ORGANOCATALYTIC STEREOSELECTIVE C-C BOND FORMATION THROUGH DESYMMETRIZATION, MICHAEL, AND ALDOL CONDENSATION REACTIONS

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INDIAN INSTITUTE OF TECHNOLOGY DELHI

NOVEMBER 2023

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by

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Submitted

in fulfilment of the requirements of the degree of Doctor of Philosophy

to the

INDIAN INSTITUTE OF TECHNOLOGY DELHI

NOVEMBER 2023

This Ph.D. thesis is dedicated to my

Mom & Dad

Special gratitude to my parents for their unconditional love, being my best friends and inspiration.

CERTIFICATE

This is to certify that the thesis entitled, **"Organocatalytic Stereoselective C-C Bond Formation Through Desymmeterization, Michael, and Aldol Condensation Reactions"**, being submitted by **Mr. Sanjay Singh** to the ***Indian Institute of Technology Delhi*** for the award of the degree of **Doctor of Philosophy** in Chemistry is a record of bonafide research work carried out by him. **Mr. Sanjay Singh** worked under my guidance and supervision and has fulfilled the requirements for the submission of a Ph.D. thesis, which to my knowledge has reached the requisite standard.

The results illustrated and incorporated in this dissertation have not been submitted in part or full to any other University or Institute for the award of any degree or diploma.

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Acknowledgments

I extend my heartfelt gratitude to all those who have contributed to the completion of this doctoral dissertation. First and foremost, I want to thank my supervisor ***Prof. Ravi P. Singh*** *without his enthusiasm, encouragement, support, and continuous optimism, this thesis would hardly have been completed. I am also very grateful to him for his scientific advice and knowledge and many insightful discussions and suggestions. He showed me different dimensions to approach a research problem and the need to be persistent to accomplish any goal. His advice on both research as well as on my career has been invaluable. I also must thank the members of my SRC committee,* ***Prof. A. J. Elias****,* ***Prof. N. G. Ramesh****, and* ***Prof. K. K. Pant*** *for their valuable suggestions and advice in general. I also thank all the past and the present Head of the Department of Chemistry, for the academic support and the facilities provided to carry out my research work. I would also like to thank* ***Prof. V. Haridas*** *(Chairman, DRC) for streamlining curricular formalities. I would like to express my special gratitude towards* ***Prof. N. G. Ramesh****, for his timely encouragement, valuable suggestions, and support. I gratefully acknowledge all the faculty members and staff for providing the necessary facilities to pursue my research activities. I would also like to thank* ***Prof. Neetu Singh****, for her kind and generous nature, constant support, and encouragement. I would also like to thank UGC-India, India, for providing the research fellowship that allowed me to undertake this research program. I would also like to greatly acknowledge* ***Prof. S. Nagendran****, coordinator of the X-ray facility, for providing me an opportunity to learn and operate the single crystal X-ray diffractometer. I would like to thank Dr. Pritam, Dr. Soumyadip, Mr. Bhuvanesh, Mr. Vivek, and Mr. Prakash for helping me to learn and solve the X-ray Crystal data. I would like to extend my sincere thanks to all the teachers of the chemistry department for their support whenever it was required.*

A supportive and healthy environment is crucial for staying and surviving in a working place. The foundation stone of this group was laid down by my senior lab mates Dr. Amol P Jadhav, Dr. Bhaskara Rao, Dr. Krishna Kumar, and Dr. Devalina Ray. I would like to thank them for not only creating a cordial working environment in the lab but also for timely guidance and enduring support in continuing and completing my research projects. I feel very lucky to have such seniors in my life and I express my special thank of gratitude to them. I would like to thank Dr. Md. Belal, Dr. Abhijeet Srivastava, Dr. Krishna Kumar, Dr. Vijay Gupta, Dr. Krishna Nand Tripathi, Dr. Manish Kumar Jaiswal, Dr. Soumyadip Hore, Dr. Diksha, and Dr. Amjad Ali for the support, and guidance at various times. I also thank Mr. Keshav, Mr. Manoj, Mrs.

Poornima, and Mr. Narugopal for helping me in recording NMR, and HRMS. I also thank Mr. Virender Sharma, in-charge III of central glass blowing facility for his timely help. I am thankful to all the members of this department who helped me in one way or the other to carry out my work successfully.

