Stereoselective Synthesis of Drug-like Molecules *via* Catalytic Enolates and Dienamines

A
Thesis
Submitted for the Degree of

Doctor of Philosophy

By

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May 2016

DEDICATED TO MY PARENTS

For all your love, support and encouragement that enabled me to achieve my dreams

DECLARATION

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

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CERTIFICATE

*Certified that the work contained in the thesis entitled "**Stereoselective Synthesis of Drug-like Molecules via Catalytic Enolates and Dienamines"** has been carried out by **Mr. Murali Krishna Patoju** under my supervision and the same has not been submitted elsewhere for a degree.*

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ACKNOWLEDGEMENTS

With high regards and profound respect, I wish to express my deep sense of gratitude to ***Prof. Dhevalapally B. Ramachary****, for his inspiring guidance and valuable suggestions throughout my research work. It has been a great privilege and honour to be associated with him.*

I would like to thank Prof. M. Durga Prasad Dean, School of Chemistry for providing all the facilities needed for our research. I extend my sincere thanks to former Deans Prof. D. Basavaiah, Prof. M. Periasamy and Prof. M. V. Rajasekharan, all the faculty members of School of Chemistry for their timely help and cooperation during my Ph. D. program.

It gives me great pleasure to thank my friends Apparao (Appu), Krishna, venkat babu, Narayana, Trinadh, Mahesh (Baaaaa) Srinu (gollu), Srinu (baddhala), Srinu (Bandi) Venu, Kranthi (mister cool), Harinadh, Ravikiran (boost), Koti, Satheesh, Vinod, Ramana, B. Nagaraju, Padmakar, Ganapathi and Anand for everything they have given to me and making my stay here, a memorable one in my life.

I am extremely thankful to my lab seniors and colleagues Dr. Vijayendar Reddy, Dr. Rosy Mallik, Dr. Sakthidevi, Dr. Venkaiah, Dr. Shiva Prasad, Dr. Suresh, Dr. Bharanishashank, Dr. Srinivasa Reddy, Dr. Madhavachary, Dr. Malli (Babai), Dr. Sreekanth, Dr. Swamy, Dr. Tirupathi, Shruthi, Karthik, Prabhakar, Jaggu, Surendra, Anif, Jyothi and Mounika for their friendly cooperation in the lab. My special thanks to Dr. K. Anebouselvy for her kind proof reading of this entire thesis.

I would like to express my special thanks to sweet buddys who brought smile on my face in my tough time Chandu (Apachi), Dr. Sunny (pandu), Dr. Ashok (ok ok), Rama Krishna, Dr. Durga rao (D), Guptha, Malli (My buddy), Koti, Prabhakar with their funny, joyful and crazy discussions.

I am very thankful to all my friends and colleagues in School of Chemistry Dr. K. Srinivas, Dr. Ganesh, Dr. Naveen, Dr. Raveendra babu, Dr. Manoj, Ramana, Thamilarsan, Sakthivel, Chandrahas, Dr. Gangadhar, Allu Srinivas, Prasad, Leela, Dr. Obul Reddy, Suresh, Satyanarayana, Mohan, Uday, Ramesh, Anand, Harish, Edukondalu, Shanmugam,

Anand, Ramusagar, Dr. Sekhar Reddy, Dr. Santosh, Chandrashekar, Veera Ragavaiah, Lingaiah, Sai, Thamilarasi, Obaiah, Vikranth, Nanda Kishore, Sathish, Karunakar, Ramavath babu, Dr. Balavardhan, Dr. Swamy, Narendra, K. S. N. Raju, Srinivas, Dr.Anand anna, Dr. Kishore, Amala, Dr. Arjun, Dr. Vikram, Dr. Sathish, Dr. Viji,. Ramesh, Dr. Ramaraju, Dr Prakash, Ramakumar, YSLV Narayana, Dr Ajay, Krishna, Ramudu, Dr. Shesadri, Dr. Venu, Dr Sudharani, Ramakrishna, Dr. Ramu Yadav, Sanathan, Dr Raja, Prabhakar, Majji, Dr. Rajgopal, Sridhar Reddy, Shashi, Yasin, Shivaramakrishna, Dr. Thirupathi Reddy, Pavan, Dr. Hari, Sowmya, Crystal heros (Sudheer, Narendhar, satheesh).

I acknowledge the help and support provided by the technical and non-teaching staff of the School of Chemistry. I also thank Dr. P. Ragavaiah, Sambashiva Rao, Satyanarayana, Mallaiah Shetty, Bhaskara Rao, Venkataramana, Asiaperwej, Vijaya Laxmi, Turab, Venky (NMR), A. R. Setty, Prasad, Santhosh, Maruthi, Sucharith and Durgesh for their timely help.

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

Finally and most importantly, I would like to thank my mother Govindamma garu, father Rajeswararao garu and my brother Rakesh kumar for their support and encouragement that deserves great appreciation. The unconditional love of my parents and their blessings made me what I am today and I owe everything to them. Dedicating this thesis to them is a minor recognition for their relentless support and love.

Murali Krishna Patoju

Stereoselective Synthesis of Drug-like Molecules via Catalytic Enolates and Dienamines

1. ABSTRACT

In chapter 1, carbonate-catalyzed keteniminate-mediated synthesis of 5-amino-1,2,3-triazoles from aryl-acetonitriles and aryl azides is reported. This cycloaddition reaction is characterized by high rate and selectivity, and easy access to a library of functioalized 5-amino-1,2,3-triazoles, giving the desired products in very good yields. This protocol overcomes the many disadvantages of previous reports such as usage of stong bases in many equivalents and highly reactive substrates. Many 5-amino-1,2,3-triazoles have found wide range of application in biological, medicinal, organic, bio-organic, polymer and material chemistry.

In chapter 2, an organocatalytic azide–ketone [3+2]-cycloaddition (OrgAKC) reaction of a variety of 1-aryl-2-(arylthio)ethanones and 1-alkyl-2-(alkylthio)ethanones with different aryl/alkyl azides is reported in dimethyl sulfoxide or solvent-free under ambient conditions to furnish the 1,5-disubstituted-4-thio-1,2,3-triazoles in a regiospecific manner, which are further converted into useful 1,5-disubstituted-1,2,3-triazoles by treatment with Raney-Ni at 25 °C for 1-3 h. The OrgAKC reaction has wonderful features such as high rate and selectivity, solvent-free, easily available substrates/catalysts, many synthetic/medicinal applications, and excellent yields generating a vast library of triazoles.

In chapter 3, we utilized Tomita zipper cyclization protocol for the synthesis of benzosultams. In this methodology, we performed the reaction of highly reactive *N*-sulfonyl *α*-ketiminoesters with unmodified ynone in the presence of organophosphine catalyst and acid co-catalyst to afford benzosultams in excellent yields at 25 °C *via* Tomita Zipper Cyclization. Many benzosultams have found wide range of applications in biological, medicinal, and also serve as intermediates in many organic synthetic transformations.

In chapter 4, an asymmetric organocatalytic arylideneacetone-olefin [4+2]-cycloaddition (OrgAOC) reaction of a variety of arylidene-acetones and 1,3-indandione with different aldehydes is reported in toluene under ambient conditions to furnish the optically pure spiro-compounds in a stereoselective manner, which are further converted into

medicinally useful spiromentins by Suzuki reaction. The asymmetric OrgAOC reaction has wonderful features such as high rate and selectivity, easily available substrates/catalysts, many synthetic/medicinal applications, and excellent yields generating a vast library of chiral spiro-compounds.

2. INTRODUCTION

One of the major challenges faced by the synthetic organic chemist, now a days, is the development of efficient synthetic methodologies which could provide rapid access to structural and stereo chemical complexity in molecules similar to biological processes. The ultimate goal of the modern synthetic organic chemistry is the achievement of desired complex chiral moieties with high reaction efficiency, liberating the environmentally benign and non toxic by-products and the use of readily available cheap starting materials, without compromising in yields and stereoselectivity. Most of these goals have been full filled by transition-metal catalysis and enzyme catalysis, each catalytic approach has its own drawbacks such as particular atmosphere and circumstances required for enzyme catalysis and the transition metal catalysis are highly toxic to bio-system even in trace amounts.

In the last decade, most of these difficulties faced by synthetic organic chemists have been overcome by the introduction of organocatalysis to the chemistry world. In organo catalysis, small organic molecules can be used in sub-stoichiometric amount for the acceleration of chemical reactions. In a short span of time, organocatalysis developed very extremely due to some advantages[1] over previous metal catalysis and enzyme catalysis. In these organocatalyzed reactions various intermediates, generated *in situ* from carbonyl compounds and amines, such as enamine,[1b,c] enolates,[2] iminium,[1] dienamine[3] and trienamine[4] have been successfully utilized in the synthesis of complex moieties with high levels of stereoselectivity either in one step or in cascade manner. The cascade protocols require neither protection nor de-protection steps and most importantly these reactions can be performed under aerobic atmosphere and does not require any dry solvents, indeed the reaction rates can be accelerated often in the presences of water.

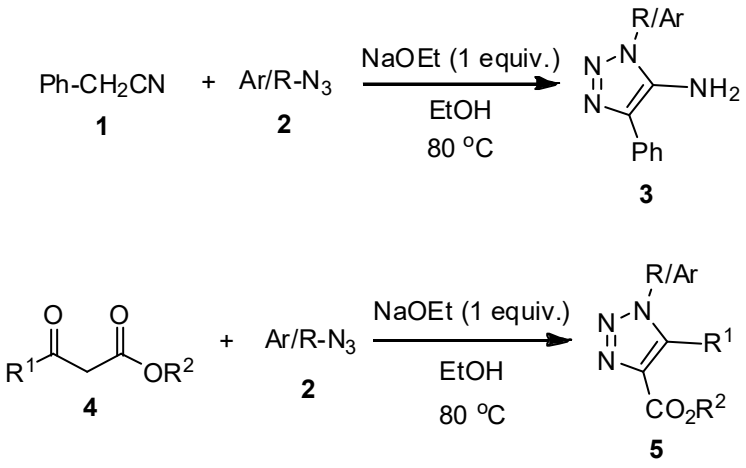
The research work described in this thesis is divided into two parts

1. Enolate mediated [3+2]-cycloaddition.
2. 2-Aminobuta-1,3-diene mediated [4+2]-cycloaddition reactions.

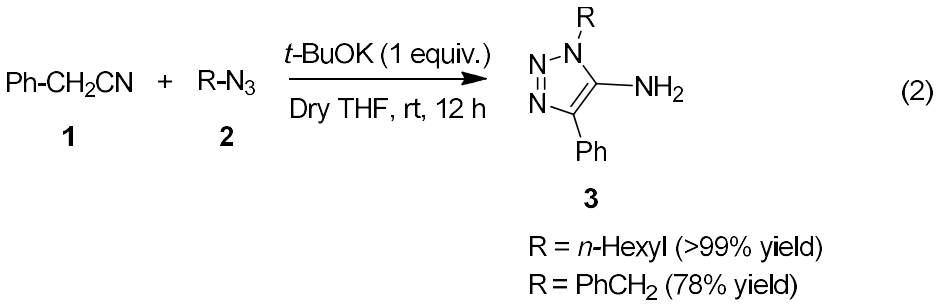
2.1. Enolate mediated [3+2]-cycloaddition for the synthesis of substituted 1,2,3-triazoles:

Recently, base catalyzed enolate-azide [3+2]-cycloadditions emerged as a solution to avoid metal residues in the synthesis of substituted 1,2,3-triazoles.[2] Such cycloadditions generally proceed through an enamine or enolate intermediate generated *in situ* from a carbonyl and an amine, which further reacts as a dipolarophile with an azide to afford the desired five-membered triazole. The enolate mediated methods have certain advantages over the respective metal-mediated transformations as they are potentially greener and considered to be non-toxic towards biological systems. These characteristics of enolated mediated method grabbed the attention of chemical community to develop new methodologies for the metal free synthesis of triazoles and also to employ different kinds of dipoles in organocatalytic [3+2]-cycloaddition reactions.

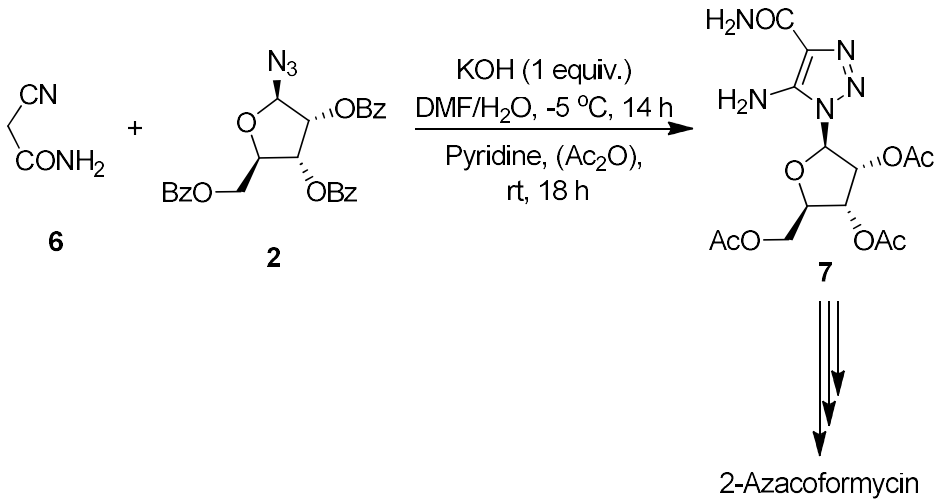
In 1902, Dimroth utilized enolate as an intermediate to synthesize highly substituted 1,2,3-triazole in a regioselective manner. In this protocol, they used stoichiometric amount of sodium ethoxide as base to pick a proton from the active methylene compounds **1** to generate the enolate, which under goes reaction with Ar/R-N_3 **2** to furnish substituted 1,2,3-triazoles in ethanol as a solvent at reflux temperature. This protocol was favor for aromatic azides, especially those with electron withdrawing substituents on the benzene ring, and the electron donating substituents on the aromatic ring retarded the process. Further, great difficulties were faced with alkyl azides under these harsh conditions and 1-substituted 5-amino-1,2,3-triazoles **3** undergo rearrangement to 5-(substituted)amino-1,2,3-triazoles under these harsh conditions (eq. 1).[5]



To overcome these limitations, in 1958, Lieber Eugene *et al.* used equimolar amount of *t*-BuOK in anhydrous THF at RT instead of using the metal alkoxide bases in absolute alcohol. By this protocol, they succeeded in the preparation of *N*-alkylated-1,2,3-triazoles **3** from aliphatic azides **2** and active methylene compounds **1** with high yields, without any further rearrangement.[6] But with methyl ketones, the yields were very poor due to dimerization of ketones and formation of other side products (eq. 2).

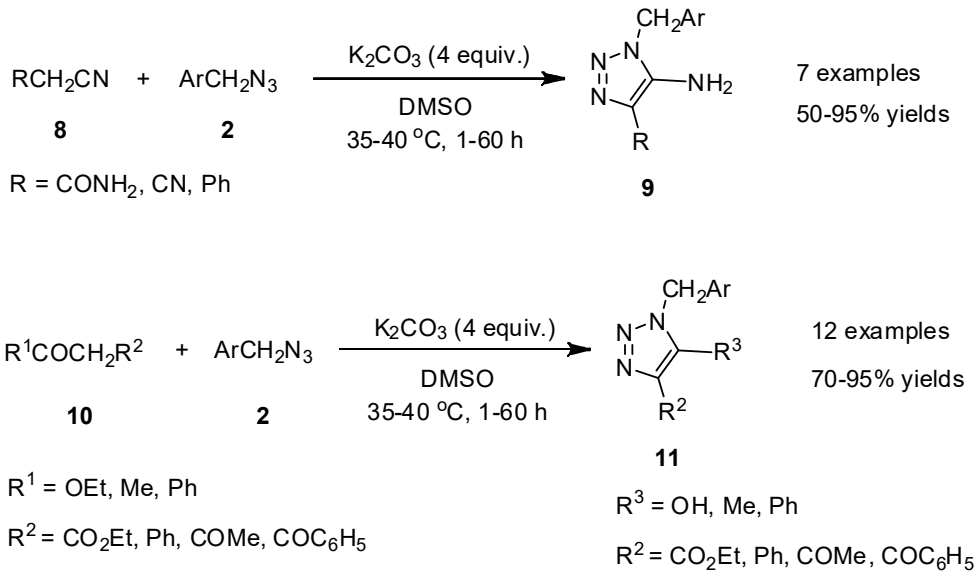


Later in 1986, Townsend *et al.* reported the synthesis of heterocyclic analogues of the nucleoside antibiotic coformycin by utilizing enolate mediated [3+2]-cycloaddition as the crucial step. In this protocol, the reaction of cyanoacetamide **6** and 2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranaosyl azide **2** in the presence of 1 equiv. of potassium hydroxide in DMF/H_2O as solvent afforded debenzoylated 5-amino-1,2,3-triazole *via* [3+2]-cycloaddition, which was *in situ* acetylated to furnish the corresponding aceylated triazole **7**. This is a crucial intermediate for the synthesis of the antibiotic coformycins (eq. 3).[7]



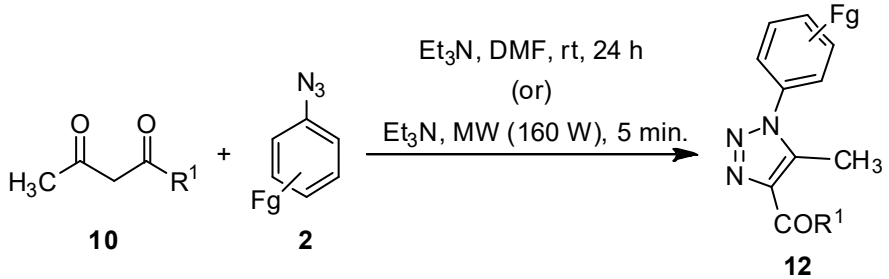
(3)

In 1991, Wright *et al.* demonstrated the preparation of 1-benzyl-1*H*-1,2,3-triazoles **9** from active methylene compounds and benzyl azides **2** using a mild base such as anhydrous potassium carbonate in DMSO as a solvent at 35-40 °C. By this method, they prepared 5-amino-1*H*-1,2,3-triazoles **9** from malononitrile, phenylacetonitrile and cyanoacetamide **8** by treating with benzyl azide **2**, which can be easily separated by filtration of the reaction mixture after addition of water. In a similar manner, 5-hydroxyl-1*H*-1,2,3-triazole **11** was obtained from diethyl malonate **10** in 80% yield.[8] Unfortunately, simple methyl ketones, such as acetones, acetophenones, ethyl fluoroacetate and ethyl nitroacetate were unsuccessful to form the corresponding required products under these conditions (eq. 4).



(4)

In 2011, Florence mongin reported the synthesis of 5-methyl-4-acyl-1,2,3-triazoles **12**, by reaction of aryl azides **2** with *β*-dicarbonyl compounds **10** under both thermal and micro wave conditions in the presence of triethylamine under neat condition as shown in eq. 5.[9] The rate of the reaction was dramatically enhanced by microwave irradiation compared with thermal condition. The regioselectivity and mechanism of the reaction was proved theoretically by DFT studies on *β*-dicarbonyl compounds **10** (eq. 5).



10 **2** **12** (5)

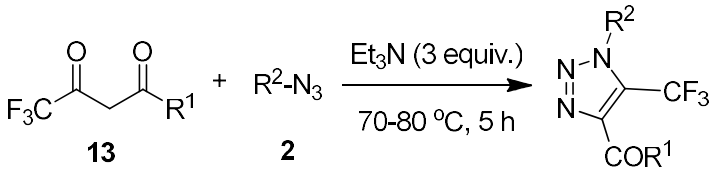
R^1 = CH_3, OCH_3

Fg = 4-Cl, 4-Br, 4-NO_2, 3-NO_2

14 examples

70-95% yields

In 2012, Bakulev and co-workers prepared 5-trifluoromethyl-1,2,3-trizoles **14** from the reaction of 1-trifluoromethyl-1,3-dicarbonyl compounds **13** and phenyl azides **2** in presence of 3 equiv. of triethylamine as a base under neat condition at 70-80 °C in 5 h with 100% regioselectivity (eq. 6). They provided experimental evidence for this exclusive regioselectivity by controlled NMR experiments and showed that the $–CF_3$ group in 1,3-dicarbonyl compounds could direct the reaction towards the formation of a single regioisomer i.e, 4-acyl-5-trifluoromethyl-1,2,3-triazoles **14**.[10]



13 **2** **14** (6)

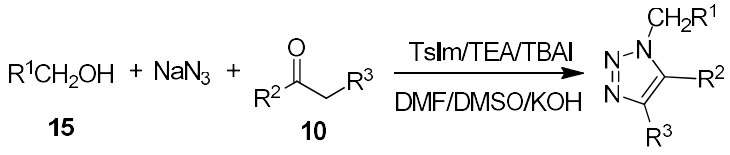
R^1 = Ph, Ar, CH_3, OEt

R^2 = Ph, Ar, CH_2CO_2Et

17 examples

50-90% yields

In the same year, Song Cao synthesized highly substituted 1,2,3-triazoles by one pot three component [3+2]-cycloaddition *via in situ* generated alkyl/aryl azides. Reaction of 1° and 2° alkyl/aryl alcohol **15**, sodium azide and active methylene ketones **10** in the presence of tetrabutylammonium iodide (TBAI), *N*-(*p*-toluenesulfonyl)imidazole (TsIm) and triethylamine (TEA) in DMF/DMSO mixture as solvent, KOH as base, furnished the corresponding products in 50-85% yields. In this protocol they generated alkyl/aryl azides *in situ* from the corresponding alcohols and utilized without any further purification, for the synthesis of respective *N*-alkyl/aryl-triazoles **16**. Generally, the preparation of highly substituted *N*-methyl, -ethyl, -propyl 1,2,3-trizoles are somewhat difficult due to toxicity and explosive nature of *N*-methyl, -ethyl, -propyl azides. However these limitations were overcome by this protocol (eq. 7).[11]



15 **10** **16** (7)

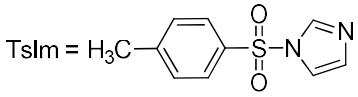
R^1 = Ph, $PhSCF_2$, Hetroaryl, *n*-alkyl, H

R^2 = Ph, CH_3

R^3 = CN, $COCH_3$, $CO_2C_2H_5$

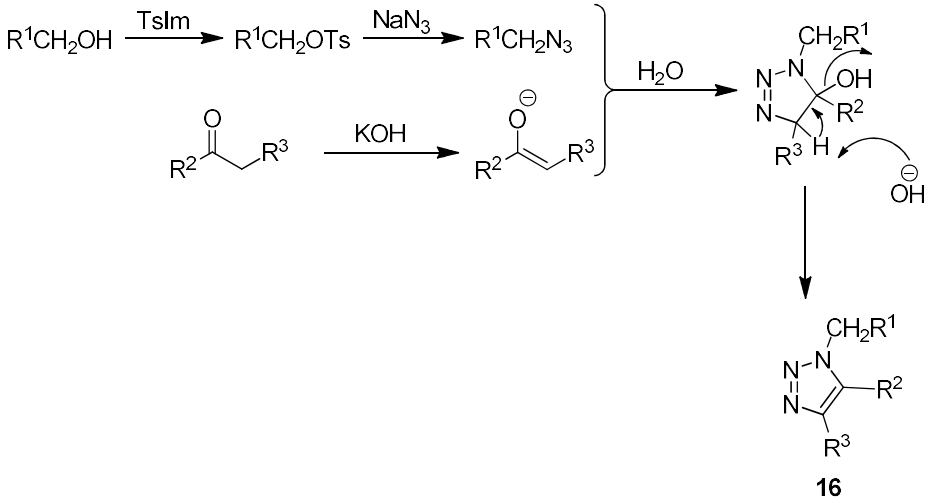
17 examples

50-85 % yields

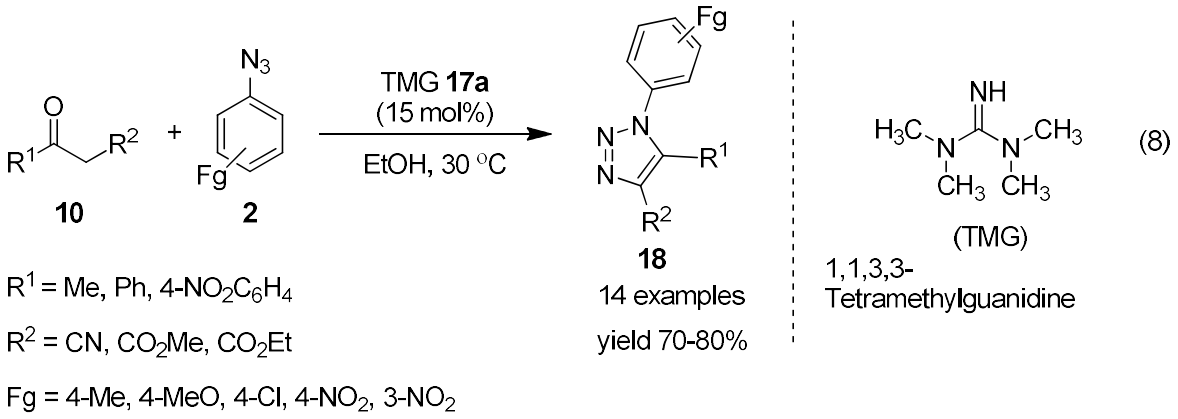


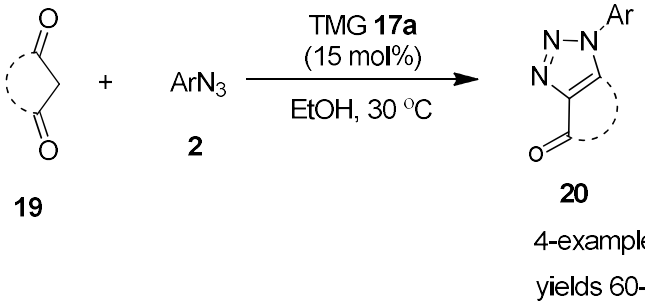
TEA = Triethyamine

TBAI = Tetrabutylammonium iodide



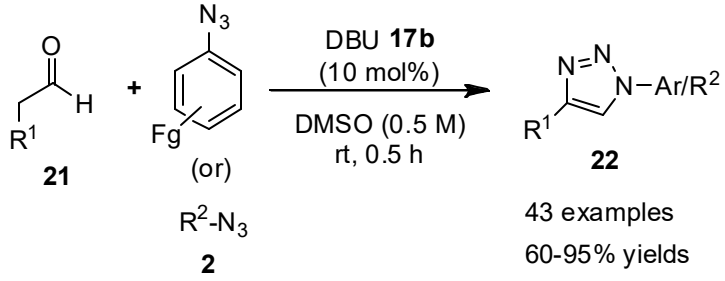
In 2013, Ayoob Bazgir *et al* demonstrated an efficient protocol for the synthesis of 1,2,3-triazoles *via* [3+2]-cycloaddition in the presence of 1,1,3,3-tetramethylguanidine **17a** (TMG) as a catalyst. Reaction of different substituted aryl azides **2** with CH-acids **10** in presence of TMG **17a** as catalyst in ethanol as solvent at 30 °C furnished the corresponding 1,2,3-triazoles **18**. By using this mild reaction condition, they synthesized bicyclic and tricyclic triazoles **20** from the corresponding cyclic 1,3-diketones **19** by reacting with aryl azides **2** with good isolated yields (eq. 8).[12]





In 2014, our group reported an efficient protocol for the synthesis of 1,4-disubstituted-1,2,3-triazoles **22** from enolizable aldehydes **21** and azides **2** in presence of 10 mol% DBU **17b** as catalyst in DMSO at 25 °C *via* [3+2]-cycloaddition (organo-click) reaction. This reaction condition favoured both electron donating and withdrawing substrates on the aromatic aldehydes **21** with aryl azides **2** containing various substituents at different positions to furnish the corresponding 1,4-disubstituted-1,2,3-traizoles **22** in high yields

within 30 min. This protocol is characterized by mild reaction condition, high rate and regioselectivity, and excellent yields with broad scope of substrates (eq. 9).[2a]



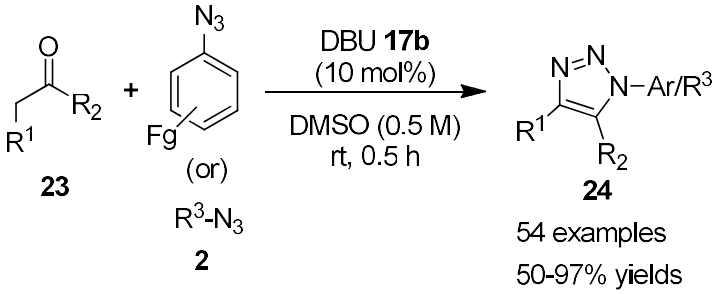
(9)

R^1 = Ph, Bn, various substituted phenyls, alkyl, H

R^2 = $PhCH_2$, CO_2Et

Fg = electron donating, withdrawing, neutral substitutions

Further, in the same year, as an extension, our group utilized enolizable arylacetones and deoxybenzoin **23** as the substrates instead of enolizable aldehydes **21,** for the synthesis of fully decorated 1,2,3-triazoles **24**. These enolizable arylacetones and deoxybenzoin **23** react with aryl azides **2** in presence of 10 mol% DBU **17b** in DMSO as solvent to furnish the corresponding triazoles in excellent yields with high regioselectivity at 25 °C in 0.5-6 h (eq. 10).[2b]



(10)

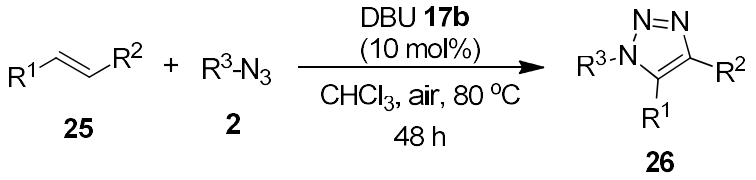
R^1 = Ph, 2-naphthyl, Bn, various substituted phenyls

R^2 = Ph, various substituted phenyl, Me, Et

Fg = H, different substituted phenyls

R^3 = 1-naphthyl, Bn, CO_2Et

In 2014, Jian Wang *et al.* discovered the first organocatalytic intermolecular azide-zwitterion [3+2]-cycloaddition followed by aerobic oxidation reaction. In this reaction, electron deficient alkenes **25** reacts with Lewis base 1,8-diazabicyclo[5.4.0]undec-7-ene **17b** to generate zwitter ion intermediate, which readily reacts with an array of azides **2** *via* [3+2] cycloaddition to generate fully or highly substituted 1,2,3-triazoles **26** in a highly regioselective manner (eq. 11).[2c]



25 **2** **26**

(11)

R^1 = aryl, heteroaryl, alkyl

R^2 = COR, CO_2R, CHO, CN, $CONR_2$, COSR etc.

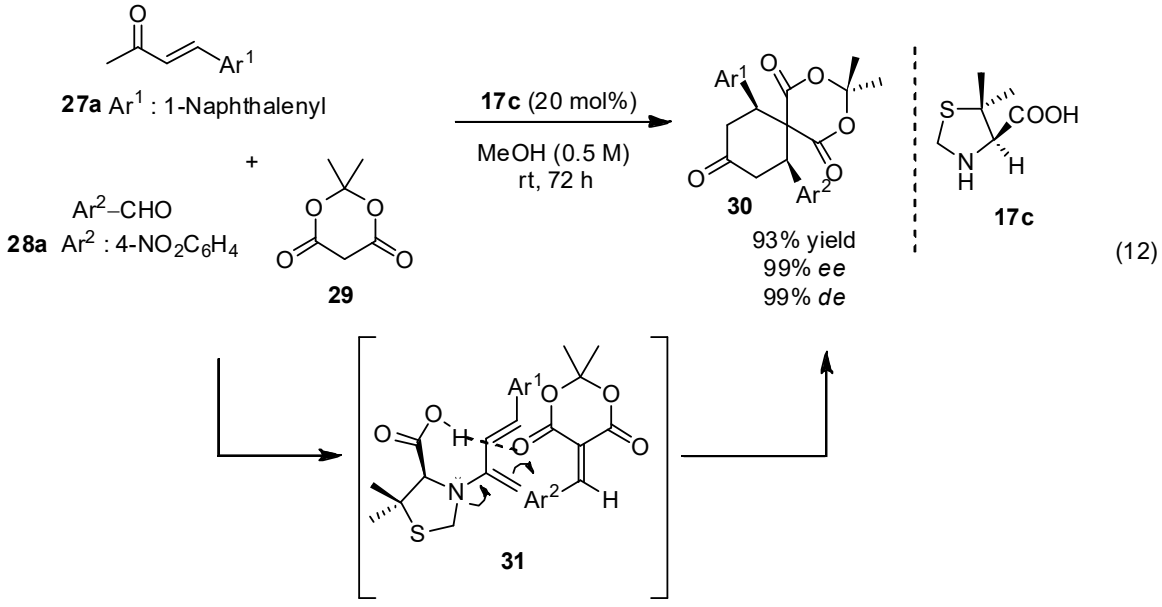
R^3 = aryl, heteroaryl, alkyl

yields: 80-90%

2.2. 2-Aminobuta-1,3-dienes mediated [4+2]-cycloaddition reactions:

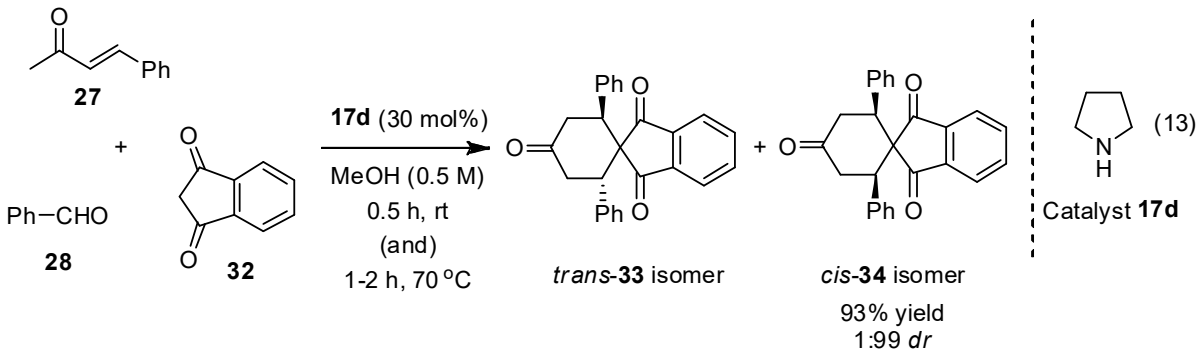
In 2002, Barbas *et al.* discovered 2-aminobuta-1,3-diene intermediate,[14c] which was generated *in situ* from the reaction of benzylideneacetone with catalytic L-proline or L-dienamine, and reacted with *β*-nitrostyrenes in Diels-Alder manner to generate [4+2]-cyclicadducts. This reaction created a domain in organic synthesis called *dienamine-catalysis*. After these preliminary studies, many groups rushed into this field to investigate the reaction scope by changing catalysts along with co-catalysts and different substrates of enones and dienophiles.

In 2003, Ramachary and Barbas demonstrated the first organo catalytic highly diastereospecific and enantioselective asymmetric three component Diels-Alder reaction.[14d] This reaction proceeds *via* domino Knoevenagel-Diels-Alder reaction to construct highly substituted spiro[5,5]undecane-1,5,9-trione **30** from the readily available 4-substituted-but-3-en-2-one **27**, aldehyde **28** and 2,2-dimethyl-1,3-dioxane-4,6-dione **29** (Meldrum's acid) with the aid of dienamine catalysis in the presence of 5,5-dimethylthiazolidium-4-carboxylic acid **17c** (L-DMTC) as catalyst. These products are very interesting building blocks in many natural products and biological chemistry (eq. 12).

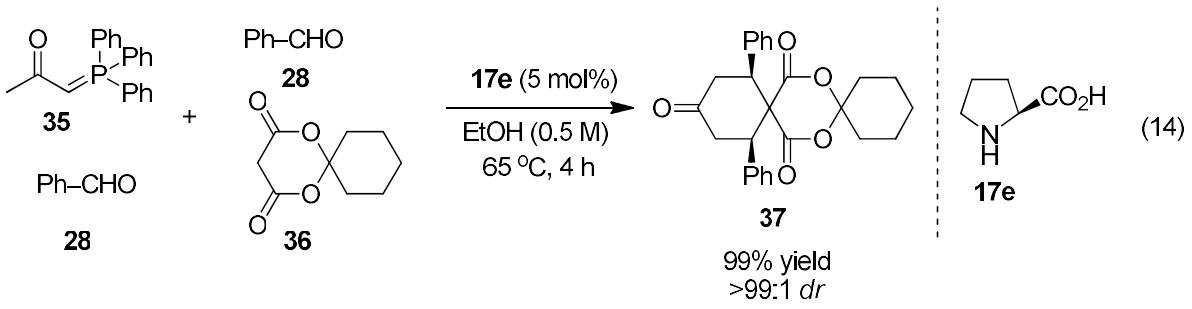


(12)

In 2003, Ramachary and Barbas reported the synthesis of highly substituted prochiral spiro[cyclohexane-1,2'-indan]-1',3',4-trione **33** and **34** *via* cascade Knoevenagel-Diels-Alder-epimerization (K-DA-E) reactions,[14e,f] with high diastereoselectivity. Reaction of commercially available chalcogens **27**, aldehydes **28** and 1,3-indandione **32** in the presence of pyrrolidine **17d** as catalyst furnished the corresponding spirocyclic ketones in excellent yields and *dr'*s, which are good starting materials for the preparation of fenestranes (eq. 13).

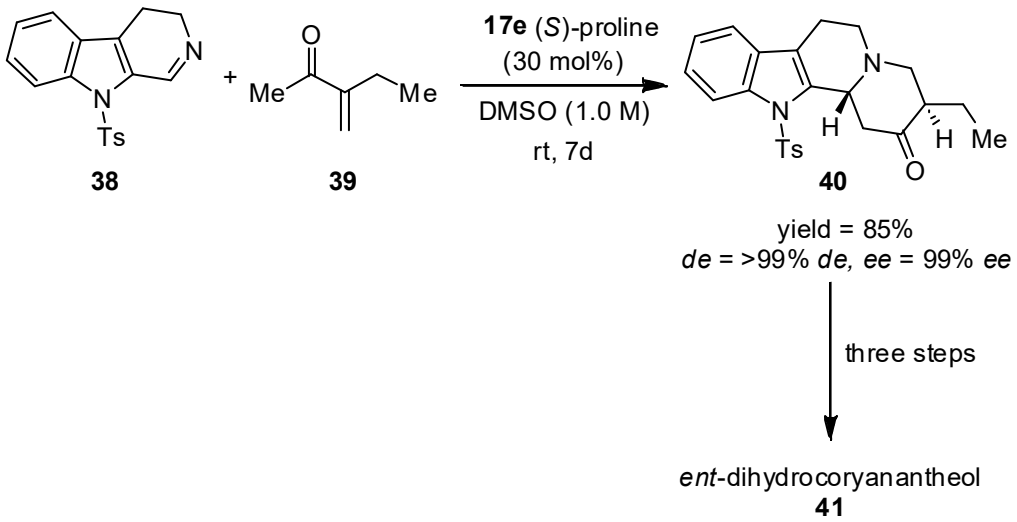


In 2004, Ramachary and Barbas reported the first organo-click reaction *via* combination of Witting, Knoevenagel and Diels-Alder reactions sequentially. Simple heating of phosphorane **35**, aldehyde **28** and spirolactone **36** with a catalytic amount of L-Proline **17e** furnished the dispiro[5.2.5.2]hexadecane **37** in quantitative yields with >99:1 diastereoselectivity as shown in eq. 14. This procedure is a manifestation of organo-click chemistry transformation.[14g]



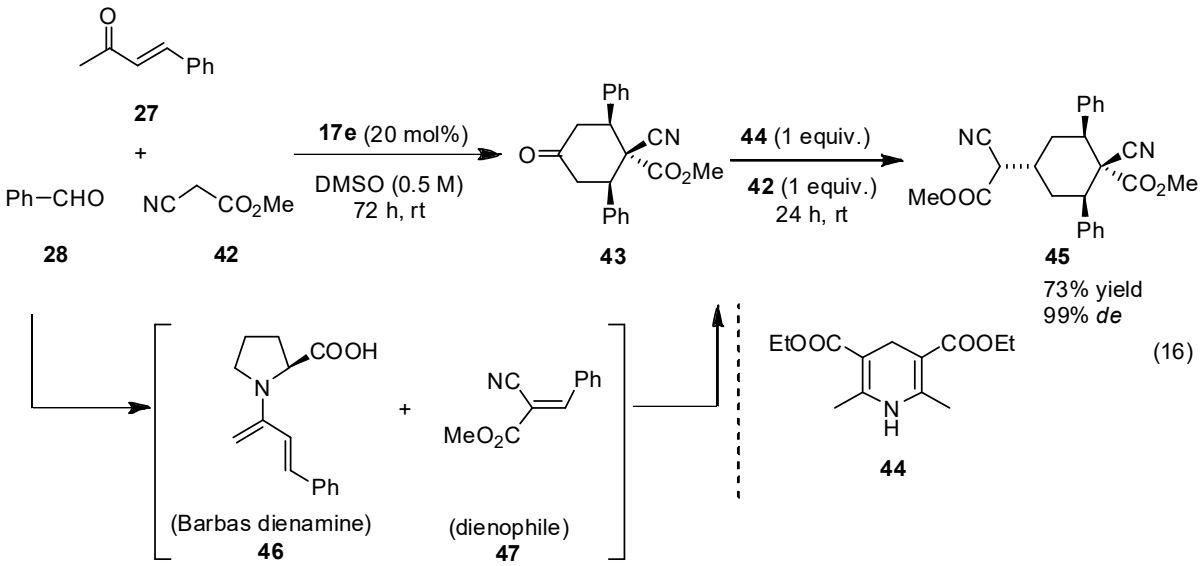
In 2006, Takashi Itoh and co-workers demonstrated the total synthesis of *ent*-dihyrocorynantheol **41** with high enantio- and diasteroselectivity by utilizing proline **17e** catalysed asymmetric addition reaction as the key step. They commenced the reaction

between carboline **38** and 3-ethyl-3-buten-2-one **39** in the presence of L-Proline **17e** to obtain the cyclic adduct **40** in very good yield with excellent enantioselectivity as shown in eq. 15. However in this article they did not give any conclusion on whether it follows stepwise (Mannich-aza-Micheal) or concerted (hetero Diels-Alder) manner.[15]

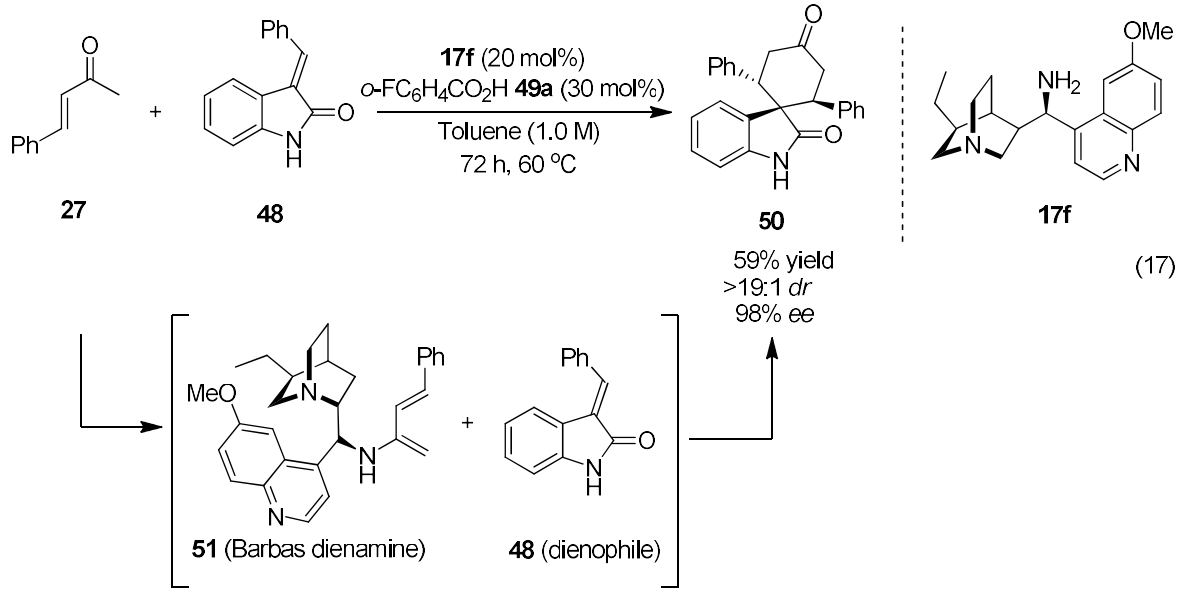


(15)

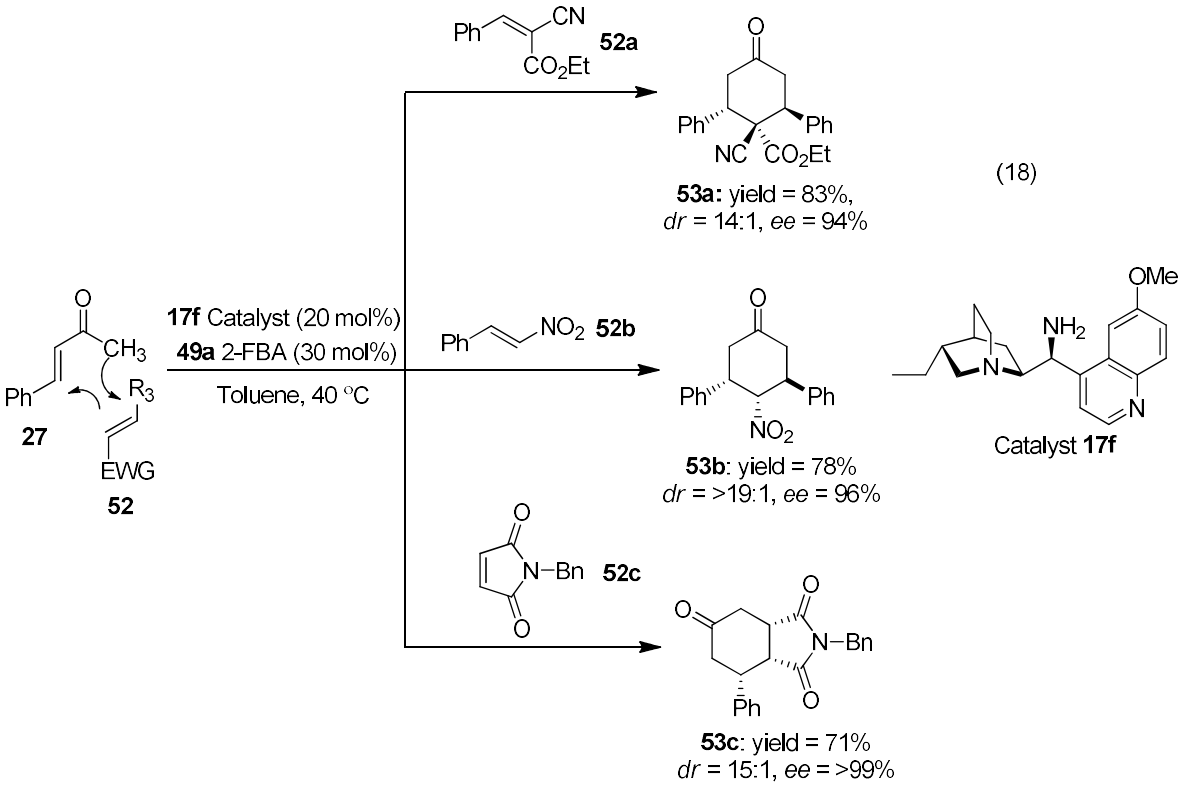
In 2008, Ramachary *et al.* demonstrated a double cascade reaction for the synthesis of highly functionalized stereoselective cyclohexanes **45** with the aid of Barbas dienamine catalysis. In this communication, they reported proline **17e** catalysed three and five component cascade reaction for the synthesis of highly substituted prochiral methyl-1-cyano-4-oxo-2,6-diphenyl-cyclohexanecarboxylate **43** and methyl-1-cyano-4(cyano-methoxycarbonyl-methyl)-2,6-diphenyl cyclohexanecarboxylate **45** in high yields with excellent *de*'s. They commenced their reactions with readily available starting materials such as 4-substituted-3-butene-2-ones **27**, aldehydes **28**, methyl cyano acetates **42** and Hantzsch ester **44** to obtain the corresponding products *via* cascade olefination-Diels-Alder-epimerization and olefination-Diels-Alder-epimerization-olefination-hydrogenation reactions respectively, as shown in eq. 16.[16]



In 2009, Melchiorre *et al.* demonstrated an asymmetric synthesis of multiple stereogenic centers containing spirocyclic oxindoles through Barbas dienamine platform. In this report, Barbas dienamine intermediate **51**, generated *in situ* from the condensation of *α*, *β*-unsaturated ketones and 1° amine, reacts with the dienophiles to afford the corresponding spiro-oxindole derivatives **50** in moderate yields with high enantioselectivities as shown in eq.17. This spirocyclic oxindole core is found in many medicinally relevant compounds as well as in natural products.[17a]

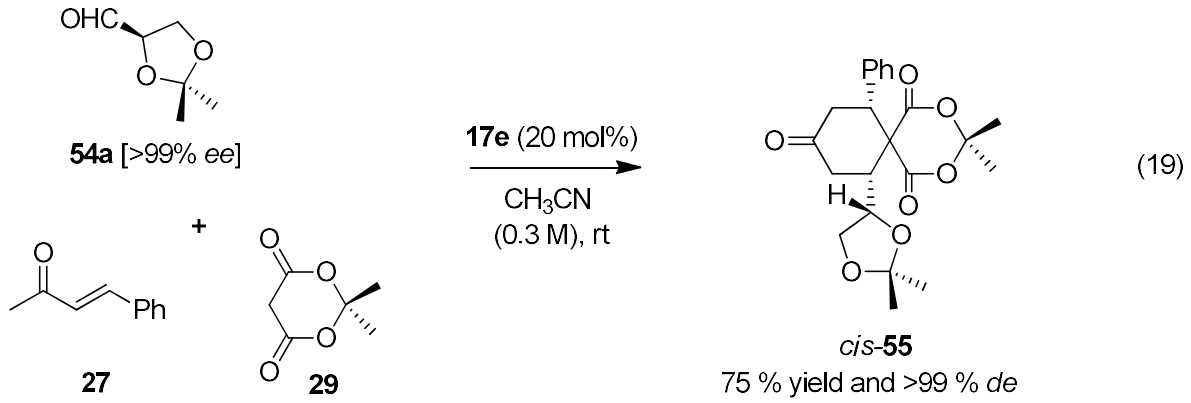


In the same year, Melchiorre *et al.* reported construction of challenging asymmetric complex scaffolds in efficient manner by utilizing chiral primary amine catalysis. In this protocol, reaction of *α,β*-unsaturated ketones **27** with different electron deficient olefins **52** such as *β*-nitrostyrene, *trans*-*α*-cyanocinnamate and *N*-phenyl or *N*-benzyl maleimides in the presence of chiral primary amine 9-amino(9-deoxy)-*epi*-hydroquinine **17f** as catalyst afforded the corresponding highly substituted cyclohexanone and bicyclic scaffolds **53** in good yields with good diesterioselectivities and excellent enantioselectivities *via* combination of enamine-iminium activation (eq. 18).[17b]



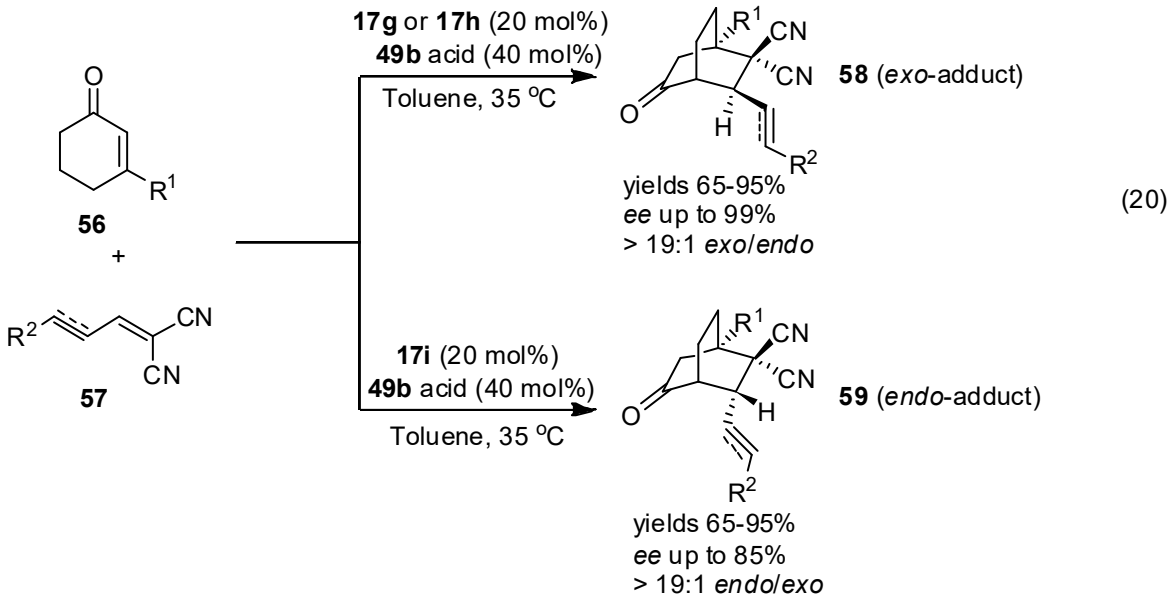
In 2011, our group demonstrated an amino acid catalyzed diastereospecific three component Diels-Alder (DTCDA) reaction that produced highly funtionalized chiralspiro[5,5]undecane-1,5,9-triones **55** with the aid of Barbas dieneamine catalysis. Reaction of 4-substituted-3-butene-2-one **27**, chiral aldehyde **54**, and 2,2 dimethyl-1,3-dioxane-4,6-dione **29** (Meldrum's acid) in the presence of catalytic amount of L-Proline **17e** yielded the corresponding product in 75% yield with >99% *de* as shown in eq. 19. These

functionalized chiral spiro[5,5]undecane-1,5,9-triones **55** are attractive building blocks in the total synthesis of natural products.[19]

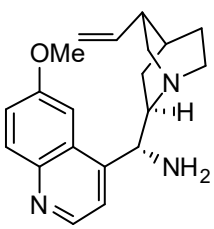


(19)

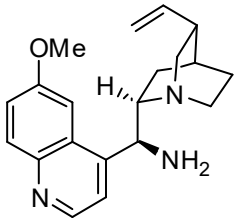
In 2012, Ying-Chun Chen *et al*. reported an amine catalyzed stereodivergent and regioselective [4+2]-cycoladdition[20] with the aid of 2-aminobutadiene catalysis. Reactions of *β*-substituted cycloenones **56** with allylidene or alkynylidenemalonanitrile **57** substrates afforded the corresponding substituted bicyclo[2,2,2]octane **58** and **59** analogous with moderate to excellent diastereo and enantioselectivity in the presence of primary amine catalyst **17**. In this unusal transformation, the hydrogen bonding interactions between the primary amine catalyst and the starting material plays a key role to achieve high diastereodivergence. By the combination of 9-amino-9-deoxyepiquinidine **17i** and salicylic acid **49b** efficiently produced an *endo* cyclo adduct **59**, while using 6'-hydroxy- 9-amino-9-deoxyepiquinine **17g** and **17h** as a catalyst obtained *exo* cyclo adducts **58** (eq. 20).



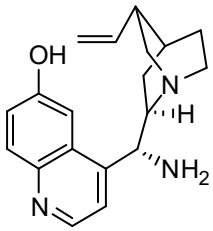
(20)



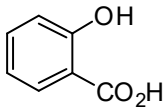
catalyst **17g**



catalyst **17h**

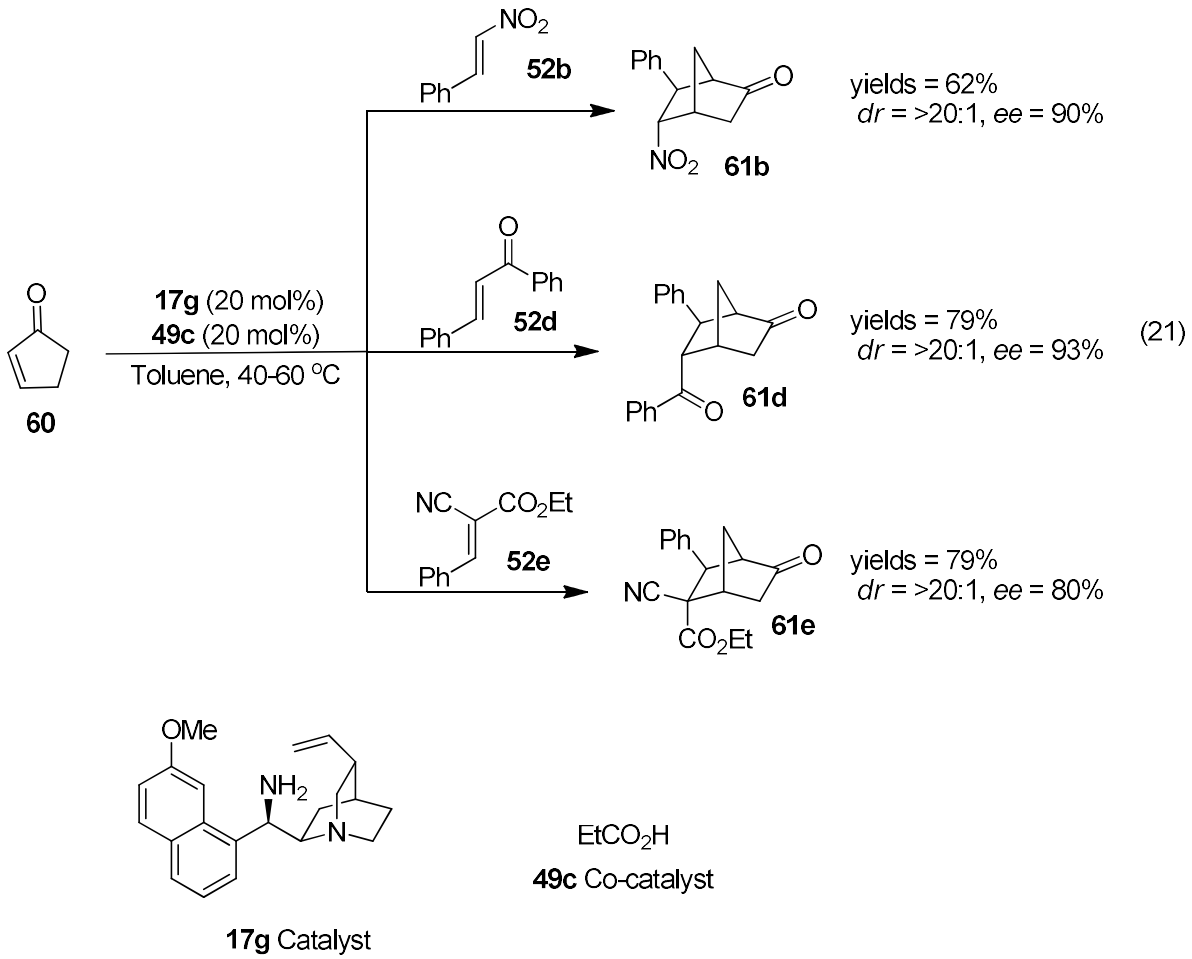


catalyst **17i**



49b Salicylic acid

In 2015, Jorgensen *et al.* reported a synthesis of norcamphor scaffold containing multifunctional chiral centers with high stereoselectivity through Barbas dienamine platform. In this protocol, they performed the reaction of cyclopentenone **60** with the most common class of different electron deficient olefins such as nitro, amide, ester and cyno substituted olefins, chalcones, conjugated malononitriles **52** in presence of primary amine quinine-based catalyst in toluene as solvent to afford the corresponding products. This protocol turned out to be very general to synthesize a variety of 5,6-substituted norcamphor **61** derivatives in high yields with excellent stereoselectivity (eq. 21).[21]



Attracted by the synthetic and biological applications of nitrogen containing heterocyclic compounds and spiro compounds, and considering the strong demand for their preparation under extreme mild conditions, we were interested to develop new synthetic protocols which could proceed under mild conditions to provide the desired products in excellent yields.

As our aim was to develop new methods for the preparation of *N*-containing hetrocyclic compounds and spiro compounds, major part of the thesis work was focused on the base/amine catalyzed enolate mediated synthesis of highly substituted 1,2,3-trizoles and sultams . In addition, another part of the thesis work was centered on the amine catalyzed 2-amino buta-1,3-diene mediated synthesis of spiro compounds. The results of these investigations have been discussed in detail in chapters 2-5.

PREFACE

*The area of organocatalysis known to mimic the characteristics of bio-molecules and enzymes, is now considered as the "third pillar of asymmetric catalysis". In recent years, organocatalytic reactions are becoming powerful tools for the construction of complex molecular skeletons. More importantly, organocatalytic approaches have become alternative to the metal mediated transformations because of their simple structure of the catalyst, simple operation technique, milder conditions, high efficiency and regiospecificity, readily available precursors and are potentially greener. Different kinds of in situ generated intermediates of carbonyl activation in amine catalysis has been developed for the construction of highly functionalized molecules with good selectivity. The present thesis entitled "**Stereoselective Synthesis of Drug-like Molecules via Catalytic Enolates and Dienamines**" describes the reactions involving enolate- and 2-aminobuta-1,3-diene intermediates in the synthesis of highly functionalized molecules of pharmaceutical and biological importance. In all sections, a brief introduction is provided to keep the present work in proper perspective, the compounds are sequentially numbered (bold), and references are marked sequentially as superscript and listed at the end of the thesis. All the figures included in the thesis were obtained by DIRECT PHOTOCOPY OF THE ORIGINAL SPECTRA, and in some of them uninformative areas have been cut to save space.*

In first chapter, a mild and efficient procedure for the synthesis of highly functionalized heterocycles such as 5-amino-1,4-disubstituted-1,2,3-triazoles has been discussed. The resulting products have found wide applications in pharmaceuticals, material chemistry, polymer, organic, and bio-organic chemistry. To construct such functionalized molecules a diversity-oriented, green, sustainable and practical synthesis is required. Here we achieved this by using simple starting materials such as monosubstituted acetonitriles and aryl azides in the presence of catalytic amount of Cs_2CO_3. The mild carbonate base-catalyzed azide–acetonitrile [3+2]-cycloaddition (AAC) reaction proceeds at high rate and regioselctivity and it is one of the best reaction conditions for the synthesis of 5-amino-1,2,3-triazoles.

In second chapter, we described enolate-mediated synthesis of 1,5-disubstituted-4-thio-1,2,3-triazoles and 1,5-disubstituted-1,2,3-triazoles by utilizing organocatalytic azide-ketone [3+2]-cycloaddition (OrgAKC) reaction in excellent yields with high regioselectivity. A variety of enolizable 1-aryl-2-(arylthio)ethanones or 1-alkyl-2-(alkylthio)ethanones and aryl azides were employed as starting materials under tertiary amine-catalysis. Further, these products were converted into medicinally important and materially useful 1,5-disubstituted-1,2,3-triazoles by treatment with Raney-Ni.

In third chapter, we demonstrated the synthesis of benzosultams from the highly reactive N-sulfonyl α-ketiminoesters, and unmodified ynones through Tomita zipper [3+2]-cycloaddition protocol. Reaction of N-sulfonyl α-ketiminoesters with unmodified ynone in the presence of organophosphine catalyst and acid co-catalyst afforded the benzosultams in excellent yields with less selectivity. Many benzosultams have found wide range of applications in biological, medicinal and organic chemistry and also serve as intermediates in many synthetic transformations.

In fourth chapter, we demonstrated a three-component [4+2]-cycloaddition reaction under the catalysis of chiral primary amines along with co-catalysts to synthesize medicinally/materialistically important chiral poly-functionalized spirocyclic ketones under the simple and ambient conditions. Here we achieved by using simple starting materials such as differently substituted benzylideneacetones, and arylaldehydes as the substrates along with 1,3-indandione which in situ generate 2-arylidene-1,3-indanediones as the dienophile and 2-aminobuta-1,3-dienes as the diene source, synergistic-catalysis of chiral primary amines and simple Brønsted acid.

LIST OF ABBREVIATIONS

AAC	azide-alkyne cycloaddition
AANC	azide-acetonitrile cycloaddition
Ac	acetyl
AcOH	acetic acid
Ac_2O	acetic anhydride
AKC	azide-ketone cycloaddition
Anal.	analysis
aq.	Aqueous
ATCDA	asymmetric three component Diels-Alder reaction
Ar	aryl
Bn	benzyl
Boc	butyloxy carbonyl
Bp	boiling point
br	broad
Bu	butyl
*t*Bu or ^{t}Bu	*tertiar*y-butyl
n-BuLi	*n*-butyl lithium
Bz	benzyl
calcd.	calculated
cat.	catalytic
cm	centimeter
$CHCl_3$	choloform
CH_3CN	acetonitrile
$C_6H_5CH_3$	toluene
Cs_2CO_3	Caesium carbonate
CSP	chiral stationary phase
D	dipole moment
DA	Diels Alder
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of a doublet
ddd	doublet of a doublet of a doublet
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DMAP	dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMTC	5,5-dimethylthiazolidium-4-carboxylic acid
DTCDA	diastereospecific three component Diels-Alder
dr	diastereomeric ratio
dt	doublet of a triplet
EDG	electron donating group
ee	enantiomeric excess
eq.	equation

equiv.	equivalent (s)
Et	ethyl
EtOH	ethyl alcohol
Et_2O	diethylether
EWG	electron withdrawing group
Fg	functional group
Fig.	figure
gm	gram (s)
h	hour (s)
Hz	hertz
Hex	hexyl
HIV	human immunodeficiency virus
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
^{i}Pr	isopropyl
IR	infrared
K_2CO_3	potassium carbonate
KOH	potassium hydroxide
$LiAlH_4$	lithium aluminum hydride
lit.	literature
m	multiplet
m-CPBA	*m*-chloro perbenzoic acid
M	molarity
Mp.	melting point
Me	methyl
mg	milligram (s)
mGluR1	metabotropic glutamate receptor 1
min	minutes
mL	milliliter
mol	mole
mmol	millimole
MW	microwave
$NaBH_4$	sodium borohydride
Ni	nickel
NMR	nuclear magnetic resonance
o	ortho
OrgAAC	organocatalytic azide-aldehyde cycloaddition
OrgAOC	organocatalytic arylideneacetone-olefin cycloaddition
PET	positron emission tomography
Ph	phenyl
PGES	Prostaglandin E synthase
Pg	protecting group
ppm	parts per million
p-TSA	*p*-toluenesulfonic acid
pr	propyl
q	quartet
RT	room temperature
s	singlet
sec	secondary
S_NAr	nucleophilic aromatic substitution

t	triplet
TBAI	tetrabutylammonium iodide
TBHP	tertiary-butyl hydroperoxide
TBPB	tertiary-butyl peroxybenzoate
*t*BuOK	Potassium tertiarybutoxide
td	triplet of a doublet
TEA	triethylamine
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
TS	transition state
TsIm	*N*-(p-toluenesulfonyl)imadazole
UV	ultraviolet
α	alpha
β	beta

Part-A

3. Azide-Acetonitrile "Click" Reaction Triggered by Cs_2CO_3: An Atom-Economic, High-yielding Synthesis of 5-Amino-1,2,3-Triazoles

3.1 Introduction

*1,2,3-T*riazoles have emerged as an important "amide isosteres" with unique chemical/physical properties and are widely used as pharmaceuticals.[22] Many of the 1,4- or 1,5-disubstituted and the 1,4,5-trisubstituted 1,2,3-triazoles have found wide range of applications in biological, medicinal, organic, bio-organic, polymer and material chemistry due to their surrogating behavior with amide bonds.[22] Several recent studies including relative planarity, strong dipole moment (4-5 D), and amphihydrogen-bonding capability of 1,2,3-triazoles indicate their bio-similarity with amide bonds. 1,2,3-Triazoles have become better choice than amide bonds in biological chemistry due to their inertness towards oxidation, hydrolysis and enzymatic degradation.[22c,22d,22h,22l]

In a search for new-type of 1,2,3-triazoles, we thought of synthesizing 5-amino-1,2,3-triazoles.[23] As these compounds posses high dipole moment compared to simple 1,2,3-triazoles, they have shown significant role in pharmaceutical/biological chemistry (Figure 1).[23] Although in the literature simple enolizable nitriles are used as substrates to furnish 5-amino-1,2,3-triazoles through preformed keteniminate-formation with excess amount of strong base and aryl azides, its further development is required due to the utilization of excess amount of base and harsh reaction conditions.[24] Herein, we have shown interest to develop a general organocatalytic protocol for their high-yielding regioselective synthesis from less reactive monosubstituted acetonitriles (Scheme 1). Owing to various applications of 1,2,3-triazoles, the last two decades have witnessed the development of novel methods to synthesize functionalized triazoles in a regioselective manner. Especially, copper-catalyzed azide-alkyne [3+2]-cycloaddition reaction (eq. a, Scheme 1),[25] ruthenium- or iridium-catalyzed azide-alkyne [3+2]-cycloaddition reaction,[26] strain-promoted azide-alkyne [3+2]-

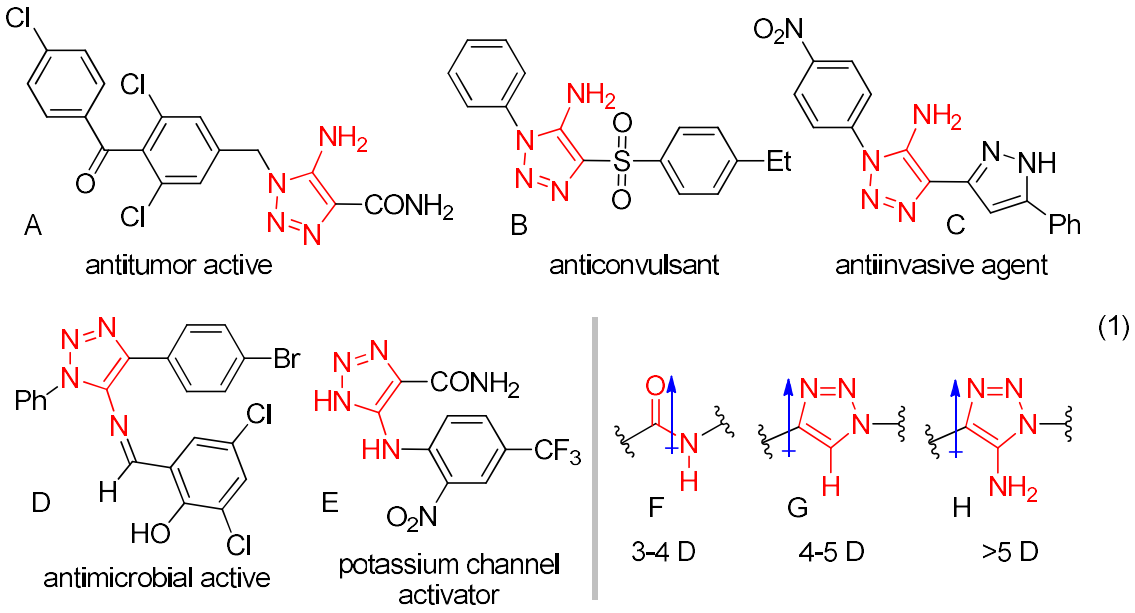
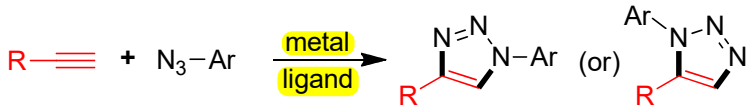


Fig.1 Potential applications based on the 5-amio-1,2,3-triazoles.

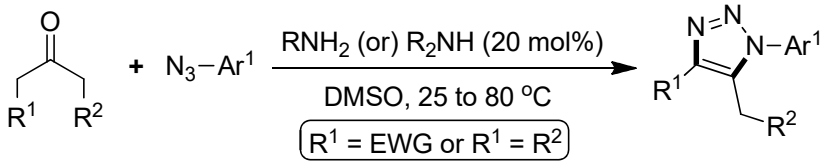
cycloaddition reaction,[27] organocatalytic enamine- or enolate-mediated azide-carbonyl [3+2]-cycloaddition reaction (eq. b-c, Scheme 1),[28, 2a-d] copper- or I_2/TBPB-promoted reaction of *N*-tosylhydrazones with anilines,[29] iodine-promoted three-component reaction of *N*-tosylhydrazones, arylketone and anilines,[30] and classical electronically controlled active olefin-azide [3+2]-cycloaddition reaction,[31] are among those novel reactions. Many of these reactions are suitable to synthesize a variety of 1,2,3-triazoles, except 5-amino-1,2,3-triazoles, because of the existence of active functional group NH_2 at the 5-position of 1,2,3-triazoles.

In view of this, we have chosen the recently discovered transition metal-free organocatalytic enolate-mediated [3+2]-cycloaddition protocol for the regioselective synthesis of 5-amino-1,2,3-triazoles from easily available aryl azides, monosubstituted acetonitriles and catalytic amount of *tert*-amines or carbonate salts (eq. d, Scheme 1). Herein, we have disclosed a general, rapid, and operationally simple azide-acetonitrile "click" (AANC) reaction for the chemo- and regioselective synthesis of fully decorated 5-amino-1,2,3-triazoles from the aryl azides and monosubstituted acetonitriles (eq. d, Scheme 1).

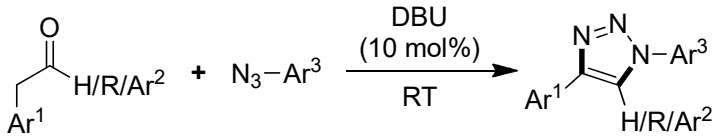
a) Metal-acetylide mediated click reaction: Meldal, Sharpless, and Fokin



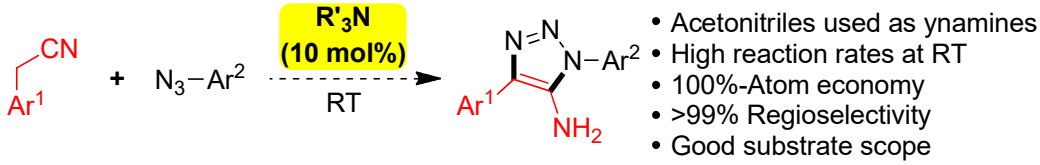
b) Amine-catalyzed enamine-mediated click reaction: Ramachary, Pons-Bressy, and Wang



c) Amine-catalyzed enolate-mediated click reaction: Ramachary



d) Amine- or base-catalyzed click synthesis of 5-amino-1,2,3-triazoles: **This work**

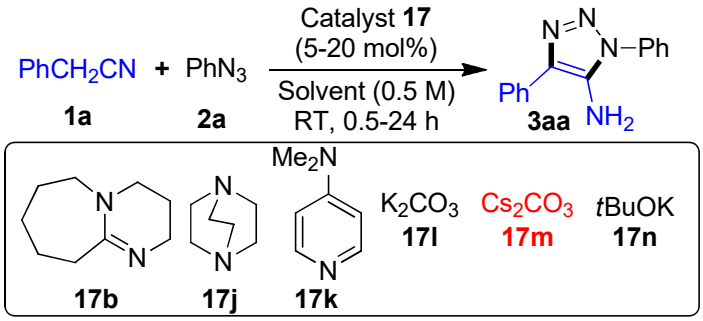


Scheme 1: Reaction design for the azide-acetonitrile "click" reaction

3.2 *Results and Discussion*

We undertook the prior optimization of the AANC reaction by screening simple amine and non-amine catalysts for the reaction of phenylacetonitrile **1a** with 1.0 to 1.5 equiv. of PhN_3 **2a** (Table 1). To our surprise, the reaction of **1a** with 1.5 equiv. of **2a** in DMSO under 20-mol% of DBU **17b**-catalysis at RT for 0.5 h furnished the expected product **3aa** as a single regioisomer with 85% yield (Table 1, entry 1). With lesser catalyst **17b** loading (10 or 5-mol-%), the reaction became inferior with respect to rate and yield (Table 1, entries 2 and 3). There is not much improvement in the above reaction by changing the solvent to DMF (Table 1, entry 4). The same AANC reaction at RT for 24 h under 20-mol% of DABCO **17j** or DMAP **17k**-catalysis furnished **3aa** in only 0% and 10% yields, respectively (Table 1, entries 5 and 6). After obtaining moderate results with *tert*-amine catalysts **17b, 17j** and **17k** through keteniminate-formation, we thought of exploring the same reaction with

Table 1: Reaction optimization[a]



Entry	Catalyst **3**	Solvent	*t* [h]	Yield **3aa** [%][b]
1	**17b** (20 mol%)	DMSO	0.5	85
2	**17b** (10 mol%)	DMSO	0.75	72
3	**17b** (5 mol%)	DMSO	24	45
4	**17b** (20 mol%)	DMF	16	45
5	**17j** (20 mol%)	DMSO	24	–
6	**17k** (20 mol%)	DMSO	24	10
7	**17l** (20 mol%)	DMSO	6	45
8	**17m** (20 mol%)	DMSO	0.5	90
9	**17m** (10 mol%)	DMSO	0.75	93
10[c]	**17m** (10 mol%)	DMSO	0.75	93
11[d]	**17m** (10 mol%)	DMSO	0.75	87
12[c,e]	**17m (10 mol%)**	**DMSO+H_2O**	**0.5**	**99**
13	**17m** (10 mol%)	H_2O	24	–
14	**17m** (10 mol%)	DMF	6	40
15	**17n** (20 mol%)	DMSO	0.5	85
16	**17n** (10 mol%)	DMSO	0.5	65

[a] Reactions were carried out in solvent (0.5 M) with 1.5 equiv. of **2a** relative to the **1a** (0.5 mmol) in the presence of 5-20-mol% of catalyst **17**. [b] Yield refers to the column-purified product. [c] 1.2 equiv. of **2a** was used. [d] 1.0 equiv. of **2a** was used. [e] DMSO/H_2O (7:3) was used as solvent.

non-amine bases **17l-n** as the catalysts (Table 1, entries 7-16). Intriguingly, the reaction of **1a** with 1.5 equiv. of **2a** in DMSO under 20-mol% of Cs_2CO_3 **17m**-catalysis at 25 °C for 0.5 h furnished **3aa** in 90% yield, but the same reaction under K_2CO_3 **17l**-catalysis furnished the product **3aa** in only 45% yield after 6 h (Table 1, entries 7 and 8). Amazingly, the same reaction with just 10-mol% of **17m**-catalysis also furnished **3aa** in 93% yield within 0.75 h

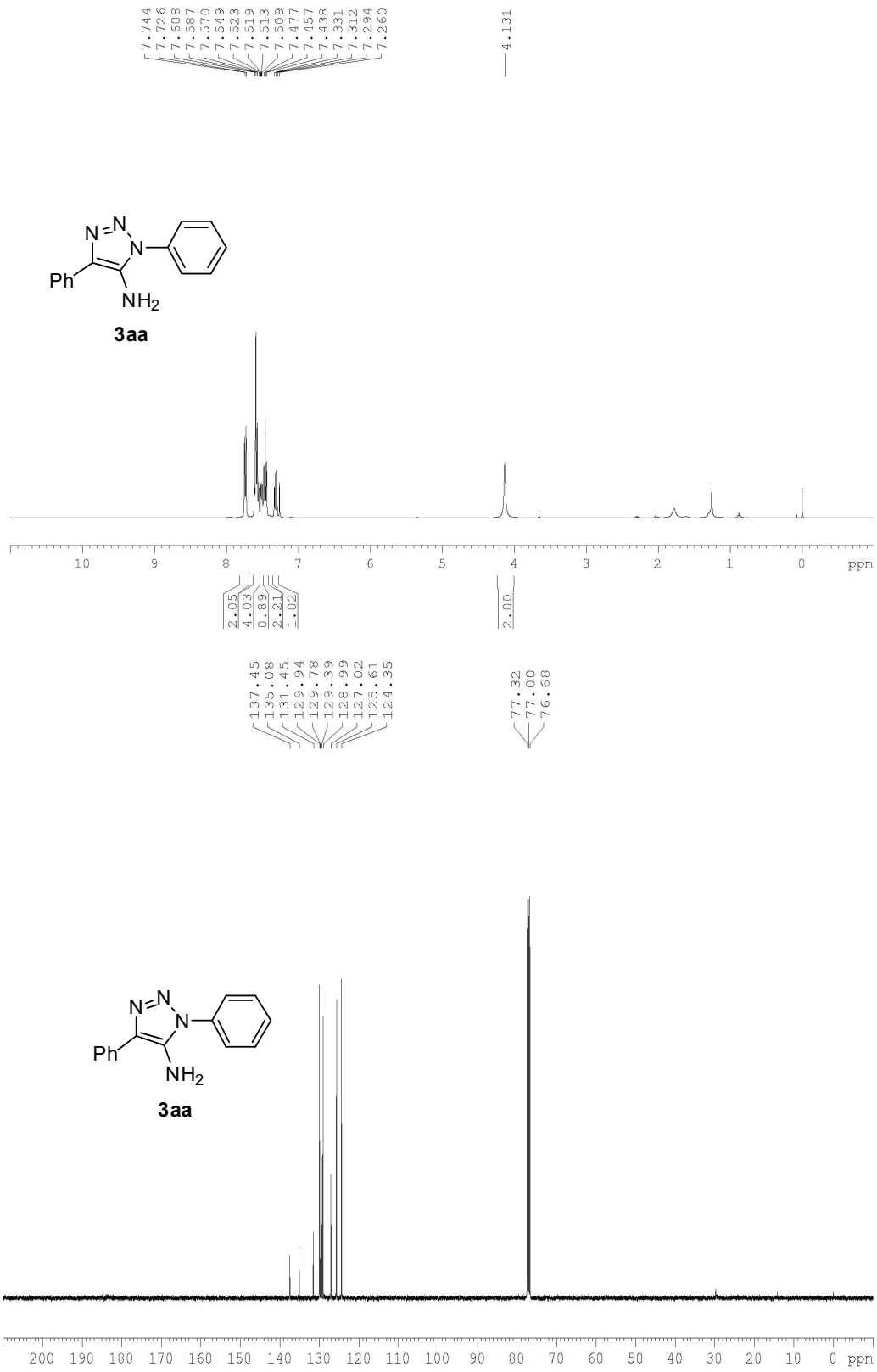
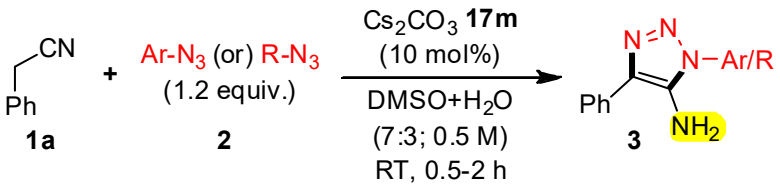


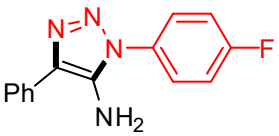
Figure-2: ^{1}H and ^{13}C NMR spectra of the product **3aa**.

