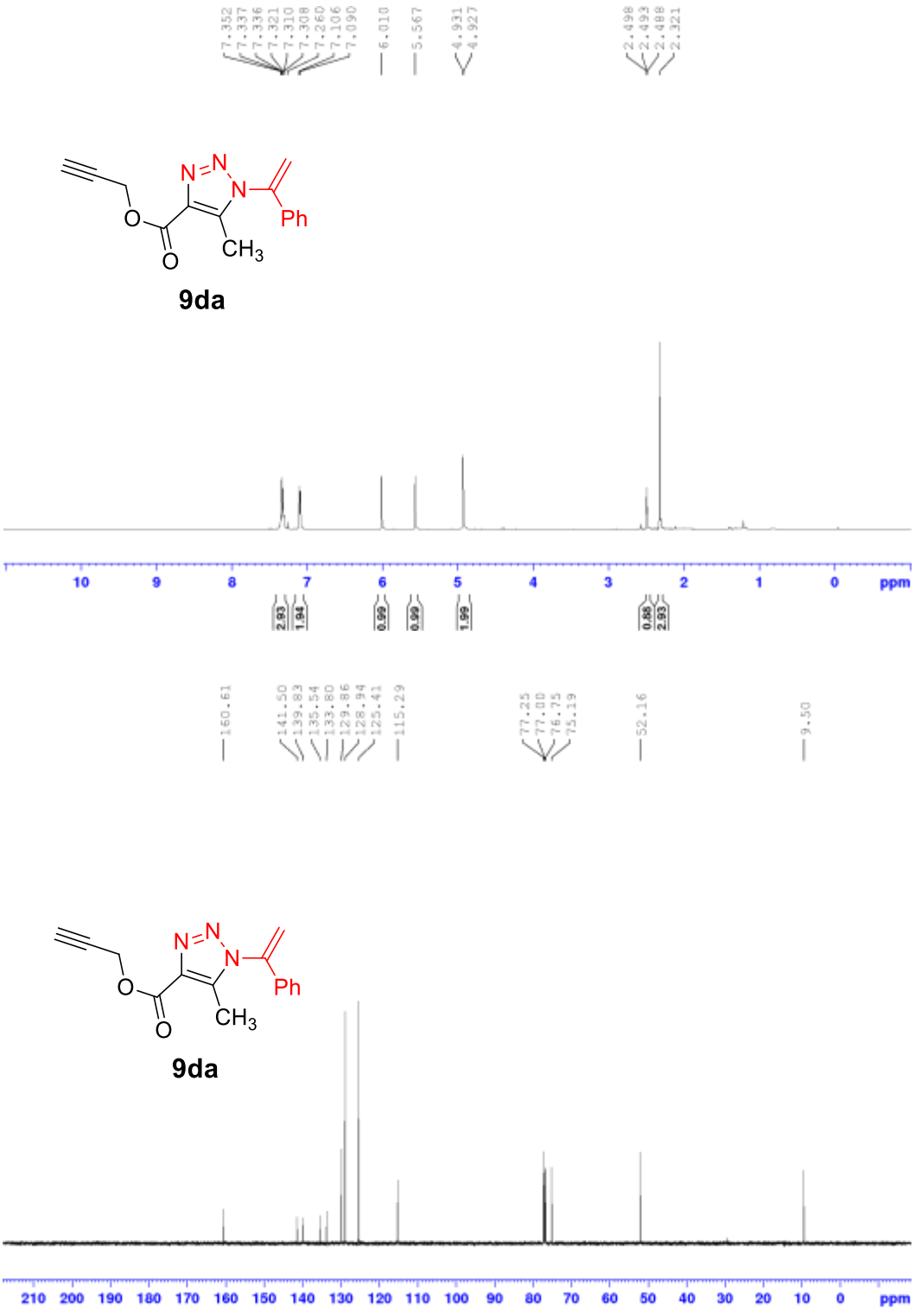


Figure-3: ^{1}H NMR and ^{13}C NMR spectrum of product **9da**.

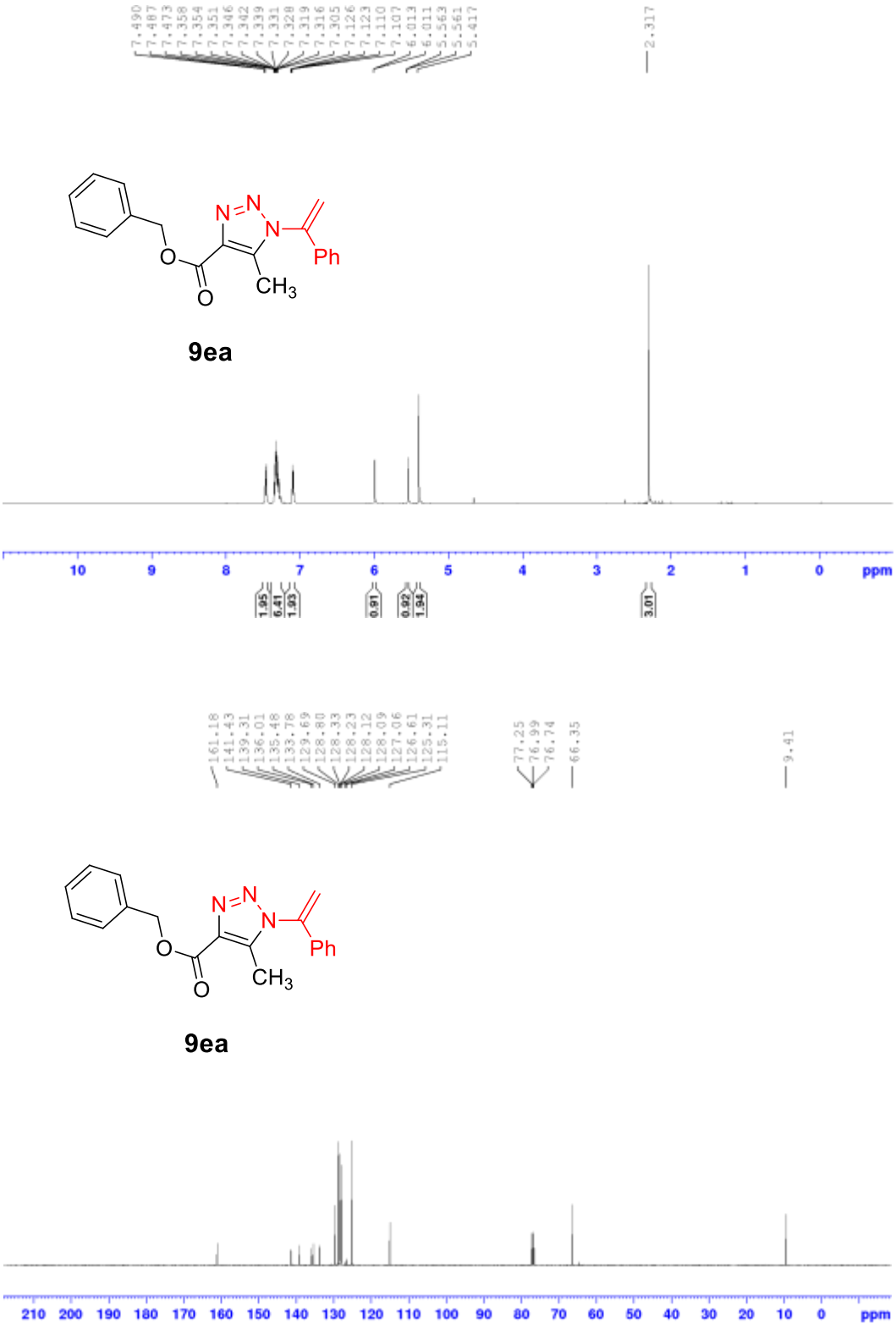


Figure-4: ^{1}H NMR and ^{13}C NMR spectrum of product **9ea**.

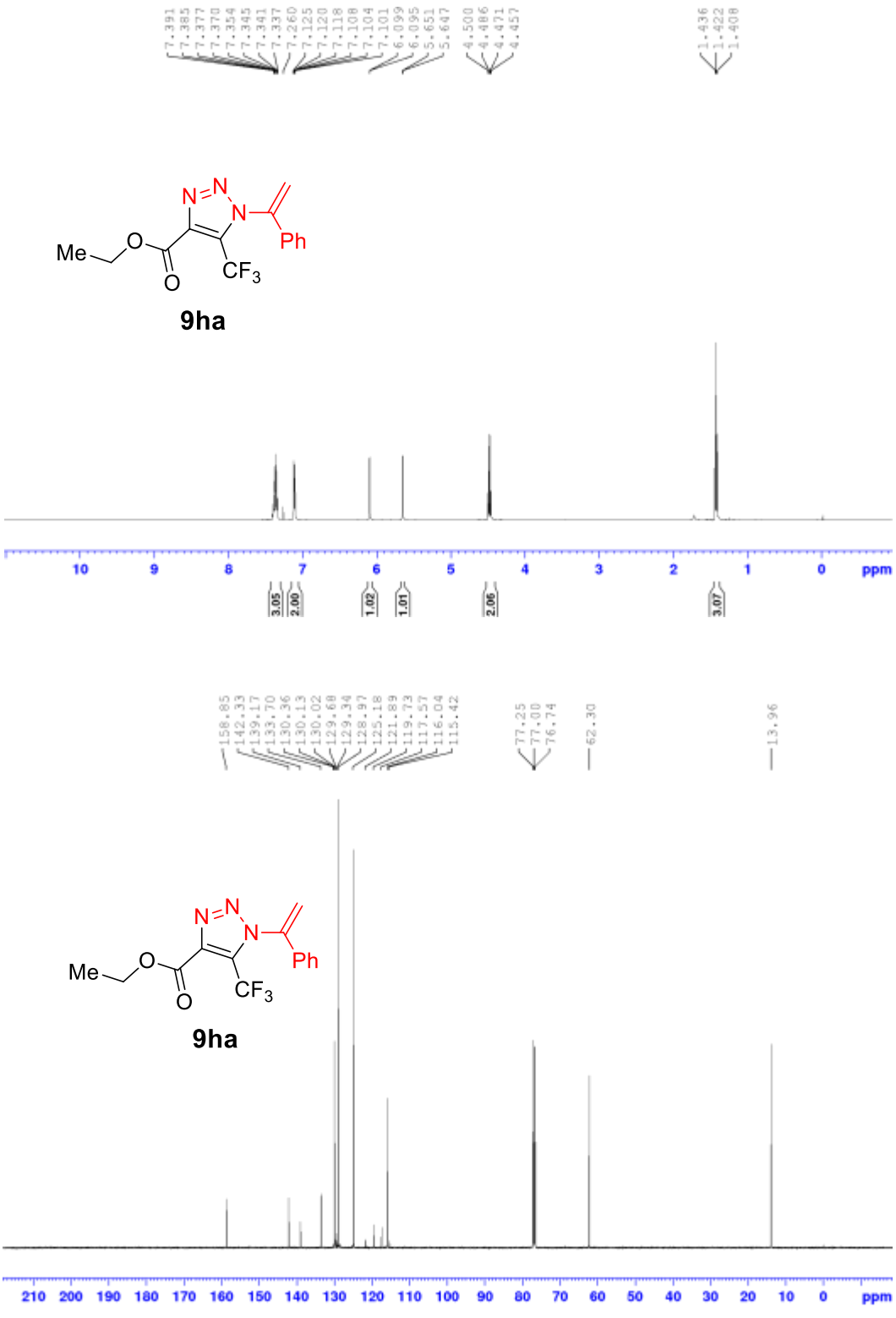


Figure-5: ^{1}H NMR and ^{13}C NMR spectrum of product **9ha**.

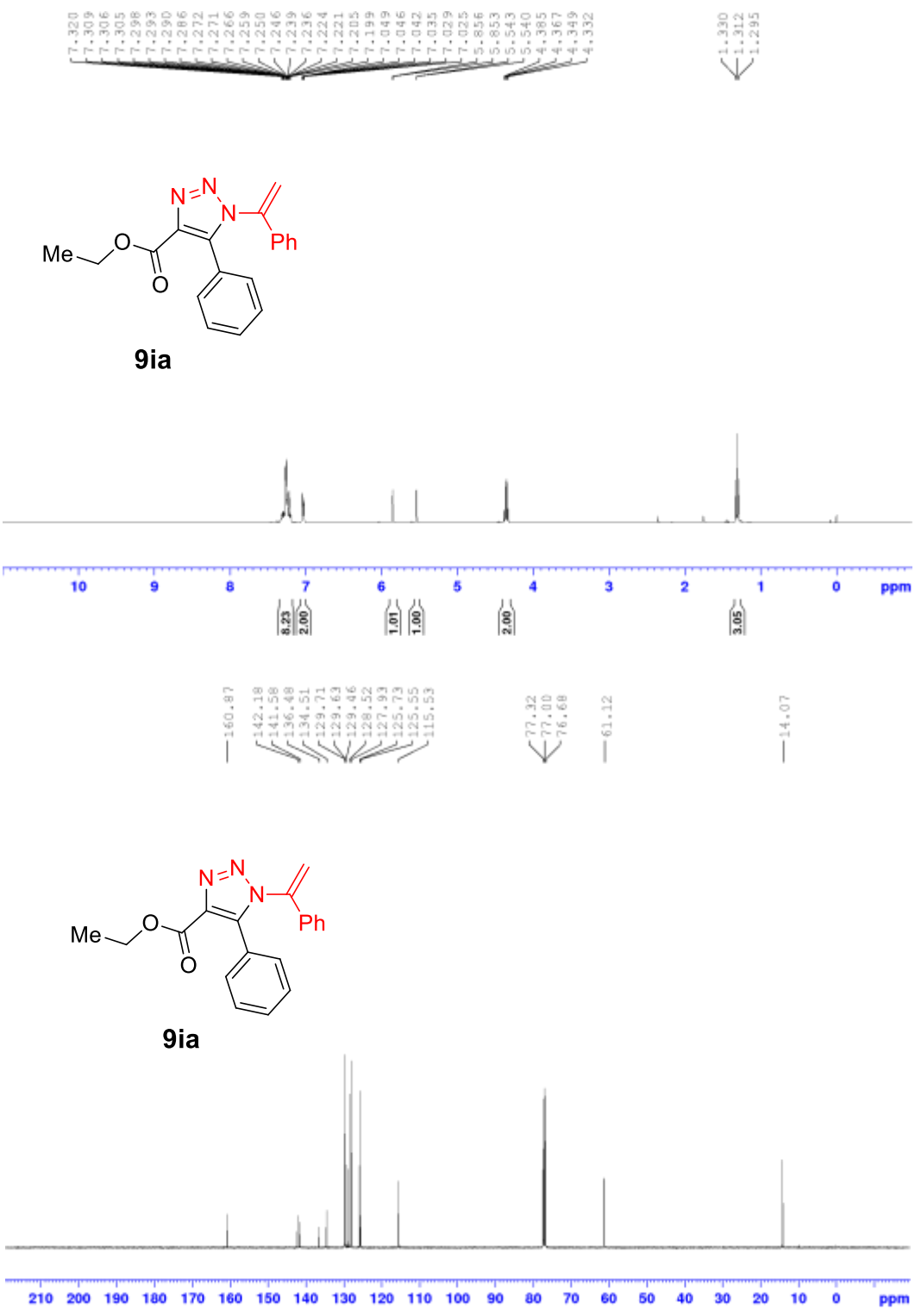


Figure-6: ^{1}H NMR and ^{13}C NMR spectrum of product **9ia**.

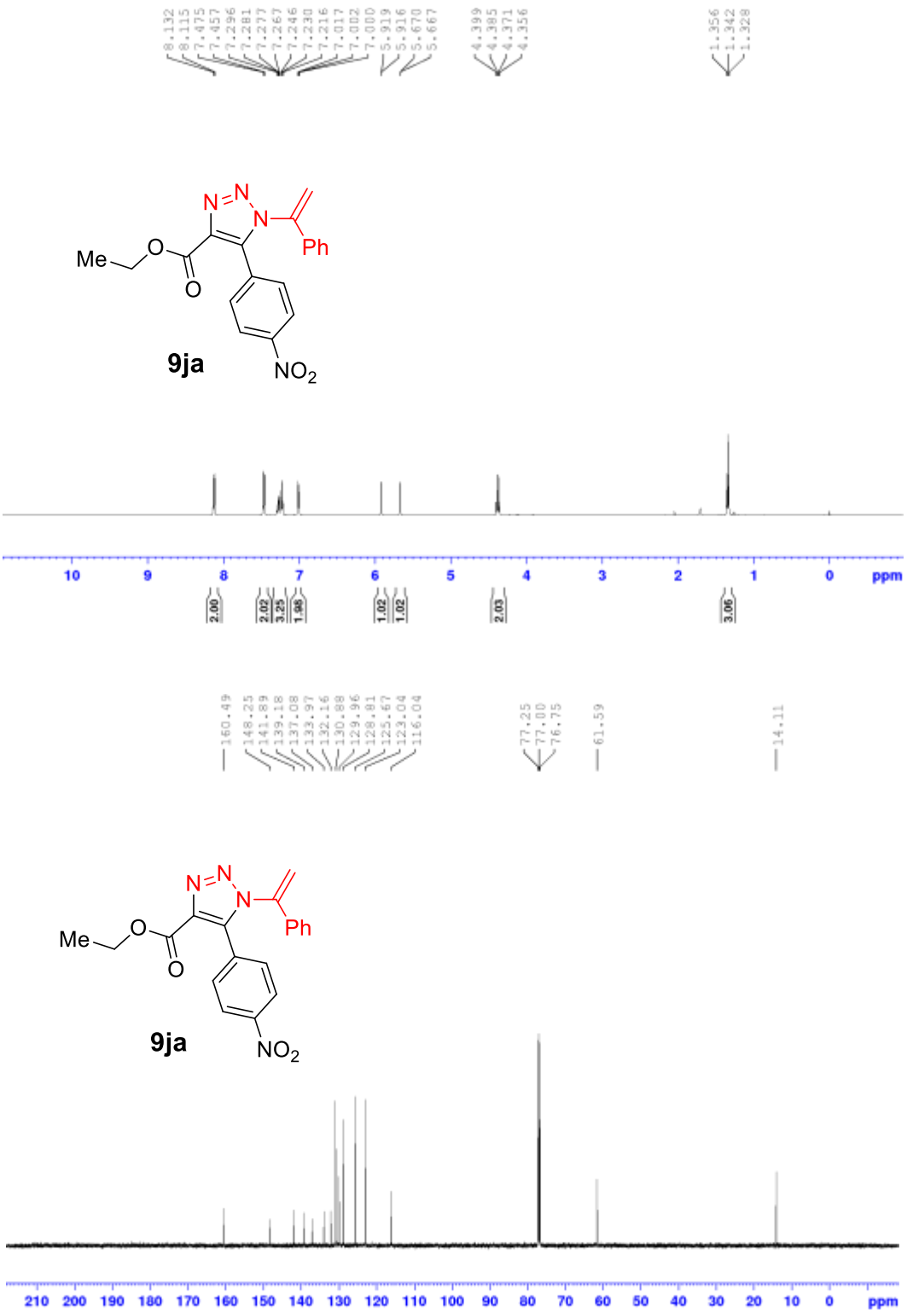


Figure-7: ^{1}H NMR and ^{13}C NMR spectrum of product **9ja**.

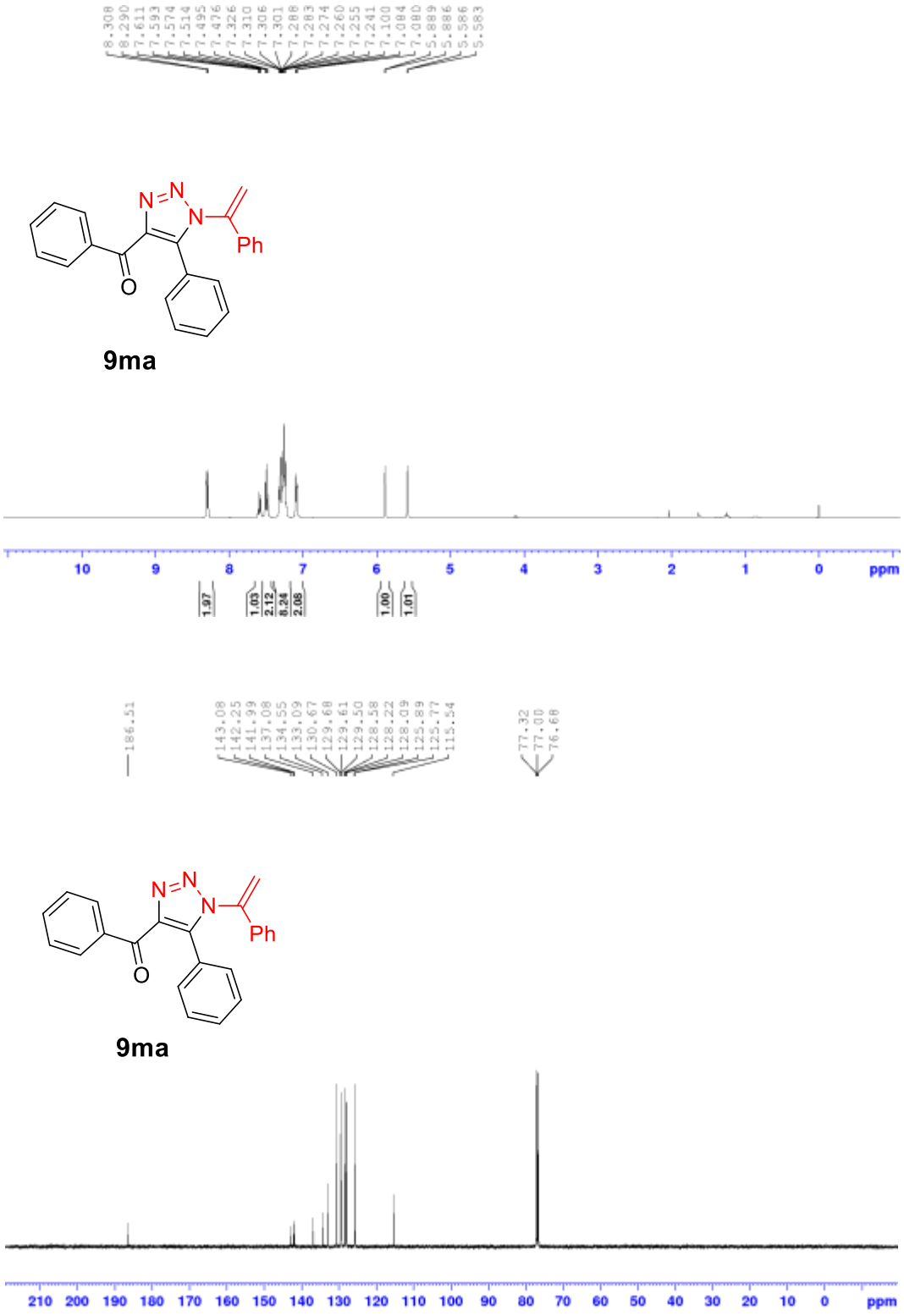


Figure-8: ^{1}H NMR and ^{13}C NMR spectrum of product **9ma**.

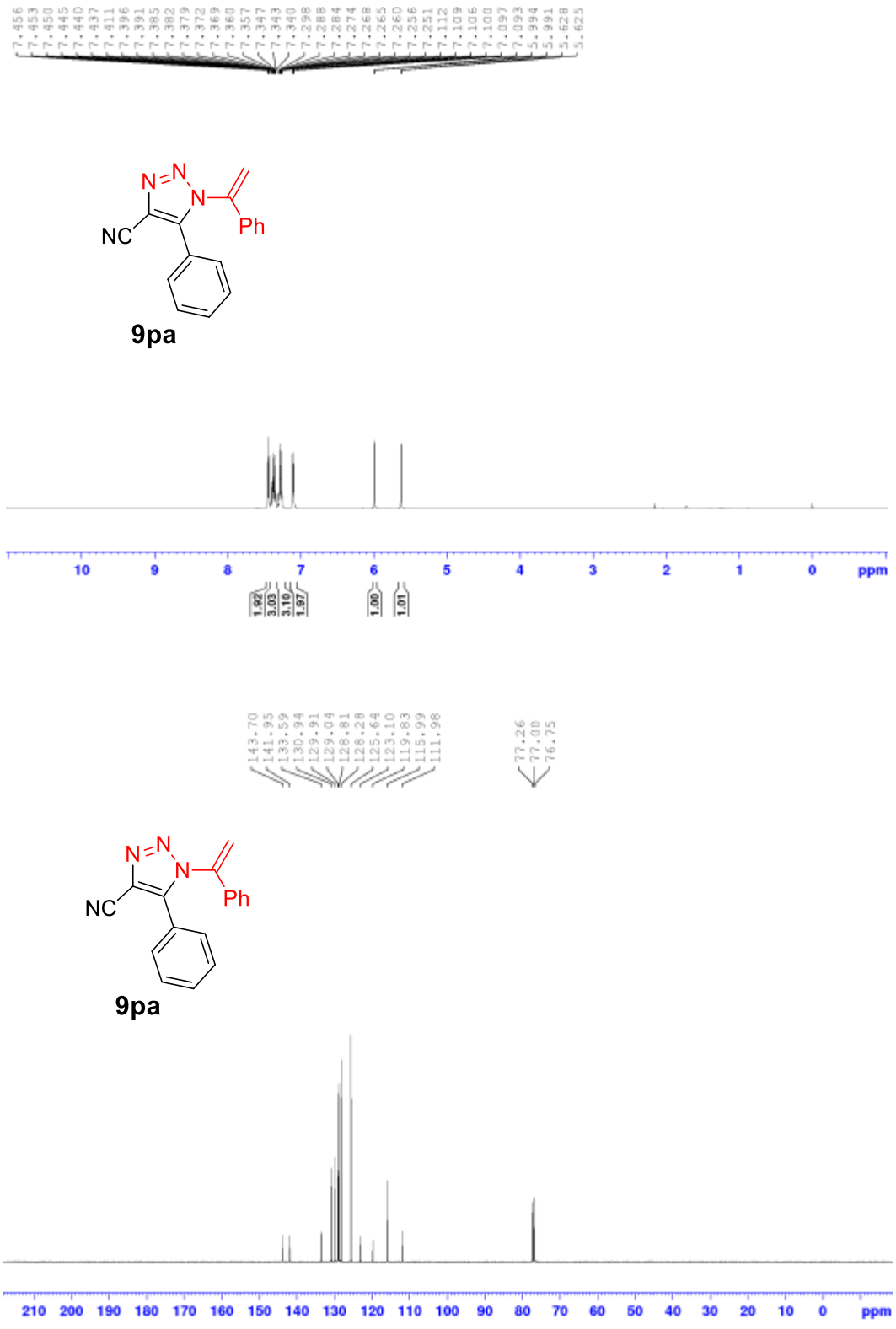


Figure-9: ^{1}H NMR and ^{13}C NMR spectrum of product **9pa**.

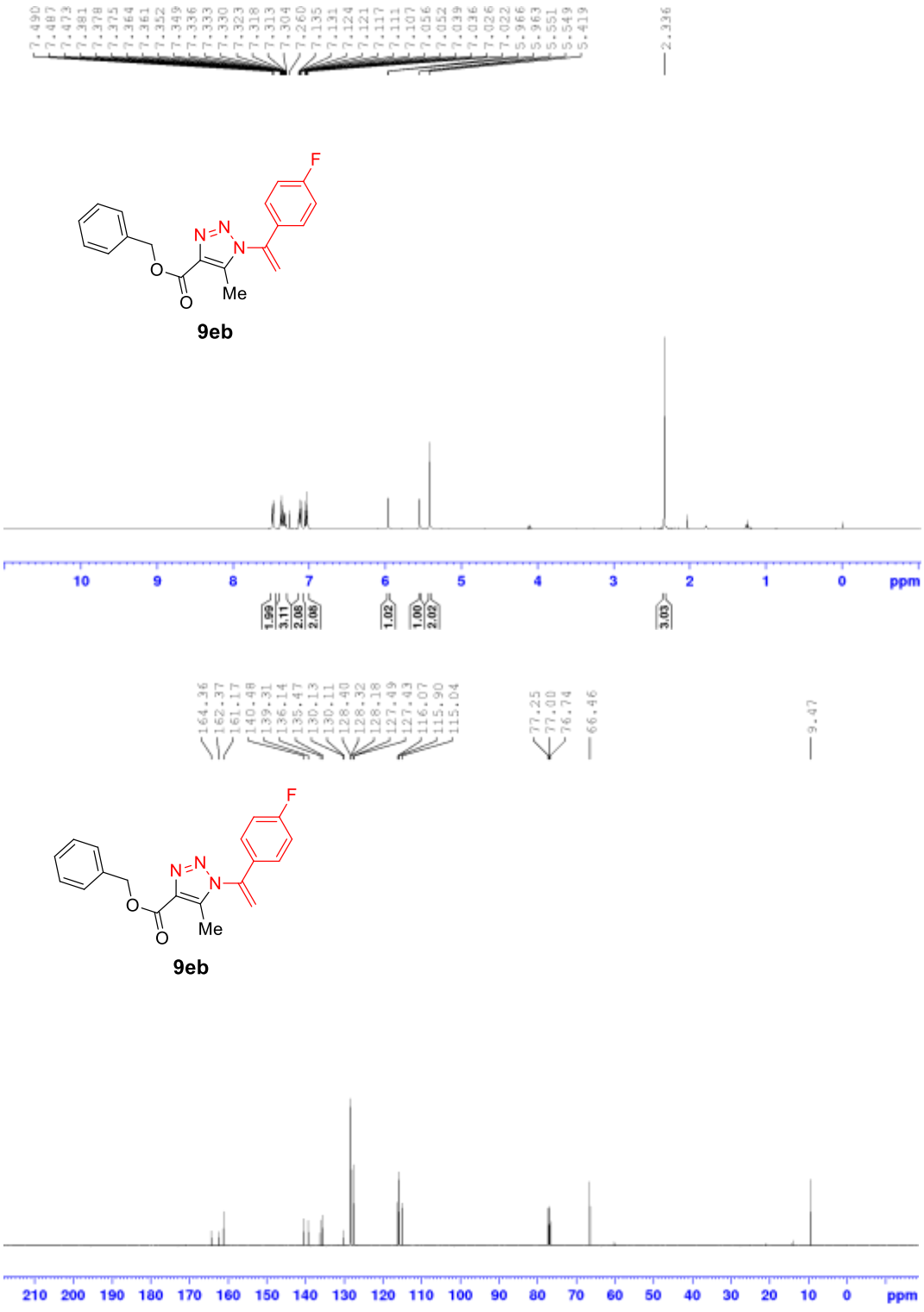


Figure-10: ^{1}H NMR and ^{13}C NMR spectrum of product **9eb**.

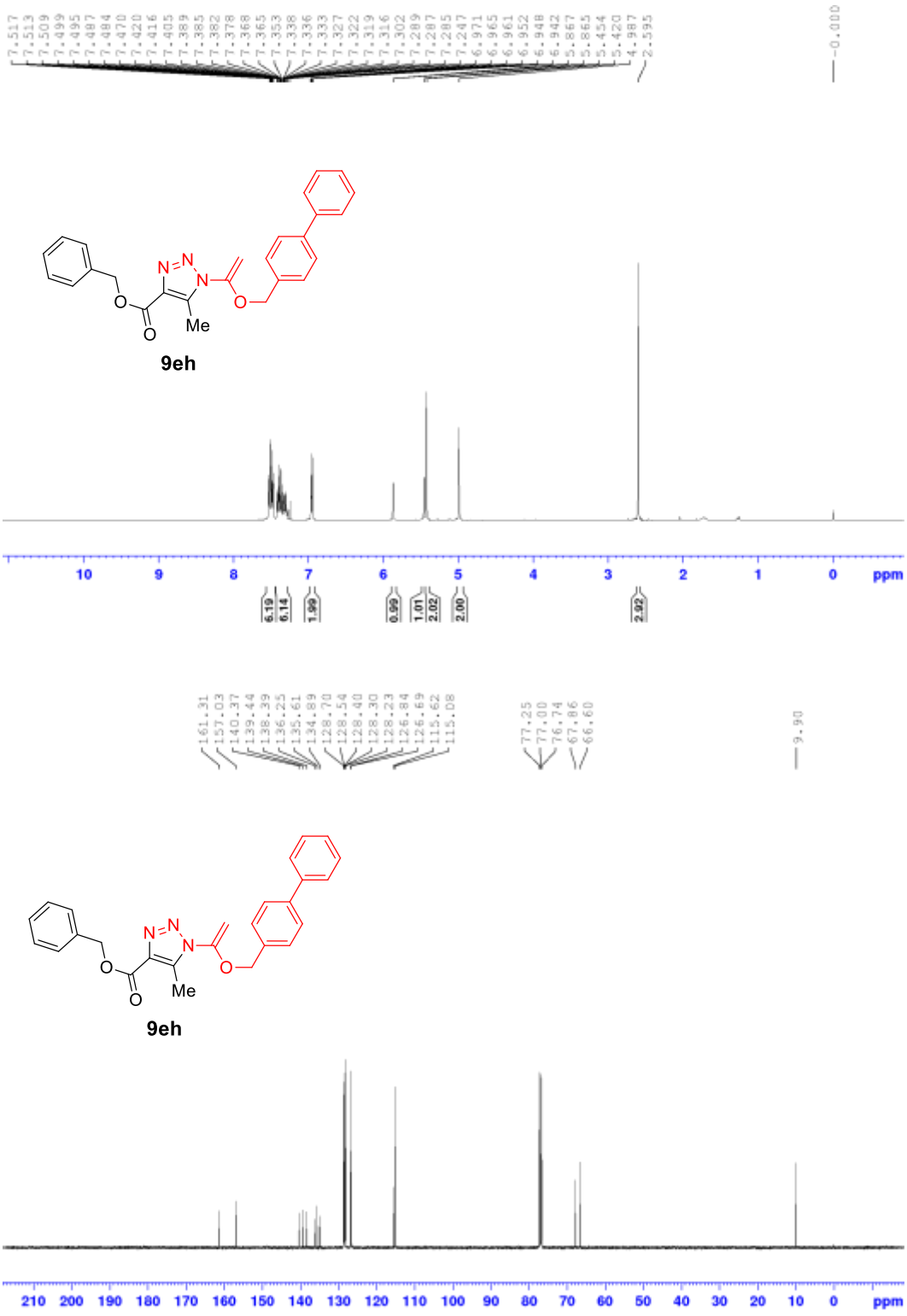


Figure-11: ^{1}H NMR and ^{13}C NMR spectrum of product **9eh**.

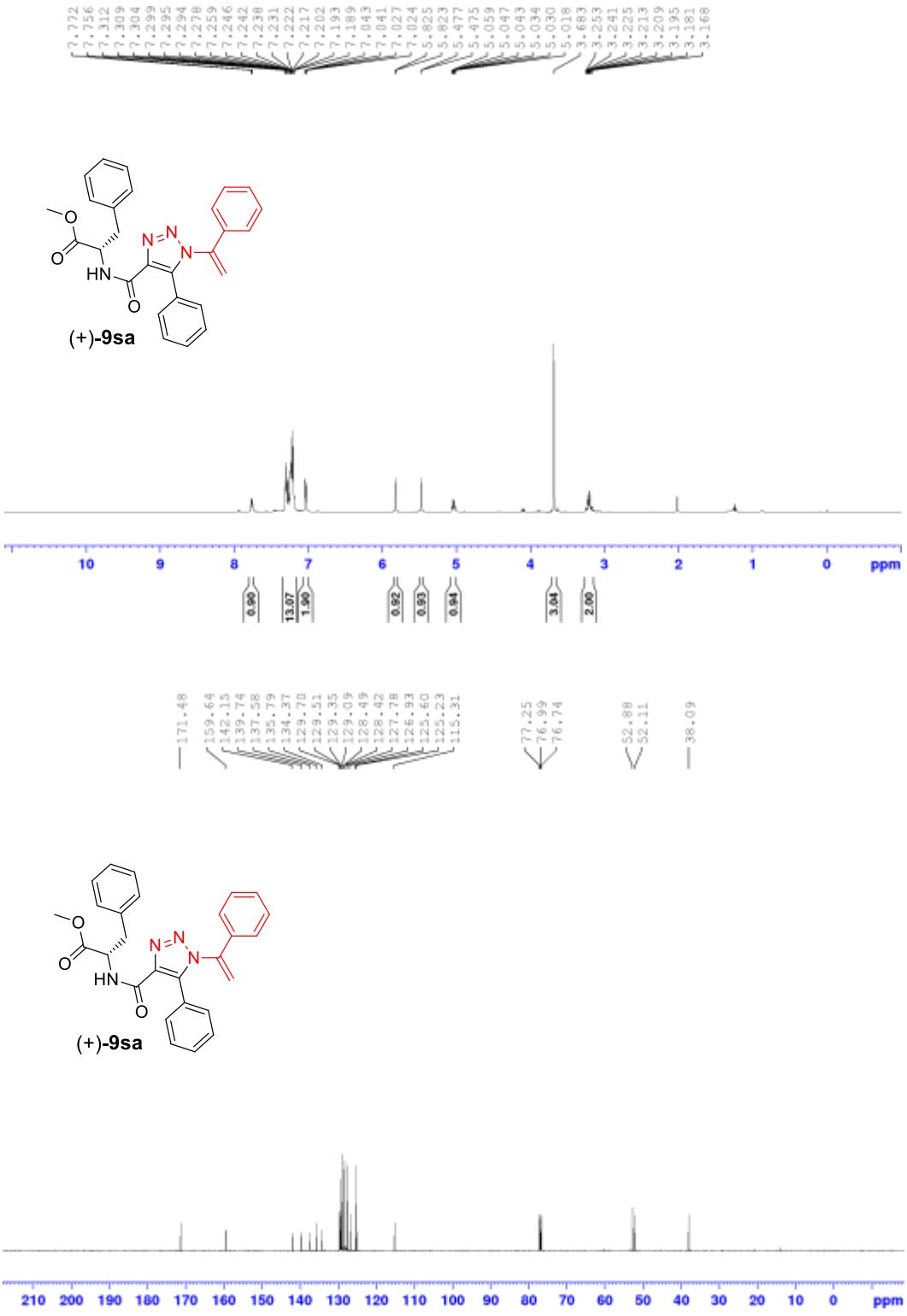


Figure-12: ^{1}H NMR and ^{13}C NMR spectrum of product (+)-**9sa**.

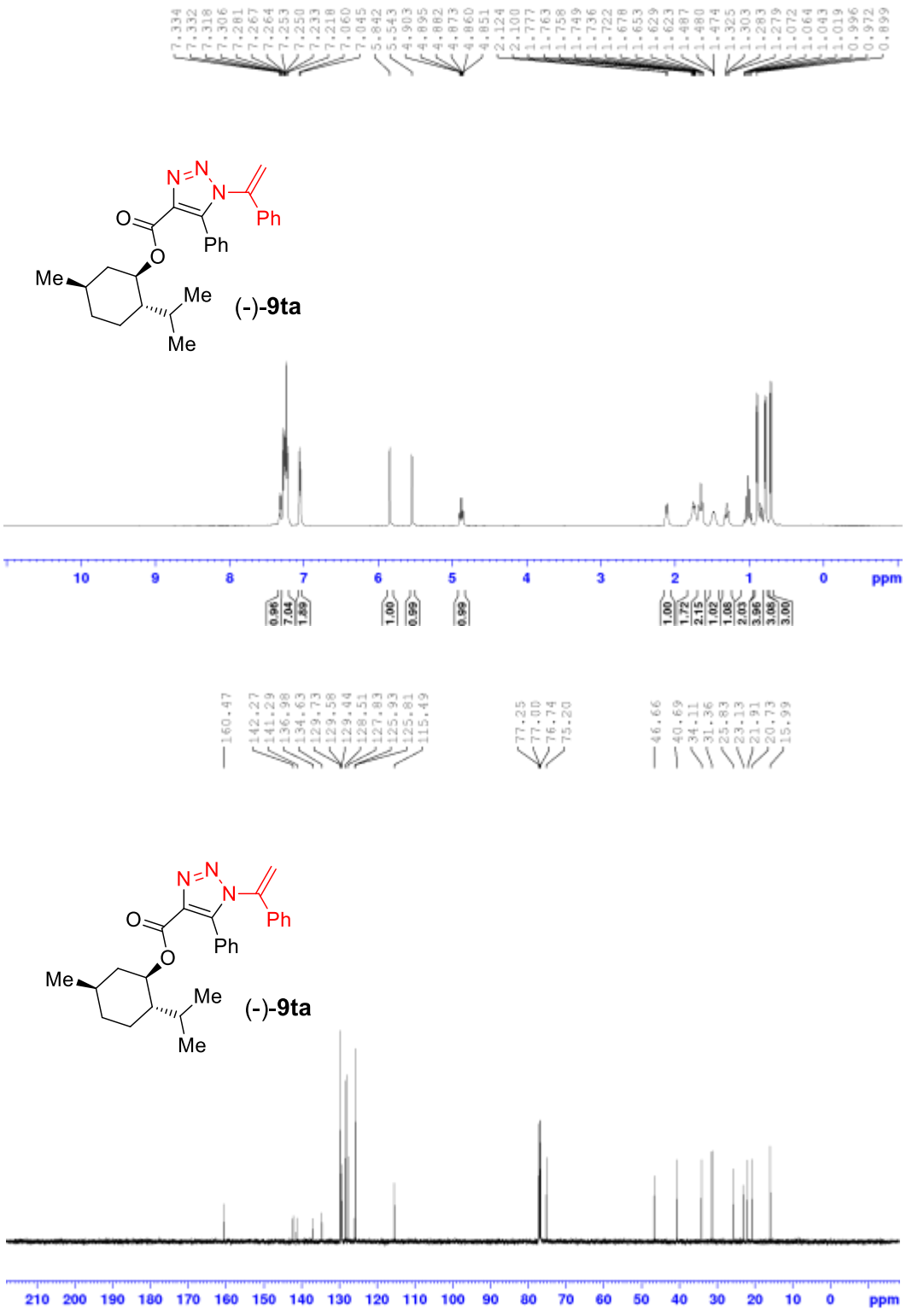


Figure-13: ^{1}H NMR and ^{13}C NMR spectrum of product (-)-**9ta**.

After clear understanding of the electronic factors of activated carbonyls **1** in the [3+2]-cycloaddition reaction, we investigated the reaction scope with different α-azidostyrenes and α-azido olefins **8b-i** with **1e** or **1a** in the presence of catalytic amount of TBD **3f** at 25 °C (Table 2). In this reaction, α-azidostyrenes **8b-f** containing different functional groups of 4-F, 4-Cl, 4-CH_3, 2-CH_3 and 4-OCH_3 were used as substrates along with **1e** for the organocatalytic click synthesis of the single isomer of 1,2,3-triazoles **9eb-ef** in excellent to good yields within 1.0-5.0 h (Table 2). Surprisingly, click reaction of α-azidostyrenes **8d-f** containing 4-CH_3, 2-CH_3 and 4-OCH_3 with **1e** under the standard conditions [10-mol% **3f** in DMSO at 25 °C] furnished the products **9ed-ef** in moderate to poor yields, but the same reaction under 30-mol% of **3f** in neat furnished the expected products **9ed-ef** in good yields (Table 2). Organo-click reaction of **1e** with 2-(1-azidovinyl)naphthalene **8g** under **3f**-catalysis at 25 °C for 4.0 h furnished the expected product **9eg** in 80% yield. With applications in mind, we performed the organo-click reaction of **1a** or **1e** with simple aliphatic α-azido olefins **8h-i** to furnish the expected click products in very good yields within 0.85 h as shown in Table 2. To test the generality of this methodology, we performed few more click reactions by using α-azidostyrenes **8b-c** containing 4-F and 4-Cl with activated carbonyls of pentane-2,4-dione **1l** and 3-oxo-3-phenylpropanenitrile **1p** to furnish the click products **9lb**, **9lc**, **9pb** and **9pc** in very good yields as shown in Table 2. With preparation of chiral functionalized 1-vinyl-1*H*-1,2,3-triazoles in mind, we performed the click reaction of (*S*)-methyl 2-(3-oxo-3-phenylpropanamido)-3-phenylpropanoate **1s** and (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 3-oxo-3-phenylpropanoate **1t** with **8a** under **3f**-catalysis to furnish the chiral click products (+)-**9sa** in 87% and (-)-**9ta** in 80% yield, respectively (Table 2). The results furnished in the Table 2 demonstrate the broad scope of this novel methodology covering a structurally diverse group of activated carbonyls **1a-t** and α -azidostyrenes/ α-azido-olefins **8a-i**. The structure and regiochemistry of the click products **9** were established through NMR analysis and also finally confirmed by the X-ray structure analysis on **9ia** (Figure 14).[30]

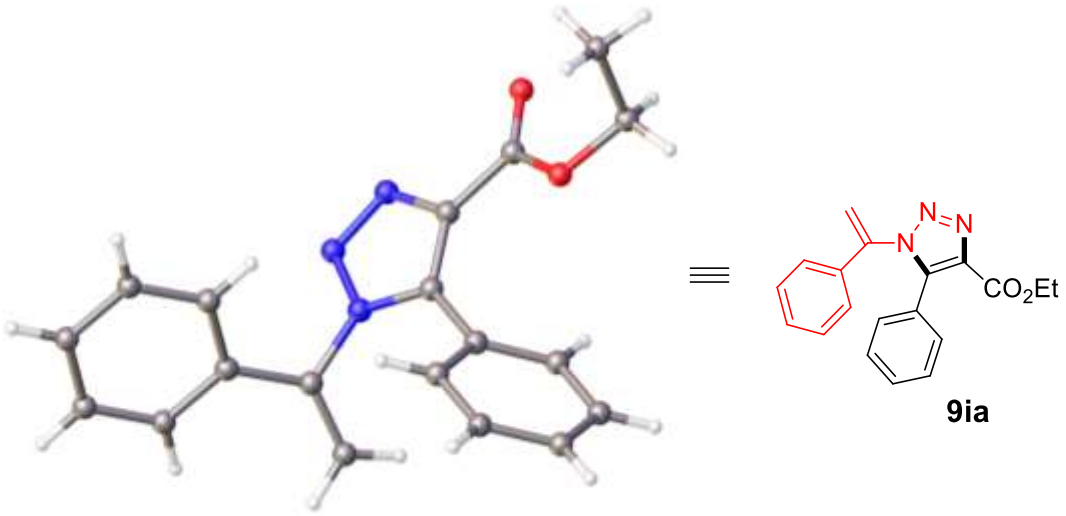
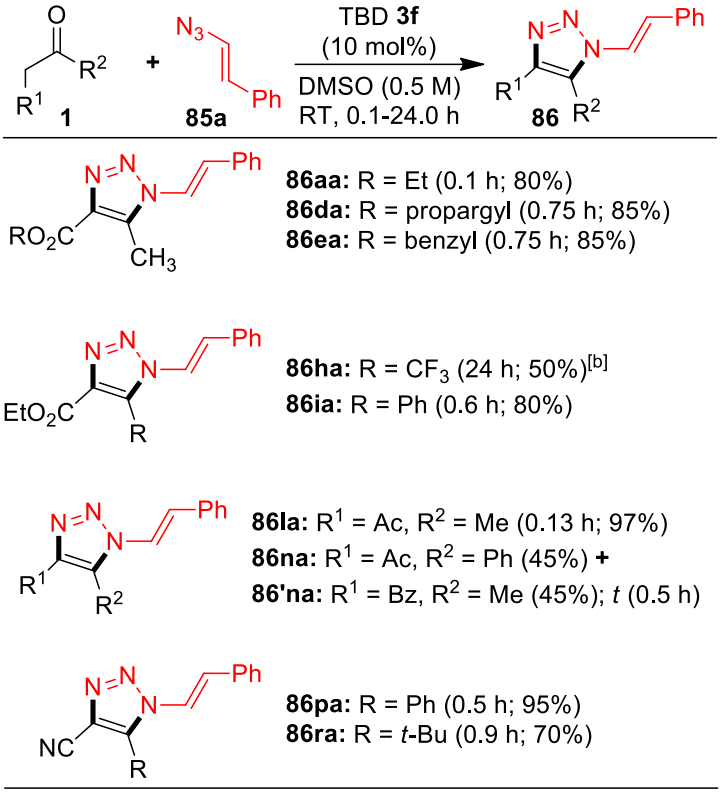


***Figure-14*:** Crystal structure of ethyl 5-phenyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazole-4-carboxylate (**9ia**).

To further understand the electronic nature of azidostyrenes in the organo-click reaction, we have chosen simple (*E*)-*β*-azidostyrene **85a**, which is having linear conjugation (Table 3). Surprisingly, the click reaction of ethyl acetoacetate **1a** with (*E*)-*β*-azidostyrene **85a** under TBD **3f**-catalysis at 25 °C within 0.1 h furnished the expected 1-styryl-1*H*-1,2,3-triazole **6aa** in 80% yield (Table 3, entry 1). Likewise, the click reaction of propargyl acetoacetate **1d** and benzyl acetoacetate **1e** with (*E*)-*β*-azidostyrene **85a** under TBD **3f**-catalysis furnished the 1-styryl-1*H*-1,2,3-triazoles **86da** and **86ea** in 85% yield within 0.75 h, respectively (Table 3, entries 2 and 3). We have also tested six more examples of functionalized activated carbonyls **1h-r** for the organo-click reaction with (*E*)-*β*-azidostyrene **85a**, which furnished the expected substituted 1-styryl-1*H*-1,2,3-triazoles **86ha-86ra** in good to excellent yields (Table 3, entries 4-9). Key point to mention here in all the above nine click reactions is that the reaction rates are very high with shorter times compared to *α*-azidostyrene **8a**. The observed high reactivity of **85a** compared to **8a** in the [3+2]-cycloaddition is mainly due to their differences in conjugation like linear versus cross; because polarizability in **85a** is more compared to **8a**, which is inducing the quick reaction with *in situ* generated enolates.

Table 3: Azide Scope.[a]



[a] Reactions were carried out in DMSO (0.5 M) with 1.5 equiv. of **85a** relative to the **1** (0.5 mmol) in the presence of 10-mol% of **3f** and yield refers to the column-purified product. [b] 1.2 equiv. of DBU **3e** was used as catalyst.

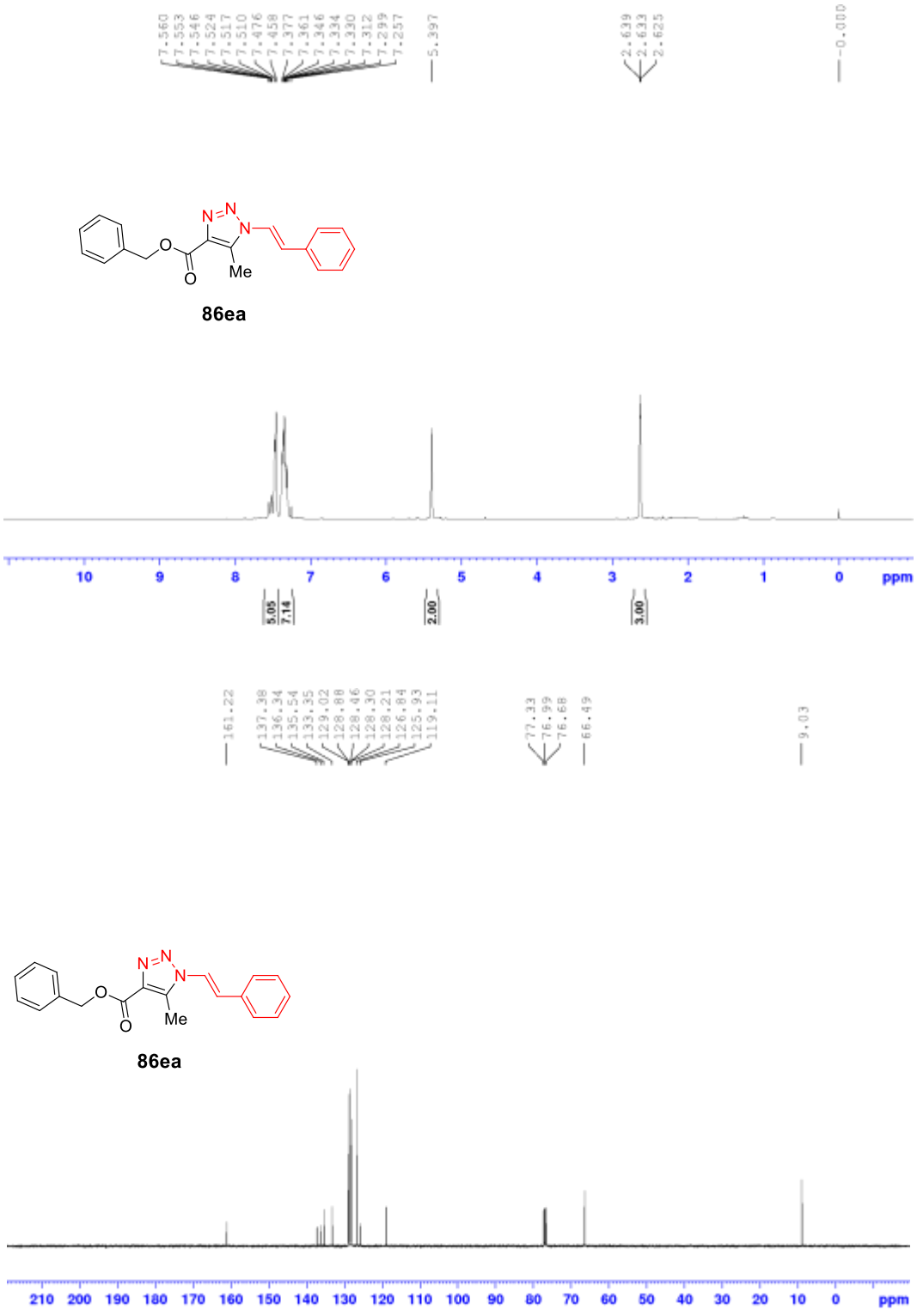


Figure-15: ^{1}H NMR and ^{13}C NMR spectrum of product **86ea**.

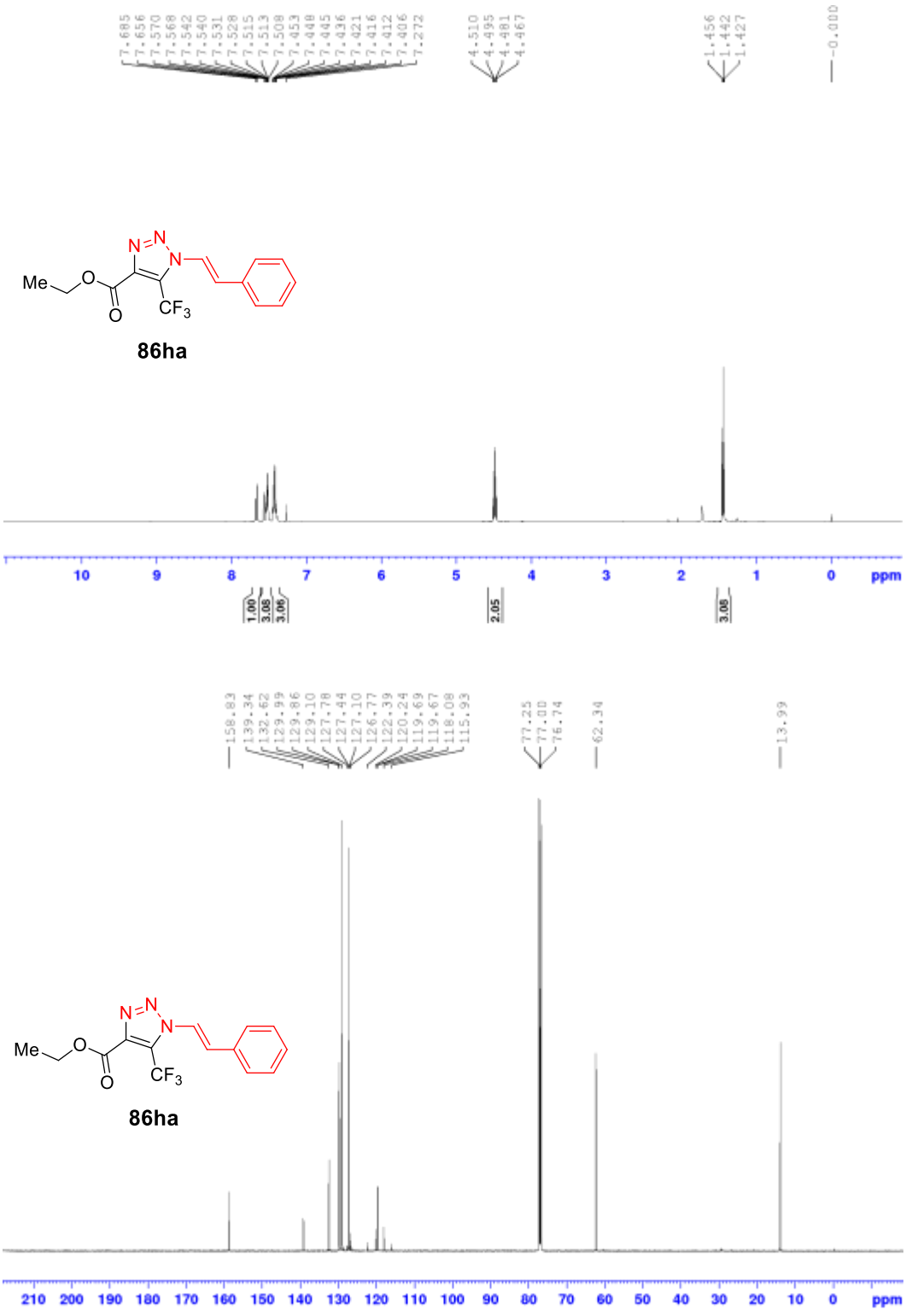


Figure-16: ^{1}H NMR and ^{13}C NMR spectrum of product **86ha**.

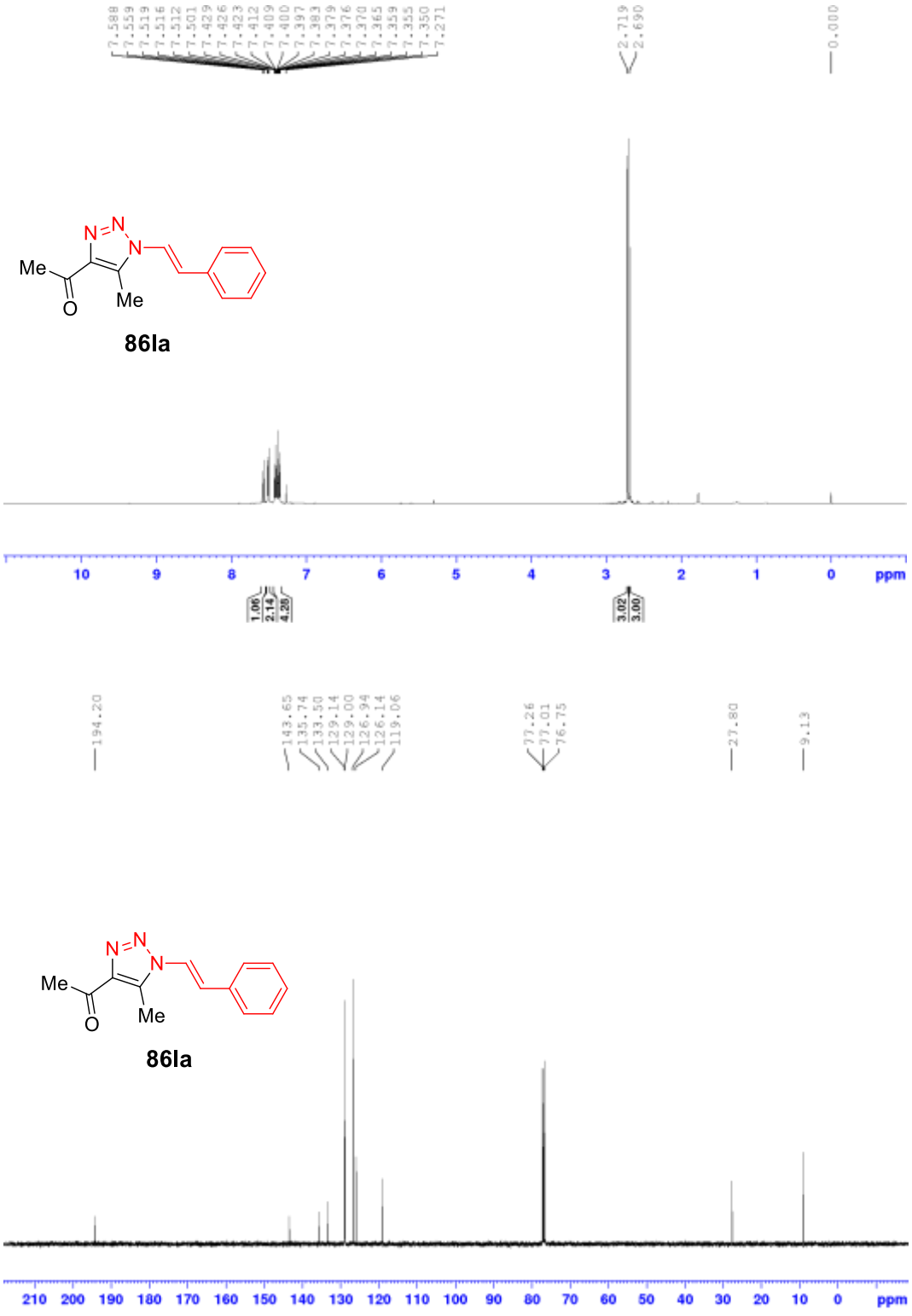


Figure-17: ^{1}H NMR and ^{13}C NMR spectrum of product **86la**.