I am forever thankful to my colleagues in the lab for their friendship and support. Their presence was very important in a process that is often felt as tremendously solitaire formed the core of my research time and we have been there for one another throughout this journey. I would like to thank all my colleagues (present and past) Ravneet, Bhuvnesh, Manju, Shashank, Harish, Ravi Saini, Abhijeet, Arindam, Kalyan, Chandan, Shreya, Najam, Saurabh, Mubarik, Pooja, Richa, Deepak, Aarti, Satish, Priyankar, Rajesh, Jitendra, Shivam, Sunil, Sameer, Akash, Neha, Gyanshree, Surjeet. It is a pleasure to thank my friends Dr. Surjeet, and Dr. Mukesh, and my teacher Prof. Sunil Uppal for creating my interest in chemistry and inspiring me to complete my Ph.D. dissertation. Words cannot express how grateful I am to my family: my parents, Sh. Karan Singh and Mrs. Rooma Devi and my brother Mr. Narinder Singh, my loving sisters Mrs. Sarita Devi, Mrs. Anita Devi, Mrs. Reena Devi and brother-in-laws Jarnail Singh, Pratap Singh, and Des Raj Singh for always supporting and encouraging me the best possible way, for unconditional support, blessings, constant love and encouragement to pursue my interests. A special credit goes to my all nieces and nephews especially Rahul, Arun, Priyanka, Sunaina, Anshu, Anshika, Tanishq, and Divyansh who have been the light of my life bringing smiles to my face and have given me extra strength and motivation to get things done. I'd like to extend a special mention to my uncle, the late Sh. Sansar Singh, whose guidance and teachings during my childhood continue to inspire me today. His wisdom and kindness left an indelible mark on my life.

In closing, I wish to thank Lord Shiva, whose benevolent blessings have showered upon me, infusing me with unwavering strength and boundless courage to fearlessly confront the formidable challenges that have graced my path.

Sanjay Singh

ABSTRACT

The thesis entitled "***Organocatalytic Stereoselective C-C Bond Formation Through Desymmetrization, Michael, and Aldol Condensation Reactions***" is divided into five chapters which are mainly focused on the development of organocatalytic stereoselective C-C bond formation. In chapters two and three, the concept of enantioselective desymmetrization has been demonstrated. Chapter four realizes the concept of remote C-H functionalization through bifunctional organocatalysis. Finally, in chapter five, stereoselective synthesis of 3-carboxamidecoumarins tethered α-trifluoromethyl styrenes has been described by employing the concept of an aldol condensation.

Chapter 1: Discloses a brief description of general organic chemistry, chirality, and its role in day-to-day life, asymmetric catalysis where special emphasis has been made on organocatalysis, and various activation modes of organocatalysis. Finally, the concept of enantioselective desymmetrization has been elaborated with the main focus on the desymmetrization of cyclopent-4-ene-1,3-dione.

Chapter 2: Herein, we have unraveled a L-*tert*-leucine derived thiourea catalyzed enantioselective homologating annulation of cyclopent-4-ene-dione with 3-cyano-4-methylcoumarins giving access to a wide range of enantioriched polycyclic multisubstituted amino pentafulvene cores. Importantly, our catalytic system efficiently catalyzed this single-step transformation involving substrates tethered with natural products and drug candidates, providing the complex homologated adducts in high yields with excellent stereocontrol. The cytotoxicity and cellular uptake experiments revealed that the enantiopurity of this novel class of polycyclic aminopentafulvenes has significant effects on their photophysical properties and cell viability.

Chapter 3: In this chapter, we have disclosed a L-*tert*-leucine dipeptide thiourea catalyzed enantioselective (4+1) carbospiroannulation between cyclohexenylidene malononitriles and cyclopent-4-ene-1,3-diones. The developed protocol can successfully be applied to a wide range of cyclopent-4-ene-1,3-diones and a few cyclohexenylidene malononitriles and the carbospiroannulated adducts could be achieved in good to high yields with moderate to excellent stereocontrol. Pleasingly, this methodology realizes an unprecedented

enantioselective vinylogous carbospiroannulation for the formation of chiral [4,4]nonane frameworks.