(Table 1, entry 9). But the same AANC reaction under 10-mol% of **17m**-catalysis with decreased equivalents (1.2 or 1.0 equiv.) of **2a** for 0.75 h furnished **3aa** in 93% and 87% yields, respectively (Table 1, entries 10 and 11). The AANC reaction of **1a** with 1.2 equiv. of **2a** in DMSO+H_2O (7:3) under 10-mol% of Cs_2CO_3 **17m**-catalysis at 25 °C for 0.5 h furnished **3aa** in 99% yield, may be due to no decomposition of the product **3aa** in an aqueous dimethyl sulfoxide (Table 1, entry 12). We were astonished to find that, there was no reaction in pure water due to the poor solubility and only starting materials were recovered under 10-mol% of **17m**-catalysis for 24 h; and the product **3aa** was obtained in only 40% yield in DMF solvent (Table 1, entries 13 and 14). The same reaction with 20 or 10-mol% of *t*-BuOK **17n**-catalysis furnished **3aa** in 85% or 65% yield, respectively (Table 1, entries 15 and 16). Finally, we envisioned the optimized condition to be 25 °C in DMSO+H_2O (7:3) under 10-mol% of Cs_2CO_3 **17m**-catalysis to furnish the single isomer of fully decorated 5-amino-1,2,3-traizole **3aa** in 99% yield from **1a** and **2a** (Table 1, entry 12).

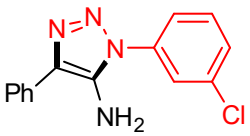
With the best optimized condition in hand, the generality of the keteniminate-mediated AANC reaction was investigated further. For this, various aryl and alkyl azides **2b-q** were reacted with phenylacetonitrile **1a** catalyzed by 10-mol% of Cs_2CO_3 **17m** at 25 °C in DMSO+H_2O (7:3; 0.5 M) for 0.5-2 h (Table 2). Fascinatingly, the aryl azides **2b-n** containing different functional groups of F, Cl, Br, Me, OMe, CF_3, CN, CO_2Et, CHO, and NO_2 at three different positions furnished the expected fully decorated 5-amino-1,2,3-triazoles **3ab-an** in good to excellent yields within 0.5-2 h. The AANC reaction of **1a** with 4-$CO_2EtC_6H_4N_3$ **2l** and 4-$CHOC_6H_4N_3$ **2m** under **17m**-catalysis in DMSO+H_2O furnished the products **3al** and **3am** in only 46-49% yields due to the decomposition, but the same reaction under the 10-mol% of DBU **17b**-catalysis in DMSO furnished **3al** in 75% and **3am** in 60% yields. Surprisingly, Cs_2CO_3 **17m** or DBU **17b**-catalyzed AANC reaction of **1a** with aliphatic azides of benzyl azide **2o** and (2-azidoethyl)benzene **2p** did not furnish the expected products **3**, but the same reaction under 20-mol% of *t*-BuOK **17n**-catalysis for 2 h furnished the 5-amino-1,2,3-triazoles **3ao** in 95% and **3ap** in 92% yields. There was no AANC reaction observed between **1a** and TsN_3 **2q** under all the three different catalytic conditions. The structure and the regiochemistry of the AANC products **3ab-ap** were confirmed by NMR analysis and also finally confirmed by the X-ray structure analysis on **3al** as shown in the Figure 8.[32]

Table 2: Azide scope with phenylacetonitrile **1a**[a,b]

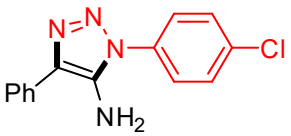




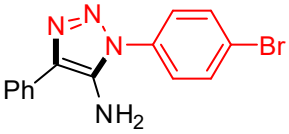
86% (**3ab**)



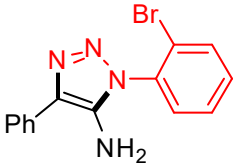
90% (**3ac**)



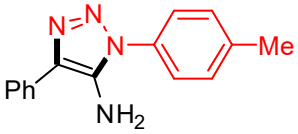
85% (**3ad**)



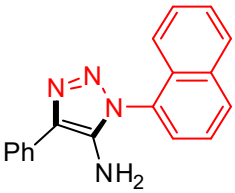
85% (**3ae**)



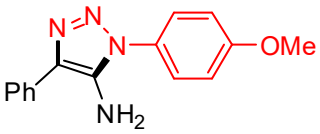
80% (**3af**)



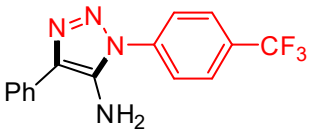
80% (**3ag**)



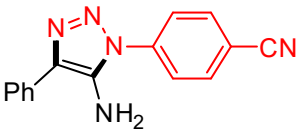
60% (**3ah**)



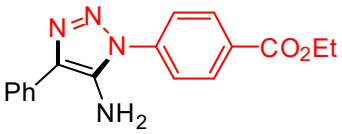
85% (**3ai**)



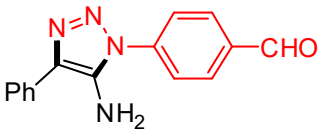
90% (**3aj**)



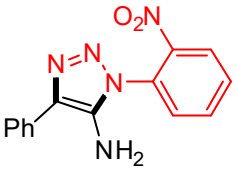
93% (**3ak**)



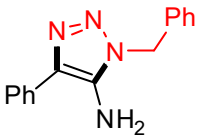
75% (**3al**)[c]



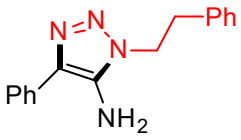
60% (**3am**)[c]



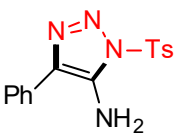
60% (**3an**)



95% (**3ao**)[d]



92% (**3ap**)[d]



<5% (**3aq**)

[a] Reactions were carried out in DMSO+H_2O (7:3; 0.5 M) with 1.2 equiv. of **2b-q** relative to the **1a** (0.5 mmol) in the presence of 10-mol% of **17m**. [b] Yield refers to the column-purified product. [c] DBU-catalysis at RT for 1-2 h. [d] *t*BuOK-catalysis at RT for 2 h.

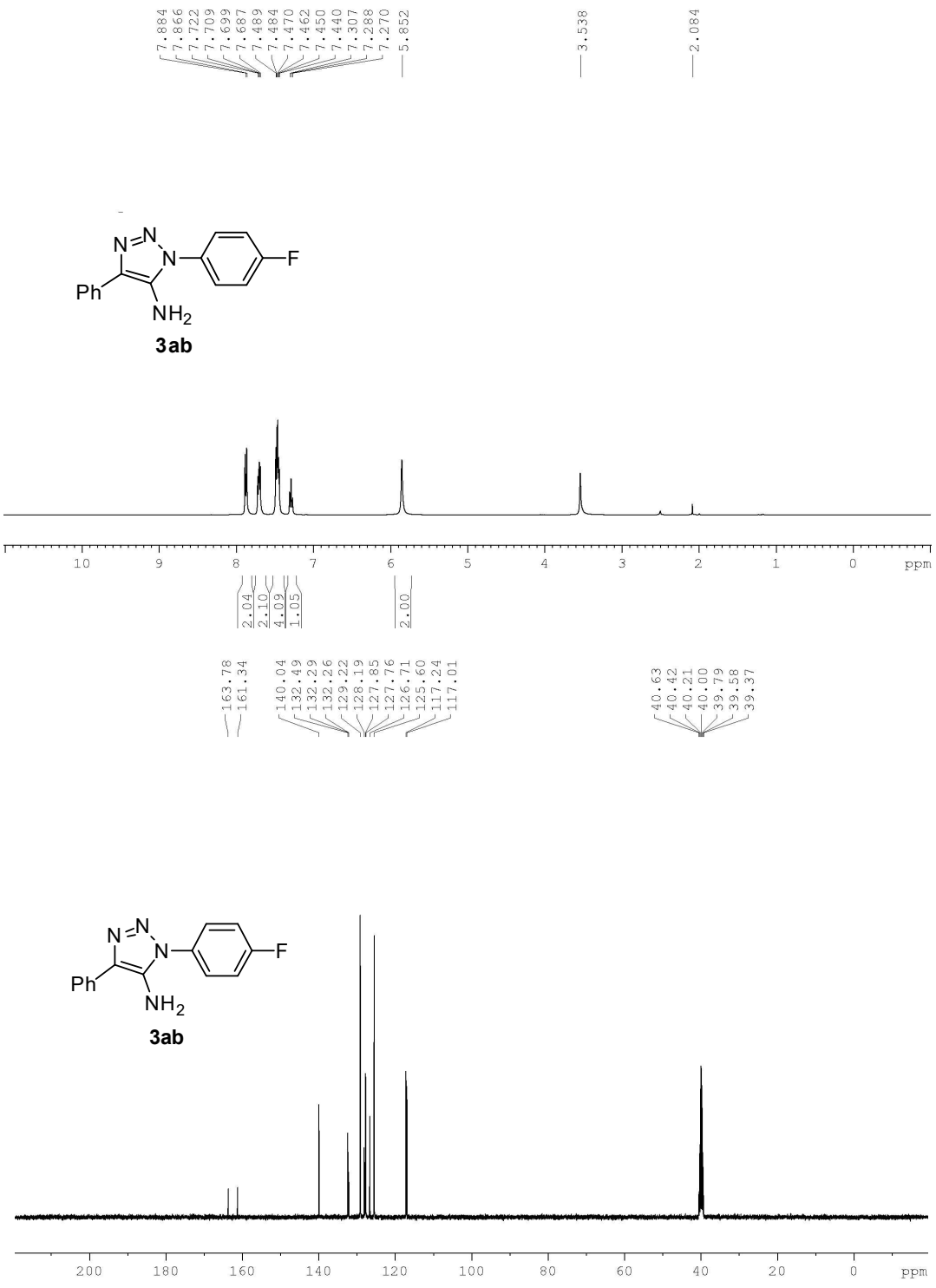


Figure-3: ^{1}H NMR and ^{13}C NMR spectrum of product **3ab.**

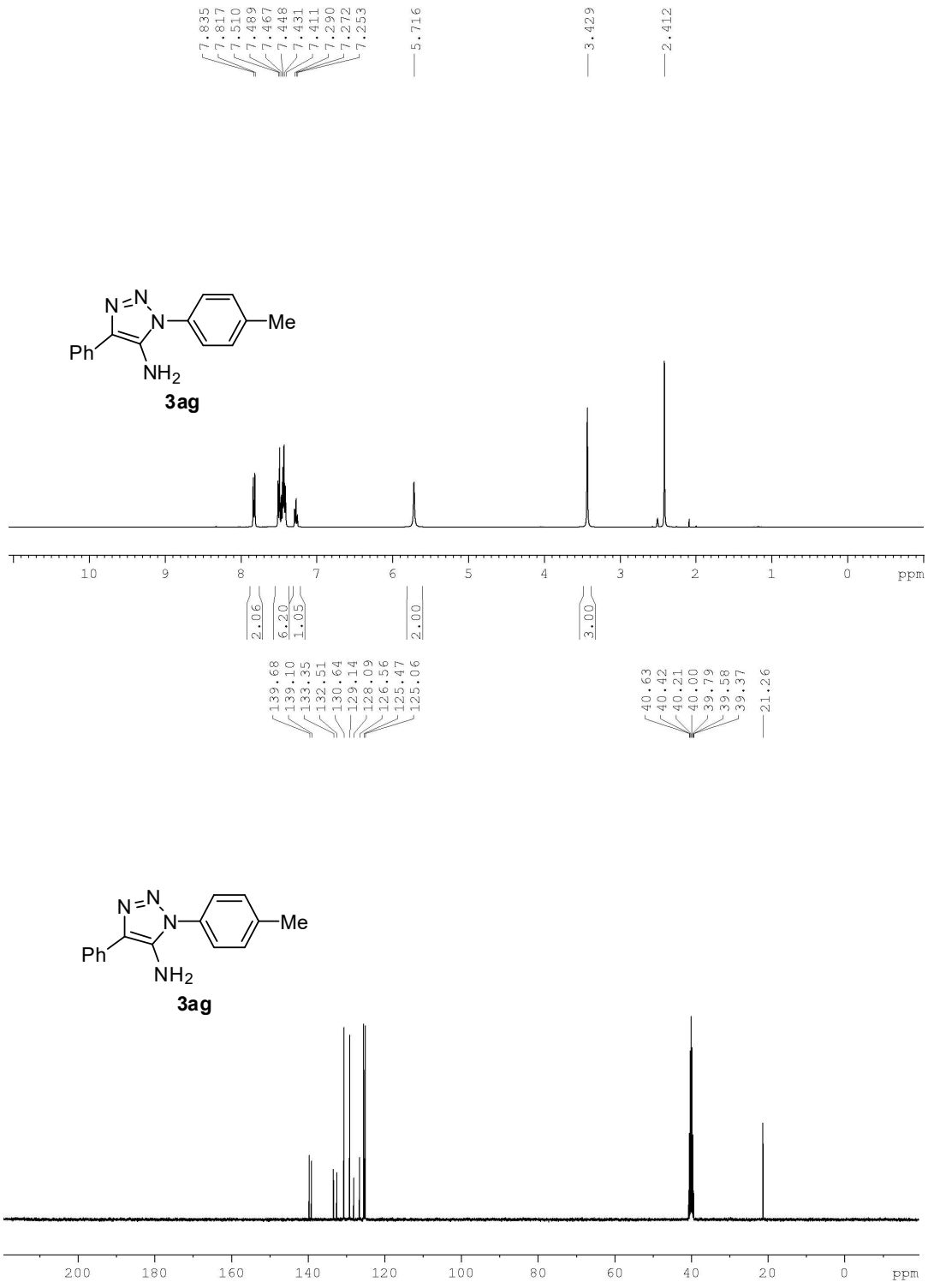


Figure-4: ^{1}H NMR and ^{13}C NMR spectrum of product **3ag.**

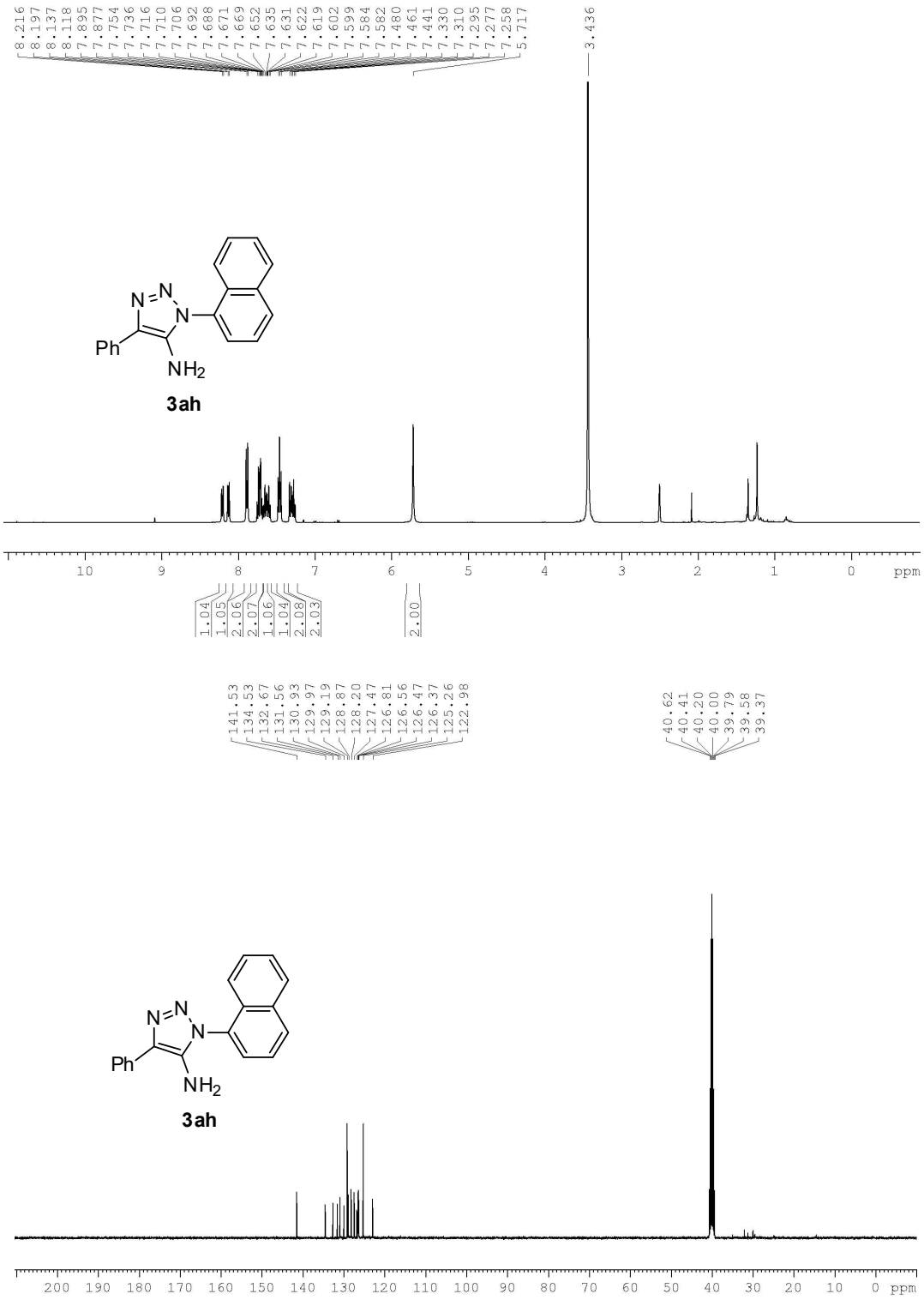


Figure-5: ^{1}H NMR and ^{13}C NMR spectrum of product **3ah.**

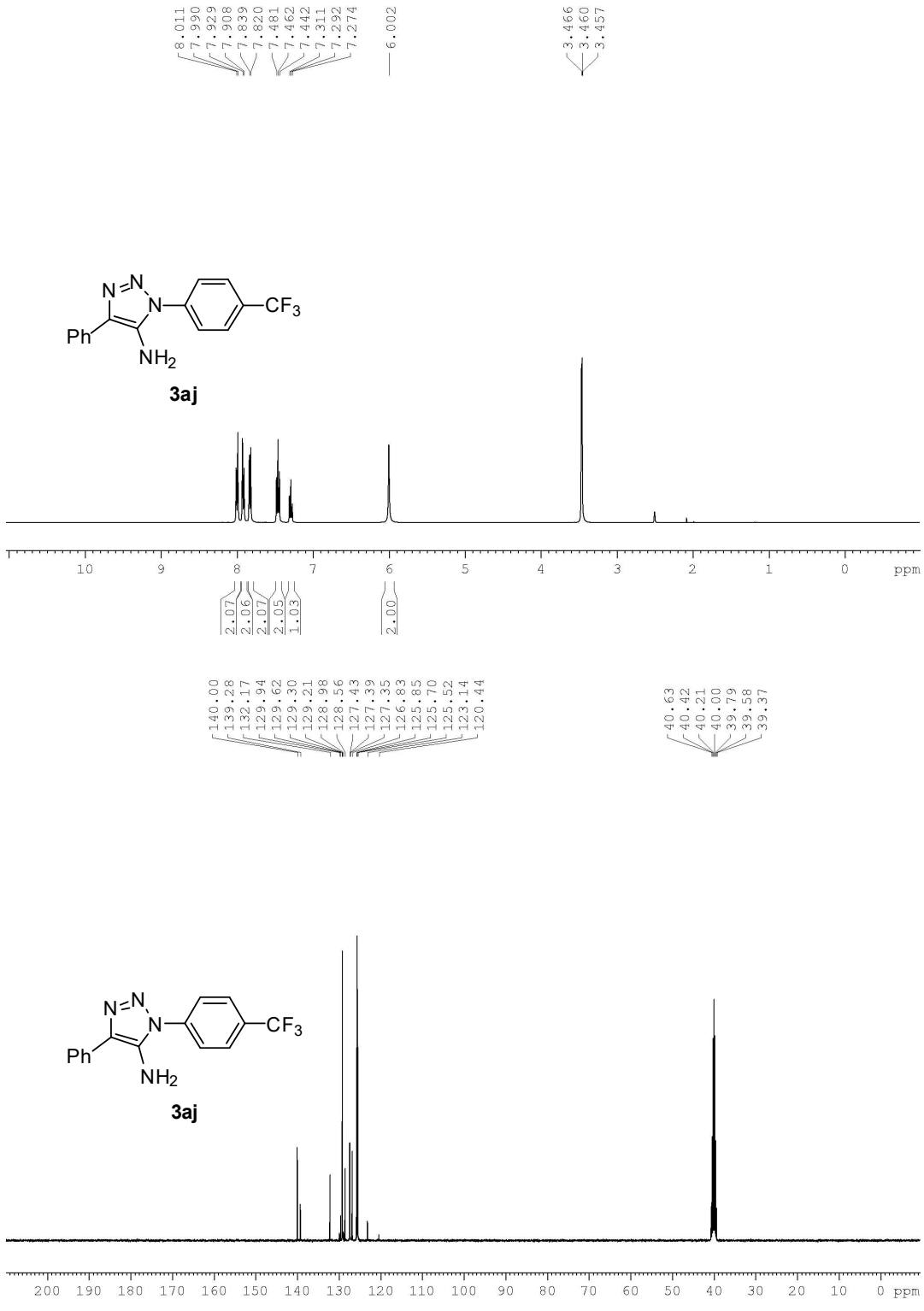


Figure-6: ^{1}H NMR and ^{13}C NMR spectrum of product **3aj.**

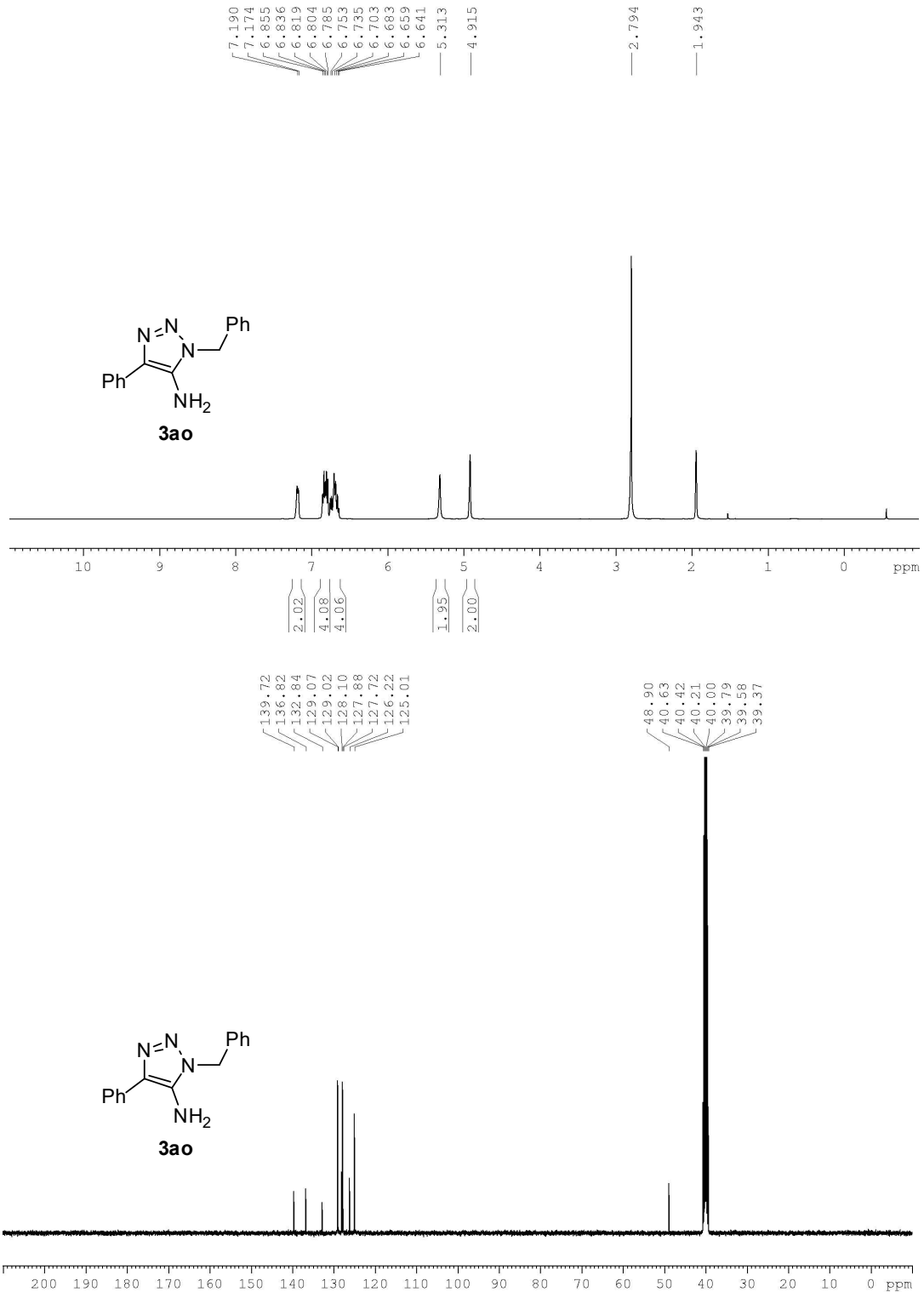


Figure-7: ^{1}H NMR and ^{13}C NMR spectrum of product **3ao.**

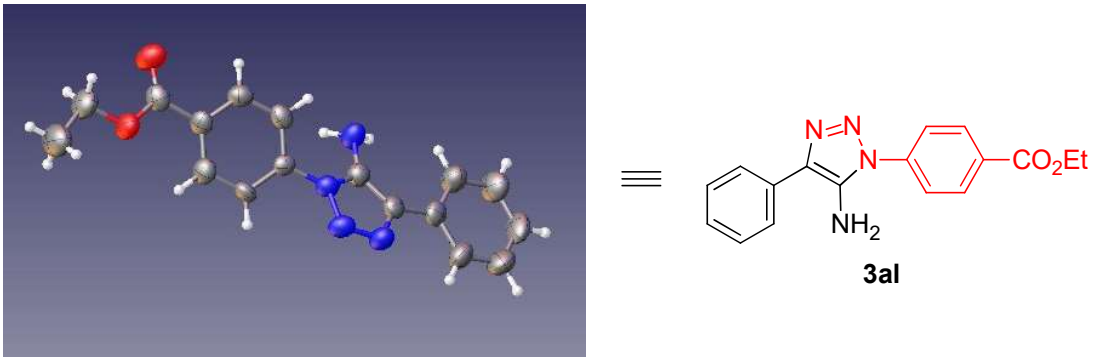
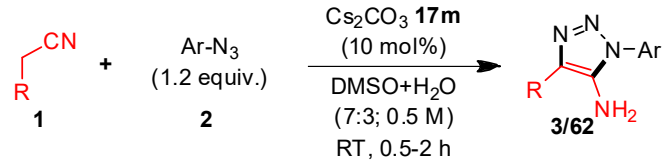


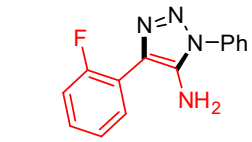
Figure 8. Crystal structure of ethyl 4-(5-amino-4-phenyl-1*H*-1,2,3-triazol-1-yl)benzoate (**3al**).

To develop a further diverse library of fully decorated 5-amino-1,2,3-triazoles **3**, and bis-5-amino-1,2,3-triazoles **62**, and also to further understand the electronic factors of monosubstituted arylacetonitriles **1** in the AANC reaction, we have chosen different arylacetonitriles **1b-p**, and simple aryl azides **2** (Table 3). The AANC reaction of 2-fluorophenylacetonitrile **1b** with less reactive PhN_3 **2a** under Cs_2CO_3-catalysis at 25 °C for 0.75 h furnished the 5-amino-1,2,3-triazole **3ba** in 93% yield (Table 3). In a similar manner, we have also tested five more examples of 3-F, 4-F, 4-Cl, 3-Br and 4-Br phenylacetonitriles **1c-g** for the AANC reaction with PhN_3 **2a** at 25 °C for 0.75 h, which furnished the 5-amino-1,2,3-triazoles 3**ca-ga** in 90-93% yields (Table 3). The AANC reaction of 3-Me, 4-Me, 4-OMe, 4-CF_3, 4-CN, and 2-NO_2-substituted phenylacetonitriles **1h-j** and **1m-o** with **2a** under **17m**-catalysis at 25 °C for 0.75-1.0 h furnished the fully decorated 5-amino-1,2,3-triazoles **3ha-ja** and **3ma-oa** in 80-93% yields, respectively without showing much electronic influence. But surprisingly, the AANC reaction of 4-OAc and 4-NHAc substituted phenylacetonitrile **1k/1l** with PhN_3 **2a** under Cs_2CO_3-catalysis needed a little higher temperature (60 °C) for 3 h and furnished the 5-amino-1,2,3-triazoles **3ka** and **3la** in only 50% and 40% yields, respectively. With applications in mind, we have prepared the bis-5-amino-1,2,3-triazoles **62pa**, **62po** and **62ar** in good yields from the treatment of 2,2'-(1,4-phenylene)diacetonitrile **1p** or **1a** with aryl azides PhN_3 **2a**, BnN_3 **2o**, or 1,4-bis(azidomethyl)benzene **2r** at 25 °C for 2 h under *t*-BuOK **17n**-catalysis. Initially, we were disappointed to find that there was no bis-5-amino-1,2,3-triazole **62pa** formation from the reaction of 2,2'-(1,4-phenylene)diacetonitrile **1p** with **2a** under Cs_2CO_3 **17m**-catalysis and only mono-triazole **3pa** was isolated in 50% yield. Later on switching to *t*-BuOK **17n** (20

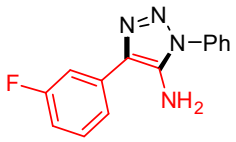
mol-%) as catalyst, we successfully synthesised the bis-5-amino-1,2,3-triazoles **62pa**, **62po** and **62ar** in 50%, 60%, and 60% yields respectively from the AANC reaction.

Table 3 : Reaction scope with different azides and phenylacetonitriles[a,b]

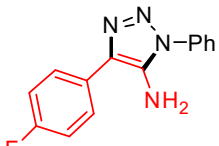




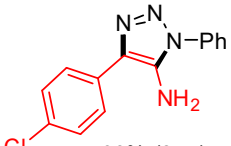
93% (**3ba**)



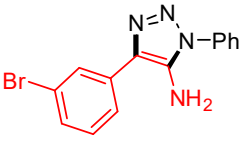
90% (**3ca**)



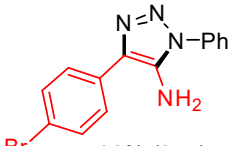
90% (**3da**)



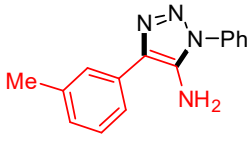
90% (**3ea**)



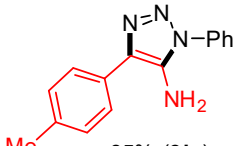
90% (**3fa**)



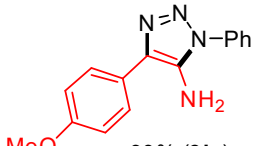
93% (**3ga**)



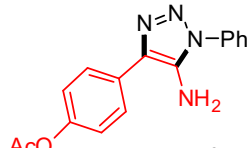
93% (**3ha**)



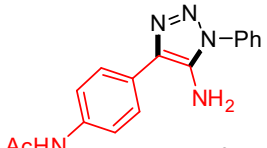
85% (**3ia**)



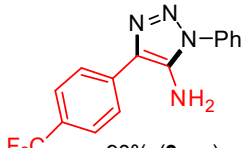
90% (**3ja**)



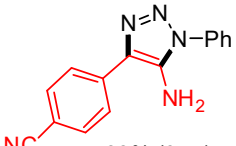
50% (**3ka**)[c]



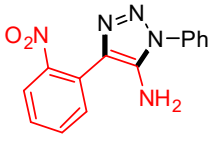
40% (**3la**)[c]



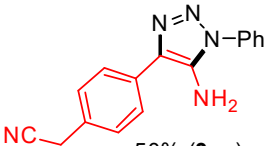
90% (**3ma**)



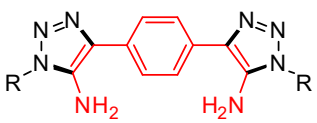
88% (**3na**)



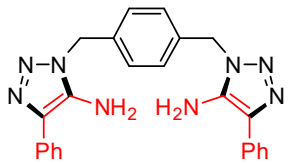
80% (**3oa**)



50% (**3pa**)



R = Ph: 50% (**62pa**)[d]
R = Bn: 60% (**62po**)[d]



60% (**62ar**)[d]

[a] Reactions were carried out in DMSO+H_2O (7:3; 0.5 M) with 1.2 equiv. of **2** relative to the **1** (0.5 mmol) in the presence of 10-mol% of **17l**. [b] Yield refers to the column-purified product. [c] Reaction performed at 60 °C for 3 h. [d] *t*BuOK-catalysis at RT for 2 h.

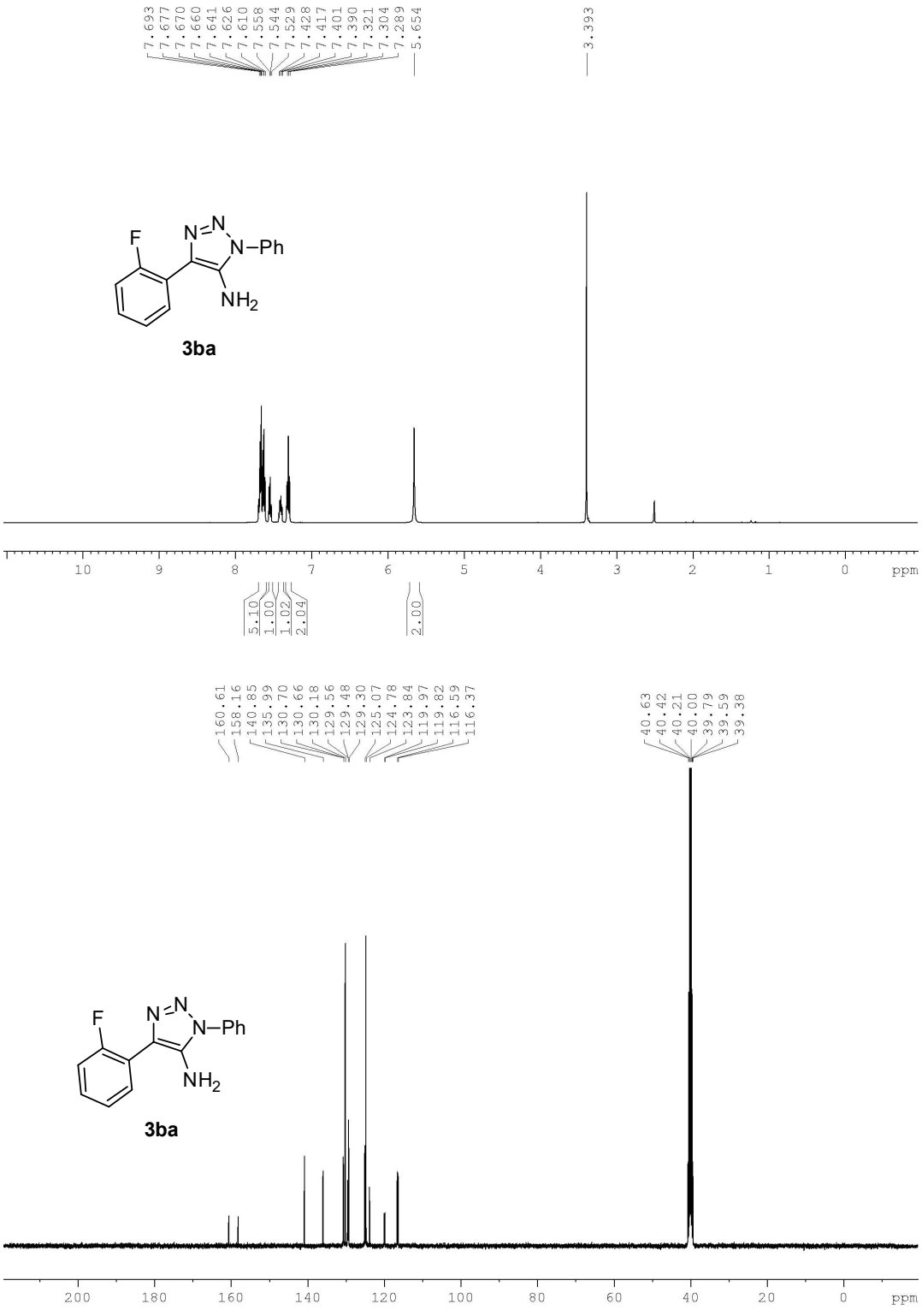


Figure-9: ^{1}H NMR and ^{13}C NMR spectrum of product **3ba.**

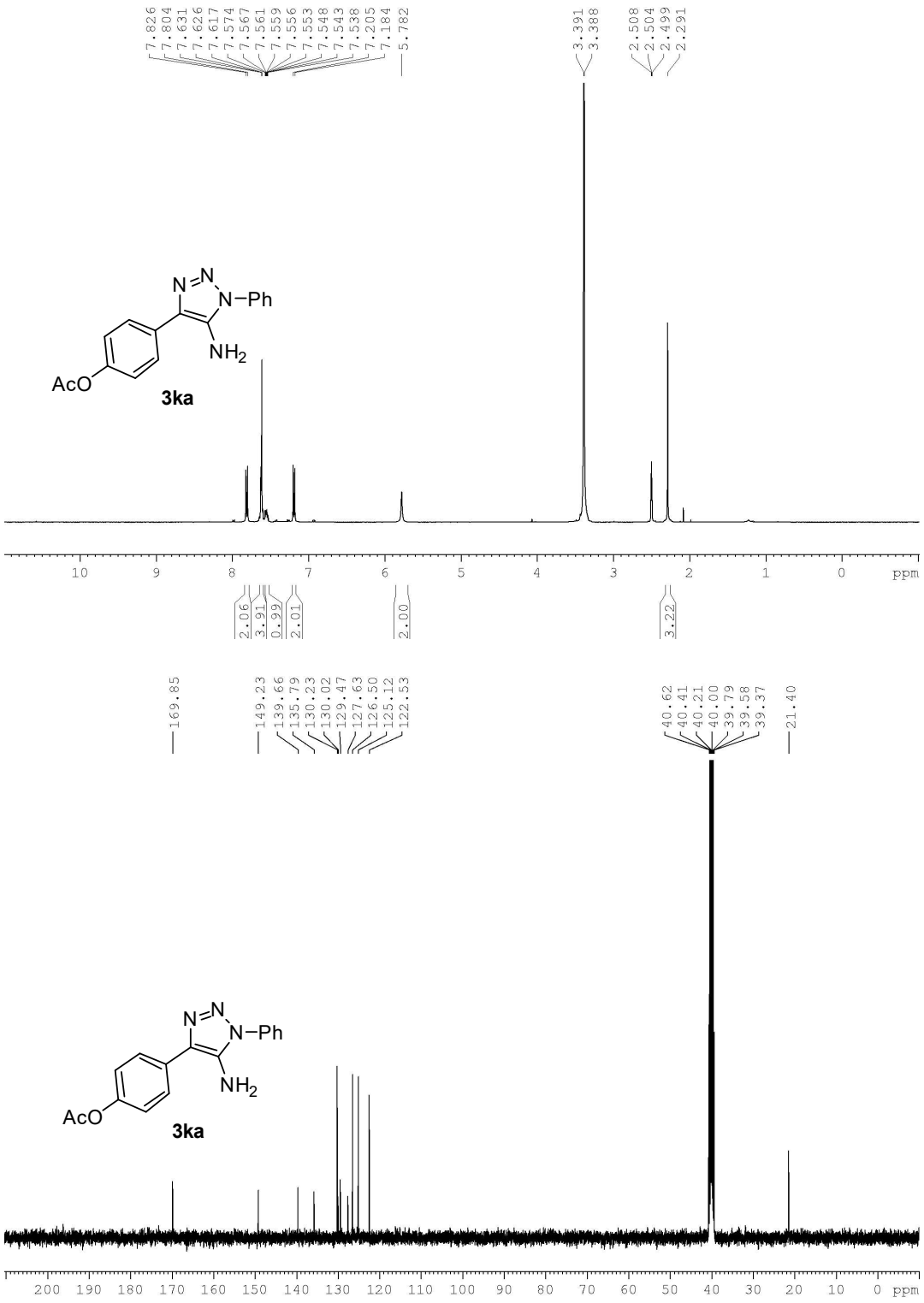


Figure-10: ^{1}H NMR and ^{13}C NMR spectrum of product **3ka.**

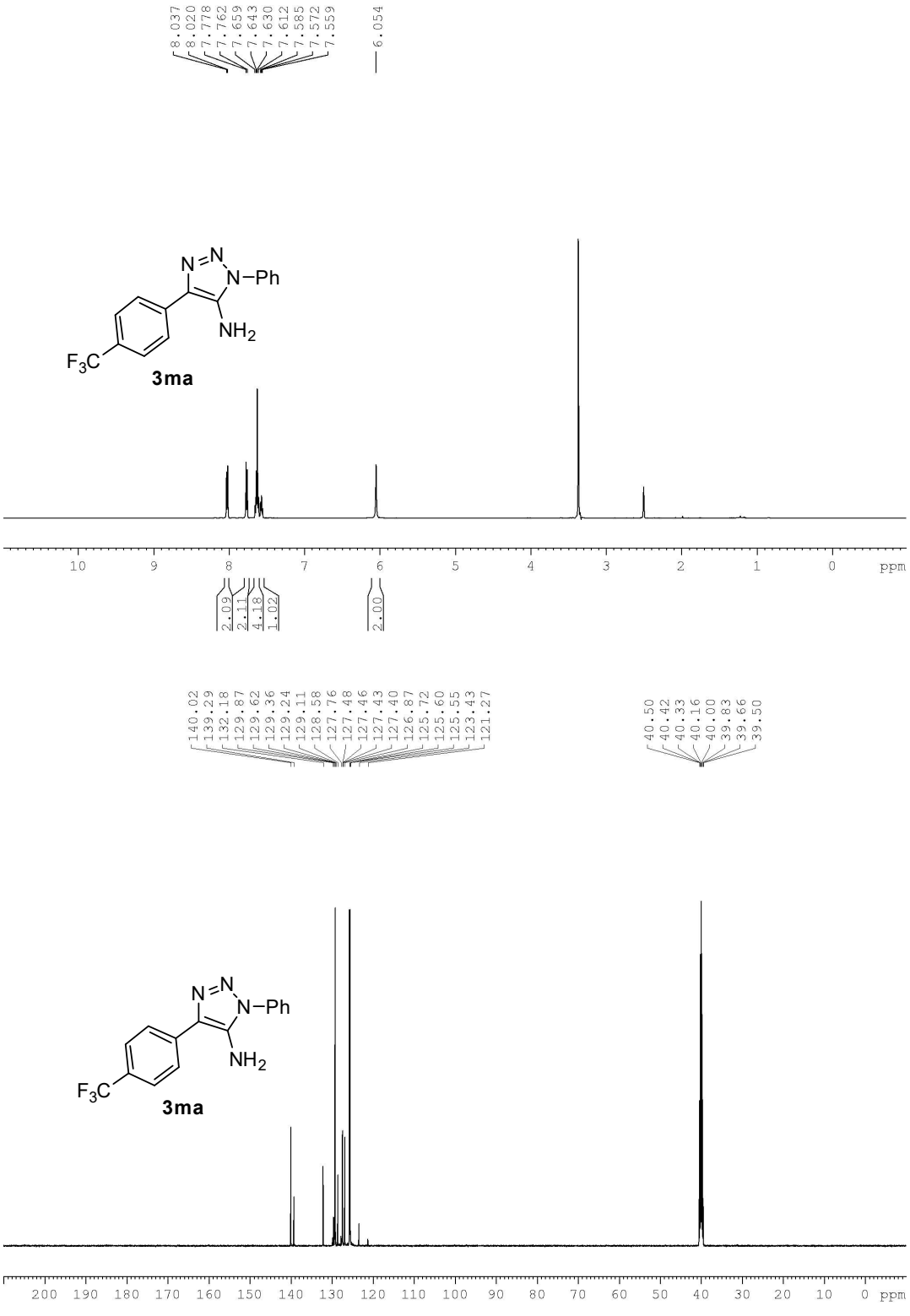


Figure-11: ^{1}H NMR and ^{13}C NMR spectrum of product **3ma.**

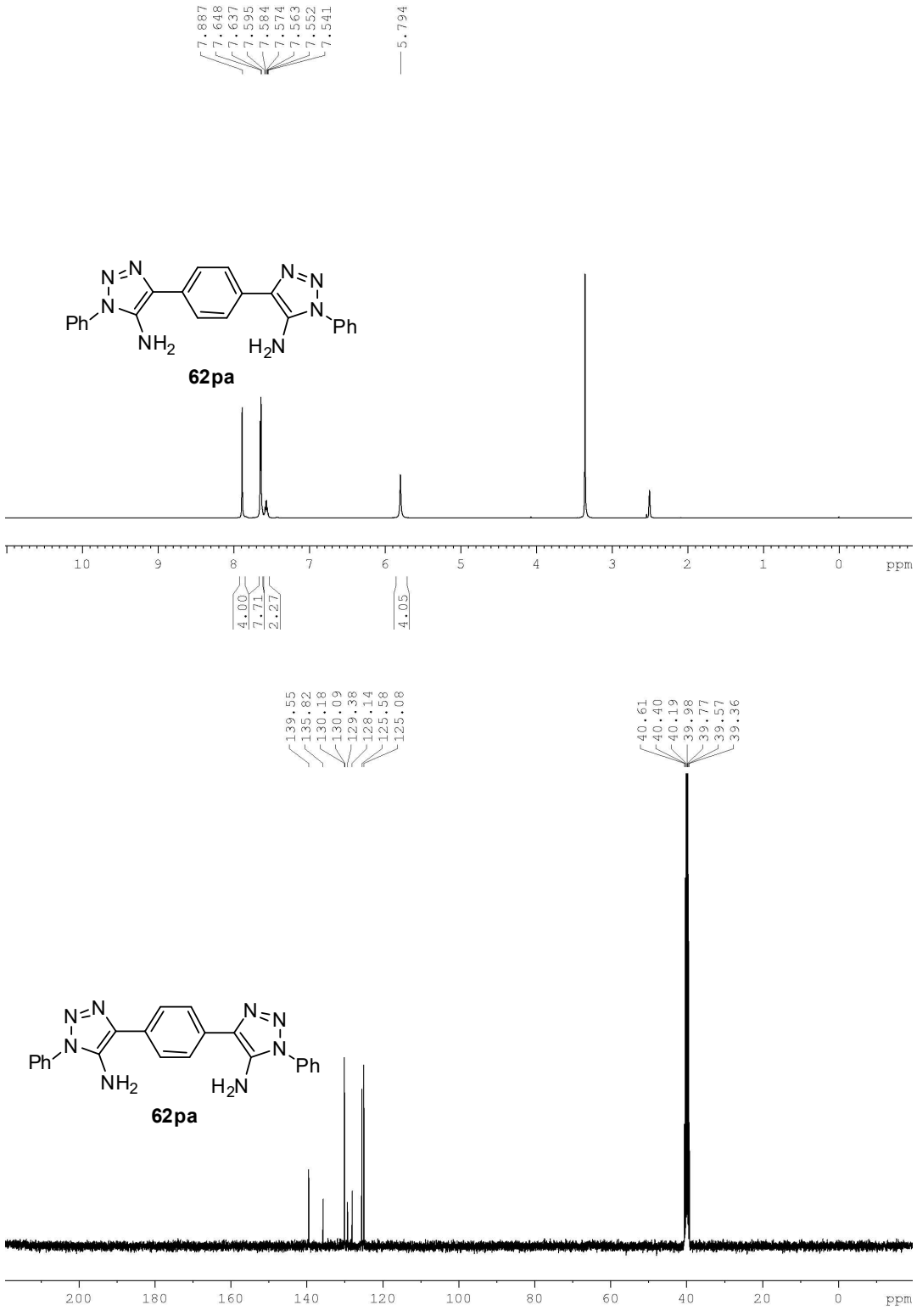


Figure-12: ^{1}H NMR and ^{13}C NMR spectrum of product **62pa.**

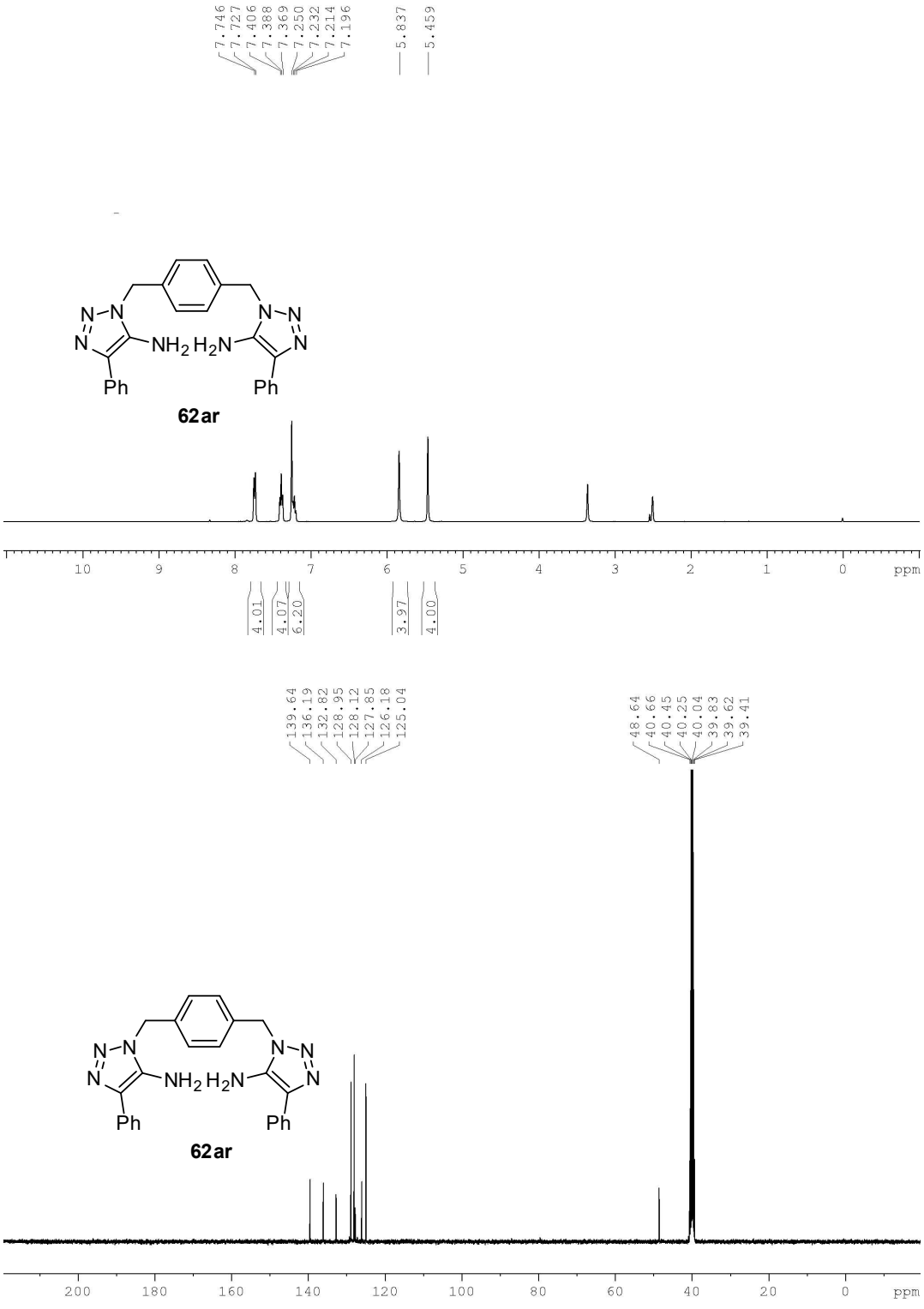
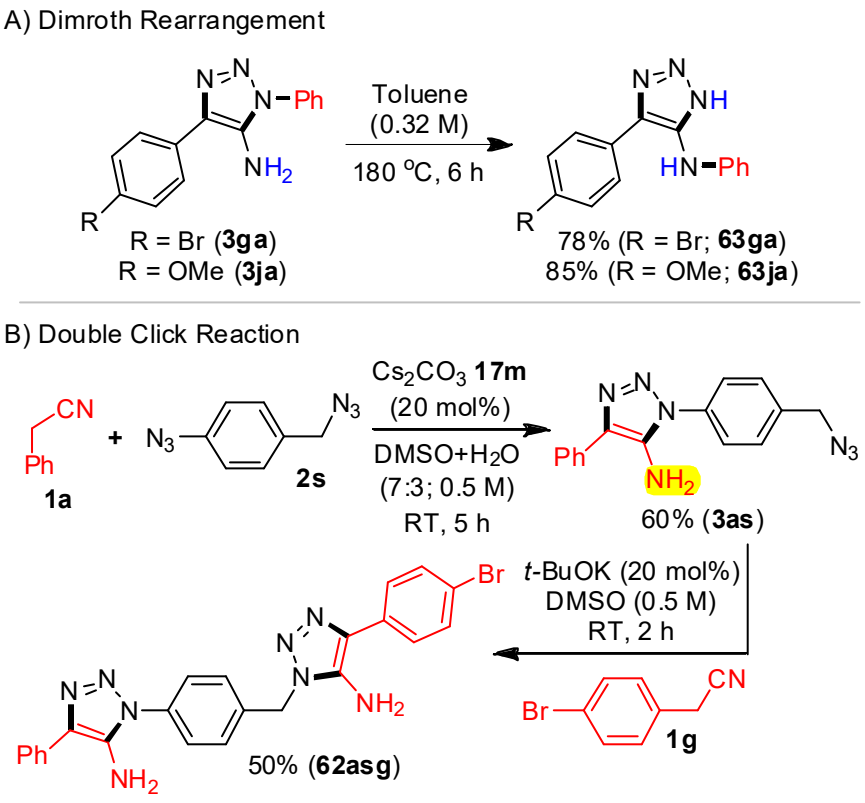


Figure-13: ^{1}H NMR and ^{13}C NMR spectrum of product **62ar.**

The utility of the AANC reaction was further represented by synthesizing medicinally useful compounds **63ga**, **63ja** and **62asg** (Scheme 2).[23] As shown in Scheme 2, analogues of potassium channel activators **63ga** and **63ja** were synthesized in very good yield from the corresponding 5-amino-1,2,3-triazoles **3ga** and **3ja** through the modified Dimroth rearrangement conditions.[33] In contrast, the literature conditions for the Dimroth rearrangement required highly basic solvent, high temperature and long reaction time.[13] Further, we synthesized the functionally rich double click compound **62asg** through the first AANC reaction of phenylacetonitrile **1a** with 1-azido-4-(azidomethyl)benzene **2s** in DMSO+H_2O at 25 °C for 5 h under **17m**-catalysis to furnish **3as** in 60% yield, which on *t*-BuOK-catalyzed second AANC reaction with 4-bromophenylacetonitrile **1g** at 25 °C for 2 h furnished **62asg** in 50% yield. These results clearly show the advantage of the AANC methodology, which enables a high-yielding metal-free synthesis of medicinally important 5-amino-1,2,3-triazoles.



Scheme 2: Application of azide-acetonitrile "click" reaction

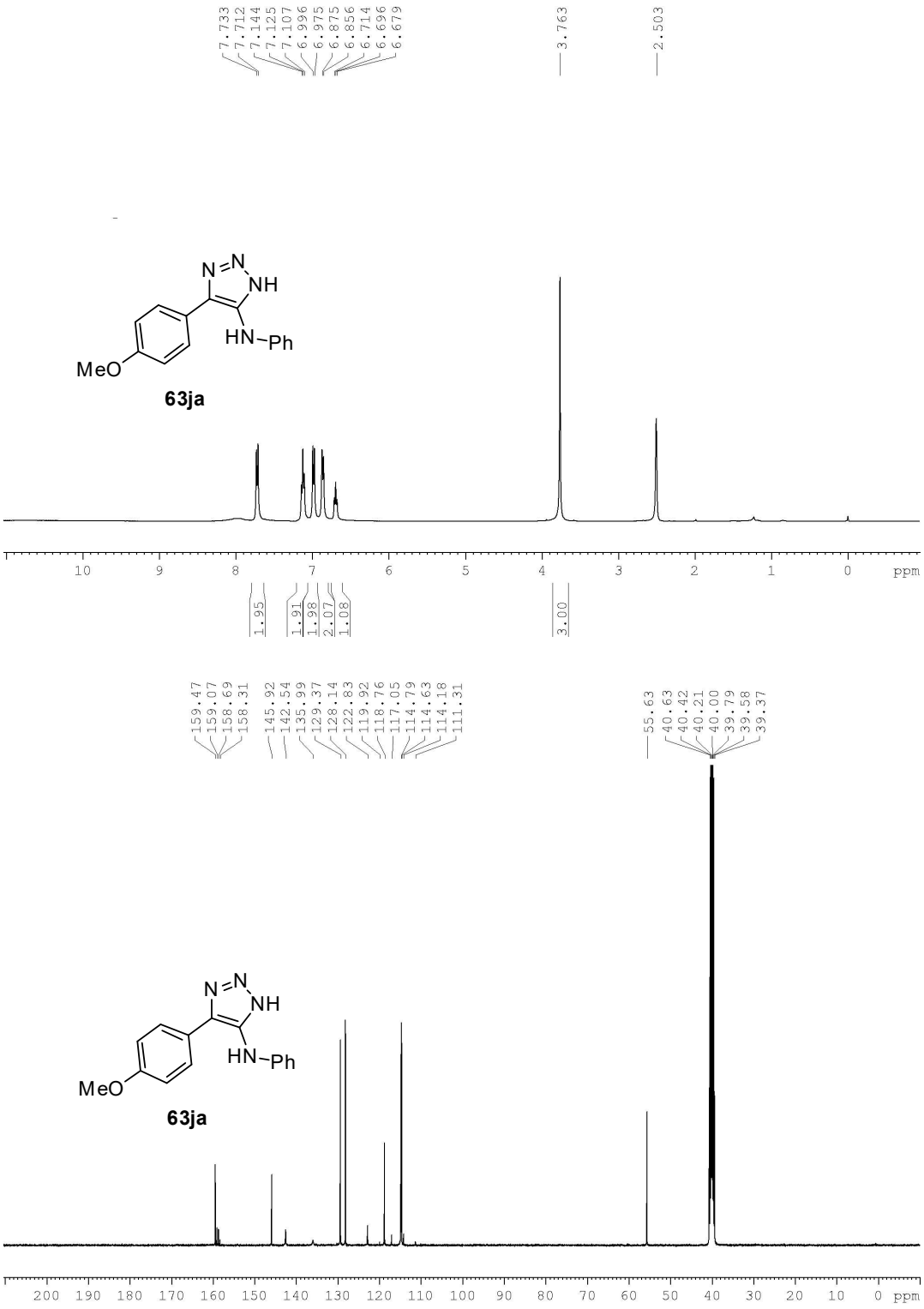


Figure-14: ^{1}H NMR and ^{13}C NMR spectrum of product **63ja.**

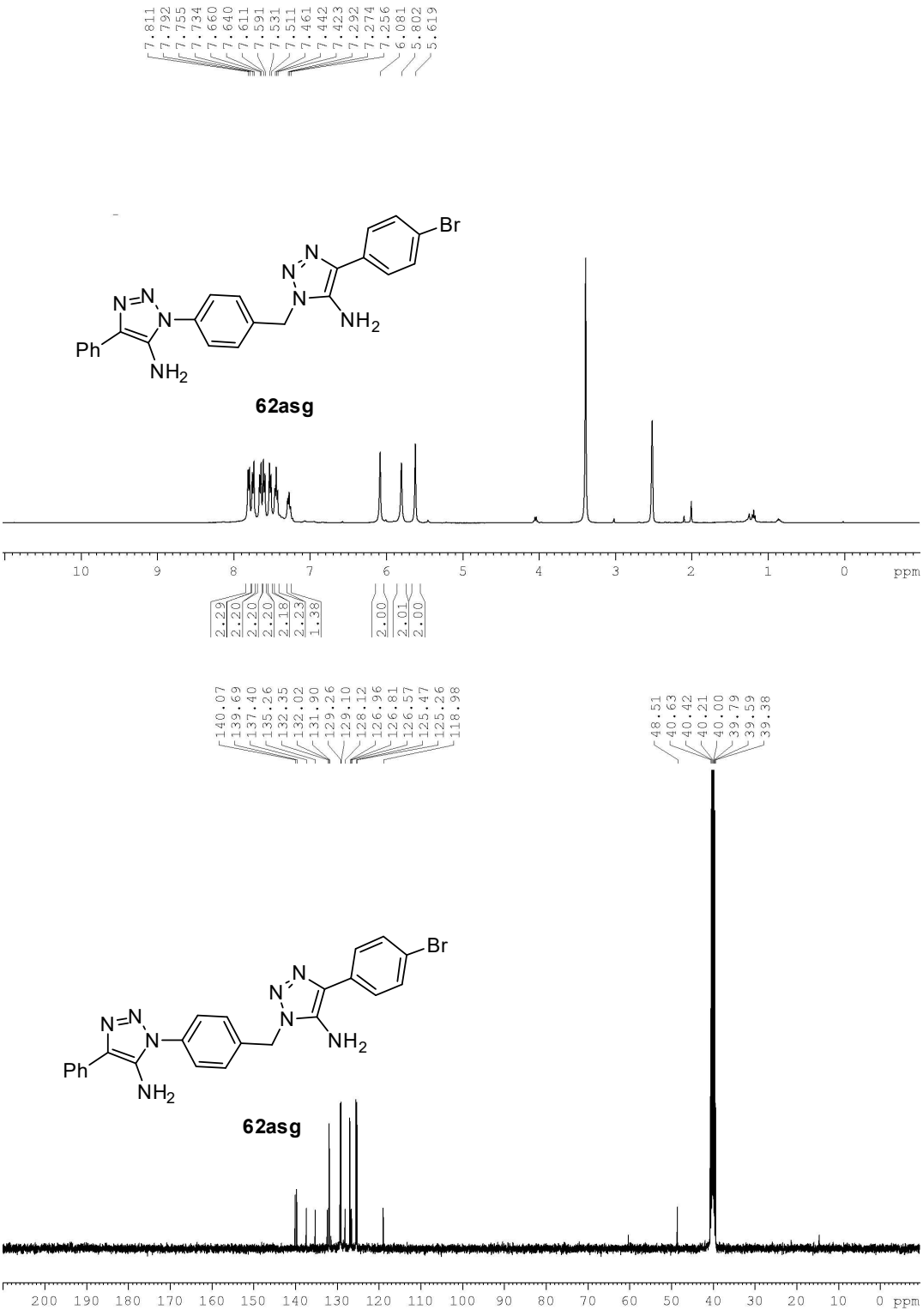
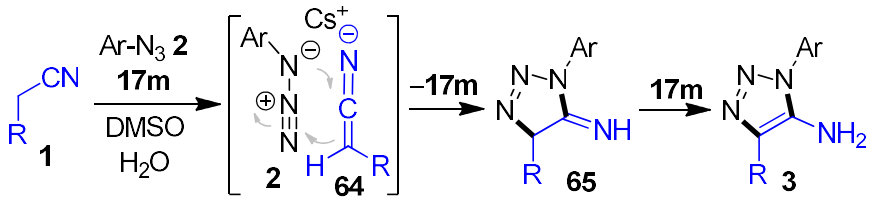


Figure-15: ^{1}H NMR and ^{13}C NMR spectrum of product **62asg.**

3.3 Mechanistic Insights

The provisional mechanism for the **17m**-catalyzed AANC reaction in DMSO+H_2O (7:3; 0.5 M) is illustrated in Scheme 3. Reaction of monosubstituted acetonitriles **1** with catalyst **17m** generates the keteniminate **64**,[34] which on *in situ* treatment with Ar-N_3 **2** furnishes selectively the adduct 1,4-diaryl-1*H*-1,2,3-triazol-5(4*H*)-imine **65** *via* concerted or stepwise [3+2]-cycloaddition reaction,[28] which on further rapid isomerisation transforms into the fully decorated 5-amino-1,2,3-triazole **3** at ambient conditions. In this AANC reaction, the formation rate and the stability of the reactive intermediates **64** and **65** seems to be induced by the presence of limited amount of water molecules in DMSO under the **17m**-catalysis.



Scheme 3: Proposed reaction mechanism for AANC reaction

3.4 Conclusion

In conclusion, we have demonstrated the keteniminate-mediated carbonate-catalyzed or organocatalytic azide-acetonitrile [3+2]-cycloaddition reaction that generates medicinally important 5-amino-1,2,3-triazoles decorated with useful functional groups. Carbonate-catalyzed AANC protocol highlights the metal-free conditions with high rate and selectivity, and easy access to a library of functionalized 5-amino-1,2,3-triazoles. Moreover, many of the reported syntheses have the disadvantage of requiring the strong bases with many equivalents or using highly reactive substrates; therefore, this catalytic protocol is very convenient. Further work is in progress to utilize the keteniminate-mediated AANC reactions in medicinal and material chemistry.

4. An Organocatalytic Regiospecific Synthesis of 1,5-Disubstituted-4-Thio-1,2,3-Triazoles and 1,5-Disubstituted-1,2,3-Triazoles

4.1 Introduction

1,4-/1,5-Disubstituted 1,2,3-triazoles and 1,4,5-trisubstituted 1,2,3-triazoles have garnered much interest as peptide bond isosteres and also as an important family of heterocycles, which exhibit a vast spectrum of properties and applications and are widely used in pharmaceuticals.[22] In particular, 1,2,3-triazoles containing 4-thiomethyl or 5-thio compounds and 1,5-disubstituted 1,2,3-triazoles have found widespread medicinal application in anticancer drugs, antifungal agents, antibacterial drugs, anti-inflammatory drugs, mPGES-1 inhibitors, bioorthogonal probes, and also as human dUTPase inhibitors (Figure 16).[35] With these applications, the development of more general and green protocols for the synthesis of their analogues is of significant interest.[36]

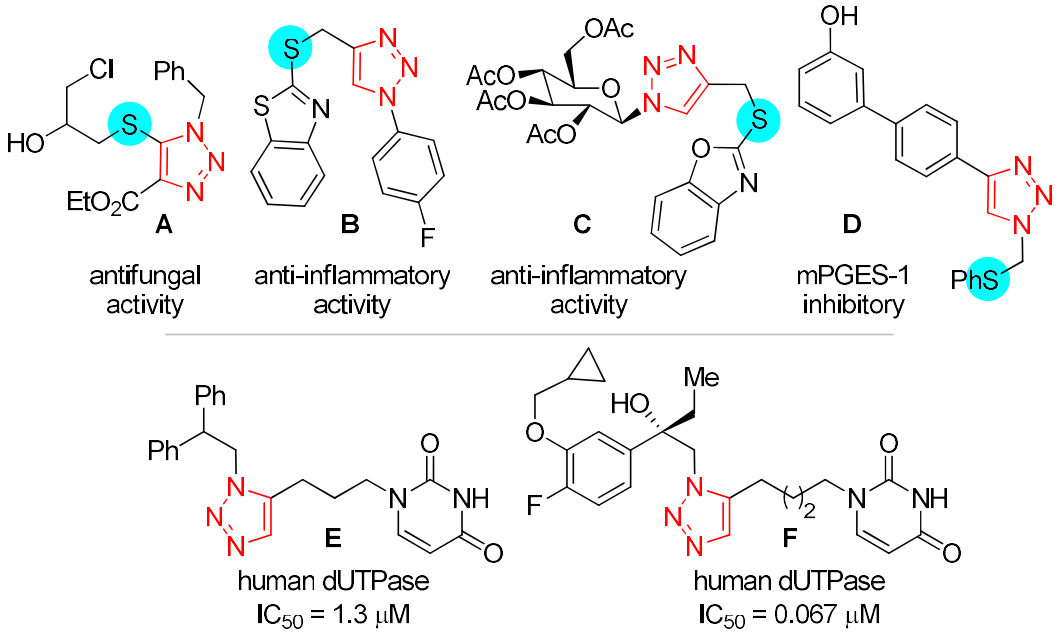
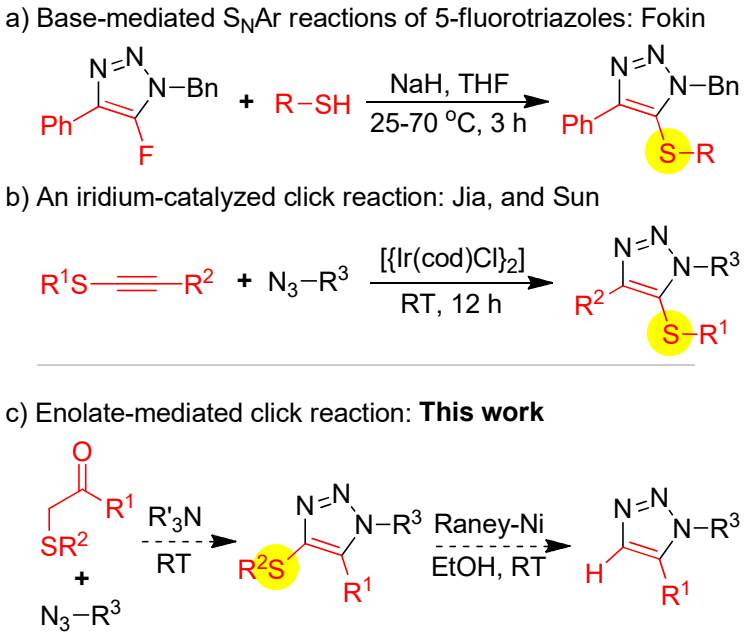


Figure 16. Potential applications based on the 1,2,3-triazoles.

The regioselective copper-catalyzed azide–alkyne [3+2]-cycloaddition (CuAAC) reaction, reported by the groups of Sharpless and Meldal in 2002, led to a huge expansion of interest in 1,4-disubstituted 1,2,3-triazoles.[25] After the discovery of this click reaction, many researchers entered this field and made significant contributions in terms of structural evolution, reaction development, and applications in the chemical and biological sciences. Novel reaction discoveries in this field have included, zinc-, ruthenium-, iridium-, and samarium-catalyzed azide–alkyne [3+2]-cycloadditions,[26] strain-promoted azide–alkyne [3+2]-cycloaddition (SPAAC),[27] base-promoted azide–alkyne [3+2]-cycloaddition,[37] azide–bromomagnesium acetylide [3+2]-cycloaddition,[38] organocatalytic enamine- or enolate-mediated azide–carbonyl [3+2]-cycloaddition,[2,28] copper- or iodine/tert-butyl peroxybenzoate-promoted reaction of *N*-tosylhydrazones with anilines,[29] iodine-promoted three-component reaction of *N*-tosylhydrazones, arylketones and anilines,[30] and electronically controlled active olefin–azide [3+2]-cycloaddition.[31] Many of these reactions are suitable to synthesize a variety of 1,2,3-triazoles, based on the availability of substrates and catalysts.

In search of the medicinally important 1,2,3-triazoles, we thought of synthesizing 1,5-disubstituted-4-thio-1,2,3-triazoles,[35] as their analogues have shown significant role in pharmaceutical/biological chemistry (Figure 16).[35] Although in the literature base-promoted S_NAr reaction of 5-fluoro-1,2,3-triazoles with alkyl thiols (eq. a, Scheme 4)[39] or iridium-catalyzed [3+2]-cycloaddition of thioalkynes with aryl azides (eq. b, Scheme 4)[26e] exist as new protocols to furnish 5-thio-1,2,3-triazoles through metal-catalysis, there is no reaction available to prepare the 4-thio-1,2,3-triazoles. Herein, we have disclosed a general, rapid, and operationally simple organocatalytic azide-ketone [3+2]-cycloaddition (OrgAKC) reaction for the chemo- and regiospecific high-yielding synthesis of fully decorated 1,5-disubstituted-4-thio-1,2,3-triazoles from the aryl/alkyl azides and 1-aryl-2-(arylthio)ethanones or 1-alkyl-2-(alkylthio)ethanones (eq. c, Scheme 4). One of the very important benefit of this protocol is that useful 1,5-disubstituted-1,2,3-triazoles could be easily synthesized from the common intermediate, 1,5-disubstituted-4-thio-1,2,3-triazoles through desulphurization reaction with Raney-Ni at room temperature (eq. c, Scheme 4).



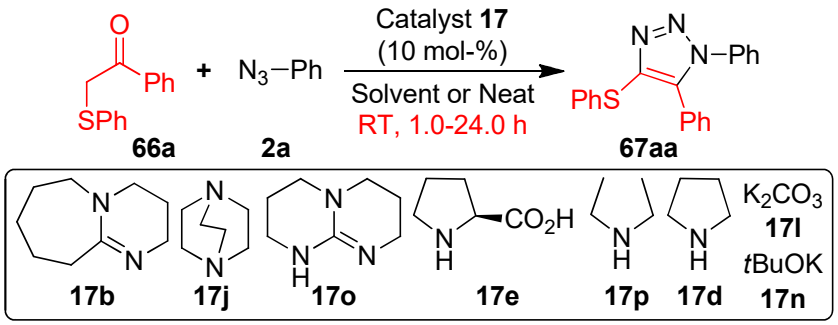
Scheme 4. Design for the enolate-mediated OrgAKC reaction

4.2 Results and Discussion

Based on our proposal, first we have chosen 1-phenyl-2-(phenylthio)ethanone **66a** and phenyl azide **2a** as substrates for the reaction optimization. We commenced optimization of the OrgAKC reaction by using commercially available DBU **17b** [pK_a of conjugate acid in DMSO = 12] as the organocatalyst for the clicking of 1-phenyl-2-(phenylthio)ethanone **66a** [pK_a of methylene CH-bonds in DMSO = 16.9] with 1.2 to 1.5 equiv. of phenyl azide **2a** (Table 4). The click reaction of ketone **66a** with 1.2 equiv. of **2a** in DMSO, catalyzed by 10-mol% of **17b** at 25 °C for 2.5 h furnished the expected 4-thio-1,2,3-triazole **67aa** as a single regioisomer in moderate yield (Table 4, entry 1). The same reaction over an extended time (6 h) at 25 °C furnished the 4-thio-1,2,3-triazole **67aa** in 85% yield (Table 4, entry 2). When the amount of azide **2a** was increased from 1.2 to 1.5 equivalents, the same reaction over 6 h furnished the 4-thio-1,2,3-triazole **67aa** in 90% yield (Table 8, entry 3). At a reaction temperature at 50 °C, the same reaction of **66a** with 1.5 equiv of **2a** furnished **67aa** in 90% yield within 1.0 h (Table 4, entry 4). To investigate whether the DBU-promoted OrgAKC reaction is solvent dependent, we carried out the click reaction in various other solvent systems, including aqueous dimethyl sulfoxide [DMSO+H_2O (7:3 v/v)], DMF, CH_3CN,

$CHCl_3$ and EtOH. However we obtained the click product **67aa** in decreased yields of 50%, 76%, 42%, <3% and <5% respectively, and longer reaction times of up to 24 h were

Table 4: Reaction optimization[a]



Entry	Catalyst **17** [10 mol-%]	Solvent [0.5 M]	Azide **2a** [equiv.]	*t* [h]	Yield [%][b] **67aa**
1	**17b**	DMSO	1.2	2.5	65
2	**17b**	DMSO	1.2	6.0	85
3	**17b**	DMSO	1.5	6.0	90
4[c]	**17b**	DMSO	1.5	1.0	90
5[d]	**17b**	DMSO+H_2O	1.5	24.0	50
6	**17b**	DMF	1.5	2.0	76
7	**17b**	CH_3CN	1.5	17.0	42
8[e]	**17b**	$CHCl_3$	1.5	24.0	<3%
9[e]	**17b**	EtOH	1.5	24.0	<5%
10[e]	**17j**	DMSO	1.5	24.0	<3%
11	**17o**	DMSO	1.5	24.0	37
12[e]	**17e**	DMSO	1.5	24.0	–
13	**17p**	DMSO	1.5	24.0	22
14[e]	**17d**	DMSO	1.5	24.0	–
15[e]	**17l**	DMSO	1.5	24.0	<5%
16[e]	**17n**	DMSO	1.5	6.5	<5%
17	**17b**	Neat	1.5	1.5	85
18[c]	**17b**	Neat	1.5	1.5	90

[a] Reactions were carried out in solvent (0.5 M) or solvent-free with 1.2-1.5 equiv. of **2a** relative to the **66a** (0.5 mmol) in the presence of 10-mol% of catalyst **17**. [b] Yield refers to product isolated by column chromatography. [c] Reaction performed at 50 °C. [d] DMSO+H_2O (7:3) was used as solvent. [e] Starting materials **66a** and **2a** were recovered.