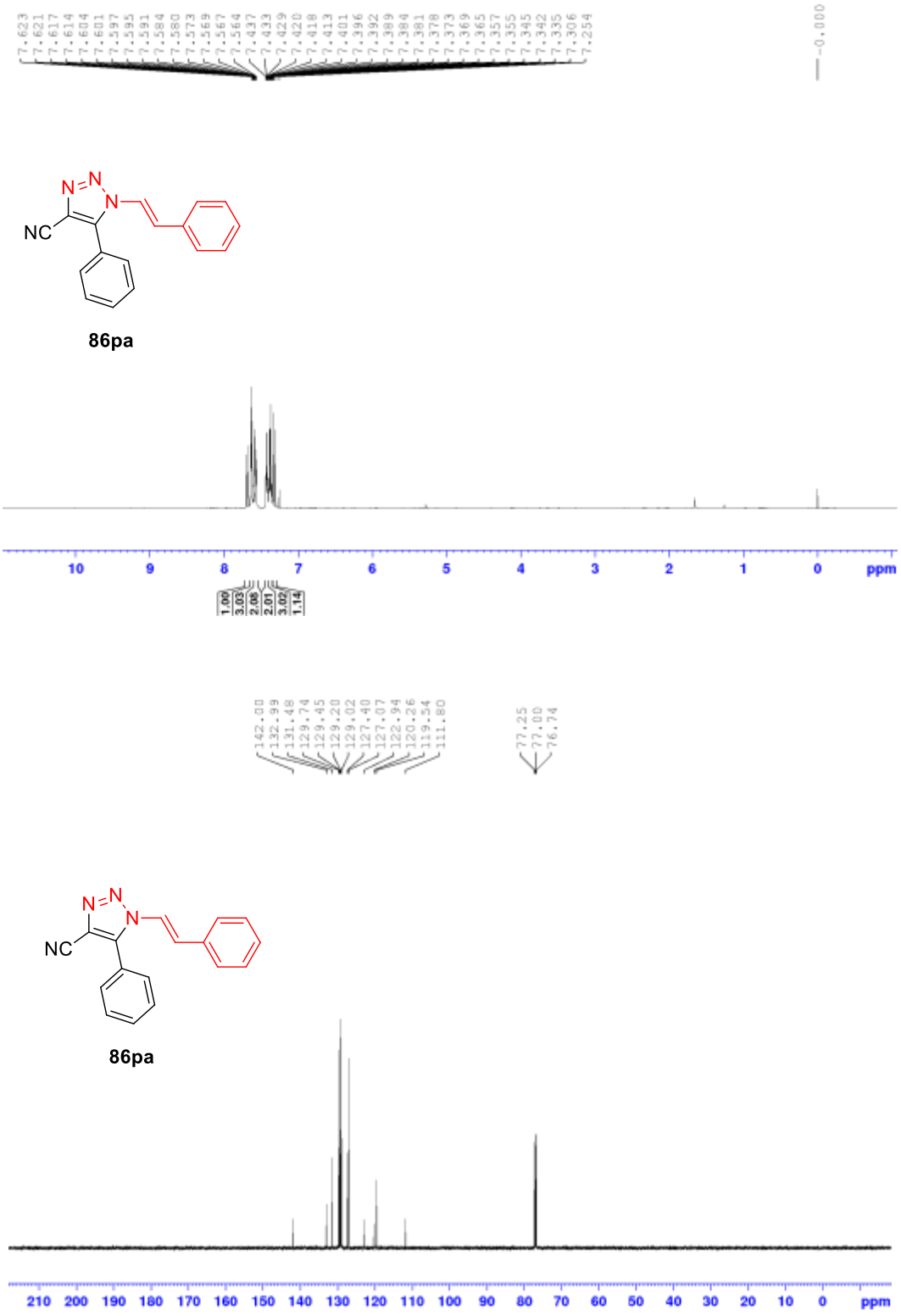
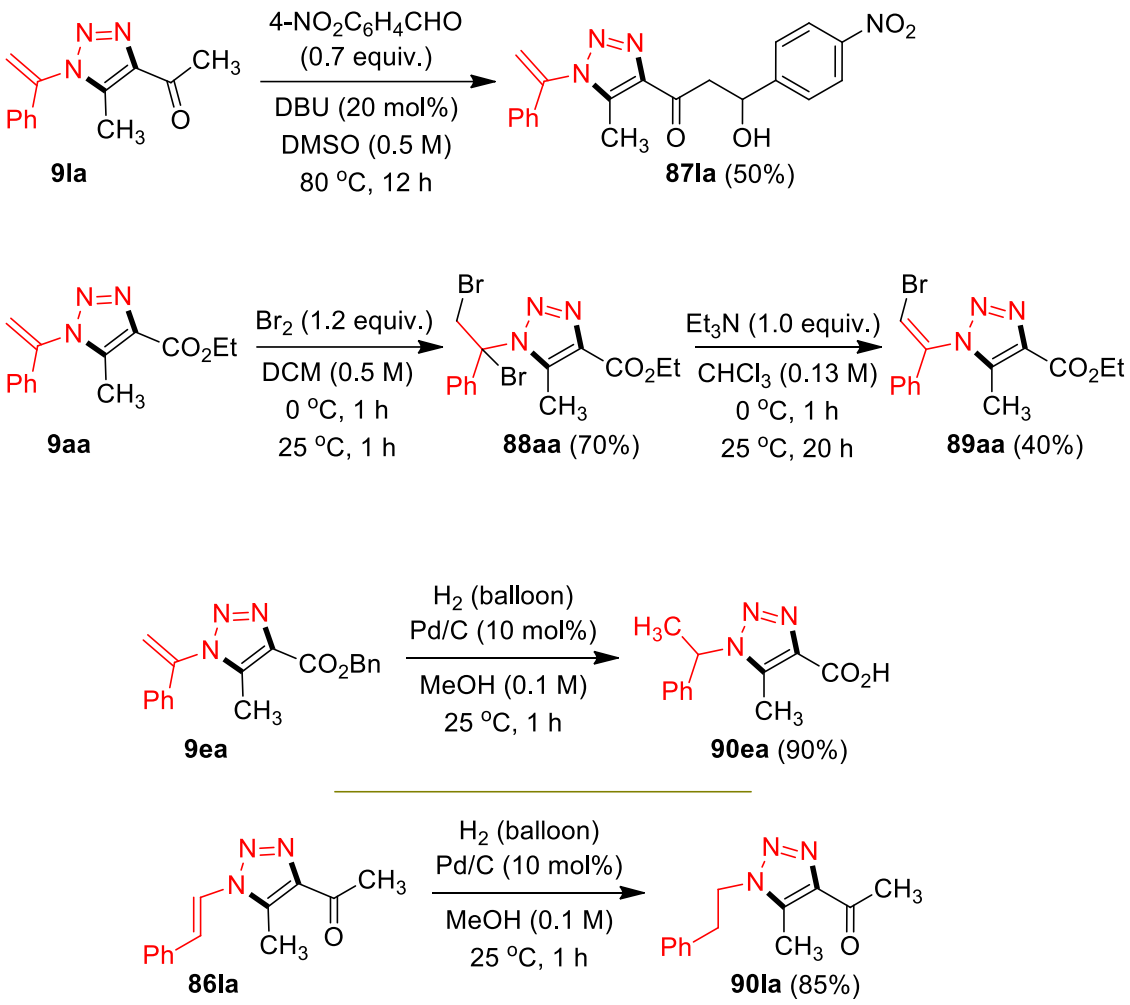


Figure-18: ^{1}H NMR and ^{13}C NMR spectrum of product **86pa**.

3.2.3 Synthetic applications of click products:

The versatility of the organo-click reaction was further exemplified by synthesizing a few useful compounds **87la**, **88aa**, **89aa**, **90ea** and **90la** (Scheme 2). We explored the utilization of **9** bearing 1,2,3-triazole-Ac in the synthesis of aldol product **87** *via* enolate-mediated aldol reaction (Scheme 2). Direct DBU-catalysed aldol reaction of 1-(5-methyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazol-4-yl)ethanone **9la** with 0.7 equiv. of 4-nitrobenzaldehyde in DMSO at 80 °C for 12 h furnished the aldol product **87la** in 50% yield (Scheme 2). Aldol products containing the 1,2,3-triazole ring will be promising probes to study the medicinal and material properties.[22] As shown in Scheme 2, ethyl 1-(1,2-dibromo-1-phenylethyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate **88aa** was synthesized in good yield from the treatment of 1.2 equiv. of bromine with 1-vinyl-1*H*-1,2,3-triazole **89aa** in DCM at 0-25 °C for 2 h; which on further treatment with 1.0 equiv. of triethylamine in $CHCl_3$ at 0-25 °C for 21 h furnished the synthetically useful triazole-based vinylbromide **89aa** in 40% yield along with fully debrominated product **9aa** in 40% yield through elimination of bromine (Scheme 2). Further, we synthesized the *N*-alkyl substituted 1,2,3-triazoles **90ea** and **90la** through hydrogenation reaction of fully substituted 1-vinyl-1*H*-1,2,3-triazole **9ea** and 1-styryl-1*H*-1,2,3-triazole **86la** using hydrogen balloon under 10-mol% of Pd/C in methanol at 25 °C for 1 h. In a single step, compound of 5-methyl-1-(1-phenylethyl)-1*H*-1,2,3-triazole-4-carboxylic acid **90ea** was isolated in 90% yield and 1-(5-methyl-1-phenethyl-1*H*-1,2,3-triazol-4-yl)ethanone **90la** was isolated in 85% yield (Scheme 2). These results highlights advantages of the organo-click reactions, which enables a quick synthesis of *N*-alkyl substituted 1,2,3-triazoles.

Scheme 2: Synthetic Applications.



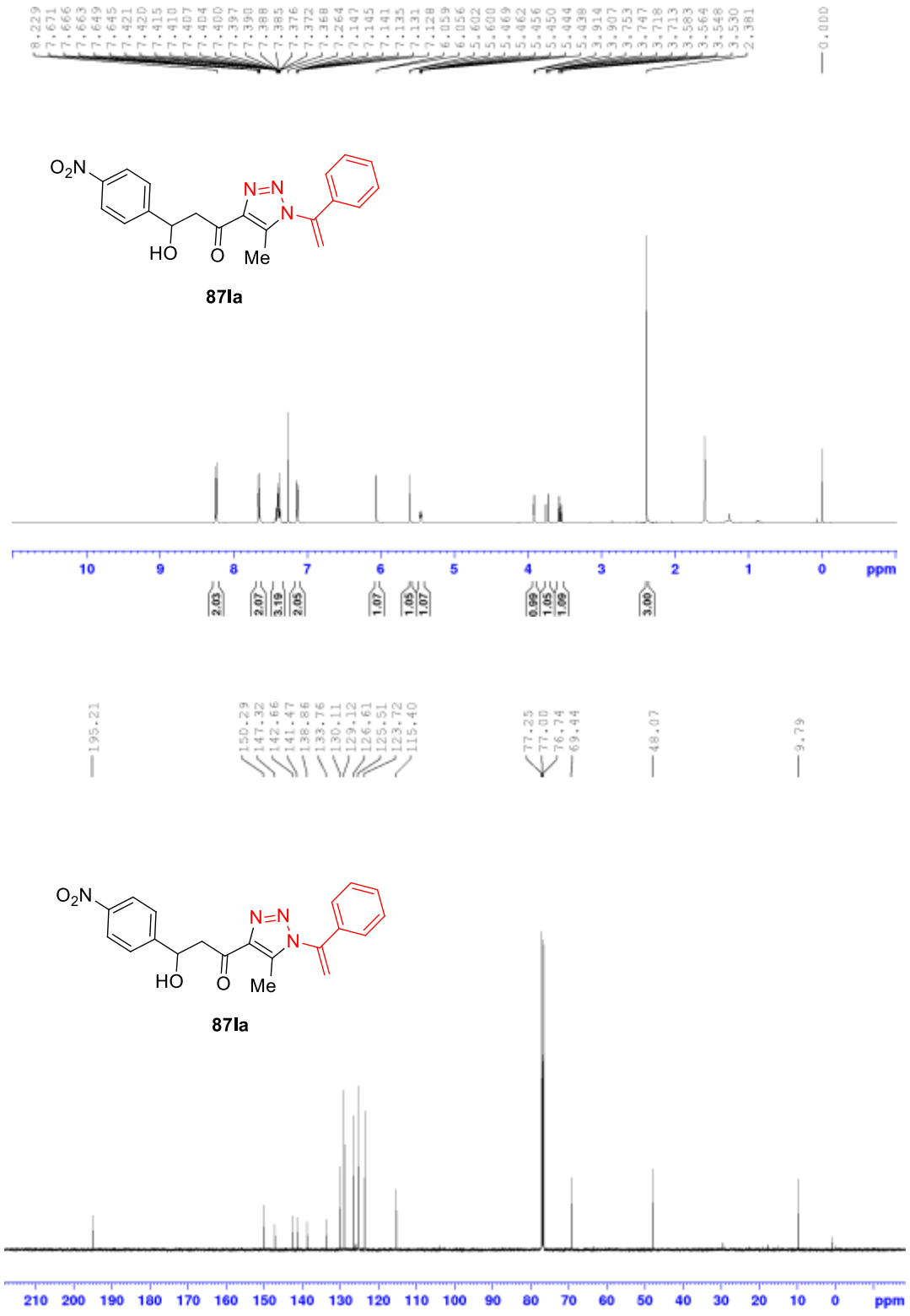


Figure-19: ^{1}H NMR and ^{13}C NMR spectrum of product **87la**.

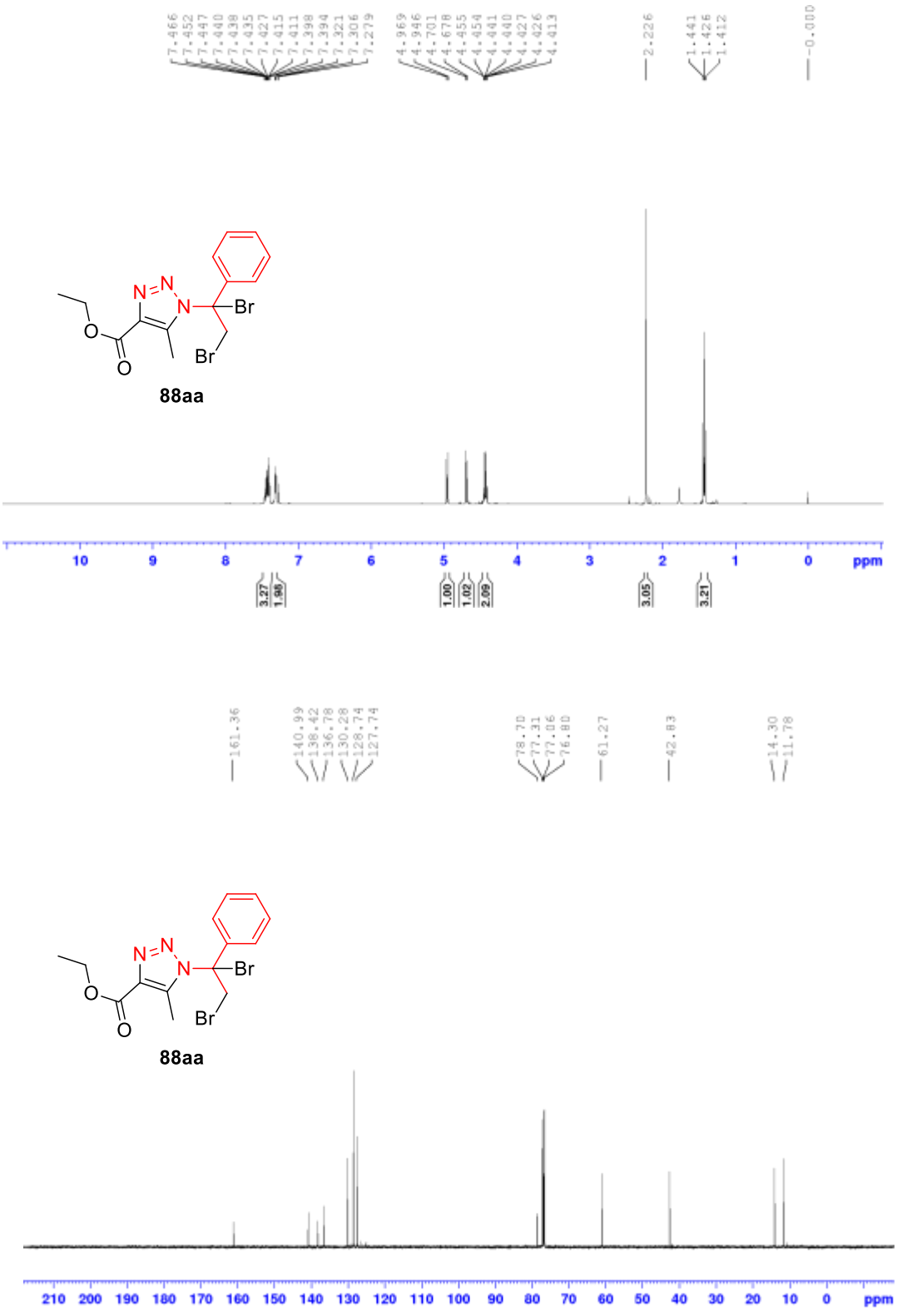


Figure-20: ^{1}H NMR and ^{13}C NMR spectrum of product **88aa**.

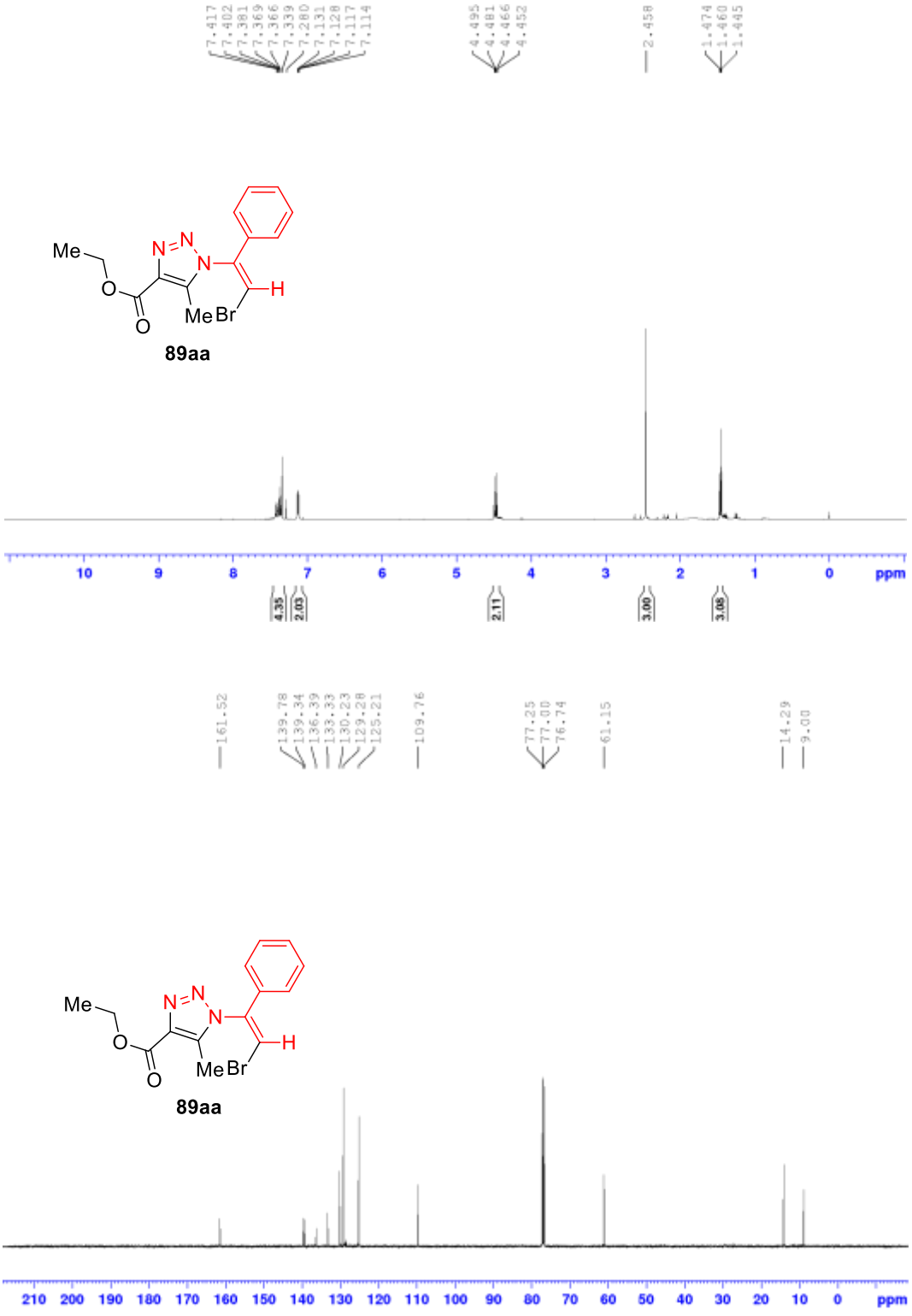


Figure-21: ^{1}H NMR and ^{13}C NMR spectrum of product **89aa**.

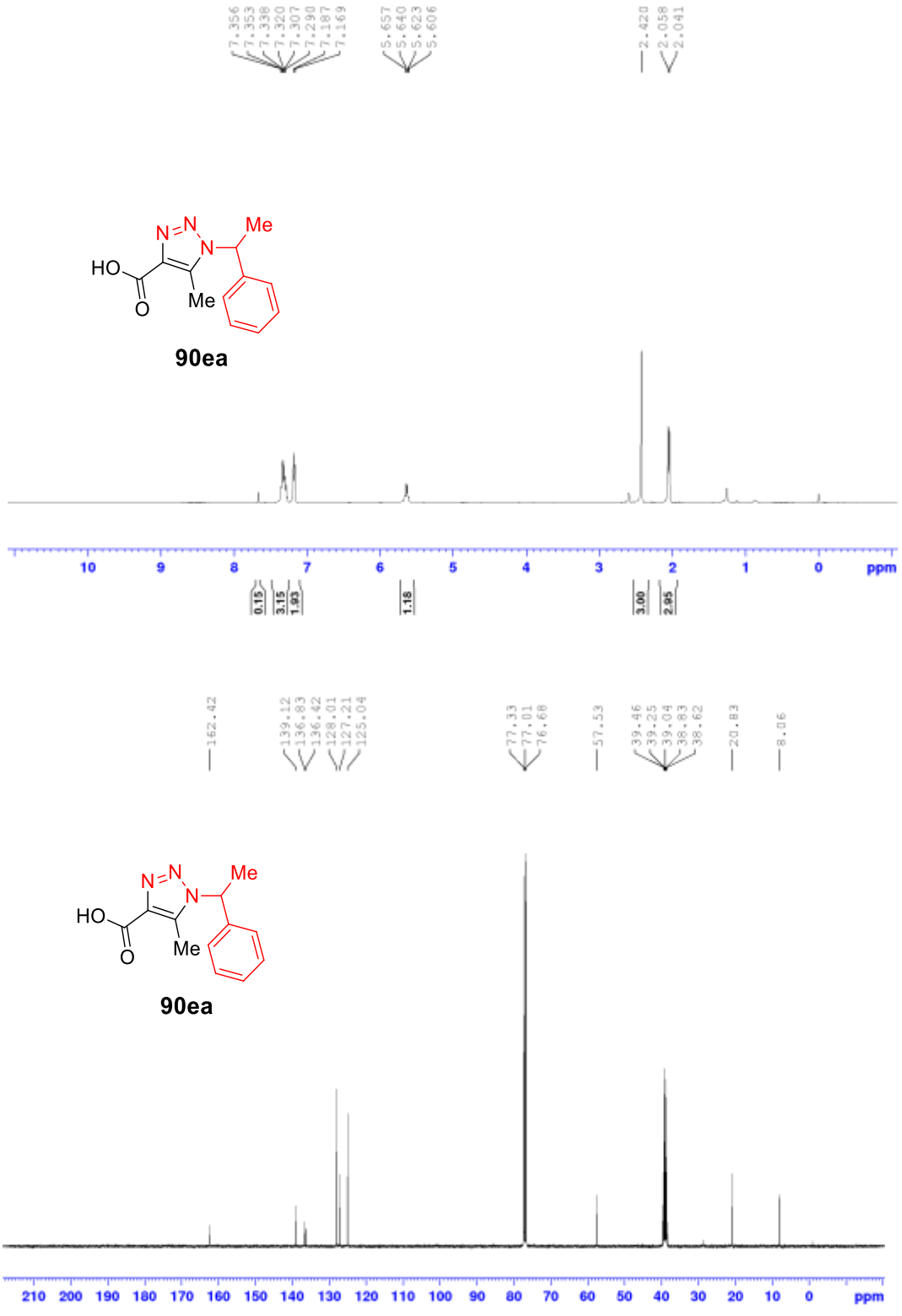


Figure-22: ^{1}H NMR and ^{13}C NMR spectrum of product **90ea**.

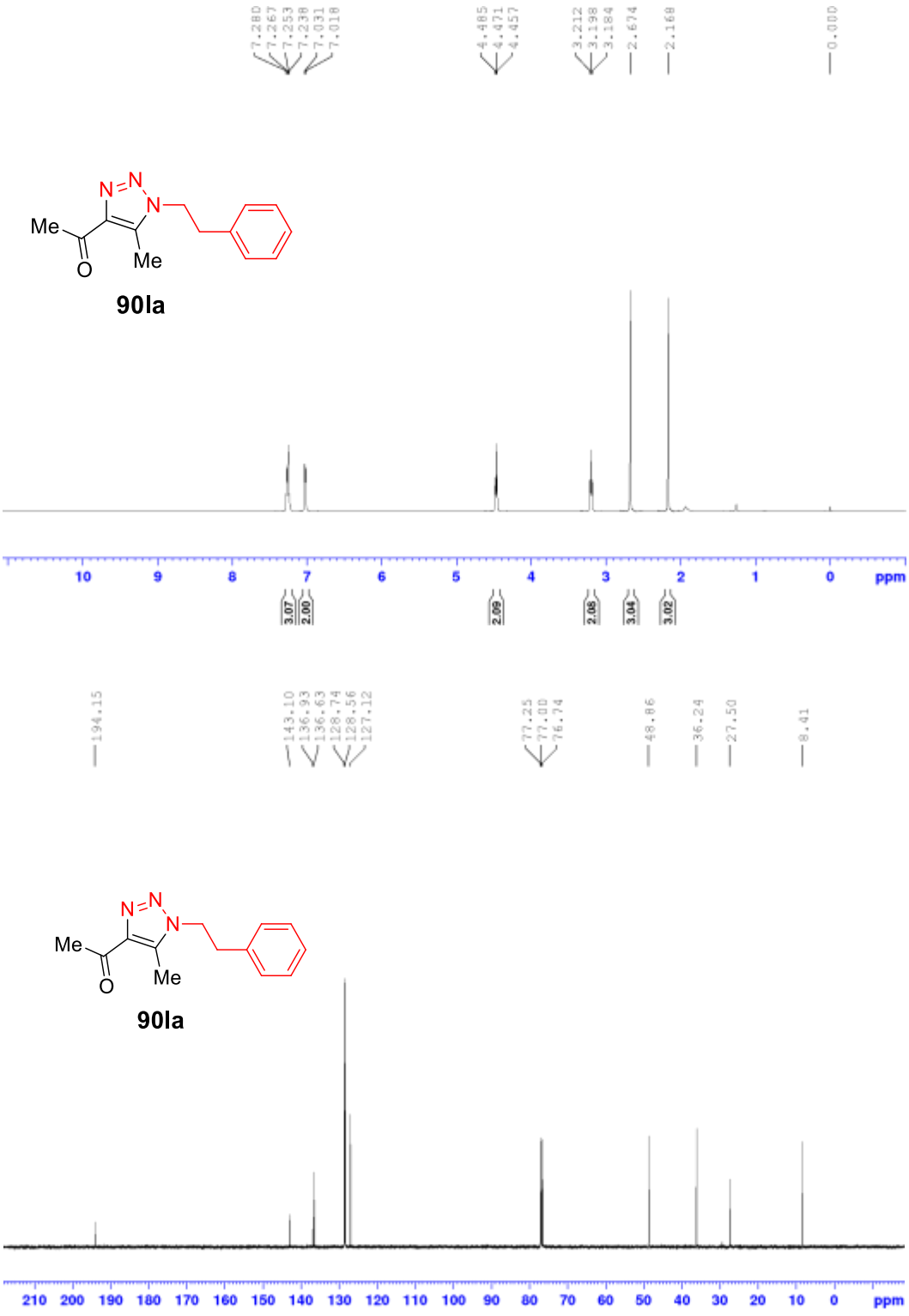
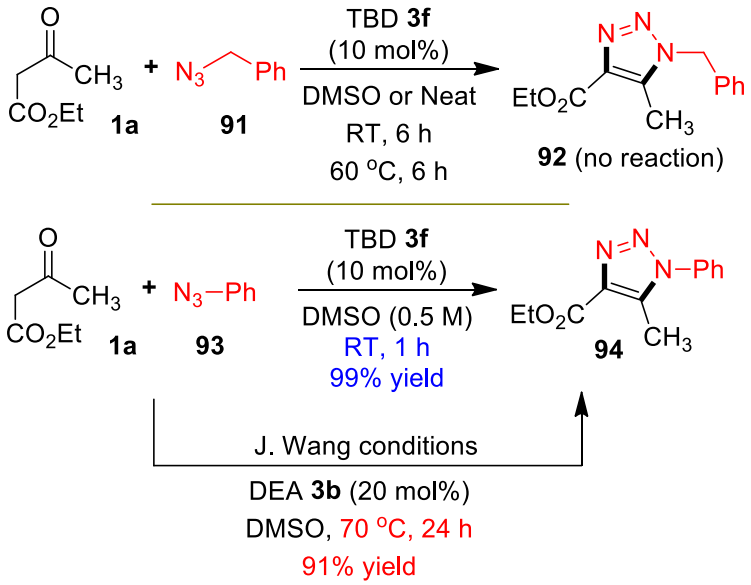


Figure-23: ^{1}H NMR and ^{13}C NMR spectrum of product **90la**.

3.2.4 Controlled experiments:

In order to further extend the understanding of catalytic power of TBD **3f** and also electronic nature of vinyl-azides **8/85**, we have done a few controlled experiments as shown in Scheme 3. Surprisingly, there is no triazole **92** formation from the reaction of ethyl acetoacetate **1a** with benzyl azide **91** under TBD **3f**-catalysis at 25 to 60 °C even after 12 h (Scheme 3). At the same time, the click reaction of ethyl acetoacetate **1a** with phenyl azide **93** under TBD **3f**-catalysis in DMSO at 25 °C within 1.0 h furnished the single isomer of 1,2,3-triazole **94** in 99% yield (Scheme 3). The same product **94** was synthesised by Wang *et al.* in 91% yield under enamine-catalysis by using 20 mol% of diethyl amine **3b** in DMSO at 70 °C in 24 h,[24c] which is rationally inferior to the present enolate-catalysis. Many of the products **9/86** yields/selectivity obtained were excellent through enolate-intermediate compared to the previous methods and vinyl-azides reactivity towards enolates was similar to the aryl azides than aliphatic azides.

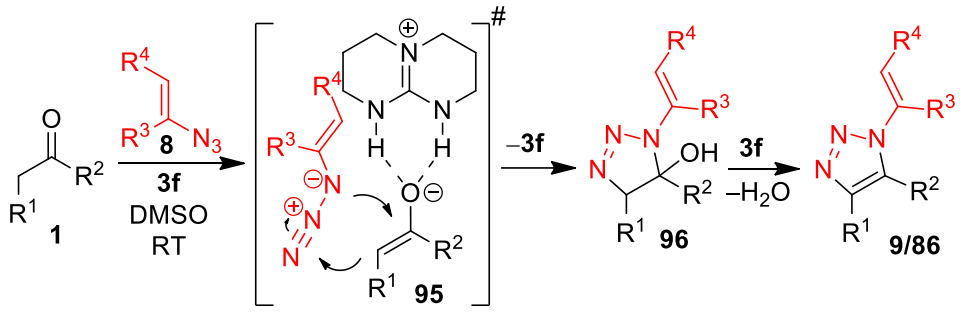
Scheme 3: Controlled Experiments.



3.2.5 Mechanistic rationale:

The mechanism for the selective synthesis of **9/86** through the reaction of **1**, **8/85** and **3f** is illustrated in Scheme 4.[25l] Reaction of the catalyst TBD **3f** (pK_a = 26.03 in CH_3CN) with activated carbonyls **1** generates the enolate **95**, which on in situ treatment with reactive vinyl-N_3 **8/85** furnishes selectively the functionalized 1,2,3-triazolines **96** via concerted [3+2]-cycloaddition or stepwise amination-cyclization reaction, which further transforms into the stable 1,2,3-triazole **9/86** through rapid elimination of water induced by the basic nature of **3f**.

Scheme 4: Reaction Mechanism.



3.3 Conclusions:

In summary, for the first time we have developed the TBD-catalyzed regiospecific synthesis of 1,4,5-trisubstituted *N*-vinyl-1,2,3-triazoles **9/86** from simple activated carbonyls **1** and *N*-vinyl azides **8/85**via [3+2]-cycloaddition reaction. The click reaction proceeds in excellent yields with high rate and selectivity using TBD **3f** as the organocatalyst within a few hours at 25 °C. Further work is in progress to develop the application of these products in medicinal to material chemistry.

4. An Aldehyde–Azomethine Imine [3+2]-Cycloaddition: High-yielding Regioselective Synthesis of Substituted *N,N*-Bicyclic Pyrazolidinones

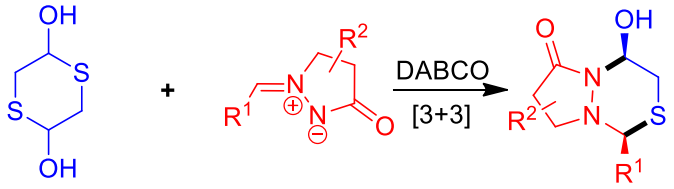
4.1 Introduction

Click chemistry since its inception, has established new paradigms in terms of reaction atom economy, sustainability, modularity and operational simplicity.[31] Before 2014, the realm of click chemistry was confined to metal mediated, strain promoted or amine catalyzed enamine mediated reactions.[23] In 2014, our group introduced catalytic enolate mediated click chemistry strategies and established it as a relevant, efficient and complimentary mechanistic approach towards click reactions.[25a,b,g,h,l,m] We explored the scope of azides as 1,3-dipole click partners, until 2016, then we envisioned to bring other dipoles under the ambit of catalytic enolate-mediated click chemistry. Our search for 1,3-dipoles led us to *N*,*N*′-cyclic azomethine imines which are conceptually 1,3-dipoles of aza-allyl type. Azomethine imines are stable, easily accessible and are a key player in numerous 1,3-dipolar cycloaddition reactions leading to a diverse array of *N*,*N*-bicyclic hetrocycles.[32]

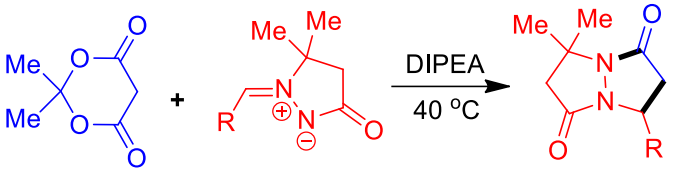
In 2013, Wang *et. al.* utilized an in situ generated mercaptoacetaldehyde in a [3+3]-cycloaddition with azomethine imines under the assistance of DABCO with sulfur acting as nucleophile instead of carbon (Scheme 5a).[33] Later, in 2014, Brière group also reported a cyclocondensation reaction of Meldrum's acid acting as ketene equivalent to azomethine imines giving pyrazolidinones as products (Scheme 5b).[34] Recently, we developed a three component [3+2]-cycloaddition reaction between azomethine imine, indane-1,3-dione and an aldehyde catalyzed by L-proline (Scheme 5d).[35] In continuation of our quest, we planned to develop an enolate-mediated azomethine imine click reaction in contrast to the amine mediated click reaction developed by us earlier.

Scheme 5: Previous and present reaction design.

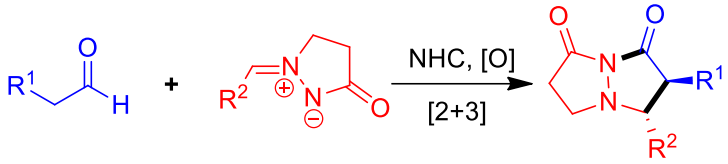
a) DABCO catalysed [3+3] cycloaddition with 1,4-dithiane-2,5-diol: Wang



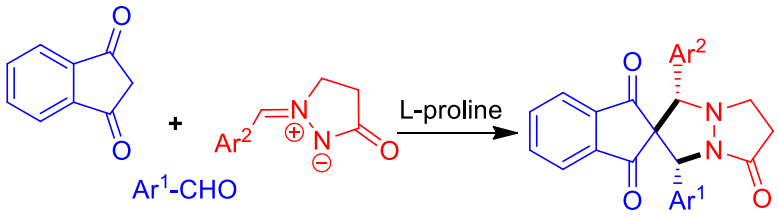
b) *tert*-Amine catalysed cyclocondensation of Meldrum's acid: Brière



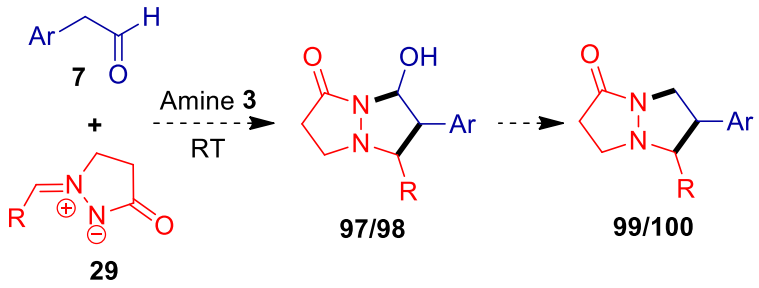
c) NHC catalysed enolate mediated click reaction: Xu and Ren



d) Amino acid catalysed azomethine imine-olefin [3+2] cycloaddition: Ramachary

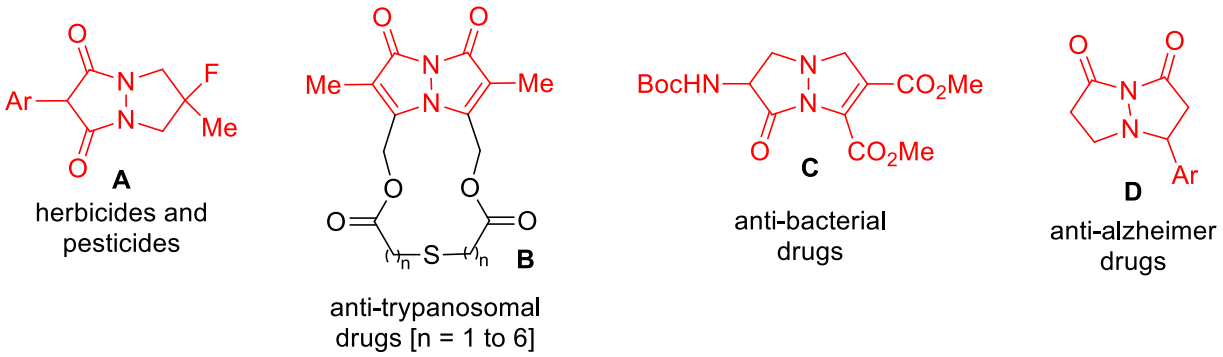


e) Amine-catalysed enolate mediated [3+2] cycloaddition: present work



To execute our vision, aldehydes with α-hydrogens were chosen as the click partners, which would give a pyrazolidinone skeleton on cycloaddition and further reductive dehydroxylation (Scheme 5e). Molecules encompassing pyrazolidine motifs have been known to have biological activities making them useful as pesticides, herbicides, antibacterial, anti-trypanosomal and anti-alzheimer's drugs to mention a few (Figure 14).[36] This gave us further impetus to develop this strategy. Recently, Xu and Ren *et. al*., reported an NHC catalysed cycloaddition of aldehydes to azomethine imines, however, their approach suffers from use of excess base and oxidant (Scheme 5c).[15] Ready *et. al.* reported a novel [3+2]-cycloaddition between azomethine imines and highly reactive lithium ynolates to synthesize bicyclic pyrazolidinones.[37a] In contrast, our enolate based approach is simple, catalytic and atom economic, which are some of the qualities highly desirable in a click reaction.[25]

Figure-24: Biologically active pyrazolidinones.



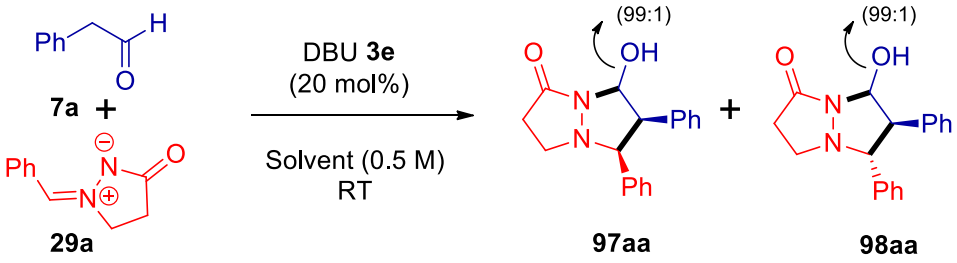
4.2 *Results and Discussion*

4.2.1 *Reaction optimization:*

Our journey to optimize azomethine imine-aldehyde click reaction commenced with performing the reaction of phenylacetaldehyde **7a** and azomethine imine **29a** in a variety of solvents under DBU catalysis (Table 4).[25a] Initially, the reaction was carried out in aprotic polar solvents such as DMSO, DMF, CH_3CN, and THF to furnish the desired click products **97aa** and **98aa** in 55%, 34%, 37% and 16% yield with 2:1 to 1:1.5 *dr*, respectively (entries 1-4, Table 4). The reaction in DMSO solvent yielded the maximum 55% of the desired click product with 2:1

dr of **97aa/98aa**. This high yield can be partly attributed to the high solubility of **7a** in DMSO. A non-polar solvent like toluene afforded the desired product **97aa/98aa** in poor yield of 37% (entry 6, Table 4). For further improvement in yield, we shifted to use of chlorinated solvents like DCE and chloroform (entries 5, 7 and 8, Table 4). To our delight, the reaction when performed in chloroform furnished the click products **97aa** and **98aa** in very good yield of 71% but with no diastereoslectivity (entry 7). To achieve selectivity, the reaction temperature was lowered to 0 °C which lead to a little excess of the *trans*-isomer **97aa**/**98aa** (1:1.6 *dr*) but at the cost of decreased yield of 47% (entry 8). This observation hints towards the fact that the formation of *trans-i*somer **98aa** is more favourable at low temperature with a lower transition state energy.

Table 4: Solvent optimization.[a]

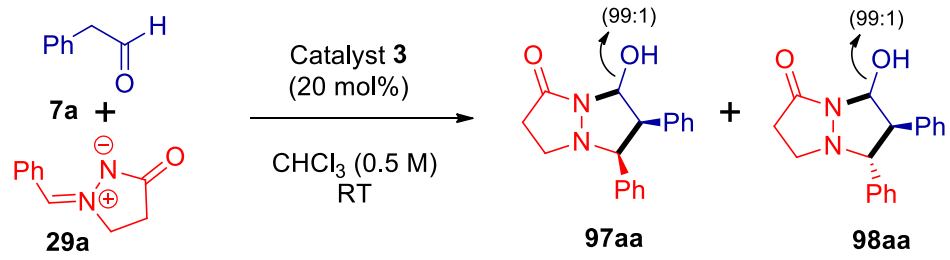


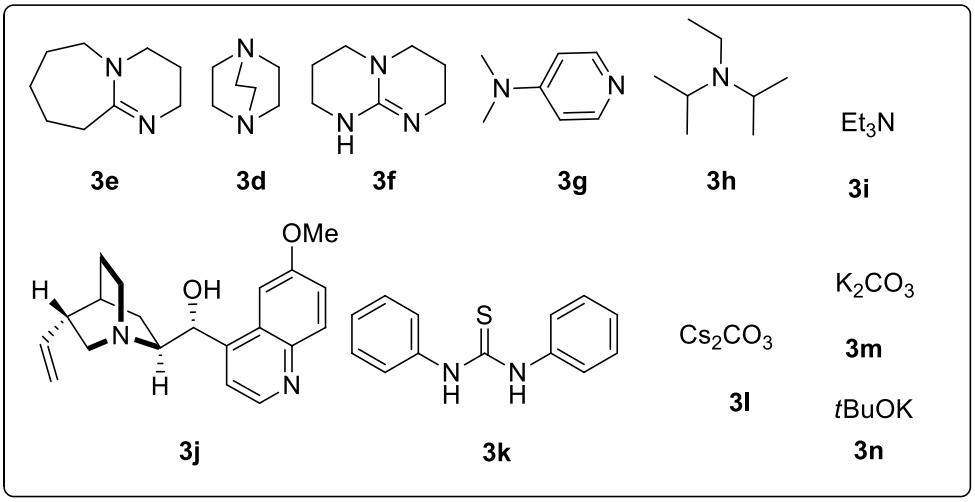
Entry	Solvent	Time (min)	Yield[b] (%)	dr[c] (**4aa:5aa**)
1	DMSO	5	55	2:1
2	DMF	5	34	1:1
3	CH_3CN	5	37	1:1
4	THF	10	16	1:1.5
5	DCE	10	58	1:1
6	Toluene	60	37	1:1.2
7	$CHCl_3$	5	71	1:1
8[d]	$CHCl_3$	18	47	1:1.6

[a] Reactions were carried out in solvent (0.5 M) with 1.5 equiv. of **29a** relative to **7a** (0.5 mmol) in the presence of 20 mol-% of catalyst **3e**; and completion of reaction was monitored by TLC. [b] Yield refers to the column purified product. [c] *dr* determined by NMR analysis.[d] Reaction performed at 0 °C.

From our previous experience in enolate chemistry,[25] various tertiary amines **3e-j** and inorganic bases **3l-n** were tested to deliver high-yielding [3+2]-cycloadducts **97aa/98aa** from **7a** and **29a** using chloroform as solvent at 25 °C (Table 5). To our dismay, all acyclic aliphatic tertiary amines **3e-i** afforded our desired click products **97aa/98aa** in very poor yields (7-8%, entries 3-5). Thereafter, we shifted our focus towards testing cyclic tertiary amines like DABCO **3d**, TBD **3f** and quinine **3j** (entries 1, 2 and 6). Surprisingly, catalyst **3h** and **3i** also produced click products **97aa/98aa** in low to moderate yields with 1:1 *dr*, but catalyst **3j** in a period of 96 h furnished the product formation of **97aa/98aa** in 64% yield with 2.4:1 *dr* and poor *ee*'s (27/14% *ee's* for major and minor isomers). Click reaction under the hydrogen bonding catalysis with **3k** showed no product formation until DBU **3e** was added to the reaction mixture to yield 41% of the click reaction products **97aa/98aa** in 30 minutes (entry 7). Prompted by these discouraging results, inorganic bases like cesium carbonate **3l**, potassium carbonate **3m** and potassium tertiary butoxide **3n** were utilized as catalysts for the click reaction. Two of the carbonates **3l** and **3m** as catalysts afforded the products **97aa/98aa** in at least 50% yield with 1:1 *dr* (entries 8-9, Table 5). Fascinatingly potassium tertiary butoxide **3n** outshined all other catalysts in providing the final click products **97aa/98aa** in very good yield of 80% with 1:1 *dr* in just 3 minutes (entry 10, Table 2). A decrease in catalyst loading to 10 mol-% and 5 mol-% was concomitant with a decrease in product yields (entries 11 and 12). Aforementioned results unequivocally made us to establish catalyst **3n** (20 mol-%) in chloroform (0.5 M) at 25 °C as the optimized condition.

Table 5: Reaction Catalyst Optimization.[a]





Entry	Catalyst **3**	Time (h)	Yield[b] (%)	dr[c] (**97aa:98aa**)
1	**3d**	14	12	1:1
2	**3f**	0.083	42	1:1
3	**3g**	17	8.3	1.2:1
4	**3h**	6	7	1:1
5	**3i**	6	8	1:1
6	**3j**	96	64	2.4:1
7[d]	**3k+3e**	0.5	41	1:1.2
8	**3l**	0.7	57	1:1
9	**3m**	3.5	52	1:1
10	**3n**	0.05	80	1:1
11[e]	**3n**	0.42	26	1:1
12[f]	**3n**	24	19	1:1

[a] Reactions were carried out in solvent (0.5 M) with 1.5 equiv. of **29a** relative to **7a** (0.5 mmol) in the presence of 20 mol-% of catalyst **3**; and completion of reaction was monitored by TLC. [b] Yield refers to the column purified product. [c] *dr* determined by NMR analysis. [d] Reaction performed in presence of 10 mol-% each of **3k** and **3e.** [e] Catalyst loading decreased to 10 mol-%. [f] Reaction carried out in presence of 5 mol-% of catalyst.

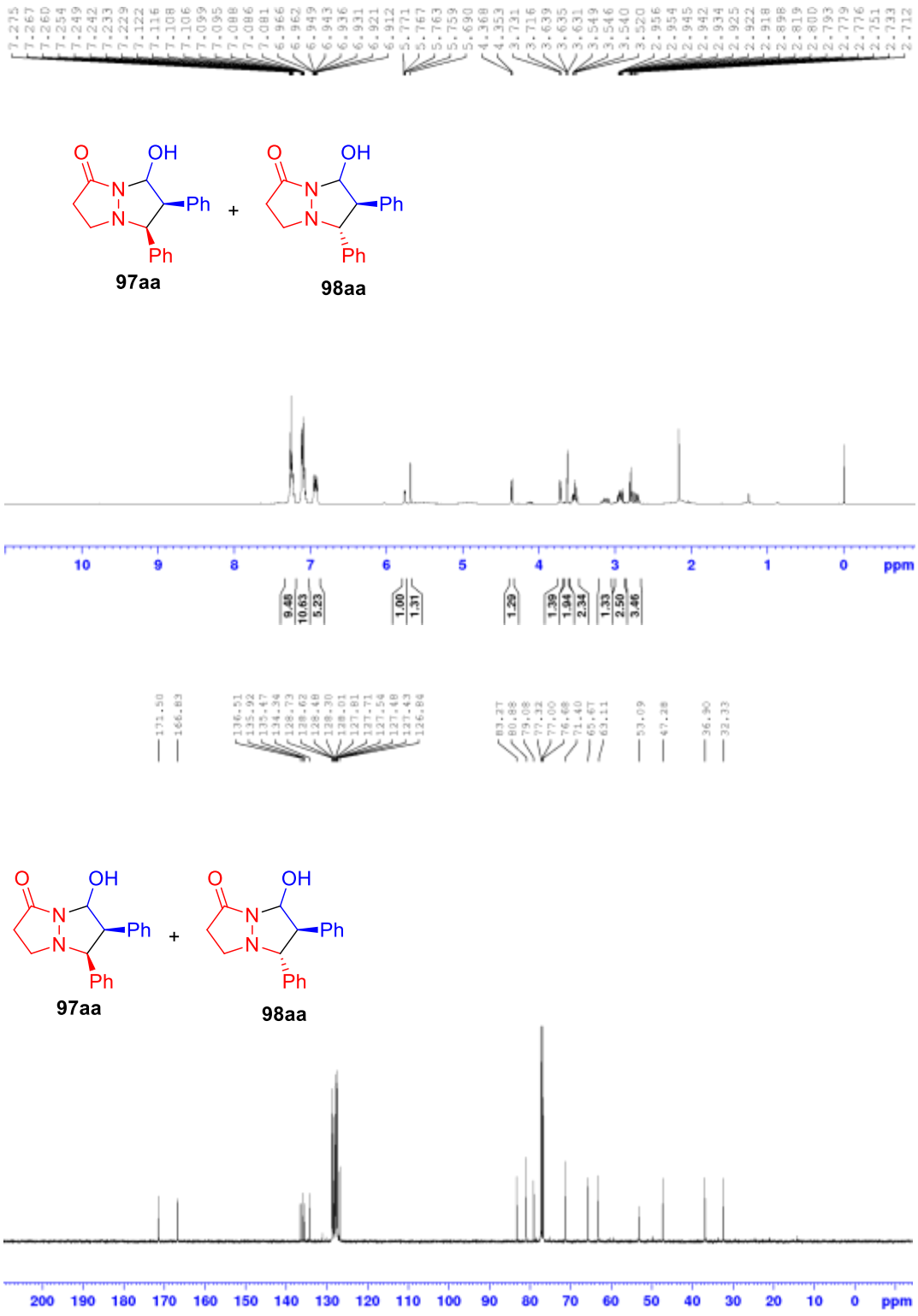
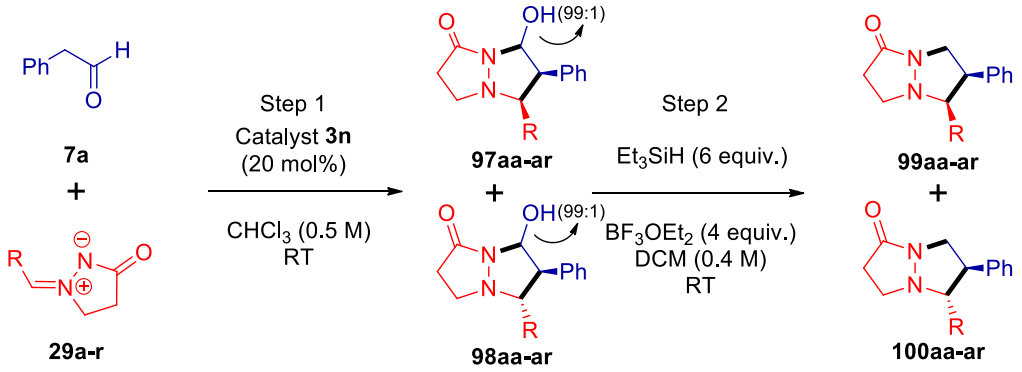


Figure-25: ^{1}H NMR and ^{13}C NMR spectrum of products **97aa** and **98aa**.

4.2.2 Scope of Aldehyde-Azomethine imine click reaction:

Under the optimal conditions, the substrate scope of the reaction was probed by reacting phenylacetaldehyde **7a** with different azomethine imines **29a-r** (Table 6). Characterization of the cycloaddition products selectivity was made feasible through reductive dehydroxylation of **97** and **98** with triethylsilane and boron trifluoride etherate to furnish the *N*,*N*-bicyclic pyrazolidinone **99** and **100** respectively in very good yields at 25 °C. Notably, the number of isomers formed in first and second step were found to be the same, means formation of hydroxyl group is stereoselective. This observation sheds light on the fact that, stereochemistry at the hydroxyl carbon is fixed in both the diastereoisomers **97/98**. This gives us the conclusion that both the stereoisomers differs stereochemically only at C-5 and C-6 positions. *N*,*N′*-Cyclic azomethine imines **29** bearing different functional groups on the benzene ring participated in the [3+2]-cycloaddition reaction with **7a** to give tetrahydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one derivatives **97/98** in very good yields within shorter reaction times followed by dehydroxylation furnished the pyrazolidinones **99/100** in excellent yields. Halogenated, electron donating and electron withdrawing substituents were well tolerated under the present protocol with slight fluctuations in the diastereomeric ratios of **99/100** from 1:1. Exceptions among them were *p*-CF_3 and *p*-OMe derivatives with 9:1 and 1:2.5 *dr* (entry 12 and 14). Surprisingly, the shift towards *trans*-selectivity began when benzene ring was replaced with a furan ring (1:3.5 *dr*) and then becomes fully visible in entries 17 and 18 (1:12 and 1:11 *dr*) with the attachment of aliphatic groups. This clearly indicates that steric and electronic factors are controlling the outcome of stereochemistry, which will be discussed in the next section.

Table 6: Azomethine imine substrate scope.[a]



Entry	**29** (**R**)	Time (h)		Yield (%)[b]		dr[c]
		Step 1	Step 2	**97+98 (%)**	**99+100 (%)**	(**99:100**)
1	**29a** (C_6H_5)	0.05	24	**97aa+98aa** (80)	**99aa+100aa** (75)	1:1
2	**29b** (2-FC_6H_4)	1	12	**97ab+98ab** (67)	**99ab+100ab** (89)	1:1
3	**29c** (4-ClC_6H_4)	1	1.5	**97ac+98ac** (70)	**99ac+100ac** (89)	1.3:1
4	**29d** (2-ClC_6H_4)	2	2	**97ad+98ad** (83)	**99ad+100ad** (83)	1.3:1
5	**29e** (4-BrC_6H_4)	0.5	2.5	**97ae+98ae** (78)	**99ae+100ae** (62)	1:1.4
6	**29f** (2-BrC_6H_4)	1	2	**97af+98af** (70)	**99af+100af** (78)	1.4:1
7	**29g** (2,4-$Cl_2C_6H_3$)	2	2	**97ag+98ag** (60)	**99ag+100ag** (68)	1.3:1
8	**29h** (4-MeC_6H_4)	2	3	**97ah+98ah** (81)	**99ah+100ah** (84)	1:1
9	**29i** (2-MeC_6H_4)	1	3	**97ai+98ai** (70)	**99ai+100ai** (74)	1.3:1
10	**29j** (4-$NO_2C_6H_4$)	2	3	**97aj+98aj** (86)	**99aj+100aj** (87)	1:1.5
11	**29k** (4-CNC_6H_4)	3	13	**97ak+98ak** (76)	**99ak+100ak** (83)	1:1
12	**29l** (4-$CF_3C_6H_4$)	1	12	**97al+98al** (75)	**99al+100al** (95)	9:1
13	**29m** (3-$NO_2C_6H_4$)	12	13	**97am+98am** (77)	**99am+100am** (84)	1.2:1
14	**29n** (4-$OMeC_6H_4$)	1.5	2	**97an+98an** (75)	**99an+100an** (97)	1:2.5
15	**29o** (2-$OMeC_6H_4$)	1.5	3	**97ao+98ao** (66)	**99ao+100ao** (62)	1.8:1
16	**29p** (Furan-2-yl)	3	5	**97ap+98ap** (62)	**99ap+100ap** (52)	1:3.5
17	**29q** ((*E*)-CH=CHC_6H_4)	0.5	12	**97aq+98aq** (57)	**99aq+100aq** (70)	1:12
18	**29r** ($CH_2CH(CH_3)_2$)	3	12	**97ar+98ar** (47)	**99ar+100ar** (57)	1:11

[a] Reactions were carried out in solvent (0.5 M) with 1.5 equiv. of **29a** relative to **7a** (0.5 mmol) in the presence of 20 mol-% of catalyst **3n**; and completion of reaction was monitored by TLC. [b] Yield refers to the column purified product. [c] *dr* determined by NMR analysis.