Chapter 4: Here, a catalytic asymmetric vinylogous Michael addition of 3-cyano-4-methylcoumarins has been developed using maleimides as Michael acceptor. Catalyzed by L-*tert*-leucine based thiourea, this reaction led to the densely functionalized product in good yields with moderate to excellent enantioselectivities. This report represents the first non-covalent organocatalytic asymmetric vinylogous Michael addition reaction of 3-cyano-4-methylcoumarins.

Chapter 5: In this chapter, I have developed an efficient base catalyzed methodology for the synthesis of 3-carboxamidecoumarins tethered α-trifluoromethyl styrenes by reacting 3-cyano-4 methylcoumarin and trifluoromethyl ketones. The corresponding products could be achieved in satisfactory yields and good to excellent stereoselectivies.

सार

"ओर्गनोकैटलिस्टिक स्टीरियोसेलेक्टिव सी-सी बॉन्ड निर्माण के माध्यम से डेसिमेट्रिजेशन, माइकल और एल्डोल कंडेंसेशन प्रतिक्रियाओं" शीर्षक थीसिस पांच अध्यायों में विभाजित है, जो मुख्य रूप से ओर्गनोकैटलिस्टिक स्टीरियोसेलेक्टिव सी-सी बॉन्ड निर्माण के विकास पर केंद्रित हैं। दो और तीसरे अध्यायों में विकल्पी विरामीकरण के अवधारणा का प्रदर्शन किया गया है। चौथे अध्याय में दूरस्थ सी-एच फंक्शनलाइजेशन के अवधारणा को बाइफंक्शनल ओर्गनोकैटलिस्टि द्वारा प्राप्त किया गया है। अंत में, पांचवें अध्याय में, एक ऐल्डोल कंडेंसेशन के अवधारणा का उपयोग करके 3-कार्बोक्समाइडकूमारिन टेदरेड अल्फा-ट्रिफ्लुओरोमिथाइल स्टायरेन्स का स्टीरियोसेलेक्टिव संश्लेषण वर्णित किया गया है।

अध्याय 1: सामान्य जैविक रसायनिकी, किराणता और दिन-प्रतिदिन जीवन में भूमिका, विषमता की कटिबद्धता, और विशेष रूप से ओर्गनोकैटलिस्टिक के रूप में असिम्मित्र इनामीकरण, और ओर्गनोकैटलिस्टि के विभिन्न सक्रियता तरीकों का वर्णन किया गया है। अंत में, साइक्लोपेंट-4-इन-1,3-डियोन के डेसिमेट्रिजेशन पर मुख्य ध्यान दिया गया है।

अध्याय 2: इसमें, हमने एल-टर्ट-लुसीन से प्राप्त थायोयुरिया कैटलाइज्ड इनामिसेलेक्टिव होमोलगिंग अनुष्ठान की खोल दी है, जो साइक्लोपेंट-4-इन-डायन के साथ 3-सायनो-4-मिथाइलकूमारिनों के साथ सायोज्य विशाल विषम एमिनो पेन्टफुलवेन कोर्स के लिए पहुंच प्रदान करता है। महत्वपूर्ण रूप से, हमारे कैटलिटिक प्रणाली ने प्राकृतिक उत्पादों और दवा उम्मीदवारों से साथ बंधे उपकरणों को सायोज्यता के साथ जोड़ते हुए, उन्हें उच्च उत्पादन दरों में और उत्कृष्ट स्टीरियोकंट्रोल के साथ परिक्षित किया। साइटोटॉक्सिसिटी और सेल्युलर अधिग्रहण प्रयोगों ने दिखाया कि इस नई कक्षा के पॉलीसाइक्लिक एमिनोपेन्टफुल्वेन्स की एनटिओप्यूरिटी के उनके फोटोफिजिकल गुणों और सेल जीवन को उनके ऊर्जा पर प्रभाव पड़ा।