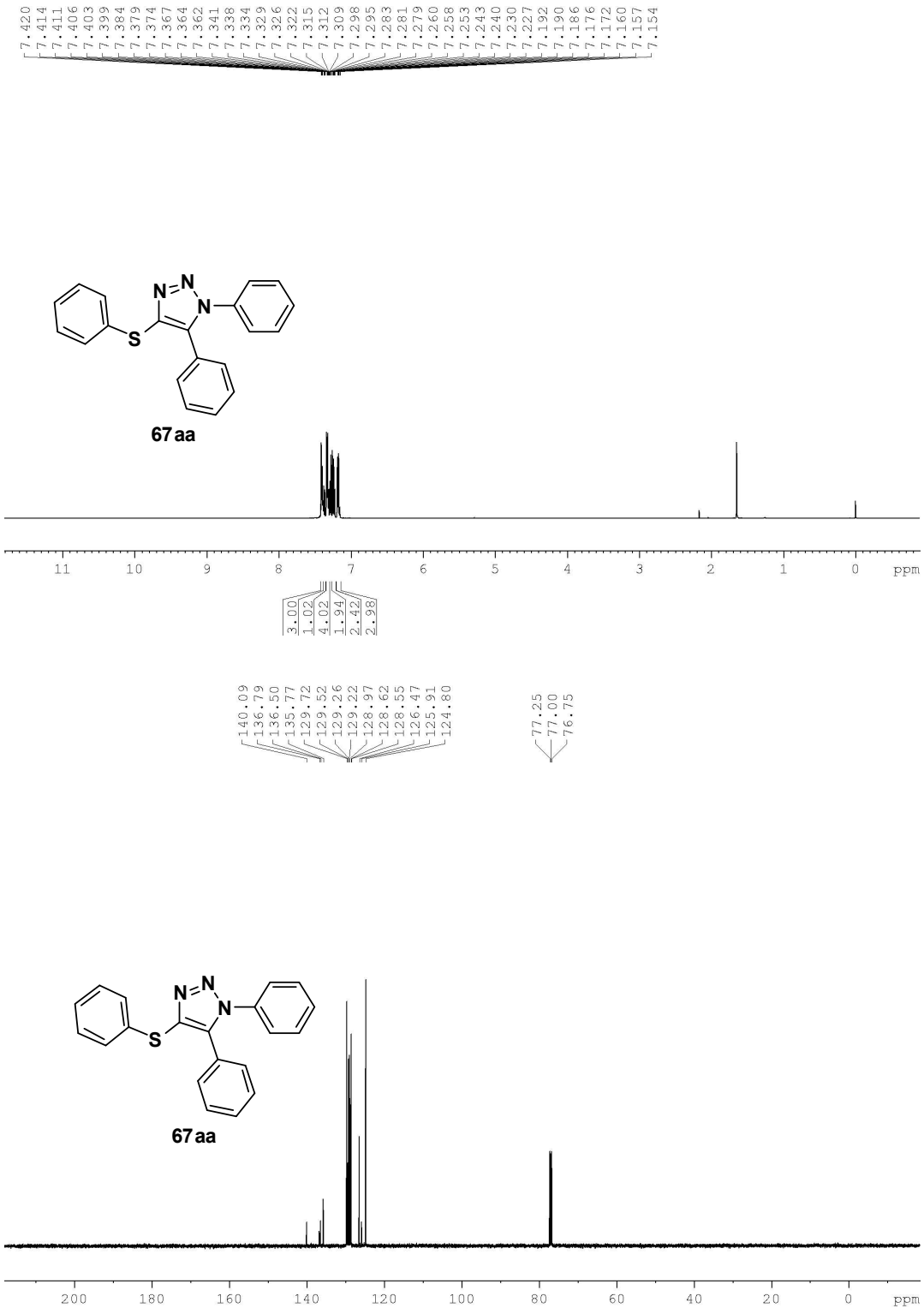
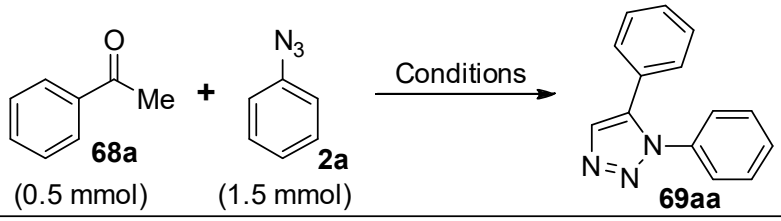


Figure-17: ^{1}H and ^{13}C NMR spectra of the product **67aa**.

required, except in DMF (Table 4, entries 5-9). These results clearly support our hypothesis of involvement of reactive *in situ* enolate formation from **66a** with **17b** during the course of the reaction To further investigate the reactivity of amine and non-amine catalysts on OrgAKC reaction, we carried out the click reaction with 10 mol-% of various catalysts like DABCO (**17j**), triazabicyclodecene (**17o**), proline (**17e**), diethylamine (**17p**), pyrrolidine (**17d**), K_2CO_3 (**17l**) and *t*-BuOK (**17n**) in DMSO at 25 °C. However, with catalysts **17o** and **17p**, we obtained the **67aa** in only 37% and 22% yield, respectively, and with the other catalysts conversions of 0–<5% were obtained (Table 4, entries 10–16). To make this click reaction greener, we tested the reaction under solvent-free conditions. Pleasingly, the solvent-free reaction of **66a** (0.5 mmol, 114 mg) and **2a** (0.75 mmol, 88.6 mL) with **17b** (0.05 mmol, 7.5 mL) at 25–50 °C for 1.5 h furnished **67aa** in 85–90% yields (Table 4, entries 17 and 18). In these reactions, the phenylthio (Ph–S) group was electronically responsible for

Table 5: Reaction design for the click reaction of acetophenone with phenyl azide.

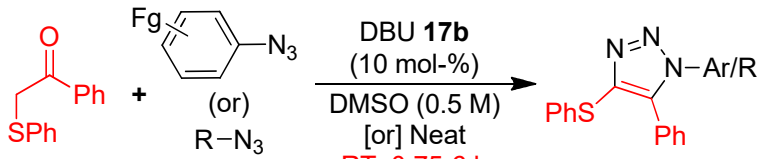


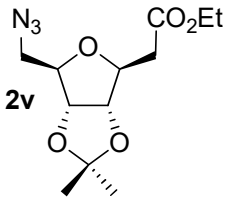
Entry	Reaction Conditions	Solvent	Product
1	*t*-BuOK **17n** (20 mol%), 25-70 °C, 24 h	DMSO	No Reaction
2	Cs_2CO_3 **17m** (20 mol%), 25-70 °C, 24 h	DMSO	No Reaction
3	NaOMe **17q** (20 mol%), 25-70 °C, 24 h	DMSO	No Reaction
4	DBU **17b** (20 mol%), 25-70 °C, 24 h	DMSO	No Reaction
5	Guanidine **17r** (20 mol%), 25-70 °C, 24 h	DMSO	No Reaction
6	Piperidine **17s** (20 mol%), 25-70 °C, 24 h	DMSO	No Reaction
7	Pyrrolidine **17d** (20 mol%), 25-70 °C, 24 h	DMSO	No Reaction
8	L-Proline **17e** (20 mol%), 25-70 °C, 24 h	DMSO	No Reaction
9	Diethylamine **17p** (20 mol%), 25-70 °C, 24 h	DMSO	No Reaction
10	$HC(OEt)_3$ (1 equiv.), TfOH (1 equiv.), 25 °C, 24 h	CCl_4	No Reaction
11	$HC(OEt)_3$ (1 equiv.), $AgSbF_6$ (0.1 equiv.), 25 °C, 24 h	DCM	No Reaction

inducing the acidity of C–H bonds in **66a**, as proven by the control experiments. No click reaction was observed between acetophenone (PhS = H) **68a** and phenyl azide through enolate or enamine formation catalyzed by amines or amino acids (Table 5). We therefore identified the optimized conditions as 25–50 °C in DMSO or solvent-free, catalyzed by 10 mol% of DBU **17b**, which furnished the single isomer **67aa** in 90% yield from **66a** and **2a** (Table 4, entries 3, 4 and 18).

With the optimized conditions in hand, the scope and the generality of the DBU-catalyzed OrgAKC reactions were investigated. A variety of substituted aryl and alkyl azides **2b-v** reacted with ketone **66a** catalyzed by 10-mol% of DBU **17b** at 25 °C both under solvent-free conditions and in DMSO for 0.75-6 h (Table 6). The aryl azides **2b–e**, **2j–m** and **2t** with substituents including NO_2, CO_2Et, CN, CF_3, CHO, F, Cl and Br furnished the expected 4-thio-1,2,3-triazoles **67ab**–**ae**, **67aj**–**am** and **67at** in excellent yields within 0.75 h under both sets of conditions, without showing much difference (Table 6, entries 1–9). Reaction rates and yields of the 4-thio-1,2,3-triazoles **67ab**–**ae**, **67aj**–**am** and **67at** were increased by electron-withdrawing substituents at the *para* position of **2**, but rate and yields slightly decreased with alkyl and electron-donating substituents. For example, the DBU-catalyzed OrgAKC reaction of the aryl azides 4-$CH_3C_6H_4N_3$ (**2g**) and 4-$OCH_3C_6H_4N_3$ (**2i**) with ketone **66a** in DMSO at 25 °C took longer time (6 h) for lower yields (65% and 25 %, respectively); but the same reactions at 50 °C for 2.0 h furnished the 4-thio-1,2,3-triazoles **67ag** and **67ai** in 90% and 55% yields, respectively (Table 6, entries 10 and 11), similar results were obtained with **2g** and **2i** under solvent-free conditions, but the yield of **67ai** was increased compared to that in DMSO. The reaction of **66a** with chiral (*R*)-**2u** having 75.9% *ee*, catalyzed by 10 mol% of **17b**, furnished (*R*)-**67au** in 65% yield with similar (75.7%) *ee* (Table 6, entry 12). Surprisingly, no reaction was observed for the **17b**-catalyzed OrgAKC reaction of **66a** with alkyl and sugar azides **2o**, **2p** and **2v** in DMSO at 25–65 °C for 24 h, but the same reaction under solvent-free conditions at 50 °C for 3, 6, and 24 h furnished **67ao**, **67ap**, and **67av** in 65%, 40%, and 60% yields, respectively (Table 6, entries 13–15). The longer reaction time (24 h) required for the OrgAKC reaction of **66a** with azido sugar **2v** may be due to the highly viscous nature of the reaction mixture because of the polar functional groups. 1,2,3-Triazole formation from alkyl or sugar azides is a useful reaction in click chemistry,[40] which highlights the importance of the OrgAKC reaction in glycoscience.

Table 6: Azide scope[a]



Entry	Ar-N_3 or R-N_3 **2**	Yield [%][b,c] **67ab-av**
1	**2b** (Fg = 4-F)	**67ab**: 95 (90)
2	**2c** (Fg = 3-Cl)	**67ac**: 96 (85)
3	**2d** (Fg = 4-Cl)	**67ad**: 95 (88)
4	**2e** (Fg = 4-Br)	**67ae**: 88 (92)
5	**2j** (Fg = 4-CF_3)	**67aj**: 97 (85)
6	**2k** (Fg = 4-CN)	**67ak**: 93 (85)
7	**2l** (Fg = 4-CO_2Et)	**67al**: 90 (90)
8	**2m** (Fg = 4-CHO)	**67am**: 87 (81)
9	**2t** (Fg = 4-NO_2)	**67at**: 93 (85)
10[d]	**2g** (Fg = 4-Me)	**67ag**: 90 (87)
11[d]	**2i** (Fg = 4-OMe)	**67ai**: 55 (72)
12[e]	**2u** [Fg = (*R*)-4-CH_3COCH_2CHOH]	**67au**: 65 (63)
13[d,f]	**2o** (R = Bn)	**67ao**: – (65)
14[d,f]	**2p** (R = CH_2CH_2Ph)	**67ap**: – (40)
15[d,f,g]	**2v** 	**67av**: – (60)

[a] Reactions were carried out in DMSO (0.5 M) or solvent-free with 1.5 equiv. of **2b-v** relative to the **66a** (0.5 mmol) in the presence of 10-mol% of **17b**. [b] Yield refers to the column-purified product. [c] Values in parentheses refer to the yields of the solvent-free reaction. [d] Reaction performed at 50 °C. [e] *ee* of the **2m** is 75.9% and that of **67am** is 75.7%, based on the chiral HPLC analysis; [f] Reaction performed in solvent-free condition only. [g] *t* = 24 h.

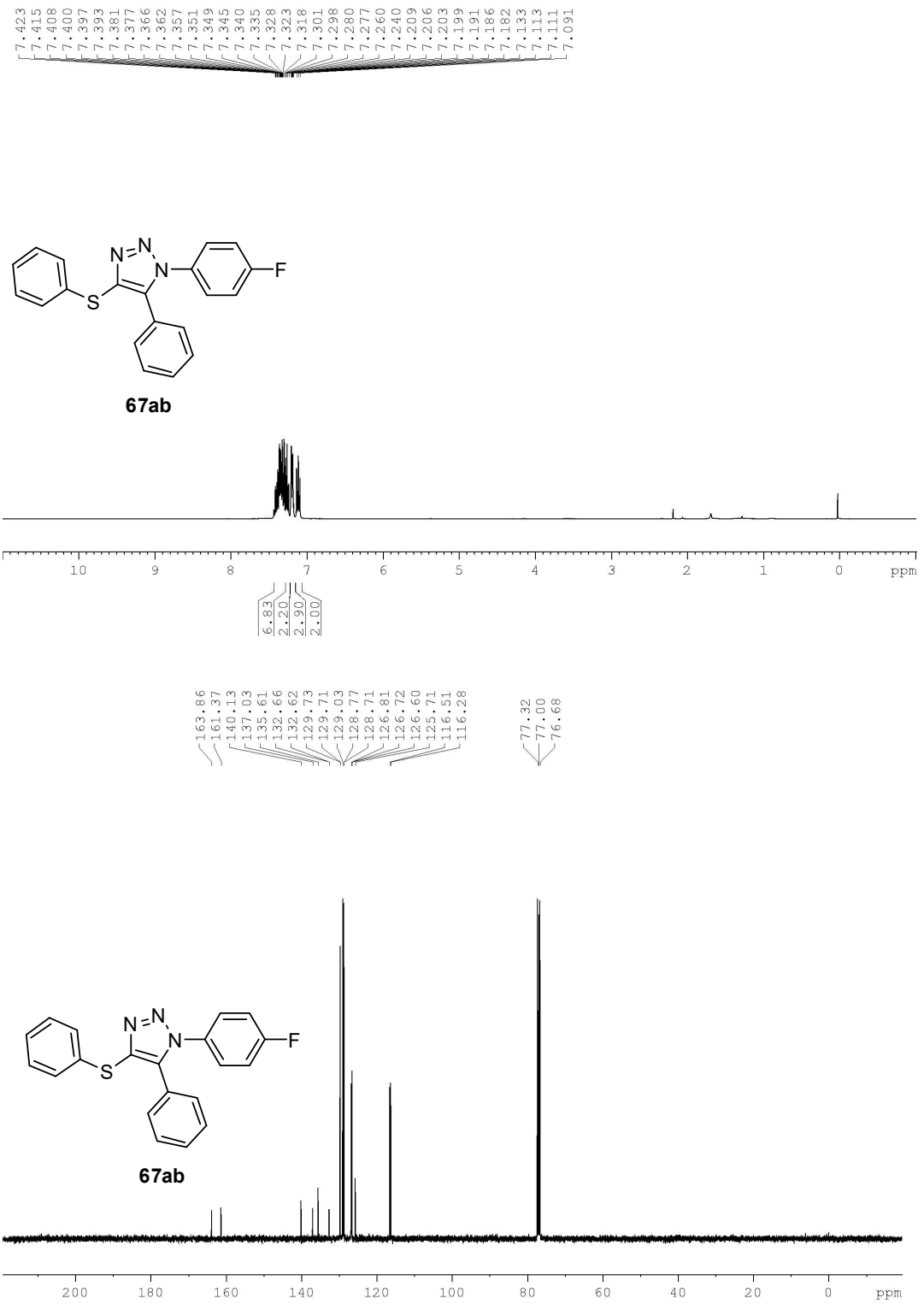


Figure-18: ^{1}H and ^{13}C NMR spectra of the product **67ab**.

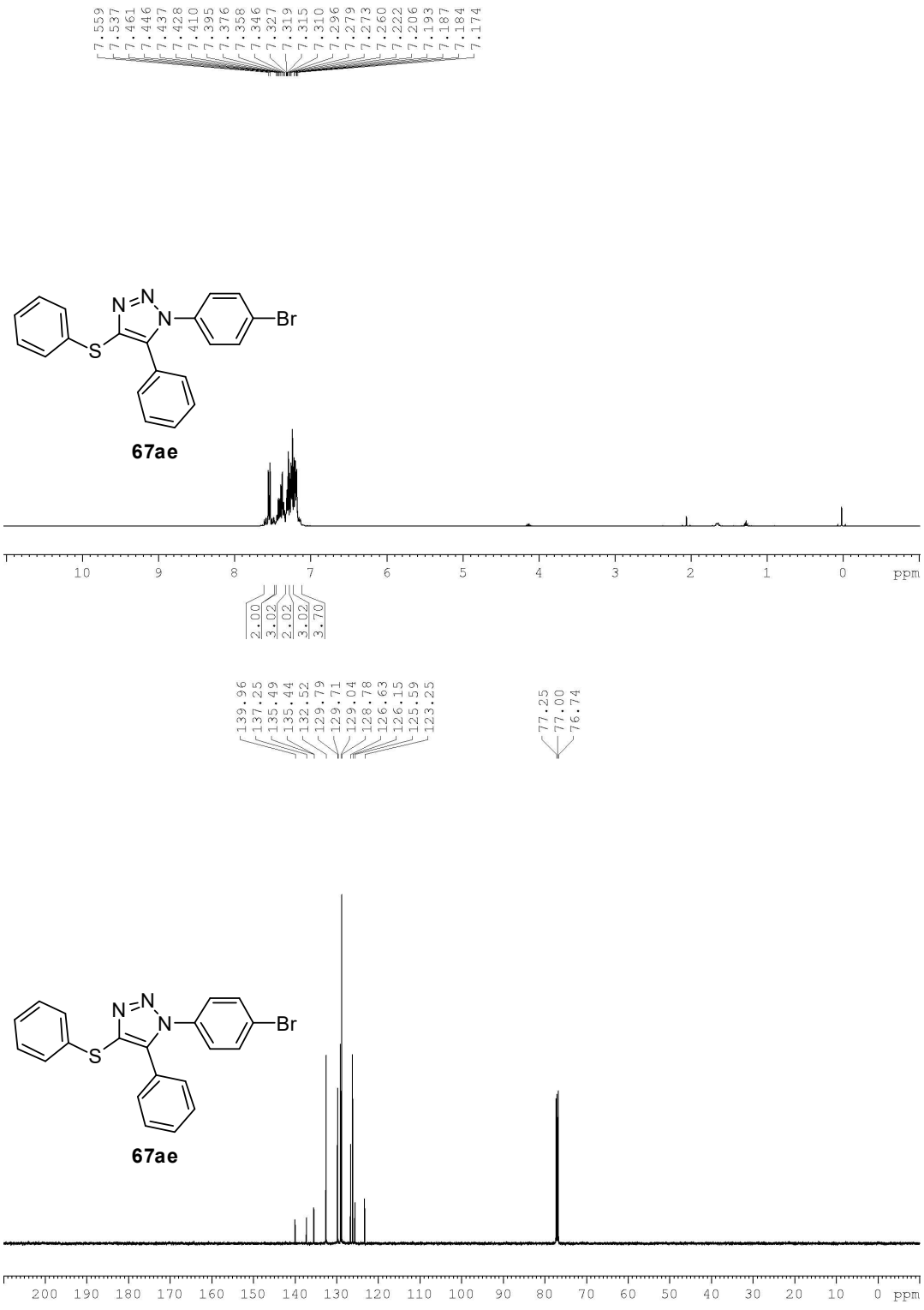


Figure 19: ^{1}H and ^{13}C NMR spectra of the product **67ae**.

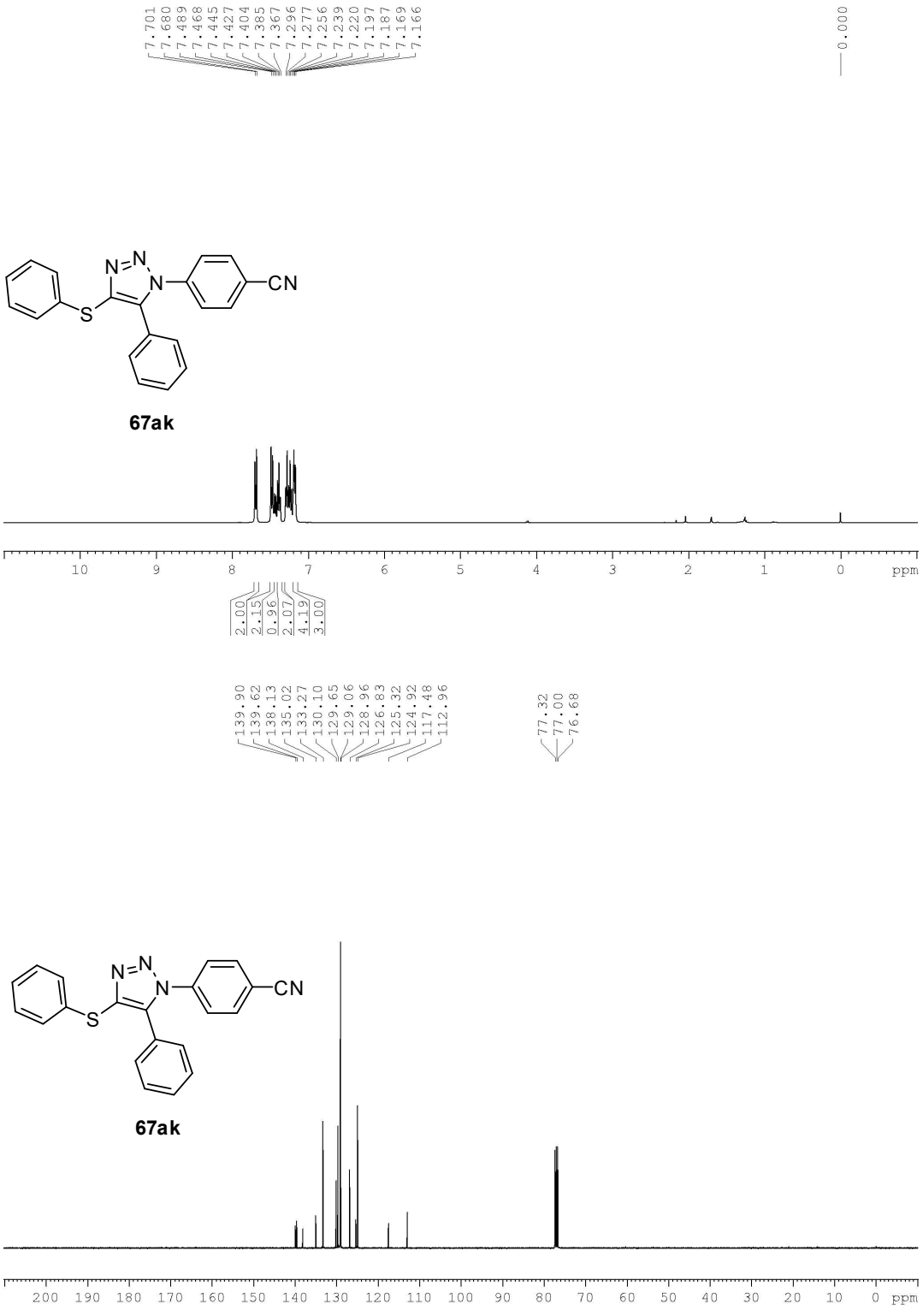


Figure-20: ^{1}H and ^{13}C NMR spectra of the product **67ak**.

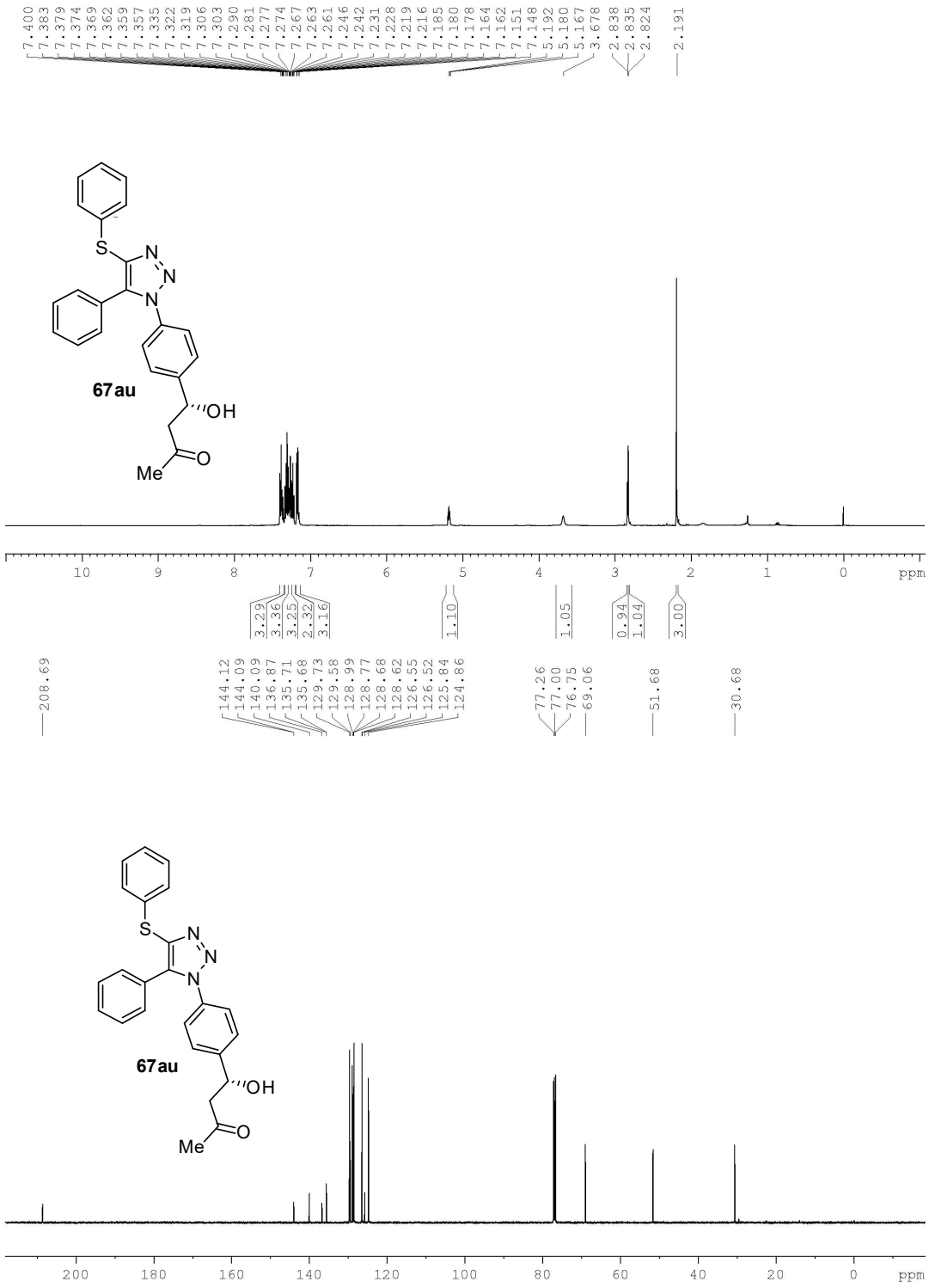


Figure-21: ^{1}H and ^{13}C NMR spectra of the product **67au**.

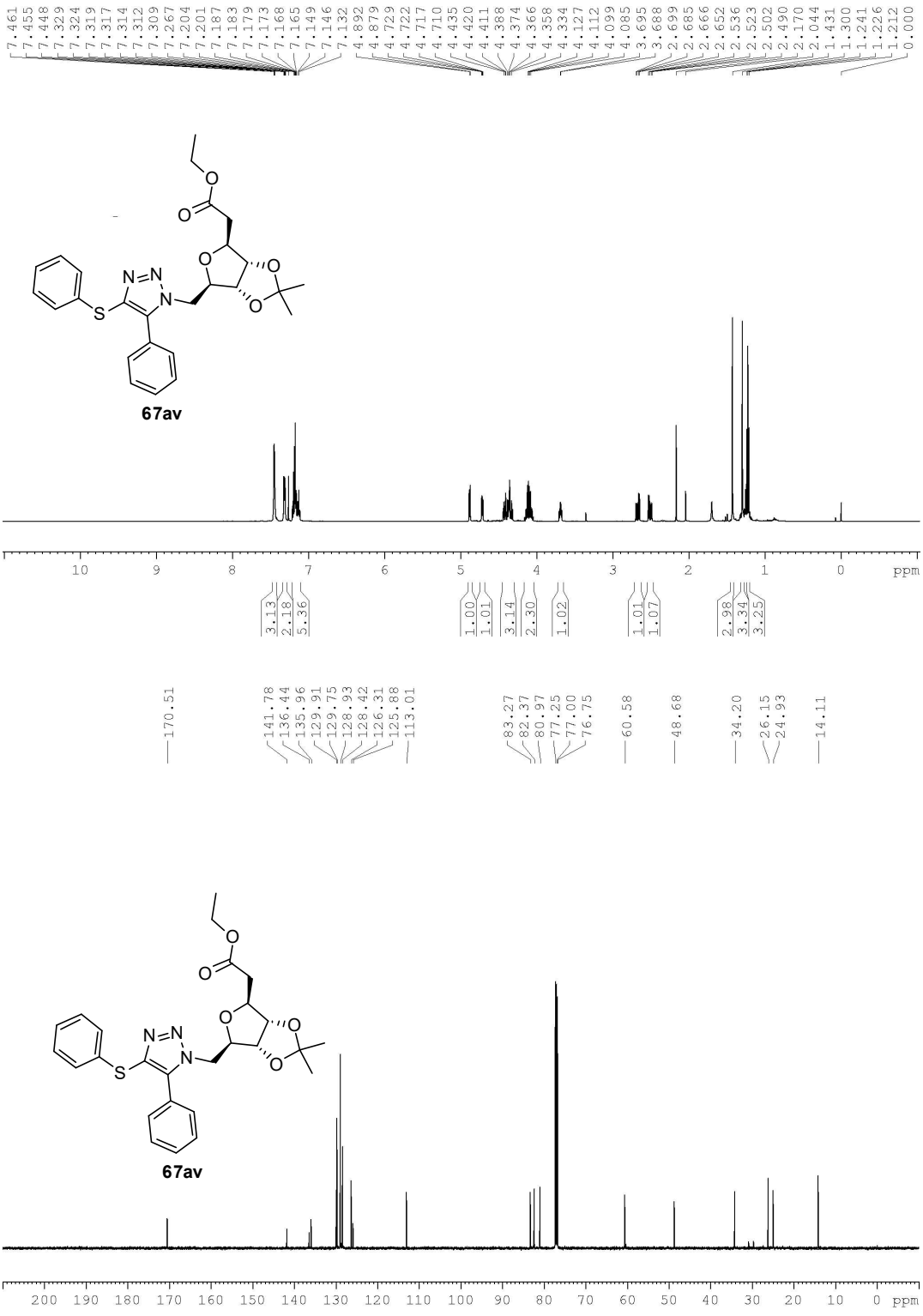


Figure-22: ^{1}H and ^{13}C NMR spectra of the product **67av**.

Having elucidated the solvent effects and the electronic and steric factors of aryl, alkyl, and sugar azides **2** in the [3+2]-cycloaddition reaction, we further investigated the reaction scope with different 1-aryl-2-(phenylthio)ethanones **66b–n** and 1-(phenylthio)propan-2-one **66o** in the OrgAKC reaction with $C_6H_5N_3$ **2a**, 4-$CF_3C_6H_4N_3$ **2j**, and 4-$FC_6H_4N_3$ **2b** under both sets of conditions (Table 7). In this reaction, 1-aryl-2-(phenylphenylthio)ethanones **66b–n**, containing functional groups including 4-NO_2, 3-NO_2, 4-CN, 4-CF_3, 4-F, 4-Cl, 4-Br, 4-I, 4-OMe, 4-Me, 2-naphthyl, 4-phenyl, and heteroaryl, were used as substrates for the organocatalytic synthesis of single isomers of 1,4,5-trisubstituted 4-thio-1,2,3-triazoles **67bj–nj**, **67fa**, and **67gb** in good to excellent yields within 0.75–1.5h (Table 7, entries 1–15). In a similar manner, the OrgAKC reaction of 1-(phenylthio)propan-2-one **66o** with aryl azides **2a** and **2j** catalyzed by **17b** at RT for 0.75 h in DMSO furnished **67oa** and **67oj** in 65% and 80% yields, respectively (Table 7, entries 16 and 17). The OrgAKC reactions of **66j**, **66n**, and **66o** with **2j** or **2a** in DMSO gave click products **67jj**, **67nj**, and **67oa** in 70 %, 62% and 65% yields, whereas the same reactions under solvent-free conditions also furnished the products in moderate yields 66 %, 56% and 61 %, respectively; (Table 7, entries 11, 15, and 16). The results in Table 7 demonstrate the broad scope of this methodology, covering a structurally diverse group of 1-aryl-2-(phenylthio)ethanones **66b–n**, 1-(phenylthio)propan-2-one **66o**, and aryl azides **2a**, **2j**, and **2b**. Many of the OrgAKC product **67** yields obtained compared very well to iridium-catalyzed azide–thioalkyne [3+2]-cycloaddition[26] (Table 7 and Scheme 4). The structure and the regiochemistry of the OrgAKC products were confirmed by NMR spectroscopy. Moreover, the structure of **67jj** was definitively established X-ray structure analysis (Figure 23).[41]

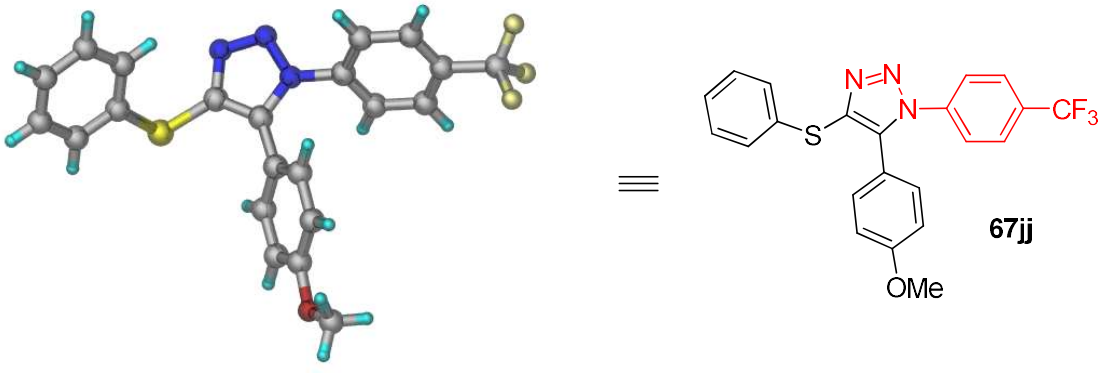
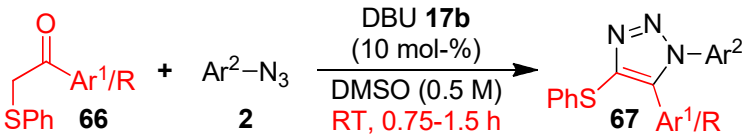


Figure 23. Crystal structure of 5-(4-methoxyphenyl)-4-(phenylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (**67jj**).

Table 7. Ketones scope:α-(Phenylthio)ketones.[a]



Entry	Ar^1 or R **66**	Ar^2-N_3 **2**	Yield [%][b] **67**
1	**66b** (Ar = 4-$NO_2C_6H_4$)	**2j**	95 (**67bj**)
2	**66c** (Ar = 3-$NO_2C_6H_4$)	**2j**	91 (**67cj**)
3	**66d** (Ar = 4-CNC_6H_4)	**2j**	90 (**67dj**)
4	**66e** (Ar = 4-$CF_3C_6H_4$)	**2j**	85 (**67ej**)
5	**66f** (Ar = 4-FC_6H_4)	**2a**	95 (**67fa**)
6	**66f** (Ar = 4-FC_6H_4)	**2j**	85 (**67fj**)
7	**66g** (Ar = 4-ClC_6H_4)	**2b**	85 (**67gb**)
8	**66g** (Ar = 4-ClC_6H_4)	**2j**	90 (**67gj**)
9	**66h** (Ar = 4-BrC_6H_4)	**2j**	83 (**67hj**)
10	**66i** (Ar = 4-IC_6H_4)	**2j**	82 (**67ij**)
11[c]	**66j** (Ar = 4-$OMeC_6H_4$)	**2j**	70 (**67jj**)
12	**66k** (Ar = 4-MeC_6H_4)	**2j**	93 (**67kj**)
13	**66l** (Ar = 2-Naphthyl)	**2j**	90 (**67lj**)
14	**66m** (Ar = 4-PhC_6H_4)	**2j**	92 (**67mj**)
15[c]	**66n** (Ar = Furan-2-yl)	**2j**	62 (**67nj**)
16[c]	**66o** (R = Me)	**2a**	65 (**67oa**)
17	**66o** (R = Me)	**2j**	80 (**67oj**)

[a] Reactions were carried out in DMSO (0.5 M) with 1.5 equiv. of **2** relative to the **66b-o** (0.5 mmol) in the presence of 10 mol-% of **17b**. [b] Yield refers to the column-purified product. [c] yields of 66% (**67jj**), 56% (**67nj**) and 61% (**67oa**) were obtained through solvent-free reaction of **66j, 66n**, and **66o** with **2j** or **2a** at RT for 1 h.

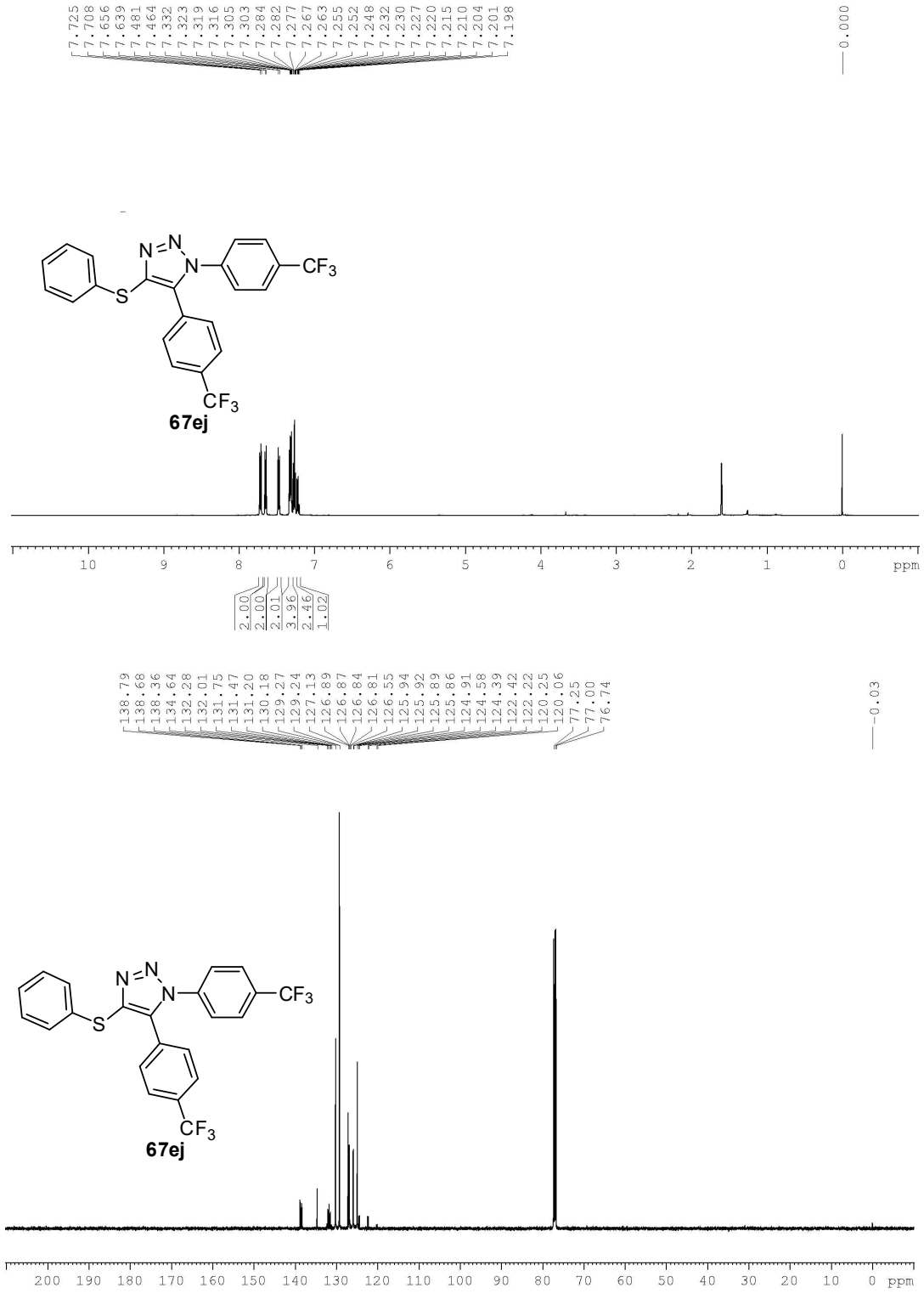


Figure-24: ^{1}H and ^{13}C NMR spectra of the product **67ej**.

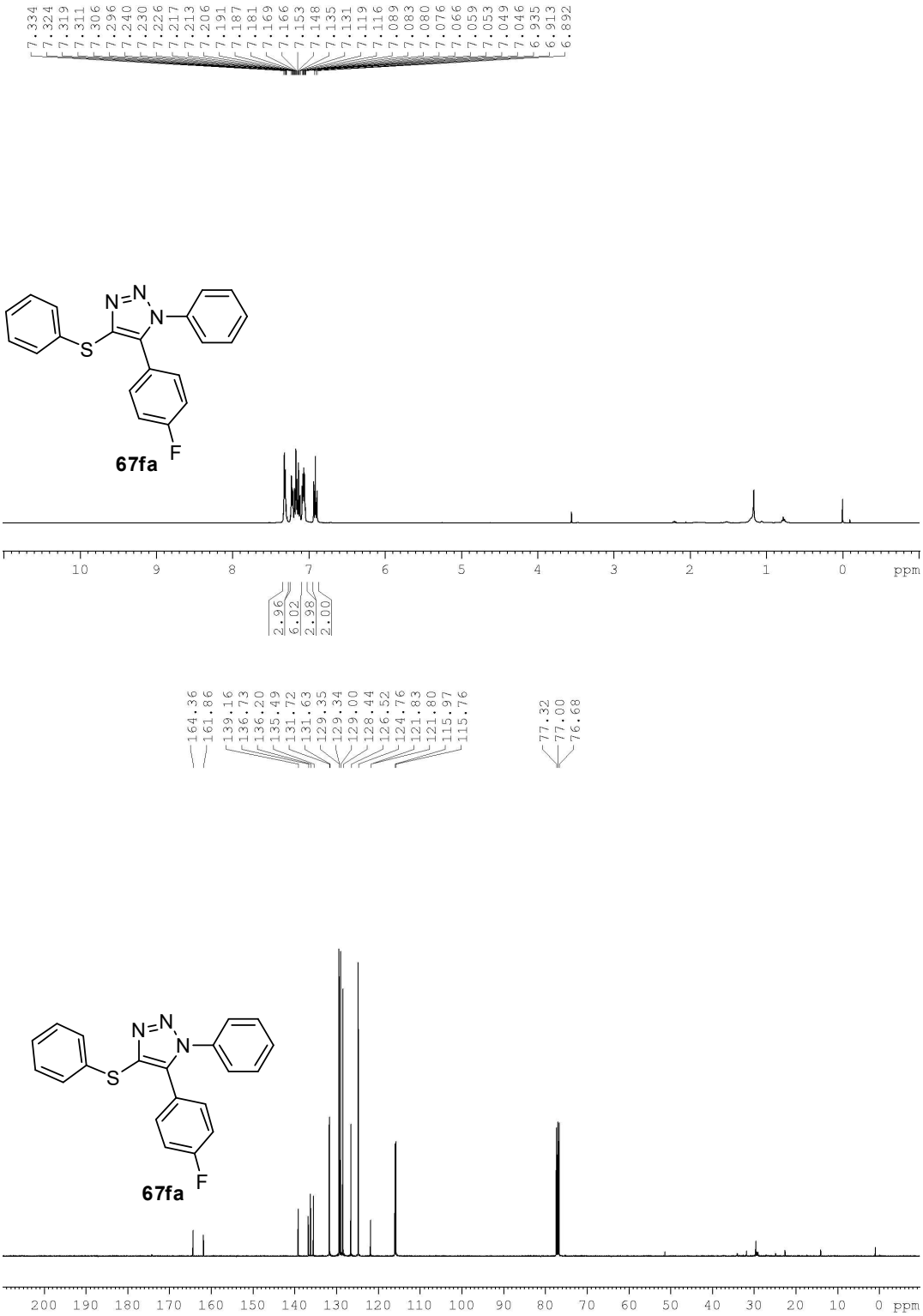


Figure-25: ^{1}H and ^{13}C NMR spectra of the product **67fa.**

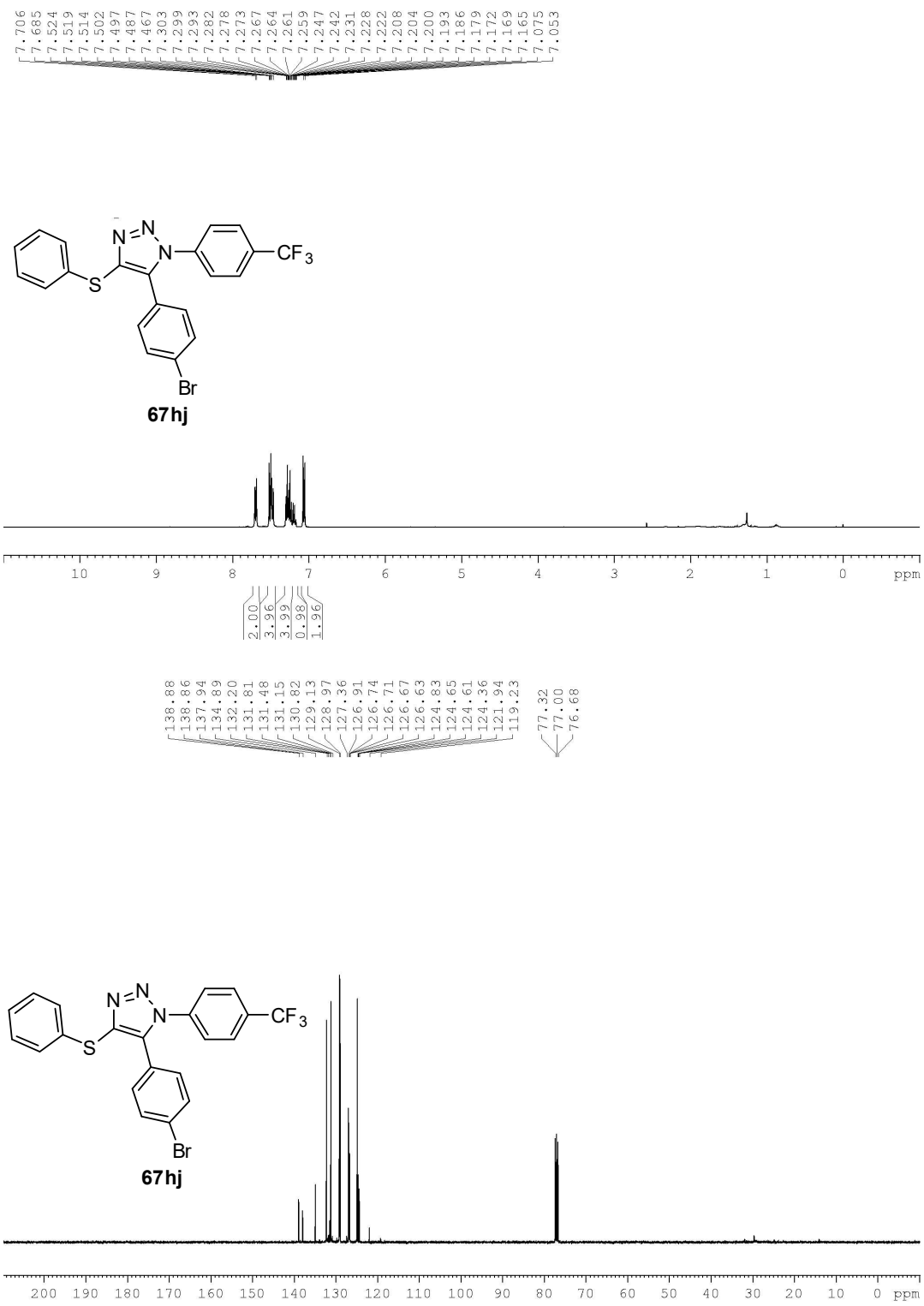


Figure-26: ^{1}H and ^{13}C NMR spectra of the product **67hj.**

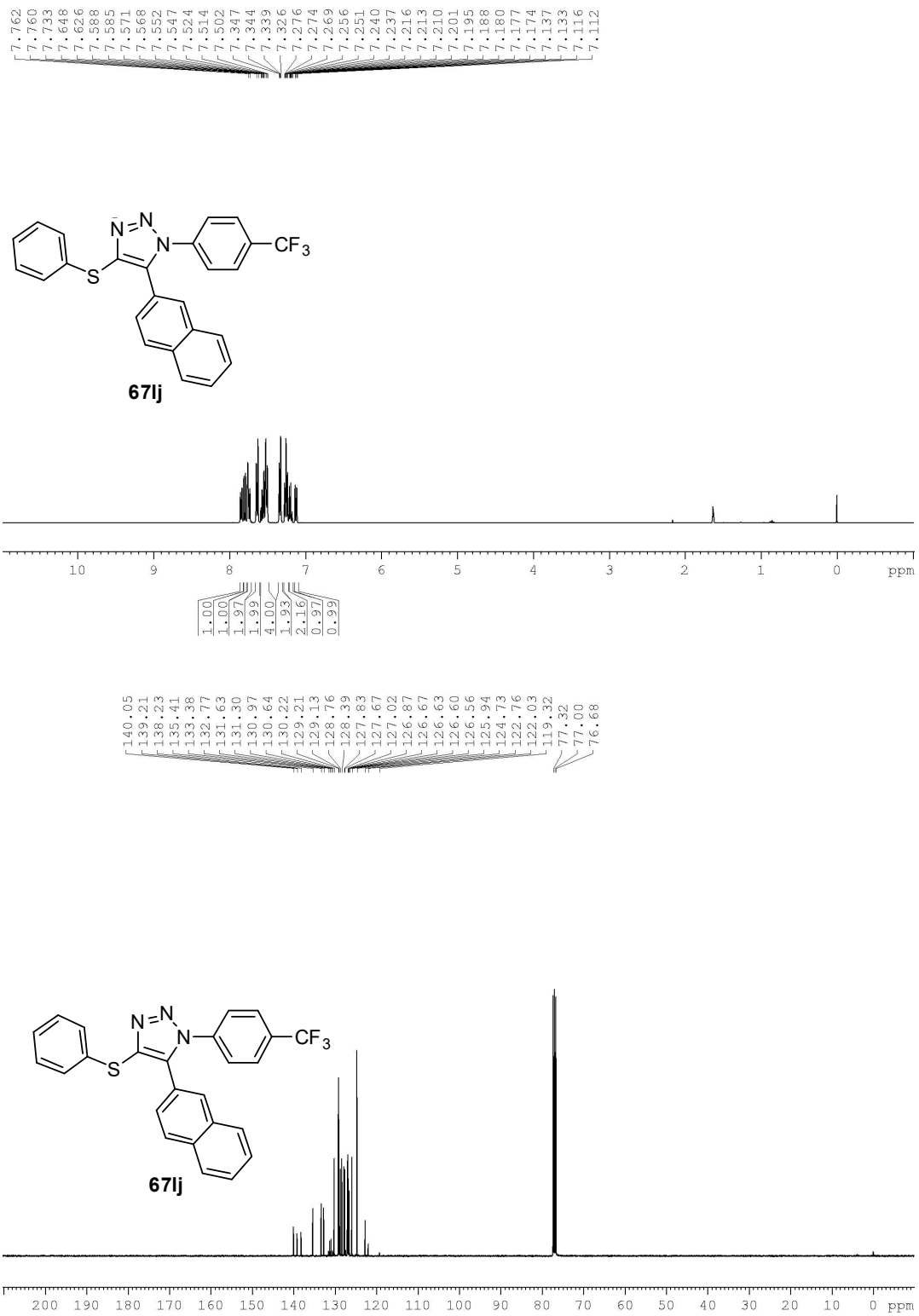


Figure-27: ^{1}H and ^{13}C NMR spectra of the product **67lj.**

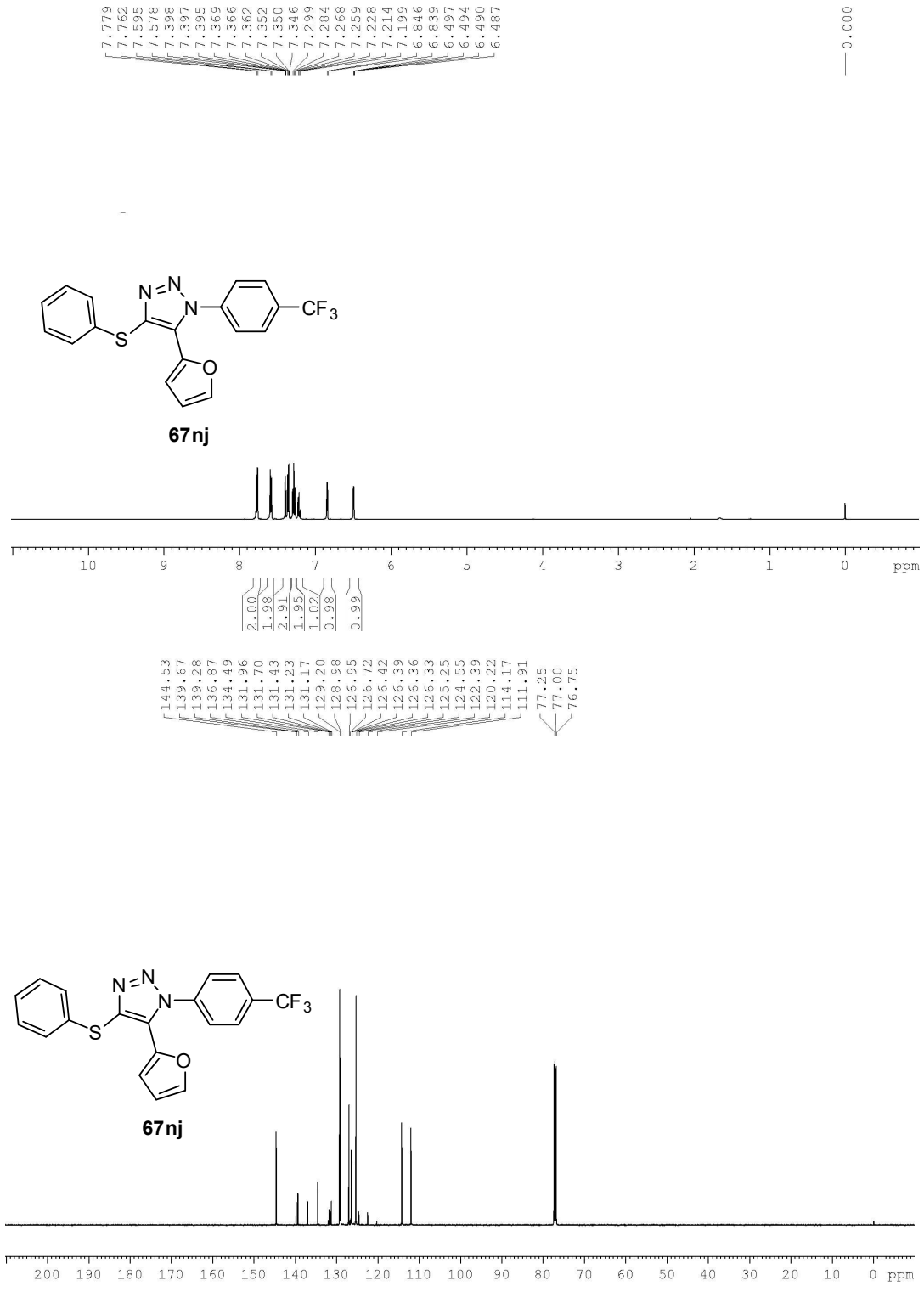


Figure-28: ^{1}H and ^{13}C NMR spectra of the product **67nj.**

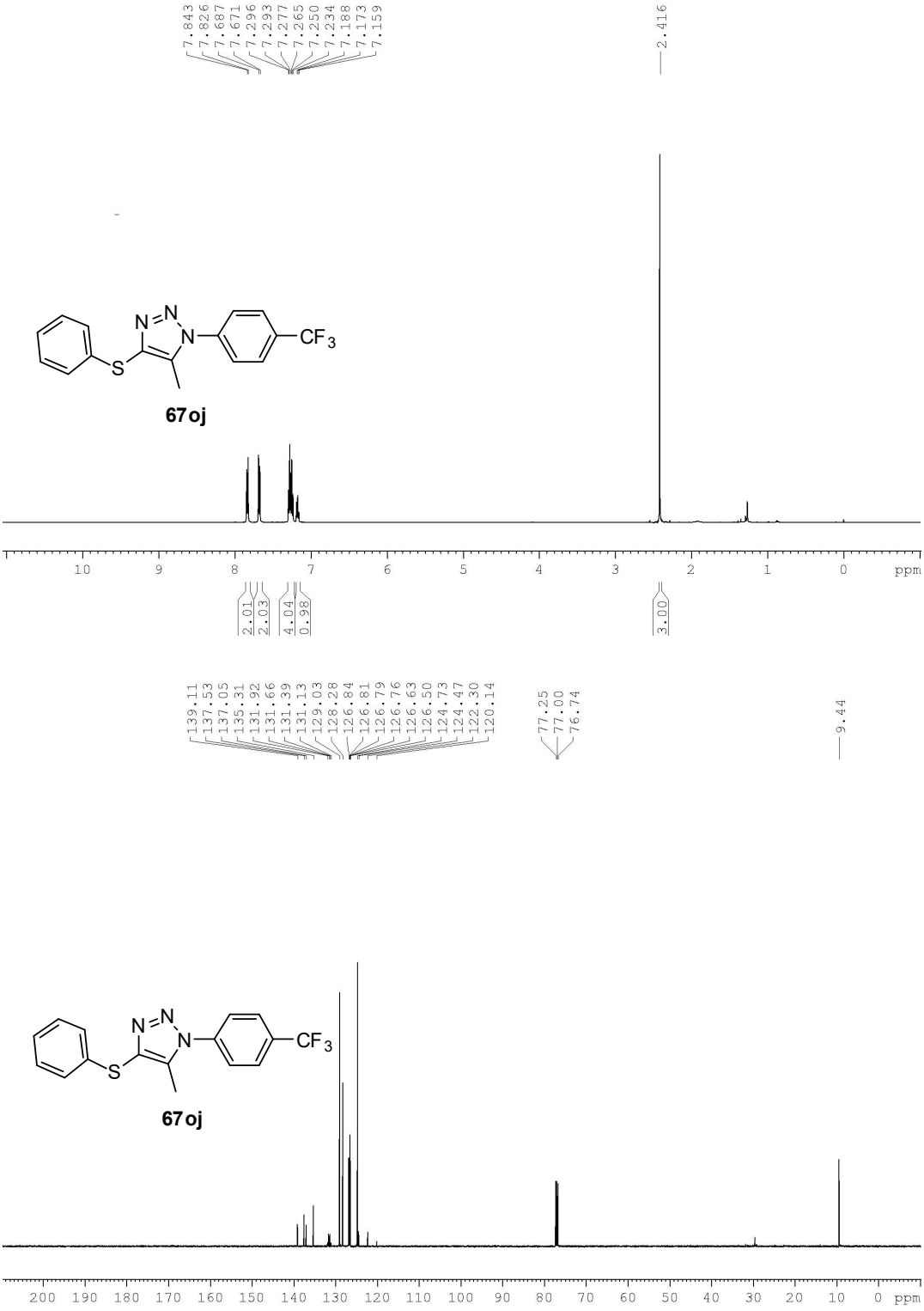
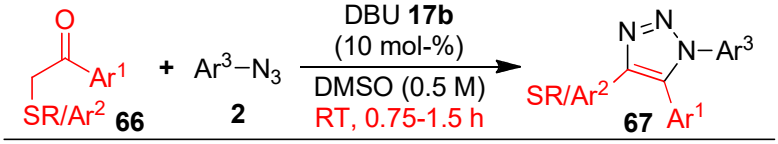


Figure-29: ^{1}H and ^{13}C NMR spectra of the product **67oj.**

To further investigate the importance of the alkyl/aryl substitution on the sulfur atom on the acidity of the α-methylene of 1-aryl-2-(arylthio)ethanones and 1-aryl-2-(alkylthio)ethanones **66p–w** in the OrgAKC reaction, we chose the highly functionalized ketones **66p–w**, which have low or high α-methylene acidity compared to 1-aryl-2-(phenylthio)ethanones **66a–o** (Table 8). The reaction of 1-[(1,1'-biphenyl)-4-yl]-2-[(2-fluorophenyl)thio]ethanone **66p** with 4-$CF_3C_6H_4N_3$ **2j** catalyzed by DBU at 25 °C for 1.5 h furnished the expected 4-thio-1,2,3-triazole **67pj** in 87% yield without showing the effects of steric or electronic factors (Table 8, entry 1). In a similar manner, the reaction of 2-chlorophenylthioethanone **66q**, 4-chlorophenylthioethanone **66r**, and 2-bromophenylthioethanone **66s** with 4-$CF_3C_6H_4N_3$ **2j** catalyzed by DBU at 25 °C for 1.5 h furnished the 4-thio-1,2,3-triazoles **67qj**–**sj**, each in 85% yield (Table 8, entries 2–4). We also utilized three examples of 1-aryl-2-(alkylthio)ethanones **66t**, **u**, and **w** for the OrgAKC reaction with **2a** or **2j** catalyzed by DBU, which furnished the expected 1,4,5-trisubstituted 4-

Table 8: Ketone scope: Other α-(arylthio)ketones.[a]



Entry	R, Ar^1, or Ar^2 **66**	Ar^3-N_3 **2**	Yield [%][b] **67**
1	**66p** (Ar^1 = 4-PhC_6H_4; Ar^2 = 2-FC_6H_4)	**2j**	87 (**67pj**)
2	**66q** (Ar^1 = 4-PhC_6H_4; Ar^2 = 2-ClC_6H_4)	**2j**	85 (**67qj**)
3	**66r** (Ar^1 = 4-PhC_6H_4; Ar^2 = 4-ClC_6H_4)	**2j**	85 (**67rj**)
4	**66s** (Ar^1 = 4-PhC_6H_4; Ar^2 = 2-BrC_6H_4)	**2j**	85 (**67sj**)
5	**66t** (Ar^1 = 4-PhC_6H_4; R = Octyl)	**2j**	92 (**67tj**)
6	**66u** (Ar^1 = 4-FC_6H_4; R = Decyl)	**2j**	92 (**67uj**)
7	**66v** (Ar^1 = 4-MeC_6H_4; Ar^2 = 4-$CF_3C_6H_4$)	**2j**	92 (**67vj**)
8	**66w** (Ar^1 = C_6H_5; R = $CH_2C_6H_5$)	**2a**	87 (**67wa**)

[a] Reactions were carried out in DMSO (0.5 M) with 1.5 equiv. of **2** relative to the **66p-w** (0.5 mmol) in the presence of 10 mol-% of **17b**. [b] Yield refers to product isolated by colum chromatography.

thio-1,2,3-triazoles **67tj**, **uj**, and **wa** in excellent yields within 0.75h without showing any electronic effects from the alkyl substitution of sulfur (Table 8, entries 5, 6, and 8). The OrgAKC reaction of richly functionalized 1-(*p*-tolyl)-2-[(4-(trifluoromethyl) phenyl)thio]ethanone **66v** with 4-$CF_3C_6H_4N_3$ **2j** catalyzed by **17b** at 25 °C for 0.75 h furnished the functionalized 4-thio-1,2,3-triazole **67vj** in 92% yield (Table 8, entry 7). The results in Table 8 highlight the efficacy of this protocol in the click synthesis of 4-thio-1,2,3-triazoles **67**. The advantage of the OrgAKC reaction was further depicted by synthesizing medicinally useful 1,5-disubstituted 1,2,3-triazoles **69** (Table 9). The reaction of 1,5-diphenyl-4 phenylthio-1,2,3-triazole (0.5 mmol) **67aa** with 1.0 g of freshly prepared Raney Ni in ethanol at 25 °C for 2.5 h furnished the 1,5-diphenyl-1,2,3-triazole **69aa** in 87% yield (Table 9, entry 1). This mild desulfurization reaction was further exploited by using differently substituted 4-arylthio-1,2,3-triazoles and 4-alkylthio-1,2,3-triazoles **67** (Table 9). A library of synthetically and medicinally useful 1,5-disubstituted 1,2,3-triazoles **69al**–**uj** were synthesized in very good yields at room temperature by treatment of the corresponding 4-thio-1,2,3-triazoles **67** with 1.0 g of Raney Ni in ethanol through the desulfurization reaction.[42] In contrast, the reported conditions for the desulfurization required high temperature and long reaction time.[42] The desulfurization reaction worked well at 25 °C with different sulfur and aryl substituents without showing the effects of steric or electronic factors, except in the case of compound **67ae**, where debromination occurred (Table 9, entry 5). The sequential one-pot OrgAKC solvent-free reaction of **66a**, **2l**, and **17b** followed by Raney Ni desulfurization furnished the product **69al** in reduced 65% yield compared to the two-pot reaction (Table 9, entry 2). Pleasingly, the reaction of 1,5-diphenyl-4-phenylthio-1,2,3-triazole **67aa** with 1.2 equivalents of *m*-chloroperbenzoicacid in DCM at 25 °C for 18 h furnished selectively the monooxidized 1,5-diphenyl-4-(phenylsulfinyl)-1*H*-1,2,3-triazole **70aa** in 55% yield [Eq. (22)]. These results clearly show the advantages of the OrgAKC methodology, which enables a high-yielding synthesis of medicinally important 1,5-disubstituted 1,2,3-triazoles **69** and **70**.

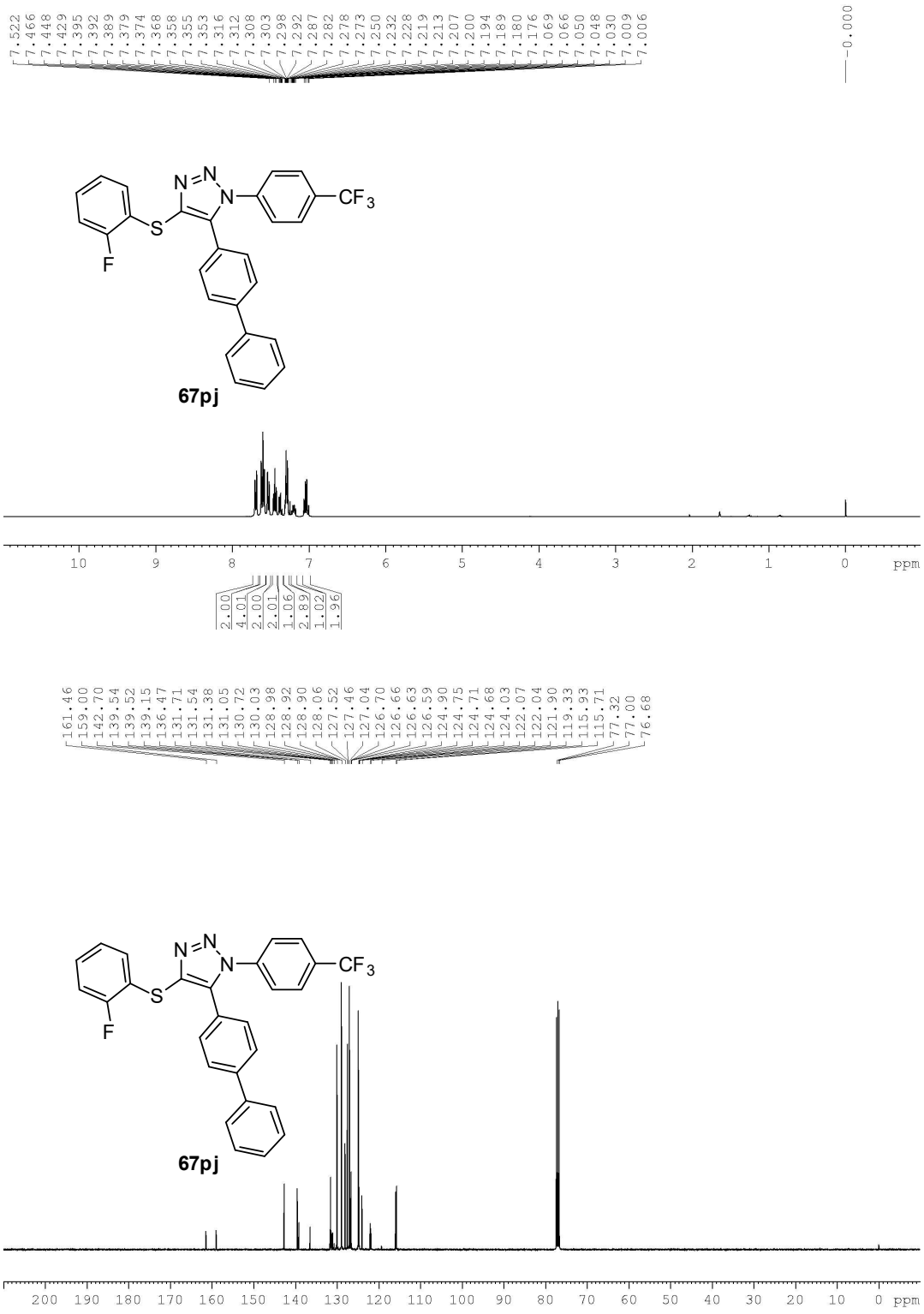


Figure-30: ^{1}H and ^{13}C NMR spectra of the product **67pj.**

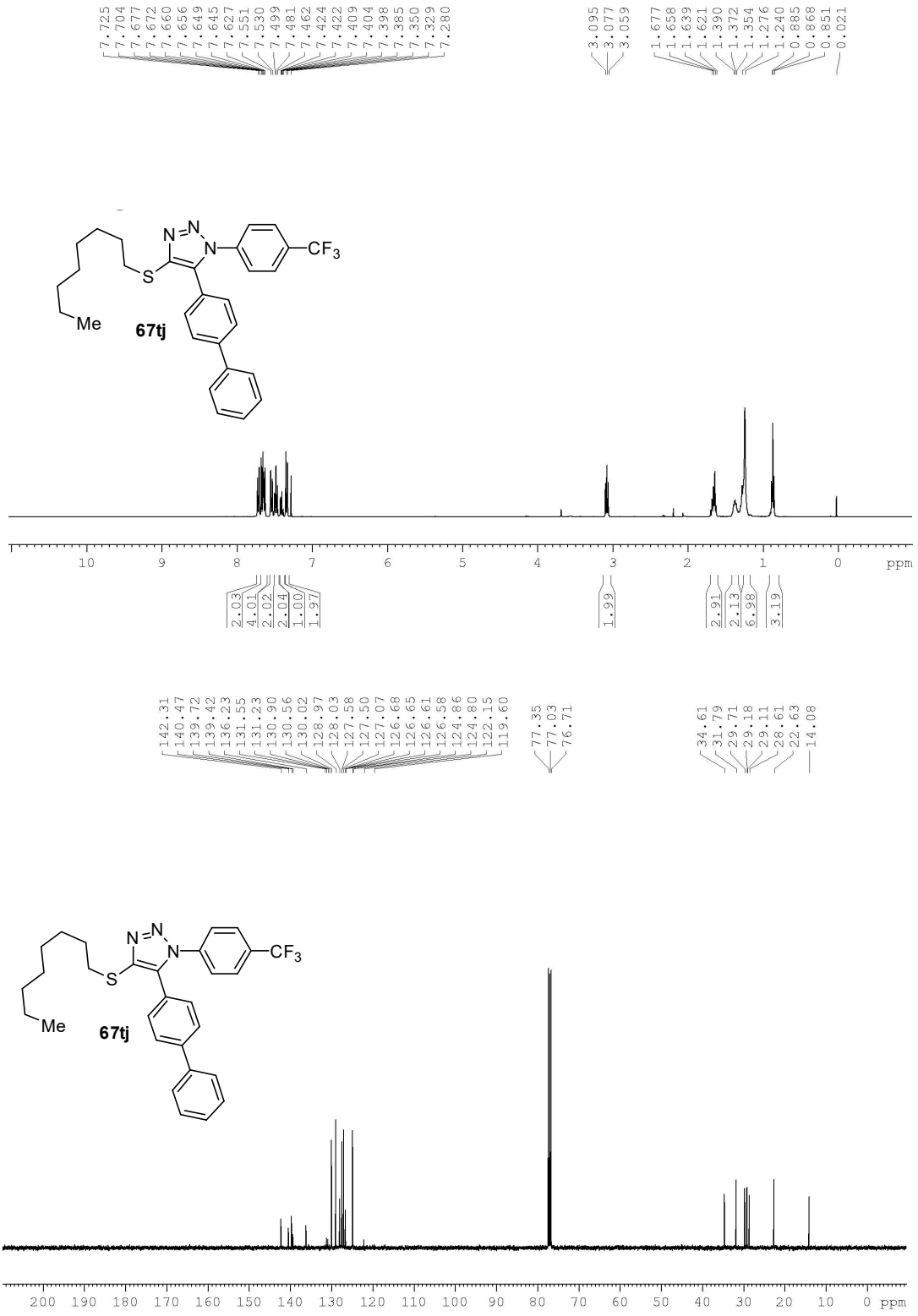


Figure-31: ^{1}H and ^{13}C NMR spectra of the product **67tj.**

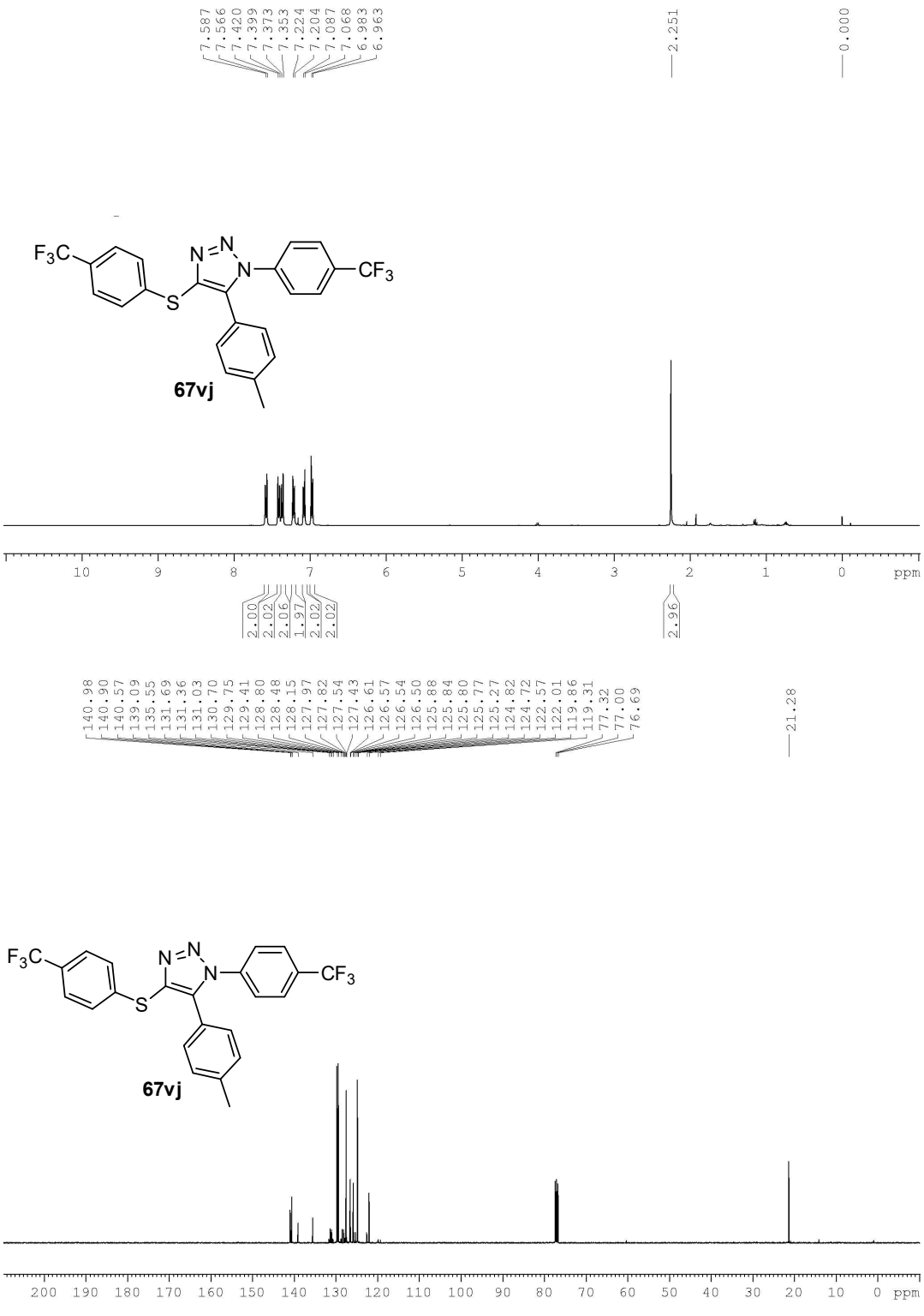
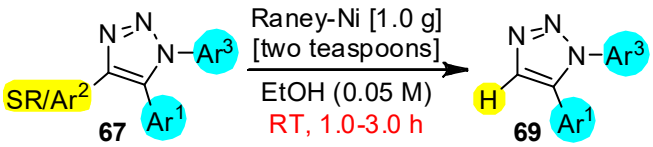


Figure-32: ^{1}H and ^{13}C NMR spectra of the product **67vj.**

Table 9: Synthesis of 1,5-disubstituted-1,2,3-triazoles **69** through desulphurization of 4-thio-1,2,3-triazoles **67**.[a]



Entry	R, Ar^1, Ar^2 or Ar^3 **67**	Yield [%][b] **69**
1	**67aa** (Ar^1 = C_6H_5; Ar^2 = C_6H_5; Ar^3 = C_6H_5)	87 (**69aa**)
2	**67al** (Ar^1 = C_6H_5; Ar^2 = C_6H_5; Ar^3 = 4-$CO_2EtC_6H_4$)	85 (**69al**)
3	**67aj** (Ar^1 = C_6H_5; Ar^2 = C_6H_5; Ar^3 = 4-$CF_3C_6H_4$)	90 (**69aj**)
4	**67ab** (Ar^1 = C_6H_5; Ar^2 = C_6H_5; Ar^3 = 4-FC_6H_4)	90 (**69ab**)
5[c]	**67ae** (Ar^1 = C_6H_5; Ar^2 = C_6H_5; Ar^3 = 4-BrC_6H_4)	70 (**69aa**)
6	**67ap** (Ar^1 = C_6H_5; Ar^2 = C_6H_5; Ar^3 = $CH_2CH_2C_6H_5$)	60 (**69ap**)
7	**67ej** (Ar^1 = 4-$CF_3C_6H_4$; Ar^2 = C_6H_5; Ar^3 = 4-$CF_3C_6H_4$)	60 (**69ej**)
8	**67lj** (Ar^1 = 2-Naphthyl; Ar^2 = C_6H_5; Ar^3 = 4-$CF_3C_6H_4$)	60 (**69lj**)
9	**67mj** (Ar^1 = 4-PhC_6H_4; Ar^2 = C_6H_5; Ar^3 = 4-$CF_3C_6H_4$)	90 (**69mj**)
10	**67rj** (Ar^1 = 4-PhC_6H_4; Ar^2 = 4-ClC_6H_4; Ar^3 = 4-$CF_3C_6H_4$)	60 (**69rj**)
11	**67tj** (Ar^1 = 4-PhC_6H_4; R = Octyl; Ar^3 = 4-$CF_3C_6H_4$)	85 (**69tj**)
12	**67uj** (Ar^1 = 4-FC_6H_4; R = Decyl; Ar^3 = 4-$CF_3C_6H_4$)	85 (**69uj**)

[a] Reactions were carried out in EtOH (0.05 M) with Raney-Ni (1.0 g) and **67** (0.5 mmol) at RT. [b] Yield refers to product isolated by column-chromatography. [c] Debromination also took place.

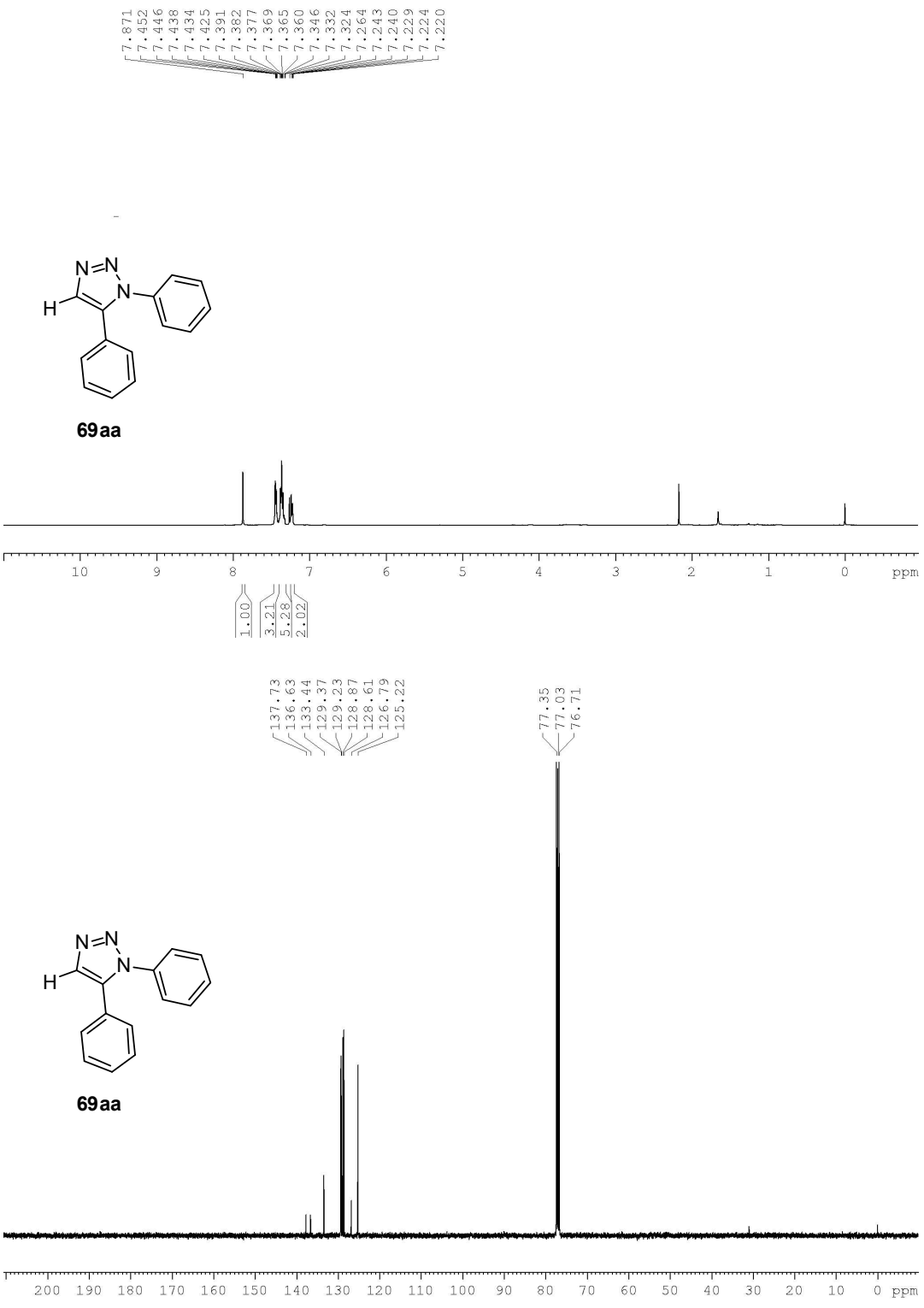


Figure-33: ^{1}H and ^{13}C NMR spectra of the product **69aa**.