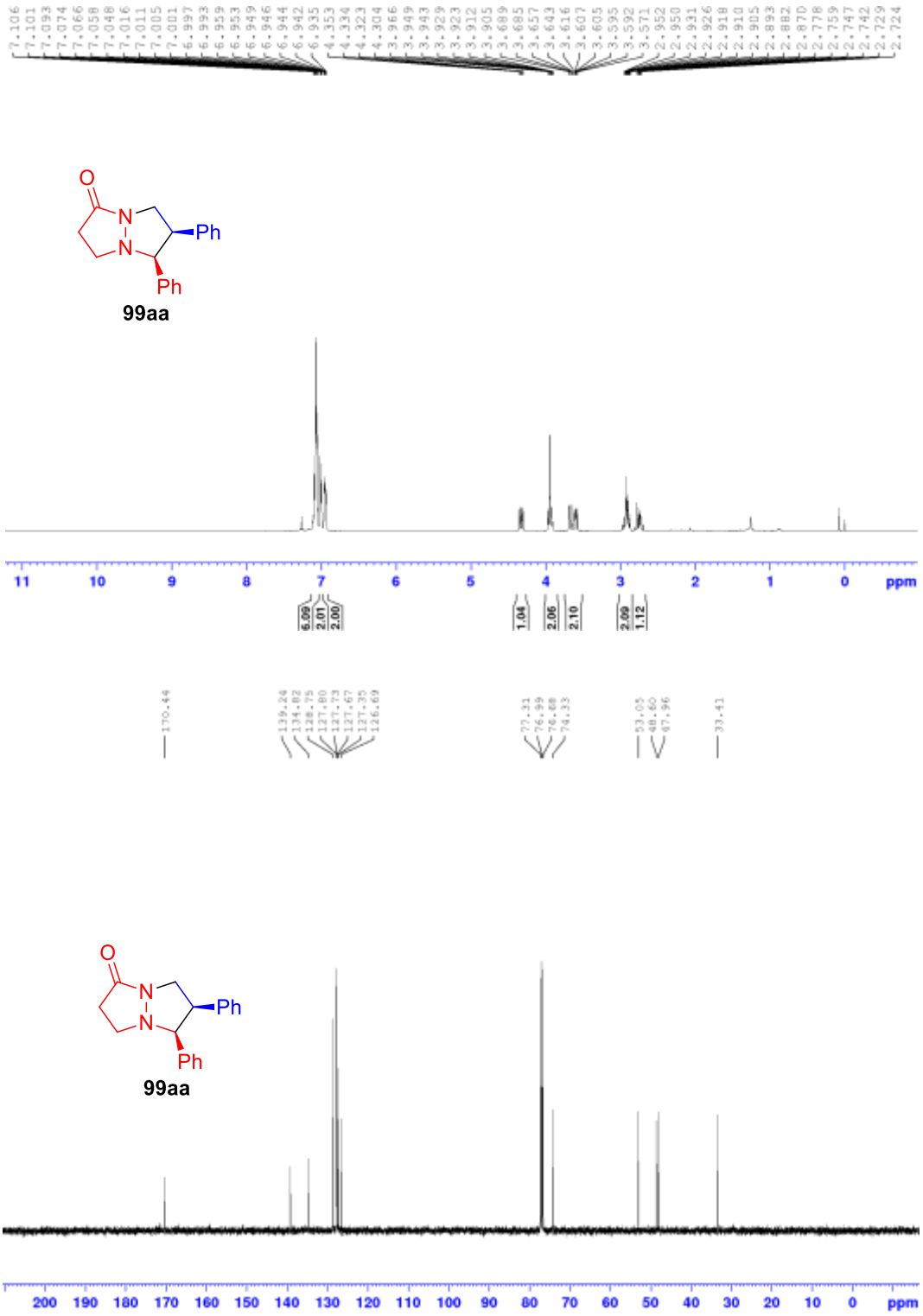


Figure-26: ^{1}H NMR and ^{13}C NMR spectrum of products **99aa.**

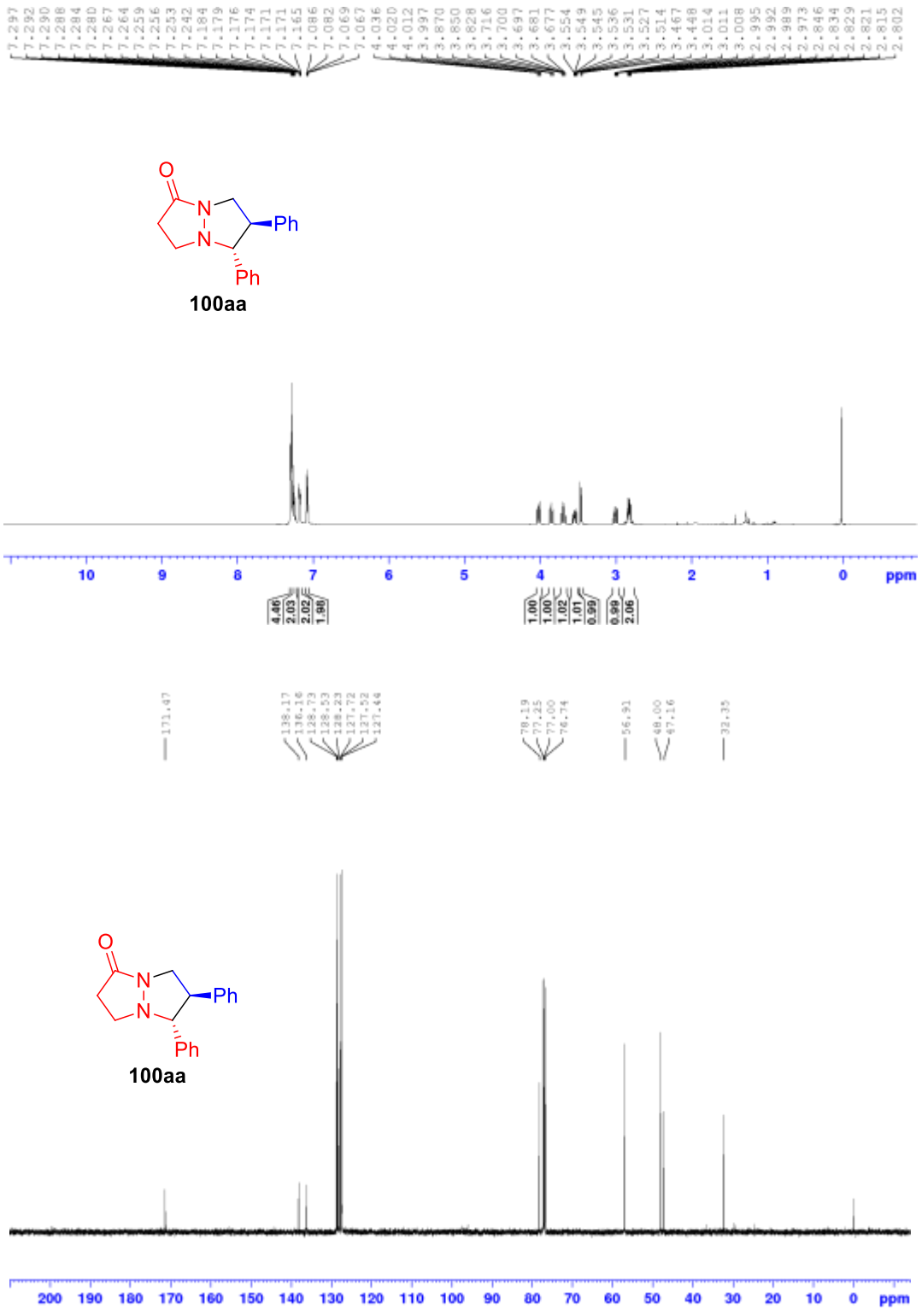


Figure-27: ^{1}H NMR and ^{13}C NMR spectrum of products **100aa.**

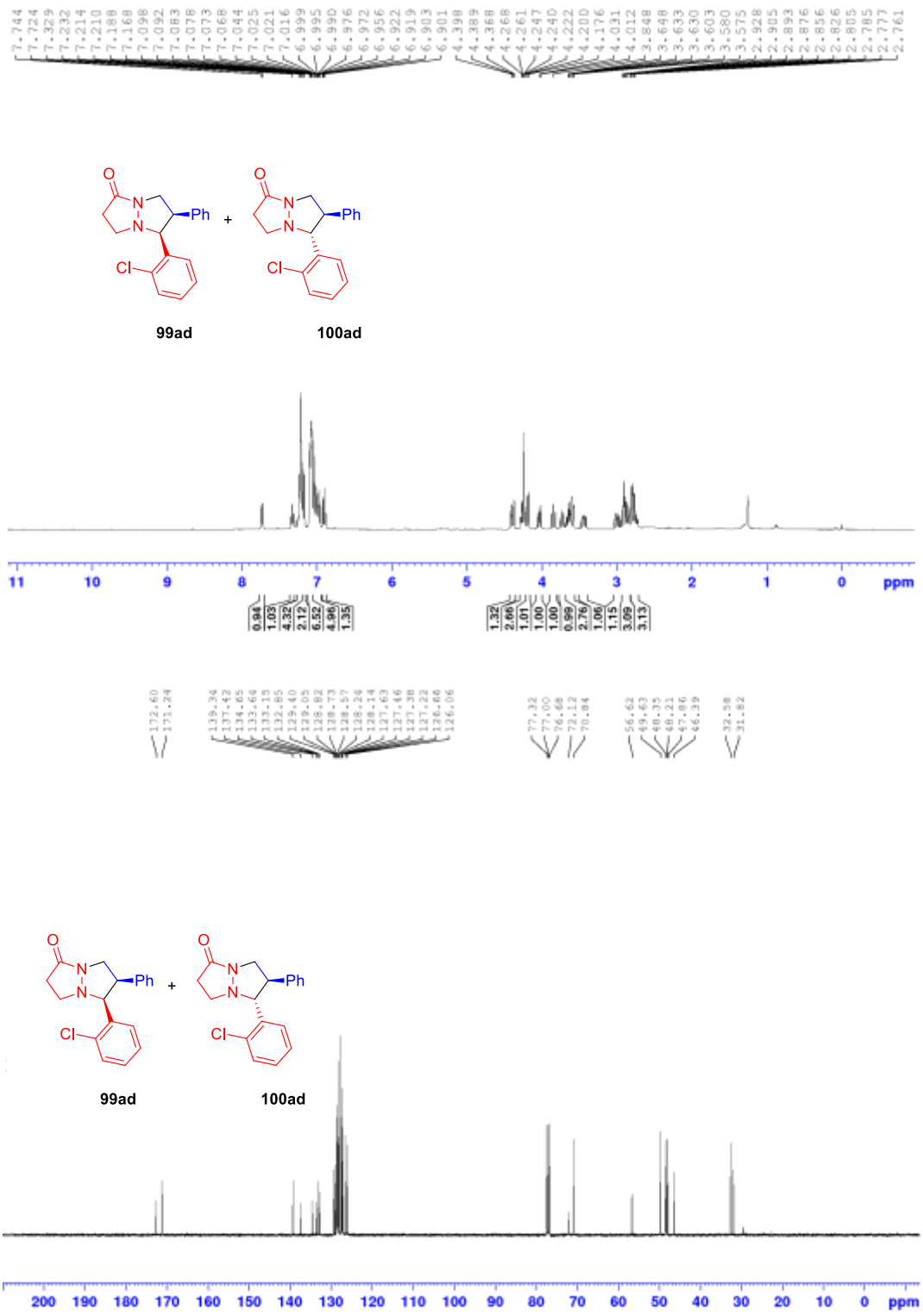


Figure-28: ^{1}H NMR and ^{13}C NMR spectrum of products **99ad** and **100ad.**

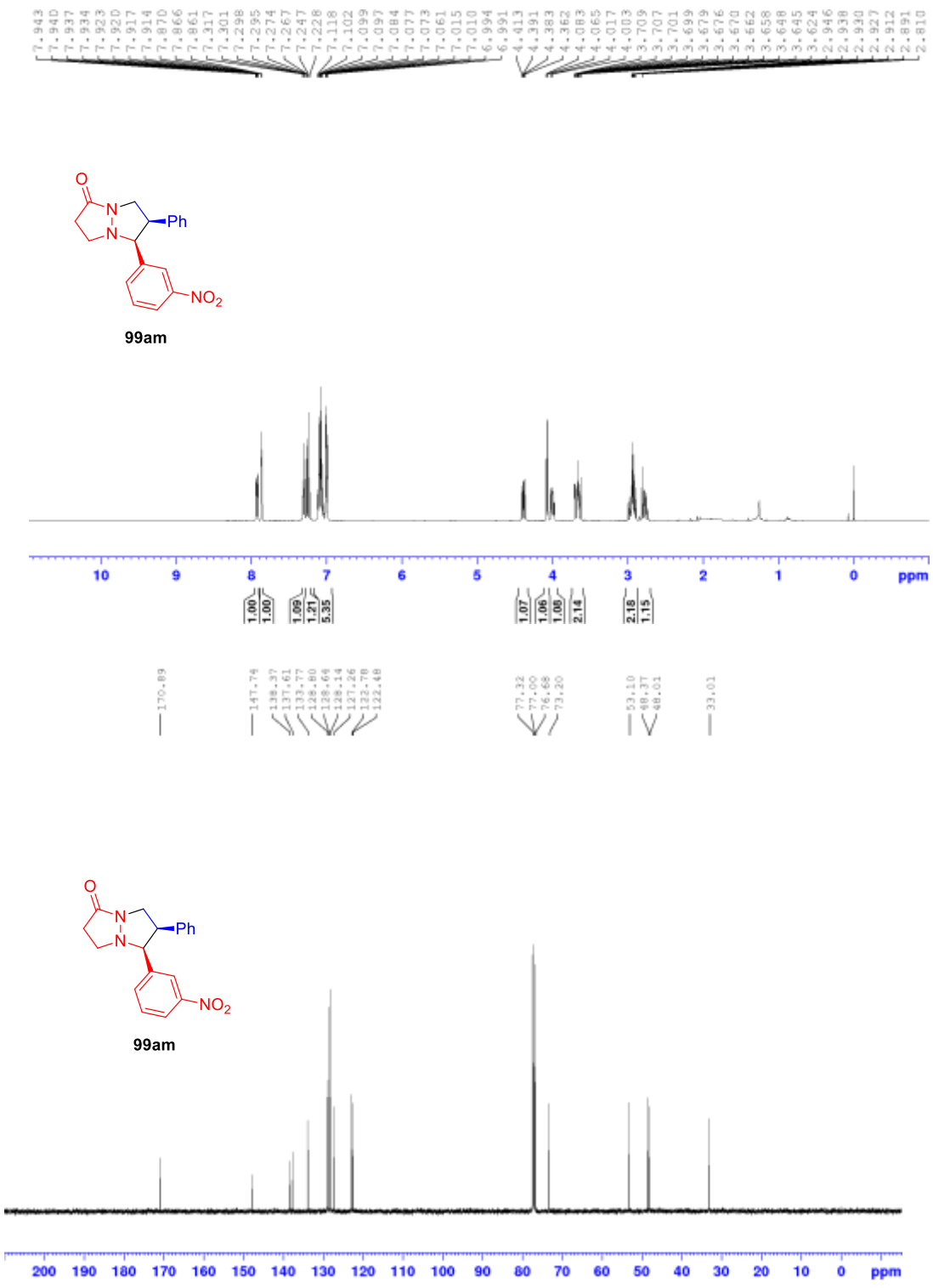


Figure-29: ^{1}H NMR and ^{13}C NMR spectrum of product **99am.**

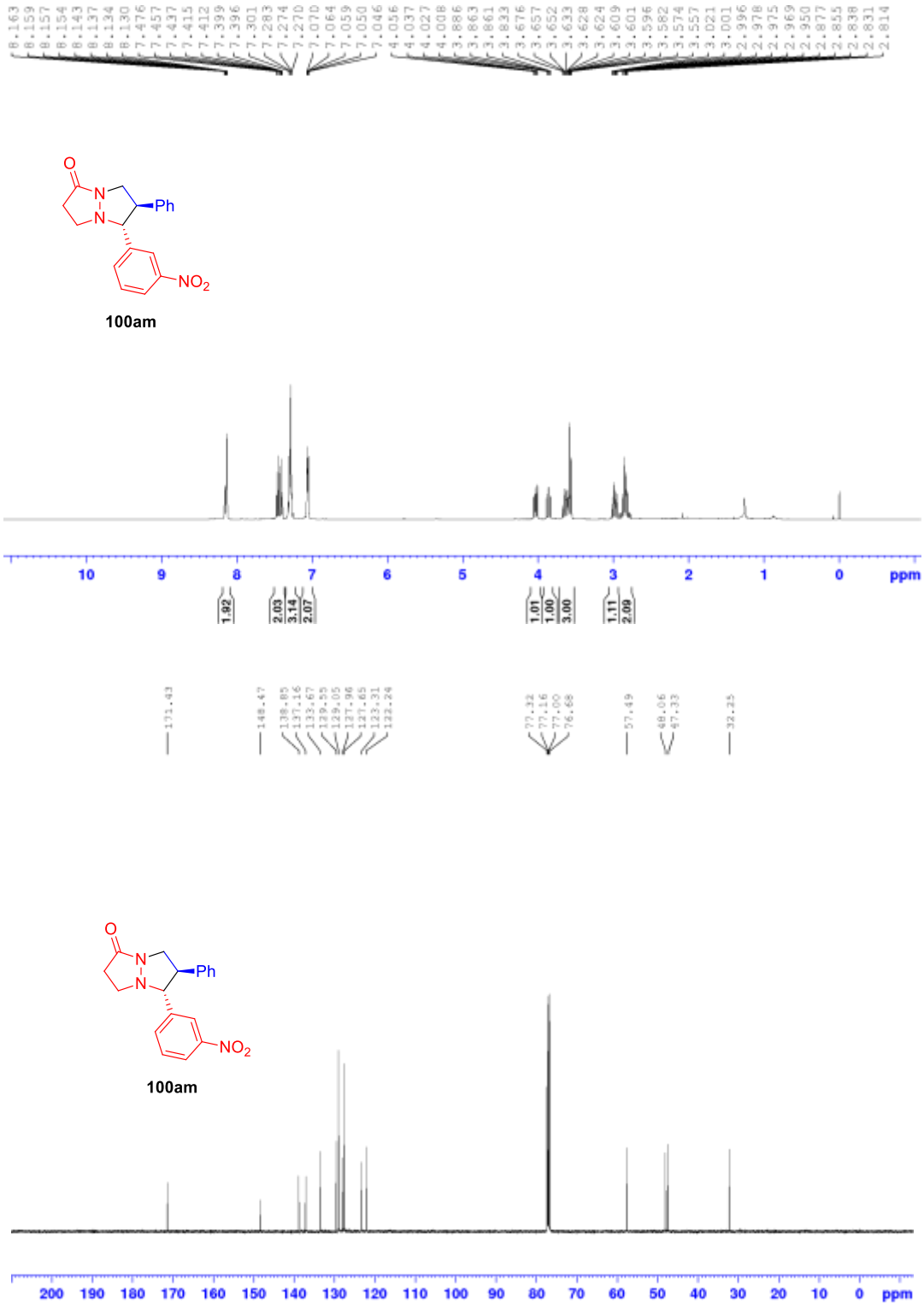


Figure-30: ^{1}H NMR and ^{13}C NMR spectrum of product **100am.**

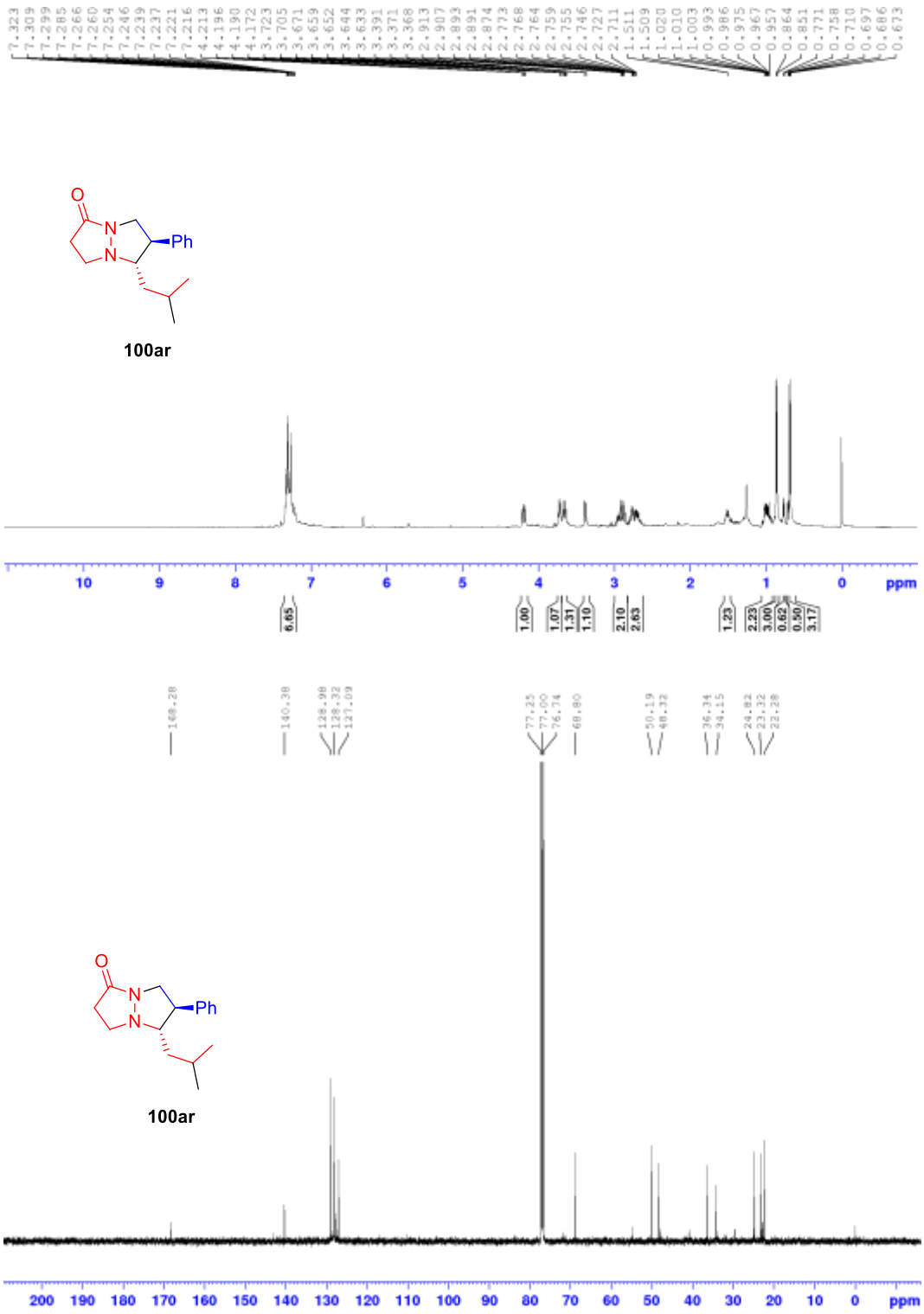
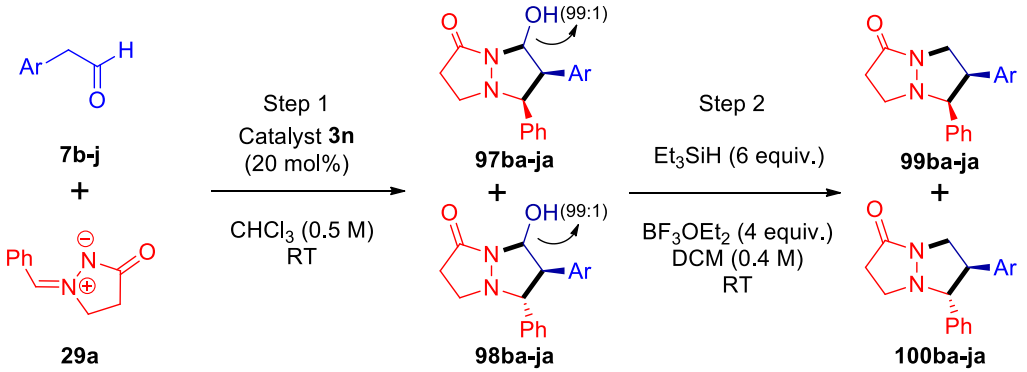


Figure-31: ^{1}H NMR and ^{13}C NMR spectrum of product **100ar.**

The aldehyde scope of the [3+2]-cycloaddition click reaction was explored by varying the substituents on the benzene ring of the aryl acetaldehydes **7** (Table 7). All halogenated aryl acetaldehydes **7b-e** (4-F, 4-Br, 2-Cl and 3-Cl; entries 1-4) gave the click products **97ba-ea/98ba-ea** in moderate to good yields (42-66%) in shorter reaction times, which on dehydroxylation furnished the pyrazolidinones **99ba-ea/100ba-ea** in excellent yields. At the same time electron withdrawing (2-NO_2), electron donating (4-OMe) and alkyl substituents (4-Me and 2-Me) on aryl acetaldehyde **7f-i** also furnished the expected click products **97fa-ia/98fa-ia** in 54-83% yields with slight influence on diastereomeric ratios, which on further dehydroxylation furnished the pyrazolidinones **99fa-ia/100fa-ia** in excellent yields (entries 5-8, Table 4). On substituting the benzene ring with naphthyl group the click product **97ka/98ka** yield decreased to 40% with 1.2:1 *dr*, but dehydroxylation gave the pyrazolidinone **99ka/100ka** in excellent yield (entry 9, Table 7).

Table 7: Aldehyde scope.[a]



Entry	**7** (Ar)	Time (h)		Yield (%)[b]		dr[c]
		Step 1	Step 2	**97+98 (%)**	**99+100 (%)**	(**99:100**)
1	**7b** (4-FC_6H_4)	0.25	12	**97ba+98ba** (42)	**99ba+100ba** (92)	1.4:1
2	**7c** (4-BrC_6H_4)	0.17	12	**97ca+98ca** (45)	**99ca+100ca** (94)	1:1
3	**7d** (2-ClC_6H_4)	0.17	12	**97da+98da** (66)	**99da+100da** (92)	1:1
4	**7e** (3-ClC_6H_4)	0.17	12	**97ea+98ea** (40)	**99ea+100ea** (95)	1.2:1
5	**7f** (2-$NO_2C_6H_4$)	0.5	3	**97fa+98fa** (73)	**99fa+100fa** (68)	1.4:1
6	**7g** (4-$OMeC_6H_4$)	0.2	12	**97ga+98ga** (54)	**99ga+100ga** (79)	1.3:1
7	**7h** (4-MeC_6H_4)	0.3	12	**97ha+98ha** (61)	**99ha+100ha** (98)	1.4:1
8	**7i** (2-MeC_6H_4)	0.42	12	**97ia+98ia** (83)	**99ia+100ia** (94)	2:1
9	**7j** (2-Naphthyl)	0.5	12	**97ja+98ja** (40)	**99ja+100ja** (97)	1.2:1

[a] Reactions were carried out in solvent (0.5 M) with 1.5 equiv. of **29a** relative to **7a** (0.5 mmol) in the presence of 20 mol% of catalyst **3n**; and completion of reaction was monitored by TLC. [b] Yield refers to the column purified product. [c] *dr* determined by NMR analysis.

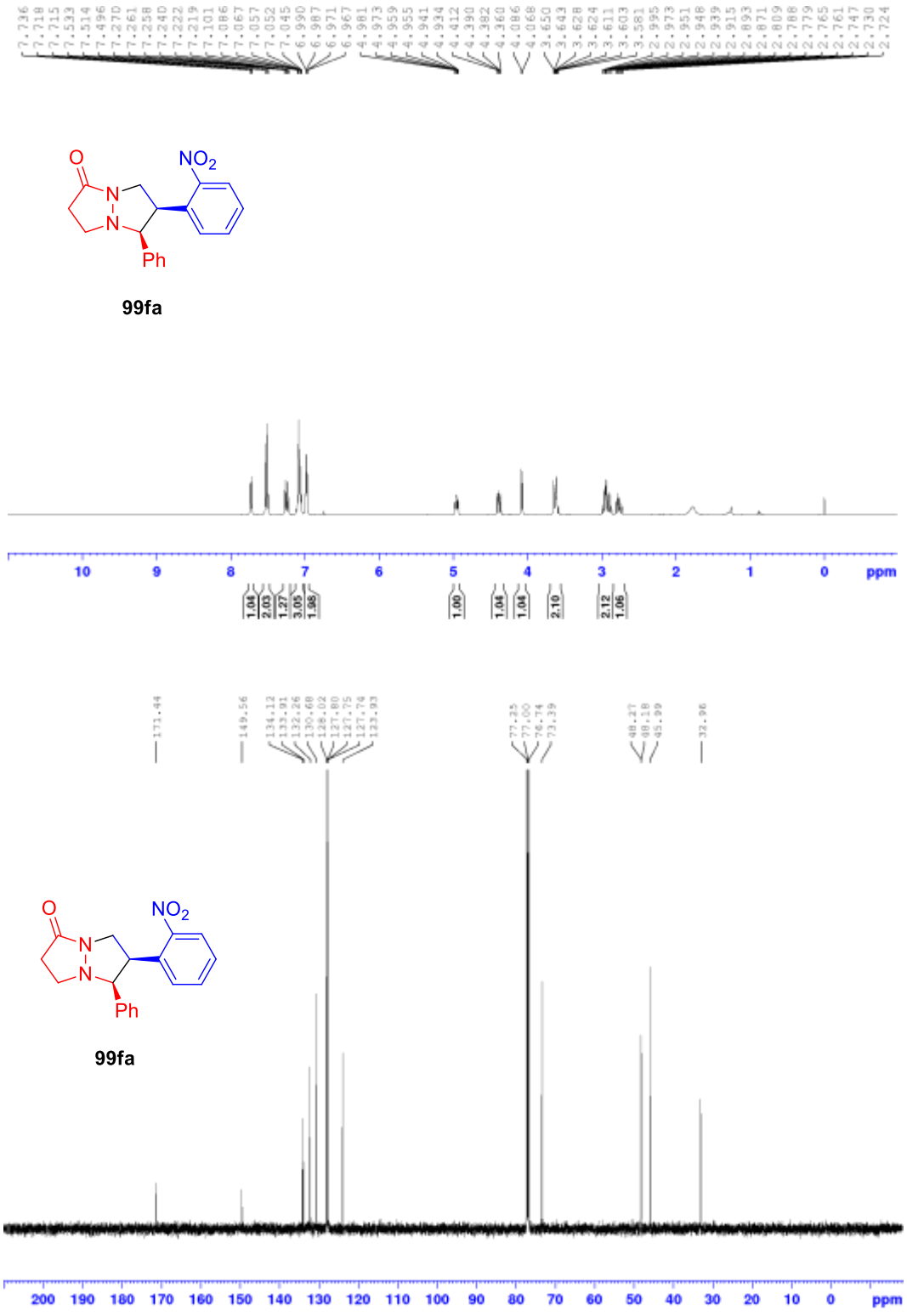


Figure-32: ^{1}H NMR and ^{13}C NMR spectrum of product **99fa.**

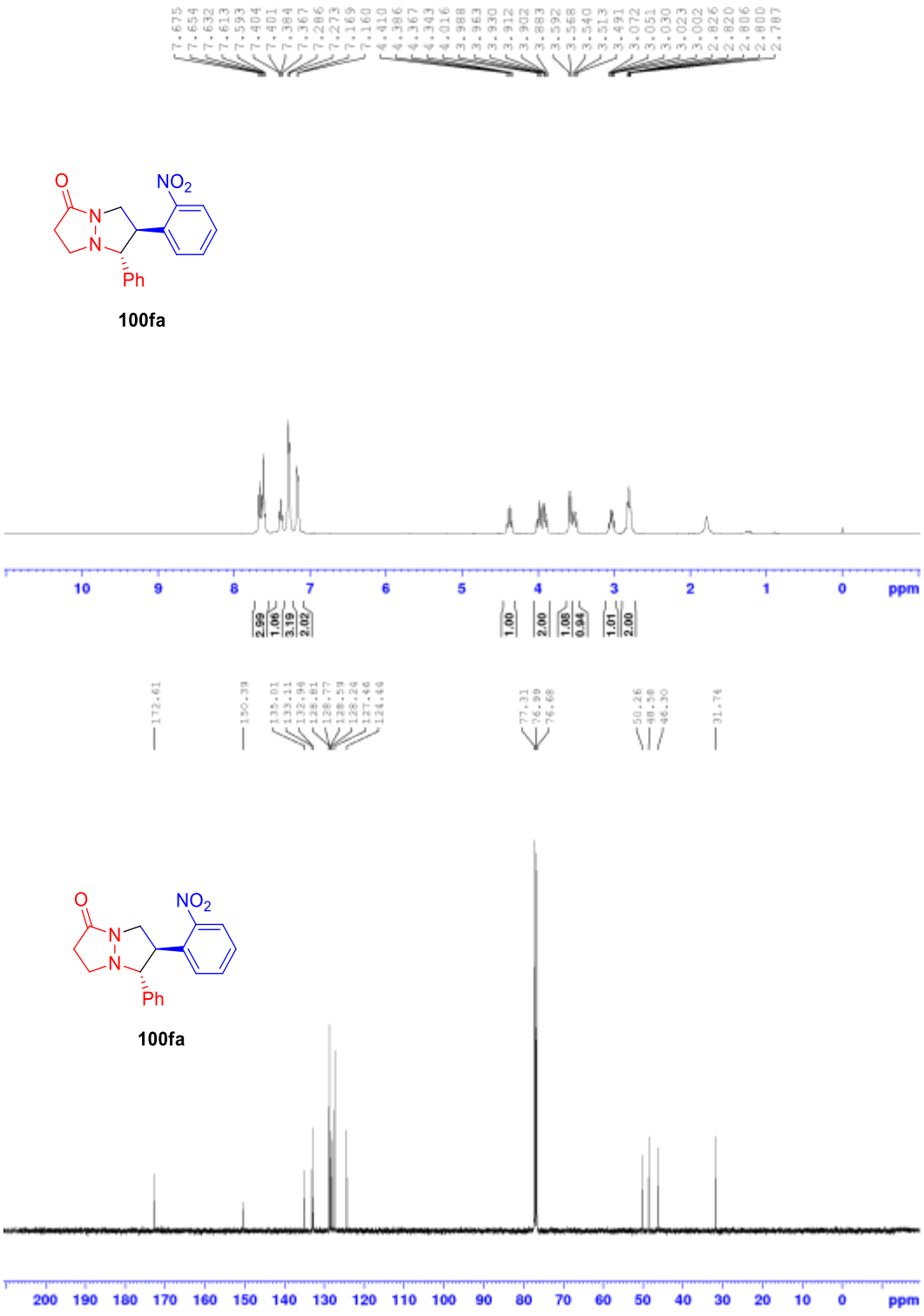


Figure-33: ^{1}H NMR and ^{13}C NMR spectrum of product **100fa.**

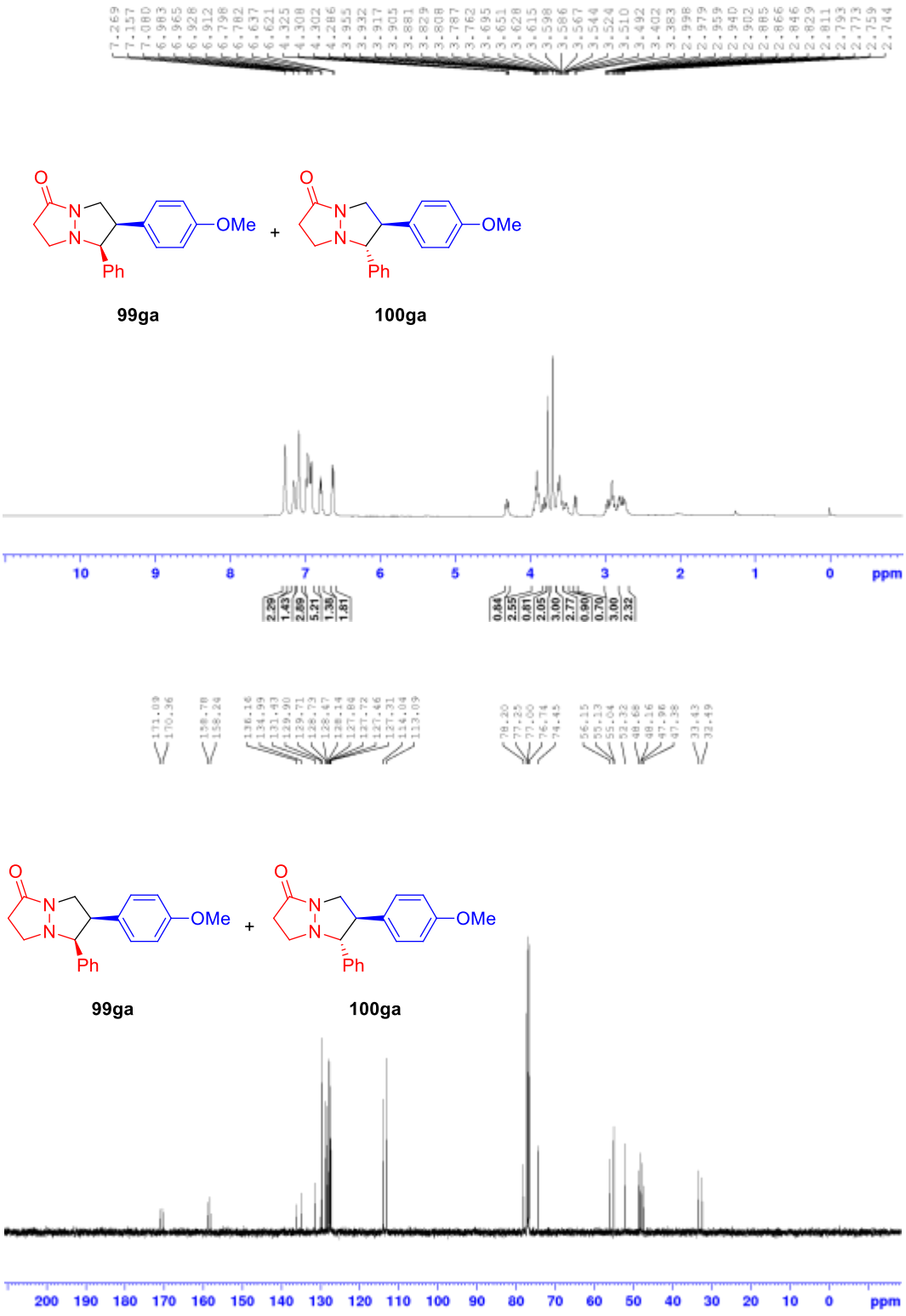


Figure-34: ^{1}H NMR and ^{13}C NMR spectrum of products **99ga** and **100ga.**

The structure and relative stereochemistry of the click products **97-100** were assigned by NMR analysis and also finally confirmed by X-ray structure analysis on **99fa** and **100fa** as shown in Figure 35 and Figure 36.[38]

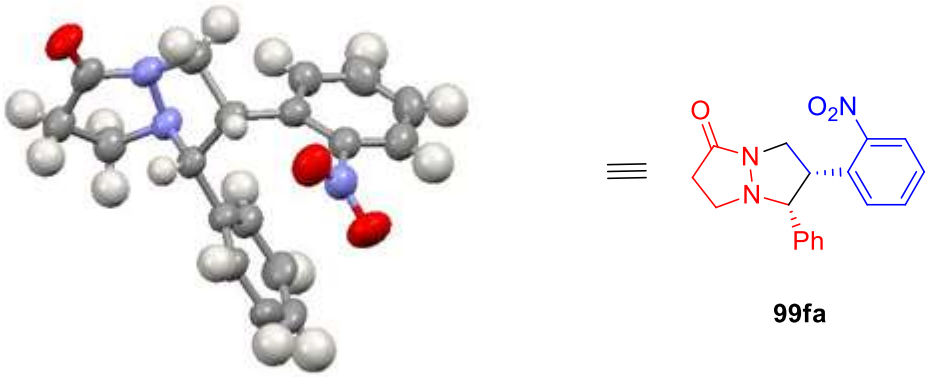


***Figure-35*:** Crystal structure of *cis*-6-(2-nitrophenyl)-5-phenyltetrahydropyrazolo [1,2-a]pyrazol-1(5*H*)-one (**99fa**).

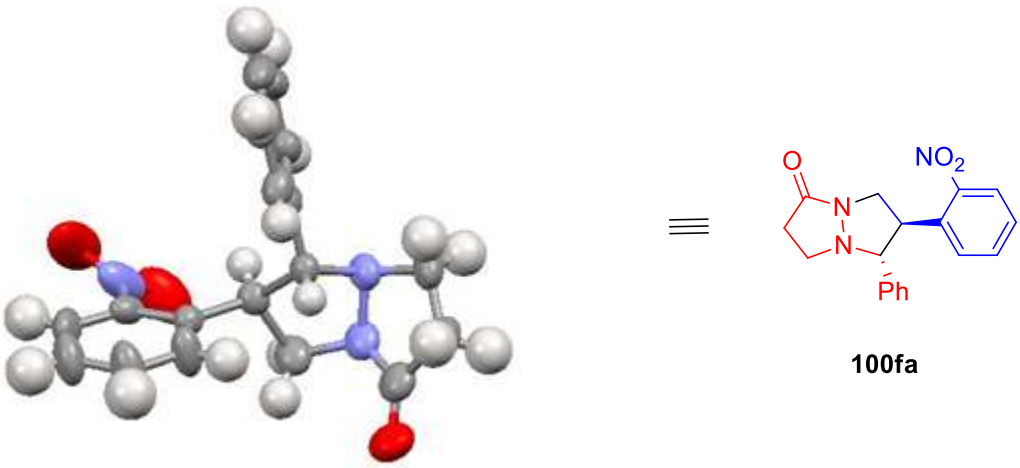
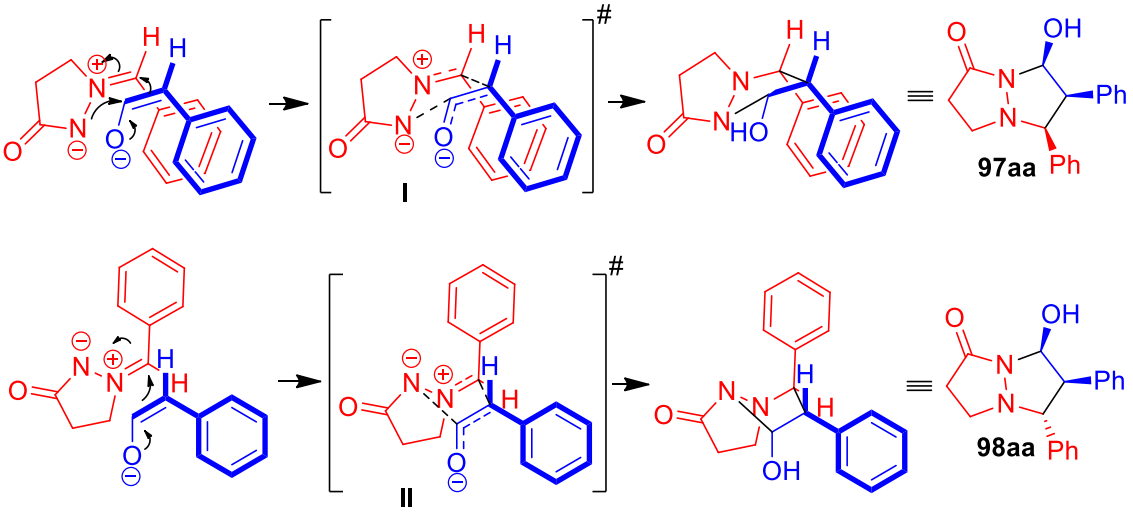


***Figure-36*:** Crystal structure of *trans*-6-(2-nitrophenyl)-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5*H*)-one (**100fa**).

4.2.3 Mechanistic Rationale:

Based on the aforementioned results and single crystal x-ray analysis of click products **99fa** and **100fa**, we proposed a plausible mechanism as illustrated in Scheme 6. According to previous literature reports,[39] in gas phase and also in polar solvents like acetonitrile phenylacetaldehyde leading to formation of *cis*-enolate as more stable form than *trans*-enolate. In contrast, in non-polar solvents like CCl_4 and cyclohexane both conformers were found to be energetically equivalent. Stability of the *cis*-conformer increases with increasing solvent polarity since it has a higher dipole moment than *trans*-conformer. Moving towards chloroform it seems probable that *cis*-conformer will have lower energy, which would lead to the formation of *cis*-enolate preferentially in the reaction mixture. As a result, the reaction may proceeds with the addition of *cis*-enolate on the azomethine imine *via* envelope shaped transition states **I** and **II** to provide the final products **97aa** and **98aa** respectively. Since, we did not observe formation of an intermediate during the course of the reaction, even though a concerted or stepwise pathway is possible, a concerted addition is more probable.

Scheme 6: Proposed reaction mechanism.



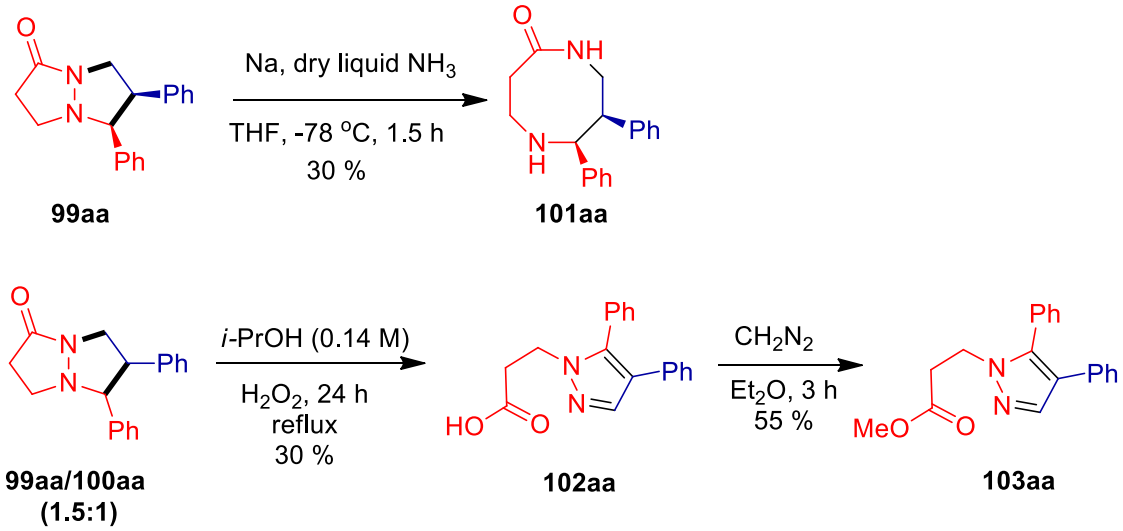
Outcome of poor to moderate diastereoselectivity from the reaction of aryl substituted **7** and **29** can be explained through competition between equally possible π-π interactions and steric hindrance between two aryl groups as shown in TS **I** and **II**. When alkyl groups are attached to

azomethine imines **29**, *trans*-isomer **98** formed as major product through TS **II** to avoid the steric hindrance between alkyl and aryl groups as shown in Scheme 6.

4.2.4 Synthetic applications of click products:

The synthetic utility of our click strategy was demonstrated by synthesizing 8-membered cyclic amide **101aa** from **99aa** through Birch reduction conditions in 30% yield (Scheme 3). Such dinitrogen cyclic compounds **101** are known as precursors to compounds acting as acrolein biomarkers and biofunctional modulators. In another application, the amide bond of the final dehydroxylated products **99aa/100aa** was cleaved and oxidized to acid **102aa** which on esterification with ethereal diazomethane yielded the product **103aa**. Analogues of compound **103aa** are known to act as inhibitor of ADP-induced human platelet aggregation and highlighting the importance of this click reaction in medicinal chemistry.[40]

Scheme 6: Synthetic applications.



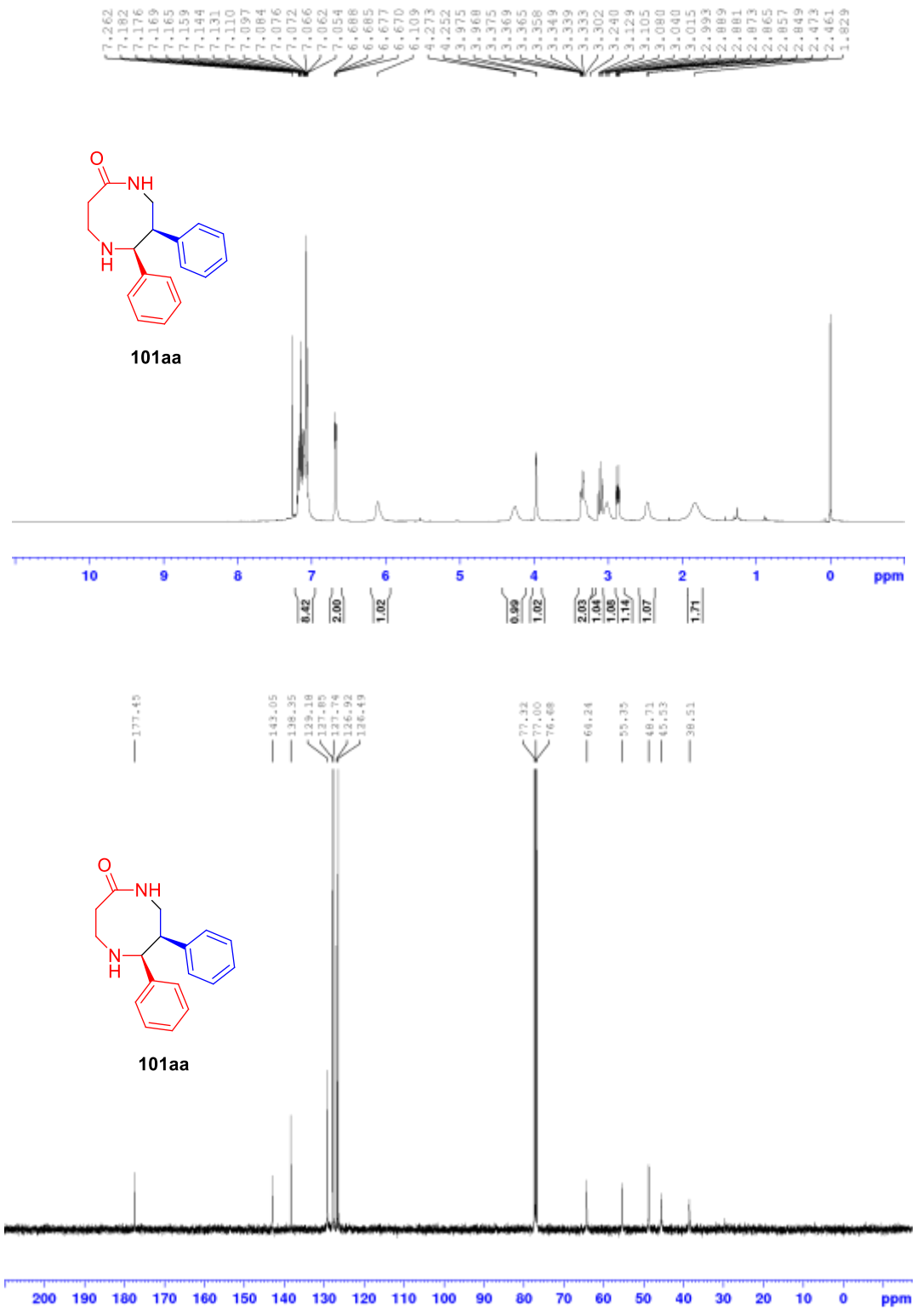


Figure-37: ^{1}H NMR and ^{13}C NMR spectrum of product **101aa.**

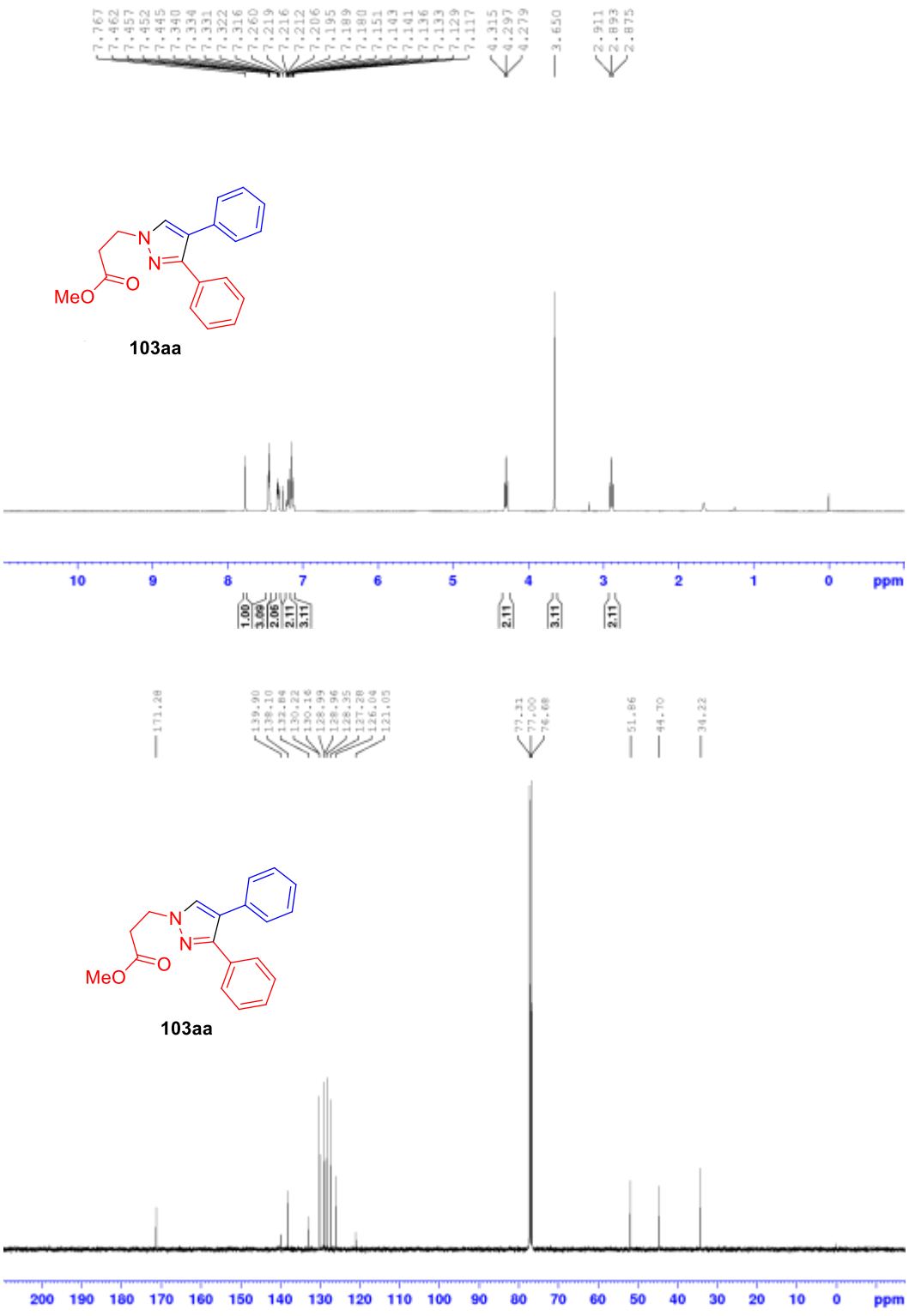


Figure-38: ^{1}H NMR and ^{13}C NMR spectrum of product **103aa.**

4.3 Conclusions

In conclusion, we presented herein an interesting example of transition metal-free amine or base-catalysed [3+2]-cycloaddition of commercially available aryl acetaldehydes with bench stable azomethine imines for the click synthesis of *N,N*-bicyclic pyrazolidinone derivatives. The key highlights of present protocol are operational simplicity, high reaction rate, low catalyst cost and ambient temperature operation.

.

5. Catalytic Ynone–Amidine Formal [4+2]–Cycloaddition for the Regioselective Synthesis of Tricyclic Heterocycles

5.1 Introduction

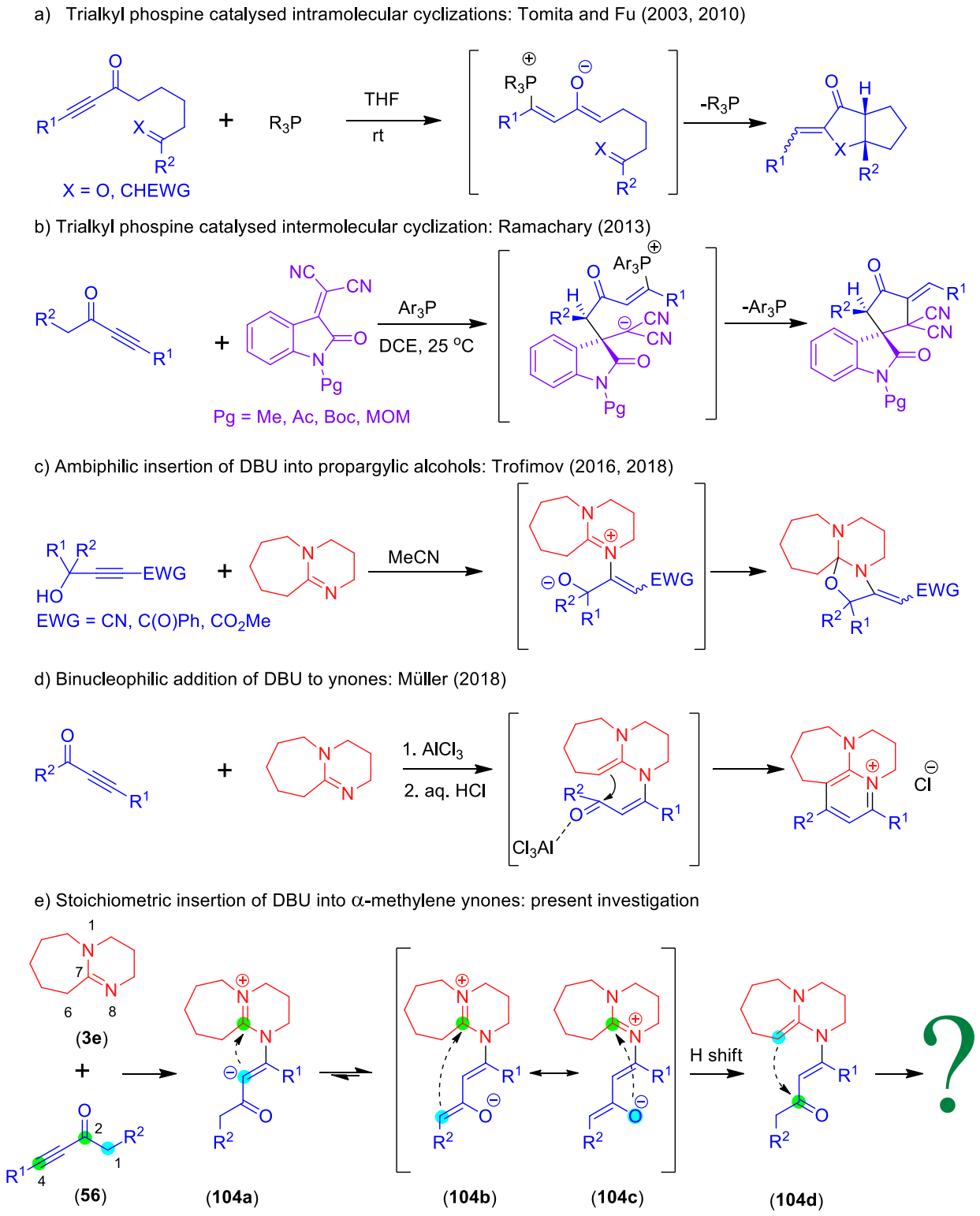
Ynones have recently surfaced as Michael acceptors with versatile reactivity, giving way to the construction of varied hetero/carbocyclic systems.[41-43] In this field, pioneering work has been done by Tomita and Fu groups exploiting ynones in trialkylphosphine-catalyzed intramolecular zipper cyclizations (Scheme 7a).[41] Influenced by their work, we developed a complimentary triphenylphosphine-catalyzed intermolecular Tomita zipper cyclization of ynones with olefins (Scheme 7b).[42f] Meticulous analysis of aforementioned reaction mechanisms brings to light some salient features of trialkylphosphine which rationalizes their excellent catalytic activity in such reactions. Primarily, the free lone pair on phosphorus renders the nucleophilic attack on C-4 carbon of ynones, resulting in a zwitterion. Finally, in the absence of alternative neutralization pathways, stabilization of this zwitterion drives the detachment of the catalyst from the substrate through novel zipper cyclization, hence regenerating it. These catalytic features that make trialkylphosphine exceptional catalysts prevent them from becoming good substrates capable of permanently bonding to its reacting partner.

Such dual behaviour, of a catalyst and a substrate, has been known to be displayed by amidine bases like DBU.[44] This is as a consequence of the fact, that following the nucleophilic attack by N-8 of DBU on ynones, the resultant zwitterion can be neutralized by proton loss from C-6 or by nucleophilic attack on the iminium ion carbon (Scheme 7e). These alternative stabilization routes, impart amidine (DBU) unparalleled nucleophilic capabilities leading to its incorporation into several acetylenic moieties like alkynoates[45a-d] and electron deficient propargylic alcohols to give fused tricyclic derivatives (Scheme 7c).[45e-h]

Even though, such diverse modes of reactivity of DBU with triple bond exist, stoichiometric addition to ynones has seldom been explored. An attempt was made in this

direction recently, by Müller's group,[46] where DBU's binucleophilic nature was exploited in annulation to ynones yielding tricyclic aminopyridinium salts (Scheme 7d). This protocol's major drawback lies in its use of ynones bearing only aromatic substituents. The absence of α-acidic hydrogens largely restricts the ynones to behave only as bielectrophiles (at C-2 and C-4). In contrast, nucleophilic capabilities of ynones with an enolizable methylene next to the carbonyl (C-1) have been demonstrated earlier by our group.[42-43] Hence, our present experimental quest is focused on reacting α-enolizable ynones with an ambiphilic DBU as a substrate, in turn taping into the complete reactivity competence of ynones with DBU (Scheme 7e). Achieving exclusively a ynone-DBU addition poses a grave challenge since this addition is in direct competition with ynone self-addition.[42k] Such an insertion of DBU to ynones is further complicated by possibility of diverse cyclization modes from intermediates **104a**, **104b**, **104c** and **104d** (Scheme 7e).

Scheme 7: Previous and present reaction design for the annulation of ynones with olefins.

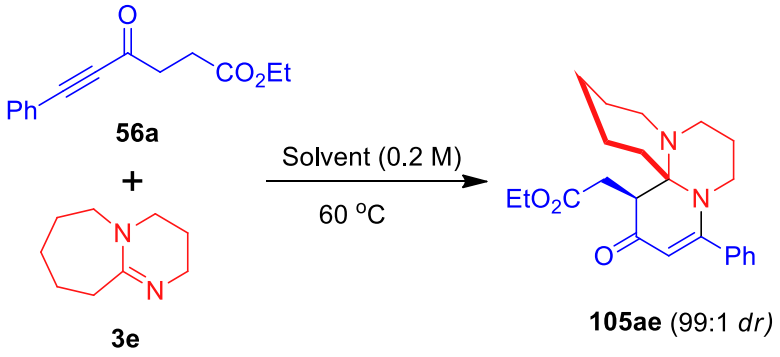


5.2 Results and Discussion

5.2.1 Reaction optimization:

The preliminary reaction was tested under the self-catalysis between ynone **56a** and 1.3 equiv. of DBU **3e** at 60 °C in DCE. To our astonishment, from a plethora of possible products (Scheme 7e) a single cyclized product **105ae** was obtained in 65% yield with 99:1 *dr* within 1.5 h (Table 8, entry 1). Product **105ae** turned out to be quite different from that obtained by Müller's work (Scheme 7d). For increasing the product **105ae** yields, an extensive solvent screening was carried out (Table 8). To begin with, non-polar aprotic solvents like DCM, chloroform, and toluene furnished **105ae** in poor yields (Table 8, entries 2-4) and no reaction was observed in 1,1,2,2-terachloroethane (Table 8, entry 5). These disappointing results directed our investigation towards more polar solvents like EtOH (61% yield, entry 6) and other solvents like THF, DMF, and DMSO gave just above average yields of 38%, 65% and 62% respectively (Table 8, entries 7-9). Self-catalyzed cyclization reaction of **56a** and 1.3 equiv. of **3e** in MeCN (0.2 M) at 60 °C for within 24 minutes furnished the product **105ae** in a very good yield (78%, entry 10). Further all attempts to improve the yield either by increasing the **3e** equiv. to 1.5 or decreasing to 1.1, carrying out the reaction at a lower temperature (30 °C) or lower concentration (0.15 M) went in vain (Table 8, entries 11-14). Thus MeCN (0.2 M) at 60 °C was fixed as the best condition for the self-catalyzed cyclization protocol.