अध्याय 3: इस अध्याय में, हमने एल-टर्ट-लुसीन डाइपेप्टाइड थायोयुरिया कैटलाइज्ड (4+1) कार्बोस्पिरोअनुष्ठान का खुलासा किया है, जो साइक्लोहेक्सेनिलिडीन मैलोनोनाइट्राइल्स और साइक्लोपेंट-4-इन-1,3-डाइयन के बीच होता है। विकसित प्रोटोकॉल सफलतापूर्वक विभिन्न साइक्लोपेंट-4-इन-1,3-डायनों और कुछ साइक्लोहेक्सेनिलिडीन मैलोनोनाइट्राइल्स पर लागू किया जा सकता है, और कार्बोस्पिरोअनुष्ठान के परिणामस्वरूप प्रशस्त कईचे उच्च उत्पादन दरों में और उच्च विरामीकरण के साथ प्राप्त किए जा सकते हैं। खुशी होती है, यह प्राथमिक रूप से भिन्नांतरगत संरचना के लिए एक अभूतपूर्व एनटियोसेलेक्टिव वायोलोगिक भविष्यात्मक कार्बोस्पिरोअनुष्ठान का साक्षात्कार करता है।

अध्याय 4: यहां, मेलिमिड्स का उपयोग करके 3-सायनो-4-मिथाइलकूमारिनों का कैटलाइज्ड विरामी विरामी माइकल उपकरण विकसित किया गया है। एल-टर्ट-लुसीन आधारित थायोयुरिया द्वारा संचालित यह प्रतिक्रिया उच्च उत्पादन दरों में मध्यम से उत्कृष्ट एनटिओसेलेक्टिविटिस के साथ घनत्वपूर्ण संयोजन उत्पन्न करती है। यह रिपोर्ट 3-सायनो-4-मिथाइलकूमारिनों के गैर-संयुक्त ओर्गनोकैटलिस्टिक विरामी माइकल उपकरण प्रतिक्रिया का प्रतिनिधित्व करती है।

अध्याय 5: इस अध्याय में, हमने विभिन्न त्रिफ्लुओरोमिथाइल केटोन्स के साथ 3-सायनो-4 मिथाइलकूमारिन और योजित करने के लिए एक अधिक उपकरण विकसित किया है। उस संबंधित उत्पादों को संतुष्टकारक उपज और अच्छे से उत्कृष्ट स्टीरियोसेलेक्टिविटियों के साथ प्राप्त किया जा सकता है।

TABLE OF CONTENTS

			Page
Certificate			I
Acknowledgments			II
Abstract			IV
Table of Contents			VIII
List of Figures			XII
List of Schemes			XIV
List of Tables			XVII
Abbreviations			XVIII
Chapter	**1**	**Introduction**	
	1.1	General Information	02
	1.2	Chirality	02
	1.2.1	What are stereoisomers?	03
	1.3.	Why Chirality?	04
	1.3.1	Role of Chirality in taste	04
	1.3.2	Role of Chirality in odour	05
	1.3.3	Role of Chirality in pharmacology	06
	1.4	Chirality Induction	07
	1.4.1	Chiral Pool	07
	1.4.2	Chiral Auxiliary	08
	1.4.3	Asymmetric Catalysis	08
	1.5.	Organocatalysis	09
	1.5.1	Background	09
	1.5.2	Classification of Organocatalysis	11
	1.5.2.1	Covalent Organocatalysis	11
	1.5.2.2	Non-Covalent Organocatalysis	12
	1.5.2.2.1	Brønsted Acid Catalysis	13
	1.5.2.2.2	Brønsted Base Catalysis	14
	1.5.2.2.3	Ion Pair Catalysis	15
	1.7	Principle of Vinylogy	16
	1.7	Desymmetrization	17
	1.8	Thesis Overview	19
	1.8.1	Desymmetrizing Homologated Annulation for the Synthesis of Chiral Aminofulvenes	19
	1.8.2	Catalytic Enantioselective Desymmetrizing (4+1) Carbospiroannulation of Cylcopent-4-ene-1,3-dione	20
	1.8.3	Enantioselective Distal Functionalization of 3-Cyano-4-methylcoumarins through	