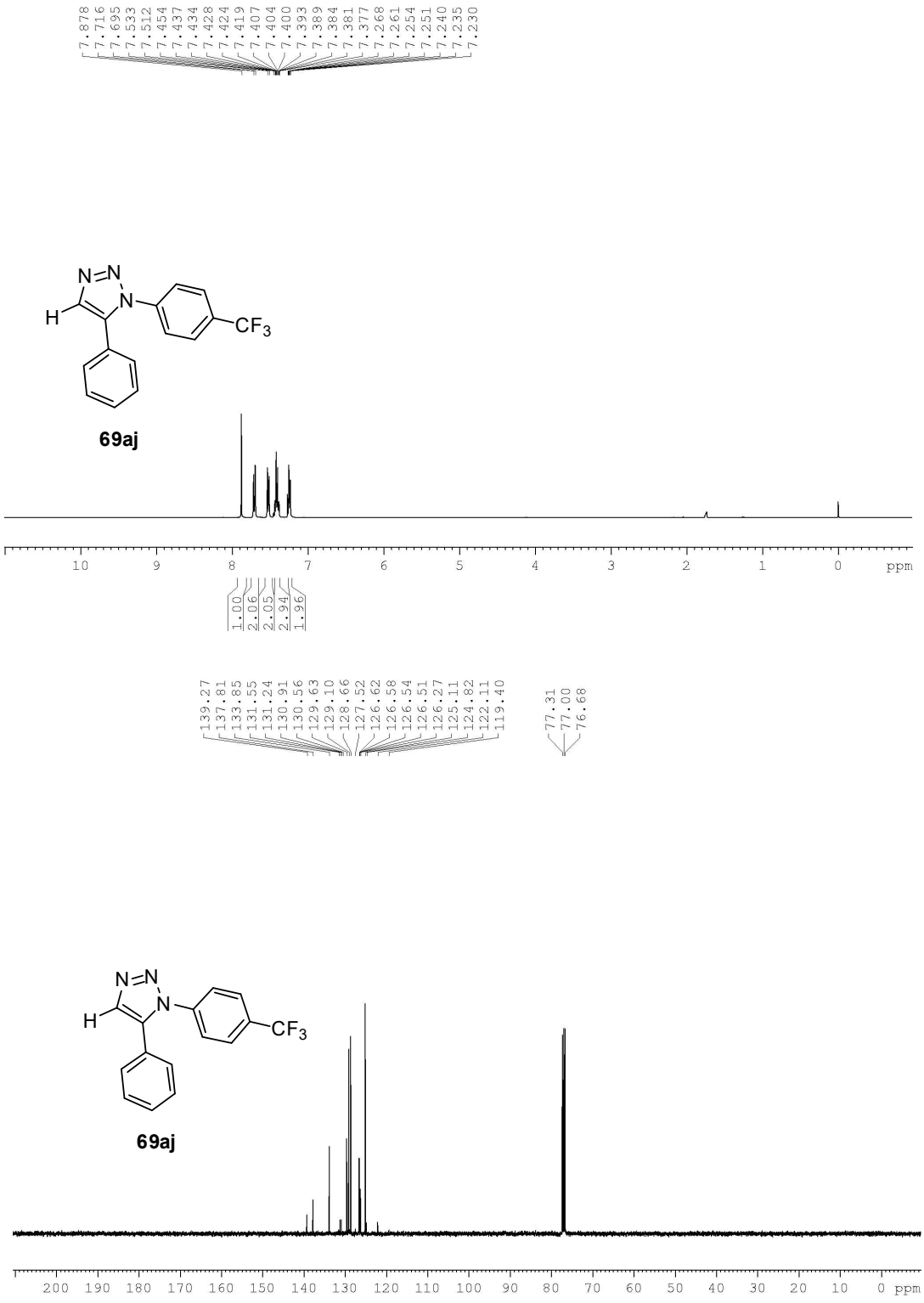


Figure-34: ^{1}H and ^{13}C NMR spectra of the product **69aj**.

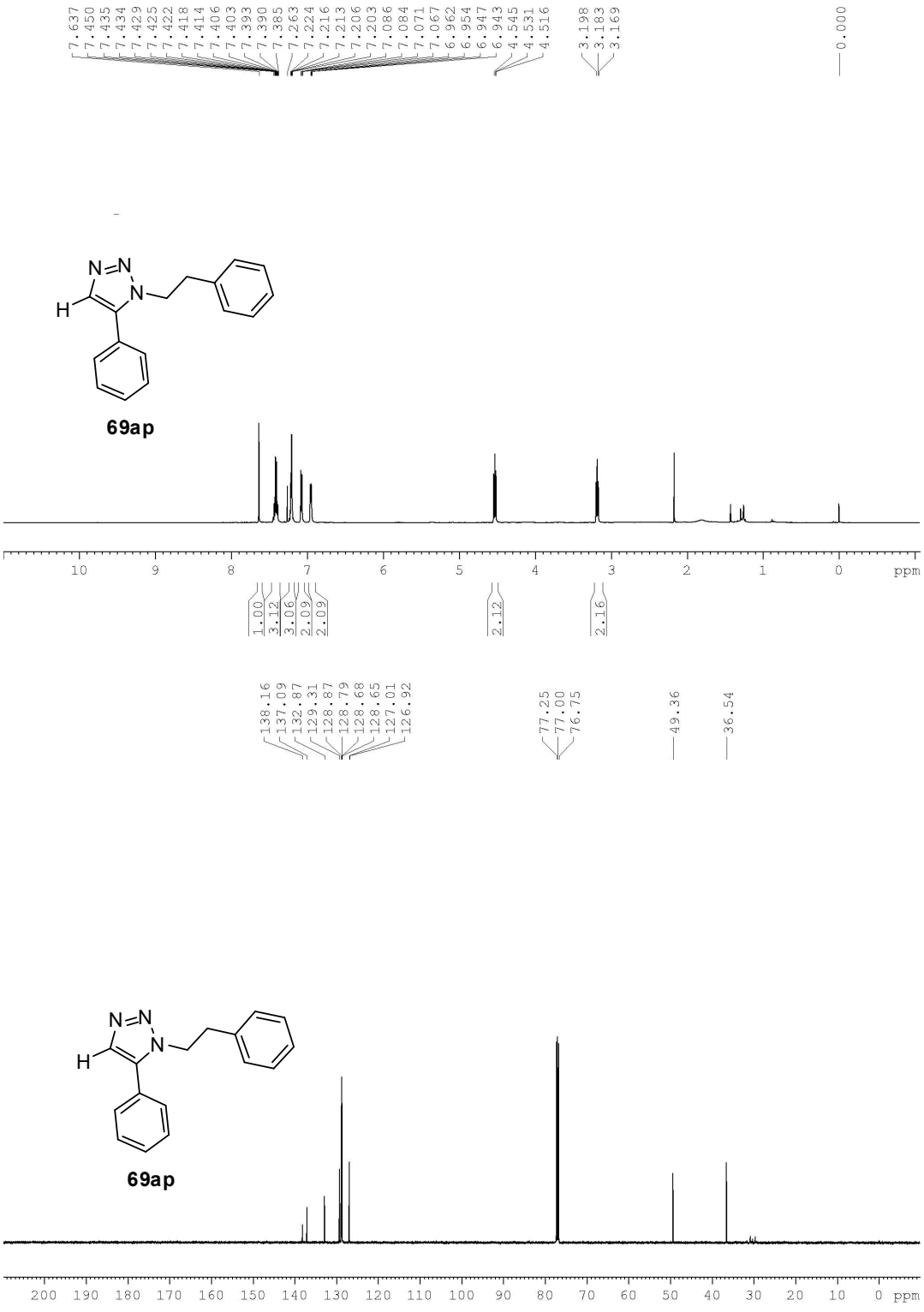


Figure-35: ^{1}H and ^{13}C NMR spectra of the product **69ap**.

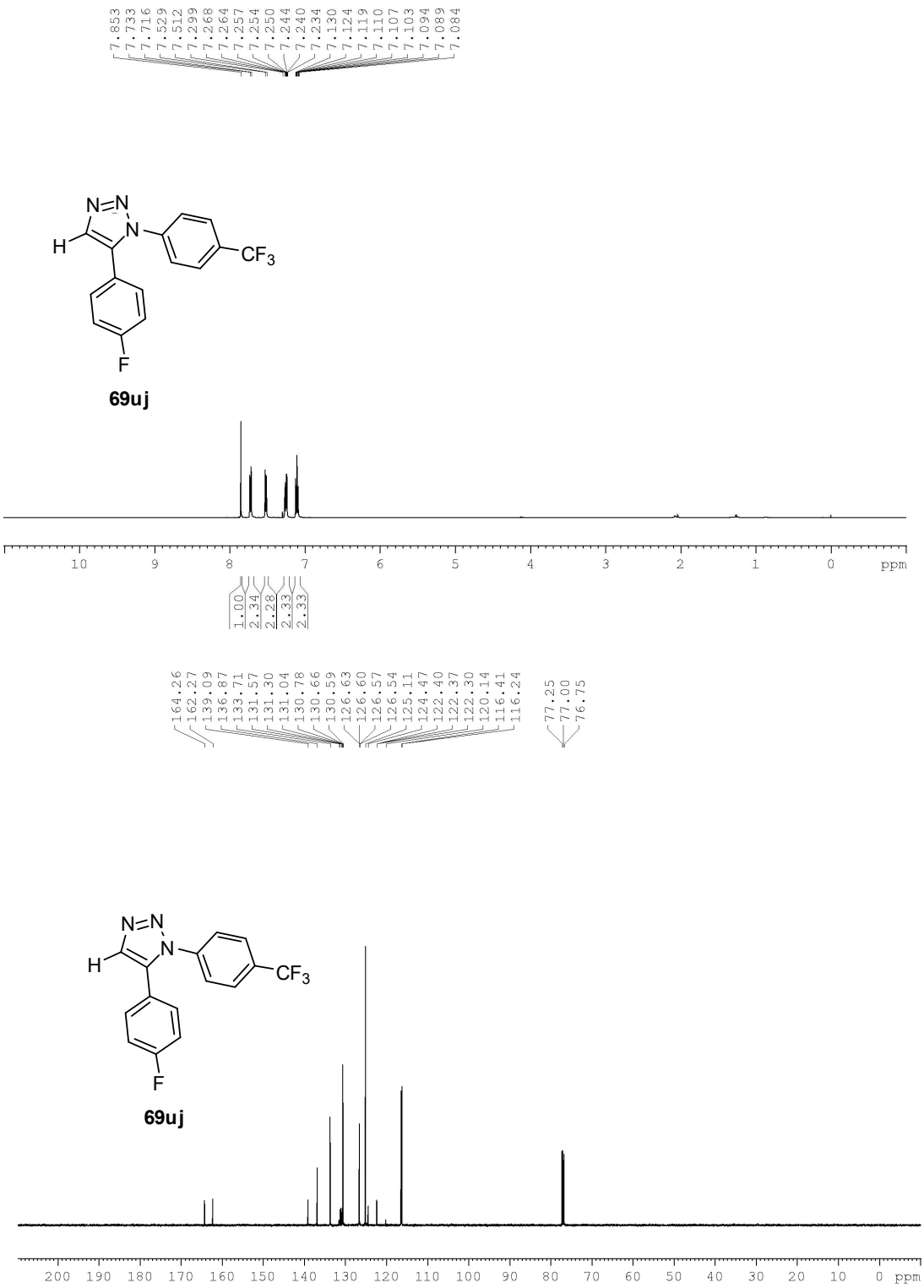
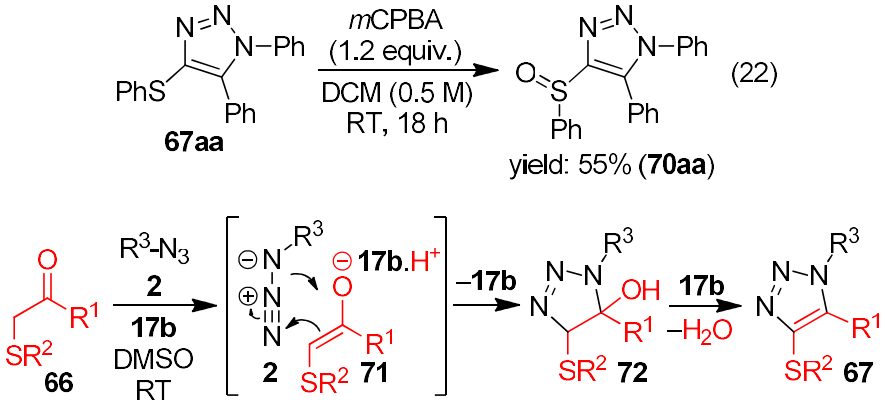


Figure-36: ^{1}H and ^{13}C NMR spectra of the product **69uj**.

4.3 Mechanistic Insights

A proposed mechanism for the regiospecific synthesis of **67** through the reaction of **66**, **2**, and **17b** is shown in Scheme 5. Reaction of the amine **17b** with ketone **66** generates the catalytic enolate **71**, which, on *in situ* treatment with Ar/R-N_3 **2**, furnishes selectively the adduct 1,2,3-triazoline **72** in a concerted or stepwise manner, which further converts into the 4-thio-1,2,3-triazole **67** through rapid elimination of water induced by the basic nature of amine **17b**.



Scheme 5: Reaction mechanism for the OrgAKC.

4.4 Conclusion

In summary, we have developed DBU-catalyzed and Raney Ni-mediated regiospecific synthesis of 1,4,5-trisubstituted 4-thio-1,2,3-triazoles **67** and 1,5-disubstituted 1,2,3-triazoles **69** from the easily available substrates 1-aryl-2-(arylthio)ethanones and 1-alkyl-2-(alkylthio)ethanones **66** with aryl or alkyl azides **2** by [3+2]-cycloaddition and subsequent desulfurization, respectively. The OrgAKC reaction proceeds in very good yields with high rate and selectivity using DBU as the catalyst in 0.75 h at 25 °C; and desulfurization of **67** performed with only 1.0 g of Raney Ni at 25 °C for 1–3 h, which highlights the efficacy of this mild procedure. Further work is in progress to develop related organocatalytic enolate-mediated asymmetric click reactions.

5. Synthesis of Benzosultams through Tomita Zipper Cyclization

5.1 Introduction

Sultams are unnatural five membered cyclic sulfonamides, which exist in many biologically active compounds. In particular, benzosultams gained more attention due to their extensive biological activities.[43] Some of the compounds containing benzosultams as core structure include human leukocyte elastase inhibitors, selective CRTh2 antagonists, active saccharin, HIV-1 inhibitor, 5-HT2 receptor antagonists and recently discovered pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines which are new agents for the treatment of chronic myelogenous leukemia (Figure 37).[44] The increased interest on the benzosultams is, particularly, due to the availability of simple coupling pathways for their preparation and few impressive chemical properties such as the stability towards hydrolysis, crystalline nature and polarity. In addition, they have also been widely employed in modern synthetic chemistry for instance, few benzosultams have found application in various asymmetric reactions, stereoselective oxidation as an oxidant[45] and monofluorination of ketones as electrophillic fluorinating agent.[46] Although many synthetic methods have been developed for the synthesis of benzosultams due to their vast biological activities and synthetic utility, the development of novel and efficient approaches are still in demand.

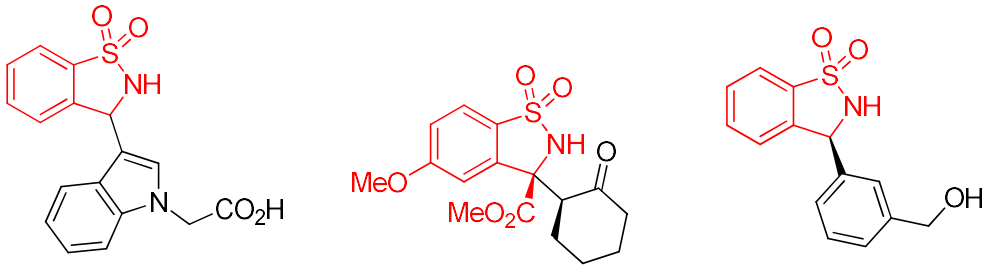
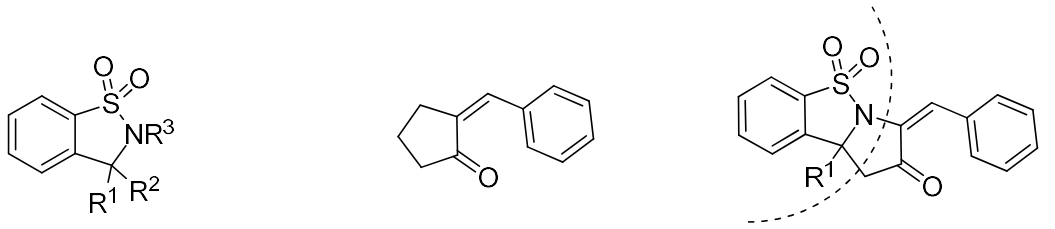


Figure 37. Selected bioactive benzosultams

On the other hand, alkylidene cycloketones are versatile intermediates in organic synthesis,[47] as well as common building blocks in many biologically active compounds [48] and natural products. Some of the literature methods for the construction of exocyclic olefins are Wittig,[49] Julia[50] and Horner-Wadsworth-Emmons[51] reactions. These methods are not significant due to the difficulty in preparation of the corresponding ylides or sulfones, and low reactivity of these species. Aldol reaction followed by dehydration under catalyzed or uncatalyzed condition is one of the alternative approaches for the synthesis of exocyclic olefins.[52] Unfortunately, regioselectivity issues and bis-condensation are serious problems with unsymmetrical ketones. Owing to the above difficulties, novel and efficient methods are still in high demand. In addition molecules containing both sultam and alkylidene cycloketone fragments are less explored (Figure 38).



Cyclic sulfonamides, **A** Alkylidene cycloketones, **B** Combination of **A** and **B**, **C**

Figure 38. Biological structures containing cyclic sulfonamides and alkylidene cycloketones

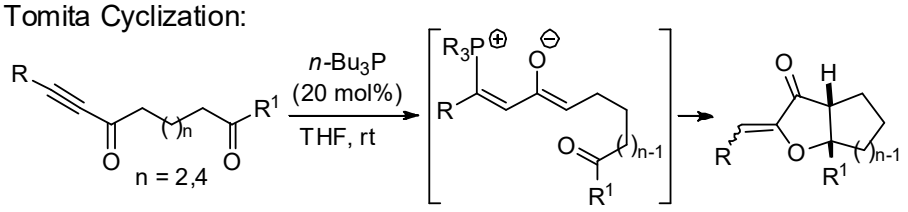
Construction of molecules containing both sultam and alkylidene cycloketone sub-unit is very interesting and challenging task for synthetic chemists. To achieve this goal, we designed the reaction between highly reactive *N*-sulfonyl α-ketiminoesters and unmodified ynones using organophosphine-catalyzed Tomita Zipper Cyclization.

Recently, our group reported phospine catalyzed intermolecular Tomita Zipper Cyclization (TZC)[53] reaction between unmodified ynones and 3-alkylidene indoline-2-one that delivers efficiently five membered spirooxinodoles.[54] Here intermolecular TZC reaction takes place on electron deficient alkenes. In continuation to our research, now we are interested in intermolecular Tomita Zipper Cyclization (TZC) reaction between unmodified ynone and *N*-sulfonyl α-ketiminoesters.

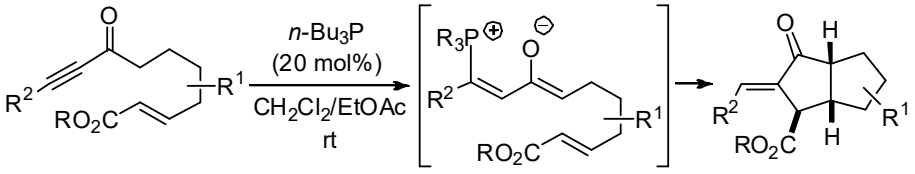
Scheme 6: Tomita Zipper Cyclization (TZC) of Ynone with *N*-Tosylimines

Previous Approaches Based on Intramolecular Cyclization:

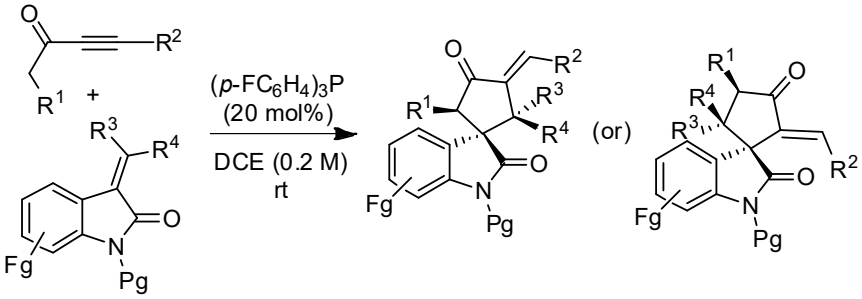
Tomita Cyclization:



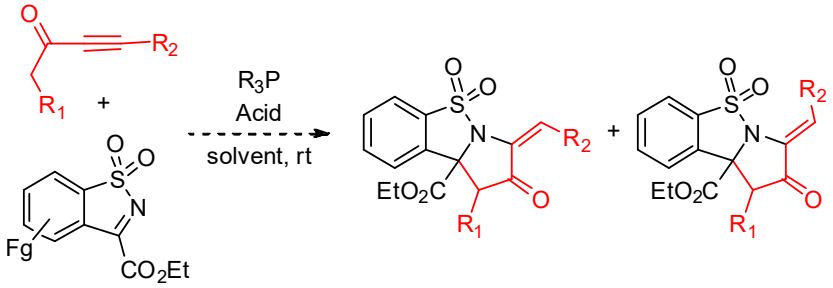
Fu Cyclization:



Intermolecular Tomita Zipper Cyclization:



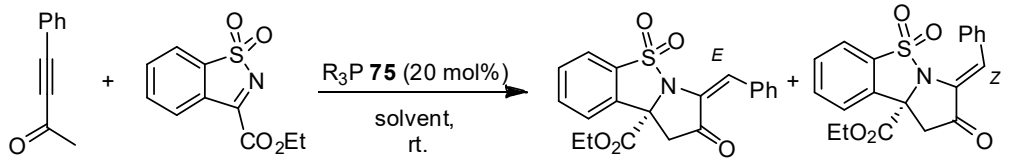
This Work: Intramolecular Tomita Zipper Cyclization of Ynone with *N*-Tosylimines



5.2 *Results and Discussion*

To find the best optimization condition, we screened a number of known aromatic and aliphatic phosphorous catalysts for the reaction of ynone **73a** with ketimine **74a** (Table 10). To our surprise, reaction of **74a** with 2 equiv. of **73a** under 20 mol% of triphenyl phospine **75a** in DCE at 25 °C for 24 h furnished the products **76aa**+**77aa** in 52% yield with 3.1:1 *E*/*Z* ratio (Table 10, entry 1). The same reaction with (*p*-$FC_6H_4)_3P$ **75b** as catalyst

Table 10. Reaction Preliminary Optimization[a]



73a **74a** **76aa** **77aa**

Ph_3P (**75a**), (p-$FC_6H_4)_3P$ (**75b**), (p-$OMeC_6H_4)_3P$ (**75c**), Ph_2EtP (**75d**), $^nBu_3P$ (**75e**), $(C_6H_{11})_3P$ (**75f**)

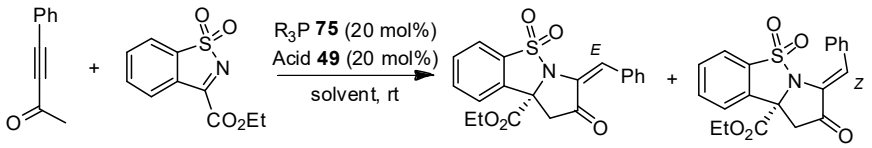
Entry	Catalyst **75** (20 mol%)	Solvent (0.2 M)	Time (h)	Yield (%)[b]	Ratio[c] (**76aa**:**77aa**)
1	**75a**	DCE	24	52	3.1:1
2	**75b**	DCE	24	54	3.4:1
3[d]	**75b**	DCE	15	47	1.8:1
4	**75c**	DCE	36	53	1.8:1
5	**75d**	DCE	72	traces	-
6	**75e**	DCE	72	traces	-
7	**75f**	DCE	36	36	1.7:1
8	**75e**	DCM	72	traces	-
9	**75a**	DCM	24	52	2.6:1
10	**75b**	DCM	36	51	2.8:1
11	**75b**	$C_6H_5CH_3$	36	55	1.2:1
12[d]	**75b**	$C_6H_5CH_3$	11	53	1.7:1
13	**75b**	THF	36	52	2.8:1
14	**75a**	[bmim]BF_4	12	52	1:2.7

[a] Reactions were carried out in solvent (0.2 M) with 2 equiv. of **73a** relative to the **74a** (0.2 mmol) in the presence of 20 mol% of catalyst **75**. [b] Yields refers to the column purified products of both the isomers.[c] *E*/*Z* ratio was determined by ^{1}H NMR analysis.[d] Reaction performed at 50 °C.

at 25 °C and 50 °C furnished 3.4:1 and 1.8:1 *E*/*Z* ratio of products **76aa**/**77aa** in 54% and 47% yields in 24 h and 15 h, respectively (Table 10, entries 2 and 3). From these results, it was observed that temperature plays a significant role on the rate of the reaction and the *E*/*Z* ratio. The reaction under electron rich phosphine catalyst such as (p-$OMeC_6H_4)_3P$ **75c**

furnished the products with good *E*/*Z* ratio in 53% yield in 36 h (Table 10, entry 4). Next we performed the reaction with ethyldiphenylphosphine **75d** and tri-*n*-butylphosphine **75e** as the catalysts under the same reaction condition, but these phosphorous catalysts did not furnish the product **76aa** and **77aa** (Table 10, entries 5 and 6). The reaction under tricyclohexylphosphine **75f** catalysis furnished the TZC product in lower yield with good **76aa**/**77aa** *E*/*Z* ratio (Table 10, entry 7). From this investigation of catalysts **75a**-**75f** on the TZC reaction, we found that catalysts **75a** and **75b** are good to obtain better yields and good *E*/*Z* ratio. Further, we tested the reactivity of the catalysts **75a** and **75b** on the TZC reaction in other solvents such as DCM, Toluene, THF and ionic liquid [Bmim]BF_4. The reaction of **73a** with **74a** under **75a** and **75b** as catalysts in DCM as solvent furnished identical yields as

Table 11: Brönsted acid effect on TZC reaction.[a]



73a **74a** **76aa** **77aa**

Ph_3P (**75a**), (p-$FC_6H_4)_3P$ (**75b**), (p-$OMeC_6H_4)_3P$ (**75c**), Ph_2EtP (**75d**), nBu_3P (**75e**), $(C_6H_{11})_3P$ (**75f**), $C_6H_5CO_2H$ (**49d**),*o*-$FC_6H_4CO_2H$ (**49a**), 2,4-$(NO_2)_2C_6H_3CO_2H$ (**49e**), $C_6H_5CH_2CO_2H$ (**49f**), CH_3CO_2H (**49g**), $C_2H_5CO_2H$ (**49c**), $C_6H_{11}CO_2H$ (**49h**).

Entry	Catalyst **75** (20 mol%)	Co-Catalyst **49** (20 mol%, p*K*a)	Solvent (0.2 M)	Time (h)	Yield (%)[b]	Ratio[c] (**76aa:77aa**)
1[d]	**75b**	H_2O (pK_a = 15.7)	DCE	72	51	2.8:1
2[e]	**75b**	MeOH (pK_a = 16.0)	DCE	48	54	2.6:1
3	**75a**	**49d** (pK_a = 4.20)	DCE	9	75	2.0:1
4	**75b**	**49d** (pK_a = 4.20)	DCE	10	52	1.4:1
5	**75a**	**49a** (pK_a = 3.27)	DCE	7	72	2.2:1
6	**75a**	**49e** (pK_a = 1.43)	DCE	8	66	1.8:1
7	**75a**	**49f** (pK_a = 4.31)	DCE	6	93	2.3:1
8	**75a**	**49g (pK_a = 4.76)**	**DCE**	**6**	**95**	**2.2:1**
9	**75a**	**49c** (pK_a = 4.88)	DCE	6	94	2.4:1
10	**75a**	**49h** (pK_a = 4.90)	DCE	7	91	1.9:1

[a] Reactions were carried out in solvent (0.2 M) with 2 equiv. of **73a** relative to the **74a** (0.2 mmol) in the presence of 20/20 mol% of catalyst **75/49**. [b] Yields refers to the column purified products of both the isomers. [c] *E*/*Z* ratio was determined by ^{1}H NMR analysis.[d] H_2O (1 equiv.) was used. [e] MeOH (1 equiv.) was used.

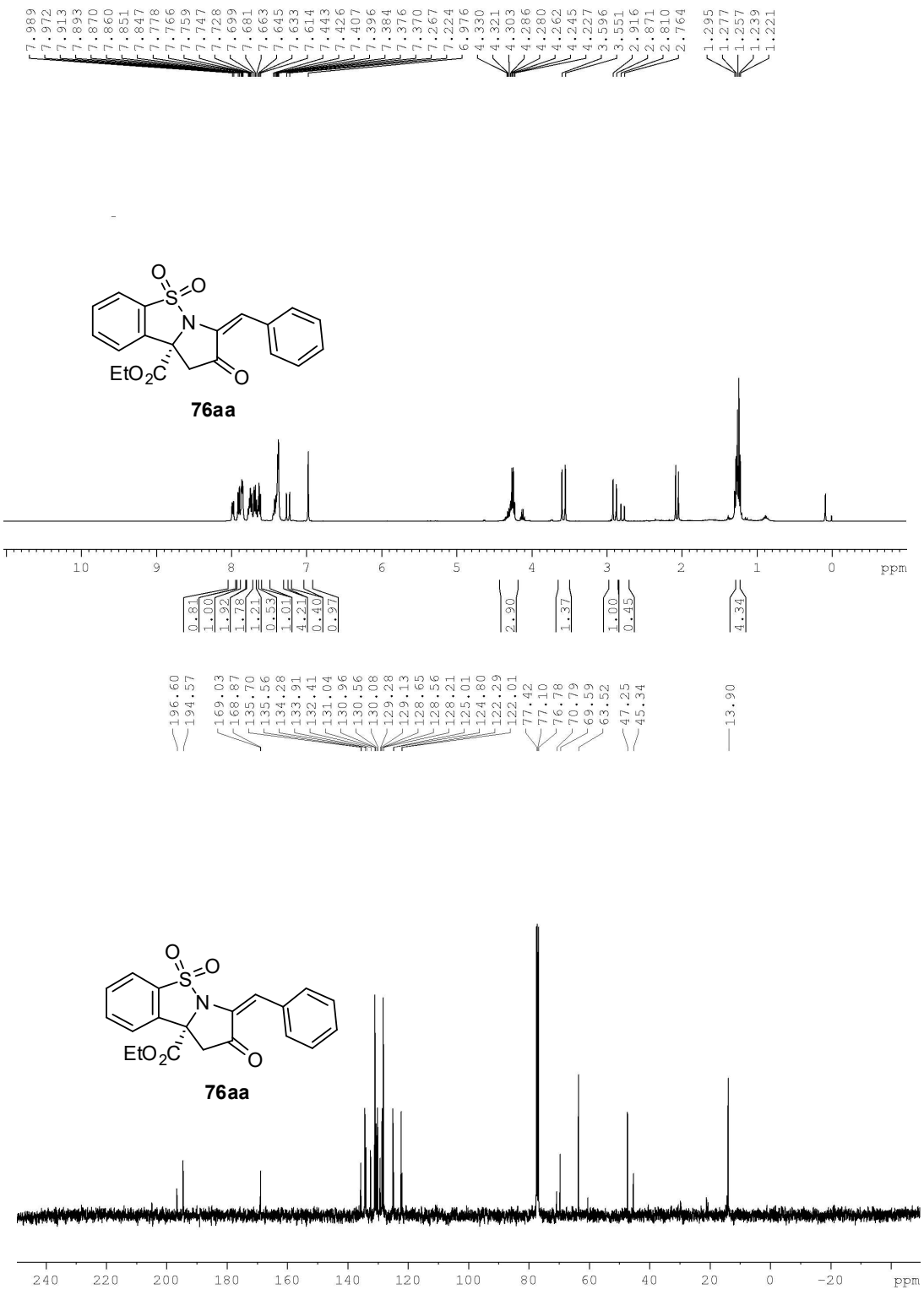


Figure-39: ^{1}H NMR and ^{13}C NMR Spectrum of Product **76aa**.

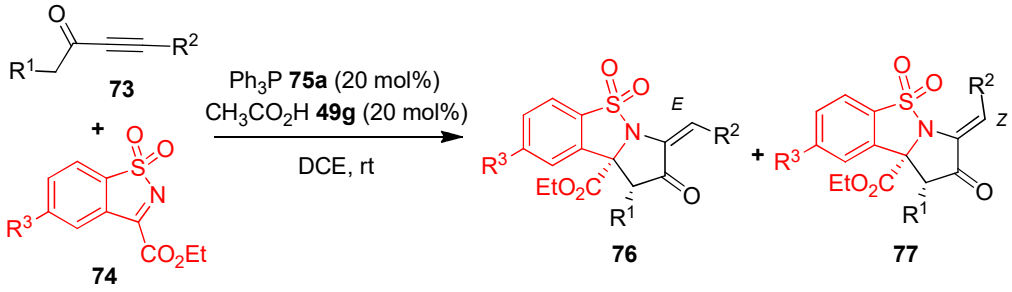
like DCE solvent but *E*/*Z* ratio are not that much good (Table 10, entries 9 and 10). When (*p*-$FC_6H_4)_3P$ **75b** catalyzed the reaction in toluene at 25 °C and 50 °C the TZC products were obtained with *E*/*Z* ratio of 1.2:1 and 1.7:1 in 55% and 53% yields within 36 and 11 h, respectively. The same reaction under **75b** catalysis in THF furnished the product in 2.8:1 *E*/*Z* ratio in 52% yield (Table 10, entries 11-13). Surprisingly, we obtained reverse *E*/*Z* ratio when we performed the same reaction under **75a** catalysis in [Bmim]BF_4 as solvent with the products in 1:2.7 *E*/*Z* ratio in 52% yield (Table 10, entry 14).

To further improve the TZC reaction, especially to increase the rate of the reaction and to get a good *E*/*Z* ratio, we tested the TZC reaction of **73a** with **74a** catalyzed by **75b** in the presence of H_2O (1 equiv.) and MeOH (1 equiv.) in DCE at 25 °C to obtain 2.8:1 and 2.6:1 *E*/*Z* ratio of products **76aa**/**77aa** in 51% and 54% yields, respectively (Table 11, entries 1 and 2). As we did not observe any noticeable improvement in the rate of the reaction by H_2O or MeOH, we tested the TZC reaction of **73a** with **74a** catalyzed by PPh_3 **75a** or (*p*-$FC_6H_4)_3P$ **75b** using different acid co-catalysts **49** in DCE at 25 °C (Table 11, entries 3-10). Reaction of **74a** with 2.0 equiv. of **73a** catalyzed by **75a** and **75b** with benzoic acid **49d** (20 mol%, pk_a= 4.20) as co-catalyst at 25 °C for 9 h and 10 h furnished the TZC products with 2.0:1 and 1.4:1 *E*/*Z* ratio in 75% and 52% yields, respectively (Table 11, entries 3 and 4). Based on these results, we concluded that the co-catalyst plays an important role on the rate of reaction and yield, and also catalyst **75a** gave better result than **75b** in the presence of co-catalyst **49d**. Further, we tested the reaction with other acid co-catalysts (Table 11, entries 5-10). The same reaction under the combination of catalyst **75a** with 2-fluoro benzoic acid **49a** (20 mol%, pk_a = 3.27) and 2,4-dinitro benzoic acid **49e** (20 mol%, pk_a= 1.43) gave the TZC product **76aa**+**77aa** in 72% and 66% yields with 2.2:1 and 1.8:1 *E*/*Z* ratio in 7 and 8 h respectively (Table 11, entries 5 and 6). As we go from benzoic acid **49d** to **49a** and **49e**, though there is a light increase in the rate of the reaction as the acidity of the co-catalyst increases, there seems to be a decrease in the product yields with maintained *E*/*Z* ratio (Table 11, entries 5 and 6). We also tested the reaction with less acidic co-catalysts than benzoic acid such as phenylacetic acid **49f** (20 mol%, pk_a = 4.31), acetic acid **49g** (20 mol%, pk_a = 4.76), propionic acid **49c** (20 mol%, pk_a = 4.88) and cyclohexane carboxylic acid **49h** (20 mol%, pk_a = 4.90) (Table 11, entries 7-10). While decreasing the acidity of the co-catalyst surprisingly, we observed excellent yields of the products with high reaction rate and

maintained *E*/*Z* ratio (Table 11, entries 7-10). Compared to all other co-catalysts, the reaction of **73a** with **74a** catalysed by **75a** and the co-catalyst acetic acid **49g** in DCE furnished the product in excellent yield 95% with 2.2:1 *E*/*Z* ratio within 6 h (Table 11, entry 8).

With the best optimized reaction condition in hand, we decided to investigate the scope and limitations of the TZC reaction. A series of ketimines containing various substituents on benzene ring **74a-d** were reacted with 2.0 equiv. of different ynones **73a-g** catalyzed by 20/20 mol% of **75a/49g** at 25 °C in DCE, for 2-9 h, to furnish the TZC products in 80-95% yields with poor *E*/*Z* ratio (Table 12). First we reacted the simple ketimine **74a** with methyl substituted ynone **73b** to furnish the product **76ba**+**77ba** in 93% yield with 3.6:1 *E*/*Z* ratio in 8 h (Table 12, entry 2). Fluoro substituted ynone **73c** gave the desired product **76ca**+**77ca** in 93% yield with 3.3:1 *E*/*Z* ratio within 7 h (Table 12, entry 3). Unfortunately, methoxy substituted ynone **73d** gave the desired product **76da**+**77da** with very poor *E*/*Z* ratio 1.7:1 in 89% yield (Table 12, entry 4). Further we were interested to investigate the effect of the halogen present on the benzene ring of the ketimine **74b** with different substituted ynones **73a**-**c** and **73e**. All of these gave the desired products in good yields but with poor *E*/*Z* ratio within 6 h (Table 12, entries 5-8). Reaction of the methyl ketimine **74c** with different ynones **73a**-**73c** gave the desired products **76ac**-**cc**/**77ac**-**cc** in good yields with moderate *E*/*Z* ratios in 7-9 h (Table 12, entries 9-13). Surprisingly, reaction of 4-methoxy ynone **73d** with **74c** gave **76dc**+**77dc** in 86% yield with good *E*/*Z* ratio 6.7:1 in 7 h (Table 12, entry 12). MOMO substituted ynone **73e** with **74c** also gave the product **76ec**+**77ec** in 92% yield but with very poor *E*/*Z* ratio 1.7:1 in 9 h (Table 12, entry 13). Ketimine substituted with methoxy **74d** reacted with ynones **73a**-**73c** to give the desired products in good yields with moderate *E*/*Z* ratio in 6-7 h (Table 12, entries 14-16). Next we were interested to study the effect of the alkyl chain on the ketone of the ynone **73f** and **73g** with simple cyclic ketimine **74a**. To our delight, both the reactions furnished the corresponding products with good yields in 2-3 h, surprisingly **73g** afforded **76ga**+**77ga** with very good *E*/*Z* ratio (Table 12, entries 17 and 18).

Table 12: Scope of TZC reaction with other ynones and imines.[a]



73a: R^2, R^1 = C_6H_5, H; **73b**: R^2, R^1 = 4-MeC_6H_4, H; **73c**: R^2, R^1 = 4-FC_6H_4, H; **73d**: R^2, R^1 = 4-$MeOC_6H_4$, H; **73e**: R^2, R^1 = 4-$MOMOC_6H_4$, H; **73f**: R^2, R^1 = C_6H_5, CH_3; **73g**: R^2, R^1 = C_6H_5, C_2H_5; **74a**: R^3 = H; **74b**: R^3 = Cl; **74c**: R^3 = CH_3; **74d**: R^3 = OMe.

Entry	Ynone **73**	Imine **74**	Time(h)	Products**76**/**77**	Yield (%)[b]	Ratio[c] (**76**:**77**)
1	**73a**	**74a**	6	**76aa/77aa**	95	2.2:1
2	**73b**	**74a**	8	**76ba/77ba**	93	3.6:1
3	**73c**	**74a**	7	**76ca/77ca**	93	3.3:1
4	**73d**	**74a**	7	**76da/77da**	89	1.7:1
5	**73a**	**74b**	6	**76ab/77ab**	91	1.5:1
6	**73b**	**74b**	6	**76bb/77bb**	80	1.3:1
7	**73c**	**74b**	6	**76cb/77cb**	93	1.5:1
8	**73e**	**74b**	6	**76eb/77eb**	88	1.6:1
9	**73a**	**74c**	7	**76ac/77ac**	86	2.9:1
10	**73b**	**74c**	7	**76bc/77bc**	88	2.3:1
11	**73c**	**74c**	9	**76cc/77cc**	78	3.7:1
12	**73d**	**74c**	7	**76dc/77dc**	86	6.7:1
13	**73e**	**74c**	9	**76ec/77ec**	92	1.7:1
14	**73a**	**74d**	6	**76ad/77ad**	90	3.2:1
15	**73b**	**74d**	6	**76bd/77bd**	91	5.5:1
16	**73c**	**74d**	7	**76cd/77cd**	91	2.9:1
17	**73f**	**74a**	3	**76fa/77fa**	78	2:1[d]
18	**73g**	**74a**	3	**76ga/77ga**	81	11.1:1

[a] Reactions were carried out in solvent (0.2 M) with 2 equiv. of **73** relative to the **74** (0.2 mmol) in the presence of 20/20 mol% of catalyst **75a/49g**. [b] Yields refers to the column purified products of both the isomers. [c] *E/Z* ratio was determined by ^{1}H NMR analysis.[d] *cis:trans* = 2.8:1 ratio determined by ^{13}C NMR analysis.

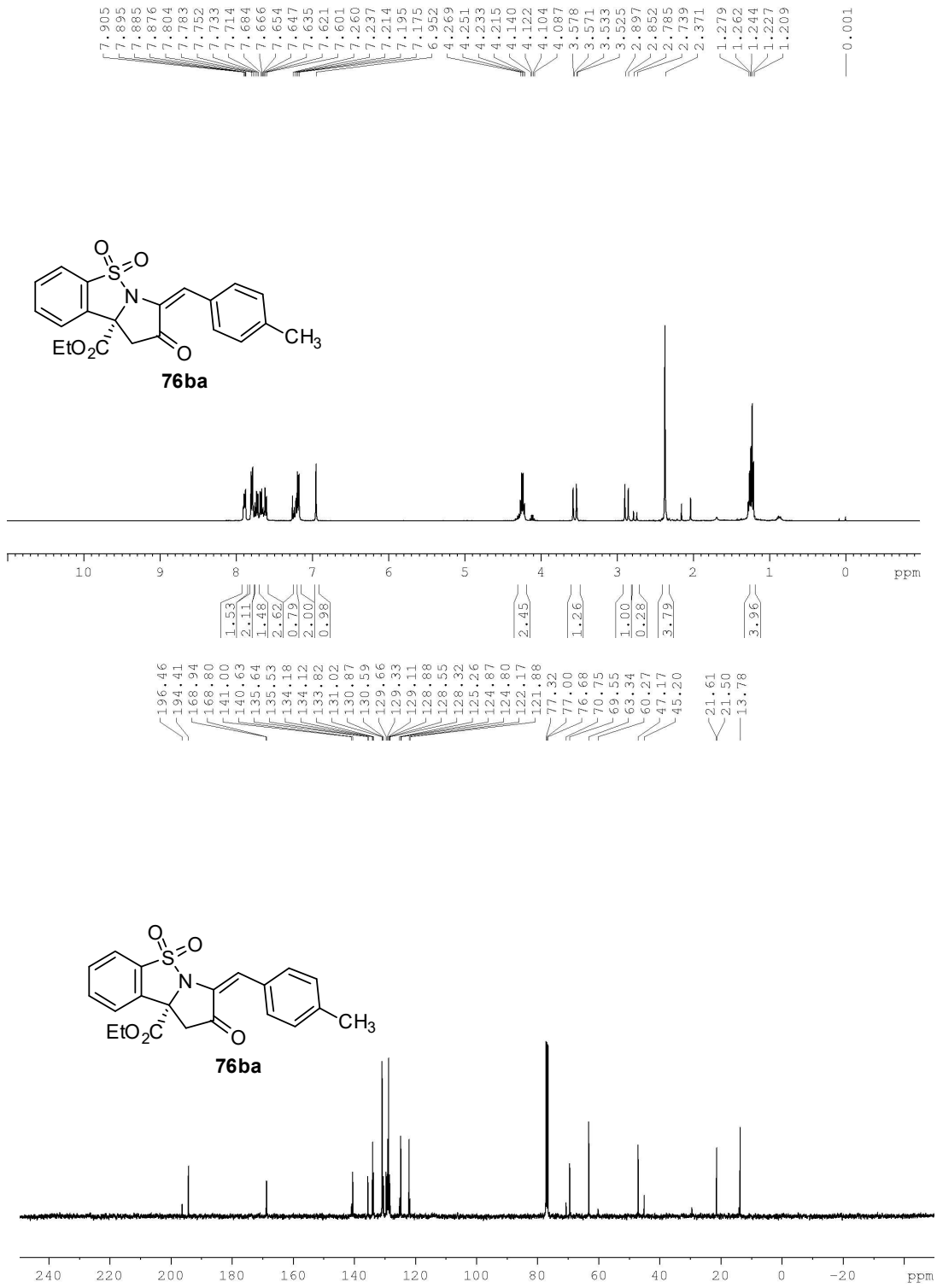


Figure-40: ^{1}H NMR and ^{13}C NMR Spectrum of Product **76ba**.

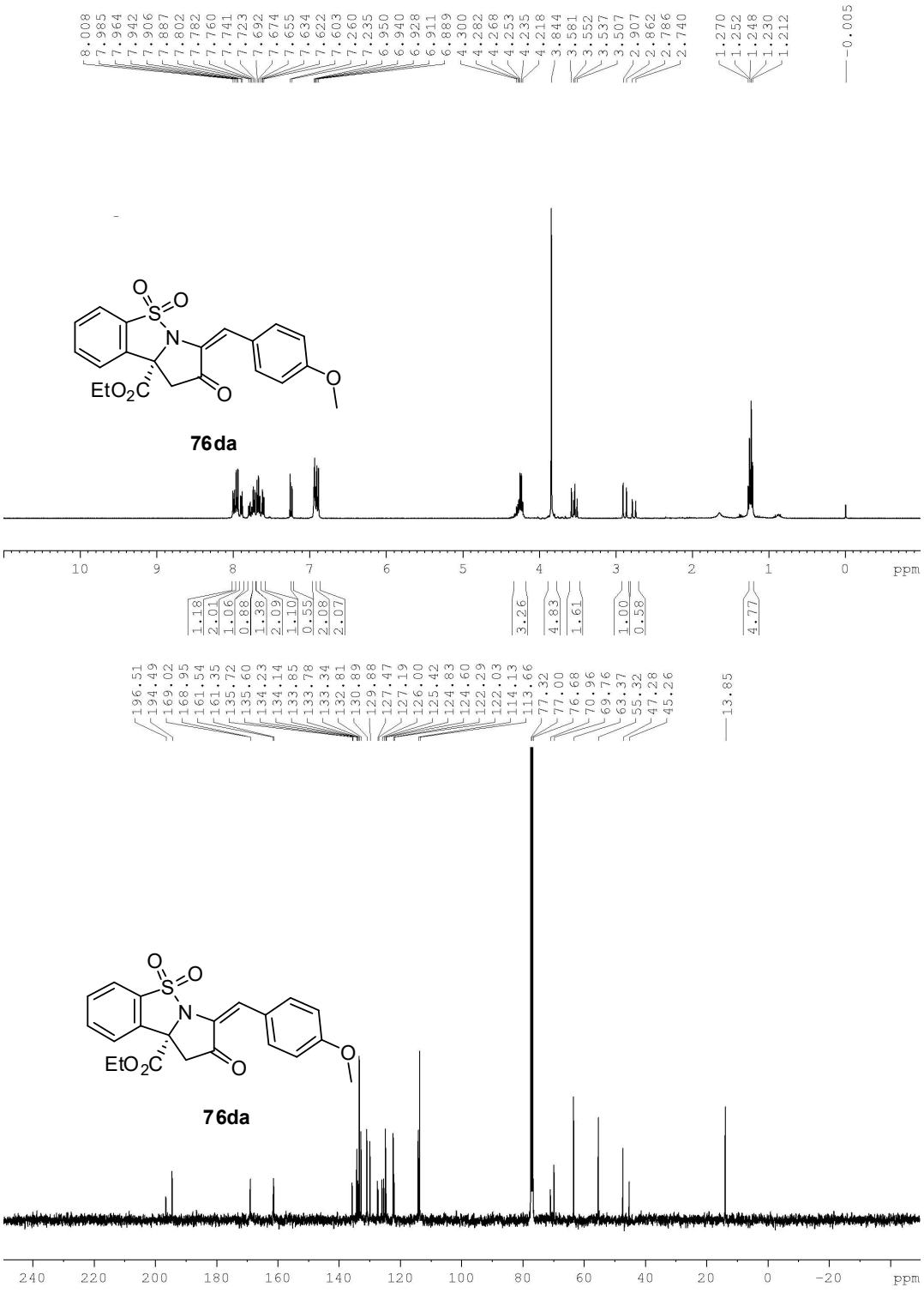


Figure-41: ^{1}H NMR and ^{13}C NMR Spectrum of Product **76da**.

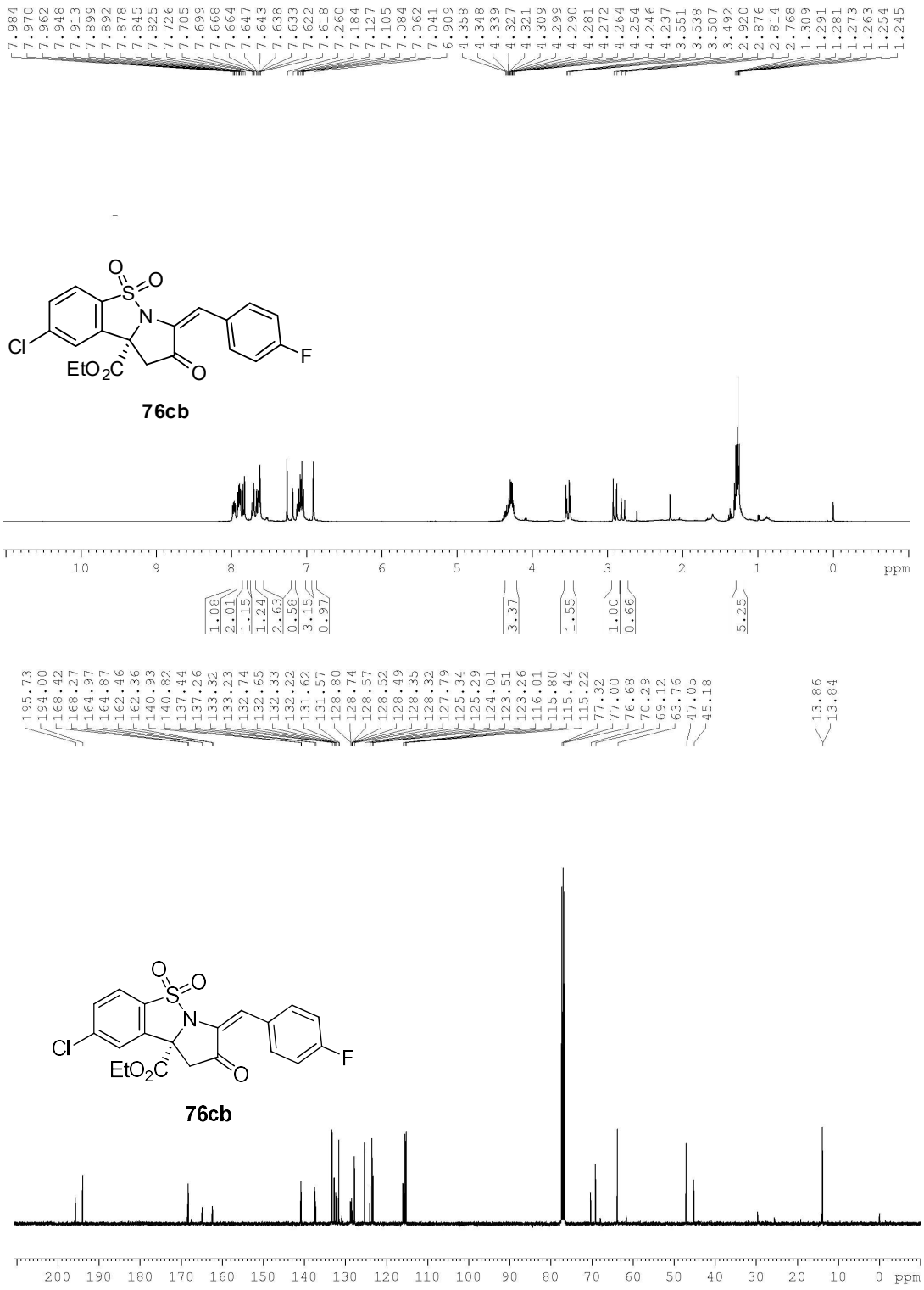


Figure-42: ^{1}H NMR and ^{13}C NMR Spectrum of Product **76cb**.

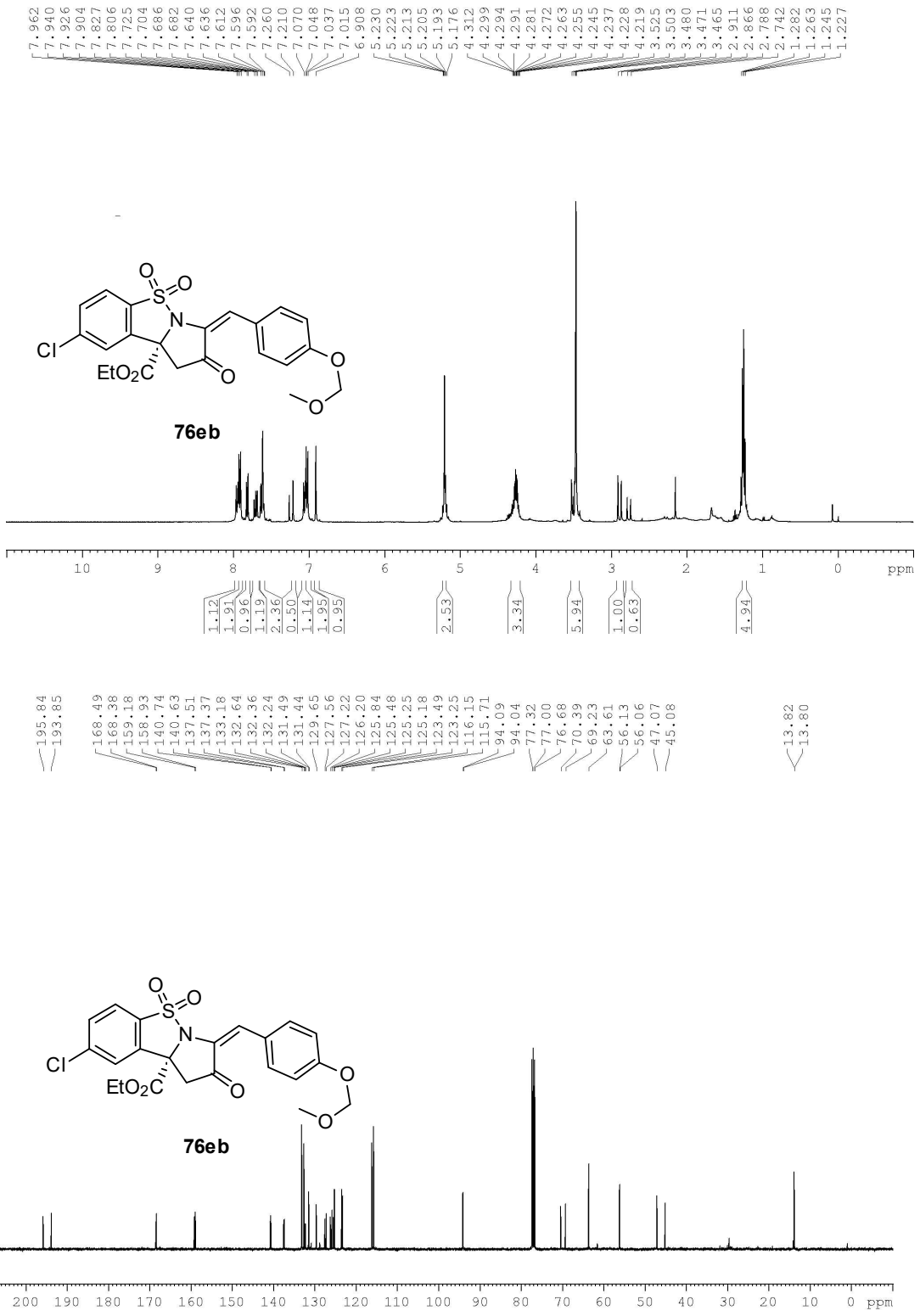


Figure-43: ^{1}H NMR and ^{13}C NMR Spectrum of Product **76eb.**

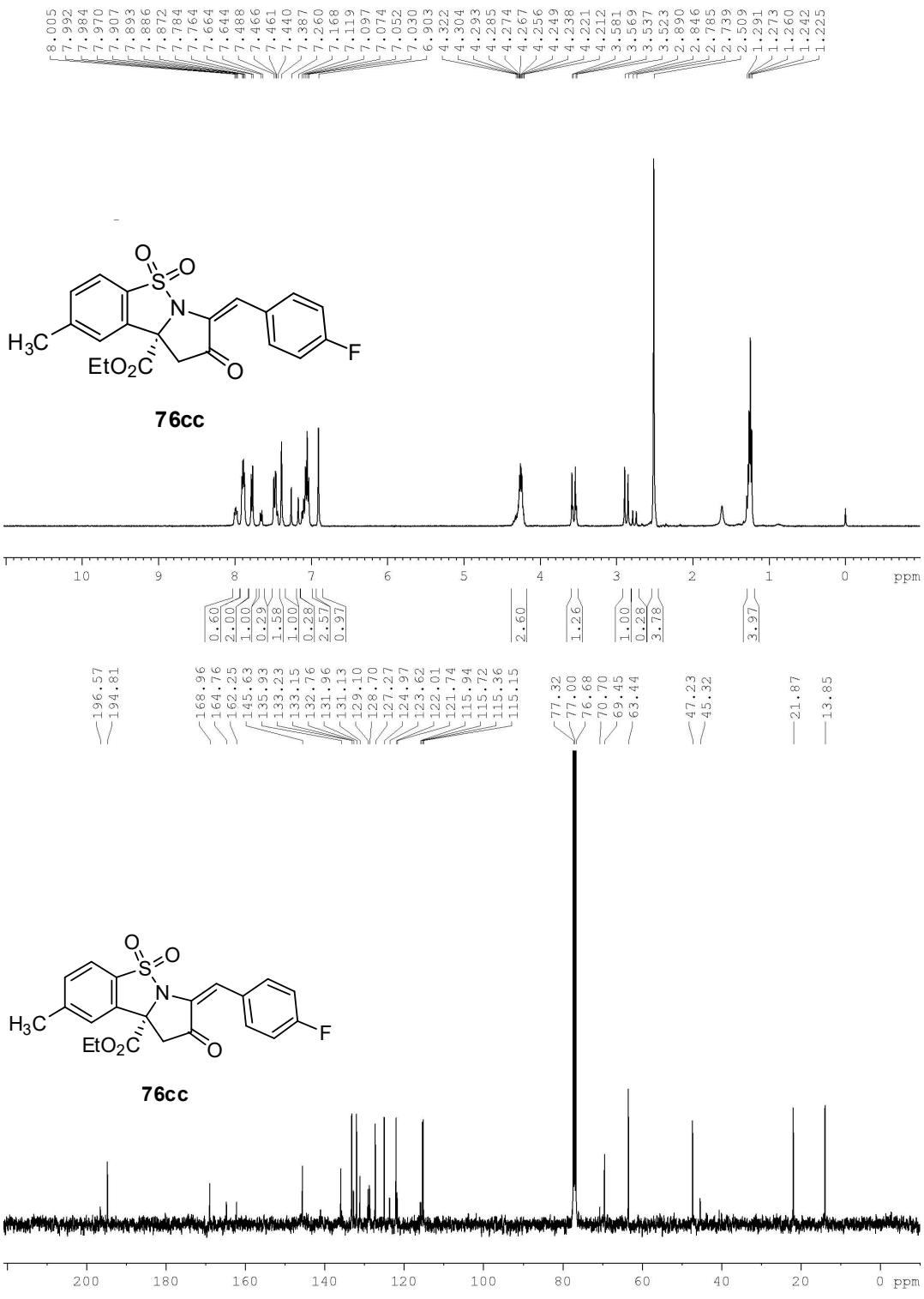


Figure-44: ^{1}H NMR and ^{13}C NMR Spectrum of Product **76cc.**

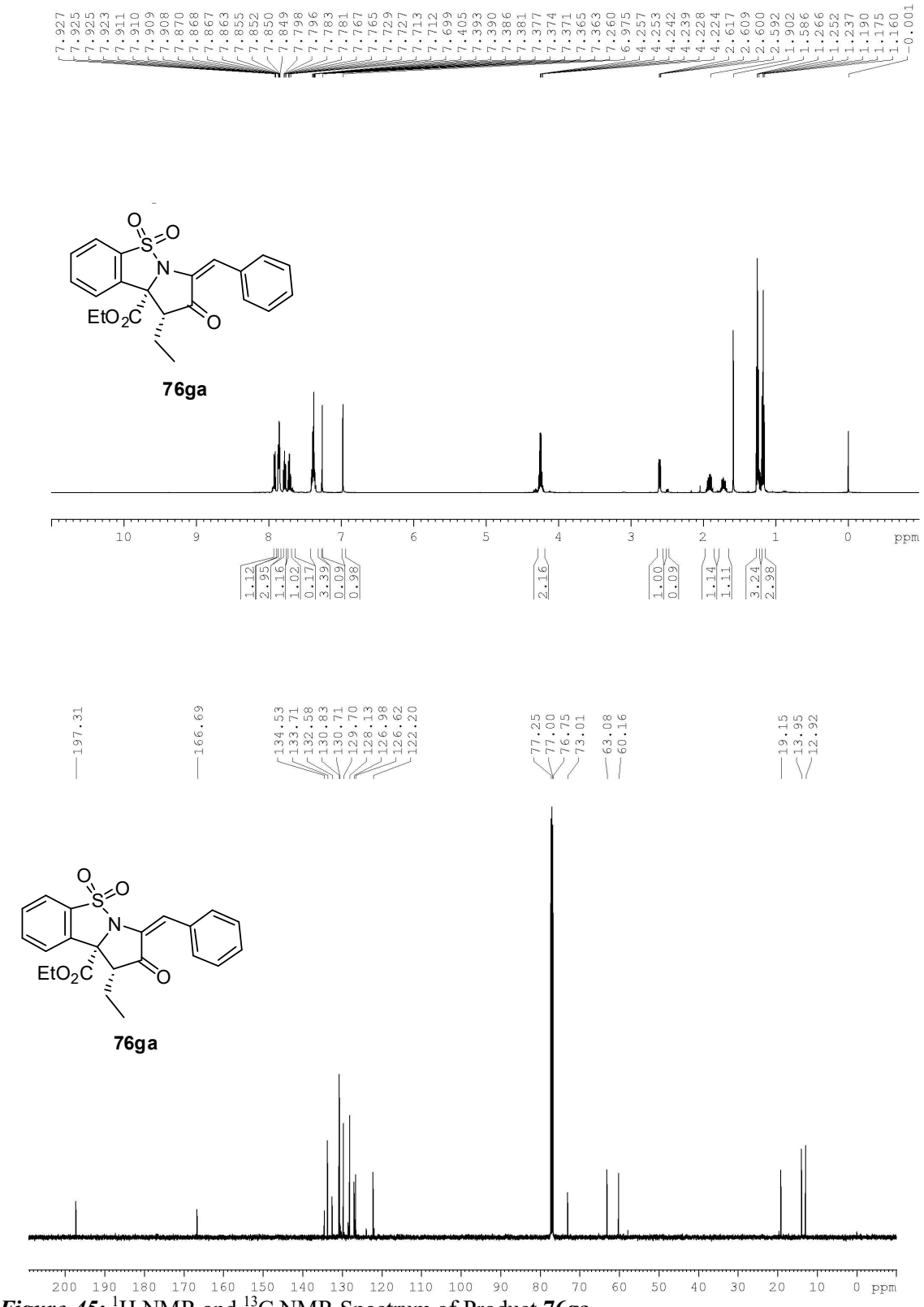
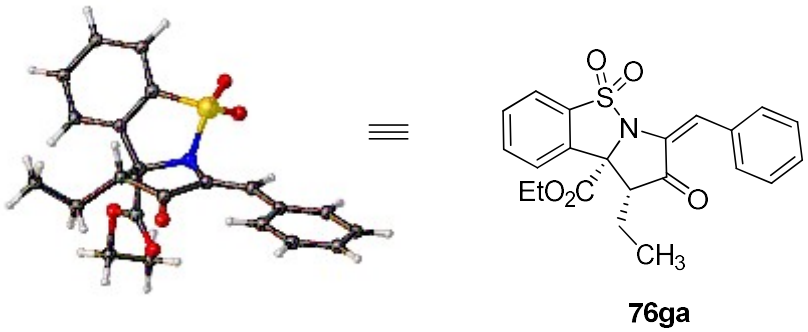


Figure-45: ^{1}H NMR and ^{13}C NMR Spectrum of Product **76ga.**

The structure and the regiochemistry of the TZC products **76** and **77** were confirmed by NMR analysis and also finally confirmed by the X-ray structure analysis on **76ga** as shown in the Figure 46.



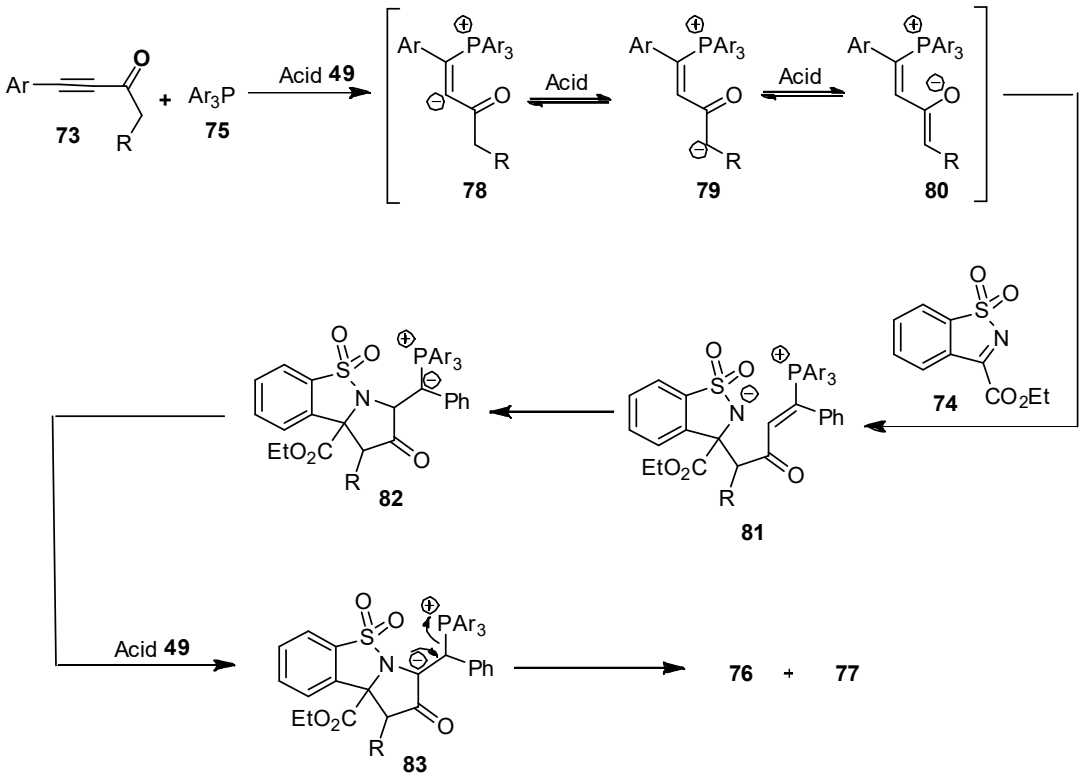
76ga

Figure 46: (1R,9bS,E)-ethyl 3-benzylidene-1-ethyl-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (**76ga**).

5.3 Mechanistic Insights

The most accelerated reaction pathway is shown in Scheme 7, which was confirmed based on the controlled ^{31}P NMR analysis and HRMS experiments between ynone **73a** and triphenyl phosphine **75a**.[54] Based on these experiments, a zwitterionic intermediate **78** is obtained by the conjugated addition of triarylphoshine catalyst **75** to the ynones **73**, which further undergoes intramolecular proton migration from α-position of the carbonyl group to produce the intermediate **79**. This *in situ* generated catalytic intermediate **79** is in equilibrium with catalytic (*Z*)-4-(triarylphosphonio)buta-1,3-dien-2-olates **80**. The reaction follows a stepwise manner, the nucleophilic enolate intermediate attacks the ketimine to produce nitrogen anion species **81**, which further undergoes an intramolecular cyclization to furnish the phosphorane **82**. Finally, proton transfer generates the intermediate **83**, followed by elimination of Ph_3P to afford the desired product **76** and **77** (Scheme 7).

Scheme 7. Reaction Mechanism:



5.4 Conclusion

In summary, building on a commanding but largely unexploited mode of catalytic *(Z)-4-(triarylphosphonio)buta-1,3-dien-2-olates* reactivity discovered by Tomita, we have developed an efficient synthesis of benzosultams by utilizing Tomita zipper cyclization method between highly reactive *N*-sulfonyl *α*-ketiminoesters and unmodified ynones in the presence triphenylphosphine and co-catalyst acetic acid at room-temperature in excellent yields.

Part-B

6. Asymmetric Synthesis of Nature-inspired Bioactive Spiro-compounds through Organocatalytic Diels-Alder Reactions

6.1 Introduction

In 2002, Barbas discovered the L-proline- or L-diamine-catalysed 2-aminobuta-1,3-diene-mediated intermolecular [4+2]-cycloaddition reaction of benzylideneacetone with *β*-nitrostyrenes, which created a new realm in organic chemistry called as dienamine-catalysis.[14] After this preliminary studies, many chemists entered in this field to investigate the reaction scope by changing the catalysts along with co-catalysts and different substrates of cyclic/acyclic enones and dienophiles.[55] In this relation, in order to increase the yields, rate and selectivity of Barbas 2-aminobuta-1,3-diene-mediated [4+2]-cycloaddition reaction, 2,4-dinitrobenzenesulfonic acid,[56] 4-$CF_3C_6H_4CO_2H$,[57] *o*-$FC_6H_4CO_2H$,[17] 4-BrC_6H_4OH[17c] and simple Brønsted acids like AcOH/BzOH[58] were used as co-catalysts along with L-amino acids,[14,55] (*S*)-(−)-5-(2-pyrrolidinyl)-1*H*-tetrazole,[59] (*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine,[60](*S*)-2-((pyrrolidin-2-ylmethyl)thio)pyridine,[61] (*S*)-N^1-cyclohexyl-3,3-dimethylbutane-1,2-diamine[62] or quinine/quinidine based primary amines[63] as catalysts. Even though various combination of catalysts/co-catalysts were studied to achieve both rate and selectivity for Barbas [4+2]-cycloaddition reaction, the quest for best catalytic conditions for the asymmetric version of three-component Diels-Alder (ATCDA) reaction of benzylideneacetones and arylaldehydes with 1,3-indandione was fruitless so far (Scheme 8).

In 2003-2004, Barbas *et al*. developed the L-amino acid or amine-catalyzed 2-aminobuta-1,3-diene-mediated three-component Diels-Alder reaction of benzylideneacetones and arylaldehydes with 1,3-indandione to furnish the functionalized spiro[cyclohexane-1,2'-indan]-1',3',4-triones in good yields and high *dr*'s but with poor enantioselectivity (Scheme 8). [14e, f]

Later Roberti *et al*. used this non-enantioselective Barbas [4+2]-cycloaddition protocol along with Suzuki reaction to synthesize highly functionalized single isomer of *cis*-(±)-spiro[cyclohexane-1,2'-indan]-1',3',4-triones to study their anti-cancer properties.[64] Interestingly, many of this functionalized racemic *cis*-spirocyclic ketones **A-C** showed well-defined activity on apoptosis and differentiation, making them potential leads for development as new anticancer agents and chemical probes to study signaling networks in neoplastic cells (Figure 47).

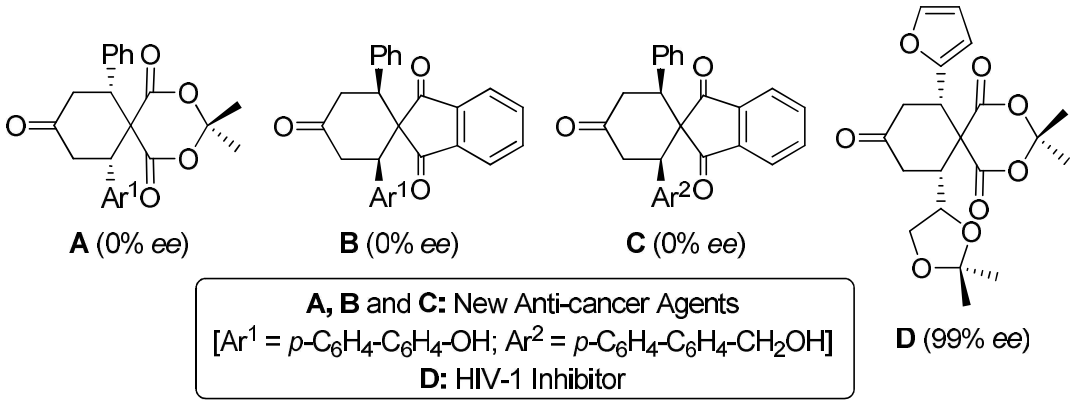
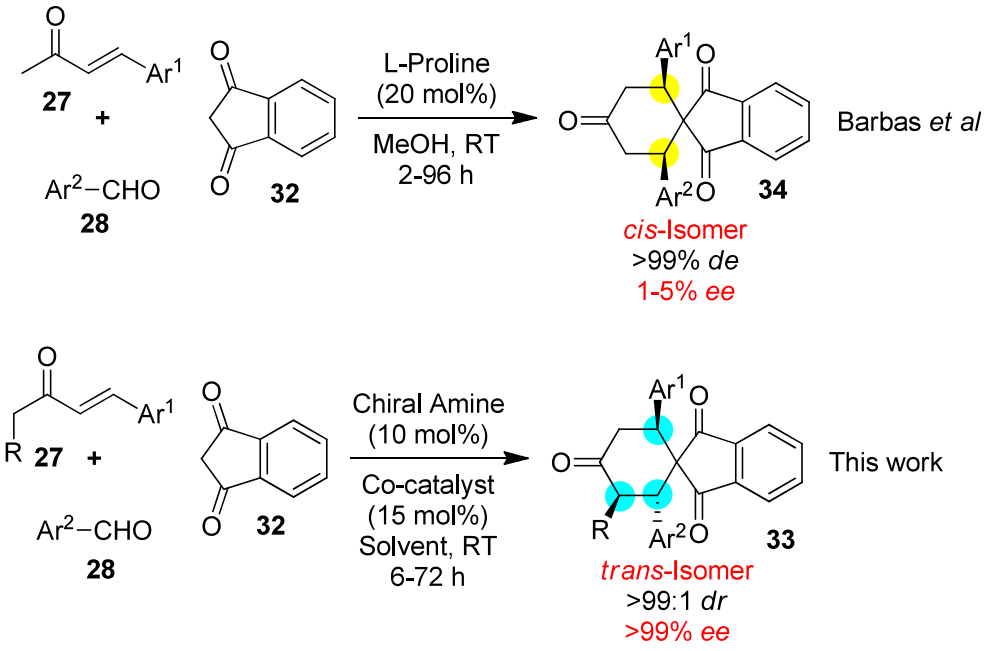


Figure-47: Potential applications of spirocyclic ketones.

These preliminary pharmaceutical studies on racemic *cis*-(±)-spirocyclic ketones **A-C** inspired us to develop a common catalytic asymmetric protocol to synthesize both the isomers of optically pure spirocyclic ketones, so that the process of finding novel anti-cancer drug discovery will advance.

In continuation of our recent interest in the development of novel organocatalytic cascade protocols for the drugs and drug-like molecules synthesis (Figure 47, **D**),[19] herein we have chosen three-component differently substituted benzylideneacetones, and arylaldehydes as the substrates along with 1,3-indandione to study the enhancement in reaction rate and selectivity (*ee* and *de*) of Barbas [4+2]-cycloaddition reaction under the catalysis of chiral primary amines along with co-catalysts (Scheme 8). Our main focus in this study is to develop a common protocol for the asymmetric synthesis of both the isomers of chiral poly-functionalized spirocyclic ketones, which contain medicinally/materialistically important biphenyl groups under the simple ambient catalytic conditions.[64] For this design, we have chosen both *in situ* generated 2-arylidene-1,3-indanediones as the dienophile and 2-

aminobuta-1,3-dienes as the diene source with synergistic-catalysis of chiral primary amines and simple Brønsted acid (Scheme 8).

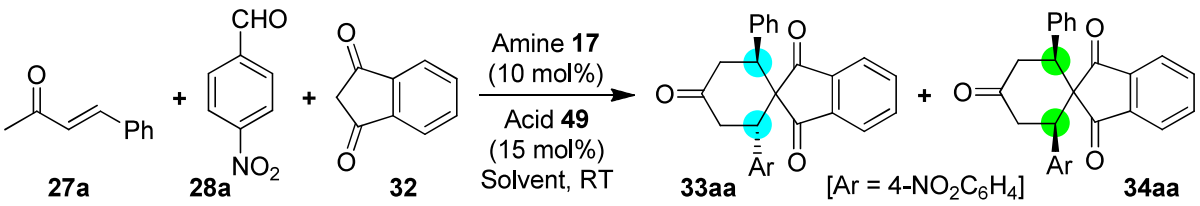


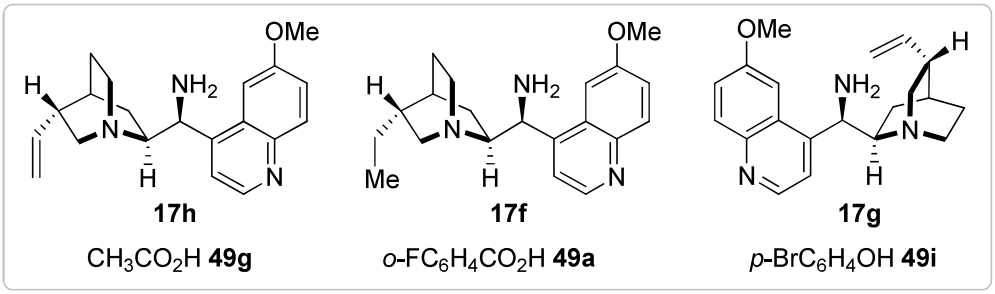
Scheme-8: Summary of previous work and the design plan of this work.