Table 8: Reaction solvent optimization.[a]



Entry	(**3e**) equiv.	Solvent (0.2 M)	Time (h)	Yield (%)[b] **105ae**
1	1.3	DCE	1.5	65
2	1.3	DCM	1	35
3	1.3	$CHCl_3$	2.5	44
4	1.3	Toluene	1	13
5	1.3	$Cl_2CHCHCl_2$	48	NR
6	1.3	EtOH	2.5	61
7	1.3	THF	1.5	38
8	1.3	DMF	0.7	65
9	1.3	DMSO	0.5	62
10	1.3	MeCN	0.4	78.2
11	1.5	MeCN	0.5	73
12	1.1	MeCN	0.6	61
13[c]	1.3	MeCN	0.5	65
14[d]	1.3	MeCN	2.5	73

[a] Reactions were carried out in solvent (0.2 M) with **3e** relative to **56a** (0.3 mmol). [b] Yield refers to the column purified product.[c] Reaction performed in solvent (0.15 M). [d] Reaction performed at 30 °C. Note: Complete consumption of **56a** was observed in all reactions.

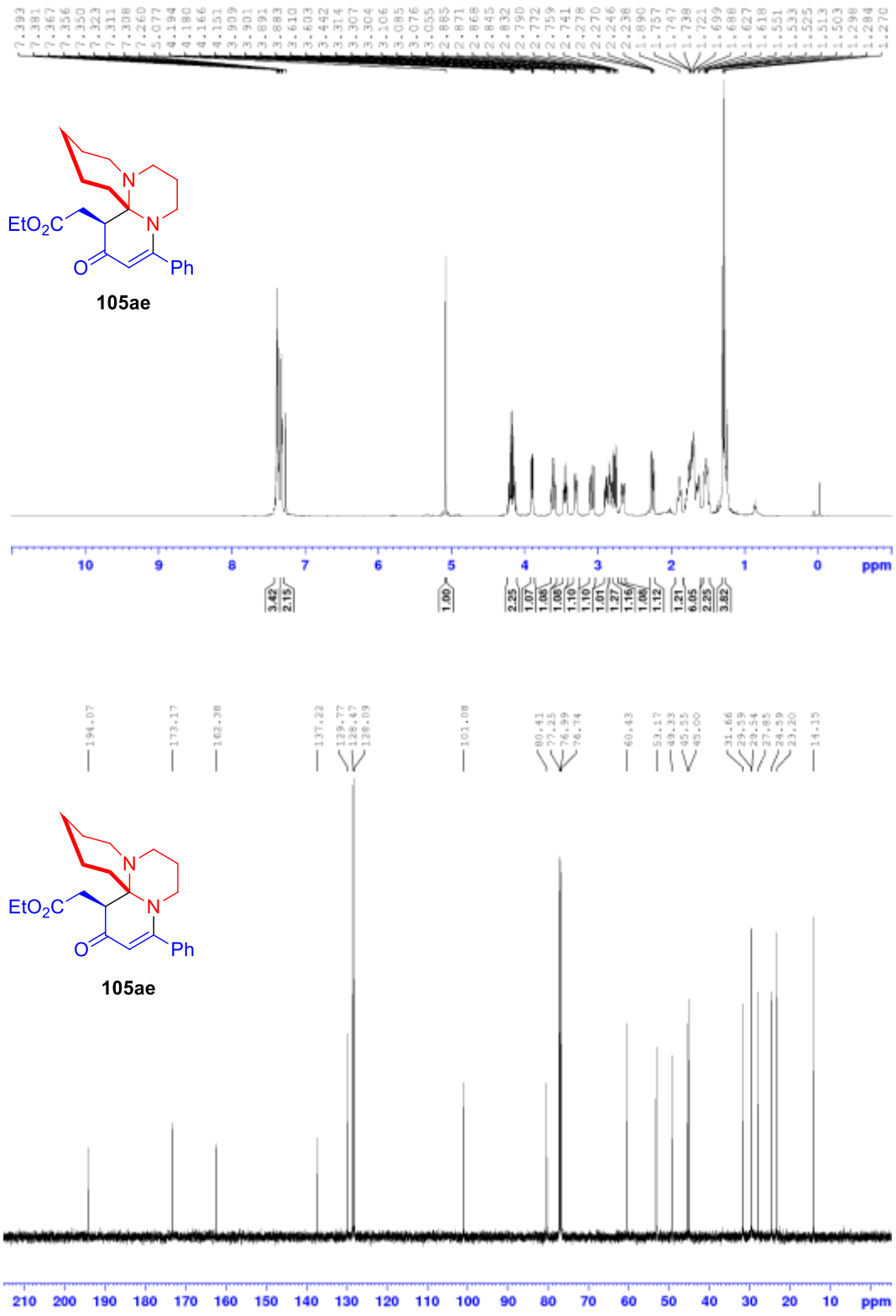
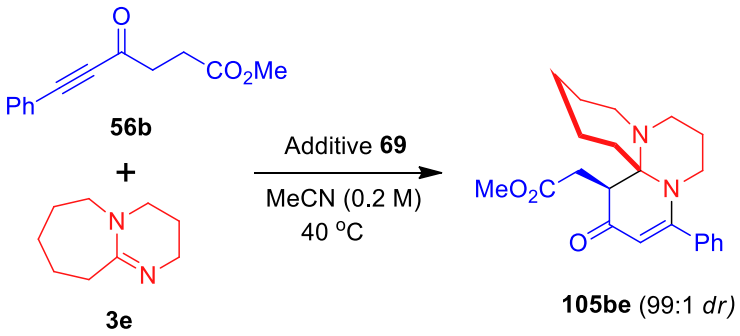


Figure-39: ^{1}H NMR and ^{13}C NMR spectrum of products **105ae.**

Surprisingly, subjecting the methyl ester **56b** to the optimized self-catalyzed condition with **3e** resulted in a moderate yield of 45% of **105be** (Table 9, entry 1). Even reversal of reactant equivalents by taking 1.3 equiv. of **56b** with respect to **3e** caused a further reduction in yield to 23% (Table 9, entry 2). Such dismal results compelled us to reanalyze the optimized condition with **56b** in the presence of various additives **69** at 40 °C (Table 9). By addition of catalytic amount of Brønsted acids **69a-e** like CH_3CO_2H, *o*-$FC_6H_4CO_2H$, $PhCO_2H$, *p*-$MeOC_6H_4CO_2H$ and 2-naphthoic acid were initially employed with the aim of slightly activating the ynone carbonyl without deactivating DBU. However, all of the aforementioned additives **69a-e** had detrimental effect on the product yields furnishing just 19-64% of **105be** (Table 9, entries 3-7). As a consequence, the reaction was again performed in the presence of a mild base like DMAP **69f** and (±)-BINOL **69g** both of which gave poor yields of 32% and 41% respectively (Table 9, entries 8 and 9). Such, discouraging results shifted our focus towards testing Lewis acids like metal triflates **69h-n** for promoting the formation of **105be** in higher yields. Out of all the metal triflates **69h-n** screened, AgOTf **69h** and $Ca(OTf)_2$ **69n** proved promising as additives by furnishing the **105be** in 66% and 70% yields respectively (Table 9, entries 10-16). Hence, we narrowed down on 1.3 equiv. of **3e** with **56b** in the presence of 10 mol% of $Ca(OTf)_2$ **69n** at 40 °C in MeCN (0.2 M) as the final optimized condition (Table 9, entry 16).

Table 9: Reaction additive optimization.[a]



Entry	Additive **69** (mol %)	Time (h)	Yield (%)[b] **105be**
1[c]	_	0.3	45
2[d]	_	0.25	23
3	**69a:** CH_3CO_2H (20 mol%)	2.5	19
4	**69b:** *o*-$FC_6H_4CO_2H$ (20 mol%)	21.0	50
5	**69c:** $PhCO_2H$ (20 mol%)	5.5	64
6	**69d:** *p*-$MeOC_6H_4CO_2H$ (20 mol%)	4.5	53
7	**69e:** 2-Naphthoic acid (20 mol%)	4.5	51
8	**69f:** DMAP (20 mol%)	2.0	32
9	**69g:** (±)-BINOL (10 mol%)	3.0	41
10	**69h:** AgOTf (10 mol%)	4.0	66
11	**69i:** $Cu(OTf)_2$ (10 mol%)	1.0	36
12	**69j:** $Zn(OTf)_2$ (10 mol%)	2.5	36
13	**69k:** $In(OTf)_3$ (10 mol%)	4.0	48
14	**69l:** $Sc(OTf)_3$ (10 mol%)	2.5	51
15	**69m:** $Mg(OTf)_2$ (10 mol%)	3.0	46
16	**69n:** $Ca(OTf)_2$ (10 mol%)	3.0	70

[a] Unless otherwise mentioned, reactions were carried out in solvent (0.2 M) with 1.3 equiv. of **3e** relative to **56b** (0.3 mmol) in presence of additive **5**. [b] Yield refers to the column purified product.[c] Reaction performed at 60 °C.[d] Reaction was carried out in solvent (0.2 M) with 1.3 equiv. of **56b** relative to **3e** (0.3 mmol). Note: Complete consumption of **56b** was observed in all reactions.

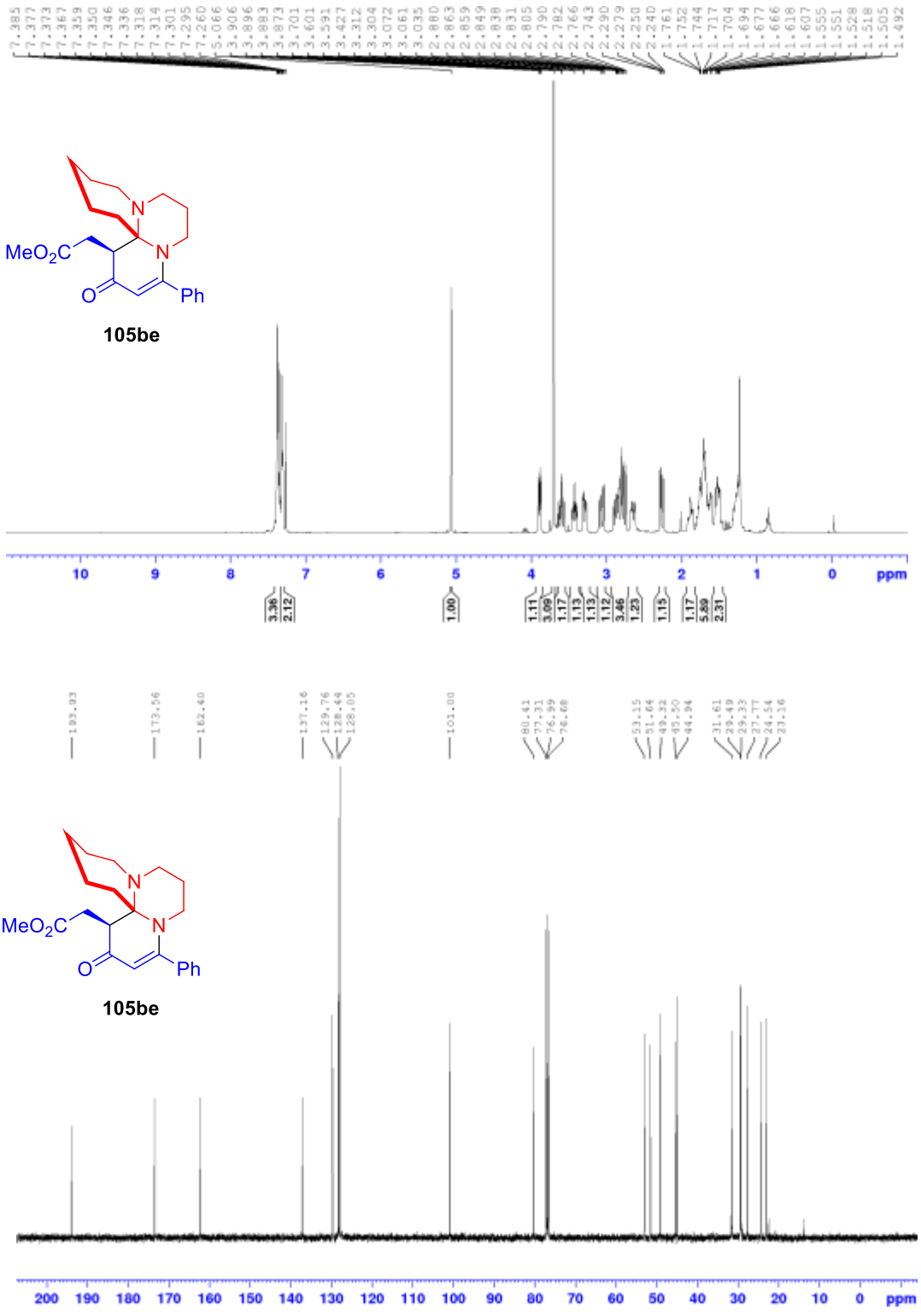
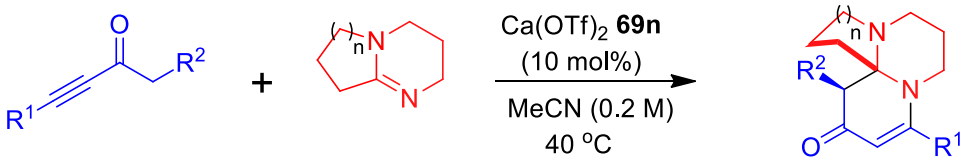


Figure-40: ^{1}H NMR and ^{13}C NMR spectrum of products **105be.**

5.2.2 Scope of Ynone-Amidine formal [4+2]-cycloaddition reaction:

Having established the optimum conditions, a variety of α-enolizable ynones **56** and amidine bases **3** were tested under the catalytic protocol to explore the formal [4+2]-cycloaddition scope. Initially, just extending the aliphatic chain as R^2 substituent from methyl to ethyl by utilizing **56c-d** had negligible effect on reaction outcome with **3e** yielding the products **105ce-105de** in very good yields of 84-83% (Table 10, entries 1-2). Hence, our substrate variation was guided towards varying the R^1 group as differently substituted aromatics with R^2 fixed as Me. Phenyl groups bearing halogens F and Cl at *para* positions (Table 10, entries 3 and 4) and electron donating substituents like *p*-Me and *p*-OMe (Table 10 entries 5 and 6) delivered good yields of the desired products **105ge-105he** (68-80% yields). Exceptionally, electron withdrawing groups like *p*-NO_2 substituted phenyl rings provided an inseparable mixture of compounds within a short span of 12 minutes (Table 10, entry 7). Hetero-aromatics like 3-thiophenyl were also well tolerated under the present catalytic protocol (Table 10, entry 8). However, the ynone **56k** when made completely aromatic by substituting both R^1 and R^2 as Ph groups gave complete decomposition of the starting material during the reaction (entry 9). This indicates that an increased reactivity on account of stabilization of the α-anion (Scheme 7e, **104b**) via electron withdrawing or delocalizing groups, both lead to occurrence of multiple side reactions. Therefore, a fine balance of ynone reactivity was found to be crucial for success of this strategy. On similar lines, due to –I effect of OCH_2Ph group as R^2 the product **105le** yield diminished to 38% (Table 10, entry 10). Subsequently, locking R^1 as Ph or *p*-FC_6H_4 group in conjunction with substituting R^2 as methylene esters like ethyl, benzyl and isopropyl generated the desired products **105ae-105oe** in good to excellent yields of 72-87% (Table 10, entries 11-14). Even complex chiral substituents like methylene ester of (-)-menthyl as R^2 also fared well under this reaction strategy furnishing **105pe** in excellent 88% yield with 1:1 *dr* (entry 15). Fully aliphatic ynone **56q** also produced the final product **105qe** in 42% yield (Table 10, entry 16).

Table 10: Reaction substrate scope.[a]



56a-q **3** **105** (99:1 *dr*)

Entry	Ynone (**56**)	Amidine (n, **3**)	Time (h)	Yield **105** (%)
1	**56c:** R^1, R^2 = Ph, Me	3, **3e**	5.0	84 (**105ce**)
2	**56d:** R^1, R^2 = Ph, CH_2Me	3, **3e**	5.0	83 (**105de**)
3	**56e:** R^1, R^2 = *p*-FC_6H_4, Me	3, **3e**	5.0	76 (**105ee**)
4	**56f:** R^1, R^2 = *p*-ClC_6H_4, Me	3, **3e**	5.0	80 (**105fe**)
5	**56g:** R^1, R^2 = *p*-MeC_6H_4, Me	3, **3e**	5.0	68 (**105ge**)
6	**56h:** R^1, R^2 = *p*-$MeOC_6H_4$, Me	3, **3e**	6.0	78 (**105he**)
7[b]	**56i:** R^1, R^2 = *p*-$NO_2C_6H_4$, Me	3, **3e**	0.2	- (**105ie**)
8	**56j:** R^1, R^2 = 3-Thiophenyl, Me	3, **3e**	5.0	75 (**105je**)
9[b]	**56k:** R^1, R^2 = Ph, Ph	3, **3e**	0.5	- (**105ke**)
10	**56l:** R^1, R^2 = Ph, OCH_2Ph	3, **3e**	1.0	38 (**105le**)
11	**56a:** R^1, R^2 = Ph, CH_2CO_2Et	3, **3e**	3.0	87 (**105ae**)
12	**56m:** R^1, R^2 = Ph, $CH_2CO_2CH(Me)_2$	3, **3e**	3.0	74 (**105me**)
13	**56n:** R^1, R^2 = Ph, $CH_2CO_2CH_2Ph$	3, **3e**	3.0	72 (**105ne**)
14	**56o:** R^1, R^2 = *p*-FC_6H_4, CH_2CO_2Et	3, **3e**	3.0	81 (**105oe**)
15[c]	**56p:** R^1, R^2 = Ph, $CH_2CO_2R^3$	3, **3e**	1.5	88 (**105pe**)
16	**56q:** R^1, R^2 = $CH_2(CH_2)_2CH_3$, Me	3, **3e**	6.0	42 (**105qe**)
17	**56a:** R^1, R^2 = Ph, CH_2CO_2Et	1, **3o**	1.0	70 (**105ao**)
18	**56c:** R^1, R^2 = Ph, Me	1, **3o**	2.0	50 (**105co**)
19	**56e:** R^1, R^2 = *p*-FC_6H_4, Me	1, **3o**	3.0	40 (**105eo**)
20	**56o:** R^1, R^2 = *p*-FC_6H_4, CH_2CO_2Et	1, **3o**	1.0	56 (**105oo**)
21	**56b:** R^1, R^2 = Ph, CH_2CO_2Me	2, **3p**	1.0	20 (**105bp**)

[a] Yield refers to the column purified product.[b] Complete decomposition of **56** was accompanied with formation of multiple spots on **TLC.** [c] R^3 **=** (-)-Menthyl and distereomeric product mixture with 1:1 *dr* (**105pe:105'pe)** obtained.

Note: Complete consumption of **56** was observed in all reactions.

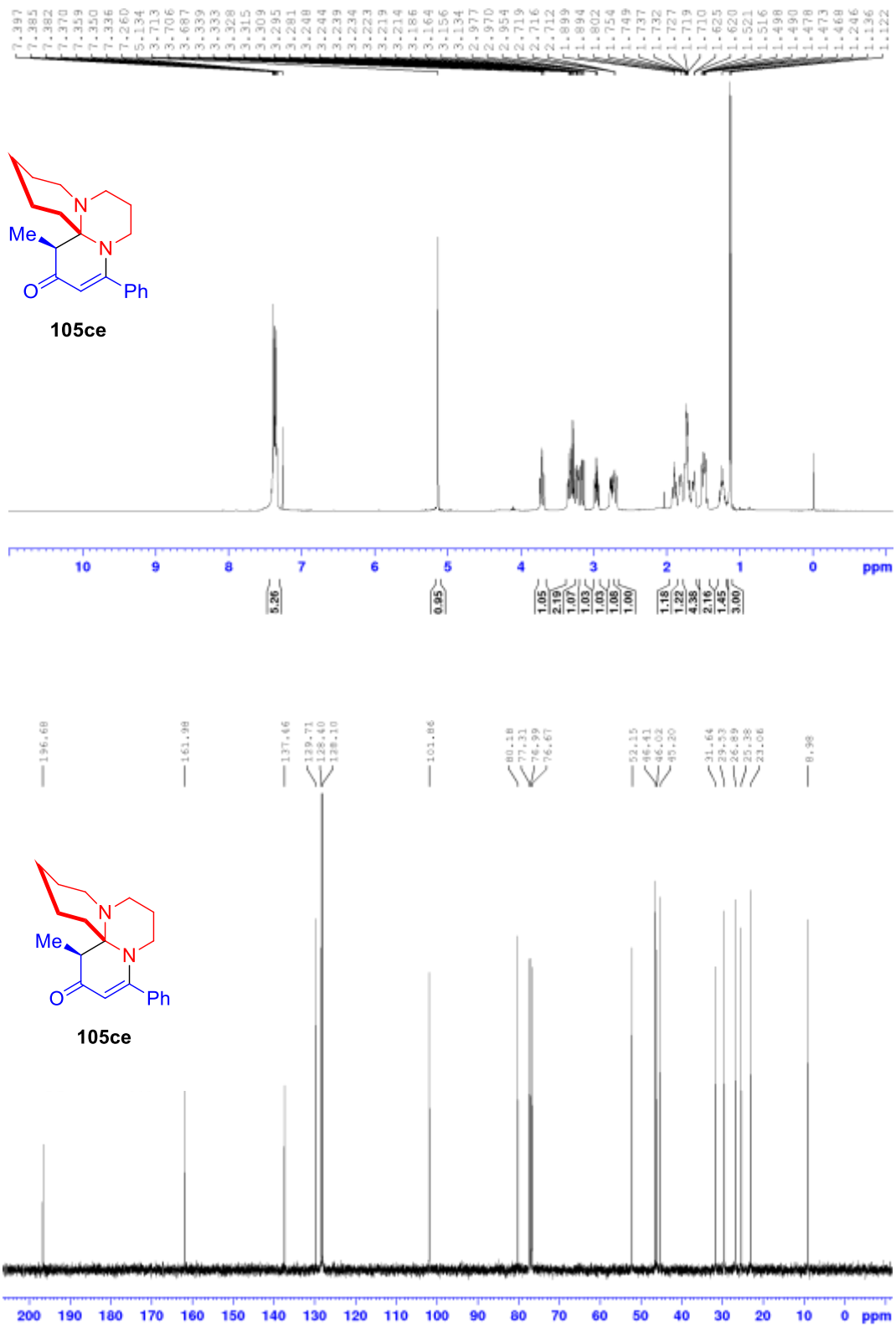


Figure-41: ^{1}H NMR and ^{13}C NMR spectrum of products **105ce.**

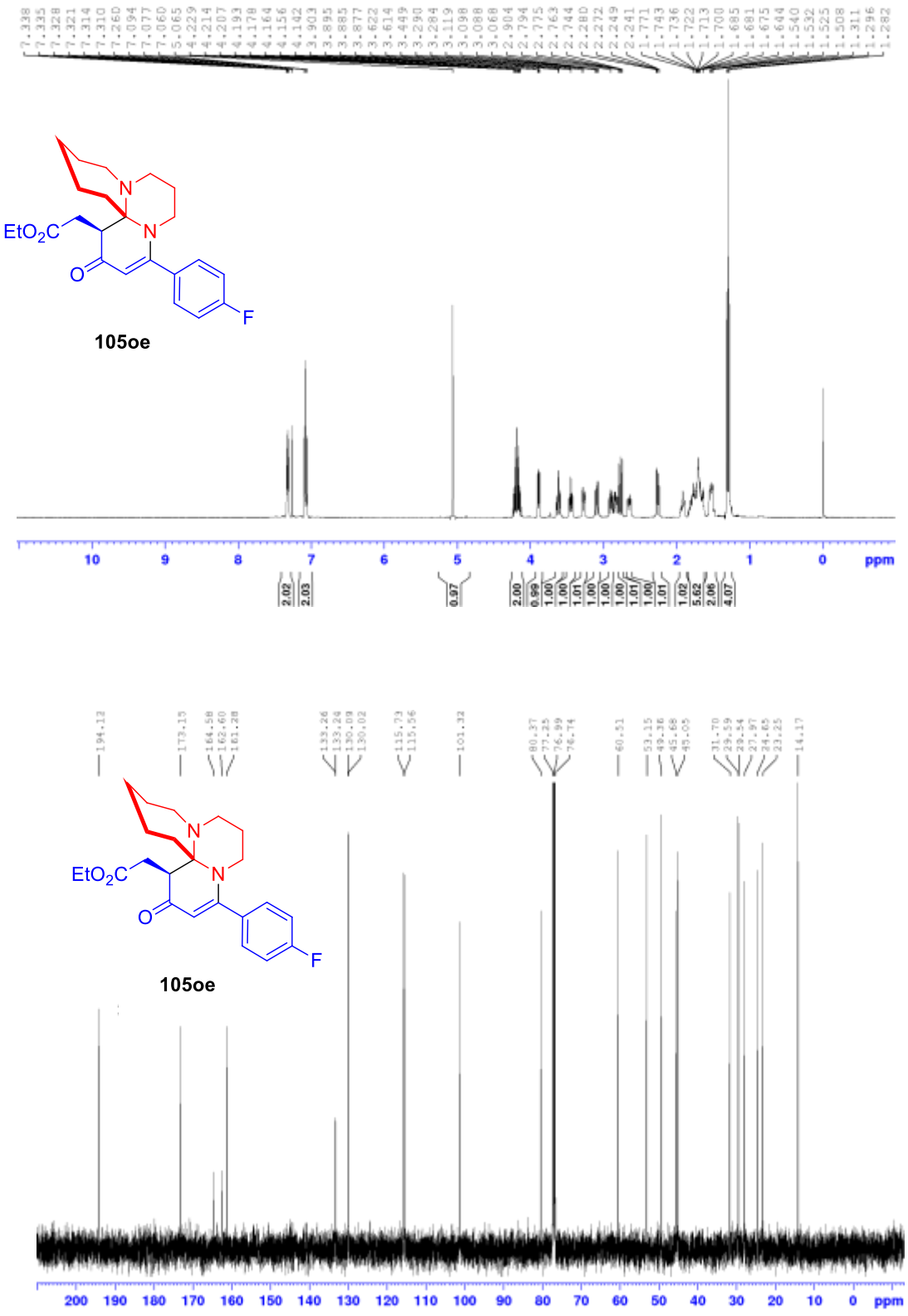
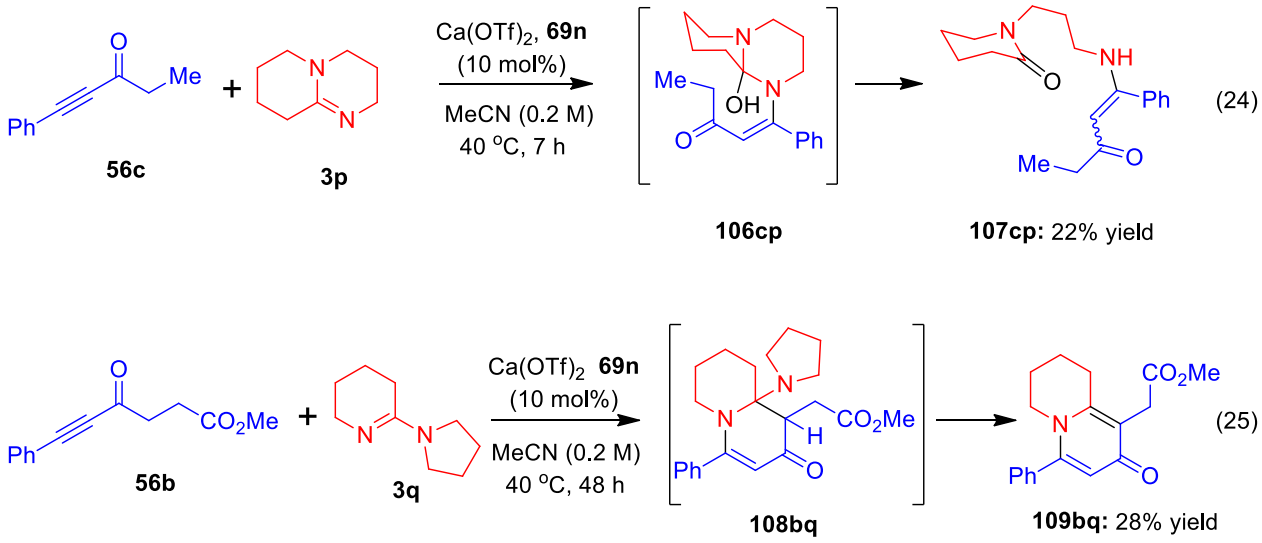


Figure-42: ^{1}H NMR and ^{13}C NMR spectrum of products **105oe.**

This protocol's scope was further broadened by utilizing other amidine bases like DBN **3o** in reaction with a handful of ynones **56a-o** delivering the respective products **105ao-105oo** in 40-70% yields (Table 10, entries 17-20). Further some unanticipated results were obtained with other amidine bases like **3p** where reaction with **56b** gave a very poor yield (20%) of the product **105bp** (Table 10, entry 21). However, utilizing the same amidine **3p** in reaction with ynone **56c** proceeded to give a unique open ring product **107cp** via the intermediate **106cp** with incorporation of a molecule of water from the solvent (Scheme 8, Eq. 24). Another peculiar reactivity was observed in the interaction of amidine **3q** with ynone **56b**, where a molecule of pyrrolidine was eliminated from the expected product **108bq** to yield stable compound **109bq** in 28% yield (Scheme 8, Eq. 25).

Scheme 8: Unexpected reactivity of ynones with amidine bases.



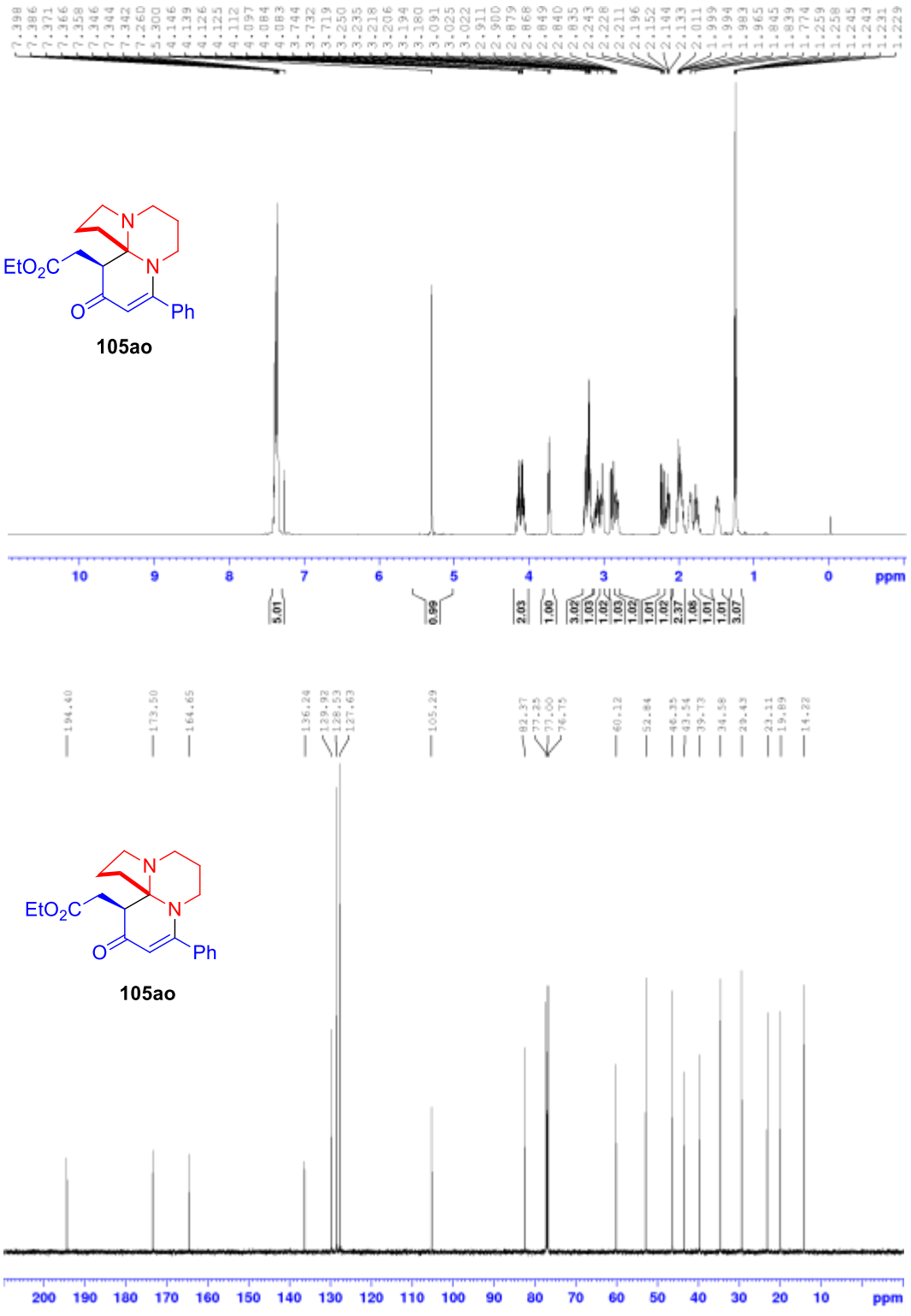


Figure-43: ^{1}H NMR and ^{13}C NMR spectrum of products **105ao.**

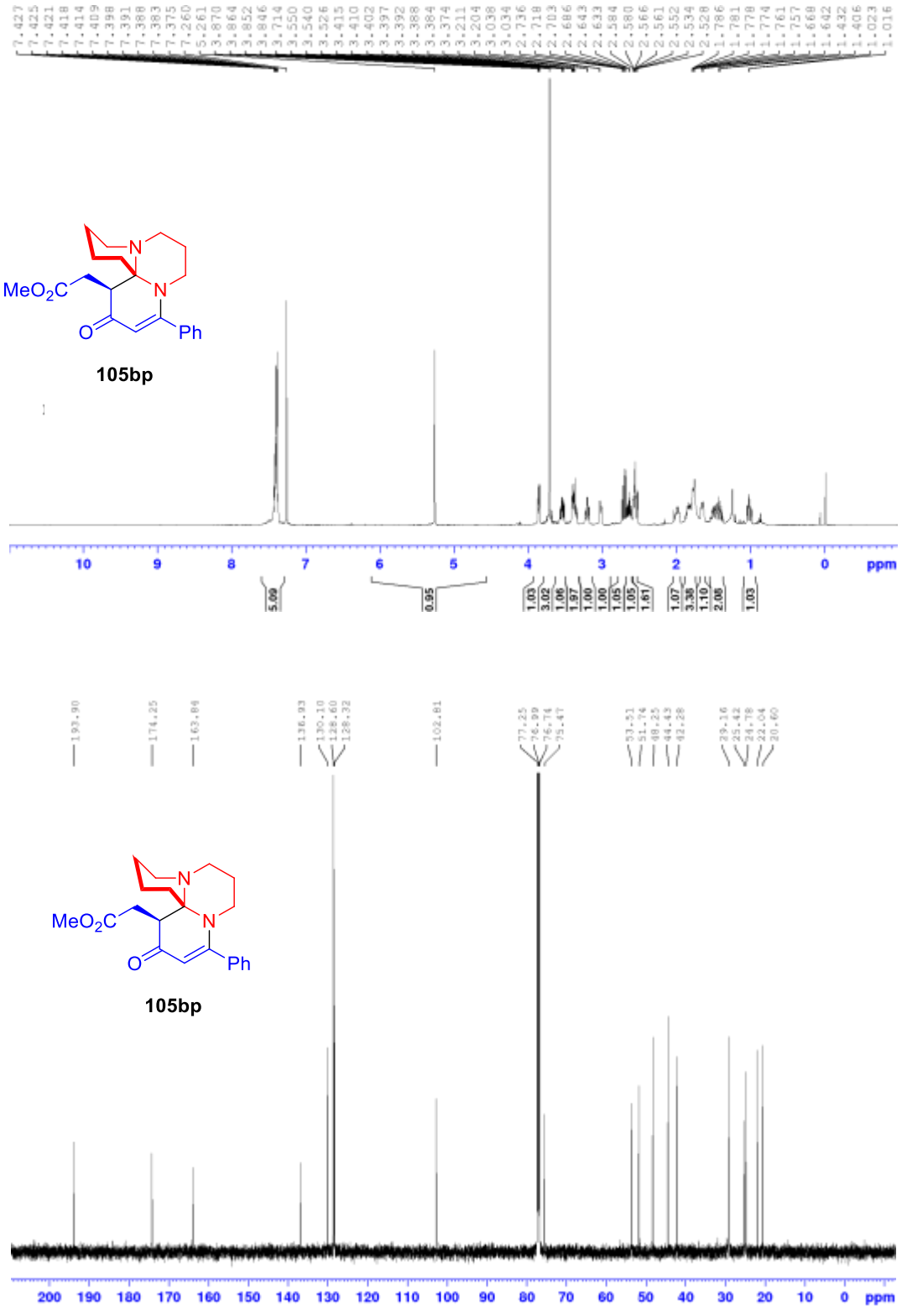


Figure-44: ^{1}H NMR and ^{13}C NMR spectrum of products **105bp.**

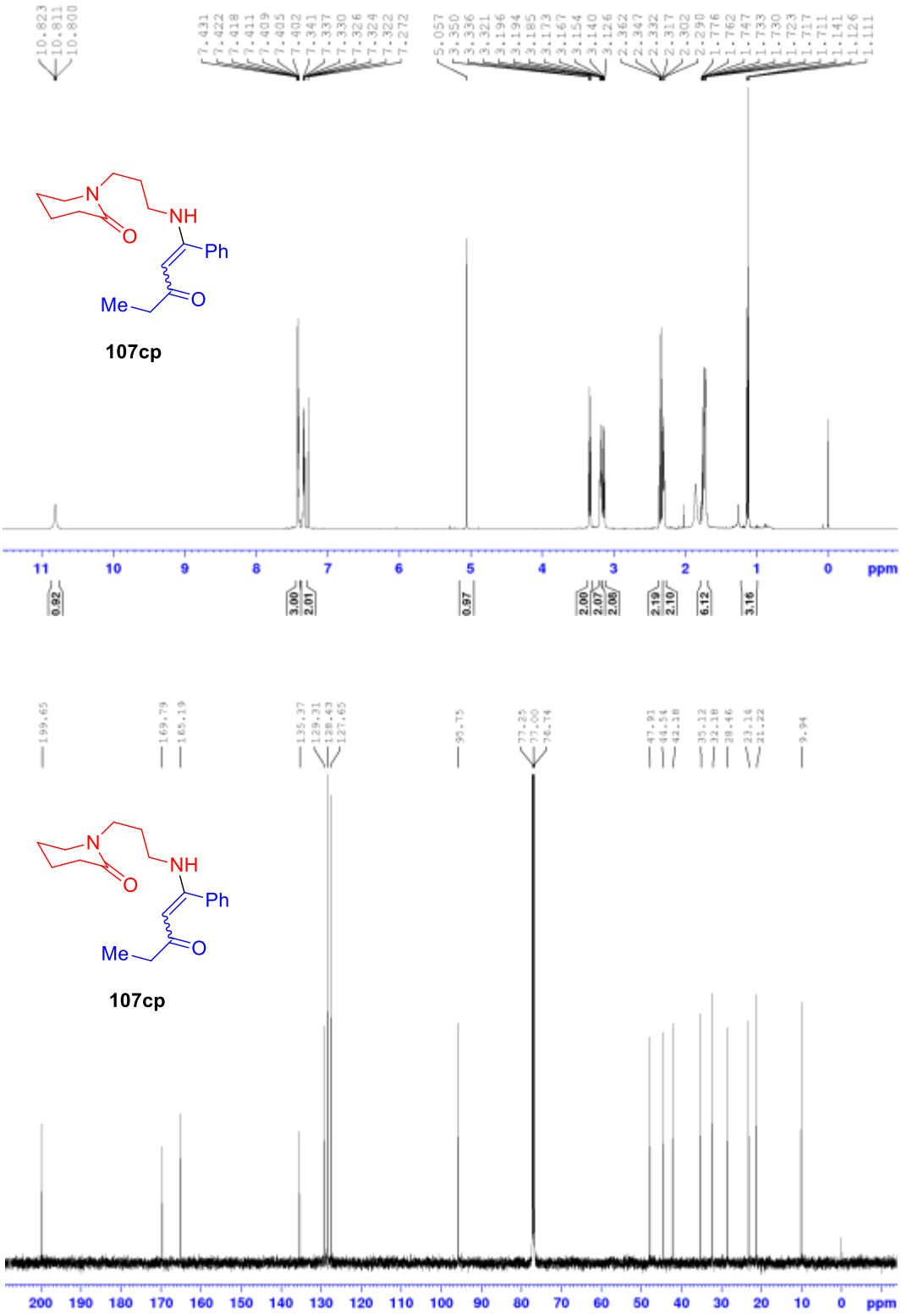


Figure-45: ^{1}H NMR and ^{13}C NMR spectrum of products **107cp.**

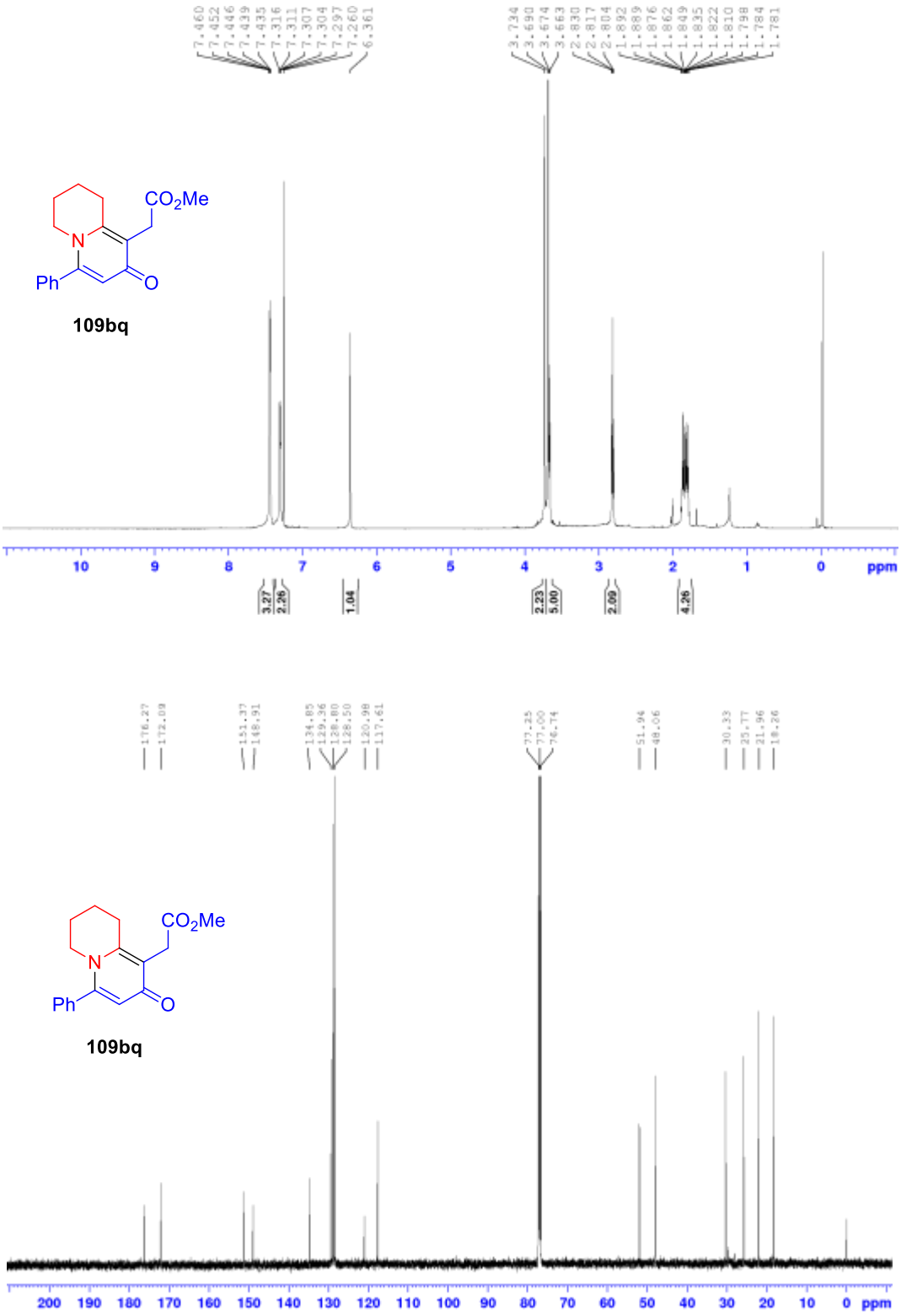


Figure-46: ^{1}H NMR and ^{13}C NMR spectrum of products **109bq.**

The structure and relative stereochemistry of the products **105** were assigned by NMR analysis and also finally confirmed by X-ray structure analysis on **105oe** as shown in Figure 47 .[47]

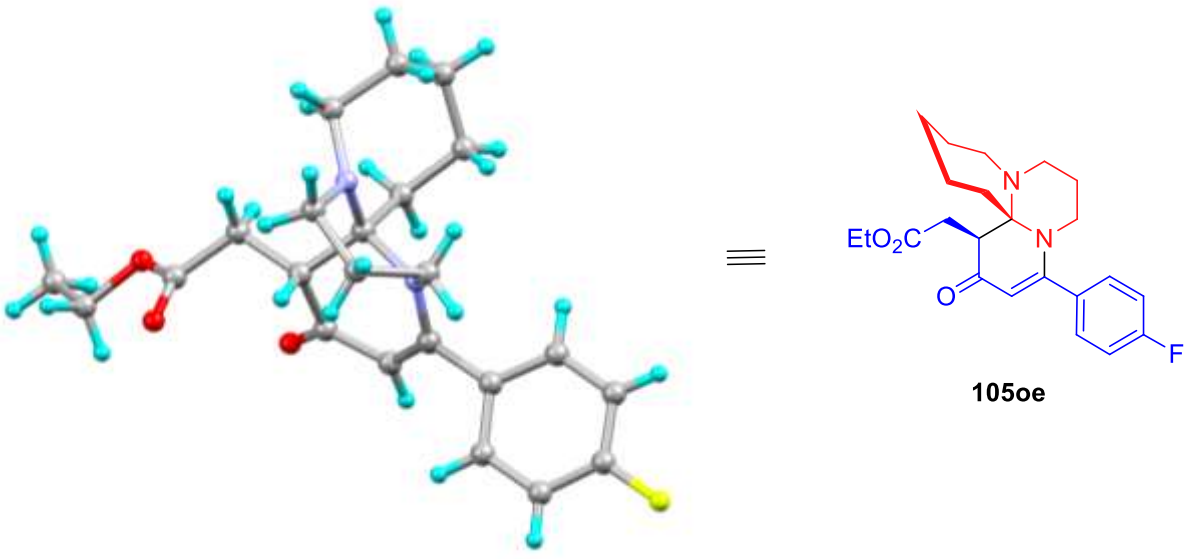
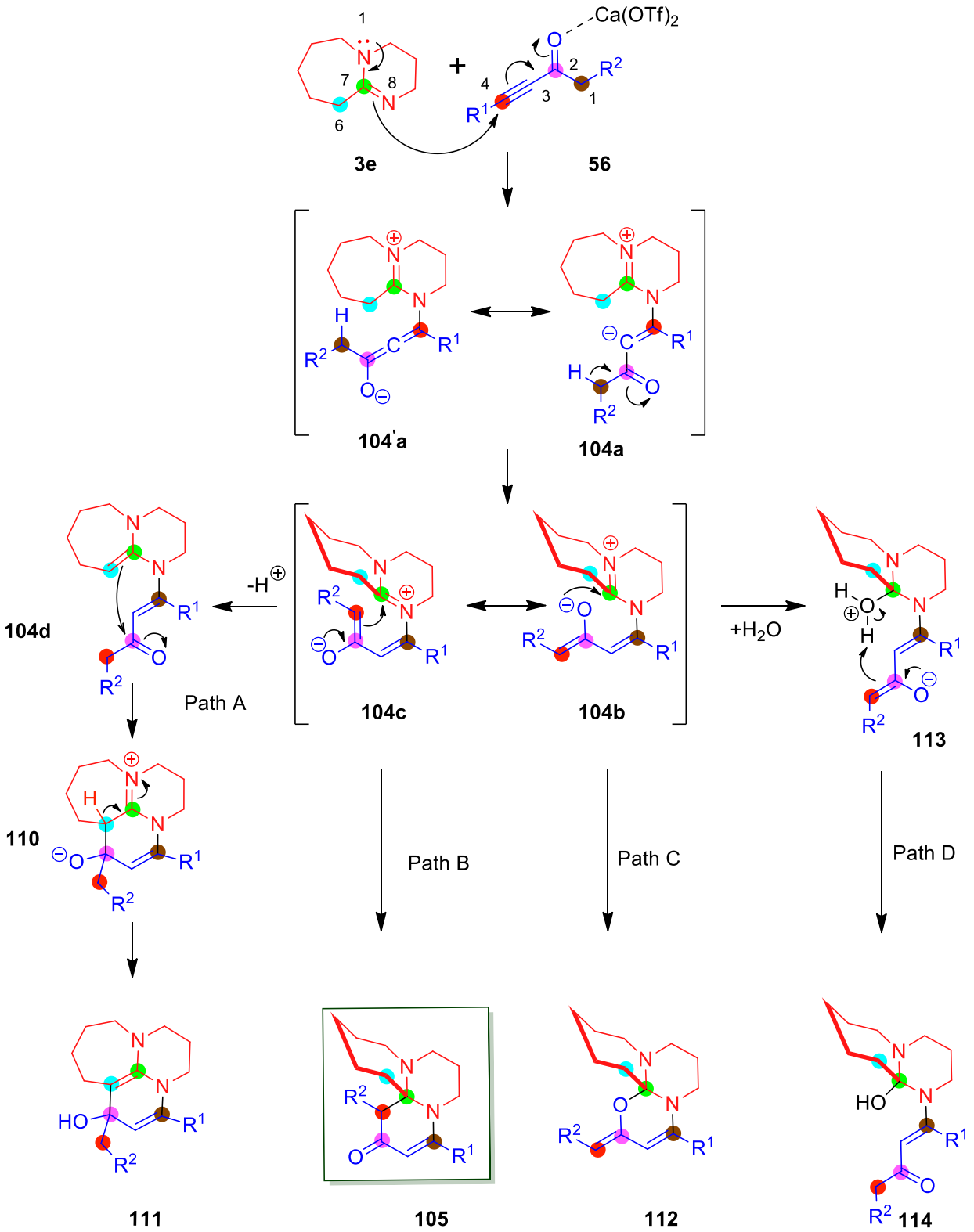


***Figure-47*:** Crystal structure of ethyl-2-(*cis*-4-(4-fluorophenyl)-2-oxo-1,2,6,7,8,10,11,12,13,14-decahydropyrido[2',1':2,3] pyrimido[1,2-*a*]azepin-1-yl)acetate (**105oe**).

5.2.3 Mechanistic rationale:

Taking cognizance of the crystal structure of **56oa** and activation of the carbonyl **56** by calcium salts,[48] a mechanism was hypothesized as elucidated in Scheme 9. In the present mechanism, oxophilicity of calcium drives the coordination of $Ca(OTf)_2$ **69n** to ynone carbonyl **56**, in turn activating the ynone towards Michael addition at C-4 by DBU's N-8. The zwitterion intermediate **104a** thus formed, undergoes a [1,3]-hydrogen shift to yield resonance hybrid intermediates **104b** and **104c**. Such, intermediates could be neutralized through a myriad of reaction pathways. Loss of an adjacent proton at DBU's C-6 followed by a nucleophilic attack on ynone C-2 could lead to addition product **111** similar to as obtained by Müller's group (Scheme 7d) via path-A. The path-B dictates a selective nucleophilic enolate attack by the carbon α to the carbonyl moiety on iminium C-7 furnishing cyclized products **105**. Same intermediate **104b** could also yield cyclized products **112** through path-C. Finally, this reaction sequence could also be truncated intermolecularly with addition of water from solvent at C-7 giving entities like **114** through path-D. Amidst such manifold reaction possibilities, present reaction design yields singularly products **105** via route-B. Reaction pathway-D even elucidates the formation of product **107cp** via **106cp**. Isolation of **107cp** additionally, is a testament to the existence of intermediates **104a**, **104b**, **104c** and **104d** along with initial regiochemistry of interaction between DBU **3e** and ynone **56**. In the zwitterionic intermediate **104c** for reaction with ester ynones, a larger 'R' group of ester functionality sterically locks the ester carbonyl in a conformation favouring stabilizing interactions between the ester carbonyl's 'O' and the positively charged iminium nitrogen. Thus, rationalizing the decrease in yield on moving from ethyl ynone ester **56a** to methyl ynone ester **56b**.

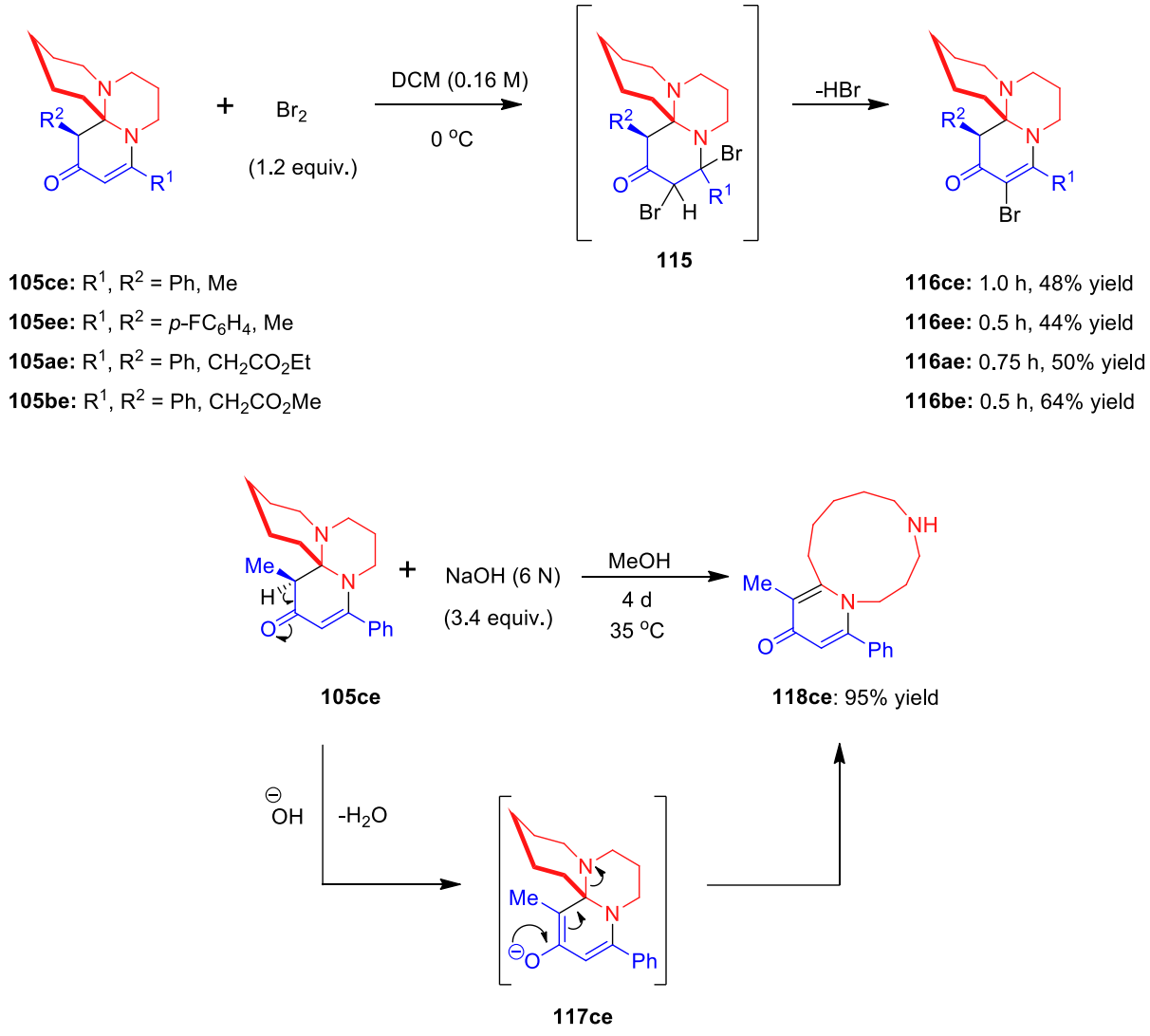
Scheme 9: Proposed reaction mechanism.



5.2.4 Synthetic applications of click products:

The final cyclized products **105** were further scrutinized for their chemical reactivity, paving way for their synthetic applications (Scheme 10). Hence, intentionally library of compounds **105** were made to undergo facile bromination succeeded by bromination addition followed by dehydrohalogenation to yield mono-brominated products **116** in good yields. In addition, compound **105ce** underwent C-N bond cleavage on treatment with aqueous NaOH (6.0 N) in methanol via formation of enolate **117ce** to generate an eleven-membered fused heterocycle **118ce** in excellent yield.

Scheme 10: Synthetic applications.