		Direct Addition to Maleimides.	21
	1.8.4	Stereoselective Synthesis of 3-Carboxamide coumarins Tethered a- Trifluoromethyl Styrenes	21
	1.9	References	22
Chapter	**2**	**Desymmetrizing Homologated Annulation for the Synthesis of Chiral Aminofulvenes**	
	2.1	Introduction	26
	2.2	Our Strategy	28
	2.3	Results and Discussion	30
	2.4	Conclusion	39
	2.5	Experimental section	41
	2.5.1	General Information	41
	2.5.2	Material and Methods	41
	2.5.3	Reaction monitoring through NMR and ESI-MS analysis	42
	2.5.4	Emission Spectra with excitation at 360 nm and MTT assay	44
	2.5.5	General procedure for the preparation catalysts	45
	2.5.6	General procedure for the preparation of 3-Cyano-4-methylcoumarins	45
	2.5.7	General procedure for the synthesis of cyclopenta-1,3-dienones	56
	2.5.12	General procedure for the reparation of racemic homologated adducts	48
	2.5.13	General procedure for the reparation of chiral homologated adducts	48
	2.5.14	Characterization of starting materials and products	49
	2.5.15	Representative ^{1}H, and ^{13}C Spectra	81
	2.5.16	Representative HPLC Chromatograms	64
	2.5.17	Crystal data and ORTEP diagram for 65a	125
	2.6	References	127
Chapter	**3**	**Catalytic Enantioselective Desymmetrizing (4+1) Carbospiroannulation of Cylcopent-4-ene-1,3-dione**	
	3.1	Introduction	132
	3.2	Our Strategy	135
	3.3	Results and Discussion	136
	3.4	Conclusion	140
	3.5	Experimental Section	141
	3.5.1	General Information	141
	3.5.2	Preparation of catalysts	141

	3.5.3	Preparation of substrates	141
	3.5.5	General procedure for the synthesis of racemic carbospiroannulated adducts	142
	3.5.6.	General procedure for the synthesis of chiral carbospiroannulated adducts	143
	3.5.7	Characterization of carbospiroannulated products	143
	3.5.8	^{1}H, ^{13}C and ^{19}F Spectra	156
	3.5.9	Representative HPLC Chromatograms	173
	3.5.10	Single Crystal X-ray Data of compound **95b**	106
	3.7	References	132
Chapter	**4**	**Enantioselective Distal Functionalization of 3-Cyano-4-methylcoumarins through Direct Addition to Maleimides**	
	4.1	Introduction	191
	4.2	Objective	195
	4.3	Results and discussion	195
	4.4	Conclusion	201
	4.5	Experimental Section	202
	4.5.1	General Information	202
	4.5.2	Optimization studies	203
	4.5.2.1	Catalyst screening	203
	4.5.2.2	Preparation of the catalysts	205
	4.5.3	Synthesis of 3-Cyano-4-methylcoumarins	205
	4.5.4	Synthesis of *N*-substituted maleimides	206
	4.5.6	General procedure for the reparation of racemic Michael adducts	207
	4.5.7	General procedure for asymmetric vinylogous Michael reaction	207
	4.5.8	Characterization data of the compounds	
	4.5.9	^{1}H, and ^{13}C, NMR spectra	226
	4.5.10	Representative HPLC Chromatograms	245
	4.5.11	Single crystal XRD data **95a**	265
	4.6	References	266
Chapter	**5**	**Stereoselective Synthesis of 3-Carboxamide-coumarins Tethered α-Trifluoromethyl Styrenes**	
	5.1	Introduction	270
	5.2	Our Strategy	273
	5.3	Results and Discussion	274
	5.4	Conclusion	278

	5.5	Experimental Section	279
	5.5.1	General Information	279
	5.5.2	General procedure for the preparation of 3-carboxamide derivatives.	279
	5.5.3	Characterization of products	285
	5.5.4	Representative ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra	287
	5.5.5	Crystal data and ORTEP diagram for compound **147q**	321
	5.5.6	References	323
Bio-Data			423

List of Figures

Figure No.	Figure Caption	Page
1.1	Non-superimposable mirror image of the hand	02
1.2	Representative example of enantiomers	03
1.3	Role of chirality in taste	05
1.4	Role of chirality in odor	06
1.5	Role of chirality in pharmacology	07
1.6	Representative examples of amino and NHC catalysts.	12
1.7	Chiral phosphoric acid activation mode	13
1.8	Representative examples of chiral Brønsted acid.	13
1.9	Chiral Brønsted base activation mode	14
1.10	Representative examples of chiral Brønsted base catalysts	14
1.11	Representative examples of chiral ion pair catalysts	15
1.12	SCOPUS report 2022	16
1.13	Representative examples of vinylogous nucleophiles.	17
1.14	Enantioselective desymmetrization of meso/archiral scaffolds	18
1.15	Challenges poised during enantioselective symmetry breaking process	
2.2.1	(A) Our reaction design (B) unprecedented deysmmetric homologation annulation	28
2.2.2	Biologically relevant and electrochromic motifs containing pentafulvenes	28
2.3.1	Proposed reaction pathway and Mechanistic insights	35
2.3.2	Crystal Packing	37
2.3.3	Bioimaging	39
2.5.1	Reaction monitoring through ^{1}H NMR	42
2.5.2	^{1}H NMR and HRMSanalysis showing silica gel promoted transition of intermediate **V** into **65a**	43
2.5.3a	Emission spectra of chiral and racemic homologated adducts.	44
2.5.3b	MTT and *in-vitro* cytocompatibility of the developed chiral homologated adducts	44
2.5.4	ORTEP drawing of **65a**.	126
3.1.1	Biologically relevant and chiral ligands containing spiro[4.4]nonane core	132
3.6.1	ORTEP drawing of **95b**	186
4.3.1	Representative coumarin containing chiral drugs	191