6.2 *Results and Discussion*

In the reaction optimization, directly we have chosen 9-amino-9-deoxyepiquinine **17h** (10 mol%) as the catalyst in toluene for the three-component [4+2]-cycloaddition reaction, as this catalyst **17h** proved suitable for cycloaddition reactions[63] and also for aminoenyne-catalysis.[60a] Interestingly, three-component one-pot reaction of benzylideneacetone **27a** and 4-nitrobezaldehyde **28a** with 1,3-indandione **32** at room temperature for 26 h under the catalysis of **17h** (10 mol%), furnished the spirocyclic *exo*-product *anti*-(+)-**33aa** in only 26% yield with 81% *ee* and *endo*-product *syn*-(−)-**34aa** in only 8% yield with 33% *ee* in 3:1 *dr* (Table 13, entry 1). On obtaining very low yield/*ee*/*dr*, we further investigated co-catalysts (**49g**, **49a** and **49i**) effect on the primary amine **17h**-catalyzed three-component reaction of **27a**, **28a** and **32** in toluene, $CHCl_3$ and CH_3CN at room temperature for 7-24 h (Table 13, entries 2-8). Among the tested co-catalysts in three different solvents, *o*-$FC_6H_4CO_2H$ **49a**[17] gave promising results for *anti*-(+)-**33aa** formation in terms of yield (86%), *ee* (98%) and *dr* (>99:1) in toluene solvent at 25 °C within 7 h (Table 13, entry 3). But, surprisingly the same

Table-13: Reaction optimization[a]





Entry	Catalyst **17/49**	Solvent (0.25 M)	Time [h]	Yields [%][b] **33aa**	**34aa**	*dr*[c] [anti:syn]	*ee* [%][d] **33aa**	**34aa**
1	**17h**	$C_6H_5CH_3$	26	26	8	3:1	81	33
2	**17h/49g**	$C_6H_5CH_3$	24	41	12	3.4:1	92	58
3	**17h/49a**	$C_6H_5CH_3$	7	86	-	>99:1	98	-
4	**17h/49a**	$C_6H_5CH_3$	24	73	8	9:1	99	83
5	**17h/49a**	$CHCl_3$	19	63	-	>99:1	97	-
6	**17h/49a**	CH_3CN	19	25	-	>99:1	93	-
7	**17h/49i**	$C_6H_5CH_3$	21	40	25	1.6:1	90	34
8	**17h/49i**	$CHCl_3$	21	10	9	1:1	87	21
9[e]	**17f/49a**	$C_6H_5CH_3$	6	78	-	>99:1	98	-
10	**17f/49a**	$C_6H_5CH_3$	8	78	-	>99:1	99	-
11[f]	**17f/49i**	$C_6H_5CH_3$	6	26	26	1:1	89	25
12	**17g/49a**	$C_6H_5CH_3$	6	85	-	>99:1	-98	-

[a] Reactions were carried out in solvent (0.3 M) with 2 equiv. of **27a** relative to **28a** (0.3 mmol) and **32** (0.3 mmol) in the presence of 10/15 mol% of catalysts **17/49**. [b] Yield refers to the coloumn-purified product. [c] *dr* determined by crude ^{1}H NMR analysis and also based on coloumn purified compounds. [d] *ee* determined by CSP-HPLC analysis. [e] Reaction performed under the catalysis of **17f/49a** (20/30 mol%). [f] Reaction performed under the catalysis of **17f/49i** (20/20 mol%).

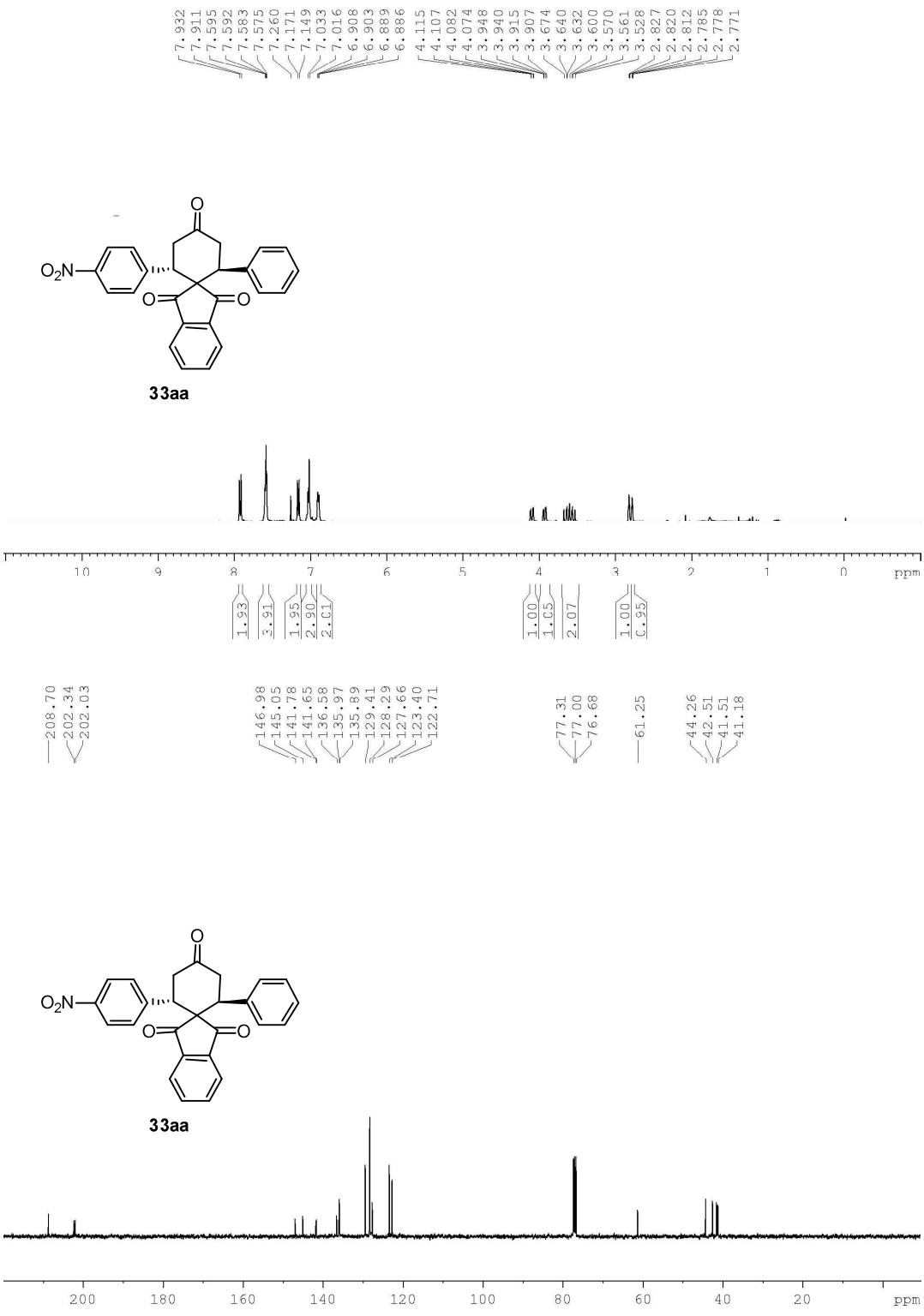


Figure-48: ^{1}H and ^{13}C NMR spectra of the product **33aa**.

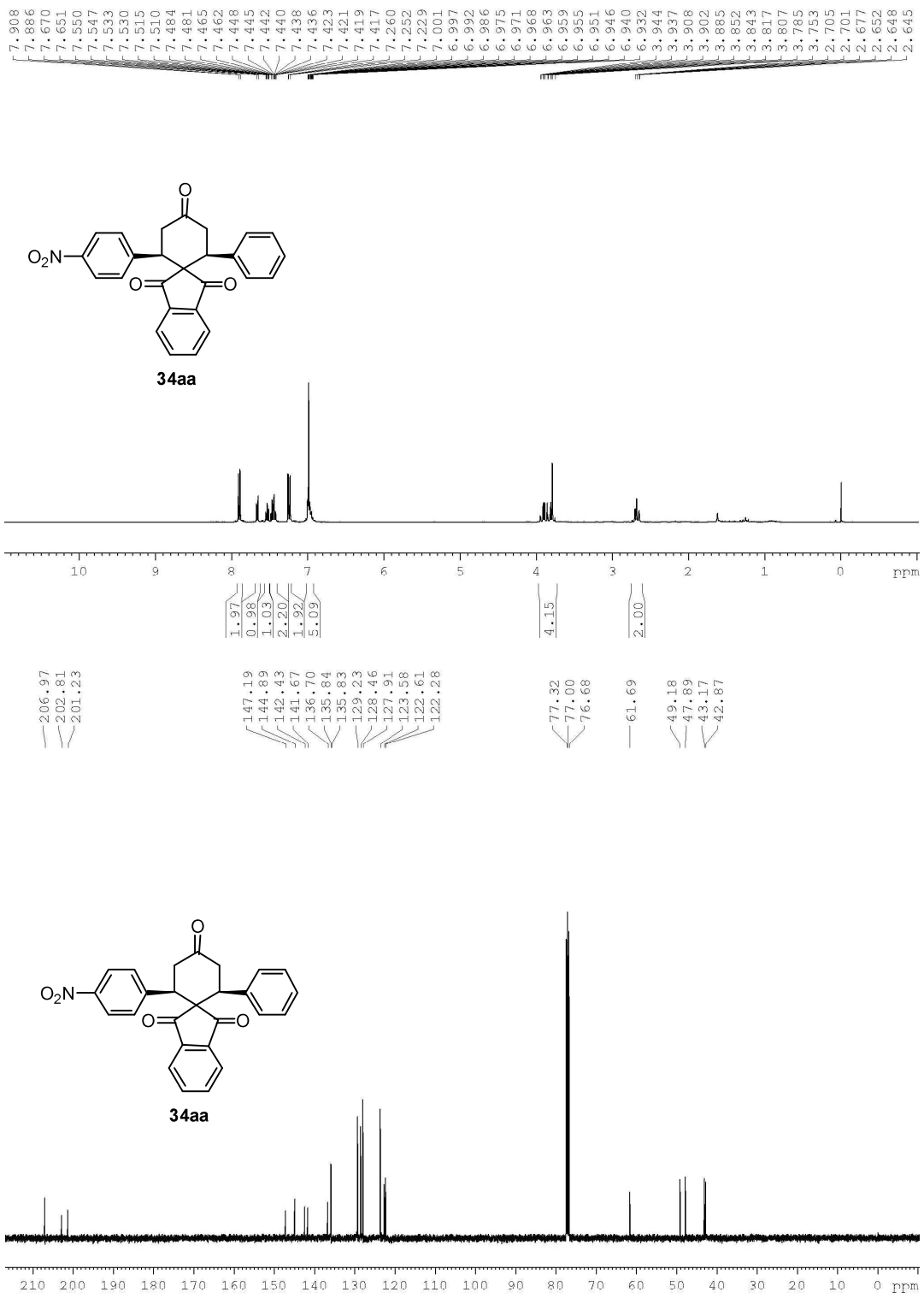
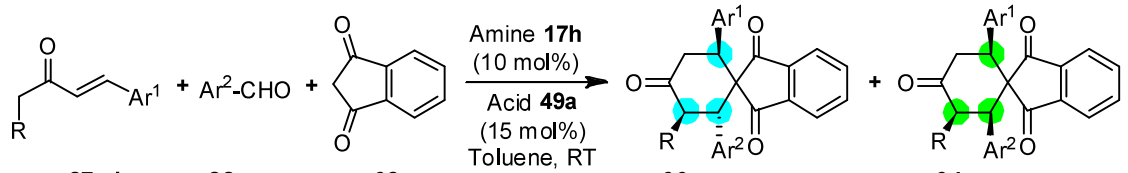


Figure-49: ^{1}H and ^{13}C NMR spectra of the product **34aa**.

reaction at 25 °C for prolonged reaction time (24 h) furnished *anti*-(+)-**33aa** in reduced yield (73%) with 99% *ee* along with *syn*-(−)-**34aa** in 8% yield with 83% *ee* in 9:1 *dr* (Table 13, entry 4). This result clearly suggests that primary amine **17h/49a** is able to catalyze the epimerization of kinetic *exo*-product *anti*-(+)-**33aa** to thermodynamically stable *endo*-product *syn*-(−)-**34aa** in moderate yield with decreased selectivity. More information regarding epimerization of kinetic products **33** will be discussed in the next section. After realizing the importance of the role played by *o*-$FC_6H_4CO_2H$ **49a** along with **17h** in boosting the rate/yield/*ee*/*dr*, we were curious to know how well it works when used along with 9-amino-9-deoxyepidihydroquinine **17f** and 9-amino-9-deoxyepiquinidine **17g**. Disappointingly, under the catalysis of **17f/49a** (10/15 mol% or 20/30 mol-%), we observed a noticeable drop in the yield but there is no change in *ee* and *dr* (Table 13, entries 9 and 10). In the case of **17g/49a**-catalysis, we were able to obtain the opposite enantiomer *anti*-(−)-**33aa** in 85% yield with 98% *ee* and >99:1 *dr* (Table 13, entry 12). Shockingly, the same reaction under the catalysis of **17f/49i** furnished the spirocyclic ketones *anti*-(+)-**33aa** in 26% yield with 89% *ee* and *syn*-(−)-**34aa** in 26% yield with 25% *ee* in 1:1 *dr* (Table 13, entry 11). Finally the best optimised reaction conditions were found to be the combination of catalysts **17h** (10 mol%) and **49a** (15 mol-%) in toluene at room temperature. The acidity of *o*-$FC_6H_4CO_2H$ **49a**, structure of the primary amine **17h**, solvent nature and many other weak interactions between the substrates and the catalysts seem to be playing essential role in controlling the rate and selectivity, which will be discussed elaborately in mechanistic section.

We further focused our attention to study the scope of the asymmetric three-component Diels-Alder (ATCDA) reaction utilizing various functionalised benzylideneacetones **27a-j** and arylaldehydes **28a-o** with 1,3-indandione **32**. Initially, the ATCDA reaction was carried out on simple, 4-OMe, 4-Me, 4-Br, 3-Br, and 2-Br substituted benzaldehydes **28b-28g** with benzylideneacetone **27a** and **32** using the best optimised catalyst **17h/49a** system to furnish the spirocyclic products *anti*-(−)-**33ab** to *anti*-(+)-**33ag** in very good yields with good *dr* and excellent *ee* (Table 14, entries 1-6). 2-Bromobenzaldehyde **28g** gave the spirocyclic product *anti*-(+)-**33ag** in 85% yield and >99:1 *dr* but with less *ee* (78%), may be due to the neighboring 2-bromo group participation (Table 14, entry 6). Benzaldehyde possessing an

Table 14: Reaction scope[a]



27a-j **28a-o** **32** **33** (major) **34** (minor)

Entry	Enone **27**	Ar^2-CHO **28**	*t* [h]	Yield **33** [%][b]	*dr*[c] [anti:syn]	*ee* [%][d]
1	**27a**: R = H, Ar^1 = C_6H_5	**28b**: Ar^2 = C_6H_5	5	78 (**33ab**)	22:1	96
2	**27a**	**28c**: Ar^2 = 4-$OMeC_6H_4$	6	80 (**33ac**)	9:1	98
3	**27a**	**28d**: Ar^2 = 4-$CH_3C_6H_4$	11	93 (**33ad**)	11:1	99
4	**27a**	**28e**: Ar^2 = 4-BrC_6H_4	2	88 (**33ae**)	5:1	97
5	**27a**	**28f**: Ar^2 = 3-BrC_6H_4	5	95 (**33af**)	7:1	97
6	**27a**	**28g**: Ar^2 = 2-BrC_6H_4	5	85 (**33ag**)	>99:1	78
7	**27a**	**28h**: Ar^2 = 4-$CF_3C_6H_4$	5	85 (**33ah**)	9:1	98
8	**27a**	**28i**: Ar^2 = 4-$CO_2MeC_6H_4$	5	86 (**33ai**)	7:1	97
9	**27a**	**28j**: Ar^2 = 4-CNC_6H_4	3	82 (**33aj**)	>99:1	99
10	**27a**	**28k**: Ar^2 = 3-CNC_6H_4	6	86 (**33ak**)	7:1	97
11	**27a**	**28l**: Ar^2 = 3-$NO_2C_6H_4$	12	81 (**33al**)	15:1	95
12	**27b**: R = H, Ar^1 = 2-Naphthyl	**28e**: Ar^2 = 4-BrC_6H_4	3	92 (**33be**)	>99:1	98
13	**27c**: R = H, Ar^1 = 4-$NO_2C_6H_4$	**28e**: Ar^2 = 4-BrC_6H_4	6	73 (**33ce**)	>99:1	99
14	**27c**: R = H, Ar^1 = 4-$NO_2C_6H_4$	**28j**: Ar^2 = 4-CNC_6H_4	6	60 (**33cj**)	10:1	97
15	**27d**: R = H, Ar^1 = 4-$OMeC_6H_4$	**28a**: Ar^2 = 4-$NO_2C_6H_4$	3	76 (**33da**)	37:1	99
16	**27e**: R = H, Ar^1 = 2,6-$Cl_2C_6H_3$	**28a**: Ar^2 = 4-$NO_2C_6H_4$	9	58 (**33ea**)	7:1	>99
17	**27f**: R = H, Ar^1 = 4-BrC_6H_4	**28b**: Ar^2 = C_6H_5	7	84 (**33fb**)	7:1	96
18	**27g**: R = H, Ar^1 = 2-Thiophenyl	**28a**: Ar^2 = 4-$NO_2C_6H_4$	12	82 (**33ga**)	15:1	99
19	**27h**: R = H, Ar^1 = (*E*)-PhCH=CH	**28a**: Ar^2 = 4-$NO_2C_6H_4$	6	35 (**33ha**)	99:1	96
20	**27i**: R = CH_3, Ar^1 = C_6H_5	**28a**: Ar^2 = 4-$NO_2C_6H_4$	12	73 (**33ia**)	3:1	95 (98)[e]
21	**27j**: R = C_2H_5, Ar^1 = C_6H_5	**28a**: Ar^2 = 4-$NO_2C_6H_4$	12	78 (**33ja**)	25:1	99
22[f]	**27a**	**28m**: Ar^2 = 4-$CHOC_6H_4$	6	9 (**33am**) 46 (**33'am**)	99:1 99:1	94 94
23	**27a**	**28n**: Ar^2 = 4-$OHC_6H_4C_6H_4$	72	65 (**33an**)	8:1	98
24	**27a**	**28o**: Ar^2 = 4-$OHCH_2C_6H_4C_6H_4$	72	73 (**33ao**)	5:1	99

[a] Reactions were carried out in toluene (0.3 M) with 2 equiv. of **27** relative to **28** (0.3 mmol) and **32** (0.3 mmol) in the presence of 10/15 mol% of catalyst **17h/49a**. [b] Yield refers to the column-purified products of both the isomers. [c] *dr* determined by coloumn purified products. [d] *ee* determined by CSP-HPLC analysis of major *trans*-isomer. [e] *ee* values in parentheses obtained for minor *cis*-isomer. [f] Compound **33'am** represents the dimer.

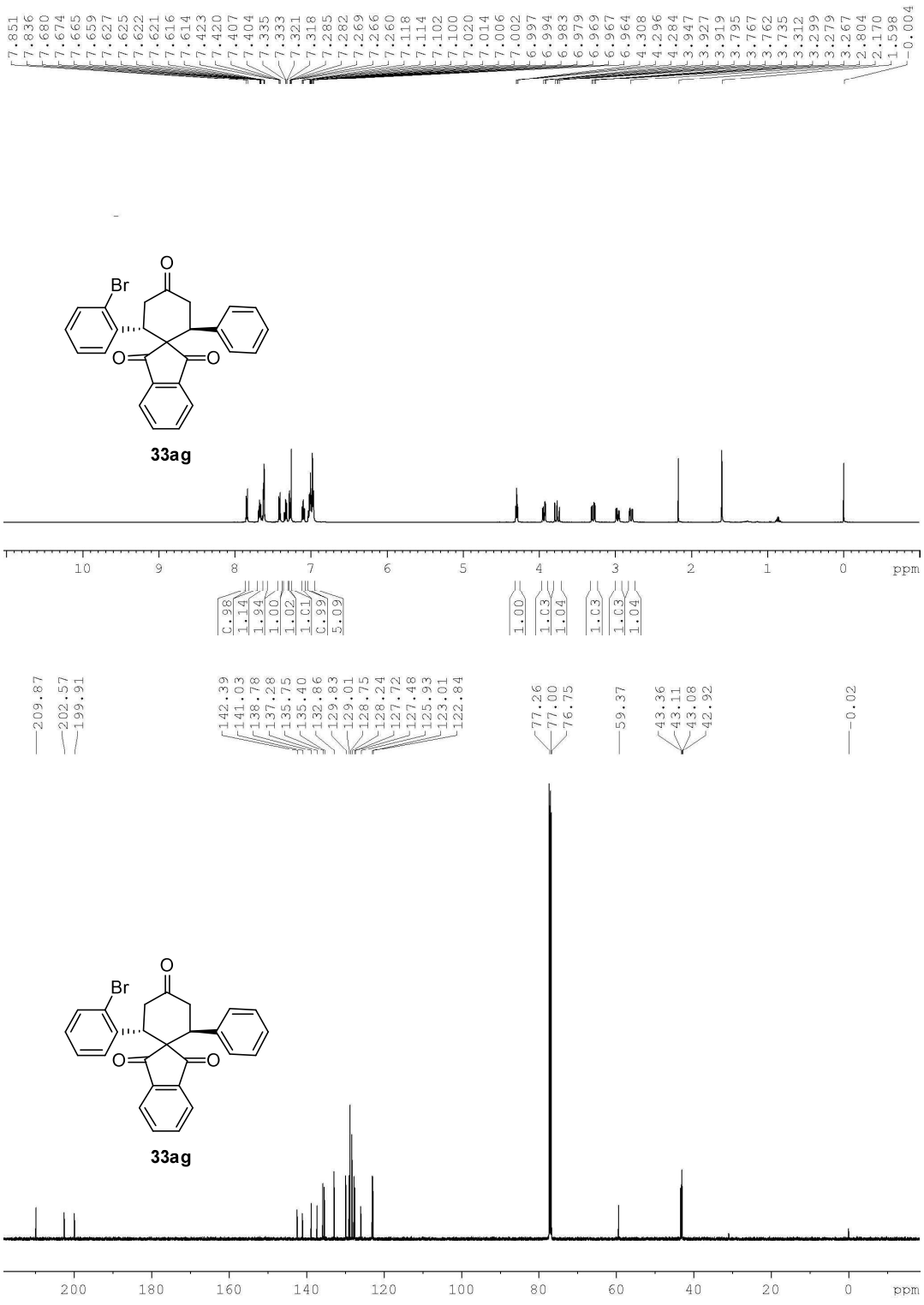


Figure-50: ^{1}H and ^{13}C NMR spectra of the product **33ag**.

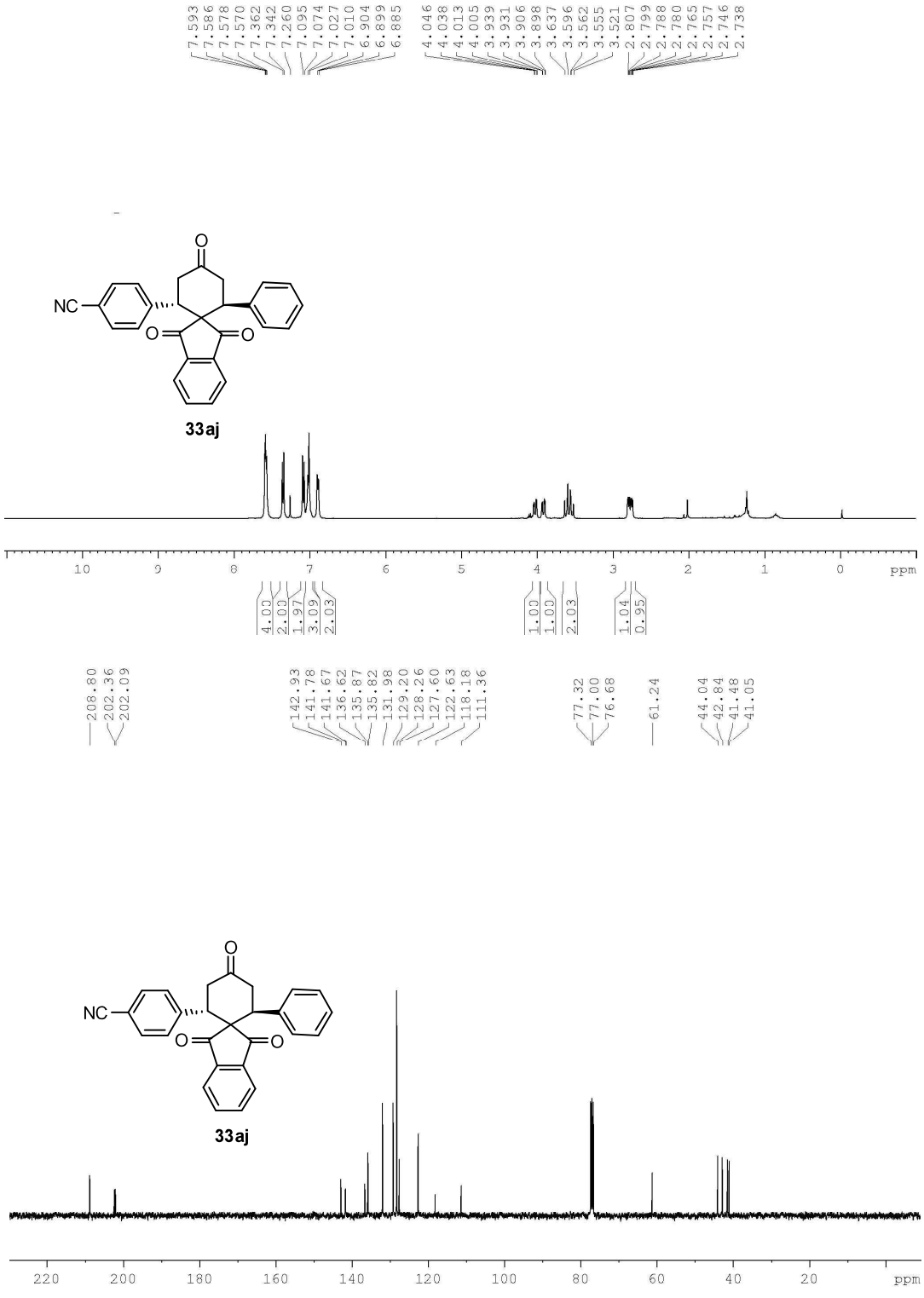


Figure-51: ^{1}H and ^{13}C NMR spectra of the product **33aj**.

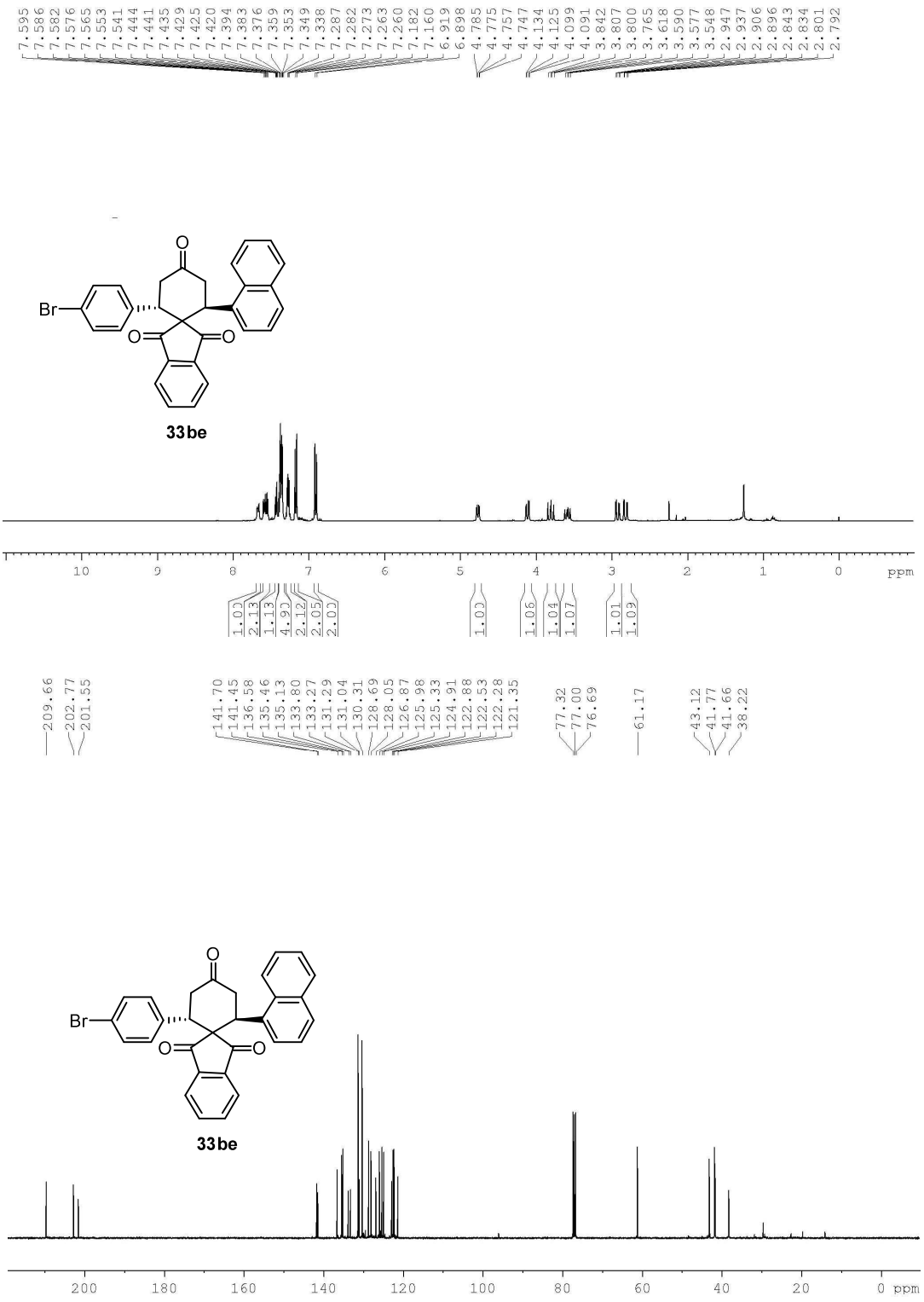


Figure-52: ^{1}H and ^{13}C NMR spectra of the product **33be**.

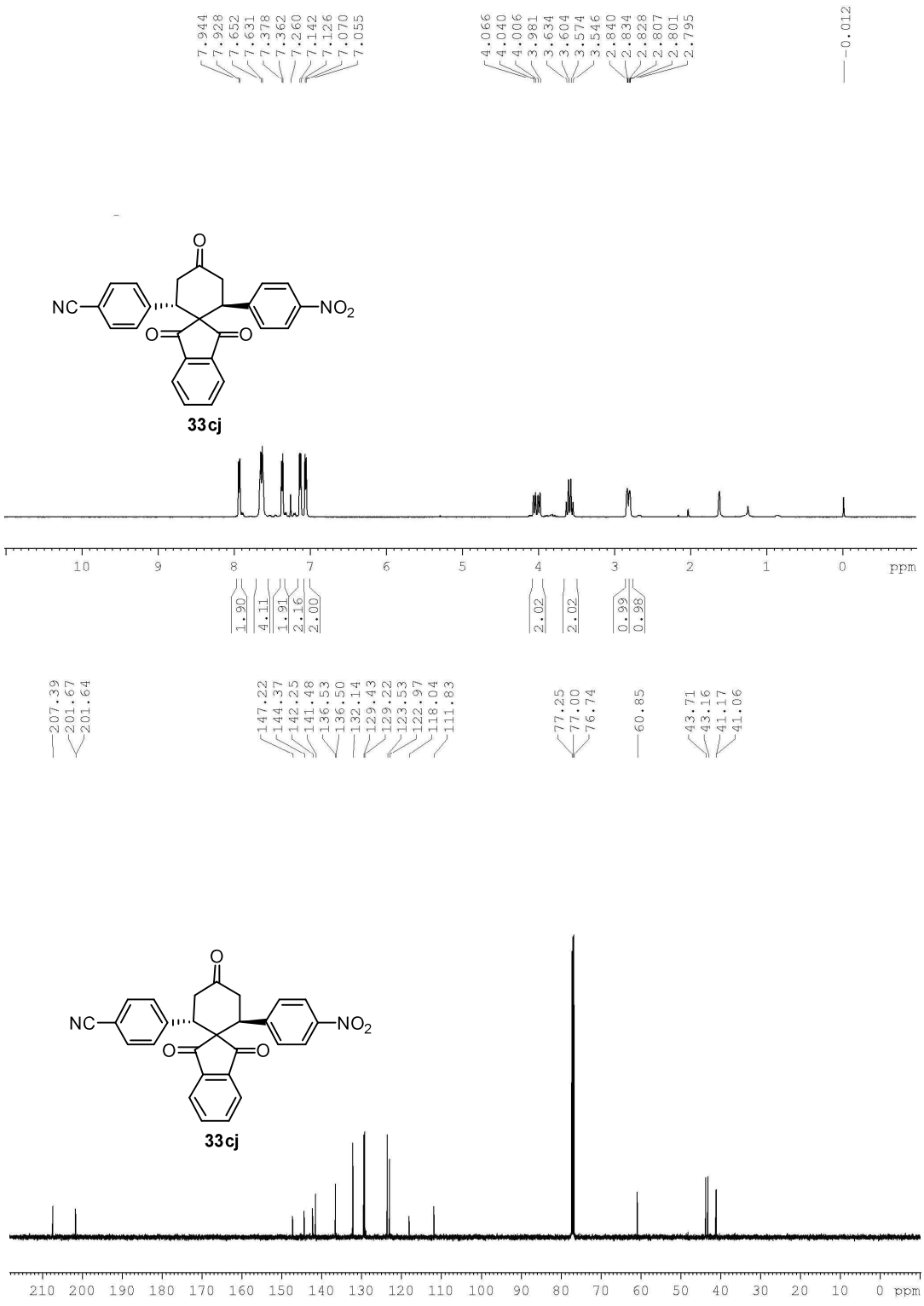


Figure-53: ^{1}H and ^{13}C NMR spectra of the product **33cj**.

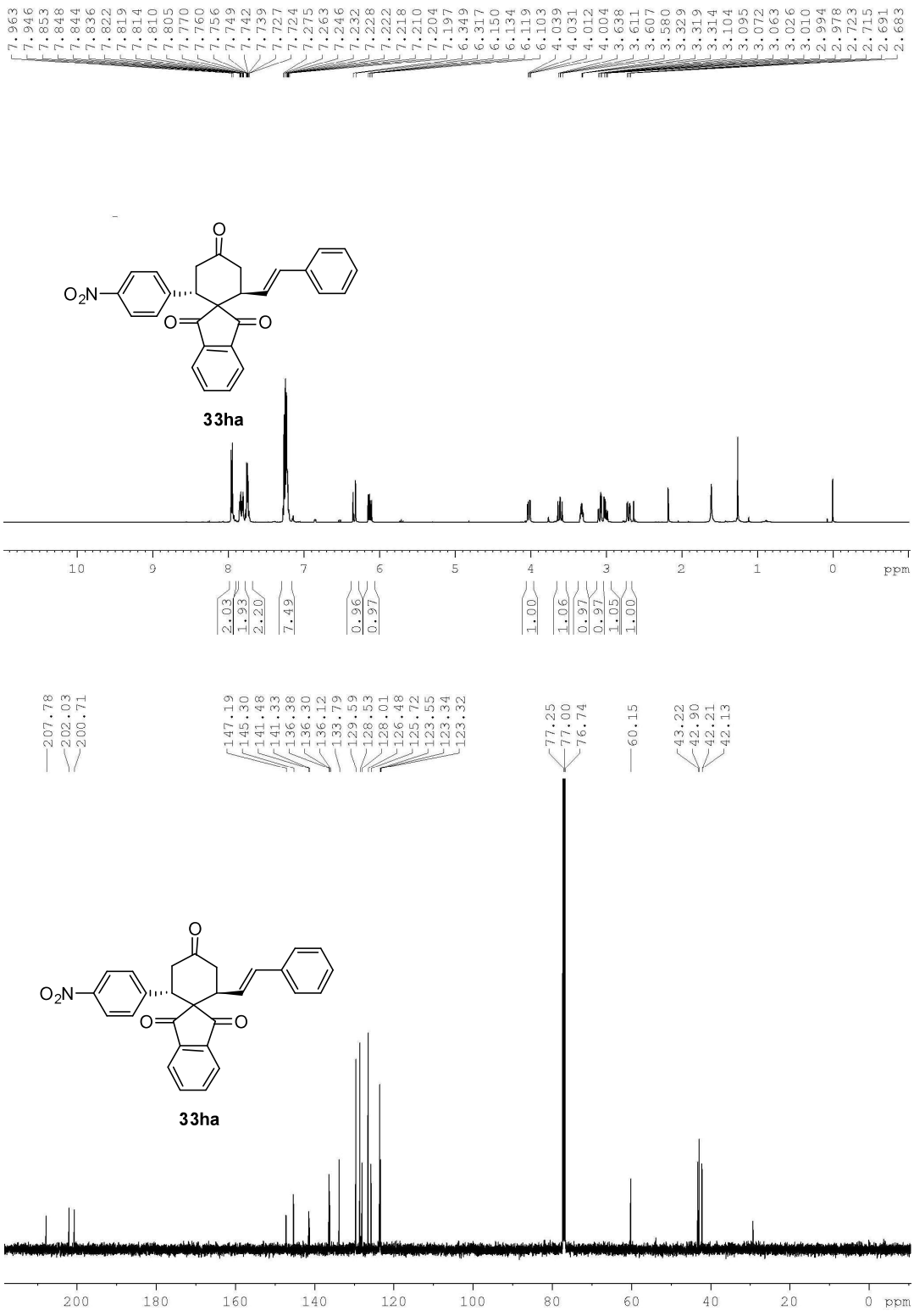


Figure-54: ^{1}H and ^{13}C NMR spectra of the product **33ha**.

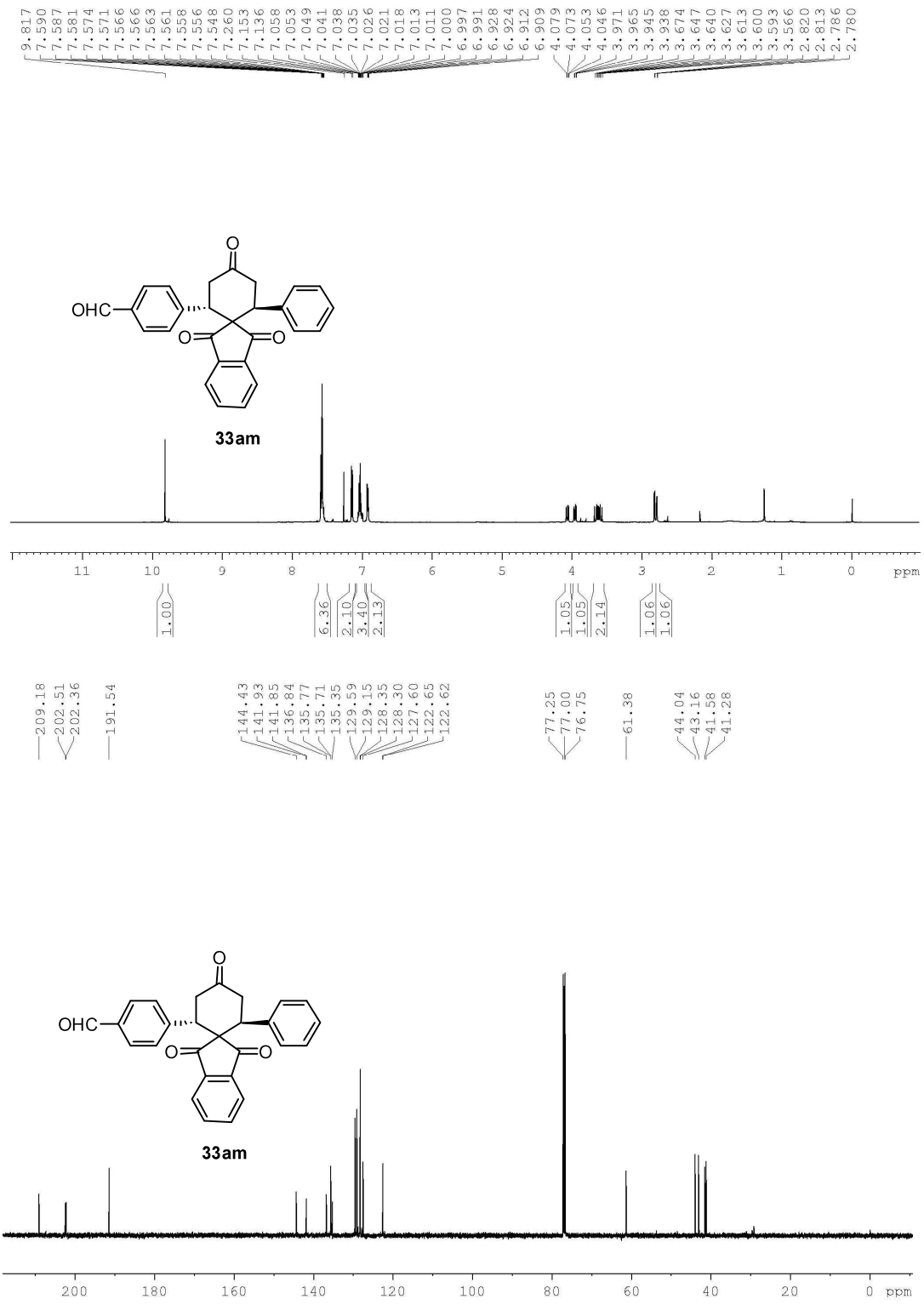


Figure-55: ^{1}H and ^{13}C NMR spectra of the product **33am**.

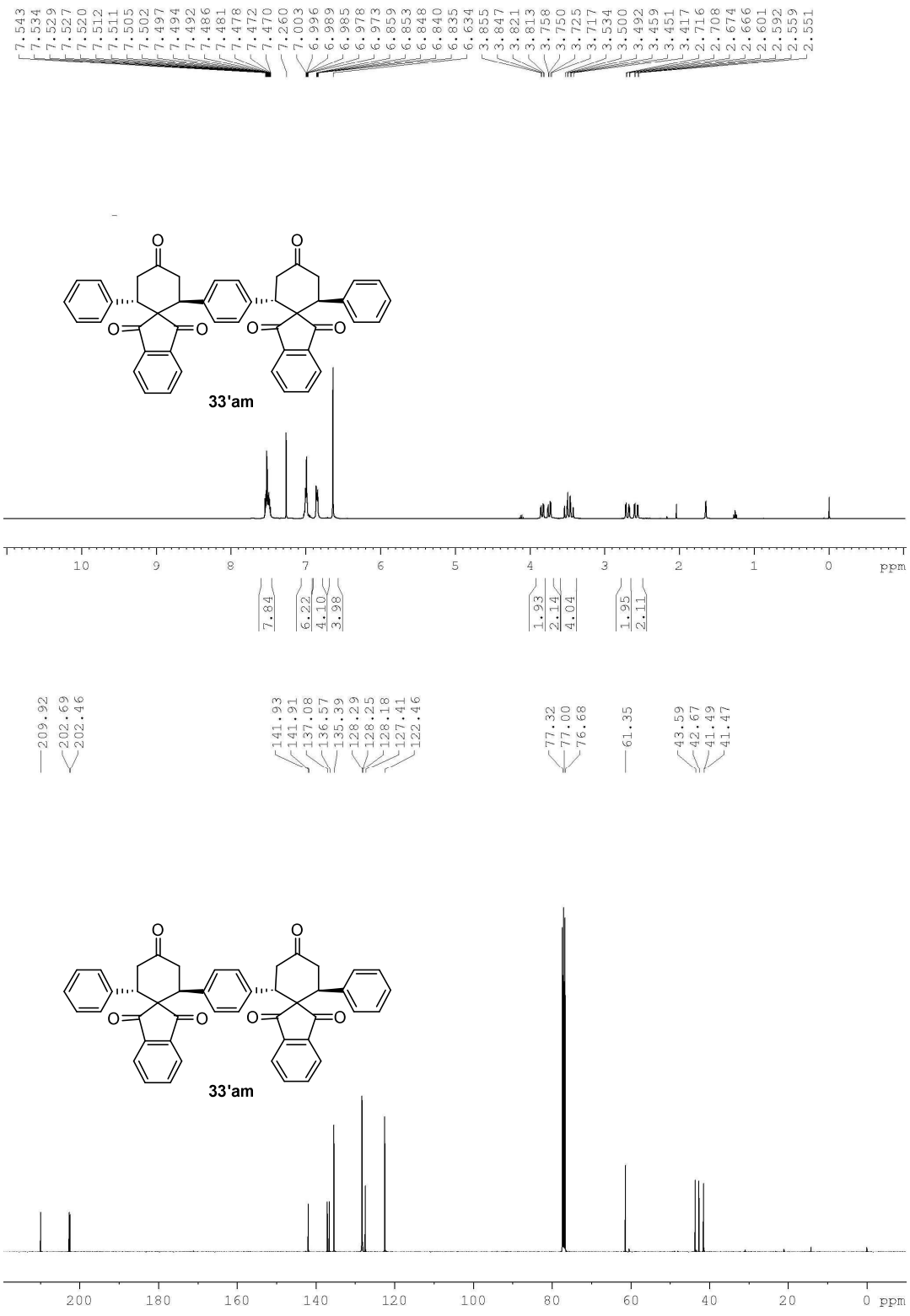


Figure-56: ^{1}H and ^{13}C NMR spectra of the product **33'am**.

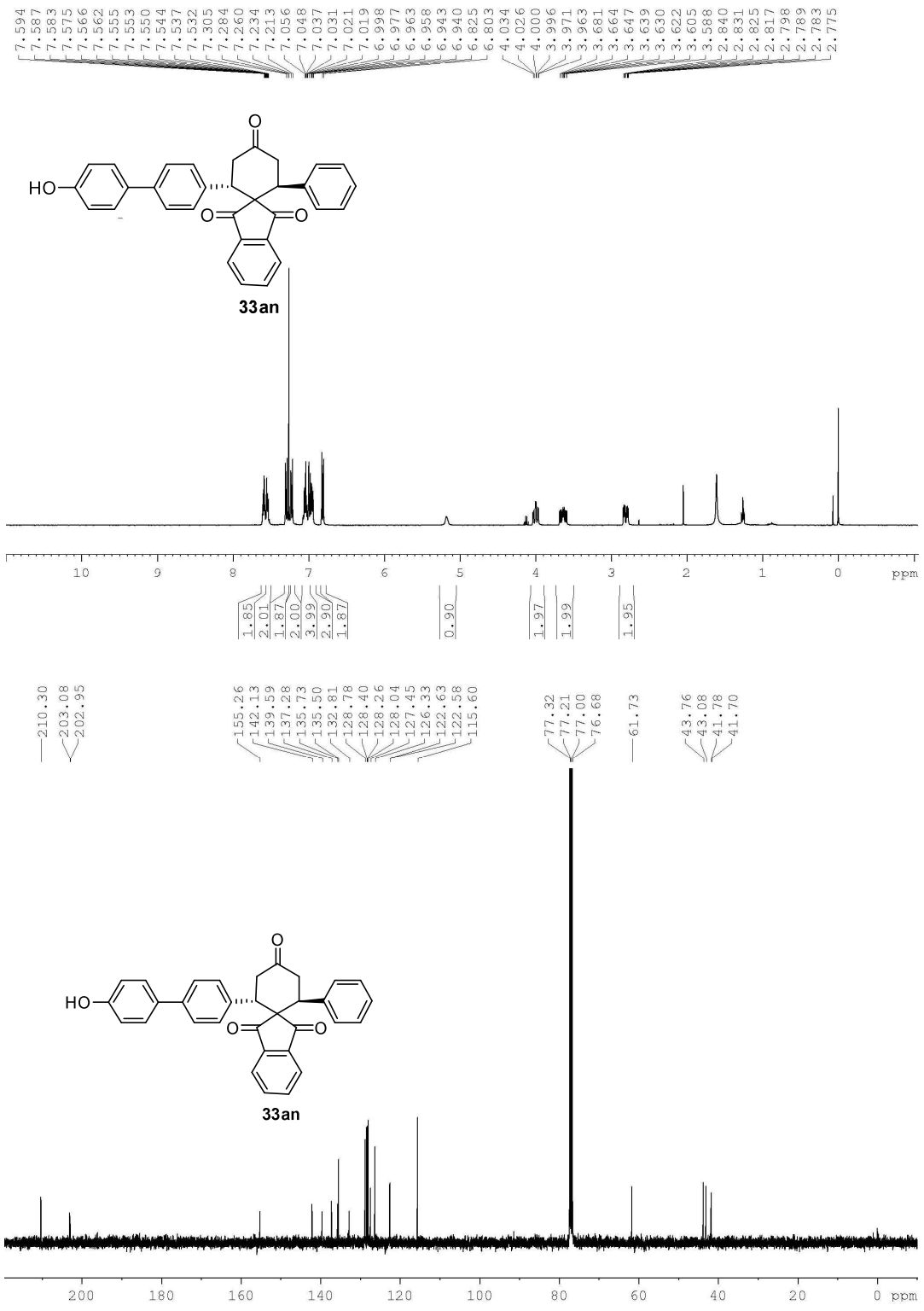


Figure-57: ^{1}H and ^{13}C NMR spectra of the product **33an**.

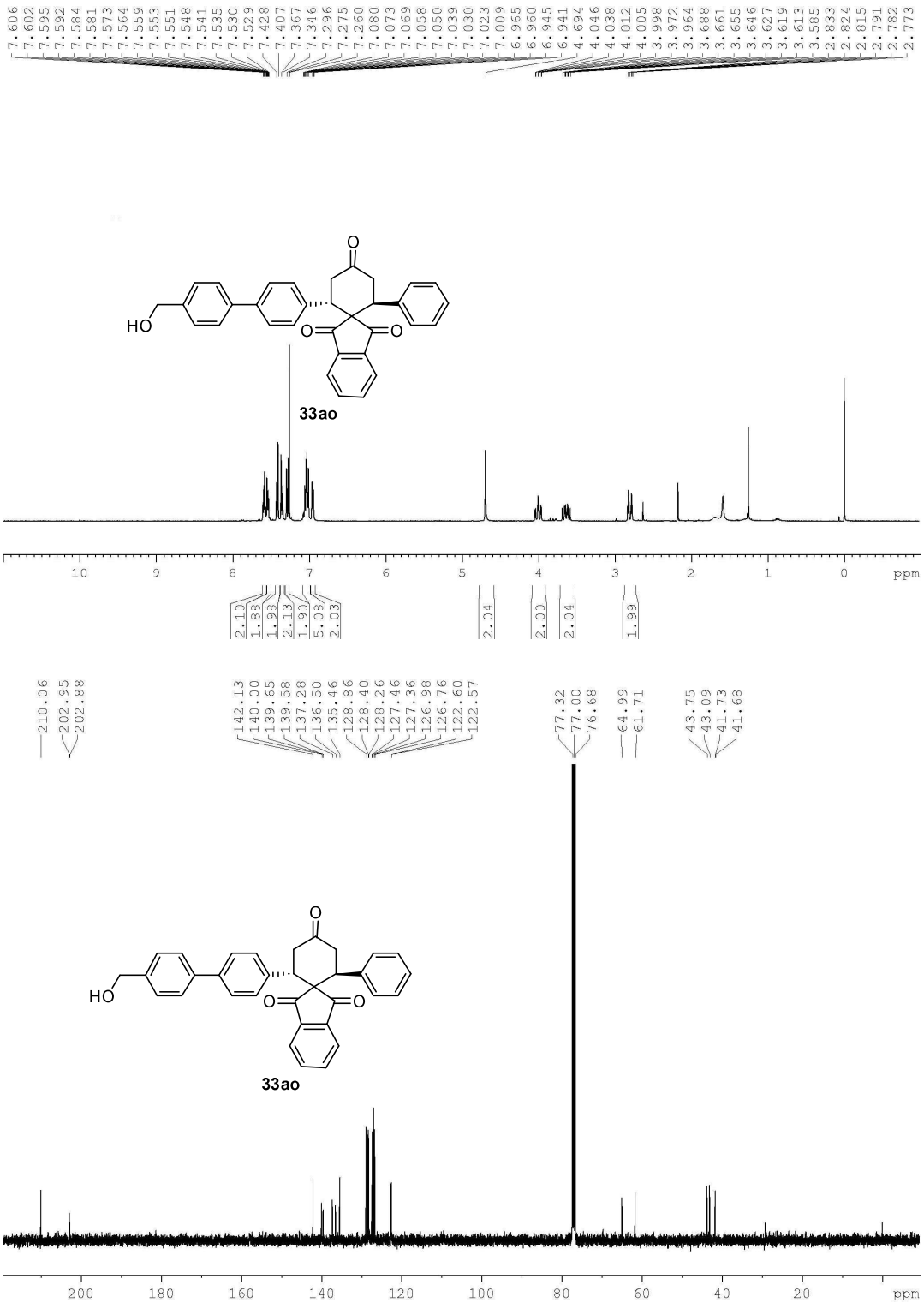
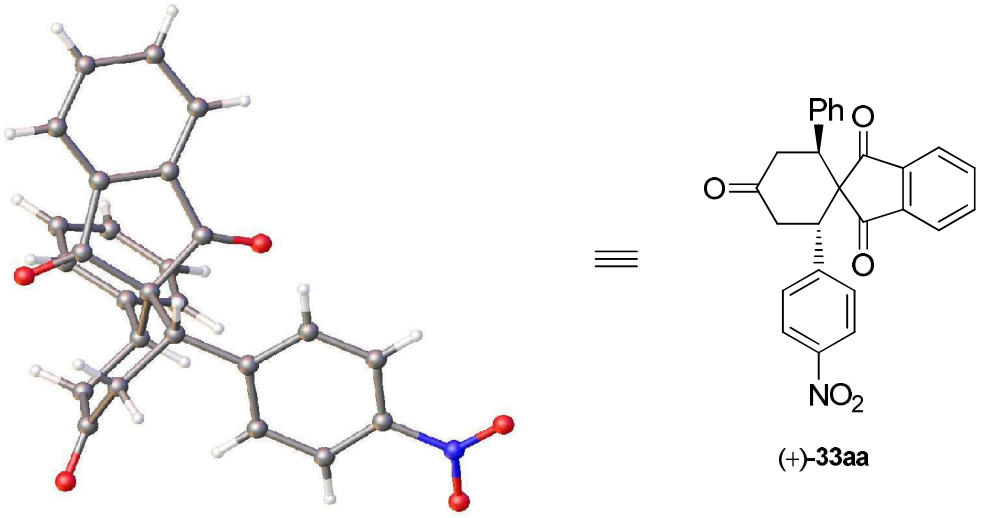


Figure-58: ^{1}H and ^{13}C NMR spectra of the product **33ao**.

electron withdrawing group such as 4-CF_3, 4-CO_2Me, 4-CN, 3-CN, and 3-NO_2 **28h** to **28l** also underwent the ATCDA reaction with **27a** and **32** to provide the spirocyclic products *anti*-(−)-**33ah** to *anti*-(−)-**33al** in very good yields with good *dr* and excellent *ee* (Table 14, entries 7-11).

After studying the scope of the ATCDA reaction of **27a** and **32** with various functionalised benzaldehydes **28a-l**, we extended our studies further in order to investigate the generality of the ATCDA reaction on various arylideneacetones **27b-j** (Table 14, entries 12-21). The arylideneacetones containing neutral, electron-withdrawing, electron-donating, halogenated, hetero-atom substituted, olefin conjugated and alkyl substituted **27b-27j** on subjecting to the ATCDA reaction with medicinally important functional group (4-H, 4-Br, 4-CN, and 4-NO_2) substituted benzaldehydes **28a-j** and **32** under the **17h/49a**-catalysis at 25 °C for 3-12 h resulted in the formation of products *anti*-(−)-**33be** to *anti*-(−)-**33ja** as major isomers in 35-92% yields with good *dr* and 95-99% *ee* (Table 14, entries 12-21). Surprisingly, the ATCDA reaction of both the electron withdrawing groups containing (*E*)-4-(4-nitrophenyl)but-3-en-2-one **27c** and 4-formylbenzonitrile **28j** with **32** under the **17h/49a**-catalysis furnished the spirocyclic product *anti*-(−)-**33cj** as the major isomer in 60% yield with 10:1 *dr* and 97% *ee* (Table 14, entry 14). Another fascinating element of surprise in this ATCDA reaction was that we observed the exclusive formation of a single isomer of enantiomer *anti*-(−)-**33ha** in moderate yield from (3*E*,5*E*)-6-phenylhexa-3,5-dien-2-one **27h** with **28a** and **32** under the given reaction conditions through the formation of the key intermediate 2-aminohexa-1,3,5-triene (Table 14, entry 19). Herein, few different alkyl substituted enones **27i-j** were also used as the source for the *in situ* generation of 2-aminobuta-1,3-dienes in the ATCDA reaction with **28a** and **32** to furnish the spirotriones *anti*-(+)-**33ia** in 73% yield with 95% *ee* and 3:1 *dr*; and *anti*-(−)-**33ja** in 78% yield with 99% *ee* and 25:1 *dr* (Table 14, entries 20-21). The ATCDA reaction of enone **27a** with terephthalaldehyde **28m** and **32** at 25 °C for 6 h furnished the spirotrione *anti*-(−)-**33am** in only 9% yield, 94% *ee* and 99:1 *dr*; which was accompanied by the functionally rich double Diels-Alder product *anti*-(−)-**33'am** in 46% yield with 94% *ee* and 99:1 *dr* as shown in Table 14, entry 22. Next, with medicinal applications in mind, we focused our attention on the synthesis of optically pure **33an** and **33ao**, which are analogous to the previously discussed anti-

cancer agents of racemic compounds **B** and **C** (Figure 47).[64] For this purpose, we needed to first synthesis the biphenyl group containing arylaldehydes **28n** and **28o** and were prepared by the conventional Suzuki coupling reaction in 71% and 68% yields respectively. The ATCDA reaction of enone **27a** with 1,3-indandione **32** and 4'-hydroxy-[1,1'-biphenyl]-4-carbaldehyde **28n** under the **17h/49a**-catalysis in toluene at 25 °C for 72 h furnished the highly substituted spirotrione *anti*-(−)-**33an** in 65% yield with 98% *ee* and 8:1 *dr* (Table 14, entry 23). In a similar manner, another important highly substituted spirotrione *anti*-(−)-**33ao** was prepared in 73% yield with 99% *ee* and 5:1 *dr* (Table 14, entry 24). Even though in both of these cases, the products *anti*-(−)-**33an** and *anti*-(−)-**33ao** were obtained in good yield and excellent *ee*, it was disappointing with respect to reaction rate (as it has taken 72 h) and *dr*. In the near future this ATCDA protocol could help medicinal chemists to design new drugs. The structure, regioselectivity and absolute stereochemistry of the ATCDA products **33** and **34** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on *anti*-(+)-**33aa** as shown in Figure-59.[66]

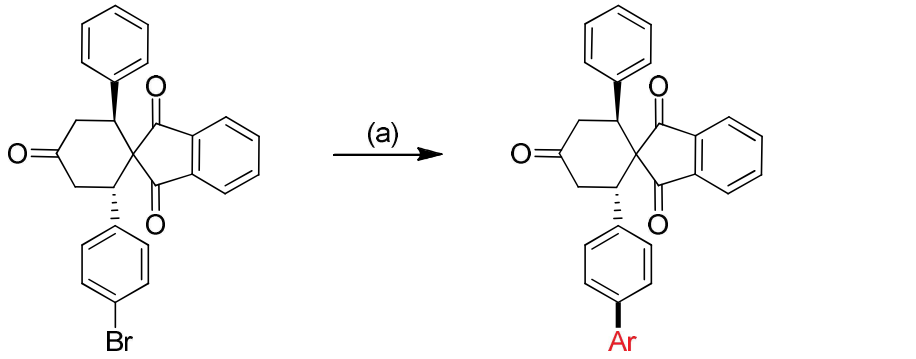


(+)-**33aa**

Figure 59: Crystal structure of chiral (2*S*,6*S*)-2-(4-nitrophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (**33aa**).

Given our interest to develop general protocol to synthesize library of isomerically pure chiral biphenyls to study their anti-cancer properties,[64] herein as an alternative, we envisioned another route, wherein instead of preparing the biphenyl containing arylaldehydes **28n** and **28o** and then subjecting them to ATCDA reaction, we wanted to

see the outcome of the Suzuki coupling reaction on the ATCDA product *anti*-(−)-**33ae** with the correspondingly substituted phenyl boronic acids in order to obtain the same compounds, *anti*-(−)-**33an** and *anti*-(−)-**33ao**. Interestingly, Pd-catalyzed Suzuki coupling of *anti*-(−)-**33ae** [97% *ee* and 99% *de*] bearing an aryl bromide with 4-hydroxyphenylboronic acid, $Pd(PPh_3)_4$ and sodium succinate in toluene/ethanol/water (4:2:1) at 80 °C for 8 h furnished the product *anti*-(−)-**33an** in 35% yield with 98% *ee* and 6:1 *dr* (Scheme 9). In a similar manner, chiral spirotrione *anti*-(−)-**33ao** was also prepared in 43% yield with 99% *ee* and 15:1 *dr* (Scheme 9). These Suzuki coupling reactions were performed on purified *anti*-(−)-**33ae**, nevertheless, we ended up with mixture of diastereomers, which may be attributed to isomerisation at the benzylic position under the harsh reaction conditions of Suzuki coupling. Looking back and judging, we feel that the first route is better and advantageous in terms of reaction yield and *ee*. This sequential Suzuki/ATCDA protocol will be helping to find the suitable drug-like molecules for the treatment of cancer cells, which is emphasizing the value of this approach to the pharmaceuticals.[64]

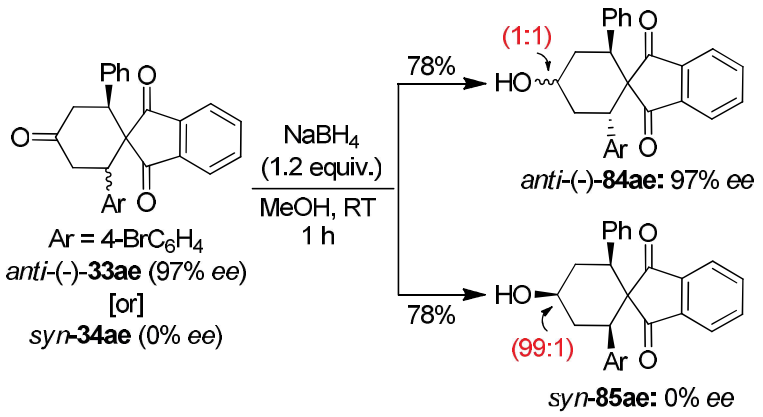


Scheme 9: Asymmetric synthesis of *trans*-isomers of anti-cancer agents **B** and **C**. For reaction conditions, see: (a) Ar-$B(OH)_2$ (2.0 equiv.), $Pd(PPh_3)_4$ (0.055 equiv.), $C_6H_5CH_3$ (2.0 mL), Sodium succinate (2.1 equiv.), $C_6H_5CH_3$: H_2O (1.14 : 1; 1.5 mL), EtOH (1.4 mL), 80 °C, 8 h.

With material applications in mind, we explored the utilization of spiranes *anti*-(−)-**33ae** and *syn*-(±)-**34ae** in the synthesis of hydroxyl-spiranes **84-85**, which are starting materials for the synthesis of [*m.n.o.p*]fenestranes (Scheme 10).[67] Reduction of chiral spirotrione *anti*-(−)-**33ae** with 1.2 equiv. of $NaBH_4$ in dry CH_3OH at 0-25 °C for 1.0 h

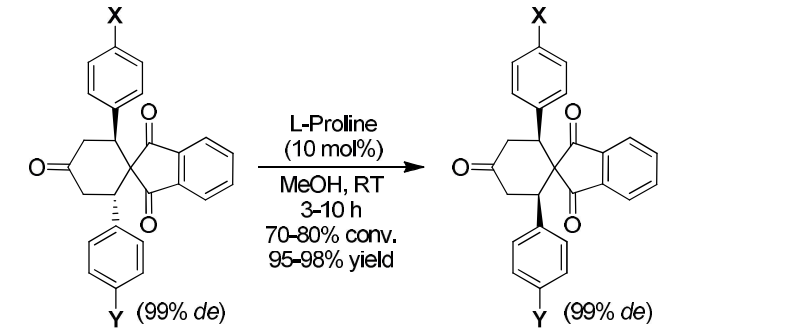
furnished the alcohol *anti*-(−)-**84ae** in 78% yield with 97% *ee* and 1:1 *dr*; but similar reaction on *syn*-(±)-**34ae** furnished the *syn*-(±)-**85ae** in 78% yield with 99:1 *dr* (Scheme 10).

Scheme 10: Reduction of spiroketones.



ATCDA major *anti*-isomeric products of *anti*-(+)-**33aa**, *anti*-(−)-**33ae**, and *anti*-(−)-**33da** were epimerized to the *syn*-isomers of *syn*-(−)-**34aa**, *syn*-(±)-**34ae**, and *syn*-(+)-**34da** under proline-catalysis in very good yields with 70-80% conversion at 25 °C for 3-10 h (Scheme 11). Epimerized *syn*-isomers **34** were obtained in 0-91% *ee* although single enantiomer of *anti*-isomer **33** was used. Outcome *ee* of epimerization products **34** is totally controlled by electronic nature of aryl functional groups, which is thoroughly discussed in the next mechanistic section. Organocatalytic epimerization is important method for the synthesis of chiral spiranes **34**, which could become good candidates for

Scheme 11: Organocatalytic epimerization reactions.



33aa [X = H; Y = NO_2: 99% *ee*]
33ae [X = H; Y = Br: 97% *ee*]
33da [X = OMe; Y = NO_2: 99% *ee*]

34aa [X = H; Y = NO_2: 65% *ee*]
34ae [X = H; Y = Br: 0% *ee*]
34da [X = OMe; Y = NO_2: 91% *ee*]

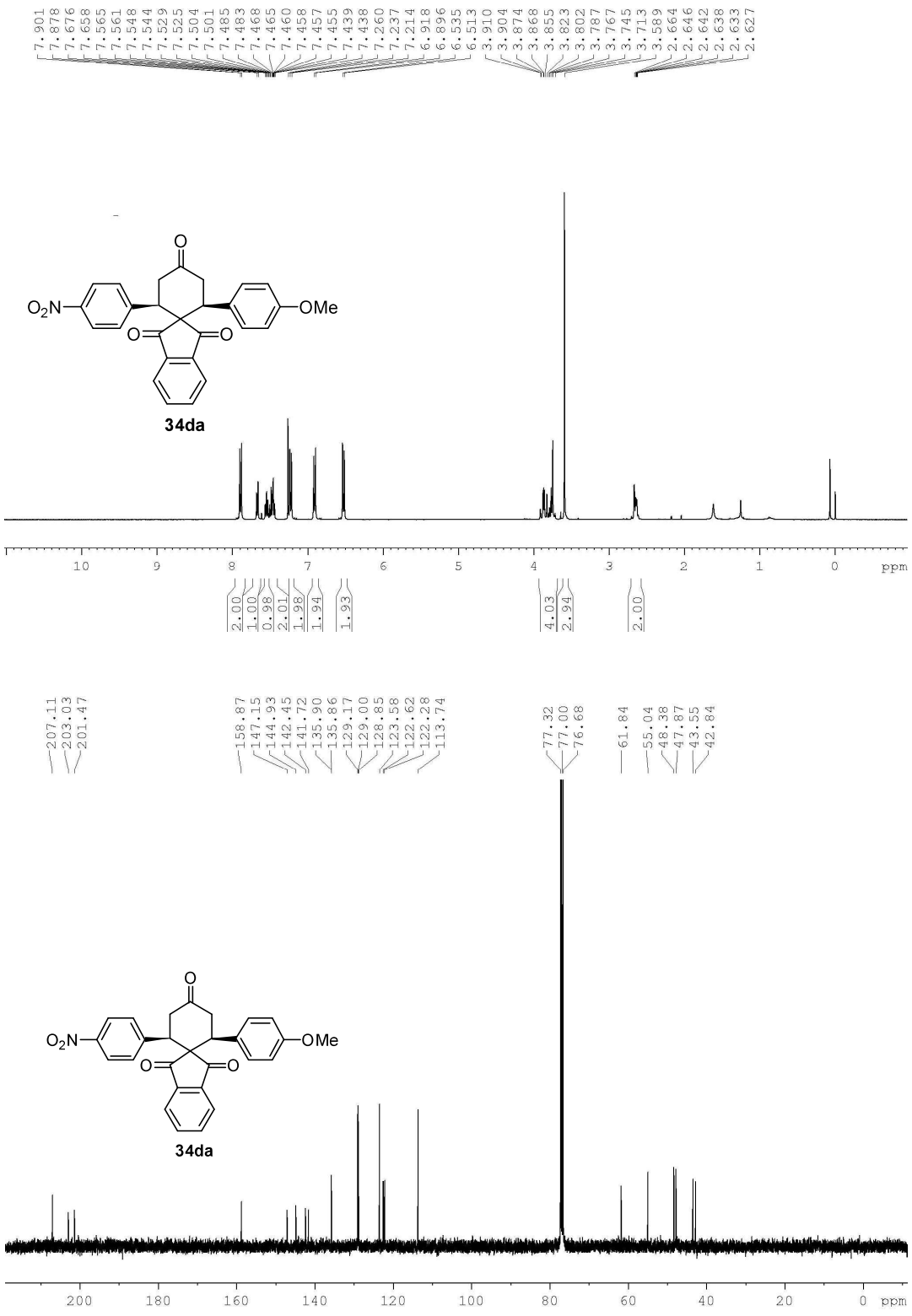
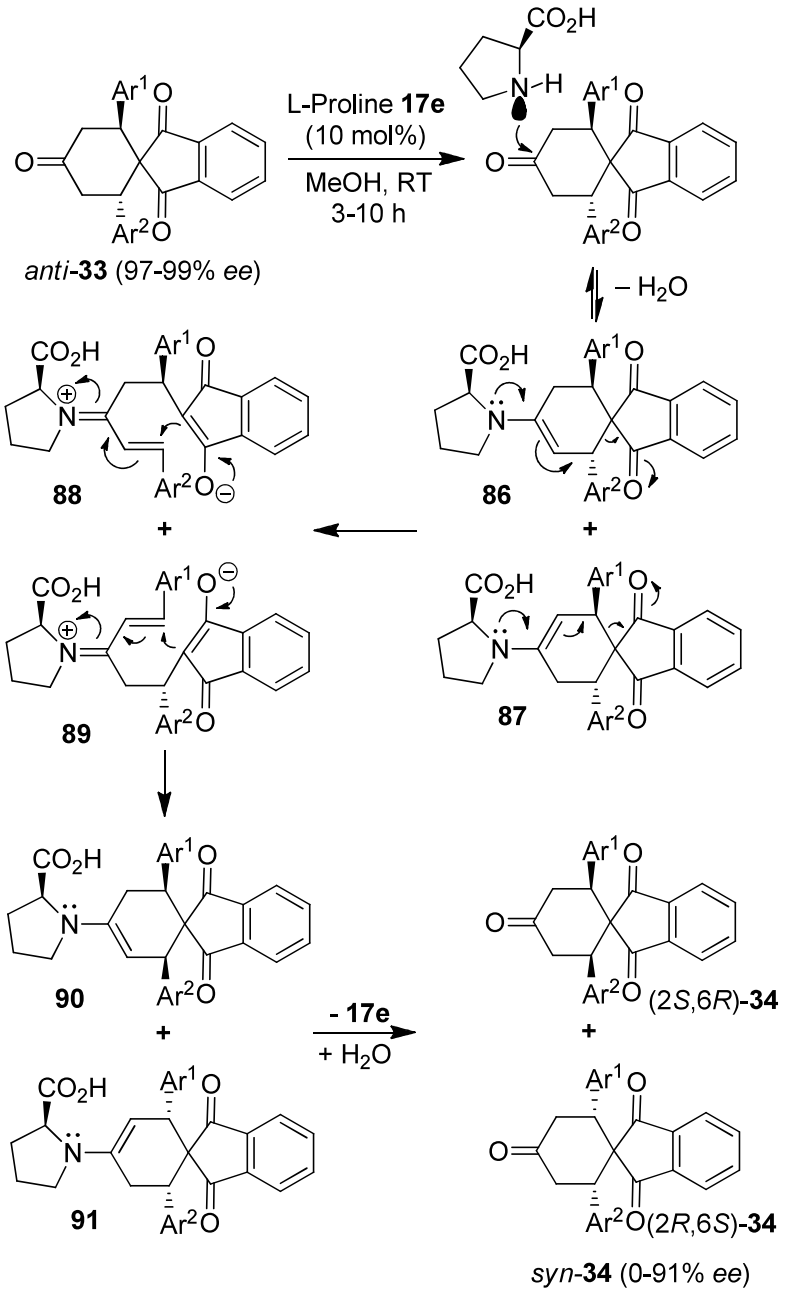


Figure-60: ^{1}H and ^{13}C NMR spectra of the product **34da**.

the anticancer studies.[64]

For the mechanism of organocatalytic epimerization at *β*-position to carbonyl of *anti*-isomer **33**, we are proposing that *anti*-(−)-**33** (97-99% *ee*) reacts sharply with the catalyst L-proline **17e** to generate the 1:1 mixture of enamines **86** and **87**, which exist in equilibrium with *anti*-(−)-**33** (Scheme 12). The solvent induced *retro*-Michael reaction furnished the ring-opened imine-enolates **88** and **89** through hydrogen bonding with

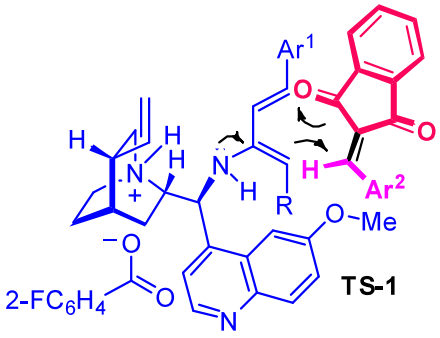
Scheme 12. Proposed mechanism for the L-proline catalyzed epimerization



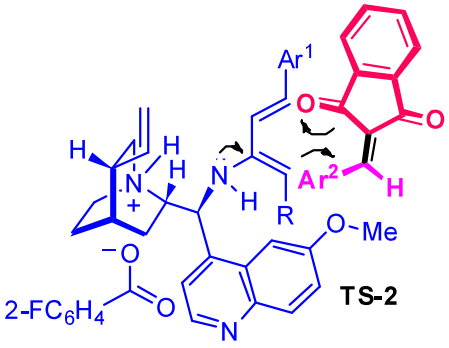
MeOH. Both of the imine-enolates **88** and **89** then undergo Michael reaction to furnish the enamines of the thermodynamically stable *syn*-isomer **90** and **91**, which undergo *in situ* hydrolysis to furnish the two enantiomers of *syn*-isomer (2*S*,6*R*)-**34** and (2*R*,6*S*)-**34**. Overall *ee* of the *syn*-isomer **34** (0-91% *ee*) depends on the ratio of the *in situ* generated imine-enolates **88** and **89**, which is totally controlled by the stereoelectronic nature of the aryl groups attached to *anti*-**33**.

Herein, we attempted to explain the mechanistic aspects of the synergistic 9-amino-9-deoxyepiquinine **17h**/*o*-$FC_6H_4CO_2H$ **49a** catalyzed ATCDA reaction and L-proline **17e**-catalyzed epimerization reactions based on the few controlled experiments (Schemes 11 and 12). From the optimization studies we came to know that primary amine **17h** and acid **49a** in toluene solvent facilitates the ATCDA reaction through cascade olefination followed by [4+2]-cycloaddition, most probably due to the stabilization of the catalyst cluster through acid/base and weak interactions. Although further studies are needed to firmly elucidate the mechanism of the ATCDA reactions through **17h/49a**-catalysis, the reaction proceeds by stepwise manner between in situ generated Barbas dienamines (2-aminobuta-1,3-dienes) and 2-arylidene-indan-1,3-diones (Scheme 13). Based on the X-ray crystal structure studies, we can rationalize the observed high stereoselectivity through an allowed transition state where the *si*-face of olefin approaches the *si*-face of Barbas dienamine due to the strong hydrogen-bonding/electrostatic/CH-π interactions and less steric hindrance as shown in **TS-1**. Formation of the minor diastereomer may be explained by model **TS-2**, in which there is

Scheme 13: Reaction Mechanism.



Stable TS Model for [4+2]-Cycloaddition *via* 2-Aminobuta-1,3-diene-Catalysis [***Si*-face Approach**]



Unstable TS Model for [4+2]-Cycloaddition *via* 2-Aminobuta-1,3-diene-Catalysis [***Re*-face approach**]

strong steric hindrance between the alkyl portion of the catalyst and the aryl group of olefin (Scheme 13).

6.3 Conclusion

In summary, we have described for the first time highly asymmetric 9-amino-9-deoxyepiquinine **17h**/*o*-$FC_6H_4CO_2H$ **49a**-catalyzed ATCDA reaction of arylideneacetones, arylaldehydes and 1,3-indandione through Barbas dienamine-platform under ambient conditions. The ATCDA reaction proceeds in very good yields with high *exo*-selectivity using a synergistic combination of primary amine, 9-amino-9-deoxyepiquinine with simple Brønsted acid *o*-$FC_6H_4CO_2H$. Furthermore, we have demonstrated the direct application of the ATCDA into the asymmetric synthesis of anti-cancer products *anti*-(−)-**33an** and *anti*-(−)-**33ao** through two different sequences of Suzuki-ATCDA or ATCDA-Suzuki reactions. We explained the mechanistic synergy of **17h** with **49a** to perform the ATCDA reaction of **27**, **28** and **32** in toluene and also organocatalytic epimerization. Further work is in progress to utilize the chiral ATCDA products *anti*-(−)-**33** as intermediates for the bioactive molecules synthesis.

7. Experimental Section

7.1 General Methods:

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 500 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. *In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 experiment, and is given in parentheses.* The coupling constants *J* are given in Hz. Column chromatography was performed using Acme's silica gel (particle size 0.063-0.200 mm). High-resolution mass spectra (HRMS) were recorded on ESI-TOF maXis. GCMS mass spectrometry was performed on Shimadzu GCMS-QP2010 mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010 A mass spectrometer. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-Kα (λ = 0.71073 Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube (λ = 0.71073 Å). For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

7.2 General Procedure for the Cs_2CO_3-catalyzed Domino [3+2]-Cycloaddition Reactions :

In an ordinary glass vial equipped with a magnetic stirring bar, to 0.05 mmol of catalyst **17m** in DMSO+H_2O (7:3; 0.5 M), was added 0.6 mmol of aryl azide **2** and 0.5 mmol of monosubstituted acetonitrile **1** and the reaction mixture was stirred at 25 °C for 0.5-2.0 h. 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 domino products **3** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

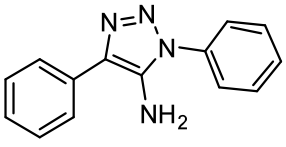
7.3 General Procedure for the tBuOK-catalyzed Domino [3+2]-Cycloaddition Reactions:

In an ordinary glass vial equipped with a magnetic stirring bar, to 0.1 mmol of catalyst **17n** in DMSO (0.5 M), was added 0.6 mmol of aryl azide **2** and 0.5 mmol of monosubstituted acetonitrile **1** and the reaction mixture was stirred at 25 °C for 0.5-2.0 h. 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 domino products **3** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

7.4 General Procedure for the DBU-catalyzed Domino [3+2]-Cycloaddition Reactions:

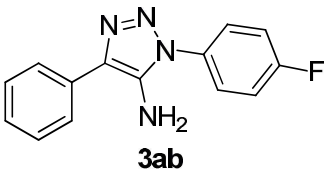
In an ordinary glass vial equipped with a magnetic stirring bar, to 0.1 mmol of catalyst **17b** in DMSO (0.5 M), was added 0.75 mmol of aryl azide **2** and 0.5 mmol of monosubstituted acetonitrile **1** and the reaction mixture was stirred at 25 °C for 0.5-2.0 h. The crude reaction mixture was worked 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 domino products **3** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

1,4-Diphenyl-1*H*-1,2,3-triazlo-5-amine (3aa): Prepar117ed following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 170-172 °C; IR (KBr): ν_{max} 3443, 3364, 1600, 1515, 1381, 1270, 1239, 1103, 1070, 969, 763 and 713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (2H, d, *J* = 7.2 Hz), 7.61-7.55 (4H, m), 7.52-7.51 (1H, m), 7.46 (2H, t, *J* = 8.0 Hz), 7.31 (1H, t, *J* = 7.6 Hz), 4.13 (2H, s, N*H*$_2$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 137.4 (C), 135.1 (C), 131.4 (C), 129.9 (2 x CH), 129.8 (C), 129.4 (CH), 129.0 (2 x CH), 127.0 (CH), 125.6 (2 x CH), 124.3 (2 x CH); HRMS m/z 237.1131 ($M + H^+$), calcd for $C_{14}H_{12}N_4H$ 237.1140.