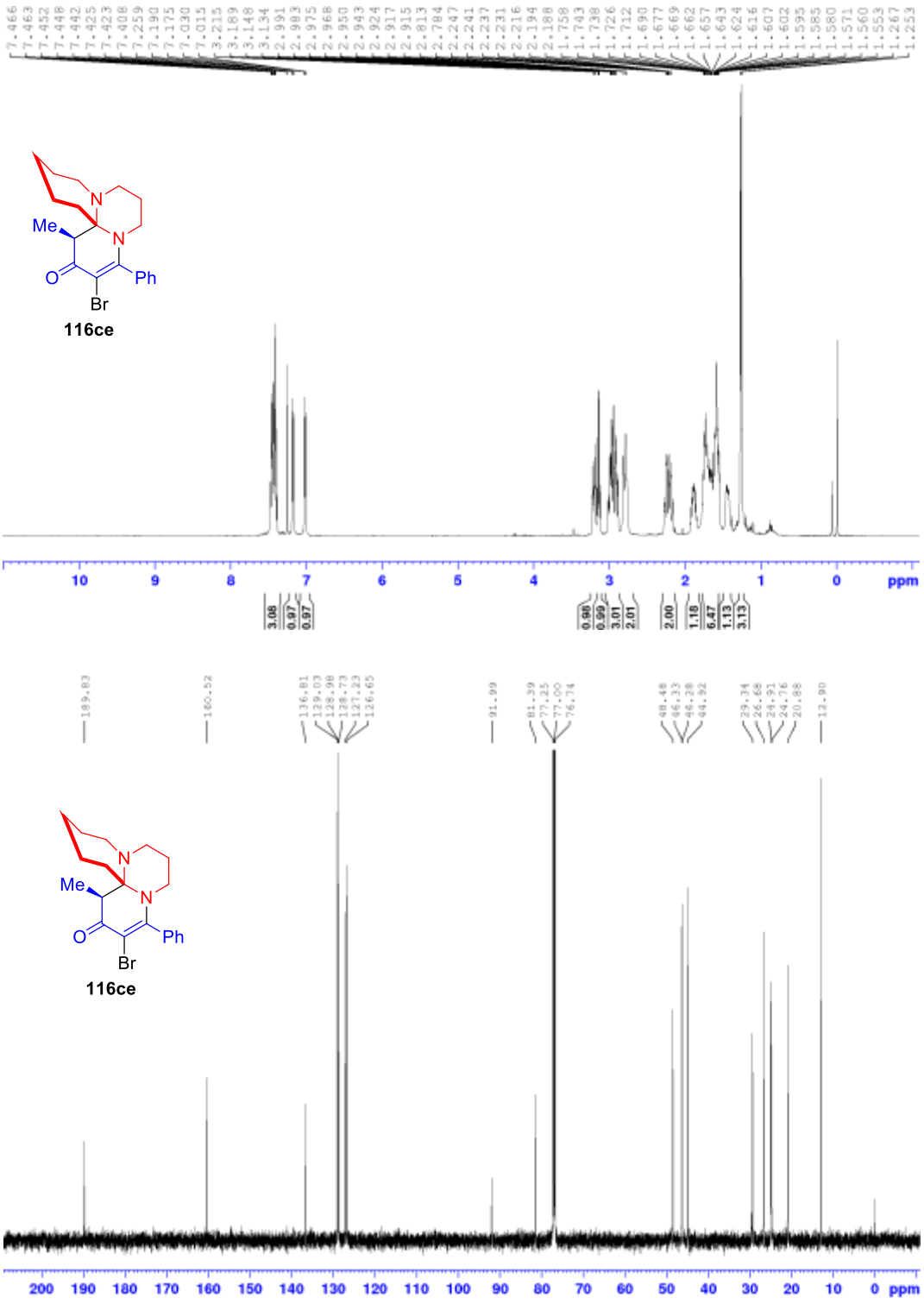


Figure-48: ^{1}H NMR and ^{13}C NMR spectrum of products **116ce.**

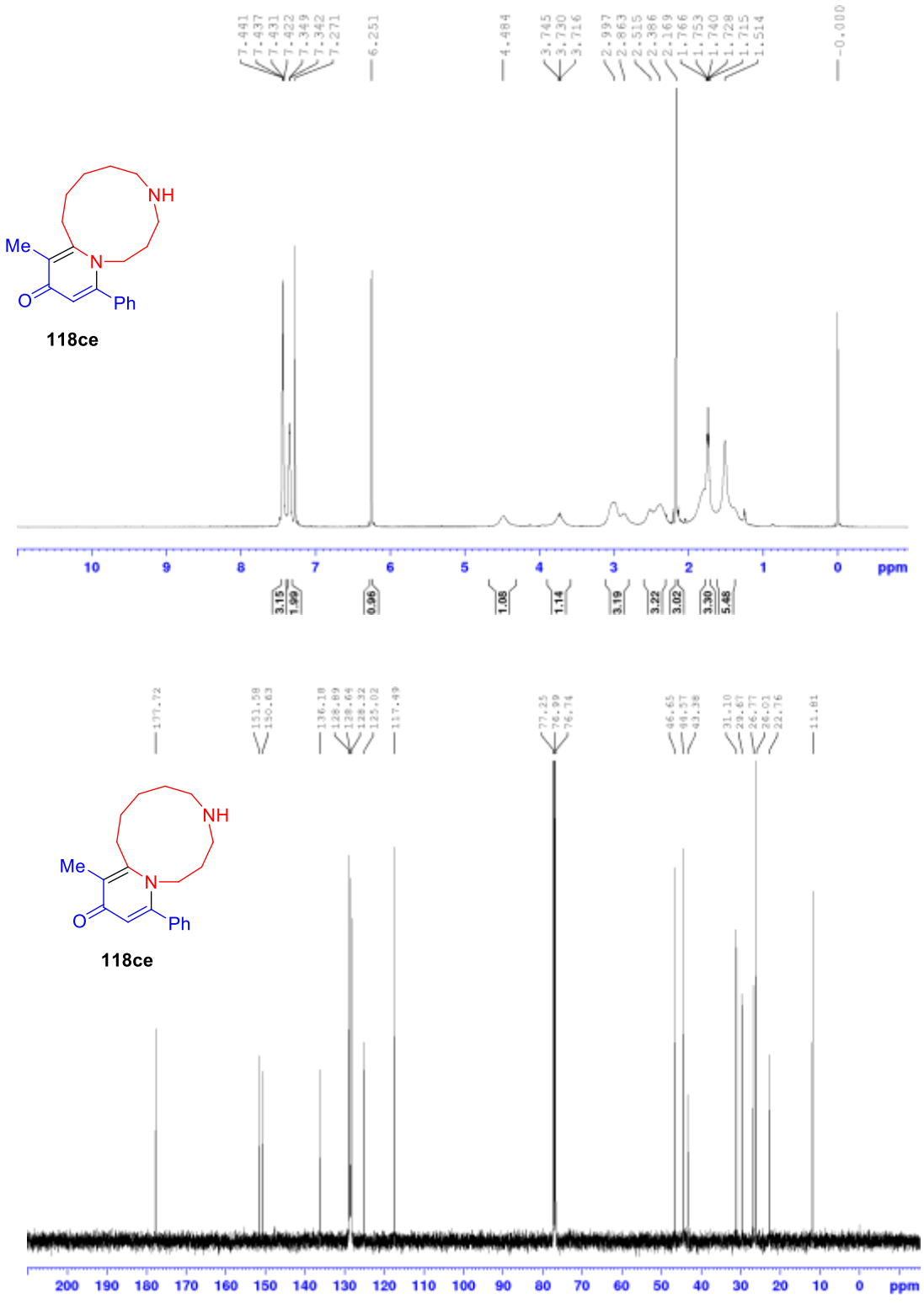


Figure-49: ^{1}H NMR and ^{13}C NMR spectrum of products **118ce.**

The structure and relative stereochemistry of the products **116** were assigned by NMR analysis and also finally confirmed by X-ray structure analysis on **116ce** as shown in Figure 50 .[47]

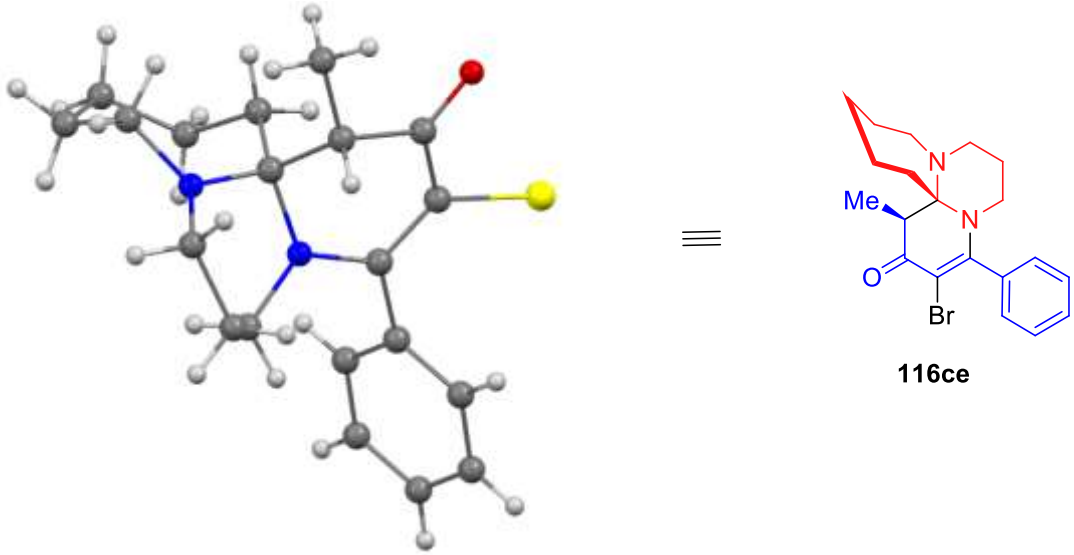


***Figure-50*:** Crystal structure of *cis*-3-bromo-1-methyl-4-phenyl-6,7,8,10,11,12,13,14-octahydropyrido[2',1':2,3]pyrimido [1,2-*a*]azepin-2(1*H*)-one (**116ce**).

5.3 Conclusions

In essence, an unprecedented ambiphilic addition of ynones across a carbon nitrogen bond of amidines has been achieved in a formal [4+2]-cycloaddition fashion under self- or calcium-catalysis. Furthermore, a single ynone-amidine adduct was obtained among many possibilities, highlighting the unique regioselectivity of the present reaction strategy. Our future efforts would be directed towards applying the profitable insights gained about reactivity of amidines and ynones from the present study to new reactions and substrate designs.

6. 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 (HRMS) were recorded on ESI-TOF maXis. IR spectra were recorded on JASCO FT/IR-5300 and Thermo Nicolet FT/IR-5700. 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 ($\lambda = 0.71073$ 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 ($\lambda = 0.71073$ 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 and/or by treatment with a solution of 1.5 g $KMnO_4$, 10 g K_2CO_3, and 1.25 mL 10% NaOH in 200 mL water.

1. General experimental procedures for Triazabicyclodecene as an Organocatalyst for Regiospecific Synthesis of 1,4,5-Trisubstituted *N*-Vinyl-1,2,3-Triazoles

Procedure A: General procedure for the TBD-catalyzed [3+2]-cycloaddition reactions in DMSO: In an ordinary glass vial equipped with a magnetic stirring bar, containing a solution of 0.75 mmol of vinyl azide **8/85** and 0.5 mmol of active methylene compound 1 in DMSO (1.0 mL), 0.05 mmol of catalyst TBD **3f** was added. The reaction mixture was stirred at 25 °C and the reaction progress was monitored by TLC. After completion of the reaction, the crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and

concentrated. Pure organo-click products **9/86** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure B: General procedure for the TBD-catalyzed [3+2]-cycloaddition reactions in solvent-free conditions: In an ordinary glass vial equipped with a magnetic stirring bar, containing a solution of 0.75 mmol of vinyl azide **8/85** and 0.5 mmol of active methylene compound **1**, 0.05 mmol of catalyst TBD **3f** was added. The reaction mixture was stirred at 25 °C in solvent-free conditions. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure organo-click products **9/86** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure C: General procedure for the DBU-catalyzed [3+2]-cycloaddition reactions: In an ordinary glass vial equipped with a magnetic stirring bar, containing a solution of 0.75 mmol of vinyl azide **8/85** and 0.5 mmol of active methylene compound **1** in DMSO (1.0 mL), 0.6 mmol of catalyst DBU **3e** was added. The reaction mixture was stirred at 25 °C and the reaction progress was monitored by TLC. After completion of the reaction, the crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. Pure click products **9/86** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

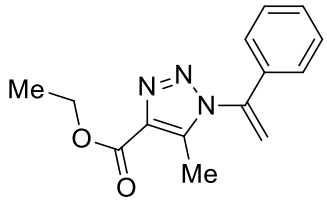
Procedure D: General procedure for the DBU-catalyzed Aldol reaction: In an ordinary glass vial equipped with a magnetic stirring bar, containing a solution of 0.57 mmol of **9la** and 0.38 mmol of *p*-nitrobenzaldehyde in DMSO (0.76 mL), 0.076 mmol of catalyst DBU **3e** was added. The reaction mixture was stirred at 80 °C for 12 h followed by work up with aqueous NH_4Cl solution and extraction of the aqueous layer with dichloromethane (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. Pure aldol product **87la** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure E: Procedure for dibromination of product 9aa: In an ordinary glass vial equipped with a magnetic stirring bar, a solution of 0.19 mmol of **9aa** in dichloromethane (0.37 mL) was taken. The stirred reaction mixture was cooled to 0 °C followed by dropwise addition of 0.011 mL of bromine. The reaction mixture was stirred at 0 °C for 1 h and at 25 °C for an additional 1 h. The reaction mixture was quenched with saturated sodium thiosulfate solution followed by extraction of the aqueous layer with dichloromethane (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. Pure product **88aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure F: Procedure for debromohydrogenation of 88aa: In an ordinary glass vial equipped with a magnetic stirring bar, a solution of 0.13 mmol of **88aa** in chloroform (1.0 mL) was taken. The stirred reaction mixture was cooled to 0 °C followed by dropwise addition of 0.018 mL (0.13 mmol) of triethylamine. The reaction mixture was allowed to warm to 25 °C and was stirred at the same temperature for 20 h. The reaction mixture was quenched with saturated ammonium chloride solution followed by extraction of the aqueous layer with dichloromethane (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. Pure product **89aa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure G: Procedure for reduction of products 9ea and 86la: In an 10 mL round bottomed flask, a solution of 0.3 mmol of **9ea** or **86la** in dry methanol (3 mL) was taken followed by addition of 30 mg Pd/C (10 mol%). The reaction mixture was purged with nitrogen gas followed by hydrogen gas. The reaction mixture was allowed to stir at 25 °C under the pressure of a hydrogen gas filled balloon for 1 h. The crude reaction mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure. The concentrate was subjected to column chromatography (silica gel, mixture of hexane/ethyl acetate) to obtain the pure compounds **90ea** and **90la**, respectively.

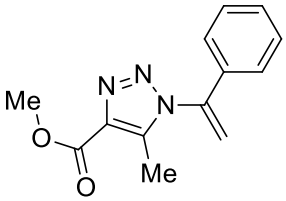
Ethyl 5-methyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazole-4-carboxylate (9aa):[49] Prepared



9aa

following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow viscous oil; IR (Neat): ν_{max} 2986, 2931, 1715, 1649, 1572, 1452, 1260, 1172, 1107, 1014, 915, 844 and 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.34 (3H, m), 7.15-7.13 (2H, m), 6.02 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.59 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 4.44 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 2.34 (3H, s), 1.43 (3H, t, *J* = 7.5 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.6 (C, O=*C*-O), 141.7 (C), 139.3 (C), 136.4 (C), 134.0 (C), 129.9 (CH), 129.0 (2 x CH), 125.5 (2 x CH), 115.2 (CH_2), 61.0 (CH_2), 14.3 (CH_3), 9.5 (CH_3); HRMS m/z 280.1060 (M + Na^+), calcd for $C_{14}H_{15}N_3O_2Na$ 280.1062.

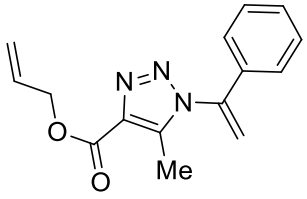
Methyl 5-methyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazole-4-carboxylate (9ba): Prepared



9ba

following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a pale yellow liquid; IR (Neat): ν_{max} 2848, 1718, 1637, 1578, 1444, 1267, 1246, 1214, 1166, 1112, 1026, 914, 828, 780 and 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.32 (3H, m), 7.13-7.11 (2H, m), 6.02 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 5.59 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 3.96 (3H, s), 2.33 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 162.0 (C, O=*C*-O), 141.7 (C), 139.4 (C), 136.2 (C), 134.0 (C), 129.9 (CH), 129.0 (2 x CH), 125.5 (2 x CH), 115.2 (CH_2), 51.9 (CH_3), 9.5 (CH_3); HRMS m/z 266.0907 (M + Na^+), calcd for $C_{13}H_{13}N_3O_2Na$ 266.0905.

Allyl 5-methyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazole-4-carboxylate (9ca): Prepared following

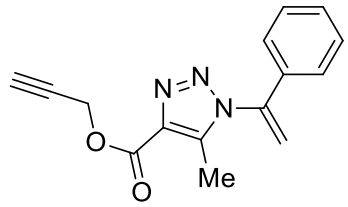


9ca

the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a pale yellow liquid; IR (Neat) ν_{max} 2931, 1720, 1644, 1567, 1496, 1441, 1425, 1260, 1238, 1205, 1167, 1101, 1057, 1025, 981, 920, 844, 778 and 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.30 (3H, m), 7.11-7.09 (2H, m), 6.10-5.99 (1H, m), 6.00 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.57 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.40 (1H, dd, *J* = 17.0, 1.5 Hz, olefinic-*H*), 5.26 (1H, dd, *J* = 10.5, 1.0 Hz, olefinic-*H*), 4.85 (2H, dd, *J* = 5.5, 1.0 Hz, olefinic-*H*), 2.31 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.2 (C, O=*C*-O), 141.5

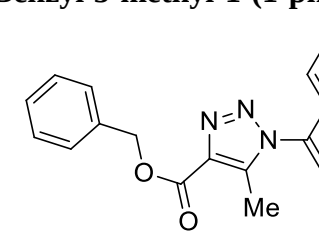
(C), 139.4 (C), 136.1 (C), 133.8 (C), 131.7 (CH), 129.8 (CH), 128.9 (2 x CH), 125.4 (2 x CH), 118.9 (CH_2), 115.2 (CH_2), 65.5 (CH_2), 9.5 (CH_3); HRMS m/z 292.1062 ($M + Na^+$), calcd for $C_{15}H_{15}N_3O_2$ Na 292.1062.

Prop-2-yn-1-yl 5-methyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazole-4-carboxylate (9da): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow liquid; IR (Neat): ν_{max} 3282, 3266, 1722, 1640, 1567, 1443, 1345, 1257, 1237, 1154, 1102, 1051, 973, 916, 834, 782 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34-7.31 (3H, m), 7.10 (2H, d, *J* = 8.0 Hz), 6.01 (1H, s, olefinic-*H*), 5.57 (1H, s, olefinic-*H*), 4.93 (2H, d, *J* = 2.0 Hz), 2.49 (1H, t, *J* = 2.5 Hz), 2.32 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 160.6 (C, O=*C*-O), 141.5 (C), 139.8 (C), 135.5 (C), 133.8 (C), 129.9 (CH), 128.9 (2 x CH), 125.4 (2 x CH), 115.3 (CH_2), 77.2 (C), 75.2 (CH), 52.2 (CH_2), 9.5 (CH_3); HRMS m/z 290.0913 ($M + Na^+$), calcd for $C_{15}H_{13}N_3O_2Na$ 290.0905.



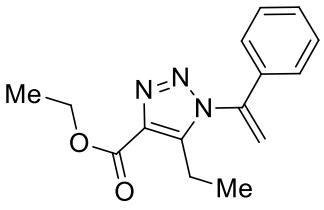
9da

Benzyl 5-methyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazole-4-carboxylate (9ea): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a pale yellow liquid; IR (Neat): ν_{max} 3034, 1727, 1660, 1593, 1459, 1314, 1262, 1232, 1175, 1118, 1035, 989, 953 and 911 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48 (2H, d, *J* = 7.0 Hz), 7.36-7.30 (6H, m), 7.12 (2H, dd, *J* = 8.0, 1.5 Hz), 6.01 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.56 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.42 (2H, s), 2.32 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.2 (C, O=*C*-O), 141.4 (C), 139.3 (C), 136.0 (C), 135.5 (C), 133.8 (C), 129.7 (CH), 128.8 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 128.1 (CH), 125.3 (2 x CH), 115.1 (CH_2), 66.3 (CH_2), 9.4 (CH_3); HRMS m/z 320.1406 ($M + H^+$), calcd for $C_{19}H_{17}N_3O_2H$ 320.1399.



9ea

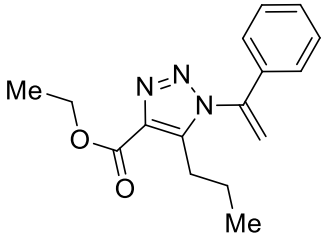
Ethyl 5-ethyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazole-4-carboxylate (9fa): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a pale yellow liquid; IR (Neat): 2981, 2915, 2844, 1715, 1644, 1556, 1446, 1381, 1293, 1244, 1167,



9fa

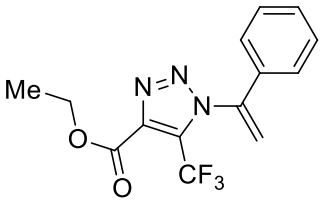
1112, 1025, 920, 773 and 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.29 (3H, m), 7.13-7.10 (2H, m), 6.02 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 5.56 (1H, d, *J* = 0.8 Hz, olefinic-*H*), 4.42 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.78 (2H, q, *J* = 7.6 Hz), 1.40 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$), 1.00 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.4 (C, O=*C*-O), 144.6 (C), 141.8 (C), 135.9 (C), 134.2 (C), 129.8 (CH), 128.9 (2 x CH), 125.5 (2 x CH), 115.3 (CH_2), 60.9 (CH_2), 16.9 (CH_2), 14.2 (CH_3), 12.7 (CH_3); HRMS m/z 272.1399 ($M + H^+$), calcd for $C_{15}H_{17}N_3O_2H$ 272.1399.

Ethyl 1-(1-phenylvinyl)-5-propyl-1*H*-1,2,3-triazole-4-carboxylate (9ga): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a pale yellow liquid; IR (Neat): ν_{max} 2964, 2926, 2871, 1715, 1644, 1562, 1446, 1381, 1271, 1238, 1222, 1173, 1123, 1019, 915, 783, 696 and 526 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.31 (3H, m), 7.12 (2H, dd, *J* = 8.2, 1.0 Hz), 6.02 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.57 (1H, d, *J* = 0.5 Hz, olefinic-*H*), 4.42 (2H, q, *J* = 7.5 Hz, OC*H*$_2$CH$_3$), 2.72 (2H, t, *J* = 8.0 Hz, ArC*H*$_2$CH$_2$CH$_3$), 1.43 (2H, sextet, *J* = 7.0 Hz, ArCH$_2$C*H*$_2$CH$_3$), 1.41 (3H, t, *J* = 7.0 Hz), 0.79 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.5 (C, O=*C*-O), 143.3 (C), 142.0 (C), 136.3 (C), 134.3 (C), 129.9 (CH), 128.9 (2 x CH), 125.5 (2 x CH), 115.3 (CH_2), 60.9 (CH_2), 25.2 (CH_2), 21.8 (CH_2), 14.2 (CH_3), 13.7 (CH_3); HRMS m/z 286.1555 ($M + H^+$), calcd for $C_{16}H_{19}N_3O_2H$ 286.1556.



9ga

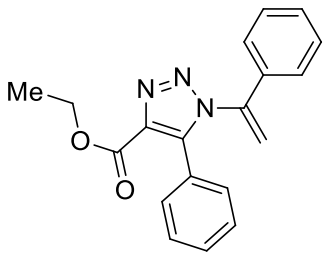
Ethyl 1-(1-phenylvinyl)-5-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (9ha): Prepared following the procedure **C** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow viscous oil; IR (Neat): ν_{max} 3720, 3671, 1742, 1556, 1441, 1293, 1260, 1216, 1156, 1129, 1046 and 767 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39-7.34 (3H, m), 7.12-7.10 (2H, m), 6.10 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 5.65 (1H, d, *J* = 2.0 Hz, olefinic-*H*), 4.48 (2H, q, *J* = 7.5 Hz, OC*H*$_2$CH$_3$), 1.42 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 158.8 (C, O=*C*-O), 142.3 (C), 139.2 (C), 133.7 (C), 130.1 (CH), 129.8 (C, q, *J* = 42.5 Hz), 129.0 (2 x CH), 125.2 (2 x CH), 118.6 (C, q, *J* = 270.0



9ha

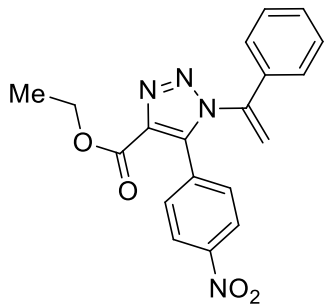
Hz, *C*F_3), 116.0 (CH_2), 62.3 (CH_2), 14.0 (CH_3); HRMS m/z 334.0781 (M + Na^+), calcd for $C_{14}H_{12}F_3N_3O_2Na$ 334.0779.

Ethyl 5-phenyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazole-4-carboxylate (9ia):[49] Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp: 124-126 °C; IR (Neat): ν_{max} 1709, 1633, 1562, 1485, 1452, 1419, 1381, 1315, 1288, 1255, 1183, 1112, 1052, 920, 849, 762 and 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.20 (8H, m), 7.05-7.02 (2H, m), 5.85 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 5.54 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 4.36 (2H, q, *J* = 7.2 Hz, OC$H_2$$CH_3$), 1.31 (3H, t, *J* = 6.8 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 160.9 (C, O=*C*-O), 142.2 (C), 141.6 (C), 136.5 (C), 134.5 (C), 129.7 (CH), 129.6 (2 x CH), 129.5 (CH), 128.5 (2 x CH), 127.9 (2 x CH), 125.7 (2 x CH), 125.5 (C), 115.5 (CH_2), 61.1 (CH_2), 14.1 (CH_3); HRMS m/z 320.1396 (M + H^+), calcd for $C_{19}H_{17}N_3O_2H$ 320.1399.



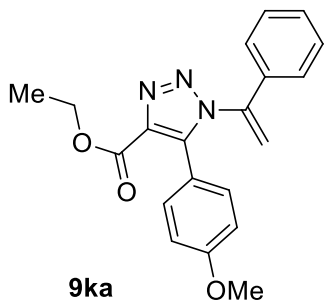
9ia

Ethyl 5-(4-nitrophenyl)-1-(1-phenylvinyl)-1*H*-1,2,3-triazole-4-carboxylate (9ja): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp: 148-150 °C; IR (Neat): ν_{max} 2919, 2849, 1730, 1601, 1525, 1433, 1347, 1260, 1190, 1098, 1044, 915, 861 and 736 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (2H, d, *J* = 8.5 Hz), 7.47 (2H, d, *J* = 9.0 Hz), 7.30-7.22 (3H, m), 7.02-7.00 (2H, m), 5.92 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 5.67 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 4.38 (2H, q, *J* = 7.0 Hz, OC$H_2$$CH_3$), 1.34 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 160.5 (C, O=*C*-O), 148.2 (C), 141.9 (C), 139.2 (C), 137.1 (C), 134.0 (C), 132.1 (C), 130.9 (2 x CH), 130.0 (CH), 128.8 (2 x CH), 125.7 (2 x CH), 123.0 (2 x CH), 116.0 (CH_2), 61.6 (CH_2), 14.1 (CH_3); HRMS m/z 387.1062 (M + Na^+), calcd for $C_{19}H_{16}N_4O_4Na$ 387.1069.



9ja

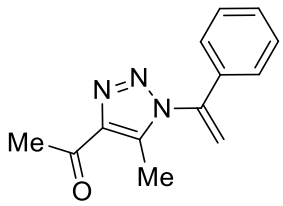
Ethyl 5-(4-methoxyphenyl)-1-(1-phenylvinyl)-1*H*-1,2,3-triazole-4-carboxylate (9ka): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. Mp: 82-84 °C; IR (Neat): ν_{max} 2959, 2931, 2833, 1726, 1611,



9ka

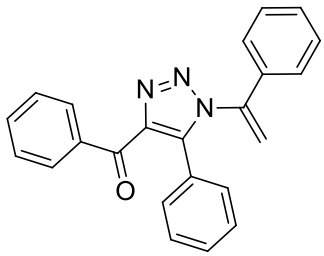
1578, 1501, 1430, 1386, 1304, 1255, 1173, 1096, 1046, 855, 800 and 696 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.21 (5H, m), 7.07-7.04 (2H, m), 6.79 (2H, d, *J* = 7.2 Hz), 5.88 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 5.53 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 4.38 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.76 (3H, s), 1.35 (3H, t, *J* = 6.8 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.1 (C, O=*C*-O), 160.6 (C), 142.3 (C), 141.6 (C), 136.1 (C), 134.5 (C), 131.1 (2 x CH), 129.5 (CH), 128.6 (2 x CH), 125.7 (2 x CH), 117.3 (C), 115.5 (CH_2), 113.5 (2 x CH), 61.1 (CH_2), 55.2 (CH_3), 14.2 (CH_3); HRMS m/z 372.1325 ($M + Na^+$), calcd for $C_{20}H_{19}N_3O_3Na$ 372.1324.

1-(5-Methyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazol-4-yl)ethanone (9la):[49] Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a pale yellow liquid. IR (Neat): 2931, 1682, 1644, 1551, 1496, 1425, 1364, 1255, 1227, 1145, 1074, 1030, 948, 915, 778 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.31 (3H, m), 7.13-7.10 (2H, m), 6.02 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 5.56 (1H, d, *J* = 0.8 Hz, olefinic-*H*), 2.72 (3H, s), 2.33 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.2 (C, *C*=O), 143.3 (C), 141.5 (C), 137.9 (C), 133.9 (C), 129.9 (CH), 129.0 (2 x CH), 125.4 (2 x CH), 115.1 (CH_2), 27.7 (CH_3), 9.6 (CH_3); HRMS m/z 250.0957 ($M + Na^+$), calcd for $C_{13}H_{13}N_3ONa$ 250.0956.



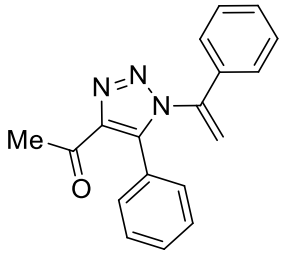
9la

Phenyl (5-phenyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazol-4-yl)methanone (9ma):[49] Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow solid. Mp: 90-92 °C; IR (Neat): 3052, 3030, 1655, 1605, 1540, 1485, 1452, 1419, 1282, 1260, 1173, 1008, 909, 773 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.30 (2H, d, *J* = 7.2 Hz), 7.59 (1H, t, *J* = 7.2 Hz), 7.49 (2H, t, *J* = 7.6 Hz), 7.33-7.24 (8H, m), 7.10-7.08 (2H, m), 5.89 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 5.58 (1H, d, *J* = 1.2 Hz olefinic-*H*); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 186.5 (C, *C*=O), 143.1 (C), 142.2 (C), 142.0 (C), 137.1 (C), 134.5 (C), 133.1 (CH), 130.7 (2 x CH), 129.7 (CH), 129.6 (2 x CH), 129.5 (CH), 128.6 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 125.9 (C), 125.8 (2 x CH), 115.5 (CH_2); HRMS m/z 374.1265 ($M + Na^+$), calcd for $C_{23}H_{17}N_3ONa$ 374.1269.



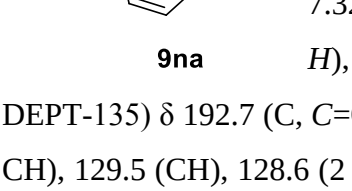
9ma

1-(5-Phenyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazol-4-yl)ethanone (9na): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow solid. Mp: 96-98 °C; IR (Neat): ν_{max} 3057, 3003, 2920, 1688, 1638, 1551, 1490, 1419, 1342, 1244, 1151, 1025, 953, 767 and 685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.20 (8H, m), 7.06-7.03 (2H, m), 5.85 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 5.51 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 2.76 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 192.7 (C, *C*=O), 143.0 (C), 142.2 (C), 139.8 (C), 134.5 (C), 129.8 (CH), 129.6 (2 x CH), 129.5 (CH), 128.6 (2 x CH), 128.0 (2 x CH), 125.7 (2 x CH), 125.5 (C), 115.5 (CH_2), 28.3 (CH_3); HRMS m/z 290.1294 ($M + H^+$), calcd for $C_{18}H_{15}N_3OH$ 290.1293.



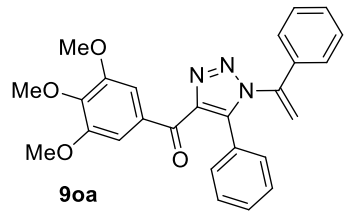
9na

(5-Methyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone (9′na): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a colourless liquid. IR (Neat): 3063, 2992, 2926, 1737, 1644, 1605, 1540, 1452, 1425, 1266, 1178, 1030, 915, 783 and 685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.41 (2H, br d, *J* = 8.0 Hz), 7.61 (1H, br t, *J* = 8.0 Hz), 7.52 (2H, br t, *J* = 8.0 Hz), 7.40-7.36 (3H, m), 7.20-7.17 (2H, m), 6.06 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 5.63 (1H, d, *J* = 0.8 Hz, olefinic-*H*), 2.44 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 187.3 (C, *C*=O), 143.2 (C), 141.7 (C), 140.4 (C), 137.3 (C), 134.0 (C), 132.8 (CH), 130.5 (2 x CH), 129.9 (CH), 129.0 (2 x CH), 128.2 (2 x CH), 125.5 (2 x CH), 115.2 (CH_2), 10.1 (CH_3); HRMS m/z 312.1113 ($M + Na^+$), calcd for $C_{18}H_{15}N_3ONa$ 312.1113.



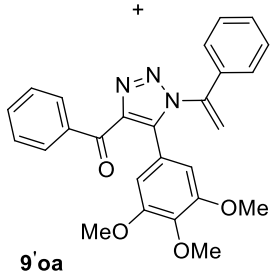
9′na

(5-Phenyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazol-4-yl)(3,4,5-trimethoxyphenyl)methanone (9oa) and phenyl(1-(1-phenylvinyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methanone (9′oa): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow viscous oil; IR (Neat): ν_{max} 3003, 2937, 2827, 1666, 1583, 1507, 1452, 1425, 1326, 1244, 1123, 1008, 937, 844, 773 and 696 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, 1:1 mixture) δ 8.28-



9oa

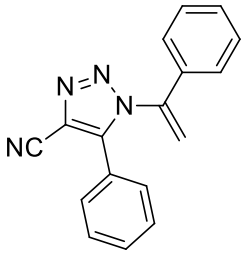
+



9′oa

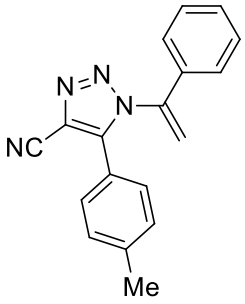
8.27 (2H, br d, *J* = 8.0 Hz), 7.76 (2H, s), 7.61 (1H, br t, *J* = 8.0 Hz), 7.51 (2H, br t, *J* = 8.0 Hz), 7.33-7.23 (11H, m), 7.14-7.09 (4H, m), 6.52 (2H, s), 5.93 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.88 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.64 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 5.58 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 3.95 (3H, s), 3.93 (6H, s), 3.79 (3H, s), 3.65 (6H, s); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture) δ 186.7 (C, O=*C*), 184.6 (C, O=*C*), 152.73 (2 x C), 152.70 (2 x C), 143.2 (C), 142.8 (C), 142.7 (C), 142.5 (C), 142.3 (C), 142.2 (C), 141.7 (C), 139.1 (C), 137.1 (C), 134.7 (C), 134.5 (C), 133.1 (CH), 131.9 (C), 130.6 (CH), 129.6 (CH), 129.55 (2 x CH), 129.54 (CH), 129.51 (2 x CH), 128.6 (2 x CH), 128.56 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 126.1 (C), 125.8 (2 x CH), 125.7 (2 x CH), 120.8 (C), 115.5 (CH_2), 115.4 (CH_2), 108.4 (2 x CH), 107.4 (2 x CH), 60.9 (CH_3), 60.7 (CH_3), 56.2 (2 x CH_3), 56.0 (2 x CH_3); HRMS m/z 464.1585 (M + Na^+), calcd for $C_{26}H_{23}N_3O_4Na$ 464.1586.

5-Phenyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazole-4-carbonitrile (9pa): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow crystalline solid. Mp: 127-128 °C; IR (KBr): ν_{max} 2236 (C, *C*N), 1627, 1573, 1496, 1452, 1348, 1288, 1238, 1101, 1052, 1025, 915, 822, 767, 696, 636, 564 and 477 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46-7.44 (2H, m), 7.41-7.34 (3H, m), 7.30-7.25 (3H, m), 7.11-7.09 (2H, m), 5.99 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 5.63 (1H, d, *J* = 1.5 Hz, olefinic-*H*); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 143.7 (C), 141.9 (C), 133.6 (C), 130.9 (CH), 129.9 (CH), 129.0 (2 x CH), 128.8 (2 x CH), 128.3 (2 x CH), 125.6 (2 x CH), 123.1 (C), 119.8 (C), 116.0 (CH_2), 112.0 (C, *C*N); HRMS m/z 295.0960 (M + Na^+), calcd for $C_{17}H_{12}N_4Na$ 295.0960.



9pa

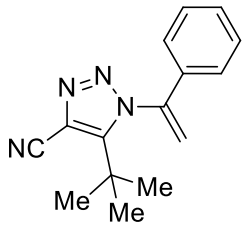
1-(1-Phenylvinyl)-5-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carbonitrile (9qa): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as yellow oil. IR (Neat): 3063, 3025, 2236 (CN), 1622, 1507, 1446, 1353, 1288, 1238, 1183, 1041, 909, 833, 773 and 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (2H, br t, *J* = 8.0 Hz), 7.31-7.26 (3H, m), 7.17 (2H, d, *J* = 8.0 Hz), 7.12-7.10 (2H, m), 5.99 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 5.60 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 2.32 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 143.9 (C), 142.0 (C), 141.5 (C), 133.7 (C), 129.9 (CH), 129.8 (2 x CH), 128.8 (2 x CH), 128.2 (2 x CH), 125.6 (2 x CH), 120.2 (C), 119.6 (C),



9qa

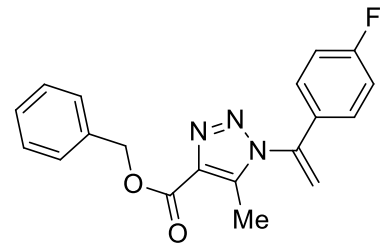
116.0 (CH_2), 112.2 (C, *C*N), 21.3 (CH_3); HRMS m/z 309.1111 ($M + Na^+$), calcd for $C_{18}H_{14}N_4Na$ 309.1116.

5-(*tert*-Butyl)-1-phenyl-1*H*-1,2,3-triazole-4-carbonitrile (9ra): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a white crystalline solid. Mp: 130-132 °C; IR (Neat): ν_{max} 3123, 2981, 2926, 2871, 2241, 1961, 1868, 1726, 1622, 1567, 1529, 1490, 1441, 1419, 1342, 1298, 1244, 1194, 1134, 1019, 948, 772 and 679 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.36 (3H, m), 7.08-7.07 (2H, m), 6.20 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 5.64 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 1.37 (9H, s, 3 x C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 151.8 (C), 143.8 (C), 134.9 (C), 130.1 (CH), 129.2 (2 x CH), 125.1 (2 x CH), 119.2 (C), 117.1 (CH_2), 113.2 (C, *C*N), 32.4 (C), 29.9 (3 x CH_3); HRMS m/z 275.1274 ($M + Na^+$), calcd for $C_{15}H_{16}N_4Na$ 275.1273.



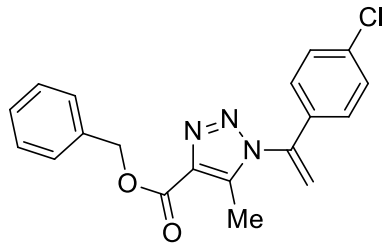
9ra

Benzyl 1-(1-(4-fluorophenyl)vinyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (9eb): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow liquid; IR (Neat): ν_{max} 3063, 3036, 2953, 1715, 1638, 1600, 1501, 1425, 1255, 1156, 1096, 1052, 909, 849, 745 and 701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.49-7.47 (2H, m), 7.38-7.30 (3H, m), 7.13-7.11 (2H, m), 7.06-7.02 (2H, m), 5.96 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 5.55 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.42 (2H, s), 2.34 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 163.4 (C, d, *J* = 248.7 Hz, *C*F), 161.2 (C, O=*C*-O), 140.5 (C), 139.3 (C), 136.1 (C), 135.5 (C), 130.1 (C, d, *J* = 2.5 Hz), 128.4 (2 x CH), 128.3 (2 x CH), 128.2 (CH), 127.5 (2 x CH, d, *J* = 7.5 Hz), 116.0 (2 x CH, d, *J* = 21.2 Hz), 115.0 (CH_2), 66.5 (CH_2), 9.5 (CH_3); HRMS m/z 360.1128 ($M + Na^+$), calcd for $C_{19}H_{16}FN_3O_2Na$ 360.1124.



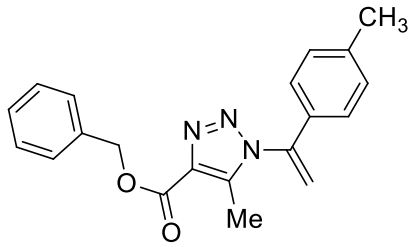
9eb

Benzyl 1-(1-(4-chlorophenyl)vinyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (9ec): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a yellow viscous liquid. IR (Neat): ν_{max} 3057, 3025, 2953, 1715, 1633, 1567, 1496, 1425, 1266, 1156, 1096, 981, 915, 838 and 701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.47 (2H, br d, *J* = 8.0 Hz), 7.38-7.30 (5H, m), 7.07 (2H, br td, *J* = 8.0, 2.0 Hz), 6.03 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 5.59 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 5.42 (2H, s), 2.34 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.0 (C, O=*C*-O), 140.3 (C), 139.3 (C), 136.1 (C), 135.7 (C), 135.4 (C), 132.3 (C), 129.0 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 128.1 (CH), 126.7 (2 x CH), 115.7 (CH_2), 66.4 (CH_2), 9.4 (CH_3); HRMS m/z 376.0831 (M + Na^+), calcd for $C_{19}H_{16}ClN_3O_2Na$ 376.0829.



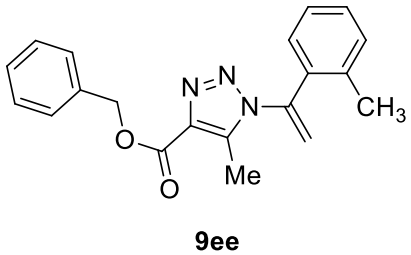
9ec

Benzyl 5-methyl-1-(1-(*p*-tolyl)vinyl)-1*H*-1,2,3-triazole-4-carboxylate (9ed): Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow semi-solid. IR (Neat): ν_{max} 3030, 2909, 1715, 1633, 1567, 1425, 1353, 1255, 1167, 1107, 1046, 986, 904, 827 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.49 (2H, br d, *J* = 8.0 Hz), 7.39-7.33 (3H, m), 7.16 (2H, d, *J* = 8.0 Hz), 7.02 (2H, d, *J* = 8.0 Hz), 5.97 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.52 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.43 (2H, s), 2.36 (3H, s), 2.32 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.4 (C, O=*C*-O), 141.6 (C), 140.1 (C), 139.5 (C), 136.2 (C), 135.6 (C), 131.2 (C), 129.7 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 128.3 (CH), 125.4 (2 x CH), 114.2 (CH_2), 66.6 (CH_2), 21.2 (CH_3), 9.6 (CH_3); HRMS m/z 334.1553 (M + H^+), calcd for $C_{20}H_{19}N_3O_2H$ 334.1556.



9ed

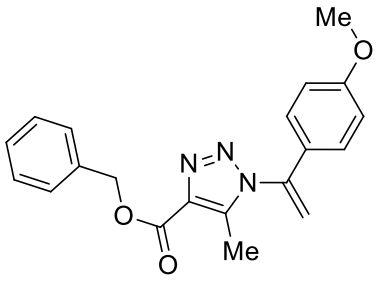
Benzyl 5-methyl-1-(1-(*o*-tolyl)vinyl)-1*H*-1,2,3-triazole-4-carboxylate (9ee): Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane and was isolated as an off white solid. Mp: 82-84 °C; IR (KBr): ν_{max} 3063, 3030, 2959, 2920, 1704, 1638, 1567, 1452, 1419, 1271, 1167, 1101, 975, 909, 833, 778 and 696 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz)



9ee

δ 7.47-7.46 (2H, m), 7.38-7.29 (4H, m), 7.24-7.22 (2H, m), 7.19-7.18 (1H, m), 5.88 (1H, d, *J* = 0.5 Hz, olefinic-*H*), 5.62 (1H, d, *J* = 0.5 Hz, olefinic-*H*), 5.40 (2H, s), 2.17 (3H, s), 2.01 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.4 (C, O=*C*-O), 141.9 (C), 138.8 (C), 136.4 (C), 135.9 (C), 135.5 (C), 133.9 (C), 131.1 (CH), 129.6 (CH), 129.3 (CH), 128.4 (2 x CH), 128.3 (2 x CH), 128.2 (CH), 126.3 (CH), 116.7 (CH_2), 66.4 (CH_2), 19.4 (CH_3), 9.7 (CH_3); HRMS m/z 334.1552 ($M + H^+$), calcd for $C_{20}H_{19}N_3O_2H$ 334.1556.

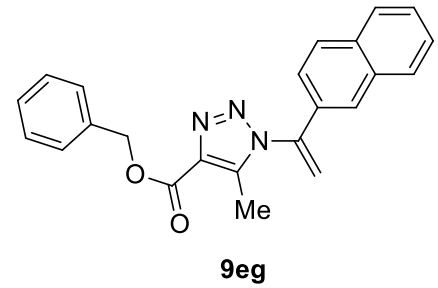
Benzyl 1-(1-(4-methoxyphenyl)vinyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (9ef):



9ef

Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow viscous liquid. IR (Neat): ν_{max} 2926, 2844, 1720, 1600, 1512, 1414, 1255, 1162, 1101, 1036, 838, 734 and 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (2H, br d, *J* = 8.0 Hz), 7.40-7.33 (3H, m), 7.05 (2H, br td, *J* = 8.0, 2.0 Hz), 6.86 (2H, br td, *J* = 8.0, 2.0 Hz), 5.89 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 5.45 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 5.42 (2H, s), 3.81 (3H, s), 2.33 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.5 (C, O=*C*-O), 160.9 (C), 141.4 (C), 139.5 (C), 136.2 (C), 135.7 (C), 128.6 (2 x CH), 128.5 (2 x CH), 128.3 (CH), 127.0 (2 x CH), 126.6 (C), 114.4 (2 x CH), 113.1 (CH_2), 66.7 (CH_2), 55.4 (CH_3), 9.7 (CH_3); HRMS m/z 372.1326 ($M + Na^+$), calcd for $C_{20}H_{19}N_3O_3Na$ 372.1324.

Benzyl 5-methyl-1-(1-(naphthalen-2-yl)vinyl)-1*H*-1,2,3-triazole-4-carboxylate (9eg):

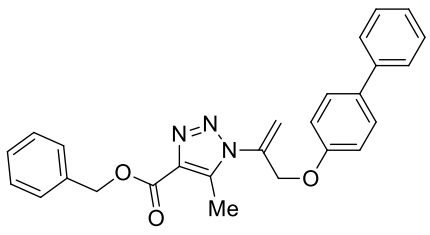


9eg

Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as viscous yellow oil. IR (Neat): ν_{max} 3063, 3046, 1709, 1633, 1567, 1425, 1353, 1277, 1238, 1162, 1101, 981, 904, 816 and 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84 (2H, br t, *J* = 8.0 Hz), 7.74 (1H, br d, *J* = 8.0 Hz), 7.53-7.47 (4H, m), 7.40-7.32 (5H, m), 6.16 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 5.67 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 5.45 (2H, s), 2.35 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.3 (C, O=*C*-O), 141.5 (C), 139.5 (C), 136.1 (C), 135.5 (C), 133.5 (C), 132.7 (C), 131.1 (C), 128.9 (CH), 128.4 (2 x CH), 128.33 (2 x CH), 128.3 (CH), 128.2 (CH), 127.5 (CH), 127.1 (CH) 126.8 (CH), 125.1 (CH), 122.3 (CH),

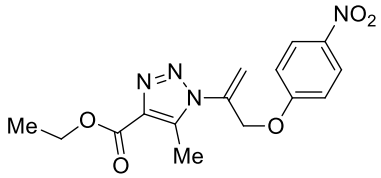
115.6 (CH_2), 66.5 (CH_2), 9.5 (CH_3); HRMS m/z 392.1376 ($M + Na^+$), calcd for $C_{23}H_{19}N_3O_2Na$ 392.1375.

Benzyl 1-(3-([1,1'-biphenyl]-4-yloxy)prop-1-en-2-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (9eh): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid. Mp: 104-106 °C; IR (Neat): ν_{max} 3029, 1712, 1665, 1614, 1578, 1526, 1490, 1423, 1355, 1237, 1144, 1045, 834, 756 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.53-7.47 (6H, m), 7.42-7.28 (6H, m), 6.96 (2H, br td, *J* = 8.0, 2.0 Hz), 5.87 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.45 (1H, s, olefinic-*H*), 5.42 (2H, s), 4.99 (2H, s), 2.59 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.3 (C, O=*C*-O), 157.0 (C), 140.4 (C), 139.4 (C), 138.4 (C), 136.2 (C), 135.6 (C), 134.9 (C), 128.7 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 128.3 (CH), 128.2 (2 x CH), 126.8 (CH), 126.7 (2 x CH), 115.6 (CH_2), 115.1 (2 x CH), 67.9 (CH_2), 66.6 (CH_2), 9.9 (CH_3); HRMS m/z 426.1817 ($M + H^+$), calcd for $C_{26}H_{23}N_3O_3H$ 426.1818.



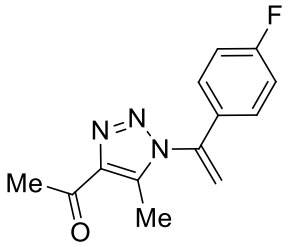
9eh

Ethyl 5-methyl-1-(3-(4-nitrophenoxy)prop-1-en-2-yl)-1*H*-1,2,3-triazole-4-carboxylate (9ai): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a yellow solid. Mp: 68-70 °C; IR (Neat): ν_{max} 2982, 1722, 1665, 1598, 1510, 1423, 1345, 1299, 1252, 1175, 1149, 1118, 1071, 1046, 844, 777 and 746 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.21 (2H, d, *J* = 9.0 Hz), 7.01 (2H, d, *J* = 9.0 Hz), 5.89 (1H, s, olefinic-*H*), 5.54 (1H, s, olefinic-*H*), 5.11 (2H, s), 4.45 (2H, q, *J* = 7.0 Hz, O*CH*$_2$CH$_3$), 2.65 (3H, s), 1.44 (3H, t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 162.2 (C, O=*C*-O), 161.2 (C), 142.0 (C), 139.1 (C), 137.1 (C), 136.5 (C), 125.8 (2 x CH), 116.0 (CH_2), 114.7 (2 x CH), 68.1 (CH_2), 61.0 (CH_2), 14.1 (CH_3), 9.8 (CH_3); HRMS m/z 333.1199 ($M + H^+$), calcd for $C_{15}H_{16}N_4O_5H$ 333.1199.



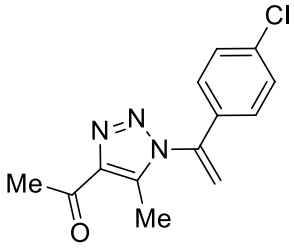
9ai

1-(1-(1-(4-Fluorophenyl)vinyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone (9lb): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp: 42-44 °C; IR (Neat): ν_{max} 3123, 3068, 3003, 1682, 1644, 1594, 1545, 1507, 1408, 1227, 1156, 1008, 953, 838 and 778 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.13-7.08 (2H, m), 7.05-6.99 (2H, m), 5.96 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 5.52 (1H, d, *J* = 0.8 Hz, olefinic-*H*), 2.69 (3H, s), 2.33 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.1 (C, *C*=O), 163.5 (C, d, *J* = 250.0 Hz, *C*F), 143.3 (C), 140.5 (C), 137.8 (C), 130.2 (C, d, *J* = 3.0 Hz), 127.5 (2 x CH, d, *J* = 9.0 Hz), 116.2 (2 x CH, d, *J* = 22.0 Hz), 114.9 (CH_2, d, *J* = 1.0 Hz), 27.7 (CH_3), 9.6 (CH_3); HRMS m/z 268.0862 ($M + Na^+$), calcd for $C_{13}H_{12}FN_3ONa$ 268.0862.



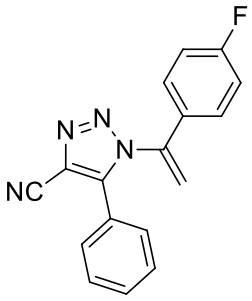
9lb

1-(1-(1-(4-Chlorophenyl)vinyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone (9lc): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as an off white solid. Mp: 58-60 °C; IR (Neat): ν_{max} 1688, 1627, 1589, 1562, 1496, 1425, 1277, 1238, 1145, 1096, 1014, 959, 844 and 723 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32 (2H, br td, *J* = 8.0, 2.0 Hz), 7.06 (2H, br td, *J* = 8.0, 2.0 Hz), 6.02 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 5.58 (1H, d, *J* = 1.2 Hz, olefinic-*H*), 2.71 (3H, s), 2.34 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.2 (C, *C*=O), 143.3 (C), 140.5 (C), 137.8 (C), 136.0 (C), 132.5 (C), 129.3 (2 x CH), 126.8 (2 x CH), 115.6 (CH_2), 27.8 (CH_3), 9.7 (CH_3); HRMS m/z 284.0567 ($M + Na^+$), calcd for $C_{13}H_{12}ClN_3ONa$ 284.0567.



9lc

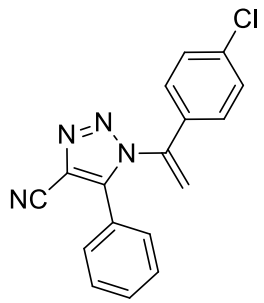
1-(1-(1-(4-Fluorophenyl)vinyl)-5-phenyl-1*H*-1,2,3-triazole-4-carbonitrile (9pb): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a light red solid. Mp: 98-100 °C; IR (Neat): ν_{max} 3068, 2246 (CN), 1638, 1600, 1512, 1452, 1419, 1348, 1288, 1238, 1167, 1107, 1041, 931, 833, 773 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.37 (5H, m), 7.10-7.07 (2H, m), 6.97-6.93 (2H, m), 5.92 (1H, d, *J* = 1.6 Hz, olefinic-*H*), 5.63 (1H, d, *J* = 1.6 Hz, olefinic-*H*); ^{13}C



9pb

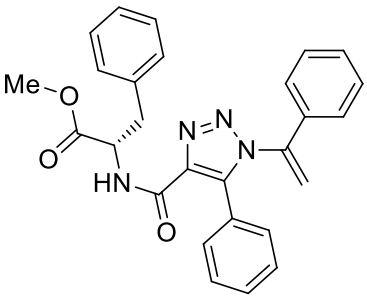
NMR ($CDCl_3$, DEPT-135) δ 163.4 (C, d, *J* = 250.0 Hz, *C*F), 143.6 (C), 141.0 (C), 131.1 (CH), 129.9 (C, d, *J* = 3.0 Hz), 129.2 (2 x CH), 128.3 (2 x CH), 127.8 (2 x CH, d, *J* = 8.0 Hz), 123.0 (C), 120.0 (C), 116.0 (2 x CH, d, *J* = 22.0 Hz), 115.9 (CH_2), 111.9 (C, *C*N); HRMS m/z 291.1046 ($M + H^+$), calcd for $C_{17}H_{11}FN_4H$ 291.1046.

1-(1-(4-Chlorophenyl)vinyl)-5-phenyl-1*H*-1,2,3-triazole-4-carbonitrile (9pc): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp: 114-116 °C; IR (Neat): ν_{max} 2362, 2323, 2241, 1627, 1589, 1539, 1496, 1457, 1425, 1392, 1353, 1277, 1101, 1008, 915, 833 and 767 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.46-7.36 (5H, m), 7.25 (2H, br td, *J* = 8.0, 2.0 Hz), 7.05 (2H, br td, *J* = 8.0, 2.0 Hz), 5.99 (1H, d, *J* = 1.6 Hz, olefinic-*H*), 5.66 (1H, d, *J* = 1.6 Hz, olefinic-*H*); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 143.7 (C), 141.0 (C), 136.1 (C), 132.1 (C), 131.2 (CH), 129.2 (2 x CH), 129.1 (2 x CH), 128.2 (2 x CH), 127.0 (2 x CH), 122.9 (C), 120.0 (C), 116.6 (CH_2), 111.9 (C, *C*N); HRMS m/z 329.0570 ($M + Na^+$), calcd for $C_{17}H_{11}ClN_4Na$ 329.0570.



9pc

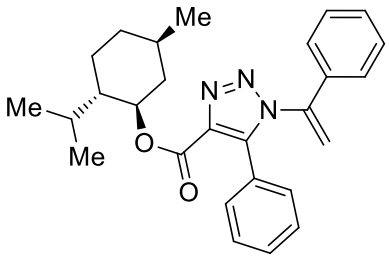
(*S*)-Methyl 3-phenyl-2-(5-phenyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazole-4-carboxamido)propanoate (9sa): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow flaky semi-solid. **$[\alpha]_D^{25}$ = +35.1° (*c* = 0.32 g/100 mL, $CHCl_3$);** IR (Neat): 3403, 3063, 3030, 2953, 2855, 1742, 1677, 1567, 1507, 1452, 1337, 1293, 1205, 1118, 1025, 915, 783 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.76 (1H, d, *J* = 8.0 Hz, N*H*), 7.31-7.19 (13H, m), 7.04-7.02 (2H, m), 5.82 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.48 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.06-5.02 (1H, m), 3.68 (3H, s), 3.25-3.17 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.5 (C, O=*C*-O), 159.6 (C, O=*C*-NH), 142.1 (C), 139.7 (C), 137.6 (C), 135.8 (C), 134.4 (C), 129.7 (2 x CH), 129.5 (CH), 129.3 (CH), 129.1 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.8 (2 x CH), 126.9 (CH), 125.6 (2 x CH),



9sa

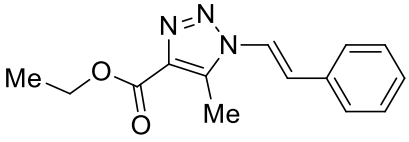
125.2 (C), 115.3 (CH_2), 52.9 (CH_3, OCH_3), 52.1 (CH), 38.1 (CH_2); HRMS m/z 475.1749 (M + Na^+), calcd for $C_{27}H_{24}N_4O_3Na$ 475.1746.

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 5-phenyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazole-4-carboxylate (9ta): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow flaky semi-solid. **$[\alpha]_D^{21}$ = -45.9° (*c* = 0.28 g/100 mL, $CHCl_3$);** IR (Neat): 3065, 2951, 2915, 2864, 1722, 1640, 1578, 1490, 1448, 1386, 1185, 1040, 958, 916, 844, 767 and 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33-7.22 (8H, m), 7.05 (2H, d, *J* = 7.5 Hz), 5.84 (1H, s, olefinic-*H*), 5.54 (1H, s, olefinic-*H*), 4.88 (1H, dt, *J* = 11.0, 4.0 Hz), 2.11 (1H, br d, *J* = 11.5 Hz), 1.78-1.72 (2H, m), 1.65 (2H, br t, *J* = 12.6 Hz), 1.48 (1H, br s), 1.32-1.28 (1H, m), 1.07-0.97 (2H, m), 0.89 (3H, d, *J* = 6.5 Hz), 0.78 (3H, d, *J* = 6.9 Hz), 0.71 (3H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 160.5 (C, O=*C*-O), 142.3 (C), 141.3 (C), 137.0 (C), 134.6 (C), 129.7 (2 x CH), 129.6 (CH), 129.4 (CH), 128.5 (2 x CH), 127.8 (2 x CH), 125.9 (C), 125.8 (2 x CH), 115.5 (CH_2), 75.2 (CH), 46.7 (CH), 40.7 (CH_2), 34.1 (CH_2), 31.4 (CH), 25.8 (CH), 23.1 (CH_2), 21.9 (CH_3), 20.7 (CH_3), 16.0 (CH_3); HRMS m/z 452.2314 (M + Na^+), calcd for $C_{27}H_{31}N_3O_2Na$ 452.2314.



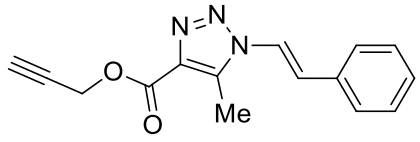
9ta

(*E*)-Ethyl 5-methyl-1-styryl-1*H*-1,2,3-triazole-4-carboxylate (86aa): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp: 108-110 °C; IR (Neat): ν_{max} 3059, 2982, 1717, 1562, 1417, 1371, 1350, 1304, 1242, 1195, 1092, 978, 942, 849, 787, 746 and 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 (1H, d, *J* = 14.0 Hz, olefinic-*H*), 7.50 (2H, br d, *J* = 7.0 Hz), 7.42-7.35 (4H, m), 4.44 (2H, q, *J* = 7.0 Hz, O$CH_2$$CH_3$), 2.69 (3H, s), 1.44 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.6 (C, O=*C*-O), 137.2 (C), 136.7 (C), 133.5 (C), 129.1 (CH), 129.0 (2 x CH), 126.9 (2 x CH), 126.1 (CH), 119.3 (CH), 61.0 (CH_2), 14.3 (CH_3), 9.1 (CH_3); HRMS m/z 258.1239 (M + H^+), calcd for $C_{14}H_{15}N_3O_2H$ 258.1243.



86aa

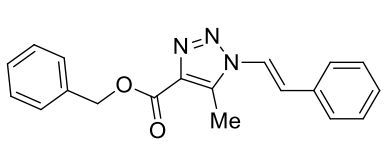
(*E*)-Prop-2-yn-1-yl 5-methyl-1-styryl-1*H*-1,2,3-triazole-4-carboxylate (86da): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and



86da

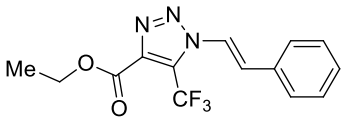
was isolated as a white solid. Mp: 104-106 °C; IR (Neat): ν_{max} 3266, 1717, 1578, 1443, 1376, 1350, 1273, 1226, 1190, 1082, 973, 947, 782, 751, 694 and 607 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56 (1H, d, *J* = 14.4 Hz, olefinic-*H*), 7.50 (2H, br d, *J* = 7.2 Hz), 7.43-7.28 (4H, m), 4.96 (2H, d, *J* = 2.4 Hz), 2.70 (3H, s), 2.53 (1H, t, *J* = 2.4 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 160.6 (C, O=*C*-O), 137.8 (C), 135.8 (C), 133.3 (C), 129.1 (CH), 128.9 (2 x CH), 126.9 (2 x CH), 126.2 (CH), 119.0 (CH), 77.27 (C), 75.3 (CH), 52.2 (CH_2), 9.1 (CH_3); HRMS m/z 290.0914 ($M + Na^+$), calcd for $C_{15}H_{13}N_3O_2Na$ 290.0905.

(*E*)-Benzyl 5-methyl-1-styryl-1*H*-1,2,3-triazole-4-carboxylate (86ea): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp: 116 °C; IR (Neat): ν_{max} 1712, 1572, 1448, 1423, 1355, 1221, 1180, 1092, 978, 947, 803, 741 and 689 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56-7.46 (5H, m), 7.38-7.30 (7H, m), 5.40 (2H, s), 2.63 (3H, t, *J* = 3.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.2 (C, O=*C*-O), 137.4 (C), 136.3 (C), 135.5 (C), 133.3 (C), 129.0 (CH), 128.9 (2 x CH), 128.5 (2 x CH), 128.3 (2 x CH), 128.2 (CH), 126.8 (2 x CH), 125.9 (CH), 119.1 (CH), 66.5 (CH_2), 9.0 (CH_3); HRMS m/z 342.1224 ($M + Na^+$), calcd for $C_{19}H_{17}N_3O_2Na$ 342.1218.



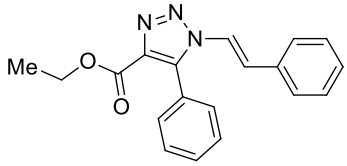
86ea

(*E*)-Ethyl 1-styryl-5-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (86ha): Prepared following the procedure **C** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp: 70-72 °C; IR (Neat): ν_{max} 2988, 1727, 1562, 1443, 1366, 1340, 1231, 1144, 1051, 953, 854, 746 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.67 (1H, d, *J* = 14.0 Hz, olefinic-*H*), 7.57-7.51 (3H, m), 7.45-7.41 (3H, m), 4.49 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 1.44 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 158.8 (C, O=*C*-O), 139.3 (C), 132.6 (C), 130.0 (CH), 129.9 (CH), 129.1 (2 x CH), 127.4 (2 x CH), 127.3 (C, q, *J* = 41.2 Hz), 119.3 (CH, q, *J* = 2.5 Hz), 119.2 (C, q, *J* = 278.7 Hz, CF_3), 62.3 (CH_2), 14.0 (CH_3); HRMS m/z 334.0777 ($M + Na^+$), calcd for $C_{14}H_{12}F_3N_3O_2Na$ 334.0779.