4.3.1	Plausible mechanism and ESI-MS analysis for dual mode of activation	200
4.5.1	Structure of catalysts used	205
5.1.1	Representative biological and material relevant 3-carboxamidecoumarin and α- trifluoromethylstyrenes motifs	270
5.3.1	Plausible Mechanism	277
5.5.1	ORTEP diagram for compound **147q.**	322

List of Schemes

Scheme No.	Scheme Caption	Page
1.1	The procedure for the RAMP-/SAMP-hydrazone methodology	08
1.2.	Hydrocynation of aldehydes through cinchona alkaloids catalysis	10
1.3	Hajos–Parrish–Eder–Sauer–Wiechert reaction	10
1.4	First L-proline catalyzed asymmetric aldol reaction through HOMO raising strategy	11
1.5	First organocatalytic aldol reaction through LUMO lowering strategy	11
1.6	Asymmetric vinylogous desymmetrizing homologated annulation of cyclopent-4-ene-1,3- dione.	20
1.7	organocatalytic asymmetric vinylogous (4+1) carbospiroannulation of cyclopent-4-ene- 1,3-dione.	20
1.8	organocatalytic asymmetric vinylogous Michael addition reaction of 3-cyano-4- methylcoumarins.	21
1.9	Stereoselective synthesis of 3-carboxamidecoumarins tethered α-trifluoromethyl styrenes	21
2.1.1	NHC catalyzed desymmetrizing construction of arenes with all carbon quaternary chiral center.	26
2.1.2	NHC catalyzed desymmetrizing construction of arenes with all carbon quaternary chiral center.	27
2.1.3	Chiral phosphonium salt-enabled desymmetrizing construction of arenes	27
2.1.4	Secondary amine catalyzed construction of polycyclic Arenes	27
2.2.1	Chiral aluminum Lewis acid catalyzed desymmetrizing asymmetric ring expansion of cyclohexanones with α-diazoacetates	29
2.2.2	Asymmetric synthesis of 2-aryl cycloalkanones by Sc-catalyzed carbon insertion	29
2.2.3	Asymmetric ring expansion reaction of isatins and α-alkyl-adiazoesters	30
2.3.1	Scope of Coumarin	32
2.3.2	Scope of diketone	33
2.3.3	Post synthetic transformations	36
3.1.1	Synthesis of spiro[4.4]nonane core through Pd(II)/Brønsted acid catalyzed enantioselective allylic C−H activation.	133
3.1.2	Organocatalytic Construction of Chiral Spiro[4.4]nonane-1,6-diones	134