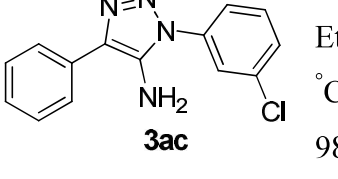
3aa

1-(4-Fluorophenyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (3ab): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 132-134 °C ; IR (neat): ν_{max} 3413, 3320, 1604, 1517, 1440, 1243, 991, 832, 760 and 700 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.87 (2H, br d, *J* = 7.2 Hz), 7.72-7.69 (2H, m), 7.49-7.44 (4H, m), 7.29 (1H, t, *J* = 7.6 Hz), 5.85 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 162.6 (C, d, *J* = 244.0 Hz, *C*-F), 140.0 (C), 132.5 (C), 132.3 (C, d, *J* = 3.0 Hz), 129.2 (2 x CH), 128.2 (C), 127.8 (2 x CH, d, *J* = 9.0 Hz), 126.7 (CH), 125.6 (2 x CH), 117.1 (2 x CH, d, *J* = 23.0 Hz); HRMS m/z 255.1038 (M + H^+), calcd for $C_{14}H_{11}FN_4H$ 255.1046.



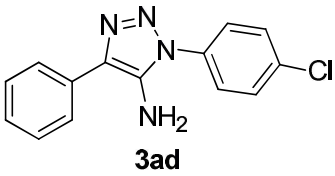
3ab

1-(3-Chlorophenyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (3ac): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp 124-126 °C; IR (neat): ν_{max} 3294, 1621, 1594, 1425, 1382, 1261, 1221, 1074, 984, 783, 764 and 715 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.81 (2H, d, *J* = 7.5 Hz), 7.74 (1H, m), 7.65-7.61 (3H, m), 7.45 (2H, t, *J* = 8.0 Hz), 7.28 (1H, t, *J* = 7.5 Hz), 5.92 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.9 (C), 137.1 (C), 134.3 (C), 132.2 (C), 131.8 (CH), 129.3 (CH), 129.1 (2 x CH), 128.2 (C), 126.7 (CH), 125.5 (2 x CH), 125.0 (CH), 123.8 (CH); HRMS m/z 271.0735 (M + H^+), calcd for $C_{14}H_{11}ClN_4H$ 271.0750.



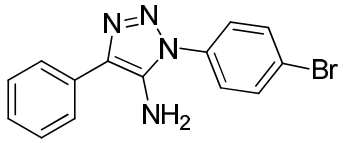
3ac

1-(4-Chlorophenyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (3ad): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp 156-158 °C; IR (neat): ν_{max} 3419, 3323, 1612, 1498, 1444, 1407, 1382, 1259, 1093, 982, 819, and 769 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.81 (2H, d, *J* = 7.5 Hz), 7.68 (4H, m), 7.45 (2H, t, *J* = 7.5 Hz), 7.28 (1H, t, *J* = 7.5 Hz), 5.86 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.9 (C), 134.7 (C), 133.9 (C), 132.3 (C), 130.2 (2 x CH), 129.1 (2 x CH), 128.2 (C), 127.0 (2 x CH), 126.7 (CH), 125.5 (2 x CH); HRMS m/z 271.0750 (M + H^+), calcd for $C_{14}H_{11}ClN_4H$ 271.0750.



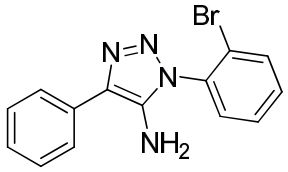
3ad

1-(4-Bromophenyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (3ae): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 132-134 °C; IR (neat): ν_{max} 3314, 2920, 2851, 1610, 1508, 1444, 1259, 1070, 980, 908, 832, 815, 769 and 716 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.81 (2H, br d, *J* = 7.2 Hz), 7.79 (2H, br d, *J* = 7.2 Hz), 7.60 (2H, br d, *J* = 8.8 Hz), 7.44 (2H, t, *J* = 8.0 Hz), 7.27 (1H, t, *J* = 7.2 Hz), 5.86 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.8 (C), 135.1 (C), 133.1 (2 x CH), 132.2 (C), 129.1 (2 x CH), 128.2 (C), 127.2 (2 x CH), 126.6 (CH), 125.5 (2 x CH), 122.3 (C); HRMS m/z 315.0249 (M + H^+), calcd for $C_{14}H_{11}BrN_4H$ 315.0245.



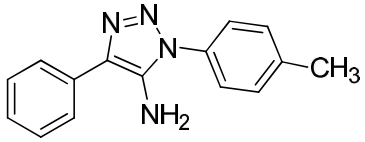
3ae

1-(2-Bromophenyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (3af): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 120-122 °C; IR (neat): ν_{max} 3402, 3161, 3073, 1599, 1561, 1467, 1308, 1265, 1020, 991, 914 and 739 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.91 (1H, br d, *J* = 7.6 Hz), 7.83 (2H, br d, *J* = 7.2 Hz), 7.65-7.54 (3H, m), 7.43 (2H, t, *J* = 7.6 Hz), 7.25 (1H, t, *J* = 7.2 Hz), 5.82 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 140.9 (C), 134.6 (C), 134.1 (CH), 132.7 (CH), 132.6 (C), 130.8 (CH), 129.6 (CH), 129.1 (2 x CH), 126.5 (C), 126.3 (CH), 125.0 (2 x CH), 122.3 (C); HRMS m/z 315.0249 (M + H^+), calcd for $C_{14}H_{11}BrN_4H$ 315.0245.



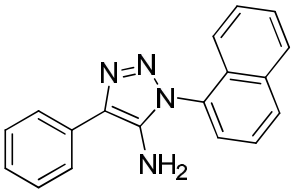
3af

4-Phenyl-1-(p-tolyl)-1*H*-1,2,3-triazol-5-amine (3ag): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 144-146 °C; IR (Neat): ν_{max} 3375, 3282, 1600, 1517, 1441, 1260, 1106, 986, 832, 772, 695 and 498 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.83 (2H, d, *J* = 7.2 Hz), 7.51-7.41 (6H, m), 7.27 (1H, t, *J* = 7.2 Hz), 5.72 (2H, s, N*H*$_2$), 3.43 (3H, s, Ar-C*H*$_3$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.7 (C), 139.1 (C), 133.3 (C), 132.5 (C), 130.6 (2 x CH), 129.1 (2 x CH), 128.1 (C), 126.6 (CH), 125.5 (2 x CH), 125.1 (2 x CH), 21.3 (CH_3); HRMS m/z 251.1290 (M + H^+), calcd for $C_{15}H_{14}N_4H$ 251.1297.



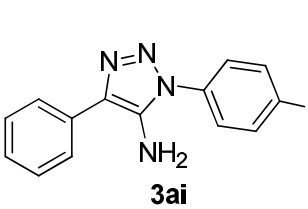
3ag

1-(Naphthalen-1-yl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (3ah): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and isolated as a semi solid; IR (neat): ν_{max} 3315, 3194, 1625, 1606, 1508, 1404, 1264, 1023, 991, 803, 770, 733 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.21 (1H, d, *J* = 7.6 Hz), 8.13 (1H, d, *J* = 7.6 Hz), 7.89 (2H, d, *J* = 7.2 Hz), 7.75-7.69 (2H, m), 7.67-7.635 (1H, m), 7.63-7.58 (1H, m), 7.46 (2H, t, *J* = 7.6 Hz), 7.33-7.26 (2H, m), 5.72 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 141.5 (C), 134.5 (C), 132.7 (C), 131.6 (C), 130.9 (CH), 130.0 (C), 129.2 (2 x CH), 128.9 (CH), 128.2 (CH), 127.5 (CH), 126.8 (C), 126.6 (CH), 126.5 (CH), 126.4 (CH), 125.3 (2 x CH), 123.0 (CH); HRMS m/z 287.1288 (M + H^+), calcd for $C_{18}H_{14}N_4H$ 287.1297.



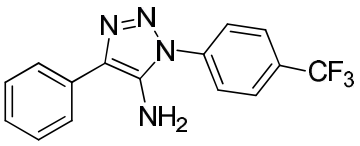
3ah

1-(4-Methoxyphenyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (3ai): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 135-137 °C; IR (neat): ν_{max} 3458, 3305, 2851, 1623, 1507, 1463, 1440, 1248, 1036, 979, 908, 832 and 771 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.79 (2H, d, *J* = 7.6 Hz), 7.50 (2H, d, *J* = 8.8 Hz), 7.43 (2H, t, *J* = 7.6 Hz), 7.26 (1H, t, *J* = 7.2 Hz), 7.15 (2H, d, *J* = 9.2 Hz), 5.64 (2H, s, N*H*$_2$), 3.85 (3H, s, OC*H*$_3$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 160.1 (C), 139.8 (C), 132.5 (C), 129.1 (2 x CH), 128.6 (C), 127.8 (C), 127.0 (2 x CH), 126.5 (CH), 125.4 (2 x CH), 115.3 (2 x CH), 56.1 (CH_3); HRMS m/z 267.1240 (M + H^+), calcd for $C_{15}H_{14}N_4OH$ 267.1246.



3ai

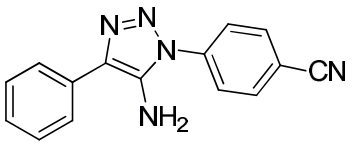
4-Phenyl-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-5-amine (3aj): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 170-172 °C; IR (neat): 3079, 2920, 2859, 1714, 1643, 1467, 1380, 1319, 991, 914 and 722 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.00 (2H, d, *J* = 8.4 Hz), 7.92 (2H, d, *J* = 8.4 Hz), 7.83 (2H, d, *J* = 7.6 Hz), 7.46 (2H, t, *J* = 7.6 Hz), 7.29 (1H, t, *J* = 7.6 Hz), 6.00 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 140.0 (C), 139.3 (C), 132.2 (C), 129.5 (C, q, *J* = 32.0 Hz), 129.2 (2 x CH), 128.6 (C), 127.3 (2 x CH, q, *J* = 4.0 Hz), 126.8 (CH), 125.7 (2 x CH), 125.5 (2 x CH),



3aj

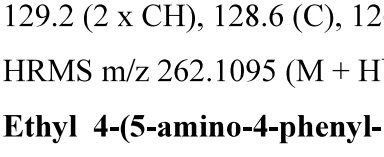
124.5 (CF_3, q, J = 270.0 Hz); HRMS m/z 305.1002 (M + H^+), calcd for $C_{15}H_{11}F_3N_4H$ 305.1014.

4-(5-Amino-4-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile (3ak): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp 150-152 °C; IR (neat): ν_{max} 3409, 3320, 2233, 1609, 1516, 1444, 1413, 1381, 1262, 1128, 1070, 982, 847, and 771 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.10 (2H, br d, J = 8.4 Hz), 7.90 (2H, br d, J = 8.4 Hz), 7.81 (2H, br d, J = 7.2 Hz), 7.46 (2H, br t, J = 8.0 Hz), 7.29 (1H, br t, J = 7.2 Hz), 6.02 (2H, s, NH_2); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.9 (C), 139.6 (C), 134.4 (2 x CH), 132.0 (C), 129.2 (2 x CH), 128.6 (C), 126.9 (CH), 125.7 (2 x CH), 125.4 (2 x CH), 118.8 (C), 111.7 (C); HRMS m/z 262.1095 (M + H^+), calcd for $C_{15}H_{11}N_5H$ 262.1093.



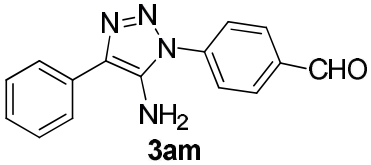
3ak

Ethyl 4-(5-amino-4-phenyl-1*H*-1,2,3-triazol-1-yl)benzoate (3al): Prepared following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp 110-112 °C; IR (neat): ν_{max} 3413, 3320, 2920, 1715, 1621, 1419, 1271, 1106, 865, 772, 695 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.18 (2H, br d, J = 8.0 Hz), 7.82 (2H, br d, J = 8.0 Hz), 7.80 (2H, br d, J = 8.0 Hz), 7.45 (2H, br t, J = 7.6 Hz), 7.28 (1H, br t, J = 7.2 Hz), 5.95 (2H, s, NH_2), 4.37 (2H, q, J = 6.8 Hz), 1.35 (3H, t, J = 6.8 Hz); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 165.6 (C, *C*=O), 139.9 (C), 139.6 (C), 132.2 (C), 131.2 (2 x CH), 130.3 (C), 129.2 (2 x CH), 128.5 (C), 126.8 (CH), 125.7 (2 x CH), 124.8 (2 x CH), 61.7 (CH_2), 14.7 (CH_3); HRMS m/z 309.1346 (M + H^+), calcd for $C_{17}H_{16}N_4O_2H$ 309.1352.



3al

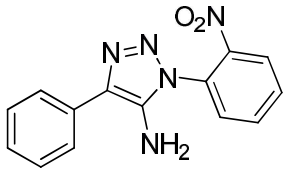
4-(5-Amino-4-phenyl-1*H*-1,2,3-triazol-1-yl)benzaldehyde (3am): Prepared following the procedure **7.4** and purified by column chromatography using EtOAc/hexane and isolated as a White solid. Mp 120-122 °C; IR (neat): ν_{max} 3385, 3277, 1705, 1603, 1578, 1514, 1443, 1420, 1375, 1302, 1203, 1167, 1023, 982, 829 and 766 cm^{-1}; ^1H NMR (DMSO-d6, 500 MHz) δ 10.13 (1H, s, C*H*O), 8.15 (2H, d, J = 8.5 Hz), 7.91 (2H, d, J = 8.0 Hz), 7.80 (2H, d, J = 7.5 Hz), 7.46 (2H, t, J = 7.5 Hz), 7.29 (1H, t, J = 7.5 Hz), 6.00 (2H, s, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 193.0 (*C*HO, C), 140.5 (C), 139.9 (C), 136.1



3am

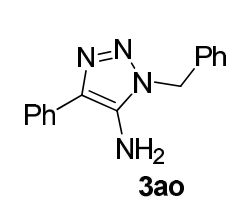
(C), 132.1 (C), 131.4 (2 x CH), 129.2 (2 x CH), 128.5 (C), 126.8 (CH), 125.6 (2 x CH), 125.0 (2 x CH); HRMS m/z 265.1078 ($M + H^+$), calcd for $C_{15}H_{12}N_4OH$ 265.1089.

1-(2-Nitrophenyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (3an): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and isolated as a White solid. Mp 135-137 °C; IR (neat): ν_{max} 3303, 3150, 1615, 1588, 1522, 1440, 1347, 1270, 1139, 980, 766, 739 and 700 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.28 (1H, dd, *J* = 8.0, 1.2 Hz), 7.98 (1H, dt, *J* = 7.6, 1.2 Hz), 7.89-7.81 (4H, m), 7.45 (2H, t, *J* = 7.6 Hz), 7.28 (1H, t, *J* = 7.2 Hz), 6.06 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 145.8 (C), 141.2 (CH), 135.3 (CH), 132.2 (C), 131.8 (C), 130.3 (CH), 129.1 (2 x CH), 128.3 (C), 127.1 (C), 126.5 (CH), 126.1 (CH), 125.2 (2 x CH); LCMS m/z 282.40 ($M + H^+$), calcd for $C_{14}H_{11}N_5O_2H$ 282.0991.



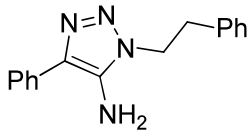
3an

1-Benzyl-4-phenyl-1*H*-1,2,3-triazol-5-amine (3ao): Prepared following the procedure **7.3** and purified by column chromatography using EtOAc/hexane and was isolated as a White solid. Mp 118-120 °C; IR (neat): ν_{max} 3314, 3203, 1637, 1605, 1586, 1518, 1496, 1445, 1368, 1251, 1225, 1114, 1073, 993, 803, 767 and 718 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.18 (2H, br d, *J* = 6.4 Hz), 6.85-6.78 (4H, m), 6.75-6.64 (4H, m), 5.31 (2H, s, N*H*$_2$), 4.91 (2H, s, NC*H*$_2$Ph); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.7 (C), 136.8 (C), 132.8 (C), 129.1 (2 x CH), 129.0 (2 x CH), 128.1 (CH), 127.9 (2 x CH), 127.7 (C), 126.2 (CH), 125.0 (2 x CH), 48.9 (CH_2); HRMS m/z 251.1299 ($M + H^+$), calcd for $C_{15}H_{14}N_4H$ 251.1297.



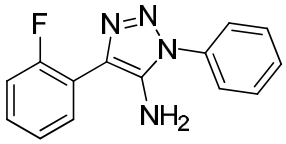
3ao

1-Phenethyl-4-phenyl-1*H*-1,2,3-triazol-5-amine (3ap): Prepared following the procedure **7.3** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 126-128 °C; IR (neat): ν_{max} 3298, 3177, 1632, 1582, 1528, 1445, 1265, 1073, 1007, 760, and 706 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.74 (2H, br d, *J* = 7.2 Hz), 7.41 (2H, br t, *J* = 7.6 Hz), 7.32-7.31 (4H, m), 7.25-7.21 (2H, m), 5.80 (2H, s, N*H*$_2$), 4.41 (2H, t, *J* = 8.0 Hz), 3.10 (2H, t, *J* = 8.0 Hz); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.4 (C), 138.4 (C), 132.9 (C), 129.4 (2 x CH), 129.0 (2 x CH), 128.8 (2 x CH), 127.7 (C), 126.9 (CH), 126.1 (CH), 125.0 (2 x CH), 46.9 (CH_2), 35.0 (CH_2); LCMS m/z 265.00 ($M + H^+$), calcd for $C_{16}H_{16}N_4H$ 265.1453.



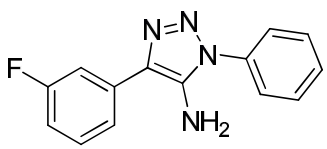
3ap

4-(2-Fluorophenyl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (3ba): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 168-170 °C; IR (neat): ν_{max} 3352, 1606, 1512, 1451, 1374, 1222, 1197, 1106, 979, 820 and 760 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.70-7.61 (5H, m), 7.54 (1H, tt, *J* = 7.0, 1.2 Hz), 7.43-7.39 (1H, m), 7.32-7.29 (2H, m), 5.65 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 159.4 (C, d, *J* = 245.0 Hz, *C*-F), 140.8 (C), 136.0 (C), 130.7 (CH, d, *J* = 3.0 Hz), 130.2 (2 x CH), 129.5 (CH, d, *J* = 8.0 Hz), 129.3 (CH), 125.1 (CH), 124.8 (2 x CH), 123.8 (C), 119.9 (C, d, *J* = 14.0 Hz), 116.4 (CH, d, *J* = 21.0 Hz); HRMS m/z 255.1037 (M + H^+), calcd for $C_{14}H_{11}FN_4H$ 255.1046.



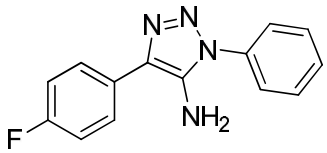
3ba

4-(3-Fluorophenyl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (3ca): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 152-154 °C; IR (neat): 3401, 3330, 1161, 1500, 1434, 1383, 1278, 1263, 1191, 1161, 1024, 987, 869, and 756 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.70 (1H, d, *J* = 8.0 Hz), 7.64-7.63 (5H, m), 7.58-7.55 (1H, m), 7.48 (1H, q, *J* = 8.0 Hz), 7.09 (1H, t, *J* = 8.5 Hz), 5.95(2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 163.0 (C, d, *J* = 240 Hz), 140.1 (C), 135.6 (C), 134.7 (C, d, *J* = 12.5 Hz), 131.0 (CH, d, *J* = 8.75 Hz), 130.2 (2 x CH), 129.5 (CH), 126.9 (C), 125.2 (2 x CH), 121.3 (CH, d, *J* = 2.5 Hz), 113.0 (CH, d, *J* = 21.25 Hz); 111.7 (CH, d, *J* = 22.5 Hz); LRMS m/z 255.00 (M + H^+), calcd for $C_{14}H_{11}FN_4H$ 255.1046.



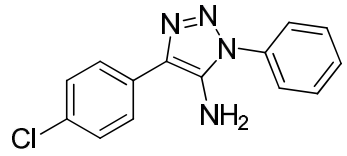
3ca

4-(4-Fluorophenyl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (3da): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 112-114 °C; IR (neat): ν_{max} 3286, 3192, 1612, 1576, 1517, 1452, 1381, 1221, 1091, 983, 909, 835 and 816 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.84 (2H, m), 7.63-7.62 (4H, m), 7.56 (1H, m), 7.28 (2H, br t, *J* = 9.0 Hz), 5.79 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 161.2 (C, d, *J* = 241 Hz), 139.5 (C), 135.8 (C), 130.2 (2 x CH), 129.4 (CH), 128.9 (C, d, *J* = 2.5 Hz), 127.5 (C), 127.4 (2 x CH, d, *J* = 8.75 Hz), 125.1 (2 x CH), 115.9 (2 x CH, d, *J* = 21.25 Hz); HRMS m/z 255.1047 (M + H^+), calcd for $C_{14}H_{11}FN_4H$ 255.1046.



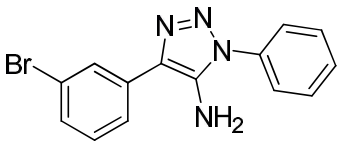
3da

4-(4-Chlorophenyl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (3ea): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow solid. Mp 134-136 °C; IR (Neat): νmax 3398, 3280, 1623, 1509, 1454, 1402, 1380, 1257, 1093, 986, 910, 832, 823, 768, 750, and 720 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.83 (2H, d, *J* = 8.5 Hz), 7.65-7.61 (4H, m), 7.57-7.55 (1H, m), 7.49 (2H, d, *J* = 9.0 Hz), 5.87 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.9 (C), 135.7 (C), 131.3 (C), 130.8 (C), 130.2 (2 x CH), 129.5 (CH), 129.0 (2 x CH), 127.0 (2 x CH, C), 125.2 (2 x CH); HRMS m/z 271.0743 (M + H^+), calcd for $C_{14}H_{11}ClN_4H$ 271.0750.



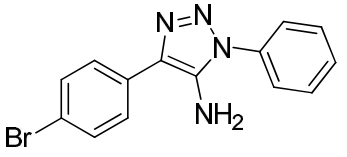
3ea

4-(3-Bromophenyl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (3fa): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow solid. Mp 112-114 °C; IR (neat): ν_{max} 3348, 1601, 1574, 1510, 1452, 1410, 1379, 1278, 1254, 1122, 1068, 993, 983, 877, 787, 767, 752 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.98 (1H, t, *J* = 2.0 Hz), 7.83 (1H, td, *J* = 8.0, 1.0 Hz), 7.65-7.61 (4H, m), 7.58-7.55 (1H, m), 7.46-7.44 (1H, m), 7.41-7.38 (1H, t, *J* = 8.0 Hz), 5.96 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 140.2 (C), 135.6 (C), 134.8 (C), 131.2 (CH), 130.2 (2 x CH), 129.6 (CH), 129.1 (CH), 127.6 (CH), 126.6 (C), 125.3 (2 x CH), 124.1 (CH), 122.7 (C); HRMS m/z 315.0239 (M + H^+), calcd for $C_{14}H_{11}BrN_4H$ 315.0245.



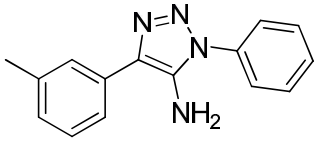
3fa

4-(4-Bromophenyl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (3ga): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a semi solid; IR (KBr): 3364, 3298, 1616, 1512, 1457, 1402, 1265, 1073, 1002, 832, 767 and 701 cm-1; ^1H NMR (DMSO-d_6, 500 MHz) δ 7.80 (2H, d, *J* = 8.5 Hz), 7.63-7.62 (6H, m), 7.56 (1H, m), 5.91 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.9 (C), 135.7 (C), 131.9 (2 x CH), 131.6 (C), 130.2 (2 x CH), 129.5 (CH), 127.4 (2 x CH), 127.1 (C), 125.1 (2 x CH), 119.3 (C); HRMS m/z 315.0246 (M + H^+), calcd for $C_{14}H_{11}BrN_4H$ 315.0245.



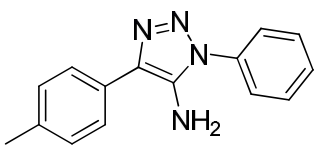
3ga

1-Phenyl-4-(m-tolyl)-1*H*-1,2,3-triazol-5-amine (3ha): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and isolated as a White solid. Mp 122-124 °C; IR (neat): νmax 3298, 3208, 1631, 1598, 1515, 1455, 1369, 1270, 1044, 980, 916, 854, 781 and 722 cm-1; ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 7.64-7.61 (6H, m), 7.58-7.53 (1H, m), 7.33 (1H, t, *J* = 7.6 Hz), 7.09 (1H, br d, *J* = 7.6 Hz), 5.76 (2H, s, N*H*$_2$), 2.38 (3H, s, Ar-C*H*$_3$) ; ^{13}C NMR (DMSO-d$_6$, DEPT-135) δ 139.6 (C), 138.2 (C), 135.9 (C), 132.3 (C), 130.2 (2 x CH), 129.4 (CH), 129.0 (CH), 128.2 (C), 127.3 (CH), 126.1 (CH), 125.0 (2 x CH), 122.7 (CH), 21.7 (CH$_3$); LCMS m/z 249.10 (M - H$^+$), calcd for $C_{15}H_{13}N_4$ 249.1140.



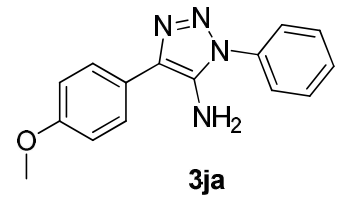
3ha

1-Phenyl-4-(p-tolyl)-1*H*-1,2,3-triazol-5-amine (3ia): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow solid. Mp 122-124 °C; IR (neat): νmax 3274, 3195, 1616, 1594, 1579, 1518, 1503, 1452, 1378, 1245, 980 and 708 cm-1; ^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 7.69 (2H, br d, *J* = 8.0 Hz), 7.63-7.61 (4H, m), 7.57-7.53 (1H, m), 7.25 (2H, br d, *J* = 7.6 Hz), 5.66 (2H, s, N*H*$_2$), 2.34 (3H, s, Ar-C*H*$_3$); ^{13}C NMR (DMSO-d$_6$, DEPT-135) δ 139.4 (C), 135.9 (C), 135.8 (C), 130.2 (2 x CH), 129.7 (2 x CH), 129.6 (C), 129.4 (CH), 128.4 (C), 125.5 (2 x CH), 125.1 (2 x CH), 21.3 (CH$_3$); HRMS m/z 251.1294 (M + H$^+$), calcd for $C_{15}H_{14}N_4H$ 251.1297.



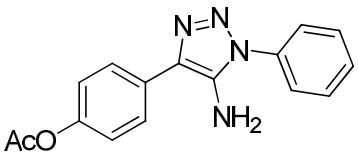
3ia

4-(4-Methoxyphenyl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (3ja): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 162-164 °C; IR (KBr): νmax 3362, 1599, 1565, 1509, 1453, 1382, 1237, 1105, 1026, 833 and 771cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 500 MHz) δ 7.44 (2H, d, *J* = 8.5 Hz), 7.33-7.31 (4H, m), 7.26-7.24 (1H, m), 6.73 (2H, d, *J* = 8.5 Hz), 5.34 (2H, s, N*H*$_2$), 3.50 (3H, s, Ar-OC*H*$_3$); ^{13}C NMR (DMSO-d$_6$, DEPT-135) δ 158.2 (C), 138.9 (C), 135.9 (C), 130.1 (2 x CH), 129.3 (CH), 128.5 (C), 127.0 (2 x CH, C), 124.9 (2 x CH), 114.5 (2 x CH), 55.6 (CH$_3$); HRMS m/z 267.1244 (M + H$^+$), calcd for $C_{15}H_{14}N_4OH$ 267.1246.



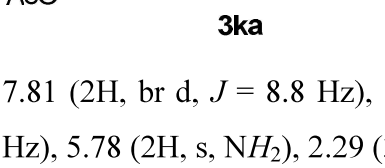
3ja

4-(5-Amino-1-phenyl-1*H*-1,2,3-triazol-4-yl)phenyl acetate (3ka): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a oily liquid; IR (Neat): ν_{max} 3430, 3331, 1751, 1620, 1515, 1370, 1274, 1217, 1190, 983, 911, 851, 767 and 718 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.81 (2H, br d, *J* = 8.8 Hz), 7.63-7.62 (4H, m), 7.57-7.54 (1H, m), 7.19 (2H, br d, *J* = 8.4 Hz), 5.78 (2H, s, N*H*$_2$), 2.29 (3H, s, Ar-OCOC*H*$_3$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 169.8 (C, O-*C*=O), 149.2 (C), 139.7 (C), 135.8 (C), 130.2 (2 x CH), 130.0 (C), 129.5 (CH), 127.6 (C), 126.5 (2 x CH), 125.1 (2 x CH), 122.5 (2 x CH), 21.4 (CH_3); HRMS m/z 295.1188 (M + H^+), calcd for $C_{16}H_{14}N_4O_2H$ 295.1195.



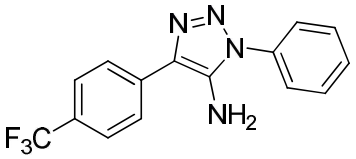
3ka

N-(4-(5-Amino-1-phenyl-1*H*-1,2,3-triazol-4-yl)phenyl)acetamide (3la): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a semi solid; IR (neat): ν_{max} 3575, 3301, 2923, 1661, 1601, 1514, 1442, 1408, 1373, 1318, 1286, 1110, 1019, 909, 810, 752, 694 and 653 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 10.00 (1H, s), 7.72 (2H, d, *J* = 8.5 Hz), 7.66 (2H, d, *J* = 8.5 Hz), 7.63-7.62 (4H, m), 7.55 (1H, m), 5.69 (2H, s, N*H*$_2$), 2.07 (3H, s, Ar-NHCOC*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 168.6 (NH-*C*=O, C), 139.1 (C), 138.0 (C), 135.9 (C), 130.1 (2 x CH), 129.3 (CH), 128.2 (C), 127.1 (C), 125.8 (2 x CH), 125.0 (2 x CH), 119.6 (2 x CH), 24.5 (CH_3); HRMS m/z 294.1353 (M + H^+), calcd for $C_{16}H_{15}N_5OH$ 294.1355.



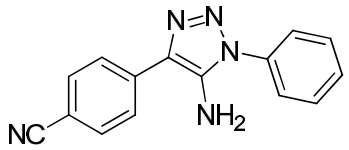
3la

1-Phenyl-4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-5-amine (3ma): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp 168-170 °C; IR (neat): ν_{max} 3435, 3326, 1617, 1506, 1453, 1412, 1318, 1280, 1239, 1166, 1072, 982, 840, 736 and 712 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.03 (2H, d, *J* = 8.5 Hz), 7.77 (2H, d, *J* = 8.0 Hz), 7.66-7.61 (4H, m), 7.59-7.56 (1H, m), 6.05 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 140.0 (C), 139.3 (C), 132.2 (C), 129.5 (C, q, *J* = 32.5 Hz), 129.2 (2 x CH), 128.6 (C), 127.4 (2 x CH, q, *J* = 3.75 Hz), 126.9 (CH), 125.7 (2 x CH), 125.5 (2 x CH), 124.5 (C, q, *J* = 270 Hz); HRMS m/z 305.1016 (M + H^+), calcd for $C_{15}H_{11}F_3N_4H$ 305.1014.



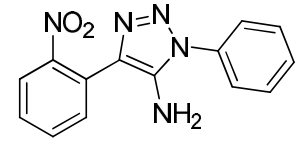
3ma

4-(5-Amino-1-phenyl-1*H*-1,2,3-triazol-4-yl)benzonitrile (3na): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a semi solid; IR (neat): ν_{max} 3405, 3282, 2229, 1613, 1503, 1452, 1408, 1260, 1226, 1128, 1047, 1024, 984, 909, 844 and 759 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.00 (2H, br d, *J* = 8.4 Hz), 7.86 (2H, br d, *J* = 8.4 Hz), 7.66-755 (5H, m), 6.15 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 141.1 (C), 137.1 (C), 135.4 (C), 133.1 (2 x CH), 130.3 (2 x CH), 129.7 (CH), 126.2 (C), 125.43 (2 x CH), 125.38 (2 x CH), 119.7 (C), 108.2 (C, *C*N); LCMS m/z 262.25 ($M + H^+$), calcd for $C_{15}H_{11}N_5H$ 262.1093.



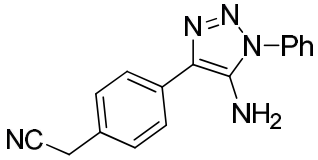
3na

4-(2-Nitrophenyl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (3oa): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 185-187 °C; IR (KBr): ν_{max} 3450, 3354, 1625, 1524, 1494, 1358, 1307, 1268, 1219, 1073, 983, 951, 855, 781, 768, 733 and 718 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.96 (1H, dd, *J* = 8.0, 1.0 Hz), 7.77-7.11 (2H, m), 7.65-7.63 (4H, m), 7.58-7.55 (2H, m), 6.00 (2H, s, N*H*$_2$); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 148.6 (C), 140.8 (C), 135.7 (C), 133.0 (CH), 130.8 (CH), 130.2 (2 x CH), 129.4 (CH), 128.5 (CH), 125.4 (C), 124.7 (2 x CH), 124.7 (CH), 124.1 (C); HRMS m/z 282.0992 ($M + H^+$), calcd for $C_{14}H_{11}N_5O_2H$, 282.0991.



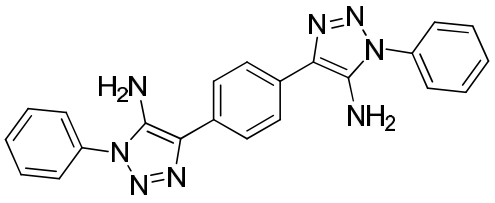
3oa

2-(4-(5-Amino-1-phenyl-1*H*-1,2,3-triazol-4-yl)phenyl)acetonitrile (3pa): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow solid. Mp 146-148 °C; IR (neat): ν_{max} 3463, 3377, 1603, 1416, 1262, 1235, 1117, 971, 827, 728, 711 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.82 (2H, br d, *J* = 8.0 Hz), 7.63-7.61 (4H, m), 7.58-7.54 (1H, m), 7.41 (2H, br d, *J* = 8.4 Hz), 5.82 (2H, s, N*H*$_2$), 4.07 (2H, s, Ar-C*H*$_2$CN); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.8 (C), 135.8 (C), 131.8 (C), 130.2 (2 x CH), 129.5 (CH), 129.3 (C), 128.9 (2 x CH), 127.5 (C), 125.9 (2 x CH), 125.2 (2 x CH), 119.9 (C), 22.6 (CH_2, Ar-*C*H$_2$CN); LCMS m/z 276.15 ($M + H^+$), calcd for $C_{16}H_{13}N_5H$ 276.1249.



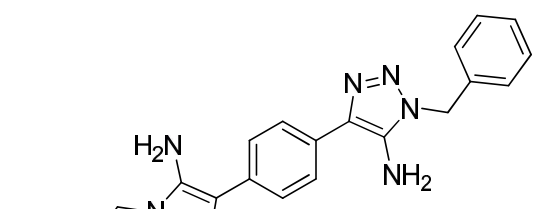
3pa

4,4'-(1,4-Phenylene)bis(1-phenyl-1*H*-1,2,3-triazol-5-amine) (62pa): Prepared following the procedure **7.3** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 200-202 °C; IR (neat): ν_{max} 3402, 3319, 1617, 1523, 1505, 1451, 1413, 1378, 1294, 1256, 1242, 1132, 1052, 982, 907, 839 and 754 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.89 (4H, s), 7.65-7.64 (8H, m), 7.57 (2H, m), 5.79 (4H, s, 2 x NH_2); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.5 (2 x C), 135.8 (2 x C), 130.2 (4 x CH), 130.1 (2 x C), 129.4 (2 x CH), 128.1 (2 x C), 125.6 (4 x CH), 125.1 (4 x CH); HRMS m/z 395.1744 ($M + H^+$), calcd for $C_{22}H_{19}N_8H$ 395.1733.



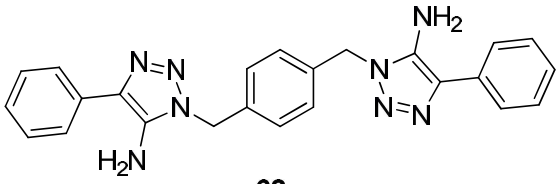
62pa

4,4'-(1,4-Phenylene)bis(1-benzyl-1*H*-1,2,3-triazol-5-amine) (62po): Prepared following the procedure **7.3** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp 220-222 °C; IR (neat): νmax 3390, 3326, 3210, 1640, 1588, 1538, 1361, 1251, 1117, 848 and 731 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.78 (4H, s), 7.39-7.35 (4H, m), 7.32-7.26 (6H, m), 5.85 (4H, s, 2 x NH_2), 5.48 (4H, s, 2 x ArCH_2N); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.5 (2 x C), 136.8 (2 x C), 130.2 (2 x C), 129.0 (4 x CH), 128.1 (2 x CH), 127.9 (4 x CH), 127.8 (2 x C), 125.0 (4 x CH), 48.9 (2 x CH_2); LRMS m/z 423.65 ($M + H^+$), calcd for $C_{24}H_{22}N_8H$ 423.2046.



62po

1,1'-(1,4-Phenylenebis(methylene))bis(4-phenyl-1*H*-1,2,3-triazol-5-amine) (62ar): Prepared following the procedure **7.3** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow solid. Mp 220-222 °C; IR (neat): ν_{max} 3321, 3213, 1644, 1589, 1548, 1521, 1273, 1254, 1120, 989, 910, 833, 800, 764, 752 and 716 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.74 (4H, d, *J* = 7.6 Hz), 7.39 (4H, t, *J* = 7.6 Hz), 7.25-7.20 (6H, m), 5.84 (4H, s, 2 x NH_2), 5.46 (4H, s, 2 x ArCH_2N); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.6 (2 x C), 136.2 (2 x C), 132.8 (2 x C), 128.9 (4 x CH), 128.1 (4 x CH), 127.8 (2 x C),



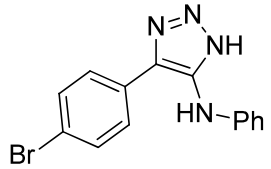
62ar

126.2 (2 x CH), 125.0 (4 x CH), 48.6 (2 x CH_2); HRMS m/z 423.2044 ($M + H^+$), calcd for $C_{24}H_{22}N_8H$ 423.2046.

7.5 General Procedure for the Dimroth Rearrangement of Triazoles 63ga and 63ja:

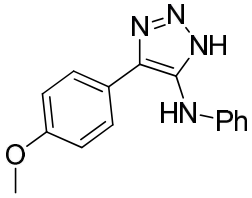
4-(4-Methoxyphenyl)-1-phenyl-1*H*-1,2,3-triazol-5-amine **3ga** (0.5 mmol) and toluene (2.0 ml) were added in a seal tube and resulting suspension was refluxed at 180 °C for 6 h. Pure product **63ga** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

4-(4-Bromophenyl)-N-phenyl-1*H*-1,2,3-triazol-5-amine (63ga): Prepared following the procedure **7.5** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp 140-142 °C; IR (neat): ν_{max} 3391, 3161, 2920, 1610, 1545, 1501, 1402, 1315, 1068, 1019, 986, 827, 756, 695 cm^{-1}; ^1H NMR (DMSO-d_6 + TFA (three drops), 400 MHz) δ 7.74 (2H, d, *J* = 8.4 Hz), 7.61 (2H, d, *J* = 8.8 Hz), 7.14 (2H, t, *J* = 7.6 Hz), 6.91 (2H, d, *J* = 7.6 Hz), 6.72 (1H, t, *J* = 7.2 Hz); ^{13}C NMR (DMSO-d_6 + TFA (three drops), DEPT-135) δ 145.4 (C), 143.5 (C), 135.3 (C), 132.2 (2 x CH), 130.1 (C), 129.5 (2 x CH), 128.8 (2 x CH), 121.5 (C), 119.3 (CH), 115.2 (2 x CH); HRMS m/z 315.0230 ($M + H^+$), calcd for $C_{14}H_{11}BrN_4H$ 315.0245.



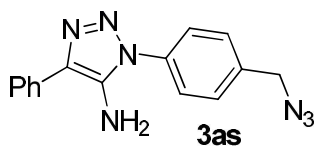
63ga

4-(4-Methoxyphenyl)-N-phenyl-1*H*-1,2,3-triazol-5-amine (63ja): Prepared following the procedure **7.5** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp 160-162 °C; IR (neat): ν_{max} 3409, 3168, 1598, 1552, 1497, 1463, 1322, 1252, 1181, 1020, 982, 837, 744 cm^{-1}; ^1H NMR (DMSO-d_6 + TFA (three drops), 400 MHz) δ 7.72 (2H, d, *J* = 8.4 Hz), 7.12 (2H, t, *J* = 7.6 Hz), 6.98 (2H, d, *J* = 8.4 Hz), 6.86 (2H, d, *J* = 7.6 Hz), 6.70 (1H, t, *J* = 7.2 Hz), 3.76 (3H, s, Ar-OC*H*$_3$); ^{13}C NMR (DMSO-d_6 + TFA (three drops), DEPT-135) δ 159.5 (C), 145.9 (C), 142.5 (C), 136.0 (C), 129.4 (2 x CH), 128.1 (2 x CH), 122.8 (C), 118.8 (CH), 114.8 (2 x CH), 114.6 (2 x CH), 55.6 (CH_3); HRMS m/z 267.1237 ($M + H^+$), calcd for $C_{15}H_{14}N_4OH$ 267.1246.



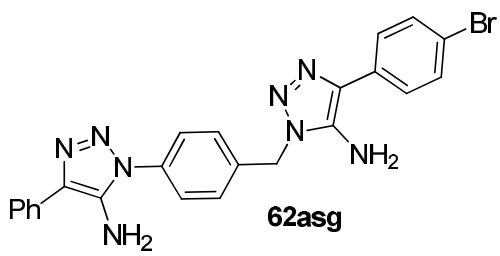
63ja

1-(4-(Azidomethyl)phenyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (3as): Prepared following the procedure **7.2** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp 125-127 °C; IR (neat): ν_{max} 3435, 3347, 3068, 2926, 2849, 2093, 1627, 1523, 1419, 1342, 986, 827, 767, 695 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.81 (2H, br d, *J* = 7.2 Hz), 7.67 (2H, d, *J* = 8.4 Hz), 7.62 (2H, d, *J* = 8.4 Hz), 7.45 (2H, t, *J* = 7.6 Hz), 7.27 (1H, t, *J* = 7.6 Hz), 5.82 (2H, s, NH_2), 4.60 (2H, s, Ar-CH_2N_3); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 139.7 (C), 137.0 (C), 135.5 (C), 132.3 (C), 130.0 (2 x CH), 129.1 (2 x CH), 128.2 (C), 126.6 (CH), 125.5 (2 x CH), 125.2 (2 x CH), 53.5 (CH_2); HRMS m/z 292.1301 ($M + H^+$), calcd for $C_{15}H_{13}N_7H$ 292.1311.



3as

1-(4-((5-Amino-4-(4-bromophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)phenyl)-4-phenyl-1H-1,2,3-triazol-5-amine (62asg):



62asg

Prepared following the procedure **7.3** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp 180-182 °C; IR (neat):ν_{max} 3384(br), 1636, 1603, 1519, 1374, 1270, 1175, 1048, 1023, 995, 823, 761 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.80 (2H, d, *J* = 7.6 Hz), 7.74 (2H, d, *J* = 8.4 Hz), 7.65 (2H, d, *J* = 8.0 Hz), 7.60 (2H, d, *J* = 8.0 Hz), 7.52 (2H, d, *J* = 8.0 Hz), 7.44 (2H, t, *J* = 7.6 Hz), 7.27 (1H, t, *J* = 7.2 Hz), 6.08 (2H, s, NH_2), 5.80 (2H, s, NH_2), 5.62 (2H, s, Ar-CH_2N); ^{13}C NMR (DMSO-d_6, DEPT-135) δ 140.1 (C), 139.7 (C), 137.4 (C), 135.3 (C), 132.3 (C), 132.0 (C), 131.9 (2 x CH), 129.3 (2 x CH), 129.1 (2 x CH), 128.1 (C), 127.0 (2 x CH), 126.8 (C), 126.6 (CH), 125.5 (2 x CH), 125.3 (2 x CH), 119.0 (C), 48.5 (CH_2); HRMS m/z 487.0983 ($M+H^+$), calcd for $C_{23}H_{19}N_8BrH$ 487.0994.

7.6 General procedure for the DBU-catalyzed domino [3+2]-cycloaddition reactions in DMSO:

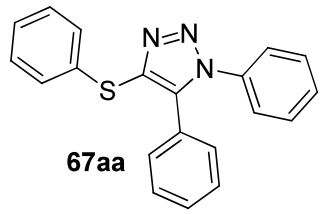
In an ordinary glass vial equipped with a magnetic stirring bar, to 0.05 mmol of DBU (**17b**) in DMSO (1.0 mL), was added 0.75 mmol of azide **2** and 0.5 mmol of 1-aryl-2-(arylthio)ethanones or 1-alkyl-2-(alkylthio)ethanones and the reaction mixture was stirred at 25 °C for 0.75-6.0 h. The crude reaction 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 domino products **67** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

7.7 General procedure for the DBU-catalyzed domino [3+2]-cycloaddition reactions in solvent-free conditions:

In an ordinary glass vial equipped with a magnetic stirring bar, to 0.05 mmol of DBU **17b** was added 0.75 mmol of azide **2** and 0.5 mmol of 1-aryl-2-(arylthio)ethanones or 1-alkyl-2-(alkylthio)ethanones and the reaction mixture was stirred at 25 °C for 0.75-6.0 h in solvent-free conditions. 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 domino products **67** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

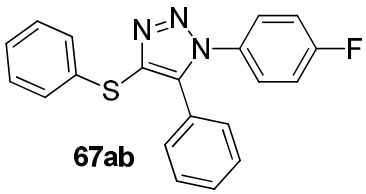
1,5-Diphenyl-4-(phenylthio)-1*H*-1,2,3-triazole (67aa):



67aa

Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 110-112 °C; IR (KBr): ν_{max} 1583, 1495, 1441, 1293, 1265, 1090, 1063, 997, 832, 772, 723 and 597 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.39 (3H, m), 7.37 (1H, m), 7.35-7.30 (4H, m), 7.30-7.22 (2H, m), 7.26-7.20 (2H, m), 7.20-7.15 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT-135) δ 140.1 (C), 136.8 (C), 136.5 (C), 135.8 (C), 129.7 (2 x CH), 129.5 (CH), 129.26 (2 x CH), 129.2 (CH), 128.97 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 126.5 (CH), 125.9 (C), 124.8 (2 x CH); HRMS m/z 330.1064 ($M + H^+$), calcd for $C_{20}H_{15}N_3SH$ 330.1065.

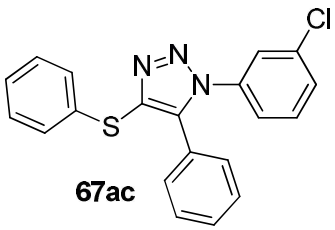
1-(4-Fluorophenyl)-5-phenyl-4-(phenylthio)-1*H*-1,2,3-triazole (67ab): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 106-108 °C; IR (KBr): ν_{max} 3063, 1895, 1600, 1583, 1501, 1479, 1298, 1265, 1145, 1073, 1002, 767, 832 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.30 (7H, m), 7.28-7.24 (2H, m), 7.21-7.18 (3H, m), 7.13-7.09 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 162.6 (C, d, J = 249.0 Hz,



67ab

C-F), 140.1 (C), 137.0 (C), 135.6 (C), 132.6 (C, d, *J* = 4.0 Hz), 129.73 (2 x CH), 129.71 (CH), 129.0 (2 x CH), 128.8 (2 x CH), 128.7 (2 x CH), 126.8 (2 x CH, d, *J* = 9.0 Hz), 126.6 (CH), 125.7 (C), 116.4 (2 x CH, d, *J* = 23.0 Hz); HRMS m/z 348.0970 ($M + H^+$), calcd for $C_{20}H_{14}FN_3SH$ 348.0971.

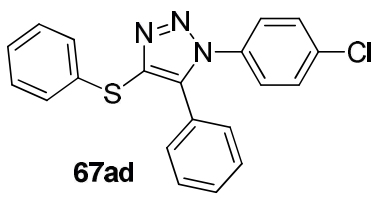
1-(3-Chlorophenyl)-5-phenyl-4-(phenylthio)-1*H*-1,2,3-triazole (67ac): Prepared following



67ac

the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow liquid. IR (KBr): ν_{max} 1901, 1578, 1495, 1463, 1441, 1271, 1095, 1057, 986, 832, 778, 739 and 547 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47(1H, t, *J* = 2.0 Hz), 7.45-7.41 (2H, m), 7.40-7.37 (2H, m), 7.34-7.28 (4H, m), 7.26-7.25 (1H, m), 7.22-7.18 (3H, m), 7.17-7.15 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 140.1 (C), 137.35 (C), 137.26 (C), 135.5 (C), 135.1 (C), 130.2 (CH), 129.9 (CH), 129.7 (2 x CH), 129.4 (CH), 129.1 (2 x CH), 128.78 (2 x CH), 128.76 (2 x CH), 126.6 (CH), 125.5 (C), 125.0 (CH), 122.8 (CH); HRMS m/z 364.0675 ($M + H^+$), calcd for $C_{20}H_{14}ClN_3SH$ 364.0675.

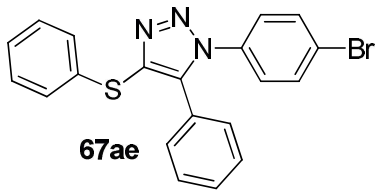
1-(4-Chlorophenyl)-5-phenyl-4-(phenylthio)-1*H*-1,2,3-triazole (67ad): Prepared following



67ad

the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 94-96 °C; IR (KBr) ν_{max} 3068, 2361, 1572, 1501, 1473, 1441, 1271, 1057, 991, 843, 734, 695 and 547 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.37 (5H, m), 7.32-7.26 (6H, m), 7.21-7.20 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 140.0 (C), 137.2 (C), 135.5 (C), 135.3 (C), 135.0 (C), 129.8 (CH), 129.7 (2 x CH), 129.6 (2 x CH), 129.1 (2 x CH), 128.8 (4 x CH), 126.7 (CH), 125.9 (2 x CH), 125.6 (C); HRMS m/z 364.0670 ($M + H^+$), calcd for $C_{20}H_{14}ClN_3SH$ 364.0675.

1-(4-Bromophenyl)-5-phenyl-4-(phenylthio)-1*H*-1,2,3-triazole (67ae): Prepared following

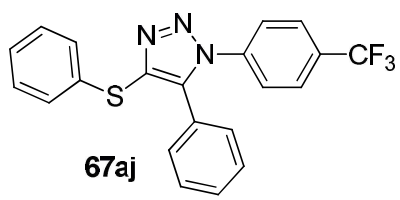


67ae

the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 128-130 °C; IR (KBr): 2356, 1572, 1490, 1473, 1435, 1298, 1265, 1057, 986, 827, 815, 690, 778 and 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (2H, br d, *J* = 8.8 Hz), 7.46-7.35 (3H, m), 7.33-

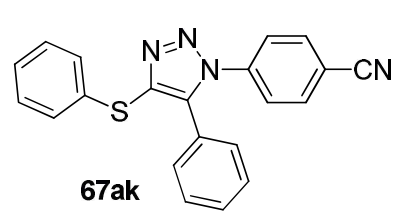
7.30 (2H, m), 7.28-7.26 (3H, m), 7.22-7.17 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 140.0 (C), 137.2 (C), 135.5 (C), 135.4 (C), 132.5 (2 x CH), 129.8 (CH), 129.7 (2 x CH), 129.0 (2 x CH), 128.8 (4 x CH), 126.6 (CH), 126.1 (2 x CH), 125.6 (C), 123.2 (C); HRMS m/z 408.0174 ($M + H^+$), calcd for $C_{20}H_{14}BrN_3SH$ 408.0170.

5-Phenyl-4-(phenylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67aj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 76-78 °C; IR (KBr): ν_{max} 3073, 1917, 1615, 1572, 1517, 1402, 1319, 1056, 991, 843, 744, 695, 525 and 432 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (2H, br d, *J* = 8.4 Hz), 7.51 (2H, br d, *J* = 8.4 Hz), 7.48-7.38 (3H, m), 7.34-7.31 (2H, m), 7.30-7.26 (2H, m), 7.23-7.19 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 140.0 (C), 139.2 (C), 137.8 (C), 135.3 (C), 131.1 (C, q, *J* = 34.0 Hz), 130.0 (CH), 129.7 (2 x CH), 129.1 (2 x CH), 129.0 (2 x CH), 128.9 (2 x CH), 126.8 (CH), 126.6 (2 x CH, q, *J* = 3.0 Hz), 125.5 (C), 124.8 (2 x CH), 123.4 (CF_3, q, *J* = 271.0 Hz); HRMS m/z 398.0940 ($M + H^+$), calcd for $C_{21}H_{14}F_3N_3SH$ 398.0939.



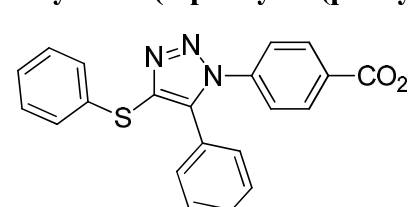
67aj

4-(5-Phenyl-4-(phenylthio)-1*H*-1,2,3-triazol-1-yl)benzonitrile (67ak): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow solid. Mp 104-106 °C; IR (KBr): ν_{max} 2241, 1605, 1578, 1506, 1473, 1271, 1073, 986, 849, 734, 695 and 575 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (2H, br d, *J* = 8.4 Hz), 7.48 (2H, br d, *J* = 8.4 Hz), 7.44-7.43 (1H, m), 7.40-7.37 (2H, br t, *J* = 8.4 Hz), 7.30-7.22 (4H, m), 7.20-7.17 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 139.9 (C), 139.6 (C), 138.1 (C), 135.0 (C), 133.3 (2 x CH), 130.1 (CH), 129.6 (2 x CH), 129.1 (4 x CH), 129.0 (2 x CH), 126.8 (CH), 125.3 (C), 124.9 (2 x CH), 117.5 (C), 113.0 (C, *C*N); HRMS m/z 355.1014 ($M + H^+$), calcd for $C_{21}H_{14}N_4SH$ 355.1017.



67ak

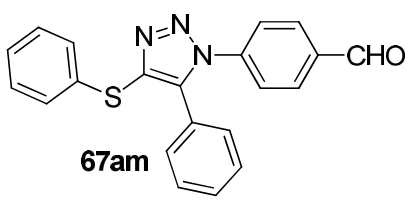
Ethyl 4-(5-phenyl-4-(phenylthio)-1*H*-1,2,3-triazol-1-yl)benzoate (67al): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 66-68 °C; IR (KBr): ν_{max} 1719, 1604, 1478, 1276, 1171, 1095, 859, 771, 700, 547



67al

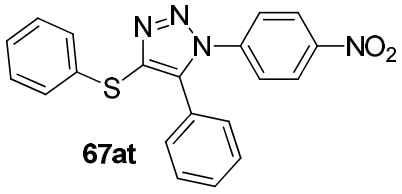
and 443 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (2H, d, *J* = 8.8 Hz), 7.43-7.39 (3H, m), 7.37-7.33 (2H, m), 7.31-7.28 (2H, m), 7.26-7.23 (2H, m), 7.20-7.17 (3H, m), 4.39 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 1.39 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.3 (C, O-*C*=O), 140.1 (C), 139.7 (C), 137.5 (C), 135.4 (C), 131.0 (C), 130.7 (2 x CH), 129.8 (CH), 129.7 (2 x CH), 129.0 (2 x CH), 128.82 (2 x CH), 128.79 (2 x CH), 126.7 (CH), 125.6 (C), 124.4 (2 x CH), 61.4 (CH_2, OCH_2CH_3), 14.2 (CH_3, OCH_2CH_3); HRMS m/z 402.1278 ($M + H^+$), calcd for $C_{23}H_{19}N_3O_2SH$ 402.1276.

4-(5-Phenyl-4-(phenylthio)-1*H*-1,2,3-triazol-1-yl)benzaldehyde (67am): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 98-100 °C; IR (KBr): ν_{max} 3057, 2728, 1704, 1600, 1578, 1473, 1293, 1200, 832, 739 and 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.06 (1H, s, *H*C=O), 7.94 (2H, br d, *J* = 8.4 Hz), 7.55 (2H, br d, *J* = 8.4 Hz), 7.47-7.43 (1H, m), 7.39 (2H, br t, *J* = 8.4 Hz), 7.33-7.31 (2H, m), 7.29-7.25 (2H, m), 7.22-7.19 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 190.7 (CH, H-*C*=O), 140.8 (C), 140.1 (C), 137.9 (C), 136.2 (C), 135.3 (C), 130.7 (2 x CH), 130.0 (CH), 129.7 (2 x CH), 129.1 (2 x CH), 129.0 (2 x CH), 128.9 (2 x CH), 126.8 (CH), 125.6 (C), 125.0 (2 x CH); HRMS m/z 358.1007 ($M + H^+$), calcd for $C_{21}H_{15}N_3OSH$ 358.1014.



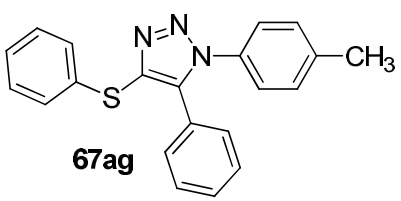
67am

1-(4-Nitrophenyl)-5-phenyl-4-(phenylthio)-1*H*-1,2,3-triazole (67at): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow solid. Mp 166-168 °C; IR (KBr): 3084, 1594, 1512, 1495, 1473, 1347, 1276, 1063, 854, 745, 684 and 542 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.28 (2H, d, *J* = 8.4 Hz), 7.57 (2H, d, *J* = 8.8 Hz), 7.50-7.47 (1H, m), 7.44-7.40 (2H, m), 7.33-7.31 (2H, m), 7.29-7.25 (2H, m), 7.23-7.21 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 147.4 (C), 141.0 (C), 140.0 (C), 138.3 (C), 134.9 (C), 130.2 (CH), 129.6 (2 x CH), 129.1 (4 x CH), 129.0 (2 x CH), 126.9 (CH), 125.2 (C), 125.0 (2 x CH), 124.8 (2 x CH); HRMS m/z 375.0911 ($M + H^+$), calcd for $C_{20}H_{14}N_4O_2SH$ 375.0916.



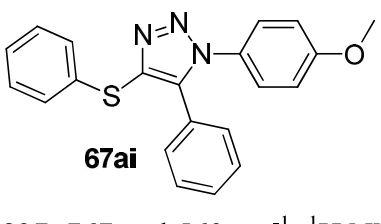
67at

5-Phenyl-4-(phenylthio)-1-(p-tolyl)-1*H*-1,2,3-triazole (67ag): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 108-110 °C; IR (KBr): 3068, 1572, 1512, 1468, 1441, 1271, 1057, 986, 821, 766, 701 and 575 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.15 (14H, m), 2.39 (3H, s, Ar-C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 140.1 (C), 139.4 (C), 136.5 (C), 135.9 (C), 134.0 (C), 129.8 (2 x CH), 129.7 (2 x CH), 129.4 (CH), 128.9 (2 x CH), 128.50 (2 x CH), 128.46 (2 x CH), 126.4 (CH), 126.0 (C), 124.6 (2 x CH), 21.1 (CH_3); HRMS m/z 344.1222 ($M + H^+$), calcd for $C_{21}H_{17}N_3SH$ 344.1221.



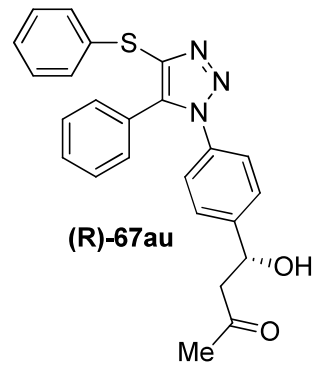
67ag

1-(4-Methoxyphenyl)-5-phenyl-4-(phenylthio)-1*H*-1,2,3-triazole (67ai): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 76-78 °C; IR (KBr): ν_{max} 3052, 2964, 2920, 2832, 1895, 1610, 1578, 1512, 1479, 1304, 1249, 1172, 1068, 827, 767 and 569 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.21 (9H, m), 7.20-7.13 (3H, m), 6.88 (2H, d, *J* = 8.8 Hz), 3.81 (3H, s, OC*H*$_3$); ^{13}C NMR ($CDCl_3$ DEPT-135) δ 160.0 (C), 140.1 (C), 136.4 (C), 135.9 (C), 129.7 (2 x CH), 129.49 (C), 129.45 (CH), 129.0 (2 x CH), 128.54 (2 x CH), 128.47 (2 x CH), 126.4 (CH), 126.2 (2 x CH), 126.0 (C), 114.4 (2 x CH), 55.5 (CH_3, O*C*H$_3$); HRMS m/z 360.1172 ($M + H^+$), calcd for $C_{21}H_{17}N_3OSH$ 360.1171.



67ai

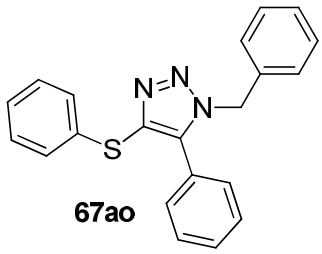
(*R*)-4-Hydroxy-4-(4-(5-phenyl-4-(phenylthio)-1*H*-1,2,3-triazol-1-yl)phenyl)butan-2-one (67au): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and isolated as a white semi-solid. **$[\alpha]_D^{25}$ = +17.5° (*c* = 0.42 g/100 mL, $CHCl_3$, 69% *ee*)**; IR (KBr): ν_{max} 3430 (br), 1704, 1578, 1521, 1473, 1358, 1265, 1161, 1068, 1002, 838, 772, 734, 695, 515 and 454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.36 (3H, m), 7.33-7.30 (3H, m), 7.29-7.26 (3H, m), 7.25-7.22 (2H, m), 7.18-7.15 (3H, m), 5.18 (1H, t, *J* = 6.5 Hz), 3.68 (1H, br s, O*H*), 2.83 (2H, br d, *J* = 6.0 Hz), 2.19 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$ DEPT-135) δ 208.7 (C, C=O), 144.1 (C), 140.1 (C), 136.9 (C), 135.71 (C), 135.68 (C), 129.7 (2 x CH), 129.6 (CH), 129.0 (2 x CH), 128.7 (2 x CH), 128.6 (2 x CH),



(R)-67au

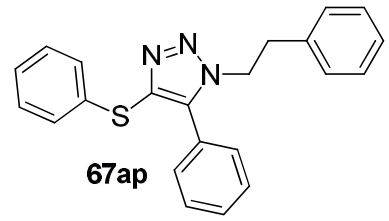
126.55 (2 x CH), 126.52 (CH), 125.8 (C), 124.9 (2 x CH), 69.1 (CH), 51.7 (CH_2), 30.7 (CH_3); HRMS m/z 416.1433 ($M + H^+$), calcd for $C_{24}H_{21}N_3O_2SH$ 416.1433.

1-Benzyl-5-phenyl-4-(phenylthio)-1*H*-1,2,3-triazole (67ao): Prepared following the procedure **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow oily liquid. IR (KBr): 2920, 2854, 1742, 1578, 1479, 1452, 1238, 1068, 1030, 750, 684 and 547 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.43 (1H, tt, *J* = 6.5, 1.5 Hz), 7.37 (2H, tt, *J* = 6.5, 1.5 Hz), 7.28-7.25 (3H, m), 7.22-7.17 (4H, m), 7.15-7.12 (3H, m), 7.07-7.04 (2H, m), 5.49 (2H, s, NC*H*$_2$Ph); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 141.0 (C), 136.4 (C), 136.1 (C), 134.97 (C), 129.8 (CH), 129.6 (2 x CH), 128.9 (2 x CH), 128.8 (2 x CH), 128.7 (2 x CH), 128.34 (2 x CH), 128.3 (CH), 127.3 (2 x CH), 126.3 (CH), 125.9 (C), 52.8 (CH_2); HRMS m/z 344.1222 ($M + H^+$), calcd for $C_{21}H_{17}N_3SH$ 344.1221.



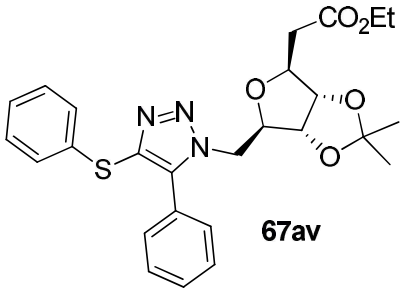
67ao

1-Phenethyl-5-phenyl-4-(phenylthio)-1*H*-1,2,3-triazole (67ap): Prepared following the procedure **7.7** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. IR (KBr): ν_{max} 3063, 2920, 2849, 1742, 1578, 1473, 1441, 1271, 1238, 1068, 931, 750, 690 and 536 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.39 (1H, m), 7.35-7.31 (2H, m), 7.22-7.13 (6H, m), 7.11-7.08 (2H, m), 6.90-6.88 (2H, m), 6.86-6.84 (2H, m), 4.50 (2H, t, *J* = 6.8 Hz, NC*H*$_2$CH$_2$Ph), 3.18 (2H, t, *J* = 6.8 Hz, NCH$_2$C*H*$_2$Ph); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 141.6 (C), 136.8 (C), 136.4 (C), 135.6 (C), 129.6 (CH), 129.4 (2 x CH), 128.9 (2 x CH), 128.72 (2 x CH), 128.67 (4 x CH), 128.0 (2 x CH), 127.0 (CH), 126.1 (CH), 125.8 (C), 50.2 (CH_2, NCH$_2$CH$_2$Ph), 36.3 (CH_2, NCH$_2$*C*H$_2$Ph); HRMS m/z 358.1374 ($M + H^+$), calcd for $C_{22}H_{19}N_3SH$ 358.1378.



67ap

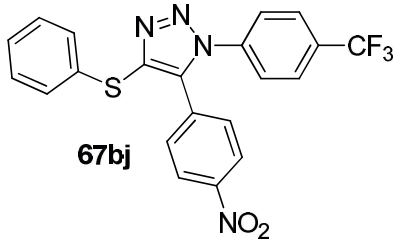
Ethyl-2-((1S,3S,3aS,6aR)-5,5-dimethyl-3-((5-phenyl-4-(phenylthio)-1*H*-1,2,3-triazol-1-yl)methyl)hexahydro-1*H*-cyclopenta[c]furan-1-yl)acetate (67av):



67av

Prepared following the procedure **7.7** and purified by column chromatography using EtOAc/hexane and isolated as a colourless oily liquid. **$[\alpha]_D^{25}$ = +24.7° (*c* = 0.33 g/100 mL, $CHCl_3$, >99% *ee***); IR (KBr): ν_{max} 3063, 2991, 2969, 2931, 1726, 1616, 1583, 1479, 1435, 1380, 1315, 1156, 898, 832, 783, 734 and 526 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.46-7.45 (3H, m), 7.33-7.31 (2H, m), 7.22-7.11 (5H, m), 4.88 (1H, d, *J* = 6.5 Hz), 4.72 (1H, dd, *J* = 6.0, 3.5 Hz), 4.44-4.32 (3H, m), 4.16-4.05 (2H, m, OCH_2CH_3), 3.69 (1H, dt, *J* = 7.0, 4.0 Hz), 2.67 (1H, dd, *J* = 16.5, 7.0 Hz), 2.51 (1H, dd, *J* = 17.0, 6.5 Hz), 1.43 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.23 (3H, t, *J* = 7.5 Hz, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT-135) δ 170.5 (C, O-*C*=O), 141.8 (C), 136.4 (C), 135.9 (C), 129.9 (CH), 129.7 (2 x CH), 128.9 (4 x CH), 128.4 (2 x CH), 126.3 (CH), 125.9 (C), 113.0 (C, O-*C*-O), 83.3 (CH), 82.4 (CH), 81.0 (CH), 77.2 (CH), 60.6 (CH_2, OCH_2CH_3), 48.7 (CH_2), 34.2 (CH_2), 26.1 (CH_3), 24.9 (CH_3), 14.1 (CH_3, OCH_2CH_3); HRMS m/z 496.1907 ($M + H^+$), calcd for $C_{26}H_{29}N_3O_5SH$ 496.1906.

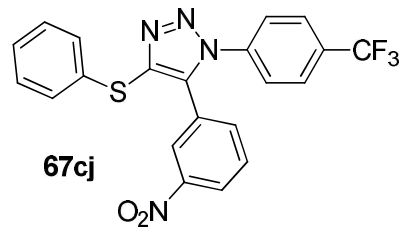
5-(4-Nitrophenyl)-4-(phenylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67bj):



67bj

Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp 110-112 °C; IR (KBr): ν_{max} 1610, 1528, 1342, 1315, 1167, 1123, 1063, 854, 843, 734 and 679 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.25 (2H, br d, *J* = 8.8 Hz), 7.74 (2H, br d, *J* = 8.4 Hz), 7.49 (2H, br d, *J* = 8.4 Hz), 7.41 (2H, td, *J* = 8.8, 2.0 Hz), 7.35-7.24 (5H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 148.3 (C), 139.1 (C), 138.6 (C), 137.5 (C), 134.2 (C), 131.9 (C), 131.8 (C, q, *J* = 33.0 Hz), 130.8 (2 x CH), 129.34 (2 x CH), 129.30 (2 x CH), 127.3 (CH), 127.0 (2 x CH, q, *J* = 4.0 Hz), 125.0 (2 x CH), 124.0 (2 x CH), 123.2 (CF_3, q, *J* = 271.0 Hz); HRMS m/z 443.0781 ($M + H^+$), calcd for $C_{21}H_{13}F_3N_4O_2SH$ 443.0790.

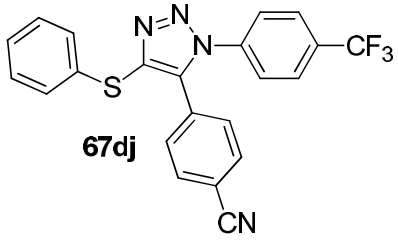
5-(3-Nitrophenyl)-4-(phenylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67cj):



67cj

Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a off white solid. Mp 126-128 °C; IR (KBr): ν_{max} 3063, 1786, 1676, 1610, 1567, 1402, 1320, 1063, 1008, 838, 794, 739, 690 and 619 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.29 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz), 8.15 (1H, t, *J* = 2.0 Hz), 7. 73 (2H, br d, *J* = 8.0 Hz), 7.59 (1H, t, *J* = 8.0 Hz), 7.50 (2H, br d, *J* = 8.5 Hz), 7.45 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz), 7.37-7.35 (2H, m), 7.31-7.27 (2H, m), 7.26-7.22 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 148.3 (C), 139.3 (C), 138.6 (C), 137.3 (C), 135.3 (CH), 134.1 (C), 131.8 (C, q, *J* = 33.75 Hz), 130.1 (CH), 129.7 (2 x CH), 129.3 (2 x CH), 127.42 (CH), 127.38 (C), 127.0 (2 x CH, q, *J* = 3.7 Hz), 125.0 (2 x CH), 124.8 (CH), 124.6 (CH), 123.2 (CF_3, q, *J* = 270.0 Hz); HRMS m/z 443.0792 ($M + H^+$), calcd for $C_{21}H_{13}F_3N_4O_2SH$ 443.0790.

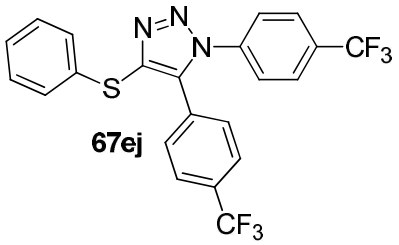
4-(4-(Phenylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-5-yl)benzonitrile



67dj

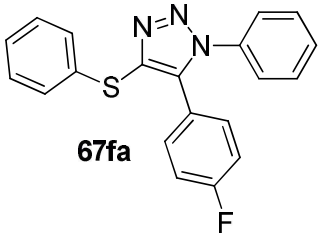
(67dj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow oily liquid. IR (KBr): ν_{max} 3079, 2235, 1928, 1616, 1578, 1512, 1473, 1315, 1024, 986, 832, 728, 619, 569, 547 and 471 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (2H, br d, *J* = 8.4 Hz), 7.67 (2H, br d, *J* = 8.8 Hz), 7.46 (2H, br d, *J* = 8.4 Hz), 7.34-7.20 (7H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 139.0 (C), 138.7 (C), 137.8 (C), 134.3 (C), 132.5 (2 x CH), 131.8 (C, q, *J* = 33.0 Hz), 130.4 (2 x CH), 130.2 (C), 129.4 (2 x CH), 129.3 (2 x CH), 127.3 (CH), 126.9 (2 x CH, q, *J* = 4.0 Hz), 124.9 (2 x CH), 123.2 (CF_3, q, *J* = 270.8 Hz), 117.7 (C), 113.8 (C, *C*N); HRMS m/z 423.0898 ($M + H^+$), calcd for $C_{22}H_{13}N_4F_3SH$ 423.0891.

4-(Phenylthio)-1,5-bis(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67ej): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 80-82 °C; IR (KBr): ν_{max} 3046, 2920, 1715, 1616, 1578, 1512, 1479, 1315, 1019, 997, 838, 635 and 591 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (2H, d, *J* = 6.8 Hz), 7.65 (2H, d, *J* = 6.8 Hz), 7.47 (2H, d, *J* = 6.8 Hz), 7.33-7.03 (4H, m), 7.28-7.25 (2H, m), 7.23-7.20 (1H, m); ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT-135) δ 138.8 (C), 138.7 (C), 138.4 (C), 134.6 (C), 131.85 (C, q, *J* = 33.0 Hz), 131.6 (C, q, *J* = 33.0 Hz), 130.2 (2 x CH), 129.3 (C), 129.2 (4 x CH), 127.1 (CH), 126.8 (2 x CH, q, *J* = 3.75 Hz), 125.9 (2 x CH, q, *J* = 3.75 Hz), 124.9 (2 x CH), 123.3 (CF_3, q, *J* = 271.25 Hz), 123.5 (CF_3, q, *J* = 270.0 Hz); HRMS m/z 466.0813 ($M + H^+$), calcd for $C_{22}H_{13}F_6N_3SH$ 466.0813.



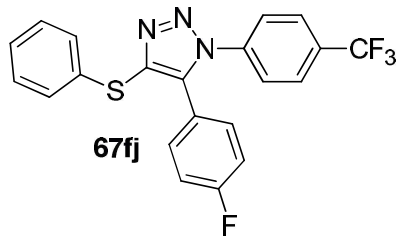
67ej

5-(4-Fluorophenyl)-1-phenyl-4-(phenylthio)-1*H*-1,2,3-triazole (67fa): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and isolated as a yellow liquid. IR (KBr): ν_{max} 3057, 2920, 2843, 1731, 1594, 1539, 1484, 1260, 1216, 1068, 920, 849, 767 and 684 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.30 (3H, m), 7.24-7.12 (6H, m), 7.09-7.05 (3H, m), 6.91 (2H, t, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 163.1 (C, d, *J* = 249.7 Hz, *C*-F), 139.2 (C), 136.7 (C), 136.2 (C), 135.5 (C), 131.7 (2 x CH, d, *J* = 9.0 Hz), 129.35 (CH), 129.34 (2 x CH), 129.0 (2 x CH), 128.4 (2 x CH), 126.5 (CH), 124.8 (2 x CH), 121.8 (C, d, *J* = 3.0 Hz), 115.9 (2 x CH, d, *J* = 21.0 Hz); HRMS m/z 348.0974, ($M + H^+$), calcd for $C_{20}H_{14}FN_3SH$ 348.0971.



67fa

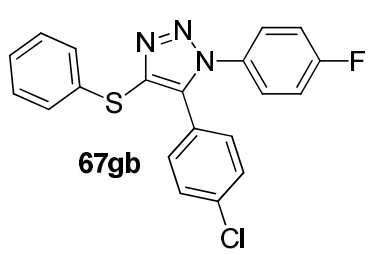
5-(4-Fluorophenyl)-4-(phenylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67fj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 52-54 °C; IR (KBr): ν_{max} 3057, 2926, 1616, 1545, 1484, 1430, 1331, 1232, 1156, 1117, 1057, 838, 761, 734 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (2H, d, *J* = 8.8 Hz), 7.48 (2H, d, *J* = 8.4 Hz), 7.30-7.23 (4H, m), 7.20-7.16 (3H, m), 7.09-7.05 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 163.4 (C, d, *J* = 250.5 Hz), 139.1 (C), 139.0 (C), 137.8 (C), 135.0 (C), 131.8 (2 x CH, d, *J* = 8.0 Hz), 131.3



67fj

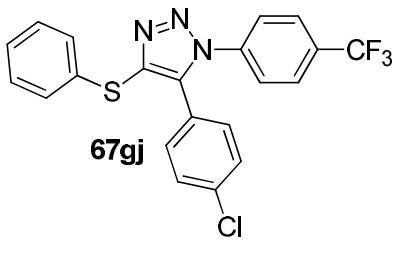
(C, q, *J* = 32.0 Hz), 129.1 (2 x CH), 128.9 (2 x CH), 126.8 (CH), 126.6 (2 x CH, q, *J* = 4.0 Hz), 124.8 (2 x CH), 123.3 (CF_3, q, *J* = 271.0 Hz), 121.5 (C, d, *J* = 3.0 Hz), 116.3 (2 x CH, d, *J* = 22.0 Hz); HRMS m/z 416.0845 ($M + H^+$), calcd for $C_{21}H_{13}F_4N_3SH$ 416.0845.

5-(4-Chlorophenyl)-1-(4-fluorophenyl)-4-(phenylthio)-1*H*-1,2,3-triazole (67gb): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a colourless oily liquid. IR (KBr): ν_{max} 3063, 2915, 2849, 2356, 1512, 1463, 1227, 1150, 1090, 997, 838, 750, 684 and 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.25 (8H, m), 7.22-7.18 (1H, m), 7.17-7.11 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 162.7 (C, d, *J* = 250.0 Hz), 139.0 (C), 137.3 (C), 136.0 (C), 135.3 (C), 132.4 (C, d, *J* = 3.0 Hz), 131.0 (2 x CH), 129.1 (4 x CH), 128.8 (2 x CH), 126.79 (2 x CH, d, *J* = 8.0 Hz), 126.77 (CH), 124.1 (C), 116.6 (2 x CH, d, *J* = 23.0 Hz); HRMS m/z 382.0580 ($M + H^+$), calcd for $C_{20}H_{13}ClFN_3SH$ 382.0581.



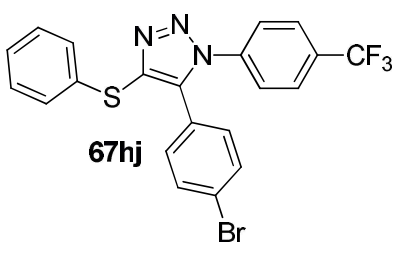
67gb

5-(4-Chlorophenyl)-4-(phenylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67gj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a colourless viscous liquid; IR (KBr): ν_{max} 3079, 3057, 2854, 1912, 1736, 1616, 1578, 1479, 1265, 1019, 838, 695 and 526 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (2H, d, *J* = 8.4 Hz), 7.48 (2H, d, *J* = 8.4 Hz), 7.35 (2H, br d, *J* = 8.8 Hz), 7.30-7.23 (4H, m), 7.21-7.18 (1H, m), 7.13 (2H, br d, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 138.9 (2 x C), 138.0 (C), 136.3 (C), 134.9 (C), 131.3 (C, q, *J* = 33.0 Hz), 131.0 (2 x CH), 129.3 (2 x CH), 129.1 (2 x CH), 129.0 (2 x CH), 126.9 (CH), 126.7 (2 x CH, q, *J* = 4.0 Hz), 124.8 (2 x CH), 123.9 (C), 123.3 (CF_3, q, *J* = 271.0 Hz); HRMS m/z 432.0544 ($M + H^+$), calcd for $C_{21}H_{13}ClF_3N_3SH$ 432.0549.