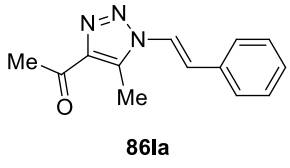
86ha

(*E*)-Ethyl 5-phenyl-1-styryl-1*H*-1,2,3-triazole-4-carboxylate (86ia): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp: 156-158 °C; IR (Neat): ν_{max} 2931, 1722, 1562, 1485, 1443, 1423, 1381, 1257, 1216, 1200, 1046, 947, 844, 767 and 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.65 (1H, d, *J* = 14.0 Hz, olefinic-*H*), 7.58-7.54 (3H, m), 7.48-7.46 (2H, m), 7.38-7.31 (5H, m), 7.18 (1H, d, *J* = 14.5 Hz, olefinic-*H*), 4.34 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 1.30 (3H, t, *J* = 7.5 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 160.7 (C, O=*C*-O), 139.7 (C), 136.9 (C), 133.5 (C), 130.4 (CH), 130.3 (2 x CH), 128.94 (CH), 128.86 (2 x CH), 128.6 (2 x CH), 126.9 (2 x CH), 125.6 (CH), 125.2 (C), 119.9 (CH), 66.1 (CH_2), 14.0 (CH_3); HRMS m/z 342.1222 ($M + Na^+$), calcd for $C_{19}H_{17}N_3O_2Na$ 342.1218.



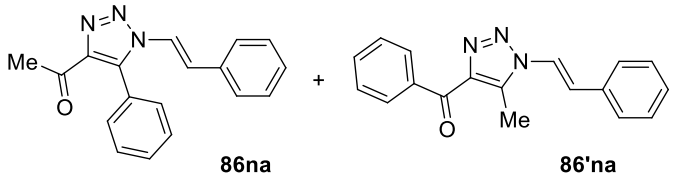
86ia

(*E*)-1-(5-Methyl-1-styryl-1*H*-1,2,3-triazol-4-yl)ethanone (86la): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp: 148-150 °C; IR (neat): ν_{max} 1670, 1552, 1417, 1324, 1273, 1221, 1180, 1077, 978, 942, 798, 751 and 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.57 (1H, d, *J* = 14.5 Hz, olefinic-*H*), 7.52-7.50 (2H, m), 7.43-7.35 (4H, m), 2.72 (3H, s), 2.69 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.2 (C, *C*=O), 143.6 (C), 135.7 (C), 133.5 (C), 129.1 (CH), 129.0 (2 x CH), 126.9 (2 x CH), 126.1 (CH), 119.1 (CH), 27.8 (CH_3), 9.1 (CH_3); HRMS m/z 250.0956 ($M + Na^+$), calcd for $C_{13}H_{13}N_3ONa$ 250.0956.



86la

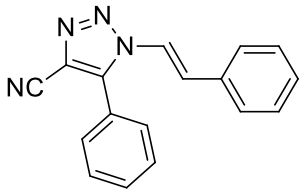
(*E*)-1-(5-Phenyl-1-styryl-1*H*-1,2,3-triazol-4-yl)ethanone (86na) and (*E*)-(5-Methyl-1-styryl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone (86′na): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. IR (Neat): ν_{max} 3060, 1691, 1645, 1552, 1485, 1448, 1417, 1361, 1242, 1175, 1128, 1035, 947, 927, 803, 751 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 1:1 mixture) δ 8.34-8.32 (2H, m), 7.67-7.31 (21H, m), 7.21 (1H, d, *J* = 14.4 Hz, olefinic-*H*), 2.77 (3H, s), 2.73 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture) δ 192.6 (C, *C*=O), 187.4 (C, *C*=O), 143.54 (C), 143.50 (C), 138.2 (C), 138.0 (C), 137.3 (C), 133.6 (2 x C), 132.9 (CH), 130.6



86na 86'na

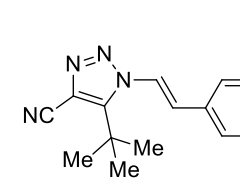
(2 x CH), 130.5 (2 x CH), 130.3 (2 x CH), 129.2 (CH), 129.0 (2 x CH), 128.9 (2 x CH), 128.7 (2 x CH), 128.2 (2 x CH), 127.0 (2 x CH), 126.9 (2 x CH), 126.2 (CH), 125.7 (CH), 125.2 (C), 119.9 (CH), 119.1 (CH), 28.2 (CH_3), 9.6 (CH_3); HRMS m/z 312.1119 ($M + Na^+$), calcd for $C_{18}H_{15}N_3ONa$ 312.1113.

(*E*)-5-Phenyl-1-styryl-1*H*-1,2,3-triazole-4-carbonitrile (86pa): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp: 124-126 °C; IR (Neat): ν_{max} 3081, 3029, 2239, 1490, 1454, 1423, 1350, 1268, 1066, 999, 947, 808, 751 and 689 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.68 (1H, d, *J* = 14.5 Hz, olefinic-*H*), 7.64-7.61 (3H, m), 7.58-7.56 (2H, m), 7.44-7.43 (2H, m), 7.40-7.35 (3H, m), 7.32 (1H, d, *J* = 14.5 Hz, olefinic-*H*); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 142.0 (C), 133.0 (C), 131.5 (CH), 129.7 (2 x CH), 129.4 (CH), 129.2 (2 x CH), 129.0 (2 x CH), 127.4 (CH), 127.1 (2 x CH), 122.9 (C), 120.3 (C), 119.5 (CH), 111.8 (C, *C*N); HRMS m/z 273.1140 ($M + H^+$), calcd for $C_{17}H_{12}N_4H$ 273.1140.



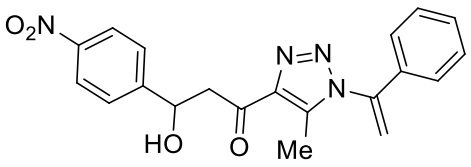
86pa

(*E*)-5-(*tert*-Butyl)-1-styryl-1*H*-1,2,3-triazole-4-carbonitrile (86ra): Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp: 122-124 °C; IR (Neat): ν_{max} 3127, 2977, 2941, 2879, 2233, 1526, 1469, 1402, 1371, 1273, 1242, 1206, 1159, 1082, 1051, 1025, 942, 808, 756 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.52-7.47 (4H, m), 7.45-7.38 (3H, m), 1.59 (9H, s, 3 x C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 149.3 (C), 133.1 (C), 129.6 (CH), 129.5 (CH), 129.1 (2 x CH), 127.1 (2 x CH), 121.2 (CH), 118.9 (C), 113.2 (C, *C*N), 31.8 (C), 29.6 (3 x CH_3); HRMS m/z 253.1453 ($M + H^+$), calcd for $C_{15}H_{16}N_4H$ 253.1453.



86ra

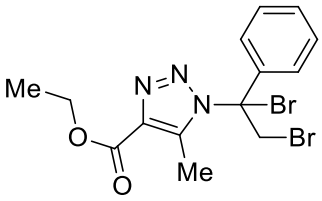
3-Hydroxy-1-(5-methyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazol-4-yl)-3-(4-nitrophenyl)propan-1-one (87la): Prepared following the procedure **D** and purified by column chromatography using EtOAc/hexane and was isolated as a pale yellow liquid. IR (Neat): ν_{max} 3437 (OH), 2926, 2848, 1686, 1598, 1557, 1521, 1423, 1335, 1283, 1108, 1061, 1009, 968, 911, 844, 777 and 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.24 (2H, td, *J* = 9.0, 2.0 Hz), 7.65 (2H, td, *J* = 9.0, 2.0 Hz),



87la

7.42-7.37 (3H, m), 7.15-7.13 (2H, m), 6.06 (1H, d, *J* = 1.5 Hz, olefinic-*H*), 5.60 (1H, d, *J* = 1.0 Hz, olefinic-*H*), 5.45 (1H, td, *J* = 9.0, 3.5 Hz), 3.91 (1H, d, *J* = 3.5 Hz), 3.73 (1H, dd, *J* = 17.5, 3.0 Hz), 3.56 (1H, dd, *J* = 17.5, 9.5 Hz), 2.38 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.2 (C, *C*=O), 150.3 (C), 147.3 (C), 142.7 (C), 141.5 (C), 138.9 (C), 133.8 (C), 130.1 (CH), 129.1 (2 x CH), 126.6 (2 x CH), 125.5 (2 x CH), 123.7 (2 x CH), 115.4 (CH_2), 69.4 (CH), 48.1 (CH_2), 9.8 (CH_3); HRMS m/z 379.1406 ($M + H^+$), calcd for $C_{20}H_{18}N_4O_4H$ 379.1406.

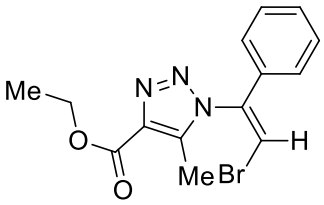
Ethyl 1-(1,2-dibromo-1-phenylethyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (88aa):



88aa

Prepared following the procedure **E** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow oil; IR (KBr): ν_{max} 1717, 1567, 1526, 1443, 1412, 1376, 1299, 1231, 1185, 1164, 1118, 1071, 1015, 978, 937 and 844 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47-7.39 (3H, m), 7.31 (2H, d, *J* = 7.5 Hz), 4.96 (1H, d, *J* = 11.5 Hz), 4.69 (1H, d, *J* = 11.5 Hz), 4.43 (2H, q, *J* = 7.5 Hz, OC*H*$_2$CH$_3$), 2.23 (3H, s), 1.43 (3H, t, *J* = 7.5 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.4 (C, O=*C*-O), 141.0 (C), 138.4 (C), 136.8 (C), 130.3 (CH), 128.7 (2 x CH), 127.7 (2 x CH), 78.7 (C), 61.3 (CH_2), 42.8 (CH_2), 14.3 (CH_3), 11.8 (CH_3); HRMS m/z 415.9607 ($M + H^+$), calcd for $C_{14}H_{15}Br_2N_3O_2H$ 415.9609.

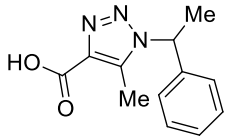
(*Z*)-Ethyl 1-(2-bromo-1-phenylvinyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (89aa):



89aa

Prepared following the procedure **F** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow liquid. IR (Neat): ν_{max} 3086, 2988, 2920, 2853, 1717, 1609, 1567, 1448, 1428, 1371, 1273, 1242, 1164, 1102, 1015, 978, 911, 849, 767 and 705 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.34 (3H, m), 7.34 (1H, s), 7.13-7.11 (2H, m), 4.47 (2H, q, *J* = 7.5 Hz, OC*H*$_2$CH$_3$), 2.46 (3H, s), 1.46 (3H, t, *J* = 7.5 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.5 (C, O=*C*-O), 139.8 (C), 139.3 (C), 136.4 (C), 133.3 (C), 130.2 (CH), 129.3 (2 x CH), 125.2 (2 x CH), 109.8 (CH), 61.1 (CH_2), 14.3 (CH_3), 9.0 (CH_3); HRMS m/z 336.0348 ($M + H^+$), calcd for $C_{14}H_{14}BrN_3O_2H$ 336.0348.

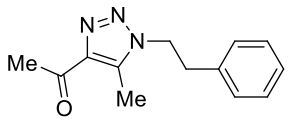
5-Methyl-1-(1-phenylethyl)-1*H*-1,2,3-triazole-4-carboxylic acid (90ea): Prepared following the procedure **G** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp: 118-120 °C; IR (Neat):



90ea

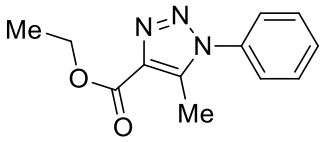
ν_{max} 1694, 1579, 1448, 1400, 1381, 1332, 1265, 1221, 1191, 1105, 971, 792, 773, 736 and 702 cm^{-1}; ^1H NMR ($CDCl_3$ + few drops DMSO-d_6, 400 MHz) δ 7.36-7.30 (3H, m), 7.18 (2H, d, *J* = 7.2 Hz), 5.63 (1H, q, *J* = 6.8 Hz), 2.42 (3H, s), 2.05 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$+ few drops DMSO-d_6, DEPT-135) δ 162.4 (C, O=*C*-O), 139.1 (C), 136.8 (C), 136.4 (C), 128.0 (2 x CH), 127.2 (CH), 125.0 (2 x CH), 57.5 (CH), 20.8 (CH_3), 8.1 (CH_3); HRMS m/z 254.0906 (M + Na^+), calcd for $C_{12}H_{13}N_3O_2Na$ 254.0905.

1-(5-Methyl-1-phenethyl-1*H*-1,2,3-triazol-4-yl)ethanone (90la): Prepared following the procedure **G** and purified by column chromatography using EtOAc/hexane and isolated as a yellow viscous liquid. IR (Neat): ν_{max} 3065, 3024, 2920, 1676, 1567, 1423, 1361, 1268, 1175, 1066, 947, 736, 699 and 493 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28-7.24 (3H, m), 7.02 (2H, d, *J* = 6.5 Hz), 4.47 (2H, t, *J* = 7.0 Hz), 3.20 (2H, t, *J* = 7.0 Hz), 2.67 (3H, s), 2.17 (3H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.1 (C, *C*=O), 143.1 (C), 136.9 (C), 136.6 (C), 128.7 (2 x CH), 128.6 (2 x CH), 127.1 (CH), 48.9 (CH_2), 36.2 (CH_2), 27.5 (CH_3), 8.4 (CH_3); HRMS m/z 252.1113 (M + Na^+), calcd for $C_{13}H_{15}N_3ONa$ 252.1113.



90la

Ethyl 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylate (94):[50] Prepared following the procedure **A** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp: 46-48 °C; IR (KBr): ν_{max} 3057, 2981, 2931, 2904, 1709, 1567, 1501, 1425, 1375, 1342, 1244, 1222, 1101, 1036, 986, 926, 844, 783, 767, 690, 668, 504 and 438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58-7.54 (3H, m), 7.45-7.42 (2H, m), 4.45 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.58 (3H, s), 1.43 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 161.7 (C, O=*C*-O), 138.8 (C), 136.7 (C), 135.4 (C), 130.0 (CH), 129.6 (2 x CH), 125.3 (2 x CH), 61.0 (CH_2), 14.3 (CH_3), 9.9 (CH_3); HRMS m/z 232.1081 (M + H^+), calcd for $C_{12}H_{13}N_3O_2H$ 232.1086.



94

2. General experimental procedures for An Aldehyde-Azomethine Imine [3+2]-Cycloaddition: High-yielding Regioselective Synthesis of Substituted *N,N*-Bicyclic Pyrazolidinones.

Procedure A: **General procedure for [3+2]-cycloaddition of azomethine imines and aldehydes:** To an ordinary glass vial equipped with a magnetic stirring bar, containing a solution of 0.5 mmol of enolizable aldehyde **7** and 0.75 mmol of azomethine imine **29** in dry chloroform (1.0 mL), 0.1 mmol of catalyst *t*BuOK **3k** was added. The reaction mixture was stirred at 25 °C and the reaction progress was monitored by TLC. After completion of the reaction, the crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Pure click products **97/99** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

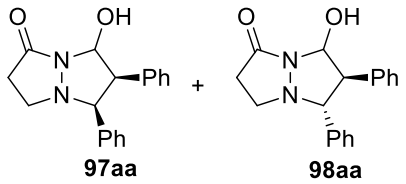
Procedure B: **General procedure for reductive dehydroxylation of click products 97/99:** In an 10 mL round bottomed flask fitted with a rubber septum, a solution of 0.3 mmol of **97/99** in dry dichloromethane (1.0 mL) was taken under N_2 atmosphere. To the vigorously stirred reaction mixture at 0 °C consecutive addition of 2.0 mmol of Et_3SiH and 1.13 mmol of $BF_3.Et_2O$ was added. The reaction mixture was brought to room temperature (25 °C) and stirred till reaction completion, as monitored by TLC. After completion, reaction was quenched with saturated $NaHCO_3$ solution and extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The concentrate was subjected to column chromatography (silica gel, mixture of hexane/ethyl acetate) to obtain the pure compounds **100.**

Procedure C: **Procedure for reductive cleavage of bicyclopyrazolidinone *N-N* bond of product 99aa:** Dry liquid ammonia was condensed at –78 °C in a three-necked round bottom flask equipped with a Dewar condenser cooled with liquid nitrogen in ethyl acetate. A solution of bicyclopyrazolidinone **99aa** (0.5 mmol) in dry degassed THF (24 mL) was added followed by sodium metal (1.5 mmol). The solution became blue in 5 minutes and then discolored to a white cloudy solution. The resulting mixture was stirred for 1.5 hour at -78 °C before an excess of solid NH_4Cl was added. The reaction mixture was slowly warmed to room temperature until NH_3 had been distilled off. Water was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (hexane/ethyl acetate) to afford product **101aa**.

Procedure D: **Procedure for hydrogen peroxide oxidation and further esterification of 99aa/100aa:** 0.41 mmol of **99aa/100aa** was dissolved in isopropanol (3 mL) and hydrogen peroxide (1.4 mL, 30% in

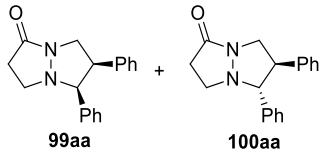
water) was added. The solution was heated under reflux for 24 h, the solvent was removed under reduced pressure, and the resulting residue was recrystallized from ethyl acetate to give product **102aa.** A 50 mL conical flask with stir bar was filled with 10 mL of Et_2O and 475 mg of *N*-methyl-*N*-nitrosourea. The flask was then placed in an ice bath and 2 mL of 50 % KOH (aq.) solution was added slowly. After stirring for 10 minutes, the neon-yellow ether layer was separated, dried over KOH and added into a solution of **102aa** in diethyl ether (10 mL). After reaction completion, as monitored by TLC, the reaction mixture was kept in hot water bath (50 °C) for excess diazomethane to evaporate. The resulting solution was concentrated and the concentrate was subjected to column chromatography (hexane/ethyl acetate) to yield the pure product **103aa**.

***cis*-7-Hydroxy-5,6-diphenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (97aa) and *trans*-7-hydroxy-5,6-diphenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (98aa):** Prepared following the procedure **A** and isolated as off white solid. *dr* = 1:1; IR (Neat): ν_{max} 3339, 3029, 2838, 1676, 1490, 1448, 1423, 1371, 1268, 1180, 1066, 756 and 705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.23 (7H, m), 7.12-7.08 (8H, m), 6.97-6.91 (5H, m), 5.76 (1H, dd, *J* = 3.2, 1.6 Hz), 5.69 (1H, s), 4.36 (1H, d, *J* = 6.0 Hz), 3.72 (1H, d, *J* = 6.0 Hz), 3.64-3.63 (2H, m), 3.57-3.50 (2H, m), 3.18-3.09 (1H, m), 2.98-2.90 (2H, m), 2.82-2.69 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.6 (C, *C*=O), 166.8 (C, *C*=O), 136.5 (C), 135.9 (C), 135.5 (C), 134.3 (C), 128.7 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.3 (CH), 128.0 (2 x CH), 127.8 (2 x CH), 127.7 (2 x CH), 127.5 (2 x CH), 127.48 (2 x CH), 127.4 (2 x CH), 126.8 (CH), 83.3 (CH), 80.9 (CH), 79.1 (CH), 71.4 (CH), 65.7 (CH), 63.1 (CH), 53.1 (CH_2), 47.3 (CH_2), 36.9 (CH_2), 32.3 (CH_2); HRMS m/z 317.1268 ($M + Na^+$), calcd for $C_{18}H_{18}N_2O_2Na$ 317.1266.



97aa **98aa**

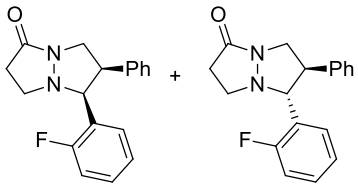
***cis*-5,6-Diphenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99aa) and *trans*-5,6-Diphenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100aa):** Prepared following the procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as white solids. Mp 120-122 °C (**99aa**) and 88-90 °C (**100aa**); *dr* = 1:1; IR (Neat): ν_{max} 3062, 3029, 2929, 2839, 1674, 1603, 1454, 1421, 1354, 1206, 1072, 1030, 859, 754, 665, 598, 548 and 512 cm^{-1}; **For compound 99aa:** ^1H NMR ($CDCl_3$, 400 MHz) δ 7.10-7.04 (6H, m), 7.01-7.00 (2H, m), 6.96-6.93 (2H, m), 4.32 (1H, dd, *J* = 12.0, 8.0 Hz), 3.95 (1H, d, *J* = 6.8 Hz), 3.94 (1H, dt, *J* = 7.0, 2.8 Hz), 3.69-3.57 (2H, m), 2.97-2.87 (2H, m), 2.77-2.74 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.4 (C, *C*=O), 139.2 (C), 134.8 (C), 128.7 (2 x CH), 127.8 (2 x CH), 127.7 (2 x CH), 127.67 (2 x CH), 127.3 (CH), 126.7 (CH), 74.3 (CH), 53.0 (CH), 48.6 (CH_2), 48.0 (CH_2), 33.4 (CH_2); **For compound 100aa:** ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30-7.24



99aa **100aa**

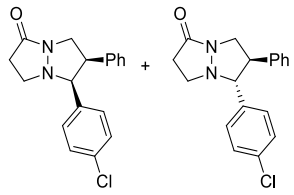
(4H, m), 7.30-7.24 (2H, m), 7.18-7.16 (2H, m), 7.09-7.07 (2H, m), 4.02 (1H, dd, *J* = 11.7, 7.5 Hz), 3.85 (1H, t, *J* = 10.0 Hz), 3.72-3.66 (1H, m), 3.57-3.51 (1H, m), 3.46 (1H, d, *J* = 9.5 Hz), 3.03-2.97 (1H, m), 2.85-2.80 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.5 (C, *C*=O), 138.2 (C), 136.2 (C), 128.7 (2 x CH), 128.5 (2 x CH), 128.2 (CH), 127.7 (2 x CH), 127.5 (2 x CH), 127.4 (CH), 78.2 (CH), 56.9 (CH), 48.0 (CH_2), 47.2 (CH_2), 32.3 (CH_2); HRMS m/z 279.1407 ($M + H^+$), calcd for $C_{18}H_{18}N_2OH$ 279.1497.

***cis*-5-(2-fluorophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ab) and *trans*-5-(2-fluorophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ab):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a semi-solid. *dr* = 1:1; IR (Neat): ν_{max} 3064, 3030, 29 62, 1699, 1586, 1492, 1455, 1356, 1229, 1085, 1033, 770 and 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (1H, dt, *J* = 6.8, 1.6 Hz), 7.26-7.25 (5H, m), 7.12-7.02 (9H, m), 6.95-6.78 (3H, m), 4.39 (1H, dd, *J* = 12.0, 8.8 Hz), 4.20 (1H, d, *J* = 7.2 Hz), 4.12-4.07 (1H, m), 4.00 (1H, dd, *J* = 11.2, 7.2 Hz), 3.92-3.75 (3H, m), 3.71-3.64 (1H, m), 3.59 (1H, dd, *J* = 12.0, 2.8 Hz), 3.53-3.46 (1H, m), 3.05-2.73 (6H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.9 (C, *C*=O), 171.2 (C, *C*=O), 161.3 (C, d, *J* = 246.0 Hz, *C*-F), 160.2 (C, d, *J* = 244.0 Hz, *C*-F), 139.5 (C), 137.8 (C), 129.6 (CH, d, *J* = 9.0 Hz), 128.7 (2 x CH), 128.6 (CH, d, *J* = 4.0 Hz), 128.58 (CH, d, *J* = 4.0 Hz), 128.5 (2 x CH), 128.2 (CH, d, *J* = 5.0 Hz), 127.8 (2 x CH), 127.5 (CH), 127.4 (2 x CH), 126.8 (CH), 124.6 (CH, d, *J* = 3.0 Hz), 123.5 (CH, d, *J* = 3.0 Hz), 123.1 (C, d, *J* = 12.0 Hz), 122.9 (C, d, *J* = 14.0 Hz), 115.5 (CH, d, *J* = 22.0 Hz), 114.6 (CH, d, *J* = 21.0 Hz), 69.9 (CH), 67.5 (CH), 55.7 (CH), 50.9 (CH), 48.31 (2 x CH_2), 48.27 (CH_2), 47.1 (CH_2), 32.8 (CH_2), 32.2 (CH_2); LCMS m/z 297.25 ($M+H^+$), calcd. for $C_{18}H_{17}FN_2OH$ 297.1403; Anal. Calcd. for $C_{18}H_{17}FN_2O$ (296.1325): C, 72.95; H, 5.78; N, 9.45. Found: C, 72.85; H, 5.72; N, 9.51%.



99ab **100ab**

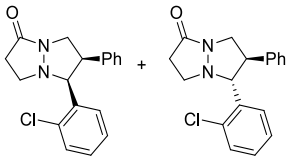
***cis*-5-(4-chlorophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ac) and *trans*-5-(4-chlorophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ac):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a yellow viscous liquid. *dr* = 1.3:1; IR (KBr): ν_{max} 3062, 2955, 2853, 1687, 1492, 1455, 1179, 1089, 1015, 832 and 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.22 (5H, m), 7.13-7.08 (5H, m), 7.06-7.02 (4H, m), 7.01-6.99 (2H, m), 6.90-6.87 (2H, m), 4.36-4.29 (1H, m), 3.99 (1H, dd, *J* = 11.6,7.6 Hz), 3.93-3.88 (2H, m), 3.81 (1H, t, *J* = 10.0 Hz), 3.67-3.61 (2H, m), 3.59-3.49 (2H, m), 3.42 (1H, d, *J* = 10.0 Hz), 2.99-2.86 (3H, m), 2.84-2.69 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.3 (C, *C*=O), 170.4 (C, *C*=O), 138.9 (C), 137.6 (C), 134.7 (C), 133.9 (C), 133.4



99ac **100ac**

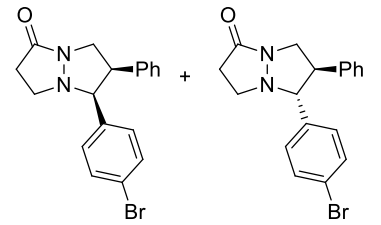
(C), 133.1 (C), 129.0 (2 x CH), 128.8 (2 x CH), 128.7 (4 x CH), 128.6 (2 x CH), 128.0 (2 x CH), 127.9 (2 x CH), 127.6 (2 x CH), 127.5 (CH), 126.9 (CH), 77.4 (CH), 73.6 (CH), 57.0 (CH), 52.9 (CH), 48.4 (CH_2), 47.9 (CH_2), 47.88 (CH_2), 47.1 (CH_2), 33.22 (CH_2), 32.24 (CH_2); LCMS m/z 312.15 (M^+), calcd. for $C_{18}H_{17}ClN_2O$ 312.1029; Anal. Calcd. for $C_{18}H_{17}ClN_2O$ (312.1029): C, 69.12; H, 5.48; N, 11.33. Found: C, 69.25; H, 5.42, N, 8.89%.

***cis*-5-(2-chlorophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ad) and *trans*-5-(2-chlorophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ad):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a gummy liquid; *dr* = 1.3:1; IR (KBr): ν_{max} 3063, 3029, 2954, 2927, 2896, 1693, 1493, 1472, 1455, 1442, 1421, 1353, 1272, 1205, 1179, 1131, 1087, 1034, 756, 701, 597 and 552 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73 (1H, d, *J* = 8.0 Hz), 7.33 (1H, dt, *J* = 8.0, 1.6 Hz), 7.25-7.21 (3H, m), 7.18 (2H, d, *J* = 8.0 Hz), 7.10-6.95 (10H, m), 6.90 (1H, dt, *J* = 7.6, 0.8 Hz), 4.39 (1H, dd, *J* = 11.6, 8.0 Hz), 4.29-4.22 (2H, m), 4.19 (1H, d, *J* = 9.6 Hz), 4.04 (1H, dd, *J* = 11.6,7.6 Hz), 3.85 (1H, t, *J* = 10.0 Hz), 3.72 (1H, q, *J* = 9.6 Hz), 3.67-3.57 (2H, m), 3.49-3.41 (1H, m), 3.03-2.72 (6H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 172.6 (C, *C*=O), 171.2 (C, *C*=O), 139.3 (C), 137.4 (C), 134.6 (C), 133.6 (C), 133.1 (C), 132.8 (C), 129.4 (CH), 129.0 (CH), 128.8 (CH), 128.7 (2 x CH), 128.6 (2 x CH), 128.2 (2 x CH), 128.1 (CH), 127.6 (2 x CH), 127.5 (2 x CH), 127.4 (CH), 127.2 (CH), 126.7 (CH), 126.1 (CH), 72.1 (CH), 70.8 (CH), 56.6 (CH), 49.6 (CH), 48.3 (CH_2), 48.2 (CH_2), 47.9 (CH_2), 46.4 (CH_2), 32.6 (CH_2), 31.8 (CH_2); LCMS m/z 312.00 (M^+), calcd. for $C_{18}H_{17}ClN_2O$ 312.1029; Anal. Calcd. for $C_{18}H_{17}ClN_2O$ (312.1029): C, 69.12; H, 5.48; N, 11.33. Found: C, 69.06; H, 5.56, N, 9.02%.



99ad **100ad**

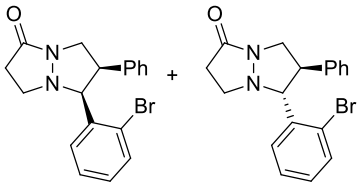
***cis*-5-(4-bromophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ae) and *trans*-5-(4-bromophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ae):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as off white semi-solid. *dr* = 1.4:1; IR (Neat): ν_{max} 3062, 3029, 2954, 2896, 2838, 1681, 1488, 1455, 1408, 1352, 1243, 1207, 1179, 1128, 1087, 1071, 1010, 823, 757, 700, 548 and 513 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.39 (2H, d, *J* = 8.5 Hz), 7.28-7.23 (4H, m), 7.19 (2H, d, *J* = 8.5 Hz), 7.11-7.10 (2H, m), 7.06-6.99 (6H, m), 6.83 (2H, d, *J* = 8.5 Hz), 4.34-4.30 (1H, m), 3.99 (1H, dd, *J* = 11.5, 7.5 Hz), 3.93-3.89 (2H, m), 3.81 (1H, t, *J* = 11.5 Hz), 3.66-3.49 (4H, m), 3.41 (1H, d, *J* = 10.0 Hz), 2.98-2.74 (6H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.4 (C, *C*=O), 170.5 (C, *C*=O), 138.8 (C), 137.6 (C), 135.3 (C), 134.0 (C), 131.6 (2 x CH), 130.9 (2 x CH),



99ae **100ae**

129.3 (2 x CH), 129.0 (2 x CH), 128.7 (2 x CH), 128.6 (2 x CH), 127.9 (2 x CH), 127.6 (2 x CH), 127.5 (CH), 126.9 (CH), 122.1 (C), 121.2 (C), 77.4 (CH), 73.6 (CH), 57.0 (CH), 52.8 (CH), 48.4 (CH_2), 48.0 (CH_2), 47.9 (CH_2), 47.0 (CH_2), 33.1 (CH_2), 32.2 (CH_2); HRMS m/z 357.0603 ($M + H^+$), calcd for $C_{18}H_{17}BrN_2OH$ 357.0603.

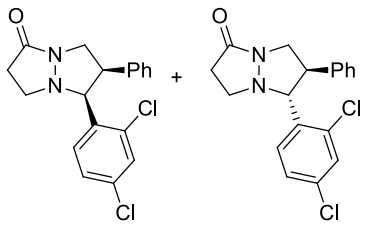
***cis*-(2-bromophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99af) and *trans*-(2-bromophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100af):**



99af 100af

Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a viscous oil. *dr* = 1.4:1; IR (KBr): ν_{max} 3062, 3029, 2955, 2895, 1688, 1493, 1468, 1439, 1422, 1353, 1272, 1206, 1087, 1026, 757 and 701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.72 (1H, d, *J* = 7.0 Hz), 7.40 (1H, dt, *J* = 8.0, 1.0 Hz,), 7.37 (2H, dd, *J* = 8.0, 1.0 Hz), 7.25-7.19 (3H,m), 7.14-6.99 (9H, m), 6.95-6.88 (2H, m), 4.39 (1H, dd, *J* = 11.5, 9.0 Hz), 4.32-4.28 (1H, m), 4.20 (1H, d, *J* = 7.0 Hz), 4.17 (1H, d, *J* = 9.5 Hz), 4.05 (1H, dd, *J* = 9.5, 7.0 Hz), 3.84 (1H, t, *J* = 10.5 Hz), 3.71 (1H, q, *J* = 9.5 Hz), 3.65-3.59 (2H, m), 3.48-3.40 (1H, m), 3.01 (1H, ddd, *J* = 11.5, 9.5, 7.0 Hz), 2.94-2.85 (2H, m), 2.84-2.72 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 173.1 (C, *C*=O), 171.4 (C, *C*=O), 139.3 (C), 137.4 (C), 135.3 (C), 134.6 (C), 132.7 (CH), 132.1 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 128.6 (2 x CH), 128.5 (CH), 128.3 (2 x CH), 127.8 (CH), 127.6 (2 x CH), 127.57 (2 x CH), 127.4 (CH), 126.7 (CH), 126.6 (CH), 125.2 (C), 123.3 (C), 74.4 (CH), 72.9 (CH), 56.9 (CH), 49.5 (CH), 48.4 (CH_2), 48.2 (CH_2), 47.7 (CH_2), 46.0 (CH_2), 32.5 (CH_2), 31.6 (CH_2); HRMS m/z 357.0606 ($M + H^+$), calcd for $C_{18}H_{17}BrN_2OH$ 357.0603.

***cis*-5-(2,4-dichlorophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ag) and *trans*-5-(2,4-dichlorophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ag):**

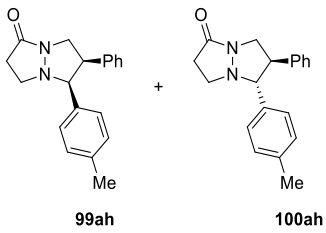


99ag 100ag

Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a white semi-solid. *dr* = 1.3:1; IR (KBr): ν_{max} 3029, 2955, 1690, 1472, 1352, 1098, 757 and 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (1H, d, *J* = 8.4 Hz), 7.32 (1H, dd, *J* = 8.4, 2.0 Hz), 7.28-7.23 (4H, m), 7.21 (1H, d, *J* = 2.4 Hz), 7.09-7.02 (8H, m), 6.90 (1H, dd, *J* = 8.4, 2.0 Hz), 4.40 (1H, dd, *J* = 11.6, 8.4 Hz), 4.22 (1H, dt, *J* = 8.4, 2.8 Hz), 4.18 (1H, d, *J* = 7.2 Hz), 4.11 (1H, d, *J* = 9.6 Hz), 4.04 (1H, dd, *J* = 11.6, 7.6 Hz), 3.84 (1H, t, *J* = 11.6 Hz), 3.69-3.57 (3H, m), 3.49-3.42 (1H, m), 3.00-2.96 (1H, m), 2.94-2.84 (2H, m), 2.83-2.71 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 172.6 (C, *C*=O), 171.5 (C, *C*=O), 139.2 (C), 137.2 (C), 135.3 (C), 134.3 (C), 133.6 (C), 133.4 (C), 132.6 (C), 132.1 (C), 129.8 (CH), 129.7 (CH), 129.3 (CH), 128.8 (CH), 128.79 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH),

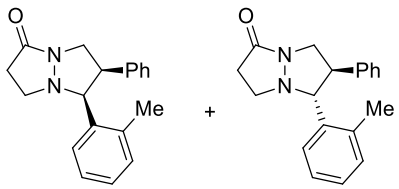
127.8 (CH), 127.7 (CH), 127.5 (2 x CH), 127.0 (CH), 126.5 (CH), 72.0 (CH), 70.5 (CH), 57.0 (CH), 49.8 (CH), 48.41 (CH_2), 48.4 (CH_2), 47.9 (CH_2), 46.5 (CH_2), 32.5 (CH_2), 31.9 (CH_2); LCMS m/z 345.85 (M^+), calcd. for $C_{18}H_{16}Cl_2N_2O$ 346.0640; Anal. calcd. for $C_{18}H_{16}ClN_2O$ (346.0640): C, 62.26; H, 4.64; N, 8.07. Found: C, 62.35; H, 4.58; N, 8.15%.

***cis*-6-phenyl-5-(*p*-tolyl)tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ah) and *cis*-6-phenyl-5-(*p*-tolyl)tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ah):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a viscous liquid. *dr* = 1:1; IR (KBr): ν_{max} 2923, 2853, 1693, 1674, 1515, 1455, 1351, 1180, 1088, 1032, 820, 758, 700, 548 and 514 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.24 (3H, m), 7.09-7.03 (11H, m), 6.88-6.81 (4H, m), 4.31 (1H, s), 3.98-3.81 (4H, m), 3.67 (2H, d, *J* = 9.5 Hz), 3.57-3.41 (3H, m), 2.99-2.73 (6H, m), 2.31 (3H, s, Ph-CH_3), 2.19 (3H, s, Ph-CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.4 (C, *C*=O), 170.4 (C, *C*=O), 139.4 (C), 138.2 (C), 138.0 (C), 137.0 (C), 132.9 (C), 131.6 (C), 129.2 (2 x CH), 128.8 (2 x CH), 128.7 (2 x CH), 128.5 (2 x CH), 127.75 (2 x CH), 127.7 (2 x CH), 127.66 (2 x CH), 127.4 (2 x CH), 127.38 (CH), 126.7 (CH), 78.0 (CH), 74.3 (CH), 56.6 (CH), 53.0 (CH), 48.6 (CH_2), 48.0 (CH_2), 47.99 (CH_2), 47.1 (CH_2), 33.4 (CH_2), 32.3 (CH_2), 21.1 (CH_3), 20.9 (CH_3); LCMS m/z 293.15 ($M+H^+$), calcd. for $C_{19}H_{20}N_2OH$ 293.1654; Anal. Calcd. for $C_{19}H_{20}N_2O$ (292.1576): C, 78.05; H, 6.89; N, 9.58. Found: C, 78.12; H, 6.83; N, 9.65%.



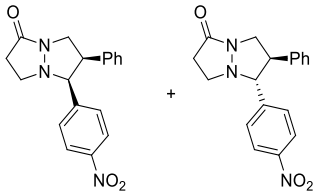
99ah **100ah**

***cis*-6-phenyl-5-(*o*-tolyl)tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ai) and *trans*-6-phenyl-5-(*o*-tolyl)tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ai):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a semi-solid. *dr* = 1.3:1; IR (Neat): ν_{max} 2953, 1698, 1492, 1456, 1357, 1085, 759, 702 and 555 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.67 (2H, d, *J* = 8.0 Hz), 7.26-7.21 (4H, m), 7.14 (1H, dt, *J* = 7.5, 1.5 Hz), 7.06-7.01 (6H, m), 6.98 (2H, d, *J* = 6.5 Hz), 6.94 (1H, dt, *J* = 8.5, 1.5 Hz), 6.84 (2H, t, *J* = 7.0 Hz), 4.40-4.36 (1H, m), 4.10-4.02 (3H, m), 3.83 (1H, dd, *J* = 11.2, 9.5 Hz), 3.73 (1H, d, *J* = 10.0 Hz), 3.69-3.59 (3H, m), 3.49-3.44 (1H, m), 2.87-2.70 (6H, m), 2.31 (3H, s, Ph-CH_3), 1.64 (3H, s, Ph-CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.8 (C, *C*=O), 171.0 (C, *C*=O), 139.5 (C), 138.1 (C), 136.9 (C), 135.0 (C), 134.3 (C), 133.2 (C), 130.2 (CH), 129.7 (CH), 128.7 (2 x CH), 128.3 (2 x CH), 127.6 (2 x CH), 127.5 (CH), 127.5 (2 x CH), 127.4 (CH), 127.2 (CH), 126.9 (CH), 126.8 (CH), 126.6 (CH), 126.4 (CH), 125.2 (CH), 74.06 (CH), 71.1 (CH), 57.3 (CH), 50.1 (CH), 48.3 (CH_2), 48.1 (CH_2), 47.7 (CH_2), 46.8 (CH_2), 32.8 (CH_2), 32.2 (CH_2), 19.3 (CH_3), 18.9 (CH_3); HRMS m/z 293.1654 ($M + H^+$), calcd for $C_{19}H_{20}N_2OH$ 293.1654.



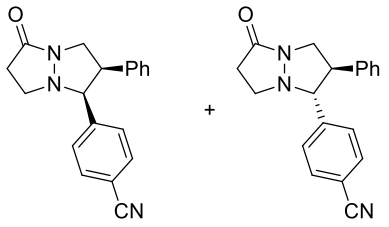
99ai **100ai**

***cis*-5-(4-nitrophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99aj) and *trans*-5-(4-nitrophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100aj):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a viscous liquid. *dr* = 1:1.5; IR (Neat): ν_{max} 2957, 2925, 2854, 1711, 1688, 1601, 1522, 1455, 1345, 1287, 1124, 1073, 857, 772, 700 and 548 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.13 (2H, d, *J* = 9.0 Hz), 7.92 (2H, d, *J* = 9.0 Hz), 7.34-7.25 (4H, m), 7.18 (2H, d, *J* = 8.5 Hz), 7.11-7.04 (6H, m), 7.00 (2H, dd, *J* = 7.5, 2.5 Hz), 4.38 (1H, dd, *J* = 12.0, 8.5 Hz), 4.08 (1H, d, *J* = 7.0 Hz), 4.03-4.00 (2H, m), 3.84 (1H, dd, *J* = 11.3, 8.3 Hz), 3.68-3.56 (5H, m), 3.00-2.74 (6H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.3 (C, *C*=O), 170.7 (C, *C*=O), 147.8 (C), 147.0 (C), 143.9 (C), 142.9 (C), 138.3 (C), 137.1 (C), 129.0 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.1 (2 x CH), 128.09 (2 x CH), 127.9 (CH), 127.6 (2 x CH), 127.2 (CH), 123.7 (2 x CH), 123.0 (2 x CH), 77.2 (CH), 73.4 (CH), 57.5 (CH), 53.1 (CH), 48.5 (CH_2), 48.1 (CH_2), 48.0 (CH_2), 47.4 (CH_2), 33.0 (CH_2), 32.3 (CH_2); LCMS m/z 324.50 ($M+H^+$), calcd. for $C_{18}H_{17}N_3O_3H$ 324.1348; Anal. Calcd. for $C_{18}H_{17}N_3O_3$ (323.1270): C, 66.86; H, 5.30; N, 13.00. Found: C, 66.75; H, 5.34; N, 13.05%.



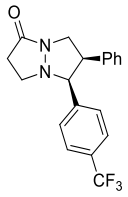
99aj **100aj**

***cis*-5-oxo-2-phenylhexahydropyrazolo[1,2-*a*]pyrazol-1-yl)benzonitrile (99ak) and *trans*-5-oxo-2-phenylhexahydropyrazolo[1,2-*a*]pyrazol-1-yl)benzonitrile (100ak):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow semi-solid. *dr* = 1:1; IR (Neat): 3062, 2956, 2929, 2898, 2850, 2227, 1668, 1608, 1497, 1455, 1416, 1354, 1208, 1179, 1129, 1088, 1031, 832, 753, 702, 666, 601 and 559 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (2H, d, *J* = 7.2 Hz), 7.36 (2H, d, *J* = 7.2 Hz), 7.29-7.26 (6H, m), 7.12-6.99 (8H, m), 4.36 (1H, t, *J* = 10.0 Hz), 4.03-3.98 (3H, m), 3.82 (1H, t, *J* = 11.2 Hz), 3.66-3.50 (5H, m), 2.97-2.76 (6H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.4 (C, *C*=O), 170.7 (C, *C*=O), 141.8 (C), 140.8 (C), 138.3 (C), 137.1 (C), 132.2 (2 x CH), 131.4 (2 x CH), 128.8 (2 x CH), 128.4 (2 x CH), 128.2 (2 x CH), 127.9 (2 x CH), 127.86 (2 x CH), 127.7 (CH), 127.5 (2 x CH), 127.0 (CH), 118.4 (C, *C*N), 118.3 (C, *C*N), 111.8 (C), 110.9 (C), 77.2 (CH), 73.3 (CH), 57.2 (CH), 52.9 (CH), 48.2 (CH_2), 47.9 (2 x CH_2), 47.0 (CH_2), 32.8 (CH_2), 32.0 (CH_2); HRMS m/z 304.1454 ($M + H^+$), calcd for $C_{19}H_{17}N_3OH$ 304.1450.



99ak **100ak**

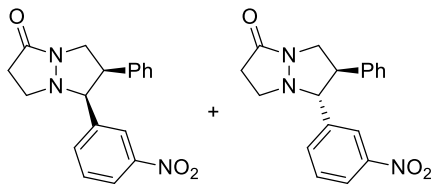
***cis*-6-phenyl-5-(4-(trifluoromethyl)phenyl)tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99al):**



99al

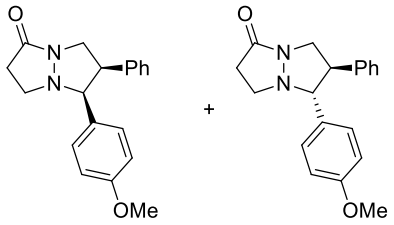
Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as off white solid. Mp 110-112 °C; *dr* = 9:1; IR (Neat): 3064, 3031, 2961, 2899, 2837, 1683, 1619, 1419, 1321, 1162, 1118, 1066, 1018, 832, 752, 701, 607 and 548 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33 (2H, d, *J* = 8.5 Hz), 7.10-7.08 (5H, m), 6.99-6.98 (2H, m), 4.35 (1H, dd, *J* = 12.0, 8.5 Hz), 4.00 (1H, dd, *J* = 7.0 Hz), 3.98-3.94 (1H, m), 3.68 (1H, dd, *J* = 12.0, 2.0 Hz), 3.63-3.59 (1H, m), 2.97-2.87 (2H, m), 2.78-2.71 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.8 (C, *C*=O), 139.3 (C), 138.6 (C), 129.5 (C, q, *J* = 32.5 Hz), 128.6 (2 x CH), 128.03 (2 x CH), 127.9 (2 x CH), 127.0 (CH), 124.7 (2 x CH, q, *J* = 3.7 Hz), 123.8 (C, q, *J* = 270.0 Hz), 73.7 (CH), 53.0 (CH), 48.4 (CH_2), 48.1 (CH_2), 33.1 (CH_2); LCMS m/z 347.25 ($M+H^+$), calcd. for $C_{19}H_{17}F_3N_2OH$ 347.1371; Anal. calcd. for $C_{19}H_{17}F_3N_2O$ (346.1293): C, 65.89; H, 4.95; N, 8.09. Found: C, 65.72; H, 4.89; N, 8.15%.

***cis*-5-(3-nitrophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99am) and *trans*-5-(3-nitrophenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100am):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a viscous liquid. *dr* = 1.2:1; IR (Neat): ν_{max} 3031, 2960, 2929, 2898, 2853,1679, 1527, 1455, 1421, 1346, 1209, 1094, 912, 836, 809, 770, 754, 707, 682, 600 and 551 cm^{-1}; **For compound 99am:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (1H, qd, *J* = 8.0, 1.2 Hz), 7.87 (1H, t, *J* = 2.0 Hz), 7.32-7.30 (1H, m), 7.27-7.23 (1H, m), 7.12-7.00 (5H, m), 4.39 (1H, dd, *J* = 12.0, 8.8 Hz), 4.07 (1H, d, *J* = 7.2 Hz), 4.02-3.98 (1H, m), 3.71-3.62 (2H, m), 3.00-2.89 (2H, m), 2.81-2.73 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 170.9 (C, *C*=O), 147.7 (C), 138.4 (C), 137.6 (C), 133.8 (CH), 128.8 (CH), 128.6 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 122.8 (CH), 122.5 (CH), 73.2 (CH), 53.1 (CH), 48.4 (CH_2), 48.0 (CH_2), 33.0 (CH_2); **For compound 100am:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16-8.13 (2H, m), 7.48-7.40 (2H, m), 7.30-7.27 (3H, m), 7.07-7.05 (2H, m), 4.03 (1H, dd, *J* = 11.6, 7.6 Hz), 3.86 (1H, t, *J* = 9.6 Hz), 3.68-3.56 (3H, m), 3.02-2.95 (1H, m), 2.88-2.81 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.4 (C, *C*=O), 148.5 (C), 138.8 (C), 137.2 (C), 133.7 (CH), 129.5 (CH), 129.0 (2 x CH), 128.0 (CH), 127.6 (2 x CH), 123.3 (CH), 122.2 (CH), 77.2 (CH), 57.5 (CH), 48.1 (CH_2), 47.3 (CH_2), 32.2 (CH_2); HRMS m/z 324.1347 ($M + H^+$), calcd for $C_{18}H_{17}N_3O_3H$ 324.1348.



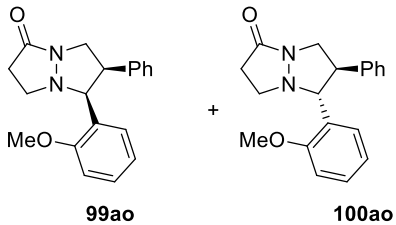
99am **100am**

***cis*-5-(4-methoxyphenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99an) and *trans*-5-(4-methoxyphenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100an):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a colourless gummy liquid. *dr* = 1:2.5; IR (KBr): ν_{max} 2956, 2925, 2854, 1695, 1613, 1514, 1463, 1365, 1245, 1175, 1032, 834, 759, 701 and 551 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.20 (3H, m), 7.14-7.10 (4H, m), 7.08-7.07 (3H, m), 7.02-7.00 (2H, m), 6.85-6.79 (4H, m), 6.62-6.59 (2H, m), 4.35-4.27 (1H, m), 4.01-3.96 (1H, m), 3.89-3.79 (2H, m), 3.77 (3H, s), 3.69 (3H, s), 3.66-3.62 (1H, m), 3.57-3.48 (4H, m), 3.38 (1H, d, *J* = 10.0 Hz), 3.01-2.94 (1H, m), 2.93-2.84 (2H, m), 2.82-2.77 (2H, m), 2.75-2.68 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.3 (C, *C*=O), 170.3 (C, *C*=O), 159.5 (C), 158.8 (C), 139.4 (C), 138.2 (C), 128.9 (2 x CH), 128.8 (2 x CH), 128.7 (2 x CH), 128.67 (2 x CH), 127.82 (C), 127.81 (CH), 127.7 (2 x CH), 127.4 (2 x CH), 126.7 (CH), 126.6 (C), 113.9 (2 x CH), 113.2 (2 x CH), 77.8 (CH), 74.0 (CH), 56.7 (CH), 55.1 (CH_3), 55.0 (CH), 53.0 (CH_3), 48.6 (CH_2), 47.9 (CH_2), 47.87 (CH_2), 47.1 (CH_2), 33.5 (CH_2), 32.4 (CH_2); LCMS m/z 307.15 ($M\text{-}H^+$), calcd. for $C_{19}H_{19}N_2O_2$ 307.1452; Anal. calcd. for $C_{19}H_{20}N_2O_2$ (308.1525): C, 74.00; H, 6.54; N, 9.08. Found: C, 74.17; H, 5.51; N, 9.18%.



99an **100an**

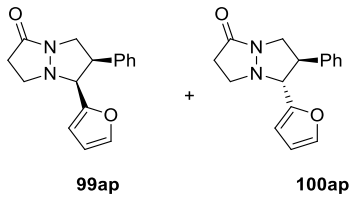
***cis*-5-(2-methoxyphenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ao) and *trans*-5-(2-methoxyphenyl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ao):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a viscous liquid. *dr* = 1.8:1; IR (Neat): 3062, 3029, 2954, 2896, 2836, 1698, 1681, 1602, 1587, 1493, 1462, 1354, 1286, 1244, 1087, 1050, 1027, 756, 702 and 555 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.59 (2H, dd, *J* = 7.6, 1.6 Hz), 7.26-7.18 (4H, m), 7.11-7.09 (2H, m), 7.04-6.99 (6H, m), 6.73 (2H, d, *J* = 8.4 Hz), 6.66-6.62 (2H, m), 4.37 (1H, dd, *J* = 12.0, 8.4 Hz), 4.19 (1H, d, *J* = 7.2 Hz), 4.17-4.11 (2H, m), 3.97 (1H, dd, *J* = 11.6, 7.6 Hz), 3.83 (1H, d, *J* = 9.6 Hz), 3.80 (3H, s), 3.72-3.62 (2H, m), 3.52 (1H, dd, *J* = 12.0, 2.8 Hz), 3.48-3.43 (1H, m), 3.32 (3H, s), 3.03-2.70 (6H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 172.0 (C, *C*=O), 171.3 (C, *C*=O), 157.9 (C), 156.4 (C), 140.2 (C), 138.8 (C), 129.0 (CH), 128.5 (2 x CH), 128.4 (2 x CH), 128.0 (CH), 127.7 (CH), 127.64 (CH), 127.6 (2 x CH), 127.5 (2 x CH), 127.1 (CH), 126.5 (CH), 124.5 (C), 123.9 (C), 120.9 (CH), 119.8 (CH), 110.8 (CH), 109.3 (CH), 69.7 (CH), 68.7 (CH), 55.8 (CH), 55.0 (CH), 54.97 (CH_3), 50.0 (CH_3), 48.35 (2 x CH_2), 48.27 (CH_2), 46.9 (CH_2), 32.8 (CH_2), 32.3 (CH_2); LCMS



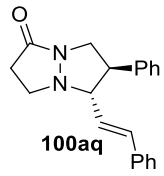
99ao **100ao**

m/z 307.15 (M-H$^+$), calcd for $C_{19}H_{19}N_2O_2$ 307.1452; Anal. Calcd. for $C_{19}H_{20}N_2O_2$ (308.1525): C, 74.00; H, 6.54; N, 9.08. Found: C, 74.12; H, 6.49; N, 9.15%.

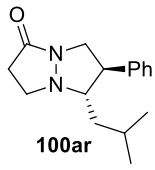
***cis*-5-(furan-2-yl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ap) and *trans*-5-(furan-2-yl)-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ap):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a white semi-solid. *dr* = 1:3.5; IR (Neat): 3029, 2956, 2896, 1697, 1496, 1455, 1422, 1346, 1271, 1208, 1179, 1150, 1085, 1031, 1012, 757, 701, 599 and 543 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.42 (2H, m), 7.38 (1H, s), 7.31-7.14 (10H, m), 6.32 (1H, dd, *J* = 3.2, 1.6 Hz), 6.27 (1H, d, *J* = 3.2 Hz), 6.11 (1H, dd, *J* = 2.8, 1.6 Hz), 4.21-4.04 (2H, m), 3.91-3.89 (3H, m), 3.79-3.50 (4H, m), 3.25-3.13 (4H, m), 2.81-2.70 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 172.1 (C, *C*=O), 171.4 (C, *C*=O), 149.0 (C), 148.8 (C), 143.2 (2 x CH), 142.1 (CH), 138.6 (C), 138.2 (C), 128.8 (2 x CH), 128.2 (CH), 128.0 (CH), 127.4 (CH), 127.3 (2 x CH), 127.0 (CH), 110.4 (2 x CH), 110.1 (CH), 109.5 (2 x CH), 70.97 (CH), 70.17 (CH), 51.9 (CH), 50.8 (CH), 47.8 (CH_2), 46.7 (CH_2), 32.7 (CH_2), 31.8 (CH_2); LCMS m/z 269.15 (M+H$^+$), calcd for $C_{16}H_{16}N_2O_2H$ 269.1290; Anal. Calcd. for $C_{16}H_{16}N_2O_2$ (268.1212): C, 71.62; H, 6.01; N, 10.44. Found: C, 71.52; H, 6.08; N, 10.36%.



***trans*-6-phenyl-5-((*E*)-styryl)tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100aq):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a white semi-solid. *dr* = 1:12; IR (Neat): 3028, 2925, 2896, 2852, 1698, 1495, 1452, 1354, 1083, 1031, 970, 746, 699 and 544 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31-7.19 (10H, m), 6.37 (1H, d, *J* = 16.0 Hz), 6.08 (1H, dd, *J* = 16.0, 8.0 Hz), 3.94 (1H, dd, *J* = 11.6, 7.6 Hz), 3.76 (1H, t, *J* = 11.2 Hz), 3.64-3.56 (2H, m), 3.12 (2H, td, *J* = 27.2, 8.8 Hz), 2.79 (2H, t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 172.1 (C, *C*=O), 138.3 (C), 135.9 (C), 134.9 (CH), 128.8 (2 x CH), 128.5 (2 x CH), 128.1 (CH), 127.7 (2 x CH), 127.4 (CH), 126.4 (2 x CH), 124.6 (CH), 76.7 (CH), 54.2 (CH), 47.8 (CH_2), 46.5 (CH_2), 31.9 (CH_2); HRMS m/z 305.1654 (M+H$^+$), calcd for $C_{20}H_{21}N_2OH$ 305.1654.

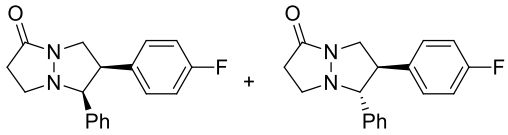


***trans*-5-isobutyl-6-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ar):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a colourless viscous liquid. *dr* = 1:11; IR (Neat): 3062, 3029, 2955, 2931, 2869, 1682, 1604, 1494, 1466, 1455, 1367, 1083, 766 and 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32-7.20 (5H, m), 4.19 (1H, dd, *J* = 11.5, 9.0 Hz), 3.74-3.63 (2H, m), 3.38 (1H, d, *J* = 10.0 Hz), 2.96-2.85 (2H, m), 2.81-2.70 (2H, m), 1.55-1.46 (1H, m), 1.02-0.93 (2H, m), 0.86 (3H, d, *J* = 6.5 Hz), 0.68 (3H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.3 (C,



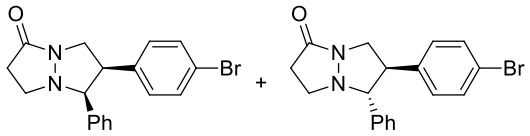
C=O), 140.4 (C), 128.9 (2 x CH), 128.3 (2 x CH), 127.1 (CH), 68.8 (CH), 50.2 (CH), 50.2 (CH_2), 48.3 (CH_2), 36.3 (CH_2), 34.1 (CH_2), 24.8 (CH), 23.3 (CH_3), 22.3 (CH_3); LCMS m/z 258.10 (M^+), calcd for $C_{16}H_{22}N_2O$ 258.1732; Anal. calcd. for $C_{16}H_{22}N_2O$ (258.1732): C, 74.38; H, 8.58; N, 10.84. Found: C, 74.46; H, 8.52; N, 10.78%.

***cis*-6-(4-fluorophenyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ba) and *trans*-6-(4-fluorophenyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ba):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as off white solid. *dr* = 1.4:1; IR (Neat): 3063, 3034, 2955, 2838, 1679, 1604, 1510, 1454, 1422, 1351, 1224, 1161, 1101, 832, 765, 732, 701, 598 and 550 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29-7.27 (2H, m), 7.16-7.14 (2H, m), 7.10-7.09 (3H, m), 7.04-7.01 (2H, m), 6.99-6.94 (7H, m), 6.78 (2H, t, *J* = 9.0 Hz), 4.33 (1H, dd, *J* = 12.0, 8.0 Hz), 3.97-3.90 (3H, m), 3.83 (1H, t, *J* = 10.0 Hz), 3.68-3.59 (3H, m), 3.57-3.50 (1H, m), 3.38 (1H, d, *J* = 10.0 Hz), 3.01-2.84 (3H, m), 2.83-2.71 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.7 (C, *C*=O), 170.8 (C, *C*=O), 162.0 (C, d, *J* = 243.7 Hz, *C*-F), 161.6 (C, d, *J* = 243.7 Hz, *C*-F), 135.9 (C), 135.1 (C, d, *J* = 3.7 Hz), 134.7 (C), 133.8 (C, d, *J* = 3.7 Hz), 130.2 (2 x CH, d, *J* = 8.7 Hz), 129.2 (2 x CH, d, *J* = 8.7 Hz), 128.6 (2 x CH), 128.3 (CH), 128.0 (2 x CH), 127.6 (2 x CH), 127.58 (2 x CH), 127.46 (CH), 115.6 (2 x CH, d, *J* = 21.2 Hz), 114.5 (2 x CH, d, *J* = 22.5 Hz), 78.2 (CH), 74.1 (CH), 56.2 (CH), 52.4 (CH), 48.4 (CH_2), 48.2 (CH_2), 48.0 (CH_2), 47.0 (CH_2), 33.2 (CH_2), 32.2 (CH_2); LCMS m/z 295.20 ($M\text{-}H^+$), calcd for $C_{18}H_{16}FN_2O$ 295.1252; Anal. calcd. for $C_{18}H_{17}FN_2O$ (296.1325): C, 72.95; H, 5.78; N, 9.45. Found: C, 72.85; H, 5.72; N, 9.38%.