3.1.3	NHC co-catalyzed desymmetrizing (3+2) spiroannulation	134
3.1.4	Construction of C-N axially chiral scaffolds via NHC catalysis	135
3.1.5	Diastereoselective synthesis of spiro[4.4]nonane cores	135
3.1.6	Enantioselective synthesis of spiro[4.4]nonane cores	135
3.3.1	Reaction Scope	137
3.3.2	Post synthetic transformation	139
3.3.3	Reaction pathway	140
4.1.1	Asymmetric vinylogous Michael addition between 3-cyano-4-methylcoumarins and α,β- unsaturated ketones	192
4.1.2	Rh-catalyzed enantioselective vinylogous asymmetric ring-opening (ARO)	193
4.1.3	$(QD)_2$PHAL catalyzed enantioselective vinylogous allylic alkylation of 3-cyano-4- methylcoumarins.	193
4.1.4	$(QD)_2$PYR catalyzed enantioselective vinylogous allylic alkylation of 3-cyano-4- methylcoumarins	193
4.1.5	Amide phosphonium salt catalyzed enantioselective Mannich reaction between 3-cyano- 4-methyl coumarins and isatin imines	193
4.1.6	Chiral brominium salt catalyzed enantioselective Mannich reaction	194
4.1.7	Organocatalytic enantioselective vinylogous Michael addition between malononitrile alkylidene and maleimide	194
4.1.8.	Asymmetric vinylogous Michael reaction of allyl alkyl ketones to maleimides	195
4.2.1	γ−C−H functionalization of 4-methylcoumarin via bifunctional organocatalysis	195
4.3.3	Post synthetic transformations	201
4.5.2	Synthesis of 3-Cyano-4-methylcoumarins	205
4.5.3	Synthesis of maleimides	206
4.5.4	Preparation of racemic vinylogous Michael products	207
4.5.5	General procedure for asymmetric vinylogous Michael products	207
5.1.1	Pd-catalyzed coupling reaction between aryl halides and α-trifluoroisopropenylzinc reagent	271
5.1.2	KF promoted olefination of alkanesulfonyl halides with aryl ketones.	271
5.1.3	Lauroyl peroxide catalyzed synthesis of α-trifluoromethylated alkenes	272
5.1.4	Palladium catalyzed cross coupling reaction between α-trifluoroacetophenone tosylhydrazone with aryl bromides.	272
5.1.5	$SOCl_2$ mediated synthesis of coumarin-3-carboxamides	272

5.1.6	$NaHCO_3$ mediated synthesis of 2-imino-2*H*-chromene-3-carboxamides	273
5.1.7	TBPB initiated regioselective synthesis of C-3-carboxamidecoumarins	273
5.2.1	Reaction design and serendipity	273
5.3.1	Coumarin scope	276

List of Tables

Table No.	Table Caption	Page
2.3.1	Optimization of reaction condition	31
3.3.1	Optimization Studies	136
4.3.1	Optimization Studies	196
4.5.2.1	Catalyst screening	203
4.5.2.2	Effect of solvent, temperature, and concentration	204
5.3.1	Optimization studies	275

List of Abbreviations

Abbreviation	Full form
Ac	Acetate
MeCN/CH_3CN/ACN	Acetonitrile
Ar	Aryl
$BF_3.OEt_2$	Boron trifluoride etherate
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
^{t}Bu	*tert*-Butyl
$CDCl_3$	Deuterated chloroform
CH_2Cl_2	Dichloromethane
CPA	Chiral Phosphoric Acid
cm-1	Wavenumbers
°C	Degrees Celsius
2,4-DNBA	2,4-Dinitrobenzoic acid
dr	Diastereomeric ratio
DIPEA	*N*, *N*-Diisopropylethylamine
DMAP	*N*, *N*-Dimethylpyridin-4-amine
DABCO	1,4-diazabicyclo[2.2.2]octane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMF	Dimethylformamide
d	Doublet
dd	Doublet of doublets
DMSO-d6	Deuterated dimethyl sulfoxide
δ	Chemical shift
er	Enantiomeric ratio
ee	Enantiomeric excess
ESI-TOF	Electrospray ionization - Time-of-flight
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
FTIR	Fourier transform infrared
H_2O	Water
h	Hour
HCN	Hydrogen cyanide
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
J	Coupling constant
λ	Wavelength
LUMO	Lowest unoccupied molecular orbital
LDA	Lithium diisopropylamide
min	Minute

MTBE	Methyl *tert*-butyl ether
m	Multiplet
MHz	Megahertz
mL	Millilitre
MeOD	Deuterated methanol
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-*2H*-tetrazolium bromide
μL	Microlitre
NHC	N-Heterocyclic carbenes
NBS	N-Bromosuccinimide
PNBA	*para*-Nitrobenzoic acid
p-TsOH	*para*-Toluenesulfonic acid
PTC	Phase Transfer Catalyst
s	Singlet
SOMO	Singly unoccupied molecular orbital
TFA	Trifluoroacetic acid
TfOH	Triflic acid
TCA	Trichloroacetic acid
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TBAF	Tetra-*N*-butylammonium fluoride
UV	Ultraviolet