67gj

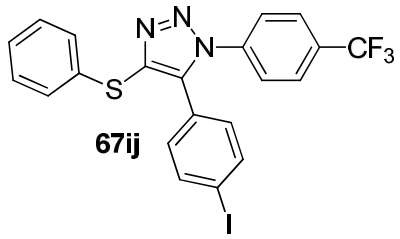
5-(4-Bromophenyl)-4-(phenylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67hj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow oily liquid. IR (KBr): ν_{max} 3068, 2920, 2843, 1616, 1528, 1320, 1161, 1123, 1057, 980, 832, 750, 684 and 531 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ



67hj

7.69 (2H, br d, *J* = 8.4 Hz), 7.52-7.47 (4H, m), 7.30-7.22 (4H, m), 7.21-7.16 (1H, m), 7.09 (2H, br d, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 138.88 (C), 138.86 (C), 137.9 (C), 134.9 (C), 132.2 (2 x CH), 131.3 (C, q, *J* = 33.0 Hz), 131.1 (2 x CH), 129.1 (2 x CH), 129.0 (2 x CH), 126.9 (CH), 126.7 (2 x CH, q, *J* = 4.0 Hz), 124.8 (2 x CH), 124.6 (C), 124.4 (C), 123.3 (CF_3, q, *J* = 271.0 Hz); HRMS m/z 476.0045 ($M + H^+$), calcd for $C_{21}H_{13}BrF_3N_3SH$ 476.0044.

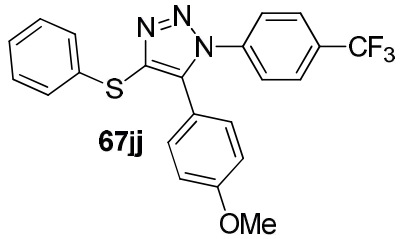
5-(4-Iodophenyl)-4-(phenylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67ij):



67ij

Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 80-82 °C; IR (KBr): ν_{max} 3846, 2915, 2356, 1610, 1583, 1528, 1468, 1320, 1271, 1117, 1002, 986, 849, 821, 690 and 619 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75-7.71 (4H, m), 7.50 (2H, br d, *J* = 8.4 Hz), 7.33-7.20 (5H, m), 6.93 (2H, br d, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 139.0 (C), 138.9 (C), 138.2 (2 x CH), 138.0 (C), 134.9 (C), 131.4 (C, q, *J* = 33.0 Hz), 131.2 (2 x CH), 129.2 (2 x CH), 129.1 (2 x CH), 127.0 (CH), 126.7 (2 x CH, q, *J* = 4.0 Hz), 125.0 (C), 124.8 (2 x CH), 123.3 (CF_3, q, *J* = 271.0 Hz), 96.6 (C, *C*-I); HRMS m/z 523.9901 ($M + H^+$), calcd for $C_{21}H_{13}F_3IN_3SH$ 523.9905.

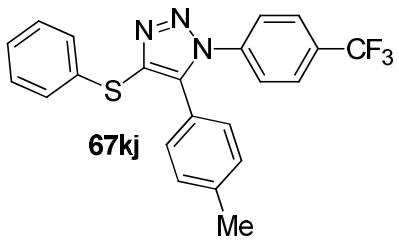
5-(4-Methoxyphenyl)-4-(phenylthio)-1-(4-(trifluoromethyl)phenyl)-*1H*-1,2,3-triazole



67jj

(67jj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp. 90-95 °C; IR (KBr): ν_{max} 1616, 1490, 1320, 1161, 1123, 986, 849, 597, 504 and 443 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (2H, d, *J* = 8.4 Hz), 7.51 (2H, d, *J* = 8.4 Hz), 7.33-7.25 (4H, m), 7.22-7.18 (1H, m), 7.14 (2H, br d, *J* = 8.8 Hz), 6.91 (2H, br d, *J* = 8.8 Hz), 3.84 (3H, s, OC*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 160.7 (C), 140.1 (C), 139.3 (C), 137.2 (C), 135.6 (C), 131.07 (C, q, *J* = 34.0 Hz), 131.14 (2 x CH), 129.1 (2 x CH), 128.7 (2 x CH), 126.7 (CH), 126.6 (2 x CH, q, *J* = 4.0 Hz), 124.8 (2 x CH), 123.4 (CF_3, q, *J* = 271.0 Hz), 117.4 (C), 114.4 (2 x CH), 55.3 (CH_3); HRMS m/z 428.1047 ($M + H^+$), calcd for $C_{22}H_{16}F_3N_3OSH$ 428.1044.

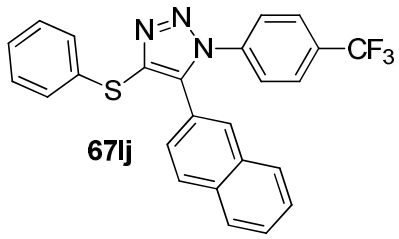
4-(Phenylthio)-5-(*p*-tolyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67kj):



67kj

Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow solid. Mp 66-68 °C; IR (KBr): ν_{max} 3079, 2926, 1616, 1578, 1479, 1413, 1315, 1172, 1123, 843, 810, 739, 684, 613 and 536 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.66 (2H, d, *J* = 8.4 Hz), 7.49 (2H, d, *J* = 8.0 Hz), 7.31-7.28 (2H, m), 7.26-7.22 (2H, m), 7.19-7.16 (3H, m), 7.07 (2H, d, *J* = 8.0 Hz), 2.36 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 140.2 (2 x C), 139.3 (C), 137.4 (C), 135.5 (C), 131.0 (C, q, *J* = 33.0 Hz), 129.63 (2 x CH), 129.56 (2 x CH), 129.0 (2 x CH), 128.8 (2 x CH), 126.6 (CH), 126.5 (2 x CH, q, *J* = 3.0 Hz), 124.8 (2 x CH), 123.4 (C, q, *J* = 272.0 Hz), 122.4 (C), 21.3 (CH_3); HRMS m/z 412.1087 ($M + H^+$), calcd for $C_{22}H_{16}F_3N_3SH$ 412.1095.

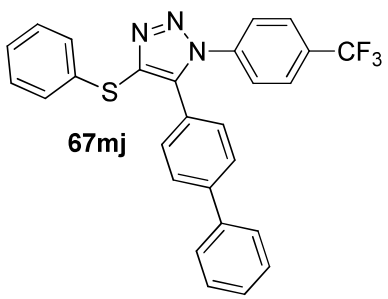
5-(Naphthalen-2-yl)-4-(phenylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole



67lj

(67lj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a off white solid. Mp 80-82 °C; IR (KBr): ν_{max} 3063, 1610, 1583, 1517, 1479, 1320, 1172, 1128, 1063, 909, 849, 750, 679, 591 and 531 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.84 (1H, d, *J* = 8.0 Hz), 7.80 (1H, d, *J* = 8.8 Hz), 7.76-7.33 (2H, m), 7.64 (2H, d, *J* = 8.8 Hz), 7.59-7.50 (4H, m), 7.35-7.33 (2H, m), 7.28-7.24 (2H, m), 7.22-7.17 (1H, m), 7.12 (1H, dd, *J* = 8.4, 1.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 140.0 (C), 139.2 (C), 138.2 (C), 135.4 (C), 133.4 (C), 132.8 (C), 131.1 (C, q, *J* = 33.0 Hz), 130.2 (CH), 129.2 (2 x CH), 129.1 (2 x CH), 128.7 (CH), 128.4 (CH), 127.8 (CH), 127.7 (CH) 127.0 (CH), 126.9 (CH), 126.6 (2 x CH, q, *J* = 4.0 Hz), 125.9 (CH), 124.7 (2 x CH), 123.4 (CF_3, q, *J* = 270.0 Hz), 122.8 (C); HRMS m/z 448.1100 ($M + H^+$), calcd for $C_{25}H_{16}F_3N_3SH$ 448.1095.

5-([1,1'-Biphenyl]-4-yl)-4-(phenylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol

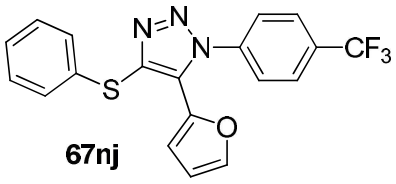


67mj

(67mj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow oily liquid. IR (KBr): ν_{max} 2926, 2860, 1742, 1616, 1578, 1517, 1479, 1424, 1320, 1161, 1106, 843, 772, 728 and 679 cm^{-1}; ^1H NMR ($CDCl_3$,

400 MHz) δ 7.72 (2H, d, *J* = 8.4 Hz), 7.64-7.61 (4H, m), 7.56 (2H, d, *J* = 8.4 Hz), 7.50-7.46 (2H, m), 7.42-7.35 (3H, m), 7.31-7.27 (4H, m), 7.24-7.20 (1H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 142.7 (C), 139.8 (C), 139.6 (C), 139.2 (C), 137.8 (C), 135.3 (C), 131.2 (C, q, *J* = 33.0 Hz), 130.1 (2 x CH), 129.1 (2 x CH), 129.0 (2 x CH), 128.9 (2 x CH), 128.1 (CH), 127.5 (2 x CH), 127.0 (2 x CH), 126.8 (CH), 126.6 (2 x CH, q, *J* = 4.0 Hz), 124.9 (2 x CH), 124.2 (C), 123.4 (CF_3, q, *J* = 271.0 Hz); HRMS m/z 474.1254 (M + H^+), calcd for $C_{27}H_{18}F_3N_3SH$ 474.1252.

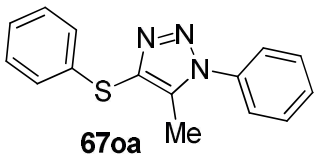
5-(Furan-2-yl)-4-(phenylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67nj):



67nj

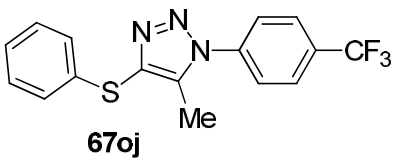
Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a off white solid. Mp. 104-106 °C; IR (KBr): ν_{max} 1615, 1521, 1478, 1322, 1168, 1127, 1060, 1023, 995, 898, 845 and 744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (2H, d, *J* = 8.5 Hz), 7.59 (2H, d, *J* = 8.5 Hz), 7.40-7.35 (3H, m), 7.30-7.27 (2H, m), 7.23-7.20 (1H, m), 6.84 (1H, d, *J* = 3.5 Hz), 6.49 (1H, dd, *J* = 3.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 144.5 (CH), 139.7 (C), 139.3 (C), 136.9 (C), 134.5 (C), 131.6 (C, q, *J* = 33.75 Hz), 131.2 (C), 129.2 (2 x CH), 129.0 (2 x CH), 126.9 (CH), 126.4 (2 x CH, q, *J* = 3.75 Hz), 125.2 (2 x CH), 123.5 (C, q, *J* = 270.0 Hz), 114.2 (CH), 111.9 (CH); HRMS m/z 388.0736 (M + H^+), calcd for $C_{19}H_{12}F_3N_3OSH$ 388.0731.

5-Methyl-1-phenyl-4-(phenylthio)-1*H*-1,2,3-triazole (67oa): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 50-52 °C; IR (KBr): 3084, 2361, 1616, 1578, 1473, 1419, 1326, 1260, 1002, 849, 745, 690 and 613 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.59-7.47 (5H, m), 7.30-7.24 (4H, m), 7.19-7.15 (1H, m), 2.36 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 137.7 (C), 136.4 (C), 136.2 (C), 135.8 (C), 129.65 (CH), 129.58 (2 x CH), 129.0 (2 x CH), 128.1 (2 x CH), 126.3 (CH), 124.7 (2 x CH), 9.4 (CH_3); HRMS m/z 290.0728 (M + Na^+), calcd for $C_{15}H_{13}N_3SNa$ 290.0728.



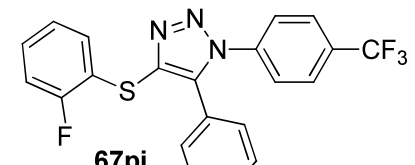
67oa

5-Methyl-4-(phenylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67oj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a light yellow semi-solid. IR (KBr): 3084, 2361, 1616, 1578, 1517, 1419, 1326, 1260, 1052, 849, 827, 690 and 613 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.83 (2H, d, *J* = 8.5 Hz), 7.68 (2H, d, *J* = 8.0 Hz), 7.30-7.23 (4H, m), 7.19-7.16 (1H, m), 2.42 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 139.1 (C), 137.5 (C), 137.0 (C), 135.3 (C), 131.5 (C, q, *J* = 32.5 Hz), 129.0 (2 x CH), 128.3 (2 x CH), 126.8 (2 x CH, q, *J* = 2.5 Hz), 126.5 (CH), 124.7 (2 x CH), 123.4 (CF_3, q, *J* = 271.2 Hz), 9.4 (CH_3); HRMS m/z 358.0594 ($M + Na^+$), calcd for $C_{16}H_{12}F_3N_3SNa$ 358.0602.



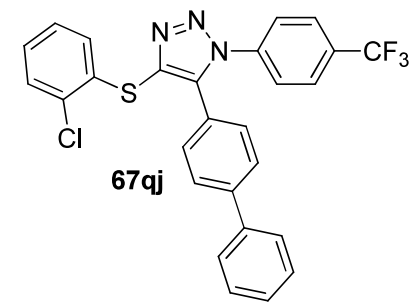
67oj

5-([1,1'-Biphenyl]-4-yl)-4-((2-fluorophenyl)thio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67pj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 98-100 °C; IR (KBr): ν_{max} 1615, 1472, 1322, 1220, 1169, 1128, 1060, 990, 844, 753 and 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70 (2H, d, *J* = 8.8 Hz), 7.62-7.58 (4H, m), 7.53 (2H, d, *J* = 8.4 Hz), 7.47-7.43 (2H, m), 7.39-7.35 (1H, m), 7.32-7.27 (3H, m), 7.23-7.18 (1H, m), 7.07-7.01 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 160.2 (C, d, *J* = 246.0 Hz), 142.7 (C), 139.54 (C), 139.52 (C), 139.1 (C), 136.5 (C), 131.5 (CH), 131.2 (C, q, *J* = 33.0 Hz), 130.0 (2 x CH), 128.92 (2 x CH), 128.94 (CH, d, *J* = 8.0 Hz), 128.1 (CH), 127.5 (2 x CH), 127.0 (2 x CH), 126.6 (2 x CH, q, *J* = 38.0 Hz), 124.9 (2 x CH), 124.7 (CH, d, *J* = 3.6 Hz), 124.0 (C), 123.4 (CF_3, q, *J* = 270.0 Hz), 122.0 (C, d, *J* = 17.0 Hz), 115.8 (CH, d, *J* = 22.0 Hz); HRMS m/z 492.1158 ($M + H^+$), calcd for $C_{27}H_{17}F_4N_3SH$ 492.1158.



67pj

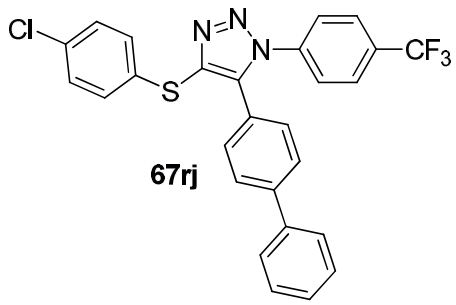
5-([1,1'-Biphenyl]-4-yl)-4-((2-chlorophenyl)thio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol (67qj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 156-158 °C; IR (KBr): ν_{max} 1615, 1478, 1450, 1322, 1169, 1128, 1109, 1060, 1031, 996, 843, 752 and 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (2H, d, *J* = 8.4 Hz), 7.61-



67qj

7.55 (6H, m), 7.46-7.42 (2H, m), 7.39-7.33 (2H, m), 7.26 (2H, br d, *J* = 8.8 Hz), 7.15-7.07 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 142.8 (C), 140.6 (C), 139.5 (C), 139.2 (C), 135.9 (C), 135.1 (C), 132.0 (C), 131.3 (C, q, *J* = 33.0 Hz), 130.0 (2 x CH), 129.8 (CH), 128.9 (2 x CH), 128.6 (CH), 128.1 (CH), 127.6 (2 x CH), 127.3 (CH), 127.2 (CH), 127.0 (2 x CH), 126.7 (2 x CH, q, *J* = 3.0 Hz), 124.9 (2 x CH), 123.8 (C), 123.4 (CF_3, q, *J* = 271.0 Hz); HRMS m/z 508.0857 ($M + H^+$), calcd for $C_{27}H_{17}ClF_3N_3SH$ 508.0862.

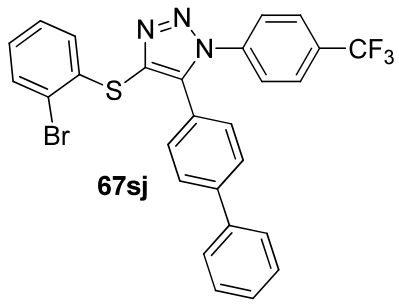
5-([1,1'-Biphenyl]-4-yl)-4-((4-chlorophenyl)thio)-1-(4-(trifluoromethyl)phenyl)-1*H*-



67rj

1,2,3-triazole (67rj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and isolated as a yellow oily liquid. IR (KBr): ν_{max} 1615, 1475, 1412, 1322, 1169, 1129, 1091, 1060, 997, 844, 766 and 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (2H, d, *J* = 8.4 Hz), 7.66-7.62 (4H, m), 7.55 (2H, d, *J* = 8.4 Hz), 7.50-7.46 (2H, m), 7.43-7.39 (1H, m), 7.31-7.24 (6H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 142.8 (C), 139.7 (C), 139.4 (C), 139.1 (C), 137.4 (C), 133.7 (C), 133.0 (C), 131.3 (C, q, *J* = 33.0 Hz), 130.4 (2 x CH), 130.1 (2 x CH), 129.2 (2 x CH), 128.9 (2 x CH), 128.1 (CH), 127.5 (2 x CH), 127.0 (2 x CH), 126.7 (2 x CH, q, *J* = 3.0 Hz), 124.9 (2 x CH), 124.0 (C), 123.4 (CF_3, q, *J* = 271.0 Hz); HRMS m/z 508.0854 ($M + H^+$), calcd for $C_{27}H_{17}ClF_3N_3SH$ 508.0862.

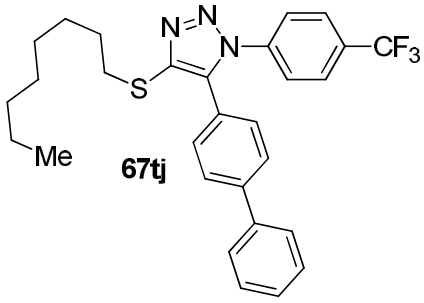
5-([1,1'-Biphenyl]-4-yl)-4-((2-bromophenyl)thio)-1-(4-(trifluoromethyl)phenyl)-1*H*-



67sj

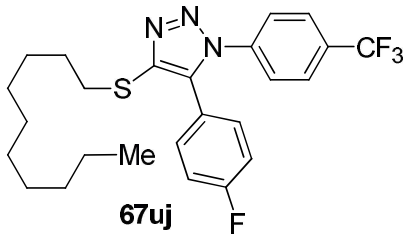
1,2,3-triazole (67sj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 130-132 °C; IR (Neat): ν_{max} 1615, 1446, 1323, 1129, 1060, 1020, 996, 950, 844, 766, 750, and 736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (2H, d, *J* = 8.0 Hz), 7.60-7.56 (6H, m), 7.52 (1H, dd, *J* = 8.0, 1.0 Hz), 7.44 (2H, br t, *J* = 8.0 Hz), 7.36 (1H, tt, *J* = 8.0, 2.0 Hz), 7.26 (2H, td, *J* = 8.5, 2.0 Hz), 7.19 (1H, dt, *J* = 7.5, 1.5 Hz), 7.05-7.01 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 142.8 (C), 140.7 (C), 139.5 (C), 139.1 (C), 137.2 (C), 136.1 (C), 133.0 (CH), 131.3 (C, q, *J* = 33.75 Hz), 129.9 (2 x CH), 128.9 (2 x CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.6 (2 x CH), 127.3 (CH), 127.0 (2 x CH), 126.7 (2 x CH, q, *J* = 3.75 Hz), 124.9 (2

x CH), 123.7 (C), 122.6 (CF_3, q, *J* = 281.25 Hz), 121.5 (C); HRMS m/z 552.0356 ($M + H^+$), calcd for $C_{27}H_{17}BrF_3N_3SH$ 552.0357.

5-([1,1'-Biphenyl]-4-yl)-4-(octylthio)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67tj): 

67tj

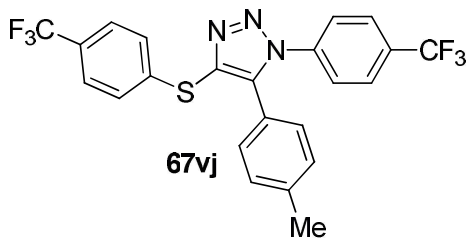
Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and was isolated as a colourless oily liquid. IR (KBr): 1616, 1495, 1326, 1161, 1128, 1106, 1068, 854, 838, 602 and 509 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.71 (2H, br d, *J* = 8.4 Hz), 7.68-7.63 (4H, m), 7.54 (2H, br d, *J* = 8.4 Hz), 7.48 (2H, br t, *J* = 8.4 Hz), 7.42 (1H, br tt, *J* = 8.4, 2.0 Hz), 7.34 (2H, br td, *J* = 8.4, 1.5 Hz), 3.07 (2H, t, *J* = 7.2 Hz), 1.68-1.62 (3H, m), 1.39-1.35 (2H, m), 1.28-1.24 (7H, m), 0.87 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 142.3 (C), 140.5 (C), 139.7 (C), 139.4 (C), 136.2 (C), 131.1 (C, q, *J* = 33.0 Hz), 130.0 (2 x CH), 129.0 (2 x CH), 128.0 (CH), 127.5 (2 x CH), 127.1 (2 x CH), 126.6 (2 x CH, q, *J* = 4.0 Hz), 124.9 (2 x CH), 124.8 (C), 123.42 (CF_3, q, *J* = 265.0 Hz), 34.6 (CH_2), 31.8 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.6 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS m/z 510.2196 ($M + H^+$), calcd for $C_{29}H_{30}F_3N_3SH$ 510.2191.

4-(Decylthio)-5-(4-fluorophenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (67uj): 

67uj

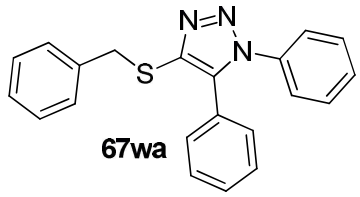
Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow liquid. IR (KBr): ν_{max} 1917, 1660, 1610, 1523, 1413, 1315, 1101, 1057, 991, 843, 723, 613 and 531 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (2H, d, *J* = 8.4 Hz), 7.47 (2H, d, *J* = 8.4 Hz), 7.28-7.23 (2H, m), 7.11 (2H, tt, *J* = 8.4, 2.0 Hz), 3.01 (2H, t, *J* = 7.2 Hz), 1.61 (2H, quintet, *J* = 7.2 Hz), 1.35-1.22 (14H, m), 0.86 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 163.1 (C, d, *J* = 250.0 Hz), 140.3 (C), 139.1 (C), 135.6 (C), 131.6 (2 x CH, d, *J* = 9.0 Hz), 131.0 (C, q, *J* = 33.0 Hz), 126.5 (2 x CH, q, *J* = 3.0 Hz), 124.7 (2 x CH), 123.3 (CF_3, q, *J* = 271.0 Hz), 122.1 (C, d, *J* = 3.0 Hz), 116.1 (2 x CH, d, *J* = 22.0 Hz), 34.5 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 29.42 (CH_2), 29.40 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.4 (CH_2), 22.5 (CH_2), 14.0 (CH_3); HRMS m/z 480.2098 ($M + H^+$), calcd for $C_{25}H_{29}F_3N_3SH$ 480.2097.

5-(*p*-Tolyl)-1-(4-(trifluoromethyl)phenyl)-4-((4-(trifluoromethyl)phenyl)thio)-1*H*-1,2,3-triazole (67vj): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and isolated as a light yellow oily liquid. IR (KBr): ν_{max} 2361, 2328, 1610, 1523, 1331, 1326, 1167, 1139, 1106, 1002, 991, 843, 597 and 460 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58 (2H, d, *J* = 8.4 Hz), 7.41 (2H, d, *J* = 8.4 Hz), 7.36 (2H, d, *J* = 8.0 Hz), 7.21 (2H, d, *J* = 8.0 Hz), 7.08 (2H, d, *J* = 7.6 Hz), 6.97 (2H, br d, *J* = 8.0 Hz), 2.25 (3H, s, Ar-C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 141.0 (C), 140.9 (C), 140.6 (C), 139.1 (C), 135.5 (C), 131.2 (C, q, *J* = 33.0 Hz), 129.7 (2 x CH), 129.4 (2 x CH), 128.3 (C, q, *J* = 33.0 Hz), 127.5 (2 x CH), 126.6 (2 x CH, q, *J* = 4.0 Hz), 125.8 (2 x CH, q, *J* = 4.0 Hz), 124.8 (2 x CH), 123.9 (CF_3, q, *J* = 270.0 Hz), 123.4 (CF_3, q, *J* = 271.0 Hz), 122.0 (C), 21.3 (CH_3, s); HRMS m/z 480.0969 ($M + H^+$), calcd for $C_{23}H_{15}F_6N_3SH$ 480.0969.



67vj

4-(Benzylthio)-1,5-diphenyl-1*H*-1,2,3-triazole (67wa): Prepared following the procedure **7.6** or **7.7** and purified by column chromatography using EtOAc/hexane and isolated as a white solid. Mp 106-108 °C; IR (KBr): ν_{max} 2926, 1589, 1495, 1446, 1419, 1260, 1200, 1084, 1063, 991 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.30 (4H, m), 7.27-7.23 (4H, m), 7.20-7.17 (3H, m), 7.16-7.13 (2H, m), 6.93-6.91 (2H, m), 4.20 (2H, s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 138.4 (C), 138.1 (C), 137.4 (C), 136.7(C), 129.7 (2 x CH), 129.2 (2 x CH), 129.12 (CH), 129.10 (CH), 129.0 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 127.2 (CH), 126.2 (C), 124.9 (2 x CH), 39.4 (CH_2); HRMS m/z 344.1218 ($M + H^+$), calcd for $C_{21}H_{17}N_3SH$ 344.1221.



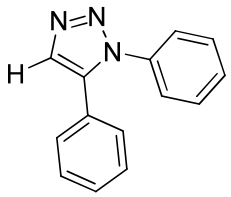
67wa

7.8 General procedure for the desulphurization of 1,5-disubtituted-4-thio-1,2,3-triazoles with Raney-nickel:

Two teaspoons of freshly prepared Raney-Nickel were added to a well stirred solution of 1,5-disubtituted-4-thio-1,2,3-triazoles **67** in ethanol (0.05 M) under argon atmosphere. The reaction mixture was allowed to stir for 1.0-3.0 h at 25 °C. After completion, the reaction mixture was filtered through a tight packing of celite on a sintered glass funnel. The filter cake was rinsed thoroughly with ethanol then sucked damp-dry. The filtrate was evaporated

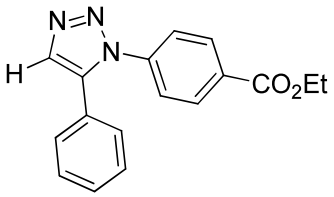
under reduced pressure to obtain crude reaction mixture. Pure products **69** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

1,5-Diphenyl-1*H*-1,2,3-triazole (69aa): Prepared following the procedure **7.8** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow solid. Mp 78-80 °C; IR (KBr): 3117, 2355, 1599, 1500, 1478, 1451, 1232, 1144, 1056, 991, 914, 848, 782, 684, 563 and 514 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.87 (1H, s), 7.45-7.42 (3H, m), 7.39-7.32 (5H, m), 7.24-7.22 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 137.7 (C), 136.6 (C), 133.4 (CH), 129.4 (2 x CH), 129.2 (2 x CH), 128.9 (2 x CH), 128.6 (2 x CH), 126.8 (C), 125.2 (2 x CH); HRMS m/z 244.0848 ($M + Na^+$), calcd for $C_{14}H_{11}N_3Na$ 244.0851.



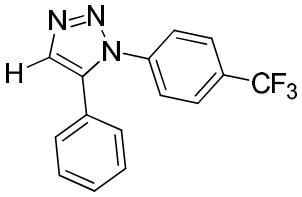
69aa

Ethyl 4-(5-phenyl-1*H*-1,2,3-triazol-1-yl)benzoate (69al): Prepared following the procedure **7.8** and purified by column chromatography using EtOAc/hexane and was isolated as a white solid. Mp 138-140 °C; IR (KBr): 2980, 2898, 1715, 1600, 1512, 1479, 1452, 1402, 1260, 1123, 986, 865, 761, 690 and 515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (2H, br d, *J* = 8.8 Hz), 7.87 (1H, s), 7.46 (2H, br d, *J* = 8.8 Hz), 7.41-7.35 (3H, m), 7.24-7.22 (2H, m), 4.40 (2H, q, *J* = 7.2 Hz), 1.41 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 165.4 (C, O-*C*=O), 139.9 (C), 137.8 (C), 133.7 (CH), 131.0 (C), 130.7 (2 x CH), 129.5 (CH), 129.0 (2 x CH), 128.6 (2 x CH), 126.4 (C), 124.7 (2 x CH), 61.4 (CH_2), 14.2 (CH_3); HRMS m/z 294.1242 ($M + H^+$), calcd for $C_{17}H_{15}N_3O_2H$ 294.1243.



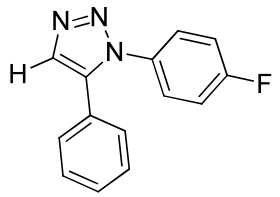
69al

5-Phenyl-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (69aj): Prepared following the procedure **7.8** and purified by column chromatography using EtOAc/hexane and was isolated as a colourless oily liquid. IR (KBr): 2931, 1747, 1610, 1457, 1419, 1232, 1068, 986, 756 and 608 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.88 (1H, s), 7.70 (2H, d, *J* = 8.4 Hz), 7.52 (2H, d, *J* = 8.4 Hz), 7.45-7.38 (3H, m), 7.26-7.23 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 139.3 (C), 137.8 (C), 133.8 (CH), 131.1 (C, q, *J* = 33.0 Hz), 129.6 (CH), 129.1 (2 x CH), 128.7 (2 x CH), 126.6 (2 x CH, q, *J* = 4.0 Hz), 126.3 (C), 125.1 (2 x CH), 123.5 (CF_3, q, *J* = 271.0 Hz); HRMS m/z 290.0903 ($M + H^+$), calcd for $C_{15}H_{10}F_3N_3H$ 290.0905.



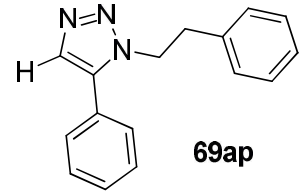
69aj

1-(4-Fluorophenyl)-5-phenyl-1*H*-1,2,3-triazole (69ab): Prepared following the procedure **7.8** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow solid. Mp 140-142 °C; IR (KBr): 1605, 1419, 1287, 1210, 1145, 1090, 1046, 843, 761 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.85 (1H, s), 7.38-7.34 (5H, m), 7.23-7.22 (2H, d, *J* = 6.5 Hz), 7.12 (2H, t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 162.5 (C, d, *J* = 247.5 Hz), 137.7 (C), 133.2 (CH), 132.5 (C, d, *J* = 3.75 Hz), 129.2 (CH), 128.8 (2 x CH), 128.4 (2 x CH), 126.9 (2 x CH, d, *J* = 8.75 Hz), 126.3 (C), 116.3 (2 x CH, d, *J* = 23.75 Hz); HRMS m/z 240.0937 (M + H^+), calcd for $C_{14}H_{10}FN_3H$ 240.0937.



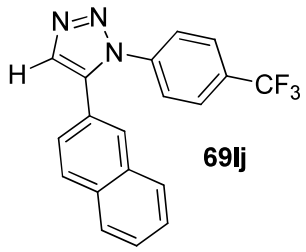
69ab

1-Phenethyl-5-phenyl-1*H*-1,2,3-triazole (69ap): Prepared following the procedure **7.8** and purified by column chromatography using EtOAc/hexane and isolated as a colourless oily liqiud. IR (KBr): ν_{max} 3057, 3024, 2920, 1731, 1600, 1452, 1232, 1112, 1079, 1013, 767, 701 and 531 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.64 (1H, s), 7.45-7.38 (3H, m), 7.22-7.20 (3H, m), 7.08 (2H, dd, *J* = 7.5, 1.0 Hz), 6.95 (2H, dd, *J* = 7.5, 2.0 Hz), 4.53 (2H, t, *J* = 7.5 Hz), 3.18 (2H, t, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2 (C), 137.1 (C), 132.9 (CH), 129.3 (CH), 128.9 (2 x CH), 128.8 (2 x CH), 128.7 (2 x CH), 128.6 (2 x CH), 127.0 (C), 126.9 (CH), 49.4 (CH_2), 36.5 (CH_2); HRMS m/z 250.1343 (M + H^+), calcd for $C_{16}H_{15}N_3H$ 250.1344.



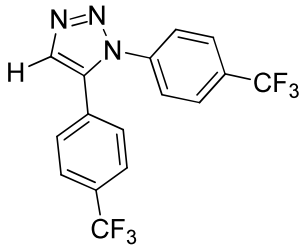
69ap

5-(Naphthalen-2-yl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (69lj): Prepared following the procedure **7.8** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow solid. Mp 98-100 °C; IR (KBr): 3134, 3079, 3046, 1610, 1517, 1495, 1424, 1326, 1271, 1243, 1068, 1046, 975, 849 and 810 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.97 (1H, s), 7.87-7.80 (4H, m), 7.68 (2H, d, *J* = 8.5 Hz), 7.57-7.55 (4H, m), 7.20 (1H, dd, *J* = 9.0, 2.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 139.4 (C), 137.9 (C), 134.2 (CH), 133.3 (C), 133.0 (C), 131.1 (C, q, *J* = 33.75Hz), 129.0 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 127.2 (CH), 126.6 (2 x CH, q, *J* = 3.75 Hz), 125.4 (CH), 125.1 (2 x CH), 123.6 (C), 123.5 (CF_3, q, *J* = 271.2 Hz); HRMS m/z 340.1049 (M + H^+), calcd for $C_{19}H_{12}F_3N_3H$ 340.1061.



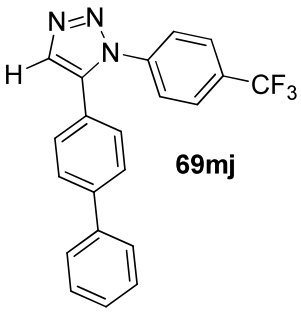
69lj

1,5-Bis(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (69ej): Prepared following the procedure **7.8** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow oily liquid. IR (KBr): 2920, 1616, 1517, 1419, 1326, 1238, 1068, 838, 712, 608 and 471 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.95 (1H, s), 7.75 (2H, d, *J* = 8.4 Hz), 7.67 (2H, d, *J* = 8.0 Hz), 7.52 (2H, d, *J* = 8.4 Hz), 7.38 (2H, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 138.9 (C), 136.5 (C), 134.3 (CH), 131.7 (C, q, *J* = 32.8 Hz), 131.6 (C, q, *J* = 33.0 Hz), 129.9 (C), 129.0 (2 x CH), 126.9 (2 x CH, q, *J* = 3.7 Hz), 126.2 (2 x CH, q, *J* = 3.7 Hz), 125.2 (2 x CH), 123.4 (CF_3, q, *J* = 270.7 Hz), 123.5 (CF_3, q, *J* = 270.8 Hz); HRMS m/z 358.0782 (M + H^+), calcd for $C_{16}H_9F_6N_3H$ 358.0779.



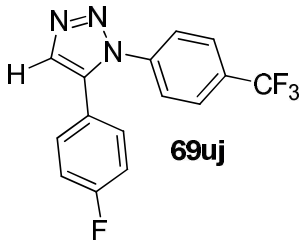
69ej

5-([1,1'-Biphenyl]-4-yl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (69mj): Prepared following the procedure **7.8** and purified by column chromatography using EtOAc/hexane and was isolated as a colourless oily liquid. IR (KBr): 1616, 1517, 1479, 1320, 1232, 1172, 991, 849, 767, 619, 569 and 493 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (1H, s), 7.73 (2H, d, *J* = 8.4 Hz), 7.64-7.56 (6H, m), 7.46 (2H, br t, *J* = 8.4 Hz), 7.41-7.37 (1H, m), 7.31 (2H, br d, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 142.5 (C), 139.7 (C), 139.4 (C), 137.6 (C), 133.9 (CH), 131.3 (C, q, *J* = 33.0 Hz), 129.04 (2 x CH), 128.98 (2 x CH), 128.1 (CH), 127.7 (2 x CH), 127.0 (2 x CH), 126.6 (2 x CH, q, *J* = 3.6 Hz), 125.2 (2 x CH), 125.1 (C), 123.5 (CF_3, q, *J* = 271.0 Hz); HRMS m/z 366.1218 (M + H^+), calcd for $C_{21}H_{14}F_3N_3H$ 366.1218.



69mj

5-(4-Fluorophenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (69uj): Prepared following the procedure **7.8** and purified by column chromatography using EtOAc/hexane and was isolated as a yellow oily liquid. IR (KBr): 1616, 1550, 1490, 1320, 1227, 1161, 1123, 1063, 1041, 986, 849, 597 and 504 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.85 (1H, s), 7.72 (2H, d, *J* = 8.5 Hz), 7.52 (2H, d, *J* = 8.5 Hz), 7.27-7.23 (2H, m), 7.11 (2H, tt, *J* = 8.5, 3.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 163.3 (C, d, *J* = 249.5Hz), 139.1 (C), 136.9 (C), 133.7 (CH), 131.2 (C, q, *J* = 33.12 Hz), 130.6 (2 x CH, d, *J* = 8.7 Hz), 126.6 (2 x CH, q, *J* = 3.6 Hz), 125.1 (2 x CH), 123.4 (CF_3, q, *J* = 271.2



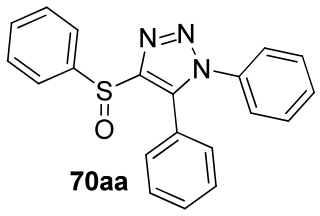
69uj

Hz), 122.4 (C, d, *J* = 3.7 Hz), 116.3 (2 x CH, d, *J* = 21.9 Hz); HRMS m/z 308.0805 (M + H^+), calcd for $C_{15}H_9F_4N_3H$ 308.0811.

7.9 General procedure for the oxidation of product 70aa:

In a round bottom flask equipped with a magnetic stirring bar, **67aa** (0.6 mmol) and DCM (4 mL) were added under argon atmosphere. In another round bottom flask, *meta*-chloroperoxybenzoic acid (1.2 equiv.) was taken in 2 mL DCM. At 0 °C, *meta*-chloroperoxybenzoic acid solution was added into the round bottom flask containing **67aa** solution under argon atmosphere for 5 min. After addition, the resulting mixture was stirred under argon at room temperature for 17.5 h. After workup with aqueous $NaHCO_3$ solution, the organic layer was dried over sodium sulphate. After evaporation of the solvents under vacuum, the compound was purified through a silica gel column using hexane and ethyl acetate as eluent to give pure product **70aa**.

1,5-Diphenyl-4-(phenylsulfinyl)-1*H*-1,2,3-triazole (70aa): Prepared following the procedure **7.9** and purified by column chromatography using EtOAc/hexane and isolated as a white semi-solid. IR (KBr): ν_{max} 3079, 3052, 2230, 1616, 1583, 1473, 1408, 1161, 1128, 1063, 843 and 734 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.68-7.66 (2H, m), 7.44-7.34 (10H, m), 7.29-7.26 (3H, m); ^{13}C NMR ($CDCl_3$ DEPT-135) δ 148.2 (C), 141.4 (C), 139.5 (C), 135.7 (C), 130.9 (CH), 130.3 (CH), 130.2 (2 x CH), 129.7 (CH), 129.4 (2 x CH), 128.9 (2 x CH), 128.8 (2 x CH), 125.1 (2 x CH), 125.0 (2 x CH), 124.4 (C); HRMS m/z 368.0831 (M + Na^+), calcd for $C_{20}H_{15}N_3OSNa$ 368.0834.

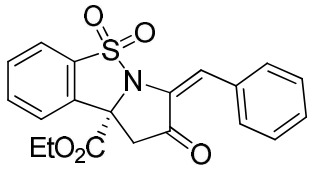


70aa

7.10 General Procedure for Phosphine-Catalyzed TZC or [3+2]-Cycloaddition of Ynones with ketimine:

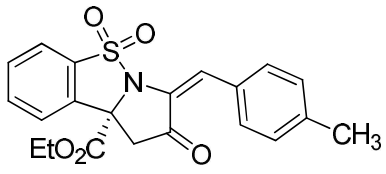
In an ordinary glass vial equipped with a magnetic stirring bar was taken a mixture phosphine catalyst **75a** (20 mol%) and acetic acid **49g** (20 mol%) in dichloroethane. Then 0.6 mmol of ynone **73**, 0.3 mmol of ketimine **74** were added sequentially to the reaction mixture was stirred at ambient temperature for 3-9 h. The reaction mixture was concentrated and pure products **76** and **77** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

(*S*,*E*)-Ethyl 3-benzylidene-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76aa): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as off white solid. Mp 102 °C; *E*/*Z* = 2.2:1; IR (KBr): ν_{max} 2919, 1742, 1636, 1606, 1444, 1323, 1181, 1126, 1070, 858, 757, 691, 611 and 580 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.98 (1H, d, *J* = 7.2 Hz), 7.90 (1H, d, *J* = 7.6 Hz), 7.87-7.85 (1H, m), 7.74 (1H, d, *J* = 7.6 Hz), 7.69 (1H, d, *J* = 7.2 Hz), 7.62 (1H, d, *J* = 7.6 Hz), 7.38-7.37 (3H, m), 7.00 (1H, s), 4.25 (2H, q, *J* = 6.8 Hz), 3.57 (1H, d, *J* = 18.0 Hz), 2.89 (1H, d, *J* = 18.0 Hz), 1.24 (3H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 194.6 (C, *C*=O), 168.9 (C, *O*-*C*=*O*), 135.7 (C), 134.3 (CH), 133.9 (C), 132.4 (C), 131.0 (2 x CH), 130.6 (CH), 130.1 (CH), 129.3 (C), 128.6 (CH), 128.2 (2 x CH), 125.0 (CH), 122.3 (CH), 69.6 (C), 63.5 (CH_2), 47.2 (CH_2), 13.9 (CH_3); ^1H NMR ($CDCl_3$, 400MHz, minor isomer) δ 7.87-7.85 (3H, m), 7.78-7.76 (2H, m), 7.65 (1H, d, *J* = 7.2 Hz), 7.43-7.40 (3H, m), 7.22 (1H, s), 4.32-4.23 (2H, m), 3.57 (1H, d, *J* = 18.0 Hz), 2.79 (1H, d, *J* = 18.4 Hz), 1.28 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, minor isomer) δ 196.6 (C, *C*=O), 169.0 (C, *O*-*C*=*O*), 135.6 (C), 134.3 (CH), 133.9 (C), 132.4 (C), 131.0 (2 x CH), 130.5 (CH), 130.1 (CH), 129.1 (C), 128.65 (2 x CH), 128.56 (CH), 124.8 (CH), 122.0 (CH), 70.8 (C), 63.5 (CH_2), 45.3 (CH_2), 13.9 (CH_3); HRMS m/z 406.0727 (M + Na^+), calcd for $C_{20}H_{17}NO_5SNa$ 406.0725.



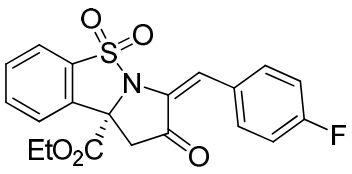
76aa

(*S*,*E*)-Ethyl 3-(4-methylbenzylidene)-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76ba): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as semi off white solid; *E*/*Z* = 3.6:1; IR (KBr): ν_{max} 2919, 1737, 1631, 1611, 1505, 1449, 1323, 1181, 1060, 904, 813, 757, 590 and 570 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.90-7.88 (1H, m), 7.79 (2H, d, *J* = 8.4 Hz), 7.75-7.71 (1H, m), 7.67 (1H, d, *J* = 7.2 Hz), 7.61 (1H, d, *J* = 8.0 Hz), 7.18 (2H, d, *J* = 8.0 Hz), 6.95 (1H, s), 4.24 (2H, q, *J* = 7.2 Hz), 3.55 (1H, d, *J* = 18.0 Hz), 2.87 (1H, d, *J* = 18.0 Hz), 2.37 (3H, s), 1.23 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 194.4 (C, *C*=O), 168.8 (C, *O*-*C*=*O*), 140.6 (C), 135.6 (C), 134.1 (CH), 133.8 (C), 131.0 (2 x CH), 130.9 (CH), 129.7 (C), 129.1 (CH), 128.9 (2 x CH), 128.5 (C), 124.9 (CH), 122.2 (CH), 69.5 (C), 63.3 (CH_2), 47.2 (CH_2), 21.5 (CH_3), 13.8 (CH_3); HRMS m/z 420.0882 (M + Na^+), calcd for $C_{21}H_{19}NO_5SNa$ 420.0882.



76ba

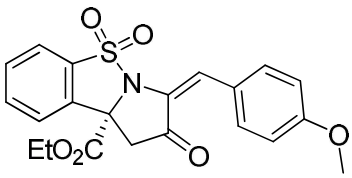
(*S*,*E*)-Ethyl 3-(4-fluorobenzylidene)-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76ca): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as off white solid.



76ca

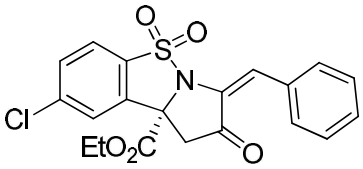
Mp 106 °C; *E*/*Z* = 3.4:1; IR (KBr): ν_{max} 1732, 1641, 1601, 1505, 1323, 1237, 1186, 1065, 833, 752, 595 and 570 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.91-7.87 (3H, m), 7.77-7.73 (1H, m), 7.69 (1H, d, *J* = 7.2 Hz), 7.62 (1H, d, *J* = 7.6 Hz), 7.05 (2H, t, *J* = 8.8 Hz), 6.92 (1H, s), 4.25 (2H, q, *J* = 7.2 Hz), 3.57 (1H, d, *J* = 18.0 Hz), 2.89 (1H, d, *J* = 18.0 Hz), 1.23 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 194.6 (C, *C*=O), 168.8 (C, *O-C=O*), 163.5 (C, d, *J* = 251.0 Hz) 135.6 (C), 134.2 (CH), 133.8 (C), 133.2 (2 x CH, d, *J* = 8.0 Hz), 140.0 (CH), 128.8 (C, d, *J* = 33.0 Hz), 127.4 (CH), 124.9 (CH + C), 122.3 (CH), 115.3 (2 x CH, d, *J* = 22.0 Hz), 69.6 (C), 63.5 (CH_2), 47.2 (CH_2), 13.8 (CH_3); HRMS m/z 424.0633 ($M + Na^+$), calcd for $C_{20}H_{16}FNO_5SNa$ 424.0631.

(*S*,*E*)-Ethyl 3-(4-methoxybenzylidene)-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76da): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as semi solid; *E*/*Z* = 1.7:1; IR (Neat): ν_{max} 2974, 2944, 1737, 1636, 1601, 1510, 1338, 1257, 1166, 1025, 858,757 and 626 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz, major isomer) δ 7.95 (2H, d, *J* = 8.8 Hz), 7.90 (1H, d, *J* = 7.6 Hz), 7.74-7.72 (1H, m), 7.69-7.67 (1H, m), 7.61 (1H, d, *J* = 7.6 Hz), 6.94 (1H, s), 6.90 (2H, d, *J* = 8.8 Hz), 4.24 (2H, q, *J* = 7.2 Hz), 3.84 (3H, s), 3.56 (1H, d, *J* = 17.6 Hz), 2.88 (1H, d, *J* = 18.0 Hz), 1.23 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 194.5 (C, *C*=O), 168.9 (C, *O-C=O*), 161.3 (C), 135.7 (C), 134.1 (CH), 133.8 (C), 133.3 (2 x CH), 130.9 (CH), 129.9 (CH), 127.5 (C), 125.4 (C), 124.8 (CH), 122.3 (CH), 113.7 (2 x CH), 69.8 (C), 63.4 (CH_2), 55.3 (CH_3), 47.3 (CH_2), 13.8 (CH_3); ^1H NMR ($CDCl_3$, 400MHz, minor isomer) δ 8.00 (2H, d, *J* = 9.2 Hz), 7.79 (1H, d, *J* = 8.0 Hz), 7.76-7.72 (1H, m), 7.69-7.65 (2H, m), 7.23 (1H, s), 6.94 (2H, d, *J* = 8.8 Hz), 4.30-4.22 (2H, m), 3.84 (3H, s), 3.53 (1H, d, *J* = 18.0 Hz), 2.76 (1H, d, *J* = 18.4 Hz), 1.25 (3H, t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, minor isomer) δ 196.5 (C, *C*=O), 169.0 (C, *O-C=O*), 161.5 (C), 135.6 (C), 134.2 (CH), 133.8 (C), 132.8 (2 x CH), 130.9 (CH), 127.2 (C), 126.0 (CH), 124.8 (CH), 124.6 (C), 122.0 (CH), 114.1 (2 x CH), 71.0 (C), 63.4 (CH_2), 55.3 (CH_3), 45.3 (CH_2), 13.8 (CH_3); HRMS m/z 436.0835 ($M + Na^+$), calcd for $C_{21}H_{19}NO_6SNa$ 436.0831.



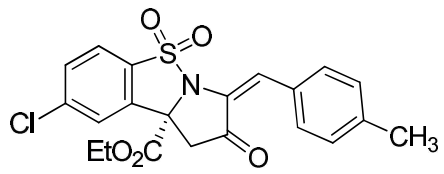
76da

(*S*,*E*)-Ethyl 3-benzylidene-8-chloro-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76ab): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as semi solid; *E*/*Z* = 1.4:1; IR (Neat): ν_{max} 3085, 2924, 2843, 1732, 1621, 1449, 1328, 1267, 1181, 1090, 823, 757 and 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz, major isomer) δ 7.96-7.94 (1H, m), 7.86-7.82 (2H, m), 7.71-7.59 (2H, m), 7.44-7.37 (3H, m), 6.96 (1H, s), 4.36-4.23 (2H, m), 3.52 (1H, d, *J* = 18.0 Hz), 2.89 (1H, d, *J* = 18.0 Hz), 1.26 (3H, t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 193.8 (C, *C*=O), 168.3 (C, *O*-*C*=*O*), 140.7 (C), 137.4 (C), 132.3 (C), 132.2 (C), 131.5 (CH), 130.9 (2 x CH), 130.4 (CH), 129.0 (C), 128.8 (CH), 128.2 (2 x CH), 125.3 (CH), 123.5 (CH), 69.0 (C), 63.7 (CH_2), 47.0 (CH_2), 13.8 (CH_3); ^1H NMR ($CDCl_3$, 400 MHz, minor isomer) δ 7.86-7.82 (2H, m), 7.71-7.59 (3H, m), 7.44-7.37 (3H, m), 7.22 (1H, s), 4.36-4.23 (2H, m), 3.52 (1H, d, *J* = 18.0 Hz), 2.79 (1H, d, *J* = 18.4 Hz), 1.29 (3H, t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, minor isomer) δ 195.8 (C, *C*=O), 168.5 (C, *O*-*C*=*O*), 140.8 (C), 137.3 (C), 132.3 (C), 132.2 (C), 131.5 (CH), 130.5 (CH), 130.1 (2 x CH), 128.8 (C), 128.6 (2 x CH), 125.2 (CH), 125.0 (CH), 123.2 (CH), 70.2 (C), 63.7 (CH_2), 45.1 (CH_2), 13.8 (CH_3); LRMS m/z 417.30 (M^+), calcd for $C_{20}H_{16}ClNO_5S$ 417.04; Anal. calcd for $C_{20}H_{16}ClNO_5S$ (417.04): C, 57.49; H, 3.86; N, 3.35. Found: C, 57.36; H, 3.92; N, 3.41%.



76ab

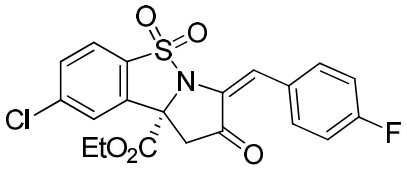
(*S*,*E*)-Ethyl 8-chloro-3-(4-methylbenzylidene)-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76bb): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as off white solid. Mp 98 °C; *E*/*Z* = 1.3:1; IR (Neat): ν_{max} 2914, 1737, 1636, 1601, 1338, 1262, 1181, 1141, 1085, 1035 and 813 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.83 (1H, d, *J* = 8.4 Hz), 7.80 (2H, d, *J* = 8.0 Hz), 7.72-7.60 (2H, m), 7.19 (2H, d, *J* = 8.0 Hz), 6.95 (1H, s), 4.34-4.21 (2H, m), 3.51 (1H, d, *J* = 18.0 Hz), 2.89 (1H, d, *J* = 17.6 Hz), 2.38 (3H, s), 1.26 (3H, t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, $CDCl_3$, major isomer) δ 193.8 (C, *C*=O), 168.4 (C, *O*-*C*=*O*), 140.9 (C), 140.7 (C), 137.5 (C), 132.4 (C), 131.5 (CH), 131.1 (2 x CH), 129.61 (CH), 129.57 (C), 129.0 (2 x CH), 128.3 (C), 125.3 (CH), 123.5 (CH), 69.2 (C), 63.7 (CH_2), 47.1 (CH_2), 21.6 (CH_3), 13.8 (CH_3); ^1H NMR ($CDCl_3$, 400MHz, minor isomer) δ 7.87 (2H, d, *J* = 8.4 Hz), 7.72-7.60 (3H, m), 7.23 (2H, d, *J* = 7.2 Hz), 7.22 (1H, s), 4.34-4.21 (2H, m), 3.51 (1H, d, *J* = 18.4 Hz), 2.78 (1H, d, *J* = 18.4 Hz), 2.38 (3H, s), 1.29 (3H, t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, $CDCl_3$, minor isomer) δ 195.9 (C, *C*=O), 168.6 (C, *O*-*C*=*O*), 141.3 (C), 140.8 (C), 137.4 (C), 132.4 (C), 131.5 (CH), 130.6 (2 x CH), 129.4 (2 x CH), 129.2 (C),



76bb

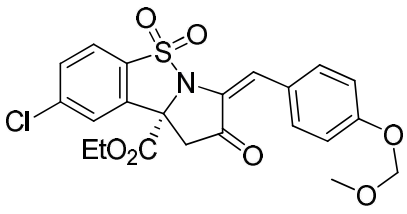
128.1 (C), 125.7 (CH), 125.2 (CH), 123.2 (CH), 70.3 (C), 63.7 (CH_2), 45.2 (CH_2), 21.7 (CH_3), 13.8 (CH_3); HRMS m/z 432.0673 ($M + H^+$), calcd for $C_{21}H_{18}ClNO_5SH$ 432.0672.

(*S*,*E*)-Ethyl 8-chloro-3-(4-fluorobenzylidene)-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76cb): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as semi solid; *E*/*Z* = 1.7:1; IR (KBr): ν_{max} 3096, 2944, 1732, 1595, 1510, 1318, 1282, 1237, 1090, 1065, 853, 833, 757 and 727 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.91-7.88 (2H, m), 7.83 (1H, d, *J* = 8.0 Hz), 7.67-7.62 (2H, m), 7.08-7.04 (2H, m), 6.91 (1H, s), 4.38-4.22 (2H, m), 3.53 (1H, d, *J* = 17.6 Hz), 2.90 (1H, d, *J* = 17.6 Hz), 1.31-1.24 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 194.0 (C, *C*=O), 168.3 (C, *O*-*C*=*O*), 163.6 (C, d, *J* = 251.0 Hz), 140.8 (C), 137.4 (C), 133.27 (2 x CH, d, *J* = 9.0 Hz), 132.3 (C), 131.6 (CH), 128.7 (C), 128.5 (C, d, *J* = 3.0 Hz), 127.8 (CH), 125.3 (CH), 123.5 (CH), 115.3 (2 x CH, d, *J* = 22.0 Hz), 69.1 (C), 63.8 (CH_2), 47.0 (CH_2), 13.9 (CH_3); ^1H NMR ($CDCl_3$, 400MHz, minor isomer) δ 7.98-7.95 (2H, m), 7.73-7.70 (3H, m), 7.18 (1H, s), 7.13-7.08 (2H, m), 4.38-4.22 (2H, m), 3.51 (1H, d, *J* = 18.4 Hz), 2.79 (1H, d, *J* = 18.4 Hz), 1.31-1.24 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, minor isomer) δ 195.7 (C, *C*=O), 168.4 (C, *O*-*C*=*O*), 163.7 (C, d, *J* = 251.0 Hz), 140.9 (C), 137.3 (C), 132.7 (2 x CH, d, *J* = 9.0 Hz), 132.2 (C), 131.6 (CH), 128.8 (C), 128.3 (C, d, *J* = 3.0 Hz) 125.3 (CH), 124.0 (CH), 123.3 (CH), 115.9 (2 x CH, d, *J* = 21.0 Hz), 70.3 (C), 63.8 (CH_2), 45.2 (CH_2), 13.9 (CH_3); HRMS m/z 436.0422 ($M + H^+$), calcd for $C_{20}H_{15}ClFNO_5SH$ 436.0422.



76cb

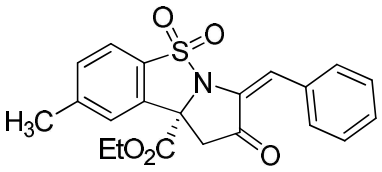
(*S*,*E*)-Ethyl 8-chloro-3-(4-(methoxymethoxy)benzylidene)-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76eb): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as semi solid; *E*/*Z* = 1.5:1; IR (Neat): ν_{max} 2934, 1727, 1631, 1606, 1510, 1333, 1242, 1176, 1146, 1080, 989, 853, 828 and 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400M Hz, major isomer) δ 7.91 (2H, d, *J* = 8.8 Hz), 7.82 (1H, d, *J* = 8.4 Hz), 7.64-7.59 (2H, m), 7.03 (2H, d, *J* = 8.8 Hz), 6.91 (1H, s), 5.23-5.18 (2H, m) 4.31-4.22 (2H, m), 3.52-3.46 (4H, m), 2.89 (1H, d, *J* = 18.0 Hz), 1.28-1.23 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 193.8 (C, *C*=O), 168.4 (C, *O*-*C*=*O*), 158.9 (C), 140.6 (C), 137.4 (C), 133.2 (2 x CH), 132.4 (C), 131.4 (CH), 129.6 (CH), 127.2 (C), 126.2 (C), 125.2 (CH), 123.5 (CH), 115.7 (CH), 94.0 (CH_2), 69.2 (C), 63.6 (CH_2), 56.1 (CH), 47.1 (CH_2), 13.8 (CH_3); ^1H NMR ($CDCl_3$, 400MHz, minor isomer) δ 7.95 (2H, d, *J* = 8.8 Hz), 7.72-7.68 (2H, m), 7.64-7.59 (1H, m), 7.21 (1H, s), 7.06 (2H, d, *J* = 8.8 Hz), 5.23-5.18 (2H, m), 4.31-4.22



76eb

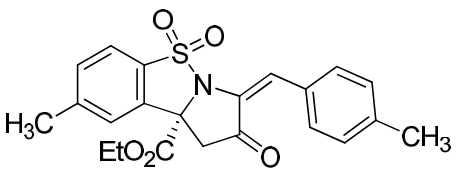
(2H, m), 3.52-3.46 (4H, m), 2.76 (1H, d, *J* = 18.4 Hz), 1.28-1.23 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, minor isomer) δ 195.8 (C, *C*=O), 168.5 (C, *O-C=O*), 159.2 (C), 140.7 (C), 137.5 (C), 132.6 (2 x CH), 132.2 (C), 131.5 (CH), 127.6 (C), 125.8 (CH), 125.5 (C), 125.2 (CH), 123.2 (CH), 116.1 (CH), 94.1 (CH_2), 70.4 (C), 63.6 (CH_2), 56.1 (CH), 45.1 (CH_2), 13.8 (CH_3); LRMS m/z 498.75 (M^+), calcd for $C_{22}H_{20}ClNO_7S$ 498.06; Anal. calcd for $C_{22}H_{20}ClNO_7S$ (498.06): C, 55.29; H, 4.22; N, 2.93. Found: C, 55.37; H, 4.28; N, 2.86%.

(*S*,*E*)-Ethyl 3-benzylidene-8-methyl-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76ac): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as off white solid. Mp 118 °C; *E*/*Z* = 2.8:1; IR (KBr): ν_{max} 2924, 1732, 1636, 1595, 1459, 1318, 1161, 808, 757 and 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.86-7.84 (2H, m), 7.77 (1H, d, *J* = 8.0 Hz), 7.48-7.36 (5H, m), 6.96 (1H, s), 4.30-4.23 (2H, m), 3.55 (1H, d, *J* = 17.6 Hz), 2.87 (1H, d, *J* = 18.0 Hz), 2.50 (3H, s), 1.24 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 194.6 (C, *C*=O), 169.0 (C, *O-C=O*), 145.5 (C), 135.9 (C), 132.4 (C), 131.9 (CH), 131.1 (C), 130.9 (2 x CH), 129.9 (CH), 129.3 (C), 128.3 (CH), 128.1 (2 x CH), 125.0 (CH), 121.9 (CH), 69.4 (C), 63.4 (CH_2), 47.2 (CH_2), 21.8 (CH_3), 13.8 (CH_3); ^{1}H NMR ($CDCl_3$, 400MHz, minor isomer) δ 7.98 (2H, d, *J* = 7.2 Hz), 7.64 (1H, d, *J* = 8.0 Hz), 7.48-7.36 (5H, m), 7.21 (1H, s), 4.33-4.23 (2H, m), 3.55 (1H, d, *J* = 17.6 Hz), 2.76 (1H, d, *J* = 18.8 Hz), 2.50 (3H, s), 1.29-1.22 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, minor isomer) δ 196.7 (C, *C*=O), 169.1 (C, *O-C=O*), 145.5 (C), 135.8 (C), 132.3 (C), 131.9 (CH), 131.1 (C), 130.5 (2 x CH), 130.3 (CH), 129.1 (C), 128.5 (2 x CH), 124.9 (CH), 124.6 (CH), 121.7 (CH), 70.6 (C), 63.4 (CH_2), 45.3 (CH_2), 21.8 (CH_3), 13.8 (CH_3); HRMS m/z 420.0884 ($M + Na^+$), calcd for $C_{21}H_{19}NO_5SNa$ 420.0882.



76ac

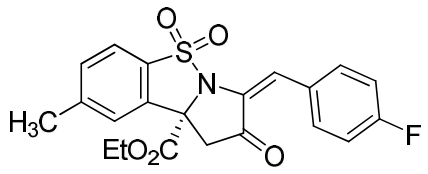
(*S*,*E*)-Ethyl 8-methyl-3-(4-methylbenzylidene)-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76bc): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as brown solid. Mp 132 °C; *E*/*Z* = 2.3:1; IR (KBr): ν_{max} 1736, 1632, 1600, 1353, 1323, 1161, 860, 810, 684, 602 and 553 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.80-7.76 (3H, m), 7.48-7.45 (1H, m), 7.39 (1H, s), 7.19 (2H, d, *J* = 8.0 Hz), 6.94 (1H, s), 4.26-4.22 (2H, m), 3.55 (1H, d, *J* = 17.6 Hz), 2.86 (1H, d, *J* = 17.6 Hz), 2.50 (3H, s), 2.37 (3H, s), 1.24 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 194.6 (C, *C*=O), 169.1 (C, *O-C=O*), 145.5 (C), 140.6 (C), 136.0 (C), 131.9 (CH), 131.2 (C), 131.1 (2 x CH), 129.1 (CH), 128.9 (2 x CH), 128.7 (C), 125.3 (C), 124.9 (CH), 122.0 (CH), 69.5 (C),



76bc

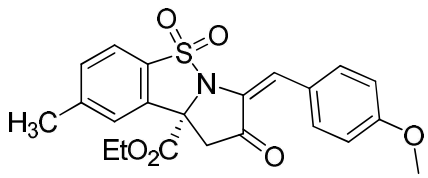
63.4 (CH_2), 47.3 (CH_2), 21.9 (CH_3), 21.6 (CH_3), 13.8 (CH_3); ^{1}H NMR ($CDCl_3$, 400MHz, minor isomer) δ 7.90 (2H, d, *J* = 8.0 Hz), 7.65 (1H, d, *J* = 8.0 Hz), 7.48-7.45 (2H, m), 7.24-7.21 (3H, m), 4.26-4.22 (2H, m), 3.54 (1H, d, *J* = 18.4 Hz), 2.75(1H, d, *J* = 18.0 Hz), 2.50 (3H, s), 2.37 (3H, s), 1.27 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, minor isomer) δ 196.7 (C, *C*=O), 169.2 (C, *O-C=O*), 145.6 (C), 141.0 (C), 135.9 (C), 131.9 (CH), 130.7 (2 x CH), 129.7 (CH), 129.44 (C), 129.37 (2 x CH), 128.4 (C), 124.9 (C), 124.8 (CH), 121.7 (CH), 70.7 (C), 63.4 (CH_2), 45.3 (CH_2), 21.9 (CH_3), 21.7 (CH_3), 13.8 (CH_3); HRMS m/z 412.1218 (M + H^+), calcd for $C_{22}H_{21}NO_5SH$ 412.1219.

(*S*,*E*)-Ethyl 3-(4-fluorobenzylidene)-8-methyl-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76cc): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as off white solid. Mp 110 °C; *E*/*Z* = 3.7:1; IR (KBr): ν_{max} 2919, 2848, 1732, 1641, 1595, 1515, 1292, 1227, 1161, 1065, 833, 752 and 676 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.91-7.87 (2H, m), 7.77 (1H, d, *J* = 8.0 Hz), 7.49-7.44 (1H, m), 7.39 (1H, s), 7.12-7.03 (2H, m), 6.90 (1H, s), 4.27-4.21 (2H, m), 3.56 (1H, d, *J* = 17.6 Hz), 2.87 (1H, d, *J* = 17.6 Hz), 2.51 (3H, s), 1.29-1.22 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 194.8 (C, *C*=O), 169.0 (C, *O-C=O*), 163.5 (C, d, *J* = 251.0 Hz), 145.6 (C), 135.9 (C), 133.2 (2 x CH, d, *J* = 8.0 Hz), 132.0 (CH), 131.1 (C), 129.1 (C), 128.7 (C), 127.3 (CH), 125.0 (CH), 122.0 (CH), 115.2 (2 x CH, d, *J* = 21.0 Hz), 69.4 (C), 63.4 (CH_2), 47.2 (CH_2), 21.9 (CH_3), 13.8 (CH_3); HRMS m/z 416.0968 (M + H^+), calcd for $C_{21}H_{18}FNO_5SH$ 416.0968.



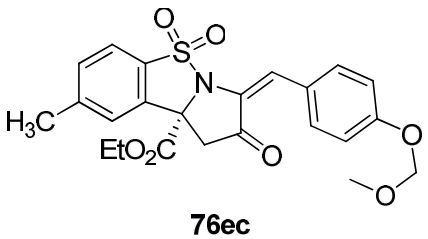
76cc

(*S*,*E*)-Ethyl 3-(4-methoxybenzylidene)-8-methyl-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76dc): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as semi solid; *E*/*Z* = 7.1:1; IR (KBr): ν_{max} 2974, 2924, 2858, 2353, 1732, 1626, 1601, 1570, 1318, 1262, 1171, 1025, 883, 833, 686 and 575 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, major isomer) δ 8.00 (2H, d, *J* = 8.8 Hz), 7.66 (1H, d, *J* = 8.8 Hz), 7.45 (2H, s), 7.22 (1H, s), 6.93 (2H, d, *J* = 8.8 Hz), 4.33-4.20 (2H, m), 3.84 (3H, s), 3.51 (1H, d, *J* = 18.4 Hz), 2.74 (1H, d, *J* = 18.4 Hz), 2.51 (3H, s), 1.25 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 196.7 (C, *C*=O), 169.2 (C, *O-C=O*), 161.5 (C), 145.6 (C), 135.9 (C), 132.8 (2 x CH), 131.9 (CH), 131.2 (C), 127.3 (C), 125.9 (CH), 124.8 (CH), 124.7 (C), 121.8 (CH), 114.1 (2 x CH), 70.9 (C), 63.3 (CH_2), 55.3 (CH_3), 45.3 (CH_2), 21.9 (CH_3), 13.9 (CH_3); HRMS m/z 428.1165 (M + H^+), calcd for $C_{22}H_{21}NO_6SH$ 428.1168.



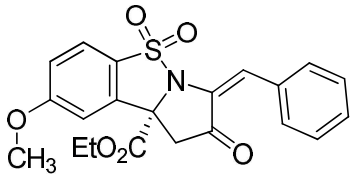
76dc

(*S*,*E*)-Ethyl 3-(4-(methoxymethoxy)benzylidene)-8-methyl-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76ec): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as semi solid; *E*/*Z* = 1.7:1; IR (Neat): ν_{max} 2954, 2919, 1737, 1631, 1601, 1510, 1328, 1242, 1166, 1080, 989, 929, 858, 737 and 681 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.92 (2H, d, *J* = 8.8 Hz), 7.76 (1H, d, *J* = 8.0 Hz), 7.45-7.43 (1H, m), 7.38 (1H, s), 7.02 (2H, d, *J* = 8.8 Hz), 6.91 (1H, s), 5.21 (2H, s), 4.30-4.21 (2H, m), 3.54 (1H, d, *J* = 18.0 Hz), 3.47 (3H, s), 2.86 (1H, d, *J* = 18.0 Hz), 2.50 (3H, s), 1.23 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, $CDCl_3$, major isomer) δ 194.7 (C, *C*=O), 169.1 (C, *O*-*C*=*O*), 158.8 (C), 145.5 (C), 136.0 (C), 133.1 (2 x CH), 131.9 (CH), 131.2 (C), 129.2 (CH), 128.0 (C), 126.4 (C), 124.9 (CH), 122.0 (CH), 115.7 (2 x CH), 94.1 (CH_2), 69.6 (C), 63.3 (CH_2), 56.1 (CH_3), 47.3 (CH_2), 21.9 (CH_3), 13.8 (CH_3); ^1H NMR ($CDCl_3$, 400MHz, minor isomer) δ 7.98 (2H, d, *J* = 8.4 Hz), 7.66 (1H, d, *J* = 8.8 Hz), 7.48-7.43 (2H, m), 7.21 (1H, s), 7.06 (2H, d, *J* = 8.8 Hz), 5.23-5.18 (2H, m), 4.30-4.21 (2H, m), 3.52 (1H, d, *J* = 18.0 Hz), 3.47 (3H, s), 2.74 (1H, d, *J* = 18.4 Hz), 2.50 (3H, s) 1.25 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, minor isomer) δ 196.7 (C, *C*=O), 169.2 (C, *O*-*C*=*O*), 159.1 (C), 145.6 (C), 135.9 (C), 132.7 (2 x CH), 131.9 (CH), 131.1 (C), 127.6 (C), 125.7 (C), 125.5 (CH), 124.8 (CH), 121.8 (CH), 116.1 (2 x CH), 94.1 (CH_2), 70.8 (C), 63.3 (CH_2), 56.1 (CH_3), 45.3 (CH_2), 21.9 (CH_3), 13.8 (CH_3); HRMS m/z 480.1093 ($M + Na^+$), calcd for $C_{23}H_{23}NO_7SNa$ 480.1093.



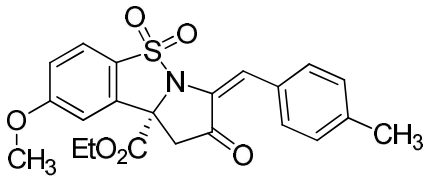
76ec

(*S*,*E*)-Ethyl 3-benzylidene-8-methoxy-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76ad): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as semi solid; *E*/*Z* = 3.6:1; IR (Neat): ν_{max} 2919, 2858, 1732, 1590, 1479, 1464, 1323, 1292, 1247, 1176, 1070, 752 and 691 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.87-7.85 (2H, m), 7.79 (1H, d, *J* = 8.4 Hz), 7.41-7.36 (3H, m), 7.17-7.08 (1H, m), 7.01 (1H, s), 6.95 (1H, s), 4.29-4.22 (2H, m), 3.91 (3H, s), 3.55 (1H, d, *J* = 17.6 Hz), 2.89 (1H, d, *J* = 17.6 Hz), 1.25 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, $CDCl_3$, major isomer) δ 194.6 (C, *C*=O), 168.9 (C, *O*-*C*=*O*), 164.3 (C), 138.1 (C), 132.4 (C), 130.9 (2 x CH), 130.0 (CH), 129.4 (C), 128.5 (CH), 128.1 (2 x CH), 125.7 (C), 123.8 (CH), 117.8 (CH), 108.8 (CH), 69.3 (C), 63.4 (CH_2), 56.1 (CH_3), 47.2 (CH_2), 13.9 (CH_3); HRMS m/z 436.0833 ($M + Na^+$), calcd for $C_{21}H_{19}NO_6SNa$ 436.0831.



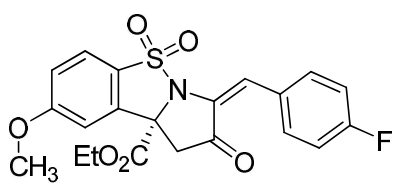
76ad

(*S*,*E*)-Ethyl 8-methoxy-3-(4-methylbenzylidene)-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76bd): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as semi solid; *E*/*Z* = 2.9:1; IR (Neat): ν_{max} 2959, 2924, 2853, 1732, 1590, 1515, 1313, 1282, 1156, 868 and 823 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.80-7.79 (3H, m), 7.23-7.11 (3H, m), 7.00 (1H, d, *J* = 2.0 Hz), 6.94 (1H, s), 4.29-4.21 (2H, m), 3.91 (3H, s), 3.54 (1H, d, *J* = 18.0 Hz), 2.89 (1H, d, *J* = 17.6 Hz), 2.37 (3H, s), 1.24 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 194.6 (C, *C*=O), 169.0 (C, *O*-*C*=*O*), 164.3 (C), 140.7 (C), 138.2 (C), 131.1 (2 x CH), 129.8 (C), 129.2 (CH), 128.9 (2 x CH), 128.7 (C), 125.7 (C), 123.8 (CH), 117.8 (CH), 108.7 (CH), 69.4 (C), 63.4 (CH_2), 56.1 (CH_3), 47.3 (CH_2), 21.6 (CH_3), 13.9 (CH_3); HRMS m/z 450.0988 (M + Na^+), calcd for $C_{22}H_{21}NO_6SNa$ 450.0987.



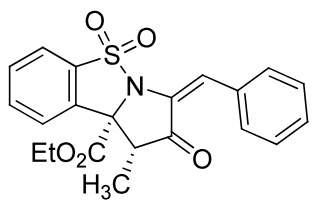
76bd

(*S*,*E*)-Ethyl 3-(4-fluorobenzylidene)-8-methoxy-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76cd): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as off white solid. Mp 120 °C; *E*/*Z* = 5.5:1; IR (KBr): ν_{max} 2924, 1732, 1606, 1464, 1328, 1166, 1010, 914, 813, 681 and 590 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.92-7.88 (2H, m), 7.80 (1H, d, *J* = 8.8 Hz), 7.19-7.16 (1H, m), 7.13-7.04 (2H, m), 7.02-7.00 (1H, m), 6.91 (1H, s), 4.33-4.23 (2H, m), 3.92 (3H, s), 3.56 (1H, d, *J* = 18.0 Hz), 2.90 (1H, d, *J* = 17.6 Hz), 1.30-1.22 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 194.8 (C, *C*=O), 168.9 (C, *O*-*C*=*O*), 164.3 (C, d, *J* = 184.0 Hz), 138.1 (C), 133.2 (2 x CH, d, *J* = 7.0 Hz), 129.1 (C), 128.7 (C), 127.4 (CH), 125.6 (C), 123.8 (CH), 117.9 (CH), 115.3 (2 x CH, d, *J* = 17.0 Hz), 108.7 (CH), 69.3 (C, d, *J* = 3.0 Hz), 63.5 (CH_2), 56.1 (CH_3), 47.2 (CH_2), 13.9 (CH_3); HRMS m/z 454.0736 (M + Na^+), calcd for $C_{21}H_{18}FNO_6SNa^+$ 454.0737.



76cd

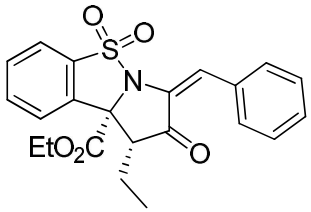
(1R,9bS,E)-ethyl 3-benzylidene-1-methyl-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76fa): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as gummy solid; *E*/*Z* = 2.1:1, *cis*:*trans* = 2.8:1; IR (KBr): ν_{max} 2924, 1737, 1641, 1454, 1333, 1232, 1181, 1025, 757, 691 and 575 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.98-7.82 (3H, m), 7.79-7.63 (3H, m), 7.42-7.37 (3H, m), 7.00 (1H, s), 4.32-4.21 (2H, m), 2.76 (1H, q, *J* = 6.8 Hz), 1.40-1.29 (3H, m), 1.27-1.23 (3H, m); ^{13}C NMR ($CDCl_3$,



76fa

DEPT-135) δ 196.8 (C, *C*=O), 166.5 (C, *O-C=O*), 134.4 (C), 133.7 (CH), 133.6 (C), 132.5 (C), 130.8 (CH), 130.4 (CH), 129.7 (CH), 128.1 (2 x CH), 127.0 (CH), 126.2 (CH), 122.1 (CH), 73.2 (C), 63.0 (CH_2), 54.1 (CH), 14.0 (CH_3), 9.3 (CH_3); ^{1}H NMR (minor isomer $CDCl_3$) δ 7.98-7.82 (3H, m), 7.79-7.63 (3H, m), 7.42-7.37 (3H, m), 7.00 (1H, s), 4.32-4.21 (2H, m), 2.76 (1H, q, *J* = 6.8 Hz), 1.40-1.29 (3H, m), 1.27-1.23 (3H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 198.8 (C, *C*=O), 166.5 (C, *O-C=O*), 134.6 (C), 133.7 (CH), 133.4 (C), 132.5 (C), 130.8 (2 x CH), 130.6 (CH), 130.2 (CH), 129.3 (C), 128.5 (2 x CH), 128.1 (CH), 126.4 (CH),122.4 (CH), 73.7 (C), 62.9 (CH_2), 51.9 (CH), 13.8 (CH_3), 9.7 (CH_3); HRMS m/z 415.1329 ($M + NH_4^+$), calcd for $C_{21}H_{19}NO_5SNH_4$ 415.1328.

(1*R*,9*bS*,*E*)-Ethyl 3-benzylidene-1-ethyl-2-oxo-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-9b-carboxylate 5,5-dioxide (76ga): Prepared following the procedure **7.10** and purified by column chromatography using EtOAc/hexane and isolated as off white solid. Mp 118 °C; *E*/*Z* = 10.6:1; IR (KBr): ν_{max} 2959, 2929, 1737, 1611, 1449, 1388, 1328, 1186, 1141, 1065, 934, 762, 696 and 580 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, major isomer) δ 7.94-7.91 (1H, m), 7.87-7.85 (3H, m), 7.78 (1H, dt, *J* = 7.5, 1.0 Hz), 7.71 (1H, dt, *J* = 8.0, 1.0 Hz), 7.41-7.36 (3H, m), 6.97 (1H, s), 4.25 (2H, dq, *J* = 7.5, 2.0 Hz), 2.60 (1H, dd, *J* = 8.5, 4.0 Hz), 1.94-1.87 (1H, m), 1.76-1.68 (1H, m), 1.25 (3H, t, *J* = 7.5 Hz), 1.17 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135, major isomer) δ 197.3 (C, *C*=O), 166.7 (C, *O-C=O*), 134.5 (C), 133.7 (CH), 132.6 (C), 130.8 (CH), 130.7 (2 x CH, C), 129.7 (CH, C), 128.1 (2 x CH), 127.0 (CH), 126.6 (CH), 122.2 (CH), 73.0 (C), 63.1 (CH_2), 60.2 (CH), 19.1 (CH_2), 13.9 (CH_3), 12.9 (CH_3); HRMS m/z 434.1037 ($M + Na^+$), calcd for $C_{22}H_{21}NO_5SNa$ 434.1038.