99ba **100ba**

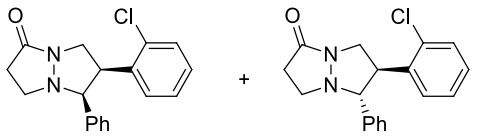
***cis*-6-(4-bromophenyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ca) and *trans*-6-(4-bromophenyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ca):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as an off white semi-solid. *dr* = 1:1; IR (KBr): ν_{max} 3029, 2954, 2896, 2838, 1677, 1489, 1454, 1352, 1207, 1128, 1010, 820, 750, 725, 701 and 547 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38 (2H, d, *J* = 8.4 Hz), 7.30-7.27 (3H, m), 7.21 (2H, d, *J* = 8.4 Hz), 7.18-7.14 (2H, m), 7.11-7.08 (3H, m), 6.96-6.88 (6H, m), 4.32 (1H, dd, *J* = 12.0, 8.4 Hz), 3.97-3.93 (2H, m), 3.88 (1H, dt, *J* = 8.8, 2.4 Hz), 3.82 (1H, t, *J* = 9.6 Hz), 3.66-3.55 (3H, m), 3.54-3.49 (1H, m), 3.37 (1H, d, *J* = 9.6 Hz), 3.02-2.87 (3H, m), 2.84-2.69 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.8 (C, *C*=O), 170.7 (C, *C*=O), 138.4 (C), 137.1 (C), 135.7 (C), 134.4 (C), 131.8 (2 x CH), 130.8 (2 x CH), 130.4 (2 x CH), 129.4 (2 x



99ca **100ca**

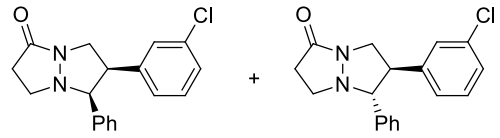
CH), 128.6 (2 x CH), 128.4 (CH), 128.0 (2 x CH), 127.6 (CH), 127.5 (2 x CH), 127.4 (2 x CH), 121.3 (C), 120.7 (C), 78.1 (CH), 73.9 (CH), 56.3 (CH), 52.5 (CH), 48.4 (CH_2), 48.0 (CH_2), 47.7 (CH_2), 46.9 (CH_2), 33.2 (CH_2), 33.13 (CH_2); LCMS m/z 357.95 ($M+H^+$), calcd for $C_{18}H_{17}BrN_2OH$ 357.0603; Anal. calcd. for $C_{18}H_{17}BrN_2O$ (356.0524): C, 60.52; H, 4.80; N, 7.84. Found: C, 60.42; H, 4.86; N, 7.78%.

***cis*-6-(2-chlorophenyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99da) and *trans*-6-(2-chlorophenyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100da):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow viscous oil. *dr* = 1:1; IR (KBr): ν_{max} 3062, 2974, 2897, 2838, 1680, 1478, 1454, 1422, 1351, 1206, 1180, 1127, 1042, 753, 734, 701 and 557 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.53 (1H, d, *J* = 7.6 Hz), 7.33 (1H, d, *J* = 7.2 Hz), 7.27-7.11 (9H, m), 7.08-7.00 (7H, m), 4.70-4.65 (1H, m), 4.37-4.30 (2H, m), 4.02 (1H, d, *J* = 7.2 Hz), 3.94-3.85 (2H, m), 3.62-3.49 (4H, m), 3.06-2.86 (3H, m), 2.83-2.71 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.8 (C, *C*=O), 171.0 (C, *C*=O), 136.9 (C), 135.8 (C), 135.7 (C), 134.2 (C), 134.17 (C), 134.0 (C), 129.9 (CH), 129.8 (CH), 128.6 (CH), 128.5 (2 x CH), 128.46 (CH), 128.3 (CH), 128.0 (CH), 127.9 (2 x CH), 127.5 (6 x CH), 127.3 (CH), 126.4 (CH), 76.4 (CH), 73.5 (CH), 52.3 (CH), 48.2 (CH_2), 47.9 (CH_2), 47.5 (CH), 47.5 (CH_2), 46.7 (CH_2), 33.1 (CH_2), 32.1 (CH_2); LCMS m/z 312.00 (M^+), calcd for $C_{18}H_{17}ClN_2O$ 312.1029; Anal. calcd. for $C_{18}H_{17}ClN_2O$ (312.1029): C, 69.12; H, 5.48; N, 8.96. Found: C, 69.23; H, 5.42; N, 8.89%.



99da **100da**

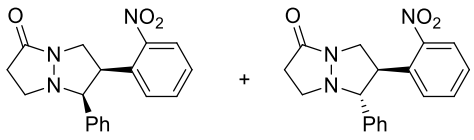
***cis*-6-(3-chlorophenyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ea) and *trans*-6-(3-chlorophenyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ea):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a semi-solid. *dr* = 1.2:1; IR (KBr): ν_{max} 3062, 3029, 2954, 2925, 2852, 1677, 1597, 1572, 1454, 1433, 1422, 1349, 1206, 1179, 1083, 1031, 785, 754, 699 and 531 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.27 (3H, m), 7.21-7.16 (4H, m), 7.10-7.01 (6H, m), 6.99-6.93 (4H, m), 6.86 (1H, d, *J* = 7.6 Hz), 4.33 (1H, dd, *J* = 11.6, 8.8 Hz), 3.96 (1H, d, *J* = 7.2 Hz), 3.93-3.86 (2H, m), 3.82 (1H, t, *J* = 11.2 Hz), 3.68-3.58 (3H, m), 3.55-3.49 (1H, m), 3.42 (1H, d, *J* = 9.6 Hz), 3.03-2.88 (3H, m), 2.82-2.69 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.7 (C, *C*=O), 170.9 (C, *C*=O), 141.4 (C), 140.2 (C), 135.7 (C), 134.5 (C), 134.4 (C), 133.6 (C), 130.0 (CH), 128.9 (CH), 128.8 (CH), 128.6 (2 x CH), 128.4 (CH), 128.0 (2 x CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.52 (2 x CH), 127.5 (2 x CH), 127.0 (CH), 126.8 (CH), 125.9 (CH), 77.9 (CH), 73.9 (CH), 56.5 (CH), 52.8 (CH), 48.2 (CH_2), 47.9



99ea **100ea**

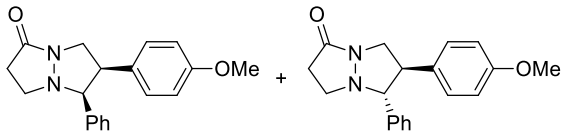
(CH_2), 47.8 (CH_2), 46.9 (CH_2), 33.1 (CH_2), 32.1 (CH_2); LCMS m/z 312.15 (M^+), calcd for $C_{18}H_{17}ClN_2O$ 312.1029; Anal. calcd. for $C_{18}H_{17}ClN_2O$ (312.1029): C, 69.12; H, 5.48; N, 8.96. Found: C, 69.21; H, 5.42; N, 8.89%.

***cis*-6-(2-nitrophenyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99fa) and *trans*-6-(2-nitrophenyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100fa):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as off white solid. Mp 108-110 °C (**6fa**) and 140-144 °C (**7fa**); *dr* = 1.4:1; IR (Neat): ν_{max} 3431, 2968, 2932, 1733, 1701, 1457, 1309, 1161, 1115, 1061, 1036, 965, 923, 770 and 654 cm^{-1}; **For compound 99fa:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (1H, d, *J* = 7.2 Hz), 7.53-7.50 (2H, m), 7.27-7.22 (1H, m), 7.10-7.04 (3H, m), 6.98 (2H, dd, *J* = 8.0, 1.2 Hz), 4.96 (1H, dt, *J* = 8.0, 2.8 Hz), 4.39 (1H, dd, *J* = 12.0, 8.8 Hz), 4.08 (1H, d, *J* = 7.2 Hz), 3.65-3.58 (2H, m), 2.99-2.87 (2H, m), 2.81-2.75 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.4 (C, *C*=O), 149.6 (C), 134.1 (C), 133.9 (C), 132.3 (2 x CH), 130.7 (2 x CH), 128.0 (CH), 127.8 (CH), 127.75 (CH), 127.74 (CH), 123.9 (CH), 73.4 (CH), 48.3 (CH_2), 48.2 (CH_2), 46.0 (CH), 33.0 (CH_2); **For compound 100fa:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67-7.59 (3H, m), 7.38 (1H, t, *J* = 7.4 Hz), 7.28 (3H, d, *J* = 5.2 Hz), 7.17-7.16 (2H, m), 4.38 (1H, dd, *J* = 17.2, 9.6 Hz), 4.02-3.88 (2H, m), 3.58 (1H, d, *J* = 9.6 Hz), 3.54-3.49 (1H, m), 3.04 (1H, dd, *J* = 19.4, 8.4 Hz), 2.83-2.79 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 172.6 (C, *C*=O), 150.4 (C), 135.0 (C), 133.1 (CH), 132.9 (C), 128.8 (2 x CH), 128.77 (CH), 128.6 (CH), 128.2 (CH), 127.5 (2 x CH), 124.4 (CH), 77.3 (CH), 50.3 (CH), 48.6 (CH_2), 46.3 (CH_2), 31.7 (CH_2); LCMS m/z 324.00 ($M+H^+$), calcd for $C_{18}H_{17}N_3O_3H$ 324.1348; Anal. calcd. for $C_{18}H_{17}N_3O_3$ (323.1270): C, 66.86; H, 5.30; N, 13.00. Found: C, 66.72; H, 5.36; N, 13.15%.



99fa **100fa**

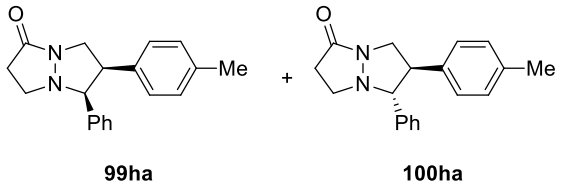
***cis*-6-(4-methoxyphenyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ga) and *trans*-6-(4-methoxyphenyl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ga):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a colourless liquid. *dr* = 1.3:1; IR (Neat): ν_{max} 3032, 2954, 2901, 2836, 1677, 1611, 1513, 1455, 1422, 1353, 1303, 1247, 1180, 1114, 1032, 829, 766, 735, 701, 599 and 552 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (3H, br s), 7.16 (2H, br s), 7.08 (3H, br s), 6.98-6.91 (6H, m), 6.79 (2H, d, *J* = 8.0 Hz), 6.63 (2H, d, *J* = 8.0 Hz), 4.30 (1H, dd, *J* = 11.0, 8.0 Hz), 3.95-3.88 (3H, m), 3.81 (1H, t, *J* = 10.5 Hz), 3.76 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.65-3.57 (3H, m), 3.54-3.49 (1H, m), 3.39 (1H, d, *J* = 9.5 Hz), 3.00-2.83 (3H, m), 2.81-2.69 (3H, m); ^{13}C



99ga **100ga**

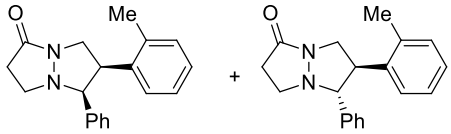
NMR ($CDCl_3$, DEPT-135) δ 171.1 (C, *C*=O), 170.4 (C, *C*=O), 158.8 (C), 158.2 (C), 136.2 (C), 135.0 (C), 131.4 (C), 129.9 (C), 129.7 (2 x CH), 128.7 (2 x CH), 128.5 (2 x CH), 128.1 (CH), 127.8 (2 x CH), 127.7 (2 x CH), 127.5 (2 x CH), 127.3 (CH), 114.0 (2 x CH), 113.1 (2 x CH), 78.2 (CH), 74.4 (CH), 56.1 (CH), 55.1 (CH_3), 55.0 (CH_3), 52.3 (CH), 48.7 (CH_2), 48.2 (CH_2), 48.0 (CH_2), 47.4 (CH_2), 33.4 (CH_2), 32.5 (CH_2); LCMS m/z 307.15 ($M\text{-}H^+$), calcd for $C_{19}H_{19}N_2O_2$ 307.1452; Anal. calcd. for $C_{19}H_{20}N_2O_2$ (308.1525): C, 74.00; H, 6.54; N, 9.08. Found: C, 74.16; H, 6.49; N, 9.15%.

***cis*-5-phenyl-6-(*p*-tolyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (99ha) and *trans*-5-phenyl-6-(*p*-tolyl)tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ha):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a yellow semi-solid. *dr* = 1.4:1; IR (KBr): ν_{max} 2953, 2923, 2853, 1677, 1603, 1515, 1454, 1350, 1215, 1031, 814, 751, 699, 665, 598 and 549 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28-7.26 (3H, m), 7.17-7.16 (2H, m), 7.09-7.06 (5H, m), 6.97-6.94 (4H, m), 6.89 (4H, br s), 4.31 (1H, dd, *J* = 11.5, 8.5 Hz), 3.98-3.88 (3H, m), 3.82 (1H, t, *J* = 11.0 Hz), 3.67-3.52 (3H, m), 3.51-3.47 (1H, m), 3.42 (1H, d, *J* = 9.5 Hz), 3.00-2.85 (3H, m), 2.83-2.70 (3H, m), 2.30 (3H, s, PhC*H*$_3$), 2.21 (3H, s, PhC*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.2 (C, *C*=O), 170.4 (C, *C*=O), 137.1 (C), 136.3 (C), 136.2 (2 x C), 135.02 (C), 135.0 (C), 129.4 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.46 (2 x CH), 128.2 (CH), 127.84 (2 x CH), 127.8 (2 x CH), 127.6 (2 x CH), 127.5 (2 x CH), 127.3 (CH), 78.2 (CH), 74.5 (CH), 56.5 (CH), 52.7 (CH), 48.7 (CH_2), 48.1 (CH_2), 48.0 (CH_2), 47.4 (CH_2), 33.5 (CH_2), 32.5 (CH_2), 21.0 (CH_3, PhC*H*$_3$), 20.9 (CH_3, PhC*H*$_3$); LCMS m/z 293.10 ($M+H^+$), calcd for $C_{19}H_{20}N_2OH$ 293.1654; Anal. calcd. for $C_{19}H_{20}N_2O$ (292.1576): C, 78.05; H, 6.89; N, 9.58. Found: C, 78.15; H, 6.83; N, 9.49%.



99ha **100ha**

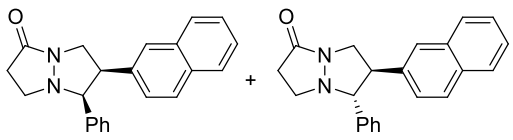
***cis*-5-phenyl-6-(*o*-tolyl)tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ia) and *trans*-5-phenyl-6-(*o*-tolyl)tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ia):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a semi-solid. *dr* = 2:1; IR (KBr): ν_{max} 3062, 3024, 2972, 2896, 2837, 1677, 1603, 1492, 1454, 1349, 1206, 1030, 852, 751, 730, 700, 665, 600, 560 and 458 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48 (1H, d, *J* = 8.0 Hz), 7.35 (1H, d, *J* = 8.0 Hz), 7.25-7.22 (2H, m), 7.18-7.15 (4H, m), 7.10-7.08 (2H, m), 7.05-6.98 (4H, m), 6.93 (2H, d, *J* = 7.5 Hz), 6.80 (2H, d, *J* = 7.5 Hz), 4.32-4.27 (2H, m), 4.04-3.99 (1H, m), 3.95-3.91 (2H, m), 3.81 (1H, t, *J* = 10.5 Hz), 3.68 (1H, d, *J* = 9.5 Hz), 3.56-3.49 (2H, m), 3.46 (1H, d, *J* = 9.5Hz), 3.02-2.71 (6H, m), 1.80 (3H, s, PhC*H*$_3$), 1.74 (3H, s, PhC*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.4 (C, *C*=O),



99ia **100ia**

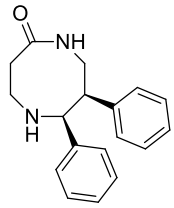
170.3 (C, *C*=O), 137.5 (C), 136.5 (C), 136.2 (C), 136.0 (2 x C), 134.4 (C), 130.2 (CH), 129.4 (CH), 128.4 (2 x CH), 128.3 (CH), 128.1 (CH), 128.07 (2 x CH), 127.6 (2 x CH), 127.5 (2 x CH), 127.1 (CH), 126.9 (CH), 126.6 (CH), 126.58 (CH), 126.4 (CH), 125.6 (CH), 78.2 (CH), 74.2 (CH), 51.8 (CH), 48.5 (CH_2), 48.2 (CH_2), 48.18 (CH_2), 47.3 (CH), 47.0 (CH_2), 33.4 (CH_2), 33.3 (CH_2), 19.5 (CH_3, Ph*C*H_3), 19.2 (CH_3, Ph*C*H_3); LCMS m/z 293.10 ($M+H^+$), calcd for $C_{19}H_{20}N_2OH$ 293.1654; Anal. calcd. for $C_{19}H_{20}N_2O$ (292.1576): C, 78.05; H, 6.89; N, 9.58. Found: C, 78.16; H, 6.83; N, 9.49%.

***cis*-6-(naphthalen-2-yl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (99ja) and *trans*-6-(naphthalen-2-yl)-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (100ja):** Prepared following the procedure **A** followed by procedure **B** and purified by column chromatography using EtOAc/hexane and isolated as a white semi-solid. *dr* = 1.2:1; IR (KBr): ν_{max} 3056, 2955, 2895, 2838, 1679, 1454, 1358, 1216, 858, 819, 748, 700 and 479 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80-7.77 (2H, m), 7.72-7.66 (3H, m), 7.55 (1H, d, *J* = 8.4 Hz), 7.47-7.43 (4H, m), 7.38 (2H, t, *J* = 3.6 Hz), 7.25-7.21 (4H, m), 7.17-7.16 (3H, m), 6.98 (5H, br s), 4.39 (1H, t, *J* = 10.0 Hz), 4.12-4.09 (2H, m), 4.02 (1H, d, *J* = 6.4 Hz), 3.92-3.80 (2H, m), 3.75 (1H, d, *J* = 11.6 Hz), 3.67-3.52 (3H, m), 3.05-2.89 (3H, m), 2.86-2.72 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.5 (C, *C*=O), 170.6 (C, *C*=O), 136.9 (C), 136.1 (C), 135.4 (C), 134.7 (C), 133.2 (C), 132.8 (C), 132.6 (C), 132.1 (C), 128.7 (CH), 128.6 (2 x CH), 128.2 (CH), 127.9 (2 x CH), 127.6 (4 x CH), 127.56 (CH), 127.5 (2 x CH), 127.46 (CH), 127.4 (CH), 127.37 (CH), 127.3 (CH), 127.0 (CH), 126.9 (CH), 126.2 (CH), 125.9 (CH), 125.8 (CH), 125.5 (CH), 125.3 (CH), 78.0 (CH), 74.3 (CH), 57.1 (CH), 53.2 (CH), 48.6 (CH_2), 48.2 (CH_2), 48.0 (CH_2), 47.2 (CH_2), 33.4 (CH_2), 32.4 (CH_2); LCMS m/z 329.35 ($M+H^+$), calcd for $C_{22}H_{20}N_2OH$ 329.1654; Anal. calcd. for $C_{22}H_{20}N_2O$ (328.1576): C, 80.46; H, 6.14; N, 8.53. Found: C, 80.32; H, 6.21; N, 8.46%.



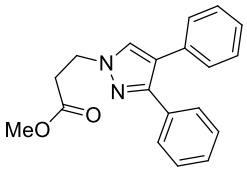
99ja **100ja**

***cis*-6,7-diphenyl-1,5-diazocan-2-one (101aa):** Prepared following the procedure **C** and purified by column chromatography using EtOAc/hexane and isolated as a colourless viscous liquid. IR (Neat): 3223, 3060, 3027, 2944, 2892, 1656, 1462 , 1398, 1301, 1219, 1180, 773, 700 and 543 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.18-7.05 (8H, m), 6.69-6.67 (2H, m), 6.11 (1H, s), 4.26 (1H, m), 3.97 (1H, d, *J* = 3.5 Hz), 3.37-3.24 (2H, m), 3.10 (1H, t, *J* = 12.5 Hz), 3.04-3.00 (1H, m), 2.87 (1H, td, *J* = 12.0, 4.0 Hz), 2.47 (1H, d, *J* = 6.0 Hz), 1.80 (1H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 177.4 (C, *C*=O), 143.0 (C), 138.3 (C), 129.2 (CH), 127.8 (2 x CH), 127.7 (2 x CH), 126.9 (CH), 126.5 (4 x CH), 64.2 (CH), 55.3 (CH), 48.7 (CH_2), 45.5 (CH_2), 38.5 (CH_2); LCMS m/z 281.1681 ($M+H^+$), calcd for $C_{18}H_{20}N_2OH$ 281.1654.



101aa

Methyl 3-(3,4-diphenyl-1*H*-pyrazol-1-yl)propanoate (103aa): Prepared following the procedure **D** and purified by column chromatography using EtOAc/hexane and isolated as a colourless liquid. IR (Neat): 2951, 1738, 1604, 1556, 1510, 1437, 1369, 1322, 1262, 1204, 1178, 1102, 992, 961, 851, 770, 698, 576 and 517 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (1H, s), 7.46-7.44 (3H, m), 7.34-7.32 (2H, m), 7.22-7.12 (5H, m), 4.30 (2H, t, *J* = 7.2 Hz), 3.65 (3H, s, OC*H*$_3$), 2.89 (2H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 171.3 (C, *C*=O), 139.9 (C), 138.1 (CH), 132.8 (C), 130.2 (2 x CH), 130.16 (C), 128.99 (2 x CH), 128.96 (CH), 128.3 (2 x CH), 127.3 (2 x CH), 126.0 (CH), 121.0 (C), 51.9 (CH_3), 44.7 (CH_2), 34.2 (CH_2); LCMS m/z 307.1508 ($M+H^+$), calcd for $C_{19}H_{18}N_2O_2H$ 307.1447.



103aa

3. General experimental procedures for Catalytic Ynone-Amidine Formal [4+2] Cycloaddition for the Regioselective Synthesis of Tricyclic Heterocycles

Procedure A: General procedure for formal [4+2]-Cycloaddition of ynones and amidines: To an ordinary glass vial with inner cap, equipped with a magnetic stirring bar, containing a solution of 0.3 mmol of ynone **56** in acetonitrile (1.5 mL), 0.03 mmol (10 mol%, 10.1 mg) of $Ca(OTf)_2$ **69n** was added under nitrogen atmosphere. The reaction mixture was capped and stirred at 25 ^{o}C for 20 seconds followed by additions of 0.39 mmol (1.3 equiv.) of amidine **3** under a nitrogen flow. The reaction mixture was again capped and stirred at 40 ^{o}C till completion. The progress of the reaction was monitored by running the TLC plate first in 1:9 (EtOAc:Hexane) solution to check the complete consumption of **56** and then running the same TLC plate in 4:6 (EtOAc:Hexane) to view the product formation. After completion of the reaction, the crude reaction mixture was diluted with chloroform and evaporated under reduced pressure. The dry crude reaction mixture was further directly loaded on to a silica gel column by dissolving in minimum amount of chloroform. The pure final product **105** was obtained by flash chromatography using EtOAc and Hexane as eluents changing the eluent (EtOAc:Hexane) in ratio 0:1, 1:9, 1.5:8.5, 2:8, 2.5:7.5 and 3:7. Owing to the nature of product sticking to silica gel, the column was completed in a time frame of 20 minutes to get maximum yield of **105**.

Procedure B: General procedure for bromination and in situ dehydrobromination of cycloadducts 105: In an ordinary glass vial equipped with a magnetic stirring bar, a solution of 0.16 mmol of **105** in dichloromethane (1 mL) was taken. The stirred reaction mixture was cooled to 0 ^{o}C followed by dropwise addition of 0.0098 mL (0.19 mmol, 30.5 mg, 1.2 equiv.) of bromine. The reaction mixture was stirred at 0 ^{o}C and monitored for completion by running the spotted TLC plate in 3:7 (EtOAc:Hexane) solution. On completion, the reaction mixture was quenched with saturated sodium thiosulfate solution followed by extraction of the aqueous layer with dichloromethane (2 x 20 mL). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated. Pure product **116** was obtained by gravity column chromatography using EtOAc and Hexane mixture as eluent.

Procedure C: Procedure for synthesis of 188ce from 105ce: To an ordinary glass vial with inner cap, equipped with a magnetic stirring bar, containing a solution of 0.2 mmol (77.8 mg) of adduct **105ce** in MeOH (1 mL), 0.1076 mL of 6 N NaOH (3.4 equiv. of NaOH) aqueous solution was added. The reaction mixture was capped and stirred at 35 ^{o}C for 4 days. The reaction completion was monitored by running the spotted TLC plate in 0.25:9.75 (EtOH:CHCl3) solution. On completion of the reaction, the crude reaction mixture was diluted with chloroform and evaporated under reduced pressure. The dry crude reaction mixture was further directly loaded on to a silica gel column by dissolving in minimum amount of chloroform. The pure final product **118ce** was obtained in 95 % yield (60.0 mg) by silica gel flash column chromatography using EtOH and chloroform as the eluent mixture.

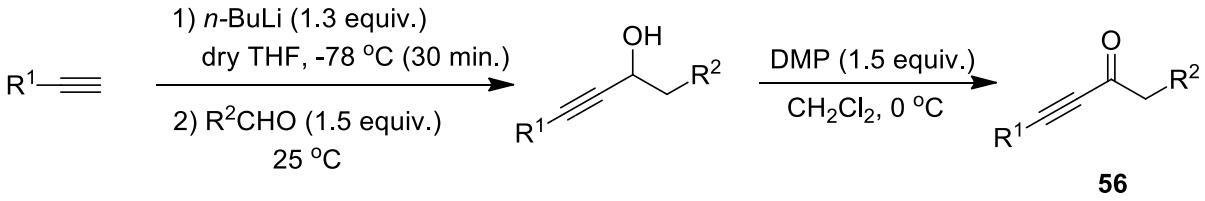
Procedure D: General procedure for synthesis of ynones 56a, 56b, 56o, 56p and 56m: In a 25mL round bottomed flask 2.5 mmol (500 mg) of 4-oxo-6-phenylhex-5-ynoic acid, dimethylaminopyridine (DMAP) (30.2 mg, 0.25 mmol, 0.1 equiv.) and 5 mmol (2 equiv.) of alcohol were taken in 8 mL of dry DCM under nitrogen atmosphere. The reaction mixture was stirred at 25 ^{o}C for 1 minute followed by addition of 662.4 mg (3.2 mmol, 1.3 equiv.) of dicyclohexylcarbodiimde (DCC) under nitrogen atmosphere. This reaction mixture was stirred at 25 ^{o}C till its completion as monitored by TLC. Upon completion, the reaction mixture was filtered and the residue was washed with diethyl ether repeatedly until it turns completely white.

The washings and the filtrate were collected, dried on anhydrous Na2SO4, evaporated under reduced pressure and pure ynone was obtained through silica gel column chromatography using EtOAc/Hexane as eluent mixture. For synthesis of ynone **56o**, 6-(4-fluorophenyl)-4-oxohex-5-ynoic acid and ethanol were used as reactants in the aforementioned procedure.

Procedure E: Procedure for synthesis of ynone 56n: In a 50 mL round bottomed flask mixture of 2.5 mmol (500 mg) of 4-oxo-6-phenylhex-5-ynoic acid and anhydrous K_2CO_3 (342.3 mg, 2.5 mmol, 1 equiv.) were taken in 10 mL dry acetone under nitrogen atmosphere. After stirring this reaction mixture for 2 minutes at 25 ^oC, 0.32 mL (2.7 mmol, 464.7 mg, 1.1 equiv.) of benzyl bromide was added and the reaction mixture was refluxed at 60 ^oC for 12 h under nitrogen atmosphere. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was filtered, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Pure ynone **56n** was obtained as a colourless liquid in 40 % yield (723 mg) after silica gel column chromatography using EtOAc/Hexane as eluent.

Procedure F: General procedure for synthesis of ynones 56c, 56d, 56e, 56k, 56l and 56q:[51] These ynones were prepared according to the Scheme 11 as described in reference 51.

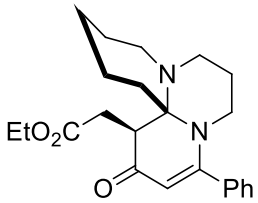
Scheme 11



Procedure G: General procedure for synthesis of ynones 56f, 56g, 56h, 56i and 56j:[52] To a solution of iodoarene (4.4 mmol, 1.1 equiv.) in diisopropylamine (5.3 mL, 38 mmol, 9.5 equiv.) was added bis(triphenylphosphine)palladium(II) dichloride (210 mg, 0.30 mmol, 0.7 mol%) and copper(I) iodide (195 mg, 1.03 mmol, 1.4 mol%). To the resultant mixture was added pent-1-yn-3-ol (336.4 mg, 4 mmol, 1.0 equiv.). The reaction mixture was allowed to come to room temperature (25 ^oC) and stirred at this temperature till completion. Reaction progress was monitored by TLC and the reaction components were visualized through U.V. light and KMnO4 stain. After completion the reaction mixture was concentrated and loaded directly onto a silica

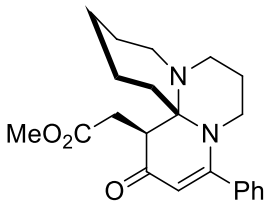
gel column. Pure ynone products were obtained by flash column chromatography using EtOAc/Hexane mixture as eluent.

***cis*-ethyl 2-(-2-oxo-4-phenyl-1,2,6,7,8,10,11,12,13,14-decahydropyrido[2',1':2,3] pyrimido [1,2-*a*]azepin-1-yl)acetate (105ae):** Prepared following the procedure A and isolated as a colourless gummy liquid. Yield: 87% (99.8 mg). IR (Neat): ν_{max} 2923, 2852, 1730, 1634, 1580, 1538, 1493, 1450, 1432, 1193, 1154, 1026, 793, 764, 701 and 665 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.35 (3H, m), 7.33-7.31 (2H, m), 5.08 (1H, s, olefinic-*H*), 4.23-4.12 (2H, m), 3.90 (1H, dd, *J* = 9.2, 4.0 Hz), 3.61 (1H, dt, *J* = 12.5, 3.8 Hz), 3.44 (1H, ddd, *J* = 12.8, 9.0, 4.0 Hz), 3.30 (1H, ddd, *J* = 12.5, 5.0, 1.8 Hz), 3.08 (1H, dd, *J* = 15.0, 10.4 Hz), 2.91-2.80 (2H, m), 2.76 (1H, dd, *J* = 15.6, 9.2 Hz), 2.68-2.64 (1H, m), 2.26 (1H, dd, *J* = 15.6, 4.0 Hz), 1.92-1.86 (1H, m), 1.81-1.61 (6H, m), 1.55-1.48 (2H, m), 1.28 (3H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.1 (C, *C*=O), 173.2 (C, O-*C*=O), 162.4 (C), 137.2 (C), 129.8 (CH), 128.5 (2 x CH), 128.1 (2 x CH), 101.1 (olefinic-*C*H), 80.4 (C, N-*C*-N), 60.4 (CH_2), 53.2 (CH_2), 49.3 (CH), 45.5 (CH_2), 45.0 (CH_2), 31.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 27.8 (CH_2), 24.6 (CH_2), 23.2 (CH_2), 14.1 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{29}N_2O_3H$ 383.2335; Found : 383.2336.



105ae

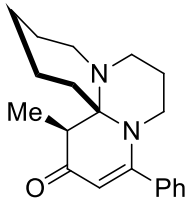
***cis*-methyl 2-(-2-oxo-4-phenyl-1,2,6,7,8,10,11,12,13,14-decahydropyrido[2',1':2,3]pyrimido [1,2-*a*]azepin-1-yl)acetate (105be):** Prepared following the procedure A and isolated as a colourless gummy liquid. Yield: 70% (99.8 mg). IR (Neat): ν_{max} 2921, 2850, 1735, 1636, 1580, 1539, 1493, 1451, 1434, 1363, 1310, 1221, 1196, 1160, 1015, 981, 929, 827, 794, 768, 733 and 702 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.34 (3H, m), 7.32-7.29 (2H, m), 5.06 (1H, s, olefinic-*H*), 3.89 (1H, dd, *J* = 9.3, 4.0 Hz), 3.70 (3H. s), 3.60 (1H, dt, *J* = 12.6, 4.0 Hz), 3.43 (1H, ddd, *J* = 12.8, 9.0, 4.0 Hz), 3.29 (1H, ddd, *J* = 12.6, 5.2, 2.0 Hz), 3.07 (1H, dd, *J* = 15.0, 10.3 Hz), 2.91-2.74 (3H, m), 2.68-2.62 (1H, m), 2.26 (1H, dd, *J* = 15.7, 4.0 Hz), 1.92-1.85 (1H, m), 1.80-1.60 (6H, m), 1.55-1.49 (2H, m). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.9 (C, *C*=O), 173.6 (C, O-*C*=O), 162.4 (C), 137.2 (C), 129.8 (CH), 128.4 (2 x CH), 128.0 (2 x CH), 101.0



105be

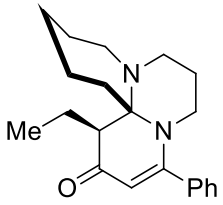
(olefinic-*C*H), 80.4 (C, N-*C*-N), 53.1 (CH_2), 51.6 (CH_3), 49.3 (CH), 45.5 (CH_2), 44.9 (CH_2), 31.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.8 (CH_2), 24.5 (CH_2), 23.2 (CH_2). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{28}N_2O_3Na$ 391.1998; Found : 391.1997.

***cis*-1-methyl-4-phenyl-6,7,8,10,11,12,13,14-octahydropyrido[2',1':2,3]pyrimido[1,2-*a*]azepin-2(1*H*)-one (105ce):** Prepared following the procedure A and isolated as a colourless liquid. Yield: 84% (78.2 mg). IR (Neat): ν_{max} 2922, 2852, 1639, 1611, 1541, 1492, 1450, 1433, 1360, 1239, 1218, 1194, 1154, 1104, 1055, 1018, 984, 926, 831, 793, 765 and 701 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.34 (5H, m), 5.13 (1H, s, olefinic-*H*), 3.71 (1H, dt, *J* = 12.6, 3.2 Hz), 3.33 (1H, ddd, *J* = 11.9, 9.3, 2.7 Hz), 3.29 (1H, q, *J* = 7.0 Hz), 3.23 (1H, ddd, *J* = 12.2, 4.5, 2.0 Hz), 3.16 (1H, dd, *J* = 15.0, 11.2 Hz), 2.96 (1H, td, *J* = 7.8, 11.3 Hz), 2.78-2.73 (1H, m), 2.70 (1H, td, *J* = 15.1, 1.6 Hz), 1.93-1.87 (1H, m), 1.84-1.61 (5H, m), 1.52-1.44 (2H, m), 1.28-1.20 (1H, m), 1.13 (3H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135) δ 196.7 (C, *C*=O), 162.0 (C), 137.5 (C), 129.7 (CH), 128.4 (2 x CH), 128.1 (2 x CH), 101.9 (olefinic-*C*H), 80.2 (C, N-*C*-N), 52.1 (CH_2), 46.4 (CH), 46.0 (CH_2), 45.2 (CH_2), 31.6 (CH_2), 29.5 (CH_2), 26.9 (CH_2), 25.4 (CH_2), 23.0 (CH_2), 9.0 (CH_3). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{26}N_2ONa$ 333.1943; Found : 333.1945.



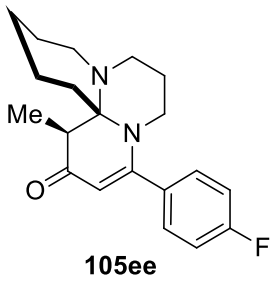
105ce

***cis*-1-ethyl-4-phenyl-6,7,8,10,11,12,13,14-octahydropyrido[2',1':2,3]pyrimido[1,2-*a*]azepin-2(1*H*)-one (105de):** Prepared following the procedure A and isolated as a colourless liquid. Yield: 83% (80.7 mg). IR (Neat): ν_{max} 2925, 2853, 1628, 1452, 1264, 734 and 704 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.32 (5H, m), 5.08 (1H, s, olefinic-*H*), 3.61 (1H, dt, *J* = 12.9, 2.6 Hz), 3.32 (1H, br s), 3.25 (1H, ddd, *J* = 12.5, 4.6, 1.8 Hz), 3.19 (1H, dd, *J* = 15.0, 11.4 Hz), 3.01-2.96 (2H, m), 2.82 (1H, dd, *J* = 14.9, 3.7 Hz), 2.73-2.68 (1H, m), 1.89 (1H, br d, *J* = 47.9 Hz), 1.79-1.68 (5H, m), 1.64-1.61 (1H, m), 1.57-1.50 (2H, m), 1.44-1.37 (1H, m), 1.30-1.23 (1H, m), 1.10 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 196.9 (C, *C*=O), 161.8 (C), 137.6 (C), 129.5 (CH), 128.4 (2 x CH), 128.0 (2 x CH), 102.3 (olefinic-*C*H), 81.2 (C, N-*C*-N), 54.1 (CH), 53.2 (CH_2), 45.7 (2 x CH_2), 45.5 (CH_2), 29.3 (CH_2), 27.7 (CH_2), 25.3 (CH_2), 23.2 (CH_2), 17.6



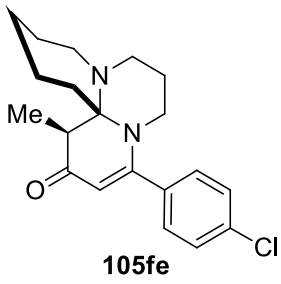
105de

(CH_2), 15.0 (CH_3). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{28}N_2ONa$ 347.2099; Found : 347.2098.

***cis*-4-(4-fluorophenyl)-1-methyl-6,7,8,10,11,12,13,14-octahydropyrido[2',1':2,3]pyrimido [1,2-*a*]azepin-2(1*H*)-one (105ee):** 

105ee

Prepared following the procedure A and isolated as a colourless oily liquid. Yield: 76% (74.8 mg). IR (Neat): ν_{max} 2918, 2849, 1727, 1632, 1602, 1545, 1506, 1444, 1372, 1265, 1219, 1156, 1104, 847, 737 and 704 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34-7.31 (2H, m), 7.08-7.04 (2H, m), 5.09 (1H, s, olefinic-*H*), 3.70 (1H, dt, *J* = 12.6, 3.0 Hz), 3.32 (1H, ddd, *J* = 11.8, 9.4, 2.6 Hz), 3.26 (1H, q, *J* = 7.1 Hz), 3.20-3.17 (1H, m), 3.15 (1H, dd, *J* = 14.7, 11.4 Hz), 2.96 (1H, td, *J* = 8.0, 11.2 Hz), 2.74-2.68 (2H, m), 1.94-1.87 (1H, m), 1.81 (1H, d, *J* = 13.6 Hz), 1.73-1.62 (4H, m), 1.51-1.43 (2H, m), 1.28-1.18 (1H, m), 1.12 (3H, d, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 196.7 (C, *C*=O), 163.6 (C, d, *J* = 248.6 Hz), 160.9 (C), 133.5 (C, d, *J* = 3.4 Hz), 130.0 (2 x CH, d, *J* = 8.2 Hz), 115.6 (2 x CH, d, *J* = 21.6 Hz), 102.1 (olefinic-*C*H), 80.3 (C, N-*C*-N), 52.2 (CH_2), 46.5 (CH), 46.1 (CH_2), 45.3 (CH_2), 31.7 (CH_2), 29.6 (CH_2), 27.0 (CH_2), 25.4 (CH_2), 23.1 (CH_2), 9.0 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{25}FN_2OH$ 329.2029; Found : 329.2029.

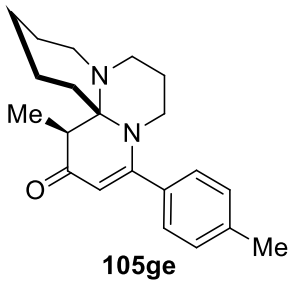
***cis*-4-(4-chlorophenyl)-1-methyl-6,7,8,10,11,12,13,14-octahydropyrido[2',1':2,3]pyrimido [1,2-*a*]azepin-2(1*H*)-one (105fe):** 

105fe

Prepared following the procedure A and isolated as a colourless oily liquid. Yield: 80% (82.7 mg). IR (Neat): ν_{max} 2924, 2853, 1623, 1594, 1572, 1490, 1438, 1358, 1238, 1213, 1080, 1064, 1313, 964, 842 and 728 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36 (2H, d, *J* = 8.7 Hz), 7.28 (2H, d, *J* = 8.4 Hz), 5.11 (1H, s, olefinic-*H*), 3.71 (1H, dt, *J* = 12.6, 3.2 Hz), 3.33 (1H, ddd, *J* = 12.0, 9.3, 2.6 Hz), 3.27 (1H, q, *J* = 7.1 Hz), 3.20-3.13 (2H, m), 2.97 (1H, td, *J* = 8.0, 11.3 Hz), 2.74-2.68 (2H, m), 1.95-1.88 (1H, m), 1.83-1.69 (4H, m), 1.67-1.62 (1H, m), 1.51-1.43 (2H, m), 1.30-1.19 (1H, m), 1.12 (3H, d, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 196.8 (C, *C*=O), 160.8 (C), 136.0 (C), 135.8 (C), 129.5 (2 x CH), 128.8 (2 x CH), 102.1 (olefinic-*C*H), 80.3 (C, N-*C*-N), 52.2 (CH_2), 46.5 (CH), 46.1 (CH_2), 45.2 (CH_2), 31.7 (CH_2), 29.6 (CH_2), 27.0 (CH_2), 25.4 (CH_2), 23.1 (CH_2),

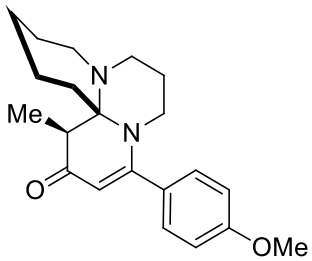
9.0 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{25}ClN_2OH$ 345.1734; Found : 345.1735.

***cis*-1-methyl-4-(*p*-tolyl)-6,7,8,10,11,12,13,14-octahydropyrido[2',1':2,3]pyrimido[1,2-*a*]azepin-2(1*H*)-one (105ge):** Prepared following the procedure A and isolated as a colourless liquid. Yield: 68% (66.2 mg). IR (Neat): ν_{max} 2924, 2852, 1628, 1541, 1508, 1451, 1361, 1264, 737 and 703 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.24 (2H, d, *J* = 8.0 Hz), 7.18 (2H, d, *J* = 7.9 Hz), 5.13 (1H, s, olefinic-*H*), 3.71 (1H, dt, *J* = 12.6, 3.2 Hz), 3.34 (1H, ddd, *J* = 12.0, 9.4, 2.8 Hz), 3.29-3.25 (2H, m), 3.17 (1H, dd, *J* = 15.0, 11.1 Hz), 2.96 (1H, td, *J* = 7.8, 11.2 Hz), 2.79-2.74 (1H, m), 2.70 (1H, td, *J* = 15.2, 1.7 Hz), 2.37 (3H, s), 1.93-1.86 (1H, m), 1.84-1.81 (1H, m), 1.76-1.68 (3H, m), 1.67-1.61 (1H, m), 1.53-1.44 (2H, m), 1.28-1.21 (1H, m), 1.13 (3H, d, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135) δ 196.8 (C, *C*=O), 162.2 (C), 140.0 (C), 134.6 (C), 129.2 (2 x CH), 128.2 (2 x CH), 101.6 (olefinic-*C*H), 80.2 (C, N-*C*-N), 52.2 (CH_2), 46.5 (CH), 46.1 (CH_2), 45.3 (CH_2), 31.7 (CH_2), 29.6 (CH_2), 27.0 (CH_2), 25.5 (CH_2), 23.1 (CH_2), 21.3 (CH_3), 9.1 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{28}N_2OH$ 325.2280; Found : 325.2280.



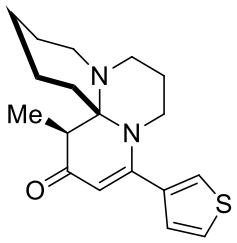
105ge

***cis*-4-(4-methoxyphenyl)-1-methyl-6,7,8,10,11,12,13,14-octahydropyrido[2',1':2,3]pyrimido [1,2-*a*]azepin-2(1*H*)-one (105he):** Prepared following the procedure A and isolated as a colourless liquid. Yield: 78% (79.6 mg). IR (Neat): ν_{max} 2926, 2852, 1626, 1606, 1542, 1508, 1440, 1360, 1264, 1174, 1107, 1031, 842 and 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30 (2H, d, *J* = 8.5 Hz), 6.90 (2H, d, *J* = 8.9 Hz), 5.13 (1H, s, olefinic-*H*), 3.83 (3H, s), 3.72 (1H, dt, *J* = 12.6, 3.2 Hz), 3.36-3.26 (3H, m), 3.16 (1H, dd, *J* = 15.1, 11.1 Hz), 2.97 (1H, td, *J* = 7.9, 11.3 Hz), 2.79-2.68 (2H, m), 1.95-1.87 (1H, m), 1.85-1.61 (5H, m), 1.54-1.43 (2H, m), 1.29-1.18 (1H, m), 1.13 (3H, d, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 196.6 (C, *C*=O), 161.8 (C), 160.9 (C), 129.6 (C), 129.6 (2 x CH), 113.8 (2 x CH), 101.3 (olefinic-*C*H), 80.0 (C, N-*C*-N), 55.2 (CH_3), 52.1 (CH_2), 46.4 (CH), 46.1 (CH_2), 45.2 (CH_2), 31.6 (CH_2), 29.5 (CH_2), 26.9 (CH_2), 25.4 (CH_2), 23.1 (CH_2), 9.0 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{28}N_2O_2H$ 341.2229; Found : 341.2229.



105he

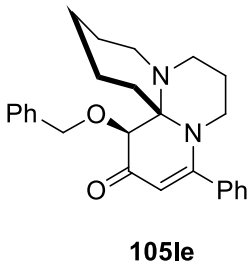
***cis*-1-methyl-4-(thiophen-3-yl)-6,7,8,10,11,12,13,14-octahydropyrido[2',1':2,3]pyrimido**



105je

[1,2-*a*]azepin-2(1*H*)-one (105je): Prepared following the procedure A and isolated as a colourless oily liquid. Yield: 75% (71.2 mg). IR (Neat): ν_{max} 2923, 2853, 1624, 1549, 1528, 1442, 1368, 1242, 1220, 1156, 1104, 797 and 697 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44 (1H, dd, *J* = 3.0, 1.1 Hz), 7.34 (1H, dd, *J* = 5.0, 3.0 Hz), 7.06 (1H, dd, *J* = 5.0, 1.0 Hz), 5.21 (1H, s, olefinic-*H*), 3.75 (1H, dt, *J* = 12.5, 3.2 Hz), 3.42 (1H, ddd, *J* = 12.3, 4.7, 2.2 Hz), 3.34 (1H, ddd, *J* = 12.0, 9.3, 2.7 Hz), 3.27 (1H, q, *J* = 7.1 Hz), 3.16 (1H, dd, *J* = 15.1, 11.2 Hz), 2.98 (1H, td, *J* = 7.9, 11.3 Hz), 2.76-2.64 (2H, m), 1.99-1.90 (1H, m), 1.82-1.62 (5H, m), 1.54-1.43 (2H, m), 1.28-1.21 (1H, m), 1.13 (3H, d, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 196.9 (C, *C*=O), 156.4 (C), 138.8 (C), 127.3 (CH), 126.0 (2 x CH), 101.2 (olefinic-*C*H), 80.1 (C, N-*C*-N), 52.2 (CH_2), 46.6 (CH), 46.1 (CH_2), 45.2 (CH_2), 31.7 (CH_2), 29.5 (CH_2), 26.9 (CH_2), 25.4 (CH_2), 23.1 (CH_2), 9.0 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{24}N_2OSH$ 317.1688; Found : 317.1686.

***cis*-1-(benzyloxy)-4-phenyl-6,7,8,10,11,12,13,14-octahydropyrido[2',1':2,3]pyrimido[1,2-**

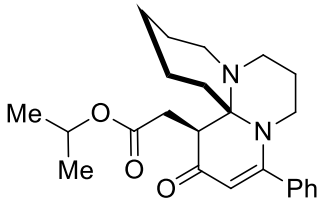


105le

***a*]azepin-2(1*H*)-one (105le):** Prepared following the procedure A and isolated as a colourless gummy liquid. Yield: 38% (45.8 mg). IR (Neat): ν_{max} 1919, 2849, 1639, 1540, 1451, 1264, 896, 733 and 703 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.45 (2H, d, *J* = 7.1 Hz), 7.41-7.28 (8H, m), 5.17 (1H, d, *J* = 11.6 Hz), 5.00 (1H, s, olefinic-*H*), 4.67 (1H, d, *J* = 11.6 Hz), 4.64 (1H, s), 3.69 (1H, dt, *J* = 12.7, 3.3 Hz), 3.50 (1H, dd, *J* = 15.0, 11.6 Hz), 3.16 (1H, ddd, *J* = 12.2, 4.6, 1.8 Hz), 2.89-2.74 (3H, m), 2.52 (1H, d, *J* = 15.2 Hz), 1.89-1.77 (3H, m), 1.74-1.68 (2H, m), 1.63-1.54 (2H, m), 1.46-1.37 (1H, m), 1.29-1.20 (1H, m). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 195.6 (C, *C*=O), 162.4 (C), 138.5 (C), 137.2 (C), 130.0 (CH), 128.8 (2 x CH), 128.5 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 127.6 (CH), 100.1 (olefinic-*C*H), 80.2 (C, N-*C*-N), 79.7 (CH), 74.3 (CH_2), 51.8 (CH_2), 45.8 (CH_2), 45.0 (CH_2), 31.5 (CH_2), 29.7 (CH_2),

27.9 (CH_2), 25.3 (CH_2), 22.8 (CH_2). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{30}N_2O_2H$ 403.2386; Found : 403.2386.

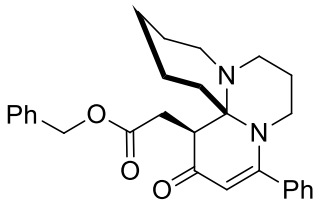
isopropyl-2-(*cis*-2-oxo-4-phenyl-1,2,6,7,8,10,11,12,13,14-decahydropyrido[2',1':2,3]



105me

pyrimido[1,2-*a*]azepin-1-yl)acetate (105me): Prepared following the procedure A and isolated as a colourless gummy liquid. Yield: 74% (87.9 mg). IR (Neat): ν_{max} 2922, 2851, 1725, 1634, 1581, 1540, 1494, 1451, 1434, 1374, 1310, 1266, 1222, 1195, 1166, 1107, 767, 736 and 702 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.35 (3H, m), 7.33-7.31 (2H, m), 5.08 (1H, s, olefinic-*H*), 5.04 (1H, sept, *J* = 6.2 Hz), 3.89 (1H, dd, *J* = 9.4, 3.9 Hz), 3.61 (1H, dt, *J* = 12.6, 3.8 Hz), 3.45 (1H, ddd, *J* = 12.6, 9.1, 3.8 Hz), 3.29 (1H, ddd, *J* = 12.5, 5.0, 1.8 Hz), 3.08 (1H, dd, *J* = 15.0, 10.5 Hz), 2.91-2.85 (1H, m), 2.82 (1H, dd, *J* = 14.9, 4.8 Hz), 2.72 (1H, dd, *J* = 15.6, 9.4 Hz), 2.68-2.64 (1H, m), 2.23 (1H, dd, *J* = 15.6, 3.9 Hz), 1.92-1.86 (1H, m), 1.82-1.61 (5H, m), 1.54-1.47 (2H, m), 1.30 (3H, d, *J* = 6.2 Hz), 1.26-1.21 (1H, m), 1.24 (3H, d, *J* = 6.3 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.2 (C, *C*=O), 172.7 (C, O-*C*=O), 162.4 (C), 137.2 (C), 129.8 (CH), 128.5 (2 x CH), 128.1 (2 x CH), 101.1 (olefinic-*C*H), 80.3 (C, N-*C*-N), 67.7 (CH), 53.1 (CH_2), 49.3 (CH), 45.6 (CH_2), 45.0 (CH_2), 31.7 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 27.9 (CH_2), 24.6 (CH_2), 23.2 (CH_2), 21.8 (CH_3), 21.6 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{32}N_2O_3H$ 397.2491; Found : 397.2492.

benzyl-2-(*cis*-2-oxo-4-phenyl-1,2,6,7,8,10,11,12,13,14-decahydropyrido[2',1':2,3]pyrimido

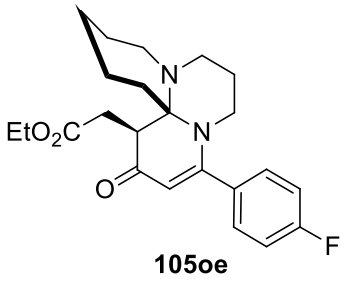


105ne

[1,2-*a*]azepin-1-yl)acetate (105ne): Prepared following the procedure A and isolated as a colourless gummy liquid. Yield: 72% (96.1 mg). IR (Neat): ν_{max} 2925, 1732, 1630, 1534, 1494, 1452, 1353, 1264, 1157, 896 and 703 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.30 (10H, m), 5.18 (2H, s, OC*H*$_2$Ph), 5.11 (1H, s, olefinic-*H*), 3.94 (1H, dd, *J* = 9.2, 4.0 Hz), 3.61 (1H, dt, *J* = 12.6, 3.8 Hz), 3.44 (1H, ddd, *J* = 12.8, 9.0, 4.0 Hz), 3.31 (1H, ddd, *J* = 12.7, 5.2, 1.9 Hz), 3.06 (1H, dd, *J* = 15.0, 10.4 Hz), 2.90-2.82 (2H, m), 2.78 (1H,

dd, *J* = 15.1, 4.9 Hz), 2.70-2.65 (1H, m), 2.33 (1H, dd, *J* = 15.8, 4.0 Hz), 1.93-1.86 (1H, m), 1.82-1.69 (4H, m), 1.65-1.60 (1H, m), 1.57-1.48 (2H, m), 1.32-1.24 (1H, m). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.0 (C, *C*=O), 173.1 (C, O-*C*=O), 162.5 (C), 137.3 (C), 136.2 (C), 129.8 (CH), 128.5 (2 x CH), 128.4 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 128.0 (CH), 101.1 (olefinic-*C*H), 80.5 (C, N-*C*-N), 66.4 (CH_2), 53.2 (CH_2), 49.4 (CH), 45.6 (CH_2), 45.0 (CH_2), 31.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 27.9 (CH_2), 24.6 (CH_2), 23.2 (CH_2). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{28}H_{32}N_2O_3Na$ 467.2311; Found : 467.2312.

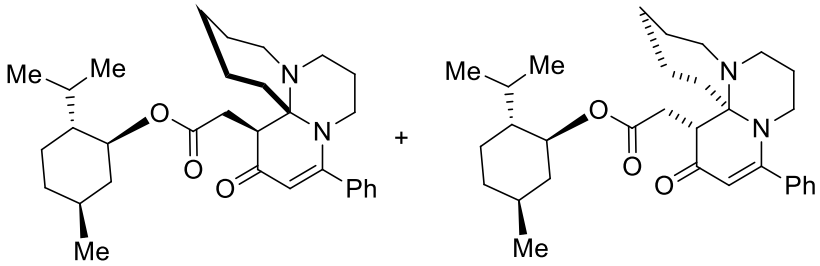
ethyl-2-(*cis*-4-(4-fluorophenyl)-2-oxo-1,2,6,7,8,10,11,12,13,14-decahydropyrido[2',1':2,3]



105oe

pyrimido[1,2-*a*]azepin-1-yl)acetate (105oe): Prepared following the procedure A and isolated as an off white solid with mp: 140-142 ^{o}C. Yield: 81% (97.3 mg). IR (Neat): ν_{max} 2925, 2853, 1730, 1637, 1599, 1543, 1505, 1440, 1363, 1283, 1310, 1223, 1193, 1155, 1096, 1028, 978, 849, 821, and 788 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34-7.31 (2H, m), 7.08 (2H, t, *J* = 8.6 Hz), 5.06 (1H, s, olefinic-*H*), 4.24-4.13 (2H, m), 3.89 (1H, dd, *J* = 9.3, 4.0 Hz), 3.62 (1H, dt, *J* = 12.5, 3.8 Hz), 3.45 (1H, ddd, *J* = 12.8, 9.0, 3.9 Hz), 3.27 (1H, ddd, *J* = 12.5, 5.1, 2.2 Hz), 3.09 (1H, dd, *J* = 15.1, 10.1 Hz), 2.93-2.86 (1H, m), 2.83 (1H, dd, *J* = 14.9, 4.8 Hz), 2.77 (1H, dd, *J* = 15.6, 9.3 Hz), 2.67-2.62 (1H, m), 2.26 (1H, dd, *J* = 15.7, 4.0 Hz), 1.95-1.88 (1H, m), 1.84-1.62 (5H, m), 1.55-1.48 (2H, m), 1.33-1.24 (1H, m), 1.30 (3H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.1 (C, *C*=O), 173.1 (C, O-*C*=O), 163.6 (C, d, *J* = 248.2 Hz), 161.3 (C), 133.2 (C, d, *J* = 2.3 Hz), 130.1 (2 x CH, d, *J* = 8.2 Hz), 115.6 (2 x CH, d, *J* = 21.6 Hz), 101.3 (olefinic-*C*H), 80.4 (C, N-*C*-N), 60.5 (CH_2), 53.1 (CH_2), 49.4 (CH), 45.7 (CH_2), 45.0 (CH_2), 31.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 28.0 (CH_2), 24.6 (CH_2), 23.2 (CH_2), 14.2 (CH_3). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{29}FN_2O_3Na$ 423.2060; Found : 423.2060.

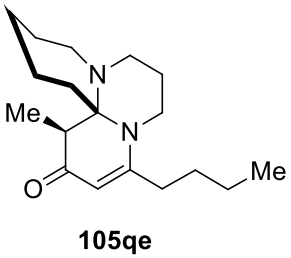
(-)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-((1*S*,14*aR*)-2-oxo-4-phenyl-1,2,6,7,8,10,11,12, 13,14-decahydropyrido [2',1':2,3]pyrimido[1,2-*a*]azepin-1-yl)acetate (105pe) and (-)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-((1*R*,14*aR*)-2-oxo-4-phenyl-1,2,6,7,8,10,11,12,13,14-decahydropyrido[2',1':2,3]pyrimido[1,2-*a*]azepin-1-yl) acetate (105′pe): Prepared



(-)-105pe **(-)-105'pe**

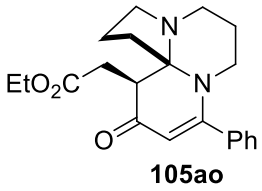
following the procedure A and isolated as a colourless oily liquid. Yield: 88% (129.9 mg). $[\alpha]_D^{25}$ = -18.41° (c = 0.201g/100mL, $CHCl_3$, 1:1 *dr*); IR (Neat): ν_{max} 2969, 2924, 2853, 1738, 1640, 1448, 1366, 1228, 1216, 901 and 527 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.31 (10H, m), 5.10 (1H, s, olefinic-*H*), 5.09 (1H, s, olefinic-*H*), 4.76-4.68 (2H, m), 3.90 (2H, dt, *J* = 9.5, 3.6 Hz), 3.65-3.58 (2H, m), 3.51-3.42 (2H, m), 3.31-3.28 (2H, m), 3.08 (2H, dd, *J* = 15.0, 10.5 Hz), 2.92-2.77 (4H, m), 2.73-2.65 (3H, m), 2.26-2.22 (2H, m), 2.16-2.08 (2H, m), 2.03-1.87 (6H, m), 1.77-1.62 (14H, m), 1.53-1.38 (8H, m), 1.30-1.22 (3H, m), 1.12-0.96 (4H, m), 0.92 (6H, d, *J* = 7.2 Hz), 0.89 (6H, d, *J* = 6.8 Hz), 0.82 (3H, d, *J* = 7.0 Hz), 0.76 (3H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.3 (C, *C*=O), 194.2 (C, *C*=O), 172.9 (C, O-*C*=O), 172.7 (C, O-*C*=O), 162.4 (C), 162.3 (C), 137.3 (C), 137.2 (C), 129.8 (CH), 129.7 (CH), 128.5 (2 x CH), 128.4 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 101.2 (olefinic-*C*H), 101.1 (olefinic-*C*H), 80.30 (C, N-*C*-N), 80.29 (C, N-*C*-N), 74.3 (CH), 74.2 (CH), 53.2 (CH_2), 53.1 (CH_2), 49.4 (CH), 49.1 (CH), 47.2 (CH), 46.9 (CH), 45.7 (CH_2), 45.6 (CH_2), 45.1 (2 x CH_2), 41.0 (CH_2), 40.4 (CH_2), 34.3 (CH_2), 34.2 (CH_2), 31.7 (2 x CH_2), 31.4 (CH), 31.3 (CH), 29.9 (CH_2), 29.7 (CH_2), 29.6 (2 x CH_2), 27.96 (CH_2), 27.94 (CH_2), 26.1 (CH), 26.0 (CH), 24.7 (2 x CH_2), 23.4 (CH_2), 23.3 (CH_2), 23.2 (CH_2), 23.18 (CH_2), 22.0 (CH_3), 21.9 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 16.3 (CH_3), 16.28 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{31}H_{44}N_2O_3H$ 493.3430; Found : 493.3437.

cis-4-butyl-1-methyl-6,7,8,10,11,12,13,14-octahydropyrido[2',1':2,3]pyrimido[1,2-*a*]azepin-2(1*H*)-one (105qe): Prepared following the procedure A and isolated as a colourless liquid. Yield: 42% (36.6 mg). IR (Neat): ν_{max} 2927, 2855, 1623, 1545, 1463, 1360, 1264, 1224, 1106 and 703 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.91 (1H, s, olefinic-*H*), 3.69 (1H, dt, *J* = 12.7, 3.8 Hz), 3.48 (1H, ddd, *J* = 12.6, 5.3, 1.4 Hz), 3.34 (1H, ddd, *J* = 12.9, 9.1, 4.4 Hz), 3.14 (1H, q, *J* = 7.1 Hz), 3.10 (1H, ddd, *J* = 15.2, 11.0, 0.8 Hz), 2.96-2.91 (1H, m), 2.75-2.71 (1H, m), 2.63-2.55 (1H, m), 2.35 (1H, ddd, *J* = 14.2, 8.0, 6.1 Hz), 2.09-1.98 (2H, m), 1.75-1.65 (2H, m), 1.61-1.54 (2H, m), 1.51-1.38 (5H, m), 1.36-1.28 (2H, m), 1.26-1.15 (1H, m), 1.05 (3H, t, *J* = 7.2 Hz), 0.89 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 196.3 (C, *C*=O), 162.5 (C), 99.5 (olefinic-*C*H), 81.1 (C, N-*C*-N), 52.6 (CH_2), 45.5 (CH), 44.8 (CH_2), 42.2 (CH_2), 34.4 (CH_2), 31.6 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 26.6 (CH_2), 25.4 (CH_2), 22.9 (CH_2), 22.1 (CH_2), 13.8 (CH_3), 9.1 (CH_3). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{30}N_2ONa$ 313.2256; Found : 313.2257.



105qe

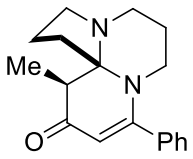
ethyl 2-(_cis_-11-oxo-9-phenyl-1,2,3,5,6,7,11,12-octahydropyrido[1,2-*a*]pyrrolo[2,1-b]pyrimidin-12-yl)acetate (105ao): Prepared following the procedure A and isolated as a colourless gummy liquid. Yield: 70% (74.4 mg). IR (Neat): ν_{max} 2977, 2945, 2870, 2824, 2824, 1726, 1629, 1582, 1536, 1496, 1451, 1370, 1301, 1211, 1237, 1155, 1125, 1075, 1029, 947, 916, 884, 748, 699, 663, 486 and 457 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.34 (5H, m), 5.30 (1H, s, olefinic-*H*), 4.17-4.05 (2H, m), 3.73 (1H, t, *J* = 6.2 Hz), 3.27-3.15 (3H, m), 3.09 (1H, ddd, *J* = 15.2, 10.2, 6.2 Hz), 3.02 (1H, dt, *J* = 7.8, 2.1 Hz), 2.89 (1H, dd, *J* = 16.0, 5.4 Hz), 2.83 (1H, ddd, *J* = 14.6, 7.0, 2.4 Hz), 2.22 (1H, dd, *J* = 16.0, 7.4 Hz), 2.15 (1H, ddd, *J* = 13.3, 9.1, 3.8 Hz), 2.03-1.92 (2H, m), 1.88-1.81 (1H, m), 1.79-1.71 (1H, m), 1.52-1.45 (1H, m), 1.24 (3H, dt, *J* = 7.0, 0.6 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.4 (C, *C*=O), 173.5 (C, O-*C*=O), 164.6 (C), 136.2 (C), 129.9 (CH), 128.5 (2 x CH), 127.6 (2 x CH), 105.3 (olefinic-*C*H), 82.4 (C, N-*C*-N), 60.1 (CH_2), 52.8 (CH_2), 46.4 (CH), 43.5 (CH_2), 39.7 (CH_2), 34.6 (CH_2), 29.4



105ao

(CH_2), 23.1 (CH_2), 19.9 (CH_2), 14.2 (CH_3). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{26}N_2O_3Na$ 377.1841; Found : 377.1841.

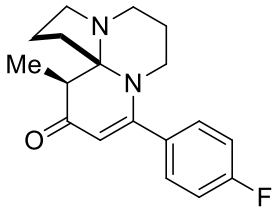
***cis*-12-methyl-9-phenyl-2,3,5,6,7,12-hexahydropyrido[1,2-*a*]pyrrolo[2,1-*b*]pyrimidin-11**



105co

(1*H*)-one (105co): Prepared following the procedure A and isolated as a colourless gummy liquid. Yield: 50% (42.3 mg). IR (Neat): ν_{max} 3056, 2936, 2866, 1654, 1632, 1626, 1562, 1495, 1451, 1368, 1322, 1213, 1174, 1110, 1063, 766, 731 and 702 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.43-7.37 (5H, m), 5.38 (1H, s, olefinic-*H*), 3.33 (1H, q, *J* = 8.6 Hz), 3.26-2.98 (6H, m), 2.16 (1H, ddd, *J* = 13.6, 9.3, 4.4 Hz), 2.08-1.97 (2H, m), 1.90-1.83 (1H, m), 1.78-1.69 (1H, m), 1.51-1.44 (1H, m), 1.08 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, DEPT-135) δ 197.3 (C, *C*=O), 164.5 (C), 136.5 (C), 129.9 (CH), 128.5 (2 x CH), 127.7 (2 x CH), 106.0 (olefinic-*C*H), 83.0 (C, N-*C*-N), 52.7 (CH_2), 43.9 (CH_2), 42.8 (CH), 39.8 (CH_2), 33.3 (CH_2), 23.0 (CH_2), 20.1 (CH_2), 7.9 (CH_3). HRMS (ESI-TOF) m/z: $[M + K]^+$ calcd for $C_{18}H_{22}N_2OK$ 321.1369; Found : 321.1367.

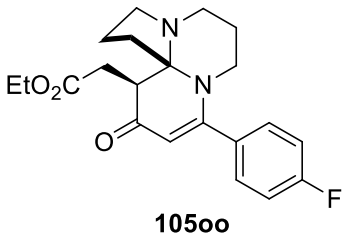
***cis*-9-(4-fluorophenyl)-12-methyl-2,3,5,6,7,12-hexahydropyrido[1,2-*a*]pyrrolo[2,1-*b*]**



105eo

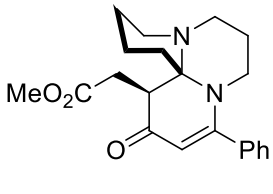
pyrimidin-11(1*H*)-one (105eo): Prepared following the procedure A and isolated as a colourless gummy liquid. Yield: 40% (36.0 mg). IR (Neat): 2918, 2850, 1639, 1600, 1569, 1506, 1453, 1411, 1368, 1323, 1217, 1157 and 846 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.39 (2H, m), 7.10-7.06 (2H, m), 5.39 (1H, d, *J* = 1.7 Hz, olefinic-*H*), 3.34 (1H, q, *J* = 7.7 Hz), 3.24-3.19 (1H, m), 3.17-2.99 (5H, m), 2.12 (1H, ddd, *J* = 13.6, 9.4, 4.4 Hz), 2.08-1.90 (2H, m), 1.89-1.82 (1H, m), 1.78-1.69 (1H, m), 1.49-1.42 (1H, m), 1.08 (3H, dd, *J* = 6.8, 0.8 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 197.5 (C, *C*=O), 163.8 (C, d, *J* = 248.7 Hz), 163.5 (C), 132.6 (C, d, *J* = 3.0 Hz), 129.7 (2 x CH, d, *J* = 8.6 Hz), 115.7 (2 x CH, d, *J* = 21.6 Hz), 107.2 (olefinic-*C*H), 82.7 (C, N-*C*-N), 52.6 (CH_2), 44.5 (CH_2), 42.4 (CH), 40.2 (CH_2), 33.7 (CH_2), 22.9 (CH_2), 20.0 (CH_2), 7.8 (CH_3). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{21}FN_2ONa$ 323.1536; Found : 323.1537.

ethyl 2-(*cis*-9-(4-fluorophenyl)-11-oxo-1,2,3,5,6,7,11,12-octahydropyrido[1,2-*a*]pyrrolo[2,1-*b*]pyrimidin-12-yl)acetate (105oo): Prepared following the procedure A and isolated as a colourless gummy liquid. Yield: 56% (62.5 mg). IR (Neat): ν_{max} 2926, 1727, 1630, 1602, 1543, 1506, 1372, 1265, 1235, 1156, 1030, 848, 736 and 704 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.39-7.35 (2H, m), 7.09-7.05 (2H, m), 5.33 (1H, s, olefinic-*H*), 4.18-4.06 (2H, m), 3.73 (1H, dd, *J* = 7.0, 5.8 Hz), 3.26 (1H, td, *J* = 6.9, 8.7 Hz), 3.19 (2H, t, *J* = 6.2 Hz), 3.12-3.06 (1H, m), 3.02 (1H, dt, *J* = 7.8, 2.8 Hz), 2.87 (1H, dd, *J* = 16.0, 5.6 Hz), 2.84 (1H, ddd, *J* = 14.6, 6.6, 2.8 Hz), 2.23 (1H, dd, *J* = 16.1, 7.2 Hz), 2.11 (1H, ddd, *J* = 13.5, 9.1, 4.1 Hz), 2.03-1.94 (2H, m), 1.88-1.81 (1H, m), 1.79-1.71 (1H, m), 1.50-1.43 (1H, m), 1.25 (3H, t, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 194.7 (C, *C*=O), 173.5 (C, O-*C*=O), 163.8 (C, d, *J* = 249.0 Hz), 163.8 (C), 132.2 (C, d, *J* = 3.4 Hz), 129.6 (2 x CH, d, *J* = 8.6 Hz), 115.7 (2 x CH, d, *J* = 21.7 Hz), 106.2 (olefinic-*C*H), 82.1 (C, N-*C*-N), 60.2 (CH_2), 52.7 (CH_2), 45.9 (CH), 44.1 (CH_2), 40.1 (CH_2), 34.9 (CH_2), 29.4 (CH_2), 23.1 (CH_2), 19.7 (CH_2), 14.2 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{25}FN_2O_3H$ 373.1927; Found : 373.1927.



105oo

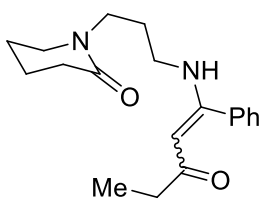
methyl 2-(*cis*-2-oxo-4-phenyl-2,6,7,8,10,11,12,13-octahydro-1*H*-dipyrido[1,2-*a*:2',1'-*b*]pyrimidin-1-yl)acetate (105bp): Prepared following the procedure A and isolated as a colourless oily liquid. Yield: 20% (21.3 mg). IR (Neat): ν_{max} 2932, 2857, 2360, 2341, 1734, 1636, 1580, 1540, 1494, 1449, 1434, 1310, 1281, 1163, 1099, 822, 768 and 703 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.44-7.37 (5H, m), 5.26 (1H, s, olefinic-*H*), 3.86 (1H, dd, *J* = 8.8, 3.0 Hz), 3.71 (3H, s), 3.55 (1H, dt, *J* = 13.3, 4.9 Hz), 3.42-3.34 (2H, m), 3.21 (1H, dt, *J* = 11.4, 3.5 Hz), 3.04-3.01 (1H, m), 2.71 (1H, dd, *J* = 16.4, 8.8 Hz), 2.64 (1H, ddd, *J* = 15.2, 10.2, 5.2 Hz), 2.59-2.53 (1H, m), 2.04-1.96 (1H, m), 1.88-1.76 (3H, m), 1.67-1.63 (1H, m), 1.55-1.37 (2H, m), 1.02 (1H, dt, *J* = 13.6, 4.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 193.9 (C, *C*=O), 174.2 (C, O-*C*=O), 163.8 (C), 136.9 (C), 130.1 (CH), 128.6 (2 x CH), 128.3 (2 x CH), 102.8 (olefinic-*C*H), 75.5 (C, N-*C*-N), 53.5 (CH_2), 51.7 (CH_3) 48.2 (CH), 44.4 (CH_2), 42.3 (CH_2), 29.2 (CH_2), 25.4



105bp

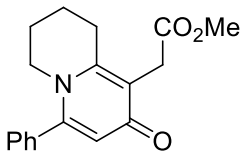
(CH_2), 24.8 (CH_2), 22.0 (CH_2), 20.6 (CH_2). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{26}N_2O_3Na$ 377.1841; Found : 377.1842.

1-(3-((3-oxo-1-phenylpent-1-en-1-yl)amino)propyl)piperidin-2-one (107cp): Prepared following the procedure A and isolated as a colourless liquid. Yield: 22% (20.7 mg). IR (Neat): ν_{max} 2931, 2871, 1635, 1605, 1567, 1483, 1350, 1293, 1178, 1132, 1050, 808, 573 and 703 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 10.81 (1H, br t, *J* = 5.8 Hz, -N*H*), 7.43-7.40 (3H, m), 7.34-7.32 (2H, m), 5.06 (1H, s, olefinic-*H*), 3.34 (2H, t, *J* = 7.2 Hz), 3.20-3.17 (2H, m), 3.15 (2H, q, *J* = 6.8 Hz), 2.34 (2H, q, *J* = 7.6 Hz), 2.32-2.29 (2H, m), 1.78-1.71 (6H, m), 1.12 (3H, t, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 199.6 (C, *C*=O), 169.8 (C, N-*C*=O), 165.2 (C), 135.4 (C), 129.3 (CH), 128.4 (2 x CH), 127.6 (2 x CH), 95.8 (olefinic-*C*H), 47.9 (CH_2), 44.5 (CH_2), 42.2 (CH_2), 35.1 (CH_2), 32.2 (CH_2), 28.4 (CH_2), 23.1 (CH_2), 21.2 (CH_2), 9.9 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{26}N_2O_2H$ 315.2073; Found : 315.2073.



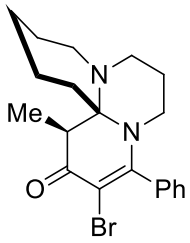
107cp

methyl 2-(8-oxo-6-phenyl-2,3,4,8-tetrahydro-1*H*-quinolizin-9-yl)acetate (109bq): Prepared following the procedure A and isolated as a colourless liquid. Yield: 28% (24.9 mg). IR (Neat): ν_{max} 2949, 1731, 1620, 1560, 1532, 1479, 1440, 1340, 1322, 1259, 1195, 1166, 863, 770 and 704 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.46-7.43 (3H, m), 7.32-7.30 (2H, m), 6.36 (1H, s, olefinic-*H*), 3.73 (3H, s), 3.69 (3H, s), 3.67 (2H, t, *J* = 5.8 Hz), 2.82 (2H, t, *J* = 6.8 Hz), 1.89-1.78 (4H, m). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 176.3 (C, *C*=O), 172.1 (C, N-*C*=O), 151.4 (C), 148.9 (C), 134.8 (C), 129.4 (CH), 128.8 (2 x CH), 128.5 (2 x CH), 121.0 (C), 117.6 (olefinic-*C*H), 51.9 (CH_3), 48.1 (CH_2), 30.3 (CH_2), 25.8 (CH_2), 22.0 (CH_2), 18.2 (CH_2). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{19}NO_3Na$ 320.1263; Found : 320.1263.



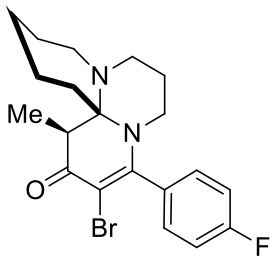
109bq

***cis*-3-bromo-1-methyl-4-phenyl-6,7,8,10,11,12,13,14-octahydropyrido[2',1':2,3]pyrimido [1,2-*a*]azepin-2(1*H*)-one (116ce):** Prepared following the procedure B and isolated as a yellow solid with mp: 155-160 ºC. Yield: 48% (29.9 mg). IR (Neat): ν_{max} 2925, 2859, 1644, 1520, 1489, 1443, 1417, 1369, 1258, 1211, 1160, 1053, 1028, 885, 772, and 701 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48-7.39 (3H, m), 7.18 (1H, d, *J* = 7.4 Hz), 7.02 (1H, d, *J* = 7.2 Hz), 3.20 (1H, td, *J* = 12.9, 3.8 Hz), 3.14 (1H, q, *J* = 7.0 Hz), 3.01-2.88 (3H, m), 2.82-2.75 (2H, m), 2.28-2.16 (2H, m), 1.93-1.84 (1H, m), 1.77-1.55 (6H, m), 1.47-1.41 (1H, m), 1.26 (3H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 189.8 (C, *C*=O), 160.5 (C), 136.8 (C), 129.0 (CH), 128.9 (CH), 128.7 (CH), 127.2 (CH), 126.6 (CH), 92.0 (C), 81.4 (C, N-*C*-N), 48.5 (CH_2), 46.3 (CH_2), 46.27 (CH), 44.9 (CH_2), 29.3 (CH_2), 26.7 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 20.9 (CH_2), 12.9 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{25}BrN_2OH$ 389.1229; Found : 389.1229.



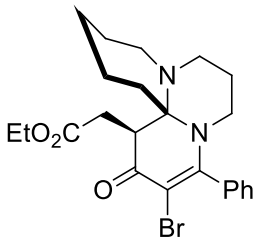
116ce

***cis*-3-bromo-4-(4-fluorophenyl)-1-methyl-6,7,8,10,11,12,13,14-octahydropyrido[2',1':2,3] pyrimido[1,2-*a*]azepin-2(1*H*)-one (116ee):** Prepared following the procedure B and isolated as a light yellow coloured liquid. Yield: 44% (28.7 mg). IR (Neat): ν_{max} 2924, 2853, 1646, 1602, 1525, 1496, 1436, 1360, 1206, 1156, 1101, 1058, 1016, 985, 869, 840, 799 and 732 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.26 (2H, br s), 7.14-7.10 (2H, m), 3.61 (1H, dt, *J* = 12.8, 3.3 Hz), 3.45 (1H, q, *J* = 7.1 Hz), 3.34 (1H, ddd, *J* = 12.2, 9.3, 2.9 Hz), 3.13 (1H, dd, *J* = 15.1, 10.8 Hz), 3.03 (1H, ddd, *J* = 12.4, 4.6, 2.1 Hz), 2.96 (1H, td, *J* = 7.6, 11.5 Hz), 2.73-2.69 (1H, m), 2.62 (1H, dd, *J* = 15.2, 8.4 Hz), 1.95-1.89 (1H, m), 1.83-1.62 (6H, m), 1.54 (1H, dd, *J* = 15.2, 10.4 Hz), 1.49-1.41 (1H, m), 1.19 (3H, d, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 189.6 (C, *C*=O), 163.3 (C, d, *J* = 248.5 Hz), 159.1 (C), 132.4 (C, d, *J* = 3.5 Hz), 130.9 (2 x CH, br s), 115.8 (2 x CH, d, *J* = 21.8 Hz), 93.5 (C), 80.4 (C, N-*C*-N), 52.3 (CH_2), 47.2 (CH), 46.9 (CH_2), 45.1 (CH_2), 31.6 (CH_2), 29.5 (CH_2), 27.4 (CH_2), 25.3 (CH_2), 23.0 (CH_2), 9.8 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{24}BrFN_2OH$ 407.1134; Found : 407.1130.



116ee

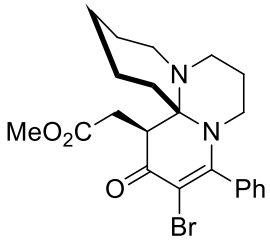
ethyl-2-(*cis*-3-bromo-2-oxo-4-phenyl-1,2,6,7,8,10,11,12,13,14-decahydropyrido[2',1':2,3]



116ae

pyrimido[1,2-a]azepin-1-yl)acetate (116ae): Prepared following the procedure B and isolated as a light yellow coloured liquid. Yield: 50% (36.9 mg). IR (Neat): ν_{max} 2923, 2852, 2360, 1730, 1646, 1518, 1487, 1441, 1371, 1203, 1160, 1028, 734 and 701 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45-7.39 (3H, m), 7.22 (2H, br s), 4.23-4.11 (2H, m), 4.07 (1H, dd, *J* = 9.8, 3.8 Hz), 3.51-3.42 (2H, m), 3.14-3.10 (1H, m), 3.06 (1H, dd, *J* = 15.0, 10.2 Hz), 2.89-2.83 (2H, m), 2.80 (1H, dd, *J* = 15.6, 9.6 Hz), 2.53 (1H, dd, *J* = 13.8, 8.4 Hz), 2.33 (1H, dd, *J* = 15.6, 3.6 Hz), 1.91-1.84 (1H, m), 1.79-1.59 (6H, m), 1.54-1.45 (1H, m), 1.34-1.27 (1H, m), 1.28 (3H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 187.4 (C, *C*=O), 172.8 (C, O-*C*=O), 160.7 (C), 136.2 (C), 129.6 (CH), 128.6 (2 x CH), 128.4 (2 x CH, br s), 91.8 (C), 80.8 (C, N-*C*-N), 60.6 (CH_2), 53.4 (CH_2), 49.7 (CH), 46.2 (CH_2), 44.7 (CH_2), 31.6 (CH_2), 30.2 (CH_2), 29.4 (CH_2), 28.2 (CH_2), 24.3 (CH_2), 23.1 (CH_2), 14.1 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{29}BrN_2O_3H$ 461.1440; Found : 461.1442.

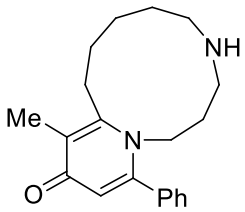
methyl-2-(*cis*-3-bromo-2-oxo-4-phenyl-1,2,6,7,8,10,11,12,13,14-decahydropyrido[2',1':2,3]



116be

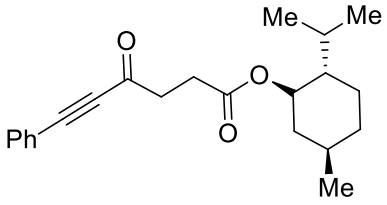
pyrimido[1,2-*a*]azepin-1-yl)acetate (116be): Prepared following the procedure B and isolated as a light yellow solid with mp: 160-162 °C. Yield: 64% (45.8 mg). IR (Neat): ν_{max} 3352, 2923, 1732, 1640, 1511, 1485, 1433, 1362, 1264, 1202, 1158, 1049, 1013, 979, 930, 761, 731 and 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45-7.42 (3H, m), 7.23 (2H, br s), 4.08 (1H, dd, *J* = 9.8, 3.6 Hz), 3.72 (3H, s), 3.52-3.42 (2H, m), 3.13 (1H, ddd, *J* = 12.8, 5.4, 1.6 Hz), 3.05 (1H, dd, *J* = 14.9, 10.0 Hz), 2.90-2.82 (2H, m), 2.81 (1H, dd, *J* = 15.6, 9.8 Hz), 2.54 (1H, dd, *J* = 14.2, 8.6 Hz), 2.35 (1H, dd, *J* = 15.6, 3.6 Hz), 1.91-1.85 (1H, m), 1.79-1.71 (4H, m), 1.67-1.59 (2H, m), 1.54-1.47 (1H, m), 1.35-1.25 (1H, m). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 187.4 (C, *C*=O), 173.2 (C, O-*C*=O), 160.8 (C), 136.2 (C), 129.7 (CH), 128.6 (2 x CH), 128.5 (2 x CH, br s), 91.8 (C), 80.8 (C, N-*C*-N), 53.4 (CH_2), 51.9 (CH_3), 49.7 (CH), 46.2 (CH_2), 44.7 (CH_2), 31.6 (CH_2), 30.0 (CH_2), 29.4 (CH_2), 28.2 (CH_2), 24.3 (CH_2), 23.1 (CH_2). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{27}BrN_2O_3H$ 447.1283; Found : 447.1285.

10-methyl-13-phenyl-2,3,4,5,6,7,8,9-octahydropyrido[1,2-*e*][1,5]diazacycloundecin-11(1*H*)-one (118ce): Prepared following the procedure C and isolated as a colourless liquid. Yield: 95% (60.0 mg). IR (Neat): ν_{max} 2925, 2851, 1617, 1599, 1534, 1489, 1463, 1372, 1258, 1206, 1147, 1049, 862, 767 and 704 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.44-7.42 (3H, m), 7.35-7.34 (2H, m), 6.25 (1H, s, olefinic-*H*), 4.48 (1H, br s), 3.74-3.72 (1H, m), 3.04-2.86 (3H, m), 2.52-2.39 (3H, m), 2.17 (3H, s), 1.74 (3H, p, *J* = 6.2 Hz), 1.51 (5H, br s). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 177.7 (C, *C*=O), 151.6 (C), 150.6 (C), 136.2 (C), 128.9 (CH), 128.6 (2 x CH), 128.3 (2 x CH), 125.0 (C), 117.5 (olefinic-*C*H), 46.6 (CH_2), 44.6 (CH_2), 43.4 (CH_2), 31.1 (CH_2), 29.7 (CH_2), 26.8 (CH_2), 26.0 (CH_2), 22.8 (CH_2), 11.8 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{26}N_2OH$ 311.2123; Found : 311.2123.



118ce

(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl-4-oxo-6-phenylhex-5-ynoate (56p): Prepared following the procedure D and isolated as a pale yellow coloured liquid. Yield: 23% (193.0 mg). IR (Neat): ν_{max} 2953, 2924, 2868, 2202, 1730, 1676, 1456, 1369, 1209, 1174, 1095, 983, 963, 758 and 689 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56-7. 54 (2H, m), 7.46-7.41 (1H, m), 7.38-7.33 (2H, m), 4.68 (1H, dt, *J* = 10.9, 4.4 Hz), 3.00-2.96 (2H, m), 2.69-2.65 (2H, m), 1.98-1.95 (1H, m), 1.90-1.83 (1H, m), 1.65-1.62 (2H, m), 1.50-1.33 (2H, m), 1.07-0.90 (2H, m), 0.87-0.85 (1H, m), 0.86 (6H, dd, *J* = 6.6, 2.0 Hz), 0.73 (3H, dd, *J* = 7.0, 2.0 Hz). ^{13}C NMR ($CDCl_3$, DEPT-135) δ 185.4 (C, *C*=O), 171.5 (C, O-*C*=O), 132.9 (2 x CH), 130.6 (CH), 128.5 (2 x CH), 119.7 (C), 91.1 (C), 87.3 (C), 74.6 (CH), 46.8 (CH), 40.7 (CH_2), 39.9 (CH_2), 34.1 (CH_2), 31.2 (CH), 28.4 (CH_2), 26.1 (CH), 23.3 (CH_2), 21.9 (CH_3), 20.6 (CH_3), 16.2 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{28}O_3H$ 341.2117; Found : 341.2116.



56p

7. REFERENCES

1. G. L'abbe´, A. Hassner, *J. Heterocycl. Chem*. **1970**, *7*, 361-366.
2. P. Ykvan, G. Mathys, G. L'abbe´, G. Syet, *J. Org. Chem*. **1972**, *97*, 3213-3216.
3. T. L. Gilchrist, G. E. Gymer, C. W. Rees**,** *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1-8.
4. Y. Nomura, Y. Takuechi, S. Tomoda, M. M. Ito, *Bull. Chem. Soc. Jpn.* **1981, *54,*** 261-266.
5. F. Shi, J. P. Waldo, Y. Chen, R. C. Larock, Org. Lett. **2008**, *10*, 2409-2412.
6. H. Nulwala, D. J. Burke, A. Khan, A. Serrano, C. J. Hawker, *Macromolecules* **2010**, *43*, 5474-5477.
7. E. P. J. Ng, Y.-F. Wang, B. W.-Q. Hui, G. Lapointe, S. Chiba, *Tetrahedron*, **2011,** 67, 7728-7737.
8. A. K. Shil, S. Kumar, S. Sharma, A. Chaudhary, P. Das, *RSC Adv*. **2015**, *5*, 11506-11514.
9. R. Shintani, G. C. Fu, *J. Am. Chem. Soc*. **2003**, *125*, 10778-10779.
10. W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang, and Y.-C. Chen, *Angew. Chem. Int. Ed*. **2007**, *46*, 7667-7670.
11. R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, J. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard, III, H. Guo, O. Kwon, *J. Am. Chem. Soc*. **2011**, *133*, 13337-13348.
12. Z. Li, H. Yu, H. Liu, L. Zhang, H. Jiang, B. Wang, H. Guo, *Chem. Eur. J.* **2014**, *20*, 1731-1736.
13. D. B. Ramachary, T. P. Reddy, A. S. Kumar, *Org. Biomol. Chem*. **2016**, *14*, 6517-6522.
14. X. Liu, Y. Wang, D. Yang, J. Zhang, D. Liu, W. Su, *Angew. Chem. Int. Ed*. **2016**, *55*, 1–5.
15. S. Yuan, Y. Luo, J. Peng, M. Miao, J. Xu, H. Ren, *Org. Lett.* **2017,** *19*, 6100-6103.
16. Z. Lian, Q.-Y. Zhao, Y. Wei, M. Shi, *Eur. J. Org. Chem.* **2012**, 3338-3341.
17. D. B. Ramachary, C. Venkaiah and P. M. Krishna, *Chem. Commun.* **2012**, *48*, 2252–2254.
18. D. B. Ramachary, C. Venkaiah, R. Madhavachary, *Org. Lett*. **2013**, *15*, 3042-3045.
19. Q. Wang, Z. Lian, Q. Xu, M. Shi, *Adv. Synth. Catal*. **2013**, *355*, 3344-3350.
20. X. Gao, Z. Li, W. Yang, Y. Liu, W. Chen, C. Zhang, L. Zheng, H. Guo, *Org. Biomol. Chem.* **2017**, *15*, 5298-5307.
21. For the applications of 1,2,3-triazoles, see: a) L. S. Kallander, et al. *J. Med. Chem.* **2005**, *48*, 5644-5647; b) S. Ito, A. Satoh, Y. Nagatomi, Y. Hirata, G. Suzuki, T. Kimura, A. Satow, S. Maehara, H. Hikichi, M. Hata, H. Kawamoto, H. Ohta, *Bioorg. Med. Chem.* **2008**, *16*, 9817–9829; c) S. Ito, Y. Hirata, Y. Nagatomi, A. Satoh, G. Suzuki, T. Kimura, A. Satow, S. Maehara, H. Hikichi, M. Hata, H. Ohta, H. Kawamoto, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5310–5313; d) T. Tsuritani, H. Mizuno, N. Nonoyama, S. Kii, A. Akao, K. Sato, N. Yasuda, T. Mase, *Org. Process Res. Dev.*

2009, *13*, 1407-1412; e) S. G. Agalave, S. R. Maujan, V. S. Pore, *Chem. Asian J.* **2011**, *6*, 2696–2718.

22. For the 1,2,3-triazoles as amide isosteres, see: a) Y. L. Angell, K. Burgess, *Chem. Soc. Rev.* **2007**, *36*, 1674–1689; b) A. Tam, U. Arnold, M. B. Soellner, R. T. Raines, *J. Am. Chem. Soc.* **2007**, *129*, 12670-12671; c) J. M. Holub, K. Kirshenbaum, *Chem. Soc. Rev.* **2010**, *39*, 1325–1337; d) I. E. Valverde, A. Bauman, C. A. Kluba, S. Vomstein, M. A. Walter, T. L. Mindt, *Angew. Chem.* **2013**, *125*, 9126–9129; *Angew. Chem. Int. Ed.* **2013**, *52*, 8957–8960.
23. For CuAAC reactions, see: a) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057-3064; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599; c) L. V. Lee, M. L. Mitchell, S. J. Huang, V. V. Fokin, K. B. Sharpless, C. H. Wong, *J. Am. Chem. Soc.* **2003**, *125*, 9588-9589; d) A. E. Speers, G. C. Adam, B. F. Cravatt, *J. Am. Chem. Soc.* **2003**, *125*, 4686-4687; e) J. -F. Lutz, Z. Zarafshani, *Adv. Drug Deliv. Rev.* **2008**, *60*, 958-970; For a strain-promoted AAC reactions, see: f) N. J. Agard, J. A. Preschner, C. R. Bertozzi, *J. Am. Chem. Soc.* **2004**, *126*, 15046-15047; g) N. J. Agard, J. M. Baskin, J. A. Prescher, A. Lo, C. R. Bertozzi, *ACS Chem. Biol.* **2006**, *1*, 644-648; h) J. M. Baskin, C. R. Bertozzi, *QSAR Comb. Sci.* **2007**, *26*, 1211-1219; i) S. T. Laughlin, J. M. Baskin, S. L. Amacher, C. R. Bertozzi, *Science* **2008**, *320*, 664-667; j) B. Gold, G. B. Dudley, I. V. Alabugin, *J. Am. Chem. Soc.* **2013**, *135*, 1558-1569; For the enamine-mediated organocatalytic [3+2]-cycloaddition reactions, see: k) D. B. Ramachary, K. Ramakumar, V. V. Narayana, *Chem. Eur. J.* **2008**, *14*, 9143–9147; l) M. Belkheira, D. E. Abed, J.-M. Pons, C. Bressy, *Chem. Eur. J.* **2011**, *17*, 12917–12921; m) L. J. T. Danence, Y. Gao, M. Li, Y. Huang, J. Wang, *Chem. Eur. J.* **2011**, *17*, 3584–3587; n) L. Wang, S. Peng, L. J. T. Danence, Y. Gao, J. Wang, *Chem. Eur. J.* **2012**, *18*, 6088–6093; o) N. Seus, L. C. Goncalves, A. M. Deobald, L. Savegnago, D. Alves, M. W. Paixao, *Tetrahedron* **2012**, *68*, 10456-10463; p) D. B. Ramachary, A. B. Shashank, *Chem. Eur. J.* **2013**, *19*, 13175–13181; q) W. Li, Q. Jia, Z. Du, J. Wang, *Chem. Commun.* **2013**, *49*, 10187-10189; r) D. K. J. Yeung, T. Gao, J. Huang, S. Sun, H. Guo, J. Wang, *Green Chem.* **2013**, *15*, 2384-2388; s) N. Seus, B. Goldani, E. J. Lenardão, L. Savegnago, M. W. Paixão, D. Alves, *Eur. J. Org. Chem*. **2014**, 1059–1065; t) W. Li, Z. Du, J. Huang, Q. Jia, K. Zhang, J. Wang, *Green Chem.* **2014**, *16*, 3003-3006; u) W. Li, Z. Du, K. Zhang, J. Wang, *Green Chem.* **2015**, *17*, 781-784; v) Q. Jia, G. Yang, L. Chen, Z. Du, J. Wei, Y. Zhong, J. Wang, *Eur. J. Org. Chem.* **2015**, 3435-3440; w) X. Xu, Z. Shi, W. Li, *New J. Chem.* **2016**, *40*, 6559-6563.
24. For the enamine-mediated organocatalytic click reactions, see: a) D. B. Ramachary, K. Ramakumar, V. V. Narayana, *Chem. Eur. J.* **2008**, *14*, 9143–9147; b) M. Belkheira, D. E. Abed,

J.-M. Pons, C. Bressy, *Chem. Eur. J.* **2011**, *17*, 12917–12921; c) L. J. T. Danence, Y. Gao, M. Li, Y. Huang, J. Wang, *Chem. Eur. J.* **2011**, *17*, 3584–3587; d) L. Wang, S. Peng, L. J. T. Danence, Y. Gao, J. Wang, *Chem. Eur. J.* **2012**, *18*, 6088–6093; e) N. Seus, L. C. Goncalves, A. M. Deobald, L. Savegnago, D. Alves, M. W. Paixao, *Tetrahedron* **2012**, *68*, 10456-10463; f) D. B. Ramachary, A. B. Shashank, *Chem. Eur. J.* **2013**, *19*, 13175–13181; g) W. Li, Q. Jia, Z. Du, J. Wang, *Chem. Commun.* **2013**, *49*, 10187-10189; h) D. K. J. Yeung, T. Gao, J. Huang, S. Sun, H. Guo, J. Wang, *Green Chem.* **2013**, *15*, 2384-2388; i) N. Seus, B. Goldani, E. J. Lenardão, L. Savegnago, M. W. Paixão, D. Alves, *Eur. J. Org. Chem*. **2014**, 1059–1065; j) W. Li, Z. Du, J. Huang, Q. Jia, K. Zhang, J. Wang, *Green Chem.* **2014**, *16*, 3003-3006; k) W. Li, Z. Du, K. Zhang, J. Wang, *Green Chem.* **2015**, *17*, 781-784; l) Q. Jia, G. Yang, L. Chen, Z. Du, J. Wei, Y. Zhong, J. Wang, *Eur. J. Org. Chem.* **2015**, 3435-3440; m) X. Xu, Z. Shi, W. Li, *New J. Chem.* **2016**, *40*, 6559-6563.

25. For the enolate-mediated organocatalytic click reactions, see: a) D. B. Ramachary, A. B. Shashank, S. Karthik, *Angew. Chem.* **2014**, *126*, 10588-10592; *Angew. Chem. Int. Ed.* **2014**, *53*, 10420–10424; b) A. B. Shashank, S. Karthik, R. Madhavachary, D. B. Ramachary, *Chem. Eur. J.* **2014**, *20*, 16877–16881; c) W. Li, J. Wang, *Angew. Chem.* **2014**, *126*, 14410–14414; *Angew. Chem. Int. Ed.* **2014**, *53*, 14186–14190; d) S. S. V. Ramasastry, *Angew. Chem.* **2014**, *126*, 14536-14538; *Angew. Chem. Int. Ed.* **2014**, *53*, 14310-14312; e) C. G. S. Lima, A. Ali, S. S. van Berkel, B. Westermann, M. W. Paixão, *Chem. Commun.* **2015**, *51*, 10784-10796; f) J. John, J. Thomas, W. Dehaen, *Chem. Commun.* **2015**, *51*, 10797-10806; g) P. M. Krishna, D. B. Ramachary, P. Sruthi, *RSC Adv.* **2015**, *5*, 62062-62066; h) D. B. Ramachary, P. M. Krishna, J. Gujral, G. S. Reddy, *Chem. Eur. J.* **2015**, *21*, 16775–16780; i) D. González-Calderón, A. Fuentes-Benítes, E. Díaz-Torres, C. A. González-González, C. González-Romero, *Eur. J. Org. Chem.* **2016**, 668–672; j) X. Zhou, X. Xu, K. Liu, H. Gao, W. Wang, W. Li, *Eur. J. Org. Chem.* **2016**, 1886–1890; k) X. Zhou, X. Xu, Z. Shi, K. Liu, H. Gao, W. Li, *Org. Biomol. Chem.* **2016**, *14*, 5246-5250; l) D. B. Ramachary, G. S. Reddy, S. Peraka, J. Gujral, *ChemCatChem* **2016**, *8*, 263-267; m) D. B. Ramachary, J. Gujral, S. Peraka, G. S. Reddy, *Eur. J. Org. Chem*., **2017**, 459-464.

26. For other metal-free methods, see: a) S. S. van Berkel, S. Brauch, L. Gabriel, M. Henze, S. Stark, D. Vasilev, L. A. Wessjohann, M. Abbas, B. Westermann, *Angew. Chem.* **2012**, *124*, 5437-5441; *Angew. Chem. Int. Ed.* **2012**, *51*, 5343-5346; b) Z. Chen, Q. Yan, Z. Liu, Y. Xu, Y. Zhang, *Angew. Chem.* **2013**, *125*, 13566-13570; *Angew. Chem. Int. Ed.* **2013**, *52*, 13324-13328; c) Z. –J. Cai, X. –M. Lu, Y. Zi, C. Yang, L. –J. Shen, J. Li, S. –Y. Wang, S. –J. Ji, *Org. Lett.* **2014**, *16*, 5108−5111; d) Z. Chen, Q. Yan, Z. Liu, Y. Zhang, *Chem. Eur. J.* **2014**, *20*, 17635–17639; e) J. Thomas, J.

John, N. Parekh, W. Dehaen, *Angew. Chem.* **2014**, *126*, 10319–10323; *Angew. Chem. Int. Ed.* **2014**, *53*, 10155–10159; f) A. Ali, A. G. Corrêa, D. Alves, J. Zukerman-Schpector, B. Westermann, M. A. B. Ferreira, M. W. Paixao, *Chem. Commun.* **2014**, *73*, 11926-11929; g) G. Cheng, X. Zeng, J. Shen, X. Wang, X. Cui, *Angew. Chem.* **2013**, *125*, 13507–13510; *Angew. Chem. Int. Ed.* **2013**, *52*, 13265–13268; h) J. John, J. Thomas, N. Parekh, W. Dehaen, *Eur. J. Org. Chem.* **2015**, 4922-4930; i) J. Thomas, V. Goyvaerts, S. Liekens, W. Dehaen, *Chem. Eur. J.* **2016**, *22*, 9966-9970.

27. a) N. Jung, S. Brase, *Angew. Chem. Int. Ed.* **2012**, *51*, 12169-12171 and references cited therein; b) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188-5240; c) G. L'abbe, *Chem. Rev.* **1969**, *69*, 345-363.

28. a) Y. Nomura, Y. Takeuchi, S. Tomoda, M. M. Ito, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 261-266; d) D. Sikora, T. Gajda, *Tetrahedron* **1998**, *54*, 2243-2250; b) S. Kamijo, Z. Huo, T. Jin, C. Kanazawa, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 6389-6397; c) H. Duan, W. Yan, S. Sengupta, X. Shi, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3899–3902; d) E. P. J. Ng, Y. –F. Wang, B. W. –Q. Hui, G. Lapointe, S. Chiba, *Tetrahedron* **2011**, *67*, 7728-7737; e) M. Kavitha, B. Mahipal, P. S. Mainkar, S. Chandrasekhar, *Tetrahedron Lett.* **2011**, *52*, 1658–1662; f) L. Kupracz, J. Hartwig, J. Wegner, S. Ceylan, A. Kirschning, *Beilstein J. Org. Chem.* **2011**, *7*, 1441–1448; g) M. –H. Wei, D. Wu, R. Sun, S. –R. Sheng, *J. Chem. Res.* **2013**, *37*, 422-424; h) F. Alonso, Y. Moglie, G. Radivoy, M. Yus, *J. Org. Chem.* **2013**, *78*, 5031−5037; i) C. Vidal, J. García-Álvarez, *Green Chem.* **2014**, *16*, 3515–3521; j) A. K. Shil, S. Kumar, S. Sharma, A. Chaudhary, P. Das, *RSC Adv.* **2015**, *5*, 11506-11514.

29. R. C. Pratt, B. G. G. Lohmeijer, D. A. Long, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2006**, *128*, 4556-4557 and references cited therein.

30. CCDC-1505414 (**9ia**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

31. H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021; *Angew. Chem.* **2001**, *113*, 2056–2075.

32. a) N. Foroughifar, A. Mobinikhaledi, *Asian J. Chem.* **2002**, *14*, 1441-1452; b) L. Pezdirc, V. Jovanovski, D. Bevk, R. Jaksě, S. Pirc, A. Meden, B. Stanovnik, J. Svete, *Tetrahedron* **2005**, *61*,

3977-3990; c) M. Keller, A. S. S. Sido, P. Pale, J. Sommer, *Chem. Eur. J.* **2009**, *15*, 2810-2817; d) N. Mizuno, K. Kamata, Y. Nakagawa, T. Oishi, K. Yamaguchi, *Catal. Today* **2010**, *157*, 359-363; e) A. Novak, J. Bezenšek, L. Pezdirc, U. Grošelj, M. Kasunič, Č. Podlipnik, B. Stanovnik, P. Šimůnek, J. Svete, *Tetrahedron* **2011**, *67*, 9729-9735; f) K. Yoshimura, T. Oishi, K. Yamaguchi, N. Mizuno, *Chem. Eur. J.* **2011**, *17*, 3827-3831; g) R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, J. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard III, H. Guo, O. Kwon, *J. Am. Chem. Soc.* **2011**, *133*, 13337-13348; h) Y. Liu, W. Zhen, W. Dai, F. Wang, X. Li, *Org. Lett.* **2013**, *15*, 874-877; i) D. Wang, H. P. Deng, Y. Wei, Q. Xu, M. Shi, *Eur. J. Org. Chem*. **2013**, 401-406; j) X. Xu, Y. Qian, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc*. **2013**, *135*, 1244-1247; k) X. Chen, C. Jia, L. Cao, D. Zhang, S. Liu, Q. Zhang, *Chem. Res. Chin. Univ*. **2015**, *31*, 543-548; l) F. Li, J. Chen, Y. Hou, Y. Li, X. -Y. Wu, X. Tong, *Org. Lett*. **2015**, *17*, 5376-5379; m) S. E. Winterton, J. M. Ready, *Org. Lett.* **2016**, *18*, 2608−2611; n) X. Wang, L. Wu, P. Yang, X. -J. Song, H. -X. Ren, L. Peng, L. -X. Wang, *Org. Lett*. **2017**, *19*, 3051−3054; o) L. Yu, Y. Zhong, J. Yu, L. Gan, Z. Cai, R. Wang, X. Jiang, *Chem. Commun*. **2018**, *54*, 2353-2356.

33. X. Fang, J. Li, H. –Y. Tao, C. –J. Wang, *Org. Lett*. **2013**, *15*, 5554-5557.

34. E. Pair, C. Berini, R. Noël, M. Sanselme, V. Levacher, J. –F. Brière, *Chem. Commun*. **2014**, *50*, 10218-10221.

35. D. B. Ramachary, T. P. Reddy, A. S. Kumar, *Org. Biomol. Chem.* **2016**, *14*, 6517-6522.

36. a) E. M. Kosower, A. E. Radkowsky, A. H. Fairlamb, S. L. Croft, R. A. Neal, *Eur. J. Med. Chem.* **1995**, *30*, 659-671; *b*) S. Hanessian, G. McNaughton-Smith, H.-G. Lombart, W. D. Lubell, *Tetrahedron* **1997**, *53*, 12789-12854; *c*) L. Pezdirc, V. Jovanovski, D. Bevk, R. Jakše, S. Pirc, A. Meden, B. Stanovnik, J. Svete, *Tetrahedron* **2005**, *61*, 3977-3990; *d*) L. Pezdirc, D. Bevk, U. Grošelj, A. Meden, B. Stanovnik, J. Svete, *J. Comb. Chem.* **2007**, *9*, 717-723; *e*) S. Yao, D. Gallenkamp, K. Wölfel, B. Lüke, M. Schindler, J. Scherkenbeck, *Bioorg. Med. Chem*. **2011**, *19*, 4669-4678; f) E. M. Kosower, E. Hershkowitz, Isr. Patent ISXXAQ IL 94658 [Chem. Abstr., **1994**, *122*, 214077]; g) R. Fischer, T. Bretschneider, E. R. F. Gesing, D. Feucht, K.-H. Kuck, P. Loesel, O. Malsam, C. Arnold, T. Auler, M. J. Hills, H. Kehne, PCT Int. Appl. WO 2005016873 [Chem. Abstr., **2005**, *142*, 261530].

37. a) S. E. Winterton, J. M. Ready, *Org. Lett*. **2016**, *18*, 2608-2611 and references cited therein; b) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 5334-5335 and references cited therein.

38. CCDC-1838956 (**99fa**) and CCDC-1838942 (**100fa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

39. a) G. J. Karabatsos, N. Hsi, *J. Am. Chem. Soc*. **1965**, *87*, 2864-2870; b) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, J. Lampe, *J . Org.* Chem. **1980**, *45***,** 1066-1081.

40. N. A. Meanwell, M. J. Rosenfeld, J. J. Kim Wright, C. L. Brassard, J. O. Buchanan, M. E. Federici, J. S. Fleming, S. M. Seiler, *J . Med.* Chem. **1992**, *35***,** 389-397.

41. a) J. E. Wilson, J. Sun, G. C. Fu, *Angew. Chem. Int. Ed*. **2010**, *49*, 161-163. b) H. Kuroda, I. Tomita, T. Endo, *Org. Lett*. **2003**, *5*, 129-131.

42. For trialkyl phosphine catalyzed ynone annulations see: a) Y. Liang, S. Liu, Z.-X. Yu, *Synlett* **2009**, 905-909. b) Z. Lian, M. Shi, *Eur. J. Org. Chem*. **2012**, 581-586. c) Z. Lian, M. Shi, *Org. Biomol. Chem*. **2012**, *10*, 8048-8050. d) L. Yang, P. Xie, E. Li, X. Li, Y. Huang, R. Chen, *Org. Biomol. Chem*. **2012**, *10*, 7628-7634. e) L. Liang, E. Li, P. Xie, Y. Huang, *Chem. Asian J*. **2014**, *9*, 1270-1273. f) D. B. Ramachary, C. Venkaiah, P. M. Krishna, *Org. Lett*. **2013**, *15*, 4714-4717. g) D. B. Ramachary, P. M. Krishna, T. P. Reddy, *Org. Biomol. Chem*. **2016**, *14*, 6413-6416. h) M. Raghu, J. Grover, S. S. V. Ramasastry, *Chem. Eur. J*. **2016**, *22*, 18316-18321. i) L. Liang, Y. Huang, *Org. Lett*. **2016**, *18*, 2604-2607. j) X. Gao, Z. Li, W. Yang, Y. Liu, W. Chen, C. Zhang, L. Zheng, H. Guo, *Org. Biomol. Chem*. **2017**, *15*, 5298-5307. k) D. B. Ramachary, T. P. Reddy, A. S. Kumar, *Org. Biomol. Chem*. **2017**, *15*, 9785-9789.

43. For amine catalyzed ynone annulations see: a) Z. Lian, Q.-Y. Zhao, Y. Wei, M. Shi, *Eur. J. Org. Chem*. **2012**, 3338-3341. b) See reference 17. c) Q. Wang, Z. Lian, Q. Xu, M. Shi, *Adv. Synth. Catal*. **2013**, *355*, 3344-3350. d) Y. Liu, T.-R. Kang, Q.-Z. Liu, L.-M. Chen, Y.-C. Wang, J. Liu, Y.-M. Xie, J.-L. Yang, L. He, *Org. Lett*. **2013**, *15*, 6090-6093. e) See reference 18. f) Q. Wang, Q. Xu, M. Shi, *Org. Chem. Front*. **2015**, *2*, 211-215. g) L. Liang, E. Li, X. Dong, Y. Huang, *Org. Lett*. **2015**, *17*, 4914-4917.

44. For reactions utilizing DBU as a substrate see: a) L. L. McCoy, D. Mai, *J. Org. Chem.* **1981**, 1016-1018. b) M. Perbost, M. Lucas, C. Chavis, J. –L. Imbach, *J. Heterocyclic Chem.* **1993**, *30*, 627-

629. c) H. Lammers, P. C.-Femandes, C. L. Habraken, *Teterahedron* **1994**, *50*, 865-870. d) L. Ma, D. Dolphin, *Tetrahedron* **1996**, *52*, 849-860. e) R. D. Chambers, A. J. Roche, *J. Fluor. Chem*. **1996**, *79*, 121-124. f) M. G. Johnson, R. J. Foglesong, *Tetrahedron Lett*. **1997**, *38*, 7003-7006. g) J. K. Sutherland, *Chem. Commun*. **1997**, 325-326. h) J.-E. S. Lönnqvist, L. F. Jalander, *J. Chem. Research (S)* **2000**, 102-105. i) J. Balogh, Á. Kuik, L. Ürge, F. Darvas, J. Bakos, R. S.- Földes, *J. Mol. Catal. A-Chem*. **2009**, *302*, 76-79. j) I. Polenz, A. Laue, T. Uhrin, T. Rüffer, H. Lang, F. G. Schmidt, S. Spange, *Polym. Chem.* **2014**, *5*, 6678-6686. k) M. Chakrabarty, N. Ghosh, S. Khasnobis, M. Chakrabarty, *Synth. Commun.* **2014**, *44*, 2955-2960. l) G. Parhizkar, A. R. Khosropour, I. M.-Baltork, E. Parhizkar, H. A. Rudbari *Teterahedron* **2017**, *73*, 1397-1406. m) Q. Fu, R. Wang, F. Liang, W. Guan, *Org. Biomol. Chem.* **2018**, *16*, 8950-8954. n) D. Peixoto, G. Malta, H. Cruz, S. Barroso, A. L. Carvalho, L. M. Ferreira, P. S. Branco, *J. Org. Chem*. **2019**, *84*, 3793-3800.

45. For Interaction of DBU with acetylenic moieties see: a) L. Ma, D. Dolphin, *J. Chem. Soc., Chem. Commun.* **1995**, 2251-2252. (b) L.-Q. Nie, Z.-J. Shi, W.-Q. Cao, *Bopuxue Zazhi* **2002**, *19*, 377 (in Chinese). c) Z. Shi, L. Nie, *Fenxi Huaxue* **2003**, *31*, 573 (in Chinese). d) Z.-J. Shi, L.-Q. Nie, W.-Q. Cao, *Fenxi Kexue Xuebao* **2004**, *20*, 586 (in Chinese). e) B. A. Trofimov, O. A. Shemyakina, A. G. Mal'kina, A. V. Stepanov, O. G. Volostnykh, I. A. Ushakov, A. V. Vashchenko, *Eur. J. Org. Chem*. **2016**, 5465-5469. f) B. A. Trofimov, O. A. Shemyakina, A. V. Stepanov, O. G. Volostnykh, A. G. Mal'kina *Russ. J. Org. Chem.* **2017**, *53*, 1893-1895. g) O. A. Shemyakina, O. G. Volostnykh, A. V. Stepanov, A. G. Mal'kina, I. A. Ushakov, K. A. Apartsin, V. V. Kireeva, B. A. Trofimov, *Mendeleev Commun.***2018**, *28*, 128-130. h) O. A. Shemyakina, O. G. Volostnykh, A. V. Stepanov, A. G. Mal'kina, I. A. Ushakov, B. A. Trofimov, *Synthesis* **2018**, *50*, 853-858.

46. O. Bakulina, F. K. Merkt, T.-O. Knedel, C. Janiak, T. J. J. Müller, *Angew. Chem. Int. Ed.* **2018**, *57*, 17240-17244.

47. CCDC-2024822 (**105oe**) and CCDC-2024821 (**116ce**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

48. For interaction of Ca (II) salts with oxygen containing moieties see: a) J.-M. Begouin, M. Niggemann, *Chem. Eur. J*. **2013**, *19*, 8030-8041. b) S. Gao, T. Stopka, M. Niggemann, *Org. Lett*. **2015**, *17*, 5080-5083. c) A. N. Parker, M. C. Martin, R. Shenje, S. France, *Org. Lett.* **2019**, *21*, 7268-7273. d) C. Qi, S. Yang, V. Gandon, D. Lebœuf, *Org. Lett*. **2019**, *21*, 7405-7409. e) R. Dada, M. Sulthan, S. Yaragorla, *Org. Lett.* **2020**, *22*, 279-283. f) C. Qi, F. Hasenmaile, V. Gandon, D. Lebœuf, *ACS Catal*. **2018**, *8*, 1734-1739. h) S. Yaragorla, R. Dada, *ACS Omega* **2017**, *2*, 4859-4869. i) L. Marin, V. Gandon, E. Schulz, D. Lebœuf, *Adv. Synth. Catal.* **2017**, *359*, 1157-1163.

49. E. P. J. Ng, Y.-F. Wang, B. W.-Q. Hui, G. Lapointe, S. Chiba, *Tetrahedron* **2011**, *67*, 7728-7737.

50. a) L. J. T. Danence, Y. Gao, M. Li, Y. Huang, J. Wang, *Chem. Eur. J.* **2011**, *17*, 3584–3587; b) L. Wang, S. Peng, L. J. T. Danence, Y. Gao, J. Wang, *Chem. Eur. J.* **2012**, *18*, 6088–6093.

51. X. Liu, D. Hong, Z. She, W. H. Hersh, B. Yoo, Y. Chen, *Tetrahedron* **2018**, *74*, 6593-6606.

52. D. R. Sutherland, L. Kinsman, S. M. Angiolini, G. M. Rosair, A.-L. Lee, *Chem. Eur. J.* **2018**, *24*, 7002-7009.

ABOUT THE AUTHOR

The author, **Mr. Jagjeet Gujral** was born on 3rd September 1990 in New Delhi, Delhi. After his initial schooling at Sahoday School, New Delhi. He obtained his B.Sc. (H) Chemistry degree in 2012 from Sri Venkateswara College, affiliated to University of Delhi. Thereafter, he obtained his M.Sc. degree with specialization in organic chemistry in 2014 from University of Delhi. Henceforth, he worked as a "Project Fellow" at CSIR-NCL Pune during 14-8-2014 to 20-11-2014. He continued as a research scholar at School of Chemistry, University of Hyderabad for Ph. D. course from December 2014 onwards.

LIST OF PUBLICATIONS

1) An Organocatalytic Regiospecific Synthesis of 1,5-Disubstituted 4– Thio-1,2,3-triazoles and 1,5-Disubstituted 1,2,3-Triazoles, D. B. Ramachary, P. M. Krishna, **Jagjeet Gujral** and G. S. Reddy, *Chem. Eur. J.* **2015,** 21, 16775-16780.

2) Triazabicyclodecene as an Organocatalyst for Regiospecific Synthesis of 1,4,5-Trisubstituted *N*-Vinyl-1,2,3-Triazoles, D. B. Ramachary, **Jagjeet Gujral**, S. Peraka, G. S. Reddy, *Eur. J. Org. Chem*. **2017**, 459-464.

3) Organocatalytic Vinyl Azide-Carbonyl [3+2]-Cycloaddition: High-Yielding Synthesis of Fully Decorated *N*-Vinyl-1,2,3-Triazoles, D. B. Ramachary, G. Surendra Reddy, Swamy Peraka and Jagjeet Gujral, *ChemCatChem*, **2017,** 9, 263–267.

4) Construction of 2-Thiabicyclo[3.3.1]nonanes by Organocatalytic Asymmetric Formal [3+3] Cycloaddition, D. B. Ramachary, P. S. Reddy, **Jagjeet Gujral**, *Eur. J. Org. Chem.* **2018,** 1852-1857.

5) An Aldehyde-Azomethine Imine [3+2]-Cycloaddition: High-yielding Regioselective Synthesis of Substituted *N,N*-Bicyclic Pyrazolidinones, **Jagjeet Gujral**, T. P. Reddy, B. Gorachand, D. B. Ramachary, *ChemistrySelect* **2018** , *3* , 7900-7905.

6) Catalytic Ynone-Amidine Formal [4+2]-Cycloaddition for the Regioselective Synthesis of Tricyclic Heterocycles, T. P. Reddy,♣ **Jagjeet. Gujral**,♣ P. Roy, D. B. Ramachary, [♣both contributed equally and manuscript under preparation].

Posters and Presentations

1. **Poster presentation:** "XIV- JNOST conference" 28 November to 1 December, 2018 CSIR-IICT, Hyderabad, India**.**
   Organizers: CSIR-IICT, Hyderabad.
2. **Poster presentation**: **"**ChemFest-2019" (16th Annual In-House Symposium), School of Chemistry, University of Hyderabad, March 2019.
   Organizers: University of Hyderabad, Hyderabad
3. **Oral prasenatation: "**ChemFest-2019" (16th Annual In-House Symposium), School of Chemistry, University of Hyderabad. Won Best Oral Presentation award.
   Organizers: University of Hyderabad, Hyderabad.

Development of Organocatalytic [3+2] and [4+2] cycloadditions: Scope and Applications

by Jagjeet Gujral

Development of Organocatalytic [3+2] and [4+2] cycloadditions: Scope and Applications

ORIGINALITY REPORT

51%	12%	50%	12%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Dhevalapally B. Ramachary, Jagjeet Gujral, Swamy Peraka, G. Surendra Reddy. " Triazabicyclodecene as an Organocatalyst for the Regiospecific Synthesis of 1,4,5-Trisubstituted -Vinyl-1,2,3-triazoles ", European Journal of Organic Chemistry, 2017 Publication	22%
2	Jagjeet Gujral, T. Prabhakar Reddy, B. Gorachand, Dhevalapally B. Ramachary. " An Aldehyde-Azomethine Imine [3+2]-Cycloaddition: High-Yielding Regioselective Synthesis of Substituted -Bicyclic Pyrazolidinones ", ChemistrySelect, 2018 Publication	17%
3	Submitted to Indian Institute of Technology, Madras Student Paper	3%
4	Submitted to Chonnam National University Student Paper	2%

Prof. D.B. Ramachary
School of Chemistry
University of Hyderabad
Hyderabad - 500 046, India.

5	Submitted to University of Hyderabad, Hyderabad Student Paper	2%
6	onlinelibrary.wiley.com Internet Source	2%
7	Submitted to University of St Andrews Student Paper	1%
8	Submitted to University of Michigan, Dearborn Student Paper	1%
9	baadalsg.inflibnet.ac.in Internet Source	1%
10	Surendra Reddy G., Anebouselvy K., Dhevalapally Ramachary. "[3+2]-Cycloaddition for the Fully Decorated Vinyl-1,2,3-Triazoles: Design, Synthesis and Applications", Chemistry – An Asian Journal, 2020 Publication	<1%
11	Hongchao Guo, Yi Chiao Fan, Zhanhu Sun, Yang Wu, Ohyun Kwon. "Phosphine Organocatalysis", Chemical Reviews, 2018 Publication	<1%
12	Dhevalapally B. Ramachary, T. Prabhakar Reddy, A. Suresh Kumar. "Organocatalytic azomethine imine-olefin click reaction: high-yielding stereoselective synthesis of	<1%

spiroindane-1,3-dione-pyrazolidinones", Organic & Biomolecular Chemistry, 2016
Publication

---

13 Ling Liang, You Huang. "Phosphine-Catalyzed [3 + 3]-Domino Cycloaddition of Ynones and Azomethine Imines To Construct Functionalized Hydropyridazine Derivatives", Organic Letters, 2016 <1%
Publication

---

14 Hélène Pellissier. "Asymmetric Metal Catalysis in Enantioselective Domino Reactions", Wiley, 2019 <1%
Publication

---

15 George W. Kabalka, Su Yu, Nan-Sheng Li, Ute Lipprandt. "The reaction of α,β-acetylenic ketones with dicyclohexylborane: Stereoselective synthesis of functionalized trisubstituted olefins", Tetrahedron Letters, 1999 <1%
Publication

---

16 www.ingentaconnect.com <1%
Internet Source

---

17 Girija S. Singh, Zelalem Y. Desta. "Isatins As Privileged Molecules in Design and Synthesis of Spiro-Fused Cyclic Frameworks", Chemical Reviews, 2012 <1%
Publication

Ana L. Cardoso, Maria I.L. Soares. "1,3-Dipolar

18 Cycloadditions Involving Allenes: Synthesis of Five-Membered Rings", Current Organic Chemistry, 2020 <1%

Publication

Exclude quotes	On	Exclude matches	< 14 words
Exclude bibliography	On		