76ga

7.11 General procedure for the primary amine/acid-catalyzed asymmetric Barbas [4+2]-cycloaddition reaction:

Primary amine catalyst **17h** (0.03 mmol) and 2-fluoro benzoic acid **49a** (0.045 mmol) in toluene (1.0 mL) were taken in an ordinary glass vial equipped with a magnetic bar at 25 °C. After stirring for 5 min, aldehyde **28** (0.3 mmol) and 1,3-indandione **32** (0.3 mmol) were added and stirred for an additional 5 min followed by addition of enone **27** (0.6 mmol) which were stirred at ambient temperature for 2–72 h. The crude reaction mixture was treated with saturated aqueous ammonium chloride solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, and concentrated. Pure products **33** and **34** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

7.12 General procedure for the primary amine/acid-catalyzed asymmetric double Barbas [4+2]-cycloaddition reaction:

Primary amine catalyst **17h** (0.06 mmol) and 2-fluoro benzoic acid **49a** (0.09 mmol) in toluene (1.0 mL) were taken in an ordinary glass vial equipped with a magnetic bar at 25 °C. After stirring for 5 min, terepthaldehyde **28m** (0.3 mmol) and 1,3-indandione **3** (0.6 mmol) were added which were stirred for an additional 5 min followed by addition of enone **27a** (1.2 mmol) and stirring at ambient temperature for 72 h. The crude reaction mixture was treated with saturated aqueous ammonium chloride solution; the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, and concentrated. Pure products **33am** and **33'am** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

7.13 General procedure for the primary amine/acid-catalyzed racemic Barbas [4+2]-cycloaddition reaction:

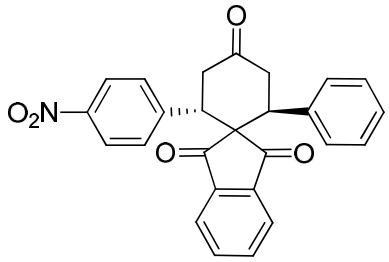
Primary amine catalysts **17h/17g** (each 0.015 mmol) and 2-fluoro benzoic acid **49a** (0.045 mmol) in toluene (1.0 mL) were taken in an ordinary glass vial equipped with a magnetic bar at 25 °C. After stirring for 5 min, aldehyde **28** (0.3 mmol) and 1,3-indandione **32** (0.3 mmol) were added which were stirred for an additional 5 min followed by addition of enone **27** (0.6 mmol) and stirring at ambient temperature for 2-72 h. The crude reaction mixture was treated with saturated aqueous ammonium chloride solution and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, and concentrated. Pure racemic products **33** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

7.14 General procedure for the Suzuki coupling on chiral Barbas [4+2]-cycloaddition product 33ae:

To 25 mL round bottom flask equipped with magnetic stir bar added solution of sodium succinate hexahydrate (100 mg, 0.37 mmol) and chiral product **33ae** (80 mg, 0.18 mmol) in toluene (0.8 mL) and H_2O (0.7 mL) under nitrogen atmosphere followed by addition of $Pd(PPh_3)_4$ (4.47 mg, 0.0039 mmol) in toluene (0.8 mL) and boronic acid (19.45 mg, 0.13 mmol) in EtOH (0.35 mL). The resulting mixture was stirred at 80 °C for 1 h. The addition of $Pd(PPh_3)_4$ (2.23 mg, 0.0019 mmol) in toluene (0.4 mL) and boronic acid (9.72 mg, 0.06 mmol) in the EtOH (0.35 mL) were repeated for further three times at 60 min intervals. Then

mixture was stirred for further 4 h. Then reaction was cooled to 25 °C and the crude reaction mixture was worked up with mixture of H_2O and Et_2O. The aqueous layer was extracted with Et_2O (2 x 5 mL) and the combined organic layers were washed with 1.0 M NaOH, brine and dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to gave crude product, which was purified by column chromatography (silica gel, hexane/ethyl acetate).

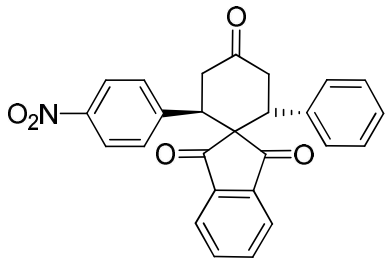
(2*S*,6*S*)-2-(4-nitrophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (33aa):



33aa

Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid, Mp 135 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 43.32 min (major), t_R = 66.72 min (minor); **$[\alpha]_D^{25}$ = +120° (*c* = 1.57 g/100 mL, $CHCl_3$, 99% *ee* and 99:1 *dr*)**, IR (KBr): ν_{max} 3057, 2920, 2849, 1704, 1599, 1517, 1347, 1254, 1106, 1035, 876, 860, 734 and 706 cm^{-1}; ^1H NMRS ($CDCl_3$, 400 MHz) δ 7.92 (2H, d, *J* = 8.4 Hz), 7.59-7.57 (4H, m), 7.16 (2H, d, *J* = 8.8 Hz), 7.03-7.02 (3H, m), 6.91-6.89 (2H, m), 4.09 (1H, dd, *J* = 13.2, 3.2 Hz), 3.93 (1H, dd, *J* = 13.2, 3.2 Hz), 3.64 (1H, dd, *J* = 16.8, 13.6 Hz), 3.56 (1H, dd, *J* = 16.8, 13.2 Hz), 2.80 (2H, td, *J* = 16.8, 2.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.7 (C, *C*=O), 202.3 (C, *C*=O), 202.0 (C, *C*=O), 147.0 (C), 145.0 (C), 141.8 (C), 141.6 (C), 136.6 (C), 136.0 (CH), 135.9 (CH), 129.4 (2 x CH), 128.3 (4 x CH), 127.7 (CH), 123.4 (2 x CH), 122.7 (2 x CH), 61.2 (C), 44.3 (CH), 42.5 (CH), 41.5 (CH_2), 41.2 (CH_2); HRMS m/z 448.1161 ($M + Na^+$), calcd for $C_{26}H_{19}NO_5Na$ 448.1160.

(2*R*,6*R*)-2-(4-nitrophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (33aa):

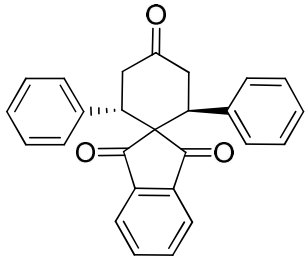


33aa

Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as yellow solid, Mp 135 °C. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 43.32 min (minor), t_R =

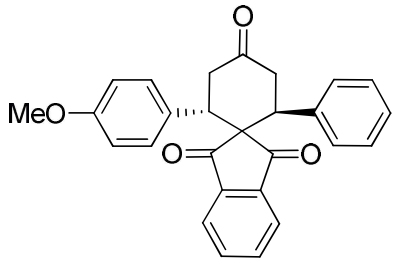
66.72 min (major); **$[\alpha]_D^{25}$ = -142.5° (*c* = 0.37 g/100 mL, $CHCl_3$, 97% *ee*, >99:1 *dr*);** IR (KBr): ν_{max} 3057, 2920, 2849, 1704, 1599, 1517, 1347, 1254, 1106, 1035, 876, 860, 734 and 706 cm^{-1}.

(2*S*,6*S*)-2,6-diphenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (33ab): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as off white gummy liquid; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.34 min (major), t_R = 27.75 min (minor); **$[\alpha]_D^{25}$ = −143.56° (*c* = 1.07 g/100 mL, $CHCl_3$, 96% *ee* and 22:1 *dr*);** IR (Neat): ν_{max} , 2360, 2341, 1720, 1696, 1592, 1495, 1456, 1351, 1329, 1285, 1249, 1215, 1159 and 874 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58-7.51 (4H, m), 7.06-7.00 (6H, m), 6.95-6.93 (4H, m), 3.97 (2H, dd, *J* = 13.2, 3.2 Hz), 3.62 (2H, dd, *J* = 16.8, 13.6 Hz), 2.77 (2H, dd, *J* = 16.8, 3.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.1 (C, *C*=O), 202.9 (2 x C, *C*=O), 142.0 (2 x C), 137.2 (2 x C), 135.4 (2 x CH), 128.3 (4 x CH), 128.2 (4 x CH), 127.3 (2 x CH), 122.4 (2 x CH), 61.6 (C), 43.5 (2 x CH), 41.6 (2 x CH_2); HRMS m/z 403.1310 ($M + Na^+$), calcd for $C_{26}H_{20}O_3Na$ 403.1310.



33ab

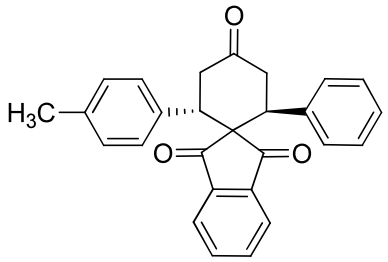
(2*S*,6*S*)-2-(4-methoxyphenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (33ac): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as white gummy liquid; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 75:25, flow rate 1.0 mL/min, λ = 254 nm), t_R = 35.95 min (major), t_R = 53.66 min (minor); **$[\alpha]_D^{25}$ = –195.7° (*c* = 0.80 g/100 mL, $CHCl_3$, 98% *ee* and 9:1 *dr*);** IR (Neat): ν_{max} 2926, 1740, 1701, 1606, 1512, 1333, 1252, 1180, 1035, 880, 834, 761 and 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61-7.53 (4H, m), 7.06-6.99 (3H, m), 6.95-6.93 (2H, m), 6.87 (2H, d, *J* = 8.8 Hz), 6.57 (2H, d, *J* = 8.8 Hz), 3.95 (2H, td, *J* = 14.0, 3.6 Hz), 3.63 (3H, s, OCH_3), 3.62-3.55 (2H, m), 2.75 (2H, ddd, *J* = 16.8, 9.2, 3.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.2 (C, *C*=O), 203.1 (C, *C*=O), 203.0 (C, *C*=O), 158.6 (C),



33ac

142.1 (2 x C), 137.4 (C), 135.4 (CH), 135.3 (CH), 129.4 (2 x CH), 129.3 (C), 128.3 (2 x CH), 128.2 (2 x CH), 127.3 (CH), 122.51 (CH), 122.46 (CH), 113.6 (2 x CH), 61.8 (C), 55.0 (CH_3), 43.6 (CH), 42.8 (CH), 42.0 (CH_2), 41.6 (CH_2); HRMS m/z 411.1596 ($M + H^+$), calcd for $C_{27}H_{22}O_4H$ 411.1596.

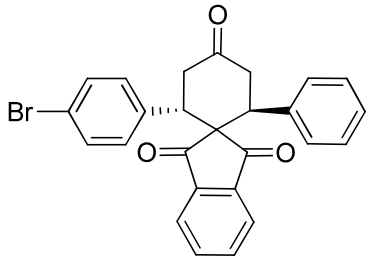
(2*S*,6*S*)-2-phenyl-6-(p-tolyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione (33ad):



33ad

Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 210 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 85:15 flow rate 1.0 mL/min, λ = 254 nm), t_R = 14.12 min (major), t_R = 28.15 min (minor); **$[\alpha]_D^{25}$ = –132.03° (*c* = 0.78 g/100 mL, $CHCl_3$, 99% *ee* and 11:1 *dr*);** IR (KBr): ν_{max} 3057, 2909, 1698, 1605, 1517, 1452, 1413, 1249, 1167, 832, 767, 717 and 564 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.59-7.56 (2H, m), 7.56-7.53 (2H, m), 7.05-6.98 (3H, m), 6.94-6.93 (2H, m), 6.86-6.82 (4H, m), 3.97-3.91 (2H, m), 3.63-3.55 (2H, m), 2.76 (2H, dd, *J* = 16.5, 3.0 Hz), 2.12 (3H, s, C*H*$_3$); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.2 (C, *C*=O), 202.93 (C, *C*=O), 202.86 (C, *C*=O), 142.1 (C), 142.0 (C), 137.4 (C), 136.9 (C), 135.3 (2 x CH), 134.3 (C), 128.9 (2 x CH), 128.3 (2 x CH), 128.21 (2 x CH), 128.16 (2 x CH), 127.3 (CH), 122.5 (CH), 122.46 (CH), 61.6 (C), 43.6 (CH), 43.1 (CH), 41.8 (CH_2), 41.7 (CH_2), 20.8 (CH_3); HRMS m/z 395.1647 ($M + H^+$), calcd for $C_{27}H_{22}O_3H$ 395.1647.

(2*S*,6*S*)-2-(4-bromophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (33ae):

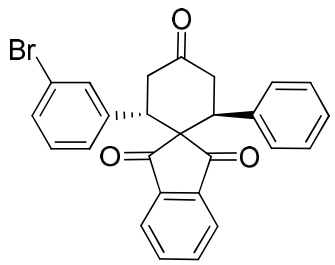


33ae

Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as pale yellow solid. Mp 142 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 85:15, flow rate 0.5 mL/min, λ = 254 nm), t_R = 17.75 min (major), t_R = 35.19 min (minor); **$[\alpha]_D^{25}$ = –143.5° (*c* = 1.14 g/100 mL, $CHCl_3$, 97% *ee* and 5:1 *dr*);** IR (KBr): ν_{max} 3030, 2904, 1693, 1594, 1484, 1452, 1413, 1353, 1238, 1008, 876, 756, 701 and 558 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.63-7.56 (4H, m), 7.18 (2H, d, *J* = 8.4 Hz), 7.06-6.98 (3H, m), 6.92-6.90 (2H, m), 6.84 (2H, d, *J* = 8.4 Hz), 3.93 (2H, ddd, *J* = 13.6, 10.4, 3.2 Hz),

3.62-3.51 (2H, m), 2.75 (2H, dt, *J* = 16.8, 3.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.6 (C, *C*=O), 202.8 (C, *C*=O), 202.5 (C, *C*=O), 142.0 (C), 141.9 (C), 137.0 (C), 136.5 (C), 135.68 (CH), 135.66 (CH), 131.4 (2 x CH), 130.1 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.5 (CH), 122.7 (CH), 122.6 (CH), 121.4 (C), 61.4 (C), 43.9 (CH), 42.5 (CH), 41.6 (2 x CH_2); HRMS m/z 481.0416 ($M + Na^+$), calcd for $C_{26}H_{19}BrO_3Na$ 481.0415.

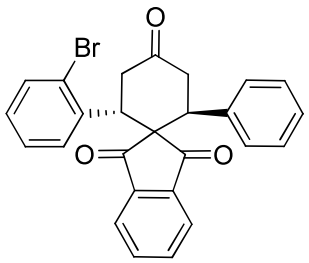
(2*S*,6*S*)-2-(3-bromophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (33af):



33af

Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as gummy liquid; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 85:15, flow rate 0.7 mL/min, λ = 254 nm), t_R = 21.19 min (major), t_R = 40.61 min (minor); **$[\alpha]_D^{25}$ = –58.89° (*c* = 0.17 g/100 mL, $CHCl_3$, 97% *ee* and 7:1 *dr*);** IR (KBr): ν_{max} 2920, 2849, 1698, 1588, 1561, 1424, 1358, 1254, 1079, 734 and 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62-7.60 (1H, m), 7.59-7.55 (3H, m), 7.14 (1H, td, *J* = 7.5, 2.0 Hz), 7.09-7.08 (1H, m), 7.05-7.00 (3H, m), 6.93-6.88 (4H, m), 3.93 (2H, ddd, *J* = 13.5, 5.5, 3.5 Hz), 3.57 (2H, ddd, *J* = 16.5, 13.5, 3.0 Hz), 2.76 (2H, dt, *J* = 17.0, 3.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.4 (C, *C*=O), 202.5 (C, *C*=O), 202.4 (C, *C*=O), 142.0 (C), 141.9 (C), 139.7 (C), 137.0 (C), 135.61 (CH), 135.58 (CH), 131.5 (CH), 130.5 (CH), 129.7 (CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.5 (CH), 127.0 (CH), 122.6 (2 x CH), 122.2 (C), 61.4 (C), 43.7 (CH), 42.8 (CH), 41.5 (CH_2), 41.4 (CH_2); HRMS m/z 459.0596 ($M + H^+$), calcd for $C_{26}H_{19}BrO_3H$ 459.0596.

(2*R*,6*S*)-2-(2-bromophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione

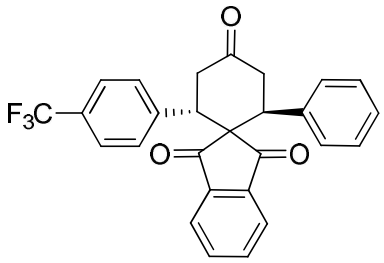


33ag

(33ag): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as off white solid. Mp 132 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AS-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 22.56 min (major), t_R = 34.04 min (minor); **$[\alpha]_D^{25}$ = +15.39° (*c* = 0.10 g/100 mL, $CHCl_3$, 78% *ee* and >99:1 *dr*);** IR (KBr): ν_{max} 3068, 2925, 2849, 1704, 1594, 1468, 1347, 1254, 1024, 887 and 695 $cm^{-}1$; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84 (1H, d, *J* = 7.5 Hz), 7.69-7.66 (1H, m), 7.63-7.61 (2H, m), 7.41

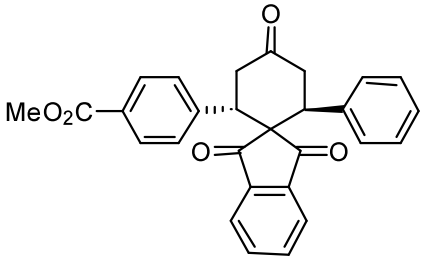
(1H, dd, *J* = 8.0, 1.5 Hz), 7.33 (1H, dt, *J* = 8.0, 1.5 Hz), 7.27 (1H, dd, *J* = 8.0, 1.5 Hz), 7.10 (1H, dt, *J* = 8.0, 1.5 Hz), 7.04-6.97 (5H, m), 4.30 (1H, t, *J* = 6.0 Hz), 3.94 (1H, dd, *J* = 14.0, 4.0 Hz), 3.76 (1H, dd, *J* = 16.5, 14.0 Hz), 3.29 (1H, dd, *J* = 16.5, 6.0 Hz), 2.97 (1H, dd, *J* = 16.0, 5.5 Hz), 2.79 (1H, dd, *J* = 16.5, 3.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.9 (C, *C*=O), 202.6 (C, *C*=O), 199.9 (C, *C*=O), 142.4 (C), 141.0 (C), 138.8 (C), 137.3 (C), 135.7 (CH), 135.4 (CH), 132.9 (CH), 129.8 (CH), 129.0 (CH), 128.7 (2 x CH), 128.2 (2 x CH), 127.7 (CH), 127.5 (CH), 125.9 (C), 123.0 (CH), 122.8 (CH), 59.4 (C), 43.4 (CH), 43.11 (CH_2), 43.08 (CH), 42.9 (CH_2); HRMS m/z 459.0593 (M + H^+), calcd for $C_{26}H_{19}BrO_3H$ 459.0596.

(2*S*,6*S*)-2-phenyl-6-(4-(trifluoromethyl)phenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione (33ah): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 178 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 15.90 min (major), t_R = 27.07 min (minor); **$[\alpha]_D^{25}$ = −188.7° (*c* = 0.71 g/100 mL, $CHCl_3$, 98% *ee* and 9:1 *dr*);** IR (Neat): ν_{max} 2360, 2342, 1739, 1701, 1595, 1424, 1324, 1256, 1246, 1162, 1114, 1068, 864, 841, 756, 719 and 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61-7.55 (4H, m), 7.32 (2H, d, *J* = 8.0 Hz), 7.09 (2H, d, *J* = 8.5 Hz), 7.05-7.01 (3H, m), 6.93-6.91 (2H, m), 4.04 (1H, dd, *J* = 13.5, 3.5 Hz), 3.94 (1H, dd, *J* = 13.5, 3.5 Hz), 3.63 (1H, dd, *J* = 16.5, 13.5 Hz), 3.58 (1H, dd, *J* = 17.0, 13.5 Hz), 2.79 (2H, ddd, *J* = 17.0, 10.5, 3.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.2 (C, *C*=O), 202.6 (C, *C*=O), 202.3 (C, *C*=O), 141.93 (C), 141.86 (C), 141.6 (C), 136.9 (C), 135.74 (CH), 135.68 (CH), 129.6 (C, q, *J* = 32.5 Hz), 128.8 (2 x CH), 128.34 (2 x CH), 128.28 (2 x CH), 127.6 (CH), 125.2 (2 x CH, q, *J* = 3.75 Hz), 123.7 (C, *C*F_3, q, *J* = 270.0 Hz), 122.6 (2 x CH), 61.4 (C), 44.1 (CH), 42.8 (CH), 41.59 (CH_2), 41.39 (CH_2); HRMS m/z 471.1184 (M + Na^+), calcd for $C_{27}H_{19}F_3O_3Na$ 471.1184.



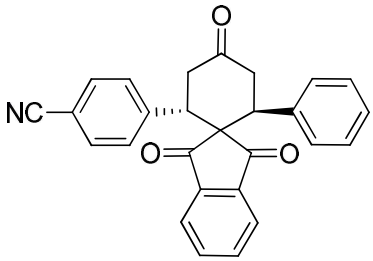
33ah

Methyl 4-((2*S*,6*S*)-1',3',4-trioxo-2-phenyl-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-6-yl)benzoate (33ai): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as off white gummy liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 27.26 min (major), t_R = 43.34 min (minor); **$[\alpha]_D^{25}$ = −177° (*c* = 0.86 g/100 mL, $CHCl_3$, 97% *ee* and 7:1 *dr*);** IR (KBr): ν_{max} 3424, 3062, 2843, 1720, 1610, 1424, 1287, 1112, 1024, 964, 887 and 739 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.70 (2H, d, *J* = 8.5 Hz), 7.57-7.52 (4H, m), 7.03-6.99 (5H, m), 6.91-6.90 (2H, m), 4.03 (1H, dd, *J* = 13.5, 3.0 Hz), 3.94 (1H, dd, *J* = 13.5, 3.0 Hz), 3.78 (3H, s), 3.62 (1H, dd, *J* = 17.0, 13.5 Hz), 3.58 (1H, dd, *J* = 17.0, 13.5 Hz), 2.76 (2H, ddd, *J* = 17.0, 6.0, 3.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.4 (C, *C*=O), 202.5 (C, *C*=O), 202.4 (C, *C*=O), 166.4 (C, *O-C=O*), 142.6 (C), 141.9 (C), 141.8 (C), 136.9 (C), 135.62 (CH), 135.58 (CH), 129.4 (2 x CH), 129.1 (C), 128.4 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.5 (CH), 122.55 (CH), 122.53 (CH), 61.3 (C), 51.9 (CH_3), 43.9 (CH), 43.0 (CH), 41.5 (CH_2), 41.3 (CH_2); HRMS m/z 439.1545 ($M + H^+$), calcd for $C_{28}H_{22}O_5H$ 439.1545.



33ai

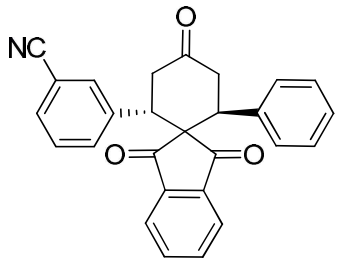
4-((2*S*,6*S*)-1',3',4-trioxo-2-phenyl-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-6-yl)benzonitrile (33aj): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 160 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 43.61 min (major), t_R = 73.70 min (minor); **$[\alpha]_D^{25}$ = –120° (*c* = 0.96 g/100 mL, $CHCl_3$, 99% *ee* and >99:1 *dr*);** IR (KBr): ν_{max} 2925, 2854, 2224, 1742, 1698, 1594, 1452, 1260, 761 and 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.59-7.57 (4H, m), 7.35 (2H, d, *J* = 8.0 Hz), 7.08 (2H, d, *J* = 8.4 Hz), 7.03-7.01 (3H, m), 6.90-6.88 (2H, m), 4.02 (1H, dd, *J* = 13.2, 3.2 Hz), 3.92 (1H, dd, *J* = 13.2, 3.2 Hz), 3.64-3.52 (2H, m), 2.77 (2H, ddd, *J* = 16.8, 7.6, 3.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.8 (C, *C*=O), 202.4 (C, *C*=O), 202.1 (C, *C*=O), 142.9 (C), 141.8 (C), 141.7 (C),



33aj

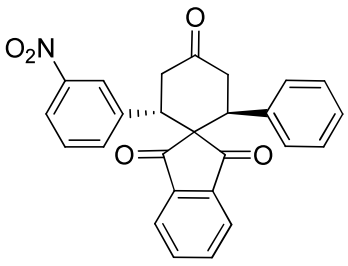
136.6 (C), 135.9 (CH), 135.8 (CH), 132.0 (2 x CH), 129.2 (2 x CH), 128.3 (4 x CH), 127.6 (CH), 122.6 (2 x CH) 118.2 (C), 111.4 (C, *CN*), 61.2 (C), 44.0 (CH), 42.8 (CH), 41.5 (CH_2) 41.0 (CH_2); HRMS m/z 423.1707 ($M + NH_4^+$), calcd for $C_{27}H_{19}NO_3NH_4$ 423.1709.

3-((2*S*,6*S*)-1',3',4-trioxo-2-phenyl-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-6-yl)benzonitrile (33ak): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as pale yellow gummy liquid; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 26.31 min (major), t_R = 40.06 min (minor); **$[\alpha]_D^{25}$ = –104.7° (*c* = 0.95 g/100 mL, $CHCl_3$, 97 % *ee* and 7:1 *dr*);** IR (KBr): ν_{max} 3062, 2920, 2849, 2230, 1704, 1594, 1452, 1347, 1265, 898, 756 and 706 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.63-7.60 (4H, m), 7.36 (1H, d, *J* = 7.5 Hz), 7.26-7.20 (3H, m), 7.08-7.03 (3H, m), 6.93-6.91 (2H, m), 4.01 (1H, dd, *J* = 13.5, 3.5 Hz), 3.93 (1H, dd, *J* = 13.5, 3.5 Hz), 3.61 (1H, dd, *J* = 16.5, 13.5 Hz), 3.57 (1H, dd, *J* = 16.5, 13.5 Hz), 2.80 (2H, dt, *J* = 16.0, 3.5 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.8 (C, *C*=O), 202.4 (C, *C*=O), 202.1 (C, *C*=O), 141.9 (C), 141.8 (C), 139.2 (C), 136.7 (C), 135.9 (CH), 135.8 (CH), 132.9 (CH), 132.0 (CH), 131.2 (CH), 129.2 (CH), 128.3 (4 x CH), 127.7 (CH), 122.8 (CH), 122.7 (CH), 118.2 (C, *CN*), 112.5 (C), 61.3 (C), 44.1 (CH), 42.5 (CH), 41.6 (CH_2), 41.3 (CH_2); HRMS m/z 428.1263 ($M + Na^+$), calcd for $C_{27}H_{19}NO_3Na$ 428.1262.



33ak

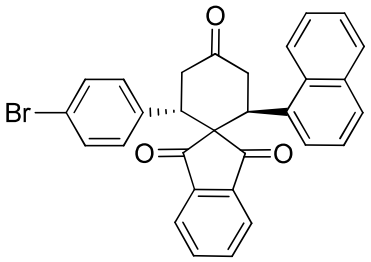
(2*S*,6*S*)-2-(3-nitrophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (33al): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as yellow liquid; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 26.37 min (major), t_R = 32.19 min (minor); **$[\alpha]_D^{25}$ = –255° (*c* = 0.65 g/100 mL, $CHCl_3$, 95% *ee* and 15:1 *dr*);** IR (Neat): ν_{max} 2922, 2852, 1731, 1691, 1636, 1603, 1587, 1517, 1339, 1308, 1233, 1202, 1091, 991, 962, 856, 785, 748, 736 and 717 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.95 (1H, qd, *J* = 4.0, 1.2 Hz), 7.86 (1H, t, *J* =



33al

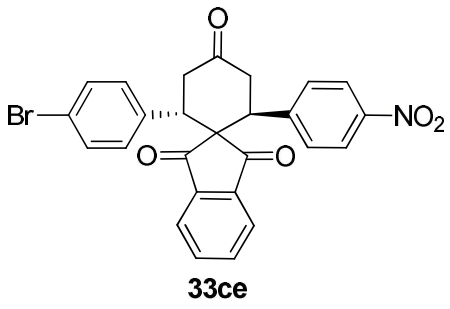
1.6 Hz), 7.64-7.59 (4H, m), 7.37-7.28 (2H, m), 7.10-7.04 (3H, m), 6.95-6.93 (2H, m), 4.11 (1H, dd, *J* = 13.2, 3.2 Hz), 3.96 (1H, dd, *J* = 12.8, 3.2 Hz), 3.67 (1H, dd, *J* = 16.8, 13.2 Hz), 3.61 (1H, dd, *J* = 17.2, 13.2 Hz), 2.85 (2H, br td, *J* = 16.8, 4.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.8 (C, *C*=O), 202.3 (C, *C*=O), 202.1 (C, *C*=O), 147.9 (C), 141.9 (C), 141.8 (C), 139.8 (C), 136.7 (C), 136.0 (CH), 135.8 (CH), 134.4 (CH), 129.3 (CH), 128.4 (4 x CH), 127.7 (CH), 123.5 (CH), 122.9 (CH), 122.7 (CH), 122.6 (CH), 61.3 (C), 44.2 (CH), 42.5 (CH), 41.6 (CH_2), 41.4 (CH_2); HRMS m/z 448.1161 ($M + Na^+$), calcd for $C_{26}H_{19}NO_5Na$ 448.1161.

(2*S*,6*S*)-2-(4-bromophenyl)-6-(naphthalen-1-yl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione (33be): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 180 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 52.44 min (major), t_R = 81.52 min (minor); **$[\alpha]_D^{25}$ = −62.62° (*c* = 0.91 g/100 mL, $CHCl_3$, 98% *ee* and >99:1 *dr*)**; IR (Neat): ν_{max} 1739, 1700, 1609, 1513, 1489, 1302, 1251, 1181, 1035, 1010, 821, 777 and 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68-7.66 (1H, m), 7.60-7.54 (2H, m), 7.44-7.42 (1H, m), 7.39-7.34 (5H, m), 7.29-7.26 (2H, m), 7.17 (2H, d, *J* = 8.8 Hz), 6.91 (2H, d, *J* = 8.4 Hz), 4.77 (1H, dd, *J* = 11.2, 4.0 Hz), 4.11 (1H, dd, *J* = 14.0, 3.6 Hz), 3.80 (1H, dd, *J* = 16.8, 14.0 Hz), 3.58 (1H, dd, *J* = 16.4, 11.2 Hz), 2.92 (1H, dd, *J* = 16.4, 4.0 Hz), 2.82 (1H, dd, *J* = 16.8, 3.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135,) δ 209.7 (C, *C*=O), 202.8 (C, *C*=O), 201.5 (C, *C*=O), 141.7 (C), 141.4 (C), 136.6 (C), 135.5 (CH), 135.1 (CH), 133.8 (C), 133.3 (C), 131.3 (2 x CH), 131.0 (C), 130.3 (2 x CH), 128.7 (CH), 128.0 (CH), 126.9 (CH), 126.0 (CH), 125.3 (CH), 124.9 (CH), 122.9 (CH), 122.5 (CH), 122.3 (CH), 121.3 (C), 61.2 (C), 43.1 (CH_2), 41.8 (CH), 41.7 (CH_2), 38.2 (CH); HRMS m/z 531.0572 ($M + Na^+$), calcd for $C_{30}H_{21}BrO_3Na$ 531.0572.



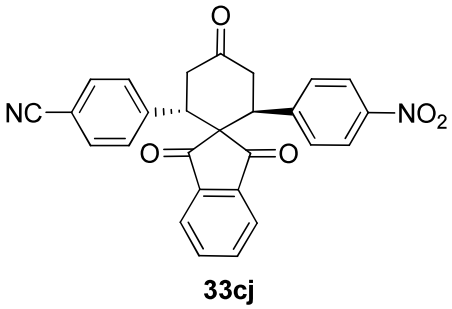
33be

(2*S*,6*S*)-2-(4-bromophenyl)-6-(4-nitrophenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione (33ce): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as pale yellow solid. Mp 140 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 85:15 flow rate 0.8 mL/min, λ = 254 nm), t_R = 61.69 min (major), t_R = 103.17 min (minor); **$[\alpha]_D^{25}$ = –94.71° (*c* = 0.83 g/100 mL, $CHCl_3$, 99% *ee* and >99:1 *dr*);** IR (Neat): ν_{max} 1739, 1701, 1595, 1520, 1488, 1407, 1346, 1255, 1175, 1075, 1011, 889, 824, 807, 755 and 713 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.91 (2H, d, *J* = 8.8 Hz), 7.63-7.61 (4H, m), 7.16 (2H, d, *J* = 8.4 Hz), 7.13 (2H, d, *J* = 8.8 Hz), 6.79 (2H, d, *J* = 8.4 Hz), 4.04 (1H, dd, *J* = 13.2, 3.2 Hz), 3.89 (1H, dd, *J* = 13.2, 3.2 Hz), 3.58 (1H, dd, *J* = 16.4, 13.2 Hz), 3.53 (1H, dd, *J* = 16.8, 13.2 Hz), 2.78 (2H, ddd, *J* = 16.0, 11.2, 3.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.1 (C, *C*=O), 202.0 (C, *C*=O), 201.9 (C, *C*=O), 147.0 (C), 144.7 (C), 141.6 (C), 141.5 (C), 136.25 (CH), 136.20 (CH), 135.8 (C), 131.5 (2 x CH), 130.0 (2 x CH), 129.4 (2 x CH), 123.4 (2 x CH), 122.9 (CH), 122.8 (CH), 121.7 (C), 60.9 (C), 43.3 (CH), 42.9 (CH), 41.5 (CH_2), 41.1 (CH_2); LCMS m/z 504.45 (M + 1), calcd for $C_{26}H_{18}BrNO_5$ 503.0368; calcd for $C_{26}H_{18}BrNO_5$ (503.0368): C, 61.92; H, 3.60; N, 2.78. Found C, 61.85; H, 3.56; N, 2.72%.



33ce

4-((2*S*,6*S*)-2-(4-nitrophenyl)-1',3',4-trioxo-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-6-yl)benzonitrile (33cj):

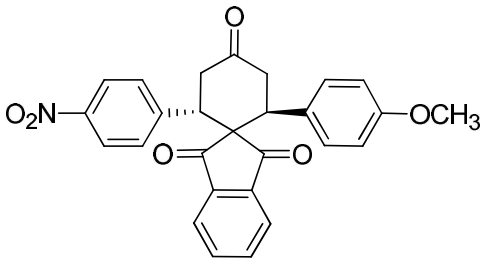


33cj

Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 230 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 70:30, flow rate 1.0 mL/min, λ = 254 nm), t_R = 47.75 min (minor), t_R = 57.03 min (major); **$[\alpha]_D^{25}$ = –260° (*c* = 0.86 g/100 mL, $CHCl_3$, 97% *ee* and 10:1 *dr*);** IR (KBr): ν_{max} 3051, 2925, 2235, 1747, 1704, 1605, 1517, 1430, 1347, 1260, 887, 701, 596 and 487 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.94 (2H, d, *J* = 8.0 Hz),

7.65-7.63 (4H, m), 7.37 (2H, d, *J* = 8.0 Hz), 7.13 (2H, d, *J* = 8.0 Hz), 7.06 (2H, d, *J* = 7.5 Hz), 4.05 (1H, br d, *J* = 13.0 Hz), 3.99 (1H, br d, *J* = 12.5 Hz), 3.62 (1H, br d, *J* = 15.0 Hz), 3.56 (1H, br d, *J* = 14.0 Hz), 2.83 (2H, br td, *J* = 16.5, 3.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.4 (C, *C*=O), 201.67 (C, *C*=O), 201.64 (C, *C*=O), 147.2 (C), 144.4 (C), 142.2 (C), 141.5 (2 x C), 136.53 (CH), 136.5 (CH), 132.1 (2 x CH), 129.4 (2 x CH), 129.2 (2 x CH), 123.5 (2 x CH), 123.0 (2 x CH), 118.0 (C), 111.8 (C), 60.8 (C), 43.7 (CH), 43.2 (CH), 41.2 (CH_2), 41.1 (CH_2); HRMS m/z 473.1114 (M + Na^+), calcd for $C_{27}H_{18}N_2O_5Na$ 473.1113.

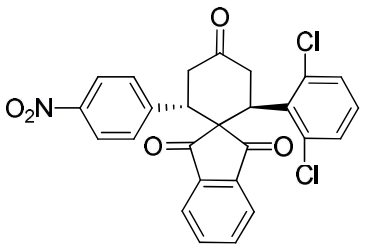
(2*S*,6*S*)-2-(4-methoxyphenyl)-6-(4-nitrophenyl)spiro[cyclohexane-1,2'-indene]-1',3',4



33da

trione (33da): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 220 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 56.46 min (major), t_R = 74.50 min (minor); **$[\alpha]_D^{25}$ = –218° (*c* = 1.07 g/100 mL, $CHCl_3$, 99% *ee* and 37:1 *dr*);** IR (KBr): ν_{max} 2968, 1698, 1596, 1520, 1346, 1256, 1160, 1128, 949, 858, 778, 755 and 718 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (2H, d, *J* = 8.4 Hz), 7.62 (4H, br s), 7.18 (2H, d, *J* = 8.8 Hz), 6.84 (2H, d, *J* = 8.4 Hz), 6.57 (2H, d, *J* = 8.4 Hz), 4.09 (1H, dd, *J* = 13.2, 3.6 Hz), 3.91 (1H, dd, *J* = 12.8, 3.2 Hz), 3.66-3.51 (2H, m), 3.63 (3H, s), 2.80 (2H, ddd, *J* = 16.5, 9.2, 3.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.7 (C, *C*=O), 202.4 (C, *C*=O), 202.1 (C, *C*=O), 158.7 (C), 146.9 (C), 145.1 (C), 141.8 (C), 141.6 (C), 135.9 (CH), 135.8 (CH), 129.35 (2 x CH), 129.33 (2 x CH), 128.5 (C), 123.3 (2 x CH), 122.7 (CH), 122.6 (CH), 113.6 (2 x CH), 61.3 (C), 54.9 (O*C*H_3), 43.5 (CH), 42.6 (CH), 41.9 (CH_2), 41.1 (CH_2); HRMS m/z 478.1264 (M + Na^+), calcd for $C_{27}H_{21}NO_6Na$ 478.1267;

(2*R*,6*S*)-2-(2,6-dichlorophenyl)-6-(4-nitrophenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-

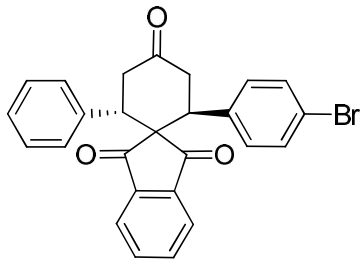


33ea

trione (33ea): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as pale yellow solid. Mp 190 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol =

85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 39.71 min (minor), t_R = 53.18 min (major); **$[\alpha]_D^{25}$ = –42.2° (*c* = 0.73 g/100 mL, $CHCl_3$, >99% *ee* and 7:1 *dr*);** IR (KBr): ν_{max} 1734, 1698, 1595, 1519, 1346, 1248, 877, 854, 750, 739 and 707 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.90 (1H, br d, *J* = 7.6 Hz), 7.86 (2H, br d, *J* = 8.8 Hz), 7.74 (1H, dt, *J* = 7.6, 1.2 Hz), 7.66 (1H, dt, *J* = 7.6, 1.2 Hz), 7.57 (1H, br d, *J* = 7.6 Hz), 7.38 (1H, dd, *J* = 7.6, 1.6 Hz), 7.21-7.14 (4H, m), 4.57 (1H, dd, *J* = 6.8, 5.6 Hz), 4.48 (1H, dd, *J* = 13.6, 4.8 Hz), 3.54 (1H, dd, *J* = 17.6, 13.2 Hz), 3.25-3.24 (2H, m), 2.84 (1H, dd, *J* = 17.6, 4.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 206.7 (C, *C*=O), 202.1 (C, *C*=O), 198.8 (C, *C*=O), 147.1 (C), 145.2 (C), 142.2 (C), 140.4 (C), 137.4 (C), 136.4 (CH), 136.0 (CH), 135.2 (C), 135.0 (C), 130.6 (CH), 129.8 (2 x CH), 129.4 (CH), 128.7 (CH), 123.4 (2 x CH), 123.2 (CH), 122.9 (CH), 59.3 (C), 43.8 (CH), 41.8 (CH_2), 41.0 (CH), 40.7 (CH_2); HRMS m/z 494.0561 ($M + H^+$), calcd for $C_{26}H_{17}Cl_2NO_5H$ 494.0562.

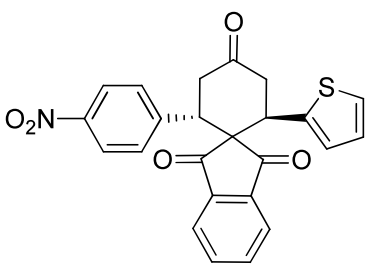
(2*S*,6*S*)-2-(4-bromophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (33fb):



33fb

Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as pale yellow solid. Mp 142 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 85:15, flow rate 0.5 mL/min, λ = 254 nm), t_R = 17.75 min (major), t_R = 35.19 min (minor); **$[\alpha]_D^{25}$ = –141.7° (*c* = 0.8 g/100 mL, $CHCl_3$, 96% *ee* and 7:1 *dr*);** IR (KBr): ν_{max} 3030, 2904, 1693, 1594, 1484, 1452, 1413, 1353, 1238, 1008, 876, 756, 701 and 558 cm^{-1}.

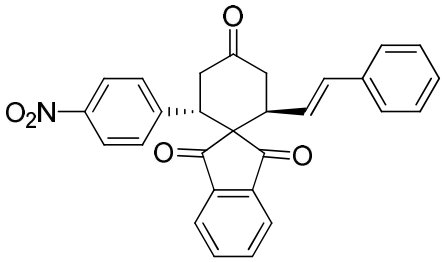
(2*S*,6*R*)-2-(4-nitrophenyl)-6-(thiophen-2-yl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione (33ga): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as off pale yellow solid. Mp 150 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 56.83 min (major), t_R = 63.83 min (minor); **$[\alpha]_D^{25}$ = –200.2° (*c* = 1.67 g/100 mL, $CHCl_3$, 99% *ee* and 15:1 *dr*);** IR (KBr): ν_{max} 3073, 2925, 1698, 1599, 1517, 1424, 1347,



33ga

1013, 860, 739 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.96 (2H, d, *J* = 8.8 Hz), 7.74-7.68 (4H, m), 7.16 (2H, d, *J* = 8.8 Hz), 6.98 (1H, dd, *J* = 5.2, 0.8 Hz), 6.73 (1H, dd, *J* = 5.2, 3.6 Hz), 6.65-6.64 (1H, m), 4.21 (1H, dd, *J* = 12.0, 3.6 Hz), 4.06 (1H, dd, *J* = 12.8, 3.6 Hz), 3.55 (1H, dd, *J* = 16.4, 12.4 Hz), 3.49 (1H, dd, *J* = 16.8, 12.0 Hz), 3.00 (1H, dd, *J* = 16.8, 4.0 Hz), 2.84 (1H, dd, *J* = 16.4, 4.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.6 (C, *C*=O), 201.8 (C, *C*=O), 201.4 (C, *C*=O), 147.1 (C), 145.0 (C), 141.8 (C), 141.7 (C), 139.4 (C), 136.2 (CH), 136.1 (CH), 129.5 (2 x CH), 126.8 (CH), 126.7 (CH), 124.8 (CH), 123.5 (2 x CH), 123.1 (CH), 123.0 (CH), 60.9 (C), 43.14 (CH), 43.08 (CH_2), 41.5 (CH_2), 39.7 (CH); HRMS m/z 454.0725 ($M + Na^+$), calcd for $C_{24}H_{17}NO_5SNa$ 454.0725.

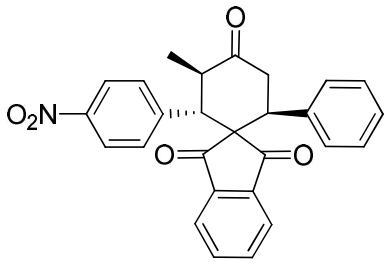
(2*S*,6*S*)-2-(4-nitrophenyl)-6-((*E*)-styryl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione



33ha

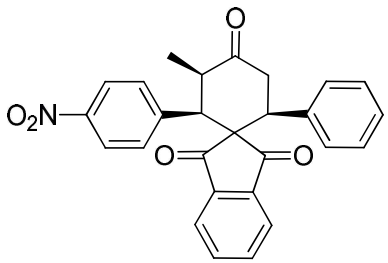
(33ha): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as gummy liquid; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 31.46 min (major), t_R = 40.52 min (minor); **$[\alpha]_D^{25}$ = –148.6° (*c* = 0.18 g/100 mL, $CHCl_3$, 96% *ee* and 99:1 *dr*);** IR (KBr): ν_{max} 2923, 2853, 1731, 1698, 1593, 1519, 1345, 1299, 1242, 1109, 776 and 750 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.95 (2H, d, *J* = 8.5 Hz), 7.85-7.80 (2H, m), 7.77-7.72 (2H, m), 7.27-7.20 (7H, m), 6.33 (1H, d, *J* = 16.0 Hz), 6.13 (1H, dd, *J* = 15.5, 8.0 Hz), 4.02 (1H, dd, *J* = 13.5, 4.0 Hz), 3.61 (1H, dd, *J* = 13.5, 15.5 Hz), 3.32 (1H, dt, *J* = 8.0, 5.0 Hz), 3.08 (1H, dd, *J* = 16.0, 4.5 Hz), 3.00 (1H, dd, *J* = 16.0, 8.0 Hz), 2.70 (1H, dd, *J* = 16.0, 4.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.8 (C, *C*=O), 202.0 (C, *C*=O), 200.7 (C, *C*=O), 147.2 (C), 145.3 (C), 141.5 (C), 141.3 (C), 136.4 (CH), 136.3 (CH), 136.1 (C), 133.8 (CH), 129.6 (2 x CH), 128.5 (2 x CH), 128.0 (CH), 126.5 (2 x CH), 125.7 (CH), 123.5 (2 x CH), 123.34 (CH), 123.32 (CH), 60.1 (C), 43.2 (CH), 42.9 (CH), 42.2 (CH_2), 42.1 (CH_2); HRMS m/z 452.1497 ($M + H^+$), calcd for $C_{28}H_{21}NO_5H$ 452.1498.

(2*S*,3*R*,6*S*)-3-methyl-2-(4-nitrophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (33ia): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as off white solid. Mp 200 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 19.18 min (major), t_R = 33.91 min (minor); **$[\alpha]_D^{25}$ = +13.6° (*c* = 0.43 g/100 mL, $CHCl_3$, 95% *ee* and 3:1);** IR (KBr): ν_{max} 3062, 2920, 2849, 1698, 1599, 1528, 1457, 1353, 1254, 904, 854, 739 and 706 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.89 (2H, d, *J* = 8.8 Hz), 7.64 (1H, d, *J* = 7.6 Hz), 7.53-7.49 (1H, m), 7.46-7.39 (2H, m), 7.22 (2H, d, *J* = 8.8 Hz), 7.00-6.91 (5H, m), 3.95-3.87 (2H, m), 3.74 (1H, dd, *J* = 14.4, 3.6 Hz), 3.54 (1H, d, *J* = 12.8 Hz), 2.70 (1H, dd, *J* = 13.6, 3.6 Hz), 0.88 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.7 (C, *C*=O), 203.0 (C, *C*=O), 201.2 (C, *C*=O), 147.0 (C), 144.6 (C), 142.5 (C), 141.5 (C), 136.8 (C), 135.8 (2 x CH), 129.6 (2 x CH, poor resolution), 128.4 (2 x CH), 127.9 (3 x CH), 123.6 (2 x CH), 122.6 (CH), 122.3 (CH), 62.7 (C), 54.8 (CH), 49.3 (CH), 44.3 (CH), 43.1 (CH_2), 12.2 (CH_3); HRMS m/z 462.1318 ($M + Na^+$), calcd for $C_{27}H_{21}NO_5Na$ 462.1317.



33ia

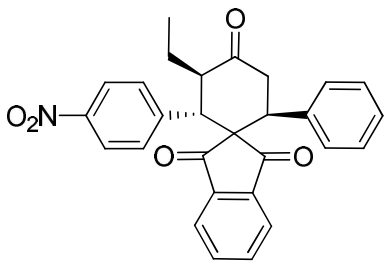
(2*R*,3*R*,6*S*)-3-methyl-2-(4-nitrophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (34ia): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as gummy liquid; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 80:20, flow rate 0.5 mL/min, λ = 254 nm), t_R = 23.56 min (major), t_R = 35.15 min (minor); **$[\alpha]_D^{25}$ = −172.5° (*c* = 0.57 g/100 mL, $CHCl_3$, 98% *ee* and 3:1 *dr*);** IR (KBr): ν_{max} 1736, 1695, 1594, 1516, 1495, 1345, 1271, 1247, 1141, 877, 854, 762 and 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (2H, br, s), 7.70-7.68 (1H, m), 7.64-7.53 (3H, m), 7.20-7.09 (5H, m), 6.90-6.88 (2H, m), 3.88 (1H, dd, *J* = 10.8, 4.4 Hz), 3.83-3.80 (1H, m), 3.76-3.70 (1H, m), 3.39 (1H, dd, *J* = 16.8, 10.8 Hz), 3.02 (1H, dd, *J* = 16.8, 4.4 Hz), 1.0 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.4 (C, *C*=O), 202.9 (C, *C*=O), 201.1 (C, *C*=O), 146.9 (C), 144.3 (C), 141.6 (C), 141.3 (C), 137.4 (C), 136.1 (CH), 135.9 (CH), 130.5



34ia

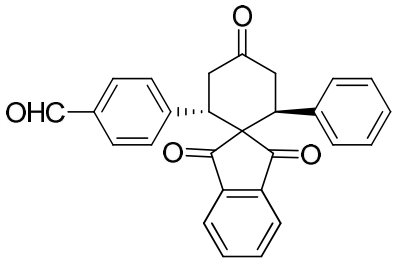
(2 x CH, poor resolution), 128.5 (2 x CH), 128.4 (2 x CH), 127.7 (CH), 123.3 (2 x CH), 122.9 (CH), 122.8 (CH), 62.4 (C), 49.1 (CH), 44.4 (CH), 43.1 (CH), 41.3 (CH_2), 12.6 (CH_3); HRMS m/z 462.1319 ($M + Na^+$), calcd for $C_{27}H_{21}NO_5Na$ 462.1317.

(2*S*,3*R*,6*S*)-3-ethyl-2-(4-nitrophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (33ja): Prepared following the procedure **7.11** and purified by column chromatography using EtOAc/hexane and isolated as white solid. Mp 174 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 11.86 min (minor), t_R = 13.67 min (major); **$[\alpha]_D^{25}$ = −13.2° (*c* = 1.28 g/100 mL, $CHCl_3$, 99% *ee* and 25:1 *dr*);** IR (Neat): ν_{max} 3051, 2914, 1704, 1605, 1523, 1452, 1353, 1265 and 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.87 (2H, d, *J* = 9.2 Hz), 7.62 (1H, d, *J* = 7.6 Hz), 7.50-7.46 (1H, m), 7.44-7.37 (2H, m), 7.22 (2H, d, *J* = 8.4 Hz), 6.97-6.89 (5H, m), 3.89 (1H, t, *J* = 14.0 Hz), 3.81-3.68 (3H, m), 2.66 (1H, dd, *J* = 13.6, 3.6 Hz), 1.39-1.32 (2H, m), 0.83 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 208.0 (C, *C*=O), 203.0 (C, *C*=O), 201.3 (C, *C*=O), 146.9 (C), 144.5 (C), 142.3 (C), 141.4 (C), 136.7 (C), 135.7 (2 x CH), 129.7 (2 x CH, poor resolution), 128.3 (2 x CH), 127.8 (3 x CH), 123.4 (2 x CH), 122.5 (CH), 122.2 (CH), 62.6 (C), 52.2 (CH), 49.8 (CH), 49.1 (CH), 43.4 (CH_2), 18.9 (CH_2), 11.0 (CH_3); HRMS m/z 454.1654 ($M + H^+$), calcd for $C_{28}H_{23}NO_5H$ 454.1654 and m/z 476.1474 ($M + Na^+$), calcd for $C_{28}H_{23}NO_5Na$ 476.1474.



33ja

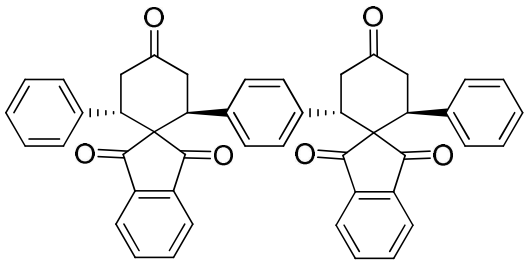
4-((2*S*,6*S*)-1',3',4-trioxo-2-phenyl-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-6-yl)benzaldehyde (33am): Prepared following the procedure **7.12** and purified by column chromatography using EtOAc/hexane and isolated as solid. Mp 232 °C; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 36.28 min (major), t_R = 60.17 min (minor); **$[\alpha]_D^{25}$ = – 60.2° (*c* = 0.92 g/100 mL, $CHCl_3$, 94% *ee* and 99:1 *dr*);** IR (KBr): ν_{max} 1718, 1698, 1606, 1306, 1255, 1214, 1171, 865, 853, 753 and 712 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.82 (1H, s), 7.59-7.55 (6H, m),



33am

7.14 (2H, d, *J* = 8.5 Hz), 7.06-6.99 (3H, m), 6.93-6.91 (2H, m), 4.06 (1H, dd, *J* = 13.0, 3.0 Hz), 3.95 (1H, dd, *J* = 13.0, 3.0 Hz), 3.64 (1H, dd, *J* = 17.0, 13.5 Hz), 3.60 (1H, dd, *J* = 17.0, 3.5 Hz), 2.80 (2H, dd, *J* = 17.0, 3.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.2 (C, *C*=O), 202.5 (C, *C*=O), 202.4 (C, *C*=O), 191.5 (C, *HC*=O), 144.4 (C), 141.9 (C), 141.8 (C), 136.8 (C), 135.8 (CH), 135.7 (CH), 135.3 (C), 129.6 (2 x CH), 129.1 (2 x CH), 128.35 (2 x CH), 128.3 (2 x CH), 127.6 (CH), 122.65 (CH), 122.62 (CH), 61.4 (C), 44.0 (CH), 43.2 (CH), 41.6 (CH_2), 41.3 (CH_2); HRMS m/z 431.1259 (M + Na), calcd for $C_{27}H_{20}O_4Na$ 431.1254.

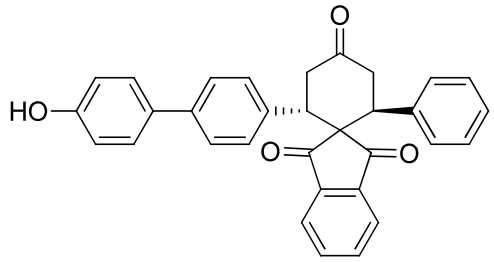
(2*S*,6*S*)-2-phenyl-6-(4-((2*S*,6*S*)-1',3',4-trioxo-2-phenyl-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-6-yl)phenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione (33'am):



33'am

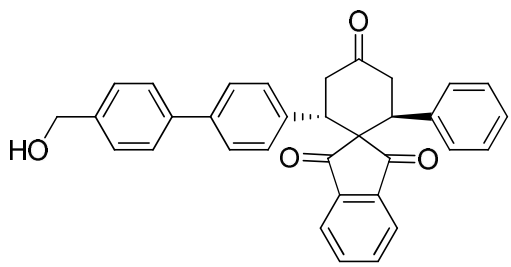
Prepared following the procedure **7.12** and purified by column chromatography using EtOAc/hexane and isolated as gummy liquid; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 34.99 min (major), t_R = 55.48 min (minor); **$[\alpha]_D^{25}$ = –176.4° (*c* = 0.87 g/100 mL, $CHCl_3$, 94% *ee* and 99:1 *dr*);** IR (Neat): ν_{max} 2958, 2914, 1693, 1594, 1501, 1408, 1358, 1249, 876, 767, 695 and 586 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54-7.47 (8H, m), 7.00-6.97 (6H, m), 6.86-6.83 (4H, m), 6.63 (4H, s), 3.83 (2H, dd, *J* = 13.6, 3.2 Hz), 3.74 (2H, dd, *J* = 13.2, 3.2 Hz), 3.53-3.42 (4H, m), 2.69 (2H, dd, *J* = 16.8, 3.2 Hz), 2.58 (2H, dd, *J* = 16.8, 3.2 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 209.9 (2 x C, *C*=O), 202.7 (2 x C, *C*=O), 202.5 (2 x C, *C*=O), 141.93 (2 x C), 141.91 (2 x C), 137.1 (2 x C), 136.6 (2 x C), 135.4 (4 x CH), 128.3 (4 x CH), 128.25 (4 x CH), 129.18 (4 x CH), 127.4 (2 x CH), 122.5 (4 x CH), 61.3 (2 x C), 43.6 (2 x CH), 42.7 (2 x CH), 41.49 (2 x CH_2), 41.47 (2 x CH_2); HRMS m/z 705.2255 (M + Na), calcd for $C_{46}H_{34}O_6Na$ 705.2253.

(2*S*,6*S*)-2-(4'-hydroxy-[1,1'-biphenyl]-4-yl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (33an): Prepared following the procedures **7.11** or **7.14** and purified by column chromatography using EtOAc/hexane and isolated as gummy liquid; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 80:20, flow rate 0.8 mL/min, λ = 254 nm), t_R = 23.35 min (major), t_R = 34.71 min (minor); **$[\alpha]_D^{25}$ = –160.25° (*c* = 1.40 g/100 mL, $CHCl_3$, 98.6% *e* and 8:1 *dr*);** IR (Neat): ν_{max} 3380, 2925, 2854, 1704, 1588, 1495, 1457, 1353, 1265, 1172, 876, 838, 756 and 701 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.61-7.57 (2H, m), 7.56-7.53 (2H, m), 7.29 (2H, d, *J* = 8.4 Hz), 7.22 (2H, d, *J* = 8.4 Hz), 7.08-7.02 (3H, m), 7.00-6.94 (4H, m), 6.81 (2H, d, *J* = 8.8 Hz), 5.18 (1H, br s), 4.00 (2H, dt, *J* = 13.6, 3.2 Hz), 3.65 (1H, dd, *J* = 13.6, 6.8 Hz), 3.61 (1H, dd, *J* = 13.6, 6.8 Hz), 2.83 (1H, dd, *J* = 6.0, 3.6 Hz), 2.79 (1H, dd, *J* = 5.6, 3.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.3 (C, *C*=O), 203.1 (C, *C*=O), 202.9 (C, *C*=O), 155.3 (C), 142.1 (2 x C), 139.6 (C), 137.3 (C), 135.7 (C), 135.5 (2 x CH), 132.8 (C), 128.8 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 127.5 (CH), 126.3 (2 x CH), 122.63 (CH), 122.58 (CH), 115.6 (2 x CH), 61.7 (C), 43.8 (CH), 43.1 (CH), 41.8 (CH_2), 41.7 (CH_2); HRMS m/z 495.1573 (M + Na), calcd for $C_{32}H_{24}O_4Na$ 495.1572.



33an

(2*S*,6*S*)-2-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (33ao): Prepared following the procedures **7.11, 7.14** and purified by column chromatography using EtOAc/hexane and isolated as gummy liquid; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 80:10, flow rate 0.8 mL/min, λ = 254 nm), t_R = 33.81 min (major), t_R = 38.05 min (minor); **$[\alpha]_D^{25}$ = –193.2° (*c* = 1.42 g/100 mL, $CHCl_3$, >99% *ee* and 15:1 *dr*);** IR (Neat): ν_{max} 3424, 3030, 1704, 1583, 1490, 1463, 1413, 1353, 1249, 1052, 997, 871, 816, 767 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.61-7.56 (2H, m), 7.56-7.52 (2H, m), 7.42 (2H, d, *J* = 8.4 Hz), 7.36 (2H, d, *J* = 8.4 Hz), 7.28 (2H, d, *J* = 8.4 Hz), 7.08-7.01 (5H, m), 6.96-6.94



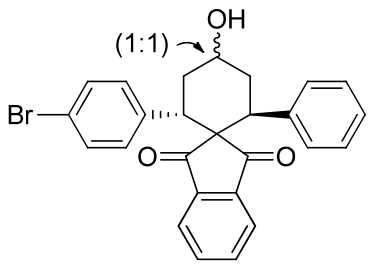
33ao

(2H, m), 4.69 (2H, s), 4.02 (1H, dd, *J* = 13.6, 3.2 Hz), 3.98 (1H, dd, *J* = 13.6, 3.2 Hz), 3.65 (1H, dd, *J* = 16.8, 10.8 Hz), 3.62 (1H, dd, *J* = 16.8, 11.2 Hz), 2.80 (2H, td, *J* = 16.8, 3.6 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 210.1 (C, *C*=O), 202.95 (C, *C*=O), 202.88 (C, *C*=O), 142.1 (2 x C), 140.0 (C), 139.65 (C), 139.58 (C), 137.3 (C), 136.5 (C), 135.5 (2 x CH), 128.9 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 127.5 (CH), 127.4 (2 x CH), 127.0 (2 x CH), 126.8 (2 x CH), 122.60 (CH), 122.57 (CH), 65.0 (CH_2), 61.7 (C), 43.7 (CH), 43.1 (CH), 41.73 (CH_2), 41.68 (CH_2); HRMS m/z 509.1725 (M + Na), calcd for $C_{33}H_{26}O_4Na$ 509.1729.

7.15 General procedure for the reduction of chiral Barbas [4+2]-cycloaddition products 33:

To 25 mL round bottom flask equipped with magnetic stir bar added product **33/34** (0.3 mmol) in dry methanol (2.0 mL) followed by addition of $NaBH_4$ (0.36 mmol) at 0 °C. Slowly reaction mixture was brought to room temperature and stirred for 0.5 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, and concentrated. Pure alcohols **84** and **85** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

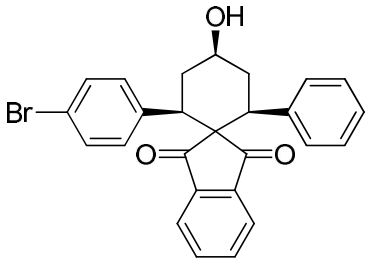
(2*S*,6*S*)-2-(4-bromophenyl)-4-hydroxy-6-phenylspiro[cyclohexane-1,2'-indene]-1',3'-dione (84ae): Prepared following the procedure **7.15** and purified by column chromatography using EtOAc/hexane and isolated as gummy liquid; IR (Neat): ν_{max} 3441, 3057, 2925, 1736, 1698, 1588, 1490, 1413, 1353, 1260, 1090, 1013, 827 and 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, 1:1 mixture of isomers) δ 7.57-7.47 (8H, m), 7.13 (4H, dd, *J* = 8.0, 6.0 Hz), 7.01-6.92 (10H, m), 6.87 (4H, dd, *J* = 8.4, 2.8 Hz), 4.59-4.58 (2H, m), 3.87 (2H, dt, *J* = 12.8, 2.4 Hz), 3.53 (2H, dt, *J* = 12.0, 2.0 Hz), 3.01-2.91 (2H, m), 2.76-2.66 (2H, m), 2.35-2.26 (2H, m), 1.96-1.89 (4H, m); ^{13}C NMR ($CDCl_3$, DEPT-135, 1:1 mixture of isomers) δ 203.9 (C, *C*=O), 203.6 (C, *C*=O), 203.5 (C, *C*=O), 203.4 (C, *C*=O), 142.13 (2 x C), 142.08 (2 x C), 139.1 (C), 138.8 (C), 138.6 (C), 138.4 (C), 135.24 (2 x CH), 135.21 (CH), 135.18 (CH), 131.1 (4 x CH), 130.2 (2 x CH), 130.1 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 128.0 (4 x CH), 126.9 (2 x CH), 122.4 (CH), 122.3 (2 x CH), 122.2 (CH), 120.8 (C), 120.7 (C), 66.59 (CH), 66.57 (CH), 62.7 (C), 62.6 (C), 43.4 (CH), 42.3 (CH), 42.0 (CH), 40.8 (CH), 34.3



84ae

(CH_2), 34.2 (CH_2), 33.4 (CH_2), 33.3 (CH_2); HRMS m/z 461.0751 (M + H^+), calcd for $C_{26}H_{21}BrO_3H$ 461.0752.

(2*R*,4*S*,6*S*)-2-(4-bromophenyl)-4-hydroxy-6-phenylspiro[cyclohexane-1,2'-indene]-1',3'-dione (85ae): Prepared following the procedure **7.15** and purified by column chromatography using EtOAc/hexane and isolated as gummy liquid; IR (KBr): ν_{max} 3402, 3057, 2925, 1731, 1698, 1594, 1490, 1249, 1035, 876, 827, 772 and 690 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.54 (1H, td, *J* = 7.0, 1.0 Hz), 7.45-7.38 (3H, m), 7.10 (2H, td, *J* = 8.5, 1.0 Hz), 6.99-6.93 (4H, m), 6.91-6.89 (3H, m), 4.15-4.08 (1H, m), 3.42 (2H, td, *J* = 13.5, 4.0 Hz), 2.83-2.75 (2H, m), 2.19-2.11 (2H, m), 2.08 (1H, br s); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 203.5 (C, *C*=O), 203.0 (C, *C*=O), 142.7 (C), 141.8 (C), 138.7 (C), 138.2 (C), 135.2 (CH), 135.0 (CH), 131.2 (2 x CH), 130.1 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 127.2 (CH), 122.1 (CH), 122.0 (CH), 121.0 (C), 70.0 (CH), 62.1 (C), 48.0 (CH), 46.8 (CH), 36.44 (CH_2), 36.38 (CH_2); HRMS m/z 461.0753 (M + H^+), calcd for $C_{26}H_{21}BrO_3H$ 461.0752.

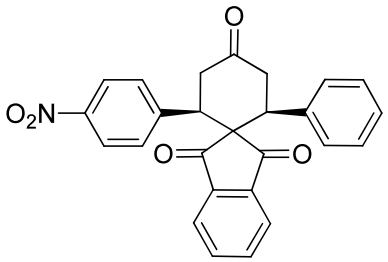


85ae

7.16 General procedure for the epimerization of chiral anti-33:

In an oven dried round bottom flask, L-proline (10 mol-%) was added to the stirred solution of *anti*-**33** (0.3 mmol) in dry methanol (2.0 mL) at 25 °C for 3-10 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, and concentrated. Pure isomer of *syn*-**34** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

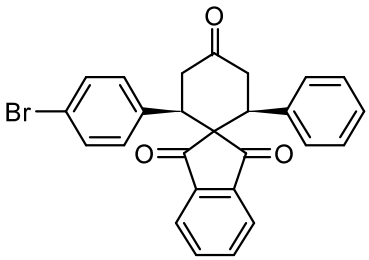
(2*R*,6*S*)-2-(4-nitrophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (34aa): Prepared following the procedure **7.16** and purified by column chromatography using EtOAc/hexane and isolated as gummy liquid. The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralcel OD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 24.68 min (minor), t_R = 31.49 min (major); **$[\alpha]_D^{25}$ = –32.55° (*c* = 0.60 g/100 mL, $CHCl_3$, 65% *ee* and >99:1 *dr*);** IR (KBr): ν_{max} 3073, 2931, 2849, 1693, 1605, 1528, 1358, 1243, 1117, 887, 854, 772 and 695 cm^{-1}; ^1H



34aa

NMR ($CDCl_3$, 400 MHz) δ 7.90 (2H, d, *J* = 8.8 Hz), 7.66 (1H, d, *J* = 7.6 Hz), 7.53 (1H, dt, *J* = 6.8, 1.2 Hz), 7.48-7.42 (2H, m), 7.24 (2H, d, *J* = 9.2 Hz), 7.02-6.91 (5H, m), 3.94-3.75 (4H, m), 2.74-2.64 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.0 (C, *C*=O), 202.8 (C, *C*=O), 201.2 (C, *C*=O), 147.2 (C), 144.9 (C), 142.4 (C), 141.7 (C), 136.7 (C), 135.84 (CH), 135.83 (CH), 129.2 (2 x CH), 128.5 (2 x CH), 127.9 (3 x CH), 123.6 (2 x CH), 122.6 (CH), 122.3 (CH), 61.7 (C), 49.2 (CH), 47.9 (CH), 43.2 (CH_2), 42.9 (CH_2); LCMS m/z 426.30 ($M^+ + 1$), calcd for $C_{26}H_{19}NO_5$ 425.1263; calcd for $C_{26}H_{19}NO_5$ (425.1263): C, 73.40; H, 4.50; N, 3.29. Found C, 73.51; H, 4.47; N, 3.36%.

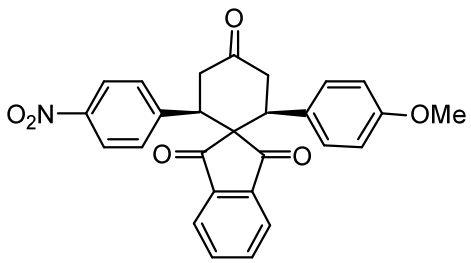
(2*R*, 6*S*)-2-(4-bromophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (34ae): Prepared following the procedure **7.15** and purified by column chromatography using EtOAc/hexane and isolated as gummy liquid; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 85:15, flow rate 1.0 mL/min, λ = 254 nm), t_R = 20.25 min, t_R = 24.52 min;



34ae

0% *ee* and >99:1 *dr*; IR (KBr): ν_{max} 1753, 1704, 1632, 1588, 1490, 1419, 1249, 1123, 1041 and 969 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.65 (1H, d, *J* = 7.5 Hz), 7.52 (1H, br t, *J* = 7.5 Hz), 7.47-7.42 (2H, m), 7.14 (2H, br d, *J* = 7.5 Hz), 6.99-6.98 (4H, m), 6.95-6.93 (1H, m), 6.91 (2H, d, *J* = 8.5 Hz), 3.82-3.73 (4H, m), 2.63 (2H, dd, *J* = 15.5, 12.0 Hz); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.8 (C, *C*=O), 203.2 (C, *C*=O), 201.6 (C, *C*=O), 142.6 (C), 141.8 (C), 137.0 (C), 136.6 (C), 135.54 (CH), 135.52 (CH), 131.5 (2 x CH), 129.8 (2 x CH), 128.4 (2 x CH), 127.9 (2 x CH), 127.7 (CH), 122.5 (CH), 122.1 (CH), 121.6 (C), 61.8 (C), 49.0 (CH), 47.8 (CH), 43.3 (CH_2), 43.2 (CH_2); HRMS m/z 459.0595 ($M + H^+$), calcd for $C_{26}H_{19}BrO_3H$ 459.0596.

(2*S*,6*R*)-2-(4-methoxyphenyl)-6-(4-nitrophenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione (33da): Prepared following the procedure **7.15** and purified by column chromatography using EtOAc/hexane and isolated as gummy liquid; The enantiomeric excess (*ee*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (hexane/2-propanol = 85:15, flow rate 1.0



33da

mL/min, λ = 254 nm), t_R = 61.46 min (major), t_R = 72.25 min (minor); **$[\alpha]_D^{25}$ = +35.23° (*c* = 0.33 g/100 mL, $CHCl_3$, 91% *ee* and >99:1 *dr*);** IR (KBr): ν_{max} 3079, 2925, 2838, 1704, 1605, 1517, 1358, 1249, 1183, 1035, 887, 761, 695 and 558 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.89 (2H, d, *J* = 8.8 Hz), 7.66 (1H, br d, *J* = 7.2 Hz), 7.54 (1H, dt, *J* = 6.8, 1.6 Hz), 7.48 (1H, dt, *J* = 6.8, 1.6 Hz), 7.45 (1H, br d, *J* = 7.2 Hz), 7.23 (2H, d, *J* = 8.8 Hz), 6.91 (2H, d, *J* = 8.8 Hz), 6.52 (2H, d, *J* = 8.8 Hz), 3.91-3.71 (4H, m), 3.59 (3H, s), 2.66-2.63 (2H, m); ^{13}C NMR ($CDCl_3$, DEPT-135) δ 207.1 (C, *C*=O), 203.0 (C, *C*=O), 201.5 (C, *C*=O), 158.9 (C), 147.1 (C), 144.9 (C), 142.4 (C), 141.7 (C), 135.90 (CH), 135.86 (CH), 129.2 (2 x CH), 129.0 (2 x CH), 128.8 (C), 123.6 (2 x CH), 122.6 (CH), 122.3 (CH), 113.7 (2 x CH), 61.8 (C), 55.0 (CH_3), 48.4 (CH), 47.9 (CH), 43.5 (CH_2), 42.8 (CH_2); HRMS m/z 478.1267 ($M + Na^+$), calcd for $C_{27}H_{21}NO_6Na$ 478.1267.

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STEREOSELECTIVE SYNTHESIS OF DRUG-LIKE MOLECULES

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2	Ramachary, Dhevalapally, and Krishna Patoju M.. "Asymmetric Synthesis of Nature-inspired Bioactive Spiro-compounds through Organocatalytic Diels-Alder Reactions", Asian Journal of Organic Chemistry, 2016. Publication	3%
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4	Dhevalapally B. Ramachary. "Dienamine Catalysis: An Emerging Technology in Organic Synthesis", European Journal of Organic Chemistry, 02/2012 Publication	1%
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6	Shashank, Adluri B., S. Karthik, R. Madhavachary, and Dhevalapally B. Ramachary. "An Enolate-Mediated Organocatalytic Azide-Ketone [3+2]-Cycloaddition Reaction: Regioselective High-Yielding Synthesis of Fully Decorated 1,2,3-Triazoles", Chemistry - A European Journal, 2014. Publication	1%
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The author, **Mr. P. Murali Krishna** was born on 10th June 1985 in Bobbili, Andhra Pradesh. After his initial schooling in Parvathipuram, he obtained his B.Sc. degree in 2005 from Maha Raja degree college,Vizianagaram and he obtained his M.Sc. degree with organic chemistry specialization in 2007 from G.I.T.A.M College, Andhra University, he worked in GVK BIO Hyderabad during 2007-2009. He continued as a research scholar in the School of Chemistry, University of Hyderabad for the Ph. D. programme from Dec 2010 onwards.

LIST OF PUBLICATIONS

1. D. B. Ramachary, Chintalapudi Venkaiah and **P. Murali Krishna**, "Discovery of 2-aminobuta-1,3-enynes in asymmetric organocascade catalysis: construction of spirocyclic cyclohexanes having five to six contiguous stereocenters" *Chem. Commun.*, **2012**, *48*, 2252-2254.
2. D. B. Ramachary, Chintalapudi Venkaiah and **P. Murali Krishna**, "Stereoselective synthesis of drug-like five-membered spirooxindoles through Tomita zipper cyclization" *Org. Lett*, **2013**, *15*, 4714-4717
3. **P Murali. Krishna**, D. B. Ramachary, and Sruthi Peesapati, "Azide-Acetonitrile "Click" Reaction Triggered by Cs_2CO_3: The Atom-Economic, High-yielding Synthesis of 5-Amino-1,2,3-Triazoles" *RSC Adv.* **2015**, *5*, 62062–62066.
4. D. B. Ramachary, **P. Murali. Krishna**, Jagjeet Gujral and G. Surendar Reddy "An Organocatalytic Regiospecific Synthesis of 1,5-Disubstituted-4-Thio-1,2,3-Triazoles and 1,5-Disubstituted-1,2,3-Triazoles" *Chem. Eur. J.* **2015**, *21*, 16775-16780.
5. D. B. Ramachary and **P. Murali. Krishna** "The Synthesis of Benzosultams through Tomita Zipper Cyclization" (*to be communicated*).
6. D. B. Ramachary and **P. Murali. Krishna** "Asymmetric Synthesis of Nature-inspired Bioactive Spiro-compounds through Organocatalytic Diels-Alder Reactions" *Asian J Org Chem.* **2016**, *5*, 0000-0000, [DOI: 10.1002/ajoc.201600145].

Poster and Oral Presentations

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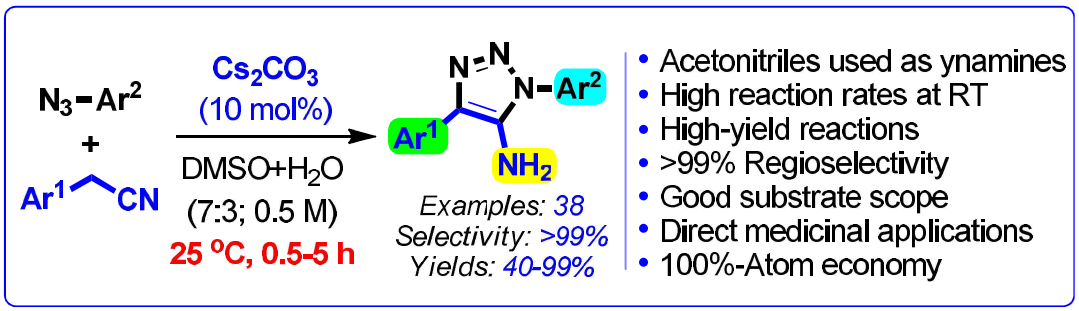
1. **Oral Presentation**: “CHEM-FEST 2015”, School of Chemistry, Hyderabad, India. Organizer: University of Hyderabad, INDIA.

Azide-Acetonitrile "Click" Reaction Triggered by Cs_2CO_3: The Atom-Economic, High-yielding Synthesis of 5-Amino-1,2,3-Triazoles



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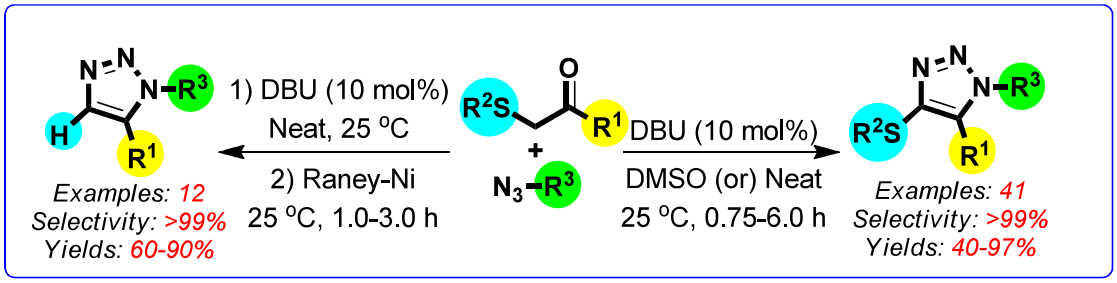
An Organocatalytic Regiospecific Synthesis of 1,5-Disubstituted-4-Thio-1,2,3-Triazoles and 1,5-Disubstituted-1,2,3-Triazoles.



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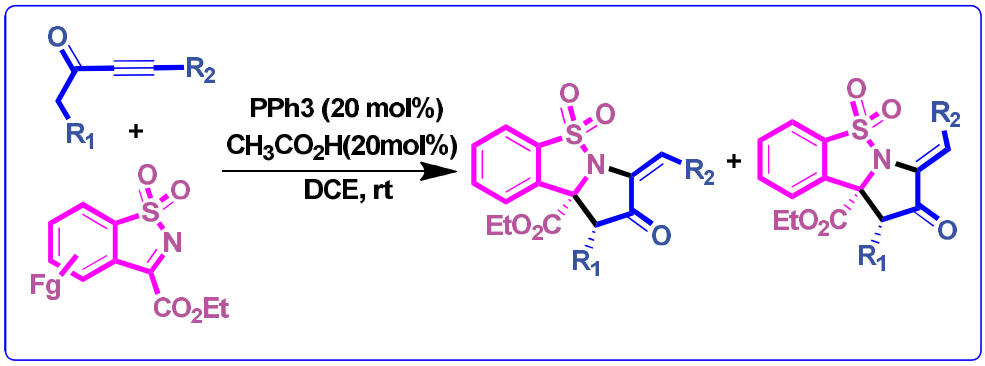

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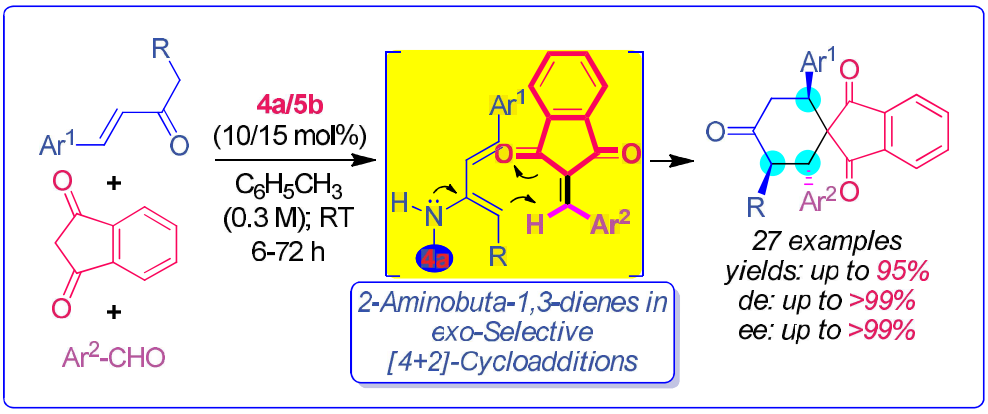

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